Collective Volume

1. ACETAL
2. ACETAMIDE
3. ACETAMIDINE HYDROCHLORIDE
4. P-ACETAMINOBENZENESULFINIC ACID
5. P-ACETAMINOBENZENESULFONYL CHLORIDE
6. ACETONEDICARBOXYLIC ACID
7. ACETYLMANDELIC ACID AND ACETYLMANDELYL CHLORIDE
8. ACID AMMONIUM O-SULFOBENZOATE
9. ACROLEIN
10. ADIPIC ACID
11. DL-ALANINE
12. ALKYL AND ALKYLENE BROMIDES
13. ALLYL ALCOHOL
14. ALLYL CYANIDE
15. α-AMINO-N-CAPROIC ACID
16. 1,4-AMINONAPHTHOL HYDROCHLORIDE
17. P-AMINOPHENYLACETIC ACID
18. AMMONIUM SALT OF AURIN TRICARBOXYLIC ACID
19. ANHYDRO-2-HYDROXYMERCURI-3-NITROBENZOIC ACID
20. ANISOLE
21. ANTHRONE
22. APPARATUS FOR CATALYTIC REDUCTION
23. L-ARABINOSE
24. ARSANILIC ACID
25. ARSONO- AND ARSENOACETIC ACIDS
26. P-ARSONOPHENOXYACETIC ACID
27. BENZALACETONE
28. BENZALACETOPHENONE
29. BENZALANILINE
30. BENZALPINACOLONE
31. BENZANILIDE
32. BENZENESULFONYL CHLORIDE
33. BENZIL
34. BENZILIC ACID
35. BENZOHYDROL

36. BENZOIC ANHYDRIDE
37. BENZOIN
38. BENZOPHENONE
39. BENZOYL PIPERIDINE
40. BENZYLACETOPHENONE
41. BENZYLANILINE
42. BENZYL BENZOATE
43. BENZYL CYANIDE
44. P-BROMOACETOPHENONE
45. 3-BROMO-4-AMINOTOLUENE
46. P-BROMOBIPHENYL
47. α-BROMO-N-CAPROIC ACID
48. 2-BROMOETHANOL
49. β-BROMOETHYLPHTHALIMIDE
50. α-BROMONAPHTHALENE
51. M-BROMONITROBENZENE
52. 2-BROMO-3-NITROBENZOIC ACID
53. P-BROMOPHENACYL BROMIDE
54. P-BROMOPHENOL
55. β-BROMOPROPIONIC ACID
56. M-BROMOTOLUENE
57. O-BROMOTOLUENE
58. P-BROMOTOLUENE
59. N-BUTYL N-BUTYRATE
60. N-BUTYL CARBAMATE
61. N-BUTYL CHLORIDE
62. TERT.-BUTYL CHLORIDE
63. N-BUTYL P-TOLUENESULFONATE
64. N-BUTYRYL CHLORIDE
65. CATECHOL
66. CHLOROACETAMIDE
67. O-CHLOROBENZOYL CHLORIDE
68. γ-CHLOROBUTYRONITRILE
69. 2-CHLOROCYCLOHEXANOL
70. P-CHLOROMERCURIBENZOIC ACID
71. O-CHLOROMERCURIPHENOL
72. M-CHLORONITROBENZENE
73. P-CHLOROPHENYL ISOTHIOCYANATE

74. β-CHLOROPROPIONIC ACID
75. O-CHLOROTOLUENE AND P-CHLOROTOLUENE
76. CREATININE
77. P-CRESOL
78. CUPFERRON
79. CYANOACETAMIDE
80. α-CYANO-β-PHENYLACRYLIC ACID
81. CYCLOHEXENE
82. CYCLOHEXENE OXIDE
83. 3-CYCLOHEXYL-2-BROMOPROPENE
84. CYCLOHEXYLCARBINOL
85. 3-CYCLOHEXYLPROPINE
86. CYCLOPENTANONE
87. L-CYSTINE
88. DIACETONAMINE HYDROGEN OXALATE
89. DIACETONE ALCOHOL
90. DIALLYLAMINE
91. DIALLYLCYANAMIDE
92. DIBENZOYLMETHANE
93. 9,10-DIBROMOANTHRACENE
94. 2,3-DIBROMOPROPENE
95. α,γ-DICHLOROACETONE
96. P-DIMETHYLAMINOBENZALDEHYDE
97. P-DIMETHYLAMINOBENZOPHENONE
98. 3,5-DINITROANISOLE
99. DI-O-NITROPHENYL DISULFIDE
100. DIPHENIC ACID
101. DIPHENYLACETIC ACID
102. 1,1-DIPHENYLETHYLENE
103. DIPHENYLMERCURY
104. 1,1-DI-P-TOLYLETHANE
105. DI-P-TOLYLMERCURY
106. EPICHLOROHYDRIN
107. ETHYL ACETOACETATE
108. ETHYL ACETONEDICARBOXYLATE
109. ETHYL ACETOPYRUVATE
110. ETHYL P-AMINOBENZOATE
111. ETHYL BENZOYLFORMATE

112. ETHYL BROMOMALONATE
113. ETHYL β-BROMOPROPIONATE
114. ETHYL N-BUTYLACETOACETATE
115. ETHYL N-BUTYLMALONATE
116. ETHYL CINNAMATE
117. ETHYL CYANOACETATE
118. ETHYLENE CYANOHYDRIN
119. ETHYL ORTHOFORMATE
120. ETHYL OXALATE
121. ETHYL OXOMALONATE
122. ETHYL PHENYLACETATE
123. ETHYL PHTHALIMIDOMALONATE
124. ETHYL PROPANE-1,1,2,3-TETRACARBOXYLATE
125. FURAN
126. 2-FURANCARBOXYLIC ACID AND 2-FURYLCARBINOL
127. FURFURAL
128. 2-FURFURALACETONE
129. 2-FURYLMETHYL ACETATE
130. D-GLUTAMIC ACID
131. GLUTARIC ACID
132. GLYCEROL α,γ-DICHLOROHYDRIN
133. GLYCEROL α-MONOCHLOROHYDRIN
134. α-GLYCERYL PHENYL ETHER
135. GLYCINE
136. GUANIDINE NITRATE
137. N-HEPTYL ALCOHOL
138. N-HEXYL ALCOHOL
139. HYDRAZINE SULFATE
140. HYDROCINNAMIC ACID
141. HYDROGEN CYANIDE (ANHYDROUS)
142. HYDROXYHYDROQUINONE TRIACETATE
143. HYDROXYLAMINE HYDROCHLORIDE AND ACETOXIME
144. β-HYDROXYPROPIONIC ACID
145. IODOBENZENE
146. P-IODOBENZOIC ACID
147. O-IODOPHENOL
148. ISATIN
149. KETENE

150. LEVULINIC ACID
151. MANDELIC ACID
152. L-MENTHONE
153. MESITYLENE
154. MESITYL OXIDE
155. METHYLAMINE HYDROCHLORIDE
156. METHYL N-AMYL KETONE
157. β-METHYLANTHRAQUINONE
158. METHYLENEAMINOACETONITRILE
159. METHYLENE BROMIDE
160. METHYLENE IODIDE
161. 4-METHYLESCULETIN
162. DL-METHYLETHYLACETIC ACID
163. α-METHYL D-GLUCOSIDE
164. METHYL-N-HEXYLCARBINOL
165. α-METHYL MANNOSIDE
166. METHYL M-NITROBENZOATE
167. METHYL RED
168. MONOCHLOROMETHYL ETHER
169. MYRISTIC ACID
170. β-NAPHTHOL PHENYLAMINOMETHANE
171. 1,4-NAPHTHOQUINONE
172. NICOTINIC ACID
173. O-NITROANILINE
174. NITROANTHRONE
175. M-NITROBENZOIC ACID
176. P-NITROBENZOIC ACID
177. P-NITROBENZOYL CHLORIDE
178. P-NITROBENZYL CYANIDE
179. M-NITROCINNAMIC ACID
180. NITROGUANIDINE
181. NITROMETHANE
182. M-NITROPHENOL
183. P-NITROPHENYLACETIC ACID
184. 3-NITROPHTHALIC ACID
185. 3-NITROPHTHALIC ANHYDRIDE
186. NITROSO-β-NAPHTHOL
187. NITROSTYRENE

188. M-NITROTOLUENE
189. NITROUREA
190. D- AND L-OCTANOL-2
191. OXALIC ACID (ANHYDROUS)
192. PENTAERYTHRITOL
193. PENTAMETHYLENE BROMIDE
194. 2-PENTENE
195. PERBENZOIC ACID
196. γ-PHENOXYPROPYL BROMIDE
197. PHENYLACETIC ACID
198. PHENYLACETYLENE
199. PHENYLETHYLENE
200. PHENYLHYDRAZINE
201. β-PHENYLHYDROXYLAMINE
202. PHENYL ISOTHIOCYANATE
203. 4-PHENYLSEMICARBAZIDE
204. PHENYLSUCCINIC ACID
205. PHENYLUREA AND SYM.-DIPHENYLUREA
206. PHLOROGLUCINOL
207. PHTHALIMIDE
208. PINACOL HYDRATE
209. PINACOLONE
210. PLATINUM CATALYST FOR REDUCTIONS
211. N-PROPYLBENZENE
212. PYRROLE
213. PYRUVIC ACID
214. QUINIZARIN
215. QUINOLINE
216. QUINONE
217. SEMICARBAZIDE SULFATE
218. SODIUM P-ARSONO-N-PHENYLGLYCINAMIDE
219. SODIUM P-HYDROXYPHENYLARSONATE
220. SODIUM P-TOLUENESULFINATE
221. STYRENE OXIDE
222. O-SULFOBENZOIC ANHYDRIDE
223. DL-TARTARIC ACID
224. AC-TETRAHYDRO-β-NAPHTHYLAMINE
225. THIOPHENOL

226. THIOPHOSGENE
227. THYMOQUINONE
228. O-TOLUNITRILE AND P-TOLUNITRILE
229. P-TOLUYL-O-BENZOIC ACID
230. P-TOLYLMERCURIC CHLORIDE
231. 1,2,3-TRIBROMOPROPANE
232. TRICARBALLYLIC ACID
233. TRIMETHYLACETIC ACID
234. TRIMETHYLAMINE
235. TRIMETHYLAMINE HYDROCHLORIDE
236. TRIMETHYLENE CHLOROHYDRIN
237. TRIMETHYLENE CYANIDE
238. TRIMETHYLGALLIC ACID
239. TRIMYRISTIN
240. 1,3,5-TRINITROBENZENE
241. 2,4,6-TRINITROBENZOIC ACID
242. TRIPHENYLAMINE
243. TRIPHENYLMETHANE
244. TRIPHENYLSTIBINE
245. XANTHONE
246. XANTHYDROL
247. α-ACETAMINOCINNAMIC ACID
248. ACETO-P-CYMENE
249. ACETOL
250. ACETONE CYANOHYDRIN
251. 2-ACETOTHIENONE
252. ACETYLENEDICARBOXYLIC ACID
253. ACETYLGLYCINE
254. ACONITIC ACID
255. ACRIDONE
256. ACROLEIN ACETAL
257. β-ALANINE
258. ALLANTOIN
259. ALLYLAMINE
260. γ-AMINOBUTYRIC ACID
261. ε-AMINOCAPROIC ACID
262. α-AMINOISOBUTYRIC ACID
263. 2-AMINO-4-METHYLTHIAZOLE

264. 1,2-AMINONAPHTHOL HYDROCHLORIDE
265. 1,4-AMINONAPHTHOL HYDROCHLORIDE
266. 1-AMINO-2-NAPHTHOL-4-SULFONIC ACID
267. 4-AMINOVERATROLE
268. N-AMYLBENZENE
269. D-ARGININE HYDROCHLORIDE
270. AZELAIC ACID
271. AZLACTONE OF α-BENZOYLAMINO-β-(3,4-DIMETHOXYPHENYL)-ACRYLIC ACID
272. AZOXYBENZENE
273. BARBITURIC ACID
274. BENZALPHTHALIDE
275. BENZANTHRONE
276. BENZIMIDAZOLE
277. BENZOHYDROXAMIC ACID
278. BENZOIN ACETATE
279. BENZOPHENONE OXIME
280. BENZOPINACOL
281. β-BENZOPINACOLONE
282. ε-BENZOYLAMINO-α-BROMOCAPROIC ACID
283. ε-BENZOYLAMINOCAPROIC ACID
284. BENZOYLENE UREA
285. β-BENZOYLPROPIONIC ACID
286. BENZYL PHTHALIMIDE
287. BETAINE HYDRAZIDE HYDROCHLORIDE
288. BROMAL
289. BROMOACETONE
290. P-BROMOBENZALDEHYDE
291. β-BROMOETHYLAMINE HYDROBROMIDE
292. α-BROMOISOVALERIC ACID
293. BROMOMESITYLENE
294. O-BROMOPHENOL
295. 4-BROMORESORCINOL
296. 1,3-BUTADIENE
297. N-BUTYL BORATE
298. N-BUTYL NITRITE
299. N-BUTYL PHOSPHATE
300. N-BUTYL SULFATE

301. N-BUTYL SULFITE
302. BUTYROIN
303. 2-CARBETHOXYCYCLOPENTANONE
304. CASEIN
305. CELLOBIOSE
306. α-CELLOBIOSE OCTAACETATE
307. CHELIDONIC ACID
308. α-CHLOROANTHRAQUINONE
309. M-CHLOROBENZALDEHYDE
310. P-CHLOROBENZALDEHYDE
311. O-CHLOROBENZOIC ACID
312. β-CHLOROETHYL METHYL SULFIDE
313. β-CHLOROPROPIONALDEHYDE ACETAL
314. CHOLESTANONE
315. CITRACONIC ANHYDRIDE AND CITRACONIC ACID
316. COPPER CHROMITE CATALYST
317. COUPLING OF O-TOLIDINE AND CHICAGO ACID
318. CYANOGEN BROMIDE
319. CYCLOHEXYLBENZENE
320. DECAMETHYLENE GLYCOL
321. DESOXYBENZOIN
322. DESYL CHLORIDE
323. 2,4-DIAMINOTOLUENE
324. DIAZOAMINOBENZENE
325. DIAZOMETHANE
326. DIBENZALACETONE
327. 1,4-DIBENZOYLBUTANE
328. 1,2-DIBROMOCYCLOHEXANE
329. 2,6-DIBROMO-4-NITROPHENOL
330. 2,6-DIBROMOQUINONE-4-CHLOROIMIDE
331. α,β-DIBROMOSUCCINIC ACID
332. DI-N-BUTYLCARBINOL
333. DICHLOROACETIC ACID
334. β-DIETHYLAMINOETHYL ALCOHOL
335. DIETHYL ZINC
336. 4,4'-DIFLUOROBIPHENYL
337. DIHYDROCHOLESTEROL
338. 3,4-DIHYDRO-1,2-NAPHTHALIC ANHYDRIDE

339. 2,6-DIIODO-P-NITROANILINE
340. 2,4-DIMETHYL-5-CARBETHOXYPYRROLE
341. 5,5-DIMETHYL-1,3-CYCLOHEXANEDIONE
342. 2,4-DIMETHYL-3,5-DICARBETHOXYPYRROLE
343. DIMETHYLGLYOXIME
344. SYM.-DIMETHYLHYDRAZINE DIHYDROCHLORIDE
345. UNSYM.-DIMETHYLHYDRAZINE HYDROCHLORIDE
346. 2,6-DIMETHYLPYRIDINE
347. 2,4-DIMETHYLPYRROLE
348. 2,5-DIMETHYLPYRROLE
349. 2,4-DINITROANILINE
350. 2,4-DINITROBENZALDEHYDE
351. P-DINITROBENZENE
352. 2,4-DINITROPHENYLHYDRAZINE
353. 1,4-DIPHENYLBUTADIENE
354. 4,5-DIPHENYLGLYOXALONE
355. DIPHENYLMETHANE
356. DIPHENYLMETHANE IMINE HYDROCHLORIDE
357. β,β-DIPHENYLPROPIOPHENONE
358. DIPHENYL SELENIDE
359. DIPHENYLSELENIUM DICHLORIDE AND TRIPHENYLSELENONIUM CHLORIDE
360. DIPHENYL SULFIDE
361. DIPHENYL TRIKETONE
362. N-DODECYL BROMIDE
363. DURENE
364. DUROQUINONE
365. EPICHLOROHYDRIN AND EPIBROMOHYDRIN
366. ERUCIC ACID
367. ETHOXYACETIC ACID AND ETHYL ETHOXYACETATE
368. ETHYL ACETOSUCCINATE
369. ETHYL ADIPATE
370. ETHYL BENZOYLACETATE
371. ETHYL BENZOYLDIMETHYLACETATE
372. ETHYL α,β-DIBROMO-β-PHENYLPROPIONATE
373. ETHYL ETHOXALYLPROPIONATE
374. ETHYL ETHYLENETETRACARBOXYLATE
375. ETHYL HYDROGEN SEBACATE

376. ETHYL N-METHYLCARBAMATE
377. ETHYL METHYLMALONATE
378. ETHYL α-NAPHTHOATE
379. ETHYL α-PHENYLACETOACETATE
380. ETHYL PHENYLCYANOPYRUVATE
381. ETHYL PHENYLMALONATE
382. N-ETHYL-MTOLUIDINE
383. ETHYL N-TRIDECYLATE
384. FLUOROBENZENE
385. P-FLUOROBENZOIC ACID
386. FUMARIC ACID
387. GALLACETOPHENONE
388. DL-GLYCERALDEHYDE
389. DL-GLYCERALDEHYDE ETHYL ACETAL
390. GLYCEROL α,γ-DIBROMOHYDRIN
391. GLYCINE ETHYL ESTER HYDROCHLORIDE
392. UNSYM.-HEPTACHLOROPROPANE
393. HEPTALDOXIME
394. N-HEPTANOIC ACID
395. 2-HEPTANOL
396. N-HEPTYLAMINE
397. N-HEXADECANE
398. N-HEXADECYL IODIDE
399. N-HEXALDEHYDE
400. HEXAMETHYLENE GLYCOL
401. HIPPURIC ACID
402. L-HISTIDINE MONOHYDROCHLORIDE
403. HOMOVERATRIC ACID
404. α-HYDRINDONE
405. HYDROGEN BROMIDE (ANHYDROUS)
406. P-HYDROXYBENZOIC ACID
407. 2-HYDROXY-3,5-DIIODOBENZOIC ACID
408. β-HYDROXYETHYL METHYL SULFIDE
409. P-IODOANILINE
410. 5-IODOANTHRANILIC ACID
411. IODOBENZENE
412. M-IODOBENZOIC ACID
413. P-IODOPHENOL

414. 2-IODOTHIOPHENE
415. ISOBUTYL BROMIDE
416. ISODURENE
417. ISONITROSOPROPIOPHENONE
418. ISOPROPYL LACTATE
419. ISOPROPYL THIOCYANATE
420. ITACONIC ANHYDRIDE AND ITACONIC ACID
421. 2-KETOHEXAMETHYLENIMINE
422. LAURYL ALCOHOL
423. DL-LYSINE HYDROCHLORIDES
424. MALONIC ACID
425. MALONONITRILE
426. MERCURY DI-β-NAPHTHYL
427. MESACONIC ACID
428. DL-METHIONINE
429. METHOXYACETONITRILE
430. METHYL BENZYL KETONE
431. 5-METHYLFURFURAL
432. METHYLHYDRAZINE SULFATE
433. METHYLIMINODIACETIC ACID
434. METHYL IODIDE
435. METHYL ISOPROPYL CARBINOL
436. METHYL ISOPROPYL KETONE
437. S-METHYL ISOTHIOUREA SULFATE
438. METHYL NITRATE
439. METHYL OXALATE
440. 3-METHYLPENTANOIC ACID
441. α-METHYL-α-PHENYLHYDRAZINE
442. 1-METHYL-2-PYRIDONE
443. 6-METHYLURACIL
444. 1,2-NAPHTHALIC ANHYDRIDE
445. α-NAPHTHOIC ACID
446. β-NAPHTHOIC ACID
447. 1,2-NAPHTHOQUINONE
448. β-NAPHTHYLMERCURIC CHLORIDE
449. M-NITROACETOPHENONE
450. 1-NITRO-2-ACETYLAMINONAPHTHALENE
451. NITROBARBITURIC ACID

452. P-NITROBENZALDEHYDE
453. P-NITROBENZYL BROMIDE
454. P-NITRODIPHENYL ETHER
455. 2-NITROFLUORENE AND 2-AMINOFLUORENE
456. NITROMESITYLENE
457. 1-NITRO-2-NAPHTHOL
458. P-NITROPHENYL ISOCYANATE
459. O-NITROPHENYLSULFUR CHLORIDE
460. 4-NITROPHTHALIC ACID
461. 4-NITROPHTHALIMIDE
462. N-NITROSOMETHYLANILINE
463. NITROSOMETHYLUREA
464. NITROSOMETHYLURETHANE
465. 2-NITROTHIOPHENE
466. OLEYL ALCOHOL
467. ORTHANILIC ACID
468. PELARGONIC ACID
469. PENTAERYTHRITYL BROMIDE AND IODIDE
470. N-PENTANE
471. PHENACYL BROMIDE
472. 2- AND 3-PHENANTHRENESULFONIC ACIDS
473. PHENOXTHIN
474. α-PHENYLACETOACETONITRILE
475. DL-β-PHENYLALANINE
476. PHENYLARSONIC ACID
477. PHENYLBENZOYLDIAZOMETHANE
478. α-PHENYL-β-BENZOYLPROPIONITRILE
479. γ-PHENYLBUTYRIC ACID
480. O-PHENYLENEDIAMINE
481. α-PHENYLETHYLAMINE
482. D- AND L-α-PHENYLETHYLAMINE
483. PHENYLGLYOXAL
484. PHENYLNITROMETHANE
485. PHENYLPROPIOLIC ACID
486. 2-PHENYLPYRIDINE
487. PHENYLPYRUVIC ACID
488. PHENYL THIENYL KETONE
489. PHLOROACETOPHENONE

490. PHTHALALDEHYDIC ACID
491. PHTHALIDE
492. SYMMETRICAL AND UNSYMMETRICAL O-PHTHALYL CHLORIDES
493. PIMELIC ACID
494. PIPERONYLIC ACID
495. POTASSIUM ANTHRAQUINONE-α-SULFONATE
496. PROPIONALDEHYDE
497. O-PROPIOPHENOL AND P-PROPIOPHENOL
498. L-PROPYLENE GLYCOL
499. N-PROPYL SULFIDE
500. PROTOCATECHUALDEHYDE
501. PYROMELLITIC ACID
502. QUINONE
503. REINECKE SALT
504. β-RESORCYLIC ACID
505. SODIUM 2-BROMOETHANESULFONATE
506. SUCCINIC ANHYDRIDE
507. SUCCINIMIDE
508. TAURINE
509. TETRAHYDROFURAN
510. α-TETRALONE
511. TETRAMETHYLENE CHLOROHYDRIN
512. THIOBENZOPHENONE
513. P-THIOCYANODIMETHYLANILINE
514. β-THIODIGLYCOL
515. THIOPHENE
516. THIOSALICYLIC ACID
517. P-TOLUALDEHYDE
518. O-TOLUAMIDE
519. O-TOLUIC ACID
520. P-TOLYL CARBINOL
521. SYM.-TRIBROMOBENZENE
522. TRICARBETHOXYMETHANE
523. TRICARBOMETHOXYMETHANE
524. TRICHLOROETHYL ALCOHOL
525. TRIETHYL CARBINOL
526. 1,2,3-TRIIODO-5-NITROBENZENE

527. TRIPHENYLETHYLENE
528. TRIPHENYLMETHYLSODIUM
529. SYM.-TRITHIANE
530. L-TRYPTOPHANE
531. URAMIL
532. VERATRALDEHYDE
533. VERATRONITRILE
534. ACENAPHTHENEQUINONE
535. ACENAPHTHENOL-7
536. β-(3-ACENAPHTHOYL)PROPIONIC ACID
537. ACETOACETANILIDE
538. ACETOBROMOGLUCOSE
539. 2-ACETOTHIENONE
540. ACETYLACETONE
541. ACETYLBENZOYL
542. 1-ACETYLCYCLOHEXENE
543. 2-ACETYLFLUORENE
544. 9-ACETYLPHENANTHRENE
545. ACID ANHYDRIDES
546. ACRYLIC ACID
547. β-ALANINE
548. ALLOXAN MONOHYDRATE
549. ALLOXANTIN DIHYDRATE
550. 2-ALLYLCYCLOHEXANONE
551. ALLYL LACTATE
552. ALUMINUM TERT-BUTOXIDE
553. AMINOACETAL
554. 9-AMINOACRIDINE
555. O-AMINOBENZALDEHYDE
556. M-AMINOBENZALDEHYDE DIMETHYLACETAL
557. O-AMINOBENZYL ALCOHOL
558. 2-AMINO-P-CYMENE
559. α-AMINODIETHYLACETIC ACID
560. 5-AMINO-2,3-DIHYDRO-1,4-PHTHALAZINEDIONE
561. 4-AMINO-2,6-DIMETHYLPYRIMIDINE
562. AMINOGUANIDINE BICARBONATE
563. 2-AMINO-6-METHYLBENZOTHIAZOLE
564. 3-AMINO-2-NAPHTHOIC ACID

565. 2-AMINO-4-NITROPHENOL
566. DL-α-AMINOPHENYLACETIC ACID
567. P-AMINOPHENYL DISULFIDE
568. DL-α-AMINO-α-PHENYLPROPIONIC ACID
569. DL-β-AMINO-β-PHENYLPROPIONIC ACID
570. β-AMINOPROPIONITRILE AND BIS-(β-CYANOETHYL)-AMINE
571. 3-AMINO-1H-1,2,4-TRIAZOLE
572. 4-AMINO-4H-1,2,4-TRIAZOLE
573. 9-ANTHRALDEHYDE; 2-ETHOXY-1-NAPHTHALDEHYDE
574. D-ARABINOSE
575. AZOBENZENE
576. BENZALACETONE DIBROMIDE
577. 1,2,3-BENZOTRIAZOLE
578. BENZOYLACETANILIDE
579. β-BENZOYLACRYLIC ACID
580. BENZOYL CYANIDE
581. BENZOYLFORMIC ACID
582. BENZOYL DISULFIDE
583. BENZYL CHLOROMETHYL KETONE
584. BIALLYL
585. BROMOACETAL
586. α-BROMOBENZALACETONE
587. α-BROMOHEPTALDEHYDE
588. 3-BROMO-4-HYDROXYTOLUENE
589. 6-BROMO-2-NAPHTHOL
590. 9-BROMOPHENANTHRENE
591. 2-BROMOPYRIDINE
592. 4-BROMO-O-XYLENE
593. O-N-BUTOXYNITROBENZENE
594. TERT-BUTYL ACETATE
595. N-BUTYL ACRYLATE
596. TERT-BUTYLAMINE
597. N-BUTYLBENZENE
598. 1-N-BUTYLPYRROLIDINE
599. N-CAPROIC ANHYDRIDE
600. 3-CARBETHOXYCOUMARIN
601. CARBOBENZOXY CHLORIDE AND DERIVATIVES
602. β-CARBOMETHOXYPROPIONYL CHLORIDE

603. CARBOXYMETHOXYLAMINE HEMIHYDROCHLORIDE
604. O-CARBOXYPHENYLACETONITRILE
605. CATALYST, RANEY NICKEL, W-6
606. CATALYST, RANEY NICKEL, W-2
607. P-CHLOROACETYLACETANILIDE
608. O-CHLOROBROMOBENZENE
609. 4-CHLOROBUTYL BENZOATE
610. 2-CHLOROCYCLOHEXANONE
611. ω-CHLOROISONITROSOACETOPHENONE
612. 2-CHLOROLEPIDINE
613. 1-CHLOROMETHYLNAPHTHALENE
614. 2-CHLOROMETHYLTHIOPHENE
615. M-CHLOROPHENYLMETHYLCARBINOL
616. γ-CHLOROPROPYL ACETATE
617. M-CHLOROSTYRENE
618. CHOLESTENONE
619. COUMARILIC ACID
620. 9-CYANOPHENANTHRENE
621. 1,1-CYCLOBUTANEDICARBOXYLIC ACID AND CYCLOBUTANECARBOXYLIC ACID
622. TRANS-1,2-CYCLOHEXANEDIOL
623. α-CYCLOHEXYLPHENYLACETONITRILE
624. CYCLOPROPANECARBOXYLIC ACID
625. CYCLOPROPYL CYANIDE
626. CYSTEIC ACID MONOHYDRATE
627. DECAMETHYLENE BROMIDE
628. DECAMETHYLENEDIAMINE
629. DEHYDROACETIC ACID
630. NOR-DESOXYCHOLIC ACID
631. 3,12-DIACETOXY-BISNOR-CHOLANYLDIPHENYLETHYLENE
632. 4,4'-DIAMINODIPHENYLSULFONE
633. 1,2-DIAMINO-4-NITROBENZENE
634. DIAZOMETHANE
635. TRANS-DIBENZOYLETHYLENE
636. DIBENZOYLMETHANE
637. β-DI-N-BUTYLAMINOETHYLAMINE
638. γ-DI-N-BUTYLAMINOPROPYLAMINE
639. DI-β-CARBETHOXYETHYLMETHYLAMINE

640. α,α-DICHLOROACETAMIDE
641. 2,6-DICHLOROANILINE AND 2,6-DIBROMOANILINE
642. 2,6-DICHLOROPHENOL
643. DI-(P-CHLOROPHENYL)ACETIC ACID
644. 4,7-DICHLOROQUINOLINE
645. DIETHYLAMINOACETONITRILE
646. 2,3-DIHYDROPYRAN
647. DIHYDRORESORCINOL
648. 2,5-DIHYDROXYACETOPHENONE
649. 2,6-DIHYDROXYACETOPHENONE
650. 2,5-DIHYDROXY-P-BENZENEDIACETIC ACID
651. 3,5-DIHYDROXYBENZOIC ACID
652. DIISOVALERYLMETHANE
653. 2,6-DIMETHOXYBENZONITRILE
654. 3,3'-DIMETHOXYBIPHENYL AND 3,3'-DIMETHYLBIPHENYL
655. 6,7-DIMETHOXY-3,4-DIHYDRO-2-NAPHTHOIC ACID
656. β,β-DIMETHYLACRYLIC ACID
657. β-DIMETHYLAMINOPROPIOPHENONE HYDROCHLORIDE
658. 3,4-DIMETHYLANILINE
659. 2,3-DIMETHYLANTHRAQUINONE
660. 2,3-DIMETHYL-1,3-BUTADIENE
661. 3,5-DIMETHYL-4-CARBETHOXY-2-CYCLOHEXEN-1-ONE AND 3,5-DIMETHYL-2-CYCLOHEXEN-1-ONE
662. DIMETHYLETHYNYLCARBINOL
663. 5,5-DIMETHYLHYDANTOIN
664. 2,5-DIMETHYLMANDELIC ACID
665. 1,5-DIMETHYL-2-PYRROLIDONE
666. 2,4-DIMETHYLQUINOLINE
667. 2,4-DIMETHYLTHIAZOLE
668. 2,5-DINITROBENZOIC ACID
669. 3,5-DINITROBENZOIC ACID
670. 2,2'-DINITROBIPHENYL
671. 1,4-DINITRONAPHTHALENE
672. α,α-DIPHENYLACETONE
673. DIPHENYLACETONITRILE
674. DIPHENYLACETYLENE
675. DIPHENYLDIAZOMETHANE
676. 2,3-DIPHENYLINDONE (2,3-DIPHENYL-1-INDENONE)

677. DIPHENYLIODONIUM IODIDE
678. DIPHENYLKETENE
679. 2,4-DIPHENYLPYRROLE
680. DITHIZONE
681. N-DODECYL (LAURYL) MERCAPTAN
682. N-DODECYL (LAURYL) P-TOLUENESULFONATE
683. DYPNONE
684. β-ETHOXYETHYL BROMIDE
685. β-ETHOXYPROPIONALDEHYDE ACETAL
686. β-ETHOXYPROPIONITRILE
687. ETHYL β-ANILINOCROTONATE
688. ETHYL AZODICARBOXYLATE
689. ETHYL BENZALMALONATE
690. ETHYL BENZOYLACETATE
691. ETHYL BROMOACETATE
692. ETHYL N-BUTYLCYANOACETATE
693. 2-ETHYLCHROMONE
694. ETHYL DIACETYLACETATE
695. ETHYL DIAZOACETATE
696. ETHYLENE THIOUREA
697. ETHYL ETHOXYMETHYLENEMALONATE
698. ETHYL (1-ETHYLPROPENYL)METHYLCYANOACETATE
699. ETHYL (1-ETHYLPROPYLIDENE)CYANOACETATE
700. ETHYL 1,16-HEXADECANEDICARBOXYLATE
701. ETHYL HYDRAZINECARBOXYLATE AND DIAMINOBIURET
702. ETHYL α-ISOPROPYLACETOACETATE
703. ETHYL β-PHENYL-β-HYDROXYPROPIONATE
704. 4-ETHYLPYRIDINE
705. ETHYL 2-PYRIDYLACETATE
706. ETHYL N-TRICARBOXYLATE
707. 1-ETHYNYLCYCLOHEXANOL
708. O-EUGENOL
709. FLUORENONE-2-CARBOXYLIC ACID
710. FUMARYL CHLORIDE
711. FURYLACRYLIC ACID
712. β-GENTIOBIOSE OCTAACETATE
713. D-GLUCOSAMINE HYDROCHLORIDE
714. β-D-GLUCOSE-1,2,3,4-TETRAACETATE

715. β-D-GLUCOSE-2,3,4,6-TETRAACETATE
716. GLYCOLONITRILE
717. GLYOXAL BISULFITE
718. GUANIDOACETIC ACID
719. HEMIN
720. O-N-HEPTYLPHENOL
721. HEXAMETHYLENE CHLOROHYDRIN
722. HOMOPHTHALIC ACID AND ANHYDRIDE
723. HYDROQUINONE DIACETATE
724. M-HYDROXYBENZALDEHYDE
725. 2-HYDROXYCINCHONINIC ACID
726. β-(2-HYDROXYETHYLMERCAPTO)PROPIONITRILE
727. 4(5)-HYDROXYMETHYLIMIDAZOLE HYDROCHLORIDE
728. 2-HYDROXY-1-NAPHTHALDEHYDE
729. 2-HYDROXY-1,4-NAPHTHOQUINONE
730. 2-HYDROXY-5-NITROBENZYL CHLORIDE
731. 5-HYDROXYPENTANAL
732. IMIDAZOLE
733. INDAZOLE
734. INDOLE
735. IODOBENZENE DICHLORIDE
736. IODOSOBENZENE
737. IODOXYBENZENE
738. ISATOIC ANHYDRIDE
739. ISOBUTYRAMIDE
740. ISOBUTYRONITRILE
741. DL-ISOLEUCINE
742. ISOPRENE CYCLIC SULFONE
743. 2-ISOPROPYLAMINOETHANOL
744. DL-ISOPROPYLIDENEGLYCEROL
745. JULOLIDINE
746. KETENE DIETHYLACETAL
747. KETENE DIMER
748. α-KETOGLUTARIC ACID
749. KRYPTOPYRROLE
750. LACTAMIDE
751. LEPIDINE
752. DL-LEUCINE

753. LINOLEIC ACID
754. LINOLENIC ACID
755. MALONONITRILE
756. MANDELAMIDE
757. MANDELIC ACID
758. D-MANNOSE
759. L-MENTHOXYACETIC ACID
760. L-MENTHOXYACETYL CHLORIDE
761. MESITALDEHYDE
762. MESITOIC ACID
763. MESITYLACETIC ACID
764. METHACRYLAMIDE
765. ω-METHOXYACETOPHENONE
766. M-METHOXYBENZALDEHYDE
767. 2-METHOXYDIPHENYL ETHER
768. 6-METHOXY-8-NITROQUINOLINE
769. 1-METHYLAMINOANTHRAQUINONE
770. 1-METHYLAMINO-4-BROMOANTHRAQUINONE
771. METHYL β-BROMOPROPIONATE
772. METHYL 5-BROMOVALERATE
773. 4-METHYLCARBOSTYRIL
774. 4-METHYLCOUMARIN
775. METHYL ω-CYANOPELARGONATE
776. N-METHYL-3,4-DIHYDROXYPHENYLALANINE
777. N-METHYLFORMANILIDE
778. β-METHYLGLUTARIC ACID
779. 2-METHYL-4-HYDROXYQUINOLINE
780. 1-METHYL-2-IMINO-β-NAPHTHOTHIAZOLINE
781. 2-METHYLINDOLE
782. METHYL ISOTHIOCYANATE
783. METHYL 4-KETO-7-METHYLOCTANOATE
784. METHYL MYRISTATE AND METHYL PALMITATE AND THE CORRESPONDING ACIDS
785. N-METHYL-1-NAPHTHYLCYANAMIDE
786. 1-METHYL-1-(1-NAPHTHYL)-2-THIOUREA
787. METHYL PYRUVATE
788. METHYL SEBACAMATE
789. METHYLSUCCINIC ACID

790. METHYLTHIOUREA
791. MONOPERPHTHALIC ACID
792. MUCOBROMIC ACID
793. MUCONIC ACID
794. β-NAPHTHALDEHYDE
795. α-NAPHTHONITRILE
796. 1,2-NAPHTHOQUINONE-4-SULFONATE, AMMONIUM AND POTASSIUM
797. NAPHTHORESORCINOL
798. O-NITROBENZALDEHYDE
799. M-NITROBENZALDEHYDE DIMETHYLACETAL
800. P-NITROBENZONITRILE
801. P-NITROBENZOYL PEROXIDE
802. P-NITROBENZYL ACETATE
803. P-NITROBENZYL ALCOHOL
804. 2-NITRO-P-CYMENE
805. 5-NITRO-2,3-DIHYDRO-1,4-PHTHALAZINEDIONE
806. M-NITRODIMETHYLANILINE
807. 5-NITROINDAZOLE
808. 2-NITRO-4-METHOXYANILINE
809. 4-NITRO-1-NAPHTHYLAMINE
810. P-NITROPHENYLARSONIC ACID
811. P-NITROPHENYL SULFIDE
812. NITROSOBENZENE
813. OLEYL ALCOHOL
814. OZONE
815. PALLADIUM CATALYSTS
816. PENTAACETYL D-GLUCONONITRILE
817. PENTAMETHYLENE BROMIDE
818. 1,5-PENTANEDIOL
819. 3-PENTEN-2-OL
820. 4-PENTEN-1-OL
821. PHENANTHRENE-9-ALDEHYDE
822. DL-PHENYLALANINE
823. 1-PHENYL-3-AMINO-5-PYRAZOLONE
824. PHENYL AZIDE
825. P-PHENYLAZOBENZOIC ACID
826. P-PHENYLAZOBENZOYL CHLORIDE

827. PHENYL CINNAMATE
828. α-PHENYLCINNAMONITRILE
829. α-PHENYLETHYLAMINE
830. β-PHENYLETHYLAMINE
831. β-PHENYLETHYLDIMETHYLAMINE
832. 2-PHENYLINDOLE
833. PHENYLMETHYLGLYCIDIC ESTER
834. 1-PHENYLNAPHTHALENE
835. PHENYLPROPARGYL ALDEHYDE
836. α-PHENYLPROPIONALDEHYDE
837. α-PHENYLTHIOUREA
838. PHTHALALDEHYDIC ACID
839. PICOLINIC ACID HYDROCHLORIDE
840. γ-N-PROPYLBUTYROLACTONE AND β-(TETRAHYDROFURYL) PROPIONIC ACID
841. PROTOCATECHUIC ACID
842. PSEUDOIONONE
843. PSEUDOTHIOHYDANTOIN
844. PYOCYANINE
845. 1-(α-PYRIDYL)-2-PROPANOL
846. PYROGALLOL 1-MONOMETHYL ETHER
847. RESACETOPHENONE
848. RHODANINE
849. SALICYL-O-TOLUIDE
850. SEBACONITRILE AND ω-CYANOPELARGONIC ACID
851. SELENOPHENOL
852. DL-SERINE
853. SODIUM AMIDE
854. SORBIC ACID
855. STEAROLIC ACID
856. TRANS-STILBENE
857. TEREPHTHALALDEHYDE
858. TEREPHTHALIC ACID
859. TETRAHYDROFURFURYL BROMIDE
860. TETRAHYDROPYRAN
861. TETRAIODOPHTHALIC ANHYDRIDE
862. α-TETRALONE
863. 2,3,4,6-TETRAMETHYL-D-GLUCOSE

864. TETRANITROMETHANE
865. TETRAPHENYLCYCLOPENTADIENONE
866. TETRAPHENYLPHTHALIC ANHYDRIDE
867. M-THIOCRESOL
868. 2-THIOPHENEALDEHYDE
869. DL-THREONINE
870. O-TOLUALDEHYDE
871. O-TOLUIC ACID
872. P-TOLUIC ACID
873. O-TOLUIDINESULFONIC ACID
874. M-TOLYLBENZYLAMINE
875. 1,3,5-TRIACETYLBENZENE
876. TRIBIPHENYLCARBINOL
877. 1,2,5-TRIHYDROXYPENTANE
878. TRIMETHYLENE OXIDE
879. 2,4,7-TRINITROFLUORENONE
880. TRIPHENYLCARBINOL
881. TRIPHENYLCHLOROMETHANE
882. UNDECYL ISOCYANATE
883. DL-VALINE
884. VINYLACETIC ACID
885. VINYL CHLOROACETATE
886. ABIETIC ACID
887. 3-ACETAMIDO-2-BUTANONE
888. N-(P-ACETYLAMINOPHENYL)RHODANINE
889. 9-ACETYLANTHRACENE
890. α-ACETYL-δ-CHLORO-γ-VALEROLACTONE
891. 1-ACETYLCYCLOHEXANOL
892. 2-P-ACETYLPHENYLHYDROQUINONE
893. δ-ACETYL-N-VALERIC ACID
894. ACROLEIN ACETAL
895. ALLOXAN MONOHYDRATE
896. ALLOXANTIN DIHYDRATE
897. 2-AMINO-4-ANILINO-6-(CHLOROMETHYL)-S-TRIAZINE
898. P-AMINOBENZALDEHYDE
899. 2-AMINOBENZOPHENONE
900. ε-AMINOCAPROIC ACID
901. 2-AMINO-3-NITROTOLUENE

902. 3-AMINOPYRIDINE
903. P-AMINOTETRAPHENYLMETHANE
904. ARYLUREASI. CYANATE METHODP-BROMOPHENYLUREA
905. ARYLUREASII. UREA METHODP-ETHOXYPHENYLUREA
906. DL-ASPARTIC ACID
907. ATROLACTIC ACID
908. AZELANITRILE
909. 1,1'-AZO-BIS-1-CYCLOHEXANENITRILE
910. BENZENEBORONIC ANHYDRIDE
911. BENZHYDRYL β-CHLOROETHYL ETHER
912. BENZOFURAZAN OXIDE
913. BENZOGUANAMINE
914. BENZOYLACETANILIDE
915. BENZOYLCHOLINE IODIDE AND CHLORIDE
916. 3-BENZOYLPYRIDINE
917. 2-BENZYLAMINOPYRIDINE
918. 3-BENZYL-3-METHYLPENTANOIC ACID
919. BENZYLTRIMETHYLAMMONIUM ETHOXIDE
920. BISCHLOROMETHYL ETHER
921. N-BROMOACETAMIDE
922. β-BROMOETHYLPHTHALIMIDE
923. 4-BROMO-2-HEPTENE
924. P-BROMOMANDELIC ACID
925. 2-BROMO-3-METHYLBENZOIC ACID
926. N-BUTYLACETYLENE
927. SEC-BUTYL α-N-CAPROYLPROPIONATE
928. N-BUTYL GLYOXYLATE
929. TERT-BUTYL HYPOCHLORITE
930. 2-BUTYN-1-OL
931. BUTYRCHLORAL
932. β-CARBETHOXY-γ,γ-DIPHENYLVINYLACETIC ACID
933. β-(O-CARBOXYPHENYL)PROPIONIC ACID
934. CETYLMALONIC ESTER
935. CHLOROACETONITRILE
936. 3-(O-CHLOROANILINO)PROPIONITRILE
937. CHLORO-P-BENZOQUINONE
938. N-CHLOROBETAINYL CHLORIDE
939. TRANS-2-CHLOROCYCLOPENTANOL

940. 1-CHLORO-2,6-DINITROBENZENE
941. 2-CHLORO-2-METHYLCYCLOHEXANONE AND 2-METHYL-2-CYCLOHEXENONE
942. 2-CHLORONICOTINONITRILE
943. α-CHLOROPHENYLACETIC ACID
944. O-CHLOROPHENYLCYANAMIDE
945. α-(4-CHLOROPHENYL)-γ-PHENYLACETOACETONITRILE
946. 1-(P-CHLOROPHENYL)-3-PHENYL-2-PROPANONE
947. P-CHLOROPHENYL SALICYLATE
948. O-CHLOROPHENYLTHIOUREA
949. 2-CHLOROPYRIMIDINE
950. 2-CHLORO-1,1,2-TRIFLUOROETHYL ETHYL ETHER
951. β-CHLOROVINYL ISOAMYL KETONE
952. Δ4-CHOLESTEN-3,6-DIONE
953. Δ4-CHOLESTEN-3-ONE
954. CHOLESTEROL, Δ5-CHOLESTEN-3-ONE, AND Δ4-CHOLESTEN-3-ONE
955. COUMALIC ACID
956. CREOSOL
957. N-2-CYANOETHYLANILINE
958. CYANOGEN IODIDE
959. 3-CYANO-6-METHYL-2(1)-PYRIDONE
960. 1-CYANO-3-PHENYLUREA
961. 1,2-CYCLODECANEDIOL
962. CYCLODECANONE
963. CYCLOHEPTANONE
964. 1,2-CYCLOHEXANEDIONE DIOXIME
965. CYCLOHEXENE SULFIDE
966. CYCLOHEXYLIDENECYANOACETIC ACID AND 1-CYCLOHEXENYLACETONITRILE
967. CYCLOPENTADIENE AND 3-CHLOROCYCLOPENTENE
968. DIACETYL-D-TARTARIC ANHYDRIDE
969. 2,5-DIAMINO-3,4-DICYANOTHIOPHENE
970. 2,4-DIAMINO-6-HYDROXYPYRIMIDINE
971. DIAMINOURACIL HYDROCHLORIDE
972. DIAZOMETHANE
973. DIBROMOACETONITRILE
974. 4,4'-DIBROMOBIPHENYL

975. DI-N-BUTYLDIVINYLTIN
976. DI-TERT-BUTYL MALONATE
977. 4,4'-DICHLORODIBUTYL ETHER
978. 1,1-DICHLORO-2,2-DIFLUOROETHYLENE
979. 2,2-DICHLOROETHANOL
980. 1,1'-DICYANO-1,1'-BICYCLOHEXYL
981. 1,2-DI-1-(1-CYANO)CYCLOHEXYLHYDRAZINE
982. DICYANOKETENE ETHYLENE ACETAL
983. DICYCLOPROPYL KETONE
984. 1-DIETHYLAMINO-3-BUTANONE
985. N,N'-DIETHYLBENZIDINE
986. DIETHYL BENZOYLMALONATE
987. DIETHYL 1,1-CYCLOBUTANEDICARBOXYLATE
988. DIETHYL Δ2-CYCLOPENTENYLMALONATE
989. DIETHYL ETHYLIDENEMALONATE
990. DIETHYL MERCAPTOACETAL
991. DIETHYL METHYLENEMALONATE
992. DIETHYL γ-OXOPIMELATE
993. DIETHYL CIS-Δ4-TETRAHYDROPHTHALATE AND DIETHYL CIS-HEXAHYDROPHTHALATE
994. DIETHYLTHIOCARBAMYL CHLORIDE
995. 3,4-DIHYDRO-2-METHOXY-4-METHYL-2H-PYRAN
996. 9,10-DIHYDROPHENANTHRENE
997. 9,10-DIHYDROXYSTEARIC ACID
998. 1,4-DIIODOBUTANE
999. 1,6-DIIODOHEXANE
1000. DIISOPROPYL METHYLPHOSPHONATE
1001. 2,3-DIMETHOXYCINNAMIC ACID
1002. DIMETHYL ACETYLENEDICARBOXYLATE
1003. P-DIMETHYLAMINOBENZALDEHYDE
1004. β-DIMETHYLAMINOETHYL CHLORIDE HYDROCHLORIDE
1005. 2-(DIMETHYLAMINO)PYRIMIDINE
1006. 4,6-DIMETHYLCOUMALIN
1007. N,N-DIMETHYLCYCLOHEXYLMETHYLAMINE
1008. DIMETHYLFURAZAN
1009. β,β-DIMETHYLGLUTARIC ACID
1010. DIMETHYLKETENE
1011. 5,5-DIMETHYL-2-N-PENTYLTETRAHYDROFURAN

1012. 3,5-DIMETHYLPYRAZOLE
1013. 2,2-DIMETHYLPYRROLIDINE
1014. 5,5-DIMETHYL-2-PYRROLIDONE
1015. N,N-DIMETHYLSELENOUREA
1016. ASYM-DIMETHYLUREA
1017. 2,6-DINITROANILINE
1018. P,P'-DINITROBIBENZYL
1019. 1,4-DINITROBUTANE
1020. 3,4-DINITRO-3-HEXENE
1021. DIPHENYLACETALDEHYDE
1022. DIPHENYLACETYLENE
1023. 1,4-DIPHENYL-5-AMINO-1,2,3-TRIAZOLE AND 4-PHENYL-5-ANILINO-1,2,3-TRIAZOLE
1024. N,N'-DIPHENYLBENZAMIDINE
1025. α,β-DIPHENYLCINNAMONITRILE
1026. DIPHENYL SUCCINATE
1027. 2,3-DIPHENYLSUCCINONITRILE
1028. P-DITHIANE
1029. TRANS-2-DODECENOIC ACID
1030. ETHANEDITHIOL
1031. ETHOXYACETYLENE
1032. ETHYL α-ACETYL-β-(2,3-DIMETHOXYPHENYL)-PROPIONATE
1033. ETHYL AZODICARBOXYLATE
1034. ETHYL BENZOYLACETATE
1035. ETHYL TERT-BUTYL MALONATE
1036. N-ETHYL-P-CHLOROANILINE
1037. ETHYL CHLOROFLUOROACETATE
1038. ETHYL DIAZOACETATE
1039. ETHYL DIETHOXYACETATE
1040. ETHYL ENANTHYLSUCCINATE
1041. ETHYLENIMINE
1042. 2-ETHYLHEXANONITRILE
1043. ETHYL ISOCYANIDE
1044. β-ETHYL-β-METHYLGLUTARIC ACID
1045. 4-ETHYL-2-METHYL-2-OCTENOIC ACID
1046. 5-ETHYL-2-METHYLPYRIDINE
1047. ETHYL α-NITROBUTYRATE
1048. ETHYL ORTHOCARBONATE

1049. ETHYL β,β-PENTAMETHYLENEGLYCIDATE
1050. ETHYL PHENYLCYANOACETATE
1051. ETHYL (1-PHENYLETHYLIDENE)CYANOACETATE
1052. ETHYL N-PHENYLFORMIMIDATE
1053. ETHYL α-(1-PYRROLIDYL)PROPIONATE
1054. ETHYL PYRUVATE
1055. 1,1'-ETHYNYLENE-BIS-CYCLOHEXANOL
1056. FERROCENE
1057. FLAVONE
1058. 9-FLUORENECARBOXYLIC ACID
1059. 5-FORMYL-4-PHENANTHROIC ACID
1060. FUMARONITRILE
1061. FURFURAL DIACETATE
1062. 2-FURFURYL MERCAPTAN
1063. 2-FUROIC ACID
1064. GLUTARIC ACID AND GLUTARIMIDE
1065. GUANYLTHIOUREA
1066. D-GULONIC-γ-LACTONE
1067. HEMIMELLITENE
1068. HENDECANEDIOIC ACID
1069. N-HEPTAMIDE
1070. 3-N-HEPTYL-5-CYANOCYTOSINE
1071. HEXAHYDRO-1,3,5-TRIPROPIONYL-S-TRIAZINE
1072. HEXAMETHYLBENZENE
1073. HEXAMETHYLENE DIISOCYANATE
1074. N-HEXYL FLUORIDE
1075. 4-HYDROXY-1-BUTANESULFONIC ACID SULTONE
1076. 6-HYDROXYNICOTINIC ACID
1077. 3-HYDROXYTETRAHYDROFURAN
1078. INDAZOLE
1079. INDOLE-3-ALDEHYDE
1080. IODOCYCLOHEXANE
1081. 2-IODOTHIOPHENE
1082. 4-IODOVERATROLE
1083. ISODEHYDROACETIC ACID AND ETHYL ISODEHYDROACETATE
1084. ISOPHORONE OXIDE
1085. ITACONYL CHLORIDE
1086. 6-KETOHENDECANEDIOIC ACID

1087. β-KETOISOÖCTALDEHYDE DIMETHYL ACETAL
1088. LAURONE
1089. LAURYLMETHYLAMINE
1090. 2-MERCAPTO-4-AMINO-5-CARBETHOXYPYRIMIDINE AND 2-MERCAPTO-4-HYDROXY-5-CYANOPYRIMIDINE
1091. 2-MERCAPTOBENZIMIDAZOLE
1092. METHANESULFONYL CHLORIDE
1093. O-METHOXYPHENYLACETONE
1094. P-METHOXYPHENYLACETONITRILE
1095. METHYL P-ACETYLBENZOATE
1096. O-METHYLBENZYL ALCOHOL
1097. 2-METHYLBENZYLDIMETHYLAMINE
1098. O-METHYLCAPROLACTIM
1099. 3-METHYLCOUMARONE
1100. METHYL CYCLOPENTANECARBOXYLATE
1101. METHYL CYCLOPROPYL KETONE
1102. 2-METHYL-2,5-DECANEDIOL
1103. N-METHYL-2,3-DIMETHOXYBENZYLAMINE
1104. N-METHYL-1,2-DIPHENYLETHYLAMINE AND HYDROCHLORIDE
1105. TRANS-2-METHYL-2-DODECENOIC ACID
1106. METHYLENECYCLOHEXANE AND N,N-DIMETHYLHYDROXYLAMINE HYDROCHLORIDE
1107. 2-METHYLENEDODECANOIC ACID
1108. 1-METHYL-3-ETHYLOXINDOLE
1109. 9-METHYLFLUORENE
1110. 5-METHYLFURFURYLDIMETHYLAMINE
1111. 3-METHYL-2-FUROIC ACID AND 3-METHYLFURAN
1112. β-METHYLGLUTARIC ANHYDRIDE
1113. METHYLGLYOXAL-ω-PHENYLHYDRAZONE
1114. METHYL HYDROGEN HENDECANEDIOATE
1115. 4-METHYL-6-HYDROXYPYRIMIDINE
1116. 1-METHYLISOQUINOLINE
1117. METHYLISOUREA HYDROCHLORIDE
1118. METHYL 3-METHYL-2-FUROATE
1119. METHYL γ-METHYL-γ-NITROVALERATE
1120. 3-METHYL-4-NITROPYRIDINE-1-OXIDE
1121. 3-METHYLOXINDOLE
1122. 3-METHYL-1,5-PENTANEDIOL

1123. β-METHYL-β-PHENYL-α,α'-DICYANOGLUTARIMIDE
1124. β-METHYL-β-PHENYLGLUTARIC ACID
1125. 1-METHYL-3-PHENYLINDANE
1126. METHYL 2-THIENYL SULFIDE
1127. METHYL β-THIODIPROPIONATE
1128. 3-METHYLTHIOPHENE
1129. METHYL P-TOLYL SULFONE
1130. β-METHYL-δ-VALEROLACTONE
1131. MONOBENZALPENTAERYTHRITOL
1132. MONOBROMOPENTAERYTHRITOL
1133. MONOVINYLACETYLENE
1134. MUCOBROMIC ACID
1135. 1-NAPHTHALDEHYDE
1136. NAPHTHALENE-1,5-DISULFONYL CHLORIDE
1137. 1,5-NAPHTHALENEDITHIOL
1138. 1,4-NAPHTHOQUINONE
1139. α-NAPHTHYL ISOTHIOCYANATE
1140. NEOPHYL CHLORIDE
1141. NICOTINAMIDE-1-OXIDE
1142. NICOTINONITRILE
1143. O-NITROACETOPHENONE
1144. 9-NITROANTHRACENE
1145. O- AND P-NITROBENZALDIACETATE
1146. M-NITROBENZAZIDE
1147. M-NITROBIPHENYL
1148. O-NITROCINNAMALDEHYDE
1149. 1-NITROÖCTANE
1150. 1-(P-NITROPHENYL)-1,3-BUTADIENE
1151. TRANS-O-NITRO-α-PHENYLCINNAMIC ACID
1152. M-NITROSTYRENE
1153. 6-NITROVERATRALDEHYDE
1154. NORBORNYLENE
1155. OLEOYL CHLORIDE
1156. PARABANIC ACID
1157. 1,4-PENTADIENE
1158. PENTAERYTHRITYL TETRABROMIDE
1159. 4-PENTYN-1-OL
1160. PHENANTHRENEQUINONE

1161. PHENYLACETAMIDE
1162. PHENYLACETYLENE
1163. γ-PHENYLALLYLSUCCINIC ACID
1164. N-PHENYLBENZAMIDINE
1165. TRANS-1-PHENYL-1,3-BUTADIENE
1166. α-PHENYL-α-CARBETHOXYGLUTARONITRILE
1167. α-PHENYLCINNAMIC ACID
1168. 2-PHENYLCYCLOHEPTANONE
1169. PHENYLDICHLOROPHOSPHINE
1170. 4-PHENYL-M-DIOXANE
1171. O-PHENYLENE CARBONATE
1172. α-PHENYLGLUTARIC ANHYDRIDE
1173. 1-PHENYL-1-PENTEN-4-YN-3-OL
1174. 1-PHENYLPIPERIDINE
1175. 3-PHENYL-1-PROPANOL
1176. PHENYLPROPARGYLALDEHYDE DIETHYL ACETAL
1177. PHENYLSUCCINIC ACID
1178. O-PHTHALALDEHYDE
1179. α-PHTHALIMIDO-O-TOLUIC ACID
1180. PROPIOLALDEHYDE
1181. PSEUDOPELLETIERINE
1182. PUTRESCINE DIHYDROCHLORIDE
1183. 2,3-PYRAZINEDICARBOXYLIC ACID
1184. PYRIDINE-N-OXIDE
1185. 2-PYRROLEALDEHYDE
1186. 2-(1-PYRROLIDYL)PROPANOL
1187. QUINACETOPHENONE MONOMETHYL ETHER
1188. SEBACIL
1189. SEBACOIN
1190. SODIUM NITROMALONALDEHYDE MONOHYDRATE
1191. SODIUM β-STYRENESULFONATE AND β-STYRENESULFONYL CHLORIDE
1192. STEAROLIC ACID
1193. STEARONE
1194. CIS-STILBENE
1195. TRANS-STILBENE OXIDE
1196. α-SULFOPALMITIC ACID
1197. SYRINGIC ALDEHYDE

1198. TETRAACETYLETHANE
1199. DL-4,4',6,6'-TETRACHLORODIPHENIC ACID
1200. TETRACYANOETHYLENE
1201. TETRAETHYLTIN
1202. 1,2,3,4-TETRAHYDROCARBAZOLE
1203. AR-TETRAHYDRO-α-NAPHTHOL
1204. CIS-Δ4-TETRAHYDROPHTHALIC ANHYDRIDE
1205. TETRAHYDROTHIOPHENE
1206. TETRALIN HYDROPEROXIDE
1207. α-TETRALONE
1208. β-TETRALONE
1209. 2,2,6,6-TETRAMETHYLOLCYCLOHEXANOL
1210. TETRAPHENYLARSONIUM CHLORIDE HYDROCHLORIDE
1211. TETRAPHENYLETHYLENE
1212. 2-THENALDEHYDE
1213. 3-THENALDEHYDE
1214. 3-THENOIC ACID
1215. 3-THENYL BROMIDE
1216. THIOBENZOIC ACID
1217. THIOBENZOPHENONE
1218. THIOLACETIC ACID
1219. O-TOLUALDEHYDE
1220. P-TOLUENESULFENYL CHLORIDE
1221. P-TOLUENESULFINYL CHLORIDE
1222. P-TOLUENESULFONIC ANHYDRIDE
1223. P-TOLYLSULFONYLMETHYLNITROSAMIDE
1224. 2,4,6-TRIBROMOBENZOIC ACID
1225. TRICHLOROMETHYLPHOSPHONYL DICHLORIDE
1226. P-TRICYANOVINYL-N,N-DIMETHYLANILINE
1227. TRIETHYL PHOSPHITE
1228. 2,4,4-TRIMETHYLCYCLOPENTANONE
1229. α,β,β-TRIPHENYLPROPIONIC ACID
1230. α,α,β-TRIPHENYLPROPIONITRILE
1231. TRIPTYCENE
1232. TRITHIOCARBODIGLYCOLIC ACID
1233. 10-UNDECYNOIC ACID
1234. VANILLIC ACID
1235. VINYL LAURATE AND OTHER VINYL ESTERS

1236. 2-VINYLTHIOPHENE
1237. O-XYLYLENE DIBROMIDE
1238. 2-ACETAMIDO-3,4,6-TRI-O-ACETYL-2-DEOXY-α-D-GLUCOPYRANOSYL CHLORIDE
1239. ACETONE DIBUTYL ACETAL
1240. 3β-ACETOXYETIENIC ACID
1241. 3-ACETYLOXINDOLE
1242. ADAMANTANE
1243. 1-ADAMANTANECARBOXYLIC ACID
1244. ALLENE
1245. 2-ALLYLCYCLOHEXANONE
1246. AMINOACETONE SEMICARBAZONE HYDROCHLORIDE
1247. 2-AMINOFLUORENE
1248. AMINOMALONONITRILE P-TOLUENESULFONATE
1249. 1-AMINO-1-METHYLCYCLOHEXANE
1250. 3(5)-AMINOPYRAZOLE
1251. 1-AMINOPYRIDINIUM IODIDE
1252. O-ANISALDEHYDE
1253. AROMATIC ALDEHYDES. MESITALDEHYDE
1254. ARYLBENZENES: 3,4-DICHLOROBIPHENYL
1255. BENZENEDIAZONIUM-2-CARBOXYLATE AND BIPHENYLENE
1256. 1,2,3-BENZOTHIADIAZOLE 1,1-DIOXIDE
1257. BENZOYL FLUORIDE
1258. 3-BENZOYLOXYCYCLOHEXENE
1259. N-BENZYLACRYLAMIDE
1260. 2-BENZYLCYCLOPENTANONE
1261. α-BENZYLIDENE-γ-PHENYL-Δβ,γ-BUTENOLIDE
1262. CIS-2-BENZYL-3-PHENYLAZIRIDINE
1263. 1-BENZYLPIPERAZINE
1264. BICYCLO[2.2.1]HEPTEN-7-ONE
1265. EXO-CIS-BICYCLO[3.3.0]OCTANE-2-CARBOXYLIC ACID
1266. BICYCLO[2.1.0]PENTANE
1267. 2,2'-BIPYRIDINE
1268. 1,2-BIS(N-BUTYLTHIO)BENZENE
1269. 4,4'-BIS(DIMETHYLAMINO)BENZIL
1270. BIS(1,3-DIPHENYLIMIDAZOLIDINYLIDENE-2)
1271. 3-BROMOACETOPHENONE
1272. 2-BROMOALLYLAMINE

1273. N-(2-BROMOALLYL)ETHYLAMINE
1274. BROMOCYCLOPROPANE
1275. P-BROMODIPHENYLMETHANE
1276. 1-BROMO-2-FLUOROBENZENE
1277. 1-BROMO-2-FLUOROHEPTANE
1278. 2-BROMO-4-METHYLBENZALDEHYDE
1279. 2-BROMONAPHTHALENE
1280. 3-BROMOPHTHALIDE
1281. 3-BROMOPYRENE
1282. 3-BROMOTHIOPHENE
1283. 7-T-BUTOXYNORBORNADIENE
1284. T-BUTYL ACETOACETATE
1285. T-BUTYL AZIDOFORMATE
1286. T-BUTYL AZODIFORMATE
1287. T-BUTYL CARBAMATE
1288. T-BUTYL CARBAZATE
1289. T-BUTYL CYANOACETATE
1290. TRANS-4-T-BUTYLCYCLOHEXANOL
1291. T-BUTYL DIAZOACETATE
1292. T-BUTYL HYPOCHLORITE
1293. 2-N-BUTYL-2-METHYLCYCLOHEXANONE
1294. 2-T-BUTYL-3-PHENYLOXAZIRANE
1295. D,L-10-CAMPHORSULFONIC ACID (REYCHLER'S ACID)
1296. D,L-10-CAMPHORSULFONYL CHLORIDE
1297. 2-CARBETHOXYCYCLOOCTANONE
1298. 1,1'-CARBONYLDIIMIDAZOLE
1299. α-CHLOROACETYL ISOCYANATE
1300. 9-CHLOROANTHRACENE
1301. N-CHLOROCYCLOHEXYLIDENEIMINE
1302. CHLORODIISOPROPYLPHOSPHINE
1303. 2-CHLORO-1-FORMYL-1-CYCLOHEXENE
1304. CHLOROMETHYLPHOSPHONOTHIOIC DICHLORIDE
1305. P-CHLOROPHENOXYMETHYL CHLORIDE
1306. P-CHLOROPHENYL ISOTHIOCYANATE
1307. CHLOROSULFONYL ISOCYANATE
1308. 2-CHLOROTHIIRANE 1,1-DIOXIDE
1309. 1-CHLORO-1,4,4-TRIFLUOROBUTADIENE
1310. 3-CHLORO-2,2,3-TRIFLUOROPROPIONIC ACID

1311. CHOLANE-24-AL
1312. CHOLESTANYL METHYL ETHER
1313. CINNAMYL BROMIDE
1314. COUMARONE
1315. γ-CROTONOLACTONE
1316. CROTYL DIAZOACETATE
1317. 1-CYANOBENZOCYCLOBUTENE
1318. 7-CYANOHEPTANAL
1319. 2-CYANO-6-METHYLPYRIDINE
1320. CYCLOBUTYLAMINE
1321. CYCLODECANONE
1322. CIS-CYCLODODECENE
1323. 1,3-CYCLOHEXADIENE
1324. 1,4-CYCLOHEXANEDIONE
1325. CYCLOHEXANONE DIALLYL ACETAL
1326. 2-CYCLOHEXENONE
1327. CYCLOHEXYLIDENECYCLOHEXANE
1328. CYCLOHEXYL ISOCYANIDE
1329. 2-CYCLOHEXYLOXYETHANOL
1330. 1,2-CYCLONONADIENE
1331. CYCLOÖCTANONE
1332. TRANS-CYCLOOCTENE
1333. CYCLOPENTANECARBOXALDEHYDE
1334. 2-CYCLOPENTENE-1,4-DIONE
1335. 2-CYCLOPENTENONE
1336. CYCLOPROPYLBENZENE
1337. M-CYMENE
1338. DEAMINATION OF AMINES. 2-PHENYLETHYL BENZOATE VIA THE NITROSOAMIDE DECOMPOSITION
1339. DEOXYANISOIN
1340. 4,4'-DIAMINOAZOBENZENE
1341. DIAMINOMALEONITRILE (HYDROGEN CYANIDE TETRAMER)
1342. 2,3-DIAMINOPYRIDINE
1343. DIAZOMETHANE
1344. DI-T-BUTYL NITROXIDE
1345. 2,2'-DICHLORO-α,α'-EPOXYBIBENZYL
1346. DICHLOROMETHYLENETRIPHENYLPHOSPHORANE AND β,β-DICHLORO-P-DIMETHYLAMINOSTYRENE

1347. DICHLOROMETHYL METHYL ETHER
1348. 2,6-DICHLORONITROBENZENE
1349. 3,4-DICHLORO-1,2,3,4-TETRAMETHYLCYCLOBUTENE
1350. DIETHYL ACETAMIDOMALONATE
1351. DIETHYL AMINOMALONATE HYDROCHLORIDE
1352. DIETHYL [O-BENZOYL]ETHYLTARTRONATE
1353. DIETHYL BIS(HYDROXYMETHYL)MALONATE
1354. DIETHYL β-KETOPIMELATE
1355. N,N-DIETHYL-1,2,2-TRICHLOROVINYLAMINE
1356. β,β-DIFLUOROSTYRENE
1357. 2,2-DIFLUOROSUCCINIC ACID
1358. α,α-DIFLUOROTOLUENE AND BENZENESULFINYL FLUORIDE
1359. 9,10-DIHYDROANTHRACENE
1360. 1,4-DIHYDROBENZOIC ACID
1361. 2,5-DIHYDRO-2,5-DIMETHOXYFURAN
1362. 1,3-DIHYDROISOINDOLE
1363. 1,3-DIHYDRO-3,5,7-TRIMETHYL-2H-AZEPIN-2-ONE
1364. 3,3'-DIHYDROXYBIPHENYL
1365. DIHYDROXYCYCLOPENTENE
1366. 1,2-DIMERCAPTOBENZENE
1367. DIMESITYLMETHANE
1368. 7,7-DIMETHOXYBICYCLO[2.2.1]HEPTENE
1369. TRANS-4,4'-DIMETHOXYSTILBENE
1370. 6-(DIMETHYLAMINO)FULVENE
1371. N,N-DIMETHYLAMINOMETHYLFERROCENE METHIODIDE
1372. α-(N,N-DIMETHYLAMINO)PHENYLACETONITRILE
1373. DIMETHYL CYCLOHEXANONE-2,6-DICARBOXYLATE
1374. 2,7-DIMETHYL-2,7-DINITROÖCTANE
1375. 2,6-DIMETHYL-3,5-DIPHENYL-4H-PYRAN-4-ONE
1376. 4,6-DIMETHYL-1-HEPTEN-4-OL
1377. DIMETHYLKETENE β-LACTONE DIMER
1378. DIMETHYL 3-METHYLENECYCLOBUTANE-1,2-DICARBOXYLATE
1379. DIMETHYL OCTADECANEDIOATE
1380. 2,7-DIMETHYLOXEPIN
1381. α,α-DIMETHYL-β-PHENETHYLAMINE
1382. 2,4-DINITROBENZENESULFENYL CHLORIDE
1383. 2,4-DINITROIODOBENZENE
1384. 3,5-DINITRO-O-TOLUNITRILE

1385. 1,6-DIOXO-8A-METHYL-1,2,3,4,6,7,8,8A-OCTAHYDRONAPHTHALENE
1386. DIPHENALDEHYDE
1387. DIPHENALDEHYDIC ACID
1388. DIPHENYL-P-BROMOPHENYLPHOSPHINE
1389. 1,4-DIPHENYL-1,3-BUTADIENE
1390. DIPHENYLCARBODIIMIDE
1391. DIPHENYLCARBODIIMIDE
1392. 1,1-DIPHENYLCYCLOPROPANE
1393. DIPHENYLCYCLOPROPENONE
1394. DIPHENYLDIACETYLENE
1395. DIPHENYL KETIMINE
1396. 1,1-DIPHENYLPENTANE
1397. α,β-DIPHENYLPROPIONIC ACID
1398. CIS- AND TRANS-1,2-DIVINYLCYCLOBUTANE
1399. DOCOSANEDIOIC ACID
1400. 3-ETHOXY-2-CYCLOHEXENONE
1401. N-ETHYLALLENIMINE
1402. ETHYL γ-BROMOBUTYRATE
1403. ETHYL CYCLOHEXYLIDENEACETATE
1404. ETHYL 6,7-DIMETHOXY-3-METHYLINDENE-2-CARBOXYLATE
1405. ETHYL P-DIMETHYLAMINOPHENYLACETATE
1406. 1-ETHYL-3-(3-DIMETHYLAMINO)PROPYLCARBODIIMIDE HYDROCHLORIDE AND METHIODIDE
1407. ETHYL 2,4-DIPHENYLBUTANOATE
1408. ETHYLENE SULFIDE
1409. ETHYL β-HYDROXY-β,β-DIPHENYLPROPIONATE
1410. ETHYL INDOLE-2-CARBOXYLATE
1411. α-ETHYL-α-METHYLSUCCINIC ACID
1412. N-ETHYLPIPERIDINE
1413. FERROCENYLACETONITRILE
1414. 2-FLUOROHEPTANOIC ACID
1415. FORMAMIDINE ACETATE
1416. 3-(2-FURYL)ACRYLONITRILE
1417. GLYCINE T-BUTYL ESTER
1418. 4-HEPTANONE
1419. HEXAHYDROGALLIC ACID AND HEXAHYDROGALLIC ACID TRIACETATE

1420. HEXAHYDROXYBENZENE
1421. 2,3,4,5,6,6-HEXAMETHYL-2,4-CYCLOHEXADIEN-1-ONE
1422. HEXAMETHYLPHOSPHOROUS TRIAMIDE
1423. HEXAPHENYLBENZENE
1424. 1,3,5-HEXATRIENE
1425. HOMOPHTHALIC ACID
1426. 3-HYDROXYGLUTARONITRILE
1427. 2-HYDROXYISOPHTHALIC ACID
1428. HYDROXYMETHYLFERROCENE
1429. 2-HYDROXY-3-METHYLISOCARBOSTYRIL
1430. P-HYDROXYPHENYLPYRUVIC ACID
1431. 3-HYDROXYPYRENE
1432. 3-HYDROXYQUINOLINE
1433. 2-HYDROXYTHIOPHENE
1434. HYDROXYUREA
1435. 2-INDANONE
1436. INDAZOLE
1437. INDOLE-3-ACETIC ACID
1438. INDOLE-3-CARBONITRILE
1439. IODOSOBENZENE
1440. IODOSOBENZENE DIACETATE
1441. N-IODOSUCCINIMIDE
1442. IODOXYBENZENE
1443. ISOPHTHALALDEHYDE
1444. 3-ISOQUINUCLIDONE
1445. β-ISOVALEROLACTAM-N-SULFONYL CHLORIDE AND β-ISOVALEROLACTAM
1446. KETENE
1447. KETENE DI(2-METHOXYETHYL) ACETAL
1448. α-KETOGLUTARIC ACID
1449. DL-KETOPINIC ACID
1450. 18,20-LACTONE OF 3β-ACETOXY-20β-HYDROXY-5-PREGNENE-18-OIC ACID
1451. LEVOPIMARIC ACID
1452. 2-MERCAPTOPYRIMIDINE
1453. MESITOIC ACID
1454. METHANESULFINYL CHLORIDE
1455. 1-(2-METHOXYCARBONYLPHENYL)PYRROLE

1456. 1-(P-METHOXYPHENYL)-5-PHENYL-1,3,5-PENTANETRIONE
1457. 2-(P-METHOXYPHENYL)-6-PHENYL-4-PYRONE
1458. METHYL BENZENESULFINATE
1459. 10-METHYL-10,9-BORAZAROPHENANTHRENE
1460. METHYL BUTADIENOATE
1461. N-METHYLBUTYLAMINE
1462. 1-METHYLCYCLOHEXANECARBOXYLIC ACID
1463. 2-METHYL-1,3-CYCLOHEXANEDIONE
1464. 2-METHYLCYCLOPENTANE-1,3-DIONE
1465. METHYLENECYCLOHEXANE
1466. METHYLENECYCLOHEXANE OXIDE
1467. N-METHYLETHYLAMINE
1468. 3-METHYLHEPTANOIC ACID
1469. 5-METHYL-5-HEXEN-2-ONE
1470. 1-METHYLINDOLE
1471. METHYL ISOCYANIDE
1472. METHYL KETONES FROM CARBOXYLIC ACIDS: CYCLOHEXYL METHYL KETONE
1473. 2-METHYLMERCAPTO-N-METHYL-Δ2-PYRROLINE
1474. 3-METHYLPENTANE-2,4-DIONE
1475. 3-METHYL-1-PHENYLPHOSPHOLENE OXIDE
1476. METHYL PHENYL SULFOXIDE
1477. 4-METHYLPYRIMIDINE
1478. 1-METHYL-3-P-TOLYLTRIAZENE AND ITS USE IN THE ESTERIFICATION OF ACIDS
1479. N-MONO- AND N,N-DISUBSTITUTED UREAS AND THIOUREAS
1480. MONOPERPHTHALIC ACID
1481. 1-MORPHOLINO-1-CYCLOHEXENE
1482. 2,3-NAPHTHALENEDICARBOXYLIC ACID
1483. 2,6-NAPHTHALENEDICARBOXYLIC ACID
1484. N-β-NAPHTHYLPIPERIDINE
1485. NEOPENTYL ALCOHOL
1486. NICOTINIC ANHYDRIDE
1487. O-NITROBENZALDEHYDE
1488. 2-NITROCARBAZOLE
1489. 2-NITROETHANOL
1490. N-NITROMORPHOLINE
1491. M-NITROPHENYL DISULFIDE

1492. 4-NITRO-2,2,4-TRIMETHYLPENTANE
1493. 2,4-NONANEDIONE
1494. 2-NORBORNANONE
1495. NORCARANE
1496. EXO/ENDO-7-NORCARANOL
1497. NORTRICYCLANOL
1498. NORTRICYCLANONE
1499. Δ1(9)-OCTALONE-2
1500. OCTANAL
1501. 2-OXA-7,7-DICHLORONORCARANE
1502. D-2-OXO-7,7-DIMETHYL-1-VINYLBICYCLO[2.2.1]HEPTANE
1503. PALLADIUM CATALYST FOR PARTIAL REDUCTION OF ACETYLENESCHECKERS' NOTE: AMONG ORGANIC CHEMISTS THIS CATALYST IS COMMONLY CALLED "LINDLAR CATALYST."
1504. [2.2]PARACYCLOPHANE
1505. 2,3,4,5,6-PENTA-O-ACETYL-D-GLUCONIC ACID AND 2,3,4,5,6-PENTA-O-ACETYL-D-GLUCONYL CHLORIDE
1506. PENTACHLOROBENZOIC ACID
1507. 1,2,3,4,5-PENTACHLORO-5-ETHYLCYCLOPENTADIENE
1508. 3,3-PENTAMETHYLENEDIAZIRINE
1509. PERCHLOROFULVALENE
1510. PEROXYBENZOIC ACID
1511. PHENACYLAMINE HYDROCHLORIDE
1512. PHENOLS: 6-METHOXY-2-NAPHTHOL
1513. PHENYLBROMOETHYNE
1514. PHENYL T-BUTYL ETHER
1515. PHENYL T-BUTYL ETHER
1516. PHENYLCYCLOPROPANE
1517. R(+)- AND S(−)-α-PHENYLETHYLAMINE
1518. PHENYLGLYOXAL
1519. 2-PHENYLINDAZOLE
1520. N-PHENYLMALEIMIDE
1521. 2-PHENYL-5-OXAZOLONE
1522. 2-PHENYLPERFLUOROPROPENE
1523. 9-PHENYLPHENANTHRENE
1524. 2-PHENYL-3-N-PROPYLISOXAZOLIDINE-4,5-CIS-DICARBOXYLIC ACID N-PHENYLIMIDE
1525. PHENYLSULFUR TRIFLUORIDE

1526. 3-PHENYLSYDNONE
1527. 1-PHENYL-2-THIOBIURET
1528. PHENYL(TRICHLOROMETHYL)MERCURY
1529. N-PHTHALYL-L-β-PHENYLALANINE
1530. 4-PYRIDINESULFONIC ACID
1531. α-PYRONE
1532. P-QUINQUEPHENYL
1533. 3-QUINUCLIDONE HYDROCHLORIDE
1534. REDUCTION OF CONJUGATED ALKENES WITH CHROMIUM(II) SULFATE: DIETHYL SUCCINATE
1535. REDUCTION OF ORGANIC HALIDES. CHLOROBENZENE TO BENZENE
1536. RUTHENOCENE
1537. STYRYLPHOSPHONIC DICHLORIDE
1538. TETRACYANOETHYLENE OXIDE
1539. TETRAHYDROXYQUINONE
1540. TETRAMETHYLAMMONIUM 1,1,2,3,3-PENTACYANOPROPENIDE
1541. TETRAMETHYLBIPHOSPHINE DISULFIDE
1542. TETRAMETHYL-P-PHENYLENEDIAMINE
1543. 2,3,4,5-TETRAMETHYLPYRROLE
1544. 2,2,5,5-TETRAMETHYLTETRAHYDRO-3-KETOFURAN
1545. α,α,α',α'-TETRAMETHYLTETRAMETHYLENE GLYCOL
1546. 2,4,5,7-TETRANITROFLUORENONE
1547. (+)- AND (–)-α-(2,4,5,7-TETRANITRO-9-FLUORENYLIDENEAMINOOXY)PROPIONIC ACID
1548. 1,2,3,4-TETRAPHENYLNAPHTHALENE
1549. TETROLIC ACID
1550. THIOBENZOYLTHIOGLYCOLIC ACID
1551. 2A-THIOHOMOPHTHALIMIDE
1552. P-TOLUENESULFONYLHYDRAZIDE
1553. 1-P-TOLYLCYCLOPROPANOL
1554. O-TOLYL ISOCYANIDE
1555. 2-(P-TOLYLSULFONYL)DIHYDROISOINDOLE
1556. 2,4,5-TRIAMINONITROBENZENE
1557. 1,2,4-TRIAZOLE
1558. α,α,α-TRICHLOROACETANILIDE
1559. 1,1,3-TRICHLORO-N-NONANE
1560. TRIETHYLOXONIUM FLUOBORATE

1561. 1,1,1-TRIFLUOROHEPTANE
1562. M-TRIFLUOROMETHYL-N,N-DIMETHYLANILINE
1563. 4,6,8-TRIMETHYLAZULENE
1564. 2,6,6-TRIMETHYL-2,4-CYCLOHEXADIENONE
1565. TRIMETHYLOXONIUM FLUOBORATE
1566. TRIMETHYLOXONIUM 2,4,6-TRINITROBENZENESULFONATE
1567. 2,2,4-TRIMETHYL-3-OXOVALERYL CHLORIDE
1568. 2,4,6-TRIMETHYLPYRYLIUM PERCHLORATE
1569. 2,4,6-TRIMETHYLPYRYLIUM TETRAFLUOROBORATE
1570. 2,4,6-TRIMETHYLPYRYLIUM TRIFLUOROMETHANESULFONATE
1571. TRIPHENYLALUMINUM
1572. TRIPHENYLENE
1573. 2,3,5-TRIPHENYLISOXAZOLIDINE
1574. 2,4,6-TRIPHENYLNITROBENZENE
1575. 2,4,6-TRIPHENYLPHENOXYL
1576. 2,4,6-TRIPHENYLPYRYLIUM TETRAFLUOROBORATE
1577. TROPYLIUM FLUOBORATE
1578. UNSOLVATED N-BUTYLMAGNESIUM CHLORIDE
1579. VINYL TRIPHENYLPHOSPHONIUM BROMIDE
1580. ACYLAMIDOALKYL ACETOPHENONES FROM SUBSTITUTED PHENETHYLAMINES: 2-(2-ACETAMIDOETHYL)-4,5-DIMETHOXYACETOPHENONE
1581. THIOL PROTECTION WITH THE ACETAMIDOMETHYL GROUP: S-ACETAMIDOMETHYL-L-CYSTEINE HYDROCHLORIDE
1582. ACETIC FORMIC ANHYDRIDE
1583. ACETONE HYDRAZONE
1584. PREPARATION OF HYDRAZONES: ACETOPHENONE HYDRAZONE
1585. 3β-ACETOXY-5α-CYANOCHOLESTAN-7-ONE
1586. P-ACETYL-α-BROMOHYDROCINNAMIC ACID
1587. α,β-DEHYDROGENATION OF β-DICARBONYL COMPOUNDS BY SELENOXIDE ELIMINATION: 2-ACETYL-2-CYCLOHEXEN-1-ONE
1588. 2-ACETYL-1,3-CYCLOPENTANEDIONE
1589. 3-ACETYL-2,4-DIMETHYLFURAN
1590. 2-ACETYL-6-METHOXYNAPHTHALENE
1591. COPPER CATALYZED ARYLATION OF β-DICARBONYL COMPOUNDS: 2-(1-ACETYL-2-OXOPROPYL)BENZOIC ACID
1592. 5-ACETYL-1,2,3,4,5-PENTAMETHYLCYCLOPENTADIENE
1593. 2-ADAMANTANECARBONITRILE

1594. TERTIARY ALCOHOLS FROM HYDROCARBONS BY OZONATION ON SILICA GEL: 1-ADAMANTANOL
1595. ADAMANTANONE
1596. ENONE REDUCTION-ENOLATE ALKYLATION SEQUENCE: 2-ALLYL-3-METHYLCYCLOHEXANONE
1597. PREPARATION OF N-AMINOAZIRIDINES: TRANS-1-AMINO-2,3-DIPHENYLAZIRIDINE, 1-AMINO-2-PHENYLAZIRIDINE, AND 1-AMINO-2-PHENYLAZIRIDINIUM ACETATE
1598. REDUCTION OF KETONES BY USE OF THE TOSYLHYDRAZONE DERIVATIVES: ANDROSTAN-17 β-OL
1599. ALDEHYDES FROM 4,4-DIMETHYL-2-OXAZOLINE AND GRIGNARD REAGENTS: O-ANISALDEHYDE
1600. [18]ANNULENE
1601. AZETIDINE
1602. AZOETHANE
1603. DIELS-ALDER ADDITION OF PERCHLOROBENZYNE: BENZOBARRELENE
1604. BENZOCYCLOPROPENE
1605. α-CHLORINATION OF CARBOXYLIC ACIDS MEDIATED BY CHLOROSULFONIC ACID: ε-BENZOYLAMINO-α-CHLOROCAPROIC ACID
1606. 1-N-ACYLAMINO-1,3-DIENES FROM 2,4-PENTADIENOIC ACIDS BY THE CURTIUS REARRANGEMENT: BENZYL TRANS-1,3-BUTADIENE-1-CARBAMATE
1607. BENZYL CHLOROMETHYL ETHER
1608. 1-BENZYLINDOLE
1609. N-ALKYLINDOLES FROM THE ALKYLATION OF SODIUM INDOLIDE IN HEXAMETHYLPHOSPHORIC TRIAMIDE: 1-BENZYLINDOLE
1610. 3-ALKYLATED AND 3-ACYLATED INDOLES FROM A COMMON PRECURSOR: 3-BENZYLINDOLE AND 3-BENZOYLINDOLE
1611. ALKYLATION OF ISOQUINOLINES VIA 2-BENZOYL-1,2-DIHYDROISOQUINALDONITRILES: 1-BENZYLISOQUINOLINE
1612. THE FORMATION AND ALKYLATION OF SPECIFIC ENOLATE ANIONS FROM AN UNSYMMETRICAL KETONE: 2-BENZYL-2-METHYLCYCLOHEXANONE AND 2-BENZYL-6-METHYLCYCLOHEXANONE
1613. SULFIDE SYNTHESIS: BENZYL SULFIDE

1614. BICYCLO[1.1.0]BUTANE
1615. BORANES IN FUNCTIONALIZATION OF DIENES TO CYCLIC KETONES: BICYCLO[3.3.1]NONAN-9-ONE
1616. BICYCLO[3.2.1]OCTAN-3-ONE
1617. BICYCLO[2.1.0]PENT-2-ENE
1618. DEHYDROXYLATION OF PHENOLS; HYDROGENOLYSIS OF PHENOLIC ETHERS: BIPHENYL
1619. CONTROLLED-POTENTIAL ELECTROLYTIC REDUCTION: 1,1-BIS (BROMOMETHYL)CYCLOPROPANE
1620. BIS(TRIFLUOROMETHYL)DIAZOMETHANE
1621. BIS[2,2,2-TRIFLUORO-1-PHENYL-1-(TRIFLUOROMETHYL) ETHOXY] DIPHENYL SULFURANE
1622. ACYLOIN CONDENSATION IN WHICH CHLOROTRIMETHYLSILANE IS USED AS A TRAPPING AGENT: 1,2-BIS(TRIMETHYLSILYLOXY)CYCLOBUTENE AND 2-HYDROXYCYCLOBUTANONE
1623. 2-BORNENE
1624. SELECTIVE α-BROMINATION OF AN ARALKYL KETONE WITH PHENYLTRIMETHYLAMMONIUM TRIBROMIDE: 2-BROMOACETYL-6-METHOXYNAPHTHALENE AND 2,2-DIBROMOACETYL-6-METHOXYNAPHTHALENE
1625. MERCURY(II) OXIDE-MODIFIED HUNSDIECKER REACTION: 1-BROMO-3-CHLOROCYCLOBUTANE
1626. PARA-BROMINATION OF AROMATIC AMINES: 4-BROMO-N,N-DIMETHYL-3-(TRIFLUOROMETHYL)ANILINE
1627. BROMOHYDRINS FROM ALKENES AND N-BROMOSUCCINIMIDE IN DIMETHYL SULFOXIDE: ERYTHRO-2-BROMO-1,2-DIPHENYLETHANOL
1628. CHAIN ELONGATION OF ALKENES VIA GEM-DIHALOCYCLOPROPANES: 2-BROMO-3,3-DIPHENYL-2-PROPEN-1-YL ACETATE
1629. 2-BROMOHEXANOYL CHLORIDE
1630. 1-BROMO-3-METHYL-2-BUTANONE
1631. TRANS,TRANS-1,3-BUTADIENE-1,4-DIYL DIACETATE
1632. A NEW REAGENT FOR TERT-BUTOXYCARBONYLATION: 2-TERT-BUTOXYCARBONYLOXYIMINO-2-PHENYLACETONITRILE
1633. TERT-BUTOXYCARBONYL-L-PROLINE
1634. TERT-BUTYL AZIDOFORMATE

1635. TERT-BUTYLCYANOKETENE
1636. CIS-4-TERT-BUTYLCYCLOHEXANOL
1637. POLYMERIC CARBODIIMIDE. MOFFAT OXIDATION: 4-TERT-BUTYLCYCLOHEXANONE
1638. OXIDATION OF ALCOHOLS BY METHYL SULFIDE – N-CHLOROSUCCINIMIDE – TRIETHYLAMINE: 4-TERT-BUTYLCYCLOHEXANONE
1639. 2-TERT-BUTYL-1,3-DIAMINOPROPANE
1640. PHOTOCHEMICAL RING CONTRACTION OF 2-ETHOXYPYRROLIN-5-ONES TO CYCLOPROPANONE DERIVATIVES: TERT-BUTYL N-(1-ETHOXYCYCLOPROPYL)CARBAMATE
1641. PHASE-TRANSFER HOFMANN CARBYLAMINE REACTION: TERT-BUTYL ISOCYANIDE
1642. SULFIDE SYNTHESIS IN PREPARATION OF UNSYMMETRICAL DIALKYL DISULFIDES: SEC-BUTYL ISOPROPYL DISULFIDE
1643. 3-BUTYL-2-METHYLHEPT-1-EN-3-OL
1644. MONOALKYLATION OF α,β-UNSATURATED KETONES VIA METALLOENAMINES: 1-BUTYL-10-METHYL-Δ1(9)-2-OCTALONE
1645. β-DIKETONES FROM METHYL ALKYL KETONES: 3-N-BUTYL-2,4-PENTANEDIONE
1646. SECONDARY AND TERTIARY ALKYL KETONES FROM CARBOXYLIC ACID CHLORIDES AND LITHIUM PHENYLTHIO (ALKYL)CUPRATE REAGENTS: TERT-BUTYL PHENYL KETONE
1647. REMOVAL OF Nα-BENZYLOXYCARBONYL GROUPS FROM SULFUR-CONTAINING PEPTIDES BY CATALYTIC HYDROGENATION IN LIQUID AMMONIA: O-TERT-BUTYL-L-SERYL-S-TERT-BUTYL-L-CYSTEINE TERT-BUTYL ESTER
1648. ESTERIFICATION OF HINDERED ALCOHOLS: TERT-BUTYL P-TOLUATE
1649. PEPTIDE SYNTHESES USING N-ETHYL-5-PHENYLISOXAZOLIUM-3'-SULFONATE: CARBOBENZOXY-L-ASPARAGINYL-L-LEUCINE METHYL ESTER AND N-CARBOBENZOXY-3-HYDROXY-L-PROLYLGLYCYLGLYCINE ETHYL ESTER
1650. CARBONYL CYANIDE
1651. 3-CHLOROCYCLOBUTANECARBOXYLIC ACID
1652. (Z)-4-CHLORO-4-HEXENYL TRIFLUOROACETATE
1653. M-CHLOROPERBENZOIC ACID
1654. 3-(4-CHLOROPHENYL)-5-(4-METHOXYPHENYL)ISOXAZOLE

1655. α-CHLORO ENAMINES, REACTIVE INTERMEDIATES FOR SYNTHESIS: 1-CHLORO-N,N,2-TRIMETHYLPROPENYLAMINE
1656. MODIFIED CLEMMENSEN REDUCTION: CHOLESTANE
1657. CONJUGATE REDUCTION OF α,β-UNSATURATED P-TOLUENESULFONYLHYDRAZONES TO ALKENES WITH CATECHOLBORANE: 5β-CHOLEST-3-ENE
1658. 5β-CHOLEST-3-ENE-5-ACETALDEHYDE
1659. 18-CROWN-6
1660. CINNAMONITRILE
1661. PREPARATION OF CYANO COMPOUNDS USING ALKYLALUMINUM INTERMEDIATES: 1-CYANO-6-METHOXY-3,4-DIHYDRONAPHTHALENE
1662. CYCLOBUTADIENEIRON TRICARBONYL
1663. ALDEHYDES FROM ACID CHLORIDES BY REDUCTION OF ESTER-MESYLATES WITH SODIUM BOROHYDRIDE: CYCLOBUTANECARBOXALDEHYDE
1664. CYCLIC KETONES FROM 1,3-DITHIANE: CYCLOBUTANONE
1665. CYCLOBUTANONE FROM METHYLENECYCLOPROPANE VIA OXASPIROPENTANE
1666. CYCLOBUTANONE VIA SOLVOLYTIC CYCLIZATION
1667. ONE-CARBON RING EXPANSION OF CYCLOALKANONES TO CONJUGATED CYCLOALKENONES: 2-CYCLOHEPTEN-1-ONE
1668. NITRILES FROM KETONES: CYCLOHEXANECARBONITRILE
1669. ALDEHYDES FROM OLEFINS: CYCLOHEXANECARBOXALDEHYDE
1670. CATALYTIC OSMIUM TETROXIDE OXIDATION OF OLEFINS: CIS-1,2-CYCLOHEXANEDIOL
1671. STEREOSELECTIVE HYDROXYLATION WITH THALLIUM(I) ACETATE AND IODINE: TRANS- AND CIS-1,2-CYCLOHEXANEDIOLS
1672. CLEAVAGE OF METHYL ETHERS WITH IODOTRIMETHYLSILANE: CYCLOHEXANOL FROM CYCLOHEXYL METHYL ETHER
1673. PREPARATION OF α,β-UNSATURATED ALDEHYDES VIA THE WITTIG REACTION: CYCLOHEXYLIDENEACETALDEHYDE
1674. CYCLOPROPENONE
1675. CYCLOPROPYLDIPHENYLSULFONIUM TETRAFLUOROBORATE
1676. RING CONTRACTION VIA A FAVORSKII-TYPE REARRANGEMENT: CYCLOUNDECANONE

1677. HYDROGENATION OF AROMATIC NUCLEI: 1-DECALOL
1678. OXIDATION WITH THE CHROMIUM TRIOXIDE-PYRIDINE COMPLEX PREPARED IN SITU:1-DECANAL
1679. REDUCTION OF ALKYL HALIDES AND TOSYLATES WITH SODIUM CYANOBOROHYDRIDE IN HEXAMETHYLPHOSPHORIC TRIAMIDE (HMPA):A. 1-IODODECANE TO N-DECANEB. 1-DODECYL TOSYLATE TO N-DODECANE
1680. DIAMANTANE: PENTACYCLO[7.3.1.14,12.02,7.06,11]TETRADECANE
1681. MACROCYCLIC DIIMINES: 1,10-DIAZACYCLOÖCTADECANE
1682. DIAZOACETOPHENONE
1683. 2-DIAZOCYCLOALKANONES: 2-DIAZOCYCLOHEXANONE
1684. 2-DIAZOPROPANE
1685. MACROCYCLIC POLYETHERS: DIBENZO-18-CROWN-6 POLYETHER AND DICYCLOHEXYL-18-CROWN-6 POLYETHER
1686. 1,2-DIAROYLCYCLOPROPANES: TRANS-1,2-DIBENZOYLCYCLOPROPANE
1687. α,α'-DIBROMODIBENZYL SULFONE
1688. PHOSPHINE–NICKEL COMPLEX CATALYZED CROSS-COUPLING OF GRIGNARD REAGENTS WITH ARYL AND ALKENYL HALIDES: 1,2-DIBUTYLBENZENE
1689. OXIDATION WITH BIS(SALICYLIDENE) ETHYLENEDIIMINOCOBALT(II) (SALCOMINE): 2,6-DI-TERT-BUTYL-P-BENZOQUINONE
1690. DIAZO TRANSFER BY MEANS OF PHASE-TRANSFER CATALYSIS: DI-TERT-BUTYL DIAZOMALONATE
1691. DI-TERT-BUTYL DICARBONATE
1692. CIS-3,4-DICHLOROCYCLOBUTENE
1693. CIS-DICHLOROALKANES FROM EPOXIDES: CIS-1,2-DICHLOROCYCLOHEXANE
1694. 2,3-DICYANOBUTADIENE AS A REACTIVE INTERMEDIATE BY IN SITU GENERATION FROM 1,2-DICYANOCYCLOBUTENE: 2,3-DICYANO-1,4,4A,9A-TETRAHYDROFLUORENE
1695. DIDEUTERIODIAZOMETHANE
1696. DIETHYLALUMINUM CYANIDE
1697. DIETHYLAMINOSULFUR TRIFLUORIDE
1698. DIETHYL TERT-BUTYLMALONATE
1699. 2-TRIMETHYLSILYLOXY-1,3-BUTADIENE AS A REACTIVE DIENE: DIETHYL TRANS-4-TRIMETHYLSILYLOXY-4-CYCLOHEXENE-1,2-

DICARBOXYLATE
1700. DIETHYL 2-(CYCLOHEXYLAMINO)VINYLPHOSPHONATE
1701. RADICAL ANION ARYLATION: DIETHYL PHENYLPHOSPHONATE
1702. DIETHYL TRANS-Δ4-TETRAHYDROPHTHALATE
1703. HOMOGENEOUS CATALYTIC HYDROGENATION: DIHYDROCARVONE
1704. TRANS-1,2-DIHYDROPHTHALIC ACID
1705. 5,6-DIHYDRO-2H-PYRAN-2-ONE AND 2H-PYRAN-2-ONE
1706. 2,4-DIMETHOXYBENZONITRILE
1707. BIARYLS FROM SIMPLE ARENES VIA ORGANOTELLURIUM INTERMEDIATES: 4,4'-DIMETHOXY-1,1'-BIPHENYL
1708. 6,7-DIMETHOXY-3-ISOCHROMANONE
1709. REGIOSELECTIVE MANNICH CONDENSATION WITH DIMETHYL (METHYLENE)AMMONIUM TRIFLUOROACETATE: 1-(DIMETHYLAMINO)-4-METHYL-3-PENTANONE
1710. DIRECTED LITHIATION OF AROMATIC COMPOUNDS: (2-DIMETHYLAMINO-5-METHYLPHENYL)DIPHENYLCARBINOL
1711. USE OF DIPOTASSIUM NITROSODISULFONATE (FREMY'S SALT): 4,5-DIMETHYL-O-BENZOQUINONE
1712. 1,2-DIMETHYLCYCLOBUTENES BY REDUCTIVE RING-CONTRACTION OF SULFOLANES: CIS-7,8-DIMETHYLBICYCLO [4.2.0]OCT-7-ENE
1713. 4,4'-DIMETHYL-1,1'-BIPHENYL
1714. N,N-DIMETHYL-5β-CHOLEST-3-ENE-5-ACETAMIDE
1715. CONVERSION OF ESTERS TO AMIDES WITH DIMETHYLALUMINUM AMIDES: N,N-DIMETHYLCYCLOHEXANECARBOXAMIDE
1716. 4,4-DIMETHYL-2-CYCLOHEXEN-1-ONE
1717. REDUCTIVE AMINATION WITH SODIUM CYANOBOROHYDRIDE: N,N-DIMETHYLCYCLOHEXYLAMINE
1718. N,N-DIMETHYLDODECYLAMINE OXIDE
1719. DIMETHYL NITROSUCCINATE
1720. DIMETHYL 2,3-PENTADIENEDIOATE
1721. ALLYLICALLY TRANSPOSED AMINES FROM ALLYLIC ALCOHOLS: 3,7-DIMETHYL-1,6-OCTADIEN-3-AMINE
1722. BICYCLIC KETONES FOR THE SYNTHESIS OF TROPINOIDS: 2α,4α-DIMETHYL-8-OXABICYCLO[3.2.1]OCT-6-EN-3-ONE
1723. 2,2-DIMETHYL-4-PHENYLBUTYRIC ACID

1724. CYCLOPENTENONES FROM α,α'-DIBROMOKETONES AND ENAMINES: 2,5-DIMETHYL-3-PHENYL-2-CYCLOPENTEN-1-ONE
1725. ALKYLATIONS OF ALDEHYDES VIA REACTION OF THE MAGNESIOENAMINE SALT OF AN ALDEHYDE: 2,2-DIMETHYL-3-PHENYLPROPIONALDEHYDE
1726. 3,5-DINITROBENZALDEHYDE
1727. 2,3-DIPHENYL-1,3-BUTADIENE
1728. REAGENTS FOR SYNTHESIS OF ORGANOSELENIUM COMPOUNDS: DIPHENYL DISELENIDE AND BENZENESELENENYL CHLORIDE
1729. AROMATIC HYDROCARBONS FROM AROMATIC KETONES AND ALDEHYDES: 1,1-DIPHENYLETHANE
1730. NUCLEOPHILIC α-SEC-AMINOALKYLATION: 2-(DIPHENYLHYDROXYMETHYL)PYRROLIDINE
1731. DIPHENYLKETENE
1732. ALKENES VIA HOFMANN ELIMINATION: USE OF ION-EXCHANGE RESIN FOR PREPARATION OF QUATERNARY AMMONIUM HYDROXIDES: DIPHENYLMETHYL VINYL ETHER
1733. 2,3-DIPHENYLVINYLENE SULFONE
1734. 1,3-DITHIANE
1735. 2,2'-DITHIENYL SULFIDE
1736. SELECTIVE EPOXIDATION OF TERMINAL DOUBLE BONDS: 10,11-EPOXYFARNESYL ACETATE
1737. 1-ETHOXY-1-BUTYNE
1738. DEMETHYLATION OF METHYL ARYL ETHERS: 4-ETHOXY-3-HYDROXYBENZALDEHYDE
1739. CARBENE GENERATION BY α-ELIMINATION WITH LITHIUM 2,2,6,6-TETRAMETHYLPIPERIDIDE: 1-ETHOXY-2-P-TOLYLCYCLOPROPANE
1740. ESTERIFICATION OF CARBOXYLIC ACIDS WITH TRIALKYLOXONIUM SALTS: ETHYL AND METHYL 4-ACETOXYBENZOATES
1741. ORTHO-ALKYLATION OF ANILINES: ETHYL 4-AMINO-3-METHYLBENZOATE
1742. ETHYL 5β-CHOLEST-3-ENE-5-ACETATE
1743. FREE-RADICAL CYCLIZATION: ETHYL 1-CYANO-2-METHYLCYCLOHEXANECARBOXYLATE
1744. 2,2-(ETHYLENEDITHIO)CYCLOHEXANONE
1745. A GENERAL SYNTHESIS OF 4-ISOXAZOLECARBOXYLIC ESTERS:

ETHYL 3-ETHYL-5-METHYL-4-ISOXAZOLECARBOXYLATE
1746. 3-ALKYL-1-ALKYNES SYNTHESIS: 3-ETHYL-1-HEXYNE
1747. β-HYDROXY ESTERS FROM ETHYL ACETATE AND ALDEHYDES OR KETONES: ETHYL 1-HYDROXYCYCLOHEXYLACETATE
1748. INDOLES FROM ANILINES: ETHYL 2-METHYLINDOLE-5-CARBOXYLATE
1749. STEREOSELECTIVE SYNTHESIS OF TRISUBSTITUTED OLEFINS: ETHYL 4-METHYL-(E)-4,8-NONADIENOATE
1750. METALATION OF 2-METHYLPYRIDINE DERIVATIVES: ETHYL 6-METHYLPYRIDINE-2-ACETATE
1751. ETHYL 1-NAPHTHYLACETATE
1752. γ-KETOESTERS FROM ALDEHYDES VIA DIETHYL ACYLSUCCINATES: ETHYL 4-OXOHEXANOATE
1753. ETHYL PYRROLE-2-CARBOXYLATE
1754. THIAZOLES FROM ETHYL ISOCYANOACETATE AND THIONO ESTERS: ETHYL THIAZOLE-4-CARBOXYLATE
1755. CARBOXYLATION OF AROMATIC COMPOUNDS: FERROCENECARBOXYLIC ACID
1756. FLUORINATIONS WITH PYRIDINIUM POLYHYDROGEN FLUORIDE REAGENT: 1-FLUOROADAMANTANE
1757. ALDEHYDES FROM AROMATIC NITRILES: 4-FORMYLBENZENESULFONAMIDE
1758. GERANYL CHLORIDE
1759. ALLYLIC CHLORIDES FROM ALLYLIC ALCOHOLS: GERANYL CHLORIDE
1760. GLUTACONALDEHYDE SODIUM SALT FROM HYDROLYSIS OF PYRIDINIUM-1-SULFONATE
1761. ALDEHYDES FROM PRIMARY ALCOHOLS BY OXIDATION WITH CHROMIUM TRIOXIDE: HEPTANAL
1762. CONVERSION OF NITRO TO CARBONYL BY OZONOLYSIS OF NITRONATES: 2,5-HEPTANEDIONE
1763. MACROCYCLIC POLYAMINES: 1,4,7,10,13,16-HEXAÄZACYCLOÖCTADECANE
1764. CUPROUS ION-CATALYZED OXIDATIVE CLEAVAGE OF AROMATIC O-DIAMINES BY OXYGEN: (Z,Z)-2,4-HEXADIENEDINITRILE
1765. HEXAFLUOROACETONE IMINE
1766. 3-TRIMETHYLSILYL-3-BUTEN-2-ONE AS MICHAEL ACCEPTOR

FOR CONJUGATE ADDITION-ANNELATION: CIS-4,4A,5,6,7,8-HEXAHYDRO-4A,5-DIMETHYL-2(3H)-NAPHTHALENONE
1767. NITRONES FOR INTRAMOLECULAR 1,3-DIPOLAR CYCLOADDITIONS: HEXAHYDRO-1,3,3,6-TETRAMETHYL-2,1-BENZISOXAZOLINE
1768. (E)-4-HEXEN-1-OL
1769. FRAGMENTATION OF α,β-EPOXYKETONES TO ACETYLENIC ALDEHYDES AND KETONES: PREPARATION OF 2,3-EPOXYCYCLOHEXANONE AND ITS FRAGMENTATION TO 5-HEXYNAL
1770. γ-HYDROXY-α,β-UNSATURATED ALDEHYDES VIA 1,3-BIS (METHYLTHIO)ALLYLLITHIUM: TRANS-4-HYDROXY-2-HEXENAL
1771. 17β-HYDROXY-5-OXO-3,5-SECO-4-NORANDROSTANE-3-CARBOXYLIC ACID
1772. DIRECTED ALDOL CONDENSATIONS: THREO-4-HYDROXY-3-PHENYL-2-HEPTANONE
1773. MACROLIDES FROM CYCLIZATION OF ω-BROMOCARBOXYLIC ACIDS: 11-HYDROXYUNDECANOIC LACTONE
1774. DIRECT IODINATION OF POLYALKYLBENZENES: IODODURENE
1775. TRANS-IODOPROPENYLATION OF ALKYL HALIDES: (E)-1-IODO-4-PHENYL-2-BUTENE
1776. 2-IODO-P-XYLENE
1777. CIS-α,β-UNSATURATED ACIDS: ISOCROTONIC ACID
1778. TRICHLOROMETHYL CHLOROFORMATE AS A PHOSGENE EQUIVALENT: 3-ISOCYANATOPROPANOYL CHLORIDE
1779. (−)-ISOPINOCAMPHEOL
1780. REACTION OF ARYL HALIDES WITH π-ALLYLNICKEL HALIDES: METHALLYLBENZENE
1781. SULFONYL CYANIDES: METHANESULFONYL CYANIDE
1782. 1,6-METHANO[10]ANNULENE
1783. VINYL SULFIDES FROM THIOACETALS WITH COPPER(I) TRIFLUOROMETHANESULFONATE: (Z)-2-METHOXY-1-PHENYLTHIO-1,3-BUTADIENE
1784. 6-METHOXY-β-TETRALONE
1785. METHYL GROUPS BY REDUCTION OF AROMATIC CARBOXYLIC ACIDS WITH TRICHLOROSILANE - TRI-N-PROPYLAMINE: 2-METHYLBIPHENYL
1786. 1-D-ALDEHYDES FROM ORGANOMETALLIC REAGENTS: 2-

METHYLBUTANAL-1-D
1787. PREPARATION OF VINYL TRIFLUOROMETHANESULFONATES: 3-METHYL-2-BUTEN-2-YL TRIFLATE
1788. PREPARATION AND REDUCTIVE CLEAVAGE OF ENOL PHOSPHATES: 5-METHYLCOPROST-3-ENE
1789. OXYMERCURATION-REDUCTION: ALCOHOLS FROM OLEFINS: 1-METHYLCYCLOHEXANOL
1790. REDUCTIVE CLEAVAGE OF ALLYLIC ALCOHOLS, ETHERS, OR ACETATES TO OLEFINS: 3-METHYLCYCLOHEXENE
1791. γ-KETOESTERS TO PREPARE CYCLIC DIKETONES: 2-METHYL-1,3-CYCLOPENTANEDIONE
1792. SULFIDE CONTRACTION VIA ALKYLATIVE COUPLING: 3-METHYL-2,4-HEPTANEDIONE
1793. ISOXAZOLE ANNELATION REACTION: 1-METHYL-4,4A,5,6,7,8-HEXAHYDRONAPHTHALEN-2(3H)-ONE
1794. ADDITION OF ORGANOLITHIUM REAGENTS TO ALLYL ALCOHOL: 2-METHYL-1-HEXANOL
1795. CONVERSION OF PRIMARY ALCOHOLS TO URETHANES VIA THE INNER SALT OF METHYL (CARBOXYSULFAMOYL) TRIETHYLAMMONIUM HYDROXIDE: METHYL N-HEXYLCARBAMATE
1796. METHYL 2-ALKYNOATES FROM 3-ALKYL-2-PYRAZOLIN-5-ONES: METHYL 2-HEXYNOATE
1797. METHYL (TRANS-2-IODO-1-TETRALIN)CARBAMATE
1798. METHYL NITROACETATE
1799. METHYL (E)-3-NITROACRYLATE
1800. 2-METHYL-2-NITROSOPROPANE AND ITS DIMER
1801. NUCLEOPHILIC ACYLATION WITH DISODIUM TETRACARBONYLFERRATE: METHYL 7-OXOHEPTANOATE AND METHYL 7-OXOÖCTANOATE
1802. ALDEHYDES FROM ALLYLIC ALCOHOLS AND PHENYLPALLADIUM ACETATE: 2-METHYL-3-PHENYLPROPIONALDEHYDE
1803. ENDOCYCLIC ENAMINE SYNTHESIS: N-METHYL-2-PHENYL-Δ2-TETRAHYDROPYRIDINE
1804. HYDROGENOLYSIS OF CARBON-HALOGEN BONDS WITH CHROMIUM(II)-EN PERCHLORATE: NAPHTHALENE FROM 1-BROMONAPHTHALENE

1805. THIOPHENOLS FROM PHENOLS: 2-NAPHTHALENETHIOL
1806. (S)-(−)-α-(1-NAPHTHYL)ETHYLAMINE
1807. ALKYL IODIDES: NEOPENTYL IODIDE AND IODOCYCLOHEXANE
1808. SULFIDE SYNTHESIS IN PREPARATION OF DIALKYL AND ALKYL ARYL SULFIDES: NEOPENTYL PHENYL SULFIDE
1809. 4-NITROBENZYL FLUORIDE
1810. 1-NITROCYCLOÖCTENE
1811. FORMATION AND PHOTOCHEMICAL WOLFF REARRANGEMENT OF CYCLIC α-DIAZO KETONES: D-NORANDROST-5-EN-3β-OL-16-CARBOXYLIC ACIDS
1812. HIGHLY REACTIVE MAGNESIUM FOR THE PREPARATION OF GRIGNARD REAGENTS: 1-NORBORNANECARBOXYLIC ACID
1813. Δ9,10-OCTALIN
1814. 2,2,7,7,12,12,17,17-OCTAMETHYL-21,22,23,24-TETRAOXAPERHYDROQUATERENE
1815. ORCINOL MONOMETHYL ETHER
1816. 1,6-OXIDO[10]ANNULENE
1817. CYANIDE-CATALYZED CONJUGATE ADDITION OF ARYL ALDEHYDES: 4-OXO-4-(3-PYRIDYL)BUTYRONITRILE
1818. ALDEHYDES FROM SYM-TRITHIANE: N-PENTADECANAL
1819. (PENTAFLUOROPHENYL)ACETONITRILE
1820. PENTAFLUOROPHENYLCOPPER TETRAMER, A REAGENT FOR SYNTHESIS OF FLUORINATED AROMATIC COMPOUNDS
1821. TRANS-3-PENTEN-2-ONE
1822. ARENE OXIDE SYNTHESIS: PHENANTHRENE-9,10-OXIDE
1823. FREE-RADICAL ALKYLATION OF QUINONES: 2-PHENOXYMETHYL-1,4-BENZOQUINONE
1824. 3-PHENYL-2H-AZIRINE-2-CARBOXALDEHYDE
1825. PHASE-TRANSFER ALKYLATION OF NITRILES: 2-PHENYLBUTYRONITRILE
1826. DIRECTED ALDOL CONDENSATIONS: β-PHENYLCINNAMALDEHYDE
1827. ALDEHYDES FROM 2-BENZYL-4,4,6-TRIMETHYL-5,6-DIHYDRO-1,3(4H)-OXAZINE: 1-PHENYLCYCLOPENTANECARBOXALDEHYDE
1828. AMINES FROM MIXED CARBOXYLIC-CARBONIC ANHYDRIDES: 1-PHENYLCYCLOPENTYLAMINE
1829. CIS-2-PHENYLCYCLOPROPANECARBOXYLIC ACID
1830. SUBSTITUTION OF ARYL HALIDES WITH COPPER(I) ACETYLIDES:

2-PHENYLFURO[3,2-B]PYRIDINE
1831. KETONES AND ALCOHOLS FROM ORGANOBORANES: PHENYL HEPTYL KETONE, 1-HEXANOL, AND 1-OCTANOL
1832. 1-PHENYL-1,4-PENTADIYNE AND 1-PHENYL-1,3-PENTADIYNE
1833. PHENYLATION WITH DIPHENYLIODONIUM CHLORIDE: 1-PHENYL-2,4-PENTANEDIONE
1834. 1-PHENYL-4-PHOSPHORINANONE
1835. 4-PHENYL-1,2,4-TRIAZOLINE-3,5-DIONE
1836. 2-PHENYL-2-VINYLBUTYRONITRILE
1837. BORANES IN FUNCTIONALIZATION OF OLEFINS TO AMINES: 3-PINANAMINE
1838. ALLYLIC OXIDATION WITH HYDROGEN PEROXIDE–SELENIUM DIOXIDE: TRANS-PINOCARVEOL
1839. BASE-INDUCED REARRANGEMENT OF EPOXIDES TO ALLYLIC ALCOHOLS: TRANS-PINOCARVEOL
1840. POLYMERIC CARBODIIMIDE. PREPARATION
1841. ALKYNES VIA PHASE TRANSFER–CATALYZED DEHYDROHALOGENATION: PROPIOLALDEHYDE DIETHYL ACETAL
1842. REARRANGEMENT OF BRIDGEHEAD ALCOHOLS TO POLYCYCLIC KETONES BY FRAGMENTATION-CYCLIZATION: 4-PROTOADAMANTANONE (TRICYCLO-[4.3.1.03,8]DECAN-4-ONE)
1843. QUADRICYCLANE
1844. 1,2,3,4-TETRAHYDRO-β-CARBOLINE
1845. AZIRIDINES FROM β-IODOCARBAMATES: 1,2,3,4-TETRAHYDRONAPHTHALENE(1,2)IMINE
1846. 2,3,4,5-TETRAHYDROPYRIDINE TRIMER
1847. 3,3,6,6-TETRAMETHOXY-1,4-CYCLOHEXADIENE
1848. 2,2,3,3-TETRAMETHYLIODOCYCLOPROPANE
1849. 4H-1,4-THIAZINE 1,1-DIOXIDE
1850. 2-THIOPHENETHIOL
1851. P-TOLYLSULFONYLDIAZOMETHANE
1852. P-TOLYLSULFONYLMETHYL ISOCYANIDE
1853. TRI-TERT-BUTYLCYCLOPROPENYL TETRAFLUOROBORATE
1854. TRICARBONYL[(2,3,4,5-η)-2,4-CYCLOHEXADIEN-1-ONE]IRON AND TRICARBONYL[(1,2,3,4,5-η)-2-METHOXY-2,4-CYCLOHEXADIEN-1-YL]IRON(1+) HEXAFLUOROPHOSPHATE(1–) FROM ANISOLE
1855. ALKYLATION OF DIMEDONE WITH A TRICARBONYL(DIENE)IRON

COMPLEX: TRICARBONYL[2-[(2,3,4,5-η)-4-METHOXY-2,4-CYCLOHEXADIEN-1-YL]-5,5-DIMETHYL-1,3-CYCLOHEXANEDIONE]IRON
1856. CYCLOBUTADIENE IN SYNTHESIS: ENDO-TRICYCLO[4.4.0.02,5]DECA-3,8-DIENE-7,10-DIONE
1857. TRIFLUOROACETYLATION OF AMINES AND AMINO ACIDS UNDER NEUTRAL, MILD CONDITIONS: N-TRIFLUOROACETANILIDE AND N-TRIFLUOROACETYL-L-TYROSINE
1858. ALDEHYDES FROM ACID CHLORIDES BY MODIFIED ROSENMUND REDUCTION: 3,4,5-TRIMETHOXYBENZALDEHYDE
1859. OXIDATION WITH THE NITROSODISULFONATE RADICAL. I. PREPARATION AND USE OF DISODIUM NITROSODISULFONATE: TRIMETHYL-P-BENZOQUINONE
1860. 2,2-(TRIMETHYLENEDITHIO)CYCLOHEXANONE
1861. TRIMETHYLENE DITHIOTOSYLATE AND ETHYLENE DITHIOTOSYLATE
1862. TRIMETHYLOXONIUM TETRAFLUOROBORATE
1863. 3,5,5-TRIMETHYL-2-(2-OXOPROPYL)-2-CYCLOHEXEN-1-ONE
1864. ALDEHYDES BY OXIDATION OF TERMINAL OLEFINS WITH CHROMYL CHLORIDE: 2,4,4-TRIMETHYLPENTANAL
1865. TRIMETHYLSILYL AZIDE
1866. 3-TRIMETHYLSILYL-3-BUTEN-2-ONE: A MICHAEL ACCEPTOR
1867. TROPOLONE
1868. REDUCTIVE COUPLING OF CARBONYLS TO ALKENES: ADAMANTYLIDENEADAMANTANE
1869. SYNTHESIS AND DIELS–ALDER REACTIONS OF 3-ACETYL-2(3H)-OXAZOLONE: 6-AMINO-3,4-DIMETHYL-CIS-3-CYCLOHEXEN-1-OL
1870. ELECTROPHILIC N-AMINATION OF IMIDE SODIUM SALTS WITH O-DIPHENYLPHOSPHINYLHYDROXYLAMINE (DPH): 7-AMINOTHEOPHYLLINE
1871. ATROPALDEHYDE
1872. AZULENE
1873. REDUCTION OF QUINONES WITH HYDRIODIC ACID: BENZ[A]ANTHRACENE
1874. CONVERSION OF KETONES TO CYANOHYDRINS: BENZOPHENONE CYANOHYDRIN
1875. 1,3-OXAZEPINES VIA PHOTOISOMERIZATION OF

HETEROAROMATIC N-OXIDES: 3,1-BENZOXAZEPINE
1876. OXIDATION OF 5-AMINOTETRAZOLES: BENZYL ISOCYANIDE
1877. PEPTIDE SYNTHESIS USING 1-(4-CHLOROPHENYL)-3-(4'-METHYL-1'-PIPERAZINYL)-2-PROPYN-1-ONE AS REAGENT: BENZYLOXYCARBONYL-L-ALANYL-L-CYSTEINE METHYL ESTER AND BENZYLOXYCARBONYL-L-ASPARTYL-(TERT-BUTYL ESTER)-L-PHENYLALANYL-L-VALINE METHYL ESTER
1878. INDOLES FROM 2-METHYLNITROBENZENES BY CONDENSATION WITH FORMAMIDE ACETALS FOLLOWED BY REDUCTION: 4-BENZYLOXYINDOLE
1879. CHIRAL MEDIA FOR ASYMMETRIC SOLVENT INDUCTIONS. (S,S)-(+)-1,4-BIS(DIMETHYLAMINO)-2,3-DIMETHOXYBUTANE FROM (R, R)-(+)-DIETHYL TARTRATE
1880. CONDENSATION OF DIMETHYL 1,3-ACETONEDICARBOXYLATE WITH 1,2-DICARBONYL COMPOUNDS: CIS-BICYCLO[3.3.0] OCTANE-3,7-DIONES
1881. BIS(2,2,2-TRICHLOROETHYL) AZODICARBOXYLATE
1882. β-HALOACETALS AND KETALS: 2-(2-BROMOETHYL)-1,3-DIOXANE AND 2,5,5-TRIMETHYL-2-(2-BROMOETHYL)-1,3-DIOXANE
1883. CONVERSION OF METHYL KETONES INTO TERMINAL ALKYNES: (E)-BUTEN-3-YNYL-2,6,6-TRIMETHYL-1-CYCLOHEXENE
1884. REDUCTIVE CLEAVAGE OF VINYL PHOSPHORODIAMIDATES: 17β-TERT-BUTOXY-Gα-ANDROST-2-ENE
1885. TERT-BUTOXYCARBONYLATION OF AMINO ACIDS AND THEIR DERIVATIVES: N-TERT-BUTOXYCARBONYL-L-PHENYLALANINE
1886. N-TERT-BUTOXYCARBONYL-L-PHENYLALANINE
1887. GENERATION AND REACTIONS OF ALKENYLLITHIUM REAGENTS: 2-BUTYLBORNENE
1888. PREPARATION OF THIOL ESTERS: S-TERT-BUTYL CYCLOHEXANECARBOTHIOATE AND S-TERT-BUTYL 3α,7α,12α-TRIHYDROXY-5β-CHOLANE-24-THIOATE
1889. PREPARATION OF O-ESTERS FROM THE CORRESPONDING THIOL ESTERS: TERT-BUTYL CYCLOHEXANECARBOXYLATE
1890. ESTERIFICATION OF CARBOXYLIC ACIDS WITH DICYCLOHEXYLCARBODIIMIDE/4-DIMETHYLAMINOPYRIDINE: TERT-BUTYL ETHYL FUMARATE
1891. ACYLOIN CONDENSATION BY THIAZOLIUM ION CATALYSIS: BUTYROIN

1892. (S)-(+)-γ-BUTYROLACTONE-γ-CARBOXYLIC ACID
1893. 3-(1-HYDROXYBUTYL)-1-METHYLPYRROLE AND 3-BUTYROYL-1-METHYLPYRROLE
1894. REDUCTIVE ARYLATION OF ELECTRON-DEFICIENT OLEFINS: 4-(4-CHLOROPHENYL)BUTAN-2-ONE
1895. SYNTHESIS OF α,β-UNSATURATED NITRILES FROM ACETONITRILE: CYCLOHEXYLIDENEACETONITRILE AND CINNAMONITRILE
1896. 1,2-CYCLOBUTANEDIONE
1897. CYCLOBUTANONE
1898. CYCLOBUTENE
1899. DEOXYGENATION OF EPOXIDES WITH LOWER VALENT TUNGSTEN HALIDES: TRANS-CYCLODODECENE
1900. MERCAPTANS FROM THIOKETALS: CYCLODODECYL MERCAPTAN
1901. EPOXIDATION OF OLEFINS BY HYDROGEN PEROXIDE-ACETONITRILE: CIS-CYCLOOCTENE OXIDE
1902. CYCLOPROPANECARBOXALDEHYDE
1903. CYCLOPROPANONE ETHYL HEMIACETAL FROM ETHYL 3-CHLOROPROPANOATE
1904. CYCLOUNDECANECARBOXYLIC ACID
1905. A GENERAL SYNTHETIC METHOD FOR THE PREPARATION OF METHYL KETONES FROM TERMINAL OLEFINS: 2-DECANONE
1906. DEOXYGENATION OF SECONDARY ALCOHOLS: 3-DEOXY-1,2:5,6-DI-O-ISOPROPYLIDENE-α-D-RIBO-HEXOFURANOSE
1907. DI-TERT-BUTYL METHYLENEMALONATE
1908. 2,6-DI-TERT-BUTYL-4-METHYLPYRIDINE
1909. α-AMINO ACETALS: 2,2-DIETHOXY-2-(4-PYRIDYL)ETHYLAMINE
1910. DIASTEREOSELECTIVE α-ALKYLATION OF β-HYDROXYCARBOXYLIC ESTERS THROUGH ALKOXIDE ENOLATES: DIETHYL (2S, 3R)-(+)-3-ALLYL-2-HYDROXYSUCCINATE FROM DIETHYL (S)-(−)-MALATE
1911. DIETHYL [(2-TETRAHYDROPYRANYLOXY)METHYL] PHOSPHONATE
1912. N-(2,4-DIFORMYL-5-HYDROXYPHENYL)ACETAMIDE
1913. STEREOCONTROLLED IODOLACTONIZATION OF ACYCLIC OLEFINIC ACIDS: THE TRANS AND CIS ISOMERS OF 4,5-DIHYDRO-5-IODOMETHYL-4-PHENYL-2(3H)-FURANONE

1914. OZONOLYTIC CLEAVAGE OF CYCLOHEXENE TO TERMINALLY DIFFERENTIATED PRODUCTS: METHYL 6-OXOHEXANOATE, 6,6-DIMETHOXYHEXANAL, METHYL 6,6-DIMETHOXYHEXANOATE
1915. PALLADIUM-PHOSPHINE-COMPLEX-CATALYZED REACTION OF ORGANOLITHIUM COMPOUNDS AND ALKENYL HALIDES: (Z)-β-[2-(N,N-DIMETHYLAMINO)PHENYL]STYRENE
1916. COPPER(I)-CATALYZED PHOTOCYCLOADDITION: 3,3-DIMETHYL-CIS-BICYCLO[3.2.0]HEPTAN-2-ONE
1917. ANODIC OXIDATION OF ACIDS: DIMETHYL DECANEDIOATE
1918. (2SR,3RS)-2,4-DIMETHYL-3-HYDROXYPENTANOIC ACID
1919. (2SR,3SR)-2,4-DIMETHYL-3-HYDROXYPENTANOIC ACID
1920. 1,3-DIMETHYLIMIDAZOLE-2-THIONE
1921. β-DIMETHYLAMINOMETHYLENATION: N,N-DIMETHYL-N'-P-TOLYLFORMAMIDINE
1922. 1,6-DIMETHYLTRICYCLO[4.1.0.02,7]HEPT-3-ENE
1923. PREPARATION OF CHLOROPHENYLDIAZIRINE AND THERMAL GENERATION OF CHLOROPHENYL CARBENE: 1,2-DIPHENYL-3-METHYLCYCLOPROPENE
1924. DIPHENYL PHOSPHORAZIDATE
1925. THE STORK–DANHEISER KINETIC ALKYLATION PROCEDURE: 3-ETHOXY-6-METHYL-2-CYCLOHEXEN-1-ONE
1926. ETHYL α-(BROMOMETHYL)ACRYLATE
1927. ALIPHATIC AND AROMATIC β-KETO ESTERS FROM MONOETHYL MALONATE: ETHYL 2-BUTYRYLACETATE
1928. YEAST REDUCTION OF ETHYL ACETOACETATE: (S)-(+)-ETHYL 3-HYDROXYBUTANOATE
1929. ETHYL 4-HYDROXYCROTONATE
1930. OSMIUM-CATALYZED VICINAL OXYAMINATION OF OLEFINS BY N-CHLORO-N-ARGENTOCARBAMATES: ETHYL THREO-[1-(2-HYDROXY-1,2-DIPHENYLETHYL)]CARBAMATE
1931. ETHYL ISOCROTONATE
1932. THE C-ARYLATION OF β-DICARBONYL COMPOUNDS: ETHYL 1-(P-METHOXYPHENYL)-2-OXOCYCLOHEXANECARBOXYLATE
1933. α-ALLENIC ESTERS FROM α-PHOSPHORANYLIDENE ESTERS AND ACID CHLORIDES: ETHYL 2,3-PENTADIENOATE
1934. ADDITION OF AN ETHYLCOPPER COMPLEX TO 1-OCTYNE: (E)-5-ETHYL-1,4-UNDECADIENE
1935. DICHLOROVINYLATION OF AN ENOLATE: 8-ETHYNYL-8-METHYL-

1,4-DIOXASPIRO[4.5]DEC-6-ENE
1936. PALLADIUM-CATALYZED SYNTHESIS OF 1,4-DIENES BY ALLYLATION OF ALKENYLALANES:α-FARNESENE
1937. ALKYLATION OF THE ANION FROM BIRCH REDUCTION OF O-ANISIC ACID: 2-HEPTYL-2-CYCLOHEXENONE
1938. HEXAFLUOROACETONE
1939. HEXAHYDRO-2-(1H)-AZOCINONE
1940. HEXAMETHYL DEWAR BENZENE
1941. SELECTIVE HYDROBORATION OF A 1,3,7-TRIENE: HOMOGERANIOL
1942. α-HYDROXYLATION OF A KETONE USING O-IODOSYLBENZOIC ACID: α-HYDROXYACETOPHENONE VIA THE α-HYDROXY DIMETHYLACETAL
1943. SILYLATION OF 2-METHYL-2-PROPEN-1-OL DIANION: 2-(HYDROXYMETHYL)ALLYLTRIMETHYLSILANE
1944. 2-HYDROXYMETHYL-2-CYCLOPENTENONE
1945. ONE-STEP HOMOLOGATION OF ACETYLENES TO ALLENES: 4-HYDROXYNONA-1,2-DIENE
1946. HYDROXYLATION OF ENOLATES WITH OXODIPEROXYMOLYBDENUM(PYRIDINE)(HEXAMETHYLPHOSPHORIC TRIAMIDE), MOO5·PY·HMPA (MOOPH): 3-HYDROXY-1,7,7-TRIMETHYLBICYCLO[2.2.1]HEPTAN-2-ONE
1947. α-HYDROXY KETONES FROM THE OXIDATION OF ENOL SILYL ETHERS WITH M-CHLOROPERBENZOIC ACID: 6-HYDROXY- 3,5,5-TRIMETHYL-2-CYCLOHEXEN-1-ONE
1948. IMIDAZOLE-2-CARBOXALDEHYDE
1949. Z-1-IODOHEXENE
1950. CONVERSION OF EPOXIDES TO β-HYDROXY ISOCYANIDES: TRANS-2-ISOCYANOCYCLOHEXANOL
1951. 2,3-O-ISOPROPYLIDENE-D-ERYTHRONOLACTONE
1952. O-ISOTHIOCYANATO-(E)-CINNAMALDEHYDE
1953. PHOTOPROTONATION OF CYCLOALKENES: LIMONENE TO P-MENTH-8-EN-1-YL METHYL ETHER
1954. ANODIC OXIDATION OF N-CARBOMETHOXYPYRROLIDINE: 2-METHOXY-N-CARBOMETHOXYPYRROLIDINE
1955. PREPARATION AND DIELS–ALDER REACTION OF A HIGHLY NUCLEOPHILIC DIENE: TRANS-1-METHOXY-3-

TRIMETHYLSILOXY-1,3-BUTADIENE AND 5β-METHOXYCYCLOHEXAN-1-ONE-3β,4β-DICARBOXYLIC ACID ANHYDRIDE
1956. PHOTOCYCLIZATION OF AN ENONE TO AN ALKENE: 6-METHYLBICYCLO[4.2.0]OCTAN-2-ONE
1957. METHYL α-(BROMOMETHYL)ACRYLATE
1958. METHYL DIFORMYLACETATE
1959. SELECTIVE HALOGEN-LITHIUM EXCHANGE REACTIONS OF 2-(2'-HALOPHENYL)ETHYL HALIDES: SYNTHESIS OF 4,5-METHYLENEDIOXYBENZOCYCLOBUTENE AND 1-PHENYL-3,4-DIHYDRO-6,7-METHYLENEDIOXYISOQUINOLINE
1960. METHYLENE KETONES AND ALDEHYDES BY SIMPLE, DIRECT METHYLENE TRANSFER: 2-METHYLENE-1-OXO-1,2,3,4-TETRAHYDRONAPHTHALENE
1961. METHYL 4-HYDROXY-2-BUTYNOATE
1962. ASYMMETRIC HYDROBORATION OF 5-SUBSTITUTED CYCLOPENTADIENES: SYNTHESIS OF METHYL (1 R,5R)-5-HYDROXY-2-CYCLOPENTENE-1-ACETATE
1963. PREPARATION OF LOW-HALIDE METHYLLITHIUM
1964. β-ALKYL-α,β-UNSATURATED ESTERS FROM ENOL PHOSPHATES OF β-KETO ESTERS: METHYL 2-METHYL-1-CYCLOHEXENE-1-CARBOXYLATE
1965. OPTICALLY ACTIVE EPOXIDES FROM VICINAL DIOLS VIA VICINAL ACETOXY BROMIDES: (S)-(–)- AND (R)-(+)-METHYLOXIRANE
1966. METHYL PHENYLACETYLACETATE FROM PHENYLACETYL CHLORIDE AND MELDRUM'S ACID
1967. 2-METHYL-3-PHENYLPROPANAL
1968. (+)-(7AS)-7A-METHYL-2,3,7,7A-TETRAHYDRO-1 H-INDENE-1,5-(6H-DIONE
1969. (S)-8A-METHYL-3,4,8,8A-TETRAHYDRO-1,6(2H, 7H)-NAPHTHALENEDIONE
1970. THIATION WITH 2,4-BIS(4-METHOXYPHENYL)-1,3,2,4-DITHIADIPHOSPHETANE 2,4-DISULFIDE: N-METHYLTHIOPYRROLIDONE
1971. OSMIUM-CATALYZED VICINAL OXYAMINATION OF OLEFINS BY CHLORAMINE-T: CIS-2-(P-TOLUENESULFONAMIDO) CYCLOHEXANOL AND 2-METHYL-3-(P-TOLUENESULFONAMIDO)-

2-PENTANOL
1972. 2-METHYL-2-(TRIMETHYLSILOXY)PENTAN-3-ONE
1973. (R,S)-MEVALONOLACTONE-2-13C
1974. REDUCTION OF KETONES TO HYDROCARBONS WITH TRIETHYLSILANE: M-NITROETHYLBENZENE
1975. 2-NITROPROPENE
1976. CARBOXYLIC ACIDS FROM THE OXIDATION OF TERMINAL ALKENES BY PERMANGANATE: NONADECANOIC ACID
1977. SUBSTITUTED γ-BUTYROLACTONES FROM CARBOXYLIC ACIDS AND OLEFINS: γ-(N-OCTYL)-γ-BUTYROLACTONE
1978. ASYMMETRIC REDUCTION OF α,β-ACETYLENIC KETONES WITH B-3-PINANYL-9-BORABICYCLO[3.3.1]NONANE: (R)-(+)-1-OCTYN-3-OL
1979. PREPARATION OF CHIRAL, NONRACEMIC γ-LACTONES BY ENZYMECATALYZED OXIDATION OF MESO-DIOLS: (+)-(1R,6S)-8-OXABICYCLO[4.3.0]NONAN-7-ONE
1980. HOMOCONJUGATE ADDITION OF NUCLEOPHILES TO CYCLOPROPANE-1,1-DICARBOXYLATE DERIVATIVES: 2-OXO-1-PHENYL-3-PYRROLIDINECARBOXYLIC ACID
1981. SYNTHESIS OF 1,4-DIKETONES FROM SILYL ENOL ETHERS AND NITROOLEFINS: 2-(2-OXOPROPYL)CYCLOHEXANONE
1982. ASYMMETRIC HYDROGENATION OF KETOPANTOYL LACTONE: D-(–)-PANTOYL LACTONE
1983. PREPARATION OF 4-ALKYL-AND 4-HALOBENZOYL CHLORIDES: 4-PENTYLBENZOYL CHLORIDE
1984. α-TERT-ALKYLATION OF KETONES: 2-TERT-PENTYLCYCLOPENTANONE
1985. PERHYDRO-9B-BORAPHENALENE AND PERHYDRO-9B-PHENALENOL
1986. 2-PHENYL-2-ADAMANTANAMINE HYDROCHLORIDE
1987. CYANIC ACID ESTERS FROM PHENOLS: PHENYL CYANATE
1988. TOSYLHYDRAZONE SALT PYROLYSES: PHENYLDIAZOMETHANES
1989. CONJUGATE ALLYLATION OF α,β-UNSATURATED KETONES WITH ALLYLSILANES: 4-PHENYL-6-HEPTEN-2-ONE
1990. ENANTIOSELECTIVE ADDITION OF BUTYLLITHIUM IN THE PRESENCE OF THE CHIRAL COSOLVENT DDB: (R)-(+)-1-PHENYL-1-PENTANOL

1991. FORMYL TRANSFER TO GRIGNARD REAGENTS WITH N-FORMYLPIPERIDINE: 3-PHENYLPROPIONALDEHYDE
1992. PHENYL VINYL SULFONE AND SULFOXIDE
1993. 2-ALKENYL CARBINOLS FROM 2-HALO KETONES: 2-E-PROPENYLCYCLOHEXANOL
1994. ENANTIOSELECTIVE EPOXIDATION OF ALLYLIC ALCOHOLS: (2S,3S)-3-PROPYLOXIRANEMETHANOL
1995. ACID CHLORIDES FROM α-KETO ACIDS WITH α,α-DICHLOROMETHYL METHYL ETHER: PYRUVOYL CHLORIDE
1996. RICINELAIDIC ACID LACTONE
1997. SPIRO[5.7]TRIDECA-1,4-DIEN-3-ONE
1998. 2,2' : 6',2' -TERPYRIDINE
1999. ELECTROHYDRODIMERIZATION OF AN ACTIVATED ALKENE: TETRAETHYL 1,2,3,4-BUTANETETRACARBOXYLATE
2000. INDIRECT ELECTROLYSIS: TETRAMETHYL 1,1,2,2-ETHANETETRACARBOXYLATE
2001. DIELS-ALDER REACTION OF 1,2,4,5-HEXATETRAENE: TETRAMETHYL[2.2]PARACYCLOPHANE-4,5,12,13-TETRACARBOXYLATE
2002. THIETE 1,1-DIOXIDE AND 3-CHLOROTHIETE 1,1-DIOXIDE
2003. (S)-(+)-2-(P-TOLUENESULFINYL)-2-CYCLOPENTENONE: PRECURSOR FOR ENANTIOSELECTIVE SYNTHESIS OF 3-SUBSTITUTED CYCLOPENTANONES
2004. CIS-N-TOSYL-3-METHYL-2-AZABICYCLO[3.3.0]OCT-3-ENE
2005. TRIFLOROACETYL TRIFLATE
2006. M-TRIFLUOROMETHYLBENZENESULFONYL CHLORIDE
2007. SILYLATION OF KETONES WITH ETHYL TRIMETHYLSILACETATE: (Z)-3-TRIMETHYLSILOXY-2-PENTENE
2008. TRIMETHYLSILYL CYANIDE: CYANOSILATION OF P-BENZOQUINONE
2009. IN SITU CYANOSILYLATION OF CARBONYL COMPOUNDS: O-TRIMETHYLSILYL-4-METHOXYMANDELONITRILE
2010. STEREOSPECIFIC REDUCTION OF PROPARGYL ALCOHOLS: (E)-3-TRIMETHYLSILYL-2-PROPEN-1-OL
2011. TRIS(DIMETHYLAMINO)SULFONIUM DIFLUOROTRIMETHYLSILICATE
2012. REDUCTION OF α-AMINO ACIDS: L-VALINOL
2013. ACETONE TRIMETHYSILYL ENOL ETHER

2014. SYNTHESIS OF A KEY β-LACTAM INTERMEDIATE BY A [2 + 2] CYCLOADDITION ROUTE: 4-ACETOXYAZETIDIN-2-ONE
2015. STEREOSELECTIVE 1,4-FUNCTIONALIZATIONS OF CONJUGATED DIENES: CIS- AND TRANS-1-ACETOXY-4-(DICARBOMETHOXYMETHYL)-2-CYCLOHEXENE
2016. 1,4-FUNCTIONALIZATION OF 1,3-DIENES VIA PALLADIUM-CATALYZED CHLOROACETOXYLATION AND ALLYLIC AMINATION: 1-ACETOXY-4-DIETHYLAMINO-2-BUTENE AND 1-ACETOXY-4-BENZYLAMINO-2-BUTENE
2017. PALLADIUM(0)-CATALYZED SYN-1,4-ADDITION OF CARBOXYLIC ACIDS TO CYCLOPENTADIENE MONOEPOXIDE: CIS-3-ACETOXY-5-HYDROXYCYCLOPENT-1-ENE
2018. N-ACETYL-N-PHENYLHYDROXYLAMINE VIA CATALYTIC TRANSFER HYDROGENATION OF NITROBENZENE USING HYDRAZINE AND RHODIUM ON CARBON
2019. ACETYLTRIMETHYLSILANE
2020. ALLYLTRIBUTYLTIN
2021. (S)-(–)-1-AMINO-2-METHOXYMETHYLPYRROLIDINE (SAMP) AND (R)-(+)-1-AMINO-2-METHOXYMETHYLPYRROLIDINE (RAMP), VERSATILE CHIRAL AUXILIARIES
2022. IMINIUM ION-BASED DIELS–ALDER REACTIONS: N-BENZYL-2-AZANORBORNENE
2023. MIXED HIGHER-ORDER CYANOCUPRATE-INDUCED EPOXIDE OPENINGS: 1-BENZYLOXY-4-PENTEN-2-OL
2024. REDUCTIVE ANNULATION OF VINYL SULFONES: BICYCLO[4.3.0.]NON-1-EN-4-ONE
2025. INTRAMOLECULAR CYCLIZATION OF CIS,CIS-1,5-CYCLOOCTADIENE USING HYPERVALENT IODINE: BICYCLO[3.3.0]OCTANE-2,6-DIONE
2026. (R)-(+)-1,1'-BINAPHTHALENE-2,2'-DIOL
2027. ENANTIOMERIC (S)-(+)- AND (R)-(–)-1,1'-BINAPHTHYL-2,2'-DIYL HYDROGEN PHOSPHATE
2028. (R)-(+)- AND (S)-(–)-2,2'-BIS(DIPHENYLPHOSPHINO)-1,1'-BINAPHTHYL (BINAP)
2029. 1,4-BIS(TRIMETHYLSILYL)BUTA-1,3-DIYNE
2030. N-TERT-BUTOXYCARBONYL-L-LEUCINAL
2031. TERT-BUTYL ACETOTHIOACETATE AND ITS USE IN SYNTHESIS: 3-ACETYL-4-HYDROXY-5,5-DIMETHYLFURAN-2(4H)-ONE

2032. P-TERT-BUTYLCALIX[4]ARENE
2033. P-TERT-BUTYLCALIX[6]ARENE
2034. P-TERT-BUTYLCALIX[8]ARENE
2035. 3-BUTYLCYCLOBUTENONE
2036. 9-N-BUTYL-1,2,3,4,5,6,7,8-OCTAHYDROACRIDIN-4-OL
2037. TERT-BUTYL-TERT-OCTYLAMINE
2038. PALLADIUM-CATALYZED COUPLING OF VINYL TRIFLATES WITH ORGANOSTANNANES: 4-TERT-BUTYL-1-VINYLCYCLOHEXENE AND 1-(4-TERT-BUTYLCYCLOHEXEN-1-YL)-2-PROPEN-1-ONE
2039. (+)-(2R,8AS)-10-(CAMPHORYLSULFONYL)OXAZIRIDINE
2040. (–)-D-2,10-CAMPHORSULTAM
2041. CONJUGATE ADDITION–CYCLIZATION OF A CYANOCUPRATE: 2-CARBOMETHOXY-3-VINYLCYCLOPENTANONE
2042. 7-CHLORO-7-CYANOBICYCLO[4.2.0]OCTAN-8-ONE
2043. (S)-2-CHLOROALKANOIC ACIDS OF HIGH ENANTIOMERIC PURITY FROM (S)-2-AMINO ACIDS: (S)-2-CHLOROPROPANOIC ACID
2044. 1-CHLORO-1-(TRICHLOROETHENYL)CYCLOPROPANE
2045. PALLADIUM-CATALYZED REDUCTION OF VINYL TRIFLUOROMETHANESULFONATES TO ALKENES: CHOLESTA-3,5-DIENE
2046. HOFMANN REARRANGEMENT UNDER MILDLY ACIDIC CONDITIONS USING [I,I-BIS(TRIFLUOROACETOXY)] IODOBENZENE: CYCLOBUTYLAMINE HYDROCHLORIDE FROM CYCLOBUTANECARBOXAMIDE
2047. ALLYLIC ACETOXYLATION OF CYCLOALKENES: 2-CYCLOHEPTEN-1-YL ACETATE
2048. CONDENSATION OF (–)-DIMENTHYL SUCCINATE DIANION WITH 1,ω-DIHALIDES: (+)-(1S,2S)-CYCLOPROPANE-1,2-DICARBOXYLIC ACID
2049. TRIPLE-BOND ISOMERIZATIONS: 2- TO 9-DECYN-1-OL
2050. 1-DEOXY-2,3,4,6-TETRA-O-ACETYL-1-(2-CYANOETHYL)-α-D-GLUCOPYRANOSE
2051. 4,13-DIAZA-18-CROWN-6
2052. 1,4-DI-O-ALKYL THREITOLS FROM TARTARIC ACID: 1,4-DI-O-BENZYL-L-THREITOL
2053. DIALKOXYACETYLENES: DI-TERT-BUTOXYETHYNE, A VALUABLE SYNTHETIC INTERMEDIATE
2054. 4-CHLORINATION OF ELECTRON-RICH BENZENOID COMPOUNDS:

2,4-DICHLOROMETHOXYBENZENE
2055. PREPARATION AND THREE-CARBON + TWO-CARBON CYCLOADDITION OF CYCLOPROPENONE 1,3-PROPANEDIOL KETAL: 5,5-DICYANO-4-PHENYL-2-CYCLOPENTEN-1-ONE 1,3-PROPANEDIOL KETAL
2056. REARRANGEMENT OF 4-ARYL-4-HYDROXY-2,3-DIALKOXYCYCLOBUTENONES TO ANNULATED HYDROQUINONES AND QUINONES: 5,6-DIETHOXYBENZOFURAN-4,7-DIONE
2057. (R)-(−)-N,N-DIETHYL-(E)-CITRONELLALENAMINE AND (R)-(+)-CITRONELLAL VIA ISOMERIZATION OF N,N-DIETHYLGERANYLAMINE OR N,N-DIETHYLNERYLAMINE
2058. ADDITION OF DIALKYLAMINES TO MYRCENE: N,N-DIETHYLGERANYLAMINE
2059. TELOMERIZATION OF ISOPRENE WITH DIALKYLAMINE: N,N-DIETHYLNERYLAMINE
2060. 6-DIETHYLPHOSPHONOMETHYL-2,2-DIMETHYL-1,3-DIOXEN-4-ONE
2061. DIAZO KETONE CYCLIZATION ONTO A BENZENE RING: 3,4-DIHYDRO-1(2H)-AZULENONE
2062. DIISOPROPYL (2S,3S)-2,3-O-ISOPROPYLIDENETARTRATE
2063. (S)-N,N-DIMETHYL-N'-(1-TERT-BUTOXY-3-METHYL-2-BUTYL) FORMAMIDINE
2064. 4,4-DIMETHYL-2-CYCLOPENTEN-1-ONE
2065. 3,3-DIMETHYL-1,5-DIPHENYLPENTANE-1,5-DIONE
2066. A GENERAL SYNTHETIC METHOD FOR THE PREPARATION OF CONJUGATED DIENES FROM OLEFINS USING BROMOMETHANESULFONYL BROMIDE: 1,2-DIMETHYLENECYCLOHEXANE
2067. 1,3-DIMETHYL-3-METHOXY-4-PHENYLAZETIDINONE
2068. APROTIC DOUBLE MICHAEL ADDITION: 1,3-DIMETHYL-5-OXOBICYCLO[2.2.2]OCTANE-2-CARBOXYLIC ACID
2069. CYCLOPENTADIENE ANNULATION VIA THE SKATTEBØL REARRANGEMENT: (1R)-9,9-DIMETHYLTRICYCLO-[6.1.1.02,6]DECA-2,5-DIENE
2070. PROPARGYLATION OF ALKYL HALIDES: (E)-6,10-DIMETHYL-5,9-UNDECADIEN-1-YNE AND (E)-7,11-DIMETHYL-6,10-DODECADIEN-2-YN-1-OL

2071. N-BENZYL-N-METHOXYMETHYL-N-(TRIMETHYLSILYL) METHYLAMINE AS AN AZOMETHINE YLIDE EQUIVALENT: 2,6-DIOXO-1-PHENYL-4-BENZYL-1,4-DIAZABICYCLO[3.3.0]OCTANE
2072. THE CARROLL REARRANGEMENT: 5-DODECEN-2-ONE
2073. ASYMMETRIC SYNTHESIS OF 4,4-DIALKYLCYCLOHEXENONES FROM CHIRAL BICYCLIC LACTAMS: (R)-4-ETHYL-4-ALLYL-2-CYCLOHEXEN-1-ONE
2074. UTILIZATION OF β-CHLORO ALKYLIDENE/ARYLIDENE MALONATES IN ORGANIC SYNTHESIS: ETHYL CYCLOPROPYLPROPIOLATE
2075. ETHYL (E,Z)-2,4-DECADIENOATE
2076. SYNTHESIS OF ALKYL PROPANOATES BY A HALOFORM REACTION OF A TRICHLORO KETONE: ETHYL 3,3-DIETHOXYPROPANOATE
2077. ENANTIOMERICALLY PURE ETHYL (R)- AND (S)- 2-FLUOROHEXANOATE BY ENZYME-CATALYZED KINETIC RESOLUTION
2078. ETHYL α-(HEXAHYDROAZEPINYLIDENE-2)ACETATE FROM O-METHYLCAPROLACTIM AND MELDRUM'S ACID
2079. ETHYL α-(HYDROXYMETHYL)ACRYLATE
2080. PALLADIUM-CATALYZED COUPLING OF ACID CHLORIDES WITH ORGANOTIN REAGENTS: ETHYL (E)-4-(4-NITROPHENYL)-4-OXO-2-BUTENOATE
2081. ETHYL 5-OXO-6-METHYL-6-HEPTENOATE FROM METHACRYLOYL CHLORIDE AND ETHYL 4-IODOBUTYRATE
2082. COPPER-CATALYZED CONJUGATE ADDITION OF A ZINC HOMOENOLATE: ETHYL 3-[3-(TRIMETHYLSILYLOXY)CYCLOHEX-2-ENYL]PROPIONATE
2083. ETHYNYL P-TOLYL SULFONE
2084. N-FLUOROPYRIDINIUM TRIFLATE: AN ELECTROPHILIC FLUORINATING AGENT
2085. PALLADIUM-CATALYZED SYNTHESIS OF CONJUGATED DIENES: (5Z,7E)-5,7-HEXADECADIENE
2086. DOMINO DIELS–ALDER REACTION: 3,3A,3B,4,6A,7A-HEXAHYDRO-3,4,7-METHENO-7H-CYCLOPENTA[A]PENTALENE-7,8-DICARBOXYLIC ACID
2087. CHIRAL 1,3-OXATHIANE FROM (+)-PULEGONE: HEXAHYDRO-4,4,7-TRIMETHYL-4H-1,3-BENZOXATHIIN

2088. A GENERAL SYNTHESIS OF CYCLOBUTANONES FROM OLEFINS AND TERTIARY AMIDES: 3-HEXYLCYCLOBUTANONE
2089. 3-HYDROXY-1-CYCLOHEXENE-1-CARBOXALDEHYDE
2090. YEAST REDUCTION OF 2,2-DIMETHYLCYCLOHEXANE-1,3-DIONE: (S)-(+)-3-HYDROXY-2,2-DIMETHYLCYCLOHEXANONE)
2091. NUCLEOPHILIC HYDROXYMETHYLATION BY THE (ISOPROPOXYDIMETHYLSILYL)METHYL GRIGNARD REAGENT: 1-(HYDROXYMETHYL)CYCLOHEXANOL FROM CYCLOHEXANONE
2092. SELECTIVE CYCLOPROPANATION OF (S)-(–)-PERILLYL ALCOHOL: 1-HYDROXYMETHYL-4-(1-METHYLCYCLOPROPYL)-1-CYCLOHEXENE
2093. 3-HYDROXY-3-METHYL-1-PHENYL-1-BUTANONE BY CROSSED ALDOL REACTION
2094. ERYTHRO-DIRECTED REDUCTION OF A β-KETO AMIDE: ERYTHRO-1-(3-HYDROXY-2-METHYL-3-PHENYLPROPANOYL) PIPERIDINE
2095. ENANTIOSELECTIVE SAPONIFICATION WITH PIG LIVER ESTERASE (PLE): (1S,2S,3R)-3-HYDROXY-2-NITROCYCLOHEXYL ACETATE
2096. DIASTEREOSELECTIVE ALDOL CONDENSATION USING A CHIRAL OXAZOLIDINONE AUXILIARY: (2S*,3S*)-3-HYDROXY-3-PHENYL-2-METHYLPROPANOIC ACID
2097. DIRECT NUCLEOPHILIC ACYLATION BY THE LOW-TEMPERATURE, IN SITU GENERATION OF ACYLLITHIUM REAGENTS; α-HYDROXY KETONES FROM KETONES: 3-HYDROXY-2,2,3-TRIMETHYLOCTAN-4-ONE FROM PINACOLONE
2098. A GENERAL [3+2] ANNULATION: CIS-4-EXO-ISOPROPENYL-1,9-DIMETHYL-8-(TRIMETHYLSILYL)BICYCLO[4.3.0]NON-8-EN-2-ONE
2099. TRANSESTERIFICATION OF METHYL ESTERS OF AROMATIC AND α,β-UNSATURATED ACIDS WITH BULKY ALCOHOLS: (–)-MENTHYL CINNAMATE AND (–)-MENTHYL NICOTINATE
2100. DIASTEROSELECTIVE FORMATION OF α-METHOXYCARBONYL LACTONES THROUGH AN INTRAMOLECULAR DIELS–ALDER REACTION: (4RS,4ARS,6RS,8ARS)-, (4S,4AS,6S,8AS)- AND (4R,4AR,6R,8AR)-4-METHOXYCARBONYL-1,1,6-TRIMETHYL-1,4,4A,5,6,7,8,8A-OCTAHYDRO-2,3-BENZOPYRONE [RAC-5, (+)-5, AND (–)-5]
2101. 4-METHOXY-3-PENTEN-2-ONE

2102. REGIOSELECTIVE SYNTHESIS OF TETRAHYDROPYRIDINES: 1-(4-METHOXYPHENYL)-1,2,5,6-TETRAHYDROPYRIDINE
2103. 6-BROMO-6-DEOXY HEXOSE DERIVATIVES BY RING OPENING OF BENZYLIDENE ACETALS WITH N-BROMOSUCCINIMIDE: METHYL 4-O-BENZOYL-6-BROMO-6-DEOXY-α-D-GLUCOPYRANOSIDE
2104. A GENERAL SYNTHETIC METHOD FOR THE OXIDATION OF PRIMARY ALCOHOLS TO ALDEHYDES: (S)-(+)-2-METHYLBUTANAL
2105. ALKOXYCARBONYLATION OF PROPARGYL CHLORIDE: METHYL 4-CHLORO-2-BUTYNOATE
2106. METHYL 2-CHLORO-2-CYCLOPROPYLIDENACETATE
2107. VICINAL DICARBOXYLATION OF AN ALKENE: CIS-1-METHYLCYCLOPENTANE-1,2-DICARBOXYLIC ACID
2108. VINYL RADICAL CYCLIZATION VIA ADDITION OF TIN RADICALS TO TRIPLE BONDS: 3-METHYLENE-4-ISOPROPYL-1,1-CYCLOPENTANEDICARBOXYLIC ACID, DIMETHYL ESTER
2109. METHYLENATION OF CARBONYL COMPOUNDS: (+)-3-METHYLENE-CIS-P-METHANE
2110. PREPARATION AND USE OF LITHIUM ACETYLIDE: 1-METHYL-2-ETHYNYL-ENDO-3,3-DIMETHYL-2-NORBORNANOL
2111. 3-METHYL-2(5H)-FURANONE
2112. ASYMMETRIC SYNTHESES USING THE SAMP-/RAMP-HYDRAZONE METHOD: (S)-(+)-4-METHYL-3-HEPTANONE
2113. METHYL 7-HYDROXYHEPT-5-YNOATE
2114. DIRECTED HOMOGENEOUS HYDROGENATION: METHYL ANTI-3-HYDROXY-2-METHYLPENTANOATE
2115. ALLYLCARBAMATES BY THE AZA-ENE REACTION: METHYL N-(2-METHYL-2-BUTENYL)CARBAMATE
2116. SYNTHESIS OF BIARYLS VIA PALLADIUM-CATALYZED CROSS-COUPLING: 2-METHYL-4'-NITROBIPHENYL
2117. (R)-ALKYLOXIRANES OF HIGH ENANTIOMERIC PURITY FROM (S)-2-CHLOROALKANOIC ACIDS VIA (S)-2-CHLORO-1-ALKANOLS: (R)-METHYLOXIRANE
2118. KETONES FROM CARBOXYLIC ACIDS AND GRIGNARD REAGENTS: METHYL 6-OXODECANOATE
2119. PREPARATION AND INVERSE-ELECTRON-DEMAND DIELS–ALDER REACTION OF AN ELECTRON-DEFICIENT DIENE: METHYL 2-OXO-5,6,7,8-TETRAHYDRO-2H-1-BENZOPYRAN-3-CARBOXYLATE AND

6-METHOXY-7-METHOXYCARBONYL-1,2,3,4-TETRAHYDRONAPHTHALANE

2120. GEMINAL ACYLATION-ALKYLATION AT A CARBONYL CENTER USING DIETHYL N-BENZYLIDENEAMINOMETHYLPHOSPHONATE: 2-METHYL-2-PHENYL-4-PENTENAL
2121. METHYL (Z)-3-(PHENYLSULFONYL)PROP-2-ENOATE
2122. ALKYLATIONS USING HEXACARBONYL(PROPARGYLIUM) DICOBALT SALTS: 2-(1-METHYL-2-PROPYNYL)CYCLOHEXANONE
2123. ENANTIOSELECTIVE OXIDATION OF A SULFIDE: (S)-(−)-METHYL P-TOLYL SULFOXIDE
2124. INTRAMOLECULAR OXIDATIVE COUPLING OF A BISENOLATE: 4-METHYLTRICYCLO[2.2.2.03,5]OCTANE-2,6-DIONE
2125. A GENERAL METHOD FOR THE SYNTHESIS OF ALLENYLSILANES: 1-METHYL-1-(TRIMETHYLSILYL)ALLENE
2126. α-DIPHENYLMETHYLSILYLATION OF ESTER ENOLATES: 2-METHYL-2-UNDECENE FROM ETHYL DECANOATE
2127. VINYLATION OF ENOLATES WITH A VINYL CATION EQUIVALENT: TRANS-3-METHYL-2-VINYLCYCLOHEXANONE
2128. CYCLOPENTANONES FROM CARBOXYLIC ACIDS VIA INTRAMOLECULAR ACYLATION OF ALKYLSILANES: 2-METHYL-2-VINYLCYCLOPENTANONE
2129. OXIDATIVE CLEAVAGE OF AN AROMATIC RING: CIS,CIS-MONOMETHYL MUCONATE FROM 1,2-DIHYDROXYBENZENE
2130. 4-NITROINDOLE
2131. 3'-NITRO-1-PHENYLETHANOL BY ADDITION OF METHYLTRIISOPROPOXYTITANIUM TO M-NITROBENZALDEHYDE
2132. REDUCTION OF CARBOXYLIC ACIDS TO ALDEHYDES: 6-OXODECANAL
2133. (1-OXO-2-PROPENYL)TRIMETHYLSILANE
2134. 1,2,3,4,5-PENTAMETHYLCYCLOPENTADIENE
2135. HYDROMAGNESIATION REACTION OF PROPARGYLIC ALCOHOLS: (E)-3-PENTYL-2-NONENE-1,4-DIOL FROM 2-OCTYN-1-OL
2136. ENOL ETHERS BY METHYLENATION OF ESTERS: 1-PHENOXY-1-PHENYLETHENE AND 3,4-DIHYDRO-2-METHYLENE-2H-1-BENZOPYRAN
2137. LIPASE-CATALYZED KINETIC RESOLUTION OF ALCOHOLS VIA

CHLOROACETATE ESTERS: (−)-(1R,2S)-TRANS-2-PHENYLCYCLOHEXANOL AND (+)-(1S,2R)-TRANS-2-PHENYLCYCLOHEXANOL
2138. (−)-8-PHENYLMENTHOL
2139. (S)-4-(PHENYLMETHYL)-2-OXAZOLIDINONE
2140. PALLADIUM-CATALYZED REACTION OF 1-ALKENYLBORONATES WITH VINYLIC HALIDES: (1Z,3E)-1-PHENYL-1,3-OCTADIENE
2141. α-UNSUBSTITUTED γ,δ-UNSATURATED ALDEHYDES BY CLAISEN REARRANGEMENT: 3-PHENYL-4-PENTENAL
2142. 2-(PHENYLSULFONYL)-1,3-CYCLOHEXADIENE
2143. DIENOPHILE ACTIVATION VIA SELENOSULFONATION: 1-(PHENYLSULFONYL)CYCLOPENTENE
2144. (±)-TRANS-2-(PHENYLSULFONYL)-3-PHENYLOXAZIRIDINE
2145. (PHENYLTHIO)NITROMETHANE
2146. (−)-α-PINENE BY ISOMERIZATION OF (−)-β-PINENE
2147. SYNTHESIS OF CYCLOBUTANONES VIA 1-BROMO-1-ETHOXYCYCLOPROPANE: (E)-2-(1-PROPENYL)CYCLOBUTANONE
2148. A GENERAL METHOD FOR THE PREPARATION OF 9-, 10-, AND 11-MEMBERED UNSATURATED MACROLIDES: SYNTHESIS OF 8-PROPIONYL-(E)-5-NONENOLIDE
2149. 2-PROPYL-1-AZACYCLOHEPTANE FROM CYCLOHEXANONE OXIME
2150. (−)-SALSOLIDINE
2151. RING EXPANSION AND CLEAVAGE OF SUCCINOIN DERIVATIVES: SPIRO[4.5]DECANE-1,4-DIONE AND ETHYL 4-CYCLOHEXYL-4-OXOBUTANOATE
2152. 1,3,4,6-TETRA-O-ACETYL-2-DEOXY-α-D-GLUCOPYRANOSE
2153. AMBIENT-TEMPERATURE ULLMAN REACTION: 4,5,4',5'-TETRAMETHOXY-1,1'-BIPHENYL-2,2'-DICARBOXALDEHYDE
2154. SYNTHESIS OF MACROCYCLIC SULFIDES USING CESIUM THIOLATES: 1,4,8,11-TETRATHIACYCLOTETRADECANE
2155. PREPARATION AND INVERSE-ELECTRON-DEMAND DIELS–ALDER REACTION OF AN ELECTRON-DEFICIENT HETEROCYCLIC AZADIENE: TRIETHYL 1,2,4-TRIAZINE-3,5,6-TRICARBOXYLATE AND 2,3,6-TRICARBOETHOXYPYRIDINE
2156. CONVERSION OF ESTERS TO ALLYLSILANES: TRIMETHYL(2-METHYLENE-4-PHENYL-3-BUTENYL)SILANE
2157. TRIMETHYLSILYLACETYLENE

2158. (Z)-4-(TRIMETHYLSILYL)-3-BUTEN-1-OL
2159. TRIMETHYLSILYLDIAZOMETHANE
2160. TRISAMMONIUM GERANYL DIPHOSPHATE
2161. THE STETTER REACTION: 2,5-UNDECANEDIONE AND 3-METHYL-2-PENTYL-2-CYCLOPENTEN-1-ONE (DIHYDROJASMONE)
2162. SYNTHESIS OF 2-SUBSTITUTED NAPHTHALENEDIOL DERIVATIVES USING CHROMIUM CARBENE COMPLEXES: 1-ACETOXY-2-BUTYL-4-METHOXYNAPHTHALENE
2163. STEREOCONTROLLED PREPARATION OF 3-ACYLTETRAHYDROFURANS FROM ACID-PROMOTED REARRANGEMENTS OF ALLYLIC KETALS: (2S,3S)-3-ACETYL-8-CARBOETHOXY-2,3-DIMETHYL-1-OXA-8-AZASPIRO[4.5]DECANE
2164. HIGHLY REACTIVE CALCIUM FOR THE PREPARATION OF ORGANOCALCIUM REAGENTS: 1-ADAMANTYL CALCIUM HALIDES AND THEIR ADDITION TO KETONES: 1-(1-ADAMANTYL) CYCLOHEXANOL
2165. (3S,4S)-3-AMINO-1-(3,4-DIMETHOXYBENZYL)-4-[(R)-2,2-DIMETHYL-1,3-DIOXOLAN-4-YL]-2-AZETIDINONE
2166. ENANTIOMERICALLY PURE β-AMINO ACIDS FROM 2-TERT-BUTYL-1-CARBOMETHOXY-2,3-DIHYDRO-4(1H)-PYRIMIDINONE: (R)-3-AMINO-3-(P-METHOXYPHENYL)PROPIONIC ACID
2167. N-TERT-BUTOXYCARBONYL-L-SERINE β-LACTONE AND (S)-3-AMINO-2-OXETANONE P-TOLUENESULFONIC ACID SALT
2168. BENZOCYCLOBUTENONE BY FLASH VACUUM PYROLYSIS
2169. 4-BENZYL-10,19-DIETHYL-4,10,19-TRIAZA-1,7,13,16-TETRAOXACYCLOHENEICOSANE (TRIAZA-21-CROWN-7)
2170. (–)-2-O-BENZYL-L-GLYCERALDEHYDE AND ETHYL (R,E)-4-O-BENZYL-4,5-DIHYDROXY-2-PENTENOATE
2171. (E)-1-BENZYL-3-(1-IODOETHYLIDENE)PIPERIDINE: NUCLEOPHILE-PROMOTED ALKYNE-IMINIUM ION CYCLIZATIONS
2172. DIASTEREOSELECTIVE HOMOLOGATION OF D-(R)-GLYCERALDEHYDE ACETONIDE USING 2-(TRIMETHYLSILYL) THIAZOLE: 2-O-BENZYL-3,4-ISOPROPYLIDENE-D-ERYTHROSE
2173. SYNTHESIS OF N-PROTECTED α-AMINO ACIDS FROM N-(BENZYLOXYCARBONYL)-L-SERINE VIA ITS β-LACTONE: Nα-(BENZYLOXYCARBONYL)-β-(PYRAZOL-1-YL)-L-ALANINE
2174. N-(BENZYLOXYCARBONYL)-L-VINYLGLYCINE METHYL ESTER
2175. ENANTIOSELECTIVE, CATALYTIC DIELS-ALDER REACTION: (1S-

ENDO)-3-(BICYCLO[2.2.1]HEPT-5-EN-2-YLCARBONYL)-2-OXAZOLIDINONE
2176. 2,2'-BI-5,6-DIHYDRO-1,3-DITHIOLO[4,5-B][1,4]DITHIINYLIDENE (BEDT-TTF)
2177. (S)-(–)- AND (R)-(+)-1,1'-BI-2-NAPHTHOL
2178. [3+2]-ANIONIC ELECTROCYCLIZATION USING 2,3-BIS (PHENYLSULFONYL)-1,3-BUTADIENE: TRANS-4,7,7-TRICARBOMETHOXY-2-PHENYLSULFONYLBICYCLO[3.3.0]OCT-1-ENE
2179. BIS(TRIFLUOROETHYL) (CARBOETHOXYMETHYL)PHOSPHONATE
2180. BIS(TRIMETHYLSILYL) PEROXIDE (BTMSPO)
2181. 9-BORABICYCLO[3.3.1]NONANE DIMER
2182. 3-MORPHOLINO-2-PHENYLTHIOACRYLIC ACID MORPHOLIDE AND 5-(4-BROMOBENZOYL-2-(4-MORPHOLINO)-3-PHENYLTHIOPHENE
2183. 9-BROMO-9-PHENYLFLUORENE
2184. PALLADIUM(0)-CATALYZED REACTION OF 9-ALKYL-9-BORABICYCLO[3.3.1]NONANE WITH 1-BROMO-1-PHENYLTHIOETHENE: 4-(3-CYCLOHEXENYL)-2-PHENYLTHIO-1-BUTENE
2185. AN IMPROVED PREPARATION OF 3-BROMO-2H-PYRAN-2-ONE: AN AMBIPHILIC DIENE FOR DIELS-ALDER CYCLOADDITIONS
2186. SYNTHESIS OF FUNCTIONALIZED ENYNES BY PALLADIUM/ COPPER-CATALYZED COUPLING REACTIONS OF ACETYLENES WITH (Z)-2,3-DIBROMOPROPENOIC ACID ETHYL ESTER: (Z)-2-BROMO-5-(TRIMETHYLSILYL)-2-PENTEN-4-YNOIC ACID ETHYL ESTER
2187. 2-SUBSTITUTED PYRROLES FROM N-TERT-BUTOXYCARBONYL-2-BROMOPYRROLE: N-TERT-BUTOXYCARBONYL-2-TRIMETHYLSILYLPYRROLE
2188. SYNTHESIS OF 7-SUBSTITUTED INDOLINES VIA DIRECTED LITHIATION OF 1-(TERT-BUTOXYCARBONYL)INDOLINE: 7-INDOLINECARBOXALDEHYDE
2189. PREPARATION OF 3-BROMOPROPIOLIC ESTERS:METHYL AND TERT-BUTYL 3-BROMOPROPIOLATES
2190. (4R)-(+)-TERT-BUTYLDIMETHYLSILOXY-2-CYCLOPENTEN-1-ONE
2191. (4S)-(–)-TERT-BUTYLDIMETHYLSILOXY-2-CYCLOPENTEN-1-ONE
2192. 3-(S)-[(TERT-BUTYLDIPHENYLSILYL)OXY]-2-BUTANONE

2193. ALLYLIC ALCOHOLS BY ALKENE TRANSFER FROM ZIRCONIUM TO ZINC: 1-[(TERT-BUTYLDIPHENYLSILYL)OXY]-DEC-3-EN-5-OL
2194. PREPARATION AND REACTIONS OF 2-TERT-BUTYL-1,1,3,3-TETRAMETHYLGUANIDINE: 2,2,6-TRIMETHYLCYCLOHEXEN-1-YL IODIDE
2195. (–)-(1S,4R)-CAMPHANOYL CHLORIDE
2196. RHODIUM-CATALYZED HETEROCYCLOADDITION OF A DIAZOMALONATE AND A NITRILE: 4-CARBOMETHOXY-5-METHOXY-2-PHENYL-1,3-OXAZOLE
2197. SCHWARTZ'S REAGENT
2198. PYRIDINE-DERIVED TRIFLATING REAGENTS: N-(2-PYRIDYL)-TRIFLIMIDE AND N-(5-CHLORO-2-PYRIDYL)TRIFLIMIDE
2199. ASYMMETRIC HYDROGENATION OF ALLYLIC ALCOHOLS USING BINAP-RUTHENIUM COMPLEXES: (S)-(–)-CITRONELLOL
2200. A STABLE CHIRAL 1,4-DIHYDROPYRIDINE EQUIVALENT FOR THE ASYMMETRIC SYNTHESIS OF SUBSTITUTED PIPERIDINES: 2-CYANO-6-PHENYLOXAZOLOPIPERIDINE
2201. BENZOANNELATION OF KETONES: 3,4-CYCLODODECENO-1-METHYLBENZENE
2202. 2-CYCLOHEXENE-1,4-DIONE
2203. 1,3,5-CYCLOOCTATRIENE
2204. CONVERSION OF AMINES TO PHOSPHO ESTERS: DECYL DIETHYL PHOSPHATE
2205. DETRIFLUOROACETYLATIVE DIAZO GROUP TRANSFER: (E)-1-DIAZO-4-PHENYL-3-BUTEN-2-ONE
2206. 4,5-DIBENZOYL-1,3-DITHIOLE-1-THIONE
2207. 2,3-DIBROMO-1-(PHENYLSULFONYL)-1-PROPENE AS A VERSATILE REAGENT FOR THE SYNTHESIS OF FURANS AND CYCLOPENTENONES: 2-METHYL-4-[(PHENYL-SULFONYL) METHYL]FURAN AND 2-METHYL-3-[(PHENYLSULFONYL) METHYL]-2-CYCLOPENTEN-1-ONE
2208. (+)-(2R,8AR)-[(8,8-DIMETHOXYCAMPHORYL)SULFONYL] OXAZIRIDINE AND (+)-(2R,8AR)-[(8,8-DICHLOROCAMPHORYL) SULFONYL]OXAZIRIDINE
2209. DIETHYL (2S,3R)-2-(N-TERT-BUTOXYCARBONYL)AMINO- 3-HYDROXYSUCCINATE
2210. DIETHYL (DICHLOROMETHYL)PHOSPHONATE. PREPARATION AND USE IN THE SYNTHESIS OF ALKYNES: (4-METHOXYPHENYL)

ETHYNE
2211. GENERATION OF N,N-DIETHYLCARBAMOYLLITHIUM VIA LITHIUM-TELLURIUM EXCHANGE AND ITS REACTION WITH 3-PHENYLPROPANAL: N,N-DIETHYL-2-HYDROXY-4-PHENYLBUTANAMIDE
2212. DIETHYL 1-PROPYL-2-OXOETHYLPHOSPHONATE
2213. 3,4-DIETHYLPYRROLE AND 2,3,7,8,12,13,17,18-OCTAETHYLPORPHYRIN
2214. (3,3-DIFLUOROALLYL)TRIMETHYLSILANE
2215. 3-[(1S)-1,2-DIHYDROXYETHYL]-1,5-DIHYDRO-3H-2,4-BENZODIOXEPINE
2216. 2,2'-DIMETHOXY-6-FORMYLBIPHENYL
2217. 5,7-DIMETHOXY-3-METHYLINDAZOLE FROM 3,5-DIMETHOXYACETOPHENONE
2218. TETRAHYDRO-3-BENZAZEPIN-2-ONES BY LEAD TETRAACETATE OXIDATION OF ISOQUINOLINE ENAMIDES: 7,8-DIMETHOXY-1,3,4,5-TETRAHYDRO-2H-3-BENZAZEPIN-2-ONE
2219. PREPARATION OF BICYCLO[3.2.0]HEPT-3-EN-6-ONES: 1,4-DIMETHYLBICYCLO[3.2.0]HEPT-3-EN-6-ONE
2220. MESITYLENESULFONYLHYDRAZINE, AND (1α,2α,6β)-2,6-DIMETHYLCYCLOHEXANECARBONITRILE AND (1α,2β,6α)-2,6-DIMETHYLCYCLOHEXANECARBONITRILE AS A RACEMIC MIXTURE
2221. SYNTHESIS OF EPOXIDES USING DIMETHYLDIOXIRANE: TRANS-STILBENE OXIDE
2222. SYNTHESIS OF β-LACTONES AND ALKENES VIA THIOL ESTERS: (E)-2,3-DIMETHYL-3-DODECENE
2223. 1,1,-DIMETHYLETHYL (S)- OR (R)-4-FORMYL-2,2-DIMETHYL-3-OXAZOLIDINECARBOXYLATE: A USEFUL SERINAL DERIVATIVE
2224. 1,3-DIOLS FROM LITHIUM β-LITHIOALKOXIDES GENERATED BY THE REDUCTIVE LITHIATION OF EPOXIDES: 2,5-DIMETHYL-2,4-HEXANEDIOL
2225. DIASTEREOSELECTIVE FORMATION OF TRANS-1,2-DISUBSTITUTED CYCLOHEXANES FROM ALKYLIDENEMALONATES BY AN INTRAMOLECULAR ENE REACTION: DIMETHYL (1'R,2'R,5'R)-2-(2'-ISOPROPENYL-5'-METHYLCYCLOHEX-1'-YL)-PROPANE-1,3-DIOATE
2226. DIALKYL MESOXALATES BY OZONOLYSIS OF DIALKYL

BENZALMALONATES: DIMETHYL MESOXALATE
2227. REGIO- AND STEREOSELECTIVE CARBOXYLATION OF ALLYLIC BARIUM REAGENTS: (E)-4,8-DIMETHYL-3,7-NONADIENOIC ACID
2228. (1R,5S)-(−)-6,6-DIMETHYL-3-OXABICYCLO[3.1.0]HEXAN-2-ONE. HIGHLY ENANTIOSELECTIVE INTRAMOLECULAR CYCLOPROPANATION CATALYZED BY DIRHODIUM(II) TETRAKIS [METHYL 2-PYRROLIDONE-5(R)-CARBOXYLATE]
2229. MANGANESE-COPPER-CATALYZED CONJUGATE ADDITION OF ORGANOMAGNESIUM REAGENTS TO α,β-ETHYLENIC KETONES: 2-(1,1-DIMETHYLPENTYL)-5-METHYL-CYCLOHEXANONE FROM PULEGONE
2230. PREPARATION AND DIELS-ALDER REACTION OF A REACTIVE, ELECTRON-DEFICIENT HETEROCYCLIC AZADIENE: DIMETHYL 1,2,4,5-TETRAZINE-3,6-DICARBOXYLATE. 1,2-DIAZINE (DIMETHYL 4-PHENYL-1,2-DIAZINE-3,6-DICARBOXYLATE) AND PYRROLE (DIMETHYL 3-PHENYLPYRROLE-2,5-DICARBOXYLATE) INTRODUCTION
2231. (S)-N-(9-PHENYLFLUOREN-9-YL)ALANINE AND (S)-DIMETHYL N-(9-PHENYLFLUOREN-9-YL)ASPARTATE
2232. SPIROANNELATION VIA ORGANOBIS(CUPRATES): 9,9-DIMETHYLSPIRO[4.5]DECAN-7-ONE
2233. REARRANGEMENT OF TRANS-STILBENE OXIDE TO DIPHENYLACETALDEHYDE WITH CATALYTIC METHYLALUMINUM BIS(4-BROMO-2,6-DI-TERT-BUTYLPHENOXIDE)
2234. (R)-(−)-2,2-DIPHENYLCYCLOPENTANOL
2235. CYCLOPROPANATION USING AN IRON-CONTAINING METHYLENE TRANSFER REAGENT: 1,1-DIPHENYLCYCLOPROPANE
2236. (R,R)-1,2-DIPHENYL-1,2-ETHANEDIOL (STILBENE DIOL)
2237. (1R,2R)-(+)- AND (1S,2S)-(−)- 1,2-DIPHENYL-1,2-ETHYLENEDIAMINE
2238. (R)-(+)-2-(DIPHENYLHYDROXYMETHYL)PYRROLIDINE
2239. INVERSE ELECTRON-DEMAND DIELS-ALDER CYCLOADDITION OF A KETENE DITHIOACETAL. COPPER HYDRIDE-PROMOTED REDUCTION OF A CONJUGATED ENONE. 9-DITHIOLANOBICYCLO [3.2.2]NON-6-EN-2-ONE FROM TROPONE
2240. 4-DODECYLBENZENESULFONYL AZIDES

2241. ALKYLIDENATION OF ESTER CARBONYL GROUPS: (Z)-1-ETHOXY-1-PHENYL-1-HEXENE
2242. CONVERSION OF METHYL KETONES INTO TERMINAL ACETYLENES: ETHYNYLFERROCENE
2243. STEREOSPECIFIC SYNTHESIS OF ETHYL (Z)-3-BROMO-2-PROPENOATE
2244. REGIOSELECTIVE SYNTHESIS OF 3-SUBSTITUTED INDOLES: 3-ETHYLINDOLE
2245. SYNTHESIS OF FURANS VIA RHODIUM(II) ACETATE-CATALYZED REACTION OF ACETYLENES WITH α-DIAZOCARBONYLS: ETHYL 2-METHYL-5-PHENYL-3-FURANCARBOXYLATE
2246. ETHYL 1-NAPHTHYLACETATE: ESTER HOMOLOGATION VIA YNOLATE ANIONS
2247. ETHYL 3-OXO-4-PENTENOATE (NAZAROV'S REAGENT)
2248. α-ACETYLENIC ESTERS FROM α-ACYLMETHYLENEPHOSPHORANES: ETHYL 4,4,4-TRIFLUOROTETROLATE
2249. STEREOSELECTIVE SYNTHESIS OF 2,2-DISUBSTITUTED 1-FLUORO-ALKENES: (E)-[[FLUORO(2-PHENYLCYCLOHEXYLIDENE)-METHYL]SULFONYL]BENZENE AND (Z)-[2-(FLUOROMETHYLENE)-CYCLOHEXYL]BENZENE
2250. REACTION OF SULFOXIDES WITH DIETHYLAMINOSULFUR TRIFLUORIDE: FLUOROMETHYL PHENYL SULFONE, A REAGENT FOR THE SYNTHESIS OF FLUOROALKENES
2251. D-(R)-GLYCERALDEHYDE ACETONIDE
2252. L-(S)-GLYCERALDEHYDE ACETONIDE
2253. S-(−)-5-HEPTYL-2-PYRROLIDINONE. CHIRAL BICYCLIC LACTAMS AS TEMPLATES FOR PYRROLIDINES AND PYRROLIDINONES
2254. A SELECTIVE, HETEROGENEOUS OXIDATION USING A MIXTURE OF POTASSIUM PERMANGANATE AND CUPRIC SULFATE: (3AS,7AR)-HEXAHYDRO-(3S,6R)-DIMETHYL-2(3H)-BENZOFURANONE
2255. CYCLOPENTANONE ANNULATION VIA CYCLOPROPANONE DERIVATIVES: (3Aβ,9Bβ)-1,2,3A,4,5,9B-HEXAHYDRO-9B-HYDROXY-3A-METHYL-3H-BENZ[E]INDEN-3-ONE
2256. PREPARATION AND REACTIONS OF ALKENYLCHROMIUM REAGENTS: 2-HEXYL-5-PHENYL-1-PENTEN-3-OL
2257. ALKYNYL(PHENYL)IODONIUM TOSYLATES: PREPARATION AND

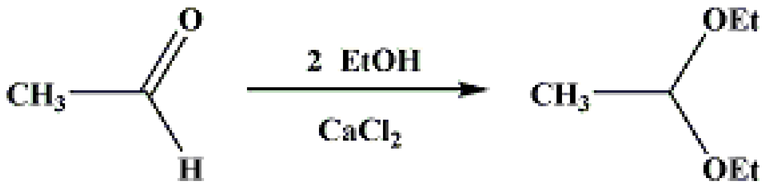
STEREOSPECIFIC COUPLING WITH VINYLCOPPER REAGENTS. FORMATION OF CONJUGATED ENYNES. 1-HEXYNYL(PHENYL) IODONIUM TOSYLATE AND (E)-5-PHENYLDODEC-5-EN-7-YNE
2258. DIRECT DEGRADATION OF THE BIOPOLYMER POLY[(R)-3-HYDROXYBUTYRIC ACID] TO (R)-3-HYDROXYBUTANOIC ACID AND ITS METHYL ESTER
2259. ENANTIOSELECTIVE HYDROLYSIS OF CIS-3,5-DIACETOXYCYCLOPENTENE: (1R,4S)-(+)-4-HYDROXY-2-CYCLOPENTENYL ACETATE
2260. PREPARATION AND USE OF (METHOXYMETHOXY) METHYLLITHIUM: 1-(HYDROXYMETHYL)CYCLOHEPTANOL
2261. STEREOSELECTIVE ALDOL REACTION OF DOUBLY DEPROTONATED (R)-(+)-2-HYDROXY-1,2,2-TRIPHENYLETHYL ACETATE (HYTRA): (R)-3-HYDROXY-4-METHYLPENTANOIC ACID
2262. 1,2-ADDITION OF A FUNCTIONALIZED ZINC-COPPER ORGANOMETALLIC [RCU(CN)ZNI] TO AN α,β-UNSATURATED ALDEHYDE: (E)-2-(4-HYDROXY-6-PHENYL-5-HEXENYL)-1H-ISOINDOLE-1,3(2H)-DIONE
2263. (R)-(+)-2-HYDROXY-1,2,2-TRIPHENYLETHYL ACETATE
2264. A SIMPLE AND CONVENIENT METHOD FOR THE PREPARATION OF (Z)-β-IODOACROLEIN AND OF (Z)- OR (E)-γ-IODO ALLYLIC ALCOHOLS: (Z)- AND (E)-1-IODOHEPT-1-EN-3-OL
2265. IODOLACTAMIZATION: 8-EXO-IODO-2-AZABICYCLO[3.3.0]OCTAN-3-ONE
2266. A SIMPLE AND CONVENIENT METHOD FOR THE OXIDATION OF ORGANOBORANES USING SODIUM PERBORATE: (+)-ISOPINOCAMPHEOL
2267. TITANIUM-MEDIATED ADDITION OF SILYL DIENOL ETHERS TO ELECTROPHILIC GLYCINE: 4-KETOPIPECOLIC ACID HYDROCHLORIDE
2268. 4-KETOUNDECANOIC ACID
2269. ACETYLENIC ETHERS FROM ALCOHOLS AND THEIR REDUCTION TO Z- AND E-ENOL ETHERS: PREPARATION OF 1-MENTHOXY-1-BUTYNE FROM MENTHOL AND CONVERSION TO (Z)- AND (E)-1-MENTHOXY-1-BUTENE
2270. REGIO- AND STEREOSELECTIVE INTRAMOLECULAR HYDROSILYLATION OF α-HYDROXY ENOL ETHERS: 2,3-SYN-2-METHOXYMETHOXY-1,3-NONANEDIOL

2271. (E,Z)-1-METHOXY-2-METHYL-3-(TRIMETHYLSILOXY)-1,3-PENTADIENE
2272. 4-METHOXY-4'-NITROBIPHENYL
2273. 7-METHOXYPHTHALIDE
2274. DOUBLE HYDROXYLATION REACTION FOR CONSTRUCTION OF THE CORTICOID SIDE CHAIN: 16α-METHYLCORTEXOLONE
2275. 2-METHYL-1,3-CYCLOPENTANEDIONE
2276. METHOXYCARBONYLMETHYLATION OF ALDEHYDES VIA SILOXYCYCLOPROPANES: METHYL 3,3-DIMETHYL-4-OXOBUTANOATE
2277. STEREOSELECTIVE ALKENE SYNTHESIS VIA 1-CHLORO-1-[(DIMETHYL)PHENYLSILYL]ALKANES AND α-(DIMETHYL)PHENYLSILYL KETONES: 6-METHYL-6-DODECENE
2278. 2-METHYLENE-1,3-DITHIOLANE
2279. ASYMMETRIC HYDROGENATION OF 3-OXO CARBOXYLATES USING BINAP-RUTHENIUM COMPLEXES: (R)-(−)-METHYL 3-HYDROXYBUTANOATE
2280. ASYMMETRIC CATALYTIC GLYOXYLATE-ENE REACTION: METHYL (2R)-2-HYDROXY-4-PHENYL-4-PENTENOATE
2281. INDOLE-2-ACETIC ACID METHYL ESTERS: METHYL 5-METHOXYINDOLE-2-ACETATE
2282. A GENERAL PROCEDURE FOR MITSUNOBU INVERSION OF STERICALLY HINDERED ALCOHOLS: INVERSION OF MENTHOL. (1S,2S,5R)-5-METHYL-2-(1-METHYLETHYL)CYCLOHEXYL 4-NITROBENZOATE
2283. (R)-(−)-10-METHYL-1(9)-OCTAL-2-ONE
2284. SYNTHESIS OF β-KETO ESTERS BY C-ACYLATION OF PREFORMED ENOLATES WITH METHYL CYANOFORMATE: PREPARATION OF METHYL (1α,4Aβ,8Aα)-2-OXODECAHYDRO-1-NAPHTHOATE
2285. SYNTHESIS OF (S)-2-METHYLPROLINE: A GENERAL METHOD FOR THE PREPARATION OF α-BRANCHED AMINO ACIDS
2286. OXIDATION OF SECONDARY AMINES TO NITRONES: 6-METHYL-2,3,4,5-TETRAHYDROPYRIDINE N-OXIDE
2287. NITROACETALDEHYDE DIETHYL ACETAL
2288. CONJUGATE ADDITION OF A VINYLZIRCONIUM REAGENT: 3-(1-OCTEN-1-YL)CYCLOPENTANONE
2289. SPIROANNELATION OF ENOL SILANES: 2-OXO-5-METHOXYSPLRO

[5.4]DECANE
2290. NICKEL-CATALYZED, GEMINAL DIMETHYLATION OF ALLYLIC DITHIOACETALS: (E)-1-PHENYL-3,3-DIMETHYL-1-BUTENE
2291. 1-PHENYL-2,3,4,5-TETRAMETHYLPHOSPHOLE
2292. PHENYLTHIOACETYLENE
2293. PHENYL VINYL SULFIDE
2294. 3-PYRROLINE
2295. PREPARATION OF POLYQUINANES BY DOUBLE ADDITION OF VINYL ANIONS TO SQUARATE ESTERS: 4,5,6,6A-TETRAHYDRO-3A-HYDROXY-2,3-DIISOPROPOXY-4,6A-DIMETHYL-1(3AH)-PENTALENONE
2296. (S)-TETRAHYDRO-1-METHYL-3,3-DIPHENYL-1H,3H-PYRROLO-[1,2-C][1,3,2]OXAZABOROLE-BORANE COMPLEX
2297. SUBSTITUTION REACTIONS OF 2-BENZENESULFONYL CYCLIC ETHERS: TETRAHYDRO-2-(PHENYLETHYNYL)-2H-PYRAN
2298. 9-THIABICYCLO[3.3.1]NONANE-2,6-DIONE
2299. ASYMMETRIC SYNTHESIS OF TRANS-2-AMINOCYCLOHEXANECARBOXYLIC ACID DERIVATIVES FROM PYRROLOBENZODIAZEPINE-5,11-DIONES: (1S,2S)-2-(N-TOSYLAMINO)CYCLOHEXANECARBOXYLIC ACID
2300. A HYDROXYMETHYL ANION EQUIVALENT: TRIBUTYL [(METHOXYMETHOXY)METHYL]STANNANE
2301. TRIBUTYL(3-METHYL-2-BUTENYL)TIN
2302. 1-TRIFLUOROMETHYL-1-CYCLOHEXANOL
2303. (2S,4S)-2,4,5-TRIHYDROXYPENTANOIC ACID 4,5-ACETONIDE METHYL ESTER
2304. CHIRAL (ACYLOXY)BORANE COMPLEX-CATALYZED ASYMMETRIC DIELS-ALDER REACTION: (1R)-1,3,4-TRIMETHYL-3-CYCLOHEXENE-1-CARBOXALDEHYDE
2305. NICKEL-CATALYZED SILYLOLEFINATION OF ALLYLIC DITHIOACETALS: (E,E)-TRIMETHYL(4-PHENYL-1,3-BUTADIENYL) SILANE
2306. 1,2,3-TRIPHENYLCYCLOPROPENIUM BROMIDE
2307. A WATER-SOLUBLE TIN HYDRIDE: TRIS[3-(2-METHOXYETHOXY) PROPYL]STANNANE
2308. TRIS(TRIMETHYLSILYL)SILANE
2309. UBIQUINONE-1
2310. (1R,5R)-(+)-VERBENONE OF HIGH OPTICAL PURITY

Organic Syntheses, CV 1, 1

ACETAL



Submitted by Homer Adkins and B. H. Nissen.
Checked by H. T. Clarke and J. H. Bishop.

1. Procedure

In a 1-gallon (4-l.) bottle are placed 1050 g. (1305 cc., 21.7 moles) of 95 per cent ethyl alcohol and 200 g. (1.8 moles) of granulated anhydrous calcium chloride (Note 1). The mixture is cooled to 8° or below by immersion in ice water, and 500 g. (620 cc., 11.4 moles) of freshly distilled acetaldehyde (b. p. 20–22°) is slowly added down the sides of the bottle so that it forms a layer on the alcoholic calcium chloride. The bottle is then tightly closed with a cork stopper and shaken vigorously for a few minutes (Note 2). It is then allowed to stand at room temperature with intermittent shaking for one to two days. The mixture divides into two layers after one to two hours; after the first twenty-four hours no appreciable change in volume of the two layers takes place.

The upper layer, which weighs 1280–1285 g., is separated and washed three times with 330 cc. portions of water. The weight has now fallen to 990–995 g. The oil is dried by standing over 25 g. of anhydrous potassium carbonate and is then fractionally distilled with the use of an efficient column at least 90 cm. long (Note 3), and the fraction which boils at 101–103.5° collected as pure acetal. In this way 700–720 g. can be obtained by one or two fractionations. The yield can be further increased by washing the low-boiling fractions and residue with small quantities of water, drying, and again fractionally distilling, so that a total of 790–815 g. is obtained (61–64 per cent of the theoretical amount). (Note 4)

2. Notes

1. It is essential that the calcium chloride should be anhydrous; if it contains water of crystallization, stratification may be long delayed and the yield be much decreased. On the other hand, no great advantage is observed by substituting absolute alcohol for the 95 per cent material.
2. On mixing the acetaldehyde and the alcoholic calcium chloride solution, a considerable rise in temperature takes place; for this reason it is necessary to chill the reagents and to close the stopper before mixing intimately, otherwise losses might occur by volatilization.
3. A fractionating column containing a condensing unit at the head[1] has been found satisfactory.

4. It is suggested that acetaldehyde be distilled directly into the mixture of alcohol and calcium chloride. The aldehyde is generated by warming paraldehyde with a little sulfuric acid. The yield of acetal thus obtained is somewhat lower than that in the procedure described (V. H. Wallingford, private communication).

3. Discussion

Acetal can be prepared by the action of acetaldehyde upon alcohol in the presence of small quantities of mineral acid,[2] or Twitchell's reagent,[3] or certain metallic salts;[4] by the action of acetylene on alcohol in the presence of sulfuric acid and mercuric salts;[5] by the action of acetaldehyde on tetraethyl silicate with hydrogen chloride as a catalyst;[6] from paraldehyde and ethyl alcohol with hydrogen chloride or *p*-toluenesulfonic acid as catalyst;[7] and from metaldehyde and ethyl alcohol in the presence of calcium chloride and a trace of hydrogen chloride.[8] The procedure described is essentially that of Adkins and Nissen.[9]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Twitchell's reagent

mercuric salts

metaldehyde

ACETAL (105-57-7)

ethyl alcohol, alcohol (64-17-5)

calcium chloride (10043-52-4)

acetaldehyde (75-07-0)

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

acetylene (74-86-2)

tetraethyl silicate (78-10-4)

hydrogen chloride (7647-01-0)

p-toluenesulfonic acid (104-15-4)

paraldehyde (123-53-7)

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Organic Syntheses, CV 1, 3

ACETAMIDE

Submitted by G. H. Coleman and A. M. Alvarado.
Checked by H. T. Clarke and E. R. Taylor.

1. Procedure

In a 5-l. flask is placed 3 kg. (2860 cc., 50.0 moles) of glacial acetic acid and to this is added a weight of ammonium carbonate corresponding to 400 g. (23.5 moles) of ammonia (Note 1). The flask is fitted with a one-hole stopper holding an efficient fractionating column 90 cm. long with condenser and receiver. An air condenser 150–200 cm. long may be employed. The mixture in the flask is heated to gentle boiling and the flame so regulated that the rate of distillation does not exceed 180 cc. per hour. The distillation is continued in this way for eight to ten hours, until the temperature at the head of the column reaches 110°. The distillate, which is a mixture of water and acetic acid, amounts to 1400–1500 cc. The receiver is changed, the flame under the flask is gradually increased, and the distillation is continued at about the same rate until the temperature at the head of the column rises to 140°. The distillate, which amounts to 500–700 cc., is largely acetic acid and may be used in the next run.

The contents of the flask are transferred to a 2-l. flask for fractional distillation (p. 130), having a column 40–50 cm. long, and distilled under atmospheric pressure, using an air condenser. The fraction boiling below 210°, amounting to 250–300 cc., is collected separately. The material remaining in the flask is nearly pure acetamide and may all be distilled, 1150–1200 g. passing over at 210–216°. By redistilling the fraction boiling below 210°, the yield may be increased to 1200–1250 g. (87–90 per cent of the theoretical amount). The acetamide thus obtained is pure enough for most purposes, but if a purer product is desired it may be recrystallized from a mixture of benzene and ethyl acetate; 1 l. of benzene and 300 cc. of ethyl acetate are used for 1 kg. of acetamide (Note 2). Colorless needles melting at 81° are thus obtained (Note 3). The solvent and the acetamide it contains may be recovered by distillation.

2. Notes

1. Ammonium carbonate of commerce is often extremely impure, and care must be taken to obtain a representative sample for the determination of the ammonia content by titration with standard acid. The ammonium carbonate used in this preparation contained 27.2 per cent of ammonia, and 1470 g. was used in each

run.
2. Crystallization of acetamide, by solution in hot methyl alcohol (0.8 cc. per g.) and dilution with ether (8–10 cc. per g.), has been recommended as the best method of purification.[1]
3. As acetamide is somewhat hygroscopic, it cannot be exposed to the air unless precautions are taken to have the air dry.

3. Discussion

Acetamide can be prepared by the rapid distillation of ammonium acetate;[2] by heating ammonium acetate in a sealed tube and distilling the product;[3] by treating acetic anhydride with ammonia;[4] by heating a mixture of ammonium chloride and sodium acetate to 240°;[5] by the action of cold aqueous ammonia on ethyl acetate;[6] by boiling a mixture of glacial acetic acid and ammonium thiocyanate for four days;[7] by saturating glacial acetic acid with dry ammonia and then refluxing;[8] by distillation of ammonium acetate through a reflux condenser filled first with glacial acetic acid and then with aniline until the temperature of the mixture reaches 220°;[9] by passing a stream of ammonia through heated acetic acid;[10] and from formamide and hydrogen at 200–500°.[11]

The procedure described is based on the method of Noyes and Goebel,[12] in which equimolecular proportions of ammonium acetate and acetic acid are heated together, the acetic acid having been shown to accelerate both the dehydration of ammonium acetate and the hydrolysis of acetamide.

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Acetamide (60-35-5)

acetic acid (64-19-7)

ammonium carbonate

ammonia (7664-41-7)

Benzene (71-43-2)

ethyl acetate (141-78-6)

methyl alcohol (67-56-1)

ether (60-29-7)

ammonium acetate (631-61-8)

acetic anhydride (108-24-7)

ammonium chloride (12125-02-9)

sodium acetate (127-09-3)

ammonium thiocyanate (1762-95-4)

aniline (62-53-3)

formamide (75-12-7)

hydrogen (1333-74-0)

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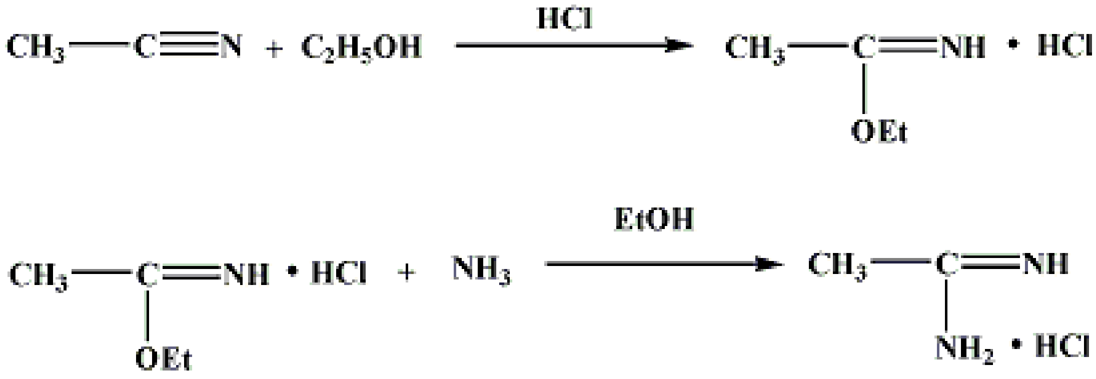
Organic Syntheses, CV 1, 5

ACETAMIDINE HYDROCHLORIDE



Submitted by A. W. Dox
Checked by Frank C. Whitmore

1. Procedure

Dry hydrogen chloride (p. 293) (Note 1) is passed into a solution of 100 g. (2.44 moles) of thoroughly dry acetonitrile (Note 2) in 113 g. (143 cc., 2.5 moles) of absolute ethyl alcohol (Note 1) contained in a 1-l. weighed suction flask (Note 3) surrounded by a freezing mixture of ice and salt, until an increase in weight of 95 g. (2.6 moles) is obtained. This requires about four hours (Note 4) but the time is diminished considerably if proper mechanical stirring is used. The flask is now tightly stoppered, the side arm being attached to a calcium chloride tube, and allowed to stand until the mixture has set to a solid mass of crystals. Usually this requires two or three days.

A solution of dry ammonia gas in absolute ethyl alcohol is prepared and titrated against standard hydrochloric acid, using methyl orange as the indicator. The solution should contain at least 9 per cent of ammonia by weight (Note 5).

The solid crystalline mass of acetimido ethyl ether hydrochloride is broken up and transferred to a dry mortar in which it is ground to a paste with 100 cc. of absolute alcohol and returned to the flask (Note 6). It is then stirred mechanically with an excess of the alcoholic ammonia solution (500 cc. of 9 per cent solution or an equivalent amount of a more concentrated solution). The crystals gradually dissolve and ammonium chloride separates. After stirring for three hours the ammonium chloride is filtered by suction and the filtrate evaporated on the steam bath to a volume of about 200 cc. when a considerable quantity of crystals separates. On cooling, the acetamidine hydrochloride separates in long colorless prisms. These are filtered by suction, washed with 10 cc. of cold alcohol, and dried in a desiccator over sulfuric acid. Concentration of the mother liquor gives a second crop. The product melts at 164–166° and is readily soluble in alcohol and in water. The yield varies from 185 to 210 g. (80–91 per cent of the theoretical amount). The product is somewhat

deliquescent and should be kept in a tightly stoppered bottle.

2. Notes

1. Moisture in the reagents affects the yield seriously because of the ease with which the intermediate imido ether is hydrolyzed. The hydrogen chloride must be thoroughly dried by passing it through two wash bottles containing sulfuric acid. If the wash bottles are not effective, a tube containing glass beads mixed with phosphorus pentoxide should be used after the wash bottles. It is well to protect the side arm of the flask by means of a calcium chloride tube. The absolute alcohol used should be at least 99.5 per cent (p. 249).

2. If commercial acetonitrile is used directly, the yields are poor. It should be dried over calcium chloride for at least a week, filtered, and distilled, the fraction boiling at 76–81° being used.

3. If a thinner flask is used, there is danger of its being cracked during the experiment.

4. If a proper safety bottle is placed between the drying train and the flask of acetonitrile, the treatment with hydrogen chloride does not require constant attention during this time.

5. When weaker solutions of ammonia were used, the yields were lower.

6. The grinding of the imido ether hydrochloride is very important, as lumps of this material become coated with ammonium chloride, which prevents the complete action of the ammonia.

7. By a similar procedure benzamidine hydrochloride can be prepared. Dry hydrogen chloride is passed into a cooled solution of 51.5 g. (51 cc., 0.5 mole) of benzonitrile in 25 g. of absolute ethyl alcohol until 21.3 g. of the gas is absorbed. The reaction mixture is allowed to stand for forty-eight hours, and the solid cake of imido ether hydrochloride is quickly crushed in a dry mortar. The solid is transferred to a liter flask, and an 8 per cent solution of dry ammonia in absolute ethyl alcohol containing 12 g. of ammonia is added slowly in small portions. The reaction mixture is shaken for twenty-four hours, then allowed to stand for forty-eight hours and filtered to remove the ammonium chloride which has precipitated. (During the shaking the solution may develop a faint pink color. This is probably due to the presence of traces of glyoxal in the alcohol for this material in basic solution furnishes colored condensation products with benzamidine.) The filtrate is allowed to evaporate to dryness in the open air, and the benzamidine hydrochloride thus obtained is dissolved in water. The solution is acidified with concentrated hydrochloric acid, decolorized with charcoal, filtered, and the filtrate is evaporated almost to dryness at room temperature. The crystals of benzamidine hydrochloride dihydrate are filtered and air-dried. The yield is 60–70 g. of material which melts at 70–73°. The filtrate on evaporation to dryness furnishes 15–30 g. of less pure product, melting at 74–82°, which contains a small amount of ammonium chloride but which can be used satisfactorily in most reactions. The total yield is 80–95 per cent. (A. R. Ronzio and J. B. Ekeley, private communication.)

3. Discussion

The only practical method of preparation is that of Pinner,[1] on which the procedure described is based.

References and Notes

1. Pinner, Ber. **16**, 1654 (1883), **17**, 178 (1884).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

acetimido ethyl ether hydrochloride

imido ether

imido ether hydrochloride

ethyl alcohol, alcohol (64-17-5)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrogen chloride, hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ammonium chloride (12125-02-9)

Acetamidine hydrochloride (124-42-5)

acetonitrile (75-05-8)

Benzamidine hydrochloride (1670-14-0)

benzonitrile (100-47-0)

glyoxal (107-22-2)

benzamidine (618-39-3)

benzamidine hydrochloride dihydrate

phosphorus pentoxide (1314-56-3)

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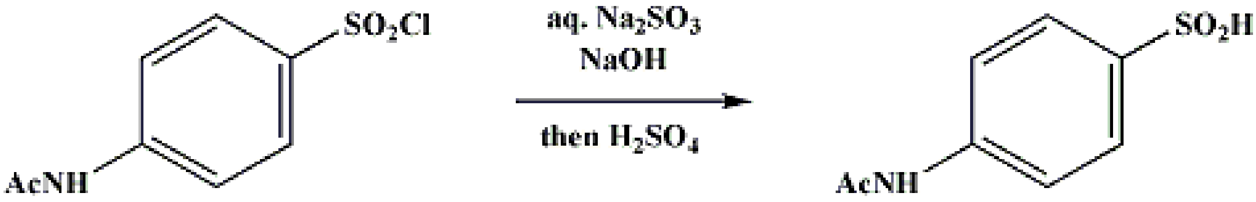
Organic Syntheses, *CV 1*, *7*

p-ACETAMINOBENZENESULFINIC ACID

[Benzenesulfinic acid, *p*-acetamido-]



Submitted by S. Smiles and C. M. Bere.
Checked by Henry Gilman and F. Schulze.

1. Procedure

The crude *p*-acetaminobenzenesulfonyl chloride (p. 8) obtained from 67.5 g. (0.5 mole) of acetanilide is shaken for two hours with a solution of 252 g. (1 mole) of crystallized sodium sulfite ($Na_2SO_3 \cdot 7H_2O$) in 500 cc. of water. The reaction mixture is kept slightly alkaline by the addition at intervals of small portions of 50 per cent sodium hydroxide solution. The total volume of alkali used varies from 10 to 50 cc. After the alkaline mixture has been shaken for the two-hour period (Note 1) it is filtered, and the filtrate is acidified with 60 per cent sulfuric acid. If the acid is added slowly, the sulfinic acid comes down in fine crystals which, after filtering and drying, melt at 155° with decomposition (Note 2). The yield is 50–55 g.. (43–47 per cent of the theoretical amount based on the acetanilide used).

The product may be purified by crystallization from 400 cc. of hot water, but this is unnecessary when the above procedure is followed carefully.

2. Notes

1. The solution does not clear up when reduction is complete on account of the formation of a gelatinous impurity. Two hours suffice for the completion of reduction.
2. The melting point given in the literature (180°) is incorrect, its publication being due to a typographical error. The observed melting point varies slightly with the rate of heating during the determination of the melting point.

3. Discussion

p-Acetaminobenzenesulfinic acid can be prepared by the reduction of *p*-acetaminobenzenesulfonyl chloride.[1]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 8
- Org. Syn. Coll. Vol. 6, 727

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfinic acid

sulfuric acid (7664-93-9)

Acetanilide (103-84-4)

sodium sulfite (7757-83-7)

sodium hydroxide (1310-73-2)

p-Acetaminobenzenesulfonyl chloride (121-60-8)

p-Acetaminobenzenesulfinic acid, Benzenesulfinic acid, p-acetamido- (710-24-7)

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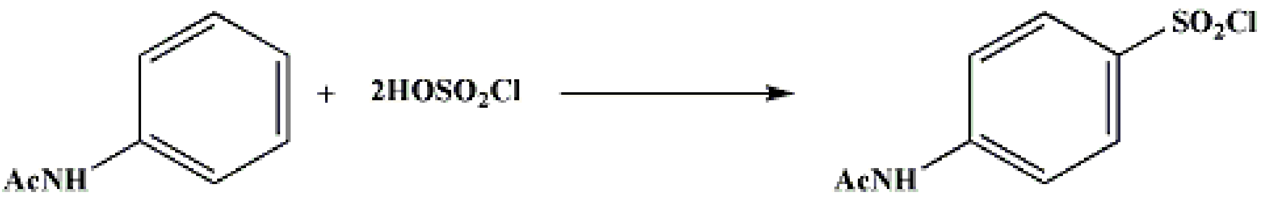
Organic Syntheses, CV 1, 8

p-ACETAMINOBENZENESULFONYL CHLORIDE

[Sulfanilyl chloride, N-acetyl-]



Submitted by S. Smiles and Jessie Stewart.
Checked by Henry Gilman and F. Schulze.

1. Procedure

In a 500-cc. round-bottomed flask, fitted with a mechanical stirrer, is placed 290 g. (165 cc., 2.49 moles) of chlorosulfonic acid (Note 1). The flask is surrounded by a cooling bath and cooled with running water to about 12–15°. To the chlorosulfonic acid is added gradually 67.5 g. (0.5 mole) of acetanilide. This requires about fifteen minutes if the temperature is maintained at approximately 15°. Since large volumes of hydrogen chloride are evolved, the reaction should be conducted in a good hood, or a gas absorption trap (Fig. 7 on p. 97) might be used. After all the acetanilide has been added, the mixture is heated to 60° for two hours to complete the reaction (Note 2).

The sirupy liquid is poured slowly, with stirring (Note 3), into 1 kg. of ice to which just enough water has been added to make stirring easy. This decomposition of the excess chlorosulfonic acid should be carried out in the hood. The solid sulfonyl chloride which separates is collected on a suction funnel (Note 4) and washed with water. The yield of crude material is 90–95 g. (77–81 per cent of the theoretical amount based on the acetanilide).

This crude material may be used directly in many preparations such as *p*-acetaminobenzenesulfinic acid (p. 7). If a pure product is desired, the crude material is dried by pressing on a porous plate and then crystallized from dry benzene. The acid chloride is slightly soluble in benzene, and only 1.5 to 2 g. will dissolve in 100 cc. of hot benzene. On cooling, about 75 per cent of the material separates from the benzene in thick, colorless prisms melting at 149° (Note 5).

2. Notes

1. The chlorosulfonic acid should be freshly distilled. Smaller amounts of this reagent may be used without reducing the yield or affecting the quality of the product. However, with smaller amounts the time required for the reaction must be increased. Thus, if 175 g. (1.5 moles) of chlorosulfonic acid is used with 67.5 g. (0.5 mole) of acetanilide, an additional hour of heating is required to obtain the

yields mentioned above.
2. The hydrogen chloride which is liberated during the reaction fills the mixture with tiny bubbles. When these disappear the reaction is complete.
3. Mechanical stirring is most convenient but not necessary.
4. A rather large suction funnel (125 mm. or more) should be used in the filtration as the sulfonyl chloride has a tendency to clog the filter.
5. The purification is the least satisfactory part of the preparation. The material must not be heated while water is still present, or excessive decomposition will occur. As the sulfonyl chloride is only slightly soluble in hot benzene, it is inconvenient to crystallize more than a small amount at a time. The crude product does not keep well and must be used at once. After recrystallization it may be kept indefinitely.

3. Discussion

p-Acetaminobenzenesulfonyl chloride can be prepared by the action of phosphorus pentachloride[1] or chlorosulfonic acid[2] on sodium *p*-acetaminobenzenesulfonate and by the action of chlorosulfonic acid on acetanilide.[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 7

References and Notes

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2. Goldyrev and Postovskii, J. Applied Chem. (U.S.S.R.) **11**, 316 (1938) [C. A. **32**, 5800 (1938)].
3. Stewart, J. Chem. Soc. **121**, 2558 (1922).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfonyl chloride

acid chloride

hydrogen chloride (7647-01-0)

Benzene (71-43-2)

Acetanilide (103-84-4)

Sulfanilyl chloride, N-acetyl-, p-Acetaminobenzenesulfonyl chloride (121-60-8)

chlorosulfonic acid (7790-94-5)

phosphorus pentachloride (10026-13-8)

p-Acetaminobenzenesulfinic acid (710-24-7)

sodium p-acetaminobenzenesulfonate

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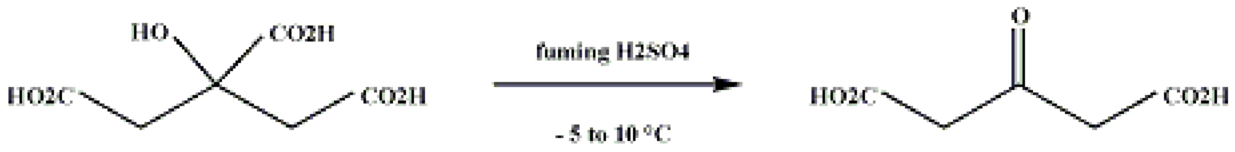
Organic Syntheses, CV 1, 10

ACETONEDICARBOXYLIC ACID

[Glutaric acid, β-oxo]



Submitted by Roger Adams, H. M. Chiles, and C. F. Rassweiler.
Checked by H. T. Clarke and T. F. Murray.

1. Procedure

In a 5-l. round-bottomed flask (Note 1), fitted with a mechanical stirrer, is placed 3 kg. (1555 cc.) of fuming sulfuric acid (20 per cent of free sulfur trioxide). Then the flask is cooled very efficiently with a thick pack of ice and salt, until the temperature of the acid reaches –5° (Note 2). The stirring is started, and 700 g. (3.64 moles) of finely powdered u. s. p. citric acid is added gradually. The speed of the addition is regulated according to the temperature of the reaction mixture. The temperature should not rise above 0° until half of the citric acid has been added, after which the temperature should not be allowed to exceed 10° until the reaction is complete. The addition requires three to four hours, provided efficient cooling is used. The citric acid should be in solution at the end of this time; if not, the stirring should be continued until it has dissolved completely.

The temperature of the reaction mixture is allowed to rise gradually until a vigorous evolution of gas commences; at this point the flask is cooled with ice water to stop the excessive frothing, but cooling is not carried far enough to stop the evolution of gas entirely (Note 3). After the more vigorous foaming has ceased, the reaction mixture is raised to about 30° and kept there until no more foaming occurs. A convenient way of determining this point is to stop the stirring for a moment and allow the mixture to remain quiet. After a minute or so, a clear brown liquid giving off very few gas bubbles should result. This general procedure requires two to three hours.

The reaction mixture is cooled down again with ice and salt until the temperature reaches 0°, then 2400 g. of finely cracked ice is added in small portions at such a rate that the temperature does not rise above 10° until one-third of the ice has been added. Then the temperature may be allowed to rise to 25–30°. The addition of the ice requires about two hours; after this, the mixture is cooled again to 0° (Note 4) and then filtered as rapidly as possible through a funnel fitted with a filtros plate (Note 5). The crystals are thoroughly pressed and sucked as dry as possible. The acetonedicarboxylic acid is light gray to white in color. After the suction and pressing have removed practically all of the sulfuric acid, the crystals are transferred to a beaker and stirred with sufficient ethyl acetate (about 200–250 cc.) to make a thick paste. The crystals

are filtered with suction. If acetonedicarboxylic acid entirely free from sulfuric acid is desired, the washing with ethyl acetate should be repeated. The yield of practically dry acetonedicarboxylic acid varies from 450–475 g. (85–90 per cent of the theoretical amount) (Note 6). This may be used directly for the preparation of the ester (p. 237). The acid itself is not stable and after a few hours gradually decomposes (Note 7).

2. Notes

1. The reaction must be carried out in a good hood, since a large amount of carbon monoxide is liberated.

2. The use of a very efficient ice and salt mixture around the reaction flask is necessary if the reaction is to be carried out within the time indicated. It is very necessary to regulate the temperature as directed, since a considerably lower yield is obtained if the temperature rises.

3. Some cooling is necessary, or the rapid evolution of gas will cause the reaction mixture to foam over with consequent loss of material.

4. Vigorous cooling before final filtration of the acetonedicarboxylic acid is essential to good yields, since the acid is fairly soluble in the reaction mixture.

5. The filtros plate for filtration can be very conveniently sealed into the Büchner funnel with a paste of water-glass and amorphous silica which is then hardened with concentrated sulfuric acid.

6. If the acid is to be esterified at once, careful drying from ethyl acetate is not necessary.

7. However, it has been observed that if the acid is purified by recrystallization from ethyl acetate and thoroughly dried it undergoes no decomposition, at least over a seven-month period, when kept at room temperature in a desiccator.[1]

3. Discussion

Acetonedicarboxylic acid can be prepared from citric acid by the action of concentrated[2] or fuming sulfuric acid.[3] The procedure described is a slight modification of that by Willstätter and Pfannenstiehl.[3] While it is more complex than the details given by Ingold and Nickolls,[3] it gives somewhat higher yields. The method of Ingold and Nickolls has been checked and found to have the advantage of requiring much less time.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 237
- Org. Syn. Coll. Vol. 1, 408
- Org. Syn. Coll. Vol. 1, 485
- Org. Syn. Coll. Vol. 4, 816

References and Notes

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2. Pechmann, Ber. **17**, 2543 (1884).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

ethyl acetate (141-78-6)

Acetonedicarboxylic acid

Glutaric acid, β-oxo (542-05-2)

sulfur trioxide (7446-11-9)

citric acid (77-92-9)

carbon monoxide (630-08-0)

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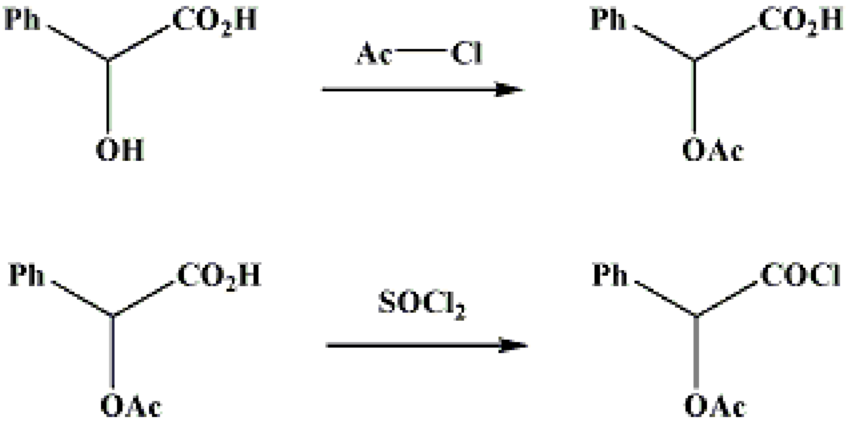
Organic Syntheses, CV 1, 12

ACETYLMANDELIC ACID and ACETYLMANDELYL CHLORIDE

[(Mandelic acid, acetate) (Mandelyl chloride, acetate)]



Submitted by F. K. Thayer
Checked by Roger Adams and E. E. Dreger.

1. Procedure

(*A*) In a 500-cc. Claisen distilling flask with a low side tube connected to a condenser, are placed 105 g. (0.69 mole) of mandelic acid (p. 336) (m.p. 118°) and 151 g. (137 cc., 1.92 moles) of acetyl chloride. A reaction sets in without the application of heat (Note 1). As soon as a clear solution results, the flask is warmed on a water bath and the excess acetyl chloride is distilled. The last trace of acetyl chloride may be removed by prolonged drying in a vacuum. The acetylmandelic acid then crystallizes in large, round, white clusters after one or two days' standing. The yield is 130–133 g. (97–99 per cent of the theoretical amount) (Note 2).

(*B*) To the crude acetylmandelic acid still containing some acetyl chloride obtained as described above, is added 250 g. (149 cc., 2.1 moles) of thionyl chloride. The reaction starts at once without warming but it is necessary to reflux for four hours to complete the reaction (Note 3). The excess thionyl chloride is then distilled and the residue distilled under reduced pressure (Note 4). The yield is 115–120 g. (79–82 per cent of the theoretical amount) of almost colorless liquid boiling at 125–130°/10 mm. (150–155°/33 mm.).

2. Notes

1. Occasionally the application of a little heat is necessary to bring about a more rapid acetylation.
2. The melting points given in the literature range from 39 to 80°. The acetylmandelic acid is difficult to crystallize but may be purified from benzene

or chloroform, preferably the former. The product thus obtained melts at about 79–80°.

3. Prolonged refluxing of the acetylmandelic acid with the thionyl chloride tends to lower the yield.

4. The boiling point of acetylmandelyl chloride has been reported[1] as 129°/10 mm. The pressure should be reduced as low as possible, to avoid the formation of tar during the distillation.

3. Discussion

Acetylmandelic acid can be prepared by the action of acetyl chloride[1] or acetic anhydride[2] on mandelic acid.

Acetylmandelyl chloride can be prepared by the action of phosphorus pentachloride[1] or thionyl chloride[3] on acetylmandelic acid.

References and Notes

1. Anschütz and Böcker, Ann. **368**, 57, 59 (1909).
2. Kaufler and Herzog, Ber. **42**, 3872 (1909).
3. v. Braun and Müller, Ber. **51**, 244 (1918).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Benzene (71-43-2)

acetic anhydride (108-24-7)

phosphorus pentachloride (10026-13-8)

Acetylmandelic acid

Acetylmandelyl chloride (1638-63-7)

Mandelic acid, acetate (5438-68-6)

Mandelyl chloride, acetate

Mandelic acid (90-64-2)

acetyl chloride (75-36-5)

thionyl chloride (7719-09-7)

chloroform (67-66-3)

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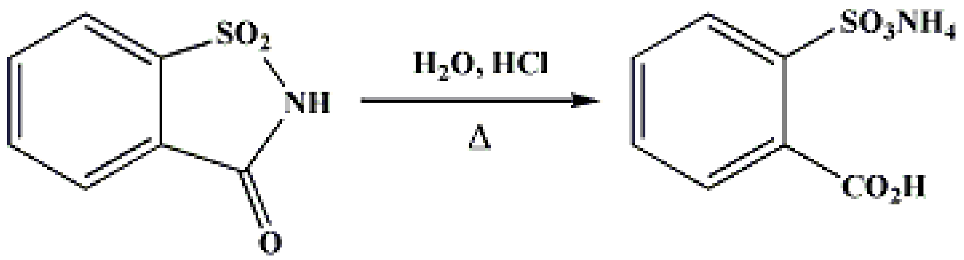
Organic Syntheses, CV 1, 14

ACID AMMONIUM *o*-SULFOBENZOATE

[Benzoic acid, *o*-sulfo-, ammonium H salt]



Submitted by H. T. Clarke and E. E. Dreger.
Checked by Henry Gilman and J. E. Kirby.

1. Procedure

In a 12-l. flask fitted with a stirrer and reflux condenser are placed 188 g. (1 mole) of *o*-sulfobenzoic imide ("saccharin insoluble"), 565 cc. of distilled water and 188 g. (158 cc.) of concentrated hydrochloric acid (sp. gr. 1.19). The mixture is boiled over a free flame with continual stirring (Note 1) until all the solid is in solution; this requires two and one-half to three hours. A second quantity of 188 g. of *o*-sulfobenzoic imide is then added, and the mixture again heated with stirring until a clear solution results, which requires one and one-half to two hours. Heating is then continued for one hour longer, whereupon the solution is poured into a crock and allowed to cool.

The crystals which separate are collected on a suction funnel, washed as free from hydrochloric acid as possible (Note 2) with ice-cold distilled water, and dried. The mother liquor and washings are concentrated on a steam bath under reduced pressure until the separation of crystals causes bumping, when the solution is again allowed to crystallize. This procedure is repeated, the final mother liquor being evaporated nearly to dryness. The main product, together with that from the mother liquors, weighs 410–427 g. (91–95 per cent of the theoretical amount) and is sufficiently pure for conversion into *o*-sulfobenzoic anhydride (p. 495). In order to obtain a purer product the material may be recrystallized from an equal weight of distilled water; the yield on recrystallizing is about 90 per cent.

2. Notes

1. The mixture tends to foam somewhat during the first few minutes of boiling.
2. If much hydrochloric acid is allowed to remain with the crystals, drying is extremely difficult.

3. Discussion

Acid ammonium *o*-sulfobenzoate can be prepared by the hydrolysis of saccharin with

concentrated hydrochloric acid.[1] The procedure described is a modification of that of White and Acree.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 495

References and Notes

1. Fahlberg and Barge, Ber. **22**, 755 (1889); Remsen and Linn, Am. Chem. J. **11**, 74 (1889).
2. White and Acree, J. Am. Chem. Soc. **41**, 1197 (1919).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ACID AMMONIUM o-SULFOBENZOATE

hydrochloric acid (7647-01-0)

saccharin (81-07-2)

o-Sulfobenzoic anhydride (81-08-3)

Benzoic acid, o-sulfo-, ammonium

o-sulfobenzoic imide

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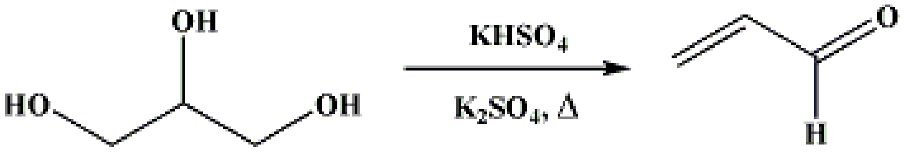
Organic Syntheses, CV 1, 15

ACROLEIN

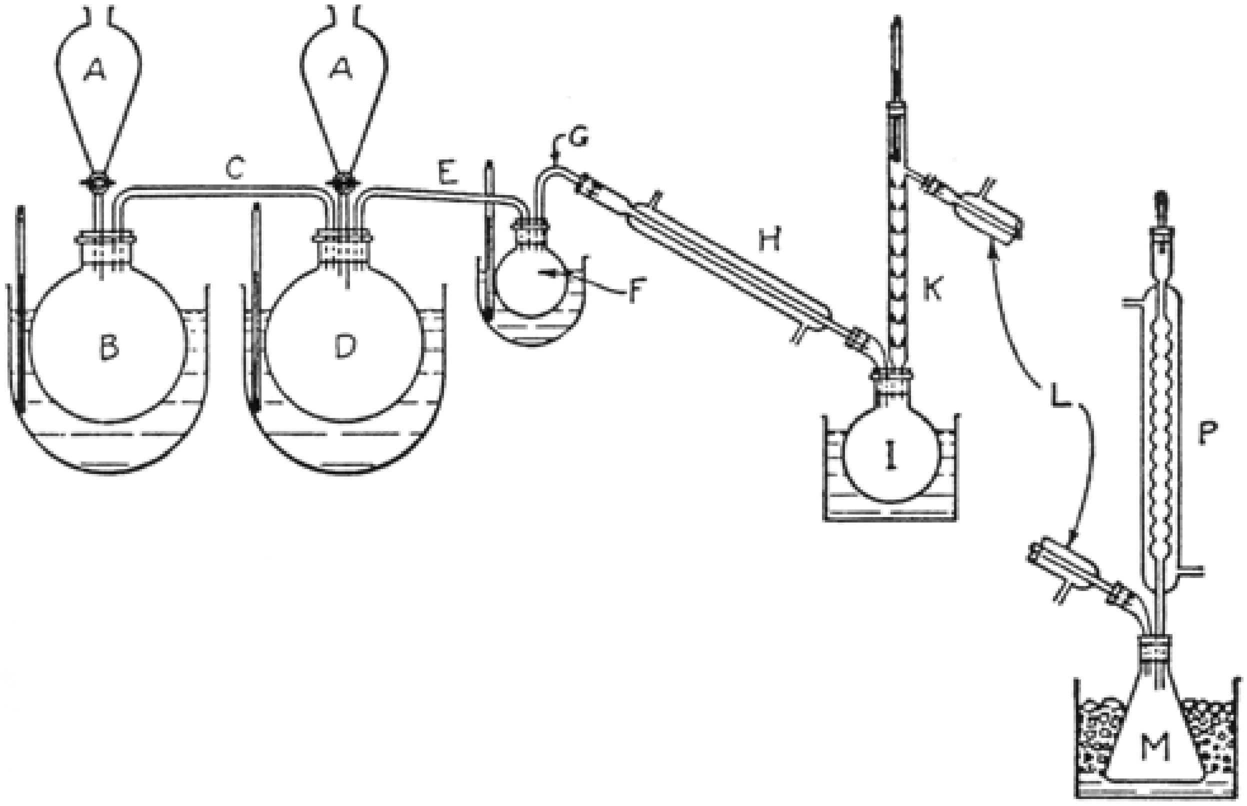


Submitted by Homer Adkins and W. H. Hartung.
Checked by Frank C. Whitmore and M. L. Wolfrom.

1. Procedure

The apparatus is assembled according to Fig. 1. B and D are 5-l. round-bottomed flasks, immersed to about two-thirds of their height in deep oil baths heated by large burners. Each bath is provided with a thermometer reaching to the level of the bottom of the flask. Flask B is fitted with a specially treated two-holed cork stopper (Note 1), in one hole of which is fitted a 500-cc. separatory funnel A and in the other a delivery tube C of 12-mm. diameter. The tubes must not extend more than 3 mm. below the stopper. Flask D is fitted with a three-holed cork stopper connected with a separatory funnel, the delivery tube from B, and the delivery tube E of 12-mm. tubing leading to flask F. F is a 500-cc. round-bottomed flask immersed to two-thirds of its height in an oil bath heated by a Bunsen burner and provided with a thermometer.

Fig. 1.



Flask F is provided with a two-holed cork stopper connected with tube E, and with tube G which connects with the first condenser H and may be of smaller bore than tubes C and E. H

is a condenser with a 30-cm. water jacket. H is connected with I by means of an adapter. I is a 1-l. round-bottomed flask supported in a pan which is at first filled with ice and later used as a water bath. Flask I is fitted with a two-holed cork stopper carrying the adapter connected with condenser H and a Vigreux column K of 2-cm. diameter and a length of 30 cm. to the side arm. Flask I and condenser H are covered with black cloth (Note 2). The side arm of K is connected with a 90-cm. water-jacketed condenser L which leads into M through an adapter. M is a 750-cc. Erlenmeyer flask immersed in an ice bath. Flask M is provided with a two-holed stopper connected with the adapter from L and an upright bulb condenser that is provided with a tube leading through a window or to a hood.

Before the final assembling of the apparatus, the flasks are charged as follows: One kilo of freshly fused and finely powdered acid potassium sulfate, 200 g. of powdered potassium sulfate, and 300 g. (238 cc.) of dry glycerol (Note 3) are thoroughly mixed in each of flasks B and D. In each of flasks I and M is placed about 1 g. of hydroquinone to act as a stabilizer for the acrolein.[1]

The apparatus is assembled as indicated and the oil baths under B and D are heated to about 190–200° (Note 4), and the oil bath under F to about 110–120°. The bath under I is filled with ice. The volatile products are collected in I which is kept carefully protected from light. When the reaction is well started 300 g. of dry glycerol is placed in each separatory funnel, and added drop by drop during the heating. After the first violent reaction has abated (about one hour) the baths under B and D are raised to 215–230° and maintained there until no more volatile product comes over (a total time of heating of about four and one-half hours). After B and D have been heated about four hours the ice under I is replaced by water which is heated to 75–80° to distil the acrolein into flask M, which is packed in ice. Near the end of the distillation the water under I is heated to boiling.

The product in M is treated with small amounts of solid sodium bicarbonate to neutralize any acid present. The cold liquid is filtered through a small filter into a 1500-cc. distilling flask containing about 1 g. of hydroquinone. It is then distilled into a tared dark bottle containing about 1 g. of hydroquinone. The yield of product boiling at 52.5–55.5° (Note 5) obtained from 1200 g. (13 moles) of dry glycerol is 240–350 g. (33–48 per cent of the theoretical amount).

2. Notes

1. The corks used in the apparatus are made tight and heat-resistant by treatment with sodium silicate solution. After being properly fitted and bored they are placed in the silicate solution contained in a bottle that is connected with a suction pump. The solution is forced into the pores of the corks by alternately making and breaking the reduced pressure and shaking the solution vigorously. After the excess of solution has been wiped off, the corks are put in place while still wet. After this the outside of each cork is given an extra coat of the silicate solution. When corks treated in this way were used no odor of acrolein was noted in the laboratory.
Acrolein has pronounced lachrymatory properties and is also highly toxic.
2. The exclusion of light slows up the polymerization of the acrolein. If the condensers are not protected from light a solid polymer collects in them.
3. The glycerol is dried by heating slowly in an open dish in a hood until the temperature of the liquid is 170°. A sand bath is used and the heating requires about

three hours. "Dynamite glycerine," 96–98 per cent, may be used instead of the dried glycerol.

4. The heating must not be too rapid nor too high at first as there is danger of frothing followed by a clogging of the apparatus.

5. Pure acrolein boils at 52.5°/760 mm.[2]

3. Discussion

Acrolein can be prepared by heating glycerol with magnesium or alkali sulfates under various conditions,[3] by heating glycerol with a "bleaching earth" catalyst,[4] from glycerol with iron and lithium phosphates as catalysts,[5] from epichlorohydrin by heating with water and an inorganic acid,[6] and from propylene with aqueous sulfuric acid and mercuric sulfate.[7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 166
- Org. Syn. Coll. Vol. 1, 506
- Org. Syn. Coll. Vol. 2, 137
- Org. Syn. Coll. Vol. 3, 502

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3. Wohl and Mylo, Ber. **45**, 2046 (1912); Witzemann, J. Am. Chem. Soc. **36**, 1766 (1914); Moureu and Lepape, Compt. rend. **169**, 885 (1919); Ann. chim. (9) **15**, 176 (1921); Evans and Haas, J. Am. Chem. Soc. **48**, 2703 (1926).
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6. Shell Development Company, U. S. pat. 2,106,347 [C. A. **32**, 2542 (1938)].
7. E. I. du Pont de Nemours and Co., U. S. pat. 2,197,258 [C. A. **34**, 5468 (1940)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

acid potassium sulfate

Dynamite glycerine

alkali sulfates

lithium phosphates

sulfuric acid (7664-93-9)

Acrolein (107-02-8)

potassium sulfate (37222-66-5)

glycerol (56-81-5)

hydroquinone (123-31-9)

sodium bicarbonate (144-55-8)

sodium silicate

silicate (15593-90-5)

magnesium (7439-95-4)

iron (7439-89-6)

Epichlorohydrin (106-89-8)

propylene (115-07-1)

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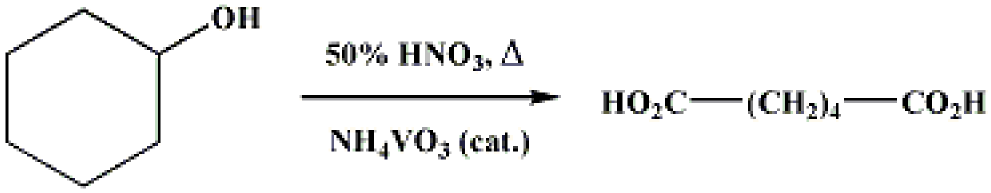
Organic Syntheses, CV 1, 18

ADIPIC ACID



Submitted by B. A. Ellis
Checked by Roger Adams and C. D. Thompson.

1. Procedure

In a 5-l. round-bottomed flask fitted with a mechanical stirrer, a thermometer, and a 1-l. separatory funnel, is placed 2100 g. (16.6 moles) of 50 per cent nitric acid (sp. gr. 1.32) (Hood). The acid is heated nearly to boiling, and 1 g. of ammonium vanadate (Note 1) is added. The stirrer is started, and 500 g. (5 moles) of cyclohexanol (Note 2) is introduced slowly through the separatory funnel. At first 40–50 drops of cyclohexanol are admitted and the reaction mixture is stirred until the reaction has started (four to five minutes) as is indicated by the evolution of oxides of nitrogen (Note 3). Then the reaction flask is placed in an ice-water bath and cooled until the temperature of the oxidizing mixture is 55–60°. The cyclohexanol is then added as rapidly as possible while the temperature of the mixture is kept within these limits. Toward the end of the oxidation (after about 475 g. of cyclohexanol has been added) the ice bath must be removed and sometimes heat must be applied in order to maintain the temperature and avoid crystallization of adipic acid.

Stirring is continued for about one hour after the addition of the last of the cyclohexanol. Then the mixture is cooled to about 0° and the adipic acid is collected on a suction filter, washed with 500 cc. of ice water, and dried in the air overnight. The yield is 395–410 g. of white crystals which melt at 146–149°. Evaporation of the nitric acid mother liquors yields an additional 30–40 g. of product which melts at 141–144° (Note 4). The total yield of crude adipic acid is 425–440 g. (58–60 per cent of the theoretical amount) (Note 5). This product is pure enough for most purposes. However, a purer product may be obtained by recrystallizing this crude material from 700 cc. of concentrated nitric acid (sp. gr. 1.42). The loss in this purification is about 5 per cent. The recrystallized acid melts at 151–152° (Note 6) and (Note 7).

2. Notes

1. It is suggested that no catalyst is necessary if the temperature of the reaction mixture, once the reaction has started, is maintained at 85–90°. (W. W. Hartman, private communication.)
2. The cyclohexanol used was a commercial grade, which contained practically

no phenol. Over 90 per cent of the product boiled between 158–163°.
3. It is important that the oxidation start before a large amount of cyclohexanol has been added or the reaction will become violent. The reaction must be carried out in a good hood.
4. The nitric acid mother liquors contain considerable amounts of adipic acid mixed with glutaric and succinic acids. It has not proved practicable to separate these acids by crystallization. However, if the nitric acid is removed by evaporation and the resulting mixture of acids is esterified with ethyl alcohol, a mixture of ethyl succinate (b.p. 121–126°/20 mm.), ethyl glutarate (b.p. 133–138°/20 mm.), and ethyl adipate (b.p. 142–147°/20 mm.) can be obtained. These esters can be separated quite satisfactorily by distillation.
5. The following modified procedure is reported to give better yields. In a 3-l. three-necked flask provided with a stirrer, reflux condenser, and dropping funnel set in asbestos-sodium silicate stoppers, are placed 1900 cc. of 50 per cent nitric acid (1262 cc. of nitric acid, sp. gr. 1.42, diluted to 1900 cc.) and 1 g. of ammonium vanadate. The flask is surrounded by a water bath heated to 50–60°, and, while the mixture is stirred, 357 g. (3.5 moles) of commercial cyclohexanol is added very slowly so that the temperature of the bath is maintained at 50–60°. This requires about six to eight hours. The reaction is completed by heating the water bath to boiling until the evolution of nitrogen oxides has ceased (about one hour). The hot reaction mixture is siphoned off and allowed to cool. The yield of crude adipic acid is 372 g. (72 per cent of the theoretical amount). (Duncan G. Foster, private communication.)
The asbestos-sodium silicate stoppers are prepared by cutting thin asbestos paper into strips about 2.5 cm. wide, moistening the strips in water-glass solution, and then winding them around the end of the condenser, for example, until a stopper of the correct size is obtained. After the apparatus is assembled the stoppers are coated with water-glass and allowed to harden overnight.
6. The nitric acid mother liquors from the crystallization may be used as part of the acid for a subsequent oxidation.
7. Adipic acid may also be recrystallized from 2.5 times its weight of water or 50 per cent alcohol. However, these solvents are less satisfactory than nitric acid.

3. Discussion

Adipic acid can be prepared by the oxidation of cyclohexanol and cyclohexanone with nitric acid[1] or potassium permanganate.[2] The procedure described is adapted from the patent of the Deutsche Hydrierwerke A.-G.[1]

Other methods of preparing adipic acid are the oxidation of cyclohexene with dichromate and sulfuric acid[3] and the interaction of γ-bromobutyric ester with sodium malonic ester followed by hydrolysis and decarboxylation of the resulting triethyl 1,4,4-butanetricarboxylate.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 123
- Org. Syn. Coll. Vol. 1, 192
- Org. Syn. Coll. Vol. 1, 289
- Org. Syn. Coll. Vol. 2, 169

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3. Zal'kind and Markov, Russ. pat. 50,394 [C. A. **31**, 8548 (1937)]; Zal'kind and Markov, C. A. **31**, 3875 (1937).
4. Boorman, Linstead, and Rydon, J. Chem. Soc. **1933**, 573.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

oxides of nitrogen

glutaric

succinic acids

asbestos-sodium silicate

nitrogen oxides

γ-bromobutyric ester

sodium malonic ester

ethyl alcohol, alcohol (64-17-5)

sulfuric acid (7664-93-9)

Adipic acid (124-04-9)

nitric acid (7697-37-2)

ammonium vanadate (7803-55-6)

Cyclohexanol (108-93-0)

phenol (108-95-2)

ethyl succinate

ethyl glutarate (1070-62-8)

Ethyl adipate (626-86-8)

Cyclohexanone (108-94-1)

potassium permanganate (7722-64-7)

Cyclohexene (110-83-8)

dichromate

triethyl 1,4,4-butanetricarboxylate

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dl-ALANINE

$$CH_3CHO + NH_4Cl + NaCN \longrightarrow CH_3CH(NH_2)CN + NaCl$$

$$CH_3CH(NH_2)CN + 2H_2O + 2HCl \longrightarrow CH_3CH(NH_3Cl)CO_2H + NH_4Cl$$

$$2CH_3CH(NH_3Cl)CO_2H + Pb(OH)_2 \longrightarrow 2CH_3CH(NH_2)CO_2H + PbCl_2$$

Submitted by E. C. Kendall and B. F. McKenzie.
Checked by C. S. Marvel and W. W. Moyer.

1. Procedure

One hundred and thirty-one grams (3 moles) of freshly distilled acetaldehyde (Note 1) is added to 100 cc. of ether in a 2-l. bottle and cooled to 5° in an ice bath (Note 2). One hundred and eighty grams (3.4 moles) of ammonium chloride dissolved in 550 cc. of water is then added, followed by an ice-cold solution of 150 g. (3.1 moles) of sodium cyanide in 400 cc. of water. The sodium cyanide must be added slowly and with frequent cooling to prevent loss of acetaldehyde by volatilization.

After the sodium cyanide solution is added, the bottle is stoppered securely, placed in a mechanical shaker, and shaken for four hours at room temperature. At the end of this time the solution is transferred to a 3-l. distilling flask and 600 cc. of concentrated hydrochloric acid (sp. gr. 1.19) is added (Hood) (Note 3).

The solution in the flask is distilled over a free flame until separation of salt prevents further heating. It is then transferred to a large evaporating dish, placed on a steam bath and evaporated to dryness (Note 4).

The residue remaining in the dish after evaporation is stirred thoroughly with 800 cc. of 95 per cent alcohol. After filtration the alcohol is distilled on a steam bath and the last traces are removed under vacuum. While still warm the residue is dissolved in 500 cc. of 95 per cent alcohol containing 2 per cent of hydrochloric acid, and cooled. Two hundred cubic centimeters of ether is added, and the solution is filtered. This treatment should remove all but the last traces of sodium chloride and ammonium chloride. The alcohol and ether are removed by distillation and the last of the free hydrochloric acid is removed by distillation under diminished pressure.

The alanine hydrochloride remaining in the flask is dissolved in 1500 cc. of water, and transferred to a metal pail of about 2-l. capacity. Two hundred and twenty grams of yellow lead oxide is added and the mixture is boiled gently for one hour. During the boiling small amounts of water are added at intervals in order to maintain the original volume (Note 5). Upon cooling, the lead chloride crystallizes; it is filtered off and the solution is again boiled one hour with 100 g. of lead oxide. Twenty grams of freshly precipitated lead hydroxide is added slowly and the boiling is continued for ten

minutes. Following this the solution is again cooled and filtered (Note 6). The chloride content should now be equivalent to not more than 50–75 cc. of a normal solution (Note 7).

The solution is again brought to a boil and the calculated amount of silver oxide (Note 7) is added to remove the last of the chlorides. The silver chloride is filtered off and the lead is precipitated with hydrogen sulfide. After filtering off the lead sulfide, a light strawcolored solution remains.

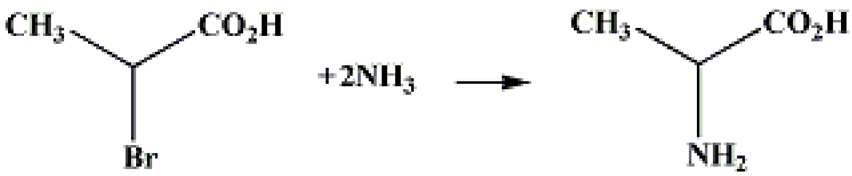
The solution is evaporated by boiling to a volume of about 400 cc., and 600 cc. of 95 per cent alcohol is added. When thoroughly cooled, 100–120 g. of alanine is filtered off. This is washed with 200 cc. of alcohol and a pure white product is obtained.

A further crop of 40–50 g. may be obtained by removing the alcohol and water until a volume of about 100 cc. remains, and then adding 250 cc. of alcohol and cooling to 0°. The total yield is 140–160 g. (52–60 per cent of the theoretical amount) (Note 8).

Alanine so prepared is sufficiently pure for most purposes. It may be recrystallized by dissolving in the least amount of hot water (about 450 cc.) and adding two volumes of alcohol.

2. Notes

1. Acetaldehyde may be conveniently prepared by distilling from paraldehyde in the presence of a trace of sulfuric acid; an efficient fractionating column should be used.
2. A one-half gallon (2-l.) ginger-ale bottle is convenient for this purpose. The necks of these bottles are small and will hold a wire securely.
3. Caution must be observed during the addition of the hydrochloric acid as much hydrogen cyanide is evolved. During the first part of the subsequent distillation it is necessary to prevent fumes from escaping from the receiver into the room.
4. During the evaporation a layer of crystals forms on the surface and must be continually broken. A blast of air blowing over the surface agitates the liquid sufficiently and allows free evaporation.
5. The volume of the solution must be kept large during the treatment with lead oxide as lead chloride will not crystallize from concentrated alanine solutions.
6. If the solution at this point still contains ammonium salts another treatment with 100 g. of lead oxide is necessary.
7. An aliquot portion of the solution is titrated with silver nitrate by the Volhard method. The result of this titration is used in calculating the amount of silver oxide which must be added.
8. A slightly lower yield of alanine may be obtained conveniently from the evaporated alanine hydrochloride by treatment with aniline (Benedict,[1] and G. J. Cox and Harriette King, private communications).



Submitted by Walter C. Tobie and Gilbert B. Ayres.
Checked by John R. Johnson and R. B. Hasbrouck.

1. Procedure

Slowly and with stirring, 100 g. (0.65 mole, 59 cc.) of cold (1–4°) α-bromopropionic acid (Note 1) is added to 3 l. (44.5 moles, 2700 g.) of cold (1–4°) concentrated aqueous ammonia (sp. gr. 0.9) (Note 2) in a 1-gal. glass-stoppered bottle, and the mixture is allowed to stand at room temperature for at least four days (Note 3). The solution is concentrated to a volume of 300 cc. (Note 4), filtered, and concentrated further to 200 cc. The solution is cooled to room temperature and 1 l. of methyl alcohol (Note 5) added. After chilling overnight in a refrigerator (0–4°) the crystals are filtered with suction and washed with 250 cc. each of methyl alcohol and ether (Note 6). The yield is 42–48 g. of crude alanine.

For purification the crude product is dissolved in 200 cc. of water (warming if necessary), 1 l. of methyl alcohol is added, and the mixture chilled overnight. After washing as before, the yield is about 38–42 g. (65–70 per cent of the theoretical amount) of purified *dl*-alanine, m. p. 295° (dec.) on the Maquenne block (Note 7). This product is free of bromide and contains only traces of ammonia. If an especially pure product is desired the material may be reprecipitated from methyl alcohol once more in the same manner (Note 8).

2. Notes

1. α-Bromopropionic acid may be prepared in 80–85 per cent yields by bromination of propionic acid, the general procedure given for α-bromoisovaleric acid (Org. Syn. **20**, 106) being followed and a fraction boiling at 100–102° at 15 mm. being collected. The commercially available α-bromopropionic acid boiling over the same range is also satisfactory.
The use of α-chloropropionic acid gives a poorer yield (43–46 per cent of theoretical) and the product is more difficult to purify owing to the fact that ammonium chloride is less soluble than the bromide in methyl alcohol.
2. The use of a large excess of ammonia (70 moles) minimizes the production of α,α'-iminodipropionic acid and similar by-products.
3. Temperatures above 40° reduce the yield, and chilling after mixing does not increase it. Less than four days' standing gives a reduced yield, but longer standing does not increase the yield.
4. Evaporation may be done in an evaporating dish under a hood, or better by

distillation at reduced pressure, using a water pump with a trap. Heating should be gentle at first to avoid violent ebullition. The ammonia may be recovered if desired by absorption in ice water.
5. The grade of technical methyl alcohol known as "Columbian Spirits" may be employed. Ethyl alcohol is much less satisfactory, since it does not dissolve ammonium bromide as well as methyl alcohol does.
6. Filtration is best done with suction on a Büchner funnel. Washing with ether can be omitted without reducing the yield.
7. In a capillary tube the product melts with decomposition at 275–280°, and the melting point varies somewhat with the rate of heating.
8. The last traces of ammonia may be removed by adding 10 g. of permutit when dissolving for the second time, then shaking the mixture thoroughly for three minutes and filtering before the methyl alcohol is added.

3. Discussion

dl-Alanine can be prepared by heating ethyl α-chloropropionate with concentrated aqueous ammonia at 100°;[2] by treatment of α-bromopropionic acid with alcoholic or aqueous ammonia;[3] by the catalytic reduction of a solution of ammonia and ammonium pyruvate,[4] or of the oxime of pyruvic acid;[5] by the action of hydrocyanic acid on aldehyde ammonia;[6] by the action of ammonium cyanide and ammonia on acetaldehyde followed by alkaline hydrolysis;[7] and by methylation of ethyl benzaminomalonate with subsequent hydrolysis and decarboxylation.[8] The procedure described in part A above is based on the modification by Zelinsky and Stadnikov[9] of the hydrocyanic acid and aldehyde ammonia method. A thorough study has been made of the preparation of alanine by the hydrogen cyanide-acetaldehyde method.[10]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 28

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

oxime of pyruvic acid

aldehyde ammonia

ethyl alcohol, alcohol (64-17-5)

acetaldehyde (75-07-0)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

methyl alcohol (67-56-1)

ether (60-29-7)

ammonium chloride (12125-02-9)

aniline (62-53-3)

sodium cyanide (143-33-9)

sodium chloride (7647-14-5)

alanine hydrochloride

lead oxide

lead chloride

lead hydroxide

silver oxide (20667-12-3)

silver chloride (7783-90-6)

lead (7439-92-1)

hydrogen sulfide (7783-06-4)

lead sulfide

alanine (56-41-7)

hydrogen cyanide, hydrocyanic acid (74-90-8)

silver nitrate (7761-88-8)

α-bromopropionic acid (598-72-1)

bromide (24959-67-9)

propionic acid (79-09-4)

α-Bromoisovaleric acid (565-74-2)

α-chloropropionic acid (598-78-7)

α,α'-iminodipropionic acid

ammonium bromide (12124-97-9)

ethyl α-chloropropionate (535-13-7)

ammonium pyruvate

ammonium cyanide

ethyl benzaminomalonate

DL-Alanine (302-72-7)

paraldehyde (123-53-7)

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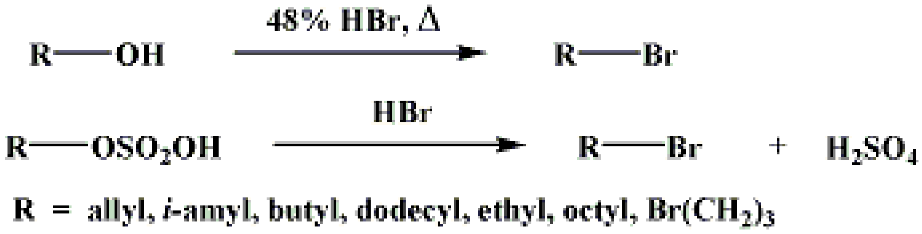
Organic Syntheses, CV 1, 25

ALKYL AND ALKYLENE BROMIDES

[I. HYDROBROMIC ACID METHOD]



Submitted by Oliver Kamm and C. S. Marvel.
Checked by H. T. Clarke and Anne W. Davis.

1. Procedure

A given primary alcohol is treated with 25 per cent excess of aqueous (48 per cent) hydrobromic acid (Note 1) together with sulfuric acid (Note 2). The mixture is refluxed (Note 3) in order to convert the alcohol as completely as possible into the corresponding bromide, and the latter is then removed from the reaction mixture by distillation. The water-insoluble layer is separated; washed successively with water, cold concentrated sulfuric acid (Note 4), and a sodium carbonate solution; separated; dried with calcium chloride (Note 5); and distilled. Slight variations from this procedure depend upon the physical and chemical properties of the alcohol used, or of the bromide formed in the reaction. For example, in the preparations of ethyl and allyl bromides, the reaction mixture is not refluxed because of the volatility of the former compound, and because of the chemical reactivity of the latter; in the preparation of *iso*-amyl bromide, too large a proportion of sulfuric acid may produce appreciable decomposition, whereas halides of high molecular weight, because of their low volatility, are separated from the reaction mixture mechanically, instead of by distillation.

The use of a modified sodium bromide-sulfuric acid method (Note 6) for the preparation of alkyl bromides is described in connection with the preparation of *n*-butyl bromide. This method has been used also for the preparations of *iso*-amyl and trimethylene bromides, but, in general, the yields were found to be somewhat lower than those obtained with the hydrobromic-sulfuric acid method.

Preparation of Hydrobromic Acid.—Hydrobromic acid may be prepared conveniently by the interaction of bromine and sulfur dioxide in the presence of water[1] (Note 7).

In a 3-l. round-bottomed flask are placed 1200 g. (377 cc., 7.5 moles) of bromine, 500 cc. of water, and 1500 g. of crushed ice. A fairly rapid stream of sulfur dioxide is allowed to pass from a pressure tank into the flask, the outlet of the gas-tube being placed below the surface of the bromine layer. The flow of sulfur dioxide is adjusted at

such a rate that the gas is completely absorbed. It is advisable to agitate the mixture occasionally during the first stage of the reduction (Note 8). About two hours will serve for the completion of the reduction, at which time the mixture will assume a yellow color (Note 9) which is not removed by further addition of sulfur dioxide, an excess of which is to be avoided (Note 10). To prevent loss by gaseous hydrogen bromide, it is advisable to cool the mixture during the progress of the reduction.

When the reduction is completed, the flask is connected with a condenser and the mixture subjected to distillation. The boiling point of constant boiling hydrobromic acid is 125–126° /760 mm., but it must be remembered that, in distilling the product from the sulfuric acid mixture, the thermometer reading should not be relied upon as an index to the composition of the distillate. Towards the end of the distillation the thermometer may rise to 130° and above, when water with only traces of acid distils from the sulfuric acid residue. Upon redistillation of the product the thermometer reading may be relied upon. For many uses a product free from traces of sulfuric acid is not required and one distillation is sufficient. In such cases the progress of the distillation is followed by determinations of the specific gravity of the distillate.

According to the above procedure, 20 kg. of 48 per cent hydrobromic acid (92 per cent of the theoretical amount) may be prepared from 10.3 kg. of bromine. The actual time required by one person for the preparation of this quantity is twenty-three hours.

For the preparation of alkyl bromides on a relatively large scale the hydrobromic acid need not be distilled but may be used directly for the subsequent preparation. The fact that 0.5 mole of sulfuric acid is present for each mole of hydrobromic acid is not a disadvantage, since the presence of sulfuric acid is desired, and consequently a correspondingly smaller quantity need be added.

(*A*) ALLYL BROMIDE, $CH_2{=}CHCH_2Br$

[Propene, 3-bromo-]

In a 3-l. round-bottomed flask, a hydrobromic acid solution is prepared (p. 26) by the sulfur dioxide reduction of 480 g. (150.5 cc., 3 moles) of bromine in the presence of 510 g. of ice water or a mixture is made of 1 kg. (5.9 moles) of aqueous 48 per cent hydrobromic acid and 300 g. (162 cc.) of concentrated sulfuric acid. To this is added 385 cc. of aqueous allyl alcohol (p. 42), which, according to bromine titration, contains 233 g. (4 moles) of pure allyl alcohol. The 3-l. round-bottomed flask is fitted with a mechanical stirrer (Note 11), separatory funnel, and an efficient condenser set for downward distillation. Stirring is started, and 300 g. (162 cc.) of concentrated sulfuric acid is added gradually through the separatory funnel to the warm solution. The allyl bromide distils over completely in about one-half to one hour. The crude allyl bromide is washed with dilute sodium carbonate solution, dried over calcium chloride, and then distilled. The yield of product boiling at 69–72° from a number of experiments varies from 445–465 g. (92–96 per cent of the theoretical amount). A small high-boiling fraction is also obtained and examination has shown this to consist

of propylene bromide.

(*B*) *iso*-AMYL BROMIDE, $(CH_3)_2CHCH_2CH_2Br$

[Butane, 1-bromo-3-methyl-]

In a 5-l. round-bottomed flask, a hydrobromic acid solution is prepared (p. 26) by passing sulfur dioxide into a mixture of 1100 g. of crushed ice and 1 kg. (314 cc., 6.25 moles) of bromine. This is equivalent to a mixture of 2.1 kg. (12.5 moles) of 48 per cent hydrobromic acid and 600 g. of concentrated sulfuric acid. There are then added, in the order mentioned, 880 g. (1086 cc., 10 moles) of *iso*-amyl alcohol (b.p. 130–132°) and 100 g. (54.5 cc.) of concentrated sulfuric acid. The clear homogeneous solution is refluxed gently during a period of five to six hours. Even during the early stages of the heating, the separation of *iso*-amyl bromide is observed, and the reaction appears to be complete after about one hour. The product is isolated as in the preparation of *n*-butyl bromide below.

A yield of 1435 g. of crude product is obtained. After purification with concentrated sulfuric acid the product weighs 1410 g. (93 per cent of the theoretical amount). Upon fractionation, however, it is found that appreciable amounts of a high-boiling product are present, and therefore the yield of fractionated material boiling over the range 116–120° varies in different experiments from 1330 to 1360 g. (88–90 per cent of the theoretical amount).

(*C*) *n*-BUTYL BROMIDE, $CH_3(CH_2)_3Br$

[Butane, 1-bromo-]

Hydrobromic-Sulfuric Acid Method.—In a 5-l. round-bottomed flask are placed 1300 g. of crushed ice and 1200 g. (376 cc., 7.5 moles) of bromine. The flask is cooled in an ice-water bath and sulfur dioxide is passed into the mixture until the red color due to free bromine has just disappeared (p. 26). This mixture is equivalent to 2500 g. (14.8 moles) of 48 per cent hydrobromic acid to which 750 g. of concentrated sulfuric acid has been added.

To the sulfuric-hydrobromic acid mixture is added 888 g. (1096 cc., 12 moles) of *n*-butyl alcohol. Following this, 600 g. (324 cc.) of concentrated sulfuric acid is added in several portions, with shaking. The flask is then attached to a reflux condenser and the mixture is refluxed during a period of five to six hours, during which time the formation of butyl bromide is carried practically to completion. The flask is now fitted with a condenser set downward and the product removed from the reaction mixture by direct distillation (about one hour). The water-insoluble layer is separated, washed first with water, then with 200 g. (109 cc.) of cold concentrated sulfuric acid, and finally with a sodium carbonate solution (50 g. of sodium carbonate in 500 cc. of water). The product is separated as completely as possible from the aqueous layer, dried during several hours with a small quantity (15–25 g.) of calcium chloride, and distilled. The yield of product boiling between 101–104° is 1560 g. (95 per cent of the theoretical

amount).

Sodium Bromide Method.—In a 5-l. round-bottomed flask is placed 1350 cc. of water, and then with stirring 1545 g. (15 moles) of finely powdered sodium bromide is added. It is advisable to add the salt to the water in this manner in place of the reverse procedure, in order to avoid caking of the sodium bromide. First, 888 g. (12 moles) of *n*-butyl alcohol and then gradually 2 kg. (1087 cc.) of concentrated sulfuric acid are added. The last half of the acid is added through a dropping funnel after the flask has been connected with a reflux condenser. The mixture is shaken occasionally during the addition of the sulfuric acid because of a tendency to separate into layers, and is finally refluxed during a period of two hours. The condenser is then set downward and the butyl bromide removed by distillation. The product is purified as in the preceding experiment for the preparation of *n*-butyl bromide by the hydrobromic-sulfuric acid method. The yield of *n*-butyl bromide boiling between 101–104° is 1480 g. (90 per cent of the theoretical amount).

(*D*) *n*-DODECYL BROMIDE, $CH_3(CH_2)_{10}CH_2Br$

[Lauryl Bromide]

In a 250-cc. round-bottomed flask are placed 70 g. (0.42 mole) of hydrobromic acid (48 per cent) (p. 26) and 22 g. (12 cc.) of concentrated sulfuric acid. To this mixture is added 40 g. (0.22 mole) of lauryl alcohol (b.p. 188–192° /110 mm.) (Org. Syn. **10**, 62), and the mixture is then refluxed for five to six hours. The bromide is isolated as described in the preparation of *n*-octyl bromide (p. 30). The product is distilled under reduced pressure and is collected from 175–180° /45 mm. The yield is 49 g. (91 per cent of the theoretical amount) (Note 12).

(*E*) ETHYL BROMIDE, CH_3CH_2Br

[Ethane, bromo-]

In the preparation of hydrobromic acid for the manufacture of ethyl bromide, particular care must be taken to avoid the presence of any excess of sulfur dioxide gas. The evolution of gas during the distillation of the ethyl bromide will invariably result in a large loss of this volatile product (b.p. 38–39°).

A hydrobromic acid solution is prepared (p. 26) in a 5-l. round-bottomed flask by the reduction of 1 kg. (314 cc., 6.25 moles) of bromine in the presence of 1.1 kg. of cracked ice. A mixture of 2075 g. (12.3 moles) of 48 per cent hydrobromic acid and 600 g. (324 cc.) of concentrated sulfuric acid may be used in place of the above reduction mixture. After the addition of 500 g. (622 cc., 10 moles) of 95 per cent ethyl alcohol, the flask is attached to a long condenser set ready for distillation, and 1 kg. (544 cc.) of concentrated sulfuric acid is slowly added through a separatory funnel. Because of the volatility of ethyl bromide, the mixture is not heated under a reflux condenser, but is subjected instead to slow distillation. The end of the condenser is provided with an adapter tube, and the distillate is collected in a flask containing ice

water. The crude ethyl bromide, weighing 1055 g., is purified as directed under the *n*-butyl bromide experiment (p. 28). The washing with concentrated sulfuric acid is almost superfluous unless a product of special purity is desired; for instance, in the present experiment a washing with 300 g. of concentrated acid results in a decrease in weight of only 10 g.

The ethyl bromide is distilled from a water bath and boils at 38.5–39.5° provided that chips of porous plate are added to prevent superheating. Final yields vary from 980 to 1035 g. (90–95 per cent of the theoretical amount) according to the precautions taken to prevent losses due to evaporation.

(*F*) *n*-OCTYL BROMIDE, $CH_3(CH_2)_6CH_2Br$

[Octane, 1-bromo-]

In a 500-cc. round-bottomed flask are placed 240 g. (1.4 moles) of hydrobromic acid (48 per cent) (p. 26), 62 g. (34 cc.) of concentrated sulfuric acid, and 71 g. (0.55 mole) of *n*-octyl alcohol (b.p. 135–140° /100 mm.). The mixture is boiled under reflux for five to six hours. The solution is diluted with water and the bromide layer is separated, washed once with a little cold concentrated sulfuric acid, then with water and finally with dilute sodium carbonate solution, after the procedure described for *n*-butyl bromide. The crude yield is 102 g.; this is dried over a little calcium chloride and distilled. The product is collected at 196–200° (91–93° /22 mm.) and amounts to 96 g. (91 per cent of the theoretical amount).

(*G*) TRIMETHYLENE BROMIDE, $Br(CH_2)_3Br$

[Propane, 1,3-dibromo-]

Hydrobromic-Sulfuric Acid Method.—In a 5-l. round-bottomed flask are placed 1200 g. (377 cc., 7.5 moles) of bromine and 1300 g. of crushed ice, and the bromine is reduced with sulfur dioxide to hydrobromic acid (p. 26). In place of the above reduction mixture, there may be used a mixture of 2.5 kg. (14.8 moles) of aqueous 48 per cent hydrobromic acid and 750 g. (408 cc.) of concentrated sulfuric acid.

First, 456 g. (433 cc., 6 moles) of trimethylene glycol (b.p. 210–215°) is added, and then 1200 g. (652 cc.) of concentrated sulfuric acid, the sulfuric acid being added slowly. The mixture is refluxed (Note 13) during a period of five to six hours and is then subjected to distillation until no water-insoluble product appears in the distillate (about one hour).

The trimethylene bromide is purified (Note 14) in accordance with the method used for *n*-butyl bromide (p. 28). A yield of 1065–1142 g. boiling at 162–165° (88–95 per cent of the theoretical amount) is obtained.

Sodium Bromide Method.—The yields of trimethylene bromide by the sodium bromide method as described for *n*-butyl bromide (p. 29) are slightly lower than those

given above. Thus, from 1350 g. of water, 1545 g. (15 moles) of sodium bromide, 456 g. (6 moles) of trimethylene glycol, and 2500 g. of sulfuric acid, a yield of 1110 g. of crude product is obtained, from which, after purification (Note 14) and distillation, a yield of 1030 g. of bromide (85 per cent of the theoretical amount) is obtained.

2. Notes

1. When an alcohol is heated with aqueous 48 per cent hydrobromic acid, a partial conversion takes place into the corresponding bromide. The reaction is more rapid and more complete, however, in the presence of sulfuric acid. Although the constant boiling hydrobromic acid obtainable on the market may be used in all the preparations described, its formation by the sulfur dioxide reduction of bromine will be considerably less expensive and equally convenient, provided that a cylinder of sulfur dioxide is available. For use in the preparation of alkyl bromides, distillation of the bromine-sulfur dioxide reduction mixture is superfluous.

2. The procedure described is quite general for the preparation of primary bromides. The presence of sulfuric acid would usually be objectionable in the preparation of secondary and tertiary bromides because of the ease of dehydration of the corresponding alcohols and the formation of isomers. This is also true of *iso*-butyl bromide and to some extent of *iso*-amyl bromide. These bromides may be obtained in good yields by the phosphorus tribromide method described in Org. Syn. **13**, 20.
In the preparations described, a more dilute hydrobromic acid solution may be used, provided that the proportion of sulfuric acid is increased. Aqueous solutions of alcohols may also be used if the proportion of sulfuric acid is suitably adjusted. In the allyl alcohol experiment, material was used as obtained from the glycerol-formic acid preparation (p. 42) after one salting out with potassium carbonate.

3. The reaction mixture is heated under the reflux condenser for several hours preliminary to the first distillation of the alkyl bromide. This is done in order to convert the alcohol as completely as possible into the corresponding bromide and thus to prevent its volatilization with the bromide. Direct distillation of the reaction mixture without refluxing will usually result in a decrease in yield of 5–15 per cent. Alkyl bromides of low molecular weight may, however, be distilled directly from the reaction mixture without the necessity of refluxing, providing the process of distillation is conducted very slowly. Alkyl halides of high molecular weight are separated from the reaction liquors mechanically instead of by distillation. This is done in order to avoid the decomposition due to heating the slightly volatile material with a gradually increasing concentration of sulfuric acid.

4. The main impurities usually found in alkyl halides are the corresponding alcohols and ethers. Cold concentrated sulfuric acid is an efficient reagent for the removal of these impurities in all cases where the alkyl halide itself is not attacked by this reagent. Whenever a product contains a considerable quantity of

unchanged alcohol, several washings with the cold concentrated acid may be required.

5. In many organic preparations too large a quantity of drying agent is usually employed, with the resulting loss of a considerable amount of material due to absorption by the drying agent. In the present experiments it is found that after a careful separation of the alkyl halide from the water layer as small a quantity as 15 g. of calcium chloride is sufficient for the drying of 1500 g. of alkyl halide.

6. The favorable results obtained in the preparation of alkyl bromides with aqueous hydrobromic acid to which sulfuric acid has been added suggest that practically the same result might be accomplished by the use of sodium bromide, water, and sulfuric acid in such ratios as approximate the proportions used in the first instance. In actual practice this modified sodium bromide method was found fairly satisfactory for the preparation of *n*-butyl bromide and of trimethylene bromide. Slightly lower yields are due to the decreased solubilities of the alcohols in the reaction mixtures because of the presence of dissolved salts. One would therefore predict that, with alcohols of still higher molecular weights, even lower yields would be obtained with the sodium bromide method. This prediction is substantiated in experiments with *iso*-amyl alcohol, where the sodium bromide method gives yields of only 70 per cent of the theoretical amount, whereas the hydrobromic acid method gives yields of almost 90 per cent. The sodium bromide method is therefore not recommended for the preparation of alkyl bromides of high molecular weight.

7. In the sulfur dioxide reduction of bromine, it should be noted that the proportion of water used depends upon whether the reduction mixture is to be distilled for the preparation of 48 per cent hydrobromic acid, or whether it is to be used directly for the manufacture of alkyl bromides.

8. During the first stage of the reduction, the flask should be shaken from time to time in order to avoid the accumulation of sulfur dioxide, or possibly of sulfuryl bromide, which would result in a violent reaction owing to a large quantity of the material reacting at one time. In more than a hundred reduction experiments conducted with quantities of bromine varying from 0.5 to 2 kg., this sudden reaction was noted in only one or two instances, in spite of the fact that there was usually no agitation other than that furnished by the entering gas stream. Mechanical stirring is frequently important in obtaining successful yields. In Fig. 2, A and B represent two convenient types of stirring devices[2] where refluxing and stirring are desired at the same time. When the stopper of the flask is so small that it will hold only the mechanical stirrer, a Y-tube such as is shown in Fig. 3 B fitted with either form of stirrer is suitable. It often happens that a separatory funnel or thermometer must also be inserted in the flask in addition to the reflux condenser. A three-necked flask such as is shown in Fig. 3 A is especially convenient, the middle opening being used for the stirrer, the two smaller ones for thermometer and reflux condenser.

Fig. 2.

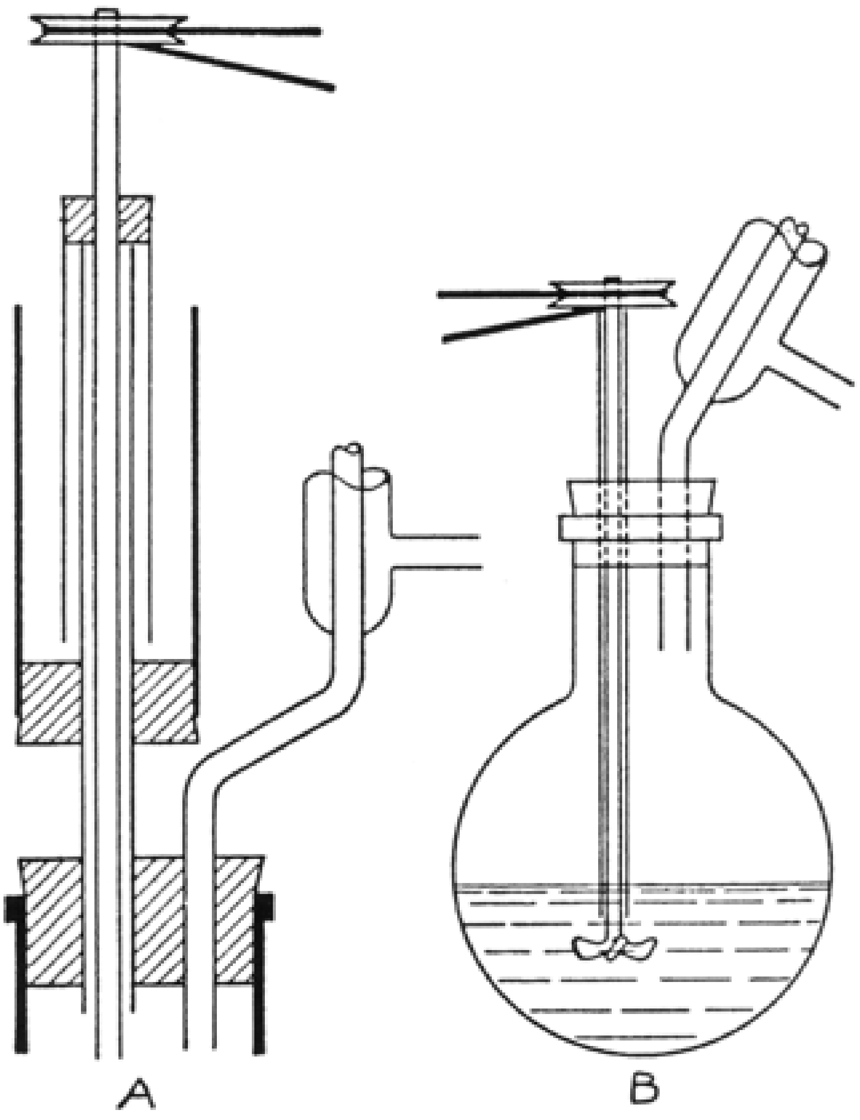
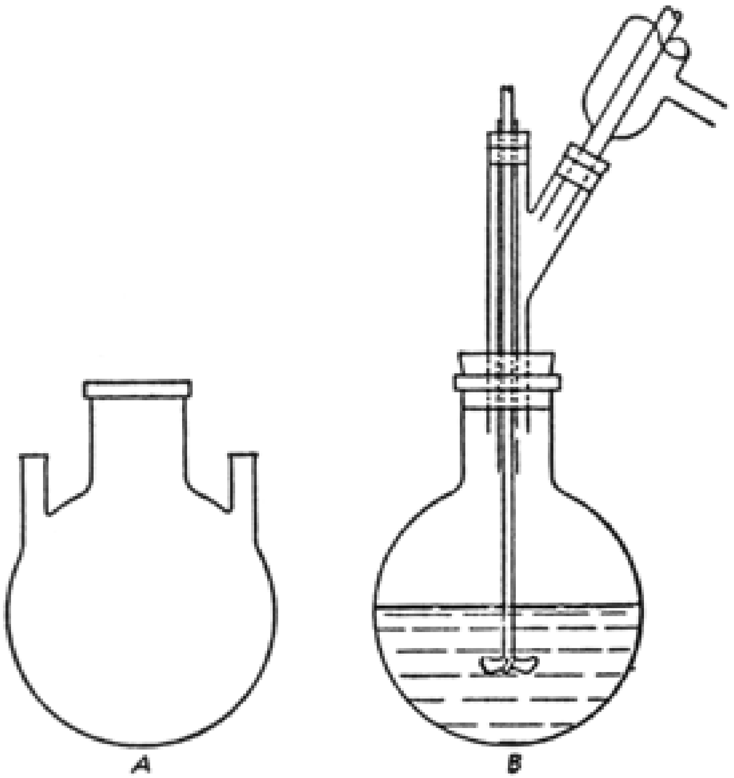


Fig. 3.



9. The intensity of the color in the reduced bromine solution depends somewhat on the quality of bromine used, and with the technical product special care is needed in noting the end point of the reduction, i.e., the transition from the bromine color to a yellowish-brown color.

10. An excess of sulfur dioxide is to be avoided for the reason that evolution of gas during the distillation of the product will result in a considerable loss of alkyl bromide through volatilization. This loss is especially marked in the preparations of ethyl and allyl bromides if this precaution is not observed.

11. In the preparation of allyl bromide, appreciable loss may occur, not only because of carbonization but primarily because of the reaction of the allyl bromide with hydrobromic acid to form propylene bromide. Stirring during the formation of the alkyl bromide prevents the formation of two layers in the reaction mixture and thus assures a rapid and smooth distillation. An efficient condenser is of course essential.

12. The troublesome emulsions often encountered when lauryl bromide is shaken with sulfuric acid may be avoided by the following alternative method of purification. The reaction mixture, after the heating is completed, is diluted with water and the layer of lauryl bromide is separated. The bromide is washed with water and then with potassium carbonate solution. The washing with water should be sufficiently thorough so that there is no appreciable foaming on shaking with the carbonate. The bromide is then dried with calcium chloride and distilled.

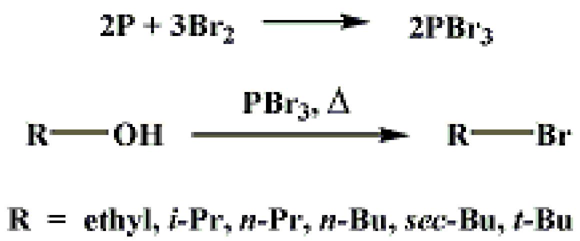
Lauryl bromide and the bromides of other primary alcohols of high molecular weight can also be prepared by saturating the alcohol at 100–120° with hydrogen bromide as described in Org. Syn. **15**, 24. This hydrogen bromide procedure has been reported to be superior for preparing lauryl bromide to the

hydrobromic acid-sulfuric acid method described above.

13. Trimethylene bromide, prepared by direct distillation of the reaction mixture without the preliminary refluxing period, contains appreciable amounts of trimethylene bromohydrin.

14. In the purification of trimethylene bromide with sulfuric acid the high specific gravity of the former (1.987) must be borne in mind. Vigorous shaking with sulfuric acid may result in the formation of emulsions.

[II. PHOSPHORUS AND BROMINE METHOD]



Submitted by R. H. Goshorn, Thomas Boyd, and E. F. Degering.
Checked by R. L. Shriner and F. J. Wolf.

1. Procedure

(*A*) ETHYL BROMIDE, CH_3CH_2Br

[Ethane, bromo-]

A 1-l. three-necked, round-bottomed flask is fitted with an Allihn condenser and a dropping funnel, the stem of which reaches to the bottom of the flask. By means of a bent glass tube the top of the Allihn condenser is connected to a Liebig condenser the end of which dips just beneath the surface of a mixture of ice and water (about 800 g.) contained in a 2-l. beaker (Note 1).

In the reaction flask are placed 363 g. of 95 per cent ethyl alcohol (7.5 moles), 25 g. of red phosphorus, and 15 g. of yellow phosphorus (1.29 gram atoms) (Note 2). The mixture is heated by means of the oil bath until gentle refluxing takes place (bath temperature at 100–110°), and 377 g. of bromine (121 cc., 2.36 moles) is slowly added through the dropping funnel over a period of three hours (Note 3), (Note 4). The water is drained from the Allihn condenser, and distillation is continued at a rate of forty to fifty drops per minute up to a temperature of about 94° (a thermometer may be placed in the flask in place of the dropping funnel) (bath at about 155°). When the distillation is complete the two condensers are disconnected first and the burner removed (Note 5).

The distillate is washed with 20 cc. of ice-cold 5 per cent sodium hydroxide solution, then with 50 cc. of ice-water. The product is dried over anhydrous calcium chloride and distilled through a short column, the distillate being collected in a dry receiver packed in an ice-salt mixture. The yield of colorless ethyl bromide distilling between 37° and 40° is 420–465 g. (82–90 per cent of the theoretical amount based on the

bromine) (Note 6).

(*B*) *iso*-PROPYL BROMIDE, $(CH_3)_2CHBr$

[Propane, 2-bromo-]

The procedure for the preparation of *iso*-propyl bromide is similar to that for ethyl bromide except for the quantities of the reactants and the temperature of the bath. A mixture of 180 g. (228 cc., 3.0 moles) of *iso*-propyl alcohol, 6 g. of red phosphorus, and 4 g. of yellow phosphorus (0.3 gram atom) is placed in the reaction flask. Then, 135 g. (43.2 cc., 0.84 mole) of bromine is added over a period of three hours, the temperature of the oil bath being maintained between 85° and 95° (preferably at 90°). The distillate is collected up to a temperature of 145° (bath temperature 155–185°). In the second distillation after washing and drying the crude product, the fraction boiling between 59° and 62° is collected. The yield of product is 143–152 g. or 69–73 per cent of the theoretical amount (Note 7).

(*C*) *n*-PROPYL BROMIDE, $CH_3CH_2CH_2Br$

[Propane, 1-bromo-]

The procedure for the preparation of *n*-propyl bromide is similar to that for ethyl bromide except for the quantities of the reactants and the temperature of the bath. A mixture of 180 g. (224 cc., 3.0 moles) of *n*-propyl alcohol, 6 g. of red phosphorus, and 4 g. of yellow phosphorus (0.3 gram atom) is placed in the reaction flask. Then 135 g. (43.2 cc., 0.84 mole) of bromine is added slowly over a period of three hours, the temperature of the oil bath being maintained between 125° and 140°. The distillate is collected up to a temperature of 140° (bath temperature 190–210°). In the second distillation, after washing and drying the crude product, the fraction boiling between 70–73° (Note 8) is collected. The yield of *n*-propyl bromide is 170–186 g. (82–90 per cent of the theoretical amount).

(*D*) *n*-BUTYL BROMIDE, $CH_3(CH_2)_3Br$

[Butane, 1-bromo-]

The same apparatus as described in the preparation of ethyl bromide may be used with the omission of the Liebig condenser.

In the reaction flask are placed 138 g. (170 cc., 1.86 moles) of *n*-butyl alcohol, 6 g. of red phosphorus, and 4 g. of yellow phosphorus (0.3 gram atom). The oil bath is heated to 175°, and 94 g. (30.1 cc., 0.58 mole) of bromine is added slowly through the dropping funnel at such a rate that the dense white vapors which form remain near the top of the Allihn condenser. The optimum period for the addition of bromine is about one hour, during which time the bath temperature slowly decreases to 165°. The mixture is distilled directly from the reaction flask which is attached to a condenser set for downward distillation. When the distillation becomes slow about 25 cc. of water is added through the dropping funnel to assist in carrying over the butyl bromide. The

final bath temperature is about 210°. The distillate is washed with 20 cc. of 5 per cent sodium hydroxide solution and then with 50 cc. of water. The product is dried with calcium chloride and distilled through a Vigreux column. The fraction boiling from 97° to 99.5° is collected and amounts to 145–150 g. (90–93 per cent of the theoretical amount).

(*E*) *sec*.-BUTYL BROMIDE, $CH_3CH_2CHBrCH_3$

[Butane, 2-bromo-]

The procedure for secondary butyl bromide is similar to that used in the preparation of *n*-butyl bromide, except that bromine is added at a bath temperature of 140–150°, and the distillate (bath temperature up to 190°) from the reaction mixture is washed with water and dried over anhydrous sodium sulfate before redistilling. The yield (b.p. 86–87°) is about 135–137 g. (84–85 per cent of the theoretical amount).

(*F*) *tert*.-BUTYL BROMIDE, $(CH_3)_3CBr$

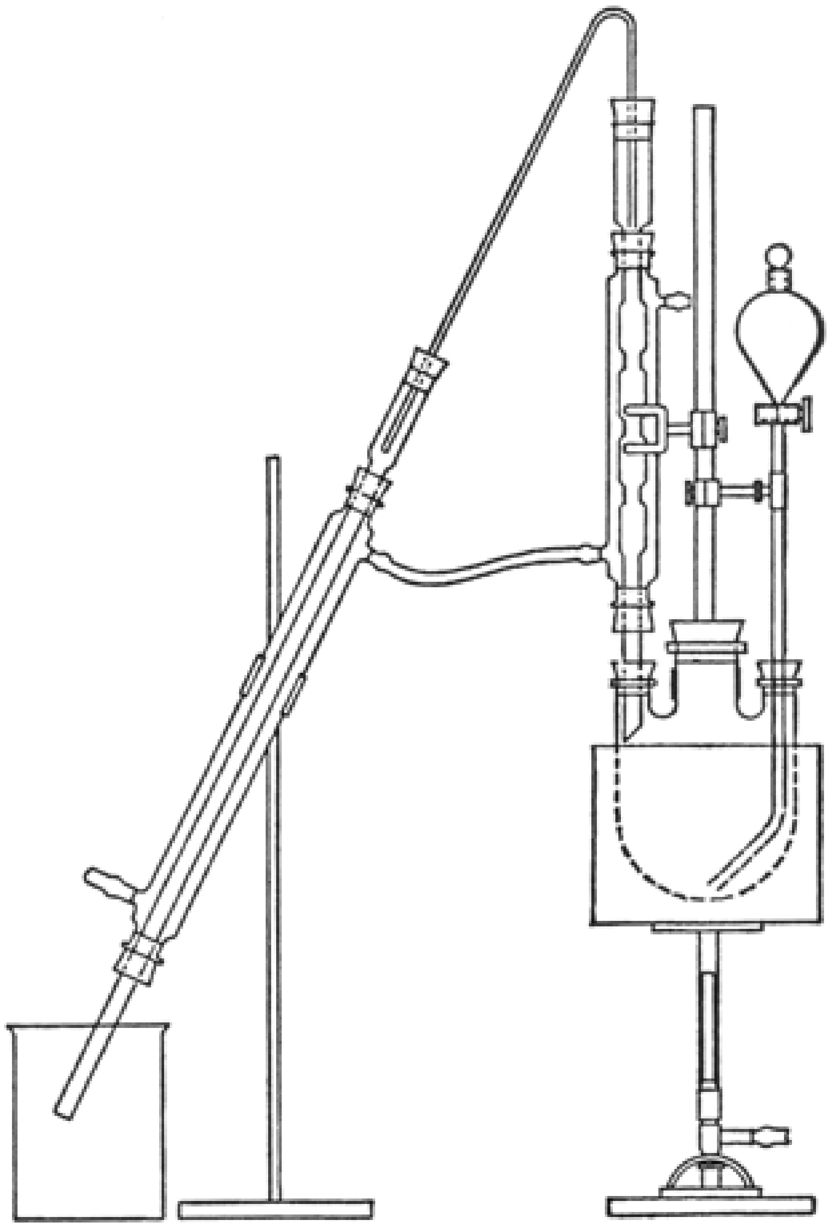
[Propane, 2-bromo-2-methyl-]

In a 500-cc. three-necked, round-bottomed flask fitted with a dropping funnel and a mechanical stirrer is placed 5 g. (0.16 gram atom) of red phosphorus. The flask is cooled on a bath of cold water, and 47 g. (15 cc., 0.29 mole) of bromine is added *very slowly* at first (Note 9). After the initial reaction has moderated the remainder of the bromine is added over a period of one and a half to two hours. The stirrer is started, and 69 g. (0.93 mole) of *tert*-butyl alcohol is placed in the separatory funnel and added slowly to the phosphorus bromide. The stirrer and separatory funnel are removed; the flask is connected to a condenser and arranged for vacuum distillation. By means of a water pump the pressure is gradually reduced to 20–30 mm. and the bromide distilled by raising the bath temperature slowly to 70–80°. The distillate is washed quickly with 50 cc. of ice-water, dried with anhydrous calcium chloride, and redistilled. The fraction boiling from 69° to 71° is collected. The yield is 32 to 34 g. (39–42 per cent of the theoretical amount).

2. Notes

1. A diagram of the apparatus used is shown in Fig. 4.

Fig. 4.



2. Nearly as good yields are obtained if yellow phosphorus is used alone. However, a much smoother and more readily controllable reaction is obtained if some red phosphorus is used along with the yellow phosphorus. Care must be exercised in handling yellow phosphorus since it ignites spontaneously in the air. It should be kept under water and transferred quickly to the flask which already contains the alcohol.

3. A vigorous reaction, with some bumping and the formation of white vapors, accompanies the first addition. As the density of the vapors decreases, the rate of addition of bromine may be increased to the extent that some of the white vapors are carried over into the Liebig condenser.

4. There is a tendency for water to be sucked from the ice bath into the apparatus because of sudden changes in pressure within the system. This difficulty may be avoided by adding the bromine at a constant rate, by maintaining a constant reflux rate, and by maintaining the temperature of the oil bath nearly constant, allowing any changes in temperature, especially lowering, to take place slowly. If water is sucked into the reaction flask, the addition of bromine may as well be

discontinued because the alcohol has become diluted and the yield will be low.
5. Care must be exercised in the disposal of the residue in the flask since it sometimes contains unreacted phosphorus which ignites spontaneously when dry and exposed to the air. After the residue has cooled, it should be drowned in a large volume of water and the mixture washed down the drain with a good stream of water.
6. Ethyl bromide is quite volatile, and hence care must be taken to keep it cold during the washing operations and to use efficient condensing systems.
7. In washing the product a lachrymator is noticed, and in the final distillation a residue of 30–36 g. possessing highly lachrymatory properties is observed.
8. The residue has lachrymatory properties and a pungent odor.
9. Care should be taken to add the bromine very slowly at first since sometimes the heat of the reaction is sufficient to ignite the phosphorus and it burns until all the oxygen is removed from the flask.

3. Discussion

Alkyl bromides are prepared most conveniently from the corresponding alcohols. The reagents commonly employed are: phosphorus bromide,[3] a metallic bromide and sulfuric acid,[4] very concentrated or fuming hydrobromic acid, often under pressure,[5] and aqueous hydrobromic acid in accordance with the method suggested by Norris.[6] Allyl, propyl, and isobutyl bromides have been prepared[7] by a modification of this last method: bromine was reduced by means of sulfur dioxide, the alcohol was added, and the mixture distilled. The procedure described has two essential modifications: the addition of concentrated sulfuric acid and a refluxing period preliminary to the distillation. The sodium bromide method has been improved by similar modifications. Purer alkyl bromides have been reported by a slight variation in the method of purification.[8] Since trimethylene glycol is now a by-product from the purification of glycerol, it is a convenient compound for the preparation of trimethylene bromide. A method involving the use of gaseous hydrobromic acid has been described,[9] but the aqueous hydrobromic-sulfuric acid method[10] has been found to be a considerable improvement.

Comparative studies of the preparation of a number of alkyl bromides show that phosphorus tribromide gives better results than red phosphorus and bromine,[11] while a comparison of different methods of preparing *n*-butyl bromide shows that the best yields are obtained with hydrogen bromide and sulfuric acid.[12]

Other procedures which have been described for the preparation of alkyl bromides include: the addition of hydrogen bromide to ethylenic hydrocarbons in the presence of an absorbent hydrous metal oxide gel;[13] heating an alcohol or its sulfuric acid ester with hydrobromic acid in aqueous solution at 110–180°, under pressure to avoid

formation of a vapor phase;[14] treatment of a dialkyl sulfate with hydrogen bromide in the vapor phase;[15] heating an alcohol saturated with hydrogen bromide in the hydrogen bromide salt of a nitrogenous heterocyclic compound such as pyridine hydrobromide;[16] and cleaving aliphatic ethers with hydrogen bromide and steam in the presence of a dehydrating catalyst.[17] Alkyl bromides have been prepared from alcohols of high molecular weight by saturating the alcohol with hydrogen bromide at 100°C.[18]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 46
- Org. Syn. Coll. Vol. 1, 117
- Org. Syn. Coll. Vol. 1, 131
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- Org. Syn. Coll. Vol. 1, 250
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- Org. Syn. Coll. Vol. 1, 435
- Org. Syn. Coll. Vol. 1, 521
- Org. Syn. Coll. Vol. 2, 128
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- Org. Syn. Coll. Vol. 2, 292
- Org. Syn. Coll. Vol. 2, 323
- Org. Syn. Coll. Vol. 2, 358
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- Org. Syn. Coll. Vol. 2, 547
- Org. Syn. Coll. Vol. 2, 602
- Org. Syn. Coll. Vol. 3, 159
- Org. Syn. Coll. Vol. 3, 363
- Org. Syn. Coll. Vol. 3, 523
- Org. Syn. Coll. Vol. 3, 601
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

red phosphorus

yellow phosphorus

ethyl alcohol (64-17-5)

calcium chloride (10043-52-4)

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

sodium hydroxide (1310-73-2)

glycerol (56-81-5)

HYDROBROMIC ACID, hydrogen bromide (10035-10-6)

sodium carbonate (497-19-8)

bromine (7726-95-6)

sulfur dioxide (7446-09-5)

Allyl bromide, Propene, 3-bromo- (106-95-6)

Allyl alcohol (107-18-6)

propylene bromide (78-75-1)

Butane, 1-bromo-3-methyl-, iso-amyl bromide (107-82-4)

Butane, 1-bromo-, Butyl bromide, n-butyl bromide (109-65-9)

sodium bromide (7647-15-6)

Lauryl Bromide, n-DODECYL BROMIDE (143-15-7)

Lauryl alcohol (112-53-8)

Ethyl bromide, Ethane, bromo- (74-96-4)

Octane, 1-bromo-, n-octyl bromide (111-83-1)

Trimethylene bromide, Propane, 1,3-dibromo- (109-64-8)

trimethylene glycol (504-63-2)

sulfuryl bromide

trimethylene bromohydrin (627-18-9)

PHOSPHORUS (7723-14-0)

Propane, 2-bromo-, iso-PROPYL BROMIDE (75-26-3)

Propane, 1-bromo-, Propyl bromide, n-PROPYL BROMIDE (106-94-5)

Butane, 2-bromo-, 2-Bromobutane, sec.-BUTYL BROMIDE (78-76-2)

sodium sulfate (7757-82-6)

Propane, 2-bromo-2-methyl-, tert.-BUTYL BROMIDE (507-19-7)

oxygen (7782-44-7)

phosphorus tribromide (7789-60-8)

pyridine hydrobromide (18820-82-1)

formic acid (64-18-6)

n-butyl alcohol (71-36-3)

iso-propyl alcohol (67-63-0)

n-propyl alcohol (71-23-8)

iso-amyl alcohol (123-51-3)

n-octyl alcohol (111-87-5)

Isobutyl bromide, iso-butyl bromide (78-77-3)

tert-butyl alcohol (75-65-0)

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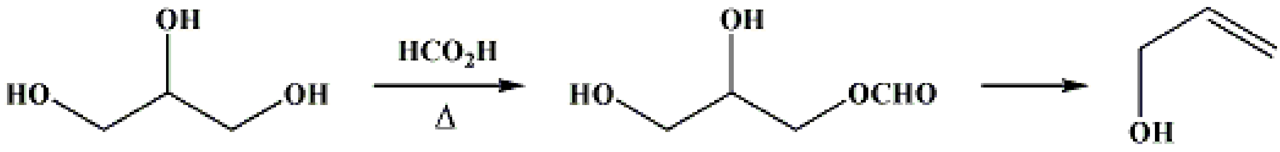
Organic Syntheses, CV 1, 42

ALLYL ALCOHOL



Submitted by Oliver Kamm and C. S. Marvel.
Checked by H. T. Clarke and E. R. Taylor.

1. Procedure

In a 5-l. round-bottomed flask are placed 2 kg. (1587 cc., 21.7 moles) of glycerol and 700 g. (585 cc., 12.9 moles) of technical 85 per cent formic acid (Note 1). The flask is connected with a condenser set for downward distillation and the temperature within the reaction mixture is indicated by a thermometer, the bulb of which is immersed in the liquid. It is advisable to use as a receiver a distilling flask attached tightly to the lower end of the condenser. A tube is then run from the side arm of the distilling flask to a bottle of strong caustic soda to dissolve and decompose any acrolein which may be formed; a few pieces of clay plate are added to the distillation flask containing the reactants in order to prevent bumping, and it is then heated *rapidly* over a good ring burner (Note 2). The first runnings should come over within fifteen minutes and a temperature of 195° should be reached in thirty to forty-five minutes. Slow heating causes charring and formation of much acrolein, and thus gives a very low yield of allyl alcohol. The distillate collected up to the point where the thermometer registers 195° is saved separately (Note 3). Heating is continued until the temperature reaches 260°, the main reaction taking place between 225° and 235°. At 260°, when the heating should be stopped, a white smoke appears and decomposition apparently begins. The distillate (about 750 cc.) coming over between the thermometer readings between 195° and 260° is saved. For this operation about four hours are required.

The contents of the flask are now allowed to cool to a temperature between 100° and 125°, and 500 g. (9.2 moles) more of the technical 85 per cent formic acid is added. The distillation is then repeated in exactly the same manner as described above and 500 cc. of distillate is collected between the temperatures from 195–260°. The reaction mixture is allowed to cool again and a third portion of 500 g. of formic acid is added. This distillation yields not more than 350 cc. of the desired fraction, indicating that the glycerol is used up and that further addition of formic acid is unnecessary; moreover, the residue left behind is now small, amounting only to 100–200 cc. The three distillations require from one to one and one-half days.

The 195–260° fractions of the distillates are treated with potassium carbonate to salt out the allyl alcohol and to neutralize the little formic acid present. This allyl alcohol is then distilled and the fraction boiling up to about 103° is collected, or if a column is used, up to 98°. In this way, 845 g. of an allyl alcohol is obtained, which by bromine titration shows a purity of about 68–70 per cent (Note 4). This is equivalent to 570–590 g. of pure allyl alcohol (45–47 per cent of the theoretical amount) (Note 5).

The alcohol may be made practically anhydrous by refluxing with successive portions of fused potassium carbonate until no further action is observed. The carbonate will remain finely divided and will not become sticky when water is absent. A considerable amount of allyl alcohol is lost

mechanically during the drying in this way, so that the potassium carbonate which is used here should be employed for the salting out of fresh portions of allyl alcohol in the first part of subsequent preparations. The allyl alcohol thus produced is dry enough for all practical purposes (98–99 per cent), and it is unnecessary to dry with lime or barium oxide as advised in the literature in order to remove all the water. The allyl alcohol obtained by this process boils at 94–97°.

The checkers have used the following method with success for obtaining a completely anhydrous product. The allyl alcohol obtained after one salting out with potassium carbonate is distilled as indicated above to give a product of about 70 per cent purity and then mixed with one-quarter of its volume of carbon tetrachloride (Note 6). The mixture is then slowly distilled from a round-bottomed flask fitted with a fractionating column at least 80 cm. long, collecting the low-boiling mixture of carbon tetrachloride, water, and allyl alcohol, drying it with potassium carbonate, and returning it to the flask (Note 7). This process is repeated several times, until only very little water passes over. The mixture is then completely distilled, taking the following cuts: Up to 80°, 80–90°, 90–95°, 95.5–97°, the last being alcohol which titrates 100 per cent pure. The lower fractions are dried separately and refractionated, thus giving an additional portion boiling at 95.5–97°.

2. Notes

1. The reaction between formic acid and glycerol runs very smoothly and without the tendency toward foaming which results when oxalic acid is used.
2. Unless heating is rapid, the yields are very unsatisfactory.
3. The lower fraction which distils up to the point where the thermometer registers 195° contains a considerable amount of formic acid, and in large-scale production it would undoubtedly pay to recover it.
4. To determine the purity of any sample of allyl alcohol, 1 cc. is run into 15–25 cc. of carbon tetrachloride and this solution is then treated in the cold with a carbon tetrachloride solution of bromine (standardized with potassium iodide and sodium thiosulfate) until a permanent bromine coloration is obtained. The amount of allyl alcohol present in any solution may also be determined roughly by conversion to allyl bromide. From several experiments it was found that the allyl bromide obtained was equivalent to the amount of allyl alcohol as determined by bromine titration.
When the crude allyl alcohol is distilled from a steam bath under reduced pressure, the distillate is considerably richer in allyl alcohol (sometimes up to 90 per cent). The strength can be readily determined by measuring the specific gravity and comparing with the following figures:

Per cent allyl alcohol..	65	70	75	80	85	90	95	100
Density at 20°.......	0.920	0.911	0.902	0.893	0.884	0.875	0.865	0.854

The best results are obtained when working at a pressure of 200–300 mm. Some boiling points of the watery alcohol are: 60°/200 mm., 70°/300 mm., and 78°/500 mm.
5. A large amount of work was carried out upon the oxalic acid and glycerol method for the production of allyl alcohol. The results were not satisfactory and therefore are not included here. It might be said, however, that, when oxalic acid is used in place of formic acid, the reaction requires a longer time for completion and is not nearly so smooth. There is a much greater tendency toward foaming and the reaction must be continually watched in order to prevent this, especially after the first distillation with oxalic acid, when more oxalic acid is

added and heating is continued. Another disadvantage is that large amounts of acrolein are produced when oxalic acid is used. In general, the yield by this method amounts to not over 20–30 per cent, whereas with formic acid a yield of 45–47 per cent is easily obtained. As far as the preparation of allyl alcohol is concerned, in amounts such as are used in the above experiments, the formic acid method is greatly to be preferred. The method of employing anhydrous oxalic acid, which has been reported as giving particularly good yields, did not give satisfactory results when tried.
Experiments were also made with 90 per cent formic acid, and yields of 50–54 per cent of allyl alcohol were obtained.
6. It is suggested that ethylene chloride rather than carbon tetrachloride be used to dehydrate the allyl alcohol because of its more rapid effect. (W. W. Hartman, private communication.)
7. The apparatus described on p. 262 may be used for these operations.

3. Discussion

The two most practical methods for the preparation of allyl alcohol are by the action of either formic[1] or oxalic acid[2] on glycerol. Both methods have been studied, and the formic acid method has been shown to be much the superior. Improved yields are obtainable[3] by reworking the fractions obtained in accordance with the procedure described in this volume, but such improvement was found to be only 2 per cent in an experiment carried out by one of the editors.

Allyl alcohol has also been prepared, together with propionaldehyde, by passing propylene oxide mixed with nitrogen over activated alumina at 200–400°,[4] and from propylene oxide, an alkali alum, and an oxidation catalyst such as vanadium pentoxide at 200–300°.[5] The thermal decomposition of allyl sulfite also furnishes allyl alcohol.[6]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 25

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

caustic soda

formic

alumina

alcohol (64-17-5)

potassium carbonate (584-08-7)

Acrolein (107-02-8)

glycerol (56-81-5)

bromine (7726-95-6)

Allyl bromide (106-95-6)

Allyl alcohol (107-18-6)

carbonate (3812-32-6)

formic acid (64-18-6)

barium oxide

carbon tetrachloride (56-23-5)

Oxalic acid (144-62-7)

potassium iodide (7681-11-0)

sodium thiosulfate (7772-98-7)

ethylene chloride (107-06-2)

Propionaldehyde (123-38-6)

propylene oxide (75-56-9)

nitrogen (7727-37-9)

vanadium pentoxide

allyl sulfite

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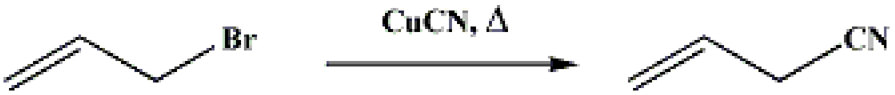
Organic Syntheses, CV 1, 46

ALLYL CYANIDE

[3-Butenenitrile]

$$2CuSO_4 + 4NaCN \longrightarrow 2CuCN + (CN)_2 + 2Na_2SO_4$$



Submitted by J. V. Supniewski and P. L. Salzberg.
Checked by Frank C. Whitmore, H. F. Herzog, and Gladys E. Woodward.

1. Procedure

(*A*) *Preparation of Cuprous Cyanide*.—(Note 1)—In a 6-l. round-bottomed flask fitted with a stopper carrying a mechanical stirrer, a separatory funnel, and a gas exit tube leading to a good hood (Note 2), is placed a solution of 650 g. (2.6 moles) of crystallized copper sulfate in 4 l. of water. The flask is surrounded by an oil bath and heated to about 80°. The stirrer is started and a solution of 255 g. (5.2 moles) of sodium cyanide (Note 3) in 650 cc. of water is added from the separatory funnel over a period of about one-half hour. Then the mixture is boiled until no more cyanogen gas is evolved. This requires about five to ten minutes.

The cuprous cyanide, which begins to separate as a light tan precipitate as soon as any of the cyanide solution is added, is allowed to settle and the solution is decanted. The precipitate is filtered, then washed with water (1 l.) and finally with alcohol (500 cc.) and ether (300 cc.). After drying at 110° for about thirty-six hours, the product weighs 200–210 g. (85–90 per cent of the theoretical amount).

(*B*) *Allyl Cyanide*.—In a 1-l. round-bottomed flask fitted with a condenser (Note 4) and a mechanical stirrer are placed 220 g. (1.83 moles) of allyl bromide (Note 5) and 170 g. (1.9 moles) of dry cuprous cyanide (Note 6). The mixture is heated in a water bath and the stirrer rotated slowly by hand until the reaction starts (about fifteen to thirty minutes). When the reaction once begins, it becomes vigorous, and the heating bath must be replaced by a cooling mixture of ice and water in order to avoid loss of product through the condenser. After the vigorous reaction has subsided, the water bath is replaced, the mechanical stirrer is started and the mixture is heated until no more allyl bromide refluxes. This requires about one hour.

The condenser is then set for distillation and the allyl cyanide is distilled from the flask by heating it in an oil bath with stirring (Note 7) and (Note 8). Upon redistillation, the allyl cyanide is pure and boils at 116–121° with almost no loss. The yield is 98–103 g. (80–84 per cent of the theoretical amount).

2. Notes

1. Technical cuprous cyanide dried at 110° gives as good results as the specially prepared substance.
2. The cyanogen evolved in this reaction should be led into a flue with good suction draft or removed by a gas absorption trap (Fig. 7 on p. 97). It may be burned if a trap is placed in the system to allow the moisture to condense.
3. The ordinary technical sodium cyanide is used.
4. A very efficient condenser is needed as the mixture refluxes vigorously during the first part of the reaction. A condenser of the bulb type about 90 cm. long is satisfactory. If a less efficient condenser is used, the upper end should be fitted with a tube leading into an empty flask to catch any material forced out.
5. The allyl bromide (p. 27) should be dried over calcium chloride, filtered and redistilled, the fraction boiling at 69–71° being used.
6. The cuprous cyanide must be dry, as small amounts of moisture reduce the yield considerably (about 15 per cent). With some samples of technical cuprous cyanide a larger amount must be used.
7. Toward the end of this distillation it is advisable to connect with the suction to remove the last of the allyl cyanide from the solid residue in the flask.
8. The residue in the flask is very tarry. It is best removed by careful treatment with strong nitric acid, then with water, and finally with hot alcohol. If necessary, the treatment is repeated several times.

3. Discussion

Allyl cyanide can be prepared from potassium cyanide and allyl chloride,[1] allyl bromide[2] and allyl iodide.[3] The procedure described is essentially that of Bruylants,[4] who has shown that the yields are much better when dry cuprous cyanide is treated with allyl bromide. Allyl cyanide can also be prepared from allyl chloride and cuprous cyanide or from allyl alcohol, cuprous cyanide and hydrochloric acid.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 851

References and Notes

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2. Pomeranz, Ann. **351**, 357 (1907); Lespieau, Compt. rend. **137**, 262 (1903); Bull. soc. chim. (3) **33**, 58 (1905).
3. Rinne and Tollens, Ann. **159**, 106 (1871).
4. Bruylants, Bull. soc. chim. Belg. **31**, 175 (1922).
5. Breckpot. ibid. **39**, 465 (1930); Glattfield and Rietz, J. Am. Chem. Soc. **62**, 974 (1940).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alcohol (64-17-5)

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

ether (60-29-7)

nitric acid (7697-37-2)

sodium cyanide (143-33-9)

Allyl bromide (106-95-6)

Allyl alcohol (107-18-6)

Allyl cyanide, 3-Butenenitrile (109-75-1)

Cuprous Cyanide (544-92-3)

copper sulfate (7758-98-7)

cyanogen

potassium cyanide (151-50-8)

allyl chloride (107-05-1)

allyl iodide (556-56-9)

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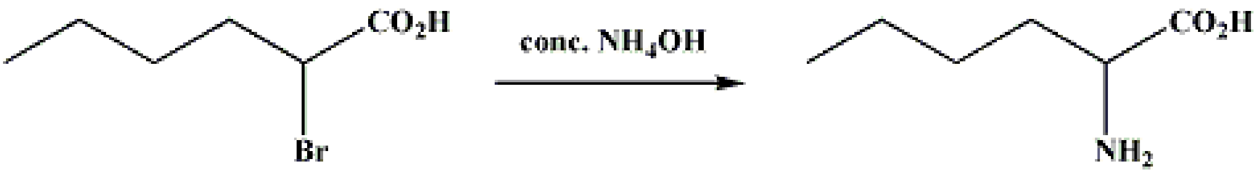
Organic Syntheses, CV 1, 48

α-AMINO-*n*-CAPROIC ACID

[Norleucine]



Submitted by C. S. Marvel and V. du Vigneaud.
Checked by H. T. Clarke and E. R. Taylor.

1. Procedure

In a 1-l. round-bottomed flask is placed 760 g. (844 cc.) of concentrated aqueous ammonia (sp. gr. 0.9) and to this is slowly added 150 g. (0.77 mole) of α-bromocaproic acid (Note 1). The flask is well stoppered and allowed to stand in a warm place (50-55°) for twenty to thirty hours. The amino acid separates and is filtered off with suction and washed with methyl alcohol (Note 2). This crop of crystals weighs 51–56 g. The aqueous filtrate is evaporated nearly to dryness on a steam bath and then treated with about 250 cc. of methyl alcohol. This precipitates a second crop of amino acid contaminated with ammonium bromide. On washing with methyl alcohol and recrystallizing from water, there is obtained 10–15 g. more of pure product. The total yield is 63–68 g. (62–67 per cent of the theoretical amount).

2. Notes

1. The once-distilled bromocaproic acid (p. 115) is satisfactory.
2. If the amino acid is not carefully washed with alcohol, it contains ammonium bromide and may possess an objectionable odor. Methyl alcohol is preferable to ethyl alcohol since it dissolves ammonium bromide more readily.

3. Discussion

α-Amino-*n*-caproic acid can be prepared by the action of ammonia on α-bromo-*n*-caproic acid,[1] and by the alkylation with butyl bromide of benzoylaminomalonic ester with subsequent hydrolysis.[2]

References and Notes

1. Hüfner, J. prakt. Chem. (2) **1**, 7 (1870); Fischer, Ber. **33**, 2381 (1900); Abderhalden, Froehlich and Fuchs, Z. physiol. Chem. **86**, 456 (1913); Adams and Marvel, J. Am. Chem. Soc. **42**, 320 (1920); E. I. du Pont de Nemours & Co., U. S. pat. 2,109,929 [C. A. **32**, 3424 (1938)].

2. Painter, J. Am. Chem. Soc. **62**, 232 (1940).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

benzoylaminomalonic ester

ethyl alcohol, alcohol (64-17-5)

ammonia (7664-41-7)

methyl alcohol (67-56-1)

ammonium bromide (12124-97-9)

Butyl bromide (109-65-9)

Norleucine (327-57-1)

α-Bromocaproic acid, α-bromo-n-caproic acid (616-05-7)

bromocaproic acid (4224-70-8)

α-AMINO-n-CAPROIC ACID (616-06-8)

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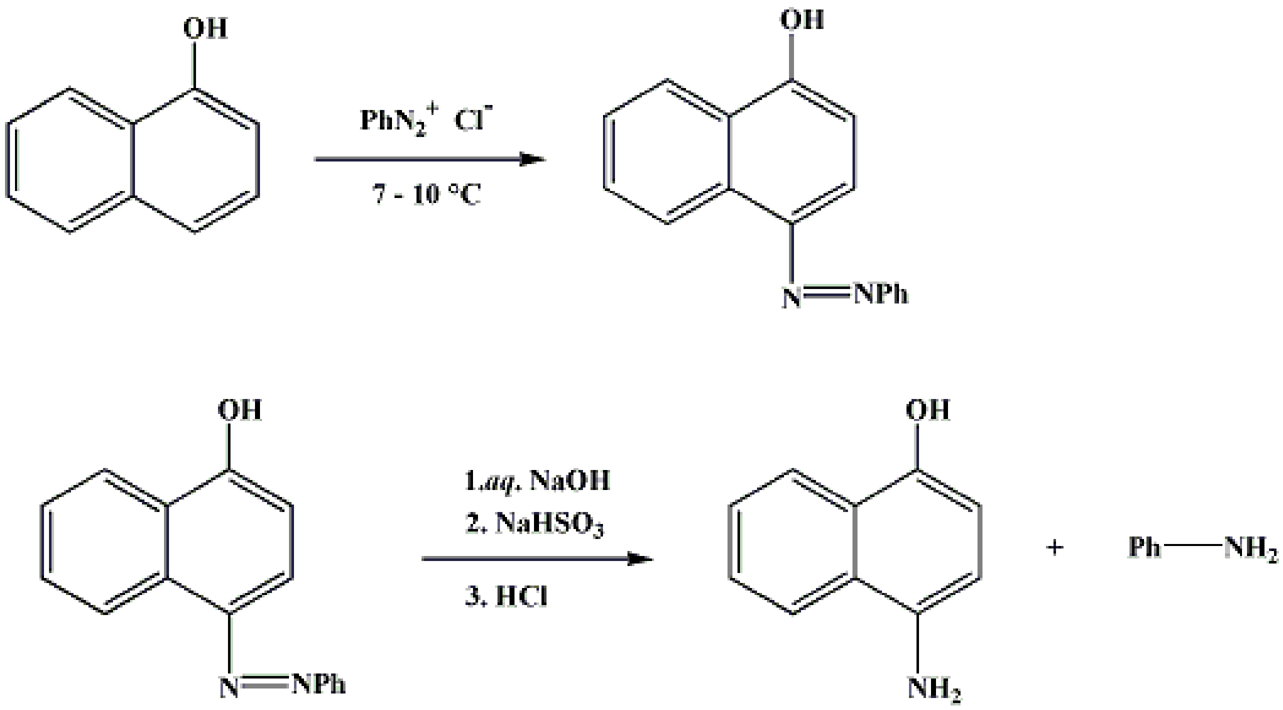
Organic Syntheses, CV 1, 49

1,4-AMINONAPHTHOL HYDROCHLORIDE

[1-Naphthol, 4-amino-, hydrochloride]



Submitted by J. B. Conant, R. E. Lutz, and B. B. Corson.
Checked by H. T. Clarke and J. H. Bishop.

1. Procedure

In a 6-l. wide-mouthed bottle, fitted with a mechanical stirrer and a separatory funnel, are placed 200 g. (1.39 moles) of α-naphthol melting at 91° or higher (Note 1) and 910 cc. of 10 per cent sodium hydroxide solution (2.5 moles). The mixture is stirred for ten minutes, at the end of which time it has become a homogeneous solution.

While the naphthol is dissolving, a solution of benzenediazonium chloride is prepared. In a 3-l. wide-mouthed bottle are placed 128 g. (125 cc., 1.38 moles) of aniline and 1.5 kg. of cracked ice (Note 2), and upon this mixture while it is stirred (by hand) is poured 410 cc. of concentrated hydrochloric acid (31.5 per cent; sp. gr. 1.16). Some crystals of aniline hydrochloride separate at this point. A solution of 100 g. (1.45 moles) of sodium nitrite in 200 cc. of water is now run in slowly from a 500-cc. separatory funnel. The tip of the stem of the separatory funnel should dip well below the surface of the liquid. The mixture is stirred (by hand if desired) and a drop is tested from time to time with starch-iodide paper. This is best done by diluting the test-drop on a watch glass with about 1 cc. of water and then placing a drop of this solution on the starch-iodide paper. The sodium nitrite solution is added until there is a test for nitrous acid which is permanent for five minutes. The diazotization is then complete; all but 2–5 per cent of the nitrite is required.

To the alkaline solution of α-naphthol is now added 1 kg. of cracked ice, the stirrer is started and the diazonium solution run in through a separatory funnel, the stem of which dips below the surface of the solution. The stirring must be uniform and efficient during the addition (Note 3).

The addition of the diazonium solution should take ten minutes. Ice is added if necessary to keep the solution below 10°. The mixture is stirred for one-half hour after the addition of the diazonium solution and then allowed to stand for three hours at 7–10° (Note 4). It is then filtered on a Büchner funnel, washed with 1 l. of water and sucked as dry as possible.

The moist benzeneazo-α-naphthol is next transferred to a 5-l. wide-mouthed bottle or a 2-gallon (8-l.) crock equipped with a mechanical stirrer and containing 3 l. of 10 per cent sodium hydroxide solution. The mixture is stirred for ten minutes to insure solution of the dye, and then filtered. The insoluble solid is stirred up with 500 cc. of 10 per cent sodium hydroxide, filtered again and washed with water. The solid, which weighs 10–90 g., consists mainly of the 2,4-disazo derivative (m. p. 197–198°), together with any benzeazo-β-naphthol that may be present.

To the deep-red solution is added 550 g. of sodium hydrosulfite (of at least 80 per cent purity); the mixture is stirred for five minutes and then for five thirty-second periods during one-half hour (Note 5). The solution slowly loses its red color (a thin layer of aniline collects on the surface), and the temperature rises from 25–50°. At the end of one-half hour the solution should no longer be red; it is then rapidly cooled to 20° in a freezing bath and by the addition of about 500 g. of ice.

To the solution is now added, with stirring, 625 cc. (6.3 moles) of concentrated (31.5 per cent; sp. gr. 1.16) hydrochloric acid (Note 6) or its equivalent of acid of approximately the same strength. A cream-colored precipitate of the aminonaphthol forms. It is rapidly filtered off on a Büchner funnel (Note 7) and washed with one portion (200 cc.) of water about half saturated with sulfur dioxide. The precipitate soon darkens on exposure to air and is therefore rapidly transferred to a 2-gallon (8-l.) crock containing 2 l. of water and 340 cc. of concentrated hydrochloric acid. The soft lumps are broken up with a cork stopper set on the end of a stirring rod. Steam is passed into the mixture for forty-five minutes, and during the last thirty minutes the mixture is stirred mechanically. At the end of this time the amine will have passed completely into solution. An insoluble impurity weighing 25–30 g. is removed by filtering with suction. The filtrate is cooled to 25° and if it is not clear is filtered again. To the clear solution at 25° is added 1200 cc. of concentrated hydrochloric acid with stirring, when a light gray precipitate of the aminonaphtholhydrochloride immediately forms. The solution is allowed to stand for two to three hours and is then filtered with suction. The hydrochloride is sucked as free from mother liquor as possible, washed very thoroughly with hydrochloric acid (1 volume acid to 1 volume of water), and dried on a porous plate. The liquors are concentrated, under reduced pressure, to a small volume, and a second crop is thus obtained. The product is of a light purplish tint (Note 8) and weighs 175–200 g. (65–74 per cent of the theoretical amount, based on the quantity of α-naphthol employed) (Note 9).

2. Notes

1. Technical α-naphthol varies widely in purity, but material melting at 91° or above is substantially free of β-naphthol; unsatisfactory results will be obtained with material of an inferior grade, but when not more than 2 per cent of β-naphthol is present yields of 70 per cent should readily be obtained.
2. During the diazotization of the aniline the temperature must be kept at 0–5°. The amount of ice stated is usually enough for this, but if not, more must be added.
3. The stirring must be very uniform and vigorous during the addition of the benzenediazonium chloride solution to the α-naphthol; otherwise the precipitate collects in gummy balls. If properly carried out, the operation produces a fine red precipitate which filters easily and is not at all gummy. A more powerful motor than that ordinarily used is

required for effective stirring.
4. The temperature at which the coupling takes place and the mixture is allowed to stand has a great influence on the amount of disazo compound formed, as much as 120 g. being produced if no external cooling is provided.
5. The reduction with hydrosulfite may be carried out in an atmosphere of illuminating gas or hydrogen sulfide. The first precipitate of the free aminophenol is a little lighter in color when prepared in an inert atmosphere, but the final aminonaphthol hydrochloride has the usual light purple color.
6. If too much hydrochloric acid is added in the precipitation of the free aminophenol, some will, of course, redissolve. The amount given above will give satisfactory results if the indicated quantities are adhered to.
7. The completeness of the precipitation should be tested by adding a little acid to one portion of the filtrate and a little sodium carbonate solution to another; no further precipitate should be produced in either case.
8. The aminophenol hydrochloride can be further purified by dissolving in hot water, cooling, and adding concentrated hydrochloric acid. It crystallizes in beautiful crystals, but the light violet color is very difficult to remove.
9. A yield of 85–90 per cent is obtainable when the best grade of α-naphthol is used. In this case it is suggested that the alkali-insoluble precipitate from the benzeneazo-α-naphthol be not filtered as it is very slight in amount and very difficult to filter. If the best grade of α-naphthol is used the amounts of water and hydrochloric acid to be used with the crude product should be multiplied by 1.3 (R. B. Whitney, private communication).

3. Discussion

1,4-Aminonaphthol can be prepared by the reduction of 1,4-nitronaphthol by tin and hydrochloric acid,[1] and by the action of phenylhydrazine on 1,4-nitrosonaphthol.[2]The more usual preparative method has been to start with α-naphthol orange (Orange I) and reduce it with stannous chloride.[3] Orange I has also been reduced with sodium hydrosulfite, using stannous chloride as an antioxidant in preparing and crystallizing the amine hydrochloride.[4] The procedure described above makes possible the use of crude, technical α-naphthol.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 162
- Org. Syn. Coll. Vol. 2, 39

References and Notes

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2. Plancher, Gazz. chim. ital. **25** (2), 393 (1895) [Chem. Zentr. I, 436 (1896)].
3. Seidel, Ber. **25**, 423 (1892); Russig, J. prakt. Chem. (2) **62**, 31 (1900); Liebermann and Jacobson, Ann. **211**, 61 (1882).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

1,4-Aminonaphthol hydrochloride

2,4-disazo derivative

benzeazo-β-naphthol

1,4-Aminonaphthol

1,4-nitronaphthol

1,4-nitrosonaphthol

α-naphthol orange

hydrochloric acid (7647-01-0)

aniline (62-53-3)

sodium hydroxide (1310-73-2)

hydrogen sulfide (7783-06-4)

sodium carbonate (497-19-8)

sulfur dioxide (7446-09-5)

1-Naphthol, 4-amino-, hydrochloride (5959-56-8)

α-naphthol, naphthol (90-15-3)

benzenediazonium chloride

aniline hydrochloride (142-04-1)

sodium nitrite (7632-00-0)

nitrous acid (7782-77-6)

nitrite (14797-65-0)

benzeneazo-α-naphthol

sodium hydrosulfite (7775-14-6)

aminonaphthol

aminonaphtholhydrochloride, aminonaphthol hydrochloride (41772-23-0)

β-naphthol (135-19-3)

hydrosulfite

aminophenol (95-55-6)

aminophenol hydrochloride (51-19-4)

tin (7440-31-5)

Phenylhydrazine (100-63-0)

stannous chloride

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p-AMINOPHENYLACETIC ACID

[α-Toluic acid, *p*-amino-]

$$p\text{-}NO_2C_6H_4CH_2CO_2H + 3(NH_4)_2S + 3H_2O \longrightarrow p\text{-}NH_2C_6H_4CH_2CO_2NH_4 + 3S + 5NH_4OH$$

$$p\text{-}NH_2C_6H_4CH_2CO_2NH_4 + CH_3CO_2H \longrightarrow p\text{-}NH_2C_6H_4CH_2CO_2H + CH_3CO_2NH_4$$

Submitted by G. Ross Robertson
Checked by H. T. Clarke and J. H. Bishop.

1. Procedure

A 1500-cc. flask is fitted with a two-holed rubber stopper carrying a glass tube which ends below the middle of the flask. The second hole is fitted with a common glass stopcock (Note 1). To the flask is added 500 cc. of 6 *N* aqueous ammonia (sp. gr. about 0.95), and 100 g. (0.55 mole) of *p*-nitrophenylacetic acid (p. 406) is now slowly introduced, with shaking. The flask is then placed in an ice bath, and the mixture saturated with hydrogen sulfide, the temperature being held below 50°.

The stopper is removed from the reaction flask, and the solution of ammonium *p*-aminophenylacetate gently boiled under the hood until nearly all the excess hydrogen sulfide and ammonia have escaped. The solution changes from a dark orange-red to a pale yellow. The deposited sulfur is filtered off by suction, and 40 cc. of glacial acetic acid rapidly stirred into the hot filtrate. The *p*-aminophenylacetic acid which crystallizes out weighs 69–70 g., but it is contaminated with a small amount of free sulfur. On evaporating the mother liquor to a small volume, about 5 g. more can be obtained. The crude material is recrystallized from 4 l. of distilled water, 69–70 g. (83–84 per cent of the theoretical amount) of a product which melts at 199–200° being thus obtained (Note 2).

2. Notes

1. The use of a stopcock in the reaction flask during the saturation with hydrogen sulfide permits the occasional expulsion of hydrogen gas, which would otherwise accumulate. Apparently, commercial ferrous sulfide contains free iron as an impurity.
2. The procedure avoids the troubles of filtration incidental to the method of reduction with ferrous sulfate and ammonia, and the yield is better. Inasmuch as the only by-product is the very soluble ammonium acetate, a large yield can be secured by close evaporation.

3. Discussion

p-Aminophenylacetic acid can be prepared by the hydrolysis of *p*-aminobenzyl cyanide with concentrated hydrochloric acid,[1] and by the reduction of *p*-nitrophenylacetic acid with

tin and hydrochloric acid[2] or with ferrous sulfate and ammonia.[3] Reduction of *p*-nitrophenylacetic acid with a platinum oxide catalyst is reported to furnish a quantitative yield of *p*-aminophenylacetic acid, but, because of more favorable solubilities, it is recommended that the ethyl ester be reduced and the reduction product then hydrolyzed to the acid.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 63

References and Notes

1. Friedländer, Ber. **17**, 237 (1884); Gabriel, Ber. **15**, 835 (1882).
2. Radziszewski, Ber. **2**, 209 (1869); Bedson, J. Chem. Soc. **37**, 92 (1880).
3. Jacobs and Heidelberger, J. Am. Chem. Soc. **39**, 1437 (1917); Robertson and Stieglitz, ibid. **43**, 180 (1921).
4. Ferber and Bendix, Ber. **72**, 839 (1939).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethyl ester

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ammonia (7664-41-7)

ammonium acetate (631-61-8)

hydrogen (1333-74-0)

iron (7439-89-6)

hydrogen sulfide (7783-06-4)

tin (7440-31-5)

α-Toluic acid (65-85-0)

sulfur (7704-34-9)

ferrous sulfide

ferrous sulfate (13463-43-9)

platinum oxide

p-AMINOPHENYLACETIC ACID (1197-55-3)

p-Nitrophenylacetic acid (104-03-0)

ammonium p-aminophenylacetate

p-aminobenzyl cyanide (3544-25-0)

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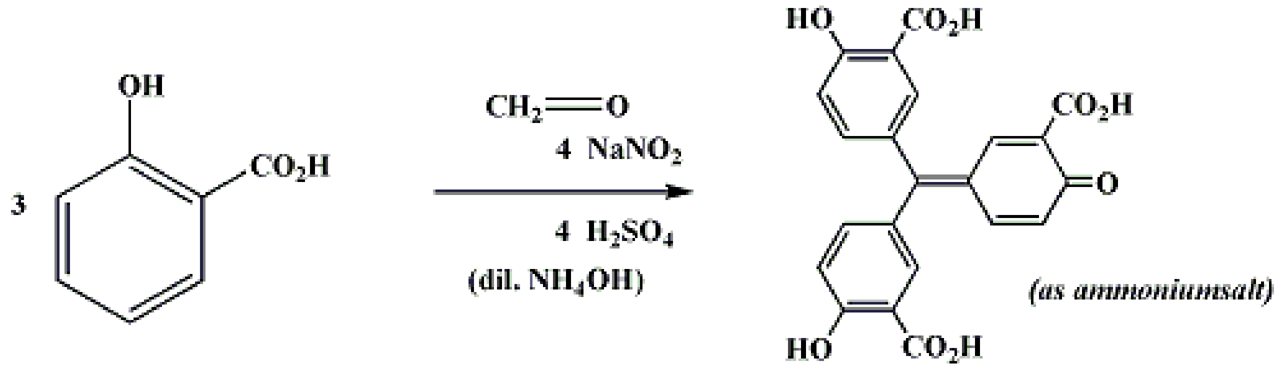
AMMONIUM SALT OF AURIN TRICARBOXYLIC ACID



Submitted by G. B. Heisig and W. M. Lauer.
Checked by H. T. Clarke and Ross Phillips.

1. Procedure

To 70 cc. of concentrated sulfuric acid (Note 1) in a 1-l. short-necked flask fitted with a mechanical stirrer and immersed in an ice-water bath is added, with vigorous stirring, 10 g. (0.145 mole) of solid sodium nitrite in small portions. The addition is made at such a rate that only a very small amount of nitrogen oxide is evolved. When solution is complete, 20 g. (0.145 mole) of salicylic acid is added in small portions with stirring; about fifteen minutes is required. The mixture is stirred at 20° until all the solid is in solution (Note 2). The mixture should then be light red to brown in color, very viscous, and quite homogeneous. It is surrounded by an ice-salt bath, and, when the temperature reaches 0°, 5 cc. (0.065 mole) of a 35–40 per cent solution of formaldehyde (formalin) (see Note 1 on p. 378) is slowly added with extremely vigorous stirring, at such a rate that the temperature does not rise above 5° (Note 3). The reaction is complete a few minutes after all the formaldehyde has been added. About 100 g. of finely crushed ice is then added, followed by 500 cc. of ice water; the stirring should be vigorous during the addition (Note 4). The contents of the flask are stirred until the aurin tricarboxylic acid has disintegrated into small pieces.

The solid is washed several times by decantation, using cold water, and finally filtered with suction. It is then dissolved in dilute ammonia (1 volume of concentrated ammonia with 2 volumes of water) while it is still on the filter paper in the suction funnel (Note 5). The filtrate is evaporated to dryness on a steam bath. The resulting glassy, light yellowish-brown ammonium salt, which weighs 19–22 g. (83–96 per cent of the theoretical amount) is sufficiently pure (Note 6) for use as a test for aluminum.[1]

2. Notes

1. The reaction may be carried out somewhat less satisfactorily with the use of 55 cc. of sulfuric acid.
2. If solution is not complete, unchanged salicylic acid will be present in the final product.

3. If the stirring is quite violent, the temperature may be allowed to rise somewhat higher, say to 15–20°, but if the temperature is allowed to rise with only moderate stirring, the yield is lowered, owing to the formation of tars.
4. Foaming may occur during the addition of the water but this can be controlled by adding a few drops of ether.

5. The purification of the crude aurin tricarboxylic acid by extracting with hot water[1] is undesirable, for the hot water causes the acid to soften, and results in the formation of large viscous semiliquid masses which cannot be washed readily.
6. The method suggested by Caro[2] for the purification of aurin tricarboxylic acid seems to be unnecessary when the dye is to be used as a test for aluminum.[1] In the method the crude product is dissolved in sodium hydroxide, sodium bisulfite is added until the solution is decolorized, and the addition compound of the free acid is precipitated by adding hydrochloric acid.

3. Discussion

The preparation of aurin tricarboxylic acid was first described in a patent[3] granted to Geigy, in which the foregoing method is embodied in one of the examples; another method, involving the action of sodium nitrite upon a warm solution of salicylic acid in a mixture of methyl alcohol and sulfuric acid, is also described in the same patent. It can also be prepared[2] by the action of sulfuric acid and nitrite upon a mixture of salicylic acid and 3,3'-dicarboxy-4,4'-dihydroxydiphenylmethane ("methylene disalicylic acid"), which is formed from salicylic acid with formaldehyde in presence of hydrochloric acid.

References and Notes

1. Hammett and Sottery, J. Am. Chem. Soc. **47**, 142 (1925).
2. Caro, Ber. **25**, 939 (1892).
3. Geigy, Ger. pat. 49,970 [Frdl. **2**, 50 (1891)]; Holaday, J. Am. Chem. Soc. **62**, 989 (1940).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

methyl alcohol (67-56-1)

ether (60-29-7)

sodium hydroxide (1310-73-2)

formaldehyde, formalin (630-08-0)

sodium nitrite (7632-00-0)

nitrite (14797-65-0)

AMMONIUM SALT OF AURIN TRICARBOXYLIC ACID (569-58-4)

nitrogen oxide

salicylic acid

aurin tricarboxylic acid

aluminum (7429-90-5)

sodium bisulfite (7631-90-5)

3,3'-dicarboxy-4,4'-dihydroxydiphenylmethane

methylene disalicylic acid

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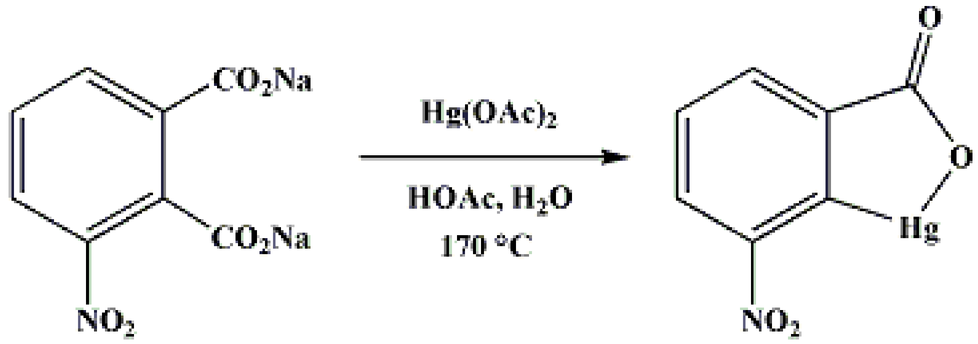
ANHYDRO-2-HYDROXYMERCURI-3-NITROBENZOIC ACID

[Benzoic acid, anhydro-2-hydroxymercuri-3-nitro-]



Submitted by Frank C. Whitmore, P. J. Culhane, and H. T. Neher.
Checked by Henry Gilman and C. C. Vernon.

1. Procedure

A solution of 80 g. (2 moles) of sodium hydroxide in 800 cc. of water is prepared in a 2-l. beaker. To the warm solution is added 211 g. (1 mole) of 3-nitrophthalic acid (p. 408) (Note 1). A small amount of insoluble material is removed by filtration through a large preheated Büchner funnel (Note 2). A solution of 350 g. (1.1 moles) of mercuric acetate (Note 3) in a mixture of 50 cc. of glacial acetic acid and 700 cc. of water is prepared by heating and filtering while hot (Note 4). The two hot solutions are poured into a 3-l. long-necked flask and mixed by shaking. No precipitate should separate (Note 5). The flask is clamped in a large oil bath (Note 6) with the level of the oil almost to the neck of the flask. It is fitted with a reflux condenser provided with a tube leading to a large beaker placed on the desk (Note 7).

The temperature of the oil bath is raised to 170° over a period of about one hour. If any considerable amount of material is driven through the condenser, it is poured back through the top of the condenser as soon as the reaction slackens. The heating at 165–175° is continued for about seventy hours. After about sixty hours the end of the tube leading from the top of the condenser is introduced below the surface of about 1 cc. of mercury in a small test tube. The evolution of carbon dioxide can be followed by observing the bubbles which pass through the mercury. When not more than one or two bubbles escape per minute, the heating is discontinued (Note 8).

The product is allowed to settle and the hot supernatant liquid is poured through a preheated suction filter. The filtrate deposits less than 10 g. of crude product on cooling. The product in the flask is shaken with several 100-cc. portions of water, and all the fine material is transferred to the filter. Some lumpy material is usually left in the flask. This is transferred to a large mortar and ground to a paste with a little water

and then transferred to the filter. After sucking as dry as possible, the suction is shut off, and 100 cc. of alcohol is poured over the material on the filter. After standing a few minutes, suction is again applied. The product is then dried to constant weight (Note 9). The yield of anhydro-2-hydroxymercuri-3-nitrobenzoic acid is 300–330 g. (82–90 per cent of the theoretical amount based on the 3-nitrophthalic acid used). It is a cream-colored powder which dissolves in an excess of dilute sodium hydroxide, leaving only a slight turbidity (Note 10) and (Note 11).

2. Notes

1. 3-Nitrophthalic acid melting above 200° (sealed tube) is pure enough for this preparation.
2. Although the insoluble material is very small in amount, filtration without suction is too slow.
3. Commercial mercuric acetate, about 90 per cent pure, was used. The equivalent amounts of mercuric oxide and acetic acid may be used if the acetate is not available.
4. A small amount of mercurous compounds is removed by the filtration.
5. If more concentrated solutions are used, the mercuric salt precipitates and the reaction runs less smoothly.
6. A large galvanized pail containing extra heavy lubricating oil was used. This oil does not fume even after heating for long periods.
7. This beaker serves to catch any material which is carried over during a slightly violent reaction which sometimes takes place at the beginning.
8. If a more accurate indication of the end of the reaction is desired, a tube containing mercury may be inverted in a small beaker of mercury and any gas evolved during the later stages of the reaction may be collected over the mercury.
9. The wet material may be used without drying for the preparation of 2-bromo-3-nitrobenzoic acid (p. 125).
10. To dissolve the mercury compound it should be dusted into boiling sodium hydroxide solution.
11. By a similar procedure phthalic anhydride may be converted into anhydro-*o*-hydroxymercuribenzoic acid. Thus, 300 g. (2 moles) of phthalic anhydride and 750 g. (2.2 moles) of commercial mercuric acetate (Note 3) give 550 g. of the mercury compound (85 per cent of the theoretical amount). With phthalic anhydride the reaction is complete in six to ten hours.

3. Discussion

Anhydro-2-hydroxymercuri-3-nitrobenzoic acid has been prepared only in accordance with the procedure described.[1]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 125

References and Notes

1. Whitmore and Culhane, J. Am. Chem. Soc. **51**, 602 (1929).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Anhydro-2-hydroxymercuri-3-nitrobenzoic acid

Benzoic acid, anhydro-2-hydroxymercuri-3-nitro-

mercurous compounds

mercuric salt

mercury compound

Anhydro-o-hydroxymercuribenzoic acid

alcohol (64-17-5)

acetic acid (64-19-7)

sodium hydroxide (1310-73-2)

3-Nitrophthalic acid (603-11-2)

mercuric acetate (1600-27-7)

mercury (7439-97-6)

carbon dioxide (124-38-9)

mercuric oxide (21908-53-2)

acetate

2-Bromo-3-nitrobenzoic acid (573-54-6)

phthalic anhydride (85-44-9)

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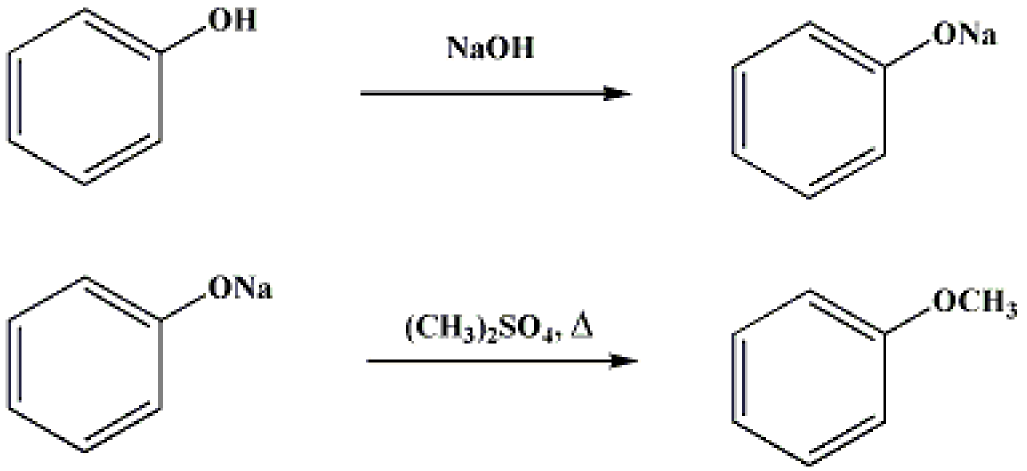
ANISOLE



Submitted by G. S. Hiers and F. D. Hager.
Checked by Henry Gilman, S. A. Harris, and G. F. Wright.

1. Procedure

In a 5-l., three-necked, round-bottomed flask fitted with an efficient stirrer, separatory funnel, and reflux condenser is placed a mixture of 235 g. (2.5 moles) of phenol and 100 g. (2.5 moles) of sodium hydroxide (Note 1) in 1 l. of water. The mixture is cooled, with stirring, in an ice-salt bath to below 10°. There is then added through the separatory funnel, with stirring, 315 g. (235 cc., 2.5 moles) of dimethyl sulfate (Note 2). This addition requires about one hour, and the cooling bath is not removed until the addition is complete. The mixture is then heated on a water bath for one-half hour. At the end of this time there is added through the separatory funnel a mixture of 235 g. (2.5 moles) of phenol and 100 g. (2.5 moles) of sodium hydroxide in 1 l. of water. This addition requires about fifteen minutes. The mixture is then refluxed vigorously over a free flame for fifteen hours (Note 3).

The mixture is cooled and the anisole layer is separated. The aqueous portion is extracted with about 200 cc. of benzene (Note 4). The combined anisole-benzene portion is washed once with water, dried over calcium chloride and distilled from a modified Claisen flask (p. 130). The portion boiling at 100–153° is refractionated. The main fraction distils at 153–154°/748 mm. The yield is 388–405 g. (72–75 per cent of the theoretical amount) (Note 5) and (Note 6).

2. Notes

1. The sodium hydroxide was a high quality technical grade.
2. Dimethyl sulfate is toxic, but with due care to avoid spattering of the liquid and inhaling of the vapor the operation may be carried out without the use of a hood. Ammonia is a specific antidote for dimethyl sulfate and should be kept at

hand to destroy any of the ester accidentally spilled.
A good technical grade of dimethyl sulfate was used.

3. When the period of refluxing is shorter, the yield is materially decreased. The first methyl group reacts easily but the second only with considerable difficulty. A longer period of refluxing does not give much larger yields. As the sodium sulfate concentration increases, the dimethyl sulfate hydrolyzes less readily. It is recommended that the addition of dimethyl sulfate is best effected at the lowest temperature where reaction takes place readily. With phenol this is 25–35°. For the second methyl group, the mixture is not refluxed but the anisole is boiled out, during which time the reaction completes itself (W. W. Hartman, private communication).

4. A separate fractional distillation of this benzene extract yields 9–18 g. of anisole. The major part of the anisole contained in the aqueous layer may be recovered by steam distillation instead of a benzene extraction. Neither method of recovery is wholly satisfactory.

5. When only one-half the amount of phenol is used, the yield is 85–92 per cent but with fairly inexpensive phenol it is more profitable to operate in such a manner that both methyl groups of the dimethyl sulfate are used.

6. Other methyl ethers may be prepared by a similar procedure. Methyl β-naphthyl ether is obtained in a 65–73 per cent yield by adding the dimethyl sulfate over a period of thirty minutes to equivalent quantities of β-naphthol and sodium hydroxide kept cool by an ice-water bath, then heating for one hour at 75–78°, and, finally, crystallizing from benzene to obtain the pure methyl ether which melts at 71°.

3. Discussion

Anisole can be prepared from phenol or its salts by the use of the following methylating agents: methyl chloride;[1] sodium methyl sulfate;[2] methyl alcohol in the presence of thorium oxide;[3] methyl alcohol and β-naphthalenesulfonic acid[4] or potassium hydrogen sulfate[5] or boron fluoride;[6] dimethyl sulfate;[7] and methyl ether and boron fluoride.[8]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

anisole-benzene

calcium chloride (10043-52-4)

ammonia (7664-41-7)

Benzene (71-43-2)

methyl alcohol (67-56-1)

sodium hydroxide (1310-73-2)

phenol (108-95-2)

sodium sulfate (7757-82-6)

β-naphthol (135-19-3)

Anisole (100-66-3)

dimethyl sulfate (77-78-1)

Methyl β-naphthyl ether (93-04-9)

methyl ether (115-10-6)

methyl chloride (74-87-3)

sodium methyl sulfate (512-42-5)

thorium oxide

β-naphthalenesulfonic acid (120-18-3)

potassium hydrogen sulfate (7646-93-7)

boron fluoride (7637-07-2)

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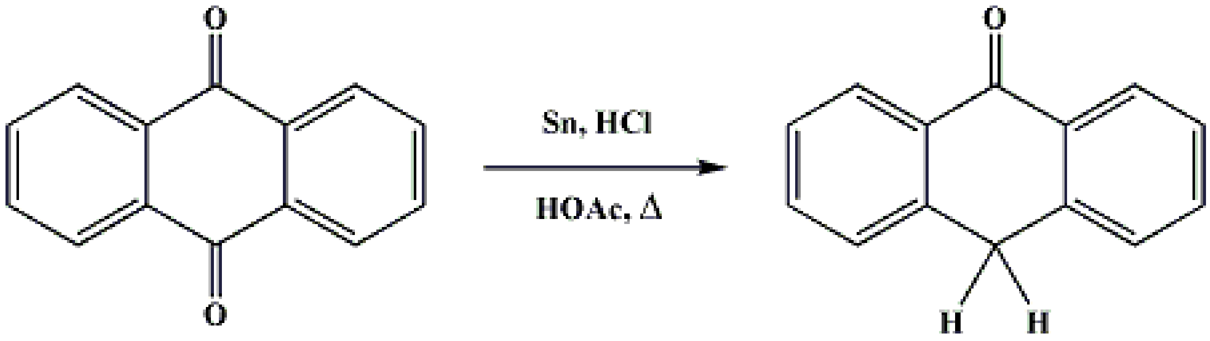
ANTHRONE



Submitted by Kurt H. Meyer
Checked by J. B. Conant and W. C. Boyd.

1. Procedure

In a 2-l. round-bottomed flask with a reflux condenser, 104 g. (0.5 mole) of anthraquinone, m.p. 276–280° (corr.), is mixed with 100 g. (0.86 atom) of granulated tin, and 750 cc. of glacial acetic acid is added. The contents of the flask are heated to boiling, and in the course of two hours, 298 g. (250 cc., 8.2 moles) of c.p. hydrochloric acid (sp. gr. 1.19) is added in 10-cc. portions to the boiling mixture. At the end of this time all the anthraquinone should have gone into solution; if not, more tin and hydrochloric acid are added.

The liquid is filtered with suction through a Gooch crucible with a fixed porous plate (Note 1), and 100 cc. of water is added. The anthrone crystallizes when the solution is cooled to about 10°. The crystals are filtered with suction on a Büchner funnel and washed with water. After drying on a porous plate the melting point of the material is about 153°. The yield is 80 g. (82.5 per cent of the theoretical amount). On recrystallization from a 3:1 mixture (Note 2) of benzene and petroleum ether about 60 g. of anthrone melting at 154–155° (corr.) is obtained (62 per cent of the theoretical amount).

2. Notes

1. The liquid can also be filtered through a fluted filter paper, but this is slower.
2. The proportions do not make much difference as far as the yield is concerned, but the substance is more soluble in mixtures rich in benzene. About 10–12 cc. of the 3:1 mixture is required for each gram of anthrone. The anthrone may be more readily dissolved if it is added to the estimated quantity of hot benzene on the steam bath, and the petroleum ether is then added. About two-thirds of the mother liquor may be distilled off through a condenser and used in later runs. The residual mother liquor deposits about 12 g. of rather impure anthrone.

3. Discussion

Anthrone can be prepared by the reduction of anthraquinone with tin and hydrochloric acid,[1] and with aluminum bronze,[2] or by cyclization of *o*-benzylbenzoic acid with liquid hydrogen fluoride.[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 390

References and Notes

1. Meyer, Ann. **379**, 55 (1911).
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3. Fieser and Hershberg, J. Am. Chem. Soc. **61**, 1278 (1939).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

aluminum bronze

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

tin (7440-31-5)

Anthrone (90-44-8)

Anthraquinone (84-65-1)

hydrogen fluoride (7664-39-3)

o-benzylbenzoic acid (612-35-1)

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APPARATUS FOR CATALYTIC REDUCTION

Submitted by Roger Adams and V. Voorhees.
Checked by Henry Gilman and S. A. Harris.

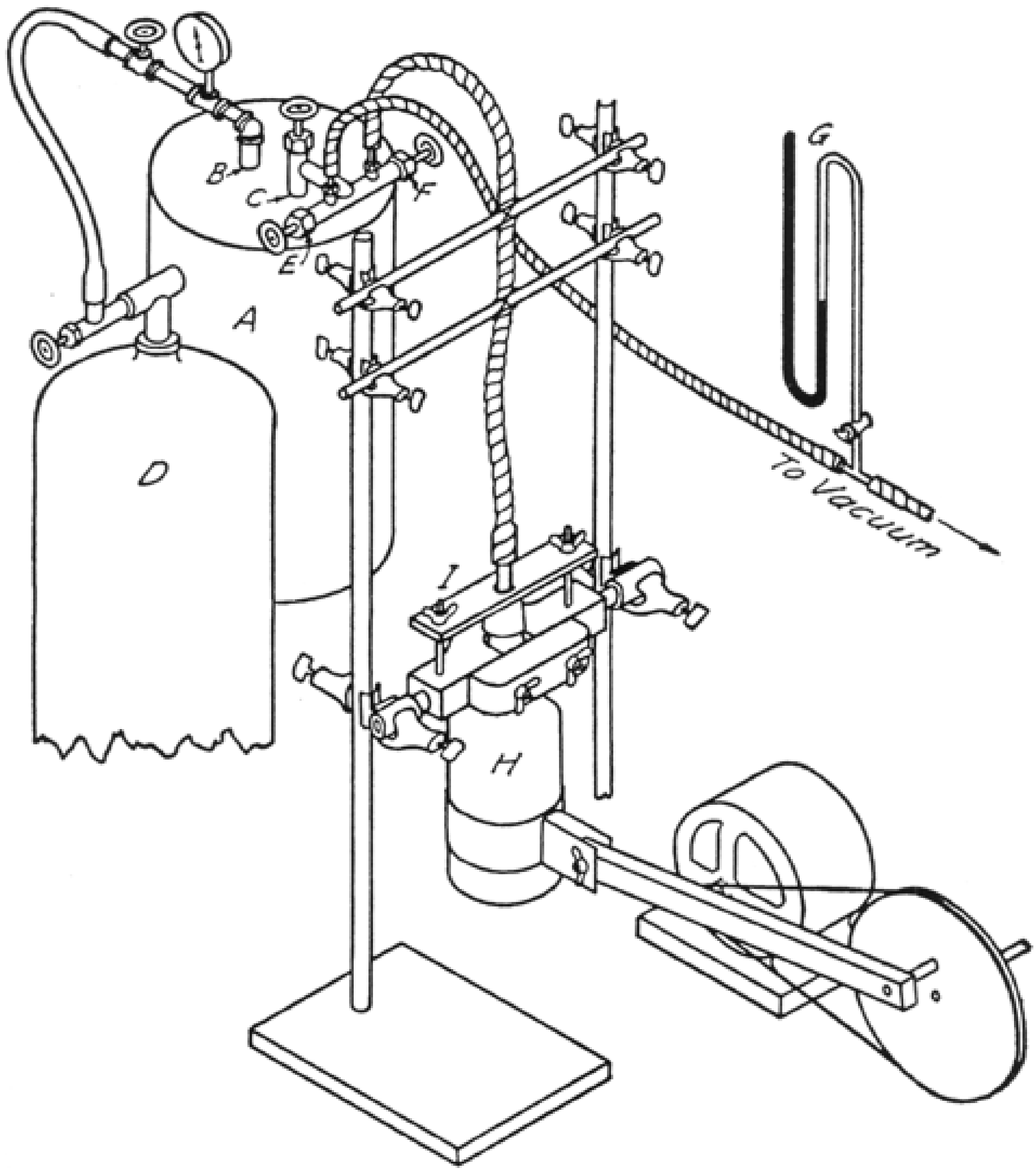
1. Procedure

(*A*) *Apparatus* (Fig. 5).—A Prest-o-lite tank A from which the filling has been removed (Note 1), or any other similar tank of about 8- to 10-l. capacity, may be conveniently used as a container for hydrogen. The top of the tank contains two openings B and C. In B is welded a tube holding a gauge and valve, and through this tube the hydrogen from a large cylinder D is introduced into the tank. In C is welded another tube controlled by a needle valve. E is used for the vacuum, a manometer G being introduced into this system, and F for a tube leading to the reaction bottle H. These outlets are so arranged that it is possible to shut off the tank from either outlet and also to make a direct connection between the vacuum and the bottle H, leaving tank A out of the circuit. The connection between the tank A and the bottle H is a heavy taped rubber tube (Note 2) which is in turn connected to a glass tube inserted through the stopper of the bottle. The rubber tube and stopper should be of high grade and must be carefully boiled with alkali before being used (Note 3). The arrangement for shaking the bottle is shown in the diagram (Note 4). The driving pulley is connected to the reaction bottle by a wooden or preferably a metal rod. The rod in turn is attached by a yoke to a metal ring which circles the bottom of the bottle. The ring opens on the back side of the bottle and is held together by a wing-nut and bolt. In order to hold the stopper in the bottle when the latter is filled with hydrogen under pressure, a metal strip I is clamped tightly over the stopper. This strip is screwed to the long wooden bottle holder which extends between the bearings, and a short wooden piece which fits around the neck of the bottle is attached to the longer one by means of screws held by wingnuts. This arrangement permits removal of the bottle from the apparatus without detaching the metal strip.

The chief precautions in setting up this reduction outfit are, first, to have every piece free from catalytic poisons, and second, to be certain that there are no leaks (Note 5). The latter are sometimes an annoying factor, and the complete apparatus should be carefully tested before attempting any reductions for standardizing the hydrogen tank. The apparatus is put together in final form with the empty reduction bottle attached to the hydrogen tank exactly as it is arranged in a reduction. The tank is then filled with hydrogen until the gauge reads 2.5–3 atm. (40–45 lb.) and the temperature of the tank recorded. The reading of the gauge is observed as soon as equilibrium is reached and the bottle is then shaken for six to eight hours. Observations are made of the drop in pressure, taking into account any change of temperature which may occur during this time. In general if the drop in pressure is less than 0.03 atm. (0.5 lb.) in the time indicated the apparatus may be considered sufficiently free from leaks for ordinary work.

For some reactions it is advantageous to heat the mixture, and the following arrangement is very satisfactory for this purpose. The bottle H is wrapped with moistened asbestos paper to a thickness of about 3 mm. and the paper is then allowed to dry. When the asbestos is thoroughly dry the bottle is wound with a coil of No. 24 Nichrome wire, beginning the coil at the bottom of the bottle and making the turns about 9 mm. apart. The wire is then covered with a 3-mm. layer of asbestos, which is moistened and allowed to dry, after which the wire is wound around the bottle in another coil from top to

Fig. 5.



bottom. The second coil is covered with asbestos as before, and the ends of the wire are connected to the terminal wires from a source of current. These wires are led along the bottle to the neck and held by means of tape in order to avoid excessive shaking. A variable resistance in the circuit is used to regulate the temperature.

(*B*) *Use of Apparatus*.—The tank A is filled with hydrogen to a pressure of 3–3.5 atm. from the cylinder D (Note 6). The solution in a suitable solvent, of the substance to be reduced is poured into the bottle H and the platinum oxide (p. 463) is added (Note 7) and (Note 8). The bottle is attached to the apparatus and evacuated by opening valves E and F and closing C. In the case of low-boiling solvents, the evacuation is continued only until the solvent begins to boil; in other cases it is continued until the pressure as recorded by the manometer remains fairly constant. The valve E is then closed and hydrogen is admitted to the bottle H from the tank A by opening valve C (Note 9) and (Note 10). When the pressure in the bottle has become adjusted the pressure of the hydrogen and the temperature of the tank A are recorded. Shaking is started. Within a few minutes the brown platinum oxide turns black (see Note 6 on p. 467), and the absorption of hydrogen begins. The shaking is continued until the theoretical amount of hydrogen has been absorbed.

The hydrogen remaining in the bottle is removed, air is admitted and the mixture allowed to stand or, if necessary, shaken for a few minutes in order to aid the settling of the catalyst. In certain cases where the catalyst settles spontaneously at the end of the reduction it is not necessary to shake the mixture with air. The solution may be decanted from the main portion of the catalyst and a second reduction carried out. In cases where the catalyst cannot be used directly for another reduction (see Note 9 on p. 468) the solution is filtered, preferably through an asbestos filter (Note 11), and fresh solvent is used for washing. The reduction product is isolated from the filtrate, usually by distilling off the solvent. The reduction of ethyl *p*-nitrobenzoate to ethyl *p*-aminobenzoate (p. 240) and benzalacetophenone to benzylacetophenone (p. 101) is described in detail.

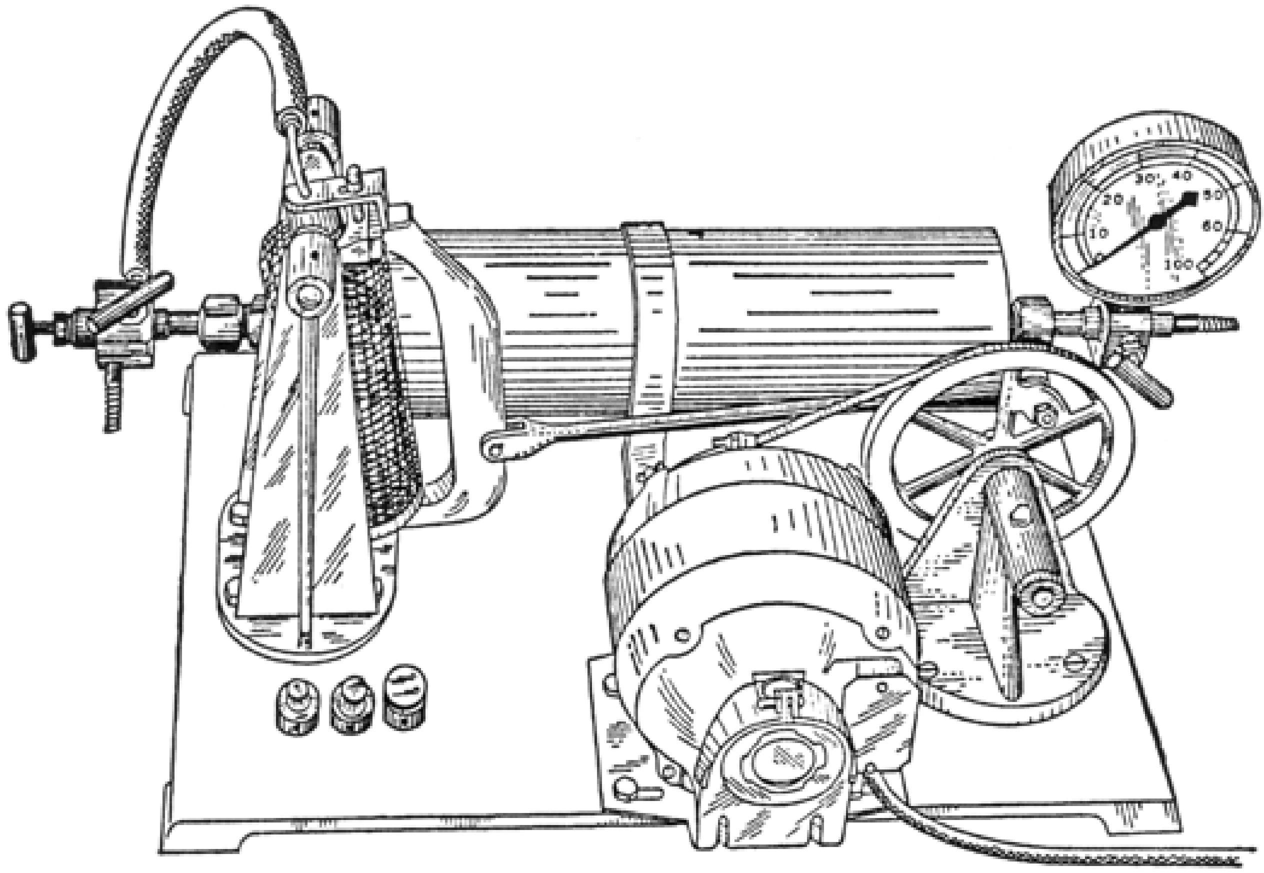
(*C*) *Standardization of Apparatus*.—After making certain that there are no leaks in the apparatus (Note 5) the hydrogen tank may be standardized by reducing 11.6 g. (0.1 mole) of pure maleic acid (Note 12) dissolved in 150 cc. of 95 per cent alcohol using 0.1 g. of catalyst (p. 463). The reduction is carried out according to the procedure described in part (*B*). Shaking of the mixture is continued until no more hydrogen is absorbed; the theoretical amount is absorbed by 0.1 mole of maleic acid within twenty or thirty minutes. The temperature of the tank is recorded. The decrease in pressure corresponds to 0.1 mole of hydrogen at the observed temperature. If the succinic acid is desired it may be recovered merely by filtering the platinum, evaporating the alcohol and crystallizing from about 10–15 cc. of boiling water. The yield of product is 10–11.5 g. (84–98 per cent of the theoretical amount) depending on the care used in crystallization.

2. Notes

1. The bottom of the tank is cut off, the filling removed, and the bottom welded on again.
2. A copper tube may be used for this connection but is less satisfactory since the shaking tends to wear it out at the joints.
3. It is advisable to boil the tube and stopper with several portions of 20 per cent sodium hydroxide until the solution is no longer colored yellow, after which the boiling is carried out several times with distilled water.
4. The motor, pulley and the supports for the reaction vessel must be attached firmly to a heavy wooden stand which will allow as little motion as possible in the apparatus during shaking, thus reducing to a minimum the possibility of the gradual formation of leaks.

The arrangement for shaking should be so made that the reaction bottle is agitated at a rate above which no difference in the speed of reduction is observed. A suitable motor is a 1/30 h. p., 1760 r.p.m., the pulley on the motor 2.5 cm. in radius, and the wooden driving pulley 7.5 cm. in radius. The distance from the center of the pulley to the hole for attaching the rod to the reaction bottle is 3.2 cm.; the distance from the center of the pulley on the motor to the center of the driving pulley to the bottle attachment is 30 cm. Considerable latitude is possible in these measurements. Although the apparatus in Fig. 5 is readily set up in any laboratory, a more compact and more stable form is shown in Fig. 6. An apparatus similar to this can be purchased complete from the Parr Instrument Co., Moline, Ill.

Fig. 6.



5. It is quite necessary that the welding of the tank be perfect and free from pin holes. Leaks frequently appear where the tubes are welded in the top of the tank. These may be eliminated by brazing the joints. A less satisfactory way is to use a cement of litharge and glycerol. This cement may also be used with success on leaky valves. Occasionally leaks occur in the rubber tubing or its connections with the bottle or tank, but these are unusual.

6. Electrolytic hydrogen was used in all experiments. This hydrogen is essentially free from all impurities except oxygen. Since oxygen in general has no harmful effect upon the reduction, no purification is necessary. If, however, oxygen-free hydrogen is needed, it must be passed over heated platinized asbestos.

7. This procedure may be varied in certain cases where it seems advantageous to reduce the platinum oxide to platinum black in the presence of the solvent alone (see Note 12 on p. 469).

8. During the course of the catalytic hydrogenation of carotin, using hexahydrobenzene and acetic acid as the solvent, it became necessary to add fresh platinum oxide catalyst. The reaction bottle was opened and immediately the powdered catalyst was added. As soon as the catalyst came in contact with the gas in the bottle an explosion resulted (H. A. Spoehr, private communication).

The above experience warrants precaution during addition of the catalyst. However, the experience of the editors in hundreds of catalytic reduction operations extending over more than ten years shows that such explosions are extraordinarily rare.

9. During the reductions it is usually advisable not to allow the pressure in the tank A to drop below about 2 atm. if the reduction is to be carried out in minimum time. When the gauge registers 2 atm. the tank is closed off from the reducing bottle and the pressure is increased to about 3–3.5 atm. by the admission of more hydrogen from D.

10. Ordinarily traces of air in the hydrogen have no deleterious effect upon the reductions. If, in any experiment, absolute freedom from air is desired the bottle may be evacuated and refilled with hydrogen two or more times. In this way the air is all washed out of the bottle.

11. When paper filters are used, the rapid suction of air through the paper in the presence of the catalyst often causes spontaneous combustion of the filter. Paper filters may be used,

however, if care is taken to keep the filter covered with solvent while suction is being applied; just before the last portion of solvent has run through, the suction is stopped.
12. Instead of pure maleic acid, 10.6 g. (0.1 mole) of pure benzaldehyde may be used for the standardization. In this case 1 cc. of 0.1 molar ferrous sulfate is added to the mixture of benzaldehyde, alcohol and catalyst before the reduction is started (see Note 13 on p. 469). The reduction is complete in fifteen to thirty minutes.

3. Discussion

Other forms of catalytic reduction apparatus which may be used in the laboratory are described in the following articles.[1]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 101
- Org. Syn. Coll. Vol. 1, 240
- Org. Syn. Coll. Vol. 1, 463
- Org. Syn. Coll. Vol. 2, 191
- Org. Syn. Coll. Vol. 2, 566
- Org. Syn. Coll. Vol. 3, 63
- Org. Syn. Coll. Vol. 3, 501
- Org. Syn. Coll. Vol. 3, 519
- Org. Syn. Coll. Vol. 4, 304
- Org. Syn. Coll. Vol. 4, 603
- Org. Syn. Coll. Vol. 4, 928
- Org. Syn. Coll. Vol. 5, 60
- Org. Syn. Coll. Vol. 5, 239
- Org. Syn. Coll. Vol. 5, 346
- Org. Syn. Coll. Vol. 5, 552

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

carotin

alcohol (64-17-5)

acetic acid (64-19-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

glycerol (56-81-5)

oxygen (7782-44-7)

ferrous sulfate (13463-43-9)

platinum oxide

Benzalacetophenone (94-41-7)

Benzylacetophenone (1083-30-3)

maleic acid (110-16-7)

Succinic acid (110-15-6)

platinum (7440-06-4)

copper (7440-50-8)

hexahydrobenzene (110-82-7)

benzaldehyde (100-52-7)

Ethyl p-aminobenzoate (94-09-7)

ethyl p-nitrobenzoate (99-77-4)

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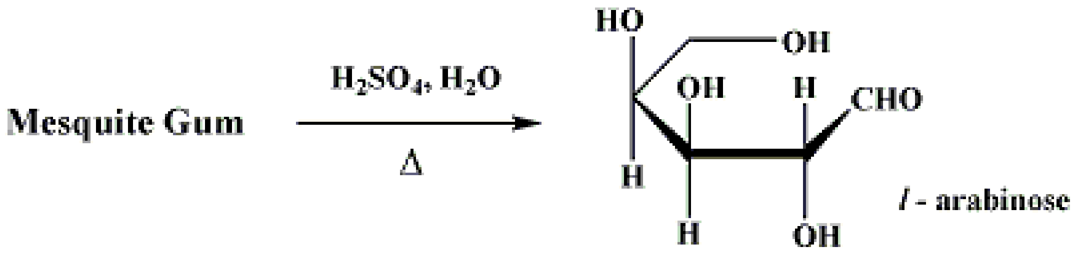
l-ARABINOSE



Submitted by Ernest Anderson and Lila Sands.
Checked by H. T. Clarke and H. J. Bean.

1. Procedure

Five hundred grams of mesquite gum (Note 1) is dissolved (Note 2) in 3 l. of cold water in a 5-l. round-bottomed flask; a cold solution of 125 g. of concentrated sulfuric acid in 80 cc. of water is added and the mixture warmed at 80° for six hours (Note 3) in a large water bath. The acid is neutralized by gradual addition of 140 g. of powdered calcium carbonate (Note 4), and the solution with excess calcium carbonate is heated in a boiling water bath for one hour to complete the neutralization. The calcium sulfate is filtered off and washed with about 2 l. of hot water. The filtrate is concentrated in an evaporating dish (Note 5) on the boiling water bath to a volume of 650–700 cc.

The solution is transferred to a 3-l. flask, using about 50 cc. of water for rinsing, and to it is added, with violent (Note 6) shaking, twice its volume (1400–1500 cc.) of 95 per cent ethyl alcohol. The solution is decanted from the gummy residue and the latter extracted three times with methyl alcohol under reflux, each time with 500 cc. of the solvent. In order to remove all the arabinose from the salts the precipitate is dissolved in 200–220 cc. of water, transferred to an evaporating dish, and 400 cc. of 95 per cent ethyl alcohol is stirred in with a heavy rod. The clear alcohol solution is decanted and the solid triturated twice with 300-cc. portions of methyl alcohol. All the alcoholic extracts (both ethyl and methyl) are combined, shaken thoroughly, and 95 per cent ethyl alcohol added as long as any appreciable precipitate forms (Note 7). The solution is allowed to stand for some hours until it is clear, decanted, and concentrated under reduced pressure on a boiling-water bath to a thin sirup (Note 8). Crystallization usually begins as soon as the sirup is cool, though it is sometimes necessary to seed with arabinose.

After crystallization has begun, 100 cc. of 95 per cent ethyl alcohol is stirred in, care being taken not to precipitate any appreciable amount of gum. Crystallization is allowed to become complete in a cool place, occasionally stirring with a heavy rod. After about two days the crystalline arabinose is filtered off and washed with 200 cc. of 95 per cent ethyl alcohol. To secure further crops of arabinose from the mother

liquor and washings, the solvent is distilled off under reduced pressure on the boiling-water bath, and the residual gum dissolved in 200 cc. of hot methyl alcohol (Note 9). The solution is cooled, seeded with arabinose if necessary, set in the refrigerator for at least one day and the arabinose filtered off.

After the first two crops of crystals have been secured, the organic salts that originally dissolved along with the arabinose begin to interfere with the crystallization. To remove these, the solvent is distilled off under reduced pressure on the boiling-water bath, the residue dissolved in approximately 200 cc. of boiling methyl alcohol, and 95 per cent ethyl alcohol added slowly with shaking until no more precipitate forms (about 40 cc. is necessary). The solution is allowed to cool and is decanted from the gummy salts; the solvent is then distilled from the sugar on the steam bath, finally under reduced pressure. The sugar is dissolved in a minimum volume of hot methyl alcohol, cooled, seeded with arabinose if necessary, set in the refrigerator to crystallize and the arabinose filtered off. If an appreciable amount of mother liquor is obtained, a fourth crop of crystals can be secured without again removing the gummy salts. In this way a total yield of 180–230 g. of crude arabinose can be obtained from the gum. The first two crops of crystals are easily obtained and amount to approximately 90 per cent of the total yield. The melting point of the crude sugar varies from 147 to 152°.

The crude powdered sugar is purified by heating 200 g. of it for forty-five minutes on the boiling-water bath with 300 g. of glacial acetic acid,[1] allowing to cool, filtering off the arabinose, washing it with 500 cc. of 95 per cent ethyl alcohol in four portions, and drying at 50–60°. It then weighs about 182 g. and melts at 155–157°. It may be recrystallized from five times its weight of 76 per cent ethyl alcohol, with the use of 10 g. of decolorizing charcoal (Norite). The yield is about 127 g., and the melting point is 155–157°; the crystals are now perfectly colorless.

2. Notes

1. Mesquite gum is collected in the southwestern United States and northern Mexico. It is carried by most drug stores in this region and may be purchased from the Martin Drug Company of Tucson, Arizona.
2. If the mixture of mesquite gum and water is allowed to stand for ten hours with frequent shaking it will form a clear solution. If the mixture of gum and water is heated in the boiling water for one hour with frequent stirring the gum will also dissolve but the resulting solution is turbid.
3. Most of the arabinose is liberated during the first three hours' heating. The longer heating is necessary only in case the highest yield of arabinose is desired or the salts are to be used later for the preparation of galactose. No galactose is liberated by heating to 80° for six hours. However, some of this sugar is produced at 100° and seriously interferes with crystallization of the arabinose.
4. The solution is apt to foam over during neutralization. This may be prevented by adding to the foaming solution from time to time small amounts of *n*-butyl alcohol to break up the bubbles.

5. The solution may foam so badly that it is difficult to distil off the water under reduced pressure. In checking, it has been found possible to do so if as much as 200–300 cc. of butyl alcohol has been added during neutralization.

6. If the mixture is merely gently shaken at this point much arabinose is contained with the precipitate, and the yield falls to as low as 30 per cent of the amount obtained otherwise.

7. Appreciable amounts of organic salts dissolve during the extraction of the sugar and interfere seriously with the crystallization of the latter. Most of the salts are precipitated by addition of 95 per cent ethyl alcohol, leaving the sugar in solution.

8. If all the water is removed at this stage by heating the gum under reduced pressure for some time, the sugar will not crystallize readily.

9. Methyl alcohol, purified by distillation over quicklime, is the most satisfactory solvent for use in crystallizing the arabinose from the gummy mixture; ethyl alcohol at this stage usually causes the precipitation of a gum.

3. Discussion

Arabinose can be prepared by the hydrolysis of cherry gum,[2] beet pulp, cholla gum,[3] gum acacia[4] and mesquite gum.[5] The chief advantages of the preparation from mesquite gum are that the material is readily available in large amounts, the process is simple, and the yield relatively large. The present procedure is a modification of the original method of Anderson and Sands.[6]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethyl alcohol (64-17-5)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

methyl alcohol (67-56-1)

calcium carbonate (471-34-1)

calcium sulfate (7778-18-9)

arabinose (28697-53-2)

sugar

galactose

butyl alcohol, n-butyl alcohol (71-36-3)

decolorizing charcoal (Norite) (7782-42-5)

l-ARABINOSE

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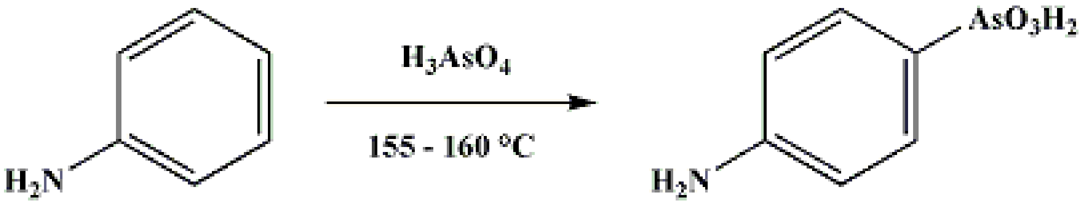
ARSANILIC ACID



Submitted by W. Lee Lewis and H. C. Cheetham.
Checked by Oliver Kamm and A. O. Matthews.

1. Procedure

To 1035 g. of sirupy arsenic acid (80–85 per cent, sp. gr. 2.00/20°; (Note 1) in a 12-inch evaporating dish, is added 828 g. (800 cc.) of aniline (Note 2) in 100-cc. portions; meanwhile the lumps of aniline arsenate which are formed are broken up by rapid stirring with a porcelain spatula. When all the aniline has been added, the powdered solid is transferred to a 3-l. round-bottomed flask equipped with a mechanical stirrer, a thermometer reaching to the lower part of the vessel, and a condenser arranged for downward distillation (Note 3); an additional 800 cc. of aniline is added and the flask heated on an oil bath at 155–160° with stirring for four and one-half hours. The mass will have assumed an intense violet color.

The reaction mixture is poured into 700 cc. of water and the flask is washed out with a portion of a previously prepared solution of 330 g. of sodium hydroxide in 1400 cc. of water, the washings being added to the reaction mixture. The remainder of the alkali is then added and the mixture agitated and cooled under the tap. At this point two distinct layers are present, a lower pink-colored alkaline water layer, and an upper strongly colored aniline layer. The water layer is, while warm, carefully separated from the purple-colored oil by means of a separatory funnel (heated to prevent the separation of sodium arsanilate) and after treatment with 15 g. of decolorizing carbon is filtered through paper.

The arsanilic acid can be obtained from the aqueous alkaline solution either as the free acid or as the sodium salt. To obtain the free acid the solution is acidified with concentrated hydrochloric acid until the purple color of tetrabromophenolsulfonphthalein is changed to a faint yellow. Care should be taken in the addition of the acid not to overstep the end-point (Note 4). Crystallization is stimulated by scratching, and the flask is allowed to stand overnight to complete the precipitation. The crystals of pinkish-yellow acid (Note 5) are filtered off, digested with 340 cc. of ethyl alcohol, filtered, and recrystallized from 2.5 l. of boiling water, adding 5–6 g. of Norite and filtering hot. This crystallization always produces a white product. The yield of thoroughly dry arsanilic acid is 147–184 g. (10.9–14.5 per cent of the theoretical amount) (Note 6), (Note 7) and (Note 8).

2. Notes

1. Arsenic acid obtained by oxidizing arsenious acid with nitric acid is satisfactory, providing all oxides of nitrogen are removed. If commercial arsenic acid is used it should be evaporated first on the water bath and then with a free flame practically to the stage of the anhydrous acid, when most of the oxides of nitrogen are driven out. water is added just before the material solidifies, and if necessary, the acid is again concentrated.
2. A good commercial grade of aniline, light in color and boiling with not more than a 1° range, may be used. It is not necessary to use a freshly distilled product.
3. During the reaction a considerable amount of water escapes, together with aniline vapors, from the reaction flask. The condenser is provided to condense and collect the distillate outside the reaction flask, and thus minimize any danger from the aniline vapors. About 200 cc. of distillate will be obtained.
4. The precipitation of arsanilic acid from the reaction mixture may cause difficulty if care is not taken to attain a definite hydrogenion concentration. The indicator consists of a 0.5 per cent solution of bromophenol blue. Filter paper dipped into this solution and dried forms a convenient test paper. That concentration of hydrogen ion at which the color of this indicator changes from purple to a faint yellow is considered the end-point. Congo red paper may also be used, but it is somewhat less sensitive.
5. A highly colored acid is occasionally obtained; under such circumstances it may become necessary to effect its purification by conversion into the sodium salt, followed by precipitation of the hot concentrated solution with alcohol, and regeneration of the acid. Colored impurities may also be eliminated by a process of fractional precipitation during the decomposition of the sodium salt, the impurities being separated with the first 25 g. fraction of the acid.
6. It is necessary to air dry the crystals of arsanilic acid at least twenty-four hours before they come to constant weight.
7. Additional amounts of arsanilic acid may be obtained from the various mother liquors. The products thus obtained are usually rather impure and hence are not considered in the yields quoted. On larger-scale production it would be economical to recover this material as well as excess aniline.
8. In preparing arsanilic acid upon a larger scale it was found that doubling the amount of aniline used and continuing the heating at 155° during twelve to sixteen hours resulted in a yield of 190–240 g. of recrystallized acid. For small-scale work, when aniline is not recovered and time is an important factor, the directions as presented seem preferable, particularly so since the arsanilic acid prepared during a short heating period is purified more readily.

3. Discussion

p-Arsanilic acid can be prepared from aniline and arsenic acid.[1] Various temperatures ranging from 150–200° and various ratios of aniline and arsenic acid have been recommended. From most of the published methods it might be inferred that this is a

smooth reaction; whereas an important side reaction consists in the oxidizing action of arsenic acid on aniline, with the production of a deeply purple-colored dye as well as much tarry material and some diarylarsonic acid. It can also be prepared by the reduction of *p*-nitrobenzenearsonic acid with iron and hydrochloric acid,[2] or by reduction of the salts of *p*-nitrobenzenearsonic acid in the presence of a nickel catalyst.[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 488

References and Notes

1. Fichter and Elkind, Ber. **49**, 239 (1916); Kober and Davis, J. Am. Chem. Soc. **41**, 451 (1919); Cheetham and Schmidt, ibid. **42**, 828 (1920); Nijk, Rec. trav. chim. **41**, 484 (1922).
2. Les Etablissements Poulenc Frères, Ger. pat. 408,575 [C. A. **23**, 849 (1929)]; Fr. pat. 636,660 [C. A. **23**, 848 (1929)].
3. Inoue and Kimura, J. Pharm. Soc. Japan **53**, 1105 (1933) [C. A. **28**, 3391 (1934)]; Stevinson and Hamilton. J. Am. Chem. Soc. **57**, 1298 (1935).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

oxides of nitrogen

arsenious acid

bromophenol blue

ethyl alcohol (64-17-5)

hydrochloric acid (7647-01-0)

aniline (62-53-3)

sodium hydroxide (1310-73-2)

iron (7439-89-6)

nitric acid (7697-37-2)

Arsanilic acid, p-Arsanilic acid (98-50-0)

arsenic acid (1327-52-2)

aniline arsenate

sodium arsanilate (127-85-5)

tetrabromophenolsulfonphthalein

nickel (7440-02-0)

decolorizing carbon, Norite (7782-42-5)

p-nitrobenzenearsonic acid (98-72-6)

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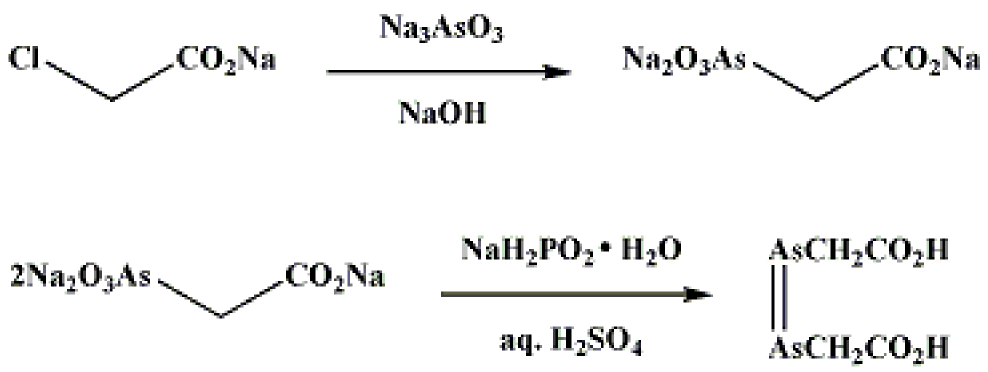
ARSONO- AND ARSENOACETIC ACIDS

[Acetic acid, arsono-, and Acetic acid, arsenodi-]



Submitted by C. S. Palmer
Checked by Oliver Kamm

1. Procedure

(*A*) *Arsonoacetic Acid*.—One hundred grams (0.51 mole) of powdered arsenious oxide is added to the hot solution obtained by dissolving 160 g. (4 moles) of sodium hydroxide in 300 cc. of water. After the solution has cooled to 20°, 48 g. (0.51 mole) of chloroacetic acid is added. The suspension is well stirred during about five minutes, when a strongly exothermic reaction begins, the temperature rises to 70–75°, and a clear solution results.

The reaction mixture is permitted to stand at room temperature during one hour, or longer if desired (Note 1). The solution is acidified with 160 cc. of glacial acetic acid and, after the temperature has been lowered to 40° by cooling, the precipitated arsenious oxide is filtered off by suction and washed with 50 cc. of water.

The filtrate is poured into a solution containing 185 g. (0.76 mole) of crystallized barium chloride dissolved in 600 cc. of hot water. Barium arsonoacetate, Ba $(O_2CCH_2AsO_3Ba)_2$ (hydrated), forms a thick, finely divided precipitate. The mixture is stirred for several minutes and then allowed to stand until the following day, when it is filtered upon a 15-cm. Büchner funnel and washed thoroughly with water (Note 2). The yield of air-dried product is 220 g. (96 per cent of the theoretical amount) (Note 3).

Sodium arsonoacetate is prepared by adding the freshly filtered and washed barium arsonoacetate as obtained above (without drying) to a solution of 108 g. (0.76 mole) of anhydrous sodium sulfate in 500 cc. of hot water. The mixture is mechanically stirred for one hour, the barium sulfate filtered off, and the filtrate concentrated on the steam bath until crystallization commences. Upon cooling and stirring (Note 4), sodium arsonoacetate separates and is filtered by suction, the filtrate being concentrated to obtain a second crop of crystals. The yield of the combined fractions is 100–110 g.

(80–88 per cent of the theoretical amount).

(*B*) *Arsenoacetic Acid*.—A solution of 12.5 g. of sodium arsonoacetate and 30 g. of sodium hypophosphite ($NaH_2PO_2 \cdot H_2O$) in 150 cc. of cold 15 per cent sulfuric acid is allowed to stand at room temperature. After two or three days, the yellow precipitate is filtered off, washed with water, and dried in a vacuum over sulfuric acid or phosphorus pentoxide. A second crop is obtained by allowing the mother liquid to stand for two days longer.

The arsenoacetic acid consists of minute yellow needles, which do not melt below 260° although they undergo considerable decomposition above 200°. The yield is 5 g. (74 per cent of the theoretical amount).

2. Notes

1. The reaction between sodium arsenite and chloroacetic acid is very rapid, as may easily be demonstrated by titrating 1-cc. portions of the solution with 0.1 *N* iodine, according to the usual volumetric method for arsenious acid, before and after the reaction with chloroacetic acid. The excess of sodium arsenite is necessary, as was learned by means of an iodimetric study of the reaction.
2. If the thick paste is not allowed to stand overnight, filtration is more cumbersome and it is extremely difficult to wash the precipitate free from arsenites. With this precaution, it is found that after five washings with 250-cc. portions of water, the final filtrate, as well as the desired barium salt, is practically free from iodine-reducing compounds.
3. The air-dried sample contains 13 per cent of water of hydration, as determined by actual analysis.
4. Stirring is required during the crystallization process, since otherwise the product tends to form a solid cake. The sodium salt is obtained without water of crystallization. Usually it contains a trace of sulfate but this does not interfere with its subsequent use. The sulfate may be removed by recrystallization from water.

3. Discussion

Arsonoacetic acid can be prepared by the action of sodium arsenite with sodium chloroacetate followed by isolation as the calcium,[1] lead[2] or barium[3] salt. The procedures described for the preparation of arsono- and arsenoacetic acids have been published.[3]

References and Notes

1. Friedr. Bayer and Co., U. S. pat. 1,445,685 [Chem. Zentr. I, 965 (1924)]; Austrian pat. 93,325 [Chem. Zentr. II, 721 (1923)]; Swiss pat. 97,977 [Chem. Zentr. II, 721 (1923)].
2. Ramberg and Ohman, Svensk. Kem. Tids. **36**, 119 (1924) [C. A. **19**, 36 (1925)].
3. Palmer, J. Am. Chem. Soc. **45**, 3023 (1923); Marquez, Anales asoc. quím. argentina **27**,

258 (1939) [C. A. **34**, 4726 (1940)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

arsenious acid

ARSONO- AND ARSENOACETIC ACIDS

Acetic acid, arsenodi-

arsenious oxide

Arsenoacetic acid

sodium hypophosphite ($NaH_2PO_2 \cdot H_2O$

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

sodium hydroxide (1310-73-2)

sodium sulfate (7757-82-6)

Acetic acid, arsono-, Arsonoacetic acid (107-38-0)

chloroacetic acid (79-11-8)

barium chloride (10361-37-2)

Barium arsonoacetate

Sodium arsonoacetate (27152-51-8)

barium sulfate (7727-43-7)

sodium arsenite

iodine (7553-56-2)

sulfate (14808-79-8)

sodium chloroacetate (3926-62-3)

phosphorus pentoxide (1314-56-3)

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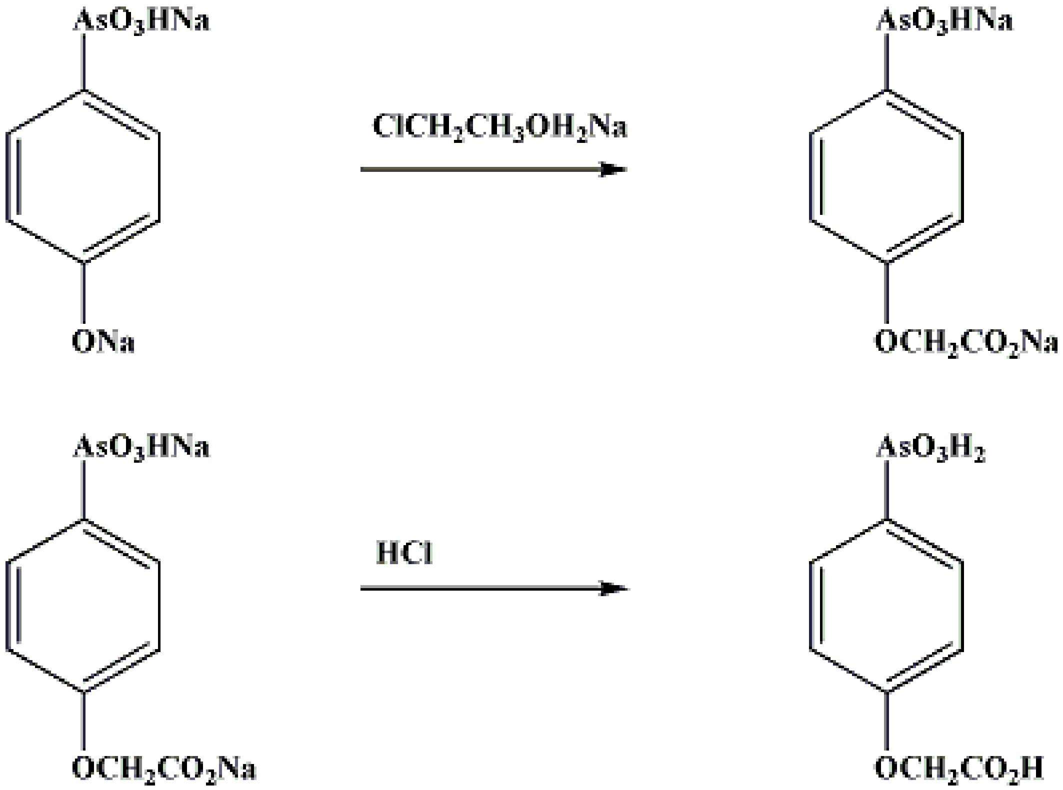
p-ARSONOPHENOXYACETIC ACID

[Acetic acid, *p*-arsonophenoxy-]



Submitted by C. S. Palmer and E. B. Kester.
Checked by J. B. Conant

1. Procedure

In a 2-l. round-bottomed flask are placed 218 g. (1 mole) of *p*-hydroxyphenylarsonic acid (Note 1) and 375 cc. of water. A solution of 180 g. (4.5 moles) (Note 2) of sodium hydroxide in 375 cc. of water is added, and the mixture shaken until a homogeneous solution is obtained. After cooling to 40–50° there is added 189 g. (2 moles) of chloroacetic acid in small portions (Note 3) with stirring, and the clear solution is refluxed for four hours. At the end of this time the mixture is cooled to 20°, filtered to remove a slight flocculent precipitate, and the *p*-arsonophenoxyacetic acid precipitated (Note 4) by the addition of 200 cc. (2.1 moles) of hydrochloric acid (sp. gr. 1.19).

The product is filtered on a 10-cm. Büchner funnel and washed with three successive 100-cc. portions of cold water. It is then crystallized from 2 l. of hot water (Note 5), filtered, and washed twice with 100-cc. portions of cold water, once with 25 cc. of acetone, and once with 25 cc. of ether. After drying at 110° for one hour, there remains a pure white, anhydrous product weighing 110–120 g. (40–43 per cent of the

theoretical amount) (Note 6). An arsenic analysis shows the product to be about 99 per cent pure.

2. Notes

1. Commercial phenolarsonic acid may be used, or 240 g. of sodium *p*-hydroxyphenylarsonate (p. 490) and 140 g. of sodium hydroxide may be substituted for the acid and the larger amount of base.
2. The use of less than 4.5 moles of alkali lowers the yield; an increase in the alkali concentration does not increase the yield.
3. Unless the chloroacetic acid is added cautiously, there may be a violent reaction and the yield of *p*-arsonophenoxyacetic acid is lowered.
4. The product sometimes does not precipitate readily without vigorous agitation and rubbing the inside wall of the vessel with a stirring rod.
5. It is sometimes necessary to use decolorizing carbon in order to get a white recrystallized product.
6. The odor of phenol is strong at the end of the reaction, but most of the *p*-hydroxyphenylarsonic acid which does not react with the chloroacetic acid is not hydrolyzed and can be recovered in the filtrate from the *p*-arsonophenoxyacetic acid.

3. Discussion

p-Arsonophenoxyacetic acid can be made by heating aqueous sodium *p*-hydroxyphenylarsonate, 2 moles of chloroacetic acid, and 4 moles of sodium hydroxide.[1]

References and Notes

1. Meister, Lucius and Brüning, Ger. pat. 216,270 [Frdl. **9**, 1047 (1908–10)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium hydroxide (1310-73-2)

phenol (108-95-2)

chloroacetic acid (79-11-8)

acetone (67-64-1)

phenolarsonic acid

decolorizing carbon (7782-42-5)

p-ARSONOPHENOXYACETIC ACID, Acetic acid, p-arsonophenoxy- (53663-15-3)

p-hydroxyphenylarsonic acid (98-14-6)

sodium p-hydroxyphenylarsonate (53663-20-0)

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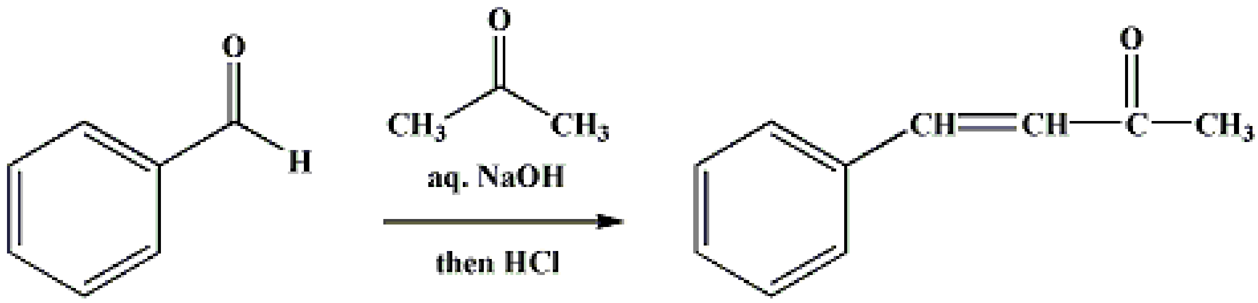
BENZALACETONE

[3-Buten-2-one, 4-phenyl-]



Submitted by N. L. Drake and P. Allen, Jr.
Checked by C. S. Marvel and A. W. Sloan.

1. Procedure

In a 2-l. bottle equipped with a mechanical stirrer are mixed 635 g. (800 cc., 11.0 moles) of u. s. p. acetone (Note 1) and (Note 2), 420 g. (400 cc., 4.0 moles) of freshly distilled benzaldehyde boiling at 178–180° (shaken with dilute sodium carbonate just before distillation), and 400 cc. of water. To this mixture, 100 cc. of 10 per cent aqueous sodium hydroxide is slowly added from a dropping funnel (Note 3), while the solution is stirred, and cooled by a water bath. The rate of addition of the alkali is so regulated that the temperature remains between 25–31°. This requires from one-half to one hour. The mixture is now stirred for two and one-quarter hours at room temperature (Note 4). At the end of this time dilute hydrochloric acid is added until the mixture is acid to litmus. The two layers which form are separated in a separatory funnel. The lower aqueous layer is extracted with 100 cc. of benzene, and the benzene solution added to the yellow oil which formed the upper layer in the first separation. This benzene solution is shaken with 100 cc. of water and separated.

The benzene is then removed by distilling from a steam bath, and the residue distilled under reduced pressure (Note 5), any water which condenses with the forerun being separated (Note 6). A special distilling flask with a fractionating side arm (p. 130) is best employed. The material which distils at 148–160° /25 mm., 133–143° /16 mm., or 120–130° /7 mm. weighs 430–470 g.; it solidifies to a crystalline mass on standing, and is pure enough for all practical purposes. On redistillation there is obtained 375–450 g. (65–78 per cent of the theoretical amount) of material boiling at 137–142° /16 mm. or 123–128° /8 mm., which solidifies on standing to crystals which melt at 40–42° (Note 7) and (Note 8).

2. Notes

1. Benzalacetone acts as an irritant, and care should be taken to prevent it from

coming in contact with the skin.

2. A large excess of acetone is taken, so as to diminish the formation of dibenzalacetone.

3. If the sodium hydroxide is added too rapidly and without cooling, the mixture darkens and the yield is lowered. The rate of addition is best determined by watching the temperature of the reaction mixture.

4. Instead of stirring the mixture after the addition of the sodium hydroxide, the bottle may be securely stoppered and shaken on a shaking machine for the same length of time.

5. The lower the pressure used in the distillation the less decomposition occurs, and the less residue is left in the distilling flask. This residue contains some dibenzalacetone.

6. The first few cubic centimeters of the distillate have a greenish color, but the rest is light yellow. For this reason it is desirable to collect the first of the distillate separately, if a very light colored product is desired.

7. On exposure to air benzalacetone gradually turns brown, especially if it is slightly impure. Pure material can be kept for months in an ordinary stoppered bottle without changing color.

8. By a like procedure in which benzaldehyde is replaced by an equivalent quantity (540 g.) of anisaldehyde, anisalacetone (b.p. 180–185° /18 mm., m.p. 72–74°) has been obtained in a yield of 83 per cent of the theoretical amount. The distillation residue, on recrystallization from ethyl acetate, yields 18 g. of dianisalacetone (m.p. 128–129°).

3. Discussion

Benzalacetone can be prepared by condensing benzaldehyde and acetone by means of dilute alkali[1] and from benzaldehyde and diketene.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 105

References and Notes

1. Claisen and Ponder, Ann. **223**, 139 (1884); Vorländer, Ann. **294**, 275 (footnote) (1897); Claisen, Ber. **14**, 2468 (1881); Lewinsohn, Perfumery Essent. Oil Record, **15**, 118 (1924) [C. A. **18**, 2222 (1924)].
2. Carbide and Carbon Chemicals Corp., U. S. pat. 2,108,427 [C. A. **32**, 2956 (1938)]; Hurd and Roe, J. Am. Chem. Soc. **61**, 3355 (1939).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ethyl acetate (141-78-6)

sodium hydroxide (1310-73-2)

sodium carbonate (497-19-8)

benzaldehyde (100-52-7)

acetone (67-64-1)

Benzalacetone, 3-Buten-2-one, 4-phenyl- (122-57-6)

Dibenzalacetone (35225-79-7)

Anisalacetone (943-88-4)

dianisalacetone (2051-07-2)

diketene (674-82-8)

anisaldehyde (123-11-5)

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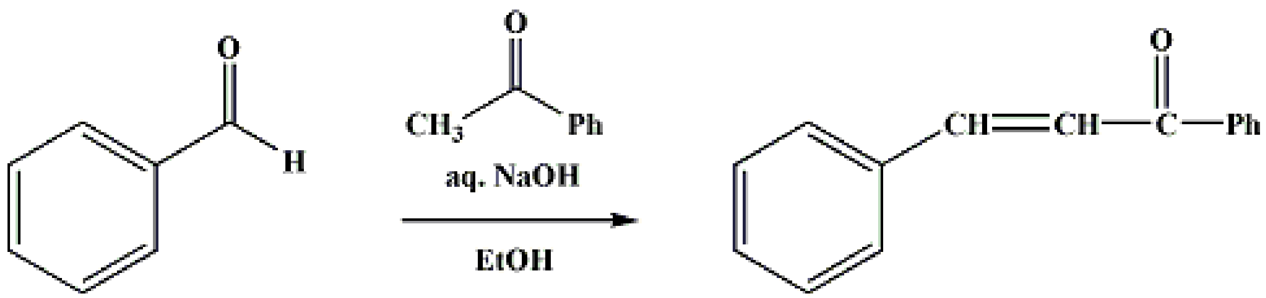
BENZALACETOPHENONE

[Chalcone]



Submitted by E. P. Kohler and H. M. Chadwell.
Checked by H. T. Clarke and R. P. Leavitt.

1. Procedure

A solution of 218 g. (5.5 moles) of sodium hydroxide in 1960 g. of water and 1000 g. (1225 cc.) of 95 per cent alcohol are introduced into a 5.5-l. bottle which is loosely covered with a perforated disk of cardboard, supplied with an effective stirrer, and supported in a larger vessel so as to permit cooling with cracked ice. Into the alkaline solution, 520 g. (4.3 moles) of pure acetophenone (Note 1) is poured, the bottle is rapidly surrounded with cracked ice, and the stirrer started; 460 g. (4.3 moles) of u. s. p. benzaldehyde (Note 2) is then added at once. The temperature of the mixture should not be below 15° and it should not be allowed to rise above 30° during the reaction (Note 3). If it tends to do so, the stirring is not sufficiently vigorous.

It is advantageous, though not essential, to inoculate the mixture with a little powdered benzalacetophenone after stirring for one-half hour. After two to three hours, the mixture becomes so thick that the stirring is no longer effective. The stirrer is then removed and the mixture left to itself in an ice box for about ten hours. The mixture now is a thick paste composed of small shot-like grains suspended in an almost colorless liquid. It is cooled in a freezing mixture and then either centrifuged or filtered on a large Büchner funnel, washed with water until the washings are neutral to litmus, and finally washed with 200 cc. of 95 per cent alcohol, which has previously been cooled to 0°. After thorough drying in the air, the crude product weighs about 880 g. (97 per cent of the theoretical amount) and melts at 50–54°. It is sufficiently pure for most purposes but tenaciously holds traces of water. It is most readily purified by recrystallization from four to four and one-half times its weight of 95 per cent alcohol (Note 4). Eight hundred and eighty grams of crude product give 770 g. (85 per cent of the theoretical amount) of light yellow material (m. p. 55–57°) and 40–50 g. that require recrystallization.

2. Notes

1. The acetophenone should be as pure as possible (m. p. 20°). Commercial acetophenone contains variable quantities of impurities which reduce the yield. By

distilling commercial acetophenone with the help of a good still-head (preferably under diminished pressure) and using only the fraction which boils at 201–202° (76–77° /10 mm.) greater quantities of benzalacetophenone can be obtained than by using the entire sample.
2. Commercial benzaldehyde can be used in place of the purer product, but the amount used must be increased to make up for the impurities which are present.
3. If the temperature is too low, or the stirring too slow, the product separates as an oil, which later solidifies in large lumps. If the temperature is allowed to rise above 30°, secondary reactions diminish both the yield and the purity of the product. The most favorable temperature is 25°.
4. In recrystallizing benzalacetophenone, the alcohol should be saturated at 50°. If the solution is saturated above this temperature, the benzalacetophenone tends to separate as an oil. The solution should be allowed to cool gradually, and should finally be chilled in a freezing mixture.

3. Discussion

Benzalacetophenone can be prepared from benzaldehyde and acetophenone, by the use of either acid[1] or alkaline condensing agents. The alkaline agents are superior and those generally used are a 30 per cent solution of sodium methoxide at low temperatures[2] and alcoholic sodium hydroxide.[3] Preliminary experiments showed that condensation with sodium methoxide requires a long time and gives a product which is difficult to handle in large quantities.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 101
- Org. Syn. Coll. Vol. 1, 205
- Org. Syn. Coll. Vol. 2, 167
- Org. Syn. Coll. Vol. 2, 236
- Org. Syn. Coll. Vol. 2, 498
- Org. Syn. Coll. Vol. 5, 1135

References and Notes

1. Claisen and Claparède, Ber. **14**, 2463 (1881); Straus and Grindel, Ann. **439**, 276 (1924); Breslow and Hauser, J. Am. Chem. Soc. **62**, 2385 (1940).
2. Claisen, Ber. **20**, 657 (1887).
3. Kostanecki and Rossbach, Ber. **29**, 1492 (1896); Schlenck and Bergmann, Ann. **463**, 234 (1928).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alcohol (64-17-5)

sodium hydroxide (1310-73-2)

Benzalacetophenone, Chalcone (94-41-7)

benzaldehyde (100-52-7)

Acetophenone (98-86-2)

sodium methoxide (124-41-4)

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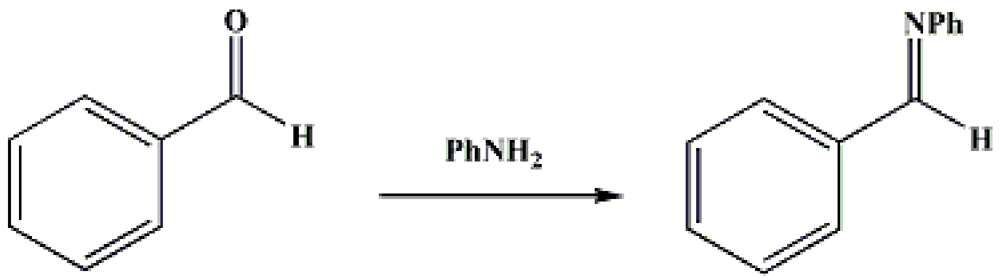
BENZALANILINE

[Aniline, N-benzylidene-]



Submitted by Lucius A. Bigelow and Harry Eatough.
Checked by Henry Gilman and J. D. Robinson.

1. Procedure

In a 500-cc. three-necked, round-bottomed flask provided with a mechanical stirrer is placed 106 g. (1 mole) of benzaldehyde (Note 1), and 93 g. (1 mole) of aniline is added with rapid stirring. After a few seconds a reaction occurs with evolution of heat and separation of water. The mixture is allowed to stand fifteen minutes and is then poured, with vigorous stirring, into 165 cc. of 95 per cent alcohol in a 600-cc. beaker. Crystallization begins in about five minutes, and the mixture is allowed to stand, first ten minutes at room temperature, and then thirty minutes in ice water. The almost solid mass is next transferred to a large Büchner funnel, filtered by suction, pressed out, and air-dried. The yield of pure benzalaniline melting at 52° is 152–158 g. (84–87 per cent of the theoretical amount).

By concentrating the mother liquor to about one-half of its original volume at room temperature or lower, under reduced pressure by means of a water pump, an additional 10 g. of benzalaniline may be obtained. This is of good quality and melts at 51° (Note 2).

2. Notes

1. Freshly distilled reagents must be used to obtain the yields described. Distillation through a column is recommended. The benzaldehyde should be washed with 5 per cent sodium carbonate solution before being distilled under reduced pressure with minimum atmospheric exposure.
2. Removal of the alcohol by distillation at ordinary pressure gives a much darker product.
If a product of high purity is desired, it may be obtained by recrystallization from 85 per cent alcohol.

3. Discussion

Benzalaniline can be prepared from aniline and benzaldehyde[1] either without a solvent or in dilute alcohol saturated with carbon dioxide.[2]

References and Notes

1. Laurent and Gerhardt, Jahresber. 488 (1850); Bogert, Org. Syn. **5**, 13 (1925).
2. Pyl, Ber. **60**, 287 (1927).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alcohol (64-17-5)

aniline (62-53-3)

sodium carbonate (497-19-8)

carbon dioxide (124-38-9)

benzaldehyde (100-52-7)

Benzalaniline, Aniline, N-benzylidene- (538-51-2)

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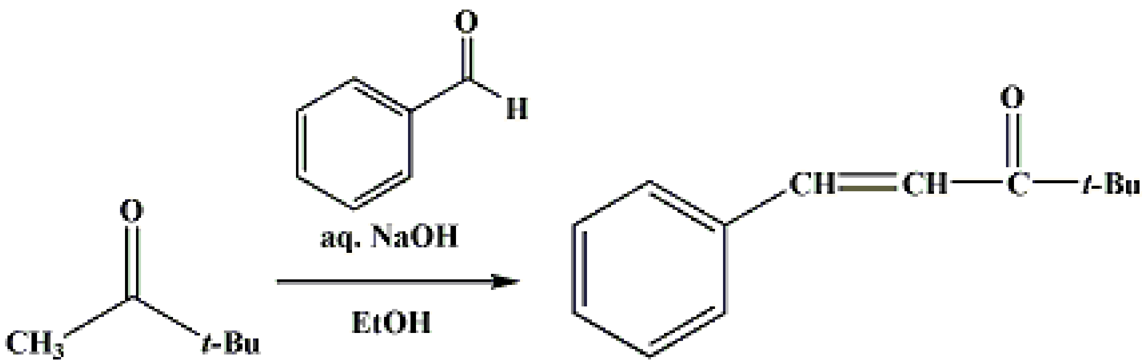
BENZALPINACOLONE

[1-Penten-3-one, 4,4-dimethyl-1-phenyl-]



Submitted by G. A. Hill and G. M. Bramann.
Checked by C. S. Marvel and A. B. Adams.

1. Procedure

In a 1500-cc. bottle are placed 100 g. (1 mole) of pinacolone (p. 462), 120 g. (1.13 moles) of freshly distilled benzaldehyde, 380 cc. of 95 per cent alcohol, 130 cc. of water, and 100 cc. of 10 per cent sodium hydroxide solution. The bottle is stoppered tightly, placed on a shaking machine, and agitated vigorously for about thirty-two hours (Note 1).

The reaction mixture is poured into a separatory funnel and diluted with an equal volume of water. The benzalpinacolone is separated by extracting three times with 300-cc. portions of benzene. The benzene extracts are combined and washed, first with water until the alkali is entirely removed, then with a saturated solution of sodium bisulfite, and finally two or three times with water. After drying over calcium chloride, the benzene is removed by distilling from a steam bath, and the residue is distilled under reduced pressure. The yield of distilled benzalpinacolone boiling at 143–146° /10 mm. is 165–175 g. (88–93 per cent of the theoretical amount). This product is slightly yellow and melts at 41–42°. It is pure enough for most purposes. It may be recrystallized from 95 per cent alcohol and is then obtained in almost pure white crystals, melting at 43°.

2. Notes

1. The time may be shortened to twenty-four hours without greatly reducing the yield.

3. Discussion

Benzalpinacolone can be prepared by the action of benzaldehyde on pinacolone in the

presence of aqueous-alcoholic alkalies.[1] The procedure described is a modification of the method by Vorländer and Kalkow.[1]

References and Notes

1. Vorländer and Kalkow, Ber. **30**, 2269 (1897); Hill, Spear and Lachowicz, J. Am. Chem. Soc. **45**, 1559 (1923).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alcohol (64-17-5)

calcium chloride (10043-52-4)

Benzene (71-43-2)

sodium hydroxide (1310-73-2)

sodium bisulfite (7631-90-5)

benzaldehyde (100-52-7)

Benzalpinacolone, 1-Penten-3-one, 4,4-dimethyl-1-phenyl- (538-44-3)

Pinacolone (75-97-8)

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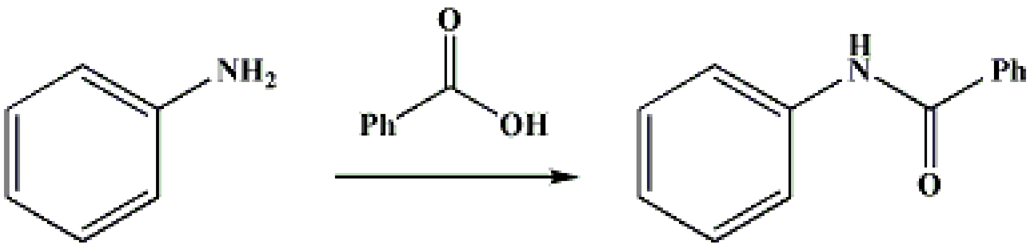
BENZANILIDE



Submitted by Carl N. Webb
Checked by C. S. Marvel and P. L. Salzberg.

1. Procedure

In a 3-l. round-bottomed flask are placed 750 g. (8.1 moles) of aniline (Note 1) and 1 kg. (8.2 moles) of benzoic acid. When about two-thirds of the benzoic acid is in the flask the mixture is melted to make room for the rest. The flask is placed in a large oil bath and connected to a condenser for distillation. The temperature of the oil is raised quickly to 180–190°, at which point distillation starts. The bath is held at this temperature until practically no more aniline and water distil (about two hours), and then the temperature is slowly raised to 225° and maintained at this temperature until no further distillation takes place (one to two hours). The oil bath is now removed and the contents of the flask are allowed to cool below 180° and 550 g. (5.9 moles) of aniline is added. The distillations at 190° and 225° are repeated (about six hours). The hot mixture is poured into two 20-cm. evaporating dishes (Hood) and is allowed to cool. The crude product weighs 1600–2000 g., depending on the amount of aniline retained.

The purplish-gray solid is ground (Note 2) in a large mortar and is poured with vigorous stirring into a 12-l. (3-gallon) crock containing 6 l. of approximately normal hydrochloric acid (5.5 l. of water and 500 cc. of concentrated hydrochloric acid). The stirring is continued for one hour after all the benzanilide has been added, and then the solid is filtered on a 20-cm. Büchner funnel. The process of stirring with acid and filtering is repeated twice to remove the excess of aniline. The solid is stirred for two hours with 6 l. of water and is filtered. It is stirred for one hour with 6 l. of normal sodium hydroxide solution to remove the excess of benzoic acid and is then filtered. The stirring with alkali and filtering is repeated. The solid is next stirred for two hours with 7 l. of water and is filtered, sucked dry, and air-dried overnight on paper.

After drying on paper the purplish solid is dried to constant weight in three 20-cm. evaporating dishes at 90–100° (about two days) and is then repowdered. The product is light purplish-gray and weighs 1270–1325 g. (80–84 per cent of the theoretical amount). It melts at 157–160°. The product is pure enough for use in the preparation of *p*-dimethylaminobenzophenone (p. 217) and for most synthetic purposes. When 100 g. of benzanilide is dissolved in 750 cc. of hot alcohol (Note 3) and the solution is boiled

with about 10 g. of decolorizing carbon (Norite), filtered, and cooled at 10° overnight, 80–86 g. of an almost colorless product melting at 160–161° separates. A second crystallization from alcohol using decolorizing carbon gives a white product with approximately the same loss in the mother liquors as in the first crystallization.

2. Notes

1. The ordinary "pure" aniline of commerce gives as good yields and as pure a product as redistilled aniline.
2. The benzanilide must be finely ground in order that aniline and benzoic acid may be completely extracted.
3. Very little of the solid fails to go into solution. The hot solution must be filtered rapidly as the benzanilide crystallizes easily.

3. Discussion

Benzanilide can be prepared by the treatment of aniline with benzoyl chloride,[1] benzoic anhydride,[2] or benzoic acid.[3]. Benzanilide has also been prepared from benzamide, aniline, and boron fluoride.[4] The method described in the procedure is essentially that of Nägeli.[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 217
- Org. Syn. Coll. Vol. 4, 383

References and Notes

1. Gerhardt, Ann. **60**, 311 (1846); Dehn and Ball, J. Am. Chem. Soc. **36**, 2096 (1914).
2. Meyer and Sundmacher, Ber. **32**, 2123 (1899).
3. Hübner, Ann. **208**, 291 (1881); Nägeli, Bull. soc. chim. (3) **11**, 892 (1894).
4. Sowa and Nieuwland, J. Am. Chem. Soc. **59**, 1202 (1937).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alcohol (64-17-5)

hydrochloric acid (7647-01-0)

aniline (62-53-3)

sodium hydroxide (1310-73-2)

Benzoic acid (65-85-0)

Benzanilide (93-98-1)

decolorizing carbon (Norite), carbon (7782-42-5)

benzoyl chloride (98-88-4)

Benzoic anhydride (93-97-0)

benzamide (55-21-0)

boron fluoride (7637-07-2)

p-Dimethylaminobenzophenone (530-44-9)

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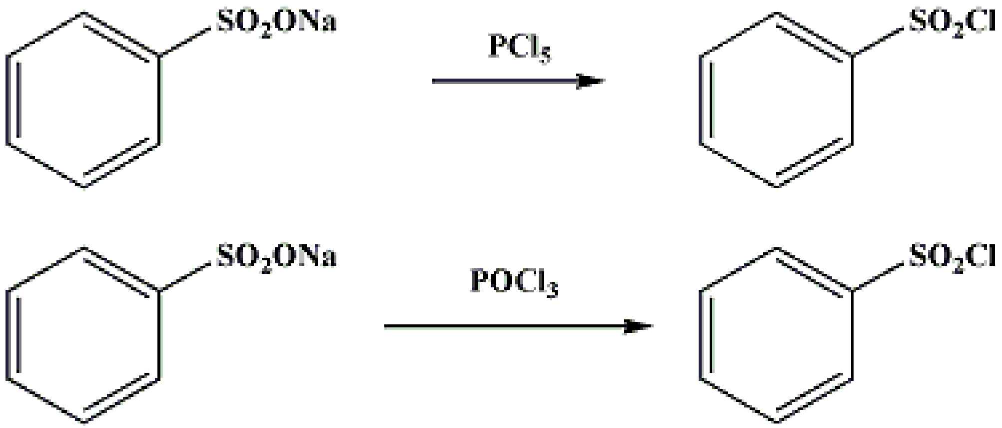
BENZENESULFONYL CHLORIDE

[(*A*) and (*B*) (*from Sodium Benzenesulfonate*)]



Submitted by Roger Adams and C. S. Marvel.
Checked by H. T. Clarke and W. W. Hartman.

1. Procedure

(*A*) *Phosphorus Pentachloride Method*.—In a 2-l. round-bottomed flask is placed a mixture of 250 g. (1.2 moles) of finely divided phosphorus pentachloride and 450 g. (2.5 moles) of sodium benzenesulfonate which has previously been dried for three hours at 140°. The mixture is heated in an oil bath at 170–180° (Note 1) for fifteen hours (Note 2). It is advisable to have a reflux condenser attached to the flask, although very little active refluxing takes place. Every four hours during the heating period, the flask should be removed from the oil bath, cooled for fifteen minutes, stoppered and shaken thoroughly until the mass becomes pasty (sometimes ten to fifteen minutes are required to accomplish this). At the end of the heating period, the mixture is cooled and 1 l. of water with 1 kg. of cracked ice are added. Benzenesulfonyl chloride sinks to the bottom, is separated, washed once with water, filtered if necessary, and distilled under reduced pressure for purification. The forerun, consisting of a little chlorobenzene, water, and a little benzenesulfonyl chloride, is discarded and the fraction boiling between 145–150° /45 mm. is collected. This weighs 330–360 g. (75–80 per cent of the theoretical amount) (Note 3).

The yields in this procedure are likely to vary widely on account of the variability in the different samples of sodium benzenesulfonate. With certain samples a solid impurity is left as a residue from the distillation of the crude benzenesulfonyl chloride.

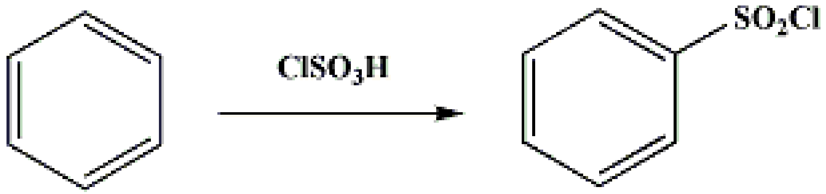
(*B*) *Phosphorus Oxychloride Method*.—Benzenesulfonyl chloride may be prepared by the same procedure described above from a mixture of 270 g. (1.5 moles) of sodium benzenesulfonate and 180 g. (1.17 moles) of phosphorus oxychloride. It is advisable to observe the same precaution of shaking every few hours. The yield of product boiling

at 145–150° /45 mm. is 195–230 g. (74–87 per cent of the theoretical amount) (Note 3).

2. Notes

1. The temperature must be maintained between 170–180°. A lower temperature does not give so good a yield.
2. It is advisable to heat the mixture as long as fifteen hours to be certain that the reaction is complete. The reaction is chiefly over, however, at the end of ten hours.
3. If a means of mechanical stirring were provided, the yields would undoubtedly be much better, and the time required shorter. The mixtures, however, are so thick that in the laboratory mechanical stirring is impracticable. Experiments using a larger excess of phosphorus pentachloride or phosphorus oxychloride were made but no particular advantage was so obtained.

[(*C*) (*from Benzene*)]



Submitted by H. T. Clarke, G. S. Babcock, and T. F. Murray.
Checked by Frank C. Whitmore and A. M. Griswold.

1. Procedure

In a 5-l. flask, fitted with stirrer, separatory funnel, exit tube, and thermometer, is placed 3.5 kg. (2 l., 30 moles) of chlorosulfonic acid (Note 1), and to it is slowly added, with continuous stirring, 780 g. (888 cc., 10 moles) of benzene (Note 2), keeping the temperature between 20° and 25° by means of cold water. The hydrogen chloride which is evolved is led to a hood or absorbed in water (Fig. 7, p. 97). The addition requires two to three hours; when this is complete, the mixture is stirred for one hour, and poured upon 6–7 kg. of crushed ice (Note 3). One liter of carbon tetrachloride is then added, the oil is separated as soon as possible (Note 4), and the watery layer is shaken with 500 cc. of carbon tetrachloride. The combined extracts are washed with dilute sodium carbonate, and the bulk of the carbon tetrachloride is distilled under atmospheric pressure (Note 5); the pressure is then reduced (Note 6) and the benzenesulfonyl chloride collected at 113–115° /10 mm. (118–120° /15 mm.). The yield is 1320–1360 g. (75–77 per cent of the theoretical amount) of a colorless liquid which on cooling sets to a crystalline solid melting at 13–14°.

A small amount (50–100 g.) of higher-boiling material remains in the flask. This is mainly diphenyl sulfone, which may be isolated by distillation under reduced pressure (b.p. 225° /10 mm.) and recrystallization from methyl alcohol. It forms colorless

crystals which melt at 128°.

2. Notes

1. If less than 50 per cent excess of chlorosulfonic acid is taken, the yield of diphenyl sulfone increases at the expense of the sulfonyl chloride.
2. A good commercial grade of benzene, boiling over a 1° range, is satisfactory. The benzene must be added to the acid (not vice versa); otherwise, a larger proportion of sulfone is formed.
3. The benzenesulfonyl chloride separates at first as a crystalline solid which melts as the temperature rises. It was found impracticable to filter off this solid, owing to its tendency to melt on the funnel.
4. The sulfonyl chloride should be removed from the water as soon as possible; otherwise, the yield falls, owing to hydrolysis. In one run in which the mixture was allowed to stand overnight before separating, only 1220 g. (69 per cent) was obtained. If difficulty is experienced in the separation, owing to the presence of suspended solid matter, the oil may first be filtered with suction through a hardened paper or felt cloth. As a rule, it is merely necessary to filter the sludgy layer lying between the oil and the water.
5. The carbon tetrachloride vapor carries with it any moisture that may be present. If this were not removed at a relatively low temperature, hydrolysis of the chloride would take place, with the formation of sulfonic acid which would promote decomposition of the sulfonyl chloride during its distillation.
6. The pressure should be reduced gradually, and the first runnings, mainly carbon tetrachloride, collected separately.

3. Discussion

Benzenesulfonyl chloride can be prepared by the action of phosphorus pentachloride on benzenesulfonic acid or its salts;[1] by the action of phosphorus oxychloride upon the salts of benzenesulfonic acid;[2] by the action of chlorosulfonic acid on benzene[3] or sodium benzenesulfonate;[4] and by the action of sulfuryl chloride on benzene in the presence of anhydrous aluminum chloride.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 504
- Org. Syn. Coll. Vol. 3, 159

References and Notes

1. Gerhardt and Chiozza, Ann. **87**, 299 (1853); Vogt, Ann. **119**, 143 (footnote) (1861); Otto, Z. Chem. 106 (1866); Barbaglia and Kekulé, Ber. **5**, 876 (1872); Bourgeois, Rec. trav. chim. **18**, 432 (1899); Mohrmann, Ann. **410**, 379 (1915); Rosenmund and Struck,

Ber. **54**, 439 (1921).
2. Gerhardt and Chancel, Compt. rend. **35**, 690 (1852).
3. Knapp, Z. Chem. 41 (1869); Pummerer, Ber. **42**, 1802, 2274 (1909); Ullmann, Ber. **42**, 2057 (1909); Saccharinfabrik A.-G., Ger. pat. 224,386 [Frdl. **10**, 114 (1913)].
4. Heumann and Köchlin, Ber. **15**, 1118 (1882).
5. Böeseken, Rec. trav. chim. **30**, 382 (1911).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfonyl chloride

hydrogen chloride (7647-01-0)

Benzene (71-43-2)

methyl alcohol (67-56-1)

chlorosulfonic acid (7790-94-5)

phosphorus pentachloride (10026-13-8)

sodium carbonate (497-19-8)

sulfone (7446-09-5)

carbon tetrachloride (56-23-5)

Benzenesulfonyl chloride (98-09-9)

Sodium Benzenesulfonate (515-42-4)

chlorobenzene (108-90-7)

Phosphorus Oxychloride (21295-50-1)

diphenyl sulfone (127-63-9)

benzenesulfonic acid (98-11-3)

sulfuryl chloride (7791-25-5)

aluminum chloride (3495-54-3)

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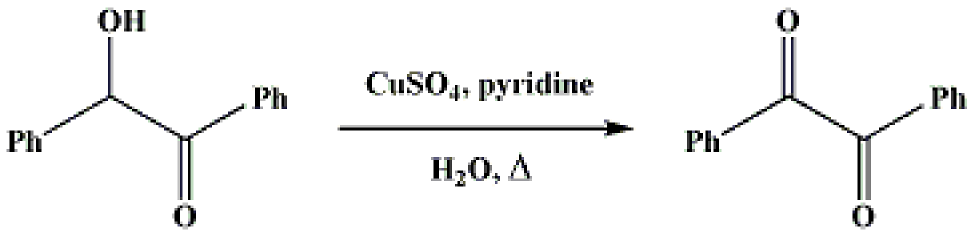
BENZIL



Submitted by H. T. Clarke and E. E. Dreger.
Checked by Roger Adams and Gerald H. Coleman.

1. Procedure

In a 12-l. flask, fitted with a mechanical stirrer and mercury seal, a reflux condenser and an inlet tube for the introduction of air, is placed a mixture of 4100 g. (16.4 moles) (Note 1) of crystalline copper sulfate (Note 2), 4000 g. of technical pyridine and 1600 g. of water. This is heated on a steam bath with stirring until the copper sulfate is completely dissolved and then 1696 g. (8 moles) of benzoin (p. 94; unrecrystallized material is satisfactory) is added and heating and stirring continued for two hours. The reaction mixture becomes dark green in color and the melted benzil forms the upper layer. After cooling, the copper sulfate-pyridine solution is decanted and the benzil washed with water and then heated with 3–4 l. of 10 per cent hydrochloric acid. After cooling, the benzil is filtered, washed with water, dried and recrystallized from carbon tetrachloride (2 l. of solvent per kg. of benzil). By concentration of the mother liquors a certain amount of benzil is always obtained. The total yield is 1450 g. (86 per cent of the theoretical amount) of recrystallized material melting at 94–95° (Note 3).

The copper sulfate-pyridine mixture is readily reoxidized by passing a current of air through it for thirty-six hours (Note 4). To this resulting solution is now added 200 g. of pyridine and it is then used for oxidizing another 1696 g. portion of benzoin.

2. Notes

1. In checking this preparation, runs about 25 per cent of the size described were made. The yields were about 3 per cent less than in the larger runs. For the reoxidization of the smaller amount of copper sulfate-pyridine solution, air was passed through for fifteen hours.
2. Copper hydroxide (or carbonate) does not dissolve in pyridine.
3. In comparing the copper sulfate-pyridine method with the nitric acid method (Org. Syn. **1**, 25) it should be pointed out that the constants on the samples are as follows:

Method	M. P. Crude	M. P. Recryst.	Fehling's Test on Recryst.
Copper sulfate-pyridine............	94–95°	94–95°	Negative
Nitric acid.......................	88°	93–94°	Positive

In other words, by the nitric acid oxidation it is difficult to obtain a product completely free from benzoin. The yields by the nitric acid method are generally about 95–96 per cent, whereas with the copper sulfate-pyridine method the yield drops to approximately 86 per cent.

The melting temperatures of mixtures of benzil and benzoin show[1] that the maximum possible depression is 10°.

4. Fifteen hours was found not long enough to effect a complete oxidation.

3. Discussion

Benzil is readily formed by the oxidation of benzoin with nitric acid,[2] chlorine,[3] iodine,[4] electrolytically[5] and catalytically.[6] The procedure described is based on the observation[7] that benzoin reduces Fehling's solution in the cold. Pyridine was selected because it prevents precipitation of cuprous oxide, is not so volatile as ammonia, and acts as a partial solvent for benzoin. It has been shown[8] that copper, pyridine and air oxidize benzoin to benzoic acid. The same oxidation also takes place in the absence of copper. Benzil can also be prepared from desoxybenzoin with selenium dioxide.[9]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 496
- Org. Syn. Coll. Vol. 4, 377

References and Notes

1. Vanstone, J. Chem. Soc. **95**, 600 (1909).
2. Zinin, Ann. **34**, 188 (1840); Adams and Marvel, Org. Syn. **1**, 25 (1921).
3. Laurent, Ann. **17**, 91 (1836).
4. Corson and McAllister, J. Am. Chem. Soc. **51**, 2822 (1929).
5. James, ibid. **21**, 893 (1899).
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7. Fischer, Ann. **211**, 214 (footnote) (1882).
8. Mohler, Helv. Chim. Acta, **8**, 740 (1925).
9. Hatt, Pilgrim, and Hurran, J. Chem. Soc. **1936**, 93.

Appendix

Compounds Referenced (Chemical Abstracts Registry Number)

copper sulfate-pyridine

Fehling's solution

Desoxybenzoin

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

nitric acid (7697-37-2)

carbon tetrachloride (56-23-5)

copper sulfate (7758-98-7)

Benzoic acid (65-85-0)

copper (7440-50-8)

iodine (7553-56-2)

Benzil (134-81-6)

pyridine (110-86-1)

Benzoin (119-53-9)

Copper hydroxide (20427-59-2)

chlorine (7782-50-5)

cuprous oxide

selenium dioxide (7446-08-4)

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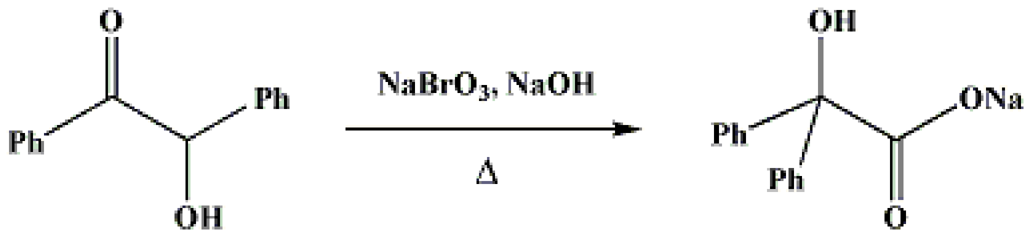
BENZILIC ACID



Submitted by Donald A. Ballard and William M. Dehn.
Checked by C. S. Marvel and Tse-Tsing Chu.

1. Procedure

The reaction mixture of benzoin, prepared by the method described on p. 94, is permitted to stand until the next day, when it is filtered, washed with water but is not dried or purified. In a 30-cm. evaporating dish 500 g. (12.5 moles) of sodium hydroxide and 115 g. (0.76 mole) of sodium bromate (or 125 g. of potassium bromate) are dissolved in 880 cc. of water. The moist benzoin (450–460 g.) is added in portions to this solution and the mixture is stirred, preferably with a mechanical stirrer, while heated on the steam bath (Note 1). As heating continues the mixture thickens and more water is added from time to time. A total of 750–800 cc. is needed. The heating and stirring are continued for about five to six hours or until a test portion is completely or almost completely soluble in water.

The mixture is diluted with about 4 l. of water and is permitted to stand overnight. A small quantity of oily or solid impurity (benzohydrol) is removed by filtration, and dilute sulfuric acid (about 1300 cc. of a solution of 3 parts of water and 1 part of concentrated sulfuric acid, sp. gr. 1.84) is added to a point short of liberation of bromine. The product is filtered, washed with water and dried. Thus 450–484 g. (84–90 per cent of the theoretical amount based on the benzaldehyde) of benzilic acid melting at 149–150° is obtained (Note 2).

2. Notes

1. If the reaction mixture is heated to boiling, large quantities of benzohydrol are obtained. The temperature reached by heating on the steam bath is about 85–90°.
2. The high purity of the product obtained by this procedure really makes recrystallization unnecessary. Should further purification be desired it is best effected by crystallization from benzene. It may also be accomplished by crystallizing from hot water with the use of animal charcoal or by dissolving in alkali and reprecipitating by means of hydrochloric acid.

3. Discussion

Benzilic acid can be prepared by the action of potassium hydroxide on benzil, in concentrated aqueous solution,[1] in alcoholic solution[2] or in ether;[3] and by heating benzil in toluene with sodamide and then treating with water.[4] The procedure described has been published.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 224

References and Notes

1. Fischer and Bösler, Ber. **14**, 326 (footnote) (1881); Staudinger, Ann. **356**, 71 (1907).
2. Liebig, Ann. **25**, 27 (1838); Zinin, Ann. **31**, 329 (1839); Jena, Ann. **155**, 79 (1870); Liebig, Ber. **41**, 1644 (1908); Schönberg and Keller, Ber. **56**, 1638 (1923); Adams and Marvel, Org. Syn. **1**, 29 (1921).
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4. Kasiwagi, Bull. Chem. Soc. Japan **1**, 66 (1926) [C. A. **20**, 2491 (1926)].
5. Evans and Dehn, J. Am. Chem. Soc. **52**, 3649 (1930).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Benzohydrol

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether (60-29-7)

sodium hydroxide (1310-73-2)

bromine (7726-95-6)

benzaldehyde (100-52-7)

Benzil (134-81-6)

Benzoin (119-53-9)

Benzilic acid (76-93-7)

sodium bromate (7789-38-0)

potassium bromate (7758-01-2)

potassium hydroxide (1310-58-3)

toluene (108-88-3)

sodamide (7782-92-5)

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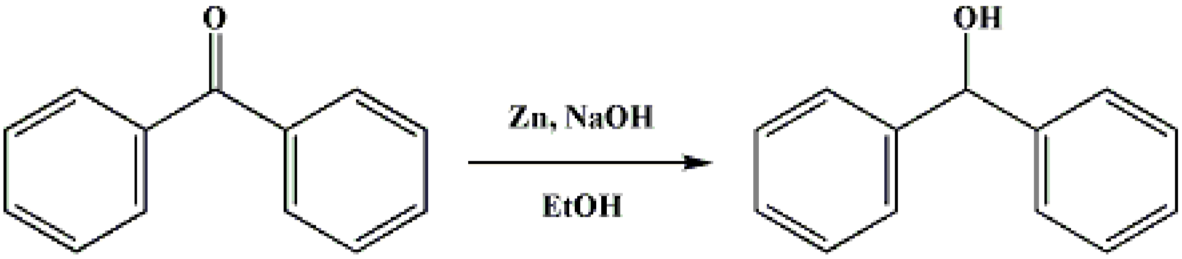
BENZOHYDROL



Submitted by F. Y. Wiselogle and H. Sonneborn, III.
Checked by C. S. Marvel and J. F. Kaplan.

1. Procedure

In a 3-l. round-bottomed flask fitted with a mechanical stirrer are placed 200 g. of technical flake sodium hydroxide, 200 g. of benzophenone, 2 l. of 95 per cent alcohol, and 200 g. of technical zinc dust. The stirrer is started and the mixture slowly warms to about 70° spontaneously. After two to three hours the mixture, which has started to cool, is filtered with suction, and the residue is washed twice with 100-cc. portions of hot alcohol (Note 1).

The filtrate is poured into five volumes of ice water acidified with about 425 cc. of concentrated commercial hydrochloric acid. The benzohydrol separates as a white crystalline mass and is filtered by suction. The yield of crude air-dried product melting at 65° is 194–196 g. (96–97 per cent of the theoretical amount). From 200 g. of crude product in 200 cc. of hot alcohol there is obtained, after cooling in an ice-salt mixture, filtering, and drying, 140–145 g. of product melting at 68°. The benzohydrol remaining in the mother liquors may be precipitated with water.

2. Notes

1. The filtered zinc dust is inflammable; it must not be allowed to dry in contact with combustible material.

3. Discussion

Benzohydrol can be prepared by reducing benzophenone with sodium amalgam;[1] with metallic calcium and alcohol;[2] with hydrogen in the presence of a catalyst;[3] with zinc, aluminum, or sodium in strongly alkaline solutions;[4] with zinc dust and alcoholic potassium hydroxide solution;[5] electrolytically;[6] with magnesium and absolute alcohol;[7] with magnesium and ammonium chloride in 95 per cent alcohol;[7] with isopropyl alcohol and a little sodium isopropoxide;[8] and with aluminum isopropoxide.[9]

References and Notes

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2. Marschalk, Ber. **43**, 642 (1910).
3. Vavon, Compt. rend. **155**, 287 (1912).
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9. Lund, Ber. **70**, 1520 (1937).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Benzohydrol

alcohol (64-17-5)

hydrochloric acid (7647-01-0)

ammonium chloride (12125-02-9)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

magnesium (7439-95-4)

aluminum (7429-90-5)

potassium hydroxide (1310-58-3)

Benzophenone (119-61-9)

zinc (7440-66-6)

calcium (7440-70-2)

sodium (13966-32-0)

isopropyl alcohol (67-63-0)

sodium isopropoxide (683-60-3)

aluminum isopropoxide

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BENZOIC ANHYDRIDE

$$C_6H_5CO_2H + (CH_3CO)_2O \longrightarrow C_6H_5COOCOCH_3 + CH_3CO_2H$$

$$C_6H_5CO_2H + C_6H_5COOCOCH_3 \longrightarrow (C_6H_5CO)_2O + CH_3CO_2H$$

Submitted by H. T. Clarke and E. J. Rahrs.
Checked by Roger Adams and P. K. Porter.

1. Procedure

In a 5-l. flask, provided with a two-holed stopper fitted with a 90-cm. fractionating column[1] and a dropping funnel, are placed 1500 g. (12.3 moles) of benzoic acid, 1500 g. (1390 cc., 14.7 moles) of acetic anhydride (or an equivalent quantity of 95 per cent acetic anhydride), and 1 cc. of sirupy phosphoric acid. The mixture is very slowly distilled, at such a rate that the temperature of the vapor at the head of the column does not exceed 120° (Note 1). When 250 cc. of distillate has been collected, 250 g. of acetic anhydride is added, and distillation is continued. This process is again repeated, so that in all 2000 g. (1850 cc., 19.6 moles) of acetic anhydride has been taken. Fractionation is then continued, fractions which distil respectively below 120°, at 120–130°, and at 130–140° being collected. Heating is continued until the temperature of the reaction mixture in the flask reaches 270°.

The residue is fractionally distilled under reduced pressure, resulting in the collection of fractions which boil respectively below 165°, at 165–210°, and at 210–220°, all under 19–20 mm. pressure (Note 2). The lower fractions are mixed with the fraction which boils at 120–130°, and distilled as before after the addition of one drop of phosphoric acid, when a further quantity of material boiling at 210–222° /20 mm. is obtained. This fraction, amounting to 1100–1200 g., consists of crude benzoic anhydride. The lower-boiling fractions may be redistilled until they become too small to justify further work.

The fraction which boils at 120–130° under atmospheric pressure is redistilled, yielding further quantities of acetic acid (below 120°) and acetic anhydride (130–140°).

The crude benzoic anhydride (which is apt to supercool without crystallizing) contains a small proportion of an oily impurity which causes the product to turn yellow on standing; it is recrystallized by dissolving in benzene (50 cc. for each 100 g.) then adding just enough petroleum ether to cause a cloudiness (about 100 cc. is required) and chilling, when the pure anhydride separates in perfectly colorless and odorless crystals melting at 43°. The first crop amounts to about 50 per cent of the crude material taken; the mother liquors are freed of solvent by distillation on the water bath, and the residue distilled under reduced pressure, when a further quantity of pure material can be obtained by recrystallizing the distillate boiling at 210–220° /19 mm. If this process is repeated until the mother liquor becomes too small in amount to

redistil satisfactorily, the yield of pure benzoic anhydride melting at 43° amounts to 1000–1030 g. (72–74 per cent of the theoretical amount) (Note 3). It is generally more convenient to distil the mother liquors only once or possibly twice, under which conditions a somewhat lower yield is obtained. The remaining mother liquors may then be mixed with a subsequent preparation.

2. Notes

1. As it is probable that the equilibria between the two acids and the three anhydrides are established in reactions of relatively low velocity, the distillation must be carried on very slowly, in spite of the catalytic action of the phosphoric acid. The intermediate fractions contain the mixed anhydride, detectable by its odor, which resembles that of acetophenone.
2. Owing to the high boiling point of the end-product, the second stage must be conducted under reduced pressure. The temperatures indicated depend, of course, upon the pressure under which the distillation is carried out, and allowances will have to be made for pressures differing materially from 20 mm.
3. Although the yield is by no means quantitative, the only reason why it should not be made nearly so by continual redistillation of the various fractions in presence of the catalyst lies in the length of time required for the process. This, however, could be avoided if a large number of runs were to be made, when the intermediate fractions could be worked over repeatedly with each subsequent batch, until practically nothing but acetic acid and benzoic anhydride remain.

3. Discussion

Benzoic anhydride can be prepared from benzoyl chloride and benzoic acid;[2] from benzoyl chloride and lead nitrate,[3] or potassium pyrosulfite,[4] or sodium carbonate;[5] from benzotrichloride and sulfuric acid;[6] from benzoic acid and acetic anhydride;[7] from benzoic acid and phosphorus in benzene solution by shaking with air or oxygen;[8] and from diphenyldichloromethane and sodium benzoate.[9] Numerous patented procedures have been described for preparing benzoic anhydride from salts of benzoic acid and inorganic acid chlorides and inorganic acid anhydrides. Some of these would be more suitable for the commercial preparation of benzoic anhydride, but the procedure described is satisfactory for the laboratory.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 560
- Org. Syn. Coll. Vol. 3, 28

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

potassium pyrosulfite

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

Benzene (71-43-2)

acetic anhydride (108-24-7)

sodium carbonate (497-19-8)

PHOSPHORUS (7723-14-0)

oxygen (7782-44-7)

Benzoic acid (65-85-0)

Acetophenone (98-86-2)

benzoyl chloride (98-88-4)

Benzoic anhydride (93-97-0)

phosphoric acid (7664-38-2)

lead nitrate (10099-74-8)

benzotrichloride (98-07-7)

diphenyldichloromethane (2051-90-3)

sodium benzoate (532-32-1)

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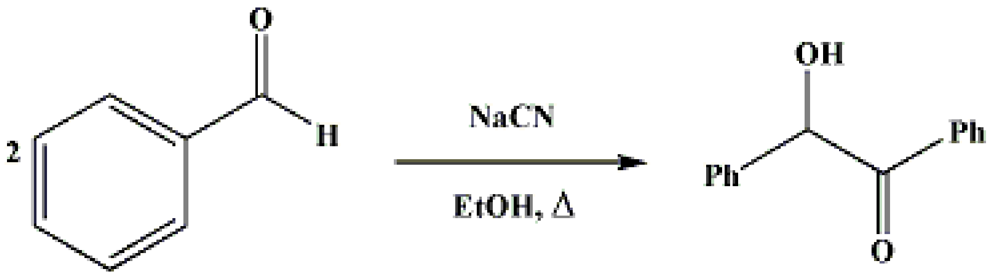
Organic Syntheses, CV 1, 94

BENZOIN



Submitted by Roger Adams and C. S. Marvel.
Checked by J. B. Conant and C. E. Bills.

1. Procedure

In a 3-l. round-bottomed flask (Note 1) fitted with a reflux condenser are placed 625 cc. of 95 per cent alcohol (Note 2), 500 cc. of water, 500 g. (476 cc., 4.7 moles) of pure benzaldehyde (Note 3), and 50 g. of sodium cyanide (96–98 per cent). The mixture is then heated and kept boiling for one-half hour (Note 4). In the course of about twenty minutes, crystals begin to separate from the hot solution. At the end of the thirty minutes, the solution is cooled, filtered with suction, and washed with a little water. The yield of dry crude benzoin, which is white or light yellow, is 450–460 g. (90–92 per cent of the theoretical amount). In order to obtain it completely pure, the crude substance is recrystallized from 95 per cent alcohol, 90 g. of crude material being dissolved in about 700 cc. of boiling alcohol; upon cooling, a yield of 83 g. of white, pure benzoin which melts at 129° is obtained.

2. Notes

1. The reaction sometimes takes place with considerable violence and material may be lost through the condenser. Accordingly, a somewhat larger flask is generally desirable, or the upper end of the reflux condenser is provided with a wide tube leading to an empty flask.
2. The procedure described requires 50 per cent of the amount of dilute alcohol which is ordinarily recommended in the literature. This allows one to prepare just double the amount of material in the same sized flask. The product obtained in this way, however, is slightly yellower than that obtained when more alcohol is used, but upon recrystallization it gives just as pure a product as that obtained by recrystallization of crude material made in the presence of more solvent. The results of many experiments lead to the conclusion that, if large amounts of benzoin are to be prepared, the method described above is the better one. If, however, only a small amount is needed and a good grade of crude material is satisfactory, the larger amount of solvent is perhaps more desirable.
3. It is absolutely necessary that pure benzaldehyde be used for this reaction.

The crude benzaldehyde which is obtained on the market should be washed with sodium carbonate solution, dried, distilled with minimum atmospheric exposure, and a fraction collected at 178–180°. Crude material will never give much more than a 50 per cent yield of benzoin.

4. Several times when benzoin was being prepared, the condensation took place and was complete after boiling five to ten minutes or even less, the product separating out in the hot solution with evolution of heat. The yield under these conditions was always good and the color better than when the reaction took a longer time. The cause of this occasional rapid reaction was not discovered, but it was probably due to inoculation with a little benzoin in certain of the experiments. When it takes place as just described, the flask and efficient condenser used will be sufficient to condense the sudden, rapid evolution of alcohol vapors caused by the heat of crystallization of the benzoin.

3. Discussion

Benzoin can be prepared by the action of an alkali cyanide on an alcoholic solution of benzaldehyde[1] and by the condensation of benzene with phenylglyoxal in the presence of aluminum chloride.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 87
- Org. Syn. Coll. Vol. 1, 89
- Org. Syn. Coll. Vol. 2, 69
- Org. Syn. Coll. Vol. 2, 159
- Org. Syn. Coll. Vol. 2, 231
- Org. Syn. Coll. Vol. 7, 95

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alkali cyanide

alcohol (64-17-5)

Benzene (71-43-2)

sodium cyanide (143-33-9)

sodium carbonate (497-19-8)

benzaldehyde (100-52-7)

aluminum chloride (3495-54-3)

Benzoin (119-53-9)

Phenylglyoxal (1074-12-0)

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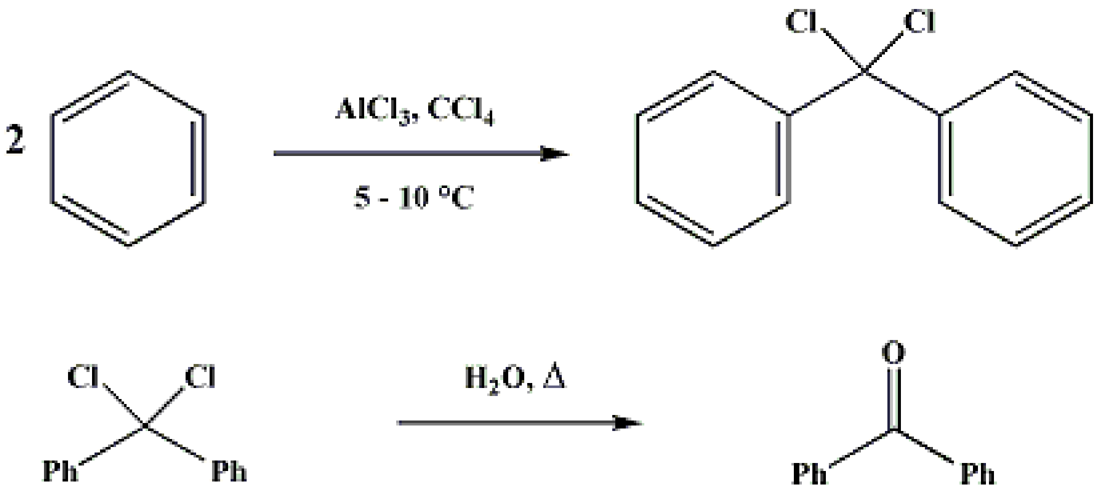
BENZOPHENONE



Submitted by C. S. Marvel and W. M. Sperry.
Checked by J. B. Conant and G. M. Bramann.

1. Procedure

In a 5-l. two-necked, round-bottomed flask fitted with a good mechanical stirrer (Note 1), a separatory funnel, a thermometer, and a reflux condenser connected with a trap (Note 2) for absorbing the hydrogen chloride evolved, are placed 455 g. (3.4 moles) of anhydrous aluminum chloride (Note 3) and 1 l. (10.2 moles) of dry carbon tetrachloride (Note 4). The flask is surrounded by an ice bath (Note 5). The stirrer is started and when the temperature of the carbon tetrachloride has dropped to 10–15°, 50 cc. of dry thiophene-free benzene (Note 6) is added all at once. The reaction begins immediately as is indicated by the evolution of hydrogen chloride and a rising temperature. As soon as the reaction has started, salt is added to the ice in the cooling bath in order to get more effective cooling. When the temperature begins to fall after the reaction has started, a mixture of 550 cc. (a total of 6.7 moles) of thiophene-free benzene and 550 cc. (a total of 14.5 moles) of carbon tetrachloride is run in at such a rate that the temperature is kept between 5° and 10° (Note 5). If efficient cooling is maintained, this addition requires one to two hours. The stirring is continued for about three hours after the benzene-carbon tetrachloride solution has been added, while the temperature is held at about 10°. The stirring is then discontinued and the mixture is allowed to stand about twelve hours. During this time the mixture comes to room temperature.

The stirrer is then again started and about 500 cc. of water is slowly added. External cooling is used in order that the water may be added more rapidly. The excess carbon tetrachloride usually refluxes during this part of the procedure. The reaction mixture is then first heated on a steam bath to remove most of the excess of carbon tetrachloride, then the mixture is distilled with steam to carry over the remaining carbon

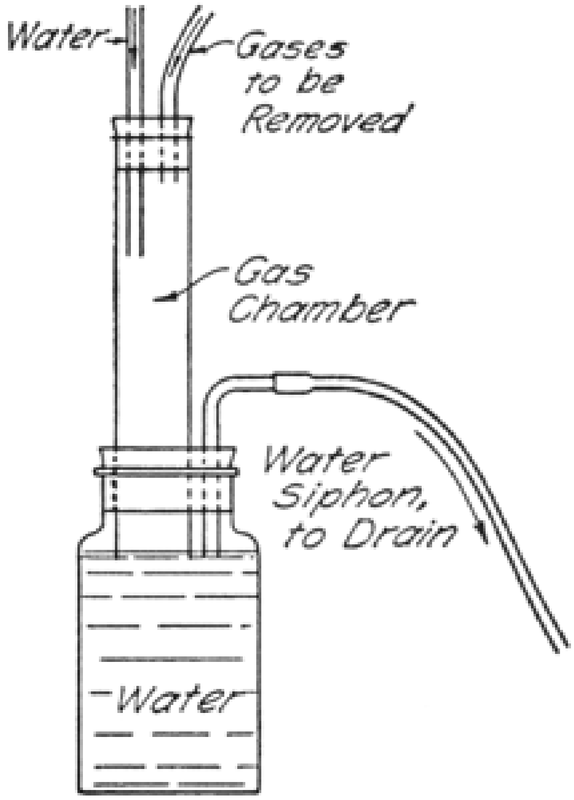
tetrachloride (Note 7), and to hydrolyze the benzophenone dichloride to benzophenone. The carbon tetrachloride comes over in about thirty minutes but the steam distillation is continued for about one hour to insure complete hydrolysis. The upper benzophenone layer is then separated from the aqueous layer and the latter is extracted with about 200 cc. of benzene. The benzene solution and the benzophenone are transferred to a 1-l. modified Claisen flask (p. 130) for distillation. The benzene and any water that is present are removed under ordinary pressure and the benzophenone is distilled under reduced pressure (Note 8). The yield is 490–550 g. (80–89 per cent of the theoretical amount based on the benzene) of a product boiling at 187–190° /15 mm., and solidifying to a white solid melting at 47–48°. The material sometimes has a bluish tinge. This color may be removed and a colorless product obtained by moistening the material with benzene and centrifuging.

2. Notes

1. The stirrer should be very efficient, as otherwise the aluminum chloride tends to cake on the sides of the flask. This makes cooling very difficult and thus increases the time necessary for the addition of the benzene-carbon tetrachloride mixture.

2. *Gas Absorption Trap*.—A convenient trap (Fig. 7) devised by John R. Johnson for the absorption of hydrogen chloride, or for the elimination of sulfur dioxide, hydrogen cyanide, etc., may be arranged as shown in the figure.

Fig. 7.



The gases are led into a chamber in which a stream of water (from the reflux condenser in this case) flows downward into a large bottle. The bottle is provided with a bent tube which serves as a siphon drain. The gases are thus brought into contact with a flowing stream of water so that the heat of solution is dissipated, and the level of the water in the lower bottle serves as a seal to prevent escape of the gases into the atmosphere. Water-insoluble gases are drawn out through the siphon drain directly into the sink.

If the gas chamber is of sufficient capacity there is practically no danger of water being drawn back into the reaction vessel, but care should be exercised when the reaction flask is cooled. For the reaction described here, a gas chamber about 2.5 cm. in diameter and 20–25 cm. in length was

found to be satisfactory.
An alternative, and simpler, gas absorption trap is described in Org. Syn. **14**, 2. In reactions involving compounds sensitive to water it is desirable to introduce a drying tube between the condenser and the trap in order to absorb any moisture which might diffuse up from the trap.
3. A good grade of technical anhydrous aluminum chloride was used to obtain the results given in the procedure. The yield decreases considerably when the quality of this reagent is not good.
4. No difference in yield is noticed in using the ordinary "pure" grade of carbon tetrachloride and the sulfur-free c.p. grade. It is easily dried by distilling the commercial product and rejecting the first 10 per cent of the distillate.
5. It is necessary to allow the reaction to start before packing in an ice-salt mixture. If the temperature is too low (below 10°) the reaction does not start. After the reaction has started, the cooling should be as efficient as possible so that the mixture of benzene and carbon tetrachloride may be added in the minimum amount of time. If the temperature drops below 5° the reaction is too slow. If the temperature goes above 10° there is increasing formation of tarry matter and lowering of the yield.
6. The yield is 5 to 10 per cent lower if the ordinary technical grade of benzene is used. The benzene is dried in the same manner as the carbon tetrachloride (Note 4).
7. About 1050–1150 cc. of carbon tetrachloride is recovered. This contains a small amount of benzene. However, it may be used in a succeeding run if it is dried over calcium chloride and distilled. No difference in the yield is noticed when recovered carbon tetrachloride is used.
8. There is considerable tendency for the benzophenone to foam over during the early part of the distillation under reduced pressure and care must be taken to prevent this.

3. Discussion

Benzophenone can be prepared by the distillation of calcium benzoate,[1] by the action of benzoyl chloride on benzene in the presence of aluminum chloride,[2] by the action of phosgene on benzene in the presence of aluminum chloride,[3] by the action of carbon tetrachloride on benzene in the presence of aluminum chloride followed by hydrolysis,[4] by treating benzoic anhydride in benzene and acetic anhydride with aluminum chloride,[5] by heating *o*-benzoyl-benzoic acid with a small amount of its copper salt,[6] by oxidizing diphenylmethane with nitric acid in the presence of lead acetate,[7] and by adding phenylmagnesium chloride to benzoyl chloride.[8]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 8

- Org. Syn. Coll. Vol. 1, 46
- Org. Syn. Coll. Vol. 1, 84
- Org. Syn. Coll. Vol. 1, 109
- Org. Syn. Coll. Vol. 1, 121
- Org. Syn. Coll. Vol. 1, 142
- Org. Syn. Coll. Vol. 1, 147
- Org. Syn. Coll. Vol. 1, 166
- Org. Syn. Coll. Vol. 1, 241
- Org. Syn. Coll. Vol. 1, 256
- Org. Syn. Coll. Vol. 1, 292
- Org. Syn. Coll. Vol. 1, 323
- Org. Syn. Coll. Vol. 1, 341
- Org. Syn. Coll. Vol. 1, 394
- Org. Syn. Coll. Vol. 1, 473
- Org. Syn. Coll. Vol. 1, 495
- Org. Syn. Coll. Vol. 1, 506
- Org. Syn. Coll. Vol. 1, 517
- Org. Syn. Coll. Vol. 1, 533
- Org. Syn. Coll. Vol. 1, 544
- Org. Syn. Coll. Vol. 1, 548
- Org. Syn. Coll. Vol. 2, 3
- Org. Syn. Coll. Vol. 2, 70
- Org. Syn. Coll. Vol. 2, 71
- Org. Syn. Coll. Vol. 2, 606
- Org. Syn. Coll. Vol. 3, 547
- Org. Syn. Coll. Vol. 4, 178
- Org. Syn. Coll. Vol. 6, 520
- Org. Syn. Coll. Vol. 9, 151

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8. Gilman and Mayhue, Rec. trav. chim. **51**, 47 (1932).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

calcium chloride (10043-52-4)

hydrogen chloride (7647-01-0)

Benzene (71-43-2)

acetic anhydride (108-24-7)

hydrogen (1333-74-0)

nitric acid (7697-37-2)

sulfur dioxide (7446-09-5)

carbon tetrachloride (56-23-5)

cyanide (57-12-5)

sulfur (7704-34-9)

benzoyl chloride (98-88-4)

Benzoic anhydride (93-97-0)

aluminum chloride (3495-54-3)

Benzophenone (119-61-9)

benzene-carbon tetrachloride

benzophenone dichloride

calcium benzoate (2090-05-3)

phosgene (75-44-5)

Diphenylmethane (101-81-5)

lead acetate

phenylmagnesium chloride (100-59-4)

o-benzoyl-benzoic acid (85-52-9)

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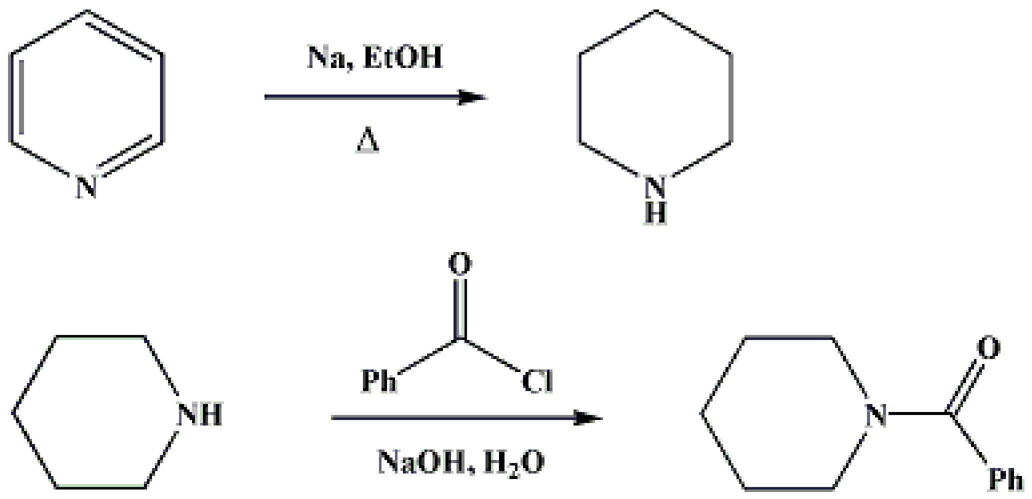
BENZOYL PIPERIDINE

[Piperidine, 1-benzoyl-]



Submitted by C. S. Marvel and W. A. Lazier.
Checked by J. B. Conant, J. S. Andrews, and C. O. Tongberg.

1. Procedure

In a 5-l., two-necked, round-bottomed flask, fitted with an efficient reflux condenser (Note 1), is placed a mixture of 130 g. (131 cc., 1.64 moles) of dry pyridine (Note 2) and 3 l. of absolute alcohol (see Note 2 on p. 249). During the course of forty to fifty minutes 450 g. (19.6 atoms) of sodium is added gradually. The sodium is added in as large pieces as can be inserted through the second opening in the flask. One and one-half liters of absolute alcohol is now added and the mixture heated over an oil bath for two to three hours until the sodium disappears. It is desirable not to allow the reaction mixture to cool (Note 3) at this point but to separate the piperidine immediately. The condenser is set for distillation and a separatory funnel is inserted through the stopper in the second opening of the flask. The alcohol is then distilled using an oil bath (Note 4). The addition of a piece of zinc facilitates an even distillation. During this procedure, water to the amount of 1700–1800 cc. is added to the reaction mixture through the separatory funnel, slowly at first and later as rapidly as possible. At the beginning, this addition must be very cautious as the heat evolved causes a very distillation of alcohol. After about 200 cc. of water has been added, the mixture begins to solidify and remains semi-solid until most of the water has been added. The distillation is continued until practically all the alcohol has distilled (three to four hours). At the end of this time there remains in the distilling flask about 1500 cc. of residue, which is discarded. The distillate is about 5 l. in volume. To this is added 200 cc. of concentrated hydrochloric acid (sp. gr. 1.19) and the mixture is then returned to the distilling flask. The alcohol is removed by distillation on a steam bath until the residual volume in the flask amounts to about 600–800 cc.; this requires two to three

hours.

The residue is then transferred to a 2-l. round-bottomed flask fitted with a mechanical stirrer and separatory funnel. The mixture is treated with stirring with a solution of 186 g. of technical sodium hydroxide or 170 g. (4.25 moles) of c.p. sodium hydroxide in about 300 cc. of water. With continuous stirring 235 g. (1.67 moles) of benzoyl chloride is now added during the course of one hour, keeping the temperature down by cooling with running water. After the addition, the reaction mixture is cooled, the amide separated (Note 5), washed with a little water (Note 6) and distilled (Note 7) under reduced pressure. The product boils at 180–184° /20 mm., 191–194° /27 mm., 240–244° /130 mm., and weighs 240–250 g. (77–81 per cent of the theoretical amount).

Benzoyl piperidine thus obtained is a straw-colored viscous liquid. Upon long standing or seeding with crystalline benzoyl piperidine, the compound crystallizes in long, colorless needles which melt at 44°. The literature reports 48° as the melting point of the pure material.

Using 180 g. of pyridine in place of the 130 g. suggested, and a corresponding increase in the other chemicals except the sodium and alcohol, a yield of 300–326 g. of benzoyl piperidine is obtained. This is a smaller percentage yield (70–75 per cent of the theoretical amount) but the actual yield more than repays for the excess of pyridine used (Note 8).

2. Notes

1. A reflux condenser 180 cm. long with inner tube 2 cm. in diameter is recommended. If a smaller condenser is employed, the reaction cannot be run as rapidly as is desirable to give the best results. If the reaction is not run rapidly sodium ethoxide separates in the flask.
2. Unless the purity of the pyridine is known, it should be dried with solid sodium hydroxide and distilled before use. For this work a fraction boiling at 112–117° was used.
3. If the alcohol solution is allowed to cool before the addition of the water, it solidifies and is remelted only with difficulty. If it is desired to suspend the process, the water should be added first and then the solution will not solidify.
4. In distilling the piperidine from the strong alkaline solution, the flask must be suspended in the oil bath. Direct heating raises the temperature of the flask to such a point that the alkali rapidly etches through it.
5. A troublesome emulsion sometimes results after benzoylation. This usually may be broken up by the addition of more strong sodium hydroxide solution. In case an emulsion is formed which cannot be broken it is possible to extract the product with benzene.
6. Any sodium hydroxide carried into the distilling flask causes decomposition of the benzoyl piperidine during distillation and consequently a considerably lower yield results. For this reason it is well to wash the product carefully in the

separatory funnel with a little water after the alkaline solution has been drawn off.
7. Benzoyl piperidine is much given to superheating, making distillation difficult.
8. If piperidine is available, benzoyl piperidine for use in the preparation of pentamethylene bromide (p. 428) may be prepared by direct benzoylation. A mixture of 105 g. of sodium hydroxide (2.6 moles), 170 g. of piperidine (2.0 moles) (b.p. 104–109°), and 800 cc. of water is treated with 280 g. (2 moles) of benzoyl chloride using the apparatus and procedure described above; the temperature is kept at 35–40°. The oily product is separated after dilution with 250 cc. of benzene if necessary (Note 5), dried with a small quantity of potassium carbonate and distilled. The portion boiling at 172–174° /12 mm. weighs 330–345 g. (87–91 per cent of the theoretical amount). The first few cubic centimeters of the distillate may be colored by a reddish impurity, in which case a forerun is collected separately.

3. Discussion

Benzoyl piperidine can be prepared by the action of benzoyl chloride on piperidine in the presence of alkalies.[1]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 428
- Org. Syn. Coll. Vol. 3, 432
- Org. Syn. Coll. Vol. 8, 326

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alcohol (64-17-5)

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

sodium hydroxide (1310-73-2)

benzoyl chloride (98-88-4)

pyridine (110-86-1)

zinc (7440-66-6)

sodium (13966-32-0)

BENZOYL PIPERIDINE, Piperidine, 1-benzoyl- (776-75-0)

piperidine (110-89-4)

sodium ethoxide (141-52-6)

pentamethylene bromide (111-24-0)

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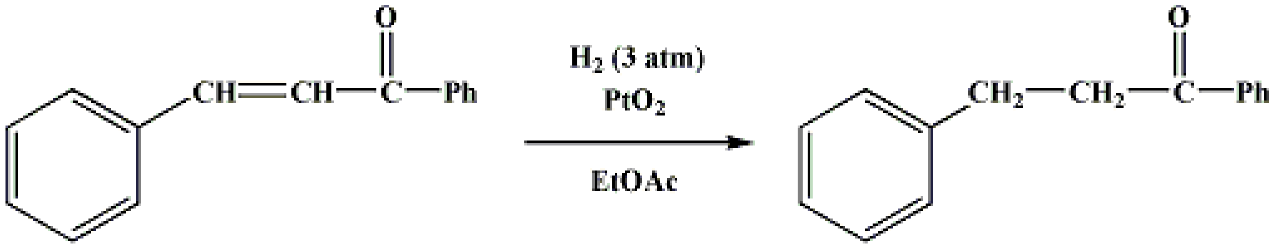
BENZYLACETOPHENONE

[Propiophenone, β-phenyl-]



Submitted by Roger Adams, J. W. Kern, and R. L. Shriner.
Checked by Henry Gilman and S. A. Harris.

1. Procedure

A solution of 20.8 g. (0.1 mole) of benzalacetophenone (p. 78) (Note 1) in 150 cc. of c.p. ethyl acetate (Note 2) is placed in the reaction bottle of the catalytic reduction apparatus (p. 61), and 0.2 g. of platinum oxide catalyst (p. 463) is added. The apparatus is evacuated, then filled with hydrogen, and the mixture shaken with hydrogen until 0.1 mole has been absorbed. The time required is usually about fifteen to twenty-five minutes (Note 3). The platinum is filtered off and the solvent removed from the filtrate by distillation. The benzylacetophenone is recrystallized from about 25 cc. of alcohol and melts at 72–73°. The yield is 17–20 g. (81–95 per cent of the theoretical amount).

2. Notes

1. The benzalacetophenone should be freshly recrystallized from alcohol just before using and should melt at 57°.
2. Owing to the comparatively slight solubility of benzalacetophenone in alcohol, ethyl acetate is used as a solvent during the reduction.
3. If 0.1 g. of catalyst is used the reduction requires about three hours; an increase in catalyst to 0.5 g. causes the reduction to take place in three or four minutes. The exact time depends to a considerable extent on the grade of benzalacetophenone used and it is not certain that the purest will necessarily be reduced in the shortest time.

3. Discussion

Benzylacetophenone can be prepared by the reduction of benzalacetophenone with zinc and acetic acid[1] and catalytically with palladium and hydrogen;[2] by the oxidation of the corresponding carbinol with chromic acid;[3] and by the hydrolysis of ethyl benzylbenzoylacetate.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 61

- Org. Syn. Coll. Vol. 1, 463

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alcohol (64-17-5)

acetic acid (64-19-7)

ethyl acetate (141-78-6)

hydrogen (1333-74-0)

platinum oxide

Benzalacetophenone (94-41-7)

Benzylacetophenone, Propiophenone, β-phenyl- (1083-30-3)

platinum (7440-06-4)

zinc (7440-66-6)

palladium (7440-05-3)

chromic acid (7738-94-5)

ethyl benzylbenzoylacetate

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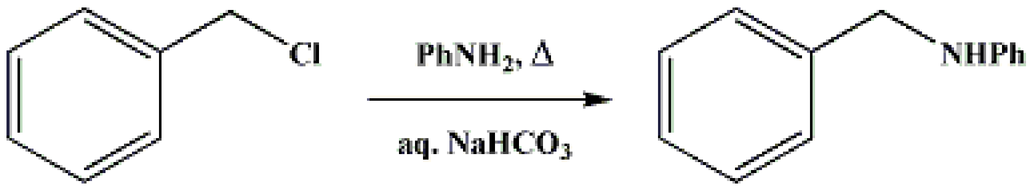
Organic Syntheses, CV 1, 102

BENZYLANILINE

[Benzylamine, N-phenyl-]



Submitted by F. G. Willson and T. S. Wheeler.
Checked by Henry Gilman and R. McCracken.

1. Procedure

A 1500-cc. flask is fitted with a reflux condenser, a mechanical stirrer, and a 200-cc. separatory funnel. In the flask are placed 372 g. (4 moles) of aniline (Note 1), 105 g. (1.25 moles) of sodium bicarbonate (Note 2), and 100 cc. of water. The flask and contents are then heated on a steam bath to 90–95°, and 127 g. (115 cc., 1 mole) of benzyl chloride (Note 3) is run in slowly from the separatory funnel, vigorous agitation being maintained. The addition of benzyl chloride should take not less than one and one-half to two hours, and the reaction is complete in four hours.

The mixture is then cooled, filtered with suction, the layers of water and organic liquid separated, and the latter washed with saturated salt solution (Note 4). The amines are then dried by shaking with about 20 g. of anhydrous sodium sulfate, and again filtered with suction. The excess of aniline is removed by distillation under reduced pressure (Note 5) using a modified Claisen flask with a fractionating side arm (p. 130). The aniline distils at 81° /12 mm., and then the temperature rises quickly to the boiling point of benzylaniline, 180° /12 mm. or 190° /16 mm. When the temperature has risen to within about 5° of the boiling point of the benzylaniline, the receiver is again changed and the benzylaniline collected from 170–200° /12 mm., practically all boiling at 178–180° /12 mm. (Note 6).

The aniline recovered amounts to 250–260 g. (89–92 per cent of the theoretical amount), and the yield of benzylaniline is 155–160 g. (85–87 per cent of the theoretical amount based on the benzyl chloride). The product solidifies on cooling and melts at 33–36°. It is practically colorless and sufficiently pure for most synthetic purposes. A pure compound melting at 36° may be obtained by crystallizing the product from about 100 cc. of ligroin (b.p. 85–90°). The solution is cooled in a freezing mixture to cause crystallization, the crystals filtered with suction, washed with a little cold ligroin, pressed, and dried. The recovery is about 90 per cent of the original product.

2. Notes

1. Benzylaniline reacts with benzyl chloride to form dibenzylaniline. If the proportion of aniline used is less than that given, the yield of benzylaniline is lowered, and separation rendered more difficult.
2. Sodium bicarbonate is used on account of its high purity and convenience in handling. An equivalent amount of the normal carbonate may be substituted, but reagents of stronger basicity increase the proportion of high-boiling by-products.
3. The benzyl chloride should be freshly distilled and collected at 176–178°.
4. Saturated salt solution is used here in preference to water, as separation of the liquids is more rapid and clean.
5. The aniline may also be quite satisfactorily removed by distillation under atmospheric pressure, using an efficient fractionating column, the distillation being interrupted when the thermometer in the still-head registers 235°.
6. Benzylaniline distils without appreciable decomposition at atmospheric pressure at 298–300°. It assumes, however, a yellow color, and separation from any higher-boiling impurities is more difficult than when distillation is carried out under reduced pressure.

3. Discussion

Benzylaniline can be prepared from aniline and benzyl chloride by heating at 160° in a reaction which may be violent and always leads to mixtures;[1] at low temperatures with an excess of aniline;[2] and in a sodium carbonate solution.[3] It can also be prepared by the reduction of benzalaniline with sodium and alcohol,[4] and by the reductive alkylation of nitrobenzene or aniline with benzaldehyde, hydrogen, and a catalyst in the presence of sodium acetate.[5]

References and Notes

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3. Gomberg and Buchler, J. Am. Chem. Soc. **42**, 2059 (1920).
4. Fischer, Ann. **241**, 330 (1887).
5. Emerson and Walters, J. Am. Chem. Soc. **60**, 2023 (1938); Emerson and Mohrman, ibid. **62**, 69 (1940).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ligroin

alcohol (64-17-5)

sodium acetate (127-09-3)

aniline (62-53-3)

hydrogen (1333-74-0)

sodium bicarbonate (144-55-8)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

benzaldehyde (100-52-7)

Benzalaniline (538-51-2)

sodium (13966-32-0)

Benzylaniline, Benzylamine, N-phenyl- (103-32-2)

benzyl chloride (100-44-7)

dibenzylaniline (91-73-6)

Nitrobenzene (98-95-3)

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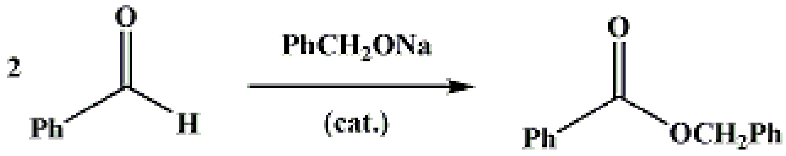
Organic Syntheses, CV 1, 104

BENZYL BENZOATE

[Benzoic acid, benzyl ester]



Submitted by O. Kamm and W. F. Kamm.
Checked by Roger Adams and R. L. Jenkins.

1. Procedure

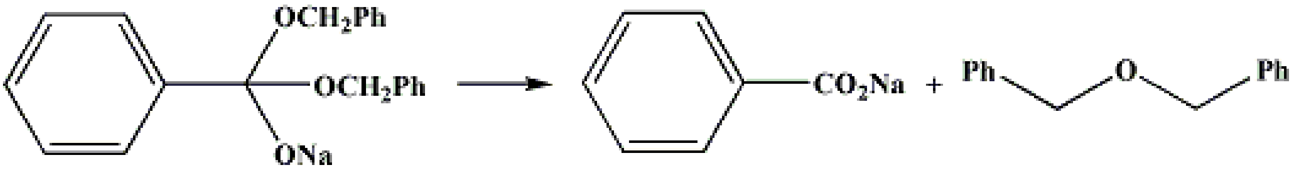
Three grams (0.13 atom) of metallic sodium is dissolved by warming for one-half hour in 70 g. (0.65 mole) of pure benzyl alcohol (Note 1), and after the mixture has cooled to room temperature the solution is added gradually, with thorough mixing, to 454 g. (4.3 moles) of c.p. benzaldehyde (which must contain *less* than 1 per cent of benzoic acid) (Note 2). The reaction mixture has a tendency to become warm, but the temperature should be kept slightly below 50–60° by cooling, if necessary (Note 3). A pasty gelatinous mass results. After about one-half hour the temperature of the mixture no longer rises; it is then warmed on the water bath for about one or two hours, with occasional shaking (Note 4).

The cooled reaction product is treated with 200 cc. of water (Note 5), the layer of oil separated, washed once with a second portion of water, and subjected to distillation under reduced pressure. The first fraction of the distillate contains benzyl alcohol together with unchanged aldehyde (Note 6), as well as a small quantity of water. The temperature then rises rapidly to the boiling point of benzyl benzoate, when the receiver is changed. The product boils at 184–185° /15 mm., and analysis by saponification shows it to consist of 99 per cent ester. The yield is 410–420 g. (90–93 per cent of the theoretical amount). This benzyl benzoate supercools readily, but after solidifying melts within one degree of the highest recorded value (19.4°) and therefore need not be refractionated, unless material of exceptional purity is required.

2. Notes

1. The benzyl alcohol used in this preparation must be free from impurities, especially aldehyde. One cubic centimeter dissolved in 50 cc. of water and treated with a freshly prepared clear solution of phenylhydrazine acetate should give no appreciable precipitate. If it is not pure, it must first be treated with alkali as described in (Note 6).
2. The benzaldehyde should be titrated in order to determine its acidity. If it is found to contain sufficient benzoic acid to react with a considerable proportion of the sodium alcoholate, a poor yield of ester will be obtained. Less than 1 per cent of benzoic acid will not interfere seriously with the yields obtained, but the presence of larger quantities of acid will be found to be detrimental and must be removed by washing the benzaldehyde with a sodium carbonate solution and redistilling with the precautions necessary to prevent too free an access of air to the distillate.
3. The order of mixing the reagents and the temperature of the ingredients at the time of mixing are the most important factors in the experiment.

In the presence of sodium benzoxide two molecules of benzaldehyde react with the alkoxide to form an addition product. When the reaction mixture is overheated an important side reaction may occur, as follows:



Dibenzyl ether no doubt forms the chief impurity in benzyl benzoate. Since the boiling point of the former lies near that of the ester, it is not removed during the process of purification by distillation.
The causes of variations in yield by the use of the older methods can now be explained. When benzaldehyde is added *to the alkoxide*, and especially when the latter is still warm, local overheating results; in fact, the temperature may rise far above 100° with the result that benzyl ether is formed. Simultaneously, the sodium benzoxide is converted into sodium benzoate, which is of no value for inducing the desired reaction, and consequently very little benzyl benzoate is obtained. The same side reactions explain the failure of this experiment when the benzyl alcohol used in preparing the catalyst (sodium benzoxide) is contaminated with benzaldehyde.

4. The temperature at which the reaction mixture is maintained after mixing, provided that it is held below 100°, has no great effect on the purity of product.

5. The reaction mixture is not treated with acetic acid, as usually recommended, for the reason that such a procedure yields a final product contaminated with benzoic acid, unless an alkaline wash is applied subsequently.

6. The recovered benzyl alcohol can be used for the preparation of a second lot of benzyl benzoate only after it has been boiled with strong sodium hydroxide to remove all traces of benzaldehyde.

3. Discussion

Benzyl benzoate can be prepared by the action of benzyl chloride on sodium benzoate, even in aqueous solution,[1] and by the action of alkoxides on benzaldehyde.[2] The sodium alkoxide method, used in the procedure described, is most convenient and practical. Unfortunately, it has been found to be extremely erratic in regard to yield (10–95 per cent), as well as in regard to the purity of the product (87–97 per cent ester).[3] As a result of the present study,[4] causes for variations are accounted for and the procedure has been converted into a satisfactory method of preparation.

References and Notes

1. Gomberg and Buchler, J. Am. Chem. Soc. **42**, 2059 (1920); Scelba, Boll. chim. farm. **62**, 33 (1923) [C. A. **17**, 2166 (1923)].
2. Claisen, Ber. **20**, 649 (1887); Kohn and Tranton, J. Chem. Soc. **75**, 1155 (1899); Matheson, Brit. pat. 270,651 [C. A. **22**, 1597 (1928)]; Grignard and Fluchaire, Ann. chim. **9**, 19 (1928).
3. Anon., Rep. Lab. Am. Med. Assoc. **12**, 84 (1919) [C. A. **14**, 3500 (1920)].
4. Kamm and Matthews, J. Am. Pharm. Assoc. **11**, 599 (1922).

Appendix

Compounds Referenced (Chemical Abstracts Registry Number)

sodium alcoholate

sodium benzoxide

acetic acid (64-19-7)

sodium hydroxide (1310-73-2)

sodium carbonate (497-19-8)

Benzoic acid (65-85-0)

benzaldehyde (100-52-7)

metallic sodium (13966-32-0)

sodium benzoate (532-32-1)

benzyl chloride (100-44-7)

BENZYL BENZOATE, Benzoic acid, benzyl ester (120-51-4)

Benzyl alcohol (100-51-6)

phenylhydrazine acetate

Dibenzyl ether, benzyl ether (103-50-4)

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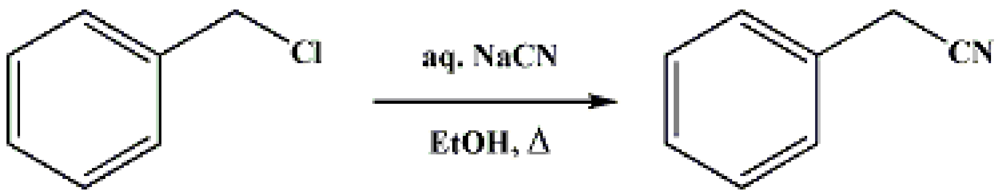
Organic Syntheses, CV 1, 107

BENZYL CYANIDE

[α-Tolunitrile]



Submitted by Roger Adams and A. F. Thal.
Checked by O. Kamm and A. O. Matthews.

1. Procedure

In a 5-l. round-bottomed flask, fitted with a stopper holding a reflux condenser and separatory funnel, are placed 500 g. (10 moles) of powdered sodium cyanide (96–98 per cent pure) and 450 cc. of water. The mixture is warmed on a water bath in order to dissolve most of the sodium cyanide, and then 1 kg. (8 moles) of benzyl chloride (b.p. 170–180°) (Note 1) mixed with 1 kg. of 95 per cent alcohol is run in through the separatory funnel in the course of one-half to three-quarters of an hour. The mixture is then heated under a reflux condenser on the steam bath for four hours, cooled and filtered with suction to remove most of the sodium chloride. It is well to wash the filtered salt with a small portion of alcohol in order to remove any benzyl cyanide which may have been mechanically held.

The flask is now fitted with a condenser, and as much alcohol as possible is distilled off on the steam bath. The residual liquid is cooled, filtered if necessary, and the layer of benzyl cyanide separated. This crude benzyl cyanide is now placed in a Claisen distilling flask and distilled under reduced pressure, the water and alcohol coming over first, and finally the cyanide (Note 2). It is advantageous to use a fractionating column or, better still, a Claisen flask with a modified side arm[1] (p. 130), which gives the same effect as a fractionating column (Note 3). The material is collected at 135–140° /38 mm. (115–120° /10 mm.) (Note 4). The yield is 740–830 g. (80–90 per cent of the theoretical amount).

2. Notes

1. The quality of the benzyl chloride markedly affects the yield of pure benzyl cyanide. If a poor technical grade is used, the yields will not be more than 60–75 per cent of the theoretical, whereas consistent results of about 85 per cent or more may always be obtained when a product is used that boils over 10°. The technical benzyl chloride at hand yielded on distillation about 8 per cent of high-boiling material; a technical grade from another source was of unusual purity

and boiled over a 2° range for the most part.
2. It is advisable to distil off the last portion of alcohol and water and also to distil the benzyl cyanide under reduced pressure, since under ordinary pressures a white solid invariably separates during the distillation.
3. One method of purifying the benzyl cyanide is to steam distil it after the alcohol has been first distilled from the reaction mixture. At ordinary pressures, this steam distillation is very slow and, with an ordinary condenser, requires eighteen to twenty hours in order to remove all the volatile product from a run of 500 g. of benzyl chloride. The distillate separates into two layers; the benzyl cyanide layer is removed and distilled. The product obtained in this way is very pure and contains no tarry material, and, after the excess of benzyl chloride has been removed, boils at practically constant temperature. This steam distillation is hardly advisable in the laboratory.
4. Benzyl cyanide, prepared according to the procedure just described and collected over a 5° range, is perfectly satisfactory for many purposes, such as the preparation of phenylacetic acid (p. 436) or ester (p. 270). However, the cyanide has a disagreeable odor due to the presence of benzyl isocyanide and often develops appreciable color on standing. The following treatment, suggested by John R. Johnson, removes the isocyanide and furnishes a water-white product which develops no color on standing for several months. The once-distilled benzyl cyanide is shaken vigorously for five minutes with an equal volume of warm (60°) 50 per cent sulfuric acid, prepared by adding 275 cc. of concentrated sulfuric acid to 500 cc. of water. The benzyl cyanide is separated and washed with an equal volume of saturated sodium bicarbonate solution followed by an equal volume of half-saturated sodium chloride solution. It is then dried and distilled under reduced pressure. The loss in the washings is negligible.

3. Discussion

Benzyl cyanide can be prepared from alcoholic potassium cyanide and benzyl chloride.[2] The less expensive sodium cyanide is just as satisfactory and therefore is the better compound to use. An aqueous solution of sodium cyanide has been used.[3] It has been prepared by passing phenylacetic acid and ammonia over silica gel at 500°,[4] and by the catalytic reduction of mandelonitrile.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 270
- Org. Syn. Coll. Vol. 1, 396
- Org. Syn. Coll. Vol. 1, 436
- Org. Syn. Coll. Vol. 2, 287
- Org. Syn. Coll. Vol. 2, 487
- Org. Syn. Coll. Vol. 2, 512

- Org. Syn. Coll. Vol. 3, 715
- Org. Syn. Coll. Vol. 3, 720
- Org. Syn. Coll. Vol. 4, 387
- Org. Syn. Coll. Vol. 4, 760

References and Notes

1. Noyes and Skinner, J. Am. Chem. Soc. **39**, 2718 (1917).
2. Cannizzaro, Ann. **96**, 247 (1855); Radziszewski, Ber. **3**, 198 (1870); Mann, Ber. **14**, 1645 (1881); Staedel, Ber. **19**, 1950 (1886).
3. Gomberg and Buchler, J. Am. Chem. Soc. **42**, 2059 (1920).
4. Mitchell and Reid, ibid. **53**, 328 (1931).
5. Zelinsky, Packendorff, and Leder-Packendorff, Ber. **67**, 300 (1934).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

alcohol (64-17-5)

sulfuric acid (7664-93-9)

ammonia (7664-41-7)

α-Tolunitrile (100-47-0)

sodium bicarbonate (144-55-8)

sodium cyanide (143-33-9)

sodium chloride (7647-14-5)

cyanide, isocyanide (57-12-5)

potassium cyanide (151-50-8)

benzyl chloride (100-44-7)

Benzyl cyanide (140-29-4)

Phenylacetic acid (103-82-2)

Benzyl isocyanide (10340-91-7)

mandelonitrile (532-28-5)

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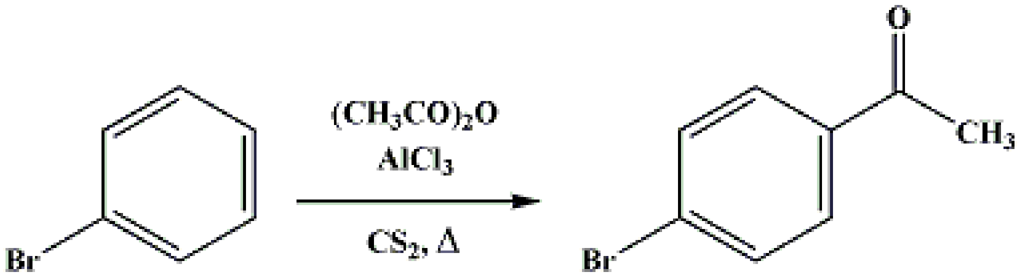
Organic Syntheses, CV 1, 109

p-BROMOACETOPHENONE

[Acetophenone, *p*-bromo-]



Submitted by Roger Adams and C. R. Noller.
Checked by J. B. Conant and C. R. Kinney.

1. Procedure

In a 5-l. round-bottomed, three-necked flask, fitted with a mechanical stirrer, separatory funnel, and reflux condenser connected with a gas absorption trap (Fig. 7 on p. 97) for disposing of the evolved hydrogen chloride, is placed 392 g. (2.5 moles) of bromobenzene in 1-l. of dry carbon disulfide (Note 1). To this is added 750 g. (5.6 moles) (Note 2) of anhydrous aluminum chloride. The mixture is heated on a steam bath until gentle refluxing starts, and then 204 g. (2 moles) of acetic anhydride (Note 3) is added slowly through the dropping funnel. The time of addition is about one hour. Gentle refluxing should be continued throughout the time of addition of the anhydride and for one hour afterward. The reaction is accompanied by a copious evolution of hydrogen chloride which does not entirely cease even after this subsequent heating.

A condenser is attached to one of the side necks, and the carbon disulfide is distilled without removing the flask from the steam bath. After the removal of the solvent (Note 4), the reaction mixture is allowed to cool somewhat (Note 5); but while it is still warm, it is poured slowly with stirring over cracked ice to which hydrochloric acid has been added. In this way only a small amount of the aluminum chloride addition product remains in the flask. This is decomposed with ice and hydrochloric acid and added to the main product. The volume is now about 5 l. Each 2-l. portion is extracted twice with 300-cc. and 200-cc. portions of benzene or ether. The extracts are combined and washed twice with water, once with 10 per cent sodium hydroxide solution, and twice more with water. The final water washings should be practically colorless and the separation sharp, any precipitate being allowed to separate with the water.

The extract is dried for one hour with about 30 g. of calcium chloride and filtered, and the solvent is distilled from a steam bath. The residue is distilled under reduced

pressure with a short column (p. 130). Some low-boiling material comes over first, and then the temperature rises rapidly. If care has been taken in the water decomposition to remove all the aluminum salts (Note 6), the product comes over water-white and crystallizes to a white solid melting at 49–50.5°. The yield is 340–395 g. (69–79 per cent of the theoretical amount) of a product boiling over a 3° range (Note 7) and (Note 8). On redistillation the boiling point is 117°/7 mm.; 129–130°/15 mm.; and 255.5°/736 mm.

2. Notes

1. If the carbon disulfide-bromobenzene solution is not clear it should be dried over calcium chloride and filtered before the aluminum chloride is added. In using such large amounts of carbon disulfide, particular precautions must be taken to prevent fires.
2. The aluminum chloride should be added in about this excess. When the excess is larger the yield does not seem to be increased, and when only 2 equivalents are used it is diminished by 10 to 15 per cent.
3. The acetic anhydride should boil at 136–139°. Some commercial grades are satisfactory, whereas others have been found to contain almost 50 per cent of acetic acid.
4. About 600–800 cc. of carbon disulfide is recovered and may be used in the next run.
5. If the product is allowed to come to room temperature before decomposition with water, it becomes semi-solid and is not easily removed from the flask.
6. If the aluminum chloride double compound is not entirely decomposed by water and the aluminum salts thus removed, the distillate comes over slightly red and does not crystallize well on cooling. Redistillation, however, gives a pure product.
7. This method is an improvement over the older methods for the preparation of substituted acetophenone derivatives. The yields obtained by the use of acetyl chloride in place of acetic anhydride in the preparation of *p*-bromoacetophenone were invariably lower.
The yield is based on the bromobenzene, because a side reaction between the acetic acid, aluminum chloride, and bromobenzene also produces some ketone.
8. Under the same general conditions, satisfactory yields of other acetophenones may be obtained. Thus, from 281 g. of chlorobenzene, 750 g. of aluminum chloride, and 205 g. of acetic anhydride, a consistent yield of 285–300 g. (74–78 per cent of the theoretical amount) of *p*-chloroacetophenone, boiling at 124–126° /24 mm. and melting at 20–21°, is obtained. Similarly, acetophenone may be obtained in 76–83 per cent yields, *p*-methylacetophenone in 85–89 per cent yields, and *p*-methoxyacetophenone in 90–94 per cent yields.

3. Discussion

p-Bromoacetophenone can be prepared by the action of acetyl chloride in carbon

disulfide on bromobenzene in the presence of anhydrous aluminum chloride,[1] and by the use of acetic anhydride in place of the acetyl chloride.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 127
- Org. Syn. Coll. Vol. 2, 503
- Org. Syn. Coll. Vol. 4, 110

References and Notes

1. Schweitzer, Ber. **24**, 550, 3766 (1891); Hale and Thorp, J. Am. Chem. Soc. **35**, 266 (1913).
2. Noller and Adams, ibid. **46**, 1892 (1924).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

carbon disulfide-bromobenzene

calcium chloride (10043-52-4)

hydrogen chloride, hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

ether (60-29-7)

acetic anhydride (108-24-7)

sodium hydroxide (1310-73-2)

acetyl chloride (75-36-5)

aluminum (7429-90-5)

Acetophenone (98-86-2)

chlorobenzene (108-90-7)

aluminum chloride (3495-54-3)

bromobenzene (108-86-1)

carbon disulfide (75-15-0)

p-Bromoacetophenone, Acetophenone, p-bromo- (99-90-1)

p-Chloroacetophenone (99-91-2)

p-Methylacetophenone (122-00-9)

p-Methoxyacetophenone (100-06-1)

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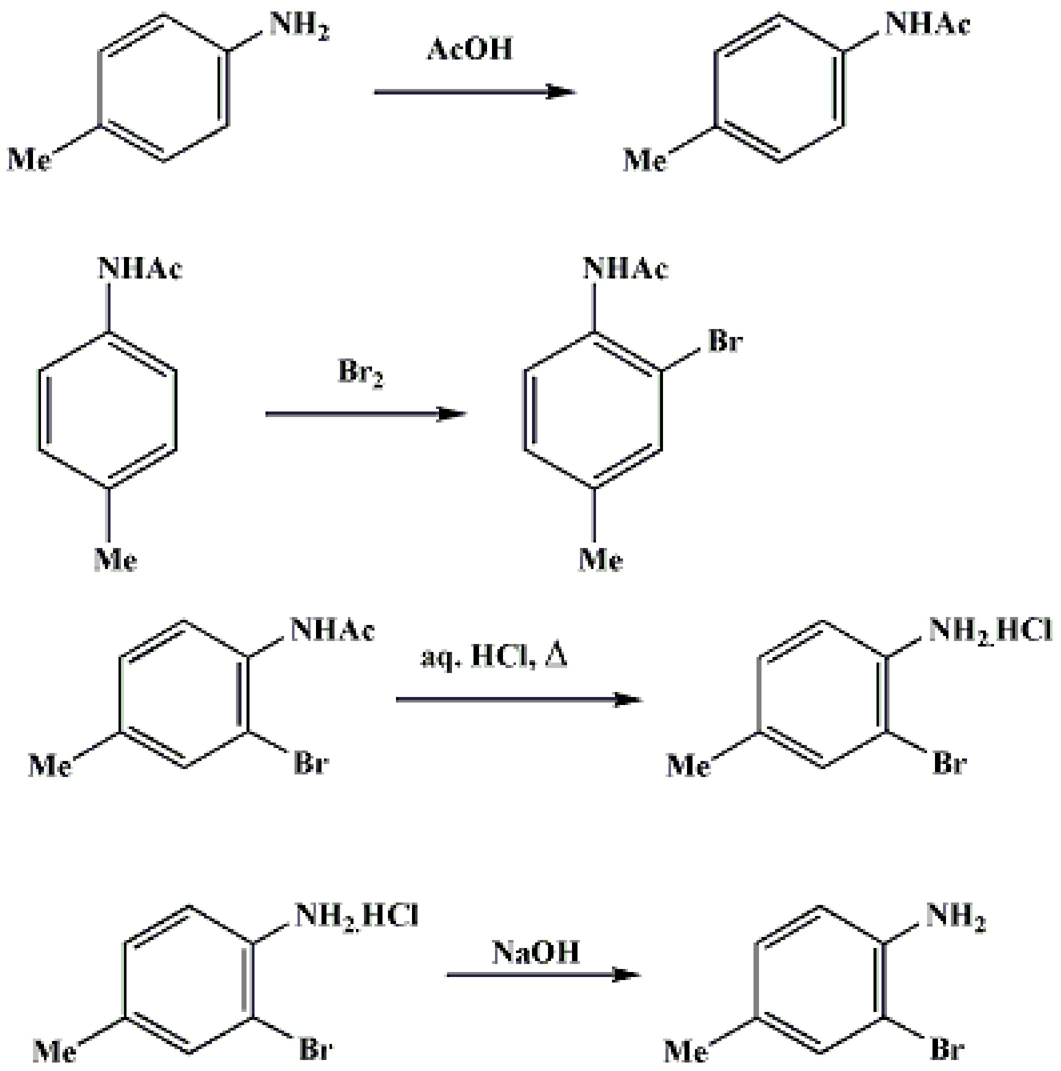
Organic Syntheses, *CV 1*, *111*

3-BROMO-4-AMINOTOLUENE

[*p*-Toluidine, 2-bromo-]



Submitted by J. R. Johnson and L. T. Sandborn.
Checked by Frank C. Whitmore and A. M. Griswold.

1. Procedure

p-Acetotoluide is prepared by refluxing 214 g. (2 moles) of commercial *p*-toluidine with 800 cc. of glacial acetic acid in a 2-l. round-bottomed flask for two hours. The reflux condenser is replaced by a mechanical stirrer and the mixture is stirred and cooled to 45°. Part of the product may separate in small crystalline flakes. The mixture is thoroughly stirred and 325 g. (102 cc., 2.03 moles) of bromine is added slowly from a separatory funnel at such a rate that the temperature of the mixture is maintained at 50–55°. During the course of this addition, which requires about forty minutes, a precipitate may separate; this later dissolves. The mixture is stirred one-half hour after the bromine has been added, and is then poured in a thin stream (Note 1) with efficient

stirring into 10 l. of cold water to which has been added 25 g. of sodium bisulfite (Note 2).

The 3-bromo-4-acetaminotoluene separates in crystalline flocks. It is filtered by suction and washed well with water and pressed dry. The wet crude material is dried until its weight does not exceed 500 g. before proceeding with the hydrolysis (Note 3).

The partially dried 3-bromo-4-acetaminotoluene is refluxed with 500 cc. of 95 per cent ethyl alcohol in a 3-l. round-bottomed flask. To the boiling solution is added 500 cc. of concentrated hydrochloric acid and the refluxing is continued for three hours. During this time, crystals of the hydrochloride of 3-bromo-4-aminotoluene separate. The hot mixture is poured into a 2-l. beaker and cooled thoroughly in running water. The hydrochloride is filtered by suction and washed rapidly with two 100-cc. portions of chilled alcohol. The weight of the hydrochloride is 250–300 g. (Note 4).

The hydrochloride is suspended in 800 cc. of water in a 2-l. beaker provided with a mechanical stirrer. The base is liberated by the addition of a solution of 140 g. of technical sodium hydroxide in 700 cc. of water, and settles as a heavy brownish oil. After cooling to room temperature, the oil is separated and weighed. The yield of the crude base is 225–250 g. (60–67 per cent of the theoretical amount based on the amount of *p*-toluidine used). The crude material may be used directly for the preparation of *m*-bromotoluene (p. 133).

The base may be purified by steam distillation but distillation under reduced pressure is more satisfactory. The oil is dried over 5 g. of solid sodium hydroxide and distilled under reduced pressure. The first portion of the distillate may contain *p*-toluidine and must be carefully separated, as it causes rapid discoloration. The 3-bromo-4-aminotoluene is obtained as a colorless liquid of b.p. 120–122°/30 mm. or 92–94°/3 mm. It solidifies on cooling and melts at 16–18°. The loss on purification is about 15 per cent of the weight of the crude base.

2. Notes

1. The bromine compound often separates at first as a heavy oil. To avoid the formation of lumps, this material should be seeded or allowed to crystallize spontaneously before the main portion is poured into water.
2. If the color of bromine persists, more sodium bisulfite should be added.
3. If the material is not partly dried before hydrolysis, the yield of the hydrochloride is diminished because of its solubility. If pure 3-bromo-4-acetaminotoluene is desired, the crude material may be crystallized from 50 per cent alcohol with the addition of decolorizing carbon (Norite) as almost colorless needles, m.p. 116–117°. The yield is 360 g. (79 per cent of the theoretical amount). This purification has no advantage when the acetamino compound is to be hydrolyzed to the amine.
4. The dark filtrate from the hydrochloride does not contain enough dissolved salt to justify recovery unless the acetamino compound is insufficiently dried

before the hydrolysis.

3. Discussion

3-Bromo-4-aminotoluene can be prepared by the bromination of *p*-acetotoluide, followed by hydrolysis of the resulting bromoacetotoluidide.[1] The procedure described is a modification of Feitler's method.[1]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 133
- Org. Syn. Coll. Vol. 2, 480
- Org. Syn. Coll. Vol. 3, 130
- Org. Syn. Coll. Vol. 3, 791
- Org. Syn. Coll. Vol. 5, 139

References and Notes

1. Wroblevsky, Ann. **168**, 153 (1873); Feitler, Z. physik. Chem. **4**, 77 (1889).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloride of 3-bromo-4-aminotoluene

ethyl alcohol, alcohol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

sodium hydroxide (1310-73-2)

bromine (7726-95-6)

sodium bisulfite (7631-90-5)

decolorizing carbon (Norite) (7782-42-5)

3-Bromo-4-aminotoluene, p-Toluidine, 2-bromo- (583-68-6)

3-Bromo-4-acetaminotoluene (614-83-5)

bromoacetotoluidide

p-toluidine (106-49-0)

p-Acetotoluide (103-89-9)

m-Bromotoluene (591-17-3)

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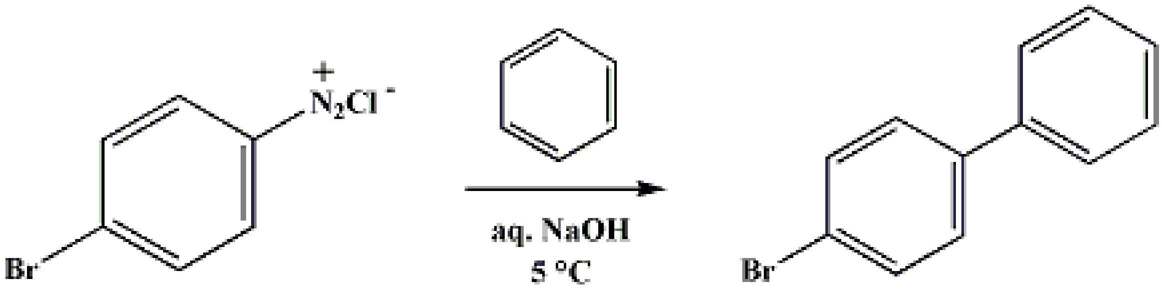
Organic Syntheses, CV 1, 113

p-BROMOBIPHENYL

[Biphenyl, 4-bromo-]



Submitted by M. Gomberg and W. E. Bachmann.
Checked by C. S. Marvel and L. T. Sandborn.

1. Procedure

Forty-three grams (0.25 mole) of *p*-bromoaniline (Note 1) and 20 cc. of water are warmed in a 400-cc. beaker until the bromoaniline melts, and then 50 cc. of concentrated hydrochloric acid (sp. gr. 1.19) is added with mechanical stirring. The mixture is heated and stirred until solution is practically complete (Note 2). The beaker is then set in a dish of ice water and the solution is stirred as it cools in order to precipitate the *p*-bromoaniline hydrochloride in fine crystals. A few small pieces of ice are added, and the cold (about 0–5°) suspension is diazotized with a solution of 18 g. (0.26 mole) of sodium nitrite in 36 cc. of water to an end-point with starch-iodide paper.

The diazotized solution is poured into a 1.5-l. wide-mouthed flask or bottle which is surrounded by ice water. Three hundred cubic centimeters of cold benzene is now poured into the diazonium solution, and by means of a good stirrer the two liquids are intimately mixed. The mixture, which is at the temperature of melting benzene, is now ready for the addition of alkali.

To this well-stirred mixture is added 58 cc. of 5 *N* sodium hydroxide solution over a period of one-half to three-quarters of an hour. This may be added drop by drop from a separatory funnel or in portions of a few cubic centimeters. The addition of the alkali causes the formation of a yellow precipitate which, on being stirred into the benzene, reacts with the benzene and gives *p*-bromobiphenyl. If too much of this reactive "oxide" is precipitated at one time, some of it may decompose to a dark brown product. The alkali is, therefore, added at such a rate that the amount of precipitate is at no time greater than can readily react with the benzene, and the stirring must be efficient. The temperature during the reaction is kept at about 5°; when all the alkali has been added, the mixture is allowed to warm to room temperature.

If an emulsion has formed, it may be broken by acidifying with hydrochloric acid,

whereupon two clear layers are obtained. The benzene solution may be dried and then fractionated or, preferably, it may be steam distilled. In the latter case it is transferred to a 1-l. Claisen flask, the flask is set in an oil bath (Note 3), and the benzene distilled. Steam is then passed in, and after the last of the benzene is removed, the *p*-bromobiphenyl distils with the steam. The temperature of the oil bath is held at 170° in order to hasten the distillation. The product solidifies in the condenser and receiving flask. There is obtained 23–24 g. of *p*-bromobiphenyl which melts at 85–86.5°.

The crude product is usually yellow or orange in color. The color may be readily removed by dissolving the crude product in 200 cc. of hot ethyl alcohol and treating this solution with 5 g. of zinc dust and about 5 cc. of concentrated hydrochloric acid (sp. gr. 1.19). This solution is then filtered and the *p*-bromobiphenyl allowed to crystallize. This gives a white product melting at 89.5–90°. The yield is 20–21 g. (34–35 per cent of the theoretical amount).

2. Notes

1. The *p*-bromoaniline used was somewhat colored and melted at 62.5–63°.
2. The volume of the diazonium solution is kept as small as possible in order that the proportion of benzene to water may be as large as possible. The bromoaniline does not completely dissolve in this quantity but is entirely converted to the salt.
3. There is some tendency toward foaming during the steam distillation. To avoid this the flask should be submerged almost completely in the oil bath.

3. Discussion

p-Bromobiphenyl can be obtained along with some of the ortho derivative from the bromination of biphenyl.[1] However, according to Schlenk,[2] the product so obtained is contaminated with some *p,p'*-dibromobiphenyl which is very difficult to remove. Bamberger obtained *p*-bromobiphenyl from the action of benzene on solid *p*-bromobenzenediazoanhydride.[3] The procedure described has been reported in the literature.[4] *p*-Bromobiphenyl has also been prepared from *p*-dibromobenzene, activated magnesium, and cyclohexanol by a series of reactions which involves the formation and dehydrogenation of 1-bromo-4-cyclohexenylbenzene.[5]

References and Notes

1. Schultz, Ann. **174**, 207 (1874).
2. Schlenk, Ber. **46**, 1477 (1913).
3. Bamberger, Ber. **29**, 470 (1896).
4. Gomberg and Bachmann, J. Am. Chem. Soc. **46**, 2339 (1924).
5. v. Braun, Irmisch, and Nelles, Ber. **66**, 1478 (1933).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

p-bromobenzenediazoanhydride

ethyl alcohol (64-17-5)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

sodium hydroxide (1310-73-2)

magnesium (7439-95-4)

Cyclohexanol (108-93-0)

sodium nitrite (7632-00-0)

zinc (7440-66-6)

Biphenyl, 4-bromo-, p-Bromobiphenyl (92-66-0)

bromoaniline

Biphenyl (92-52-4)

1-bromo-4-cyclohexenylbenzene

p-dibromobenzene (106-37-6)

p-bromoaniline (106-40-1)

p-bromoaniline hydrochloride

p,p'-dibromobiphenyl (92-86-4)

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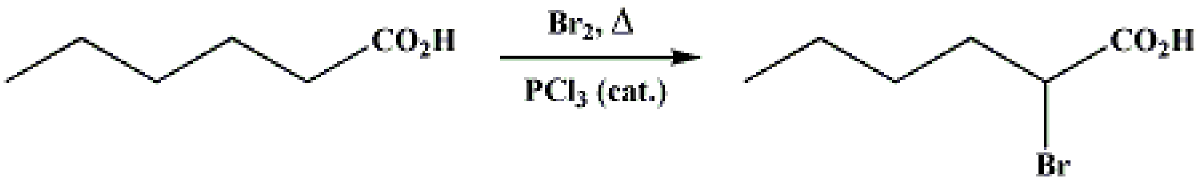
α-BROMO-*n*-CAPROIC ACID

[Caproic acid, α-bromo-]



Submitted by H. T. Clarke and E. R. Taylor.
Checked by C. S. Marvel and R. L. Shriner.

1. Procedure

Two hundred grams (1.72 moles) of freshly distilled dry *n*-caproic acid (Note 1) is placed in a 1-l. flask with 300 g. (96 cc., 1.88 moles) of bromine which has been dried by washing once with 200 cc. of concentrated sulfuric acid (Note 2). A 3-cc. portion of phosphorus trichloride is cautiously added and the flask connected to a reflux condenser (Note 3), the top of which is connected with a trap and absorption bottle containing water. The mixture is then heated in a water or oil bath to 65–70°, at which temperature the reaction commences and hydrogen bromide is given off smoothly. After five to six hours, the bromine has all reacted (Note 4). Towards the end of the reaction, the temperature is allowed to rise to about 100°. The contents of the flask are now distilled under diminished pressure (Note 5). The fraction boiling at 132–140°/15 mm. is collected and weighs 280–298 g. (83–89 per cent of the theoretical amount).

2. Notes

1. The *n*-caproic acid can be prepared by the general procedure described in Org. Syn. **11**, 78, Note 8.
2. The reagents must be dry or the yield will be lowered.
3. A flask fitted with a ground-glass connection to the reflux condenser will assist in reducing the amount of tar.
4. For larger runs, a longer time is required. A run of 2 kg. of caproic acid requires about fifteen hours.
5. It is best to distil the first low-boiling fractions with a water pump, since a considerable amount of hydrogen bromide is evolved. In order to obtain a light-colored product, the distillation should take place under as low pressure as possible. The α-bromo-*n*-caproic acid boils at 116–125°/8 mm. The product obtained is sufficiently pure for most purposes; upon redistillation, however, it comes over almost entirely between 128° and 131°/10 mm.

3. Discussion

α-Bromo-*n*-caproic acid can be prepared by heating *n*-caproic acid with bromine in a sealed tube to 140°[1] and with bromine and phosphorus;[2] and by the action of heat on α-bromo-α-butylmalonic acid.[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 48

References and Notes

1. Hüfner, Z. Chem. 616 (1868); J. prakt. Chem. (2) **1**, 7 (1870).
2. Auwers and Benhardi, Ber. **24**, 2222 (1891); Fischer, Ber. **33**, 2381 (1900); Abderhalden, Froehlich and Fuchs, Z. physiol. Chem. **86**, 455 (1913).
3. Adams and Marvel, J. Am. Chem. Soc. **42**, 319 (1920); Marvel and du Vigneaud, Org. Syn. **11**, 22.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

hydrogen bromide (10035-10-6)

bromine (7726-95-6)

PHOSPHORUS (7723-14-0)

Caproic acid, α-bromo-, α-bromo-n-caproic acid (616-05-7)

phosphorus trichloride (7719-12-2)

Caproic acid, n-caproic acid (142-62-1)

α-bromo-α-butylmalonic acid

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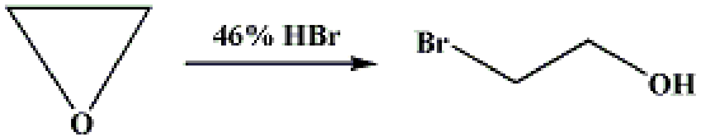
Organic Syntheses, CV 1, 117

2-BROMOETHANOL

[Ethanol, 2-bromo-]

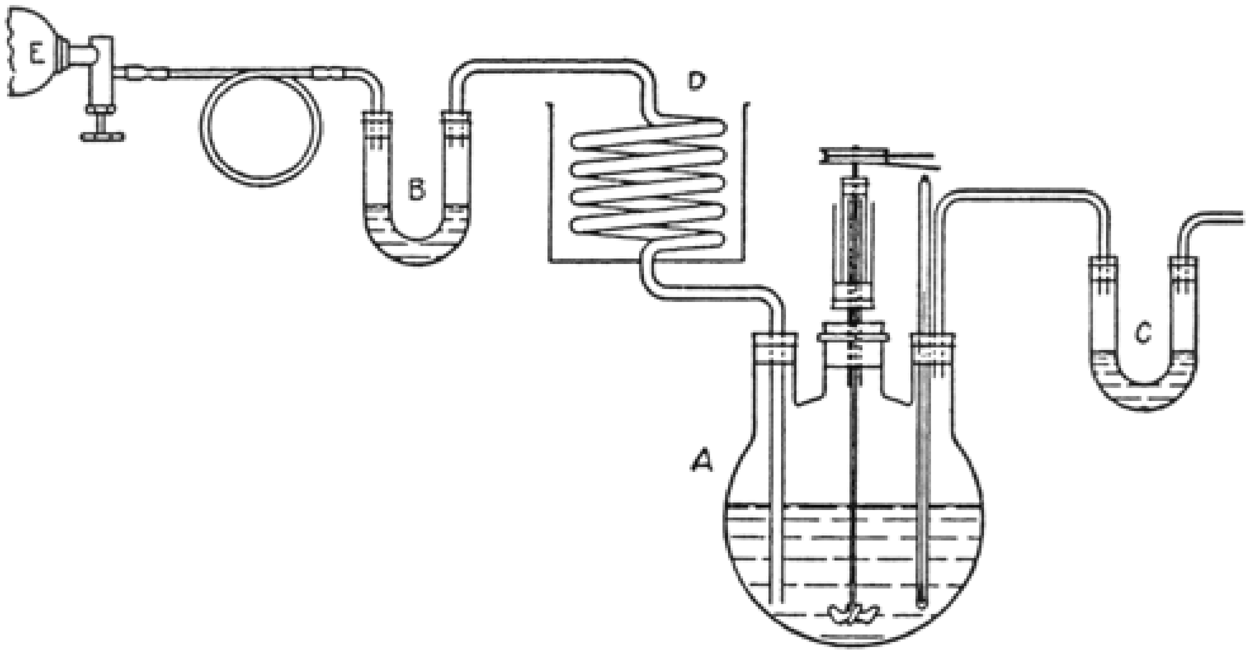


Submitted by F. K. Thayer, C. S. Marvel, and G. S. Hiers.
Checked by Henry Gilman and F. Schulze.

1. Procedure

In the 1-l. three-necked flask A (Fig. 8) is placed 550 cc. (4.56 moles) of 46 per cent hydrobromic acid (sp. gr. 1.46) (Note 1). Ethylene oxide (Note 2) is led into the acid solution as indicated in Fig. 8. The tank E is arranged on a balance so that the amount of ethylene oxide which is used can be weighed. B is a U-tube containing water to indicate the rate of flow of the gas. D is a glass coil surrounded by ice and salt which cools the gas nearly to the liquefaction temperature. C is another U-tube containing water which shows whether or not the gas is being completely absorbed.

Fig. 8.



The flask A is surrounded by an ice-salt bath and the stirrer is started. When the temperature of the acid has dropped to 10°, 132 g. (3 moles) of ethylene oxide is added over a period of about two and one-half hours (Note 3). The stirring is continued for one hour (Note 4) after all of the ethylene oxide has been added and the temperature is maintained below 10° during the reaction.

After this time the excess hydrobromic acid is neutralized with excess sodium carbonate, of

which about 100 g. of anhydrous salt is required. To the aqueous solution is then added about 100 g. of anhydrous sodium sulfate until some of the solid does not dissolve. A layer of ethylene bromohydrin separates and is collected in 200 cc. of ether. The ether layer is below the aqueous layer. The solid sodium sulfate is filtered from the solution and washed once or twice with a small amount of ether (Note 5) to remove any mechanically held bromohydrin. The aqueous filtrate is twice extracted with 200-cc. portions of ether (Note 6). The combined ether extracts are dried overnight with anhydrous sodium sulfate, filtered and distilled from a steam bath (Note 7). The remaining bromohydrin is distilled under reduced pressure (Note 8). After two distillations the fraction boiling at 55–59°/22 mm. (Note 9) is pure ethylene bromohydrin. The yield is 327–345 g. (87–92 per cent of the theoretical amount).

2. Notes

1. An equivalent amount of hydrobromic acid of greater strength may be used. Acid of lower concentration gives a much lower yield. The preparation of 48 per cent hydrobromic acid is described on p. 26.

2. Ethylene oxide attacks rubber very rapidly. Hence if rubber is used to connect the glass tubes which conduct the gas to the reaction flask, care must be taken to have the glass tubes meet inside the rubber tubing.
Undue exposure to ethylene oxide should be avoided because of its toxicity.

3. The ethylene oxide must be added quite rapidly in order to complete the addition in the time specified. It should be added at a maximum possible rate consistent with practically no loss of ethylene oxide through tube C. The best absorption of ethylene oxide appears to take place when the temperature is kept between 0° and 10°. Absorption cannot be complete in two and one-half hours when the temperature is kept at 0°.

4. When the mixture is stirred too long or the temperature is allowed to rise much above 10° the yields are lower.

5. The ether used to wash the sodium sulfate crystals may be used for the extraction of the aqueous solution.

6. When the bromohydrin is removed by the first treatment with ether, the ethereal layer is on the bottom. Subsequent ethereal extractions float on the aqueous layer.

7. About 300–335 cc. (50–55 per cent) of ether is recovered.

8. A modified Claisen flask (p. 130) is used to fractionate the compound. Distillation under atmospheric pressure causes some decomposition.[1]

9. In the first distillation the fraction boiling at 50–65°/22 mm. is collected. Boiling points observed at other pressures are as follows: 47–51°/15 mm.; 59–63°/25 mm.; and 90–94°/80 mm.

3. Discussion

Ethylene bromohydrin can be prepared by the reaction between ethylene glycol and hydrobromic acid[2] and phosphorus tribromide;[3] by the direct addition of hypobromous acid to ethylene;[4] and by the reaction between ethylene and dilute bromine water.[5] With ethylene oxide now available at a reasonable price, the procedure described has been selected because of the high yields and the convenience of reaction.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 314
- Org. Syn. Coll. Vol. 1, 528

References and Notes

1. Read and Williams, J. Chem. Soc. **117**, 1216 (1920).
2. Henry, Jahresber. 304 (1872); Norris, Watt and Thomas, J. Am. Chem. Soc. **38**, 1079 (1916); Karvonen, Acad. Sci. Fennicae, **5**A, 1–103 (1914) [C. A. **14**, 2176 (1920)].
3. Demole, Ber. **9**, 48 (1876).
4. Mokievsky, J. Russ. Phys. Chem. Soc. **30**, 900 (1898) [Chem. Zentr. I, 591 (1899)].
5. Read and Williams, J. Chem. Soc. **111**, 241 (1917); **117**, 359 (1920); Read and Hook, ibid. **117**, 1214 (1920); McDowall, ibid. **129**, 499 (1926).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

bromine water

ether (60-29-7)

HYDROBROMIC ACID (10035-10-6)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

phosphorus tribromide (7789-60-8)

2-BROMOETHANOL, Ethanol, 2-bromo-, ethylene bromohydrin (540-51-2)

Ethylene oxide (75-21-8)

ethylene glycol (107-21-1)

hypobromous acid (13517-11-8)

ethylene (9002-88-4)

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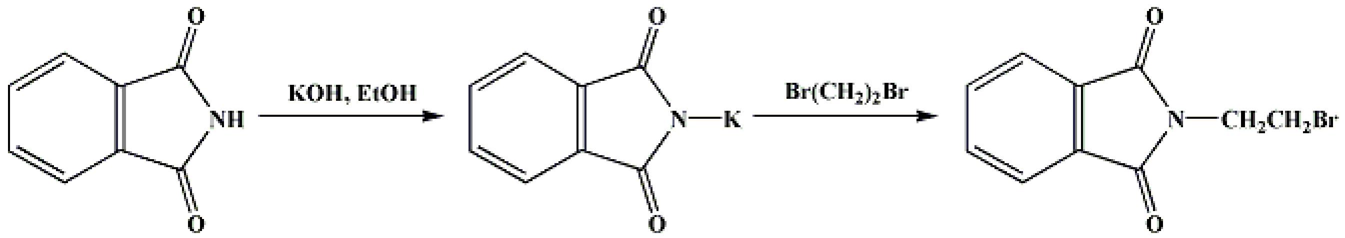
β-BROMOETHYLPHTHALIMIDE

[Phthalimide, *N*-(2-bromoethyl)-]



Submitted by P. L. Salzberg and J. V. Supniewski.
Checked by F. C. Whitmore and H. C. Benedict, Jr.

1. Procedure

(*A*) *Potassium Phthalimide*.—In a 2-l. round-bottomed flask fitted with a reflux condenser are placed 80 g. (0.54 mole) of phthalimide (Note 1) and 1600 cc. of absolute alcohol (p. 249). The mixture is gently boiled for about fifteen minutes or until no more of the phthalimide dissolves (Note 2). The hot solution is decanted from any solid into a specially prepared solution of 30.5 g. (0.54 mole) of potassium hydroxide (Note 3). A precipitate of potassium phthalimide separates at once. The mixture is stirred and cooled quickly to room temperature, and the precipitate is filtered with suction. To the alcoholic mother liquors a second 80-g. portion of phthalimide is added, and the entire process is repeated. The two crops of crystals are united (Note 4) and washed with 200 cc. of acetone to remove any unchanged phthalimide. The yield of air-dried potassium phthalimide is 160–180 g. (80–90 per cent of the theoretical amount).

(*B*) β-*Bromoethylphthalimide*.—In a 1-l. two-necked round-bottomed flask fitted with an efficient stirrer and a reflux condenser are placed 150 g. (0.81 mole) of potassium phthalimide and 450 g. (2.4 moles) of ethylene dibromide (Note 5). The stirrer is started and the mixture is heated for about twelve hours in an oil bath maintained at 180–190°. The condenser is then set for distillation, and the excess of ethylene dibromide is distilled under reduced pressure. The recovery of the bromide amounts to 290–295 g. (Note 6).

The crude bromoethylphthalimide is extracted from the potassium bromide by refluxing with 300 cc. of alcohol (98–100 per cent) (Note 7) until the dark oil is entirely dissolved. This requires about one-half. hour. The hot solution is filtered with suction, and the residue of salt is washed with a little hot alcohol. The alcohol is distilled under reduced pressure, and the dry residue is refluxed with 500 cc. of carbon disulfide for about fifteen minutes in order to separate the soluble bromoethylphthalimide from the insoluble diphthalimidoethane (Note 8). The warm solution is filtered with suction. The carbon disulfide is distilled under diminished pressure (Note 9). The bromoethylphthalimide remains as light tan crystals which melt at 78–80°. The yield is 140–160 g. (69–79 per cent of the theoretical amount).

The product thus obtained is pure enough for most purposes. However, a purer product may be obtained by recrystallization from dilute alcohol in the presence of decolorizing carbon. When 50 g. of crude product is dissolved in 200 cc. of 75 per cent alcohol, boiled for about ten minutes with 5 g. of decolorizing carbon (Norite), filtered, and the solution cooled to 0°, 40 g. of white product is obtained. The recrystallized product melts at 80–81°. A second recrystallization raises the melting point to 82–83°.

2. Notes

1. The phthalimide used was the crude product obtained as described on p. 457.
2. The crude product always contains a small amount of material insoluble in alcohol.
3. It is convenient to prepare enough potassium hydroxide solution for the two precipitations at one time. This solution is prepared by dissolving 61 g. of potassium hydroxide in 60 cc. of water. To this solution is then added 180 cc. of absolute alcohol. One-half of the resulting solution is used for each 80-g. portion of phthalimide.
4. After the first crop has been filtered, most of it should be removed and the second crop should be filtered through the same paper. The alcoholic filtrate on distillation yields about 1500 cc. of 98 per cent alcohol.
5. The ethylene dibromide which was used boiled at 129–131°.
6. The last 15 to 20 g. of this recovered product distils very slowly.
7. The alcohol recovered from the preparation of the potassium phthalimide may be used for this extraction.
8. About 10 g. of crude diphthalimidoethane is obtained.
9. If the carbon disulfide is distilled at ordinary pressures, the residue melts and turns very dark. The crude yield is not

lowered, but the purification is made more difficult.

3. Discussion

The procedure described is based on that of Gabriel.[1]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 271
- Org. Syn. Coll. Vol. 2, 25
- Org. Syn. Coll. Vol. 3, 256
- Org. Syn. Coll. Vol. 4, 106

References and Notes

1. Gabriel, Ber. **20**, 2225 (1887); **21**, 566 (1888); **22**, 1137 (1889).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alcohol (64-17-5)

bromide (24959-67-9)

acetone (67-64-1)

decolorizing carbon, decolorizing carbon (Norite) (7782-42-5)

potassium hydroxide (1310-58-3)

carbon disulfide (75-15-0)

β-Bromoethylphthalimide, bromoethylphthalimide

Potassium Phthalimide (1074-82-4)

Phthalimide (85-41-6)

ethylene dibromide (106-93-4)

potassium bromide (7758-02-3)

diphthalimidoethane

Phthalimide, N-(2-bromoethyl)- (574-98-1)

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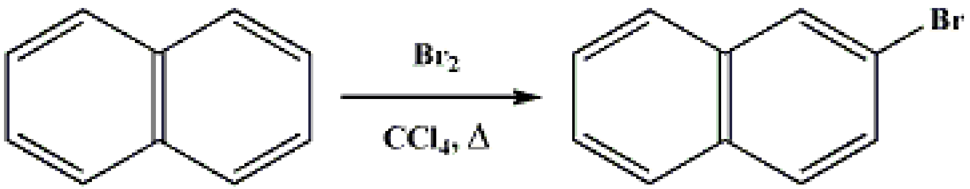
α-BROMONAPHTHALENE

[Naphthalene, 2-bromo-]



Submitted by H. T. Clarke and M. R. Brethen.
Checked by J. B. Conant and G. W. Wheland.

1. Procedure

In a 2-l. flask are placed 512 g. (4 moles) of naphthalene and 275 g. (170 cc.) of carbon tetrachloride. The flask is equipped with a stirrer, an efficient reflux condenser, and a dropping funnel, the stem of which extends below the level of the liquid. From the top of the reflux condenser a tube leads to a water trap similar to that described in Fig. 7 on p. 97. The mixture is warmed on a steam bath to gentle boiling, and 707 g. (220 cc., 4.4 moles) of bromine is run in at such a rate that practically none of it is carried over with the hydrogen bromide into the trap. This requires from twelve to fifteen hours, during which time the mixture is gently warmed on the steam bath, with continual stirring, until the evolution of hydrogen bromide ceases (about six hours). The mixture is now distilled from the steam bath under slightly reduced pressure (using a condenser) until free of carbon tetrachloride; the residue is mixed with 20–30 g. of powdered or granulated sodium hydroxide and stirred at 90–100° for four hours (Note 1). The liquid is transferred to a flask for fractional distillation and distilled under reduced pressure. The forerun contains a considerable proportion of unchanged naphthalene, the bulk of which is removed by chilling and filtering with suction; the main fraction, consisting of bromonaphthalene, passes over at 132–135°/12 mm. (145–148°/20 mm.), and a high-boiling fraction, consisting of dibromonaphthalene, is collected. The intermediate fractions and the filtrates from the foreruns are systematically redistilled; in this way 600–620 g. of colorless α-bromonaphthalene (72–75 per cent of the theoretical amount) and about 30 g. of a mixture of dibromonaphthalenes (m.p., about 60°) are obtained.

2. Notes

1. If this treatment with sodium hydroxide is omitted, the final product contains impurities which gradually give off hydrogen bromide.

3. Discussion

α-Bromonaphthalene can be prepared by the action of bromine upon naphthalene without a solvent[1] and in carbon disulfide;[2] by treating a suspension of naphthalene in a solution of bromine in alkali with hydrochloric acid;[3] and by treating a suspension of naphthalene in warm water with bromine.[4] The procedure described has been found to be more convenient and to give considerably better yields than that reported previously.[4] An essentially similar procedure has been described.[5] The method in which a suspension of naphthalene in alkaline hypobromite solution is treated with hydrochloric acid in aqueous solution[3] was found to give a satisfactory yield, but it presented considerable difficulties in the recovery of the hydrobromic acid. Iodine monobromide has been used successfully to brominate naphthalene.[6]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 425

References and Notes

1. Laurent and Wahlforss, Z. Chem. 3 (1865).
2. Glaser, Ann. **135**, 40 (1865); Otto, Ann. **147**, 166 (1868).
3. Merz and Weith, Ber. **15**, 2721 (1882).
4. Clarke and Schram, Org. Syn. **1**, 35 (1921).
5. Blicke, J. Am. Chem. Soc. **49**, 2846 (1927).
6. Militzer, ibid. **60**, 257 (1938).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

mixture of dibromonaphthalenes

hydrochloric acid (7647-01-0)

sodium hydroxide (1310-73-2)

HYDROBROMIC ACID, hydrogen bromide (10035-10-6)

bromine (7726-95-6)

carbon tetrachloride (56-23-5)

carbon disulfide (75-15-0)

α-Bromonaphthalene, bromonaphthalene (90-11-9)

Naphthalene, 2-bromo- (580-13-2)

Naphthalene (91-20-3)

dibromonaphthalene

hypobromite

Iodine monobromide (7789-33-5)

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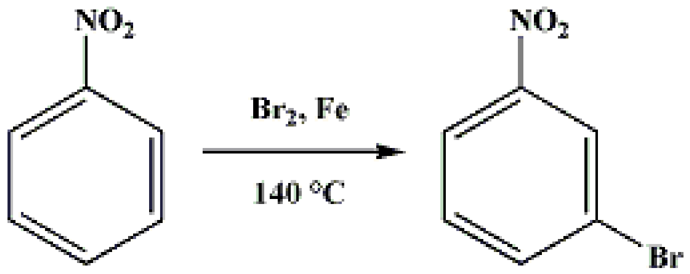
Organic Syntheses, CV 1, 123

m-BROMONITROBENZENE

[Benzene, 1-bromo-3-nitro-]



Submitted by John R. Johnson and C. G. Gauerke.
Checked by Frank C. Whitmore and T. Otterbacher.

1. Procedure

In a 3-l. three-necked, round-bottomed flask, provided with an efficient reflux condenser bearing an outlet tube held above a surface of water, a 100-cc. separatory funnel, and a mercury-sealed mechanical stirrer (Note 1), is placed 270 g. (2.2 moles) of freshly distilled dry nitrobenzene (Note 2). The joints in the apparatus are made of asbestos paper covered with water glass (see Note 5, p. 19). The flask is heated in an oil bath maintained at 135–145°, and 26 g. of iron powder and 562 g. (180 cc., 3.5 moles) of dry bromine (Note 3) are added in the following manner: Eight grams of iron powder ("ferrum reductum") (Note 4) is added through the side neck to the stirred nitrobenzene. From the separatory funnel 60 cc. of bromine is added at such a rate that the bromine vapors do not traverse the condenser. This addition requires about one hour, and the mixture is stirred and heated for another hour before the addition of a second portion of iron and bromine. Two portions, each of 8 g. of iron powder and 60 cc. of bromine, are added under the same conditions as the first addition, and the mixture is stirred and heated for one hour between the completion of one addition and the beginning of another. The evolution of hydrogen bromide slackens considerably toward the last of the heating, and there is practically no more bromine vapor in the condenser. A final addition of 2 g. of iron powder is made, and the heating continued for one hour longer.

The reaction product, which is a dark reddish-brown liquid, is poured or siphoned (Note 5) into 1.5 l. of water to which 50 cc. of a saturated solution of sodium bisulfite has been added (Note 6). The mixture is distilled with steam (p. 479) and the first portion of the distillate is collected separately to remove a small amount of unchanged nitrobenzene. It is necessary to collect about 12 l. of distillate in order to obtain all the *m*-bromonitrobenzene. The yellow crystalline solid is filtered with suction and pressed well on the funnel to remove water and traces of nitrobenzene. The yield of crude product varies from 270 to 340 g. (60–75 per cent of the theoretical amount). It melts

at 51.5–52° and boils at 117–118°/9 mm. This product is satisfactory for most purposes. If a purer material is desired, the crude *m*-bromonitrobenzene may be distilled under reduced pressure. The recovery on purification is about 85 per cent. Brühl recorded the b.p. as 138°/18 mm. and the m.p. as 56° for pure *m*-bromonitrobenzene.[1]

2. Notes

1. With small amounts, up to 90 g. of nitrobenzene, mechanical stirring is not essential, and occasional shaking is sufficient.
2. The nitrobenzene is dried by distillation under atmospheric or reduced pressure, by rejecting the first 5 per cent of the distillate.
3. The bromine is dried by shaking with an equal volume of concentrated sulfuric acid and separating.
4. A number of other forms of iron were used, but none gave as good results as the "ferrum reductum."
5. If a series of successive runs is to be made, it is convenient to siphon the reaction product, and carry out a second preparation in the same apparatus without dismantling it.
6. The sodium bisulfite is added to remove any free bromine. A large excess should not be used as secondary reactions may occur during the steam distillation.

3. Discussion

m-Bromonitrobenzene can be obtained through *m*-nitrobenzenediazonium salts[2] and by elimination of the amino group from 4-bromo-2-nitroaniline.[3] It has been prepared by the bromination of nitrobenzene in the presence of various catalysts.[4] The procedure given is adapted from that described by Wheeler and McFarland.[5]

References and Notes

1. Brühl, Z. physik. Chem. **22**, 379 (1897).
2. Griess, Phil. Trans. Roy. Soc. London **154**, III, 711 (1864); Jahresber. 457 (1866); Fittig and Mager, Ber. **8**, 364 (1875).
3. Wurster, Ber. **6**, 1543 (1873); Wurster and Grubenmann, Ber. **7**, 416 (1874).
4. Scheufelen, Ann. **231**, 165 (1885).
5. Wheeler and McFarland, Am. Chem. J. **19**, 366 (1897).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

nitrobenzenediazonium salts

sulfuric acid (7664-93-9)

iron (7439-89-6)

hydrogen bromide (10035-10-6)

bromine (7726-95-6)

sodium bisulfite (7631-90-5)

Nitrobenzene (98-95-3)

Benzene, 1-bromo-3-nitro-, m-Bromonitrobenzene (585-79-5)

Bromonitrobenzene (577-19-5)

4-bromo-2-nitroaniline (875-51-4)

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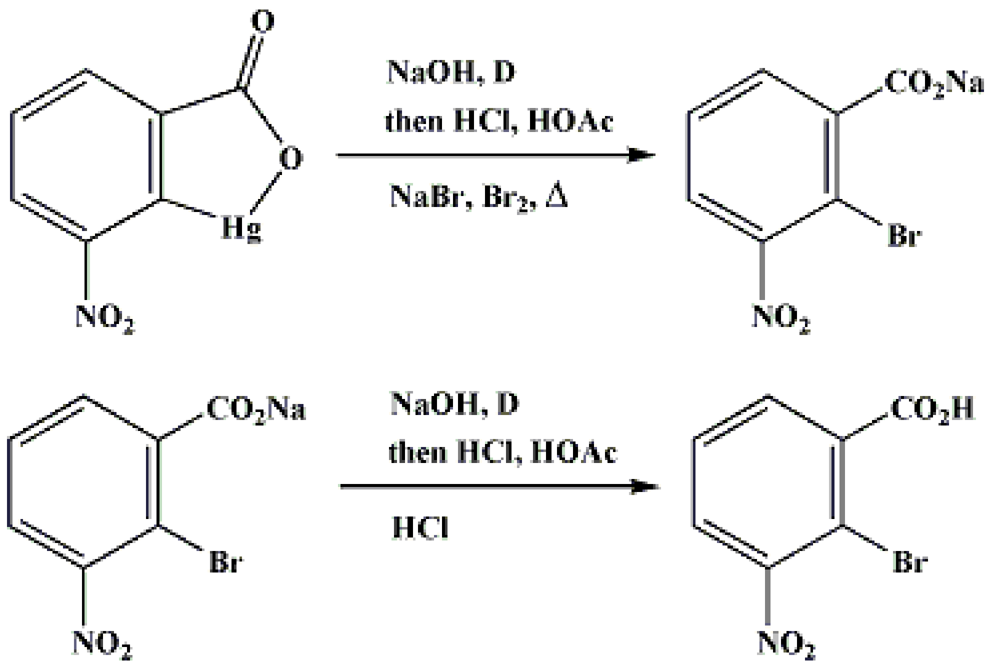
2-BROMO-3-NITROBENZOIC ACID

[Benzoic acid, 2-bromo-3-nitro-]



Submitted by Paul J. Culhane
Checked by Henry Gilman and C. C. Vernon.

1. Procedure

A solution of 50 g. (1.25 moles) of sodium hydroxide in 1.5 l. of water is prepared in a 5-l. flask, and the solution is heated to gentle boiling. To the hot solution is added, in small quantities, 330 g. (0.9 mole) of anhydro-2-hydroxymercuri-3-nitrobenzoic acid (p. 56) (Note 1). The mixture is stirred after the addition of each portion of about 50 g. until the material has gone into solution except for a small residue. The flask is then fitted with a stirrer and addition tube (Note 2) and with a connection to a reflux condenser. The material is heated to boiling and stirred vigorously. There is slowly added, with continuous stirring, 101 g. (85 cc., 0.95 mole) (Note 3) of concentrated hydrochloric acid (sp. gr. 1.19). Heating is discontinued at this point, and 31.5 g. (30 cc., 0.5 mole) of glacial acetic acid (sp. gr. 1.05) (Note 3) is added slowly. A curdy precipitate forms.

A solution of bromine is prepared by dissolving 103 g. (1 mole) of sodium bromide and 160 g. (50.2 cc., 1 mole) of bromine in 150 cc. of water (Note 4). The mixture is stirred, and the bromine solution is added as rapidly as possible through the shaft of the stirrer. The precipitate dissolves. The solution is heated to boiling for five minutes after the last of the bromine has been added. The solution is then made slightly alkaline by the addition of 20 g. (0.5 mole) of solid sodium hydroxide and filtered

through a fluted filter. The filtrate is then made acid to Congo red, using about 150 cc. of concentrated hydrochloric acid. The precipitated 2-bromo-3-nitrobenzoic acid is filtered with suction and sucked as dry as possible. It is then crystallized from 1 l. of hot 30 per cent alcohol. The yield of product melting at 185–187° is 130–150 g. (53–61 per cent of the theoretical amount, based on the 3-nitrophthalic acid used). About 25 g. of material melting at about 175° can be recovered from the mother liquor.

2. Notes

1. The reaction product from the mercuration of 3-nitrophthalic acid (1 mole) is used. The mercury compound can be used without drying if desired. If this is done, solution takes place much more readily.
2. A rapid distribution of the added material is necessary to prevent a local excess of the reagent added. This is very important when hydrochloric acid is added, as this tends to decompose the mercury compound. A convenient arrangement consists of a three-way tube of about 15-mm. bore. The stirrer operates through the center tube. The other arms are used for the condenser and for the addition of material. A three-necked flask provided with a long-stemmed separatory funnel reaching below the stirrer may be used.
3. The addition of one mole of hydrochloric acid allows the formation of one mole of sodium chloride, which is of advantage in the subsequent addition of halogen, owing to the formation of a sodium salt of the chloromercuric acid, this being more soluble and hence more reactive than the anhydro compound. Acetic acid is used for the final acidification because it does not decompose the mercury compound. The replacement by bromine takes place best in a slightly acid medium.
4. The mercury can be replaced by iodine in a similar manner. An iodine solution is made by dissolving 166 g. (1 mole) of potassium iodide and 255 g. (1 mole) of iodine in 250 cc. of water. This is used instead of the bromine solution. The mixture is filtered from the mercuric iodide and the filtrate acidified with 200 cc. of concentrated hydrochloric acid. The precipitate is filtered and then stirred with a solution of 10 g. of potassium iodide in 250 cc. of water to remove mercuric iodide. The mixture is filtered with suction and the precipitate crystallized from 1 l. of 50 per cent alcohol. The yield is 180 g. of 2-iodo-3-nitrobenzoic acid melting at 204–205.5° (61 per cent of the theoretical amount, based on the 3-nitrophthalic acid used).

3. Discussion

2-Bromo-3-nitrobenzoic acid can be prepared by the nitration of 2-bromobenzoic acid, the 2,3 acid being separated from the 2,5 acid, which is the principal product of the nitration, by fractional crystallization of the potassium salts from water.[1]

2-Iodo-3-nitrobenzoic acid can be prepared by the diazotization of 3-nitroanthranilic acid.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 56

References and Notes

1. Holleman and de Bruyn, Rec. trav. chim. **20**, 211 (1901).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Anhydro-2-hydroxymercuri-3-nitrobenzoic acid

sodium salt of the chloromercuric acid

alcohol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

bromine (7726-95-6)

sodium bromide (7647-15-6)

potassium iodide (7681-11-0)

3-Nitrophthalic acid (603-11-2)

mercury (7439-97-6)

2-Bromo-3-nitrobenzoic acid, Benzoic acid, 2-bromo-3-nitro- (573-54-6)

iodine (7553-56-2)

mercuric iodide (7774-29-0)

2-iodo-3-nitrobenzoic acid (5398-69-6)

2-bromobenzoic acid (88-65-3)

3-nitroanthranilic acid

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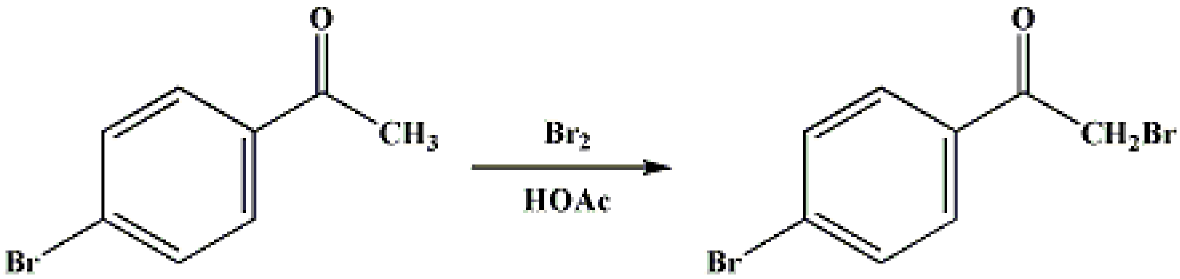
p-BROMOPHENACYL BROMIDE

[Acetophenone, α, *p*-dibromo-]



Submitted by W. D. Langley
Checked by H. T. Clarke and P. W. Boutwell.

1. Procedure

In a 500-cc. flask are placed 50 g. (0.25 mole) of *p*-bromoacetophenone (p. 109) and 100 cc. of glacial acetic acid. To the resulting solution is very slowly added 40 g. (12.5 cc., 0.25 mole) of bromine, keeping the temperature below 20°. The mixture is vigorously shaken by hand during the addition. *p*-Bromophenacyl bromide begins to separate as needles when about one-half of the bromine has been added. The addition requires about thirty minutes.

When all the bromine has been added, the flask is cooled in ice-water and the product filtered with suction. The crude crystals are washed with 50 per cent ethyl alcohol until colorless (about 100 cc. is required). The material so obtained, when air-dried, melts at 106–108° and weighs 55–60 g. It is recrystallized from 400 cc. of 95 per cent ethyl alcohol, from which it separates as colorless needles melting at 108–109°. The yield is 48–50 g. (69–72 per cent of the theoretical amount) (Note 1).

2. Notes

1. A further quantity of less pure material may be obtained from the mother liquor from the recrystallization. If the acetic acid mother liquor is treated with water until turbid and then chilled, 4–5 g. of yellow crystals may be obtained. The material recovered from both liquors (6–8 g. in all) cannot be obtained in a perfectly colorless condition but the melting point is correct after recrystallization from alcohol.

2. Judefind and Reid[1] have shown that many acids may be identified by conversion into their *p*-bromophenacyl esters by the action of *p*-bromophenacyl bromide on the sodium salts.

3. Discussion

p-Bromophenacyl bromide can be prepared by the interaction of bromobenzene and bromoacetyl chloride in the presence of aluminum chloride,[2] and by the bromination of *p*-bromoacetophenone.[1], [3]

References and Notes

1. Judefind and Reid, J. Am. Chem. Soc. **42**, 1045 (1920).
2. Collet, Compt. rend. **125**, 717 (1897).
3. Collet, Bull. soc. chim. (3) **21**, 67 (1899).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

p-bromophenacyl esters

ethyl alcohol (64-17-5)

acetic acid (64-19-7)

bromine (7726-95-6)

Acetophenone (98-86-2)

aluminum chloride (3495-54-3)

bromobenzene (108-86-1)

bromoacetyl chloride (22118-09-8)

p-Bromophenacyl bromide (99-73-0)

p-Bromoacetophenone (99-90-1)

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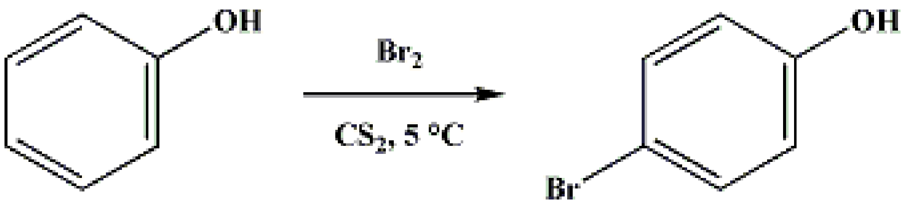
p-BROMOPHENOL

[Phenol, *p*-bromo-]



Submitted by Roger Adams and C. S. Marvel.
Checked by Oliver Kamm and R. W. Hufferd.

1. Procedure

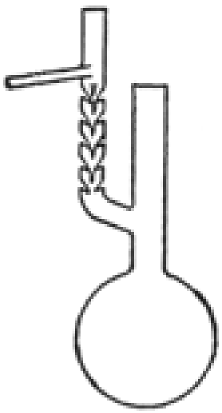
In a 5-l. round-bottomed flask fitted with a rubber stopper, holding a mechanical stirrer, reflux condenser and separatory funnel, is placed 1 kg. (10.6 moles) of phenol dissolved in 1 l. of carbon disulfide. To the top of the condenser is attached a calcium chloride tube (Note 1) and from this a glass tube leads into a beaker holding about 1200 cc. of cracked ice and water for the absorption of the hydrogen bromide evolved. In the separatory funnel is placed 1702 g. (546 cc., 10.7 moles) of bromine dissolved in 500 cc. of carbon disulfide. The flask is well cooled (below + 5°) in a salt and ice mixture (Note 2), stirring is started, and the bromine solution is allowed to run in. The addition requires about two hours. When this is completed, the flask is disconnected, and a condenser set for downward distillation is attached to it. By having a distilling flask as a receiver attached tightly to the lower end of the condenser, the dissolved hydrogen bromide which is evolved at the beginning of the heating may be led into the water used for collecting the first hydrogen bromide.

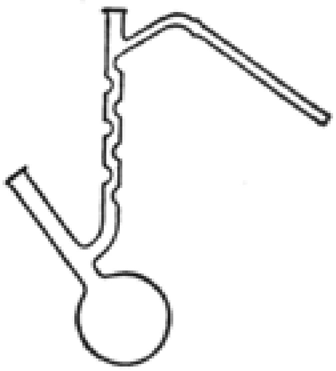
The carbon disulfide is distilled off; it amounts to about 1200 cc. (Note 3). The residual liquid is then slowly distilled under reduced pressure with a good fractionating column (Note 4) in a 1.5- or 2-l. Claisen flask which must be slightly modified (Fig. 9, p. 130) so that the *p*-bromophenol after coming in contact with cork or rubber will not be carried into the condenser (Note 5); if it does, it becomes pinkish. The yield is 1475–1550 g. (80–84 per cent of the theoretical amount) of *p*-bromophenol boiling at 145–150° /25–30 mm. In addition, there is obtained 250–350 g. of lower-boiling material consisting of a mixture of *o*-bromophenol and *p*-bromophenol from which it is very difficult to extract either constituent in pure form, and a small quantity of high-boiling material consisting chiefly of 2,4-dibromophenol. The *p*-bromophenol on cooling solidifies to a solid white mass containing practically no oil. By centrifuging the product, perfectly dry white crystals are obtained, m.p. 63°. There is also produced in this preparation about 1.5–1.6 l. of hydrobromic acid with a specific gravity of about 1.3 (Note 6).

2. Notes

1. Moisture prevents the *p*-bromophenol from crystallizing, so that particular care should be taken to keep it out of the reaction mixture.
2. Although it is not absolutely necessary that the reaction mixture be cooled with salt and ice, it is highly desirable, since this reduces the amount of *o*-bromophenol and hence the amount of low-boiling fraction; the recovery of carbon disulfide is also more satisfactory. A run of the same size as is described above was made, keeping the solution at room temperature, and under these conditions the yield of pure *p*-bromophenol was diminished.
3. The loss of carbon disulfide is due to its great volatility, the consequent passing off with the hydrogen bromide and the general loss during experimental manipulations.
The experiments may be run with a larger amount of carbon disulfide with satisfactory results. This, however, involves a longer time for distillation and is therefore undesirable. More concentrated solutions were not tried.
4. The *p*-bromophenol if distilled without using a fractionating column and collected over a 5° range, as already described, will generally amount to 1600–1660 g. (87–90 per cent of the theoretical amount). This material on cooling, however, never solidifies completely but always contains a certain amount of oil; it is satisfactory for most purposes, just as it is. Even though the once-distilled material may be freed from oil and then redistilled without special fractionation, some oil remains. To obtain a very pure product this material must be cooled to 10° and then centrifuged. In this way, hard white crystals which melt sharply at 63° result. During this process about 15–20 per cent of the product goes to the filtrate which, however, can be chilled again so that a certain amount of pure *p*-bromophenol may be obtained from it. Although a number of solvents were used in an attempt to crystallize *p*-bromophenol, none was found that was entirely satisfactory.
5. The flasks shown in Fig. 9 are particularly suited for distilling liquids which attack rubber or cork. Figure 9(a) illustrates a flask which is a modification of one already described in the literature;[1] the side arm outlet tube extends a short distance into the neck of the flask, thus preventing any vapor which has touched the cork or rubber

Fig. 9.


(a)


(b)

from condensing and flowing down the side arm into the condenser. Figure 9(b) shows a flask of the type used in the Eastman Kodak Company Laboratories. It has a longer column than the standard Claisen flask so that larger amounts of liquid can be distilled from it than from a standard Claisen flask of the same size and there is less danger from bumping. The upward angle on the first portion of the side arm outlet tube serves the same purpose as the inset side arm in the flask 9(a).

6. A complete run may be made in less than five hours.

3. Discussion

The methods for preparing *p*-bromophenol are: the action of bromine on phenol in carbon disulfide,[2] in glacial acetic acid,[3] and in a mixture of sulfuric and acetic acids;[4] and the diazotization of *p*-bromoaniline and subsequent heating with water.[5] The relative yields of ortho and para derivatives have been studied[6] in a miscellany of solvents, including water and carbon tetrachloride, and under varying temperatures.

In this investigation it was found that the diazo reaction did not give a good yield of pure compound. Bromination in glacial acetic acid is satisfactory except that the acetic acid cannot be recovered conveniently. The bromination in sulfuric acid (75 per cent) is unsatisfactory since the phenol does not dissolve readily at 0°, and, if a temperature high enough to dissolve it is used, a considerable amount of *o*-bromophenol is produced. Carbon tetrachloride might appear preferable to carbon disulfide on account of its non-inflammability; however, this advantage is offset because it must be used in much larger quantities to dissolve the phenol at 0°; it is much less easily removed, and the proportion of *o*-bromophenol is slightly greater.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 3
- Org. Syn. Coll. Vol. 1, 58
- Org. Syn. Coll. Vol. 1, 77
- Org. Syn. Coll. Vol. 1, 95

- Org. Syn. Coll. Vol. 1, 102
- Org. Syn. Coll. Vol. 1, 107
- Org. Syn. Coll. Vol. 1, 109
- Org. Syn. Coll. Vol. 1, 117
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- Org. Syn. Coll. Vol. 1, 166
- Org. Syn. Coll. Vol. 1, 183
- Org. Syn. Coll. Vol. 1, 186
- Org. Syn. Coll. Vol. 1, 188
- Org. Syn. Coll. Vol. 1, 191
- Org. Syn. Coll. Vol. 1, 235
- Org. Syn. Coll. Vol. 1, 238
- Org. Syn. Coll. Vol. 1, 246
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- Org. Syn. Coll. Vol. 1, 524
- Org. Syn. Coll. Vol. 1, 533
- Org. Syn. Coll. Vol. 1, 544
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3. Hübner and Brenken, Ber. **6**, 171 (1873); Hand, Ann. **234**, 136 (1886).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric and acetic acids

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

phenol (108-95-2)

HYDROBROMIC ACID, hydrogen bromide (10035-10-6)

bromine (7726-95-6)

carbon tetrachloride (56-23-5)

carbon disulfide (75-15-0)

2,4-dibromophenol (615-58-7)

o-Bromophenol (95-56-7)

p-bromoaniline (106-40-1)

p-Bromophenol, Phenol, p-bromo- (106-41-2)

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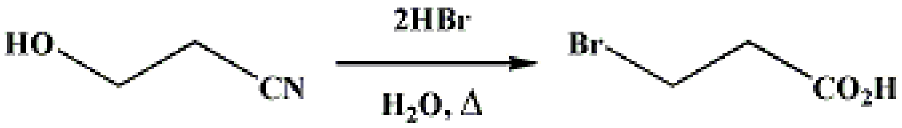
β-BROMOPROPIONIC ACID

[Propionic acid, β-bromo-]



Submitted by E. C. Kendall and B. McKenzie.
Checked by H. T. Clarke and M. R. Brethen.

1. Procedure

To 2750 g. (2 l., 13.6 moles) of 40 per cent hydrobromic acid (Note 1) in a 3-l. flask is added 317 g. (4.5 moles) of ethylene cyanohydrin (p. 256), and the mixture is boiled for two hours under a reflux condenser. The condenser is then arranged for downward distillation and a thermometer immersed in the reaction mixture; dilute hydrobromic acid is distilled off until the temperature in the flask reaches 121°, whereupon the receiver is changed and a fraction consisting of stronger hydrobromic acid is collected over the range 121–129°. When the temperature of the mixture reaches 129°, very little hydrobromic acid remains, and on cooling, the mass sets to an almost colorless solid. This is now dissolved in 2000 cc. of carbon tetrachloride (Note 2), and the ammonium bromide is filtered off and washed with 500 cc. more of the solvent; a thin aqueous layer is separated and 1500 cc. of the carbon tetrachloride distilled from the filtrate. On cooling, about 470 g. of β-bromopropionic acid crystallizes from the residue; on filtering and drying, this melts at 62.5–63.5°. With further concentration, the mother liquor yields a second crop of β-bromopropionic acid, amounting to 60–70 g.

The aqueous layer separated from the main carbon tetrachloride solution is shaken with 100 cc. of carbon tetrachloride, and thus yields about 10 g. of pure acid; when the dilute and the concentrated hydrobromic acid fractions are extracted in the same way, about 5 g. and 15 g. respectively of β-bromopropionic acid are obtained. The total yield is 560–570 g. (82–83 per cent of the theoretical amount).

2. Notes

1. The 2 l. (2750 g.) of 40 per cent hydrobromic acid may advantageously be replaced by a corresponding quantity (1550 cc.) of constant-boiling 48 per cent hydrobromic acid, should this be available. Directions for the preparation of hydrobromic acid are given on p. 26.
2. In no case should benzene be used in place of carbon tetrachloride, as it has been found impossible to separate this solvent from β-bromopropionic acid,

even on repeated fractionation with an efficient column.

3. Discussion

β-Bromopropionic acid can be prepared by the action of hydrobromic acid on acrylic acid,[1] on hydracrylic acid,[2] and on ethylene cyanohydrin;[3] and by the oxidation of β-bromopropionaldehdye[4] and of trimethylene bromohydrin[5] with nitric acid.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 246

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

β-bromopropionaldehdye

Benzene (71-43-2)

nitric acid (7697-37-2)

ammonium bromide (12124-97-9)

HYDROBROMIC ACID (10035-10-6)

trimethylene bromohydrin (627-18-9)

carbon tetrachloride (56-23-5)

β-Bromopropionic acid, Propionic acid, β-bromo- (590-92-1)

Ethylene cyanohydrin (109-78-4)

Acrylic acid (9003-01-4)

hydracrylic acid (503-66-2)

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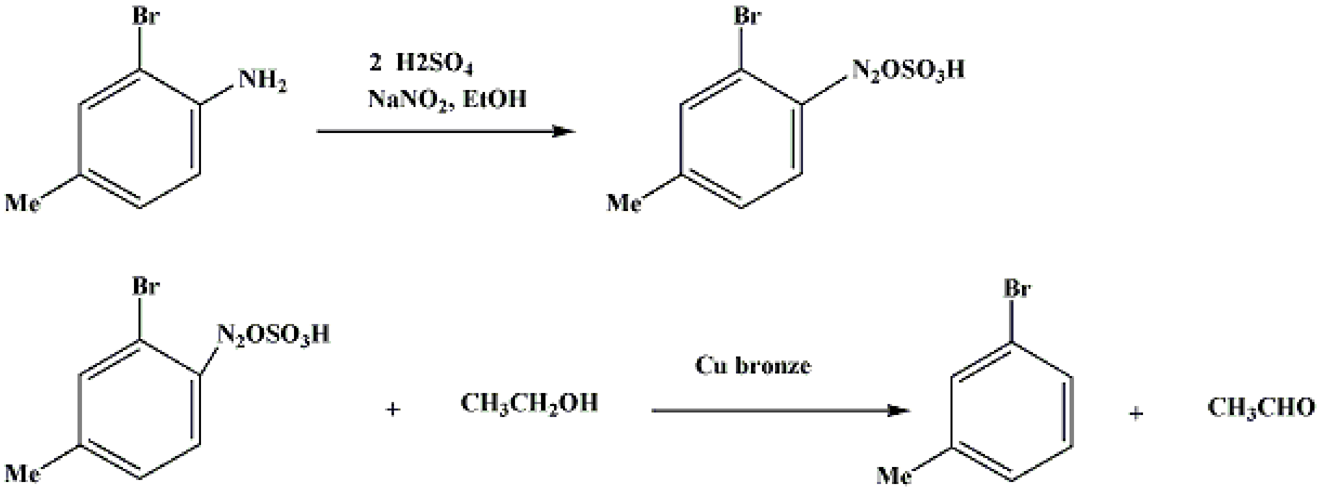
m-BROMOTOLUENE

[Toluene, *m*-bromo-]



Submitted by L. A. Bigelow, J. R. Johnson, and L. T. Sandborn.
Checked by Frank C. Whitmore and A. M. Griswold.

1. Procedure

To a cold mixture of 800 cc. of 95 per cent ethyl alcohol and 200 cc. of concentrated sulfuric acid (Note 1) in a 5-l. round-bottomed flask, provided with an efficient mechanical stirrer, is added 250 g. (1.33 moles) of crude 3-bromo-4-aminotoluene (p. 111). The solution is stirred and cooled to 10°, and a solution of 148 g. (2.05 moles) of u.s.p. sodium nitrite in 260 cc. of water is added from a separatory funnel. During this addition, the temperature of the mixture must not be allowed to rise above 10°. After all of the nitrite solution has been added, the mixture is stirred twenty minutes longer to complete the diazotization.

To the diazotized solution is added 35 g. (0.55 atom) of copper bronze (Note 2) which has been washed with ether. The stirrer is replaced by a long, efficient reflux condenser. A bath of ice water is prepared for cooling the flask when the reaction becomes too vigorous. The flask is warmed cautiously until a vigorous evolution of gas starts. It is then immersed in the ice water to prevent loss through the condenser by too rapid evolution of nitrogen and acetaldehyde. When the reaction has moderated, the flask is again warmed, and finally the mixture is heated for ten minutes on a steam bath. At the end of the reaction the color changes from reddish brown to yellow.

After the addition of 2 l. of water, the mixture is steam-distilled as long as any oil comes over. The crude, heavy, yellow oil is separated and washed with two 200-cc. portions of 10 per cent sodium hydroxide, once with 100 cc. of water, twice with 150-cc. portions of concentrated sulfuric acid, and finally with 100 cc. of 5 per cent sodium carbonate solution. It is dried with about 5 g. of calcium chloride, filtered through glass wool, and distilled using a long air condenser. Most of the product boils at 180–183°/750 mm. The yield of pure colorless material, b.p. 183°/760 mm., is 125–135 g. (36–39 per cent of the theoretical amount, based on the amount of *p*-toluidine originally used (p. 111), or 54–59 per cent based on the amount of 3-bromo-4-aminotoluene).

2. Notes

1. Proper care must be exercised in mixing the alcohol and sulfuric acid. The mixture is best cooled in the flask with stirring.
2. Reduced copper powder and various grades of copper bronze were used with practically the same results.

3. Discussion

m-Bromotoluene can be prepared by the diazotization of *m*-toluidine followed by treatment with cuprous bromide,

potassium bromide and hydrobromic acid,[1] and by elimination of the amino group from 3-bromo-4-aminotoluene[2] and 5-bromo-2-aminotoluene.[3] The procedure described is a modification of the method of Feitler.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 111

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

copper bronze

ethyl alcohol, alcohol (64-17-5)

calcium chloride (10043-52-4)

acetaldehyde (75-07-0)

sulfuric acid (7664-93-9)

ether (60-29-7)

sodium hydroxide (1310-73-2)

HYDROBROMIC ACID (10035-10-6)

sodium carbonate (497-19-8)

nitrogen (7727-37-9)

sodium nitrite (7632-00-0)

nitrite (14797-65-0)

copper powder (7440-50-8)

3-Bromo-4-aminotoluene (583-68-6)

potassium bromide (7758-02-3)

cuprous bromide (7787-70-4)

5-bromo-2-aminotoluene (583-75-5)

p-toluidine (106-49-0)

m-toluidine (108-44-1)

m-Bromotoluene, Toluene, m-bromo- (591-17-3)

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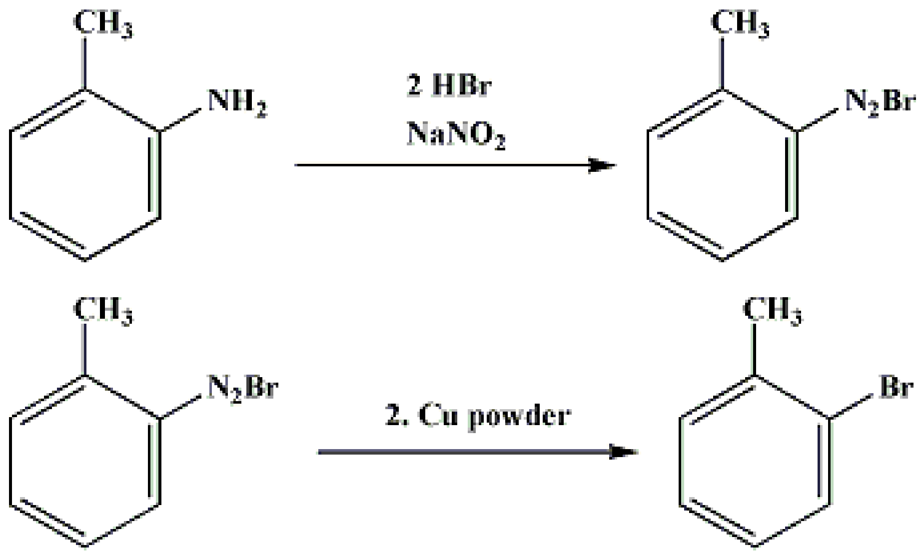
o-BROMOTOLUENE

[Toluene, *o*-bromo-]



Submitted by L. A. Bigelow
Checked by C. S. Marvel and S. V. Puntambeker.

1. Procedure

A solution of 162 g. (1.5 moles) of commercial *o*-toluidine in 880 cc. (6 moles) of 40 per cent commercial hydrobromic acid (Note 1) in a 3-l. flask is cooled to 10° and diazotized with 116 g. (1.7 moles) of coarsely powdered commercial sodium nitrite, added about 10 g. at a time. After each addition the flask is stoppered and shaken until all the red fumes are absorbed. The temperature must be kept below 10°. When diazotization is complete, 5 g. of copper powder (Note 2) is added, the flask is attached to a reflux condenser and heated very cautiously. As soon as the first sign of reaction is observed, the flask is cooled with ice. Nitrogen is evolved vigorously. When the reaction subsides, the mixture is heated one-half hour on the steam bath.

Then 1 l. of water is added and the mixture is distilled with steam until about 1.5 l. has passed over. The distillate is made alkaline with about 10 g. of powdered sodium hydroxide and the lower red layer of crude *o*-bromotoluene separated (Note 3). This weighs about 140 g. It is washed with concentrated sulfuric acid, which removes almost all the color, and then twice with water. It is dried over a little calcium chloride, filtered and distilled twice from a modified Claisen flask (p. 130). The yield of pure product boiling at 178–181° is 110–120 g. (43–47 per cent of the theoretical amount).

2. Notes

1. If 48 per cent (constant boiling) hydrobromic acid is used the diazotization is

very difficult to control. The reaction becomes very vigorous and forces out the stopper.

2. Either reduced copper or fine copper filings may be used.

3. This gives as good results as when the *o*-bromotoluene is extracted from the alkaline mixture with ether.

3. Discussion

o-Bromotoluene can be prepared by the bromination of toluene;[1] by the bromination of potassium *p*-toluenesulfonate and subsequent hydrolysis;[2] and by the diazotization of *o*-toluidine under different conditions.[3]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

ether (60-29-7)

sodium hydroxide (1310-73-2)

HYDROBROMIC ACID (10035-10-6)

nitrogen (7727-37-9)

sodium nitrite (7632-00-0)

copper, copper powder, copper filings (7440-50-8)

toluene (108-88-3)

o-Bromotoluene, Toluene, o-bromo- (95-46-5)

o-toluidine (95-53-4)

potassium p-toluenesulfonate

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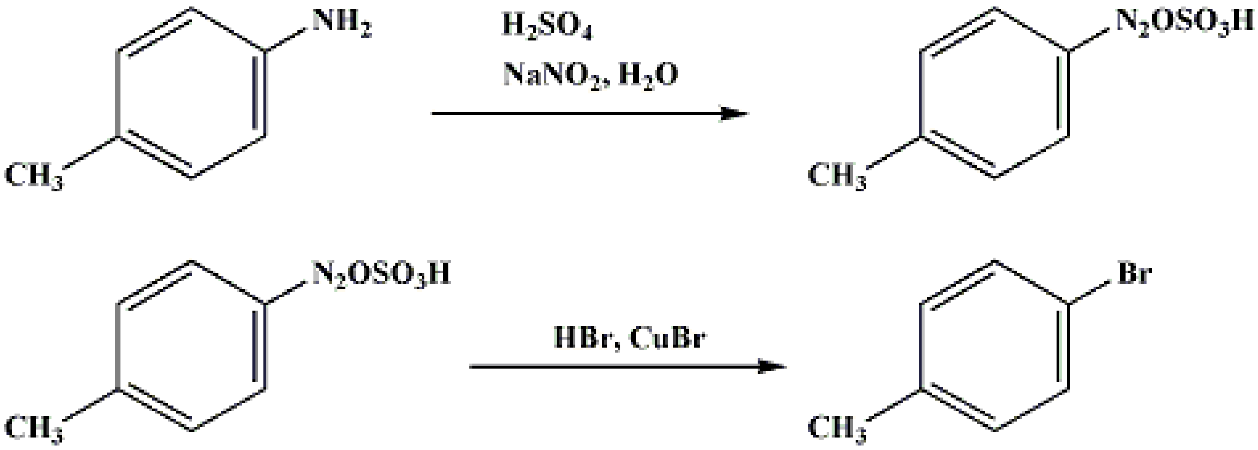
p-BROMOTOLUENE

[Toluene, *p*-bromo-]



Submitted by L. A. Bigelow
Checked by C. S. Marvel and A. E. Broderick.

1. Procedure

A mixture of 63 g. (0.25 mole) of crystallized copper sulfate, 20 g. (0.31 atom) of copper turnings, 154 g. (1.1 moles) of sodium bromide dihydrate, 30 g. (16.3 cc., 0.28 mole) of concentrated sulfuric acid (sp. gr. 1.84), and 1 l. of water is refluxed over a flame for three to four hours until the color becomes yellowish (Note 1).

When the hydrobromic acid-cuprous bromide solution is ready for use, the diazonium solution is prepared. A solution of 107 g. (1 mole) of *p*-toluidine and 196 g. (107 cc., 1.9 moles) of concentrated sulfuric acid (sp. gr. 1.84) in 1 l. of water is cooled below 20° and diazotized with a solution of 70 g. (1 mole) of sodium nitrite in 125 cc. of water. This requires about twenty to thirty minutes when the temperature is maintained between 15° and 20° by means of an ice bath.

A 5-l. round-bottomed flask containing the hydrobromic acid-cuprous bromide solution, is arranged for steam distillation. After the copper solution is heated to boiling, the diazonium solution is gradually added from a separatory funnel and a vigorous current of steam is passed through the reaction mixture at the same time. This procedure requires about two hours.

The aqueous distillate is made alkaline with sodium hydroxide solution and the *p*-bromotoluene is separated from the water layer (Note 2). The crude product weighs 131–137 g. For purification the crude product is washed once with concentrated sulfuric acid (Note 3) and then with water. It is dried over a little calcium chloride, filtered, and distilled. The yield of pure product amounts to 120–126 g. (70–73 per cent of the theoretical amount) boiling at 183–185° and melting at 25–26°.

2. Notes

1. If the color of the solution has not been discharged after heating for three to four hours, a few grams of sodium sulfite may be added to complete the reduction.
2. A small amount of ether or benzene may be used to aid in the separation if it is needed.
3. The sulfuric acid treatment is necessary if a colorless product is to be obtained. If ether is used in the extraction of the *p*-bromotoluene, it must be removed before washing with sulfuric acid.

3. Discussion

p-Bromotoluene can be prepared by the bromination of toluene with bromine[1] or hypobromous acid;[2] and, preferably, by the diazotization of *p*-toluidine followed by replacement of the diazonium group by bromine.[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 550
- Org. Syn. Coll. Vol. 2, 89

References and Notes

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2. Stark, Ber. **43**, 673 (1910).
3. Acree, Ber. **37**, 994 (1904); Neogi and Mitra, J. Chem. Soc. 1332 (1928).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

Benzene (71-43-2)

ether (60-29-7)

sodium sulfite (7757-83-7)

sodium hydroxide (1310-73-2)

bromine (7726-95-6)

copper sulfate (7758-98-7)

sodium nitrite (7632-00-0)

copper turnings (7440-50-8)

toluene (108-88-3)

hypobromous acid (13517-11-8)

sodium bromide dihydrate

hydrobromic acid-cuprous bromide

p-toluidine (106-49-0)

p-Bromotoluene, Toluene, p-bromo- (106-38-7)

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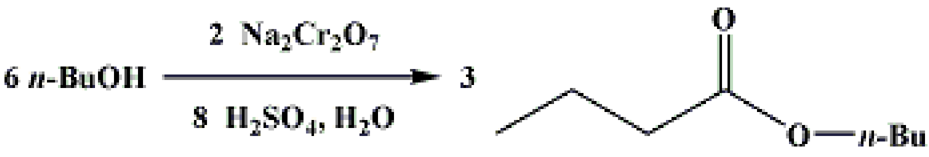
n-BUTYL *n*-BUTYRATE

[Butyric acid, butyl ester]



Submitted by G. Ross Robertson
Checked by Henry Gilman and J. E. Kirby.

1. Procedure

In a 2-l. flask fitted with a mechanical stirrer, a thermometer, and a separatory funnel, are placed a cool solution of 240 cc. (4.3 moles) of commercial sulfuric acid (sp. gr. 1.84) in 240 cc. of water, and 240 g. (296 cc., 3.24 moles) of technical *n*-butyl alcohol (Note 1). The whole is placed in a large, efficient ice-salt bath.

A solution of 320 g. (1.07 moles) of crystalline sodium dichromate (350 g. of the ordinary moist technical hydrated salt is also suitable) in 200 cc. of water is dropped from the funnel into the vigorously stirred alcohol mixture as rapidly as can be done without running the temperature above 20°. When most of the dichromate has been added, the viscosity of the reaction mixture becomes so great that the stirring is rendered inefficient. The temperature is now allowed to rise to 35° if necessary (Note 2), to accelerate the reaction.

The resulting green sirupy emulsion is diluted with an equal volume of water, whereupon 220–225 cc. of an oil containing the desired ester (Note 3), slowly separates. This oil is washed three times with water, separated, and treated with a few grams of anhydrous sodium sulfate in order to remove most of the water. It is now distilled slowly through a large, efficient fractionating column. The fraction boiling at 150–170° is collected, and should amount to 170–175 cc. It is washed with five 15-cc. portions of 60 per cent sulfuric acid (sp. gr. about 1.5) (Note 4), is then washed free of acids with dilute sodium hydroxide, and finally washed free of alkali with cold water. It is rapidly dried, as before, with sodium sulfate, and fractionated through the same distilling column. The fraction boiling at 162–166° (uncorr.) consists of *n*-butyl *n*-butyrate, containing a small percentage of residual butyl alcohol. The yield is 96–110 g. (41–47 per cent of the theoretical amount).

If higher purity is desired, the fractionation must be repeated. An additional yield may be secured by further fractionation of the lower-boiling fractions (Note 5) and (Note 6).

2. Notes

1. When *n*-butyl alcohol is oxidized to butyric acid in the presence of a high concentration of sulfuric acid, esterification takes place at once, even in the cold, as long as an excess of the alcohol is present.
2. If the temperature of the reaction mixture is allowed to rise much above 35°, considerable material escapes in the form of butyraldehyde (b.p. 74°).
3. The oil obtained as the first crude product contains, in addition to the desired ester, much unchanged butyl alcohol, a little butyraldehyde, and a little free butyric acid.
4. The 60 per cent sulfuric acid is chosen as a wash liquid because it is miscible with butyl alcohol but not with the ester. The volatile aldehyde disappears in the two fractionations, while the butyric acid is removed by the alkali.
5. The low-boiling fractions could no doubt be returned to a new batch if this process were carried out repeatedly in quantity production. About 25 per cent of the original butyl alcohol can be recovered if desired. The very small fractions boiling above 166° may contain esters of other alcohols occurring in the technical product used, and possibly butyl succinate and related by-products.
6. It is suggested that improved yields are obtainable when 2 moles of *n*-butyl alcohol are added to 0.62 mole of crystallized sodium dichromate and 5.1 moles of concentrated sulfuric acid. The temperature is kept between 30° and 40° during the addition, and then the mixture is heated on the steam bath (90–100°) for two to six hours until the supernatant liquid is practically colorless. The mixture is then worked up as described (W. J. Hickinbottom, private communication; [1]).

3. Discussion

n-Butyl *n*-butyrate can be prepared by the interaction of *n*-butyl alcohol and *n*-butyric acid in the presence of sulfuric acid;[2] by the action of aluminum butoxide on butyraldehyde;[3] by oxidizing *n*-butyl alcohol with sodium dichromate and concentrated sulfuric acid;[1] and by oxidizing *n*-butyl alcohol with sodium chlorate and dilute sulfuric acid with vanadium pentoxide as a catalyst,[4] a reaction which may lead to violent explosions if the sodium chlorate is replaced by potassium chlorate and if the temperature is not carefully controlled.[5] A number of catalytic procedures, more suitable for industrial than laboratory operation, have been described for preparing *n*-butyl *n*-butyrate by esterification,[6] or from butyric acid and hydrogen,[7] or from *n*-butyl alcohol alone.[8]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alcohol (64-17-5)

sulfuric acid (7664-93-9)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

dichromate

sodium sulfate (7757-82-6)

vanadium pentoxide

butyl alcohol, n-butyl alcohol (71-36-3)

Butyric acid, butyl ester, n-BUTYL n-BUTYRATE (109-21-7)

sodium dichromate (7789-12-0)

butyric acid, n-butyric acid (107-92-6)

butyraldehyde (123-72-8)

butyl succinate (925-21-3)

aluminum butoxide

sodium chlorate (7775-09-9)

potassium chlorate (3811-04-9)

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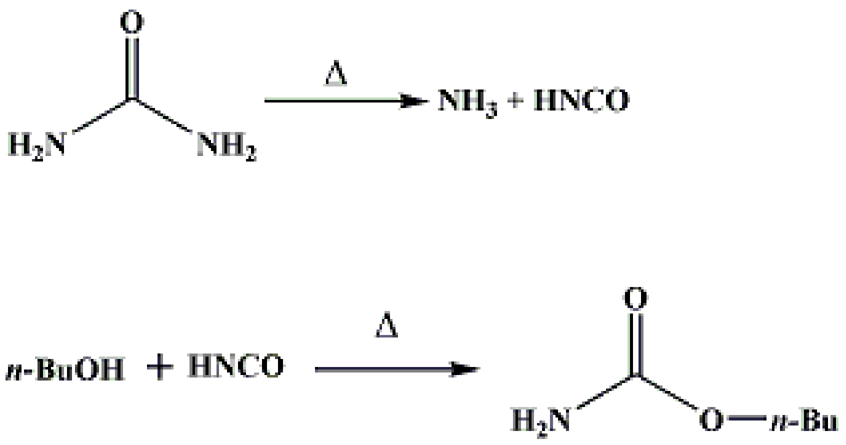
n-BUTYL CARBAMATE

[Carbamic acid, butyl ester]



Submitted by Tenney L. Davis and Stanley C. Lane.
Checked by H. T. Clarke and L. G. S. Brooker.

1. Procedure

In a 2-l. round-bottomed flask fitted with a reflux condenser is placed 970 g. (1200 cc., 13.1 moles) of *n*-butyl alcohol. This is warmed, and 180 g. (3 moles) of urea is added to the warm liquid in small portions, with shaking. While the temperature rises, care must be taken that the urea goes into solution without melting and does not form a layer of molten urea beneath the solution (Note 1). The last portions of the urea are finally dissolved by boiling the liquid. The solution is then refluxed for thirty hours (Note 2), during which time ammonia escapes from the top of the condenser (Note 3). The reflux condenser is then removed and the liquid is distilled through an efficient column until the temperature of the liquid reaches 150°. The distillate consists of butyl alcohol containing ammonia and may be used directly in another run. The material which remains in the flask solidifies on cooling. It is boiled with 1 l. of ligroin (b.p. 60–90°) (Note 4), filtered, and the undissolved solid again boiled with two 100-cc. portions of ligroin, filtered, and finally washed on the filter with 100 cc. more of warm ligroin. The white gritty material which remains undissolved is practically pure cyanuric acid (Note 5). The yield of cyanuric acid is 12–18 g. (9–14 per cent of the theoretical amount).

The combined ligroin filtrates and washings are distilled under atmospheric pressure, using a column, until the temperature of the liquid reaches 150°. The residue is then distilled under reduced pressure and the fraction boiling at 108–109°/14 mm. (Note 6) is collected. The product is pure and melts at 53–54°. The yield is 263–266 g. (75–76 per cent of the theoretical amount).

2. Notes

1. If molten urea settles to the bottom near the source of heat, it will cause the liquid to bump and will decompose to produce cyanuric acid to the detriment of the yield of butyl carbamate.
2. If thirty hours of continuous heating is impracticable, care must be taken, on resuming the heating, that the urea goes into solution without melting.
3. A small amount of ammonium carbamate collects in the condenser during the reaction and may cause clogging. This should be removed from time to time by pushing it down by means of a glass tube which fits snugly into the condenser. The gases evolved when the solid falls into the hot liquid are carried off through the tube.
4. "Aviation" gasoline (86° Baumé) may also be employed if it is first distilled and the fraction boiling above 120° rejected.
5. The extraction with ligroin may be completed satisfactorily by means of the apparatus described on p. 375. Butyl allophanate is not soluble in ligroin and, if present, would remain with the cyanuric acid. However, when the material which is insoluble in ligroin is washed with hot acetone the washings yield no appreciable residue on evaporation. This is evidence that butyl allophanate and urea are not present in the cyanuric acid.
6. *n*-Butyl carbamate boils under atmospheric pressure at 203–204° with some decomposition. The products of the decomposition are butyl alcohol and cyanuric acid.

3. Discussion

No reference to the preparation of *n*-butyl carbamate is to be found in the literature. The procedure described is adapted from that of Cahours,[1] who prepared *n*-propyl carbamate by heating propyl alcohol with urea. *n*-Butyl carbamate has also been prepared by one of the editors by the action of *n*-butyl chloroformate upon ammonia. The preparation of carbamates of the higher alcohols can be carried out by heating the carbamate of a volatile alcohol with a higher alcohol.[2]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ligroin

ammonia (7664-41-7)

butyl alcohol, n-butyl alcohol (71-36-3)

acetone (67-64-1)

Carbamic acid, butyl ester, butyl carbamate, n-BUTYL CARBAMATE (592-35-8)

urea (57-13-6)

cyanuric acid (108-80-5)

ammonium carbamate (1111-78-0)

Butyl allophanate

propyl alcohol (71-23-8)

n-propyl carbamate (627-12-3)

n-butyl chloroformate (592-34-7)

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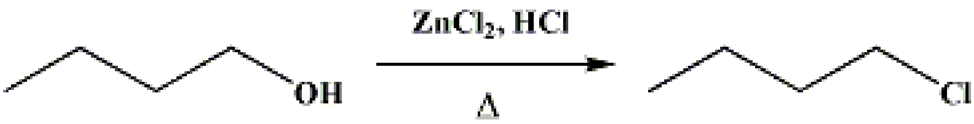
n-BUTYL CHLORIDE

[Butane, 1-chloro-]



Submitted by J. E. Copenhaver and A. M. Whaley.
Checked by R. L. Shriner and S. C. Kelton, Jr.

1. Procedure

In a 3-l. round-bottomed, short-necked flask, 1363 g. (10 moles) of anhydrous zinc chloride is dissolved in 864 cc. (10 moles) of concentrated hydrochloric acid, the flask being cooled to prevent loss of hydrogen chloride (Note 1). To this solution is added 371 g. (5 moles) of *n*-butyl alcohol. The flask is attached to a vertical, water-cooled reflux condenser (Note 2), the top of which carries a thermometer and a goose-neck tube connected with an efficient downward condenser. To the end of the downward condenser is attached a 1-l. Florence flask which is connected to a 250-cc. Erlenmeyer flask by a bent tube. A tube from the second receiving vessel is connected with a gas-absorption trap (Note 3) or to a funnel inverted over 800 cc. of 10 per cent sodium hydroxide solution in a 1-l. beaker. Rubber stoppers are used throughout. Both the receiving vessels are cooled in a large ice-salt bath.

The flask is heated by an oil bath to 150° (bath temperature), at which temperature the solution starts to boil and butyl chloride begins to distil. After a few moments, it is necessary to control the temperature in the reflux condenser at 75–80° by a very slow stream of water. The temperature of the oil bath is gradually raised to 155°, and one hour from the time of initial boiling practically all the butyl chloride has distilled. If necessary, however, heating at 155° may be continued for ten to fifteen minutes longer and the temperature of the bath then raised to 160–165°, the reflux temperature not being allowed to get above 80°. The distillate is washed with 100 cc. of cold water, 50 cc. of cold concentrated sulfuric acid (in four portions), 10 cc. of water, and finally with 25 cc. of 10 per cent sodium carbonate solution. It is dried over 10 g. of calcium chloride and distilled (Note 4) and (Note 5). The fraction boiling from 75.5° to 77.5° weighs 352–361 g. (76–78 per cent of the theoretical amount). (Note 6).

2. Notes

1. The sticks of zinc chloride are crushed before being mixed with the acid, and then the mixture is agitated with frequent cooling under the water tap. After the initial heat of solution is over (about five minutes), and there is no further tendency for the mixture to heat up, the flask is closed with a rubber stopper

which is wired on and the solution process completed by thirty minutes of mechanical shaking. If a few grams of zinc chloride remain, they will dissolve soon after the beginning of the reaction.

2. A five-bulb Allihn condenser provides sufficient refluxing to insure separation of the butyl chloride and the alcohol. When the reflux temperature reaches 75°, a very slow stream of water is necessary to keep it within the desired range.

3. The gas-absorption trap described on p. 97 may be used.

4. Distillation of the crude product was carried out through a Carborundum-filled column about 1 in. in diameter and 18 in. long. The forerun and residue were both small but may be reduced still further by mixing, drying, and redistilling.

5. The zinc chloride may be recovered for future runs by removing the reflux condenser and connecting the reaction flask directly to the downward condenser and absorber. The oil bath is gradually raised to 250–260° and held at that temperature until the zinc chloride begins to crystallize. Much time is saved in dissolving the zinc chloride in the hydrochloric acid for the next run if it is stirred while cooling. Seven runs have been made with the same zinc chloride; the same or better yields being obtained each time regardless of the fact that the zinc chloride changes to a light brown color.

6. This method may be used to prepare other alkyl chlorides. The temperatures for *n*-propyl and *sec*.-butyl chlorides are, respectively, as follows: bath, 125–130° and 138–140°; reflux, 45–50° and 65–69°. Yields: 65–70 per cent and 85–88 per cent of the theoretical amounts.

3. Discussion

n-Butyl chloride can be prepared by the interaction of *n*-butyl alcohol and hydrochloric acid or hydrogen chloride either with[1] or without a catalyst;[2] and from *n*-butyl alcohol with phosphorus pentachloride[3] or thionyl chloride.[3] The method described above is based on a recently published study.[4]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alcohol (64-17-5)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrogen chloride, hydrochloric acid (7647-01-0)

sodium hydroxide (1310-73-2)

phosphorus pentachloride (10026-13-8)

thionyl chloride (7719-09-7)

sodium carbonate (497-19-8)

n-butyl alcohol (71-36-3)

Butane, 1-chloro-, Butyl chloride, n-BUTYL CHLORIDE (109-69-3)

zinc chloride (7646-85-7)

sec.-butyl chloride (78-86-4)

n-propyl chloride (540-54-5)

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Organic Syntheses, CV 1, 144

tert.-BUTYL CHLORIDE

[Propane, 2-chloro-2-methyl-]

Submitted by James F. Norris and Alanson W. Olmsted.
Checked by Henry Gilman and L. L. Heck.

1. Procedure

In a 500-cc. separatory funnel are placed 74 g. (95 cc., 1 mole) of *tert*.-butyl alcohol (Note 1) and 247 cc. (3 moles) of c.p. concentrated hydrochloric acid (sp. gr. 1.19). After shaking, the layers are allowed to separate (fifteen to twenty minutes) and the upper layer is drawn off and washed first with a 5 per cent sodium bicarbonate solution, then with water until neutral to moist litmus paper (Note 2) and (Note 3). The chloride is treated with 10 g. of calcium chloride and shaken thoroughly, then transferred to a 125-cc. distilling flask. It is then distilled, using a long water condenser. The fraction boiling at 49.5–52° weighs 72–82 g. (78–88 per cent of the theoretical amount).

2. Notes

1. As it is difficult to prepare *tert*.-butyl alcohol free from water, 84 g. of the constant-boiling mixture of the alcohol and water can be used. This mixture boils at 80°, contains 88.24 per cent alcohol when the distillation is carried out at 760 mm., and can be readily obtained by distilling a sample of the dilute alcohol.
2. The chloride is very slowly hydrolyzed by cold water.
3. It is suggested that calcium chloride be added to the saturation point after the *tert*.-butyl alcohol and hydrochloric acid are mixed in order to salt out the *tert*.-butyl chloride and to concentrate the hydrochloric acid (W. W. Hartman, private communication).

3. Discussion

tert.-Butyl chloride can be prepared by passing hydrogen chloride into the alcohol kept cold in a freezing mixture;[1] by distilling a mixture of the alcohol and a large excess of concentrated hydrochloric acid;[2] and from the alcohol and thionyl chloride.[3] Procedures have also been described for the isomerization of isobutyl chloride to *tert*.-

butyl chloride,[4] and for the preparation of *tert.*-butyl chloride by the catalyzed addition of hydrogen chloride to the butene fraction from cracking gases.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 524

References and Notes

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4. Dow Chemical Co., U. S. pat. 1,993,719 [C. A. **29**, 2549 (1935)].
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alcohol (64-17-5)

calcium chloride (10043-52-4)

hydrogen chloride, hydrochloric acid (7647-01-0)

thionyl chloride (7719-09-7)

sodium bicarbonate (144-55-8)

Propane, 2-chloro-2-methyl-, tert.-BUTYL CHLORIDE (507-20-0)

isobutyl chloride (513-36-0)

butene (106-98-9)

tert.-butyl alcohol (75-65-0)

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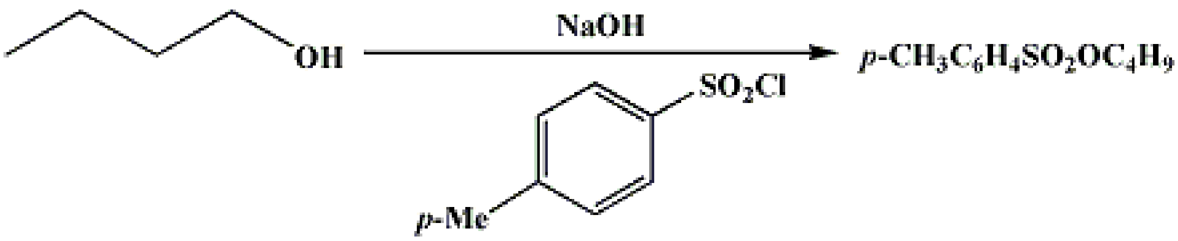
Organic Syntheses, CV 1, 145

n-BUTYL *p*-TOLUENESULFONATE

[*p*-Toluenesulfonic acid, butyl ester]



Submitted by A. T. Roos, Henry Gilman, and N. J. Beaber.
Checked by H. T. Clarke and G. S. Babcock.

1. Procedure

In a 2-l., three-necked flask, fitted with a mechanical stirrer, a thermometer, and a 250-cc. separatory funnel, are placed 148 g. (2 moles) of *n*-butyl alcohol and 210 g. (1.1 moles) of pure *p*-toluenesulfonyl chloride (Note 1). From the separatory funnel 320 cc. (1.6 moles) of 5 *N* sodium hydroxide is run in at a rate that does not cause the temperature of the reaction mixture to exceed 15° (Note 2); the addition requires three to four hours.

Another portion of 210 g. (1.1 moles) of *p*-toluenesulfonyl chloride is added and then 320 cc. of 5 *N* sodium hydroxide solution is slowly introduced, again keeping the temperature below 15°. Stirring is continued for four hours longer, and the oily layer is separated from the water layer and any unchanged *p*-toluenesulfonyl chloride. Enough petroleum ether (b.p. 60–70°) or benzene is added to the oil to cause it to float on water; the solution is washed thoroughly with 50 cc. of 10 per cent sodium hydroxide and dried by standing overnight over 20 g. of anhydrous potassium carbonate. The solution is filtered, and the solvent is distilled. This is conveniently accomplished by adding the solution from a separatory funnel to a 500-cc. Claisen flask heated on a steam bath. The oily ester is then distilled under reduced pressure (Note 3), and, after a forerun boiling to 170°/10 mm., the pure ester distils at 170–171°/10 mm. The yield is 250–270 g. (50–54 per cent of the theoretical amount) (Note 4).

2. Notes

1. Technical *p*-toluenesulfonyl chloride is dissolved in benzene, washed with 5 per cent sodium hydroxide, dried by shaking with a small amount of potassium carbonate, and then distilled under reduced pressure. If the distillation must be interrupted, it is recommended that the liquid be allowed to cool before breaking the vacuum; otherwise, when distillation is resumed later, considerable decomposition takes place.

2. The cooling may be effected conveniently by immersing the flask in a water bath containing a small amount of ice, or by cold running water. If the bath is cooled to 0°, the time required for the completion of the reaction is appreciably longer.
3. It is best to distil the ester under greatly reduced pressure. Appreciable decomposition takes place even at 10-mm. pressure, and the distilled ester becomes quite dark after standing a week. To avoid superheating and consequent decomposition, it is recommended that the ester be distilled in small lots (from 250-cc. Claisen flasks when large runs are made). A sample of 100 g. distilled at 132–133°/3 mm. remained water-white after standing for two months.
4. Methyl *p*-toluenesulfonate may be prepared in a somewhat similar manner with good yields. One kilogram of methyl alcohol (90–95 per cent) is placed in a round-bottomed flask, contained in an ice-salt bath. One kilogram of powdered pure *p*-toluenesulfonyl chloride (crude material may be used but the yield of product drops to about 75 per cent) is added with mechanical stirring. From a separatory funnel 840 g. of 25 per cent sodium hydroxide solution is added drop by drop. The temperature must be held at about 23–27° for the best results. When all this alkaline solution is added the reaction mixture is tested with litmus; if not alkaline, more alkali is added until the neutral point is reached. Upon standing several hours the ester sinks and the alcohol forms the top layer. The alcohol may be siphoned off and used in subsequent experiments; the methyl *p*-toluenesulfonate is washed with water to remove a little salt and then with 5 per cent hydrochloric acid to dissolve iron, if an iron stirrer was used. Finally it is washed with 5 per cent sodium carbonate and water. The ester is then distilled and boils at 161°/10 mm. (m.p. 27–28°). The yield is 90 per cent of the theoretical amount.
The spent alcohol is distilled from a steam bath, and alcohol of 84–91 per cent purity is obtained which is suitable for subsequent runs.

3. Discussion

Other alkyl esters have been prepared by this general method.[1] The *n*-butyl ester can be prepared by treating an ethereal solution of *p*-toluenesulfonyl chloride and butyl alcohol with powdered potassium hydroxide,[2] by refluxing the acid chloride with a 10 per cent excess of alcohol,[2] and by heating the acid chloride with the alcohol and anhydrous sodium carbonate.[3] By using pyridine as the condensing agent the yield can be increased to 86 per cent.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 47
- Org. Syn. Coll. Vol. 3, 366

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

n-butyl ester

alcohol (64-17-5)

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

methyl alcohol (67-56-1)

sodium hydroxide (1310-73-2)

iron (7439-89-6)

sodium carbonate (497-19-8)

butyl alcohol, n-butyl alcohol (71-36-3)

pyridine (110-86-1)

potassium hydroxide (1310-58-3)

p-Toluenesulfonyl chloride (98-59-9)

n-BUTYL p-TOLUENESULFONATE, p-Toluenesulfonic acid, butyl ester (778-28-9)

Methyl p-toluenesulfonate (80-48-8)

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n-BUTYRYL CHLORIDE

Submitted by B. Helferich and W. Schaefer.
Checked by Henry Gilman and S. A. Harris.

1. Procedure

In a 125-cc. distilling flask, provided with a water-cooled side arm to act as reflux condenser (Note 1), is placed 56 g. (33.4 cc., 0.47 mole) of thionyl chloride (Note 2). This is heated on a water bath, and to it is added during the course of one hour 35.2 g. (0.4 mole) of *n*-butyric acid (Note 3) by means of a separatory funnel attached to the neck of the flask. The evolved gases are absorbed in water (Note 4).

When all the acid has been added, the mixture is heated for one-half hour on the water bath and then distilled directly from an oil bath into a second distilling flask. The crude acid chloride thus obtained boils between 70° and 110°; it is purified by distillation through a column and boils almost entirely at 100–101°, only a few drops of forerun being obtained. The yield is 36 g. (85 per cent of the theoretical amount) (Note 5).

2. Notes

1. If a Claisen distilling flask is used for the preparation of the acid chloride the side arm is plugged by a small cork; the short neck holds the reflux condenser, and the long neck the separatory funnel.
2. The yield is influenced by the purity of the thionyl chloride; the results reported above were obtained with a pure product which boiled over a two-degree range.
3. The presence of traces of water in the butyric acid is of no disadvantage if a correspondingly larger quantity (1 mole for 1 mole of water) of thionyl chloride is used.
4. The gas-absorption trap shown in Fig. 7 on p. 97 may be used.
5. It is reported that the major loss in this preparation is due to the formation of butyric anhydride and that, if the thionyl chloride is kept cool by means of a water bath during the addition of the acid, the formation of anhydride is suppressed with a consequent improvement in the yield of the acid chloride (R. R. Read, private communication).

3. Discussion

n-Butyryl chloride can be prepared from *n*-butyric acid with phosphorus trichloride,[1] with phosphorus pentachloride,[1] with benzotrichloride and zinc chloride,[2] with phthaloyl chloride,[3] and with benzoyl chloride.[4] A study has been made of the preparation of butyryl chloride using phosphorus pentachloride, phosphorus trichloride, and thionyl chloride.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 312

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

phosphorus pentachloride (10026-13-8)

thionyl chloride (7719-09-7)

benzoyl chloride (98-88-4)

benzotrichloride (98-07-7)

phosphorus trichloride (7719-12-2)

butyric acid, n-butyric acid (107-92-6)

zinc chloride (7646-85-7)

butyric anhydride (106-31-0)

phthaloyl chloride (88-95-9)

Butyryl chloride, n-BUTYRYL CHLORIDE (141-75-3)

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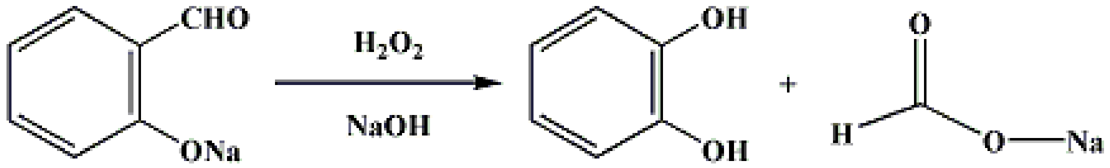
CATECHOL

[Pyrocatechol]

[(*A*) (*from Salicylaldehyde*)]



Submitted by H. D. Dakin
Checked by H. T. Clarke and E. R. Taylor.

1. Procedure

To a solution of 122 g. (1 mole) of pure salicylaldehyde (Note 1) in 1000 cc. of normal sodium hydroxide solution at room temperature, is added 1420 g. (1.2 moles) of 3 per cent hydrogen peroxide. The mixture darkens slightly in color and the temperature rises to 45–50°. The solution is allowed to stand for fifteen to twenty hours, whereupon a few drops of acetic acid are added in order to neutralize any excess alkali, and the solution evaporated to complete dryness on the water bath under reduced pressure.

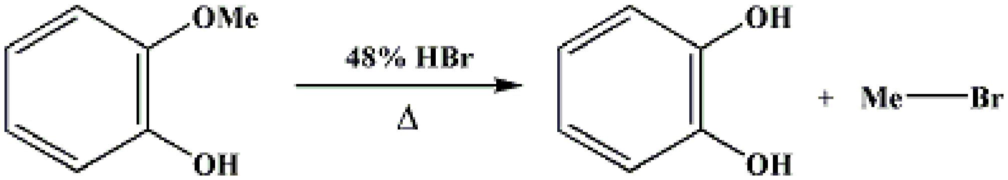
The solid residue is finely crushed and warmed nearly to boiling with 500 cc. of toluene; the mixture is then poured into the folded filter paper of an extraction apparatus (p. 375) and extracted with boiling toluene for five hours. The toluene is allowed to cool and is decanted from the catechol, which crystallizes out. The insoluble material is again ground up and extracted in the apparatus with the decanted toluene. The combined product, weighing 70–76 g., consists of light brown plates melting at 104°, and is thus pure enough for many purposes. A further 6–12 g. of catechol can be obtained on distilling off the bulk of the toluene from the mother liquor. In order to obtain an entirely pure product, the crude catechol should be distilled under reduced pressure, when it passes over entirely at 119–121° /10 mm. (or 113–115° /8 mm.), and the distillate recrystallized from about five times its weight of toluene. In this way, colorless plates melting at 104–105° are obtained. The yield of the purified product is 76–80 g. (69–73 per cent of the theoretical amount) (Note 2).

2. Notes

1. A considerably lower yield is obtained (50 per cent or less) if technical salicylaldehyde (not purified through the bisulfite compound) is employed.
2. The procedure described is applicable to almost all hydroxyaldehydes in which the hydroxyl and carbonyl groups occupy ortho or para positions relatively to each other;[1] in the latter case derivatives of hydroquinone are produced. When the hydroxyl and carbonyl groups occupy the meta position with respect to each other, no reaction takes place, as is also the case with certain ortho and para compounds containing nitro groups and iodine atoms. *o*-Hydroxyacetophenone and *p*-hydroxyacetophenone are

also capable of yielding catechol and hydroquinone, respectively, under the above conditions.
3. Catechol may also be produced from salicylaldehyde by the use of certain derivatives of hydrogen peroxide, such as persulfates or sodium peroxide, but the method is far less convenient.

[(*B*) (*from Guaiacol*)]

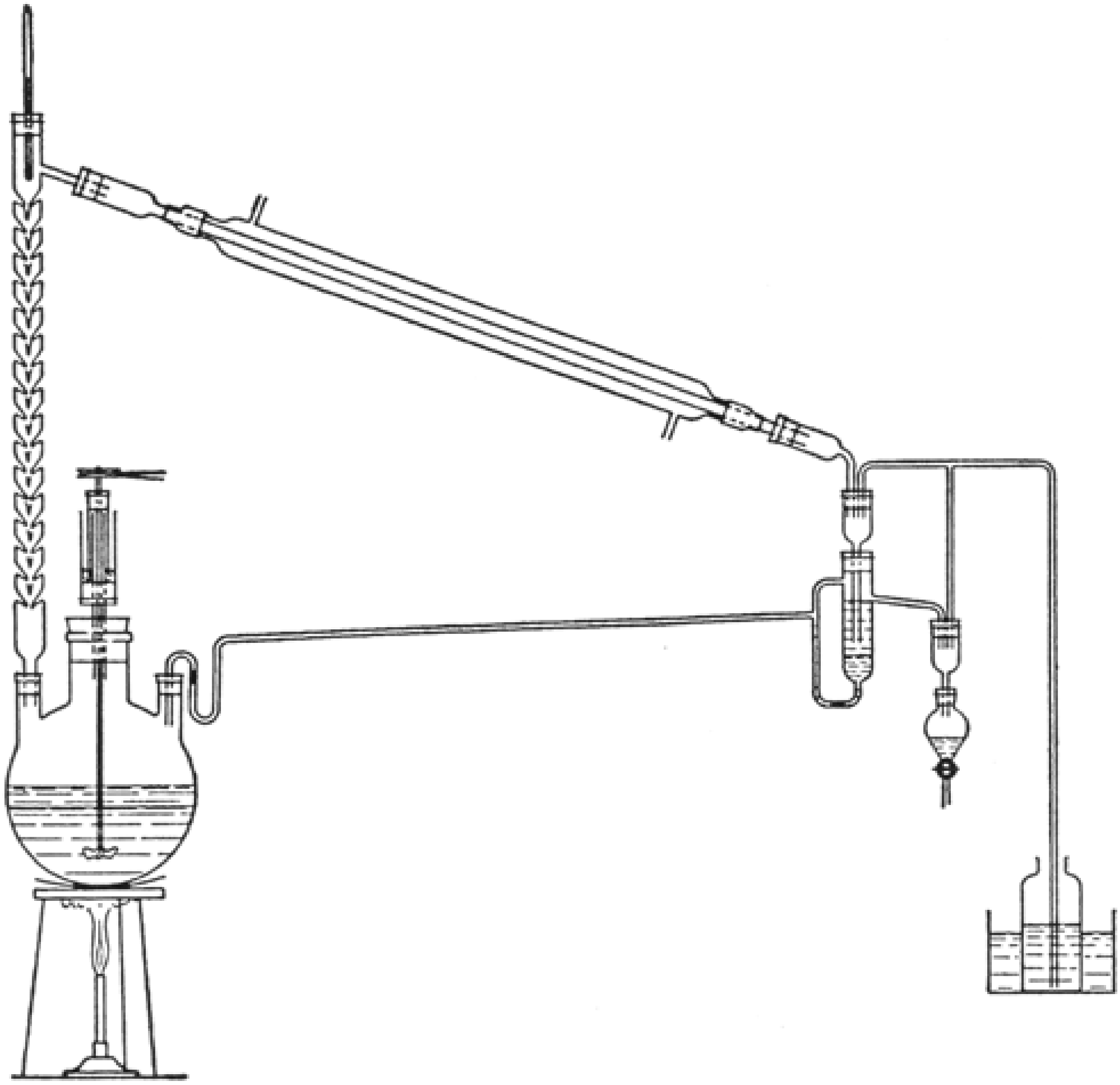


Submitted by H. T. Clarke and E. R. Taylor.
Checked by C. S. Marvel and W. B. King.

1. Procedure

In a 5-l. flask fitted with a stirrer, a thermometer reaching to the bottom, a fractionating column about 40 cm. long (Note 1), and a return inlet tube, are placed 912 g. (7.4 moles) of crystalline guaiacol and 1500 g. (1015 cc., 8.8 moles) of 48 per cent hydrobromic acid (p. 26). This apparatus is connected with a condenser, an automatic separator, and an absorption vessel, as shown in Fig. 10 (Note 2). The mixture is gently heated, with continual stirring, at such a rate that the vapor at the head of the column maintains a temperature of 85–95°. The mixture of water and guaiacol which condenses passes through the automatic separator (Note 3), the guaiacol being returned to the reaction vessel and the water collected in the tap funnel, from which it is removed from time to time. The gaseous methyl bromide is collected in an ice-cooled bottle containing a weighed quantity (about 1600 g.) of methyl alcohol (Note 4).

Fig. 10.



After six to seven hours, the temperature at the head of the column begins to rise above 95° and finally reaches 98°, at which point practically no more guaiacol passes over with the distillate. This requires about one hour more, after which the heating is stopped (Note 5). The increase in weight of the absorption bottle amounts to 400–500 g. (57–72 per cent of the theoretical amount of methyl bromide); the water collected weighs 550–560 g. (Note 6).

The residue in the flask, which has become pink in color, is extracted at 85–95° with three 1500-cc. portions of toluene (Note 7), and the united extracts are distilled under reduced pressure on the steam bath until no more moisture passes over with the vapor. The solution (2–2.5 l.) is then allowed to cool, whereupon 385–390 g. of catechol separates in colorless plates melting at 104–105°. The mother liquor is further concentrated under reduced pressure and the residue finally distilled, pure catechol passing over at 124–125° / 12 mm. The distillate, on recrystallization from a small quantity of toluene, yields 8–10 g. of pure material.

The aqueous residue from the three extractions with toluene yields, when the bulk of the water has been distilled off on the steam bath under reduced pressure, a further quantity of catechol by extraction with hot toluene, but the crystals so obtained are contaminated with a

red impurity. It is therefore preferable to distil the entire residue, again collecting the fraction boiling at 124–125° /12 mm. and recrystallizing it from fresh toluene. In this way 295–305 g. of pure product is obtained. The forerun contains a little aqueous hydrobromic acid, which may be employed in a subsequent batch. The total yield of pure catechol is 690–705 g. (85–87 per cent of the theoretical amount) (Note 8).

2. Notes

1. Any column of standard form is suitable; to work satisfactorily, it is unnecessary for it to be more than 40 cm. in length.
2. In the diagram (Fig. 10) no indication is made of joints in the glass tubing. These are, however, applicable at almost any desired point; but care should be taken to arrange them so that the ends of the glass tube come into contact, since methyl bromide appears to pass readily through the walls of the rubber tubing. It is necessary to make certain that the outlets from the automatic separator descend in an even incline and that the tubing itself is of sufficiently large diameter to prevent any siphoning effects.
3. It is noteworthy that the guaiacol which condenses is saturated with methyl bromide at the condensation temperature, so that it is necessary to prevent it from becoming warmer during its passage through the separator; otherwise the evolution of gas may hinder the ready formation of layers.
4. In order to secure satisfactory absorption of the methyl bromide, the methyl alcohol should be kept below 5° by ice-cooling.
5. Since the formation of the red by-product appears to depend upon the time during which the catechol is heated with hydrobromic acid, it is well to carry out the reaction as rapidly as possible; due care must be taken, however, that the temperature at the head of the column does not rise prematurely above 95°.
6. The water collected during the reaction contains practically no hydrobromic acid but is saturated with guaiacol and methyl bromide. Nevertheless, it scarcely pays to recover the dissolved compounds, for on distillation only 1–2 g. of wet guaiacol can be collected; while the value of the methyl bromide is in any case not very great.
7. It is suggested that carbon tetrachloride rather than toluene be used in the extraction because toluene gives a product which gradually colors, whereas the catechol extracted with carbon tetrachloride remains colorless for a considerably longer time (W. W. Hartman, private communication).
8. The reaction appears to be applicable to many other cases where the constitution of the molecule permits of boiling with strong hydrobromic acid.

3. Discussion

Catechol can be prepared by the oxidation of salicylaldehyde[1] and of phenol;[2] by the demethylation of guaiacol with aluminum chloride[3] and hydriodic acid;[4] by hydrolysis of ortho halogen-substituted phenols or ortho dihalobenzenes under suitable conditions;[5] and by the replacement of sulfonic groups by alkali fusion.[6] A series of reactions involving the oxidation of safrole, opening of the methylenedioxy ring, and decarboxylation also furnishes catechol.[7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 759

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ortho halogen-substituted phenols

ortho dihalobenzenes

acetic acid (64-19-7)

methyl alcohol (67-56-1)

sodium hydroxide (1310-73-2)

hydroquinone (123-31-9)

phenol (108-95-2)

HYDROBROMIC ACID (10035-10-6)

carbon tetrachloride (56-23-5)

aluminum chloride (3495-54-3)

toluene (108-88-3)

Catechol, Pyrocatechol (120-80-9)

Salicylaldehyde (90-02-8)

hydrogen peroxide (7722-84-1)

sodium peroxide

Guaiacol (90-05-1)

methyl bromide (74-83-9)

hydriodic acid (10034-85-2)

safrole (94-59-7)

o-Hydroxyacetophenone (118-93-4)

p-hydroxyacetophenone (99-93-4)

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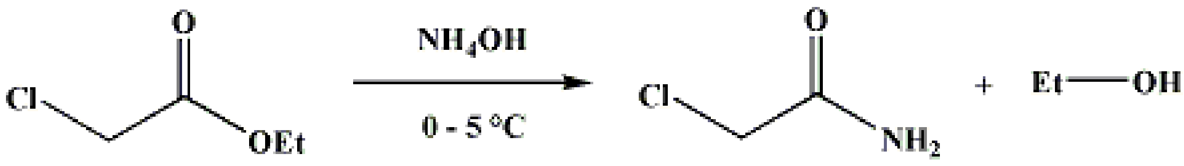
Organic Syntheses, CV 1, 153

CHLOROACETAMIDE

[Acetamide, α-chloro-]



Submitted by W. A. Jacobs and M. Heidelberger.
Checked by C. S. Marvel and D. D. Coffman.

1. Procedure

In a 2-l. round-bottomed flask fitted with a mechanical stirrer and surrounded by an ice-salt bath is placed 215 g. (1.75 moles) of ethyl chloroacetate (Note 1). Vigorous stirring is started, and to the cold ester (Note 2) 200 cc. of chilled aqueous ammonia (sp. gr. 0.9) is added. The solution is stirred in the cold for about fifteen minutes; then another 200-cc. portion of aqueous ammonia is added, and the stirring is continued for about fifteen minutes. The mixture is then allowed to stand for thirty minutes, filtered with suction, and washed with two 25-cc. portions of cold water to remove ammonium chloride. The yield of air-dried material melting at 118–119° (Note 3) is 128–138 g. (78–84 per cent of the theoretical amount).

This product contains traces of ammonium chloride which may be removed by crystallization from water. When 100 g. of crude product is recrystallized from 400 cc. of water, about 80 g. of product is obtained. The recrystallized product melts at 119–120°.

2. Notes

1. The ethyl chloroacetate used may be a commercial grade which boils at 141–146°. The ethyl chloroacetate and the chloroacetamide have the usual irritating effect of chloroacetyl compounds.
2. The temperature is best maintained at 0–5°. At higher temperatures there is more replacement of the chlorine and the yields are considerably lower.
3. Traces of moisture lower the melting point considerably.

3. Discussion

Chloroacetamide can be prepared from chloroacetyl chloride and dry ammonia gas,[1] and by the treatment of ethyl chloroacetate[2] or methyl chloroacetate[3] with cold aqueous ammonia solutions. The procedure described was developed from the methods of Scholl[2] and Tröger and Hille.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 488
- Org. Syn. Coll. Vol. 4, 144

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

chloroacetyl compounds

ammonia (7664-41-7)

ammonium chloride (12125-02-9)

chlorine (7782-50-5)

CHLOROACETAMIDE, Acetamide, α-chloro- (79-07-2)

Ethyl chloroacetate (105-39-5)

chloroacetyl chloride (79-04-9)

methyl chloroacetate (96-34-4)

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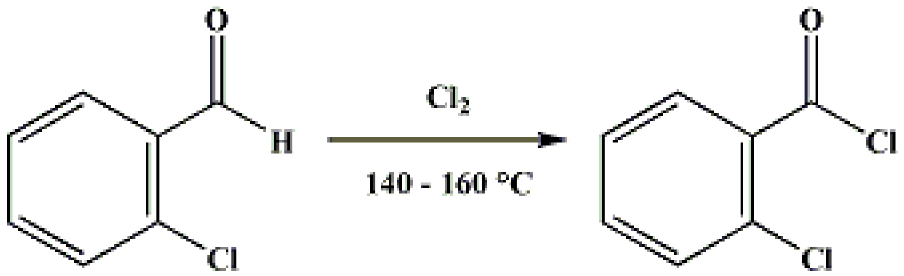
o-CHLOROBENZOYL CHLORIDE

[Benzoyl chloride, *o*-chloro-]



Submitted by H. T. Clarke and E. R. Taylor.
Checked by F. C. Whitmore and H. H. Rowley.

1. Procedure

In a 3-l. round-bottomed flask, fitted with a thermometer, a reflux condenser, and an inlet tube extending nearly to the bottom, is placed 141 g. (1 mole) of freshly distilled *o*-chlorobenzaldehyde (Note 1). To the upper end of the condenser is attached a tube leading to a flask containing water for the absorption of hydrogen chloride. The reaction vessel and absorption flask are weighed accurately, and a current of chlorine, dried by sulfuric acid, is passed into the aldehyde, the temperature of which is maintained at 140–160°. The rate of the current of gas is so regulated that little or no chlorine escapes. The reaction and absorption flasks are removed and weighed about every three hours. After about fifteen hours (Note 2) the absorption of chlorine at 160° practically ceases.

The total increase in weight (Note 3) amounts to 26–29 g. (75–84 per cent of the theoretical amount). The reaction product is distilled under reduced pressure, when the pure *o*-chlorobenzoyl chloride passes over at 93–95° /10 mm. or 137–139° /60 mm., leaving a small quantity of high-boiling residue which appears to consist mainly of an intermediate compound (Note 2). The yield is 122–126 g. (70–72 per cent of the theoretical amount) (Note 4).

2. Notes

1. Technical *o*-chlorobenzaldehyde of high purity is available. After one distillation under reduced pressure (b.p. 84° /10 mm., 125° /85 mm.), it melts at 7–10°.
2. If the mixture is kept at 125–140°, the reaction requires about thirty hours for completion. When about one-half of the necessary amount of chlorine has been added, the reaction mixture, if allowed to cool, sets to a colorless mass of an addition compound of the aldehyde and acid chloride; this on further chlorination yields *o*-chlorobenzoyl chloride.

3. The increase in weight is distributed between the reaction flask and hydrochloric acid absorption flask in the ratio of about 45: 55.

4. The use of large quantities and vigorous mechanical stirring gives much better yields. Thus, a run of 2665 g. (18.9 moles) of the aldehyde gave a yield of 2700 g. (82 per cent of the theoretical amount.

3. Discussion

o-Chlorobenzoyl chloride can be prepared by the treatment of *o*-chlorobenzoic acid with phosphorus pentachloride[1] or thionyl chloride.[2] The procedure described is based on that for the preparation of benzoyl chloride from benzaldehyde and chlorine.[3]

References and Notes

1. Emmerling, Ber. **8**, 883 (1875); Clark and Bell, Trans. Roy. Soc. Canada, III, **27**, 97 (1933) [C. A. **28**, 3053 (1934)].
2. Meyer, Monatsh. **22**, 427 (1901); Frankland, Carter and Adams, J. Chem. Soc. **101**, 2476 (1912).
3. Wöhler and Liebig, Ann. **3**, 262 (1832).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

aldehyde

sulfuric acid (7664-93-9)

hydrogen chloride, hydrochloric acid (7647-01-0)

phosphorus pentachloride (10026-13-8)

thionyl chloride (7719-09-7)

benzaldehyde (100-52-7)

benzoyl chloride (98-88-4)

chlorine (7782-50-5)

o-Chlorobenzoyl chloride, Benzoyl chloride, o-chloro- (609-65-4)

o-chlorobenzaldehyde (89-98-5)

o-Chlorobenzoic acid (118-91-2)

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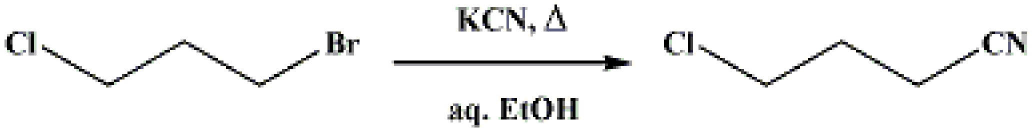
γ-CHLOROBUTYRONITRILE

[Butyronitrile, γ-chloro-]



Submitted by Charles F. H. Allen
Checked by C. S. Marvel and C. G. Gauerke.

1. Procedure

In a 2-l. three-necked, round-bottomed flask, fitted with a stirrer, a reflux condenser and a separatory funnel are placed 82 g. (1.2 moles) of potassium cyanide (95 per cent) (Note 1) and 100 cc. of water. The mixture is warmed and stirred until the cyanide is completely dissolved. To this solution is added 350 cc. of 95 per cent alcohol, followed by 158 g. (1 mole) of trimethylene chlorobromide (Note 2), and the mixture is heated under a reflux condenser (best on a water bath) with stirring for about one and one-half hours.

The solution is cooled and then diluted with 450 cc. of water. The oily layer of chloronitrile is collected in about 80 cc. of chloroform and separated from the water solution. The chloroform solution is washed with about 125–150 cc. of calcium chloride solution (prepared by adding one volume of water to an equal volume of a saturated solution of crystallized calcium chloride) and once with 125–150 cc. of water, and then dried over fused calcium chloride.

The dried solution is then fractionally distilled in a modified 100-cc. Claisen flask (p. 130). The chloroform is removed by distilling at ordinary pressure until the temperature reaches 120° (Note 3). The remainder may be fractionated under ordinary pressure but it is better to use reduced pressure. After two or three distillations the yield of pure product boiling at 93–96°/26 mm. (Note 4) and (Note 5) is 42–49 g. (60–70 per cent of the theoretical amount based on the chlorobromide used, or 40–47 per cent based on the total amount of chlorobromide taken) (Note 5) and (Note 6).

2. Notes

1. An equivalent amount (58 g., 1.2 moles) of sodium cyanide dissolved in 90 cc. of water may be used instead of the potassium salt without materially altering the yields.
2. The trimethylene chlorobromide used boiled at 142–147°. It may be prepared in 75–85 per cent yields from trimethylene chlorohydrin (p. 533) by the general

method for the preparation of alkyl bromides described on p. 25. Directions are also available[1] for its preparation in higher yields by the action of phosphorus tribromide on trimethylene chlorohydrin.

3. The chloroform fraction has a very strong odor of isonitrile. Only a trace is noted in the redistilled product.

4. When the distillation is carried out under ordinary pressures (about 745 mm.) the product boils at 194–197°.

5. The lower-boiling fraction is mainly unchanged trimethylene chlorobromide and amounts to 15–20 g. It may be refractionated or used directly in a subsequent run. The high-boiling residue is mainly trimethylene cyanide. If the residues from several runs are combined and redistilled, an average of 6–7 g. per run of product boiling at 160–165°/26 mm. is obtained.

6. Larger runs have been made and the yields are proportional; thus a five-mole run gives 210–245 g. of chlorobutyronitrile and 30–35 g. of trimethylene cyanide.

3. Discussion

γ-Chlorobutyronitrile has always been prepared by the action of potassium cyanide on trimethylene chlorobromide.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 25
- Org. Syn. Coll. Vol. 3, 221
- Org. Syn. Coll. Vol. 3, 223

References and Notes

1. Cloke, Anderson, Lachmann and Smith, J. Am. Chem. Soc. **53**, 2794 (1931).
2. Henry, Compt. rend. **101**, 1158 (1885); Bull. soc. chim. (2) **45**, 341 (1886); Gabriel, Ber. **23**, 1771 (1890) and **42**, 1252 (1909); Conant, Segur and Kirner, J. Am. Chem. Soc. **46**, 1884 (1924); Dewael, Bull. soc. chim. Belg. **39**, 87 (1930).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

potassium salt

alcohol (64-17-5)

calcium chloride (10043-52-4)

chloroform (67-66-3)

sodium cyanide (143-33-9)

phosphorus tribromide (7789-60-8)

cyanide, isonitrile (57-12-5)

potassium cyanide (151-50-8)

γ-Chlorobutyronitrile, Butyronitrile, γ-chloro-, chlorobutyronitrile (628-20-6)

Trimethylene chlorobromide (109-70-6)

chloronitrile (7790-93-4)

Trimethylene chlorohydrin (627-30-5)

Trimethylene cyanide (544-13-8)

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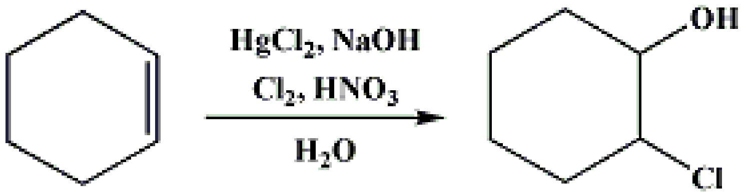
2-CHLOROCYCLOHEXANOL

[Cyclohexanol, 2-chloro-]



Submitted by G. H. Coleman and H. F. Johnstone.
Checked by C. S. Marvel and A. B. Adams.

1. Procedure

To a solution of 25 g. of mercuric chloride in 500 cc. of water in a 5-l. flask, 800 g. of cracked ice is added. A cold solution of 190 g. of sodium hydroxide in 500 cc. of water is added, and a rapid stream of chlorine is passed into the mixture, which must be kept below 5°. The addition of chlorine is continued in this way until the yellow precipitate of mercuric oxide just disappears. Then 1600 cc. of cold nitric acid (1.5 *N*) is added slowly, with stirring.

The concentration of the hypochlorous acid solution is determined by adding a measured volume to an excess of potassium iodide solution acidified with hydrochloric acid, and titrating with standard thiosulfate solution. Usually the concentration is found to be between 3.5 and 4 per cent. The amount necessary to react with 123 g. (1.5 moles) of cyclohexene is calculated.

In a 5-l. round-bottomed flask equipped with a good mechanical stirrer (Note 1) is placed 123 g. (1.5 moles) of cyclohexene (p. 183), and to it is added about one-fourth the calculated amount of the hypochlorous acid solution. The mixture is kept between 15° and 20°, and stirred vigorously until a 1-cc. test portion gives no yellow color when it is treated with potassium iodide solution and dilute hydrochloric acid. When the first portion of the hypochlorous acid has reacted, a second is added and the process is repeated. When all the hypochlorous acid has been added and the reaction is complete, the oily layer should be on the bottom and a very slight excess of hypochlorous acid should be present, as indicated by the potassium iodide test. If these conditions are not fulfilled, 100-cc. portions of the hypochlorous acid solution are added until the reaction is shown to be complete.

The solution is now saturated with salt and distilled with steam (Note 2). About 2 l. of distillate is required before all of the 2-chlorocyclohexanol passes over. The distillate is saturated with salt and the oily layer separated. The aqueous layer is extracted once with about 250 cc. of ether. This is added to the main portion, which is dried with

anhydrous sodium sulfate. The ether is removed by distillation and the product distilled under reduced pressure. The fraction boiling at 88–90°/20 mm. (104–106°/45 mm.) is collected. The yield is 142–148 g. (70–73 per cent of the theoretical amount).

2. Notes

1. If a mechanical stirrer is not available, shaking the flask by hand will give as good results.
2. In the separation of the product from the hypochlorous acid solution, steam distillation seems to be desirable. In several runs in which this was not carried out, a larger amount of a dark-colored high-boiling residue remained in the flask after distillation, and the yield of 2-chlorocyclohexanol was smaller.

3. Discussion

2-Chlorocyclohexanol can be prepared by the action of hypochlorous acid on cyclohexene.[1]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 185

References and Notes

1. Fortey, J. Chem. Soc. **73**, 948 (1898); Detoeuf, Bull. soc. chim. (4) **31**, 177 (1922); Osterberg and Kendall, J. Am. Chem. Soc. **42**, 2621 (1920).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium hydroxide (1310-73-2)

nitric acid (7697-37-2)

Cyclohexene (110-83-8)

sodium sulfate (7757-82-6)

potassium iodide (7681-11-0)

mercuric oxide (21908-53-2)

chlorine (7782-50-5)

2-Chlorocyclohexanol, Cyclohexanol, 2-chloro- (1561-86-0)

mercuric chloride (7487-94-7)

hypochlorous acid (7790-92-3)

thiosulfate

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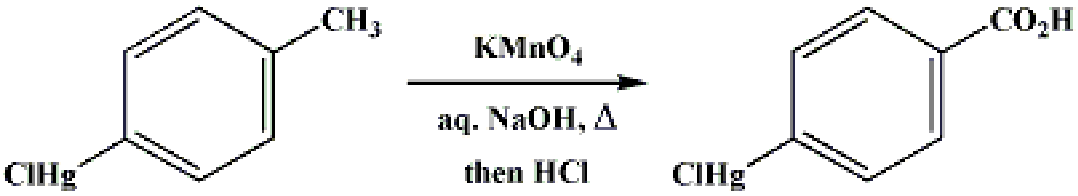
p-CHLOROMERCURIBENZOIC ACID

[Benzoic acid, *p*-chloromercuri-]



Submitted by Frank C. Whitmore and Gladys E. Woodward.
Checked by Henry Gilman and J. D. Robinson.

1. Procedure

Five hundred grams (1.5 moles) of crude *p*-tolylmercuric chloride (p. 519) and 720 g. (4.6 moles) of potassium permanganate are added to a solution of 1200 g. (30 moles) of sodium hydroxide in 18 l. of water contained in a large enameled pail (or similar vessel) placed on a 15-cm. Fletcher burner and provided with a mechanical stirrer. The mixture is stirred and heated as near boiling as possible for fifteen minutes. The highest temperature conveniently obtainable is 95°. The tolylmercuric chloride dissolves (Note 1), forming the sodium salt of *p*-hydroxymercuribenzoic acid. The solution is cooled somewhat and alcohol is added to react with the excess of potassium permanganate (250 cc. is generally required to completely decolorize the solution). The manganese dioxide thus precipitated is removed by filtering with suction (Note 2). The filtrate should be clear and colorless. (If it is green, not enough alcohol has been added.)

After the filtrate has become thoroughly cool (Note 3), it is acidified with hydrochloric acid, about 1700 cc. of technical concentrated acid being necessary. The precipitated *p*-chloromercuribenzoic acid is difficult to filter because of its flocculent character. It is best to allow it to stand at least overnight and then filter by suction after siphoning most of the clear supernatant liquid. The acid retains much water and should be dried at 110° (Note 4). The yield is 350–420 g. (61–74 per cent of the theoretical amount). The crude acid may be purified by reprecipitation with hydrochloric acid from a solution in sodium hydroxide (Note 5). The crude acid is sufficiently pure for the preparation of *p*-iodobenzoic acid (p. 325). It can be used for this purpose without drying.

2. Notes

1. The chief impurity in the *p*-tolylmercuric chloride is mercurous chloride, which is converted to the oxide and remains in the manganese dioxide precipitate.

2. In filtering the manganese dioxide from the strongly alkaline solution, it is best to support the filter paper by means of a cloth which is cut to fit the funnel and placed under the filter paper.
3. It is necessary that the filtrate be cooled at least to 20° before acidifying to avoid the splitting of the carbon-mercury linkage.
4. The caked acid loses water very slowly, even at 110°. Since the chief use of the acid is in preparing the *p*-halogen compounds (p. 325), it need not be dried, but can be mixed with water while still wet.
5. The pure acid melts at 273°.[1]

3. Discussion

p-Chloromercuribenzoic acid can be prepared by the oxidation of *p*-tolylmercuric chloride[2] and by heating the corresponding boric acid,[3] $(HO)_2BC_6H_4CO_2H$, with mercuric chloride.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 325

References and Notes

1. Nesmeyanov and Makarova, J. Gen. Chem. (U.S.S.R.) **1**, 1162 (1931) [C. A. **26**, 5295 (1932)].
2. Whitmore and Woodward, J. Am. Chem. Soc. **48**, 534 (1926).
3. Michaelis, Ann. **315**, 35 (1901).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

corresponding boric acid

p-halogen compounds

hydrochloric acid (7647-01-0)

sodium hydroxide (1310-73-2)

potassium permanganate (7722-64-7)

mercuric chloride (7487-94-7)

tolylmercuric chloride, p-tolylmercuric chloride (539-43-5)

manganese dioxide (1313-13-9)

mercurous chloride (7546-30-7)

p-Chloromercuribenzoic acid, Benzoic acid, p-chloromercuri- (59-85-8)

sodium salt of p-hydroxymercuribenzoic acid

p-iodobenzoic acid (619-58-9)

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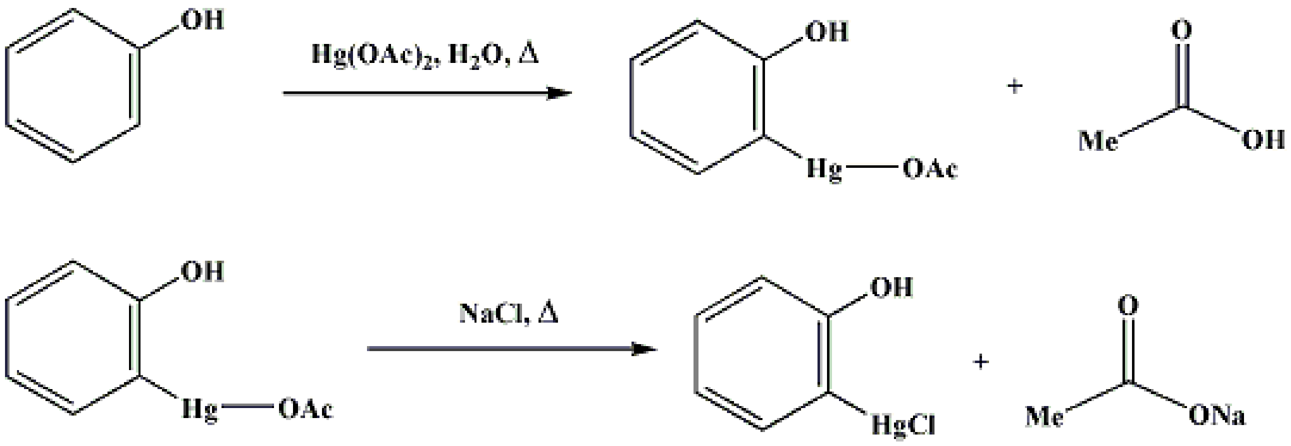
o-CHLOROMERCURIPHENOL

[Phenol, *o*-chloromercuri-]



Submitted by F. C. Whitmore and E. R. Hanson.
Checked by J. B. Conant and R. M. Granara.

1. Procedure

Two liters of water is heated to boiling in a 3-l. flask. Mean-while 50 g. (0.53 mole) of phenol, in a 250-cc. tall beaker provided with a small glass mechanical stirrer, is heated to 170° on an electric heater (Note 1). The heat is then turned off and 100 g. (0.31 mole) of powdered mercuric acetate is added gradually (five to ten minutes) to the stirred phenol. After all of the mercuric acetate has dissolved in the phenol, the mercuration mixture is poured slowly into the hot water, the burner having previously been removed (Note 2). The beaker is rinsed out with some of the hot water. The mixture is boiled for five minutes and then filtered through filter paper in a large Büchner funnel which has been previously heated by blowing steam through it. The pink residue (Note 3) consists of a small amount of dimercurated phenol and some polymerization products.

The filtrate is again brought to boiling in a clean flask and treated with a solution of 20 g. (0.34 mole) of sodium chloride in 200 cc. of boiling water. The precipitate formed is *p*-chloromercuriphenol together with some colored impurities (Note 4). The mixture is heated to boiling and filtered through a large preheated Büchner funnel. The filtrate on cooling deposits white feathery crystals of *o*-chloromercuriphenol. The mixture is allowed to stand at least twelve hours and then filtered. The crystals are air-dried. They should be colorless and should melt above 147° (m.p. of pure substance 152°). If the product is pink or melts low it should be recrystallized from hot water. The average yield of fifteen experiments was 45 g. of ortho compound melting above 147°, which corresponds to 44 per cent of the theoretical amount (Note 5).

2. Notes

1. Mercuration at lower temperatures than that recommended gives a poorer yield of the ortho compound.
2. If the heat is not removed from under the water before the mercurated phenol is added, the mixture is likely to froth over.
3. Long heating of the mercuration mixture increases the amount of pink by-product.
4. The yield of impure para compound obtained as a by-product varies from 10 to 30 g.
5. A saturated solution of bromine in glycerol should be kept at hand as an antidote for phenol

burns. If all undissolved bromine is allowed to settle out before the solution is used, there is no danger of bromine burns.
Limewater is also highly recommended for phenol burns.

3. Discussion

o-Chloromercuriphenol can be prepared by the mercuration of phenol in water solution[1] and with only phenol as the solvent.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 326

References and Notes

1. Dimroth, Ber. **35**, 2855 (1902).
2. Whitmore and Middleton, J. Am. Chem. Soc. **43**, 622 (1921).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

dimercurated phenol

mercurated phenol

para compound

Limewater

glycerol (56-81-5)

phenol (108-95-2)

sodium chloride (7647-14-5)

bromine (7726-95-6)

mercuric acetate (1600-27-7)

o-Chloromercuriphenol, Phenol, o-chloromercuri-

p-chloromercuriphenol

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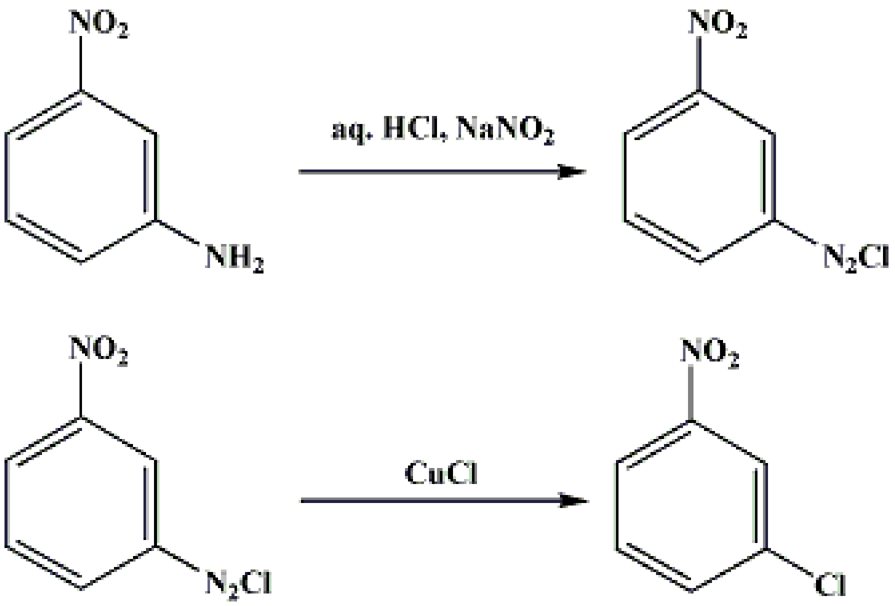
m-CHLORONITROBENZENE

[Benzene, 1-chloro-3-nitro-]



Submitted by W. W. Hartman and M. R. Brethen.
Checked by C. S. Marvel and C. R. Noller.

1. Procedure

To a solution of 1200 g. (4.8 moles) of crystallized copper sulfate and 400 g. (6.9 moles) of sodium chloride in 4 l. of water at 60–70° is added a concentrated solution of 200 g. (1.7–1.8 moles) of (90–95 per cent) sodium bisulfite (prepared if desired by saturating a solution of 100 g. of sodium carbonate with sulfur dioxide). The white precipitate of cuprous chloride is filtered off, sucked dry as rapidly as possible, and suspended in a mixture of 2 l. of water and 1.5 l. of concentrated hydrochloric acid (sp. gr. 1.19) (Note 1).

In the meantime, 552 g. (4 moles) of good commercial *m*-nitroaniline, melting at 110° or above (Note 2), is dissolved in a mixture of 500 cc. of hydrochloric acid (sp. gr. 1.19) and 1 l. of hot water; 1100 cc. of hydrochloric acid (sp. gr. 1.19) is then added, and the solution is cooled rapidly, with stirring. It is then surrounded with a freezing mixture, and diazotized at a temperature below 1° by adding, with constant stirring, a solution of 288 g. (4 moles) of technical (95 per cent) sodium nitrite in 700 cc. of water, care being taken to avoid adding an excess over that necessary to produce a distinct reaction with starch-iodide paper (p. 49). This point is reached when all but about 25 cc. of the nitrite solution has been added; the addition requires about one and one-half hours. The cold solution is now filtered in order to remove some amorphous insoluble matter; this solid, when dry, weighs 50–55 g.

The clear filtrate, which has only a pale yellow color, is now run, with stirring, into the cuprous chloride solution in a 12-l. flask, while the temperature is kept at 25–30° (Note 3). A somewhat sticky precipitate first forms, which later becomes crystalline; nitrogen is evolved in a continuous stream. The addition requires about thirty minutes. The mixture is then warmed on a steam bath under an efficient reflux condenser until the evolution of nitrogen ceases. It is then distilled in a current of steam (using the apparatus described on p. 479) until no more chloronitrobenzene passed over; 9–10 l. of distillate collects during this process (Note 4). When quite cold, the water is decanted off, and the solid shaken with 1–2 l. of 1 per cent sodium hydroxide solution at 50°. The mixture is again allowed to cool, and the light yellow alkaline solution is decanted from the solid product, which is then collected on a filter, washed with a little cold water, dried, and distilled under reduced pressure. It boils completely at 116–117°/12 mm. or 124–125°/18 mm., and the distillate solidifies to a pale yellow solid which melts at 44–45° and weighs 430–450 g. (68–71 per cent of the theoretical amount).

2. Notes

1. It is more convenient to prepare cuprous chloride by reducing copper sulfate with sodium bisulfite than by the action of copper upon cupric chloride. It is well to test a sample of the filtrate with sodium bisulfite solution; no further cuprous chloride should separate.

One mole of cuprous chloride should be used with one mole of diazonium salt. If less cuprous chloride is used the yield is decreased.

2. The yield will, of course, depend upon the quality of the nitroaniline. The pure amine should yield none of the insoluble substance on diazotization, but the cost of purification would be prohibitive. It may be noted that if the weight of the insoluble residue be deducted, the yield amounts to 75–78 per cent of the theoretical amount.

3. It is important that the temperature should be held at 25–30° during the addition of the diazonium chloride to the cuprous chloride solution. At lower temperatures the decomposition of the unstable additive compound proceeds too slowly, and would cause too violent an evolution of nitrogen on warming; at higher temperatures the formation of tarry by-product increases.

4. If desired, the steam distillation may be omitted, since the proportion of non-volatile resinous impurities is very low. In this case the reaction mixture is allowed to cool, and the watery solution is decanted; the residue is then dissolved in 1–2 l. of benzene, and the benzene solution washed with water and with dilute alkali, after which the solvent is removed by distillation on the steam bath and the residue distilled under reduced pressure. The yield and purity of the final product are equally satisfactory.

An iron condenser should not be used in the steam distillation of the crude *m*-chloronitrobenzene, as some reduction takes place and the yield is lowered by 10 to 15 per cent. The product is also deeply colored.

3. Discussion

m-Chloronitrobenzene can be prepared by the chlorination of nitrobenzene with the use of a catalyst such as iodine,[1] ferric chloride,[2] antimony trichloride[3] or iron and iodine;[4] and from *m*-nitroaniline by diazotization.[5]

References and Notes

1. Laubenheimer, Ber. **7**, 1765 (1874).
2. Varnholt, J. prakt. Chem. (2) **36**, 25 (1887).
3. Beilstein and Kurbatov, Ann. **182**, 102 (1876).
4. Fierz-David, Naturwissenschaften, **17**, 13 (1929).
5. Griess, Jahresber. 423 (1863) and 457 (1866); Hollemann and Van Der Linden, Rec. trav. chim. **30**, 317 (1911); Kohman, J. Phys. Chem. **29**, 1052 (1925).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

diazonium chloride

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

sodium hydroxide (1310-73-2)

iron (7439-89-6)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

sulfur dioxide (7446-09-5)

nitrogen (7727-37-9)

copper sulfate (7758-98-7)

sodium nitrite (7632-00-0)

nitrite (14797-65-0)

sodium bisulfite (7631-90-5)

copper (7440-50-8)

iodine (7553-56-2)

Nitrobenzene (98-95-3)

Benzene, 1-chloro-3-nitro-, m-Chloronitrobenzene (121-73-3)

cuprous chloride (7758-89-6)

chloronitrobenzene (88-73-3)

cupric chloride (7758-89-6)

nitroaniline

ferric chloride (7705-08-0)

antimony trichloride

m-nitroaniline (99-09-2)

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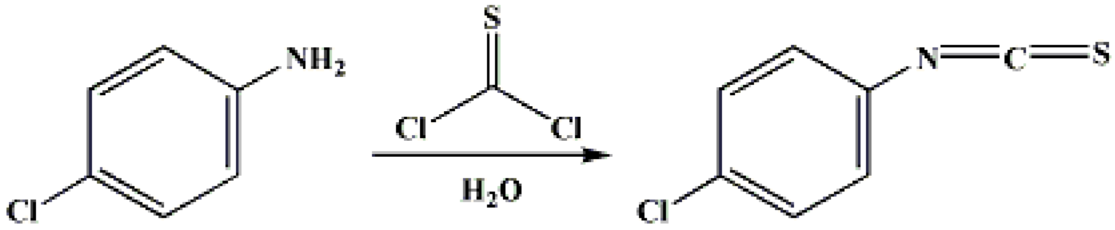
p-CHLOROPHENYL ISOTHIOCYANATE

[Isothiocyanic acid, *p*-chlorophenyl ester]



Submitted by G. Malcolm Dyson
Checked by Frank C. Whitmore and P. L. Cramer.

1. Procedure

In a 5-l. crock or battery jar, provided with a powerful mechanical stirrer, are placed 3.5 l. of water and 249 g. (165 cc., 2.16 moles) of thiophosgene (p. 506) (Note 1). To the vigorously stirred (Note 2) mixture is added slowly 255 g. (2 moles) of *p*-chloroaniline during about one-half hour. The stirring is continued for about an additional one-half hour. The dark brown oil is separated, washed with 50 cc. of 10 per cent hydrochloric acid, and placed in a flask for steam distillation.

The flask is immersed in an oil bath heated to 120° and dry steam is then passed through the reaction mixture. The first few cubic centimeters of distillate contain the excess of thiophosgene and are discarded. The isothiocyanate passes over with the water as an oil that solidifies on cooling. The steam distillation requires about four hours. The crude material is crystallized from two parts of ethyl alcohol at 50°, from which it separates as white needles melting at 44–45°. The yield is 245–275 g. (72–81 per cent of the theoretical amount) (Note 3).

2. Notes

1. Because of the objectionable properties of thiophosgene, care should be exercised in its use.
2. The stirring at the start must be very vigorous or the yield is decreased.
3. The method is general for alkyl- and halogen-substituted aromatic amines. An alternative procedure which gives lower yields but avoids the use of thiophosgene will be found on p. 447.

3. Discussion

p-Chlorophenyl isothiocyanate can be prepared by treating an alcoholic solution of *sym*-di-*p*-chlorophenyl thiourea with iodine;[1] from ammonium *p*-

chlorophenyldithiocarbamate and lead nitrate;[2] and by the action of thiophosgene on *p*-chloroaniline.[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 700
- Org. Syn. Coll. Vol. 5, 223

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethyl alcohol (64-17-5)

hydrochloric acid (7647-01-0)

iodine (7553-56-2)

lead nitrate (10099-74-8)

Thiophosgene (463-71-8)

isothiocyanate (302-04-5)

p-Chlorophenyl isothiocyanate, Isothiocyanic acid, p-chlorophenyl ester (2131-55-7)

p-chloroaniline (106-47-8)

di-p-chlorophenyl thiourea

ammonium p-chlorophenyldithiocarbamate

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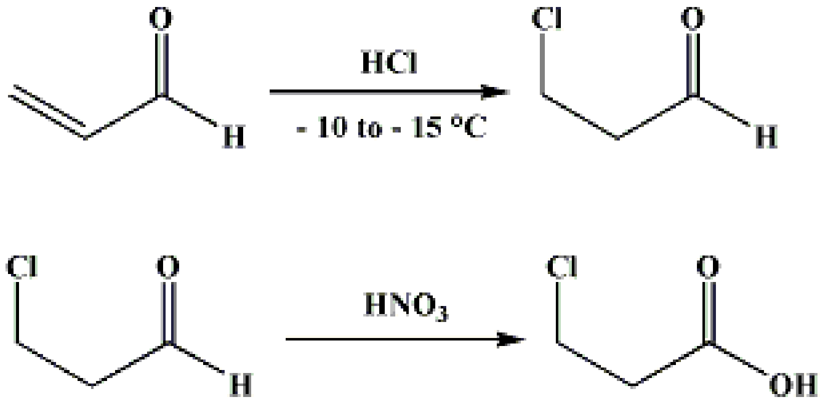
Organic Syntheses, CV 1, 166

β-CHLOROPROPIONIC ACID

[Propionic acid, β-chloro-]

[(*A*) (*from Acrolein*)]



Submitted by C. Moureu and R. Chaux.
Checked by C. S. Marvel and L. F. Martin.

1. Procedure

In a tared Erlenmeyer flask surrounded by an ice-salt bath is placed 100 g. (119 cc., 1.78 moles) of acrolein (p. 15) (Note 1). When the temperature has dropped to –10 to –15° a current of dry hydrogen chloride (p. 293) is passed into the acrolein until it shows a gain in weight of 65 g.(1.78 moles). This requires about two hours. The product thus obtained is a clear, viscous, slightly yellow liquid which becomes very turbid and dark colored on standing one or two days (Note 2).

The oxidation of the crude β-chloropropionaldehyde is carried out in a 200-cc. flask fitted with a cork stopper held about 2 cm. above the opening of the neck by means of a clamp. The stopper carries a mechanical stirrer, a separatory funnel, a thermometer, and a glass delivery tube about 10 mm. in diameter which is connected to a water pump. The space between the stopper and the flask is closed by winding a strip of asbestos paper around it (Note 3).

In the flask is placed 64 g. (43 cc., 0.9 mole) of fuming nitric acid (sp. gr. 1.49) (Note 4), the stirrer is started, and about one-sixth (Note 5) of the crude β-chloropropionaldehyde is added (Note 6) very slowly through the separatory funnel. About 1 cc. of the aldehyde is added to the acid. The temperature remains constant for one or two minutes and then slowly rises. As the oxidation begins, oxides of nitrogen are evolved and are drawn off by means of the water pump. When the temperature of the reaction mixture reaches about 30° (Note 7), the flask is immersed in a water bath (at 15–20°) and the rate of addition of the aldehyde is regulated so that the temperature of the reaction mixture is 30–35°. After the addition of the last portion of the aldehyde,

stirring is continued until the temperature drops below 25°. This oxidation requires about twenty-five minutes.

The products of six successive oxidations are combined in a 1-l. long-necked flask. Oxides of nitrogen are evolved but there is no danger of a violent reaction. The entire quantity of liquid is heated gradually on a water bath until the bath is boiling. This should be done under a hood as large quantities of oxides of nitrogen are evolved (Note 8). After about one and one-half hours the oxidation is complete and a yellow-brown liquid remains.

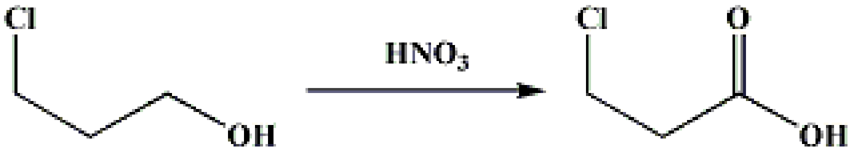
The liquid is placed in a modified Claisen flask (p. 130) and distilled (Note 9) from an oil bath with a water pump, care being taken to protect the manometer (placed in shunt in order to avoid the passage of a current of vapors) by a tube containing solid sodium hydroxide. A water condenser 40–50 cm. long should be used. At first oxides of nitrogen are evolved and it is difficult to obtain a low pressure. Then the pressure drops (to about 20–25 mm.) and nitric acid distils at 40–70°. When the distillation has nearly stopped, the temperature of the bath is raised until the boiling point of the distilling vapors reaches 100°. This fraction weighs 160–170 g. and is nitric acid having a specific gravity of 1.25–1.30. It may contain a small amount of acrylic acid. The condenser is now removed from the apparatus, a distilling flask attached as receiver, and the residue is fractionated at 20 mm., collecting about 4–5 g. boiling up to 105°, and 116–125 g. of β-chloropropionic acid boiling at 105–107° (60–65 per cent of the theoretical amount). The product melts at 35–40° (purest acid melts at 42°). The fraction boiling below 105° contains a large proportion of β-chloropropionic acid and should be redistilled with a subsequent run.

2. Notes

1. The acrolein used by the checker was obtained by distilling the commercial material (stabilized by hydroquinone) purchased from Poulenc Frères. Acrolein has pronounced lachrymatory properties and is also highly toxic.
2. β-Chloropropionaldehyde is a very unstable substance which polymerizes rapidly, especially in the presence of traces of hydrochloric acid. The crude material must be oxidized without delay as standing before oxidation will cause a lowering of the yield.
3. This constitutes a safety device, since it prevents diffusion of the oxides of nitrogen, but in case the reaction becomes violent it permits a free expansion of a sudden surge of gases.
4. The concentration and purity of the fuming nitric acid are of considerable importance. It should have a specific gravity of not less than 1.49 and should leave no residue on distillation.
5. It is not advantageous to work with larger quantities as an explosive reaction is likely to occur if stirring is stopped.
6. It is absolutely necessary to introduce the aldehyde into the nitric acid. When the reverse is attempted the reaction starts slowly but soon becomes explosive.
7. The temperature interval most favorable for the reaction is 30–35°.

8. A gas-absorption trap (Fig. 7, p. 97) may also be used.
9. The reaction mixture may also be worked up by pouring it into water and extracting the β-chloropropionic acid with ether. This is less satisfactory as the nitric acid is lost and some of the β-chloropropionic acid remains in the water.

[(*B*) (*from Trimethylene Chlorohydrin*)]



Submitted by S. G. Powell, E. H. Huntress, and E. B. Hershberg.
Checked by L. F. Fieser and A. M. Seligman.

1. Procedure

A 3-l. long-necked Pyrex flask containing 880 g. (620 cc., 10 moles) of concentrated nitric acid (sp. gr. 1.42) is supported in an ice bath in a hood and supplied with a mechanical stirrer and a thermometer suspended in the liquid. While the temperature is kept between 25° and 30° by means of the ice bath, 200 g. (2.12 moles) of trimethylene chlorohydrin (p. 533) is run in from a dropping funnel (Note 1). The addition takes two to three hours. Stirring is continued for a half hour longer.

The reaction mixture is allowed to stand overnight and is then heated for one hour on the steam bath. It is transferred to a modified Claisen flask (p. 130), and the β-chloropropionic acid is isolated by distillation under reduced pressure, employing a water pump. Nitric acid is collected up to 100°/20 mm., using a water condenser (Note 2). The condenser is replaced by a distilling flask, and the residual material is fractionated. The yield of β-chloropropionic acid boiling at 107–109°/20 mm. and freezing at 39° is 179–181 g. (78–79 per cent of the theoretical amount).

2. Notes

1. There is sometimes difficulty in starting the reaction using pure nitric acid. Once started, the oxidation proceeds rapidly under the catalytic influence of the oxides of nitrogen formed. The checkers found it convenient, in order to start the reaction, to oxidize a few drops of the chlorohydrin with nitric acid by heating in a test tube and to add this to the nitric acid in the flask without stirring. A small portion of the chlorohydrin is then added and allowed to react for a few minutes before starting the stirrer and continuing the oxidation of the main lot.
2. About 500 cc. of nitric acid (sp. gr. 1.27) is obtained. If desired the oxidation mixture may be diluted with water and the β-chloropropionic acid extracted with ether and distilled. Some material is lost in the water by this procedure.

3. Discussion

β-Chloropropionic acid can be prepared by the hydrolysis of ethylene cyanohydrin with hydrochloric acid;[1] by the oxidation of β-chloropropionaldehyde with nitric acid;[2] by the oxidation of trimethylenechlorohydrin with nitric acid[3] or permanganate;[4] and by hydrolysis of the condensation product of phosgene and ethylene.[5]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

oxides of nitrogen

aldehyde

chlorohydrin

hydrogen chloride, hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium hydroxide (1310-73-2)

Acrolein (107-02-8)

hydroquinone (123-31-9)

nitric acid (7697-37-2)

nitrogen (7727-37-9)

phosgene (75-44-5)

ethylene (9002-88-4)

Ethylene cyanohydrin (109-78-4)

Acrylic acid (9003-01-4)

Trimethylene chlorohydrin, trimethylenechlorohydrin (627-30-5)

β-Chloropropionic acid, Propionic acid, β-chloro- (107-94-8)

β-chloropropionaldehyde

permanganate

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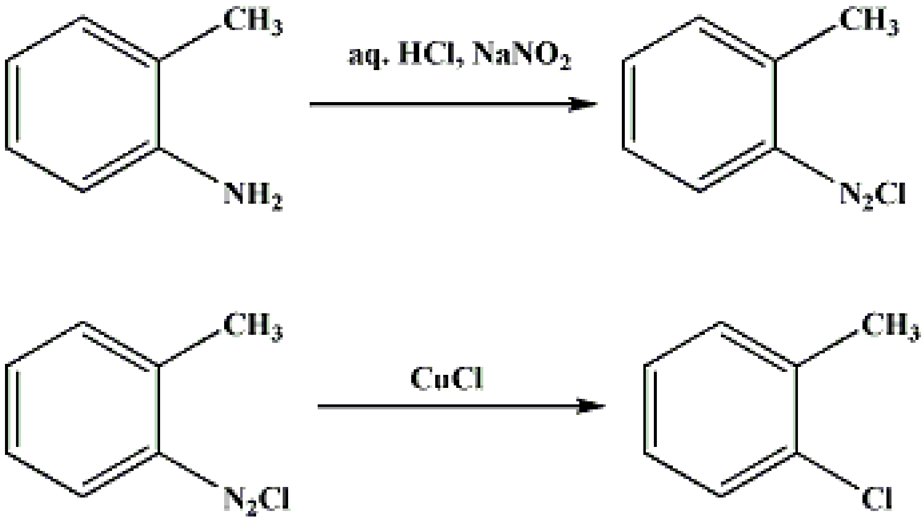
Organic Syntheses, CV 1, 170

o-CHLOROTOLUENE AND *p*-CHLOROTOLUENE

[Toluene, *o*-chloro- and *p*-chloro-]



Submitted by C. S. Marvel and S. M. McElvain.
Checked by Oliver Kamm

1. Procedure

(*A*) *Preparation of Cuprous Chloride Solution* (Note 1).—A solution of 1250 g. (5 moles) of crystallized copper sulfate and 325 g. (5.6 moles) of sodium chloride in 4 l. of hot water is prepared in a 12-l. flask. The flask is fitted with a mechanical stirrer, and an alkaline solution of sodium sulfite (265 g. of sodium bisulfite and 175 g. of sodium hydroxide in 2 l. of water) is added during a period of five to ten minutes. The mixture is allowed to cool to room temperature and washed by decantation. The cuprous chloride is obtained as a white powder, which, however, darkens on exposure to the air. The crude product is dissolved in 2 kg. of commercial 28 per cent hydrochloric acid (sp. gr. 1.14) and the solution is used in the following preparation (Note 2).

(*B*) *o-Chlorotoluene*.—In a 10-l. stone jar fitted with a mechanical stirrer are placed 2 kg. (1755 cc.) of commercial 28 per cent hydrochloric acid (sp. gr. 1.14) and 428 g. (427 cc., 4 moles) of *o*-toluidine. The mixture is cooled to 0° by adding cracked ice (about 1 kg. is required). The *o*-toluidine hydrochloride separates as a finely divided precipitate. The stirrer is started, and to the cold suspension is added a solution of 280 g. (4.05 moles) of sodium nitrite in 800 cc. of water; the diazotization is carried out at 0–5° and requires about fifteen minutes. Cracked ice is added from time to time to keep the temperature within the proper limits. The volume of the final solution is 5–6 l.

While the diazotization is being carried out the cuprous chloride solution (*A*) is cooled to 0°. The cold diazonium solution is now poured rapidly into the well-stirred cuprous

chloride solution. The solution becomes very thick, owing to the separation of an addition product between the diazonium salt and the cuprous chloride. The cold mixture is allowed to warm up to room temperature, and stirring is continued for two and one-half to three hours at this temperature (Note 3). When the temperature reaches about 15°, the solid addition compound begins to break down with the formation of nitrogen and *o*-chlorotoluene. After the specified time the solution is placed on a steam bath and heated to 60° to complete the decomposition of the addition product. The *o*-chlorotoluene forms a layer on top of the copper salt solution. The water solution is drawn off through a siphon until only 5–6 l. remains. The remaining material is steam-distilled from a 12-l. round-bottomed flask (Note 4) until about 3.5–4 l. is collected in the distillate. The *o*-chlorotoluene layer is separated from the water, washed with cold concentrated sulfuric acid (Note 5) and then with water, and finally dried over calcium chloride. The product boiling at 155–158° weighs 375–400 g. 74–79 per cent of the theoretical amount).

(*C*) *p-Chlorotoluene*.—*p*-Chlorotoluene is prepared in exactly the same way starting with *p*-toluidine. The yields are 70–79 per cent of the theoretical amount of a product which boils at 158–162° and melts at 4–7°.

2. Notes

1. The cuprous chloride solution prepared as described is more satisfactory and less expensive than one prepared by reducing cupric chloride with copper turnings.
2. If less cuprous chloride is used the yield is lowered. It seems desirable to use 1 mole of cuprous chloride (CuCl) to 1 mole of diazonium salt. Increasing the amount of cuprous chloride beyond this point does not improve the yield.
3. The literature directions usually call for mixing the diazonium solution and the cuprous chloride solution at about 30–40°. This procedure gives a yield considerably lower than that obtained by mixing the solutions cold and allowing to warm up gradually. If the mixture obtained by adding the diazonium solution to the cuprous chloride solution is heated at once, the yield falls to 55–65 per cent.
4. The steam distillation can be conveniently carried out in the apparatus described on p. 479.
5. The treatment with sulfuric acid is necessary to remove cresol and a trace of azo compound that usually colors the crude product and cannot be removed by distillation.

3. Discussion

o-Chlorotoluene can be prepared by the action of chlorine[1] and of sulfuryl chloride[2] on toluene in the presence of various catalysts; by the chlorination of *p*-toluenesulfonyl chloride followed by hydrolysis;[3] and by the diazotization of *o*-

toluidine followed by replacement of the diazonium salt group by chlorine.[4]

p-Chlorotoluene can be prepared by the action of chlorine[5] and of sulfuryl chloride[6] on toluene in the presence of various catalysts, and by the diazo reaction with *p*-toluidine.[7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 514
- Org. Syn. Coll. Vol. 2, 133
- Org. Syn. Coll. Vol. 2, 135
- Org. Syn. Coll. Vol. 2, 583

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

diazonium salt

copper salt

diazonium solution

Toluene, o-chloro- and p-chloro-

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

sodium sulfite (7757-83-7)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

copper sulfate (7758-98-7)

sodium nitrite (7632-00-0)

sodium bisulfite (7631-90-5)

copper turnings (7440-50-8)

sulfuryl chloride (7791-25-5)

chlorine (7782-50-5)

toluene (108-88-3)

cuprous chloride (7758-89-6)

cupric chloride (7758-89-6)

o-Chlorotoluene (95-49-8)

p-Chlorotoluene (106-43-4)

cresol (95-48-7)

p-toluidine (106-49-0)

o-toluidine (95-53-4)

p-Toluenesulfonyl chloride (98-59-9)

o-toluidine hydrochloride (636-21-5)

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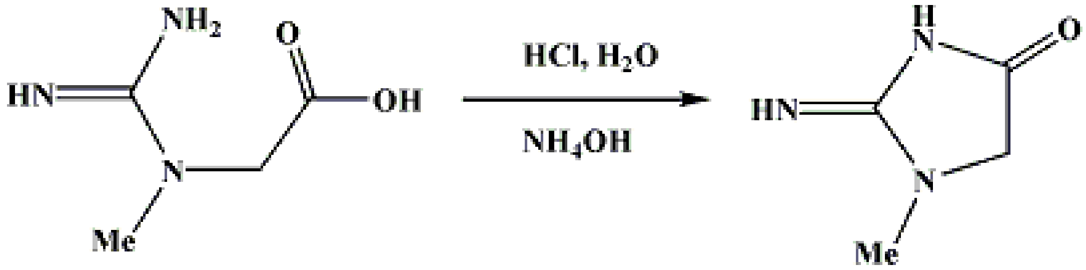
CREATININE



Submitted by Graham Edgar and W. S. Hinegardner.
Checked by H. T. Clarke and Ross Phillips.

1. Procedure

(*A*) *Creatinine*.—A mixture of 900 g. (6 moles) of commercial creatine hydrate (Note 1) with 550 cc. of concentrated hydrochloric acid (sp. gr. 1.19) and 150 cc. of water is warmed in a 3-l. flask on the steam bath for twenty-four hours (Note 2). The hot solution is filtered and chilled to 0–5° in an ice bath, and to it is added 1 l. of 28 per cent aqueous ammonia (sp. gr. 0.90). The flask is immersed in an ice-salt bath, and the mixture is stirred vigorously until the temperature falls to 0°, when the crystalline creatinine is filtered off, washed with ice-cold 28 per cent aqueous ammonia (Note 3) until the filtrate is free of chlorides, and finally with ice-cold methyl alcohol; the product (Note 4) is then dried to constant weight at 40–50°. The yield (Note 5) is 545–555 g. (80–81 per cent of the theoretical amount).

(*B*) *Creatinine Zinc Chloride*.—An intimate mixture of 400 g. (2.7 moles) of commercial creatine hydrate and 400 g. (2.9 moles) of fused zinc chloride is heated in a porcelain dish over a small flame. The mixture melts to a viscous liquid which soon solidifies. The flame is removed when the mixture can no longer be stirred. The mass, when cold, is broken up, and stirred with 500 cc. of cold water until the lumps are softened; the crude creatinine zinc chloride is filtered off with suction on a hardened filter paper and washed with ice water to remove excess zinc chloride. The crude material is now dissolved in 6 l. of boiling 25 per cent aqueous acetic acid, filtered with the use of a little decolorizing carbon, and the solution allowed to stand for forty-eight hours. The crystals that have separated are filtered off, washed with ice water, and dried. The weight is 220–230 g. The filtrate and washings are evaporated to 4.5 l. under reduced pressure in a 12-l. flask; 6.5 l. of methyl alcohol is added and the mixture allowed to stand in a cool place for twenty-four hours. The crystals that separate are filtered off, washed with cold water and dried, and an additional 150–160 g. is thus obtained. The total yield is 370–380 g. (76–78 per cent of the theoretical amount).

(*C*) *Creatinine Picrate*.—A mixture of 300 g. (2 moles) of commercial creatine hydrate with 190 cc. of concentrated hydrochloric acid (sp. gr. 1.19) and 50 cc. of

water is warmed in a glass or porcelain dish on a steam bath for twenty-four hours. The resulting mass of creatinine hydrochloride crystals is dissolved in 1 l. of water, boiled with a little decolorizing carbon, and filtered. The solution is then diluted to 4 l. with distilled water, and heated to boiling in a 12-l. flask under a reflux condenser. To the hot solution is added, with good stirring, a solution of 500 g. (2 moles) of technical picric acid (containing 10 per cent of water) in 1250 cc. of warm methyl alcohol. Stirring is continued for one hour on the steam bath and the solution allowed to cool. The crystalline precipitate of creatinine picrate is filtered off, washed well with cold water, and dried. It forms long needles which melt at 220°; the melting point (Note 6) is unchanged on recrystallization from hot water. The yield is 620–630 g. (89–90 per cent of the theoretical amount).

2. Notes

1. As a rule, the commercial product, which contains one mole of water of crystallization, is entirely satisfactory; but if it is dark in color, it may be recrystallized from water with the use of decolorizing carbon.
2. It is suggested that the hydrochloric acid solution of creatine should be thoroughly decolorized with Norite before precipitation inasmuch as any color tends to come down with the creatinine. Some of the commercial creatine contains traces of iron, in which case the addition of 3–4 g. of tartaric acid before treating with ammonia will retain the iron in solution, keeping it from precipitating with and staining the creatinine (W. W. Hartman, private communication).
3. Creatinine dissolves readily in pure water but is only slightly soluble in cold concentrated ammonia, while ammonium chloride is freely soluble.
4. The creatinine so prepared is practically 100 per cent pure; its recrystallization, while not recommended, may be carried out by dissolving, as rapidly as possible, 1 part by weight in 5 parts of water previously warmed to 65°, and then immediately adding to the warm solution double its volume of acetone, chilling in ice, and filtering after a few hours. The product is finally washed with acetone and dried. About one-third is lost in the filtrate.
5. The yield could be slightly increased by so modifying the conditions that the total volume of filtrate would be small er, but this would involve an undue amount of trouble.
6. Special attention was given to the melting-point determination, since two values, 205° and 212–213°, have been recorded in the literature.

3. Discussion

Creatinine can be prepared from creatine by the action of mineral acids,[1] by heating in an autoclave[2] and by treatment with zinc chloride;[3] and from sarcosine and arginine.[4] The procedure described was developed[5] since creatine has become available in relatively large quantities as a by-product.[6]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 586

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

chlorides

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ammonia (7664-41-7)

methyl alcohol (67-56-1)

ammonium chloride (12125-02-9)

iron (7439-89-6)

acetone (67-64-1)

decolorizing carbon, Norite (7782-42-5)

zinc chloride (7646-85-7)

Creatinine (60-27-5)

creatine hydrate (6020-87-7)

Creatinine Zinc Chloride (62708-52-5)

Creatinine Picrate

creatinine hydrochloride

picric acid (88-89-1)

creatine (57-00-1)

tartaric acid (87-69-4)

sarcosine (107-97-1)

arginine (74-79-3)

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p-CRESOL

Submitted by W. W. Hartman
Checked by Roger Adams and A. W. Sloan.

1. Procedure

One kilogram of technical sodium hydroxide and .400 g. of technical potassium hydroxide (Note 1) are melted together in a cast-iron flat-bottomed kettle, 18 cm. in depth and 18 cm. in diameter. The fused mass is well stirred by means of a piece of iron pipe closed at one end, containing a thermometer; the hand is protected by a rubber glove wrapped with a cloth. The temperature of the fused mass is allowed to fall to 230°, and 150 g. (0.73 mole) of technical sodium *p*-toluenesulfonate (Note 2) is stirred in. The temperature is now slowly raised while 450 g. (2.2 moles) more of sodium *p*-toluenesulfonate is added slowly, the additions being made whenever the melt becomes sufficiently thin to stir in the solid. When all has been added, the temperature should be about 270°; the addition requires about thirty minutes. The temperature is now raised to 300°, with occasional stirring. At this point there is a layer of heavy froth on the surface of the thin melt, and as the temperature rises this is stirred in, the whole melt becoming frothy and showing a tendency to foam over. On continuing to raise the temperature, the foaming suddenly disappears at about 330°; the melt becomes dark and evolution of hydrogen sets in. The mixture is now thin and of uniform consistency; it is poured at once into an iron tray and allowed to cool.

The solidified product is dissolved in 6-7 l. of water in a 12-l. flask, and a solution of concentrated (95 per cent) sulfuric acid (about 880 cc.) in about 2 l. of water is added until the liquor has a distinct odor of sulfur dioxide. The heat of neutralization is sufficient to cause the solution to boil; it is at once distilled in a current of steam (Note 3) until a sample of the distillate gives only a slight precipitate with bromine water. The distillate (about 6–7 l.) is saturated with salt and the oil separated. The watery solution may be again distilled with steam in order to recover the small amount of cresol in solution. The oil is at once distilled under reduced pressure, and the fraction which boils at 95–96° /15 mm. is collected. The forerun is freed of water and redistilled, yielding a further quantity. On cooling, the product solidifies to a white, crystalline mass melting at 31° (Note 4). The yield is 200–230 g. (63–72 per cent of the theoretical amount based on sodium *p*-toluenesulfonate of 95 per cent purity).

2. Notes

1. Fusion with sodium hydroxide alone yields no cresol, the fused sodium

hydroxide appearing to have no solvent action on the sodium *p*-toluenesulfonate. On the other hand, potassium hydroxide works entirely satisfactorily, as do mixtures of sodium hydroxide and potassium hydroxide containing not less than 28 per cent of potassium hydroxide. In the above directions the minimum amount of potassium hydroxide is indicated.

2. Technical sodium *p*-toluenesulfonate is, as a rule, of about 95 per cent purity; it contains about 2 per cent of sodium chloride and some moisture. Attempts to prepare a *p*-cresol of higher melting point by fusion of recrystallized sodium *p*-toluenesulfonate (which should presumably contain no isomers) have failed; it has been found impossible to raise the melting point above 31.4°.

3. Since distillation in a current of steam in a laboratory is apt to be a tedious process when only the regular form of Liebig condenser is employed, much time can be saved by the use of the apparatus described on p. 479.

4. Traces of isomeric cresols can be removed by treatment with quinone chloroimide.[1]

3. Discussion

p-Cresol can be prepared from diazotized *p*-toluidine,[2] and by the fusion of *p*-toluenesulfonic acid with potassium hydroxide.[3]

References and Notes

1. Gibbs, J. Am. Chem. Soc. **49**, 839 (1927).
2. Kekulé, Jahresber. 458 (1866); Körner, Z. Chem. 326 (1868).
3. Wurtz, Ann. **144**, 122 (1867); **156**, 258 (1870); Engelhardt and Latschinov, Z. Chem. 618 (1869).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

bromine water

cresols

sulfuric acid (7664-93-9)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

sulfur dioxide (7446-09-5)

potassium hydroxide (1310-58-3)

cresol (95-48-7)

quinone chloroimide

p-toluidine (106-49-0)

p-toluenesulfonic acid (104-15-4)

p-CRESOL (106-44-5)

sodium p-toluenesulfonate (657-84-1)

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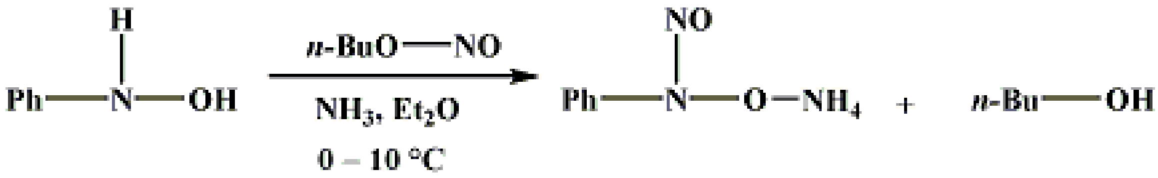
Organic Syntheses, CV 1, 177

CUPFERRON



Submitted by C. S. Marvel
Checked by Oliver Kamm

1. Procedure

The moist phenylhydroxylamine obtained from 1 kg. (8.1 moles) of nitrobenzene, by the procedure described on p. 445, is weighed and dissolved in 4.5 l. of ordinary ether (Note 1). The ether-insoluble material (sodium chloride and water) is also weighed, the difference between the two weighings being a fairly accurate measure of the amount of phenylhydroxylamine in solution.

The ether solution is filtered through a dry filter paper into a 5-l. round-bottomed flask which is fitted with an efficient mechanical stirrer and immersed in an ice-salt bath. When the temperature of the solution has fallen to 0° (Note 2), a rapid stream of dry ammonia, from a cylinder of the compressed gas, is passed into the solution.

After about fifteen minutes, the theoretical amount of freshly distilled *n*-butyl nitrite (95 g. for every 100 g. of phenylhydroxylamine) is added slowly through a dropping funnel (Note 3) and (Note 4). The addition of butyl nitrite usually requires about one hour (Note 5), during which time the stream of ammonia gas is continued in order that ammonia may always be in excess. If this precaution is not observed, a colored product will result. The temperature of the reaction mixture should be maintained below 10° and this may be done best by controlling the rate at which the butyl nitrite is added (Note 6). An appreciable rise in temperature will cause the volatilization of considerable quantities of ether and of ammonia (Note 7).

After the butyl nitrite has been added, the reaction mixture is stirred for about ten minutes longer in order to insure completion of the reaction, after which the cupferron is filtered off and washed several times with small portions of fresh ether. The product is spread on sheets of paper until all traces of ether have been lost, and is then stored in bottles where it is exposed to the vapors of ammonium carbonate. This may be done by protecting each cork with a double sheet of filter paper and placing a lump of ammonium carbonate between the cork and the filter paper (Note 8).

The yield of cupferron based on a given weight of phenylhydroxylamine averages 85–90 per cent of the theoretical amount.

2. Notes

1. The solvent ether may be replaced by benzene, but this modification offers no advantages for the preparation of cupferron on a laboratory scale.
2. The temperature must be kept low. If it is not, the material is generally colored brown and the reaction does not run smoothly. Probably the most important factor in securing successful results is always to have an excess of ammonia present.
3. The butyl nitrite is freshly distilled as a general precaution, because a product which has stood for some time is often partially decomposed.
4. It is suggested that gaseous ethyl nitrite be passed in until the precipitate ceases to increase (W. W. Hartman, private communication). However, it is probable that butyl nitrite is more convenient for a laboratory method. A method for the preparation of ethyl nitrite is described in Org. Syn. **10**, 22.
5. In the preparation of cupferron, it has been recommended that the butyl nitrite be added all at one time. This procedure is satisfactory only when the amount of phenylhydroxylamine used is less than 200 g.; otherwise the reaction becomes extremely vigorous and an excessive proportion of ether is lost. The directions given above, on the other hand, are adaptable for the preparation of large quantities of cupferron. For the rapid preparation of small quantities of material, the butyl nitrite may be added all at one time, provided sufficient excess of ammonia is present.
6. If ammonia is kept in a definite excess at all times, a rise of temperature to the boiling point of ether appears to do no harm. The lower temperature was used because it makes possible a more rapid addition of the nitrite.
7. It is found that 75 per cent of the ether and 95 per cent of the butyl alcohol used may be recovered, and that one person, working six to seven hours, is able to prepare 800 g. of cupferron. The recovered ether may be used over again, provided the following procedure is observed: The phenylhydroxylamine is dissolved in a little fresh ether, the solution cooled and treated with ammonia, then the recovered ether added. This precaution is necessary owing to the presence of some butyl nitrite in the recovered ether.
8. The addition of a small quantity of acetophenetidide to a solution of cupferron reagent tends to prevent its decomposition.[1]
Cupferron has been kept in dark bottles sealed with viscose caps for a year without decomposition.

3. Discussion

Nitroso-β-phenylhydroxylamine, of which cupferron is the ammonium salt, can be prepared by the action of sodium nitrite and hydrochloric acid on β-phenylhydroxylamine,[2] from a mixture of alkyl nitrite and β-phenylhydroxylamine in the presence of ammonia in ether or benzene solution,[3] and by the zinc dust reduction

of nitrobenzene in the presence of amyl nitrite and ammonium hydroxide solution.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 445

References and Notes

1. Germuth, Chemist-Analyst, **17**, No. 3, 3; 15 (1928) [C. A. **22**, 3372 (1928)].
2. Wohl, Ber. **27**, 1435, 1554 (1894); Bamberger and Landau, Ber. **52**, 1839 (1919); Marvel and Kamm, J. Am. Chem. Soc. **41**, 280 (1919).
3. Baudisch, Chem. Ztg. **35**, 913 (1911); Baudisch and King, J. Ind. Eng. Chem. **3**, 629 (1911); Kasanof, ibid. **12**, 799 (1920); Marvel and Kamm, J. Am. Chem. Soc. **41**, 280 (1919); Slotta and Jacobi, Z. anal. Chem. **80**, 97 (1930); This last method, using ethyl nitrite, is promising but has not been checked completely.
4. Baudisch, Ger. pat. 227, 659 [Frdl. **10**, 126 (1910–12)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Nitroso-β-phenylhydroxylamine

ammonium salt

β-Phenylhydroxylamine

hydrochloric acid (7647-01-0)

ammonium carbonate

ammonia (7664-41-7)

Benzene (71-43-2)

ether (60-29-7)

sodium chloride (7647-14-5)

sodium nitrite (7632-00-0)

nitrite (14797-65-0)

butyl alcohol (71-36-3)

Nitrobenzene (98-95-3)

Cupferron (135-20-6)

Phenylhydroxylamine (100-65-2)

Butyl nitrite, n-butyl nitrite (544-16-1)

ethyl nitrite (109-95-5)

acetophenetidide (62-44-2)

amyl nitrite (463-04-7)

ammonium hydroxide (1336-21-6)

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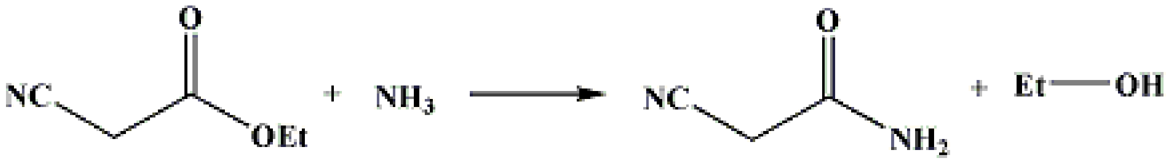
CYANOACETAMIDE



Submitted by B. B. Corson, R. W. Scott, and C. E. Vose.
Checked by C. S. Marvel and L. H. Bock.

1. Procedure

Four hundred grams (3.5 moles) of ethyl cyanoacetate (p. 254) is poured into 300 cc. (4.5 moles) of concentrated aqueous ammonia (sp. gr. 0.90) (Note 1) contained in a 1-l. wide-mouthed Erlenmeyer flask. The mixture, which is cloudy at first, is shaken; it then warms up a little and becomes clear in about three minutes. The flask is allowed to stand one hour in an ice-salt mixture. The product is then filtered by suction (Note 2) and the solid washed with two 50-cc. portions of ice-cold ethyl alcohol (Note 3). After drying in the air, the slightly yellowish, crystalline amide weighs 205–225 g. A snow-white product is easily obtained by crystallizing from hot alcohol (Note 4) and (Note 5). For this purpose 200 g. of amide is dissolved in 350 cc. (Note 6) of hot 95 per cent alcohol and the solution cooled; pure amide is deposited with practically no loss.

An additional yield of amide is obtained by evaporating (Note 7) the original mother liquor to dryness under reduced pressure while heating the flask in a boiling water bath. The damp, brownish residue in the flask is dissolved in 100 cc. of hot alcohol. The hot solution is shaken a few minutes with decolorizing charcoal, filtered by suction while still hot, and then cooled in ice. Forty-six to fifty-eight grams of yellowish amide is deposited. One more crystallization with charcoal yields 44–56 g. of pure product.

The total yield is 255–261 g. (86–88 per cent of the theoretical amount). The product melts at 119–120°.

2. Notes

1. Gaseous ammonia was tried with poor success, the ammonia being passed into the ester (both cold and at room temperature) and also into an alcoholic solution of the ester.
2. The product must be filtered rapidly while the mother liquor is cold because of the solubility of the amide.
3. Cyanoacetamide may be washed with ice water but cold alcohol is preferable because of its lower solubility in the latter.
4. The solubility of cyanoacetamide in 100 cc. of 95 per cent alcohol follows:

1.3 g. at 0°	9.5 g. at 52°
1.7 g. at 12°	14.0 g. at 62°
3.1 g. at 26°	16.3 g. at 66°
5.0 g. at 38°	18.7 g. at 69°
7.0 g. at 44°	21.5 g. at 71°

5. The alcoholic mother liquor from the crystallization usually contains a small amount of malonamide which melts at 170–171°.
6. If the treatment with decolorizing charcoal is necessary, about 450 cc. of alcohol should be used in order to avoid crystallization during the filtration.
7. A few cubic centimeters of an oil, presumably unchanged ethyl cyanoacetate, comes over with the water.
8. This work was done with the aid of a grant to the submitters from the Cyrus M. Warren Fund of the American Academy of Arts and Sciences.

3. Discussion

Cyanoacetamide can be prepared by the action of aqueous[1] or alcoholic[2] ammonia on cyanoacetic ester.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 379
- Org. Syn. Coll. Vol. 4, 210

References and Notes

1. Van't Hoff, Ber. **7**, 1383 (1874); Henry, Bull. soc. chim. (2) **48**, 656 (1887); Hesse, Am. Chem. J. **18**, 724 (1896); Thole and Thorpe, J. Chem. Soc. **99**, 429 (1911).
2. Hesse, Am. Chem. J. **18**, 724 (1896); Ott and Löpmann, Ber. **55**, 1258 (1922).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ester

cyanoacetic ester

ethyl alcohol, alcohol (64-17-5)

ammonia (7664-41-7)

CYANOACETAMIDE (107-91-5)

Ethyl cyanoacetate (105-56-6)

malonamide (108-13-4)

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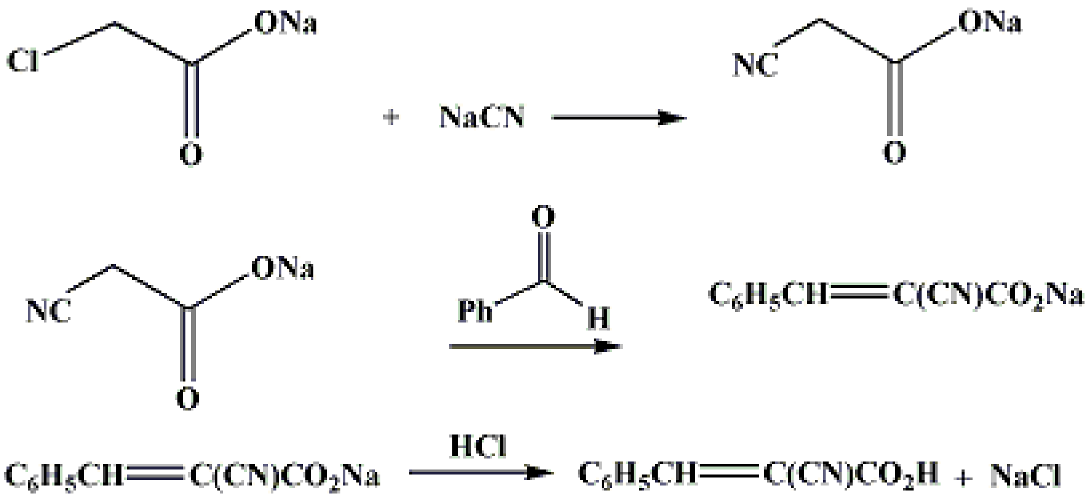
α-CYANO-β-PHENYLACRYLIC ACID



Submitted by Arthur Lapworth and Wilson Baker.
Checked by J. B. Conant and W. C. Boyd.

1. Procedure

(*A*) *Preparation of Sodium Cyanoacetate Solution.*—In a 3-l. round-bottomed flask is placed 250 g. (2.65 moles) of monochloroacetic acid. To this are added 100 cc. of water and 375 g. (1.3 moles) of crystalline sodium carbonate (decahydrate) (Note 1), the mixture being gently warmed. The neutralization is completed by adding sodium carbonate solution using litmus paper as an indicator. The flask is transferred to the hood, and a solution of 130 g. (2.65 moles) of sodium cyanide in 250 cc. of warm water is added in two approximately equal portions, waiting after the first addition until no further evolution of heat occurs, or the mixture ceases to boil. The cooled solution is neutralized with hydrochloric acid, using methyl orange as an outside indicator. The solution is then diluted with water to 1 l. and filtered; it should be of a light straw color. It can be kept for long periods of time in a stoppered bottle, although the color deepens somewhat.

(*B*) *Condensation with Benzaldehyde.*—To 400 cc. (1.06 moles) of the sodium cyanoacetate solution is added a solution of 5 g. (0.13 mole) of sodium hydroxide in 400 cc. of water. The resulting alkaline solution is warmed to 40° and treated with 100 g. (0.94 mole) of benzaldehyde which has been shaken with sodium carbonate solution and distilled under reduced pressure. The benzaldehyde dissolves after vigorous shaking for a few minutes. After standing one hour, during which time some of the sodium cyanophenylacrylate crystallizes (Note 2), the mixture is acidified with concentrated hydrochloric acid until acid to litmus and 40 cc. additional concentrated acid added, and the whole is shaken vigorously. After another hour, the crystalline cyanophenylacrylic acid is filtered on a Büchner funnel, washed thoroughly with cold water, and dried in a steam oven. It is then shaken with 100 cc. of benzene, filtered on

a Büchner funnel, and further washed with 50 cc. of benzene and dried. The yield of product melting at 178–179° is 105–115 g. (65–70 per cent of the theoretical amount). This product may have a slight pinkish color, which can be removed by recrystallization from 740 cc. of alcohol or 10 l. of hot water. The recovery is about 57 per cent from alcohol and 92 per cent from water (Note 3). The melting point remains unchanged.

2. Notes

1. In place of the crystallized sodium carbonate, the equivalent amount of dehydrated material (138 g.) and water (240 cc.) may be used.
2. If the sodium salt is crystallized out by chilling externally, then separated and acidified, it gives a purer α-cyano-β-phenylacrylic acid. The yield of acid is 90–105 g., and this purer acid is more satisfactory for the preparation of phenylsuccinic acid (p. 451) (C. F. H. Allen and C. V. Wilson, private communication).
3. Owing to hydrolysis in alkaline or neutral solutions, it is very difficult to free the acid from a slight odor of benzaldehyde if it is recrystallized from water, but a final washing with benzene removes this odor.

3. Discussion

α-Cyanophenylacrylic acid can be prepared by the hydrolysis of the corresponding ester obtained by the condensation of benzaldehyde with cyanoacetic ester in the presence of sodium alkoxide or acetic anhydride.[1] The direct condensation of benzaldehyde and cyanoacetic acid or its sodium salt takes place when the substances are heated[2] for some time at 180°. The most convenient method for the preparation of the acid (as the sodium or potassium salt) is by the action of benzaldehyde on an alkaline aqueous solution of sodium or potassium cyanoacetate prepared by the interaction of salts of bromoacetic[3] or chloroacetic acids[4] with potassium or sodium cyanide in aqueous solution.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 451

References and Notes

1. Carrick, J. prakt. Chem. (2) **45**, 501 (1892).
2. Fiquet, Ann. chim. phys. (6) **29**, 442 (1893); Bull. soc. chim. (3) **7**, 11 (1892).
3. Clarke and Francis, Ber. **44**, 273 (1911).
4. Lapworth and McRae, J. Chem. Soc. **121**, 1699 (1922).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

cyanoacetic ester

sodium alkoxide

sodium or potassium cyanoacetate

bromoacetic

chloroacetic acids

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

acetic anhydride (108-24-7)

sodium hydroxide (1310-73-2)

sodium cyanide (143-33-9)

sodium carbonate (497-19-8)

benzaldehyde (100-52-7)

monochloroacetic acid (79-11-8)

sodium (13966-32-0)

α-Cyano-β-phenylacrylic acid, cyanophenylacrylic acid, α-Cyanophenylacrylic acid (1011-92-3)

Sodium cyanoacetate (1071-36-9)

sodium carbonate (decahydrate) (6132-02-1)

sodium cyanophenylacrylate

Phenylsuccinic acid (635-51-8)

cyanoacetic acid (372-09-8)

potassium (7440-09-7)

sodium salt (824-79-3)

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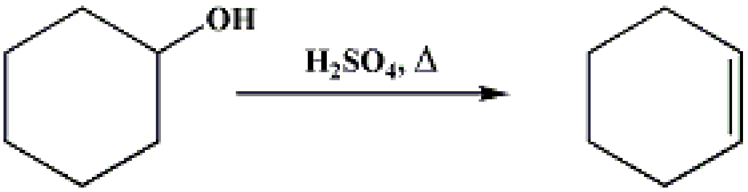
CYCLOHEXENE



Submitted by G. H. Coleman and H. F. Johnstone.
Checked by C. S. Marvel and A. B. Adams.

1. Procedure

In a 500-cc. modified Claisen flask (p. 130) are placed 400 g. (4 moles) of cyclohexanol (Note 1) and 12 cc. of concentrated sulfuric acid, and the flask is connected to a condenser and receiver surrounded by an ice bath. It is then placed in an oil bath which is heated to a temperature of 130–140°. The distillation is continued until only a small residue remains and the odor of sulfur dioxide is apparent. Toward the end of the distillation the temperature of the bath may be raised to 150°. The receiver is kept cold (Note 2) during the entire distillation, which requires from five to six hours (Note 3).

The distillate is saturated with salt, and the cyclohexene is separated from the water layer. It is dried with calcium chloride and fractionated through an efficient column (Note 4). The fraction boiling at 80–82° (uncorr.) is collected separately. It may be necessary to refractionate the low- and high-boiling portions once or twice (Note 5). The high-boiling fraction is finally added to the next run. The yield of cyclohexene is 260–285 g. (79–87 per cent of the theoretical amount) (Note 6).

2. Notes

1. The ordinary commercial grade of cyclohexanol was used in these experiments. It contained no more than a trace of phenol, and 90–95 per cent of it distilled at 158–163°.
2. In transferring cyclohexene, it is best to keep it well cooled to avoid small losses by evaporation.
3. The time required for this distillation can be reduced to about two hours by boiling the mixture in a round-bottomed flask provided with a reflux condenser with water maintained at about 75°. A tube at the top of the reflux condenser leads to a downward cold-water condenser.[1]
4. The partial condenser illustrated in Org. Syn. **20**, 27, which is a modification of an apparatus described by Hahn,[2] is very efficient in the purification of cyclohexene (A. W. Hutchison, private communication).
5. It has been suggested that the crude fraction be refluxed with sodium to

remove cyclohexanol prior to a final fractionation.[3]
6. For the preparation of cyclohexene in large quantity, distillation of cyclohexanol over silica gel[4] or, better, activated alumina is more rapid and efficient. Using a 25-mm. tube packed with 8- to 14- mesh activated alumina (Aluminum Company of America) and heated to 380–450° over a 30-cm. length, 1683 g. of cyclohexanol was dehydrated in about four hours. After separating the water, drying with sodium sulfate, and fractionating with a simple column, 1222 g. (89 per cent yield) of cyclohexene, b.p. 82–84°, was obtained. (E. B. Hershberg and John R. Ruhoff, private communication, and Org. Syn. **17**, 27.)

3. Discussion

Cyclohexene can be prepared from cyclohexanol by dehydration with potassium bisulfate,[5] oxalic acid,[6] sulfuric acid,[7] *p*-toluenesulfonic acid,[8] phosphoric acid,[9] iodine,[10] and at elevated temperatures over various catalysts.[4, 11] Cyclohexene has also been prepared from cyclohexyl chloride by passage with steam over activated carbon at 260–300°,[12] and from benzene by treatment with the substance $Ca(NH_3)_6$.[13] The procedure described is a slight modification of that described by Senderens[7] and later modified by Osterberg and Kendall.[7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 158
- Org. Syn. Coll. Vol. 2, 102
- Org. Syn. Coll. Vol. 2, 151
- Org. Syn. Coll. Vol. 2, 171
- Org. Syn. Coll. Vol. 3, 217
- Org. Syn. Coll. Vol. 3, 231

References and Notes

1. Kistiakowsky, Ruhoff, Smith, and Vaughan, J. Am. Chem. Soc. **58**, 140 (1936).
2. Hahn, Ber. **43**, 419 (1910).
3. Waterman and van Westen, Rec. trav. chim. **48**, 637 (1929).
4. Bartlett and Berry, J. Am. Chem. Soc. **56**, 2684 (1934).
5. Brunel, Bull. soc. chim. (3) **33**, 270 (1905); Willstätter and Hatt, Ber. **45**, 1466 (1912).
6. Zelinsky and Zelikov, Ber. **34**, 3252 (1901); Willstätter and Hatt, Ber. **45**, 1466 (1912); Zelinsky, J. Russ. Phys. Chem. Soc. **43**, 1222 (1911) [Chem. Zentr. I, 139 (1912)]; Juery, Bull. soc. chim. (4) **17**, 174 (1915).
7. Senderens, Compt. rend. **154**, 1169 (1912); **177**, 1183 (1923); Osterberg and Kendall, J. Am. Chem. Soc. **42**, 2620 (1920).
8. Evans and Witzemann, Bull. soc. chim. Belg. **26**, 304 (1912) [Chem. Zentr. II, 1006 (1912)].

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10. Hibbert, J. Am. Chem. Soc. **37**, 1754 (1915).
11. Ipatiev, Ber. **43**, 3385 (1910); Friedr. Bayer and Co., Ger. pat. 241,895 [Frdl. **10**, 1032 (1910–12)]; Senderens, Ann. chim. phys. (8) **25**, 461, 500 (1912).
12. Zal'kind and Markov, Narodnyi Komissariat Tyazheloi Prom. S. S. S. R. Nauch.-Issledovatel. Inst. Plasticheskikh Mass., Plasticheskie Massy. Sbornik, **2**, 331 (1937) [C. A. **31**, 3875 (1937)].
13. Kazanskii and Glushnev, J. Gen. Chem. (U.S.S.R.) **8**, 642 (1938) [C. A. **33**, 1279 (1939)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alumina

silica gel

$Ca(NH_3)_6$

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

Benzene (71-43-2)

Cyclohexanol (108-93-0)

phenol (108-95-2)

Cyclohexene (110-83-8)

sulfur dioxide (7446-09-5)

sodium sulfate (7757-82-6)

Oxalic acid (144-62-7)

potassium bisulfate (7646-93-7)

iodine (7553-56-2)

activated carbon (7782-42-5)

sodium (13966-32-0)

phosphoric acid (7664-38-2)

cyclohexyl chloride (542-18-7)

p-toluenesulfonic acid (104-15-4)

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CYCLOHEXENE OXIDE

[Cyclohexane, 1,2-epoxy-]

Submitted by A. E. Osterberg
Checked by C. S. Marvel and A. B. Adams.

1. Procedure

In a 2-l. round-bottomed flask fitted with a mechanical stirrer is placed a solution of 70 g. (1.75 moles) of sodium hydroxide in 400 cc. of water. To this solution is then added 230 g. (1.71 moles) of 2-chlorocyclohexanol (p. 158). The mixture is stirred vigorously for about one hour (Note 1). The stirring is then stopped and the upper layer is separated and fractionated carefully through an efficient column.

The fractions collected are 100–129°, 129–134°, and 134–175° (Note 2). The first fraction is mainly cyclohexene oxide but contains some water which is separated with a separatory funnel before the second fractionation. After the fraction boiling at 100–129° is collected, the condenser should be removed and dried thoroughly before collecting the second fraction, in order to insure anhydrous material. After two or three fractionations, the yield of cyclohexene oxide boiling at 129–134° is 117–122 g. (70–73 per cent of the theoretical amount).

2. Notes

1. If the stirring is continued for much longer than one and one-half hours, the yield may be lessened somewhat.
2. There is a slight high-boiling residue which begins to decompose if the temperature is raised above this point. The products of decomposition are hard to remove from the distilling flask.

3. Discussion

Cyclohexene oxide can be prepared from 2-iodocyclohexanol[1] or 2-chlorocyclohexanol[2] and alkalies; and by the oxidation of cyclohexene with perbenzoic acid.[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 232

References and Notes

1. Brunel, Compt. rend. **136**, 384 (1903); **137**, 62 (1903); Bull. soc. chim. (3) **29**, 883 (1903).
2. Godchot and Bedos, Bull. soc. chim. (4) **37**, 1454 (1925).
3. Godchot and Bedos, Compt. rend. **174**, 462 (1922).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium hydroxide (1310-73-2)

Cyclohexene (110-83-8)

2-Chlorocyclohexanol (1561-86-0)

Cyclohexene oxide, Cyclohexane, 1,2-epoxy- (286-20-4)

2-iodocyclohexanol

Perbenzoic acid (93-59-4)

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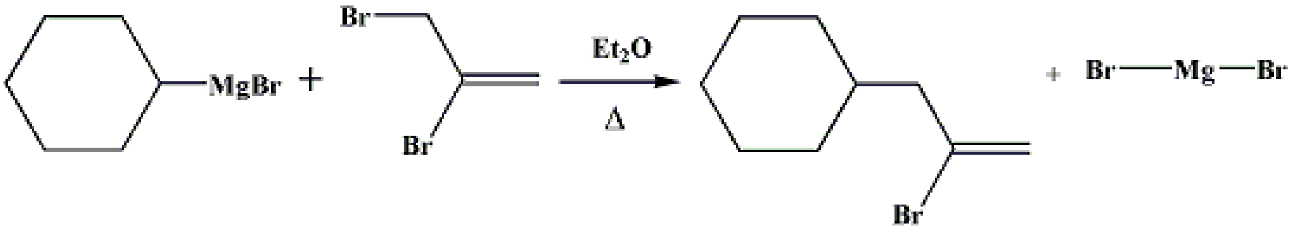
Organic Syntheses, CV 1, 186

3-CYCLOHEXYL-2-BROMOPROPENE

[Propene, 2-bromo-3-cyclohexyl-]



Submitted by R. Lespieau and M. Bourguel.
Checked by Roger Adams and M. M. Brubaker.

1. Procedure

A 3-l. three-necked round-bottomed flask is fitted with a mechanical stirrer through a mercury seal, a reflux condenser and a 1-l. separatory funnel. A mixture of 200 g. (1 mole) of 2,3-dibromopropene (p. 209) and 200 cc. of dry ether is added. The flask is now cooled in an ice bath, the stirrer is started, and one molecular equivalent of cyclohexylmagnesium bromide, prepared from 31 g. (1.28 atoms) of magnesium, 204 g. (1.25 moles) of cyclohexyl bromide, and 400 cc. of dry ether (Note 1), is added at such a rate that the mixture refluxes gently (Note 2). The addition takes about one-half to three-quarters of an hour. Two layers are formed, and magnesium bromide may separate.

The stirring should be continued and the ice bath replaced by a hot-water bath, and the mixture refluxed gently for two hours. The flask is again cooled, and 30 cc. of concentrated hydrochloric acid in 350 cc. of water is added through the separatory funnel. This should be added slowly as long as heat is evolved. The contents of the flask are then transferred to a separatory funnel, the ether layer separated and dried over calcium chloride.

The ether is distilled on a steam bath (Note 3) and the residue fractionated under reduced pressure by means of a 20-cm. column (p. 130). After three fractionations, there is obtained 32–44 g. of a product boiling up to 100° /25 mm., which is mainly unchanged dibromopropene (b.p. 42–43° /18 mm.), and 123–130 g. (60.5–64 per cent of the theoretical amount, not taking into account recovered dibromopropene) of cyclohexylbromopropene (Note 4) boiling at 100–105° /25 mm. This material is satisfactory for most purposes. On redistillation it boils at 88–89° /14 mm.

2. Notes

1. The preparation of cyclohexylmagnesium chloride is described on p. 188. The solution may be standardized by titrating against 0.5 *N* hydrochloric acid, and exactly one mole equivalent is used in the preparation. Five cubic centimeters of cyclohexylmagnesium bromide solution is slowly added to 20 cc. of water, an excess of the standard acid is added, and the excess acid titrated with sodium hydroxide. If 85 g. (3.5 atoms) of magnesium, 1 l. of dry ether, and 571 g. of cyclohexyl bromide (3.5 moles) are used, a solution results which is about 2 molar.
Excess of Grignard reagent may be employed and the same yield obtained, so that the titration is an aid to conserving Grignard reagent. About an 80 per cent yield of cyclohexylmagnesium bromide from cyclohexyl bromide and magnesium can generally be depended upon. Superior yields for both cyclohexylmagnesium chloride and bromide have been reported.[1] Directions for the preparation of cyclohexylmagnesium chloride in superior yields are given in the preparation

of cyclohexylcarbinol on p. 188.

2. The reaction is instantaneous and is not stopped by moderate cooling. The cooling may be dispensed with and the cyclohexylmagnesium bromide added more slowly (two hours).

3. The ether solution may be added in several portions to a 500-cc. modified Claisen flask (p. 130) and the ether distilled after each addition.

4. By a similar procedure[2] benzylmagnesium chloride and 2,3-dibromopropene give 4-phenyl-2-bromobutene in about 45 per cent yield, b.p. 119° /20 mm.; and heptylmagnesium bromide and 2,3-dibromopropene give 2-bromodecene in 60–65 per cent yields, b.p. 76–77° /3 mm.

3. Discussion

3-Cyclohexyl-2-bromopropene can be prepared by the action of cyclohexylmagnesium bromide on 2,3-dibromopropene[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 191
- Org. Syn. Coll. Vol. 6, 488

References and Notes

1. Gilman and Zoellner, J. Am. Chem. Soc. **53**, 1945 (1931).
2. Johnson and McEwen, J. Am. Chem. Soc. **48**, 469 (1926).
3. Lespieau, Bull. soc. chim. (4) **29**, 528 (1921).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

cyclohexylmagnesium chloride and bromide

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium hydroxide (1310-73-2)

magnesium (7439-95-4)

3-Cyclohexyl-2-bromopropene, Propene, 2-bromo-3-cyclohexyl- (53608-85-8)

2,3-Dibromopropene (513-31-5)

cyclohexylmagnesium bromide

Cyclohexyl bromide (108-85-0)

magnesium bromide (7789-48-2)

dibromopropene (13195-80-7)

cyclohexylbromopropene

cyclohexylmagnesium chloride

Cyclohexylcarbinol (100-49-2)

benzylmagnesium chloride (6921-34-2)

4-phenyl-2-bromobutene

heptylmagnesium bromide (13125-66-1)

2-bromodecene

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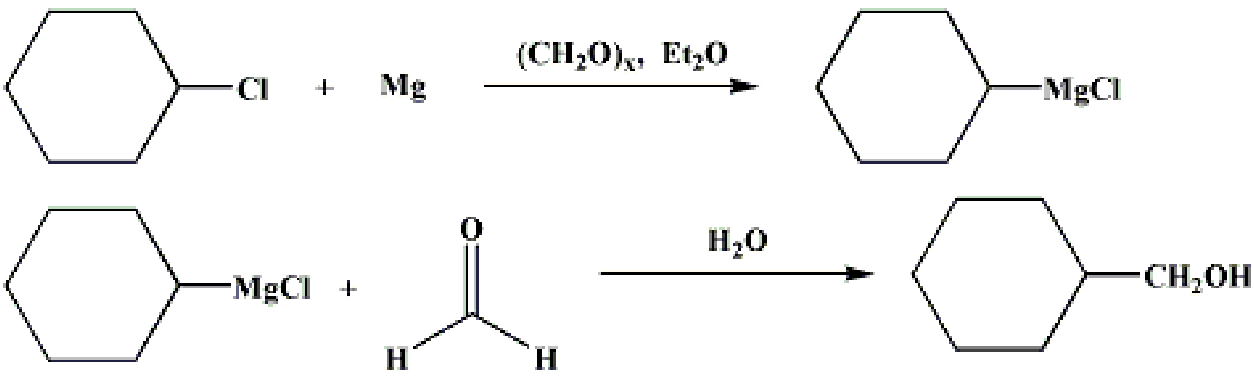
Organic Syntheses, CV 1, 188

CYCLOHEXYLCARBINOL

[Cyclohexanecarbinol]



Submitted by Henry Gilman and W. E. Catlin.
Checked by C. S. Marvel and H. R. Snyder.

1. Procedure

In a dry 1-l. three-necked, round-bottomed flask fitted with a mercury-sealed stirrer, a 500-cc. dropping funnel, and an efficient reflux condenser to the upper end of which a calcium chloride tube is attached, is placed 26.7 g. (1.1 atoms) of magnesium turnings. The reaction requires 450 cc. of ether and 118.5 g. (121 cc., 1 mole) of cyclohexyl chloride (Note 1). About 100 cc. of the ether, 15 cc. of the pure halide, and a crystal of iodine are added to the magnesium. Heat is applied, without stirring, for five to ten minutes after the iodine color has disappeared. When reaction has set in, sufficient ether is added to cover the magnesium while it is stirred, and the remainder of the halide in ether is added in one-half to three-quarters of an hour, the flask being cooled with ice water if necessary. When all the halide has been added, stirring and refluxing are continued fifteen to twenty minutes.

The separatory funnel is now replaced by a wide glass tube (about 12 mm. internal diameter) which reaches almost to, but not below, the surface of the liquid (Note 2). This tube connects directly with a 500-cc. round-bottomed flask containing 50 g. of paraformaldehyde which has been previously dried for two days in a vacuum desiccator over phosphorus pentoxide. This flask contains an inlet tube for admitting dry nitrogen. The stirrer is started (Note 3), and the flask containing the paraformaldehyde is heated in an oil bath to 180–200°. The formaldehyde formed by depolymerization (Note 4) and (Note 5) is carried over into the Grignard reagent by a slow current of dry nitrogen. At the end of about one and three-quarters hours the reaction is complete, as is indicated by a negative color test for Grignard reagent (Note 6).

The reaction mixture is then transferred to a 2-l. wide-necked, round-bottomed flask; 300 g. of cracked ice is added all at once; and the mixture is rapidly agitated until the decomposition is complete (Note 7). Twice the theoretical amount of 30 per cent

sulfuric acid is added to dissolve the magnesium hydroxide, and the mixture is then steam-distilled until no more oil is collected (Note 8). The distillate, which amounts to 1500–2500 cc., is saturated with sodium chloride and the ether-alcohol layer separated. The aqueous layer is extracted with two 100-cc. portions of ether and the ether extract added to the ether-alcohol layer. The ether solution is dried over anhydrous potassium carbonate, filtered, and heated carefully on a steam cone until all the ether is distilled. The crude alcohol is warmed one-half hour with 5 g. of freshly dehydrated lime (Note 9). After filtering and washing the lime with a little ether, the ether is distilled, and then the residual alcohol distilled from a Claisen flask (Note 10) under reduced pressure. The carbinol distils at 88–93°/18 mm. (practically all distilling at 91°). The yield is 72.5–78.5 g. (64–69 per cent of the theoretical amount).

2. Notes

1. The cyclohexyl chloride should be pure to insure a prompt reaction with magnesium, using iodine as a catalyst. Reaction between cyclohexyl bromide and magnesium sets in more rapidly than that between cyclohexyl chloride and magnesium. However, the yield of cyclohexylmagnesium bromide is less than that of cyclohexylmagnesium chloride.[1]
Cyclohexyl chloride can be prepared by heating cyclohexanol, concentrated hydrochloric acid, and anhydrous calcium chloride, with stirring, on a steam bath (W. W. Hartman, private communication).
2. Since a considerable amount of formaldehyde repolymerizes on the walls of the side tube, a wide tube is used to prevent clogging. Clogging by deposition of the reaction product is reduced by having the entry tube about 1 cm. above the surface of the solution.
3. Vigorous stirring is desirable as it materially affects the rate of absorption of the gaseous formaldehyde.
4. The amount of paraformaldehyde used is considerably in excess of 1 mole since it is difficult to tell when the reaction is complete because of repolymerization. For larger runs, the amount of paraformaldehyde need not be increased in direct proportion, as the 20 g. excess used here is sufficient to insure complete reaction in a run of almost any size. An excess of formaldehyde apparently does not decrease the yield provided that the product is steam-distilled from sulfuric acid solution (Note 8) to hydrolyze the acetal.
5. If paraformaldehyde is used directly without depolymerization, the yield is only 40–50 per cent.
6. At the end of about one and one-quarter hours, tests are made at fifteen-minute intervals for the presence of Grignard reagent. The reaction need not be interrupted. About a -cc. sample is pipetted out for each test. To this is added an equal volume of a 1 per cent solution of Michler's ketone in dry benzene. The reaction product is then hydrolyzed by the slow addition of 1 cc. of water. The subsequent addition of several drops of a 0.2 per cent solution of iodine in glacial acetic acid develops a characteristic greenish-blue color when Grignard reagent is present. The reaction is complete when no positive test is obtained for the

Grignard reagent.[2]
7. The ice must be added all at once so that the mixture stays cold at all times and local overheating does not occur. If this happens, the reaction becomes very vigorous, and the mixture is likely to foam out of the flask.
8. A high-boiling by-product, the cyclohexylcarbinol acetal of formaldehyde, is sometimes obtained, and in particularly large quantities if the steam distillation of the reaction mixture is omitted. The by-product can usually be minimized if twice the amount of 10 per cent sulfuric acid calculated to decompose the Grignard reagent is added to the reaction mixture before steam distillation is carried out. The acetal which may be present is thus hydrolyzed.
If acetal has been isolated, it may best be hydrolyzed by boiling with an equivalent weight of ethyl alcohol and concentrated hydrochloric acid (2 cc. for each 50 cc. of alcohol used) for four or five hours, then distilling off the ethyl alcohol and treating with water.
9. The heating with freshly dehydrated lime not only removes traces of water, but also gives a product which is entirely free from halogen.
10. It is advisable to use a flask with fractionating side arm (p. 130).

3. Discussion

Cyclohexylcarbinol can be prepared by the reduction of ethyl hexahydrobenzoate[3] and of benzyl alcohol,[4] and from cyclohexylmagnesium bromide or chloride with paraformaldehyde.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 186
- Org. Syn. Coll. Vol. 6, 606

References and Notes

1. Gilman and Zoellner, J. Am. Chem. Soc. **53**, 1945 (1931).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

halide

Michler's ketone

cyclohexylcarbinol acetal

cyclohexylmagnesium bromide or chloride

ACETAL (105-57-7)

ethyl alcohol, alcohol (64-17-5)

calcium chloride (10043-52-4)

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

ether (60-29-7)

formaldehyde (630-08-0)

magnesium, magnesium turnings (7439-95-4)

Cyclohexanol (108-93-0)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

iodine (7553-56-2)

Benzyl alcohol (100-51-6)

cyclohexyl chloride (542-18-7)

cyclohexylmagnesium bromide

Cyclohexyl bromide (108-85-0)

cyclohexylmagnesium chloride

Cyclohexylcarbinol, Cyclohexanecarbinol (100-49-2)

magnesium hydroxide

ethyl hexahydrobenzoate (3289-28-9)

phosphorus pentoxide (1314-56-3)

paraformaldehyde (30525-89-4)

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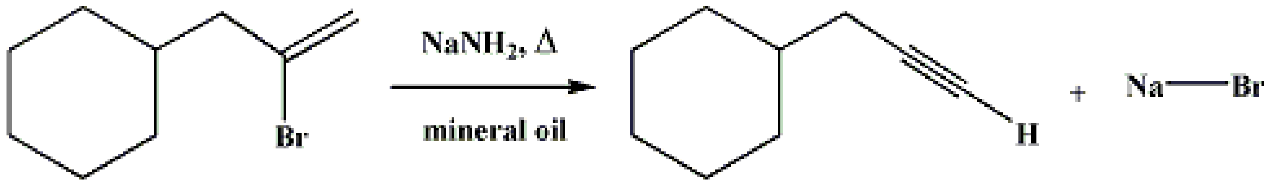
Organic Syntheses, CV 1, 191

3-CYCLOHEXYLPROPINE

[Propyne, 3-cyclohexyl-]



Submitted by R. Lespieau and M. Bourguel.
Checked by Roger Adams and M. M. Brubaker.

1. Procedure

A mixture of 120 g. (3.1 moles) of sodamide (Note 1) and 200 cc. of purified mineral oil (Note 2) is ground together in a mortar until the amide is finely pulverized (Note 3). This suspension is transferred to a 2-l. round-bottomed, three-necked flask fitted with a reflux condenser holding a calcium chloride tube, a 500-cc. separatory funnel, and an efficient mechanical stirrer through a mercury seal. The mortar and pestle are rinsed with an additional 250 cc. of the oil which is then added to the reaction flask. This is heated in an oil bath maintained at 160–165°, the stirrer is started, and 203 g. (1 mole) of cyclohexylbromopropene (p. 186) is dropped in during one and one-half hours. Ammonia is evolved, and this is allowed to pass through the condenser and is collected in water.

After all the cyclohexylbromopropene has been run in, heating is continued for about two hours, the mixture is cooled and 500 cc. of ether is added. This mixture is poured on 1.5 kg. of cracked ice in a 5-l. flask and then acidified with 280 cc. of concentrated hydrochloric acid. The ether layer is separated, dried over calcium chloride, and transferred to a 1-l. modified Claisen flask (p. 130) for distillation. The ether is distilled at ordinary pressure and then the cyclohexylpropine under diminished pressure. The product boiling up to 115°/20 mm. is collected and fractionated. The cyclohexylpropine boils at 58–63°/20 mm. The higher-boiling material is chiefly unchanged cyclohexylbromopropene which may be used again in a subsequent run. The yield of cyclohexylpropine is 80 g. (66 per cent of the theoretical amount not taking into consideration the recovered cyclohexylbromopropene which amounts to about 10 g.) (Note 4). The pure compound boils at 61–63°/24 mm.

2. Notes

1. The sodamide must be free from sodium hydroxide and may be conveniently weighed under the 250 cc. of purified mineral oil which is used to rinse out the mortar. Care must be exercised in the use of old sodamide as it sometimes contains an explosive compound that might cause trouble. The nature of this explosive compound is not definitely known; however, it appears to be associated with the development of a lemon yellow color. Should any part of the sodamide develop this

color it is recommended that the whole be destroyed at once.
Directions for preparing sodamide are to be found in Org. Syn. **20**, 86.
2. Any clean, high-boiling petroleum oil may be used. None of it should boil below 250°.
3. It is essential that the sodamide be very finely divided. The state of subdivision of the sodamide particles seriously affects the yield of product. A mechanical grinder was used by the original authors, who obtained better yields than those reported here.
4. By a similar procedure[1] decine may be made from 2-bromodecene in 68 per cent yield, b.p. 80–82°/22 mm., and 4-phenylbutine from 4-phenyl-2-bromobutene in 60 per cent yield, b.p. 95–99°/17 mm.

3. Discussion

3-Cyclohexylpropine can be prepared by heating 3-cyclohexyl-1-bromopropene with alcoholic potassium hydroxide[1] or by the action of sodamide on 3-cyclohexyl-2-bromopropene[2]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ether (60-29-7)

sodium hydroxide (1310-73-2)

potassium hydroxide (1310-58-3)

3-Cyclohexyl-2-bromopropene (53608-85-8)

cyclohexylbromopropene

4-phenyl-2-bromobutene

2-bromodecene

3-CYCLOHEXYLPROPINE, Propyne, 3-cyclohexyl-, cyclohexylpropine (17715-00-3)

decine (764-93-2)

4-phenylbutine (16520-62-0)

3-cyclohexyl-1-bromopropene

sodamide (7782-92-5)

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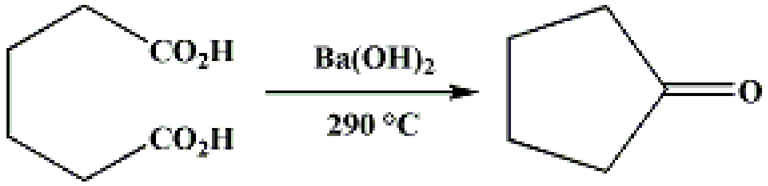
CYCLOPENTANONE



Submitted by J. F. Thorpe and G. A. R. Kon.
Checked by Roger Adams and C. R. Noller.

1. Procedure

In a 1-l. distilling flask (Note 1), fitted with a thermometer reaching within 5 mm. of the bottom, is placed an intimate mixture of 200 g. (1.34 moles) of powdered adipic acid (Note 2) and 10 g. of finely ground crystallized barium hydroxide. The mixture is gradually heated in a fusible alloy bath (Note 3) to 285–295° (Note 4) during about one and one-half hours, and maintained at that temperature until only a small amount of dry residue remains in the flask. This requires about two hours longer. The cyclopentanone distils slowly, accompanied by small quantities of adipic acid.

The ketone is separated from the water in the distillate, either by salting out with calcium chloride or by extracting with a little ether (Note 5). It is washed with a little aqueous alkali and then with water, dried over calcium chloride, and distilled through a good fractionating column (Note 6). The fraction boiling at 128–131° is cyclopentanone. The yield is 86–92 g. (75–80 per cent of the theoretical amount).

2. Notes

1. If larger runs are made, a three-necked flask provided with a mechanical stirrer should be used for the reaction.
2. The unrecrystallized adipic acid, prepared as described on p. 18, may be used.
3. An air bath may be used, but the metal bath insures better temperature control.
4. If the temperature goes above 300°, the adipic acid begins to distil quite rapidly. It is best to hold the temperature as near 290° as is possible.
5. It is reported that potassium carbonate is more satisfactory than calcium chloride for salting out the product from the distillate; traces of adipic acid are removed, and the loss which attends washing with alkali is avoided.[1]
6. Cyclopentanone is quite volatile with ether vapor, and careful fractionation is necessary when ether is used for the separation of the ketone from the water.

3. Discussion

Cyclopentanone can be prepared from adipic acid by distilling the calcium salt,[2]

heating alone[3] or with acetic anhydride,[4] or in the presence of various catalysts such as barium hydroxide,[5] barium oxide,[6] thorium oxide,[7] manganous oxide,[7] uranium nitrate,[5] ferrous sulfate[5] and others.[8] A yield of 94 per cent has been reported using barium carbonate as a catalyst.[9]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

calcium salt

calcium chloride (10043-52-4)

potassium carbonate (584-08-7)

ether (60-29-7)

acetic anhydride (108-24-7)

Adipic acid (124-04-9)

barium oxide

ferrous sulfate (13463-43-9)

thorium oxide

Cyclopentanone (120-92-3)

barium hydroxide (17194-00-2)

uranium nitrate

barium carbonate (513-77-9)

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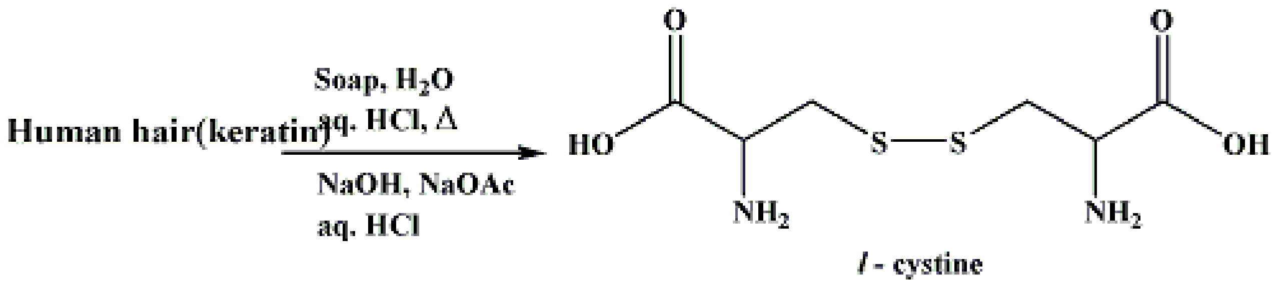
Organic Syntheses, CV 1, 194

l-CYSTINE



Submitted by R. A. Gortner and W. F. Hoffman.
Checked by H. T. Clarke and E. E. Dreger.

1. Procedure

Human hair (Note 1) is freed from foreign matter (Note 2), washed well with a lukewarm solution of soap (Note 3), then twice with cold distilled water, and dried. This washing removes the natural oils from the hair (Note 4). Two kilos of the dry, washed hair is pushed into a 12-l. round-bottomed Pyrex flask, and 4 l. of 20 per cent hydrochloric acid (Note 5) is added. An air-cooled reflux condenser, consisting of a wide glass tube, is attached to the flask. The hair is hydrolyzed by heating on the steam bath (Note 6) until the biuret reaction is entirely negative; this requires one hundred twenty to one hundred forty-four hours.

The mixture is filtered hot, and the insoluble residue is washed with distilled water. The total filtrate is now partially neutralized with 300 cc. of 40 per cent sodium hydroxide solution, while the mixture is well stirred and cooled, and then a saturated solution of 3750 g. of crystallized sodium acetate is added. The Congo red test for mineral acid should then be entirely negative. Care must be taken *not to make the solution alkaline* with sodium hydroxide (Note 7). After standing for three days at room temperature, the precipitated cystine is filtered on a suction funnel. This crude material, containing, in addition to the cystine, some "humin" pigments and tyrosine, is dissolved in 3 l. of 3 per cent hydrochloric acid. The solution is filtered and completely decolorized by two to five treatments with 20–25 g. portions of decolorizing carbon (Norite) which has been completely freed from calcium phosphate by boiling with dilute hydrochloric acid and washing with cold water. The filtrate after decolorizing should be water-clear, or at the most only slightly yellow. If it shows more color, the treatment with decolorizing carbon should be carried out again. The solution should finally be filtered once by gravity to remove traces of a solid impurity which is apt to pass through the suction funnel.

The cystine is precipitated from the clear solution by adding a filtered saturated solution of 900–1000 g. of crystallized sodium acetate until the Congo red reaction is negative. After standing five to six hours (Note 8), the cystine is filtered and washed twice with 100–200 cc. portions of hot, distilled water to remove the last traces of tyrosine. By this method the typical colorless hexagonal plates of cystine are obtained. The yield is 100–106 g. (5.0–5.3 per cent of the weight of the starting material).

2. Notes

1. Crude sheep's wool may also be employed, but the yield is not so high (about 2.6 per cent).
2. Hair obtained from barber shops generally contains matches, paper, hair-pins, and cigarette butts, and similar impurities which should be sorted out by hand as completely as possible. The other principal contamination is sand which causes little trouble and need not be removed.
3. A high grade of soap should be employed. Hair kept in hot dilute sodium carbonate solution for one to two hours yields little or no cystine.
4. The oily material may also be removed by extracting with gasoline or benzene, but this procedure involves considerably more labor.
5. The constant-boiling (20 per cent) hydrochloric acid may be prepared by adding 2000 cc. of water to 2700 cc. of concentrated hydrochloric acid (sp. gr. 1.20).
6. The hydrolysis can be carried out in a much shorter time by heating over a flame or on a sand bath, but there is great danger of breaking the flask on account of bumping, and of racemizing the cystine.
7. An alkaline reaction must always be avoided, as even dilute sodium carbonate decomposes cystine. For this reason some have preferred to omit the partial neutralization with sodium hydroxide and to employ sodium acetate only.
8. If the mixture is allowed to stand for a longer time, tyrosine tends to crystallize out with the cystine.

3. Discussion

l-Cystine may be obtained by the hydrolysis of a large number of proteins. However, the keratins are the only common proteins rich enough in cystine to serve as a source for this amino acid. Many investigators have devised methods for its isolation from the hydrolytic products of human hair,[1] wool,[2] horn,[3] nail,[3] feathers,[3] and horse hair.[4] The method of Folin[5] is the basis for most of the others. The procedure described does not claim to give so high a yield as some of those reported in the literature, but is convenient and gives consistent results.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

gasoline

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

sodium acetate (127-09-3)

sodium hydroxide (1310-73-2)

sodium carbonate (497-19-8)

decolorizing carbon, decolorizing carbon (Norite) (7782-42-5)

cystine, L-Cystine (56-89-3)

tyrosine (60-18-4)

calcium phosphate

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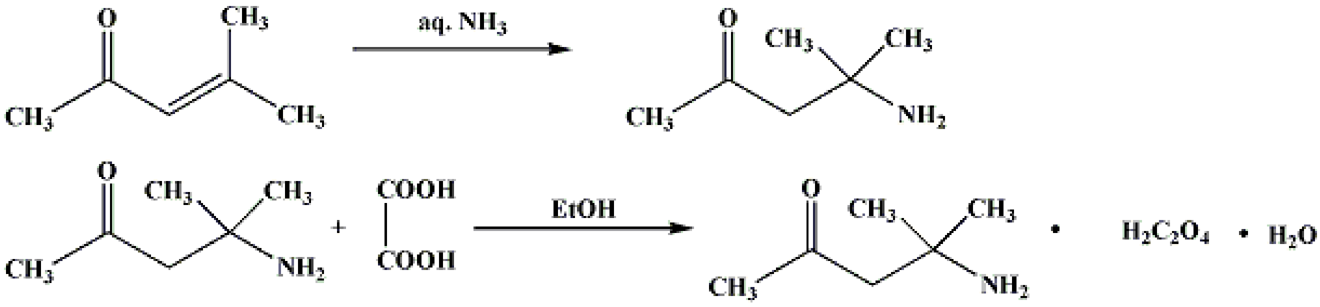
DIACETONAMINE HYDROGEN OXALATE

[Diacetonamine, acid oxalate]



Submitted by P. R. Haeseler
Checked by Roger Adams and G. S. Hiers.

1. Procedure

A mixture of 200 g. (2 moles) of mesityl oxide (p. 345) and 280 cc. of aqueous ammonia (27 per cent) is placed in a 1-l. round-bottomed flask which is equipped with an efficient mechanical stirrer. The stirrer should be inserted through a stopper in such a way that the flask is nearly air-tight. Because of the heat generated during the reaction it is desirable to keep tap water running over the flask. After stirring for several hours (Note 1) the system becomes homogeneous. When this point is reached the stirring is discontinued, and the well-stoppered flask is allowed to stand at room temperature for three days (Note 2).

Dry air is blown through the solution to remove the excess of ammonia, and the solution is then dissolved in its own volume of absolute alcohol. A sample of this solution is titrated with standard oxalic acid, litmus being used as an outside indicator (Note 3). The amount of oxalic acid (Note 4) necessary to form the acid salt is placed in a large evaporating dish and dissolved in 4 l. of 95 per cent alcohol. The amine solution is then slowly run into the acid with constant stirring. During the addition of the last half of the amine solution, the container must be cooled in order to avoid the formation of the neutral oxalate.

The resulting mixture is then heated on a steam cone or an air bath with constant stirring until the temperature of the mixture reaches 70°. The mixture is filtered, while hot, through a previously heated Büchner funnel. The filtrate is immediately placed in a large beaker or evaporating dish for the crystallization of the diacetonamine hydrogen oxalate (Note 5). The residue is treated with boiling alcohol and filtered, the filtrate containing a small additional quantity of the amine hydrogen oxalate. The mother liquor is distilled until nothing further passes over at 78° (Note 6), and the residue is allowed to stand for a day in a cool place. The crystals that separate are washed with cold absolute alcohol and dried. A total yield of 285–320 g. (63–70 per cent of the theoretical amount) of product that melts at 126–127° is obtained (Note 7).

2. Notes

1. The time required varies between three and eight hours, and the lower time limit is very materially favored when the reaction is carried out in the sunlight.
2. The period of three days seems to be the most desirable length of time to allow the reaction mixture to stand; the reaction is not complete in less time and the yields tend to become smaller if a much longer time is employed.
3. The volume of the diluted amine is usually between 800 and 860 cc. A 10-cc. portion of this may be conveniently drawn off with a pipette and usually requires from 35 to 50 cc. of 0.5 *N* oxalic acid.
4. The end point to litmus occurs when the neutral salt is formed. As the acid salt is desired, twice the amount of oxalic acid calculated above is used. This is usually between 230 and 260 g.
5. If the crystals are allowed to remain in contact with the mother liquor for several hours without filtering, they become somewhat dark in color. This color may be removed by washing with hot absolute alcohol.
6. The alcohol recovered in this way may be used as a solvent in subsequent runs. When about 3.5 l. of

alcohol has been distilled, the residue gives a small yield (10–15 g.) of dark crystals which must be washed several times with warm absolute alcohol to remove most of the color.

7. The product is entirely free from triacetonamine, triacetondiamine, and other troublesome condensation products, thus making its purification very simple. There is, however, a small quantity of ammonium hydrogen oxalate (1–1.2 per cent) mixed with this salt, but since it offers no difficulty when the product is used for synthetic purposes it is usually ignored. A small amount of ammonium salt has practically no effect on the melting point. It is possible to get pure diacetonamine hydrogen oxalate by recrystallizing from absolute alcohol.

3. Discussion

Diacetonamine can be prepared from a mixture of commercial acetone and calcium chloride by treatment with anhydrous ammonia;[1] from acetone and ammonia in the presence of a "promoter" such as ammonium nitrate;[2] and from mesityl oxide with aqueous ammonia[3] or liquid ammonia.[4]

References and Notes

1. Everest, J. Chem. Soc. **115**, 588 (1919).
2. Suzuki and Horie, Bull. Inst. Phys.-Chem. Research (Tokyo) **11**, 383 (1932) [C. A. **26**, 4302 (1932)].
3. Sokoloff and Latschinoff, Ber. **7**, 1387, 1776 (1874); Haeseler, J. Am. Chem. Soc. **47**, 1195 (1925).
4. Smith and Adkins, ibid. **60**, 408 (1938).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ammonium salt

Diacetonamine, acid oxalate

alcohol (64-17-5)

calcium chloride (10043-52-4)

ammonia (7664-41-7)

Oxalic acid (144-62-7)

acetone (67-64-1)

DIACETONAMINE HYDROGEN OXALATE (53608-87-0)

Mesityl oxide (141-79-7)

oxalate

amine hydrogen oxalate

triacetonamine

triacetondiamine

ammonium hydrogen oxalate (5972-72-5)

Diacetonamine

ammonium nitrate

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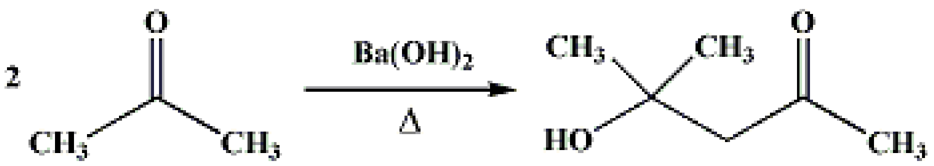
DIACETONE ALCOHOL

[2-Pentanone, 4-hydroxy-4-methyl-]



Submitted by J. B. Conant and Neal Tuttle.
Checked by Roger Adams and H. C. N. Heckel.

1. Procedure

A 2-l. round-bottomed flask is fitted with a rubber stopper carrying a Soxhlet extractor (Note 1) which in turn is fitted with an efficient reflux condenser. In the flask are placed 1190 g. (1500 cc., 20.5 moles) of commercial acetone (Note 2) and a few pieces of porous plate to produce even boiling. Two of the usual paper thimbles are placed in the extractor, one above the other. The lower one is filled nearly full of barium hydroxide; the top one is filled about three-quarters full of the same substance (Note 3), and the remainder of the space is filled with glass wool.

The flask is heated on a steam bath or in an oil bath. The heat is so regulated that the acetone refluxes back into the extractor rather rapidly. As the reaction proceeds the boiling point of the mixture rises and more steam has to be turned on or the temperature of the oil bath has to be raised. The flask should finally be lowered as far as possible into the cone of the steam bath. The reaction is complete when the liquid no longer boils when heated as hot as possible on the steam bath. This usually requires ninety-five to one hundred and twenty hours (Note 4). The refluxing may be interrupted at any time for as long as desired. The liquid in the flask has now a specific gravity of about 0.91 (20°) which corresponds to about 80 per cent of diacetone alcohol (Note 5). The only loss of material is by volatilization of the acetone through the top of the condenser; this generally amounts to several per cent.

The crude diacetone alcohol is purified by distillation. The 2-l. round-bottomed flask is fitted with a three-bulbed Glinsky fractionating column and a well-cooled condenser. The flask is heated in an oil bath, the temperature of which is gradually raised to 125°. The temperature of the bath is held at this point until no more acetone distils over, the temperature at the top of the column registering about 70° when the process is complete. The recovered acetone, containing a few per cent of diacetone alcohol, amounts to about 200 g. and can be used to prepare more material. The residual liquid has a specific gravity of 0.928 (20°) and contains about 95 per cent of diacetone alcohol. It is transferred to a 2-l. Claisen flask and distilled under reduced pressure (Note 6). A little acetone first comes over and then the diacetone alcohol distils smoothly at 71–74°/23 mm. The yield is 850 g. (71 per cent of the theoretical

amount based on the total acetone employed). The entire distillation requires about four hours.

2. Notes

1. Almost any form of a Soxhlet extractor and condenser will serve. It is advisable to use as much barium hydroxide as possible and to have the extractor empty as often and as completely as possible. The use of glass wool and care in filling the cups prevents any solid hydroxide from being carried down into the lower flask.
The use of tartaric acid in the flask has been recommended to neutralize any barium hydroxide that is carried down. This has been found unnecessary.
2. With some samples of commercial acetone containing considerable water, it has been found advisable to dry the acetone first with calcium chloride. This is usually not necessary.
3. If hydrated barium hydroxide $[Ba(OH)_2 \cdot 8H_2O]$ is used in the thimbles this becomes dehydrated after one run; the anhydrous form is just as satisfactory and may be used over and over again.
4. The time of refluxing depends on the rapidity with which the liquid boils and on the way in which the Soxhlet extractor empties. Similarly, the point at which the liquid ceases to boil will vary somewhat with the way in which it is heated. The amount of diacetone alcohol produced will, thus, vary somewhat in similar experiments. Refluxing for forty to fifty hours produces about a 70 per cent mixture which is perfectly suitable for preparing the pure product, except that more acetone is recovered unchanged.
5. Acetone and diacetone alcohol are in equilibrium with each other. The speed of both reactions is greatly accelerated by the presence of a base. The equilibrium mixture contains only a few per cent of diacetone alcohol, but the dissociation of diacetone alcohol to acetone proceeds so slowly in the absence of barium hydroxide that it is possible to increase the concentration to 80 per cent by this procedure.
6. The final distillation of diacetone alcohol must be carried out under reduced pressure as otherwise some of the material decomposes into acetone.

3. Discussion

Diacetone alcohol can be prepared from acetone by the action of alkali metal hydroxides,[1] calcium hydroxide,[2] and barium hydroxide.[3] Barium hydroxide reacts more rapidly than calcium hydroxide,[3] and was accordingly used in the procedure described.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 345

References and Notes

1. Heintz, Ann. **169**, 114 (1873); Locquin, Ann. chim. (9) **19**, 32 (1923); Thomson, U. S. pat. 1,654,103 [C. A. **22**, 787 (1928)]; Ellis, U. S. pat. 1,701,473 [C. A. **23**, 1419 (1929)].
2. Hoffman, Ger. pat. 229,678 [Frdl. **10**, 998 (1910–12)]; U. S. pat. 1,082,424 [C. A. **8**, 788 (1914)]; Edmonds, U. S. pat. 1,550,792 [C. A. **20**, 51 (1926)].
3. Kyriakides, J. Am. Soc. **36**, 534 (1914).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Diacetone alcohol

calcium chloride (10043-52-4)

acetone (67-64-1)

tartaric acid (87-69-4)

barium hydroxide (17194-00-2)

2-Pentanone, 4-hydroxy-4-methyl- (123-42-2)

hydroxide (14280-30-9)

calcium hydroxide

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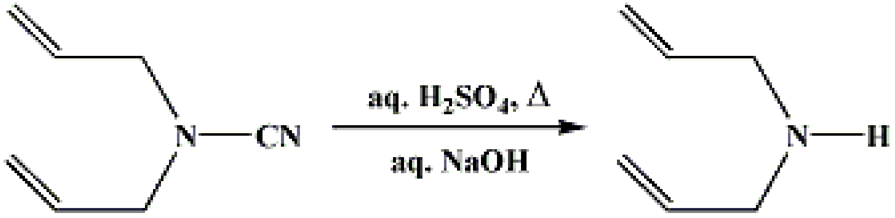
DIALLYLAMINE



Submitted by E. B. Vliet
Checked by Roger Adams and E. E. Dreger.

1. Procedure

A solution of 123 g. (67 cc., 1.2 moles) of sulfuric acid (sp. gr. 1.84) in 370 cc. of water is placed in a 2-l. round-bottomed flask equipped with a reflux condenser. To this is added 98.5 g. (0.81 mole) of diallylcyanamide (p. 203) and a few pieces of clay plate to prevent bumping. The mixture is refluxed gently for six hours. During the first fifteen minutes of heating, some bumping occurs. However, the mixture gradually becomes homogeneous and the boiling then proceeds smoothly (Note 1).

After six hours, the solution is cooled to room temperature and a cold solution of 192 g. (4.8 moles) of sodium hydroxide in 350 cc. of water is poured down the side of the flask so that most of it settles to the bottom without mixing with the solution in the flask. The flask is then connected to a condenser for downward distillation and is shaken to mix the two layers. The resulting free amine separates. The flask is heated and the amine, together with some water, distils. The distillation is continued until no amine separates from a test portion of the distillate. There is a small quantity of an oily liquid left floating in the flask. This is probably an impurity from the diallylcyanamide.

The weight of water in the distillate is estimated, and about one-half of this amount of potassium hydroxide is added in the form of sticks, so that it will dissolve slowly. The mixture should be kept cool while the potassium hydroxide is dissolving. Bubbles of ammonia gas will be evolved. When solution of the potassium hydroxide is complete, the amine is separated and dried for several hours over solid sodium hydroxide which has been freshly broken up into small lumps. It is then filtered into a distilling flask and distilled at atmospheric pressure. If the product has been thoroughly dried, there should be no low-boiling material. All the diallylamine should come over at 108–111° and only a very small amount of higher-boiling material should remain. The yield is 62–68 g. (80–88 per cent of the theoretical amount) (Note 2).

2. Notes

1. Alkali may be used for this hydrolysis instead of acid; but it is not so satisfactory, since the reaction mixture remains in two layers, thus causing the hydrolysis to proceed more slowly. Furthermore, any slight leak in the apparatus

during refluxing permits a loss of product.
2. This reaction represents a general method for the preparation of secondary amines; thus, di-*n*-butylamine has been obtained from di-*n*-butylcyanamide in yields of 75 per cent of the theoretical amount.

3. Discussion

Diallylamine can be prepared from allylamine with allyl bromide[1] or with allyl chloride.[2] Experiments on these methods showed that the resulting product contained relatively large amounts of mono- and triallylamine, and it was very difficult to isolate pure diallylamine. The procedure described from diallylcyanamide[3] is more satisfactory.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 159

References and Notes

1. Ladenburg, Ber. **14**, 1879 (1881).
2. Liebermann and Hagen, Ber. **16**, 1641 (1883).
3. Vliet, J. Am. Chem. Soc. **46**, 1307 (1924); "Versuche mit Diallylderivaten," Thesis by Paul Graf, Eidgen. Techn. Hochsch., Zürich, p. 29 (1922).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

mono- and triallylamine

sulfuric acid (7664-93-9)

ammonia (7664-41-7)

sodium hydroxide (1310-73-2)

Allyl bromide (106-95-6)

allyl chloride (107-05-1)

potassium hydroxide (1310-58-3)

Diallylamine (124-02-7)

Diallylcyanamide (538-08-9)

Allylamine (107-11-9)

di-n-butylamine (111-92-2)

di-n-butylcyanamide (2050-54-6)

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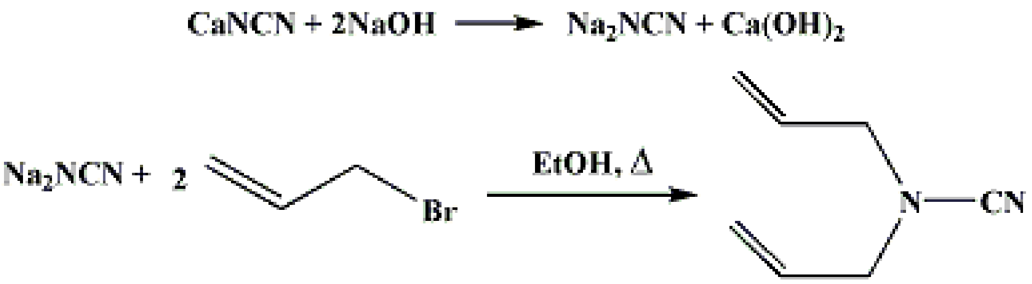
DIALLYLCYANAMIDE

[Cyanamide, diallyl-]



Submitted by E. B. Vliet
Checked by Roger Adams and E. E. Dreger.

1. Procedure

In a 5-l. round-bottomed, two-necked flask, fitted with a reflux condenser and a mechanical stirrer with a mercury seal, are placed 660 cc. of cold water and 135 g. of cracked ice. Two hundred grams (containing about 1.4 moles of pure calcium cyanamide) of fresh lime-nitrogen (Note 1) is added slowly, with stirring. As soon as the lime-nitrogen is suspended thoroughly in the water, a cold solution of 110 g. (2.75 moles) of sodium hydroxide in 200 cc. of water is added slowly, with stirring. Then the suspension is stirred quite briskly during one hour. If the temperature rises above 25°, small amounts of ice should be added (Note 2).

To the solution of sodium cyanamide thus prepared, 380 g. (3.14 moles) of allyl bromide (Note 3) and 660 cc. of 95 per cent alcohol are added. The mixture is then heated on a water bath with good stirring until it refluxes gently, and the heating and stirring are continued for two and one-half hours. Then the reflux condenser is replaced by one set downward for distillation. The stirring is continued and the alcohol is distilled until about 500 cc. has been collected. The distillate may be discarded or used for the recovery of alcohol (Note 4).

The reaction mixture is cooled to room temperature and filtered with suction through a large Büchner funnel. The residue is washed with alcohol. The filtrate which will be in two layers, is extracted twice with benzene, first with 270 cc. and then with 130 cc. The combined benzene extracts are dried with sodium sulfate and then filtered into a distilling flask. The benzene is distilled from a water bath, and then the diallylcyanamide is distilled under reduced pressure. It boils at 105–110°/18 mm.; at 128–133°/57 mm.; and at 140–145°/90 mm. There is a small residue of higher-boiling material. The yield of diallylcyanamide, boiling over a 5° range, is 90–97 g. (52–56 per cent of the theoretical amount based on the calcium cyanamide) (Note 5).

2. Notes

1. The lime-nitrogen used in this preparation should be the crude untreated product sold as fertilizer under the name "Cyanamid." It contains approximately 55 per cent calcium cyanamide, 20 per cent calcium oxide, 12 per cent graphite, and small amounts of various impurities. Lime-nitrogen should be protected from moisture when stored, in order to prevent slow polymerization to dicyanodiamide. It is advisable to use a fresh supply of lime-nitrogen for this synthesis.
2. Stirring for one hour in the cold permits the relatively insoluble calcium cyanamide to react with sodium hydroxide and go into solution as sodium cyanamide. If the temperature is not kept below 25° during this time, there is some tendency for polymerization to dicyanodiamide.
3. A good grade of allyl bromide should be used. A method for the preparation of allyl bromide is described on p. 27.
4. No allyl bromide is recovered. When water is added to the alcohol distillate, which would undoubtedly contain any unused allyl bromide, none separates. The excess probably reacts to form allyl alcohol. However, no attempt has been made to isolate it.
5. This represents a general procedure for the preparation of dialkylcyanamides; for example, di-*n*-butylcyanamide has been prepared in a similar manner, in yields of about 50 per cent of the theoretical amount.

3. Discussion

Diallylcyanamide can be prepared by the action of allyl bromide on disodium cyanamide.[1]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 201

References and Notes

1. Vliet, J. Am. Chem. Soc. **46**, 1307 (1924); U. S. pat. 1,659,793 [C. A. **22**, 1365 (1928)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

calcium cyanamide

sodium cyanamide

graphite

dicyanodiamide

disodium cyanamide

alcohol (64-17-5)

Benzene (71-43-2)

sodium hydroxide (1310-73-2)

Allyl bromide (106-95-6)

Allyl alcohol (107-18-6)

sodium sulfate (7757-82-6)

Diallylcyanamide, Cyanamide, diallyl- (538-08-9)

calcium oxide

di-n-butylcyanamide (2050-54-6)

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DIBENZOYLMETHANE

[1,3-Propanedione, 1,3-diphenyl-]

$$C_6H_5CHBrCHBrCOC_6H_5 + 2NaOCH_3 \longrightarrow C_6H_5C(OCH_3){=\!=}CHCOC_6H_5 + CH_3OH + 2NaBr$$

$$C_6H_5C(OCH_3){=\!=}CHCOC_6H_5 + H_2O(HCl) \longrightarrow C_6H_5C(OH){=\!=}CHCOC_6H_5 + CH3OH$$

$$C_6H_5C(OH){=\!=}CHCOC_6H_5 \rightleftharpoons C_6H_5COCH_2COC_6H_5$$

Submitted by C. F. H. Allen, R. D. Abell, and J. B. Normington.
Checked by Roger Adams and P. R. Shildneck.

1. Procedure

In a 2-l. three-necked, round-bottomed flask, fitted with a stirrer, reflux condenser, and dropping funnel, are placed 184 g. (0.5 mole) of benzalacetophenone dibromide (Note 1) and 165 cc. of methyl alcohol (Note 2). A solution of sodium methoxide, previously prepared (Note 3) from 23 g. (1 atom) of sodium and 230 cc. of absolute methyl alcohol (p. 249), is added rapidly to the stirred solution, and the mixture is then refluxed for one hour.

Sufficient concentrated hydrochloric acid (about 8 cc.) is added to neutralize the mixture, and then an additional 4 cc. After refluxing for five minutes (Note 4), 160 cc. of cold water is added, and the flask is cooled by ice water. The cooling and rapid stirring induce the formation of small crystals which are separated by filtration and washed once with 50 cc. of cold 50 per cent methyl alcohol and then with water until free of acid. The yield of crude, air-dried, dibenzoylmethane is 83–89 g. (74–80 per cent of the theoretical amount). The crude product is very pure but, if desired, may be recrystallized from 150 cc. of hot methyl alcohol. The first crop, obtained by cooling to 0°, weighs 74–80 g. (66–71 per cent of the theoretical amount) and melts at 77–78° (Note 5). Partial evaporation of the solvent yields 3–5 g. of less pure product (Note 6).

2. Notes

1. The yield depends somewhat upon the quality of the dibromide. The product which gave the results described in the procedure was prepared by dissolving 208 g. (1 mole) of benzalacetophenone (p. 78) in 600 cc. of carbon tetrachloride or carbon disulfide, cooling the solution in an ice bath, and adding with stirring 160 g. (51.2 cc., 1 mole) of bromine. After the reaction was complete, the dibromide was filtered off and washed with two 250-cc. portions of hot alcohol. The product obtained in this way melted at 156–157° and weighed about 310 g.
2. Pure methyl alcohol is essential. Synthetic methyl alcohol of 99 per cent purity is satisfactory. Methyl alcohol from wood distillation must be made absolute, by heating with quicklime or by some other means.
3. The time required for the preparation of the sodium methoxide solution is significantly reduced if all the sodium, cut in small pieces (about 1 cm. or less), is placed in a flask which is attached to a reflux condenser and immersed in cold water, and the alcohol added slowly through the condenser. When the initial vigorous reaction moderates, the cooling bath can be removed. The time required is about one-half hour.
4. Prolonged heating with mineral acids should be avoided because of extensive hydrolysis to benzoic acid and acetophenone.
5. In one experiment, the checkers first obtained a product of needle-like crystals which melted

at 71–72°. On standing overnight, the pure compound melting at 77–78° formed.
6. If, instead of partial evaporation to obtain the second crop of product, the mother liquor is thrown into water and the resulting oil taken up in ether, and the ether solution shaken with a saturated aqueous solution of copper acetate, about 8 g. of the light green copper derivative is obtained. When this copper salt of dibenzoylmethane is suspended in a solution of 20 cc. of concentrated sulfuric acid and 80 cc. of water and shaken intermittently with 70 cc. of ether, solution takes place and the separated ether layer after drying over calcium chloride and evaporating to dryness under reduced pressure yields about 6 g. of dibenzoylmethane melting at 77–78°.

3. Discussion

Dibenzoylmethane can be prepared by the hydrolysis of dibenzoylacetic acid;[1] by the slow spontaneous decomposition of acetyl dibenzoylmethane;[2] by the action of metallic sodium,[3] sodium ethoxide,[3] sodium methoxide,[4] alcoholic potash,[4] or sodamide[5] on mixtures of acetophenone and ethyl benzoate; by the action of alcoholic potash,[6] sodium methoxide,[7] or sodium ethoxide[8] on benzalacetophenone dibromide; by the action of sodamide on acetophenone and ethyl benzoate in ether;[9] and by the action of sodium ethoxide on certain alkyl benzoates.[10]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 244
- Org. Syn. Coll. Vol. 3, 125
- Org. Syn. Coll. Vol. 3, 251

References and Notes

1. Baeyer and Perkin, Ber. **16**, 2134 (1883); Perkin, J. Chem. Soc. **47**, 250 (1885).
2. Claisen, Ann. **291**, 83 (1896).
3. Claisen, Ann. **291**, 52 (1896).
4. Bülow and von Sicherer, Ber. **34**, 2372 (1901).
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6. Wislicenus, Ann. **308**, 219 (1899); Abell, J. Chem. Soc. **101**, 1002 (1912).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

dibromide

copper derivative

copper salt of dibenzoylmethane

alcoholic potash

alcohol (64-17-5)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

methyl alcohol (67-56-1)

ether (60-29-7)

bromine (7726-95-6)

carbon tetrachloride (56-23-5)

Benzoic acid (65-85-0)

Benzalacetophenone (94-41-7)

Acetophenone (98-86-2)

sodium methoxide (124-41-4)

sodium, metallic sodium (13966-32-0)

sodium ethoxide (141-52-6)

carbon disulfide (75-15-0)

Dibenzoylmethane, 1,3-Propanedione, 1,3-diphenyl- (120-46-7)

Benzalacetophenone dibromide (611-91-6)

copper acetate (142-71-2)

dibenzoylacetic acid

acetyl dibenzoylmethane

ethyl benzoate (93-89-0)

sodamide (7782-92-5)

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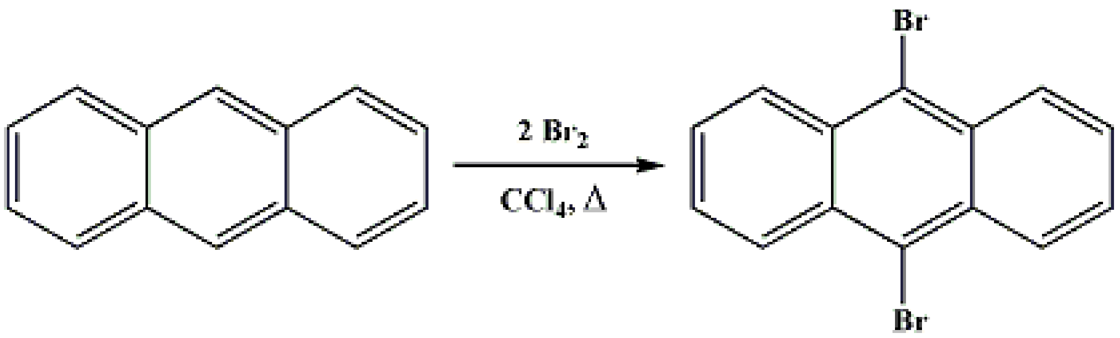
9,10-DIBROMOANTHRACENE

[Anthracene, 9,10-dibromo-]



Submitted by I. M. Heilbron and J. S. Heaton.
Checked by H. T. Clarke and T. F. Murray.

1. Procedure

To a suspension of 300 g. (1.35–1.43 moles) of anthracene of 80–85 per cent purity in 3 l. of carbon tetrachloride (Note 1), in a 5-l. flask fitted with dropping funnel, stirrer, and reflux condenser, is added slowly 567 g. (182 cc., 3.55 moles) of bromine. The bromination takes place in the cold with separation of the sparingly soluble 9,10-dibromoanthracene; in order to prevent undissolved anthracene from becoming coated over, it is necessary to maintain vigorous stirring throughout the reaction. A tube from the top of the condenser conducts hydrogen bromide to cold water, in which it is absorbed (Note 2). The addition of the bromine occupies about one-half hour; the rate is so adjusted that a minimum of bromine is carried over with the hydrogen bromide.

When all the bromine has been added, the mixture is gently warmed on a steam bath with continual stirring, care being taken not to heat so rapidly as to cause undue loss of bromine by entrainment. Heating is continued until the mixture has boiled gently for one hour. The mixture is then allowed to cool for some hours, without stirring, and the crude dibromoanthracene is filtered off, washed with a little cold carbon tetrachloride, and dried. In this way 270-425 g. of a bright yellow product, which melts (Note 3) at 218–219° (corr.), is obtained. On concentrating the mother liquors, 15–150 g. more of crude material, m.p. about 216° (corr.), can be obtained.

To prepare a purer product, the crude dibromoanthracene is extracted with carbon tetrachloride (Note 4) in an apparatus similar to that described on p. 375, the extraction is carried to the point at which crystals just begin to separate from the boiling solvent, and a fresh quantity of carbon tetrachloride is then taken. About eight extractions are necessary, 1 l. being used each time. The 9,10-dibromoanthracene so purified consists of brilliant yellow needles melting at 221–222° (corr.) (Note 5). A further quantity of pure product may be obtained by concentrating the mother liquor and recrystallizing

the second crop so obtained. The recovered solvent may be employed for further extractions. The yield amounts to 400–420 g. (83–88 per cent of the theoretical quantity based on anthracene of 85 per cent purity).

2. Notes

1. The reaction may be carried out equally well with a larger proportion of solvent, but if less than the amount indicated is taken, difficulty may arise in stirring. Carbon disulfide may be employed instead of carbon tetrachloride, but this solvent presents no essential advantages and it is necessary to use a larger volume for the same amount of anthracene.

2. The watery solution of hydrogen bromide, on fractional distillation, readily yields 48 per cent hydrobromic acid, boiling at 125–126° /760 mm. (p. 26).

3. The observed melting points of the various products are 5–6° lower than the corrected values.

4. The crude product may be recrystallized from toluene, in which it is somewhat more soluble than in carbon tetrachloride; the color of the product is, however, not quite so light, although the melting point is as high as if carbon tetrachloride were used. If desired, recrystallization may be effected from toluene without using the extraction apparatus, in which case about 10 l. of solvent in all will be required; for the filtration of the hot solution, a plug of glass wool, previously wetted with boiling toluene, may be employed, care being taken to warm the funnel adequately.

The bromination products of the impurities with which commercial anthracene is contaminated appear to be more soluble in carbon tetrachloride than is 9,10-dibromoanthracene; the yield can be slightly increased by fractional recrystallization of the products contained in the original mother liquor, but under laboratory conditions the gain does not compensate for the time involved.

5. When crystallized from xylene, samples have been obtained that melt as high as 226° (uncorr.) (E. de Barry Barnett, private communication).

3. Discussion

9,10-Dibromoanthracene can be prepared by the bromination of anthracene in dilute carbon disulfide solution.[1]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

HYDROBROMIC ACID, hydrogen bromide (10035-10-6)

bromine (7726-95-6)

carbon tetrachloride (56-23-5)

toluene (108-88-3)

carbon disulfide (75-15-0)

9,10-Dibromoanthracene, Anthracene, 9,10-dibromo- (523-27-3)

anthracene (120-12-7)

dibromoanthracene

xylene (106-42-3)

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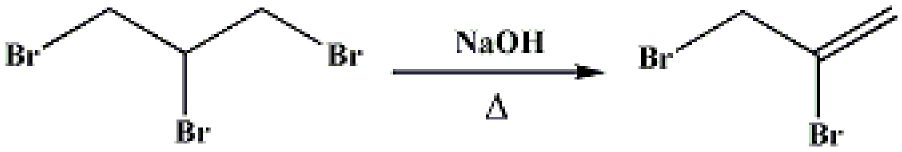
Organic Syntheses, CV 1, 209

2,3-DIBROMOPROPENE

[Propene, 2,3-dibromo-]



Submitted by R. Lespieau and M. Bourguel.
Checked by C. S. Marvel, John R. Johnson, and W. L. McEwen.

1. Procedure

A 500-cc. round-bottomed flask is connected by a wide, bent glass tube to an efficient condenser, which is provided with an adapter leading into a 500-cc. receiving flask immersed in an ice bath. Two hundred grams (0.71 mole) of 1,2,3-tribromopropane (Note 1) and 10 cc. of water are placed in the reaction flask, and 50 g. (1.25 moles) of sodium hydroxide (Note 2) in small lumps (not pulverized) is added at once with shaking. The mixture warms up and the flask is immediately connected to the apparatus and heated directly by means of a Bunsen burner held in the hand. It is advisable to use a slightly luminous flame about 15 cm. high and to heat with a rotary motion, directing the flame against the sides of the flask.

The mixture is shaken occasionally, and the alkaline layer soon becomes partly emulsified. Heat is applied until vigorous ebullition occurs, whereupon a spontaneous distillation of the reaction product takes place (Note 3). When the reaction slackens, the flask is heated as before. The mass becomes solid as the volatile products are removed. This solid mass, which is brownish in color, is heated until no more liquid distils (Note 4). The entire operation up to this point requires twenty to thirty minutes.

The distillate in the receiving flask separates into two layers: an upper layer of water; and a heavy layer of colorless oil, consisting of a mixture of 2,3-dibromopropene and unchanged tribromopropane. The distillate is transferred to a 500-cc. separatory funnel and thoroughly agitated with an additional 150 cc. of water (Note 5). The lower layer is decanted and found to weigh 140–145 g. It is subjected to a preliminary distillation under reduced pressure to separate most of the unchanged tribromopropane. The material that passes over below 95° /75 mm. consists of 2,3-dibromopropene containing a small amount of water and tribromopropane, and weighs 120–130 g. The residue in the distilling flask consists of unchanged tribromopropane (15–25 g.) (Note 6).

The crude product is dried over calcium chloride and fractionally distilled under reduced pressure (Note 7). The yield of pure, colorless, 2,3-dibromopropene boiling at 73–76° /75 mm. is 105–120 g. (74–84 per cent of the theoretical amount). A small

quantity of tribromopropane, usually about 5 per cent of the crude material, remains in the distilling flask (Note 6).

2. Notes

1. The crude tribromopropane, obtained as described on p. 521, may be used without lowering the yield.
2. Potassium hydroxide may be used in place of sodium hydroxide, but it was found that the reaction is much more violent and irregular and the yields are somewhat lower. If potassium hydroxide is used, it is advisable to provide the receiving flask with a reflux condenser to avoid loss when the initial violent reaction occurs. Since the reaction is so rapid, it would be very dangerous to use more than 200 g. of tribromopropane in a single run with potassium hydroxide.
3. In the initial vigorous ebullition, about one-half of the material distils during a few minutes and it is necessary to wait for this reaction to slacken before continuing to heat the flask. If sodium hydroxide is used, the reaction is vigorous but not violent, and it is possible to use 600 g. of tribromopropane in a 1-l. flask in a single run without danger if the reaction flask is connected with the condenser by means of a wide tube. The yields in larger runs are as good as when smaller runs are made.
4. A small additional quantity of distillate may be obtained by partially evacuating the apparatus, after replacing the adapter and receiving flask by a 250-cc. distilling flask. The amount of material obtained in this way amounts to only 1–2 g. if the reaction flask has been properly heated. It is well to note that flasks which have been repeatedly heated with very strong alkalies become fragile, and care should be used not to reduce the pressure too greatly.
5. The dibromopropene and the wash water have a strong lachrymatory effect and should be manipulated carefully.
6. When a sufficient quantity of these crude residues of tribromopropane has been collected, it may be used for preparing 2,3-dibromopropene. If allowance is made for this recovered material, the yield of 2,3-dibromopropene is 82–87 per cent of the theoretical amount.
7. The separation of 2,3-dibromopropene from tribromopropane is effected easily since their boiling points are quite different:

Pressure	2,3-Dibromopropene	Tribromopropane
18 mm.	42–43°	101–102°
75 mm.	75–76°	140–142°
760 mm.	140–143°	219–221°

These substances may be distilled under atmospheric pressure with only slight decomposition, but the products become highly colored on standing.

3. Discussion

2,3-Dibromopropene can be prepared by the action of potassium[1] or sodium hydroxide[2] on tribromopropane, and by the action of metallic sodium on an ethereal solution of tribromopropane.[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 186
- Org. Syn. Coll. Vol. 5, 121
- Org. Syn. Coll. Vol. 5, 124

References and Notes

1. Reboul, Ann. chim. phys. (3) **60**, 42 (1860); Lespieau, ibid. (7) **11**, 235 (1897); Bull. soc. chim. (4) **29**, 530 (1921); Henry, Ann. **154**, 371 (1870); Ber. **14**, 404 (1881).
2. Lespieau, Ann. chim. phys. (7) **11**, 235 (1897); Bull. soc. chim. (4) **29**, 530 (1921).
3. Tollens, Ann. **156**, 168 (1870).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

calcium chloride (10043-52-4)

sodium hydroxide (1310-73-2)

potassium hydroxide (1310-58-3)

metallic sodium (13966-32-0)

potassium (7440-09-7)

2,3-Dibromopropene, Propene, 2,3-dibromo- (513-31-5)

dibromopropene (13195-80-7)

1,2,3-Tribromopropane (96-11-7)

tribromopropane

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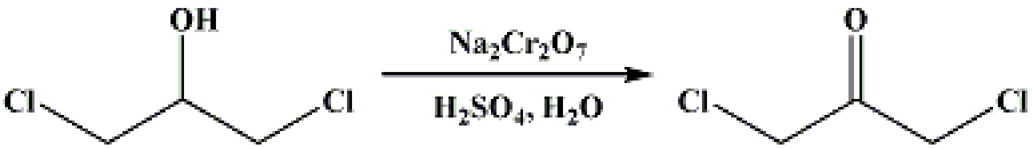
α,γ-DICHLOROACETONE

[2-Propanone, 1,3-dichloro-]



Submitted by J. B. Conant and O. R. Quayle.
Checked by O. Kamm, A. D. Dox, and L. Yoder.

1. Procedure

In a 2-l. flask are placed 375 g. (1.3 moles) of commercial sodium dichromate (Note 1), 225 cc. of water, and 300 g. (2.3 moles) of glycerol α,γ-dichlorohydrin (p. 292) (b. p. 68–75°/14 mm.). The flask is set in a water bath and equipped with a thermometer and a mechanical stirrer (Note 2). The contents are vigorously stirred, and 450 g. (245 cc.) of concentrated sulfuric acid, diluted with 115 g. of water, are introduced during the course of seven to eight hours. It is convenient to add the acid at ten-minute intervals. The temperature is kept between 20° and 25° during the entire reaction; this is accomplished by adding a little ice to the water bath from time to time. The stirring is continued for sixteen to seventeen hours after all the acid has been added; as there is very little heat evolved during this part of the reaction, the water bath may be allowed to come to room temperature (Note 3).

Sufficient water (300–800 cc.) is now added to the mixture to dissolve the pasty chromium salts (Note 4). The mass of crystals is then rapidly filtered on a Büchner funnel and sucked as dry as possible. The crystals are then transferred to a small laboratory centrifuge and centrifuged for several minutes. The crystals are washed in the centrifuge with about 15–25 cc. of ice water, then with 10–15 cc. of cold petroleum ether, and finally centrifuged until as dry as possible (Note 5). The crude dichloroacetone is dried in a vacuum desiccator over sulfuric acid overnight. It weighs about 220 g.

The crude product is best purified by distillation from a 250-cc. distilling flask fitted with an air condenser. A very small fraction (10–15 g.) of low-boiling material is obtained, and the dichloroacetone (170–175°) is then collected. It solidifies in the receiver to a white crystalline mass which weighs 200–220 g. (68–75 per cent of the theoretical amount). A few grams more may be obtained by chilling the low-boiling fraction and filtering off the water.

2. Notes

1. Commercial sodium dichromate is hygroscopic and contains varying amounts

of water. The 375 g. required in these directions is equivalent to 319 g. of anhydrous material.

2. Great caution should be exercised in working with dichloroacetone, as it is extremely lachrymatory and blisters the skin.

3. The total time required for the oxidation is twenty-four hours. It is convenient to start the reaction in the morning. In this way the last part of the reaction, which requires no attention, will be accomplished during the night. The regulation of the temperature is necessary, as the reaction proceeds very slowly below 20°; on the other hand, the dichloroacetone itself is oxidized at a somewhat higher temperature than 25°.

4. In transferring the crystals from the reaction flask to the Büchner funnel it is necessary to use a certain amount of water to dissolve the pasty chromium salts which are otherwise quite impossible to filter. The amount necessary varies greatly in different runs, according to the manner in which the chromium salts separate. The amount of this water is kept low in order to dissolve as little of the product as possible. Nevertheless, 10–15 g. of dichloroacetone are thus dissolved; this material, together with a little unchanged dichlorohydrin, may be recovered by a long procedure involving extraction with ether and sodium bisulfite. This is not profitable, however.

5. It is not necessary to wash the crystals in the centrifuge until they are white. A small amount of chromic salt will not interfere with the subsequent purification.

3. Discussion

α,γ-Dichloroacetone can be prepared by the direct chlorination of acetone;[1] by the oxidation of glycerol α,γ-dichlorohydrin;[2] by the action of hypochlorous acid on 2,3-dichloropropene;[3] and by the action of sulfur monochloride on epichlorohydrin.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 292

References and Notes

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2. Glutz and Fischer, Jahresber. 531 (1871); J. prakt. Chem. (2) **4**, 52 (1871); Markownikov, Ber. **6**, 1210 (1873); Ann. **208**, 355 (1881); Hoermann, Ber. **13**, 1706 (1880); Grimaux and Adam, Bull. soc. chim. (2) **36**, 19 (1881); Clöez, Ann. chim. phys. (6) **9**, 145 (1886); Erlenbach, Ann. **269**, 46 (1892); Posner and Rohde, Ber. **42**, 3233 (1909).
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4. Malinovskii, J. Gen. Chem. (U.S.S.R.) **9**, 832 (1939) [C. A. **34**, 375 (1940)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

Glycerol α,γ-dichlorohydrin

chromium salts

dichlorohydrin

chromic salt

sulfuric acid (7664-93-9)

ether (60-29-7)

Epichlorohydrin (106-89-8)

sodium bisulfite (7631-90-5)

acetone (67-64-1)

sodium dichromate (7789-12-0)

hypochlorous acid (7790-92-3)

α,γ-Dichloroacetone, 2-Propanone, 1,3-dichloro- (534-07-6)

dichloroacetone (513-88-2)

2,3-dichloropropene (78-88-6)

sulfur monochloride

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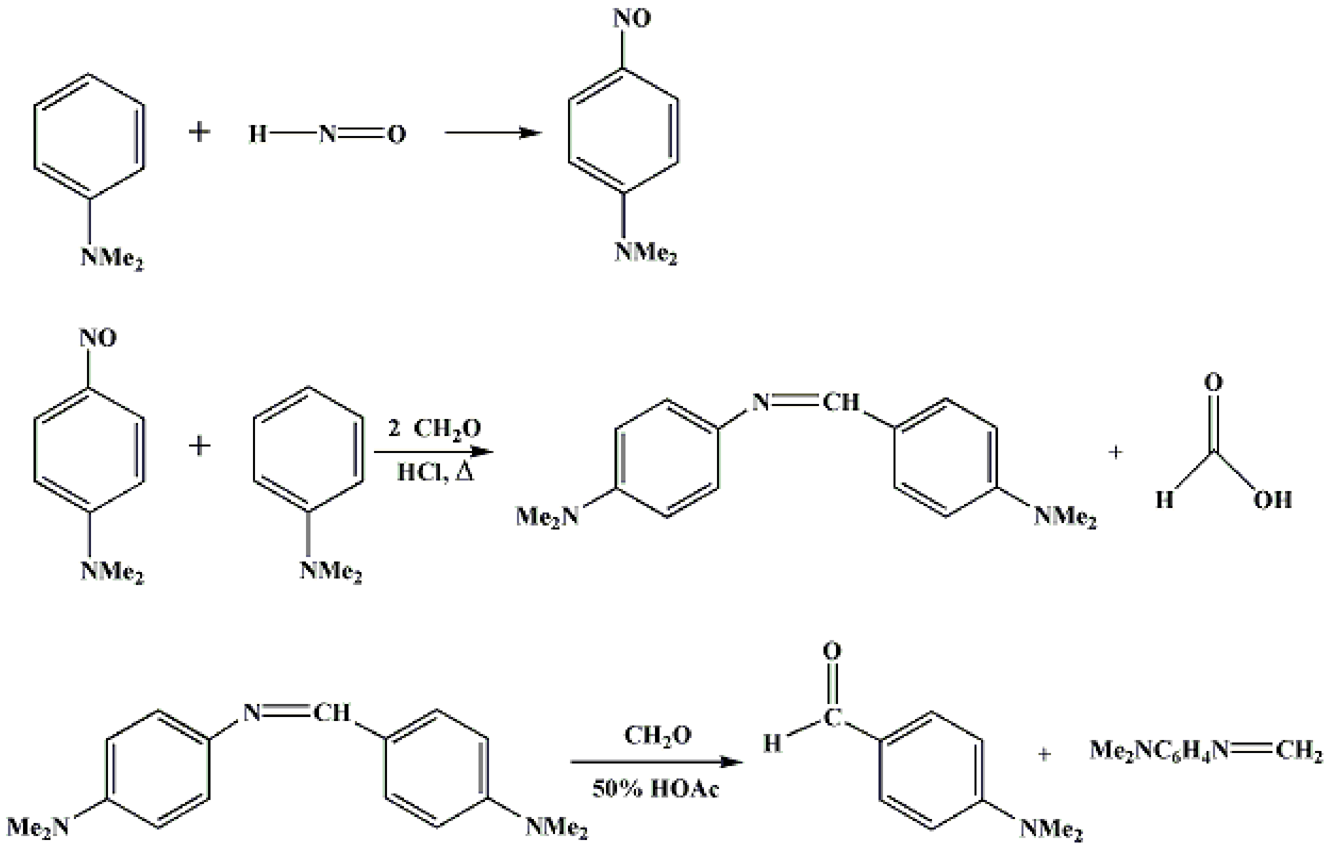
p-DIMETHYLAMINOBENZALDEHYDE

[Benzaldehyde, *p*-dimethylamino-]



Submitted by Roger Adams and Gerald H. Coleman.
Checked by H. T. Clarke and W. W. Hartman.

1. Procedure

In a 3-l. round-bottomed flask fitted with a mechanical stirrer 150 g. (1.24 moles) of technical dimethylaniline is dissolved in 750 cc. of dilute hydrochloric acid (1 part concentrated acid to 1 part water). This solution is now cooled to 0°, and a solution (previously cooled to 0°) of 90 g. (1.24 moles) of technical sodium nitrite in 150 cc. of water is added through a separatory funnel. During the addition of the nitrite solution, mechanical stirring should be employed and the flask cooled well with ice and salt, or the contents can be cooled directly by the addition of ice. The addition is made at such a rate (thirty to forty minutes) that the temperature does not rise above 5°. The precipitate of *p*-nitrosodimethylaniline hydrochloride is filtered off with suction, then washed with about 300 cc. of dilute (1:1) hydrochloric acid.

In a 2-l. beaker, 180 g. (1.5 moles) of technical dimethylaniline, 125 cc. of formaldehyde (technical 40 per cent) (see Note 1 on p. 378), and 300 cc. of concentrated hydrochloric acid are mixed and heated for ten minutes on a steam bath. The mixture is now placed in a hood and the *p*-nitrosodimethylaniline hydrochloride added all at once, or as rapidly as possible. The beaker is then covered with a watch glass. A vigorous reaction soon occurs and is complete in about five minutes. The resulting solution is transferred to a 5-l. flask and diluted to 4 l.; stirring is started, and a 25 per cent solution of sodium hydroxide is added until the red color disappears (about 650 cc. is required). The yellow benzylidene compound separates, is filtered with suction, and washed with water. The moist precipitate is transferred to a 4-l. glass jar, covered with 1 l. of 50 per cent acetic acid and 250 cc. of formaldehyde, and stirred until twenty minutes after the benzylidene compound has gone into solution. While the mixture is being stirred vigorously (Note 1) to prevent lumping of the precipitate, 400 cc. of water and 200 g. of cracked ice are added during the course of five minutes. The dimethylaminobenzaldehyde generally separates gradually in fifteen to twenty minutes, but in some cases does not. If the precipitate does not form, the solution is placed in a refrigerator for a few hours or overnight. The mixture is filtered with suction and washed at least ten times with 300-cc. portions of water

(Note 2). The precipitate is sucked as dry as possible for fifteen to thirty minutes (Note 3).

The slightly moist aldehyde is distilled under diminished pressure from an oil bath, by means of a 1-l. Claisen flask (Note 4). A small amount of water comes over first, then the thermometer rises rapidly to the boiling point of the aldehyde (180°/22 mm.). In changing receivers between the water fraction and the aldehyde, care should be taken to keep the side arm of the distilling flask warm; otherwise, on starting the distillation again, the aldehyde will solidify in the side arm and cause trouble. It is advisable not to collect the very last portion of the distillate with the main portion, as the former is frequently quite red. This is best added to crude material from another run. The main distillate is dissolved in 100 cc. of alcohol in a 2-l. beaker, then 1 l. of water is gradually added with vigorous mechanical stirring to prevent lumping. The aldehyde separates, and is filtered with suction. The product, when dry, weighs 125–130 g. (56–59 per cent of the theoretical amount) and melts at 73°.

The aldehyde prepared in this way is in the form of small granular crystals, which vary in different runs from a flesh color to a lemon yellow. For practically all purposes, this slightly colored product is entirely satisfactory and is essentially pure, as can be judged by the melting point. For reagent purposes it is desirable to remove the color completely, particularly since the product obtained as just described has a tendency to take on a reddish tinge on exposure to light. Further purification can be accomplished by dissolving the aldehyde (it dissolves slowly) in dilute hydrochloric acid (1 part of concentrated acid, sp. gr. 1.19, to 6 parts of water), 125 g. of aldehyde requiring 700 cc. of the acid (Note 5). The solution is placed in a jar and diluted with half its volume of water, and dilute sodium hydroxide solution (15–20 per cent) (Note 6) is added slowly with mechanical stirring. At the beginning, the aldehyde comes down slightly colored. After about 10–30 g. are precipitated, however, the product appears white (Note 7); this point can be readily seen. The first precipitate is filtered off and added to the next run of crude material or fractionally precipitated again from hydrochloric acid (Note 2). The rest of the aldehyde is now precipitated by means of more sodium hydroxide solution, and comes down almost white. At the very end of the neutralization, particularly if the original product was quite yellow, the last 4–5 g. of aldehyde should be precipitated separately, as this is inclined to be slightly colored. If too much alkali is added towards the end of the neutralization, a brown color appears, but the addition of a little hydrochloric acid will destroy this color. The main portion of the precipitate is filtered and dried; it weighs 95–100 g. and melts at 73°. The succeeding runs yield 115–128 g. of finished product, on account of the extra crude material obtained from the distillation and reprecipitation of the previous run (Note 8).

2. Notes

1. Vigorous mechanical stirring must be employed during the precipitation of the crude aldehyde, as otherwise large lumps are formed which make washing difficult.
2. Thorough washing of the crude aldehyde is particularly desirable, as it removes a reddish impurity which tends to distil over and color the product lemon yellow or sometimes even brownish yellow. When such a brownish product is obtained, it is quite necessary to make a second precipitation later, as well as to observe the directions mentioned in the purification of the crude aldehyde, namely, to precipitate the first few grams and the last few grams of the aldehyde separately. The precaution of rejecting the first and last portions of the precipitate is unnecessary in the reprecipitation. In the reprecipitation of a deeply colored product, the portion of aldehyde at the end may be even purplish in color, and particular care must be taken to keep this separate.
3. A previous investigator has mentioned that the crude product must be dried before distilling. This, however, is unnecessary.
4. If the aldehyde is dried before distilling, a 500-cc. distilling flask may be used.
5. In purifying the aldehyde by dissolving in acid and reprecipitating, it is essential not to use stronger acid than that specified (1:6), as stronger acid causes a deepening of the color of the solution. If the concentrated acid, which is to be diluted and used in this procedure, does not have a sp. gr. of 1.19, it will be necessary to add the equivalent amount of weaker acid in order to dissolve the *p*-dimethylaminobenzaldehyde.
6. Sodium carbonate may be used in place of sodium hydroxide for precipitation, but it causes much foaming.
7. The aldehyde that is obtained without reprecipitation gradually takes on a pinkish tinge on exposure to light. After the reprecipitation, however, this characteristic disappears.
8. When the apparatus for distilling, etc., is all set up, a run such as described requires about five to six hours for completion.

3. Discussion

The most satisfactory method for the preparation of *p*-dimethylaminobenzaldehyde is the condensation of dimethylaniline, formaldehyde and *p*-nitrosodimethylaniline, followed by hydrolysis,[1] a method for which details have been perfected.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 331

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

acid

alcohol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

sodium hydroxide (1310-73-2)

formaldehyde (630-08-0)

sodium carbonate (497-19-8)

sodium nitrite (7632-00-0)

dimethylaniline (121-69-7)

benzylidene

dimethylaminobenzaldehyde

p-Dimethylaminobenzaldehyde, Benzaldehyde, p-dimethylamino- (100-10-7)

p-Nitrosodimethylaniline hydrochloride (42344-05-8)

p-nitrosodimethylaniline (138-89-6)

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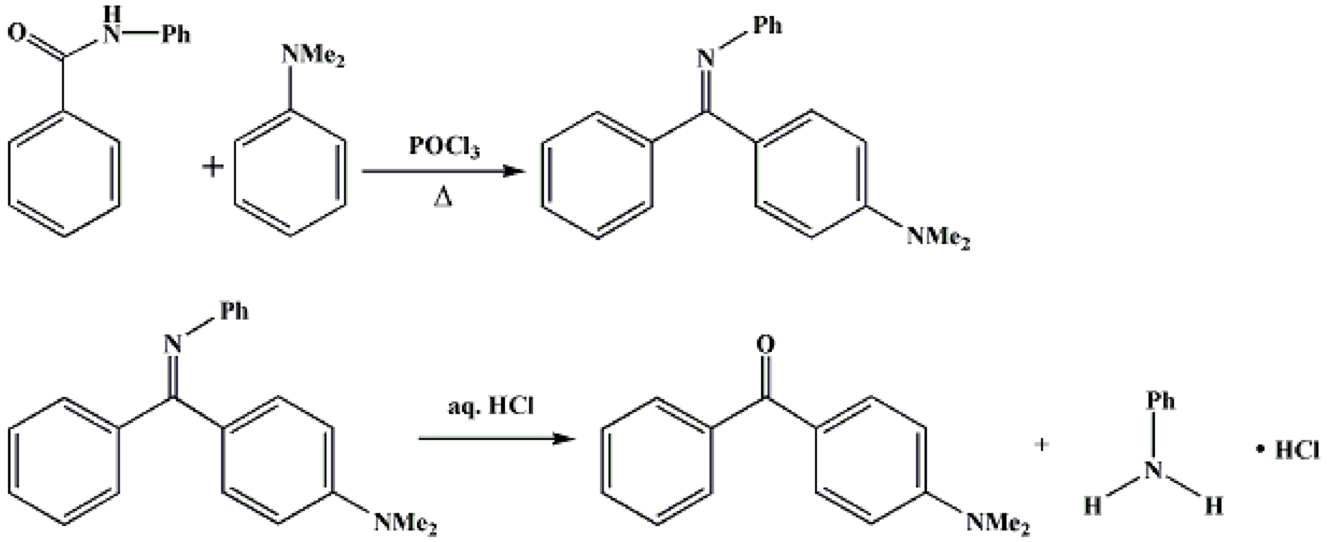
Organic Syntheses, *CV 1*, *217*

p-DIMETHYLAMINOBENZOPHENONE

[Benzophenone, *p*-dimethylamino-]



Submitted by Charles D. Hurd and Carl N. Webb.
Checked by C. S. Marvel and P. L. Salzberg.

1. Procedure

Five hundred grams (2.5 moles) of dry, powdered benzanilide (p. 82), 1025 g. (8.5 moles) of technical dimethylaniline, and 525 g. (307 cc., 3.4 moles) of phosphorus oxychloride are mixed (Note 1) in a 3-l. round-bottomed Pyrex flask (Note 2). The flask is fitted with a two-holed cork stopper which carries a reflux condenser and a thermometer. The top of the condenser is provided with a calcium chloride tube; the bulb of the thermometer reaches beneath the surface of the liquid.

The flask is warmed in a water bath until the appearance of a sudden exothermic reaction (Note 3), at which point the flask must be cooled at once by rotating it underneath the surface of cold water. The cooling is continued until the thermometer indicates a temperature of 125° or less. The flask is then immersed in a bath of boiling water for about three hours, after which the mixture is cooled to about 50°, and poured slowly into 2.5 l. of warm (Note 4) dilute hydrochloric acid, made from 325 cc. (about 4 moles) of concentrated acid, contained in a large crock of about 15 l. (4 gal.) capacity. The mixture is left for about three hours until hydrolysis is complete (Note 5).

About 8 l. of water is added to precipitate the *p*-dimethylaminobenzophenone. The solution, milky at first, soon deposits sandy crystals of light green color, which are collected on a 20-cm. Büchner funnel. They are transferred to a beaker and washed with 1.5 l. of water, after which they are again collected on the filter, washed, pressed as dry as possible, and air dried. With no further purification the melting point is 88–90°. The yield is 350–390 g. An additional 85–100 g. of inferior product, m.p. 70–80°, is obtained by treating the combined filtrates with a solution of 250 g. (6.2 moles) of sodium hydroxide. This product, air-dried as before, is dissolved in 300–400 cc. of hot alcohol from which, by partial evaporation and cooling, more than half separates in good crystalline form, m.p. 88–90.5°. This material may be combined with the first product of similar melting point. The total yield is 410–440 g. (72–77 per cent of the theoretical amount) (Note 6).

The crude product melts fairly sharply, but it is colored light green. The color may be almost completely removed by recrystallization from hot alcohol. The best result is obtained by dissolving 100 g. of the crude product in 600 cc. of boiling alcohol, heating with 5 g. of decolorizing carbon (Norite), filtering, and cooling the solution in an ice-salt bath. The crystals are then separated from the mother liquor by centrifuging (Note 7). The yield of almost colorless crystals melting at 89.5–90.5° is 80 g.

2. Notes

1. This causes an elevation in temperature to about 50°.
2. Pyrex is essential to avoid breakage when the hot flask is cooled rapidly.
3. This exothermic reaction usually begins at 90–110°, and the temperature rises in a few seconds to about 180°. In smaller runs, e.g., with 100 g. of benzanilide, it is not advisable to cool the flask before the temperature has reached about 180°, as some benzanilide may remain unchanged. The flask and the attached condenser should be readily detachable from the supporting ringstand so that the whole can be lifted and cooled quickly. A pail of cold water should be at hand for this purpose.
4. The temperature of the acid is 50° at the start and about 80° during the addition.
5. This should give a homogeneous solution. Should there be unused benzanilide, it will appear at this point and should be removed by filtration.
6. It is impracticable to obtain a further yield of ketone by the addition of more sodium hydroxide to the filtrate. Nor does it seem practical to recover the aniline and the excess of dimethylaniline.
7. If the crystals are separated by suction filtration, it is very hard to remove all the mother liquor. When such crystals are air-dried, the alcohol evaporates and leaves the outer layer of material colored deep green.

3. Discussion

p-Dimethylaminobenzophenone can be prepared from benzanilide, dimethylaniline, and phosphorus oxychloride;[1] from malachite green by prolonged exposure to direct sunlight,[2] or by heating with concentrated hydrochloric acid to 180°;[3] from the imide chloride of benzanilide with dimethylaniline;[4] and by methylation of *p*-aminobenzophenone with methyl iodide at 180°,[5] or with methyl sulfate.[6] The ketone has not been prepared by methods involving the use of zinc chloride, and attempts to prepare it by the Friedel-Crafts reaction have given very poor yields.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 82

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

malachite green

imide chloride of benzanilide

alcohol (64-17-5)

hydrochloric acid (7647-01-0)

aniline (62-53-3)

sodium hydroxide (1310-73-2)

Benzanilide (93-98-1)

decolorizing carbon (Norite) (7782-42-5)

Phosphorus Oxychloride (21295-50-1)

zinc chloride (7646-85-7)

dimethylaniline (121-69-7)

Methyl iodide (74-88-4)

methyl sulfate (75-93-4)

p-Dimethylaminobenzophenone, Benzophenone, p-dimethylamino- (530-44-9)

p-aminobenzophenone (1137-41-3)

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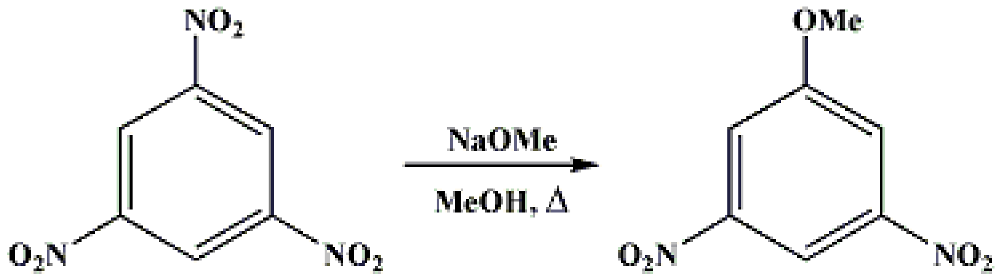
Organic Syntheses, CV 1, 219

3,5-DINITROANISOLE

[Anisole, 3,5-dinitro-]



Submitted by Frederic Reverdin
Checked by C. S. Marvel and Dorothy E. Bateman.

1. Procedure

A solution of sodium methoxide is prepared by dissolving 6.3 g. (0.27 atom) of sodium in 150 cc. of absolute methyl alcohol (Note 1) in a 1-l. flask provided with a reflux condenser. To this is added a solution of 50 g. (0.23 mole) of 1,3,5-trinitrobenzene (p. 541) in 550 cc. of absolute methyl alcohol. The mixture is boiled for about twenty minutes. The reflux condenser is then replaced by a still head and condenser, and about 300–350 cc. of alcohol is distilled. The residue in the flask is cooled to 20° and filtered.

The crude product is purified by recrystallization from hot ordinary methyl alcohol. On account of the low solubility of the dinitroanisole in hot methyl alcohol, the best results are obtained by boiling the crude product with a few grams of decolorizing carbon (Norite) in about 500 cc. of methyl alcohol, filtering the hot solution through a hot funnel, cooling the solution, filtering, and using the mother liquors for another extraction. After five extractions no more of the product is dissolved. The yield of pure product melting at 105° is 29–35 g. (63–77 per cent of the theoretical amount).

2. Notes

1. One liter of ordinary absolute methyl alcohol was treated with 5 g. of magnesium turnings and 0.1 g. of mercuric chloride, and then distilled as soon as the magnesium had dissolved.

3. Discussion

3,5-Dinitroanisole can be prepared by the action of sodium methoxide on 1,3,5-trinitrobenzene.[1]

References and Notes

1. Lobry de Bruyn, Rec. trav. chim. **9**, 208 (1890).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alcohol (64-17-5)

methyl alcohol (67-56-1)

magnesium, magnesium turnings (7439-95-4)

sodium methoxide (124-41-4)

decolorizing carbon (Norite) (7782-42-5)

sodium (13966-32-0)

mercuric chloride (7487-94-7)

3,5-DINITROANISOLE, Anisole, 3,5-dinitro- (5327-44-6)

1,3,5-Trinitrobenzene (99-35-4)

dinitroanisole

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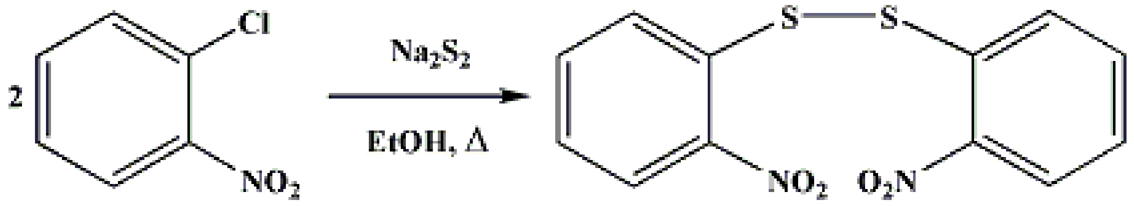
Organic Syntheses, CV 1, 220

DI-*o*-NITROPHENYL DISULFIDE

[Disulfide, bis (*o*-nitrophenyl)]



Submitted by Marston T. Bogert and Arthur Stull.
Checked by Frank C. Whitmore, W. F. Singleton, and F. E. Smith.

1. Procedure

In a 3-l. round-bottomed flask fitted with a reflux condenser are placed 360 g. (1.5 moles) of crystalline sodium sulfide (Note 1) and 1.5 l. of 95 per cent alcohol. The flask is heated on a steam bath until the sulfide dissolves. Then 48 g. (1.5 atoms) of finely ground sulfur is added, and the heating is continued until the sulfur has dissolved, forming a brownish-red solution of sodium disulfide (Note 2). A solution of 315 g. (2 moles) of *o*chloronitrobenzene (Note 3) in 500 cc. of 95 per cent alcohol is prepared in a 5-l. round-bottomed flask fitted with a reflux condenser. The sodium disulfide solution is added slowly to this solution through a funnel placed in the top of the reflux condenser. The addition should be slow until the violence of the reaction abates somewhat.

The mixture is then heated on a steam bath, gently at first (Note 4), and then at full heat for two hours. After cooling, it is filtered by suction. The mixture of the organic disulfide and the sodium chloride is transferred to a 1-l. beaker and stirred thoroughly with 500 cc. of water to remove the sodium chloride. It is then filtered by suction and the crystalline residue is washed on the filter with 100 cc. of alcohol to remove any *o*-chloronitrobenzene. The product melting at 192–195° weighs 180–210 g. (58–66 per cent of the theoretical amount).

2. Notes

1. Crystals as dry as possible should be selected. If desired, an equivalent amount of analyzed fused sodium sulfide may be used. In this case, solution takes a longer time. Since an excess of sodium sulfide is added, slight inaccuracies in the amount used are not important.
2. In case a small amount of sodium disulfide separates in a layer at the bottom, it should be taken up with a little more alcohol and added to the chloronitrobenzene solution.
3. Commercial *o*-chloronitrobenzene containing 95–98 per cent of the ortho

compound was used.
4. If too much heat is applied at first, the reaction becomes very violent.

3. Discussion

Di-*o*-nitrophenyl disulfide can be prepared by heating *o*-chloronitrobenzene in alcohol with sodium sulfide and sulfur[1] and from *o*-nitrophenylsulfur chloride and potassium hydrosulfide.[2] The procedure described is that of Blanksma[3] as elaborated by Wohlfahrt.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 455
- Org. Syn. Coll. Vol. 2, 471
- Org. Syn. Coll. Vol. 5, 843

References and Notes

1. Elgersma, Rec. trav. chim. **48**, 752 (1929).
2. Dougherty and Haas, J. Am. Chem. Soc. **59**, 2469 (1937).
3. Blanksma, Rec. trav. chim. **20**, 127 (1901).
4. Wohlfahrt, J.prakt. Chem. (2) **66**, 553 (1902).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alcohol (64-17-5)

sodium chloride (7647-14-5)

sulfur (7704-34-9)

chloronitrobenzene, o-chloronitrobenzene, ochloronitrobenzene (88-73-3)

sodium sulfide (1313-82-2)

sodium disulfide

potassium hydrosulfide (1310-61-8)

Di-o-nitrophenyl disulfide, Disulfide, bis (o-nitrophenyl) (1155-00-6)

o-Nitrophenylsulfur chloride (7669-54-7)

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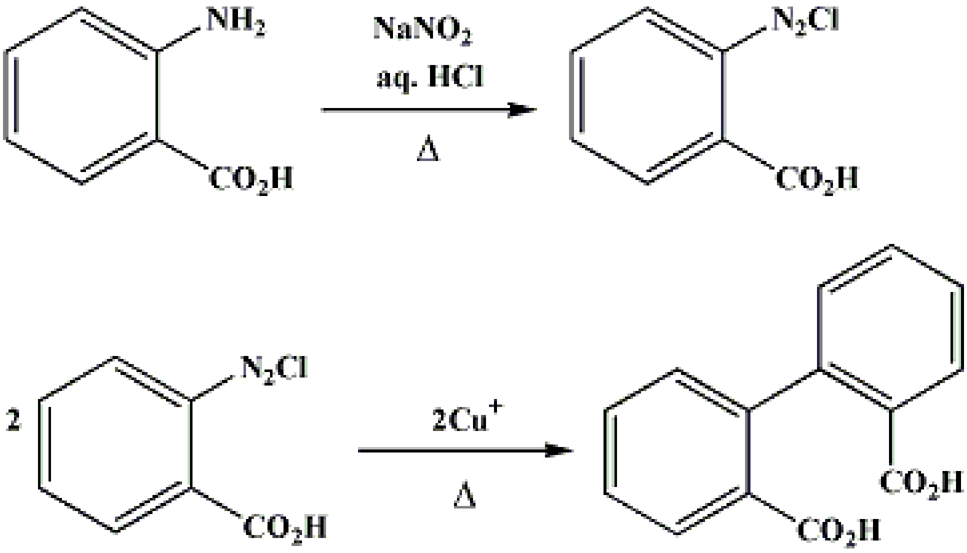
Organic Syntheses, CV 1, 222

DIPHENIC ACID



Submitted by E. R. Atkinson and H. J. Lawler.
Checked by R. L. Shriner and Roy D. Johnson.

1. Procedure

(*A*) *Diazotization of Anthranilic Acid*.—Fifty grams (0.365 mole) of anthranilic acid (m.p. 143–144°) is ground in a mortar with 150 cc. of water and 92 cc. of concentrated hydrochloric acid (sp. gr. 1.19). The suspension is transferred to a 1-l. round-bottomed flask which is equipped with a mechanical stirrer. The flask is surrounded by an ice bath. When the contents have cooled to 0–5°, a solution of 26.3 g. (0.38 mole) of sodium nitrite in 350 cc. of water is added from a dropping funnel during thirty minutes. The resulting diazonium solution is kept at a temperature below 5° and, unless it is entirely clear, is filtered by suction through a chilled Büchner funnel immediately before use.

(*B*) *Preparation of the Reducing Agent*.—One hundred and twenty-six grams (0.505 mole) of hydrated cupric sulfate is dissolved in 500 cc. of water in a 2-l. beaker and 210 cc. of concentrated ammonium hydroxide (sp. gr. 0.90) is added. The solution is then cooled to 10°. A solution of 42 g. (0.256 mole) of commercial hydroxylammonium sulfate (Note 1) in 120 cc. of water is prepared and cooled to 10°; to this latter solution there is added 85 cc. of 6 *N* sodium hydroxide solution, and the resulting solution of hydroxylamine is then filtered by suction if not clear. The hydroxylamine solution is immediately added to the ammoniacal cupric sulfate solution with hand stirring. Reduction occurs at once; a gas is evolved during the process, and the solution becomes pale blue in color. If this solution is not to be used at once it should be protected from the air.

(*C*) *Synthesis of Diphenic Acid*.—The reducing solution in the 2-l. beaker is surrounded by an ice bath so that the temperature of the solution is Kept at about 10°.

The beaker is fitted with a mechanical stirrer. The stem of a 100-cc. cylindrical dropping funnel is fitted with a glass tube which dips well below the surface of the solution and is bent upward at the end and constricted so that the opening is about 2 mm. (Note 2). An 80- to 90-cc. portion of the diazonium solution is placed in the dropping funnel and added at the rate of about 10 cc. per minute (Note 3). The remainder of the diazonium solution is added at the same rate and stirring is continued for five minutes longer.

The solution is then rapidly heated to boiling and carefully acidified with 250 cc. of concentrated hydrochloric acid (Note 4). Diphenic acid precipitates as light brown crystals. After the solution has stood overnight the solid is removed by filtration and washed free of mother liquor while on the filter with about 50 cc. of cold water. When dried, the product melts at 222–227° (corr.) and weighs 39–40 g. (88–91 per cent of the theoretical amount).

The crude product is suspended in 200 cc. of water, and 40 g. of solid sodium bicarbonate is added. The resulting solution is filtered by gravity, then boiled with 0.1 g. of Norite. The mixture is filtered and the yellowish-brown filtrate is acidified while still hot with an excess of 6 *N* hydrochloric acid. The precipitated diphenic acid is collected on a filter and washed with 40 cc. of cold water. When dried at 100° the product melts at 225–228° and weighs 32–37 g. (72–84 per cent of the theoretical amount). It is a light cream color (Note 5).

2. Notes

1. This material may be purchased from the Commercial Solvents Corporation, New York City. It may be replaced by 35.6 g. (0.512 mole) of hydroxylamine hydrochloride.
2. This trap arrangement prevents premature reaction of the entering diazonium solution with ammonia which otherwise would be carried up the stem by ascending bubbles of nitrogen.
3. It is advisable to calibrate the dropping funnel so that the proper rate of addition may be used.
4. Rapid addition of acid near the neutral point (about 160 cc. of acid) causes the formation of small lumps of copper compounds which then contaminate the product. These are easily removed during the purification.
5. This color may be removed by further leachings with hot water. It is characteristic of the product formed when reducing agents containing hydroxylamine are used. If a colorless product is desired the use of a cupro-ammonia-sulfite reducing agent is preferable.[1]

3. Discussion

This procedure is based on a detailed study[1] of the preparation of symmetrical biaryls by the action of reducing agents on diazotized amines. The reducing agent used above was introduced by Vorländer and Meyer.[2] Although the yield of diphenic acid is not

appreciably greater than that obtained with two other reducing agents,[1] there are economies of time and materials which recommend it.

Diphenic acid can be prepared by oxidizing phenanthrenequinone with chromic acid;[3] and by heating potassium *o*-bromobenzoate with copper powder.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 872
- Org. Syn. Coll. Vol. 5, 493

References and Notes

1. Atkinson, Lawler, Heath, Kimball, and Read, J. Am. Chem. Soc. **63**, 730 (1941).
2. Vorländer and Meyer, Ann. **320**, 122 (1902).
3. Roberts and Johnson, J. Am. Chem. Soc. **47**, 1399 (1925).
4. Hurtley, J. Chem. Soc. 1870 (1929).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Diphenic acid

ammoniacal cupric sulfate

copper compounds

cupro-ammonia-sulfite

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

nitrogen (7727-37-9)

cupric sulfate (7758-98-7)

sodium nitrite (7632-00-0)

copper powder (7440-50-8)

Norite (7782-42-5)

chromic acid (7738-94-5)

ammonium hydroxide (1336-21-6)

Anthranilic Acid (118-92-3)

hydroxylammonium sulfate

Hydroxylamine hydrochloride (5470-11-1)

phenanthrenequinone (84-11-7)

potassium o-bromobenzoate

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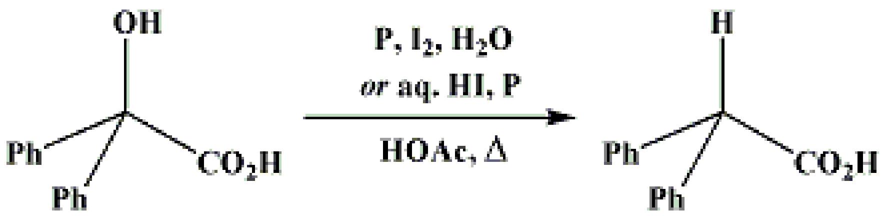
DIPHENYLACETIC ACID

[Acetic acid, diphenyl-]



Submitted by C. S. Marvel, F. D. Hager, and E. C. Caudle.
Checked by J. B. Conant and A. W. Sloan.

1. Procedure

In a 1-l. round-bottomed flask are placed 250 cc. of glacial acetic acid, 15 g. of red phosphorus, and 5 g. of iodine. The mixture is allowed to stand for fifteen to twenty minutes until the iodine has reacted, and then 5 cc. of water (Note 1) and 100 g. (0.44 mole) of benzilic acid (p. 89) are added. A reflux condenser is attached, and the mixture is boiled continuously for at least two and one-half hours. After the reaction is complete, the hot mixture is filtered with suction to remove the excess red phosphorus (Note 2). The hot filtrate is slowly poured into a cold, well-stirred, filtered solution of 20–25 g. of sodium bisulfite in 1 l. of water (Note 3). This procedure removes the excess iodine and precipitates the diphenylacetic acid as a fine white or slightly yellow powder (Note 4). The product is filtered with suction, washed with cold water, and dried thoroughly on filter paper. The yield is 88–90 g. (94–97 per cent of the theoretical amount) of a solid melting at 141–144° (Note 5). If a crystalline product is desired, the acid is dissolved in about 500 cc. of hot 50 per cent alcohol and then cooled. The melting point after recrystallization is 144–145°.

2. Notes

1. In place of phosphorus, iodine, and water, a dilute solution of hydriodic acid and phosphorus may be used.
2. If difficulties are encountered in filtering the hot acetic acid solution through filter paper, an asbestos filter may be prepared and used to advantage.
3. Some samples of sodium bisulfite caused part of the diphenyl-acetic acid to dissolve. This can always be avoided if, after the solution of sodium bisulfite is prepared, a current of sulfur dioxide is passed in, until the solution is acid to litmus.
4. Sometimes, if the acetic acid solution is poured into the water too rapidly, the product will be slightly pink and a reprecipitation from acetic acid solution will be necessary.

5. The melting points of benzilic acid and diphenylacetic acid lie very close together. However, it is very easy to test for complete reduction by treating a little of the product with cold concentrated sulfuric acid. If even a trace of benzilic acid remains the sulfuric acid will turn red.

3. Discussion

Diphenylacetic acid can be prepared by the reduction of benzilic acid with hydriodic acid and red phosphorus,[1] by carbonation of the reaction product of phenylsodium and diphenylmethane,[2] and by hydrolysis of 1,1-dichloro-2,2-diphenylethylene.[3]

References and Notes

1. Jena, Ann. **155**, 84 (1870); Klingemann, Ann. **275**, 84 (1893); Zinssen, Ber. **24**, 3556 (1891); Chichibabin, Ber. **44**, 442 (1911).
2. I. G. Farbenind. A.-G., Ger. pat. 671, 098 [C. A. **33**, 3391 (1939)].
3. Sheibley and Prutton, J. Am. Chem. Soc. **62**, 840 (1940).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

red phosphorus

alcohol (64-17-5)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

sulfur dioxide (7446-09-5)

PHOSPHORUS (7723-14-0)

sodium bisulfite (7631-90-5)

iodine (7553-56-2)

Benzilic acid (76-93-7)

Diphenylmethane (101-81-5)

hydriodic acid (10034-85-2)

Diphenylacetic acid, Acetic acid, diphenyl-, diphenyl-acetic acid (117-34-0)

phenylsodium

1,1-dichloro-2,2-diphenylethylene

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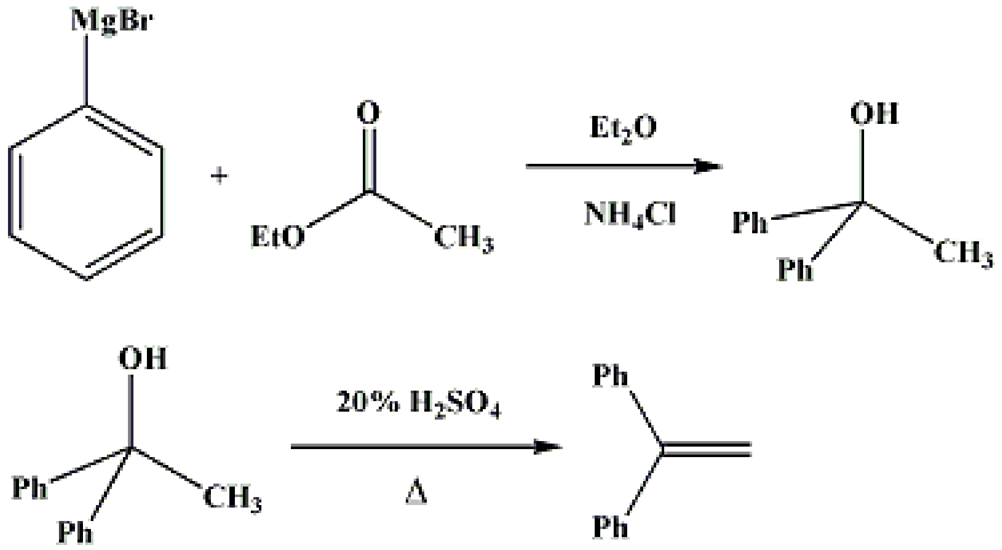
1,1-DIPHENYLETHYLENE

[Ethylene, 1,1-diphenyl-]



Submitted by C. F. H. Allen and S. Converse.
Checked by Henry Gilman and N. J. Beaber.

1. Procedure

In a 2-l. three-necked flask, fitted with a separatory funnel, reflux condenser, and stirrer, is placed 27 g. (1.1 atoms) of magnesium turnings. A mixture of 30 g. of bromobenzene and 70 cc. of dry ether is run in and the flask warmed gently until the reaction becomes rapid. Stirring is then started, and the vessel is surrounded by a dish of cold water. A mixture of 151 g. of bromobenzene (total: 181 g., 1.15 moles) and 380 cc. of dry ether is run in at such a rate as to cause vigorous refluxing; when the addition is complete (one hour) the whole is stirred for ten minutes.

After the flask has been cooled by immersion in ice water, 44 g. (0.5 mole) of dry ethyl acetate (Note 1) in an equal volume of ether is added over a period of twelve minutes. The cooling bath is removed and stirring is continued for ten minutes. When the reaction flask has again been cooled by the ice-water bath, a previously prepared ammonium chloride solution (Note 2) is added, very slowly at first, over a period of ten minutes, during which a pasty solid separates.

The ether layer is decanted into a separatory funnel, and to it is added a 50-cc. ether extract of the pasty residue. The ether is removed by dropping the solution into a 500-cc. round-bottomed flask attached to a condenser and immersed in an oil bath heated to 210–215°. The flask is removed from the oil bath, cooled, and disconnected from the condenser; 100 cc. of 20 per cent sulfuric acid is added. The flask is fitted with a reflux condenser, and the contents are boiled for one hour. The aqueous layer is now removed, and the residual oil, without being washed, is distilled at a pressure of about

30 mm. and a bath temperature of about 210° (Note 3). At first a low-boiling fraction consisting of bromobenzene (12–14 g.) and traces of water distils, after which the diphenylethylene comes over as a colorless liquid, the last portions being slightly yellowish. The brownish residue contains polymerization and decomposition products. On redistillation, the pure hydrocarbon boils at 113°/2 mm. (Note 4). The yield is 60–66 g. (67–70 per cent of the theoretical amount based on ethyl acetate) (Note 5).

2. Notes

1. The grade of ethyl acetate is very important. If ordinary ethyl acetate is used it may be purified by washing with twice its volume of water, drying over fused potassium carbonate, refluxing with phosphorus pentoxide, filtering, and fractionating, whereupon practically all comes over at constant temperature. The addition to the Grignard reagent should be cautious at first, to avoid a vigorous reaction that frequently occurs after about 15 cc. has been added.
2. The ammonium chloride solution is prepared by dissolving 50 g.> of ammonium chloride in 150 cc. of water at 25–30°. The literature recommends 30 per cent sulfuric acid for decomposing the magnesium compound; when this is used, the yield drops to 50–55 per cent, probably owing to the ready polymerization of the hydrocarbon in the presence of mineral acids.
3. This treatment obviates the necessity of isolating the intermediate carbinol. The carbinol, if desired, can be obtained in yields up to 75 per cent from the combined, dried, ether extracts.
4. The hydrocarbon is reported to boil at 123–5°/5 mm.; 134°/10 mm.[1]; 139°/11 mm.[2]; 156°/25 mm.[3]; 164°/34 mm.[3]; and at 277°/760 mm.[4]
5. The yield is decreased by about 10 per cent if only an equivalent molecular quantity of phenylmagnesium bromide is used.

3. Discussion

1,1-Diphenylethylene can be prepared by the action of alcoholic potassium hydroxide on unsymmetrical diphenylchloroethane;[4] by the action of aluminum chloride on benzene and tribromoethylene;[5] and by dehydration of the carbinol which can be prepared by the action of methylmagnesium iodide on benzophenone,[1236] or phenylmagnesium bromide on acetophenone[7] or ethyl acetate.[8] The procedure described is adapted from that of Stadnikov.[8]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 353
- Org. Syn. Coll. Vol. 3, 562
- Org. Syn. Coll. Vol. 3, 729
- Org. Syn. Coll. Vol. 3, 771

- Org. Syn. Coll. Vol. 3, 839
- Org. Syn. Coll. Vol. 5, 1124
- Org. Syn. Coll. Vol. 9, 507

References and Notes

1. Lebedew, Ber. **56**, 2349 (1923);
2. Lipp, Ber. **56**, 567 (1923);
3. Klages, Ber. **35**, 2646 (1902);
4. Hepp, Ber. **7**, 1409 (1874).
5. Anschütz, Ann. **235**, 336 (1886).
6. Gilman and Crawford, J. Am. Chem. Soc. **45**, 554 (1923).
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8. Anschütz and Hilbert, Ber. **54**, 1856 (1921); Stadnikov, J. Russ. Phys. Chem. Soc. **47**, 2037, 2115 (1915) [C. A. **10**, 1355 (1916)]; Schlenck and Bergmann, Ann. **463**, 24 (1928).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

magnesium compound

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

Benzene (71-43-2)

ethyl acetate (141-78-6)

ether (60-29-7)

ammonium chloride (12125-02-9)

magnesium turnings (7439-95-4)

Acetophenone (98-86-2)

aluminum chloride (3495-54-3)

potassium hydroxide (1310-58-3)

Benzophenone (119-61-9)

bromobenzene (108-86-1)

1,1-Diphenylethylene, Ethylene, 1,1-diphenyl-, diphenylethylene (530-48-3)

Phenylmagnesium bromide (100-58-3)

diphenylchloroethane

tribromoethylene (598-16-3)

methylmagnesium iodide (917-64-6)

phosphorus pentoxide (1314-56-3)

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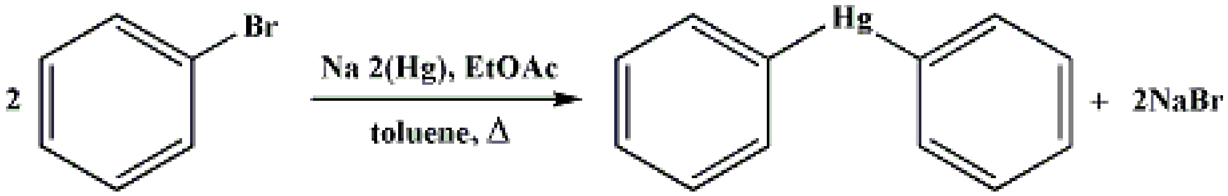
Organic Syntheses, CV 1, 228

DIPHENYLMERCURY

[Mercury, diphenyl-]



Submitted by H. O. Calvery
Checked by Frank C. Whitmore and R. W. Beattie.

1. Procedure

In a 1-l. round-bottomed flask fitted with a reflux condenser are placed 900 g. of 3 per cent sodium amalgam (Note 1), 180 g. (1.15 moles) of bromobenzene, 200 cc. of dry toluene or dry xylene, and 10 cc. of ethyl acetate. The mixture is refluxed with frequent shaking for twelve hours in an oil bath at 130°.

The mixture is transferred (Hood) (Note 2) while still hot to a fluted filter paper in a 20-cm. glass funnel, leaving behind as much mercury as possible (Note 3). The funnel is made part of a special extraction apparatus as described on p. 375. The diphenylmercury is extracted with 600 cc. of boiling benzene for about ten hours (Note 4).

The solution is distilled under reduced pressure on an oil bath, the temperature of which is raised to 110° near the end of the distillation. The solid residue left in the flask after removal of the solvent is taken out and washed until nearly white with 95 per cent alcohol which has been cooled in an ice bath. This requires about four washings of 50 cc. of alcohol each (Note 5). The yield is 65–75 g. (32–37 per cent of the theoretical amount). The melting point is 121–123°.

2. Notes

1. For the preparation of sodium amalgam see Note 1 on p. 554.
2. Diphenylmercury is very poisonous. The vapors of the benzene solution must not be breathed.
3. Care must be taken to remove all the diphenylmercury; but if too much mercury is removed, it may break the filter paper or weight it down so that the benzene vapors cannot rise around it. It is sometimes best to put stirring rods down around the sides of the paper to insure a free path for the benzene vapors.
4. In some cases the extraction may not be complete in this length of time.
5. Some diphenylmercury may be recovered by combining the washings from

several runs.

3. Discussion

Diphenylmercury can be prepared by the action of sodium on a mixture of bromobenzene and mercuric chloride;[1] from sodium amalgam and phenylmercuric iodide[2] or bromobenzene;[3] from phenyl-mercuric bromide and potassium sulfide;[2] from phenylmercuric acetate and sodium stannite;[4] from the double salt of benzenediazonium chloride and mercuric chloride by the action of powdered copper;[5] and from phenylmagnesium bromide and mercuric chloride[6] or bromide.[7]

References and Notes

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2. Dreher and Otto, Ber. **2**, 542 (1869).
3. Wurtz, Compt. rend **68**, 1300 (1869); Calvery, J. Am. Chem. Soc. **48**, 1009 (1926).
4. Dimroth, Ber. **35**, 2853 (1902); Maynard, J. Am. Chem. Soc. **46**, 1510 (1924).
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7. Bachmann, ibid. **55**, 2830 (1933).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

double salt of benzenediazonium chloride

powdered copper

alcohol (64-17-5)

Benzene (71-43-2)

ethyl acetate (141-78-6)

bromide (24959-67-9)

mercury (7439-97-6)

toluene (108-88-3)

sodium (13966-32-0)

bromobenzene (108-86-1)

mercuric chloride (7487-94-7)

xylene (106-42-3)

Phenylmagnesium bromide (100-58-3)

Diphenylmercury, Mercury, diphenyl- (587-85-9)

phenylmercuric iodide

phenyl-mercuric bromide

potassium sulfide (1312-73-8)

phenylmercuric acetate

sodium stannite

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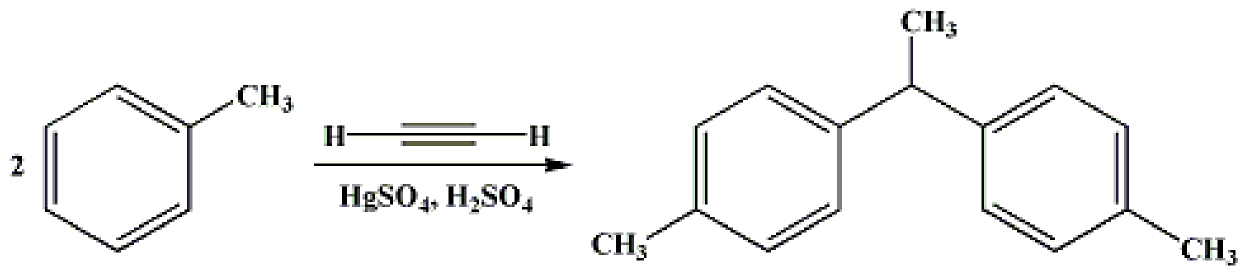
1,1-DI-*p*-TOLYLETHANE

[Ethane, 1,1-di-*p*-tolyl-]

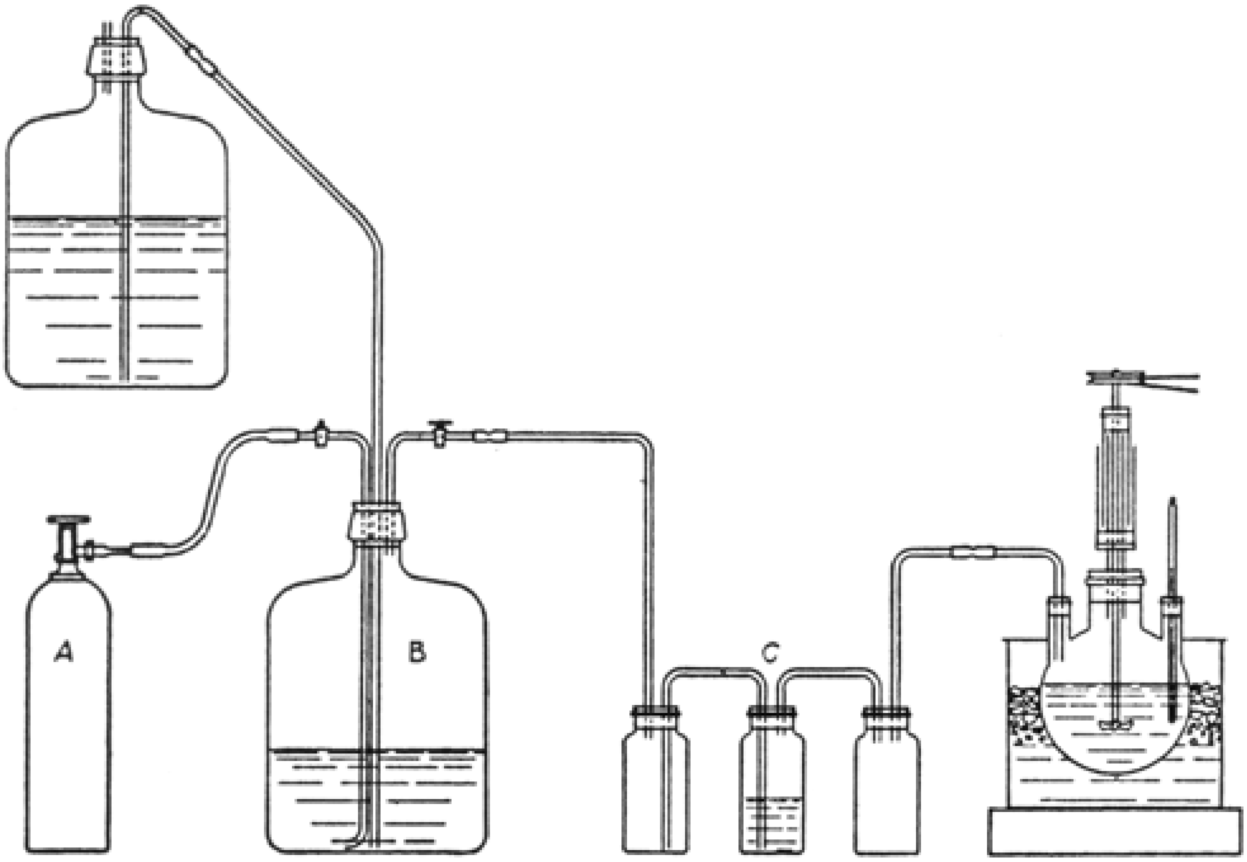


Submitted by J. S. Reichert and J. A. Nieuwland.
Checked by Oliver Kamm

1. Procedure

A 2-l. three-necked flask, containing 606 g. (700 cc., 6.6 moles) of toluene, 70 cc. of concentrated sulfuric acid, and 7 g. of mercuric sulfate, is fitted with a stirrer, a thermometer reaching into the liquid, and an inlet tube connected with a gasometer containing acetylene, as shown in Fig. 11 (Note 1). The flask and its contents are tared and cooled to 10° before the absorption of acetylene is begun. The gas from the tank, A, is washed free from acetone by being passed first through water in the gasometer, B, and then through the concentrated sulfuric acid wash bottle, C.

Fig. 11.



The acetylene is absorbed rapidly, with the evolution of considerable heat. The temperature of the reaction mixture is maintained at 10–15° by immersing the flask in a freezing mixture. When at intervals the reaction slows down, it becomes necessary to sweep the system free from air which accumulates in the flask. The absorption is continued until about 60 g. (2.3 moles) of acetylene has been absorbed, which requires a period of about two hours (Note 2). During the absorption, the mixture turns first a reddish brown, then a dark brown, and finally almost black.

The reaction mixture is freed from the acid by washing once with pure water and then with sodium carbonate solution, to which some sodium chloride is added to aid the separation of the hydrocarbon layer. If emulsification takes place, the addition of ether will remedy the difficulty.

The toluene layer is transferred to a 1-l. flask, without drying, and the unchanged toluene distilled off; the ditolylethane is then collected over a range of 295–310°. There is practically no intermediate fraction, but a tarry residue of about 75 g. remains in the flask. Upon redistillation, the ditolylethane is collected at 295–300°. The yield is 290–310 g. (60–64 per cent of the theoretical amount) (Note 3) and (Note 4).

2. Notes

1. The acetylene is absorbed with unexpected rapidity so that it is unnecessary to deliver the gas beneath the surface of the liquid. In an ordinary reaction involving a gas it would be advisable to use a special stirrer, and to deliver the gas beneath the distributing tube of the stirrer.
2. It is scarcely necessary to remove the flask for weighing until near the end of the

experiment, since the volume of acetylene is known and practically complete absorption takes place. If a tank of compressed gas is not available, the acetylene may be prepared from calcium carbide by the usual laboratory methods.[1]

3. Subsequent redistillation yields a product boiling practically over a 2° range. The best product was obtained by a final fractionation under diminished pressure, when the boiling point was found to be 144–145° /8 mm.

4. Xylene, mesitylene, ethylbenzene, and benzene condense with acetylene in a manner similar to that described above for toluene, although the yields are usually lower.[2]

3. Discussion

1,1-Di-*p*-tolylethane can be prepared from paraldehyde and toluene in the presence of sulfuric acid[3] and by the reduction of 1,1-di-*p*-tolylethylene with sodium in absolute alcohol.[4] The procedure described is essentially that of Reichert and Nieuwland.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 290
- Org. Syn. Coll. Vol. 8, 391

References and Notes

1. Steinkopf, Chem. Ztg. **33**, 969 (1909) [C. A. **3**, 2887 (1909)].
2. Reichert and Nieuwland, J. Am. Chem. Soc. **45**, 3090 (1923).
3. Fischer, Ber. **7**, 1193 (1874).
4. Anschütz and Hilbert, Ber. **57**, 1699 (1924).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

calcium carbide

alcohol (64-17-5)

sulfuric acid (7664-93-9)

acetylene (74-86-2)

Benzene (71-43-2)

ether (60-29-7)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

acetone (67-64-1)

toluene (108-88-3)

sodium (13966-32-0)

xylene (106-42-3)

mercuric sulfate (7783-35-9)

ditolylethane, 1,1-DI-p-TOLYLETHANE, Ethane, 1,1-di-p-tolyl- (530-45-0)

Mesitylene (108-67-8)

ethylbenzene (100-41-4)

1,1-di-p-tolylethylene (2919-20-2)

paraldehyde (123-53-7)

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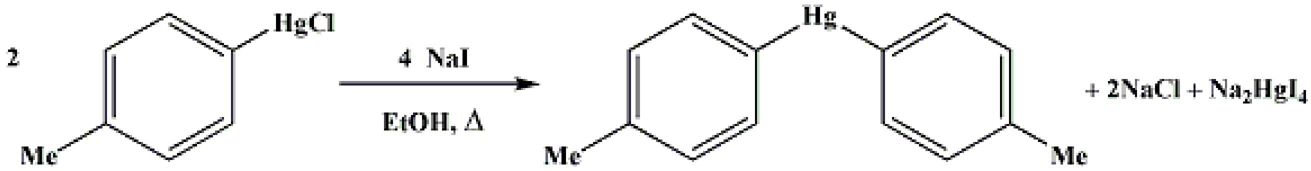
DI-*p*-TOLYLMERCURY

[Mercury, di-*p*-tolyl-]



Submitted by F. C. Whitmore, N. Thurman, and Frances H. Hamilton.
Checked by J. B. Conant and F. C. Whidden.

1. Procedure

In a 2-l. round-bottomed flask fitted with a reflux condenser and an efficient glass stirrer, are placed 700 cc. of 95 per cent ethyl alcohol, 100 g. (0.3 mole) of recrystallized *p*-tolylmercuric chloride (p. 519), and 160 g. (1.1 moles) of sodium iodide (Note 1) (75 per cent excess). The mixture is boiled with vigorous stirring (Note 2) for fifteen hours; the solid does not entirely enter into solution at any time. The mixture is then thoroughly cooled and filtered by suction and the solid washed with water until free of inorganic halide. It is then dried in an air oven at 40° and recrystallized from 500 cc. of boiling xylene (Note 3). In this way 45–50 g. (78–85 per cent of the theoretical amount) of a product melting at 238° is obtained.

2. Notes

1. Mercury compounds of the type RHgX can be changed to those of the type R_2Hg, by almost any neutral or alkaline reagent which tends to change mercuric ions to metallic mercury or to a stable complex ion. Some of these reagents are inorganic iodides, thiocyanates, thiosulfates, sulfides, hydrosulfites, ferrous hydroxide, sodium amalgam, metallic sodium, and sodium stannite. Preliminary experiments indicated that potassium thiocyanate was a good reagent for preparing di-*p*-tolylmercury; but it was later found that the use of sodium iodide with vigorous stirring gave even better results.
2. Stirring decreases the time required for the reaction and increases the yield. Without stirring it is practically impossible to obtain a product which is free from halogen.
3. Since the di-*p*-tolylmercury has practically the same solubility in xylene as the tolylmercuric iodide and chloride, the latter will be present in the recrystallized product if the reaction has not gone to completion. A trace of unchanged product may readily be detected by the metallic sodium test for inorganic halides.

3. Discussion

Di-*p*-tolylmercury can be prepared from *p*-bromotoluene with sodium amalgam;[1] from *p*-tolylmercuric chloride with copper in pyridine,[2] or with hydrazine hydrate and sodium carbonate;[3] from *p*-tolyllithium and mercuric chloride;[4] and from the double salt of *p*-toluene-diazonium chloride and mercuric chloride with copper powder in cold acetone.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 381

References and Notes

1. Dreher and Otto, Ann. **154**, 171 (1870); Wurtz, Compt. rend. **68**, 1298 (1869); La Coste and Michaelis, Ann.

201, 246 (1880).
2. Hein and Wagler, Ber. **58**, 1499 (1925).
3. Gilman and Barnett, Rec. trav. chim. **55**, 565 (1936).
4. Austin, J. Am. Chem. Soc. **54**, 3726 (1932).
5. Nesmejanov and Kahn, Ber. **62**, 1018 (1929).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

mercuric ions

metallic mercury

inorganic iodides

thiocyanates

thiosulfates

sulfides

hydrosulfites

tolylmercuric iodide and chloride

double salt of p-toluene-diazonium chloride

ethyl alcohol (64-17-5)

sodium carbonate (497-19-8)

copper, copper powder (7440-50-8)

acetone (67-64-1)

pyridine (110-86-1)

sodium, metallic sodium (13966-32-0)

mercuric chloride (7487-94-7)

p-tolylmercuric chloride (539-43-5)

xylene (106-42-3)

sodium stannite

sodium iodide (7681-82-5)

ferrous hydroxide

potassium thiocyanate (333-20-0)

hydrazine hydrate (7803-57-8)

p-Bromotoluene (106-38-7)

DI-p-TOLYLMERCURY, Mercury, di-p-tolyl- (537-64-4)

p-tolyllithium

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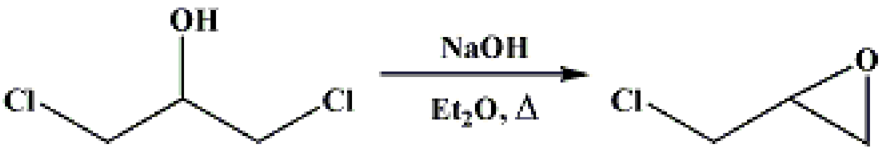
EPICHLOROHYDRIN

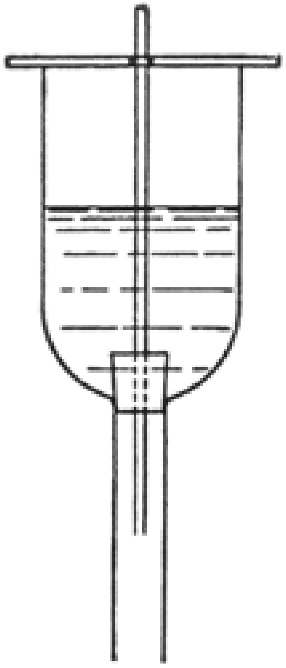


Submitted by H. T. Clarke and W. W. Hartman.
Checked by Roger Adams and H. O. Calvery.

1. Procedure

In a 5-l. flask (Note 1) provided with a mechanical stirrer, a reflux condenser, and a hopper which can be opened or closed at the bottom by means of a rubber bung attached to a glass rod (Fig. 12),

Fig. 12.



are placed 3 l. of anhydrous ether and 1290 g. (943 cc., 10 moles) of glycerol α,γ-dichlorohydrin (p. 292). The flask is surrounded by a cold-water bath, and 440 g. (11 moles) of finely powdered sodium hydroxide (Note 2), which has been passed through a 20-mesh sieve, is added through the hopper in small portions, with continual stirring, while the temperature is kept at 25–30°. The addition requires about twenty minutes. The cold water is replaced by water at 40–45°, and the mixture boiled gently with stirring for four hours. It is necessary to cool the vessel at least once every hour during this period and break up with a rod or wire any lumps which cling to the side of the flask and are not incorporated by the stirrer.

The mixture is finally cooled and the ethereal solution carefully decanted from the solid, which is carefully rinsed twice with 250-cc. portions of dry ether. The united liquids are then distilled from a water bath held at 46–60°, the residue is fractionated with a column, and the fractions boiling at the following points are collected: up to 110°; at 110–115°; at 115–117°; and at 117–140°. The portion boiling at 115–117° is pure epichlorohydrin; the lower and higher fractions are systematically redistilled, yielding a further quantity of pure material. The yield is 705–747 g. (76–81 per cent of the theoretical amount). The residue, varying from 16 to 150 g., consists of nearly pure glycerol dichlorohydrin, and may be employed in subsequent runs (Note 3).

2. Notes

1. A three-necked flask is very satisfactory for this reaction; if it is not available, the tubes leading from the reflux condenser and the hopper must be bent at slight angles to prevent congestion of apparatus.

2. The principal difficulties in the preparation are connected with the use of finely powdered alkali. Care must be taken to expose the powder as little as possible to a moist atmosphere, for if it becomes at all damp it tends to clump together and difficulty is experienced in adding it to the mixture. For this reason, and also on account of the irritating action of alkali on the mucous membranes, the sieve should be provided with well-fitting cover and receiver; the sifted material should be weighed out into a stoppered bottle and placed in the apparatus directly from this container. The hopper (Fig. 12) from which the alkali is added to the mixture should be covered with a card with a hole through which the rod passes. The bung on the rod may conveniently be constructed from a rubber stopper of appropriate size.
3. It is not essential to redistil the recovered dichlorohydrin, since the glycerol which forms the principal by-product is retained by the excess alkali and does not enter the ether.

3. Discussion

Epichlorohydrin can be prepared by the action of alkalies on glycerol α- and β-dichlorohydrins.[1] An alternative procedure involving the use of calcium hydroxide has also been described.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 256
- Org. Syn. Coll. Vol. 4, 10

References and Notes

1. Claus, Ber. **10**, 557 (1877); Reboul, Ann. Suppl. **1**, 221 (1861); Münder and Tollens, Z. Chem. 252 (1871); Prevost, J. prakt. Chem. (2) **12**, 160 (1875); Fairbourne, Gibson and Stephens, Chemistry and Industry **49**, 1021 (1930) [C. A. **25**, 915 (1931)].
2. Griesheim, Ger. pat. 246,242 [Frdl. **10**, 22 (1910–1912)]; Braun, J. Am. Chem. Soc. **54**, 1248 (1932); Org. Syn. **16**, 30.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Glycerol α,γ-dichlorohydrin

glycerol dichlorohydrin

glycerol α- and β-dichlorohydrins

ether (60-29-7)

sodium hydroxide (1310-73-2)

glycerol (56-81-5)

Epichlorohydrin (106-89-8)

calcium hydroxide

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Organic Syntheses, CV 1, 235

ETHYL ACETOACETATE

[Acetoacetic acid, ethyl ester]

$$2CH_3CO_2C_2H_5 + Na \longrightarrow CH_3C(ONa){=}CHCO_2C_2H_5 + C_2H_5OH + (H)$$

$$CH_3C(ONa){=}CHCO_2C_2H_5 + CH_3CO_2H \longrightarrow CH_3COCH_2CO_2C_2H_5 + CH_3CO_2Na$$

Submitted by J. K. H. Inglis and K. C. Roberts.
Checked by C. S. Marvel and F. E. Kendall.

1. Procedure

In a 2-l. round-bottomed flask, fitted with an efficient reflux condenser, are placed 500 g. (531 cc., 5.7 moles) of ethyl acetate (Note 1), and 50 g. (2.2 atoms) of clean sodium wire or finely sliced sodium (Note 2) is added. The reaction is at first quite slow, and must be started by warming on a water bath (Note 3). After the reaction is once started it proceeds vigorously and cooling is then necessary in order to avoid loss of material through the condenser. When the rapid reaction slows down, the reaction mixture is heated on a water bath until the sodium has completely dissolved. This usually requires about one and one-half hours. At this stage the reaction mixture should be a clear red liquid with a green fluorescence.

This solution is then cooled and made slightly acid by adding about 275 cc. of 50 per cent acetic acid (Note 4). Salt is added if necessary to cause the ester to separate. The ester layer is separated, dried over calcium chloride, and fractionally distilled under reduced pressure from a modified Claisen flask (p. 130).

The yield of ester boiling at 76–80°/18 mm. is 105–110 g. (28–29 per cent of the theoretical amount based on the ethyl acetate) (Note 5).

2. Notes

1. The grade of ethyl acetate used is very important. It must be entirely free from water and should contain about 2–3 per cent of alcohol. The absolute ethyl acetate of the U. S. Industrial Alcohol Company is satisfactory for use. If this grade is not available, ordinary ethyl acetate may be purified by washing it with twice its volume of water and drying over fused potassium carbonate, from which it is decanted, and used directly. The ethyl acetate purified in this way contains enough ethyl alcohol to allow the reaction to run well. The ethyl acetate in the wash water may be recovered by distilling through a short column from a steam cone until the vapors reach a temperature of 72°. Dry ethyl acetate containing 2–3 per cent of alcohol has a boiling point range of 2 to 3°.
If the ester is dry enough to use in this reaction it will not give a gelatinous mass of sodium hydroxide when treated with a little sodium.
2. Sodium wire and finely sliced sodium are equally good to use in this reaction. It is

important to avoid exposure of the sodium to the air which converts part of it into sodium hydroxide.

3. It is convenient to arrange the water bath so that it may be heated by passing in steam or cooled by running in cold water.

4. It is advisable to avoid a large excess of acetic acid since it increases the solubility of the ester in water.

5. When larger runs are made, the yields increase; thus 2000 g. of ethyl acetate and 200 g. of sodium give 515–568 g. of ethyl acetoacetate. From a run of this size it is possible to recover about 700 cc. of ethyl acetate. An approximately proportional recovery is obtained in smaller runs.

The yield is based on ethyl acetate and not on sodium, because it is uncertain whether one atom or two atoms of sodium react with one mole of ethyl acetate.

3. Discussion

Ethyl acetoacetate can be prepared from ethyl acetate by the action of sodium,[1] sodium ethoxide,[2] sodamide,[3] and calcium.[4] When the condensation, using sodium ethoxide, is carried out in such a manner as to remove the alcohol formed, the yield is reported to be 80 per cent of the theoretical amount.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 248
- Org. Syn. Coll. Vol. 1, 360
- Org. Syn. Coll. Vol. 2, 202
- Org. Syn. Coll. Vol. 2, 262
- Org. Syn. Coll. Vol. 2, 266
- Org. Syn. Coll. Vol. 2, 422

References and Notes

1. Geuther, Jahresber. 323 (1863); ibid. 302 (1865); Z. Chem. 5 (1866); Wislicenus, Ann. **186**, 214 (1877); Friessner, J. prakt. Chem. (2) **65**, 528 (1902); Claisen, Ber. **38**, 709 (1905); Tingle and Gorsline, Am. Chem. J. **40**, 76 (1908); J. Am. Chem. Soc. **30**, 1876 (1908); Backhaus, U.S. pat. 1,425,626 [C. A. **16**, 3314 (1922)]; Carter, U. S. pat. 1,472,324 [C. A. **18**, 400 (1924)]; Robert, J. Soc. Chem. Ind. **43**, 295T (1924).
2. Geuther, Z. Chem. 653 (1868); Michael, Ber. **33**, 3735 (1900); Claisen, Ber. **38**, 709 (1905); Higley, Am. Chem. J. **37**, 299 (1907); Snell and McElvain, J. Am. Chem Soc. **53**, 2310 (1931); Alexander Wacker Ges. für elektrochemische Industrie, Ger. pat. 526,691 [C. A. **25**, 4891 (1931)].
3. Titherley, J. Chem. Soc. **81**, 1527 (1902); Freund and Speyer, Ber. **35**, 2321 (1902).
4. Perkin and Pratt, J. Chem. Soc. **95**, 161 (1909).
5. Roberts and McElvain, J. Am. Chem. Soc. **59**, 2007 (1937).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethyl alcohol, alcohol (64-17-5)

calcium chloride (10043-52-4)

potassium carbonate (584-08-7)

acetic acid (64-19-7)

ethyl acetate (141-78-6)

sodium hydroxide (1310-73-2)

calcium (7440-70-2)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

Ethyl acetoacetate, Acetoacetic acid, ethyl ester (141-97-9)

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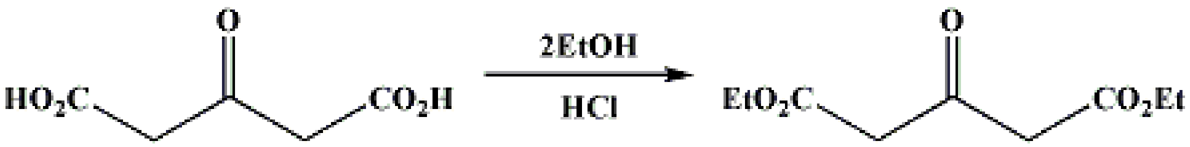
Organic Syntheses, CV 1, 237

ETHYL ACETONEDICARBOXYLATE

[Glutaric acid, β-oxo-, diethyl ester]



Submitted by Roger Adams and H. M. Chiles.
Checked by H. T. Clarke and T. F. Murray.

1. Procedure

The crude acetonedicarboxylic acid from 700 g. (3.64 moles) of citric acid, as described on p. 10, is treated with 700 g. (882 cc.) of absolute ethyl alcohol (pp. 249 and 259) (Note 1) to which has been added at least 130–150 g. of *dry* hydrogen chloride (p. 293). The mixture is placed in a flask fitted with a stopper holding a calcium chloride tube and then is heated to 45°. It is kept in a water bath at 45° (bath temperature) with frequent shaking until all the acid is dissolved (fifteen to twenty minutes). The solution is allowed to cool down to room temperature in the bath and finally to stand about twelve hours (Note 2).

The contents of the flask are then poured into 1300–1400 cc. of ice water, the ester layer separated, and the water-alcohol layer extracted twice with 700-cc. portions of benzene. The benzene extracts are added to the original ester, which has been separated. The total solution thus obtained is washed with about 400 cc. of 10 per cent sodium carbonate solution to remove the acid, then once with dilute sulfuric acid, and finally twice with 400-cc. portions of water (Note 3). The benzene is distilled on a water bath, and the ester is distilled under reduced pressure. A small low-boiling fraction comes over first, and then the ester, which boils at 131–136°/9–10 mm. or 145–148°/17 mm. (Note 4). The yield of product amounts to 284–315 g. (39–43 per cent of the theoretical amount based on the citric acid).

2. Notes

1. The directions given in the literature call for a smaller amount of alcohol than that given in the procedure, but more consistent results were obtained with the method described.
2. The ester should be isolated from the reaction mixture after twelve hours. Longer standing causes a decreased yield.
3. One of the chief precautions which must be observed, if good yields are to be obtained, is thorough and careful washing of the benzene and ester mixture. If this is not done, decomposition occurs during distillation and the yields are lowered by about one-third.

4. The ester must be distilled under low pressure (less than 20 mm.) or considerable decomposition occurs.

3. Discussion

Ethyl acetonedicarboxylate can be prepared by the esterification of acetonedicarboxylic acid[1] and of ethyl γ-cyanoacetoacetate.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 10

References and Notes

1. Pechmann, Ann. **261**, 159 (1891); Jerdan, J. Chem. Soc. **75**, 809 (footnote) (1899); Ingold and Nickolls, ibid. **121**, 1642 (1922); Willstätter and Pfannenstiel, Ann. **422**, 6 (1921).
2. Haller and Held, Compt. rend. **111**, 683 (1890).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethyl alcohol (64-17-5)

sulfuric acid (7664-93-9)

hydrogen chloride (7647-01-0)

Benzene (71-43-2)

Acetonedicarboxylic acid

citric acid (77-92-9)

sodium carbonate (497-19-8)

Ethyl acetonedicarboxylate

Glutaric acid, β-oxo-, diethyl ester (105-50-0)

ethyl γ-cyanoacetoacetate

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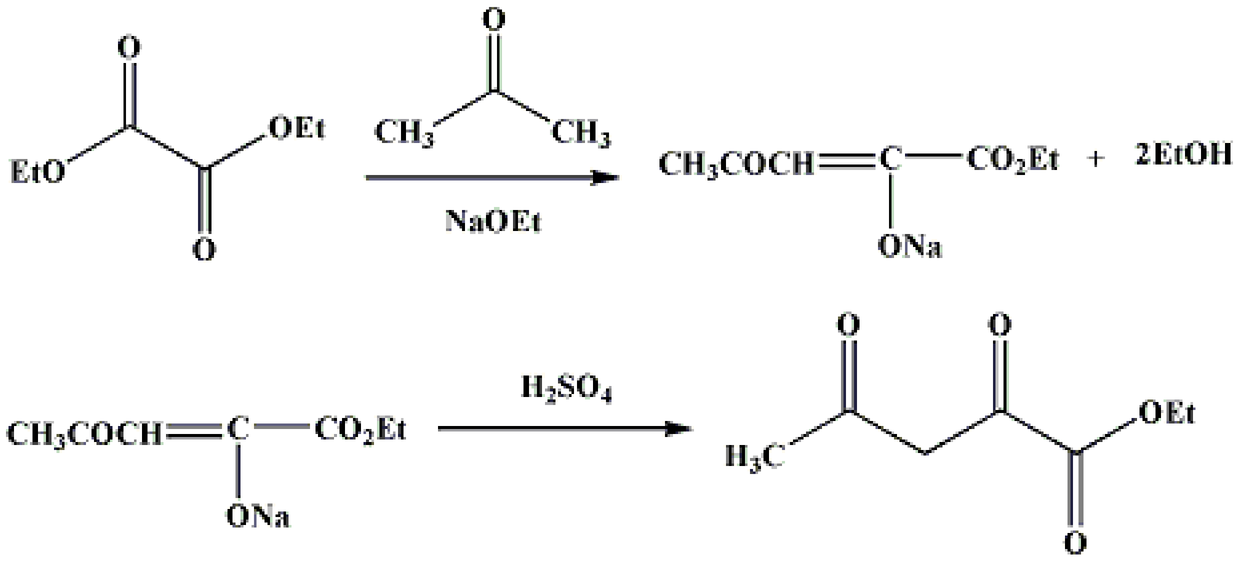
Organic Syntheses, *CV 1*, *238*

ETHYL ACETOPYRUVATE

[Valeric acid, α,γ-dioxo-, ethyl ester]



Submitted by C. S. Marvel and E. E. Dreger.
Checked by Frank C. Whitmore and Gladys E. Woodward.

1. Procedure

In a 5-l. round-bottomed flask fitted with a reflux condenser, a mechanical stirrer (Note 1) and a 1-l. separatory funnel, is placed 2800 cc. of absolute ethyl alcohol (Note 2), and to this is added 125 g. (5.4 atoms) of sodium over a period of one to two hours. The stirrer is started and the mixture allowed to cool to room temperature (Note 3), and a mixture of 730 g. (673 cc., 5 moles) of ethyl oxalate (Note 4) and 290 g. (366 cc., 5 moles) of acetone (Note 5) is added slowly over a period of two to three hours. At first a white precipitate forms; this is followed by a yellow precipitate that darkens as the reaction proceeds and later turns yellow again. The temperature rises to about 40°. Toward the end the mixture becomes so thick that stirring is difficult. Stirring is continued for one hour after the addition of the oxalate and acetone mixture. The yellow sodium salt is filtered by suction on two 20-cm. Büchner funnels (Note 6). The reaction flask is rinsed with 200 cc. of absolute ethyl alcohol, which is then used to wash the salt. The filtrate is turbid as a rule, but there is not enough sodium salt in suspension or solution to warrant recovery.

When the sodium salt has been sucked dry, it is returned to the 5-l. flask and treated with 1.5 l. of water and 1 kg. of cracked ice. The stirrer is started and there is added rapidly a cold sulfuric acid solution made by adding enough ice to 200 cc. of concentrated sulfuric acid (sp. gr. 1.84) (Note 7) so that some of the ice is not melted. The stirring is continued for five or ten minutes or until the yellow lumps of the sodium salt disappear. The mixture is then extracted with three 600-cc. portions of

benzene (Note 8). The benzene is distilled (Note 9) from the extracts on a water bath and the residue is transferred to a special 2-l. Claisen flask (p. 130) and distilled under diminished pressure. The product boils at 130–132°/37 mm. or 117–119°/29 mm. A small high-boiling fraction is redistilled to yield 20–30 g. more of the ethyl acetopyruvate. The total yield is 480–520 g. (61–66 per cent of the theoretical amount) (Note 10).

2. Notes

1. The stirrer used is a bent glass rod which nearly scrapes the sides of the flask. A simple paddle stirrer is not efficient enough to stir the semi-solid mass.
2. The quality of the absolute alcohol (p. 249) influences the yields decidedly. The amount of alcohol indicated is the smallest which can be used effectively.
3. No better yields were obtained at lower temperatures.
4. The ethyl oxalate used (p. 261) was dried over calcium chloride for a week.
5. The acetone used was commercial acetone dried over calcium chloride for a week and then distilled. Some acetone is lost in this operation as it combines chemically with the calcium chloride.[1] See, Org. Syn. **20**, 7.
6. The filtration is likely to be slow and may take as much as two or three hours. When a 40-cm. Büchner funnel was used, it was complete in less than one hour.
7. This is sufficient acid to turn Congo red paper distinctly blue. If less acid is used, a troublesome emulsion is likely to form. If such an emulsion forms it can be broken by pouring into it a small amount of sulfuric acid cooled by the addition of ice.
8. If less than 600-cc. portions of benzene are used, the danger of emulsion formation is greater.
9. About 1 l. of benzene is recovered.
10. Care should be exercised in storing ethyl acetopyruvate because spontaneous decomposition, accompanied by gas evolution, may shatter the container.

3. Discussion

Ethyl acetopyruvate can be prepared by the condensation of ethyl oxalate and acetone in the presence of sodium ethoxide.[2] The procedure described is based on that of Claisen and Stylos.[2] It is reported that the condensation of ethyl oxalate and acetone by means of sodium methoxide furnishes methyl acetopyruvate in excellent yields and that the reaction requires less care than when the ethoxide is used.[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 459

References and Notes

1. Bagster, J. Chem. Soc. **111**, 494 (1917).
2. Claisen and Stylos, Ber. **20**, 2189 (1887); Meister, Lucius and Brüning, Ger. pat. 43,847 [Winther, I, 98 (1877–1905)]; Ger. pat. Anmeldung, F. 3,299 [Frdl. **1**, 218 (1877-87)]; Clark, J. Phys. Chem. **12**, 4 (1908); Meldrum and Perkin, J. Chem. Soc. **95**, 1896 (1909).
3. Freri, Gazz. chim. ital. **68**, 616 (1938).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethyl alcohol, alcohol (64-17-5)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

Benzene (71-43-2)

acetone (67-64-1)

sodium methoxide (124-41-4)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

Ethyl acetopyruvate, Valeric acid, α,γ-dioxo-, ethyl ester (615-79-2)

Ethyl oxalate

methyl acetopyruvate (20577-61-1)

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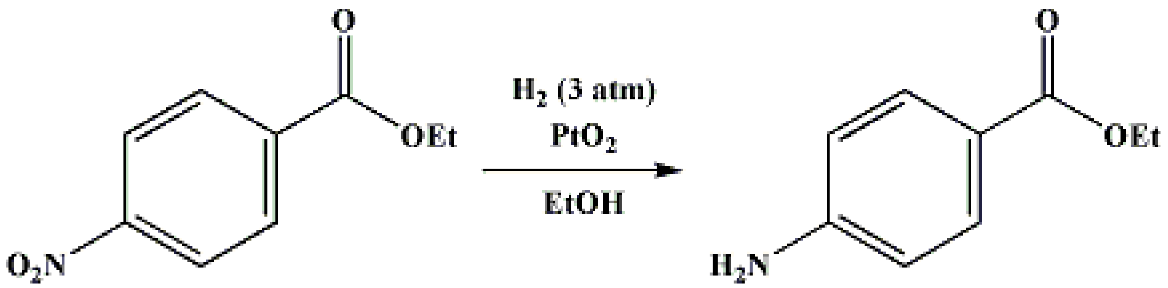
Organic Syntheses, CV 1, 240

ETHYL *p*-AMINOBENZOATE

[Benzocaine]



Submitted by Roger Adams and F. L. Cohen.
Checked by Henry Gilman and S. A. Harris.

1. Procedure

A solution of 19.5 g. (0.1 mole) of ethyl *p*-nitrobenzoate (Note 1) in 150 cc. of 95 per cent alcohol is placed in the reaction bottle of the catalytic reduction apparatus (p. 61), and 0.2 g. of platinum oxide catalyst (p. 463) is added. The mixture is shaken with hydrogen until three molecular equivalents have been absorbed. The time required is about seven minutes. The platinum is filtered off and the alcohol removed from the filtrate by distillation. The ethyl *p*-aminobenzoate, recrystallized from about 40 cc. of ether, melts at 89–90°. The yield is 15–16.5 g. (91–100 per cent of the theoretical amount).

2. Notes

1. The ethyl *p*-nitrobenzoate should be freed from acid and recrystallized from alcohol until it melts at 57°.

3. Discussion

Ethyl *p*-aminobenzoate can be prepared by the esterification of *p*-aminobenzoic acid,[1] and by the reduction of ethyl *p*-nitrobenzoate with ammonium sulfide,[2] electrolytically,[3] and with tin and alcoholic hydrochloric acid.[4] Although the reducing agent used commercially is generally iron and water in the presence of a little acid, the catalytic reduction procedure described is by far the most convenient for the laboratory. The catalytic reduction of ethyl *p*-nitrobenzoate has been described in the literature.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 61
- Org. Syn. Coll. Vol. 1, 463
- Org. Syn. Coll. Vol. 2, 299

References and Notes

1. Salkowski, Ber. **28**, 1921 (1895); Vorländer and Meyer, Ann. **320**, 135 (1902); Chemnitius, Pharm. Zentralh. **68**, 765 (1927) [C. A. **22**, 583 (1928)]; Org. Syn **13**, 54.
2. Limpricht, Ann. **303**, 278 (1898).
3. Alvarez, Mon. farm. therap. **34**, 281 (1928) [C. A. **23**, 1575 (1929)].
4. Hill and Cox, J. Am. Chem. Soc. **48**, 3218 (1926).
5. Ferber and Bendix, Ber. **72**, 841 (1939).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Benzocaine

alcohol (64-17-5)

hydrochloric acid (7647-01-0)

ether (60-29-7)

hydrogen (1333-74-0)

iron (7439-89-6)

tin (7440-31-5)

platinum oxide

platinum (7440-06-4)

aminobenzoic acid (118-92-3)

ammonium sulfide

Ethyl p-aminobenzoate (94-09-7)

ethyl p-nitrobenzoate (99-77-4)

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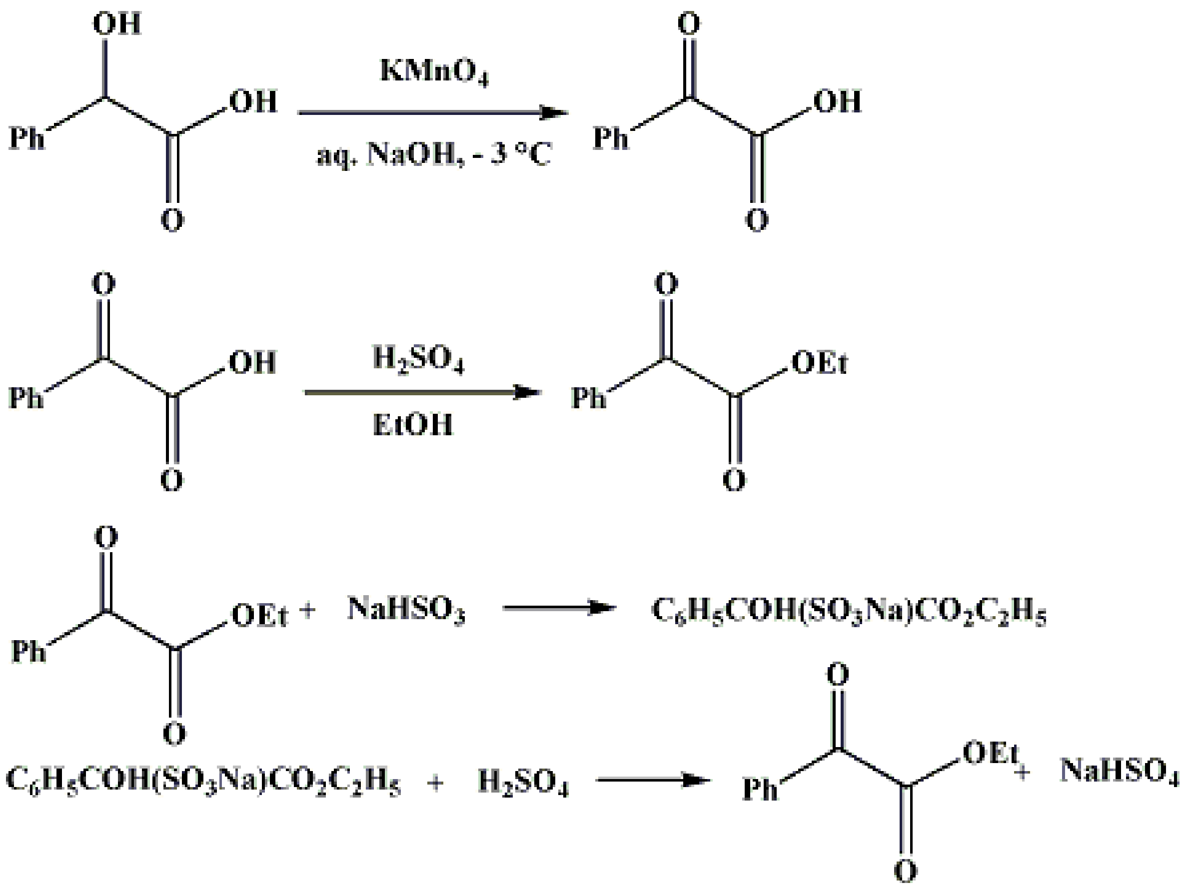
Organic Syntheses, CV 1, 241

ETHYL BENZOYLFORMATE

[Gloyoxylic acid, phenyl-, ethyl ester]



Submitted by B. B. Corson, Ruth A. Dodge, S. A. Harris, and R. K. Hazen.
Checked by C. S. Marvel and F. E. Kendall.

1. Procedure

In a 12-l. earthenware crock equipped with an efficient stirrer and a strong motor are placed 375 g. (2.5 moles) of mandelic acid (p. 336) and 500 cc. of water. The stirrer is started, and a cool solution of 110 g. (2.8 moles) of sodium hydroxide (or 115 g. of technical sodium hydroxide) in 500 cc. of water is added. This is followed by the addition of 2000 g. of cracked ice and then after a few minutes by 275 g. (1.74 moles) of finely ground u.s.p. potassium permanganate in portions over a period of one-half hour. The mixture is stirred for one and one-half hours, the temperature being maintained at –2° to –4°. About 5 kg. of ice is necessary. At the end of one and one-half hours the mixture is tested for excess permanganate by placing a drop on a piece of filter paper; a black or brown center of manganese dioxide is formed, a greenish ring around this, and an outer ring which is colorless in the absence and pink in the presence of excess permanganate. Any excess is removed by adding ethyl alcohol, generally about 200–300 cc.

When the permanganate has been destroyed, the stirrer is stopped and the manganese dioxide allowed to coagulate for one hour. The mixture is filtered through two 20-cm. Büchner funnels; the filter cakes are washed with 1000 cc. of water (Note 1) and sucked dry again (Note 2). The filtrate is evaporated to 800–1000 cc. over a free flame. While the volume of solution is large, two 30-cm. evaporating dishes are used, but toward the end the two solutions are combined in one dish. The evaporation requires two to three hours. Sometimes a little manganese dioxide will be coagulated during the evaporation; this should be removed by filtration.

The yellowish solution is transferred to a 3-l. round-bottomed, wide-necked flask and cooled with running water while 300 cc. of concentrated sulfuric acid is added slowly from a separatory funnel. This acidification process requires thirty minutes, during which time the temperature should not rise much above 25°. The liquid froths and about 30 g. of benzoic acid separates but it is not filtered. Extraction of the reaction mixture with 200-cc. portions of ether until 1500 cc. of extract has been collected is now carried out in a separatory funnel. The ether is distilled on a steam bath from a 1-l. round-bottomed, wide-necked flask connected with a water condenser, the extract being added from a separatory funnel as fast as the ether distils. After most of the ether has been removed, the heating is continued for an additional one-half hour.

The crude liquid acid (about 300 g.) is cooled with running water, and 15 cc. of concentrated sulfuric acid is added; the clear yellow oil becomes cloudy. The acid is esterified by passing the vapor of ethyl alcohol into the hot solution as in the preparation of ethyl fumarate in Org. Syn. **10**, 48, or by the method described for ethyl cyanoacetate in Org. Syn. **3**, 54, with the following changes: all three flasks, the alcohol flask, the trap, and the esterification flask are 1-l. round-bottomed, wide-necked flasks. The alcohol flask and the trap are set on adjacent steam baths. The esterification flask is placed in an oil bath which is heated by a free flame. A safety tube leads from the alcohol flask and dips under 7.5 cm. of mercury contained in a side-arm tube. This mercury safety valve avoids all dangers which might result from the development of excess pressure within the system (Note 3). The temperature of the esterification mixture is kept at 105–110° and ethyl alcohol vapor is passed through until 500 cc. of distillate has been collected. This requires about three hours. The distillate consists of alcohol, water, and a little ether.

The crude ester is cooled, an equal volume of benzene is added, then the free acid is neutralized by shaking with about 250 cc. of a 10 per cent solution of sodium carbonate (Note 4). The benzene solution is poured into 1300 cc. of a saturated solution of sodium bisulfite (about 60 g. of technical sodium bisulfite per 100 cc.), contained in a wide-necked bottle equipped with an efficient stirrer, and the mixture stirred for two and one-half hours. The mixture soon warms up a little and becomes semi-solid. It is filtered through a 20-cm. Büchner funnel and carefully washed, first with 200 cc. of a saturated solution of sodium bisulfite, finally with two 150-cc. portions of benzene (Note 5) and (Note 6). The white pearly flakes of the sodium bisulfite addition product are transferred to a 3-l. round-bottomed, wide-necked flask equipped with a mechanical stirrer and containing 700 cc. of water, 175 cc. of

concentrated sulfuric acid, and 500 cc. of benzene. The flask is heated on a steam bath under a hood, the temperature being kept at 55°, and the mixture is stirred for thirty minutes (Note 7).

The solution is then poured into a separatory funnel, the benzene separated, and the water layer extracted with a 200-cc. portion of benzene. The combined benzene solution is shaken with excess of 10 per cent sodium carbonate solution to remove free acid and sulfur dioxide (Note 8). The benzene is washed with a little water and then dried over anhydrous potassium carbonate (Note 9). The benzene is distilled at ordinary pressure over a free flame from a 500-cc. Claisen flask, the solution being added from a separatory funnel as fast as the benzene distils. It is advisable to distil the ester under reduced pressure although it can be done under ordinary pressure. The fraction distilling around 118°/5 mm., 130°/10 mm., 138°/15 mm., 148°/25 mm., 155° 35 mm., or 254°/760 mm. is collected. The yield of ethyl benzoylformate is 155–175 g. (35–40 per cent of the theoretical amount) (Note 10) and (Note 11).

2. Notes

1. In order to wash the manganese dioxide cake it must be removed from the funnel and stirred into a thin paste with water.
2. It is advisable not to stop the experiment until after filtration since manganese dioxide slowly oxidizes benzoylformic acid to benzoic acid.
3. If it is necessary to generate the steam from a can or similar contrivance, the steam generator should be connected with a safety tube dipping under 20–25 cm. of mercury.
4. The sodium carbonate solution contains 8–15 g. of unesterified acid which can be easily recovered by acidification with concentrated hydrochloric acid followed by extraction with ether.
5. The benzene contains 80 g. of impure ethyl benzoate boiling at 180–260° and containing about 20 per cent of ethyl benzoylformate. In the preparation of the methyl ester the benzene contains 60 g. of impure methyl benzoate, boiling at 170–250°, and containing about 20 per cent of methyl benzoylformate.
6. If the stirring is not very efficient the benzene layer should be stirred with the bisulfite solution a second time.
7. Longer contact with acid tends to hydrolyze the ester. The reaction should be performed under a hood since considerable sulfur dioxide is generated. A gas-absorption trap (Fig. 7 on p. 97) may be used.
8. This sodium carbonate solution contains about 4 g. of impure benzoylformic acid.
9. The potassium carbonate holds some ester which may be recovered by adding water and separating the ester layer.
10. The methyl ester is easily made by substituting methyl for ethyl alcohol. It boils at 250–255°/760 mm. The yield is about 175 g. (43 per cent of the theoretical amount).
11. By a slight modification of the procedure, crystalline benzoylformic acid

(phenylglyoxylic acid) can be isolated. The oxidation of 375 g. (2.5 moles) of mandelic acid by cold alkaline potassium permanganate is performed exactly as described in the first paragraph (p. 241). After removal of the manganese dioxide, the combined filtrates are evaporated to 2500–3000 cc. and acidified carefully, so as to precipitate only benzoic acid, by the addition of 100 cc. (190 g.) of concentrated sulfuric acid (sp. gr. 1.84) previously diluted with an equal volume of water and cooled. The benzoic acid (25–30 g.) which separates is removed by filtration. The filtrate is made alkaline with 75 g. of sodium hydroxide and concentrated to 800–1000 cc. The subsequent acidification, with 280–300 cc. of concentrated sulfuric acid, and ether extraction are performed as described in the third paragraph (p. 242). After the ether is removed, about 280 g. of crude, liquid benzoylformic acid remains.

Since, at this stage, enough water is present to render the acid immiscible with carbon disulfide, the liquid residue is dried by placing it in a distilling flask with 70–90 cc. of toluene and distilling off the water and toluene (preferably under slightly reduced pressure). The dried liquid residue is taken up in an equal volume of carbon disulfide; with adequate precautions to exclude moisture, the solution is cooled thoroughly in an ice-salt mixture. The yield of product melting at 58–61° is 190–250 g. (50–67 per cent of the theoretical amount). (Charles D. Hurd and R. W. McNamee, private communication. Checked by Reynold C. Fuson and W. E. Ross.)

12. This work was done with the aid of a grant to the submitters from the Cyrus M. Warren fund of the American Academy of Arts and Sciences.

3. Discussion

Benzoylformic acid can be prepared by the hydrolysis of benzoyl cyanide,[1] and the oxidation of acetophenone[2] and of mandelic acid.[3] The ester can be prepared from the acid by direct esterification.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 114

References and Notes

1. Claisen, Ber. **10**, 429, 844 (1877); **12**, 626 (1879); Buchka, Ber. **20**, 395 (1887); Simon, Ann. chim. phys. (7) **9**, 508 (1896).
2. Glücksmann, Monatsh. **11**, 248 (1890); Claus and Neukranz, J. prakt. Chem. (2) **44**, 80 (1891).
3. Hunaeus and Zincke, Ber. **10**, 1489 (1877); Acree, Am. Chem. J. **50**, 391 (1913).
4. Claisen, Ber. **10**, 846 (1877); Acree, Am. Chem. J. **50**, 392, 393 (1913).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Gloyoxylic acid, phenyl-, ethyl ester

ethyl alcohol (64-17-5)

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

methanol (67-56-1)

ether (60-29-7)

sodium hydroxide (1310-73-2)

Mandelic acid (90-64-2)

potassium permanganate (7722-64-7)

sodium carbonate (497-19-8)

sulfur dioxide (7446-09-5)

Benzoic acid (65-85-0)

sodium bisulfite (7631-90-5)

Acetophenone (98-86-2)

toluene (108-88-3)

carbon disulfide (75-15-0)

manganese dioxide (1313-13-9)

Ethyl cyanoacetate (105-56-6)

ethyl benzoate (93-89-0)

Ethyl benzoylformate (1603-79-8)

ethyl fumarate (2459-05-4)

Benzoylformic acid, phenylglyoxylic acid (611-73-4)

methyl benzoate (93-58-3)

Methyl benzoylformate (15206-55-0)

Benzoyl cyanide (613-90-1)

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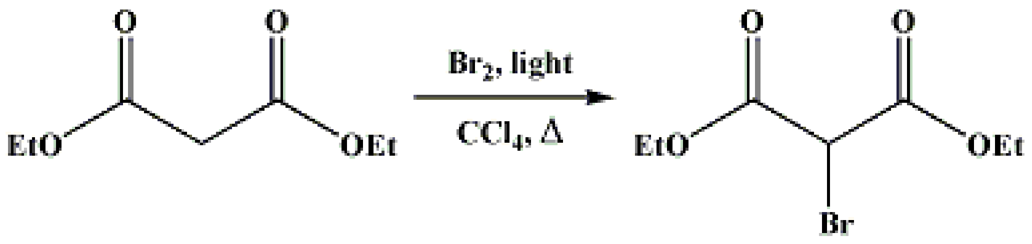
Organic Syntheses, CV 1, 245

ETHYL BROMOMALONATE

[Malonic acid, bromo-, ethyl ester]



Submitted by C. S. Palmer and P. W. McWherter.
Checked by Roger Adams and M. M. Brubaker.

1. Procedure

A 1-l. three-necked flask is fitted with a stirrer, a reflux condenser with a tube leading to a flask of water for absorption of hydrogen bromide, and a separatory funnel with a stem drawn to a fine tip which reaches almost to the blades of the stirrer. In the flask are placed 160 g. (1 mole) of diethyl malonate (Note 1) and 150 cc. of carbon tetrachloride. In the separatory funnel is placed 165 g. (53 cc., 1.03 moles) of dry bromine (Note 2). The stirrer is started, and a few cubic centimeters of bromine are run into the solution. A large electric bulb is held under the flask until the reaction starts. Then the rest of the bromine is added gradually at such a rate as to keep the liquid boiling gently. It is then refluxed until no more hydrogen bromide is evolved (about one hour).

The mixture is cooled and washed five times with 50-cc. portions of 5 per cent sodium carbonate solution. It is then distilled under reduced pressure, fractions being taken up to 130°/40 mm. and at 130–150°/40 mm. The residue amounts to about 20 g. (Note 3). The lower-boiling fraction is redistilled. The combined fractions boiling at 130–150°/40 mm. are redistilled under reduced pressure. The product boiling at 132–136°/33 mm. (121–125°/16 mm.) amounts to 175–180 g. (73–75 per cent of the theoretical amount). Redistillation of the low fractions gives about 15 g. more of the product.

2. Notes

1. Commercial diethyl malonate distilled under reduced pressure and collected over a 3° range was used.
2. Commercial bromine was dried by shaking with an equal volume of concentrated sulfuric acid. A slight excess of bromine is used to insure complete bromination.
3. A part of the higher-boiling fractions consists of ethyl dibromomalonate (W. W. Hartman, private communication).

3. Discussion

Ethyl bromomalonate can be prepared by the bromination of diethyl malonate either without a solvent[1] or in carbon tetrachloride as described in the procedure.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 271
- Org. Syn. Coll. Vol. 2, 273

References and Notes

1. Knoevenagel, Ber. **21**, 1356 (1888).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

hydrogen bromide (10035-10-6)

sodium carbonate (497-19-8)

bromine (7726-95-6)

carbon tetrachloride (56-23-5)

Ethyl bromomalonate, Malonic acid, bromo-, ethyl ester

diethyl malonate (105-53-3)

ethyl dibromomalonate

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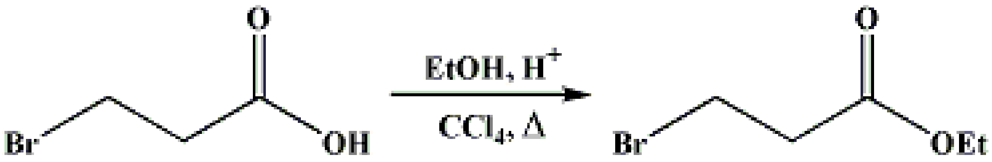
Organic Syntheses, CV 1, 246

ETHYL β-BROMOPROPIONATE

[Propionic acid, β-bromo-, ethyl ester]



Submitted by E. C. Kendall and B. McKenzie.
Checked by H. T. Clarke and M. R. Brethen.

1. Procedure

To the crude mixture of ammonium bromide and β-bromopropionic acid, prepared as described on p. 131, from 317 g. of ethylene cyanohydrin, are added 1200 cc. of carbon tetrachloride (Note 1) and 200 cc. of the same solvent which has been shaken with the aqueous distillates; the ammonium bromide is filtered off and washed with 200 cc. of carbon tetrachloride. The watery layer, amounting to about 350 cc., is separated and shaken with 100 cc. of carbon tetrachloride. To the united carbon tetrachloride solutions are added 450 cc. of 95 per cent ethyl alcohol and 10 g. of sulfosalicylic acid or phenolsulfonic acid to act as a catalyst (Note 2).

The mixture is now boiled in a 3-l. flask, the vapors being passed through an efficient condenser and the condensed liquid run into an automatic separator (p. 422) so arranged that the heavy liquid is returned to the flask and the lighter aqueous liquid discarded. If the boiling is sufficiently vigorous no more water will separate after two to two and one-half hours' boiling (Note 3). The reaction mixture is now cooled, washed with dilute sodium carbonate solution, and distilled with the use of a column until the temperature of the vapor reaches 85° and that of the liquid in the flask about 115°. The residue is then transferred to a flask provided with a column for distillation under reduced pressure (Fig. 9, p. 130) and distilled. The fraction boiling at 60–65°/15 mm. is collected, 690–700 g. of pure ethyl β-bromopropionate being obtained (85–87 per cent of the theoretical amount). A high-boiling residue, probably consisting of ethyl hydracrylate, remains in the flask, but the amount is practically negligible.

2. Notes

1. As in the preparation of the β-bromopropionic acid (p. 131), benzene must not be substituted for the carbon tetrachloride, as it has been found impossible to make a satisfactory separation of this solvent from the ester.
2. The esterification may be carried out without the addition of a sulfonic acid, as traces of hydrobromic acid generally remain in the crude material; but since the time of operation must be kept as short as possible this omission is not

recommended. It has been found that, if the water is not removed and the mixture boiled under a reflux condenser for two hours before the distillate is passed through the automatic separator, the yield falls to 70–75 per cent of the theoretical amount.
3. It is important to carry out the esterification as rapidly as possible in order to cut down to a minimum the formation of ethyl hydracrylate, which takes place by the action of water on the β-bromopropionic acid or ester; an efficient condenser is therefore necessary. For the same reason it is necessary to remove all residual water from the mixture before adding the alcohol.

3. Discussion

Ethyl β-bromopropionate can be prepared by the esterification of β-bromopropionic acid,[1] and by the addition of hydrogen bromide to ethyl acrylate.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 262

References and Notes

1. Lederer, J. prakt. Chem. (2) **42**, 384 (1890); Barthe, Compt. rend. **118**, 1268 (1894).
2. Org. Syn. **20**, 64.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ester

sulfonic acid

ethyl alcohol, alcohol (64-17-5)

Benzene (71-43-2)

ammonium bromide (12124-97-9)

HYDROBROMIC ACID, hydrogen bromide (10035-10-6)

sodium carbonate (497-19-8)

carbon tetrachloride (56-23-5)

β-Bromopropionic acid (590-92-1)

Ethylene cyanohydrin (109-78-4)

Ethyl β-bromopropionate, Propionic acid, β-bromo-, ethyl ester (539-74-2)

sulfosalicylic acid

phenolsulfonic acid

ethyl hydracrylate (687-47-8)

ethyl acrylate (140-88-5)

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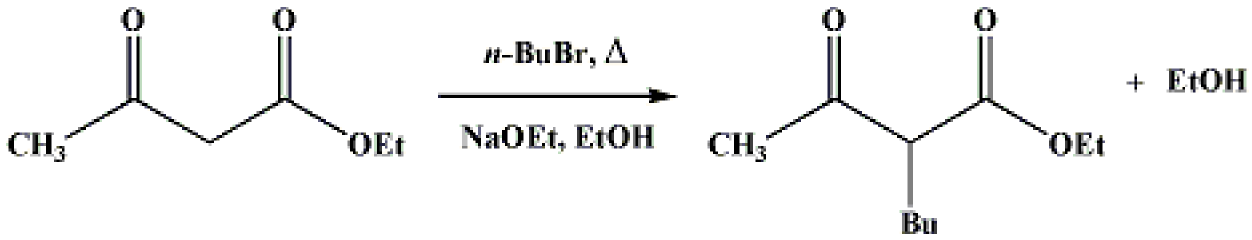
ETHYL *n*-BUTYLACETOACETATE

[Caproic acid, α-acetyl-, ethyl ester]



Submitted by C. S. Marvel and F. D. Hager.
Checked by Frank C. Whitmore and W. F. Singleton.

1. Procedure

A 5-l. round-bottomed flask, fitted with an efficient mechanical stirrer (Note 1), a reflux condenser, the upper end of which is protected by a calcium chloride tube, and a separatory funnel, is arranged for heating on a steam bath.

In the flask is placed 2.5 l. of absolute alcohol (Note 2), and then there is added gradually 115 g. (5 atoms) of metallic sodium cut into pieces. This requires three to four hours. After all the sodium has dissolved, 650 g. (5 moles) of ethyl acetoacetate (Note 3) is added. The stirrer is started and the solution heated to gentle boiling. To the boiling solution 750 g. (5.47 moles) of *n*-butyl bromide (Note 4) is added over a period of about two hours. The refluxing and stirring are continued until a sample of the solution is neutral to moist litmus paper. The time varies from six to ten hours.

When the reaction is complete, the mixture is cooled, and the solution is decanted from the sodium bromide. The salt is washed with 100 cc. of absolute alcohol, and the washings are added to the main solution. The alcohol (Note 5) is separated from the substituted acetoacetic ester by distilling through a short column from a steam bath. The crude residue after removal of the alcohol weighs about 925 g. It is satisfactory for hydrolysis to give the corresponding ketone (p. 351). If the pure ester is desired, the crude product is distilled under reduced pressure. The yield of product boiling at 112–117°/16 mm. is 642–672 g. (69–72 per cent of the theoretical amount) (Note 6).

2. Notes

1. The stirrer should be efficient in order to prevent bumping due to the settling of the sodium bromide which is formed during the reaction.
2. *Absolute Alcohol.*—The grade of absolute alcohol is important. Alcohol dried with sodium ethoxide (p. 259) is satisfactory. It is more effective to dry alcohol with magnesium methoxide if the presence of methyl alcohol in the absolute

alcohol is permissible. This may be done by dissolving 24 g. of magnesium turnings in 200 cc. of absolute methyl alcohol (the reaction is very vigorous) and then adding 3 l. of the ordinary grade of absolute alcohol (about 99.5 per cent). The mixture is refluxed for about five hours and distilled into the flask in which the absolute alcohol is to be used.

A like principle has been suggested recently for the preparation of anhydrous alcohols in general. It involves the addition of magnesium and a little iodine to the alcohol which is to be dehydrated.[1]

3. The ethyl acetoacetate used in these experiments boiled over a 5° range under reduced pressure. The product prepared as described on p. 235 is satisfactory.

4. The *n*-butyl bromide (p. 28) boiled over a range of three degrees. The excess was used in order to decrease the time necessary to complete the reaction.

5. The alcoholic solution should be protected from moisture, and the alcohol which is recovered by the distillation should be treated with sodium and boiled under a reflux condenser to remove the excess of alkyl halide. After distillation the alcohol may then be used in a subsequent preparation.

6. This reaction is very general and other substituted acetoacetic esters may be obtained in approximately the same yields if this procedure is followed.

3. Discussion

Ethyl *n*-butylacetoacetate can be prepared by the action of *n*-butyl bromide on the sodium salt of ethyl acetoacetate.[2] The procedure described is the usual one for alkylating ethyl acetoacetate.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 5
- Org. Syn. Coll. Vol. 1, 99
- Org. Syn. Coll. Vol. 1, 119
- Org. Syn. Coll. Vol. 1, 205
- Org. Syn. Coll. Vol. 1, 237
- Org. Syn. Coll. Vol. 1, 238
- Org. Syn. Coll. Vol. 1, 250
- Org. Syn. Coll. Vol. 1, 254
- Org. Syn. Coll. Vol. 1, 258
- Org. Syn. Coll. Vol. 1, 261
- Org. Syn. Coll. Vol. 1, 272
- Org. Syn. Coll. Vol. 1, 296
- Org. Syn. Coll. Vol. 1, 351
- Org. Syn. Coll. Vol. 1, 451
- Org. Syn. Coll. Vol. 1, 528
- Org. Syn. Coll. Vol. 2, 318
- Org. Syn. Coll. Vol. 2, 372

- Org. Syn. Coll. Vol. 3, 16
- Org. Syn. Coll. Vol. 4, 630

References and Notes

1. Lund and Bjerrum, Ber. **64**, 210 (1931).
2. Tafel and Jürgens, Ber. **42**, 2555 (1909); Ryan and Shannon, Proc. Roy. Irish Acad. **36**B, 322 (1924) [C. A. **19**, 470 (1925)]; Hess and Bappert, Ann. **441**, 153 (1925).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

acetoacetic ester

acetoacetic esters

sodium salt of ethyl acetoacetate

alcohol (64-17-5)

methyl alcohol (67-56-1)

magnesium, magnesium turnings (7439-95-4)

n-butyl bromide (109-65-9)

sodium bromide (7647-15-6)

iodine (7553-56-2)

sodium, metallic sodium (13966-32-0)

sodium ethoxide (141-52-6)

Ethyl acetoacetate (141-97-9)

Caproic acid, α-acetyl-, ethyl ester, ETHYL n-BUTYLACETOACETATE (1540-29-0)

magnesium methoxide

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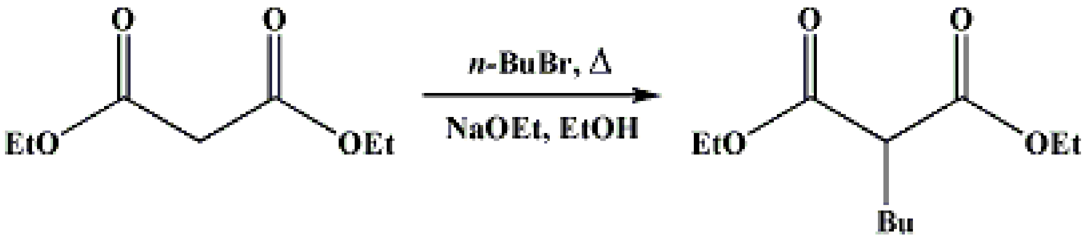
Organic Syntheses, CV 1, 250

ETHYL *n*-BUTYLMALONATE

[Malonic acid, butyl-, ethyl ester]



Submitted by Roger Adams and R. M. Kamm.
Checked by F. C. Whitmore and Milton Puterbaugh.

1. Procedure

A 5-l. round-bottomed flask, fitted with a rubber stopper holding a reflux condenser, a separatory funnel, and a mechanical stirrer, is clamped over a steam or water bath. In the flask is placed 2.5 l. of absolute alcohol (Note 1) and then there is added gradually, through the condenser, 115 g. (5 atoms) of clean sodium cut into pieces of suitable size. If the action becomes too violent, the mixture may be cooled by water poured over the outside of the flask. The sodium ethoxide solution is stirred, and cooled to about 50°, after which 825 g. (780 cc., 5.15 moles) of diethyl malonate (Note 2) is added slowly through the separatory funnel. To the clear solution is added gradually 685 g. (535 cc., 5.0 moles) of *n*-butyl bromide (Note 3). The reaction commences almost immediately and considerable heat is generated. If the addition is too rapid, the reaction may become violent enough to require cooling of the flask by pouring water over it. Up to this point, the time required is about two hours.

The reaction mixture is refluxed until neutral to moist litmus; this requires about two hours. The flask is then connected with a condenser set for distillation. As much alcohol as possible is distilled off by means of the steam or water bath. A period of about six hours is required for this distillation, and about 2 l. of alcohol is recovered.

The residue from which no more alcohol can be distilled is treated with about 2 l. of water and shaken thoroughly. The upper layer of *n*-butylmalonic ester is separated (Note 4) and distilled under diminished pressure from a 2- or a 3-l. Claisen flask. First a low-boiling portion is collected, consisting of alcohol, water, and butyl bromide; then a small intermediate fraction of unchanged malonic ester comes over; and finally *n*-butylmalonic ester boiling at 140–145°/40 mm., 130–135°/20 mm., and 235–240°/760 mm. The first fractions amount to less than 100 cc., while the main fraction weighs 860–970 g. (80–90 per cent of the theoretical amount).

2. Notes

1. The quality of the absolute alcohol used has a very marked effect upon the yield. It is desirable to reflux ordinary "absolute" alcohol with about one-twentieth of its weight of sodium and then to distil it directly into the flask in which it is to be used. See Note 2 on p. 249.

A trial run with alcohol of 98.4 per cent purity gave only a 66 per cent yield.

2. The malonic ester used should be redistilled, preferably under diminished pressure, and a 2° fraction used in the preparation. Ordinary commercial malonic ester contains up to 15 per cent of low-boiling impurities.

3. Redistilled *n*-butyl bromide (p. 28) boiling over a 1° range should be used.

4. It is not practical to filter off the sodium bromide either before or after the distillation of the alcohol, as the separation of the ester from the water layer is then very difficult.

3. Discussion

Ethyl *n*-butylmalonate can be prepared by the action of *n*-butyl halides on sodium malonic ester,[1] and by the catalytic reduction of a mixture of butyraldehyde, malonic ester, and piperidine in the presence of Raney nickel.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 258
- Org. Syn. Coll. Vol. 2, 93
- Org. Syn. Coll. Vol. 2, 194
- Org. Syn. Coll. Vol. 2, 284
- Org. Syn. Coll. Vol. 2, 416
- Org. Syn. Coll. Vol. 2, 487

References and Notes

1. Bischoff, Ber. **28**, 2622 (1895); Adams and Marvel, J. Am. Chem. Soc. **42**, 316 (1920); Levene and Taylor, J. Biol. Chem. **54**, 351 (1922); Bhide and Sudborough, J. Indian Inst. Sci. A, **8**, 89 (1925) [Chem. Zentr. I, 81 (1926)]; Dolique, Ann. chim. **15**, 439 (1931).
2. Wojcik and Adkins, J. Am. Chem. Soc. **56**, 2424 (1934).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alcohol (64-17-5)

n-butyl bromide (109-65-9)

sodium bromide (7647-15-6)

Raney nickel (7440-02-0)

sodium (13966-32-0)

piperidine (110-89-4)

sodium ethoxide (141-52-6)

butyraldehyde (123-72-8)

diethyl malonate (105-53-3)

Malonic acid, butyl-, ethyl ester, ETHYL n-BUTYLMALONATE

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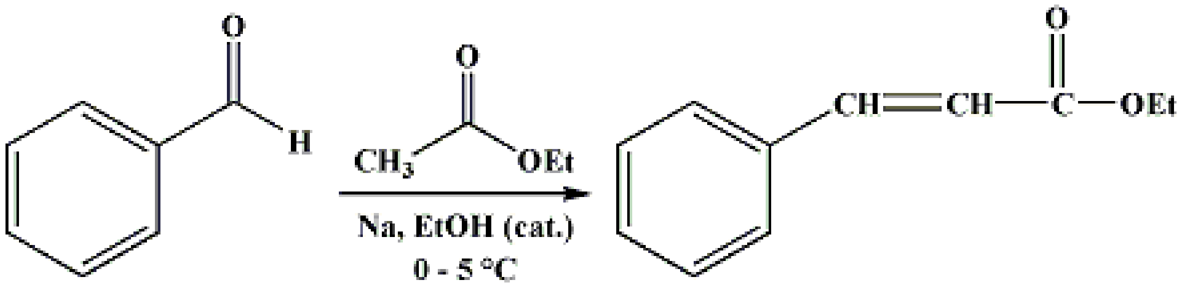
ETHYL CINNAMATE



Submitted by C. S. Marvel and W. B. King.
Checked by Henry Gilman, R. E. Fothergill, and R. E. Brown.

1. Procedure

In a 2-l. two-necked flask fitted with a short reflux condenser and mechanical stirrer (Note 1) are placed 400 cc. of dry xylene (Note 2) and 29 g. (1.26 atoms) of clean sodium (Note 3) cut in small pieces. The flask is surrounded by an oil bath and heated until the sodium has melted. At this point the stirrer is started and the sodium is broken up into very small particles (Note 4). The oil bath is removed, but stirring is continued until the sodium has solidified in very fine particles. The xylene is then poured off, and to the sodium is added 460 cc. (4.7 moles) of absolute ethyl acetate (Note 5) containing 3–4 cc. of absolute ethyl alcohol (Note 6). The flask is quickly cooled to 0° and 106 g. (1 mole) of pure benzaldehyde (Note 7) is added slowly from a separatory funnel while the mixture is stirred. The temperature is held between 0 and 5° (Note 8). The reaction starts as soon as the benzaldehyde is added, as is shown by the production of a reddish substance on the particles of the sodium. About one and one-half to two hours are required for this addition. The stirring is continued until practically all of the sodium has reacted (one hour after all the aldehyde has been added).

When most of the sodium (Note 9) has disappeared, 90–95 cc. of glacial acetic acid is added and the mixture is carefully diluted with water. The ester layer is separated, the water layer is extracted with about 25–50 cc. of ethyl acetate, and the combined ester portions are washed with 300 cc. of 6 *N* hydrochloric acid and then dried with sodium sulfate. The ethyl acetate is distilled from a water bath and the remaining liquid is transferred to a Claisen flask and distilled from an oil bath under reduced pressure. A small fraction comes over below 128°/6 mm. and is discarded. The ethyl cinnamate (Note 10) boils at 128–133°/6 mm.; 168–173°/46 mm. The yield is 120–130 g. (68–74 per cent of the theoretical amount).

2. Notes

1. The stirrer must be very efficient in order to powder the sodium without

splashing it onto the walls of the flask above the solvent.

2. The use of sodium powdered under xylene allows the reaction to be carried out much more rapidly than is the case if the sodium is cut into small pieces with a knife. Toluene may be used in place of xylene. The sodium should be as free as possible from oxide.

3. To obtain the maximum yield it is necessary to use slightly more than one equivalent of sodium. When exactly one equivalent is used the yield is about 60 per cent of the theoretical amount.

4. The powdered sodium may also be prepared by melting the sodium under hot xylene and shaking in a tightly stoppered flask wrapped in a heavy cloth.

5. The grade of ethyl acetate used in the preparation is very important. The absolute ethyl acetate (99.5 per cent) sold by the U. S. Industrial Alcohol Company is very satisfactory. If this grade is not available the ordinary ester may be purified by washing first with sodium carbonate solution, then with saturated calcium chloride solution and finally drying over anhydrous potassium carbonate.

6. A small amount of absolute alcohol is needed to start the reaction. When no alcohol is added the yields are consistently 55–60 per cent of the theoretical amount. When too much alcohol (10–15 cc.) is added the yields drop again.

7. Technical benzaldehyde is washed with sodium carbonate and distilled under reduced pressure with minimum atmospheric exposure before use. The material used in checking these directions boiled over a 3° range.

8. The temperature should never be allowed to go above 10° and the best yields of pure product are obtained when the temperature is kept within the limits mentioned in the procedure.

9. Usually during the reaction a certain amount of sodium is thrown on the upper part of the flask out of the reaction mixture and forms a cake. In decomposing the mixture with glacial acetic acid and water care must be taken that this sodium does not react violently and thus cause a fire.

10. During the distillation of the ester a reddish semi-solid mass sometimes appears in the flask. This mass melts down if the oil bath is heated to 220–230° and the distillation continues smoothly.

3. Discussion

Ethyl cinnamate can be prepared by the action of ethyl alcohol on cinnamic acid in the presence of hydrogen chloride or sulfuric acid,[1] and by the condensation of ethyl acetate and benzaldehyde in the presence of sodium.[2] The procedure described is a slight modification of that by Claisen.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 194
- Org. Syn. Coll. Vol. 2, 270

- Org. Syn. Coll. Vol. 4, 910

References and Notes

1. Kopp, Ann. **95**, 318 (1855); Weger, Ann. **221**, 75 (1883); Brühl, Ann. **235**, 19 (1886); Fischer and Speier, Ber. **28**, 3254 (1895).
2. Claisen, Ber. **23**, 977 (1890); Stoermer and Kippe, Ber. **38**, 3034 (1905).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethyl alcohol, alcohol (64-17-5)

calcium chloride (10043-52-4)

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

hydrogen chloride, hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ethyl acetate (141-78-6)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

benzaldehyde (100-52-7)

toluene (108-88-3)

sodium (13966-32-0)

xylene (106-42-3)

Ethyl cinnamate (103-36-6)

cinnamic acid (621-82-9)

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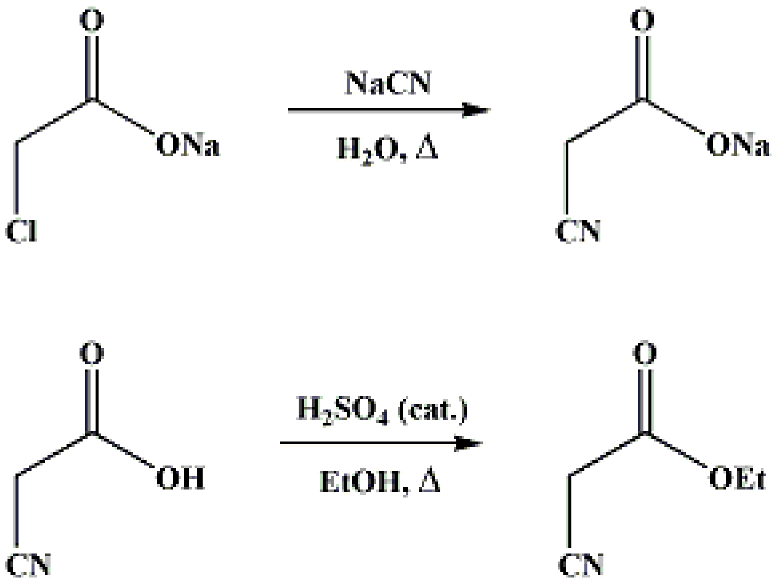
Organic Syntheses, CV 1, 254

ETHYL CYANOACETATE

[Acetic acid, cyano-, ethyl ester]



Submitted by J. K. H. Inglis
Checked by C. S. Marvel, W. F. Tuley, and S. V. Puntambeker.

1. Procedure

In a 5-l. round-bottomed flask, 500 g. (5.3 moles) of chloroacetic acid is dissolved in 700 cc. of water. The solution is warmed to 50° and neutralized with anhydrous sodium carbonate of which about 290 g. (2.7 moles) is required (a slight excess of sodium carbonate is not disadvantageous). Meanwhile 294 g. (5.8 moles) of sodium cyanide (97 per cent) is dissolved in 750 cc. of water warmed to 55°. The sodium cyanide solution is then added to the sodium chloroacetate solution, which has been cooled to room temperature, with rapid mixing of the two solutions and cooling under the water tap. The temperature rapidly rises; when it reaches 95° the solution should be cooled by adding 200 cc. of cold water and this repeated, if necessary, until the temperature no longer rises (Note 1). The solution is heated to the boiling point and boiled for five minutes (Note 2), and finally cooled with running water for one-half hour.

The solution is filtered if not clear, and the cyanoacetic acid is set free (Hood) by adding with thorough stirring 694 g. (600 cc., 5.8 moles) (a slight excess) of commercial hydrochloric acid (sp. gr. 1.156). The solution is evaporated on a water bath at 60–70° (Note 3) under a pressure of 20–30 mm. and the evaporation continued until practically no more distillate (Note 4) comes over. To the residue is added 600 cc. of 95 per cent alcohol. The solution is filtered (Note 5) from the sodium chloride, and the residue is washed with another 500-cc. portion of alcohol.

On evaporating the alcoholic solution under reduced pressure from a water bath held at 50–60° (Note 6) the residue weighs about 540 g. A mixture of 600 cc. of absolute alcohol (p. 249) and 10 cc. of concentrated sulfuric acid (Note 7) is then added. The mixture is then heated on the water bath under a reflux condenser for three hours. The excess of alcohol and some of the water formed are removed by distillation under reduced pressure and the residue again heated for two hours with 300 cc. of absolute alcohol and an additional 4 cc. of concentrated sulfuric acid. The alcohol is removed by distillation under reduced pressure, and when the ester has cooled to room temperature, the sulfuric acid is neutralized with a concentrated solution of sodium carbonate; the ester (upper layer) is separated, and the aqueous solution extracted with ether, or preferably benzene; about one-tenth of the yield is in the extract. The combined products are placed in a 1-l. distilling flask and distilled under reduced pressure after the solvent and alcohol and water have been removed. The ester is collected at 94–99°, chiefly at 97–98°/16 mm. (Note 8). The yield of a product analyzing about 97–98 per cent ethyl cyanoacetate amounts to 474–492 g. (77–80 per cent of the theoretical amount) (Note 9) and (Note 10).

2. Notes

1. If the reaction between the cyanide and chloroacetate becomes too vigorous, hydrogen cyanide is set free and partly changed to brown material and a corresponding amount of glycolate is formed.
2. The color at this stage should be yellow or a light brown.
3. If the mixture is heated to a higher temperature there is a considerable loss due to decomposition of the cyanoacetic acid.
4. Toward the end of the distillation, hydrochloric acid should be present in the distillate if excess was added in the first place. During the addition of the hydrochloric acid the excess of cyanide is decomposed, giving off hydrogen cyanide.
5. It is much easier to remove the salt by means of a centrifuge. If this method is used the salt should be washed first with 500 cc. and then with 250 cc. of alcohol.
6. The solution containing mineral acid must not be evaporated at a high temperature or diethyl malonate will be formed.
7. The addition of sulfuric acid will probably produce a slight precipitate, but this may be ignored if the original treatment with hydrochloric acid was properly carried out.
8. Ethyl cyanoacetate boils at 97°/16 mm.; 101°/19 mm.; and 107°/27 mm.
9. The product was analyzed for nitrogen by the Kjeldahl method.
10. The procedure described in Org. Syn. **10**, 48, for the esterification of fumaric acid can probably be used for the preparation of the methyl and the ethyl esters of cyanoacetic acid.

3. Discussion

Ethyl cyanoacetate can be prepared by the action of sodium[1] or potassium cyanide[2] on ethyl chloroacetate, and by the action of sodium cyanide on sodium chloroacetate, followed by esterification.[3] The procedure described differs from that given in Org. Syn. **3**, 53, mainly in the use of hydrochloric acid in place of sulfuric acid in the liberation of the cyanoacetic acid from the sodium salt, and in the simplified esterification process. These are slight but very important differences and make the procedure much easier to carry out in the laboratory. Moreover, the yields are higher. The preparation from ethyl chloroacetate and potassium cyanide in methyl alcoholic solution[4] gives a mixture of methyl and ethyl esters.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 179

References and Notes

1. Stephens, J. Soc. Chem. Ind. **43**, 313 T, 327 T (1924).
2. Finkelstein, Ann. **133**, 339 (1865); van't Hoff, Jahresber. 561 (1874); Henry, Bull. soc. chim. **46**, 62 (1886); Noyes, J. Am. Chem. Soc. **26**, 1545 (1904); Scarborough, Proc. Chem. Soc. **30**, 307 (1914).
3. Kohler and Allen, Org. Syn. **3**, 53 (1923); Phelps and Tillotson, Am. J. Sci. **26**, 264, 275 (1908); Stephens, J. Soc. Chem. Ind. **43**, 313 T, 327 T (1924).
4. Noyes, J. Am. Chem. Soc. **26**, 1545 (1904).
5. Urushibara, Bull. Chem. Soc. Japan, **2**, 143 (1927) [C. A. **21**, 2879 (1927)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

methyl and the ethyl esters of cyanoacetic acid

alcohol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether (60-29-7)

sodium cyanide (143-33-9)

sodium chloride (7647-14-5)

hydrogen cyanide (74-90-8)

sodium carbonate (497-19-8)

nitrogen (7727-37-9)

potassium cyanide (151-50-8)

chloroacetic acid (79-11-8)

sodium chloroacetate (3926-62-3)

sodium (13966-32-0)

Ethyl chloroacetate (105-39-5)

Ethyl cyanoacetate, Acetic acid, cyano-, ethyl ester (105-56-6)

cyanoacetic acid (372-09-8)

diethyl malonate (105-53-3)

Fumaric acid (110-17-8)

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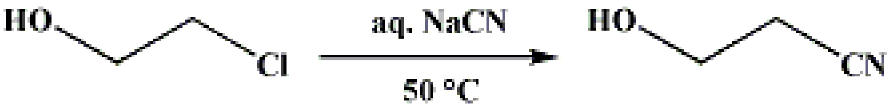
ETHYLENE CYANOHYDRIN

[Hydracrylonitrile]



Submitted by E. C. Kendall and B. McKenzie.
Checked by H. T. Clarke and W. M. Sperry.

1. Procedure

In a 5-l. flask is placed 612 g. (12.5 moles) of finely powdered sodium cyanide (passed through a meat grinder and then sifted through a 20-mesh sieve) (Note 1); the flask is equipped with a thermometer in a well, an efficient stirrer, and a reflux condenser (Note 2). The whole vessel is then set in a water bath into which warm and cold water can be run at will and if necessary rapidly removed.

A mixture of 250 cc. of water and 1 kg. (807 cc., 12.4 moles) of pure ethylene chlorohydrin (b.p. 126–127°) is then added, the stirring is started, and the temperature of the mixture raised to 45° by external application of warm water. At this point the warm water is rapidly removed (Note 3) and the temperature of the contents of the flask carefully held at 45° by jacketing with water at a suitable temperature (33–35°). After the mixture has been held at 45° for one hour it is allowed to warm up to 48° by allowing the temperature of the water bath to rise about 2°. After an hour at 48° the temperature is raised to 50° and held at this point until the reaction is over; it is necessary to raise the temperature of the bath gradually, and the end of the reaction is noted when the bath temperature reaches 50°. A period of four and one-half to five hours is necessary for this last stage.

Cold water is now placed in the water bath, while the stirrer is kept always in motion, and the temperature of the mixture is reduced to 20–22°. The mass is then filtered by suction and the sodium chloride sucked as dry as possible. This is then washed with about 800 cc. of acetone in small quantities, the washings being collected separately, and then transferred to a flask from which the acetone and water are distilled off with the use of a short fractionating column until the temperature of the vapor reaches 90°. The residue in the flask is then cooled and again filtered from a further small quantity of sodium chloride which separates during the distillation, the filtrate being added to the main product (Note 4).

This is then distilled under reduced pressure from an oil bath, and the fraction boiling at 107–109°/12 mm. (116–118°/20 mm.) is collected as pure material. The yield is 700–705 g. (79–80 per cent of the theoretical amount). There is practically no residue beyond a little salt; the foreruns consist of water, a small amount of unchanged

ethylene chlorohydrin, and some ethylene cyanohydrin.

2. Notes

1. The sodium cyanide should be finely powdered since it never completely enters into solution, and any lumps present would run the risk of becoming coated over with sodium chloride. For the same reason, the stirring must be vigorous throughout the operation.
2. Under the correct conditions no appreciable amount of hydrogen cyanide escapes from the reflux condenser, but it is wise to carry out the reaction under a hood, or to lead a tube from the top of the condenser into the open air or to a gas-absorption trap (Fig. 7 on p. 97).
3. It is most important that the temperature of the reaction mixture be not allowed to rise prematurely, since if it reaches 50° during the early stages the reaction velocity increases so rapidly that the contents are likely to boil out of the flask. For the same reason it appears necessary that a certain ratio between reacting mass and cooled surface be not exceeded. Runs of twice the above size have been carried out in a 5-l. flask without mishap, but temperature control was difficult and these conditions are extremely hazardous. A run of 4 kg. of ethylene chlorohydrin in a 12-l. flask was attempted, but rapidly went out of control.
4. When the reaction has been carried out exactly as described, the final product before distillation is very nearly colorless; if the temperature has been allowed to rise too high, a brown color is produced and ammonia is formed, with corresponding decrease in yield.

3. Discussion

Ethylene cyanohydrin can be prepared from ethylene oxide and anhydrous hydrogen cyanide;[1] from ethylene oxide and calcium cyanide in aqueous solution at 10–20°;[2] and from ethylene chlorohydrin and alkali cyanide in the absence of a solvent by heating to 100° in a closed vessel,[3] by boiling the reagents in 50 per cent aqueous-alcoholic solution,[4] by adding a concentrated aqueous solution of potassium or sodium cyanide to a boiling solution of the chlorohydrin in absolute alcohol,[5] or in aqueous solution at 45°.[6]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 131
- Org. Syn. Coll. Vol. 1, 321

References and Notes

1. Erlenmeyer, Ann. **191**, 270 (1878); Wislicenus, Ann. **167**, 346 (1873).

2. I. G. Farbenind. A.-G., Ger. pat. 561,397 [C. A. **27**, 998 (1933)].
3. Wislicenus, Ann. **128**, 4 (1863).
4. Erlenmeyer, Ann. **191**, 268 (1878).
5. Moureu, Bull. soc. chim. (3) **9**, 426 (1893); Moureu and Brown, ibid. (4) **27** 902 (1920); Jacobs and Heidelberger, J. Am. Chem. Soc. **39**, 1465 (1917).
6. Bauer, U. S. pat. 1,388,016 [C. A. **15**, 4011 (1921)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alkali cyanide

potassium or sodium cyanide

alcohol (64-17-5)

ammonia (7664-41-7)

sodium cyanide (143-33-9)

sodium chloride (7647-14-5)

hydrogen cyanide (74-90-8)

acetone (67-64-1)

Ethylene oxide (75-21-8)

Ethylene cyanohydrin, Hydracrylonitrile (109-78-4)

ethylene chlorohydrin (107-07-3)

calcium cyanide (592-01-8)

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ETHYL ORTHOFORMATE

[Orthoformic acid, triethyl ester]

Submitted by W. E. Kaufmann and E. E. Dreger.
Checked by F. C. Whitmore and H. F. Herzog.

1. Procedure

In a 5-l. round-bottomed flask, fitted with an 80-cm. reflux condenser, are placed 3 l. of absolute alcohol (Note 1) and 490 g. (327 cc., 4.1 moles) of chloroform (Note 2). The flask is arranged for outside cooling by running water. To the solution, 207 g. (9 atoms) of clean sodium cut into pieces which will conveniently drop through the condenser is added during the course of about two hours. In order to add the sodium at this rate, the flask must be cooled during the addition. When the sodium has entirely reacted and the mixture has been cooled to room temperature, the sodium chloride which has separated is removed by suction filtration with the use of thoroughly dry apparatus (Note 3). The salt is washed on the filter with 200 cc. of absolute alcohol, and the washings are allowed to run into the main filtrate.

The solution is placed in a 3-l. flask fitted with an 80-cm. fractionating column (Note 4), and the excess chloroform and most of the alcohol are distilled off on a steam or water bath. The distillate is caught in a 2-l. suction flask protected from moisture by a drying tube. This distillation requires five or six hours. A mixture of chloroform and alcohol, weighing about 2000 g., is recovered and saved for the next run (Note 3). The liquid remaining in the flask is decanted from the small amount of salt which has separated, into a Claisen flask with a 30-cm. fractionating column (Note 5). The mixture is distilled at atmospheric pressure. The fraction boiling below 85° is mainly alcohol and is discarded. An intermediate fraction of about 100 g., boiling at 85–140°, contains about one-fourth of the total yield. This may be fractionated but is best added to a subsequent run. The orthoformic ester is collected at 140–146° and weighs 120–140 g. (27–31 per cent of the theoretical amount). There is practically no higher-boiling material. Another distillation gives almost all the material boiling over a 2° range.

After the first run, 400 g. of chloroform and enough absolute alcohol (800–1000 cc.) are added to the recovered chloroform-alcohol mixture to give a total volume of 3 l. The sodium is then added as before. After the excess of chloroform and alcohol has been distilled through the fractionating column, the intermediate fraction from the previous run is added before fractionating. The yield from such a run is about 200 g. (45 per cent of the theoretical amount) (Note 6) and (Note 7).

2. Notes

1. *Absolute Alcohol.*—Good absolute alcohol is essential. The use of alcohol of about 98 per cent gives only about two-thirds the yields obtained with absolute alcohol. Alcohol dried over lime usually runs about 98.5–99.5 per cent. A good method of obtaining a higher grade of absolute alcohol is to treat this alcohol with a little sodium. When the sodium has dissolved, the alcohol is distilled from a steam bath. Under these conditions, any trace of water that may be present on account of the equilibrium

$$C_2H_5OH \quad + \quad NaOH \quad \rightleftharpoons \quad C_2H_5ONa \quad + \quad H_2O$$

remains in the concentrated solution of sodium ethoxide and sodium hydroxide. See, also, p. 249 and, Note 1, on p. 251.

2. Sufficient chloroform must be used to keep the solution from being alkaline at the end of the reaction.

3. If care is taken to prevent moisture from getting into the recovered alcohol-chloroform mixture, this mixture may be used repeatedly. After it has been used four or five times, the yield begins to fall.

4. The long fractionating column used by Clarke and Rahrs[1] is satisfactory. If such a column is not available, an 80-cm. reflux condenser without any water in it, may be used, connecting it at the top by means of a wide, bent glass tube to a condenser set downward for distillation.

5. A satisfactory type of flask for the distillation is that illustrated on p. 130.

6. The present method is better than that which uses dry ether as a solvent.

7. Yields equally good as those mentioned in the above procedure are obtained by first preparing a sodium ethoxide solution, taking the quantities given above and adding this to an alcohol-chloroform solution. One decided disadvantage in this alternative procedure is that, unless a great deal more alcohol is employed, the sodium ethoxide solution tends to become semi-solid and cannot be introduced easily into the chloroform-alcohol solution. If one attempts to use recovered alcohol, containing chloroform, the sodium chloride which separates as soon as sodium is added increases the tendency to become semi-solid.

The reaction is carried out best without stirring, thus allowing the sodium to float on top. In this way, the hydrogen escapes rapidly and little reduction of the chloroform takes place.

3. Discussion

Orthoformic ester can be prepared by the treatment of a mixture of chloroform and alcohol with sodium;[2] by the action of dry sodium ethoxide on chloroform[3] or on an ether solution of chloroform;[4] by the action of alcoholic sodium hydroxide on chloroform;[5] and by the action of alcoholic hydrochloric acid on ethyl formimido ester[6] or its mercuric chloride double salt.[7] A method[8] has been published for the

preparation of orthoformic ester, in which sodium and chloroform are added alternately to the absolute alcohol. A few runs were made according to its directions but the results were not so satisfactory as those obtained by the procedure described.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 237
- Org. Syn. Coll. Vol. 1, 248
- Org. Syn. Coll. Vol. 1, 272
- Org. Syn. Coll. Vol. 2, 126
- Org. Syn. Coll. Vol. 2, 137
- Org. Syn. Coll. Vol. 2, 262
- Org. Syn. Coll. Vol. 2, 287
- Org. Syn. Coll. Vol. 2, 323
- Org. Syn. Coll. Vol. 4, 291
- Org. Syn. Coll. Vol. 4, 630

References and Notes

1. Clarke and Rahrs, Ind. Eng. Chem. **15**, 349 (1923).
2. Sawitsch, Jahresber. 391 (1860); Ladenburg and Wichelhaus, Ann. **152**, 164 (1869); Deutsch, Ber. **12**, 116 (1879); Wood and Comley, J. Soc. Chem. Ind. **42**, 430 T (1923).
3. Williamson, Ann. **92**, 346 (1854); Stapaff, Z. Chem. 186 (1871).
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6. Pinner, Ber. **16**, 356 (1883); Claisen, Ber. **31**, 1010 (1898).
7. Hill and Black, Am. Chem. J. **31**, 209 (1904).
8. Wood and Comley, J. Soc. Chem. Ind. **42**, 430 T (1923).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

orthoformic ester

alcohol-chloroform

mercuric chloride double salt

alcohol (64-17-5)

hydrochloric acid (7647-01-0)

ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium chloride (7647-14-5)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

Ethyl orthoformate

Orthoformic acid, triethyl ester (122-51-0)

chloroform-alcohol

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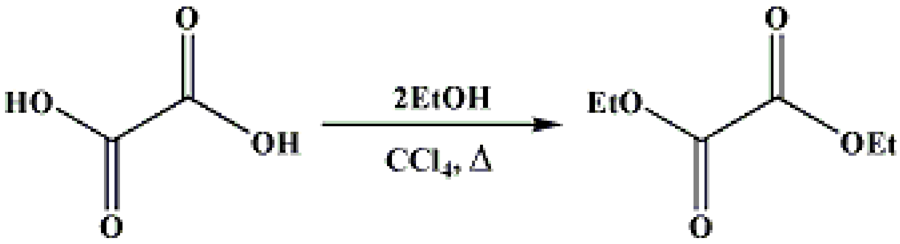
Organic Syntheses, CV 1, 261

ETHYL OXALATE

[Oxalic acid, ethyl ester]



Submitted by H. T. Clarke and Anne W. Davis.
Checked by Roger Adams and W. B. Burnett.

1. Procedure

In a 5-l. flask are placed 1 kg. (7.9 moles) of crystallized (hydrated) oxalic acid, 1.66 kg. (2034 cc.) of 95 per cent ethyl alcohol, and 1.33 kg. (887 cc.) of carbon tetrachloride. The flask is then fitted with a fractionating column, 1 meter long, to which are attached a condenser and an automatic separator so arranged that the lighter liquid flows off to a receiver (Fig. 13) (Note 1). The heavier liquid flows through a tower of anhydrous potassium carbonate, and then returns to the reaction flask. The bottom of the tower is connected with a small separatory funnel through which any potassium carbonate solution, which flows from the solid in the tower, may be withdrawn from time to time.

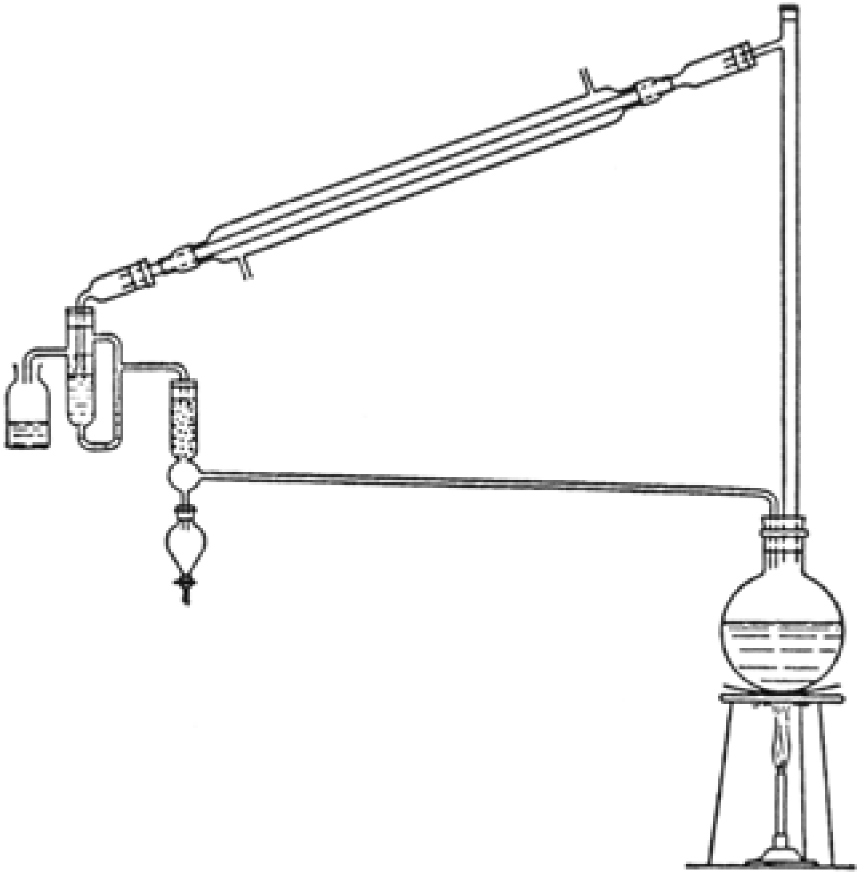
The mixture in the flask is slowly distilled (Note 2). As soon as about 500 cc. of the lighter liquid has collected, it is placed in a fractionating apparatus and distilled, the material which boils up to 79° being collected separately. This fraction, which consists principally of alcohol, with a little carbon tetrachloride and moisture, is dried with potassium carbonate and returned to the reaction mixture (Note 3). The higher fractions are redistilled.

The above process is continued until the distillate no longer separates into two phases (about twenty-seven hours). The liquid in the flask is then distilled with the use of a column until the temperature of the vapor reaches 85°; the residue is then distilled under reduced pressure, and the fraction which boils at 106–107°/25 mm. is collected. The yield is 920–960 g. of a colorless liquid (80–83 per cent of the theoretical amount) (Note 4).

2. Notes

1. The apparatus shown in Fig. 13 may be somewhat more simply constructed by using rubber connections in several places, thus eliminating

Fig. 13.



a certain amount of glass blowing, and making a more flexible piece of apparatus. The side arm of the separator may be made with two rubber connections—one above and one below the tube leading to the potassium carbonate tube. The long return tube to the flask may be constructed with a rubber joint very near the carbonate tube and one near the flask.

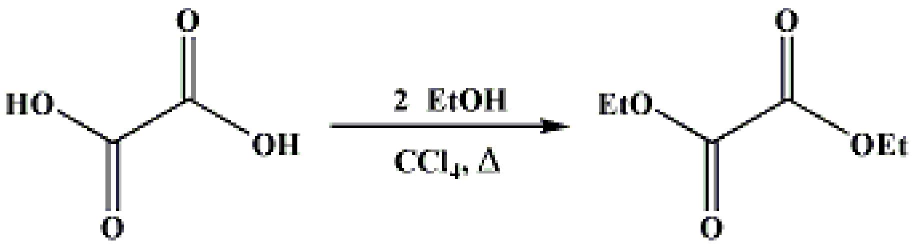
2. Water, ethyl alcohol, and carbon tetrachloride form a ternary mixture boiling at about 61°. This vapor mixture, on condensation, separates into two phases; the heavier liquid consists of carbon tetrachloride and alcohol with only small amounts of water; the lighter liquid consists of approximately 65 per cent alcohol, 25 per cent water, and 10 per cent carbon tetrachloride. By taking advantage of this fact, it is possible to conduct the esterification at a temperature so low that the ethyl hydrogen oxalate first formed does not decompose into ethyl formate and other products, as it does when the customary methods of esterification are employed.

The reaction may be carried out somewhat more expeditiously if the oxalic acid is dehydrated independently (p. 421) before it is mixed with the alcohol; indeed, it is also possible to remove the bulk of the water from the alcohol itself by a similar method, before mixing it with the oxalic acid. However, since water is formed during the esterification, little is gained by this procedure.

3. It is not absolutely necessary to remove the last traces of water from the alcohol-carbon tetrachloride layer by means of potassium carbonate before returning it to the reaction mixture; this process is, however, so simple and requires so little attention that there is no doubt that it is of material aid in cutting down the time of operation. The advantages of using crystallized oxalic

acid and commercial 95 per cent alcohol, instead of the anhydrous reagents, are obvious. When technical oxalic acid is used, the yields are usually smaller by 5–10 per cent.

4. Ethyl oxalate can also be prepared in about the same yield by the esterification procedure described in Org. Syn. **10**, 48.

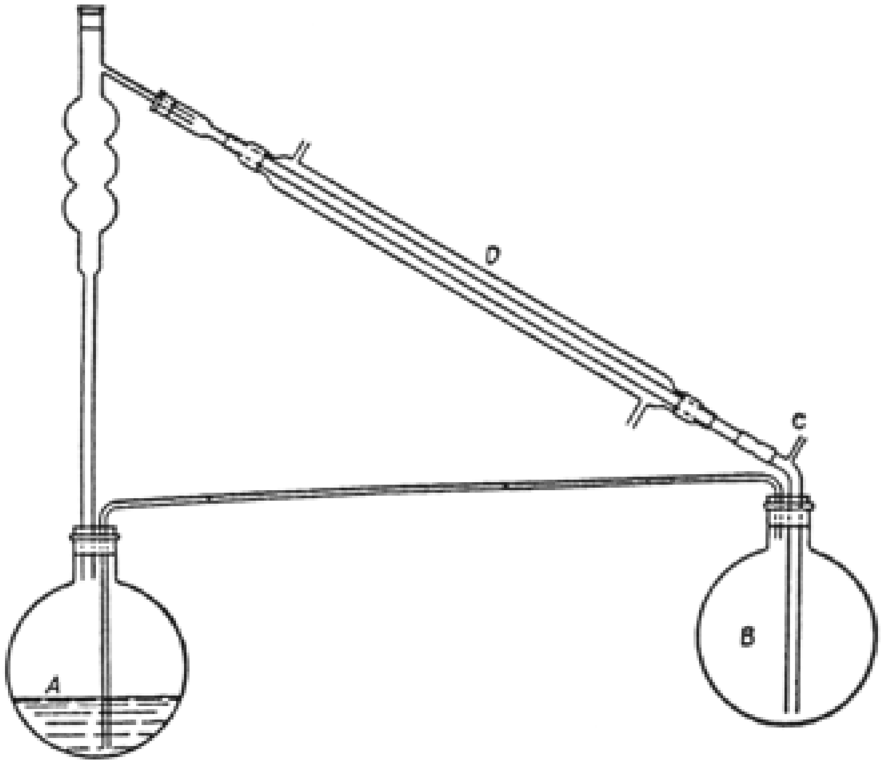


Submitted by Joseph Kenyon
Checked by C. S. Marvel and A. B. Adams.

1. Procedure

In a large evaporating dish is placed 252 g. (2 moles) of crystalline oxalic acid. The acid is heated on a steam bath for six to eight hours, with occasional stirring, until all the water of crystallization (72 g.) has been expelled (Note 1). The oxalic acid, which is almost anhydrous (weighing approximately 180 g.), is placed in a 1.5-l. round-bottomed flask, A, containing 500 cc. of absolute alcohol (p. 249) and fitted up as shown in Fig. 14.

Fig. 14.



The flask A is heated by means of an oil bath maintained at 120–125° (Note 2); the

mixed vapors of alcohol and water, passing through the fractionating column, are condensed in D, and the moist alcohol is delivered under the surface of the alcohol contained in flask B. In flask B are placed 250 cc. of absolute alcohol and about 200 g. of freshly ignited potassium carbonate. Flask B is heated in an oil bath maintained at about 95–100°. The moist alcohol delivered to the flask B is dried by the potassium carbonate and subsequently returned as vapor under the surface of the liquid in flask A. The tube C, which is provided with a calcium chloride tube and is open to the air, acts as a vent for the otherwise closed system. The reaction is run for about five hours. The excess alcohol is then distilled, the residue of ethyl oxalate is distilled under reduced pressure, and the fraction boiling at 98–101°/21 mm. is collected. The yield is 234–264 g. (80–90 per cent of the theoretical amount) (Note 3).

2. Notes

1. The oxalic acid may be dehydrated by the procedures described on p. 421.
2. The temperature varies slightly with the length of the fractionating column. This temperature was noted when an ordinary two-bulb column (about 30 cm. long) was used.
3. A similar procedure may be used for the preparation of methyl oxalate. Instead of distilling this ester, it is better to cool the solution in an ice bath and separate the crystals of methyl oxalate from the mother liquors in a basket centrifuge. The product thus obtained from 252 g. of crystallized oxalic acid weighs 120–125 g. Upon concentrating the mother liquors, cooling, and again centrifuging the mixture, a further crop of crystals weighing 30–35 g. may be obtained. Thus the total yield of methyl oxalate is 150–160 g. (63–67 per cent of the theoretical amount).
Another method for the preparation of methyl oxalate is described in Org. Syn. **10**, 70.

3. Discussion

Ethyl oxalate can be prepared by distilling a mixture of anhydrous oxalic acid and absolute alcohol, the vapor of absolute alcohol being passed simultaneously into the mixture;[1] and by adding sufficient alcohol to remove as the azeotropic mixture all the water formed in the reaction and then heating the mixture until the water is removed.[2] A modification of this method is the use of a dehydrating agent in the system,[3] as illustrated in (*B*) of the procedure. Good yields have been obtained by saturating a mixture of crystallized oxalic acid and alcohol with hydrogen chloride, removal of the alcohol and water by distillation under reduced pressure, and repetition of the treatment with alcohol and hydrogen chloride;[4] and by stirring for several hours at room temperature a mixture of anhydrous oxalic acid, 95 per cent ethyl alcohol, sulfuric acid, and benzene.[5]

Other procedures which have been employed include: The use of Twitchell's reagent

as a catalyst;[6] the distillation of a mixture of anhydrous oxalic acid, absolute alcohol, sulfuric acid and toluene;[7] and the distillation of a mixture of oxalic acid, absolute alcohol, and a liquid which forms a ternary mixture with the alcohol and water, distillation being arranged so that the vapors are condensed and returned to the reaction mixture after passing through a thimble containing calcium carbide.[8]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 42
- Org. Syn. Coll. Vol. 1, 238
- Org. Syn. Coll. Vol. 2, 126
- Org. Syn. Coll. Vol. 2, 194
- Org. Syn. Coll. Vol. 2, 272
- Org. Syn. Coll. Vol. 2, 287
- Org. Syn. Coll. Vol. 2, 288
- Org. Syn. Coll. Vol. 2, 414

References and Notes

1. Steyer and Seng, Monatsh. **17**, 613 (1869); Dutt, J. Chem. Soc. **123**, 2714 (1923). A similar procedure given in Org. Syn. **10**, 48 (1930), for the preparation of high-boiling esters can be used either with 95 per cent or absolute alcohol.
2. Contzen-Crowet, Bull. soc. chim. Belg. **35**, 165 (1926); Jewell and Butts, J. Am. Chem. Soc. **53**, 3560 (1931).
3. Frankland and Aston, J. Chem. Soc. **79**, 517 (1901).
4. Anschütz, Ber. **16**, 2414 (1883).
5. Wahl, Bull. soc. chim. (4) **35**, 304 (1924). Wahl, ibid. (4) **37**, 713 (1925), has also used essentially the procedure described in (*A*).
6. Zaganiaris and Varvoglis, Ber. **69**, 2281 (1936).
7. Micovic, Bull. soc. chim. (5) **4**, 1666 (1937).
8. Thielepape and Fulde, Ber. **66**, 1458 (1933).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ester

ethyl hydrogen oxalate

alcohol-carbon tetrachloride

ethyl alcohol, alcohol (64-17-5)

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

hydrogen chloride (7647-01-0)

Benzene (71-43-2)

carbon tetrachloride (56-23-5)

Oxalic acid (144-62-7)

toluene (108-88-3)

Ethyl oxalate, Oxalic acid, ethyl ester

ethyl formate (109-94-4)

Methyl oxalate

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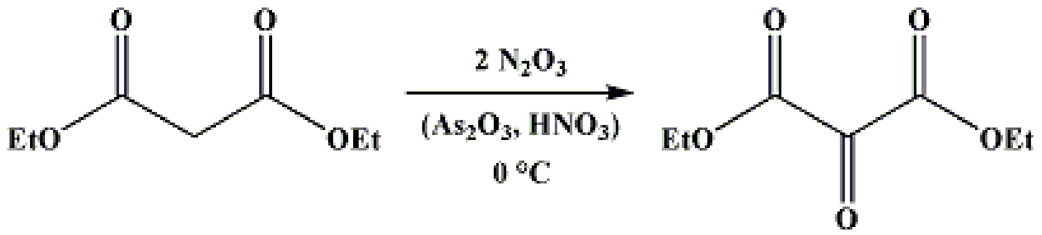
ETHYL OXOMALONATE

[Mesoxalic acid, ethyl ester]

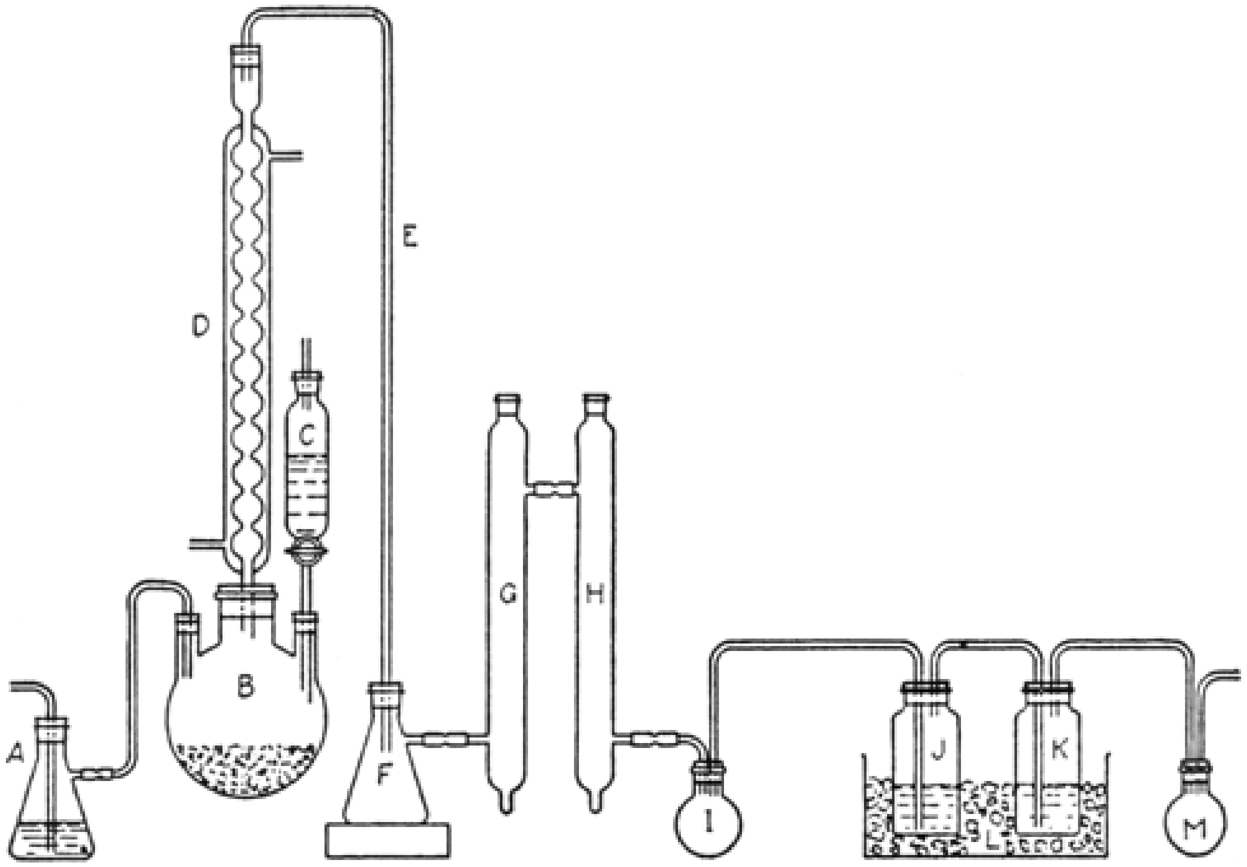


Submitted by A. W. Dox
Checked by C. S. Marvel and R. L. Shriner.

1. Procedure

(*A*) *Apparatus.*[1]—The apparatus is assembled according to Fig. 15. A is a 500-cc. Pyrex filter flask. B is a 2-l. three-necked, round-bottomed flask; into one of the side necks is fitted a 300-cc. dropping funnel C

Fig. 15.



(Note 1), and the second side neck is closed with a loose-fitting, well-greased rubber stopper, which serves as a safety valve against any sudden increase of pressure in the generator. A long (75-cm.) water-cooled bulb condenser D is connected to the middle neck of the generator flask B. The large-bore glass tube E connects the top of the condenser D

with trap F, a 500-cc. filter flask, which is connected by means of a short rubber tube to the drying towers G and H (Note 2). These towers are conveniently made from glass condenser jackets; the bottom ends are sealed and the top ends closed with rubber stoppers (Note 3). Tower H is connected to "sight flask"; I, a 500-cc. round-bottomed flask. This in turn is connected to the absorption vessels J and K (500-cc. gas washing bottles), which are immersed in an ice-salt bath contained in dish L. Absorption bottle K is connected to "sight flask" M, a 500-cc. round-bottomed flask similar to I. By means of the sight flasks I and M the efficiency of absorption can be judged by the depth of color. Flask I also serves to catch any liquid sucked back from the absorption vessels.

Before finally assembling the apparatus, the various units are charged as follows: A is one-third filled with water to serve as a bubble counter. Generator B is about one-quarter filled with dry arsenious oxide, pea size or powdered. Drying towers G and H are filled with anhydrous calcium chloride. (It is well to place a wad of glass wool in front of the entrance and exit tubes.) In each of the two absorption bottles, J and K, is placed 200 g. (1.25 moles) of ethyl malonate. Dish L is filled with an ice-salt freezing mixture.

When assembled as indicated, the apparatus is ready for operation. Concentrated nitric acid is run, in small portions, into generator B from dropping funnel C. After the action has started, the nitric acid must be forced into flask B by applying a small air pressure at the top of dropping funnel C and then opening the stopcock. Later on, when the gas generation slackens, flask B is heated with a smoky flame. The evolution of gas is maintained at a steady rate by increasing the heat until finally all the arsenious oxide has dissolved and the frothing has ceased. During the whole operation a slow stream of compressed air (Note 4) is passed through the apparatus from "bubble counter" A. The stream of air is insufficient if any colorless gas, which turns brown on coming in contact with the air, leaves the apparatus at M. When the arsenious oxide is exhausted, as shown by a slackening in gas evolution, the old generator is removed and a fresh one put in its place. (If the generator is first allowed to cool somewhat, this change can be accomplished without much discomfort.) The moist oxides of nitrogen, in passing up through the condenser D, lose most of their moisture and the gas on passing down through tube E should deposit very little water in trap F. The gas is then thoroughly dried in the towers G and H. When the calcium chloride in G becomes wet (after several runs) the tower is refilled; at the same time G and H are interchanged. After passing through the drying towers and through flask I, the gas is absorbed by the cold ethyl malonate in vessels J and K (Note 5).

(*B*) *Ethyl Oxomalonate*.—A rapid stream of nitrous anhydride is passed into the cold ethyl malonate, which becomes dark green in color. There should be an increase in weight of about 200 g. in absorption bottle J in two to three hours (Note 6).

The liquid is left in the freezing mixture for several hours, then gradually allowed to come to room temperature (Note 7). Red gases are slowly evolved. After standing for two days or more at room temperature, the liquid is transferred to a distilling flask provided with a capillary air intake, and the delivery tube connected with a water-cooled condenser and receiver. The distillation is performed under reduced pressure, by the use of a water pump. Considerable nitric oxide is evolved before the pressure drops to about 70 mm. (Note 8).

The first fraction consists mainly of water, a little ethyl acetate, and some ethyl oxomalonate which recombines with the water to form ethyl mesoxalate. When the pressure has dropped

to 45 mm. and the temperature has risen to 110°, the receiver is changed (Note 9). The main product, ethyl oxomalonate, now distils at 110–135°/45–50 mm. If the oxidation has been complete, very little residue is left (Note 10). Redistillation gives a golden-yellow liquid boiling between 103–108°/15 mm. The yield is 160–165 g. (74–76 per cent of the theoretical amount).

2. Notes

1. All the stoppers in this apparatus are of rubber, well greased with vaseline.
2. All rubber connections of this apparatus must be of thick tubing, well greased inside.
3. Ordinary gas-drying towers may also be used for G and H. The yield of ethyl oxomalonate is decreased if the nitrous anhydride is not dried.
4. The reaction between arsenious oxide and concentrated nitric acid yields a mixture of nitric oxide and nitrogen dioxide. It also contains some nitrogen tetroxide and perhaps trioxide, the amount in equilibrium depending upon the temperature of the gas. The compressed air forced in via flask A insures an excess of oxygen, and thus complete oxidation. Only a slow stream is necessary, two to three bubbles per second.
5. This work was assisted by a grant, to the submitters of the apparatus, from the Cyrus M. Warren fund of the American Academy of Arts and Sciences.
6. A complete run should if possible be made without stopping. However, if the preparation must be stopped before completion, the absorption vessels should be disconnected, weighed, and protected against moisture by calcium chloride tubes. They lose weight on standing owing to decomposition of the intermediate compound. Considerable gas escapes from J and is taken up by K. If large quantities of ethyl oxomalonate are being prepared, J is removed when it has gained 200 g.; K is connected in the position previously occupied by J; and a bottle with fresh ethyl malonate is used to back up K.
7. If the temperature is raised too rapidly, the liberation of gases causes the mixture to boil too vigorously.
8. A motor pump is not recommended because the nitric oxide is apt to cause corrosion. If the pressure is reduced too much at first, a residue of ethyl isonitrosomalonate may remain.
9. The remainder of the distillation must be conducted with extreme care. As soon as the ethyl oxomalonate has partly distilled over and the temperature has risen somewhat, the remaining isonitroso compound begins to decompose and sometimes liberates gases so rapidly that the thermometer and capillary tube may be blown out of the flask. If the manometer is watched closely, and at the first sign of liberation of gas, as evinced by a sudden increase in pressure, a wet towel is placed around the flask, the reaction can be slowed down.
10. In case any considerable amount of residue remains above 135° at 45 mm., it is heated at ordinary pressure to a higher temperature until no more nitric oxide is given off, then distilled as before.
11. Upon adding the calculated amount of water to ethyl oxomalonate, decolorization takes place immediately with evolution of heat and, on cooling, a solid mass of ethyl dihydroxymalonate results. After recrystallization from chloroform the product melts at 56–57° (Elizabeth Gilman and T. B. Johnson, private communication).

3. Discussion

Ethyl oxomalonate can be prepared by the action of nitric acid on sucrose under carefully controlled conditions;[2] by heating an aqueous solution of dihydroxyacetone with cupric acetate;[3] and by the oxidation of ethyl malonate by means of oxides of nitrogen[4] or selenium dioxide.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 326
- Org. Syn. Coll. Vol. 3, 609
- Org. Syn. Coll. Vol. 3, 771
- Org. Syn. Coll. Vol. 9, 314

References and Notes

1. The apparatus for this preparation was submitted by B. B. Corson and R. K. Hazen.
2. Chattaway and Harris, J. Chem. Soc. **121**, 2704 (1922).
3. Evans and Waring, J. Am. Chem. Soc. **48**, 2680 (1926).
4. Bouveault and Wahl, Compt. rend. **137**, 196 (1903); Schmitt, ibid. **140**, 1400 (1905); Curtiss, Am. Chem. J. **33**, 603 (1905); ibid. **35**, 477 (1906); Meyer, Bull. soc. chim. (4) **9**, 423 (1911).
5. Astin, Newman, and Riley, J. Chem. Soc. **1933**, 393; Müller, Ber. **66**, 1668 (1933).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

oxides of nitrogen

arsenious oxide

vaseline

calcium chloride (10043-52-4)

ethyl acetate (141-78-6)

chloroform (67-66-3)

nitric acid (7697-37-2)

oxygen (7782-44-7)

sucrose

selenium dioxide (7446-08-4)

nitrogen dioxide (10102-44-0)

cupric acetate (142-71-2)

Ethyl oxomalonate, Mesoxalic acid, ethyl ester, ethyl mesoxalate

ethyl malonate (1071-46-1)

nitrous anhydride

nitric oxide

nitrogen tetroxide

ethyl isonitrosomalonate

ethyl dihydroxymalonate

dihydroxyacetone

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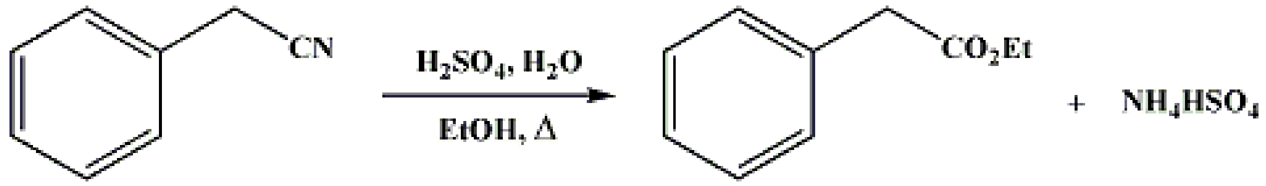
ETHYL PHENYLACETATE

[α-Toluic acid, ethyl ester]



Submitted by Roger Adams and A. F. Thal.
Checked by Oliver Kamm

1. Procedure

In a 3-l. round-bottomed flask, fitted with an efficient reflux condenser, are mixed 750 g. (918 cc.) of 95 per cent alcohol, 750 g. (408 cc.) of concentrated sulfuric acid and 450 g. (3.85 moles) of benzyl cyanide (Note 1). The mixture, which soon separates into two layers, is heated to boiling over a low flame, for six to seven hours, cooled, and poured into 2 l. of water, and the upper layer is separated. This is washed with a little 10 per cent sodium carbonate solution (Note 2) to remove small amounts of phenylacetic acid which may have been formed, and then distilled under reduced pressure. A small amount of water goes over first and then a pure product boiling 132–138°/32 mm. (120–125°/17–18 mm.) (Note 3). The yield is 525–550 g. (83–87 per cent of the theoretical amount).

2. Notes

1. The benzyl cyanide can be prepared according to the directions on p. 107; the product which boils over a 5° range should be used.
2. In washing the layer of ethyl phenylacetate with sodium carbonate it is sometimes advisable to add a certain amount of sodium chloride so that the ester will separate more readily.
3. The product obtained is water-clear and practically colorless. Although the product is collected over a 5° range, most of the liquid is found to boil over a 1° range, if distilled slowly without superheating. The boiling point of ethyl phenylacetate is near that of benzyl cyanide. However, a Kjeldahl analysis of the product shows that only a trace of nitrogen compounds is present.

3. Discussion

Ethyl phenylacetate can be prepared by the esterification of phenylacetic acid and alcohol by hydrochloric[1] or sulfuric acid;[2] and by the treatment of benzyl cyanide with alcohol and hydrogen chloride[3] or sulfuric acid, which is much more convenient in the laboratory.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 107
- Org. Syn. Coll. Vol. 2, 288

References and Notes

1. Radziszewski, Ber. **2**, 208 (1869).
2. Volhard, Ann. **296**, 2 (footnote) (1897); Senderens and Aboulenc, Compt. rend. **152**, 1855 (1911).
3. Wislicenus, Ber. **20**, 592 (1887); Ann. **296**, 361 (1897).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric

alcohol (64-17-5)

sulfuric acid (7664-93-9)

hydrogen chloride (7647-01-0)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

Benzyl cyanide (140-29-4)

Phenylacetic acid (103-82-2)

α-Toluic acid, ethyl ester (93-89-0)

Ethyl phenylacetate (101-97-3)

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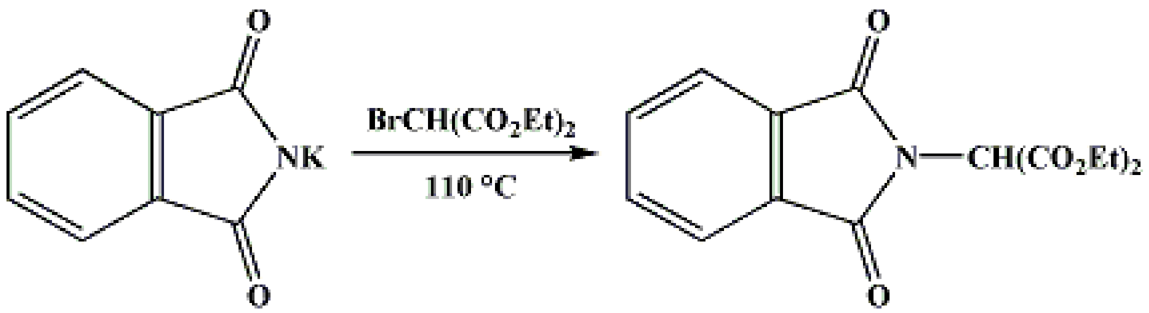
ETHYL PHTHALIMIDOMALONATE

[Malonic acid, phthalimido-, diethyl ester]



Submitted by A. E. Osterberg
Checked by Frank C. Whitmore and H. C. Benedict, Jr.

1. Procedure

In a 600-cc. beaker 210 g. (0.88 mole) of ethyl bromomalonate (p. 245) (Note 1) and 165 g. (0.89 mole) of potassium phthalimide (p. 119) are intimately stirred together. The mixture is stirred approximately every ten minutes. If no spontaneous reaction starts within one-half hour (Note 1), it is necessary to initiate the reaction by heating to 110–120°. The mixture then becomes liquid and can be stirred easily. It turns to a light brown color, especially near the top where it comes in contact with the air. When the temperature begins to drop, the mixture is heated in an oil bath at 110° for one hour to insure completion of the reaction.

The mixture is then poured into a mortar where it solidifies to a solid mass (Note 2). When cold, the mixture is ground up with water to remove most of the potassium bromide and filtered. The precipitate is then reground with water and refiltered, finally being washed well with water. The solid material on the filter consists of some potassium bromide, some phthalimide, and the ethyl phthalimidomalonate. Without drying, it is put into a 1-l. flask with 400 cc. of benzene and heated to boiling. After cooling, the insoluble bromide and phthalimide are removed by filtration. The filtrate contains some water, which is removed by means of a separatory funnel.

The benzene solution is dried with 20 g. of calcium chloride and the benzene removed by distillation under diminished pressure on a water bath. The residue is poured into a mortar where it solidifies. The crystalline mass is then ground with small amounts of ether (200 cc. in all), filtered, and washed with ether (about 100 cc.) until pure white. The yield of ethyl phthalimidomalonate melting at 73–74° is 155–162 g. From the ether filtrate after distilling the ether, there may be recovered a further amount by washing with a small amount of ether to remove the brown color. The total weight of ester obtained in the two crops is 180–190 g. (67–71 per cent of the theoretical amount).

2. Notes

1. When freshly prepared ethyl bromomalonate is used, the temperature of the mixture may rise spontaneously to 140°. In such event no heat should be applied until the temperature falls again.
2. If the solidification does not take place as soon as the mixture is cold, about 100 cc. of water should be added. This accelerates the solidification.

3. Discussion

The procedure described is adapted from that of Sörensen.[1]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 384

References and Notes

1. Sörensen, Compt. rend. trav. lab. Carlsberg **6**, 1 (1903) [Chem. Zentr. II, 33 (1903)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ester

calcium chloride (10043-52-4)

Benzene (71-43-2)

ether (60-29-7)

Potassium Phthalimide (1074-82-4)

Phthalimide (85-41-6)

potassium bromide (7758-02-3)

Ethyl bromomalonate

Ethyl phthalimidomalonate, Malonic acid, phthalimido-, diethyl ester (5680-61-5)

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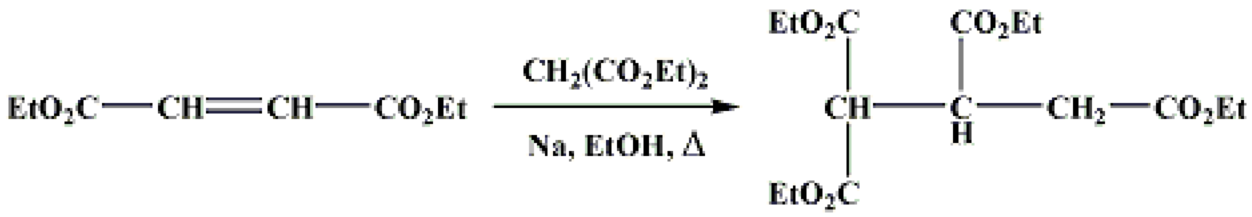
ETHYL PROPANE-1,1,2,3-TETRACARBOXYLATE

[1,1,2,3-Propanetetracarboxylic acid, tetraethyl ester]



Submitted by H. T. Clarke and T. F. Murray.
Checked by C. S. Marvel and M. M. Brubaker.

1. Procedure

In a 5-l. flask, fitted with a stirrer, a reflux condenser, and a dropping funnel, is placed 1 kg. (1266 cc.) of absolute ethyl alcohol (p. 249 and p. 259); 92 g. (4 atoms) of sodium, cut into strips, is then added through the condenser at such a rate that the alcohol does not boil too vigorously. When all the sodium is in solution, the flask is cooled and 800 g. (754 cc., 5 moles) of diethyl malonate added through the condenser, with stirring. The mixture is warmed gently on the steam bath and 700 g. (658 cc., 4.1 moles) of diethyl fumarate (Note 1) added from the dropping funnel. During this addition the solution is kept boiling gently, heat being applied if necessary (Note 2). The mixture is boiled for one hour after the diethyl fumarate has been added. It is then cooled and 250 g. (238 cc., 4.2 moles) of glacial acetic acid is added.

Most of the alcohol is distilled off under slightly reduced pressure on the steam bath and the residue is poured into sufficient distilled water to dissolve all the solid. The water layer is separated and extracted four times with carbon tetrachloride, which is added to the ester layer. The ester-carbon tetrachloride mixture is washed twice with water and the water washings extracted once with carbon tetrachloride. The carbon tetrachloride is distilled off under atmospheric pressure through a column, the moisture being carried over simultaneously.

The residue is then distilled under reduced pressure, when the ethyl propane-1,1,2,3-tetracarboxylate comes over at 182–184°/8 mm. The yield is 1261–1273 g. (93–94 per cent of the theoretical amount).

2. Notes

1. The diethyl malonate and diethyl fumarate should be redistilled under reduced pressure, and the material boiling over a 2° range collected. Directions for the preparation of diethyl fumarate are given in Org. Syn. **10**, 48, and for fumaric acid in Org. Syn. **11**, 46.

2. Heat is developed during the reaction, and the mixture may be kept boiling by adding the ethyl fumarate at a suitable rate.

3. Discussion

Ethyl propane-1,1,2,3-tetracarboxylate can be prepared by condensing malonic ester with ethyl chlorosuccinate,[1] ethyl ethoxysuccinate,[2] diethyl fumarate[3] or diethyl maleate.[4] The last two methods are now most convenient because of the commercial availability of fumaric and maleic acids.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 523

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ester-carbon tetrachloride

fumaric and maleic acids

ethyl alcohol (64-17-5)

acetic acid (64-19-7)

carbon tetrachloride (56-23-5)

sodium (13966-32-0)

ethyl fumarate (2459-05-4)

diethyl malonate (105-53-3)

Fumaric acid (110-17-8)

Ethyl propane-1,1,2,3-tetracarboxylate

1,1,2,3-Propanetetracarboxylic acid, tetraethyl ester (635-03-0)

diethyl fumarate (623-91-6)

ethyl chlorosuccinate

ethyl ethoxysuccinate

diethyl maleate (141-05-9)

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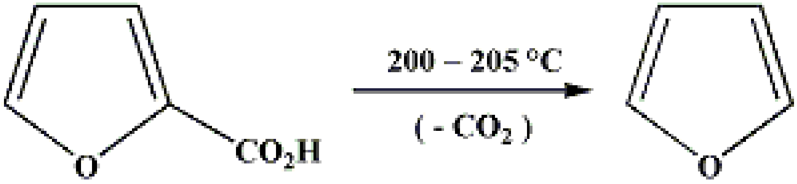
Organic Syntheses, CV 1, 274

FURAN



Submitted by W. C. Wilson
Checked by Roger Adams and C. G. Gauerke.

1. Procedure

In a 200-cc. round-bottomed flask is placed 80 g. (0.68 mole) of crude 2-furancarboxylic acid (p. 276) (usually about 95 per cent pure). To the neck of the flask is fitted an upright tube 2.5 cm. in diameter and 15 cm. long, with a side arm of the same diameter leading out about 2 cm. from the top of the tube. This side arm is extended into the bottom of an efficient (25-cm.) soda-lime tower (Note 1) immersed in a water bath held at 40° to prevent condensation of the furan. From the top of the soda-lime tower an outlet tube (0.5 cm. in diameter) is extended to the top of an upright water condenser, to the lower end of which is attached a receiving flask surrounded by ice and salt (Note 2).

The top of the upright tube in the reaction flask is closed by a cork stopper holding a glass plunger which may be used for pushing back into the flask any sublimed 2-furancarboxylic acid.

The acid is heated just to its boiling point (200–205°) (Note 3), when it decomposes with the evolution of furan and carbon dioxide. The small amounts of 2-furancarboxylic acid that sublime are pushed back from time to time. The distillate is finally redistilled, when it is found to boil at 31–34°/745 mm. The yield is 33–36 g. (72–78 per cent of the theoretical amount based on 2-furancarboxylic acid of 95 per cent purity) (Note 4).

2. Notes

1. The drying column removes carbon dioxide, moisture, and some of the other by-products which are formed. The product which is collected is nearly pure, and the redistillation completes the purification.
2. In a number of experiments a second receiver was used in addition to the first one, but it was found that practically all of the furan condensed in the first receiver.
3. Care should be taken in heating 2-furancarboxylic acid. If the temperature is too low, decomposition takes place too slowly; if too high, much 2-furancarboxylic acid sublimes and causes difficulty. In one run a thermometer

was placed in the melted acid. It read 200–205° during the evolution of the furan.
4. In the preparation of considerable quantities of furan it is desirable to pass the gas through one or two wash bottles of potassium hydroxide before it reaches the soda-lime tower. The heat of absorption of carbon dioxide keeps these bottles warm enough to prevent condensation of furan. Also, the substitution of a 120–150 cm. column for the 15-cm. column allows greater volume and speed. By these modifications 200–300 g. of furan can be prepared per hour without difficulty (F. N. Peters, private communication).

3. Discussion

Furan can be prepared by heating 2-furancarboxylic acid in a sealed tube;[1] by the dry distillation of barium 2-furancarboxylate;[1] and by heating barium 2-furancarboxylate with soda-lime.[2] Considerably improved yields have been reported to result from heating 2-furancarboxylic acid with a small amount of copper sulfate or copper oxide in a high-boiling coal-tar base[3] or in quinoline.[4] Furan has also been prepared from furfural by passing it over hot soda-lime or dropping it into a fused mixture of sodium and potassium hydroxides.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 566

References and Notes

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3. Gilman and Lousinian, Rec. trav. chim. **52**, 156 (1933).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

soda-lime

sodium and potassium hydroxides

copper sulfate (7758-98-7)

carbon dioxide (124-38-9)

Furan (110-00-9)

2-furancarboxylic acid (88-14-2)

barium 2-furancarboxylate

copper oxide (1317-38-0)

Quinoline (91-22-5)

Furfural (98-01-1)

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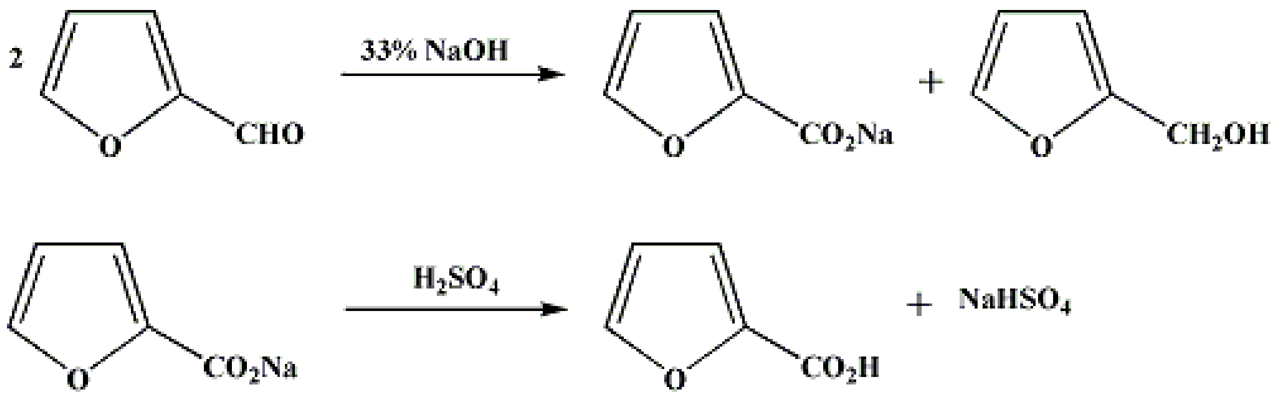
Organic Syntheses, CV 1, 276

2-FURANCARBOXYLIC ACID and 2-FURYLCARBINOL

[(2-Furoic acid) (Furfuryl alcohol)]



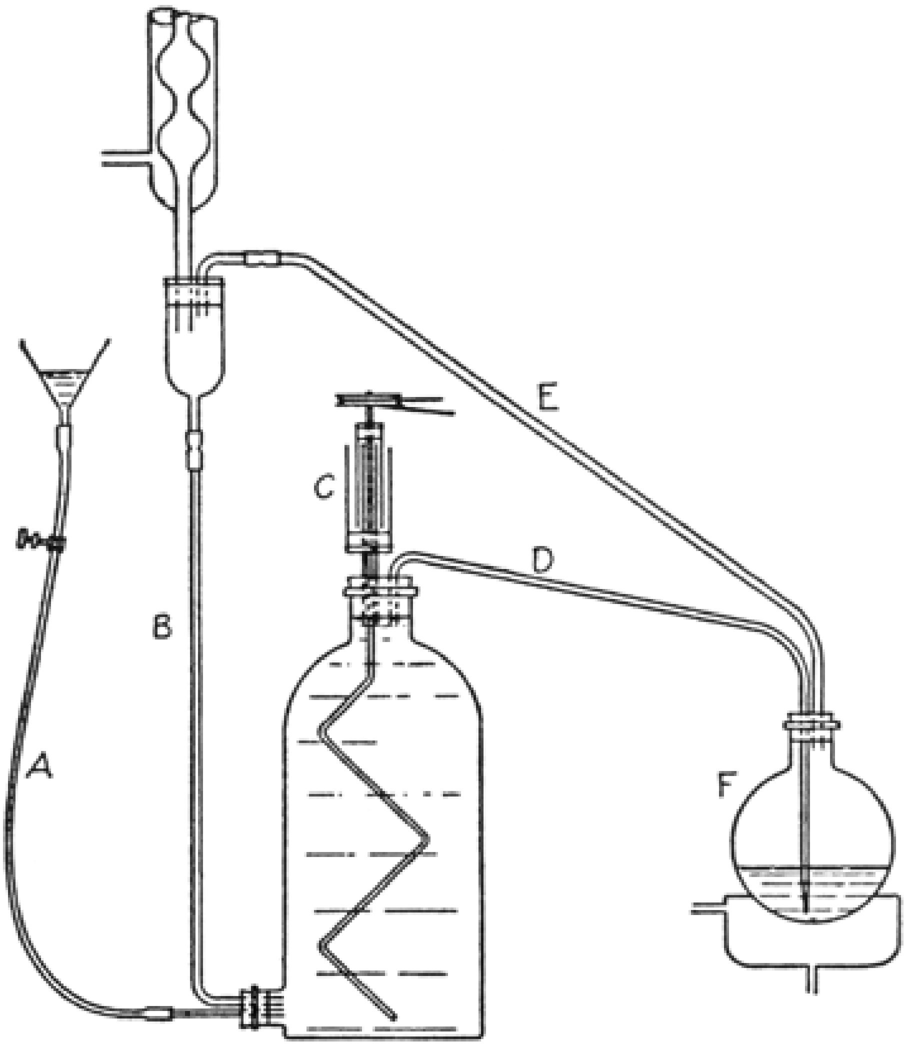
Submitted by W. C. Wilson
Checked by C. S. Marvel and C. G. Gauerke.

1. Procedure

One kilogram (862 cc., 10.2 moles) of furfural (Note 1) is placed in a 4-l. copper can (Note 2) provided with a mechanical stirrer and surrounded by an ice bath. The stirrer is started and the furfural is cooled to 5–8°. When the temperature has fallen to this range, 825 g. of 33.3 per cent technical sodium hydroxide solution (Note 3) is added from a separatory funnel at such a rate that the temperature of the reaction mixture does not exceed 20°. This requires twenty to twenty-five minutes. The rate of addition will depend on the efficiency of the cooling. The stirring is continued for one hour after the addition of the sodium hydroxide solution.

During the reaction considerable sodium 2-furancarboxylate separates in fine scale-like crystals. The reaction mixture is allowed to come to room temperature and just enough water is added to dissolve this precipitate. This requires about 325 cc. The solution is then placed in a continuous extraction apparatus (Fig. 16) and the 2-furylcarbinol is extracted with 1500–2000 cc. of ether (Note 4). The extraction is complete after six to seven hours (Note 5).

Fig. 16.



When extraction is complete the ether solution of 2-furylcarbinol is distilled until the temperature of the liquid (not the vapor) reaches 95°. Then the residue is distilled under diminished pressure. Some ether and water come over first, and the temperature then rises rapidly to the boiling point of 2-furylcarbinol. The yield of 2-furylcarbinol boiling at 75–77°/15 mm. is 310–325 g. (61–63 per cent of the theoretical amount) (Note 6).

The water solution containing the sodium 2-furancarboxylate is made acid to Congo red paper with 40 per cent sulfuric acid. This requires about 400 cc. On cooling, the 2-furancarboxylic acid crystallizes and is filtered with suction. The crude acid contains considerable sodium hydrogen sulfate and is deeply colored. For purification it is dissolved in 2300 cc. of boiling water containing about 60 g. of decolorizing carbon (Norite) and the solution is boiled for about forty-five minutes. It is then filtered and cooled with stirring to 16–20° (Note 7) and the 2-furancarboxylic acid which crystallizes is filtered by suction. The product thus obtained is light yellow in color but darkens somewhat on standing. The yield is 360–380 g. (60–63 per cent of the theoretical amount) (Note 8). This acid melts at 121–124° and by titration is 93–95 per cent pure. It is pure enough for many purposes.

For further purification the material may be recrystallized from hot water, or dissolved in alkali and reprecipitated, or distilled under reduced pressure or sublimed. Each of these operations involves considerable loss of product, either through solubility or through decomposition by heat. The best-appearing product is obtained by distillation under reduced pressure. The crude acid is distilled from a Claisen flask with a delivery tube set low in order

that the acid need not be heated much above the boiling point. The product boiling at 141–144°/20 mm. is pure white and melts at 125–132° (Note 9). The yield of distilled acid is about 75–85 per cent of the weight of the crude acid.

2. Notes

1. Technical furfural (sp. gr. 1.15) (p. 280) was used in this preparation. It boiled over a range of 140–160° and contained about 2 per cent water.
2. A 1-gallon (4-l.) ice-cream freezer is a very convenient apparatus to use for the reaction, and a copper container is not necessary.
3. This amounts to about 28 per cent pure sodium hydroxide or 5.77 moles.
4. The apparatus shown (Fig. 16) is a very convenient form of continuous extractor for the laboratory. In the flask F is placed two-thirds of the solvent to be used for the extraction. The remainder is placed in the bottle, which should be just large enough to accommodate the solution to be extracted and the rest of the solvent. The flask is heated on a bath, causing the vapors to pass through E into the condenser, and the liquid therefrom flows through B into the bottom of the bottle, the contents of which must be mechanically stirred during the extraction in order to obtain efficient contact of the liquids. The stirrer and mercury seal are represented by C. For emptying and filling the bottle without disconnecting the apparatus, the tube A with pinchcock is provided. The only precaution to be mentioned is that occasionally the solution in the flask F becomes too concentrated, and consequently so hot that the ether cannot flow back through D owing to its rapid vaporization. If this happens, the contents of the flask must be removed and replaced by fresh solvent.
Carbon tetrachloride may be used for the extraction of the 2-furylcarbinol. This requires altering the extraction apparatus to remove the solvent from the bottom of the extraction bottle. Some difficulties are met in working with carbon tetrachloride, due to the liberation of acid which causes the 2-furylcarbinol to change into the water-insoluble form. The yields of both 2-furancarboxylic acid and 2-furylcarbinol are much lower when carbon tetrachloride is used as a solvent.
5. It is reported that the necessity of extracting the carbinol with ether after completion of the Cannizzaro reaction can be avoided and the yields improved if the excess alkali is neutralized with furoic acid or ammonium sulfate or if a slight deficiency of alkali is used in the first place.[1]
6. The 2-furylcarbinol thus obtained is entirely soluble in water and has only a slight yellow tinge. If it is to be stored, about 0.5 to 1 per cent of its weight of urea should be added as a stabilizer.
7. If the solution is cooled lower than 16°, sodium hydrogen sulfate ($NaHSO_4 \cdot 10H_2O$) begins to separate with the 2-furancarboxylic acid.
8. The low yields of 2-furancarboxylic acid are due partly to the formation of tarry by-products and partly to loss through water solubility. The mother liquors contain about 2.5 g. of 2-furancarboxylic acid per 100 cc. This may be recovered by extraction with ether.
9. The melting point of the 2-furancarboxylic acid is not very sharp. The distilled acid which titrates 100 per cent softens noticeably at 125° and melts completely at 132°.[2]
It is suggested that the 2-furancarboxylic acid is satisfactorily purified by recrystallizing from carbon tetrachloride. A few cubic centimeters of water should be added to coagulate and float the dark impurities. The clear lower layer is separated and

deposits colorless crystals of correct melting point. It has also been suggested that the addition of water be omitted and the carbon tetrachloride solution be heated with Norite and then filtered.

3. Discussion

2-Furancarboxylic acid can be prepared from furfural by oxidation with dichromate,[3] or permanganate,[4] or oxygen in an alkaline solution in the presence of a suitable catalyst;[5] and by condensation using sodamide[6] or concentrated alkali.[7]

2-Furylcarbinol can be prepared from furfural by reduction with sodium amalgam[8] and catalytically,[9] and by condensation using sodamide[6] or concentrated alkali.[7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 274
- Org. Syn. Coll. Vol. 1, 285
- Org. Syn. Coll. Vol. 2, 531
- Org. Syn. Coll. Vol. 3, 621
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- Org. Syn. Coll. Vol. 4, 834

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

oxygen in an alkaline solution

sulfuric acid (7664-93-9)

ether (60-29-7)

sodium hydroxide (1310-73-2)

carbon tetrachloride (56-23-5)

Norite, decolorizing carbon (Norite) (7782-42-5)

sodium (13966-32-0)

urea (57-13-6)

2-furancarboxylic acid, 2-Furoic acid, furoic acid (88-14-2)

Furfural (98-01-1)

2-FURYLCARBINOL, Furfuryl alcohol (98-00-0)

sodium 2-furancarboxylate

sodium hydrogen sulfate (7681-38-1)

ammonium sulfate (7783-20-2)

sodamide (7782-92-5)

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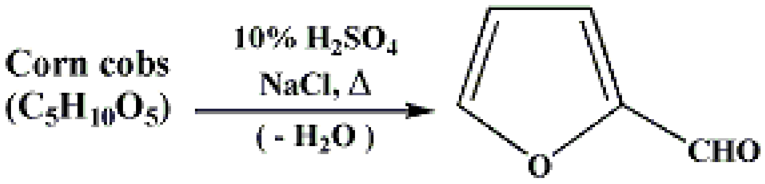
Organic Syntheses, CV 1, 280

FURFURAL

[2-Furaldehyde]



Submitted by Roger Adams and V. Voorhees.
Checked by H. T. Clarke and E. R. Taylor.

1. Procedure

In a 12-l. round-bottomed flask are placed 1.5 kg. of dry corn cobs (ground to about the size of corn kernels) (Note 1), 5 l. of 10 per cent sulfuric acid, and 2 kg. of salt. The flask is shaken in order to secure a homogeneous mixture and is then connected with an upright tube, water condenser, and return tube as shown in Fig. 17, p. 282 (Note 2). Heat is applied from a ring burner, the flame being adjusted so that the liquid distils at a rapid rate.

The distillation process is continued until practically no more furfural can be seen collecting in the distilling flask used as a receiver. The above operation requires from five to ten hours.

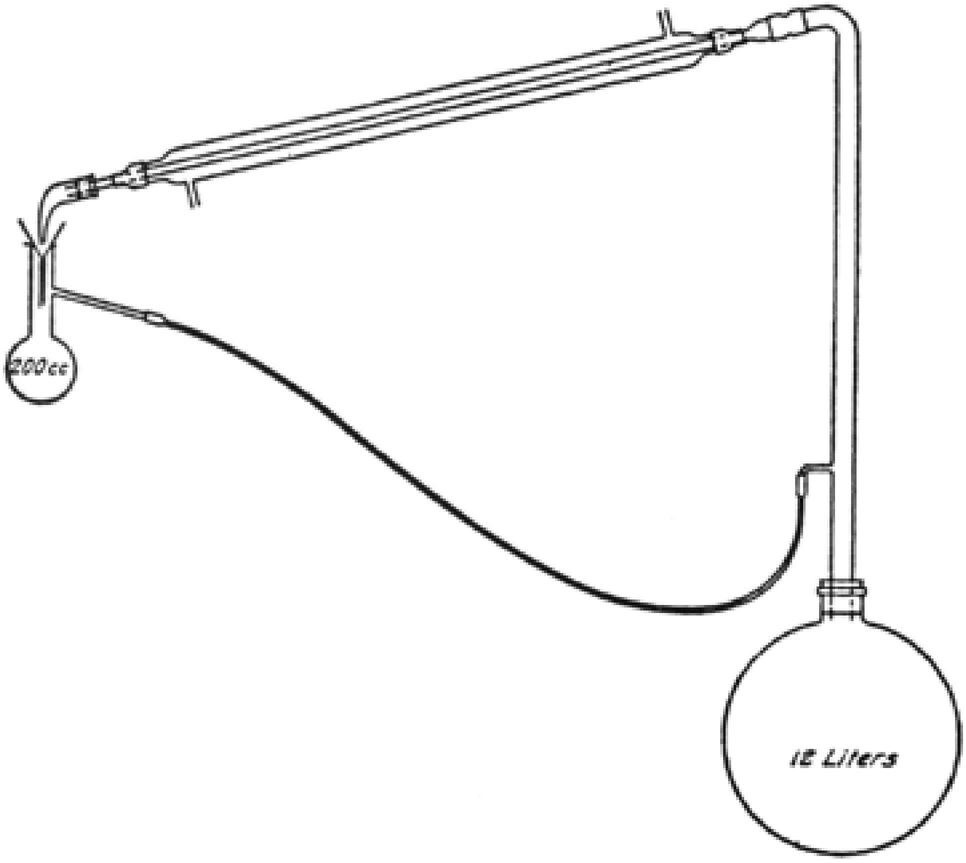
This distillate is now treated with enough sodium hydroxide so that the mixture is left just faintly acid, and the furfural separated. It amounts to 180–220 g. The wet furfural is distilled under reduced pressure from a Claisen flask which is heated in an oil bath (Note 3). The temperature of the bath is never permitted to rise above 130°. At first, water together with some furfural distils, and this fraction is separated to be worked up with a later portion. Finally, 165–200 g. of pure furfural (b.p. 90°/65 mm.; 159°/745 mm.) distils, and this fraction, collected separately, is found to be practically colorless. The distillation of the crude material must not be carried out under ordinary pressure; otherwise the product turns dark rapidly on standing. After one distillation under reduced pressure as described, however, a distillation under atmospheric pressure may be carried out without the objectionable results just mentioned (Note 4).

2. Notes

1. Certain samples of ground cobs which had remained in the laboratory for a year did not give nearly such good yields of furfural as fresher ones.
2. The apparatus described (Fig. 17) is very convenient for laboratory use, but may be modified in many ways as long as a few essential points are kept in mind. A modification worth mentioning is the use as a receiver of a vessel the

bottom of which has a stopcock attached, thus allowing the furfural to be drawn off at any time. It is necessary to have the receiver several inches higher than the opening in the upright tube so that the aqueous liquors will flow back to the reaction flask; the lower end of the funnel in the receiver must be below the side arm of the receiver in order to prevent bubbles of furfural from collecting on the surface of the liquid and being carried back to the reaction flask; the entrance of the returning liquid into the upright tube must be at such a point that a vigorous stream of vapor passes through the returning liquid, thus extracting much of the furfural carried back in the water; the tube for returning the aqueous liquors must at some point be lower than the entrance to the upright tube so that a trap of liquid will be formed and prevent the vapors from the reaction flask entering the side tube. If the return tube is small and swings too low, it happens occasionally that a bubble of air gets into the tube and prevents the regular flow of liquid; this can be remedied by shaking the tube until the difficulty is overcome. It was found that the more efficient the upright tube was as a fractionating column, the more complete was the separation of furfural.

Fig. 17.



3. Distillation of the product under reduced pressure is essential. Moreover, in this final distillation the precautions mentioned (the use of an oil bath and an outside temperature of less than 130°) must be carefully observed. When the furfural is distilled under ordinary pressure or when it is distilled under reduced pressure with a free flame, a practically colorless product is at first obtained. After a few days and sometimes after a few hours this product will gradually darken until finally a black liquid results. This change, although most marked in

the presence of light, takes place readily even when the aldehyde is stored in brown glass bottles. On the other hand, when the crude furfural is distilled under reduced pressure and is never heated above 130° during the process of distillation, a product is obtained that develops only a slight color when exposed to direct sunlight during several days. Further purification according to methods described in the literature does not give a product which will remain colorless on standing.

4. The low yield of furfural from straw and other materials makes it desirable to extract the aqueous furfural distillate after acid hydrolysis by a solvent heavier than water, such as chloroform. This is done by adding a funnel to the end of the condenser so that the distillate passes directly into a layer of chloroform contained in a receiver. Distillation is continued until the chloroform layer does not increase. The furfural is obtained by distillation of the chloroform layer, and practically all the chloroform is recovered (H. I. Waterman, private communication).

3. Discussion

Practically quantitative yields of furfural are obtained when pentoses are subjected to the action of hydrochloric acid.[1] Carbohydrate materials such as corn cobs, wood, the hulls of oats, rice, peanuts, etc., when heated with steam under pressure or distilled with dilute hydrochloric or sulfuric acids, yield appreciable quantities of furfural. Practically all the furfural now prepared technically is from oat hulls.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 276
- Org. Syn. Coll. Vol. 1, 283
- Org. Syn. Coll. Vol. 2, 302

References and Notes

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2. The literature on the preparation of furfural is too extensive for citation here. This literature has been reviewed in "Furfural and Its Derivatives," Bulletin 2 (1928), The Miner Laboratories, Chicago, Ill. Some additional references are: Heuser and Scherer, Brennstoff-Chem. **4**, 97 (1923); Gierisch, Cellulosechem. **6**, 61 (1925); Scurti, Atti II congresso naz. chim. pura applicata 317 (1926) [C. A. **22**, 4665 (1928)]; Vickers Ltd. and Lucas, Brit. pat. 298,800 [C. A. **23**, 3098 (1929)]; Brownlee, Ind. Eng. Chem. **19**, 422 (1927); Clemen, Agr. Expt. Sta. Circ. **339**, 1 (1928) [C. A. **23**, 1969 (1929)]; Oborin Zhur. Prikladnoi Khimii **3**, 231 (1930) [C. A. **24**, 4029 (1930)]; Klingstedt, Zellstoff u. Papier **8**, 471 (1928) [C. A. **24**, 4784 (1930)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

aldehyde

pentoses

hydrochloric or sulfuric acids

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

Furfural, 2-Furaldehyde (98-01-1)

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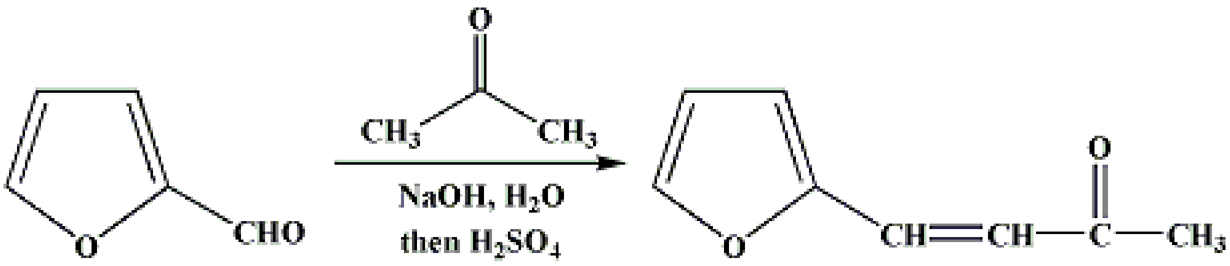
Organic Syntheses, CV 1, 283

2-FURFURALACETONE

[3-Buten-2-one, 4-(2-furyl)-]



Submitted by G. J. Leuck and L. Cejka.
Checked by Frank C. Whitmore and H. H. Rowley.

1. Procedure

In a 5-l. round-bottomed flask equipped with a mechanical stirrer are mixed 385 g. (335 cc., 3.8 moles) of 95 per cent furfural (p. 280) (Note 1) and 3 l. of water. Then 500 g. (630 cc., 8.6 moles) of acetone (Note 1) is added. The mixture is stirred and cooled to 10° and to it is added 75 cc. of 33 per cent sodium hydroxide solution, whereupon some heat is generated. Without cooling, the stirring is continued for four hours. At the end of this time 10 per cent sulfuric acid is added until the mixture is acid to litmus (about 350 cc.) (Note 2). The two layers which have formed are separated and the upper aqueous layer is distilled (Note 3) under ordinary pressure until the distillate no longer forms two layers.

The bottom layer of this distillate is added to the original lower layer and distilled under reduced pressure from a 1-l. modified Claisen flask (p. 130) provided with an air condenser and heated in an oil bath. The receiving flask is placed in a large funnel connected with the drain. A stream of cold water is run over the receiver. When a solid appears in the receiver, distillation is interrupted, the liquid distillate is discarded, and the distillation is continued. The product which distils at 114–118°/10 mm. (135–145°/50 mm.) (Note 4) weighs 310–340 g. (60–66 per cent of the theoretical amount, based on the furfural used). The yellow crystals melt at 37–39° and when melted show a sharp freezing point of 37° (Note 5).

2. Notes

1. Commercial chemicals were used. The use of purer chemicals, including furfural distilled over a 2° range under diminished pressure, gives no higher yield, but the product is lighter colored, although the boiling point and melting point are the same as with the crude materials.
Some commercial grades of acetone have a markedly deleterious effect on the yield of furfuralacetone (F. N. Peters, private communication). Accordingly, it is

recommended that acetone of reasonably high purity be used.

2. When the alkali is neutralized, the mixture loses its milky appearance and forms definite layers.

3. The distillation of the water layer may be omitted, since it yields only 10–20 g. of the product.

4. A large residue of higher-boiling material remains in the flask. This residue contains much difurfuralacetone, the formation of which takes place to a considerable extent in spite of the large excess of acetone used.

5. The highest melting point recorded in the literature is 39–40°. The crystals gradually become reddish on standing even in the dark. This change is much slower when freshly distilled furfural is used.

3. Discussion

2-Furfuralacetone can be prepared by the condensation of furfural with acetone in the presence of bases.[1]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

sodium hydroxide (1310-73-2)

acetone (67-64-1)

Furfural (98-01-1)

2-Furfuralacetone

3-Buten-2-one, 4-(2-furyl)- (623-15-4)

furfuralacetone

difurfuralacetone

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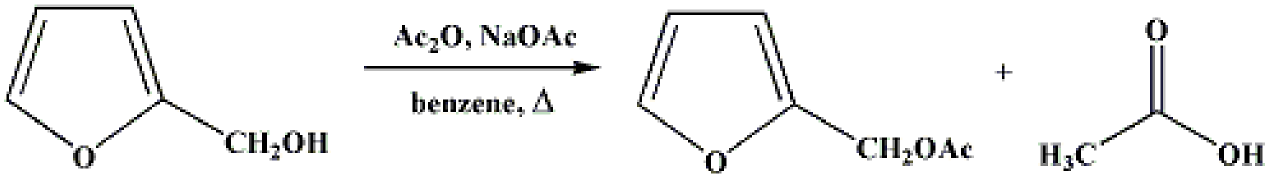
Organic Syntheses, CV 1, 285

2-FURYLMETHYL ACETATE

[Furfuryl alcohol, acetate]



Submitted by The Miner Laboratories
Checked by Roger Adams and C. G. Gauerke.

1. Procedure

A mixture of 1 l. of benzene, 600 g. (529 cc., 6.1 moles) of 2-furylcarbinol (p. 276) (Note 1), 225 g. (2.7 moles) of fused powdered sodium acetate, and 650 g. (602 cc., 6.4 moles) of a good grade of acetic anhydride are placed in a 5-l. round-bottomed flask (Note 2) fitted with a mechanical stirrer and a reflux condenser provided with a calcium chloride tube. The flask is heated on a steam bath (Note 1) for four hours with stirring to prevent caking of the sodium acetate.

The reaction mixture is allowed to cool and is poured into 4 l. of cold water (Note 3). The upper layer is separated and allowed to stand for two hours over about 500 cc. of 5 per cent sodium carbonate solution with frequent shaking or mechanical stirring. This decomposes any excess of acetic anhydride. It is finally washed with about 3 l. of water. The benzene solution is distilled under ordinary pressure to remove the benzene (800–900 cc. is recovered). The 2-furylmethyl acetate is distilled under diminished pressure, b.p. 69–70°/7 mm. The yield is 750–800 g. (87–93 per cent of the theoretical amount) (Note 4).

2. Notes

1. If the water-insoluble form of the alcohol (p. 278) is used, the mixture should be allowed to stand under a reflux condenser for about two hours before it is heated. During this period a certain amount of heat is evolved, and sometimes it is sufficient to cause the benzene to boil vigorously, thus making cooling necessary. After it has stood the required time, the mixture is refluxed as described above.
2. If a two- or three-necked flask is available it can be used to advantage.
3. The washing can best be done in a large separatory apparatus prepared by cutting the bottom out of an 18-l. (5-gallon) glass carboy and wiring into its neck a piece of glass tubing carrying a rubber tube and pinch clamp. The inverted carboy forms a useful separatory funnel of large capacity.
4. Saponification of the product with standard potassium hydroxide shows 93–94 per cent ester. It contains some furfuryl alcohol, the removal of which by fractional distillation is difficult, because the boiling points of the alcohol (169°/752 mm.) and the ester (175°/764 mm.) are so close together. Furfuryl acetate darkens on standing. It may be redistilled with little loss to give an almost colorless product.

3. Discussion

2-Furylmethyl acetate can be prepared by heating 2-furylcarbinol with acetic anhydride alone, or with acetic anhydride and sodium acetate.[1]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Benzene (71-43-2)

acetic anhydride (108-24-7)

sodium acetate (127-09-3)

sodium carbonate (497-19-8)

potassium hydroxide (1310-58-3)

2-FURYLCARBINOL, Furfuryl alcohol (98-00-0)

2-Furylmethyl acetate

Furfuryl alcohol, acetate, Furfuryl acetate (623-17-6)

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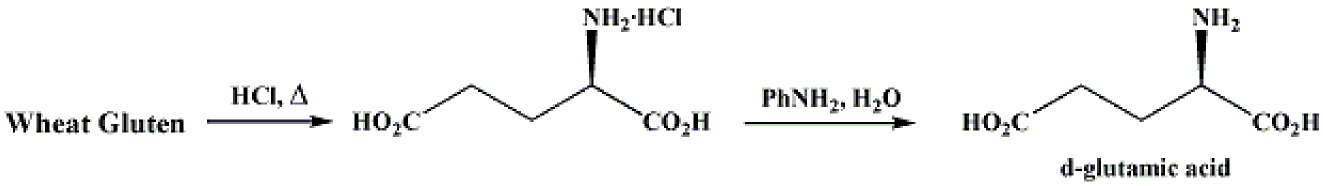
Organic Syntheses, CV 1, 286

d-GLUTAMIC ACID



Submitted by Harold King
Checked by H. T. Clarke and S. Gurin.

1. Procedure

(*A*) *Glutamic Acid Hydrochloride*.—A mixture of 300 cc. of concentrated hydrochloric acid and 100 g. (corrected for moisture) of gluten flour is boiled under reflux for six hours. When the solution has cooled to room temperature it is treated with 20 g. of decolorizing carbon and filtered by suction through two thicknesses of linen covered with a thin layer of infusorial earth; 15 cc. of concentrated hydrochloric acid is employed for rinsing the flask and washing the residue. The light yellow filtrate is concentrated under reduced pressure to 175 cc. (Note 1) and allowed to stand overnight at –8°. The crystals which separate, amounting to 25–26 g., are filtered off on hardened paper. The mother liquor is further concentrated to 75 cc. and again allowed to stand overnight at –8°. A second crop amounting to 16–18 g. is thus obtained. Further concentration yields no more crystals.

The crude product, which is yellow in color, is dissolved in 40 cc. of hot water, decolorized with 1 g. of charcoal, and treated with 33 cc. of concentrated hydrochloric acid. After standing overnight in the refrigerator, the first crop, weighing about 23 g., is obtained. This melts with decomposition at 208–209° (corr.). On concentrating the mother liquors two further crops of equal purity can be obtained, giving a total yield (Note 2) of 26–27 g. of glutamic acid hydrochloride of satisfactory quality.

(*B*) *Glutamic Acid*.—To a solution of 36.7 g. (0.2 mole) of pure glutamic acid hydrochloride in 200 cc. of hot water is added 18.6 g. (0.2 mole) of aniline. The mixture, after heating for a few minutes on the steam bath, is cooled, treated with 200 cc. of 95 per cent ethyl alcohol, and allowed to stand overnight in the refrigerator. The crystalline glutamic acid is filtered off and washed with 95 per cent ethyl alcohol until free of chloride. It is then pure, and melts with decomposition at 211–213° (corr.). The yield (Note 3) and (Note 4) is 27–28 g. (92–95 per cent of the theoretical amount).

2. Notes

1. In checking this preparation no crystals were obtained on chilling the original unconcentrated filtrate to –8° and holding it at this temperature for seventy-two hours.
2. The yield will depend in a large measure on the quality of the gluten flour; that employed for checking (Battle Creek Gluten flour) contained 8.7 per cent moisture, and 7.4 per cent nitrogen on the dry basis.
3. The glutamic acid so obtained is of high quality, which cannot be improved by recrystallization from water. In fact such recrystallization is attended with loss owing to the formation of pyrrolidone-carboxylic acid. The mother liquor yields no further crystals on concentration under reduced pressure to 75 cc. and treatment with 75 cc. of alcohol.

4. Glutamic acid may also be obtained from "Ajinomoto,"[1] a Japanese food product in powder form, consisting mainly of the monosodium salt of glutamic acid. The exact amount of this constituent may be determined by the Van Slyke amino nitrogen method and by igniting a sample of the material in a platinum crucible and titrating the residue of sodium carbonate. The calculated quantity of normal hydrochloric acid is added to a solution of the Ajinomoto in four times its weight of water, and then the solution is boiled with a little decolorizing carbon and filtered hot; the clear solution is allowed to stand overnight in the ice box and the crystallized glutamic acid is filtered and washed with ice water. In this way, 72–73 per cent of the theoretical amount can be obtained; thus, 100 g. of Ajinomoto, found to contain 84 g. of monosodium glutamate, was dissolved in 400 cc. of water and treated with 500 cc. of normal hydrochloric acid, when 54–55 g. of pure glutamic acid was obtained.

3. Discussion

d-Glutamic acid hydrochloride can be prepared by the hydrolysis of gliadin from wheat,[2] casein,[3] and technical residues like beet-sugar molasses[4] or alcohol-extracted soybean cake.[5] The acid has been synthesized from acrolein through β-aldehydobutyric acid,[6] and by the alkylation of benzoylaminomalonic ester with β-bromopropionic ester followed by hydrolysis.[7]

d-Glutamic acid can be prepared from the hydrochloride by treating a water solution with strong alkalies,[3] alkali carbonates,[8] aqueous ammonia,[9] aniline,[10] and by adding 6–8 volumes of alcohol to a concentrated aqueous solution.[11]

The preparation of *d*-glutamic acid from Ajinomoto[12] is very convenient, but more expensive than that from flour.

References and Notes

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11. Hopkins, ibid. **15**, 293 (1921).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

benzoylaminomalonic ester

β-aldehydobutyric acid

β-bromopropionic ester

ethyl alcohol, alcohol (64-17-5)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

aniline (62-53-3)

Acrolein (107-02-8)

sodium carbonate (497-19-8)

nitrogen (7727-37-9)

decolorizing carbon (7782-42-5)

Glutamic Acid Hydrochloride (138-15-8)

Glutamic Acid (56-86-0)

pyrrolidone-carboxylic acid

monosodium salt of glutamic acid, monosodium glutamate

D-Glutamic acid (617-65-2)

d-Glutamic acid hydrochloride

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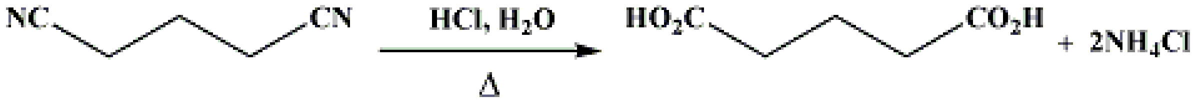
Organic Syntheses, CV 1, 289

GLUTARIC ACID

[(*A*) (*from Trimethylene Cyanide*)]



Submitted by C. S. Marvel and W. F. Tuley.
Checked by H. T. Clarke and E. E. Dreger.

1. Procedure

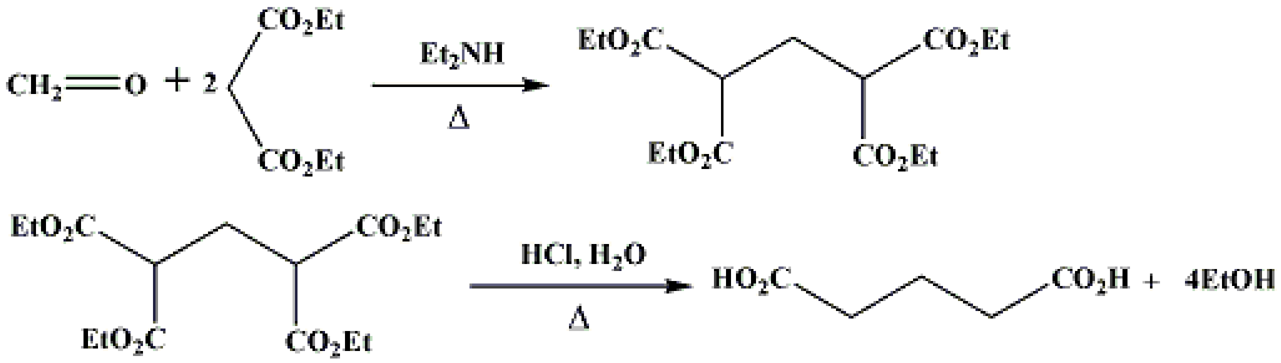
In a 2-l. round-bottomed flask are placed 100 g. (1.06 moles) of trimethylene cyanide (p. 536) and 500 g. (424 cc., 4.8 moles) of hydrochloric acid (sp. gr. 1.18). The mixture is refluxed for about four hours and then the solution is evaporated to dryness, preferably under reduced pressure. The dry residue, consisting of glutaric acid and ammonium chloride, is extracted with about 300 cc. of boiling ether. The ether solution is filtered and the residue is further extracted with two 100-cc. portions of boiling ether. The combined ether extracts containing the glutaric acid are evaporated (Note 1) to about 150–200 cc., whereupon the acid begins to crystallize. Then 1 l. of benzene (Note 2) is added, and the mixture is heated until the glutaric acid dissolves. On cooling in an ice-salt bath, the acid crystallizes. The first crop weighs 103–105 g. (Note 3). The filtrate is concentrated to about one-third its original volume and cooled, whereupon a second crop of 13–14 g. of pure glutaric acid is obtained. The total yield is thus 116–119 g. (83–85 per cent of the theoretical amount) of a product melting at 97–98° (Note 4).

2. Notes

1. Most of the ether can be recovered by concentrating the solution in a flask attached to a condenser set for distillation.
2. The glutaric acid may be directly extracted from the ammonium chloride with benzene, but on a small scale this is less satisfactory than the procedure given.
3. When the benzene solution is chilled to 0° or lower, almost all the glutaric acid separates in the first crop of crystals.
4. It is reported that glutaric acid can be easily and cheaply prepared by the oxidation of cyclopentanone according to the following procedure, which is similar to that for the preparation of adipic acid from cyclohexanone—compare p. 18. The oxidation needs careful control, for if it gets out of hand succinic acid results.
In a 2-l. round-bottomed, three-necked flask fitted with a stirrer and two large-bore condensers are placed 200 cc. of 50 per cent nitric acid and 0.25 g. of vanadium pentoxide. The flask is heated to 65–70° in a water bath (thermometer in the water), and 1 cc. of cyclopentanone is added. Oxidation is indicated by the production of brown fumes. The water bath is removed, and 42 g. (less the 1 cc.) of the cyclic ketone is added from a dropping funnel through the condenser at the rate of a drop every three seconds. The heat of the reaction keeps the flask at about 70°. If the temperature drops, oxidation ceases until the ketone has accumulated, when it may proceed almost explosively. In such a case, or if the temperature is higher, much succinic acid is formed. After addition

has been completed, the water bath is replaced and the mixture heated to boiling. The contents of the flask are poured into an evaporating dish (Hood), and the volume reduced one-half. When cold, the acid is filtered and the operation repeated twice; the last time the acid is yellowish, and the color is removed by washing with dilute hydrochloric acid. The crude glutaric acid is white and weighs 50–55 g. (80–85 per cent); m.p. 92–94°. If any succinic acid is present owing to lack of proper control, it separates in the first crop. It is more convenient to allow the mother liquors from several runs to accumulate and work them up separately; from each run 2–3 g. more of glutaric acid may be so obtained. Further purification is accomplished, if desired, by crystallization from benzene. The acid as prepared above always contains traces of nitric acid, but is satisfactory for conversion into the anhydride. If the catalyst is omitted, the yield is less by 10 per cent. (C. F. H. Allen and W. L. Ball, private communication).

[(*B*) (*from Ethyl Malonate*)]



Submitted by T. J. Otterbacher
Checked by F. C. Whitmore and F. L. Carnahan.

1. Procedure

Ethyl Propane-1,1,3,3-tetracarboxylate.—To a mixture of 1600 g. (1510 cc., 10 moles) of ethyl malonate (Note 1) and 400 g. of 40 percent formalin (5.3 moles) in a 5-l. round-bottomed flask, cooled to 5° by immersion in ice, is added 25 g. (35 cc.) of diethylamine. The mixture is then allowed to come to room temperature and remain for fifteen hours, after which the flask is heated under a reflux condenser on a boiling water bath for six hours. The aqueous layer is then separated, and the residue is distilled under reduced pressure (Note 2) from a 3-l. special Claisen flask (p. 130). The ester distils at 190–200°/12 mm. (210–215° /20 mm.). The yield (Note 3) is 1000 g. (61 per cent of the theoretical amount).

Glutaric Acid.—A mixture of 125 g. (0.37 mole) of the above product, 125 cc. of concentrated hydrochloric acid, and 125 cc. of water is heated (Note 4) in a 1-l. flask under a reflux condenser until it becomes homogeneous (six to eight hours). The contents of the flask are then evaporated to dryness, and the residual glutaric acid is transferred to a 100-cc. Claisen flask and distilled under diminished pressure. The fraction boiling at 185–195° /10 mm. is collected. It is moistened with water (Note 5) and heated gently, after which it is dried at 30°. On recrystallization from benzene, it separates in colorless needles, m.p. 96–97°. The yield is 38–40 g. (76–80 per cent of the theoretical amount).

2. Notes

1. The ethyl malonate used was a fraction of the technical grade boiling over a 3° range under diminished pressure.
2. The ester is distilled slowly at first in order to vaporize the water at a temperature below 50°.
3. The high-boiling residue (500 g.) is stated[1] to contain considerable amounts of ethyl pentanehexacarboxylate.
Directions are also available for the preparation of ethyl propane-1,1,3,3-tetracarboxylate in high yield from ethyl malonate, paraformaldehyde, and alcoholic potassium hydroxide.[2] Prior to distillation of the ester a little hydrochloric acid is added to destroy the catalyst.
4. In order to prevent loss of material through the condenser by bumping, the flask should be heated in an oil bath at 115° or its contents stirred vigorously.
5. The product is moistened to convert any anhydride, formed at the high temperature of distillation, into the acid.

3. Discussion

Glutaric acid can be prepared by the hydrolysis of trimethylene cyanide with acids or alkalies;[3] the hydrolysis of methylene dimalonic ester[4] or methylene dicyanoacetic ester;[5] and the oxidation of cyclopentanone with nitric acid[6] or catalytically.[7] Glutaric acid can also be prepared from methylcyclohexane by catalytic oxidation,[8] and from pentamethylene glycol by oxidation with permanganate.[9]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 496

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ester

cyclic ketone

methylene dimalonic ester

methylene dicyanoacetic ester

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether (60-29-7)

ammonium chloride (12125-02-9)

formalin (630-08-0)

Adipic acid (124-04-9)

nitric acid (7697-37-2)

Cyclohexanone (108-94-1)

vanadium pentoxide

Succinic acid (110-15-6)

potassium hydroxide (1310-58-3)

Trimethylene cyanide (544-13-8)

Cyclopentanone (120-92-3)

ethyl malonate (1071-46-1)

Glutaric acid (110-94-1)

Ethyl propane-1,1,3,3-tetracarboxylate

diethylamine (109-89-7)

ethyl pentanehexacarboxylate

methylcyclohexane (108-87-2)

pentamethylene glycol (111-29-5)

paraformaldehyde (30525-89-4)

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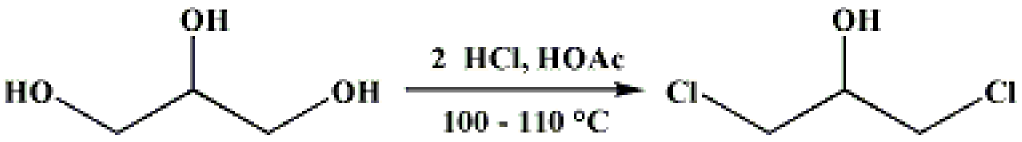
GLYCEROL α,γ-DICHLOROHYDRIN

[2-Propanol, 1,3-dichloro-]



Submitted by J. B. Conant and O. R. Quayle.
Checked by O. Kamm and A. O. Matthews.

1. Procedure

One kilogram (805 cc., 9.8 moles) of 90 per cent glycerol (sp. gr., 1.243) and 20 g. of acetic acid are placed in a weighed 2-l. flask which is immersed in an oil bath heated to 100–110° (Note 1). The flask is fitted with a two-holed stopper, which carries a long tube reaching to the bottom of the flask and a short exit tube. The long tube is connected to a hydrogen chloride generator (Note 2); the short one, to a catch-bottle and some system for absorbing any excess of hydrogen chloride (see Fig. 7 on p. 97). A stream of dry hydrogen chloride is passed into the mixture. The absorption of gas is very rapid at the start but gradually falls off towards the end of the reaction; the stream of hydrogen chloride should be regulated accordingly. The flask is removed from time to time and weighed; when the absorption of gas practically ceases, the increase in weight will be about 875 g. (25 per cent more than the theoretical amount).

The product is now cooled, placed in a 4-l. beaker, and treated with solid sodium carbonate until just alkaline to litmus. water is added from time to time, to facilitate the reaction with the sodium carbonate and to prevent the separation of salt; about 500 cc. is required. The mixture is transferred to a separatory funnel and the aqueous layer separated. The crude dichlorohydrin, which weighs 1250 g., is distilled under reduced pressure. The first fraction boiling below 68°/14 mm. weighs 225 g., and consists of water and some dichlorohydrin; the dichlorohydrin is collected between 68° and 75°/14 mm., and weighs about 775 g. The water is separated from the first fraction, which is then redistilled and yields 100 g. of dichlorohydrin. A further amount of material (40–45 g.) may be obtained by extracting the aqueous layer obtained in the neutralization process with benzene. This is, however, hardly profitable. The neutralization and distillation will require about four hours.

The 875 g. of dichlorohydrin thus obtained boils over a 7° range; this is 70 per cent of the theoretical amount (Note 3). Redistillation yields 700–720 g. boiling at 70–73°/14 mm. (55–57 per cent of the theoretical amount).

2. Notes

1. The oil bath can be conveniently heated on an electric hot plate.
2. *Hydrogen Chloride*.—The most convenient hydrogen chloride generator is that described by Sweeney.[1] Concentrated hydrochloric acid is introduced into concentrated sulfuric acid by means of a dropping funnel and a *capillary tube leading to the bottom of the sulfuric acid container*. It is convenient to use a 3-l. bottle for this container and a 1-l. funnel to contain the hydrochloric acid. The gas is dried by passing through a wash bottle containing concentrated sulfuric acid. An empty catch-flask should be connected between the generator and the absorption flask in case any glycerol tends to suck back at the start of the reaction. About 6 kg. of concentrated hydrochloric acid and 10 kg. of concentrated sulfuric acid are required in one run. The generating flask will have to be recharged every six hours; it should be half filled with sulfuric acid. Aside from this, the apparatus needs no attention.
It is suggested that hydrogen chloride can be readily and conveniently prepared by dropping concentrated sulfuric acid on dry lumps of ammonium chloride (D. T. Gibson, private communication).
Large quantities of hydrogen chloride can be prepared by adding concentrated sulfuric acid to a paste of sodium chloride and concentrated hydrochloric acid (see Note 1 on p. 534).
3. The dichlorohydrin boiling over a 7° range is sufficiently pure for most purposes. It contains very little, if any, isomeric dichlorohydrin, since on oxidation it gives dichloracetone (p. 211) in good yields.

3. Discussion

Glycerol α,γ-dichlorohydrin can be prepared by the action of hydrogen chloride on glycerol,[2] on glycerol mixed with an equal volume of acetic acid,[3] on glycerol containing 1–2 per cent of some organic acid, as acetic, as a catalyst;[4] by the action of aqueous hydrochloric acid[5] or hydrogen chloride[6] on glycerol containing acetic acid as a catalyst; and by the action of hydrogen chloride on glycerol in the presence of a water-immiscible solvent, such as dibutyl ether, and at a temperature such that steam distillation takes place.[7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 5
- Org. Syn. Coll. Vol. 1, 166
- Org. Syn. Coll. Vol. 1, 211
- Org. Syn. Coll. Vol. 1, 233
- Org. Syn. Coll. Vol. 1, 237
- Org. Syn. Coll. Vol. 1, 294
- Org. Syn. Coll. Vol. 1, 314
- Org. Syn. Coll. Vol. 1, 364

- Org. Syn. Coll. Vol. 1, 377
- Org. Syn. Coll. Vol. 1, 451
- Org. Syn. Coll. Vol. 1, 533
- Org. Syn. Coll. Vol. 2, 256
- Org. Syn. Coll. Vol. 2, 284
- Org. Syn. Coll. Vol. 4, 169
- Org. Syn. Coll. Vol. 4, 238
- Org. Syn. Coll. Vol. 4, 605

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Glycerol α,γ-dichlorohydrin

acetic

sulfuric acid (7664-93-9)

hydrogen chloride, hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

ammonium chloride (12125-02-9)

glycerol (56-81-5)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

dichloracetone (513-88-2)

2-Propanol, 1,3-dichloro- (96-23-1)

dibutyl ether (142-96-1)

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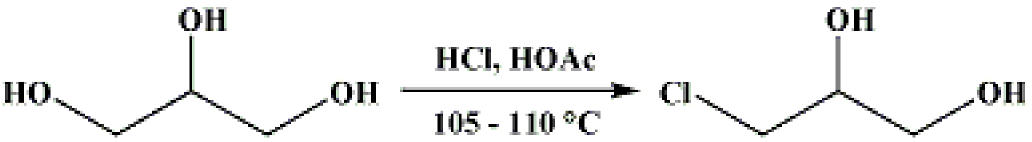
GLYCEROL α-MONOCHLOROHYDRIN

[1,2-Propanediol, 3-chloro-]



Submitted by J. B. Conant and O. R. Quayle.
Checked by O. Kamm and A. O. Matthews.

1. Procedure

Five hundred grams (402 cc., 4.9 moles) of 90 per cent glycerol and 10 g. of glacial acetic acid are mixed in a weighed 1-l. flask, which is placed in an oil bath heated to 105–110° (Note 1). A rapid stream of dry hydrogen chloride (Note 2) is introduced into the mixture. The flask is removed from the bath from time to time and reweighed. At the end of about four hours the flask will have gained 190 g. in weight. The reaction is then complete.

The product is distilled under reduced pressure. Below 114°/14 mm., 220–250 g. distil; this portion is mostly water. The monochlorohydrin is collected between 114° and 120°/14 mm. (Note 3), and weighs 360 g. (66 per cent of the theoretical amount) (Note 4). About 20 g. more may be obtained by neutralizing the first fraction and separating the aqueous layer.

2. Notes

1. The same apparatus is employed as in the preparation of glycerol α,γ-dichlorohydrin (p. 292).
2. Two kilograms of concentrated sulfuric acid and 750 g. of concentrated hydrochloric acid are sufficient to produce the necessary amount of hydrogen chloride. See pp. 293 and 534 for the generation of hydrogen chloride.
3. The portion boiling 120–130°/14 mm. amounts to only 15–30 g., showing that very little of the β-compound is formed. This is further shown by the fact that the dichlorohydrin formed by continued action of hydrogen chloride under the same conditions contains very little, if any, α,β-dichlorohydrin.
4. A light straw-colored final product is obtained in some cases.
An alternative procedure which is slower and gives slightly lower yields, but which does not require a hydrogen chloride generator, is as follows:
Three hundred grams of 90 per cent glycerol, 600 cc. of hydrochloric acid (sp. gr. 1.19), and 15 g. of glacial acetic are heated under a reflux condenser for ten hours, in a 2-l. flask. The boiling should be very gentle in the early stage of the reaction, as considerable hydrogen chloride vapor is evolved. As the reaction

progresses, and the evolution of acid vapors diminishes, the mixture is more strongly heated.
The reaction products are distilled under ordinary pressure until the temperature of the liquid has reached 140° (thermometer bulb immersed in the liquid). The residual products are distilled under diminished pressure, and the following fractions obtained: (1) up to 115°/11 mm.; (2) 115–117°/11 mm.; and (3) 117–170°/11 mm. (1) is mostly aqueous hydrochloric acid; (2) is the monochlorohydrin; and (3) is glycerol. The second fraction is redistilled, and the portion boiling at 115–118°/11 mm. or 133–136°/20 mm. is collected. The yield is 190–205 g., 59–63 per cent of the theoretical amount. Higher yields are possible by reworking the residues in a procedure which is in essential accordance with that outlined.[1]

3. Discussion

Glycerol α-monochlorohydrin can be prepared by the action of hydrogen chloride on glycerol[2] or on glycerol mixed with an equal volume of acetic acid[3] or other organic acid[4] as catalyst, or on glycerol with the ester of an organic or inorganic acid as a catalyst;[5] by the action of aqueous hydrochloric acid on glycerol[6] alone or with an organic acid (1–2 per cent), such as acetic, as a catalyst;[7] and by heating epichlorohydrin with water in the presence of sulfuric acid as a catalyst.[8]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 296

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ester

Glycerol α,γ-dichlorohydrin

acetic

Glycerol α-monochlorohydrin

sulfuric acid (7664-93-9)

hydrogen chloride, hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

glycerol (56-81-5)

Epichlorohydrin (106-89-8)

1,2-Propanediol, 3-chloro- (96-24-2)

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Organic Syntheses, CV 1, 296

α-GLYCERYL PHENYL ETHER

[1,2-Propanediol, 3-phenoxy-]

Submitted by T. S. Wheeler and F. G. Willson.
Checked by H. T. Clarke and E. R. Taylor.

1. Procedure

To 500 cc. of absolute alcohol (Note 1) in a 1-l. flask fitted with a reflux condenser is added gradually 46 g. (2 atoms) of sodium in thin slices (Note 2) at such a rate that the mixture boils steadily. When all the sodium has been added, the mixture is heated on the steam bath until the few remaining pieces of sodium barely react. Pure commercial molten phenol is now added gradually through the condenser until all the sodium has reacted, and then the remainder of 188 g. (2 moles) of phenol is added. This is followed by the addition of 221 g. (2 moles) of redistilled glycerol α-monochlorohydrin (p. 294) in small portions, the rather vigorous reaction being allowed to complete itself before each subsequent addition.

When all has been added, the mixture is heated on the steam bath for about one hour. The end of the reaction is determined by withdrawing a sample, filtering it, and heating the filtrate in which little or no precipitate should form. The mixture is filtered hot by suction through filter cloth or heavy filter paper (Note 3), the precipitate being washed with three 50-cc. portions of absolute alcohol. The filtrate and washings are distilled on the steam bath under slightly reduced pressure until no more alcohol comes over; the residue, which sets to a white waxy solid on cooling, is transferred to a distilling flask and distilled under reduced pressure, the fraction boiling at 175–190°/15 mm. being collected. In this way 235–275 g. of a product melting at 43–49° is obtained. On redistillation, 205–215 g. (61–64 per cent of the theoretical amount) of a fraction which boils at 185–187°/15 mm. and melts at 48–53° is obtained (Note 4).

2. Notes

1. Absolute alcohol (p. 249) is required in order that all the sodium chloride formed may be precipitated and that none may remain to contaminate the product.
2. More rapid solution of the sodium can be obtained if the metal is granulated prior to its addition to the alcohol. This is done by covering the sodium with ten times its weight of dry xylene and heating to 120° in a stout round-bottomed

flask.[1] The flask is then well corked, wrapped in a thick, dry cloth, and well shaken for a short time. The metal is thus obtained in the form of small spheres, the size of which is controlled by the time and rapidity of the shaking. A dry bucket should be kept at hand so that the flask can be dropped into it in case of breakage. Not more than 30 g. of sodium should be treated at one time. Vigorous mechanical stirring (Fig. 2, p. 33) may be used to advantage in place of shaking by hand.

3. The precipitate of sodium chloride obtained is very sludgy and filters poorly through fine-fibered papers.

4. Small traces of impurity lower the melting point very considerably, and by repeated recrystallization from anhydrous ether the melting point can be raised to 70°. The product crystallizes from the ether in very long, flexible needles, forming a spongy mass which filters with some difficulty. In order to obtain a high melting point, complete removal of the solvent, preferably by warming to 50° under reduced pressure, is essential.

3. Discussion

α-Glyceryl phenyl ether can be prepared by heating phenol with excess of glycerol and anhydrous sodium acetate,[2] and by heating phenol with α-monochlorohydrin and caustic alkali.[3]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Glycerol α-monochlorohydrin

α-monochlorohydrin

caustic alkali

alcohol (64-17-5)

ether (60-29-7)

sodium acetate (127-09-3)

glycerol (56-81-5)

phenol (108-95-2)

sodium chloride (7647-14-5)

sodium (13966-32-0)

xylene (106-42-3)

α-Glyceryl phenyl ether

1,2-Propanediol, 3-phenoxy- (538-43-2)

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Organic Syntheses, CV 1, 298

GLYCINE

[(*A*) (*from Methyleneaminoacetonitrile*)]

$$H_2C{=}NCH_2CN + 2C_2H_5OH + H_2SO_4 \longrightarrow (H_2NCH_2CN)\cdot H_2SO_4 + CH_2(OC_2H_5)_2$$

$$2(H_2NCH_2CN)\cdot H_2SO_4 + 3Ba(OH)_2 \longrightarrow (H_2NCH_2CO_2)_2Ba + 2BaSO_4 + 2H_2O + 2NH_3$$

$$(H_2NCH_2CO_2)_2Ba + H_2SO_4 \longrightarrow 2H_2NCH_2CO_2H + BaSO_4$$

Submitted by W. K. Anslow and Harold King.
Checked by H. T. Clarke and Letha Davies Behr.

1. Procedure

(*A*) *Alcoholysis of Methyleneaminoacetonitrile*.—To a solution of 51.5 g. (28 cc., 0.5 mole) of 95 per cent sulfuric acid in 125 cc. of 95 per cent ethyl alcohol at 45–50°, contained in a wide-mouthed 250-cc. conical flask, is added 34 g. (0.5 mole) of methyleneaminoacetonitrile (p. 355) (Note 1). The flask is closed with a rubber stopper (Note 2) and vigorously shaken by hand. Solution takes place with evolution of heat, the temperature rising about 10–15° (Note 3). The liquid separates into two layers, the upper one consisting of methylene diethyl ether; crystallization of the aminoacetonitrile hydrogen sulfate sets in rapidly. The mixture is shaken vigorously at intervals to prevent the formation of a hard cake of crystals. After the mass has stood overnight in the refrigerator at 0–5°, the salt is filtered off and washed with a minimum quantity (20–25 cc.) of ice-cold alcohol. The yield is 57–62 g. (75–81 per cent of the theoretical amount) (Note 4).

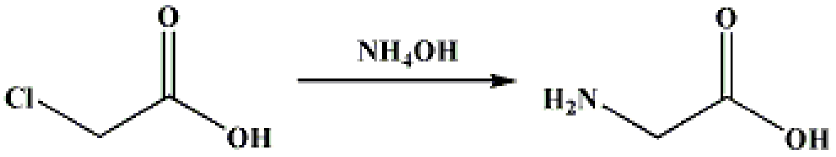
(*B*) *Preparation of Glycine*.—To a boiling suspension of 253 g. (0.8 mole) of barium hydroxide octahydrate in 500 cc. of water in a 1-l. beaker is added, in portions, 61.6 g. (0.4 mole) of aminoacetonitrile hydrogen sulfate at such a rate that the mixture does not froth over. The beaker is then covered with a 1-l. round-bottomed flask containing cold running water, and boiling is continued until no more ammonia is evolved. This requires six to eight hours. The barium is then quantitatively precipitated by the addition of exactly the necessary amount of 50 per cent sulfuric acid (Note 5). The filtrate is concentrated on a water bath to a volume of 50–75 cc.; on chilling, crude glycine crystallizes and is filtered off. The filtrate is again concentrated and chilled and the crystals removed. This process is continued until the final filtrate amounts to about 5 cc. The yield of crude glycine so obtained amounts to 25–27 g. This is systematically recrystallized from water, decolorizing with Norite and collecting the material which melts (with decomposition) at 246° (corr.) or above. Washing of the successive crops with 50 per cent ethyl alcohol is of great assistance in freeing the crystals of mother liquor. The yield of pure glycine is 20–26 g. (67–87 per cent of the theoretical amount).

2. Notes

1. The yields obtained with the crude material are as good as those with the recrystallized nitrile. Recrystallization of the nitrile is attended with considerable loss, only 65–70 per cent of the original weight being recovered.
2. Moistening of the portion of the stopper in contact with the glass should be avoided as

this lubrication tends to permit the stopper to escape unless forcibly held down.
3. If the initial temperature of the acid mixture is below that indicated, there is a tendency for the aminoacetonitrile hydrogen sulfate to separate before the nitrile is completely dissolved; if the temperature is too high, there is danger that the alcohol may boil.
4. The mother liquor contains a further quantity of aminoacetonitrile hydrogen sulfate which cannot, however, be recovered as such; in one experiment it yielded 2.3 g. of crude glycine on hydrolysis with excess barium hydroxide.
5. It is well to add a very slight excess of sulfuric acid, heat on the water bath until the precipitate filters readily, and finally complete the operation by adding dilute barium hydroxide solution until no further precipitation takes place. It is also feasible to finish with a slight excess of barium hydroxide and to remove this by the addition of ammonium carbonate to the boiling solution.

[(*B*) (*from Chloroacetic Acid*)]



Submitted by James M. Orten and Robert M. Hill.
Checked by C. S. Marvel and C. F. Woodward.

1. Procedure

In a 12-l. round-bottomed flask is placed 8 l. (120 moles) of aqueous ammonia (sp. gr. 0.90) and to it is gradually added, with stirring, 189 g. (2 moles) of monochloroacetic acid. The solution is stirred until the chloroacetic acid is dissolved and is then set aside for about forty-eight hours at room temperature. The solution, which is colorless or faintly yellow, is concentrated on a water bath under reduced pressure (Note 1) to a volume of about 200 cc.

The concentrated solution of glycine and ammonium chloride is transferred to a 2-l. beaker, the flask is rinsed with a little water, and this is added to the main portion. The volume of the solution is finally brought to 250 cc. with water, and the glycine is precipitated by the gradual addition of 1500 cc. of methyl alcohol (Note 2). The solution is well stirred during the addition of the methyl alcohol and is cooled in an ice box for four to six hours to allow complete crystallization. The solution is filtered, and the glycine crystals are washed by suspending them in 500 cc. of 95 per cent methyl alcohol; they are again collected on the filter and washed with a little methyl alcohol and then with ether. After air drying the yield is 108–112 g. of glycine.

This product contains small amounts of chloride and ammonia. For purification it is dissolved in 200 to 215 cc. of water with warming. This solution is shaken with 10 g. of permutit (Note 3) and filtered. The glycine is then precipitated by the addition of approximately five volumes (about 1250 cc.) of methyl alcohol. The glycine is collected on a Büchner funnel, washed with methyl alcohol and ether, and dried in the air. The yield is 96–98 g. (64–65 per cent of the theoretical amount) of a product which darkens at 237° and melts at 240° with decomposition. It gives no test for chlorides and is free from ammonium salts as indicated by the test with Nessler's reagent.

2. Notes

1. The distillate can be saved and the aqueous ammonia used in subsequent preparations.
2. The technical grade of methyl alcohol is satisfactory.
3. If permutit is not available, a third crystallization of the glycine from water and methyl alcohol yields a product free from ammonium salts with very little loss. The second crystallization without the use of permutit gives a very good grade of glycine which is pure enough for any ordinary work.

3. Discussion

Glycine hydrochloride can be prepared by the action of hydrochloric acid on hippuric acid,[1] aminoacetonitrile,[2] methyleneaminoacetonitrile,[3] and on ethyl phthaliminoacetate.[4] Aniline has been recommended for its conversion into free glycine.[5] Glycine can also be prepared by the interaction of chloroacetic acid and ammonia;[6] by the hydrolysis of methyleneaminoacetonitrile by successive treatments with barium hydroxide and sulfuric acid;[7] and by the hydrolysis of aminoacetonitrile by means of barium hydroxide.[8] A thorough study has been reported for its preparation in improved yields by the sulfuric acid hydrolysis of aminoacetonitrile, and in satisfactory yields from chloroacetic acid and ammonia.[9] Other methods of preparation include the reduction of cyanoformic esters,[10] a modified Curtius degradation of ethyl cyanoacetate,[11] and the hydrolysis of the neck ligaments of cattle.[12]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 11
- Org. Syn. Coll. Vol. 2, 29
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

nitrile

cyanoformic esters

Nessler's reagent

ethyl alcohol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ammonium carbonate

ammonia (7664-41-7)

methyl alcohol (67-56-1)

ether (60-29-7)

ammonium chloride (12125-02-9)

aniline (62-53-3)

chloroacetic acid, monochloroacetic acid (79-11-8)

Norite (7782-42-5)

Ethyl cyanoacetate (105-56-6)

barium hydroxide (17194-00-2)

Glycine (513-29-1)

Methyleneaminoacetonitrile (109-82-0)

methylene diethyl ether (142-68-7)

aminoacetonitrile hydrogen sulfate (5466-22-8)

barium hydroxide octahydrate (12230-71-6)

barium (7440-39-3)

Glycine hydrochloride (6000-43-7)

Hippuric acid (495-69-2)

aminoacetonitrile (540-61-4)

ethyl phthaliminoacetate

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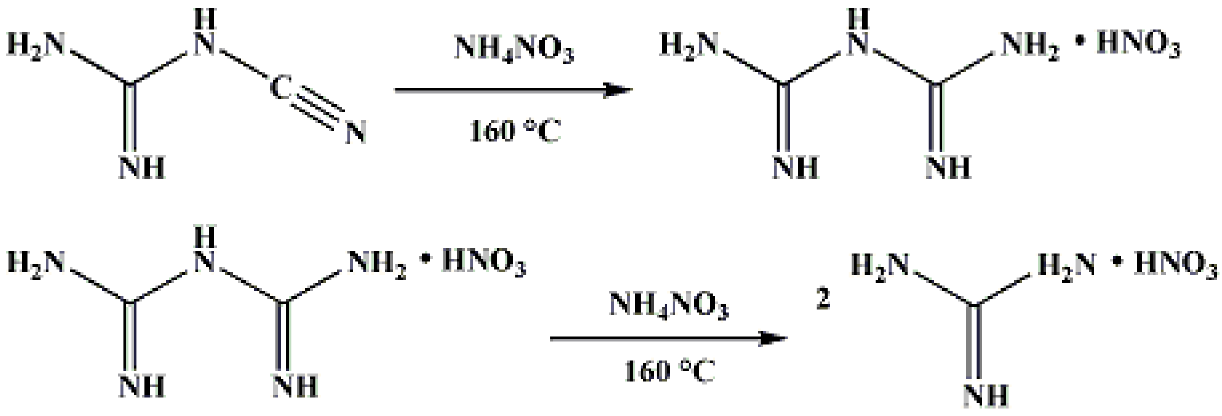
Organic Syntheses, CV 1, 302

GUANIDINE NITRATE



Submitted by Tenney L. Davis
Checked by H. T. Clarke and Ross Phillips.

1. Procedure

It is strongly recommended that this procedure not be used to prepare guanidine nitrate. Mixtures of ammonium nitrate and organic materials not much different from the mixture in the procedure are now used extensively as commercial explosives. The aqueous mixture of (Note 10) is similar to some aqueous mixtures used in sizable quantities for rock blasting; a confined mixture of this sort is especially hazardous. Only a few laboratories devoted to explosives research have the barricades and remote control devices needed to run this preparation of guanidine nitrate without risk.

Guanidine nitrate can be bought from Eastman Organic Chemicals and other suppliers.

In a 1-l. round-bottomed flask is placed an intimate mixture of 210 g. of dicyanodiamide (2.5 moles) and 440 g. of ammonium nitrate (5.5 moles) (Note 1) and (Note 10). The flask is introduced into an oil bath at 110–120°, and the temperature of the oil is raised during about one-half hour to 160°. The bath is then held at this temperature (Note 2) and (Note 10) for three hours. During the first hour the mass melts to a clear liquid which begins to deposit crystals and finally sets to a solid cake (Note 3). At the end of three hours the flask is removed from the bath; the product is allowed to cool and is extracted on the steam bath with successive quantities of water (about 2 l. is necessary to bring all soluble material into solution) (Note 4). The solution is filtered to remove white amorphous insoluble material (ammeline and ammelide) (Note 5).

The filtrate contains guanidine nitrate along with a small amount of ammonium nitrate

and very small amounts of dicyanodiamide and biguanide nitrate (Note 6). The solution is concentrated to about 1 l., and the guanidine nitrate which crystallizes on cooling is filtered off. A second crop is obtained by concentrating to 250 cc. (Note 7). The combined yield of crude guanidine nitrate is 520–560 g. (85–92 per cent of the theoretical amount). The product may be purified by recrystallization from 1 l. of water (Note 8), a second crop being taken after the mother liquor has been concentrated to 250 cc. The yield of recrystallized guanidine nitrate melting at 213–214° amounts to 500–520 g. (Note 9).

2. Notes

1. A 10 per cent excess of ammonium nitrate is used because the biguanide mononitrate which is formed as an intermediate is strongly basic and tends to attack the unreacted ammonium nitrate, as is evidenced by the liberation of ammonia during the heating. The excess of ammonium nitrate can be easily separated from the guanidine nitrate by the crystallization from water, and it does not interfere with the conversion of guanidine nitrate into nitroguanidine by the action of strong sulfuric acid.
2. When the molten mass reaches 160° its temperature begins to rise above that of the bath, generally reaching 200° during the course of five or six minutes. The mass should not be stirred at any time, especially before the mixture has completely melted; otherwise, the temperature may run somewhat higher.
3. The guanidine nitrate begins to crystallize soon after the temperature of the mixture begins to fall.
4. The hard cake goes into solution slowly, and sufficient time must be given for each portion of water to become saturated before it is decanted.
5. When the hot filtrate cools, it will deposit flocks of ammelide along with the crystals of guanidine nitrate. water may conveniently be added until the crystals dissolve, and the cold solution again filtered for the removal of ammelide.
6. This filtrate on evaporation to dryness and baking at 100° leaves a residue of 650 g., which is suitable for the preparation of nitroguanidine (p. 399).
7. At this point the mother liquor (about 200 cc.) may be discarded as it contains mainly ammonium nitrate.
8. Alcohol is a satisfactory solvent for guanidine nitrate but appears to have no advantage over water. A saturated solution of guanidine nitrate in water contains about 10 per cent at 15°.
9. The second mother liquor may advantageously be worked up with a subsequent run.
10. The submitter has prepared guanidine nitrate in batches of about 1 kg. by heating dicyanodiamide and ammonium nitrate in 2-l. flasks in oil baths heated to 160°. If the oil bath is kept at 160° the temperature of the reacting materials rises at times considerably above that point, but apparently the temperature does not mount dangerously high with such sized runs.
It is suggested that the best way to carry out the preparation, particularly on a large scale, is to heat the reagents in an autoclave, with a convenient amount of

water, at 160° for two to three hours. The autoclave is emptied while still warm. The liquid is filtered hot for the removal of white insoluble material, and the guanidine nitrate crystallizes out as the liquid cools. (T. L. Davis, private communication.)

3. Discussion

Guanidine salts can be prepared by heating ammonium thiocyanate;[1] by hydrolysis of dicyanodiamide by acids[2] (whereby one molecule of the guanidine salt is produced); and by the action of ammonium salts on dicyanodiamide,[3] from which two molecules of guanidine salt result. The nitrate can be prepared from the thiocyanate by the action of nitric acid[4] or by conversion to the sulfate and treatment with calcium nitrate.[5] The nitrate is also obtained by heating ammonium nitrate and calcium cyanamide.[6] A detailed study has been made of the preparation of guanidine nitrate in improved yields from dicyanodiamide and ammonium nitrate.[7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 399
- Org. Syn. Coll. Vol. 5, 589

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

calcium cyanamide

dicyanodiamide

Guanidine salts

acids

guanidine salt

ammonium salts

alcohol (64-17-5)

sulfuric acid (7664-93-9)

ammonia (7664-41-7)

ammonium thiocyanate (1762-95-4)

nitric acid (7697-37-2)

sulfate (14808-79-8)

ammonium nitrate

Guanidine nitrate (506-93-4)

ammelide (645-93-2)

biguanide nitrate, biguanide mononitrate

Nitroguanidine (556-88-7)

nitrate

thiocyanate

calcium nitrate (10124-37-5)

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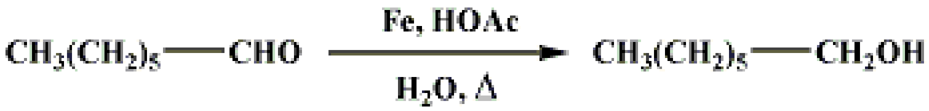
n-HEPTYL ALCOHOL



Submitted by H. T. Clarke and E. E. Dreger.
Checked by C. S. Marvel and L. T. Sandborn.

1. Procedure

In a 12-l. flask fitted with a mechanical stirrer and a short reflux condenser are placed 1800 g. (32.2 atoms) of iron filings (Note 1), 3 l. (52.5 moles) of glacial acetic acid, 3 l. of water, and 450 g. (3.95 moles) of heptaldehyde (Note 2). The mixture is heated on the steam bath, with stirring, for six to seven hours (Note 3). The flask is then fitted to an apparatus for steam distillation (p. 479) and the mixture distilled in a current of steam (Note 4) until no more oil passes over (7–8 l. of distillate). The oil is then separated, and the aqueous part distilled to recover a small quantity of dissolved or suspended heptyl alcohol.

The combined product is mixed with 1 l. of 20 per cent sodium hydroxide solution and stirred on the steam bath for four hours, in order to hydrolyze a small proportion of heptyl acetate. The oil is then separated and distilled, and the portion boiling at 172–176° is collected. The residue in the flask is mixed with about 100 cc. of water and distilled, whereupon a further small quantity of oil passes over with the steam. This distillate and the forerun are freed of the bulk of the water in a separatory funnel and distilled from a smaller flask. In this way the total yield of *n*-heptyl alcohol boiling at 172–176° (uncorr.) is 350–370 g. (75–81 per cent of the theoretical amount). The alcohol may be redistilled under reduced pressure, when it passes over almost without loss at 71–72°/12 mm.

2. Notes

1. The iron filings used were free from grease and oil. Ninety-five per cent passed an 80-mesh screen, and 60 per cent passed a 100-mesh screen. Certain lots of iron filings are not satisfactory for this reduction. Less difficulty is encountered with iron powder reduced with hydrogen than iron obtained in any other way, but some lots of iron reduced with hydrogen are not effective. Ruhoff and Reid[1] observed that the addition of a solution of nickel chloride hexahydrate will cause the reduction of heptaldehyde to start at once and will greatly increase the rate of reduction.
It is suggested, therefore, that, with a run of the size described above, a solution of 20 g. of nickel chloride hexahydrate in 50 cc. of water be added to the reaction mixture immediately after the addition of the aldehyde. If this is done,

the reduction starts at once and is complete in two hours instead of the usual six to seven hours.
It is also recommended that the reaction mixture be divided between two 12-l. flasks and that 3 l. of water be added to each flask immediately at the end of the reaction. This prevents the reaction mixture from setting to a hard mass if the steam distillation is not carried out at once, and it also reduces the amount of foaming. (C. R. Noller and R. Bannerot, private communication.)
2. The heptaldehyde should be a freshly distilled product, boiling at 154–156°.
3. The reaction may be successfully carried out without a stirrer, but the time of heating must then be lengthened to twelve to fifteen hours.
4. It is advisable to begin the steam distillation at once, while the mixture is hot, and to avoid the use of a free flame, which might cause breakage of the flask. If foaming, or too great a volume, hinders a rapid distillation, it is well to decant part of the contents of the flask and to conduct the steam distillation in two portions. (Compare (Note 1).)

3. Discussion

Heptyl alcohol can be prepared by the reduction of heptaldehyde with zinc dust and acetic acid,[2] sodium amalgam and acetic acid,[3] sodium in toluene and acetic acid,[4] and hydrogen and a catalyst.[5] Other methods include the reaction between pentane and ethylene oxide in the presence of anhydrous aluminum bromide,[6] and the action of amylmagnesium bromide on ethylene oxide.[7] The procedure described is based on a method by Hill and Nason for the reduction of cinnamaldehyde.[8]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

acetic acid (64-19-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

iron, iron filings, iron powder (7439-89-6)

toluene (108-88-3)

zinc (7440-66-6)

sodium (13966-32-0)

Ethylene oxide (75-21-8)

Heptyl alcohol, n-HEPTYL ALCOHOL (111-70-6)

heptyl acetate (112-06-1)

nickel chloride hexahydrate (7791-20-0)

Pentane (109-66-0)

aluminum bromide

amylmagnesium bromide (693-25-4)

cinnamaldehyde

heptaldehyde (111-71-7)

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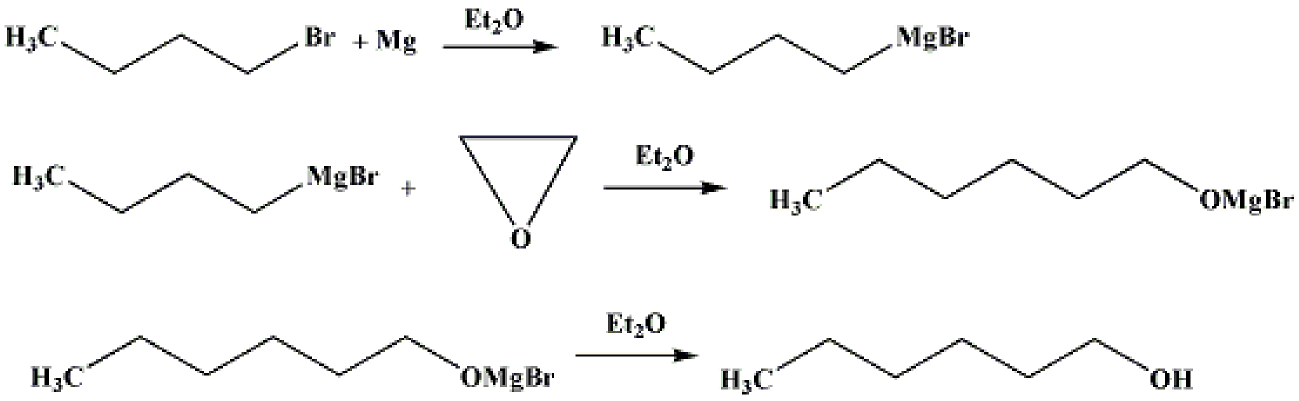
Organic Syntheses, CV 1, 306

n-HEXYL ALCOHOL



Submitted by E. E. Dreger
Checked by Roger Adams and G. S. Hiers.

1. Procedure

In a 5-l. round-bottomed flask, fitted with a stirrer, separatory funnel, and a reflux condenser to the upper end of which a calcium chloride tube is attached, is placed 150 g. (6.2 atoms) of magnesium turnings. A small crystal of iodine (Note 1) and about 100 cc. of a mixture of 822 g. (6 moles) of *n*-butyl bromide (p. 28) and 2 l. of anhydrous ethyl ether are added. As soon as the reaction starts, 350 cc. of anhydrous ether is added, and the remainder of the *n*-butyl bromide solution is dropped in at such a rate that the mixture boils continuously. The time of addition (one and one-half hours) may be decreased by cooling the flask externally. Stirring is started as soon as enough liquid is present in the flask.

When all has been added (Note 2), 278 g. (6.3 moles) of ethylene oxide (Note 3) (previously dried with soda lime) is added through a tube (3 or 4 mm. in diameter) the end of which is about 20 mm. above the surface of the liquid (Note 4), the temperature being kept below 10° by cooling in an efficient ice-and-salt bath (Note 5). This addition requires four to six hours. When all has been added the ice bath is removed; the temperature of the mixture generally rises enough to cause gentle boiling. When this ceases the mixture is warmed on a steam bath for one hour longer.

The condenser is then arranged for downward distillation, and when about 1 l. of ether has distilled (Note 6) the receiver is changed and 1 l. of dry benzene (Note 7) is added; distillation is continued with stirring until the temperature of the distilling vapor reaches 65°. The mixture is then boiled under reflux for one hour. Usually by this time it has become so viscous that stirring is no longer efficient. The mixture is then allowed to cool and is decomposed with 2 l. of an ice-water mixture. The precipitated magnesium hydroxide is dissolved by adding a sufficient quantity of 30 per cent sulfuric acid and enough ice to keep the mixture cold.

The mixture of benzene and hexyl alcohol is now distilled in a current of steam; about 7 l. of distillate must be collected before all the product is distilled. The oily layer is separated and the watery portion distilled until free of hexyl alcohol. The oil so obtained is added to the main quantity and the watery portion again distilled. The united product is now stirred on the steam bath for one to two hours with 1 l. of 20 per cent sodium hydroxide solution and again subjected to steam distillation, as before. The oily product so obtained is then distilled under atmospheric pressure with the use of a good fractionating column. The fraction boiling up to 85° is mostly benzene and water. The fraction boiling between 85° and 154° is collected separately for redistillation, and the fraction boiling at 154–157° collected as pure material. There is practically no high-boiling residue. The yield (Note 7) is 368–380

g. (60–62 per cent of the theoretical amount) (Note 8).

2. Notes

1. The reaction between the ethereal solution of *n*-butyl bromide and the magnesium frequently starts without any assistance, but the presence of a trace of iodine is of no disadvantage and renders more certain the beginning of the reaction.
2. The butyl bromide appears to react as fast as it is added, so that there is no need of stirring or warming the butylmagnesium bromide solution before adding the ethylene oxide. The small amount of unattacked magnesium has no influence on the subsequent reactions.
3. A convenient arrangement consists of placing the ethylene oxide tank on suitable scales and noting the proper decrease in weight. The gas may be passed through a short tower filled with soda lime and then through a spiral condenser surrounded with salt and ice.
4. If the mouth of the delivery tube is beneath the surface, troublesome clogging occurs.
5. The first reaction appears to consist of the formation of an oxonium addition product of the ethylene oxide and the butylmagnesium bromide.
6. Careful watching is necessary at this point, since if the distillation is carried too far a violent reaction, apparently a rearrangement of the initial addition product, may set in.
7. By the use of benzene as a diluent the reaction referred to in (Note 6) takes place smoothly and without violence; without it the yield is only about 200 g.
8. Instead of adding the condensed ethylene oxide, it may be dissolved in 350 cc. of chilled anhydrous ether which is added during the course of one to two hours. In this case, however, the yields are lower, apparently owing to the vaporization of some of the ethylene oxide.

3. Discussion

n-Hexyl alcohol can be prepared by the reduction of ethyl caproate by sodium and absolute alcohol[1] alone or in anhydrous ammonia solution;[2] by the reduction of *n*-caproamide by sodium and absolute alcohol;[3] by the reduction of *n*-caproaldehyde by sodium amalgam in dilute sulfuric acid;[4] by the action of nitrous acid on *n*-hexylamine;[5] by the interaction of *n*-propylmagnesium bromide and trimethylene oxide,[6] benzene being employed as a diluent; and by the procedure described.[7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 334

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

soda lime

oxonium addition product of the ethylene oxide

alcohol (64-17-5)

sulfuric acid (7664-93-9)

ammonia (7664-41-7)

Benzene (71-43-2)

ether, ethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

magnesium, magnesium turnings (7439-95-4)

Butyl bromide, n-butyl bromide (109-65-9)

nitrous acid (7782-77-6)

iodine (7553-56-2)

sodium (13966-32-0)

Ethylene oxide (75-21-8)

magnesium hydroxide

Hexyl alcohol, n-HEXYL ALCOHOL (111-27-3)

Butylmagnesium bromide (693-03-8)

ethyl caproate (123-66-0)

caproamide

caproaldehyde

Trimethylene oxide (503-30-0)

n-propylmagnesium bromide

n-hexylamine (111-26-2)

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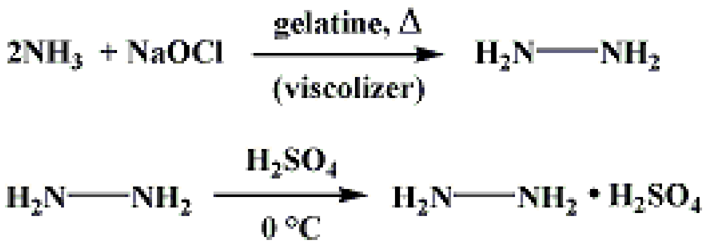
Organic Syntheses, CV 1, 309

HYDRAZINE SULFATE



Submitted by Roger Adams and B. K. Brown.
Checked by J. B. Conant and W. L. Hanaway.

1. Procedure

A normal solution of sodium hypochlorite is prepared as follows: in a 5-l. round-bottomed flask are placed 1800 g. of sodium hydroxide solution [300 g. (7.5 moles) of sodium hydroxide to 1500 g. of water] and 1500 g. of ice. Chlorine gas is then passed into the solution until it has gained in weight approximately 213 g. (3 moles). During this addition, the solution must be kept thoroughly cooled with ice, in order that chlorates will not be formed (Note 1). After all the chlorine has been passed in, it is necessary to be certain that the mixture is slightly alkaline, since any free chlorine in the solution prevents the formation of hydrazine.

In a 36-cm. evaporating dish are placed 1350 g. (1.5 l., 23 moles) of c.p. aqueous ammonia (sp. gr. 0.90), 900 cc. of distilled water (Note 2), 375 cc. of 10 per cent gelatine solution (Note 3), and 1200 cc. of the normal sodium hypochlorite solution prepared as above. This mixture is heated as rapidly as possible and boiled down until one-third of the original volume is left. This solution is then cooled thoroughly with ice and filtered with suction, first through two layers of toweling and then through one thickness of ordinary filter paper over cloth, in order to remove finely divided solid impurities. The solution is then placed in a precipitating jar, and cooled thoroughly (0°) with ice and salt; 10 cc. of concentrated sulfuric acid for each 100 cc. of solution is gradually added with constant stirring (Note 4). A precipitate of hydrazine sulfate ($NH_2NH_2 \cdot H_2SO_4$) forms. The mixture is allowed to stand in the cold for a few hours in order to complete the precipitation, and is then filtered by suction in the usual way and the precipitate washed with cold alcohol. The yield varies from 53 g. to 58 g. per 1.5 l. of aqueous ammonia (34–37 per cent of the theoretical amount). The product is perfectly white and crystalline, and satisfactory for almost any purpose. If a very pure product is desired, it must be recrystallized from water. For every 21 g. of crude product, 100 g. of boiling water is used. If the crude hydrazine is brown, it is advisable to use a little animal charcoal. After the mixture has been filtered and cooled to 0°, 19 g. of pure white crystals are obtained (Note 5).

2. Notes

1. In the preparation of the sodium hypochlorite solution it is quite necessary that the mixture be kept cold and be alkaline to litmus paper at the end of the reaction, if good yields of hydrazine are to be obtained.

2. Since iron is an anti-catalyzer, it is necessary to use distilled water throughout the process.

3. As a viscolizer, a substance such as starch, glycerol, glue, or gelatine may be used; the last, however, gives by far the most satisfactory results.

4. In order to obtain a pure white hydrazine sulfate as the first precipitate, it is necessary to cool the hydrazine solution thoroughly and filter it twice before the sulfuric acid is added. Morever, the sulfuric acid must be added slowly and with stirring. If these conditions are not followed, material containing brown particles results.

5. The mother liquor obtained from the crystallized hydrazine sulfate contains a small amount of hydrazine. If 200 g. of copper sulfate is dissolved in water and added to 10 l. of the filtrates from the above processes, a light-blue crystalline precipitate of the double salt of copper sulfate and hydrazine sulfate will be formed after ten hours. This salt, when suspended in ten times its weight of distilled water and treated with hydrogen sulfide, decomposes into copper sulfide and hydrazine sulfate. After the copper sulfide has been filtered off, the solution is concentrated until the hydrazine sulfate crystallizes. The yield of product is small, so that it is hardly advisable to undertake this recovery in the laboratory.

It is possible for one person, simultaneously evaporating six dishes of the hydrazine mixture, to turn out from 20 to 25 runs in nine hours. The time for the evaporation of a solution, such as is mentioned in the experimental part, with a four-flame Bunsen burner, is two to three hours; if the evaporation is carried out more slowly than this, the yield of product is distinctly diminished.

3. Discussion

Hydrazine salts can be prepared by the action of hypochlorites on ammonia[1] or urea;[2] by the reduction of nitrates or nitrites with zinc in neutral solution;[3] and by the action of ammonia on dichlorourea.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 450
- Org. Syn. Coll. Vol. 2, 85
- Org. Syn. Coll. Vol. 2, 208
- Org. Syn. Coll. Vol. 2, 228
- Org. Syn. Coll. Vol. 2, 395
- Org. Syn. Coll. Vol. 2, 496
- Org. Syn. Coll. Vol. 3, 73

- Org. Syn. Coll. Vol. 3, 656
- Org. Syn. Coll. Vol. 4, 74
- Org. Syn. Coll. Vol. 4, 351

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

double salt of copper sulfate

Hydrazine salts

alcohol (64-17-5)

sulfuric acid (7664-93-9)

ammonia (7664-41-7)

sodium hydroxide (1310-73-2)

glycerol (56-81-5)

iron (7439-89-6)

hydrogen sulfide (7783-06-4)

copper sulfate (7758-98-7)

chlorine (7782-50-5)

zinc (7440-66-6)

urea (57-13-6)

Hydrazine sulfate (10034-93-2)

sodium hypochlorite (7681-52-9)

hydrazine (302-01-2)

copper sulfide

dichlorourea

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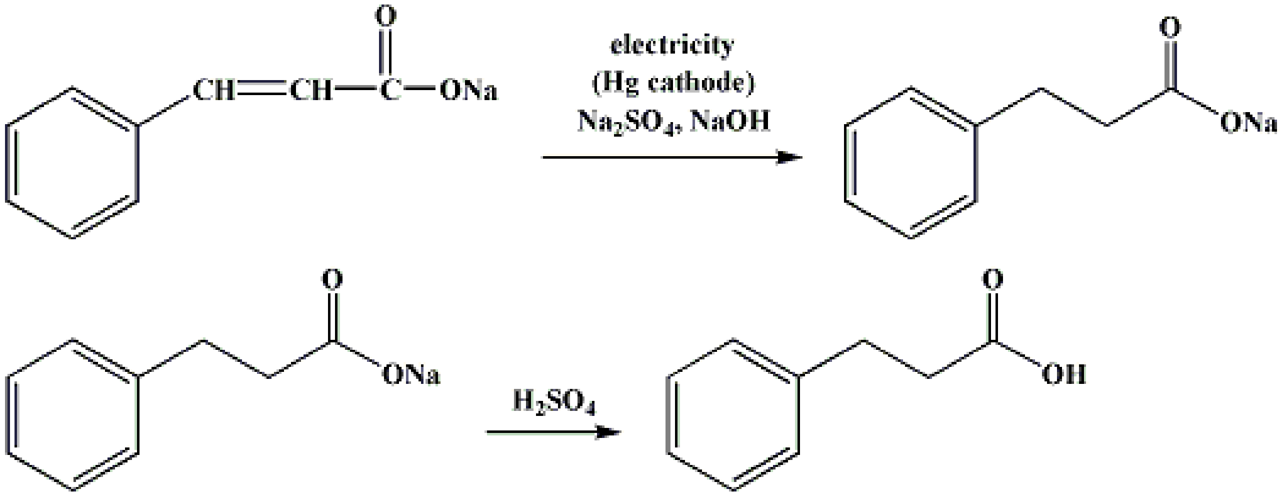
Organic Syntheses, CV 1, 311

HYDROCINNAMIC ACID



Submitted by A. W. Ingersoll
Checked by Henry Gilman and L. C. Heckert.

1. Procedure

(*A*) *Apparatus*.—The reduction is carried out in an 18 by 25 cm. battery jar (Note 1) which is surrounded by a vessel of cold water. The bottom of the battery jar is just covered with mercury which serves as the cathode of the cell. The anode is a coil of heavy sheet lead separated from the catholyte by suspending it in a porous cup. The latter is supported in the battery jar so that it just clears the surface of the mercury (Note 2). The cathode is connected with the circuit by means of a copper wire well insulated with rubber except for one-eighth inch at the end which is immersed in the mercury. Efficient mechanical stirring is provided for the catholyte. The current used for these experiments was drawn from a storage battery delivering 30 volts, through a rheostat and ammeter each capable of carrying 15 amperes. Current may be taken from any source which will supply 80 to 85 ampere-hours at the rate of 5 to 10 amperes. Several reduction cells of the size described may be run at one time by connecting them in series. The diagram given on p. 486 shows the arrangement of the apparatus.

(*B*) *Reduction of Cinnamic Acid*.—After the apparatus is assembled, 2 l. of 7–8 per cent sodium sulfate solution (Note 3) is placed in the battery jar and the porous cup is filled to the same level with more of this solution. The stirrer is started, and 200 g. (1.35 moles) of a good grade of cinnamic acid (Note 4) is suspended in the catholyte. A solution of 35 g. (0.88 mole) of sodium hydroxide in 150 cc. of water is then added at such a rate as to avoid forming lumps of sodium cinnamate (Note 5). The current is turned on and the rheostat adjusted until a steady current of 5 to 10 amperes is flowing (Note 6). From this point only occasional attention is required. The suspended sodium cinnamate and cinnamic acid gradually dissolve as the reduction proceeds. Portions adhering to the walls of the cell should be worked down with a stirring rod and finally with a little water from a wash bottle. The liquor inside the porous cup should be kept alkaline by adding very concentrated sodium hydroxide solution at about one-half hour intervals (Note 5). About 110 g. (2.7 moles) will be required. The reduction will require 76 to 80 ampere-hours (Note 7); considerable hydrogen is evolved near the end. The temperature need not be controlled (Note 8).

When reduction is complete (Note 7) the cathode liquor is decanted or siphoned from the mercury, filtered from traces of solid matter, and acidified with an excess of sulfuric acid (sp. gr. 1.1). The hydrocinnamic acid separates as an oil and solidifies on thorough cooling. The yield of crude product, which contains water and other impurities, is 180–200 g. It is purified by distillation under reduced pressure. The product boiling at 194–197°/75 mm. (145–147°/18 mm.) is colorless and melts at 47.5–48°. The yield of distilled acid is 160–180 g. (80–90 per cent of the theoretical amount) depending upon the quality of the cinnamic acid used (Note 4).

2. Notes

1. This is a commercial size. Any sturdy glass vessel of similar dimensions may be used.
2. The lead anode should have about the same surface area as the cathode. The porous cup used was 8 by 21 cm., but similar sizes will do. A three-legged desiccator plate makes a convenient support for the cup.
3. Any dilute solution of sodium sulfate may be used. If several runs are to be made, the solution recovered from the filtration of the hydrocinnamic acid should be neutralized with sodium hydroxide, diluted if necessary, and used again. Traces of hydrocinnamic acid contained in this solution are thus saved. Chemically pure reagents are not necessary.
4. The quality of the cinnamic acid used is important. The yield from a commercial c.p. acid melting at 132.5–133° was 86–90 per cent. From a lot melting at 131.5–133° obtained by recrystallizing a crude acid with the use of animal charcoal the yield was 81–83 per cent. With a technical grade of material the yield fell, in some runs, below 60 per cent, the reduction mixture foamed considerably, and much high-boiling residue was left on distillation.
5. The addition of too much sodium hydroxide at this point produces a thick sludge which does not stir well. It should be noted that during the reduction two molecular equivalents of sodium hydroxide are produced at the cathode and an equivalent amount of sulfuric acid at the anode.
6. The current may vary somewhat, especially if the anode liquor becomes too dilute or highly acid. The sodium hydroxide solution added to the anolyte should be concentrated so that the diffusion which always occurs will not dilute the catholyte excessively. High amperage shortens the time required but promotes heating. Seven amperes is a convenient rate.
7. The theoretical quantity of current is 72 ampere-hours. It is necessary to pass an excess of 4 to 8 ampere-hours to insure complete reduction. The end of the reduction is reached when a sample of the catholyte on acidification with excess sulfuric acid precipitates an oil and no solid.
8. The reaction is favored by moderately high temperatures. Excessive heating may be avoided by reducing the amperage or by placing cold water in the cooling bath.
9. It may be noted that this process is essentially a sodium amalgam reduction. By the same procedure β-furylacrylic acid was reduced to β-furylpropionic in yields of 60–70 per cent. With suitable modifications it may be applied to the reduction of other substances reducible with sodium amalgam.

3. Discussion

Hydrocinnamic acid can be prepared by the reduction of cinnamic acid with sodium amalgam,[1] with hydriodic acid at 100°,[2] with phosphorus and hydriodic acid,[3] with amalgamated zinc and hydrochloric acid,[4] electrolytically in alkaline solution on cathodes of lead[5] and mercury,[6]

catalytically with palladium black[7] and by the action of potassium cyanide on β-phenylethyl chloride followed by hydrolysis.[8]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

β-furylpropionic

amalgamated zinc

palladium black

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

PHOSPHORUS (7723-14-0)

sodium sulfate (7757-82-6)

potassium cyanide (151-50-8)

mercury (7439-97-6)

sodium (13966-32-0)

hydriodic acid (10034-85-2)

cinnamic acid (621-82-9)

Hydrocinnamic acid (501-52-0)

sodium cinnamate

β-furylacrylic acid (539-47-9)

β-phenylethyl chloride (622-24-2)

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HYDROGEN CYANIDE (ANHYDROUS)

[Hydrocyanic acid]

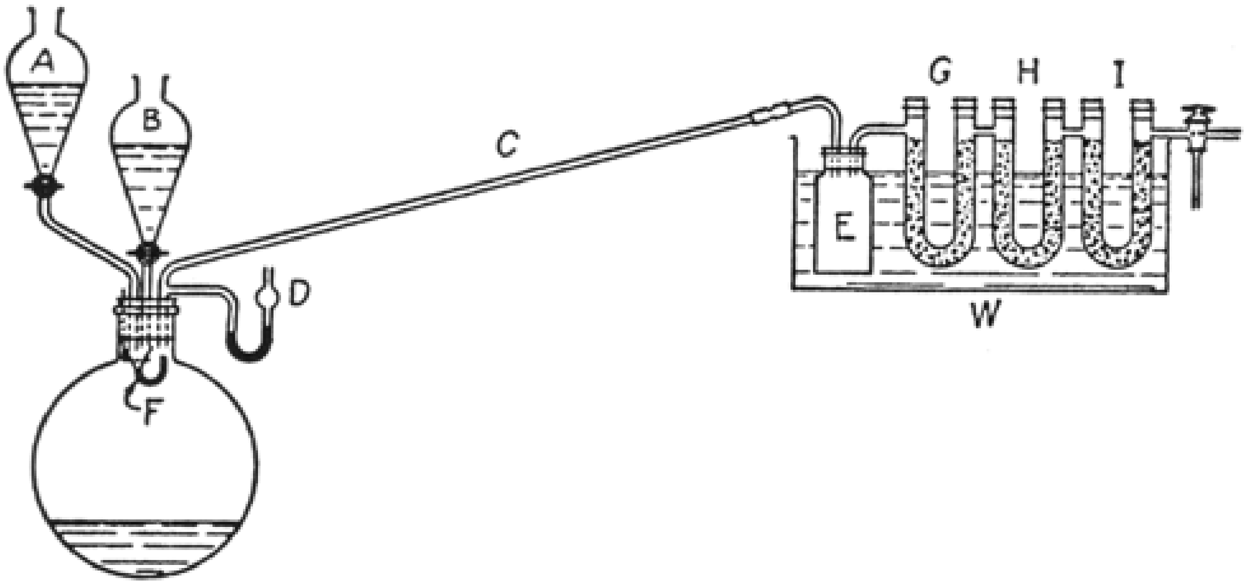
$$NaCN + H_2SO_4 \xrightarrow{H_2O} HCN + NaHSO_4$$

Submitted by K. Ziegler
Checked by Henry Gilman and L. C. Heckert.

1. Procedure

A 5-l. round-bottomed flask, set up in a good hood (Note 1), is fitted with a three-holed rubber stopper that holds two 250-cc. separatory funnels, A and B (Fig. 18). A small funnel F (about 3–4 cm. in diameter) is suspended directly under the outlets of the two separatory funnels and is attached to the rubber stopper by a loop of stiff copper wire. The discharge tube of the funnel is bent in the shape of a U so that its end is about 1 cm. below the top of the funnel. In the third hole of the rubber stopper is inserted an inclined glass tube, C, of about 10-mm. internal bore and approximately 50 cm. long. A mercury safety vent, D, is sealed in the side of this tube. C acts as an air condenser and leads to an empty gas bottle, E, of about 250-cc. capacity and then to three large U-tubes, G, H, and I, filled with anhydrous calcium chloride. The gas bottle and the U-tubes are contained in a water bath, W, warmed to 30–40°. The last calcium chloride tube is fitted with a three-way glass stopcock so that the gaseous anhydrous hydrogen cyanide may be used directly or diverted to an efficient condenser for liquefaction. The condenser is a glass coil of 4–5 mm. bore and about 50 cm. long that is surrounded by ice (Note 2) contained in a percolator arrangement like that described on p. 117.

Fig. 18.



One of the separatory funnels is filled with dilute sulfuric acid prepared by the careful addition of 392 g. (213 cc., 4 moles) of concentrated sulfuric acid to 830 cc. of water. The

other separatory funnel is filled with a solution of 203 g. (4 moles) of commercial sodium cyanide (about 96 per cent) dissolved in sufficient water to make 500 cc. of solution. Evolution of hydrogen cyanide takes place on the simultaneous addition of the two solutions. Practically all the reaction occurs in the funnel, F, and the sodium bisulfate solution continuously drains into the flask so that fresh solutions are always present. The solution in the funnel remains clear as long as sufficient sulfuric acid is present. An excess of sodium cyanide colors the solution yellow and leads to the formation of a muddy brown precipitate (Note 3). By adjusting the flow of solutions the rate of evolution is easily controlled, and the preparation requires no attention beyond that involved in the occasional replenishment of the solutions in the separatory funnels. The last part of the hydrogen cyanide can be driven from the apparatus by boiling the bisulfate solution for a few minutes. The yield of acid melting at – 15° to – 14.5° is 100–105 g. (93–97 per cent of the theoretical amount) (Note 4) and (Note 5).

2. Notes

1. Gattermann[1] recommends that the operator smoke during the preparation, for he found that a trace of hydrogen cyanide is sufficient to give the tobacco smoke a highly characteristic flavor. This preliminary warning is useful in case of leaky apparatus or a faulty hood.
2. It is essential that the coil be cooled with ice only. A freezing mixture causes solidification of the hydrogen cyanide with consequent clogging of the apparatus.
3. If the reaction is slowed up considerably or interrupted so that the solution becomes cool, sodium bisulfate crystallizes both in the funnel and in the generating flask.
4. The hydrogen cyanide is best kept over anhydrous calcium chloride. In this way it remains clear and water-white for months; otherwise, it soon becomes yellow, owing to the formation of azulmic acid. Concentrated hydrochloric acid (two drops per 500 g. of hydrogen cyanide) has also been recommended as a stabilizer.[2]
5. If larger quantities of hydrogen cyanide are desired, the apparatus may be modified as suggested by Lindemann[3] by using a four-holed rubber stopper in the generating flask and fitting it with a siphon tube by means of which the sodium bisulfate solution can be removed from time to time. With this modification the generating flask need be of only 2- to 3-l. capacity.
Hydrogen cyanide may be prepared conveniently, probably in lower yields than in the procedure described, by adding the saturated sodium cyanide solution one-half inch below the surface of 50 per cent sulfuric acid contained in a flask. The residual amount is expelled by warming the flask on a steam bath. The apparatus is the same as that used for generating hydrogen chloride (p. 293) by passing aqueous hydrochloric acid into sulfuric acid (W. W. Hartman, private communication).

3. Discussion

Hydrogen cyanide can be prepared by the action of sulfuric acid on potassium ferrocyanide,[1] potassium cyanide[4] or sodium cyanide.[5] The procedure described is based on the methods of Ziegler[5] and Lindemann.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 14
- Org. Syn. Coll. Vol. 6, 334

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

azulmic acid

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrogen chloride, hydrochloric acid (7647-01-0)

sodium cyanide (143-33-9)

hydrogen cyanide, hydrocyanic acid (74-90-8)

potassium cyanide (151-50-8)

sodium bisulfate (7681-38-1)

potassium ferrocyanide

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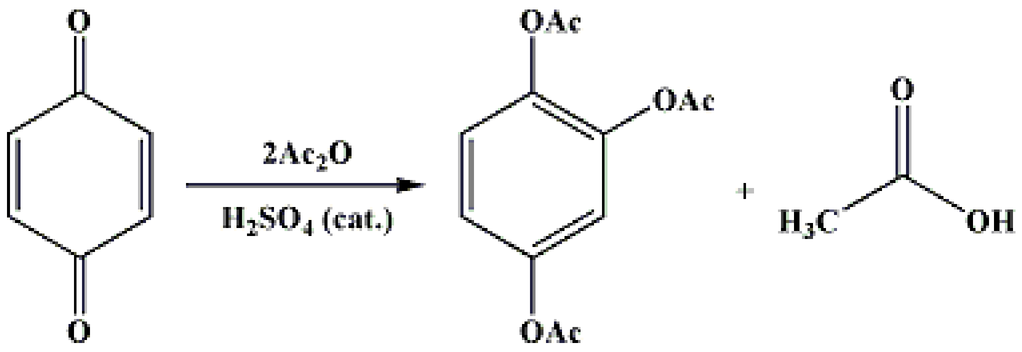
Organic Syntheses, CV 1, 317

HYDROXYHYDROQUINONE TRIACETATE

[1,2,4-Benzenetriol, triacetate]



Submitted by E. B. Vliet
Checked by Roger Adams and H. O. Calvery.

1. Procedure

Twelve grams of concentrated sulfuric acid is added to 180 g. (167 cc., 1.8 moles) of acetic anhydride in a 600-cc. beaker, after which 60 g. (0.55 mole) of quinone (Note 1) is added gradually in small portions with constant mechanical stirring. The temperature rises and should be held at 40–50° during the addition of the quinone. A temperature higher than 50° leads to decomposition of the product whereas a temperature lower than 40° causes a much slower reaction. Good temperature control can be obtained by using care in adding the quinone and by the use of a cooling bath and efficient stirring. The reaction goes smoothly and does not evolve an excessive amount of heat.

After all the quinone has been added, the solution is allowed to stand. It should be watched closely at first to see that the temperature does not rise above 50°, but at the same time it is well not to cool it below 40°. When the mixture starts to cool of its own accord, a precipitate begins to form. As soon as the mixture has cooled to about 25° (Note 2), it is poured into 750 cc. of cold water, whereupon a white precipitate separates. The mixture is cooled to about 10° and filtered with suction. The product is recrystallized from 250 cc. of 95 per cent ethyl alcohol and dried. The drying is best done in a vacuum desiccator, through which a very small stream of air is allowed to sweep. Calcium chloride is the best drying agent.

The product is practically white and rather granular; it melts at 96–97°. The yield is 120–123 g. (86–87 per cent of the theoretical amount). The product is fairly reactive and tends to decompose upon standing (Note 3), especially if care is not used in drying and handling. If it is to be used as a starting material for other syntheses, it is advisable to use it as soon as possible.

2. Notes

1. The quality of the product depends to a large extent upon the purity of the quinone; if the latter is dark, it is advisable to crystallize it from benzene before using it. Directions for the preparation and purification of quinone are given on p. 482.
2. It is quite desirable to have the reaction mixture cooled to about 25° before it is added to the water. If it is warm when added to the water, an oil will separate which solidifies slowly in the form of lumps.
3. The hydroxyhydroquinone triacetate keeps quite satisfactorily in an atmosphere of carbon dioxide.

3. Discussion

Hydroxyhydroquinone triacetate can be prepared by acetylating hydroxyhydroquinone formed by the alkali fusion of hydroquinone,[1] and by the procedure described which is essentially that of Thiele.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 360

References and Notes

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2. Thiele, Ber. **31**, 1247 (1898); Bayer and Co., Ger. pat. 101,607 and 107,508 [Frdl. **5**, 155, 156 (1901)]; Bargellini and Avrutin, Gazz. chim. ital. **40** (2), 349 (1910).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethyl alcohol (64-17-5)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

Benzene (71-43-2)

acetic anhydride (108-24-7)

hydroquinone (123-31-9)

carbon dioxide (124-38-9)

Hydroxyhydroquinone triacetate, 1,2,4-Benzenetriol, triacetate (613-03-6)

Quinone (106-51-4)

hydroxyhydroquinone (533-73-3)

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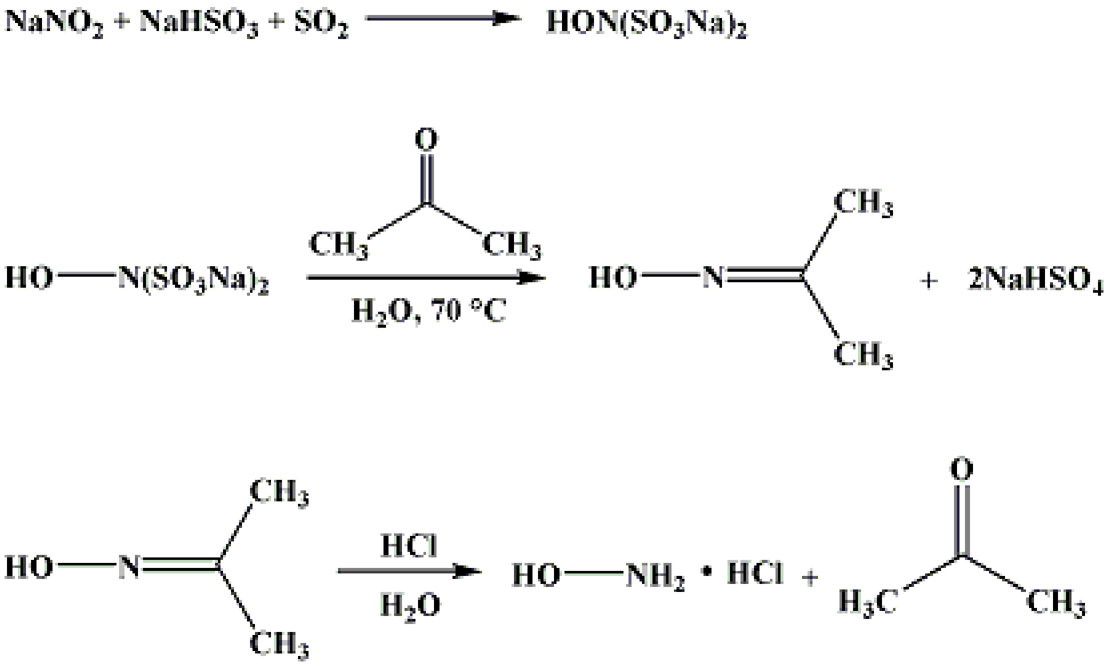
Organic Syntheses, CV 1, 318

HYDROXYLAMINE HYDROCHLORIDE and ACETOXIME



Submitted by Waldo L. Semon
Checked by H. T. Clarke and Ross Phillips.

1. Procedure

In a 2-gallon (8-l.) wide-mouthed bottle (Note 1) packed in ice-salt mixture are placed 630 g. (8.7 moles) of commercial (95 per cent) sodium nitrite and 5 kg. of chopped ice, and the mixture is well stirred. A cold (0–5°) solution of sodium bisulfite, made by saturating with sulfur dioxide a solution of 495 g. (4.7 moles) of anhydrous sodium carbonate in 1500 cc. of water, is now added slowly with hand stirring. When all is in, a sufficiently large quantity of the ice will have melted to allow a mechanical stirrer to be fitted. A stream of sulfur dioxide is now passed in, with continual stirring, the temperature being kept at 0–2°, until an acid reaction to Congo red paper is obtained and the dark color, which appears just before the reaction is complete, has faded. During the addition of the sulfur dioxide, 500 g. more of ice may be added.

The mixture is now transferred to a 12-l. flask, 495 g. (625 cc., 8.5 moles) of acetone is added, and the solution is heated on the steam bath to 70°. Heating is then discontinued, the flask wrapped in burlap in order to retard loss of heat, and the mixture allowed to stand overnight. The acid is then neutralized with a concentrated (50 per cent) solution of sodium hydroxide (about 720 g. of alkali is required), until a distinctly alkaline reaction to litmus is just obtained.

The resulting acetoxime is now distilled in a current of steam (Note 2), and the

distillation is continued until a 5-cc. sample, shaken with 2 cc. of ether, yields no appreciable residue on evaporating the ether. To the distillate (2–2.5 l.) is added 600 cc. of concentrated hydrochloric acid, and the acid solution is distilled at atmospheric pressure until the distillate is free of acetone (Note 3). The residual liquor is then evaporated to dryness on the steam bath, either in an open dish or preferably under reduced pressure. The crude hydroxylamine hydrochloride so obtained, weighing 296–470 g. (49–77 per cent of the theoretical amount), is suitable for many purposes, but is best purified by recrystallization from half its weight of water. By systematic recrystallization of the product from several batches, the yield of pure product, which crystallizes in long flat needles, melting when dry at 150–154°, may be brought as high as 70 per cent of the theoretical amount (Note 4).

In order to prepare pure acetoxime (Note 5), the procedure is modified in the following way: After neutralizing the solution of acetoxime formed after the addition of acetone, the oily layer is separated and the aqueous solution shaken with two or three 150-cc. portions of benzene. The oil and benzene solutions are mixed, the water thereby thrown out is removed, and the oil fractionally distilled with the use of a column, the portion boiling 133–136° being collected as pure acetoxime. This product, which weighs 420–480 g. (67–76 per cent of the theoretical amount), solidifies in the receiver to colorless needles melting at 60–61°. The foreruns and aqueous liquors are best distilled with steam and the distillate converted into hydroxylamine hydrochloride as above, whereupon 75–90 g. of pure salt is obtained.

2. Notes

1. The preparation can be run in larger batches than that indicated. Earthenware crocks may suitably replace the glass bottle; but since the external cooling in such vessels is not so efficient, it will be necessary, in case they are used, to add a larger proportion of ice during the reaction in order to maintain the correct temperature. This, however, is no great disadvantage, since the formation of the oxime appears to take place equally well in more dilute solution. Metal cans are entirely satisfactory for the distillation of the faintly alkaline liquids.
2. The acetoxime may be distilled by direct heating rather than by injection of steam; when the prescribed quantities are taken, however, it will be found that the liquor becomes saturated with sodium sulfate at a point just before the expulsion of the oxime is complete, so that addition of water during the distillation is necessary. More rapid distillation can be obtained by the use of a current of steam, especially if a condensing receiver (p. 479) is employed. The oxime can also, if desired, be isolated for hydrolysis by separation of the oily layer and extraction with benzene; the resulting crude hydroxylamine hydrochloride is, however, apt to be dark in color and to contain inorganic salts.
3. By redistillation of the aqueous acetone with the use of a column, 60 per cent or more of the material taken can readily be recovered and employed in a subsequent batch.
4. The final mother liquors from the recrystallization of the hydroxylamine hydrochloride contain a high proportion of ammonium chloride. The

hydroxylamine present therein is best recovered by reconversion into acetoxime, which is isolated by steam distillation of the faintly alkaline solution.
5. Acetoxime can be obtained in long needles by allowing the first portions of the steam distillate (which are saturated with oxime) to cool, and filtering off the crystals which separate; unfortunately, this product cannot be obtained in a perfectly dry condition without considerable loss by volatilization.

3. Discussion

Hydroxylamine hydrochloride can be prepared technically by the electrolytic reduction of nitric acid[1] and by the action of sodium bisulfite on sodium nitrite.[2] Raschig, who discovered the latter process, suggested the use of calcium nitrite and bisulfite so that the bulk of the inorganic salts could be removed in the form of calcium sulfate.[3] He also showed that sodium hydroxylamine disulfonate yields acetoxime on treatment with acetone,[4] and it has long been known that acetoxime readily yields hydroxylamine hydrochloride on treatment with hydrochloric acid;[5] but apparently these facts in combination were only used advantageously at a later time.[6] Excellent yields have been reported by the reaction of acetone and sodium nitrite with zinc dust. [7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 327
- Org. Syn. Coll. Vol. 2, 67
- Org. Syn. Coll. Vol. 2, 70
- Org. Syn. Coll. Vol. 2, 76
- Org. Syn. Coll. Vol. 2, 313
- Org. Syn. Coll. Vol. 2, 622
- Org. Syn. Coll. Vol. 3, 172

References and Notes

1. Tafel, Z. anorg. Chem. **31,** 322 (1902); Boehringer and Sons, Ger. pat. 133,457 [Chem. Zentr. II, 313 (1902)]; Ger. pat. 137,697 [Chem. Zentr. I, 106 (1903)]; Ponzio and Pichetto, Ann. chim. applicata **14**, 250 (1924) [C. A. **19**, 239 (1925)]; Shcherbakov and Libina, Z. Elektrochem. **35**, 70 (1929) [C. A. **23**, 2372 (1929)].
2. Raschig, Ann. **241**, 161 (1887); Ger. pat. 41,987 [Chem. Zentr. I, 246 (1888)]; Divers and Haga, J. Chem. Soc. **69**, 1665 (1896); **77**, 673 (1900); Adams and Kamm, J. Am. Chem. Soc. **40**, 1281 (1918).
3. Raschig, Ger. pat. 216,747 [Chem. Zentr. I, 308 (1910)].
4. Raschig, Ann. **241**, 187 (1887).
5. Janny, Ber. **16**, 170 (1883).
6. Semon, J. Am. Chem. Soc. **45**, 188 (1923).
7. Ogata and Hirano, J. Pharm. Soc. Japan **50**, 555 (1930) [C. A. **24**, 4758 (1930)]

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether (60-29-7)

ammonium chloride (12125-02-9)

sodium hydroxide (1310-73-2)

nitric acid (7697-37-2)

sodium carbonate (497-19-8)

sulfur dioxide (7446-09-5)

sodium sulfate (7757-82-6)

sodium nitrite (7632-00-0)

sodium bisulfite (7631-90-5)

calcium sulfate (7778-18-9)

acetone (67-64-1)

zinc (7440-66-6)

Hydroxylamine hydrochloride (5470-11-1)

ACETOXIME

hydroxylamine (7803-49-8)

calcium nitrite

sodium hydroxylamine disulfonate

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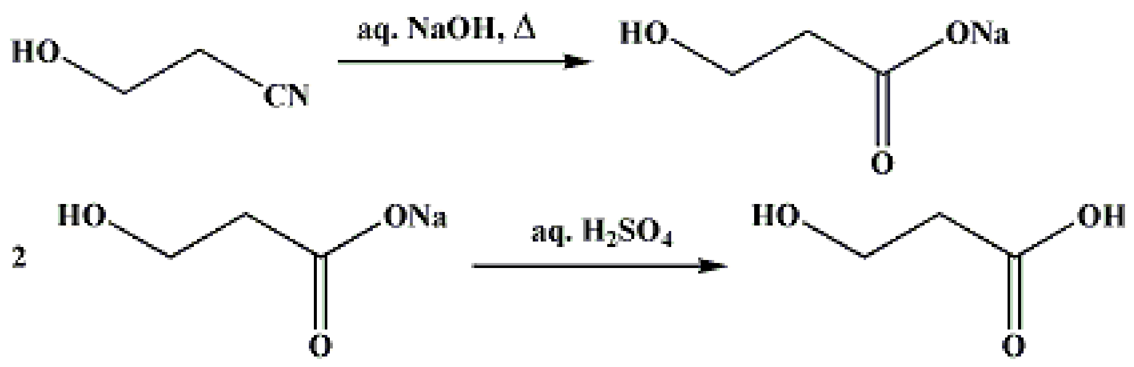
Organic Syntheses, CV 1, 321

β-HYDROXYPROPIONIC ACID

[Hydracrylic acid]



Submitted by R. R. Read
Checked by H. T. Clarke and C. R. Nollep.

1. Procedure

To a cold solution of 160 g. (4 moles) of sodium hydroxide in 500 cc. of water in a 2-l. round-bottomed flask provided with a mechanical stirrer is added slowly 250 g. (3.5 moles) of ethylene cyanohydrin (p. 256), the temperature being kept below 30° (Note 1) by means of a cold water bath. The mixture is allowed to stand overnight in the bath, when the flask is fitted with a two-holed rubber stopper bearing a capillary tube reaching almost to the bottom and a delivery tube bent slightly downward for attachment to a suction pump. The flask is then heated slowly to 80° during four hours by raising the temperature of the surrounding water. A rapid current of air is drawn through the mixture during the heating. The mixture is now evaporated to dryness under reduced pressure by heating in an oil bath, the temperature of which is raised as rapidly as the boiling of the material will permit. The oil bath is finally held at 125° until the product becomes pasty. The flask is allowed to cool, and 50 cc. of water is poured down one side of the flask, and the solid material at that point worked carefully into a paste with a stout stirring rod.

A cooled mixture of 200 g. (109 cc.) of concentrated sulfuric acid (2 moles) and 300 cc. of water is now added slowly with careful cooling (Note 2), the pasty mixture being stirred with a thermometer and the temperature not being allowed to rise above 35°. Sodium sulfate crystallizes during this addition. The mass is now shaken vigorously with 400 cc. of ether and allowed to stand for some minutes. The ether is then decanted as completely as possible and the residue filtered with suction. The sodium sulfate is now shaken with six successive 300-cc. portions of ether, the ether solutions being subsequently employed for extraction of the filtrate. This latter requires 10–14 such extractions (each with 300–400 cc. of ether) for the satisfactory extraction of the β-hydroxypropionic acid. The combined ethereal solution is dried over 50 g. of anhydrous sodium sulfate and the ether distilled from a water bath, the

temperature of which is not allowed to rise above 50°. The product is then concentrated under reduced pressure from a water bath maintained at 55–60°. The residue should have attained constant weight after four to six hours of this treatment; it consists of a sirupy liquid of pale straw color which contains 75–80 per cent of β-hydroxypropionic acid (by titration) (Note 3). The yield is 120–125 g. (28–31 per cent of the theoretical amount).

2. Notes

1. If the temperature of the mixture of nitrile and sodium hydroxide is allowed to rise too soon or too rapidly, the evolution of ammonia may become almost explosive, as the reaction is strongly exothermic.
2. The temperature during the addition of the sulfuric acid must be carefully controlled, as the heat of neutralization is sufficient to decompose the product. The use of a minimum amount of water is desirable in order to decrease the number of extractions.
3. β-Hydroxypropionic acid is an uncrystallizable and hygroscopic sirup. The 20–25 per cent of impurity remaining in the final product is largely water.

3. Discussion

β-Hydroxypropionic acid can be prepared by the hydrolysis of β-bromopropionic acid;[1] by the action of alkali on acrylic acid;[2] and by the hydrolysis of ethylene cyanohydrin with acid[3] or preferably with alkali.[4]

References and Notes

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2. Linnemann, Ber. **8**, 1095 (1875); Erlenmeyer, Ann. **191**, 281 (1878).
3. Erlenmeyer, Ann. **191**, 269 (1878).
4. Wislicenus, Ann. **128**, 6 (1863).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

ammonia (7664-41-7)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium sulfate (7757-82-6)

β-Bromopropionic acid (590-92-1)

Ethylene cyanohydrin (109-78-4)

Acrylic acid (9003-01-4)

hydracrylic acid, β-Hydroxypropionic acid (503-66-2)

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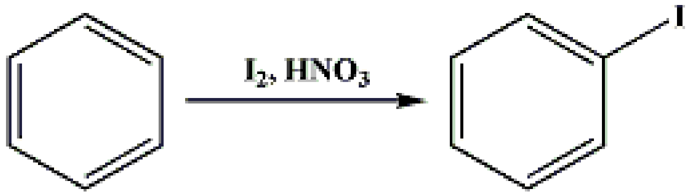
Organic Syntheses, CV 1, 323

IODOBENZENE

[Benzene, iodo-]



Submitted by F. B. Dains and R. Q. Brewster.
Checked by Henry Gilman and J. Robinson.

1. Procedure

In a 1-l. three-necked flask fitted with mechanical stirrer, reflux condenser, and separatory funnel, are placed 381 g. (1.5 moles) of iodine and 400 g. (455 cc., 5.1 moles) of benzene. The mixture is heated to about 50° on a water bath, and 275 cc. (6.15 moles) of nitric acid (sp. gr. 1.50) is added slowly from the separatory funnel; the time required for the addition should be about one and one-quarter hours. A copious evolution of oxides of nitrogen takes place, and the gases are carried off from the upper end of the condenser to an open window or hood, or absorbed by means of a gas trap (Fig. 7 on p. 97). The reaction proceeds smoothly (Note 1), and the temperature rises slowly without the application of heat until the mixture boils gently. When all the nitric acid has been added, the solution is refluxed for about fifteen minutes. If iodine still remains, more nitric acid should be added slowly to the warm solution until the purple color of the iodine has been discharged and the solution becomes brownish red.

The lower reddish oily layer is separated, mixed with an equal volume of 10 per cent sodium hydroxide solution, and steam-distilled from a 2-l. flask until no more oil passes over. Towards the end of the distillation a yellow solid begins to collect in the receiver; this consists of nitro compounds, which are removed by vigorously stirring the oil for about three hours with 20 cc. of concentrated hydrochloric acid, 300 cc. of water, and 200 g. of iron filings in a 2-l. flask connected with a reflux condenser.

The mixture is allowed to cool and is then filtered. The filtrate is rendered distinctly acid to Congo red with hydrochloric acid and again distilled with steam. The oil so obtained is separated and distilled under normal pressure with the use of a fractionating column (Note 2). The fraction boiling at 180–190° is redistilled, and the pure compound is collected at 184–186°. The yield is 523–531 g. (86–87 per cent of the theoretical amount) (Note 3).

2. Notes

1. The reaction proceeds smoothly without stirring; however, the time of addition is decreased somewhat by stirring. Ordinary rubber stoppers may be used; although they are somewhat attacked, this is not sufficiently serious to warrant any special apparatus. In very large runs it may be desirable to use stoppers made from asbestos paper and water glass. Rubber stoppers have been used in a run five times the size of that described.
2. A good separation is obtained by means of a 500-cc. modified Claisen flask (p. 130) without the use of diminished pressure.
3. Iodobenzene prepared by this procedure may contain traces of nitro compounds. The test for these is to reduce a sample with stannous chloride (or tin) and hydrochloric acid, and treat the resulting acid solution in the cold with a solution of sodium nitrite. If a phenolic odor is obtained on boiling the solution, nitro compounds are still present. A more delicate test can be made by adding the reduced solution, after treatment with sodium nitrite, to an alkaline solution of β-naphthol; an azo dye is formed if nitro compounds were originally present.

3. Discussion

The procedure described is essentially that of Datta and Chatterjee.[1] Oxidizing agents other than nitric acid can be used in the preparation of iodobenzene from benzene and iodine, but no one of them appears to be so effective and so convenient as nitric acid. Those that have been used are iodic acid,[2] fuming sulfuric acid,[3] mercuric oxide,[4] and ferric chloride.[5] It can also be made by the diazo reaction from aniline.[6]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 351

References and Notes

1. Datta and Chatterjee, J. Am. Chem. Soc. **39**, 437 (1917).
2. Kekulé, Ann. **137**, 162 (1866); Klages and Liecke, J. prakt. Chem. (2) **61**, 311 (1900).
3. Rupp, Ber. **29**, 1629 (1896); Neumann, Ann. **241**, 84 (1887).
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6. Griess, Jahresber. 477 (1866); Org. Syn. **19**, 55.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

fuming sulfuric acid

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

aniline (62-53-3)

sodium hydroxide (1310-73-2)

iron filings (7439-89-6)

nitric acid (7697-37-2)

sodium nitrite (7632-00-0)

β-naphthol (135-19-3)

tin (7440-31-5)

stannous chloride

mercuric oxide (21908-53-2)

iodine (7553-56-2)

ferric chloride (7705-08-0)

Iodobenzene, Benzene, iodo- (591-50-4)

iodic acid (7782-68-5)

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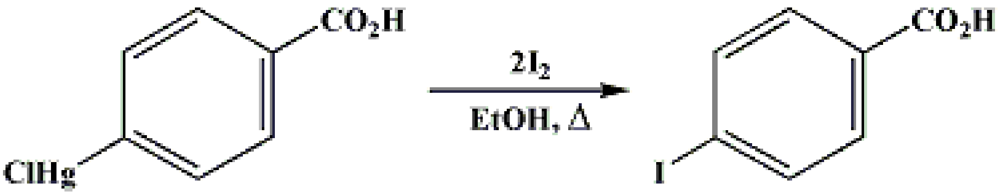
Organic Syntheses, CV 1, 325

p-IODOBENZOIC ACID

[Benzoic acid, *p*-iodo-]



Submitted by Frank C. Whitmore and Gladys E. Woodward.
Checked by Henry Gilman and C. C. Vernon.

1. Procedure

One hundred fifty grams (0.59 mole) of iodine is dissolved in 2.5 l. of 95 per cent ethyl alcohol in a 5-l. round-bottomed flask set on a tripod and provided with a mechanical stirrer and a reflux condenser. To this solution is added 300 g. (0.84 mole) of powdered dry crude *p*-chloromercuribenzoic acid (p. 159) (Note 1). The mixture is stirred and heated. The acid gradually goes into solution and the color of iodine disappears. The hot stirred mixture is treated with iodine until a yellow color persists for at least ten minutes. This is conveniently done by weighing out iodine in 10-g. portions, dissolving in a little alcohol, and adding through the condenser. The total amount of iodine required depends on the purity of the mercurated acid. It should not exceed 210 g. (0.83 mole)If any insoluble material is left after an excess of iodine has been added, it is removed by rapid filtration through a preheated suction filter.

On cooling, the filtrate yields about 175 g. of *p*-iodobenzoic acid. Concentration of the mother liquor yields crystals which are contaminated with mercuric iodide. The latter may be removed by grinding the crystals in a mortar with water and enough sodium iodide or potassium iodide to destroy the red color of the mercuric iodide (Note 2). The mixture is filtered and the crystals are washed with a little sodium iodide solution and then with water. The washed *p*-iodobenzoic acid melts at 266–267°. The total yield is 150–170 g. (72–81 per cent of the theoretical amount).

2. Notes

1. The crude *p*-chloromercuribenzoic acid (p. 159) may be sucked as dry as possible and transferred in this pasty form to the iodine solution. If, however, it has caked at all, it must be thoroughly dried and powdered. A respirator should be worn, as the dust is rather irritating.
2. Another method of removing most of the mercuric iodide is to grind the crystals, suspend them in a little water, and pour off the lighter suspension of iodobenzoic acid, leaving the heavy mercuric iodide behind. Washing with

iodide solution is necessary to remove the last of the mercuric iodide.

3. Discussion

p-Iodobenzoic acid can be prepared by the oxidation of *p*-iodotoluene with chromic acid mixture[1] and with nitric acid;[2] by hydrolysis of the nitrile obtained from *p*-iodonitrobenzene and potassium cyanide;[3] and from *p*-aminobenzoic acid by diazotization.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 159

References and Notes

1. Körner, Z. Chem. 327 (1868).
2. Cohen and Raper, J. Chem. Soc. **85**, 1273 (1904).
3. Richter, Ber. **4**, 553 (1871).
4. Marshall, Ber. **28**, 338 (1895).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethyl alcohol (64-17-5)

nitric acid (7697-37-2)

potassium iodide (7681-11-0)

potassium cyanide (151-50-8)

iodine (7553-56-2)

chromic acid (7738-94-5)

mercuric iodide (7774-29-0)

sodium iodide (7681-82-5)

iodobenzoic acid (88-67-5)

p-iodotoluene (624-31-7)

p-Chloromercuribenzoic acid (59-85-8)

p-iodobenzoic acid, Benzoic acid, p-iodo- (619-58-9)

p-iodonitrobenzene (636-98-6)

p-aminobenzoic acid (150-13-0)

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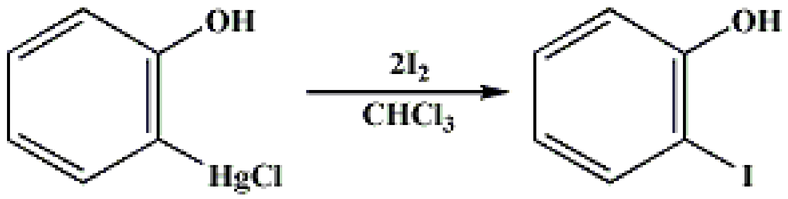
Organic Syntheses, *CV 1*, *326*

o-IODOPHENOL

[Phenol, *o*-iodo-]



Submitted by F. C. Whitmore and E. R. Hanson.
Checked by J. B. Conant and R. M. Granara.

1. Procedure

A 2-l. round-bottomed, short-necked flask is equipped with a glass mechanical stirrer. A suspension of 165 g. (0.5 mole) of *o*-chloromercuriphenol (p. 161) (m.p. 147° or higher) in 500 cc. of chloroform is placed in the flask and treated with 127 g. (0.5 mole) of iodine, the stirring being continued until a small sample on filtration shows no unreacted iodine. This requires from one to two hours. The solid inorganic mercury compounds are removed by suction filtration. The filtrate is distilled from a 1-l. distilling flask on the water bath to remove most of the chloroform, which is saved for later runs (Note 1). The residual liquid is shaken vigorously with a solution of 5 g. of potassium iodide in 10 cc. of water, to remove dissolved mercuric iodide. The heavier layer, which still possesses a reddish color, is transferred without drying to a 200-cc. Claisen flask and distilled under reduced pressure. At first a small amount of chloroform and water distils over, after which the higher-boiling material is collected in a separate receiver. Small amounts of inorganic mercury compounds remain in the flask (Note 2).

The *o*-iodophenol solidifies upon cooling. The yield of material melting at 32–34° is 70 g. (63 per cent of the theoretical amount). The product obtained in this way is slightly yellow. If a purer product is desired, it may be redistilled under reduced pressure. Most of the crude material will distil over a 5° range (b.p. 130°/18 mm. and 186°/160 mm., m.p. 43°).

2. Notes

1. About 460 cc. of chloroform can be recovered, the time required being one hour.
2. The first distillation of the iodophenol should be carried out under distinctly reduced pressure, 40 mm. or lower. The redistillation may be conducted at a higher pressure if desired.
3. Since the iodophenol has a most persistent odor, care should be exercised in working with it.

3. Discussion

o-Iodophenol can be prepared by diazotization from *o*-aminophenol[1] and from *o*-iodoaniline;[2] by heating *o*-iodosalicylic acid;[3] by treating a dilute phenol solution with iodine and iodic acid;[4] from an alcoholic solution of phenol and iodine in the presence of mercuric oxide;[5] from dry sodium phenoxide and iodine in carbon disulfide;[6] and by treating *o*-chloromercuriphenol with iodine in aqueous potassium iodide.[7]

References and Notes

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6. Schall, Ber. **16**, 1897 (1883); Ber. **20**, 3363 (1887).
7. Chi, Trans. Sci. Soc. China **7**, 169 (1932) [C. A. **26**, 5552 (1932)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

mercury compounds

chloroform (67-66-3)

phenol (108-95-2)

potassium iodide (7681-11-0)

o-aminophenol (95-55-6)

mercury (7439-97-6)

mercuric oxide (21908-53-2)

iodine (7553-56-2)

carbon disulfide (75-15-0)

mercuric iodide (7774-29-0)

iodic acid (7782-68-5)

iodophenol, o-Iodophenol, Phenol, o-iodo- (533-58-4)

sodium phenoxide

o-iodosalicylic acid

o-Chloromercuriphenol

o-iodoaniline (615-43-0)

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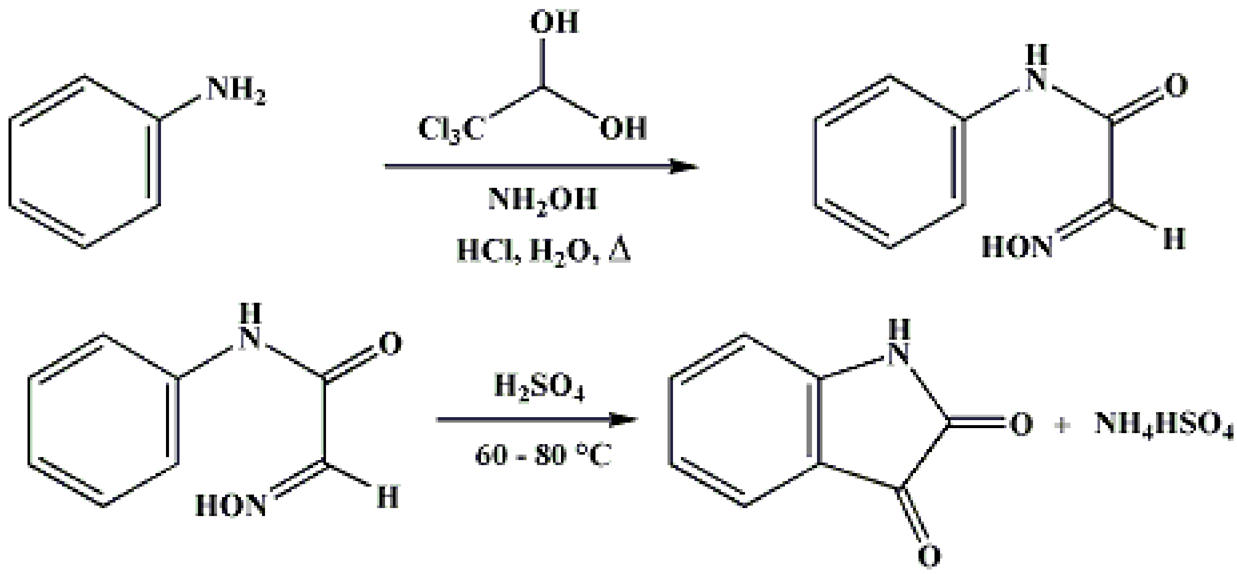
Organic Syntheses, CV 1, 327

ISATIN



Submitted by C. S. Marvel and G. S. Hiers.
Checked by J. B. Conant

1. Procedure

(*A*) *Isonitrosoacetanilide*.—In a 5-l. round-bottomed flask are placed 90 g. (0.54 mole) of chloral hydrate and 1200 cc. of water. To this solution are then added, in order: 1300 g. of crystallized sodium sulfate (Note 1); a solution of 46.5 g. (0.5 mole) of aniline (Note 2) in 300 cc. of water to which 51.2 g. (43 cc., 0.52 mole) of concentrated hydrochloric acid (sp. gr. 1.19) has been added to dissolve the amine (Note 3); and, finally, a solution of 110 g. (1.58 moles) of hydroxylamine hydrochloride (Note 4) in 500 cc. of water. The flask is heated over a wire gauze by a Meker burner so that vigorous boiling begins in about forty to forty-five minutes. After one to two minutes (Note 5) of vigorous boiling the reaction is complete. During the heating period, some crystals of isonitrosoacetanilide separate. On cooling the solution in running water the remainder crystallizes, is filtered with suction, and air-dried. The yield is 65–75 g. (80–91 per cent of the theoretical amount) of a product melting at 175°.

(*B*) *Isatin*.—Six hundred grams (326 cc.) of concentrated sulfuric acid (sp. gr. 1.84) is warmed to 50° in a 1-l. round-bottomed flask fitted with an efficient mechanical stirrer, and, to this, 75 g. (0.46 mole) of dry (Note 6) isonitrosoacetanilide is added at such a rate as to keep the temperature between 60° and 70° but not higher (Note 7). External cooling should be applied at this stage so that the reaction can be carried out more rapidly. After the addition of the isonitroso compound is finished, the solution is heated to 80° and kept at this temperature for about ten minutes to complete the reaction. Then the reaction mixture is cooled to room temperature and poured upon ten to twelve times its volume of cracked ice. After standing for about one-half hour, the

isatin is filtered with suction, washed several times with cold water to remove the sulfuric acid, and then dried in the air. The yield of crude isatin, which melts at 189–192°, is 47–52 g. (71–78 per cent of the theoretical amount). This product is pure enough for many purposes (Note 8).

For purification, 200 g. of the crude product is suspended in 1 l. of hot water and treated with a solution of 88 g. of sodium hydroxide in 200 cc. of water. The solution is stirred mechanically and the isatin passes into solution. Dilute hydrochloric acid is then added, with stirring, until a slight precipitate appears. This requires about 290–300 cc. of an acid made by diluting one volume of concentrated hydrochloric acid (sp. gr. 1.19) with two volumes of water (Note 9). The mixture is then filtered at once, the precipitate is rejected, and the filtrate is made acid to Congo red paper with hydrochloric acid. The solution is then cooled rapidly, and the isatin which separates is filtered with suction and dried in the air. The pure product thus obtained weighs 150–170 g. (Note 10) and (Note 11) and melts at 197–200° (corr.).

Isatin may also be crystallized from three times its weight of glacial acetic acid. In this case it is obtained in large brown-red crystals which melt at 196–197°.

2. Notes

1. Several runs were made in which the amounts of water and sodium sulfate were varied over a considerable range, and this concentration was found to give the best yield of product of good quality. The sodium sulfate seems to have more than a salting-out effect. If a saturated solution of sodium chloride is used no product is obtained.
2. Redistilled aniline boiling over a 2° range was used in these experiments. The ordinary "pure" grade gives slightly lower yields.
3. If the aniline is not in solution, a considerable quantity of tarry material is formed during the heating period. No tar is formed when the method described is used.
4. The hydroxylamine hydrochloride used was the crude material prepared as described on p. 318. Preliminary experiments showed that this reagent must be present in considerable excess. Equally good results were obtained by using a solution of crude hydroxylamine sulfate which also contained sodium sulfate and ammonium sulfate with a little excess sulfuric acid. The hydroxylamine content was determined in this solution by titration with potassium permanganate solution. When this crude solution is used, the addition of sodium sulfate is not always necessary.
5. Longer heating of the reaction mixture gives a lower yield of dark-colored product.
6. If too much moisture is left in the isonitrosoacetanilide it is not easy to control the reaction with sulfuric acid.
7. The reaction does not start below 45–50° but becomes too violent above 75–80°. If the temperature becomes too high, the entire run is lost by charring.

Stirring is needed to prevent local overheating.
8. In some smaller preparations when the sulfuric acid solution was poured on ice a yellow compound precipitated, which was shown to be the oxime of isatin. It has also been isolated from the acid mother liquors from which the isatin has separated. The oxime probably owes its formation to the hydrolysis of some unaltered isonitrosoacetanilide (J. P. Wibaut,[1] private communication).
9. The correct amount of acid that must be added to precipitate the impurities but not the isatin will vary with different samples of crude isatin. If too much acid is added, some isatin comes down with the impurities. This may be saved and added to a subsequent run.
10. The yield of isatin is lower than for some of its derivatives. The explanation given in the literature is that some sulfonation occurs during the treatment with sulfuric acid, with corresponding loss of product.
11. This method can be applied successfully to other isatin derivatives. Thus, under the same conditions, 54 g. of *p*-toluidine gives 75–77 g. (83–86 per cent of the theoretical amount) of isonitrosoaceto-*p*-toluidine melting at 162°. Eighty grams of this isonitroso compound treated as described under isonitrosoacetanilide gives 65–68 g. (90–94 per cent of the theoretical amount) of crude 5-methyl isatin melting at 179–183°. This is purified as described under isatin by solution in sodium hydroxide and partial neutralization to throw out the impurities or by recrystallization from three parts of glacial acetic acid. The purified 5-methyl isatin melts at 187°.

3. Discussion

Isatin can be prepared by the oxidation of indigo;[2] and the condensation of aniline, chloral hydrate, and hydroxylamine salts, followed by the action of sulfuric acid.[3] The latter method by Sandmeyer[3] seemed most promising and has been studied in detail. The procedure described differs from it in the use of hydroxylamine hydrochloride itself instead of a crude solution of hydroxylamine sulfate, and in the use of sodium sulfate to salt out the isonitroso compound.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 635

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

isonitroso compound

indigo

hydroxylamine salts

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

aniline (62-53-3)

sodium hydroxide (1310-73-2)

potassium permanganate (7722-64-7)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

Hydroxylamine hydrochloride (5470-11-1)

ammonium sulfate (7783-20-2)

hydroxylamine (7803-49-8)

Isatin (91-56-5)

chloral hydrate (302-17-0)

isonitrosoacetanilide (1769-41-1)

hydroxylamine sulfate (10046-00-1)

5-methyl isatin (608-05-9)

p-toluidine (106-49-0)

isonitrosoaceto-p-toluidine

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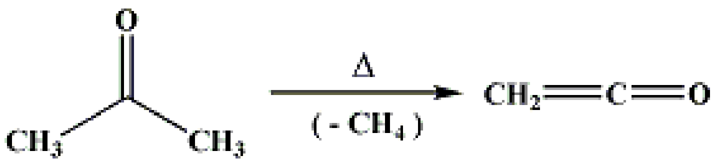
Organic Syntheses, CV 1, 330

KETENE

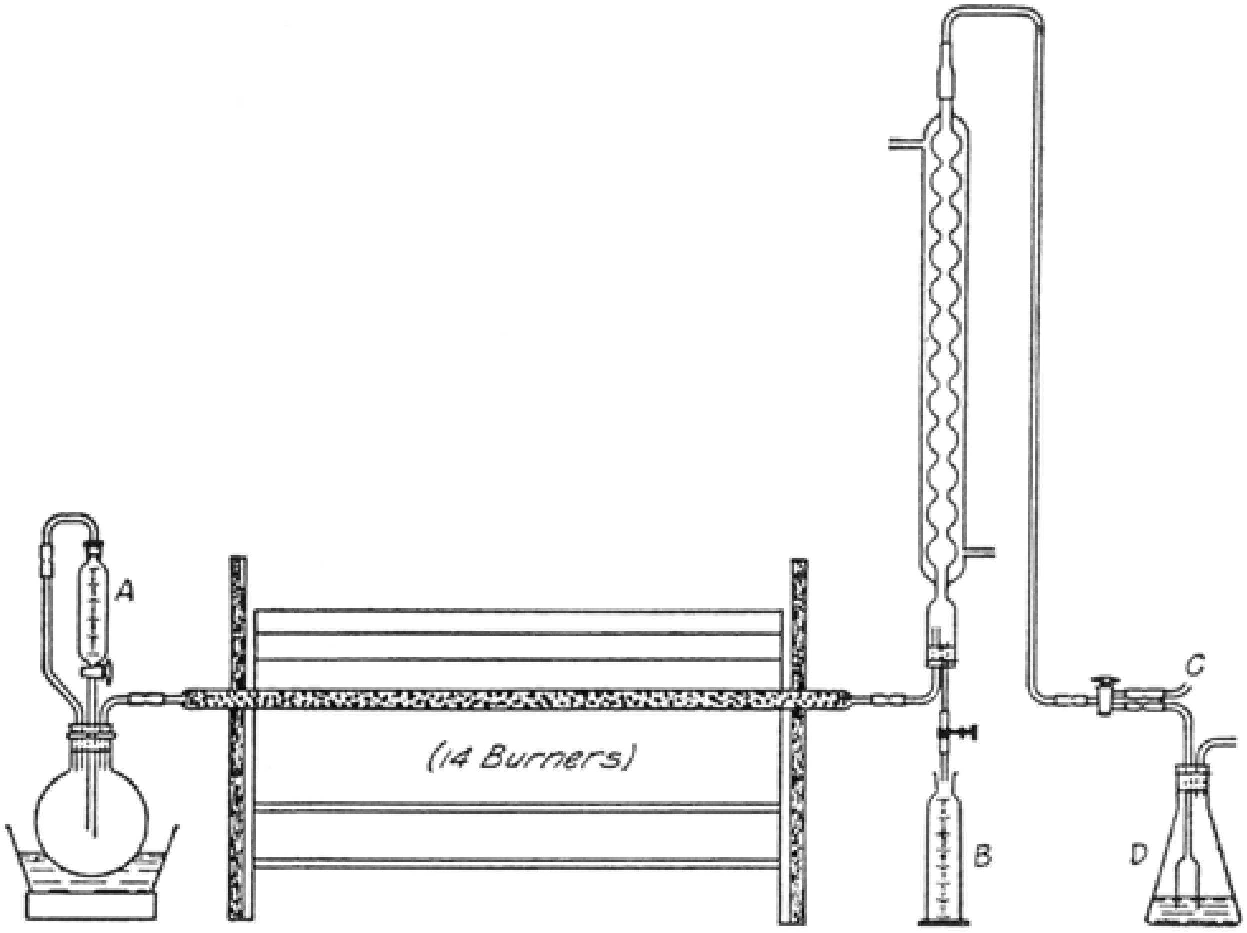


Submitted by C. D. Hurd
Checked by Oliver Kamm

1. Procedure

(*A*) *Preparation of Ketene*.—The arrangement of the apparatus is shown in Fig. 19 (Note 1). The graduated separatory funnel, shown in the diagram, filled with 100 g. (126 cc., 1.7 moles) of commercial acetone, leads into a 500-cc. round-bottomed flask which, in turn, is connected by gas-tight joints (Note 2) to a glass combustion tube filled with broken porcelain, a spiral or bulb condenser, a three-way stopcock, and a reaction flask. In the reaction flask is placed the material with which the ketene is to react (Note 3). A second reaction flask may be placed in series, if desired, to ascertain if any ketene escaped reaction in the first flask.

Fig. 19.



Prior to either of these steps, fourteen of the twenty burners of the combustion furnace are lighted (Note 4) and tiles are placed over the lighted burners, which finally must be adjusted to yield a maximum temperature. The first two and last four burners are unused.

When the furnace is fully heated, boiling water is placed beneath the round-bottomed flask and cold water passed through the condenser. Acetone is now dropped in at the rate of 3–4 cc. per minute. About one-half the acetone should be recovered as distillate in cylinder B (Note 5). Ketene, admixed with methane, carbon monoxide, and ethylene, passes into the reaction flasks (Note 6) in 25–29 per cent yields of the theoretical amount. The flow may be interrupted at will by checking the acetone flow (Note 7).

(*B*) *Preparation of Acetanilide*.—Since ketene is a highly reactive gas, it is usually prepared for immediate consumption instead of being isolated as such. It reacts with various groups which contain hydrogen, such as hydroxyl, amino, mercaptan, hydroxylamino, etc., forming acetyl derivatives.

Twenty-five grams (0.27 mole) of aniline is placed in the reaction flask, D, and 50 cc. of dry ether added as solvent (Note 8). A second reaction flask is connected at C, in which is placed 5 g. of aniline, dissolved in 20 cc. of dry ether. This prevents the escape of ketene vapor at the beginning and at the close of the operation (Note 5). In all, 85 cc. of acetone is passed through the apparatus, 39 cc. of which is recovered as distillate. Therefore, 44 cc. (or 35 g.) of acetone is decomposed. The duration of the run is about thirty minutes. Twenty-one grams of acetanilide, which corresponds to a yield of 25.8 per cent of the theoretical amount, based upon the amount of acetone decomposed, is isolated from the reaction mixture (Note 9).

2. Notes

1. *Apparatus*. A graduated dropping funnel and a graduated cylinder for the distillate are chosen because of convenience in determining the volume of decomposed acetone. The bulb (or spiral) condenser is chosen because of its efficiency. With an ordinary condenser, it is necessary to insert two U-tubes, cooled by ice, between the condenser and the reaction flask, to remove all the acetone from the ketene. In many reactions, however, this admixed acetone will do no harm. This part of the apparatus is designed to eliminate the loss of ketene by solvent action, prior to its entry into the reaction flask.
A wide-mouthed delivery tube in the reaction flask is essential to prevent clogging, when a solid product is formed. Automatic stirring in the reaction flask may be used to advantage in certain instances. There is constant agitation, of course, as the gaseous decomposition products bubble through.
Either Scotland glass or Pyrex is satisfactory for the combustion tube. An estimate of the temperature is 650° (Note 4). The life of the tube is lengthened if it rests upon a layer of thin asbestos paper. The tube is filled with pieces of broken porcelain, to serve as a "heat reservoir"; there is no catalytic effect. The porcelain blackens during the reaction.
2. *Care in Assembly*.—Since this is a gaseous reaction, it is essential that the apparatus be free from leaks; thus, corks are eliminated whereever possible. The ends of the combustion tube and the top of the condenser are drawn to the diameter of the connecting tubes and joined by a piece of thick-walled rubber tubing. Care should be

taken to have the ends of the glass tubes come into contact. The rubber tube situated between the furnace and condenser is protected by the asbestos screen, but a further essential precaution is taken, namely, that this end of the combustion tube extend a considerable distance from the furnace.
The stoppers in the reaction flask and at the top of the dropping funnel are of rubber; the other two are well-selected corks, bored perfectly and painted both inside and out with water-glass, one day previous to being used.
3. The apparatus may be calibrated by allowing the ketene to react with 5 *N* alkali and titrating the excess alkali with acid.
4. With an electric combustion furnace, wherein a temperature of 695–705° is maintained, consistent yields of 35–40 per cent ketene are produced. The best rate of flow in such a case is 4–6 cc. per minute, with recovery of 60–80 per cent of the original acetone as distillate. Although yields of ketene ranging above 45 per cent have been obtained frequently with this apparatus, they could not be duplicated consistently.
5. The thermal decomposition of ketene into carbon monoxide and ethylene is prevented, as far as possible, by the rapid removal of ketene from the hot tube, which is accomplished by the undecomposed acetone vapor. About half the acetone originally used should be collected unchanged as distillate by the vertical condenser. The yield of ketene will fall considerably if less distillate is formed.
6. Ketene gas is very irritant when inhaled, and hence proper cautions should be taken to avoid inhalation.
7. The generator, Fig. 19, is easily assembled from apparatus which can be found in almost every laboratory. Offsetting these advantages is the low yield of ketene obtained. If the necessary equipment is available, the generator described by Williams and Hurd[1] is recommended in place of the one shown above. With the Williams and Hurd generator, the yield of ketene is 80–90 per cent based on the acetone decomposed, and the output is 0.45 mole of ketene per hour. The generator may be run intermittently, or continuously for a period of twenty-four hours, and requires a minimum of attention (Jonathan L. Williams and Charles D. Hurd, private communication checked by N. L. Drake).
8. An ice bath surrounding the reaction flask is usually employed not only to prevent the vaporization of the solvent, but also to promote a greater solubility of ketene.
It has been found that the formation of acetanilide from ketene and aniline takes place more satisfactorily if the ketene is passed directly into excess aniline without any dry ether present. The excess aniline may then be removed by distillation under reduced pressure until the temperature of the vapors is 10–15° higher than the boiling point of aniline. An alternative plan is to remove excess aniline by dilute hydrochloric acid, to filter the acetanilide, and to wash with water.
9. It is suggested that improved yields of ketene may be obtained by directly dropping the acetone in at a rate of about 2 cc. per second instead of slowly distilling it into the hot tube (C. D. Hurd, private communication).

3. Discussion

Ketene can be prepared by the pyrogenic decomposition of acetic anhydride,[2] triacetin,[3] acetone,[4] and other ketones;[5] and by the action of zinc on an ethereal solution of

bromoacetyl bromide.[6] The procedure described is based on work of Schmidlin and Bergmann[4] as modified by Hurd and Cochran.[4] The preparation of ketene from acetone has been the subject of numerous articles and patents.[7] The more recent work usually involves either the use of hot metallic filaments or of metallic oxide catalysts.[8]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 102
- Org. Syn. Coll. Vol. 3, 508
- Org. Syn. Coll. Vol. 5, 679
- Org. Syn. Coll. Vol. 9, 28

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3. Ott, Ber. **47**, 2393 (1914).
4. Schmidlin and Bergmann, Ber. **43**, 2881 (1910); Hurd and Cochran, J. Am. Chem. Soc. **45**, 515 (1923); Hurd and Tallyn, ibid. **47**, 1427 (1925); Hurd, ibid. **45**, 3095 (1923); Biltz, Z. angew. Chem. **36**, 232 (1923); Ketoid Co., Brit. pat. 237,573 [C. A. **20**, 1415 (1926)]; Clarke and Waring, U. S. pat. 1,723,724 [C. A. **23**, 4485 (1929)]; Goldschmidt and Orthner, Z. angew. Chem. **42**, 40 (1929); Mitchell and Reid, J. Am. Chem. Soc. **53**, 332 (1931); Rice, Greenberg, Waters, and Vollrath, ibid. **56**, 1763 (1934).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

ether (60-29-7)

acetic anhydride (108-24-7)

aniline (62-53-3)

hydrogen (1333-74-0)

Acetanilide (103-84-4)

carbon monoxide (630-08-0)

acetone (67-64-1)

methane (7782-42-5)

zinc (7440-66-6)

ethylene (9002-88-4)

Ketene (463-51-4)

triacetin (102-76-1)

bromoacetyl bromide (598-21-0)

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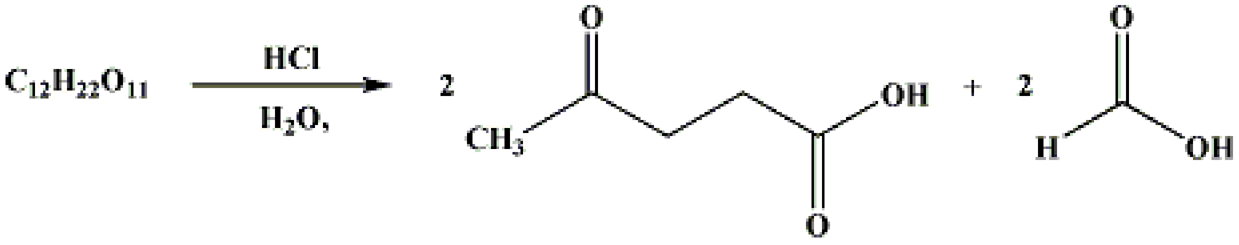
Organic Syntheses, CV 1, 335

LEVULINIC ACID



Submitted by B. F. McKenzie
Checked by H. T. Clarke and R. Phillips.

1. Procedure

To a solution of 500 g. (1.46 moles) of cane sugar (Note 1) in 1 l. of water in a 2-l. flask is added 250 cc. of concentrated hydrochloric acid (sp. gr. 1.16). The flask is heated on a steam bath for twenty-four hours, during which time considerable carbonization takes place. The black solid is filtered off with suction and washed with 300 cc. of water. The filtrate is placed in a large evaporating dish on a steam bath and allowed to evaporate overnight. The black solid residue obtained on the following morning is ground to a powder and placed in a folded filter paper of 34-cm. diameter. This is placed in a 25-cm. funnel fitted with a water-cooled 12-l. flask as described on p. 375. The solid is extracted with 500 cc. of ether for six to eight hours. The ether is distilled and the residue (Note 2) fractionated under reduced pressure. The fraction distilling at 150–160°/15 mm. or 135–140°/10 mm. forms a rather dark liquid which does not completely solidify on cooling.

On redistillation under reduced pressure a fraction boiling over a range of not more than 2° (e.g., 137–139°/10 mm.) is obtained with very little loss; this fraction solidifies almost completely at 30°. The yield is 72–76 g. (21–22 per cent of the theoretical amount).

2. Notes

1. Equally good results may be obtained with starch; the mixture however, must be warmed more slowly as it is apt to foam at the outset.
2. When larger quantities of levulinic acid are to be prepared it has been found by the checkers to be more convenient to fractionally distil the first filtrate under reduced pressure, without evaporating to dryness and extracting with ether. In this case a considerable quantity of tarry residue remains in the distilling flask. The yields are equally good.

3. Discussion

The only practical methods for preparing levulinic acid depend upon the action of

mineral acids upon carbohydrates, a reaction discovered by Grote and Tollens,[1] who heated cane sugar with dilute sulfuric acid. The procedure described is essentially that of Conrad,[2] descriptions of which frequently have appeared[3] in the subsequent literature. Improved yields have been reported[4] by digesting sucrose under pressure for one hour with dilute hydrochloric acid at 162° in the presence of water vapor. The use of distillation under reduced pressure was suggested by Kent and Tollens.[5] Levulinic acid can also be prepared from starch[6] and from glucose[7] by the action of hydrochloric acid, and from furfuryl alcohol or hydroxymethylfurfural by the action of dilute mineral acids.[8]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

cane sugar

starch

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ether (60-29-7)

sucrose

Furfuryl alcohol (98-00-0)

LEVULINIC ACID (123-76-2)

glucose (492-62-6)

hydroxymethylfurfural

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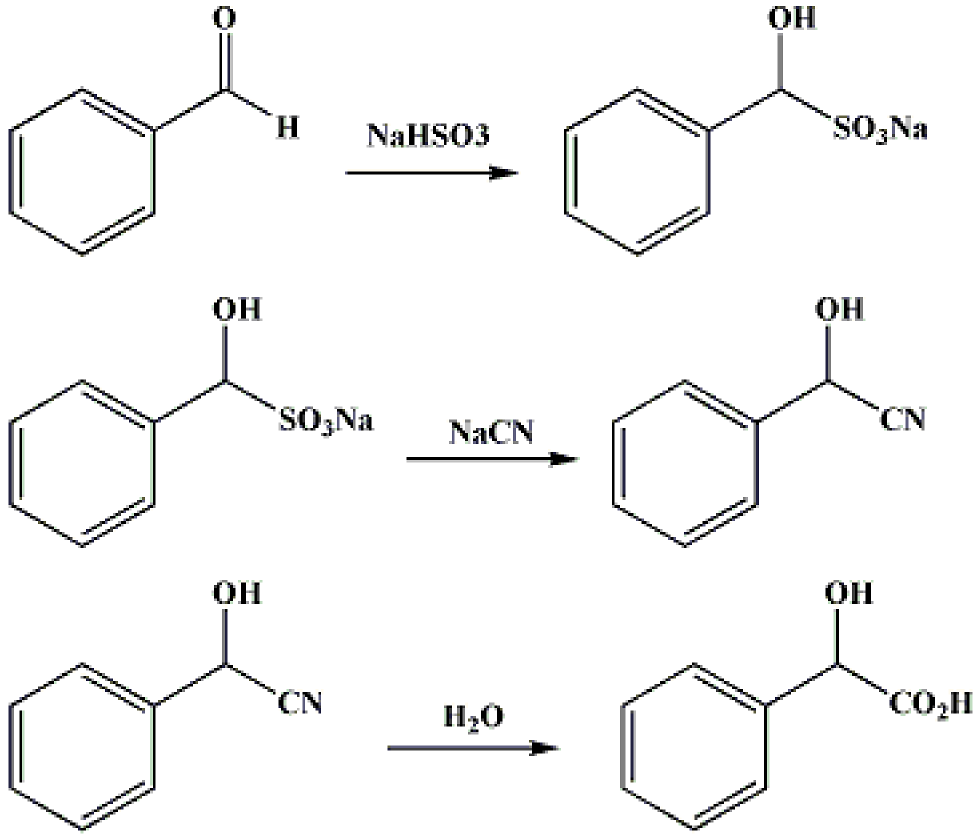
MANDELIC ACID



Submitted by B. B. Corson, Ruth A. Dodge, S. A. Harris, and J. S. Yeaw.
Checked by C. S. Marvel and M. M. Brubaker.

1. Procedure

In a 4-l. wide-mouthed glass jar, fitted with a mechanical stirrer, is placed a solution of 150 g. (3 moles) of sodium cyanide (Note 1) in 500 cc. of water and 318 g. (3 moles) of u.s.p. benzaldehyde. The stirrer is started, and 850 cc. of a saturated solution of sodium bisulfite (Note 2) is added to the mixture, slowly at first and then in a thin stream. The time of addition is ten to fifteen minutes. During the addition of the first half of this solution, 900 g. of cracked ice is added to the reaction mixture, a handful at a time. The layer of mandelonitrile which appears during the addition of the sulfite solution is separated from the water in a separatory funnel. The water is extracted once with about 150 cc. of benzene, the benzene is evaporated, and the residual mandelonitrile is added to the main portion.

The crude nitrile (about 290 cc.) is placed at once (Note 3) in a 25-cm. evaporating dish, and 425 cc. of c.p. concentrated hydrochloric acid (sp. gr. 1.19) is added. The hydrolysis is allowed to proceed in the cold (Note 4) for about twelve hours, after which the mixture is heated on a steam bath to remove the water and excess hydrochloric acid. After heating for five to six hours it is advisable to cool the mixture

(Note 5) and filter the ammonium chloride and mandelic acid mixture that separates. The filtrate is then evaporated to dryness. This residue is added to the solid material obtained before. The product is deeply colored and must be dried in the air and light for at least twenty-four hours. The total yield of the crude mandelic acid-ammonium chloride mixture is 370–390 g., depending on the amount of moisture. The mixture of ammonium chloride and mandelic acid is ground in a mortar, transferred to a 2-l. flask, and washed twice with 750-cc. portions of cold benzene (Note 6). The insoluble portion is transferred to a suction funnel and sucked dry.

Either of two methods may be used to extract the mandelic acid from the ammonium chloride.

(*A*) *Extraction with Benzene*.—The mandelic acid is separated from the ammonium chloride by extraction with hot benzene. This is best done by dividing the solid mixture into ten approximately equal parts (Note 7). One of these portions is placed in a flask with 1 l. of boiling benzene. After a few minutes the hot benzene solution is decanted through a suction funnel (Note 8). The filtrate is cooled in an ice bath and the mandelic acid that crystallizes is filtered with suction. The benzene is returned to the extraction flask containing the residue from the first extraction, and a new portion of the ammonium chloride-mandelic acid mixture is added and extracted as before. The process is repeated until the mandelic acid is completely removed from the ammonium chloride (Note 9).

The yield of pure white mandelic acid melting at 118° is 229–235 g. (50–52 per cent of the theoretical amount based on benzaldehyde).

(*B*) *Extraction with Ether* (Note 10).—The solid mixture is transferred to a 2-l. flask and shaken ten minutes with 750 cc. of ether. The ether solution is decanted through a suction filter and the solid thrown onto the filter and pressed dry. The solid is then returned to the flask and shaken with 400 cc. of ether. This mixture is filtered by suction and the solid washed twice on the filter with 250-cc. portions of ether. Each portion is allowed to drain through the filter several times while the solid is kept porous with a spatula. The combined ether filtrate is then filtered through an ordinary funnel (Note 11). The ether solution is placed in a 3-l. round-bottomed flask, and 750 cc. of toluene (Note 12) is added. The mixture is distilled on a steam bath through an efficient fractionating column as long as it distils easily, and about 1100–1400 cc. of distillate is collected. The temperature of the vapor rises to about 70°. The mixture is then heated over a free flame until the temperature in the column is 95°; about 300 cc. distils (Note 13). The residual liquid is poured while still hot into a large beaker immersed in ice water. The liquid (about 900 cc.) is stirred by hand until it has become a thick crystal mush. The cooling is continued for two hours with occasional stirring so as to bring the temperature down to 5–10°. The mixture is filtered with suction and the solid pressed dry. It is then thoroughly washed on the filter with 300 cc. of toluene in several portions (Note 14).

The yield is the same as that obtained by method (*A*) (Note 15).

2. Notes

1. This reaction and the subsequent hydrolysis should be carried out in a good hood as some hydrogen cyanide is liberated. The sodium cyanide used was the technical "cyan-egg," containing about 92–95 per cent of cyanide.

2. This saturated solution is best prepared by stirring 1500 g. of technical sodium bisulfite (97–100 per cent) with 2 l. of water and filtering to remove the excess salt. The specific gravity of this solution is 1.37–1.39.

3. The mandelonitrile should be mixed with hydrochloric acid as soon as it is separated from the water. This appears necessary in order to avoid a rapid conversion to the acetal of benzaldehyde and mandelonitrile, $C_6H_5CH[OCH(CN)C_6H_5]_2$. Hence if it is allowed to stand long before the hydrolysis, the yield of mandelic acid is reduced.

4. The hydrolysis can be carried out in the hot, but the final product may be deeply colored.

5. It is advisable to stir the mixture during the cooling in order to break up the lumps and thus obtain a product that can be more easily filtered.

6. If the crude product is not first washed with cold benzene the final product is usually colored. Very little mandelic acid is lost by this washing.

7. The entire amount of the ammonium chloride-mandelic acid mixture may be boiled with the benzene, but this gives a supersaturated solution of the acid in the benzene and much difficulty is met in the filtration. The solubility of mandelic acid in hot benzene is approximately 1 g. in 50 cc.

It may be better to carry out the extraction in a Soxhlet apparatus or an apparatus of the type described on p. 375.

8. The funnel should be previously heated and have fairly large holes so as not to be clogged by the mandelic acid that begins to crystallize as soon as the solution cools slightly. Only slight suction should be applied during filtration.

9. Usually two or three extractions of the ammonium chloride residues after the addition of the last portion of the crude mixture are necessary in order to obtain all the mandelic acid. On concentrating the benzene used for the extraction, about 5 g. of impure mandelic acid may be obtained. To diminish mechanical losses it is recommended that the same container be used to collect and crystallize the several filtrates.

10. The ether extraction method (*B*) is quicker, especially when several runs are to be made. Mandelic acid is obtained in the same yield by this method. The benzene extraction may be better for small preparations, or when a single run is to be made.

11. An occasional water layer should be removed in a separatory funnel.

12. Benzene works almost as well as toluene; xylene can also be used.

13. The temperature in the column is a better guide than the volume of distillate. A few porous chips should be added to prevent bumping. The ether-toluene solution should not stand long before distillation as mandelic acid is apt to separate. The heating with steam and with the free flame should be done quickly

since prolonged heating lowers the yield.
14. The mother liquors are worked up for toluene, but it is not profitable to try to recover the small amount of impure mandelic acid which they contain.
15. The following modification is suggested for small-scale operations: When the hydrolysis of mandelonitrile is complete, the mixture is cooled, sufficient water is added to bring the solid matter into solution, and the solution is extracted thoroughly with ether. The ethereal solution is dried with sodium sulfate, the ether is distilled off from a water bath, and the mandelic acid, which does not at once solidify, is taken up in benzene and allowed to crystallize (L. F. Fieser, private communication).

3. Discussion

Mandelic acid can be prepared by the hydrolysis of amygdalin with sulfuric acid[1] or of mandelonitrile with hydrochloric acid.[2] The mandelonitrile can be prepared by the action of hydrocyanic acid on benzaldehyde,[3] and by the action of sodium or potassium cyanide on the sodium bisulfite addition product of benzaldehyde.[4] The procedure described differs from earlier methods in that the sodium bisulfite addition compound of benzaldehyde is prepared in the presence of sodium cyanide and the nitrile is formed immediately.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 12
- Org. Syn. Coll. Vol. 1, 241
- Org. Syn. Coll. Vol. 3, 538

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

nitrile

ammonium chloride-mandelic acid

acetal of benzaldehyde

mandelonitrile, $C_6H_5CH[OCH(CN)C_6H_5]_2$

amygdalin

sodium or potassium cyanide

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether (60-29-7)

ammonium chloride (12125-02-9)

Mandelic acid (90-64-2)

sodium cyanide (143-33-9)

hydrogen cyanide, hydrocyanic acid (74-90-8)

sodium sulfate (7757-82-6)

cyanide (57-12-5)

sodium bisulfite (7631-90-5)

benzaldehyde (100-52-7)

toluene (108-88-3)

mandelonitrile (532-28-5)

xylene (106-42-3)

mandelic acid-ammonium chloride

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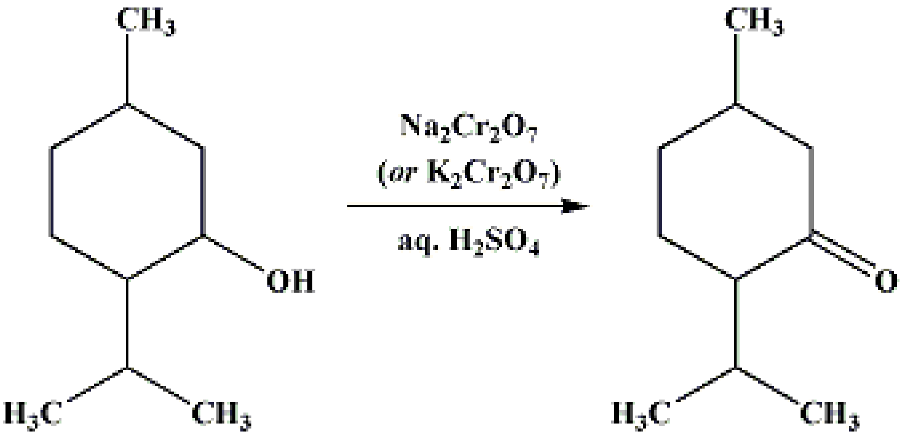
Organic Syntheses, CV 1, 340

l-MENTHONE



Submitted by L. T. Sandborn
Checked by H. T. Clarke and Ross Phillips.

1. Procedure

In a 1-l. round-bottomed flask provided with a mechanical stirrer is placed 120 g. (0.4 mole) of crystallized sodium dichromate (or an equivalent amount of potassium dichromate), and to this is added a solution of 100 g. (54.3 cc., 0.97 mole) of concentrated sulfuric acid (sp. gr. 1.84) in 600 cc. of water. To this mixture 90 g. (0.58 mole) of menthol (crystals, m.p. 41–42°) is added in three or four portions and the mixture stirred (Note 1). Heat is evolved, and the temperature of the mixture rises to about 55° (Note 2). As soon as the reaction is complete the temperature falls. The oil is mixed with an equal volume of ether, separated in a separatory funnel, and washed with three 200-cc. portions of 5 per cent sodium hydroxide solution (Note 3). The ether is then removed by distillation and the residue distilled under reduced pressure, the menthone being collected at 98–100°/18 mm. If distilled under atmospheric pressure it boils at 204–207°. The yield is 74–76 g. (83–85 per cent of the theoretical amount).

2. Notes

1. On addition of the menthol a black spongy mass forms which softens as the temperature rises and finally forms a dark brown oil.
2. The temperature may not reach 55°, in which case the mixture may be warmed gently with a small flame. If the reaction is slow in starting, gentle heating with a small flame is advantageous.
3. The oil, which is dark brown before washing with sodium hydroxide, becomes light yellow. If three washings are not sufficient to remove the dark color another portion of sodium hydroxide solution is used.

3. Discussion

l-Menthone can be prepared by the oxidation of rhodinol with a chromic-sulfuric acid mixture;[1] by heating menthol with copper at 300°;[2] and by heating 3-menthene oxide alone or in the presence of a catalyst.[3] The procedure described is that of Beckmann.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 522

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

rhodinol

sulfuric acid (7664-93-9)

ether (60-29-7)

sodium hydroxide (1310-73-2)

copper (7440-50-8)

sodium dichromate (7789-12-0)

potassium dichromate (7778-50-9)

menthol (15356-60-2)

menthone, l-MENTHONE (1196-31-2)

chromic-sulfuric acid (15244-38-9)

3-menthene oxide

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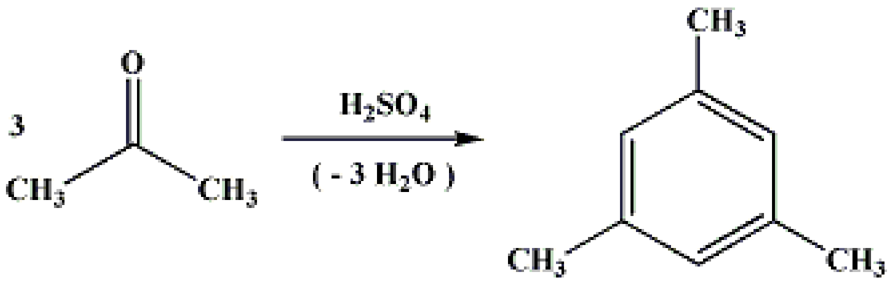
Organic Syntheses, CV 1, 341

MESITYLENE



Submitted by Roger Adams and R. W. Hufferd.
Checked by H. T. Clarke and W. W. Hartman.

1. Procedure

In a 12-l. round-bottomed flask, arranged so that the contents can be mechanically stirred, is placed 4600 g. (5750 cc., 79 moles) of technical acetone. The flask is then well cooled with an ice and salt mixture, until the temperature of the acetone is between 0° and 5° (Note 1). Stirring is started, and 4160 cc. of commercial concentrated sulfuric acid is run in at such a rate that the temperature of the mixture never rises above about 10°. This addition is accomplished in about five to ten hours. The stirring is continued for three to four hours longer, while the flask still remains immersed in the original freezing mixture to which no further amount of ice is added. The mixture is then allowed to stand at room temperature for eighteen to twenty-four hours (Note 2).

A 5-l. round-bottomed flask is fitted with a rubber stopper or a cork stopper coated with pitch (Note 3), carrying two glass tubes, one of which (for the entrance of steam) reaches to the bottom of the flask, while the other extends into the open end of a condenser set for downward distillation. The stopper should be wired into the flask. The glass delivery tube into the condenser should not be less than a 12-mm. bore, and the condenser should consist of two 120-cm. water-cooled condensers attached end to end. To the end of the condensing system, an adapter is attached, the small end of which is at least 8 mm. in bore and is fitted tightly into a stopper in a 2-l. suction flask. To the side arm of the suction flask is attached a tube leading to an exhaust fan, in order to carry away the gases which are evolved during the subsequent distillation (Note 4). In the 5-l. flask is placed about 2 l. of the sulfuric acid-acetone reaction mixture (Note 5), and the flask is then heated with a free flame and shaken occasionally. A reaction starts at the end of about fifteen or twenty minutes, as shown by the evolution of gas (chiefly sulfur dioxide), and is allowed to run for about three minutes (Note 6). At the end of this time, a current of steam is passed in and continued for about three minutes. During this period a large proportion of the mesitylene distils and should be kept separate from the subsequent distillate. The steam distillation is continued at such a rate that about 800 cc. distils in twenty-five to thirty minutes and is collected as a second distillate. At the end of this time, the distillation is stopped, the

water poured off from the distilling flask, and the tarry material emptied out while hot into waste jars.

The total amount of original reaction mixture requires five distillations similar to the one just described. The first distillates from each of the five distillations are mixed, and the layer of mesitylene is separated from the water. This is shaken with sodium hydroxide solution until no more odor of sulfur dioxide is noticeable, then washed twice with water and distilled. The first portion of the distillate consists of a small amount of water and mesitylene and is added to the combined second distillates. The fraction which distils up to 210° is saved. The second distillates are combined, washed in the same way as the first, and then distilled; the fraction which distils up to 210° is combined with the corresponding fraction from the first distillates.

These combined fractions (which boil up to 210°) and 15 g. of sodium are placed in a 2-l. distilling flask, the side arm of which is closed with a rubber tube and pinchcock and which is fitted with a reflux condenser. The mixture is heated just below the boiling point for about three hours, during which time the impurities are attacked by the molten sodium, and a gelatinous, reddish mass forms. The reflux condenser is now removed and one set for downward distillation is attached to the side arm. The mixture is distilled and about two-thirds of the liquid removed in this way. The residue is cooled, the liquid poured off from solid material and distilled up to 210°.

The distillates from the sodium treatment are now fractionated with a good column (at least 30 cm. long), and the portion which boils at 163–167° is collected. The yield of this fraction varies from 430 to 470 g. (13–15 per cent of the theoretical amount), but very often will be as high as 500 g., and has reached, in certain experiments, 600 g. (Note 7) and (Note 8).

2. Notes

1. The cooling of the reaction flask must be very efficient, a 10–15 cm. blanket of a thorough mixture of ice and salt being used. If this precaution is not employed, the time for the addition of the sulfuric acid is greatly increased, provided the temperature of the reaction mixture is still kept within the limits mentioned.
2. While the original reaction mixture is standing, the temperature gradually rises to 40° or 50° in the course of six to ten hours, and then gradually cools off again. It is probable that at the end of this time (when the flask has cooled again) the reaction mixture could be distilled with nearly as good a yield as is obtained after standing eighteen to twenty-four hours.
3. If a cork is used for the steam distillation of the reaction mixture of acetone and sulfuric acid, it should be coated well with pitch and wired into the flask. This is necessary because the vapors of the reaction mixture attack an ordinary cork very badly, and soften it so much that it is necessary to rewire it to prevent it from slipping out. A rubber stopper is satisfactory and may be used in several runs.
4. The evolved gases may be disposed of by means of a gas-absorption trap (Fig.

7 on p. 97). However, the trap may be inadequate when large volumes of gas are liberated in a short time.

5. The evolution of gas is so vigorous that it is not possible to distil more than 2 l. of the original reaction mixture at one time in the apparatus described. The connections on the apparatus, in which the mesitylene is obtained from the crude reaction mixture, should be tight, since the fumes evolved during the heating are very irritating.

6. The product which distils during the initial heating and the three minutes of steam distillation is mainly satisfactory material; the rest of the steam distillation yields only a small amount of pure product. The two portions of the distillate are, therefore, kept separate, since the second distillate always contains a considerable amount of high-boiling product which tends to cause emulsification of the alkali in the purification. No recovery of acetone is made. The mechanism of the reaction is undoubtedly as follows: when the sulfuric acid and acetone are in contact for long periods of time, several molecules of the acetone condense to form aldol condensation products. These do not break down into mesitylene until the temperature is raised in the second part of the experiment.

7. The wide variation in yields which is mentioned in the experimental part is probably due to a slight change in the grade of the chemicals which are used in this preparation. The average yield of a large number of runs made in recent years is 510 g. This improvement is due in part to a better grade of technical acetone.

8. An alternative method for the purification of the crude material has been employed by the checkers, and yields a slightly higher-grade product than the sodium method. It is as follows:

The combined distillates are treated with an equal volume of concentrated sulfuric acid and the solution warmed on a water bath for one hour, under a reflux condenser, with occasional shaking or, better, with mechanical stirring. Upon cooling, mesitylenesulfonic acid crystallizes and the unsulfonated material remains as an oil on the surface. The mixture is filtered through flannel or a filtros plate, and the crystals are washed with 60–70 per cent sulfuric acid. The oily layer is again warmed with sulfuric acid, as before. The acid and oily filtrates from the two sulfuric acid treatments are steam distilled, and the distillate combined with the next batch of material. The crystals are mixed with 2 l. of 15 per cent hydrochloric acid and heated under a reflux condenser for two to three hours. The reaction mixture is now steam distilled, the mesitylene separated, dried over calcium chloride and fractionated; the portion which boils at 163–167° is collected.

3. Discussion

Mesitylene can be prepared by the action of sulfuric acid[1] on acetone; by the action of hydrochloric acid on acetone, under pressure and at temperatures varying from 100 to 200°;[2] by the condensation of acetone using silica gel or alumina as a catalyst;[3] and by

the methylation of benzene, toluene, or *m*-xylene.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 95
- Org. Syn. Coll. Vol. 2, 449

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alumina

silica gel

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

sodium hydroxide (1310-73-2)

sulfur dioxide (7446-09-5)

acetone (67-64-1)

toluene (108-88-3)

sodium (13966-32-0)

Mesitylene (108-67-8)

sulfuric acid-acetone

mesitylenesulfonic acid

m-xylene (108-38-3)

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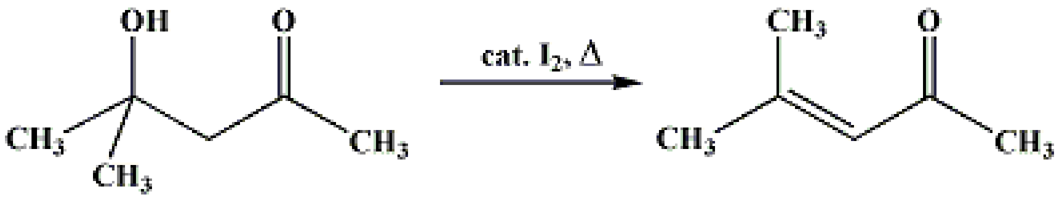
Organic Syntheses, CV 1, 345

MESITYL OXIDE



Submitted by J. B. Conant and Neal Tuttle.
Checked by Roger Adams and H. C. N. Heckel.

1. Procedure

A 1-l. round-bottomed flask is fitted with a three-bulbed Glinsky fractionating column connected to a water-cooled condenser set for distillation. The crude diacetone alcohol (p. 199) which will usually weigh about 1100 g. (9.5 moles) and will have a specific gravity of about 0.91 is placed in the flask together with 0.1 g. of iodine. The mixture is now distilled steadily but not too rapidly (Note 1) with a small free flame, and three portions are collected as follows: I, 56–80°; II, 80–126°; III, 126–131° (Note 2). The first portion is acetone containing a small amount of mesityl oxide and water (Note 3). The second portion separates into two layers—water and crude mesityl oxide. The third portion is pure mesityl oxide.

While the third fraction is distilling, the aqueous layer in fraction II is separated in a separatory funnel and the crude mesityl oxide is dried with anhydrous calcium chloride and distilled through a Glinsky column; by this means a further amount of acetone and a small intermediate fraction (85-126°), which is best discarded, are separated. The pure mesityl oxide itself then distils between 126° and 130° and is added to the pure product already obtained as the third portion of the first distillation. The first complete distillation will require about five hours; the redistillation of portion III will take about one hour. The yield is 650 g. (65 per cent of the theoretical amount based on the total acetone employed) (Note 4). About 300 g. of acetone is recovered (Note 3).

2. Notes

1. The first distillation should not be interrupted but should be carried out at a slow uniform rate until complete.
2. The very last portion of fraction III is sometimes slightly colored, apparently by some iodine which comes over at the end of the distillation. A small amount of high-boiling residue is always left.
3. The acetone recovered from the preparation of mesityl oxide can be mixed with fresh acetone and used successfully in preparing more crude diacetone alcohol (p. 199).

4. If the crude diacetone alcohol contains less than 80 per cent of diacetone alcohol (when the refluxing is not carried out long enough, for example) the yield of mesityl oxide will be, of course, correspondingly low.

3. Discussion

There are two general methods for the preparation of mesityl oxide: the action of condensing agents (hydrochloric acid, etc.) on acetone, [1] and the dehydration of diacetone alcohol. [2] The action of acid condensing agents is very unsatisfactory; the yields are poor and considerable quantities of phorone and similar substances are invariably produced. The direct production of mesityl oxide from acetone and calcium oxide[3] was tried, but without success; diacetone alcohol was the principal product. Several methods proposed for the dehydration of diacetone alcohol were investigated. That of Hibbert[2] (using a very small quantity of iodine) is superior to the action of either concentrated sulfuric acid or aluminum phosphate.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 196
- Org. Syn. Coll. Vol. 2, 200

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Diacetone alcohol

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

iodine (7553-56-2)

acetone (67-64-1)

Mesityl oxide (141-79-7)

calcium oxide

aluminum phosphate (7784-30-7)

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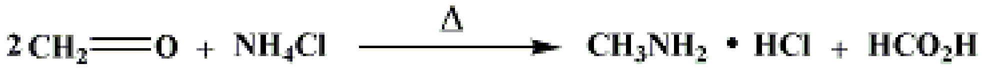
Organic Syntheses, CV 1, 347

METHYLAMINE HYDROCHLORIDE



Submitted by C. S. Marvel and R. L. Jenkins.
Checked by J. B. Conant and F. C. Whidden.

1. Procedure

In a 5-l. round-buttoned flask, fitted with a stopper holding a condenser set for downward distillation and a thermometer which will extend well into the liquid, are placed 4 kg. (3711 cc., 47–53 moles) of technical formaldehyde (35–40 per cent; sp. gr. 1.078 at 20°) (see Note 1 on p. 378) and 2 kg. (37 moles) of technical ammonium chloride. The mixture is heated on the steam bath until no more distillate comes over and then over a flame until the temperature of the solution reaches 104°. The temperature is held at this point until no more distillate comes over (four to six hours). The distillate, which consists of methylal, methyl formate, and water, may be treated as described in (Note 1).

The contents of the reaction flask are cooled to room temperature (Note 2), and the ammonium chloride which separates is filtered off and centrifuged (Note 3). The mother liquor is concentrated on the steam bath under reduced pressure to 2500 cc., and again cooled to room temperature, whereupon a second crop of ammonium chloride is obtained. The total recovery of ammonium chloride up to this point amounts to 780–815 g.

The mother liquor is again concentrated under reduced pressure until crystals begin to form on the surface of the solution (1400–1500 cc.). It is then cooled to room temperature, and a first crop of methylamine hydrochloride, containing some ammonium chloride, is obtained by filtering the cold solution and centrifuging the crystals (Note 3). At this point 625–660 g. of crude product is obtained. The mother liquor is now concentrated under reduced pressure to about 1000 cc. and cooled; a second crop of methylamine hydrochloride (170–190 g.) is then filtered off and centrifuged. This crop of crystals is washed with 250 cc. of cold chloroform, filtered, and centrifuged, in order to remove most of the dimethylamine hydrochloride which is present; after the washing with chloroform the product weighs 140–150 g. The original mother liquor is then evaporated under reduced pressure, as far as possible, by heating on a steam bath, and the thick sirupy solution (about 350 cc.) which remains is poured into a beaker and allowed to cool, with occasional stirring, in order to prevent the formation of a solid cake (Note 2). The thick paste so obtained is centrifuged, and the crystals (170–190 g.) are washed with 250 cc. of cold chloroform; the solution is filtered and the crystals are centrifuged, thus yielding 55–65 g. of product. There is no advantage in further concentrating the mother liquor.

The total yield of crude centrifuged methylamine hydrochloride is 830–850 g. This product contains, as impurities, water, ammonium chloride, and some dimethylamine hydrochloride. In order to obtain a pure product, the crude methylamine hydrochloride is recrystallized from absolute alcohol (Note 4). The crude salt is placed in a 5-l. round-bottomed flask fitted with a reflux condenser protected at the top with a calcium chloride tube; 2 l. of absolute alcohol is added and the mixture heated to boiling. After about one-half hour the undissolved material is allowed to settle and the clear solution is poured off. When the alcoholic solution is cooled, methylamine hydrochloride crystallizes out. It is filtered off and centrifuged, and the alcohol used for another extraction. The process is repeated until the alcohol dissolves no more of the product (about five extractions are necessary). In the flask 100–150 g. of ammonium chloride remains, making the total recovery of ammonium chloride 850–950 g. The yield of recrystallized methylamine hydrochloride is 600–750 g. (45–51 per cent of the theoretical amount, based on the ammonium chloride used up in the process) (Note 5) and (Note 6).

2. Notes

1. Methylal and sodium formate may be obtained from the first distillate of the main reaction mixture. The crude distillate is placed in a flask fitted with a reflux condenser, and to it is added a solution of 200 g. of sodium hydroxide in 300 cc. of water. The methyl formate is hydrolyzed to sodium formate. The methylal layer is separated, dried over calcium chloride, and distilled. In this way 240–260 g. of methylal, boiling at 37–42°, is obtained. By evaporating the watery portion to dryness, a residue of about 280 g. of crude sodium formate is obtained.

2. The methylamine hydrochloride solutions should be cooled rapidly in order to bring the salt down in small crystals which may be easily purified.

3. Centrifuging the precipitates is the only satisfactory method of drying, as all the products tend to take up water when allowed to stand in the air.

4. Since ammonium chloride is not absolutely insoluble in 100 per cent ethyl alcohol (100 g. dissolve 0.6 g. at 15°), the methylamine hydrochloride purified in the manner described contains appreciable traces of it. A purer product can be prepared by recrystallizing from *n*-butyl alcohol, in which the solubility of ammonium chloride even at the boiling temperature is negligibly small. Methylamine hydrochloride is somewhat less soluble in this solvent than in ethyl alcohol, but as a rule three extractions carried out at 90–100° with 4–6 parts of fresh butyl alcohol for each extraction result in a substantially complete separation. Since the last traces of the solvent are not readily removed by exposure to air, a solution of the recrystallized material in a small quantity of water should be distilled until free of alcohol, and allowed to crystallize.
An entirely different method for preparing pure methylamine hydrochloride free of ammonium chloride has been described.[1] It is based on the fact that when a mixture of methylamine and ammonia reacts with an insufficient quantity of

hydrochloric acid the methylamine is preferentially neutralized and the ammonia left free.

5. The literature[2] claims a yield of methylamine hydrochloride amounting to 79 per cent of the weight of ammonium chloride used up in the reaction. This figure is probably based on the weight of crude methylamine hydrochloride and not of the recrystallized material.

6. Methylamine can be purified through its benzal derivative, which is distilled and then hydrolyzed by concentrated hydrochloric acid.[3] This method has been checked and found satisfactory by one of the editors.

3. Discussion

Methylamine can be prepared by the action of ammonia on methyl iodide,[4] methyl chloride,[5] dimethyl sulfate,[6] methyl *p*-toluenesulfonate[7] and methyl alcohol with a catalyst and at elevated temperatures;[8] by the action of bromine and alkali[9] and of bleaching powder[10] on acetamide; by the action of sodamide on methyl iodide;[11] by the reduction of chloropicrin,[12] hydrocyanic or ferrocyanic acid,[13] hexamethylenetetramine,[14] nitromethane,[15] methyl nitrite,[16] or formaldoxime;[17] from acetyl chloride and sodium azide;[18] and by the action of formaldehyde on ammonium chloride.[19]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

benzal derivative

chloropicrin

hydrocyanic or ferrocyanic acid

ethyl alcohol, alcohol (64-17-5)

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

Acetamide (60-35-5)

ammonia (7664-41-7)

methyl alcohol (67-56-1)

ammonium chloride (12125-02-9)

sodium hydroxide (1310-73-2)

formaldehyde (630-08-0)

acetyl chloride (75-36-5)

chloroform (67-66-3)

bromine (7726-95-6)

dimethyl sulfate (77-78-1)

methyl chloride (74-87-3)

butyl alcohol, n-butyl alcohol (71-36-3)

Methyl iodide (74-88-4)

Methylamine hydrochloride (593-51-1)

methylal (109-87-5)

methyl formate (107-31-3)

dimethylamine hydrochloride (506-59-2)

sodium formate

methylamine (74-89-5)

hexamethylenetetramine (100-97-0)

Nitromethane (75-52-5)

methyl nitrite (624-91-9)

sodium azide (26628-22-8)

sodamide (7782-92-5)

Methyl p-toluenesulfonate (80-48-8)

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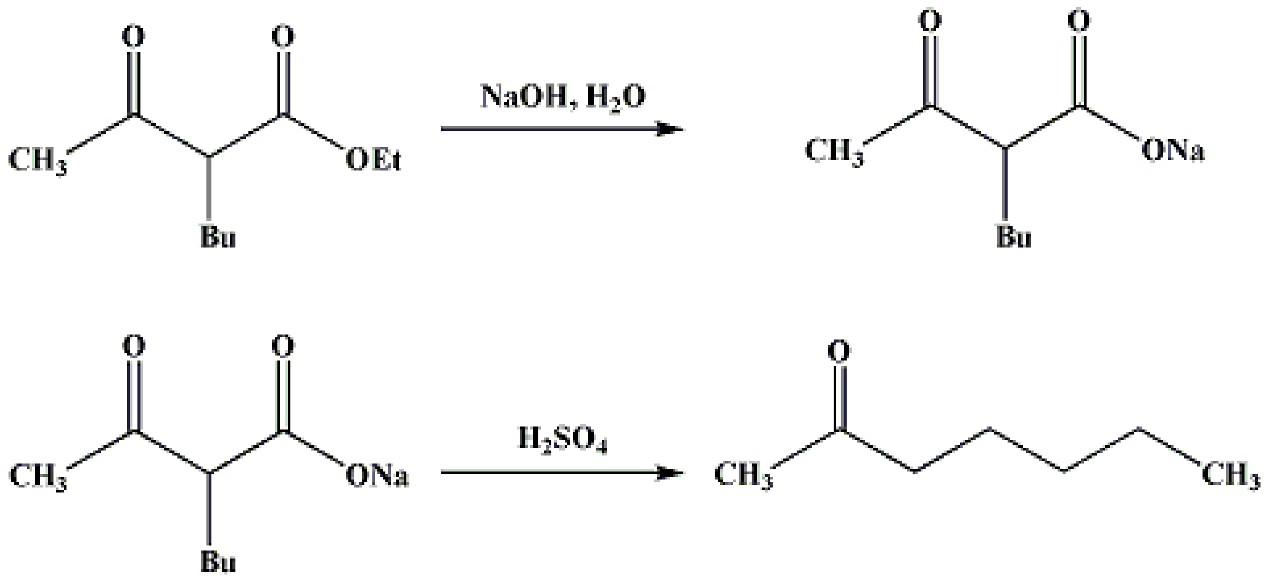
Organic Syntheses, CV 1, 351

METHYL *n*-AMYL KETONE

[2-Heptanone]



Submitted by John R. Johnson and F. D. Hager.
Checked by Frank C. Whitmore and W. F. Singleton.

1. Procedure

In a 12-l. round-bottomed flask, fitted with an efficient mechanical stirrer, is placed 5 l. of a 5 per cent solution of sodium hydroxide (6.25 moles). To this is added the crude ethyl *n*-butylacetoacetate (about 925 g.) obtained (p. 248) from 5 moles of ethyl acetoacetate. The mixture is stirred at room temperature for four hours, during which time the monosubstituted acetoacetic ester is completely saponified and passes into solution. The mixture is then allowed to stand until the unsaponified material separates completely as an oily layer. The aqueous layer is separated (Note 1) and transferred to a flask provided with a stopper fitted with a separatory funnel and a large bent glass tube leading to a condenser set for distillation.

Through the separatory funnel is added slowly 500 cc. of 50 per cent (sp. gr. 1.40) sulfuric acid (3.6 moles), which is somewhat more than the amount required to neutralize the alkali (6.25 moles) used in the saponification of the ester. When the evolution of carbon dioxide ceases to be vigorous, the reaction mixture is heated slowly to boiling, and from one-third to one-half of the total volume is distilled. The distillate is made alkaline with solid sodium hydroxide (Note 2) and redistilled until 80–90 per cent has been collected.

In the distillate the ketone layer is separated from the water, and the latter is distilled until one-third has been collected. The ketone layer in this distillate is separated, and the water layer is again distilled. This procedure is repeated as long as any considerable amount of ketone is obtained in the distillate (Note 3). The combined ketone fraction is

washed four times with one-third its volume of a concentrated solution of calcium chloride (sp. gr. 1.3 or greater) to remove alcohol (Note 4), then dried over 50 g. of solid calcium chloride, filtered, and distilled. The yield of methyl *n*-amyl ketone boiling at 148–151°/750 mm. is 300–350 g. (52–61 per cent of the theoretical amount, based upon the original ethyl acetoacetate) (Note 5).

2. Notes

1. The insoluble layer is usually quite small in amount and may be discarded. On distillation it yields but a small amount of ketone and monosubstituted ester, along with considerable high-boiling material, presumably the disubstituted ester, which was present in the crude ethyl *n*-butylacetoacetate.
2. The distillate is rendered alkaline to remove any acids formed by the acid decomposition of the substituted acetoacetic ester or unreacted ethyl acetoacetate.
3. With methyl *n*-amyl ketone this process was repeated three times after the first separation. In the case of higher ketones, fewer separations are required; with the simpler ketones a greater number is advisable, on account of their solubility in water.
4. With the lower-molecular-weight ketones it is advantageous to distil the calcium chloride solution to recover the dissolved ketone. This is carried out exactly as described for the separation from the water. With methyl *n*-amyl ketone the loss is slight if a sufficiently concentrated solution of calcium chloride is employed.
5. Other ketones may be prepared by the same general procedure. Based upon the ethyl acetoacetate used, the following yields were obtained:
Methyl *n*-butyl ketone (hexanone-2) b.p. 126–128°, 50 per cent.
Methyl *iso*-butyl ketone (4-methylpentanone-2) b.p. 115–119°, 20 per cent.
Methyl β-methylbutyl ketone (4-methylhexanone-2) b.p. 139–142°, 30 per cent.
The lower yields are due in some cases to the difficulty of isolating the products, and, in the last two, to the less complete reaction between the secondary alkyl bromide and the sodium derivative of ethyl acetoacetate.

3. Discussion

Methyl *n*-amyl ketone can be prepared by the hydration of heptine-1 and of heptine-2;[1] by heating *n*-amylpropiolic acid with potassium hydroxide;[2] by the oxidation of methyl-*n*-amylcarbinol;[3] and by the ketone decomposition of ethyl *n*-butylacetoacetate[4] which is adapted from that used by Michael and Wolgast[5] for ethyl ethylacetoacetate.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 248
- Org. Syn. Coll. Vol. 2, 317

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

monosubstituted acetoacetic ester

sodium derivative of ethyl acetoacetate

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

sodium hydroxide (1310-73-2)

carbon dioxide (124-38-9)

potassium hydroxide (1310-58-3)

Ethyl acetoacetate (141-97-9)

ETHYL n-BUTYLACETOACETATE (1540-29-0)

2-Heptanone, METHYL n-AMYL KETONE (110-43-0)

hexanone-2, Methyl n-butyl ketone (591-78-6)

4-methylpentanone-2, Methyl iso-butyl ketone (108-10-1)

Methyl β-methylbutyl ketone, 4-Methylhexanone-2

heptine-1 (628-71-7)

heptine-2

ethyl ethylacetoacetate (607-97-6)

methyl-n-amylcarbinol (543-49-7)

n-amylpropiolic acid (5663-96-7)

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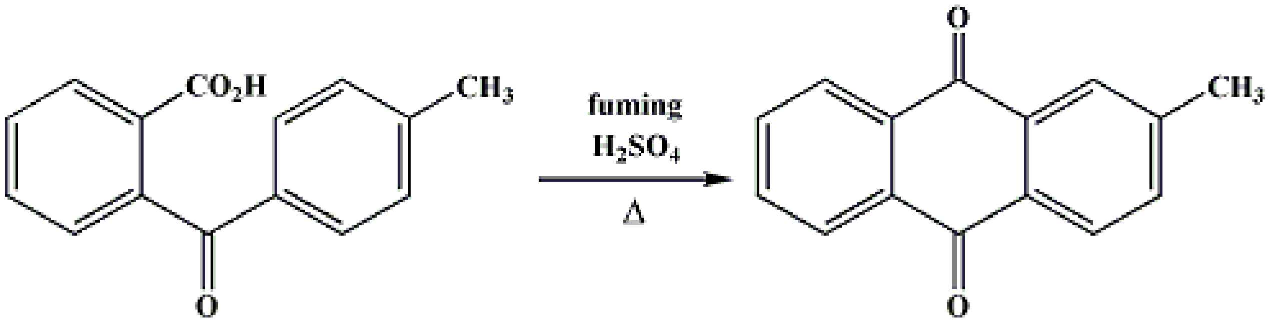
Organic Syntheses, *CV 1*, 353

β-METHYLANTHRAQUINONE

[Anthraquinone, 2-methyl-]



Submitted by L. F. Fieser
Checked by Roger Adams and R. L. Shriner.

1. Procedure

The *p*-toluyl-*o*-benzoic acid which is obtained from 100 g. of phthalic anhydride (p. 517), and which should weigh 157 g. (0.65 mole), is mixed with 1400 g. (725 cc.) of fuming sulfuric acid (20 per cent anhydride) (Note 1) in a 2-l. flask protected by a calcium chloride tube, and the mixture is heated on the steam bath for two hours with occasional shaking (Note 2). The clear, deep red solution is poured when cold upon cracked ice in a 4-l. beaker. The methyl anthraquinone separates and is digested for twenty minutes by passing in steam, after which it is filtered by suction. A flannel cloth is used in the filter, or a filtros plate may be cemented into a Büchner funnel with water-glass. The precipitate is washed well with hot water, after which it is returned to the beaker and digested as before with hot water to which is added a slight excess of ammonia, beyond that required to neutralize any acid present.

The product is filtered and dried to constant weight. The filtrate will be clear and will give no precipitate with hydrochloric acid if the conditions of condensation have been correct.

The β-methylanthraquinone is pale tan in color and weighs from 118 to 130 g. (81–90 per cent of the theoretical amount, based upon the weight of acid taken). It is practically pure, melting at 173°. Upon crystallization from alcohol in the presence of animal charcoal, it forms long, silken, almost colorless needles, melting constantly at 173.5° (176° corr.).

2. Notes

1. Some investigators have used concentrated instead of fuming sulfuric acid for the condensation, but the yield is usually low and the product is always colored bright yellow by some impurity which cannot be removed by crystallization.
2. The time allowed for condensation may be shortened to one-half, without affecting the yield, by maintaining the temperature at 125–130°.

3. Discussion

β-Methylanthraquinone can be prepared by the oxidation of β-methylanthracene[1] and material of the same origin, obtained by the benzene-extraction of crude commercial anthraquinone;[2] from the intramolecular condensation of *p*-toluyl-*o*-benzoic acid;[3] and from *o*-carbomethoxybenzoyl chloride and toluene.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 517

References and Notes

1. Fischer, Ber. **8**, 675 (1875); J. prakt. Chem. (2) **79**, 560 (1909); Fischer and Gross, J. prakt. Chem. (2) **82**, 232 (1910); Fischer, Falco, and Gross, ibid. (2) **83**, 210 (1911); Lavaux, Ann. chim. phys. (8) **20**, 445 (1910); I. G. Farbenind. A.-G., Brit. pat. 253,911 and Swiss pat. 124,266 [Chem. Zentr. II, 1820 (1928)].
2. Perkin and Cope, J. Chem. Soc. **65**, 843 (1894); Wachendorff and Zincke, Ber. **10**, 1485 (1877); Börnstein, Ber. **15**, 1820 (1882); Römer and Link, Ber. **16**, 696 (1883).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

p-Toluyl-o-benzoic acid

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

phthalic anhydride (85-44-9)

Anthraquinone (84-65-1)

toluene (108-88-3)

β-Methylanthraquinone, Anthraquinone, 2-methyl- (84-54-8)

methyl anthraquinone

β-methylanthracene (613-12-7)

o-carbomethoxybenzoyl chloride

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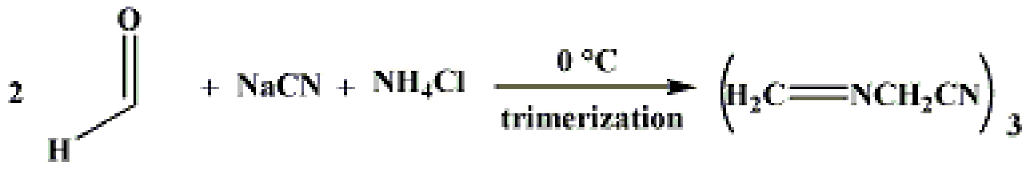
Organic Syntheses, CV 1, 355

METHYLENEAMINOACETONITRILE

[α-Hydroformamine cyanide]



Submitted by Roger Adams and W. D. Langley.
Checked by H. T. Clarke and E. R. Taylor.

1. Procedure

In a 5-l. round-bottomed flask, fitted with a mechanical stirrer and surrounded by an ice-salt bath, are placed 1620 g. (1.5 l., 18.9 moles) of technical formaldehyde (sp. gr. 1.078/20°) (Note 1) and 540 g. (10 moles) of ammonium chloride. A thermometer is placed in the liquid, which is cooled to 0°. This temperature is maintained throughout the entire reaction (Note 2). Stirring is commenced (Note 3), and a solution of 490 g. (9.8 moles) of 98 per cent sodium cyanide in 850 cc. of water is dropped into the mixture of ammonium chloride and formaldehyde at such a rate (about 90 drops per minute) that at least six hours will be required for this addition.

When one-half the sodium cyanide solution has been added, all the ammonium chloride will be in solution. At this point, the addition of 380 cc. of glacial acetic acid is started at such a rate (2–2.5 cc. per minute) that the addition of both the acid and the remainder of the sodium cyanide solution will be completed at the same time. The methyleneaminoacetonitrile begins to separate in white crystals shortly after the addition of the glacial acetic acid has commenced. After all the sodium cyanide solution and acetic acid have been added, the mixture is stirred for one and one-half hours longer; then the precipitate is filtered off, transferred to a beaker, and stirred with 1.5 l. of water. The product is filtered with suction, washed with 500 cc. of water (Note 4), and dried on filter paper. The yield is 410–475 g. (61–71 per cent of the theoretical amount) of a product melting at 129° (Note 5), (Note 6), and (Note 7).

2. Notes

1. The formalin should contain no suspended paraformaldehyde. An aqueous formaldehyde solution of specific gravity 1.078/20° contains 35 per cent formaldehyde by weight. As pointed out in Note 1, p. 378, however, technical formalin contains methanol, and the formaldehyde content of technical formalin is greater than that calculated from the specific gravity of methanol-free formaldehyde solutions. Accordingly, the figure 18.9 moles for the amount of formaldehyde present is too low. The exact amount of formaldehyde present

cannot be given, but formaldehyde in excess is used and the percentage yield is based on the sodium cyanide.

2. During the reaction, the temperature should be kept as near 0° as possible and should never rise above 5°. If the temperature goes higher, a heavy oil is sometimes obtained instead of the crystalline product. It is not difficult to maintain the low temperature when the formaldehyde and ammonium chloride are cooled to 0° before any of the sodium cyanide is added.

3. In order to obtain good yields, the stirring must be vigorous throughout the entire reaction.

4. With careful washing, 500 cc. of cold water should be sufficient to remove all chlorides.

5. For most purposes, the product is pure enough as it is obtained from the reaction mixture, but it may be crystallized from water. This recrystallization, however, is attended with considerable loss.

6. It is suggested that like yields may be obtained by the following modifications: Instead of chilling the formaldehyde-ammonium chloride mixture from the outside, ice is added during the addition of the sodium cyanide to keep the temperature down, and the first half of the sodium cyanide is added during fifteen to twenty minutes. The remainder of the sodium cyanide and the acetic acid are added during thirty to forty-five minutes, the temperature being kept below 5° throughout by means of cracked ice. The slight solubility of methyleneaminoacetonitrile in the liquor makes a larger final volume of no particular disadvantage (W. W. Hartman, private communication).

7. If a less pure product in lower yield is satisfactory the following procedure, which effects a considerable saving in time, may be used. The mixture of formaldehyde and ammonium chloride is cooled by the addition of crushed ice or solid carbon dioxide, and the acetic acid is added rapidly. Then, the temperature being maintained below 20° by adding ice or solid carbon dioxide, the sodium cyanide solution is added from a dropping funnel over a period of fifteen to twenty minutes. Stirring is continued for fifteen minutes after the cyanide has been added; then the product is filtered. The yield is 200–267 g. (45–55 per cent of the theoretical amount) of a product melting at 126–128°. (Lawrence H. Amundsen and Ruth Velitzkin, private communication.[1])

3. Discussion

Methyleneaminoacetonitrile can be prepared by the action of formaldehyde on a mixture of ammonium chloride, potassium cyanide, and acetic acid,[1] and by the action of formaldehyde on aminoacetonitrile.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 298
- Org. Syn. Coll. Vol. 2, 310

References and Notes

1. Jay and Curtius, Ber. **27**, 59 (1894); Klages, Ber. **36**, 1507 (1903); Curtius and Welde, Ber. **43**, 868 (1910); Johnson and Rinehart, J. Am. Chem. Soc. **46**, 768, 1653 (1924); Amundsen and Velitzkin, ibid. **61**, 212 (1939).
2. Klages, J. prakt. Chem. (2) **65**, 192 (1902).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

α-Hydroformamine cyanide

acetic acid (64-19-7)

methanol (67-56-1)

ammonium chloride (12125-02-9)

formaldehyde, formalin (630-08-0)

sodium cyanide (143-33-9)

cyanide (57-12-5)

carbon dioxide (124-38-9)

Methyleneaminoacetonitrile (109-82-0)

formaldehyde-ammonium chloride

ammonium chloride, potassium

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Organic Syntheses, CV 1, 357

METHYLENE BROMIDE

[Methane, dibromo-]

$$CHBr_3 + Na_3AsO_3 + NaOH \xrightarrow{\Delta} CH_2Br_2 + Na_3AsO_4 + NaBr$$

Submitted by W. W. Hartman and E. E. Dreger.
Checked by Frank C. Whitmore and C. J. Korpi.

1. Procedure

In a 2-l. round-bottomed flask placed on a steam bath and fitted with a stirrer, a separatory funnel, and a reflux condenser is placed 540 g. (1.9 moles) of commercial (88 per cent) bromoform (Note 1). There is then added 10 cc. of a solution of sodium arsenite made by dissolving 230 g. (1.16 moles) of c. p. arsenious oxide and 440 g. (11 moles) of sodium hydroxide in 1.4 l. of water. The mixture is warmed gently to start the reaction, and then the remainder of the sodium arsenite solution is added during about one hour at such a rate that the solution refluxes gently. When the addition is complete, the flask is heated for four hours on the steam bath. The reaction mixture is distilled with steam, the lower layer of methylene bromide separated, and the water layer extracted once with 100 cc. of ether (Note 2). The methylene bromide is dried with 10 g. of calcium chloride and distilled. The yield of slightly yellow liquid boiling at 97–100° is 290–300 g. (88–90 per cent of the theoretical amount).

2. Notes

1. The commercial bromoform used contained 12 per cent of alcohol. Its specific gravity was 2.59/25° as compared with 2.88/25° for pure bromoform.
2. The chief function of the extraction is to collect the fine droplets of methylene bromide which remain in the water layer.

3. Discussion

Methylene bromide can be prepared by the reaction of bromine with methylene iodide.[1] The procedure described is adapted from the preparation of methylene iodide given below, and a like method giving a lower yield has been described.[2]

References and Notes

1. Butlerow, Ann. **111**, 251 (1859).
2. Kocheshkov, J. Russ. Phys. Chem. Soc. **60**, 1191 (1928) [C. A. **23**, 2931 (1929)]; Ber. **61**, 1659 (1928).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

arsenious oxide

alcohol (64-17-5)

calcium chloride (10043-52-4)

ether (60-29-7)

sodium hydroxide (1310-73-2)

bromine (7726-95-6)

sodium arsenite

Methylene bromide, Methane, dibromo- (74-95-3)

bromoform (75-25-2)

Methylene iodide (75-11-6)

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Organic Syntheses, CV 1, 358

METHYLENE IODIDE

[Methane, diiodo-]

$$CHI_3 + Na_3AsO_3 + NaOH \xrightarrow{65\ ^\circ C} CH_2I_2 + NaI + Na_3AsO_4$$

Submitted by Roger Adams and C. S. Marvel.
Checked by H. T. Clarke and Katharine Ogden.

1. Procedure

One kilogram (2.5 moles) of iodoform (Note 1) is placed in a 5-l. round-bottomed flask fitted with a rubber stopper holding a mechanical stirrer (Note 2), a reflux condenser, a separatory funnel, and a thermometer with bulb immersed in the liquid. To this is added 500 cc. of the sodium arsenite solution [prepared from 274 g. (1.38 moles) of c. p. arsenious oxide, 532 g. (13.3 moles) of sodium hydroxide, and 2600 cc. of water] (Note 3). Stirring is started, and heat is applied until the temperature of the thermometer reaches 60–65°, where it is held constant during the whole reaction (Note 4). If the temperature is allowed to go much higher, especially at the beginning of the experiment, the reaction becomes too vigorous, and at the same time a little methyl iodide is formed. The remainder of the sodium arsenite solution is added gradually during the course of one-half hour. The whole mixture is then kept one hour at 60–65° to make sure that the reaction is completed.

The reaction mixture is allowed to cool somewhat (to about 40°) and is filtered with suction in order to remove the mechanical impurities which have come from the technical arsenious oxide and sodium hydroxide. The filtrate consists of a clear water solution with a pale yellow oil underneath. It is better not to allow the reaction mixture to cool completely before filtering or else a precipitate of sodium arsenate will gradually separate and this will tend to make an emulsion of the methylene iodide and hinder filtration and separation. The methylene iodide is now separated from the filtrate, dried with a little calcium chloride, and then distilled under reduced pressure. Practically all of it (Note 5) comes over as a light straw-colored oil between 106° and 107°/70 mm. (Note 6), the bath being kept at 130–135°. The yield of crude product is 610–660 g. (90–97 per cent of the theoretical amount). On redistillation not more than 10–20 g. is lost. The crude product is quite satisfactory for most purposes.

2. Notes

1. Experiments were made on 100-g. lots of iodoform, using varying amounts (between 1 mole and 2 moles) of sodium arsenite. The yield is, in general, best when only a very slight excess over 1 mole of arsenious oxide is used. In every case the amount of sodium hydroxide employed was that called for by the theory.

In making methylene iodide from 100-g. or even 200-g. lots of iodoform, the sodium arsenite solution may be added all at once. When the runs become larger, however, it is inadvisable to do this, and directions similar to those described above in running 1 kg. of iodoform must be used.

2. Mechanical stirring is quite necessary in order to get the best yields in the shortest time.

3. The dilution of the solution makes very little difference, the yields remaining about the same. It is, therefore, better to use as concentrated a solution as possible so that large runs may be made in a comparatively small apparatus. A more concentrated solution, however, than the one advised above is not satisfactory, since too much sodium arsenate tends to separate out during the cooling after the methylene iodide has formed and causes some trouble in the purification. If sodium arsenate does separate, the methylene iodide is obtained either by distilling with steam, or by diluting and boiling to dissolve the crystals, this last to be followed by filtering and separating.

4. If the reaction is carried out at refluxing temperature instead of at 60–65°, the yield of product is diminished by 5–10 per cent, the formation of a little methyl iodide accounting for the loss.

5. After distillation under reduced pressure, a residue of 1 to 2 g. is left in the flask. When air is admitted to the flask, a single flash of light sometimes occurs. In one case, the thermometer and stopper were even blown out of the flask. The cause was not determined.

6. The methylene iodide obtained after distillation under reduced pressure melts at 6°.

3. Discussion

Methylene iodide can be prepared by the action of iodine,[1] sodium ethoxide,[2] hydriodic acid,[3] and sodium arsenite[4] on iodoform. This last method is very simple, and several pounds of pure methylene iodide may be prepared in a few hours. It can also be prepared from methylene chloride and potassium iodide,[5] and in an excellent yield by the oxidation of iodoacetic acid by potassium persulfate.[6]

References and Notes

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2. Butlerow, Ann. chim. phys. (3) **53**, 313 (1858).
3. Lieben, Z. Chem. 712 (1868).
4. Auger, Compt. rend. **145**, 810 (1907); **146**, 1282 (1908); Gutmann, Ber. **52**, 212 (1919).
5. Perkin and Scarborough, J. Chem. Soc. **119**, 1400 (1921).
6. Panopoulos and Petzetakis, Chem. Ztg. **54**, 310 (1930).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

arsenious oxide

calcium chloride (10043-52-4)

sodium hydroxide (1310-73-2)

potassium iodide (7681-11-0)

sodium arsenite

sodium ethoxide (141-52-6)

hydriodic acid (10034-85-2)

Methyl iodide (74-88-4)

Methylene iodide, Methane, diiodo- (75-11-6)

iodoform (75-47-8)

sodium arsenate

methylene chloride (75-09-2)

iodoacetic acid (64-69-7)

potassium persulfate (7727-21-1)

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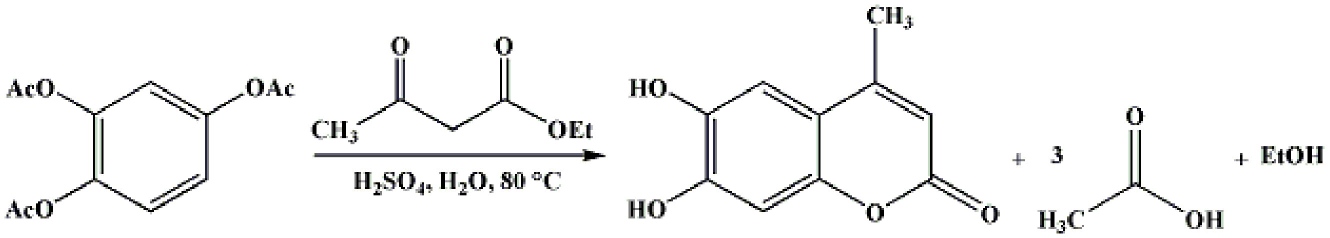
Organic Syntheses, CV 1, 360

4-METHYLESCULETIN

[Esculetin, 4-methyl-]



Submitted by E. B. Vliet
Checked by Roger Adams and E. E. Dreger.

1. Procedure

A smooth, uniform paste is made by thoroughly mixing 60 g. (0.45 mole) of ethyl acetoacetate (p. 235) (Note 1) and 114 g. (0.45 mole) of hydroxyhydroquinone triacetate (p. 317). This requires several minutes of stirring. To this mixture is added 450 cc. of 75 per cent sulfuric acid (Note 2). The paste slowly dissolves with the evolution of heat, giving a deep red solution; the latter is heated on a warm bath with occasional stirring until it reaches 80°, at which temperature it is maintained for one-half hour. It is then allowed to cool to room temperature and poured into 1850 cc. of cold water. The resulting mixture is cooled to room temperature, filtered with suction, and the precipitate washed with cold water to free it from excess acid. The 4-methylesculetin thus obtained is dried at 100° and is generally gray in color. The yield is about 80 g. (92 per cent of the theoretical amount).

A pure product may be obtained by dissolving, with the aid of heat and stirring, 100 g. of 4-methylesculetin in a solution of 200 g. of borax in 700 cc. of water. The solution obtained is filtered while hot and then cooled, whereupon the esculetin borate separates (Note 3). This is filtered off and dissolved in 1800 cc. of water, and the solution thus obtained added to 50 g. (27.2 cc.) of concentrated sulfuric acid in 500 cc. of water. 4-Methylesculetin separates and, after the mixture has been cooled, is filtered, washed, and dried. From 100 g. of the crude material, 85 g. of pure product melting at 272–274° (uncorr.) is obtained. This is generally nearly colorless but occasionally possesses a slight grayish tinge.

2. Notes

1. In order to obtain a fairly pure product without recrystallization, the intermediate ethyl acetoacetate and hydroxyhydroquinone triacetate must be pure.
2. It is important to use 75 per cent sulfuric acid in this reaction, because more concentrated acid gives a very dark product and a lower yield, while more dilute acid will not induce the reaction.
3. The exact nature of the precipitate has not been determined.

3. Discussion

4-Methylesculetin can be prepared by condensing hydroxyhydroquinone triacetate and ethyl acetoacetate with sulfuric acid or zinc chloride.[1]

References and Notes

1. v. Pechmann and v. Krafft, Ber. **34**, 423 (1901); Bargellini and Martegiani, Gazz. chim. ital. **41** (2), 613 (1911).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

zinc chloride (7646-85-7)

Ethyl acetoacetate (141-97-9)

Hydroxyhydroquinone triacetate (613-03-6)

4-Methylesculetin, Esculetin, 4-methyl- (529-84-0)

esculetin borate

borax (1303-96-4)

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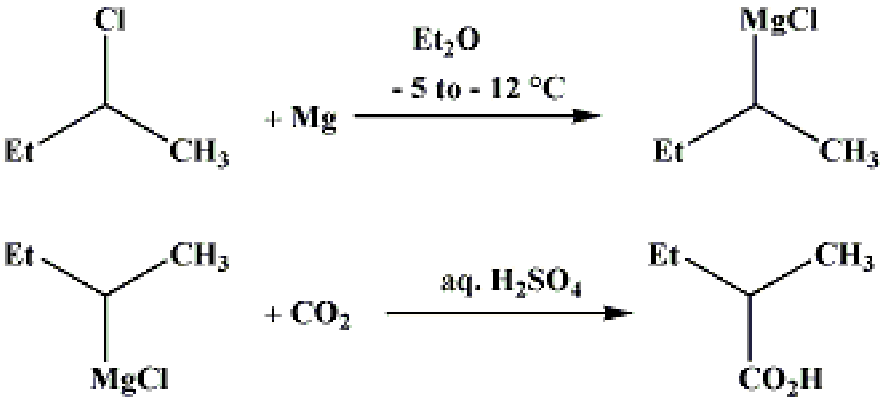
Organic Syntheses, *CV 1*, *361*

dl-METHYLETHYLACETIC ACID

[Butyric acid, α-methyl-]



Submitted by Henry Gilman and R. H. Kirby.
Checked by H. T. Clarke and L. L. Engel.

1. Procedure

In a 1-l. three-necked flask, fitted with a mechanical stirrer, condenser, and 500-cc. separatory funnel, is placed 13.4 g. (0.55 atom) of magnesium shavings (Note 1). The shavings are then covered with 50 cc. of anhydrous ether. A crystal or two of iodine and 3 g. of *sec*.-butyl chloride (Note 2) are added. The reaction is started by warming the flask with a microburner and is then allowed to proceed by its own heat for twenty minutes. A second addition of 50 cc. of anhydrous ether is made. A solution of 43 g. (the remainder of 0.5 mole) of *sec*.-butyl chloride in 300 cc. anhydrous ether is added over a period of twenty minutes. Vigorous refluxing is avoided by externally cooling the flask with water. The heat from the reaction causes refluxing to continue for twenty minutes after the addition of the halide solution. The reaction mixture is then gently refluxed for one hour with a microburner. The reaction flask is surrounded by an ice and salt mixture and the solution cooled to – 12° in an atmosphere of nitrogen (Note 3). The nitrogen gas, obtained directly from a cylinder, is dried by passing through two wash bottles containing concentrated sulfuric acid and a phosphorus pentoxide tower. It is admitted to the flask through an entry tube 10 mm. in diameter at a height of about 60 mm. above the surface of the ether solution. An additional 100 cc. of ether is added, and the separatory funnel is replaced by a thermometer.

The cylinder of nitrogen is then replaced by a cylinder of carbon dioxide. The gas after passing through the drying train enters the reaction flask through the entry tube (Note 4). The rate of flow is regulated so that the temperature of the reaction mixture does not rise above – 5° when rapid stirring is in progress. After one and one-half hours (Note 5) the temperature drops to – 12° and does not rise on increasing the rate of flow of carbon dioxide. The drop in temperature is taken as an end-point for the carbonation.

The reaction mixture is then hydrolyzed in the flask with about 500 cc. of 25 per cent sulfuric acid (Note 6). Cooling the solution with ice and water permits of rapid hydrolysis without danger of loss of material through too vigorous refluxing. The mixture is transferred to a 1-l. separatory funnel and the ether layer separated. The water layer is extracted with three 50-cc. portions of ether. The combined ether extracts are washed with about 150 cc. of 25 per cent sodium hydroxide solution until all the organic acid is converted to the salt and thus removed (Note 7) and (Note 8).

The alkaline extract is boiled in a distillation apparatus, to remove ether and other volatile impurities, until its volume is decreased by 10 per cent. It is then acidified with concentrated hydrochloric acid and the acid layer separated. The water layer is then distilled from a 1-l. flask until no more oily acid comes over (Note 9). The distillate is saturated with salt and the acid layer separated. This water layer, together with the low-boiling fraction from the acid distillation, is distilled, and the distillate salted out as before.

The combined acid layers are distilled from a 75-cc. flask connected to an air condenser. The product is collected at 173–174°. The yield of acid is 39–44 g. (76–86 per cent of the theoretical amount based on the quantity of *sec.*-butyl chloride used) (Note 10).

2. Notes

1. The magnesium shavings must circulate freely through the solution when stirred. Shavings having a width of 5.6 mm., a thickness of 0.36 mm., and a length of 3 to 16 mm. are satisfactory for this purpose.
2. If the *sec*.-butyl chloride is of a good commercial quality it need not be redistilled.
3. The preliminary sweeping with dry nitrogen was used in order to avoid decomposition of the Grignard reagent by the air which is drawn in when the flask and contents are cooled. This procedure may be omitted in some cases because the decrease in yield when nitrogen is not used is only about 3 per cent.
4. Both the nitrogen and carbon dioxide are admitted to the flask through the same entry tube. Troublesome clogging of the tube is avoided by having it above the solution instead of immersed in it.
5. The checkers found it necessary to admit carbon dioxide for two and one-half hours before the noted temperature drop was observed.
6. The reaction product solidifies if it is allowed to stand too long in the reaction flask, thus causing difficulty with the hydrolysis. Time will be saved if the acid is added immediately after the addition of the carbon dioxide is completed. A rather concentrated acid solution is used in order to keep the volume of the water layer as small as possible. For this reason, 250 cc. of 50 per cent sulfuric acid (by weight) might be used in place of the more dilute solution.
7. The products of the reaction cannot be separated smoothly by fractional distillation prior to the extraction with alkali.
8. Considerable heat is evolved in the neutralization of the acid with the sodium

hydroxide. The extraction can be effected in less time and without loss if the solution is cooled by the direct addition of ice. Two extractions were used, one with 100 cc. and one with 50 cc. of 25 per cent alkali. It is convenient to test the extracts with phenolphthalein to determine when all the acid has been removed.

9. The methylethylacetic acid may also be obtained by extraction of the acidified solution with ether. This method is not recommended, as small amounts of alcohol, which are invariably present in this solvent, contaminate the product by the formation of ethyl ester.

10. By the same general method, *n*-butyl chloride gives *n*-valeric acid in a 72–73 per cent yield, bromobenzene gives benzoic acid in an 80–85 per cent yield, and cyclohexyl chloride gives cyclohexane-carboxylic acid in an 85 per cent yield.[1]

3. Discussion

dl-Methylethylacetic acid can be prepared from methylethyl-malonic ester, by hydrolysis and subsequent heating of the methylethylmalonic acid;[2] from methylethylacetoacetic ester;[3] and by the oxidation of the corresponding alcohol or aldehyde.[4] The procedure described is preferred to that which starts with *sec*.-butyl bromide[5] because of the higher yield of acid and the lesser cost of *sec*.-butyl chloride.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 524
- Org. Syn. Coll. Vol. 2, 425
- Org. Syn. Coll. Vol. 3, 541
- Org. Syn. Coll. Vol. 8, 507

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1. Gilman and Zoellner, J. Am. Chem. Soc. **53**, 1945 (1931).
2. Auwers, Ann. **298**, 167 (1897).
3. Saur, Ann. **188**, 257 (1877).
4. Lieben and Zeisel, Monatsh. **7**, 56 (1886).
5. Gilman and Parker, Org. Syn. **5**, 75. Marvel, Blomquist, and Vaughn, J. Am. Chem. Soc. **50**, 2810 (1928).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alkali

methylethyl-malonic ester

methylethylacetoacetic ester

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium hydroxide (1310-73-2)

magnesium shavings (7439-95-4)

sec.-BUTYL BROMIDE (78-76-2)

nitrogen (7727-37-9)

Benzoic acid (65-85-0)

carbon dioxide (124-38-9)

iodine (7553-56-2)

bromobenzene (108-86-1)

n-BUTYL CHLORIDE (109-69-3)

cyclohexyl chloride (542-18-7)

Butyric acid, α-methyl-, methylethylacetic acid, DL-Methylethylacetic acid (600-07-7)

phenolphthalein (77-09-8)

cyclohexane-carboxylic acid (98-89-5)

methylethylmalonic acid

phosphorus pentoxide (1314-56-3)

n-valeric acid (109-52-4)

sec.-butyl chloride (78-86-4)

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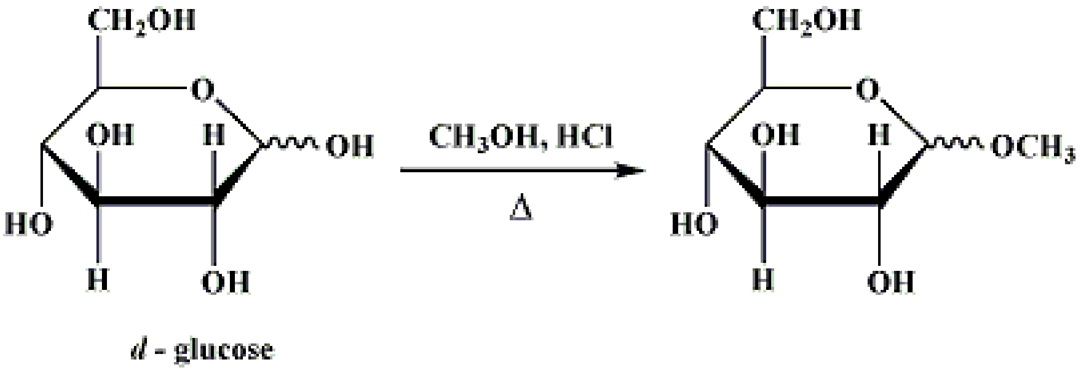
α-METHYL *d*-GLUCOSIDE

[Glucoside, α-methyl-, *d*-]



Submitted by B. Helferich and W. Schäfer.
Checked by H. T. Clarke and M. R. Brethen.

1. Procedure

Dry hydrogen chloride (p. 293), is passed into 200 g. (251 cc., 6.2 moles) of anhydrous methyl alcohol (Note 1), with ice cooling and exclusion of moisture, until the increase in weight amounts to 5 g. This solution is then diluted with 1800 g. of methyl alcohol, a 0.25 per cent solution of hydrogen chloride being thus obtained. To this is added 500 g. (2.77 moles) of finely powdered anhydrous *d*-glucose (Note 2), and the mixture boiled under reflux for seventy-two hours, a clear solution being obtained after the first fifteen minutes' boiling. It is well to attach a soda-lime tube to the upper end of the condenser, in order to exclude moisture. The clear pale yellow solution is cooled to 0°, and crystallization induced by scratching or by inoculation with a trace of α-methyl *d*-glucoside. After twelve hours at 0° the first crop is filtered by suction and washed twice with 100-cc. portions of cold methyl alcohol. The yield is 85–120 g. of a product melting at 165°.

The mother liquor and washings are returned to the flask and again boiled for seventy-two hours under reflux. The liquid is concentrated to 800 cc. and again chilled to 0°, inoculated, and allowed to stand at 0° for twenty-four hours. The second crop of glucoside so obtained is filtered by suction and washed with three 100-cc. portions of cold methyl alcohol. This yield is 110–145 g., melting at 164–165°. The mother liquor and washings are combined and concentrated to about 300 cc., chilled to 0°, and again inoculated and allowed to stand for twenty-four hours. The resulting mush of crystals is diluted with twice its weight of absolute methyl alcohol, and, after standing twenty-four hours at 0°, the third crop of glucoside is filtered (Note 3). This is recrystallized from 2.5 parts of methyl alcohol. The yield is 30–36 g., melting at 164–165°.

The total yield amounts to 260–266 g. (48.5–49.5 per cent of the theoretical amount). The product is contaminated by slight traces of *d*-glucose and possesses a very faint

reducing power towards Fehling's solution. For complete purification it is recrystallized (with practically no loss and practically no change in melting point) from five parts of methyl alcohol with the use, if necessary, of decolorizing carbon.

2. Notes

1. All the methyl alcohol used in this preparation must be anhydrous and free of acetone.
2. Slight impurities in the *d*-glucose are apt strongly to color the reaction mixture but do not materially affect the yield.
3. The final mother liquor, on long standing, deposits a further crop (about 6 g.) of crystals which melt at 94–96° and consist largely of β-methyl glucoside. A further quantity of the α-glucoside may be obtained by distilling all the methyl alcohol and boiling the residue with methyl alcoholic hydrogen chloride; it is questionable, however, whether the yield repays the time spent on the operation.

3. Discussion

α-Methyl *d*-glucoside can be prepared by heating glucose with an alcoholic solution of hydrochloric acid,[1] and biochemically from glucose, methyl alcohol and water.[2] The procedure described is based on that of Fischer,[1] with simplifications due to Bourquelot;[1] and good yields have been reported with 3 per cent hydrochloric acid with a shorter period of refluxing.[3]

References and Notes

1. Fischer, Ber. **28**, 1151 (1895); Bourquelot, Ann. chim. (9) **3**, 298 (1915); Zemplen and Tulok; Abderhalden, "Biochemisches Handlexikon," **10**, 770 (1923) (unpublished observation); Patterson and Robertson, J. Chem. Soc. 300 (1929).
2. Bourquelot, Hérissey and Bridel, Compt. rend. **156**, 491 (1913); Aubry, J. pharm. chim. (7) **10**, 202 (1914).
3. Patterson and Robertson, J. Chem. Soc. 300 (1929).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

β-methyl glucoside

α-METHYL d-GLUCOSIDE

Glucoside, α-methyl-, d-

hydrogen chloride, hydrochloric acid (7647-01-0)

methyl alcohol (67-56-1)

acetone (67-64-1)

decolorizing carbon (7782-42-5)

glucose, d-Glucose (492-62-6)

glucoside

α-glucoside (492-62-6)

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Organic Syntheses, CV 1, 366

METHYL-*n*-HEXYLCARBINOL

[2-Octanol]

Submitted by Roger Adams and C. S. Marvel.
Checked by Oliver Kamm and W. S. Marloth.

1. Procedure

For the most satisfactory preparation of methylhexylcarbinol from castor oil, in moderately large-sized runs, a copper vessel should be used (*B*). Since such a vessel is often not available in the average laboratory, directions are also included using an ordinary can (*A*), although in such cases the yields are much lower, and relatively smaller quantities of materials are used.

(*A*) *Preparation in Tin Vessel*.—In a large dish pan, 1900 g. (6.4 moles) of No. AAA castor oil (Note 1) is treated with occasional stirring with a solution of 500 g. (12.5 moles) of sodium hydroxide in 300 cc. of water. A reaction takes place, some heat is developed, and within ten or fifteen minutes a very hard solid soap is produced. This soap is broken up into small pieces and placed in a 3-gallon (12-l.) can (Note 2). In this preparation, a petroleum ether can was used, but any kind available would be just as satisfactory. The container is now fitted with an efficient reflux condenser, and it is then heated over a ring burner as long as hydrogen is evolved. The heating is regulated to produce a fairly rapid evolution of gas as shown by leading a tube from the top of the condenser into a small beaker of water. The time required for the complete evolution of the hydrogen is about nine to ten hours.

If the above reaction is not completed at one time and intermediate cooling is allowed, the reaction mixture sets to a solid mass and certain precautions *must* be taken before proceeding further. Either before heating is renewed the mass must be punched full of holes by means of an iron rod, or when the heating is started care must be taken to heat the upper part of the can first and gradually to approach the bottom. If the under part of the solid soap were heated directly, it would decompose before the upper part, and the hydrogen, being unable to escape, would cause the can to burst.

The condenser is now set downward for distillation and the heating is continued. If intermediate cooling is allowed, one of the precautions mentioned above must be observed before starting the distillation. The alcohol distils over with the water and is separated from time to time, the water being returned to the distillation can by means of a separatory funnel inserted through a rubber stopper in the top of the can. The addition of this water must be very slow in order to prevent foaming (Note 3). The heating should be regulated so that the distillate is coming over in rapid drops, not in a stream. If desired, the same sort of gravity separator described below under the large-sized experiment (*B*) may be used in this small run. About twelve hours are required for this distillation (Note 4). Toward the end, high-boiling products are obtained and considerable gas is liberated. Difficulty is almost always encountered during this part of the preparation because the long heating causes the solder in the bottom edge of the can to melt and leaks thus develop which allow a certain amount of soap to run out. The distillation need not be stopped, because the soap fills the holes, but under these conditions the temperature cannot be maintained at a point high

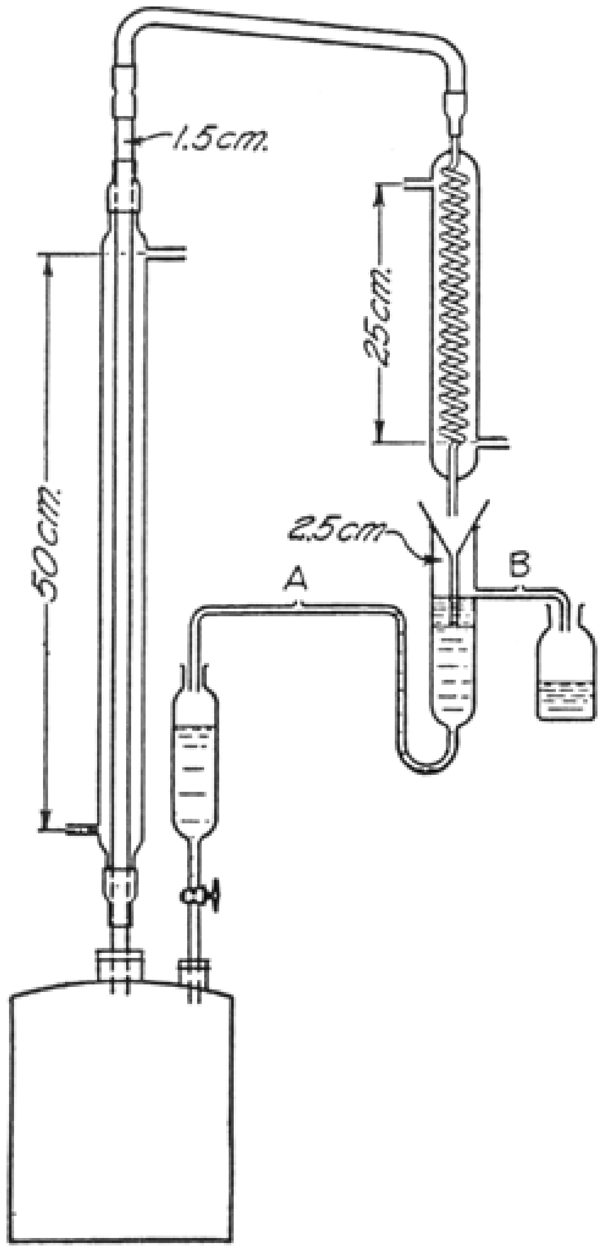
enough for the complete distillation without material loss from increased leakage. The upper layer of crude alcohol is separated from the water and fractionated. The portion boiling from 100–120° is chiefly water with a little alcohol in it. The second fraction between 120° and 175° contains a considerable quantity of ketones along with the alcohol (Note 4). The main portion distilling between 175° and 185° is the methylhexylcarbinol. Upon refractionation, 190–200 g. (23–25 per cent of the theoretical amount) of alcohol boiling at 175–180° is obtained.

This product is satisfactory for most purposes. If, however, a very pure product is desired, this may be made by shaking carefully the alcohol with 15 per cent sodium bisulfite solution, separating the alcohol, and steam distilling it from alkaline solution. The alcohol is finally distilled, and the fraction boiling at 177–179° is collected. If saturated sodium bisulfite is employed, a crystalline material which contains alcohol is formed and causes difficulty in the separation (Note 5).

Two runs of 6 kg. of castor oil with the same relative proportions of alkali and water were made in 8-gallon (30-l.) cans. The yields of pure alcohol were 650 g. and 730 g. (25.8 per cent and 29 per cent, respectively, of the theoretical amount on the basis of pure ester).

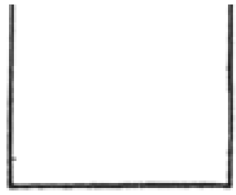
(*B*) *Preparation in Copper Vessel*.—To the cover of a 12-gallon (45-l.) copper kettle (Note 6) is fitted an apparatus to which a continuous separator may be attached (see Fig. 20).

Fig. 20.



This apparatus consists of an upright water condenser through the jacket of which steam is passed; a connecting tube leads from the top of this condenser to a second spiral condenser the bottom of which extends into a gravity separator. This allows the alcohol to run off into a receiver and the heavier aqueous layer to return through a separatory funnel to the copper kettle. A few essential points in the apparatus should be indicated: it is necessary that the return arm of the gravity separator be below the tube through which the alcohol flows into the receiver; the lower end of the funnel must be below the return side arm in order to prevent water being carried along with the methylhexylcarbinol; the capillaries A and B are necessary to prevent siphoning in the respective tubes.

A soap is made as already described (*A*) from 11.2 kg. (37.6 moles) of No. AAA castor oil (Note 1) and 2900 g. (73 moles of sodium hydroxide in 5800 g. of water (Note 7). This is broken up, placed in the kettle, and gradually heated. Much gas is evolved, and care should be taken not to lose alcohol, particularly at the beginning. The separator is not adjusted and the stopcock of the separatory funnel is kept closed until about 3 l. of distillate is collected; any small amount of alcohol is separated and the water discarded (Note 7). The separator is



now put in place to return the water to the kettle. The separatory funnel is allowed to fill with liquid and then the stopcock regulated so that the liquid flows back to the copper vessel as fast as it distils over. A return tube similar to the one illustrated in Fig. 22, p. 422, may be used, but in making methylhexylcarbinol the separatory funnel has the advantage that, if foaming occurs in the reaction flask, further addition of water can be immediately and easily stopped (Note 3).

The distillation is continued until no more alcohol comes over, a process which requires forty-eight to seventy-two hours of continuous heating. Superheating must be avoided, since foaming will then occur and may cause considerable difficulty. It is therefore advisable to adjust the heating so that the distillate comes over in rapid drops but not in a stream. If cooling is allowed to take place before the distillation is complete, it is advisable to break up the reaction cake before heating again, or to start the heating at the top of the cake and to approach the bottom gradually (Note 8). The crude product obtained is very much lighter in color than that produced when cans are used (*A*), and when it is distilled only very small fractions of low- or high-boiling material result. Moreover, the amount of ketones is small. The yields of the redistilled fraction boiling at 175–180° in three successive experiments were 1854 g., 1955 g., and 1894 g. (40–42 per cent of the theoretical amount), quantities about twice those obtained when cans are used (*A*). The time that one actually devotes to the production of methylhexylcarbinol is not great, but the total time necessary for carrying out a large experiment is almost a week.

2. Notes

1. The best grade of castor oil gives much better results than the poorer grades.
2. The container which is used in the production of methylhexylcarbinol should not be filled more than one-half with the reaction mixture, since foaming occurs to a considerable extent during the heating.
3. Upon adding to the reaction mixture the water which distils over with the alcohol, the special precaution must be taken of making the addition slowly or else the contact of the cold liquid with the hot reaction mass causes very bad foaming. If the distillation is too rapid, superheating occurs, and excessive foaming is liable to take place.
4. It is probable that stirring during the decomposition of the soap would increase the speed of the reaction and decrease the by-products.
5. It is suggested that the methylhexylcarbinol be purified as follows: The 190–200 g. of material boiling at 175–180° and 20 g. of phenylhydrazine are warmed on the steam bath for one hour and then steam distilled; the upper oily layer in the distillate is first washed with dilute hydrochloric acid, and then stirred and refluxed with 20 g. of stannous chloride and 35 cc. of hydrochloric acid for about one hour. During this time the material becomes very dark in color. The cooled oily layer is washed once with water, steam distilled, the distillate washed with water and dilute potassium carbonate, and finally distilled under reduced pressure after drying over potassium carbonate (W. W. Hartman, private communication).
6. It is worthy of special note that the yield is much larger when the reaction is carried out in a copper vessel that is capable of being heated to a high temperature without leaking. An iron vessel cannot be substituted for copper. Several runs in iron gave about the same weight of crude product, but this always contained high and low fractions that did not appear when copper was used.
7. It will be noticed that 5800 g. of water is used in the large runs (*B*) and then 3000 g. is distilled off and discarded before the alcohol begins to come over rapidly. This quantity of water helps in the formation of the soap, but it is not absolutely necessary; only 2000 or 2500 g. may be used, under which conditions the alcohol begins to come over immediately

with the water.
8. After all the methylhexylcarbinol has been distilled from the reaction mixture, the residue in the copper vessel should not be allowed to cool directly, as a solid cake that will have to be chiseled out will be formed. After the heating is stopped, it is advisable to add water to the hot residue, very slowly at first, then, as the kettle cools, more rapidly. While still fairly hot, however, the mixture is poured into a crock and allowed to cool.

3. Discussion

Methylhexylcarbinol can be prepared by the action of methylmagnesium iodide on heptaldehyde,[1] but it is less expensively obtained in a state of purity satisfactory for most purposes by heating castor oil with sodium hydroxide.[12] This gives sodium ricinoleate which upon fusion with caustic soda yields methylhexylcarbinol.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 418

References and Notes

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2. Moschnin, Ann. **87**, 111 (1853); Bouis, Ann. **97**, 34 (1856); Schorlemmer, Ann. **147**, 222 (1868); Freund and Schönfeld, Ber. **24**, 3351 (1891).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

caustic soda

ketones

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

iron (7439-89-6)

Phenylhydrazine (100-63-0)

stannous chloride

sodium bisulfite (7631-90-5)

copper (7440-50-8)

methylmagnesium iodide (917-64-6)

2-Octanol, Methylhexylcarbinol, METHYL-n-HEXYLCARBINOL (123-96-6)

sodium ricinoleate (5323-95-5)

heptaldehyde (111-71-7)

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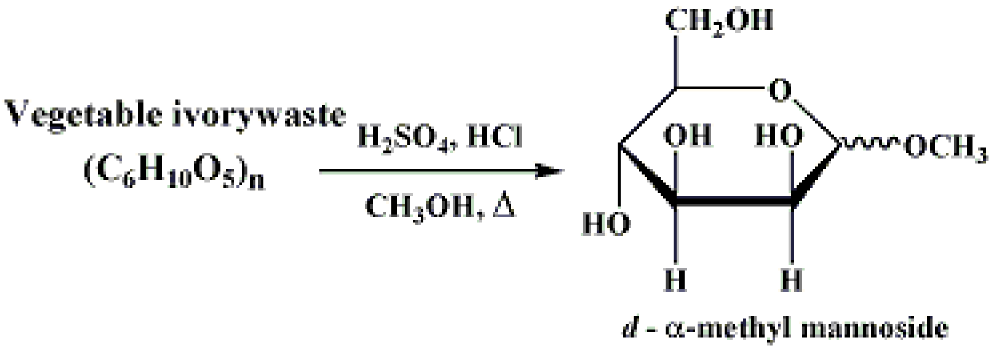
Organic Syntheses, CV 1, 371

α-METHYL MANNOSIDE

[Mannoside, α-methyl-, *d*-]



Submitted by C. S. Hudson
Checked by Frank C. Whitmore and R. D. Greene.

1. Procedure

One kilogram of dry finely ground vegetable ivory waste (Note 1) is added gradually to 1250 g. of 85 per cent sulfuric acid in an 8-l. (2-gallon) enameled vessel (Note 2) at such a rate as to keep the temperature at 30–35° (one to two hours). The mass is well kneaded (Note 3) and then kept at about 25° for fifteen hours (Note 4). A mixture of 1 l. of acetone-free methyl alcohol and 250 cc. of pure concentrated hydrochloric acid (sp. gr. 1.19) (Note 5) is kneaded into the soft mass, which is then transferred to a 12-l. flask. The flask is adjusted on a large steam bath (Note 6); 6 l. of absolute methyl alcohol is added; and the mixture is refluxed eight hours.

At the end of this time the mixture is cooled somewhat, and 100 g. of decolorizing carbon and 150 g. of infusorial earth or fuller's earth are added, and refluxing is resumed for one-half hour. The solution is filtered hot with suction through a Büchner funnel previously heated by blowing steam into the side neck of the suction flask (Note 7). The cake is washed with 500 cc. of hot absolute methyl alcohol. The filtration is likely to be slow unless a large funnel (30 cm.) is used. The light yellow filtrate soon begins to deposit crystals (Note 8). It is kept in an ice box twenty to fifty hours. The crystals are filtered by suction, washed with 50 cc. of absolute methyl alcohol, then with 50 cc. of dry acetone, and dried on porous plates at room temperature. The yield is 480–520 g. The mannoside is pure enough for most chemical purposes. It melts at about 170° and has a rotation in water of + 78.6°. If a purer product is desired, the mannoside may be crystallized from four parts of 80 per cent ethyl alcohol with 80–90 per cent recovery if the mother liquors are worked up. Slight acidity in the solution used in recrystallization should be carefully neutralized with ammonia. The recrystallized mannoside melts at 188–189° and has a rotation of $[\alpha]_D^{20}$ + 80.8°.

2. Notes

1. The ivory nut waste was obtained from the Rochester Button Company, Rochester, N. Y. It was ground in a mill, dried to constant weight at 100°, and sifted through a 20-mesh screen (8 per cm.).
2. The bottom of an Elyria enameled kettle was used. A crock can be used almost as conveniently. On smaller runs a large porcelain mortar was used.
3. The kneading can conveniently be done by means of a heavy stick, the end of which has been thoroughly charred in a fire and then polished to remove loose carbon. Stirring is not practicable.
4. A convenient method of heating is to suspend a 60-watt electric light about 20 cm. above the mixture.
5. Later experiments indicate that the addition of hydrochloric acid is not essential since the sulfuric acid is sufficient to cause the formation of the mannoside (C. S. Hudson, private communication).
6. The flask may be immersed half way in a large kettle of water heated on a large radial burner.
7. Another convenient device for rapid filtration is to use a large Witt plate in a steam funnel attached to a suction flask.
8. In some runs spontaneous crystallization is slow to start. It is advantageous to inoculate the solution with a crystal of the mannoside.

3. Discussion

α-Methyl mannoside can be prepared from mannose[1] or mannan triacetate[2] by the action of methyl alcohol and hydrochloric acid.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 541

References and Notes

1. Fischer and Beensch, Ber. **29**, 2928 (1896).
2. Patterson, J. Chem. Soc. **123**, 1139 (1923).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

α-METHYL MANNOSIDE

mannan triacetate

Mannoside, α-methyl-, d-

ethyl alcohol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

methyl alcohol (67-56-1)

acetone (67-64-1)

decolorizing carbon, carbon (7782-42-5)

mannose

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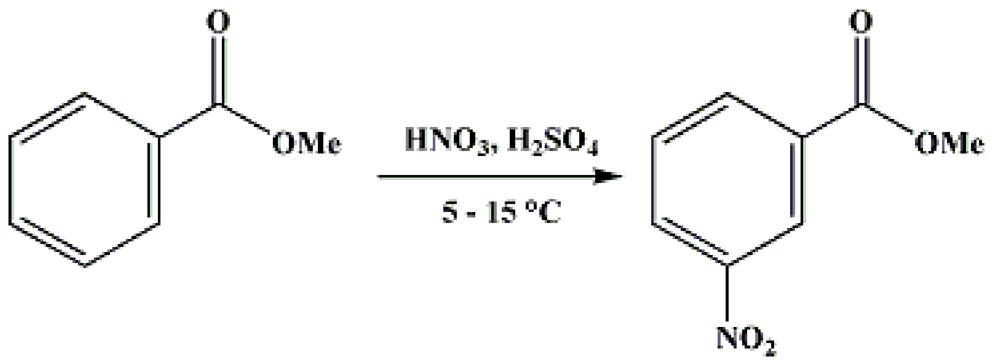
METHYL *m*-NITROBENZOATE

[Benzoic acid, *m*-nitro-, methyl ester]



Submitted by Oliver Kamm and J. B. Segur.
Checked by H. T. Clarke and E. R. Taylor.

1. Procedure

Into a 2-l. round-bottomed flask fitted with a mechanical stirrer are placed 400 cc. of concentrated sulfuric acid cooled to 0° and 204 g. (1.5 moles) of pure methyl benzoate (Note 1). The mixture is cooled by means of an ice bath to 0–10° and then, with stirring, there is added gradually, by means of a dropping funnel, a mixture of 125 cc. (1.96 moles) of concentrated nitric acid (sp. gr. 1.42) and 125 cc. of concentrated sulfuric acid. During the addition of the nitrating acid, which requires about one hour, the temperature of the reaction mixture should be kept within the range 5–15° (Note 2).

After the nitric acid has been added, stirring is continued for fifteen minutes longer; the mixture is then poured upon 1300 g. of cracked ice. The crude methyl *m*-nitrobenzoate separates as a solid and is filtered off by means of suction and washed with water. The product is placed in a flask and agitated with 200 cc. of ice-cold methyl alcohol in order to remove a small amount of *o*-nitrobenzoic ester and other impurities that are present. The cooled mixture is then filtered by means of suction, washed with another 100-cc. portion of cold methyl alcohol (Note 3), and the solid dried. The yield is 220–230 g. (81–85 per cent of the theoretical amount) (Note 4) of an almost colorless product melting at 74–76°. In order to obtain a product of maximum purity, which melts at 78°, it is advisable to recrystallize the ester from an equal weight of methyl alcohol.

2. Notes

1. It is necessary that the methyl benzoate should be of high purity and dissolve in sulfuric acid without color. Commercial methyl benzoate which does not meet the latter specification may give yields about 10 per cent lower. Directions

for the preparation of methyl benzoate are given in Org. Syn. **10**, 51, Note 13.
2. The nitration of methyl benzoate runs unusually smoothly, but it is essential to keep the temperature within the specified limits, otherwise the yield falls; at 50°, 193 g. of solid product is obtained, while at 70° the yield falls to 130 g.
3. On diluting the methyl alcoholic filtrate with water, 10–20 cc. of oil separates; more of this oil is formed by nitrating at higher temperatures, amounting to 57 cc. at 50° and 100 cc. at 70°. The oil consists not merely of methyl *o*-nitrobenzoate with some of the meta compound but contains also traces of dinitrobenzoic ester and nitrophenolic compounds. Unchanged methyl benzoate does not appear to be present.
4. The nitration method is also adaptable to the preparation of ethyl *m*-nitrobenzoate. The yield is, however, slightly lower, owing to the greater solubility of the ethyl ester.

3. Discussion

Methyl *m*-nitrobenzoate can be prepared by the esterification of *m*-nitrobenzoic acid;[1] this method is, however, obviously much less satisfactory than nitration of methyl benzoate. Nitration by means of fuming nitric acid can also be applied to methyl benzoate,[2] but the use of the ordinary nitration mixture of concentrated sulfuric acid and concentrated nitric acid is more satisfactory. Treatment of ω-trichloro-*m*-nitroacetophenone with methyl alcohol and sodium methoxide also furnishes methyl *m*-nitrobenzoate.[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 391

References and Notes

1. Chancel, Ann. **72**, 275 (1849).
2. Taverne, Rec. trav. chim. **17**, 97, 100 (1898).
3. Houben and Fischer, Ber. **64**, 2639 (1931).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

methyl alcohol (67-56-1)

nitric acid (7697-37-2)

sodium methoxide (124-41-4)

methyl benzoate (93-58-3)

m-Nitrobenzoic acid (121-92-6)

Methyl m-nitrobenzoate, Benzoic acid, m-nitro-, methyl ester (618-95-1)

methyl o-nitrobenzoate (606-27-9)

Ethyl m-nitrobenzoate (618-98-4)

ω-trichloro-m-nitroacetophenone

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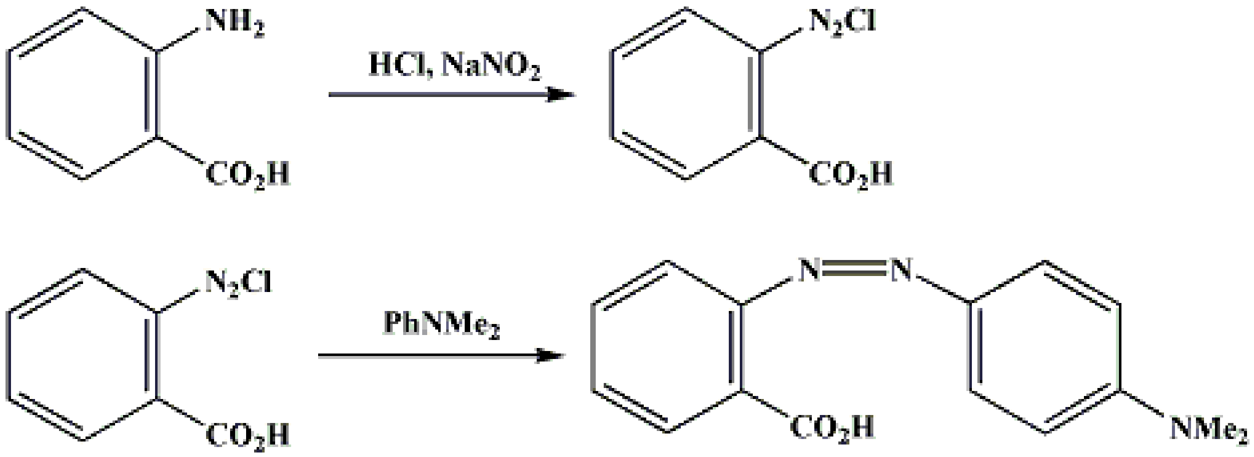
Organic Syntheses, CV 1, 374

METHYL RED



Submitted by H. T. Clarke and W. R. Kirner.
Checked by Roger Adams and J. B. Davis.

1. Procedure

Six hundred and eighty-five grams (4.75 moles) of technical anthranilic acid (generally about 95 per cent pure) (Note 1) is dissolved in 1.5 l. of water and 500 cc. of concentrated hydrochloric acid (sp. gr. 1.17) (Note 2), by heating. The insoluble dark impurity present in small amounts is filtered off, and the filtrate is transferred to a 16-l. crock and chilled with stirring. It is then mixed with a mush of 2.5 kg. of ice and 750 cc. of concentrated hydrochloric acid. The crock is cooled externally with ice, and the contents stirred continuously. When the temperature reaches about 3°, a filtered solution of 360 g. (5 moles) of sodium nitrite in 700 cc. of water is dropped in slowly, through a long capillary tube reaching below the surface of the liquid (Note 3), until a faint but permanent reaction to starch-potassium iodide paper is obtained; the temperature is kept between 3 and 5° (Note 4). This operation requires all but about 30 cc. of the nitrite solution and occupies one and one-half to two hours.

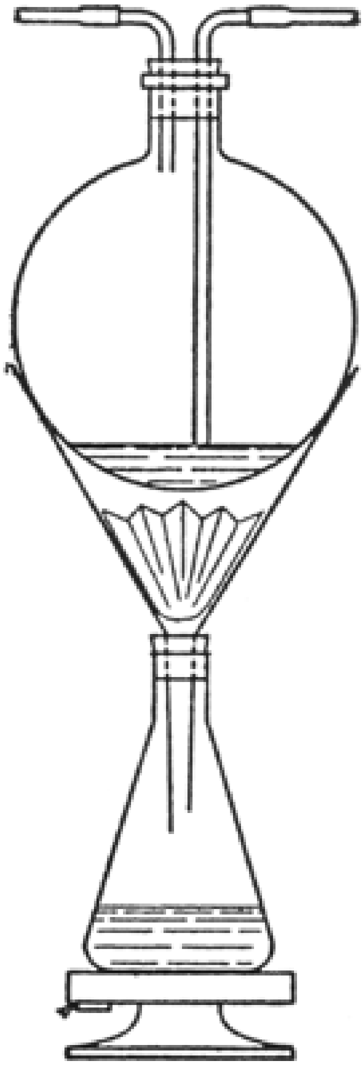
To the solution of the diazonium salt is now added 848 g. (885 cc., 7 moles) of dimethylaniline; this may be done rapidly, as the temperature does not rise appreciably. Stirring is continued for one hour, the temperature being kept at 5°. Five hundred cubic centimeters of a filtered solution of 680 g. (8.3 moles) of crystallized sodium acetate diluted to 1200 cc. is then added, and the stirring continued for four hours. If a foamy solid rises to the surface during this time and refuses to become incorporated by the stirrer, a few drops of ethyl acetate may be added to reduce the foam. The mixture is allowed to stand overnight in an ice bath which is well insulated by several thicknesses of burlap; the temperature must be kept below 7° to get a good yield of product. The remainder of the sodium acetate solution is then added with stirring, and, after the mixture has been stirred for an additional period of one to three hours, the temperature is allowed to rise slowly to 20–25° in the course of twenty-four

hours. Just enough sodium hydroxide solution is then added, with stirring, to cause the mixture to have a distinct odor of dimethylaniline (about 240 cc. of a 40 per cent solution is generally required), and the mixture is allowed to stand for forty-eight hours or longer at room temperature (20–25°) (Note 5).

The solid is then filtered off, washed first with water, then with 400 cc. of 10 per cent acetic acid (to remove the dimethylaniline), and finally with distilled water. The last filtrate is generally pale pink. The solid is sucked as dry as possible, spread out on a tray in order to allow most of the water to evaporate (fifteen to twenty hours), and then suspended in 4 l. of methyl alcohol in a 12-l. flask. This mixture is stirred on the steam bath under a reflux condenser for one to two hours, allowed to cool slowly, and then chilled in an ice bath and filtered. The solid product is washed with a second 4 l. of cold methyl alcohol (Note 6). After being dried in air, it varies in weight from 820 to 870 g.

The product is extracted with boiling toluene in the following manner: 150 g. is placed in a fluted filter paper of 29-cm. diameter in a 25-cm. glass funnel which passes through the cork of a 2-l. flat-bottomed conical flask containing 1250 cc. of toluene (Fig. 21).

Fig. 21.



The flask is heated on an electric stove, and a 12-l. round-bottomed flask, clamped to a ring stand, is placed on the funnel to act as a condenser, cold water being run through the flask. The toluene is boiled until the condensed liquid runs through almost colorless (this requires from four to ten hours). The heating is then discontinued, and, as soon as the liquid ceases to boil, the flask is removed to a bath containing water at 90–100°; the level of the water should be slightly above the level of the liquid in the flask. This arrangement permits the temperature to fall slowly so that large crystals are obtained. In the meantime a second conical flask containing 1250 cc. of toluene is attached to the funnel, and a new charge of 150 g. of crude methyl red is placed in the paper. The process is repeated until all the crude material has been so treated. When extraction is complete it is found that a certain amount of black amorphous insoluble matter remains on the filter; this is discarded. The crystals of methyl red (Note 7) are filtered off and washed with a little toluene. The weight of pure material is 755–805 g. The mother liquors are concentrated to one-fourth of their volume, and the crystals which separate on cooling are recrystallized from fresh toluene. The recovered toluene can, of course, be employed again. The total yield of pure methyl red is 790–840 g. (62–66 per cent of the theoretical amount) (Note 8). It melts at 181–182°.

The watery mother liquors from the crude methyl red are rendered alkaline with sodium hydroxide and distilled until no more dimethylaniline passes over. In this way 250 to 400 g. of moist dimethylaniline is recovered.

2. Notes

1. It is advisable to titrate the crude anthranilic acid with standard alkali and phenolphthalein before starting the experiment.

2. The amount of hydrochloric acid indicated must not be reduced; otherwise, diazoamino compounds are formed.

3. The use of a capillary tube for the addition of sodium nitrite prevents loss of nitrous acid by local reaction at the surface of the acid solution. The tube should not be tightly connected to the dropping funnel, but should be so arranged that air is sucked through with every drop. In this way, the entrance of the acid liquor into the capillary is prevented.

4. It is essential to keep the temperature low while unreacted diazobenzoic acid remains in solution, in order to avoid decomposition. If this precaution is not taken, the yields are considerably diminished, through the formation of tarry by-products.

5. The formation of the azo compound takes place slowly on the addition of the dimethylaniline, but the speed of the reaction is greatly increased when the hydrogen-ion concentration is lowered by the addition of the sodium acetate. It is nevertheless necessary to allow the reaction mixture to stand a long time; if the product is filtered off after only twenty-four hours, a further quantity of dye will separate from the filtrate on standing. The hydrochloride of methyl red is only sparingly soluble in cold water, and is apt to separate in blue needles if the acidity is not sufficiently reduced.

6. The alcoholic filtrate, obtained on digesting and washing the crude methyl red, contains a more soluble red by-product which gives a brownish-yellow solution in alkali. The methyl alcohol may be recovered with very little loss by distillation; it is, however, impracticable to attempt to recover any methyl red from the residue, owing to the tarry nature of the by-product. The proportion of this by-product is greatly increased if the temperature of the mixture is allowed to rise too soon after the addition of the sodium acetate.

7. Methyl red is described as crystallizing in needles from glacial acetic acid; on recrystallization from toluene it separates in plates.

When the methyl red is crystallized from toluene, it sometimes separates in the form of bright-red lumps, probably on account of too rapid crystallization. Under these conditions it is advisable to crystallize again, using a somewhat larger amount of toluene. The sodium salt may be prepared by dissolving the crude product in an equal weight of 35 per cent sodium hydroxide which has been diluted to 3 or 4 liters, filtering, and evaporating under diminished pressure. The isolation of methyl red as the sodium salt avoids the toluene extraction, and yields a water-soluble product (orange leaflets) which is very convenient for use as an indicator.

8. In checking these directions, an 80 per cent anthranilic acid was used; it gave a correspondingly lower yield of methyl red (650–700 g.).

3. Discussion

Methyl red can be prepared by diazotization of anthranilic acid in alcoholic solution, the product being allowed to react with dimethylaniline in the same solvent,[1] or both operations can be carried out in aqueous solution.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 140
- Org. Syn. Coll. Vol. 1, 149
- Org. Syn. Coll. Vol. 1, 207
- Org. Syn. Coll. Vol. 1, 228
- Org. Syn. Coll. Vol. 1, 335
- Org. Syn. Coll. Vol. 1, 336
- Org. Syn. Coll. Vol. 1, 538
- Org. Syn. Coll. Vol. 2, 580
- Org. Syn. Coll. Vol. 3, 310
- Org. Syn. Coll. Vol. 3, 822

References and Notes

1. Rupp and Loose, Ber. **41**, 3905 (1908); Ostromisslenski and Babodshan, J. Russ. Phys. Chem. Soc. **42**, 609 (1910) [Chem. Zentr. II, 1561 (1910)].
2. Tizard, J. Chem. Soc. **97**, 2485 (1910); Pozzi-Escot, Bull. assoc. chim. sucr. dist. **27**, 560 (1909) [Chem. Zentr. I, 960 (1910)]; Desvergnes, Ann. chim. anal. chim. appl. **2**, 209 (1920) [C. A. **14**, 3406 (1920)]; Howard and Pope, J. Chem. Soc. **99**, 1334 (1911); Schorger, Ind. Eng. Chem. **15**, 742 (1923).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Methyl Red

diazoamino compounds

hydrochloride of methyl red

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ethyl acetate (141-78-6)

methyl alcohol (67-56-1)

sodium acetate (127-09-3)

sodium hydroxide (1310-73-2)

sodium nitrite (7632-00-0)

nitrous acid (7782-77-6)

nitrite (14797-65-0)

toluene (108-88-3)

dimethylaniline (121-69-7)

Anthranilic Acid (118-92-3)

phenolphthalein (77-09-8)

diazobenzoic acid

hydrogen-ion

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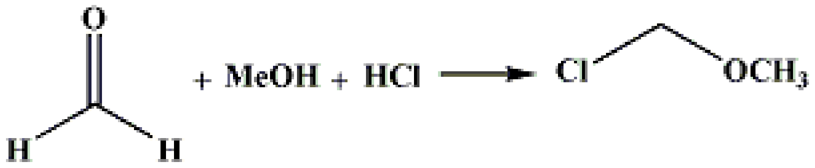
Organic Syntheses, CV 1, 377

MONOCHLOROMETHYL ETHER

[Ether, chloromethyl methyl]



Submitted by C. S. Marvel and P. K. Porter.
Checked by H. T. Clarke and E. R. Taylor.

1. Procedure

In a 2-l. round-bottomed flask fitted with a stopper carrying a reflux condenser and a glass tube reaching nearly to the bottom of the flask are placed 350 g. (438 cc., 10.9 moles) of methyl alcohol and 900 g. of technical formalin containing 252 g. (8.4 moles) of formaldehyde (Note 1).

A rapid stream of hydrogen chloride (Note 2) is run into the mixture, which is cooled with running water. In about two hours a layer of chloromethyl ether begins to appear. The stream of hydrogen chloride is continued for two or three hours longer until the solution is saturated. The layer of chloromethyl ether is then separated. The water layer is saturated with calcium chloride (Note 3), and more ether separates. This is added to the main portion, which is then dried over calcium chloride and fractionally distilled. The yield of product boiling at 55–60° is 580–600 g. (86–89 per cent of the theoretical amount based on the formaldehyde).

2. Notes

1. The following table, showing the relation between the density of formalin solutions and their formaldehyde content, has been found useful. It is copied from Beilstein's "Handbuch der organischen Chemie," 4th Ed., Julius Springer, Berlin, 1918, Vol. I, p. 561.

d_4^{18}	g. CH_2O in 100 cc.	g. CH_2O in 100 g.
1.0054	2.24	2.23
1.0126	4.66	4.60
1.0311	11.08	10.74
1.0410	14.15	13.59
1.0568	19.89	18.82
1.0719	25.44	23.73
1.0853	30.17	27.80

1.1057	37.72	34.11
1.1158	41.87	37.53

The values in this table are affected by the presence of methyl alcohol in the formalin solution; since it has been pointed out that technical formalin contains 8–10 per cent of methyl alcohol, the table is not satisfactory for determining the formaldehyde content of *technical* formalin solutions. For example, a solution containing 37 per cent of formaldehyde and 10 per cent of methyl alcohol would have a density of 1.09 and correspond to 28 per cent of formaldehyde in pure water. In view of this the percentage yield in the preparation described above should probably be 64–66 instead of 86–89 (Norman D. Scott, private communication).

2. The hydrogen chloride was generated by the method described on p. 293. About 390–420 g. of hydrogen chloride is required for saturation.

3. Chloromethyl ether is soluble in the aqueous hydrochloric acid used so that the salting-out with calcium chloride is necessary to obtain the maximum yield.

3. Discussion

Monochloromethyl ether can be prepared by saturating an aqueous solution of formaldehyde and methyl alcohol with hydrogen chloride[1] and by saturating a solution of trioxymethylene in methyl alcohol with hydrogen chloride.[2] The procedure described is essentially that developed by Henry.[1]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 54
- Org. Syn. Coll. Vol. 1, 214
- Org. Syn. Coll. Vol. 1, 347
- Org. Syn. Coll. Vol. 1, 355
- Org. Syn. Coll. Vol. 2, 610
- Org. Syn. Coll. Vol. 3, 436

References and Notes

1. Henry, Bull. sci. acad. roy. Belg. (3) **25**, 439 (1893) [Ber. **26** (2), 933 (1893)]; Litterscheid and Thimme, Ann. **334**, 10 (1904).
2. Wedekind, Ger. pat. 135,310 [Chem. Zentr. II, 1164 (1902)]; Ber. **36**, 1384 (1903); Houben and Arnold, Ber. **40**, 4307 (1907); Litterscheid, Ann. **330**, 109 (1904); Reychler, Bull. soc. chim. (4) **1**, 1195 (1907).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

trioxymethylene

calcium chloride (10043-52-4)

hydrogen chloride, hydrochloric acid (7647-01-0)

methyl alcohol (67-56-1)

hydrogen (1333-74-0)

formaldehyde, formalin (630-08-0)

MONOCHLOROMETHYL ETHER, chloromethyl ether (542-88-1)

Ether, chloromethyl methyl (107-30-2)

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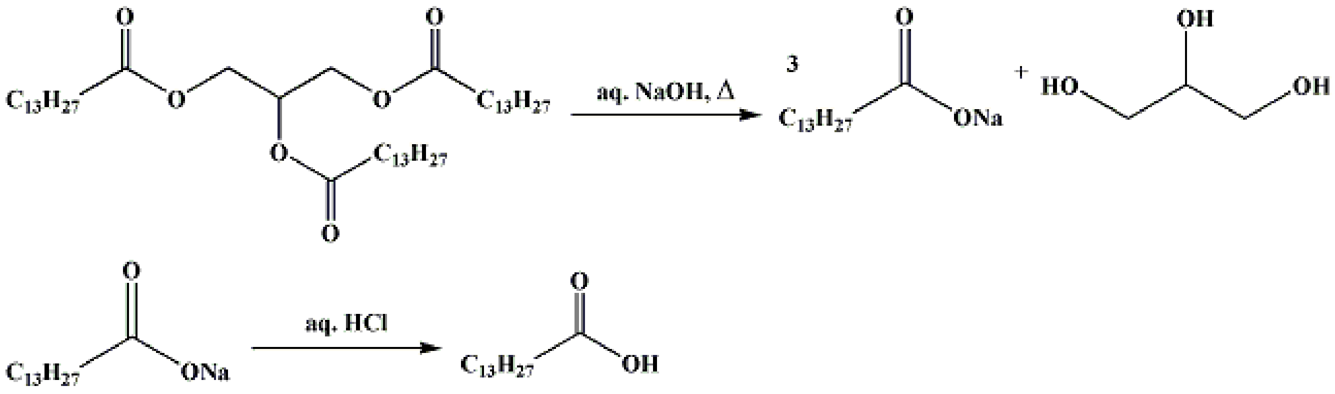
Organic Syntheses, CV 1, 379

MYRISTIC ACID



Submitted by G. D. Beal
Checked by H. T. Clarke and E. R. Taylor.

1. Procedure

In a 2-l. round-bottomed flask are placed 100 g. (0.14 mole) of pure (Note 1) trimyristin (p. 538) and 200 cc. of 10 per cent sodium hydroxide solution. The mixture is heated on a steam bath for two hours, with frequent shaking or stirring until the trimyristin has become emulsified. It is then diluted with 300 cc. of water and the heating is continued for another one-half hour, by which time the solution should be almost clear, indicating complete saponification. The solution is now poured with stirring into a hot solution of 650 cc. of water and 100 cc. of 20 per cent hydrochloric acid. The free acid which separates is not entirely clear, owing to the presence of unchanged sodium salt (Note 2). A gentle current of steam is passed into the hot mixture until the oily layer is transparent; this requires about fifteen minutes. The acid is allowed to cool and solidify; it is removed and freed of small quantities of salt and water by filtering through paper in a steam-jacketed funnel. The yield is 84–90 g. (89–95 per cent of the theoretical amount) of a colorless product (Note 3) which melts at 52–53° (Note 4).

2. Notes

1. If the trimyristin is not pure white and free of nutmeg oil, it will be necessary to purify the resulting acid by distillation under reduced pressure. It boils at 250°/100 mm. and 195°/15 mm.
2. As much as 15–20 g. of sodium salt may be found in the acid at this point if care is not taken to insure its decomposition. A corresponding amount of 35 per cent hydrochloric acid may be used. An excess of acid does no harm.
3. If desired, the acid may be recrystallized from petroleum ether (b.p., 40–60°) (F. H. Carr, private communication).
4. The melting point is not appreciably raised by recrystallization from petroleum ether. The highest melting point recorded in the literature is 53.8°.

3. Discussion

Myristic acid can be obtained by the hydrolysis of trimyristin contained in coconut oil,[1] nutmegs[2] (p. 538), or the seeds of *Virola venezuelensis*,[3] and by the hydrolysis of methyl myristate obtained from bayberry wax.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 605

References and Notes

1. Gorgey, Ann. **66**, 314 (1848).
2. Krafft, Ber. **12**, 1668 (1879); Verkade and Coops, Rec. trav. chim. **46**, 528 (1927).
3. Thoms and Mannich, Ber. pharm. Ges. **11**, 263 (1901) [Chem. Zentr. II, 189 (1901)].
4. Org. Syn. **20**, 67.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

hydrochloric acid (7647-01-0)

sodium hydroxide (1310-73-2)

Myristic acid (544-63-8)

trimyristin (555-45-3)

Methyl myristate (124-10-7)

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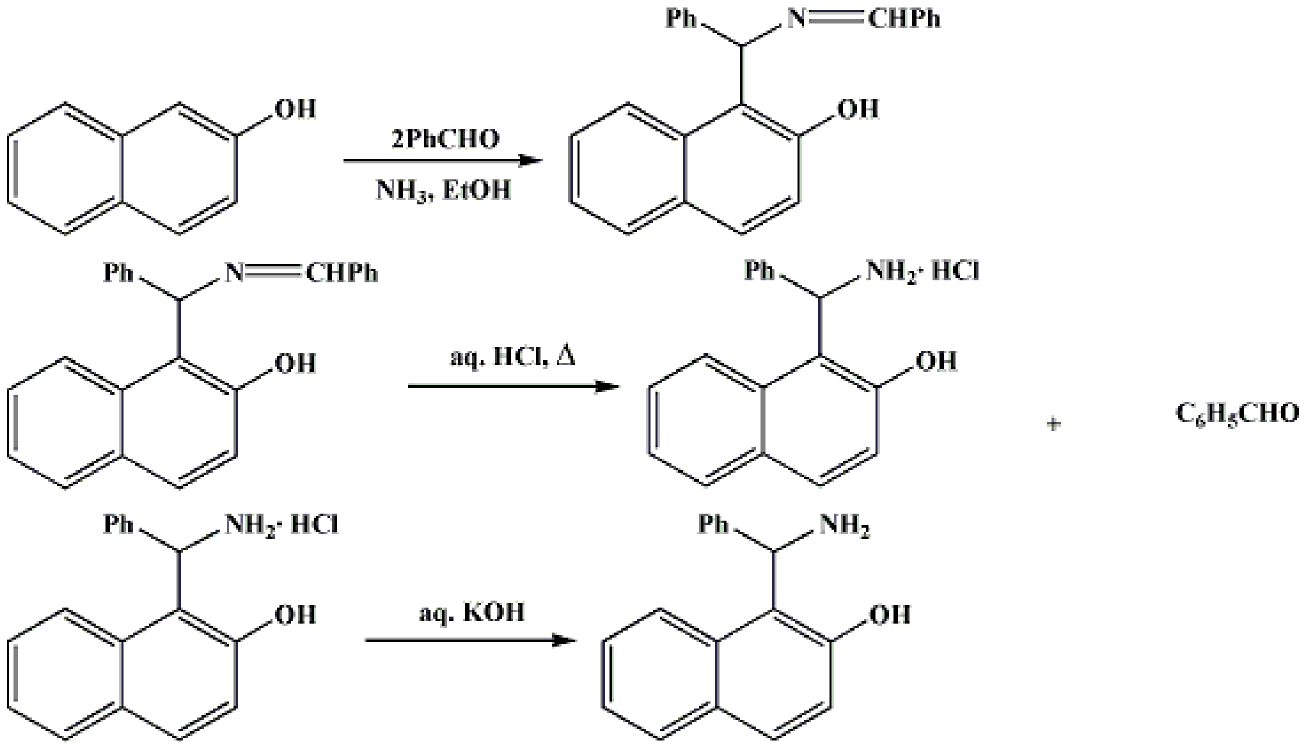
Organic Syntheses, CV 1, 381

β-NAPHTHOL PHENYLAMINOMETHANE

[2-Naphthol, 1-(α-aminobenzyl)-]



Submitted by M. Betti
Checked by C. S. Marvel and G. S. Hiers.

1. Procedure

In a 1-l. round-bottomed flask is placed a cold solution of 144 g. (1 mole) of β-naphthol in 200 cc. of 95 per cent alcohol (Note 1). To this solution is added first 212 g. (2 moles) of freshly distilled benzaldehyde (which has been previously freed from acid by shaking with 5 per cent sodium carbonate solution) and then about 200 cc. of 95 per cent alcohol which has been saturated with ammonia at room temperature. The solution becomes red and warms up spontaneously. The flask is stoppered and allowed to stand for two hours. Then the stopper is removed, and the excess ammonia is allowed to escape. After about twelve hours, the condensation product, which has separated as white needles, is filtered with suction and washed with 50 cc. of alcohol. The mother liquors on standing for three days deposit an additional quantity of the condensation product (Note 2). The yield is 284–306 g. (84–91 per cent of the theoretical amount) of a product which melts at 148–150°.

The condensation product thus obtained is introduced into a 5-l. round-bottomed flask arranged for steam distillation, and treated with three to four times its volume of 20 per cent hydrochloric acid. The mixture is steam distilled to remove all benzaldehyde formed by the hydrolysis (about two hours) (Note 3). Meanwhile, an abundant flocculent precipitate of light pink or white needles separates. The mixture in the flask is cooled thoroughly and filtered with suction. The yield is 240–260 g. (84–91 per cent of the theoretical amount) of a product which melts at 190–220° with decomposition (Note 4).

The hydrochloride thus obtained varies from pure white to a light red in color, depending on the purity of the original reagents and on the length of time required for the hydrolysis. However, the color does not interfere with isolation of a pure white free base when the salt is treated with alkali. The salt is somewhat more stable than the free base, and, if the reagent is to be stored for some time, it should be kept in this

form.

In order to obtain the amine, 200 g. of finely divided hydrochloride is placed in a 1500-cc. beaker and stirred into a smooth paste with 300 cc. of water. To this is added 50 g. of crushed ice, and the mixture is cooled in an ice bath (Note 5). Then 750–800 cc. of 5 per cent aqueous potassium hydroxide is added slowly and with stirring until a nearly clear solution results. The cold solution is transferred to a separatory funnel and extracted eight to ten times with 300-cc. portions of ether. The combined ether extract is dried overnight with 50 g. of anhydrous sodium sulfate, filtered, and concentrated to about 300 cc. When the solution is cooled in an ice bath, the amine crystallizes and is filtered with suction. The first crop of crystals weighs 112–115 g. Further concentration of the mother liquors to about 100 cc. and cooling yield 14–18 g. more of the product (Note 6). The total yield is 127–131 g. (73–75 per cent of the theoretical amount) of a product which melts at 124–125° (Note 7). If desired, it may be purified by dissolving in an excess of dry ether, evaporating the excess of solvent, and allowing the amine to crystallize. Thus, 24.5 g. of the amine, when dissolved in 800 cc. of dry ether and the solution filtered and evaporated in a current of air to 150 cc., yields 18–19 g. of product, melting at 124–125°

2. Notes

1. It is usually necessary to warm the alcohol in order to dissolve the β-naphthol. This solution is then cooled before the addition of the benzaldehyde.
2. Even after three days' standing, the reaction is not entirely complete, and an additional 8–10 g. of product may be obtained by allowing the mother liquors to stand for another three or four days.
3. Sometimes, when the distillation is carried on for too long a period, the hydrochloride coagulates to a hard red mass. If this happens, the product may be purified by crystallization from about 15 per cent hydrochloric acid. Even the deeply colored hydrochloride yields a colorless amine.
4. The hydrochloride is almost insoluble in cold water. It is slightly hydrolyzed by boiling water.
5. The temperature should be kept below 20° during the addition of the alkali, or the product is decomposed and ammonia is evolved.
6. A small additional amount of impure product may be obtained by evaporating the mother liquors further and cooling the solution. This product amounts to only a few grams and needs to be purified by recrystallization from ether.
7. This amine is of interest because it is readily resolved with tartaric acid to give the pure dextro and levo isomers.[1] These optically active bases are very useful in the resolution of various types of racemic substances.

3. Discussion

β-Naphthol phenylaminomethane has been prepared only by the method outlined in the procedure.[2]

References and Notes

1. Betti, Gazz. chim. ital. **36**, II, 392 (1906).
2. Betti, Gazz. chim. ital. **31**, I, 385 (1901).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

β-Naphthol phenylaminomethane

alcohol (64-17-5)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ether (60-29-7)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

β-naphthol (135-19-3)

benzaldehyde (100-52-7)

potassium hydroxide (1310-58-3)

tartaric acid (87-69-4)

2-Naphthol, 1-(α-aminobenzyl)- (481-82-3)

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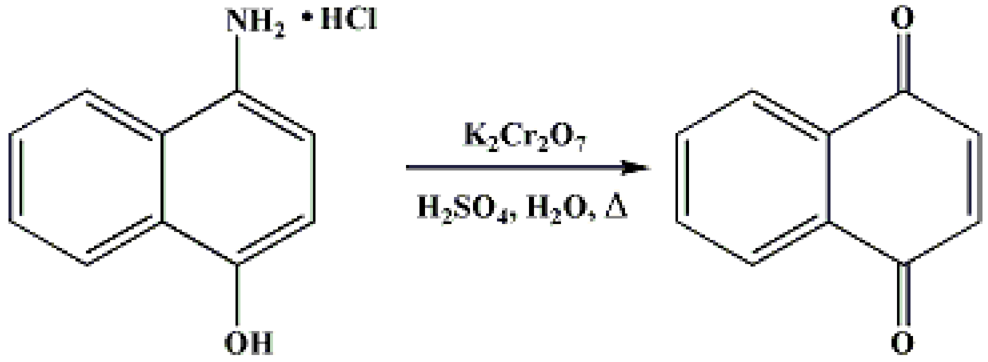
Organic Syntheses, *CV 1*, *383*

1,4-NAPHTHOQUINONE



Submitted by Louis F. Fieser
Checked by C. R. Noller and W. R. White.

1. Procedure

A mixture of 70 g. (0.36 mole) of pure 1,4-aminonaphthol hydrochloride and 2100 cc. of water at 30° in a 5-l. flask is stirred for a few minutes in order to dissolve most of the material and then treated with 100 cc. of concentrated sulfuric acid. The mixture is heated to the boiling point until all the precipitated amine sulfate has been brought into solution. The solution is somewhat pink. The hot solution is poured rapidly through a large funnel (without a paper), which has been warmed on the steam bath, into a 5-l. round-bottomed flask containing a filtered solution at room temperature of 70 g. (2.4 moles) of potassium dichromate in 1 l. of water. The flask is shaken to mix the contents thoroughly. The quinone separates at once as a mass of fine, yellow needles. After cooling to 25° the material is collected, washed with water, and dried at 30–40°. The crude product is dull yellow; it melts at 124–125° to a dark liquid and weighs 53–55 g. (Note 1).

The crude naphthoquinone is warmed gently on the steam bath with 1.5 l. of ether, when it rapidly dissolves and leaves in suspension a slight amount of dark, fluffy material. The solution is shaken for ten minutes with 10 g. of decolorizing carbon; it is then filtered, and the ether is distilled from a steam bath until crystals begin to form. The solution is then allowed to cool undisturbed, and the clear canary-yellow prisms which separate are collected and washed with ether. The mother liquor is clarified by shaking as before with 7 g. of decolorizing carbon, filtered, and evaporated to a small volume until crystals begin to separate. The crystals are again washed with ether, and the mother liquor is clarified and evaporated once more. The final crop of material is dull in color but yields a pure product on recrystallization. All the material is of a high quality and melts at 124–125° to a clear yellow liquid; the yield is 44–46 g. (78–81 per cent of the theoretical amount) (Note 2).

2. Notes

1. The method of oxidation is essentially that of Russig.[1] The product obtained is slightly but definitely better than that produced at a lower temperature, or by adding the sulfuric acid to the dichromate solution, or by using ferric chloride. These latter procedures give the same yield, but the product is less pure and contains a black, ether-soluble impurity which must be washed out carefully after crystallization from ether.

2. This procedure[2] avoids the tedious purification by distillation with superheated steam in vacuum, which was described in the original method in Org. Syn. Coll. Vol. **I**, 375 (1932).

3. Discussion

1,4-Naphthoquinone can be prepared by the oxidation of naphthalene,[3] 1,4-aminonaphthol,[4], [5] 1,4-naphthylene diamine,[4] and 1,4-naphthylamine sulfonic acid.[6] Oxidation of 1,4-aminonaphthol is the most convenient method.[7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 310
- Org. Syn. Coll. Vol. 4, 698

References and Notes

1. Russig, J. prakt. Chem. (2) **62**, 31 (1900).
2. Fieser and Fieser, J. Am. Chem. Soc. **57**, 491 (1935).
3. Groves, Ann. **167**, 357 (1873); Plimpton, J. Chem. Soc. **37**, 634 (1880); Japp and Miller, ibid. **39**, 220 (1881); Miller, J. Russ. Phys. Chem. Soc. **16**, 414 (1884); Arnold and Larson, J. Org. Chem. **5**, 250 (1940).
4. Liebermann, Ann. **183**, 242 (1876).
5. Zincke and Wiegand, Ann. **286**, 70 (1895); Russig, J. prakt. Chem. (2) **62**, 31 (1900); Conant and Fieser, J. Am. Chem. Soc. **46**, 1862 (1924); Liebermann, Ber. **14**, 1796 (1881).
6. Monnet, Reverdin, and Nölting, Ber. **12**, 2306 (1879).
7. Conant and Fieser, J. Am. Chem. Soc. **46**, 1862 (1924).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

1,4-Aminonaphthol hydrochloride

1,4-Aminonaphthol

sulfuric acid (7664-93-9)

ether (60-29-7)

decolorizing carbon (7782-42-5)

Naphthalene (91-20-3)

ferric chloride (7705-08-0)

potassium dichromate (7778-50-9)

1,4-Naphthoquinone, naphthoquinone (130-15-4)

1,4-naphthylene diamine (2243-61-0)

1,4-naphthylamine sulfonic acid (84-86-6)

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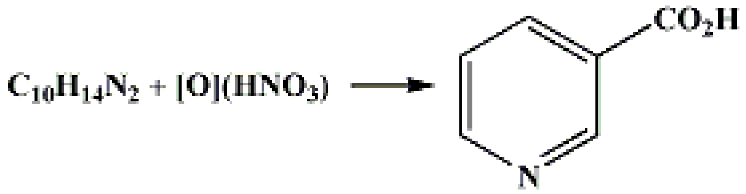
Organic Syntheses, CV 1, 385

NICOTINIC ACID



Submitted by S. M. McElvain
Checked by J. B. Conant and B. B. Corson.

1. Procedure

In a 5-l. round-bottomed flask is placed 4 kg. (2816 cc.) of c.p. concentrated nitric acid (sp. gr. 1.42) (Note 1). To this is added, in 25-cc. portions, 210 g. (1.23 moles) of nicotine (Note 2). The addition should be made carefully in order that local heating may not occur and material be lost. After each addition of nicotine, the flask should be shaken in order to insure a homogeneous solution. The addition of the nicotine causes the temperature of the liquid to rise somewhat but not sufficiently to cause evolution of nitrogen dioxide. The flask is placed on a steam bath under a hood and heated until the liquid reaches a temperature of 70°. It is then removed and the reaction allowed to continue spontaneously (Note 3), sufficient heat being evolved to cause the liquid to boil. The boiling ceases after one hour, but the flask is replaced upon the steam bath for ten to twelve hours, during which time there is a more or less continuous evolution of oxides of nitrogen.

The contents of the flask are then poured into an evaporating dish and evaporated almost to dryness on the steam bath (about ten hours). The purification which follows is best carried out with the product of two runs such as have been described above.

After the evaporation of most of the liquid, the nicotinic acid nitrate from two runs is transferred to a 1.5-l. beaker, 400 cc. of distilled water is added (Note 4), and the mixture is heated until complete solution results. On cooling, the nicotinic acid nitrate separates as yellow granular crystals and is filtered off. To obtain it absolutely pure, it may be recrystallized in a way similar to that just described but with the use of animal charcoal. It contains one molecule of water of crystallization and has a melting point of 190–192° (corr.). The yield is 420–460 g. 83–91 per cent of the theoretical amount).

The 420–460 g. of crude nicotinic acid nitrate from two runs (not necessarily dry) is dissolved in 900 cc. of boiling water in a 3-l. beaker, and 800 g. of crystalline disodium phosphate ($Na_2HPO_4 \cdot 12H_2O$) is added with constant stirring. The resulting thick mixture is stirred and heated almost to boiling for five minutes and then allowed to cool. The mixture is finally chilled to 0° by an ice bath. It is well to stir occasionally during the crystallization to prevent the formation of too solid a cake of crystalline material. The nicotinic acid is filtered off upon a 15-cm. Büchner funnel and washed

with three 100-cc. portions of cold water.

The yield is 260–300 g. of material containing a small amount of mineral salts but otherwise nearly pure. It can be purified further by recrystallization from 2.5 to 3.5 l. (Note 4) of hot water, 150–180 g. of material, which melts at 230–232° (corr.), being obtained. The yield of recrystallized material is 50–60 per cent of the theoretical amount, based upon the nicotine employed.

The recrystallization is the least satisfactory part of this procedure and involves the greatest apparent loss of material; the product before recrystallization is sufficiently pure for most purposes. By evaporation of the mother liquors, 40–45 g. of pure nicotinic acid may be obtained, making the total yield of pure material 190–225 g. (63–74 per cent of the theoretical amount); in addition, a small amount of somewhat less pure material is recovered (Note 5).

2. Notes

1. Fuming nitric acid, the use of which is advised in the literature, is not so convenient and gives no better results than concentrated nitric acid.
2. A product of 100 per cent purity gives no better results than does the crude 95 per cent material used in this experiment.
Care should be exercised in handling nicotine because of its high toxicity.
3. If the nicotine and nitric acid mixture is merely placed on a steam bath and allowed to heat without control of the temperature, an occasional run will react violently, with loss of material.
4. The amounts of solvent given for the various recrystallizations are those which result in the best yields, and it is advisable to follow them as closely as possible.
5. Nicotinic acid hydrochloride may be obtained directly from the nitrate by heating on a steam bath 460 g. of crude nitrate with 1 l. of concentrated hydrochloric acid (sp. gr. 1.19). After six to eight hours, the evolution of gas ceases and the liquid is evaporated under diminished pressure. The dry salt is again treated with 500 cc. of hydrochloric acid and heated for five hours and then evaporated as before.
After the salt has been obtained again, it is dissolved in 400 cc. of hot water and the solution diluted with four times its volume of 95 per cent alcohol. Upon cooling and stirring, the hydrochloride, melting at 273–274°, is obtained in a yield of 245–250 g. (63–65 per cent of the theoretical amount). An additional quantity of 75–80 g. may be obtained from the mother liquors.

3. Discussion

Nicotinic acid can be prepared by oxidation of nicotine with nitric acid,[1] potassium permanganate[2] or chromic acid,[3] and by carbonation of the lithium derivative made from 3-bromopyridine.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 334

References and Notes

1. Weidel, Ann. **165**, 330 (1873); Pictet and Rotschy, Ber. **34**, 702 (1901); Pictet and Sussdorff, Arch. sci. phys. nat. (4) **5**, 113 (1898) [Chem. Zentr. I, 677 (1898)]; McElvain and Adams, J. Am. Chem. Soc. **45**, 2738 (1923).
2. Laiblin, Ann. **196**, 134 (1879); Ber. **10**, 2136 (1877); Späth and Spitzer, Ber. **59**, 1482 (1926).
3. Hoogewerff and van Dorp, Rec. trav. chim. **1**, 121 (1882); Camps, Arch. Pharm. **240**, 353 (1902).
4. Gilman and Spatz, J. Am. Chem. Soc. **62**, 446 (1940).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

oxides of nitrogen

disodium phosphate ($Na_2HPO_4 \cdot 12H_2O$)

lithium derivative made from 3-bromopyridine

alcohol (64-17-5)

hydrochloric acid (7647-01-0)

nitric acid (7697-37-2)

potassium permanganate (7722-64-7)

chromic acid (7738-94-5)

nitrogen dioxide (10102-44-0)

Nicotinic acid (59-67-6)

nicotine (22083-74-5)

nicotinic acid nitrate

Nicotinic acid hydrochloride (636-79-3)

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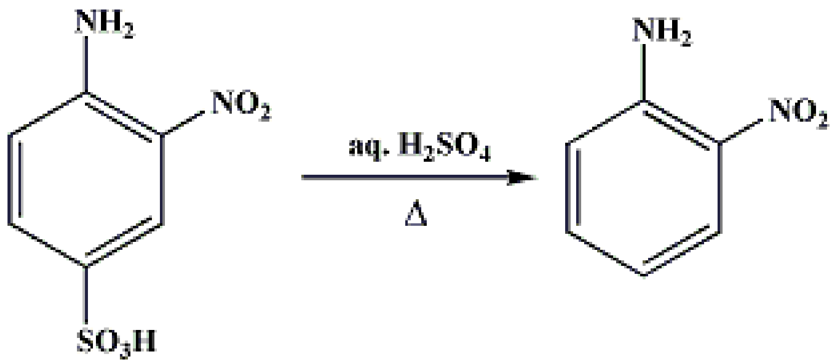
Organic Syntheses, CV 1, 388

o-NITROANILINE

[Aniline, *o*-nitro-]



Submitted by Louis Ehrenfeld and Milton Puterbaugh.
Checked by Roger Adams and S. V. Puntambeker.

1. Procedure

In a 3-l. round-bottomed flask fitted with a reflux condenser are placed 218 g. (1 mole) of coarsely powdered technical *o*-nitroaniline-*p*-sulfonic acid, and a hot mixture of 775 cc. of concentrated sulfuric acid (sp. gr. 1.84) and 950 cc. of water (Note 1). Heat is applied and the mixture is refluxed gently for one hour after solution is practically complete (total about three hours). The resulting dark solution is allowed to cool and is poured slowly into 12 l. of cold water in a crock (Note 2).

After cooling, the dense orange-yellow precipitate is filtered with suction. This crop of crystals after air-drying weighs about 70 g. and melts at 68–70°. The filtrate is returned to the crock and made slightly alkaline with 50 per cent sodium hydroxide solution (about 2.25 l.). It is then made barely acid to litmus with sulfuric acid. This neutralization will produce considerable heat, and the mixture should be thoroughly cooled before filtering. This second crop of crystals weighs about 22–25 g. and melts at 69–70.5°. The total crude yield is 90–95 g.

The two crops of crystals may be combined for recrystallization from boiling water, using 1 l. for each 9 g. The hot solution is filtered quickly, and the filtrate is cooled thoroughly and filtered with suction. The crystals are dried at 50°. The product melts at 69–71°. An alternative method of purification is to dissolve the crude product in about 250 cc. of 95 per cent alcohol, filter the solution, dilute with 1 l. of hot water, and warm on a steam bath if a precipitate forms. On cooling this solution, the product separates in orange-brown needles, and is filtered and air-dried. The yield is about 78 g. (56 per cent of the theoretical amount), m.p. 69.5–70.5°.

2. Notes

1. If cold, diluted acid is used, stirring must be employed during the heating to

prevent caking and consequent charring.
2. The dark solution may be poured slowly over sufficient ice to half-fill a 16-l. (4-gallon) crock. A good yield was obtained in this way, but at this point the temperature is not likely to rise much and the use of cold water is less expensive and sufficiently satisfactory.

3. Discussion

o-Nitroaniline can be obtained together with some *p*-nitroaniline in the nitration and subsequent hydrolysis of acetanilide[1] and of benzanilide;[2] by the sulfonation, nitration, and subsequent hydrolysis of oxanilide[3] and of acetanilide;[4] by the nitration of aniline and separation of the mixture of isomers;[5] and by heating *o*-chloronitrobenzene with ammonium acetate.[6]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 501

References and Notes

1. Walker and Zincke, Ber. **5**, 114 (1872); Remsen and Graham, Am. Chem. J. **11**, 320 (1889); Weida, Am. Chem. J. **19**, 547 (1897); Pokorny, Bull. Soc. Indus. Mulhouse 280 (1894) [Chem. Zentr. II, 556 (1894)].
2. Lellmann, Ann. **221**, 6 (1883).
3. Anilinoel-Fabrik A. Wülfing, Ger. pat. 65,212; 66,060 [Frdl. **3**, 44, 45 (1892)].
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5. Bruns, Ber. **28**, 1954 (1895).
6. Soc. Chimique De La Grande-Paroisse, Brit. pat. 169,688 [C. A. **16**, 721 (1922)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

oxanilide

alcohol (64-17-5)

sulfuric acid (7664-93-9)

ammonium acetate (631-61-8)

aniline (62-53-3)

Acetanilide (103-84-4)

sodium hydroxide (1310-73-2)

Benzanilide (93-98-1)

o-chloronitrobenzene (88-73-3)

o-NITROANILINE, Aniline, o-nitro- (88-74-4)

o-nitroaniline-p-sulfonic acid (616-84-2)

p-nitroaniline (100-01-6)

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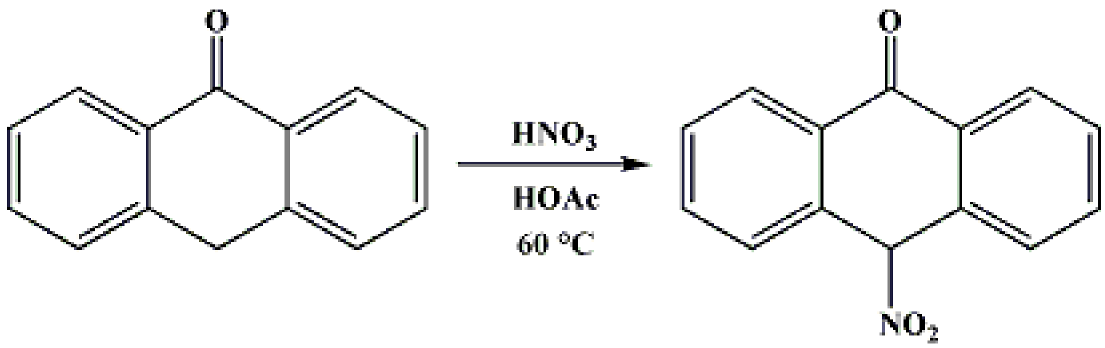
NITROANTHRONE

[Anthrone, 10-nitro-]



Submitted by Kurt H. Meyer
Checked by J. B. Conant and W. C. Boyd.

1. Procedure

In a 1-l. beaker equipped with a separatory funnel, a mechanical stirrer, and a thermometer, 20 g. (0.1 mole) of anthrone (p. 60) is dissolved in 300 cc. of glacial acetic acid. While the mixture is kept at 60° and stirred, a solution of 10.5 g. (7 cc., 0.16 mole) of fuming nitric acid (sp. gr. 1.5) in 50 cc. of glacial acetic acid is run in during one hour.

On cooling to about 10°, 15 g. of nitroanthrone separates out in long yellowish-white needles. After the addition of 100 cc. of water to the mother liquor, 6 g. more, somewhat darker in color, crystallizes in three to four hours.

On recrystallization from about 300 cc. of a 1:1 benzene-petroleum ether (40–60°) mixture, 16.5 g. of nitroanthrone melting at 140° (corr.) is obtained (67 per cent of the theoretical amount) (Note 1).

2. Notes

1. By dissolving in hot alkali (about 300 cc. of water and 30 g. of sodium hydroxide per gram of nitroanthrone) and precipitating with acid below 10°, the red nitroanthranol may be obtained, which on standing slowly changes back to the nitroanthrone.

3. Discussion

Nitroanthrone can be prepared by the nitration of anthracene in isobutyl alcohol,[1] and by the nitration of anthrone.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 445

References and Notes

1. Perkin and Mackenzie, J. Chem. Soc. **61**, 868 (1892); Meisenheimer and Connerade, Ann. **330**, 177 (1904).
2. Meyer and Sander, Ann. **396**, 149 (1913).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

benzene-petroleum ether

acetic acid (64-19-7)

sodium hydroxide (1310-73-2)

nitric acid (7697-37-2)

Anthrone (90-44-8)

anthracene (120-12-7)

Nitroanthrone

Anthrone, 10-nitro- (6313-44-6)

nitroanthranol

isobutyl alcohol (78-83-1)

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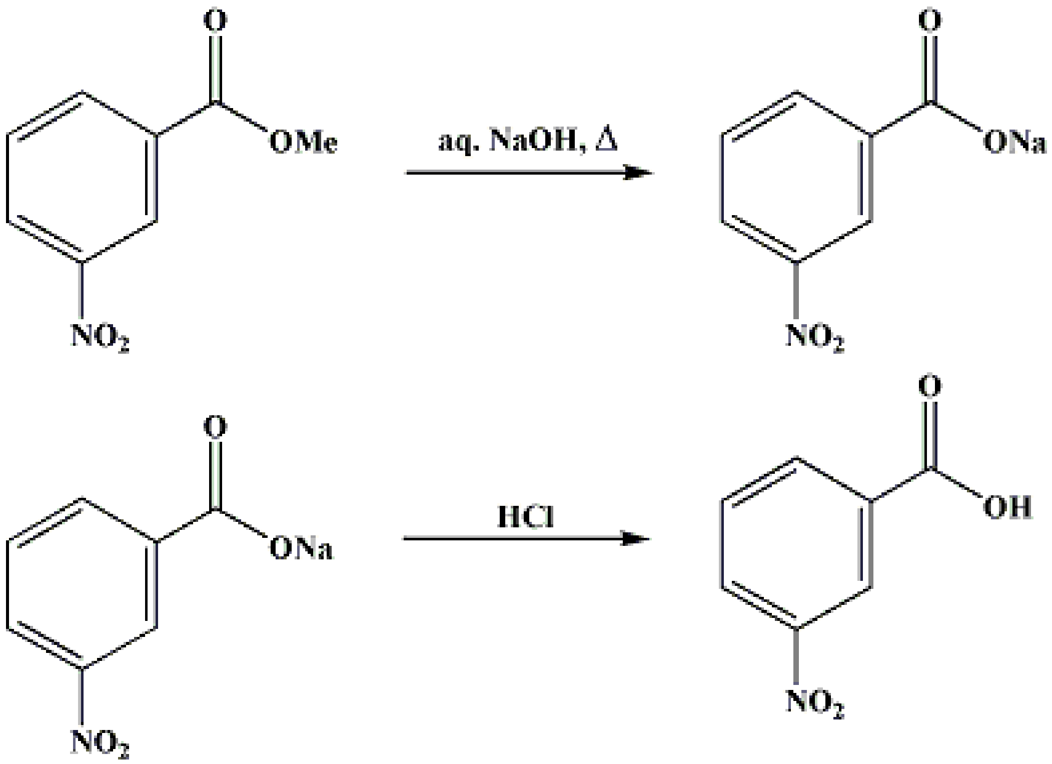
Organic Syntheses, CV 1, 391

m-NITROBENZOIC ACID

[Benzoic acid, *m*-nitro-]



Submitted by Oliver Kamm and J. B. Segur.
Checked by H. T. Clarke and E. R. Taylor.

1. Procedure

In a 2-l. round-bottomed flask fitted with a reflux condenser are placed a solution of 80 g. (2 moles) of sodium hydroxide in 320 cc. of water (Note 1) and 181 g. (1 mole) of methyl *m*-nitrobenzoate (not recrystallized, p. 372). The mixture is heated to boiling during five to ten minutes or until the saponification is complete as shown by the disappearance of the ester.

The reaction mixture is now diluted with a equal volume of water, and when cool is poured, with stirring, into 250 cc. of concentrated hydrochloric acid (Note 2). After the solution has cooled to room temperature, the *m*-nitrobenzoic acid is filtered off by means of suction. This crude acid when dry weighs 150–160 g. (90–96 per cent of the theoretical amount). It has a light brownish color, melts at 140°, and should be completely soluble in ether, thus showing the absence of salts. This acid is satisfactory for many purposes, but in order to prepare a perfectly pure product it must be crystallized once from 1 per cent aqueous hydrochloric acid (Note 3). A light cream-colored product is thus obtained with a loss of about 5 per cent of the material (Note 4).

2. Notes

1. The use of a more dilute sodium hydroxide solution than that recommended above has been found to yield unsatisfactory results in the saponification of the ester. Prolonged boiling may lead to the production of colored products.
2. After the hydrolysis of the methyl *m*-nitrobenzoate it is essential that the solution of the sodium salt be poured into the acid. If acid is added to the salt in the usual way, a less soluble acid salt separates; and, as this cannot be entirely removed from the *m*-nitrobenzoic acid even on long digestion with hydrochloric acid, a product is obtained which does not dissolve completely in ether.
3. *m*-Nitrobenzoic acid is soluble to the extent of 1 part in 300 parts of water at 20°, and 20 parts at 100°. The crystallization from water or dilute hydrochloric acid is therefore quite satisfactory.
4. *m*-Nitrobenzoic acid is obtained in a higher yield by nitration of methyl benzoate (p. 372) with subsequent hydrolysis than by the direct nitration of benzoic acid; this method is also preferable on account of the laborious nature of the methods necessary for the separation of the meta acid from the small quantities of the para isomer formed in the latter process.

3. Discussion

m-Nitrobenzoic acid can be prepared by the nitration of benzoic acid by means of nitric acid,[1] a mixture of nitric and sulfuric acids,[2] or mixtures of nitrates and sulfuric acid;[3] all these methods lead to the production of a mixture containing principally the *m*-nitrobenzoic acid with a smaller proportion of the ortho and 1–2 per cent of the para isomer. Nitration of benzotrichloride with subsequent hydrolysis also furnishes *m*-nitrobenzoic acid.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 715

References and Notes

1. Mulder, Ann. **34**, 297 (1840); Hübner, Ann. **222**, 72 (1884).
2. Gerland, Ann. **91**, 186 (1854); Varma and Kulkarni, J. Am. Chem. Soc. **47**, 143 (1925).
3. Gerland, Ann. **91**, 185 (1854); Liebermann, Ber. **10**, 862 (1877).
4. Sah, Lei, and Wang, Science Repts. Natl. Tsinghua Univ. **A2**, 137 (1933) [C. A. **28**, 118 (1934)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

nitric and sulfuric acids

nitrates and sulfuric acid

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium hydroxide (1310-73-2)

nitric acid (7697-37-2)

Benzoic acid (65-85-0)

benzotrichloride (98-07-7)

methyl benzoate (93-58-3)

m-Nitrobenzoic acid, Benzoic acid, m-nitro- (121-92-6)

Methyl m-nitrobenzoate (618-95-1)

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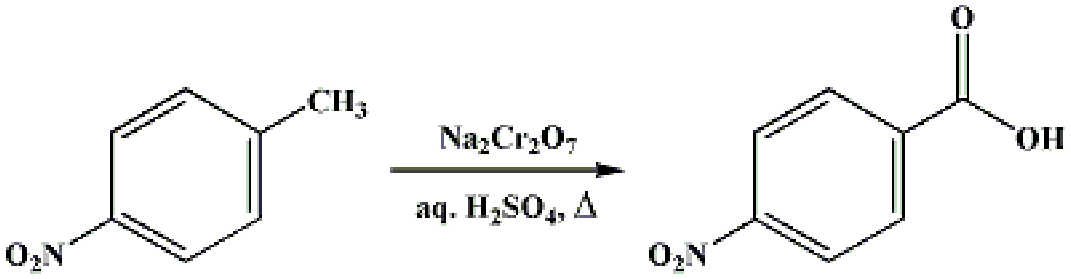
p-NITROBENZOIC ACID

[Benzoic acid, *p*-nitro-]



Submitted by O. Kamm and A. O. Matthews.
Checked by H. T. Clarke and W. W. Hartman.

1. Procedure

In a 5-l. round-bottomed flask, fitted with a mechanical stirrer, are placed 680 g. (2.3 moles) of sodium dichromate, 1500 cc. of water, and 230 g. (1.7 moles) of *p*-nitrotoluene. Stirring is started, and 1700 g. of concentrated sulfuric acid is allowed to flow in during about thirty minutes (Note 1). The heat of dilution of the sulfuric acid will cause the nitrotoluene to melt, and rapid oxidation will soon take place. The last half of the sulfuric acid must be added gradually, in order to prevent too violent a reaction. Since a small amount of nitrotoluene is volatilized, it is advisable to carry on this work under a hood.

After the sulfuric acid has been added and the spontaneous heating of the reaction mixture has subsided, the mixture is heated to gentle boiling for about one-half hour (Note 2). When the reaction mixture has cooled, 2 l. of water is added, the cooled solution is filtered through a cloth filter, and the product washed with about 1 l. of water. In order to remove the chromium salts as completely as possible, the crude *p*-nitrobenzoic acid is warmed on the water bath and agitated with 1 l. of dilute (5 per cent) sulfuric acid solution (Note 3). After cooling, the product is again filtered. It is then dissolved in 5 per cent sodium hydroxide solution, filtered from any chromium hydroxide remaining, and also from unchanged nitrotoluene. The filtrate, which should be light yellow or greenish in color, is acidified with dilute sulfuric acid, with stirring. It is usually preferable to run the alkaline solution into the dilute sulfuric acid, rather than to use the reverse procedure, for the precipitation of the nitro acid (Note 4). The precipitated product is filtered with suction, washed thoroughly, and dried. The product should have only a light lemon color. The yield is 230–240 g. (82–86 per cent of the theoretical amount).

For a product of special purity, crystallization from benzene is advisable. For most purposes, however, the nitrobenzoic acid may be used without crystallization, since its

melting point is found to be within 2° of the correct value of 238°.

2. Notes

1. The above procedure differs from that recorded in the literature, mainly in the use of a fairly large excess of sulfuric acid. This shortens the reaction time from forty hours to about one hour, which is especially convenient in the preparation of the acid on a laboratory scale. Because of the use of this large excess of sulfuric acid, the reaction is apt to be rather violent if the directions given are not carefully followed. The oxidation should be carried out under a hood. Small amounts of nitrotoluene are lost by volatilization, but this loss is not serious, as can be seen from the yield of product obtained.
2. Ten or 20 g. of unchanged nitrotoluene can be recovered from the reaction mixture by steam distillation, but the value of the by-product would not pay for the time spent in recovery.
3. The washing of the crude reaction product with dilute sulfuric acid is advisable, if good material is to be obtained. If an efficient centrifuge is available for use at this stage of the operation, this separate washing may prove to be less essential.
4. When a sparingly soluble organic acid is precipitated from fairly concentrated solution, the precipitate is liable to carry down with it some of the salt of the organic acid. Addition of the salt solution to the mineral acid, with stirring, avoids this difficulty.

3. Discussion

p-Nitrobenzoic acid can be prepared by the oxidation of *p*-nitrotoluene with nitric acid,[1] chromic acid,[2] permanganates,[3] and electrolytically.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 394
- Org. Syn. Coll. Vol. 3, 334

References and Notes

1. Fischer, Ann. **127**, 137 (1863); Wilbrand and Beilstein, Ann. **128**, 257 (1863); Lloyd and Gershon, U. S. pat. 1,458,715 [C. A. **17**, 2587 (1923)].
2. Beilstein and Geitner, Ann. **139**, 335 (1866).
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4. Boehringer and Sons, Ger. pat. 117,129 [Frdl. **6**, 112 (1900–02)]; Dunbrook and Lowy, Trans. Am. Electrochem. Soc. **45** (pre-print) (1924) [C. A. **18**, 1088 (1924)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

permanganates

sulfuric acid (7664-93-9)

Benzene (71-43-2)

sodium hydroxide (1310-73-2)

nitric acid (7697-37-2)

chromic acid (7738-94-5)

sodium dichromate (7789-12-0)

nitrotoluene (88-72-2)

chromium hydroxide

nitrobenzoic acid (552-16-9)

p-NITROBENZOIC ACID, Benzoic acid, p-nitro- (62-23-7)

p-nitrotoluene (99-99-0)

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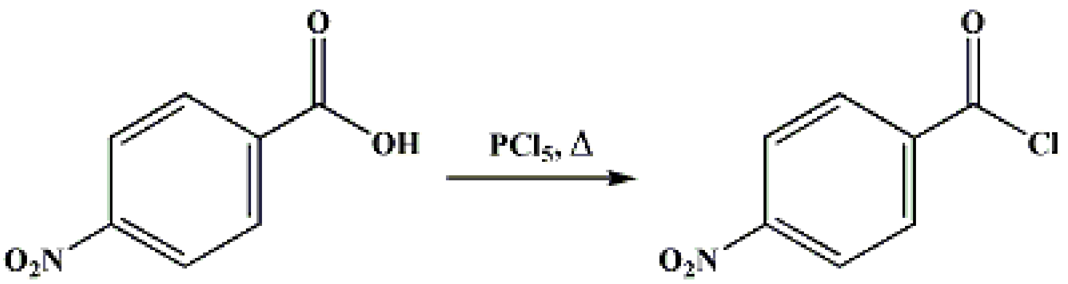
p-NITROBENZOYL CHLORIDE

[Benzoyl chloride, *p*-nitro-]



Submitted by Roger Adams and R. L. Jenkins.
Checked by Oliver Kamm

1. Procedure

In a 3-l. round-bottomed flask are mixed 501 g. (3 moles) of pure *p*-nitrobenzoic acid (p. 392) and 626 g. (3 moles) of pure phosphorus pentachloride (Note 1). The flask is provided with a calcium chloride tube from which emerges a tube leading to the surface of a flask of water, in order to absorb the hydrogen chloride formed during the reaction (Note 2). The flask is placed on a water bath and heated with occasional shaking until the reaction starts (fifteen to forty-five minutes). Vigorous evolution of hydrogen chloride takes place, and the heating is continued until the reaction is complete (fifteen to thirty minutes after the reaction starts). There is thus formed a light yellow, homogeneous liquid.

The reaction mixture is now transferred to a Claisen flask connected with a water-cooled condenser, and the phosphorus oxychloride is removed at ordinary pressure by raising the temperature of the oil bath (Note 3) gradually to 200–220°. The water condenser is then replaced by a *short* air-cooled condenser, and the residual liquid is distilled under reduced pressure (Note 4). A small quantity of phosphorus oxychloride first distils over, after which the receiver is changed and the temperature rises rapidly to the boiling point of *p*-nitrobenzoyl chloride, 197°/73 mm. (155°/20 mm.). During this distillation the oil bath should be kept at a temperature of about 230–250° (or at 210–215° if 20 mm. pressure is used). The yield is 500–534 g. (90–96 per cent of the theoretical amount). The distillate solidifies to a yellow crystalline mass melting at 71° (Note 5). The product may be recrystallized from ligroin or carbon tetrachloride, from which it separates in fine yellow needles melting at 73° (Note 6).

2. Notes

1. The yield of *p*-nitrobenzoyl chloride depends to a great extent upon the quality of the reagents used. With impure phosphorus pentachloride and pure *p*-

nitrobenzoic acid, yields of 70–80 per cent of the product are obtained. With pure phosphorus pentachloride and a less pure grade of *p*-nitrobenzoic acid, yields of 85–90 per cent are obtained. When neither reagent is of high grade, yields may fall as low as 40–50 per cent of the theoretical amount. In all such cases the color of the original reaction mixture varies from a deep yellow to a black.

Phosphorus pentachloride purchased as pure is occasionally of inferior quality and gives poor results. It is not a difficult matter to prepare in the laboratory a product suitable for this reaction. To 1 kg. (620 cc., 7.3 moles) of phosphorus trichloride, chlorine is added until the increase in weight is 500 g. The gas should be added above the surface of the liquid, which is stirred occasionally during the addition. The stirring should not be continuous, however, as this tends to allow the formation of the pentachloride in the tube, which thus becomes clogged. At the end of the reaction the mixture becomes practically solid.

2. A gas-absorption trap (Fig. 7 on p. 97) may be used for this purpose.

3. If the reaction mixture is heated with a free flame during the distillation under reduced pressure, there is considerable danger of superheating and consequent decomposition (sometimes violent) of the *p*-nitrobenzoyl chloride.

Experience with many preparations of this acid chloride has shown that it is desirable to have a safety water bottle between the receiving flask and the manometer to use during the distillation under reduced pressure. This avoids the passage of vapors of phosphorus oxychloride or acid chloride into the pump.

4. At the beginning of the distillation under reduced pressure the air condenser is warmed gently with a free flame to prevent solidification of the first portion of the distillate.

5. The product is best placed while hot in small wide-mouthed bottles and allowed to solidify. This prevents any moisture from the air from decomposing more than the surface layer of the acid chloride.

6. It is suggested that *p*-nitrobenzoyl chloride can be prepared in excellent yields by heating *p*-nitrobenzoic acid under reflux with an excess of thionyl chloride, the *p*-nitrobenzoyl chloride being distilled under reduced pressure after the excess of thionyl chloride has been removed by distillation at atmospheric pressure (J. Kenyon, private communication).

3. Discussion

p-Nitrobenzoyl chloride can be prepared from *p*-nitrobenzoic acid with phosphorus pentachloride;[1] with phosphorus trichloride, oxychloride, and chlorine;[2] with thionyl chloride;[3] and with thionyl chloride and pyridine.[4]

References and Notes

1. Gevekoht, Ann. **221**, 335 (1883).
2. E. I. du Pont de Nemours and Co., U. S. pat. 2,048,768 [C. A. **30**, 6010 (1936)].

3. J. Kenyon, private communication.
4. Carré and Libermann, Compt. rend. **199**, 1422 (1934).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ligroin

hydrogen chloride (7647-01-0)

phosphorus pentachloride (10026-13-8)

thionyl chloride (7719-09-7)

carbon tetrachloride (56-23-5)

Phosphorus Oxychloride (21295-50-1)

pyridine (110-86-1)

chlorine (7782-50-5)

phosphorus trichloride (7719-12-2)

phosphorus trichloride, oxychloride

p-NITROBENZOIC ACID (62-23-7)

p-Nitrobenzoyl chloride, Benzoyl chloride, p-nitro- (122-04-3)

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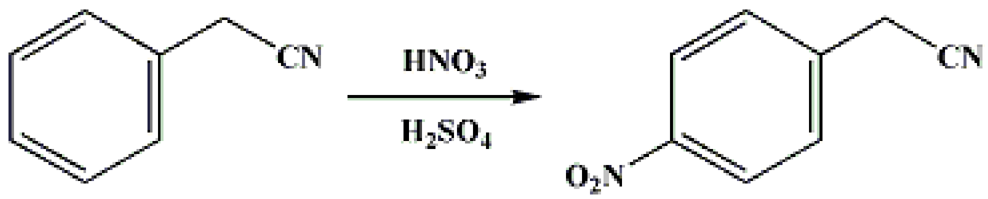
Organic Syntheses, CV 1, 396

p-NITROBENZYL CYANIDE

[α-Tolunitrile, *p*-nitro-]



Submitted by G. R. Robertson
Checked by Roger Adams and H. O. Calvery.

1. Procedure

In a 2-l. round-bottomed flask, fitted with a stopper holding a dropping funnel and a mechanical stirrer, is placed a mixture of 275 cc. (4.3 moles) of concentrated nitric acid (sp. gr. 1.42) (Note 1) and 275 cc. (4.9 moles) of concentrated sulfuric acid (sp. gr. 1.84). This is cooled to 10° in a freezing mixture, and 100 g. (0.85 mole) of benzyl cyanide (free from alcohol and water) (Note 2) is run in slowly, at such a rate that the temperature remains at about 10° and does not exceed 20°. After all the benzyl cyanide has been added (about one hour), the ice bath is removed, and the mixture is stirred for one hour and then poured onto 1200 g. of crushed ice. A pasty mass slowly separates; more than half of this mass is *p*-nitrobenzyl cyanide, the other constituents being *o*-nitrobenzyl cyanide, and a variable amount of an oil which resists hydrolysis; apparently no dinitro compounds are formed. The mass is filtered on a porcelain funnel with suction, pressed well to remove as much oil as possible, and dissolved in 500 cc. of boiling 95 per cent alcohol. On cooling, *p*-nitrobenzyl cyanide crystallizes; the mother liquor, on distillation, gives an impure alcohol which can be used for the next run. Recrystallization from 550 cc. of 80 per cent alcohol (sp. gr. 0.86 to 0.87) yields 70–75 g. (50–54 per cent of the theoretical amount) (Note 3) of a product which melts at 115–116°.

This product is satisfactory for most purposes, and incidentally for the preparation of *p*-nitrophenylacetic acid (p. 406). Occasionally it must be free even from traces of the ortho compound; if so, it should be crystallized again from 80 per cent alcohol; it then melts at 116–117°.

2. Notes

1. Fuming nitric acid may be used, but the procedure described is less expensive.
2. The yield of 70–75 g. is obtained from benzyl cyanide, which boils over a 5° range, prepared as described on p. 107. Very pure benzyl cyanide will give a slightly higher yield, whereas commercial grades may give only 50 g. of *p*-

nitrobenzyl cyanide and much oil.
3. The reaction has been also carried out with 500 g. of benzyl cyanide. Under these conditions a 5-l. flask was used, and it required two and one-half hours to add the benzyl cyanide. The yield of product was 325–370 g. (47–54 per cent of the theoretical amount).

3. Discussion

p-Nitrobenzyl cyanide has hitherto been prepared by the action of fuming nitric acid[1] on benzyl cyanide.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 406

References and Notes

1. Salkowski, Ber. **17**, 505 (1884); Pschorr, Ber. **33**, 170 (1900); Koessler and Hanke, J. Biol. Chem. **39**, 585 (1919); Robertson and Stieglitz, J. Am. Chem. Soc **43**, 180 (1921); Baker, Cooper, and Ingold, J. Chem. Soc. 426 (1928).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alcohol (64-17-5)

sulfuric acid (7664-93-9)

nitric acid (7697-37-2)

Benzyl cyanide (140-29-4)

p-Nitrophenylacetic acid (104-03-0)

p-Nitrobenzyl cyanide (555-21-5)

α-Tolunitrile, p-nitro- (619-72-7)

o-nitrobenzyl cyanide (610-66-2)

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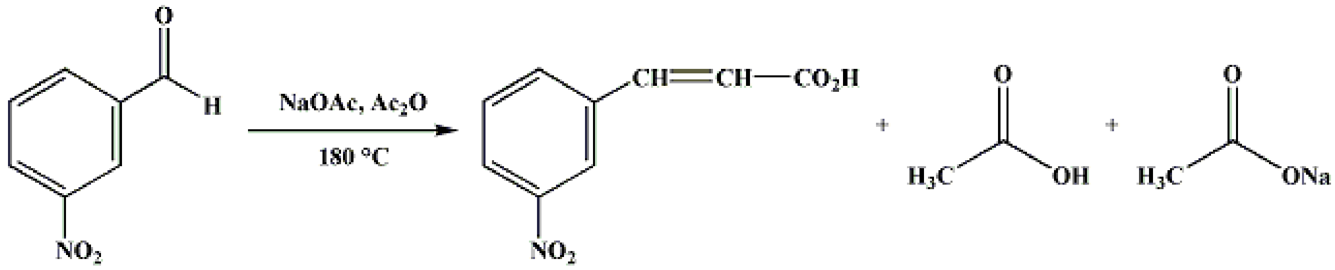
Organic Syntheses, CV 1, 398

m-NITROCINNAMIC ACID

[Cinnamic acid, *m*-nitro-]



Submitted by F. K. Thayer
Checked by Roger Adams and A. B. Adams.

1. Procedure

In a 200-cc. round-bottomed flask, fitted with a reflux condenser, are placed 50 g. (0.33 mole) of *m*-nitrobenzaldehyde (Note 1), 40 g. (0.48 mole) of freshly fused sodium acetate, and 70 g. (0.68 mole) of acetic anhydride. The contents of the flask are well mixed and the mixture heated in an oil bath held at 180° for about thirteen hours. After the reaction product has been allowed to cool slightly, it is poured into 200–300 cc. of water and then filtered by suction (Note 2). After the solid has been washed several times with water, it is dissolved in a solution of 20 cc. of aqueous ammonia (sp. gr. 0.9) in about 200 cc. of water. The solution of the ammonium salt, after filtering, is poured into a solution of 15 cc. of sulfuric acid (sp. gr. 1.84) in about 200 cc. of water (Note 3). The precipitated *m*-nitrocinnamic acid is filtered, redissolved in aqueous ammonia, and again precipitated by pouring the solution into dilute sulfuric acid (Note 4).

After the last precipitation, the *m*-nitrocinnamic acid is washed with a little water and then sucked as dry as possible (Note 5). The product, which still contains considerable water, is dissolved in 250–300 cc. of boiling 95 per cent alcohol from which the nitrocinnamic acid crystallizes on cooling. The yield is 47–49 g. (74–77 per cent of the theoretical amount). The product is pale yellow and melts at 192–194°. If a purer product is desired, it may be recrystallized from benzene or alcohol (Note 6).

2. Notes

1. The *m*-nitrobenzaldehyde used was the technical grade and melted at 50–53°.
2. In one run, the product was extracted from the reaction mixture with benzene, removed from the benzene by a sodium carbonate solution, and this solution in turn acidified to obtain the *m*-nitrocinnamic acid. Neither the product nor the yield was as satisfactory by this method.
3. If acid is added to the solution of the ammonium salt, the precipitated *m*-nitrocinnamic acid carries down a considerable quantity of ammonium salts.
4. There is always a small amount of material that is insoluble in the aqueous ammonia. This is removed by the second treatment.
5. The product is very difficult to dry. If it is removed from the filter after washing, several days are required for it to become dry. This dry product melts at about 190–193°.
6. The melting point of *m*-nitrocinnamic acid is given in the literature as 195° and 196–197°. Alcohol is mentioned as a good solvent for recrystallization, but experience in this work showed that benzene is also satisfactory, a white *m*-nitrocinnamic acid being obtained from this solvent.

3. Discussion

m-Nitrocinnamic acid can be prepared by the condensation of *m*-nitrobenzaldehyde with malonic acid in the presence of bases such as aniline,[1] ammonia,[1] and pyridine;[2] and from *m*-nitrobenzaldehyde with sodium acetate and acetic anhydride.[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 731

References and Notes

1. Knoevenagel, Ber. **31**, 2610 (1898).
2. Dutt, Quart. J. Indian Chem. Soc. **1**, 297 (1925); Kurien, Pandya, and Surange, ibid. **11**, 824 (1934).
3. Schiff, Ber. **11**, 1782 (1878); Tiemann and Oppermann, Ber. **13**, 2060 (1880); Reich and Koehler, Ber. **46**, 3732 (1913); Posner, J. prakt. Chem. (2) **82**, 425 (1910); Böck, Lock, and Schmidt, Monatsh. **64**, 408 (1934).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alcohol (64-17-5)

sulfuric acid (7664-93-9)

ammonia (7664-41-7)

Benzene (71-43-2)

acetic anhydride (108-24-7)

sodium acetate (127-09-3)

aniline (62-53-3)

sodium carbonate (497-19-8)

pyridine (110-86-1)

nitrocinnamic acid

Malonic acid (141-82-2)

m-Nitrobenzaldehyde (99-61-6)

m-Nitrocinnamic acid, Cinnamic acid, m-nitro- (555-68-0)

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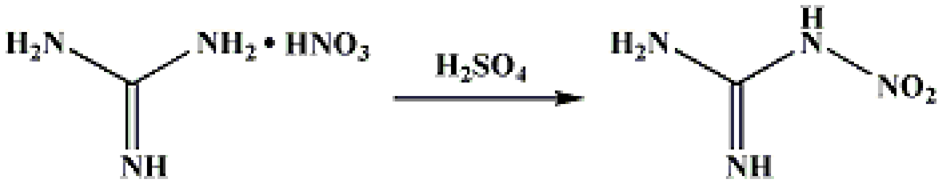
Organic Syntheses, CV 1, 399

NITROGUANIDINE

[Guanidine, nitro-]



Submitted by Tenney L. Davis
Checked by H. T. Clarke and Ross Phillips.

1. Procedure

To 500 cc. (Note 1) of concentrated sulfuric acid (sp. gr. 1.84), previously cooled in a freezing mixture, is added, in small portions and with hand stirring, 560 g. of crude (Note 2) guanidine nitrate (obtained from 210 g. of dicyanodiamide as described on p. 302). The temperature is not allowed to rise above 20° during the addition. When all has been added, the milky mixture is allowed to stand at room temperature with occasional stirring until it is homogeneous and free from crystals (Note 3). It is then poured with stirring into 6 l. of a mixture of cracked ice and water. The precipitated nitroguanidine is filtered, washed free from acid, and recrystallized from the least possible amount (4–5 l.) of boiling water (Note 4). The yield (Note 5) is 380–390 g. (73–75 per cent of the theoretical amount, based on the dicyanodiamide used). The product melts with decomposition at about 232° (Note 6).

2. Notes

1. It has been found in checking that the use of 800 cc. of acid, though not necessary, gives a much less viscous solution, which becomes homogeneous more rapidly.
2. This contains ammonium nitrate, which, however, does not interfere with the reaction.
3. The mixture has to stand fifteen to twenty hours before solution is complete.
4. The solution should be allowed to cool slowly, preferably overnight, when the nitroguanidine separates in long needles which resemble sublimed phthalic anhydride. The mother liquor contains only 3–4 g. per liter, and may be discarded.
5. In checking, yields amounting to 85–90 per cent of the theoretical quantity were obtained from pure guanidine nitrate.
6. Melting points varying between 220° and 250° have been obtained on the same sample, according to the rate of heating.

3. Discussion

Nitroguanidine can be prepared by the nitration of guanidine salts by means of nitric acid,[1] or by the action of concentrated sulfuric acid, or fuming nitric acid upon guanidine nitrate.[2] The nitration of guanidine thiocyanate yields a product which retains a small proportion of sulfur compounds, and the nitration of the sulfate requires vigorous treatment and gives poor yields. The procedure described, which yields the *alpha* form,[3] is simple and economical, and furnishes a good yield. A detailed study of the preparation from guanidine nitrate and sulfuric acid has been published.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 302
- Org. Syn. Coll. Vol. 3, 73

References and Notes

1. Thiele, Ann. **270**, 16 (1892).
2. Jousselin, Compt. rend. **88**, 1087 (1879); Pellizzari, Gazz. chim. ital. **21** (II), 406 (1891); Ewan and Young, J. Soc. Chem. Ind. **40**, 109 T (1921); Kato, Sugino, and Koidzumi, J. Electrochem. Assoc. (Japan) **2**, 187 (1934) [C. A. **28**, 7250 (1934)].
3. Davis, Ashdown, and Couch, J. Am. Chem. Soc. **47**, 1063 (1925).
4. Smith, Sabetta, and Steinbach, Ind. Eng. Chem. **23**, 1124 (1931).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

dicyanodiamide

sulfuric acid (7664-93-9)

nitric acid (7697-37-2)

phthalic anhydride (85-44-9)

ammonium nitrate

Guanidine nitrate (506-93-4)

Nitroguanidine, Guanidine, nitro- (556-88-7)

guanidine thiocyanate

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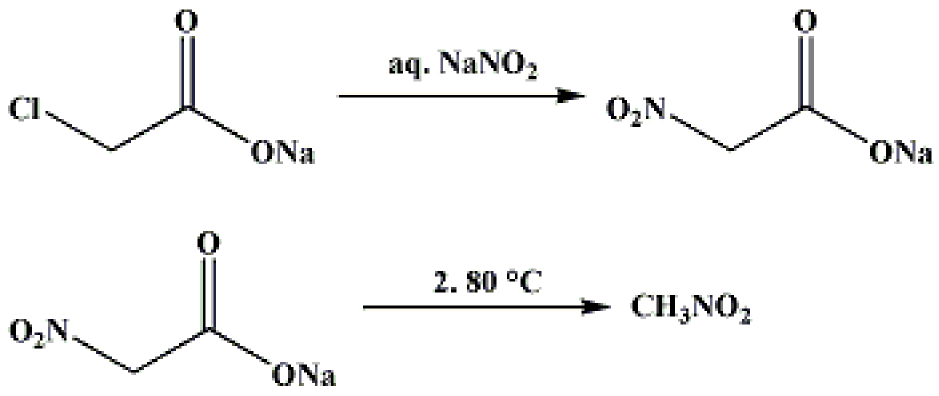
Organic Syntheses, CV 1, 401

NITROMETHANE

[Methane, nitro-]



Submitted by F. C. Whitmore and Marion G. Whitmore.
Checked by H. T. Clarke and J. H. Bishop.

1. Procedure

To a mixture of 500 g. (5.3 moles) of chloroacetic acid and 500 g. of cracked ice, is added, with stirring, just sufficient cold 40 per cent sodium hydroxide solution to make the solution faintly alkaline to phenolphthalein. About 360 cc. is required; the temperature should not rise above 20° (Note 1). The solution is then mixed with 365 g. (5.3 moles) of sodium nitrite dissolved in 500 cc. of water and heated in a 3-l. round-bottomed flask fitted with a two-holed stopper containing a bent tube of large diameter connecting with an efficient condenser (set downward for distillation) and a thermometer dipping into the liquid. The receiver should be so arranged that it can be cooled, if necessary, by a stream of water.

The solution is heated slowly until the first appearance of bubbles of carbon dioxide, which occurs when the temperature has reached about 80°. The flame is then removed and the reaction allowed to proceed by itself (Note 2). If no rise in temperature occurs, heat is very cautiously applied until the temperature rises to 85°, when the flame is again removed (Note 3). At this temperature the exothermic decomposition of the sodium nitroacetate becomes so rapid that the temperature rises almost to 100° without further application of external heat. If heat is applied after the temperature of the liquid reaches 85°, violent frothing will occur, with serious loss of nitromethane. If the reaction becomes too vigorous it may be checked by applying a wet towel to the flask. Nitromethane starts to distil over at about 90°. During the spontaneous heating, about 120 cc. of nitromethane distils over, accompanied by about 170 cc. of water (Note 4). This water is saved for redistillation.

When the mixture ceases to maintain its temperature spontaneously at 95–100°, heat is applied cautiously until the temperature reaches 110°. About 13 cc. of nitromethane

and 200 cc. of water distil over. Further distillation gives water which contains too little nitromethane to pay for recovery. At this point enough sodium chloride and sodium carbonate have separated to cause serious bumping.

The water separated from the nitromethane distillates is mixed with one-fourth of its weight of salt, and redistilled, yielding 10–12 cc. of nitromethane and about 100 cc. of water. This water on distillation gives 3–4 cc. of nitromethane and about 45 cc. of water (Note 5).

The total yield of moist product is 125–135 g.; on drying with a little calcium chloride and distilling, 115–125 g. of pure nitromethane, boiling at 98–101°, is obtained (35–38 per cent of the theoretical amount). A small forerun distils over below 98°, and a little dark brown residue remains (Note 6).

2. Notes

1. In making the sodium chloroacetate, the use of sodium hydroxide with proper cooling is much more rapid than the use of sodium carbonate. In the case of sodium hydroxide it is essential to keep the solution cool in order to prevent the formation of sodium glycolate. If it is preferred to employ sodium carbonate, about 300 g. of the anhydrous material will be required to make the solution slightly alkaline.
2. The thermometer dipping *in the liquid* is absolutely necessary, as the success of the preparation depends on proper temperature control. The vital point of the whole preparation is to remove all external heat as soon as the reaction is well started. This is between 80 and 85°. No frothing ever occurs when this precaution is rigidly adhered to.
3. Several of these distilling sets can be set up and run by one operator, if each lot is started only when the preceding one has reached 85° and external heat has been removed. The corresponding water layers from different sets can be united and distilled at once.
4. It has been recommended[1] that use be made of a gravity separator connected with the adapter in order to separate the nitromethane as fast as it condenses. It was found inadvisable to use such a separator, as the nitromethane is so little heavier than water that a rapid separation is not possible; drops of nitromethane remain suspended and pass over with the water. It is best to allow the distillates to stand in cylinders for at least one-half hour before separating the nitromethane by means of a separatory funnel. During this standing, as much as 2 per cent more of nitromethane sometimes settles out.
5. If the time consumed is an important consideration, it is well to note that the spontaneous heating from 85° to 100° gives three-fourths of all the nitromethane obtained in the preparation. This takes less than one hour. The further heating above 100° and the distillations of the water layers take over two hours, and give only one-fourth of the total yield.
6. It is suggested that improved yields are obtainable when 374 g. of crystalline boric acid is added subsequent to the sodium nitrite and prior to the heating. In

this way, carbon dioxide together with some oxides of nitrogen are evolved at about 45°. The reason offered for the higher yields is the destruction of sodium bicarbonate by the boric acid, which thereby prevents alkaline hydrolysis of the sodium chloroacetate (C. L. Tseng, private communication; [2]).
The yield is somewhat improved by using 625 g. of chloroacetic acid and about 450 cc. of 40 per cent sodium hydroxide solution instead of the 500 g. and 360 cc., respectively, now specified (H. Adkins, private communication; [2]).

3. Discussion

Nitromethane can be prepared by the action of dimethyl sulfate on potassium nitrite,[3] or of methyl *p*-toluenesulfonate[4] or methyl chloride[5] on sodium nitrite; and from potassium nitrite and potassium chloroacetate,[2] or, preferably, the corresponding sodium salts.[6] Nitromethane is now commercially available as a product of the vapor-phase nitration of the lower paraffin hydrocarbons.[7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 413

References and Notes

1. Steinkopf, Ber. **42**, 3438 (1909).
2. Kolbe, J. prakt. Chem. (2) **5**, 427 (1872); Preibische, ibid. (2) **8**, 316 (1874); Steinkopf, Ber. **41**, 4457 (1908).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

oxides of nitrogen

calcium chloride (10043-52-4)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

sodium nitrite (7632-00-0)

carbon dioxide (124-38-9)

dimethyl sulfate (77-78-1)

methyl chloride (74-87-3)

chloroacetic acid (79-11-8)

sodium chloroacetate (3926-62-3)

Nitromethane, Methane, nitro- (75-52-5)

phenolphthalein (77-09-8)

sodium nitroacetate

sodium glycolate (2836-32-0)

boric acid (10043-35-3)

potassium nitrite (7758-09-0)

potassium chloroacetate

Methyl p-toluenesulfonate (80-48-8)

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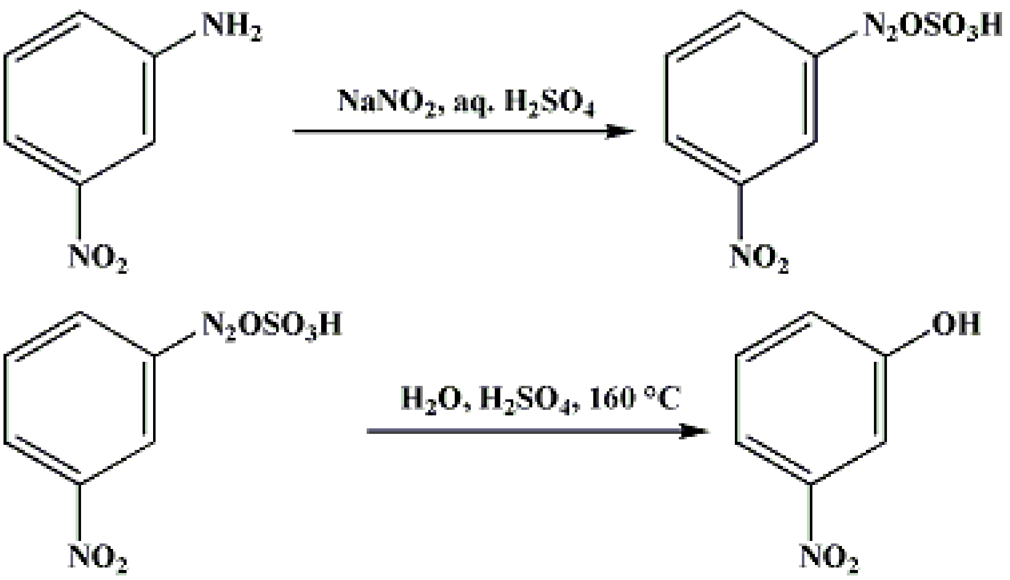
Organic Syntheses, CV 1, 404

m-NITROPHENOL

[Phenol, *m*-nitro-]



Submitted by R. H. F. Manske
Checked by H. T. Clarke and M. R. Brethen.

1. Procedure

In a 4-l. beaker is placed 210 g. (1.5 moles) of finely powdered *m*-nitroaniline (Note 1). A cold mixture of 450 cc. of water and 330 cc. of concentrated sulfuric acid is added with hand or mechanical stirring, and then about 800 g. of finely crushed ice. When a homogeneous mixture has resulted, a solution of 105 g. (1.52 moles) of sodium nitrite in 250 cc. of water is added rapidly over a period of eight to ten minutes at the bottom of the mixture through a separatory funnel (Note 2) until a permanent color is given to starch-iodide paper (about 25–30 cc. of nitrite solution remains unused). The temperature during diazotization should be maintained at 0–5°. Stirring is continued for five to ten minutes longer, and the solution allowed to settle for another five minutes. A heavy crystalline deposit of *m*-nitrobenzenediazonium sulfate settles at the bottom of the beaker, from which the supernatant liquid is decanted (Note 3).

While the diazotization is in progress, 1 l. of concentrated sulfuric acid is added to 750 cc. of water in a 5-l. round-bottomed flask and the mixture heated to boiling (160°) with a large ring burner. The liquor from the diazotization is then added from a separatory funnel at such a rate that the acid mixture boils very vigorously. About fifty minutes is required for this addition. The crystalline diazonium sulfate is then added in small portions at such a rate that the evolved nitrogen does not cause loss of material by excessive foaming. Boiling is continued for a few minutes longer, and the contents of the flask are poured into a large beaker (Note 4) set in running cold water, and

vigorously stirred to obtain a homogeneous crystal magma.

When completely cold, the nitrophenol is filtered, thoroughly pressed out, drained with suction, and washed with several portions of iced water, 450 cc. in all being used. It is spread on large sheets of filter paper and dried in a warm room. As thus prepared it has a yellowish brown appearance with darker particles intermixed. The yield is 170–180 g. (81–86 per cent of the theoretical amount) (Note 5).

It may be purified by recrystallization from hot hydrochloric acid, as recommended in Org. Syn. **3**, 89, but on account of the difficulty of filtration this procedure is satisfactory on a small scale only. It is preferably distilled in 200-g. lots from a 500-cc. Claisen flask under 10–15 mm. pressure, b.p. 160–165°/12 mm. It is important that no air inlet be used to prevent bumping, since under these conditions the nitrophenol partly sublimes and causes trouble by stopping up the connections. A filter or distilling flask is used as a receiver, and only a short but wide-bore (10-mm.) air condenser is necessary (Note 6). The product is pale yellow and melts at 95–96°. The yield from 200 g. of crude product is 180–185 g.

2. Notes

1. The *m*-nitroaniline used in these experiments was a commercial specimen of 98.4 per cent purity. A less pure specimen did not give a greatly decreased yield. The *m*-nitroaniline may also be added to the mixture prepared by adding the ice to the diluted acid, but this procedure is not quite so satisfactory.
2. The addition of the sodium nitrite solution should be as rapid as possible. If it is too rapid, however, considerable foaming occurs.
3. The filtration of this solution is slow and usually unnecessary. Occasionally undetermined impurities are present, and then washing of the diazonium salt with iced water by decantation, followed by filtration, becomes desirable.
4. In the first part of the addition the solution remains pale yellow to brown, but when the solution becomes saturated with the nitrophenol the nitrophenol separates as a dark oil which is not filtered off. The final volume of the solution is about 3.5 l., and the boiling temperature about 120°.
5. By using the same molecular proportions the following *m*-nitrophenols were prepared in equally good yields from the corresponding *m*-nitroanilines: 3-methoxy-5-nitrophenol and 3-nitro-4,6-xylenol. For the first compound it is advisable to use slightly more ice in the diazotization and add the diazonium solution to a mixture of equal volumes of sulfuric acid and water.
6. After the *m*-nitrophenol has been distilled the flask should be allowed to cool before air is admitted. Otherwise the residue may decompose with explosive violence (W. E. Bachmann and B. W. Rottschaefer, private communication).

3. Discussion

m-Nitrophenol can be prepared by diazotizing *m*-nitroaniline and subsequently heating with a large volume of water;[1] by treating benzene with mercury nitrate and nitric acid

in an atmosphere of carbon dioxide;[2] and by boiling *m*-nitrophenetole (from phenacetin by nitration, hydrolysis, and diazotization in alcohol) with hydrobromic acid,[3] a method which is better than that given in Org. Syn. **3**, 87, but far inferior to the present procedure.

References and Notes

1. Fittig, Ber. **7**, 179 (1874); Henriques, Ann. **215**, 323 (1882); De Bruyn, Rec. trav. chim. **2**, 216 (1883); Holleman and Wilhelmy, ibid. **21**, 433 (1902); Adams and Wilson, Org. Syn. **3**, 87 (1923).
2. Macdonald and Calvert, U. S. pat. 1,320,076 [C. A. **14**, 71 (1920)]; Davis, U. S. pat. 1,417,368 [C. A. **16**, 2518 (1922)].
3. Unpublished experiments by one of the editors.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

m-nitrophenols

m-nitroanilines

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

nitric acid (7697-37-2)

HYDROBROMIC ACID (10035-10-6)

nitrogen (7727-37-9)

sodium nitrite (7632-00-0)

nitrite (14797-65-0)

carbon dioxide (124-38-9)

phenacetin (62-44-2)

nitrophenol (88-75-5)

3-Methoxy-5-nitrophenol

3-Nitro-4,6-xylenol

mercury nitrate

m-nitroaniline (99-09-2)

m-Nitrophenol, Phenol, m-nitro- (554-84-7)

m-nitrobenzenediazonium sulfate

m-nitrophenetole (621-52-3)

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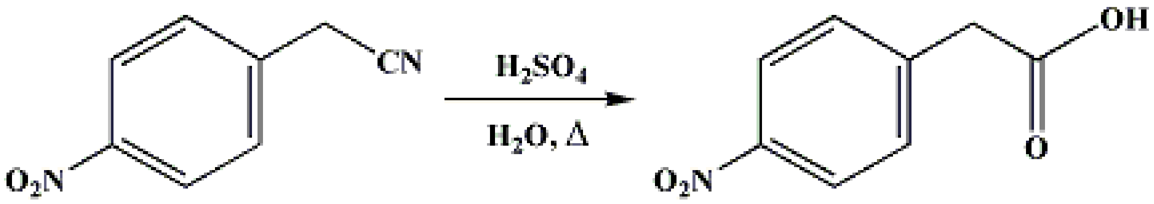
Organic Syntheses, CV 1, 406

p-NITROPHENYLACETIC ACID

[α-Toluic acid, *p*-nitro-]



Submitted by G. Ross Robertson
Checked by Roger Adams and H. O. Calvery.

1. Procedure

In a 1-l. round-bottomed flask is placed 100 g. (0.62 mole) of *p*-nitrobenzyl cyanide (p. 396). A solution of 300 cc. (5.4 moles) of concentrated sulfuric acid (sp. gr. 1.84) in 280 cc. of water is prepared, and two-thirds of this solution is poured onto the *p*-nitrobenzyl cyanide. The mixture is shaken well, until the solid is all moistened with the acid. Any solid material adhering to the walls of the vessel is now washed down into the liquid with the remainder of the acid; the flask is attached to a reflux condenser, then set, without shaking, over a 10-cm. hole in a large sheet of asbestos board which rests on a tripod, and heated until the mixture boils (Note 1). The boiling is continued for fifteen minutes (Note 2).

The reaction mixture, which becomes rather dark, is diluted with an equal volume of cold water and cooled to 0° or below. The solution is filtered; the precipitate is washed several times with ice water and then dissolved in 1600 cc. of boiling water (Note 3). This solution is filtered as rapidly as possible through a large folded filter, preferably with a steam funnel (Note 4). In spite of all precautions, however, some solid usually separates on the filter. This must be redissolved in a minimum quantity of boiling water, and this solution then filtered into the main solution. The *p*-nitrophenylacetic acid separates in long, pale yellow needles, which melt at 151–152°. The yield is 103–106 g. (92–95 per cent of the theoretical amount).

2. Notes

1. If the flask is not protected with an asbestos board or the equivalent, decomposition occurs where the substance is superheated on the side walls of the flask. If crystals of the cyanide are allowed to remain on the upper walls of the flask, they are not easily washed down and so are not hydrolyzed.
2. In making experiments with 500 g. of *p*-nitrobenzyl cyanide, it was found that the time for hydrolysis was about the same as when smaller amounts were used.
3. If a good grade of cyanide is used, it is not necessary to add animal charcoal in order to obtain the acid in a pure state. With technical *p*-nitrobenzyl cyanide,

a few grams of animal charcoal are added in dissolving the precipitate.
4. The solubility curve of *p*-nitrophenylacetic acid is very steep at temperatures near 100°, so that the filtering of the boiling solution should be rapid.

3. Discussion

p-Nitrophenylacetic acid can be prepared by the nitration of phenylacetic acid[1] and by the hydrolysis of its nitrile with hydrochloric acid.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 52
- Org. Syn. Coll. Vol. 1, 396
- Org. Syn. Coll. Vol. 3, 444

References and Notes

1. Maxwell, Ber. **12**, 1765 (1879); Borsche, Ber. **42**, 3596 (1909).
2. Gabriel, Ber. **15**, 834 (1882).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

Phenylacetic acid (103-82-2)

p-Nitrophenylacetic acid (104-03-0)

p-Nitrobenzyl cyanide (555-21-5)

α-Toluic acid, p-nitro-

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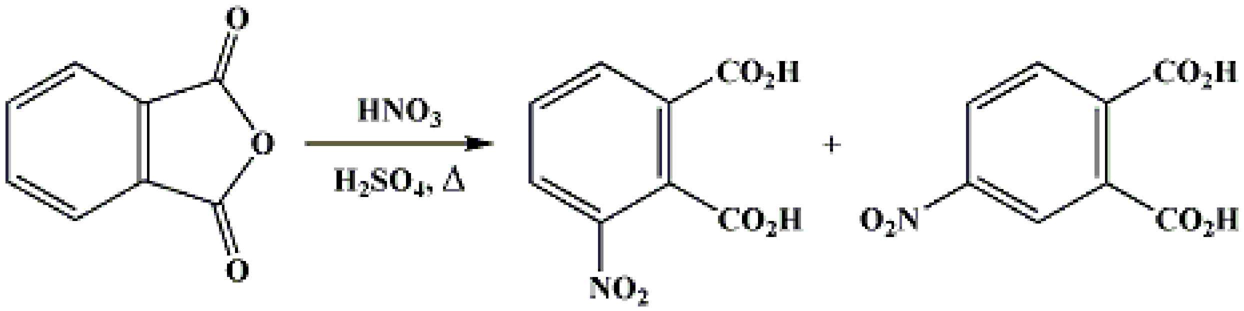
Organic Syntheses, CV 1, 408

3-NITROPHTHALIC ACID

[Phthalic acid, 3-nitro-]



Submitted by P. J. Culhane and Gladys E. Woodward.
Checked by Henry Gilman and C. C. Vernon.

1. Procedure

A 2-l. beaker placed on a piece of board in the bottom of a 4-l. (1-gallon) crock is fitted with a mechanical stirrer (Note 1). In the beaker are placed 650 cc. of commercial sulfuric acid (sp. gr. 1.84) and 500 g. (3.4 moles) of technical phthalic anhydride. The mixture is stirred, and steam is passed into the crock. When the mixture reaches 80°, the steam is shut off and 210 cc. of fuming nitric acid (sp. gr. 1.51) is added slowly from a separatory funnel at such a rate as to maintain the temperature of the stirred mixture at 100–110°. The addition requires one to two hours. After the fuming acid has been added, 900 cc. of concentrated nitric acid (sp. gr. 1.42) is added as rapidly as possible without causing the temperature to rise above 110° (Note 2). The mixture is then stirred and heated by passage of steam into the crock for two hours longer.

The mixture is allowed to stand overnight and then poured into 1.5 l. of water in a 4-l. (1-gallon) crock. After cooling, the solid mixture of 3- and 4-nitrophthalic acids is filtered by suction through a Büchner funnel without a filter paper (Note 3) or through a filtros plate (p. 11). The wet cake is returned to the crock and stirred thoroughly with 200 cc. of water, which dissolves a large amount of the 4-nitrophthalic acid. The mixture is again filtered by suction (Note 4), and the wet cake is dissolved by boiling with 200–300 cc. of water (Note 5). The solution is filtered hot and stirred mechanically until crystallization starts. It is then allowed to stand overnight, as the crystallization is slow. The crystals are filtered by suction and air-dried. The product melts at 205–210° in a sealed tube. The yield is 200–220 g. (28–31 per cent of the theoretical amount) (Note 6). Recrystallization of 200 g. of the crude acid from 300 cc. of water gives 170 g. of acid melting at 215–218° (capillary tube sealed 2 cm. from bottom). The washings and mother liquor from the crystallization may be saved for the recovery of 4-nitrophthalic acid (Note 7).

2. Notes

1. A large steam bath may be used instead of the crock. A motor should not be placed directly above the nitration mixture because of the fumes evolved. The motor should be connected with the stirrer by a belt, or, better still, a stirrer of the wind turbine type should be used. If a hood is not available, a 3-l. three-necked flask provided with a glass tube to conduct the fumes outside has been found satisfactory. When a beaker is used, it is recommended that two rectangular glass plates be placed across the top to reduce the danger of acid spattering.
2. The indicated proportions of fuming nitric acid and concentrated acid give as good results as fuming acid alone. The addition of the concentrated acid first does not work well.
3. The filtrate is repeatedly poured through the filter until clear. The mother liquor containing sulfuric acid and nitric acid cannot be worked up profitably for the recovery of the nitrophthalic acids.
4. The mother liquor is saved for the recovery of 4-nitrophthalic acid (Note 7). The product, if air-dried at this point, weighs about 500 g.
5. The amount of water needed depends on the dryness of the cake of crude acids.
6. The yields may be increased by various refinements, but the cost of the 3-nitrophthalic acid obtained is also increased. Because of the extreme cheapness of phthalic anhydride, it is inadvisable to increase the labor cost unduly in order to improve the yield. If a purer product is desired, crystallization from acetic acid will give 3-nitrophthalic acid melting at about 217° (closed tube).
7. The washings and mother liquors from crystallizations may be evaporated and esterified to separate the isomeric acids.[1]
About 370 g. of air-dried solid material may be recovered from the mother liquors and washings. Care must be exercised in concentrating these solutions, as the solid material chars readily when the solution becomes concentrated.

3. Discussion

3-Nitrophthalic acid can be prepared by the oxidation of nitronaphthalene,[2] and by the nitration of phthalic acid in a variety of ways.[3] The procedure described is based on that of Bogert and Boroschek[1] and of Lawrance.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 56
- Org. Syn. Coll. Vol. 1, 410
- Org. Syn. Coll. Vol. 2, 457
- Org. Syn. Coll. Vol. 3, 656

References and Notes

1. Bogert and Boroschek, J. Am. Chem. Soc. **23**, 743 (1901).
2. Beilstein and Kurbatow, Ann. **202**, 217 (1880); de Aguiar, Ber. **5**, 899 (1872)
3. Faust, Ann. **160**, 57 (1871); Miller, Ann. **208**, 224 (1881); Kenner and Mathews, J. Chem. Soc. **105**, 2476 (1914); Cohen, Woodroffe, and Anderson, ibid. **109**, 232 (1916); Littmann, J. Am. Chem. Soc. **47**, 1980 (1925).
4. Lawrance, ibid. **42**, 1872 (1920).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

3- and 4-nitrophthalic acids

nitrophthalic acids

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

nitric acid (7697-37-2)

3-Nitrophthalic acid, Phthalic acid, 3-nitro- (603-11-2)

phthalic anhydride (85-44-9)

4-nitrophthalic acid (610-27-5)

nitronaphthalene (86-57-7)

phthalic acid (88-99-3)

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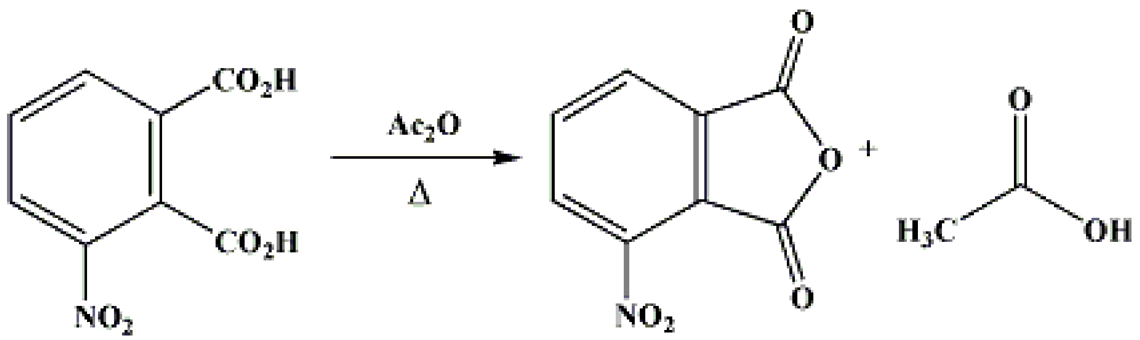
Organic Syntheses, CV 1, 410

3-NITROPHTHALIC ANHYDRIDE

[Phthalic anhydride, 3-nitro-]



Submitted by B. H. Nicolet and J. A. Bender.
Checked by Frank C. Whitmore and W. F. Singleton.

1. Procedure

To 211 g. (1 mole) of 3-nitrophthalic acid (p. 408) in a 300-cc. round-bottomed flask fitted with a reflux condenser is added 205 g. (190 cc., 2 moles) of acetic anhydride (99–100 per cent). The mixture is heated to gentle boiling until the acid is completely dissolved and then for about ten minutes longer. The hot mixture is poured (Hood) into a 15-cm. porcelain dish and allowed to cool. The crystal mass is ground thoroughly in a mortar and filtered by suction. The crystals are returned to the mortar and the filtrate (about 140 cc.) is placed in a 300-cc. distilling flask. The crystals are ground with 150 cc. of alcohol-free ether (Note 1) and filtered. They are again returned to the mortar and similarly washed.

After drying in the air for a short time, the product is dried to constant weight at 105°. The yield of product melting at 163–164° is 170–180 g. (88–93 per cent of the theoretical amount). The acetic acid filtrate is distilled with a thermometer in the liquid until the temperature is 150°. The distillate amounts to about 120 cc. The residue is poured into the mortar and, after cooling, is ground with some of the ether used in washing the original crystals. Thus about 10 g. of a product melting at 160–163° is obtained.

2. Notes

1. Dry ether is recommended because ordinary ether contains alcohol, and some monoethyl ester may form. Ordinary u.s.p. ether which has stood over calcium chloride for two days is satisfactory.

3. Discussion

3-Nitrophthalic anhydride can be prepared by heating 3-nitrophthalic acid under

various conditions[1] and by the action of acetic anhydride,[2] essentially as in the procedure described. The direct nitration of phthalic anhydride yields 3-nitrophthalic anhydride together with the isomeric 4-nitro compound.[3]

References and Notes

1. Kahn, Ber. **35**, 3859 (1902).
2. McKenzie, J. Chem. Soc. **79**, 1137 (1901).
3. Hayashi and Kawasaki, J. Soc. Chem. Ind. Japan **36**, Suppl. binding 121 (1933) [C. A. **27**, 2947 (1933)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alcohol-free ether

alcohol (64-17-5)

calcium chloride (10043-52-4)

acetic acid (64-19-7)

ether (60-29-7)

acetic anhydride (108-24-7)

3-Nitrophthalic acid (603-11-2)

phthalic anhydride (85-44-9)

3-Nitrophthalic anhydride, Phthalic anhydride, 3-nitro- (641-70-3)

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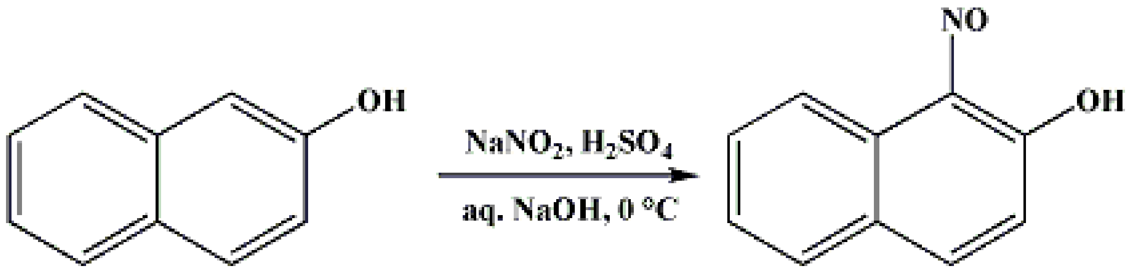
Organic Syntheses, *CV 1*, *411*

NITROSO-β-NAPHTHOL

[2-Naphthol, 1-nitroso-]



Submitted by C. S. Marvel and P. K. Porter.
Checked by H. T. Clarke and W. W. Hartman.

1. Procedure

In a 12-l. round-bottomed flask (Note 1) fitted with a mechanical stirrer is placed 500 g. (3.5 moles) of technical β-naphthol dissolved in a warm solution of 140 g. (3.5 moles) of sodium hydroxide in 6 l. of water. The solution is cooled to 0° in an ice and salt bath, and 250 g. (3.5 moles) of powdered technical sodium nitrite is added. Stirring is started, and 1100 g. (833 cc., 4.6 moles) of sulfuric acid (sp. gr. 1.32) is added from a dropping funnel at such a rate that the whole is added in one to one and one-half hours, the temperature being kept at 0°. During the reaction, crushed ice is added from time to time to maintain the temperature at 0°; about 1 kg. is generally used (Note 2). After all the sulfuric acid has been added, the solution should react acid to Congo red paper. The mixture is stirred one hour longer at the low temperature, and then the nitroso-β-naphthol, which has gradually separated during the reaction, is filtered with suction and washed thoroughly with water. The product is at first light yellow in color, but after three to four days it gradually changes to a dark brown. The moisture content seems to have some effect on the color.

After the product has been air-dried for about four days, the yield is about 665 g.; it melts at 97°. A sample of this partially dried product, on drying in a vacuum desiccator over sulfuric acid for twenty hours, loses about 10 per cent of its weight, and the melting point is 106°. By longer drying under ordinary conditions, the melting point of 106° is reached (Note 3). The total yield of dry product is about 595 g. (99 per cent of the theoretical amount).

This product is satisfactory for most purposes. It may be obtained in a crystalline condition, however, by recrystallizing from hot ligroin (b.p. 60–90°). About 2 g. of nitroso-β-naphthol will dissolve in 15 cc. of boiling ligroin. The product is not very soluble in cold ligroin, so that nearly all is recovered.

2. Notes

1. A large vessel is needed for the reaction, as the nitroso-β-naphthol separates in a finely divided condition and there is some tendency to foam.
It has been suggested that instead of a flask there be used a 13–14 l. bottle or crock with an opening of 20–22 cm. and equipped with a stirrer of heavy glass rod having four or five right-angle bends which extend to the top of the bottle and which are just small enough to fit the mouth. If the salt-ice mixture in the cooling bath is stirred well, a temperature of 0° may be maintained without internal cooling (L.F. Fieser, private communication).
2. It is very necessary to keep the temperature near 0° while adding the sulfuric acid, or a tarry product will be obtained. Vigorous stirring and the addition of the sulfuric acid at the proper rate are essential for a good product. Instead of the 1100 g. of sulfuric acid (sp. gr. 1.32) there can, of course, be added an equivalent amount of concentrated acid and sufficient ice to give a cold solution.
3. The final air-dried product is pure except for its moisture content, as is shown by the fact that on drying in a vacuum desiccator it has a very good melting point.

3. Discussion

Nitroso-β-naphthol can be prepared by the action of sulfuric acid upon a solution of potassium or sodium nitrite and the sodium salt of β-naphthol;[1] by the action of sodium nitrite upon an alcoholic solution of zinc chloride and β-naphthol;[2] by the action of sodium nitrite upon β-naphthol suspended in zinc sulfate solution;[3] and electrolytically from β-naphthol.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 33
- Org. Syn. Coll. Vol. 2, 42

References and Notes

1. Fuchs, Ber. **8**, 1026 (1875); Groves, J. Chem. Soc. **45**, 295 (1884); Lagodzinski and Hardine, Ber. **27**, 3076 (1894).
2. Henriques and Ilinski, Ber. **18**, 705 (1885).
3. Koehler, Ger. pat. 25,469 [Frdl. **1**, 335 (1877–87)].
4. Emi, Repts. Imp. Ind. Research Inst., Osaka (Japan) **15**, No. I, 1 (1934) [C. A. **29**, 2457 (1935)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ligroin

potassium or sodium nitrite

sulfuric acid (7664-93-9)

sodium hydroxide (1310-73-2)

sodium nitrite (7632-00-0)

β-naphthol (135-19-3)

zinc chloride (7646-85-7)

Nitroso-β-naphthol, 2-Naphthol, 1-nitroso- (131-91-9)

sodium salt of β-naphthol

zinc sulfate (7733-02-0)

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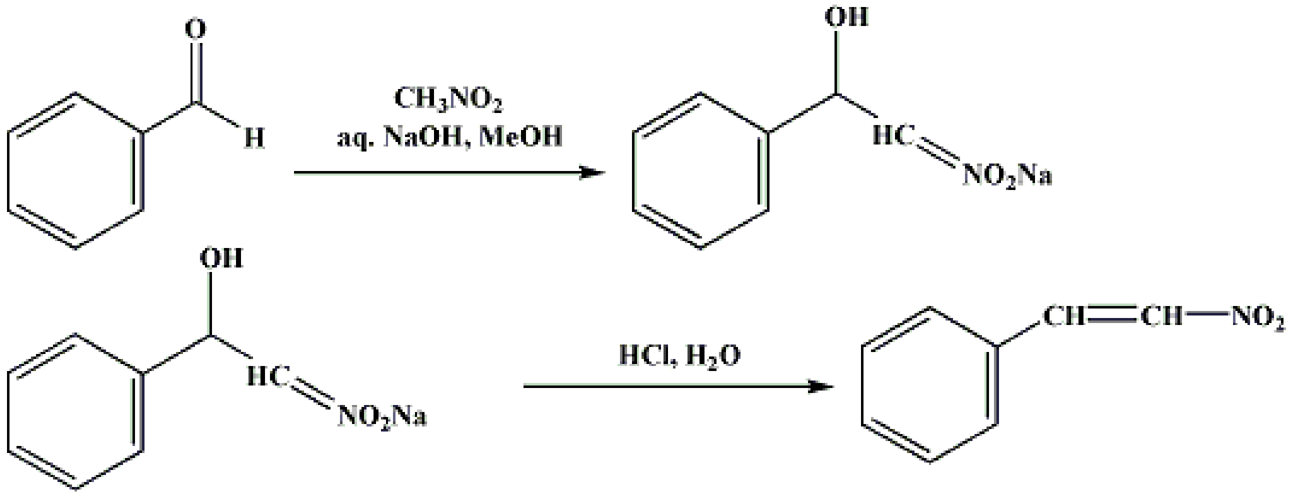
Organic Syntheses, CV 1, 413

NITROSTYRENE

[Styrene, β-nitro-]



Submitted by David E. Worrall
Checked by C. S. Marvel and W. H. Lycan.

1. Procedure

In a 6-l. wide-mouthed bottle, packed in a pail with a freezing mixture of ice and salt and fitted with a mechanical stirrer, a thermometer, and a separatory funnel, are placed 305 g. (5 moles) of nitromethane (p. 401), 530 g. (5 moles) of benzaldehyde (Note 1), and 1000 cc. of methyl alcohol. A solution of sodium hydroxide is prepared by dissolving 210 g. (5.25 moles) of sodium hydroxide in approximately an equal volume of water and cooling. It is then diluted to 500 cc. with ice and water, poured into the funnel, and added with stirring to the nitromethane mixture at such a rate that the temperature is kept at 10–15° (Note 2) and (Note 3).

A bulky white precipitate forms rapidly during the addition of the alkali. The mixture gets so thick that stirring becomes difficult and it may be advisable to add 100 cc. more of methyl alcohol. After fifteen minutes' standing, the pasty mass is converted to a clear solution by the addition of 3–3.5 l. of ice water containing crushed ice (Note 4). Hydrochloric acid (made by diluting 1000 cc. of concentrated hydrochloric acid with 1500 cc. of water) is placed in a 15-l. mixing jar and the reaction mixture run into this from the separatory funnel at such a rate that the stream just fails to break into drops (Note 5). A pale yellow crystalline mass separates almost immediately as the alkaline solution comes in contact with the acid. After the stirring is stopped, the solid settles to the bottom of the jar. The major part of the cloudy liquid layer is removed by decantation, and the residue filtered by suction and washed with water until free from chlorides. This product is freed from all but a negligible amount of water by melting in a beaker immersed in hot water. Two layers are formed, and on cooling again the lower layer of nitrostyrene freezes; the water may then be poured off. The crude nitrostyrene is purified by dissolving in 420 cc. of hot ethyl alcohol (Note 6), filtering the solution into a warm suction flask to remove solid impurities, and then cooling until crystallization is complete. The yield of crude product melting at 56–58° is 650–670 g. The yield of recrystallized nitrostyrene melting sharply at 57–58° is 600–620 g. (80–83 per cent of the theoretical amount). The whole procedure, including purification, can be done in a day.

2. Notes

1. Technical benzaldehyde which had been washed with sodium carbonate solution, dried, and distilled under reduced pressure, was used in this preparation.
2. The first few cubic centimeters of sodium hydroxide solution should be added cautiously to the nitromethane mixture since, after a short induction period, there is a considerable evolution of heat and the temperature may rise from – 10° to 30° or even higher in spite of good stirring. If necessary, this rise in temperature is easily checked by adding a handful of crushed ice directly to the mixture. After this initial reaction the rest of the alkali may be added more rapidly.
3. The condensation induced by sodium hydroxide is almost instantaneous above 10°. The procedure may be interrupted with safety after the addition of alkali, and the product will not change on standing overnight in an ice chest.
4. After the product has been dissolved in water the resulting alkaline solution is much more sensitive and should be used up as rapidly as possible and the temperature kept below 5°.
5. The alkaline solution must be added slowly to the acid, for the reverse procedure always forms an oil containing a saturated nitro alcohol. A large excess of acid at room temperature is used, conditions which facilitate the formation of the desired unsaturated nitro compound.
6. The vapors of hot solutions of nitrostyrene are very irritating to the eyes and nose, and the skin of the face is sensitive to the solid substance.

3. Discussion

Nitrostyrene can be prepared by the condensation of benzaldehyde and nitromethane. This may be accomplished by the use of small amounts of a primary aliphatic amine,[1] a method which requires a number of days for the reaction to go to completion, or preferably by the use of alkali as first discovered by Thiele.[2] Alternatively, nitrostyrene can be prepared from benzil, nitromethane, and sodium ethoxide,[3] or from styrene and nitrosyl chloride.[4]

References and Notes

1. Knoevenagel and Walter, Ber. **37**, 4507 (1904).
2. Thiele, Ber. **32**, 1293 (1899); Thiele and Haeckel, Ann. **325**, 7 (1902).
3. Fujise, Takeuchi, Kamioka, and Tiba, Ber. **68**, 1274 (1935).
4. Perrot, Compt. rend. **202**, 494 (1936).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethyl alcohol (64-17-5)

hydrochloric acid (7647-01-0)

methyl alcohol (67-56-1)

sodium hydroxide (1310-73-2)

sodium carbonate (497-19-8)

benzaldehyde (100-52-7)

Benzil (134-81-6)

sodium ethoxide (141-52-6)

Nitromethane (75-52-5)

NITROSTYRENE, Styrene, β-nitro- (102-96-5)

styrene (100-42-5)

nitrosyl chloride (2696-92-6)

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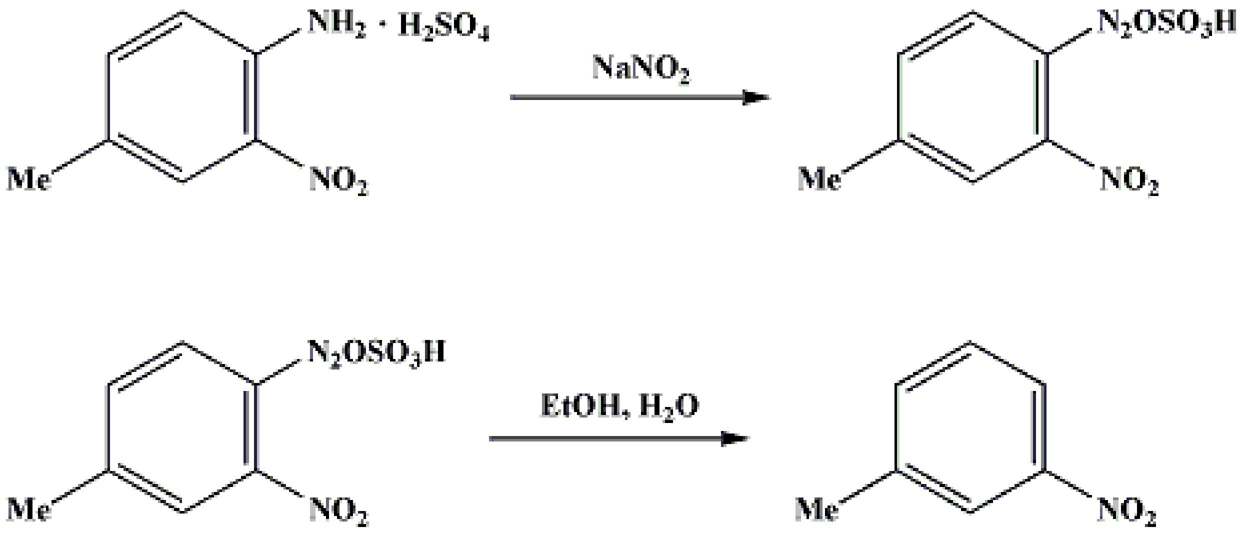
Organic Syntheses, CV 1, 415

m-NITROTOLUENE

[Toluene, *m*-nitro-]



Submitted by H. T. Clarke and E. R. Taylor.
Checked by J. B. Conant and L. F. Lea.

1. Procedure

To 500 g. of 95 per cent ethyl alcohol in a 5-l. flask are added 170 g. (1.1 moles) of "*m*-nitro-*p*-toluidine" (3-nitro-4-aminotoluene, m.p. 112–114°, (Note 1)) and 250 g. of concentrated sulfuric acid. The solution is chilled to 10° by means of an ice bath, and a solution of 85 g. (1.2 moles) of technical sodium nitrite in the minimum quantity of water is slowly added, with stirring, the temperature being kept below 10°. The mixture is now warmed very gently on the water bath under an efficient reflux condenser (from the upper end of which a tube leads to a hood or through water) until evolution of gas ceases (Note 2). The alcohol and aldehyde are then carefully distilled off, using a fractionating column and heating in an oil or brine bath (Note 3); when the temperature of the vapors reaches 80° fractionation is stopped and the residue is distilled in a current of steam.

The oil is separated from the distillate, and the aqueous portion is shaken out once with 150–200 cc. of benzene. The united oil and extract are dried with a small quantity of calcium chloride and distilled, first under atmospheric pressure to remove the benzene, and finally under reduced pressure. The *m*-nitrotoluene passes over entirely at 113–114°/15 mm. On cooling, it forms a pale yellow solid which melts at 16°. The yield of pure material is 95–110 g. (62–72 per cent of the theoretical amount).

2. Notes

1. "*m*-Nitro-*p*-toluidine" of good quality is readily available, since it is employed

as an intermediate in the preparation of certain important pigments.
2. The decomposition of the diazonium sulfate in the presence of alcohol may take place with considerable violence, and it is necessary to watch the reaction carefully so as to be able to check it, if necessary, by the external application of cold water. Acetaldehyde is rapidly evolved, and some will generally escape from the condenser. It is therefore advisable to lead the escaping gases through water, not only in order to avoid possibility of fire, but also to retain any nitrotoluene which may be entrained.
3. If, after the reaction, the alcohol is distilled off without the use of a column it will contain an appreciable quantity of *m*-nitrotoluene, amounting to 5 or more per cent of the yield. The use of an oil or brine bath is recommended on account of the presence of solid inorganic salts in the mixture.

3. Discussion

The procedure described is substantially that of Buchka.[1] *m*-Nitrotoluene can also be prepared by a similar process from 5-nitro-2-aminotoluene.[2]

References and Notes

1. Buchka, Ber. **22**, 829 (1889); Bigelow, J. Am. Chem. Soc. **41**, 1565 (1919).
2. Beilstein and Kuhlberg, Ann. **158**, 348 (1871).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

diazonium sulfate

ethyl alcohol (64-17-5)

calcium chloride (10043-52-4)

acetaldehyde (75-07-0)

sulfuric acid (7664-93-9)

Benzene (71-43-2)

sodium nitrite (7632-00-0)

nitrotoluene (88-72-2)

3-nitro-4-aminotoluene (89-62-3)

5-nitro-2-aminotoluene (99-52-5)

m-Nitrotoluene, Toluene, m-nitro- (99-08-1)

m-nitro-p-toluidine (119-32-4)

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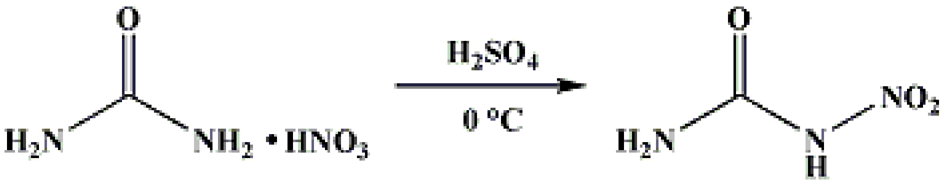
Organic Syntheses, CV 1, 417

NITROUREA

[Urea, nitro-]



Submitted by A. W. Ingersoll and B. F. Armendt.
Checked by Henry Gilman and C. C. Vernon.

1. Procedure

In a 2-l. Erlenmeyer flask provided with a mechanical stirrer and thermometer, and surrounded by an ice-salt mixture, is placed 700 cc. of concentrated sulfuric acid. The stirrer is started, and when the acid is cooled to –3° or below, 200 g. (1.62 moles) of dry, powdered urea nitrate is added in small portions at such a rate that the temperature does not rise above 0°. The addition will require about one-half hour. Stirring is continued for another one-half hour, the temperature being kept below + 3° (Note 1). Then the mixture is poured upon 1 kg. of ice.

The white, finely divided precipitate of nitrourea is filtered upon a 12-cm. Büchner funnel. A hardened filter paper (Note 2) is used in this operation, and the nitrourea is pressed as dry as possible. The product is washed in the funnel with four portions of cold water just sufficient to cover it, and pressed dry each time (Note 3). Then it is dried in the air (Note 4). By strongly cooling the filtrates, a further small amount of nitrourea may be obtained and added to the main portion. The yield of air-dried material is 120–150 g. (70–87 per cent of the theoretical amount). It melts with decomposition at 150–164° and is sufficiently pure for use in the preparation of semicarbazide (Note 5) and (Note 6).

2. Notes

1. If bubbles of gas begin to be evolved while stirring, the mixture should be poured at once upon ice.
2. A hardened filter is necessary. Whatman's No. 50 is satisfactory.
3. Cracks appear when the nitrourea is filtered; hence, care must be taken that the water used for washing does not go through the cracks instead of through the material. If desired, the nitrourea may be removed from the funnel, made into a paste with about 800 cc. of cold water, and again filtered.
4. The product may be dried on a steam plate if the heating is not continued too long.
5. Various samples of nitrourea prepared in this way melt differently, and

therefore the melting point is not a suitable indication of purity. A uniform product can also be obtained by crystallizing one-half of the crude material obtained in one run from 1 l. of water at a temperature not over 55°, and using the filtrate to crystallize the second half. Even this recrystallized material does not have a definite melting point.

6. Nitrourea may be obtained in a pure condition by recrystallization from ether, benzene, or chloroform, in which solvents it does not dearrange, and melts sharply at 158.4–158.8° with decomposition.[1]

3. Discussion

Nitrourea can be prepared by the action of concentrated sulfuric acid on urea nitrate.[2] The procedure described is essentially that of Thiele and Lachmann.[2] A modified procedure[3] uses a lesser quantity of sulfuric acid.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 485
- Org. Syn. Coll. Vol. 4, 361

References and Notes

1. Willstätter and Pfannenstiel, Ber. **59**, 1870 (1926); Davis and Blanchard, J. Am. Chem. Soc. **51**, 1790 (1929).
2. Thiele and Lachmann, Ann. **288**, 281 (1895); Backer, Rec. trav. chim. **31**, 21 (1912); Willstätter and Pfannenstiel, Ber. **59**, 1870 (1926).
3. Davis and Blanchard, J. Am. Chem. Soc. **51**, 1794 (1929).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

Benzene (71-43-2)

ether (60-29-7)

chloroform (67-66-3)

Nitrourea, Urea, nitro- (556-89-8)

urea nitrate

semicarbazide (57-56-7)

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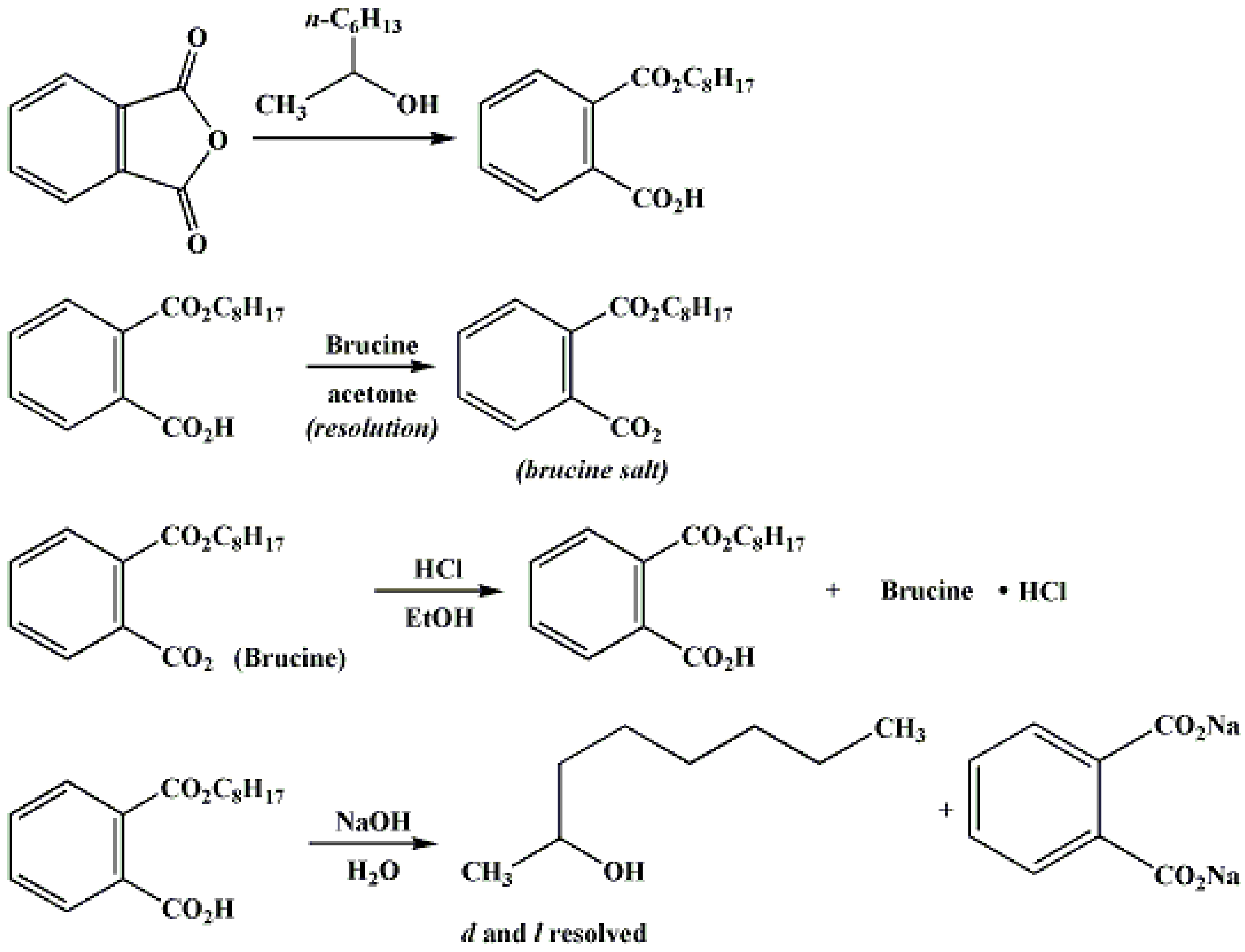
Organic Syntheses, CV 1, 418

d- and *l*-OCTANOL-2

[2-Octanol, *d*- and *l*-]



Submitted by Joseph Kenyon
Checked by Roger Adams and F. E. Kendall.

1. Procedure

(*A*) *Preparation of sec.-Octyl Hydrogen Phthalate*.—A mixture of 130 g. (1 mole) of *sec*.-octyl alcohol (p. 366) and 148 g. (1 mole) of phthalic anhydride is heated for twelve to fifteen hours in a flask surrounded by an oil bath at 110–115° (Note 1). During the heating the mixture should be mechanically stirred or shaken occasionally to give a homogeneous liquid. The cooled reaction mixture is added to about 8 l. of water which contains 150 g. (1.4 moles) of anhydrous sodium carbonate. The solid material gradually goes into solution, and if the resulting solution is perfectly clear, dilute hydrochloric acid is added in slight excess, thus precipitating the *sec*.-octyl hydrogen phthalate as an oil which rapidly turns to a solid; if the alkaline solution is not clear, owing to the presence of methyl hexyl ketone in the original alcohol, it should be extracted with ether to remove the ketone before acidifying with hydrochloric acid.

The octyl hydrogen phthalate is filtered, washed with water, ground thoroughly with water in a mortar, and finally filtered and dried. For complete purification it may be crystallized either from petroleum ether (b.p. 60–70°) or glacial acetic acid, from which it separates as needles melting at

55°. The crude material, however, is perfectly satisfactory for the following experiments. The yield is nearly quantitative if the *sec.*-octyl alcohol is pure (Note 2) and (Note 3).

(*B*) *Resolution*.—A warm solution of 278 g. (1 mole) of *sec.*-octyl hydrogen phthalate and 600 cc. of acetone is treated with 394 g. (1 mole) of brucine and the mixture warmed until the solution is clear. Upon cooling, the crystals of brucine salt (A) form. These are filtered, pressed, and washed in the funnel with 250 cc. of acetone. The combined filtrate and washings are concentrated to about 50 per cent of their original volume and then poured into dilute hydrochloric acid (slightly more than the calculated amount), which causes the precipitation of the *sec.*-octyl hydrogen phthalate. After the precipitate sets to a crystalline mass, it is filtered, washed with cold water, and dried. This weighs approximately one-half of the original ester used and has a rotation $[\alpha]_{5461}$ – 47° in absolute alcohol solution (Note 4).

The crystals (A) are dissolved in the minimum amount of hot ethyl alcohol and decomposed by pouring the solution into dilute hydrochloric acid. The weight of the ester thus obtained is about one-half of that originally taken, and its rotation in absolute alcohol is about $[\alpha]_{5461}$ +47°, $[\alpha]_D$ +44°.

The two lots of crude active *sec.*-octyl hydrogen phthalate are now separately crystallized twice from acetic acid (about 2 g. of 90 per cent acetic acid should be used for each gram of solid). They are thus obtained in an optically pure condition and possess the rotations $[\alpha]_{5461}$ – 58.5°, $[\alpha]_D$ – 48.4° and $[\alpha]_{5461}$ +58.3°, $[\alpha]_D$ +48.4°, respectively. The amount of pure product, m.p. 75°, obtained in each case is respectively about 99 g. and 96 g. (about 70 per cent of the theoretical amount). The *sec.*-octyl hydrogen phthalate of low optical activity obtained by adding water to the acetic acid filtrates can be collected and used in a subsequent preparation.

(*C*) *Hydrolysis*.—Optically pure *l*- and *d*-*sec.*-octyl alcohols are obtained by distillation in a current of steam of the *sec.*-octyl hydrogen phthalate and 2 moles of sodium hydroxide in 30 per cent solution. The alcohols are practically insoluble in water and are separated, dried with potassium carbonate, and distilled. Each boils at 86°/20 mm. and has a rotation $[\alpha]^{17°}_{5461}$ + 11.8°, $[\alpha]^{17°}_{D}$ + 9.9° or $[\alpha]^{17°}_{5461}$ – 11.8°, $[\alpha]^{17°}_{D}$ – 9.9°. The yields of alcohol from the *sec.*-octyl hydrogen phthalates are about 95 per cent of the calculated amounts.

2. Notes

1. If this temperature is exceeded the yield of octyl phthalate is reduced and the color of the product is very dark. The color is carried through with the *l*-fraction, making it difficult to read rotations.
2. The yield of *sec.*-octyl hydrogen phthalate from the crude *sec.*-octyl alcohol used in this preparation was 61–64 per cent.
3. It is reported that *sec.*-octyl hydrogen phthalate may be prepared in a purer state and with better yields if the reaction is carried out in the presence of pyridine according to the procedure of Levene and Mikeska for preparing the acid phthalate of cyclohexyl phenyl carbinol[1] (H. L. Haller, private communication).
4. Frequently this product is so dark that a determination of rotation is impossible.

3. Discussion

The resolution of *sec.*-octyl alcohol was first described by Pickard and Kenyon.[2] The method employed by these authors differs from the procedure described in the following respects. The brucine salt of *sec.*-octyl hydrogen phthalate was crystallized several times from acetone until it

reached optical purity and was then decomposed to give pure *d-sec.*-octyl hydrogen phthalate. The partly levorotatory hydrogen phthalic ester obtained by the decomposition of the more soluble fractions of the brucine salt was then combined with cinchonidine and the cinchonidine salt crystallized some half-dozen times from acetone until optical purity was reached. Decomposition of this salt yielded the optically pure *l-sec.*-octyl hydrogen phthalate.

The procedure described[3] is much more convenient.

References and Notes

1. Levene and Mikeska, J. Biol. Chem. **75**, 594 (1927).
2. Pickard and Kenyon, J. Chem. Soc. **91**, 2058 (1907).
3. Kenyon, ibid. **121**, 2540 (1922).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

ester

brucine salt

acid phthalate

hydrogen phthalic ester

cinchonidine salt

D- and L-Octanol-2

2-Octanol, d- and l-

d-sec.-octyl alcohols

sec.-octyl hydrogen phthalates

brucine salt of sec.-octyl hydrogen phthalate

ethyl alcohol, alcohol (64-17-5)

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium carbonate (497-19-8)

phthalic anhydride (85-44-9)

acetone (67-64-1)

pyridine (110-86-1)

sec.-octyl alcohol (123-96-6)

sec.-Octyl Hydrogen Phthalate, d-sec.-octyl hydrogen phthalate, l-sec.-octyl hydrogen phthalate

(5393-19-1)

methyl hexyl ketone (111-13-7)

octyl hydrogen phthalate, octyl phthalate

brucine

cyclohexyl phenyl carbinol

cinchonidine

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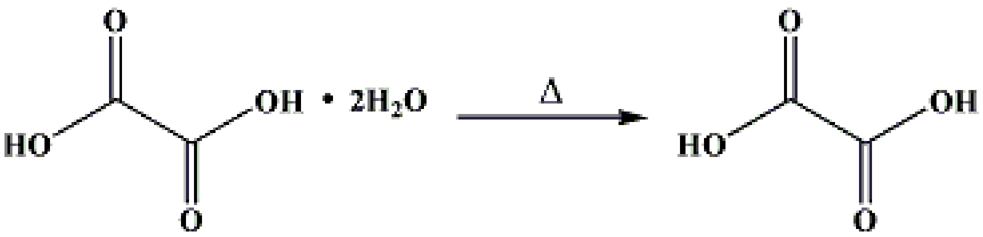
Organic Syntheses, CV 1, 421

OXALIC ACID (ANHYDROUS)

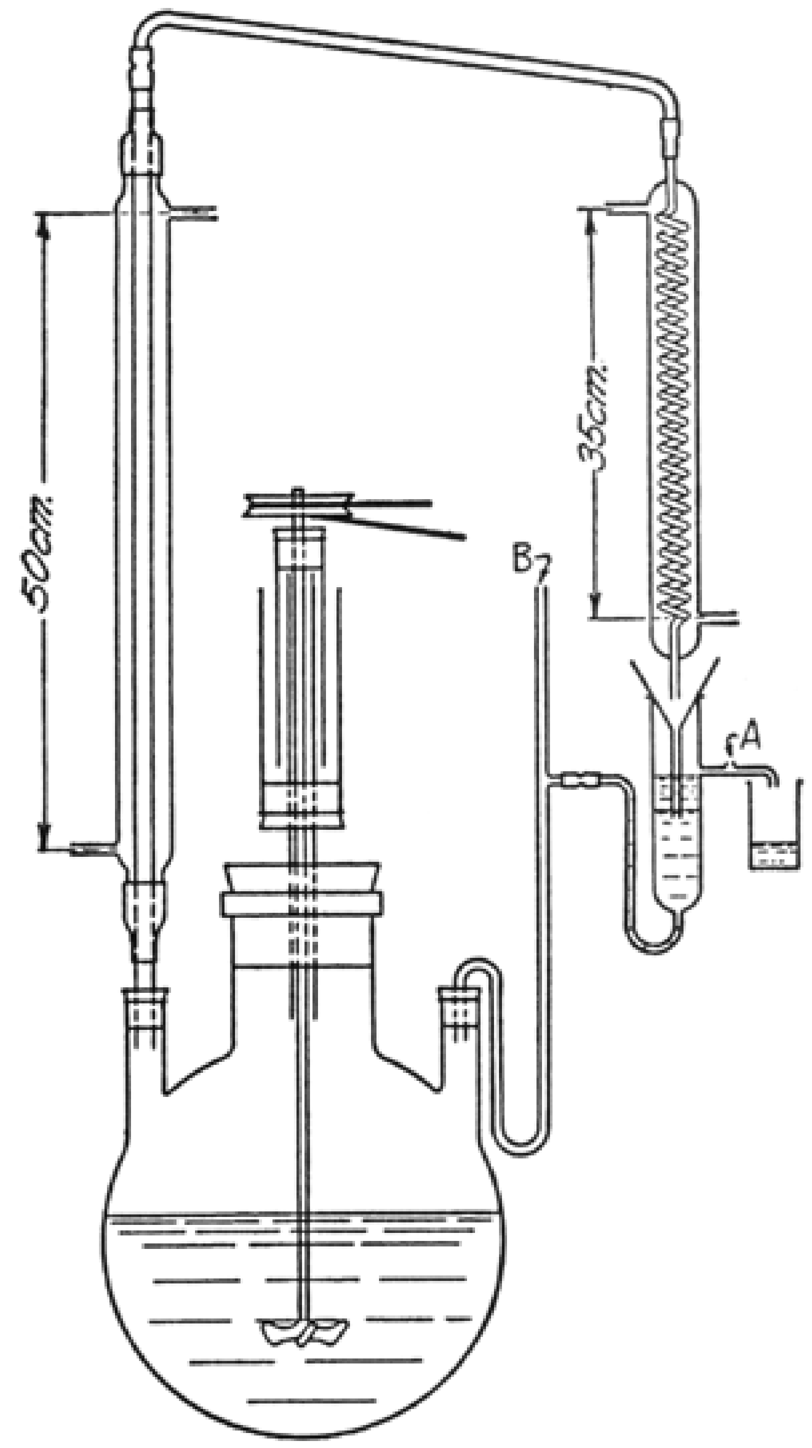


Submitted by H. T. Clarke and Anne W. Davis.
Checked by Roger Adams and V. Voorhees.

1. Procedure

In a 5-l. round-bottomed flask are placed 2 kg. (15.9 moles) of pure crystallized oxalic acid which has been passed through a 10-mesh sieve, and 3 l. of carbon tetrachloride (Note 1). The flask is then fitted (Note 2) with a mechanical stirrer and the apparatus shown in Fig. 22.

Fig. 22.



This apparatus consists of an upright water condenser through the jacket of which steam is passed. A connecting tube leads from the top of this condenser to the top of a second efficient spiral condenser (Note 3), the bottom of which extends into a gravity separator. The water runs off into a receiver, and the heavier carbon tetrachloride layer returns to the reaction flask. A few essential points in the apparatus should be mentioned: it is necessary that the return arm of the gravity separator be below the tube through which the water flows into the receiver; the bottom of the funnel should be below the water outlet as in the diagram; the openings A and B are necessary to prevent siphoning in the respective tubes; and the last bend in the return tube before entering the reaction flask serves as a trap to prevent vapors from entering that tube.

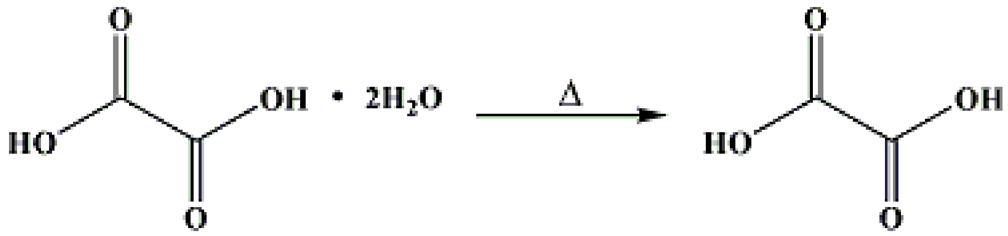
The flask is placed up to its neck (Note 4) in hot water, stirring is started, and the steam is allowed to flow through the first upright condenser. The heating of the flask (Note 5) and vigorous stirring are continued until no more water passes through into the condenser. This point is indicated by the fact that no more water flows from the side arm of the separator. A slight milkiness in the carbon tetrachloride, which persists even when practically no more water comes over, need not be considered. The time of heating depends to a large extent on the rate with which the vapors are distilled over, and this rate in turn depends largely on the efficiency of the condenser. With an ordinary apparatus, such as that described, the time necessary will be approximately eighteen to twenty-four hours.

The reaction mixture is now filtered with suction, care being taken that any oxalic acid which is crusted above the surface of the carbon tetrachloride is not removed with the main portion of the product. The carbon tetrachloride may be used again for another run (Note 6), and the anhydrous oxalic acid is dried by short exposure to a warm dry atmosphere. The yield of product amounts to more than 90 per cent of the theoretical amount.

2. Notes

1. Carbon tetrachloride is in every way the most suitable liquid. It is not inflammable; the boiling temperature is such that water is readily evolved but sublimation of anhydrous acid is slight; and, inasmuch as the density is near to that of oxalic acid, an efficient mixing can be obtained. In benzene, the first and third conditions are not fulfilled; in toluene, apparently none of them, for although the water is more rapidly driven off than with carbon tetrachloride the sublimation is so great as to be troublesome, and, owing to the less efficient stirring in the liquid of lower density, the acid shows a great tendency to clump. However, toluene has been used.[1]
2. The stopper should be of good cork, covered if desired with tin foil. Rubber stoppers are rapidly attacked by the carbon tetrachloride vapors and rendered useless after one run.
3. As the time necessary for the dehydration depends almost entirely on the rate of boiling, care must be taken to select an efficient condenser. If a long spiral condenser is not available, a very successful device is to join the top of the upright tube to an ordinary long condenser placed in a slanting position, with its lower end connected by a bent tube of rather large bore to another condenser also in a slanting position, and leading back to the top of the gravity separator, the arrangement being > shaped.
4. It is well to place as much liquid in the flask as consistent with rapid boiling, since a slight crust of partially dehydrated acid is likely to collect around the upper edges of the carbon tetrachloride; this stays behind when the anhydrous acid is fIltered off and must not be included in the main product. Complete immersion of the flask in hot water will greatly minimize this trouble, and it is therefore recommended.
5. The heat may be applied to the flask either by direct flame, water bath, or

steam bath.
6. A considerable portion of carbon tetrachloride is lost in the experiment, and this is the chief disadvantage in the procedure. It is almost impossible to filter the oxalic acid and recover more than about 80 per cent of the carbon tetrachloride. About 18 per cent remains attached to the anhydrous oxalic acid and evaporates when the oxalic acid is dried. The last 2 per cent is lost by evaporation during the dehydration.



Submitted by Everett Bowden
Checked by C. S. Marvel and E. H. Woodruff.

1. Procedure

A laboratory oven (Note 1) is equipped with as many clay plates or enameled pie plates or trays as it will accommodate and is adjusted to operate at 98–99° (Note 2) and (Note 3). When the temperature has become constant the plates are removed, rapidly covered with a layer (not over 3–4 mm. deep) of pulverized (Note 4) hydrated oxalic acid, and then quickly replaced in the oven. The temperature will drop slightly for a few minutes (Note 5). After the oven has regained the temperature for which it was adjusted, it is heated for two hours longer at this temperature. The product is then removed, crushed if slightly caked, and quickly bottled. The yield from 100 g. of hydrated oxalic acid is 69–70 g. (96–98 per cent of the theoretical amount) (Note 6). The product is 99.5–100 per cent pure, as indicated by titration with standard alkali (Note 7).

2. Notes

1. Any type of oven may be used, but the automatic electric requires least attention. As many trays may be used as there are shelves in the oven. The trays are heated with the oven to decrease the subsequent first drop in temperature.
2. Some *slight* sublimation is always noticed, and the acid tends to cake. At higher temperatures heavy losses are caused by sublimation, and the caked material is very imperfectly dehydrated; there is also some darkening. Under the conditions described a white product is formed.
3. The dehydration is faster at higher temperatures. Numerous experiments showed that one hour and twenty minutes at a temperature of 113–115° gave a nearly theoretical yield of slightly colored material containing 97 per cent of oxalic acid. A one-hour heating at the same temperature gave an apparent yield of 102 per cent containing 94 per cent of oxalic acid. This result applies to a c.p. starting material; technical acid gives somewhat less favorable results.

4. The acid should be powdered so that 50 per cent will pass a 60-mesh sieve and all will pass a 40-mesh sieve. A 23-cm. plate can be used for about 50 to 100 g. of acid.
5. The oven temperature always drops a few degrees, owing to the cooling effect of the cold acid and the evaporation of a relatively large quantity of water. This drop in temperature is much less noticeable in a large oven than in a small one, and in one having thermostatic control in contrast to manual control.
6. The amount of material which may be dried will depend entirely on the size of the oven and the size and number of trays used. By repeating the runs several kilograms of material may be dried in a day with very little attention.
7. The success of this method of dehydration depends upon an exact control of all conditions specified.

3. Discussion

Oxalic acid can be dehydrated by heating to about 100° in an oven[2] or at 145–150° in an oil bath;[3] by treatment with concentrated sulfuric acid;[4] and by the use of an organic compound like carbon tetrachloride to distil off the water.[5] A preliminary trial of the concentrated sulfuric acid method showed it to be less suitable than the other methods. The weakness of the method involving the direct application of heat has been chiefly a lack of standardization.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 246
- Org. Syn. Coll. Vol. 1, 261
- Org. Syn. Coll. Vol. 1, 366
- Org. Syn. Coll. Vol. 2, 414
- Org. Syn. Coll. Vol. 2, 416
- Org. Syn. Coll. Vol. 3, 203
- Org. Syn. Coll. Vol. 3, 381

References and Notes

1. Johnson and Partington, J. Chem. Soc. 1510 (1930).
2. Villiers, Bull. soc. chim. (2) **33**, 415 (1880); Rising and Stieglitz, J. Am. Chem. Soc. **40**, 726 (1918).
3. Peter, Bull. soc. chim. (2) **38**, 406 (1882).
4. Maumené, Jahresber. 371 (1864); Villiers, Bull. soc. chim. (2) **33**, 415 (1880); Lescoeur, Ann. chim. (6) **19**, 58 (1890); Fisher, Proc. Chem. Soc. **8**, 186 (1892).
5. Hultman, Davis, and Clarke, J. Am. Chem. Soc. **43**, 368 (1921); Johnson and Partington, J. Chem. Soc. 1510 (1930).

Appendix

Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

Benzene (71-43-2)

carbon tetrachloride (56-23-5)

Oxalic acid, OXALIC ACID (ANHYDROUS) (144-62-7)

toluene (108-88-3)

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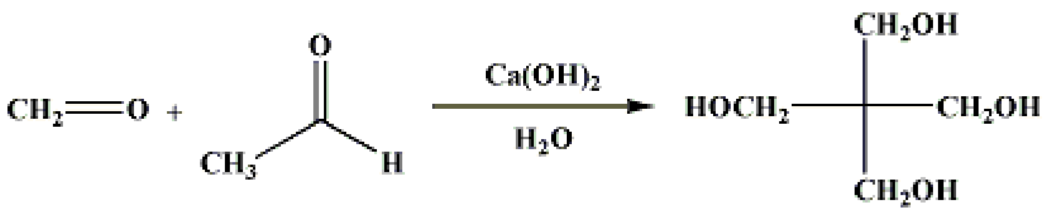
Organic Syntheses, CV 1, 425

PENTAERYTHRITOL



Submitted by H. B. J. Schurink
Checked by H. T. Clarke and S. Gurin.

1. Procedure

To a suspension of 800 g. of paraformaldehyde (corresponding to 26.7 moles of formaldehyde) (Note 1) in 5.5 l. of water containing 210 g. (4.77 moles) of acetaldehyde there is added 180 g. (3.22 moles) of powdered quicklime in small portions with vigorous mechanical stirring (Note 2). The rate of addition is so adjusted that the temperature rises to 50° in thirty minutes, and during the subsequent additions the temperature of the mixture is not allowed to exceed 55°. The mixture takes on a slightly yellow color. After the addition is complete, stirring is continued for three hours, the mixture is filtered by gravity, and the yellow filtrate is acidified with just enough dilute hydrochloric acid to give an acid reaction to litmus. Subsequent to the addition of 30 g. of Norite and stirring for five minutes, the solution is again filtered.

The filtrate, which should be colorless, is concentrated on the steam bath under reduced pressure (Fig. 23) (Note 3) until crystalline material begins to separate. The liquor, amounting to approximately 3 l., is heated on the steam bath at atmospheric pressure and filtered with suction while hot, any crystals remaining on the filter being washed through by aspiration of wet steam. The filtrate is allowed to stand in the refrigerator overnight and the first crop of crystals filtered off. This weighs approximately 300 g. and melts at about 237° (corr.). The mother liquor is concentrated to approximately 2 l. and a second crop obtained as above; this weighs 60–70 g. and melts at 242° (corr.). A third crop of 50–60 g. melting at 249° (corr.) is obtained by concentrating the mother liquor to 1.2 l. The mother liquor is finally concentrated to a sirup, when a fourth crop weighing about 10 g. and melting at 248° (corr.) is obtained.

The combined product, weighing 410-420 g., is recrystallized from an equal weight of hot water containing 10 cc. of concentrated hydrochloric acid. The color is removed by the addition of 5 g. of Norite. By suitably concentrating the mother liquors, second, third, and fourth crops may be obtained, all of which appear to be of the same purity as the first crop. The total yield is 360–370 g. (55-57 per cent of the theoretical amount) of a product melting at 258–260° (corr.) and containing negligible amounts of calcium (Note 4). The final residue, amounting to 20–30 g., leaves a considerable quantity of ash on ignition.

2. Notes

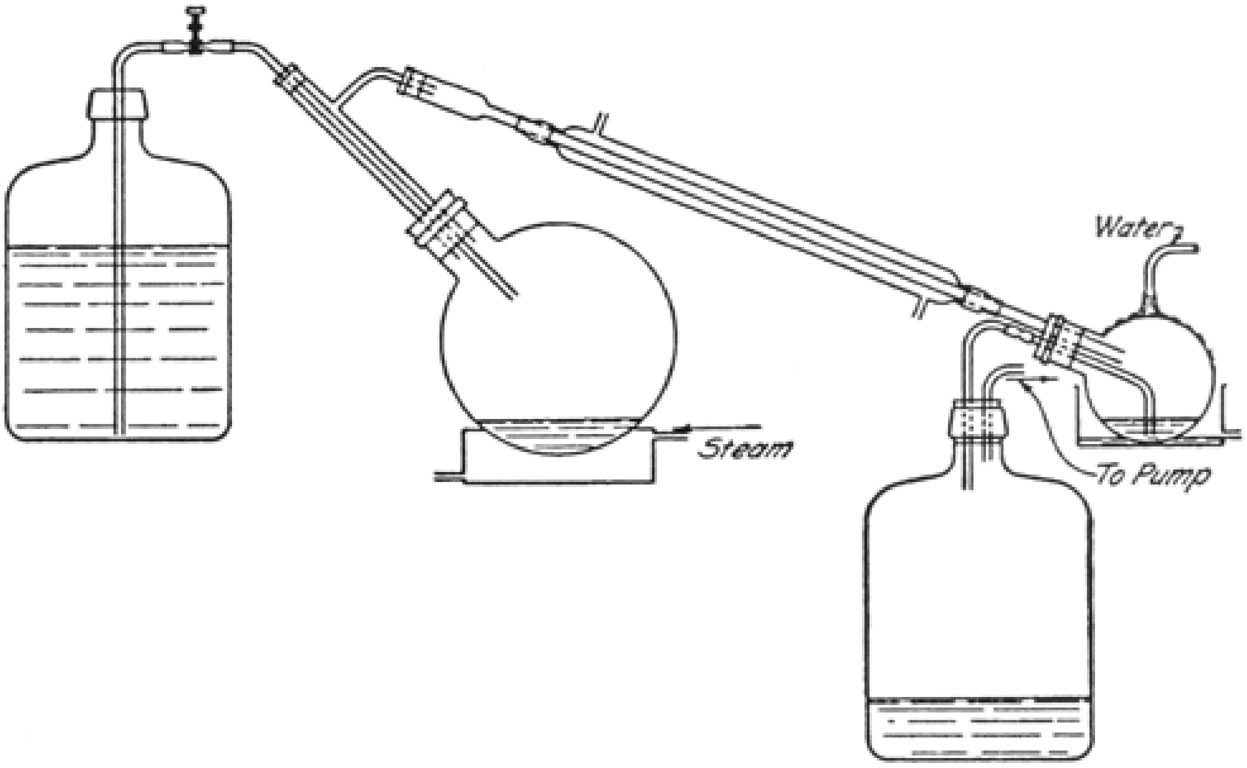
1. Since commercial paraformaldehyde contains varying amounts of moisture, the latter must be determined and the amount taken must be based on the actual

paraformaldehyde content.

2. The reaction may conveniently be carried out in a crock covered to minimize losses by evaporation.

3. The apparatus shown in Fig. 23 has been found convenient for such evaporations under reduced pressure. The distillation is started with 3.5–4 l. in the 12-l. flask, and the level of liquid is maintained by controlling the rate of addition by means of a screw clamp. A 2-l. flask has been found satisfactory for the condensing intermediate receiver, provided that the outside is completely wetted by the cold water.

Fig. 23.



It has been recommended that some paraffin wax be added to prevent severe frothing during evaporation.

4. The product should give only a slight opalescence when a concentrated solution is treated with ammonium oxalate.

It has been shown[1] that pentaerythritol prepared as above always contains an appreciable proportion of dipentaerythrityl ether, m.p. 221°, which cannot be removed by recrystallization from hot water but forms a more soluble tetranitrate. Pure pentaerythritol, prepared from the purified tetranitrate, is stated to melt at 260°.

3. Discussion

Pentaerythritol can be prepared by condensing acetaldehyde with formaldehyde in aqueous solution by means of calcium hydroxide or barium hydroxide.[2] The patents covering this process are too numerous to review. The procedure described has proved rather more convenient than that previously published in this series.[3] Paraformaldehyde is stated[4] to give a better yield than formalin.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 49
- Org. Syn. Coll. Vol. 2, 135
- Org. Syn. Coll. Vol. 2, 476
- Org. Syn. Coll. Vol. 2, 545

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2. Tollens and Wigand, Ann. **265**, 316 (1891); Rave and Tollens, Ann. **276**, 58 (1893); Stettbacher, Z. ges. Schiess-Sprengstoffw. **2**, 182 (1916) [C. A. **11**, 2543 (1917)]; Rheinisch-Westfälische Sprengstoff-A. G., Ger. pat. 298,932 [Frdl. **13**, 86 (1923)]; Ger. pat. 390,622 [Frdl. **14**, 167 (1926)]; Burke, U. S. pat. 1,716,110 [C. A. **23**, 3717 (1929)]; Friedrich and Brün, Ber. **63**, 2681 (1930); Backer and Schurink, Rec. trav. chim. **50**, 923 (1931); Corbellini and Langini, Giorn. chim. ind. applicata **15**, 53 (1933) [C. A. **27**, 4256 (1933)].
3. Chemical Laboratory, Picatinny Arsenal, Org. Syn. **4**, 53 (1925); Aaronson, U. S. pat. 1,678,623 [C. A. **22**, 3418 (1928)].
4. Radulescu and Tanasescu, Bull. soc. sci. Cluj **1**, 528 (1923) [C. A. **19**, 494 (1925)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

quicklime

tetranitrate

acetaldehyde (75-07-0)

hydrochloric acid (7647-01-0)

formaldehyde, formalin (630-08-0)

Norite (7782-42-5)

calcium (7440-70-2)

barium hydroxide (17194-00-2)

calcium hydroxide

Pentaerythritol (115-77-5)

ammonium oxalate (1113-38-8)

dipentaerythrityl ether

paraformaldehyde (30525-89-4)

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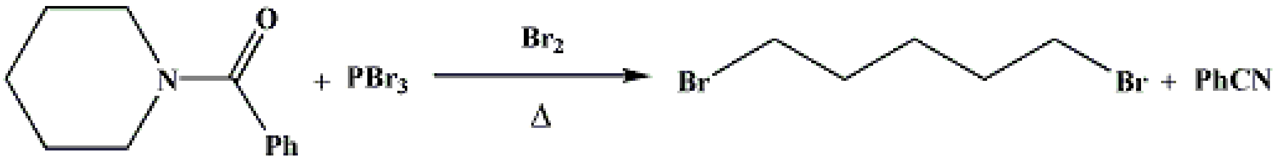
Organic Syntheses, CV 1, 428

PENTAMETHYLENE BROMIDE

[Pentane, 1,5-dibromo-]



Submitted by J. von Braun
Checked by J. B. Conant and J. S. Andrews.

1. Procedure

In a 500-cc. Claisen distilling flask is placed 80 g. (0.42 mole) of benzoyl piperidine (p. 99). To this is added with cooling 115 g. (0.43 mole) of phosphorus tribromide; this results in the formation of a light-colored solution. With careful cooling, this solution is treated, with shaking, with 65 g. (20.8 cc., 0.405 mole) of bromine. The flask is now connected for distillation under reduced pressure, and the solution is heated gradually for a few minutes until the rapid evolution of gas ceases. The product is then distilled under reduced pressure. At about 70°/20 mm. a mixture of pentamethylene bromide, phosphorus oxybromide, and benzonitrile begins to distil over into the receiver; a yellow solid collects in the condenser. This is then followed by a black decomposition product, at which point the distillation is stopped. The distillate is poured upon ice and allowed to stand in order to decompose the phosphorus oxybromide, a process which requires about one hour if carried out in a flask fitted with a reflux condenser and mechanical stirrer.

The heavy oil is removed from the water; it consists of pentamethylene bromide and benzonitrile. This oily layer is treated with 125 cc. of 40 per cent hydrobromic acid solution and boiled under a reflux condenser with vigorous stirring for about three hours in order to hydrolyze completely the benzonitrile to benzoic acid (Note 1). The mixture is then distilled with steam, an air condenser being placed between the distillation flask and the receiving flask to which is fitted a reflux condenser cooled with water. This apparatus is necessary to avoid clogging of the condenser tubes with the benzoic acid. The pentamethylene bromide is separated from the water layer, washed with sodium carbonate, dried over calcium chloride, and distilled under reduced pressure. The product boils at 108–110°/20 mm. and amounts to 63–70 g. (65–72 per cent of the theoretical amount).

2. Notes

1. It has been reported that pentamethylene bromide prepared by the procedure described contains a considerable amount of benzonitrile, and the following procedure is given for removing the nitrile. The crude product, after removal of the phosphorus oxybromide, is washed with water and distilled, the portion boiling up to 105°/10 mm. being collected. The distillate is dissolved in two volumes of ligroin (b.p. 40°) and extracted seven times with concentrated sulfuric acid — 3 cc. for each 10 cc. of distillate. The ligroin solution is then washed with dilute sodium hydroxide solution, any emulsions being broken by

filtration, dried over calcium chloride, and distilled.[1] Alternatively, it is reported[2] that the procedure of v. Braun and Steindorff[3] removes benzonitrile satisfactorily. In this procedure the distillate containing the pentamethylene bromide, benzonitrile and phosphorus oxybromide is poured carefully into 85–95 cc. of water, while cooling and stirring. The resulting mixture is refluxed for eight to ten hours with occasional additions of 3–4 cc. of alcohol to decrease resinification. The product is then extracted with ether, washed with sodium carbonate solution, steam-distilled, dried, and, finally, distilled *in vacuo*.

In the laboratory it has been found that shaking pentamethylene bromide with concentrated sulfuric acid results in the formation of emulsions. The use of a solvent such as petroleum ether usually prevents the emulsification but lowers the yield of the final product.

3. Discussion

Pentamethylene bromide can be prepared by the action of fuming hydrobromic acid on pentamethylene glycol,[4] or 1, 5-diphenoxypentane;[5] by the action of hydrobromic acid on an acetic acid solution of 1,5-diisoamyloxypentane;[6] and by the action of phosphorus pentabromide on benzoyl piperidine.[7] Pentamethylene bromide can also be prepared from tetrahydrofurfuryl alcohol by conversion to 1,2-dihydropyran, reduction to 1,5-epoxypentane, and treatment of this last product with hydrogen bromide in glacial acetic acid.[8]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 99
- Org. Syn. Coll. Vol. 3, 692

References and Notes

1. Johnson, J. Chem. Soc. 1531 (1933). Compare, Clarke, ibid. **103**, 1703 (footnote) (1913), Dox and Yoder, J. Am. Chem. Soc. **43**, 1368 (1921).
2. Müller, Ber. **68**, 1013 (1935).
3. v. Braun and Steindorff, Ber. **38**, 2339 (1905).
4. Gustavson and Demjanoff, J. prakt. Chem. (2) **39**, 542 (1889); Haworth and Perkin, Ber. **26**, 2247 (1893); Hochstetter, Monatsh. **23**, 1071 (1902); Müller and Rölz, ibid. **50**, 105 (1928).
5. v. Braun and Steindorff, Ber. **38**, 960 (1905).
6. Hamonet, Compt. rend. **138**, 1611 (1904); Bull. soc. chim. (3) **33**, 530 (1905).
7. v. Braun, Ber. **37**, 3211 (1904); v. Braun and Steindorff, Ber. **38**, 2338 (1905); Merck, Ger. pat. 164,365 [Chem. Zentr. II, 1563 (1905)]; Clarke, J. Chem. Soc. **103**, 1703 (footnote) (1913); Dox and Yoder, J. Am. Chem. Soc. **43**, 1367 (1921).
8. Paul, Bull. soc. chim. (4) **53**, 1489 (1933).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ligroin

alcohol (64-17-5)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

ether (60-29-7)

benzonitrile (100-47-0)

sodium hydroxide (1310-73-2)

HYDROBROMIC ACID, hydrogen bromide (10035-10-6)

sodium carbonate (497-19-8)

bromine (7726-95-6)

phosphorus tribromide (7789-60-8)

Benzoic acid (65-85-0)

BENZOYL PIPERIDINE (776-75-0)

pentamethylene bromide, Pentane, 1,5-dibromo- (111-24-0)

pentamethylene glycol (111-29-5)

1,5-epoxypentane (142-68-7)

phosphorus oxybromide

1, 5-diphenoxypentane (40339-96-6)

1,5-diisoamyloxypentane

phosphorus pentabromide (7789-69-7)

tetrahydrofurfuryl alcohol (97-99-4)

1,2-dihydropyran

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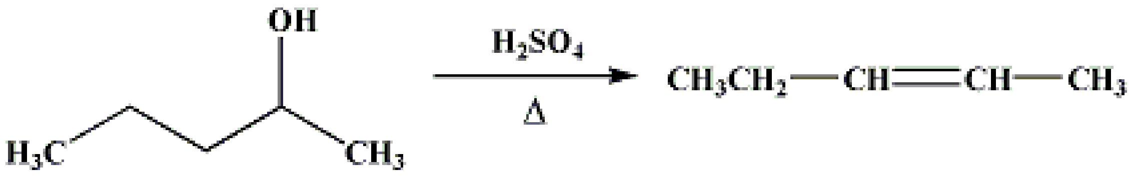
Organic Syntheses, CV 1, 430

2-PENTENE



Submitted by James F. Norris
Checked by Frank C. Whitmore

1. Procedure

To a cooled mixture of 200 cc. of water and 200 cc. of concentrated sulfuric acid in a 1-l. round-bottomed flask is added slowly 176 g. (214 cc., 2 moles) of pentanol-2 (b.p. 118–120°) (Note 1). The flask is connected with a long efficient condenser for distillation (Note 2). The end of the condenser is provided with an adapter which passes well into a receiver surrounded by ice water (Note 2). The flask is heated on a boiling-water bath as long as distillation takes place (two to three hours).

The distillate is shaken in the receiver with about 25 cc. of a 5 per cent solution of sodium hydroxide to remove any trace of sulfur dioxide that may be present. The hydrocarbon is separated and dried with 10 g. of anhydrous calcium chloride. It is then distilled, the fraction boiling at 35–41° (Note 3) being collected. The yield is 92–112 g. (65–80 per cent of the theoretical amount).

2. Notes

1. Pentanol-2 is now manufactured on a large scale from petroleum. As the quality of the commercial alcohol varies, the product should be distilled before use and the proper fraction taken. The material was kindly supplied by the Petroleum Chemical Corporation, Cambridge, Mass. (A. D. Little, Inc.).
2. Because of the volatility of the product, unusual precautions must be taken in its preparation to avoid loss.
3. Most of the product distils at 36–37°. The product may contain a small amount of the isomeric pentene-1. By redistilling it through a 25-cm. fractionating column containing small pieces of glass rod, the pure hydrocarbon can be readily obtained. Pentene-2 boils at 36.39° ± 0.04°/760 mm., melts at –138° ± 2°, has the density $d^{15°}_{4°}$ 0.6555 and n^{25}_{D} 1.3839.

3. Discussion

Pentene-2 can be prepared by the action of alcoholic potash on 3-iodopentane[1] or 3-bromopentane;[2] by dehydration of pentanol-2,[3] or pentanol-3;[4] by pyrolysis of the

acetate of pentanol-3;[5] and by the catalytic reduction of pentine-2.[6]

References and Notes

1. Wagner and Saytzev, Ann. **175**, 373 (1875).
2. Lucas and Moyse, J. Am. Chem. Soc. **47**, 1461 (1925); Sherrill, Otto, and Pickett, ibid. **51**, 3028 (1929).
3. Tissier, Bull. soc. chim. (3) **9**, 100 (1893); Sherrill, Baldwin, and Haas, J. Am. Chem. Soc. **51**, 3037 (1929).
4. Sherrill, Otto, and Pickett, J. Am. Chem. Soc. **51**, 3028 (1929); Leendertse, Tulleners, and Waterman, Rec. trav. chim. **53**, 715 (1934).
5. Wibaut and van Pelt, Jr., ibid. **57**, 1057 (1938).
6. Bourguel, Bull. soc. chim. (4) **41**, 1475 (1927).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alcoholic potash

acetate of pentanol-3

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

sodium hydroxide (1310-73-2)

sulfur dioxide (7446-09-5)

2-Pentene, Pentene-2 (646-04-8)

pentanol-2 (6032-29-7)

pentene-1 (109-67-1)

3-iodopentane (1809-05-8)

3-bromopentane (1809-10-5)

pentanol-3 (584-02-1)

pentine-2 (627-21-4)

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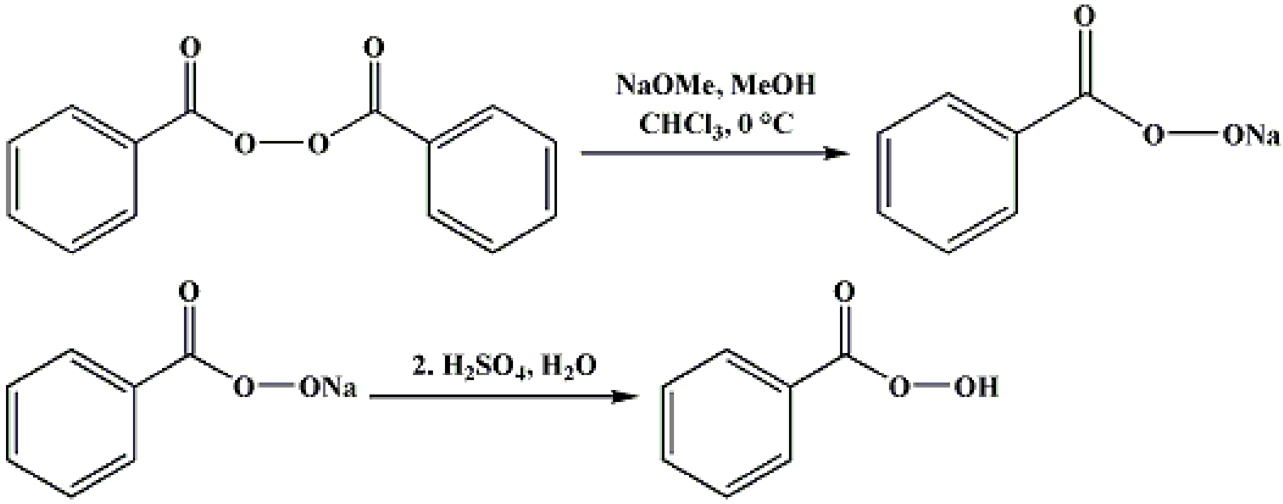
Organic Syntheses, CV 1, 431

PERBENZOIC ACID



Submitted by Géza Braun
Checked by C. R. Noller and Poe Liang.

1. Procedure

In a 500-cc. Erlenmeyer flask (Note 1), 5.2 g. (0.22 gram atom) of sodium is dissolved in 100 cc. of absolute methyl alcohol with moderate cooling. The resulting solution of sodium methoxide (Note 2) is cooled to – 5° in a freezing mixture. A solution of 50 g. (0.21 mole) of pure commercial benzoyl peroxide (m.p. 104°) (Note 3) in 200 cc. of chloroform (Note 4) is prepared, cooled to 0°, and added without delay to the sodium methoxide solution (Note 2) with shaking and cooling at such a rate that the temperature does not rise above 0°. The mixture is kept for four or five minutes in an ice-salt bath with continuous shaking; it turns milky, but no precipitate appears. The reaction mixture is now transferred to a 1-l. separatory funnel, and the sodium perbenzoate is extracted with 500 cc. of water containing much chopped ice (Note 5). The chloroform layer is then separated and the aqueous layer is extracted twice with 100-cc. portions of cold chloroform to remove the methyl benzoate. The aqueous solution contains the sodium salt of perbenzoic acid. The perbenzoic acid is liberated by the addition of 225 cc. of cold 1 *N* sulfuric acid and is removed from solution by extracting three times with 100-cc. portions of cold chloroform (Note 6). The united chloroform solutions are washed twice with 50-cc. portions of water, and the chloroform layer is carefully separated.

The volume of the moist (milky) chloroform solution is about 308 cc., and iodometric titration indicates that it contains 23.5–24.5 g. of perbenzoic acid (82.5–86 per cent of the theoretical amount) (Note 7), (Note 8), and (Note 9). Water is the only impurity present in the moist solution; the solution may therefore be used as such for oxidations that are to be carried out in the presence of water.

To obtain crystalline perbenzoic acid, the moist chloroform solution is dried with a small amount of anhydrous sodium sulfate for an hour (Note 6). Then the sodium sulfate is removed by filtration and washed with dry chloroform; from the filtrate the chloroform is completely removed under reduced pressure while carbon dioxide is introduced through a capillary tube. The white or pale yellow residue is dried for several hours under 10 mm. pressure at 30–35°. The yield is 22–

23 g. of crystalline mass which contains several per cent less active oxygen than the theoretical owing to a slight contamination with benzoic acid (Note 8) and (Note 9). The perbenzoic acid is very soluble in the usual organic solvents, such as chloroform, ether, ethyl acetate; it is slightly soluble in cold water and in cold ligroin.

2. Notes

1. All the glassware used in the preparation should be carefully cleaned. Either cork or thoroughly cleaned rubber stoppers may be used.
2. Sodium methoxide is preferred to sodium ethoxide because it is more soluble in the excess of alcohol and it does not precipitate provided that the solution is not cooled below – 5°. If sodium ethoxide is used the sodium perbenzoate precipitates immediately as a white powder when the sodium ethoxide is added to the chloroform solution of benzoyl peroxide. With sodium methoxide the solution turns milky, but no precipitate appears.
3. The commercial (Eastman) benzoyl peroxide may be used if it gives a colorless or pale yellow chloroform solution; otherwise it should be recrystallized from a small amount of hot chloroform. It should always be analyzed before use, since the melting point is not a safe criterion of purity. The following method of analysis is convenient and satisfactory: In a 300-cc. Erlenmeyer flask, 0.5 g. of benzoyl peroxide is dissolved in 15 cc. of chloroform. The solution is cooled to – 5°, and 25 cc. of 0.1 *N* ice-cold sodium methoxide solution is added at once with cooling and shaking. After four to five minutes at – 5°, 100 cc. of iced water, 5 cc. of 10 per cent sulfuric acid, and 2 g. of potassium iodide in 20 cc. of 10 per cent sulfuric acid are added in the order mentioned with violent stirring. The liberated iodine is titrated with 0.1 *N* sodium thiosulfate solution. One cubic centimeter of 0.1 *N* sodium thiosulfate solution is equivalent to 0.0121 g. of benzoyl peroxide.
4. The chloroform (u. s. p. grade) used in the preparation can be recovered by careful drying with anhydrous sodium sulfate and subsequent fractional distillation and used over and over again. The by-product is methyl benzoate, which is purified by vacuum distillation.
5. The preparation should be carried out as quickly as possible; the temperature must be kept around 0° by the addition of chopped ice, especially before the free acid is liberated from the sodium salt. Failure to observe this precaution leads to very uncertain results, whereas under correct conditions the yield of perbenzoic acid is invariably as high as 82–86 per cent of the theoretical amount.
6. After the perbenzoic acid is liberated with sulfuric acid, it may be extracted from the aqueous solution with any appropriate organic solvent (*e.g.* ether or ethyl acetate). Even if concentrated solutions of perbenzoic acid are required, it is better to apply the amount of solvent specified (or more) and then to concentrate the solution under reduced pressure at a temperature not above 30–35°. The solution may, but need not, be dried before concentration. Anhydrous sodium sulfate is the only satisfactory drying agent. Calcium chloride sometimes causes a sudden decomposition of the peracid.
7. The yield is calculated on the benzoyl peroxide content of the material used. These directions are equally satisfactory for the preparation of perbenzoic acid on a smaller or larger scale. Experiments in which the amount of benzoyl peroxide used ranged from 10 to 250 g. gave an average yield of 85 per cent of the theoretical. However, amounts from 25 to 50 g. are preferred because the experiments can easily be completed in a short time.
8. The perbenzoic acid thus prepared is fairly stable, especially when kept in the dark in a cold place. A sample kept in moist chloroform solution showed the following change in active oxygen:

1 cc. of the solution required:	
Immediately after preparation............	13.2 cc. of 0.1 *N* $Na_2S_2O_3$
After 21 days at 2° in the dark...........	12.5 cc. of 0.1 *N* $Na_2S_2O_3$
After 5 days more at room temperature.....	7.8 cc. of 0.1 *N* $Na_2S_2O_3$

9. The amount of active oxygen is estimated by iodometric titration. One or two grams of sodium iodide is dissolved in 50 cc. of water, and then about 5 cc. of glacial acetic acid and 5 cc. of chloroform are added. To this mixture a chloroform solution of perbenzoic acid is added with violent shaking. The iodine liberated is titrated with 0.1 *N* sodium thiosulfate solution, of which 1 cc. is equivalent to 0.0069 g. of perbenzoic acid.

3. Discussion

Perbenzoic acid can be prepared by the action of sodium methoxide[1] or ethoxide[2] on benzoyl peroxide followed by acidification with dilute sulfuric acid; from benzoyl chloride, hydrogen peroxide, and sodium peroxide;[3] and from benzaldehyde and acetic anhydride in acetone and an atmosphere of oxygen.[4]

The procedure described above, which is taken from Org. Syn. **13**, 86, is a considerable improvement in ease of manipulation, time required, and yield obtained, over that given in the original Collective Volume I, 422. Chloroform is a better solvent than ether or toluene for benzoyl peroxide. A further improvement is the substitution of sodium methoxide for sodium ethoxide. Sodium methoxide is much more soluble in the excess of alcohol, and the sodium perbenzoate remains in solution, thus assuring a quantitative conversion.

The directions in the original Collective Volume I, 422, contain two errors. The amount of sodium specified (23 g.) is twice the correct amount, and the percentage yield, stated as 90, is only 65.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 494
- Org. Syn. Coll. Vol. 5, 904
- Org. Syn. Coll. Vol. 5, 900

References and Notes

1. Braun, J. Am. Chem. Soc. **51**, 239 (1929).
2. Baeyer and Villiger, Ber. **33**, 858, 1569 (1900); Levy and Lagrave, Bull. soc. chim. (4) **37**, 1597 (1925); Pummerer and Reindel, Ber. **66**, 336 (1933).
3. Bergmann and Witte, Ger. pat. 409,779 [Chem. Zentr. I, 1911 (1925)]; Brooks and Brooks, J. Am. Chem. Soc. **55**, 4310 (1933).
4. Jorissen and Van der Beek, Rec. trav. chim. **45**, 245 (1926).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ligroin

sodium perbenzoate

sodium salt of perbenzoic acid

peracid

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

ethyl acetate (141-78-6)

methyl alcohol (67-56-1)

ether (60-29-7)

acetic anhydride (108-24-7)

chloroform (67-66-3)

sodium sulfate (7757-82-6)

oxygen (7782-44-7)

potassium iodide (7681-11-0)

sodium thiosulfate (7772-98-7)

Benzoic acid (65-85-0)

carbon dioxide (124-38-9)

benzaldehyde (100-52-7)

iodine (7553-56-2)

acetone (67-64-1)

sodium methoxide (124-41-4)

benzoyl chloride (98-88-4)

toluene (108-88-3)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

hydrogen peroxide (7722-84-1)

sodium peroxide

sodium iodide (7681-82-5)

methyl benzoate (93-58-3)

benzoyl peroxide (94-36-0)

Perbenzoic acid (93-59-4)

sodium salt (824-79-3)

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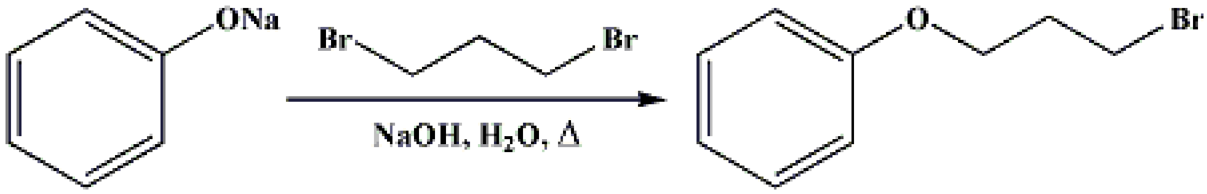
Organic Syntheses, CV 1, 435

γ-PHENOXYPROPYL BROMIDE

[Propane, 1-bromo-2-phenoxy-]



Submitted by C. S. Marvel and A. L. Tanenbaum.
Checked by H. T. Clarke and C. J. Malm.

1. Procedure

In a 5-l. round-bottomed flask, fitted with a stopper carrying a long reflux condenser, a mechanical stirrer (Note 1), and a separatory funnel, are placed 2 l. of water (Note 2), 1 kg. (4.95 moles) of trimethylene bromide (p. 30) (Note 3), and 370 g. (3.9 moles) of phenol. The stirrer is started, and the mixture is heated to boiling. To the boiling solution is added a solution of 150 g. (3.75 moles) of sodium hydroxide in 500 cc. of water at such a rate that all is added in about one hour. The mixture is refluxed for five to six hours longer to complete the reaction, then cooled, and the upper water layer is separated and discarded.

The lower layer consists of trimethylene bromide, phenoxypropyl bromide, and diphenoxypropane. This mixture is distilled under reduced pressure, a Claisen flask with a modified side arm (p. 130) being used. The first fraction is collected up to 136°/20 mm.; it consists of water and recovered trimethylene bromide with a little phenoxypropyl bromide (Note 4). The water is separated and discarded. The recovered trimethylene bromide weighs 340–450 g. (Note 5). The next fraction is pure phenoxypropyl bromide, which boils at 136–142°/20 mm. The yield is 495–600 g. (84–85 per cent of the theoretical amount based on the trimethylene bromide not recovered) (Note 6). On cooling, the phenoxypropyl bromide crystallizes to a white solid, m.p. 7–8°. A small amount (50–80 g.) of diphenoxypropane is left as a residue in the distilling flask.

2. Notes

1. The reaction may be run without stirring, but a longer period of refluxing is necessary and the yield is lower.
2. If less water is used in the reaction mixture, sodium bromide separates.
3. The large excess of trimethylene bromide must be used in order to avoid the formation of large amounts of diphenoxypropane.
4. Phenoxypropyl bromide attacks rubber stoppers quite readily, and the side

arm of the distillation flask should be set in (p. 130), in order to avoid contamination of the distillate.

5. The use of recovered trimethylene bromide does not result in so good a yield of phenoxypropyl bromide, because a little phenoxypropyl bromide is already present and during the reaction is converted to diphenoxypropane.

6. Phenoxyethyl bromide may be made in a similar manner. Two kilos (10.7 moles) of ethylene bromide, 785 g. (8.5 moles) of phenol, and 2 l. of water, upon treatment with 375 g. (9.4 moles) of sodium hydroxide, yield 960–970 g. of phenoxyethyl bromide (55–56 per cent of the theoretical amount) boiling at 125–130° /18 mm.

3. Discussion

γ-Phenoxypropyl bromide can be prepared by the action of sodium phenoxide on trimethylene bromide in alcohol solution.[1] The procedure described has been published.[2]

References and Notes

1. Lohmann, Ber. **24**, 2631 (1891); Salonina, Ber. **26**, 2987 (1893); v. Braun and Beschke, Ber. **39**, 4120 (1906).
2. Marvel and Tanenbaum, J. Am. Chem. Soc. **44**, 2647 (1922).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alcohol (64-17-5)

sodium hydroxide (1310-73-2)

phenol (108-95-2)

sodium bromide (7647-15-6)

Trimethylene bromide (109-64-8)

ethylene bromide (106-93-4)

sodium phenoxide

γ-Phenoxypropyl bromide, phenoxypropyl bromide (588-63-6)

Propane, 1-bromo-2-phenoxy-

diphenoxypropane

Phenoxyethyl bromide (589-10-6)

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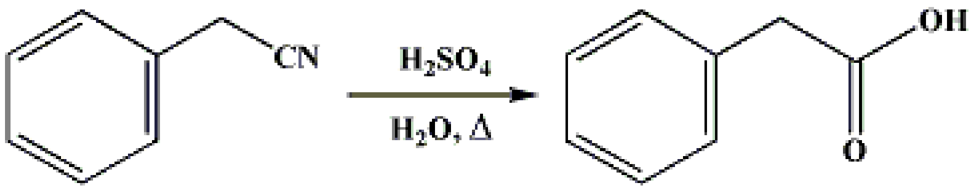
Organic Syntheses, CV 1, 436

PHENYLACETIC ACID

[α-Toluic acid]



Submitted by Roger Adams and A. F. Thal.
Checked by O. Kamm and A. O. Matthews.

1. Procedure

In a 5-l. round-bottom flask, fitted with a mechanical stirrer and reflux condenser, are mixed 1150 cc. of water, 840 cc. of commercial sulfuric acid (Note 1) and 700 g. (6 moles) of benzyl cyanide (p. 107). The mixture is heated under a reflux condenser and stirred for three hours (Note 2), cooled slightly, and then poured into 2 l. of cold water. The mixture should be stirred so that a solid cake is not formed; the phenylacetic acid is then filtered off. This crude material is melted under water and washed by decantation several times with hot water. These washings, on cooling, deposit a small amount of phenylacetic acid which is filtered off and added to the main portion of material. The last of the hot water is poured off from the material while it is still molten, and it is then transferred to a 2-l. Claisen distilling flask and distilled under reduced pressure. A small amount of water comes over first and is rejected; about 20 cc., containing an appreciable amount of benzyl cyanide, then distils. This fraction is used in the next run. The distillate boiling at 176–189°/50 mm. is collected separately and solidifies on standing. It is practically pure phenylacetic acid, m.p. 76–76.5°, and weighs 630 g. (77.5 per cent of the theoretical amount) (Note 3). As the fraction which is returned to the second run of material contains a considerable portion of phenylacetic acid, the yield actually amounts to at least 80 per cent.

For the preparation of small quantities of phenylacetic acid, it is convenient to use the modified method given in (Note 3).

2. Notes

1. The standard directions for the preparation of phenylacetic acid specify that the benzyl cyanide is treated with dilute sulfuric acid prepared by adding three volumes of sulfuric acid to two volumes of water. The reaction, however, goes so vigorously that it is always necessary to have a trap for collecting the benzyl cyanide which is blown out of the apparatus. The use of the more dilute acid, as described in the above directions, is more satisfactory.

The odor of phenylacetic acid is disagreeable and persistent.
2. The phenylacetic acid may also be made by boiling under a reflux condenser for eight to fifteen hours, without a stirrer, but this method is not nearly so satisfactory as that described in the procedure.
3. The following modified procedure can be used for the preparation of small quantities of the acid. One hundred grams of benzyl cyanide is added to a mixture containing 100 cc. of water, 100 cc. of concentrated sulfuric acid, and 100 cc. of glacial acetic acid. After this has been heated for forty-five minutes under a reflux condenser, the hydrolysis is practically complete. The reaction mixture is then poured into water, and the phenylacetic acid is isolated in the usual manner.

3. Discussion

The standard method for the preparation of phenylacetic acid is the hydrolysis of benzyl cyanide with either alkali[1] or acid.[2] The acid hydrolysis runs by far the more smoothly and so was the only one studied. Phenylacetic acid can also be prepared by the carbonation of benzylmagnesium chloride[3] and by the catalytic reduction of mandelic acid.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 107
- Org. Syn. Coll. Vol. 2, 61
- Org. Syn. Coll. Vol. 2, 156
- Org. Syn. Coll. Vol. 2, 229
- Org. Syn. Coll. Vol. 2, 389
- Org. Syn. Coll. Vol. 4, 760
- Org. Syn. Coll. Vol. 4, 777

References and Notes

1. Cannizzaro, Ann. **96**, 247 (1855); Mann, Ber. **14**, 1465 (1881); Bodroux, Compt. rend. **151**, 236 (1910).
2. Staedel, Ber. **19**, 1950 (1886).
3. Austin and Johnson, J. Am. Chem. Soc. **54**, 655 (1932).
4. Zelinsky, Packendorff, and Leder-Packendorff, Ber. **67**, 301 (1934).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

Mandelic acid (90-64-2)

α-Toluic acid (65-85-0)

Benzyl cyanide (140-29-4)

Phenylacetic acid (103-82-2)

benzylmagnesium chloride (6921-34-2)

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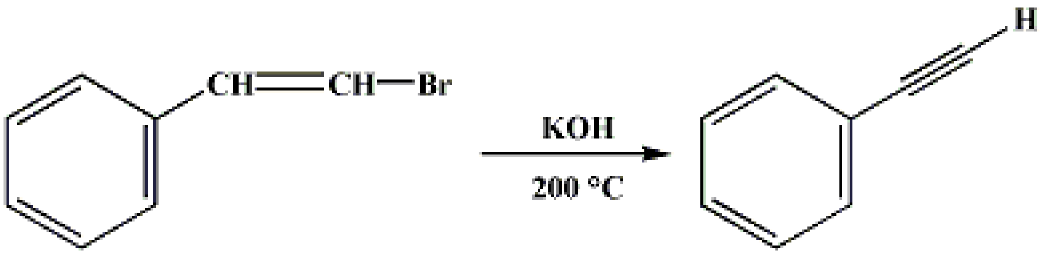
Organic Syntheses, CV 1, 438

PHENYLACETYLENE

[Benzene, ethynyl-]



Submitted by John C. Hessler
Checked by J. B. Conant and G. R. Barrett.

1. Procedure

In a 500-cc. Pyrex distilling flask (Note 1) is placed 150 g. (2.7 moles) of potassium hydroxide. The mouth of the flask is provided with a one-holed stopper holding a dropping funnel; the side tube of the flask is connected with a condenser set for downward distillation.

The distilling flask is gradually heated in an oil bath until the temperature of the bath is 200°, and 100 g. (0.55 mole) of β-bromostyrene is then dropped in upon the molten potassium hydroxide (Note 2), at the rate of somewhat less than a drop a second. Since the boiling point of phenylacetylene is 142–143°, and that of bromostyrene is 218–220°, the phenylacetylene distils away from the unchanged bromostyrene.

While the bromostyrene is being dropped in (Note 3), the temperature of the oil bath is raised very gradually to 215–220° and is kept there until all the bromostyrene has been added. Finally the temperature is raised to 230° and is held there until no more distillate comes over. The distillate is colorless; it consists of two layers, the lower one being water. The upper layer is separated and dried with solid potassium hydroxide. It is then distilled. The yield of the distilled phenylacetylene, boiling at 142–144°, is 37 g. (67 per cent of the theoretical amount) (Note 4).

2. Notes

1. A single Pyrex flask can be used for only three or four runs. The flask should be emptied while still very hot. The use of steel or copper vessels in place of a glass flask seems to diminish the yield slightly.
2. The potassium hydroxide usually available contains sufficient moisture so that it will liquefy at 200°. If pure dry potassium hydroxide is used, it is necessary to add a little water so that the fusion point will be lowered to the temperature indicated.

It is suggested that equally good yields can be obtained if the eutectic of sodium hydroxide and potassium hydroxide is used, under which conditions the alkali is molten at 200° and the reaction takes place very readily.[1]

3. Toward the end of the reaction, a crust of potassium bromide may tend to cover the melted potassium hydroxide. The crust can be broken by shaking the distilling flask gently, or by using a glass rod inserted through a second hole in the stopper holding the dropping funnel.

It is convenient to have such a rod or stirrer passing through a mercury seal in the stopper of the flask. An occasional turn of this stirrer breaks the crust and facilitates the operation. Mechanical stirring should not be employed, as it reduces the yield tremendously. Apparently this is because it facilitates the solution of bromostyrene in the tarry by-products and thus causes it to polymerize instead of reacting with the potassium hydroxide.

4. The yield of material can be somewhat increased by working with small lots (25 g. of β-bromostyrene).

3. Discussion

Two methods are available for preparing phenylacetylene: the elimination of carbon dioxide from phenylpropiolic acid, and the elimination of halogen acid from either styrene dibromide or an α- or β-halostyrene. Phenylpropiolic acid has been converted to phenylacetylene by means of phenol[2] or aniline[3] or by heating with barium hydroxide.[4] Styrene dibromide has been converted to phenylacetylene by treatment with sodium in liquid ammonia,[5] or sodamide,[6 7] or potassium hydroxide in alcohol.[8] α-Chlorostyrene and α-bromostyrene have been converted to phenylacetylene by means of sodamide.[7,9] β-Chlorostyrene and β-bromostyrene have been converted to phenylacetylene by treatment with sodium ethoxide or potassium hydroxide in alcohol[10] with sodium in liquid ammonia,[5] with sodamide,[7] with molten potassium hydroxide,[11] and with the sodium derivative of aniline.[12]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 763

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

α- or β-halostyrene

sodium derivative of aniline

alcohol (64-17-5)

ammonia (7664-41-7)

aniline (62-53-3)

sodium hydroxide (1310-73-2)

phenol (108-95-2)

carbon dioxide (124-38-9)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

potassium bromide (7758-02-3)

barium hydroxide (17194-00-2)

Phenylacetylene, Benzene, ethynyl- (536-74-3)

β-bromostyrene, bromostyrene (103-64-0)

Phenylpropiolic acid (637-44-5)

styrene dibromide (93-52-7)

α-Chlorostyrene

α-bromostyrene (98-81-7)

β-Chlorostyrene (622-25-3)

sodamide (7782-92-5)

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Organic Syntheses, CV 1, 440

PHENYLETHYLENE

[Styrene]

Submitted by T. W. Abbott and John R. Johnson.
Checked by H. T. Clarke and M. R. Brethen.

1. Procedure

In a 500-cc. flask, fitted with a 24-cm. fractionating column (Note 1) and (Note 2) attached to a water-jacketed condenser, are placed 148 g. (1 mole) of dry powdered cinnamic acid, 2 g. of hydroquinone, and several small pieces of clay plate. One-half gram of hydroquinone is also placed in the flask in which the distillate is to be collected (Note 3). The acid is rapidly heated over a wire gauze with a free flame until phenylethylene begins to distil, the heating being regulated so that the temperature of the vapors at the head of the column never exceeds 130°, and mainly remains below 120° (Note 4) and (Note 2). The cinnamic acid refluxes, but very little should escape and collect in the condenser. The decomposition is complete in three and one-half to five hours, when no more phenylethylene distils and the temperature at the head of the column rises rapidly.

The distillate consists of a straw-colored oil and a little water; a dark tarry residue (50–60 g.) remains in the reaction flask. About 100 cc. of water is added to the distillate, and the aqueous mixture is distilled. The phenylethylene is easily volatile with steam and separates in the distillate as a colorless oil. The oil (45–48 g.) is separated, dried with a small amount of calcium chloride, and carefully distilled under reduced pressure, the condenser and receiver being cooled to 0–5° by means of iced (or very cold) water. The phenylethylene is collected at 44–46°/40 mm. or 60–63°/60 mm. (Note 5). The yield is 40–42 g. (38–41 per cent of the theoretical amount) (Note 6).

2. Notes

1. The column consists of a glass tube of 13–14 mm. internal diameter, 24 cm. long from lower end to the side arm, which has an internal diameter of 7 mm. It is important that these dimensions be observed in order to avoid polymerization of the product. It has been found in checking that better results are obtained by making indentations in the tube at frequent intervals and at different angles; these tend to reduce the number of cinnamic acid particles which are carried

over with the vapor. A column of the Vigreux type would no doubt also be suitable.
2. If the fractionating column does not have the exact dimensions designated in (Note 1) the temperature of the vapors at the head of the column will vary from those given. However, no difficulty will arise in obtaining the yield of product indicated if the general directions for heating the cinnamic acid, so as to avoid the carrying of the cinnamic acid into the distillate, are followed.
3. An anti-oxidant such as catechol or hydroquinone is used to prevent polymerization. Hydroquinone should be added in the ratio of one part per thousand unless the phenylethylene is to be used immediately.[1]
4. If the temperature of the escaping vapor rises above 130°, appreciable amounts of cinnamic acid pass into the condenser and the yield falls materially.
5. Phenylethylene should not be distilled under atmospheric pressure since the temperature (146°) required for the distillation causes a considerable loss by polymerization. The decomposition of cinnamic acid cannot be effected by distillation under diminished pressure, since the acid under these conditions distils below the temperature required for decomposition (approximately 300°).
6. On increasing the scale of the preparation, the yield is somewhat higher.

3. Discussion

Phenylethylene can be prepared by the addition of hydrobromic or hydriodic acid to cinnamic acid and subsequent treatment with alkali;[2] from methylphenylcarbinol by distillation of the benzoic ester or by the action of phosphoric acid;[3] by distilling β-phenylethyl phenylacetate;[4] by pyrogenic decomposition of ethylbenzene[5] or β-phenylethyl chloride;[6] from phenyl-α,β-dibromoethane and magnesium;[7] and by heating β-phenylethyl alcohol with potassium hydroxide.[8] The procedure described is that of Böeseken and Bastet.[9] The method of Sabetay[8] has been reported[10] to be superior to that described above.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 494

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrobromic or hydriodic acid

benzoic ester

calcium chloride (10043-52-4)

hydroquinone (123-31-9)

magnesium (7439-95-4)

potassium hydroxide (1310-58-3)

phosphoric acid (7664-38-2)

Catechol (120-80-9)

ethylbenzene (100-41-4)

cinnamic acid (621-82-9)

β-phenylethyl chloride (622-24-2)

styrene, Phenylethylene (100-42-5)

phenyl-α,β-dibromoethane (93-52-7)

methylphenylcarbinol (98-85-1)

β-phenylethyl phenylacetate (102-20-5)

β-phenylethyl alcohol (60-12-8)

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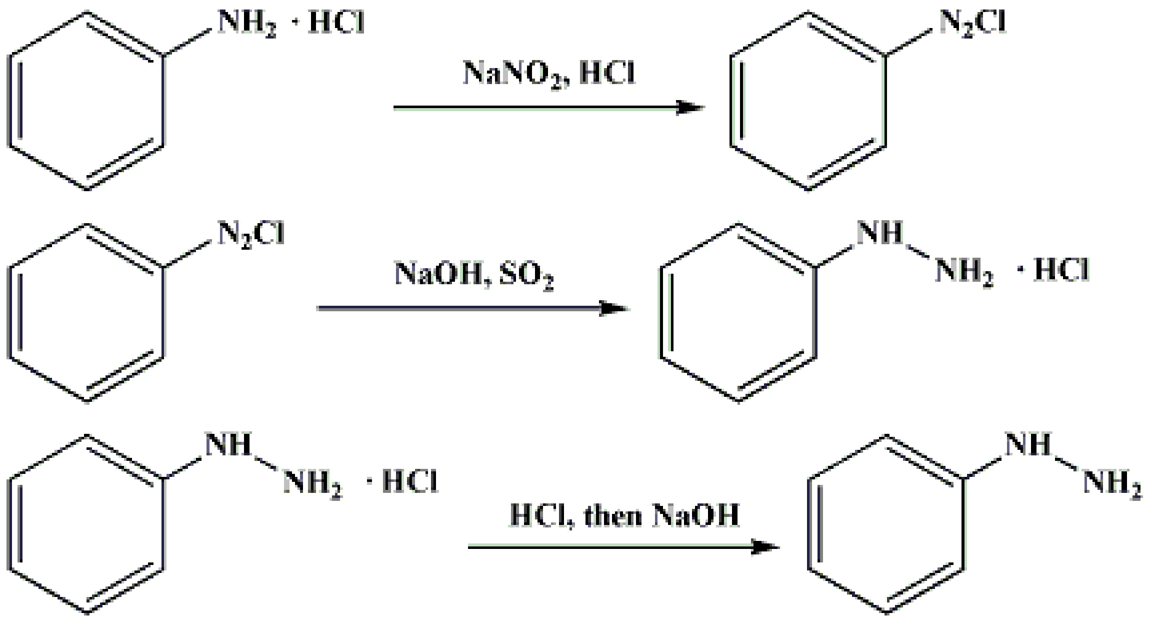
Organic Syntheses, CV 1, 442

PHENYLHYDRAZINE

[Hydrazine, phenyl-]



Submitted by G. H. Coleman
Checked by J. B. Conant and H. R. Thompson.

1. Procedure

In a 12-l. round-bottomed flask, fitted with a mechanical stirrer, is placed 1045 cc. of concentrated commercial hydrochloric acid (sp. gr. 1.138). The flask is surrounded with a freezing mixture of ice and salt, and, when the contents are at 0°, stirring is started and 500 g. of cracked ice is added, or more ice can be added and the external cooling dispensed with; then 372 g. (364 cc., 4 moles) of aniline, also cooled to 0°, is run in during five minutes. The mixture is treated with 500 g. more of cracked ice, and a cold solution (0°) of 290 g. (4 moles) of technical sodium nitrite dissolved in 600 cc. of water is allowed to run in slowly (twenty to thirty minutes) from a separatory funnel, the end of which is drawn to a small tip and reaches nearly to the bottom of the flask. During this addition, the stirrer is operated rather vigorously, and the temperature is kept as near 0° as possible by the frequent addition of cracked ice (about 1 kg.).

In the meantime, a sodium sulfite solution is prepared by dissolving 890 g. (20 moles) of sodium hydroxide, of about 90 per cent purity, in about 1 l. of water and then diluting to 6 l. A few drops of phenolphthalein solution are added and sulfur dioxide passed in, first until an acid reaction is indicated and then for two or three minutes longer. During the addition of the sulfur dioxide, the solution is cooled with running water. On account of the strong alkaline solution, the original color produced by the phenolphthalein is very faint, but this slowly increases until it becomes deep just

before the acid point is reached. It is best to remove a small sample of the liquid from time to time, dilute with three or four volumes of water, and add a drop more of phenolphthalein (Note 1).

The sodium sulfite solution is placed in a 12-l. flask and cooled to about 5°. Approximately 500 g. of cracked ice is added, and then, with mechanical stirring, the diazonium salt solution is run in as rapidly as possible (Note 2). The mixture becomes a bright orangered. The flask is now warmed to about 20° on a steam bath, until the solid sodium sulfite, which has separated while cooling, redissolves. The total amount of liquid is now about 10 l. One-half of this is poured into another 12-l. flask, and both halves are warmed on the steam bath to 60–70°, until the color becomes quite dark (thirty to sixty minutes). Sufficient hydrochloric acid (300–400 cc.) is now added (Note 3) to each flask to make the solutions acid to litmus. The heating is continued and the color gradually becomes lighter until, after four to six hours, the solutions have become nearly colorless; they may be heated overnight, if desired.

To the hot solutions is now added about one-third of their volume of concentrated hydrochloric acid (2 l. to each portion), and the mixtures are cooled, first in running water, then in a freezing mixture, to 0° (Note 4). The phenylhydrazine hydrochloride precipitates in the form of slightly yellowish or pinkish crystals which may be filtered off and dried (Note 5).

The free base is liberated by adding to the phenylhydrazine hydrochloride 1 l. of a 25 per cent solution of sodium hydroxide. The phenylhydrazine separates and is taken up with benzene (two 300-cc. portions). The combined extractions are well dried with 200 g. of solid sodium hydroxide (Note 6), poured off, and distilled. Most of the benzene may be distilled under ordinary pressure, and the remainder, and any low-boiling impurities, under diminished pressure. The pure phenylhydrazine boils at 137–138°/18 mm., and is obtained as a pale yellow liquid (Note 7). It can be crystallized on cooling in an ice bath; the crystals melt at 23°. The crude phenylhydrazine from two lots of aniline (744 g.) is best distilled at one time and gives 695–725 g. of pure product (80–84 per cent of the theoretical amount).

2. Notes

1. If the sodium sulfite solution contains an excess of alkali, a black tar tends to form when the solution is warmed, and very little phenylhydrazine is obtained. Great care must be taken in determining the end point in the neutralization of the sodium hydroxide by the sulfur dioxide.
It is best to use freshly prepared sodium sulfite for the reduction, since the commercial quality is poor and gives a lower yield of phenylhydrazine. A cylinder of liquid sulfur dioxide should, of course, be available.
2. The rapid addition of the diazonium salt solution to the sodium sulfite seems to be advantageous.
3. If the sodium sulfite-diazonium salt mixture is acidified before warming or

before becoming dark, the red color of the solution does not disappear on heating, and the precipitated phenylhydrazine hydrochloride obtained is colored red.

Most published directions for the preparation of phenylhydrazine specify the use of zinc dust and acetic acid following the reduction with sodium sulfite. No improvement in the quality or quantity of the product was obtained by using zinc and acetic acid.

4. In order to obtain the maximum yield, it is necessary to cool the hydrochloric acid solution of the phenylhydrazine hydrochloride from 20° to 0°, before filtration. From 5 to 10 per cent of product separates between these two temperatures. When this is done, no more phenylhydrazine hydrochloride is obtained by concentration of the mother liquor. An increase in the amount of hydrochloric acid above 2 l. for the precipitation of the hydrochloride produces no increase in yield of product.

5. The phenylhydrazine hydrochloride may be purified by crystallizing from water. A 600-cc. portion of water is used for 100 g. of crude hydrochloride, and the solution boiled a short time with a few grams of animal charcoal. After filtering, 200 cc. of concentrated hydrochloric acid is added, and the mixture cooled to 0°. Pure white crystals in a yield of 85–90 g. are obtained.

6. The benzene solution of phenylhydrazine should be well dried before distilling, since the presence of moisture causes an increased amount of foaming to take place just after the benzene has distilled off. When the distillation is carried out carefully, practically no phenylhydrazine distills with the benzene or other low-boiling impurities.

Care should be taken that the free base contains no trace of hydrochloride, for this compound catalyzes the decomposition of phenylhydrazine above 100°.

7. Pure phenylhydrazine dissolves in dilute acetic acid to yield a perfectly clear solution.

Care should be taken when working with large quantities of phenylhydrazine, since the product may cause serious injury to the skin. The vapors of phenylhydrazine should not be inhaled.

3. Discussion

Phenylhydrazine can be prepared by the reduction of benzenediazonium salts by means of a miscellany of reducing agents, of which sodium sulfite[1] is preferred. Although this method is given in several laboratory manuals, the results were not found entirely satisfactory. The present directions provide for a lengthy but essential heating of the diazonium-sulfite mixture, omit the useless zinc dust reduction, and supply exact details for preparation on a fairly large laboratory scale. The electrolytic reduction of benzenediazonium salts has been reported to furnish a quantitative yield of phenylhydrazine.[2]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium sulfite-diazonium salt

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

aniline (62-53-3)

sodium sulfite (7757-83-7)

sodium hydroxide (1310-73-2)

sulfur dioxide (7446-09-5)

sodium nitrite (7632-00-0)

Phenylhydrazine, Hydrazine, phenyl- (100-63-0)

zinc (7440-66-6)

phenolphthalein (77-09-8)

phenylhydrazine hydrochloride (59-88-1)

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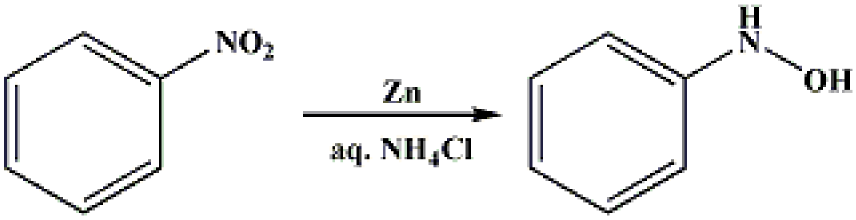
Organic Syntheses, CV 1, 445

β-PHENYLHYDROXYLAMINE

[Hydroxylamine, N-phenyl-]



Submitted by Oliver Kamm
Checked by C. S. Marvel

1. Procedure

In a 16-l. earthenware jar are placed 250 g. (4.7 moles) of technical ammonium chloride, 8 l. of water, and 500 g. (416 cc., 4.1 moles) of nitrobenzene. The mixture is stirred vigorously by means of a mechanical stirrer, and 620 g. (8.1 atoms) of zinc dust of 85 per cent purity is added (Note 1) during the course of fifteen to twenty minutes (Note 2). As the reduction proceeds, the temperature rises to 60–65°. Stirring is continued for fifteen minutes after all the zinc dust has been added, at the end of which time the reaction is complete, as indicated by the fact that the temperature of the mixture ceases to rise.

While still hot, the solution is filtered with suction in order to remove the zinc oxide, which is washed with 1 l. of hot water. The filtrate is placed in an enameled pan, saturated with salt, about 3 kg. being required, and cooled to 0° by being placed in an ice-salt mixture. The phenylhydroxylamine, which crystallizes out in long, light yellow needles (Note 3), is filtered by suction. The yield of crude product varies considerably, depending upon the amount of salt solution present, but averages 350–400 g. This corresponds to 275–300 g. (62–68 per cent of the theoretical amount) of actual phenylhydroxylamine, as determined by its separation from inorganic materials by solution in ether (Note 4).

Since phenylhydroxylamine deteriorates upon storage, it is generally used promptly, as illustrated in the preparation of cupferron (p. 177). The oxalate is somewhat more stable.

2. Notes

1. The zinc dust must be analyzed (Gattermann, "Practical Methods of Organic Chemistry," 3rd ed., p. 390), and a proportional quantity used if the zinc content is not 85 per cent. Technical nitrobenzene is satisfactory if it distils over a range of not more than 5° and is not acid in reaction.

2. When the reaction is run more slowly, the temperature does not reach 60–65° and the yield is poorer. At 50–55°, the yield is about 55 per cent.
3. It is important that the phenylhydroxylamine solution be kept at 0° for at least one-half hour or considerable material will be lost in the solution. The use of an enameled pail saves a great deal of time at this step.
4. Phenylhydroxylamine is soluble in saturated salt solution at 0° to the extent of about 9 g. per liter, but this amount is not included in the yields given. Occasional yields of 300–310 g. of dry phenylhydroxylamine have been obtained.

3. Discussion

β-Phenylhydroxylamine can be prepared by the reduction of nitrobenzene by zinc dust,[1] a method in which various solvents and catalysts have been used, and in which copper-coated and amalgamated zinc, as well as aluminum amalgam,[2] have been substituted for the zinc dust; by ammonium sufide;[3] by sodium in liquid ammonia;[4] and by the oxidation of anilinomagnesium bromide with an ether solution of hydrogen peroxide.[5] The procedure described is like an earlier method,[6] but it has been found[7] that cooling is not essential. The preparation of the oxalate has been described.[8]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 177
- Org. Syn. Coll. Vol. 5, 957
- Org. Syn. Coll. Vol. 5, 1124
- Org. Syn. Coll. Vol. 8, 16

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

β-Phenylhydroxylamine

copper-coated and amalgamated zinc

ammonium sufide

sodium in liquid ammonia

ether (60-29-7)

ammonium chloride (12125-02-9)

aluminum (7429-90-5)

zinc (7440-66-6)

Nitrobenzene (98-95-3)

hydrogen peroxide (7722-84-1)

Cupferron (135-20-6)

Phenylhydroxylamine, Hydroxylamine, N-phenyl- (100-65-2)

zinc oxide

anilinomagnesium bromide

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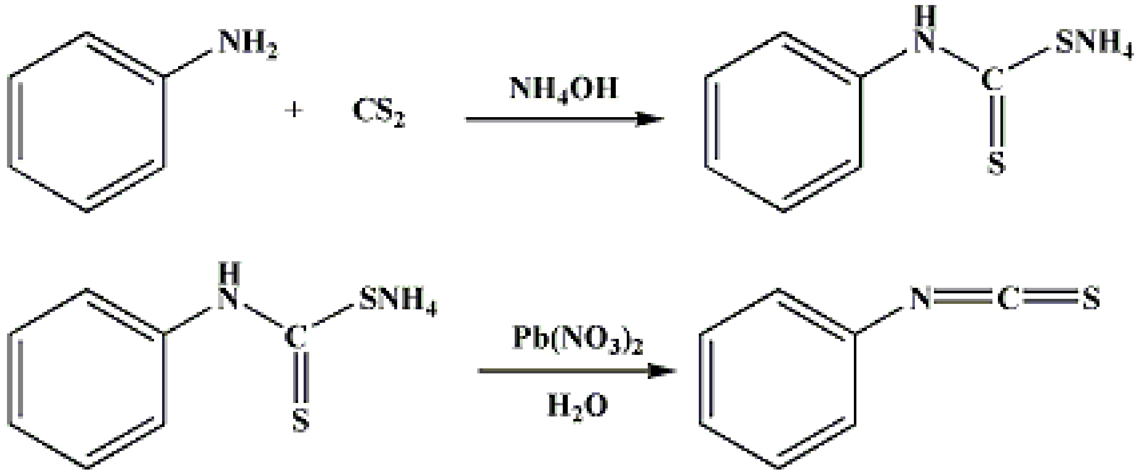
Organic Syntheses, CV 1, 447

PHENYL ISOTHIOCYANATE

[Isothiocyanic acid, phenyl ester]



Submitted by F. B. Dains, R. Q. Brewster, and C. P. Olander.
Checked by C. S. Marvel and L. T. Sandborn.

1. Procedure

In a 500-cc. round-bottomed flask (Note 1), fitted with a mechanical stirrer and surrounded by an ice-salt cooling bath, are placed 54 g. (43 cc., 0.71 mole) of carbon disulfide and 90 cc. (1.3 moles) of concentrated aqueous ammonia (sp. gr. 0.9). The stirrer is started, and 56 g. (0.6 mole) of aniline (Note 2) is run into the mixture from a separatory funnel at such a rate that the addition is complete in about twenty minutes. The stirring is continued for thirty minutes after all the aniline has been added, and then the reaction mixture is allowed to stand for another thirty minutes. During this time a heavy precipitate of ammonium phenyldithiocarbamate separates and may even stop the stirrer.

The salt is dissolved in 800 cc. of water (Note 3) and transferred to a 5-l. round-bottomed flask. To the solution is added with constant stirring a solution of 200 g. (0.6 mole) of lead nitrate in 400 cc. of water. Lead sulfide separates as a heavy brown precipitate which soon turns black. The mixture is then distilled with steam into a receiver containing 5–10 cc. of 1 *N* sulfuric acid as long as any oil comes over (Note 4). About 2–3 l. of distillate is collected. The product is separated from the water and weighs 63–66 g.

The oil is dried over a little calcium chloride and distilled under reduced pressure. The yield of phenyl isothiocyanate boiling at 120–121°/35 mm. is 60–63 g. (74–78 per cent of the theoretical amount) (Note 5) and (Note 6).

2. Notes

1. If the reaction is carried out in a beaker, so much ammonia is lost by volatilization that the crystalline ammonium phenyldithiocarbamate is not formed. The temperature should be from 0° to 10° to avoid loss of ammonia.
2. Ordinary technical aniline was used in these experiments.
3. The transfer of the salt to the 5-l. flask is conveniently made by the addition of four successive 200-cc. portions of water to the flask containing the salt.
4. The sulfuric acid is added to react with any ammonia that may be carried over. Otherwise the ammonia may react with the product to give phenylthiourea.
5. Larger runs give somewhat lower percentage yields; thus 280 g. of aniline gives about 250 g. (61 per cent of the theoretical amount) of redistilled phenyl isothiocyanate.
6. The following slightly modified procedure is generally applicable to the preparation of aryl isothiocyanates.
To a solution of 90 g. (0.50 mole) of *p*-bromoaniline, 60 g. (0.78 mole) of carbon disulfide and 90 cc. of 95 per cent alcohol at 10–15° is added 81.6 g. (0.63 mole) of concentrated aqueous ammonia. The milky suspension, in a stoppered flask covered with a towel, is shaken occasionally until a clear solution is obtained. Considerable heat is evolved, and crystals of the intermediate dithiocarbamate soon separate. After standing overnight the crystals are filtered, washed with ether, dissolved in 3 l. of cold water, and stirred while a solution of 174 g. (0.5 mole) of lead nitrate is slowly added. Stirring is continued for fifteen to twenty minutes, and then the *p*-bromophenylisothiocyanate is steam-distilled into a flask acidified with sulfuric acid. The product, which solidifies, is separated and dried. It weighs 30.5 g. (a yield of 27 per cent) and melts at 60–61°.
In this procedure the use of alcohol is essential; without it no isothiocyanate is obtained. It is also advisable with very reactive aromatic amines to add the ammonia in small portions so as to avoid a too vigorous reaction and to keep the temperature of the contents of the stoppered flask below 35°. With some substituted anilines the intermediate dithiocarbamate does not crystallize although the heat evolved indicates that a reaction has taken place. When this happens the solution can be diluted with water and treated with lead nitrate, but the yield will usually be small.
Using this procedure the following isothiocyanates have been prepared with the percentage yields indicated: *p*-iodophenyl, 26–50; *p*-isopropylphenyl, 34; *m*-(trifluoromethyl) phenyl, 50; *p*-acetylphenyl, trace; *m*-bromophenyl, 20; β-naphthyl, 8; *p*-dimethylaminophenyl, 13; 2-methyl-4-isopropylphenyl, 5. The reaction did not work with 2-aminopyridine. (C. J. Kibler, private communication.)

3. Discussion

Phenyl isothiocyanate can be prepared from thiocarbanilide by the action of

phosphorus pentoxide,[1] hydrochloric acid,[2] iodine,[3] phosphoric acid,[4] acetic anhydride,[5] and dilute sulfuric acid;[6] from ammonium phenyldithiocarbamate by the action of ethyl chlorocarbonate,[7] copper sulfate,[8], [9] lead nitrate,[9] ferrous sulfate,[9] and zinc sulfate;[9] and from methylene aniline by heating with sulfur.[10]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 165
- Org. Syn. Coll. Vol. 3, 312
- Org. Syn. Coll. Vol. 4, 700
- Org. Syn. Coll. Vol. 5, 223

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1. Hofmann, Jahresber. 349 (1858).
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3. Hofmann, Ber. **2**, 453 (1869); Rudnev, J. Russ. Phys. Chem. Soc. **10**, 184 (1878).
4. Hofmann, Ber. **15**, 985 (1882).
5. Werner, J. Chem. Soc. **59**, 396 (1891).
6. Bly, Perkins and Lewis, J. Am. Chem. Soc. **44**, 2896 (1922).
7. Kaluza, Monatsh. **33**, 367 (1912).
8. Losanitsch, Ber. **24**, 3021 (1891).
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10. Kawaoka, J. Soc. Chem. Ind., Japan **43**, No. 2, Suppl. binding 53 (1940) [C. A. **34**, 6131 (1940)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ß-naphthyl isothiocyanate

alcohol (64-17-5)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ether (60-29-7)

acetic anhydride (108-24-7)

aniline (62-53-3)

lead sulfide

copper sulfate (7758-98-7)

sulfur (7704-34-9)

ferrous sulfate (13463-43-9)

iodine (7553-56-2)

phosphoric acid (7664-38-2)

lead nitrate (10099-74-8)

carbon disulfide (75-15-0)

zinc sulfate (7733-02-0)

PHENYL ISOTHIOCYANATE, Isothiocyanic acid, phenyl ester (103-72-0)

ammonium phenyldithiocarbamate

phenylthiourea (103-85-5)

dithiocarbamate

2-aminopyridine (504-29-0)

thiocarbanilide (102-08-9)

ethyl chlorocarbonate (541-41-3)

methylene aniline (100-62-9)

phosphorus pentoxide (1314-56-3)

p-bromoaniline (106-40-1)

p-bromophenylisothiocyanate (1985-12-2)

p-iodophenyl isothiocyanate

p-isopropylphenyl isothiocyanate

m-(trifluoromethyl) phenyl isothiocyanate

p-acetylphenyl isothiocyanate

m-bromophenyl isothiocyanate

p-dimethylaminophenyl isothiocyanate

2-methyl-4-isopropylphenyl isothiocyanate

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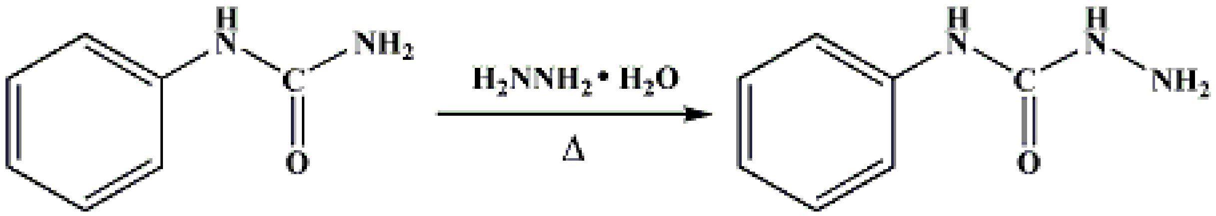
Organic Syntheses, CV 1, 450

4-PHENYLSEMICARBAZIDE

[Semicarbazide, 4-phenyl-]



Submitted by A. S. Wheeler
Checked by C. S. Marvel and M. M. Brubaker.

1. Procedure

In a 500-cc. round-bottomed flask fitted with a reflux condenser are placed 68 g. of phenylurea (0.5 mole) (Note 1) and 120 cc. (1 mole) of 42 per cent hydrazine hydrate solution (Note 2). The flask is heated on a steam bath for about twelve hours. The hot mixture is treated with a small amount of decolorizing charcoal (Norite) and filtered. The charcoal is washed with two 15-cc. portions of warm water, and the filtrate and washings are then concentrated on a steam bath to about 100 cc. On cooling in an ice bath a crop of crystals separates which is collected on a filter and washed with two 15-cc. portions of cold water. The filtrate and washings are concentrated to about 25 cc., and another crop of crystals is obtained as before. The total yield of crude compound is 47–52 g. It is white at first but sometimes turns brown on drying. It usually melts below 115° because of some unchanged phenylurea.

The product is purified (Note 3) by conversion to the hydrochloride, which is then changed into the free base.

A filtered solution of the crude product in 200 cc. of hot absolute alcohol is treated with 250 cc. of concentrated hydrochloric acid. Most of the hydrochloride precipitates at once and is filtered, washed with alcohol, and dried. The filtrate is cooled in an ice-salt bath and again filtered, and the precipitate is washed, dried, and added to the previous portion. The yield is 46–48 g. of material melting at about 215° (Note 4). The hydrochloride is dissolved in three times its weight of water, previously heated nearly to boiling (Note 5). The solution is filtered if necessary and then treated with sodium hydroxide solution (2.2 g. of 10 per cent sodium hydroxide solution for each gram of hydrochloride used). The free base separates at once, and the solution is cooled in an ice bath and filtered. This product melts at 120–123°. The yield of pure base is 28–30 g. (37–40 per cent of the theoretical amount) (Note 6).

2. Notes

1. The phenylurea was prepared as described on p. 453 and melted at 146–147°.
2. An equivalent amount of hydrazine sulfate (p. 309) and sodium hydroxide in 80 per cent alcohol may be used in place of the hydrazine hydrate solution without greatly diminishing the yield.
3. The crude product contains about 9–10 g. of unchanged phenylurea which cannot be satisfactorily removed by crystallization from benzene or water. When the hydrochloride of the phenylsemicarbazide is formed, the phenylurea may be recovered from the alcoholic filtrates.
4. Inasmuch as the melting point of the salt varies somewhat with the rate of heating, this temperature is not particularly significant.
5. The salt should not be boiled with water any longer than is necessary, as some decomposition occurs, and diphenylurea, melting at about 235–240°, is produced.
6. It is suggested that an improved yield is obtainable by heating 34 g. of phenylurea, 25 cc. of 100 per cent hydrazine hydrate, and 25 cc. of absolute alcohol for twenty-four hours on a steam bath. This procedure would eliminate the need of purification by passing through the hydrochloride and back to the base (A. S. Wheeler, private communication).

3. Discussion

4-Phenylsemicarbazide can be prepared by the action of hydrazine hydrate on phenylurea;[1] and by hydrolysis of benzal-4-phenylsemicarbazone[2] and of α-benzoyl β-phenylcarbamyl hydrazine.[3]

References and Notes

1. Curtius, J. prakt. Chem. (2) **58**, 216 (1898).
2. Curtius and Hofmann, ibid. (2) **53**, 526 (1896).
3. Bailey and McPherson, J. Am. Chem. Soc. **39**, 1333 (1917).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

benzal-4-phenylsemicarbazone

α-benzoyl β-phenylcarbamyl hydrazine

alcohol (64-17-5)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

sodium hydroxide (1310-73-2)

hydrazine hydrate (7803-57-8)

Hydrazine sulfate (10034-93-2)

4-PHENYLSEMICARBAZIDE, Semicarbazide, 4-phenyl- (537-47-3)

Phenylurea (64-10-8)

phenylsemicarbazide (103-03-7)

diphenylurea (603-54-3)

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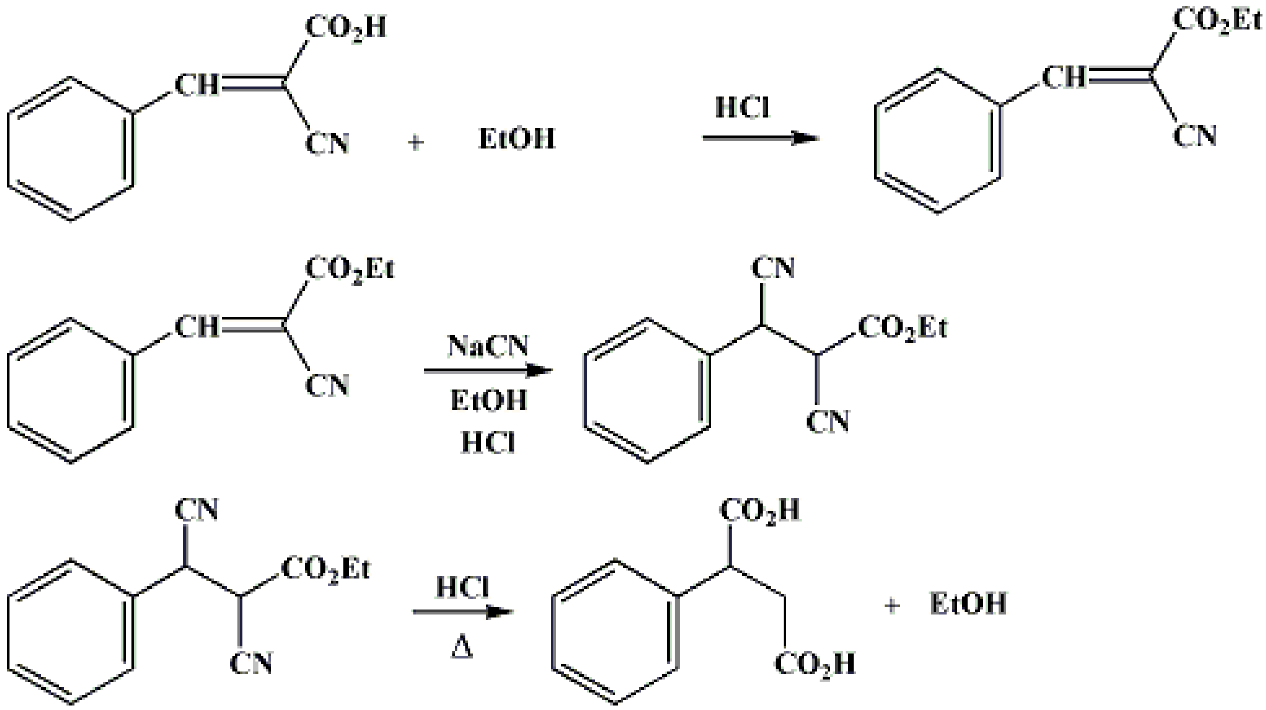
Organic Syntheses, CV 1, 451

PHENYLSUCCINIC ACID

[Succinic acid, phenyl-]



Submitted by Arthur Lapworth and Wilson Baker.
Checked by J. B. Conant and Mildred Evans.

1. Procedure

(*A*) *Esterification of α-Cyano-β-phenylacrylic Acid*.—In a 200-cc. round-bottomed flask fitted with a reflux condenser, 50 g. (0.29 mole) of dry α-cyano-β-phenylacrylic acid (p. 181) is boiled for four and one-half hours with 100 cc. of absolute alcohol (p. 249) containing 3–4 g. of anhydrous hydrogen chloride (p. 293). The resulting solution is filtered rapidly while hot and allowed to stand overnight. Long, flat, colorless prisms separate which are filtered off with suction, washed with a little cold alcohol, and dried in air. A further small quantity may be obtained by working up the mother liquor. The melting point of the ethyl α-cyano-β-phenylacrylate is 50°, and the yield is 46.5–53 g. (80–91 per cent of the theoretical amount) (Note 1).

(*B*) *Addition of Sodium Cyanide to Ethyl α-Cyano-β-phenylacrylate*.—Twenty grams (0.1 mole) of cyanophenylacrylic ester is treated with 40 cc. of 50 per cent alcohol and 10 g. (0.2 mole) of finely powdered sodium cyanide. The mixture becomes warm and the ester rapidly dissolves, the reaction being completed by heating on the steam bath for two minutes. To this is added 200 cc. of water, and the resulting clear, colorless solution of the addition product is decomposed with hydrochloric acid. This causes the precipitation of ethyl α,β-dicyano-β-phenylpropionate as a yellowish oil, which on standing overnight and being stirred vigorously, or seeded if possible, sets to a yellowish solid mass. This is

filtered off with suction and washed with cold water.

(*C*) *Hydrolysis of Ethyl α,β-Dicyano-β-phenylpropionate*.—The product thus obtained is hydrolyzed by boiling under a reflux condenser for four hours with 80 cc. of concentrated hydrochloric acid (sp. gr. 1.19). The substance goes into solution, and this clear solution, on cooling, deposits phenylsuccinic acid in small crystals which are nearly colorless. These are filtered off, washed with cold water, and dried. The yield of product melting at 164–166° is 17.6–18.4 g. (91–95 per cent of the theoretical amount based on the weight of ester used) (Note 2) and (Note 3).

2. Notes

1. It is suggested that the esterification may be more conveniently carried out by substituting 95 per cent for absolute alcohol, and 25 g. concentrated sulfuric acid for the hydrogen chloride, without affecting either the yield or quality of ester (W. E. Barker, private communication).
2. The phenylsuccinic acid, if slightly off color, may be recrystallized easily from a hot water solution by rapid cooling. Five grams is dissolved in 400 cc. of hot water, and then 60 cc. more of hot water is added. This solution is filtered and cooled in ice water with stirring until crystals separate. After standing, the crystals are filtered off. The yield is 4.5 g. (90 per cent) of product melting at 167°.
3. The quantities of material used may be doubled from (*B*) on, in which case the refluxing in (*C*) requires at least one-half hour longer for complete solution. One run with double quantities yielded 32.6 g.

3. Discussion

Phenylsuccinic acid can be prepared by the action of potassium cyanide and alcohol upon α-chlorostyrene;[1] by the reaction of ethoxyphenylmaleic anhydride and fuming hydriodic acid at 165°;[2] by the hydrolysis of phenylcyanopropionic acid, obtained by heating ethyl benzalmalonate and aqueous potassium cyanide;[3] by the action of potassium cyanide on ethyl benzalmalonate and saponification of the product with potassium hydroxide;[4] by the hydrolysis with hydrochloric acid of ethyl α,β-dicyano-β-phenylpropionate, obtained from sodium ethyl cyanoacetate and mandelonitrile;[5] and by the hydrolysis of the addition product of hydrogen cyanide and ethyl α-cyano-β-phenylacrylate.[6]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 181
- Org. Syn. Coll. Vol. 4, 804

References and Notes

1. Rügheimer, Ber. **14**, 428 (1881).
2. Volhard and Henke, Ann. **282**, 83 (1894).

3. Bredt and Kallen, Ann. **293**, 348 (1896).
4. Wegscheider and Hecht, Monatsh. **24**, 417 (1903).
5. Higson and Thorpe, J. Chem. Soc. **89**, 1471 (1906).
6. Lapworth and McRae, J. Chem. Soc. **121**, 1704 (1922); Manske, J. Am. Chem. Soc. **53**, 1106 (1931).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ester

cyanophenylacrylic ester

alcohol (64-17-5)

sulfuric acid (7664-93-9)

hydrogen chloride, hydrochloric acid (7647-01-0)

sodium cyanide (143-33-9)

hydrogen cyanide (74-90-8)

potassium cyanide (151-50-8)

potassium hydroxide (1310-58-3)

mandelonitrile (532-28-5)

hydriodic acid (10034-85-2)

α-Cyano-β-phenylacrylic acid (1011-92-3)

Phenylsuccinic acid, Succinic acid, phenyl- (635-51-8)

α-Chlorostyrene

Ethyl α-cyano-β-phenylacrylate (2025-40-3)

Ethyl α,β-dicyano-β-phenylpropionate

ethoxyphenylmaleic anhydride

phenylcyanopropionic acid

Ethyl benzalmalonate

sodium ethyl cyanoacetate

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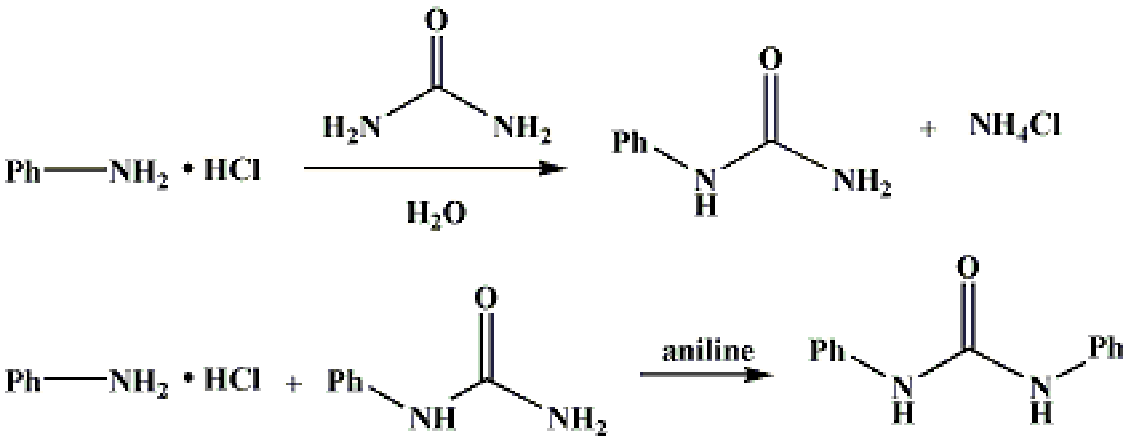
Organic Syntheses, CV 1, 453

PHENYLUREA and *sym.*-DIPHENYLUREA

[Urea, phenyl-, and Carbanilide]



Submitted by Tenney L. Davis and K. C. Blanchard.
Checked by C. S. Marvel and W. B. King.

1. Procedure

A solution of 390 g. (3 moles) of aniline hydrochloride and 190 g. (3.2 moles) of urea in 1500 cc. of water is boiled in a 3-l. flask under a reflux condenser (Note 1) and (Note 2). After about one hour, crystals begin to separate; at the end of one and one-half to two hours, the mixture, which bumps considerably, is filtered rapidly by suction, and the crystals of carbanilide washed with 100 cc. of boiling water. The filtrate is chilled, and the phenylurea which crystallizes out is filtered off and rinsed with a little cold water, the washings being discarded. The filtrate is again boiled under a reflux condenser for one and one-half to two hours, or until it begins to bump, and the process is repeated. The above operations are repeated a third time, and each time the phenylurea is collected from the cold filtrate. The mother liquor is finally evaporated to one-half its original volume, and additional crops of carbanilide and phenylurea are so obtained. Further evaporation is not profitable.

The crude carbanilide (symmetrical diphenylurea) is practically pure, and may be obtained in large colorless needles melting at 235° by recrystallization from alcohol with the use of decolorizing carbon; 1 l. of alcohol is required for every 25 g. of product (Note 3). The weight of the crude carbanilide is 122–128 g. (38–40 per cent of the theoretical amount).

The crude phenylurea is somewhat colored and contains a little carbanilide. It may be purified by dissolving in a minimum quantity of boiling water, adding a little decolorizing carbon, and filtering. When the filtrate first begins to cool, a flocculent precipitate of carbanilide is deposited; this must be filtered off while the liquid is still

hot. The filtrate, on cooling, yields colorless stout needles or flakes of phenylurea melting at 147° (Note 4). The total weight of pure product is 212–225 g. (52–55 per cent of the theoretical amount).

2. Notes

1. The reaction can undoubtedly be explained by the formation of an equilibrium mixture of urea and ammonium cyanate in boiling solution; the ammonium cyanate reacts at the moment of its formation with aniline hydrochloride, yielding phenylurea. Phenylurea also undergoes a secondary reaction, involving the intermediate formation of phenyl isocyanate, which reacts with aniline hydrochloride, forming carbanilide; so that in order to obtain the best yield it is necessary to interrupt the process from time to time and remove the phenylurea first formed.
That the reaction proceeds to completion under the above conditions is shown by the fact that although the mixture ultimately becomes faintly alkaline (on account of the formation of ammonia by hydrolysis of the excess of urea) at no time does the mixture appear to contain aniline.
2. In the above directions the concentration is as high as it is safe to make it; if less water is used the yield of phenylurea decreases and there is grave danger of loss due to the sudden heating of the mixture by rapid separation of crystals. This phenomenon has been observed with a more concentrated mixture even on heating on the steam bath.
3. The carbanilide can also be obtained in long needles from glacial acetic acid or preferably ethyl acetate.
4. If the solution of phenylurea is allowed to cool slowly, the product separates in needles several centimeters in length.

3. Discussion

Phenylurea can be prepared from aniline salts with potassium cyanate in aqueous solution,[1] a method which suffers from the disadvantage that potassium cyanate is not easily prepared in the laboratory and rapidly undergoes spontaneous decomposition in storage; by heating aniline with urea,[2] whereby carbanilide is formed in rather larger proportion than phenylurea; and from aniline and nitrourea in aqueous solution.[3] A method analogous to the procedure described has been patented for the preparation of *p*-phenetylurea,[4] in which *p*-phenetidine is heated with urea nitrate (or *p*-phenetidine hydrochloride with urea) in aqueous solution. This reaction appears to be generally applicable to aromatic primary amines; it does not, however, appear to be so well suited to the preparation of the corresponding derivatives of secondary amines.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 450

References and Notes

1. Hofmann, Ann. **57**, 265 (1846); Weith, Ber. **9**, 820 (1876).
2. Fleischer, Ber. **9**, 995 (1876); Davis and Underwood, J. Am. Chem. Soc. **44**, 2600 (1922).
3. Davis and Blanchard, J. Am. Chem. Soc. **51**, 1790 (1929).
4. Riedel, Ger. pat. 76,596 [Frdl. **4**, 1268 (1894–97)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

aniline salts

aromatic primary amines

secondary amines

sym.-DIPHENYLUREA

p-phenetylurea

alcohol (64-17-5)

acetic acid (64-19-7)

ammonia (7664-41-7)

ethyl acetate (141-78-6)

aniline (62-53-3)

aniline hydrochloride (142-04-1)

decolorizing carbon (7782-42-5)

urea (57-13-6)

Nitrourea (556-89-8)

urea nitrate

Phenylurea, Urea, phenyl- (64-10-8)

diphenylurea (603-54-3)

Carbanilide (102-07-8)

ammonium cyanate

phenyl isocyanate (103-71-9)

potassium cyanate (590-28-3)

p-phenetidine (156-43-4)

p-phenetidine hydrochloride (637-56-9)

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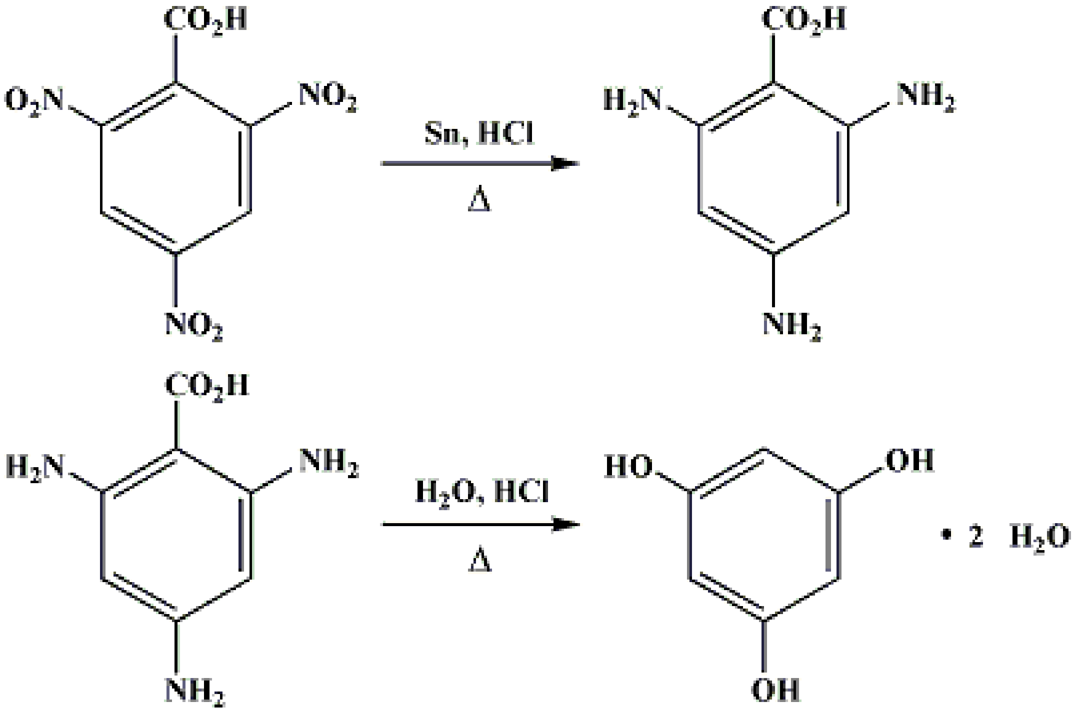
Organic Syntheses, CV 1, 455

PHLOROGLUCINOL



Submitted by H. T. Clarke and W. W. Hartman.
Checked by C. S. Marvel and A. T. Blomquist.

1. Procedure

To 225 g. (0.87 mole) of crude 2,4,6-trinitrobenzoic acid (p. 543) (Note 1) and (Note 2) is added 2100 g. (1800 cc., 19.6 moles) of concentrated hydrochloric acid (sp. gr. 1.17) in a 5-l. flask provided with a reflux condenser, the inner tube of which is 15–20 mm. in diameter. To this mixture is added 830 g. (7.0 atoms) of granulated tin in small portions, the reaction being started after the addition of 30–40 g. of the tin by immersing the flask in a hot-water bath (Note 3). The rest of the tin is added through the condenser at such a rate that the reaction proceeds briskly. It is advisable to carry out this reaction under a hood since hydrogen chloride is likely to escape at the beginning of the reaction. The mixture is finally heated on a steam bath for one hour in order to complete the reaction, and is then filtered hot through glass wool in order to remove unreacted tin.

The filtrate is made up to exactly 2 l., and a 50-cc. sample is titrated with sodium hydroxide solution of known concentration (35–40 per cent in a suitable strength). The volume of alkali necessary to produce a slight permanent precipitate is noted (it usually requires 6–8 cc. of 40 per cent alkali). More alkali is run in until the liquid is neutral to litmus paper: this second value represents the acid combined with tin. To the filtrate in the 5-l. flask are added 1 kg. of cracked ice and then sufficient alkali to neutralize the free acid as well as 60 per cent of that combined with the tin (about 800

cc. of 40 per cent sodium hydroxide is required). The mixture is diluted, without filtering, to 6 l. and boiled in a 12-l. flask under a reflux condenser in an atmosphere of coal gas (Note 4) for twenty hours. The precipitate is then filtered off and washed very thoroughly with boiling water (2–3 l. of water); the combined filtrates are concentrated to 3 l., then rendered slightly acid to litmus with hydrochloric acid, and chilled to 0°, when crystals of phloroglucinol separate. This crop is filtered off; it should weigh 70–80 g. It is then dissolved in 700 cc. of hot water, filtered, and allowed to crystallize at 0°. In this way 65–75 g. (46–53 per cent of the theoretical amount) of almost colorless (Note 5) phloroglucinol dihydrate melting at 217–218° is obtained.

2. Notes

1. It is unnecessary to remove the small amount of trinitrotoluene with which the crude trinitrobenzoic acid is contaminated, since it has been found that no trace of the methyl homologue of phloroglucinol is obtained on treating trinitrotoluene in the above manner.
2. An equivalent quantity of 1,3,5-trinitrobenzene (p. 541) may be employed in place of trinitrobenzoic acid with exactly the same result; but, as the most convenient method of preparing trinitrobenzene in the laboratory is through trinitrobenzoic acid, nothing is gained by the substitution.
3. In carrying out the reduction, care must be taken that not more than 5 per cent of the tin is added before the reaction starts; otherwise the interaction begins with such violence that the product may be lost. The reaction may be readily checked by immersion of the flask in water. The application of wet towels to the upper half of the flask is often of great assistance to condensation though only slightly checking the reaction itself.
4. Coal gas is recommended as being the most convenient inert gas in which to carry out the hydrolysis; carbon dioxide or nitrogen should serve equally well.
5. If it is found impossible to obtain a white product by crystallization, purification may be effected by dissolving the phloroglucinol dihydrate in four times its weight of boiling water and passing in sulfur dioxide until no further bleaching effect is observed (about one-half minute is usually sufficient).

3. Discussion

Phloroglucinol can be prepared by the following fusion reactions: resorcinol with sodium hydroxide;[1] 1,3,5-benzenetrisulfonic acid with sodium hydroxide;[2] and 3,5-dibromophenol with potassium hydroxide.[3] Better yields, however, are obtained by boiling a dilute solution of triaminobenzene hydrochloride[4] or triaminobenzoic acid hydrochloride[5] with water.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 522

References and Notes

1. Barth and Schreder, Ber. **12**, 503 (1879).
2. Barth and Schreder, Ber. **12**, 422 (1879).
3. Blau, Monatsh. **7**, 632 (1886).
4. Weidel and Pollak, ibid. **21**, 20 (1900).
5. Cassella and Co., Ger. pat. 102,358 [Frdl. **5**, 156 (1897–1900)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

methyl homologue of phloroglucinol

hydrogen chloride, hydrochloric acid (7647-01-0)

sodium hydroxide (1310-73-2)

sulfur dioxide (7446-09-5)

nitrogen (7727-37-9)

tin (7440-31-5)

carbon dioxide (124-38-9)

potassium hydroxide (1310-58-3)

1,3,5-Trinitrobenzene (99-35-4)

Phloroglucinol (108-73-6)

2,4,6-Trinitrobenzoic acid (129-66-8)

phloroglucinol dihydrate (6099-90-7)

trinitrotoluene (118-96-7)

trinitrobenzoic acid

trinitrobenzene

resorcinol (108-46-3)

1,3,5-benzenetrisulfonic acid

3,5-dibromophenol

triaminobenzene hydrochloride

triaminobenzoic acid hydrochloride

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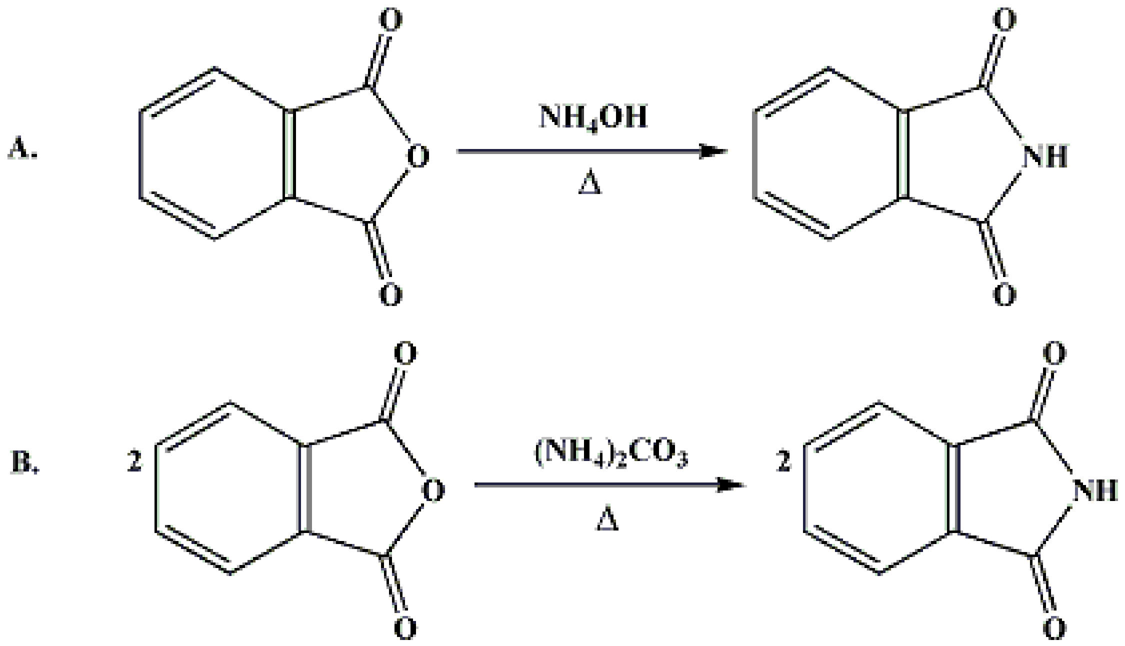
Organic Syntheses, CV 1, 457

PHTHALIMIDE



Submitted by W. A. Noyes and P. K. Porter.
Checked by H. T. Clarke and J. H. Bishop.

1. Procedure

(*A*) In Pyrex 5-l. round-bottomed flask is placed a mixture of 500 g. (3.4 moles) of phthalic anhydride and 400 g. (444 cc., 6.6. moles) of 28 per cent aqueous ammonia. The flask is fitted with an air condenser not less than 10 mm. in diameter and is then slowly heated with a free flame until the mixture is in a state of quiet fusion at a temperature of about 300° (Note 1). It requires about one hour before all the water has gone and about one and one-half to two hours before the temperature of the reaction mixture reaches 300° and the mixture is a homogeneous melt. It is advisable, during the heating, to shake the flask occasionally; some material sublimes into the condenser and must be pushed down with a glass rod. The hot reaction mixture is now poured out into a crock, covered with a paper to prevent loss by sublimation, and allowed to cool (Note 2). The product is practically pure without further treatment, and melts at 232–235° (Note 3). The yield is 470–480 g. (95–97 per cent of the theoretical amount) (Note 4).

(*B*) Phthalimide may also be made by fusing 500 g. (3.4 moles) of phthalic anhydride and 500 g. (4.4 moles) of ammonium carbonate which has been previously ground in a mortar. The subsequent procedure is the same as when aqueous ammonia is used. Frequent shaking is necessary, and the sublimed material must be pushed back occasionally into the reaction flask. About two hours are required for completion.

2. Notes

1. On a large scale, it would be advisable to collect the small amount of ammonia given off during the reaction.
2. If desired, the product obtained by pouring the reaction mass into the crock may be treated with hot water to soften the cake, broken up with a glass rod, transferred to a flask, and boiled with water for a few minutes. This treatment, however, is quite unnecessary; for all preparative purposes, the crude cake, as it is obtained, may be ground up and used directly.
3. Phthalimide may be recrystallized from water, but only about 4 g. of phthalimide will dissolve in a liter of boiling water. It may also be crystallized from alcohol, in which solvent it dissolves to the extent of five parts in a hundred at boiling temperature.
4. Several smaller runs of 25 g. of phthalic anhydride gave the same percentage yield.

3. Discussion

Phthalimide can be prepared by heating ammonium phthalate,[1] by heating acid ammonium phthalate,[2] and by passing dry ammonia over heated phthalic anhydride.[3] It was found that the last of these methods was by no means easy to bring about: dry phthalic anhydride is apparently only superficially affected by the dry ammonia, and it was difficult to introduce sufficient heat into the loose mass of crystals to initiate reaction.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 119
- Org. Syn. Coll. Vol. 2, 526

References and Notes

1. Laurent, Ann. **19**, 47 (1836); Ann. **41**, 110 (1842); Marignac, Ann. **42**, 220 (1842); Wagner, Jahresber. 549 (1868); Cohn, Ann. **205**, 300 (1880); Landsberg, Ann. **215**, 181 (1882).
2. Marignac, Jahresber. 590 (1847–48).
3. Kuhara, Am. Chem. J. **3**, 29 (1881).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

acid ammonium phthalate

alcohol (64-17-5)

ammonium carbonate

ammonia (7664-41-7)

phthalic anhydride (85-44-9)

Phthalimide (85-41-6)

ammonium phthalate (523-24-0)

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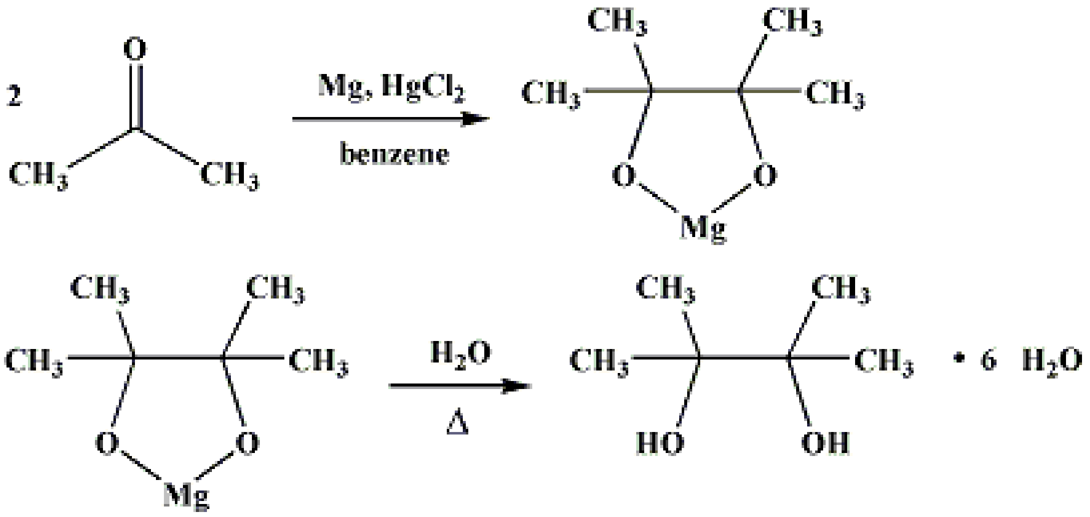
Organic Syntheses, CV 1, 459

PINACOL HYDRATE



Submitted by Roger Adams and E. W. Adams.
Checked by H. T. Clarke and Ross Phillips.

1. Procedure

In a 5-l. round-bottomed flask, fitted with a stopper holding a separatory funnel and an efficient reflux condenser (Note 1) closed at the top with a calcium chloride tube (Note 2), are placed 80 g. (3.29 atoms) of magnesium turnings and 800 cc. of dry benzene (Note 3). Through the dropping funnel is added gradually a solution of 90 g. of mercuric chloride in 400 g. (505 cc., 6.9 moles) of acetone (Note 4), carefully at first and then more rapidly after the reaction starts. The time of addition is about five to ten minutes (Note 5). Sometimes the reaction does not commence until a considerable proportion of the acetone solution of mercuric chloride has been added. In this case the reaction proceeds very vigorously when it does start, and the flask must be cooled in running water to avoid loss through the condenser. As soon as the first vigorous reaction is over, a mixture of 200 g. (258 cc., 3.45 moles) of acetone and 200 cc. of benzene is added (Note 6). When the reaction slows down, the flask is heated on a water bath until no further reaction is evident (about two hours). During this time the magnesium pinacolate swells until it fills the flask about three-fourths full. The flask is removed from the condenser and shaken until the reaction mass is well broken up (Note 7). The condenser is again attached and the heating continued for another hour.

Through the separatory funnel is then added 200 cc. of water, and the reaction mixture is heated for another hour. The flask should be shaken occasionally during this time. The reaction mixture is cooled to about 50° and filtered. The solid is returned to the flask and heated for ten minutes with a fresh 500-cc. portion of benzene to dissolve any remaining pinacol. The original filtrate and the second portion of benzene, after it is filtered from the magnesium hydroxide, are mixed and distilled to one-half the original volume in order to remove the acetone; the remaining benzene solution is

treated with 300 cc. of water and cooled to 10–15°. The pinacol hydrate separates, and after about thirty minutes (Note 8) it is collected on a suction filter and washed with benzene, or better, the mixture is centrifuged in a basket centrifuge. The pinacol hydrate, air-dried at room temperature (Note 9), weighs 325–375 g. (43–50 per cent of the theoretical amount based on the magnesium used) (Note 2). The product melts at 46–47°. It is sufficiently pure for most purposes. Occasionally the product is slightly yellow. If such a product is dissolved in an equal weight of boiling water, treated with a little animal charcoal, filtered, and the filtrate cooled in ice, over 95 per cent of the material may be recovered in large white crystals (Note 10).

2. Notes

1. The condenser should have an inner tube with a fairly large diameter (12–15 mm.) in order to take care of the acetone vapors during the vigorous reaction.
2. The reaction mixture must be guarded carefully from moisture throughout the reaction; if moisture is present the magnesium becomes coated with oxide or hydroxide and the reaction does not take place smoothly.
Scrupulous drying improves the yield of pinacol hydrate reported in these directions (G. A. Hill, private communication).
3. If a larger amount of benzene is used, the reaction is too slow in starting. Commercial benzene is satisfactory if it has been distilled and the first portion containing the water rejected.
4. The acetone used is the ordinary commercial grade dried over calcium chloride. The dryness of the acetone is important and determines the time required for the reaction to start; if it is perfectly dry (two to three days over calcium chloride with occasional agitation) the reaction starts at once. See Note 5, p. 239.
5. The reaction should be allowed to proceed with the maximum speed without loss of acetone through the condenser. If the reaction is made to run slowly, the yields are lower.
6. It is important that the second portion of acetone and benzene be added to the reaction mixture before the refluxing stops, as otherwise heat must be applied to start the reaction again.
7. Mechanical stirring is rendered somewhat difficult in the laboratory because the mass becomes almost solid at the end of the reaction. A centrifugal tube type stirrer will give satisfactory results.
8. Generally, from one-half to three hours are necessary for maximum crystallization. The shorter period is frequently sufficient if the cooling is thorough.
9. If dried at a temperature above that of the room, there is a tendency for the product to melt and for pinacol to be lost by volatilization.
10. The pinacol hydrate contains a small quantity of an organic mercury compound or compounds, the vapors of which are harmful. This contaminant may be removed by a thorough washing with benzene or preferably by melting under benzene and then cooling with stirring (H. S. King,[1] and H. B. J.

Schurink, private communications). Alternatively, the contaminant can be destroyed by distilling with steam.[2]

3. Discussion

Pinacol hydrate can be prepared by the reduction of acetone by means of magnesium amalgam,[3] aluminum amalgam,[4] sodium,[5] sodium amalgam,[6] and electrolytically.[7] The procedure described is a modification of that by Holleman.[3] The catalyzed addition of hydrogen peroxide to tetramethylethylene also furnishes pinacol.[8] Satisfactory methods have been described for the preparation of anhydrous pinacol.[1]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 462
- Org. Syn. Coll. Vol. 3, 312

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

organic mercury compound or compounds

calcium chloride (10043-52-4)

Benzene (71-43-2)

magnesium, magnesium turnings (7439-95-4)

aluminum (7429-90-5)

acetone (67-64-1)

sodium (13966-32-0)

hydrogen peroxide (7722-84-1)

mercuric chloride (7487-94-7)

magnesium hydroxide

Pinacol hydrate (6091-58-3)

magnesium pinacolate

pinacol (76-09-5)

tetramethylethylene (563-79-1)

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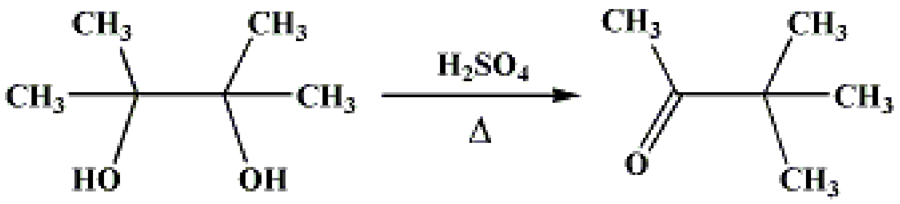
Organic Syntheses, CV 1, 462

PINACOLONE



Submitted by G. A. Hill and E. W. Flosdorf.
Checked by C. S. Marvel and A. E. Gray.

1. Procedure

In a 2-l. round-bottomed flask, fitted with a stopper carrying a dropping funnel and a connection to a condenser set for distillation, are placed 750 g. of 6 *N* sulfuric acid (Note 1) and 250 g. of pinacol hydrate (Note 2). The mixture is then distilled until the upper layer of distillate ceases to increase in volume (Note 3). This requires about fifteen to twenty minutes. The pinacolone layer in the distillate is separated from the water and the water is returned to the reaction flask. First, 60 cc. of concentrated sulfuric acid is added to the water, and then a second 250-g. portion of pinacol hydrate. The distillation is repeated. This process is repeated twice more until 1 kg. (4.42 moles) of pinacol hydrate has been used (Note 4).

The combined pinacolone fraction is dried over calcium chloride, filtered, and fractionally distilled. There is first a small low-boiling portion; then the pinacolone comes over at 103–107°; and finally there is a higher-boiling portion which yields more pinacolone on redistillation. The yield from a run, as described, is 287–318 g. (65–72 per cent of the theoretical amount). This product occasionally turns slightly yellow on standing, but redistillation removes the color with almost no loss of product.

2. Notes

1. Phosphoric acid (50 per cent) or hydrated oxalic acid may be used to bring about this rearrangement. When these reagents are used, the reaction mixture should be boiled for three to four hours. A yield of pinacolone corresponding to 60–65 per cent of the theoretical amount is thus obtained.
2. The pinacol hydrate is the unrecrystallized product obtained as described on p. 459. The use of recrystallized pinacol hydrate increases the yield of pinacolone by about 4 per cent.
3. An oily layer always remains behind in the distilling flask.
4. Larger or smaller runs of pinacolone may be made without materially affecting the yield.

3. Discussion

Pinacolone can be prepared by heating pinacol hydrate with dilute sulfuric or dilute hydrochloric acid;[1] by treating anhydrous pinacol[2] with concentrated sulfuric acid at 0°; by heating pinacol or its hydrate with 5 per cent oxalic acid[3] for twelve hours, or with 50 per cent tartaric, phosphoric, or oxalic acid[3] for three to four hours. Pinacolone can also be prepared from pivalamide and methylmagnesium halides[4] and from *tert.*-butylmagnesium chloride and acetyl chloride[5] or sodium acetate.[6]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 81
- Org. Syn. Coll. Vol. 1, 524

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric or dilute hydrochloric acid

pinacol or its hydrate

tartaric, phosphoric, or oxalic acid

methylmagnesium halides

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

sodium acetate (127-09-3)

acetyl chloride (75-36-5)

Oxalic acid (144-62-7)

Pinacolone (75-97-8)

phosphoric acid (7664-38-2)

Pinacol hydrate (6091-58-3)

pinacol (76-09-5)

pivalamide (754-10-9)

tert.-butylmagnesium chloride (677-22-5)

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PLATINUM CATALYST FOR REDUCTIONS

[Platinic oxide]

$$H_2PtCl_6 + 6NaNO_3 \longrightarrow Pt(NO_3)_4 + 6NaCl + 2HNO_3$$

$$Pt(NO_3)_4 \xrightarrow{\Delta} PtO_2 + 4NO_2 + O_2$$

$$PtO_2 + H_2O \longrightarrow PtO_2 \cdot H_2O$$

Submitted by Roger Adams, V. Voorhees, and R. L. Shriner.
Checked by Henry Gilman and S. A. Harris.

1. Procedure

In a porcelain casserole (a Pyrex beaker may be used) is prepared a solution of 3.5 g. (Note 1) of a commercial c.p. chloroplatinic acid (Note 2) and (Note 3) in 10 cc. of water, and to this is added 35 g. of c.p. sodium nitrate (Note 4). The mixture is evaporated to dryness by heating gently over a Bunsen flame while stirring with a glass rod. The temperature is then raised, 350–370° being reached within about ten minutes. Fusion takes place, brown oxides of nitrogen are evolved, and a precipitate of brown platinum oxide gradually separates. During this procedure foaming often occurs, in which case the mass must be more vigorously stirred and an additional flame directed at the top of the reaction mixture. If the burner under the casserole is removed when foaming starts, the top of the fused mass solidifies and foaming may become sufficient to carry material over the sides of the casserole. By the end of fifteen minutes, when the temperature has reached about 400°, the evolution of gas has greatly decreased. At the end of twenty minutes the temperature should be 500–550°. At this point the vigorous evolution of oxides of nitrogen has practically ceased, and a gentle evolution of gas takes place. The temperature is held at this point (best with the full force of the burner directly on the casserole) until about thirty minutes have elapsed, when the fusion should be complete. This temperature (500–550°) is most satisfactory for the fusion (Note 5) in order to obtain a catalyst of maximum activity and minimum lag (Note 6). The temperature indicated is generally attained by means of one ordinary Bunsen burner turned on as high as possible; where the gas pressure is lower a Meker burner may be necessary.

The mass is allowed to cool and is then treated with 50 cc. of water. The brown precipitate settles to the bottom and can be washed by decantation once or twice, then filtered (preferably through a hardened filter paper on a Gooch crucible), and washed on the filter until practically free from nitrates. If the fusion has been properly carried out no difficulty is encountered in this procedure; but if the temperature of fusion has not been high enough or has not been maintained for a sufficiently long time the precipitate tends to become colloidal on addition of water and does not filter well; moreover, under these conditions, the yield of product and its activity as a catalyst are diminished. Sometimes the precipitate becomes colloidal only when practically all the

nitrates are removed; in this case it is better to stop washing as soon as the colloid starts to form, since small traces of the salt do not affect the efficiency of the catalyst. The filtrates should be tested for platinum and saved if any is present (Note 7). The oxide is either used directly, or more generally it is dried in a desiccator and portions of the dried material weighed out for reductions. The yield is 1.57–1.65 g. (95–100 per cent of the theoretical amount) (Note 5) and (Note 8). The use of platinum oxide is illustrated in the reduction of ethyl *p*-nitrobenzoate to ethyl *p*-aminobenzoate (p. 240) and of benzalacetophenone to benzylacetophenone (p. 101).

The platinum black by reduction of the oxide may sometimes be used a second, third, or even more times in the reduction of certain compounds merely by reactivating (Note 9) with air or oxygen. A spent catalyst must be reworked (Note 3) along with the platinum recovered from filtrates (Note 7), filter papers (Note 10) and the casserole (Note 11). In the use of platinum oxide-platinum black for reductions, certain types of compounds require different physical conditions from others in order to obtain the best results in each case, and factors such as the following must be taken into consideration: the temperature, the medium in which the reduction of platinum oxide to platinum black occurs (Note 12), the effect of traces of inorganic salts (Note 13), and the solvent employed (Note 14). Palladous oxide-palladium black has been used for catalytic reduction, and in some cases has proved a more efficient catalyst than the platinum oxide-platinum black, though generally this has not been found true (Note 15).

2. Notes

1. If a considerable quantity of platinum oxide is desired it is more satisfactory to prepare several runs of the size indicated than one large run, since spattering and the evolution of gases make large amounts inconvenient to handle. The activity of the catalyst appears in certain cases to decrease after standing for several weeks and therefore the oxide should preferably be prepared as required.
2. Commercial c.p. chloroplatinic acid varies somewhat in its purity. In this work that from the Mallinckrodt Chemical Works, St. Louis, was used and gave very satisfactory results. Since small amounts of impurities in the catalyst are important factors in the rate of reduction of certain types of compounds, this question of impurities in the chloroplatinic acid must be taken into account (Note 13). In a large proportion of the reductions studied, platinum oxide prepared from the chloroplatinic acid mentioned gave as good results as that from spectroscopically pure chloroplatinic acid made according to the directions of Wichers.[1]
If only platinum metal is available this is dissolved in aqua regia and evaporated to dryness several times with hydrochloric acid, until free from nitrates (Note 3) and the product purified according to the method of Wichers.
3. Platinum residues may be reworked by dissolving them in aqua regia, filtering, evaporating the filtrate to dryness, taking up with a little water, and fusing with sodium nitrate. If organic matter is present in the chloroplatinic acid, as it generally is when recovered platinum is used, it will be oxidized during the

fusion and, except in cases requiring a spectroscopically pure platinum, seems to have no deleterious effect. Repeated reworking does seem to cause an accumulation of poison in the catalyst, and under these conditions it should be purified as described by Wichers.[1]

The following alternative procedure for the preparation of the catalyst is particularly time-saving when scrap platinum or spent catalyst is used, for after conversion to chloroplatinic acid a purification is conveniently effected by precipitating the ammonium salt, and the direct fusion of this salt with sodium nitrate eliminates the tedious process of reconversion to chloroplatinic acid. Furthermore ammonium chloroplatinate is not hygroscopic and can be weighed accurately. The amount of catalyst obtained is almost exactly half the weight of the ammonium salt employed.

A mixture of 3 g. of ammonium chloroplatinate and 30 g. of sodium nitrate in a casserole or Pyrex beaker is heated gently at first until the rapid evolution of gas slackens and then more strongly until a temperature of 500° is reached. This operation requires about fifteen minutes, and there is no spattering. The temperature is held at 500–520° for one-half hour and the mixture is then allowed to cool. The platinum oxide catalyst, collected in the usual way by extracting the soluble salts with water, weighs 1.5 g. and is comparable in appearance and in activity to the material prepared from chloroplatinic acid. [William F. Bruce, private communication, and J. Am. Chem. Soc. **58**, 687 (1936). Checked by L. F. Fieser, R. P. Jacobsen, and M. S. Newman.]

4. u.s.p. sodium nitrate could probably be used in place of the c.p. grade in most instances, but in one type of reduction at least (that of aminophenols to cyclic amino alcohols) the small amount of impurities in the u.s.p. grade affected the activity of the catalyst. It has been reported that the use of potassium nitrate instead of sodium nitrate yields a more active catalyst.[2]

5. The relation of temperature of fusion to the properties of the catalyst produced was determined[3] by carrying out the fusion at various temperatures, which were recorded by stirring continuously with a thermocouple encased in a Pyrex glass tube, and reading the temperature on a pyrometer. The product prepared at lower temperatures is usually light brown in color and has a greater tendency to become colloidal on washing. The catalyst prepared at intermediate temperatures is brown; at 600° it is a very deep brown. The color may vary even when the catalyst is prepared under conditions which are essentially the same, but if the temperature indicated in the procedure is used the oxide will be satisfactory.

The products prepared at temperatures below 450° and above 600° have a lower activity and require a longer time for reduction to platinum black than those prepared at temperatures between 450° and 600°.

If the fusion temperature is about 300°, the yield of platinum oxide is very low; at higher temperatures the yield increases; and at temperatures of 450° and above it is practically quantitative. With a proper fusion a slightly lower yield than quantitative is generally not due to non-precipitation of the platinum but to loss by spattering and to deposition of a small amount on the casserole.

It has been suggested[4] that the fusion be conducted in a Pyrex beaker or casserole resting in a cavity in a copper block heated with a burner and provided with a thermometer well. This permits more accurate temperature control and is claimed to furnish a catalyst of maximum and reproducible activity.

6. The brown oxide is a heavy granular powder which settles to the bottom of the solution in the bottle in which the reduction is carried out (p. 61). It must be reduced to platinum black before it becomes a catalyst for the reduction. When the hydrogen is admitted and the bottle shaken the brown oxide becomes black and whips up into a fine suspension. The time necessary for the change of the oxide to platinum black is called the lag. The lag varies usually from several seconds to two or three minutes, depending upon the conditions under which the platinum oxide is reduced to platinum black. In general the lag is short provided that the reduction of the oxide is carried out merely in the presence of solvent; if carried out in the presence of solvent and substance to be reduced, as is more common practice, the character of the substance being reduced has a considerable effect, and sometimes a lag of ten to fifteen minutes occurs. In experiments where foreign salts are added as promoters or poisons, the lag varies widely, though generally within a maximum of ten to fifteen minutes; exceptions occur, and it was found that the lag was forty to sixty minutes or more when the platinum oxide was reduced in the presence of a little sodium nitrite and an alcoholic solution of benzaldehyde. It is probable also that the temperature at which the platinum oxide is formed from the chloroplatinic acid and the solvent present have some effect on the ease with which it is reduced to platinum black.

7. It is advisable to test for platinum in all the filtrates before discarding any of them, since there is sometimes a tendency for small amounts of platinum to remain in solution. A very satisfactory and delicate test for platinum, described by Wöhler,[5] consists in making the solution acid with hydrochloric acid and adding a few drops of stannous chloride. A yellow color develops when platinum is present and a brown color when it is in large amount. If any doubt exists as to whether or not the solution is yellow, it should be shaken with a small amount of ether; the yellow color concentrates in the ether layer, indicating the presence of platinum. From the sodium nitrate filtrates a large proportion of the platinum can be recovered by adding excess of formaldehyde and sodium hydroxide and heating. Upon standing, platinum black separates and may be filtered and worked up with other platinum black residues. The platinum which still remains in solution after this precipitation can be recovered by acidifying the solution and heating with zinc.

8. Quantitative analyses show the oxide to be $PtO_2 \cdot H_2O$.[3] It usually contains a very small amount of glaze from the casserole, but this does not affect its use or activity. The oxide dissolves only slightly in hot aqua regia even after long heating; it is insoluble in boiling concentrated nitric acid, and only slightly, or at least only slowly, soluble in boiling concentrated hydrochloric acid. Constant-boiling hydrobromic acid, on the other hand, dissolves it completely in the cold

with the evolution of bromine and the formation of a solution of bromoplatinic acid from which the red potassium salt can be readily precipitated or the solution may be evaporated and the residue used directly in a subsequent fusion.

9. The platinum oxide-platinum black, like any other platinum black, gradually loses its activity with use. In the reduction of certain types of compounds, notably aldehydes, the catalyst can be revivified by shaking with air or oxygen for a few minutes.[6] Frequently this must be done in order to have the reduction go to completion, and often it is desirable to do so during a reduction so as to increase the rate of reaction. In other reductions, attempted reactivation as described results in the complete inactivation and frequently the coagulation of the catalyst. In reducing certain substances, the catalyst tends to coagulate in lumps during the reduction, particularly toward the end of the reduction. In these instances reworking of catalyst is necessary (Note 3) before it can be used satisfactorily for a second run. On the other hand, in the reduction of many substances, the catalyst does not coagulate, but after the reduction is complete it gradually settles if allowed to stand, and the supernatant liquid may be decanted; when a second run is made with this catalyst it is frequently not much inferior to new catalyst and forms a fine suspension as soon as shaking is again started.

10. There is always a certain amount of the oxide which adheres to the filter paper during filtration, so that these papers should be ignited and the residue added to any platinum catalyst which has already become inactive and requires redissolving and reprecipitation (Note 3).

11. The thin film of oxide which remains in the casserole is dissolved by treating with a little constant-boiling hydrobromic acid (Note 8); the solution obtained may then be evaporated and the residue added to the next fusion mixture.

12. In certain reductions it is an advantage to reduce the platinum oxide to platinum black by shaking with hydrogen in the presence of solvent only, before the substance to be reduced is added to the mixture. More often the catalyst is reduced in the presence of the substance to be reduced; with aldehydes, for example, the platinum black is usually more finely divided and generally more active if prepared in presence of the aldehyde.

13. Certain inorganic salts promote or retard the action of the catalyst.[7] Thus, in the reduction of aldehydes, iron salts in mere traces have a remarkable effect in increasing the rate of reduction and in inhibiting the tendency of the catalyst to lose its activity. To a lesser extent manganese, nickel, and other salts have the same effect. On the other hand, with the majority of substances studied, these salts retard the reduction.

14. The solvent used is an important factor influencing the rate of reduction,[7] and no generalization can be made beyond the one that alcohol, either 95 per cent or absolute, has proved to be the best solvent for most of the compounds thus far studied. Ethyl acetate and glacial acetic acid may be used to advantage in some cases.

15. Palladous oxide,[8] PdO, may be prepared by the fusion of palladous chloride with sodium nitrate; it is an effective catalyst in hydrogenation, the most active form being produced when the fusion temperature is 600°.

3. Discussion

Platinic oxide can be prepared by the interaction of platinic chloride and excess sodium hydroxide,[9] and by the fusion of chloroplatinic acid with sodium nitrate.[10] The catalyst itself is platinum black, and this can be prepared by the reduction of chloroplatinic acid with formaldehyde,[11] the details for which have been improved by Willstätter and Hatt,[12] Willstätter and Waldschmidt-Leitz,[13] and Feulgen,[14] and by the reduction of platinum oxide with hydrogen.[10] A platinum catalyst can also be prepared from platinum black by heating with oxygen under pressure.[15] Colloidal platinum or palladium catalysts, reported to be particularly valuable for the reduction of nitriles, oximes, and nitrostyrenes to amines, have also been described.[16]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 61
- Org. Syn. Coll. Vol. 1, 101
- Org. Syn. Coll. Vol. 1, 240
- Org. Syn. Coll. Vol. 2, 489
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

oxides of nitrogen

chloroplatinic acid

platinum black

platinum oxide-platinum black

Palladous oxide-palladium black

aminophenols

cyclic amino alcohols

bromoplatinic acid

alcohol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ethyl acetate (141-78-6)

ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

formaldehyde (630-08-0)

nitric acid (7697-37-2)

HYDROBROMIC ACID (10035-10-6)

bromine (7726-95-6)

oxygen (7782-44-7)

sodium nitrite (7632-00-0)

stannous chloride

platinum oxide, Platinic oxide

Benzalacetophenone (94-41-7)

Benzylacetophenone (1083-30-3)

platinum (7440-06-4)

benzaldehyde (100-52-7)

zinc (7440-66-6)

palladium (7440-05-3)

sodium nitrate

ammonium chloroplatinate

potassium nitrate (7757-79-1)

manganese, nickel

Palladous oxide

palladous chloride

platinic chloride

Ethyl p-aminobenzoate (94-09-7)

ethyl p-nitrobenzoate (99-77-4)

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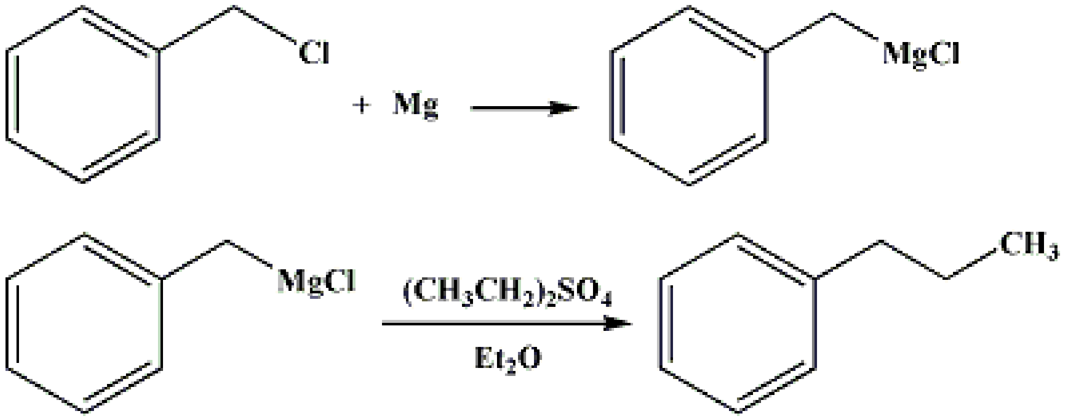
Organic Syntheses, CV 1, 471

n-PROPYLBENZENE

[Benzene, propyl-]



Submitted by Henry Gilman and W. E. Catlin.
Checked by C. S. Marvel and H. R. Snyder.

1. Procedure

In a dry 3-l. flask, fitted with a mercury-sealed stirrer, a 500-cc. dropping funnel, and a condenser provided at its upper end with a drying tube containing a mixture of calcium chloride and soda-lime (Note 1), is placed 48.6 g. (2 atoms) of magnesium turnings. There are then added 200 cc. of dry ether, a small crystal of iodine, and about 25 cc. of a solution of 253 g. (230 cc., 2 moles) of freshly distilled benzyl chloride in 1 l. of dry ether. If the reaction does not start at once, the flask is partially immersed in a bath containing water heated to about 40°. As soon as the ether begins to boil, and reaction sets in, the bath is removed and stirring is commenced. The remainder of the benzyl chloride in ether can be added during the course of one-half hour if the reaction is regulated by cooling the greater part of the flask by immersion in ice water (Note 2). The reaction will continue for about fifteen minutes after all the benzyl chloride has been added, and then the mixture is refluxed gently for about fifteen minutes.

To the stirred benzylmagnesium chloride is then added 616 g. (522 cc., 4 moles) of freshly distilled diethyl sulfate (Note 3). The addition of diethyl sulfate is so regulated that gentle refluxing takes place throughout the reaction. Once reaction is started with a few cubic centimeters of diethyl sulfate, it is necessary to cool the reaction flask by ice water in order to complete addition within about one hour. When all the ester has been added, stirring is continued with gentle boiling for fifteen minutes (Note 4).

The cooled mixture is next poured, with stirring, upon a mixture of 1 kg. of crushed ice, 1 l. of water, and 200 cc. of concentrated hydrochloric acid. After stirring a few minutes to dissolve the sludge, the major part of the water layer is siphoned off and the ethereal solution is separated. The water layer is washed once with about 50 cc. of

ether, and this washing is added to the ethereal solution of *n*-propylbenzene. The ether is removed by distillation from a water or steam bath through a fractionating column. The residue is poured into 1 l. of 10 per cent sodium hydroxide solution in about 50 per cent alcohol, and this mixture is refluxed for one hour (Note 5). After the *n*-propylbenzene is thrown out by the addition of a large volume of water, the hydrocarbon is separated, combined with an ether extract of the aqueous layer, dried by standing over 10–15 g. of solid potassium hydroxide, and fractionally distilled through an efficient column. The yield of *n*-propylbenzene, distilling at 155–160°, is 165–180 g. (70–75 per cent of the theoretical amount).

2. Notes

1. The function of the calcium chloride and soda-lime is to absorb any moisture and carbon dioxide which might diffuse into the reaction flask. The deleterious effect of another constituent of the atmosphere, oxygen, may be decreased by first sweeping out the flask with dry nitrogen or hydrogen. The initial use of a dry inert atmosphere may also be supplemented by the use of a trap[1] to exclude the air, particularly in those operations requiring extensive periods.
2. Benzylmagnesium chloride is one of a group of Grignard reagents which can be prepared in satisfactory yields by the rapid addition of the halide to magnesium in ether.[2]
3. If the diethyl sulfate is dark in color it should be washed, prior to distillation, with ice water and then with a sodium bicarbonate solution until all free acid is removed.
4. At the end of this time a negative color test shows that the Grignard reagent has been used up.
5. The solution is refluxed with alcoholic alkali to decompose any unaltered diethyl sulfate.

3. Discussion

n-Propylbenzene can be prepared by the action of sodium on propylbromide and bromobenzene;[3] by the action of diethylzinc[4] or ethylmagnesium bromide[5] on benzyl chloride; by the action of diethyl sulfate[6] or ethyl *p*-toluenesulfonate[7] on benzylmagnesium chloride; and by the reduction of ethyl phenyl ketone,[8] methyl benzyl ketone,[8] or propenylbenzene.[9] Propylbenzene can also be obtained from benzene by a variety of alkylation processes: With cyclopropane and aluminum chloride[10] or hydrogen fluoride;[11] with propylene and phosphorus pentoxide;[12] with propyl bromide and aluminum chloride;[13] and with propyl alcohol and aluminum chloride[14] or sulfuric acid.[15]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 47
- Org. Syn. Coll. Vol. 4, 605

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ester

soda-lime

hydrocarbon

alcohol (64-17-5)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

magnesium, magnesium turnings (7439-95-4)

propylene (115-07-1)

propylbromide, Propyl bromide (106-94-5)

oxygen (7782-44-7)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

hydrogen fluoride (7664-39-3)

iodine (7553-56-2)

aluminum chloride (3495-54-3)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

benzyl chloride (100-44-7)

bromobenzene (108-86-1)

propyl alcohol (71-23-8)

benzylmagnesium chloride (6921-34-2)

Benzene, propyl-, Propylbenzene, n-PROPYLBENZENE (103-65-1)

diethyl sulfate (64-67-5)

diethylzinc (557-20-0)

ethylmagnesium bromide (925-90-6)

ethyl phenyl ketone (93-55-0)

Methyl benzyl ketone (103-79-7)

propenylbenzene

cyclopropane (75-19-4)

phosphorus pentoxide (1314-56-3)

ethyl p-toluenesulfonate (80-40-0)

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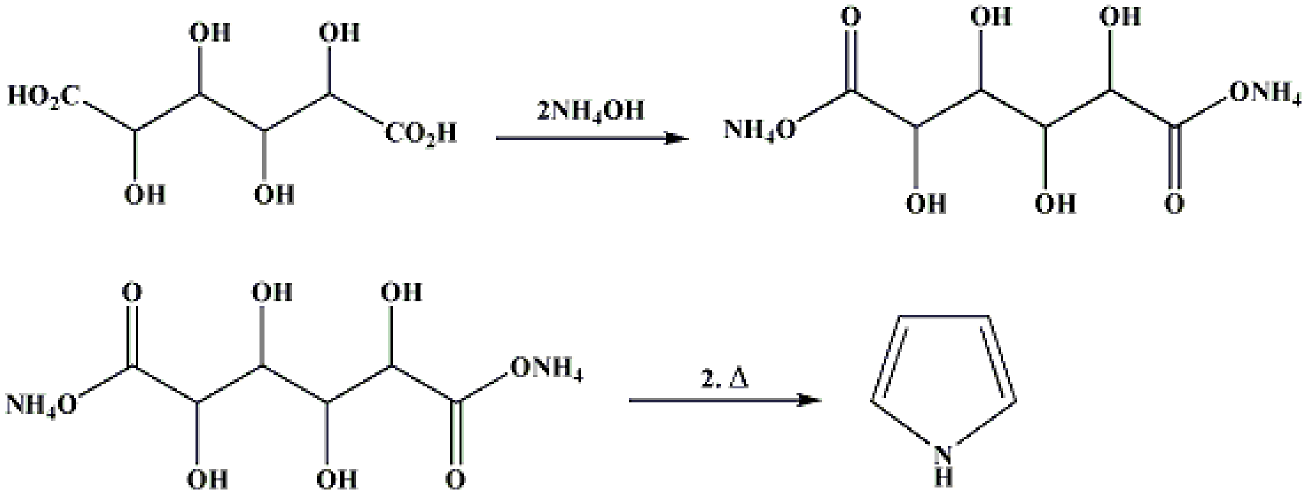
Organic Syntheses, CV 1, 473

PYRROLE



Submitted by S. M. McElvain and K. M. Bolliger.
Checked by H. T. Clarke and E. R. Taylor.

1. Procedure

In a 30-cm. evaporating dish or a Pyrex tray are placed 630 g. (3 moles) of mucic acid (Note 1) and 900 cc. of aqueous ammonia (sp. gr. 0.9); this mixture is rapidly stirred to a smooth paste under the hood. The paste is evaporated to complete dryness on a steam bath, and the resulting ammonium mucate is powdered and mixed with 350 cc. of glycerol (Note 2) in a 5-l. round-bottomed Pyrex flask. After standing overnight, the mixture is carefully distilled over a free flame, the heat being applied to one side of the flask alone, so that only a portion of the mass is heated to the reaction temperature. The gases, which are evolved with considerable foaming (Note 3), are led away to a gas trap (Fig. 7, p. 97) or to the open air, on account of their disagreeable nature. The heating is extended throughout the mass as rapidly as appears possible from the state of the mixture. Distillation is continued until a sample of distillate no longer shows oily drops when treated with solid potassium hydroxide; the total volume of distillate amounts to 900–1000 cc.

The entire distillate is redistilled until no further oil separates in the distillate; the watery layer is then separated and returned to the reaction flask, together with the water remaining in the distilling flask. Two liters more of water is added, and about 800 cc. is distilled. The distillate is redistilled until 250–300 cc. has collected in the receiver. This final distillate, on treatment with solid potash, yields a further 2 g. of oil.

The united oil is rapidly dried with a small quantity of solid potassium hydroxide (Note 4) and distilled. The fraction which boils at 127–131° is collected; this is a colorless liquid which darkens on exposure to light (Note 5). The yield is 75–80 g. (37–40 per cent of the theoretical amount).

2. Notes

1. Mucic acid is now manufactured on a large scale by the oxidation of the galactan occurring in certain species of wood.
2. By the use of more glycerol the yield may be slightly increased, but the foaming is very difficult to control. Medicinal mineral oil may be substituted for the glycerol, but the yield is then considerably reduced.
3. Unless the flame is properly adjusted before the foaming becomes very pronounced, there may be difficulty in controlling the distillation. The best method consists in removing the flame from below the flask and allowing it to play on the upper portion of the vessel above the surface of the boiling mixture.

4. When pyrrole is allowed to stand over potassium hydroxide for more than a few hours, combination takes place, lowering the yield.
5. A product of rather better quality, which shows less tendency to darken, may be obtained by finally distilling under reduced pressure. The darkening may also be almost entirely avoided by storing the product in a sealed vessel.

3. Discussion

Pyrrole can be obtained by fractional distillation of bone oil and purification through the potassium derivative.[1] The only synthetic method offering any possibilities involves the thermal decomposition of ammonium mucate, either alone[2] or in the presence of glycerol.[3]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ammonium mucate

potash

galactan

ammonia (7664-41-7)

glycerol (56-81-5)

potassium hydroxide (1310-58-3)

Pyrrole (109-97-7)

mucic acid

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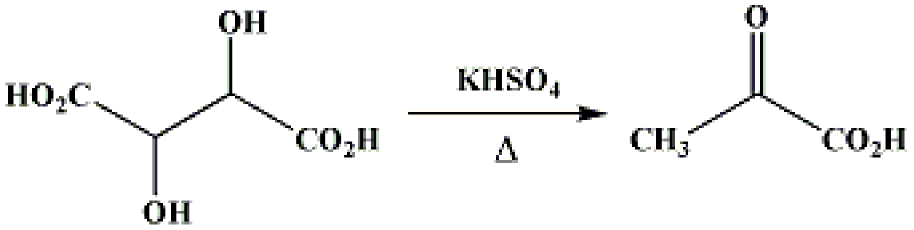
Organic Syntheses, CV 1, 475

PYRUVIC ACID



Submitted by J. W. Howard and W. A. Fraser.
Checked by C. S. Marvel and R. L. Shriner.

1. Procedure

An intimate mixture of 600 g. (4.4 moles) of finely powdered, freshly *fused* potassium acid sulfate and 400 g. (2.7 moles) of powdered tartaric acid, prepared by grinding them together in a mortar, is placed in a 3-l. round-bottomed Pyrex flask connected with a condenser which is filled with water but does not have any water flowing through it. The mixture is heated by means of an oil bath maintained at a temperature between 210 and 220° until liquid no longer distils over. Some foaming takes place (Note 1), but, if fused potassium acid sulfate is used and the temperature of the bath does not rise above 220°, it is not difficult to control. The distillate is then fractionated under reduced pressure. Pyruvic acid passes over at 75–80°/25 mm. and the yield is 117–128 g. (50–55 per cent of the theoretical amount) (Note 2).

2. Notes

1. If the mixture foams badly, it may be kept from frothing over by heating the upper part of the flask with a free flame.
2. The cake left in the reaction flask may be removed readily by inverting over a steam jet.

3. Discussion

Pyruvic acid can be prepared by the hydrolysis of α,α-dichloropropionic acid,[1], [2] α,α-dibromopropionic acid,[2] acetyl cyanide,[3] and oxal-acetic ester;[3] and by the distillation of tartaric acid or glyceric acid.[4] Better results are obtained, however, by the distillation of tartaric acid in the presence of a dehydrating agent such as potassium bisulfate,[5] and the procedure described was adopted after a study of a variety of dehydrating agents and various experimental conditions. The ethyl ester can be prepared by the catalytic oxidation of ethyl lactate,[6] and the acid has been obtained by the oxidation of methylglyoxal bisulfite.[7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 610

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethyl ester

potassium acid sulfate

oxal-acetic ester

potassium bisulfate (7646-93-7)

tartaric acid (87-69-4)

Pyruvic acid (127-17-3)

α,α-dichloropropionic acid (75-99-0)

α,α-dibromopropionic acid

acetyl cyanide (631-57-2)

glyceric acid (600-19-1)

ethyl lactate (687-47-8)

methylglyoxal bisulfite

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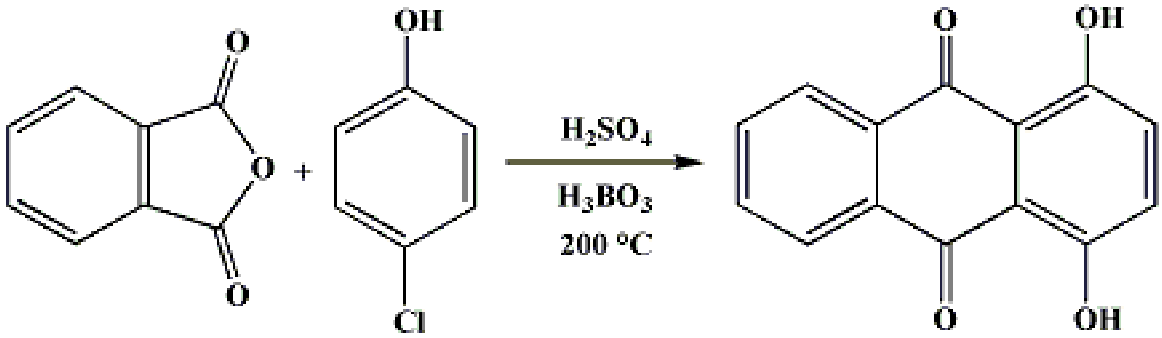
Organic Syntheses, CV 1, 476

QUINIZARIN



Submitted by L. A. Bigelow and H. H. Reynolds.
Checked by Roger Adams and G. S. Hiers.

1. Procedure

One hundred fifteen grams (0.9 mole) of *p*-chlorophenol, 300 g. (2.0 moles) of phthalic anhydride, 50 g. of crystallized boric acid, and 2 kg. (1090 cc.) of 95 per cent sulfuric acid are thoroughly mixed in a 1.5-l. round-bottomed flask. The flask is then immersed to the neck in an oil bath and the temperature gradually raised to 200° during the course of one-half to three-quarters of an hour (Note 1). It is then kept constant at 200° for three and one-half hours. Owing to the tendency of the phthalic anhydride to sublime, the mouth of the flask is covered with a piece of porous plate. When cool, the colored melt is poured slowly into 5 l. of cold water with continuous stirring, and filtered. The precipitate is boiled with 10 l. of water and filtered hot to remove the excess of phthalic anhydride which goes into solution. The residue is then suspended in 10 l. of boiling water, and to this suspension is added a sufficient quantity of 10 *N* potassium hydroxide solution to produce a purple color (about 30 cc.), followed by 300 cc. more (Note 2). The alkaline solution is filtered hot, and the residue (about 5–10 g.) is washed with 200 cc. of hot 2 per cent potassium hydroxide solution and discarded.

The purple quinizarin solution is next saturated with carbon dioxide and the precipitated quinizarin again filtered. The product is then boiled with 5 l. of a 10 per cent solution of sodium carbonate until it appears black (probably the monosodium salt) to dissolve the last traces of purpurin. The mixture is cooled to room temperature and filtered, and the precipitate is boiled with 5 l. of 5 per cent hydrochloric acid to liberate the quinizarin. The mixture is again cooled to room temperature, and the final product is filtered, washed with cold water, and dried at 100°.

The yield is 147–160 g. (68–74 per cent of the theoretical amount). It sinters at 190–191° and melts at 199–200° (corr.). A sample twice recrystallized from glacial acetic acid melted at 200–202° (corr.) (Note 3). The crystal form of this product compares very favorably with that of quinizarin of the highest purity, as observed under the

microscope.

2. Notes

1. An enameled bucket placed on a Fletcher radial burner serves well for this purpose.
2. The "purple color" end-point is not sharp, but as soon as the red hue of the mixture has distinctly changed toward purple, this point is considered reached. A variation of 5–10 cc. either way has little effect, but a large excess gives a large alkali-insoluble residue.

3. Purified quinizarin is reported as melting at 194–195°.[1] A melting point of 191–193°, probably uncorrected, is also given.[2]

3. Discussion

Quinizarin can be prepared by heating *p*-chlorophenol, phthalic anhydride, and either sulfuric acid[3] or aluminum chloride;[4] by diazotizing *p*-chloroaniline, condensing it with phthalic anhydride, and hydrolyzing;[5] by heating hydroquinone with phthalic anhydride;[6] by heating hydroquinone, phthalic anhydride, and c. p. sulfuric acid;[7] by oxidizing anthraquinone with ammonium persulfate in sulfuric acid solution[8] or with nitrosylsulfuric acid in the presence of mercury or a mercury compound;[9] by treating anthraquinone and 2-hydroxyanthraquinone with sulfuric and nitric acids in the presence of boric acid;[10] by heating anthraquinone with sulfuric acid in the presence of boric acid to 260–280°;[11] by chlorination of hydroxy-anthraquinone followed by hydrolysis with sulfuric acid in the presence of boric acid;[12] and by a method like the procedure described, in which a mixture of *o*- and *p*-chlorophenol is heated above 200°.[13]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

monosodium salt

purpurin

mercury or a mercury compound

sulfuric and nitric acids

o- and p-chlorophenol

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

hydroquinone (123-31-9)

sodium carbonate (497-19-8)

carbon dioxide (124-38-9)

phthalic anhydride (85-44-9)

Anthraquinone (84-65-1)

aluminum chloride (3495-54-3)

potassium hydroxide (1310-58-3)

boric acid (10043-35-3)

Quinizarin (81-64-1)

ammonium persulfate (7727-54-0)

nitrosylsulfuric acid (7782-78-7)

2-hydroxyanthraquinone (605-32-3)

hydroxy-anthraquinone (129-43-1)

p-chloroaniline (106-47-8)

p-chlorophenol (106-48-9)

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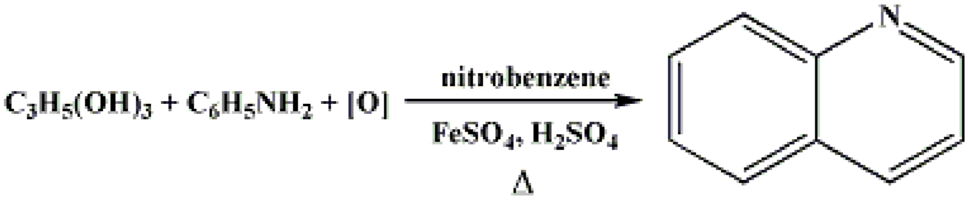
QUINOLINE



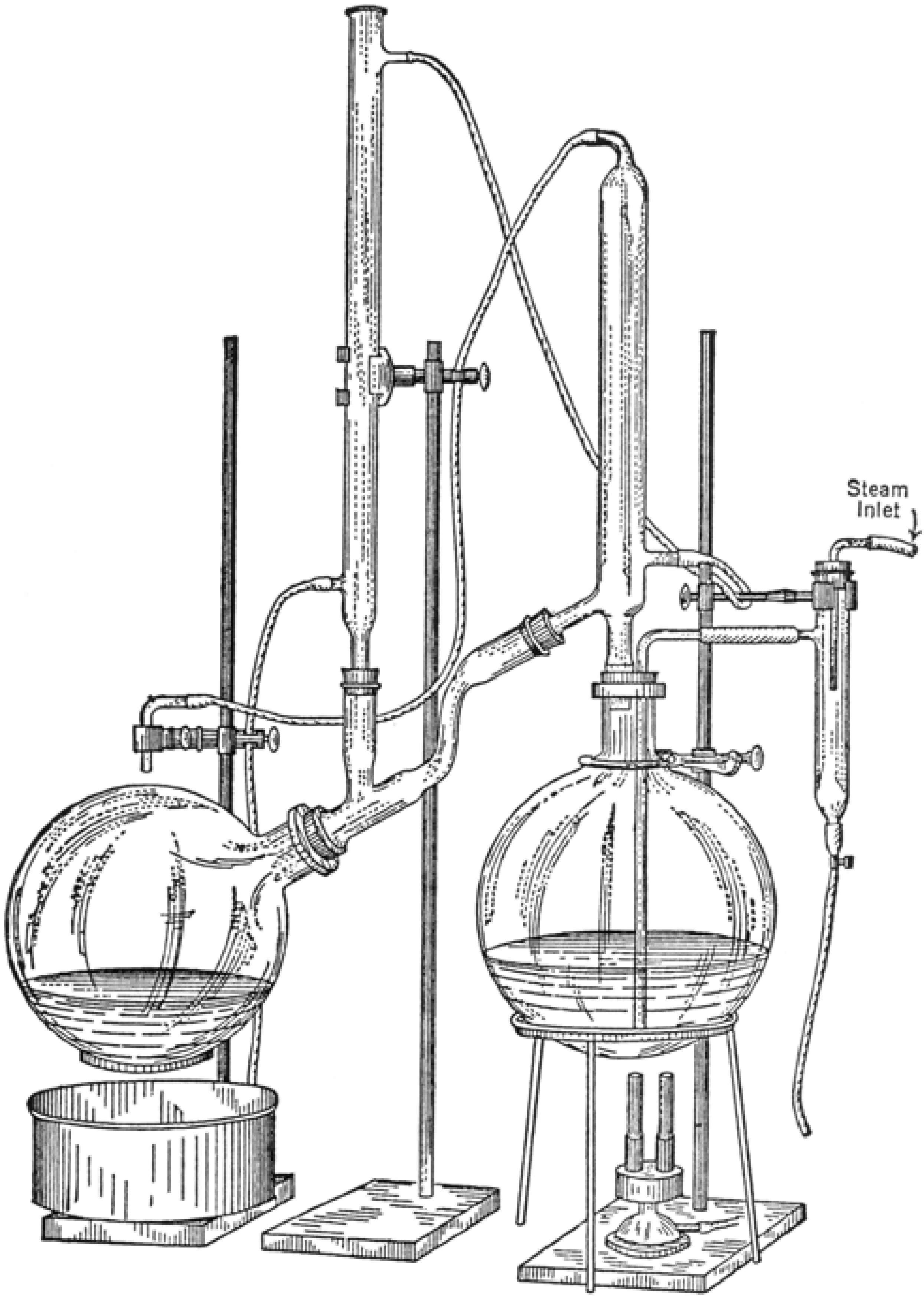
Submitted by H. T. Clarke and Anne W. Davis.
Checked by Roger Adams and A. W. Sloan.

1. Procedure

In a 5-l. round-bottomed flask, fitted with an efficient reflux condenser of wide bore, are placed, in the following order, 80 g. of powdered crystalline ferrous sulfate (Note 1), 865 g. (687 cc., 9.4 moles) of c.p. glycerol (Note 2), 218 g. (213 cc., 2.3 moles) of aniline, 170 g. (141 cc., 1.4 moles) of nitrobenzene, and 400 cc. of concentrated sulfuric acid (sp. gr. 1.84) (Note 3). The contents of the flask are well mixed and the mixture heated gently over a free flame. As soon as the liquid begins to boil, the flame is removed, since the heat evolved by the reaction is sufficient to keep the mixture boiling for one-half to one hour. If the reaction proceeds too violently at the beginning, the reflux condenser may be assisted by placing a wet towel over the upper part of the flask. When the boiling has ceased the heat is again applied and the mixture boiled for five hours. It is then allowed to cool to about 100° and transferred to a 12-l. flask; the 5-l. flask is rinsed out with a small quantity of water.

The 12-l. flask is then connected with the steam-distillation apparatus shown in Fig. 24, a 12-l. flask being used as a receiver (Note 4); steam is passed in (without external heat) until 1500 cc. has distilled (ten to thirty minutes). This removes all the unchanged nitrobenzene (10–20 cc.). The current of steam is then interrupted, the receiver is changed, and 1.5 kg. of 40 per cent sodium hydroxide solution is added cautiously through the steam inlet. The heat of neutralization is sufficient to cause the liquids to boil and thus become thoroughly mixed. Steam is then passed in as rapidly as possible until all the quinoline has distilled. In this process, 6–8 l. of distillate is collected (two and one-half to three and one-half hours are required, unless a very efficient condensing apparatus is used, under which conditions the distillation may be complete in one-half to one and one-half hours). The distillate is allowed to cool, and the crude quinoline separated. The aqueous layer of the distillate is again distilled with steam until all the quinoline has been volatilized and collected in about 3 l. of distillate.

Fig. 24.



This 3 l. of distillate is then mixed with the first yield of quinoline, and 280 g. (150 cc.) of concentrated sulfuric acid is added. The solution is cooled to 0–5°, and a saturated solution of sodium nitrite added until a distinct excess of nitrous acid is present (as shown either by starch-potassium iodide paper or by the odor). This generally requires 50 to 70 g. of sodium

nitrite. The mixture is then warmed on a steam bath for one hour, or until active evolution of gas ceases, and is then distilled with steam until all the volatile material has been expelled (4 l. of distillate will result). The receiver is then changed and the mixture in the distillation flask is neutralized, as before, with 700 g. of 40 per cent sodium hydroxide solution. The quinoline is distilled exactly as described above, the aqueous portions of the distillate being distilled with steam until all the quinoline has been isolated. The crude product is then distilled under reduced pressure, and the fraction which boils at 110–114°/14 mm. is collected. The forerun is separated from any water which may be present, dried with a little solid alkali, and redistilled. The total yield is 255–275 g. (84–91 per cent of the theoretical amount based on the aniline taken) (Note 5).

2. Notes

1. In the Skraup synthesis of quinoline the principal difficulty has always been the violence with which the reaction generally takes place; it occasionally proceeds relatively smoothly, but in the majority of cases gets beyond control, with consequent loss of material through the condenser. By the addition of ferrous sulfate, which appears to function as an oxygen carrier, the reaction is extended over a longer period of time. It is thus possible to work with much larger quantities of material when ferrous sulfate is employed.

2. In a number of experiments, the glycerol used contained an appreciable amount of water. Under these conditions, the yield of product is much lower. "Dynamite" glycerol containing less than one-half per cent of water is best employed; u.s.p. glycerol contains 5 per cent of water and usually gives lower yields.

3. It is important that the materials should be added in the correct order; should the sulfuric acid be added before the ferrous sulfate, the reaction may start at once. It is also important to mix the materials well before applying heat; the aniline sulfate should have dissolved almost completely, and the ferrous sulfate should be distributed throughout the solution. To avoid danger of overheating, it is well to apply the flame away from the center of the flask where any solids would be liable to congregate.

4. The apparatus for steam distillation shown in Fig. 24 requires little desk space. In this apparatus the greater portion of the condensation is effected by the stream of water passing over the receiver. It is, therefore, necessary that the stream passing through the condenser should be sufficiently rapid to cause it to form a uniform film over the receiving flask.

Much time can be saved by the use of the steam distillation apparatus described, especially when large quantities have to be handled. The above directions avoid the use of extraction methods, which not only consume more time but may lead to appreciable losses of material.

5. Although these directions have been used many times with results exactly as described, in a few cases the yields have dropped to 60–65 per cent without any apparent reason. At present no explanation can be given for this.

The percentage yields have been based on the amount of aniline taken. It would probably be more legitimate to base the calculation on the amounts of aniline taken and of nitrobenzene not recovered, since undoubtedly the latter is reduced to aniline during the course of the reaction. If this is done, the yield is found to be only 55 to 60 per cent of the calculated amount.

3. Discussion

Quinoline can be prepared by heating a mixture of aniline, glycerol, and sulfuric acid[1] alone or with an oxidizing agent like nitrobenzene,[2] arsenic acid,[3] ferric oxide,[4] and vanadic acid.[5] With the use of nitrobenzene, the reaction, according to the original method, takes place with extreme violence. The procedure followed here gives higher yields than those obtained with the ferric oxide method[4] and is the most satisfactory for the preparation of quinoline, but its homologs are preferably prepared by the use of arsenic acid because of the somewhat greater yields. The violence of the original nitrobenzene method may also be moderated by the use of acetic[6] or boric[7] acid. Copper sulfate has been used as a catalyst in the Skraup synthesis,[8] and the iron salt of *m*-nitrobenzenesulfonic acid has been employed as the oxidizing agent.[9] Preliminary experiments on the boric acid method showed that the reaction runs smoothly but gives yields somewhat lower than those reported.[7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 123
- Org. Syn. Coll. Vol. 1, 162
- Org. Syn. Coll. Vol. 1, 170
- Org. Syn. Coll. Vol. 1, 175
- Org. Syn. Coll. Vol. 1, 304
- Org. Syn. Coll. Vol. 1, 318
- Org. Syn. Coll. Vol. 1, 511
- Org. Syn. Coll. Vol. 1, 514
- Org. Syn. Coll. Vol. 2, 217
- Org. Syn. Coll. Vol. 2, 474
- Org. Syn. Coll. Vol. 2, 569
- Org. Syn. Coll. Vol. 3, 6

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alkali

sulfuric acid (7664-93-9)

aniline (62-53-3)

sodium hydroxide (1310-73-2)

glycerol (56-81-5)

oxygen (7782-44-7)

copper sulfate (7758-98-7)

sodium nitrite (7632-00-0)

nitrous acid (7782-77-6)

ferrous sulfate (13463-43-9)

arsenic acid (1327-52-2)

Nitrobenzene (98-95-3)

Quinoline (91-22-5)

boric acid (10043-35-3)

aniline sulfate

ferric oxide (1309-37-1)

vanadic acid

iron salt of m-nitrobenzenesulfonic acid

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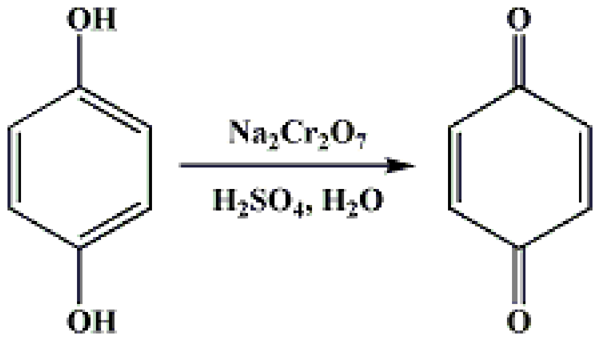
Organic Syntheses, CV 1, 482

QUINONE



Submitted by E. B. Vliet
Checked by Roger Adams and E. E. Dreger.

1. Procedure

In a 2.5-l. beaker, 100 g. (0.91 mole) of hydroquinone is dissolved in 2 l. of water heated to about 50°. After the solid is completely dissolved, the solution is cooled to 20°, 100 g. (54.4 cc.) of concentrated sulfuric acid is slowly poured in, and the mixture is again cooled to 20° (Note 1). A concentrated solution of technical sodium dichromate is prepared by dissolving 140 g. (0.47 mole) in 65 cc. of water (Note 2). This solution is then added gradually to the hydroquinone solution, with the use of a mechanical stirrer (Note 3), the mixture being cooled so that the temperature never rises above 30°. At first a greenish-black precipitate forms, but, upon further addition of the sodium dichromate solution, the color changes to yellowish green. As soon as this color remains permanent (a slight excess of sodium dichromate does no harm) the reaction is complete. This requires about one-half to three-quarters of an hour; 90–110 cc. of sodium dichromate solution is necessary. The mixture is then cooled to about 10° and filtered with suction. As much water as possible is pressed out of the crystals.

The filtrate is extracted twice, 150 cc. of benzene being used for each extraction. The precipitate of quinone is transferred to a 1-l. beaker, and 500 cc. of benzene, including the 300 cc. used to extract the filtrate, is added. The mixture is now heated with stirring on a steam bath, and as soon as most of the quinone has dissolved the benzene layer is decanted into another beaker. It is dried while hot by stirring a short time with a little calcium chloride, and then filtered through an ordinary funnel into a 1-l. distilling flask before it cools. There is a certain amount of quinone which does not go into the 500 cc. of benzene, so that the residue is extracted a second time with about 100 cc. of benzene, which is dried and filtered with the first extract. During these extractions (Note 4), the benzene should not be at the boiling point, as this will cause a considerable volatilization of the quinone.

The distilling flask is now attached to a condenser set for downward distillation, and the benzene is distilled. As soon as the quinone starts to separate, the residue in the

flask is transferred to a beaker and cooled in an ice bath. The precipitate is filtered off with suction and the product spread out for a short time to dry. The product is yellow in color and weighs 75 to 80 g. (76–81 per cent of the theoretical amount). Material made in this way will hold its yellow color over long periods of time, provided it is protected from light.

The benzene distillate is yellow and contains some quinone. This, as well as the benzene from the final filtration of the quinone crystals, may be used in a subsequent run and thus raises the yield of the subsequent runs to about 85–90 g. (86–92 per cent of the theoretical amount) (Note 5).

2. Notes

1. If impure hydroquinone is used, a black, sticky precipitate will usually appear after the addition of the sulfuric acid to the hydroquinone solution. This should be removed, before the oxidation is started, by filtration without suction through a fluted filter.
2. When technical sodium dichromate is used, the solution should be filtered with suction, before it is added to the hydroquinone, in order to remove any insoluble impurities.
3. As the mixture becomes thick during the oxidation, it is very necessary to use a stirrer which will keep the whole mass agitated by reaching to the sides and bottom of the beaker.
4. In the laboratory it is convenient to make several small runs of the size indicated, as far as the oxidation is concerned; but the benzene extractions can be combined.
5. It is also possible to obtain good yields of quinone in the following manner: 1500 cc. of water, 465 g. of concentrated sulfuric acid, and 300 g. (2.7 moles) of hydroquinone are mixed in a 3-l. beaker. The mixture is cooled to 0°, and 330 g. (1.1 moles) of sodium dichromate is added in powdered form, the temperature being kept below 5° at all times. This method requires a longer time and much more care in the control of conditions than the procedure described.

3. Discussion

Quinone can be prepared by the oxidation of benzene,[1] aniline,[2] and hydroquinone[3] by a miscellany of oxidizing agents. The oxidation of hydroquinone is rapid and convenient and therefore desirable for the laboratory.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 317
- Org. Syn. Coll. Vol. 2, 553

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

Benzene (71-43-2)

aniline (62-53-3)

hydroquinone (123-31-9)

sodium dichromate (7789-12-0)

Quinone (106-51-4)

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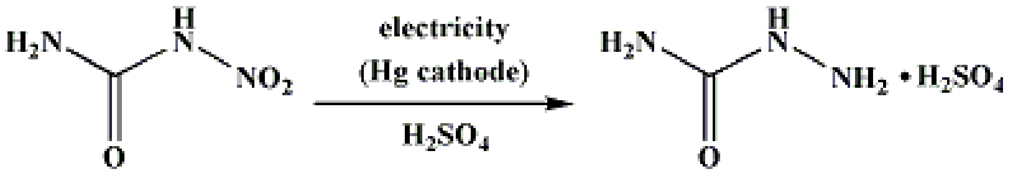
Organic Syntheses, *CV 1*, 485

SEMICARBAZIDE SULFATE

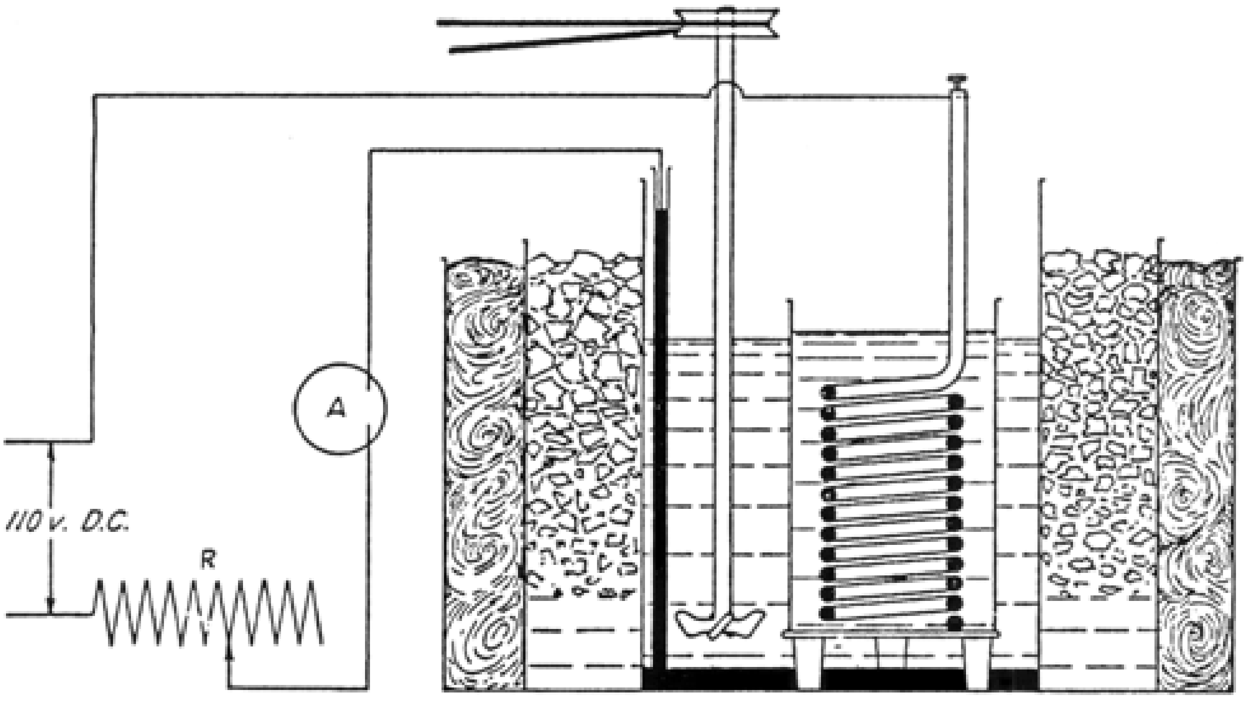


Submitted by A. W. Ingersoll, L. J. Bircher, and M. M. Brubaker.
Checked by Henry Gilman and L. C. Heckert.

1. Procedure

(*A*) *Apparatus*.—The reduction is carried out in a 15 by 23 cm. battery jar (Note 1), which is surrounded by a vessel suitable for a cooling bath. The bottom of the battery jar is covered with mercury, which serves as the cathode of the cell. The anode is a heavy lead coil separated from the catholyte by being suspended in a porous cup. This cup is set upon a support which holds it just above the cathode surface and does not appreciably diminish the latter (Note 2). The cathode is connected with the circuit by means of a glass tube partially filled with mercury and carrying a small piece of platinum wire sealed through the lower end. An efficient mechanical stirrer is provided in the catholyte. The current used in these experiments was 110 d.c., with a field rheostat, having a resistance of 8 ohms and a capacity of 20 amperes, for controlling the current. Any source of current supplying 30–110 volts and 15–20 amperes and any rheostat capable of carrying this current may be used. An ammeter reading to at least 15 amperes is connected in the circuit. Several reduction cells of the size described above may be run at one time, if they are connected in series. Figure 25 shows the general set-up.

Fig. 25.



(*B*) *Reduction of Nitrourea*.—After the apparatus is assembled, 600 cc. of 20 per cent sulfuric acid (Note 3) is placed in the battery jar, and the lead anode in the porous cup is also covered with acid of the same strength. The cell is surrounded by an ice-salt bath, the stirrer is started, and, while the solution is cooling, 50 g. (0.48 mole) of nitrourea (Note 4) is added to the catholyte. A thermometer is placed in the catholyte, and when the temperature drops to +5° the current is turned on as follows: with the rheostat set for maximum resistance, the current is switched on, then the rheostat is gradually adjusted until the current flowing through the cell is about 0.06 ampere per square centimeter of cathode surface (Note 5). The cell must be efficiently cooled with ice and salt so as to keep the temperature at all times below 10° (Note 6). The reduction requires five to six hours. The nitrourea is quite insoluble but gradually dissolves as it is reduced. The foam and clumps of solid are worked down into the liquid occasionally. When almost all the nitrourea is in solution, some of the catholyte should be drawn up with a pipette and used to wash down the nitrourea that adheres to the walls of the vessel. The reduction is continued for about ten to twenty minutes after the nitrourea has dissolved. When the reduction is complete, as is indicated by a marked evolution of hydrogen, the current is shut off, and the porous cup is washed down with a little distilled water and removed.

The solution of semicarbazide sulfate is removed from the cell and filtered (Note 7). The filtered solution is concentrated under reduced pressure on a water bath (Note 8) to a volume of 125–150 cc. Meanwhile, considerable semicarbazide sulfate will have crystallized. The mixture is cooled thoroughly in ice and the crystals are collected on a hardened filter paper, or better, on a filtros plate (see Note 5, on p. 11), and washed several times with absolute alcohol to remove sulfuric acid. The crystals are dried on clay plate or paper. The yield is 50–57 g. (61–69 per cent of the theoretical amount) of a product melting at 144–145° with decomposition.

2. Notes

1. This is a commercial size. The internal diameter of these battery jars is 15–17 cm. Any sturdy glass vessel of the same dimensions may be used.
2. The lead anode should have about the same surface area as the cathode. In these experiments the porous cup used was 8 by 21 cm., but slightly larger sizes would do. A three-legged desiccator plate makes a convenient support for the cup. The latter should be immersed as deeply as possible in the catholyte, to decrease the resistance and consequent heating in the cell. It should not be more than 4–5 mm. thick, or the resistance will be too great and excessive heating will occur. Another convenient arrangement for the reduction cell is to divide the battery jar into two compartments by sealing in a diaphragm of thin cork-pine wood by means of paraffin. This offers very little resistance to the passage of the current and allows the reduction to be carried on very rapidly. A filtros plate may also be used as a diaphragm to separate the two solutions.
3. For runs of this size, sulfuric acid as dilute as 15 per cent may be used with good results. In larger runs or in runs using moist nitrourea, the 20 per cent acid is preferable.
4. Various grades of nitrourea (p. 417) may be used in the reduction without noticeably affecting the purity of the semicarbazide sulfate. In order to obtain the yields given in the procedure, the nitrourea was well washed, sucked dry on the filter,

and air-dried. The moist material obtained after filtration is equally good (see (Note 3)). Runs in which 60–70 g. of nitrourea was used gave slightly lower yields than those in which 50 g. was used.

5. The current varies somewhat with changes in temperature and concentration and must be adjusted occasionally. If very efficient cooling can be had, currents as high as 0.07 ampere per square centimeter may be used. The current efficiency and speed of reduction are decreased with currents below 0.06 ampere per square centimeter. A current of 13.5 amperes was satisfactory for the cell described.

6. The yield falls off rapidly at temperatures above 10°. The control of temperature is much easier if the porous cup is immersed as deeply as possible in the catholyte (Note 2).

7. If another run is to be made immediately, the reduced liquor may be removed by means of a siphon or pipette. If it is decanted, a little vaseline rubbed on the edge of the vessel will aid in pouring off the aqueous liquor from the mercury.

8. The evaporation must be conducted on a water bath whose temperature does not exceed 50–55°, in order to avoid decomposition of the product. The evaporation may also be conveniently carried out by placing the solution in a beaker, warming to 50–55°, and blowing air over the surface of the solution. This takes a somewhat longer time but requires no watching.

3. Discussion

Salts of semicarbazide can be prepared by the action of potassium cyanate on hydrazine sulfate;[1] by the action of hydrazine hydrate on urea;[2] by heating hydrazine ammonium carbonate;[3] by the reduction of nitrourea with zinc dust and hydrochloric acid;[4] and by electrolytic reduction with iron cathodes and ammonium chloride solution,[5] with tin cathodes and sulfuric acid solution,[6] with lead cathodes and hydrochloric acid solution,[7] and with cathodes of copper, nickel, lead, and mercury in hydrochloric or sulfuric acid solution.[8]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 311

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Salts of semicarbazide

hydrochloric or sulfuric acid

alcohol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ammonium chloride (12125-02-9)

hydrogen (1333-74-0)

mercury (7439-97-6)

zinc (7440-66-6)

urea (57-13-6)

hydrazine hydrate (7803-57-8)

Hydrazine sulfate (10034-93-2)

Nitrourea (556-89-8)

potassium cyanate (590-28-3)

Semicarbazide sulfate

hydrazine ammonium carbonate

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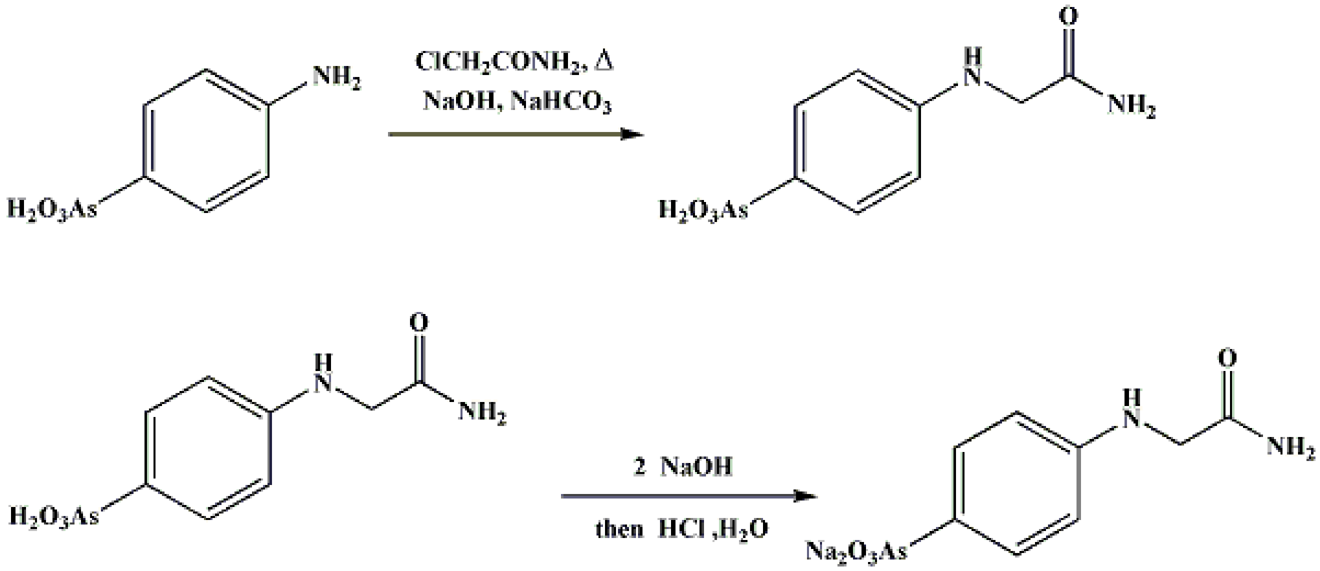
Organic Syntheses, CV 1, 488

SODIUM *p*-ARSONO-*N*-PHENYLGLYCINAMIDE

[Tryparsamide]



Submitted by W. A. Jacobs and M. Heidelberger.
Checked by Roger Adams and L. F. Martin.

1. Procedure

To a solution of 130 g. (0.6 mole) of arsanilic acid (p. 70) in 600 cc. (0.6 mole) of normal sodium hydroxide are added 52 g. (0.62 mole) of sodium bicarbonate and 70 g. (0.75 mole) of chloroacetamide (p. 153). The mixture is heated on a water bath to 90–100°, and a steady evolution of carbon dioxide occurs. At the end of two hours, when gas evolution has practically ceased, the mixture is cooled to 40°, stirred vigorously, and 150 cc. of 20 per cent hydrochloric acid poured in rapidly. *p*-Arsonophenylglycinamide crystallizes at once and, after cooling to room temperature, is filtered by suction and washed once with 2 per cent hydrochloric acid (Note 1), then with cold water.

The crude product thus obtained is contaminated with some arsanilic acid and possibly other products. These are removed during purification. The crude product is suspended in about 400 cc. of water, and, with vigorous stirring, treated carefully with 25 per cent aqueous sodium hydroxide until solution is just complete. At this point the mixture is still acid to litmus, and an excess of sodium hydroxide is to be avoided to prevent decomposition of the product. About 15 g. of animal charcoal is added, the mixture stirred for five minutes without heating, and filtered. The filtrate is treated during vigorous stirring with 100 cc. of 20 per cent hydrochloric acid, and the pure acid at once separates. After cooling, it is filtered by suction and washed thoroughly with small portions of ice-cold water until the filtrate is practically halogen-free (Note 2).

The acid, without drying, is suspended in about 200 cc. of distilled water and, with vigorous stirring, cautiously (Note 3) treated with 25 per cent sodium hydroxide solution until dissolved and the solution reacts neutral to litmus. The solution is then filtered through folded filter paper which should be free from soluble calcium salts, otherwise the filtrate will remain clouded by a suspension of the calcium salt. The clear, faintly yellow or colorless filtrate is then vigorously stirred and treated with 1.5 volumes of 95 per cent alcohol. Crystallization is induced by rubbing with a rod, and then an additional volume of alcohol is added. The mixture should be allowed to cool to about 20° and stand for at least two hours to complete the precipitation of the salt, which is then filtered by suction and washed thoroughly with 85 per cent alcohol. The salt is then air-dried. The yield is 73–77 g. (38–40 per cent of the theoretical amount).

2. Notes

1. From this filtrate approximately 15–30 g. of arsanilic acid may be recovered by just neutralizing to Congo red with sodium hydroxide.
2. If the free acid is desired it may be obtained by drying the product at this stage. The yield of free acid is about 100 g. (60 per cent of the theoretical amount).
3. If sodium hydroxide is added too rapidly some solid precipitates which does not redissolve.

3. Discussion

This procedure described for the preparation of sodium *p*-arsono-*N*-phenylglycinamide has been reported in the literature.[1]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alcohol (64-17-5)

hydrochloric acid (7647-01-0)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

carbon dioxide (124-38-9)

Arsanilic acid (98-50-0)

CHLOROACETAMIDE (79-07-2)

Sodium p-arsono-N-phenylglycinamide (834-03-7)

p-Arsonophenylglycinamide

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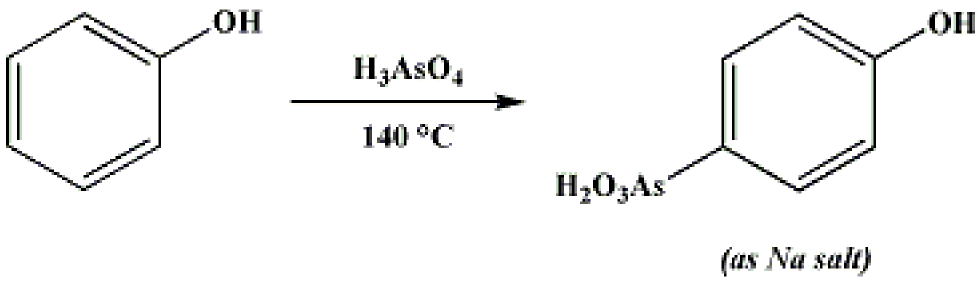
Organic Syntheses, CV 1, 490

SODIUM *p*-HYDROXYPHENYLARSONATE

[Benzenearsonic acid, *p*-hydroxy-, sodium salt]



Submitted by W. G. Christiansen and A. J. Norton.
Checked by Oliver Kamm

1. Procedure

Seven hundred and twenty grams (3.8–4 moles) of sirupy arsenic acid (75–80 per cent) is boiled in a beaker until the temperature of the acid is 150°; about 120 g. of water is driven off, leaving a sirup containing approximately 95 per cent of orthoarsenic acid, which is then added to 300 g. (3.2 moles) of phenol in a 1-l. round-bottomed, three-necked Pyrex flask provided with an efficient stirrer, a thermometer, and a connection with a downward condenser. The flask is set in an oil bath which is heated at once to 155–160°, and the stirrer is run at a rate high enough to insure thorough mixing.

When the inside temperature reaches 140°, boiling commences and water with a very little phenol begins to distil. The distillation is allowed to continue until 60 cc. (one molecular equivalent) of water has been collected; this usually requires one hour, and the inside temperature rises to 146°. The downward condenser is then replaced by a reflux condenser (Note 1) and the reaction is allowed to continue until a total of four hours has elapsed from the time the contents of the flask first reached 140°. After the return condenser has been attached, the inside temperature declines slowly to 141° or 142° and the reaction mixture becomes thicker and somewhat tarry. After the contents of the flask have been partially cooled, they are poured into 4 l. of water and mechanically stirred; the agitation is continued for a short time in order to break up the tarry material and enable the water to dissolve the hydroxyphenylarsonic acids completely.

Finely ground barium hydroxide is added gradually to the well-stirred water solution until the material is slightly alkaline to litmus, in order to remove the excess of arsenic acid; when this point is reached, the solution becomes pink. If the procedure is carried out properly, 700–800 g. of $Ba(OH)_2{\cdot}8H_2O$ should suffice (Note 2). The time required by this method is greater than when a hot solution of barium hydroxide is used, but the method is more convenient and does not cause such a great increase in volume. After removal of the barium arsenate by filtration, the mother liquor and washings are

treated with sulfuric acid until the solution contains neither barium nor sulfate ions. When the barium sulfate has been separated and thoroughly washed (Note 3), the filtrate is concentrated on a steam bath to about 3 l., neutralized to litmus with sodium hydroxide, filtered, evaporated until the solution becomes well coated with crystals, and then treated with 2.5 volumes of alcohol. After the mixture has cooled in an ice box, the sodium *p*-hydroxyphenylarsonate is separated, washed with alcohol, and dried in an oven at 80°. A second crop may be secured from the filtrate by concentrating it further and precipitating with alcohol. The total yield of anhydrous sodium *p*-hydroxyphenylarsonate is 252 g. (33 per cent of the theoretical amount). By proper manipulation, it is possible to obtain as much as 240 g. in the first crop and to have it free from sulfate, arsenate, and sodium *o*-hydroxyphenylarsonate which is one of the by-products formed in this reaction (Note 4).

2. Notes

1. When the downward condenser is not replaced by a reflux condenser, the total volume of water that distils is 90–120 cc. and the mass becomes very tarry, owing to the oxidation of phenol or of some intermediate substance formed in the reaction. *p*-Hydroxyphenylarsonic acid is not destructively oxidized by hot arsenic acid.

2. In removing the excess arsenic acid with barium hydroxide, the solution should not be permitted to become strongly alkaline, as the barium salt of the hydroxyphenylarsonic acid may commence to separate, thereby decreasing the yield.

3. The filtration of large quantities of barium sulfate is usually tedious; but if filtering carbon is added to the suspension to be filtered and if a mat of this carbon is prepared on the filter by filtering an aqueous suspension of carbon, the barium sulfate may be removed rapidly and completely, even when it is precipitated from cold solutions.

4. When phenol is arsonated with arsenic acid, small amounts of *o*-hydroxyphenylarsonic acid, *p,p'*-dihydroxyphenylarsinic acid, and *o,p'*-dihydroxyphenylarsinic acid are formed as by-products. As the sodium salts of the secondary acids are soluble in alcohol, they will not appear in the material precipitated by the addition of alcohol. The sodium salt of *o*-hydroxyphenylarsonic acid, although insoluble in alcohol, will not be precipitated if the solution is not concentrated too far before addition of the alcohol. To test the material for the presence of the ortho compound, ferric chloride is added to an aqueous solution of a small amount of the solid; the ortho hydroxy acid gives a deep purple color, whereas the para acid gives no coloration. The sodium salt which is precipitated with alcohol contains water of crystallization, which is driven off by drying at 80°. The product can be purified by dissolving in hot water and adding hot alcohol until a slight permanent turbidity is produced. Upon cooling, the material separates in a crystalline condition. Occasionally, the second crops of sodium *p*-hydroxyphenylarsonate

contain small amounts of arsenious oxide which is formed from the arsenic acid during the oxidation mentioned above.

3. Discussion

p-Hydroxyphenylarsonic acid can be prepared by diazotization of arsanilic acid and replacement of the diazo group by hydroxyl;[1] by directly introducing the arsonic group into phenol;[2] and by diazotization of *p*-aminophenol followed by treatment with sodium arsenite.[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 75

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

arsenious oxide

hydroxyphenylarsonic acids

$Ba(OH)_2 \cdot 8H_2O$

barium salt of the hydroxyphenylarsonic acid

p,p'-dihydroxyphenylarsinic acid

alcohol (64-17-5)

sulfuric acid (7664-93-9)

sodium hydroxide (1310-73-2)

phenol (108-95-2)

Arsanilic acid (98-50-0)

arsenic acid, orthoarsenic acid (1327-52-2)

barium sulfate (7727-43-7)

sodium arsenite

carbon (7782-42-5)

ferric chloride (7705-08-0)

barium hydroxide (17194-00-2)

barium arsenate

p-aminophenol (123-30-8)

sodium salt (824-79-3)

p-hydroxyphenylarsonic acid (98-14-6)

sodium p-hydroxyphenylarsonate, Benzenearsonic acid, p-hydroxy-, sodium salt (53663-20-0)

sodium o-hydroxyphenylarsonate, sodium salt of o-hydroxyphenylarsonic acid

o-hydroxyphenylarsonic acid

o,p'-di-hydroxyphenylarsinic acid

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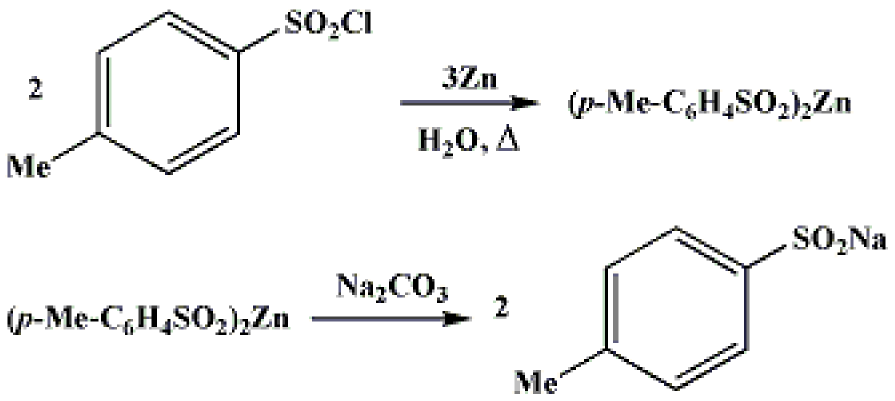
Organic Syntheses, CV 1, 492

SODIUM *p*-TOLUENESULFINATE

[*p*-Toluenesulfinic acid, sodium salt]



Submitted by Frank C. Whitmore and Frances H. Hamilton.
Checked by J. B. Conant and Paul Allen, Jr.

1. Procedure

Five hundred grams (2.6 moles) of technical *p*-toluenesulfonyl chloride is ground in a mortar to break up all lumps. Three liters of water is placed in a 12-l. crock provided with a large brass stirrer and a tube for passing steam directly into the liquid. Dry steam is passed into the water until the temperature reaches 70°. The steam is then shut off and 400 g. (5.5–6.1 atoms) of zinc dust (90 to 100 per cent pure) is added. The sulfonyl chloride is then added in small portions by means of a porcelain spoon. The addition takes about ten minutes. The temperature rises to about 80°. Stirring is continued for ten minutes after the last of the chloride has been added. Steam is then passed into the mixture until the temperature reaches 90°. If it is heated any hotter, bumping takes place. The steam is shut off, and 250 cc. of 12 *N* sodium hydroxide solution is added. Finely powdered sodium carbonate is then added in 50-g. portions until the mixture is strongly alkaline. The mixture froths considerably, but this causes no trouble unless too small a crock is used. The stirrer is loosened and the crock is removed.

The mixture is filtered by suction in a large funnel. The filtrate has a volume of about 4.5 l. The cake of unchanged zinc dust and zinc compounds is transferred to a 3-l. battery jar and placed under the stirrer, and the latter is clamped in place. water (750 cc.) is added, the stirrer is started, and steam is passed in until the mixture starts to froth too violently. The steam is then shut off, but the stirring is continued for ten minutes. The mixture is filtered and the filtrate is added to the main solution in a large evaporating dish. The liquid is evaporated over a large burner to a volume of about 1 l., or until a considerable crust forms around the edges. The mixture is then cooled. Large, flat, transparent crystals separate. The thoroughly cooled mixture is filtered by suction, and the crystals are air-dried until efflorescence just starts. They are then bottled. The product is *p*-$CH_3C_6H_4SO_2Na{\cdot}2H_2O$. The yield is 360 g. (64 per cent of

the theoretical amount). Careful acidification of the mother liquor with dilute hydrochloric acid yields 15 g. of the free sulfinic acid (Note 1).

2. Notes

1. The free sulfinic acid may be prepared by dissolving the sodium salt in cold water and carefully acidifying the solution with hydrochloric acid. An excess of hydrochloric acid must be avoided, as it dissolves the acid to a certain extent. The sulfinic acid is difficult to dry without partial conversion into the sulfonic acid and thiosulfonic ester.
It is suggested that an office ledger press is convenient for rapid drying between sheets of filter paper (D. T. Gibson, private communication).

3. Discussion

p-Toluenesulfinic acid and its salts can be prepared by the following general methods: the reduction of the sulfonyl chloride by sodium amalgam,[1] zinc dust in alcohol and water,[2] sodium sulfite,[3] sodium sulfide,[4] potassium hydrosulfide[5] (the thio acid being first formed), and sodium arsenite;[6] from toluene, aluminum chloride, sulfur dioxide, and hydrogen chloride;[7] from *p*-toluidine by diazotization and subsequent treatment with sulfur dioxide and finely divided copper;[8] and from *p*-tolylmagnesium bromide and sulfur dioxide.[9]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 519
- Org. Syn. Coll. Vol. 4, 937

References and Notes

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3. Blomstrand, Ber. **3**, 965 (1870).
4. Meister, Lucius, and Brüning, Ger. pat. 224,019 [Chem. Zentr. II, 513 (1910)].
5. Fromm and Erfurt, Ber. **42**, 3821 (1909).
6. Gutmann, Ber. **41**, 3351 (1908); Ber. **42**, 480 (1909).
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8. Gattermann, Ber. **32**, 1141 (1899); Thomas, J. Chem. Soc. **95**, 344 (1909).
9. Unpublished directions.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfinic acid

sulfonic acid

thiosulfonic ester

p-$CH_3C_6H_4SO_2Na\cdot 2H_2O$

p-Toluenesulfinic acid and its salts

alcohol (64-17-5)

hydrogen chloride, hydrochloric acid (7647-01-0)

sodium sulfite (7757-83-7)

sodium hydroxide (1310-73-2)

sodium carbonate (497-19-8)

sulfur dioxide (7446-09-5)

copper (7440-50-8)

sodium arsenite

aluminum chloride (3495-54-3)

toluene (108-88-3)

zinc (7440-66-6)

sodium (13966-32-0)

sodium sulfide (1313-82-2)

potassium hydrosulfide (1310-61-8)

p-toluidine (106-49-0)

p-Toluenesulfonyl chloride (98-59-9)

p-tolylmagnesium bromide (4294-57-9)

p-toluenesulfinic acid, sodium salt, Sodium p-toluenesulfinate

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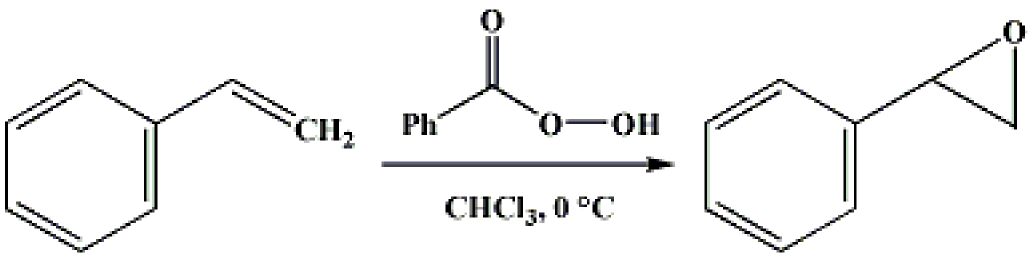
Organic Syntheses, CV 1, 494

STYRENE OXIDE

[Oxirane, 2-phenyl-]



Submitted by Harold Hibbert and Pauline Burt.
Checked by Roger Adams and F. E. Kendall.

1. Procedure

To a solution of 42 g. (0.30 mole) of perbenzoic acid (p. 431) in 500 cc. of chloroform is added 30 g. (0.29 mole) of styrene (b.p. 141–143°) (p. 440). The solution is kept at 0° for twenty-four hours and is shaken frequently during the first hour. At the end of twenty-four hours, titration of an aliquot part of the solution shows that only the slight excess of perbenzoic acid remains (Note 1).

The benzoic acid is removed from the chloroform solution by shaking with an excess of 10 per cent sodium hydroxide solution, the alkali is removed by washing with water, and the chloroform solution is dried with anhydrous sodium sulfate. It is then fractionated through an efficient distilling column (p. 130). Removal of the chloroform leaves a practically colorless liquid which distils at 188–192° (uncorr.) (Note 2). The yield is 24–26 g. (69–75 per cent of the theoretical amount).

2. Notes

1. The perbenzoic acid may be analyzed by mixing with an excess of acidified potassium iodide and titrating the liberated iodine with sodium thiosulfate (p. 434).
2. If the styrene oxide is distilled over a free flame some decomposition takes place as indicated by the formation of water. This is not observed if the product is distilled from an oil bath.

3. Discussion

Styrene oxide can be prepared by the action of iodine, water, and mercuric oxide on styrene.[1] The procedure described has been published.[2]

References and Notes

1. Fourneau and Tiffeneau, Compt. rend. **140**, 1596 (1905).
2. Hibbert and Burt, J. Am. Chem. Soc. **47**, 2240 (1925).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium sulfate (7757-82-6)

potassium iodide (7681-11-0)

sodium thiosulfate (7772-98-7)

Benzoic acid (65-85-0)

mercuric oxide (21908-53-2)

iodine (7553-56-2)

styrene (100-42-5)

Styrene oxide, Oxirane, 2-phenyl- (96-09-3)

Perbenzoic acid (93-59-4)

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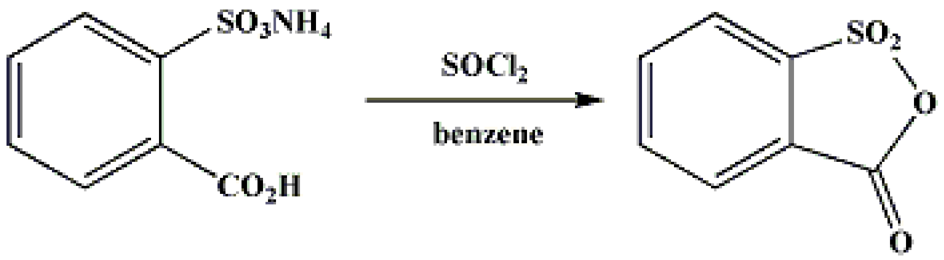
Organic Syntheses, CV 1, 495

o-SULFOBENZOIC ANHYDRIDE

[Benzoic acid, *o*-sulfo-, cyclic anhydride]



Submitted by H. T. Clarke and E. E. Dreger.
Checked by Henry Gilman and J. E. Kirby.

1. Procedure

In a 2-l. flask fitted with a mechanical stirrer, a separatory funnel, and an efficient reflux condenser are placed 219 g. (1 mole) of finely powdered acid ammonium *o*-sulfobenzoate (p. 14) and 200 cc. of dry benzene (Note 1). To this is added with stirring 145 g. (86.3 cc., 1.22 moles) of thionyl chloride (b.p. 76–78°). A tube is connected to the upper end of the reflux condenser which passes into an ice-cooled flask; from this another tube is provided to carry off the hydrogen chloride and sulfur dioxide generated during the reaction (Fig. 7, p. 97). The mixture is gently warmed on a steam bath in such a way that gases are evolved fairly briskly (Note 2); continuous stirring is essential. The bulk of the entrained benzene and thionyl chloride is condensed in the ice-cooled receiver; the condensate is returned periodically to the reaction mixture through the separatory funnel. After about fifteen hours' heating, the evolution of gases slackens; an additional 400 cc. of dry benzene is then added and the heating continued until the evolution of gases ceases; this requires about five hours longer.

The hot mixture is then filtered (Note 3) with suction into a 2-l. flask, and the solid material, consisting of ammonium chloride, is washed with 100 cc. of hot benzene. This solid is then returned to the 2-l. flask and boiled with stirring for one hour with 300 cc. of dry benzene; the mixture while hot is then filtered with suction into the same 2-l. flask. The combined filtrates and washings are then distilled until about 300 cc. of benzene has been removed, after which the solution is cooled in an ice bath; this causes the greater part of the sulfobenzoic anhydride to crystallize. The benzene mother liquor is decanted from these crystals and the bulk of the solvent removed by distillation.

The flask containing the crystals is attached to a condenser and heated until the solid has completely melted; the adhering solvent is then removed from the liquid by slightly reducing the pressure. The clear residue is poured into a dish and allowed to cool. The product thus obtained melts at 121–123°. The residue from the mother

liquor, being as a rule somewhat dark in color, is preferably distilled under reduced pressure (Note 4), the flask being heated in a metal bath. The anhydride distils at 184–186°/18 mm. The second crop may have a slightly lower melting point. The total yield of *o*-sulfobenzoic anhydride, which is of sufficient purity for the preparation of sulfonephthaleins, amounts to 118–121 g. (64–66 per cent of the theoretical amount) (Note 5). In order to convert this into a product melting at 126–127° (Note 4), it is recrystallized from three times its weight of dry benzene.

2. Notes

1. The benzene is most satisfactorily dried by distillation, the moist forerun being rejected.
2. The reaction may become so vigorous that it is necessary to interrupt the heating for a short time.
3. The filtration should be carried out under a hood, on account of the presence of some unchanged thionyl chloride.
4. It is stated in the literature that the pure compound melts at 128°. It is very sensitive to moist air, which converts it into the free acid.
5. With larger quantities the yields are significantly increased; the submitters of these directions obtained 74–81 per cent of the theoretical amount with runs of 7.5 moles.

3. Discussion

o-Sulfobenzoic anhydride can be prepared from the free acid by heating alone or with phosphorus pentoxide[1] and by treating it with acetyl chloride;[2] from the neutral potassium salt by warming with phosphorus pentachloride;[2] from the acid potassium salt by warming with phosphorus pentachloride[3] or thionyl chloride,[4] and by heating it with phosphorus pentoxide to 400°.[5] The procedure described is a modification of that of White and Acree[6] who heated the acid ammonium salt with an excess of thionyl chloride and extracted the product with benzene.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 14

References and Notes

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3. Sohon, Am. Chem. J. **20**, 258 (1898).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfonephthaleins

ACID AMMONIUM o-SULFOBENZOATE

hydrogen chloride (7647-01-0)

Benzene (71-43-2)

ammonium chloride (12125-02-9)

phosphorus pentachloride (10026-13-8)

acetyl chloride (75-36-5)

thionyl chloride (7719-09-7)

sulfur dioxide (7446-09-5)

sulfobenzoic anhydride, o-Sulfobenzoic anhydride, Benzoic acid, o-sulfo-, cyclic anhydride (81-08-3)

phosphorus pentoxide (1314-56-3)

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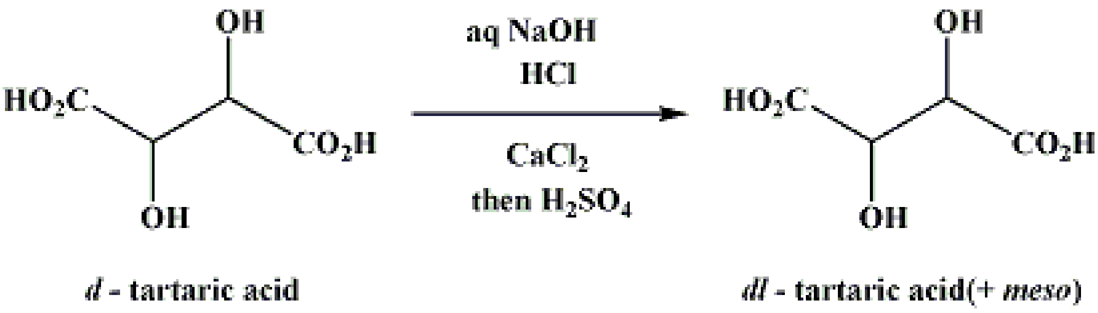
dl-TARTARIC ACID

[By-product, *meso*-Tartaric Acid]



Submitted by A. F. Holleman
Checked by H. T. Clarke and H. J. Bean.

1. Procedure

In a copper or iron kettle of 4-l. capacity is placed a solution of 200 g. (1.33 moles) of *d*-tartaric acid and 700 g. of sodium hydroxide in 1400 cc. of water. A 12-l. flask through which cold water is run is placed in the mouth of the kettle in order to prevent loss of water vapor, and the mixture is boiled gently over an open flame for four hours. The solution is now transferred to a 12-l. flask or crock and partially neutralized with 1400 cc. of commercial hydrochloric acid (sp. gr. 1.19). To the still alkaline solution is now added just enough sodium sulfide to precipitate all the iron or copper which has been dissolved from the kettle (Note 1). The filtered solution is then just acidified with hydrochloric acid, boiled to expel all hydrogen sulfide, and made very faintly alkaline to phenolphthalein with sodium hydroxide solution. To the hot solution is then added a concentrated solution of 300 g. of anhydrous calcium chloride which causes an immediate precipitation of calcium *dl*-tartrate and *meso*-tartrate.

The mixture is allowed to stand for one week (Note 2) and the precipitate filtered, washed with cold water until free of chlorides, and dried at 40–50°. The yield is 246–315 g. The product is found on analysis to consist principally of the tetrahydrate, $C_4H_4O_6Ca\cdot4H_2O$ (Note 3). It is suspended in 800 cc. of water and treated with the calculated quantity (0.4 g. for every 1.0 g.) of concentrated (95–96 per cent) sulfuric acid. The mixture is warmed on the steam bath, with occasional shaking, or mechanical stirring, for thirty to forty hours (Note 4), filtered hot, and the calcium sulfate washed well with hot distilled water.

The united filtrate is evaporated on the steam bath until the volume amounts to 200 cc., at which point crystals should have already begun to separate from the hot solution. After standing at room temperature for twenty-four hours or longer, the crystals are filtered by suction as free from mother liquor as possible and recrystallized from an equal weight of distilled water (Note 5). The filtrate from this recrystallization

is evaporated on the steam bath and the second crop of *dl*-tartaric acid filtered and recrystallized as before. The yield is 65–75 g. (29–33.4 per cent of the theoretical amount).

The sirupy filtrate from the *dl*-tartaric acid, which consists principally of *meso*-tartaric acid together with a small amount of unchanged *d*-tartaric acid, is diluted with its own volume of water and divided into two equal parts; one part is exactly neutralized with potassium hydroxide, using phenolphthalein, and the second part is added. After standing for twenty-four hours the potassium hydrogen *d*-tartrate is filtered off. The filtrate is neutralized with ammonia, then just acidified with acetic acid, and treated with an excess of calcium chloride solution (about 500 cc. of a 25 per cent solution). After standing for a week (Note 2) the precipitated calcium *meso*-tartrate is filtered and washed with cold distilled water. It may, if desired, be recrystallized from boiling water. The yield is 42–55 g. (corresponding to 13–17 per cent of the original *d*-tartaric acid). The sirupy free acid may be prepared from this salt by treatment with sulfuric acid as above.

2. Notes

1. If iron is not removed at this point it separates with the calcium salt and contaminates the final product. If desired, copper can be removed at a later stage by passing hydrogen sulfide through the acid solution.
2. The calcium salts, in particular that of *meso*-tartaric acid, separate very slowly, and the yield is appreciably lower if the mixture is allowed to stand only eighteen hours.
3. The calcium salt of the principal product, *dl*-tartaric acid, crystallizes with four molecules of water; the secondary product, *meso*-tartaric acid, forms a calcium salt which crystallizes with three molecules of water. The amount of sulfuric acid actually required may readily be calculated from the percentage of calcium found on analysis in the regular way; or it may be estimated by igniting a sample, and titrating the residue with standard acid.
4. This long treatment is necessary since, on the one hand, the calcium salts tend to be protected by the calcium sulfate which crystallizes on them, and, on the other hand, it is important to allow all the free sulfuric acid to react.
5. A very complete separation of the calcium sulfate may be effected by adding to the concentrated solution 1000 cc. of alcohol, allowing the mixture to stand for twenty-four hours, and filtering. The alcohol is then distilled from the filtrate and the procedure followed as indicated above.

3. Discussion

dl-Tartaric acid can be prepared by racemization of *d*-tartaric acid by heating to 175° with a small amount of water[1] or by boiling with a large excess of concentrated alkali;[2] and by the oxidation of fumaric acid.[3]

References and Notes

1. Jungfleisch, Compt. rend. **75**, 439 (1872); Bull. soc. chim. (2) **18**, 201 (1872).
2. Meissner, Ber. **30**, 1574 (1897); Holleman, Rec. trav. chim. **17**, 66 (1898); Campbell, Slotin, and Johnston, J. Am. Chem. Soc. **55**, 2604 (1933).
3. Kekulé and Anschütz, Ber. **13**, 2150 (1880); Hofmann, Ehrhart, and Schneider, Ber. **46**, 1667 (1913); Milas and Terry, J. Am. Chem. Soc. **47**, 1412 (1925); Standard Brands, U. S. pat. 2,000,213 [C. A. **29**, 4027 (1935)]; Milas and Sussman, J. Am. Chem. Soc. **58**, 1302 (1936).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

calcium salt

$C_4H_4O_6Ca{\cdot}4H_2O$

calcium salts

alcohol (64-17-5)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ammonia (7664-41-7)

sodium hydroxide (1310-73-2)

iron (7439-89-6)

hydrogen sulfide (7783-06-4)

copper (7440-50-8)

calcium sulfate (7778-18-9)

potassium hydroxide (1310-58-3)

calcium (7440-70-2)

dl-tartaric acid (87-69-4)

sodium sulfide (1313-82-2)

Fumaric acid (110-17-8)

phenolphthalein (77-09-8)

D-tartaric acid (147-71-7)

meso-Tartaric Acid (147-73-9)

calcium dl-tartrate (3164-34-9)

meso-tartrate

potassium hydrogen d-tartrate

calcium meso-tartrate

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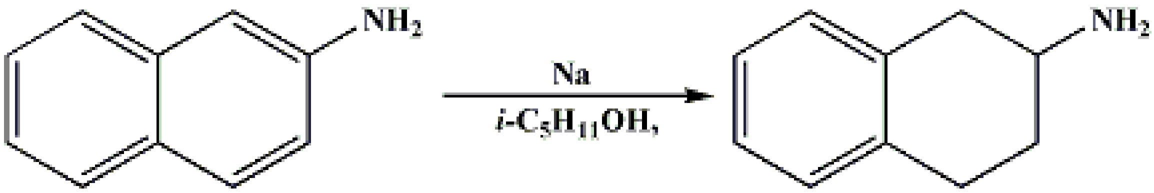
Organic Syntheses, *CV 1*, 499

ac-TETRAHYDRO-β-NAPHTHYLAMINE

[2-Naphthylamine, 1,2,3,4-tetrahydro-]



Submitted by E. B. H. Waser and H. Möllering.
Checked by Roger Adams and W. W. Moyer.

1. Procedure

A 1-l. wide-necked, round-bottomed flask is set into an iron dish of about 1.3–1.5 l. capacity and the space between is filled with fine sand so that the flask rests about 1 cm. from the bottom of the dish (Note 1). In the flask is placed 26 g. (1.1 atoms) (twice the theoretical amount) of sodium cut into thin slices (Note 2), and the flask is then closed with a tight-fitting cork stopper through which is inserted a separatory funnel (Note 3) and a long, wide, Liebig condenser through the jacket of which is passed downward a rapid current of air (Note 4).

While this set-up is being prepared a solution of 20 g. (0.14 mole) of β-naphthylamine in 250 cc. of isoamyl alcohol (dried by distilling off a moist forerun) is heated to boiling. The boiling solution is poured in a stream through the separatory funnel into the flask upon the sodium and then washed down with 50 cc. of boiling isoamyl alcohol. A very violent reaction begins immediately which slows up after about five minutes and then must be aided by warming. The flame is so regulated that the reaction mixture is always boiling very vigorously until all the sodium is dissolved. This generally requires about three or four hours. If after three hours the sodium is not completely dissolved it is advisable, in order to hasten the reaction, to add 50 cc. more of isoamyl alcohol.

When all the sodium is completely dissolved, the hot, yellow solution is allowed to cool to about 100° and then poured into 500 cc. of cold water. The mixture is allowed to cool completely with frequent shaking, and then the upper isoamyl alcohol layer is separated from the water layer which contains the principal part of the sodium hydroxide.

The reduction is repeated four times with 20 g. of β-naphthylamine so that altogether 100 g. of naphthylamine has been reduced (Note 5). The isoamyl alcohol solutions from all five portions are combined, and concentrated hydrochloric acid is added until the solution is just acid to litmus. For this purpose usually about 40–50 cc. is needed

(Note 6). The greater part of the isoamyl alcohol is now distilled from a large flask (about 900–1100 cc. is recovered). The distillation is continued until a crust of crystals starts to form, and the residue is then cooled and treated with 200–300 cc. of water and about 300 cc. of 50 per cent potassium hydroxide solution. The base which separates is extracted is the separatory funnel with four 400–500 cc. portions of ether and the ether extracts combined in a wide-necked flask.

The flask is set in ice water, and a rapid stream of carbon dioxide, which has previously passed through two wash bottles containing water (Note 7), is passed in. After about one-quarter hour the liquid begins to become cloudy, and soon after there follows a rather rapid separation of the carbonate of the strongly basic alicyclic compound; the aromatic base does not react but remains in solution. The carbondioxide is passed in continuously until no more carbonate separates; this requires about four to six hours. The carbonate is filtered by suction on a Büchner funnel and washed with a little dry ether. The filtrate is again treated with carbon dioxide; there is often obtained still more carbonate which is added to the precipitate (Note 8).

For further purification, the almost dry carbonate is dissolved in 500–600 cc. of 7 per cent acetic acid and the solution is filtered from the dark impurities. The clear, almost colorless solution is decomposed with a large excess of potassium hydroxide (about 200 cc. of a 50 per cent solution), whereupon the alicyclic base separates as a light-brown oil which collects on the surface of the water solution and is extracted as rapidly as possible by shaking three or four times with ether. The ether solution is dried for at least six hours with about 90–100 g. of potassium hydroxide (Note 9). The distillation of the ether is carried out most conveniently in a specially designed Claisen flask (Fig. 26) of 100–150 cc. capacity,

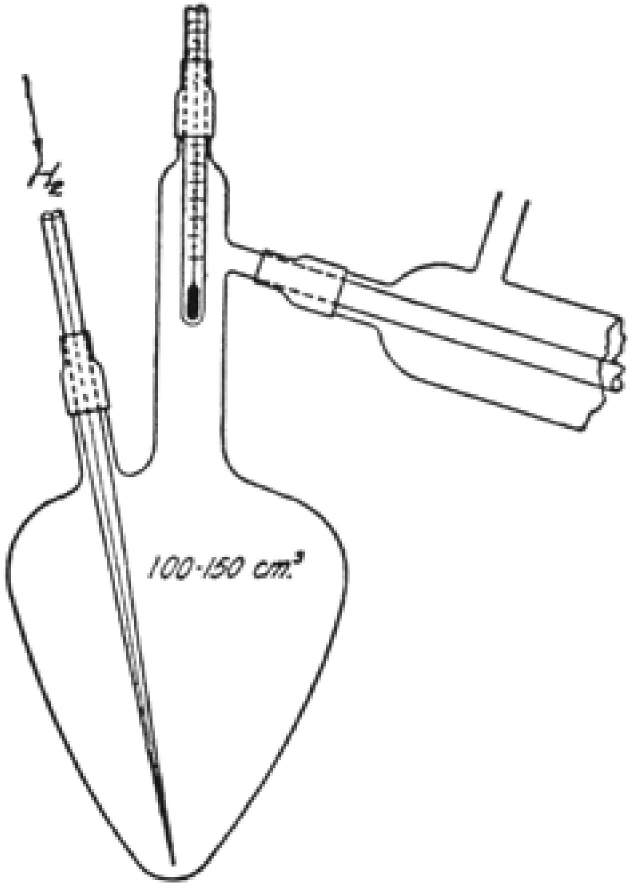
Fig. 26.

the ether solution gradually being added to the flask from the separatory funnel.

The base is distilled under the reduced pressure obtained by a water pump, because it is easily decomposed under ordinary pressure. For this distillation a flask of the form shown in Fig. 26 is recommended for use (Note 10) though it is not essential.

Since the base is sensitive to oxygen, dry hydrogen is passed through the capillary tube used in the distillation (Note 11). The distillation of the base runs very smoothly, and the liquid

distils over from beginning to end almost constantly within a degree.



The yield of pure distilled base, b.p. 118.5°/8 mm., 127.5–128°/12 mm., 140–140.5°/20 mm., amounts to 53–59 g. (51–57 per cent of the theoretical amount). The pure base can be preserved only by sealing it in ampules (containing as little air as possible) immediately after distillation. The *ac*-tetrahydro-β-naphthylamine is a colorless, water-clear liquid which shows no fluorescence (Note 12) and possesses a strong odor similar to piperidine. In the air the base soon turns brown, rapidly absorbs carbon dioxide, and changes to the carbonate.

The hydrochloride of the *ac*-tetrahydro-β-naphthylamine can be obtained readily by neutralizing a dry ether solution of the base with an ether solution of hydrogen chloride. It crystallizes from water in large plates which melt at 237° (Note 13) and (Note 14).

2. Notes

1. In place of the sand bath it is possible to use an ordinary wire gauze or a Babo's air bath, but the danger of a fire due to a sudden breaking of the flask during the very violent reaction at the beginning is considerably greater. The experiment is best carried out using a sand bath. The hands should be protected with gloves and the eyes with glasses.
2. After many experiments, this amount of sodium was found to be the optimum. By the use of smaller quantities of sodium and β-naphthylamine the yield drops; with larger amounts the danger of breaking the glass flask increases. It is probably possible to use copper flasks, but it is then impossible to see how the reaction is running.
3. The stopcock of the separatory funnel must have as wide a hole as possible so that the isoamyl alcohol can enter in a rapid stream.
4. If a water condenser is used the condensation is much more efficient but the danger of breaking is then much greater. A brass inner tube in place of a glass one is desirable. If the condenser tube is too narrow, there is danger that the violently boiling isoamyl alcohol will be thrown out at the beginning of the reaction because it cannot flow back.
5. By working up less than 100 g. of β-naphthylamine the yield decreases rather rapidly on account of the various possibilities for loss in the later operations.

6. An excess of acid does no harm but makes the recovery of the isoamyl alcohol more difficult.

7. If an efficient reflux condenser is attached to the flask the major part of the ether can be recovered. It is necessary to be sure that the carbon dioxide is actually moist because otherwise the carbonate will not form at all or only very slowly.

8. The ether filtrates contain dihydronaphthalene and *ar*-tetrahydro-β-naphthylamine.

9. Since the free base reacts very strongly alkaline and also is sensitive, it is not possible to allow it to remain long in the air or loss will occur due to carbonate formation and oxidation.

10. The suggested flask has the following advantages over other forms:
(*a*) The chance for contaminating the boiling base with rubber is reduced to a minimum; the capillary and thermometer are attached to the distillation flask by means of small rubber tubing.
(*b*) The loss due to the substance which remains on the walls of the flask is reduced to a minimum as compared to other flasks.
(*c*) The substances can, with the help of the capillary, be distilled over to the last drop, which is not possible in a round flask.

11. This apparatus has also proved itself very useful for the distillation of other substances sensitive to oxygen.

12. Fluorescence arises from aromatic by-products which, however, can be entirely separated by careful work. Pure *ac*-tetrahydro-β-naphthylamine gives no color with diazobenzenesulfonic acid.

13. According to Allewelt and Day, J. Org. Chem. **6**, 386 (1941), the crude hydrochloride can be obtained in an almost colorless condition by shaking it with 150–200 cc. of ether in the cold.

14. Of special interest is the extremely powerful physiological action of the tetrahydro base and its salts,[1] which makes it advisable to handle it carefully. The action can be called a symptom-complex to which Barger has assigned the name, "sympathomimetic," and it consists in a maximum dilation of the pupils (mydriasis), in a marked increase in the arterial blood pressure, and in an increase in the rapidity of breathing.

3. Discussion

ac-Tetrahydro-β-naphthylamine can be prepared by the reduction of β-naphthylamine with sodium and alcohol, a method first described by Bamberger and Müller.[2] It is possible to substitute ethyl alcohol for amyl alcohol, but the yield is distinctly lower. The base has been obtained recently in good yield by hydrogenation of β-naphthylamine using a nickel catalyst.[3]

References and Notes

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3. Adkins and Cramer, J. Am. Chem. Soc. **52**, 4349 (1930).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ac-Tetrahydro-β-naphthylamine

hydrochloride of the ac-tetrahydro-β-naphthylamine

ar-tetrahydro-β-naphthylamine

ethyl alcohol, alcohol (64-17-5)

hydrogen chloride, hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

oxygen (7782-44-7)

carbon dioxide, carbondioxide (124-38-9)

nickel (7440-02-0)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

piperidine (110-89-4)

2-Naphthylamine, 1,2,3,4-tetrahydro- (2954-50-9)

isoamyl alcohol (123-51-3)

naphthylamine (134-32-7)

dihydronaphthalene

diazobenzenesulfonic acid

amyl alcohol (71-41-0)

β-naphthylamine (91-59-8)

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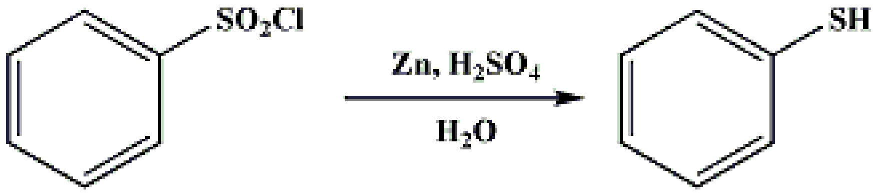
Organic Syntheses, CV 1, 504

THIOPHENOL

[Benzenethiol]



Submitted by Roger Adams and C. S. Marvel.
Checked by H. T. Clarke and Katharine Ogden.

1. Procedure

In a 12-l. round-bottomed flask are placed 7.2 kg. of cracked ice and 2.4 kg. (1300 cc., 23.4 moles) of concentrated sulfuric acid (sp. gr. 1.84). The mixture becomes very cold and is kept at –5° to 0° by means of an ice-salt bath. Mechanical stirring is started and 600 g. (3.4 moles) of crude benzenesulfonyl chloride (p. 84) is gradually introduced (one-half hour) (Note 1). Then 1.2 kg. (16.5 atoms) of zinc dust (90 per cent) is added (Note 2) in portions as rapidly as possible without allowing the temperature to rise above that mentioned (this requires about one-half hour) (Note 3). The contents of the flask are stirred for one to one and one-half hours longer, the temperature being kept at 0° or below during the whole period. A stopper holding an efficient reflux condenser (lower end not constricted) and stirrer is now attached; the ice bath is removed (Note 4); and the reaction mixture is allowed to warm up spontaneously or it may be warmed up with a low flame, the stirring being continued. Within a very few (two to five) minutes, in many runs, a rather vigorous reaction with the evolution of much hydrogen takes place. Under these circumstances it is advisable to cool the flask momentarily by a stream of water. The reflux condenser will, however, generally take care of the vapors satisfactorily.

After the first ebullition has subsided, no further attention is required, and the mixture is heated to boiling over a ring burner until the solution becomes clear. The stirring should be continued during the refluxing, and the stirrer should be arranged so as to suck the liquid downward from the surface. This helps distribute the zinc which holds hydrogen and floats on top of the liquid. About four to seven hours are required for the heating (Note 5). The thiophenol is then distilled with steam, this process requiring about one hour. The product is separated from the water, dried with calcium chloride (shaking with calcium chloride for three to five minutes is generally sufficient), and distilled. The crude material weighs 359 g. (96 per cent of the theoretical amount), and the pure compound boiling at 166–169° (71°/15mm.) weighs 340 g. (91 per cent of the theoretical amount). Ten to twelve hours are required for the whole experiment up to the final distillation.

2. Notes

1. Since benzenesulfonyl chloride solidifies at 15°, it is necessary to add it to the sulfuric acid slowly, with stirring, so that it will be as finely divided as possible when the zinc is added.

2. The directions given in the literature advise the addition of the zinc dust to the sulfuric acid and then the addition of the benzenesulfonyl chloride. This procedure has been reversed in the way described above so that the minimum amount of hydrogen will be lost during the addition of the zinc.

3. It is essential that the temperature during the first part of the reaction be kept at 0° or below, for otherwise poor yields are obtained. In order to hold the temperature at 0°, it is absolutely essential to add the zinc dust at least as slowly as described.

4. After the initial reaction at a low temperature had taken place, it was, in several instances, found convenient to allow the reaction mixture to stand overnight before proceeding further. The flask was thus left in the ice, which gradually melted, allowing the reaction mixture to warm up to room temperature. Under these conditions, however, a poor yield generally resulted. Upon closer study, it was discovered that the small amount of product obtained was due to the sudden vigorous reaction, with consequent loss through the condenser, which took place when a certain temperature was reached. The reaction mixture may be safely allowed to stand only if a very efficient condenser is used. In the checking of this experiment, no sudden reaction was observed, and heating with a small flame after the initial mixing and stirring at 0° gave excellent results. The difference in the experiments may have been due to a slightly different grade of raw materials.

5. Vigorous stirring while the reaction mixture is heated reduces materially the time of the reduction (from twelve to seven hours or less), as it brings the zinc, which otherwise floats, into intimate contact with the acid and sulfonyl chloride.

3. Discussion

Two general methods are available for the preparation of thiophenols. The first is by the treatment of aryldiazonium chlorides with potassium ethyl xanthogenate and then heating with alkali to give thiophenols.[1] This reaction has been used for the preparation of a large number of thiophenols, but it suffers from the disadvantage of having many side-reactions and in the danger of occasional violent explosions[2] when conditions are not correct. The second method involving the reduction of sulfonyl chlorides by zinc dust and sulfuric acid,[3] although limited to sulfonyl chlorides not having another group such as nitro which might be reduced, gives better yields of pure product than the xanthogenate process and avoids ether extraction and treatment with alcoholic potassium hydroxide. Thiophenol itself has also been prepared from diphenyl sulfide[4] and from chlorobenzene[5] by heating with aqueous sodium sulfide under pressure.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 695

References and Notes

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5. Vorozhtzov, Jr., and Mitzengendler, Russ. pat. 34,554 [C. A. **29**, 2977 (1935)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfonyl chloride

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

ether (60-29-7)

hydrogen (1333-74-0)

Benzenesulfonyl chloride (98-09-9)

chlorobenzene (108-90-7)

potassium hydroxide (1310-58-3)

zinc (7440-66-6)

sodium sulfide (1313-82-2)

Thiophenol, Benzenethiol (108-98-5)

potassium ethyl xanthogenate (140-89-6)

xanthogenate

Diphenyl sulfide (139-66-2)

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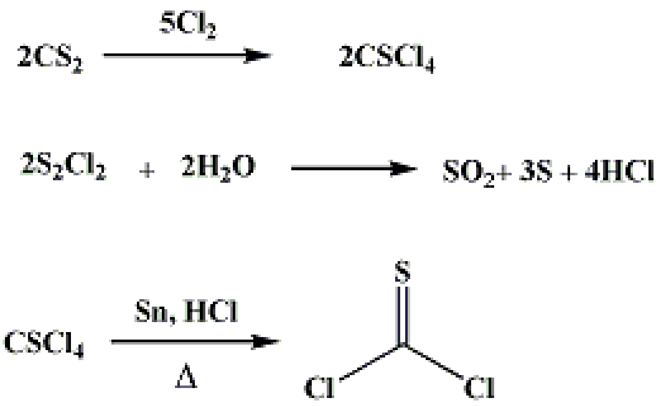
Organic Syntheses, CV 1, 506

THIOPHOSGENE



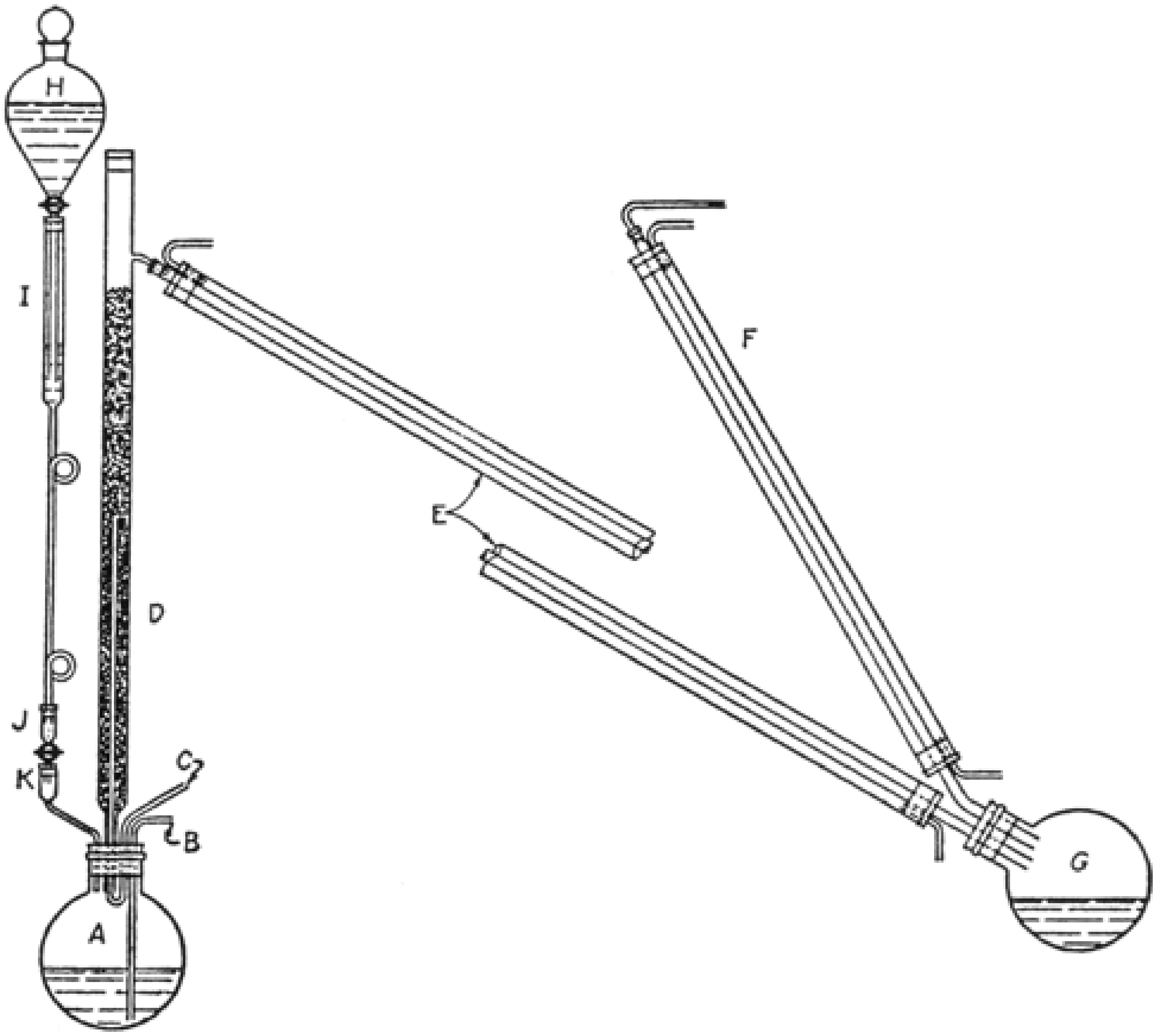
Submitted by G. Malcolm Dyson
Checked by Frank C. Whitmore and A. M. Griswold.

1. Procedure

(*A*) *Preparation of Thiocarbonyl Perchloride*.—In a 5-l. bottle arranged for cooling by running water is placed 500 g. (398 cc., 6.58 moles) of dry carbon disulfide (Note 1) to which 0.5 g. of iodine has been added. Dry chlorine is passed into the cooled carbon disulfide at such a rate that the temperature does not rise above 25°, until the liquid weighs 1770 g. (17.9 moles of chlorine) (Note 2). The time required is about forty hours. The product, a mixture of impure thiocarbonyl perchloride and sulfur chloride, is a deep red liquid.

The apparatus illustrated in Fig. 27 is assembled, in a large hood if possible (Note 3). A is a 5-l. round-bottomed flask heated by a large ring burner and provided with a specially treated four-holed cork stopper covered with tin foil (Note 4). To these holes are fitted the column D, the tube B reaching to the bottom of A, the specially bent tube C reaching up the inside of D, and the tube K connected with the tubes leading to the 2-l. separatory funnel H, so that the distance between the stopper of A and the stopcock of H is at least 100 cm. The bottom of the column D is of 20-mm. bore; the main portion is of 30 mm.

Fig. 27.



The side arm should be at least 85 cm. above the stopper of A. The tube C should reach about half way up the inside of the column D. The column is filled with pieces of 3-mm. glass tubing about 5 mm. long. Its top is provided with a cork covered with tin foil and fitted fairly loosely so as to blow out in case of a clogging of the apparatus. It should be held by a wire to prevent its being blown out entirely. Tubes B and C are connected with a steam line or steam generator of large capacity. The separatory funnel H is placed at the highest available level (Note 5) and connected with the tubes I, J, and K in such a manner as to secure a pressure of liquid sufficient to more than balance the steam pressure (Note 6). E and F are specially constructed condensers of unusual length (160 cm. and 85 cm., respectively) and bore (40 mm.) made from large glass tubing and rubber stoppers (Note 7). The top of condenser F is connected to a good draft chamber or to a gas-absorption trap (Fig. 7 on p. 97). G is a 5-l., or better, a 12-l. round-bottomed flask which is used as a receiver.

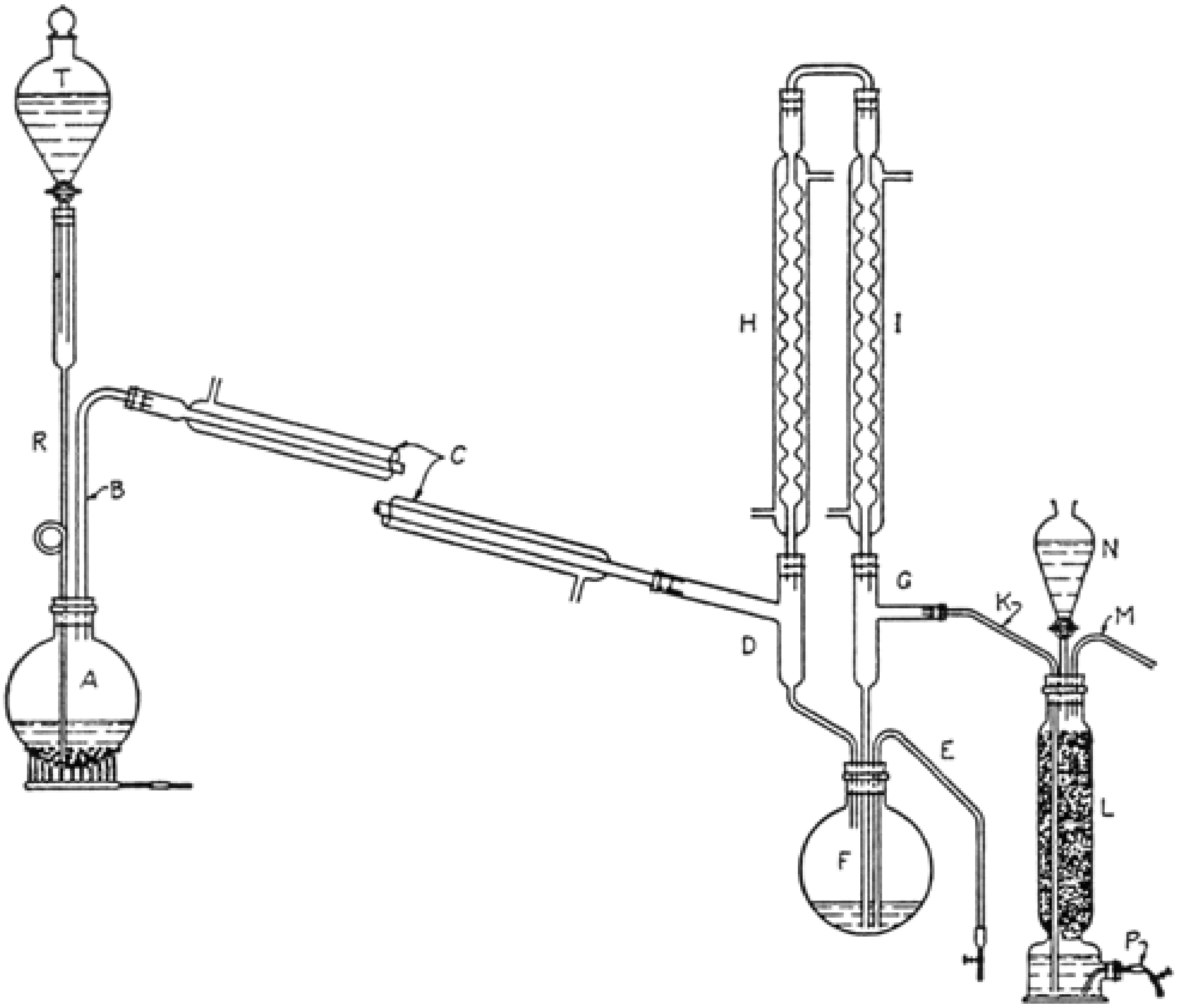
The crude chlorinated mixture is steam-distilled in this special apparatus to obtain thiocarbonyl perchloride and to decompose the sulfur chloride. In flask A is placed 1210 cc. of water which is heated to boiling by means of the ring burner. Steam is passed in through tubes B and C. The chlorinated mixture is placed in the separatory funnel H, and the connecting tubes are filled with the liquid which is allowed to pass into A at about 5 drops per second (Note 8). Sulfur begins to separate in the column and in the condensers. The steam distillation requires about five hours and gives 10–12 l. of distillate consisting of

water, sulfur, and a heavy red oil. The water is decanted and the rest of the mixture is filtered by suction through glass wool. The oil is separated and dried over about 10 g. of calcium chloride.

The crude, dry thiocarbonyl perchloride is distilled through an efficient 60-cm. column (Note 9). The distillate below 140° is discarded. The fraction boiling at 140–155° at atmospheric pressure amounts to about 600 g. The boiling point of pure thiocarbonyl perchloride is 149°.

(*B*) *Reduction of Thiocarbonyl Perchloride to Thiophosgene*.—The apparatus illustrated in Fig. 28 is assembled. A is a 5-l. round-bottomed flask heated by a ring burner and provided with a two-holed, specially treated cork (Note 4) carrying tube B of about 40-cm. length connected with condenser C of about 115-cm. length, and tube R which conveys the perchloride from the separatory funnel T (Note 6). R is 6-mm. tubing of about 90-cm. length and must reach to the bottom of A. D and G are specially blown connecting tubes, D reaching through the cork of F and G reaching to the bottom of the 5-l. flask, F. Each arm of D is about 20 cm. long and of 2-cm. bore. The vertical arm of G is of about 3-cm. bore and its side arm of about 1-cm. bore. H and I are efficient bulb condensers at least 60 cm. long. F is provided with siphon E for removing the product. L is a tall tower (about 50 cm. in length) packed with short pieces of glass tubing alternating with layers of glass wool. Its stopper carries the tube K reaching to the bottom of the tower, a separatory funnel, and an exit tube M leading to the draft. P is a siphon for removing the xylene wash liquid.

Fig. 28.



In the flask A are placed 750 g. (6.3 atoms) of granulated tin (Note 10) and 1500 cc. of commercial hydrochloric acid (about 28 per cent). The mixture is heated until the action is vigorous. The thiocarbonyl perchloride is run in from the funnel T (Note 11). The resulting reaction is very violent. The vapors are condensed in the series of condensers and in the scrubber L through which xylene is allowed to flow slowly from the separatory funnel N. Most of the crude thiophosgene collects in F, although a small amount is obtained from the distillation of the xylene wash liquid.

The crude thiophosgene is separated and dried with about 10 g. of calcium chloride, and fractionated with a good column. Very little distils below 73°. The fraction boiling at 73–76° at atmospheric pressure is pure thiophosgene and amounts to about 180 g. (24 per cent of the theoretical amount) (Note 12). The fraction above 76° is largely thiocarbonyl perchloride and may be again reduced or added to the reduction in a subsequent run.

2. Notes

1. Ordinary commercial carbon disulfide was used after drying over calcium chloride.
2. Any great excess of chlorine should be avoided as it favors the formation of carbon tetrachloride. Practically as good yields have been obtained by using only about three-fourths the amount of chlorine indicated.
3. The vapors formed in the experiment are very objectionable. It is even advisable to

transfer the liquids from one vessel to another by suction rather than by pouring in order to avoid the irritating and lachrymatory effects of the vapors.
Decided care should be exercised in the handling of thiophosgene because of its high toxicity.
4. It is advisable to saturate all corks with sodium silicate solution after fitting and boring them (Note 1 on p. 17). They are then covered with lead foil, wired in, and coated with shellac.
5. As long a column of liquid as possible is used to overcome the tendency for steam to work back up the inlet tube. If this happens, the sulfur formed is likely to clog the tube. This can be avoided by proper manipulation of the stopcock J.
6. The backing of steam up the inlet tube is one of the most serious difficulties in the experiment. This can be avoided if the tube I (Fig. 27) is once filled with the perchloride.
7. No ordinary condenser was found sufficiently effective to condense the vapors and not be clogged by the sulfur. The specially constructed wide condensers are absolutely necessary.
8. If the addition is much more rapid than this, not all the sulfur chloride is decomposed.
9. The distillation of the crude perchloride is necessary to remove carbon tetrachloride and other low-boiling impurities which could not later be separated from the thiophosgene by distillation.
10. The tin used should be in fairly large granules; otherwise the reaction is likely to become too violent. In general, the faster the reduction the better the yield of thiophosgene. In a few cases yields of 50–60 per cent have been obtained.
11. The time of addition of the perchloride should be made as short as possible consistent with safety. In runs with the above amounts of materials, the time of the addition was about ten minutes. It may again be emphasized that the yield in this reaction depends largely on the skill of the operator in running the reduction as rapidly as possible.
12. As has been stated, larger yields are occasionally obtained, but they cannot be depended on.

3. Discussion

Thiophosgene can be prepared by the reduction of thiocarbonyl perchloride.[1] A simpler method for preparing the intermediate thiocarbonyl perchloride has been described.[2] Compare Autenrieth and Hefner, Reference 1.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 165

References and Notes

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[Chem. Zentr. II, 987 (1928)]; Autenrieth and Hefner, Ber. **58**, 2153 (1925).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Thiocarbonyl Perchloride

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

sodium silicate

carbon tetrachloride (56-23-5)

tin (7440-31-5)

sulfur (7704-34-9)

iodine (7553-56-2)

chlorine (7782-50-5)

carbon disulfide (75-15-0)

Thiophosgene (463-71-8)

xylene (106-42-3)

sulfur chloride

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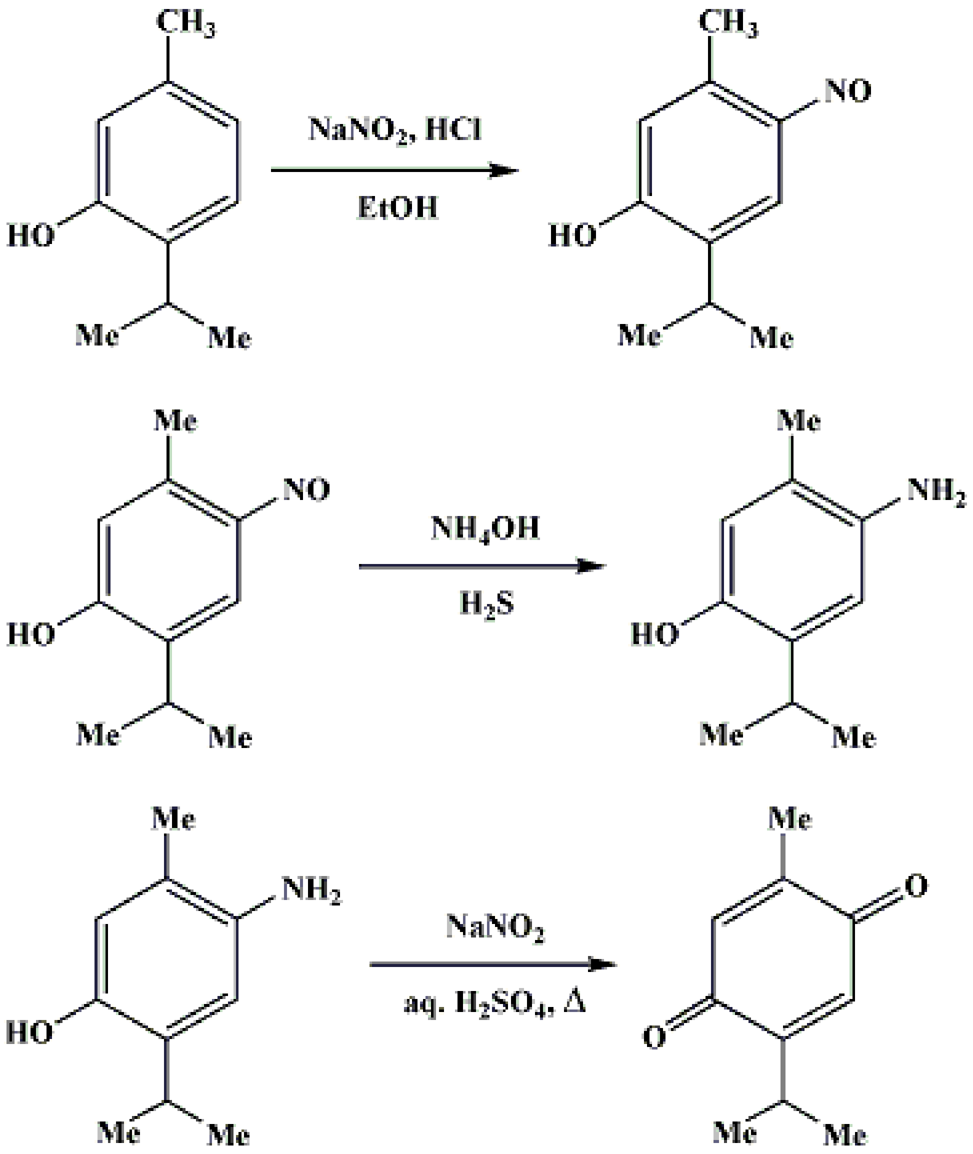
Organic Syntheses, CV 1, 511

THYMOQUINONE



Submitted by Edward Kremers, Nellie Wakeman, and R. M. Hixon.
Checked by H. T. Clarke and C. R. Noller.

1. Procedure

(*A*) *Nitrosothymol*.—To a solution of 100 g. (0.66 mole) of thymol in 500 cc. of 95 per cent ethyl alcohol is added 500 cc. of concentrated hydrochloric acid. This mixture is cooled to 0° in a 2-l. beaker set in an ice-salt bath, and to it is added 72 g. (1 mole) of commercial sodium nitrite in portions of about 5 g. each.

The mixture is stirred well after each addition (Note 1). The solution first becomes brown in color, and a green precipitate soon begins to form. After 35 g. of nitrite has been added, the mixture becomes pasty; the intervals between the additions must now be lengthened and the stirring made more vigorous. When all has been added, the bulk

of the product is transferred to a 12-l. flask containing 8 l. of cold water, and the remainder washed in with water. The product, after agitation with water, is now a light-yellow, fluffy solid; it is filtered off by suction and washed well with water (Note 2).

(*B*) *Aminothymol*.—The crude, wet nitrosothymol so obtained is worked up with a mixture of 900 cc. of 28 per cent aqueous ammonia (sp. gr. 0.90) and 1600 cc. of water; the brown solution is filtered free of a little resinous matter, and hydrogen sulfide is passed into it. The brown color disappears and a white precipitate of aminothymol forms. The passage of hydrogen sulfide is continued for thirty minutes longer (Note 3), when the base is filtered and washed well with cold water, contact with air being avoided as far as possible (Note 4).

(*C*) *Thymoquinone*.—The wet aminothymol thus prepared is immediately dissolved in 110 cc. of concentrated sulfuric acid diluted to 4 l. and contained in a 12-l. flask. To this solution is added 150 g. (2.08 moles) of sodium nitrite, in 5–10 g. portions, with shaking after each addition. The resulting mixture is heated to 60° on a steam bath, with occasional shaking, for one-half hour (Note 5), and is then distilled in a current of steam, by means of the apparatus described on p. 479 (Note 6). All the thymoquinone passes over with the first 3 l. of distillate; it solidifies on cooling, and is filtered with suction (Note 7), washed, and dried at room temperature. The yield is 80–87 g. (73–80 per cent of the theoretical amount) of bright yellow crystals, melting at 43–45° (Note 8).

2. Notes

1. No nitrous acid escapes from the mixture, since it is converted into ethyl nitrite which in turn reacts with the thymol.
2. The crude nitrosothymol may be purified by drying and subsequent recrystallization from 2 l. of benzene, from which it separates as a pale yellow solid, melting at 160–164°. A small second crop is obtained on concentrating the mother liquor, which contains in addition an orange-colored resinous impurity. The yield is 103 g. (87 per cent of the theoretical amount).
3. If the base is filtered off without passing in the excess of hydrogen sulfide, it immediately assumes a purple color on exposure to air.
4. The free base tends to become oxidized in the air but may be preserved as the hydrochloride. This is prepared by transferring it as soon as possible to 1500 cc. of distilled water containing 100 cc. of concentrated hydrochloric acid. The sparingly soluble hydrochloride separates at once. It is recrystallized from the mixture with the use of a little decolorizing carbon, whereupon it separates as colorless needles. A further crop is obtained on concentrating the mother liquor under reduced pressure to about 200 cc. The yield is 110 g. (82.1) per cent of the theoretical amount).
5. The greater part of the oxides of nitrogen escapes during this treatment; the small amount that passes over with the thymoquinone does not harm the product.
6. If an ordinary condenser is employed for the steam distillation, care must be

taken that the distilled product does not crystallize in the condenser tube and clog it.
7. The watery filtrate contains about 0.5 g. of dissolved thymoquinone; this can be recovered by distilling over 500 cc. of it and filtering the distillate.
8. The melting point is not appreciably raised by recrystallization from petroleum ether (b.p. 60–80°).

3. Discussion

Thymoquinone can be prepared directly from thymol by sulfonating and oxidizing the sulfonation mixture with manganese dioxide[1] or potassium dichromate;[2] the same process has been successfully employed with carvacrol.[3] The oxidation of salts of aminothymol with dichromate,[4] ferric chloride,[5] or nascent bromine[6] leads to satisfactory yields of thymoquinone, as does prolonged refluxing of nitrosothymol with dilute hydrochloric acid.[7] The procedure described is based on the observation[8] that the diazonium salt obtained from aminothymol is almost quantitatively converted into thymoquinone on warming in the presence of excess nitrous acid.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

oxides of nitrogen

petroleum ether

salts of aminothymol

nascent bromine

diazonium salt obtained from aminothymol

ethyl alcohol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

Benzene (71-43-2)

hydrogen sulfide (7783-06-4)

sodium nitrite (7632-00-0)

nitrous acid (7782-77-6)

nitrite (14797-65-0)

decolorizing carbon (7782-42-5)

manganese dioxide (1313-13-9)

ferric chloride (7705-08-0)

ethyl nitrite (109-95-5)

potassium dichromate (7778-50-9)

Thymoquinone (490-91-5)

Nitrosothymol (2364-54-7)

thymol (89-83-8)

Aminothymol

carvacrol (499-75-2)

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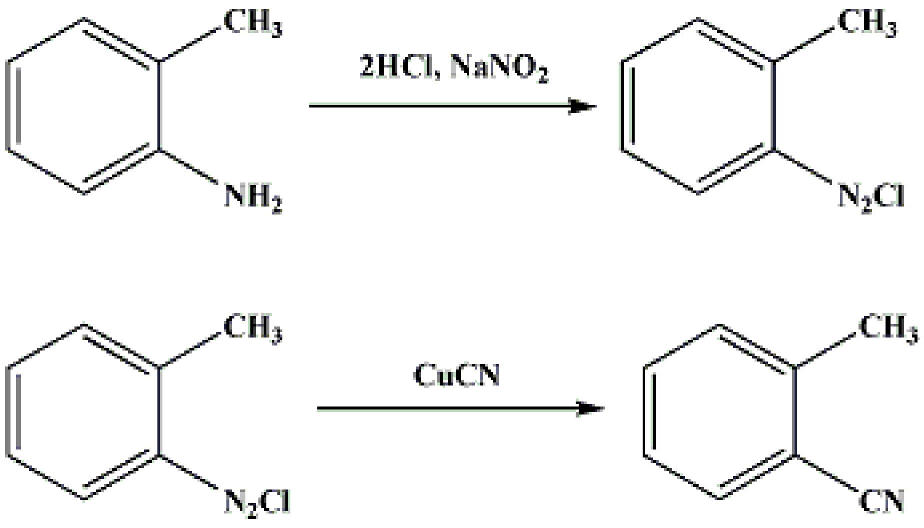
Organic Syntheses, CV 1, 514

o-TOLUNITRILE AND *p*-TOLUNITRILE



Submitted by H. T. Clarke and R. R. Read.
Checked by C. S. Marvel and M. M. Brubaker.

1. Procedure

(*A*) *Preparation of Cuprous Cyanide Solution.*—Cuprous chloride prepared from 1250 g. (5 moles) of crystallized copper sulfate, according to the directions given on p. 170, is suspended in 2 l. of cold water in a 15-l. crock fitted with a mechanical stirrer. A solution of 650 g. (12.7–13 moles) of sodium cyanide (96–98 per cent) in 1 l. of water is added and the mixture stirred, whereupon the cuprous chloride enters into solution with considerable evolution of heat (Note 1). The mixture is then cooled by surrounding the crock with cold water (Note 2).

(*B*) *o-Tolunitrile.*—While the cuprous cyanide solution is cooling, 428 g. (427 cc., 4 moles) of *o*-toluidine is mixed in a 20-l. crock with 1 l. of commercial 28 per cent hydrochloric acid (sp. gr. 1.14) and enough cracked ice, about 4 kg., to bring the temperature of the mixture to 0°. A solution of 280 g. (4.06 moles) of sodium nitrite in 800 cc. of water is added, with stirring, to the resulting suspension of *o*-toluidine hydrochloride, the temperature being kept at 0–5° by the addition of cracked ice. The addition of the nitrite occupies about fifteen minutes; at the end of the operation, the mixture must show a distinct and permanent reaction for free nitrous acid on testing with starch-iodide paper (Note 3). The final volume of the solution is 5–6 l. The mixture is now cautiously neutralized by adding dry sodium carbonate with constant stirring, using litmus paper to determine the end-point; about 200 g. of the anhydrous carbonate is required (Note 4).

The cold cuprous cyanide solution is now chilled to 0–5° by the addition of ice, and 1 l. of benzene (Note 5) is poured on the surface. To this mixture is slowly added the

cold neutralized diazonium solution. During the addition, which occupies about thirty minutes, such vigorous stirring is maintained that the benzene on the surface is constantly drawn to the stirrer, and the temperature is maintained at 0–5° by occasionally adding ice. As soon as the diazonium solution comes into contact with the cuprous cyanide, a dark yellow, oily precipitate is formed which at once begins to give off nitrogen; the resulting nitrile is taken up by the benzene as soon as it is formed (Note 6). When all has been added, the temperature is held at 0–5° for thirty minutes longer, and then is allowed to rise to that of the room (20–25°), which usually requires about three hours.

After stirring has been continued for two hours longer, the crock is surrounded by hot water or steam and warmed to 50° without stirring. The mixture is then allowed to stand until cool, when the aqueous layer is drawn off by means of a siphon. The upper oily layer is transferred to a 12-l. flask and distilled in a current of steam until no more oil passes over; about 10 l. of distillate is collected (Note 7). The water is drawn off and the benzene removed by distillation, by means of a 2-l. round-bottomed flask and a fractionating column about 90 cm. long. When benzene no longer distils over, the distillation is continued in the same apparatus under reduced pressure, and the fraction that boils at 94–96°/20 mm. is collected. A small amount of dark-colored residue remains in the flask. The yield of almost colorless *o*-tolunitrile is 300–330 g. (64–70 per cent of the theoretical amount).

(*C*) *p-Tolunitrile*.—*p*-Tolunitrile can be prepared in exactly the same manner from *p*-toluidine; the product, which distils at 104–106°/20 mm., solidifies in the receiver to a mass of nearly colorless needles which melt at 25–27°. The yield is the same as with the ortho compound (Note 8).

2. Notes

1. If desired, the cuprous chloride may be suspended in 3 l. of water and the sodium cyanide added in the solid form.
2. If several runs are to be made it may be more convenient to prepare a large quantity of cuprous cyanide solution, since this appears to be stable for several days.
3. If the sodium nitrite is not of the highest technical purity it may be necessary to employ more than the indicated quantity. It is essential that the test for nitrous acid be permanent; if any unchanged amine remains, a precipitate of the diazoamino compound is formed on neutralization. A moderate excess of nitrite does not appear to interfere with the reaction, especially since the greater portion of the free nitrous acid is removed by the carbon dioxide liberated on neutralization.
4. Sodium carbonate is preferable to sodium hydroxide because very little heat is evolved on neutralization. A slight excess of carbonate does not appear to be harmful.
5. It is suggested that 1 l. of toluene be used instead of benzene. Since the benzene freezes at 0° to 4° it does not extract the nitrile until it melts much later

in the procedure. (R. L. Shriner, private communication.)
6. It is essential that the stirring be very vigorous. If the intermediate addition compound is allowed to collect on the surface of the liquid, it decomposes spontaneously with the evolution of much heat; this decomposition may take place with almost explosive violence. The presence of the benzene tends to diminish the viscosity of the intermediate product and permit it to be readily distributed throughout the mixture. Decomposition is quite rapid at 0° and is practically complete when room temperature is reached; it appears, however, to be advisable to warm the mixture to 50°, since if this is omitted the yield is slightly decreased.
7. The apparatus described on p. 479 is suitable for the steam distillation.
8. The product, as obtained in the above procedure, is of high purity; cresols do not appear to be formed under the conditions specified. The process has the advantage over that described in the literature[1] of giving rise to no poisonous fumes during the formation of the cuprous cyanide and during the interaction of this with the diazonium salt. The yield is practically the same as in the older method.

3. Discussion

o- and *p*-Tolunitriles can be prepared by the interaction of the corresponding diazonium solutions with cuprous cyanide,[2] or alkali cupric diammino-cyanide.[3] Nickel cyanide is said to be better than copper cyanide in the preparation of nitriles by the Sandmeyer reaction.[4] A mixture of *o*- and, predominantly, *p*-tolunitrile is obtained by treating toluene with trichloroacetonitrile and aluminum chloride, then cleaving the resulting ketimines with alkali.[5] *p*-Tolunitrile can be prepared from the corresponding amide by heating it with the double salt of aluminum chloride and sodium chloride.[6]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 586
- Org. Syn. Coll. Vol. 2, 588
- Org. Syn. Coll. Vol. 3, 626
- Org. Syn. Coll. Vol. 5, 480

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

cresols

alkali cupric diammino-cyanide

double salt of aluminum chloride

o- and p-Tolunitriles

o- and, predominantly, p-tolunitrile

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

sodium hydroxide (1310-73-2)

sodium cyanide (143-33-9)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

carbonate (3812-32-6)

nitrogen (7727-37-9)

Cuprous Cyanide (544-92-3)

copper sulfate (7758-98-7)

sodium nitrite (7632-00-0)

nitrous acid (7782-77-6)

carbon dioxide (124-38-9)

aluminum chloride (3495-54-3)

toluene (108-88-3)

cuprous chloride (7758-89-6)

o-Tolunitrile (529-19-1)

p-Tolunitrile (104-85-8)

Nickel cyanide (557-19-7)

copper cyanide (544-92-3)

trichloroacetonitrile (545-06-2)

p-toluidine (106-49-0)

o-toluidine (95-53-4)

o-toluidine hydrochloride (636-21-5)

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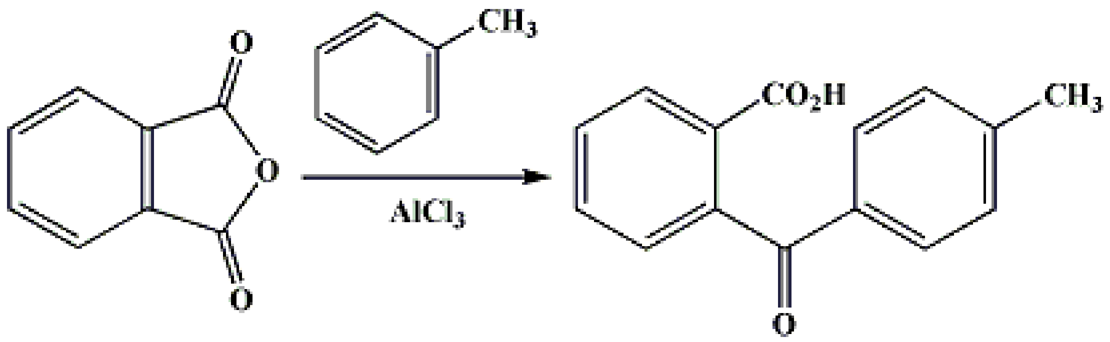
p-TOLUYL-*o*-BENZOIC ACID

[Benzoic acid, *o*-(*p*-toluyl)-]



Submitted by L. F. Fieser
Checked by Roger Adams and R. L. Shriner.

1. Procedure

A 2-l. round-bottomed flask is clamped to a ring stand and equipped with a rubber stopper carrying a glass stirrer with mercury seal, and a reflux condenser connected with a trap (Fig. 7 on p. 97) for removing the evolved hydrogen chloride.

One hundred grams (0.68 mole) of phthalic anhydride and 400 g. (462 cc., 4.35 moles) of toluene are placed in the flask, which is cooled in an ice bath while 200 g. (1.5 moles) of anhydrous aluminum chloride (Note 1) is being ground to a fine powder. The chloride is now added all at once (Note 2). Stirring is commenced at once, and the ice bath is removed. The mixture warms up considerably and becomes olive-green in color. When the evolution of hydrogen chloride begins to slacken (ten minutes) a water bath is put into place and heated to 90° in the course of forty-five minutes. The temperature of the bath is kept at 90° and vigorous stirring continued for two and one-half hours. At this point, the evolution of hydrogen chloride will have practically ceased and the reaction will have been completed. The hot water in the bath is replaced first by cold water and then by ice, while stirring is continued.

As soon as the flask is well cooled, it is disconnected and carried to the hood, and ice is slowly added, with shaking, until the dark mass is completely decomposed and the flask is about one-half filled with the mixture. After 150 cc. of crude concentrated hydrochloric acid has been added, the mass coagulates and the solution clears; the flask is then heated on the steam bath while preparations are being made for steam distillation.

This operation, which removes the excess of toluene, may be carried out in the same flask and loss by transfer thus avoided (Note 3). The aqueous solution of aluminum chloride and hydrochloric acid, after thorough cooling, is decanted through a suction filter, the residue washed with a little cold water, and that collected on the filter

returned to the flask. This residue consists almost solely of *p*-toluyl-*o*-benzoic acid, partly crystalline, partly in oily lumps.

A previously prepared and heated solution of 50 g. of sodium carbonate in 1 l. of water is added, and steam is passed in to provide heat and agitation. With a rapid stream, the acid will go into solution in about ten minutes, leaving a small amount of brown, tarry material and a little alumina undissolved (Note 4). The solution is filtered while hot and transferred to a 2-l. beaker, and the acid precipitated by the addition of 65 cc. of concentrated hydrochloric acid. The acid separates as an oil, which soon crystallizes. The solution is cooled in ice and the acid filtered and washed.

The air-dried product is pure white and weighs 170 g. (Note 5). After drying at 100°, the anhydrous acid melts at 138–139° and weighs 157 g. (96 per cent of the theoretical amount). Air-dried material is suitable for the condensation to β-methylanthraquinone, p. 353. It may be recrystallized from toluene.

2. Notes

1. Although statements are found in the literature that quantitive yields may be obtained with smaller quantities of aluminum chloride, the ratio $1C_6H_4(CO)_2O:2AlCl_3$ is essential.
2. Leakage of hydrogen chloride at any of the connections may be stopped with paraffin.
3. The steam distillation requires about fifteen minutes, and about 340–380 cc. of toluene is recovered.
4. If, in extracting the acid with sodium carbonate, more than 2–3 g. of material remains undissolved, the residue is treated with dilute hydrochloric acid to remove alumina, washed, and again extracted with a little carbonate solution. This extract is neutralized separately since some tar may separate with the *p*-toluyl-*o*-benzoic acid. In this event, it is filtered and extracted with *cold* carbonate solution, in which the tar is completely insoluble.
5. According to Limpricht,[1] the acid may crystallize either in hydrated or in the anhydrous condition, but the transition temperature is not stated. The loss of water upon drying at 100° shows the compound obtained in this experiment to be the monohydrate.

3. Discussion

p-Toluyl-*o*-benzoic acid can be prepared by the action of aluminum chloride on phthalic anhydride and toluene.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 353

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

p-Toluyl-o-benzoic acid

hydrogen chloride, hydrochloric acid (7647-01-0)

sodium carbonate (497-19-8)

phthalic anhydride (85-44-9)

aluminum chloride (3495-54-3)

toluene (108-88-3)

β-Methylanthraquinone (84-54-8)

Benzoic acid, o-(p-toluyl)- (7148-03-0)

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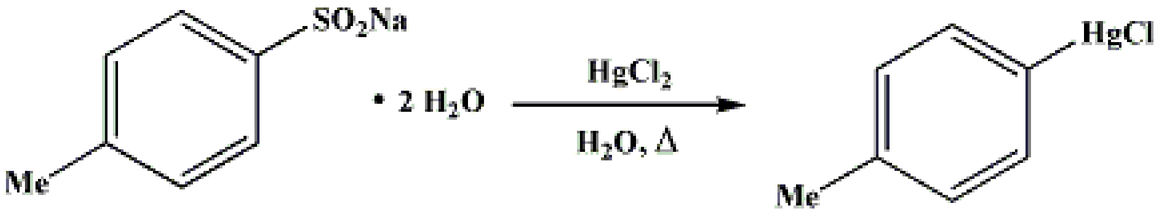
p-TOLYLMERCURIC CHLORIDE

[Mercury compounds. *p*-Tolylmercuric chloride]



Submitted by F. C. Whitmore, Frances H. Hamilton, and N. Thurman.
Checked by J. B. Conant and F. C. Whidden.

1. Procedure

To 1 l. of boiling water in a 3-l. beaker or large evaporating dish (Note 1) is added 150 g. (0.55 mole) of mercuric chloride; to this mixture is then added, with good stirring, 116 g. (0.54 mole) of sodium *p*-toluenesulfinate (p. 492). A thick, white, curdy precipitate forms at once (Note 2), and in a short time sulfur dioxide is evolved copiously. The heating and stirring are continued until no more sulfur dioxide is evolved, which requires about two hours.

The mixture is then filtered by suction, and the precipitate dried in an oven at about 80° for twelve hours. The dry precipitate is then placed in a 1-l. round-bottomed flask with reflux condenser, and covered with 800 cc. of xylene. The mixture is agitated by shaking, the xylene heated to boiling for five to ten minutes, and the solution filtered through a hot funnel to remove the calomel which is formed during the reaction (Note 2). The filtrate is cooled, the *p*-tolylmercuric chloride filtered off, and the undissolved portion extracted again with the filtrate (Note 3). This is repeated twice. In this way 90–100 g. (51–57 per cent of the theoretical amount) of a product which melts at 233° is obtained.

2. Notes

1. It is essential that the vessel employed should be of at least 3-l. capacity. If it is smaller, the contents will probably overflow during the first evolution of sulfur dioxide.
2. A large amount of calomel is formed in this reaction owing to the reduction of the mercuric chloride by the sulfurous acid formed. This reduction produces hydrochloric acid which probably changes some of the mercury compound to toluene and mercuric chloride. An attempt was made to avoid this action by adding sodium hydroxide slowly during the process to keep the solution from becoming strongly acid, but the yield was increased only slightly. The yield was not increased by adding the sulfinate to the mercuric chloride gradually or by

reversing this process.
3. There is always a considerable amount of inorganic mercury left in the filtrate, which gives very little more of the *p*-tolylmercuric chloride when treated with more of the sulfinate. This may be present largely in the form of the mercuric salt of *p*-toluenesulfonic acid produced by the oxidation of some of the sulfinic acid liberated in a side-reaction.

3. Discussion

p-Tolylmercuric chloride can be prepared from *p*-toluenesulfinic acid and mercuric chloride,[1] from *p*-toluenesulfonyl chloride and diphenylmercury at 120°,[2] by treating *p*-tolylboric acid with mercuric chloride, [3] by the direct mercuration of toluene with mercuric acetate,[4] from *p*-tolylmercuric nitrate and hydrochloric acid,[5] from hydrochloric acid and *p*-tolylmercuric hydroxide formed by the oxidation of di-*p*-tolylmercury,[6] from di-*p*-tolylmercury by heating with mercuric chloride in alcohol, [7] by heating the double salt of *p*-toluenediazonium chloride and mercuric chloride in acetone with copper powder,[8] and from *p*-toluenediazonium chloride and finely divided mercury.[9]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 159
- Org. Syn. Coll. Vol. 1, 231

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfinic acid

calomel

inorganic mercury

double salt of p-toluenediazonium chloride

alcohol (64-17-5)

hydrochloric acid (7647-01-0)

sodium hydroxide (1310-73-2)

sulfur dioxide (7446-09-5)

mercuric acetate (1600-27-7)

mercury (7439-97-6)

copper powder (7440-50-8)

acetone (67-64-1)

toluene (108-88-3)

mercuric chloride (7487-94-7)

p-tolylmercuric chloride (539-43-5)

xylene (106-42-3)

Diphenylmercury (587-85-9)

sulfurous acid (7782-99-2)

p-Toluenesulfonyl chloride (98-59-9)

p-Toluenesulfinic acid (536-57-2)

Sodium p-toluenesulfinate

DI-p-TOLYLMERCURY (537-64-4)

mercuric salt of p-toluenesulfonic acid

p-tolylboric acid

p-tolylmercuric nitrate

p-tolylmercuric hydroxide

p-toluenediazonium chloride

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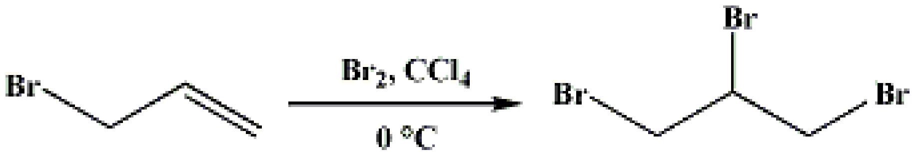
1,2,3-TRIBROMOPROPANE



Submitted by John R. Johnson and W. L. McEwen.
Checked by Roger Adams and L. T. Sandborn.

1. Procedure

A 1-l. round-bottomed flask is provided with a mechanical stirrer, a dropping funnel, a calcium chloride exit tube, and a thermometer which reaches nearly to the bottom of the flask. In the flask are placed 181.5 g. (1.5 moles) of allyl bromide (Note 1) and 250 cc. of dry carbon tetrachloride (Note 2). In the dropping funnel is placed 255 g. (80 cc., 1.56 moles) of bromine which has been washed once with an equal volume of concentrated sulfuric acid. The mechanical agitation is started and the flask is cooled in a mixture of ice and salt. When the temperature has fallen to –5°, the bromine is allowed to drop in slowly at such a rate that the temperature remains at about – 5° and never rises above 0° (Note 3). The addition of the bromine requires about one and one-half hours. The solution is usually orange-red in color at the end of the reaction, owing to the slight excess of bromine. It is allowed to warm up to room temperature with continuous stirring (about one-half hour) and is then transferred to a large separatory funnel. The flask is washed once with a 10–15 cc. portion of carbon tetrachloride.

A 500-cc. Claisen flask is arranged for distilling the solvent and the solution is dropped in from the funnel at such a rate that the flask is never more than two-thirds full. The Claisen flask is heated in an oil bath, and the carbon tetrachloride distils when the oil bath reaches about 120°. As much as possible of the solvent is removed at atmospheric pressure by allowing the temperature of the oil bath to rise to 150°. The remainder of the carbon tetrachloride is removed under a pressure of about 20 mm. by collecting a fraction until the thermometer registers a sudden rise (temperature of the oil bath about 120°).

The residue in the distilling flask is practically pure 1,2,3-tribromopropane (Note 4) and boils at 100–103°/18 mm. On cooling in an ice-salt mixture and scratching vigorously, the tribromopropane solidifies to a mass of white needles, which melt below room temperature. The yield is 406–413 g. (96–98 per cent of the theoretical amount). If an absolutely colorless product is desired, it is advisable to collect the first few drops of distillate separately, since they may be slightly yellow. The product on long standing becomes yellow, but when the colored product is used in reactions it gives yields that indicate a high degree of purity.

2. Notes

1. Allyl bromide (p. 27) was dried with calcium chloride and distilled through a fractionating column. The portion boiling at 69.5–71.5° was collected.
2. Carbon tetrachloride was purified by distilling the commercial product and rejecting the first 10 per cent of the distillate, thus eliminating the water.
3. A yield of 93 per cent of the theoretical amount is obtained when the reaction is run at a temperature of 25–30°. At the higher temperature, there is a small amount of high-boiling product left in the flask after the final distillation.
4. The crude 1,2,3-tribromopropane which remains after complete removal of the carbon tetrachloride weighs 418–420 g. It is almost pure and can be used for a number of reactions without further purification.

3. Discussion

1,2,3-Tribromopropane can be prepared by the action of phosphorus pentabromide on either epibromohydrin[1] or symmetrical dibromohydrin;[1,2] by the action of bromine, in the presence of iron, on propylene bromide;[3] by the addition of bromine to allyl bromide;[4] by the addition of hydrogen bromide to 1,3-dibromopropene;[5] and by the action of bromine and phosphorus on glycerol.[6] The procedure described is essentially that of Perkin and Simonsen.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 209

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

symmetrical dibromohydrin

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

glycerol (56-81-5)

iron (7439-89-6)

hydrogen bromide (10035-10-6)

bromine (7726-95-6)

Allyl bromide (106-95-6)

propylene bromide (78-75-1)

PHOSPHORUS (7723-14-0)

carbon tetrachloride (56-23-5)

1,2,3-Tribromopropane (96-11-7)

tribromopropane

phosphorus pentabromide (7789-69-7)

Epibromohydrin (3132-64-7)

1,3-dibromopropene

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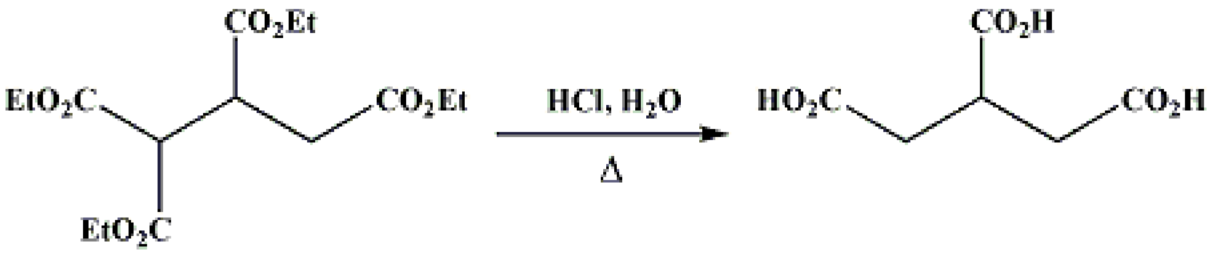
Organic Syntheses, CV 1, 523

TRICARBALLYLIC ACID



Submitted by H. T. Clarke and T. F. Murray.
Checked by C. S. Marvel and M. M. Brubaker.

1. Procedure

In a 3-l. flask, fitted with a stirrer and a fractionating column with condenser for downward distillation, are placed 912 g. (815 cc., 2.75 moles) of ethyl propane-1,1,2,3-tetracarboxylate (p. 272) and 950 cc. of a solution of equal volumes of pure concentrated hydrochloric acid and distilled water. A receiver with a side tube is attached to the condenser; this side tube leads to a water trap. The mixture is boiled, with continual stirring, at such a rate that the alcohol is removed as fast as it is formed, but without undue removal of water from the flask (Note 1). The progress of the reaction can be followed by noting the rate at which carbon dioxide passes through the trap. When the temperature at the head of the column approaches 100°, the flame is turned down so that very little liquid distils over. Heating is continued until evolution of carbon dioxide ceases (Note 2).

The flask is now disconnected from the stirrer and column, and the contents distilled off as completely as possible on the steam bath under reduced pressure. The remaining solid is freed from residual moisture and hydrochloric acid by allowing a slow current of dry air to pass over it, while still heating on the steam bath and maintaining a partial vacuum (Note 3). It is then redissolved in distilled water; the solution is filtered with the use of decolorizing carbon, and again evaporated under reduced pressure.

The residue, when completely dry, is ground up, mixed to a paste with dry ether, filtered by suction, washed with dry ether, and dried. The product so obtained (Note 4) is practically pure and melts at 160–161°. The yield is 474–479 g. (95–96 per cent of the theoretical amount).

2. Notes

1. The temperature at the head of the column will give some idea of the relative amount of water passing over with the alcohol, but allowance must be made for the lowering of the distilling temperature by the carbon dioxide evolved.
2. Twelve hours' heating is necessary to complete the reaction.
3. The dry air is best introduced through a tube leading to the bottom of the

flask; it is well not to disconnect the condenser, but to note the point at which no more drops condense. The current of dry air should be quite slow—not more than two bubbles per second in the sulfuric acid wash bottle.

4. Tricarballylic acid is readily soluble in water (requiring about twice its weight at room temperature), but may, if desired, be recrystallized from it. Dry ether may also be employed, about 50 parts by weight being necessary.

3. Discussion

Tricarballylic acid can be prepared by the hydrolysis of the nitrile obtained from glycerol tribromohydrin and potassium cyanide;[1] by reduction of aconitic acid by sodium amalgam[2] or electrolytically;[3] and by the hydrolysis of ethyl propanetetracarboxylate in alkaline solution[4] or more conveniently with hydrochloric acid.[5]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

nitrile

glycerol tribromohydrin

alcohol (64-17-5)

hydrochloric acid (7647-01-0)

ether (60-29-7)

potassium cyanide (151-50-8)

carbon dioxide (124-38-9)

decolorizing carbon (7782-42-5)

sodium (13966-32-0)

Ethyl propane-1,1,2,3-tetracarboxylate

Tricarballylic acid (99-14-9)

Aconitic acid (499-12-7)

ethyl propanetetracarboxylate

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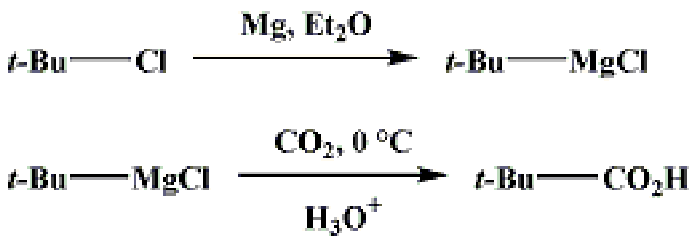
Organic Syntheses, CV 1, 524

TRIMETHYLACETIC ACID

[Pivalic acid]

[(*A*) (*from tert.- Butyl Chloride*)]



Submitted by S. V. Puntambeker and E. A. Zoellner.
Checked by J. B. Conant and A. H. Blatt.

1. Procedure

In a 3-l. three-necked, round-bottomed flask, fitted with a mechanical stirrer and mercury seal, a 500-cc. separatory funnel, and an efficient reflux condenser, is placed 61 g. (2.5 atoms) of magnesium turnings or powder (Note 1). The magnesium is then covered with 200 cc. of anhydrous ether. About 5 cc. of pure *tert.*-butyl chloride (with a crystal or two of iodine) is added to start the reaction. Stirring is begun, and a solution of 227 g. (2.5 moles) of pure *tert.*-butyl chloride (p. 144) in 1100 cc. of anhydrous ether is dropped slowly (Note 2) on the magnesium during six to eight hours. The reaction is practically complete when all the halide has been added, but stirring should be continued for fifteen minutes longer.

The reaction mixture is now surrounded by an ice and salt mixture. The separatory funnel is replaced by a two-holed rubber stopper containing a thermometer (bulb immersed in the reaction mixture) and a glass tube the outer end of which is connected to a mercury trap (Note 3). When the temperature of the reaction mixture has fallen to 0°, the condenser is replaced by a tube 10 mm. in diameter and adjusted so the end is 50 mm. above the surface of the reaction mixture. The reaction mixture is stirred and carbon dioxide is added through this tube directly from a cylinder after passing through two bottles containing concentrated sulfuric acid. The carbon dioxide is added as rapidly as it is used up. The temperature is controlled by the rate of stirring and should not go above 8+°. After two and one-half to three hours the temperature falls below 0°. Then the addition is continued for one-half hour under an excess pressure of 45 mm. (Note 3). The temperature falls to −3 to −5° at the end of this time, and the reaction is complete.

After the flask is surrounded with ice, the reaction mixture is hydrolyzed (Note 4) with 25 per cent sulfuric acid, transferred to a 2-l. separatory funnel, and then the ether layer is separated (Note 4). The water layer is extracted with four 100-cc. portions of

ether. The combined ether extracts are then washed with four 100-cc. portions of 25 per cent sodium hydroxide solution to remove the trimethylacetic acid from the ether.

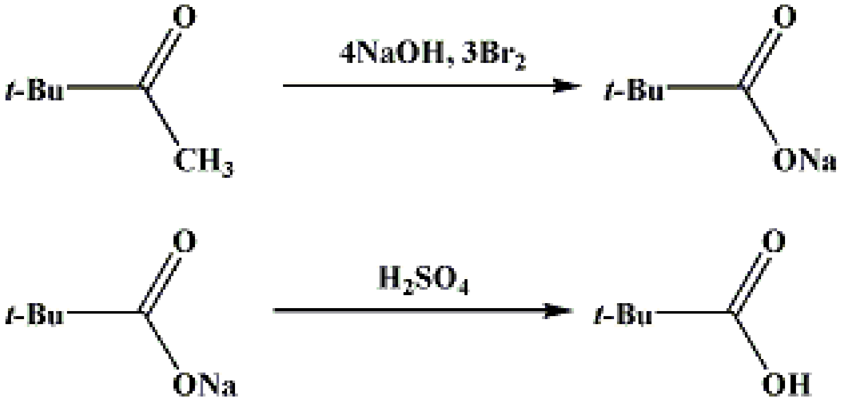
The aqueous alkaline extract is heated to 100° to remove ether and volatile impurities. The solution is then cooled with ice and acidified with 25 per cent sulfuric acid, and the organic acid separated. The water layer is distilled from a 2-l. flask until no more oily solution comes over. The distillate is saturated with salt, and the acid layer is separated. This water layer together with the low-boiling fraction from distillation of the crude trimethylacetic acid is distilled and the distillate salted out as before.

The combined acid layers are distilled from a 250-cc. Claisen flask connected to an air condenser, which in turn is connected to a side-arm flask cooled by running water. The trimethylacetic acid is collected at 162–165°/atm. press., 110–112°/124 mm. The yield, which depends somewhat on the form of magnesium, is 157–162 g. (61–63 per cent of the theoretical amount based on *tert.*-butyl chloride) when ordinary magnesium turnings are used and 177–178 g. (69–70 per cent) when 200-mesh magnesium powder is used. The acid melts at 34–35°.

2. Notes

1. The yield of product depends to a considerable extent upon the form of magnesium used. Either the finer commercial grade of turnings should be used or the 30- to 200-mesh powdered magnesium that is kept in a tightly stoppered bottle when not in use. The powdered magnesium makes possible a 5–8 per cent increase in yield.
2. The rate of addition of the halide solution is important. The slower the rate, the better the yield. A delivery constant of the separatory funnel should be determined so that the solution can be added uniformly over a period of six to eight hours. A modified procedure for preparing *tert.*-butylmagnesium chloride has been described by Whitmore and Houk.[1]
3. The mercury trap enables the operator to adjust the flow of the carbon dioxide according to the rate of absorption, and to apply a pressure of 45 mm. during the last half-hour. The pressure itself has practically no effect. The trap consists merely of a narrow glass test tube containing mercury, and the tube is made to extend beneath the surface.
4. The hydroylsis of the reaction mixture and subsequent separation of the acid is the procedure given on p. 362. Sulfuric acid should be added during the hydrolysis as long as any particles of magnesium are present. The water layer does not become clear, owing to solidification of the organic acid.

[(*B*) (*from Pinacolone*)]



Submitted by L. T. Sandborn and E. W. Bousquet.
Checked by F. C. Whitmore and T. Otterbacher.

1. Procedure

In a 5-l. round-bottomed flask fitted with a mechanical stirrer is placed a solution of 330 g. (8.25 moles) of u.s.p. stick sodium hydroxide in 2.8 l. of water, and the solution is cooled to 0° in an ice-salt bath. To the well-stirred solution 480 g. (154 cc., 3 moles) of bromine is added from a separatory funnel at such a rate as to keep the temperature below 10° (Note 1) (fifteen to twenty minutes). The solution is cooled again to 0°, and 100 g. (1 mole) of pinacolone (p. 462) is added from a separatory funnel, the temperature being kept below 10°. After the solution is decolorized (about one hour) it is stirred for three hours at room temperature.

The flask is then fitted with a separatory funnel and a condenser for distillation, and heated with a Meker burner to steam-distil the bromoform and carbon tetrabromide (Note 2) and (Note 3).

The burner is then removed, the mixture is cooled to 50°, and 400 cc. of concentrated sulfuric acid (Note 4) is added through the separatory funnel. The heat of neutralization causes some trimethylacetic acid to distil with water. When all the acid is added the flask is heated again and the trimethylacetic acid comes over with about 400 cc. of water. When all the trimethylacetic acid (70–80 cc.) has distilled, a liquid heavier than water begins to come over. The distillation is stopped and the acid separated from the water in a separatory funnel and dried either with calcium chloride or by distilling with benzene which carries over all water (Note 5). The trimethylacetic acid is further purified by distillation under reduced pressure. It boils at 75–78°/20 mm.; melts at 34–35°; and the yield is 63–65 g.

The water layer is extracted with two 100-cc. portions of ether. The combined ether solutions are dried with calcium chloride, the ether distilled, and the residue fractionated under reduced pressure, using a modified Claisen flask (p. 130). Ten to twelve grams may be obtained in this way. The total yield is 72–75 g. (71–74 per cent of the theoretical amount).

2. Notes

1. The temperature must be kept low during the reaction to prevent formation of sodium bromate.
2. The reaction between sodium hydroxide and tribromopinacolone is not complete at room temperature. Heating in this manner, rather than separation in the cold, results in an increase of 10–15 per cent in the yield.
3. The bromoform passes over with the steam rather rapidly. In some runs some carbon tetrabromide was also obtained. Toward the end of the steam distillation a heavy oil that is more or less of a lachrymator may come over. This is undoubtedly brominated pinacolone. The bromoform may be purified by distillation under reduced pressure. One run gave 115 g. of product, boiling at 78–79°/22 mm.
4. An equivalent amount of hydrochloric acid may be used without affecting the yield.
5. The trimethylacetic acid is dried very easily by distilling with about 50 cc. of benzene at ordinary pressure until all the water is removed, and then the residue is distilled under reduced pressure.

3. Discussion

Trimethylacetic acid can be prepared by the hydrolysis of *tert.*- butyl cyanide;[2] by the oxidation of dimethyl-2,2-propanol with chromic acid;[3] by the oxidation of pinacolone with sodium hypobromite,[4] potassium hypochlorite,[5] and chromic acid;[6] by the carbonation of *tert.*- butylmagnesium chloride;[7] and by treatment of butanol,[8] isobutanol,[8] or acetone[9] with carbon monoxide at high temperature and pressure.

References and Notes

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9. E. I. du Pont de Nemours and Co., U. S. pat. 2,037,654 [C. A. **30**, 3836 (1936)]; Hardy, J. Chem. Soc. 464 (1938).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

dimethyl-2,2-propanol

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether (60-29-7)

sodium hydroxide (1310-73-2)

carbon monoxide (630-08-0)

magnesium, magnesium turnings, magnesium turnings or powder, magnesium powder (7439-95-4)

bromine (7726-95-6)

mercury (7439-97-6)

carbon dioxide (124-38-9)

butanol (71-36-3)

iodine (7553-56-2)

acetone (67-64-1)

Pinacolone (75-97-8)

sodium bromate (7789-38-0)

chromic acid (7738-94-5)

tert.- Butyl Chloride, tert.-BUTYL CHLORIDE (507-20-0)

bromoform (75-25-2)

isobutanol (78-83-1)

Trimethylacetic acid, Pivalic acid (75-98-9)

carbon tetrabromide (558-13-4)

tribromopinacolone

sodium hypobromite

potassium hypochlorite

tert.- butyl cyanide (630-18-2)

tert.-butylmagnesium chloride, tert.- butylmagnesium chloride (677-22-5)

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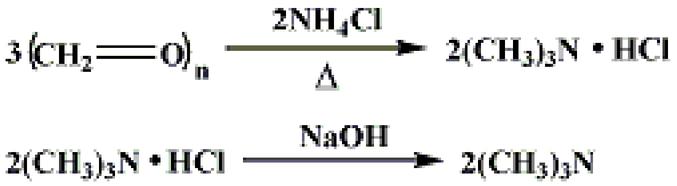
Organic Syntheses, CV 1, 528

TRIMETHYLAMINE

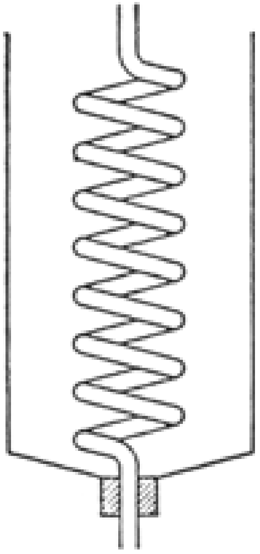


Submitted by Roger Adams and B. K. Brown.
Checked by J. B. Conant and A. McB. Kinney.

1. Procedure

Five hundred grams (9.35 moles) of technical ammonium chloride and 1330 g. (14.8 moles) of paraformaldehyde are mixed and allowed to react as in the procedure described for the preparation of trimethylamine hydrochloride (p. 531). To obtain from this crude reaction mixture a water or alcohol solution of trimethylamine, it is not satisfactory merely to treat with alkali and lead the trimethylamine through the solvent, since the gas is inefficiently absorbed; in fact, it is almost impossible to get a concentrated solution in this way without loss of material. The best way to prepare a solution is to liquefy the trimethylamine (b.p. 3.5°) and in this form run it into the solvent. For this purpose, the 5-l. flask in which the initial reaction is carried out is fitted with a rubber stopper holding a separatory funnel and a glass tube for leading off the trimethylamine (Note 1). This tube is run into one opening of a large U-tube or Wolff bottle holding soda-lime for drying the gas. The exit tube from this drying bottle has a glass tube leading to the top of an upright condenser which consists of a spiral tube cooled with a freezing mixture (Fig. 29) (Note 2).

Fig. 29.



The bottom of this condenser leads through a rubber stopper fitting tightly in a 2- or 3-l. flask, holding the solvent and immersed in an ice-salt mixture. An exit tube from this flask leads to a Wolff bottle kept at a low temperature and holding a little solvent, and through this solvent any unabsorbed trimethylamine must bubble. The exit tube of this last Wolff bottle is closed with a soda-lime tube if an anhydrous solvent is being used (Note 3).

The separatory funnel is filled with sodium hydroxide solution (1100 g. in 2 l. of water) which is then allowed to flow into the reaction mixture at such a speed that, after the air in the apparatus has been replaced by trimethylamine, a continuous stream of drops of trimethylamine flows from the condenser into the solvent and practically no gas goes through the end Wolff bottle. At the beginning, the evolution of trimethylamine is rapid, and hence the addition of the alkali must be very slow (Note 4); as soon as the reaction mixture is partly decomposed, however, the

alkali may be added more rapidly. After it has all been added, the reaction mixture is heated ten to fifteen minutes to make sure that all the amine is evolved. The time for this alkali treatment is about three to four hours.

With such an experiment as is described above, using 1000 g. of absolute alcohol (p. 249) in the solvent flask and about 150 g. in the end Wolff bottle, 1469 g. of solution is obtained in the main flask and 174 g. in the Wolff bottle, thus indicating that a total of 491 g. (89 per cent of the theoretical amount) of trimethylamine is present. There is thus obtained a 32 per cent solution in the main flask, which has a specific gravity of about 0.760 at +5° (Note 5). By titration with standard hydrochloric acid (Note 6), the same amounts of trimethylamine are indicated as are found by weighing. In several experiments, the yields were consistently 85–90 per cent of the theoretical amount (Note 7).

2. Notes

1. As trimethylamine is very volatile and easily lost, particular care must be taken to have all connections in the apparatus tight.
2. Special attention should be drawn to the condenser (Fig. 29) used since it is valuable in many other experiments wherever substances having a boiling point between –10° and +30° are being handled (see, also, p. 117). Any gallon (4-l.) can, having an opening in the top in which a stopper may be inserted, is satisfactory for a jacket. The bottom of the can is cut out, and the can is then inverted. A spiral tube such as that which may be obtained from the inside of a spiral condenser is placed in the can with the lower end fitting tightly through the stopper in the neck. By filling the can with an ice and salt mixture a condensing temperature of –10° or below can easily be obtained.
3. If water is to be used as a solvent, no soda-lime tube is necessary on the exit of the end Wolff bottle. Moreover, with water as a solvent it is not absolutely necessary to have the soda-lime tube between the generating flask and the solvent. It is advisable to have it there, however, since it tends to catch any small amount of colored liquid coming from the reaction flask and thus prevents contamination of the water solution obtained.
4. During the evolution of the trimethylamine, it is necessary occasionally to shake the flask containing the solvent. It happens that, after about a 10–15 per cent solution is formed, the trimethylamine tends to form a top layer which is not dissolved until agitated.
5. In order to avoid loss of material, the specific gravity of any trimethylamine solution must be taken at a low temperature. In this experiment, +5° was chosen.
6. Titration of the strength of the trimethylamine in the solvent is best done by pipetting out 1 cc. of the solution and allowing it to run immediately into 50 cc. of water. This is to prevent volatilization during titration. The amine is then titrated in the usual way with standard hydrochloric acid, using methyl orange as an indicator.
7. Since tests in the trimethylamine hydrochloride preparation (p. 531) indicate that only trimethylamine is formed in this reaction, it is unnecessary to purify

the trimethylamine solution.

3. Discussion

Trimethylamine can be prepared by the action of formaldehyde on ammonium chloride under pressure;[1] by the action of formaldehyde and formic acid on ammonia,[2] a method which has been checked by one of the editors and is highly recommended; from paraformaldehyde and ammonium chloride;[3] and from methyl alcohol, ammonia, and a catalyst.[4] The numerous commercial processes which lead to mixtures of methylamines have not been reviewed since they are not convenient for the laboratory.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 531
- Org. Syn. Coll. Vol. 2, 85
- Org. Syn. Coll. Vol. 3, 334
- Org. Syn. Coll. Vol. 4, 84

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

soda-lime

alcohol (64-17-5)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

methyl alcohol (67-56-1)

ammonium chloride (12125-02-9)

sodium hydroxide (1310-73-2)

formaldehyde (630-08-0)

formic acid (64-18-6)

Trimethylamine (75-50-3)

Trimethylamine hydrochloride (593-81-7)

methyl orange (547-58-0)

paraformaldehyde (30525-89-4)

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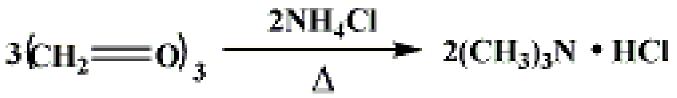
Organic Syntheses, CV 1, 531

TRIMETHYLAMINE HYDROCHLORIDE



Submitted by Roger Adams and C. S. Marvel.
Checked by J. B. Conant and A. McB. Kinney.

1. Procedure

Five hundred grams (9.35 moles) of technical ammonium chloride and 1330 g. (14.8 moles) of paraformaldehyde are thoroughly mixed and placed in a 5-l. round-bottomed flask fitted with a long reflux condenser (a jacket of about 100-cm. length and an inner tube of about 2-cm. diameter) (Note 1). By means of an oil bath, the temperature of the reaction mixture is gradually raised. Between 85° and 105° liquefaction begins to take place at the bottom of the flask, and at the same time a very vigorous evolution of carbon dioxide starts. The heat is at once withdrawn, and if the reaction is too violent, the oil bath should be removed. The reaction is allowed to continue without further heating until the gas evolution is less vigorous. This requires about one and one-half hours. Heat is again applied and the temperature of the bath raised to about 160°, where it is held until there is practically no more evolution of carbon dioxide. This takes two and one-half to three and one-half hours, after which time the reaction is complete.

To obtain the trimethylamine hydrochloride, it is now merely necessary to treat the mixture with sodium hydroxide, and to distil the free amine into hydrochloric acid. A separatory funnel is therefore inserted through the stopper of the flask and the reflux condenser is changed to a downward position for distillation. The open end of the condenser is fitted tightly into the neck of a distilling flask or suction flask, to the outside arm of which is attached, by means of rubber tubing, a glass tube which leads under hydrochloric acid in a receiver. Care must be taken to have all the joints in the apparatus tight as the trimethylamine is very volatile and can easily be lost. The object of the intermediate boiling or suction flask is to catch any water which may distil with the trimethylamine during the treatment with the sodium hydroxide. This water is often colored yellow, and if allowed to go directly into the hydrochloric acid in the receiver contaminates the trimethylamine hydrochloride.

A solution of 1100 g. of sodium hydroxide (two and one-half to three times the amount theoretically necessary to liberate the free amine) in 2 l. of water is allowed to drop through the separatory funnel into the reaction mixture, which has cooled somewhat during the change of apparatus. The amine distils, passes through the condenser, through the intermediate bottle, and into the receiver, in which is placed an amount of concentrated hydrochloric acid (930 cc. of sp. gr. 1.19) slightly more than enough to neutralize the weight of amine which should theoretically be formed. To be

certain that all the amine has been driven from the reaction flask, heat is finally applied for ten or fifteen minutes to the mixture. The whole procedure, from the beginning of the first reaction until a solution of trimethylamine hydrochloride is obtained, requires not more than six to seven hours.

To obtain the trimethylamine hydrochloride, the hydrochloric acid solution is evaporated, first over a free flame, and later, when the crystals start to form, on a steam bath. As the solution gets more and more concentrated, the trimethylamine hydrochloride crystallizes out and is filtered from time to time, dried for a few minutes in an air bath (temperature 100–110°), and then kept in a tightly closed bottle. If the trimethylamine hydrochloride as it crystallizes is centrifuged, the product is obtained pure and dry at once. The average yield from four runs is 710 g. of pure trimethylamine hydrochloride and 82 g. of product which is tinged slightly yellow (a total of 89 per cent of the theoretical amount based on the ammonium chloride) (Note 2). The coloration results from the evaporation to dryness of the very last portion of solution.

2. Notes

1. The reaction takes place with the evolution of a considerable amount of heat, and consequently a condenser as efficient as that mentioned is necessary in order to avoid loss. The wide inner tube is used to avoid any possibility of paraformaldehyde subliming and clogging the condenser.

2. The complete solubility of the product in chloroform[1] shows the trimethylamine hydrochloride to be free from ammonium chloride and methylamine hydrochloride, and the fact that no precipitate is obtained when the trimethylamine hydrochloride in aqueous solution is treated with sodium hydroxide and benzenesulfonyl chloride shows that dimethylamine hydrochloride is absent.

3. Discussion

Methods for the preparation of trimethylamine hydrochloride are essentially like those given at the end of the preceding preparation (p. 530) of trimethylamine.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 528

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

ammonium chloride (12125-02-9)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

carbon dioxide (124-38-9)

Benzenesulfonyl chloride (98-09-9)

Methylamine hydrochloride (593-51-1)

dimethylamine hydrochloride (506-59-2)

Trimethylamine (75-50-3)

Trimethylamine hydrochloride (593-81-7)

paraformaldehyde (30525-89-4)

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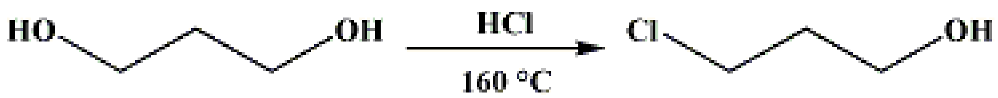
Organic Syntheses, *CV 1*, *533*

TRIMETHYLENE CHLOROHYDRIN

[1-Propanol, 3-chloro-]



Submitted by C. S. Marvel and H. O. Calvery.
Checked by H. T. Clarke and M. R. Brethen.

1. Procedure

A 100-cc. round-bottomed, wide-mouthed flask (or a large test tube 18 cm. long and 4.5 cm. wide) is fitted with a rubber stopper carrying a separatory funnel, a thermometer, an inlet tube reaching almost to the bottom of the flask, and an outlet tube leading to a condenser set for downward distillation. A receiver consisting of a suction flask is attached tightly to the end of the condenser, and the side arm of the receiver is attached to a reflux condenser. A tube is led from the top of the condenser to the hood in order to take care of excess hydrogen chloride during the distillation, or a gas-absorption trap (Fig. 7, p. 97) can be used for this purpose. About 25–30 cc. of trimethylene glycol (b.p. 210–215°) is placed in the flask and heated by means of an oil or metal bath to 150–170°. A *very* rapid stream of dry hydrogen chloride (Note 1) is now led into the hot glycol through the inlet tube. A reddish distillate consisting of water, trimethylene chlorohydrin, hydrogen chloride, and some unchanged glycol begins to distil. As rapidly as the glycol is used up in the reaction flask, more is added from the separatory funnel. It is always advisable to keep the amount of material in the reaction flask as small as possible. The rate at which the hydrogen chloride is passed through the flask controls the reaction and also has a marked effect on the yield (Note 2). The best results are obtained by passing in the gas rapidly enough to use up 2–3 cc. of trimethylene glycol in one minute. The process is continuous and can be run indefinitely without changing the apparatus. The weight of crude distillate from 1800 g. of trimethylene glycol is usually 2300–2500 g.

To obtain the trimethylene chlorohydrin, the distillate from this operation is heated for about one hour on a steam bath in order to drive out most of the excess hydrogen chloride. The distillate is then fractionated under reduced pressure (Note 3) in a modified Claisen flask (p. 130). The fractionating side arm should be 25 cm. in length. The fractions collected under 10 mm. are: to 55°, 55–57°, 57–65°, 65–85°, 85–105°, residue.

Before a further fractionation is carried out, the residue is discarded; the portion boiling at 85–105°, consisting chiefly of unchanged trimethylene glycol, is set aside for use in a later preparation; the low-boiling portion up to 55°, consisting mainly of water and hydrogen chloride with some trimethylene chloride (Note 4) and

trimethylene chlorohydrin, is neutralized carefully with powdered sodium carbonate. Two layers form, and the upper containing the chlorohydrin is separated, dried over anhydrous potassium carbonate, and again replaced as the portion boiling up to 55°. Another complete fractional distillation, carried out in the usual way, is now made except that the highest fraction boils at 65–85°/10 mm.

The material boiling above 65°/10 mm. is chiefly trimethylene glycol and is used in a succeeding experiment. The final yield of trimethylene chlorohydrin (Note 5) boiling at 60–64°/10 mm. is 835–1000 g. from 1800 g. of trimethylene glycol (50–60 per cent of the theoretical amount), and 400–450 g. of trimethylene glycol is recovered.

2. Notes

1. *Hydrogen Chloride*.—The hydrogen chloride may be generated by any method desired. Since a large quantity of gas is required, the first procedure described on p. 293 is rather expensive. A more satisfactory arrangement is to half fill a 12-l. flask with a paste of salt and concentrated hydrochloric acid and run into this commercial sulfuric acid. The gas is dried by a single wash bottle of sulfuric acid.

If sulfuric and hydrochloric acids are used, then, for the conversion of 1800 g. of trimethylene glycol, a 20-l. bottle half-filled with concentrated sulfuric acid is treated with concentrated hydrochloric acid introduced through a tube reaching to the bottom. The hydrochloric acid is added at the rate of 30–40 drops per minute. Two charges of sulfuric acid are needed and a total of about 24 kg. of hydrochloric acid.

2. The yield of chlorohydrin is largely determined by the rate at which the reaction is carried out. A very rapid stream of hydrogen chloride is absolutely essential for obtaining the yields mentioned. Moreover, it is very important to keep as small an amount of glycol as possible in the reaction flask. If larger amounts of glycol are present at any one time, the yield of product is lowered and considerable tar is produced.

3. Trimethylene chlorohydrin cannot be distilled under atmospheric pressure without some decomposition. The fractionation can be carried out at ordinary pressures when the fractions collected are up to 125°, 125–158°, 158–164°, 164–190°, 190–210° and residue. This procedure is less desirable as some hydrogen chloride is evolved and the product turns dark on standing.

4. The portion boiling up to 55°/10 mm., obtained after the second fractionation, was washed with concentrated sulfuric acid, then water, and finally dried and distilled. A certain amount of trimethylene chloride was sometimes obtained, boiling at 115–120° and amounting to about 30 per cent of the total fraction.

5. The chlorohydrin contains a very small amount (less than 0.5 per cent) of water-insoluble material, which is probably trimethylene chloride and di-γ-chloropropyl ether.

3. Discussion

Trimethylene chlorohydrin can be prepared from trimethylene glycol by the action of dry hydrogen chloride under various conditions;[1] by the action of aqueous hydrochloric acid;[2] and by the action of sulfur chloride.[3] It can also be prepared from γ-chloropropyl acetate and methyl alcoholic hydrochloric acid.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 156
- Org. Syn. Coll. Vol. 1, 166
- Org. Syn. Coll. Vol. 1, 292
- Org. Syn. Coll. Vol. 1, 294
- Org. Syn. Coll. Vol. 3, 197
- Org. Syn. Coll. Vol. 3, 203
- Org. Syn. Coll. Vol. 4, 238
- Org. Syn. Coll. Vol. 4, 605

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric and hydrochloric acids

methyl alcoholic hydrochloric acid

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

hydrogen chloride, hydrochloric acid (7647-01-0)

sodium carbonate (497-19-8)

trimethylene glycol (504-63-2)

Trimethylene chlorohydrin, 1-Propanol, 3-chloro- (627-30-5)

sulfur chloride

trimethylene chloride (142-28-9)

di-γ-chloropropyl ether (629-36-7)

γ-Chloropropyl acetate (628-09-1)

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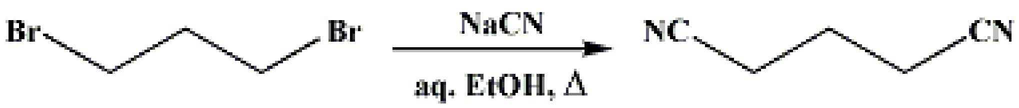
Organic Syntheses, CV 1, 536

TRIMETHYLENE CYANIDE

[Glutaronitrile]



Submitted by C. S. Marvel and E. M. McColm.
Checked by H. T. Clarke and E. E. Dreger.

1. Procedure

In a 5-l. round-bottomed flask fitted with a stopper holding a reflux condenser and a separatory funnel are placed 294 g. (6 moles) of sodium cyanide and 300 cc. of water. The flask is heated on a steam bath until most of the sodium cyanide is in solution. This requires two to three hours. A solution of 500 g. (2.47 moles) of trimethylene bromide (Note 1) in 1 l. of 95 per cent alcohol is then added through the separatory funnel over a period of forty to sixty minutes. The mixture is refluxed for thirty to forty hours (Note 2) on a steam bath. Then the solvent is removed, preferably under reduced pressure, using an oil bath.

The residue, consisting of sodium bromide, sodium cyanide, and trimethylene cyanide, is extracted with 300–400 cc. of ethyl acetate, which dissolves the trimethylene cyanide and does not dissolve the inorganic salts. This solution is filtered and the salt washed once with about 100 cc. of ethyl acetate. The ethyl acetate is distilled at ordinary pressure (Note 3) and the residual liquid is distilled under reduced pressure. The yield of trimethylene cyanide boiling at 144–147°/13 mm. or 131–134°/10 mm. is 180–200 g. (77–86 per cent of the theoretical amount).

2. Notes

1. Larger runs seem to give slightly lower yields.
2. The yield is lower if the heating is continued too long, owing to partial hydrolysis of the cyanide.
3. Very little ethyl acetate is lost in this procedure if it is distilled at ordinary pressures. If it is not entirely removed before the pressure is reduced, considerable foaming occurs.

3. Discussion

Trimethylene cyanide can be prepared by the action of potassium cyanide on trimethylene bromide.[1]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 289

References and Notes

1. Reboul, Compt. rend. **82**, 1197 (1876); Henry, ibid. **100**, 742 (1885), Bull. soc. chim. (2) **43**, 617 (1885); Perkin, J. Chem. Soc. **55**, 702 (1889).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alcohol (64-17-5)

ethyl acetate (141-78-6)

sodium cyanide (143-33-9)

sodium bromide (7647-15-6)

Trimethylene bromide (109-64-8)

cyanide (57-12-5)

potassium cyanide (151-50-8)

Trimethylene cyanide, Glutaronitrile (544-13-8)

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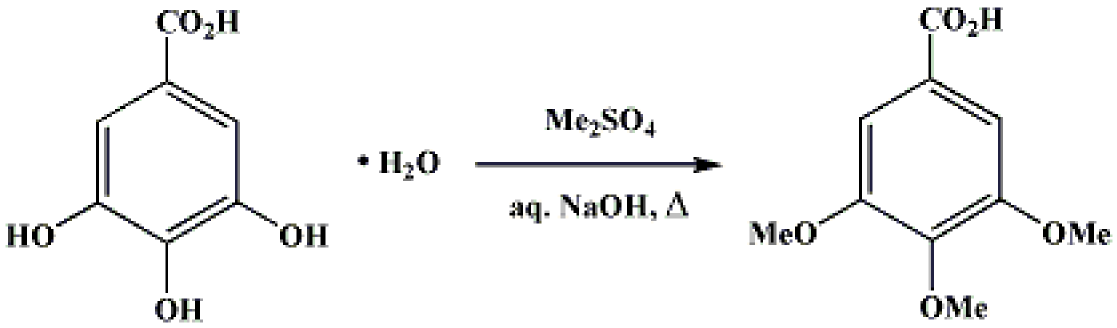
Organic Syntheses, CV 1, 537

TRIMETHYLGALLIC ACID

[Benzoic acid, 3,4,5-trimethoxy-]



Submitted by F. Mauthner
Checked by H. T. Clarke

1. Procedure

To a cold solution of 80 g. (2 moles) of sodium hydroxide in 500 cc. of water in a 1-l. flask is added 50 g. (0.266 mole) of gallic acid. The flask is immediately tightly stoppered (Note 1), and the mixture shaken occasionally until all the acid has dissolved; 89 g. (67 cc.) of dimethyl sulfate (0.71 mole) is then added (Note 2) and the flask is shaken for twenty minutes, being cooled by means of cold water in order that the temperature does not rise above 30–35°. Occasionally the stopper is raised to release any pressure. A second portion of 89 g. of dimethyl sulfate is then added and shaking continued for ten minutes longer. During this second addition the temperature may rise to 40–45°.

The flask is then fitted with a reflux condenser and the contents boiled for two hours. In order to saponify the small amount of ester which is produced, a solution of 20 g. of sodium hydroxide in 30 cc. of water is then added and boiling continued for two additional hours. The reaction mixture is then cooled and acidified with dilute hydrochloric acid; the precipitated trimethylgallic acid is filtered with suction and washed well with cold water. The product, which melts at 157–160°, is sufficiently pure for many purposes. It weighs 50–52 g. (89–92 per cent of the theoretical amount). It may be purified by recrystallization from 2 l. of boiling water with the use of decolorizing carbon, the filtration being carried out in a steam-jacketed funnel. In this way 41–43 g. (Note 3) of colorless needles melting at 167° is obtained.

2. Notes

1. The alkaline solution immediately darkens somewhat, owing to the presence of dissolved air; further oxidation must be limited by preventing access of air to the mixture. This is particularly necessary during the early stages; with increasing methylation the tendency to absorb oxygen falls off rapidly. Sodium

bisulfite has been recommended to prevent oxidation during methylation.[1] Access of air may be prevented in an apparatus that permits of mechanical stirring. For this purpose a three-necked flask is provided with a mechanical stirrer, separatory funnel, and Bunsen valve. The valve is made by cutting a vertical slit in a piece of rubber tubing, closed at one end by a solid glass plug or pinchcock and attached at the other end to a piece of glass tubing contained in a stopper. Such a valve acts in one direction, permitting release of gas pressure. A guard tube filled with sodium hyposulfite has been used to exclude oxygen.[1]
2. The toxic nature of methyl sulfate must always be borne in mind. Ammonia is a specific antidote for methyl sulfate and should be kept at hand to destroy any of the ester accidentally spilled.
3. A further quantity can be recovered by concentrating the mother liquor. The residue of decolorizing carbon is also likely to contain an appreciable proportion of trimethylgallic acid, which can be extracted by boiling it with the mother liquor.

3. Discussion

Trimethylgallic acid can be prepared by methylating gallic acid with dimethyl sulfate,[2] and by methylating methyl gallate and saponifying the product.[3]

References and Notes

1. Bogert and Coyne, J. Am. Chem. Soc. **51**, 571 (1929).
2. Graebe and Martz, Ann. **340**, 219 (1905); Perkin and Weizmann, J. Chem. Soc. **89**, 1655 (1906); Fischer and Freudenberg, Ber. **45**, 2718 (1912); Bogert and Isham, J. Am. Chem. Soc. **36**, 517 (1914); Nierenstein, J. Chem. Soc. **111**, 7 (1917); Overmyer, J. Am. Chem. Soc. **49**, 503 (1927); Bogert and Coyne, ibid. **51**, 571 (1929).
3. Will, Ber. **21**, 2022 (1888).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

sodium hydroxide (1310-73-2)

oxygen (7782-44-7)

sodium bisulfite (7631-90-5)

dimethyl sulfate (77-78-1)

decolorizing carbon (7782-42-5)

methyl sulfate (75-93-4)

Trimethylgallic acid

Benzoic acid, 3,4,5-trimethoxy- (118-41-2)

gallic acid (149-91-7)

methyl gallate (99-24-1)

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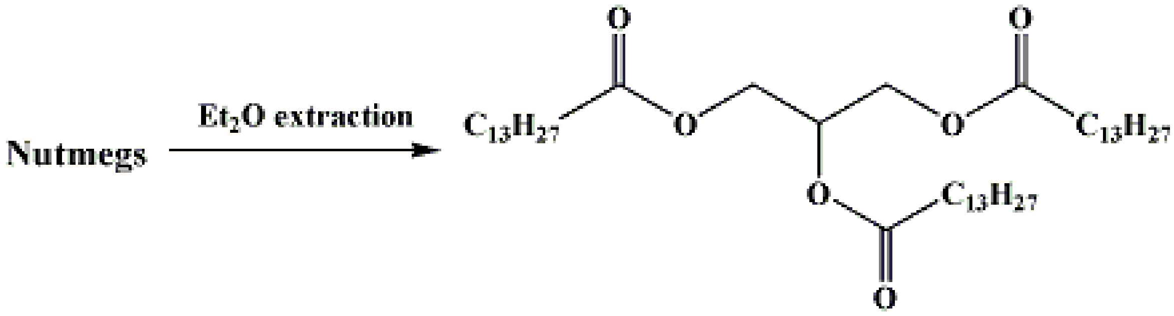
Organic Syntheses, CV 1, 538

TRIMYRISTIN

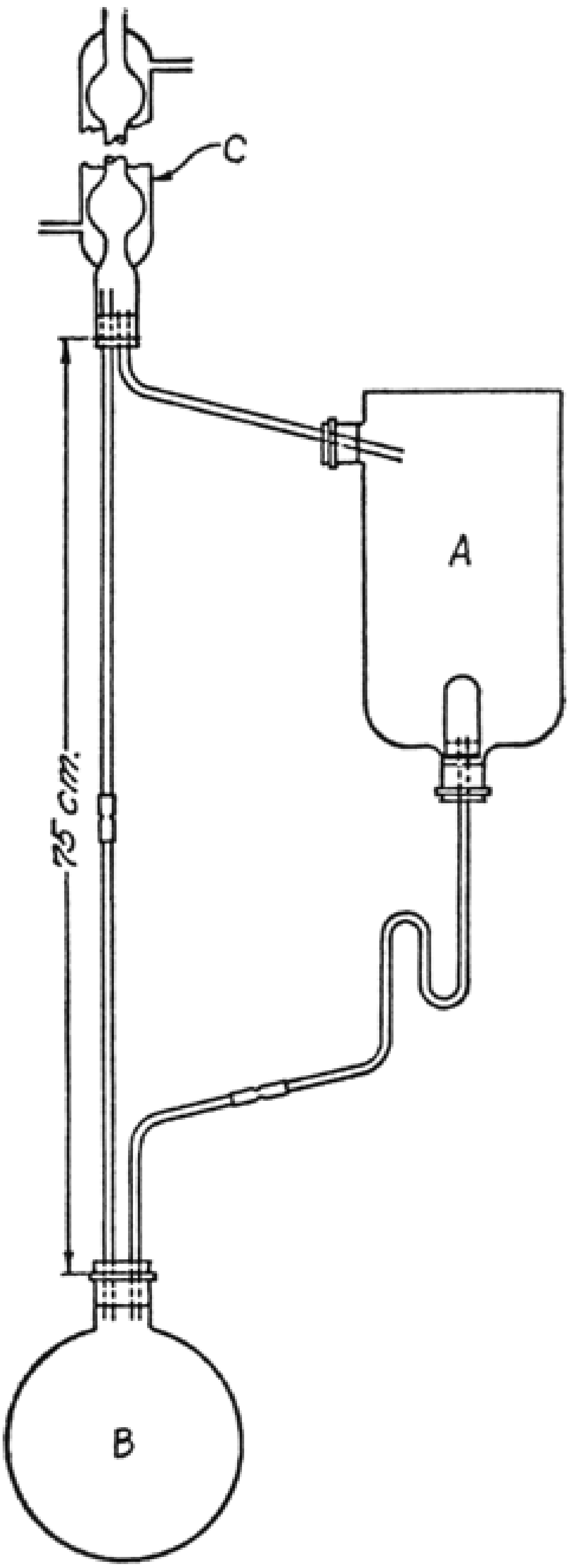


Submitted by G. D. Beal
Checked by H. T. Clarke and E. R. Taylor.

1. Procedure

In the container A (Fig. 30) is placed 1500 g. of crushed nutmegs (Note 1) moistened with ether (Note 2). A is a 3-l. inverted aspirator bottle connected by a 3-mm. glass tube to the efficient condenser C, and by 3-mm. tubing, one end of which is provided with a Soxhlet thimble to the 2-l. round-bottomed flask B. Flask B is connected by 3-mm. tubing of 75-cm. length to C. In B are placed 500 cc. of ether and a few chips of clay plate to prevent superheating. B is then heated on a steam cone so that the ether boils rapidly enough to reach the condenser C and to flow back through A.

Fig. 30.



The extraction with ether is continued until the ether leaving the insoluble solid is entirely colorless. This requires twenty-four to seventy-two hours, according to the state of subdivision of the nutmegs and the rate at which the ether is passed through.

The ethereal solution is then freed of a small quantity of entrained insoluble matter by filtering through a folded paper. This filtration may advantageously be completed in the type of extractor described on p. 375. The clear solution is now entirely freed from ether by distillation on the water bath. The residue weighs 640–690 g. On cooling it sets to a mass of crystals of trimyristin which is filtered with suction (Note 3) and washed with 225 cc. of cold 95 per cent ethyl alcohol in small portions. The product is now recrystallized from 3.5 l. of 95 per cent ethyl alcohol; it is stirred mechanically during cooling since the trimyristin tends to separate as an oil at the outset (Note 4). The crystallized trimyristin is then filtered off by suction and washed with 350-400 cc. of 95 per cent alcohol in small portions. The crystals, which are colorless and practically odorless, melt at 54–55°. The yield is 330–364 g.

2. Notes

1. If the nutmegs are crushed to No. 40 powder, as recommended by the author, the extraction is complete in twenty-four to forty-eight hours; in checking it was found more convenient merely to pass the nutmegs through a food chopper (whereby they were broken up into pieces the largest of which were 3–4 mm. across), when the extraction required sixty-six to seventy-two hours for completion.

West India nutmegs are less expensive than the East India variety, and there seems to be no difference in yields of trimyristin between the two kinds.

If nutmeg butter, a commercial fat obtained by the hot pressing of ground nutmegs, is available, the above extraction may be omitted. The only operation necessary is a double crystallization of the crude material from boiling 95 per cent alcohol. Since nutmeg butter is frequently adulterated with foreign fats, the purity of the product should be checked by the saponification number (232 for pure trimyristin).

2. The nutmeg must first be moistened with ether; otherwise the extraction takes much longer. The author has found this apparatus to be generally satisfactory for the extraction of vegetable drugs with volatile solvents.

3. The filtrate from the crude trimyristin contains the odorous oils of the nutmeg. A further quantity of trimyristin may be obtained from it by distilling with steam and recrystallizing the non-volatile residue twice from alcohol; but the amount is not commensurate with the trouble, and this operation is not advised unless the residues from at least 5 kg. of nutmegs are on hand.

4. The alcohol may be distilled from the mother liquor of the recrystallization. The residue from this distillation may be added to the mother liquor of the first crystallization, which is then concentrated to the crystallization point. The crop of crystals thus obtained will usually require double recrystallization. Alcohol recovered from the first mother liquor will contain too much volatile oil of nutmeg to be used for other purposes.

3. Discussion

Trimyristin can be isolated from nutmegs by ether extraction.[1]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 379

References and Notes

1. Playfair, Ann. **37**, 152 (1841); Masino, Ann. **202**, 172 (1880); Power and Salway, J. Chem. Soc. **93**, 1653 (1908); Krafft, Ber. **12**, 1668 (1879); Verkade and Coops, Rec. trav. chim. **46**, 528 (1927).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethyl alcohol, alcohol (64-17-5)

ether (60-29-7)

trimyristin (555-45-3)

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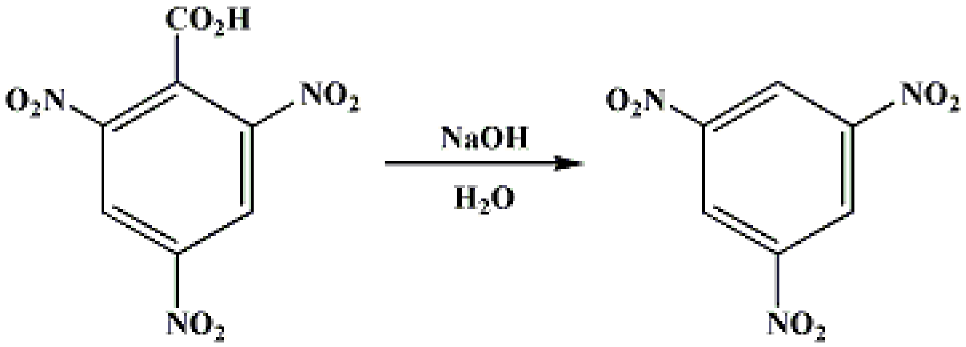
Organic Syntheses, CV 1, 541

1,3,5-TRINITROBENZENE

[Benzene, 1,3,5-trinitro-]



Submitted by H. T. Clarke and W. W. Hartman.
Checked by J. B. Conant and J. J. Toohy.

1. Procedure

The crude trinitrobenzoic acid obtained by oxidation of 360 g. (1.6 moles) of trinitrotoluene (p. 543) is mixed with 2 l. of water at 35° (Note 1) in a 5-l. flask provided with a stirrer. Fifteen per cent sodium hydroxide solution is added, with continuous stirring, until a *faint* red color is just produced (Note 2). The color is then immediately discharged by means of one or two drops of acetic acid, and the liquid is filtered from unchanged trinitrotoluene. The filtrate is transferred to a 5-l. flask, and 70 cc. of glacial acetic acid is added.

The mixture is then gently heated (Note 3), with continuous stirring, when trinitrobenzene separates in crystalline condition and floats on the surface of the liquid as a frothy layer. After about one and one-half hours the evolution of gas ceases; at this point the crystals begin to stir into the solution. The heating and stirring are continued for three-quarters of an hour, when the mixture is allowed to cool, and the crystals filtered off. A sample of the filtrate should be tested for undecomposed trinitrobenzoic acid: if a precipitate is produced by the addition of sulfuric acid the process must be continued. After recrystallization from glacial acetic acid, the product melts at 121–122°. The yield is 145–155 g. (43–46 per cent of the theoretical amount calculated from the trinitrotoluene).

2. Notes

1. During the solution of the trinitrobenzoic acid, the temperature should not be below 35°, owing to the slight solubility of trinitrobenzoic acid in cold water. The heat of neutralization raises the temperature to 45–55°, but 55° should not be exceeded, since any trinitrobenzene formed at this point would later be removed with the unreacted trinitrotoluene.

2. Care must be taken that no more alkali is added than is just sufficient to produce the faint red color. If an excess of alkali is added it produces a permanent color, which is not removed by acid and colors the final product.
3. When once the evolution of carbon dioxide sets in, the flame must be cut down so as to avoid the formation of a thick layer of froth which might foam over.

3. Discussion

1,3,5-Trinitrobenzene can be prepared by nitrating *m*-dinitrobenzene,[1] and by heating 2,4,6-trinitrobenzoic acid or its sodium salt with water, alcohol, dilute sodium carbonate, or other suitable solvent.[2] 2,4,6-Trinitrobenzaldehyde[3] and 2,4,6-trinitrobenzoic acid[4] both furnish trinitrobenzene on treatment with alcoholic ammonia —the yield from the aldehyde is reported to be quantitative.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 219
- Org. Syn. Coll. Vol. 1, 455
- Org. Syn. Coll. Vol. 1, 543

References and Notes

1. Hepp, Ber. **9**, 402 (1876), Ann. **215**, 344 (1882); Drummond, J. Soc. Chem. Ind. **41**, 338T (1922).
2. Chemische Fabrik Griesheim, Ger. pat. 77,353 [Frdl. **4**, 34 (1894–97)], Desvergnes, Chimie & industrie, **25**, 3, 291 (1931) [C. A. **25**, 2699 (1931)], which contains a comparative study of methods of preparation.
3. Secareanu, Bull. soc. chim. (4) **51**, 596 (1932).
4. Secareanu, ibid. **53**, 1399 (1933).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

2,4,6-trinitrobenzoic acid or its sodium salt

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

ammonia (7664-41-7)

sodium hydroxide (1310-73-2)

sodium carbonate (497-19-8)

carbon dioxide (124-38-9)

1,3,5-Trinitrobenzene, Benzene, 1,3,5-trinitro- (99-35-4)

2,4,6-Trinitrobenzoic acid (129-66-8)

trinitrotoluene (118-96-7)

trinitrobenzoic acid

trinitrobenzene

2,4,6-Trinitrobenzaldehyde (606-34-8)

m-dinitrobenzene (99-65-0)

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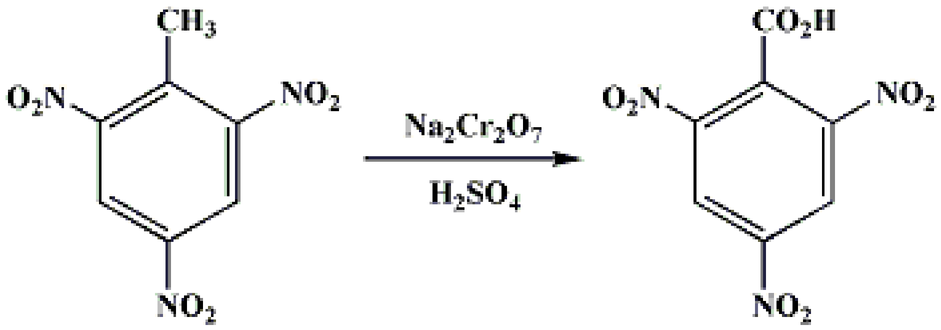
Organic Syntheses, CV 1, 543

2,4,6-TRINITROBENZOIC ACID

[Benzoic acid, 2,4,6-trinitro-]



Submitted by H. T. Clarke and W. W. Hartman.
Checked by J. B. Conant and J. J. Toohy.

1. Procedure

To 3600 g. (1960 cc.) of concentrated sulfuric acid, in a 5-l. flask placed in an empty water bath, is added 360 g. (1.6 moles) of technical trinitrotoluene, while the mixture is stirred mechanically (Note 1). Sodium dichromate is now added in small quantities (Note 2), with constant stirring, until the temperature of the mixture reaches 40°; the empty water bath is now filled with cold water and the addition of sodium dichromate continued at such a rate that the temperature remains at 45–55°. In all, 540 g. (1.8 moles) of sodium dichromate is added, the addition taking one to two hours. When all has been added, the mixture, which has now become very thick, is stirred for two hours at 45–55°, and poured into a crock containing 4 kg. of crushed ice. The insoluble trinitrobenzoic acid is filtered off and carefully washed with cold water until free from chromium salts. On drying it weighs 320–340 g.

The product is now mixed with 2 l. of distilled water at 35° in a 5-l. flask provided with a stirrer, and 15 per cent sodium hydroxide solution is dropped in with continuous stirring until a *faint* red color is just produced (Note 3). Should this disappear, it is restored by the addition of a few drops more. When it has persisted for five minutes, the color is discharged by the addition of a few drops of acetic acid, and the insoluble unattacked trinitrotoluene filtered off and washed with a little water. The trinitrobenzoic acid is precipitated from the filtrate by the addition of a slight excess of 50 per cent sulfuric acid. The solution is chilled, and the acid filtered and washed free from salts with ice water (Note 4). When dried in air it weighs 230–280 g. (57–69 per cent of the theoretical amount).

2. Notes

1. It is essential that the stirring should be most efficient, so that when the

mixture becomes thick the dichromate will be evenly distributed throughout the liquid, as rapidly as it is added. If the stirring is not efficient, local reactions of extreme violence (in certain cases leading to conflagration) will occur. An iron stirrer may be employed in the oxidation reaction, but not in the purification.
2. Technical sodium dichromate generally contains a certain amount of chlorides, and the chlorine liberated from these tends to cause a troublesome foam towards the end of the reaction. Only a very efficient stirrer, which draws down the surface of the liquid, is able to combat this difficulty. The amount of solid sodium dichromate given is for the dry crystalline compound containing two molecules of water of crystallization.
3. Great care should be taken in dissolving the crude acid in the alkali. If an excess of alkali persists for any length of time, a permanent color is produced which will discolor the final product. The acid is fairly soluble in cold water and should be washed with care.
4. The mother liquors and washings lose carbon dioxide on boiling, and the insoluble trinitrobenzene separates (p. 541); after filtering, washings, and drying, it weighs 15–20 g. (4–6 per cent of the theoretical amount).

3. Discussion

2,4,6-Trinitrobenzoic acid can be prepared by the oxidation of trinitrotoluene with a mixture of concentrated nitric and sulfuric acids,[1] a method which is unsuitable in the laboratory owing to the difficulty of devising suitable apparatus; by oxidation in nitric acid solution by means of potassium chlorate,[2] a method which has been found difficult to control on a laboratory scale; and by the procedure described, a modification of a patented process,[3] in which trinitrotoluene suspended in sulfuric acid is oxidized by chromic anhydride.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 455
- Org. Syn. Coll. Vol. 1, 541
- Org. Syn. Coll. Vol. 3, 334

References and Notes

1. Chemische Fabrik Griesheim, Ger. pat. 77,559 [Frdl. **4**, 34 (1894–97)].
2. Lüttgen, Ger. pat. 226,225 [Frdl. **10**, 167 (1910–12)].
3. Chemische Fabrik Griesheim, Ger. pat. 127,325 [Frdl. **6**, 148 (1900–02)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

nitric and sulfuric acids

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

sodium hydroxide (1310-73-2)

nitric acid (7697-37-2)

carbon dioxide (124-38-9)

chlorine (7782-50-5)

sodium dichromate (7789-12-0)

potassium chlorate (3811-04-9)

2,4,6-Trinitrobenzoic acid, Benzoic acid, 2,4,6-trinitro- (129-66-8)

trinitrotoluene (118-96-7)

trinitrobenzoic acid

trinitrobenzene

chromic anhydride

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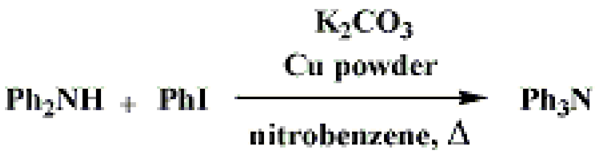
Organic Syntheses, CV 1, 544

TRIPHENYLAMINE



Submitted by F. D. Hager
Checked by Henry Gilman and R. McCracken.

1. Procedure

In a 2-l. three-necked, round-bottomed flask, fitted with a very efficient mechanical stirrer, a 100-cc. separatory funnel, and a large air-cooled reflux condenser (Note 1), the upper part of which is bent downwards and attached to a vertical water condenser, are placed 176 g. (1.04 moles) of ground diphenylamine (Note 2), 204 g. (1 mole) of iodobenzene, 1 l. of nitrobenzene (Note 3), 138 g. (1 mole) of finely powdered anhydrous potassium carbonate, and 5 g. of copper powder (Note 4).

The reaction mixture is then stirred very vigorously and boiled at such a rate that the nitrobenzene condenses in the upper third of the air-cooled reflux condenser and flows back in an almost steady stream. The water formed in the reaction passes over, together with a small amount of nitrobenzene and iodobenzene, and is condensed by the water-cooled condenser. This distillate is freed of water by shaking with a small quantity of sodium sulfate and returned at intervals through the separatory funnel to the reaction flask. Heating is continued for about twenty-four hours or until the reaction is complete, as is evidenced by the non-evolution of water (Note 5).

The reaction mixture is allowed to cool somewhat and is then transferred to a 5-l. flask, and the nitrobenzene together with a little of the excess diphenylamine is removed by steam distillation. During distillation the flask should be heated to prevent excessive condensation of steam (Note 6). Steam distillation should be continued until a liter of distillate contains less than 5 cc. of water-insoluble material (Note 7).

The reaction mixture is cooled, and the crude amines which separate are collected on a suction funnel and washed twice with 400-cc. portions of water. The filtrate and washings should be saved for the recovery of iodine (Note 8). The precipitate on the funnel is transferred to a 2-l. beaker, dissolved in about 1 l. of benzene, filtered, and the benzene-insoluble part washed three times with 75-cc. portions of benzene. The benzene solution and washings are combined and separated mechanically from as much water as possible. The water is then completely removed by distilling until the distillate comes over clear. If necessary, dry benzene is added to the solution in order to have a final volume of about 1200 cc.

When the water is entirely removed, the benzene solution is cooled and an excess of

dry hydrogen chloride is passed into it to precipitate the diphenylamine as the hydrochloride (Note 9).

After standing about three hours, the diphenylamine hydrochloride is filtered and washed with benzene (Note 10). The benzene is distilled from the filtrate (Note 11), and the residual triphenylamine is transferred to a 500-cc. modified Claisen flask (p. 130) and distilled under reduced pressure. The first fraction consists of some benzene, then the temperature rises rapidly and a few cubic centimeters of deeply colored distillate come over just before the amine fraction, which is collected at 195–205°/10–12 mm. The distillate is a yellow liquid which soon solidifies to a light yellow solid. The side arm of the distilling flask should be of rather large bore (about 10 mm.) to prevent clogging by the amine which solidifies. The crude product weighs 220–235 g. and melts at 120–124°.

In order to obtain a pure product the amine is dissolved in about 700 cc. of boiling ethyl acetate under a reflux condenser. When the amine has dissolved the solution is rapidly cooled and stirred, whereupon the amine separates in almost white crystals. Further crops of crystals may be obtained on concentrating the solution and cooling. The last portions may be colored, but one recrystallization from ethyl acetate gives a nearly colorless product (Note 12). The total yield of pale yellow product which melts at 126° is 200–210 g. (82–85 per cent of the theoretical amount) (Note 13).

2. Notes

1. The air condenser used here was 65 cm. long and of 13-mm. bore, and the vertical water condenser, 40 cm. in length. Cork stoppers were used, and it was found desirable to protect their exposed surfaces by coating them with water-glass, allowing these to dry, and then coating with lead foil. It is best to boil the mixture on a sand bath and to cover with asbestos that part of the flask not immersed in the sand.
2. Technical diphenylamine which has been distilled under reduced pressure and collected over a 5° range (159–164°/4 mm.) is satisfactory.
3. The nitrobenzene should not contain any free acid. Should there be free acid present, it can be removed by shaking with solid potassium carbonate.
4. "Natur Kupfer C" is a good catalyst, but ordinary copper bronze may be used.
5. The time required for the completion of reaction varies with the rate of stirring. When the stirring is very vigorous most of the water comes over within twelve hours.
6. This heating should be done carefully, preferably on a sand bath, because of the danger of breaking the flask due to the caking of some undissolved potassium carbonate.
7. In general, about 8–10 l. of aqueous distillate is required, and practically all but about 25 cc. of the nitrobenzene is recovered. It is recommended that the removal of nitrobenzene by steam distillation be fairly complete in order to avoid a gummy residue.
8. Most of the iodine can be recovered as potassium iodide mixed with some

potassium carbonate. A little cuprous iodide is also present.

9. The hydrogen chloride is introduced through a delivery tube at least 25 mm. in diameter and about 10 cm. under the surface of the liquid. If the gas is introduced rapidly enough and the mixture stirred occasionally there is little trouble with clogging of the delivery tube.

10. The crude diphenylamine may be recovered by decomposing the hydrochloride with water and filtering the mixture.

11. A large amount of hydrogen chloride is evolved during the distillation, and some provision must be made to keep it out of the room. A gas-absorption trap (Fig. 7 on p. 97) may be used.

12. Because of the lower solubility of triphenylamine in ethyl alcohol this solvent may be used advantageously in washing the crystals and in recrystallizing small amounts of the compound.

13. *N*-Phenylcarbazole may be made in an analogous manner by substituting carbazole for diphenylamine. If stirring and heating are both very vigorous, twelve hours suffices for the reaction. The yield of purified product is about 88 per cent of the theoretical amount, and the compound melts at 88–89°. The crystals, when crushed, emit a strong violet light.

3. Discussion

The procedure described is a modification of that by Goldberg and Nimerovsky.[1] Triphenylamine can also be prepared by the treatment of aniline or diphenylamine with potassium and then bromobenzene,[2] by the action of sodium on diphenylamine and bromobenzene,[3] and from aniline and anhydrous hydrogen chloride under pressure at about 250°.[4]

References and Notes

1. Goldberg and Nimerovsky, Ber. **40**, 2452 (1907).
2. Merz and Weith, Ber. **6**, 1514 (1873).
3. Heydrich, Ber. **18**, 2156 (1885).
4. General Aniline Works, U. S. pat. 2,051,123 [C. A. **30**, 6760 (1936)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

copper bronze

ethyl alcohol (64-17-5)

potassium carbonate (584-08-7)

hydrogen chloride (7647-01-0)

Benzene (71-43-2)

ethyl acetate (141-78-6)

aniline (62-53-3)

sodium sulfate (7757-82-6)

potassium iodide (7681-11-0)

copper powder (7440-50-8)

iodine (7553-56-2)

sodium (13966-32-0)

Nitrobenzene (98-95-3)

bromobenzene (108-86-1)

potassium (7440-09-7)

Iodobenzene (591-50-4)

Triphenylamine (603-34-9)

diphenylamine (122-39-4)

diphenylamine hydrochloride (537-67-7)

cuprous iodide (7681-65-4)

carbazole (86-74-8)

N-Phenylcarbazole (1150-62-5)

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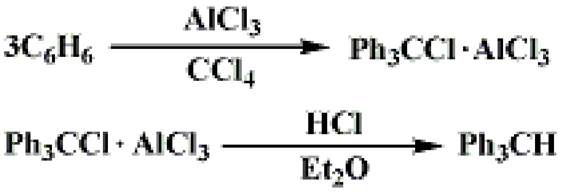
Organic Syntheses, CV 1, 548

TRIPHENYLMETHANE

[Methane, triphenyl-]



Submitted by J. F. Norris
Checked by H. T. Clarke and T. F. Murray.

1. Procedure

To a mixture of 292 g. (332 cc., 3.7 moles) of dry benzene and 116 g. (73.2 cc., 0.75 mole) of dry carbon tetrachloride (Note 1), in a 1-l. flask provided with a reflux condenser having a calcium chloride tube at its upper end, is added 100 g. (0.75 mole) of anhydrous aluminum chloride in lumps (Note 2). The flask is at once immersed in ice water to within 5 cm. of the top, and allowed to stand for twenty-four hours, the temperature of the water being allowed to rise to that of the room (Note 3). One hundred and ten grams (153 cc., 1.48 moles) of anhydrous ether is added in small portions, through the condenser, the flask being shaken occasionally during the twenty minutes required for the addition.

The mixture is allowed to stand for twenty-four hours, and is then poured into a 5-l. flask containing 650 g. of ice and 25 cc. of concentrated hydrochloric acid. One liter of benzene is then added, and the mixture heated on a steam bath under a return condenser. After gently boiling for five or ten minutes, the mixture is allowed to cool to 40–50°, when the benzene layer is separated, washed with 700 cc. of warm water containing 25 cc. of concentrated hydrochloric acid, and distilled. After the benzene has been removed under atmospheric pressure, the residue is transferred to a 300-cc. flask and distilled under reduced pressure, and a fraction boiling over the range 190–215°/10 mm. collected (Note 4). This weighs 135–160 g.; it solidifies on cooling. It is recrystallized from 550–650 cc. of ethyl alcohol (Note 5), and a colorless product, crystallizing in needles which melt sharply at 92°, is obtained. This is filtered off and washed twice with 30-cc. portions of fresh alcohol. The alcoholic mother liquor is concentrated and the residue distilled under reduced pressure, material which distils over at 190–200°/10 mm. being collected. This is recrystallized from ethyl alcohol, and 6–7 g. more of pure material is thus obtained. The total yield of recrystallized product is 125–154 g. (68–84 per cent of the theoretical amount).

2. Notes

1. A convenient method for removing moisture from the carbon tetrachloride

and the benzene consists in distilling off about one-tenth of the liquid; this first fraction contains all the moisture which may have been dissolved in the commercial products. It is, as a rule, unnecessary to distil the remaining liquid before use.

2. The aluminum chloride may be a good grade of technical anhydrous material. If a powdered product is employed, the reaction is apt to proceed too rapidly. The lump material appears to be somewhat more efficient.
The calcium chloride tube can be connected with a trap (Fig. 7 on p. 97) for removal of the evolved hydrogen chloride.

3. With shorter periods of standing and lower temperatures, the yield falls off materially. Thus, in one experiment in which the mixture was allowed to stand for twenty-four hours at 5–8°, a large proportion of a lower-boiling product (apparently diphenylmethane) was formed, and only 109 g. of crude triphenylmethane was obtained.

4. A dark, tarry residue amounting to 25–40 g. remains in the flask.

5. Methyl alcohol may also be employed, but it is necessary to use 1600–1700 cc. of it. Triphenylmethane dissolves in one-third of its weight of warm benzene; it separates from this solution with benzene of crystallization, which is lost on exposure to air or recrystallization from alcohol.

3. Discussion

Triphenylmethane can be prepared by the interaction of benzene and chloroform in the presence of aluminum chloride[1] or ferric chloride;[2] by the reduction of triphenylchloromethane by ether under the influence of aluminum chloride,[3] ferric chloride,[2] or zinc chloride;[4] by the reduction of triphenylchloromethane or triphenylcarbinol by means of alcohol in the presence of sulfuric acid;[5] by heating triphenylcarbinol with formic acid;[6] and from benzene and benzal chloride in the presence of beryllium chloride.[7]

References and Notes

1. Schwartz, Ber. **14**, 1516 (1881); Friedel and Crafts, Bull. soc. chim. (2) **37**, 6 (1882); Allen and Kölliker, Ann. **227**, 108 (1885); Biltz, Ber. **26**, 1961 (1893).
2. Meissel, Ber. **32**, 2422 (1899).
3. Gomberg, Ber. **33**, 3147 (1900); Norris and Young, J. Am. Chem. Soc. **46**, 2580 (1924).
4. Gomberg, J. Am. Chem. Soc. **35**, 204 (1913).
5. Schmidlin and Garcia-Banùs, Ber. **45**, 3188 (1912).
6. Satisfactory yields can be obtained by refluxing practical triphenylcarbinol with an excess of formic acid. (W. W. Hartman, private communication). This general method, without statement of yields, has been mentioned by the following: Guyot and Kovache, Compt. rend. **154**, 121 (1912); Kauffmann and Pannwitz, Ber. **45**, 766 (1912); Kovache, Ann. chim. (9) **10**, 196 (1918).
7. Bredereck, Lehmann, Schönfeld, and Fritzsohe, Ber. **72**, 1415 (1939).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethyl alcohol, alcohol (64-17-5)

sulfuric acid (7664-93-9)

hydrogen chloride, hydrochloric acid (7647-01-0)

Benzene (71-43-2)

methyl alcohol (67-56-1)

ether (60-29-7)

chloroform (67-66-3)

formic acid (64-18-6)

carbon tetrachloride (56-23-5)

aluminum chloride (3495-54-3)

Diphenylmethane (101-81-5)

zinc chloride (7646-85-7)

ferric chloride (7705-08-0)

Triphenylmethane, Methane, triphenyl- (519-73-3)

Triphenylchloromethane (76-83-5)

Triphenylcarbinol (76-84-6)

benzal chloride (98-87-3)

beryllium chloride (7787-47-5)

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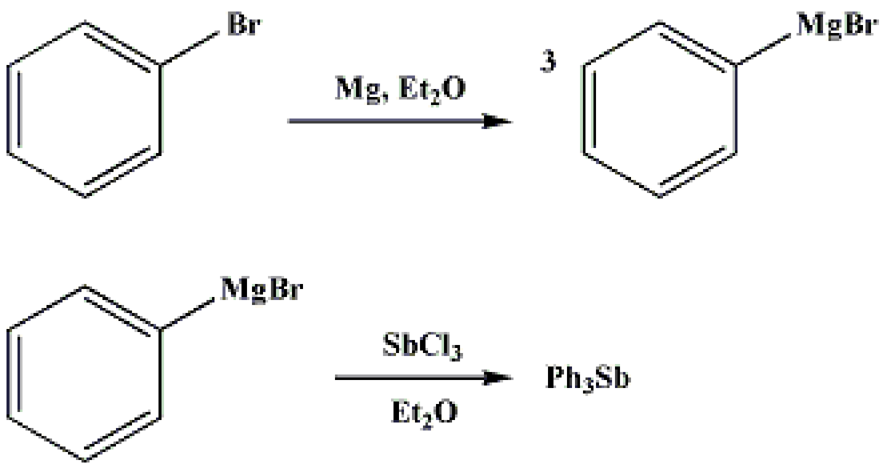
Organic Syntheses, CV 1, 550

TRIPHENYLSTIBINE

[Stibine, triphenyl-]



Submitted by G. S. Hiers
Checked by Henry Gilman and F. Schulze.

1. Procedure

In a 2-l. round-bottomed, three-necked flask fitted with a mercury-sealed mechanical stirrer, a reflux condenser, and a separatory funnel is placed 40 g. (1.65 atoms) of magnesium turnings (Note 1). This is covered with 200 cc. of dry ether, and there is then added 100 cc. of a mixture of 260 g. (1.65 moles) of dry bromobenzene and 800 cc. of dry ether. As soon as the reaction starts, 200 cc. more of dry ether is added and the remainder of the bromobenzene solution at such a rate as to cause gentle boiling (about two hours). With external cooling, the time may be shortened.

When all the bromobenzene has been added, there is added slowly through the separatory funnel a solution of 114 g. (0.5 mole) of freshly distilled antimony trichloride (m.p. 67–73°) in 300 cc. of dry ether. The reaction proceeds smoothly and even briskly with the freshly distilled chloride. However, if the latter has not been freshly prepared, gentle warming may be required to start the reaction. When all the antimony trichloride has been added (one to two hours), the mixture is heated on the steam bath for one hour longer.

When cool, the reaction mixture is poured slowly with stirring into 1 l. of ice and water (Note 2). If the stirring is thorough, most of the triphenylstibine is to be found in the ether layer. The hydrolysis mixture is filtered through a Büchner funnel and the residue on the filter extracted three times (Note 3) with 100-cc. portions of ether. The aqueous layer is separated and extracted twice with 200-cc. portions of ether. The combined ether portions are evaporated slowly on a steam bath to remove the ether, and there remains behind a yellow semi-solid which crystallizes to a white solid on

cooling (Note 4). The yield of crude product melting at 49° is 145–160 g. (82–90 per cent of the theoretical amount). For purification from a small amount of biphenyl which is present in the crude product, 90 g. of triphenylstibine is dissolved in 200 cc. of petroleum ether (b.p. 40–50°) by warming on a steam bath. There is generally a small amount of insoluble residue which is filtered and the filtrate cooled in a freezing mixture. The triphenylstibine separates as small prisms and weighs 58–65 g.; by further concentration of the filtrate to an approximate volume of 50 cc. and then cooling again, an additional 15–20 g. of product separates. Both portions melt at 50°.

2. Notes

1. The excess of the Grignard reagent insures the complete removal of all the halogen from the antimony.
2. During the hydrolysis the use of acids to dissolve the magnesium hydroxide must be avoided, for the presence of acid tends to decompose the antimony compound.
3. During the filtration some other evaporates and the stibine compound is left on the filter with the magnesium hydroxide. Extraction is necessary to remove this product.
4. The same method may be used for the preparation of tri-*p*-tolylstibine. Starting with 282 g. (1.65 moles) of *p*-bromotoluene (p. 136) and proceeding in the same manner as described there was secured 150–157 g. (77–80 per cent of the theoretical amount) of crude tri-*p*-tolylstibine. This product purified by recrystallization from methyl alcohol or ether melts at 125–126°. The reaction is somewhat more vigorous, and sometimes cooling is necessary at first.

3. Discussion

Triphenylstibine can be prepared from the interaction of chlorobenzene and antimony trichloride with sodium,[1] from antimony trichloride and phenylmagnesium bromide,[2] and from antimony and phenyllithium.[3]

References and Notes

1. Michaelis and Reese, Ann. **233**, 42 (1886); Morgan and Vining, J. Chem. Soc. **117**, 777 (1920).
2. Pfeiffer and Heller, Ber. **37**, 4621 (1904).
3. Talalaeva and Kocheshkov, J. Gen. Chem. (U.S.S.R.) **8**, 1831 (1938) [C. A. **33**, 5819 (1939)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

antimony compound

stibine compound

methyl alcohol (67-56-1)

ether (60-29-7)

magnesium turnings (7439-95-4)

chlorobenzene (108-90-7)

sodium (13966-32-0)

bromobenzene (108-86-1)

Biphenyl (92-52-4)

antimony trichloride

magnesium hydroxide

Phenylmagnesium bromide (100-58-3)

Triphenylstibine, Stibine, triphenyl- (603-36-1)

antimony (7440-36-0)

Phenyllithium (591-51-5)

p-Bromotoluene (106-38-7)

Tri-p-tolylstibine

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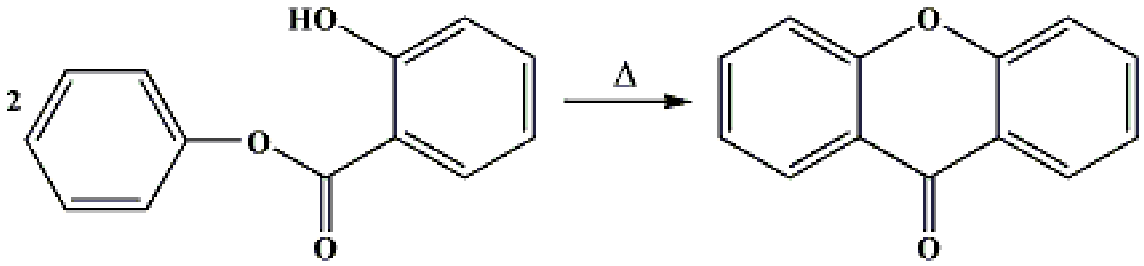
Organic Syntheses, CV 1, 552

XANTHONE



Submitted by A. F. Holleman
Checked by H. T. Clarke

1. Procedure

Five hundred grams (2.34 moles) of phenyl salicylate is heated in a 1-l. special distilling flask having a wide (Note 1) side arm 20–25 cm. long, and fitted with two thermometers, one extending to the bottom of the flask, and the other just below the side arm. When the temperature of the liquid reaches 275–285°, phenol begins to distil. The heating is so regulated that the temperature of the vapor never exceeds 175° and preferably remains below 170° (Note 2). In this way the phenol distils at the rate of 5–10 drops per minute. The temperature of the liquid rises gradually (Note 3), and after six to seven hours reaches 350–355°. At this point the distillation of the phenol practically ceases; the weight of the distillate is 220–225 g.

The receiver is now changed, the lower thermometer is raised from the liquid (Note 4), and the contents of the flask distilled as rapidly as possible (Note 5). Heating is continued until the tarry residue begins to foam; towards the end of the distillation the color of the vapor becomes deep yellow with a greenish fluorescence. The distillate weighs 165–170 g.; it is poured while still molten into a cold dish and allowed to cool, ground in a mortar with 100 cc. of 5 per cent sodium hydroxide, and warmed on the steam bath for ten to fifteen minutes with 400 cc. of this solution. When cold, the xanthone is filtered off, washed free of alkali, and dried. A small amount of low-melting impurity is removed by boiling for ten to fifteen minutes with 250 cc. of methyl alcohol, cooling, filtering, and washing with the same solvent. A few grams can be recovered from the filtrate. The product melting at 170–172°, after softening slightly at 168–170°, weighs 141–145 g. (61–63 per cent of the theoretical amount). It is pure enough for the preparation of xanthydrol (p. 554). A purer product can be obtained by recrystallization from twenty parts of 95 per cent ethyl alcohol, from which it separates as pale yellow needles, melting at 173–174°.

2. Notes

1. The side arm should have an internal diameter of at least 10 mm. in order to minimize the danger of stoppage by solidified distillate. This danger occurs

particularly when the higher-melting xanthone first begins to distil. No condenser is employed, the flask used as a receiver being cooled sufficiently by the air to condense all the vapors.
2. The regulation of temperature is difficult at first, but becomes easier after the first half-hour.
3. In consequence of this gradual rise in temperature, it is necessary to increase the size of the flame gradually.
4. Although the boiling point of xanthone is about 350°, the liquid in the flask reaches temperatures which would be dangerous to a mercury thermometer.
5. If a Pyrex flask is used, it is not only safe, but advisable, to remove the wire gauze and heat directly with the free flame. This permits the xanthone to be distilled rapidly and with a minimum loss.

3. Discussion

Xanthone can be prepared by heating phenyl salicylate[1] alone or with acetic anhydride;[2] by heating salicylic acid, phenol, and acetic anhydride;[3] and by warming *o*-phenoxybenzoic acid with concentrated sulfuric acid[4] or phosphorus pentoxide;[5] by distilling *o*-phenoxybenzoyl chloride *in vacuo*;[6] and by heating aspirin[7] or *o*-hydroxybenzophenone.[8]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 554

References and Notes

1. Graebe, Ann. **254**, 279 (1889).
2. Perkin, Ber. **16**, 339 (1883).
3. Dhar, J. Chem. Soc. **117**, 1061 (1920).
4. Graebe, Ber. **21**, 501 (1888).
5. Knapp, J. prakt. Chem. **146**, 118 (1936).
6. Lock and Kempter, Monatsh. **67**, 25 (1936).
7. Spektor, Khim. Farm. Prom. **1933**, 195 [C. A. **28**, 575 (1934)].
8. Cullinane, Morgan, and Plummer, Rec. trav. chim. **56**, 631 (1937).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethyl alcohol (64-17-5)

sulfuric acid (7664-93-9)

methyl alcohol (67-56-1)

acetic anhydride (108-24-7)

sodium hydroxide (1310-73-2)

phenol (108-95-2)

salicylic acid

Xanthone (90-47-1)

phenyl salicylate (118-55-8)

Xanthydrol (90-46-0)

aspirin (50-78-2)

phosphorus pentoxide (1314-56-3)

o-phenoxybenzoic acid (2243-42-7)

o-phenoxybenzoyl chloride

o-hydroxybenzophenone (117-99-7)

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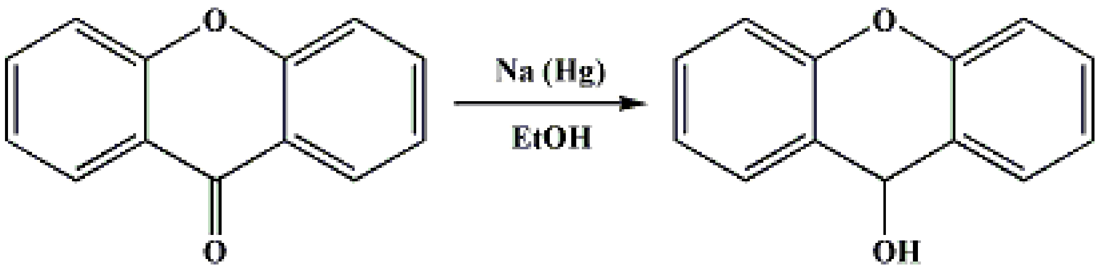
Organic Syntheses, CV 1, 554

XANTHYDROL



Submitted by A. F. Holleman
Checked by H. T. Clarke and C. R. Noller.

1. Procedure

An amalgam prepared from 9.0 g. (0.39 atom) of sodium and 750 g. (55 cc.) of mercury (Note 1) is warmed to about 50° (Note 2) in a 500-cc. Pyrex round-bottomed flask (Note 3). To it is then added a cold suspension of 25 g. (0.13 mole) of xanthone (p. 552) in 175 cc. of 95 per cent ethyl alcohol. The flask is at once stoppered, held in a cloth, and vigorously shaken, the stopper being raised from time to time to release any pressure. The temperature rises rapidly to 60–70°. The solid xanthone rapidly goes into solution, a very faint and transient blue color being developed. At the end of about five minutes the alcoholic solution is clear and practically colorless.

After a further ten-minute shaking the mercury is separated and washed with 10–15 cc. of alcohol. The alcoholic solution is filtered while warm and slowly poured with stirring into 2 l. of cold distilled water. The precipitated xanthydrol is filtered with suction, washed with water until free of alkali, and dried at 40–50° to constant weight. The crystalline product, which weighs 23–24 g. (91–95 per cent of the theoretical amount), melts at 121–123° and is practically pure (Note 4) and (Note 5).

2. Notes

1. The amalgam may be conveniently prepared by placing the sodium in the 500-cc. flask, covering it with 15–20 cc. of dry toluene, and cautiously melting the metal over a free flame. The flame is then extinguished and the mercury added in drops, with occasional shaking. The reaction is extremely vigorous at first, but the rate of addition may be rapidly increased after the first 2–3 cc. of mercury has been added. The addition is so regulated that the toluene boils continuously, and it is finally allowed to volatilize completely. The toluene vapor remaining above the amalgam tends to protect it from the action of the air.
2. The amalgam is semi-solid at room temperature, but is completely melted at 50°. If made as in (Note 1), it is merely allowed to cool to 50° before the alcoholic xanthone is added.
3. A thick-walled flask is necessary; although no great pressure is developed at

any time, the impact of the mercury during shaking might break thin glass.
4. Xanthydrol is employed as a reagent for the determination of urea, with which it forms an insoluble condensation product. The material obtained is entirely satisfactory for this purpose; if desired, however, it may be recrystallized from alcohol, whereby the melting point is raised by about 1°.
5. Because of the marked instability of xanthydrol, melting-point determination may afford little assurance of purity. It has been suggested that xanthydrol be prepared directly prior to use or else kept in an alcohol solution in which it is much more stable than in the solid state (A. M. Ward,[1] private communication).

3. Discussion

Xanthydrol can be prepared by the reduction of xanthone in alcoholic solution with zinc dust and sodium hydroxide,[2] with a low percentage sodium amalgam,[1] or with aluminum isopropoxide.[3] The procedure described is based on the method of Fosse.[1]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 228
- Org. Syn. Coll. Vol. 1, 377
- Org. Syn. Coll. Vol. 1, 552
- Org. Syn. Coll. Vol. 2, 607

References and Notes

1. Fosse, Ann. chim. (9) **6**, 58 (1916); Kny-Jones and Ward, Analyst, **54**, 574 (1929) [C. A. **24**, 39 (1930)]; Graff, Maculla, and Graff, J. Biol. Chem. **121**, 73 (1937).
2. Meyer and Saul, Ber. **26**, 1276 (1893); Adriani, Rec. trav. chim. **35**, 180 (1915); Kirkhgof and Spektor, Khim. Farm. Prom. **1934**, No. 2, 12 [C. A. **28**, 5451 (1934)].
3. Lund, Ber. **70**, 1520 (1937).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

amalgam

ethyl alcohol, alcohol (64-17-5)

sodium hydroxide (1310-73-2)

mercury (7439-97-6)

toluene (108-88-3)

zinc (7440-66-6)

sodium (13966-32-0)

aluminum isopropoxide

urea (57-13-6)

Xanthone (90-47-1)

Xanthydrol (90-46-0)

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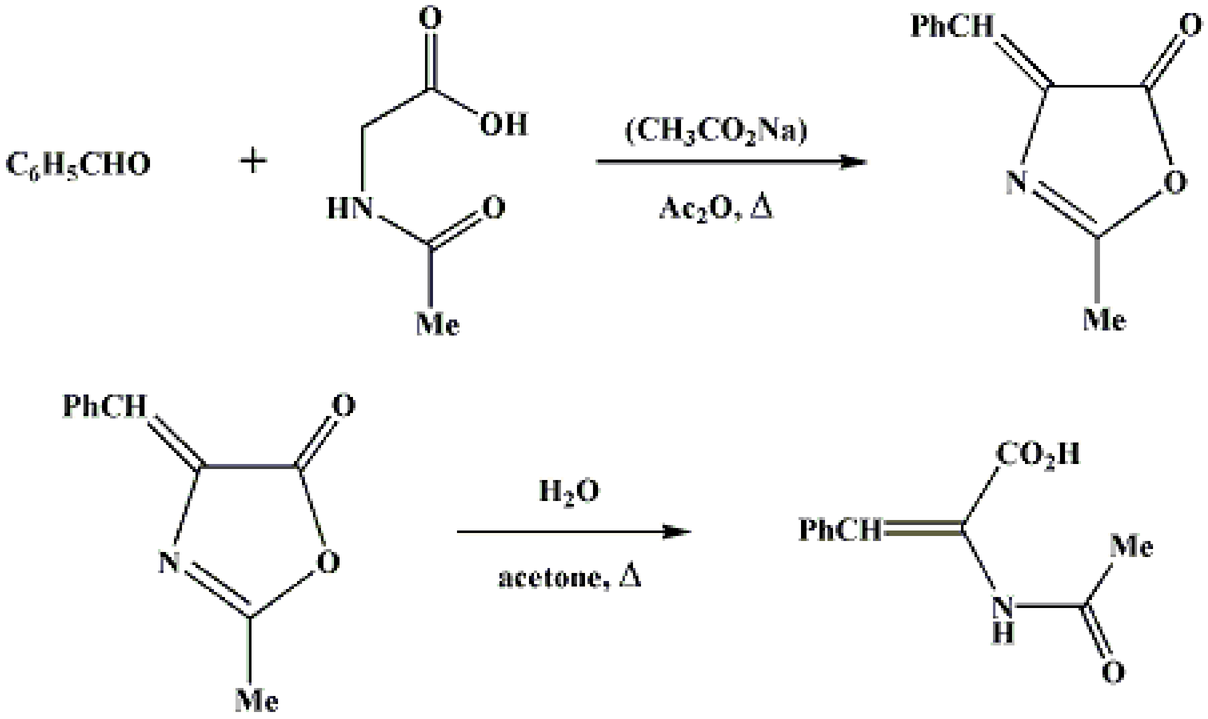
Organic Syntheses, CV 2, 1

α-ACETAMINOCINNAMIC ACID

[Cinnamic acid, α-acetamido-]



Submitted by R. M. Herbst and D. Shemin.
Checked by Reynold C. Fuson and E. A. Cleveland.

1. Procedure

A mixture of 58.5 g. (0.5 mole) of acetylglycine (p. 11) (Note 1), 30 g. (0.37 mole) of anhydrous sodium acetate, 79 g. (0.74 mole) of freshly distilled benzaldehyde, and 134 g. (1.25 moles) of 95 per cent acetic anhydride in a loosely corked 1-l. Erlenmeyer flask is warmed on the steam bath with occasional stirring until solution is complete (ten to twenty minutes). The resulting solution is boiled for one hour under reflux, cooled, and placed in a refrigerator overnight. The solid mass of yellow crystals is treated with 125 cc. of cold water and broken up with a stirring rod. The crystals are then transferred to a Büchner funnel and washed thoroughly with cold water (Note 2). After being dried in a vacuum desiccator over phosphorus pentoxide and potassium hydroxide, the crude azlactone weighs 69–72 g. (74–77 per cent of the theoretical amount). The product melts at 148–150°, and is sufficiently pure for preparative purposes (Note 3).

In a 1-l. round-bottomed, short-necked flask 47 g. (0.25 mole) of the crude azlactone of α-acetaminocinnamic acid is dissolved by boiling with a mixture of 450 cc. of acetone and 175 cc. of water. Hydrolysis is completed by boiling under reflux for four hours. Most of the acetone is then removed by distillation at ordinary pressure on a

steam bath. The residual solution is diluted with 400 cc. of water, heated to boiling for five minutes to ensure complete solution of the acetamino acid, and filtered (Note 4) and (Note 5). A small amount of undissolved material (0.2–0.5 g.) which remains on the filter is washed with 50–75 cc. of boiling water. Any crystals which separate from the filtrate are redissolved by heating, after which the solution is boiled for five minutes with 10 g. of Norite and filtered with the aid of gentle suction while still almost at the boiling point (Note 5). The Norite is washed thoroughly on the funnel with two to four 50-cc. portions of boiling water to remove the crystals which separate during the filtration, and the washings are added to the main filtrate. After standing in a refrigerator overnight the colorless, crystalline needles are collected on a Büchner funnel (Note 6), washed with 150–200 cc. of ice-cold water, and dried for several hours at 90–100°. The yield is 41–46 g. (80–90 per cent of the theoretical amount) of practically pure material, m.p. 191–192° (Note 7).

2. Notes

1. The azlactone of α-acetaminocinnamic acid may also be prepared by substituting the equivalent amount of glycine for acetylglycine and increasing the amount of acetic anhydride to three molecular proportions, but the yield is only about 45–50 per cent of the theoretical amount.
2. If the excess benzaldehyde is not almost completely removed by repeated washing with water, a final wash with 50–75 cc. of ether may be advantageous, although this causes some loss of azlactone owing to its solubility in ether.
3. The azlactone can be recrystallized from alcohol, from carbon tetrachloride, or from ethyl acetate with addition of petroleum ether. Aqueous solvents should be avoided, since the azlactone ring is easily opened by water. When alcohol is used for recrystallization, there is some danger of opening the azlactone ring with the formation of an ester, particularly on prolonged heating of the solution.
4. The solution may be filtered by gravity through a large folded filter (preferably in a steam-jacketed funnel), or through a Büchner funnel with gentle suction.
5. The solubility of α-acetaminocinnamic acid in water decreases very rapidly on cooling below the boiling point of the solution. Since the solution is very nearly saturated with the product, a large share of the acid will crystallize in the funnel during filtration if the solution is allowed to cool too much. This property of the product makes it inadvisable to work with larger quantities.
6. Occasionally after treatment with Norite the solution is green owing to traces of iron and phenylpyruvic acid. If the crystals are still yellow at this point, the treatment with Norite should be repeated before the product is collected on a filter.
7. If further purification is desired, the product may be recrystallized from 600 cc. of boiling water, with a loss of about 5 per cent. The loss is due in part to hydrolysis of the product with the formation of phenylpyruvic acid.

3. Discussion

The azlactone of α-acetaminocinnamic acid has been prepared by heating a mixture of glycine, benzaldehyde, acetic anhydride, and anhydrous sodium acetate;[1, 2] and from *N*-chloroacetylphenylalanine by treatment with acetic anhydride.[2]

α-Acetaminocinnamic acid has been prepared from the corresponding azlactone by hydrolysis with either aqueous sodium hydroxide[1] or with boiling water alone.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 489
- Org. Syn. Coll. Vol. 2, 519

References and Notes

1. Erlenmeyer, Jr., and Früstück, Ann. **284**, 48 (1895).
2. Bergmann and Stern, ibid. **448**, 26 (1926).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

Azlactone of α-Acetaminocinnamic acid

alcohol (64-17-5)

ethyl acetate (141-78-6)

ether (60-29-7)

acetic anhydride (108-24-7)

sodium acetate (127-09-3)

sodium hydroxide (1310-73-2)

iron (7439-89-6)

carbon tetrachloride (56-23-5)

benzaldehyde (100-52-7)

acetone (67-64-1)

Norite (7782-42-5)

potassium hydroxide (1310-58-3)

Glycine (513-29-1)

α-Acetaminocinnamic acid, Cinnamic acid, α-acetamido- (5469-45-4)

Acetylglycine (543-24-8)

Phenylpyruvic acid (156-06-9)

phosphorus pentoxide (1314-56-3)

N-chloroacetylphenylalanine (721-65-3)

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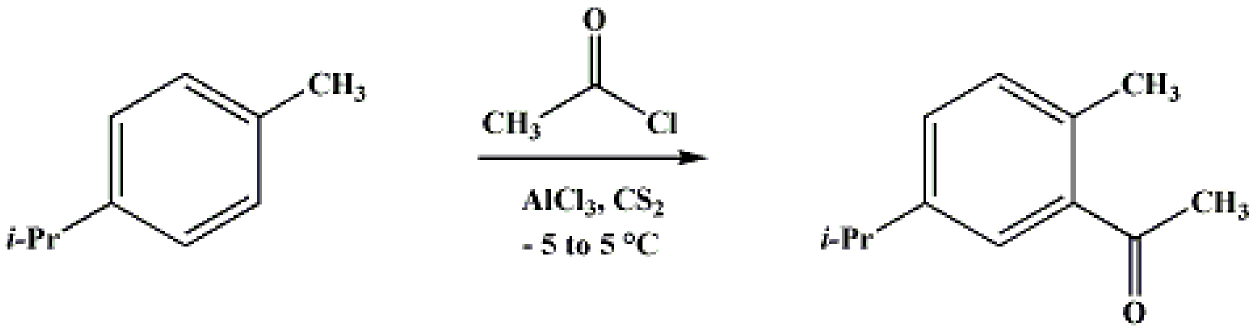
Organic Syntheses, *CV 2, 3*

ACETO-*p*-CYMENE

[Acetophenone, 5-isopropyl-2-methyl-]



Submitted by C. F. H. Allen
Checked by Reynold C. Fuson and Charles F. Woodward.

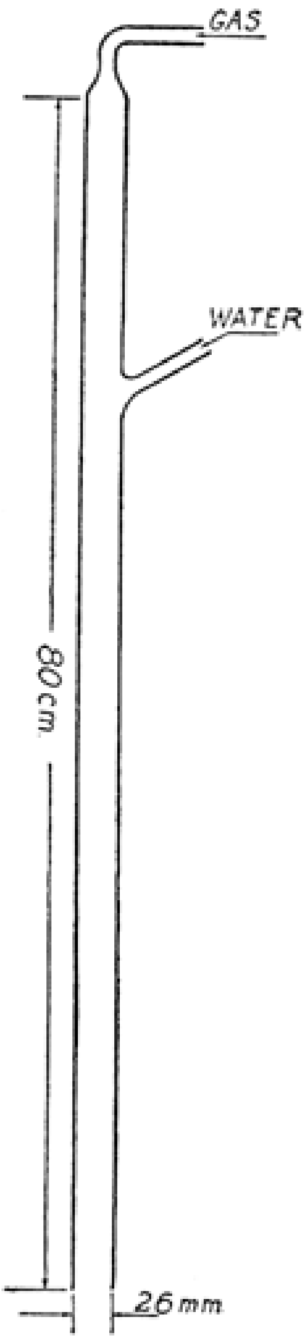
1. Procedure

A 1-l. three-necked flask is fitted with a dropping funnel, a stirrer, a thermometer for reading low temperatures (Note 1), and a condenser, to the upper end of which is attached a tube for disposing of the hydrogen chloride evolved (Note 2). A mixture of 200 cc. of carbon disulfide and 180 g. (1.35 moles) of anhydrous aluminum chloride is placed in the flask which is then immersed in an ice-salt freezing mixture and stirred very vigorously until the temperature of the mixture is –5° or below. A mixture of 175 g. (1.3 moles) of *p*-cymene and 110 g. (100 cc., 1.4 moles) of acetyl chloride is added from the dropping funnel at such a rate that the temperature never rises above 5°. This addition requires about three and one-third hours (Note 3). The mixture is allowed to stand overnight and is then poured upon 1 kg. of cracked ice to which 200 cc. of concentrated hydrochloric acid has been added. The mixture is extracted with three 700-cc. portions of ether; the ether solution is dried over anhydrous calcium chloride and distilled at ordinary pressure from a Claisen flask provided with an indented column, until the temperature reaches 190°. The material that remains in the flask is fractionally distilled twice under diminished pressure. The principal fraction is aceto-*p*-cymene, a pale yellow oil boiling at 124–125°/12 mm. (155–157°/30 mm.). It weighs 115–125 g. (50–55 per cent of the theoretical amount) (Note 4). About 50 g. of cymene is recovered (Note 5), and there is a small amount (10–12 g.) of residual oil left in the flask (Note 6).

2. Notes

1. Since it is impossible to read that part of the thermometer scale which extends into the reaction flask, a thermometer should be used which when in position has the zero point above the stopper of the flask. A thermometer reading from –50° to +50° is recommended.
2. A gas trap of the type shown in f.htmig. 1 is suitable for this purpose. Another gas trap is shown in Org. Syn. Coll. Vol. I, **1941**, 97.

Fig. 1



3. After about two-thirds of the mixture has been added the rate of addition may be increased somewhat. The time required for the addition depends on the efficiency of the cooling and stirring; the stirring must be vigorous. With one-half of these amounts in a 500-cc. flask, the time required is only about one and one-third hours since, under these conditions, it is easier to control the temperature.
4. From the first fractionation a fraction boiling over a 20° range is taken as crude ketone; e.g., at 28–30 mm. the fraction is taken which boils at 145–165°. Much trouble is caused by the tendency of the ketone to become superheated.
5. Acetyl chloride gives a better yield and less high-boiling residue than acetic anhydride.

6. This procedure has also been used successfully in the acetylation of cumene and *tert.*-butylbenzene. At the low temperatures employed there is very little

decomposition, as is shown by the small amount of high-boiling residue.

3. Discussion

Aceto-*p*-cymene can be prepared by the action of acetyl chloride on *p*-cymene in the presence of anhydrous aluminum chloride[1] or ferric chloride.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 24
- Org. Syn. Coll. Vol. 2, 543
- Org. Syn. Coll. Vol. 3, 23
- Org. Syn. Coll. Vol. 3, 446
- Org. Syn. Coll. Vol. 4, 42
- Org. Syn. Coll. Vol. 4, 62
- Org. Syn. Coll. Vol. 4, 157
- Org. Syn. Coll. Vol. 4, 162
- Org. Syn. Coll. Vol. 4, 364
- Org. Syn. Coll. Vol. 4, 387
- Org. Syn. Coll. Vol. 4, 404
- Org. Syn. Coll. Vol. 4, 554
- Org. Syn. Coll. Vol. 4, 590
- Org. Syn. Coll. Vol. 4, 715
- Org. Syn. Coll. Vol. 4, 746
- Org. Syn. Coll. Vol. 4, 755
- Org. Syn. Coll. Vol. 4, 804
- Org. Syn. Coll. Vol. 4, 807
- Org. Syn. Coll. Vol. 4, 844
- Org. Syn. Coll. Vol. 4, 960
- Org. Syn. Coll. Vol. 4, 984
- Org. Syn. Coll. Vol. 5, 196
- Org. Syn. Coll. Vol. 5, 572
- Org. Syn. Coll. Vol. 5, 580
- Org. Syn. Coll. Vol. 5, 1135

References and Notes

1. Lacourt, Bull. soc. chim. Belg. **38**, 17 (1929); Claus, Ber. **19**, 232 (1886); Klages and Lickroth, ibid. **32**, 1563 (1899); Verley, Bull. soc. chim. (3) **17**, 910 (1897).
2. Meissel, Ber. **32**, 2421 (1899).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Acetophenone, 5-isopropyl-2-methyl-

calcium chloride (10043-52-4)

hydrogen chloride, hydrochloric acid (7647-01-0)

ether (60-29-7)

acetic anhydride (108-24-7)

acetyl chloride (75-36-5)

aluminum chloride (3495-54-3)

carbon disulfide (75-15-0)

ferric chloride (7705-08-0)

cymene, p-cymene (99-87-6)

cumene (98-82-8)

Aceto-p-cymene

tert.-butylbenzene (98-06-6)

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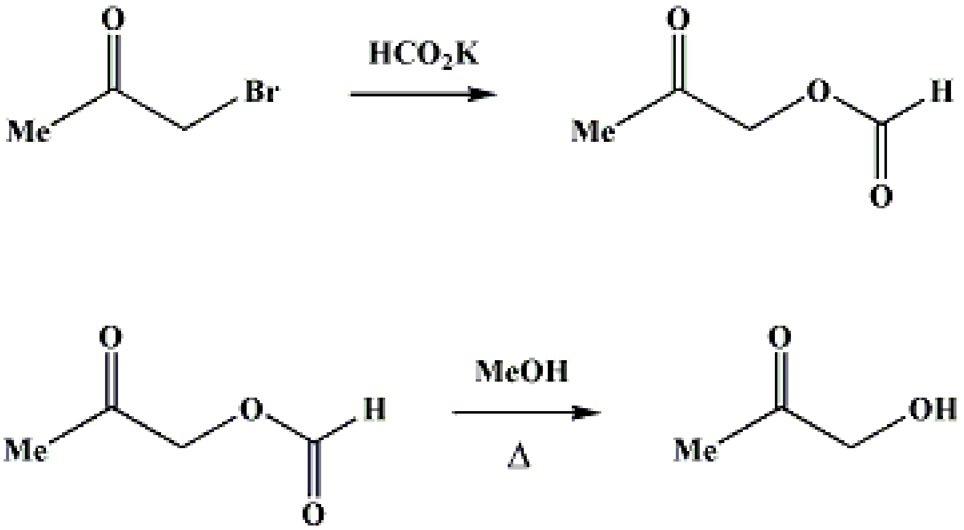
Organic Syntheses, CV 2, 5

ACETOL

[2-Propanone, 1-hydroxy-]

$$HCO_2C_2H_5 + KOH \longrightarrow HCO_2K + C_2H_5OH$$



Submitted by P. A. Levene and A. Walti.
Checked by Frank C. Whitmore and J. Pauline Hollingshead.

1. Procedure

In a 3-l. round-bottomed flask fitted with a 75-cm. Liebig condenser is placed 210 g. of potassium hydroxide (purified with alcohol) dissolved in 1.5 l. of anhydrous methyl alcohol. The solution is cooled to below 50° (Note 1), 300 g. of purified ethyl formate is added, and the mixture is refluxed for two hours (Note 2) and (Note 3).

Then 410 g. (251 cc., 3 moles) of bromoacetone (p. 88) is added, and the mixture is refluxed for sixteen hours on a water bath at 95–97°. At the end of the operation the solution is cooled to 0° in an ice-salt bath. The potassium bromide which settles is filtered on a cooled suction filter, and the filtrate is fractionated.

The fraction boiling at 23–35°/12 mm. is discarded, as it contains very little acetol. The main fraction distils at 35–47°/12 mm. and weighs 160 g. This material is refractionated, and the portion boiling at 40–43°/12 mm. is collected. The yield is 120–130 g. (54–58 per cent of the theoretical amount) (Note 4).

2. Notes

1. It is necessary to cool the mixture below 50° to prevent loss of the volatile

ethyl formate.
2. Technical ethyl formate was purified by washing with 3 per cent sodium carbonate solution, then with cold water, drying over anhydrous sodium sulfate, filtering, and fractionating. Compare p. 180. It is very important that all the materials used in the synthesis of acetol be anhydrous, as otherwise condensation products are formed.
3. If commercial potassium formate is used it should be dried under reduced pressure at 80°. One and one-half to two moles should be used per mole of the bromo compound.
4. Acetol polymerizes very readily on standing but remains unchanged when dissolved in an equal volume of methyl alcohol.

3. Discussion

Acetol has usually been prepared by the reaction between bromoacetone and sodium or potassium formate or acetate, followed by hydrolysis of the ester with methyl alcohol.[1], [2] Treatment of glycerol[3] or propylene glycol[4] at 200–300° with a dehydrogenating catalyst leads to the formation of acetol, while the direct oxidation of acetone with Baeyer and Villiger's acetone-peroxide reagent furnishes acetol together with pyruvic acid.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 88
- Org. Syn. Coll. Vol. 2, 545
- Org. Syn. Coll. Vol. 7, 356

References and Notes

1. Nef, Ann. **335**, 247, 260 (1904).
2. Urion, Ann. chim. (11) **1**, 78 (1934).
3. Holmes, Brit. pat. 428,462 [C. A. **29**, 6908 (1935)].
4. Carbide and Carbon Chemicals Corporation, U. S. pat. 2,143,383 [C. A. **33**, 2914 (1939)].
5. Pastureau, Bull. soc. chim. (4) **5**, 227 (1909).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium or potassium formate

Baeyer and Villiger's acetone-peroxide reagent

alcohol (64-17-5)

Acetol (64-19-7)

methyl alcohol (67-56-1)

glycerol (56-81-5)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

acetone (67-64-1)

potassium hydroxide (1310-58-3)

potassium bromide (7758-02-3)

ethyl formate (109-94-4)

Pyruvic acid (127-17-3)

2-Propanone, 1-hydroxy- (116-09-6)

Bromoacetone (598-31-2)

potassium formate

propylene glycol (57-55-6)

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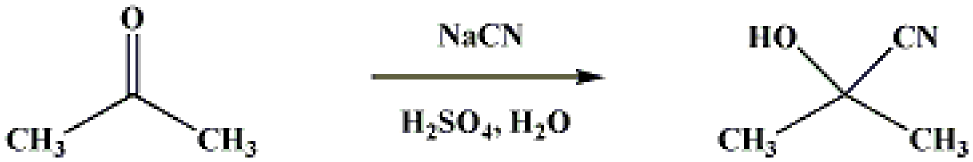
Organic Syntheses, CV 2, 7

ACETONE CYANOHYDRIN

[Isobutyronitrile, α-hydroxy-]



Submitted by R. F. B. Cox and R. T. Stormont.
Checked by Reynold C. Fuson and Madison Hunt.

1. Procedure

In a 5-l. three-necked, round-bottomed flask fitted with an efficient stirrer (Note 1), a separatory funnel, and a thermometer in a well is placed a solution of 500 g. (9.7 moles) of powdered 95 per cent sodium cyanide in 1.2 l. of water and 900 cc. (713 g., 12.3 moles) of acetone. The flask is surrounded by an ice bath, and the solution is stirred vigorously. When the temperature falls to 15°, 2.1 l. (8.5 moles) of 40 per cent sulfuric acid (Note 2) is added over a period of three hours, the temperature being kept between 10° and 20°. After all the acid has been added the stirring is continued for fifteen minutes and then the flask is set aside for the salt to settle. Usually a layer of acetone cyanohydrin forms and is decanted and separated from the aqueous layer. The sodium bisulfate is removed by filtration and washed with three 50-cc. portions of acetone. The combined filtrate and acetone washings are added to the aqueous solution, which is then extracted three times with 250-cc. portions of ether (Note 3). The extracts are combined with the cyanohydrin previously separated and dried with anhydrous sodium sulfate. The ether and acetone are removed by distillation from a water bath, and the residue is distilled under reduced pressure. The low-boiling portion is discarded, and acetone cyanohydrin is collected at 78–82°/15 mm. The yield is 640–650 g. (77–78 per cent of the theoretical amount) (Note 4).

2. Notes

1. It is advantageous to use a heavy metal stirrer because of the increased viscosity of the mixture toward the end of the reaction. Since some hydrogen cyanide may escape from the reaction mixture, the stopper carrying the stirrer should be fitted with a tube for leading off the gas or the reaction should be carried out under a hood.
2. The 40 per cent sulfuric acid is prepared by adding 650 cc. of concentrated sulfuric acid (sp. gr. 1.84) to 1.8 l. of water.
3. Extraction and distillation should be started as soon as possible after the completion of the reaction, and the distillation should be done as rapidly as possible to avoid decomposition.

4. The preparation of acetone cyanohydrin from potassium cyanide and the bisulfite addition product of acetone is described in Org. Syn. **20**, 43. The procedure given there furnishes a less pure cyanohydrin which, however, is suitable for some synthetic uses.

3. Discussion

Acetone cyanohydrin has been prepared from acetone and anhydrous hydrogen cyanide in the presence of a basic catalyst such as potassium carbonate, potassium hydroxide, or potassium cyanide;[1] by the reaction of potassium cyanide on the sodium bisulfite addition product of acetone;[2] and by the action of hydrogen cyanide, prepared directly in the reaction mixture, on an aqueous solution of acetone.[3] More modern industrial procedures employ acetone, liquid hydrogen cyanide, and a basic catalyst.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 323
- Org. Syn. Coll. Vol. 3, 560
- Org. Syn. Coll. Vol. 5, 839

References and Notes

1. Urech, Ann. **164**, 256 (1872); Ultée, Ber. **39**, 1857 (1906); Rec. trav. chim. **28**, 7 (1909).
2. Bucherer and Grolée, Ber. **39**, 1225 (1906); Ger. pat. 141,509 (Chem. Zentr. **1903**, I, 1244); Org. Syn. **20**, 43.
3. Welch and Clemo, J. Chem. Soc. **1928**, 2629.
4. Triplex Safety Glass Company Ltd., Brit. pat. 416,007 [C. A. **29**, 814 (1935)]; 452,285 [C. A. **31**, 417 (1937)]; I. G. Farbenind. A.-G., Fr. pat. 804,124 [C. A. **31**, 2615 (1937)]; Deutsche Gold- und Silber-Scheideanstalt vorm. Roessler, Fr. pat. 812,366 [C. A. **32**, 958 (1938)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium bisulfite addition product of acetone

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

ether (60-29-7)

sodium cyanide (143-33-9)

hydrogen cyanide (74-90-8)

sodium sulfate (7757-82-6)

potassium cyanide (151-50-8)

acetone (67-64-1)

potassium hydroxide (1310-58-3)

sodium bisulfate (7681-38-1)

Acetone cyanohydrin, Isobutyronitrile, α-hydroxy- (75-86-5)

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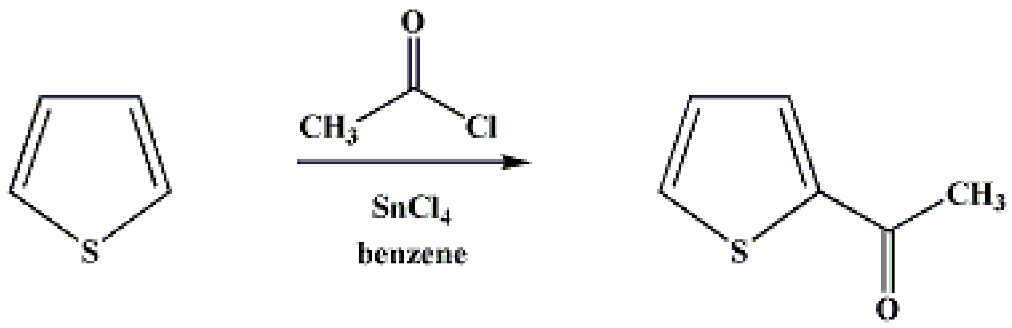
Organic Syntheses, CV 2, 8

2-ACETOTHIENONE

[Ketone, methyl 2-thienyl]



Submitted by John R. Johnson and G. E. May.
Checked by Reynold C. Fuson and E. A. Cleveland.

1. Procedure

In a 500-cc. round-bottomed, three-necked flask provided with a thermometer, dropping funnel, a liquid-sealed stirrer, and calcium chloride tube are placed 16.8 g. (0.2 mole) of thiophene (p. 578), 15.6 g. (14 cc., 0.2 mole) of acetyl chloride, and 200 cc. of dry benzene. The solution is cooled to 0°, and 52 g. (23 cc., 0.2 mole) of freshly distilled stannic chloride is added dropwise, with efficient stirring, during the course of about forty minutes. The reaction mixture assumes a purple color when the first drops of stannic chloride are added, and soon a purple solid precipitates.

After all the stannic chloride has been added, the cooling bath is removed and the mixture stirred for one hour longer. The addition product is hydrolyzed by the slow addition of a mixture of 90 cc. of water and 10 cc. of concentrated hydrochloric acid. The yellow benzene layer is separated, washed with 25 cc. of water, and dried over 5–10 g. of anhydrous calcium chloride. Benzene and unchanged thiophene (Note 1) are distilled through a short fractionating column (using an oil bath), and the residual liquid is distilled under reduced pressure. The yield of 2-acetothienone, b.p. 89–91°/9 mm., is 20–21 g. (79–83 per cent of the theoretical amount) (Note 2).

2. Notes

1. By shaking the recovered benzene-thiophene mixture with a solution of 5.5 g. of mercuric chloride, 10 g. of sodium acetate, and 10 cc. of alcohol in 80 cc. of water, the unchanged thiophene is converted to the 2-chloromercurithiophene (containing a small amount of the dimercurichloride); from this the free thiophene can be obtained by treatment with hydrochloric acid. The recovered thiophene amounts to 2–2.5 g.

2. 2-Acetothienone has the following physical constants: d_4^{20} 1.168, n_D^{20} 1.566.

Its semicarbazone melts at 186–187° (corr.).

3. Discussion

2-Acetothienone has been prepared by treating thiophene with acetyl chloride in the presence of aluminum chloride[1] or stannic chloride,[2] and by treating 2-chloromercurithiophene with acetyl chloride.[3] The present method is essentially that of Stadnikoff and Goldfarb.[2] Stannic chloride is superior to aluminum chloride as a catalyst for this reaction as aluminum chloride induces polymerization of the thiophene.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 14

References and Notes

1. Peter, Ber. **17**, 2643 (1884); Biedermann, ibid. **19**, 636 (1886).
2. Stadnikoff and Goldfarb, ibid. **61**, 2341 (1928).
3. Volhard, Ann. **267**, 178 (1892); Steinkopf and Baumeister, ibid. **403**, 69 (1914).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

benzene-thiophene

dimercurichloride

alcohol (64-17-5)

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

sodium acetate (127-09-3)

acetyl chloride (75-36-5)

aluminum chloride (3495-54-3)

mercuric chloride (7487-94-7)

Ketone, methyl 2-thienyl (88-15-3)

Thiophene (110-02-1)

stannic chloride (7646-78-8)

2-chloromercurithiophene

2-Acetothienone (88-15-3)

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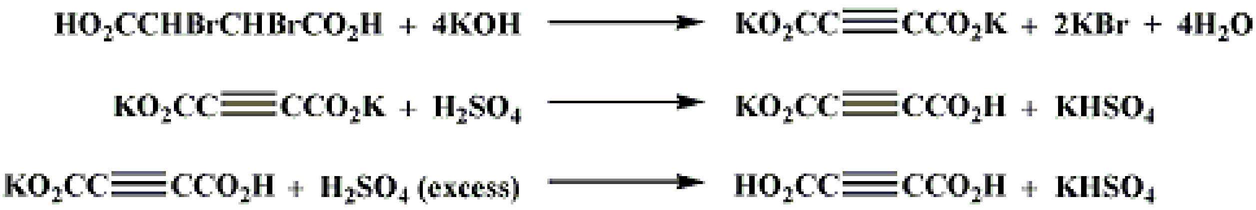
Organic Syntheses, CV 2, 10

ACETYLENEDICARBOXYLIC ACID



Submitted by T. W. Abbott, Richard T. Arnold, and Ralph B. Thompson.
Checked by Reynold C. Fuson and W. E. Holland.

1. Procedure

A solution of potassium hydroxide is prepared by dissolving 122 g. (2.2 moles; 1.5 times the theoretical amount) of potassium hydroxide in 700 cc. of 95 per cent methyl alcohol (Note 1) contained in a 2-l. round-bottomed flask provided with a reflux condenser. To this alkaline solution is added 100 g. (0.36 mole) of α,β-dibromosuccinic acid (p. 177), and the mixture is refluxed for one hour and fifteen minutes on a steam bath. The reaction mixture is cooled and filtered with suction. The mixed salts are washed with 200 cc. of methyl alcohol (Note 2) and dried by pressing between filter papers; when dry the product weighs 144–150 g.

This salt mixture is dissolved in 270 cc. of water, and the acid potassium salt is precipitated by adding 8 cc. of concentrated sulfuric acid in 30 cc. of water. After standing for three hours, or overnight, the mixture is filtered with suction (Note 3). The acid salt is then dissolved in 240 cc. of water to which 60 cc. of concentrated sulfuric acid has been added, and the solution is extracted with five 100-cc. portions of ether. The combined ether solutions are evaporated to dryness on a steam bath, leaving pure hydrated crystals of acetylenedicarboxylic acid. After drying for two days over concentrated sulfuric acid in a vacuum desiccator the crystals decompose sharply at 175–176°. The yield is 30–36 g. (73–88 per cent of the theoretical amount).

2. Notes

1. The yield is slightly lower when 95 per cent ethyl alcohol is used.
2. This salt mixture is composed of potassium bromide and potassium acetylenedicarboxylate.
3. This acid salt is practically bromine-free and does not require additional washing.

3. Discussion

The procedure described is essentially that of Bandrowski[1] and Baeyer[2] as modified by Ruggli.[3] The same general method has also been used by Backer and van der Zanden,[4] and by Moureu and Bongrand.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 329

References and Notes

1. Bandrowski, Ber. **10**, 838 (1877).
2. Baeyer, ibid. **18**, 677 (1885).
3. Ruggli, Helv. Chim. Acta **3**, 564 (1920).
4. Backer and van der Zanden, Rec. trav. chim. **47**, 776 (1928).
5. Moureu and Bongrand, Ann. chim. (9) **14**, 9 (1920).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethyl alcohol (64-17-5)

sulfuric acid (7664-93-9)

methyl alcohol (67-56-1)

ether (60-29-7)

potassium hydroxide (1310-58-3)

potassium bromide (7758-02-3)

Acetylenedicarboxylic acid (142-45-0)

α,β-Dibromosuccinic acid (526-78-3)

potassium acetylenedicarboxylate

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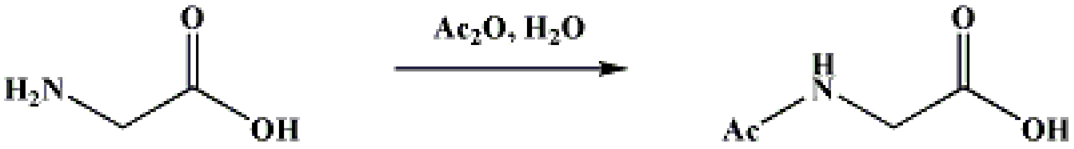
Organic Syntheses, CV 2, 11

ACETYLGLYCINE

[Aceturic acid]



Submitted by R. M. Herbst and D. Shemin.
Checked by Reynold C. Fuson and E. A. Cleveland.

1. Procedure

In a 1-l. Erlenmeyer flask provided with a mechanical stirrer are placed 75 g. (1 mole) of glycine (Org. Syn. Coll. Vol. I, **1941**, 298) and 300 cc. of water. The mixture is stirred vigorously until the glycine is almost completely dissolved, when 215 g. (2 moles) of 95 per cent acetic anhydride (Note 1) is added in one portion. Vigorous stirring is continued for fifteen to twenty minutes, during which time the solution becomes hot and acetylglycine may begin to crystallize. The solution is placed in the refrigerator (Note 2) overnight to effect complete crystallization. The precipitate is collected on a Büchner funnel, washed with ice-cold water, and dried at 100–110°. This product weighs 75–85 g. and melts at 207–208°. The combined filtrate and washings are evaporated to dryness under reduced pressure on a water bath at 50–60°. The residue on recrystallization from 75 cc. of boiling water yields a second fraction, of 20–30 g., which melts at 207–208° after being washed with ice-cold water and dried at 100–110°. An additional 4–6 g. of only slightly less pure product may be obtained from the mother liquor by concentration. The total yield is 104–108 g. (89–92 per cent of the theoretical amount) (Note 3).

2. Notes

1. The equivalent quantity of 90 per cent acetic anhydride may be used.
2. The refrigerator used by the checkers maintained a temperature of 5–7°.
3. The method may be employed to acetylate most α-amino acids with only slight modifications depending upon the solubility of the particular amino acid. When optically active amino acids are acetylated, there is little or no racemization.[1]

3. Discussion

Acetylglycine has been prepared by the interaction of acetyl chloride and the silver salt of glycine in dry ether or benzene;[2, 3] by the action of acetic anhydride on glycine suspended in warm benzene;[3] by heating glycine with acetic anhydride;[4] by treating an

aqueous solution of glycine or its sodium salt with ketene;[5] and by treating an aqueous alkaline solution of glycine with acetic anhydride.[6]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 1

References and Notes

1. Behr and Clarke, J. Am. Chem. Soc. **54**, 1631 (1932).
2. Kraut and Hartmann, Ann. **133**, 105 (1865).
3. Curtius, Ber. **17**, 1665 (1884).
4. Radenhausen, J. prakt. Chem. (2) **52**, 437 (1895).
5. Bergmann and Stern, Ber. **63**, 437 (1930).
6. Chattaway, J. Chem. Soc. **1931**, 2495.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

glycine or its sodium salt

Benzene (71-43-2)

ether (60-29-7)

acetic anhydride (108-24-7)

acetyl chloride (75-36-5)

Glycine (513-29-1)

Ketene (463-51-4)

Acetylglycine, Aceturic acid (543-24-8)

silver salt of glycine

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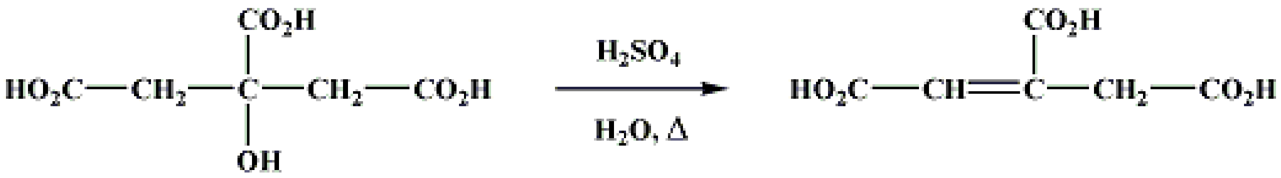
Organic Syntheses, CV 2, 12

ACONITIC ACID



Submitted by William F. Bruce
Checked by Louis F. Fieser and C. H. Fisher.

1. Procedure

In a 1-l. round-bottomed flask equipped with a reflux condenser (Note 1) are placed 210 g. (1 mole) of powdered citric acid monohydrate and a solution of 210 g. (115 cc., 2 moles) of concentrated sulfuric acid in 105 cc. of water. The mixture is heated in an oil bath kept at a temperature of 140–145° for seven hours. The light brown solution is poured into a shallow dish, and the flask is rinsed with 10 cc. of hot glacial acetic acid. The liquid is allowed to cool slowly to 41–42° (Note 2), with occasional stirring to break up the solid mass of aconitic acid which separates, and the solid is collected on a suction funnel (Note 3). The material is pressed and drained thoroughly until practically dry, when it is removed and stirred to a homogeneous paste with 70 cc. of concentrated hydrochloric acid, cooled in an ice bath. The solid is collected on a suction funnel (Note 3), washed with two 10-cc. portions of cold glacial acetic acid, sucked thoroughly, and spread out in a thin layer on porous plate or paper for final drying (Note 4). This product contains practically no sulfate and is pure enough for most purposes. It is colorless, and when dry weighs 71–77 g. (41–44 per cent of the theoretical amount) (Note 5). The point of decomposition determined under controlled conditions (Note 6) varies from 180° to 200°.

For purification the acid is crystallized from about 150 cc. of glacial acetic acid, using an acid-resistant filter for the hot solution (Note 7). Aconitic acid separates as small, colorless needles weighing 50–60 g., and about 10 g. more can be secured by concentrating the mother liquor under reduced pressure to one-third of its volume. The material is dried in the air and then in a desiccator containing sodium hydroxide in order to remove all traces of acetic acid. One crystallization usually is sufficient to bring the point of decomposition to 198–199° (Note 6).

2. Notes

1. A ground-glass connection is highly desirable.
2. By filtering at this point rather than at a lower temperature, a separation from a small amount of low-melting material is accomplished without much loss of aconitic acid.
3. This material may be filtered conveniently by means of a sintered glass funnel, or by using a pad of pure wool flannel in an 8-cm. Büchner funnel.
4. In humid weather the solid often deliquesces, and this necessitates drying in a desiccator. The material retains acetic acid very tenaciously, and drying should be continued until the odor of the solvent no longer can be noticed.
5. A determination by the method of Pucher, Vickery, and Leavenworth[1] showed that 26 g. of citric acid remained in the sulfuric acid solution. It is inadvisable to use this solution for another run; the accumulation of water and by-products reduces the yield and the

quality of the product considerably.
6. When heated in a capillary tube aconitic acid decomposes rather suddenly with vigorous gas evolution at a temperature which is closely dependent upon the rate of heating and the temperature at which the sample is introduced. In the literature[2] "melting points" ranging from 182.5° to 194.5° are recorded. The uncrystallized aconitic acid, when introduced at 180° into a small bath provided with mechanical agitation and heated at the rate of 2–3° per minute, usually decomposed at 189–190°. The once recrystallized material, introduced at 190°, decomposed at 198–199°; introduced at 195°, it decomposed at 204–205°. A determination on the Dennis bar,[3] the most reliable method for this type of compound, showed a decomposition point of 209°. The sample must be thoroughly dry to obtain the highest figures.
7. The hot solution is very destructive to filter paper. A convenient filter is made by preparing a 1–2 mm. mat of asbestos in a 6-cm. Büchner funnel, dusting onto this a 2–3 mm. layer of Norite, washing by suction, and heating the unit, together with a suction flask, in an oven at 120°. When dry and hot, the apparatus is ready for use.

3. Discussion

Aconitic acid has been prepared from citric acid by the action of sulfuric acid[4] or hydrogen chloride,[5] or by heating.[6] It has been prepared also from methyl acetylcitrate[7] and from acetylcitric anyhdride.[8] The method described is essentially that of Hentschel.[4] Phosphoric acid (85 per cent) can be used in place of sulfuric acid, but much closer regulation of the conditions seems necessary and the yield is not greatly improved.

The effects of acid strength and temperature on the reaction between sulfuric acid and citric acid have been reported by Quartaroli and Belfiori: the use of pyrosulfuric acid, cold, or sulfuric acid of less than 94 per cent strength, hot, leads to the formation of aconitic acid.[9]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

acetylcitric anyhdride

pyrosulfuric acid

sulfuric acid (7664-93-9)

hydrogen chloride, hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

sodium hydroxide (1310-73-2)

citric acid (77-92-9)

Norite (7782-42-5)

phosphoric acid (7664-38-2)

Aconitic acid (499-12-7)

citric acid monohydrate (5949-29-1)

methyl acetylcitrate

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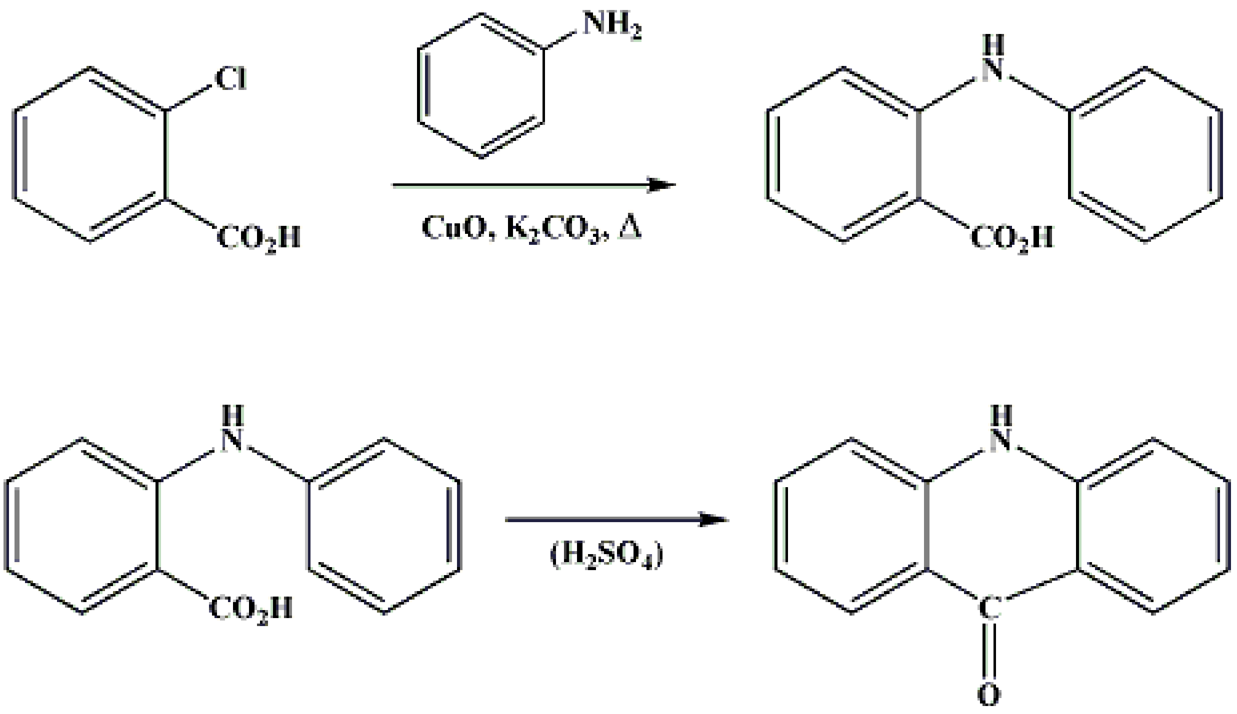
ACRIDONE



Submitted by C. F. H. Allen and G. H. W. McKee.
Checked by W. W. Hartman and A. Weissberger.

1. Procedure

(*A*) *N-Phenylanthranilic Acid*.—In a 1-l. round-bottomed flask fitted with an air-cooled condenser, a mixture of 155 g. (1.66 moles) of aniline, 41 g. (0.26 mole) of *o*-chlorobenzoic acid (Note 1), 41 g. (0.3 mole) of technical anhydrous potassium carbonate, and 1 g. of copper oxide is refluxed for two hours, using an oil bath. The excess aniline is removed by distillation with steam (about three hours is required), and 20 g. of decolorizing carbon (Note 2) is added to the brown residual solution. The mixture is boiled for fifteen minutes and filtered by suction. The filtrate is added, with stirring, to a mixture of 30 cc. of concentrated hydrochloric acid and 60 cc. of water. The precipitated acid is filtered with suction when cold. After drying to constant weight in the air, the yield is 46–52 g. (82–93 per cent of the theoretical amount) of a nearly white product; m.p. 179–181° with preliminary shrinking (Note 3), (Note 4), and (Note 5).

(*B*) *Acridone*.—In a 500-cc. flask a solution of 42.7 g. (0.2 mole) of N-phenylanthranilic acid (Note 6) in 100 cc. of concentrated sulfuric acid (sp. gr. 1.84) is heated on a boiling water bath for four hours and then poured into 1 l. of boiling water. Spattering is minimized by allowing the solution to run down the wall of the container. The yellow precipitate is filtered after boiling for five minutes, and the filtrate is saved (Note 7). The moist solid is boiled for five minutes with a solution of 30 g. (0.28 mole)

of sodium carbonate in 400 cc. of water, collected with suction (Note 8), and washed well with water. After drying in the air the crude acridone weighs 35.5–37.5 g. (91–96 per cent of the theoretical amount) and melts at 344–346° (Note 9). This material is pure enough for many purposes; it may be recrystallized from a mixture of aniline and acetic acid, using 10 cc. of aniline and 25 cc. of acetic acid for every 2 g. of solid. The recovery is about 90 per cent, and the recrystallized product melts at 348–352° (Note 10).

2. Notes

1. Sixty grams of technical *o*-chlorobenzoic acid is dissolved in 200 cc. of hot water containing 20 g. of sodium carbonate, 10 g. of decolorizing carbon is added, and, after boiling for ten minutes, the mixture is filtered by suction. The filtrate is added to hydrochloric acid prepared by diluting 31 cc. of the concentrated acid with an equal volume of water. The air-dried product weighs 41 g. and is used directly. This purification is essential to obtain a good yield and a product of good quality. If it is omitted, a blue to black acid results, from which the color is removed only with difficulty.
Directions for preparing *o*-chlorobenzoic acid by the oxidation of *o*-chlorotoluene are given on p. 135.
2. Ordinary animal charcoal and Darco gave equally good results.
3. N-Phenylanthranilic acid decomposes slowly at elevated temperatures. Before the melting point is reached, there is considerable preliminary shrinkage. If the "dip method" is used, the melting point is 182–183°. The literature values vary from 181° to 184° for the pure acid.
4. This acid is pure enough for all ordinary purposes. The melting point is only slightly raised by dissolving 5 g. in 100 cc. of water containing 2.5 g. of sodium carbonate, adding 2.5 g. of decolorizing carbon, boiling for five minutes, filtering, and acidifying. The recovery is 4.6 g. If the product is colored this procedure must be followed to get acridone of light color.
5. For recrystallization, 5 g. of the acid is dissolved in 25 cc. of boiling alcohol and 5 cc. of water added. The recovery is 4.8 g., and the melting point is 182–183°. Acetic acid (2 cc. per gram) may be substituted for alcohol; it is more convenient for recrystallizing large quantities.
6. The N-phenylanthranilic acid may be used without recrystallization if it has been prepared from purified *o*-chlorobenzoic acid. If not, the crude N-phenylanthranilic acid must be decolorized as described in (Note 4); otherwise a greenish acridone is obtained which, however, has the proper melting point.
7. On standing overnight, the filtrate deposits 1 6 to 2 g. of a very impure product which melts at about 315°.
8. On acidification of the filtrate, a little (1.5–2 g.) N-phenylanthranilic acid is always precipitated.
9. The crude acridone shrinks in a capillary tube at 330–335° and melts to a dark-colored liquid at 344–346°.
10. Isoamyl alcohol may also be used for recrystallization; 1 g. of

acridonerequires 120 cc. of solvent and yields 0.75 g. of material melting at 354°, using a Berl-Kullman copper block.[1]

3. Discussion

The practical methods of preparation of N-phenylanthranilic acid are the action of aniline on *o*-chloro- or *o*-bromobenzoic acid,[2], [3] or the action of bromobenzene on anthranilic acid,[4], [5], [6] copper or its salts being used in both instances.

The only method of preparative value for acridone is by ring closure of N-phenylanthranilic acid.[7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 135

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

copper or its salts

o-chloro- or o-bromobenzoic acid

alcohol (64-17-5)

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

aniline (62-53-3)

sodium carbonate (497-19-8)

decolorizing carbon (7782-42-5)

bromobenzene (108-86-1)

o-Chlorotoluene (95-49-8)

Anthranilic Acid (118-92-3)

copper oxide (1317-38-0)

isoamyl alcohol (123-51-3)

Acridone (578-95-0)

N-Phenylanthranilic acid (91-40-7)

o-Chlorobenzoic acid (118-91-2)

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ACROLEIN ACETAL

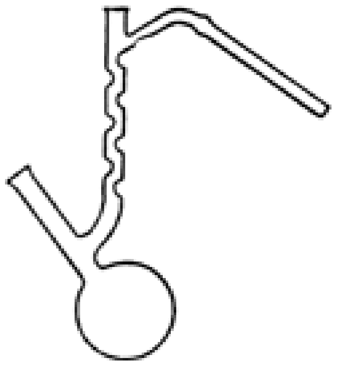
[Acrolein, diethyl acetal]

Submitted by E. J. Witzemann, Wm. Lloyd Evans, Henry Hass, and E. F. Schroeder.
Checked by Frank C. Whitmore and Harry T. Neher.

1. Procedure

To 340 g. (6 moles) of dry, powdered potassium hydroxide (Note 1) in a 500-cc. short-necked round-bottomed flask (Note 2) is added 167 g. (1 mole) of β-chloropropionaldehyde acetal (p. 137). The mixture is shaken vigorously and attached at once to a three-bulbed Glinsky or other suitable column, connected to a water condenser set for distillation (Note 3). The flask is heated in an oil bath at 210–220° until nothing more distils (Note 4). The distillate is transferred to a separatory funnel and the lower aqueous layer is removed. The acrolein acetal is dried over 10 g. of potassium carbonate, filtered, and distilled from a modified Claisen flask (.htmFig. 2). The yield is 98 g. (75 per cent of the theoretical amount) of a product which boils at 122–126°.

Fig. 2



2. Notes

1. The powdered potassium hydroxide should pass a 60-mesh sieve (24 per cm.). The dryness of the powder is of the utmost importance. Water must be avoided as much as possible. Therefore, the potassium hydroxide should be fused at 350° for two hours and then pulverized as rapidly as possible. A 24-cm. (10-in.) disk pulverizer having a capacity of about 200 g. per minute is recommended. If the

potassium hydroxide is not fused before pulverizing, the yield of acetal drops to about 60 per cent.
2. The concentrated potassium hydroxide left at the completion of the reaction attacks the glass rapidly. For this reason iron retorts made from 10-cm. (4-in.) pipe should be used when many runs are to be made.
3. The reaction between the acetal and the alkali is very vigorous.
4. A large low-boiling fraction indicates too much moisture in the potassium hydroxide used. See (Note 1).

3. Discussion

Acrolein acetal has been prepared by treatment of β-chloropropionaldehyde acetal with dry, powdered potassium hydroxide,[1] and from acrolein, ethyl orthoformate, and ammonium nitrate in boiling alcohol.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 307
- Org. Syn. Coll. Vol. 4, 21

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alcohol (64-17-5)

potassium carbonate (584-08-7)

Acrolein (107-02-8)

potassium hydroxide (1310-58-3)

ammonium nitrate

Ethyl orthoformate

Acrolein acetal

Acrolein, diethyl acetal

β-chloropropionaldehyde acetal (35573-93-4)

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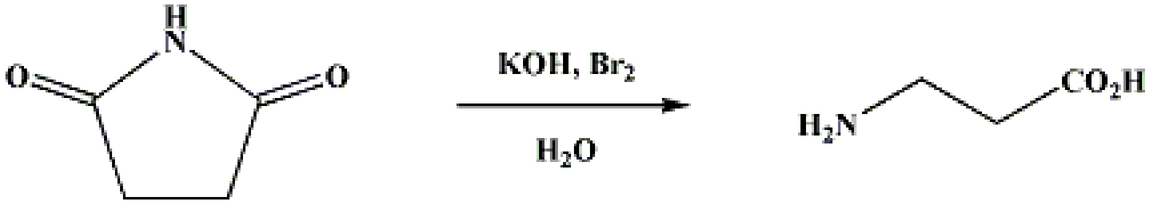
β-ALANINE



Submitted by H. T. Clarke and Letha Davies Behr.
Checked by W. H. Carothers and W. L. McEwen.

1. Procedure

To a cold (0–5°) solution of 302 g. of potassium hydroxide sticks in 2720 cc. of distilled water is added slowly, with stirring, 96.6 g. (30.8 cc., 0.6 mole) of bromine. This solution is chilled to 0°, and 59.4 g. (0.6 mole) of succinimide (p. 562) is added with hand stirring. The mixture is warmed in a water bath to 55–60°, when it becomes colorless, and is held at that temperature for two hours (Note 1). After standing overnight at room temperature, it is acidified to Congo red with concentrated hydrochloric acid (about 380 cc., sp. gr. 1.18) (Note 2) and evaporated to dryness on a steam bath under reduced pressure. The residue is treated with 1 l. of warm 95 per cent alcohol; the undissolved potassium bromide is filtered and washed with 150–200 cc. of cold alcohol in small portions. The filtrate and washings are combined and evaporated to dryness under reduced pressure, and the residue is extracted with 100 cc. of 95 per cent alcohol. The resulting solution is again evaporated to dryness and the residue finally extracted with 140 cc. of hot absolute alcohol (Note 3). After distilling the bulk of the alcohol, this extract is diluted with about 200 cc. of distilled water and shaken out twice with 80-cc. portions of ether. The ether extracts are discarded (Note 4).

The aqueous solution is freed of ether and alcohol and then boiled under reflux for one to one and a half hours in order to hydrolyze any β-alanine ester. After evaporating under reduced pressure to remove as much as possible of the excess hydrochloric acid, the residue is dissolved in water and diluted to exactly 1 l. A 5-cc. portion of this solution is withdrawn for determination of total halides. A suspension of silver oxide prepared from 10 per cent more than the equivalent quantity of silver nitrate (Note 5) is added to the remaining portion of the solution, and the mixture is stirred well in order to bring about complete precipitation of the halides. After standing overnight the precipitate is filtered and washed with water. The filtrate and washings are concentrated under reduced pressure to about 400 cc., saturated with hydrogen sulfide, and filtered through a thin layer of decolorizing carbon. The colorless filtrate is evaporated to a volume of about 100 cc., treated with decolorizing carbon if necessary, concentrated on the steam bath until crystallization begins, and chilled. The crystals are filtered with suction, washed with a little cold alcohol, and dried. A further crop is obtained by concentrating the mother liquor and again chilling (Note 6). The combined

crops (28–30 g., m.p. 189–192°) are recrystallized from water, employing the same procedure, and yield 22–24 g. (41–45 per cent of the theoretical amount) of pure β-alanine, which melts at 197–198° (corr.) with decomposition. About 2 g. of less pure product can be secured from the final mother liquors.

2. Notes

1. The odor of ammonia is perceptible, indicating some hydrolysis.
2. On acidification a small amount of bromine may be liberated; this is removed rapidly during the subsequent evaporation.
3. In the last extraction the alcohol-insoluble material may be removed advantageously with a centrifuge.
4. This ether extraction removes small quantities of succinic acid and its esters.
5. The silver oxide is prepared by dissolving the silver nitrate in about five parts of cold water and adding a slight excess of pure sodium hydroxide in 10 per cent solution. The precipitate is well stirred, collected by filtration or centrifuging, and washed free of sodium salts. It should not be dried before use.
6. The final mother liquor consists of a rather viscous solution containing uncrystallizable by-products.

3. Discussion

The above directions are based upon the methods of Hoogewerff and Van Dorp,[1] as modified by Holm[2] and by Hale and Honan.[3] β-Alanine has also been prepared by the action of hypobromite upon succinamide and hydrolysis of the resulting β-ureidopropionic acid;[4] by the action of ammonia upon β-iodopropionic acid;[5] by the hydrolysis of methyl carbomethoxy-β-aminopropionate, obtained by the action of sodium methoxide on succinbromimide;[6] by the reduction of β-nitrosopropionic acid;[7] by heating ethyl acrylate with alcoholic ammonia;[8] from succinylglycine ester by the azide synthesis;[9] by the action of liquid ammonia upon methyl acrylate;[10] and by the reduction of cyanoacetic acid,[11] or its ethyl ester followed by hydrolysis.[12]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 34

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

β-alanine ester

succinic acid and its esters

succinylglycine ester

alcohol (64-17-5)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ether (60-29-7)

sodium hydroxide (1310-73-2)

silver oxide (20667-12-3)

hydrogen sulfide (7783-06-4)

silver nitrate (7761-88-8)

bromine (7726-95-6)

sodium methoxide (124-41-4)

decolorizing carbon (7782-42-5)

potassium hydroxide (1310-58-3)

potassium bromide (7758-02-3)

hypobromite

cyanoacetic acid (372-09-8)

ethyl acrylate (140-88-5)

β-Alanine (107-95-9)

Succinimide (123-56-8)

succinamide (110-14-5)

β-ureidopropionic acid (462-88-4)

β-iodopropionic acid (141-76-4)

methyl carbomethoxy-β-aminopropionate

succinbromimide

β-nitrosopropionic acid

methyl acrylate (96-33-3)

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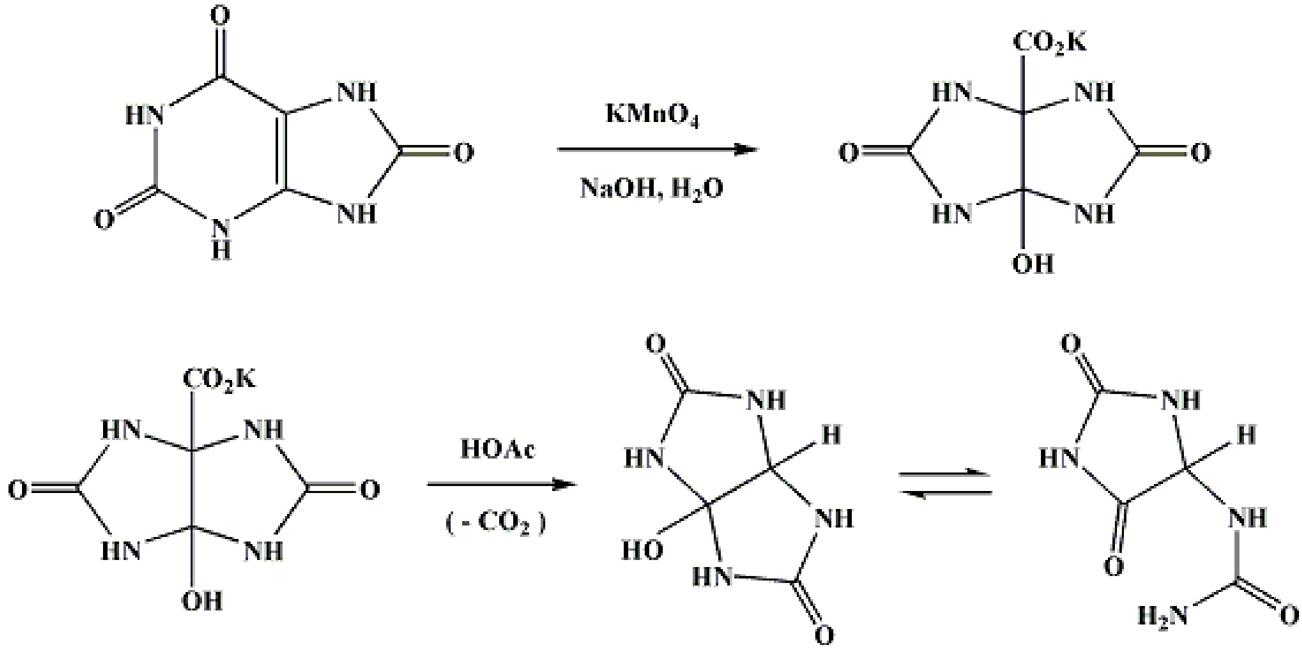
ALLANTOIN



Submitted by W. W. Hartman, E. W. Moffett, and J. B. Dickey.
Checked by W. H. Carothers and W. L. McEwen.

1. Procedure

One hundred grams of uric acid (0.595 mole) and 4.5 l. of hot (70–85°) water are placed in a 12-l. round-bottomed flask equipped with a mechanical stirrer. The stirrer is started, and a solution of 80 g. (2 moles) (Note 1) of commercial sodium hydroxide in 120 cc. of water is added. Stirring is continued until the uric acid is in solution (Note 2), after which the solution is cooled by means of a stream of water directed against the flask. When the temperature has fallen to 25–30°, 50 g. (0.32 mole) (Note 3) of potassium permanganate is added all at once (Note 4) to the vigorously stirred solution. Stirring is continued for fifteen to twenty minutes (Note 5), and the mixture is filtered (Note 6) at once through a 19-cm. Büchner funnel. The first fraction of the filtrate contains a small amount of manganese dioxide. This fraction must be collected separately and returned to the funnel. As soon as the filtrate becomes clear it is collected in a 12-l. round-bottomed flask which contains 130 cc. (137 g., 2.2 moles) of glacial acetic acid. The filtrate is tested with litmus to be sure that it is acid, and evaporated to a volume of 1.5–2 l. on a steam bath under reduced pressure (20–30 mm.). The solution thus obtained is allowed to stand in a cool place overnight, and the allantoin which crystallizes is filtered on a 9-cm. Büchner funnel (Note 7). The allantoin is dissolved in 800–900 cc. of boiling water, treated with 5 g. of Norite, and filtered rapidly through a fluted filter paper in a steam funnel. The filtrate is allowed to stand in a cool place overnight (Note 8), and the white crystals of allantoin are separated by filtration with suction. The yield of product melting at 230–231° (Note 9) is 60–71 g. (64–75 per cent of the theoretical amount). If the filtrate from the purification liquors is concentrated to 100 cc., there is obtained an additional 3–5 g. of allantoin.

2. Notes

1. The use of more than 80 g. of sodium hydroxide does not increase the yield, but, if not neutralized immediately upon completion of the reaction, it causes decomposition of some allantoin.
2. It is essential that the uric acid be completely in solution; otherwise not all of it will be oxidized. When the solution is cooled a small amount of white precipitate sometimes separates, but this does

not affect the yield.
3. The amount of potassium permanganate can be varied between 50 and 62 g. (0.32–0.39 mole) without changing the yield.
4. The potassium permanganate must be added rapidly (one to five minutes).
5. If the period of stirring is reduced to ten minutes, some unchanged uric acid is recovered. The period can be extended slightly beyond twenty minutes without decreasing the yield of allantoin, but if it is extended beyond one hour the yield is appreciably decreased.
6. Filtration must be as rapid as possible; this necessitates the use of a large Büchner funnel.
7. The filtrate is discarded since the amount of allantoin is not sufficient to repay attempts to separate it from the various other compounds present.
8. Crystallization can be hastened by stirring in an ice bath.
9. The melting point appears to depend somewhat on the rate of heating. The melting point 228–230° is observed in a capillary tube in a bath heated slowly from room temperature. If the capillary is placed in a bath already heated to 228°, the specimen melts at 233–234°. On a copper block still higher melting points are obtained.

3. Discussion

Allantoin has been prepared by the oxidation of uric acid with potassium permanganate,[1] lead dioxide,[2] potassium ferricyanide,[3] oxygen,[4] manganese dioxide,[5] ozone,[6] or hydrogen peroxide,[7] and by the electrolytic oxidation of lithium urate.[8] It is also formed by heating urea with glyoxylic acid[9] or with any one of a number of disubstituted acetic acids such as, for instance, dichloroacetic acid.[10]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

lithium urate

acetic acid (64-19-7)

sodium hydroxide (1310-73-2)

potassium permanganate (7722-64-7)

oxygen (7782-44-7)

Norite (7782-42-5)

urea (57-13-6)

hydrogen peroxide (7722-84-1)

manganese dioxide (1313-13-9)

Allantoin (97-59-6)

uric acid

potassium ferricyanide (13746-66-2)

ozone (10028-15-6)

glyoxylic acid (298-12-4)

dichloroacetic acid (79-43-6)

lead dioxide

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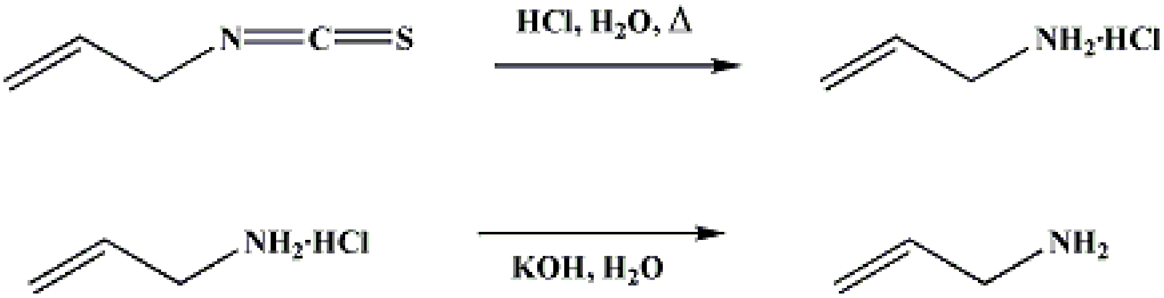
ALLYLAMINE



Submitted by M. T. Leffler
Checked by W. W. Hartman and E. J. Rahrs.

1. Procedure

In a 5-l. round-bottomed flask, equipped with a reflux condenser connected to a gas trap (Note 1), are placed 2 l. (12.1 moles) of 20 per cent hydrochloric acid and 500 g. (5.05 moles) of allyl isothiocyanate (Note 2). The mixture is refluxed over a free flame until the upper layer of allyl isothiocyanate has completely disappeared, about fifteen hours being required for the hydrolysis. When the reaction is complete, the solution is poured into a 3-l. beaker and concentrated on the steam bath until crystals begin to form in the hot solution. This occurs when the volume is approximately 400 cc. (Note 3).

The warm residue is then diluted with water to a volume of 500–550 cc. and placed in a 2-l. three-necked, round-bottomed flask equipped with a 500-cc. dropping funnel, a mercury-sealed mechanical stirrer, and a condenser arranged for distillation. The lower end of the condenser is fitted to a receiver consisting of a 500-cc. suction flask, whose side arm is connected to a reflux condenser (Note 4). The receiver is placed in an ice-salt bath and the three-necked flask in a water bath. The temperature of the water bath is raised to 95–98°, the stirrer is started, and a solution of 400 g. (7.1 moles) of potassium hydroxide in 250 cc. of water is added dropwise from the funnel. As soon as the free hydrochloric acid is neutralized, the amine begins to distil. The rate of the addition of the alkali is regulated so as to maintain a dropwise distillation of allylamine and, after the addition is complete, heating and stirring are continued until all the amine has distilled.

The distillate is then dried over solid potassium hydroxide for twenty-four hours and finally over metallic sodium (Note 5). The allylamine is distilled from a water bath held at 70–78°, through a 12-in. fractionating column, into a receiver immersed in an ice bath. Two fractions are collected: up to 54°/746 mm., and 54–57°/746 mm. The lower fraction amounts to 14–16 g. and on redistillation yields 6–8 g. of pure material. The total yield of pure allylamine boiling at 54–57°/746 mm. is 200–210 g. (70–73 per cent of the theoretical amount).

2. Notes

1. It is desirable to use a gas trap in order to prevent vapors of allyl isothiocyanate from escaping into the room. The gas trap described on p. 4 is suitable.
2. Eastman's "practical" grade (b.p. 150–152°) of allyl isothiocyanate was used in this preparation.
3. The rate of evaporation is greatly accelerated by allowing a stream of air to blow across the surface of the hot liquid. It is advantageous for the evaporation to proceed as far as possible in order to remove most of the free hydrochloric acid, and no harm is done if it continues until the solution turns to a semi-solid mass of crystals.
4. Care must be taken throughout to prevent loss of the product by volatilization. Furthermore, the vapors should not be allowed to come into contact with the nasal passages, as violent sneezing is produced.
5. The distillate should be kept cold (5–10°) during the drying process and should be separated from the potassium hydroxide before drying with sodium.

3. Discussion

Allylamine has been prepared by the hydrolysis of allyl isothiocyanate with dilute sulfuric[1] or hydrochloric[2] acid.

References and Notes

1. Hofmann, Ber. **1**, 183 (1868).
2. Gabriel and Eschenbach, ibid. **30**, 1124 (1897).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

potassium hydroxide (1310-58-3)

sodium, metallic sodium (13966-32-0)

Allylamine (107-11-9)

allyl isothiocyanate (57-06-7)

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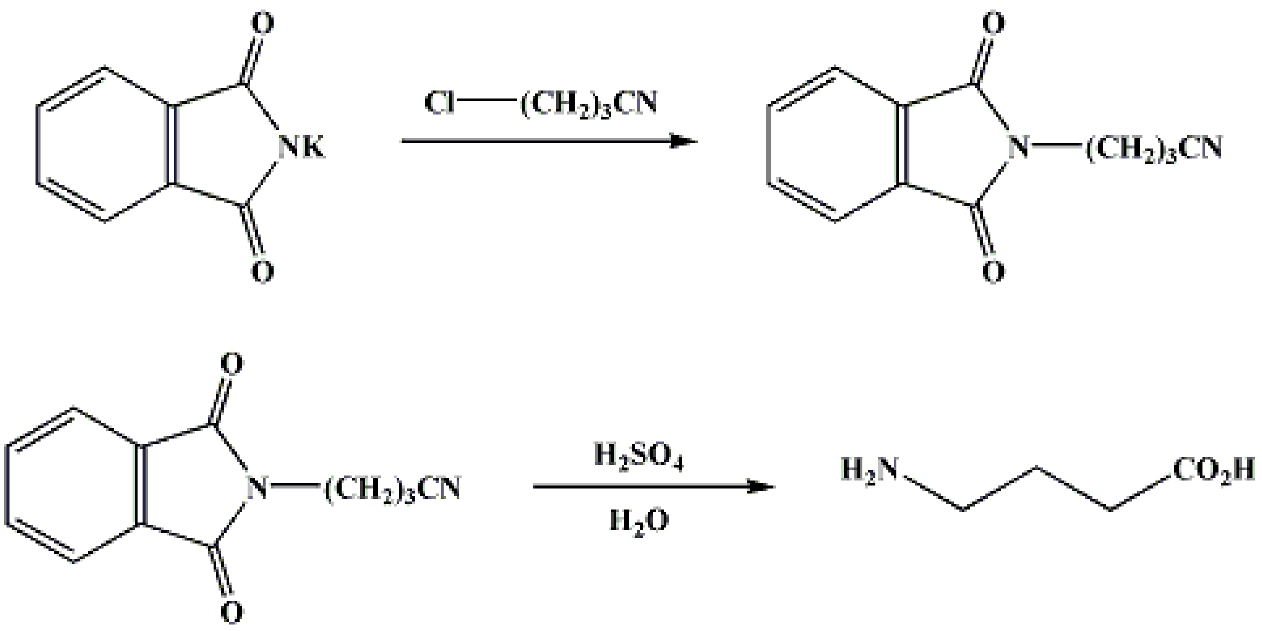
Organic Syntheses, CV 2, 25

γ-AMINOBUTYRIC ACID

[Butyric acid, γ-amino-]



Submitted by C. C. DeWitt
Checked by W. W. Hartman and A. J. Schwaderer.

1. Procedure

In a 1-l. round-bottomed flask fitted with a tightly fitting cork stopper carrying an air condenser are placed 100 g. (0.54 mole) of finely powdered potassium phthalimide (Org. Syn. Coll. Vol. I, **1941**, 119) and 52 g. (0.5 mole) of γ-chlorobutyronitrile (Org. Syn. Coll. Vol. I, **1941**, 156). The flask is heated in an oil bath maintained at 150–180° for one and one-half hours (Note 1) and then allowed to cool. The excess potassium phthalimide and the potassium chloride formed are removed by extraction with several portions of boiling distilled water until the wash water gives no test for chloride ion. The flask is then cooled and the product caused to solidify, and the remaining water is decanted as completely as possible. The solid is treated with 140 cc. of concentrated sulfuric acid, and the mixture is warmed gently in an oil bath under a reflux condenser until all the γ-phthalimidobutyronitrile is brought into solution. Through the reflux condenser 200 cc. of distilled water is added carefully and the solution is refluxed vigorously for three hours. The mixture is cooled and allowed to stand overnight, and the phthalic acid is filtered. The filtrate is transferred to a large evaporating dish, 1 l. of distilled water is added, and then an excess of barium carbonate (about 550 g.) is added in small portions (Note 2). The mixture is evaporated nearly to dryness on the steam bath, and the residue is stirred throroughly with 1 l. of distilled water and again evaporated (Note 3). Finally 1 l. of distilled water is stirred with the solid and the mixture is filtered on a large Büchner funnel. The precipitate is washed with three 200-cc. portions of hot distilled water, and the filtrate and washings are concentrated to a volume

of 200 cc. on the steam bath. After the addition of 2 g. of activated carbon the solution is filtered by suction, using a No. 42 Whatman paper, and the charcoal is washed with several small portions of hot distilled water. The filtrate is concentrated on the steam bath to the point of crystallization (about 75 cc.), and 375–500 cc. of absolute alcohol is added to precipitate the amino acid. The mixture is stirred well so that the yellow impurities are retained in the solvent, and, after cooling, the colorless, crystalline product is collected and washed with absolute alcohol.

The alcoholic filtrate is evaporated to 50 cc., and 50 g. of barium hydroxide and 150 cc. of distilled water are added (Note 4). The mixture is refluxed for two hours and the excess barium hydroxide is precipitated with carbon dioxide. The barium carbonate is removed by filtration and washed with hot distilled water. A slight excess of sulfuric acid is added to the filtrate to liberate the amino acid from its barium salt, and an excess of barium carbonate is added to remove sulfate ion. The mixture is digested on the steam bath until effervescence ceases, and then it is filtered and the precipitate is washed with hot distilled water. The filtrate and washings are concentrated on the steam bath to a volume of 100 cc., decolorized with 1 g. of active carbon, filtered, and concentrated to the point of crystallization (about 25 cc.). The amino acid is precipitated by the addition of 150 cc. of absolute alcohol, and the product is collected and washed with absolute alcohol.

The combined yield is 24–32 g. (47–62 per cent on the basis of the γ-chlorobutyronitrile used). The amino acid may be recrystallized by dissolving it in the least possible amount of distilled water and adding 5 to 7 volumes of absolute alcohol.

2. Notes

1. It is advisable to interrupt the heating after about forty-five minutes and thoroughly mix the pasty material by means of a glass rod. Longer heating of the reaction mass, although unnecessary, does no harm.
2. The reagent neutralizes the sulfuric acid and decomposes the ammonium sulfate, but it does not react with the amino acid.
3. Usually the ammonia is removed completely by these two treatments, but if it is not the thorough mixing of the solid with water and the subsequent evaporation must be repeated.
4. The alcoholic filtrate contains appreciable amounts of pyrrolidone. The treatment with excess barium hydroxide converts this into the barium salt of the amino acid.[1], [2]

3. Discussion

γ-Aminobutyric acid has been prepared by the electrolytic reduction of succinimide to pyrrolidone and hydrolysis of the pyrrolidone by means of barium hydroxide;[1] by the oxidation of piperylurethan with fuming nitric acid and treatment of the resulting product with concentrated hydrochloric acid in sealed tubes at 100°;[3] by the hydrolysis of the

condensation product of N-(β-bromoethyl)-phthalimide and sodiomalonic ester;[4] and by the method described above which is a slight modification of that of Gabriel.[2]

References and Notes

1. Tafel and Stern, Ber. **33**, 2224 (1900).
2. Gabriel, ibid. **22**, 3335 (1889); **23**, 1771 (1890).
3. Schotten, ibid. **16**, 643 (1883).
4. Aschan, ibid. **24**, 2450 (1891).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

piperylurethan

sodiomalonic ester

alcohol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

nitric acid (7697-37-2)

carbon dioxide (124-38-9)

carbon (7782-42-5)

Potassium Phthalimide (1074-82-4)

γ-Chlorobutyronitrile (628-20-6)

barium hydroxide (17194-00-2)

barium carbonate (513-77-9)

ammonium sulfate (7783-20-2)

phthalic acid (88-99-3)

Succinimide (123-56-8)

γ-Aminobutyric acid, Butyric acid, γ-amino- (56-12-2)

potassium chloride (7447-40-7)

γ-phthalimidobutyronitrile

pyrrolidone (616-45-5)

N-(β-bromoethyl)-phthalimide (574-98-1)

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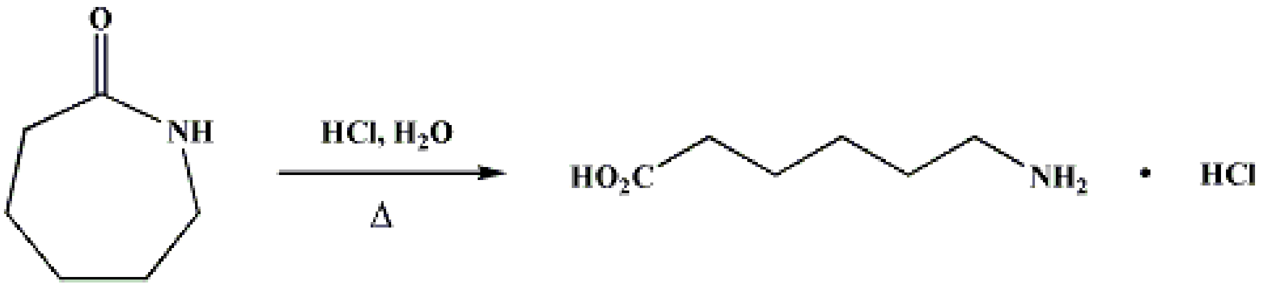
Organic Syntheses, CV 2, 28

ε-AMINOCAPROIC ACID

[Caproic acid, ε-amino-]



Submitted by J. C. Eck
Checked by Louis F. Fieser and C. H. Fisher.

1. Procedure

In a 500-cc. round-bottomed flask, 50 g. (0.44 mole) of 2-ketohexamethylenimine (p. 371) is added to a solution of 45 cc. of concentrated hydrochloric acid (sp. gr. 1.19) in 150 cc. of water. The solution is boiled for about one hour until it becomes clear (Note 1) and evaporated to dryness under reduced pressure on a steam bath.

The resulting ε-aminocaproic acid hydrochloride is converted to the free acid by a procedure similar to that used in the preparation of *dl*-alanine (Org. Syn. Coll. Vol. I, **1941**, 21). The hydrochloride is dissolved in 1 l. of water in a 1.5-l. beaker and treated successively with 50 g. of powdered litharge, 25 g. of powdered litharge, 5 g. of freshly precipitated lead hydroxide, 25 g. of powdered silver oxide (Note 2), and, finally, hydrogen sulfide. During this procedure, the original volume is maintained by the addition of small amounts of water.

After the complete removal of halogen and metallic ions, the solution is concentrated to a volume of about 100 cc., and 300 cc. of absolute alcohol is added. Then the amino acid is precipitated by slowly adding 500 cc. of ether with stirring and cooling.

The resulting ε-aminocaproic acid is collected on a suction filter and dried in a desiccator. The yield of ε-aminocaproic acid melting at 201–203° is 52.5–53.5 g. (90–92 per cent of the theoretical amount).

2. Notes

1. This indicates that the hydrolysis is complete.
2. The exact amount of silver oxide required may be determined by titrating a sample of the solution with silver nitrate by the Volhard method.

3. Discussion

ε-Aminocaproic acid has been prepared by the hydrolysis of ε-benzoylaminocapronitrile,[1] by the hydrolysis of ethyl δ-phthalimidobutylmalonate,[2] and from cyclohexanone oxime by rearrangement and hydrolysis.[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 76
- Org. Syn. Coll. Vol. 4, 39

References and Notes

1. von Braun and Steindorff, Ber. **38**, 176 (1905); von Braun, ibid. **40**, 1839 (1907); Ruzicka and Hugoson, Helv. Chim. Acta **4**, 479 (1921); Marvel, MacCorquodale, Kendall, and Lazier, J. Am. Chem. Soc. **46**, 2838 (1924).
2. Gabriel and Maass, Ber. **32**, 1266 (1899).
3. Wallach, Ann. **312**, 188 (1900); Eck and Marvel, J. Biol. Chem. **106**, 387 (1934).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alcohol (64-17-5)

hydrochloric acid (7647-01-0)

ether (60-29-7)

lead hydroxide

silver oxide (20667-12-3)

hydrogen sulfide (7783-06-4)

silver nitrate (7761-88-8)

ε-AMINOCAPROIC ACID, Caproic acid, ε-amino- (60-32-2)

2-Ketohexamethylenimine (105-60-2)

ε-aminocaproic acid hydrochloride

ε-benzoylaminocapronitrile

ethyl δ-phthalimidobutylmalonate

Cyclohexanone oxime (100-64-1)

DL-Alanine (302-72-7)

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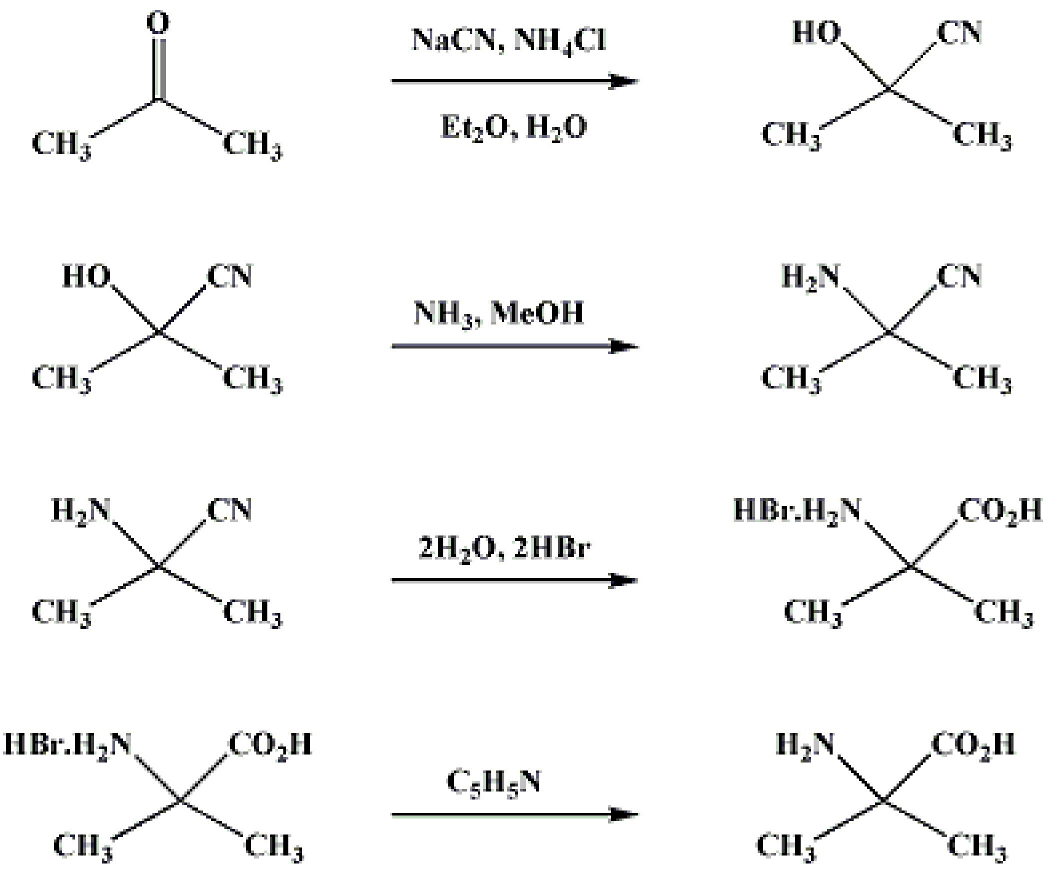
Organic Syntheses, CV 2, 29

α-AMINOISOBUTYRIC ACID

[Isobutyric acid, α-amino-]



Submitted by H. T. Clarke and H. J. Bean.
Checked by C. S. Marvel and C. F. Bailey.

1. Procedure

A filtered solution of 200 g. (3.7 moles) of ammonium chloride in 500 cc. of water is placed in a 3-l. round-bottomed flask. The flask is surrounded by an ice bath and cooled to 5–10°. A solution of 175 g. (3 moles) of acetone in 500 cc. of ether is added with stirring (Note 1). Then a solution of 160 g. (3.2 moles) of sodium cyanide in 350 cc. of water is added, with stirring, at such a rate that the temperature never exceeds 10° (Note 2).

The reaction mixture is stirred for one hour after all the cyanide has been added and then is allowed to stand overnight. The ether layer is separated and the aqueous liquor is extracted with six 300-cc. portions of ether. The ether extracts are combined and the ether is distilled. The residue, which consists mainly of acetone cyanohydrin, is diluted with 800 cc. of methyl alcohol. The solution is cooled and saturated with ammonia gas (Note 3). The reaction mixture is allowed to stand for two or three days (Note 4), and

the excess ammonia is expelled by a current of air. The methyl alcohol is removed by distillation as completely as possible, and 600 cc. of water is added to the residue. Then 1 kg. of 48 per cent hydrobromic acid is added and the mixture is refluxed for two hours.

The hydrobromic acid is distilled under reduced pressure on a steam bath. The residue is treated with 400–500 cc. of water, and the solution is again concentrated under reduced pressure to remove as much hydrobromic acid as possible (Note 5).

The residue is dissolved in fifteen to twenty times its weight of methyl alcohol (Note 6) and filtered, and an excess of pyridine (Note 7) is added. The free amino acid separates on standing overnight. It is collected on a Büchner funnel, washed thoroughly with methyl alcohol, and dried. The yield is 92–102 g. (30–33 per cent of the theoretical amount). If a pyridine-free product is desired, it is dissolved in 200 cc. of warm water and filtered, and the filtrate is poured into 2 l. of methyl alcohol (Note 8). There is less than 10 g. of product in the mother liquors. It may be isolated by evaporating to dryness, washing with methyl alcohol, and purifying by reprecipitation in the same way.

2. Notes

1. Vigorous stirring is necessary to obtain the best results.
2. The reaction temperature may rise to 15° without lowering the yield. If the temperature falls to 0°, the reaction does not take place readily.
3. The excess of ammonia is necessary to cause the formation of the aminonitrile from the acetone cyanohydrin formed in the first stage of the process.
4. In some runs this time was only twenty-four hours and no serious diminution of the yield was noted.
5. After addition of the water and subsequent evaporation almost to dryness it is well to add another small portion of water (25–75 cc.) and again evaporate to dryness to ensure the complete removal of hydrobromic acid. This should be done several times if necessary.
6. The amount of methyl alcohol should not exceed 3 l.; otherwise the amino acid will be precipitated incompletely. Long stirring in the cold may be necessary to effect complete solution, though apparently no difficulty is encountered if the residue does not dissolve completely.
7. The minimum amount of pyridine necessary is determined by the amount of hydrobromic acid remaining in the residue. An excess of pyridine does no harm. If it is desired to use the minimum amount pyridine is added in small portions until the solution is neutral to Congo red, and then an additional 250 g. is added.
8. A further small quantity may be obtained by evaporating the mother liquor to a small volume on a steam bath, allowing it to crystallize, and washing the crystals with methyl alcohol.

3. Discussion

The only satisfactory method of preparing α-aminoisobutyric acid is the Strecker synthesis[1] in one or another of its modifications.[2] The process of isolating the product by treating an alcoholic solution of the hydrobromide with pyridine is essentially the same as that developed for glycine;[3] alternatively, aniline may be used.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 88

References and Notes

1. Strecker, Ann. **75**, 28 (1850).
2. Tiemann and Friedländer, Ber. **14**, 1970 (1881); Marckwald, Neumark, and Stelzner, ibid. **24**, 3283 (1891); Gulewitsch, ibid. **33**, 1900 (1900); Hellsing, ibid. **37**, 1923 (1904); Gulewitsch and Wasmus, ibid. **39**, 1184 (1906); Zelinsky and Stadnikoff, ibid. **39**, 1726 (1906); Cocker and Lapworth, J. Chem. Soc. **1931**, 1391.
3. Org. Syn. **4**, 31 (1925).
4. Benedict, J. Am. Chem. Soc. **51**, 2277 (1929).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ammonia (7664-41-7)

methyl alcohol (67-56-1)

ether (60-29-7)

ammonium chloride (12125-02-9)

aniline (62-53-3)

sodium cyanide (143-33-9)

HYDROBROMIC ACID, hydrobromide (10035-10-6)

acetone (67-64-1)

pyridine (110-86-1)

Glycine (513-29-1)

Acetone cyanohydrin (75-86-5)

α-Aminoisobutyric acid, Isobutyric acid, α-amino- (62-57-7)

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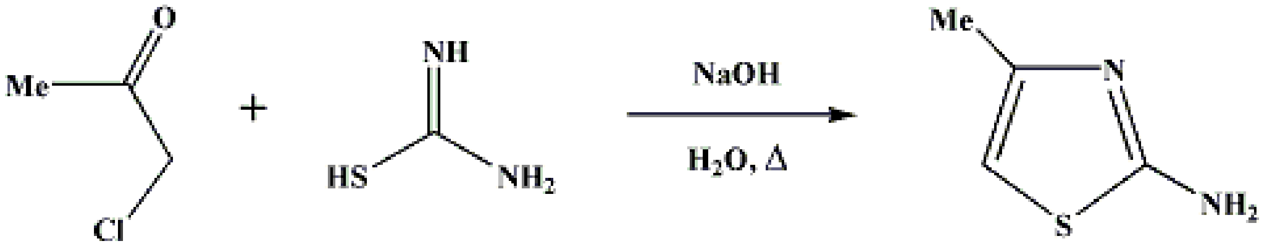
Organic Syntheses, CV 2, 31

2-AMINO-4-METHYLTHIAZOLE

[Thiazole, 2-amino-4-methyl-]



Submitted by J. R. Byers and J. B. Dickey.
Checked by Louis F. Fieser and Byron Riegel.

1. Procedure

Seventy-six grams (1 mole) of thiourea is suspended in 200 cc. of water (Note 1) in a 500-cc. flask equipped with a reflux condenser, dropping funnel, and mechanical stirrer. The stirrer is started, and 92.5 g. (80 cc., 1 mole) of chloroacetone (Note 2) is run in during thirty minutes. As the reaction proceeds the thiourea dissolves and the temperature rises. The yellow solution is refluxed for two hours and cooled, and, while the mixture is stirred continuously but not so rapidly as to produce a troublesome emulsion, 200 g. of solid sodium hydroxide is added with cooling. The upper, oily layer is separated in a separatory funnel and the aqueous layer is extracted three times with ether, using a total of 300 cc. (Note 3). The dark red oil is combined with the ethereal extract, and the solution is dried over 30 g. of solid sodium hydroxide and filtered by gravity to remove small amounts of tar. The ether is removed by distillation from a steam bath, and the oil is distilled at reduced pressure. After a very small fore-run, 2-amino-4-methylthiazole is collected at 117–120°/8 mm., or 130–133°/18 mm. The yield of material melting at 44–45° is 80–85.5 g. (70–75 per cent of the theoretical amount).

2. Notes

1. The reaction may be conducted without this diluent, but it is then likely to become violent.
2. Commercial chloroacetone was distilled and the fraction boiling at 116–122° taken; nearly all of this boiled at 118–120°.
3. If a precipitate is produced and causes an emulsion, add ice and water until it dissolves.

3. Discussion

The method given is essentially that of Traumann.[1] 2-Amino-4-methylthiazole has been prepared also from chloroacetone and ammonium thiocyanate;[2] from chloroacetone and

ammonium thiocyanate in ammonia water;[3] by the action of ammonium thiocyanate on thiocyanoacetone;[3] by saponifying and decarboxylating the cyclic ester from ethyl γ-bromoacetoacetate and thiourea;[4] and from thiocyanoacetone and ammonia in absolute ether.[5]

References and Notes

1. Traumann, Ann. **249**, 37 (1888).
2. Hantzsch and Traumann, Ber. **21**, 938 (1888); Hantzsch and Weber, ibid. **20**, 3118 (1887).
3. Tscherniac and Norton, ibid. **16**, 345 (1883); Tcherniac, J. Chem. Soc. **115**, 1071 (1919).
4. Steude, Ann. **261**, 33 (1891).
5. Hantzsch, Ber. **61**, 1785 (1928).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ammonia (7664-41-7)

ether (60-29-7)

ammonium thiocyanate (1762-95-4)

sodium hydroxide (1310-73-2)

2-Amino-4-methylthiazole, Thiazole, 2-amino-4-methyl- (1603-91-4)

thiourea (62-56-6)

chloroacetone (78-95-5)

thiocyanoacetone

ethyl γ-bromoacetoacetate

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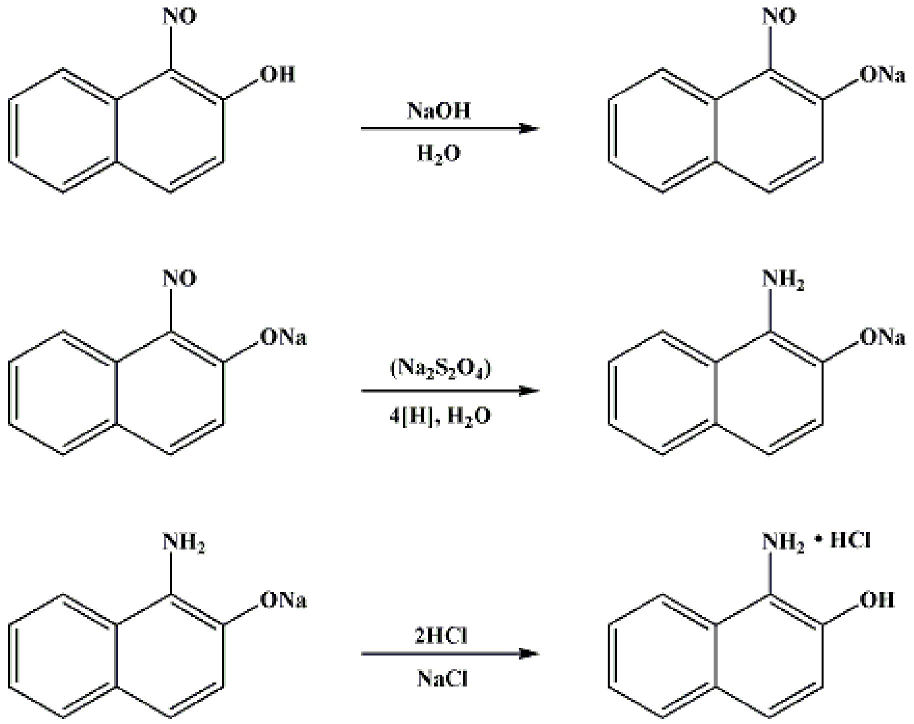
Organic Syntheses, *CV 2, 33*

1,2-AMINONAPHTHOL HYDROCHLORIDE

[2-Naphthol, 1-amino-, hydrochloride]



Submitted by J. B. Conant and B. B. Corson.
Checked by Frank C. Whitmore and A. L. Osterhof.

1. Procedure

In an 8-l. (2-gal.) earthenware crock, equipped with a mechanical stirrer and a tube for introducing steam, are placed 240 g. (1.39 moles) of nitroso-β-naphthol (from 200 g. of β-naphthol, Org. Syn. Coll. Vol. I, **1941**, 411) (Note 1), 1.5 l. of water, and 300 cc. of 5 *N* sodium hydroxide. The lumps are broken up with a rod, and the mixture is stirred for about thirty minutes. At the end of this time, practically all the nitroso compound is dissolved and 1.2 l. of 5 *N* sodium hydroxide is added. Steam is passed in until the temperature of the mixture is 35°, and then the steam is shut off and 600 g. of technical sodium hydrosulfite (at least 85 per cent pure) is added while the solution is being stirred. The solution is stirred continuously for five minutes while the temperature rises to 60–65°, and then for one minute at five-minute intervals during one-half hour. At the end of about fifteen minutes the solution becomes clear and light yellow in color. A small amount of black scum floats on the surface.

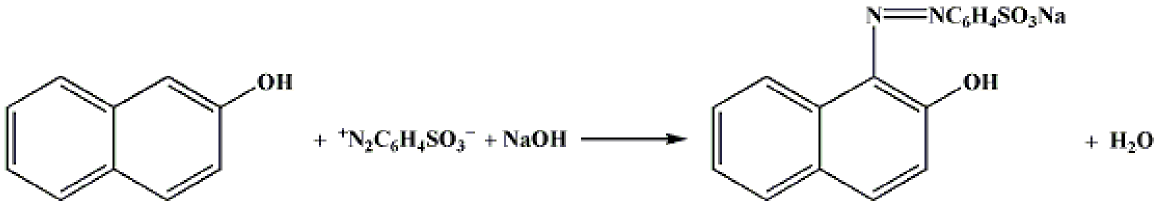
The solution is now cooled to 20° by the addition of about 1 kg. of ice and 500 cc. of technical concentrated hydrochloric acid (sp. gr. 1.16) is added with stirring. This precipitates the aminonaphthol as a voluminous, almost white precipitate (Note 2) which is collected on two 20-cm. Büchner funnels. It is rapidly pressed as free from mother liquor as possible and transferred quickly (Note 3) to an 8-l. (2-gal.) crock containing 2.5 l. of water and 250 cc. of technical concentrated hydrochloric acid. The large lumps are broken up with a rod, steam is passed in, and the stirrer is started. Steam is introduced at such a rate that a temperature of 85–90° is reached within ten minutes; the mixture is stirred at this temperature for one hour longer. The hot mixture is then filtered through a 15-cm. Büchner funnel, and the filtrate is cooled to 35–40° in an ice bath.

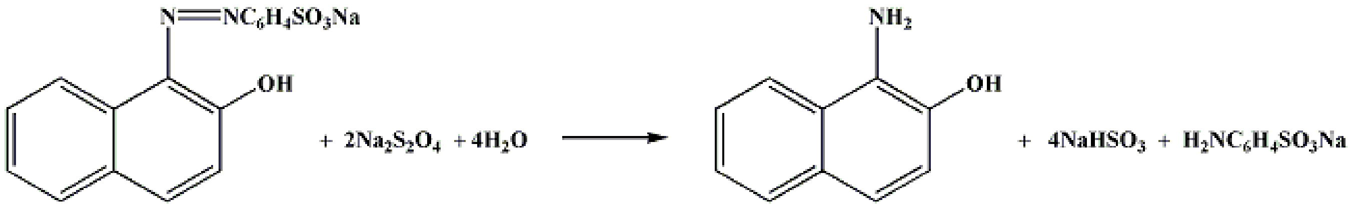
The claret-colored solution (5.2–5.8 l.) is filtered through a fluted filter paper in a 15-cm. funnel into 1.2 l. of concentrated hydrochloric acid in an 8-l. bottle. The aminonaphthol hydrochloride starts to precipitate immediately. The mixture is allowed to stand for at least two hours with occasional agitation to ensure complete precipitation. The hydrochloride is collected on a 15-cm. Büchner funnel and washed successively with three small portions of 20 per cent hydrochloric acid and three 50-cc. portions of ether (Note 4). It is then dried in the air in thin layers on filter paper. The yield is 180–200 g. of anhydrous material (Note 5) (66–74 per cent of the theoretical amount based on 200 g. of β-naphthol). The hydrochloride is unstable; in solution it decomposes rapidly, but this decomposition can largely be prevented by the addition of sodium bisulfite. The dry solid slowly changes and should be used within a few weeks of its preparation (Note 6).

2. Notes

1. It is usually not convenient to dry the nitroso-β-naphthol. The amount given in these directions corresponds to 200 g. of β-naphthol, and the yield is calculated on this basis. The nitroso-β-naphthol dissolves in one mole of sodium hydroxide, forming

a green solution. There is left in suspension a small amount of amorphous brown material which need not be removed.
2. The amounts of sodium hydroxide, sodium hydrosulfite, and hydrochloric acid used are such that complete precipitation of the aminonaphthol results at this point. It is well to test for complete precipitation, however, by adding a few drops of alkali to one portion of the filtrate and a little acid to another.
3. The aminonaphthol is very sensitive to atmospheric oxidation. When first precipitated it is white, but it becomes purple in the air and therefore should be handled rapidly. A small amount of sodium bisulfite may be added at this point to decrease the oxidation, but this is usually unnecessary since some bisulfite from the reduction adheres to the precipitate and is carried through to the final precipitation.
4. Washing with ether greatly facilitates the drying of the product and also lightens its color somewhat. If the material is to be used without being dried, the washing with ether may be omitted.
5. Air-dried material, when apparently completely dry, contains 10–15 per cent of moisture. In order to obtain the true weight of the material an aliquot sample should be dried over sodium hydroxide under reduced pressure.
6. The product, as first formed, is a very light purple but darkens on long standing. It may be purified by dissolving in hot water containing sodium bisulfite, filtering, and reprecipitating with hydrochloric acid.





Submitted by Louis F. Fieser
Checked by C. R. Noller and W. R. White.

1. Procedure

(*A*) *Diazotization of Sulfanilic Acid*.—A mixture of 105 g. (0.5 mole) of sulfanilic acid dihydrate, 26.5 g. (0.25 mole) of anhydrous sodium carbonate, and 500 cc. of water is heated and stirred until all the sulfanilic acid has dissolved, and the solution is then cooled in an ice bath to 15° (sodium sulfanilate begins to crystallize at this temperature). A solution of 37 g. (0.54 mole) of sodium nitrite in 100 cc. of water is added and the resulting solution is poured at once onto a mixture of 106 cc. (1.25 moles) (Note 1) of concentrated hydrochloric acid (sp. gr. 1.18) and 600 g. of ice contained in a 2-l. beaker. The solution, from which *p*-benzenediazonium sulfonate separates on stirring, is allowed to stand in an ice bath for fifteen to twenty-five minutes, during which time the naphthoxide solution is prepared.

(*B*) *Coupling: Orange II*.—Seventy-two grams of β-naphthol (0.5 mole) is dissolved in the warm solution obtained by dissolving 110 g. (2.75 moles) (Note 2) of sodium hydroxide in 600 cc. of water in a 5-l. flask, and the solution is cooled to about 5° by the addition of 400 g. of ice. The suspension of the diazonium salt then is added and the mixture is stirred well and allowed to stand without external cooling for one hour (Note 3). The azo compound soon separates from the red solution and eventually forms a stiff paste.

(*C*) *Reduction: 1,2-Aminonaphthol Hydrochloride*.—The suspension of Orange II is heated to 45–50°, when all the material dissolves with slight evolution of gas. About one-tenth of 230 g. (about 1.1 moles) of technical sodium hydrosulfite (Note 4) is added cautiously and the mixture is stirred until the froth subsides; the remainder is then added without delay. The yellow material which first separates (probably the hydrazo compound) soon is converted into the nearly colorless aminonaphthol. In order to complete the reduction and to give an easily filterable product the mixture is heated strongly until it begins to froth; it is then cooled to 25° by stirring in an ice bath, and the pink or cream-colored product is collected and washed free from the slightly yellow mother liquor with water.

The crude aminonaphthol is washed into a beaker containing a solution at 30° of 2 g. of stannous chloride dihydrate and 53 cc. (0.63 mole) of concentrated hydrochloric acid in 1 l. of water. When the mixture is stirred the amine soon dissolves, leaving in suspension a small amount of fluffy material which is easily distinguishable from the original lumps (Note 5). The solution is clarified by stirring (without heating) for five minutes with 10 g. of decolorizing carbon, and it is then filtered by suction. The pale yellow solution is treated with 50 cc. of concentrated hydrochloric acid and heated to the boiling point, a second 50 cc. of the acid being added as the heating progresses. The color becomes somewhat fainter during this process. The vessel containing the hot solution is

transferred to an ice bath and allowed to cool undisturbed, and the 1-amino-2-naphthol hydrochloride soon separates in the form of large, perfectly colorless needles. When fairly cold, 100 cc. of concentrated hydrochloric acid is added and the solution is cooled to 0° before collecting the product (Note 6). The hydrochloride is washed with a cold solution of 50 cc. of concentrated hydrochloric acid in 200 cc. of water and dried on a filter paper at a temperature not above 30–35°. The yield is 70–83 g. (72–85 per cent of the theoretical amount). The material will remain colorless, or very nearly so, if protected from the light in storage. The fresh solution in water is only faintly colored and leaves but a trace of residue on filtration.

Although this material is suitable for most purposes, it may be purified further in the following manner. It is dissolved by heating in a solution of 2 g. of stannous chloride and 2 cc. of concentrated hydrochloric acid in 1 l. of water, and the hot solution is clarified by filtration through a 5-mm. mat of decolorizing carbon (Note 7). The yellow or red color which may develop disappears on reheating to the boiling point. After the addition of 100 cc. of concentrated hydrochloric acid the solution is allowed to cool in an ice bath, treated with a second 100 cc. of acid, cooled to 0°, and collected and washed as before. The crystalline product is colorless, ash-free, and of analytical purity. The loss in the crystallization of an 80-g. lot amounts to 5–10 g. (6–12 per cent).

2. Notes

1. Diazotization can be accomplished by the use of just one equivalent of acid (0.5 mole), but the solution of the diazoic acid, $NaO_3SC_6H_4N{=}NOH$, so formed is much less stable than the suspension of the inner salt which results from the use of more acid.
2. The excess alkali is not required for the process of coupling, but rather to provide conditions suitable for the reduction.
3. The yield is not improved by allowing a longer period for the reaction. Under the conditions specified, the mixture during the coupling remains at a temperature of 5–10°.
4. If the hydrosulfite is of poor quality more will be needed, and an additional amount of sodium hydroxide should also be added.
5. The solution is highly supersaturated, but it will remain so unless allowed to stand for an undue amount of time. It is also a mistake to add the quantity of concentrated hydrochloric acid specified to a suspension of the aminonaphthol, for this may initiate crystallization.
6. An alternative method of crystallization is to add all the hydrochloric acid (200 cc.) to the boiling solution and to allow this to cool slowly; very large, thick needles result. In the presence of stannous chloride there is no danger of a darkening of the solution as the result of oxidation.
7. This method is preferable to the usual one when dealing with a substance sensitive to air oxidation.

3. Discussion

1-Amino-2-naphthol has been obtained from β-naphthylamine[1] and, more practically, from β-naphthol through the nitroso compound or an azo compound. Nitroso-β-naphthol has been reduced in alkaline solution with hydrogen sulfide[2, 3] or sodium hydrosulfite,[4] but early workers encountered difficulty in converting the amine into its hydrochloride without undue oxidation. Sulfur dioxide was employed as an anti-oxidant, but it is wholly inadequate. Reduction in an acidic medium, usually with stannous chloride, has been more satisfactory. The isolalation of the amine stannochloride and its tedious decomposition with hydrogen sulfide[5] are unnecessary, for the amine hydrochloride can be caused to crystallize essentially free from tin by avoiding an excess of the reducing agent.[2, 6, 7] Nitroso-β-naphthol has been reduced also with zinc dust and sulfuric acid,[8] but the quality of the material, used for conversion to the quinone, is in some doubt.

The nitroso derivative has disadvantages as an intermediate in that it involves handling either a voluminous precipitate or a large volume of solution, and in that some tar is likely to form; hence an azo compound is preferable. Technical Orange II has been reduced in a neutral or alkaline medium with sodium sulfide[2] or sodium hydrosulfite,[9] the sulfanilic acid being eliminated as the soluble sodium salt. With stannous chloride, the necessity of isolating the amine stannochloride[1] can be avoided by using just the calculated amount of reagent, the resulting mixture of amine hydrochloride and sulfanilic acid being separated with an alkaline buffer.[2] Witt[10] found that the sulfanilic acid can be kept in solution if this is sufficiently acidic, and with this improvement Russig[11] worked out a procedure for the preparation and reduction of Orange II which was reported to give excellent yields but which, judging from the results of conversion to the quinone, affords a poor product.

Orange II also has been reduced with zinc dust and hydrochloric acid,[12] by electrolysis,[13] and by catalytic hydrogenation,[14] while a number of other azo dyes derived from β-naphthol have been reduced to 1,2-aminonaphthol with hydrogen and Raney nickel.[15]

The method described above is novel chiefly in that it makes use of stannous chloride as an antioxidant in preparing and crystallizing the amine hydrochloride. The method is applicable with slight modifications to the preparation of many other aminophenols.[16]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 39

- Org. Syn. Coll. Vol. 2, 430

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6. Zincke, Ann. **268**, 274 (1892).
7. Paul, Z. angew. Chem. **10**, 48 (1897).
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10. Witt, ibid. **21**, 3472 (1888).
11. Russig, J. prakt. Chem. (2) **62**, 56 (1900); Böeseken, Rec. trav. chim. **41**, 780 (1922).
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14. Tetralin G.m.b.H., Ger. pat. 406,064 [Frdl. **14**, 395 (1921–25)].
15. Whitmore and Revukas, J. Am. Chem. Soc. **62**, 1687 (1940).
16. Fieser and Fieser, ibid. **57**, 491 (1935).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

1,2-Aminonaphthol hydrochloride

Orange II

$NaO_3SC_6H_4N{=}NOH$

1,2-aminonaphthol

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

hydrogen sulfide (7783-06-4)

sodium carbonate (497-19-8)

sulfur dioxide (7446-09-5)

sodium nitrite (7632-00-0)

sodium hydrosulfite (7775-14-6)

aminonaphthol

aminonaphthol hydrochloride (41772-23-0)

β-naphthol (135-19-3)

stannous chloride

sodium bisulfite (7631-90-5)

Raney nickel (7440-02-0)

decolorizing carbon (7782-42-5)

zinc (7440-66-6)

sodium sulfide (1313-82-2)

Quinone (106-51-4)

Nitroso-β-naphthol (131-91-9)

2-Naphthol, 1-amino-, hydrochloride, 1-amino-2-naphthol hydrochloride (1198-27-2)

sulfanilic acid dihydrate

stannous chloride dihydrate (10025-69-1)

sulfanilic acid (121-57-3)

β-naphthylamine (91-59-8)

sodium sulfanilate

1-Amino-2-naphthol

p-benzenediazonium sulfonate (305-80-6)

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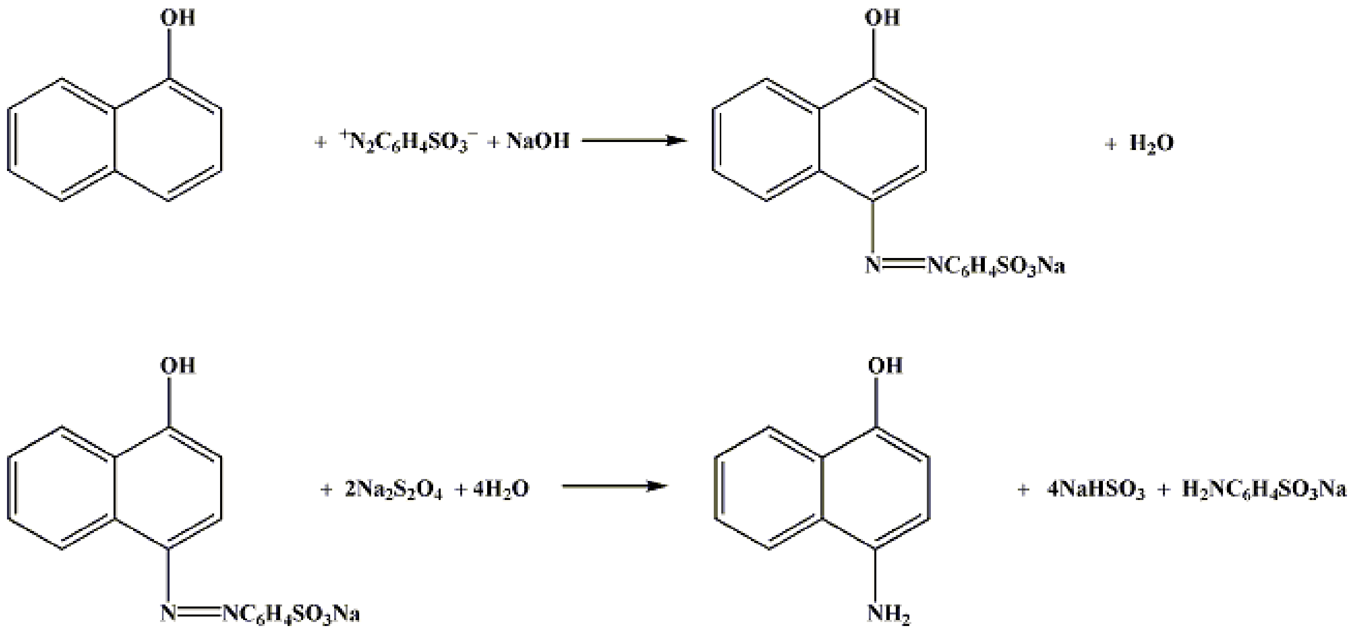
1,4-AMINONAPHTHOL HYDROCHLORIDE

[1-Naphthol, 4-amino-, hydrochloride]



Submitted by Louis F. Fieser
Checked by C. R. Noller and W. R. White.

1. Procedure

One hundred and five grams (0.5 mole) of sulfanilic acid dihydrate is diazotized exactly as described in the last paragraph of p. 35. While the suspension of *p*-benzenediazonium sulfonate is kept in an ice bath, 72 g. (0.5 mole) of α-naphthol (Note 1) is dissolved in the warm solution obtained by dissolving 110 g. (2.75 moles) of sodium hydroxide in 600 cc. of water in a 5-l. flask. The naphthoxide solution is cooled to 25°, 400 g. of ice is added, and the suspension of the diazonium salt is then introduced (Note 2). The mixture is stirred well and allowed to stand for one hour, during which time the formation of the dye, Orange I, goes to completion.

The deep purple-red solution of Orange I is warmed to 45–50°, about one-tenth of 230 g. (about 1.1 moles) of technical sodium hydrosulfite (Note 3) is added cautiously, and the mixture is stirred until the froth subsides; the remainder of the hydrosulfite is then added without delay. The tan suspension of the aminonaphthol is heated to about 70° to effect sufficient coagulation to permit filtering. It is then cooled quickly to 25° by stirring in an ice bath, and the precipitate is filtered and washed with fresh 1 per cent sodium hydrosulfite solution.

The crude aminonaphthol is transferred quickly to a beaker containing a solution of 2 g. of stannous chloride dihydrate and 63 cc. of hydrochloric acid in 800 cc. of water at 30°. On stirring and warming, the amine dissolves. The solution, which is usually a deep red, is filtered with suction; treatment with charcoal is not necessary. One hundred cubic centimeters of concentrated hydrochloric acid is added, the solution is heated to boiling for five to ten minutes, and a second 100-cc. portion of the acid is added. During this heating the color fades to a light yellow, and on cooling to 0° a mass of small, nearly colorless crystals is obtained.

This material (dry weight, 77–80 g.) (Note 4), without being dried, is dissolved by heating in a solution of 2 g. of stannous chloride and 2 cc. of concentrated hydrochloric acid in 700 cc. of water. The hot solution is clarified by filtration through a 5-mm. mat of decolorizing carbon. One hundred cubic centimeters of concentrated hydrochloric acid is added to the hot solution, which is then cooled in an ice bath, treated with a second 100-cc. portion of acid, and cooled to 0°. The precipitate is filtered and washed with a cold solution of 50 cc. of concentrated hydrochloric acid in 200 cc. of water. The 1,4-aminonaphthol hydrochloride forms small, nearly colorless needles of a high degree of purity. The solution in water is faintly pink, and the crystals may acquire a slight pink color after a few weeks. The yield is 70–73 g. (72–75 per cent of the theoretical amount) (Note 5).

2. Notes

1. The α-naphthol should be free from the β-isomer; if the material is very highly colored it is advisable to purify it by distillation at atmospheric pressure. Material melting at 95–96° is satisfactory.
2. A low temperature is required during the coupling in order to avoid the formation of the disazo compound.
3. If the hydrosulfite is of poor quality more will be needed, and an additional amount of sodium hydroxide should also be

added.
4. The material is slightly yellow and may redden on drying; it probably contains a trace of 2,4-diamino-1-naphthol.
5. These directions are very similar to the directions on p. 35 for preparing 1,2-aminonaphthol and should be compared with those directions. The differences between the two procedures are the result of the greater solubility and the greater sensitivity to air oxidation of the 1,4-aminonaphthol.

3. Discussion

The usual method of preparing 1,4-aminonaphthol has been from α-naphthol through an azo dye. The majority of investigators have reduced technical Orange I with stannous chloride;[1, 2, 3, 4, 5, 6] benzeneazo-α-naphthol has been reduced by the same reagent.[7, 8] In order to make possible the use of crude technical α-naphthol a method has been developed[9] for the preparation of the benzeneazo compound, its separation from the isomeric dye coming from the β-naphthol present as well as from any disazo compound by extraction with alkali, and the reduction of the azo compound in alkaline solution with sodium hydrosulfite. The process, however, is tedious and yields an impure product.

1,4-Aminonaphthol can be prepared by reduction of 1,4-nitrosonaphthol, but this is not practical because the starting material is not readily available.[7] The aminonaphthol can also be prepared with a 60 per cent overall yield by the reduction of α-nitronaphthalene to the naphthyl hydroxylamine and rearrangement of the hydroxylamine.[10]

The method described above is applicable with slight modifications to the preparation of both the ortho and para aminonaphthols and to many homologs, benzologs, and heterocyclic isologs of these substances. The chief feature of novelty is in the use of stannous chloride as an anti-oxidant in preparing and crystallizing the amine hydrochlorides.[11]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

1,4-Aminonaphthol hydrochloride

1,4-Aminonaphthol

1,4-nitrosonaphthol

1,2-aminonaphthol

Orange I

hydrochloric acid (7647-01-0)

sodium hydroxide (1310-73-2)

1-Naphthol, 4-amino-, hydrochloride (5959-56-8)

α-naphthol (90-15-3)

benzeneazo-α-naphthol

sodium hydrosulfite (7775-14-6)

aminonaphthol

β-naphthol (135-19-3)

stannous chloride

α-nitronaphthalene (86-57-7)

sulfanilic acid dihydrate

stannous chloride dihydrate (10025-69-1)

2,4-diamino-1-naphthol

naphthyl hydroxylamine

p-benzenediazonium sulfonate (305-80-6)

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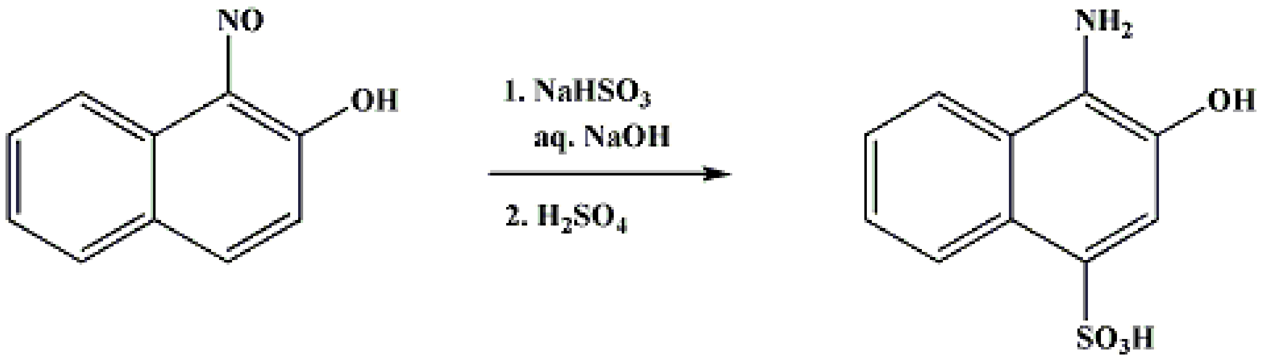
1-AMINO-2-NAPHTHOL-4-SULFONIC ACID

[2-Naphthol-4-sulfonic acid, 1-amino-]



Submitted by Louis F. Fieser
Checked by Frank C. Whitmore and D. J. Loder.

1. Procedure

Three hundred grams of β-naphthol (2.1 moles) is converted into nitroso-β-naphthol (Org. Syn. Coll. Vol. I, **1941**, 411) (Note 1), and the product is transferred to a 6-l. (1.5 gal.) crock which is wide enough to admit the Büchner funnel (30-cm.) employed. A cold solution of 600 g. (5.8 moles) of sodium bisulfite and 100 cc. of 6 *N* sodium hydroxide solution in 2 l. of water (Note 2) is used to rinse the material adhering to the funnel into the crock. The mixture is diluted with water to 4–4.5 l. and stirred until solution of the nitroso-β-naphthol is complete (about fifteen minutes). The dark solution is siphoned onto a large Büchner funnel and filtered by suction, thus removing a small amount of tarry material which is always present. The clear, yellowish brown filtrate is transferred to an 8- to 10-l. wide-mouthed bottle and diluted with water to 7 l. While the solution is vigorously stirred, 400 cc. of concentrated sulfuric acid is poured slowly down the walls of the bottle; the mixture is then placed in the hood and protected from the light (Note 3). The temperature rises from 20–25° to 35–40° at once and to about 50° in the course of two hours, when the reaction is nearly complete. After standing for a total of five hours or more (Note 4), the precipitate, which sets to a stiff paste in the bottle, is collected on a filter. The residue is transferred to a 1-l. beaker and washed with 200 cc. of water. The mixture is filtered, and the residue is washed with 300 cc. of water on the filter. The moist material weighs 700–800 g. No appreciable decomposition takes place on drying the product to constant weight at 120°. A light powder of fine, gray needles is thus obtained. The yield is 410–420 g. (82–84 per cent of the theoretical amount based on the β-naphthol used) (Note 5).

2. Notes

1. In preparing nitroso-β-naphthol in the quantity here required it is convenient to use a 7- to 8-l. bottle, with an 8- to 10-cm. opening, equipped with a stirrer of

heavy glass rod having four or five right-angle bends which extend to the top of the bottle and which are just small enough to fit the mouth. The bottle is placed in a bucket containing a salt-ice mixture which is stirred occasionally by hand. With this arrangement a temperature of 0° may be maintained without internal cooling.

2. Sodium hydroxide is added to the bisulfite solution in order to neutralize any acid which has not been removed by washing, and which would liberate sulfur dioxide and thus cause some reduction of the nitroso compound before the addition product is formed. An excess of alkali, as employed above, aids in the solution of the material.

3. The aminonaphtholsulfonic acid becomes rose colored on long exposure to the light, especially when moist.

4. The time required for the process may be shortened somewhat by adding the sodium bisulfite-sodium hydroxide solution to the suspension of the crude nitroso compound, thus avoiding a long filtration. The amounts of water employed in the various operations should be reduced to a minimum, and enough additional sodium hydroxide solution should be used to neutralize the excess acid present. The product is of a slightly inferior quality, and the yield is 4–5 per cent lower.

5. This gray material is not quite pure and contains water of crystallization so that the percentage yield reported is in error. A better product can be obtained by stirring the mixture of nitroso-β-naphthol and sodium bisulfite solution vigorously by hand with a wooden paddle thus causing all the soluble product to dissolve in three to four minutes. The suspension is then filtered as rapidly as possible using two 15-cm. Büchner funnels and changing filter papers frequently. The clear, golden-yellow filtrate is acidified immediately on completion of the filtration. The product is then light gray, whereas, if much time elapses before the bisulfite solution is acidified, the solution turns red and the aminonaphtholsulfonic acid may be deep purple-gray in color. After the product has been collected and washed with water, it is washed with warm alcohol until the filtrate is colorless, 1.5–2 l. being required. The product is washed with two 100-cc. portions of ether and dried to constant weight at 60–80° in the absence of light. A pure white, dust-dry product is thus obtained, weighing 370–380 g. (75–78 per cent of the theoretical amount based on the β-naphthol). The wash alcohol does not dissolve an appreciable amount of the aminonaphtholsulfonic acid since evaporation of the deep red wash liquor gives a dark residue weighing only 3–4 g. (E. L. Martin and Louis F. Fieser, private communication.)

3. Discussion

1-Amino-2-naphthol-4-sulfonic acid has been prepared by warming 2-naphthoquinone-1-chloroimide with sodium bisulfite solution;[1] by reduction of 1-benzeneazo-2-naphthol-4-sulfonic acid with stannous chloride and hydrochloric acid;[2] by treatment of 1-amino-2-naphthol hydrochloride with sodium sulfite;[3] and by treatment of nitroso-β-naphthol with sodium bisulfite and hydrochloric acid.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 633

References and Notes

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4. Schmidt, J. prakt. Chem. (2) **44**, 522 (1891); Böniger, Ber. **27**, 23 (1894).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

2-naphthoquinone-1-chloroimide

alcohol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium sulfite (7757-83-7)

sodium hydroxide (1310-73-2)

sulfur dioxide (7446-09-5)

β-naphthol (135-19-3)

stannous chloride

sodium bisulfite (7631-90-5)

Nitroso-β-naphthol (131-91-9)

1-amino-2-naphthol hydrochloride (1198-27-2)

1-AMINO-2-NAPHTHOL-4-SULFONIC ACID, 2-Naphthol-4-sulfonic acid, 1-amino- (116-63-2)

aminonaphtholsulfonic acid

sodium bisulfite-sodium hydroxide

1-benzeneazo-2-naphthol-4-sulfonic acid

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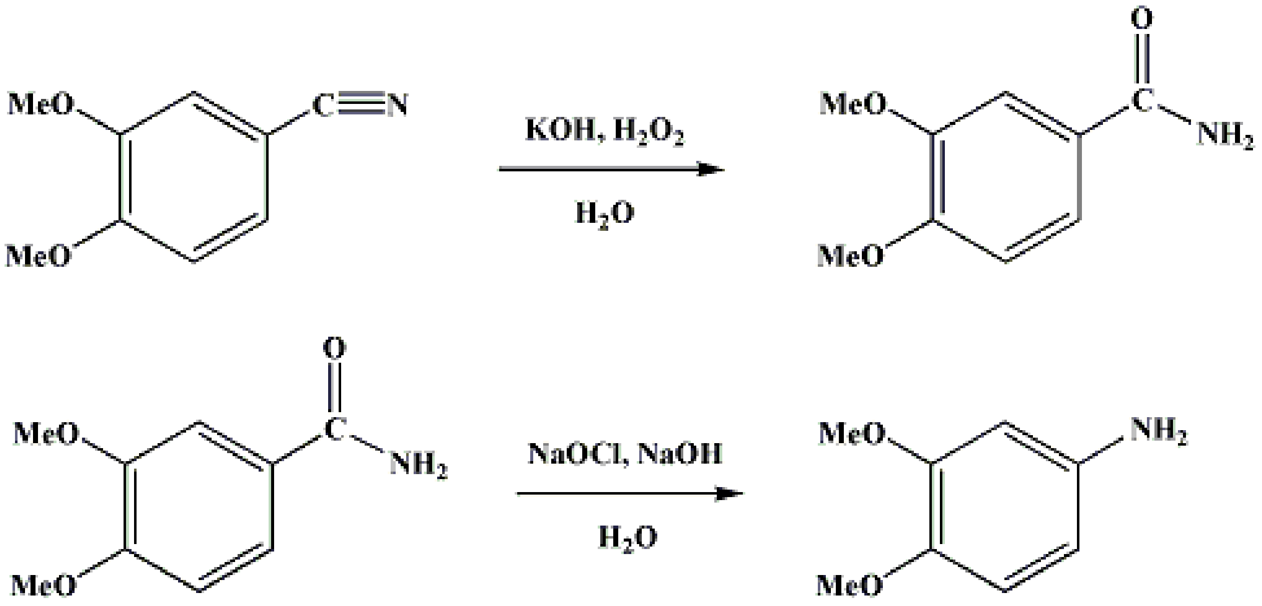
4-AMINOVERATROLE

[Aniline, 3,4-dimethoxy-]



Submitted by J. S. Buck and W. S. Ide.
Checked by John R. Johnson and H. B. Stevenson.

1. Procedure

In a 5-l. flask fitted with a mechanical stirrer are placed 1.8 kg. (1.6 moles) of fresh 3 per cent hydrogen peroxide solution, 100 g. of 25 per cent potassium hydroxide solution, and 57 g. (0.35 mole) of veratronitrile (p. 622). The mixture is warmed slowly to 45°, with stirring, and the source of heat is then withdrawn. The reaction proceeds with evolution of oxygen, and the temperature continues to rise (Note 1). The amide soon begins to separate; in about fifty minutes the reaction is complete and the temperature begins to fall. The mixture is cooled to 3–5° and allowed to remain in the cooling bath for one and one-half to two hours. The white crystalline product is filtered with suction and dried in the air. The veratric amide melts at 162.5–163.5° and weighs 55–58 g. (87–92 per cent of the theoretical amount).

An alkaline solution of sodium hypochlorite is prepared by passing chlorine (0.412 gram for each gram of the amide) (Note 2) into a mixture of 300 g. of cracked ice and a cold solution of 80 g. of sodium hydroxide in 500 cc. of water, contained in a 2-l. round-bottomed flask. The whole of the veratric amide (55–58 g.) is added in one portion, and the mixture is warmed slowly in a water bath, with mechanical stirring. The material soon darkens in color, and at 50–55° (internal temperature) oily droplets begin to separate. The temperature is raised gradually to 70° and maintained at this point for one hour. A solution of 120 g. of sodium hydroxide in 120 cc. of water is added slowly, and the temperature is increased to 80° for an additional hour.

Upon cooling the mixture, the oily layer of amine solidifies to a red crystalline mass. The crude amine is filtered with suction, washed with two 60-cc. portions of ice-cold water, pressed thoroughly, and transferred to an ordinary 125-cc. Claisen flask. The filtrate is extracted with three 60-cc. portions of benzene, the extracts are transferred separately to the Claisen flask, and the benzene is distilled at atmospheric pressure (Note 3). The residual amine is distilled under reduced pressure and is collected at 172–174°/24 mm. (Note 4). The distillate solidifies quickly to a mass of colorless crystals which melt sharply at 87.5–88° (Note 5). From 58 g. (0.32 mole) of veratric amide there is obtained 39–40 g. (80–82 per cent of the theoretical amount) of 4-aminoveratrole.

2. Notes

1. A large amount of frothing occurs, and the temperature rises to 52–55° during the reaction. The flask should be removed at intervals and shaken by hand to bring the material carried up by the froth into contact with the solution.
2. The quantity of chlorine indicated is 5 per cent more than the theoretical amount. The chlorine may be obtained from a cylinder, but for small amounts it is more accurate to generate chlorine by treating a weighed amount of potassium permanganate with an excess of concentrated hydrochloric acid (0.367 g. $KMnO_4$ 0.412 g. Cl_2). For 55–58 g. of veratric amide the weight of permanganate to be used is 20.2–21.3 g.
For generating the chlorine, the requisite weight of potassium permanganate is placed in a 500-cc. distilling flask fitted with a separatory funnel and suspended so that the flask can be agitated. Concentrated hydrochloric acid (about 130 cc. is required) is allowed to drop slowly upon the permanganate crystals, and as the reaction progresses the flask is heated. After all the acid has been added the mixture is boiled gently for a few minutes to expel the last portions of chlorine, and the delivery tube is removed rapidly from the alkaline hypochlorite solution to prevent the solution from being sucked back into the generator. A safety bottle should be inserted between the side tube of the generator and the tube which delivers the chlorine into the alkali.
3. Distillation of the benzene extracts in this way serves to remove the water, and in the subsequent distillation of the amine no watery fore-run is obtained.
4. Since the aminoveratrole tends to solidify in the side tube of the distilling flask, it is advisable to distil the material rapidly and to employ a bath temperature about 60° higher than that of the distilling vapor. Care must be taken to avoid contaminating the distillate with a small amount of colored material which comes over if the distillation is carried too far.
5. The melting point of 4-aminoveratrole obtained by reduction of 4-nitroveratrole is reported as 85–86°.[1] The amine discolors on exposure to air and light; it should be stored in a sealed, dark container.

3. Discussion

4-Aminoveratrole has been prepared by the reduction of 4-nitroveratrole with tin,[1], [2] or stannous chloride,[3] and hydrochloric acid. The present procedure is based upon a method

used for the preparation of aminopiperole (3,4-methylenedioxyaniline).[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 619

References and Notes

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3. Heinisch, Monatsh. **15**, 232 (1894).
4. Rupe and Majewski, Ber. **33**, 3401 (1900).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

aminopiperole

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

sodium hydroxide (1310-73-2)

potassium permanganate (7722-64-7)

oxygen (7782-44-7)

tin (7440-31-5)

stannous chloride

chlorine (7782-50-5)

potassium hydroxide (1310-58-3)

hydrogen peroxide (7722-84-1)

permanganate

sodium hypochlorite (7681-52-9)

4-Aminoveratrole, Aniline, 3,4-dimethoxy- (6315-89-5)

Veratronitrile (2024-83-1)

Veratric amide (1521-41-1)

aminoveratrole

4-nitroveratrole (709-09-1)

3,4-methylenedioxyaniline (14268-66-7)

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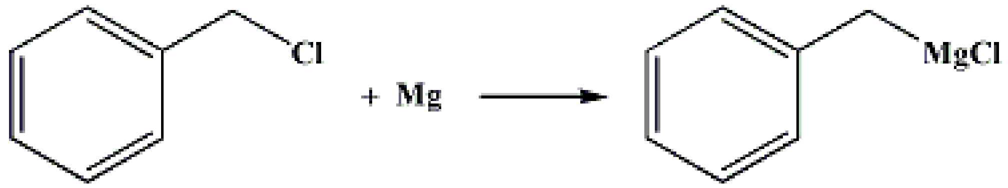
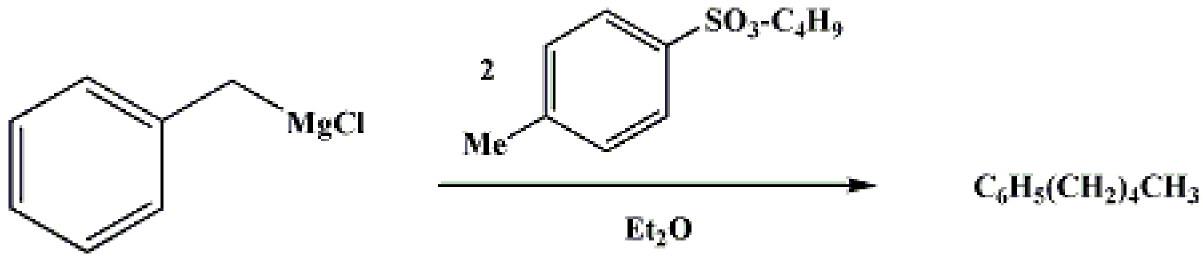
n-AMYLBENZENE

[Benzene, amyl-]





Submitted by Henry Gilman and J. Robinson.
Checked by C. S. Marvel and S. S. Rossander.

1. Procedure

One mole of benzylmagnesium chloride is prepared in a 2-l. three-necked, round-bottomed flask from 24.3 g. (1 gram atom) of magnesium turnings, 126.5 g. (115 cc., 1 mole) of benzyl chloride, and 500 cc. of anhydrous ether, according to the directions given in Org. Syn. Coll. Vol. I, **1941**, 471.

The solution of benzylmagnesium chloride is cooled with running water, and 456 g. (2 moles) of *n*-butyl *p*-toluenesulfonate (Note 1) dissolved in about twice its volume of anhydrous ether is then added slowly with stirring through the separatory funnel at such a rate that the ether just boils. The time required for the addition is about two hours. A white solid soon forms and the mixture assumes the consistency of a thick cream. Stirring is continued, without cooling, for about two hours, and the mixture is hydrolyzed by pouring onto crushed ice to which is then added about 125 cc. of concentrated hydrochloric acid (Note 2).

The ether layer is separated and combined with a 200-cc. ether extract of the aqueous layer. The combined ether solution is washed once with about 100 cc. of water and then dried by shaking for a few minutes with about 10 g. of anhydrous potassium carbonate. After filtration, the ether is distilled on a water bath. When practically all the ether has been removed, about 5 g. of sodium, freshly cut and in thin slices, is added and the mixture is boiled for about two hours (Note 3). The solution is decanted and then distilled, using an efficient fractionating column. The fraction boiling at 190–

210° is collected. This on redistillation yields 74–88 g. (50–59 per cent of the theoretical amount) of *n*-amylbenzene boiling at 198–202° (Note 4).

2. Notes

1. Directions for the preparation of *n*-butyl *p*-toluenesulfonate are given in Org. Syn. Coll. Vol. I, **1941**, 145, and in Org. Syn. **20**, 51.
2. The hydrolysis is preferably carried out in a 5-l. Erlenmeyer flask. The magnesium *p*-toluenesulfonate is sparingly soluble in hydrochloric acid, and complete solution is brought about by the subsequent addition of about 2 l. of water.
3. Refluxing with sodium helps to remove the small amount of benzyl alcohol formed by the atmospheric oxidation of benzylmagnesium chloride.
4. The major part of the *n*-amylbenzene distils at 199–201°. A careful fractionation of the distillate that comes over around 75° yields 24 g. (26 per cent of the theoretical amount) of *n*-butyl chloride boiling at 76–80°.

3. Discussion

n-Amylbenzene has been prepared by the action of sodium on a mixture of benzyl and butyl bromides;[1] by the reaction between benzyl sodium and butyl chloride;[2] by the reduction of *n*-valerophenone with formic acid over copper at 300°,[3] or with zinc and hydrochloric acid;[4] by the action of sodium ethoxide on the hydrazone[5] and the semicarbazone[6] of *n*-valerophenone; and by the procedure described, which is an adaptation of the directions of Gilman and Heck[7] and Rossander and Marvel.[8]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

benzyl and butyl bromides

hydrazone

semicarbazone

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

ether (60-29-7)

magnesium turnings (7439-95-4)

formic acid (64-18-6)

copper (7440-50-8)

zinc (7440-66-6)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

benzyl chloride (100-44-7)

Benzyl alcohol (100-51-6)

Butyl chloride, n-BUTYL CHLORIDE (109-69-3)

benzylmagnesium chloride (6921-34-2)

Benzene, amyl-, n-AMYLBENZENE (538-68-1)

benzyl sodium

n-valerophenone (1009-14-9)

n-BUTYL p-TOLUENESULFONATE (778-28-9)

magnesium p-toluenesulfonate

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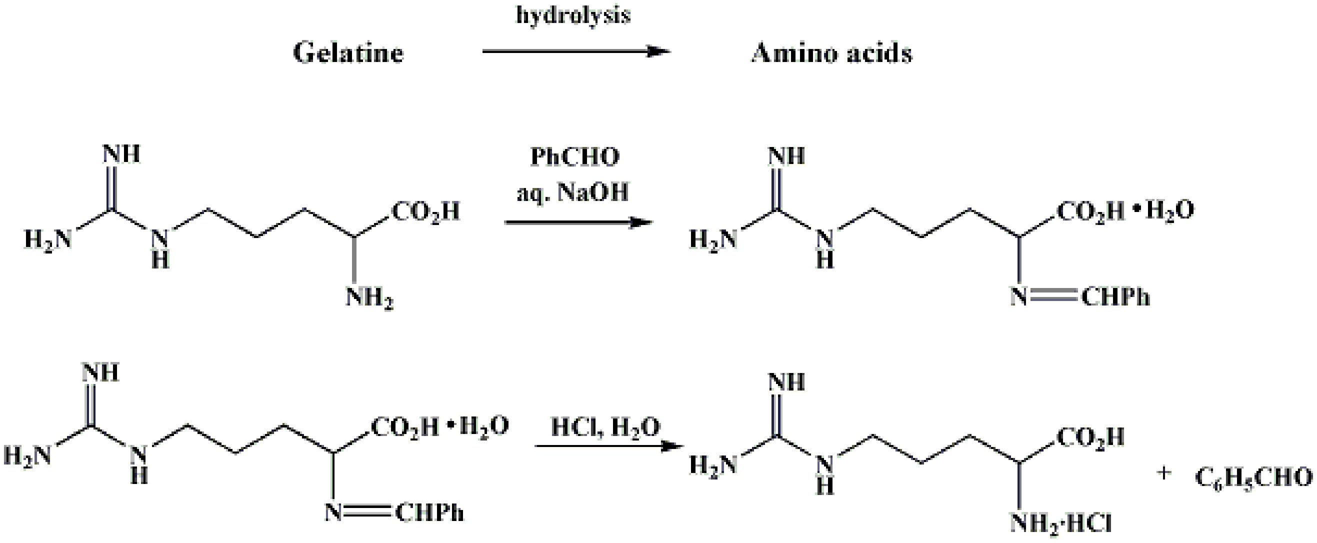
d-ARGININE HYDROCHLORIDE



Submitted by E. Brand and M. Sandberg.
Checked by H. T. Clarke and S. Graff.

1. Procedure

Benzylidenearginine, Method 1.—To 500 g. of gelatine (Note 1) is added 1.5 l. of concentrated hydrochloric acid (sp. gr. 1.19); the mixture is warmed on the steam bath for thirty minutes and boiled over a free flame for eight to ten hours (Note 2) under a reflux condenser provided with a trap for hydrogen chloride gas. The solution is concentrated to 400 cc. on the steam bath under reduced pressure, employing the apparatus shown in Org. Syn. Coll. Vol. I, **1941**, 427. The syrupy residue is then diluted with 500 cc. of distilled water and again concentrated to 400 cc. This process of dilution and evaporation is repeated twice more (Note 3). The final residue is dissolved in 500 cc. of hot distilled water and decolorized by adding 15 g. of decolorizing carbon and heating for ten minutes on the steam bath. The filtrate is chilled in an ice-salt bath and treated with 250–350 cc. of a 40 per cent solution of sodium hydroxide until slightly alkaline to litmus, keeping the temperature below 10°. An additional 70-cc. portion of 40 per cent sodium hydroxide solution is added, keeping the temperature below 5°; this is followed by the addition, in four portions, of 225 cc. of benzaldehyde, with vigorous shaking after each addition, the temperature being held below 5° throughout (Note 4). The addition of the benzaldehyde occupies about ten minutes.

The resulting emulsion is allowed to stand overnight in the refrigerator at 0–5°; the crystalline precipitate is filtered by suction and washed first with 80 cc. of ice-cold water in four portions, then with 50 cc. of a mixture of two volumes of ether and one volume of methyl alcohol, and, finally, with ether (Note 5) until the washings are colorless and free of benzaldehyde. After drying in a vacuum desiccator the product weighs 35–40 g.; it melts with decomposition at 206–207° (corr.).

Benzylidenearginine, Method 2.—The hydrolysis of 500 g. of gelatine and the removal of excess hydrochloric acid are conducted as described above. After treatment with 15 g. of decolorizing carbon the filtrate is diluted to 2.5 l., heated almost to boiling, and treated with 110 g. of 2,4-dinitro-1-naphthol-7-sulfonic acid ("flavianic acid") (Note 6) dissolved in 400 cc. of hot water. The mixture is boiled (Note 7) for about three minutes and diluted with boiling water to a total volume of 4 l. The mixture is cooled rapidly to 45° and then allowed to cool slowly to room temperature, with occasional stirring and vigorous scratching of the walls of the container. After standing for about two hours at room temperature (Note 8), practically all (Note 9) the arginine dinitronaphtholsulfonate should have separated in crystalline, readily filterable form. The product is filtered by suction and washed first with three 100-cc. portions of a 0.5 per cent solution of dinitronaphtholsulfonic acid and then with two 25-cc. portions of 95 per cent ethyl alcohol. After being dried in air, the product weighs 113–118 g. (Note 10); it decomposes at 245–265° (Note 11).

One hundred grams (0.21 mole) of finely powdered arginine dinitronaphtholsulfonate is added, all at once, to 230 cc. of cold 2 *N* sodium hydroxide; the salt dissolves readily on agitation. There is then added *without delay* (Note 12) 35 g. (0.33 mole) of benzaldehyde, in four portions and with vigorous shaking, each portion being accompanied by 75 cc. of ice-cold water. During this process, benzylidenearginine separates as a crystalline cake. The mixture is allowed to stand at 15–20° for one to two hours, whereupon the product is filtered (Note 13) and washed successively with two to four 50-cc. portions of ice-cold water, three 20-cc. portions of a mixture of 20 cc. of methyl alcohol and 40 cc. of ether, and finally two 50-cc. portions of ether (Note 5). It is then dried in air. The yield is 39–43 g., corresponding to about 44–48 g. from 500 g. of gelatine (Note 10).

Arginine Hydrochloride.—A suspension of 50 g. (0.18 mole) of benzylidenearginine in 39 cc. of 5 *N* hydrochloric acid is heated in a boiling water or steam bath for forty-five minutes, with occasional shaking. The mixture is allowed to cool and is freed of benzaldehyde by shaking with three 100–150 cc. portions of ether. The aqueous solution is filtered if necessary, decolorized with 3 g. of decolorizing carbon, filtered, and concentrated on the water bath at 70° under reduced pressure until crystallization sets in. The residue is transferred from the flask with the aid of 25 cc. of hot 70 per cent ethyl alcohol; the arginine hydrochloride is precipitated by adding 300 cc. of absolute alcohol. After filtering the product, a further small quantity of crystalline hydrochloride is obtained by adding 300 cc. of ether to the mother liquor. The combined (Note 14) yield amounts to 33–34 g. (88–90 per cent of the theoretical amount). It melts at 220° (corr.) and exhibits a rotation of $[\alpha]_D^{25°}$ = +12.2 to 12.3° (5 per cent in water).

2. Notes

1. The quality of gelatine is technically defined on the basis of its physical properties, and different samples vary widely in chemical composition. In checking, the highest yields (9.7–10.3 per cent of the weight of gelatine taken) of benzylidenearginine were secured from the "Bactogelatine" of the Digestive Ferments Company.
2. The biuret reaction is generally found to be negative after five hours.
3. The third distillate generally contains only 1–2 g. of hydrogen chloride. In checking this preparation on a larger scale, it has been found convenient to add the water continuously below the surface of the boiling syrup; this modification, which constitutes a steam distillation under reduced pressure, brings about a more rapid removal of the excess hydrochloric acid.
4. Unless the temperature is held below 5°, difficulty is experienced in emulsifying the benzaldehyde.
5. Benzylidenearginine is quite insoluble in ether but appreciably soluble in methyl alcohol and in water. Attempts to recrystallize it from the latter solvents lead to a product of inferior quality, owing to decomposition in solution. Impure or contaminated samples may be purified by hydrolysis with hot hydrochloric acid and reprecipitation with benzaldehyde after neutralization.
6. The free dinitronaphtholsulfonic acid can be prepared readily from commercial Naphthol Yellow S by treating a filtered saturated solution of the dye with three volumes of concentrated hydrochloric acid. The crystals which separate are washed with cold 20 per cent hydrochloric acid and dried, first in air and finally in a vacuum desiccator over solid sodium hydroxide.
7. The boiling prevents the precipitation of arginine diflavianate and minimizes the separation of the flavianates of other amino acids.
8. Crystallization is occasionally delayed, particularly in first runs when traces of arginine flavianate are not available in the atmosphere for spontaneous inoculation. In such cases it may be necessary to chill the solution in the refrigerator with occasional vigorous scratching.
9. The mother liquor, on long standing in the icebox, may deposit a second crop of crystals which appear to consist largely of sodium dinitronaphtholsulfonate and yield no arginine on further treatment. The filtrate thus obtained in Method 2 is suitable for the recovery of other amino acids, thereby differing from the corresponding mother liquor from Method 1.
10. This yield was obtained from a batch of gelatine from which 35–36 g. of benzylidenearginine was obtained by Method 1.
11. According to the literature,[1] pure arginine dinitronaphtholsulfonate melts at 258–260° with decomposition. The presence of moisture lowers the melting point considerably. If the mother liquor is allowed to stand for several days at 0–5°, some sodium dinitronaphtholsulfonate may crystallize.
12. Delay in adding the benzaldehyde must be avoided or sodium dinitronaphtholsulfonate may crystallize; the water is added to prevent this. The presence of the excess of benzaldehyde also appears to help prevent

this crystallization.
13. A sintered-glass suction filter is advantageous for collecting and washing the benzylidenearginine.
14. The over-all loss involved in the various steps may be estimated from the following experiment: 5.0 g. of arginine nitrate was converted through the dinitronaphtholsulfonate into benzylidenearginine and then back into arginine nitrate, when 4.2 g. was recovered.

3. Discussion

Arginine has been precipitated (*a*) in the form of its silver derivative at *p*H 10;[2] (*b*) as its dinitronaphtholsulfonate which is then decomposed by means of 33 per cent sulfuric acid,[1] by the combined action of hot dilute sulfuric acid and butyl alcohol,[3] by cold concentrated hydrochloric acid followed by aniline,[4] or by barium hydroxide.[5] Arginine has likewise been precipitated (*c*) in the form of its benzylidene derivative from solutions rendered alkaline with barium hydroxide or sodium hydroxide.[6] It has been separated as such (*d*) from protein hydrolysates by electrolysis under controlled *p*H.[7]

In the present directions, Method 1 is essentially that developed by Bergmann and Zervas;[6] Method 2 forms a combination of methods (*b* and *c*) and thus at once affords a product of high purity while avoiding the mechanical difficulties involved in the complete removal of the dinitronaphtholsulfonic acid from its arginine salt.

References and Notes

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3. Pratt, ibid. **67**, 351 (1926).
4. Cox, ibid. **78**, 475 (1928).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

gelatine

arginine diflavianate

arginine flavianate

flavianic acid

ethyl alcohol, alcohol (64-17-5)

sulfuric acid (7664-93-9)

hydrogen chloride, hydrochloric acid (7647-01-0)

methyl alcohol (67-56-1)

ether (60-29-7)

aniline (62-53-3)

sodium hydroxide (1310-73-2)

benzaldehyde (100-52-7)

butyl alcohol (71-36-3)

decolorizing carbon (7782-42-5)

arginine (74-79-3)

barium hydroxide (17194-00-2)

Benzylidenearginine

arginine dinitronaphtholsulfonate

dinitronaphtholsulfonic acid

Arginine Hydrochloride (1119-34-2)

sodium dinitronaphtholsulfonate

arginine nitrate

D-Arginine hydrochloride (627-75-8)

2,4-dinitro-1-naphthol-7-sulfonic acid

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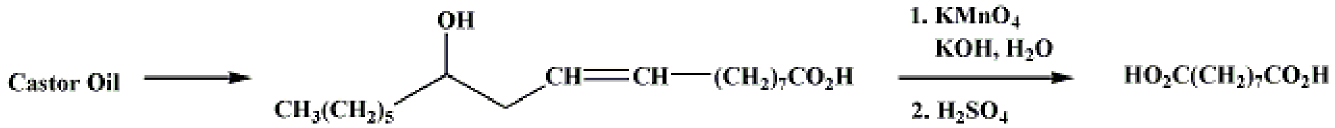
AZELAIC ACID



Submitted by Julian W. Hill and W. L. McEwen.
Checked by Reynold C. Fuson and Charles F. Woodward.

1. Procedure

Five hundred grams of castor oil (Note 1) is added to a solution of 100 g. of potassium hydroxide in 1 l. of 95 per cent alcohol. The mixture is placed in a 3-l. flask equipped with a reflux condenser and is boiled for three hours. The solution is then poured into 3 l. of water and acidified by the addition of a solution of 100 cc. of concentrated sulfuric acid in 300 cc. of water. The acid which separates is washed twice with warm water, shaken intermittently for one hour with 100 g. of anhydrous magnesium sulfate, and then filtered with suction. The yield of crude ricinoleic acid thus obtained is 480 g. The acid should be oxidized at once (Note 2).

Two hundred and forty grams (0.8 mole) of the dried ricinoleic acid is dissolved in 1.6 l. of water containing 64 g. of potassium hydroxide. A 12-l. round-bottomed flask is equipped with a powerful mechanical stirrer, and in it are placed 625 g. (3.5 moles) of potassium permanganate and 7.5 l. of water at 35°. The mixture is stirred to facilitate solution of the permanganate, and, if necessary, heat is applied to maintain the temperature at 35°. When the permanganate has completely dissolved, the alkaline solution of ricinoleic acid is added in a single portion with vigorous stirring (Note 3). The temperature rises rapidly to about 75°. Stirring is continued for a half hour, or until a test portion added to water shows no permanganate color.

The oxidation mixture is now divided into two equal portions and each portion is treated as follows: To the mixture is added a solution of 200 g. of concentrated sulfuric acid in 600 cc. of water (Note 4). The mixture is heated on a steam bath for 15 minutes to coagulate the manganese dioxide which is filtered while still very hot (Note 5). After filtration the manganese dioxide is placed in a 4-l. beaker and boiled with 2 l. of water to dissolve any azelaic acid that may adhere to it. This mixture is filtered while hot, and the filtrate is added to the main portion.

The combined filtrates and washings for the two portions of the oxidation mixture are evaporated to a volume of about 4 l., and this solution is cooled in ice. The crystals which separate are filtered with suction, washed once with cold water, and dried. The yield is 70–80 g. of material having a melting point that may vary from 95 to 105°.

The crude substance is dissolved in 1.2 l. of boiling water, filtered with suction, and allowed to cool. The crystals are filtered, washed with water, and dried. There is obtained 48–55 g. of product (32–36 per cent of the theoretical amount, based upon the amount of crude ricinoleic acid taken for oxidation). The melting point of the purified azelaic acid is 104–106°.

2. Notes

1. The castor oil used was a commercial grade designated as "Crystal." It was obtained from the Baker Castor Oil Company, New York City.
2. If ricinoleic acid is allowed to stand, polymerization occurs; Baker and Ingold report[1] that the polymerized acid gives very poor yields in the oxidation by nitric acid.
3. At this point the mixture tends to froth quite badly, and, if stirring is not vigorous, material may be lost. Addition of a small quantity of ether or benzene may be resorted to but is unnecessary if stirring is efficient.
4. The acid must be added slowly and carefully to prevent too rapid evolution of carbon dioxide with consequent foaming. If possible, each of the two portions should be placed in a large container, such as a 12-l. flask.
5. For this purpose it is advisable to use three 20-cm. Büchner funnels supported in 2-l. filter flasks.

3. Discussion

Azelaic acid can be prepared by the oxidation of castor oil with nitric acid;[2] by the oxidation of ricinoleic acid with nitric acid[1] and with alkaline permanganate;[3] by the oxidation of methyl oleate with alkaline permanganate;[4] by the

ozonization of oleic acid and decomposition of the ozonide;[5] by the ozonization of methyl ricinoleate and decomposition of the ozonide;[6] by the action of carbon dioxide upon 1,7-heptamethylenemagnesium bromide;[7] by the hydrolysis of 1,7-dicyanoheptane;[8] and by the oxidation of dihydroxystearic acid with dichromate and sulfuric acid, the dihydroxy acid being prepared from oleic acid and hydrogen peroxide.[9]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ozonide

1,7-heptamethylenemagnesium bromide

alcohol (64-17-5)

sulfuric acid (7664-93-9)

Benzene (71-43-2)

ether (60-29-7)

nitric acid (7697-37-2)

potassium permanganate (7722-64-7)

carbon dioxide (124-38-9)

potassium hydroxide (1310-58-3)

hydrogen peroxide (7722-84-1)

manganese dioxide (1313-13-9)

Azelaic acid (123-99-9)

magnesium sulfate (7487-88-9)

ricinoleic acid

methyl oleate (112-62-9)

oleic acid (112-80-1)

methyl ricinoleate (141-24-2)

1,7-dicyanoheptane (1675-69-0)

dihydroxystearic acid

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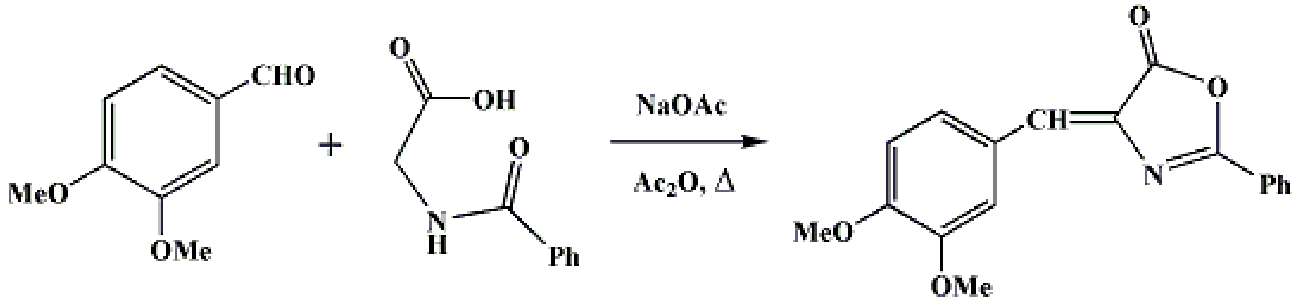
AZLACTONE OF α-BENZOYLAMINO-β-(3,4-DIMETHOXYPHENYL)-ACRYLIC ACID

[5(4)-Oxazolone, 2-phenyl-4-veratral-]



Submitted by Johannes S. Buck and Walter S. Ide.
Checked by John R. Johnson and H. R. Snyder.

1. Procedure

In a 2-l. Erlenmeyer flask, a mixture of 160 g. (0.96 mole) of veratraldehyde (Note 1), 192 g. (1.07 moles) of powdered, dry hippuric acid (p. 328), 80 g. (0.98 mole) of powdered, freshly fused sodium acetate, and 300 g. (278 cc., 2.9 moles) of high-grade acetic anhydride is heated on an electric hot plate, with constant shaking. The mixture becomes almost solid, and then, as the temperature rises, it gradually liquefies and turns deep yellow in color (Note 2). As soon as the material has liquefied completely the flask is transferred to a steam bath and heated for two hours. During this time a part of the product separates as deep yellow crystals. At the end of the heating 400 cc. of alcohol is added slowly to the contents of the flask. During this addition the flask is cooled slightly to moderate the vigor of the reaction. After allowing the reaction mixture to stand overnight, the yellow crystalline product is filtered with suction and washed on the filter with two 100-cc. portions of ice-cold alcohol and finally with two 100-cc. portions of boiling water. After drying, the product weighs 205–215 g. (69–73 per cent of the theoretical amount) and melts at 149–150°. This material is sufficiently pure for many purposes; it can be purified further by crystallization from hot benzene. In this way, using 1.2 l. of benzene, there is obtained 180–190 g. of the pure azlactone, melting at 151–152°.

2. Notes

1. The veratraldehyde obtained by methylating vanillin (p. 619) may be used without further purification.
2. The mixture should become completely liquid at a temperature of about 110°. Overheating should be avoided, since this causes the product to become red instead of bright yellow.

3. Discussion

The azlactones of α-benzoylaminocinnamic acids have always been prepared by the action of hippuric acid and acetic anhydride upon aromatic aldehydes,[1] usually in the presence of sodium acetate.[2] The procedure given here is essentially that of Kropp and Decker.[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 333

- Org. Syn. Coll. Vol. 2, 489

References and Notes

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2. Erlenmeyer, Ann. **275**, 3 (1893).
3. Kropp and Decker, Ber. **42**, 1184 (1909).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

AZLACTONE OF α-BENZOYLAMINO-β-(3,4-DIMETHOXYPHENYL)-ACRYLIC ACID

5(4)-Oxazolone, 2-phenyl-4-veratral-

azlactones of α-benzoylaminocinnamic acids

alcohol (64-17-5)

Benzene (71-43-2)

acetic anhydride (108-24-7)

sodium acetate (127-09-3)

Hippuric acid (495-69-2)

Veratraldehyde (120-14-9)

vanillin (121-33-5)

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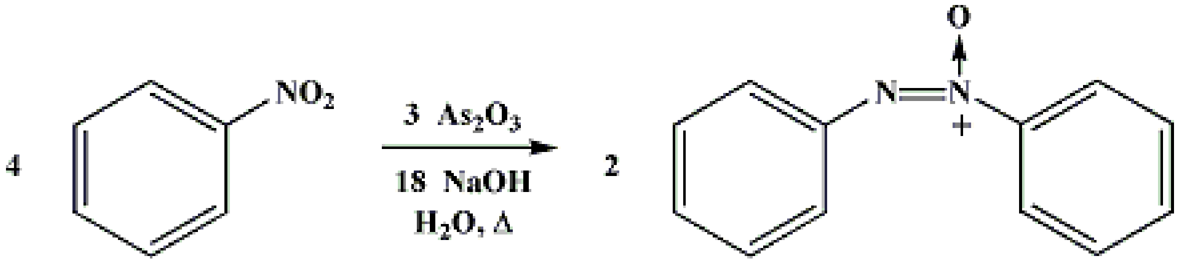
AZOXYBENZENE



Submitted by H. E. Bigelow and Albert Palmer.
Checked by Henry Gilman and H. J. Harwood.

1. Procedure

Sodium arsenite is prepared by dissolving 226 g. (1.1 moles) of powdered arsenious oxide, made into a paste with a little water, in a solution of 275 g. (6.9 moles) of sodium hydroxide dissolved in 600 cc. of water. This solution, diluted with 600 cc. of water, is poured into a 2-l. three-necked flask provided with a reflux condenser and a mechanical stirrer, and 150 g. (125 cc., 1.2 moles) of freshly distilled nitrobenzene is added (Note 1).

The mixture is refluxed on an oil bath for eight hours with constant and vigorous stirring (Note 2). After removing the oil bath, the reaction mixture is allowed to cool to about 80°, while stirring is continued, and is then transferred to a separatory funnel previously heated to about the same temperature in an oven (Note 3).

The upper layer of oil is separated (Note 4), run at once into an open vessel, and washed with water to which a little hydrochloric acid has been added. Yellow crystals form at once (Note 5), and the yield of azoxybenzene melting at 35.5–36.5° is 102 g. (85 per cent of the theoretical amount) (Note 6) and (Note 7).

2. Notes

1. The excess of sodium arsenite and the eight-hour period of heating ensure the complete utilization of nitrobenzene. This makes it unnecessary to use steam distillation or other processes for the removal of unreacted nitrobenzene. Crude nitrobenzene may be used, but a good grade is recommended. When crude nitrobenzene is used, a darker product having a slightly lower melting point is usually obtained.
2. The internal temperature should be about 104°, and the temperature of the bath should not greatly exceed 115°. A smaller flask might be used were it not for the danger of foaming which would result from accidental stopping of the stirrer. If the reaction is interrupted, the oil bath must be removed even though the stirring has been stopped; otherwise, on resumption of stirring, the

superheated material may be ejected through the condenser. With these precautions in mind it is unnecessary to have a continuous eight-hour period of heating.

Contrary to the general statement found in the literature, azoxybenzene is somewhat volatile with steam. Therefore, the presence of oil drops in the condenser at the end of the eight-hour period of refluxing is no criterion of unaltered nitrobenzene. Azoxybenzene is easily volatile with steam at 140–150°.

3. In this way the separation is effected at about 60°, and the danger of the solution's cooling to a point where sodium arsenate separates is avoided. Should the sodium arsenate separate because of undue cooling, the mixture is heated again, with stirring, until the arsenate redissolves. On dilution with sufficient water to keep the arsenate in solution, the oil settles to the bottom and does not separate readily from the liquid. Furthermore, the volume of solution is so large with such dilution that it is less easily handled.

4. The solution from which the original oil separated will yield, when diluted with an equal volume of water, a small additional quantity of azoxybenzene. This may be recovered by extraction with benzene, but the quantity of compound so obtained does not justify this extra procedure.

5. The presence of hydrochloric acid accelerates crystallization. Should crystallization be retarded, it is recommended that the oil be seeded with a crystal of azoxybenzene.

6. Recrystallization from 50 cc. of hot 95 per cent alcohol gives 72 g. of azoxybenzene. The recrystallized product melts at the same temperature, 35.5–36.5°, as the crude material but is distinctly lighter in color.

7. The following alternative procedure for preparing azoxybenzene is convenient.

In a 1-l. three-necked flask fitted with a reflux condenser and an efficient stirrer (p. 117) there are placed 60 g. of sodium hydroxide, 200 cc. of water, and 41 g. (34.2 cc., 0.33 mole) of nitrobenzene. The flask is immersed in a water bath kept at 55–60°, and 45 g. (0.23 mole) of dextrose is introduced in portions, with continuous stirring, in the course of one hour. The temperature of the bath is then raised to 100° and kept there for two hours. The hot mixture is poured into a 2-l. long-necked flask and steam-distilled to removed nitrobenzene and aniline. This requires some twenty minutes, during which time about 2 l. of distillate passes over. When the distillate is clear, the residue is poured into a beaker and cooled well in an ice bath. The azoxybenzene, which solidifies, is collected, the lumps are ground in a mortar, and the product is washed with water and dried. The yield of material melting at 34–35° is 26–27 g. (79–82 per cent of the theoretical amount). Crystallization from 15 cc. of methyl alcohol gives material melting at 35–35.5° with 90 per cent recovery. (Nicholas Opolonick, private communication. Checked by Louis F. Fieser and M. Fieser.)

3. Discussion

Azoxybenzene has been prepared by reduction of nitrobenzene with alcoholic

potassium hydroxide,[1] with sodium amalgam,[2] with hydrogen in the presence of lead oxide,[3] with methyl alcohol and sodium hydroxide,[4] with sodium methoxide and methyl alcohol,[5] with lead suboxide in alkaline suspension,[6] with dextrose in alkaline suspension (see (Note 7), above), and electrolytically;[7] by oxidation of azobenzene with chromic anhydride;[8] by treatment of β-phenylhydroxylamine with alkaline potassium permanganate,[9] with nitrobenzene,[10] with mineral acids,[11] and with mercury acetamide;[12] and by oxidation of aniline with hydrogen peroxide,[13] and with acid permanganate solution in the presence of formaldehyde.[14] The procedure described is a slight modification of one in the literature.[15]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

arsenious oxide

β-Phenylhydroxylamine

lead suboxide

alcohol (64-17-5)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

methyl alcohol (67-56-1)

aniline (62-53-3)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

formaldehyde (630-08-0)

potassium permanganate (7722-64-7)

lead oxide

sodium arsenite

sodium methoxide (124-41-4)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

Nitrobenzene (98-95-3)

hydrogen peroxide (7722-84-1)

dextrose (492-62-6)

sodium arsenate

chromic anhydride

Azoxybenzene (495-48-7)

Azobenzene (103-33-3)

mercury acetamide

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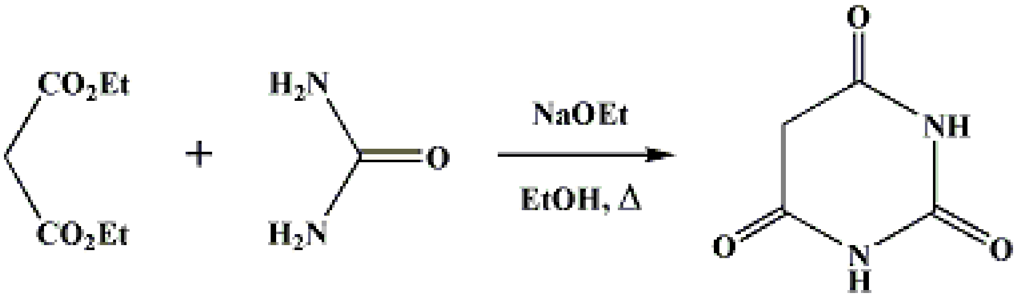
Organic Syntheses, CV 2, 60

BARBITURIC ACID



Submitted by J. B. Dickey and A. R. Gray.
Checked by Reynold C. Fuson and W. E. Ross.

1. Procedure

In a 2-l. round-bottomed flask fitted with a reflux condenser protected by a calcium chloride tube, 11.5 g. (0.5 gram atom) of finely cut sodium is dissolved in 250 cc. of absolute alcohol. To this solution is added 80 g. (0.5 mole) of ethyl malonate followed by 30 g. (0.5 mole) of dry urea dissolved in 250 cc. of hot (70°) absolute alcohol. After being well shaken the mixture is refluxed for seven hours on an oil bath heated to 110°. A white solid separates rapidly. After the reaction is completed, 500 cc. of hot (50°) water is added and then enough hydrochloric acid (sp. gr. 1.18) to make the solution acidic (about 45 cc.). The resulting clear solution is filtered and cooled in an ice bath overnight. The white product is collected on a Büchner funnel, washed with 50 cc. of cold water, and then dried in an oven at 105–110° for three to four hours. The yield of barbituric acid is 46–50 g. (72–78 per cent of the theoretical amount).

3. Discussion

Barbituric acid has been prepared by the action of phosphorus oxychloride on malonic acid and urea;[1] by treating an acetic acid solution of urea and malonic acid with acetic anhydride;[2] from ethyl malonate and urea using sodium ethoxide as a condensing agent;[3] and from ethyl malonate and the sodium derivative of urea prepared from urea and sodium in liquid ammonia.[4]

The procedure described is an adaption of that of Michael.[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 440
- Org. Syn. Coll. Vol. 3, 37

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium derivative of urea

alcohol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ammonia (7664-41-7)

acetic anhydride (108-24-7)

Phosphorus Oxychloride (21295-50-1)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

urea (57-13-6)

ethyl malonate (1071-46-1)

Malonic acid (141-82-2)

Barbituric acid (67-52-7)

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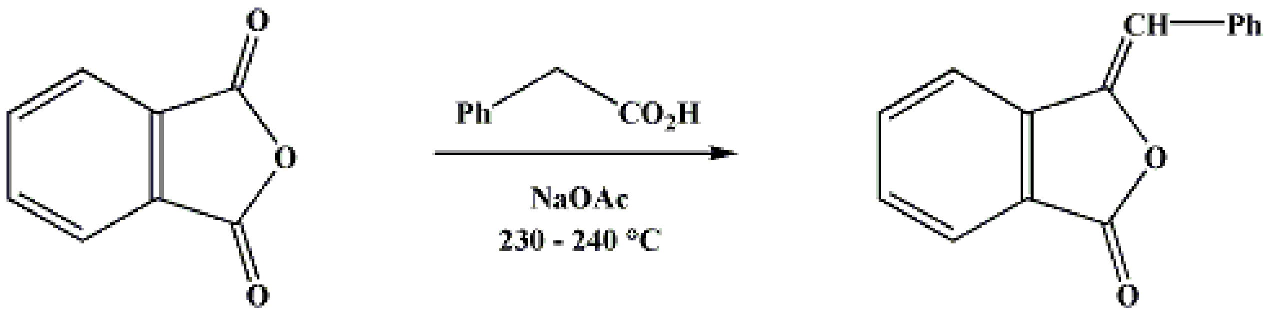
Organic Syntheses, CV 2, 61

BENZALPHTHALIDE

[Phthalide, 3-benzylidene-]



Submitted by Richard Weiss
Checked by John R. Johnson and H. R. Snyder.

1. Procedure

In a 500-cc. round-bottomed flask with a short neck (not longer than 3 cm.) are placed 100 g. (0.67 mole) of phthalic anhydride (Note 1), 110 g. (0.8 mole) of phenylacetic acid (Org. Syn. Coll. Vol. I, **1941**, 436), and 2.6 g. of freshly fused sodium acetate. A few chips of porous plate are added, and the flask is provided with a cork bearing a thermometer, which reaches almost to the bottom, and a wide, bent glass tube leading to a condenser. The tube ends just at the lower edge of the cork and does not protrude into the neck of the flask. The flask is imbedded up to the neck in a sand bath and is heated rapidly until the thermometer reaches 230°; then the temperature is raised slowly until the water produced in the reaction and some entrained organic matter pass out through the exit tube. The water is collected in a small vessel and its quantity noted from time to time in order to follow the progress of the reaction. The operation should be conducted so that the temperature rises from 230 to 240° in the course of about two hours. The reaction is maintained at 240° until the distillation of water ceases; this requires about one additional hour.

The flask now contains a brown mass covered with a film. The stopper is removed, and a test portion is taken out by means of a glass rod. The test portion is placed in a test tube or small beaker, treated with a little alcohol, and heated to boiling. When the reaction is complete, the material dissolves readily in the hot alcohol and crystallizes on cooling.

When this test has been found to be satisfactory, the flask is allowed to cool to 90–95°, and the product is dissolved in 400 cc. of boiling alcohol. The solution is filtered from insoluble matter and allowed to cool. The yellow crystals of benzalphthalide are filtered with suction and washed with 40–50 cc. of cold alcohol. The product weighs 115–116 g. and melts at 95–97°; for purification it is recrystallized from 370–380 cc. of alcohol. The yield of pure benzalphthalide, m.p. 100–101°, is 106–110 g. (71–74 per cent of the theoretical amount).

2. Notes

1. A good grade of sublimed phthalic anhydride should be used (m.p. 129–131°); if this is not available the ordinary phthalic anhydride can be purified by sublimation.

3. Discussion

Benzalphthalide has been prepared only from phthalic anhydride and phenylacetic acid in the presence of sodium acetate. The procedure given here is essentially that of Gabriel.[1]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 353

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alcohol (64-17-5)

sodium acetate (127-09-3)

phthalic anhydride (85-44-9)

Phenylacetic acid (103-82-2)

Benzalphthalide, Phthalide, 3-benzylidene- (575-61-1)

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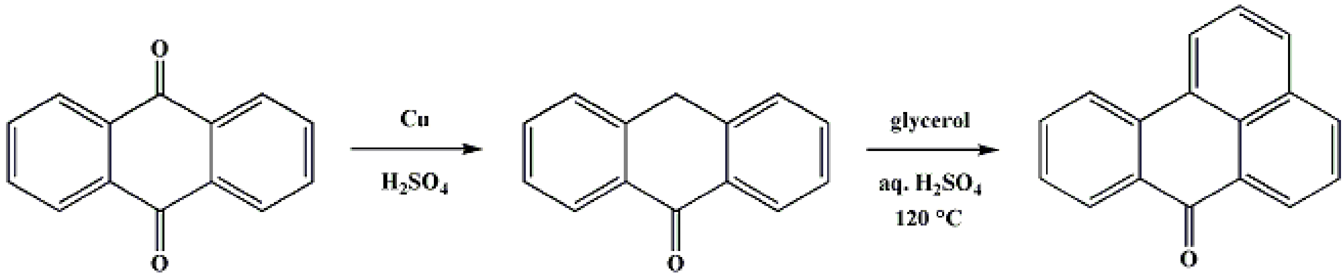
Organic Syntheses, CV 2, 62

BENZANTHRONE

[7-Benz[*de*]anthracene-7-one]



Submitted by L. C. Macleod and C. F. H. Allen.
Checked by Louis F. Fieser and Max Tishler.

1. Procedure

In a 2-l. three-necked flask fitted with a mechanical stirrer and thermometer, 72 g. (0.35 mole) of anthraquinone (p. 554) is dissolved in 1060 g. of concentrated sulfuric acid by stirring at room temperature, and 42 cc. of water is then added to the red solution (Note 1). The flask is immersed up to the neck in an oil bath, and 48 g. (0.76 gram atom) of precipitated copper (Note 2) is added during one and one-half hours, the reaction mixture being kept at a temperature of 38–42°, if necessary by external heating, until all the copper has dissolved; this requires about three hours (Note 3).

A mixture of 96 g. (1.04 moles) of glycerol (Note 4) and 96 cc. of water is slowly introduced in the course of thirty minutes and the temperature is allowed to rise to 85–90°. The mixture is carefully heated to 120° during one and one-half hours, in such a way that the temperature rises uniformly at a rate of 1° every three minutes (Note 5). A temperature of 118–120° is maintained for an additional three-hour period; then the mixture is cooled to 70–80° and carefully poured with stirring into 4 l. of boiling water (Note 6). Spattering is avoided by pouring the acid mixture down the walls of the beaker while stirring. The suspension is boiled for a few minutes and preferably allowed to stand for several hours before being filtered.

The dark green benzanthrone is filtered on a large Büchner funnel, washed well with water, and boiled for thirty to forty minutes with 1.2 l. of 1 per cent sodium hydroxide solution. The product is filtered, washed free of the dark-colored liquor, and dried at 120°; weight, 67–71 g.; benzanthrone content, about 87 per cent. The crude material is boiled with 500 cc. of technical tetrachloroethane in which all but about 8 g. of a black char easily dissolves. The solution is boiled under reflux for fifteen minutes with 25 g. of decolorizing carbon, and then filtered while hot through a Büchner funnel directly into a 2-l. round-bottomed, long-necked flask, the residue being washed with hot tetrachloroethane (100–150 cc.) until the filtrate is colorless. After the addition of 400–500 cc. of hot water the solvent is removed by steam distillation, a process which requires but little time. The benzanthrone left as a residue is filtered and dried at 120°. The yield of yellow solid, which melts at 168–170° and is pure enough for many purposes, is 56–60 g. (70–75 per cent of the theoretical amount).

In order to secure a pure product the above material is dissolved in 175 cc. of tetrachloroethane by boiling and the solution is boiled under reflux for fifteen minutes with 12 g. of decolorizing carbon, and then filtered by suction into an Erlenmeyer flask, the charcoal being washed with about 50 cc. of hot solvent. The filtrate is kept hot, treated with 750 cc. of boiling alcohol, and set aside to crystallize. The benzanthrone separates as pure yellow needles melting at 170–171°; yield, 48–52 g. (60–65 per cent of the theoretical amount) (Note 7).

2. Notes

1. The solution of the anthraquinone is slower if the water is added at the outset.
2. The precipitated copper is prepared as on p. 446, using twice the quantities given.
3. The mixture becomes yellow-brown in color and some anthranol separates, but any unreacted copper can be seen on the bottom of the flask if the stirring is stopped for a few minutes.
4. The glycerol is a commercial, anhydrous product.
5. The heating must be done very carefully, and the temperature must never be allowed to rise above 120°. At higher temperatures much material is lost by charring.
6. A more granular and easily filterable product is obtained than when cold water is used.
7. On recovery of the tetrachloroethane by steam distillation of the mother liquor, a small additional quantity of material (5 g.) is obtained, but it is quite dark and of poor quality.

3. Discussion

Benzanthrone is commonly prepared by heating a reduction product of anthraquinone with sulfuric acid and glycerol,[1 2 3 4 5] or with a derivative of glycerol,[6] or with acrolein.[7] The anthraquinone is usually reduced in sulfuric acid solution, just prior to the reaction, by means of aniline sulfate,[2] iron,[3] or copper.[4] However, the simultaneous reduction and condensation has been reported to give better yields.[8] Benzanthrone has also been prepared by dehydrogenating phenyl α-naphthyl ketone with aluminum or ferric chloride,[9] by dehydration of 1-phenylnaphthalene-2-carboxylic acid,[10] and by heating cinnamalanthrone with sodium-aluminum chloride.[11]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

aluminum or ferric chloride

7-Benz[de]anthracene-7-one

alcohol (64-17-5)

sulfuric acid (7664-93-9)

sodium hydroxide (1310-73-2)

Acrolein (107-02-8)

glycerol (56-81-5)

iron (7439-89-6)

Anthraquinone (84-65-1)

copper (7440-50-8)

decolorizing carbon (7782-42-5)

aniline sulfate

Benzanthrone (82-05-3)

tetrachloroethane (630-20-6)

anthranol (610-50-4)

phenyl α-naphthyl ketone

1-phenylnaphthalene-2-carboxylic acid

cinnamalanthrone

sodium-aluminum chloride

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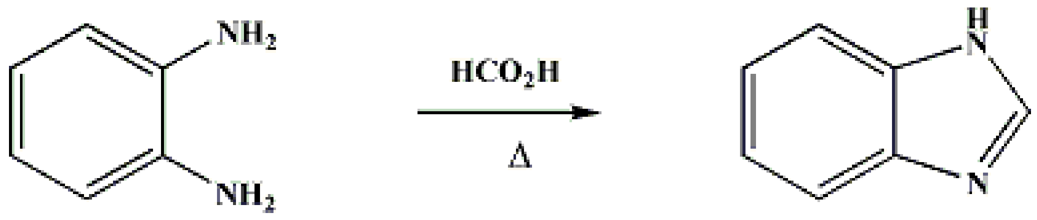
Organic Syntheses, CV 2, 65

BENZIMIDAZOLE



Submitted by E. C. Wagner and W. H. Millett.
Checked by W. W. Hartman and G. W. Sawdey.

1. Procedure

In a 500-cc. round-bottomed flask 54 g. (0.5 mole) of *o*-phenylenediamine (Note 1) is treated with 32 cc. (34.6 g.) of 90 per cent formic acid (0.75 mole) (Note 2). The mixture is heated in a water bath at 100° for two hours. After cooling, 10 per cent sodium hydroxide solution is added slowly, with thorough mixing by rotation of the flask, until the mixture is just alkaline to litmus. The crude benzimidazole is collected with suction in a 75-mm. Büchner funnel; ice-cold water is used to rinse all solid out of the reaction flask. The crude product is pressed thoroughly on the filter, washed with about 50 cc. of cold water, and then purified without previous drying (Note 3).

The benzimidazole is dissolved in 750 cc. of boiling water in a 1.5-l. beaker. The solution is digested for fifteen minutes with about 2 g. of Norite and filtered rapidly through a well-heated filter (Note 4). The filtrate is cooled to 10–15°, and the benzimidazole is filtered and washed with 50 cc. of cold water. The white (Note 5) product is dried at 100°. The melting point is 170–172°, and the yield is 49–50.5 g. (83–85 per cent of the theoretical amount) (Note 6) and (Note 7).

2. Notes

1. The *o*-phenylenediamine used was a good grade of commercial material, m.p. 99–101°. The hydrochloride can be used with or without addition of sodium formate. Directions for preparing *o*-phenylenediamine are given on p. 501.
2. The yield is not greatly affected if the amount of formic acid is decreased almost to the theoretical, but a safe excess is recommended to ensure utilization of the *o*-phenylenediamine. Formic acid of considerably less than 90 per cent concentration will form benzimidazole; good yields were obtained with 40 per cent acid.
3. The crude benzimidazole, if dried at 100°, weighs 57.5–59 g. (97–99 per cent of the theoretical amount), melts at 167–168°, and is yellow tinged. This discoloration is difficult to remove and persists after two crystallizations (Note 5).
4. The solution is almost saturated when boiling, and crystallization begins at

once on cooling. The filter must be thoroughly heated and filtration must be rapid, or crystallization will occur in the filter.

5. If the crystallized benzimidazole is discolored, the following treatment will yield a good product. The benzimidazole is dissolved in boiling water (13 cc. per gram), and a strong solution of potassium permanganate is added until the liquid becomes opaque owing to the precipitated brown oxide of manganese. To the hot mixture solid sodium bisulfite is added until clarification results. Decolorizing carbon is introduced, and the mixture is digested for fifteen minutes and filtered hot. The recovery is 90–92 per cent.

6. A small additional amount (2–2.5 g.) can be obtained by evaporation of the mother liquor to about 30 cc.

7. This is a general method of preparing benzimidazoles. Using an equivalent of acetic acid (45 g.) in place of formic acid, 2-methyl-benzimidazole, m.p. 172–174°, can be prepared in 68 per cent yield.

3. Discussion

Benzimidazole has been prepared from *o*-phenylenediamine by the action of chloroform and alcoholic potassium hydroxide[1] and of formic acid,[2] and by the reduction of *o*-nitroformanilide.[3] Less serviceable methods include the interaction of *o*-phenylenediamine and dichloromethylformamidine,[4] or diphenylformamidine,[5] or formoacetic anhydride,[6] and the thermal decarboxylation of benzimidazole-2-carboxylic acid.[7] The procedure described was developed[8] from that of Wundt.[2]

The conversion of aliphatic acids to 2-alkylbenzimidazoles, by heating with *o*-phenylenediamine, has been proposed as a general method for preparing solid derivatives for identification.[9]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 501

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Soc. **59**, 178 (1937).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

oxide of manganese

formoacetic anhydride

acetic acid (64-19-7)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

potassium permanganate (7722-64-7)

formic acid (64-18-6)

sodium bisulfite (7631-90-5)

decolorizing carbon, Norite (7782-42-5)

potassium hydroxide (1310-58-3)

sodium formate

Benzimidazole (51-17-2)

dichloromethylformamidine

diphenylformamidine

benzimidazole-2-carboxylic acid

o-Phenylenediamine (95-54-5)

2-methyl-benzimidazole (615-15-6)

o-nitroformanilide

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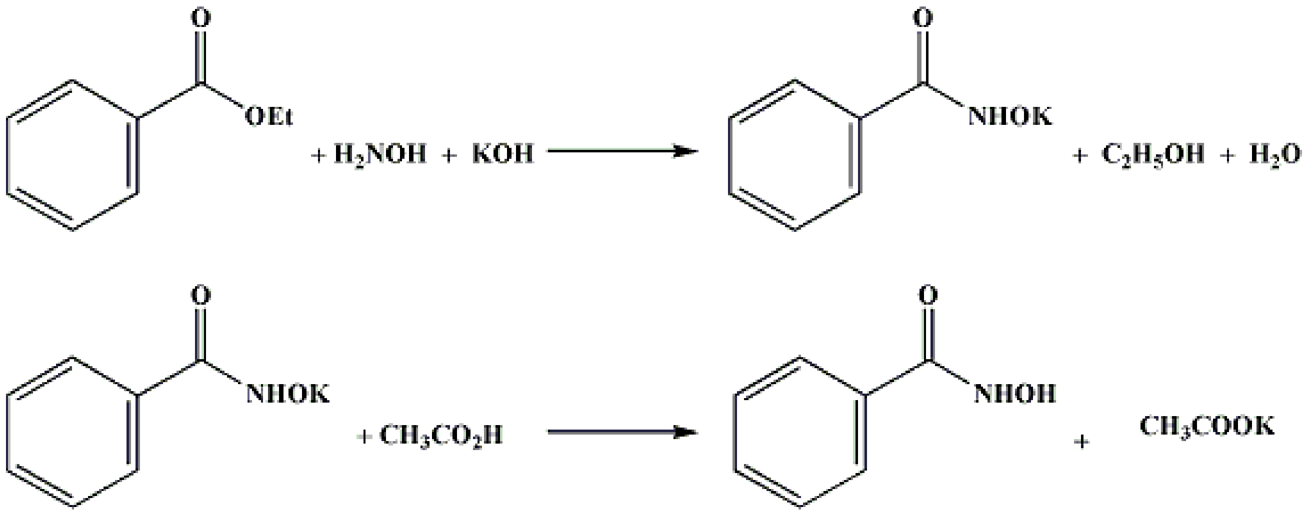
Organic Syntheses, CV 2, 67

BENZOHYDROXAMIC ACID



Submitted by C. R. Hauser and W. B. Renfrow, Jr..
Checked by C. R. Noller and M. Synerholm.

1. Procedure

(*A*) *Potassium Benzohydroxamate*.—Separate solutions of 46.7 g. (0.67 mole) of hydroxylamine hydrochloride (Org. Syn. Coll. Vol. I, **1941**, 318) in 240 cc. of methyl alcohol, and of 56.1 g. (1 mole) of c. p. potassium hydroxide in 140 cc. of methyl alcohol, are prepared at the boiling point of the solvent. Both are cooled to 30–40° (Note 1), and the one containing alkali is added with shaking to the hydroxylamine solution; any excessive rise of temperature during the addition is prevented by occasional cooling in an ice bath. After all the alkali has been added, the mixture is allowed to stand in an ice bath for five minutes to ensure complete precipitation of potassium chloride. Fifty grams (0.33 mole) of ethyl benzoate is added with thorough shaking, and the mixture filtered immediately with suction. The residue in the funnel is washed with a little methyl alcohol. The filtrate is placed in an Erlenmeyer flask and allowed to stand at room temperature. Crystals begin to form within twenty minutes to three hours, depending upon the amount of supersaturation of the solution. After forty-eight hours the crystals are filtered, washed with a little absolute ethyl alcohol, and dried in air. The yield is 33–35 g. (57–60 per cent of the theoretical amount) (Note 2), (Note 3), and (Note 4).

(*B*) *Benzohydroxamic Acid*.—A mixture of 35 g. (0.2 mole) of the potassium salt in 160 cc. of 1.25 *N* acetic acid is stirred and heated until a clear solution is obtained. The solution is allowed to cool to room temperature and finally chilled in an ice bath. Benzohydroxamic acid separates as white crystals. After filtering and drying, the product melts at 120–128° and weighs 25–26 g. (91–95 per cent of the theoretical amount). The crude material may be purified by dissolving it in 4.5 times its weight of hot ethyl acetate, filtering from a small amount of solid, and allowing the solution to cool to room temperature. The white crystals which separate are filtered, washed with a little benzene, and allowed to dry in air. The yield of recrystallized product, m.p. 125–128°, from 26 g. of crude material is 20 g. (77 per cent recovery) (Note 5).

2. Notes

1. The hydroxylamine hydrochloride solution should not be cooled too quickly or crystallization may occur before mixing. Exposure to atmospheric oxygen should be minimized after mixing the solutions, to avoid oxidation of the free hydroxylamine.
2. By concentrating the alcoholic mother liquors an additional 3–5 g. of the potassium salt may be obtained.

3. This salt can be used for the preparation of acyl derivatives; for example, when suspended in dioxane and treated with benzoyl chloride, dibenzohydroxamic acid is formed in excellent yield.
4. The potassium salts of *p*-methyl- and *p*-methoxybenzohydroxamic acid have been prepared by the submitters by this method in approximately the same yields.
5. This product has a neutralization equivalent of 137.5–138 (calculated 137.1) when determined as follows. Several drops of an alcoholic solution of 1,3,5-trinitrobenzene are added to 30–40 cc. of water in a flask, and 0.1 *N* alkali (about 0.5 cc.) is run in until a pink color is just produced. An accurately weighed sample (approximately 0.3 g.) of benzohydroxamic acid is then dissolved in the solution and titrated with standard alkali until the pink color is restored. The latter titer is used to calculate the neutralization equivalent.

3. Discussion

Benzohydroxamic acid has been prepared by the action of hydroxylamine on benzoyl chloride,[1] ethyl benzoate,[2], [3] or benzamide.[4]

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3. Tiemann and Krüger, Ber. **18**, 740 (1885); Jeanrenaud, ibid. **22**, 1272 (1889).
4. Hofmann, ibid. **22**, 2856 (1889).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

potassium salt

dibenzohydroxamic acid

potassium salts of p-methyl- and p-methoxybenzohydroxamic acid

ethyl alcohol (64-17-5)

acetic acid (64-19-7)

Benzene (71-43-2)

ethyl acetate (141-78-6)

methyl alcohol (67-56-1)

oxygen (7782-44-7)

benzoyl chloride (98-88-4)

benzamide (55-21-0)

potassium hydroxide (1310-58-3)

ethyl benzoate (93-89-0)

1,3,5-Trinitrobenzene (99-35-4)

Hydroxylamine hydrochloride (5470-11-1)

hydroxylamine (7803-49-8)

potassium chloride (7447-40-7)

Benzohydroxamic acid (495-18-1)

Potassium Benzohydroxamate (32685-16-8)

dioxane (5703-46-8)

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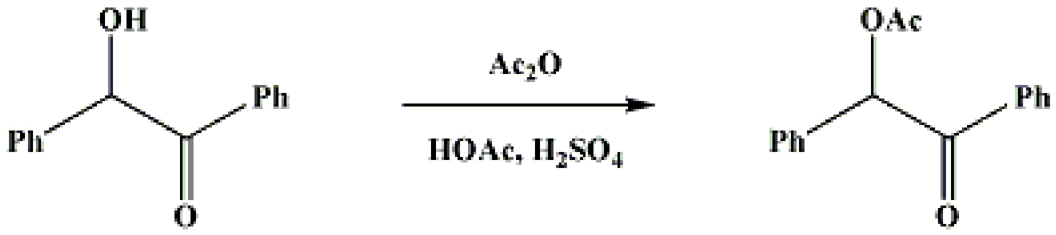
BENZOIN ACETATE



Submitted by B. B. Corson and N. A. Saliani.
Checked by Frank C. Whitmore and Marion M. Whitmore.

1. Procedure

To a mixture of 212 g. (1 mole) of benzoin (Note 1), 200 cc. of glacial acetic acid, and 200 cc. (2.1 moles) of acetic anhydride, in a 1-l. beaker provided with a mechanical stirrer, is added slowly, with stirring, 20 cc. of concentrated c.p. sulfuric acid. This requires five minutes, during which the benzoin quickly dissolves and the temperature rises to about 50°. The beaker is placed on the steam bath for twenty minutes (Note 2). The mixture is allowed to cool somewhat, transferred to a large dropping funnel, and added *slowly* to 2.5 l. of water vigorously stirred in a 4-l. (1-gal.) crock during thirty minutes (Note 3). Stirring is continued for one hour. The mixture is filtered by suction on a 30-cm. Büchner funnel, and the crystals are sucked as dry as possible and spread on filter paper. After about two hours the crystals are transferred to a 1-l. beaker and warmed to about 60° with 400 cc. of 95 per cent ethyl alcohol. The clear solution is cooled with stirring to 5° and filtered by suction. The air-dried benzoin acetate, melting at 80–82°, weighs 220–230 g. (86 to 90 per cent of the theoretical amount). Another crystallization from 400 cc. of alcohol removes the slight yellow tinge and gives a product melting at 81.5–82.5°, with a loss of about 10 g.

2. Notes

1. The benzoin (Org. Syn. Coll. Vol. I, **1941**, 94) need not be recrystallized.
2. The mixture should not be heated longer or more vigorously.
3. If the product solidifies in lumps, the lumps must be removed, crushed to a paste in a large mortar, and returned to the mixture for stirring.

3. Discussion

The only method of preparative interest is the acetylation of benzoin, either with acetyl chloride[1] or with acetic anhydride.[2] The melting point of benzoin acetate was reported by Zinin as "below 100°," by Jena and Limpricht as 75°, but by later investigators as 82–83°.

References and Notes

1. Zinin, Ann. **104**, 120 (1857); Jena and Limpricht, ibid. **155**, 92 (1870); Päpcke Ber. **21**, 1336 (1888).
2. Francis and Keane, J. Chem. Soc. **99**, 346 (1911).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethyl alcohol, alcohol (64-17-5)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

acetic anhydride (108-24-7)

acetyl chloride (75-36-5)

Benzoin (119-53-9)

Benzoin acetate (574-06-1)

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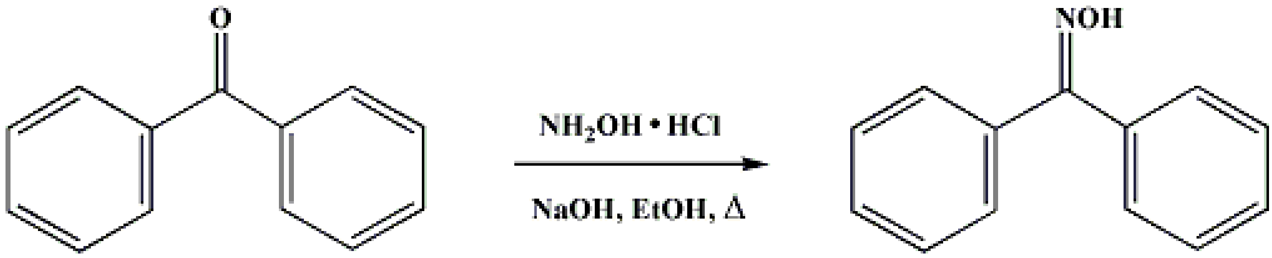
BENZOPHENONE OXIME



Submitted by Arthur Lachman
Checked by C. R. Noller

1. Procedure

A mixture of 100 g. (0.55 mole) of benzophenone (Org. Syn. Coll. Vol. I, **1941**, 95), 60 g. (0.86 mole) of hydroxylamine hydrochloride (Org. Syn. Coll. Vol. I, **1941**, 318), 200 cc. of 95 per cent ethyl alcohol, and 40 cc. of water is placed in a 2-l. round-bottomed flask. To this is added in portions, with shaking, 110 g. (2.75 moles) of powdered sodium hydroxide. If the reaction becomes too vigorous, cooling with tap water may be necessary. After all the sodium hydroxide has been added, the flask is connected to a reflux condenser, heated to boiling, and refluxed for five minutes. After cooling, the contents are poured into a solution of 300 cc. of concentrated hydrochloric acid in 2 l. of water. The precipitate is filtered with suction, thoroughly washed with water, and dried (Note 1). The yield is 106–107 g. (98–99 per cent of the theoretical amount) of a product melting at 141–142°. On crystallizing 20 g. from 80 cc. of methyl alcohol, 13 g. of crystalline material of the same melting point is obtained (Note 2).

2. Notes

1. This crude material dried overnight at about 40° is practically pure and if used at once is satisfactory for the preparation of diphenylmethane imine hydrochloride (p. 234).
2. In the presence of oxygen and traces of moisture, benzophenone oxime is gradually converted into a mixture of benzophenone and nitric acid.[1] A good method of preserving this oxime is to dry it in a vacuum desiccator, fill the desiccator with pure carbon dioxide, re-evacuate, and fill again with carbon dioxide. The preparation may then be transferred to a bottle, also filled with carbon dioxide, and sealed against access of air.

3. Discussion

Benzophenone oxime has been prepared in quantity by treating an aqueous alcoholic mixture of benzophenone and hydroxylamine hydrochloride with hydrochloric acid,[2] with sodium carbonate,[3] with alcoholic potassium hydroxide,[4] or with aqueous sodium hydroxide.[5] It has also been obtained by treating bisnitrosylbenzohydryl with alcoholic potassium hydroxide,[6] and by the oxidation of α-aminodiphenylmethane with magnesium persulfate solution.[7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 234

References and Notes

1. Hollemann, Rec. trav. chim. **13**, 429 (1894); Lachman, J. Am. Chem. Soc. **46**, 1478 (1924).
2. Beckmann, Ber. **19**, 989 (1886).
3. Janny, ibid. **15**, 2782 (1882).
4. Derick and Bornmann, J. Am. Chem. Soc. **35**, 1287 (1913).
5. Lachman, ibid. **46**, 1481 (1924); **47**, 262 (1925).
6. Behrend and Platner, Ann. **278**, 369 (1894).
7. Bamberger and Seligman, Ber. **36**, 704 (1903).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

bisnitrosylbenzohydryl

ethyl alcohol (64-17-5)

hydrochloric acid (7647-01-0)

methyl alcohol (67-56-1)

sodium hydroxide (1310-73-2)

nitric acid (7697-37-2)

sodium carbonate (497-19-8)

oxygen (7782-44-7)

carbon dioxide (124-38-9)

potassium hydroxide (1310-58-3)

Benzophenone (119-61-9)

Hydroxylamine hydrochloride (5470-11-1)

Benzophenone oxime (574-66-3)

diphenylmethane imine hydrochloride (5319-67-5)

α-aminodiphenylmethane (91-00-9)

magnesium persulfate

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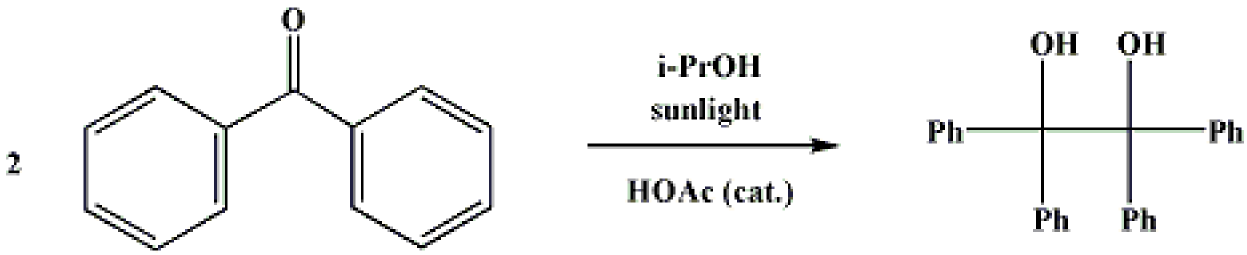
BENZOPINACOL



Submitted by W. E. Bachmann
Checked by John R. Johnson and H. R. Snyder.

1. Procedure

A mixture of 150 g. (0.82 mole) of benzophenone (Note 1), one drop of glacial acetic acid (Note 2), and 665 g. (850 cc., 11 moles) of isopropyl alcohol (Note 3) in a 1-l. round-bottomed flask is warmed to 45°. The flask is closed with a tight cork firmly wired or tied in place, and is supported in an inverted position in a tripod and exposed to direct sunlight. After three to five hours of bright sunshine crystals of benzopinacol begin to appear; after eight or ten days of exposure, depending upon the intensity of the light (Note 4), the flask is filled with crystals of benzopinacol. The solution is chilled in ice and the crystalline product is filtered with suction, washed with a small quantity of isopropyl alcohol, and allowed to dry in the air. The filtrate is reserved for subsequent reductions (see below). The yield of practically pure benzopinacol, m.p. 188–190° (Note 5), is 141–142 g. (93–94 per cent of the theoretical amount). The product is sufficiently pure for most purposes. It may be crystallized by dissolving it in 1 l. of hot benzene, filtering, and adding 400 cc. of hot ligroin (b.p. 90–100°) to the hot filtrate. After cooling in ice and filtering there is obtained 129–130 g. of purified product. The melting point is not changed by this purification.

To the isopropyl alcohol filtrate is added another 150-g. portion of benzophenone, and the solution is exposed to sunlight as in the first reduction. The benzopinacol which separates is filtered and dried. The yield in the second and subsequent runs is 142–143 g. (94–95 per cent of the calculated amount). This procedure can be repeated with the same filtrate until six or seven portions (900–1050 g.) of benzophenone have been reduced.

2. Notes

1. Although a practical grade of benzophenone can be used in this preparation, it is better to have material that has been recrystallized from alcohol. Directions for preparing benzophenone are given in Org. Syn. Coll. Vol. I, **1941**, 95.
2. No more than one drop of acetic acid should be used. The acid is added to ensure the removal of traces of alkali, which cause decomposition of the pinacol

into benzophenone and benzohydrol.

3. If isopropyl alcohol is not available, absolute ethyl alcohol can be used. With ethyl alcohol the reaction is slower and a yellow solution is obtained; nevertheless, the crystals of benzopinacol are colorless.

4. About five clear bright days are required to complete the reduction. The reaction can be interrupted at any time, the crystals filtered, and the filtrate then exposed further.

5. Since the pinacol decomposes near its melting point the latter will vary with the rate of heating. The temperatures reported here were obtained by slow heating; if the tube is placed in a bath at 150° and heated rapidly, the observed melting or decomposition point is 193–195°.

3. Discussion

Benzopinacol has been prepared by the action of phenylmagnesium bromide on benzil[1] or methyl benzilate.[1] Usually it has been obtained by reduction of benzophenone, the reducing agents being zinc and sulfuric acid[2] or acetic acid,[3] aluminum amalgam,[4] and magnesium and magnesium iodide.[5] The present method is based on a study by Cohen[6] of the photochemical reaction discovered by Ciamician and Silber.[7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 73

References and Notes

1. Acree, Ber. **37**, 2761 (1904).
2. Linnemann, Ann. **133**, 26 (1865).
3. Zagumenni, Ber. **14**, 1402 (1881).
4. Cohen, Rec. trav. chim. **38**, 75 (1919).
5. Gomberg and Bachmann, J. Am. Chem. Soc. **49**, 241 (1927).
6. Cohen, Rec. trav. chim. **39**, 243 (1920).
7. Ciamician and Silber, Ber. **33**, 2911 (1900).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Benzohydrol

ligroin

ethyl alcohol (64-17-5)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

Benzene (71-43-2)

magnesium (7439-95-4)

aluminum (7429-90-5)

Benzil (134-81-6)

Benzophenone (119-61-9)

zinc (7440-66-6)

isopropyl alcohol (67-63-0)

Phenylmagnesium bromide (100-58-3)

Benzopinacol (464-72-2)

methyl benzilate (76-89-1)

magnesium iodide

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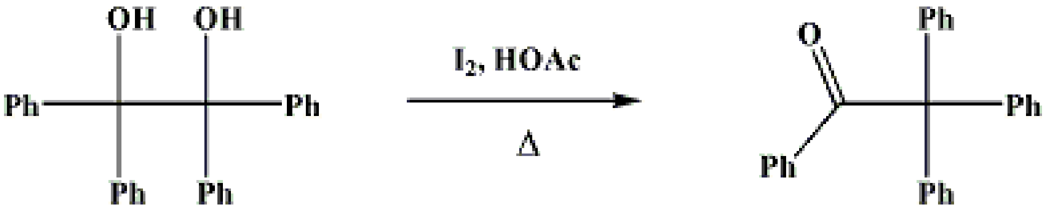
Organic Syntheses, CV 2, 73

β-BENZOPINACOLONE



Submitted by W. E. Bachmann
Checked by John R. Johnson and H. R. Snyder.

1. Procedure

In a 1-l. round-bottomed flask provided with a reflux condenser is placed a solution of 1 g. of iodine in 500 cc. of glacial acetic acid. One hundred grams (0.27 mole) of benzopinacol (Note 1) is added, and the flask is heated over a wire gauze, with shaking, until the solution boils gently. It is then refluxed for five minutes during which the solid benzopinacol disappears completely and a clear red solution is obtained (Note 2). The solution is transferred at once to a 1-l. beaker, and, upon cooling, the benzopinacolone separates in fine threads. The product is filtered with suction, washed with two or three 60-cc. portions of cold glacial acetic acid until colorless, and dried. The filtrate is reserved for subsequent preparations. The yield of practically pure benzopinacolone melting at 178–179° is 90–91 g. (95–96 per cent of the theoretical amount). If a purer product is desired the material may be dissolved in 450 cc. of hot benzene, filtered, and treated with 250 cc. of hot ligroin (b.p. 90–100°). After cooling in ice the benzopinacolone is filtered and dried. The purified product weighs 82–83 g. and melts at 179–180°.

To the acetic acid filtrate is added another 100-g. portion of benzopinacol and the reaction is carried out in the same way. The yield of benzopinacolone in the second and subsequent runs is 94–94.5 g. (98–99 per cent of the theoretical amount). This procedure can be repeated in the same filtrate until 500 g. of the pinacol has been rearranged.

2. Notes

1. The benzopinacol obtained by photochemical reduction of benzophenone (p. 71) may be used directly without purification.
2. Frequently the benzopinacolone begins to crystallize in the boiling solution during the last minute of heating.

3. Discussion

β-Benzopinacolone has been prepared by rearrangement of benzopinacol. The

rearrangement has been carried out by heating benzopinacol with benzoyl chloride,[1] with acetyl chloride,[2] with acetic acid at 180–200°,[2] with dilute sulfuric acid at 180–200°,[2] and with concentrated hydrochloric acid at 200°.[2] The present procedure is based on the method described by Gomberg and Bachmann.[3]

This preparation is referenced from:

- Org. Syn. 76, 294

References and Notes

1. Linnemann, Ann. **133**, 28 (1865).
2. Thörner and Zincke, Ber. **10**, 1475 (1877).
3. Gomberg and Bachmann, J. Am. Chem. Soc. **49**, 246 (1927).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ligroin

β-Benzopinacolone

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

acetyl chloride (75-36-5)

iodine (7553-56-2)

benzoyl chloride (98-88-4)

Benzophenone (119-61-9)

pinacol (76-09-5)

Benzopinacol (464-72-2)

benzopinacolone (466-37-5)

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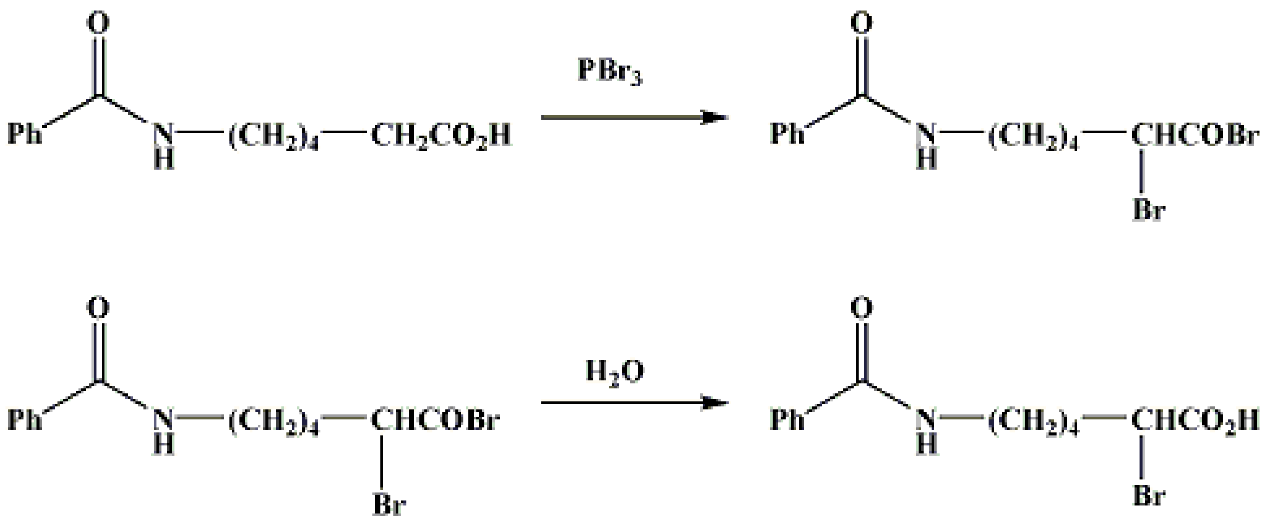
ε-BENZOYLAMINO-α-BROMOCAPROIC ACID

[Caproic acid, ε-benzamido-α-bromo-]



Submitted by J. C. Eck and C. S. Marvel.
Checked by C. R. Noller and William Munich.

1. Procedure

An intimate mixture of 150 g. (0.64 mole) of dry ε-benzoylaminocaproic acid (p. 76) and 26.4 g. (0.85 gram atom) of dry red phosphorus is placed in a 1-l. three-necked flask provided with a separatory funnel, an air-cooled condenser connected through a calcium chloride tube to a water trap, and a mechanical stirrer (Note 1). The reaction flask is surrounded by an ice-salt mixture, the stirrer started, and 408 g. (131 cc., 2.55 moles) of dry bromine added dropwise from the separatory funnel. When all the bromine has been added the cooling bath is removed. The mixture is warmed slowly at first and finally heated on a steam bath, with stirring, until the bromine vapors have practically disappeared. The hot mixture is poured slowly into 400 cc. of water in a 1-l. beaker with hand stirring. The viscous acid bromide reacts with the water with the evolution of heat, and the solid acid is formed. The lumps are pulverized, the mixture is replaced in the original reaction flask, and the whole is treated with a slow stream of sulfur dioxide to remove excess bromine. The solid product is filtered on a Büchner funnel, washed with three 50-cc. portions of water, and air-dried. The crude material is dissolved in 250 cc. of hot 95 per cent alcohol, filtered, and poured with stirring into 1 l. of cold water (Note 2). After filtering and air-drying, 130–180 g. (64–89 per cent of the calculated amount) of acid melting at 162–165° is obtained.

2. Notes

1. The stirrer must be very powerful because the mixture becomes lumpy and finally very viscous. If the material agglomerates so badly that the stirrer will not operate, hand stirring may be necessary temporarily until the mass liquefies

sufficiently to renew mechanical stirring. The checkers tried one run in which carbon tetrachloride was added to facilitate stirring, but, though it accomplished this purpose, the yield was only about half of that obtained without a liquid medium.

2. The crude product may be recrystallized from ethyl alcohol, but the melting point is the same as that of the product obtained by precipitation with water, and the yield is considerably less.

3. Discussion

The above procedure[1] is essentially that of Braun.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 374

References and Notes

1. Eck and Marvel, J. Biol. Chem. **106**, 387 (1934).
2. Braun, Ber. **42**, 839 (1909).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

red phosphorus

ethyl alcohol, alcohol (64-17-5)

bromine (7726-95-6)

sulfur dioxide (7446-09-5)

carbon tetrachloride (56-23-5)

ε-BENZOYLAMINO-α-BROMOCAPROIC ACID, Caproic acid, ε-benzamido-α-bromo- (1700-05-6)

ε-Benzoylaminocaproic acid (956-09-2)

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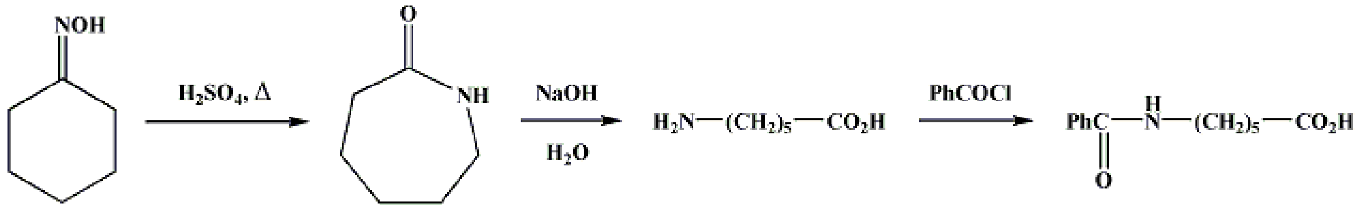
ε-BENZOYLAMINOCAPROIC ACID

[Caproic acid, ε-benzamido-]



Submitted by J. C. Eck and C. S. Marvel.
Checked by C. R. Noller and William Munich.

1. Procedure

(*A*) *Cyclohexanone Oxime*.—In a 5-l. flask, fitted with an efficient mechanical stirrer and an 8-mm. glass inlet tube reaching to within 5 cm. of the bottom of the flask, are placed 1.5 kg. of cracked ice and a solution of 182 g. (2.5 moles) of technical sodium nitrite (95 per cent) in 500 cc. of water (Note 1). The flask is placed in an ice-salt mixture, and a cold (−8°) solution of sodium bisulfite, prepared by saturating with sulfur dioxide a solution of 143 g. (1.35 moles) of anhydrous sodium carbonate in 600 cc. of water, is added. While the temperature is kept below 0°, a moderate stream of sulfur dioxide is passed into the mixture until it is acid to Congo red and then just enough longer to remove the dark color which appears shortly before the solution becomes acid.

To this solution are added 196 g. (2 moles) of technical cyclohexanone and 500 cc. of 85 per cent ethyl alcohol; the cooling bath is replaced by a steam bath, the stirrer started, and the mixture heated to 75°. The flask is then packed in mineral wool or other insulating material and allowed to cool slowly, with effective stirring, for forty-eight hours. The solution at room temperature is exactly neutralized to litmus with a 50 per cent solution of sodium hydroxide, with cooling and stirring. About 330 g. of sodium hydroxide solution is required.

The oily layer is separated and the aqueous solution extracted with two 200-cc. portions of ether. The oil and ether extracts are combined, the ether is removed, and the residue distilled from a 500-cc. modified Claisen flask having a 25-cm. fractionating side arm. The fraction boiling at 95–100° at 5 mm. weighs 170–190 g. and melts at 78–80°. This product is transferred to a large mortar, allowed to cool, and ground with 120 cc. of petroleum ether (b.p. 35–60°). After filtering with suction, and allowing the solvent to evaporate from the crystals, there is obtained 133–147 g. of cyclohexanone oxime (59–65 per cent of the calculated amount) melting at 86–88° (Note 2).

(*B*) *ε-Benzoylaminocaproic Acid*.—The rearrangement of 100 g. (0.88 mole) of pure cyclohexanone oxime (Note 3) is carried out in the following way. In a 1-l. beaker are placed a 10-g. portion of the oxime and 20 cc. of 85 per cent sulfuric acid (sp. gr. 1.783) (Note 4). The beaker is heated with a low flame and the contents are mixed with a rotary motion until bubbles first appear. The beaker is then removed from the flame immediately, and the violent reaction, which lasts a few seconds, is allowed to subside. The acid solution of ε-caprolactam is transferred to a 5-l. round-bottomed flask, and another 10-g. portion of the oxime is placed in the beaker and rearranged with sulfuric acid as before. The combined acid solution from the ten operations is diluted with 2.5 l. of water and boiled gently for one and one-half hours with 5 g. of decolorizing carbon. The solution is filtered and exactly neutralized to litmus with 50 per cent sodium hydroxide solution. About 510 g. of sodium hydroxide solution is usually required. The neutral solution is boiled for one-half hour with 5 g. of decolorizing carbon and filtered.

The filtrate is placed in a 5-l. flask fitted with a mechanical stirrer, cooled in an ice bath to 10°, and a solution of 55 g. (1.37 moles) of sodium hydroxide in 55 cc. of water added. The temperature being kept at 10°, 94 g. (0.67 mole) of benzoyl chloride is added dropwise from a separatory funnel over a period of thirty-five to forty minutes, with rapid stirring. The mixture is stirred for an hour longer, filtered, and placed in a 4-l. beaker. The cold filtrate is slowly acidified to Congo red by adding 10 per cent hydrochloric acid, with hand stirring (about 450 cc. of acid is required). The solid (Note 5) is filtered with suction, washed with water, and spread out to dry. When dry, the product is washed with two 100-cc. portions of petroleum ether (35–60°) to remove the admixed benzoic acid. The adhering petroleum ether is allowed to evaporate from the crystals, and the final drying is carried out in a vacuum desiccator over sulfuric acid. The yield of purified product, m.p. 77–80°, is 135–150 g. (65–72 per cent of the calculated amount, based on cyclohexanone oxime).

2. Notes

1. The sodium nitrite may be added directly to 2 kg. of ice, but, if this is done, the nitrite and ice should be mixed thoroughly outside the flask to prevent caking of the ice.
2. Cyclohexanone oxime can be prepared with better yields from the ketone, hydroxylamine hydrochloride (Org. Syn. Coll. Vol. I, **1941**, 318), and sodium carbonate according to the procedure given on p. 314. The preparation using hydroxylamine hydrochloride, however, is more expensive than that given above.
3. The rearrangement of the oxime is carried out in 10-g. portions and in a large open beaker because of the violence of the reaction. It is essential to use oxime of good quality or a product of inferior grade results.

4. Acid of this concentration may be prepared by mixing five volumes of concentrated sulfuric acid with one volume of water.
5. If the acid separates as an oil, it should be allowed to stand with occasional stirring until it solidifies.

3. Discussion

ε-Benzoylaminocaproic acid has been prepared by treatment of benzoylpiperidine with phosphorus pentachloride to form ε-benzoylaminoamyl chloride, conversion to the nitrile, and hydroylsis to the acid,[1] and by the procedure described above.[2]

Directions for the rearrangement of cyclohexanone oxime and isolation of ε-caprolactam and ε-aminocaproic acid are to be found on pp. 371 and 28.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 74
- Org. Syn. Coll. Vol. 2, 371
- Org. Syn. Coll. Vol. 6, 90
- Org. Syn. Coll. Vol. 8, 568

References and Notes

1. Braun, Ber. **42**, 839 (1909).
2. Eck and Marvel, J. Biol. Chem. **106**, 387 (1934).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

Congo red

ε-benzoylaminoamyl chloride

ethyl alcohol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium hydroxide (1310-73-2)

phosphorus pentachloride (10026-13-8)

Cyclohexanone (108-94-1)

sodium carbonate (497-19-8)

sulfur dioxide (7446-09-5)

sodium nitrite (7632-00-0)

Benzoic acid (65-85-0)

sodium bisulfite (7631-90-5)

decolorizing carbon (7782-42-5)

benzoyl chloride (98-88-4)

Benzoylpiperidine (776-75-0)

Hydroxylamine hydrochloride (5470-11-1)

ε-AMINOCAPROIC ACID (60-32-2)

ε-caprolactam (105-60-2)

Cyclohexanone oxime (100-64-1)

ε-Benzoylaminocaproic acid, Caproic acid, ε-benzamido- (956-09-2)

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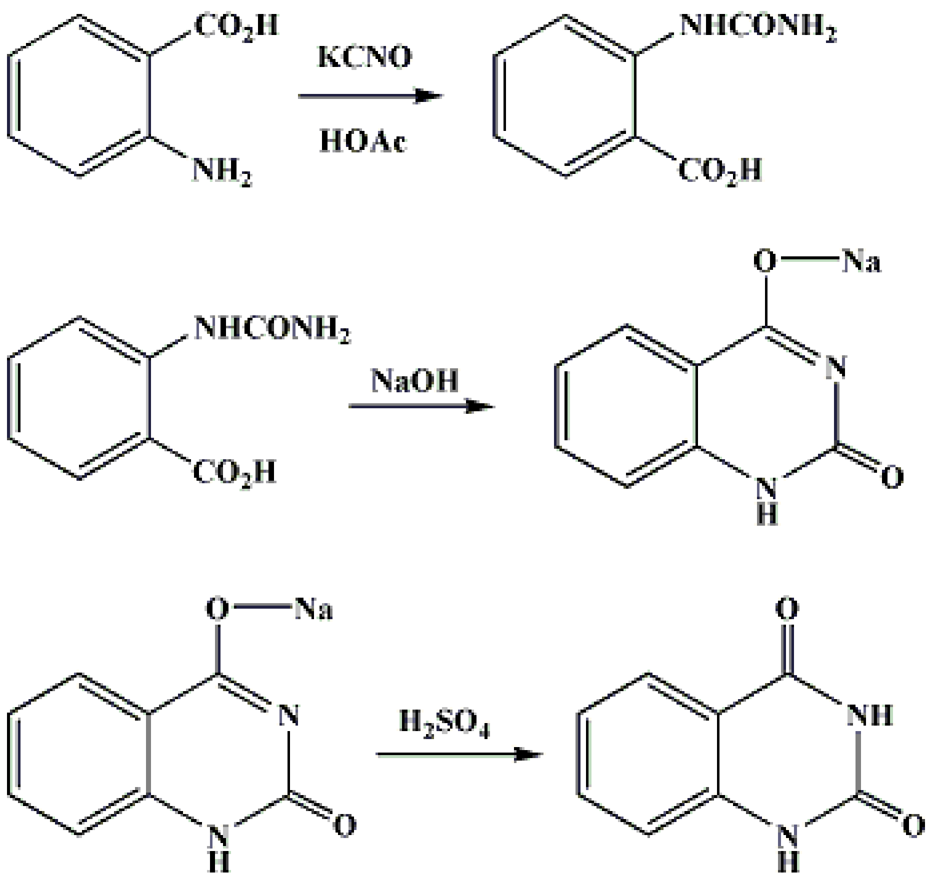
BENZOYLENE UREA

[2,4(1,3)-Quinazolinedione]



Submitted by N. A. Lange and F. E. Sheibley.
Checked by W. W. Hartman and J. B. Dickey.

1. Procedure

In a 3-l. beaker a mixture of 20 g. (0.146 mole) of anthranilic acid, 700 cc. of warm water (35°), and 11 cc. (11.6 g., 0.19 mole) of glacial acetic acid is stirred mechanically and allowed to cool to room temperature. A freshly prepared solution of 15 g. (0.185 mole) of potassium cyanate (Note 1) in 50 cc. of water is then added dropwise with stirring over a period of fifteen to twenty minutes (Note 2). The resulting pasty mixture is stirred for twenty minutes, and then 200 g. (5 moles) of flaked sodium hydroxide (Note 3) is added slowly in small portions. During this addition the reaction mixture is kept below 40° by cooling in a cold-water bath. A clear solution is obtained momentarily, but in a short time a fine granular precipitate of the hydrated monosodium salt of benzoylene urea precipitates. After the mixture has cooled overnight in an ice box, the precipitated sodium salt is collected on a Büchner funnel, using a hardened filter paper (Note 4). The colorless salt is dissolved in 1 l. of hot water (90–95°), and the solution is filtered and heated to boiling in a 3-l. beaker. The benzoylene urea is precipitated by adding dilute sulfuric acid (1:1) with vigorous

stirring until the liquor is acid to litmus. The product separates as a hydrate which forms small, lustrous, colorless needles. The material is collected on a Büchner funnel, washed with 200 cc. of water, and dried in an oven at 100°. The yield is 19.5–20.5 g. (82–87 per cent of the theoretical amount) (Note 5).

2. Notes

1. The yield is highly dependent upon the quality of the potassium cyanate employed, and some samples were found worthless for the purpose. The yields given were realized using Eastman's regular grade of potassium cyanate.
2. If the addition is too rapid the odor of isocyanic acid (remindful of that of sulfur dioxide) becomes strong and the yield is diminished.
3. The commercial grade of flaked sodium hydroxide dissolves readily and is convenient to handle. Any silica present is not objectionable since it is removed by filtering the redissolved sodium salt before precipitating the product with acid.
4. Schleicher and Schüll's hardened filters (No. 575, 9 cm.) are satisfactory.
5. The melting point of benzoylene urea is above 350°.

3. Discussion

Benzoylene urea has been prepared by passing cyanogen into a solution of anthranilic acid in alcohol and hydrolyzing the resulting 2-ethoxy-4-ketodihydroquinazoline;[1] by fusing anthranilic acid with urea;[2], [3] and by the action of aqueous cyanic acid on anthranilic acid.[2], [3], [4], [5] The procedure described is adapted from that of Bogert and Scatchard[5] with several modifications.

References and Notes

1. Griess, Ber. **2**, 415 (1869).
2. Griess, J. prakt. Chem. (2) **5**, 371 (1872).
3. Bogert and Scatchard, J. Am. Chem. Soc. **41**, 2056 (1919).
4. Gabriel and Colman, Ber. **38**, 3561 (1905); Scott and Cohen, J. Chem. Soc. **119**, 664 (1921).
5. Bogert and Scatchard, J. Am. Chem. Soc. **38**, 1611 (1916).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

2,4(1,3)-Quinazolinedione

silica

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

sodium hydroxide (1310-73-2)

sulfur dioxide (7446-09-5)

cyanogen

urea (57-13-6)

Anthranilic Acid (118-92-3)

potassium cyanate (590-28-3)

Benzoylene urea (86-96-4)

isocyanic acid (75-13-8)

2-ethoxy-4-ketodihydroquinazoline

cyanic acid (420-05-3)

monosodium salt of benzoylene urea

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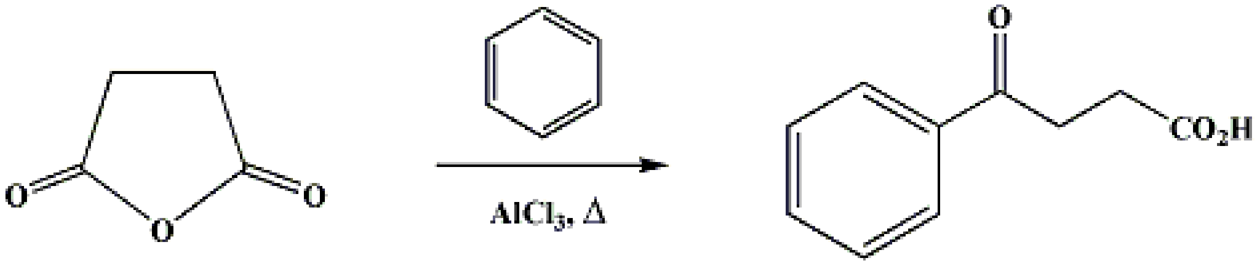
Organic Syntheses, CV 2, 81

β-BENZOYLPROPIONIC ACID

[Propionic acid, β-benzoyl-]



Submitted by L. F. Somerville and C. F. H. Allen.
Checked by Reynold C. Fuson and Don B. Forman.

1. Procedure

In a 2-l. three-necked, round-bottomed flask fitted with a mechanical stirrer and two reflux condensers are placed 68 g. (0.68 mole) of succinic anhydride (p. 560) and 350 g. (4.5 moles) of dry, thiophene-free benzene (Note 1). The stirrer is started, and 200 g. (1.5 moles) of powdered, anhydrous aluminum chloride is added all at once. Hydrogen chloride is evolved and the mixture becomes hot (Note 2). It is heated in an oil bath and refluxed, with continued stirring, for half an hour (Note 3). The flask is then surrounded by cold water, and 300 cc. of water is slowly added from a dropping funnel inserted in the top of one of the condensers (Note 4). The excess benzene is removed by steam distillation, and the hot solution is at once poured into a 2-l. beaker. After the mixture is cold the liquid is decanted from the precipitated solid and acidified with concentrated hydrochloric acid (about 20 cc. is required); 5 to 15 g. of benzoylpropionic acid separates and is filtered (Note 5). The residual suspension in the beaker is boiled for five hours with 1.5 l. of water containing 360 g. of commercial soda ash; the resulting solution is filtered with suction, the filter cake washed with hot water, and the filtrate acidified with concentrated hydrochloric acid; about 300 cc. is required (Note 6). The precipitated benzoylpropionic acid is filtered and washed with hot water (Note 7). After drying for a day it weighs 95–100 g. (77–82 per cent of the theoretical amount) and melts at 111–113° (Note 8).

If the first, colored, precipitate (weight, 5–15 g.) is separated as suggested it is unnecessary to purify the remainder. The acid may be further purified, if desired, by dissolving in dilute sodium hydroxide and precipitating with concentrated hydrochloric acid, the first portion of the precipitate being collected separately. The pure product melts at 116° (Note 9).

2. Notes

1. Commercial benzene is shaken with concentrated sulfuric acid, then with water and dried, first with anhydrous calcium chloride and then over metallic sodium.
2. If the reaction does not start at once it is initiated by gentle heating.
3. The yield is not increased by longer heating.
4. The procedure from this point on can be simplified and improved as follows. After the addition of water to the aluminum chloride complex, 100 cc. of concentrated hydrochloric acid (sp. gr. 1.18) is added and the benzene is removed by steam distillation. The hot mixture is transferred to a 1-l. beaker, and the β-benzoylpropionic acid separates as a colorless oil which soon solidifies. After cooling to 0°, it is collected, washed with a cold mixture of 50 cc. of concentrated hydrochloric acid and 150 cc. of water, and then with 200 cc. of cold water. The crude acid is dissolved in a solution of 75 g. of anhydrous sodium carbonate in 500 cc. of water by boiling for fifteen minutes. The solution is filtered by suction and the small amount of aluminum hydroxide washed twice with 50-cc. portions of hot water. Four grams of charcoal is added to the hot filtrate; the solution is stirred for three to four minutes and then filtered with suction. The clear, colorless filtrate is transferred to a 2-l. beaker, cooled to 50–60°, and carefully acidified with 130 cc. of concentrated hydrochloric acid. After cooling to 0° in an ice-salt bath the acid is filtered, washed well with water, dried overnight at room temperature, and finally dried to constant weight at 40–50°. The yield is 110–115 g. (92–95 per cent of the theoretical amount). It melts at 114–115° and needs no further purification. (E. L. Martin and Louis F. Fieser, private communication.)
5. The amount of acid isolated at this point varies according to the length of time the solution is allowed to stand before acidification.
6. The first portion of the precipitated acid is usually colored; it is best to filter it separately. The remaining acid will then be colorless and very nearly pure (m.p. 114–115°).
7. By evaporating the filtrate to a small volume and extracting with ether, a further 3 g. of acid may be obtained.
8. The acid tenaciously retains traces of water to which apparently higher yields may be due. The weights given were obtained on material that had been dried overnight in a vacuum desiccator.
9. γ-Benzoylbutyric acid may also be prepared by this method. Glutaric anhydride (0.68 mole) dissolved in part of 350 g. of benzene is added to the rest of the benzene, in which the aluminum chloride is suspended; the temperature is kept below 15° for one and one-half hours, including the time of addition; an 80–85 per cent yield of γ-benzoylbutyric acid melting at 125–126° is obtained.

3. Discussion

β-Benzoylpropionic acid can be prepared from succinic anhydride, benzene, and aluminum chloride,[1] or from succinic anhydride and phenyl-magnesium bromide.[2] It has also been obtained by prolonged heating of cinnamic aldehyde, hydrocyanic acid,

hydrochloric acid, and water;[3] by reduction of benzoylacrylic acid;[4] by the ketonic hydrolysis of benzoylsuccinic ester;[5] by heating phenylbromoparaconic, phenylbromoisoparaconic, or γ-phenyl-β,γ-dibromobutyric acids with water;[6] by the hydrolysis of phenacylbenzoylacetic ester;[7] and by heating phenacylmalonic acid.[8]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 499
- Org. Syn. Coll. Vol. 5, 80

References and Notes

1. Burcker, Ann. chim. phys. (5) **26**, 435 (1882); Kohler and Engelbrecht, J. Am. Chem. Soc. **41**, 768 (1919).
2. Komppa and Rohrmann, Ann. **509**, 263 (1934).
3. Matsmoto, Ber. **8**, 1145 (1875); Peine, ibid. **17**, 2114 (1884).
4. von Pechmann, ibid. **15**, 889 (1882).
5. Perkin, J. Chem. Soc. **47**, 276 (1885).
6. Fittig and Leoni, Ann. **256**, 81 (1890); Fittig, Obermüller, and Schiffer, ibid. **268**, 74 (1892).
7. Kapf and Paal, Ber. **21**, 1487 (1888).
8. Kues and Paal, ibid. **18**, 3325 (1885).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

soda ash

benzoylsuccinic ester

phenylbromoparaconic, phenylbromoisoparaconic, or γ-phenyl-β,γ-dibromobutyric acids

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrogen chloride, hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether (60-29-7)

sodium hydroxide (1310-73-2)

hydrocyanic acid (74-90-8)

sodium carbonate (497-19-8)

aluminum chloride (3495-54-3)

metallic sodium (13966-32-0)

phenyl-magnesium bromide (100-58-3)

cinnamic aldehyde

Thiophene (110-02-1)

β-Benzoylpropionic acid, Propionic acid, β-benzoyl-, benzoylpropionic acid (2051-95-8)

Succinic anhydride (108-30-5)

aluminum hydroxide

γ-Benzoylbutyric acid (1501-05-9)

Glutaric anhydride (108-55-4)

benzoylacrylic acid (583-06-2)

phenacylmalonic acid

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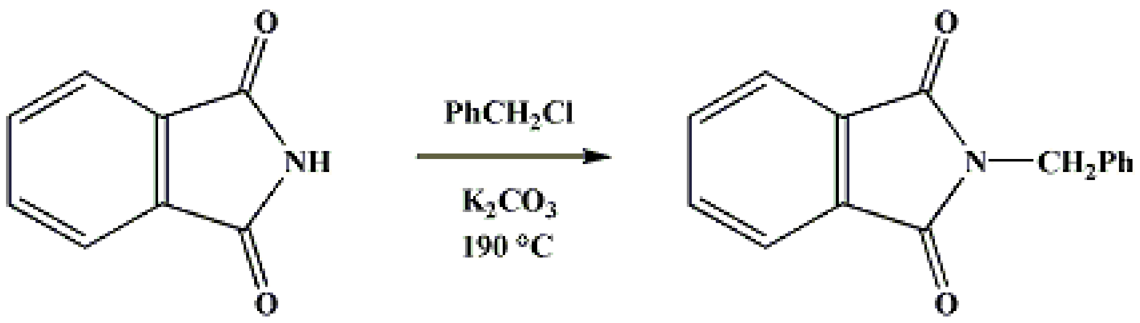
BENZYL PHTHALIMIDE

[Phthalimide, N-benzyl-]



Submitted by Richard H. F. Manske
Checked by Henry Gilman and H. J. Harwood.

1. Procedure

An intimate mixture of 166 g. (1.2 moles) of anhydrous potassium carbonate (Note 1) and 294 g. (2 moles) of phthalimide is treated with 506 g. (4 moles) of benzyl chloride (Note 2), and the mixture is heated in an oil bath at 190° under a reflux condenser for three hours (Note 3). While the mixture is still hot, the excess benzyl chloride is removed by steam distillation (Note 4). Near the end of this operation the benzyl phthalimide crystallizes. It is advisable to cool the mixture rapidly with very vigorous agitation so that the material is in as fine a state of division as possible. The solid is filtered on a large Büchner funnel, thoroughly washed with water, and drained as completely as possible by suction. It is then washed once with 400 cc. of 60 per cent alcohol and drained again. The yield of this product, melting at 100–110°, is 340–375 g. (72–79 per cent of the theoretical amount). It is conveniently purified by crystallizing from glacial acetic acid. The recovery in the crystallization is about 80 per cent, and the pure product melts at 116° (corr.) (Note 5).

2. Notes

1. The potassium carbonate is conveniently dehydrated by heating in a large basin over a moderate flame. It must be ground to a very fine powder and mixed with the phthalimide in a mortar.
2. A good grade of benzyl chloride having a boiling range of 3° was used.
3. There is no apparent advantage in using mechanical stirring.
4. The excess benzyl chloride is recovered from the distillate and dried with calcium chloride. About 200–300 g. is recovered.
5. Using the same general procedure trimethylene bromide furnishes γ-bromopropylphthalimide and, as a by-product, α,γ-diphthalimidopropane, while β-phenylethyl bromide gives β-phenylethylphthalimide.

3. Discussion

Benzyl phthalimide can be prepared from potassium phthalimide and benzyl chloride;[1] from phthalimide, potassium carbonate, and benzyl chloride;[2] and from phthalimide, sodium ethoxide, and benzyl chloride.[3] The two latter procedures avoid the preparation of potassium phthalimide. Phthalic anhydride, benzylamine, and glacial acetic acid on refluxing also furnish benzyl phthalimide.[4] The procedure described has been published.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 256

References and Notes

1. Gabriel, Ber. **20**, 2227 (1887).
2. Ing and Manske, J. Chem. Soc. **1926**, 2348.
3. Weisz and Lányi, Magyar Chem. Folyóirat **39**, 153 (1933) [C. A. **28**, 5815 (1934)].
4. Vanags, Acta Univ. Latviensis, Kim. Fakultat. Ser. 4, No. 8, 405 (1939) [C. A. **34**, 1983 (1940)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

calcium chloride (10043-52-4)

potassium carbonate (584-08-7)

acetic acid (64-19-7)

Trimethylene bromide (109-64-8)

phthalic anhydride (85-44-9)

sodium ethoxide (141-52-6)

benzyl chloride (100-44-7)

Potassium Phthalimide (1074-82-4)

Phthalimide (85-41-6)

BENZYL PHTHALIMIDE

Phthalimide, N-benzyl- (2142-01-0)

γ-bromopropylphthalimide

β-phenylethyl bromide (103-63-9)

β-phenylethylphthalimide

benzylamine (100-46-9)

α,γ-diphthalimidopropane

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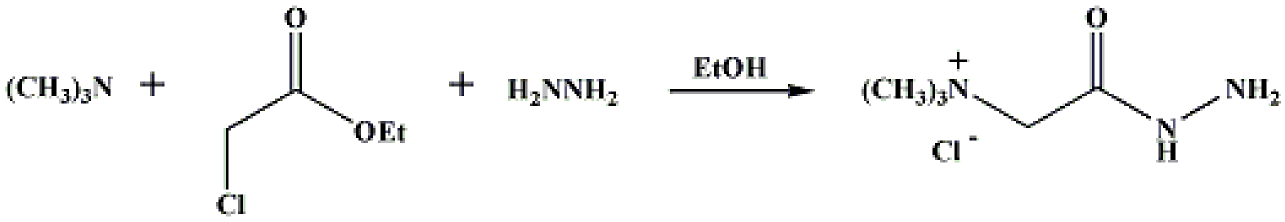
BETAINE HYDRAZIDE HYDROCHLORIDE

[Girard's Reagent]

[Ammonium compounds, substituted. (Carboxymethyl)trimethyl— chloride, hydrazide]



Submitted by André Girard
Checked by Louis F. Fieser and Robert P. Jacobsen.

1. Procedure

In a 1-l. three-necked flask fitted with a stirrer, a thermometer, and an ice-cooled spiral condenser (Org. Syn. Coll. Vol. I, **1941**, 529) is placed a solution of 98 g. (84.5 cc., 0.8 mole) of ethyl chloroacetate (Note 2, p. 263) in 200 cc. of absolute alcohol. The solution is cooled to 0° by stirring in a salt-ice bath; and, after the stirrer is stopped, 74 cc. (49 g., 0.83 mole) of trimethylamine, measured after precooling to −5°, is added all at once. The exothermic reaction is controlled sufficiently by cooling so that the temperature of the mixture rises to 60° in the course of about one hour (Note 1). When there is no longer any heat effect, the mixture is allowed to stand at room temperature for twenty hours (without replenishment of the condenser ice).

The condenser is removed, the thermometer replaced by a dropping funnel, and 40 g. (0.8 mole) of 100 per cent hydrazine hydrate (Note 2) added, with stirring, in the course of ten to fifteen minutes. After being stirred for forty-five minutes longer, the solution is cooled slightly, and, unless crystallization of the reaction product starts spontaneously, the walls of the vessel are scratched with a glass rod to induce crystallization (Note 3). The product separates in fine, colorless needles. After being thoroughly cooled in an ice bath, the highly hygroscopic salt is collected quickly on a Büchner funnel, washed with 150 cc. of cold absolute alcohol, and pressed dry under a rubber dam. Dried in a vacuum desiccator over concentrated sulfuric acid, this material weighs 100–108 g. A further crop can be obtained after distilling 200–300 cc. of solvent from the mother liquor and washings at the pressure of the water pump. The total yield of salt, m. p. 175–180°, with decomposition, is 112–120 g. (83.5–89.5 per cent of the theoretical amount) (Note 4), (Note 5), and (Note 6).

2. Notes

1. Without external cooling the temperature rises to about 75° and it is difficult to avoid some loss of amine.
2. Hydrazine hydrate may be prepared by the ammonolysis of hydrazine sulfate (Org. Syn. Coll. Vol. I, **1941**, 309) as described in Org. Syn. **21**, 70.
The 42 per cent hydrazine hydrate solution supplied by the Eastman Kodak Company is

too dilute for use as such, but may be concentrated by distillation with xylene.[1] A mixture of 144 cc. (150 g.) of the 42 per cent solution and 230 cc. of xylene is distilled from a 500-cc. flask through a 17-cm. Hempel column fitted into a cork covered with tin foil. After distillation of the xylene, with about 85 cc. of water, the residue yields on distillation 45–50 g. of 80–85 per cent hydrazine hydrate. This material, assayed best by titration with standard acid using methyl orange as indicator, may be used as such or concentrated further (see (Note 6)).

3. When more dilute hydrazine hydrate is used, the crystallization is slower, but it is not advisable to cool the solution thoroughly until crystals have begun to appear.

4. Although this material contains a small amount of the symmetrical dihydrazide, which is not easily eliminated on crystallization, it is entirely satisfactory as a reagent for the isolation of ketones. A purer product, m.p. 192°, with decomposition, can be obtained by adding the solution prepared from ethyl chloroacetate and trimethylamine to an alcoholic solution containing a considerable excess of hydrazine hydrate.

5. When stored in a dry, tightly stoppered container the reagent can be kept for long periods without deteriorating (odor), but samples withdrawn after some time are best recrystallized from absolute alcohol before use.

6. The yields obtained by the checkers when using 75 per cent and 50 per cent hydrazine hydrate were 78 per cent and 66 per cent, respectively, of the theoretical amount.

3. Discussion

The above procedure is essentially that of Girard and Sandulesco.[2]

References and Notes

1. Hurd and Bennett, J. Am. Chem. Soc. **51**, 265 (1929).
2. Girard and Sandulesco, Helv. Chim. Acta **19**, 1095 (1936).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alcohol (64-17-5)

sulfuric acid (7664-93-9)

Ethyl chloroacetate (105-39-5)

xylene (106-42-3)

hydrazine hydrate (7803-57-8)

Hydrazine sulfate (10034-93-2)

Trimethylamine (75-50-3)

BETAINE HYDRAZIDE HYDROCHLORIDE (123-46-6)

methyl orange (547-58-0)

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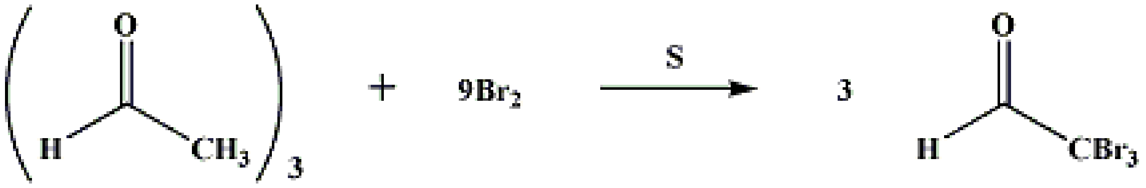
BROMAL



Submitted by F. A. Long and J. W. Howard.
Checked by W. W. Hartman and G. L. Boomer.

1. Procedure

In a 2-l. three-necked, round-bottomed flask, fitted with a liquid-sealed mechanical stirrer, a dropping funnel, and an efficient reflux condenser, are placed 720 g. (230 cc., 4.5 moles) of bromine (Note 1) and 1.5 g. of sulfur (Note 2). A glass tube is connected to the top of the condenser to carry the evolved hydrogen bromide to a gas trap. Sixty-nine grams (69 cc., 0.52 mole) of dry paraldehyde (Note 1) is added slowly, with stirring, over a period of about four hours. The reaction proceeds under its own heat during the addition of the paraldehyde; subsequently the mixture is heated externally for two hours at 60–80°. The solution is distilled and a fraction collected over the range 155–175° (Note 3).

On redistillation under reduced pressure there is obtained 220–240 g. (52–57 per cent of the theoretical amount) of reddish yellow bromal, boiling at 59–62°/9 mm., or 71–74°/18 mm.

2. Notes

1. The bromine is dried by shaking with concentrated sulfuric acid; the paraldehyde is dried over calcium chloride.
2. The use of sulfur as a catalyst increases the yield 5–10 per cent and causes no trouble in the purification.
3. The fore-run amounts to 90–180 g. and consists mostly of bromine, bromoacetaldehyde, and dibromoacetaldehyde. An additional quantity of bromal may be obtained by treating this material with a small amount of bromine, heating for two hours at 60–80°, and distilling as before.

3. Discussion

Bromal has been prepared by brominating a solution of paraldehyde in ethyl acetate,[1] by passing bromine vapor through absolute alcohol,[2] and by treatment of chloral with a metallic bromide.[3]

References and Notes

1. Pinner, Ann. **179**, 67 (1875).
2. Schäffer, Ber. **4**, 366 (1871).
3. Müller, U. S. pat. 2,057,964 [C. A. **31**, 112 (1937)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

metallic bromide

alcohol (64-17-5)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

ethyl acetate (141-78-6)

hydrogen bromide (10035-10-6)

bromine (7726-95-6)

sulfur (7704-34-9)

Bromal (115-17-3)

dibromoacetaldehyde

chloral (75-87-6)

bromoacetaldehyde (17157-48-1)

paraldehyde (123-53-7)

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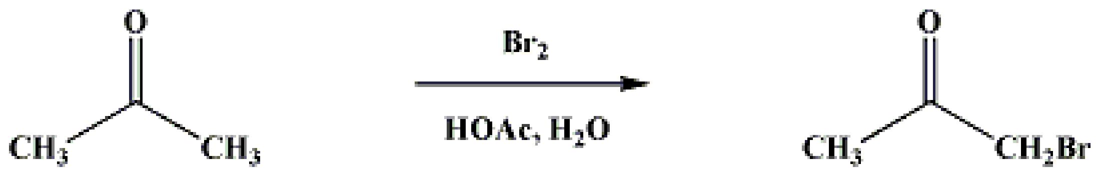
BROMOACETONE

[2-Propanone, 1-bromo-]



Submitted by P. A. Levene
Checked by Frank C. Whitmore and J. Pauline Hollingshead.

1. Procedure

A 5-l., three-necked, round-bottomed flask is provided with an efficient mechanical stirrer, a 48-cm. Allihn reflux condenser, a thermometer, and a 500-cc. separatory funnel, the stem of which reaches nearly to the bottom of the flask (Note 1).

Through the separatory funnel are introduced 1.6 l. of water, 500 cc. of c. p. acetone, and 372 cc. of glacial acetic acid. The stirrer is started and the temperature of the water bath is raised to 70–80°, so that the mixture in the flask is at about 65° (Note 2). Then 354 cc. (7.3 moles) of bromine is carefully added through the separatory funnel. The addition, which requires one to two hours, is so regulated as to prevent the accumulation of unreacted bromine (Note 3). As a rule the solution is decolorized in about twenty minutes after the bromine has been added. When the solution is decolorized, it is diluted with 800 cc. of cold water, cooled to 10°, made neutral to Congo red with about 1 kg. of solid anhydrous sodium carbonate, and the oil which separates is collected in a separatory funnel and dried with 80 g. of anhydrous calcium chloride. After drying, the oil is fractionated and the fraction boiling at 38–48°/13 mm. is collected. The yield is 470–480 g. (50–51 per cent of the theoretical amount). It may be used without further purification for the preparation of acetol (p. 5); but, if a purer product is desired, the above product is refractionated and the fraction boiling at 40–42°/13 mm. is collected. The yield is 400–410 g. (43–44 per cent of the theoretical amount).

The higher-boiling fraction contains a mixture of isomeric dibromoacetones.

2. Notes

1. The apparatus should be set up with the flask in a large container (such as a 14-qt. galvanized pail) to be used as a water bath, and under a well-ventilated hood, as both the bromine and bromoacetone are powerful irritants to the skin and mucous membranes.
2. It is necessary to warm the reaction mixture to this temperature to ensure a smooth reaction

3. It is not advisable to have too great an excess of bromine present at any time, as it sometimes reacts suddenly with great violence.

3. Discussion

Bromoacetone has been prepared by the electrolysis of a mixture of acetone and hydrobromic acid,[1] and by more orthodox methods of bromination: the addition of bromine to acetone dissolved in ten times its weight of water;[2] the addition of bromine to acetone in which marble is suspended;[3] the addition of bromine to acetone, water, and concentrated hydrochloric acid;[4] and the introduction of bromine by means of a current of air into cold acetone.[5]

A procedure similar to the one described above, except that the reaction mixture is illuminated with a powerful light, has been published.[6]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 5

References and Notes

1. Richard, Compt. rend. **133**, 879 (1901).
2. Sokolowsky, Ber. **9**, 1687 (1876).
3. Scholl and Matthaiopoulos, ibid. **29**, 1555 (1896).
4. Hughes, Watson, and Yates, J. Chem. Soc. **1931**, 3322.
5. Emmerling and Wagner, Ann. **204**, 29 (1880).
6. Gohr and Thiekötter, Biochem. Z. **305**, 374 (1940).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Congo red

dibromoacetones

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

acetic acid, Acetol (64-19-7)

HYDROBROMIC ACID (10035-10-6)

sodium carbonate (497-19-8)

bromine (7726-95-6)

acetone (67-64-1)

Bromoacetone, 2-Propanone, 1-bromo- (598-31-2)

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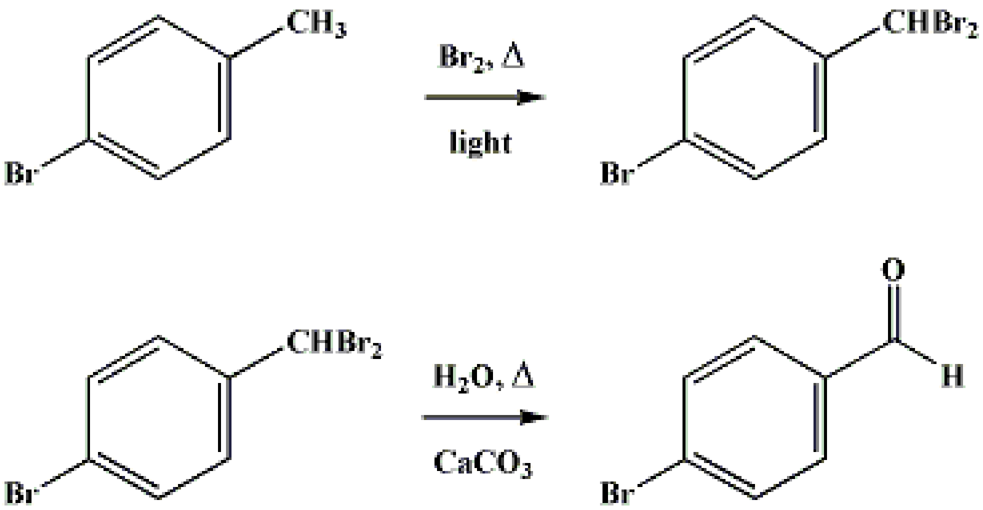
p-BROMOBENZALDEHYDE

[Benzaldehyde, *p*-bromo-]



Submitted by George H. Coleman and G. E. Honeywell.
Checked by W. W. Hartman and A. J. Schwaderer.

1. Procedure

In a 1-l. three-necked flask fitted with a mechanical stirrer, a reflux condenser, a thermometer, and a dropping funnel is placed 100 g. (0.58 mole) of *p*-bromotoluene (Org. Syn. Coll. Vol. I, **1941**, 136). The stem of the dropping funnel and the thermometer should reach nearly to the bottom of the flask. The upper end of the condenser is connected to a gas absorption trap. The flask is heated with stirring in an oil bath until the temperature of the liquid reaches 105°. The liquid is illuminated with an unfrosted 150-watt tungsten lamp, and 197 g. (61.8 cc., 1.23 moles) of bromine is added slowly from the separatory funnel (Note 1). About one-half of the bromine is added during the first hour, during which time the temperature is kept at 105–110°. The rest is added during about two hours while the temperature is raised to 135°. When all the bromine has been added the temperature is raised slowly to 150°.

The crude product (Note 2) is transferred to a 2-l. flask and mixed thoroughly with 200 g. of powdered calcium carbonate. About 300 cc. of water is added and the mixture is heated cautiously (Note 3) and then refluxed for fifteen hours to effect hydrolysis. The product is then distilled in a rapid current of steam (Note 4); the distillate is collected in 500-cc. portions and cooled; and the *p*-bromobenzaldehyde is collected and dried in a desiccator. From the first liter of distillate 50–60 g. of *p*-bromobenzaldehyde melting at 55–57° is obtained. An additional 15–20 g. of product melting at 50–56° is obtained in about 2 l. more of distillate (Note 5). This may be purified through the bisulfite addition compound (Note 6) and yields 13–18 g. of product melting at 55–57°. The total yield of pure aldehyde is 65–75 g. (60–69 per cent of the theoretical amount).

2. Notes

1. The rate of addition of the bromine should be so regulated that a large excess of unreacted bromine does not accumulate in the reaction mixture. The amount of bromine present may be roughly estimated by the color of the solution and by the amount of bromine vapor carried into the condenser.
2. *p*-Bromobenzal bromide is a lachrymator and also produces a burning sensation on the skin. Washing the affected parts with alcohol gives relief.
3. In order to avoid breaking the flask the mixture is heated first on a water bath and then on a wire gauze over a flame with continuous shaking until the liquid begins to boil. The refluxing may then be continued without danger.
4. The inlet tube for steam should reach to the bottom of the distillation flask. A 16-mm. bulb on the end of this tube with four 0.8-mm. openings helps to ensure thorough mixing of the heavy residue. If this residue is not well stirred the aldehyde distils very slowly. It is well to connect the flask to the condenser through a large Hopkins still head in order to prevent the entrainment of foam during the distillation.
5. Five to ten grams of crude *p*-bromobenzoic acid can be obtained by acidifying the solution left in the distilling flask.
6. The material is triturated with saturated sodium bisulfite solution (2 cc. per gram), and after about three hours the pasty mixture is filtered with suction. The addition product is washed with absolute alcohol and then with ether and transferred to a flask fitted for steam distillation. Excess sodium carbonate solution is added and the aldehyde is distilled in a current of steam.

3. Discussion

p-Bromobenzaldehyde has been prepared by the oxidation of *p*-bromotoluene with chromyl chloride,[1] by saponification of the acetal from *p*-bromophenylmagnesium bromide and orthoformic ester,[2] by the oxidation of ethyl *p*-bromobenzyl ether with nitric acid,[3] by the oxidation of *p*-bromobenzyl bromide with lead nitrate,[4] by the hydrolysis of *p*-bromobenzal bromide in the presence of calcium carbonate,[5] and by the procedure given on p. 442 which involves oxidation of *p*-bromotoluene with chromium trioxide in the presence of acetic anhydride, followed by hydrolysis of the resulting *p*-bromobenzaldehyde diacetate.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 200
- Org. Syn. Coll. Vol. 4, 763

References and Notes

1. Wörner, Ber. **29**, 153 (1896).
2. Tschitschibabin, ibid. **37**, 188 (1904); Bodroux, Bull. soc. chim. (3) **31**, 587 (1904); Gattermann, Ann. **393**, 223 (1912).
3. Errera, Gazz. chim. ital. **17**, 206 (1887).
4. Jackson and White, Ber. **11**, 1043 (1878); Am. Chem. J. **3**, 32 (1881).
5. Adams and Vollweiler, J. Am. Chem. Soc. **40**, 1738 (1918).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

orthoformic ester

ACETAL (105-57-7)

alcohol (64-17-5)

ether (60-29-7)

acetic anhydride (108-24-7)

nitric acid (7697-37-2)

sodium carbonate (497-19-8)

bromine (7726-95-6)

sodium bisulfite (7631-90-5)

calcium carbonate (471-34-1)

lead nitrate (10099-74-8)

chromyl chloride

chromium trioxide (1333-82-0)

p-Bromotoluene (106-38-7)

p-Bromobenzaldehyde, Benzaldehyde, p-bromo- (1122-91-4)

p-Bromobenzal bromide

p-bromobenzoic acid (586-76-5)

p-bromophenylmagnesium bromide

ethyl p-bromobenzyl ether

p-bromobenzyl bromide (589-15-1)

p-bromobenzaldehyde diacetate

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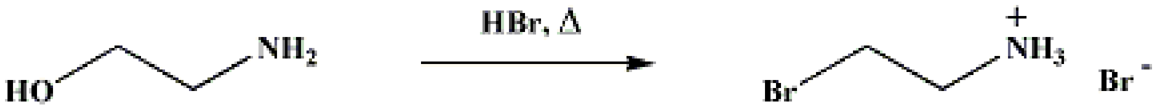
β-BROMOETHYLAMINE HYDROBROMIDE

[Ethylamine, 2-bromo-, hydrobromide]



Submitted by Frank Cortese
Checked by C. S. Marvel and C. L. Fleming.

1. Procedure

One kilogram (16.4 moles) of ice-cold ethanolamine (Note 1) is added, through a dropping funnel, with mechanical stirring, to 7 l. (9.94 kg., 52 moles) of ice-cold hydrobromic acid (sp. gr. 1.42) (Note 2) contained in a 12-l. round-bottomed flask. The flask is attached to an efficient fractionating column and heated until 1850 cc. of distillate has been collected. The rate of heating is then diminished to a point at which the liquid ceases to distil and merely refluxes. The heating under reflux is continued for one hour. At the end of this time, 700 cc. more is distilled, and the solution is again heated under reflux for one hour. This procedure is followed with 600-, 300-, 250-, 150-, 100-, and 50-cc. portions of distillate. The process may be interrupted at any time. The solution is finally heated under reflux for three hours, and 2.3 l. of crude hydrobromic acid distilled. The total volume of distillate, including that which is collected during refluxing, must not be less than 6270 cc. or more than 6330 cc.

The dark-colored residue is divided into two approximately equal portions, and each is poured, while still hot, into a 4-l. beaker. After the liquid has cooled to about 70°, 1650 cc. of acetone is added to each portion. The mixture is stirred well, so that as much as possible of the dark-colored solid is brought into contact with the acetone. After standing in the icebox overnight, the β-bromoethylamine hydrobromide is collected on a filter, washed with acetone until colorless (Note 3), and air-dried for about fifteen minutes. The filtrates are combined, concentrated to a volume of 1 l., and cooled. After seeding, a second crop of nearly pure material is obtained. By evaporation to a syrup, cooling, and seeding, a third crop of slightly colored material is obtained. (Note 4). The yield is about 2.8 kg. (83 per cent of the theoretical amount) (Note 5).

2. Notes

1. Commercial ethanolamine is fractionated in a glass apparatus, and the fraction boiling at 167–169° is used.
2. The hydrobromic acid must have a specific gravity of at least 1.42.
3. It may be advisable for effective washing to transfer the crude cake to a mortar and crush it.
4. All three crops are suitable for use in the synthesis of taurine described on p.

564.

5. The procedure has been applied to the preparation of the following β-dialkylaminoethyl bromide hydrobromides.

$BrCH_2CH_2NHR_2Br$		
R	Yield, Per Cent	Heating Periods
CH_3	83	1–1.5 hr., 2 hr.
C_2H_5	80	1 hr., 2 hr.
n-C_3H_7	55	0.75 hr., 2 hr.
n-C_4H_9	20	1 hr., 3 hr.
n-C_4H_9	59	0.5 hr., 2 hr.

The final distillation was not always carried as far as called for by the procedure of Cortese. If a faint brown or violet color appeared in the distillate, or if white fumes were given off, the distillation was discontinued; further distillation seemed to cause decomposition. However, the color always came near the end point specified in the procedure above and the total volume of the distillates was never less than 95 per cent of that called for. Since the solubilities of the products in acetone range from very slight to extreme as the molecular weights increase, the extraction of the products requires variations in the amounts of acetone specified above. [Lawrence H. Amundsen and Karl W. Krantz, private communication, and J. Am. Chem. Soc. **63**, 305 (1941).]

3. Discussion

β-Bromoethylamine hydrobromide has been prepared by the reaction of potassium phthalimide with ethylene bromide, followed by hydrolysis;[1] by the addition of hydrogen bromide to ethyleneimine;[2] from ethanolamine and hydrobromic acid;[3] and from ethanolamine and hydrogen bromide at 140–190°.[4] The preparation from ethyleneimine and hydrogen bromide is reported to succeed only if the imine is added to the acid.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 563
- Org. Syn. Coll. Vol. 3, 254
- Org. Syn. Coll. Vol. 4, 333

References and Notes

1. Gabriel, Ber. **21**, 566 (1888).

2. Gabriel, ibid. **21**, 1054 (1888); Gabriel and Stelzner, ibid. **28**, 2929 (1895).
3. Gabriel, ibid. **50**, 826 (1917); Cortese, J. Am. Chem. Soc. **58**, 191 (1936).
4. I. G. Farbenind. A.-G., Brit. pat. 468,387 [C. A. **31**, 8545 (1937)].
5. Masters and Bogert, J. Am. Chem. Soc. **64**, 2710 (1942).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

bromide (24959-67-9)

HYDROBROMIC ACID, hydrogen bromide (10035-10-6)

acetone (67-64-1)

Potassium Phthalimide (1074-82-4)

ethylene bromide (106-93-4)

β-Bromoethylamine hydrobromide, Ethylamine, 2-bromo-, hydrobromide (2576-47-8)

ethanolamine (141-43-5)

Taurine (107-35-7)

ethyleneimine (9002-98-6)

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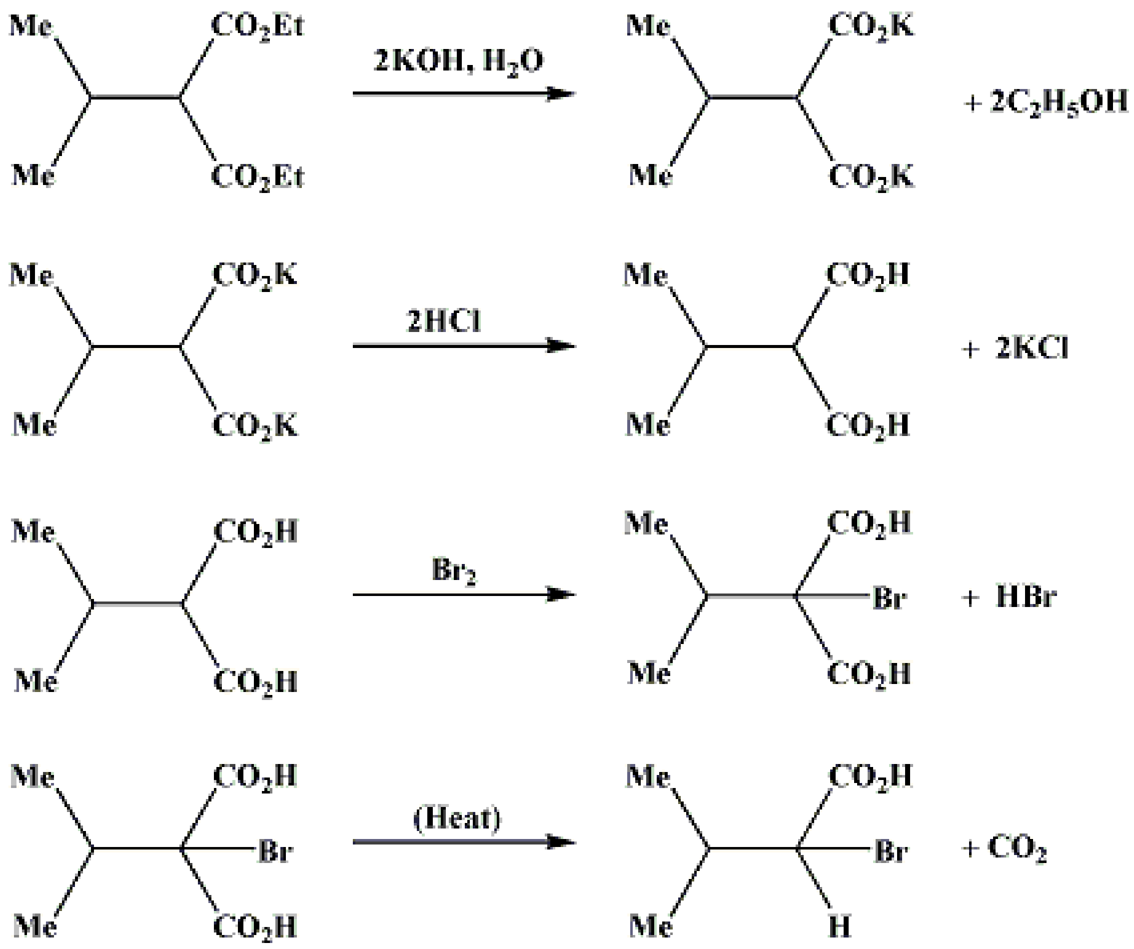
α-BROMOISOVALERIC ACID

[Isovaleric acid, α-bromo-]



Submitted by C. S. Marvel and V. du Vigneaud.
Checked by Frank C. Whitmore and A. M. Griswold.

1. Procedure

A solution of 200 g. (3.6 moles) of potassium hydroxide in 200 cc. of water is placed in a 2-l. flask fitted with a reflux condenser. The mixture is heated to about 80°, and 202 g. (1 mole) of isopropylmalonic ester (Note 1) is added through the condenser over a period of about one hour. The mixture should be shaken well to prevent the formation of two layers. The saponification proceeds rapidly, forming a clear solution. The solution is transferred to a 20-cm. evaporating dish, the flask is rinsed with 50 cc. of water, and the solution and washings are evaporated practically to dryness on a steam bath (Note 2).

The residue is dissolved in 200 cc. of water, transferred to a 1-l. flask, and cooled to 0° in an ice-salt bath. A mixture of 400 cc. of concentrated hydrochloric acid (sp. gr. 1.19) and 200 g. of cracked ice is added slowly until the mixture is acid to Congo red.

The temperature of the mixture must not rise above 10° (Note 3). Potassium chloride separates. The mixture is extracted with two 200-cc. portions and four 100-cc. portions of alcohol-free ether (Note 4) to remove the isopropylmalonic acid. The ether solution (Note 5) is placed in a flask fitted with a reflux condenser, and 160 g. (1 mole) of bromine is added gradually over a period of about two hours at such a rate that the ether boils gently (Note 6). When the bromination is complete, the ether solution is washed with 100 cc. of water to remove the hydrobromic acid, dried over 25 g. of calcium chloride, and freed from ether by distillation on the steam bath. The crude isopropylbromomalonic acid is heated in the distilling flask in an oil bath at 125–130° until no more carbon dioxide is evolved. It is then distilled under reduced pressure; the fraction distilling at 140–160°/40 mm. is collected separately and redistilled (Note 7). The yield of product boiling at 148–153°/40 mm. (125–130°/15 mm.) is 100–120 g. (55–66 per cent of the theoretical amount) (Note 8).

2. Notes

1. The isopropylmalonic ester was prepared by the method used for *n*-butylmalonic ester (Org. Syn. Coll. Vol. I, **1941**, 250). The yield of product boiling at 132–135°/44 mm. was 70–75 per cent of the theoretical amount.
2. Unless the saponification is complete, the final product will contain ethyl α-bromoisovalerate, which will appear in the low-boiling fraction. If all the alcohol is not removed, some esterification will occur on acidification.
3. A rise in temperature favors the loss of carbon dioxide with the formation of isovaleric acid, which will escape bromination.
4. The ether used for extraction is first extracted with one-tenth its volume of saturated calcium chloride solution to remove the alcohol, which would otherwise cause partial esterification of the acid.
5. No special drying is necessary before the bromination, but the ether and aqueous layers should be separated carefully.
6. Usually the bromination starts easily. Sometimes, however, the mixture has to be heated after the first few drops of bromine are added. The mixture may have to be heated to complete the bromination.
7. The product on the first distillation does not have a constant boiling point, as some carbon dioxide is liberated from undecomposed isopropylbromomalonic acid. This cannot be avoided by preliminary heating, even at temperatures much higher than those used.
8. This is a general method for preparing α-bromo acids. By using exactly analogous directions α-bromo-*n*-caproic acid may be obtained in 65–70 per cent yields from *n*-butylmalonic ester; α-bromoisocaproic acid in 65–70 per cent yields from isobutylmalonic ester; and α-bromo-β-methylvaleric acid in 75–80 per cent yields from *sec*.-butylmalonic ester.

3. Discussion

α-Bromoisovaleric acid has been prepared from bromine and isovaleric acid alone,[1] or in the presence of phosphorus,[2] or phosphorus trichloride;[3] and by the action of heat on isopropylbromomalonic acid.[4]

References and Notes

1. Ley and Popoff, Ann. **174**, 63 (1874).
2. Schleicher, ibid. **267**, 115 (1892).
3. Org. Syn. **20**, 106.
4. Koenigs and Mylo, Ber. **41**, 4437 (1908).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Congo red

isopropylmalonic ester

isobutylmalonic ester

n-butylmalonic ester

sec.-butylmalonic ester

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

ether (60-29-7)

α-Bromoisovaleric acid, Isovaleric acid, α-bromo- (565-74-2)

HYDROBROMIC ACID (10035-10-6)

bromine (7726-95-6)

PHOSPHORUS (7723-14-0)

α-bromo-n-caproic acid (616-05-7)

carbon dioxide (124-38-9)

potassium hydroxide (1310-58-3)

phosphorus trichloride (7719-12-2)

potassium chloride (7447-40-7)

isopropylmalonic acid (601-79-6)

isopropylbromomalonic acid

ethyl α-bromoisovalerate (609-12-1)

isovaleric acid (503-74-2)

α-Bromoisocaproic acid (49628-52-6)

α-Bromo-β-methylvaleric acid (42880-22-8)

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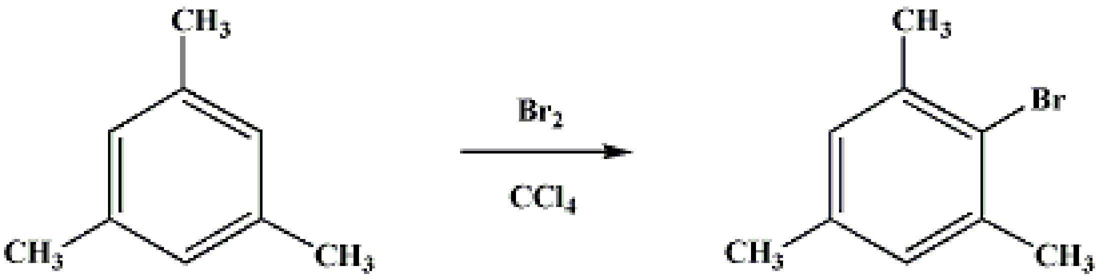
Organic Syntheses, CV 2, 95

BROMOMESITYLENE

[Mesitylene, 2-bromo-]



Submitted by Lee Irvin Smith
Checked by Roger Adams and H. A. Stearns.

1. Procedure

In a 3-l. three-necked flask, provided with a short reflux condenser, a mechanical stirrer, and a separatory funnel, is placed a solution of 636 g. (5.3 moles) of mesitylene (Note 1) in 375–440 cc. of carbon tetrachloride. The flask is placed in an ice-salt bath, and when the temperature of the reaction mixture is below 10° a solution of 900 g. (288 cc., 5.6 moles) of bromine in 565 cc. of carbon tetrachloride is added to the well-stirred solution. The bromination proceeds very readily, and the hydrogen bromide which is evolved is led off through the condenser and absorbed in water. The addition of the bromine solution requires about three hours, during which time the temperature is maintained at 10–15°.

After the addition of the bromine is complete, the reaction mixture is allowed to stand at room temperature for about one hour. It then has a light yellow color. The solution is washed with water and then with two 500-cc. portions of 20 per cent sodium hydroxide solution to remove any dissolved hydrobromic acid. The solution is dried over calcium chloride and filtered. The carbon tetrachloride is distilled through a good column until the temperature at the top of the column reaches about 120°. When the carbon tetrachloride has distilled, the oil is likely to turn dark and give off fumes.

The residue is added to a solution of 50 g. of sodium in about a liter of 95 per cent alcohol. The solution is boiled under a reflux condenser for about one hour (Note 2) and then allowed to stand overnight. The reaction mixture is diluted with about 6 l. of water and the two layers are separated. The aqueous layer is extracted with three or four 500-cc. portions of carbon tetrachloride (Note 3), and the extracts are added to the bromomesitylene. This solution is then washed thoroughly with water. The carbon tetrachloride solution is separated, dried over calcium chloride, and distilled. After the carbon tetrachloride is removed the bromomesitylene is fractionated carefully under reduced pressure from a modified Claisen flask. The fraction boiling at 105–107°/16–

17 mm. (Note 4) is bromomesitylene. The yield is 840–870 g. (79–82 per cent of the theoretical amount). There is a small low-boiling portion (about 25 g.) and also a small high-boiling residue. The bromomesitylene obtained in this way gives no precipitate on standing twenty-four hours with alcoholic silver nitrate solution. It has a melting point of −1° to +1°.

2. Notes

1. The mesitylene was prepared as described in Org. Syn. Coll. Vol. I, **1941**, 341, and boiled at 58–59°/15 mm.
2. The treatment with sodium ethoxide removes any traces of side-chain halogen derivatives. Some care has to be exercised at this point as the solution may foam at the beginning of the heating period.
3. The carbon tetrachloride distilled from the crude bromomesitylene may be used for this purpose. The total volume of solution should be about 2 l.
4. Boiling points of bromomesitylene observed at different pressures were as follows: 132°/62 mm.; 139°/70 mm.; 146°/78 mm.; 157°/100 mm.

3. Discussion

Bromomesitylene is always prepared by brominating mesitylene—a reaction that can be run in the dark,[1] or in daylight,[2] or using sulfur bromide and nitric acid,[3] or with metallic manganese as a catalyst in the absence of any solvent.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 360
- Org. Syn. Coll. Vol. 3, 848
- Org. Syn. Coll. Vol. 5, 706

References and Notes

1. Schramm, Ber. **19**, 212 (1886).
2. Fittig and Storer, Ann. **147**, 6 (1868); Smith and MacDougall, J. Am. Chem. Soc. **51**, 3002 (1929).
3. Kalle and Company, Ger. pat. 123,746 [Frdl. **6**, 53 (1900–02)].
4. Duke, Lewis, and Dunbar, Proc. S. Dakota Acad. Sci. **15**, 21 (1935) [C. A. **30**, 2556 (1936)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

metallic manganese

alcohol (64-17-5)

calcium chloride (10043-52-4)

sodium hydroxide (1310-73-2)

nitric acid (7697-37-2)

silver nitrate (7761-88-8)

HYDROBROMIC ACID, hydrogen bromide (10035-10-6)

bromine (7726-95-6)

carbon tetrachloride (56-23-5)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

Mesitylene (108-67-8)

Bromomesitylene (27129-86-8)

Mesitylene, 2-bromo- (576-83-0)

sulfur bromide

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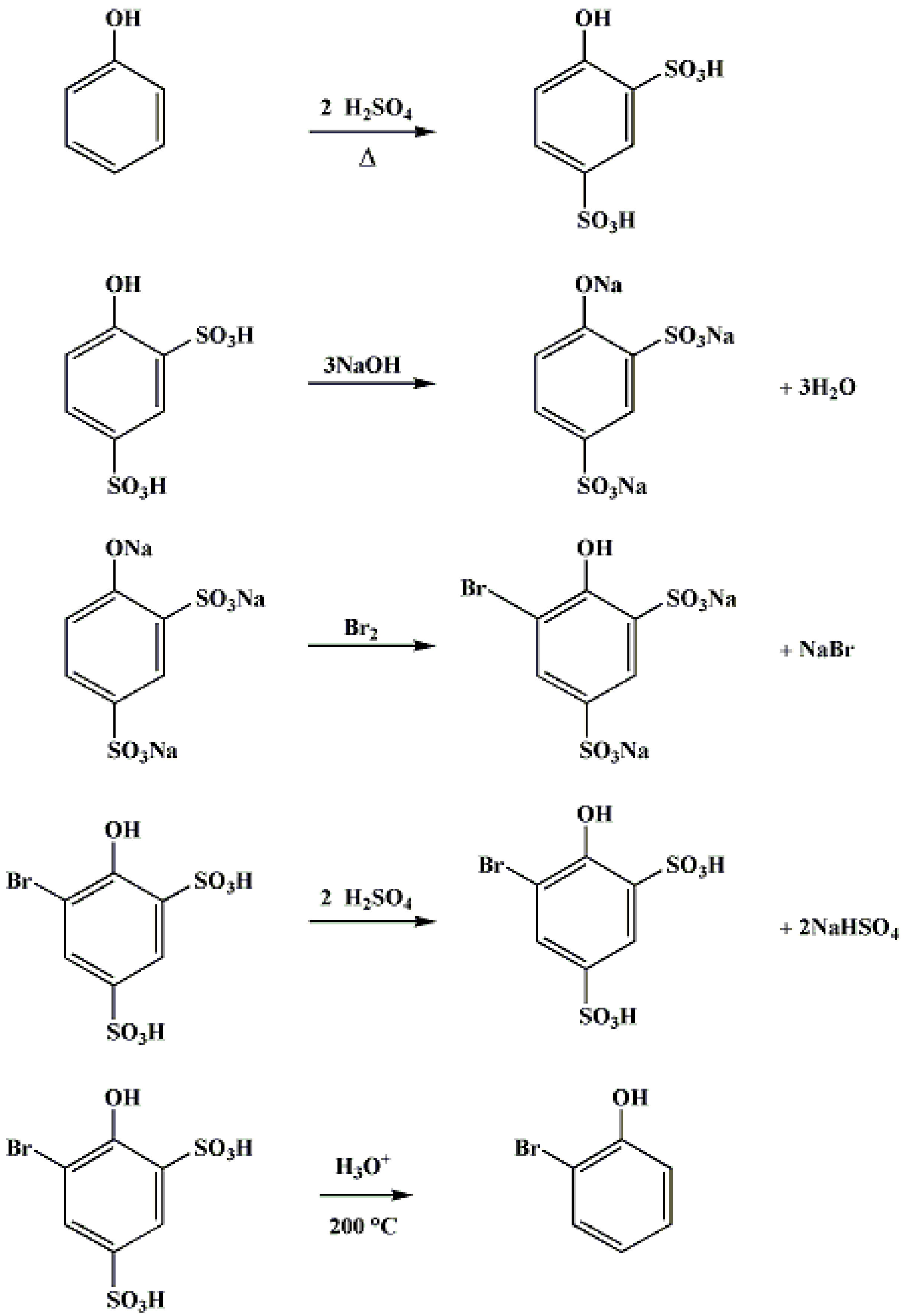
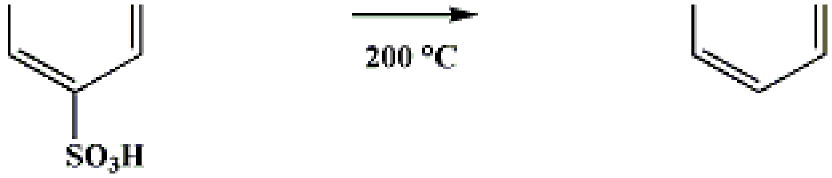
o-BROMOPHENOL

[Phenol, *o*-bromo-]





Submitted by Ralph C. Huston and Murel M. Ballard.
Checked by Louis F. Fieser and Max Tishler.

1. Procedure

In a 3-l. three-necked flask is placed a mixture of 94 g. (1 mole) of phenol and 350 g. (190 cc., 3.5 moles) of concentrated sulfuric acid, and the mixture is heated on a boiling water bath for three hours with constant mechanical stirring. At the end of this time the boiling water bath is replaced by an ice bath. When the reaction mixture has been cooled to room temperature it is made alkaline by the careful addition of a solution of 280 g. (7 moles) of sodium hydroxide in 700 cc. of water (Note 1). This must be done slowly and with good cooling to prevent boiling. A solid salt, which at first separates, largely dissolves at a later stage.

The alkaline solution is cooled to room temperature; with the stirrer still in constant operation, and after inserting a thermometer, 160 g. (1 mole) of bromine is added from a dropping funnel in the course of twenty to thirty minutes. During this operation the temperature is allowed to rise to 40–50°. Stirring is continued for one-half hour after all the bromine has been added. The solution should still be alkaline and should contain only a small amount of suspended material.

In order to evaporate the solution, the flask is then placed in an oil bath, which is brought to a temperature of 150–155°. As soon as solid material begins to separate, the mixture will bump badly unless a rather rapid current of air is passed through the reaction mixture. This has the further advantage of hastening the evaporation (Note 2). The heating is continued until a thick, pasty, gray mass is left as a residue, the process requiring thirty to forty minutes. The mixture is allowed to cool and then made strongly acid by the addition of 800 cc. of concentrated sulfuric acid. This must be done slowly and under a hood on account of the rapid evolution of hydrogen bromide.

The flask is then heated in an oil bath maintained at a temperature of 190–210° and the mixture is distilled with steam. The sulfonate groups are hydrolyzed in this process, and the bromophenol passes over as a heavy, colorless or pale yellow oil. In about one hour the distillate is clear. The product is extracted with ether, the ether is removed by distillation from the steam bath, and the residue is distilled at atmospheric pressure (Note 3). The fraction boiling at 194–200° represents practically pure *o*-bromophenol. The yield is 70–75 g. (40–43 per cent of the theoretical amount) (Note 4). *o*-Bromophenol is a colorless liquid with a very characteristic odor. It is rather unstable and decomposes on standing, becoming brown or red in color.

2. Notes

1. Too great an excess of water in the reaction mixture appears to result in the formation of higher bromination products. Insufficient water causes the reaction

mixture to solidify during bromination, preventing efficient agitation.
2. A small amount of tribromophenol is eliminated in the evaporation, the substance being volatile with steam.
3. Distillation should be as rapid as possible, as the *o*-bromophenol is somewhat unstable and decomposes rapidly at the high temperature. Distillation at reduced pressure has not been found to offer much improvement.
4. The rather large residue of higher-boiling material probably contains higher bromination products of phenol.

3. Discussion

o-Bromophenol has been prepared by the bromination of phenol in various solvents and with various brominating agents,[1] and at high temperature in the absence of a solvent.[2] It has been obtained by the decarboxylation of 2-bromo-3-hydroxybenzoic acid,[3] by the diazotization of *o*-bromoaniline,[4] and from *o*-aminophenol by the Sandmeyer reaction.[5] The method given here, which is an adaptation of the procedure of Takagi and Kutani[6] for the preparation of 2-chlorophenol, has been improved by using nitrobenzene as a solvent in the bromination of the phenolsulfonic acid.[7]

References and Notes

1. Hubner and Brenken, Ber. **6**, 171 (1873); Dinwiddie and Kastle, Am. Chem. J. **46**, 502 (1911); Skraup and Beifuss, Ber. **60**, 1077 (1927); Likhosherstov, J. Russ. Phys.-Chem. Soc. **61**, 1019 (1929) [C. A. **24**, 836 (1930)].
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3. Lellman and Grothmann, Ber. **17**, 2726 (1884).
4. Fittig and Mayer, ibid. **8**, 362 (1875).
5. Mendola and Streatfeild, J. Chem. Soc. **73**, 685 (1898).
6. Takagi and Kutani, J. Pharm. Soc. Japan, No. 517, 260 (1925) [C. A. **20**, 2669 (1926)].
7. Huston and Neeley, J. Am. Chem. Soc. **57**, 2176 (1935).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

ether (60-29-7)

sodium hydroxide (1310-73-2)

phenol (108-95-2)

hydrogen bromide (10035-10-6)

bromine (7726-95-6)

o-aminophenol (95-55-6)

Nitrobenzene (98-95-3)

phenolsulfonic acid

bromophenol, o-Bromophenol, Phenol, o-bromo- (95-56-7)

tribromophenol

2-bromo-3-hydroxybenzoic acid

2-chlorophenol (95-57-8)

o-bromoaniline (615-36-1)

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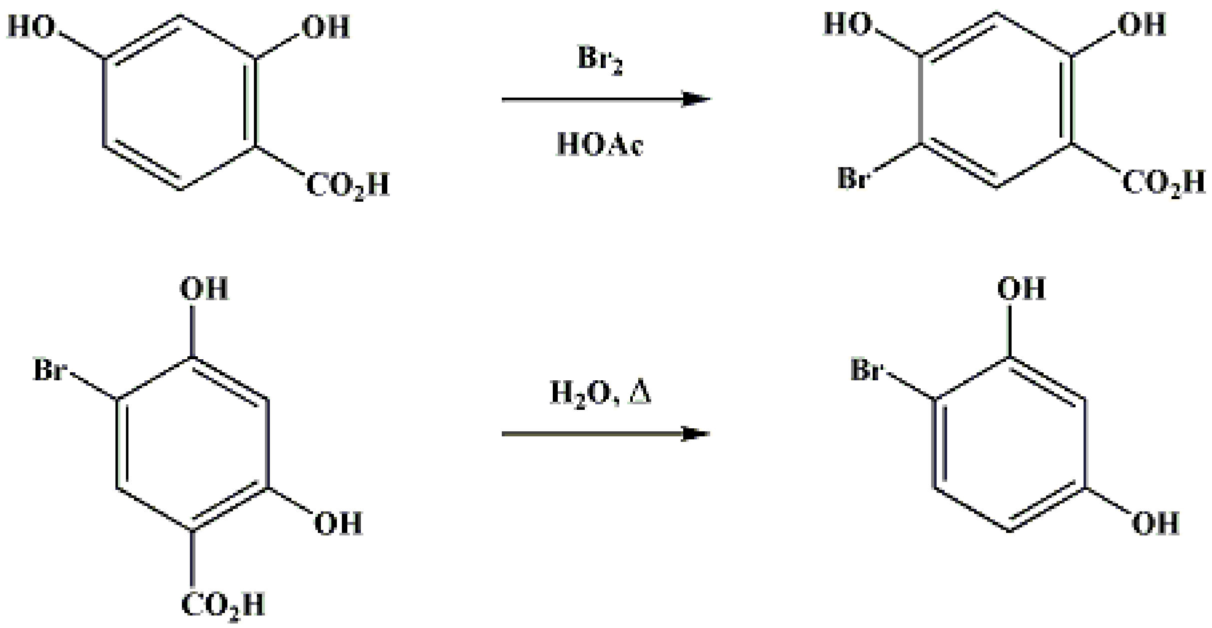
4-BROMORESORCINOL

[Resorcinol, 4-bromo-]



Submitted by R. B. Sandin and R. A. McKee.
Checked by W. W. Hartman and J. B. Dickey.

1. Procedure

In a 1-l. flask fitted with a mechanical stirrer and a dropping funnel are placed 46.2 g. (0.3 mole) of 2,4-dihydroxybenzoic acid (β-resorcylic acid, p. 557) and 350 cc. of glacial acetic acid. After the stirrer is started the mixture is warmed until solution results (45°) and then is allowed to cool to 35°. Through the dropping funnel is added a solution of 48 g. (15 cc., 0.3 mole) of bromine in 240 cc. of glacial acetic acid with vigorous stirring over a period of about one hour. The temperature of the reaction mixture remains at 30–35°. When all the bromine is added the solution is poured into 5 l. of water, and the mixture is cooled to 0–5° and allowed to stand for several hours. The fine, white crystals of 2,4-dihydroxy-5-bromobenzoic acid are collected on a 10-cm. Büchner funnel and washed with about 500 cc. of cold water. The crude product, after air drying at room temperature, melts at 194–200° and weighs 55–60 g. For purification it is dissolved in 1.5 l. of boiling water, and the solution is refluxed for one hour (Note 1), filtered while hot, and cooled in an ice bath. The material which crystallizes is collected, washed with 100 cc. of cold water, and air dried. The yield of colorless 2,4-dihydroxy-5-bromobenzoic acid, melting at 206.5–208.5° (corr.), is 40–44 g. (57–63 per cent of the theoretical amount).

Thirty grams of purified 2,4-dihydroxy-5-bromobenzoic acid is refluxed for twenty-four hours with 375 cc. of water, and the resulting solution is filtered, cooled, and

extracted with a 400-cc. and a 200-cc. portion of ether. The ether is removed by evaporation, and the 4-bromoresorcinol is dried on a steam bath. The yield of product melting at 100–102° (Note 2) is 22–22.5 g. (90–92 per cent of the theoretical amount).

2. Notes

1. The 2,4-dihydroxy-3,5-dibromobenzoic acid invariably present is in this way converted into the very soluble 2,4-dibromoresorcinol and removed. The monobromo acid is decarboxylated much more slowly.
2. Some samples were obtained with melting points ranging from 77° to 93°, but on dissolving the samples in chloroform and evaporating the solvent the values rose to 100–102°. This is not believed to be a process of purification.

3. Discussion

4-Bromoresorcinol has been prepared by the monobromination of resorcinol monobenzoate and subsequent hydrolysis;[1] from 2-bromo-5-aminophenol by the diazo reaction;[2] by treating resorcinol with dichlorourea and potassium bromide;[3] and by the bromination of 2,4-dihydroxybenzoic acid followed by decarboxylation.[4] The above procedure is based particularly upon the observations of Rice.[4]

References and Notes

1. Fries and Lindemann, Ann. **404**, 61 (1914).
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3. Likhosherstov, J. Gen. Chem. (U.S.S.R.) **3**, 172 (1933) [C. A. **28**, 1676 (1934)].
4. Zehenter, Monatsh. **2**, 480 (1881); **8**, 293 (1887); von Hemmelmayr, ibid. **33**, 977 (1912); **34**, 374 (1913); Rice, J. Am. Chem. Soc. **48**, 3125 (1926); Davis and Harrington, ibid. **56**, 129 (1934).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

acetic acid (64-19-7)

ether (60-29-7)

chloroform (67-66-3)

bromine (7726-95-6)

potassium bromide (7758-02-3)

dichlorourea

resorcinol (108-46-3)

4-Bromoresorcinol, Resorcinol, 4-bromo- (6626-15-9)

2,4-dihydroxybenzoic acid, β-Resorcylic acid (89-86-1)

2,4-Dihydroxy-5-bromobenzoic acid (7355-22-8)

2,4-dihydroxy-3,5-dibromobenzoic acid

2,4-dibromoresorcinol

resorcinol monobenzoate (136-36-7)

2-bromo-5-aminophenol

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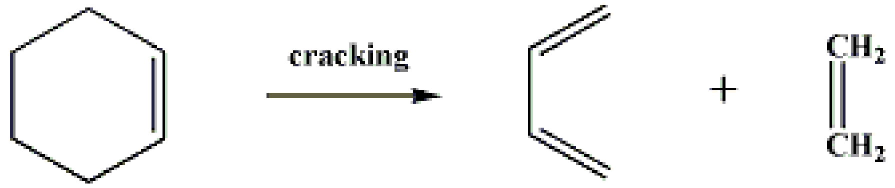
1,3-BUTADIENE

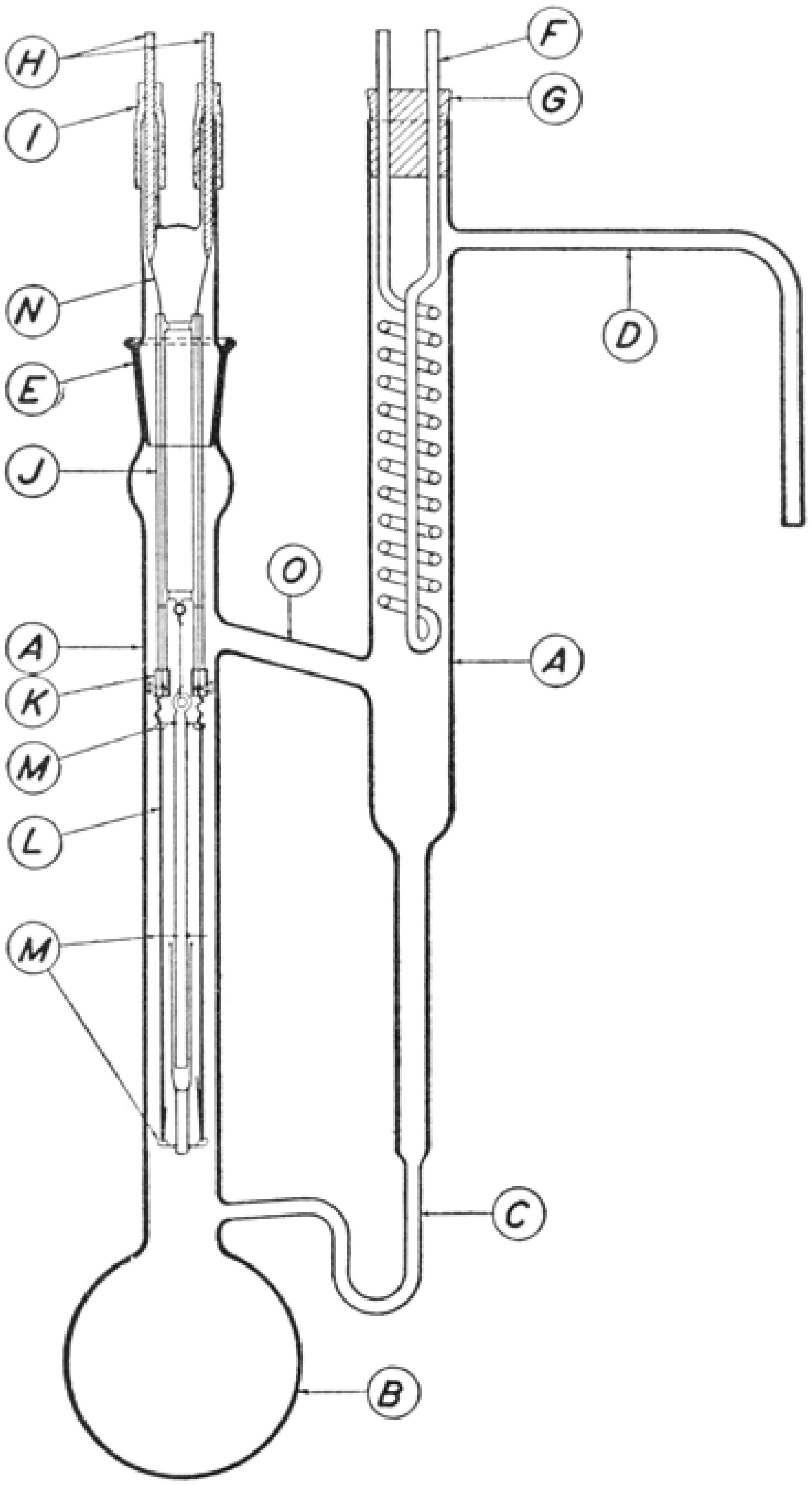


Submitted by E. B. Hershberg and John R. Ruhoff.
Checked by W. H. Carothers and J. Harmon.

1. Procedure

Cyclohexene (Org. Syn. Coll. Vol. I, **1941**, 183, and p. 152 below) is boiled in the flask B, shown in f.htmig. 3, and the vapor is passed over a cracking element consisting of an expansible grid threaded with resistance ribbon L (Note 1) and (Note 2). The boiling flask B is supported over a 250-watt bowl heater provided with a rheostat, and the current in the cracking element is taken from a 115-volt a-c. or d-c. source and controlled by a second rheostat of 10-ampere capacity (Note 3). In order to trap any cyclohexene which passes the coil condenser, the gas-delivery tube D is connected to a tube leading close to the bottom of a 500-cc. distilling flask immersed in an ice bath. The exit tube of the flask is connected with a short section of rubber tubing to a receiver for condensing the butadiene, consisting of a large test tube with the entrance tube leading halfway to the bottom and an exit tube at the top for conducting the ethylene (saturated with butadiene) to a hood or outdoors. The receiver is cooled in a Dewar flask containing solid carbon dioxide and a eutectic mixture of equal parts by weight (or volume) of chloroform and carbon tetrachloride.

Fig. 3



The flask B is two-thirds filled with cyclohexene, and, with the cooling water flowing, this is heated to vigorous boiling. When the vapor has displaced the air from the

apparatus *completely* (Note 4), the current is turned on in the cracking unit. By adjusting both the rate of boiling and the current the ribbon is maintained at a bright red heat over its entire length. Very rapid refluxing is necessary in order to prevent undue carbonization on the filament and tar formation on the glass walls (Note 5). The generator can be run intermittently or until the charge is exhausted.

The butadiene collected is purified by a bulb-to-bulb distillation, the receiver in the cooling mixture being replaced by a similar container to which it is connected by means of rubber tubing and into which the butadiene is allowed to distil. The product is quite satisfactory for most uses, as in the Diels-Alder reaction (Note 6). The cracking element uses about 500 watts at 8.7 amperes and produces 25–30 g. of butadiene per hour. The yield, based on the cyclohexene consumed (Note 7) and on redistilled product, is 65–75 per cent of the theoretical amount. High-boiling residues accumulating in the boiling flask should be removed after preparing 100–150 g. of butadiene (Note 8).

2. Notes

1. *Apparatus*.—The unit shown in f.htmig. 3 is constructed of Pyrex glass, and the following is a summary of satisfactory dimensions for the various tubings (outer diameters) and of other specifications: A, 32-mm. tubing; B, 500-cc. flask; C, 7-mm. tubing; D, 8-mm. tubing; E, No. 35 standard taper joint; F, coil of 3/16-in. copper tubing (see (Note 2)); G, cork stopper; H, 1/8-in. brass rod; I, rubber tubing; J, 3-mm. glass tubing; K, brass electrical connectors; L, Chromel C resistance ribbon No. 37 B. and S. gauge, 1.9–2 ohms per foot, width 1/16 in., length 56 to 60 in. (see below); M, tungsten wire-loop supports sealed into the suspended glass rod; the center supports are of 0.01-in. (dia.) wire, those at the top and bottom of 0.015-in. (dia.) wire; N, copper wire No. 22 B. and S. gauge; O, 12-mm. tubing.
The ribbon L of the cracking element is threaded between the tungsten loops M, of which there are five each at the top and bottom and eight at the center. The unit is suspended with a copper wire from the glass cross-support as shown. The lower end is free to drop down as the resistance wire expands; this prevents short-circuiting of the element.
The composition of the filament is of importance in determining the yield and the performance of the apparatus. With nickel-chromium alloys excessive carbonization occurs and the yield is poor. Much better results are obtained with the nickel-iron-chromium alloys called Chromel C and Nichrome Alloy Wire.
2. To provide for the proper functioning of the coil condenser even in warm weather it is advisable to increase the number of turns to 30–40, although the condenser as shown is satisfactory with tap water at 4–10°.
3. A slide-wire rheostat of 2-ampere capacity wound on a hollow enameled iron tube will carry the required current if a stream of cooling water is passed through the tube.
4. An explosion may occur if the filament is heated while an appreciable amount of air is still present. Furthermore, the heating element will burn out at once if an adequate supply of cyclohexene vapor is not supplied, since the current passing

through the wire is far above the normal rating for air.
5. In case of excessive carbonization the rate of boiling should be increased or the filament temperature slightly lowered. In general the vapor velocity should be as high as possible without exceeding the capacity of the copper condenser.
6. The crude product contains appreciable amounts of C_2, C_3, and C_6 fractions. The actual butadiene content lies between 82 and 88 per cent. If very pure material is desired the butadiene is converted into the tetrabromide, which is crystallized and reconverted to the hydrocarbon by means of zinc and alcohol.[1]
7. The cyclohexene collecting in the ice trap ordinarily is returned to the boiling flask; in determining the percentage conversion this was combined with any material left in the boiler and the pure starting material present recovered by fractionation.
8. The apparatus may be used also for the preparation of ketene from acetone (Org. Syn. Coll. Vol. I, **1941**, 330).

3. Discussion

The methods for the preparation of gaseous products containing more or less butadiene are too numerous for profitable review here. Especially is this true since the development of commercial processes which are not particularly suitable for laboratory operation. The most satisfactory procedure for preparing butadiene in the laboratory is the pyrolysis of cyclohexene,[2] which has been shown to yield a product consisting essentially of butadiene.[1, 3] For this pyrolysis, the apparatus described above and that described by Williams and Hurd[4] are available. Other laboratory preparations of butadiene start from butyl chloride,[5] 2,3-dibromobutane,[6] crotyl chloride,[6] and 1,3-butylene glycol.[7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 28

References and Notes

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Appendix

Compounds Referenced (Chemical Abstracts Registry Number)

alcohol (64-17-5)

Cyclohexene (110-83-8)

carbon tetrachloride (56-23-5)

carbon dioxide (124-38-9)

acetone (67-64-1)

zinc (7440-66-6)

ethylene (9002-88-4)

Butyl chloride (109-69-3)

1,3-Butadiene, butadiene (106-99-0)

2,3-dibromobutane (5408-86-6)

crotyl chloride (4894-61-5)

1,3-butylene glycol (107-88-0)

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n-BUTYL BORATE

Submitted by John R. Johnson and S. W. Tompkins.
Checked by W. W. Hartman and J. B. Dickey.

1. Procedure

In a 2-l. round-bottomed flask, equipped with a 200-cc. dropping funnel and a 30-cm. column filled with glass beads (Note 1), and connected to a 40–50 cm. condenser, are placed 124 g. (2 moles) of boric acid, 666 g. (9 moles) of technical *n*-butyl alcohol, and a few chips of porous plate. The reaction mixture is heated to gentle boiling, and the rate of heating is adjusted so that 90–100 cc. of distillate is collected per hour. The temperature of the vapor at the top of the column remains constant at 91° over a period of three to three and one-half hours while the azeotropic mixture of *n*-butyl alcohol and water distils (Note 2). After two hours, the upper layer of *n*-butyl alcohol in the distillate is separated from the water, dried with a little anhydrous potassium carbonate or magnesium sulfate, and returned to the reaction mixture through the separatory funnel. Likewise, after the third hour of heating, the *n*-butyl alcohol in the distillate is separated, dried, and returned to the reaction flask.

During the third hour of heating, the temperature at the top of the column rises slowly as the removal of the water approaches completion. After the fourth hour, when the temperature of the distilling vapor has attained 110–112°, the heating is discontinued, and the reaction mixture is transferred to a 2-l. Claisen flask with the least possible exposure to atmospheric moisture (Note 3). The unreacted *n*-butyl alcohol is removed by distillation under reduced pressure (Note 4) until the thermometer registers a sudden rise in temperature. The receiver is then changed, and the main fraction of *n*-butyl borate distils almost entirely at 103–105°/8 mm. or 114–115°/15 mm. A negligible residue remains in the distilling flask. The weight of the distilled *n*-butyl borate, which contains a small amount of *n*-butyl alcohol, is 410–435 g. (89–94 per cent of the theoretical amount). From the aqueous distillate and the fore-run of the vacuum distillation, 190–210 g. of *n*-butyl alcohol is recovered.

The main fraction of *n*-butyl borate is redistilled from a Claisen flask provided with an indented fractionating column (Note 5), and the first 4–6 cc. of distillate is rejected. The purified product, b.p. 103–105°/8 mm. or 114–115°/15 mm., weighs 400–425 g. (87–92 per cent of the theoretical amount) (Note 6).

2. Notes

1. Any fractionating column of a reasonably effective type can be used.

Columns longer than 30 cm. and of the most efficient types were found to give no better results than a simple Hempel column filled with glass beads or broken glass.
2. The distillate collected while the temperature remains at 91° separates into two layers; 100 cc. of this distillate contains 72 cc. of a supernatant layer of wet *n*-butyl alcohol.
3. Since *n*-butyl borate is hydrolyzed readily by atmospheric moisture, it is necessary to manipulate the reaction product so as to minimize exposure to the air.
4. *n*-Butyl borate can be purified by distillation at atmospheric pressure, but the separation from *n*-butyl alcohol is effected more readily under reduced pressure. *n*-Butyl borate is stated[1] to boil at 190°/200 mm. and at 230–235° under atmospheric pressure.
5. It is advantageous to use a Claisen flask with a 25–30 cm. side arm bearing a condenser jacket and connected to a device for collecting the fractions without interruption of the distillation or exposure to moist air.
6. *n*-Amyl borate can be prepared in a similar manner. From 792 g. (9 moles) of *n*-amyl alcohol and 124 g. (2 moles) of boric acid there is obtained 510–525 g. (93–96 per cent of the theoretical amount) of *n*-amyl borate, b.p. 146–148°/16 mm.; 210–215 g. of *n*-amyl alcohol is recovered. In this preparation the temperature of the distilling vapor remains at 95° during the first two hours and the distillate contains relatively more water (100 cc. of distillate contains 56 cc. of water and 44 cc. of *n*-amyl alcohol). After the second hour the temperature rises slowly to 136–137°. It is unnecessary, and not advantageous, to return the recovered *n*-amyl alcohol to the reaction mixture.

3. Discussion

The procedure described is essentially that disclosed in a patent.[1] *n*-Butyl borate can also be prepared by the action of *n*-butyl alcohol on boron triacetate or boric anhydride.

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

potassium carbonate (584-08-7)

n-butyl alcohol (71-36-3)

boric acid (10043-35-3)

n-amyl alcohol (71-41-0)

magnesium sulfate (7487-88-9)

boron triacetate

boric anhydride

n-BUTYL BORATE (688-74-4)

n-Amyl borate (621-78-3)

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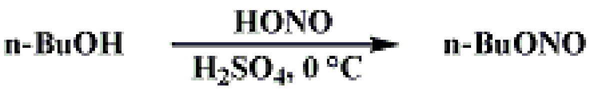
n-BUTYL NITRITE



Submitted by W. A. Noyes
Checked by C. R. Noller and B. H. Wilcoxon.

1. Procedure

In a 3-l. three-necked, round-bottomed flask, fitted with a mechanical stirrer (Note 1), a separatory funnel extending to the bottom of the flask, and a thermometer, are placed 380 g. (5.5 moles) of c.p. sodium nitrite and 1.5 l. of water. The flask is surrounded by an ice-salt mixture, and the solution is stirred until the temperature falls to 0°. A mixture of 100 cc. of water, 136 cc. (250 g., 2.5 moles) of concentrated sulfuric acid (sp. gr. 1.84) (Note 2), and 457 cc. (370 g., 5 moles) of commercial *n*-butyl alcohol is cooled to 0° and by means of the separatory funnel is introduced slowly beneath the surface of the nitrite solution, with stirring. The alcohol solution is added slowly enough so that practically no gas is evolved, and the temperature is kept at ±1°. This usually requires from one and one-half to two hours.

The resulting mixture is allowed to stand in the ice-salt bath until it separates into layers, and the liquid layers are decanted from the sodium sulfate into a separatory funnel (Note 3). The lower aqueous layer is removed and the butyl nitrite layer washed twice with 50-cc. portions of a solution containing 2 g. of sodium bicarbonate and 25 g. of sodium chloride in 100 cc. of water. After drying over 20 g. of anhydrous sodium sulfate, the yield of practically pure butyl nitrite amounts to 420–440 g. (81–85 per cent of the theoretical amount) (Note 4) and (Note 5). If desired, the product may be distilled under reduced pressure when 98 per cent distils at 24–27°/43 mm. (Note 6). Butyl nitrite boils at 75° under atmospheric pressure, with some decomposition.

2. Notes

1. A stirrer capable of keeping solid material in motion and driven by a strong motor should be used because of the precipitation of large amounts of sodium sulfate towards the end of the reaction.
2. The concentration of sulfuric acid which is used keeps the butyl alcohol in solution but does not dissolve butyl nitrite.
3. If more butyl nitrite separates from the sodium sulfate after the first decantation, a second decantation is made. Care must be exercised in handling butyl nitrite; inhalation of the vapor may cause severe headache and heart excitation.
4. The same procedure is quite satisfactory for runs of one-tenth this size. In small runs mechanical stirring is unnecessary since gentle rotation of the flask

by hand gives good mixing.
5. Isoamyl nitrite may be made in the same manner and with approximately the same yields.
6. Butyl nitrite decomposes slowly on standing and should be kept in a cool place and used within a few days or, at most, a few weeks after it is prepared. A sample which stood for five months during a warm summer seemed to contain only 20–25 per cent of the original nitrite. The products of decomposition consist of oxides of nitrogen, water, butyl alcohol, and polymerization products of butyraldehyde.

3. Discussion

Butyl nitrite has always been prepared by the action of nitrous acid on butyl alcohol.[1] The method described[2] is a modification of that of Wallach and Otto[3] for ethyl nitrite.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 363
- Org. Syn. Coll. Vol. 3, 191
- Org. Syn. Coll. Vol. 5, 623
- Org. Syn. Coll. Vol. 6, 840

References and Notes

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2. Noyes, ibid. **55**, 3888 (1933).
3. Wallach and Otto, Ann. **253**, 251 (1889).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

oxides of nitrogen

sulfuric acid (7664-93-9)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

sodium nitrite (7632-00-0)

nitrous acid (7782-77-6)

butyl alcohol, n-butyl alcohol (71-36-3)

butyraldehyde (123-72-8)

Butyl nitrite, n-butyl nitrite (544-16-1)

ethyl nitrite (109-95-5)

Isoamyl nitrite (110-46-3)

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n-BUTYL PHOSPHATE

Submitted by G. R. Dutton and C. R. Noller.
Checked by John R. Johnson and Anthony Hunt.

1. Procedure

In a 2-l. round-bottomed flask, fitted with a reflux condenser, liquid-sealed mechanical stirrer, dropping funnel (Note 1), and thermometer, are placed 222 g. (274 cc., 3 moles) of dry *n*-butyl alcohol, 260 g. (265 cc., 3.3 moles) of pyridine, and 275 cc. of dry benzene (Note 2). The solution is stirred and the flask is cooled in an ice-salt mixture until the temperature has fallen to −5°. With efficient stirring (Note 3), 153 g. (91 cc., 1 mole) of phosphorus oxychloride (b.p. 106–107°) is added dropwise at such a rate that the temperature does not exceed 10°. After the addition is completed the reaction mixture is heated slowly to the reflux temperature and held there for two hours. The mixture is cooled to room temperature, and 400–500 cc. of water is added to dissolve the pyridine hydrochloride (Note 4). The benzene layer is separated, washed with 100–150 cc. of water (Note 5), and dried over 20 g. of anhydrous sodium sulfate.

The benzene and other low-boiling materials are removed by distillation at 40–50 mm. pressure until the temperature of the distilling vapor reaches 90°. The *n*-butyl phosphate fraction is collected at 160–162°/15 mm., or 143–145°/8 mm., and weighs 190–200 g. (71–75 per cent of the theoretical amount) (Note 6).

2. Notes

1. The tip of the funnel should be placed sufficiently high above the surface of the reaction mixture of avoid encrustation with pyridine hydrochloride. It is advantageous to use a thermometer on which the scale above −5° is visible above the stopper; otherwise, the fog in the flask and the pyridine salt may obscure the scale.
2. The reactants and solvent were dried by distillation; fractions boiling over an interval of 1° were used.
3. The first 10–15 cc. of phosphorus oxychloride must be added very slowly to avoid vigorous reaction and overheating. It is essential to avoid an initial temperature so low that unreacted phosphorus oxychloride accumulates and then suddenly reacts with violence. The mechanical stirrer should be of such dimensions and operated at such speeds that the heat of reaction is dissipated rapidly without throwing solid material (and occluded reactants) against the upper walls of the flask.

4. About 50 per cent of the pyridine may be recovered by concentrating this aqueous solution over a steam bath, treating with strong caustic soda solution, and distilling the pyridine layer.
5. The solution should be neutral before distillation. The presence of hydrogen chloride promotes decomposition of phosphoric esters.[1] The benzene solution should not be washed with alkaline reagents, such as sodium carbonate solution, since alkaline reagents also cause decomposition during distillation.
6. This is a general method for preparing alkyl phosphates. Using a similar procedure, the *n*-propyl ester may be obtained in 60–65 per cent yields, the *sec.*-butyl ester in 40–45 per cent yields, and the *n*-amyl ester in 60–65 per cent yields.[2]

3. Discussion

n-Butyl phosphate has been prepared by the action of phosphorus pentachloride or oxychloride on butyl alcohol;[3] by the action of phosphorus oxychloride on aluminum butoxide[4] or sodium butoxide;[5] and by the oxidation of butyl phosphite.[6] The procedure described above[2] is similar to one which has been used for the preparation of alkyl phosphites.[7]

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2. Noller and Dutton, J. Am. Chem. Soc. **55**, 424 (1933).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

caustic soda

phosphorus pentachloride or oxychloride

n-propyl ester

sec.-butyl ester

n-amyl ester

hydrogen chloride (7647-01-0)

Benzene (71-43-2)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

butyl alcohol, n-butyl alcohol (71-36-3)

Phosphorus Oxychloride (21295-50-1)

pyridine (110-86-1)

aluminum butoxide

pyridine hydrochloride (628-13-7)

sodium butoxide

butyl phosphite

n-BUTYL PHOSPHATE (12788-93-1)

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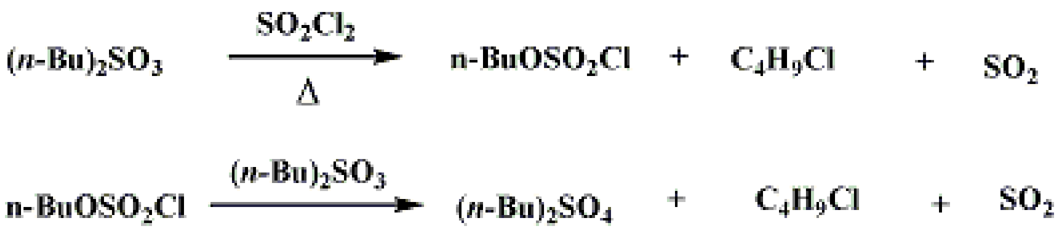
n-BUTYL SULFATE



Submitted by C. M. Suter and H. L. Gerhart.
Checked by C. R. Noller and M. Synerholm.

1. Procedure

In a 2-l. three-necked flask, fitted with a dropping funnel, mercury-sealed stirrer, and condenser, is placed 625 g. (3.2 moles) of *n*-butyl sulfite (p. 112). The condenser is connected to a gas absorption trap, and 217 g. (131 cc., 1.6 moles) of sulfuryl chloride (Note 1) is added over a period of thirty minutes, with rapid stirring and cooling with tap water. The dropping funnel is then replaced by a thermometer dipping into the liquid, and the flask is heated slowly, with stirring, until the refluxing of the butyl chloride becomes vigorous (about 100–110°). Sulfur dioxide is evolved copiously during this time. The condenser is replaced with a 40-cm. Vigreux column and downward condenser; the temperature is gradually raised to 130–135° and kept there until no more sulfur dioxide or butyl chloride distils. The heating and distillation require about two hours. The residue of crude *n*-butyl sulfate is cooled to room temperature, and 100 cc. of saturated sodium carbonate solution is added. The mixture is stirred for about ten minutes, poured into a separatory funnel, and let stand for thirty minutes to allow the layers to separate. The upper layer is dried with calcium chloride, at least overnight, and then allowed to stand over 15 g. of anhydrous sodium or potassium carbonate for a day, with occasional shaking. The product is filtered into a 500-cc. modified Claisen flask with a 25-cm. fractionating side arm, and distilled from an oil bath. The first distillation gives 250–280 g. (74–83 per cent of the calculated amount) of *n*-butyl sulfate, b.p. 110–114°/4 mm., which has a sharp odor. Redistillation gives a pure material with a slight ester odor, boiling at 109–111° at 4 mm., with only a small mechanical loss (Note 2).

2. Notes

1. Commercial sulfuryl chloride was redistilled and the fraction boiling at 69–70° was used.
2. The submitters report that *n*-propyl sulfate may be prepared in similar fashion, the yield being about 66–70 per cent. The second distillation in this case should be done through a short column to remove higher-boiling material; *n*-propyl sulfate distils at 88–91° at 4 mm.

3. Discussion

n-Butyl sulfate has been prepared by the action of *n*-butyl chlorosulfonate upon *n*-butyl orthoformate or *n*-butyl sulfite.[1] It has been obtained also by oxidation of *n*-butyl sulfite with potassium permanganate in glacial acetic acid solution.[2] The method described above appears to be the most satisfactory for laboratory-scale preparations.

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1. Levaillant, Compt. rend. **197**, 648 (1933); Barkenbus and Owen, J. Am. Chem Soc. **56**, 1204 (1934).
2. Evans, Ph.D. Dissertation, Northwestern University, 1935.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

calcium chloride (10043-52-4)

potassium carbonate (584-08-7)

acetic acid (64-19-7)

potassium permanganate (7722-64-7)

sodium carbonate (497-19-8)

sulfur dioxide (7446-09-5)

sulfuryl chloride (7791-25-5)

sodium (13966-32-0)

Butyl chloride (109-69-3)

n-butyl sulfite (626-85-7)

n-BUTYL SULFATE (15507-13-8)

n-propyl sulfate

n-butyl chlorosulfonate

n-butyl orthoformate

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Organic Syntheses, *CV 2, 112*

n-BUTYL SULFITE

Submitted by C. M. Suter and H. L. Gerhart.
Checked by C. R. Noller and M. Synerholm.

1. Procedure

In a 2-l. three-necked flask, fitted with a mercury-sealed stirrer, thermometer, condenser, and dropping funnel, is placed 684 g. (845 cc., 9.2 moles) of dry *n*-butyl alcohol (Note 1). The condenser is connected to a trap for absorbing hydrogen chloride, and 500 g. (305 cc., 4.2 moles) of thionyl chloride (Note 2) is added over a period of two hours, with stirring. The reaction mixture is kept at 35–45°, by immersing the flask in ice water, during the addition of the first half of the thionyl chloride (Note 3). After evolution of hydrogen chloride begins, the water bath is removed and a small flame applied to maintain this temperature. After all the thionyl chloride has been added the temperature is raised gradually to the boiling point, over a period of thirty minutes, to complete the reaction and remove the remainder of the hydrogen chloride. The reaction mixture is then transferred to a 1-l. modified Claisen flask with a 25-cm. fractionating side arm, and fractionated under diminished pressure. After a fore-run consisting largely of unchanged alcohol, there is obtained 625–689 g. (77–84 per cent of the calculated amount) of *n*-butyl sulfite, b.p. 109–115°/15 mm. Refractionation gives 585–674 g. (72–83 per cent) of a product distilling at 109–112° at 14 mm. (Note 4).

2. Notes

1. Commercial *n*-butyl alcohol was dried by distillation through a column; the fore-run and a small fraction collected after the vapors reached 117° were discarded.
2. Commercial thionyl chloride was redistilled, and the fraction boiling at 78–80° was employed.
3. Considerable heat is evolved until gas evolution begins, after which heat is absorbed.
4. The submitters report that *n*-propyl sulfite is obtained from *n*-propyl alcohol in somewhat smaller yields, by the same procedure.

3. Discussion

n-Butyl sulfite has been prepared from butyl alcohol and thionyl chloride by the method described,[1] and using anhydrous ether as a solvent together with dry pyridine

to take up the hydrogen chloride evolved.[2] The pyridine method has been checked, but its advantages do not offset the extra expense of the ether and pyridine used. Butyl sulfite has also been made by the action of sulfur chloride on butyl alcohol.[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 111

References and Notes

1. Voss and Blanke, Ann. **485**, 258 (1931); Barkenbus and Owen, J. Am. Chem. Soc **56**, 1204 (1934).
2. Gerrard, J. Chem. Soc. **1939**, 99.
3. Bert, Compt. rend. **178**, 1827 (1924).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrogen chloride (7647-01-0)

ether (60-29-7)

thionyl chloride (7719-09-7)

butyl alcohol, n-butyl alcohol (71-36-3)

pyridine (110-86-1)

n-propyl alcohol (71-23-8)

sulfur chloride

Butyl sulfite, n-butyl sulfite (626-85-7)

n-propyl sulfite

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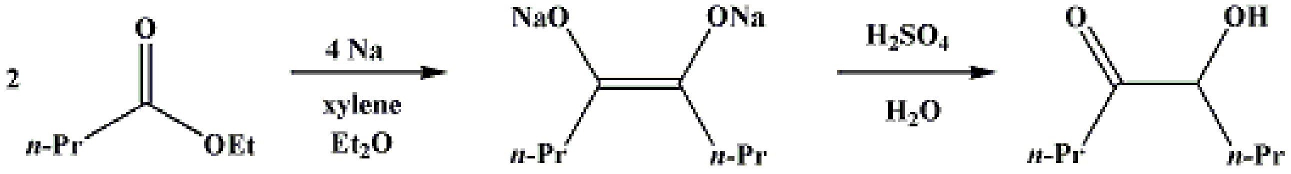
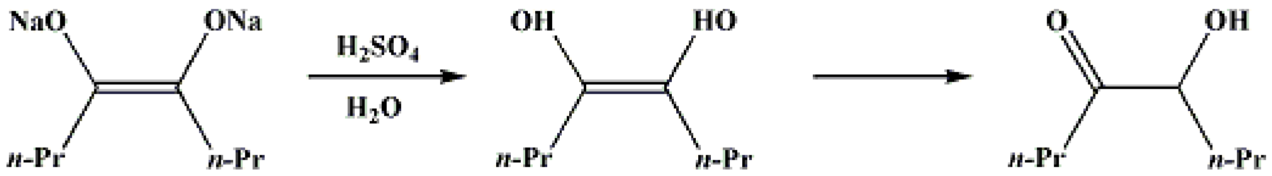
Organic Syntheses, CV 2, 114

BUTYROIN

[4-Octanone, 5-hydroxy-]





Submitted by John M. Snell and S. M. McElvain.
Checked by C. S. Marvel and M. R. Lehman.

1. Procedure

In a 3-l. three-necked, round-bottomed flask, fitted with a long reflux condenser and an efficient mechanical stirrer, are placed 92 g. (4 gram atoms) of clean metallic sodium and about 150 cc. of xylene. The sodium is finely powdered by heating the flask until the sodium melts and then cooling with very vigorous stirring. The cooled xylene is decanted, and the powdered sodium is thoroughly washed with four or five portions of dry, alcohol-free ether. About 1.2 l. of absolute ether is added (Note 1), and the flask is fitted with a reflux condenser, a 250-cc. separatory funnel, and a mechanical stirrer (Note 2).

The stirrer is started, and 232 g. (2 moles) of purified ethyl *n*-butyrate (Note 3) is slowly run in from the separatory funnel. It is advisable to add first a portion of about 25 cc.; the heat of reaction soon causes the ether to boil; the rest of the ester is then run in at such a rate that gentle ebullition is maintained. Stirring is continued until there is no further reaction and practically all the sodium has been converted into the voluminous yellow-white solid which begins to appear almost at once (Note 4).

The reaction flask is now surrounded by an ice bath, and the contents are vigorously stirred while a cooled solution of 210 g. of sulfuric acid (sp. gr. 1.84) in 350 cc. of water is carefully run in from the separatory funnel. The stirrer is now removed and the flask is allowed to stand in the ice bath until the lower layer of hydrated sodium sulfate ($Na_2SO_4 \cdot 10H_2O$) has solidified. The ether solution is decanted and the sodium sulfate crystals washed with 100–200 cc. of ether.

The combined solution and washings are shaken with about 100 cc. of 20 per cent sodium carbonate solution (Note 5) and are then dried over anhydrous potassium carbonate. The ether and alcohol are removed rapidly by distillation, and the residue is fractionated under reduced pressure in a 250-cc. modified Claisen flask (Note 6). The main fraction boils at 80–86° at 12 mm.; a fraction boiling up to about 15° above the main fraction should also be collected. The low-boiling and high-boiling fractions can be refractionated for recovery of a small additional amount of butyroin. The total yield is 94–101 g. (65–70 per cent of the theoretical amount) of product that is

colored yellow by traces of the diketone (Note 7) and (Note 8).

2. Notes

1. The reaction can be run in benzene, but it is much slower than in ether.
2. For powdering the sodium a small, rapid stirrer is best; for stirring the reaction mixture, a fairly large, slower stirrer is best.
3. The ester is purified as follows: It is washed once with 10 per cent sodium carbonate solution and twice with an equal volume of saturated sodium chloride solution; it is then dried twenty-four hours over anhydrous potassium carbonate. The potassium carbonate is filtered and the ester allowed to stand overnight with about 2 per cent of its weight of phosphorus pentoxide. The ester is then distilled through a column directly from the phosphorus pentoxide; a fraction that distils over a range of 2 degrees or less should be taken. Lower yields of butyroin may be obtained from less carefully purified ester.
4. Addition of the ester requires one and one-half to two hours, and the mixture should then be refluxed an hour longer.
5. Small amounts of butyric acid and dipropylglycollic acid are present in the reaction mixture.
6. The ether should be removed rapidly and the distillation should not be too slow, for long heating favors the formation of a high-boiling by-product of unknown structure at the expense of the butyroin.
7. Usually the amount of diketone present is negligible. The diketone may be removed by shaking the butyroin vigorously from time to time during one hour with 100 cc. of a saturated sodium bisulfite solution, washing with strong sodium chloride solution, and then redistilling.
8. These directions have been used for the following acyloins:

Propionoin b.p. 60–65°/12 mm.; 50–55 per cent yield.
Isobutyroin b.p. 70–75°/14 mm.; 70–75 per cent yield.
Pivaloin m.p. 80–81°; b.p. 85–95°/12 mm.; 52–60 per cent yield

3. Discussion

Aliphatic acyloins can be obtained by the saponification of the reaction product of sodium on moist ethereal solutions of acid chlorides, the first product being the diester of the dienolic modification of the acyloin.[1] Of greater preparative interest, however, is the reaction between ethereal solutions of aliphatic esters and sodium[2] or potassium.[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 95

References and Notes

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3. Scheibler and Emden, Ann. **434**, 265 (1923).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

Benzene (71-43-2)

ether (60-29-7)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

sodium bisulfite (7631-90-5)

sodium, metallic sodium (13966-32-0)

butyric acid (107-92-6)

potassium (7440-09-7)

xylene (106-42-3)

Butyroin, 4-Octanone, 5-hydroxy- (496-77-5)

dipropylglycollic acid

Propionoin (4984-85-4)

Isobutyroin (815-77-0)

Pivaloin (815-66-7)

ethyl n-butyrate (105-54-4)

phosphorus pentoxide (1314-56-3)

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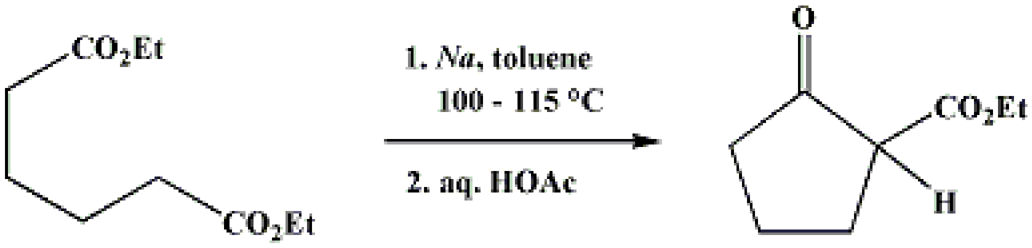
Organic Syntheses, CV 2, 116

2-CARBETHOXYCYCLOPENTANONE

[Cyclopentanecarboxylic acid, 2-oxo-, ethyl ester]



Submitted by P. S. Pinkney
Checked by Louis F. Fieser and T. L. Jacobs.

1. Procedure

A 3-l. three-necked, round-bottomed flask is fitted with a mercury-sealed mechanical stirrer (Note 1), a 250-cc. dropping funnel, and a reflux condenser protected from the air by means of a calcium chloride tube. In the flask are placed 23 g. (1 gram atom) of sodium and 250 cc. of dry toluene (Note 2). The stirrer is started, and 202 g. (1 mole) of ethyl adipate (p. 264) is added from the dropping funnel at such a rate that the addition is complete in about two hours. The reaction usually starts immediately on addition of the ethyl adipate. The temperature of the oil bath is maintained at 100–115° during the addition and for about five hours longer. Dry toluene is added through the condenser from time to time in order to keep the reaction mixture fluid enough for efficient stirring (Note 3). Between 750 cc. and 1 l. of toluene is added in this manner.

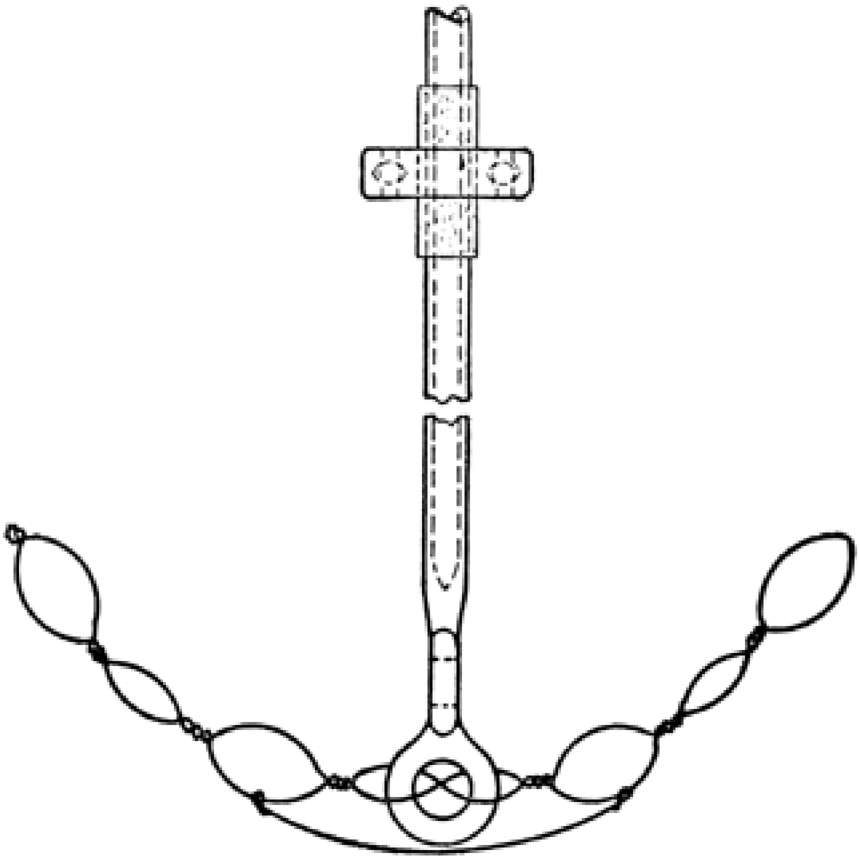
The reaction mixture is cooled in an ice bath and slowly poured into 1 l. of 10 per cent acetic acid cooled to 0° (ice-salt mixture). The toluene layer is separated, washed once with water, twice with cooled 7 per cent sodium carbonate solution, and again with water. The toluene is removed by distillation at ordinary pressure, and the residue is distilled under reduced pressure. The yield is 115–127 g. (74–81 per cent of the theoretical amount) of a product boiling at 83–88°/5 mm. or 79–84°/3 mm. (Note 4) and (Note 5).

2. Notes

1. The Hershberg[1] stirrer, shown in part in f.htmig. 4, provides very efficient agitation of this or other pasty mixtures. Two glass rings are sealed to the end of a stirrer shaft at right angles to one another, and each is threaded with B. and S. No. 18 Chromel or Nichrome wire (in the drawing the wire is shown only for the lower ring; the upper wire is not provided with a cross brace). The stirrer is easily introduced and removed through a narrow opening, and in operation it follows the contour of the flask. It is convenient to use glass tubing for the

stirrer shaft and to provide it with a pair of small ball bearings slipped on over short sections of rubber tubing (one of these bearings is shown in the drawing).

Fig. 4



The yields reported were obtained using this stirrer; with various other stirrers it was seldom possible to duplicate the results.

2. The toluene is dried by distillation from sodium.

3. If the reaction mixture is allowed to become too thick for efficient stirring, or if the temperature of the oil bath is raised above 115–120°, the solid sodium derivative will cake on the sides of the flask. This makes the complete removal of the reaction mixture from the flask and the decomposition of the sodium derivative more difficult.

4. According to the literature,[2], [3] the product obtained in this manner may contain ethyl adipate. To remove this, the product is cooled to 0° and run slowly into 600 cc. of 10 per cent potassium hydroxide solution maintained at 0° with ice-salt. Water is added until the salt which separates has dissolved, and the cold alkaline solution is extracted twice with 200-cc. portions of ether. The alkaline solution, kept at 0°, is run slowly into 900 cc. of 10 per cent acetic acid solution with stirring, the temperature remaining below 1° (ice-salt). The oil which separates is taken up in 400 cc. of ether, and the aqueous solution is extracted with four 250-cc. portions of ether. The ether extract is washed twice with cold 7 per cent sodium carbonate solution and dried over sodium sulfate. After removal of the ether the residue is distilled, b.p. 79–81°/3 mm. The recovery is only 80–85 per cent, and in a well-conducted preparation the ethyl adipate

eliminated amounts to less than 1 per cent of the total product. Unless the preparation has proceeded poorly the tedious purification ordinarily is best omitted.

If material free from all traces of ethyl adipate is desired, time and material can be saved by omitting the first distillation (observation of the checkers). The toluene solution of the crude 2-carbethoxycyclopentanone is cooled to 0° and added slowly with stirring to 300 cc. of 10 per cent potassium hydroxide solution maintained below 1°. Cold water is added until the slightly soluble potassium salt has dissolved. The toluene layer is then separated and washed twice with 150-cc. portions of cold, 10 per cent potassium hydroxide solution. After each washing, cold water is added to dissolve any solid which separates. The toluene solution, now very light yellow in color, is finally washed twice with 150-cc. portions of cold water. The aqueous solutions are combined, extracted with 250 cc. of ether, and treated as described for the alkaline solution above. The yield is 100–115 g. (64–74 per cent).

5. The following procedure gives slightly better yields.

A 3-l. round-bottomed flask, which contains 50 g. of "molecular" sodium, is fitted with a reflux condenser protected from the air by means of a calcium chloride tube, and 1250 cc. of benzene, dried by distilling over sodium, is added. Three hundred and three grams (1.5 moles) of ethyl adipate is then added, in one lot, followed by 3 cc. of absolute alcohol. The flask is warmed on the steam bath until, after a few minutes, a vigorous reaction commences and a cake of the sodio-compound begins to separate. During this stage the flask is kept well shaken by hand. After the spontaneous reaction has abated, the mixture is refluxed on the steam bath overnight, then cooled in ice. The product is decomposed with ice and 6 *N* hydrochloric acid, the acid being added until Congo red paper is turned blue. The benzene layer is separated, and the aqueous layer is extracted once with 200 cc. of benzene. The united extract is washed with 200 cc. of 5 per cent sodium carbonate solution and 300 cc. of water. The solution is placed in a 3-l. distilling flask and the benzene and water are removed by distillation under ordinary pressure. The residue is fractionated under reduced pressure. The yield is 185–192 g. (79–82 per cent of the theoretical amount) of a product boiling at 108–111°/15 mm. On redistillation the product boils at 102°/11 mm.

The significant features of this procedure are the addition of alcohol, which eliminates or greatly reduces the induction period, and the excess of sodium, which contributes to the completeness of the reaction. The benzene, used as a solvent, may be replaced by petroleum ether (b.p. 60–80°).

The once-distilled carbethoxycyclopentanone is sufficiently pure for ordinary synthetic purposes; it gives a 93 per cent yield of the Cmethyl derivative. (R. P. Linstead and E. M. Meade, private communication.[4] Checked by R. L. Shriner and N. S. Moon.)

3. Discussion

2-Carbethoxycyclopentanone has been prepared from ethyl adipate by the action of sodium,[5], [2], [3], [4] sodamide,[6] and sodium ethoxide.[7] The method in the above procedure is based upon the work of Cornubert and Borrel.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 57
- Org. Syn. Coll. Vol. 2, 128
- Org. Syn. Coll. Vol. 2, 139
- Org. Syn. Coll. Vol. 2, 539
- Org. Syn. Coll. Vol. 3, 3
- Org. Syn. Coll. Vol. 3, 16
- Org. Syn. Coll. Vol. 3, 121
- Org. Syn. Coll. Vol. 4, 68
- Org. Syn. Coll. Vol. 4, 313
- Org. Syn. Coll. Vol. 4, 771
- Org. Syn. Coll. Vol. 4, 866
- Org. Syn. Coll. Vol. 5, 76
- Org. Syn. Coll. Vol. 5, 121
- Org. Syn. Coll. Vol. 5, 300
- Org. Syn. Coll. Vol. 5, 424
- Org. Syn. Coll. Vol. 5, 572
- Org. Syn. Coll. Vol. 5, 966
- Org. Syn. Coll. Vol. 8, 522

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1. Hershberg, Ind. Eng. Chem., Anal. Ed. **8**, 313 (1936).
2. Cornubert and Borrel, Bull. soc. chim. (4) **47**, 301 (1930).
3. Bouveault, ibid. (3) **21**, 1019 (1899); Zelinsky and Ouchakoff, ibid. (4) **35**, 484 (1924).
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5. van Rysselberge, Bull. acad. roy. Belg. (Sci.) [5] **12**, 171 (1926); (Chem. Zentr. **1926**, 11, 1846).
6. Bouveault and Locquin, Bull. soc. chim. (4) **3**, 440 (1908).
7. Wislicenus and Schwanhäusser, Ann. **297**, 112 (1897).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

alcohol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

ether (60-29-7)

Ethyl adipate (626-86-8)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

potassium hydroxide (1310-58-3)

toluene (108-88-3)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

2-Carbethoxycyclopentanone, Cyclopentanecarboxylic acid, 2-oxo-, ethyl ester, carbethoxycyclopentanone (611-10-9)

sodamide (7782-92-5)

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Organic Syntheses, CV 2, 120

CASEIN

Submitted by E. J. Cohn and J. L. Hendry.
Checked by H. T. Clarke and W. M. Kennan.

1. Procedure

To 1 l. of milk, from which the cream has been largely separated (Note 1), 0.05 *M* hydrochloric acid is slowly added, with stirring, through a capillary tube extending to the bottom of the beaker. The addition is continued until the solution attains a *p*H of 4.6 (Note 2). The end point is determined by withdrawing 5-cc. samples, diluting to 50 cc., adding methyl red, and matching against a buffered series (Note 3). Approximately 1 l. of acid is required; the separation of the casein is practically complete at this point. Three liters of water is then added, stirring is discontinued, and the flocculent precipitate of casein is allowed to settle in the refrigerator for twelve to twenty-four hours. The clear supernatant liquid which contains soluble proteins and salts is removed as completely as possible by siphoning; the precipitate is collected on a suction funnel and washed with cold distilled water until the washings are free of calcium (give no precipitate with ammonium oxalate).

The casein, which is contaminated with calcium phosphate and fats, is filtered to as small a volume as possible (about 500 cc.) and transferred to a 2-l. beaker. It is then treated with 0.1 *M* sodium hydroxide, the alkali being added slowly and with stirring through a capillary extending to the bottom of the beaker (Note 4). The addition of alkali is continued until the *p*H of the mixture reaches 6.3 (Note 5); 100–150 cc. of the alkali is required. The end point is determined by matching against a buffered series (Note 6), employing dibromo-*o*-cresolsulfonphthalein ("bromocresol purple"). At this *p*H the casein is completely in solution in the form of its sodium salt; fats, calcium phosphate, and any calcium caseinate remain undissolved. Care must be taken not to add more alkali than is necessary to bring the *p*H to the above point (Note 4). The milky solution is filtered through a thick layer (10–15 mm.) of filter paper pulp tightly packed upon a suction funnel. The filtrate may be slightly opalescent; if it is less clear it is again filtered through a fresh layer of pulp.

The filtrate is brought to a *p*H of 4.6 with 0.05 *M* hydrochloric acid just as in the original precipitation, the necessary amount of acid being determined by titration of an aliquot portion, diluted fivefold, with 0.01 *M* hydrochloric acid; 220–250 cc. of 0.05 *M* acid is required. As the reprecipitation progresses, the rate at which the acid is added is decreased in order to prevent precipitation at the tip of the capillary tube; vigorous mechanical stirring is, of course, essential. When the acidification is complete, 5 l. of cold distilled water is added and the flocculent precipitate allowed to settle in the refrigerator. After siphoning off the clear supernatant liquid, the casein is collected on a suction funnel, using hardened paper, washed with cold distilled water until free of chloride, sucked as dry as possible, and dried over calcium chloride in a vacuum desiccator. The yield is 23–29 g. of a colorless coherent product which may readily be

pulverized in a mortar.

2. Notes

1. The cream is satisfactorily removed by allowing the milk to stand in a refrigerator overnight and siphoning off the lower layer.
2. Casein exists in milk in the form of a calcium derivative; *p*H 4.6 is the isoelectric point of free casein, which is soluble to the extent of only 0.11 g. per liter.[1]
3. Buffers for this range may be made up as follows:

0.1 *M* Acetic Acid	0.1 *M* Sodium Acetate	*p*H
7.35 cc.	2.65 cc.	4.2
6.3	3.7	4.4
5.1	4.9	4.6
4.0	6.0	4.8
2.95	7.05	5.0

4. It is important to avoid a local excess of alkali, which would tend to denature the casein.[2]
5. At this *p*H sodium caseinate is largely dissolved, whereas calcium caseinate is largely undissolved.[3]
6. The buffer series may conveniently be prepared as follows:

Disodium Phosphate (*M*/15)	Monopotassium Phosphate (*M*/15)	*p*H
0.78 cc.	9.22 cc.	5.8
1.2	8.8	6.0
1.85	8.15	6.2
2.65	7.35	6.4
3.75	6.25	6.6
5.0	5.0	6.8

3. Discussion

The precipitation of casein in its uncombined form by the addition to milk of one or another acid forms the basis of all methods of preparation. These differ widely, however, in the subsequent purification. In the method of Hammarsten,[4] just enough alkali is added to dissolve this casein completely. The alkalinity reached in this process somewhat modifies its physical properties but probably not its composition. In the method of Van Slyke and Bosworth[5] the last trace of calcium is removed by adding oxalate to an ammoniacal solution of the casein, but this procedure was shown to be unnecessary by Van Slyke and Baker.[6]

The present process is based in large part upon that of Van Slyke and Baker, the

modifications depending upon the observation that casein forms far more soluble compounds with univalent than with bivalent bases at neutral reactions.

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Methyl Red

casein

calcium caseinate

sodium caseinate

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

sodium acetate (127-09-3)

sodium hydroxide (1310-73-2)

calcium (7440-70-2)

calcium phosphate

oxalate

ammonium oxalate (1113-38-8)

chloride

bromocresol

Disodium Phosphate (7558-79-4)

Monopotassium Phosphate (7778-77-0)

dibromo-o-cresolsulfonphthalein

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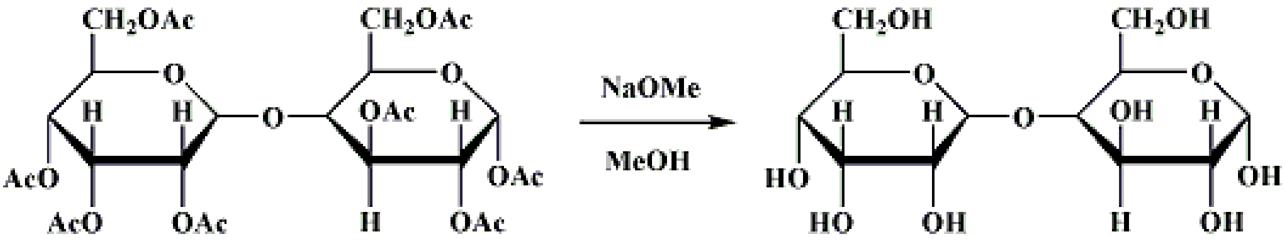
Organic Syntheses, CV 2, 122

CELLOBIOSE



Submitted by Géza Braun
Checked by Reynold C. Fuson, William E. Ross, and William P. Campbell.

1. Procedure

In a 500-cc. three-necked flask, provided with a mercury-sealed stirrer and a calcium chloride tube, 68 g. (0.1 mole) of α-cellobiose octaacetate, m.p. 220–222° (p. 124), is suspended in 300 cc. of absolute methyl alcohol. A solution, prepared by dissolving 0.25 g. (0.01 gram atom) of sodium in 50 cc. of methyl alcohol, is added, and the mixture is stirred vigorously for one hour at room temperature (Note 1). The mixture becomes thin as the hydrolysis proceeds and the solvent acquires a slight color. After the time specified the crystalline solid is collected by suction filtration, washed with four 25-cc. portions of methyl alcohol, and dried at 40°. The weight of the nearly colorless crude cellobiose corresponds closely to the theoretical amount (34 g.). For purification it is dissolved in 125 cc. of hot water containing a few drops of glacial acetic acid, and the solution is clarified with 1–2 g. of Norite and filtered by suction. The colorless filtrate is concentrated under reduced pressure to a small volume, continuing until a large portion of the cellobiose has crystallized, and the crystalline magma is washed into an Erlenmeyer flask with 100 cc. of methyl alcohol. The mixture is stirred well and allowed to stand for several hours for completion of the crystallization, and the sugar is collected on a Büchner funnel, washed with 25 cc. of methyl alcohol, and dried at 40°. The yield of pure cellobiose, $[\alpha]_D^{20°}$ + 34.8° (in 6 per cent aqueous solution), is 31 g. (91 per cent of the theoretical amount). On concentrating the mother liquor to a small volume and adding alcohol as before, 1 g. of equally pure product is obtained, making the total yield 94 per cent of the theoretical amount (Note 2).

2. Notes

1. The reaction may be carried out equally satisfactorily by shaking the mixture mechanically in a stoppered bottle.

2. Using an earlier procedure,[1] in which a solution of the octaacetate in chloroform is treated with sodium methoxide solution and then with water, the yields of pure cellobiose amounted to 67–79 per cent of the theoretical quantity.

3. Discussion

Cellobiose was prepared first by Skraup and König[2] by the saponification of the octaacetate with alcoholic potassium hydroxide, and the method was improved by Pringsheim and Merkatz.[3]

Aqueous barium hydroxide also has been employed[4] for the purpose, and methyl alcoholic ammonia has been used extensively for the hydrolysis of carbohydrate acetates. The method of catalytic hydrolysis with a small quantity of sodium methoxide was introduced by Zemplén,[1] who considered the action to be due to the addition of the reagent to the ester-carbonyl groups of the sugar acetate and the decomposition of the addition compound by reaction with alcohol.[5] The present procedure, reported by Zemplén, Gerecs, and Hadácsy,[6] is a considerable improvement over the original method[1] (see (Note 2)).

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 350

References and Notes

1. Zemplén, Ber. **59**, 1254 (1926).
2. Skraup and König, ibid. **34**, 1115 (1901).
3. Pringsheim and Merkatz, Z. physiol. Chem. **105**, 173 (1919).
4. Abderhalden and Zemplén, ibid. **72**, 58 (1911).
5. Zemplén and Kunz, Ber. **56**, 1705 (1923).
6. Zemplén, Gerecs, and Hadácsy, ibid. **69**, 1827 (1936).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

acetic acid (64-19-7)

methyl alcohol (67-56-1)

chloroform (67-66-3)

sodium methoxide (124-41-4)

Norite (7782-42-5)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

barium hydroxide (17194-00-2)

CELLOBIOSE (528-50-7)

α-Cellobiose octaacetate (5346-90-7)

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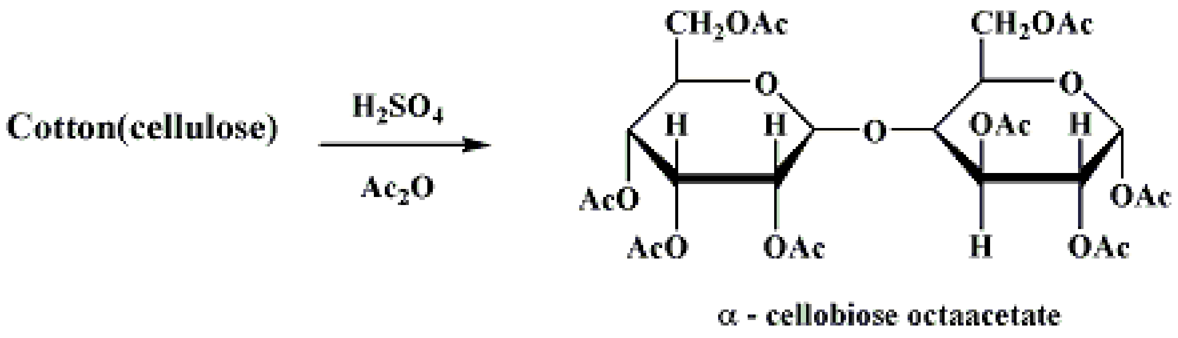
Organic Syntheses, CV 2, 124

α-CELLOBIOSE OCTAACETATE



Submitted by Géza Braun
Checked by Reynold C. Fuson, William E. Ross, and William P. Campbell.

1. Procedure

In a 1-l. wide-mouthed bottle with a glass stopper, 400 cc. of acetic anhydride is cooled to −10° in a freezing mixture and 36 cc. of concentrated sulfuric acid is added at once with constant stirring. The temperature of the solution rises to about 20°. The bottle is removed from the freezing mixture, and 20 g. of absorbent cotton (Note 1) is worked into the liquor immediately with a heavy glass rod. With constant stirring, the bottle is warmed in a water bath maintained at 60° until the temperature of the mixture reaches 45° (about ten minutes), and then it is removed and the temperature is kept from rising above 55° by suitable cooling with running water, stirring being continued throughout (Note 2). After about twenty minutes (total) the mixture becomes thin; at this point it is cooled to 50° and a second 20-g. portion of cotton is added with stirring, the temperature again being kept from rising above 55°. The process of cooling to 50° and adding 20 g. of cotton is repeated at intervals of about ten minutes until 100 g. of cotton in all has been introduced. After the final addition stirring is continued until the mixture becomes thin (about ten minutes); then the bottle is stoppered and heated in a bath maintained at 50° for one hour, during which time the cotton dissolves completely to a thin, light brown syrup. The stoppered container is kept in an oven at 35° for seven days.

The solution darkens to a deep wine-red color, and α-cellobiose octaacetate begins to crystallize on the second day (Note 3). After seven days at 35° the semi-crystalline mass is stirred into 0 l. of cold water. With good stirring the flocculent precipitate of α-cellobiose octaacetate and cellulose-dextrin acetates soon becomes crystalline; after standing for one to two hours the solid is collected on a 12.5-cm. Büchner funnel, washed free from acid with cold water, and drained thoroughly. The moist product, weighing about 250 g., is triturated with 250 cc. of warm methyl alcohol, and, after cooling to room temperature, the undissolved solid is collected on a 7-cm. Büchner funnel, washed with three 50-cc. portions of methyl alcohol, and dried at 40°. The yield of fairly pure α-cellobiose octaacetate is 69–74 g. For purification it is dissolved

in 300 cc. of chloroform and the solution is filtered by suction into a dry receiver through a pad prepared by dusting Norite onto a Büchner funnel and washing the funnel with alcohol. The chloroform solution is filtered while the pad is still wet with alcohol, and the filter is washed at once with 100 cc. of chloroform without interruption in the filtration. The colorless filtrate is concentrated at reduced pressure until the acetate begins to crystallize (about 250 cc.), the crystals are redissolved by warming, and the solution is poured into 750 cc. of warm methyl alcohol. The acetate begins to crystallize at once as small needles which eventually form a thick paste. The mixture is cooled to 0° with stirring, and after about one hour the material is collected, washed with 100 cc. of methyl alcohol, and dried at 40°. The yield of colorless α-cellobiose octaacetate, m.p. 220–222°, $[\alpha]_D^{20°}$ + 41.6°, is 65–69 g. (35–37 per cent of the theoretical amount, assuming that the cotton contains 10 per cent of moisture) (Note 4), (Note 5), and (Note 6).

For further purification a solution of the material in 350 cc. of chloroform is clarified if necessary and poured into 750 cc. of methyl alcohol, and the mixture is cooled to 0°. The yield of the pure acetate, m.p. 225–226°, $[\alpha]_D^{20°}$ + 42.5°, is 61–65 g. The constants are not altered by further crystallizations.

2. Notes

1. Pure commercial cotton or filter paper may be used. These materials ordinarily contain 7–10 per cent of moisture.
2. Effective stirring and careful control of the reaction are essential to obtain good yields. If left uncontrolled, the temperature may rise quickly above 100° with considerable decomposition.
3. The crystallization is accelerated by scratching the walls of the jar or by seeding. Seed is obtained easily by pouring a small portion of the reaction mixture into a large amount of water; the precipitate is separated, treated with alcohol, and dried at 40°.
4. In earlier experiments a temperature of 30–40° was maintained during the addition of the cotton (which then required more time), and the acetolysis was allowed to proceed at room temperature for six days. The yield of product melting at 220–222° was 50–56 g., but rose to 62–70 g. when the period of digestion was extended to eight days.
5. The quantities can be doubled without change in the procedure or the percentage yield.
6. Pringsheim's method[1] of isolating the acetate gives equally good results. Instead of pouring the acetolysis mixture into water, it is kept at 0° for one to two days and the crystalline material is collected on a large Büchner funnel and washed with 50 cc. of ice-cold acetic anhydride. Cellulose-dextrin acetates and other by-products pass into the filtrate. The crude mass is digested with 200 cc. of warm methyl alcohol, collected, and crystallized from chloroform-alcohol as above. The yield is 65–68 g., m.p. 220–222°.

3. Discussion

The preparation of α-cellobiose octaacetate by the acetolysis of cellulose was discovered by Franchimont,[2] and the process has been studied carefully by a number of other investigators.[1], [3], [4], [5] The observations of Freudenberg[4] and Klein[5] were particularly useful in developing the present procedure.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 122

References and Notes

1. Pringsheim and Merkatz, Z. physiol. Chem. **105**, 173 (1919).
2. Franchimont, Ber. **12**, 1941 (1879).
3. Skraup and König, Monatsh. **22**, 1011 (1901); Maquenne and Goodwin, Bull. soc. chim. (3) **31**, 854 (1904); Schliemann, Ann. **378**, 366 (1911); Ost, ibid. **398**, 332 (1913).
4. Freudenberg, Ber. **54**, 767 (1921).
5. Klein, Z. angew. Chem. **25**, 1409 (1912).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Cellulose-dextrin acetates

cellulose

sulfuric acid (7664-93-9)

methyl alcohol (67-56-1)

acetic anhydride (108-24-7)

chloroform (67-66-3)

Norite (7782-42-5)

chloroform-alcohol

α-Cellobiose octaacetate (5346-90-7)

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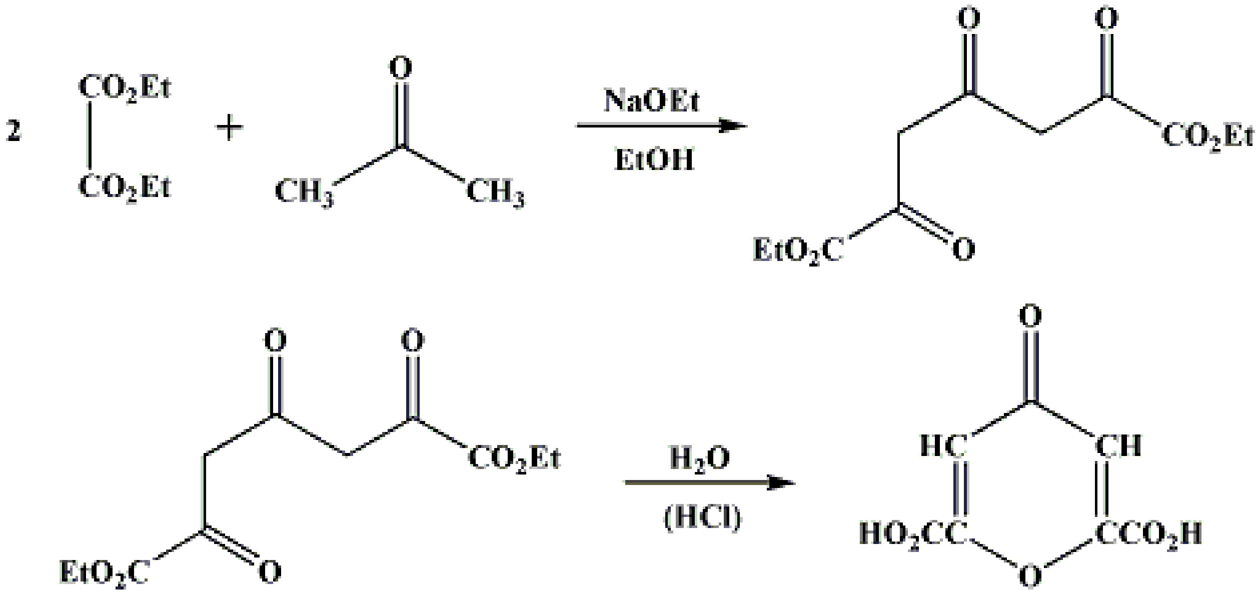
Organic Syntheses, CV 2, 126

CHELIDONIC ACID



Submitted by E. Raymond Riegel and F. Zwilgmeyer.
Checked by Reynold C. Fuson and William E. Ross.

1. Procedure

In a 1-l. round-bottomed flask, fitted with a reflux condenser protected by a calcium chloride tube, 46 g. (2 gram atoms) of sodium is dissolved in 600 cc. of absolute alcohol (Note 1). About one hour is required for the addition of the sodium, and another hour for its complete solution. Toward the end of the reaction the flask may be heated with a small smoky flame. While the sodium is being dissolved, the following materials are weighed in dry, stoppered containers: 58 g. (1 mole) of dry acetone (Note 2), 150 g. (1.03 moles) of freshly distilled ethyl oxalate (Org. Syn. Coll. Vol. I, **1941**, 261), and 160 g. (1.1 moles) of ethyl oxalate.

About half of the sodium ethoxide solution is poured into a 3-l. round-bottomed, three-necked flask provided with a liquid-sealed stirrer and a reflux condenser; the other half is kept warm by a small flame. The first half of the solution is allowed to cool until a solid begins to appear, then 58 g. of dry acetone mixed with 150 g. of ethyl oxalate is added at once and the stirrer is set in motion. Heat is evolved, and the liquid turns brown but remains clear. As soon as any turbidity appears, the other half of the hot sodium ethoxide solution is poured into the mixture together with 160 g. of ethyl oxalate, the two streams being allowed to mix as they flow into the flask. The liquid initially is clear and of a deep brown color, but after stirring for about thirty minutes the mixture becomes practically solid. The flask is then connected with a condenser for distillation and heated in an oil bath at 110° until 150 cc. of alcohol has distilled. The flask is protected by a calcium chloride tube and the reaction mixture is cooled to 20°. The sodium derivative is removed to a 3-l. beaker by means of a glass rod and

treated with a mixture of 300 cc. of concentrated hydrochloric acid (sp. gr. 1.19) and 800 g. of cracked ice (Note 3). All lumps are carefully crushed, and the creamy yellow suspension of acetonedioxalic ester is collected on a 15-cm. Büchner funnel. The ester is removed from the filter, stirred with about 100 cc. of ice water, and again collected (Note 4). For hydrolysis the crude material is heated with 300 cc. of concentrated hydrochloric acid in a 5-l. flask (Note 5) on the steam bath for twenty hours. After cooling to 20° the solid hydrated acid is collected on a 10-cm. Büchner funnel, washed with two 50-cc. portions of ice water, and dried, first at 100° for two hours, and then at 160° to constant weight to remove the water of crystallization. The yield of product decomposing at 257° (corr.) is 140–145 g. (76–79 per cent of the theoretical amount).

2. Notes

1. A good grade of absolute alcohol should be used (Org. Syn. Coll. Vol. I, **1941**, 259).
2. The acetone is dried for several days over calcium chloride, filtered, and distilled. Some acetone is lost in this operation by combination with the calcium chloride.[1]
3. The temperature must be kept as low as possible during the neutralization, for any undue rise in temperature results in a darkening of the product.
4. The crude ester, after a further washing and after drying in a vacuum desiccator over sulfuric acid, melts at 98–100° and weighs 220 g. (85 per cent of the theoretical amount).
5. A large flask is used because the mixture froths seriously at first. If the frothing becomes troublesome it may be stopped by adding a little ether.

3. Discussion

Natural chelidonic acid is obtained from the herb celandine (*Chelidonium majus*). The synthesis from ethyl oxalate and acetone was first described by Claisen;[2] the process was simplified by Willstätter and Pummerer[3] and further improved by Ruzicka and Fornasir.[4] The present procedure is modeled after that of the last-mentioned investigators.

References and Notes

1. Bagster, J. Chem. Soc. **111**, 494 (1917).
2. Claisen, Ber. **24**, 111 (1891).
3. Willstätter and Pummerer, ibid. **37**, 3744 (1904).
4. Ruzicka and Fornasir, Helv. Chim. Acta **3**, 811 (1920).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alcohol (64-17-5)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ether (60-29-7)

acetone (67-64-1)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

Ethyl oxalate

Chelidonic acid (99-32-1)

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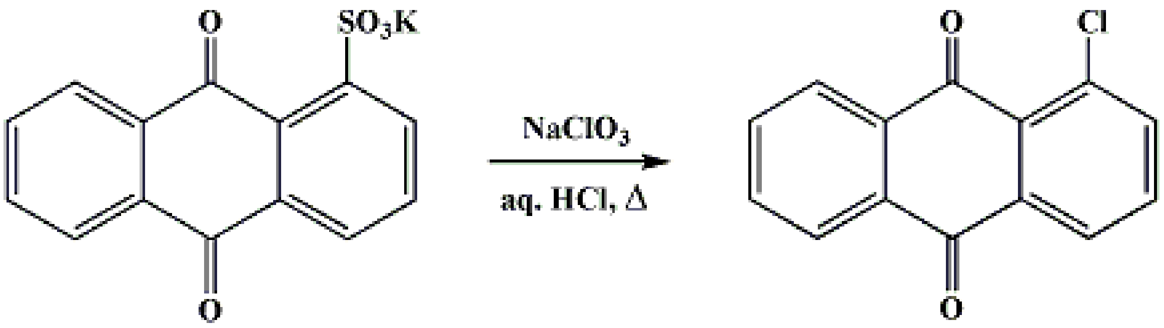
α-CHLOROANTHRAQUINONE

[Anthraquinone, 1-chloro-]



Submitted by W. J. Scott and C. F. H. Allen.
Checked by Louis F. Fieser and E. B. Hershberg.

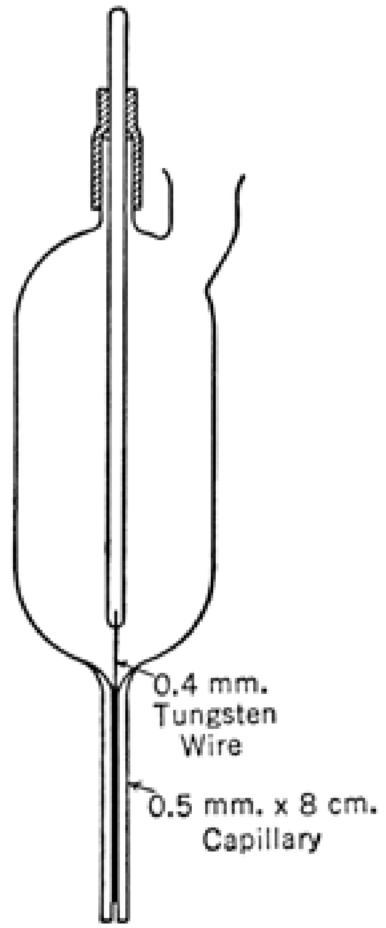
1. Procedure

A 2-l. three-necked flask fitted with a stirrer (Note 1) and (Note 2), condenser, and dropping funnel (Note 3) is mounted in the hood, and in it are placed 20 g. (0.061 mole) of potassium anthraquinone-α-sulfonate (p. 539), 500 cc. of water, and 85 cc. (1 mole) of concentrated hydrochloric acid. The solution is heated to boiling and stirred, while a solution of 20 g. (0.19 mole) of sodium chlorate (Note 4) in 100 cc. of water is added dropwise over a period of three hours (Note 5). The mixture is refluxed very slowly for an additional hour before the precipitated α-chloroanthraquinone is collected by suction filtration and washed free from acid with hot water (about 350 cc.). After drying *in vacuo* at 100°, the bright yellow product melts at 158–160° (corr.) and weighs 14.6–14.7 g. (97–98 per cent of the theoretical amount) (Note 6) and (Note 7).

2. Notes

1. Since the mixture tends to foam toward the end of the reaction, it is advisable to use an effective stirrer. A Hershberg stirrer (p. 117) of tantalum wire gave good service in the hands of the checkers; the metal was not appreciably attacked after repeated use.
2. Although a glass sleeve for the stirrer is fairly satisfactory, it is better to use a seal of the conventional type (Org. Syn. Coll. Vol. I, **1941**, 33, Fig. 2a) filled with water rather than mercury.
3. Since the usual dropping funnel has the disadvantage of requiring considerable attention from the operator, the checkers found it much more convenient to employ the device (of E. B. H.) shown in f.htmig. 5.

Fig. 5



4. Potassium chlorate is less satisfactory because of its lower solubility.

5. If the addition is too rapid or the boiling too vigorous, chlorinating gases are lost through the condenser.

6. Crystallization of the product from 200 cc. of *n*-butyl alcohol gives 13.4 g. of material in the form of yellow needles, m.p. 161–162° (corr.). Larger amounts are conveniently crystallized from toluene, using 2 cc. per gram.

7. The melting point given for highly purified α-chloroanthraquinone is 162.5° (corr.). The possible contaminants include the β-isomer, 1,5-, and 1,8-dichloroanthraquinone, all of which melt at higher temperatures but depress the melting point of the α-monochloro compound.

3. Discussion

α-Chloroanthraquinone has been prepared from α-aminoanthraquinone by the diazo reaction,[1] by the action of thionyl chloride on potassium anthraquinone-α-sulfonate under pressure,[2] and by the above process.[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 539
- Org. Syn. Coll. Vol. 3, 573
- Org. Syn. Coll. Vol. 4, 68

- Org. Syn. Coll. Vol. 4, 746
- Org. Syn. Coll. Vol. 4, 840

References and Notes

1. Bayer and Company, Ger. pat. 131,538 [Frdl. **6**, 311 (1900–02)]; Groggins, "Unit Processes in Organic Syntheses," p. 175, McGraw-Hill Book Company, New York, 1935.
2. Meister, Lucius, and Brüning, Ger. pat. 267,544 (Chem. Zentr. **1914**, I, 89).
3. Bayer and Company, Ger. pat. 205,195 (Chem. Zentr. **1909**, I, 414); Badische Anilin- und Soda-Fabrik, Ger. pat. 228,876 (Chem. Zentr. **1911**, I, 102); Ullmann and Ochsner, Ann. **381**, 1 (1911).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

1,5-, and 1,8-dichloroanthraquinone

hydrochloric acid (7647-01-0)

thionyl chloride (7719-09-7)

mercury (7439-97-6)

n-butyl alcohol (71-36-3)

toluene (108-88-3)

sodium chlorate (7775-09-9)

potassium chlorate (3811-04-9)

α-Chloroanthraquinone, Anthraquinone, 1-chloro- (82-44-0)

Potassium anthraquinone-α-sulfonate (30845-78-4)

α-aminoanthraquinone (82-45-1)

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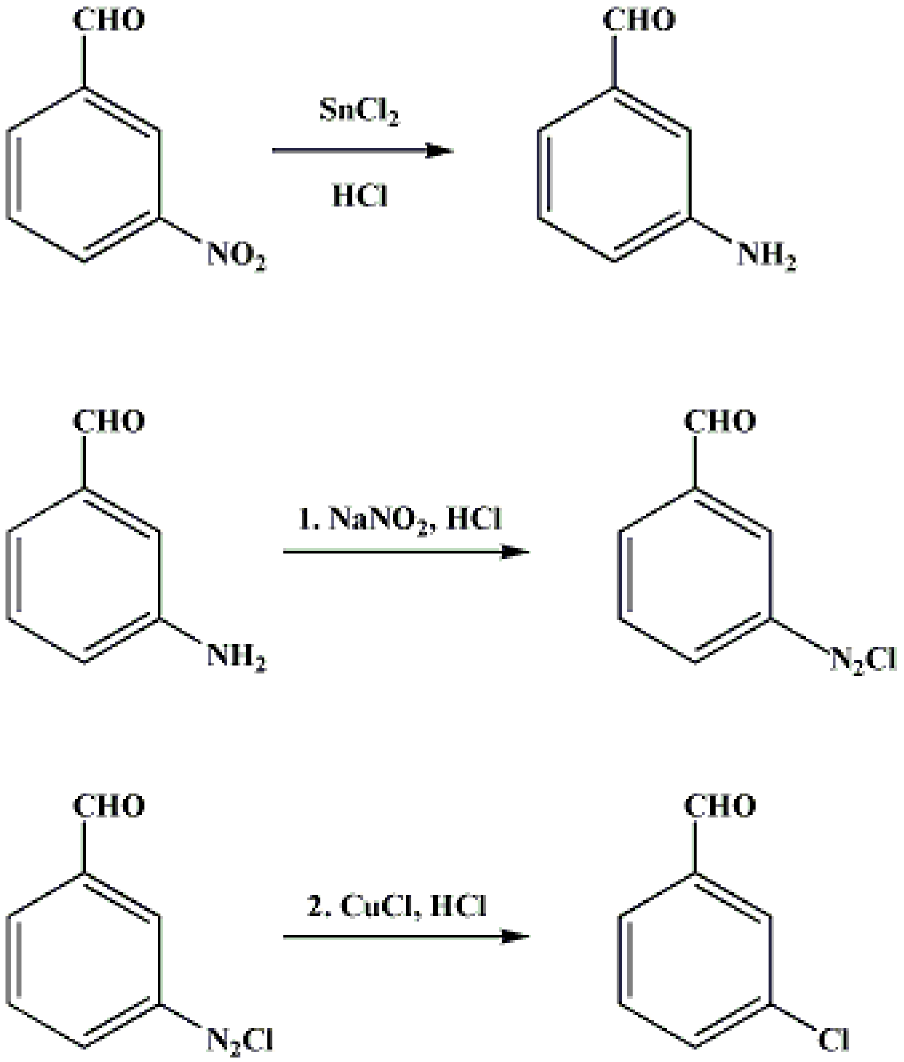
m-CHLOROBENZALDEHYDE

[Benzaldehyde, *m*-chloro-]



Submitted by Johannes S. Buck and Walter S. Ide.
Checked by John R. Johnson and Paul W. Vittum.

1. Procedure

A solution of 450 g. (2 moles) of stannous chloride crystals (Note 1) in 600 cc. of concentrated hydrochloric acid is placed in a 3-l. beaker provided with an efficient mechanical stirrer and cooled in an ice bath. When the temperature of the solution has fallen to +5°, 100 g. (0.66 mole) of *m*-nitrobenzaldehyde (Note 2) is added in one portion. The temperature rises slowly at first, reaching 25–30° in about five minutes, then rises very rapidly to about 100°. Stirring must be vigorous or the reaction mixture may be forced out of the beaker (Note 3). During the reaction the nitrobenzaldehyde dissolves, and an almost clear, red solution is obtained. The solution is cooled in an ice-salt mixture until the temperature has fallen to about +2°. During the cooling, orange-

red crystals separate and a pasty suspension results.

A 250-cc. separatory funnel is fixed so that its stem extends below the surface of the pasty suspension. A solution of 46 g. (0.67 mole) of sodium nitrite in 150 cc. of water is placed in the funnel and is slowly added to the well-stirred mixture until it shows a positive starch-iodide test for nitrous acid. The temperature of the mixture is maintained between 0° and +5° (Note 4) throughout the addition of the nitrite solution, which requires about ninety minutes. Usually, all but 5–8 cc. of the nitrite solution must be added before a positive test for nitrous acid appears.

During the latter part of the diazotization of the aminobenzaldehyde, a hot solution of cuprous chloride is prepared. In a 5-l. round-bottomed flask, 189 g. (0.75 mole) of powdered copper sulfate crystals and 161 g. of sodium chloride are dissolved in 600 cc. of hot water, and to this solution is added a solution of 41 g. (0.22 mole) of sodium metabisulfite ($Na_2S_2O_5$) and 27 g. (0.67 mole) of sodium hydroxide in 300 cc. of water. The final temperature of the resulting cuprous chloride solution should be about 75°.

The diazonium solution is added to the hot cuprous chloride solution while the latter is shaken by hand but is not cooled. After the solutions are thoroughly mixed, 840 cc. of concentrated hydrochloric acid is added and the mixture is allowed to stand overnight. The reaction mixture is steam-distilled to separate the *m*-chlorobenzaldehyde, which is collected practically completely in the first 1.5 l. of distillate. The *m*-chlorobenzaldehyde is removed from the aqueous distillate by extraction with two 150-cc. portions of ether, and the ethereal solution is dried with 10–15 g. of anhydrous calcium chloride. After being decanted from the drying agent, the ether is distilled, and the residual liquid is distilled under diminished pressure. The *m*-chlorobenzaldehyde boils at 84–86°/8 mm., 107–109°/26 mm. (Note 5). The yield is 70–74 g. (75–79 per cent of the theoretical amount) (Note 6).

2. Notes

1. A chemically pure grade of stannous chloride crystals ($SnCl_2 \cdot 2H_2O$) was used. Lower yields were obtained when technical stannous chloride was used.
2. A practical grade of *m*-nitrobenzaldehyde was used; m.p. 52–55°.
3. During the vigorous reaction it is advisable to keep the cooling bath and the reaction mixture well stirred. Less satisfactory yields were obtained when the reaction was moderated by adding the nitrobenzaldehyde in several portions.
4. At temperatures below 0° the speed of diazotization is markedly decreased. Above +5° some decomposition of the diazonium salt takes place.
5. Since *m*-chlorobenzaldehyde is oxidized easily by atmospheric oxygen, it should be stored in a tightly corked or sealed container.
6. According to the submitters *m*-bromobenzaldehyde can be prepared by the same general procedure using, in place of cuprous chloride, a solution of cuprous bromide prepared from 189 g. of copper sulfate, 91 g. of sodium

bromide, 41 g. of sodium metabisulfite, and 27 g. of sodium hydroxide. Instead of 840 cc. of concentrated hydrochloric acid, 200 cc. of 48 per cent hydrobromic acid is added after the diazonium solution has been mixed with the cuprous bromide. The *m*-bromobenzaldehyde boils at 93–98°/8 mm. The yield is 80 g. or 65 per cent of the theoretical amount.

It is reported, however, that *m*-bromobenzaldehyde prepared in this way may contain as much as 20 per cent of *m*-chlorobenzaldehyde. This contamination can be avoided by using stannous bromide as the reducing agent.

A solution of stannous bromide is prepared by heating 119 g. (1 gram atom) of mossy tin with 705 g. (4 moles) of 46 per cent hydrobromic acid for two hours on a steam bath, with mechanical stirring. The solution is cooled to 40°, and 50 g. (0.33 mole) of *m*-nitrobenzaldehyde is added in one portion, with continued stirring. The temperature rises from the heat of reaction and finally reaches about 105°. After heating for one-half hour longer on a steam bath, the reaction mixture is cooled to 0° and the aminobenzaldehyde diazotized by the gradual addition of 23 g. (0.33 mole) of sodium nitrite in 75 cc. of water. The diazonium solution is poured into a hot suspension of cuprous bromide, 100 cc. of 46 per cent hydrobromic acid is added, with stirring, and the mixture is allowed to stand overnight. The mixture is steam-distilled and the *m*-bromobenzaldehyde isolated by ether extraction and vacuum distillation; b.p. 90–92°/4 mm. The yield is 41 g. (67 per cent of the theoretical amount). (F. T. Tyson, private communication.)

3. Discussion

m-Chlorobenzaldehyde has been prepared by the chlorination of benzaldehyde[1] and by the oxidation of *m*-chlorobenzyl alcohol[2] and of *m*-chlorotoluene.[3] It is most conveniently prepared from *m*-nitrobenzaldehyde through *m*-aminobenzaldehyde and the diazonium reaction.[4] The procedure given above is essentially that described in the patent literature.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 583
- Org. Syn. Coll. Vol. 3, 453

References and Notes

1. Müller, Ger. pat. 30,329; 33,064 [Frdl. **1**, 143, 146 (1877–87)].
2. Mettler, Ber. **38**, 2812 (1905).
3. Law and Perkin, J. Chem. Soc. **93**, 1636 (1908).
4. Meister, Lucius, and Brüning, Ger. pat. 31,842 [Frdl. **1**, 144 (1877–87)]; Erdmann and Schwechten, Ann. **260**, 59 (1890); Eichengrün and Einhorn, ibid. **262**, 135 (1891).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium metabisulfite

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

HYDROBROMIC ACID (10035-10-6)

sodium bromide (7647-15-6)

oxygen (7782-44-7)

copper sulfate (7758-98-7)

sodium nitrite (7632-00-0)

nitrous acid (7782-77-6)

tin (7440-31-5)

stannous chloride

benzaldehyde (100-52-7)

cuprous bromide (7787-70-4)

cuprous chloride (7758-89-6)

nitrobenzaldehyde (552-89-6)

aminobenzaldehyde (529-23-7)

stannous bromide (10031-24-0)

m-Bromobenzaldehyde (3132-99-8)

m-Chlorobenzaldehyde, Benzaldehyde, m-chloro- (587-04-2)

m-Nitrobenzaldehyde (99-61-6)

m-chlorobenzyl alcohol (873-63-2)

m-chlorotoluene (108-41-8)

m-aminobenzaldehyde (1709-44-0)

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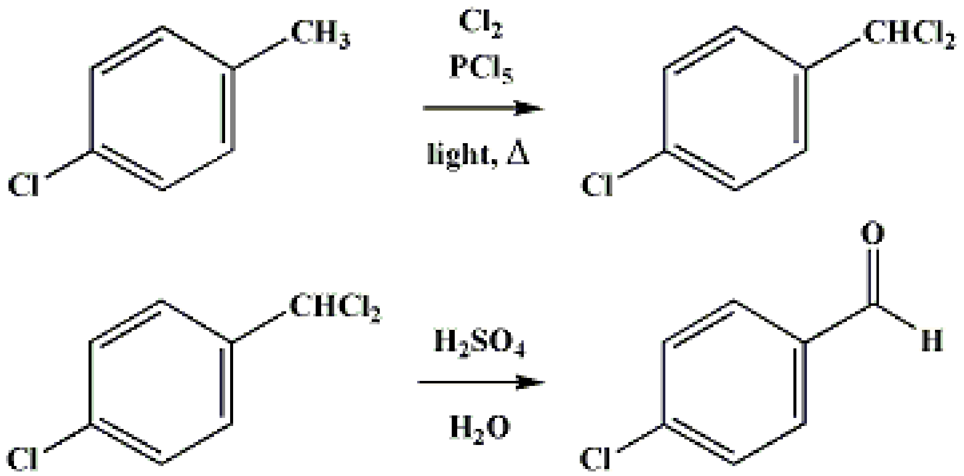
p-CHLOROBENZALDEHYDE

[Benzaldehyde, *p*-chloro-]



Submitted by W. L. McEwen
Checked by Henry Gilman and Chuan Liu.

1. Procedure

A 500-cc. two-necked, round-bottomed flask is provided with an air-cooled reflux condenser, 2 cm. in diameter and filled for a length of 60 cm. with 5–6 mm. glass pearls or rings (Note 1). Chlorine is to be introduced by means of a 4-mm. glass tube, inserted through a cork in a neck of the flask, extending close to the bottom of the flask and provided with a small bulb with fine perforations to break up the gas stream into small bubbles. The large quantities of hydrogen chloride formed can be disposed of by means of a gas absorption trap.

Into the tared flask are placed 126.5 g. (1 mole) of *p*-chlorotoluene (Org. Syn. Coll. Vol. I, **1941**, 170) and 3.8 g. of phosphorus pentachloride. The flask is heated in a bath kept at 160–170° (Note 2), and while illuminated with direct sunlight or with an unfrosted 100-watt tungsten lamp a rapid stream of chlorine is introduced directly from a cylinder until the gain in weight is 55–66 (Note 3).

The pale yellow or yellow-green product is then transferred to a 4-l. wide-mouthed bottle containing 400 cc. of concentrated sulfuric acid, and stirred vigorously (Hood) for five hours (Note 4). The viscous mixture is then transferred to a separatory funnel and allowed to stand overnight, after which the lower layer (Note 5) is run slowly, with stirring, into a 3-l. beaker three-quarters filled with cracked ice. The cream-colored solid obtained when the ice has melted is filtered by suction, washed with water, pressed dry on the funnel, and divided into three equal parts. Each portion is dissolved in a minimum of ether, and the ether solution is repeatedly shaken with 2 per cent sodium hydroxide solution until acidification of the washings gives no precipitate

of *p*-chlorobenzoic acid (Note 6).

After removal of the ether by distillation on a steam bath, the residue is distilled under diminished pressure from a Claisen flask. The yield of *p*-chlorobenzaldehyde distilling at 108–111°/25 mm. and melting at 46–47° is 76–84 g. (54–60 per cent of the theoretical amount).

2. Notes

1. The glass packing reduces the tendency of the stream of hydrogen chloride to carry away *p*-chlorotoluene as a spray.
If only one run is to be made, good-quality corks are satisfactory. If several runs are made, it is recommended that the corks be impregnated with sodium silicate solution to prevent excessive corrosion by the hydrogen chloride and chlorine.
2. The bath contains either oil or graphite.
3. The time required was four and one-half hours. In a larger run by the submitter, in which 750 g. of *p*-chlorotoluene and 23 g. of phosphorus pentachloride were used, the time required for a gain in weight of 330–360 g. was six to ten hours.
4. Vigorous stirring is necessary to prevent undue foaming. Most of the hydrogen chloride is evolved early in stirring.
5. The waxy upper layer is discarded.
6. The yield of *p*-chlorobenzoic acid is about 20 g. From the larger runs, starting with 750 g. of *p*-chlorotoluene, the yield of acid averaged 260 g.

3. Discussion

p-Chlorobenzaldehyde can be prepared from *p*-chlorobenzyl chloride or *p*-chlorobenzyl bromide with aqueous lead nitrate;[1] from *p*-chlorotoluene and chromyl chloride;[2] by the hydrolysis of *p*-chlorobenzal chloride;[3] from *p*-aminobenzaldehyde by diazotization and subsequent treatment with cuprous chloride;[4] from *p*-chlorophenylmagnesium bromide and ethyl orthoformate;[5] from *p*-chlorobenzyl chloride with hexamethylenetetramine and subsequent hydrolysis;[6] by conversion of *p*-chlorobenzonitrile to the iminochloride which is then hydrolyzed;[7] by the action of carbon monoxide and aluminum chloride on chlorobenzene;[8] and by the action of sodium carbonate on 2,5-dichlorobenzenesulfonyl-4-chlorobenzoylhydrazine.[9]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 200

References and Notes

1. Beilstein and Kuhlberg, Ann. **147**, 352 (1867); Jackson and White, Am. Chem. J. **3**, 30 (1881).
2. Law and Perkin, J. Chem. Soc. **93**, 1636 (1908).
3. Erdmann and Kirchhoff, Ann. **247**, 368 (1888); Erdmann and Schwechten, ibid **260**, 63 (1890); Kaeswurm, Ber. **19**, 742 (1886).
4. Von Walther and Raetze, J. prakt. Chem. (2) **65**, 258 (1902).
5. Bodroux, Bull. soc. chim. (3) **31**, 587 (1904).
6. Mayer and English, Ann. **417**, 78 (1918).
7. Stephen, J. Chem. Soc. **127**, 1874 (1925).
8. Boehringer and Sons, Ger. pat. 281,212 (Chem. Zentr. **1915**, I, 178).
9. McFadyen and Stevens, J. Chem. Soc. **1936**, 584.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

hydrogen chloride (7647-01-0)

ether (60-29-7)

sodium hydroxide (1310-73-2)

phosphorus pentachloride (10026-13-8)

carbon monoxide (630-08-0)

sodium silicate

sodium carbonate (497-19-8)

chlorobenzene (108-90-7)

aluminum chloride (3495-54-3)

chlorine (7782-50-5)

lead nitrate (10099-74-8)

cuprous chloride (7758-89-6)

p-Chlorotoluene (106-43-4)

Ethyl orthoformate

hexamethylenetetramine (100-97-0)

chromyl chloride

2,5-dichlorobenzenesulfonyl-4-chlorobenzoylhydrazine

p-chlorophenylmagnesium bromide

p-Chlorobenzaldehyde, Benzaldehyde, p-chloro- (104-88-1)

p-chlorobenzyl chloride (104-83-6)

p-chlorobenzoic acid (74-11-3)

p-chlorobenzyl bromide (622-95-7)

p-chlorobenzal chloride (13940-94-8)

p-Aminobenzaldehyde (17625-83-1)

p-chlorobenzonitrile (623-03-0)

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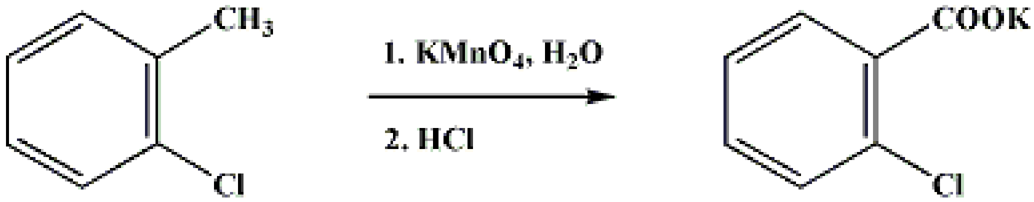
o-CHLOROBENZOIC ACID

[Benzoic acid, *o*-chloro-]



Submitted by H. T. Clarke and E. R. Taylor.
Checked by Henry Gilman and J. H. McGlumphy.

1. Procedure

In a 12-l. flask fitted with stirrer and reflux condenser are placed 600 g. (3.8 moles) of potassium permanganate, 7 l. of water, and 200 g. (1.6 moles) of *o*-chlorotoluene (Org. Syn. Coll. Vol. I, **1941**, 170). The mixture is slowly heated to boiling (Note 1) with continual stirring until the permanganate color has disappeared. This requires three to four hours. The condenser is now set downward for distillation, and the mixture is distilled, with constant stirring, until no more oil passes over with the water. The unattacked *o*-chlorotoluene thus obtained amounts to 25–30 g. The hot mixture is filtered with suction and the cake of hydrated manganese dioxide washed with two 500-cc. portions of hot water. The combined filtrate is concentrated (Note 2) to about 3.5 l.; if it is not entirely clear it may be clarified by the use of 1–2 g. of decolorizing carbon. It is now, while still hot, acidified by cautiously adding 250 cc. of concentrated hydrochloric acid (sp. gr. 1.19) with continual agitation. When the mixture is cool the white precipitate of *o*-chlorobenzoic acid is filtered and washed with cold water. The dry weight is 163–167 g. (76–78 per cent of the theoretical amount, based on the amount of *o*-chlorotoluene actually oxidized) of a very nearly pure (Note 3) product melting at 137–138°. For purification this may be recrystallized from 600 cc. of toluene, when 135–140 g. of a product melting at 139–140° is obtained. Further crops can be obtained by concentrating the mother liquor.

2. Notes

1. If the mixture is heated too rapidly the reaction may be violent at the outset; it can be controlled by laying wet towels upon the upper part of the flask.
2. This concentration is satisfactorily carried out on the steam bath under reduced pressure (Org. Syn. Coll. Vol. I, **1941**, 427).
3. It is important to use pure *o*-chlorotoluene in this preparation; otherwise the *o*-chlorobenzoic acid may be contaminated with isomeric acids which are very difficult to remove. The *o*-chlorotoluene therefore should be prepared from pure *o*-toluidine or *o*-chlorotoluenesulfonic acid.

Directions for the purification of technical *o*-chlorobenzoic acid are to be found on p. 16.

3. Discussion

The only practical methods of preparing *o*-chlorobenzoic acid consist in the oxidation of *o*-chlorotoluene and the replacement of the amino group in anthranilic acid by a chlorine atom. Both methods have been fully discussed by Graebe,[1] who recommends the former for the preparation of relatively large quantities. The oxidation of *o*-chlorotoluene by permanganate was originally described by Emmerling.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 15
- Org. Syn. Coll. Vol. 3, 28

References and Notes

1. Graebe, Ann. **276**, 54 (1893).
2. Emmerling, Ber. **8**, 880 (1875).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

potassium permanganate (7722-64-7)

decolorizing carbon (7782-42-5)

toluene (108-88-3)

manganese dioxide (1313-13-9)

o-Chlorotoluene (95-49-8)

Anthranilic Acid (118-92-3)

o-toluidine (95-53-4)

o-Chlorobenzoic acid, Benzoic acid, o-chloro- (118-91-2)

o-chlorotoluenesulfonic acid

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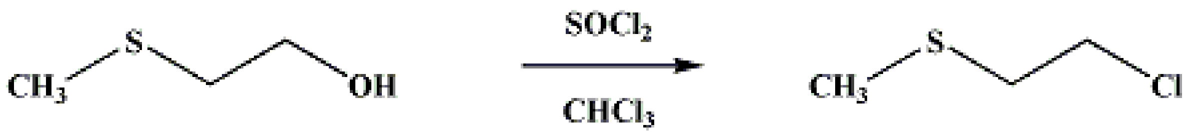
β-CHLOROETHYL METHYL SULFIDE

[Sulfide, β-chloroethyl methyl]



Submitted by W. R. Kirner and Wallace Windus.
Checked by H. T. Clarke and S. Gurin.

1. Procedure

In a 1-l. three-necked flask are mixed 150 g. (1.63 moles) of β-hydroxyethyl methyl sulfide (p. 345) (Note 1) and 200 g. of dry chloroform (Note 2). The flask is placed on a steam bath and is fitted with a dropping funnel, a mechanical stirrer, and a condenser. The condenser is fitted with a trap to remove the vapors of hydrogen chloride and sulfur dioxide. A solution of 204 g. (1.7 moles) (Note 3) of thionyl chloride in 135 cc. of dry chloroform is added dropwise to the β-hydroxyethyl methyl sulfide over a period of about two hours (Note 4). The reaction mixture is stirred vigorously during this addition and for about four hours after the addition is complete. The chloroform is distilled on the steam bath and the residue is distilled under reduced pressure. The yield is 135–153 g. (75–85 per cent of the theoretical amount) of a product boiling at 55–56°/30 mm. (Note 5).

2. Notes

1. Quantities of material seven times as large as the above may be used without decreasing the percentage yield of the product.
2. The chloroform is dried by distillation, and the fraction boiling at 60–61° is used.
3. The thionyl chloride is redistilled, and the fraction boiling over a two-degree range is employed.
4. The reaction mixture is heated once when about half the thionyl chloride has been added in order to keep the chloroform refluxing gently. Heating after the complete addition of the thionyl chloride is undesirable.
5. β-Chloroethyl methyl sulfide is a vesicant and must be handled with care. It boils at 140° under atmospheric pressure.

3. Discussion

The above method is essentially that described in the literature.[1]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 384

References and Notes

1. Kirner, J. Am. Chem. Soc. **50**, 2452 (1928).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrogen chloride (7647-01-0)

thionyl chloride (7719-09-7)

chloroform (67-66-3)

sulfur dioxide (7446-09-5)

β-Chloroethyl methyl sulfide, Sulfide, β-chloroethyl methyl (542-81-4)

β-Hydroxyethyl methyl sulfide (5271-38-5)

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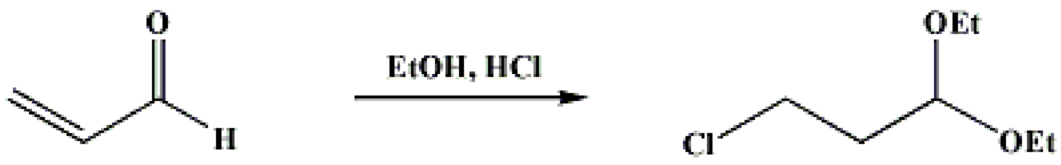
β-CHLOROPROPIONALDEHYDE ACETAL

[Propionaldehyde, β-chloro-, diethyl acetal]

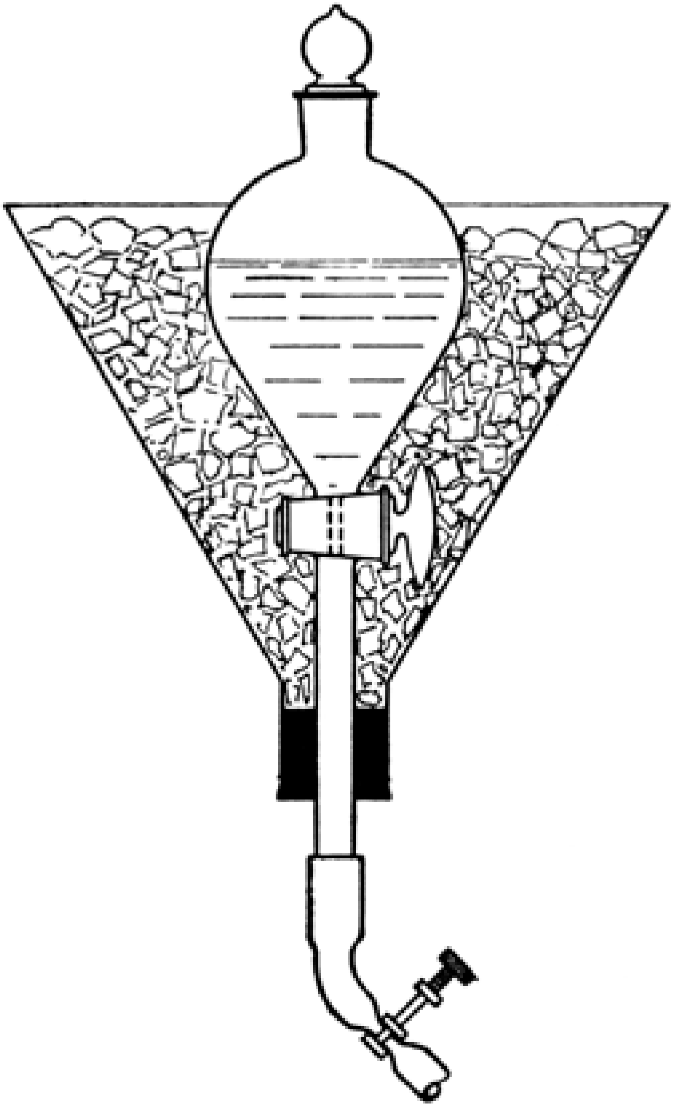


Submitted by E. J. Witzemann, Wm. Lloyd Evans, Henry Hass, and E. F. Schroeder.
Checked by Frank C. Whitmore and Harry T. Neher.

1. Procedure

In a 3-l. round-bottomed flask, fitted with a mechanical stirrer and an inlet tube, is placed 200 g. (253 cc.) of absolute alcohol (Note 1). The flask is surrounded by an ice-salt bath, and the alcohol is saturated with dry hydrogen chloride at 0°. The stem of a 200-cc. separatory funnel is fitted to a one-holed stopper inside a large short-stemmed funnel (.htmFig. 6). The space between the funnels is filled with finely cracked ice and water. In the separatory funnel is placed 112 g. (2 moles) of cold acrolein (Org. Syn. Coll. Vol. I, **1941**, 15) (Note 2).

Fig. 6



When the alcohol is saturated with hydrogen chloride, the generator is disconnected and the stem of the separatory funnel is connected to the inlet tube by a rubber tube provided with a screw clamp for adjusting the flow. The acrolein is added, with stirring, to the alcoholic hydrogen chloride solution at about 0°. The addition should require from one to two hours. After two layers have formed, the lower layer of acetal is separated and treated gradually with powdered sodium bicarbonate until all acid is neutralized (Note 3). The mixture is filtered. The filtrate is washed with two 50-cc. portions of ice water and dried over 10 g. of potassium carbonate for five to ten hours (Note 4). It is then filtered and distilled under reduced pressure. The yield of product boiling at 58–62°/8 mm. is 112 g. (34 per cent of the theoretical amount).

2. Notes

1. At least 99.5 per cent alcohol should be used (Org. Syn. Coll. Vol. I, **1941**, 259).

2. If the acrolein is not kept cold, the vapors become unbearable. The stopper of the separatory funnel should be provided with a fine glass capillary.

3. All acid must be removed before washing the product with water, because

dilute acid hydrolyzes the acetal very readily.
4. It is recommended that the ice water be prepared from distilled water as the impurities in some samples of tap water lead to decomposition of the acetal. (Private communication from C. F. H. Allen.)

3. Discussion

β-Chloropropionaldehyde acetal has been prepared by the action of acrolein on alcoholic hydrogen chloride alone,[1] or in the presence of calcium chloride.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 17

References and Notes

1. Alsberg, Jahresber. **1864**, 495; Wohl, Ber. **31**, 1797 (1898); Wohl and Emmerich, ibid. **33**, 2761 (1900); Brabant, Z. physiol. Chem. **86**, 208 (1913); Witzemann, J. Am. Chem. Soc. **36**, 1909 (1914); Spoehr and Young, Carnegie Inst. Washington Yearbook, **25**, 176 (1925–1926); Expt. Sta. Record, **57**, 817 (1927) [C. A. **22**, 2368 (1928)].
2. Crawford and Kenyon, J. Chem. Soc. **1927**, 399.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alcohol (64-17-5)

calcium chloride (10043-52-4)

potassium carbonate (584-08-7)

hydrogen chloride (7647-01-0)

Acrolein (107-02-8)

sodium bicarbonate (144-55-8)

β-chloropropionaldehyde acetal (35573-93-4)

Propionaldehyde, β-chloro-, diethyl acetal

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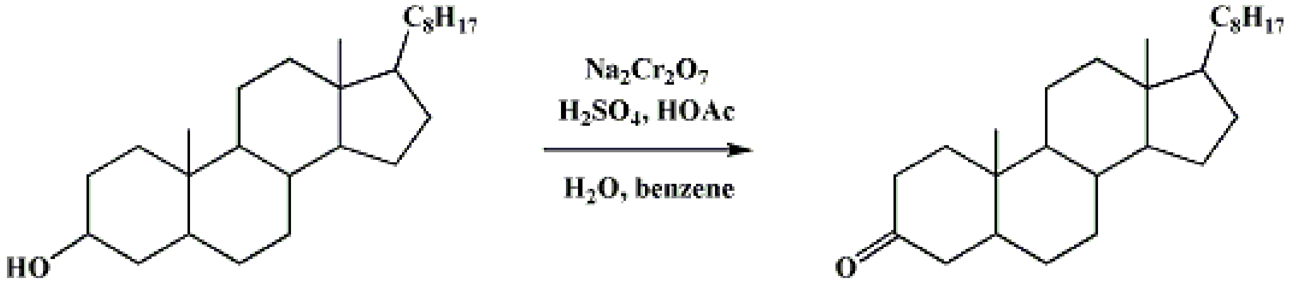
Organic Syntheses, CV 2, 139

CHOLESTANONE



Submitted by William F. Bruce
Checked by Louis F. Fieser and R. P. Jacobsen.

1. Procedure

A solution of 50 g. (0.13 mole) of dihydrocholesterol (Note 1) in 500 cc. of benzene is added slowly with cooling (Note 2) to a solution of 68 g. (0.23 mole) of crystalline sodium dichromate, 50 cc. of glacial acetic acid, and 90 cc. of concentrated sulfuric acid in 300 cc. of water in a 3-l. flask. The mixture is agitated thoroughly in a shaking device or by efficient stirring (Note 3) for six hours at 25–30° (Note 4).

The benzene solution is separated and washed twice with 100 cc. of water, once with 200 cc. of 5 per cent potassium hydroxide, and twice with water. If the solution is not colorless it is clarified with 1 g. of Norite. The benzene is removed by distillation, and the resulting syrup is dissolved in 300 cc. of alcohol by heating. The solution on cooling deposits cholestanone as well-formed needles. The yield of collected, washed, and air-dried material, m.p. 129–130°, is 41.5–42 g. (83–84 per cent of the theoretical amount). The addition of 80 cc. of water to the filtrate gives about 2 g. of material melting at 125–126°.

2. Notes

1. Material melting at 140–141° (p. 191) is satisfactory. The presence of a trace of cholesterol is not objectionable since this is converted into acidic products which are removed in the course of the purification.
2. When the solutions are mixed without cooling the temperature rises to about 60° and the yield is somewhat less.
3. The checkers employed a Hershberg stirrer (p. 117).
4. The agitation may be continued twice as long without appreciable difference in yield. Six hours is regarded as the minimum time for the quantity specified.

3. Discussion

Cholestanone has been prepared by the oxidation of dihydrocholesterol with chromic anhydride in acetic acid solution.[1] The yield is sometimes diminished as a result of the partial acetylation of the sterol.

References and Notes

1. Diels and Abderhalden, Ber. **39**, 884 (1906); Willstätter and Mayer, ibid. **41**, 2199 (1908); Vavon and

Jakubowicz, Bull. soc. chim. (4) **53**, 584 (1933).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alcohol (64-17-5)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

Benzene (71-43-2)

Norite (7782-42-5)

potassium hydroxide (1310-58-3)

sodium dichromate (7789-12-0)

chromic anhydride

Cholestanone (566-88-1)

Dihydrocholesterol (80-97-7)

Cholesterol (57-88-5)

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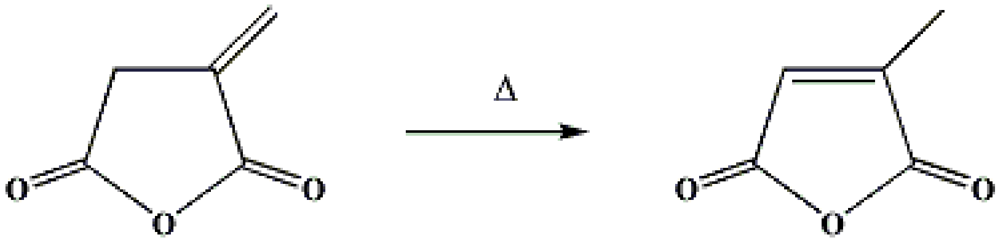
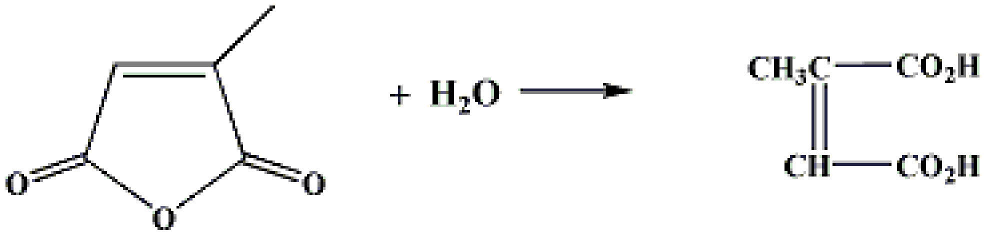
Organic Syntheses, CV 2, 140

CITRACONIC ANHYDRIDE AND CITRACONIC ACID





Submitted by R. L. Shriner, S. G. Ford, and L. J. Roll.
Checked by C. R. Noller

1. Procedure

(*A*) *Citraconic Anhydride*.—Two hundred and fifty grams of itaconic anhydride (Note 1) is distilled rapidly at atmospheric pressure in a 500-cc. modified Claisen flask with a 15-cm. (6-in.) fractionating column (Note 2). The receivers for the distillate must be changed without interrupting the distillation. The distillate passing over below 200° consists of water and other decomposition products. The fraction which distils at 200–215° consists of citraconic anhydride and is collected separately. The yield is 170–180 g. (68–72 per cent of the theoretical amount) of a product melting at 5.5–6°. On redistillation under reduced pressure there is obtained 155–165 g. (62–66 per cent of the theoretical amount) of a product which boils at 105–110°/22 mm. and melts at 7–8° (Note 3).

(*B*) *Citraconic Acid*.—To 22.4 g. (0.2 mole) of pure citraconic anhydride in a 100-cc. beaker is added from a pipet exactly 4 cc. (0.22 mole) of distilled water. The mixture is stirred on a hot plate until a homogeneous solution is formed, then covered with a watch glass and allowed to stand for forty-eight hours. At the end of this time the mixture has solidified completely. The yield is 26 g. of a product melting at 87–89°. For further purification it is finely ground in a mortar, washed with 50 cc. of cold benzene, dried in the air, and then dried for twenty-four hours in a vacuum desiccator over phosphorus pentoxide. This furnishes 24.4 g. (94 per cent of the theoretical amount) of citraconic acid which melts at 92–93°.

2. Notes

1. The crude itaconic anhydride obtained as described on p. 368 was used. Itaconic acid may be substituted for the anhydride.
2. The success of the preparation depends upon a rapid distillation and changing the receivers without interrupting the distillation. The best yields are obtained when the heating period is of short duration.
3. The crude citraconic anhydride contains a small amount of water, acetone, and citraconic acid. Vacuum distillation allows the removal of these impurities without materially decreasing the yield.

3. Discussion

Citraconic anhydride has been prepared by the distillation of citraconic acid and of citric acid.[1]

Citraconic acid has been obtained by distillation of citric acid,[2] of lactic acid,[3] and of hydroxypyrotartaric acid;[4] and by treating citric acid with hydriodic acid.[5] A mixture of citraconic and itaconic acids is obtained by flowing a concentrated aqueous solution of citric acid into a heated evacuated vessel, distilling under reduced pressure the mixture of anhydrides formed, and allowing the mixture to react with water.[6]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 368
- Org. Syn. Coll. Vol. 2, 382

References and Notes

1. Anschütz, Ber. **14**, 2788 (1881).
2. Crasso, Ann. **34**, 68 (1840); Kekulé, "Lehrbuch der organischen Chemie," **2**, 317 (1866); Wilm, Ann. **141**, 28 (1867).
3. Engelhardt, ibid. **70**, 243, 246 (1849).
4. Demarçay, Ber. **9**, 963 (1876).
5. Kämmerer, Ann. **139**, 269 (1866).
6. Boehringer Sohn A.-G., Brit. pat. 452,460 [C. A. **31**, 1045 (1937)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

citraconic and itaconic acids

Benzene (71-43-2)

citric acid (77-92-9)

acetone (67-64-1)

hydriodic acid (10034-85-2)

Citraconic anhydride (616-02-4)

Citraconic acid (498-23-7)

Itaconic anhydride (2170-03-8)

Itaconic acid (97-65-4)

lactic acid (50-21-5)

hydroxypyrotartaric acid

phosphorus pentoxide (1314-56-3)

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COPPER CHROMITE CATALYST

Submitted by W. A. Lazier and H. R. Arnold.
Checked by R. L. Shriner and J. F. Kaplan.

1. Procedure

A mixture of 26 g. (0.1 mole) of c.p. barium nitrate and 800 cc. of distilled water is warmed to 70°. After solution is complete 218 g. (0.9 mole) of c.p. copper nitrate trihydrate is added and the mixture stirred at 70° until a clear solution results (Note 2).

A solution of ammonium chromate is prepared by dissolving 126 g. (0.5 mole) of c.p. ammonium dichromate in 600 cc. of distilled water and adding 150 cc. of 28 per cent aqueous ammonia (sp. gr. 0.9) (Note 3). The warm solution of the nitrates is stirred (hand stirring is adequate) while the ammonium chromate solution is poured into it in a thin stream. Stirring is continued for a few minutes, after which the reddish brown precipitate of copper barium ammonium chromate is collected (Note 4) and pressed in a 16-cm. Büchner funnel, and dried at 110°. This dry precipitate is placed in a loosely covered nickel pan (Note 5), or one or two small porcelain casseroles covered with watch glasses, and heated in a muffle furnace for one hour at 350–450° (Note 6). At this point the yield of chromite should be about 160 g. The ignition residue is pulverized in a mortar to break up any hard lumps that may be present (Note 7) and then transferred to a 2-l. beaker containing 1.2 l. of 10 per cent acetic acid. After being stirred for ten minutes the mixture is allowed to settle. After about ten minutes, two-thirds or more of the spent acid solution is decanted and replaced by 1.2 l. of fresh 10 per cent acetic acid, and the extraction is repeated. The residue is washed by repeating the extraction procedure four times with 1.2 l. of distilled water each time (Note 8). The insoluble portion is collected by filtering with suction on a Büchner funnel, dried at 110°, and ground in a mortar to a fine black powder (Note 9). The yield is 130–140 g. (Note 10) and (Note 11).

2. Notes

1. The reactions involved in this preparation cannot be expressed quantitatively in a simple equation. The process has been investigated by Gröger.[1]
2. Barium nitrate is sparingly soluble in cold water and even less soluble in copper nitrate solution. It is therefore necessary to heat the mixture in order to bring both salts into solution together.

3. The warm, freshly prepared ammonium chromate solution may be used for the precipitation at once or may be allowed to cool to room temperature. However, the solution prepared as indicated is supersaturated at room temperature and deposits crystals on standing. If a stock solution of ammonium chromate is to be held over from day to day, a portion of the ammonia should be withheld and added immediately before precipitation. Chromic acid may be used for the preparation of the ammonium chromate solution provided that the acid solution is kept cold while a sufficient quantity of ammonia is introduced below the surface.
4. The amount of ammonia used is calculated to give a mother liquid that is neutral to litmus, allowance being made for the basic character of the precipitate. While a deviation either way affects the yield adversely, it is better not to try to adjust the end point after precipitation, but to make a slight correction on the amount of ammonia to be used for the next batch. The mother liquor serves as its own indicator: if acid, the solution is yellow; if alkaline, a deep green.
5. A convenient-sized pan, 6 cm. deep, 19 cm. long, and 10 cm. wide, can be made from a sheet of nickel 1/32 inch thick.
6. The ignition of copper ammonium chromate causes a spontaneous exothermic reaction which proceeds with a rapid evolution of gas. Although the size of the charge ignited at one time is unimportant, the retaining vessels should not be too full, else there will be considerable mechanical loss of product. It is also inadvisable to break up the lumps of dried precipitate, as the lumpy condition diminishes spraying of the chromite on ignition.
7. The unextracted catalyst should be a bluish black, friable powder. It is a satisfactory catalyst for the dehydrogenation of alcohols and for the less difficult hydrogenation reactions, such as the reduction of nitro compounds. This mixture of copper chromite and copper oxide is somewhat less active and more susceptible of reduction to metallic copper than the catalyst from which the copper oxide has been removed by acid extraction.
8. If the washing is unduly prolonged, the catalyst tends to become colloidal and is difficult to separate either by decantation or filtration.
9. No special precautions are necessary in handling or storing the copper chromite catalyst, since it is unharmed by exposure to air or moisture.
10. Barium has been included as a catalyst component on account of its protective action against sulfate poisoning and its reported stabilization of the catalyst against reduction. Alternatively, the above procedure may be used for the preparation of a copper chromite catalyst containing no barium. In this case the barium nitrate is omitted and 242 g. (1 mole) of copper nitrate is used. All other details are the same as given above.
11. An alternative procedure described by Adkins[2] is as follows: Thirty-one grams of barium nitrate is dissolved in 820 cc. of distilled water which has been heated to 80°. To this hot solution is added 260 g. of copper nitrate trihydrate, and the mixture is stirred and heated until solution is complete. Meanwhile, 151 g. of ammonium dichromate is dissolved in 600 cc. of distilled water and 225 cc.

of 28 per cent aqueous ammonia added. The hot nitrate solution is poured in a thin stream with stirring into the ammonium chromate solution. The orange precipitate is collected on a filter, pressed, and sucked as dry as possible. It is dried in an oven at 75–80° for twelve hours, pulverized, and divided into three portions. Each portion is decomposed separately in a large porcelain casserole (15-cm. diameter) by heating over a free flame. The mass should be heated just hot enough to cause decomposition to take place at the minimum temperature. During the decomposition the powder is stirred continuously with a steel spatula, and the heating is regulated so that the evolution of gases does not become violent. This is accomplished by heating only one side of the casserole and by increasing the rate of stirring when the decomposition starts to spread throughout the mass. During this process the color of the powder changes from orange to brown and finally to black. When the entire mass has become black the evolution of gases ceases, and the powder is removed from the casserole and allowed to cool. The combined product is then stirred for thirty minutes with 600 cc. of 10 per cent acetic acid solution, collected on a filter, washed by suspending it six times in 100-cc. portions of water, dried for twelve hours at 125°, and pulverized. The yield of catalyst is 170 g.

3. Discussion

Copper chromite has been made by the ignition of basic copper chromate at a red heat and by the thermal decomposition of copper ammonium chromate.[1] The procedure given here is a modification of the latter method[3] in which barium ammonium chromate is also incorporated.[4] Copper-chromium oxide hydrogenation catalysts have also been prepared by grinding or heating together copper oxide and chromium oxides, by the decomposition of copper ammonium chromium carbonates or copper-chromium nitrates,[2], [4] and by the low-temperature ignition of copper ammonium chromates.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 325
- Org. Syn. Coll. Vol. 3, 471
- Org. Syn. Coll. Vol. 3, 693
- Org. Syn. Coll. Vol. 4, 216
- Org. Syn. Coll. Vol. 4, 677
- Org. Syn. Coll. Vol. 4, 857

References and Notes

1. Gröger, Z. anorg. Chem. **58**, 412 (1908); **76**, 30 (1912).
2. Adkins, "Reactions of Hydrogen with Organic Compounds over Copper-Chromium Oxide and Nickel Catalysts," p. 12, University of Wisconsin Press, Madison, 1937.
3. Lazier, U. S. pats. 1,746,782 and 1,746,783 [C. A. **24**, 1649 (1930)]; U. S. pat.

1,964,000 [C. A. **28**, 5075 (1934)].

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

metallic copper

chromium oxides

copper ammonium chromium carbonates

copper-chromium nitrates

copper ammonium chromates

acetic acid (64-19-7)

ammonia (7664-41-7)

chromic acid (7738-94-5)

copper oxide (1317-38-0)

barium (7440-39-3)

COPPER CHROMITE

barium nitrate (10022-31-8)

copper nitrate trihydrate

ammonium chromate (7788-98-9)

ammonium dichromate

copper barium ammonium chromate

copper nitrate (3251-23-8)

copper ammonium chromate

Copper-Chromium Oxide

copper chromate

barium ammonium chromate

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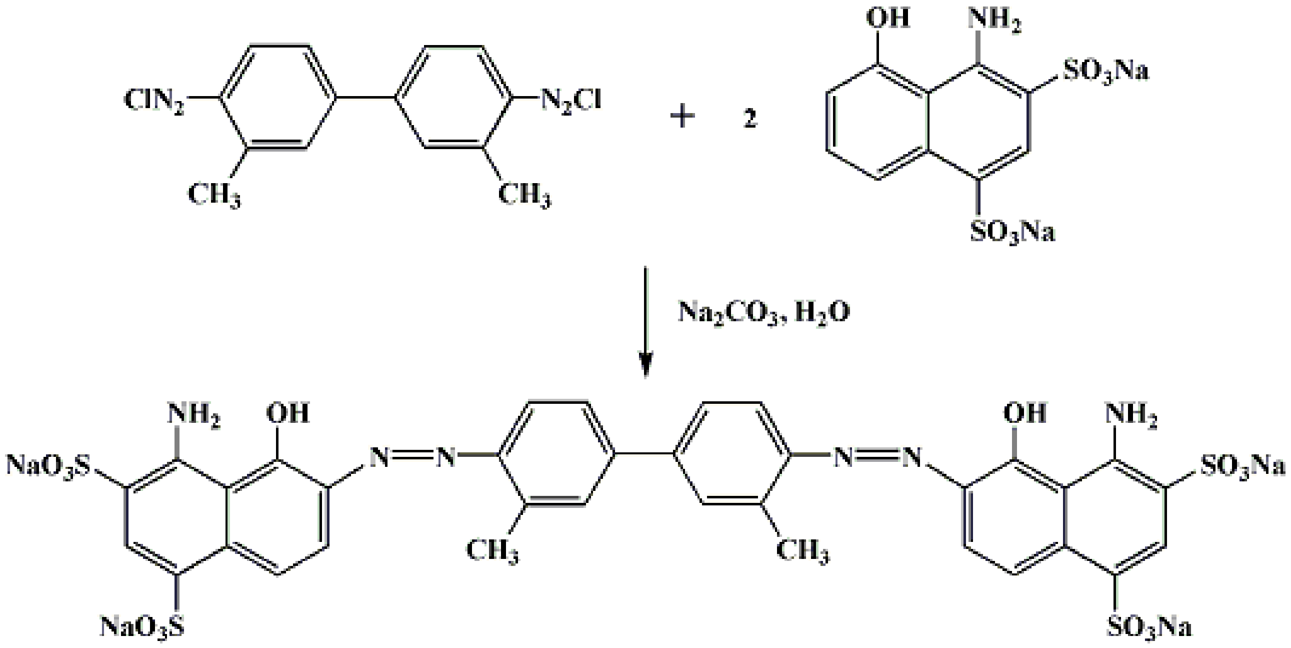
Organic Syntheses, CV 2, 145

COUPLING OF *o*-TOLIDINE AND CHICAGO ACID

[Preparation of a Salt-Free Azo Dye]

[1,3-Naphthalenedisulfonic acid, 6,6'-[(3,3'-dimethyl[1,1'-biphenyl]- 4,4'diyl) bis(azo)]bis[4-amino-5-hydroxy-, tetrasodium salt]



Submitted by J. L. Hartwell and Louis F. Fieser.
Checked by W. W. Hartman and G. L. Boomer.

1. Procedure

In a 1-l. beaker 21.2 g. (0.1 mole) of *o*-tolidine is made into a thin paste with 300 cc. of water and dissolved by the addition of 20 cc. (23.6 g., 0.23 mole) of concentrated hydrochloric acid (sp. gr. 1.18), warming a little if necessary. The solution is cooled to 10° with ice, mechanical agitation is started, and 21 cc. (25 g., 0.24 mole) more of concentrated hydrochloric acid is added (Note 1). This causes partial separation of *o*-tolidine dihydrochloride. The temperature being kept at 10–15°, a solution of 14.5 g. (0.2 mole) of 95 per cent sodium nitrite in 40 cc. of water is run in rapidly, the last 10 per cent being held back and added slowly as needed to give a distinct positive test for nitrous acid on starch-iodide paper. This excess is maintained for one-half hour. Throughout the diazotization an excess of hydrochloric acid should be present as shown by a strong test on Congo red paper. When the diazotization is complete, the excess nitrous acid is eliminated by the careful addition of a small amount of *o*-tolidine hydrochloride solution, using starch-iodide paper to arrive at an exact balance (Note 2).

In a 3-l. beaker a paste is made from 82 g. (0.21 mole) of 88 per cent technical Chicago acid (1-amino-8-naphthol-2,4-disulfonic acid) (Note 3) and 500 cc. of water, and solution effected by the addition of 8 g. (0.2 mole) of sodium hydroxide in 30 cc. of water, testing with litmus toward the end and leaving the reaction still acid (Note 4). The solution is cooled to 18° by the addition of ice, and just before the coupling 35 g. (0.33 mole) of anhydrous sodium carbonate is added.

With vigorous mechanical agitation the diazonium salt solution is run into the Chicago acid

solution rather rapidly. The blue dye which separates at first, gradually dissolves on further stirring. After one-half hour the solution is tested for alkalinity (Note 5) and for completeness of coupling (Note 6) and (Note 7).

After stirring for a total of two hours, the mixture is heated to 85°, 15 g. of decolorizing carbon is added, and the solution stirred for fifteen minutes and filtered. The filtrate is reheated to 85° with agitation and the volume estimated. For each 100 cc. of the solution 27 g. of hydrated sodium acetate (usually 450–500 g. in all) is added slowly, with vigorous stirring, in four or five portions (Note 8). The dye is thus caused to separate in an easily filterable form. On "spotting" a drop of the mixture on filter paper by means of a stirring rod, the dye should form a dark blue mass in the center of a red or violet rim (Note 9). The mixture, while still warm, is filtered with suction on a 20-cm. Büchner funnel, and as much as possible of the mother liquor is removed (Note 10). The filter cake is dissolved in 1.2 l. of water at 85° and resalted as above with about 300 g. of sodium acetate, in several portions, or until most of the dye is salted out. In a "spot" test on filter paper, little red should be left in the rim. The product is collected, redissolved in 1.2 l. of water at 85°, and salted again. This time enough sodium acetate should be added to give a small rim which shows no red impurity (Note 11). The product is collected, dried in an oven at 110° for at least twenty-four hours, ground, and passed through a 40-mesh sieve.

The sodium acetate is then extracted by digesting the sifted dye for ten to fifteen minutes with successive 500-cc. portions of boiling 95 per cent ethyl alcohol, filtering with suction after each extraction, and washing the product on the filter with a little alcohol (Note 12). After four alcohol extractions the filtrate should give a negative test for acetate. The product, which changes in appearance from bronze to green during the extraction, is dried in air at room temperature. The yield is 80–81 g. (83–84 per cent of the theoretical amount) of dye free from inorganic salts and organic impurities (Note 13).

2. Notes

1. If the hydrochloric acid is added all at once instead of in two portions as described, a solid will be obtained consisting of *o*-tolidine coated with its dihydrochloride and the diazotization will occur slowly.
2. If a clear solution is not obtained at this point, any solid may be removed by filtration.
3. Owing to the fact that this intermediate is a technical product and has been isolated by salting out, a knowledge of its purity is necessary. The compound is actually present as the acid sodium salt (molecular weight 341). A rapid method of analysis, sufficiently accurate for this preparation, is to titrate a known weight in dilute, strongly acid solution with 0.5 *N* sodium nitrite solution standardized against sulfanilic acid, using starch-iodide paper in obtaining the end points.
Some samples of technical Chicago acid may contain so much of an impurity giving rise to a red dye that the removal of this red dye by resalting, as recommended in (Note 9), presents considerable difficulty. When this occurs it is advantageous to purify the Chicago acid in the following fashion. Seven hundred grams of a Chicago acid paste, found by titration to contain 26.6 per cent of 1-amino-8-naphthol-2,4-disulfonic acid, is dissolved by heating in 2 l. of water; the solution is filtered, heated to 70°, and salted out by the addition of sodium chloride (600–650 g.) until a thick paste is obtained. The precipitate is collected at 40°, pressed well by means of a rubber dam, dissolved in 2 l. of water, and resalted exactly as before. After drying for thirty-six hours in a vacuum oven at 75°, the nearly white product weighs 150–155 g. and contains 78 per cent of active reagent. The dye ("Tolidine-1824") obtained from this material showed no red impurity in the capillary test after the second salting. (Louis F. Fieser and M. E. Gross, private communication.)

4. Aminonaphthols rapidly turn dark in alkaline solution owing to oxidation. For this reason the solution is left faintly acid until just before coupling.
5. This test is made by removing a few drops of the coupling mixture by means of a stirring rod to one of the depressions in a white porcelain spot plate, salting out the dye by stirring with a little c.p. sodium chloride, and bringing a piece of litmus paper in contact with the mass.
6. The test for completeness of coupling involves testing for excess diazonium salt (*a*) and for excess Chicago acid (*b*):

1. (*a*) A drop or two of the coupling mixture is dissolved in about 20 cc. of water in a test tube and the solution divided equally in two test tubes. To one tube is added a few drops of a 10 per cent solution of Schaeffer's salt (2-naphthol-6-sulfonic acid) or R salt (2-naphthol-3,6-disulfonic acid) prepared from 0.5 g. of the acid, 5 cc. of water, and just enough sodium carbonate solution to dissolve the material. The other tube acts as a control. Both tubes are brought rapidly nearly to boiling and the colors compared. If too dark, both tubes are diluted equally with water until the solutions are light blue. The colors may be compared by pouring solution from each tube onto filter paper. If the color of the solution in the first tube is at all redder than that in the control tube, an excess of the diazonium compound is present in the coupling mixture.
2. (*b*) A few drops of the coupling mixture are salted out as in (Note 5), the mass transferred to filter paper, and near the spot on the reverse side is placed a drop of solution of diazotized sulfanilic acid. A red or red-violet coloration at the meeting of the two spots shows the presence of excess Chicago acid.

7. Throughout the coupling an alkaline reaction should be maintained and sodium carbonate added if the alkalinity falls. If the mixture gives tests for both diazonium compound and Chicago acid, insufficient time has elapsed for complete coupling. A little more Chicago acid should be added (in alkaline solution) if a deficiency is shown.
8. The temperature of salting, speed of addition of salt, speed and duration of agitation, and alkalinity of the solution all affect the physical form of the dye and determine how well it will filter. The method described gives a product which filters rapidly.
9. The red impurity is another dye produced by coupling of the diazonium salt with an oxidation product which is present in the technical Chicago acid. It is usually easier to free the blue dye of this red impurity by resalting than to purify the Chicago acid. However, in the case of Trypan blue (tolidine coupled with two moles of H acid) the red impurity cannot be removed by salting. It may be removed completely by extraction with alcohol, in which it is more soluble than the blue component, preferably by precipitating a hot saturated aqueous solution of the dye with at least six times its volume of alcohol.
10. In this and subsequent filtrations it is advantageous to use a rubber dam held in place by rubber bands. The use of the rubber dam is especially advantageous for a slow filtration continuing overnight.
11. The most sensitive test for purity of the dye is the capillary test,[1] depending on the fact that the red impurity is more soluble in water than the blue compound and less readily adsorbed by filter paper. An amount of press cake corresponding roughly to 0.05 g. of solid dye is dissolved in 200 cc. of water in a 400-cc. beaker, 0.5 g. of common salt is added, and the temperature raised to 95°. A 2 by 15 cm. strip of filter paper is immersed in the liquid and is supported on a stirring rod pushed through it and placed across the top of the beaker. The temperature is maintained at 95° for fifteen minutes and the filter paper removed. Any red impurity will show plainly above the blue. If purification is found to be incomplete, further resalting will produce a pure product.
12. The progress of the extraction may be followed by adding three drops of concentrated

sulfuric acid to 10 cc. of the alcoholic filtrate in a test tube. If a white precipitate of sodium sulfate does not form at once, the solution is chilled in an ice bath. A precipitate will form with 0.002 g. of sodium acetate in 10 cc. of alcohol.

13. Using this procedure, other diamines such as benzidine and dianisidine may be diazotized and coupled with other aminonaphthols, such as S acid (1-amino-8-naphthol-4-sulfonic acid), J acid (2-amino-5-naphthol-7-sulfonic acid), Gamma acid (2-amino-8-naphthol-6-sulfonic acid), and H acid (1-amino-8-naphthol-3,6-disulfonic acid), or with simple naphthols such as NW acid (1-naphthol-4-sulfonic acid), Schaeffer's acid (2-naphthol-6-sulfonic acid), and R acid (2-naphthol-3,6-disulfonic acid). The procedure would be varied only in the manner of salting out the dyes, each of which would require a set of optimum conditions peculiar to itself (see (Note 8)). If the alkalinity of sodium acetate leads to a considerable increase in solubility of the dye, ammonium bromide may be used. The latter is extracted easily by hot ethyl alcohol or, better, by hot methyl alcohol.
Naphthylamines cannot be used as second components by this procedure, as coupling takes place in acid solution.

3. Discussion

Dyes of the types described in the procedure and those mentioned in (Note 13) are described in the patent literature.[2] The ordinary methods of preparation give products that contain salt and other impurities.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 295

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Trypan blue (tolidine coupled with two moles of H acid)

o-tolidine hydrochloride

1,3-Naphthalenedisulfonic acid, 6,6'-[(3,3'-dimethyl[1,1'-biphenyl]- 4,4'diyl)bis(azo)]bis[4-amino-5-hydroxy-, tetrasodium salt

ethyl alcohol, alcohol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

methyl alcohol (67-56-1)

sodium acetate (127-09-3)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

ammonium bromide (12124-97-9)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

sodium nitrite (7632-00-0)

nitrous acid (7782-77-6)

decolorizing carbon (7782-42-5)

1-amino-8-naphthol-2,4-disulfonic acid, CHICAGO ACID (82-47-3)

sulfanilic acid (121-57-3)

2-naphthol-6-sulfonic acid (61886-35-9)

2-naphthol-3,6-disulfonic acid (148-75-4)

benzidine (92-87-5)

1-amino-8-naphthol-4-sulfonic acid (83-64-7)

2-amino-5-naphthol-7-sulfonic acid (87-02-5)

2-amino-8-naphthol-6-sulfonic acid (90-51-7)

1-amino-8-naphthol-3,6-disulfonic acid (5460-09-3)

1-naphthol-4-sulfonic acid (84-87-7)

o-TOLIDINE (119-93-7)

dianisidine (119-90-4)

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Organic Syntheses, CV 2, 150

CYANOGEN BROMIDE

$$NaCN + Br_2 \xrightarrow{H_2O} BrCN + NaBr$$

Submitted by W. W. Hartman and E. E. Dreger.
Checked by Roger Adams and I. L. Ozanne.

1. Procedure

A 2-l. round-bottomed flask, surrounded by an ice-water bath and provided with a stirrer, a separatory funnel, and an outlet tube, is set up in a good hood. To the flask are added 500 g. (160 cc., 3.1 moles) of bromine and 50 cc. of water (Note 1). To the stirred mixture is added gradually a solution of 170 g. of sodium cyanide (3.5 moles) in 1.2 l. of warm water. The temperature of the reaction mixture is kept below 30°. When the reaction is complete (about two hours or less) the cyanogen bromide is distilled from a steam bath, using a 500-cc. flask (Note 2) as a receiver. The distillate is warmed with about 100 g. of anhydrous calcium chloride, filtered, and again distilled, preferably with the distilling flask used as a receiving vessel connected directly to the flask from which the cyanogen bromide is being distilled. The product boils at 60–62°. It is melted in the receiver (Note 3) (Hood) and poured into a warm tared bottle. The yield of white crystalline solid (Note 4) melting at 49–51° is 239–280 g. (73–85 per cent of the theoretical amount).

2. Notes

1. Water is used to decrease the volatilization of the bromine.
2. It is desirable to have the receiving flask close to the distilling flask because cyanogen bromide will clog a tube which is too small in diameter or too long.
3. Because of the toxic nature of the product it is best to wear a gas mask while transferring the molten product.
4. Cyanogen bromide does not keep well and may at times even become explosively unstable on standing. It is preferable to prepare it just before using.

3. Discussion

Cyanogen bromide has been prepared from an aqueous solution of potassium cyanide and bromine at 0°;[1] by the action of bromine on an alkali cyanide in the presence of carbon tetrachloride and acetic acid;[2] and from bromine and moist mercuric cyanide.[3] Detailed directions have been published by Slotta for the preparation from bromine and aqueous potassium cyanide.[1]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 608
- Org. Syn. Coll. Vol. 7, 435

References and Notes

1. Langlois, Ann. chim. phys. (3) **61**, 482 (1861); Scholl, Ber. **29**, 1823 (1896); Baum, ibid. **41**, 523 (1908); Slotta, ibid. **67**, 1028 (1934).
2. National Aniline and Chemical Company, U. S. pat. 1,938,324 [C. A. **28**, 1148 (1934)].
3. Sérullas, Ann. chim. phys. (2) **34**, 100 (1827).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

calcium chloride (10043-52-4)

acetic acid (64-19-7)

sodium cyanide (143-33-9)

bromine (7726-95-6)

carbon tetrachloride (56-23-5)

potassium cyanide (151-50-8)

Cyanogen bromide (506-68-3)

mercuric cyanide (592-04-1)

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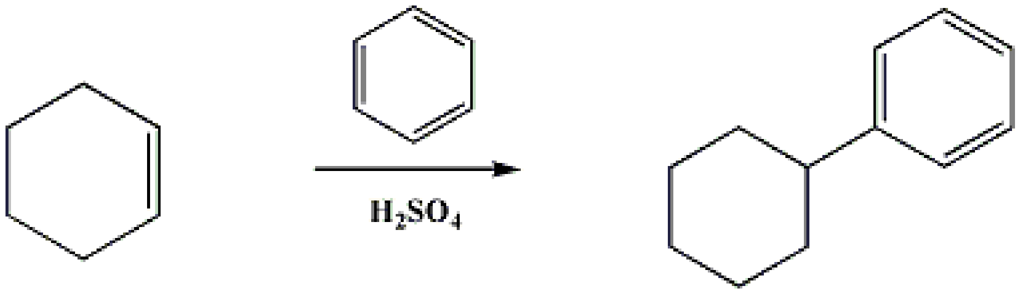
Organic Syntheses, CV 2, 151

CYCLOHEXYLBENZENE

[Cyclohexane, phenyl-]



Submitted by B. B. Corson and V. N. Ipatieff.
Checked by John R. Johnson and E. A. Cleveland.

1. Procedure

In a 1-l. three-necked flask equipped with a mechanical stirrer, dropping funnel, and thermometer are placed 468 g. (530 cc., 6 moles) of benzene and 92 g. (50 cc.) of concentrated sulfuric acid (sp. gr. 1.84). The mixture is cooled in an ice bath, and 164 g. (203 cc., 2 moles) of cyclohexene (Note 1) is added with stirring over a period of one and one-half hours, while the temperature is maintained between 5° and 10°. Stirring is continued for an additional hour after all the cyclohexene has been added.

The hydrocarbon layer is separated, cooled in ice, and washed with four 50-cc. portions of cold concentrated sulfuric acid (Note 2). The material is then washed twice with warm water (50°), twice with 3 per cent sodium hydroxide solution, and twice with pure water (Note 3). The hydrocarbon mixture is dried over anhydrous calcium chloride (Note 4) and subjected twice to fractional distillation, using a 30-cm. Vigreux or similar column; the cyclohexylbenzene is collected at 238–243° (Note 5) and (Note 6). The yield is 210–220 g. (65–68 per cent of the theoretical amount).

2. Notes

1. For the preparation of moderate amounts of cyclohexene the dehydration of cyclohexanol with 85 per cent phosphoric acid, according to the procedure of Dehn and Jackson, J. Am. Chem. Soc. **55**, 4285 (1933), is very convenient. Furthermore, very little carbonization occurs, in contrast with the sulfuric acid method described in Org. Syn. Coll. Vol. I, **1941**, 183, where there is much carbonization and the product is contaminated with sulfur dioxide.
In a 2-l. three-necked flask, carrying a separatory funnel and three-bulbed Wurtz column filled with broken glass tubing, is placed 200 g. of 85 per cent phosphoric acid. The column is attached to an *efficient* condenser leading to a receiver cooled in an ice bath, and the flask is heated in an oil bath at 165–170°.

Through the funnel 1 kg. (10 moles) of practical cyclohexanol is dropped in over a period of four to five hours. After the addition has been completed the temperature of the bath is raised gradually to 200° and maintained at 200° for one-half hour. During the whole operation the temperature at the top of the column does not rise above 90°. The upper layer of the distillate is separated (salt may be added to break up emulsions) and dried with anhydrous magnesium sulfate; the lower aqueous layer is saved for reworking if desired; likewise the spent drying agent may be treated with water to recover admixed cyclohexene. The crude cyclohexene is distilled in an efficient column, and the fraction boiling at 81–83° is collected. The yield is 660–690 g. (79–84 per cent of the theoretical amount). The residue consists largely of cyclohexanol and may be recycled as described below.

An additional 25–30 g. of cyclohexene may be obtained by combining the residue from the distillation of the crude cyclohexene with the water layer from the original distillate and distilling with 25 g. of 85 per cent phosphoric acid. This distillate is added to the low-boiling fraction from the distillation of the crude cyclohexene and separated. The upper layer is dried with anhydrous magnesium sulfate and distilled as described above.

The phosphoric acid may be recovered by diluting with water and filtering, then evaporating with a little nitric acid to the proper concentration.

The same procedure when used with 86 g. (1 mole) of cyclopentanol and 15 cc. of 85 per cent phosphoric acid gave 55 g. (81 per cent of the theoretical amount) of cyclopentene, b.p. 44–45°. No attempt was made to recover the cyclopentanol. (Oliver Grummitt and John R. Johnson, private communication.)

2. The purpose of the sulfuric acid is to convert dicyclohexyl sulfate to cyclohexyl hydrogen sulfate, which is removed by the subsequent washing operations.

3. To avoid emulsification as much as possible it is advantageous to use warm water rather than cold, and dilute alkali rather than concentrated. The milkiness of the aqueous wash liquid represents only a very small loss of material.

4. It is well to allow suspended water to settle by standing overnight and to separate again before adding the drying agent.

5. In a typical preparation the fractions collected during the second distillation were as follows: 78–85°, 296 g.; 85–235°, 2 g.; 235–238°, 2 g.; 238–243°, 215 g.; 243–265°, 2 g.; residue above 265°, 46 g.

6. The distillation residue becomes semi-solid on cooling owing to the separation of 1,4-dicyclohexylbenzene. The latter may be recovered by filtering with suction, washing with methyl alcohol, and crystallizing from acetone (using 4 cc. of acetone per gram of the crude solid). The yield of purified dicyclohexylbenzene, m.p. 100–101°, is 15–24 g.

3. Discussion

Cyclohexylbenzene has been prepared by the hydrogenation of biphenyl[1] and of

cyclohexenylbenzene;[2] by the reaction of cyclohexyl chloride[3] or bromide[4] with benzene in the presence of aluminum chloride; and from benzene and cyclohexene or cyclohexanol in the presence of aluminum chloride,[5] sulfuric acid,[6] or boron halides.[7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 102
- Org. Syn. Coll. Vol. 2, 171

References and Notes

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2. Sabatier and Murat, Compt. rend. **154**, 1390 (1912); Alder and Rickert, Ber. **71**, 379 (1938).
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5. Bodroux, Ann. chim. (10) **11**, 511 (1929); Berry and Reid, J. Am. Chem. Soc. **49**, 3142 (1927); Corson and Ipatieff, ibid. **59**, 645 (1937); Nametkin and Pokrovskaya, J. Gen. Chem. (U.S.S.R.) **7**, 962 (1937) [C. A. **31**, 5332 (1937)]; Tsukervanik and Sidorova, J. Gen. Chem. (U.S.S.R.) **7**, 641 (1937) [C. A. **31**, 5780 (1937)].
6. Deschauer, Ger. pat. 515,177 (Chem. Zentr. **1931**, I, 1829); Truffault, Compt. rend. **202**, 1286 (1936); Corson and Ipatieff, J. Am. Chem. Soc. **59**, 645 (1937).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

Benzene (71-43-2)

methyl alcohol (67-56-1)

sodium hydroxide (1310-73-2)

nitric acid (7697-37-2)

Cyclohexanol (108-93-0)

Cyclohexene (110-83-8)

sulfur dioxide (7446-09-5)

acetone (67-64-1)

aluminum chloride (3495-54-3)

phosphoric acid (7664-38-2)

Biphenyl (92-52-4)

cyclohexyl chloride (542-18-7)

magnesium sulfate (7487-88-9)

Cyclohexylbenzene, Cyclohexane, phenyl- (827-52-1)

cyclopentanol (96-41-3)

Cyclopentene (142-29-0)

dicyclohexyl sulfate

cyclohexyl hydrogen sulfate

1,4-dicyclohexylbenzene (1087-02-1)

cyclohexenylbenzene (771-98-2)

dicyclohexylbenzene

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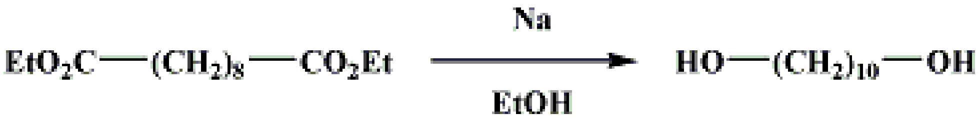
DECAMETHYLENE GLYCOL

[1,10-Decanediol]



Submitted by R. H. Manske
Checked by W. H. Carothers and W. L. McEwen.

1. Procedure

To a solution of 65 g. (0.25 mole) of ethyl sebacate (p. 277) in 800 cc. of absolute ethyl alcohol (Note 1) contained in a 3-l. round-bottomed flask, to which is attached a 60-cm. bulbed reflux condenser protected by a calcium chloride drying tube, is added 70 g. (3 gram atoms) of sodium in large pieces in one lot. The somewhat vigorous reaction is easily kept under control by immersing the entire flask in a mixture of crushed ice and water. In a short time the reaction has subsided somewhat; the flask is then removed from the cooling mixture, and the reaction is allowed to proceed without external cooling. Reduction is completed by heating the mixture on a steam bath until all the sodium has dissolved. The partly cooled mixture is diluted with 300 cc. of water and heated on the steam bath until no more alcohol distils. The remaining small amount of alcohol is removed by gently applying suction from a water pump. The residue is diluted with about 600 cc. of hot water, and the mixture is allowed to cool without being disturbed. The separated oil solidifies to a solid cake from which the lower aqueous layer is easily decanted. The solid is washed once with a little cold water, drained as completely as possible, and dried by heating in the flask on a steam bath under reduced pressure. The residue is extracted with four successive 250-cc. portions of hot benzene. The united extract is clarified with a little charcoal, filtered, and concentrated to a volume of about 60 cc. About 200 cc. of alcohol is added; the solution is filtered, concentrated to about 60 cc., and mixed with an equal volume of hot benzene. On slow cooling the mixture sets to a solid mass of large crystals, which are filtered and washed with ether. The yield of this product, which melts at 72–74° (corr.), is 32–33 g. (73–75 per cent of the theoretical amount) (Note 2), (Note 3), and (Note 4).

2. Notes

1. The alcohol must be perfectly dry, for any water present will cause immediate saponification of the ester with a consequent loss of yield. An excellent method for preparing completely anhydrous alcohol from alcohol of 99.5 per cent strength consists in dissolving 7 g. of sodium in 1 l. of the alcohol, adding 27.5 g. of a high-boiling ester such as ethyl phthalate, refluxing, and distilling.[1]

2. When several runs of the size indicated above or a single large run is made, the combined mother liquors may be evaporated free of solvent and the residue distilled under reduced pressure. The distillate on recrystallization from alcohol-benzene yields, however, only 5 to 7 grams of pure glycol per mole of sebacic ester.

3. The general method of Bouveault and Blanc has been used extensively for the preparation of glycols. Various modifications of detail have been suggested. Most of them are probably trivial or immaterial. In the experience of the checkers the rapid addition of the alcohol-ester mixture to the sodium gives results approximately equal to those described above, but mechanical stirring of the reaction mixture seriously reduces the yield.[2] The method used for isolating the glycol must be adapted to the properties of the glycol. At least for small runs the method of crystallization described here is the most suitable for decamethylene glycol. Lower members of the series are less readily crystallized. C. S. Marvel in a private communication has pointed out that for these glycols continuous ether extraction is the best method, and this has been used for hexamethylene glycol with success by the checkers.

Using the procedure described the checkers have prepared the following glycols.

		Yield, Per Cent
Heptamethylene glycol	b.p. 143–146°/8 mm.	88
Nonamethylene glycol	b.p. 147–150°/2 mm.	71
Undecamethylene glycol	m.p. 48–50°	57
Tridecamethylene glycol	m.p. 75–77°	88
Tetradecamethylene glycol	m.p. 83–85°	61
Octadecamethylene glycol	m.p. 96–98°	54

The heptamethylene glycol was separated by continuous ether extraction from the alkaline reduction solution after the latter had been diluted and distilled to remove the alcohol. The nonamethylene glycol was separated from the alkaline liquor by decantation (as above) and distilled. All the others were crystallized from benzene (without alcohol). Equally successful results have also been obtained with larger runs (e.g., 0.5 mole of ester).

4. Decamethylene glycol can also be prepared in excellent yields by the reduction of commercial butyl sebacate according to the procedure given for hexamethylene glycol on p. 325.

3. Discussion

Decamethylene glycol is best prepared by the reduction of sebacic esters either with sodium and an alcohol,[2] the Bouveault-Blanc procedure described above, or with hydrogen and a catalyst[3]—a procedure for which directions are given on p. 325. Both methods are applicable to the preparation of many other glycols.

Decamethylene glycol has also been prepared by the reduction of sebacamide with sodium and amyl alcohol[4] and by the reduction of methyl sebacate with sodium and liquid ammonia in absolute alcohol.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 262
- Org. Syn. Coll. Vol. 3, 397
- Org. Syn. Coll. Vol. 3, 637
- Org. Syn. Coll. Vol. 3, 829
- Org. Syn. Coll. Vol. 4, 427
- Org. Syn. Coll. Vol. 4, 461
- Org. Syn. Coll. Vol. 4, 630
- Org. Syn. Coll. Vol. 5, 1031

References and Notes

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2. Bouveault and Blanc, Compt. rend. **137**, 329 (1903); Bull. soc. chim. (3) **31**, 1205 (1904); Ger. pat. 164, 294 [Frdl. **8**, 1260 (1905–7)]; Franke and Kienberger, Monatsh. **33**, 1191 (1912); Chuit, Helv. Chim. Acta **9**, 264 (1926); Carothers, Hill, Kirby, and Jacobson, J. Am. Chem. Soc. **52**, 5287 (1930).
3. Folkers and Adkins, ibid. **54**, 1146 (1932).
4. Scheuble, Monatsh. **24**, 623 (1903); Scheuble and Loeble, ibid. **25**, 344 (1904); Alberti and Smieciuszewski, ibid. **27**, 411 (1906).
5. Chablay, Compt. rend. **156**, 1021 (1913); Ann. chim. (9) **8**, 216 (1917).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alcohol-benzene

ethyl alcohol, alcohol (64-17-5)

ammonia (7664-41-7)

Benzene (71-43-2)

ether (60-29-7)

hydrogen (1333-74-0)

sodium (13966-32-0)

amyl alcohol (71-41-0)

Decamethylene glycol, 1,10-Decanediol (112-47-0)

Ethyl sebacate (693-55-0)

ethyl phthalate

Hexamethylene glycol (629-11-8)

Heptamethylene glycol (629-30-1)

Nonamethylene glycol (3937-56-2)

Undecamethylene glycol (765-04-8)

Tridecamethylene glycol

Tetradecamethylene glycol (19812-64-7)

Octadecamethylene glycol

butyl sebacate

sebacamide (1740-54-1)

methyl sebacate (818-88-2)

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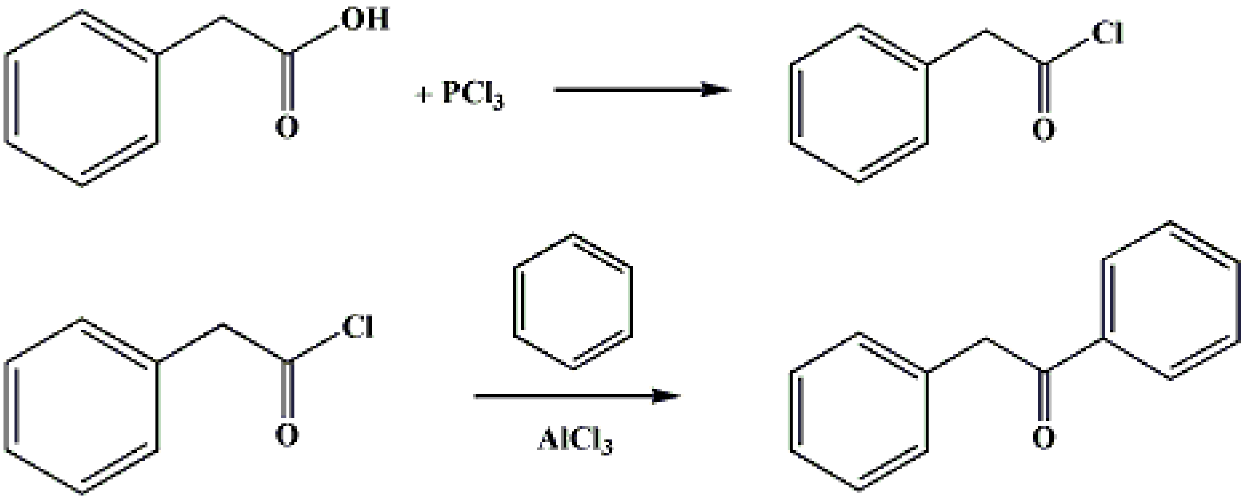
Organic Syntheses, CV 2, 156

DESOXYBENZOIN



Submitted by C. F. H. Allen and W. E. Barker.
Checked by C. S. Marvel and Tse-Tsing Chu.

1. Procedure

To 68 g. (0.5 mole) of phenylacetic acid (Note 1) in a 1-l. flask fitted with a reflux condenser and a system for absorbing hydrogen chloride, is added 35 g. (0.25 mole) of phosphorus trichloride. The mixture is heated on a steam bath for one hour. While the contents of the flask are still warm, 400 cc. of dry benzene is added. The benzene solution of phenylacetyl chloride is decanted from the residue of phosphorous acid onto 75 g. (0.56 mole) of anhydrous aluminum chloride in a dry, 1-l. flask which can be fitted to the same condenser. The reaction is vigorous at first and cooling is necessary. The mixture is refluxed for one hour on a steam bath, then cooled and poured into a mixture of 500 g. of cracked ice and 200 g. of concentrated hydrochloric acid. The benzene layer is separated, and the aqueous layer is extracted once with a mixture of 100 cc. of benzene and 100 cc. of ether (Note 2). The ether-benzene solution is washed once with 100 cc. of water (Note 3), and then dried over 40–50 g. of calcium chloride. The solution is filtered (Note 4) with suction into a 1-l. Claisen flask, and the solvent is removed by distillation under reduced pressure (Note 5); the residue consists of a brown oil which solidifies on cooling.

The crude material (91–92 g.) is purified by distillation under reduced pressure from a 250-cc. Claisen flask (Note 6). The product distils at 160°/5 mm. (172°/15 mm.; 200°/30 mm.) as a colorless oil which solidifies on cooling. The yield is 81–82 g. (82–83 per cent of the theoretical amount based on the phenylacetic acid used) of a product which melts at 53–54°. The product is recrystallized from methyl alcohol, using 4 cc. of solvent for each gram of product (Note 7); the yield is 55–56 g. of crystals melting at 55–56°. An additional 7 g. of crystals melting at 55–56° is obtained by cooling the filtrate in an ice-salt bath. On further cooling of the mother liquors, about 5 g. of

crystals melting at 54–55° is obtained. The total yield of purified product is 67–70 g. (Note 8). Further recrystallization of the product from methyl alcohol does not raise the melting point above 55–56°.

2. Notes

1. Directions for preparing phenylacetic acid are given in Org. Syn. Coll. Vol. I, **1941**, 436. A very high grade of phenylacetic acid can also be obtained from companies supplying essential oils and perfumers' supplies, and some of the acid from these commercial sources is superior to that prepared by the Organic Syntheses procedure. Since the quality of the desoxybenzoin depends upon the quality of the phenylacetic acid used, it is important to employ a superior grade of acid.
2. A mixture of benzene and ether is used instead of ether alone because a more efficient separation of the two layers is obtained.
3. Washing with sodium hydroxide at this point does not improve the quality of the product but does, as a result of the formation of emulsions, cause an 8–10 per cent loss in yield.
4. It is better to remove the calcium chloride by filtration than by decantation even though the solution looks clear. Small particles of calcium chloride and aluminum chloride not removed from the solution may cause bumping or even decomposition during the distillation.
5. Removal of the solvent by distillation under reduced pressure on the steam bath makes fractionation unnecessary during distillation of the product.
6. It is necessary to use a Claisen flask with a wide side-arm, since the desoxybenzoin may solidify and clog the apparatus. The distillation under reduced pressure is quiet if directions are followed carefully.
7. Methyl alcohol is the best solvent for purification. Desoxybenzoin tends to separate from ethyl alcohol as an oil.
8. Desoxybenzoin is somewhat unstable to light and consequently must be stored in dark bottles.

3. Discussion

Because of the availability of the starting materials, the most convenient methods of preparing desoxybenzoin are the Friedel-Crafts reaction,[1] described above, and the reduction of benzoin.[2] Desoxybenzoin can also be prepared, often with very good yields, by the treatment of bromostilbene with water in a sealed tube at 180–190°;[3] by the reduction of benzil;[4] by the action of zinc and hydrochloric acid on chlorobenzil;[5] from benzene, phenylacetic acid, and phosphorus pentoxide;[6] from benzoyl chloride and the magnesium halide derivative of sodium phenylacetate;[7] from benzylmagnesium chloride and benzamide;[8] and by alkaline hydrolysis of desylthioglycollic acid.[9]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 339

References and Notes

1. Graebe and Bungener, Ber. **12**, 1080 (1879).
2. Kohler, Am. Chem. J. **36**, 182 (1906); Irvine and Weir, J. Chem. Soc. **91**, 1388 (1907); Kohler and Nygaard, J. Am. Chem. Soc. **52**, 4133 (1930); Ballard and Dehn, ibid. **54**, 3970 (1932).
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4. Japp and Klingemann, J. Chem. Soc. **63**, 770 (1893).
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7. Ivanoff and Nicoloff, Bull. soc. chim. (4) **51**, 1331 (1932).
8. Jenkins, J. Am. Chem. Soc. **55**, 704 (1933).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Desoxybenzoin

ethyl alcohol (64-17-5)

calcium chloride (10043-52-4)

hydrogen chloride, hydrochloric acid (7647-01-0)

Benzene (71-43-2)

methyl alcohol (67-56-1)

ether (60-29-7)

sodium hydroxide (1310-73-2)

benzoyl chloride (98-88-4)

benzamide (55-21-0)

aluminum chloride (3495-54-3)

Benzil (134-81-6)

Benzoin (119-53-9)

zinc (7440-66-6)

Phenylacetic acid (103-82-2)

phosphorus trichloride (7719-12-2)

benzylmagnesium chloride (6921-34-2)

phenylacetyl chloride (103-80-0)

bromostilbene

chlorobenzil

sodium phenylacetate (114-70-5)

desylthioglycollic acid

phosphorous acid (13598-36-2)

phosphorus pentoxide (1314-56-3)

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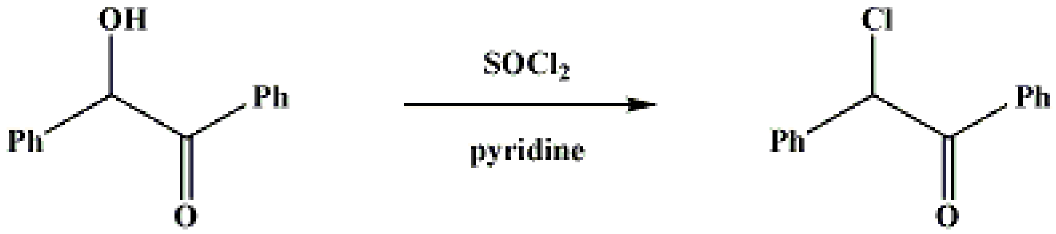
Organic Syntheses, *CV 2, 159*

DESYL CHLORIDE

[Acetophenone, α-chloro-α-phenyl-]



Submitted by A. M. Ward
Checked by C. S. Marvel and Tse-Tsing Chu.

1. Procedure

In a 1-l. beaker are placed 100 g. (0.47 mole) of benzoin (Org. Syn. Coll. Vol. I, **1941**, 94), and 50 g. (57 cc.) of pyridine. The mixture is heated until a solution is obtained, then cooled in an ice bath until solid. The mass is coarsely ground, and 75 g. (46 cc.; 0.63 mole) of thionyl chloride is added slowly with vigorous stirring and cooling in a water bath. After each addition of thionyl chloride, the reaction mixture becomes quite hot, and considerable amounts of sulfur dioxide and hydrogen chloride are evolved. At first the mass becomes pasty and then soon sets to a light yellow solid. After about an hour, water is added and the solid is coarsely ground and filtered. It is finely triturated twice with water, filtered by suction, and pressed as dry as possible. The white powder is dried to constant weight over sulfuric acid or calcium chloride. The yield of crude product is about 125 g. The compound is dissolved in 450 cc. of boiling 95 per cent alcohol (Note 1), filtered, and the filtrate cooled by running water. There is obtained 77 g. of colorless crystals which, after drying in the air, melt at 66–67°. On cooling the mother liquor in an ice-salt mixture, there is obtained an additional 9 g. of crystals melting at 65–66°. Further cooling of the filtrate yields no more product. The total yield is 80–86 g. (74–79 per cent of the theoretical amount) (Note 2) and (Note 3).

2. Notes

1. The product may be recrystallized from petroleum ether (b.p. 40–60°), but this solvent is less satisfactory for large amounts of material.
2. When the preparation is carried out with one-fifth these quantities the yield is only about 70 per cent of the theoretical amount.
3. Desyl chloride decomposes and becomes brown when exposed to sunlight, but is quite stable if kept in dark bottles.

3. Discussion

Desyl chloride has been prepared by the action of thionyl chloride on benzoin,[1] and on

l-benzoin.[2] It has also been prepared by the action of hydrogen chloride on azibenzil.[3]

References and Notes

1. Schroeter, Ber. **42**, 2348 (1909).
2. McKenzie and Wren, J. Chem. Soc. **97**, 481 (1910).
3. Curtius and Lang, J. prakt. Chem. (2) **44**, 547 (1891).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

azibenzil

alcohol (64-17-5)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrogen chloride (7647-01-0)

thionyl chloride (7719-09-7)

sulfur dioxide (7446-09-5)

pyridine (110-86-1)

Benzoin, l-benzoin (119-53-9)

Desyl chloride, Acetophenone, α-chloro-α-phenyl- (447-31-4)

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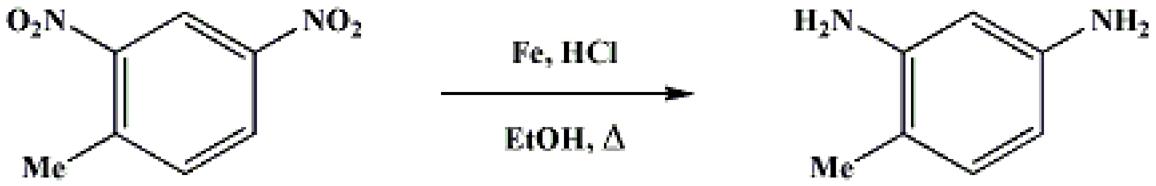
Organic Syntheses, CV 2, 160

2,4-DIAMINOTOLUENE

[2,4-Toluenediamine]



Submitted by S. A. Mahood and P. V. L. Schaffner.
Checked by Roger Adams and P. R. Shildneck.

1. Procedure

In a 500-cc. three-necked flask, fitted with a reflux condenser and a mechanical stirrer (Note 1), are placed 45.5 g. (0.25 mole) of 2,4-dinitrotoluene (Note 2), 85 g. (1.5 moles) of iron (Note 3), and 100 cc. of 50 per cent (by weight) ethyl alcohol (Note 4). The mixture is heated to boiling on a water bath, the stirrer is started (Note 5), and a solution of 5.2 cc. (0.06 mole) of concentrated hydrochloric acid in 25 cc. of 50 per cent (by weight) ethyl alcohol is added slowly (Note 6). The mixture is refluxed for two hours after addition of the acid is complete. At the end of this time the apparatus is disconnected and the hot mixture is made just alkaline to litmus by the addition of the calculated amount of 15 per cent alcoholic potassium hydroxide solution (Note 7). Without allowing the mixture to cool, the iron is removed by filtration and the reaction flask is rinsed with two 50-cc. portions of 95 per cent ethyl alcohol; the same alcohol is used to wash the iron residue. To the filtrate is added 84 cc. of 6 *N* sulfuric acid; the normal sulfate of 2,4-diaminotoluene precipitates. The mixture is cooled to 25° and filtered by suction. The product is washed with two 25-cc. portions of 95 per cent ethyl alcohol, dried in the air for two hours (Note 8) and then dried to constant weight at 110°. The yield is 49 g. (89 per cent of the theoretical amount) of a product which melts with decomposition at 249–251° (Note 9).

A solution of 20 g. of 2,4-diaminotoluene sulfate in 200 cc. of water at 60° is cooled to 40° (Note 10), and made alkaline to litmus with saturated sodium hydroxide solution (Note 11). To this solution is added 15 g. of the sulfate, which is dissolved by raising the temperature of the mixture to 55°. The solution is cooled to 40° and made slightly alkaline to litmus with saturated sodium hydroxide solution. The mixture is then cooled to 30° and filtered by suction. The remainder of the diaminotoluene sulfate (14 g.) is then dissolved in the filtrate by heating the mixture to 55°. The solution is cooled to 40° and again made alkaline to litmus with saturated sodium hydroxide solution. The mixture is cooled to 25°, and the diaminotoluene crystals are collected on a Büchner funnel. The entire product is dried to constant weight in a desiccator over calcium chloride. The yield is 26.5 g. (95 per cent of the theoretical amount based on

the diaminotoluene sulfate used) of a product melting at 97–98.5°.

The crude diaminotoluene (Note 12) is dissolved in eight times its weight of benzene (212 g.) at 70°, and the solution is filtered quickly through a hot Büchner funnel (Note 13) with moderate suction (Note 14). The filtrate is cooled to 25°, and the mother liquor is decanted from the brown crystals. The mother liquor is concentrated to a volume of 25 cc. by distillation under atmospheric pressure and then cooled to 25°. The mother liquor is decanted from the diaminotoluene, and the entire product is dried in the air. The yield is 22.5 g. (81 per cent of the theoretical amount based on the diaminotoluene sulfate used; 74 per cent based on the dinitrotoluene used) of a product which melts at 98° (Note 15).

2. Notes

1. The mechanical stirrer should extend well to the bottom of the flask in order to prevent caking of the iron during the reduction.
2. The 2,4-dinitrotoluene used must be free from oil and have the correct melting point of 71°.
3. The iron used may be either iron powder or iron filings, but it should pass a 100-mesh sieve in order to give invariable results. If iron particles of larger size are used the reduction may be incomplete, although complete reduction was obtained with a sample of iron powder contaminated with filings.
4. The concentration of the alcoholic solution is important. Incomplete reduction was obtained with 95 per cent alcohol, as well as with methylated spirit, as suggested by West.[1] Complete reduction may be obtained in aqueous solution, but the product is difficult to isolate and is not always pure.
5. The stirrer should be run at such a speed that the iron particles do not settle or the iron will cake during the reduction. A speed of about 750 r.p.m. is satisfactory.
6. The reaction between the iron and hydrochloric acid is very vigorous, especially with iron powder, and the hydrochloric acid must be added very slowly at first. About one drop every ten seconds for the first ten minutes is satisfactory, and this may be increased to one drop every four seconds after this length of time has elapsed. The addition of the hydrochloric acid should require about thirty minutes.
7. The exact amount of alcoholic potassium hydroxide is determined previously by titration of a separate sample of 5.2 cc. of concentrated hydrochloric acid with the alcoholic potassium hydroxide.
8. Most of the alcohol and any aldehyde must be removed by evaporation at room temperature since heating the wet product at once to 110° always causes the formation of orange-colored impurities.
9. The same percentage yields of the sulfate were obtained using six times the amounts of materials.
10. The solution is cooled before addition of the alkali, as this is accompanied by a rise in temperature.

11. Saturated sodium hydroxide solution is used rather than more dilute solutions since dilution of the diaminotoluene solution is to be avoided as much as possible.
12. The diaminotoluene obtained by neutralizing the sulfate contains varying amounts of sodium sulfate and possibly some diaminotoluene sulfate, both of which are insoluble in benzene.
13. A hot Büchner funnel (70° or above) is used to prevent crystallization of the diaminotoluene in the funnel.
14. Moderate suction is used to prevent boiling of the benzene since this causes crystallization of the diaminotoluene in the funnel.
15. In an attempt to prepare a pure white product, the dry recrystallized material was distilled rapidly at atmospheric pressure using a short air condenser. A yellow product distilling at 292° was obtained. On distilling the recrystallized material at 148–150°/8 mm., a white product was obtained.

3. Discussion

2,4-Diaminotoluene has been prepared by reduction of 2,4-dinitrotoluene with iron and acetic acid,[2] electrolytically,[3] or with hydrogen and Raney nickel;[4] and by reduction of 4-nitro-*o*-toluidine[5] or 2,4-dinitrobenzoyl chloride[6] with tin and hydrochloric acid.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 63

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethyl alcohol, alcohol (64-17-5)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

iron, iron filings, iron powder (7439-89-6)

sodium sulfate (7757-82-6)

tin (7440-31-5)

Raney nickel (7440-02-0)

potassium hydroxide (1310-58-3)

4-nitro-o-toluidine (99-52-5)

2,4-Diaminotoluene, 2,4-Toluenediamine, diaminotoluene (95-80-7)

2,4-dinitrotoluene, dinitrotoluene (121-14-2)

2,4-diaminotoluene sulfate, diaminotoluene sulfate

2,4-dinitrobenzoyl chloride

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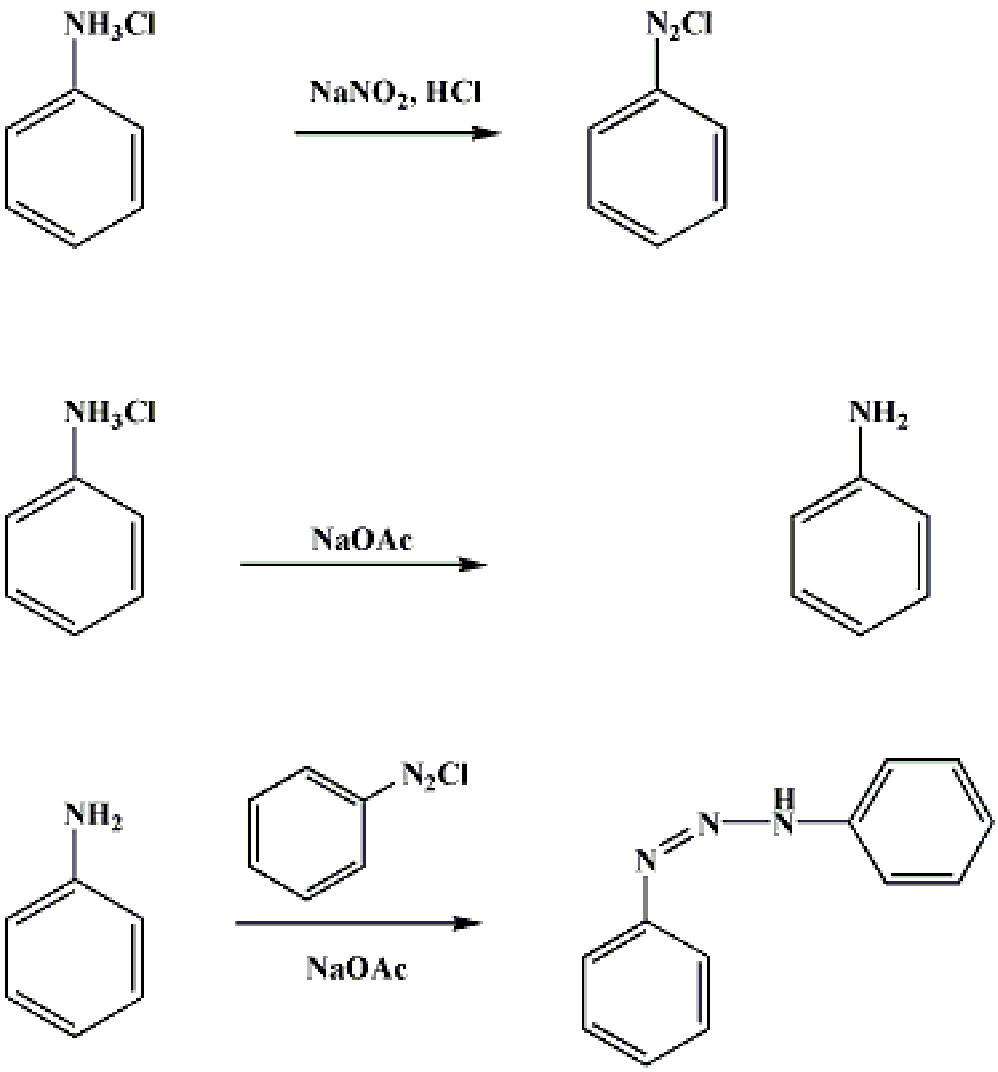
DIAZOAMINOBENZENE

[Triazene, 1,3-diphenyl-]



Submitted by W. W. Hartman and J. B. Dickey.
Checked by C. R. Noller and C. R. Kemp.

1. Procedure

In a 5-l. flask fitted with a mechanical stirrer and a dropping funnel are placed 1 kg. of cracked ice, 1.5 l. of water, 279 g. (3 moles) of a technical grade of aniline, and 458 g. (388 cc., 4.5 moles) of concentrated hydrochloric acid (sp. gr. 1.18). The stirrer is started, and a solution of 109 g. (1.5 moles) of 95 per cent sodium nitrite in 250 cc. of water is added over a period of fifteen minutes. The reaction mixture is then stirred for fifteen minutes, and a solution of 422 g. (3.1 moles) of crystalline sodium acetate dissolved in 800 cc. of water is added over a period of five minutes. A yellow precipitate of diazoaminobenzene begins to form at once. Stirring is continued for forty-five minutes, keeping the temperature below 20° (Note 1). The yellow

diazoaminobenzene is filtered on a 19-cm. Büchner funnel (Note 2), washed with 5 l. of cold water, and then sucked as dry as possible and spread out on a sheet of paper to dry (Note 3). The product thus obtained is dissolved in 4 l. of boiling ligroin (b.p. 60–90°) (Note 4), filtered, and allowed to cool to room temperature and stand overnight. When crystallization is complete, the yellow crystals are filtered on a 19-cm. Büchner funnel, washed with 500 cc. of cold ligroin (b.p. 60–90°), and dried at room temperature. The yield of yellow crystals melting at 92–94° is 242–251 g. (82–85 per cent of the theoretical amount) (Note 5). If a product of greater purity is desired, the diazoaminobenzene is dissolved in 4 l. of boiling ligroin (b.p. 60–90°) and crystallized as before. The recrystallized diazoaminobenzene weighs 204–218 g. (69–73 per cent of the theoretical amount) and melts at 94–96° (Note 6) and (Note 7).

2. Notes

1. The temperature noted is not known to be the maximum temperature at which the reaction may be run.
2. A centrifuge of suitable size is preferable.
3. A rubber dam is fitted over the top of the Büchner funnel and held in place by rubber bands in order to remove as much of the water as possible.
4. Prolonged heating of the diazoaminobenzene with ligroin causes decomposition. For this reason it is well to heat the ligroin to boiling before it is added to the product to be crystallized. Solution is effected as rapidly as possible. If the crude diazoaminobenzene is not dry, a layer of water will separate at the bottom of the flask. This should be removed as completely as possible before filtering the hot ligroin solution.
5. An additional crop of crystals weighing 20–25 g. and melting at 79–83° can be obtained by evaporating the mother liquors to 1 l. and chilling in an ice bath.
6. The size of the run may be halved; a run with half quantities gave 125 g. of product.
7. Pure diazoaminobenzene is described as faintly yellow needles melting at 100°. A procedure for the purification of diazoaminobenzene and other aminoazo compounds has been described by Dwyer.[1]

3. Discussion

Diazoaminobenzene has been prepared by the action of sodium nitrite on aniline sulfate;[2] by the action of sodium nitrite on aniline hydrochloride;[3] by the action of sodium nitrite and sodium acetate on aniline hydrochloride;[4] by the action of ammonium nitrate and hydrogen sulfide on aniline hydrochloride in the presence of iron;[5] by the action of sodium nitrite and potassium chromate or dichromate on aniline;[6] and from aniline and amyl nitrite.[7]

Diazoaminobenzene has also been prepared by the action of nitrous acid gas on aniline in alcohol;[8] by the action of silver nitrite on aniline hydrochloride;[9] and together with

phenylurea by the action of nitrosophenylurea on aniline in methyl alcohol.[10] Niementowski and Roszkowski[11] have reported studies on the diazotization of aniline, aniline hydrochloride, and aniline sulfate with sodium nitrite and silver nitrite. The procedure described is adapted from that of Fischer.[4]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ligroin

potassium chromate or dichromate

hydrochloric acid (7647-01-0)

methyl alcohol (67-56-1)

sodium acetate (127-09-3)

aniline (62-53-3)

iron (7439-89-6)

hydrogen sulfide (7783-06-4)

aniline hydrochloride (142-04-1)

sodium nitrite (7632-00-0)

nitrous acid (7782-77-6)

amyl nitrite (463-04-7)

ammonium nitrate

Phenylurea (64-10-8)

aniline sulfate

Diazoaminobenzene, Triazene, 1,3-diphenyl- (136-35-6)

silver nitrite (7783-99-5)

nitrosophenylurea

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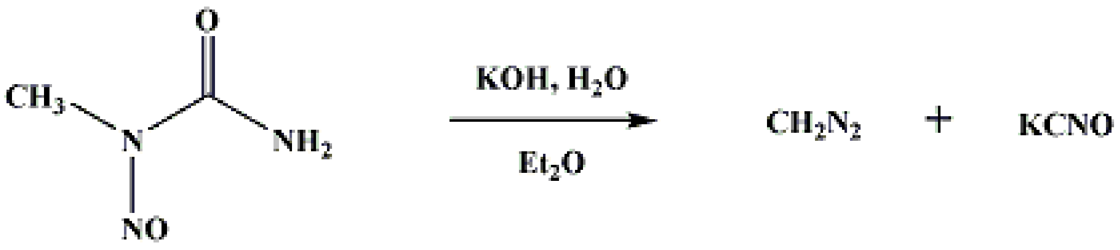
Organic Syntheses, CV 2, 165

DIAZOMETHANE

[Methane, diazo-]



Submitted by F. Arndt
Checked by C. R. Noller and I. Bergsteinsson.

1. Procedure

Diazomethane is highly toxic. The utmost care is essential in the preparation and use of this material.

In a 500-cc. round-bottomed flask are placed 60 cc. of 50 per cent aqueous potassium hydroxide solution and 200 cc. of ether. The mixture is cooled to 5°, and 20.6 g. (0.2 mole) of nitrosomethylurea (p. 461) is added with shaking. The flask is fitted with a condenser set for distillation. The lower end of the condenser carries an adapter passing through a two-holed rubber stopper and dipping below the surface of 40 cc. of ether contained in a 300-cc. Erlenmeyer flask and cooled in an ice-salt mixture. The exit gases are passed through a second 40-cc. portion of ether likewise cooled below 0°. The reaction flask is placed in a water bath at 50° and brought to the boiling point of the ether with occasional shaking. The ether is distilled until it comes over colorless, which is usually the case after two-thirds of the ether has been distilled. *Under no circumstances should all the ether be distilled*. The combined ether solutions in the receiving flasks contain from 5.3 to 5.9 g. of diazomethane (63–70 per cent of the theoretical amount) (Note 1) and (Note 2), which is sufficiently dry for most purposes (Note 3).

If a dry solution of diazomethane is required, the ether solution is allowed to stand for three hours over pellets of pure potassium hydroxide (Note 4). For extremely dry solutions, further drying is effected with sodium wire.

2. Notes

1. For analysis an aliquot portion (about one-twentieth) of the solution is allowed to react at 0° with a solution of an accurately weighed sample of about 1.3 g. of pure benzoic acid in 50 cc. of absolute ether. The benzoic acid must be in excess as evidenced by the complete decolorization of the diazomethane

solution. The unreacted benzoic acid is titrated with standard 0.2 *N* alkali.

2. The same procedure may be used for preparing two or three times the quantity obtained here.

3. The ether solution does not contain ammonia or methyl alcohol. It does contain traces of methylamine, but this is also present when diazomethane is prepared from nitrosomethylurethane.

If one does not require a pure, water-free solution, as is frequently the case when carrying out tests with small amounts of material, a simplified procedure may be used. To 100 cc. of ether is added 30 cc. of 40 per cent potassium hydroxide, and the mixture is cooled to 5°. To this, with continued cooling and shaking, is added 10 g. of finely powdered nitrosomethylurea in small portions over a period of one to two minutes. The deep yellow ether layer can be decanted readily; it contains about 2.8 g. of diazomethane, together with some dissolved impurities and water. The water may be removed by drying for three hours over pellets of pure potassium hydroxide. Solutions of diazomethane in benzene and other water-immiscible organic solvents may be prepared in the same way.

4. Broken sticks should not be used as the sharp corners facilitate the decomposition of the diazomethane.

3. Discussion

There are four methods of practical importance for the preparation of diazomethane: the action of alcoholic potassium hydroxide[1] or sodium dissolved in glycol[2] on nitrosomethylurethane; heating a mixture of potassium hydroxide, chloroform, hydrazine hydrate, and absolute alcohol;[3] the action of potassium hydroxide on nitrosomethylurea,[4] the method described above; and the action of alkoxides on the nitroso derivative of β-methylaminoisobutyl methyl ketone.[5] The choice of a method will usually depend upon the availability of the starting material. Directions for the preparation of the starting materials used in the first three methods are given in this volume; directions for preparing the nitroso derivative of β-methylaminoisobutyl methyl ketone and from it diazomethane will appear in a forthcoming volume of Organic Syntheses.

Arndt, Loewe, and Avan have discussed the merits of the various methods of preparing diazomethane,[6] as has Eistert.[7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 244
- Org. Syn. Coll. Vol. 4, 250
- Org. Syn. Coll. Vol. 5, 231
- Org. Syn. Coll. Vol. 5, 245
- Org. Syn. Coll. Vol. 5, 351
- Org. Syn. Coll. Vol. 5, 877

- Org. Syn. Coll. Vol. 5, 1099
- Org. Syn. Coll. Vol. 6, 432
- Org. Syn. Coll. Vol. 6, 613
- Org. Syn. Coll. Vol. 8, 196
- Org. Syn. Coll. Vol. 9, 300

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2. Meerwein and Burneleit, ibid. **61**, 1845 (1928).
3. Staudinger and Kupfer, ibid. **45**, 505 (1912).
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5. Adamson and Kenner, J. Chem. Soc. **1935**, 286; **1937**, 1551.
6. Arndt, Loewe, and Avan, Ber. **73**, 606 (1940).
7. Eistert, Angew. Chem. **54**, 99, 124 (1941).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

nitroso derivative of β-methylaminoisobutyl methyl ketone

alcohol (64-17-5)

ammonia (7664-41-7)

Benzene (71-43-2)

methyl alcohol (67-56-1)

ether (60-29-7)

chloroform (67-66-3)

Benzoic acid (65-85-0)

potassium hydroxide (1310-58-3)

sodium, sodium wire (13966-32-0)

hydrazine hydrate (7803-57-8)

methylamine (74-89-5)

Diazomethane, Methane, diazo- (334-88-3)

Nitrosomethylurea

Nitrosomethylurethane

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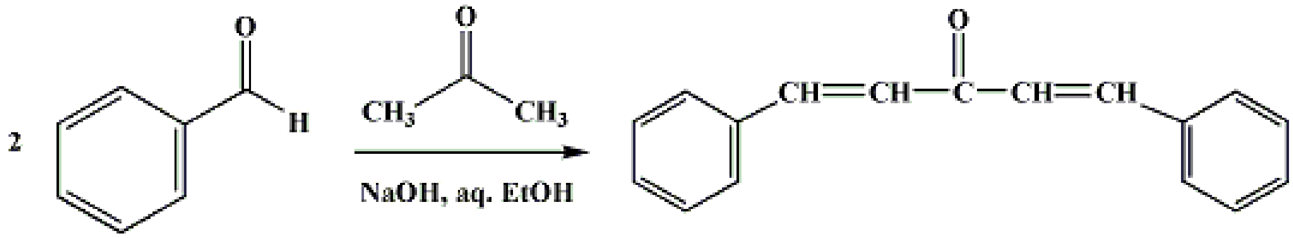
Organic Syntheses, CV 2, 167

DIBENZALACETONE

[3-Pentanone, 1,5-diphenyl-]



Submitted by Charles R. Conard and Morris A. Dolliver.
Checked by H. Lohse and C. R. Noller.

1. Procedure

A cooled solution of 100 g. of sodium hydroxide in 1 l. of water and 800 cc. of alcohol (Note 1) is placed in a 2-l. wide-mouthed glass jar which is surrounded with water and fitted with a mechanical stirrer. The solution is kept at about 20–25° and stirred vigorously (Note 2) while one-half of a mixture of 106 g. (1 mole) of benzaldehyde and 29 g. (0.5 mole) of acetone is added (Note 3). In about two or three minutes a yellow cloud forms which soon becomes a flocculent precipitate. After fifteen minutes the rest of the mixed reagents is added, and the container is rinsed with a little alcohol which is added to the mixture. Vigorous stirring is continued for one-half hour longer, and the mush is then filtered with suction on a large Büchner funnel. The product is thoroughly washed with distilled water (Note 4) and then dried at room temperature to constant weight. The yield is 105–110 g. (90–94 per cent of the theoretical amount) (Note 5) of a product which melts at 104–107°.

The crude dibenzalacetone may be recrystallized from hot ethyl acetate, using 100 cc. of solvent for each 40 g. of material. The recovery in this purification is about 80 per cent; the purified product melts at 110–111°.

2. Notes

1. Sufficient alcohol is used to dissolve the benzaldehyde rapidly and to retain the benzalacetone in solution until it has had time to react with the second molecule of aldehyde. Lower concentrations of base slow up the formation of the dibenzalacetone and thus favor side reactions which yield a sticky product. Higher concentrations of base give added difficulty in washing. These concentrations were suggested by, and are approximately the same as, those used in the preparation of benzalacetophenone described in Org. Syn. Coll. Vol. I, **1941**, 78.
2. Only temperatures between 20 and 25° were tried; it was assumed that a change of temperature would have the same effect that it has in the preparation of benzalacetophenone mentioned above.
Stirring is essential, as it makes considerable difference in the uniformity of the product.
3. The benzaldehyde was u.s.p. quality which had been washed with sodium carbonate solution and distilled. Commercial c.p. acetone was used. The theoretical quantities are used, since an excess of benzaldehyde results in a sticky product while an excess of acetone favors the production of benzalacetone. The mixture is prepared before addition in order to ensure

additions of equivalent quantities.
4. Since the product is practically insoluble in water, large amounts can be used in the washing. Sodium compounds are probably the chief impurities. The dried product contains some sodium carbonate which results from the failure to remove the sodium hydroxide completely. There remain also the impurities insoluble in water. However, the product is pure enough for use in most reactions.
5. If the mush is allowed to stand several hours, chilled, and filtered cold, a slightly larger yield is obtained, but this is not worth while. The filtrate may be used as a medium for a second run in which about 93 per cent of the theoretical yield is obtained. The melting point of the second product is slightly lower.

3. Discussion

Dibenzalacetone has been prepared by condensing benzaldehyde with acetone using as condensing agents dry hydrogen chloride,[1] 10 per cent sodium hydroxide solution,[2] and glacial acetic acid with sulfuric acid.[3] It has also been obtained by condensing benzalacetone with benzaldehyde in the presence of dilute sodium hydroxide.[4] Straus and Ecker[5] were the first to record the use of ethyl acetate for crystallization.

References and Notes

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3. Claisen and Claparède, ibid. **14**, 2460 (1881).
4. Claisen and Ponder, Ann. **223**, 141 (1884).
5. Straus and Ecker, Ber. **39**, 2988 (1906).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alcohol (64-17-5)

sulfuric acid (7664-93-9)

hydrogen chloride (7647-01-0)

acetic acid (64-19-7)

ethyl acetate (141-78-6)

sodium hydroxide (1310-73-2)

sodium carbonate (497-19-8)

Benzalacetophenone (94-41-7)

benzaldehyde (100-52-7)

acetone (67-64-1)

Benzalacetone (122-57-6)

Dibenzalacetone (35225-79-7)

3-Pentanone, 1,5-diphenyl-

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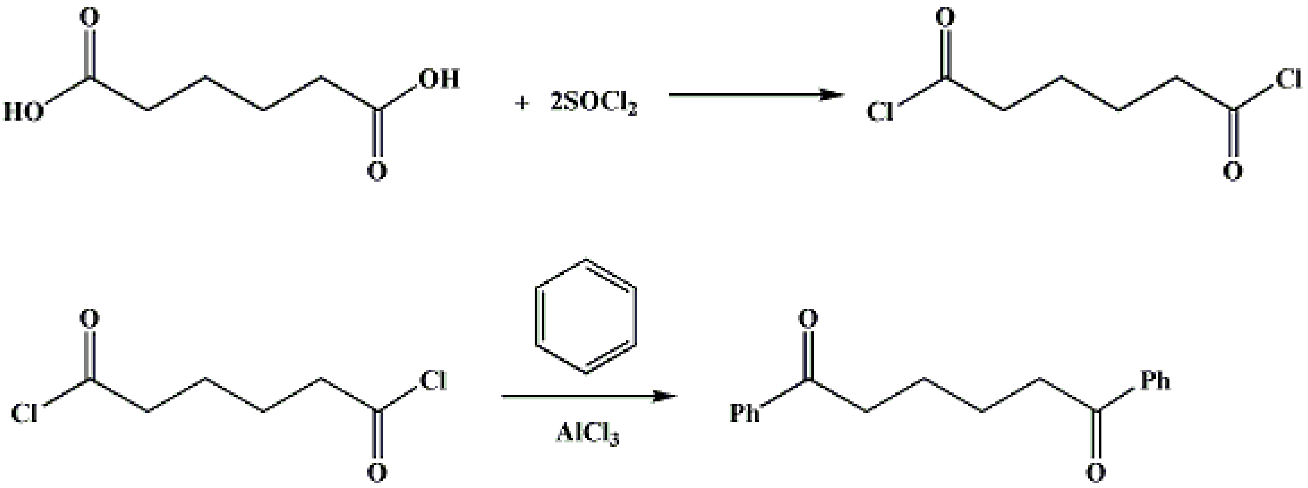
1,4-DIBENZOYLBUTANE

[1,6-Hexanedione, 1,6-diphenyl-]



Submitted by Reynold C. Fuson and Joseph T. Walker.
Checked by W. H. Carothers and W. L. McEwen.

1. Procedure

One mole (146 g.) of adipic acid (Org. Syn. Coll. Vol. I, **1941**, 18), previously dried over sulfuric acid in a vacuum, is placed in a 1-l. round-bottomed flask equipped with a condenser, and 357 g. (217 cc., 3 moles) of thionyl chloride is added at once. The mixture is heated gently on a water bath held at a temperature of 50–60°. After about four hours, solution is complete and evolution of hydrogen chloride has ceased. The flask is now connected to a downward condenser and heated under diminished pressure by a water bath to remove any excess thionyl chloride. The light yellow residue of adipyl chloride is ready for use.

A mixture of 300 g. (2.25 moles) of anhydrous aluminum chloride and 1.5 l. (17 moles) of benzene (dried over sodium and distilled) is placed in a 3-l. three-necked flask equipped with a mercury-sealed stirrer, a reflux condenser, and a dropping funnel. The reaction mixture is cooled in an ice bath, and, with rapid stirring, the adipyl chloride is added through the dropping funnel at an *even rate* during the course of forty-five minutes (Note 1). The reaction mixture darkens slowly but does not become black. After the adipyl chloride has been added, the ice bath is removed and stirring is continued for two hours at room temperature (Note 2).

The solution is then poured slowly, with constant stirring, into a mixture of 1 kg. of cracked ice and 200 cc. of concentrated hydrochloric acid in a 5-l. flask. There should be a small quantity of ice remaining after decomposition is complete. When the ice has melted, the mixture of water, precipitated dibenzoylbutane, and benzene is divided into two equal portions, and 1–1.25 l. of benzene is added to each. The solid is dissolved by shaking and gentle warming on the steam bath; the benzene layers are separated and washed, first with an equal volume of dilute sodium carbonate solution, and then with water.

The benzene solution is placed in a 5-l. flask, and 3–3.5 l. of benzene is removed by distillation. The residual liquid is set aside and allowed to cool. The dibenzoylbutane which crystallizes after several hours is filtered; it melts at 104–107° (Note 3). An equal volume of ether is added to the light brown filtrate, and a second crop of crystals is obtained (Note 4).

The yield of crude product is 199–216 g. (75–81 per cent of the theoretical amount). The material may be recrystallized by dissolving it in 1 l. of hot 95 per cent ethyl alcohol. Upon cooling, crystals which melt at 106–107° separate. The yield of recrystallized product is 190–210 g.

2. Notes

1. It is very important to keep the reaction mixture cold during the addition of the acid chloride; otherwise there will be charring which will lead to a discolored product.
2. If the reaction mixture is allowed to stand at this point the yield is materially decreased.
3. The melting point and color of the crude product seem to be influenced by the quality of the aluminum chloride. The checkers used a very pure aluminum chloride and found that the color of the reaction mixture was never darker than a bright orange, that the crude product was always colorless, and that the crude product always melted at 106–108°. If a less pure aluminum chloride is used the crude product is sometimes brown. This color may be completely removed by washing with a few cubic centimeters of cold ether, in which the diketone is only slightly soluble.
4. The checkers found that only 5–6 g. of material was precipitated by the addition of ether. For this reason it seems scarcely worth while to carry out this part of the procedure.

3. Discussion

Dibenzoylbutane has been prepared by the action of aluminum chloride on a mixture of benzene and adipyl chloride[1] or benzene and polymeric adipic anhydride.[2] It has also been obtained from adiponitrile and phenylmagnesium bromide,[3] and as a by-product in the action of zinc on α,β-dibromopropiophenone[4] and α,α'-dibromodibenzoylbutane.[5] Melting points between 102°[1] and 112°[4] have been recorded for the diketone.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 401

References and Notes

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2. Hill, J. Am. Chem. Soc. **54**, 4105 (1932).
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4. Kohler, Am. Chem. J. **42**, 384 (1909).
5. Fuson and Farlow, J. Am. Chem. Soc. **56**, 1593 (1934).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethyl alcohol (64-17-5)

sulfuric acid (7664-93-9)

hydrogen chloride, hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether (60-29-7)

thionyl chloride (7719-09-7)

Adipic acid (124-04-9)

sodium carbonate (497-19-8)

aluminum chloride (3495-54-3)

zinc (7440-66-6)

sodium (13966-32-0)

Phenylmagnesium bromide (100-58-3)

1,4-Dibenzoylbutane, 1,6-Hexanedione, 1,6-diphenyl- (3375-38-0)

adipyl chloride (111-50-2)

dibenzoylbutane

adipic anhydride

adiponitrile (111-69-3)

α,β-dibromopropiophenone

α,α'-dibromodibenzoylbutane

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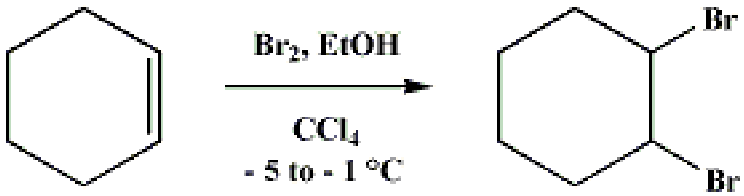
1,2-DIBROMOCYCLOHEXANE

[Cyclohexane, 1,2-dibromo-]



Submitted by H. R. Snyder and L. A. Brooks.
Checked by Lee Irvin Smith, R. T. Arnold, and John Ryan.

1. Procedure

In a 2-l. three-necked, round-bottomed flask, fitted with a 500-cc. separatory funnel, a mechanical stirrer, and a thermometer, is placed a solution of 123 g. (1.5 moles) of cyclohexene (Note 1) in a mixture of 300 cc. of carbon tetrachloride and 15 cc. of absolute alcohol. The flask is surrounded by an ice-salt bath. The stirrer is started, and, when the temperature has reached –5°, a solution of 210 g. (67 cc., 1.3 moles) of bromine in 145 cc. of carbon tetrachloride is added from the separatory funnel at such a rate that the temperature of the reaction mixture does not exceed –1° (Note 2). The addition requires about three hours.

When the bromine has been added the contents of the flask are transferred directly to a 1-l. modified Claisen flask and the carbon tetrachloride and excess cyclohexene are distilled from a water bath (Note 3), (Note 4), and (Note 5). The water bath is replaced by an oil bath and the product distilled under reduced pressure. There is a small low-boiling fraction, and then pure dibromocyclohexane distils at 99–103°/16 mm. (108–112°/25 mm.). The yield is 303 g. (95 per cent of the theoretical amount) (Note 6) and (Note 7).

2. Notes

1. Cyclohexene boiling over a two-degree range is satisfactory for this preparation. Directions for preparing cyclohexene are given in Org. Syn. Coll. Vol. I, **1941**, 183 and on p. 152 above.
2. Unless the temperature is controlled carefully, the yield is poor because of substitution reactions. Even at this low temperature some substitution occurs unless the excess of cyclohexene is used.
3. The three-necked flask may be rinsed with a little carbon tetrachloride.
4. The dibromide decomposes on continued exposure to the air and becomes very dark. Hence the product should be distilled at once.
5. The low-boiling distillate contains a trace of the dibromide as shown by the

fact that it darkens on exposure to the air.
6. The product is stored best in sealed bottles with as little exposure to the air as possible.
7. A product which will not darken may be obtained by the following purification: The crude dibromide is shaken for five minutes with about one-third its volume of 20 per cent ethyl alcoholic potassium hydroxide. The mixture is diluted with its own volume of water and the organic layer is washed free of alkali, dried, and distilled. Material so treated will stay clear indefinitely. The loss in the purification is about 10 per cent. (Wm. Von Eggers Doering and Aldrich Durant, Jr., private communication.)

3. Discussion

1,2-Dibromocyclohexane has been prepared from cyclohexene by the addition of bromine in chloroform,[1] carbon tetrachloride,[2] ether,[3] glacial acetic acid,[4] aqueous sodium bromide,[5] and in the absence of a solvent.[6] The bromination in carbon tetrachloride containing a little alcohol is more satisfactory than the bromination in carbon tetrachloride which is described in an earlier volume.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 285

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethyl alcoholic potassium hydroxide

alcohol (64-17-5)

acetic acid (64-19-7)

ether (60-29-7)

chloroform (67-66-3)

Cyclohexene (110-83-8)

bromine (7726-95-6)

sodium bromide (7647-15-6)

carbon tetrachloride (56-23-5)

1,2-Dibromocyclohexane, Cyclohexane, 1,2-dibromo- (5401-62-7)

dibromocyclohexane

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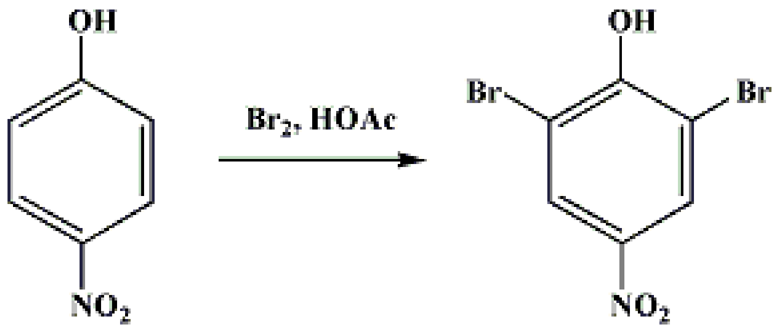
2,6-DIBROMO-4-NITROPHENOL

[Phenol, 2,6-dibromo-4-nitro-]



Submitted by W. W. Hartman and J. B. Dickey.
Checked by Louis F. Fieser and C. H. Fisher.

1. Procedure

In a 5-l. round-bottomed flask, fitted with a liquid-sealed mechanical stirrer, a dropping funnel, and a tube leading to a gas trap to carry off the hydrogen bromide, 278 g. (2 moles) of *p*-nitrophenol (m.p. 112–113°) is dissolved in 830 cc. of glacial acetic acid. To this solution at room temperature is added, dropwise with stirring during the course of three hours, a solution of 750 g. (240 cc., 4.7 moles) of bromine in 700 cc. of glacial acetic acid. After the addition of the bromine the reaction mixture is stirred for one-half hour and then warmed on the steam bath (internal temperature about 85°) for one hour in order to remove as much of the excess bromine as possible. The last traces of bromine are removed by passing a stream of air into the reaction mixture, which then has a yellow or brown color. The mixture is treated with 1.1 l. of cold water, stirred until cool (Note 1), and allowed to stand in ice, or in an ice chest, overnight. The pale yellow crystalline product is collected on a 19-cm. Büchner funnel and washed first with 500 cc. of 50 per cent aqueous acetic acid and then thoroughly with water. It is dried in an oven at 40–60° or in a vacuum desiccator over sodium hydroxide. The yield is 570–583 g. (96–98 per cent of the theoretical amount) of a nearly colorless product melting with decomposition at 138–140° (Note 2).

2. Notes

1. If the solution is stirred during cooling the product is less likely to cake on the walls of the flask and the resulting crystals are easier to wash.
2. This material is sufficiently pure for most purposes, and the quality is not greatly improved by recrystallization from 50 per cent acetic acid. Samples prepared by bromination, even after purification, invariably decompose at the melting temperature, which is somewhat dependent upon the rate of heating. The material obtained by nitration has been found to melt without

decomposition at 144–145°.[1]

3. Discussion

2,6-Dibromo-4-nitrophenol has been prepared by the nitration of 2,6-dibromophenol[1] or of dibromophenolsulfonic acid,[2] and by the action of nitric acid on 2,6-dibromo-4-nitrosophenol[3] or on 2,4,6-tribromophenol.[4] It has been obtained from the corresponding ethyl ether[5] and by the action of bromine on *p*-nitrosophenol,[6] 4,6-dibromo-2-nitrophenol,[7] 5-nitro-2-hydroxybenzoic acid,[8] and 5-nitro-2-hydroxybenzene-sulfonic acid.[9] The dibromination of *p*-nitrophenol[10, 11] has been carried out in sulfuric acid solution[12] and in the presence of aluminum chloride.[13] The method described here is essentially that of Möhlau and Uhlmann.[11]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 175

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

sodium hydroxide (1310-73-2)

nitric acid (7697-37-2)

hydrogen bromide (10035-10-6)

bromine (7726-95-6)

aluminum chloride (3495-54-3)

2,6-Dibromo-4-nitrophenol, Phenol, 2,6-dibromo-4-nitro- (99-28-5)

2,6-dibromophenol (608-33-3)

dibromophenolsulfonic acid

2,6-dibromo-4-nitrosophenol

2,4,6-tribromophenol (118-79-6)

4,6-dibromo-2-nitrophenol

5-nitro-2-hydroxybenzoic acid (96-97-9)

5-nitro-2-hydroxybenzene-sulfonic acid

p-nitrophenol (100-02-7)

p-nitrosophenol (104-91-6)

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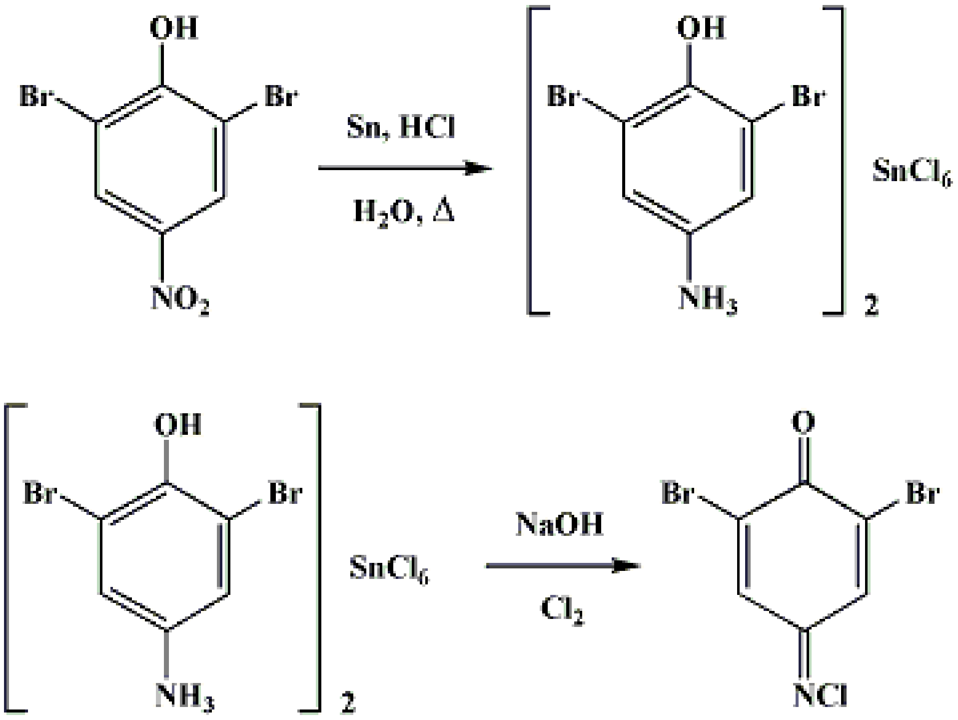
2,6-DIBROMOQUINONE-4-CHLOROIMIDE

[Quinonimine, 2,6-dibromo-N-chloro-]



Submitted by W. W. Hartman, J. B. Dickey, and J. G. Stampfli.
Checked by Louis F. Fieser and C. H. Fisher.

1. Procedure

(*A*) *2,6-Dibromo-4-aminophenol Chlorostannate*.—In a 5-l. round-bottomed flask is placed 148.5 g. (0.5 mole) of 2,6-dibromo-4-nitrophenol (p. 173) with 300 cc. (3.7 moles) of concentrated hydrochloric acid (sp. gr. 1.19), 300 cc. of water, and 185 g. (1.56 gram atoms) of mossy tin. Three cubic centimeters of capryl alcohol is added to control the foaming, and the mixture is heated in the open flask with stirring on the steam bath until the reaction starts. The reaction may proceed vigorously at the outset, and it is well to heat cautiously during the initial stages. Hydrochloric acid and water are added from time to time, and foaming can be controlled by the addition of a part of the water. A total of 520 cc. (6.4 moles) of concentrated hydrochloric acid and 900 cc. of water are added during the course of the reaction. When the first, vigorous reaction is over the mixture is heated strongly until all the dibromonitrophenol has dissolved, and the hot solution (at about 85°) is filtered through a layer of Norite on a hot Büchner funnel. The filtrate, which usually is colorless, is cooled to 0° with stirring for two hours, or allowed to stand in a cool place overnight. The product, which separates in the form of colorless or slightly yellow needles, is collected on a Büchner funnel and washed with cold dilute hydrochloric acid (one volume of concentrated acid to one volume of water). The material is usually colorless and may be used directly for the

reaction which follows (Note 1). After drying in an oven at 50–60°, or in a vacuum desiccator over sodium hydroxide, the tin salt weights 214–220 g. The theoretical weight, based on the formula assumed above, is 217 g.

(*B*) *2,6-Dibromoquinone-4-chloroimide*.—The chlorostannate is conveniently oxidized in two batches (Note 2). In a 3-l. flask is placed a solution of 115 g. (2.9 moles) of sodium hydroxide in 175 cc. of water, 1 kg. of cracked ice is added, and 108 g. (1.52 moles) of chlorine gas is passed into the mixture. About 80 per cent of the ice is melted by the operation. In a 5-l. flask 110 g. (0.127 mole) of the tin salt of 2,6-dibromo-4-aminophenol is dissolved in 1.2 l. of water and 12 cc. of concentrated hydrochloric acid. Solution is effected by warming the mixture to 40–50°, after which it is cooled to 15–17° and 600 g. of ice is added. The sodium hypochlorite solution is then added all at once with vigorous stirring (Hood). A yellow precipitate of 2,6-dibromoquinone-4-chloroimide separates immediately, and chlorine is evolved. As soon as the sodium hypochlorite solution has been stirred in, 120 cc. of concentrated hydrochloric acid is added in order to keep the tin salts in solution (Note 3). The fine, yellow precipitate is filtered under the hood on a Büchner funnel (Note 4) and washed with 1.5 l. of 5 per cent hydrochloric acid to remove tin salts and chlorine. The product is dried on a glass tray at 30–40° (Note 5), or in a vacuum desiccator over sodium hydroxide. From two such batches the yield of chloroimide melting at 80–82° is 126–130 g. (84–87 per cent of the theoretical amount based on the weight of 2,6-dibromo-4-nitrophenol used in Part A).

2. Notes

1. If the product has an appreciable yellow color, it should be recrystallized from a mixture of 150 cc. of concentrated hydrochloric acid and 375 cc. of water, heating to 85–90°. The yield of recrystallized product is 180–190 g. By evaporating the mother liquor to one-third the original volume under reduced pressure, an additional 15–25 g. of tin salt can be recovered.
2. As much as 700 g. of tin salt can be oxidized in one run by using a 70-l. crock for the reaction vessel.
3. The particle size of the chloroimide can be increased by stirring for one hour at this point.
4. The first liter of filtrate is refiltered until it is clear.
5. Care must be taken in drying as one larger run decomposed violently in an open tray when the temperature was about 60°.

3. Discussion

2,6-Dibromoquinone-4-chloroimide has been prepared by the action of sodium hypochlorite on 2,6-dibromo-4-aminophenol in the form of the chlorostannate[1] or as the hydrochloride.[2]

References and Notes

1. Möhlau, Ber. **16**, 2845 (1883); Friedländer and Stange, ibid. **26**, 2262 (1893); Möhlau and Uhlmann, Ann. **289**, 94 (1896); Mikhailov, Trans. Inst. Pure Chem. Reagents No. **16**, 83 (1939) [C. A. **34**, 3707 (1940)].
2. Gibbs, J. Biol. Chem. **72**, 653 (1927).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

sodium hydroxide (1310-73-2)

tin (7440-31-5)

Norite (7782-42-5)

chlorine (7782-50-5)

sodium hypochlorite (7681-52-9)

2,6-Dibromo-4-nitrophenol (99-28-5)

2,6-Dibromoquinone-4-chloroimide (537-45-1)

Quinonimine

capryl alcohol (111-87-5)

dibromonitrophenol

2,6-dibromo-4-aminophenol (609-21-2)

tin salt of 2,6-dibromo-4-aminophenol

2,6-Dibromo-4-aminophenol chlorostannate

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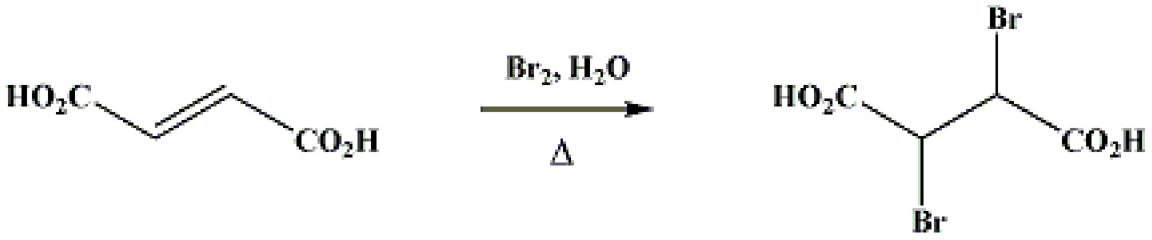
Organic Syntheses, CV 2, 177

α,β-DIBROMOSUCCINIC ACID

[Succinic acid, α,β-dibromo-]



Submitted by Herbert S. Rhinesmith
Checked by Reynold C. Fuson and W. E. Ross.

1. Procedure

In a 2-l. three-necked, round-bottomed flask, equipped with a mechanical stirrer (Note 1), dropping funnel, and Friedrichs condenser[1] (Note 2), are placed 200 g. (1.7 moles) of fumaric acid (Note 3) and 400 g. of water (Note 4). The materials are thoroughly mixed until the fumaric acid has been completely wet by the water. The resulting thick, viscous mass is then stirred vigorously (Note 5) and brought to boiling by heating on a wire gauze with a Bunsen flame (Note 6).

Two hundred and seventy-six grams (94.3 cc., 1.7 moles) of bromine (Note 7) is now added as rapidly as possible through the dropping funnel, the rate of addition being so controlled that the Friedrichs condenser is continuously about half full of the refluxing liquid (Note 8). This operation takes about one hour (Note 9). After about 100 g. of bromine has been added, the dibromosuccinic acid forms rapidly and separates in tiny white needles. At the completion of the reaction there should be a slight excess of bromine, as indicated by the red color of the solution. Occasionally 5–10 g. of bromine has to be added at this point to ensure an excess.

The reaction flask is now surrounded with ice water and cooled to 10°, with stirring. The product is then collected on a large Büchner funnel, and washed with cold water to remove the bromine liquor. The filtrate may be discarded, as it contains only impurities. The material is dried overnight at room temperature and need not be recrystallized; the yield is 343–400 g. (72–84 per cent of the theoretical amount).

2. Notes

1. A heavy stirrer with as large a paddle as possible is used, in order to rotate the mass of crystals formed during the course of the reaction. A mercury seal is unnecessary, but it is advisable to have the stirrer bearing extend beneath the surface of the liquid.
2. Glass connections or rubber stoppers should be used throughout, as corks are

rapidly disintegrated by the hot bromine.
3. Commercial fumaric acid ("practical") is sufficiently pure for this preparation. Directions for preparing fumaric acid are given on p. 302.
4. Any larger amount of water leads to the formation of monobromomalic acid, tartaric acid, and compounds of unknown composition.[2]
5. Vigorous stirring is essential to obtain good yields.
6. It is necessary to keep the reaction mixture boiling throughout the entire course of the reaction. During the addition of the bromine, however, the size of the flame should be reduced considerably, because the reaction is exothermic.
7. The apparatus should be set up under a hood, or the top of the condenser connected to a gas absorption trap for the removal of bromine vapor, small amounts of which escape continually under the conditions of the experiment.
8. By this procedure most of the unchanged bromine is washed back into the flask, so that the amount escaping from the top of the condenser is kept at a minimum.
9. If the bromine is added over a much longer period of time, the yield is materially decreased.

3. Discussion

α,β-Dibromosuccinic acid may be prepared by heating succinic acid with bromine and water in a closed tube at 180°;[3] by heating succinic acid, red phosphorus, and bromine in a closed tube at 140°;[4] by heating fumaric acid with 2 moles of bromine in acetic acid for seven hours in a sealed tube at 100°;[5] from fumaric acid, bromine, and water at 100° under pressure;[6] and by the method described above.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 10

References and Notes

1. Friedrichs, Z. angew. Chem. **33** (I) 30 (1920).
2. Kekulé, Ann. Spl. Bd. **1**, 338 (1861).
3. Kekulé, Ann. **117**, 120 (1861); Ann. Spl. Bd. **1**, 338 (1861); Bourgoin, Bull. soc. chim. (2) **19**, 148 (1873).
4. Gorodetzky and Hell, Ber. **21**, 1729 (1888).
5. Michael, J. prakt. Chem. (2) **52**, 289 (1895).
6. Kekulé, Ann. Spl. Bd. **1**, 129 (1861); Baeyer, Ber. **18**, 674 (1885).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

red phosphorus

acetic acid (64-19-7)

bromine (7726-95-6)

Succinic acid (110-15-6)

tartaric acid (87-69-4)

Fumaric acid (110-17-8)

α,β-Dibromosuccinic acid, Succinic acid, α,β-dibromo- (526-78-3)

dibromosuccinic acid

monobromomalic acid

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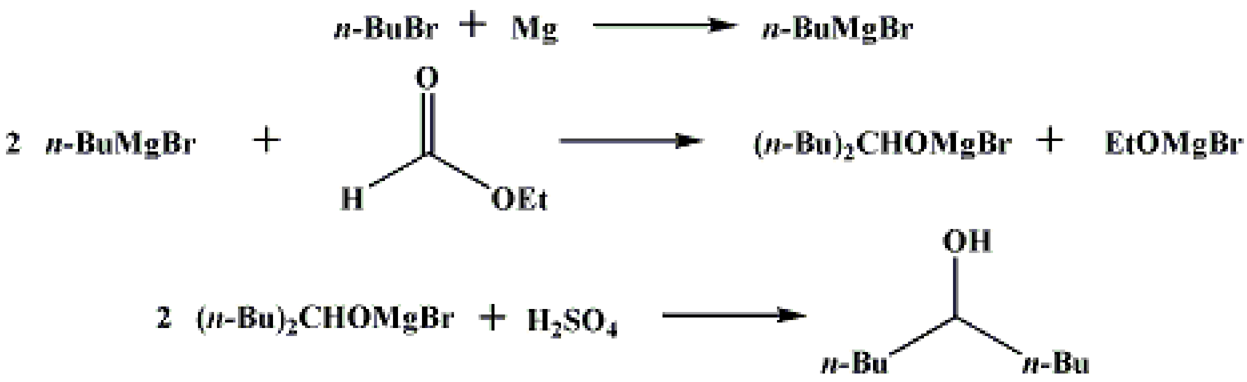
DI-*n*-BUTYLCARBINOL

[5-Nonanol]



Submitted by G. H. Coleman and David Craig.
Checked by John R. Johnson and H. B. Stevenson.

1. Procedure

In a 3-l. three-necked, round-bottomed flask, fitted with a 500-cc. separatory funnel, a liquid-sealed mechanical stirrer, and a reflux condenser, are placed 36.5 g. (1.5 gram atoms) of magnesium turnings and 500 cc. of absolute ether. A solution of 206 g. (1.5 moles) of *n*-butyl bromide (Org. Syn. Coll. Vol. I, **1941**, 28, 37) in 250 cc. of absolute ether is placed in the separatory funnel. The stirrer is started, and 10–15 cc. of the bromide solution is allowed to flow into the flask from the funnel; the reaction generally begins within a few minutes (Note 1). As soon as refluxing is vigorous, the flask is surrounded by ice and water and the rate of addition of the bromide is adjusted so that moderate refluxing occurs. After all the solution has been added (thirty to forty minutes), the cooling bath is removed. Stirring is continued for fifteen minutes longer, after which only a small residue of unreacted magnesium remains.

The flask is cooled in an ice bath and a solution of 55.5 g. (0.75 mole) of pure ethyl formate (Note 2) in 100 cc. of absolute ether is placed in the separatory funnel. The stirrer is started and the ethyl formate solution is added at such a rate that the ether refluxes gently. This addition requires about one-half hour. The cooling bath is then removed and stirring is continued for ten minutes.

With vigorous stirring (Note 3), 100 cc. of water is added through the separatory funnel at such a rate that rapid refluxing occurs. Following this, a cold solution of 85 g. (46 cc., 0.85 mole) of concentrated sulfuric acid in 400 cc. of water is added. After the addition of the acid, the two layers become practically clear. A large part of the ethereal layer is decanted into a 1-l. round-bottomed flask, and the remainder, together with the aqueous layer, is transferred to a separatory funnel. The solid remaining in the flask is washed with two 25-cc. portions of ether, which are added to the material in the separatory funnel. The ethereal layer is separated and combined with the decanted

portion. The flask is fitted with an efficient fractionating column, and the ether is distilled from a steam bath until the temperature of the vapor reaches about 50°. To the residual impure carbinol (Note 4) is added 75 cc. of 15 per cent aqueous potassium hydroxide solution and the flask is fitted with a reflux condenser. The mixture is boiled vigorously under reflux for three hours, after which the purified carbinol is removed by steam distillation, the volume in the flask being kept at 250–300 cc. The distillate is collected in a separatory funnel so that the lower aqueous layer can be drawn off periodically. The distillation is complete when about 1.5 l. of water has been collected.

The upper layer of di-*n*-butylcarbinol is separated and allowed to stand over 10 g. of anhydrous potassium carbonate for one hour. The liquid is decanted into a 500-cc. Claisen flask, and the residual potassium carbonate is washed with three 10-cc. portions of dry ether, which are added to the material in the distilling flask. After removing a small fraction of low-boiling material, there is obtained 90–92 g. (83–85 per cent of the theoretical amount) of pure di-*n*-butylcarbinol, b.p. 97–98°/ 20 mm. (Note 5).

2. Notes

1. The reaction between the ethereal solution of *n*-butyl bromide and the magnesium generally starts without any assistance; if necessary, a small amount of a previously prepared Grignard reagent or a crystal of iodine may be used to start the reaction.
2. It is best to use freshly distilled ethyl formate, which may be purified in the following way: To 100 g. of commercial ethyl formate is added 15 g. of anhydrous potassium carbonate, and the mixture is allowed to stand for one hour with occasional shaking. The ester is decanted into a dry 200-cc. flask, and 5 g. of phosphorus pentoxide is added. The flask is provided with an efficient fractionating column, and the ethyl formate is distilled into a receiver protected from atmospheric moisture. A fraction boiling at 53–54° was used in this preparation.
3. During the addition of the water it is necessary to stir efficiently so that the solid which is produced will be precipitated in a finely divided form and not in large aggregates.
4. The formic ester of di-*n*-butylcarbinol is present as an impurity in the crude product and is hydrolyzed by refluxing with potassium hydroxide solution.
5. Di-*n*-butylcarbinol can be distilled at atmospheric pressure without appreciable decomposition (b.p. 193–194°/743 mm.) but it is preferable to distil under diminished pressure. The following boiling points were observed under various pressures: 97°/20 mm., 104°/30 mm., 109°/40 mm., 117°/60 mm., 130°/100 mm.

3. Discussion

Di-*n*-butylcarbinol has been prepared by the action of *n*-butylmagnesium bromide upon *n*-valeraldehyde[1] and upon ethyl formate.[1, 2] It has also been obtained by the catalytic hydrogenation of di-*n*-butyl ketone in the presence of platinum.[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 5
- Org. Syn. Coll. Vol. 4, 210
- Org. Syn. Coll. Vol. 9, 510

References and Notes

1. Malengreau, Bull. acad. roy. Belg. cl. sei. **1906**, 802 [C. A. **1**, 1970 (1907)].
2. Dillon and Lucas, J. Am. Chem. Soc. **50**, 1713 (1928).
3. Vavon and Ivanoff, Compt. rend. **177**, 453 (1923).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

ether (60-29-7)

magnesium, magnesium turnings (7439-95-4)

n-butyl bromide (109-65-9)

platinum (7440-06-4)

iodine (7553-56-2)

potassium hydroxide (1310-58-3)

ethyl formate (109-94-4)

n-butylmagnesium bromide (693-03-8)

5-Nonanol, DI-n-BUTYLCARBINOL (623-93-8)

phosphorus pentoxide (1314-56-3)

di-n-butyl ketone (502-56-7)

n-valeraldehyde (110-62-3)

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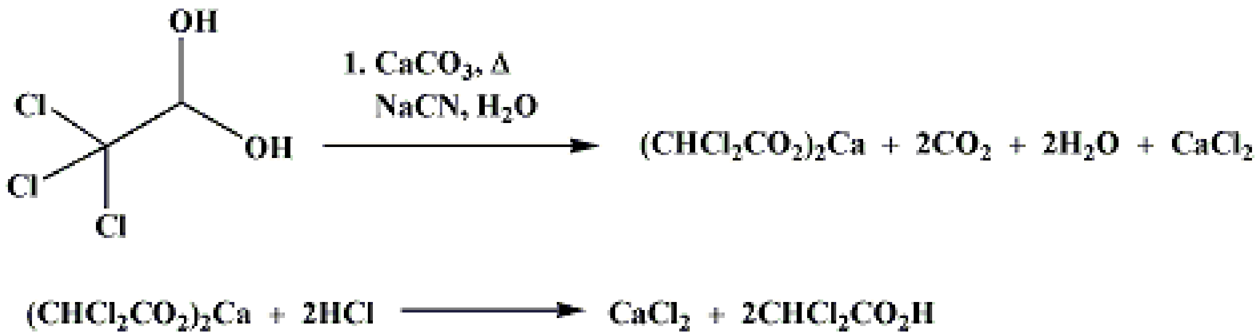
DICHLOROACETIC ACID

[Acetic acid, dichloro-]



Submitted by Arthur C. Cope, John R. Clark, and Ralph Connor.
Checked by R. L. Shriner and Neil S. Moon.

1. Procedure

A solution of 250 g. (1.5 moles) of u.s.p. chloral hydrate in 450 cc. of warm water (50–60°) is placed in a 3-l. round-bottomed flask bearing a reflux condenser and thermometer (Note 1). The condenser is temporarily removed and 152.5 g. (1.52 moles) of precipitated calcium carbonate added; this is followed by 2 cc. of amyl alcohol (Note 2) and a solution of 10 g. of technical sodium cyanide in 25 cc. of water. Although the reaction is exothermic, the reaction mixture is heated with a low flame so that it reaches 75° in about ten minutes; at this point heating is discontinued. The temperature continues to rise to 80–85° during five to ten minutes and then drops. As soon as the temperature begins to fall the solution is heated to boiling and refluxed for twenty minutes. The mixture is then cooled to 0–5° in an ice bath, acidified with 215 cc. of concentrated hydrochloric acid (sp. gr. 1.18), and extracted with five 100-cc. portions of ether (Note 3). The combined ether extracts are dried with 20 g. of anhydrous sodium sulfate, the ether is removed by distillation from a steam bath, and the residue is distilled in vacuum from a Claisen flask with a fractionating side arm (Note 4). The yield of dichloroacetic acid, b.p. 99–104°/23 mm., is 172–180 g. (88–92 per cent of the theoretical amount) (Note 5).

2. Notes

1. The amount of hydrogen cyanide evolved is small, and the reaction may be carried out in a hood without any special device for removing this gas. The use of mechanical stirring does not improve the results.
2. Amyl alcohol is added to decrease the amount of foaming.
3. The emulsion which often forms during the ether extraction may be broken by filtering through a fluted filter or with suction.
4. The product decomposes when distilled at atmospheric pressure.

5. The preparation has been carried out with equally good results using double the quantities given above.

3. Discussion

Dichloroacetic acid has been prepared by the chlorination of acetic[1] or chloroacetic[2] acid, by hydrolysis of pentachloroethane,[3] from trichloroacetic acid by electrolytic reduction[4] or the action of copper,[5] and by the action of alkali cyanides on chloral hydrate.[6] The method described here is essentially that of Delépine.[7]

References and Notes

1. Müller, Ann. **133**, 159 (1865); Dow Chemical Company, U. S. pat. 1,921,717 [C. A. **27**, 5084 (1933)].
2. Maumené, Compt. rend. **59**, 84 (1864).
3. Alais, Froges, and Camargue, Fr. pat. 773, 623 [C. A. **29**, 1437 (1935)].
4. Brand, Ger. pat. 246,661 [C. A. **6**, 2496 (1912)].
5. Doughty and Black, J. Am. Chem. Soc. **47**, 1091 (1925); Doughty and Derge, ibid. **53**, 1594 (1931).
6. Wallach, Ann. **173**, 288 (1874); Pucher, J. Am. Chem. Soc. **42**, 2251 (1920); Chattaway and Irving, J. Chem. Soc. **1929**, 1038.
7. Delépine, Bull. soc. chim. (4) **45**, 827 (1929).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium cyanide (143-33-9)

hydrogen cyanide (74-90-8)

sodium sulfate (7757-82-6)

copper (7440-50-8)

calcium carbonate (471-34-1)

chloral hydrate (302-17-0)

amyl alcohol (71-41-0)

dichloroacetic acid, Acetic acid, dichloro- (79-43-6)

pentachloroethane (76-01-7)

trichloroacetic acid (76-03-9)

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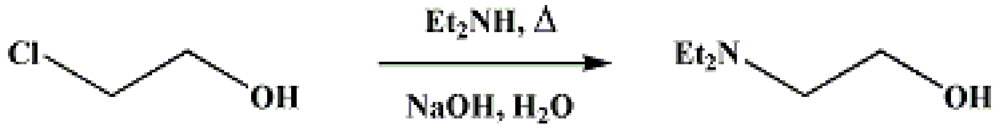
β-DIETHYLAMINOETHYL ALCOHOL

[Ethanol, 2-diethylamino-]



Submitted by W. W. Hartman
Checked by W. H. Carothers and W. L. McEwen.

1. Procedure

In a 2-l. flask provided with a reflux condenser and a dropping funnel is placed 380 g. (5.2 moles) of diethylamine (b.p. 52–60°). The diethylamine is heated to boiling over a steam bath, and 320 g. (4 moles) of ethylene chlorohydrin is added from the dropping funnel during the course of about one hour. Heating is then continued for eight hours more. The reaction mixture is allowed to cool, and a solution of 230 g. of sodium hydroxide in 350 cc. of water is added fairly rapidly with constant shaking. Two layers form immediately, and sodium chloride is precipitated. The latter is dissolved by the addition of 400 cc. of water, and then 500 cc. of benzene is added and the mixture is stirred mechanically for five minutes. The benzene layer is separated and the aqueous layer is extracted three times more, 500 cc. of benzene being used for each extraction. The combined benzene extracts are dried over about 100 g. of solid potassium carbonate, with mechanical stirring until the turbidity of the solution has disappeared. The solution is distilled from a 3-l. flask provided with a 50-cm. column (packed with glass or Carborundum) and a thermometer dipping in the liquid. Distillation is continued until the temperature of the liquid reaches 100° and that at the top of the column is 85°. The residue is transferred to a 1-l. Claisen flask having a 30-cm. column, and is distilled under reduced pressure. Cuts are taken at 45°/20 mm., 45–64°/18 mm., and 64–65°/18 mm. The last fraction amounts to about 290 g. The first two fractions are redistilled and more β-diethylaminoethyl alcohol is obtained (Note 1). The total yield is 320–330 g. (68–70 per cent of the theoretical amount).

2. Notes

1. The physical properties of β-diethylaminoethyl alcohol are described in detail by Headlee, Collett, and Lazzell.[1]

3. Discussion

β-Diethylaminoethyl alcohol has been prepared by reduction of diethylaminoacetic ester with sodium and alcohol;[2] by the action of ethylene chlorohydrin on

diethylamine;[3] by the action of ethylene oxide on diethylamine;[1] and from ethanolamine and ethyl sulfate.[4]

References and Notes

1. Horne and Shriner, J. Am. Chem. Soc. **54**, 2928 (1932); Headlee, Collett, and Lazzell, ibid. **55**, 1066 (1933).
2. Gault, Compt. rend. **145**, 126 (1907); Bull. soc. chim. (4) **3**, 369 (1908).
3. Ladenburg, Ber. **14**, 1878 (1881); Soderman and Johnson, J. Am. Chem. Soc. **47**, 1394 (1925).
4. Carbide and Carbon Chemicals Corporation, Fr. pat. 792,046 [C. A. **30**, 4176 (1936)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

diethylaminoacetic ester

alcohol (64-17-5)

potassium carbonate (584-08-7)

Benzene (71-43-2)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

sodium (13966-32-0)

Ethylene oxide (75-21-8)

ethylene chlorohydrin (107-07-3)

diethylamine (109-89-7)

ethanolamine (141-43-5)

β-Diethylaminoethyl alcohol, Ethanol, 2-diethylamino- (100-37-8)

ethyl sulfate

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DIETHYL ZINC

[Zinc, diethyl-]

Submitted by C. R. Noller
Checked by Henry Gilman, Harriet A. Southgate, and C. Mehltretter.

1. Procedure

In a 500-cc. round-bottomed flask, provided with a reflux condenser (Note 1) and a heavy stirrer (Note 2), is placed 130 g. (approximately 2 gram atoms) of zinc-copper couple (Note 3). To this is added a mixture of 78 g. (0.5 mole) of ethyl iodide and 54.4 g. (0.5 mole) of ethyl bromide (Note 4); the stirrer is started and the mixture heated to refluxing. After one-half hour of refluxing, the reaction starts (Note 5), as is evidenced by the greatly increased rate of refluxing, and the flame is removed. If the reaction becomes too vigorous, the flask is cooled with ice water, but only to the point where the reaction is again under control (Note 6). At the end of one-half hour from the time the flame is removed, the reaction is usually over. The flask is allowed to cool to room temperature (Note 7), connected with a distilling head, condenser, and receiver, and the contents are distilled under reduced pressure (Note 8) directly from the reaction flask into a 200-cc. round-bottomed flask immersed in an ice-salt mixture (Note 9). At the end of the distillation, dry carbon dioxide or purified nitrogen is admitted to the apparatus (Note 10). The yield of crude material, which is sufficiently pure for most purposes, is 53–55 g. (86–89 per cent of the theoretical amount).

For purification, a 30-cm. fractionating column of the Vigreux type is fitted with a condenser and receiving flask provided with a vent. The extension of this vent is covered with a test tube carrying another small tube for admitting carbon dioxide; the end of the test tube is then loosely plugged by a piece of cotton wool (Note 11). The apparatus is swept out with carbon dioxide, and the round-bottomed flask containing the once-distilled diethyl zinc is connected to the column. The diethyl zinc is then redistilled at atmospheric pressure. The yield of material boiling at 115–120° is 50–52 g. (81–84 per cent of the theoretical amount) (Note 5) and (Note 12).

2. Notes

1. The use of dry apparatus and the exclusion of atmospheric moisture are essential to smooth starting of the reaction. Consequently, the top of the condenser is either provided with a drying tube containing calcium chloride or attached to a trap[1] to exclude the atmosphere.

2. A slow-moving stirrer that fits the bottom and sides of the flask is necessary in order to keep the zinc thoroughly agitated.

3. The zinc-copper couple may be prepared by either of the following methods:

1. (*a*) A mixture of 120 g. of zinc dust and 10 g. of powdered copper oxide in a 200-cc. round-bottomed flask is heated gently over a free flame in a current of hydrogen with stirring or rotation of the flask until the copper oxide is reduced and a uniform gray mixture is obtained. The temperature should be kept just below the point of fusion during the heating.
2. (*b*) A zinc-copper alloy containing 5 to 8 per cent copper is prepared by melting zinc with clean brass turnings and casting into bars. This is turned into fine shavings and is ready for use.

When only small quantities of zinc alkyls are to be prepared, method (*a*) may be used to advantage. For large quantities it is believed that the zinc-copper alloy turnings (*b*) are more convenient. Zinc-copper couple prepared by method (*a*) must be used at once or stored in an atmosphere of dry inert gas, as it rapidly deteriorates on exposure to moist air.

The method recommended by Noyes[2] does not seem to yield so active a couple as either of the above methods, and, although it gives entirely satisfactory results if pure iodides are used, the yields with a mixture of iodides and bromides are lower.

4. The use of a mixture of alkyl iodide and alkyl bromide is not only less expensive but the reaction is not so vigorous as when the alkyl iodide alone is used. Directions for preparing ethyl bromide are given in Org. Syn. Coll. Vol. I, **1941**, 29, 36.

5. The submitter observed that reaction generally started in twenty to forty minutes after refluxing began. The checkers found that the time for reaction to set in was nearer one and one-quarter hours. Unless all precautions to exclude moisture are exercised, the reaction may not start for several hours. In such cases, after the preliminary period of stirring and heating externally, the mixture can be allowed to stand at room temperature without stirring. Under these conditions the reaction always started spontaneously (sometimes after five hours) and required no attention, for when reaction did set in the refluxing was not sufficiently vigorous to require cooling. When the reaction is slow in starting, the yield of diethyl zinc is somewhat lower.

6. If the mixture is cooled too much, the reaction may stop entirely and is difficult to start again. If this happens the yield will be considerably lower.

7. On cooling, the reaction mass solidifies (probably on account of the re-formation of RZnX) and may be briefly exposed to air without danger. The solid material is much less reactive than diethyl zinc.

8. The pressure should be below 30 mm. of mercury or decomposition will occur.

9. Either a special adapter with a side arm for applying suction may be used or a piece of right-angled tubing may be inserted in the same stopper with the condenser tube.

10. When the distillation is carried out under reduced pressure there is no need to

sweep out the apparatus with inert gas. At other times, exposure to air must be prevented by using an atmosphere of carbon dioxide or nitrogen.

The checkers carried out this distillation by heating the flask in an oil bath (about 200°) at a pressure of about 8 mm. The distillation was complete in about one hour. The flask can also be heated directly with a full Bunsen flame.

11. This vent can be replaced by a mercury seal formed by connecting a double right-angled glass tube from the upper part of the receiving flask to a container with mercury. The tube is only slightly immersed in the mercury. When a mercury seal is used, the receiver must be removed when distillation is completed in order that mercury may not be pulled into the receiver when the system commences to cool.

12. Using the same procedure, the yields and boiling points of higher zinc alkyls are as follows: di-*n*-propyl zinc, 85–86 per cent, b.p. 39–40°/9 mm.; di-*n*-butyl zinc, 78–79 per cent, b.p. 81–82°/9 mm.; di-isoamyl zinc, 50–55 per cent, b.p. 100–103°/12 mm. The higher zinc alkyls should always be distilled under reduced pressure.

3. Discussion

Diethyl zinc has been prepared from zinc and mercury diethyl,[3] and from ethyl bromide and zinc-copper couple using a special catalyst.[4] Diethyl zinc is usually prepared by the action of ethyl iodide on specially treated zinc,[5] the zinc-copper couple being most useful for this purpose.[6 7 2 8] The procedure described above has been published.[9] Arylzinc halides, zinc dialkyls, and zinc diaryls may be prepared by the action of the Grignard reagent on anhydrous zinc chloride in ether solution.[10]

Attention is called to an improved apparatus for the preparation, purification, and use of zinc ethyl.[11]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

mercury diethyl

zinc ethyl

calcium chloride (10043-52-4)

ether (60-29-7)

hydrogen (1333-74-0)

Ethyl bromide (74-96-4)

nitrogen (7727-37-9)

mercury (7439-97-6)

carbon dioxide (124-38-9)

copper (7440-50-8)

zinc (7440-66-6)

zinc chloride (7646-85-7)

copper oxide (1317-38-0)

Diethyl zinc, Zinc, diethyl- (557-20-0)

zinc-copper

Ethyl iodide (75-03-6)

di-isoamyl zinc

di-n-propyl zinc

di-n-butyl zinc (1119-90-0)

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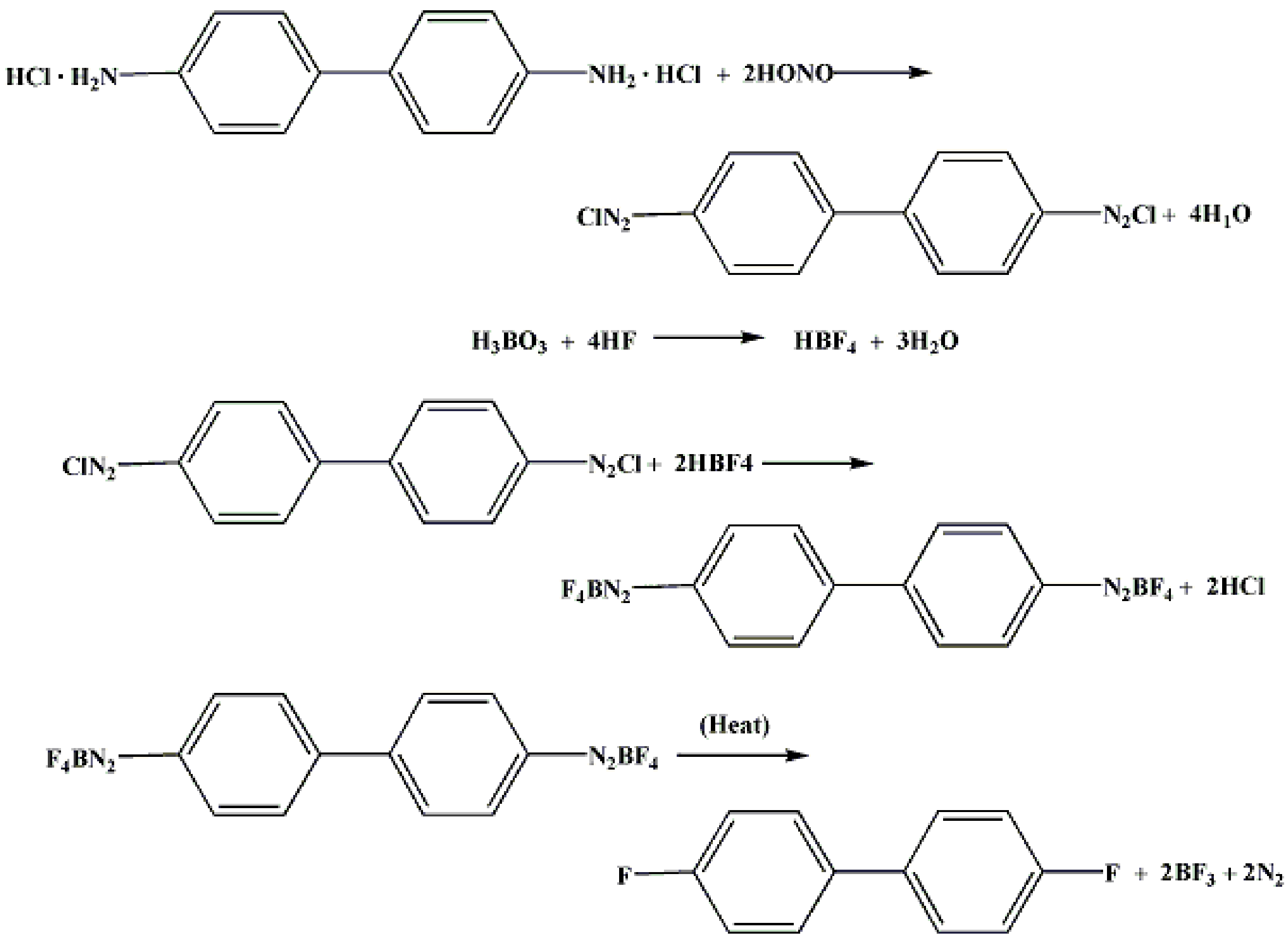
4,4'-DIFLUOROBIPHENYL

[Biphenyl, 4,4'-difluoro-]



Submitted by G. Schiemann and W. Winkelmüller.
Checked by W. W. Hartman, J. R. Byers, and J. B. Dickey.

1. Procedure

A mixture of 280 g. (1.5 moles) of commercial benzidine and 880 cc. (10.2 moles) of concentrated hydrochloric acid (sp. gr. 1.18) is placed in a 5-l. round-bottomed flask and warmed on a steam bath for one to two hours, with occasional shaking, to form the dihydrochloride. The flask is then equipped with a mechanical stirrer and a dropping funnel, and cooled, with stirring, to −10° in an ice-salt bath. When this temperature has been reached, the benzidine dihydrochloride is tetrazotized over a period of two hours with a solution of 232 g. (3.2 moles) of 95 per cent sodium nitrite in 800 cc. of water, until a faint test for nitrous acid with starch-iodide paper is obtained after twenty minutes. During this reaction, the temperature is kept below −5°.

Concurrently with the tetrazotization, 104 g. (1.68 moles) of boric acid is dissolved in 222 g. (6.66 moles) of 60 per cent hydrofluoric acid. The solution is made in a 1-l. beaker, which has been coated inside with paraffin, and is cooled in an ice bath. The boric acid is added slowly in small portions, and the mixture is stirred with a lead rod. It is necessary to keep the temperature below 20–25° in order that the heat of solution may not melt the paraffin from the walls of the beaker (Note 1).

The ice-cold fluoboric acid solution is added rather rapidly, with stirring, to the finished tetrazo solution, the temperature being kept below 10°. A thick paste of 4,4'-biphenylene-bis-diazonium borofluoride forms. The mixture is stirred at 10° for twenty to thirty minutes. It is then collected on a 19-cm. Büchner funnel and washed consecutively with about 200 cc. of cold water, 200 cc. of cold commercial methyl alcohol, and 200 cc. of

commercial ether; the cake is sucked as dry as possible between washings. It is then dried in a vacuum desiccator over concentrated sulfuric acid (sp. gr. 1.84). The yield of the dry solid is 393–400 g. (68–69 per cent of the theoretical amount). The product decomposes at 135–137°.

A 1-l. distilling flask with a wide side arm may be used for the decomposition of the tetrazonium borofluoride. A 500-cc. distilling flask is fastened directly to the side arm of the decomposition flask and cooled with running water. To the side arm of the receiver is connected a rubber tube which is placed over 2 l. of water in a 5-l. flask (Note 2). The solid to be decomposed (Note 3) is placed in the decomposition flask and heated at the upper edge with a Bunsen burner. When white fumes begin to be evolved, the burner is removed and the decomposition permitted to continue spontaneously. More heat is applied as needed. Finally vigorous heating is employed to ensure complete decomposition. Some 4,4'-difluorobiphenyl is collected in the receiver, but the larger portion remains in the decomposition flask, from which it is recovered by steam-distilling the black residue. A second steam distillation gives a pure white compound melting at 88–89°, after drying in an oven at 60–70°. When 153 g. of the tetrazonium borofluoride is decomposed in this manner, 61–62 g. of 4,4'-difluorobiphenyl is obtained (80–81.5 per cent of the theoretical amount, based on the tetrazonium borofluoride; 54–56 per cent based on the benzidine used).

2. Notes

1. A small lead jar is excellent for preparing the solution. By means of a lead stirrer of the usual shape, mechanical stirring may be used. The stirrer should be thrust through a hole in a lead cover of sufficient size to prevent splashing of the hydrofluoric acid.
Hydrofluoric acid produces extremely painful burns. Exposed parts of the body must be protected when working with this material. Compare, Note 3, p. 297. Instead of preparing fluoboric acid, 355.5 g. of commercial 40 per cent fluoboric acid may be used.
2. A convenient apparatus is made by connecting a 1-l. round-bottomed flask by means of a bent tube of large diameter (2 cm.) to a second 1-l. round-bottomed flask containing 500 cc. of water. The second flask is equipped with an exit tube, and the gases which do not dissolve in the water are led into a hood.
3. It is very necessary that the tetrazonium borofluoride be dried completely. If the solid is wet, the decomposition proceeds very vigorously. There is formed at the same time a product of higher melting point (160°) as well as some tar. These products, although not volatile with steam, lower the yield of the 4,4'-difluorobiphenyl very materially.

3. Discussion

4,4'-Difluorobiphenyl has been prepared from 4,4'-biphenyl-bis-diazonium piperidide (by diazotizing benzidine and coupling with piperidine) and concentrated hydrofluoric acid;[1] by the action of sodium on *p*-fluorobromobenzene in ether;[2] from benzidine by tetrazotization and decomposing the biphenyl-bis-diazonium salt with concentrated hydrofluoric acid;[3] by the above method in the presence of ferric chloride;[4] and by the prolonged contact of the vapors of fluorobenzene with a red-hot wire.[5] The method described here is the most satisfactory for use in the laboratory and is an improvement on the method of Balz and Schiemann.[6]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

fluoboric acid

4,4'-biphenylene-bis-diazonium borofluoride

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

methyl alcohol (67-56-1)

ether (60-29-7)

sodium nitrite (7632-00-0)

nitrous acid (7782-77-6)

hydrofluoric acid (7664-39-3)

sodium (13966-32-0)

piperidine (110-89-4)

ferric chloride (7705-08-0)

boric acid (10043-35-3)

benzidine (92-87-5)

benzidine dihydrochloride

tetrazonium borofluoride

Fluorobenzene (462-06-6)

p-fluorobromobenzene (460-00-4)

4,4'-DIFLUOROBIPHENYL, Biphenyl, 4,4'-difluoro- (398-23-2)

4,4'-biphenyl-bis-diazonium piperidide

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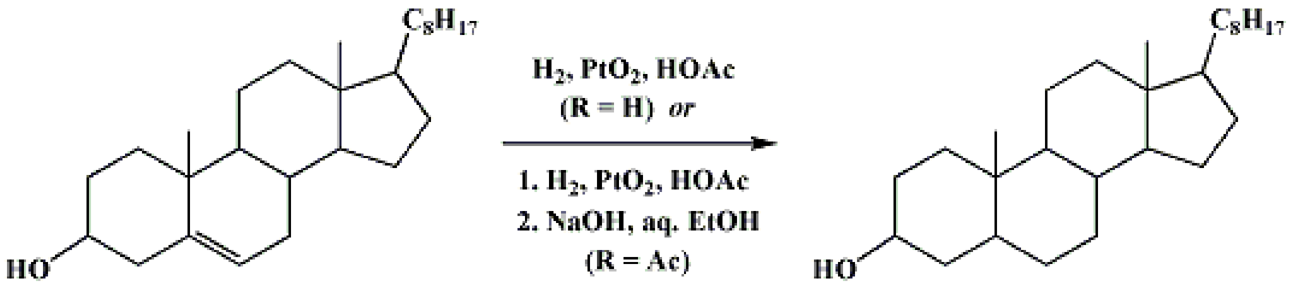
Organic Syntheses, CV 2, 191

DIHYDROCHOLESTEROL

[β-Cholestanol]



Submitted by W. F. Bruce
Checked by Louis F. Fieser, R. P. Jacobsen, and M. S. Newman.

1. Procedure

(*A*) *From Cholesterol*.—One hundred grams (0.26 mole) of commercial cholesterol is crystallized from 250 cc. of glacial acetic acid, using 1 g. of Norite if required, and the purified material (Note 1) is transferred, conveniently without being dried, to a hydrogenation vessel equipped with a thermometer and a heating device (Note 2). Three hundred cubic centimeters of purified glacial acetic acid (Note 3) and 0.5 g. of platinum oxide are added, and the hydrogenation is conducted at 65–75° at a slight positive pressure. The total amount of hydrogen usually is absorbed in two to four hours (Note 4). After the hydrogen has been replaced by air the solution is filtered hot and the product is obtained by crystallization and concentration. The total yield of air-dried, partially acetylated dihydrocholesterol, m.p. 130–135°, is 85–90 g.

Unless a specially purified product (see below) is desired, the crude material is heated for three hours on the steam bath with 400 cc. of alcohol and a solution of 25 g. of sodium hydroxide in 100 cc. of water. After cooling, the product is collected, washed, and crystallized from 500 cc. of alcohol. The yield is 75–80 g. (75–80 per cent of the theoretical amount), and a well-dried sample (Note 5) melts at 140–141°.

Submitted by J. O. Ralls
Checked by Louis F. Fieser, R. P. Jacobsen, and M. S. Newman.

1. Procedure

(*B*) *From Cholesteryl Acetate* (Note 6).—Five grams of cholesteryl acetate (Note 7) and 0.1 g. of platinum oxide are suspended in 25 cc. of absolute ether and 50 cc. of purified glacial acetic acid (Note 3), and the hydrogenation is conducted at room temperature at a slight positive pressure. The reaction is complete in ten to fifty minutes. The solution is filtered, using ether to dissolve any crystallized material, and, after removing the solvent by distillation at reduced pressure, the residue is either saponified as above or purified in the following manner.

Purification by the Method of Anderson and Nabenhauer.[1]—A solution of 20 g. of crude, partially or completely acetylated dihydrocholesterol in 200 cc. of carbon tetrachloride is placed in a separatory funnel and treated with 100 cc. of acetic anhydride. About 5 cc. of concentrated sulfuric acid is added dropwise through the stem of the inverted funnel with cooling and shaking until there

is no further increase in color. A blue or green color develops, the intensity depending on the amount of cholesterol present in the sample. After fifteen to twenty minutes about 10 cc. of water is added, by drops and with cooling and gentle shaking until two distinct layers form. The carbon tetrachloride solution (upper layer) is separated and washed free of acid with sodium chloride or sodium carbonate solution (pure water gives emulsions). After drying with sodium sulfate, the solvent is removed by distillation at diminished pressure and the residue is saponified as above with alcoholic alkali and crystallized from alcohol. The purified dihydrocholesterol weighs 12–14 g. and melts, after thorough drying (Note 5), at 142–143°. It gives a faint Liebermann-Burchard reaction (Note 8) only after ten to fifteen minutes.

2. Notes

1. The dry weight of the crystallized material is 90–95 g. Some samples may require recrystallization.
2. A suitable arrangement for heating the hydrogenation vessel is described in Org. Syn. Coll. Vol. I, **1941**, 61. An alternative arrangement is the following: a round-bottomed long-necked flask is supported at the top by a two-piece clamp with a loosened checknut, connected below to an eccentric, and heated in motion by means of a stationary microburner.
3. glacial acetic acid is purified by boiling for one hour with 5 g. of potassium permanganate per liter and distilling.
4. The catalyst sometimes loses its activity when about half of the theoretical amount of hydrogen has been absorbed, probably because of the poisoning action of impurities not removed from the commercial cholesterol. If this happens the addition of one or two 0.2-g. portions of catalyst usually suffices to bring the reaction practically to completion.
5. The sterol forms a hydrate from which the water is eliminated only after thorough drying, as in vacuum at 100°.
6. The acetyl derivative is more easily reduced than the free sterol.
7. Cholesteryl acetate is prepared by boiling for one hour a solution of 5 g. of cholesterol in 7.5 cc. of acetic anhydride, cooling, filtering, and washing the crystalline product with cold methanol. The yield of material melting at 114–115° is 5 g.
8. This test for cholesterol is made by dissolving about 5 mg. of the material in 2 cc. of carbon tetrachloride, and adding 1 cc. of acetic anhydride and 3–4 drops of concentrated sulfuric acid. Cholesterol gives rise to a succession of color changes.

3. Discussion

Dihydrocholesterol has been prepared by the reduction of cholestenone with sodium and amyl alcohol[2] and by the hydrogenation of cholesterol. In the presence of platinum black or platinum oxide, yields varying from 6.5 per cent to 40 per cent have been obtained in ether,[3] acetone,[4] ethyl acetate,[5] and acetic acid.[6]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 139
- Org. Syn. Coll. Vol. 5, 245

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2. Diels and Abderhalden, Ber. **39**, 889 (1906); Diels and Stamm, ibid. **45**, 2230 (1912); Neuberg, ibid. **39**, 1155 (1906).
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6. v. Fürth and Felsenreich, Biochem. Z. **69**, 420 (1915).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

platinum black

β-Cholestanol

alcohol (64-17-5)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether (60-29-7)

acetic anhydride (108-24-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

potassium permanganate (7722-64-7)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

carbon tetrachloride (56-23-5)

platinum oxide

acetone (67-64-1)

Norite (7782-42-5)

sodium (13966-32-0)

amyl alcohol (71-41-0)

Dihydrocholesterol (80-97-7)

Cholesterol (57-88-5)

Cholesteryl acetate (604-35-3)

Cholestenone

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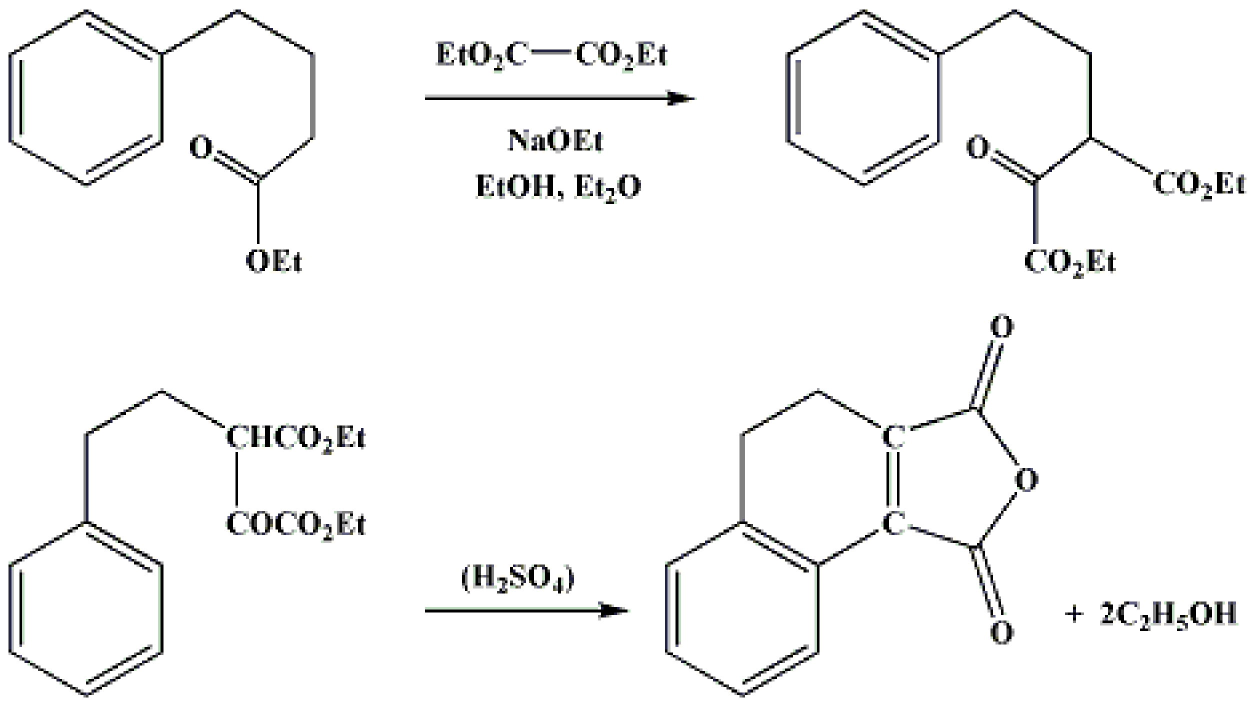
3,4-DIHYDRO-1,2-NAPHTHALIC ANHYDRIDE

[1,2-Naphthalenedicarboxylic anhydride, 3,4-dihydro-]



Submitted by E. B. Hershberg and Louis F. Fieser.
Checked by C. R. Noller and S. Kinsman.

1. Procedure

(*A*) *Ester Condensation*.—In a 1-l. round-bottomed flask, fitted with a reflux condenser equipped with a dropping funnel and a calcium chloride tube, is placed a suspension of 6.1 g. (0.27 mole) of powdered sodium (Note 1) in 150 cc. of absolute ether. A solution of 12.6 g. (0.27 mole) of absolute ethyl alcohol (Note 2) and 50 cc. of absolute ether is added, and the mixture is allowed to stand overnight to complete the reaction. To the suspension of sodium ethoxide, 57 g. (0.39 mole) of ethyl oxalate (Org. Syn. Coll. Vol. I, **1941**, 261), diluted with 50 cc. of ether, is added in portions. After the spontaneous reaction subsides, the pale yellow solution is allowed to stand for one-half hour, and 50 g. (0.26 mole) of ethyl γ-phenylbutyrate (Note 3), diluted with 50 cc. of absolute ether is added. The mixture is refluxed gently for twenty-four hours (Note 4).

The deep red solution is cooled in an ice bath and neutralized by the addition, with shaking, of an ice-cold solution of 15 cc. of concentrated sulfuric acid in 200 cc. of water. The ether layer is separated, washed with water, and dried over sodium sulfate. The ether is removed by dropping the solution from a separatory funnel the stem of which extends to the bottom of an evacuated Claisen flask heated on the steam bath.

The residue is a pale yellow oil consisting of a mixture of ethyl α-ethoxalyl-γ-phenylbutyrate and unchanged ethyl oxalate (Note 5).

(*B*) *Cyclization*.—The above oil is poured slowly into 500 cc. of concentrated sulfuric acid, the temperature being kept at 20–25° by cooling in an ice bath. After standing for one and one-half hours at 20–25°, the deep red solution is poured on 3 l. of ice and water. The anhydride, precipitated as a pale yellow solid, is collected and washed thoroughly with water. Dried *in vacuo* at 25°, the material weighs 40–45 g. and melts at 117–122°. Distillation under diminished pressure gives a light yellow product, m.p. 122–124°. The yield is 38–42 g. (73–81 per cent of the theoretical amount). This material is suitable for most purposes. Crystallization from 100 cc. of benzene with the addition of 75 cc. of ligroin (b.p. 60–80°) gives 34–41 g. of pale yellow prisms, m.p. 125–126° (Note 6).

2. Notes

1. The powdered sodium for this preparation may be prepared as in Org. Syn. Coll. Vol. I, **1941**, 252, or according to the following procedure for potassium, using xylene instead of toluene. (With certain other γ-arylbutyric esters it is better to use potassium.) Commercial potassium is cleaned by melting it under toluene, and 10.4 g. (0.27 mole) of the metal and 150 cc. of dry toluene are placed in a 1-l. flask. After the liquid is heated to boiling on a hot plate, the flask is removed and closed with a ground-glass stopper carrying a sealed-on stopcock. Apparatus with interchangeable ground joints is essential. After one shake with the stopcock open to relieve superheating, the stopcock is closed, and the flask is shaken quickly and vigorously to powder the metal. The mixture is allowed to cool undisturbed, and nitrogen is admitted. The stopper is replaced by a distilling head carrying a 500-cc. flask, into which the toluene can be decanted. The powdered metal is washed several times with absolute ether and finally covered with ether (150 cc.) and converted into the ethoxide with 12.6 g. of alcohol diluted with 150 cc. of ether. Traces of potassium in the wash liquors are destroyed safely by treatment under reflux with alcohol diluted with ether.
2. The alcohol was dried according to Org. Syn. Coll. Vol. I, **1941**, 251, Note 1.
3. Ethyl γ-phenylbutyrate is prepared in 85–88 per cent yields by refluxing for three hours a mixture of 50 g. of γ-phenylbutyric acid (p. 499), 150 cc. of alcohol dried over lime, and 5 g. of concentrated sulfuric acid. The ester is isolated by distilling 100 cc. of the alcohol under reduced pressure from a steam bath, diluting the residue with 200 cc. of water, separating, and extracting the aqueous layer twice with 50-cc. portions of ether. The combined ester and ether layers are dried with sodium sulfate, the ether removed, and the residue distilled under diminished pressure; the portion boiling at 144–147°/19 mm. is collected.
4. With potassium ethoxide the reaction is complete in twelve hours.
5. The keto ester decomposes on distillation, even under diminished pressure.
6. For the cyclization of the keto esters from γ-naphthylbutyric esters it is advisable to use 80 per cent sulfuric acid, and to heat the mixture, with stirring,

at 70–80° for one-half hour.

3. Discussion

The above procedure is a modification[1] of the method of von Auwers and Möller.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 423
- Org. Syn. Coll. Vol. 3, 300

References and Notes

1. Fieser and Hershberg, J. Am. Chem. Soc. **57**, 1851 (1935).
2. von Auwers and Möller, J. prakt. Chem. (2) **109**, 137 (1925).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ligroin

ethyl α-ethoxalyl-γ-phenylbutyrate

ethyl alcohol, alcohol (64-17-5)

sulfuric acid (7664-93-9)

Benzene (71-43-2)

ether (60-29-7)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

toluene (108-88-3)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

potassium (7440-09-7)

xylene (106-42-3)

Ethyl oxalate

3,4-Dihydro-1,2-naphthalic anhydride, 1,2-Naphthalenedicarboxylic anhydride, 3,4-dihydro- (37845-14-0)

ethyl γ-phenylbutyrate (10031-93-3)

γ-Phenylbutyric acid (1821-12-1)

potassium ethoxide (917-58-8)

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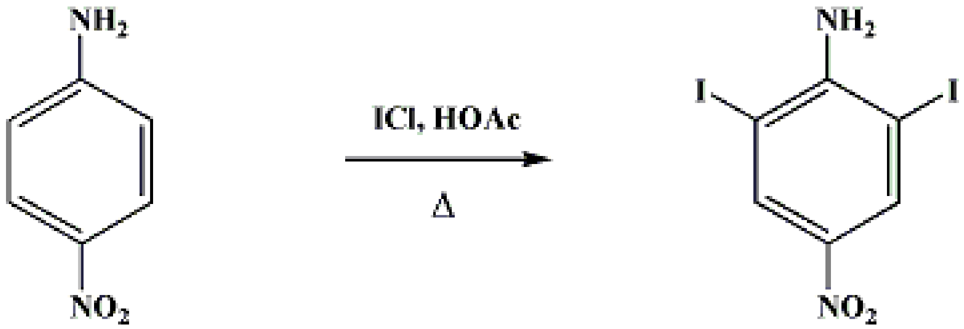
2,6-DIIODO-*p*-NITROANILINE

[Aniline, 2,6-diiodo-4-nitro-]



Submitted by R. B. Sandin, W. V. Drake, and Frank Leger.
Checked by Frank C. Whitmore and Marion M. Whitmore.

1. Procedure

One hundred thirty-eight grams (1 mole) of *p*-nitroaniline (East-man Technical grade) is dissolved in 370 cc. of boiling glacial acetic acid in a 2-l. three-necked flask provided with a mechanical stirrer, a reflux condenser, and a dropping funnel. The burner is removed, and a mixture of 325 g. (2 moles) of iodine monochloride (Note 1) in 100 cc. of glacial acetic acid is added slowly from the dropping funnel with rapid stirring during thirty minutes. Considerable heat is evolved. The mixture is heated on a rapidly boiling water bath for two hours and then transferred to a 1-l. beaker and allowed to cool. The solidified mixture is treated with 100 cc. of glacial acetic acid and any hard lumps are crushed thoroughly with a flat glass stopper (Note 2). The mixture is transferred to a large Büchner funnel and filtered by suction, two 25-cc. portions of glacial acetic acid being used to wash the last of the crystals into the funnel. The dark mother liquor is removed as completely as possible by suction. The crystals are returned to the beaker, thoroughly stirred with 200 cc. of cold glacial acetic acid, and transferred to the suction filter again. The beaker is rinsed with two 25-cc. portions of glacial acetic acid, and the crystals are sucked as dry as possible. The suction is shut off, and the crystals are wetted with 50 cc. of ether. The suction is again used to remove the ether. The product is air dried to constant weight (about twenty-four hours). The yield of air-dried diiodo-*p*-nitroaniline melting at 243–245° is 220–250 g. (56–64 per cent of the theoretical amount) (Note 3).

2. Notes

1. The iodine monochloride is made by passing dry chlorine gas into 254 g. (1 mole) of iodine in a tared 500-cc. Erlenmeyer flask until the gain in weight is 71 g. Frequent shaking is necessary. The iodine mono-chloride is used directly without distillation. Compare p. 344.

2. It is advisable to wear rubber gloves during these operations with glacial acetic acid.
3. It is reported that the following modifications increase the yield to 86 per cent: The reaction mixture is refluxed for two hours in an oil bath, cooled, filtered, and sucked as dry of solvent as possible. The cake is then made into a paste with 600 cc. of hot water, a little sodium bisulfite is added in order to remove excess iodine, and the product is filtered and dried. 2,6-Diiodo-4-nitroaniline can be crystallized from nitrobenzene followed by washing with alcohol; it then melts at 249–250°. [Carl Niemann and C. E. Redemann, private communication, and J. Am. Chem. Soc. 63, 1550 (1941)].

3. Discussion

2,6-Diiodo-*p*-nitroaniline has been made by the action of iodine chloride on a chloroform solution[1] and also on a glacial acetic acid solution[2] of *p*-nitroaniline.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 349
- Org. Syn. Coll. Vol. 2, 604

References and Notes

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2. Willgerodt and Arnold, ibid. **34**, 3344 (1901).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

acetic acid (64-19-7)

ether (60-29-7)

chloroform (67-66-3)

sodium bisulfite (7631-90-5)

iodine (7553-56-2)

chlorine (7782-50-5)

Nitrobenzene (98-95-3)

Aniline, 2,6-diiodo-4-nitro-, 2,6-Diiodo-4-nitroaniline, 2,6-Diiodo-p-nitroaniline (5398-27-6)

iodine monochloride, iodine mono-chloride, iodine chloride (7790-99-0)

p-nitroaniline (100-01-6)

diiodo-p-nitroaniline

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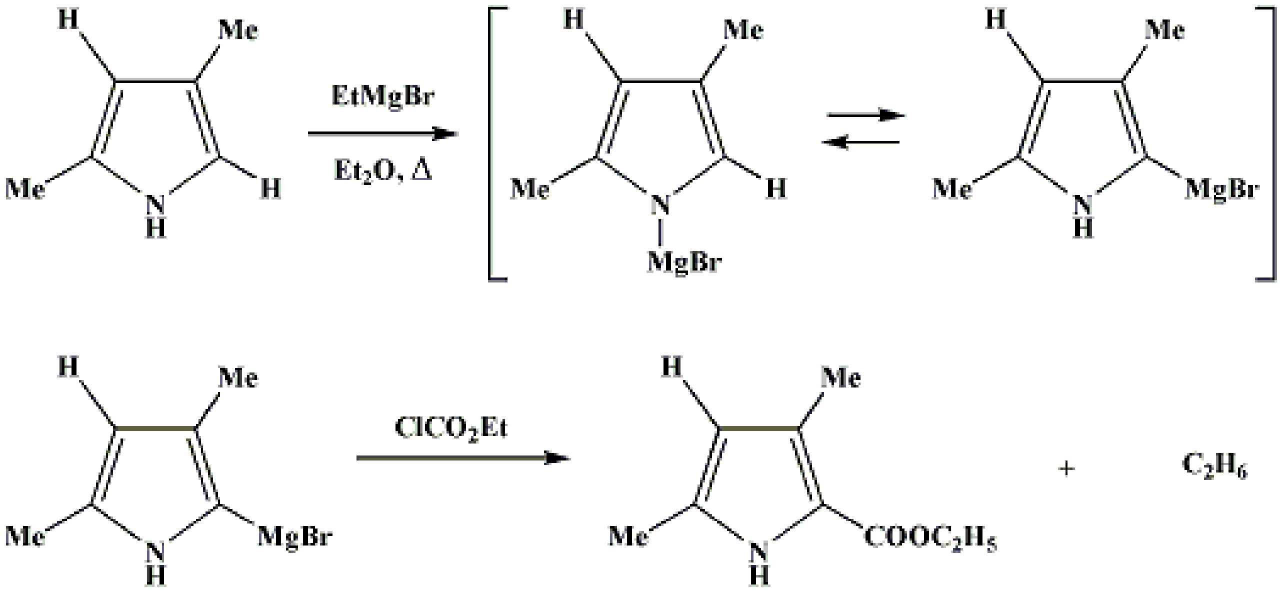
2,4-DIMETHYL-5-CARBETHOXYPYRROLE

[2-Pyrrolecarboxylic acid, 3, 5-dimethyl-, ethyl ester]



Submitted by Hans Fischer
Checked by C. R. Noller

1. Procedure

In a 1-l. round-bottomed, three-necked flask fitted with an efficient reflux condenser, liquid-sealed stirrer, and dropping funnel is placed 13 g. (0.53 gram atom) of magnesium turnings. A few cubic centimeters of a solution of 60 g. (42 cc., 0.55 mole) of pure ethyl bromide in 50 cc. of absolute ether is added and the stirrer started (Note 1). When the bromide begins to react 200 cc. of absolute ether is added, and then the balance of the bromide solution is run in as fast as the refluxing permits (about one-half hour). After allowing fifteen minutes for the completion of the reaction, a solution of 40 g. (0.42 mole) of 2,4-dimethylpyrrole (p. 217) in 100 cc. of absolute ether is added in the course of twenty minutes (Note 2) and the mixture is refluxed for one-half hour on the steam bath.

The reaction mixture is cooled to room temperature, and a solution of 58 g. (51 cc., 0.53 mole) of freshly distilled ethyl chloroformate (b.p. 92.5–93.5°) in 100 cc. of absolute ether is added dropwise in the course of one-half hour (Note 3). The mixture is heated on the steam bath for one and one-half hours and then allowed to stand overnight at room temperature.

The flask is placed in an ice-salt mixture, and the contents are decomposed by the gradual addition of 300 cc. of saturated ammonium chloride solution and 100 cc. of water (Note 4). The aqueous layer is removed by means of a 1.5-l. separatory funnel, and sufficient ether is added to dissolve the yellow precipitate. The total volume of ether solution is about 1 l. This is washed with two 200-cc. portions of water, and the three aqueous layers are extracted consecutively with a 100-cc. portion of ether. The combined ether solution is dried over 30 g. of anhydrous sodium sulfate, concentrated on the steam bath to a volume of about 200 cc., and cooled to room temperature. The product which crystallizes is collected with suction and washed with two 25-cc. portions of ether. The yield is 35–38 g. of light yellow product, m.p. 122–123°. The ether is

completely removed from the combined filtrates by heating on the steam bath, and the black oil is allowed to stand overnight. The semi-solid mass is filtered with suction and washed with a minimum amount of cold ether. In this way an additional 6–7 g. of yellow material is obtained which melts at 119–121°.

The combined crude material is crystallized from 75 cc. of 95 per cent alcohol and yields 37–39 g. of slightly colored material, m.p. 123–124°. A second crystallization from alcohol gives 34–36 g. of colorless product melting at the same temperature. By the systematic working of the alcoholic mother liquors, an additional 5–6 g. of pure material is obtained, making the total yield 40–41 g. (57–58 per cent of the theoretical amount).

2. Notes

1. Stirring is continued without interruption throughout the preparation to the point where the mixture is allowed to stand overnight.
2. The reaction is not exothermic, but the large volume of ethane evolved necessitates the regulated addition of the solution of dimethylpyrrole.
3. Considerable heat is produced during the addition of about two-thirds of the solution, after which the addition may be more rapid.
4. The first third of the ammonium chloride solution must be added quite slowly with frequent and thorough shaking.

3. Discussion

The most convenient laboratory method for the preparation of 2,4-dimethyl-5-carbethoxypyrrole is that given above.[1] A cheaper method of obtaining large quantities of the material consists in the partial hydrolysis of 2,4-dimethyl-3,5-dicarbethoxypyrrole with sulfuric acid, followed by decarboxylation.[2] The ester has been obtained also by the alcoholysis of 5-trichloroaceto-2,4-dimethylpyrrole in the presence of sodium ethoxide.[3] The free acid has been obtained from 1-[2,4-dimethylpyrrole-5]-2,4-dimethylpyrrole-5-carboxylic acid[4] and from 2,4-dimethylpyrrole-5-aldehyde.[5]

References and Notes

1. Fischer, Weiss, and Schubert, Ber. **56**, 1199 (1923); Ingraffia, Gazz. chim. ital **63**, 584 (1933).
2. Fischer and Walach, Ber. **58**, 2820 (1925).
3. Houben and Fischer, ibid. **64**, 2639 (1931).
4. Magnanini, ibid. **22**, 38 (1889).
5. Alessandri, Atti accad. Lincei **24** (II) 199 (1915) [C. A. **10**, 1350 (1916)]; Alessandri and Passerini, Gazz. chim. ital. **51** (I), 277 (1921).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

1-[2,4-dimethylpyrrole-5]-2,4-dimethylpyrrole-5-carboxylic acid

alcohol (64-17-5)

sulfuric acid (7664-93-9)

ether (60-29-7)

ammonium chloride (12125-02-9)

magnesium turnings (7439-95-4)

Ethyl bromide (74-96-4)

sodium sulfate (7757-82-6)

sodium ethoxide (141-52-6)

ethyl chloroformate (541-41-3)

2,4-Dimethyl-5-carbethoxypyrrole, 2-Pyrrolecarboxylic acid, 3, 5-dimethyl-, ethyl ester (2199-44-2)

2,4-Dimethylpyrrole (625-82-1)

ethane (74-84-0)

dimethylpyrrole

2,4-Dimethyl-3,5-dicarbethoxypyrrole (2436-79-5)

5-trichloroaceto-2,4-dimethylpyrrole

2,4-dimethylpyrrole-5-aldehyde

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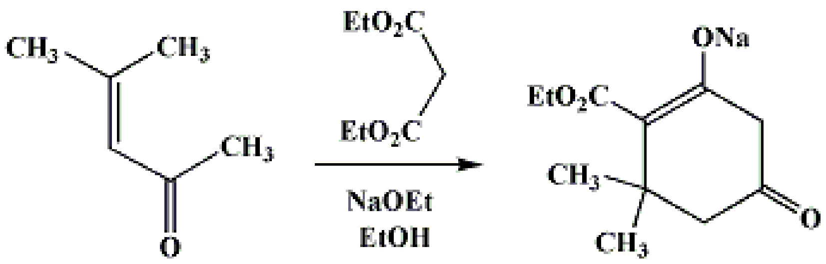
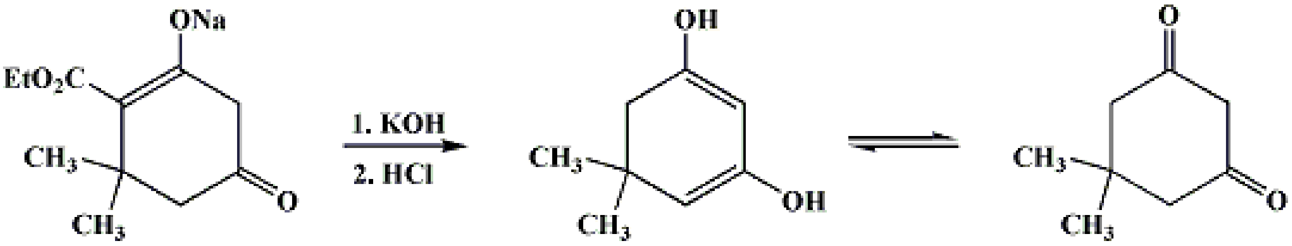
Organic Syntheses, CV 2, 200

5,5-DIMETHYL-1,3-CYCLOHEXANEDIONE

[1,3-Cyclohexanedione, 5,5-dimethyl-]





Submitted by R. L. Shriner and H. R. Todd.
Checked by W. H. Carothers and W. L. McEwen.

1. Procedure

In a dry 2-l. three-necked, round-bottomed flask, fitted with a liquid-sealed stirrer, a 500-cc. dropping funnel, and an efficient reflux condenser protected at the top with a calcium chloride tube, is placed 400 cc. of absolute alcohol. Through the condenser tube is added 23 g. (1 gram atom) of clean sodium at such a rate that the solution is kept at the boiling temperature. After the sodium has dissolved completely, 170 g. (1.06 moles) of ethyl malonate is added, and then 100 g. (1.02 moles) of mesityl oxide (Note 1) is added slowly through the dropping funnel. The solution is refluxed with constant stirring for two hours, after which a solution of 125 g. (2.2 moles) of potassium hydroxide in 575 cc. of water is added and the mixture is stirred and refluxed again on the water bath for six hours.

The mixture while still hot is made just acid to litmus with dilute hydrochloric acid (1 volume concentrated acid to 2 volumes water; sp. gr. 1.055); about 550 cc. is required. The flask is fitted with a condenser set for distillation, and as much alcohol as possible (about 550 cc.) is distilled by heating on a water bath.

The residue in the flask is boiled with about 15 g. of Norite (Note 2), filtered, and the treatment with the decolorizing charcoal repeated. The residue is again neutralized to litmus with dilute hydrochloric acid (about 150 cc.) and again boiled with charcoal. The hot, neutral or alkaline, yellow filtrate is finally made distinctly acid to methyl orange with additional dilute hydrochloric acid (50 to 100 cc.), boiled for a few minutes, and allowed to cool, whereupon the methone crystallizes. The product is filtered by suction from the acid liquid, washed with ice-cold water, and dried in the air. The yield is 96–122 g. (67–85 per cent of the theoretical amount) (Note 3).

2. Notes

1. The yield of methone depends on the purity of the mesityl oxide (Org. Syn. Coll. Vol. I,

1941, 345), which should be freshly distilled, the fraction boiling at 126–131° being collected.
2. Care is necessary when adding the decolorizing charcoal or the hot acid solution may foam vigorously owing to the liberation of carbon dioxide. A large container should be used, and the charcoal should be added very slowly.
3. The submitters in carrying out this preparation invariably obtained yields ranging from 120 to 128 g. of a product melting between 145° and 147°. Crystallization from about 1 l. of acetone gave 100 g. (70 per cent) of pure white material melting at 147°. The checkers (using mesityl oxide purchased from the Eastman Kodak Co. and freshly distilled) obtained yields ranging from 96 to 112 g., but their product melted at 147–148° and recrystallization failed to raise the melting point. The melting point of methone is given in the literature as 148–150°.

3. Discussion

5,5-Dimethyldihydroresorcinol, methone, dimedone, has always been made from mesityl oxide and malonic ester. The procedure given above is that of Vorländer.[1]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 345

References and Notes

1. Vorländer and Erig, Ann. **294**, 314 (1897); Vorländer, Z. anal. Chem. **77**, 245 (1929); Z. angew. Chem. **42**, 46 (1929); Chavanne, Miller, and Cornet, Bull. soc. chim. Belg. **40**, 673 (1931).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alcohol (64-17-5)

hydrochloric acid (7647-01-0)

carbon dioxide (124-38-9)

acetone (67-64-1)

Norite (7782-42-5)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

Mesityl oxide (141-79-7)

ethyl malonate (1071-46-1)

5,5-Dimethyl-1,3-cyclohexanedione, 1,3-Cyclohexanedione, 5,5-dimethyl-, methone, dimedone (126-81-8)

5,5-Dimethyldihydroresorcinol

methyl orange (547-58-0)

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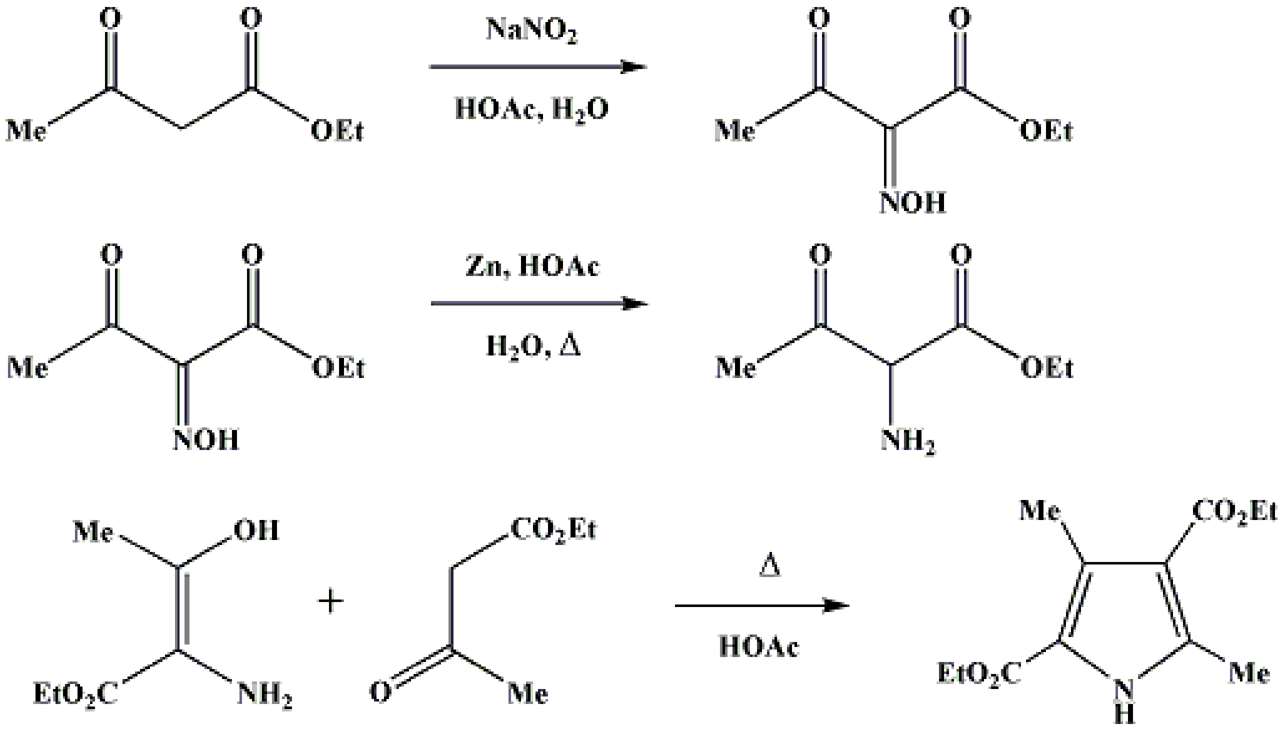
2,4-DIMETHYL-3,5-DICARBETHOXYPYRROLE

[2,4-Pyrroledicarboxylic acid, 3,5-dimethyl-, diethyl ester]



Submitted by Hans Fischer
Checked by C. R. Noller

1. Procedure

In a 3-l. three-necked, round-bottomed flask, fitted with a liquid-sealed mechanical stirrer and dropping funnel, are placed 390 g. (3 moles) of ethyl acetoacetate (Org. Syn. Coll. Vol. I, **1941**, 235) and 900 cc. of glacial acetic acid. The solution is cooled in an efficient freezing mixture to 5°, and a cold solution of 107 g. (1.47 moles) of 95 per cent sodium nitrite in 150 cc. of water is added dropwise with vigorous stirring at such a rate that the temperature remains between 5° and 7°. With efficient cooling about one-half hour is required to add the nitrite. The mixture is stirred for one-half hour longer and then allowed to stand for four hours, during which time it warms up to room temperature.

The separatory funnel is replaced by a wide-bore condenser, and the third neck of the flask is fitted with a stopper. The solution is stirred and portions of 196 g. (3 gram atoms) of zinc dust (Note 1) are added quickly through the third neck of the flask until the liquid boils and then frequently enough to keep it boiling (Note 2). After the addition has been completed, the mixture is heated by a burner and refluxed for one hour (Note 3) and (Note 4). While still hot the contents of the flask are decanted from the remaining zinc into a crock containing 10 l. of water which is being vigorously stirred. The zinc residue is washed with two 50-cc. portions of hot glacial acetic acid which are also decanted into the water. After standing overnight, the crude product is filtered by suction, washed on the filter with two 500-cc. portions of water, and dried in air to constant weight. The yield is 205–230 g. (57–64 per cent of the theoretical

amount) of material melting at 126–130°. On recrystallizing a 50-g. portion from 100 cc. of 95 per cent alcohol and washing twice with 20-cc. portions of cold alcohol, there is obtained 38.5 g. of pale yellow crystals melting at 136–137° (Note 5).

2. Notes

1. The zinc dust should be at least 80 per cent pure, and an amount equivalent to 196 g. of 100 per cent material should be used. An excess of zinc dust up to 3.5 gram atoms has been used without changing the yield.
2. Four portions of approximately 15 g. each are required to bring the solution to the boiling point, after which the remainder is added in about 5-g. portions over a period of three-quarters of an hour. Great care must be taken not to add too much zinc dust at first as the mixture foams badly. It is well to have a bath of ice and water and wet towels handy in order to control the reaction if it should become too violent.
3. For reasons unknown some runs behave entirely differently from others. Occasionally the foaming suddenly stops after about half of the zinc has been added and the remainder can be added much more rapidly, causing the solution to boil vigorously. During the period of external heating of the solution the mixture becomes thick and gummy and as much as 300 cc. of acetic acid must be added before stirring can be continued. The lower yields reported are obtained when this occurs.
4. It is reported that the yield is increased to 75 per cent by adding sodium acetate to the zinc dust reduction mixture to form a complex with the zinc acetate and so increase its solubility, and by adding the solution of the nitroso compound to the mixture of zinc dust, sodium acetate, ethyl acetoacetate, and glacial acetic acid, instead of adding the zinc dust last.[1]
5. The crude product turns pink when exposed to light whereas the recrystallized product is quite stable. A somewhat lighter product is obtained if 2 g. of decolorizing carbon is used during the crystallization, but this has no effect on the melting point.

3. Discussion

The above method, which has always been used for the preparation of 2,4-dimethyl-3,5-dicarbethoxypyrrole, is essentially that of Knorr.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 217

References and Notes

1. Corwin and Quattlebaum, Jr., J. Am. Chem. Soc. **58**, 1083 (1936).
2. Knorr, Ann. **236**, 318 (1886).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alcohol (64-17-5)

acetic acid (64-19-7)

sodium acetate (127-09-3)

sodium nitrite (7632-00-0)

decolorizing carbon (7782-42-5)

zinc (7440-66-6)

Ethyl acetoacetate (141-97-9)

2,4-Dimethyl-3,5-dicarbethoxypyrrole, 2,4-Pyrroledicarboxylic acid, 3,5-dimethyl-, diethyl ester (2436-79-5)

zinc acetate (557-34-6)

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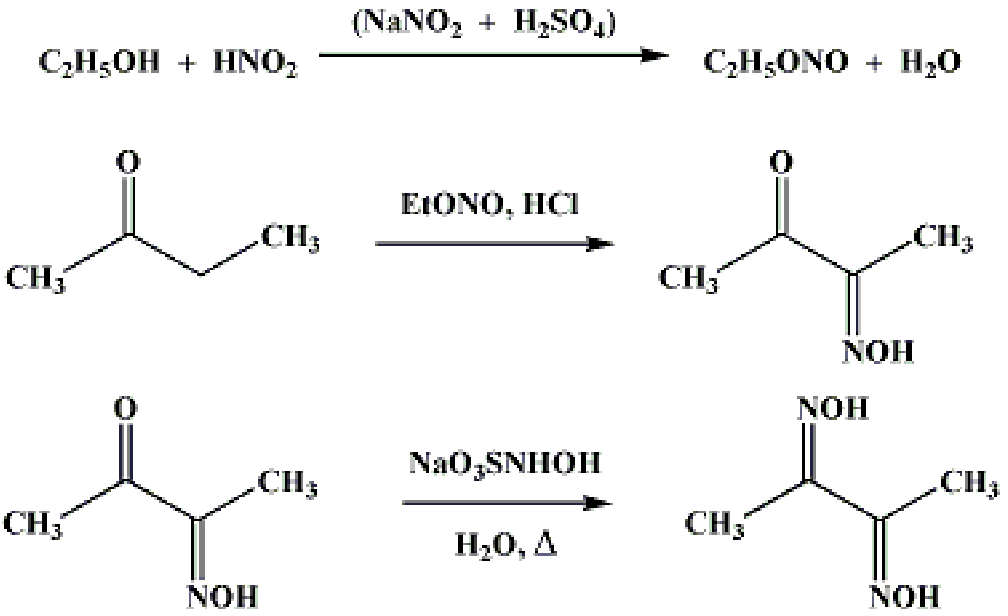
Organic Syntheses, CV 2, 204

DIMETHYLGLYOXIME

[Glyoxime, dimethyl-]



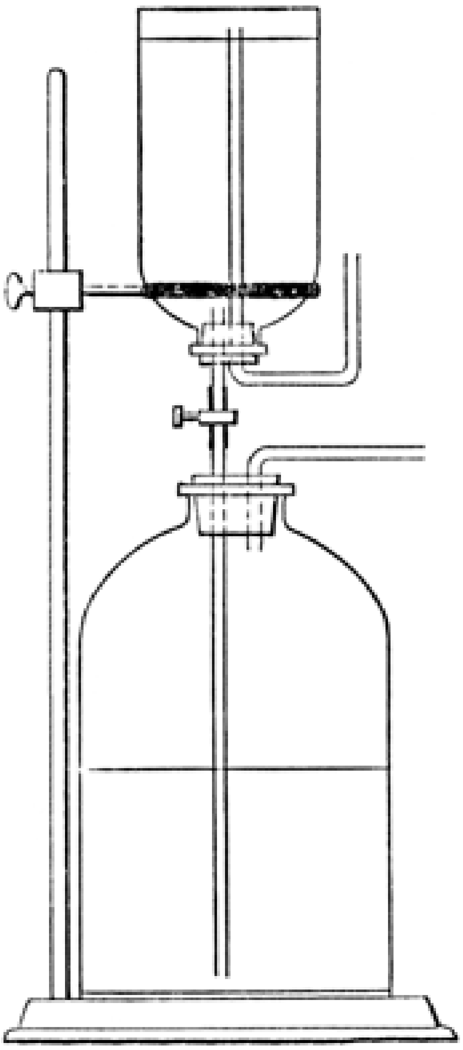
Submitted by W. L. Semon and V. R. Damerell.
Checked by Henry Gilman and R. E. Fothergill.

1. Procedure

(*A*) *Ethyl Nitrite*.—Two solutions are prepared. Solution I contains 620 g. (9 moles) of sodium nitrite (650 g. of technical 95 per cent quality), 210 g. (4.6 moles) of alcohol (285 cc. of 90 per cent denatured alcohol, or its equivalent), and water to make a total volume of 2.5 l. Solution II contains 440 g. of sulfuric acid (255 cc. of sp. gr. 1.84) and 210 g. of alcohol, diluted with water to 2.5 l. Ethyl nitrite may be generated continuously in gaseous form by allowing solution II to flow into solution I.

The gas can be conveniently made by putting solution II in a 2.5-l. bottle fitted with a two-holed rubber stopper (.htmFig. 7) and provided with glass tubing as indicated in the diagram. The rate of flow of solution II into a 6-l. bottle containing solution I is regulated by a screw clamp. The ethyl nitrite generated flows out of the second opening in the stopper of the lower bottle. The stoppers to both bottles should be wired on. A mechanical stirrer in the lower bottle is helpful in securing a steady evolution of the gas (Note 1).

Fig. 7



(*B*) *Biacetyl Monoxime*.—In a 2-l. three-necked flask provided with a condenser, a thermometer, and an inlet tube for ethyl nitrite, and arranged for external cooling, is placed 620 g. of commercial methyl ethyl ketone which has been dried with, and filtered from, 75 g. of anhydrous copper sulfate. Forty cubic centimeters of hydrochloric acid (sp. gr. 1.19) is added (Note 2) and the temperature raised to 40°. The ethyl nitrite from the preceding preparation is now bubbled in, the temperature being maintained between 40° and 55°. After all the ethyl nitrite has been passed in (Note 3) the crude product may be used in the preparation of dimethylglyoxime by distilling off the alcohol formed in the reaction until the temperature of the liquid reaches 90° (Note 4).

If pure biacetyl monoxime is desired, the crude product is neutralized with about 35 cc. of concentrated aqueous ammonia and diluted with half its volume of water. It is then distilled to remove alcohol, etc., until the distillate is no longer inflammable. The receiver is changed, and the contents are now rapidly distilled, using superheated steam. Almost all the biacetyl monoxime comes over in the first 5 l. of distillate. One to 1.5 kg. of salt is dissolved in the distillate, which is then cooled to 0°. The solid biacetyl monoxime crystallizes and may be filtered. The yield is 480–520 g. The product can be further purified, if desired, by recrystallizing from water (Note 5).

(*C*) *Sodium Hydroxylamine Monosulfonate*.—In a 12-l. crock are mixed 5 kg. of shaved ice (Note 6) and 569 g. of sodium nitrite (594 g. of the technical 95 per cent quality). Into this is stirred a suspension of sodium bisulfite containing 1.1 kg. of available sulfur dioxide (about 1775 g. of technical bisulfite) in 750 cc. of water. Then, beneath the surface of the solution is added, with constant stirring, 150 cc. of glacial acetic acid (Note 7) followed by a mixture of 550 cc. of concentrated hydrochloric acid (sp. gr. 1.19) with 400 g. of shaved ice (Note 8). The entire solution should always remain below 0°, further ice being added if there is a tendency for the temperature to rise. The solution should now become acid to Congo red paper and contain 6 or more moles of the sodium hydroxylamine disulfonate, which rapidly hydrolyzes to an acid solution of the monosulfonate.

(*D*) *Dimethylglyoxime*.—The crude biacetyl monoxime remaining after distilling to 90°, and containing about 5 moles of biacetyl monoxime, is added to the sodium hydroxylamine monosulfonate solution (which has been filtered to remove any sediment) and which is contained in a 15-l. flask. It is heated to 70° and allowed to remain warm (with occasional stirring) for several hours (Note 9). The dimethylglyoxime separates in crystals which can be filtered from the solution as soon as it has become cold (Note 10). The crystals are washed with cold water until free of sulfate. The yield of compound melting at 238–240° is 540–575 g.

Recrystallization is unnecessary since the product is pure white and free from tarry material (Note 5).

(*E*) *Sodium Dimethylglyoximate*.—To a solution of 75 g. of sodium hydroxide in 300 cc. of water is added, with stirring, 100 g. of dimethylglyoxime (Note 11). Heat is applied to effect solution (Note 12), and the mixture is filtered from any slight residue. The solution is poured while hot into 500 cc. of 95 per cent alcohol. After cooling to 5°, with stirring, the crystals which form are filtered, then suspended in 150 cc. of alcohol and again filtered, and finally dried at 25° until the solid has no odor of alcohol (Note 13). The yield is 213–230 g. (81–88 per cent of the theoretical amount) of the octahydrate.

2. Notes

1. If a mechanical stirrer is not used attention is necessary to prevent a layer of solution II from collecting at the bottom of solution I, since, under these conditions, a little shaking produces too violent an evolution of gas.
Because ethyl nitrite is harmful if inhaled continuously, the reaction should be run in a hood or out of doors.
2. The methyl ethyl ketone should not be allowed to stand any length of time between the addition of the hydrochloric acid and the treatment with ethyl nitrite, inasmuch as the acid causes a condensation of the ketone with itself, thereby lowering the yield of biacetyl monoxime.
3. The ethyl nitrite may be passed into the solution as rapidly as possible,

provided that the temperature does not exceed 55°. Very complete absorption takes place, and the time of addition is about one and one-half hours.

4. This distillation for the removal of alcohol and excess methyl ethyl ketone should not stop before the temperature of the liquid reaches 90° or continue after this temperature is attained. If the distillation is stopped too soon, the alcohol that was not removed later increases the solubility of the dimethylglyoxime; too high a temperature causes the formation of tarry products. Both factors reduce the yield.

5. About 70–80 per cent of the biacetyl monoxime is recovered on crystallization. Practically all the monoxime left in the mother liquor can be recovered by steam distillation. The recrystallized and dried compound melts at 76.5°. Purification by distillation is not recommended.

Biacetyl monoxime turns brown rapidly after preparation; it must not be allowed to stand before adding it to the hydroxylamine monosulfonate in the preparation of dimethylglyoxime if this final product is to be obtained in a colorless condition.

6. Shaved ice is used in place of crushed ice because of more efficient cooling. The use of snow is advised, if it is available.

7. The acetic acid helps to buffer the solution and maintain a low hydrogen-ion concentration, which is favorable for a good yield.

8. The acid may be added as rapidly as desired so long as the temperature remains below 0° and no evolution of gas takes place. The entire addition should require not more than fifteen minutes.

9. The mixture is warmed to hasten the hydrolysis of disulfonate to monosulfonate, and also to increase the solubility of the biacetyl monoxime in the monosulfonate solution.

10. The dimethylglyoxime should not be filtered until the mixture has become perfectly cool, because dimethylglyoxime is slightly soluble in a warm acid solution.

11. Crude or discolored dimethylglyoxime may be used since the impurities remain in solution in the aqueous alcohol.

12. The solution of dimethylglyoxime in sodium hydroxide should not be boiled, since prolonged heating causes decomposition.

13. The sodium salt may be further purified if desired by dissolving in water and reprecipitating with alcohol. Large crystals may be secured by crystallizing slowly from water.

Too long drying, or drying at too high a temperature, partially dehydrates the salt, with the result that it dissolves much more slowly in water and is therefore less desirable for making solutions for use in qualitative or quantitative analysis. Sodium dimethylglyoximate is extremely soluble in water. A 3 per cent (0.1 *M*) aqueous solution is suggested to replace the 1 per cent alcoholic solution now used in analytical work.

3. Discussion

Biacetyl monoxime has been prepared by the action of amyl nitrite on methyl ethyl

ketone using sodium hydroxide[1] or hydrochloric acid[2] as a condensing agent, and by melting nitrosolevulinic acid.[3]

Dimethylglyoxime has been prepared by the action of hydrochloric acid upon biacetyl monoxime;[4] by the action of hydroxylamine on biacetyl;[5] by the action of hydroxylamine on biacetyl monoxime;[6] and by the action of sodium hydroxylamine monosulfonate on biacetyl monoxime.[7] It is formed in small amounts, together with ethylnitrolic acid, by the action of oxides of nitrogen upon methyl ethyl ketone.[8]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 1022
- Org. Syn. Coll. Vol. 6, 542

References and Notes

1. Claisen, Ber. **38**, 696 (1905).
2. Diels and Farkas, ibid. **43**, 1957 (1910); Biltz, Z. anal. Chem. **48**, 164 (1909); Semon and Damerell, J. Am. Chem. Soc. **47**, 2038 (1925).
3. Thal, Ber. **25**, 1720 (1892).
4. Schramm, ibid. **16**, 180 (1883); Johlin, J. Am. Chem. Soc. **36**, 1218 (1914).
5. Fittig, Daimler, and Keller, Ann. **249**, 182 (1888).
6. Tschugaeff, Ber. **38**, 2520 (1905); Gandarin, J. prakt. Chem. (2) **77**, 414 (1908); Biltz, Z. anal. Chem. **48**, 164 (1909); Adams and Kamm, J. Am. Chem. Soc. **40**, 1281 (1918).
7. Semon and Damerell, ibid. **46**, 1290 (1924); **47**, 2033 (1925).
8. Behrend and Tryller, Ann. **283**, 244 (1894).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

oxides of nitrogen

ethylnitrolic acid

alcohol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ammonia (7664-41-7)

sodium hydroxide (1310-73-2)

sulfur dioxide (7446-09-5)

copper sulfate (7758-98-7)

sodium nitrite (7632-00-0)

sodium bisulfite (7631-90-5)

ethyl nitrite (109-95-5)

amyl nitrite (463-04-7)

hydroxylamine (7803-49-8)

sodium hydroxylamine disulfonate

DIMETHYLGLYOXIME, Glyoxime, dimethyl- (95-45-4)

Biacetyl monoxime (57-71-6)

methyl ethyl ketone (78-93-3)

Sodium Hydroxylamine Monosulfonate

Sodium Dimethylglyoximate

nitrosolevulinic acid

biacetyl (431-03-8)

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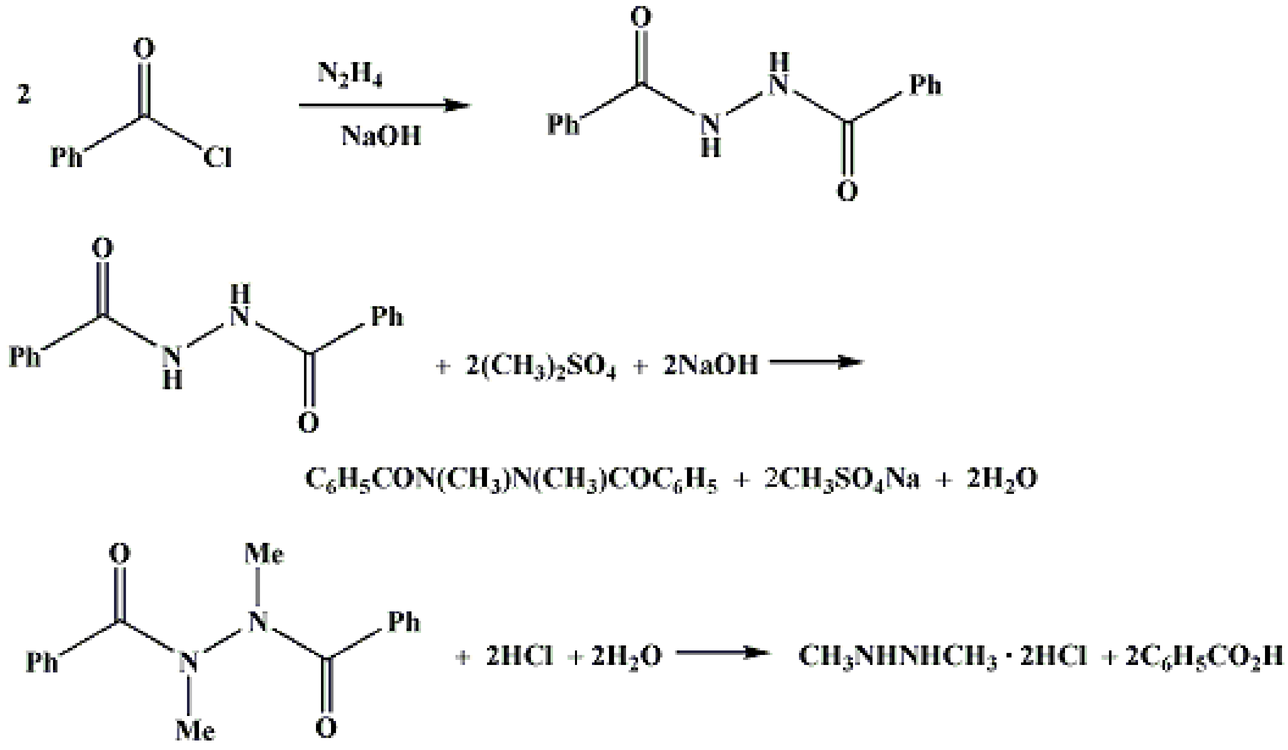
Organic Syntheses, CV 2, 208

sym.-DIMETHYLHYDRAZINE DIHYDROCHLORIDE

[Hydrazine, 1,2-dimethyl-, dihydrochloride]



Submitted by H. H. Hatt
Checked by Reynold C. Fuson and Ellsworth Ellingboe.

1. Procedure

(*A*) *Dibenzoylhydrazine*.—In a 2-l. flask, provided with a mechanical stirrer (Note 1) and cooled in a bath of cold water, are placed a solution of 48 g. (1.2 moles) of sodium hydroxide in 500 cc. of water and 65 g. (0.5 mole) of hydrazine sulfate (Org. Syn. Coll. Vol. I, **1941**, 309). With stirring, 145 g. (120 cc., 1.03 moles) of freshly distilled benzoyl chloride and 120 cc. of an aqueous solution containing 45 g. (1.1 moles) of sodium hydroxide are added slowly from separate dropping funnels. The benzoyl chloride is added over a period of one and one-half hours; the alkali is added slightly faster. After both additions are completed the mixture is stirred for two hours longer and then saturated with carbon dioxide (Note 2). The dibenzoylhydrazine is filtered with suction, pressed thoroughly, and ground to a paste with 50 per cent aqueous acetone. The material is filtered with suction, washed with water, and pressed as dry as possible. The crude product is dissolved in about 650 cc. of boiling glacial acetic acid, from which, on cooling, the dibenzoylhydrazine separates as a mass of fine white needles. These are filtered with suction, washed with cold water, and dried by heating under reduced pressure on a water bath, in a slow current of air. This first fraction, m.p. 234–238°, amounts to 80–90 g. (66–75 per cent of the theoretical amount) and is practically pure. Small quantities of less pure material can be obtained by concentration of the mother liquor.

(*B*) *Dibenzoyldimethylhydrazine*.—The following operations should be performed under a hood. In a 2-l. three-necked flask, provided with a mechanical stirrer, a thermometer, and two dropping funnels, are placed 80 g. (0.33 mole) of dibenzoylhydrazine, 10 g. (0.25 mole) of sodium

hydroxide, and 600 cc. of water. The mixture is maintained at about 90° (Note 3) by heating on a water bath. With stirring, 320 g. (240 cc., 2.54 moles) of methyl sulfate (Note 4) and 250 cc. of an aqueous solution containing 125 g. (3.1 moles) of sodium hydroxide are added from separate dropping funnels. The methyl sulfate is added in 10-cc. portions at five-minute intervals, the sodium hydroxide solution at a rate that maintains the reaction mixture slightly alkaline. When markedly alkaline the mixture has a distinctly yellow color; it is best to maintain a degree of alkalinity slightly less than that required to produce this color.

During the additions, which require about two hours, the dibenzoyldimethylhydrazine separates as a supernatant liquid (Note 5); the semisolid material thrown up on the sides of the flask must be washed down from time to time. After being heated for one-half hour longer the mixture is allowed to cool. The solid dibenzoyldimethylhydrazine is collected, crushed with water, filtered, and dissolved in 100 cc. of chloroform. The solution is filtered from insoluble impurities and dried over sodium sulfate; the chloroform is removed by heating on a water bath, finally under reduced pressure. The solid residue melts at 77–84° and is sufficiently pure for further use. The yield is 77–83 g. (86–93 per cent of the theoretical amount) (Note 6).

(*C*) *Dimethylhydrazine Dihydrochloride*.—In a 2-l. flask, a mixture of 67 g. (0.25 mole) of dibenzoyldimethylhydrazine and 250 cc. of 32 per cent hydrochloric acid (sp. gr. 1.16) is refluxed gently for two hours under a hood. To remove the benzoic acid, the mixture is steam-distilled until 10 l. of distillate has collected (Note 7); the residual liquor is evaporated to dryness under reduced pressure on a water bath. The crystalline dihydrochloride is treated with 25 cc. of absolute ethyl alcohol, and the mixture is evaporated to dryness under reduced pressure. This treatment is repeated, and the dihydrochloride is crushed with a mixture of 25 cc. of absolute alcohol and 2–3 cc. of concentrated hydrochloric acid, filtered, and washed with 10–15 cc. of cold absolute alcohol. The first fraction of dimethylhydrazine dihydrochloride, after being dried in a vacuum desiccator, weighs 22–23 g. By evaporation of the mother liquors and further treatment with 5–6 cc. of absolute alcohol and a little hydrochloric acid, a second fraction of 3 g. of the hydrochloride is obtained. Repetition of this procedure yields a third fraction amounting to about 0.5 g. (Note 8). The total yield is 25–26 g. (75–78 per cent of the theoretical amount).

2. Notes

1. The reaction flask need neither be corked nor placed under a hood if a glass tube, connected to a filter pump, is passed a short way into the neck of the flask.
2. Most of the dibenzoylhydrazine separates during the reaction as a white precipitate; if the mixture is not saturated with carbon dixoide, about 3 g. of the product remains in solution.
3. The temperature may be determined by a thermometer sheathed in a glass tube, which passes through the stopper and dips into the liquid. A section of rubber tubing slipped over the upper end of the thermometer serves to hold it in place. This device also provides a convenient method of testing the alkalinity of the solution.
4. Since methyl sulfate is very toxic, care should be exercised to avoid spilling the liquid or inhaling the vapor of the reaction mixture. Ammonia is a specific antidote.
5. The stated quantities of methyl sulfate and sodium hydroxide are merely approximations of the amounts actually required. The methyl sulfate is added at the stated rate until all the solid dibenzoylhydrazine has disappeared, and then another 25 cc. is added. Usually less than the stated amount of alkali is required.
6. The dibenzoyldimethylhydrazine can be obtained in a purer state by treating the cold, filtered chloroform solution with a 1 : 1 mixture of ether and petroleum ether (b.p. 40–60°) until crystallization begins and then adding slowly a moderate excess of petroleum ether.

The hydrazine separates in small white needles, m.p. 84–87°.

7. It is found that this treatment removes the benzoic acid almost completely. Alternatively, the benzoic acid can be extracted with a 1 : 1 benzene-ether mixture.

8. The mono- and dihydrochlorides are very hygroscopic and should not be exposed to air for any length of time. Solutions of the dihydrochloride lose hydrochloric acid on evaporation, and the dihydrochloride obtained from solutions so treated tends to be oily. In recrystallization a little concentrated hydrochloric acid is added to the alcoholic solution. The dihydrochloride may be crystallized by dissolving in boiling absolute ethyl alcohol (1 g. requires 20 cc. of alcohol), then adding a little concentrated hydrochloric acid and, after cooling slightly, about one-fifth of the volume of ether. The dimethylhydrazine dihydrochloride separates as a white crystalline powder, melting at 165–167°.

3. Discussion

Symmetrical dimethylhydrazine has been obtained by heating the methiodide of 1-methylpyrazole with potassium hydroxide.[1] It has usually been prepared by methylation of diformylhydrazine and subsequent hydrolysis with hydrochloric acid.[2] The present method is based on the observation of Folpmers that dibenzoylhydrazine may be similarly employed.[3]

References and Notes

1. Knorr and Köhler, Ber. **39**, 3257 (1906).
2. Harries and Klamt, ibid. **28**, 503 (1895); Harries and Haga, ibid. **31**, 56 (1898); Thiele, ibid. **42**, 2575 (1909).
3. Folpmers, Rec. trav. chim. **34**, 34 (1915).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

carbon dixoide

Symmetrical dimethylhydrazine

methiodide of 1-methylpyrazole

sym.-DIMETHYLHYDRAZINE DIHYDROCHLORIDE

ethyl alcohol, alcohol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ammonia (7664-41-7)

Benzene (71-43-2)

ether (60-29-7)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium sulfate (7757-82-6)

Benzoic acid (65-85-0)

carbon dioxide (124-38-9)

acetone (67-64-1)

benzoyl chloride (98-88-4)

potassium hydroxide (1310-58-3)

methyl sulfate (75-93-4)

Hydrazine sulfate (10034-93-2)

DIMETHYLHYDRAZINE DIHYDROCHLORIDE

Hydrazine, 1,2-dimethyl-, dihydrochloride (306-37-6)

Dibenzoylhydrazine

Dibenzoyldimethylhydrazine

diformylhydrazine

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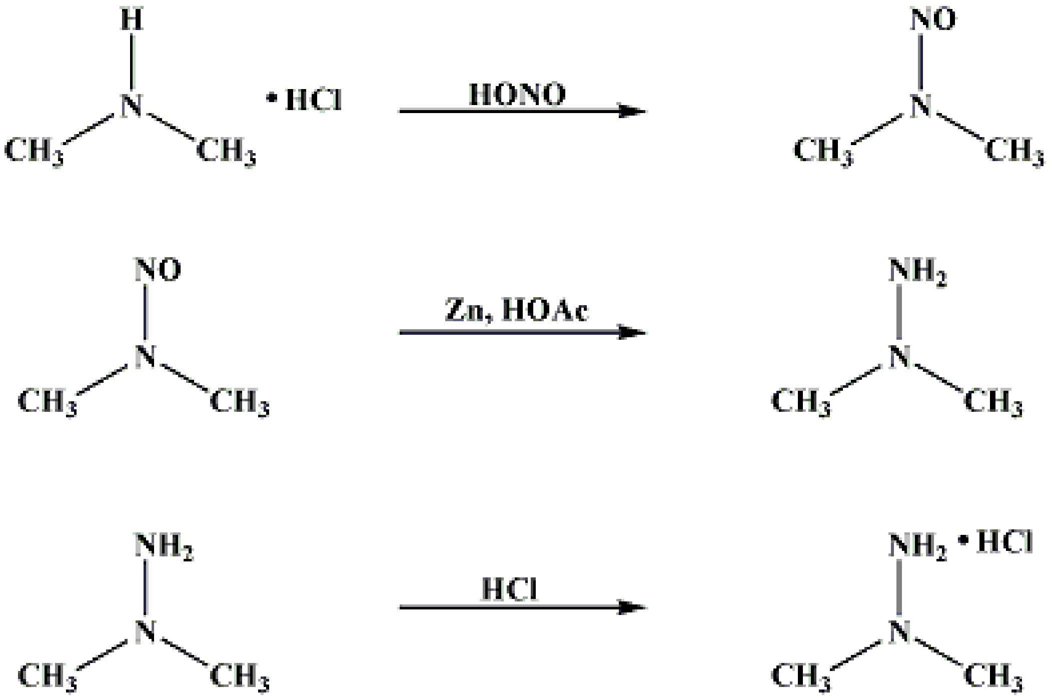
unsym.-DIMETHYLHYDRAZINE HYDROCHLORIDE

[Hydrazine, 1,1-dimethyl-, hydrochloride]



Submitted by H. H. Hatt
Checked by W. W. Hartman and W. D. Peterson.

1. Procedure

(*A*) *Nitrosodimethylamine*.—In a 2-l. round-bottomed flask provided with a mechanical stirrer are placed 245 g. (3 moles) of dimethylamine hydrochloride, 120 cc. of water, and 10 cc. of approximately 2 *N* hydrochloric acid. The resulting solution is stirred vigorously and maintained at 70–75° by heating on a water bath, while 235 g. (3.23 moles) of 95 per cent sodium nitrite suspended in 150 cc. of water is added from a dropping funnel over a period of an hour. The reaction mixture is tested frequently and maintained barely acid to litmus by further 1-cc. additions of 2 *N* hydrochloric acid when necessary (about 30–35 cc. of acid is required). Stirring and heating are continued for two hours after all the sodium nitrite has been added.

The flask is arranged for distillation, and the reaction mixture is distilled under slightly diminished pressure on a water bath until the residue is practically dry. To the residue 100 cc. of water is added, and the process of distillation to dryness is repeated. The distillates are combined and saturated with potassium carbonate (about 300 g. is required); the upper layer of dimethylnitrosoamine is removed, and the water layer is extracted with three 140-cc. portions of ether. The combined nitrosoamine and ethereal extracts are dried over anhydrous potassium carbonate and distilled through a 30-cm. fractionating column. The yield of product boiling at 149–150° /755 mm. is 195–200

g. (88–90 per cent of the theoretical amount). Nitrosodimethylamine is a yellow oil which darkens in bright light.

(*B*) *unsym.-Dimethylhydrazine Hydrochloride*.—In a 5-l. round-bottomed flask, provided with a mechanical stirrer, dropping funnel, and thermometer, are put 200 g. (2.7 moles) of nitrosodimethylamine, 3 l. of water, and 650 g. (10 gram atoms) of 100 per cent zinc dust, or an equivalent amount of lower-quality material (Note 1). While the mixture is stirred and maintained at 25–30° by immersion in a water bath, 1 l. (14 moles) of 85 per cent acetic acid is added from the dropping funnel over a period of two hours. Subsequently the reaction mixture is heated for one hour at 60°, allowed to cool, and the excess zinc dust filtered and washed with a little water. The aqueous liquors are combined and transferred to a 12-l. flask arranged for steam distillation. The flask is fitted with a dropping funnel, and the steam inlet is provided with a trap. A large filtering or distilling flask serves as the receiver, and the side tube is connected with two absorption flasks, each containing 1 : 1 hydrochloric acid (Note 2). The aqueous liquors are made distinctly alkaline by adding a concentrated solution of 1 kg. of sodium hydroxide through the dropping funnel, and the mixture is then steam-distilled until a test portion of the distillate shows only a faint reduction with Fehling's solution. Usually about 5–6 l. of distillate suffices to remove the dimethylhydrazine. The distillation is more rapid if a free flame is placed under the distillation flask.

The aqueous distillate is treated with 650 cc. of concentrated hydrochloric acid and concentrated on a steam bath, under reduced pressure, until the residual liquor becomes a syrupy mass (Note 3). This is desiccated further by adding 150 cc. of absolute ethyl alcohol and evaporating under reduced pressure. Two or three such treatments with alcohol dry the crystalline material sufficiently so that it no longer sticks to the sides of the flask. The crude product is dried in a vacuum desiccator over calcium chloride. The pale yellow, dry, crystalline solid weighs 200–215 g. (77–83 per cent of the theoretical amount). The dried product may be purified by dissolving it in an equal weight of boiling absolute ethyl alcohol and then chilling in an ice bath. The yield of pure white crystals melting at 81–82° is 180–190 g. (69–73 per cent of the theoretical amount) (Note 4).

2. Notes

1. The approximate strength of the zinc dust should be known in order to ensure complete reduction.
2. If this step is carried out under a hood, the absorption flasks are unnecessary. During the first minutes of the subsequent steam distillation, volatile nitrogen bases, consisting chiefly of ammonia and methylamine, are driven over.
3. A concentrated aqueous solution of the free hydrazine may be obtained from the syrupy residue by allowing it to drop onto a large excess of solid sodium hydroxide and distilling until the temperature reaches 100°. To obtain the anhydrous base, the concentrated aqueous solution is redistilled after standing over potassium hydroxide, the base is collected over barium oxide and after several days' standing is distilled again. The free hydrazine boils at 62–65° /765

mm.; it is extremely hygroscopic and attacks cork and rubber.
4. The product is the monohydrochloride of the base.

3. Discussion

The preparation of unsymmetrical dimethylhydrazine by reduction of nitrosodimethylamine was described by Fischer[1] and by Renouf.[2] Methylation of hydrazine,[3] reduction of nitrodimethylamine,[4] and the action of aminopersulfuric acid on dimethylamine[5] also furnish unsymmetrical dimethylhydrazine.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 12

References and Notes

1. Fischer, Ber. **8**, 1587 (1875).
2. Renouf, ibid. **13**, 2170 (1880).
3. Harries and Haga, ibid. **31**, 56 (1898).
4. Franchimont, Rec. trav. chim. **3**, 427 (1884); Backer, ibid. **31**, 150 (1912).
5. Sommer and Schulz, Ger. pat. 338,609 [Frdl. **13**, 203 (1916–21)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

aminopersulfuric acid

unsym.-Dimethylhydrazine Hydrochloride

unsymmetrical dimethylhydrazine

ethyl alcohol (64-17-5)

calcium chloride (10043-52-4)

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ammonia (7664-41-7)

ether (60-29-7)

sodium hydroxide (1310-73-2)

barium oxide

sodium nitrite (7632-00-0)

potassium hydroxide (1310-58-3)

zinc (7440-66-6)

hydrazine (302-01-2)

dimethylamine hydrochloride (506-59-2)

methylamine (74-89-5)

dimethylhydrazine (57-14-7)

Hydrazine, 1,1-dimethyl-, hydrochloride (593-82-8)

Nitrosodimethylamine, dimethylnitrosoamine (62-75-9)

dimethylamine (124-40-3)

nitrodimethylamine (4164-28-7)

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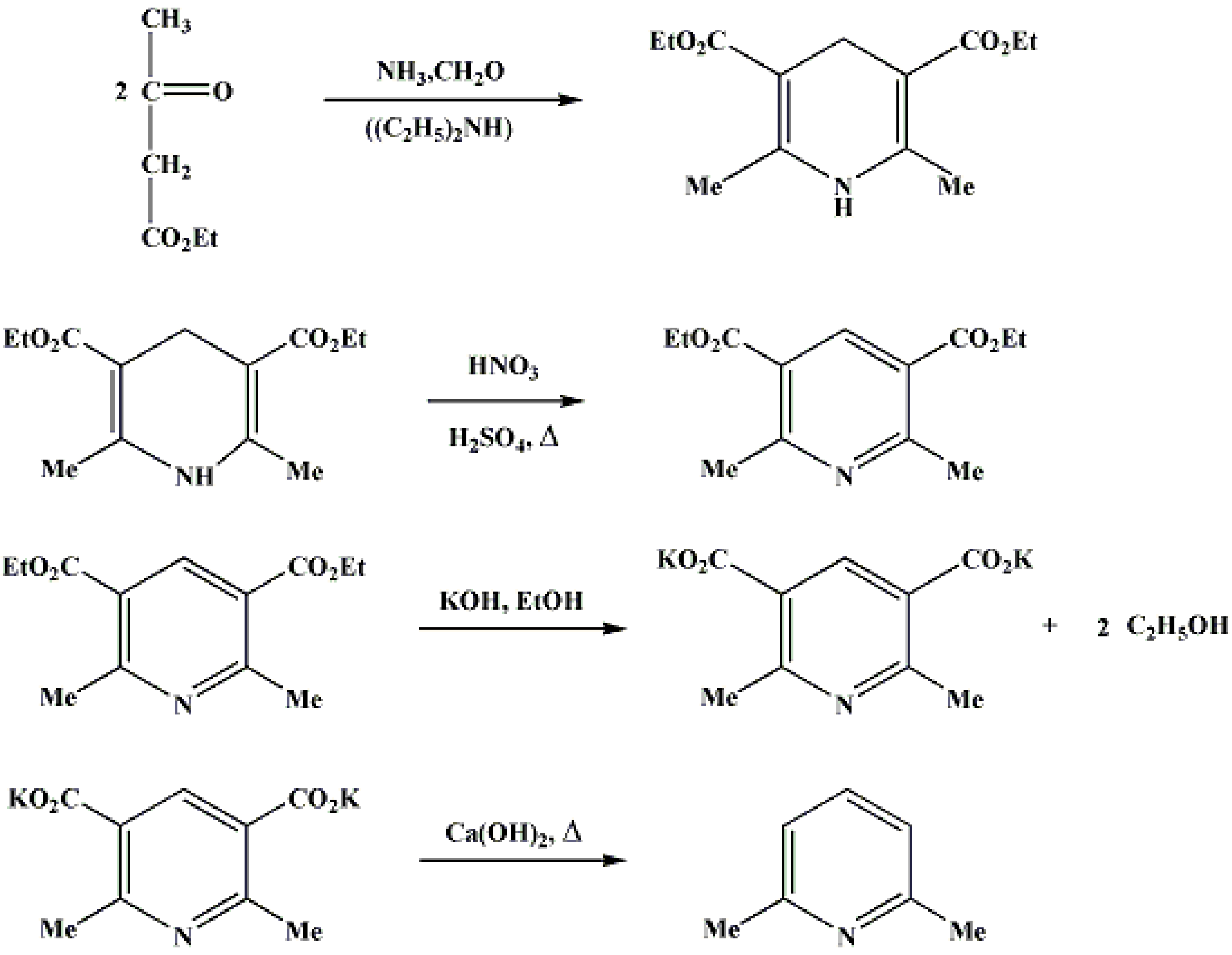
2,6-DIMETHYLPYRIDINE

[2,6-Lutidine]



Submitted by Alvin Singer and S. M. McElvain.
Checked by Reynold C. Fuson and Charles F. Woodward.

1. Procedure

To 500 g. (3.85 moles) of freshly distilled ethyl acetoacetate in a 1-l. flask, set in ice and well cooled, are added 152 g. (2 moles) of 40 per cent aqueous formaldehyde solution and 20–25 drops of diethylamine. The flask and contents are kept cold for six hours and are then allowed to stand at room temperature for forty to forty-five hours. At the end of this time two layers are present, a lower oily layer and an upper aqueous layer. The layers are separated, and the aqueous layer is extracted with 50 cc. of ether. The ether solution is added to the oily layer, and the resulting solution is dried over 30 g. of calcium chloride. The ether is then removed by distillation on a steam bath. The residue, amounting to approximately 500 g., is diluted with an equal volume of alcohol and is thoroughly cooled in an ice bath. Ammonia is then passed into the mixture until the solution is saturated. This requires from four to eight hours, and during this time the flask is kept packed in ice. The ammoniacal alcoholic solution is allowed to stand at room temperature for forty to forty-five hours. Most of the alcohol is now evaporated; the residue is cooled, and the solid 1,4-dihydro-3,5-dicarbethoxy-2,6-dimethylpyridine is removed from the remaining alcohol on a suction filter. The dried ester melts at 175–180° and weighs 410–435 g. (84–89 per cent of the theoretical amount).

To 200 g. (0.79 mole) of the ester in a 5-l. flask is added a mixture of 270 g. of water, 72 g. of concentrated nitric acid (sp. gr. 1.42), and 78 g. of concentrated sulfuric acid. The flask is then very cautiously heated, and the contents are kept in a swirling motion by a slow shaking of the flask by hand. The oxidation is accompanied by considerable foaming if the heating is too rapid, part of the reaction mixture may be lost by excessive frothing. After the foaming has subsided, the reaction mixture is again warmed cautiously until the liquid assumes a deep red color. The entire oxidation is carried out in ten to fifteen minutes. After the liquid has ceased boiling, it is treated with 500 cc. of water and 500 g. of finely chopped ice. The resulting solution is made strongly alkaline by the gradual addition of ammonium hydroxide (sp. gr. 0.90). The precipitated 3,5-dicarbethoxy-2,6-dimethylpyridine is filtered with suction, dried on a porous plate, and then distilled (Note 1). The yield of product boiling at 170–172°/8 mm. is 115–130 g. (58–65 per cent of the theoretical amount based on the dihydro ester).

A solution of 130 g. (0.52 mole) of this ester in 400 cc. of ethyl alcohol is placed in a two-necked 2-l. flask, carrying a dropping funnel and a reflux condenser, and is heated to boiling. Then one-third of a solution (Note 2) of 78.5 g. (1.4 moles) of potassium hydroxide in 400 cc. of alcohol is added from the dropping funnel, and the alcoholic solution is boiled until it becomes clear. Then a second third of the alkali solution is added, and the reaction mixture is again boiled until any precipitate disappears. Finally, the last third of the alcoholic potassium hydroxide solution is added. The addition of the alkali requires about twenty minutes. The reaction mixture is then boiled for forty minutes longer.

The contents of the flask while still hot are poured into a 30-cm. evaporating dish and the alcohol is evaporated on a steam bath. The dry salt is pulverized and thoroughly mixed with 390 g. of calcium oxide, placed in a 2-l. copper retort (Note 3), and heated with the full flame of a Meker burner. The distillate is placed in a distilling flask and heated on a steam bath; all material distilling under 90° is removed and discarded. The residue is then allowed to stand over solid potassium hydroxide for twelve hours and is finally fractionated. The dimethylpyridine distils at 142–144°/743 mm. The yield is 35–36 g. (63–65 per cent of the theoretical amount based on the 3,5-dicarbethoxy-2,6-dimethylpyridine, or 30–36 per cent based on the original ethyl acetoacetate).

2. Notes

1. Before the pressure is reduced, the 3,5-dicarbethoxy-2,6-dimethylpyridine should be melted by immersing the distilling flask in boiling water. If this is not done, considerable foaming takes place during the distillation.
2. If the entire amount of alcoholic potassium hydroxide solution is added at this point, there is precipitated a colorless solid, which does not dissolve even on prolonged heating.
3. A metal retort is very desirable for this decomposition since glass flasks soften at the temperature necessary for the reaction.

3. Discussion

2,6-Dimethylpyridine has been isolated from the basic fraction of coal tar[1] and also from the bone oil fraction distilling at 139–142°.[2] It has been prepared from ethyl acetopyruvate and ethyl β-aminocrotonate.[3] A procedure for the oxidation of the dihydroester and the saponification and decarboxylation of the product, similar to the procedure given above, has been published.[4]

References and Notes

1. Lunge and Rosenberg, Ber. **20**, 129 (1887); Heap, Jones, and Speakman, J. Am. Chem. Soc. **43**, 1936 (1921); Komatsu and Mohri, J. Chem. Soc. Japan **52**, 722 (1931) [C. A. **26**, 4936 (1932)].
2. Ladenberg and Roth, Ber. **18**, 51 (1885).

3. Mumm and Hüneke, ibid. **50**, 1568 (1917).
4. Oparina, Karasina, and Smirnov, J. Applied Chem. (U.S.S.R.) **11**, 965 (1938) [C. A. **33**, 1732 (1939)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethyl alcohol, alcohol (64-17-5)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

ammonia (7664-41-7)

ether (60-29-7)

formaldehyde (630-08-0)

nitric acid (7697-37-2)

potassium hydroxide (1310-58-3)

ammonium hydroxide (1336-21-6)

calcium oxide

Ethyl acetoacetate (141-97-9)

Ethyl acetopyruvate (615-79-2)

diethylamine (109-89-7)

2,6-Dimethylpyridine, 2,6-Lutidine (108-48-5)

1,4-Dihydro-3,5-dicarbethoxy-2,6-dimethylpyridine (1149-23-1)

3,5-Dicarbethoxy-2,6-dimethylpyridine (1149-24-2)

dimethylpyridine (583-61-9)

ethyl β-aminocrotonate (626-34-6)

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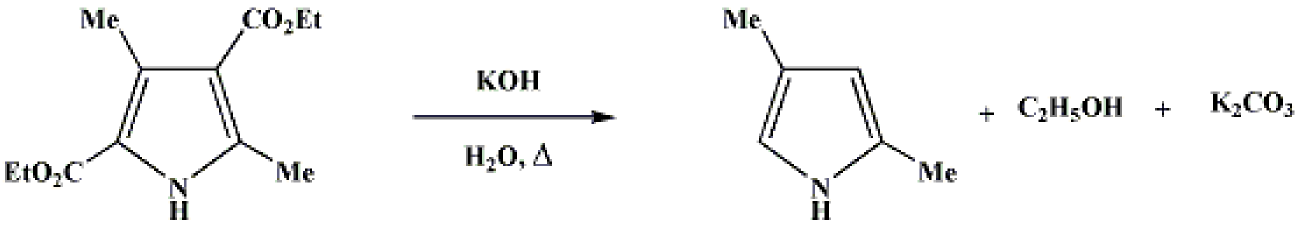
2,4-DIMETHYLPYRROLE

[Pyrrole, 2,4-dimethyl-]



Submitted by Hans Fischer
Checked by C. R. Noller

1. Procedure

A solution of 270 g. (4.8 moles) of potassium hydroxide in 150 cc. of water is prepared in a 3-l. round-bottomed flask, 120 g. (0.5 mole) of crude 2,4-dimethyl-3,5-dicarbethoxypyrrole (p. 202) and a pinch of sand are added, and the whole is mixed thoroughly by shaking. The flask is fitted with a reflux condenser, and the mixture is heated in an oil bath at 130° for two to three hours with occasional shaking until the thick paste has become partially liquefied owing to the formation of dimethylpyrrole.

The flask is next fitted for distillation with superheated steam and with a separatory funnel for the introduction of water into the center of the flask. A 3-l. round-bottomed flask fitted with a vertical condenser is used as a receiver (Org. Syn. Coll. Vol. I, **1941**, 479). The temperature of the oil bath is raised to 160°, and superheated steam at 220–250° is introduced. The temperature of the oil bath is then gradually raised to 200°. If foaming becomes too great, a few drops of water are added from the separatory funnel, care being taken that the water does not strike the hot glass walls (Note 1). Steam distillation is continued until no more dimethylpyrrole comes over. This takes from one to two hours, and the distillate amounts to 2.5–3 l. The distillate is extracted once with 200 cc. of ether and three times with 100-cc. portions, and the extract is dried for two hours over 20 g. of anhydrous potassium carbonate. The ether is removed by distillation from a 100-cc. modified Claisen flask having a 15-cm. fractionating side arm, the solution being added gradually through a separatory funnel. After the ether is removed the residue is distilled and the fraction boiling at 160–165° is collected. The yield is 27 to 30 g. (57–63 per cent of the theoretical amount) (Note 2) and (Note 3).

2. Notes

1. If the contents of the flask cake or become semi-solid, the temperature of the oil bath should be lowered and the rate of flow of superheated steam gradually decreased.
2. There is practically no fore-run, but if repeated or larger batches are made it is possible to obtain about 2 g. more of product per run from the higher-boiling fractions. If recrystallized ester is used a higher yield of dimethylpyrrole with less high-boiling products is obtained but the over-all yield is lower.
3. 2,4-Dimethylpyrrole is very readily oxidized in the air to a red resinous substance. If it is not used immediately, it should be stored under nitrogen or sealed in a glass vial under a vacuum.

3. Discussion

2,4-Dimethylpyrrole has been obtained by a large number of reactions, but the method of Knorr[1] and the condensation of acetone with aminoacetone[2] are the only ones of preparative interest. The procedure

given above is one modification of Knorr's method. In another modification, the pyrrole ester and alkali are heated in a steel bomb and the product is distilled in an inert atmosphere; a yield of 95 per cent is reported.[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 198

References and Notes

1. Knorr, Ann. **236**, 326 (1886).
2. Piloty and Hirsch, ibid. **395**, 65 (1913).
3. Corwin and Krieble, J. Am. Chem. Soc. **63**, 1830 (1941).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

potassium carbonate (584-08-7)

ether (60-29-7)

nitrogen (7727-37-9)

acetone (67-64-1)

potassium hydroxide (1310-58-3)

2,4-Dimethylpyrrole, Pyrrole, 2,4-dimethyl- (625-82-1)

dimethylpyrrole

2,4-Dimethyl-3,5-dicarbethoxypyrrole (2436-79-5)

aminoacetone (298-08-8)

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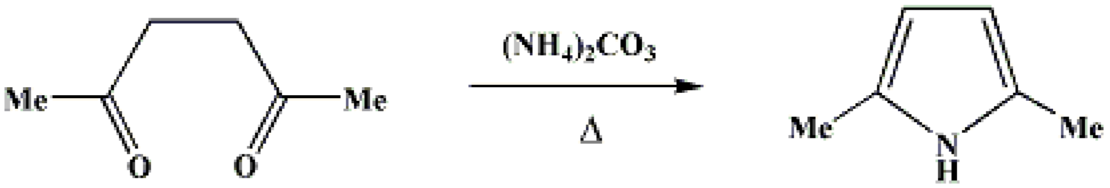
2,5-DIMETHYLPYRROLE

[Pyrrole, 2,5-dimethyl-]



Submitted by D. M. Young and C. F. H. Allen.
Checked by John R. Johnson and H. B. Stevenson.

1. Procedure

In a 500-cc. Erlenmeyer flask, fitted with an air-cooled reflux condenser of large bore (Note 1), are placed 100 g. (0.88 mole) of acetonylacetone (Note 2) and 200 g. (1.75 moles) of ammonium carbonate, in lumps. The mixture is heated in an oil bath at 100° until effervescence stops; this requires sixty to ninety minutes. The air-cooled condenser is replaced by a water-cooled condenser of large bore, and the mixture is refluxed gently at 115° (bath temperature) for thirty minutes longer (Note 1) and (Note 3). The mixture is cooled, and the upper, yellow layer of the pyrrole is separated (Note 4). The lower layer is extracted with 15 cc. of chloroform, which is added to the crude pyrrole. The whole is dried over anhydrous calcium chloride, in a tightly stoppered container which has been swept out with nitrogen beforehand.

The material is transferred (Note 4) to a modified Claisen flask having a fractionating side arm, and the chloroform is distilled completely under reduced pressure (without being condensed). The dimethylpyrrole is collected at 51–53°/8 mm. or 78–80°/25 mm.; only a small residue (4–5 g., b.p. 80–85°/25 mm.) remains. The product weighs 68–72 g. (81–86 per cent of the theoretical amount) and is quite pure (Note 5); it should be stored in an inert atmosphere in a tightly sealed, dark glass container.

2. Notes

1. Sublimed ammonium carbonate must be prevented from blocking the condenser. From time to time the sublimate is pushed back into the reaction mixture by means of a stout glass rod.
2. Acetonylacetone may be prepared conveniently by hydrolysis of 2,5-dimethylfuran. The following procedure is based upon directions supplied to the checkers by Mr. Gwyn Benson, of the Shawinigan Chemicals, Ltd. In a 500-cc. flask are placed 125 g. (1.2 moles) of 2,5-dimethylfuran (b.p. 93–96°), 60 g. of water, 50 g. of glacial acetic acid, and 3 cc. of 10 per cent sulfuric acid. The mixture is boiled gently for thirty-six hours, 1 g. of sodium acetate crystals is

added to convert the sulfuric acid to sodium sulfate, and the material is distilled at atmospheric pressure through a fractionating column. The fraction boiling up to 155° is removed, and the residual liquid is distilled under reduced pressure. The acetonylacetone is collected at 78–79°/15 mm., or 88–89°/25 mm., and weighs 128–133 g. (86–90 per cent of the theoretical amount).

3. At the end of the first and second periods of heating it is well to dissolve the sublimed ammonium carbonate, by pouring 5–10 cc. of hot water back and forth through the condenser, and return the solution to the reaction mixture.

4. In this and all the subsequent operations, the dimethylpyrrole should be manipulated with a minimum exposure to atmospheric oxygen. The distilling apparatus should be swept out with nitrogen at the start and nitrogen admitted, instead of air, whenever the vacuum is released.

5. Since 2,5-dimethylpyrrole does not form solid derivatives, the refractive index may be used as a criterion of purity. The value for a freshly distilled specimen is $n_D^{22°}$ 1.500. On standing the material gradually turns red and the refractive index rises. This change is accelerated by air and light.

3. Discussion

2,5-Dimethylpyrrole has been prepared by heating acetonylacetone with ammonium acetate in glacial acetic acid[1] or with alcoholic ammonia in a sealed tube at 150°.[2] It has also been prepared by hydrolysis and decarboxylation of 2,5-dimethyl-3,4-dicarbethoxypyrrole[3] and the monocarbethoxy compound.[4]

References and Notes

1. Ajello and Cusmano, Gazz. chim. ital. **69**, 210 (1939).
2. Paal, Ber. **18**, 2254 (1885).
3. Knorr, ibid. **18**, 299, 1565 (1885).
4. Timoshevskaya, J. Gen. Chem. (U.S.S.R.) **9**, 766 (1939) [C. A. **34**, 423 (1940)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

ammonium carbonate

ammonia (7664-41-7)

ammonium acetate (631-61-8)

sodium acetate (127-09-3)

chloroform (67-66-3)

sodium sulfate (7757-82-6)

oxygen (7782-44-7)

nitrogen (7727-37-9)

dimethylpyrrole

2,5-Dimethylpyrrole, Pyrrole, 2,5-dimethyl- (625-84-3)

Acetonylacetone (110-13-4)

2,5-dimethylfuran (625-86-5)

2,5-dimethyl-3,4-dicarbethoxypyrrole

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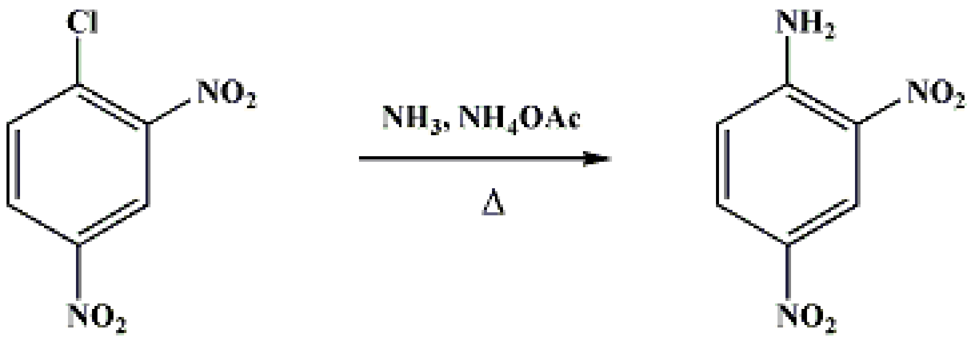
2,4-DINITROANILINE

[Aniline, 2,4-dinitro-]



Submitted by F. B. Wells and C. F. H. Allen.
Checked by Reynold C. Fuson and Chan Mann Lu.

1. Procedure

A wide-mouthed 250-cc. flask (Note 1) containing a mixture of 50 g. (0.25 mole) of technical 2,4-dinitrochlorobenzene (Note 2) and 18 g. (0.23 mole) of ammonium acetate is half immersed in an oil bath. The flask is fitted with a reflux condenser and an inlet tube, the lower end of which is at least 2 cm. wide (to prevent clogging) and which nearly touches the surface of the reaction mixture. During the operation ammonia gas is introduced through a bubble counter which contains a small amount of strong potassium hydroxide solution (12 g. of potassium hydroxide in 10 cc. of water).

The oil bath is heated to 170° and maintained at that temperature for six hours during which time ammonia gas is passed through at the rate of three to four bubbles per second. After the mixture has cooled, the solid is broken up by means of a glass rod and mixed with 100 cc. of water; the mixture is then heated to boiling and filtered while hot. The residue is dissolved in 500 cc. of boiling alcohol, and water is added (about 150 cc.) until the solution becomes turbid. Heat is applied until the turbidity disappears and then the solution is allowed to cool. After standing overnight, the crystals are filtered and dried. The yield is 31–35 g. (68–76 per cent of the theoretical amount) of 2,4-dinitroaniline, melting at 175–177° (Note 3) and (Note 4). For further purification the product is recrystallized in the same manner from alcohol and water, using 20 cc. of alcohol per gram of solid. Ninety per cent of the crude material is recovered as recrystallized product melting sharply at 180°.

2. Notes

1. The neck of the flask must be large enough to admit the wide inlet tube. A 250-cc. extraction flask is most convenient.
2. The technical dinitrochlorobenzene used had a freezing point of 45°. The higher yield given is obtained using a product once recrystallized from alcohol

(m.p. 48°).
3. Some specimens of technical dinitrochlorobenzene used contained undetermined impurities that formed double compounds with the dinitroaniline. These remained in the filtrate. It was not worth the trouble to recover the small amount of amine thus lost.
4. The value of this method is that no autoclave is required. It was not satisfactory when applied to the nitrochlorobenzenes.

3. Discussion

2,4-Dinitroaniline has been prepared by heating dinitrochlorobenzene and ammonia under pressure;[1] by heating 1,2,4-trinitrobenzene with concentrated ammonia;[2] by heating dinitrochlorobenzene with urea[3] or ammonium acetate;[4] by hydrolysis of the dinitroacetanilide obtained when dinitrochlorobenzene and acetamide are heated at 200–210°;[5] by heating 2,4-dinitroanisole or 2,4-dinitroanisic acid with aqueous or alcoholic ammonia under pressure;[6] by heating 2,4-dinitrophenol and aqueous ammonia under pressure;[7] and by the rearrangement of *p*-nitrophenylnitroamine spontaneously[8] or with concentrated sulfuric acid at 0°.[9]

References and Notes

1. Clemm, J. prakt. Chem. (2) **1**, 170 (1870); Willgerodt, Ber. **9**, 979 (1876).
2. Hepp, Ann. **215**, 362 (1882).
3. Rohm and Haas Company, U. S. pat. 1,752,998 [C. A. **24**, 2468 (1930)].
4. Soc. chim. de la Grande-Paroisse, Brit. pat. 169,688 [C. A. **16**, 721 (1922)].
5. Kym, Ber. **32**, 3539 (1899).
6. Salkowski, Ann. **174**, 263 (1874).
7. Barr, Ber. **21**, 1542 (1888).
8. Bamberger and Dietrich, ibid. **30**, 1253 (1897).
9. Hoff, Ann. **311**, 98 (1900).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alcohol (64-17-5)

sulfuric acid (7664-93-9)

Acetamide (60-35-5)

ammonia (7664-41-7)

ammonium acetate (631-61-8)

potassium hydroxide (1310-58-3)

urea (57-13-6)

2,4-Dinitroaniline, Aniline, 2,4-dinitro- (97-02-9)

2,4-dinitrochlorobenzene (97-00-7)

dinitrochlorobenzene

dinitroaniline

1,2,4-trinitrobenzene (610-31-1)

dinitroacetanilide

2,4-dinitroanisole (119-27-7)

2,4-dinitroanisic acid

2,4-dinitrophenol (51-28-5)

p-nitrophenylnitroamine

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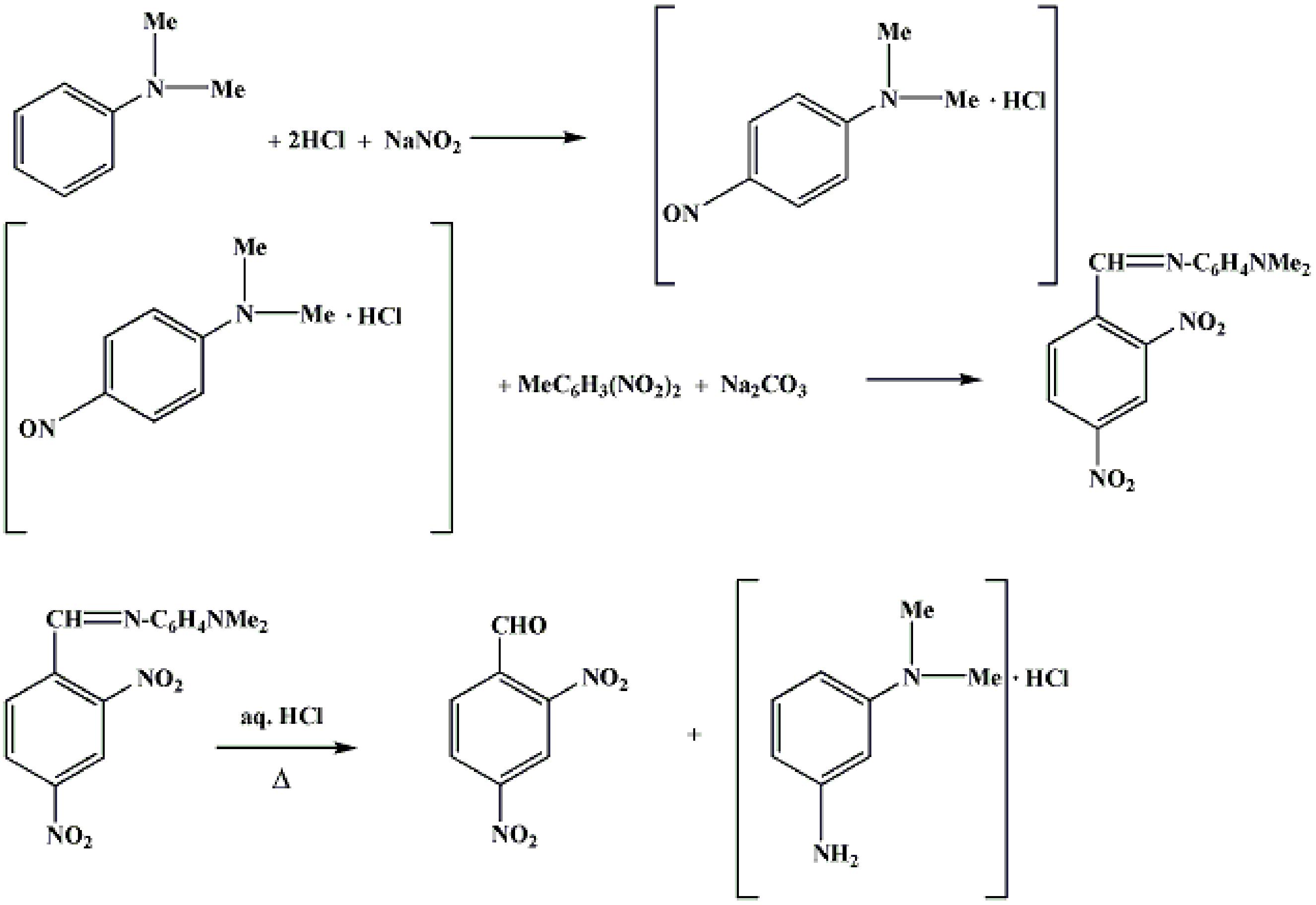
2,4-DINITROBENZALDEHYDE

[Benzaldehyde, 2,4-dinitro-]



Submitted by G. M. Bennett and E. V. Bell.
Checked by J. B. Conant and R. E. Schultz.

1. Procedure

A solution of 300 g. (2.5 moles) of technical dimethylaniline in 1050 cc. of concentrated hydrochloric acid is placed in a large jar or crock and finely divided ice is added until the temperature has fallen to 5°. The contents of the jar are then stirred mechanically, and a solution of 180 g. (2.6 moles) of sodium nitrite in 300 cc. of water is slowly added from a separating funnel, the stem of which dips beneath the surface of the liquid. The addition takes one hour, and the temperature is kept below 8° by the addition of ice if necessary. When all the nitrite has been added the mixture is allowed to stand one hour and then filtered. The solid *p*-nitrosodimethylaniline hydrochloride is washed with 400 cc. of 1:1 hydrochloric acid and then with 100 cc. of alcohol. After drying in air, it weighs 370–410 g. (80–89 per cent of the theoretical amount) (Note 1).

In a 3-l. flask a mixture of 330 g. (1.8 moles) of air-dried *p*-nitrosodimethylaniline hydrochloride (Note 2) with 100 g. of anhydrous sodium carbonate and 1.5 l. of 95 per cent alcohol is heated on the steam bath for thirty minutes and filtered to remove sodium chloride and unchanged carbonate. The filtrate is placed with 300 g. (1.6 moles) of 2,4-dinitrotoluene (m.p. 70°) in a 5-l. flask provided with a mechanical stirrer and a reflux condenser and heated on the steam bath with stirring for five hours. When the contents of the flask are cold, the condensation product is collected on a Büchner funnel and well drained by means of a suction pump and a piece of "rubber dam" fastened over the top of the funnel. The rubber is drawn down onto the solid by the suction, thus forcing the liquid out. The dark green solid is washed by transferring it to a large beaker, stirring it with 1 l. of 95 per cent alcohol on the steam bath for half an hour, cooling, and filtering again, using the rubber dam. The dinitrobenzylidene-*p*-aminodimethylaniline is placed while still damp in a large round-bottomed flask containing 500 cc. of a mixture of equal volumes of concentrated hydrochloric acid and water, and steam is blown in by a tube reaching to the lowest part of the vessel. Vigorous injection of steam is

continued for fifteen minutes after the liquid has reached a temperature of 105° (Note 3).

When cold the aqueous layer is decanted (or filtered) from the solidified product, and the process of steam-agitation with acid is repeated, another 500 cc. of dilute acid being added (Note 4). Finally the solid is filtered, washed with water, and dried *in vacuo*. The crude dinitrobenzaldehyde so obtained weighs 170–210 g. and melts at 40–50°. It is purified by heating in two lots each with 8 l. of naphtha (b.p. 90–110°) in a large flask on the steam bath with mechanical stirring for three hours, decanting the solution (temperature of liquid 80°) and allowing the aldehyde to crystallize. The purified dinitrobenzaldehyde, air-dried, weighs 79–104 g. (24–32 per cent of the theoretical amount) and melts at 69–71° (Note 5). From the mother liquors impure material may be recovered by evaporation or by distillation in steam, from which by a similar process of crystallization a further 20 g. of aldehyde of m.p. 66° can be separated.

2. Notes

1. It is reported that *p*-nitrosodiethylaniline hydrochloride can be prepared by a similar procedure and that the free base can be obtained from the hydrochloride in the following way: The reaction mixture containing the *p*-nitrosodiethylaniline hydrochloride prepared from 50 g. of once-distilled diethylaniline is stirred and kept at 5° while 580 cc. of 2 *N* sodium carbonate solution is added dropwise. The addition requires about two hours, after which the color of the reaction mixture changes to dark green and a dark green solid separates. Stirring is continued for ten minutes, then the precipitate is allowed to settle for five minutes and is filtered with suction. The precipitate is washed with three 25-cc. portions of distilled water, added dropwise by means of a pipet, then with three 20-cc. portions of a 1:1 alcohol-ether mixture, also added dropwise. The *p*-nitrosodiethylaniline is dried in a desiccator over calcium chloride. The material weighs 57 g. (95 per cent of the theoretical amount). If a very pure sample is desired, the nitrosoamine should be crystallized from petroleum ether. (M. Q. Doja and A. Mokeet, private communication.)
2. Attempts to use technical nitrosodimethylaniline in place of the freshly prepared material were not successful.
3. It is essential that the temperature reach the maximum (about 105°) and be kept at this point for sufficient time during the hydrolysis.
4. The acid aqueous liquors contain *p*-aminodimethylaniline and might be utilized in the preparation of quinoneimine dyes.
5. 2,4-Dinitrobenzaldehyde is a useful reagent since it forms crystalline condensation products with amines and with substances having a reactive methylene or methyl group.[1]

3. Discussion

Dinitrobenzaldehyde was first prepared from dinitrotoluene.[1, 2, 3] It has also been prepared from 2,4-dinitrobenzylaniline by oxidation to the benzylidene compound and subsequent hydrolysis,[4, 5] and by oxidation of dinitrobenzyl alcohol.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 825

References and Notes

1. Bennett and Pratt, J. Chem. Soc. **1929**, 1465.
2. Sachs and Kempf, Ber. **35**, 1224 (1902); Sachs, Ger. pat. 121,745 [Frdl. **6**, 1047 (1900–02)].
3. Müller, Ber. **42**, 3695 (1909).
4. Sachs and Everding, ibid. **35**, 1237 (1902).
5. Cohn and Friedländer, ibid. **35**, 1266 (1902).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

naphtha

alcohol (64-17-5)

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

sodium nitrite (7632-00-0)

dimethylaniline (121-69-7)

2,4-dinitrotoluene, dinitrotoluene (121-14-2)

quinoneimine

2,4-Dinitrobenzaldehyde, Benzaldehyde, 2,4-dinitro- (528-75-6)

dinitrobenzaldehyde

diethylaniline (91-66-7)

nitrosodimethylaniline

2,4-dinitrobenzylaniline

dinitrobenzyl alcohol

p-Nitrosodimethylaniline hydrochloride (42344-05-8)

dinitrobenzylidene-p-aminodimethylaniline

p-nitrosodiethylaniline hydrochloride (58066-98-1)

p-Nitrosodiethylaniline (120-22-9)

p-aminodimethylaniline (99-98-9)

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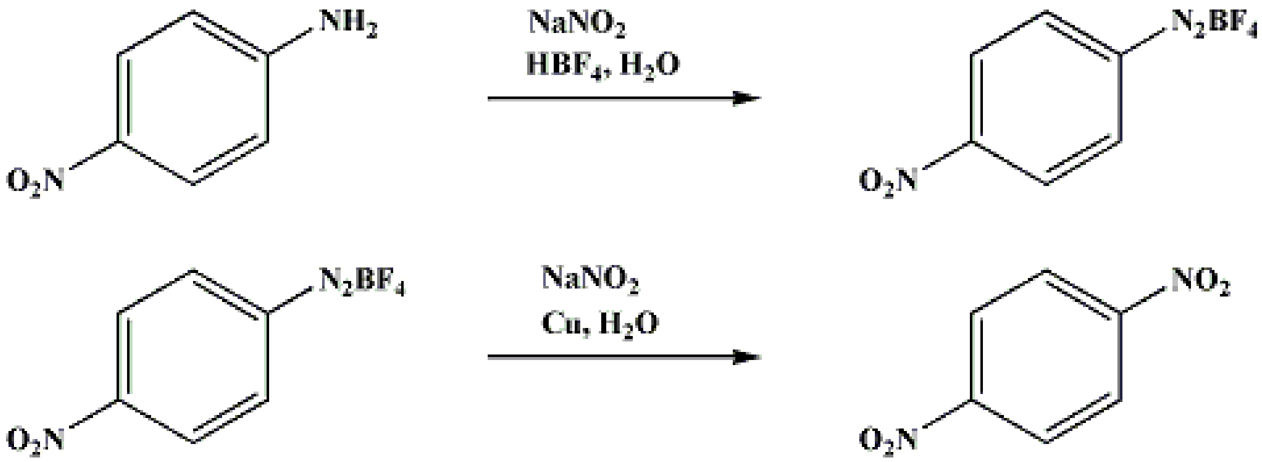
p-DINITROBENZENE

[Benzene, *p*-dinitro-]



Submitted by E. B. Starkey
Checked by Lee Irvin Smith and H. E. Ungnade.

1. Procedure

Thirty-four grams (0.25 mole) of *p*-nitroaniline is dissolved in 110 cc. of fluoboric acid solution (Note 1) in a 400-cc. beaker. The beaker is placed in an ice bath and the solution stirred with an efficient stirrer. A cold solution of 17 g. (0.25 mole) of sodium nitrite in 34 cc. of water is added dropwise. When the addition is complete, the mixture is stirred for a few minutes and filtered by suction on a sintered glass filter. The solid diazonium fluoborate is washed once with 25–30 cc. of cold fluoboric acid, twice with 95 per cent alcohol, and several times with ether (Note 2). The product weighs 56–59 g. (95–99 per cent of the theoretical amount).

Two hundred grams of sodium nitrite is dissolved in 400 cc. of water in a 2-l. beaker, and 40 g. of copper powder is added (Note 3). The mixture is stirred with an efficient stirrer (Note 4), and a suspension of the *p*-nitrophenyldiazonium fluoborate in 200 cc. of water is added slowly. Much frothing occurs, and 4–5 cc. of ether is added from time to time to break the foam. The reaction is complete when all the diazonium compound has been added. The product is filtered with suction, washed several times with water, twice with dilute sodium hydroxide solution, and again with water. The solid is dried in an oven at 110°, powdered, and extracted with 300-cc., 200-cc., and 150-cc. portions of boiling benzene. The benzene is evaporated on a water bath, and the residue is crystallized from 120–150 cc. of boiling glacial acetic acid. The resulting reddish yellow crystals, melting at 172–173°, weigh 28–34.5 g. (67–82 per cent yield) (Note 5). Recrystallization from alcohol yields pale yellow crystals melting at 173°.

2. Notes

1. Fluoboric acid is made by adding 184 g. of boric acid slowly, with constant stirring, to 450 g. of hydrofluoric acid (48–52 per cent) in a copper, lead, or silver-plated container placed in an ice bath.
Hydrofluoric acid causes very painful burns. Exposed parts of the body must be protected when working with this material. Compare Note 3, p. 297. Fluoboric acid (40 per cent) is now a commercial product.

2. A sintered glass filter should be used for filtering, and the fluoborate stirred well on the filter with each washing, before suction is applied. The diazonium fluoborate is stable and may be dried in a vacuum desiccator over phosphorus pentoxide.

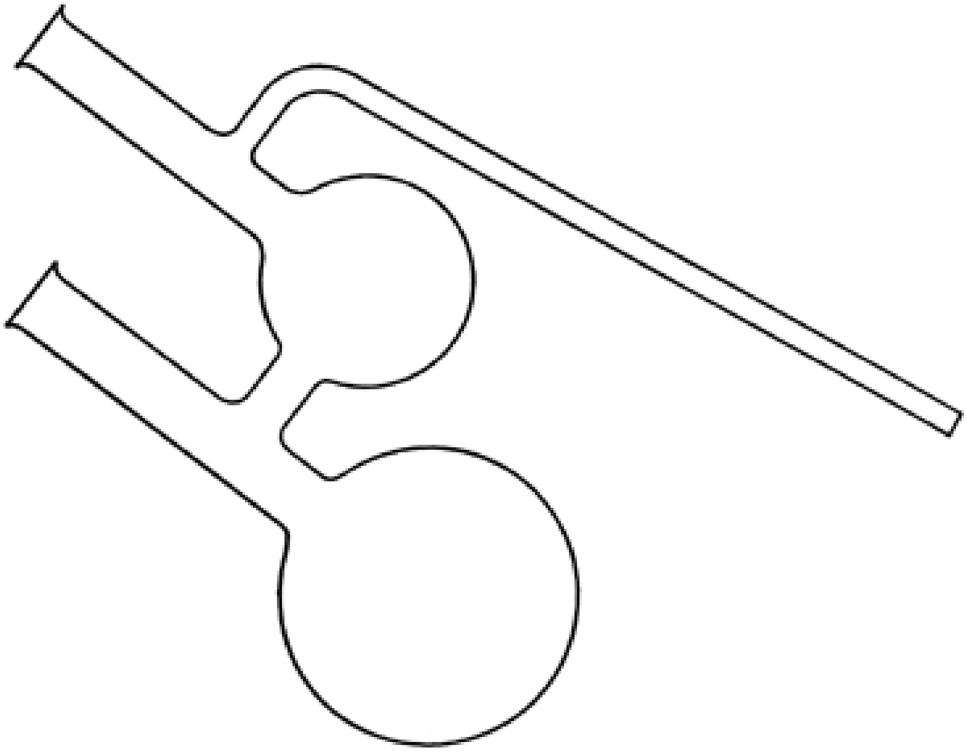
3. The copper used was "Copper metal, precipitated powder."

4. In the decomposition reaction, efficient stirring is quite essential. An off-center stirrer is best suited for the purpose. The reaction should require about two hours. Less efficient stirring and a shorter reaction time cause the formation of an impure product which is not readily purified by crystallization.

5. *o*-Dinitrobenzene may be prepared from *o*-nitroaniline by the same general method. From 34 g. (0.25 mole) of the amine there is obtained 38 g. (63 per cent yield) of dry *o*-nitrobenzenediazonium fluoborate. After carrying out the reaction of the diazonium fluoborate with sodium nitrite and copper, the *o*-dinitrobenzene is separated by steam distillation instead of filtration and extraction. A little paraffin is added to diminish the troublesome foaming and creeping during distillation, and a special flask (Note 6) designed for such operations may be used advantageously. The crystalline product is filtered from the steam distillate and recrystallized from alcohol. The yield of *o*-dinitrobenzene, m.p. 116–116.5°, is 14–16 g. (33–38 per cent of the theoretical amount).

6. A Claisen flask modified as shown in f.htmig. 8 is used in the synthetic laboratories of the Eastman Kodak Company for the distillation of liquids which foam and creep badly. The large bulb inserted in the side arm should have a capacity about one-third that of the distillation flask. During distillation the flask is supported at the angle shown in the figure.

Fig. 8



3. Discussion

p-Dinitrobenzene has been prepared from *p*-nitrosonitrobenzene by treatment with nitric acid;[1] from *p*-nitroaniline by the Sandmeyer reaction;[2] and by the oxidation of *p*-nitroaniline in concentrated sulfuric acid with ammonium persulfate.[3] *o*-Dinitrobenzene has been prepared in similar fashion from *o*-nitroaniline by the Sandmeyer reaction[4] and by oxidation with persulfate.[3] The preparation described above has been published.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 665

References and Notes

1. Bamberger and Hübner, Ber. **36**, 3808 (1903).
2. Meisenheimer and Patzig, ibid. **39**, 2528 (1906).
3. Witt and Kopetschni, ibid. **45**, 1134 (1912).
4. Körner and Contardi, Atti accad. Lincei (5) **23**, I, 283 (1914) [C. A. **8**, 3020 (1914)].
5. Starkey, J. Am. Chem. Soc. **59**, 1479 (1937).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

fluoboric acid

alcohol (64-17-5)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

Benzene (71-43-2)

ether (60-29-7)

sodium hydroxide (1310-73-2)

nitric acid (7697-37-2)

sodium nitrite (7632-00-0)

hydrofluoric acid (7664-39-3)

copper, copper powder (7440-50-8)

boric acid (10043-35-3)

ammonium persulfate (7727-54-0)

o-Dinitrobenzene (528-29-0)

o-NITROANILINE (88-74-4)

phosphorus pentoxide (1314-56-3)

p-nitroaniline (100-01-6)

p-Dinitrobenzene, Benzene, p-dinitro- (100-25-4)

p-nitrophenyldiazonium fluoborate (456-27-9)

o-Nitrobenzenediazonium fluoborate

p-nitrosonitrobenzene

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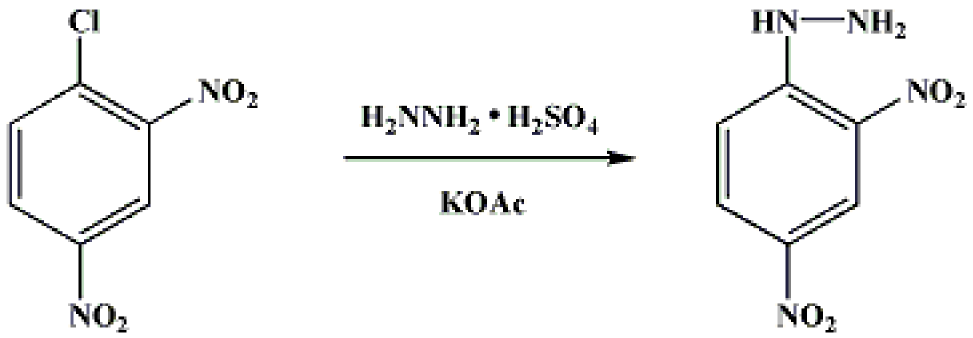
2,4-DINITROPHENYLHYDRAZINE

[Hydrazine, (2,4-dinitrophenyl)-]



Submitted by C. F. H. Allen
Checked by Reynold C. Fuson and Mark W. Farlow.

1. Procedure

Thirty-five grams (0.27 mole) of hydrazine sulfate (Org. Syn. Coll. Vol. I, **1941**, 309) is suspended in 125 cc. of hot water in a 400-cc. beaker and stirred by hand during the addition of 85 g. (0.87 mole) of potassium acetate (Note 1). The mixture is boiled five minutes and then cooled to about 70°; 75 cc. of alcohol is added, and the solid is filtered with suction and washed with 75 cc. of hot alcohol. The filtered hydrazine solution is saved for the next step.

In a 1-l. flask fitted with a stirrer and reflux condenser, 50.5 g. (0.25 mole) of technical 2,4-dinitrochlorobenzene is dissolved in 250 cc. of alcohol; the hydrazine solution is added, and the mixture is refluxed with stirring for an hour. Most of the product separates during the first ten minutes (Note 2); it is cooled well, filtered, and washed, once with 50 cc. of warm alcohol (60°) to remove unchanged halide and then with 50 cc. of hot water. The solid weighs 30 g. and melts at 190–192° with evolution of gas (Note 3); it is pure enough for most purposes. By distilling half the alcohol from the filtrate a less pure second crop is obtained; this is recrystallized from *n*-butyl alcohol (30 cc. per g.) (Note 4). The total yield is 40–42 g. (81–85 per cent of the theoretical amount) (Note 5)–(Note 10).

2. Notes

1. An equivalent amount of sodium acetate may be substituted for the potassium acetate.
2. Considerable heat is evolved during the separation.
3. The melting point is not sharp; in the capillary tube the sample shrinks about 10° below the melting point.
4. For recrystallization, *n*-butyl alcohol is the best solvent in spite of the large

amount required, but tetralin, pyridine, or dioxane (10 cc. per g.) may be used where large quantities are involved. Fortunately, most of the material as prepared does not need further purification.
5. Complete evaporation of the filtrate yields a gummy residue; the amount of dinitrochlorobenzene present is too small to justify recovery.
6. By substituting 10 g. of sodium hydroxide for every 35 g. of potassium acetate and boiling for five minutes without filtering the salt, a 70 per cent yield of dinitrophenylhydrazine results; the quality is not quite so good as that obtained by the use of potassium acetate.
7. A slightly higher yield is obtained by starting with hydrazine hydrate.
8. 2,4-Dinitrophenylhydrazine is used in qualitative organic analysis for preparing solid derivatives of carbonyl compounds.[1, 2]
9. By this procedure 2,6-dinitrophenylhydrazine can be prepared from 2,6-dinitrochlorobenzene; picryl chloride gives 2,4,6-trinitrophenylhydrazine.
10. These directions have been used equally successfully with twice, and with five times, the amounts specified.

3. Discussion

2,4-Dinitrophenylhydrazine has been prepared from hydrazine hydrate and 2,4-dinitrochlorobenzene[3, 2] or 2,4-dinitrobromobenzene,[4] and from the same halogen compounds and hydrazine acetate.[1]

References and Notes

1. Allen, J. Am. Chem. Soc. **52**, 2955 (1930).
2. Brady and Elsmie, Analyst **51**, 77 (1926); Brady, J. Chem. Sec. **1931**, 757.
3. Purgotti, Gazz. chim. ital. **24** (I) 555 (1894).
4. Curtius and Dedichen, J. prakt. chem. (2) **50**, 258 (1894).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alcohol (64-17-5)

sodium acetate (127-09-3)

sodium hydroxide (1310-73-2)

n-butyl alcohol (71-36-3)

pyridine (110-86-1)

hydrazine hydrate (7803-57-8)

Hydrazine sulfate (10034-93-2)

Tetralin (119-64-2)

dioxane (5703-46-8)

2,4-dinitrochlorobenzene (97-00-7)

dinitrochlorobenzene

2,4-Dinitrophenylhydrazine, Hydrazine, (2,4-dinitrophenyl)- (119-26-6)

potassium acetate (127-08-2)

dinitrophenylhydrazine

2,6-dinitrophenylhydrazine

2,6-dinitrochlorobenzene (606-21-3)

picryl chloride (88-88-0)

2,4,6-trinitrophenylhydrazine (653-49-6)

2,4-dinitrobromobenzene (584-48-5)

hydrazine acetate (7335-65-1)

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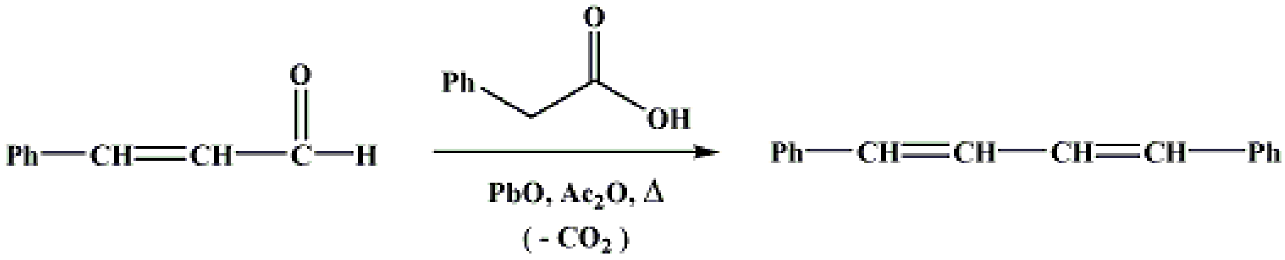
1,4-DIPHENYLBUTADIENE

[Bistyryl]



Submitted by B. B. Corson
Checked by C. R. Noller and J. F. Carson.

1. Procedure

In a 1-l. round-bottomed flask equipped with a reflux condenser and protected by a calcium chloride tube are placed 150 g. (1.1 moles) of phenylacetic acid (Org. Syn. Coll. Vol. I, **1941**, 436), 147 g. (1.1 moles) of freshly distilled cinnamic aldehyde, 122 g. of litharge, and 155 cc. of acetic anhydride. The mixture is boiled for five hours (Note 1), poured while still hot into a beaker, and allowed to stand overnight. The semisolid contents are stirred to a mush, filtered with suction in a large Büchner funnel, and pressed dry. The solid is washed on the funnel with two 35-cc. portions of ethyl alcohol, the material being stirred thoroughly before suction is applied. The cake is transferred to a beaker, stirred to a mush with 50 cc. of alcohol, and again filtered with suction. The material is washed with another 50-cc. portion of alcohol in the same manner (Note 2). The product, which is light yellow to tan in color, weighs 62–67 g. (27–29 per cent of the theoretical amount) (Note 3) and melts at 149.5–153.5°.

For purification the material is dissolved in 300 cc. of hot benzene; the solution is boiled three minutes with 5 g. of decolorizing carbon, and filtered hot, with gentle suction, through a warm Büchner funnel. The benzene filtrate is treated with 500 cc. of hot ethyl alcohol, heated to boiling, and then cooled to 10° in an ice bath, with shaking. After the crystals are filtered with suction and pressed thoroughly, 50 cc. of ethyl alcohol is allowed to soak into the cake and suction is applied again. The recrystallized product weighs 52–57 g. (23–25 per cent of the theoretical amount) (Note 4) and melts at 152.5–153.5°. This product is the trans-trans form of the diene.

2. Notes

1. During the first half hour, the flask should be heated gently and shaken several times to facilitate solution of the lead oxide.
2. Thorough washing is essential.
3. About 8 g. of crude hydrocarbon can be recovered from the original mother liquor, but the recovery is tedious and is not recommended.
4. An additional quantity of about 5.5 g. can be obtained by evaporating the mother liquor to 25 cc. and allowing to crystallize.

3. Discussion

The only method of preparative interest is the condensation of phenylacetic acid and cinnamic aldehyde.[1] The above procedure follows the method of Kuhn and Winterstein.[2] Bistyryl has been obtained also from styrylmagnesium bromide and cupric chloride,[3] or azobenzene,[4] and by the reduction of β-bromostyrene with hydrazine in the presence of palladium.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 499

References and Notes

1. Thiele and Schleussner, Ann. **306**, 198 (1899).
2. Kuhn and Winterstein, Helv. Chim. Acta **11**, 103 (1928).
3. Sakellarios and Kyrimis, Ber. **57**, 325 (1924); Gilman and Parker, J. Am. Chem. Soc. **46**, 2827 (1924).
4. Gilman and Pickens, ibid. **47**, 2410 (1925).
5. Busch and Weber, J. prakt. Chem. (2) **146**, 54 (1936).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

litharge

ethyl alcohol, alcohol (64-17-5)

Benzene (71-43-2)

acetic anhydride (108-24-7)

decolorizing carbon (7782-42-5)

palladium (7440-05-3)

Phenylacetic acid (103-82-2)

cupric chloride (7758-89-6)

cinnamic aldehyde

hydrazine (302-01-2)

β-bromostyrene (103-64-0)

Azobenzene (103-33-3)

1,4-Diphenylbutadiene, Bistyryl (886-65-7)

styrylmagnesium bromide

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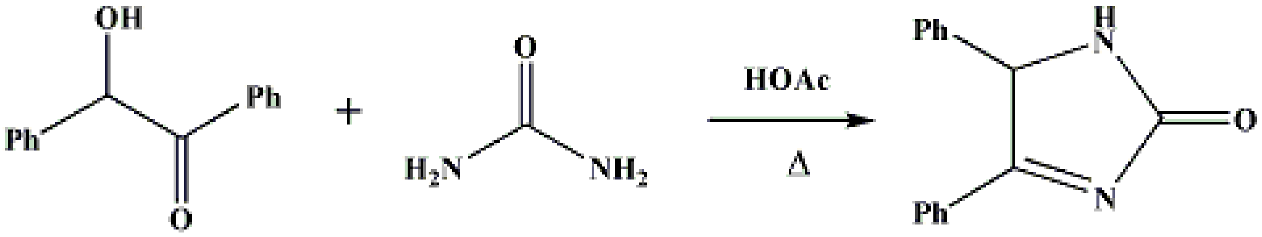
4,5-DIPHENYLGLYOXALONE

[2(5)-Imidazolone, 4,5-diphenyl-]



Submitted by B. B. Corson and Emeline Freeborn.
Checked by Frank C. Whitmore and Marion M. Whitmore.

1. Procedure

A mixture of 212 g. (1 mole) of benzoin (Note 1), 110 g. (1.8 moles) of urea and 800 cc. of glacial acetic acid in a 2-l. round-bottomed flask is heated under a reflux condenser for seven hours (Note 2). The hot solution is quickly poured into a 2-l. beaker (Note 3) and allowed to stand at least three hours. The cold mixture is then transferred by means of a large wooden spoon or spatula to a 30-cm. Büchner funnel and sucked as dry as possible with the help of a rubber dam. The crystals are pressed down during the suction filtration. The filtrate is discarded. The crystals are returned to the beaker, stirred mechanically with 500 cc. of ether for thirty minutes, filtered again by suction (Note 4), and spread out to dry at least overnight (Note 5). The product is dissolved by heating with 1 l. of glacial acetic acid in a 2-l. round-bottomed flask attached to a reflux condenser (Note 6), and the clear solution is poured, with mechanical stirring, into 2.5 l. of water in a 4-l. (1-gal.) crock. Stirring is continued for thirty minutes (Note 7). The mixture is filtered on a 30-cm. Büchner funnel and pressed and sucked as dry as possible. The crystals are transferred to the 2-l. beaker and stirred mechanically for ten minutes with 1 l. of water. After filtration, the washing with water is repeated. The product is then returned to the beaker, stirred with 750 cc. of ether, and filtered again. The material is then air-dried to constant weight. The yield of white fluffy crystals of diphenylglyoxalone melting at 330–335° (corr.) (Note 8) is 220–230 g. (93–97 per cent of the theoretical amount).

2. Notes

1. The benzoin (Org. Syn. Coll. Vol. I, **1941**, 94) need not be recrystallized.
2. At first the color is reddish orange but later it changes to dark yellow.
3. If left in the flask the product solidifies too much to be removed readily.
4. Unreacted benzoin is removed by the ether, in which diphenylglyoxalone is only sparingly soluble.
5. The product is difficult to dry completely.
6. This step is not successful if less than 1 l. of glacial acetic acid is used.

7. The water removes unreacted urea.
8. The melting point is conveniently taken on the surface of mercury heated in a test tube with the thermometer dipping in the mercury.

3. Discussion

The only method of preparative interest is the interaction between benzoin and urea in acetic acid solution as described by Biltz[1] and Chattaway.[2]

References and Notes

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2. Chattaway and Coulson, J. Chem. Soc. **1928**, 1363.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

4,5-Diphenylglyoxalone

2(5)-Imidazolone, 4,5-diphenyl-

diphenylglyoxalone

acetic acid (64-19-7)

ether (60-29-7)

mercury (7439-97-6)

Benzoin (119-53-9)

urea (57-13-6)

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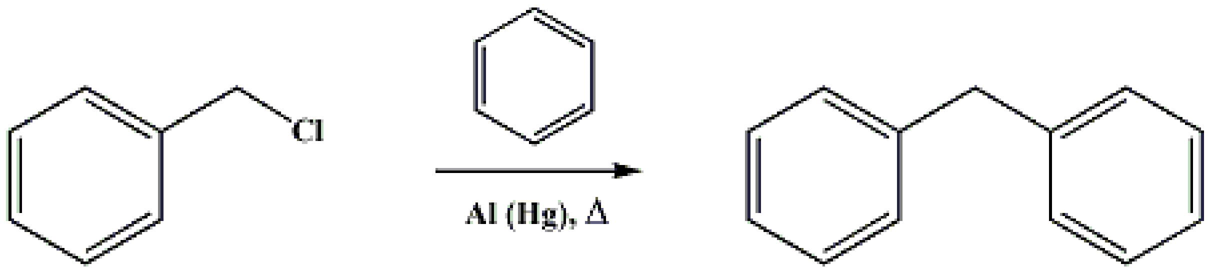
Organic Syntheses, CV 2, 232

DIPHENYLMETHANE

[Methane, diphenyl-]



Submitted by W. W. Hartman and Ross Phillips.
Checked by Reynold C. Fuson and S. H. Babcock.

1. Procedure

In a 5-l. flask, provided with a reflux condenser and an S-tube attached to a dropping funnel, are placed 2 kg. (2.3 l., 25.6 moles) of benzene, which has been dried by distilling until the distillate comes over clear, and 10 g. of amalgamated aluminum turnings (Note 1). The benzene is heated to boiling on a steam bath, the steam is turned off, and 500 g. (3.96 moles) of benzyl chloride is added at such a rate as to cause the solution to boil (Note 2). The hydrogen chloride is absorbed in water or allowed to pass out-of-doors. When all the benzyl chloride has been added (one hour), the mixture is warmed for ten to fifteen minutes, or until the evolution of hydrogen chloride ceases. When cool, the benzene solution of diphenylmethane is decanted from the small amount of tarry material (Note 3) and washed with 5 per cent sodium hydroxide solution and then with water. After a partial drying with calcium chloride, the benzene is distilled from a steam bath and the residue fractionated under diminished pressure. The fore-run is collected up to 125°/10 mm., the main product at 125–130°/10 mm., and an after-run up to 150°/10 mm. (Note 4). Redistillation of the fore-run and after-run yields a small amount of material which is added to the main fraction. The latter is chilled and a small amount of oil is decanted from the crystals. The yield of material melting at 24–25° is 330–350 g. (49.5–52.5 per cent of the theoretical amount).

2. Notes

1. Amalgamated aluminum is prepared as follows: Aluminum turnings, freed from any oil by washing with ether, are stirred with a 5 per cent mercuric chloride solution for a few minutes and then washed quickly with water followed by methyl alcohol. The amalgamated aluminum is used at once.
2. At times the reaction is slow in starting. Not more than 50–60 g. of benzyl chloride is added at first, and the mixture is heated until the evolution of

hydrochloric acid indicates that the reaction is under way. If too much benzyl chloride is present when the reaction starts, the contents of the flask may boil over.

3. Succeeding batches may be started in the same flask containing the aluminum turnings and the trace of tarry material without the addition of further catalyst; these batches do not show an induction period.

4. The material in the residue and high-boiling fraction may be partially converted into diphenylmethane by heating with one-third its weight of aluminum chloride and five times its weight of benzene.

3. Discussion

Diphenylmethane can be prepared from benzene and benzyl chloride with aluminum chloride,[1] hydrogen fluoride,[2] beryllium chloride,[3] the double salt of aluminum and sodium chlorides,[4] zinc dust,[5] zinc chloride,[6] or aluminum amalgam[7] as a condensing agent. The procedure described above is a slight modification of the last method.

Benzene and benzyl alcohol furnish diphenylmethane on treatment with boron fluoride,[8] hydrogen fluoride,[9] or beryllium chloride.[3] Diphenylmethane has also been prepared from benzene, methylene chloride, and aluminum chloride,[10] and from benzene, formaldehyde, ethanol, and concentrated sulfuric acid.[11] The reduction of benzophenone to diphenylmethane has been effected by hydriodic acid and phosphorus,[12] sodium and alcohol,[13] and fusion with zinc chloride and sodium chloride.[14] The condensation of benzylmagnesium chloride and benzene to diphenylmethane can be brought about by small amounts of magnesium and water.[15]

References and Notes

1. Friedel and Balsohn, Bull. soc. chim. (2) **33**, 337 (1880).
2. Simons and Archer, J. Am. Chem. Soc. **61**, 1521 (1939).
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7. Hirst and Cohen, J. Chem. Soc. **67**, 827 (1895).
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10. Friedel and Crafts, Bull. soc. chim. (2) **41**, 324 (1884); Schwarz, Ber. **14**, 1526 (1881).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

amalgamated aluminum turnings

Amalgamated aluminum

double salt of aluminum and sodium chlorides

ethanol (64-17-5)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrogen chloride, hydrochloric acid (7647-01-0)

Benzene (71-43-2)

methyl alcohol (67-56-1)

ether (60-29-7)

sodium hydroxide (1310-73-2)

formaldehyde (630-08-0)

magnesium (7439-95-4)

sodium chloride (7647-14-5)

PHOSPHORUS (7723-14-0)

aluminum, Aluminum turnings (7429-90-5)

hydrogen fluoride (7664-39-3)

aluminum chloride (3495-54-3)

Benzophenone (119-61-9)

zinc (7440-66-6)

sodium (13966-32-0)

Diphenylmethane, Methane, diphenyl- (101-81-5)

benzyl chloride (100-44-7)

Benzyl alcohol (100-51-6)

zinc chloride (7646-85-7)

hydriodic acid (10034-85-2)

mercuric chloride (7487-94-7)

benzylmagnesium chloride (6921-34-2)

methylene chloride (75-09-2)

beryllium chloride (7787-47-5)

boron fluoride (7637-07-2)

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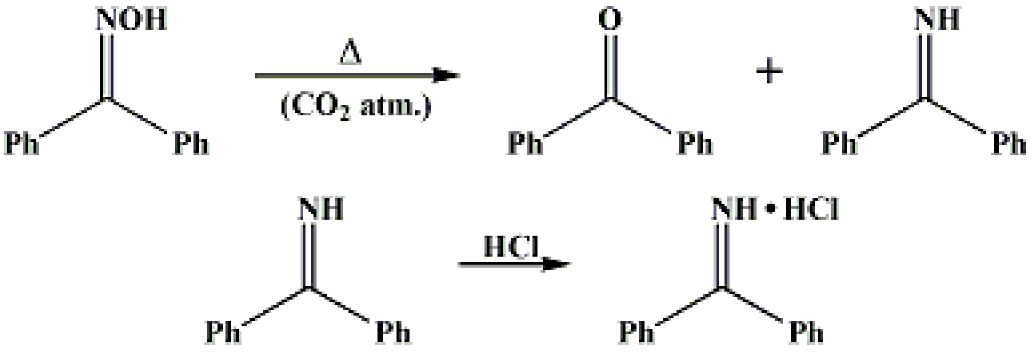
Organic Syntheses, CV 2, 234

DIPHENYLMETHANE IMINE HYDROCHLORIDE

[Benzohydrylideneimine, hydrochloride]



Submitted by Arthur Lachman
Checked by C. R. Noller

1. Procedure

A piece of glass tubing 80 cm. long and 2 cm. in internal diameter is sealed at one end and loosely packed with 49 g. (0.25 mole) of benzophenone oxime (p. 70). The tube is supported in a nearly horizontal position, dipping slightly toward the closed end, and connected to a small filter flask by means of rubber stoppers and a piece of glass tubing bent at a right angle. The system is evacuated by means of a water pump, and dry carbon dioxide is admitted; the system is re-evacuated and carbon dioxide is admitted again. The oxime is then heated with a free flame, beginning at the upper end and heating at one spot until decomposition takes place before heating a further portion (Note 1). When all the oxime has been decomposed, the mixture which has collected at the closed end of the tube (Note 2) is heated strongly for a short time to complete the decomposition, and allowed to cool. Suction is again applied to the tube, and the condensed water is driven out by gently warming the tube. The liquid is then transferred to a small distilling flask and distilled at a pressure of about 20 mm. The distillate, consisting of a mixture of benzophenone and diphenylmethane imine, is dissolved in 400 cc. of ligroin (60–90°), and the imine hydrochloride is precipitated by bubbling in dry hydrogen chloride. The salt is filtered with suction (Note 3), washed with a little ligroin, dried, and preserved in a dry atmosphere (Note 4). It sublimes without decomposition at 230–250° (Note 5). The yield is 16–18 g. (59–66 per cent of theoretical amount) (Note 6).

2. Notes

1. When the heating is carefully done, no material is carried out of the tube with the gases.
2. Care should be taken to prevent any drops of water that have condensed in the cool portion of the tube from running back and mixing with the liquid that is

being heated.
3. Benzophenone may be recovered from the filtrate.
4. In moist air the hydrochloride is changed to a mixture of benzophenone and ammonium chloride. The free base on standing in air gives off ammonia and gradually deposits crystals of benzophenone.
5. The imine salt can be converted into the free base by the method of Hantzsch and Kraft, which involves treating a solution of the salt in chloroform with dry ammonia.
6. The yield depends greatly on the quality of the benzophenone oxime. If this contains moisture or has been exposed to moist air, especially in a closed space, for any length of time, the yield is markedly decreased.

3. Discussion

Diphenylmethane imine (or its hydrochloride) has been obtained by heating diphenyldichloromethane with urethane at 130°;[1] by the action of ammonia on diphenyldibromomethane;[2] by treating benzophenonechloroimide with phosphorus pentachloride in ether solution,[3] or dry hydrogen chloride in ligroin solution;[4] by the action of phenylmagnesium bromide on N-bromobenzamide,[2] benzonitrile,[5] cyanogen bromide,[6] cyanogen chloride,[7] and alkyl thiocyanates.[8] It has also been obtained by passing a mixture of ammonia and benzophenone vapor over thorium oxide at 380–390°;[9] by the catalytic reduction of benzophenone oxime using hydrogen and a nickel catalyst in absolute alcohol solution at ordinary temperature and pressure;[10] by passing a mixture of hydrogen and benzophenone oxime vapor over reduced copper at 200°;[11] and by the action of sodium ethoxide on N-monochlorodiphenylmethylamine in alcoholic solution.[12] The method described here has been previously published by Lachman.[13]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 70
- Org. Syn. Coll. Vol. 5, 520

References and Notes

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2. Moore, ibid. **43**, 564 (1910).
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6. Grignard, Bellet, and Courtot, ibid. (9) **4**, 34 (1915).
7. Grignard, Bellet, and Courtot, ibid. (9) **12**, 379 (1919).

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ligroin

Benzohydrylideneimine, hydrochloride

Diphenylmethane imine (or its hydrochloride)

benzophenonechloroimide

alcohol (64-17-5)

hydrogen chloride (7647-01-0)

ammonia (7664-41-7)

ether (60-29-7)

ammonium chloride (12125-02-9)

hydrogen (1333-74-0)

benzonitrile (100-47-0)

phosphorus pentachloride (10026-13-8)

chloroform (67-66-3)

carbon dioxide (124-38-9)

thorium oxide

copper (7440-50-8)

nickel (7440-02-0)

Benzophenone (119-61-9)

diphenyldichloromethane (2051-90-3)

sodium ethoxide (141-52-6)

Phenylmagnesium bromide (100-58-3)

Benzophenone oxime (574-66-3)

diphenylmethane imine hydrochloride (5319-67-5)

Cyanogen bromide (506-68-3)

diphenylmethane imine (1013-88-3)

urethane (51-79-6)

diphenyldibromomethane

N-bromobenzamide

cyanogen chloride (506-77-4)

N-monochlorodiphenylmethylamine

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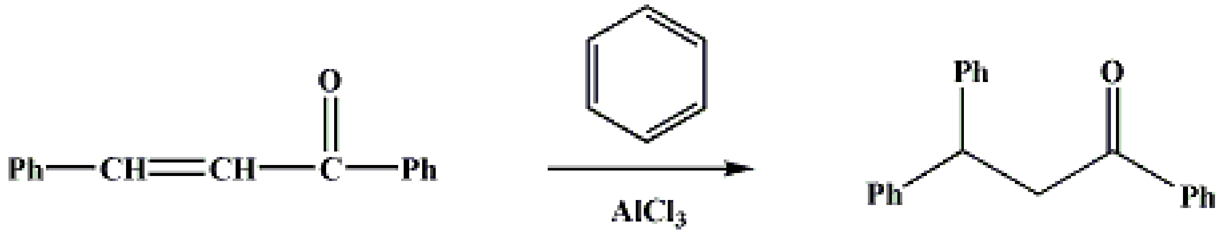
Organic Syntheses, CV 2, 236

β,β-DIPHENYLPROPIOPHENONE

[Propiophenone, β,β-diphenyl-]



Submitted by P. R. Shildneck
Checked by C. R. Noller and C. R. Kemp.

1. Procedure

In a 3-l. round-bottomed, three-necked flask fitted with a liquid-sealed mechanical stirrer, a thermometer, and a 500-cc. separatory funnel are placed 1.7 l. of dry benzene and 160 g. (1.2 moles) of powdered, anhydrous aluminum chloride (Note 1). The mixture is cooled to 10° by means of an ice-water bath and maintained at 10–20° during the addition of a solution of 120 g. (0.58 mole) of benzalacetophenone (Note 2) in 300 cc. of dry benzene. This addition requires about thirty minutes. The cooling bath is then removed and stirring continued at room temperature until all the dense, yellow precipitate formed at first has gone into solution (Note 3). The reaction is complete after stirring for an additional hour.

The bulk of the brown-colored benzene solution is decanted into a cold mixture of 100 cc. of concentrated hydrochloric acid and 1.5 l. of water in a 5-l. round-bottomed flask. The remainder is filtered on a Büchner funnel, and the lumps of aluminum chloride are washed with two 100-cc. portions of benzene. The filtrates are added to the main solution and the whole is washed thoroughly with the dilute acid. If the layers do not separate readily the mixture is filtered with gentle suction and the water separated by siphoning. The solution is washed twice with 1.5-l. portions of water and filtered again if necessary.

The clear, light yellow benzene solution is subjected to rapid steam distillation (Note 4) in the same 5-l. flask, and when no more benzene passes over the flask is cooled under the tap with shaking. The residual oil solidifies to light brown pellets. These are collected, separated from water as much as possible, and dissolved in 2250 cc. of boiling alcohol. Five grams of decolorizing carbon is added; the hot solution is filtered with suction and allowed to cool. The best results are obtained if the alcoholic solution is stirred slowly with a mechanical stirrer while cooling to room temperature. Stirring is stopped when the mixture becomes semi-solid, and the mass is then allowed to stand for twenty-four hours. The fine, colorless needles are filtered on a 15-cm. Büchner funnel and pressed as dry as possible. The yield of thoroughly air-dried, colorless

material melting at 91–92° (Note 5) amounts to 125–140 g. (76–85 per cent of the theoretical amount) (Note 6).

2. Notes

1. Trial runs demonstrated that one mole of benzalacetophenone required at least two moles of anhydrous aluminum chloride to complete the reaction at room temperature. When less aluminum chloride was used the yellow addition product failed to dissolve entirely even after stirring for twenty-four hours, and the yield was decreased.
2. The benzalacetophenone (Org. Syn. Coll. Vol. I, **1941**, 78) must be quite pure (m.p. 55–56°) and, in particular, free from benzaldehyde.
3. A change in appearance of the mixture is very noticeable at the end of the reaction. The yellow color rapidly gives way to a dark brown. A perfectly clear solution is not produced as the aluminum chloride remains in suspension.
4. If the benzene solution is steam-distilled directly from the acid mixture the crude product is darker in color, more difficult to crystallize, and less pure after crystallization.
5. The melting point of β,β-diphenylpropiophenone is given in the literature[1], [2], [3] as 96°. The product melting at 91–92° was recrystallized to constant melting point from alcohol and from ligroin, but the melting point remained at 92° (corr.). The oxime and the monobromoketone prepared according to Kohler[3] were found to melt at 133° (corr.) and 166° (corr.), respectively.
6. An additional 12–16 g. of less pure product, melting at 88–91°, may be obtained by concentrating the mother liquor to 400 cc.

3. Discussion

β,β-Diphenylpropiophenone has been prepared from benzalacetophenone with phenylmagnesium bromide,[1] and a number of other phenylmetallic compounds;[2] by the condensation of benzalacetophenone and benzene with concentrated sulfuric acid[3] or with aluminum chloride,[4] and by the action of aluminum chloride on a mixture of benzene and the hydrochloride of benzalacetophenone.[4] The procedure described here is essentially that of Vorländer and Friedberg.[4]

References and Notes

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4. Vorländer and Friedberg, Ber. **56**, 1144 (1923).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ligroin

hydrochloride of benzalacetophenone

alcohol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

Benzalacetophenone (94-41-7)

benzaldehyde (100-52-7)

decolorizing carbon (7782-42-5)

aluminum chloride (3495-54-3)

Phenylmagnesium bromide (100-58-3)

β,β-Diphenylpropiophenone, Propiophenone, β,β-diphenyl- (606-86-0)

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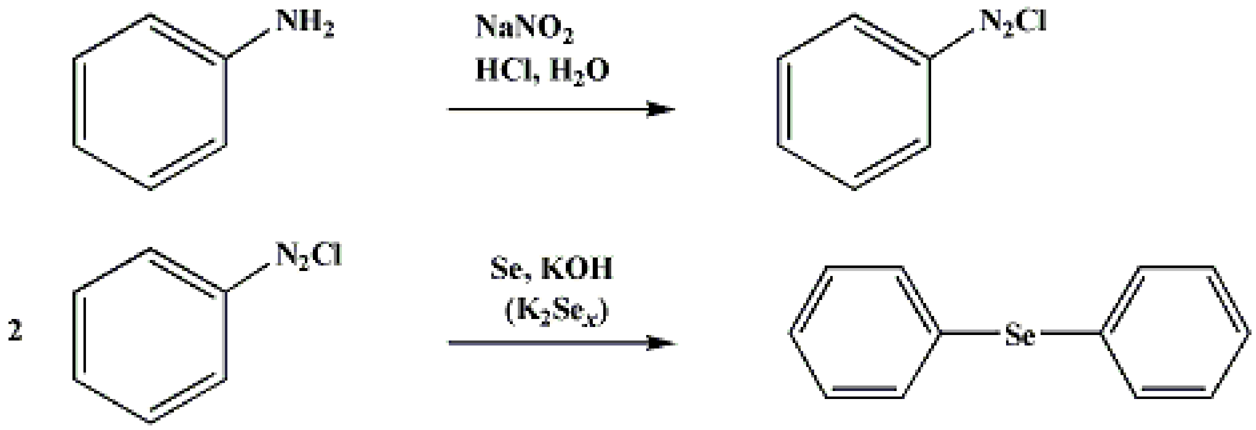
Organic Syntheses, CV 2, 238

DIPHENYL SELENIDE

[Phenyl selenide]



Submitted by Henry M. Leicester
Checked by W. W. Hartman and R. H. Bullard.

1. Procedure

In a 500-cc. beaker are placed 360 g. (6.4 moles) of powdered potassium hydroxide and 240 g. (3 gram atoms) of black powdered selenium which have been previously ground together in a mortar. This mixture is heated (Note 1) in an oil bath at 140–150° until a thick, dark red liquid is formed (Note 2), and then it is added (Note 3) in small portions to 400 cc. of ice water in a 5-l. flask. The solution is kept in an ice bath until used.

To 375 cc. (4.3 moles) of hydrochloric acid (sp. gr. 1.18) and 200 g. of ice is added 139.6 g. (1.5 moles) of aniline. The resulting solution is diazotized with a solution of 103.5 g. (1.5 moles) of c.p. sodium nitrite, ice being added to the reaction mixture, as necessary, in order to keep the temperature below 5°. The final volume of the diazotized solution is about 1 l. This solution is added in a slow stream from a dropping funnel to the potassium selenide solution, which is vigorously stirred with a mechanical stirrer. When all the diazotized solution has been added, the red aqueous solution is decanted from the dark oil which forms and is heated to boiling (Note 4). It is then poured back on the oil, the mixture is well stirred (Note 5), 200 cc. of chloroform is added, and the selenium is collected on a filter and washed with a little more chloroform (Note 6). After the chloroform layer is separated, the aqueous layer is again extracted with 200 cc. of chloroform. The combined extracts are then distilled, the diphenyl selenide being collected from 300 to 315°. The yield of yellow oil of rather unpleasant odor is 138–150 g. (79–86 per cent of the theoretical amount) (Note 7). If a purer product is desired, this material can be distilled under diminished pressure. It boils at 165–167°/12 mm.

2. Notes

1. Although no toxic gases are evolved in this reaction, the mixture has a rather unpleasant odor, so that it is best to use a hood throughout.
2. If the potassium hydroxide and selenium are absolutely dry, a thick paste is formed. The addition of a few cubic centimeters of water will form the dark red liquid mentioned.
3. If the mass is allowed to cool and solidify, it becomes very hard and is difficult to break up and dissolve.
4. Unless the aqueous layer is heated separately, the beaker containing the viscous oil always cracks, no matter how well the liquid is stirred.
5. This treatment converts the selenium from the red, colloidal form into the more easily filterable black modification.
6. The amount of selenium recovered is 101–115 g.
7. When smaller amounts of the selenide are prepared, the yield drops to 70–75 per cent. The method may be applied equally well to the preparation of the selenides from the three toluidines, giving yields of 50–70 per cent.

3. Discussion

The method described here is a modification of that of Schoeller.[1] Diphenyl selenide has also been prepared from diazotized aniline and alkali monoselenides;[2] by the Friedel-Crafts reaction with benzene and selenium tetrachloride[3] or selenium dioxide;[4] from diphenyl sulfone and selenium;[5] from phenylmagnesium bromide and selenium,[6] selenium dichloride,[7] selenium oxychloride,[7] or selenium dibromide;[8] and from sodium selenophenoxide and bromobenzene.[9]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 240

References and Notes

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3. Krafft and Kaschau, ibid. **29**, 428 (1896); Bradt and Green, J. Org. Chem. **1**, 540 (1937).
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Appendix

Compounds Referenced (Chemical Abstracts Registry Number)

sodium selenophenoxide

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

aniline (62-53-3)

chloroform (67-66-3)

sodium nitrite (7632-00-0)

diphenyl sulfone (127-63-9)

selenium dioxide (7446-08-4)

potassium hydroxide (1310-58-3)

bromobenzene (108-86-1)

Phenylmagnesium bromide (100-58-3)

Diphenyl selenide, Phenyl selenide (1132-39-4)

selenium

potassium selenide

selenium tetrachloride (10026-03-6)

selenium dichloride (14457-70-6)

selenium oxychloride

selenium dibromide (22987-45-7)

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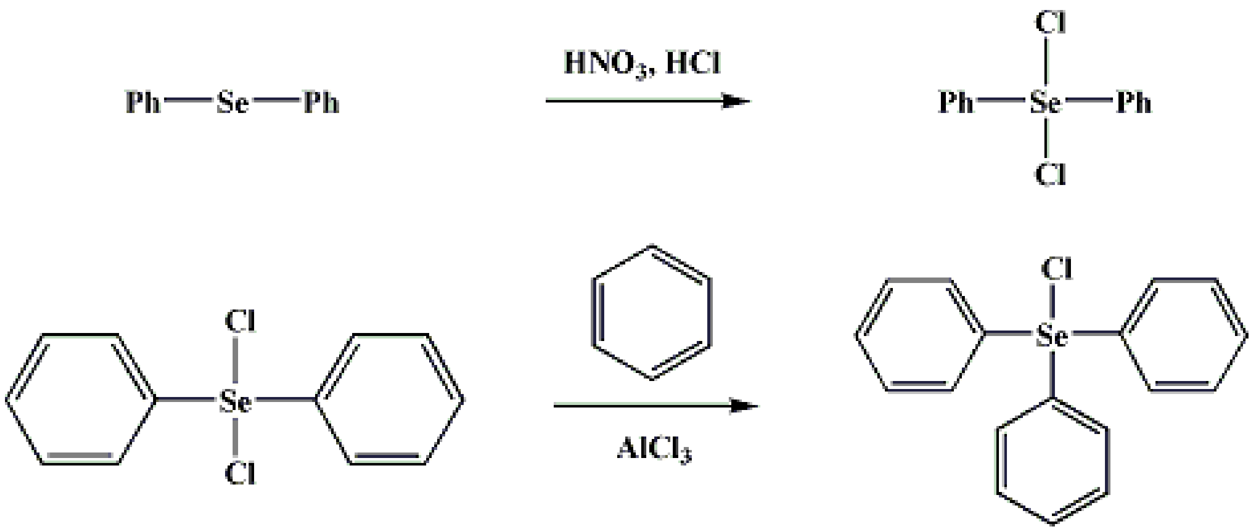
Organic Syntheses, CV 2, 240

DIPHENYLSELENIUM DICHLORIDE AND TRIPHENYLSELENONIUM CHLORIDE

[Selenium compounds, diphenyl- dichloride]

[Selenonium compounds, triphenyl- chloride]



Submitted by Henry M. Leicester
Checked by W. W. Hartman and R. H. Bullard.

1. Procedure

(*A*) *Diphenylselenium Dichloride*.—One hundred twenty-five grams (0.53 mole) of diphenyl selenide (p. 238) is added in portions to 250 cc. (4 moles) of nitric acid (sp. gr. 1.42) in a 1.5-l. beaker. Hydrochloric acid (sp. gr. 1.18) is then added until precipitation is complete. About 170 cc. (2 moles) of acid is required. The mixture is then diluted with 500 cc. of water, and the yellow precipitate is separated by filtration and air-dried. The crude product is purified by extracting with 500 cc. of boiling benzene. The crystals which separate on cooling are collected on a filter and the filtrate is used for a further extraction. Three such treatments are necessary for a complete crystallization. The yield of yellow needles, decomposing at 187–188°, is 137–141 g. (85–87 per cent of the theoretical amount).

(*B*) *Triphenylselenonium Chloride*.—To 87 g. (100 cc., 1.1 moles) of benzene in a 1-l. three-necked flask provided with a mechanical stirrer, is added 30 g. (0.22 mole) of anhydrous aluminum chloride. The suspension is cooled in an ice bath, and to it is added, with stirring, 40 g. (0.13 mole) of diphenylselenium dichloride in portions of approximately 1 g. at a time over a period of twenty-five minutes. Before each addition the temperature should be below 10° to prevent the final product from becoming dark. When the addition is complete, the reaction mixture is allowed to stand for three hours at room temperature, and then 200 cc. of water is added cautiously (Note 1). The

benzene layer is separated and discarded. If the water layer is colored, further extractions with benzene will remove most of the color without reducing the yield. The water layer is then extracted three times with 50-cc. portions of chloroform. The combined extracts are concentrated to a volume of 40 cc. and treated with 120 cc. of ether (Note 2). A yellow oil precipitates and solidifies almost at once to a white powder. The triphenylselenonium chloride is collected on a filter and recrystallized from 300 cc. of methyl ethyl ketone to which 20 cc. of water has been added (Note 3). The yield of anhydrous product, after drying at 100°, is 30 g. (67 per cent of the theoretical amount) (Note 4).

2. Notes

1. Much heat is evolved during the first part of the hydrolysis.
2. Triphenylselenonium chloride may be precipitated from aqueous solution as the zinc chloride double salt.[1]
3. Triphenylselenonium chloride is soluble in anhydrous methyl ethyl ketone only to the extent of 2 g. in 300 cc. Using the water-methyl ethyl ketone mixture, the substance crystallizes with two molecules of water. This can be removed by heating for half an hour at 100°, but is again taken up from moist solvents or moist air.
4. This method can also be used for the preparation of *p*-tolyl- or of mixed phenyl-*p*-tolylselenonium salts.

3. Discussion

Diphenylselenium dichloride has been prepared from diphenyl selenide[2], [3] by the action of chlorine and by treatment first with nitric acid and then hydrochloric acid. Triphenylselenonium chloride has been prepared by fusing together diphenylmercury and diphenylselenium dichloride,[4] and by the action of diphenylselenium dichloride on benzene in the presence of aluminum chloride.[3]

References and Notes

1. Crowell and Bradt, J. Am. Chem. Soc. **55**, 1500 (1933).
2. Foster and Brown, ibid. **50**, 1182 (1928).
3. Leicester and Bergstrom, ibid. **51**, 3587 (1929).
4. Leicester and Bergstrom, ibid. **53**, 4428 (1931); Leicester, ibid. **57**, 1901 (1935).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Selenium compounds, diphenyl- dichloride

Selenonium compounds, triphenyl- chloride

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether (60-29-7)

chloroform (67-66-3)

nitric acid (7697-37-2)

aluminum chloride (3495-54-3)

chlorine (7782-50-5)

Diphenylmercury (587-85-9)

methyl ethyl ketone (78-93-3)

Diphenyl selenide (1132-39-4)

DIPHENYLSELENIUM DICHLORIDE

Triphenylselenonium chloride (17166-13-1)

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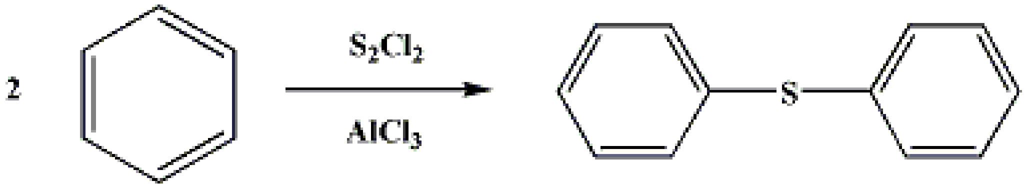
DIPHENYL SULFIDE

[Phenyl sulfide]



Submitted by W. W. Hartman, L. A. Smith, and J. B. Dickey.
Checked by Reynold C. Fuson and S. H. Babcock.

1. Procedure

In a 5-l. three-necked, round-bottomed flask, fitted with a mechanical stirrer, dropping funnel, and a condenser connected to an apparatus for removing hydrogen chloride, are placed 858 g. (980 cc., 11 moles) of dry benzene (Note 1) and 464 g. (3.48 moles) of aluminum chloride. The reaction mixture is cooled in an ice bath to 10°, and then 405.1 g. (3 moles) of commercial sulfur chloride in 390 g. (450 cc., 5 moles) of benzene is added, with stirring, over a period of one hour, the temperature being kept at about 10°. The reaction begins at once as evidenced by the evolution of hydrogen chloride and the separation of a yellow viscous aluminum chloride complex. When all the sulfur chloride has been added, the reaction mixture is removed from the ice bath, stirred at room temperature for two hours, and then heated at 30° until practically no hydrogen chloride is evolved (one hour). The mixture is then poured on 1 kg. of cracked ice, and, when hydrolysis is complete, the benzene layer is separated from the water layer by means of a separatory funnel. The benzene is distilled on a steam bath, and the resulting dark-colored oil is cooled to 0° and filtered through a Büchner funnel to remove the sulfur which separates. The residue is dissolved in 500 cc. of commercial methyl alcohol, and the solution is cooled to 0°. Stirring is continued for three hours, and the precipitated sulfur is removed as before. The alcohol is removed on a steam bath, and the residue is distilled from a 1-l. modified Claisen flask with a water-cooled side-arm receiver. After a small amount of low-boiling product passes over, there is obtained 470–490 g. (Note 2) of a yellow liquid boiling at 155–170°/18 mm. The material thus obtained is heated for one hour on a steam bath, with stirring, with 70 g. of zinc dust and 200 g. of 40 per cent sodium hydroxide solution (Note 3). The diphenyl sulfide is then separated from the sodium hydroxide, washed with two 500-cc. portions of water, dried over anhydrous sodium sulfate, and distilled. The yield of colorless diphenyl sulfide boiling at 162–163°/18 mm. is 450–464 g. (81–83 per cent of the theoretical amount).

2. Notes

1. The benzene can be dried by distilling on a steam bath until the distillate is no longer milky. About 15 per cent of the benzene is distilled.
2. On distillation of the residue in the distillation flask a fraction boiling at 170–200°/18 mm. is obtained. Crystallization of this material from methyl alcohol yields 8–10 g. of thianthrene, melting at 155–156°.
3. It is necessary to treat the diphenyl sulfide as described in order to obtain a colorless product.

3. Discussion

Diphenyl sulfide can best be prepared by treating benzene and aluminum chloride with sulfur chloride,[1] sulfur dichloride,[2] or sulfur.[3] In addition to diphenyl sulfide, traces of thiophenol and varying amounts of thianthrene are found.

References and Notes

1. Böeseken, Rec. trav. chim. **24**, 209 (1905); Böeseken and Waterman, ibid. **29**, 319 (1910); Böeseken and Koning, ibid. **30**, 116 (1911); Genvresse, Bull. soc. chim. (3) **15**, 409 (1896); Hartman, Smith, and Dickey, Ind. Eng. Chem. **24**, 1317 (1932).
2. Böeseken, Rec. trav. chim. **24**, 217 (1905); Böeseken and Koning, ibid. **30**, 116 (1911).
3. Friedel and Crafts, Ann. chim. phys. (6) **14**, 437 (1888); Böeseken, Rec. trav. chim. **24**, 17, 219 (1905); Dougherty and Hammond, J. Am. Chem. Soc. **57**, 117 (1935).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrogen chloride (7647-01-0)

Benzene (71-43-2)

methyl alcohol (67-56-1)

sodium hydroxide (1310-73-2)

sodium sulfate (7757-82-6)

sulfur (7704-34-9)

aluminum chloride (3495-54-3)

zinc (7440-66-6)

sulfur chloride

Thiophenol (108-98-5)

Diphenyl sulfide, Phenyl sulfide (139-66-2)

thianthrene (92-85-3)

sulfur dichloride (10545-99-0)

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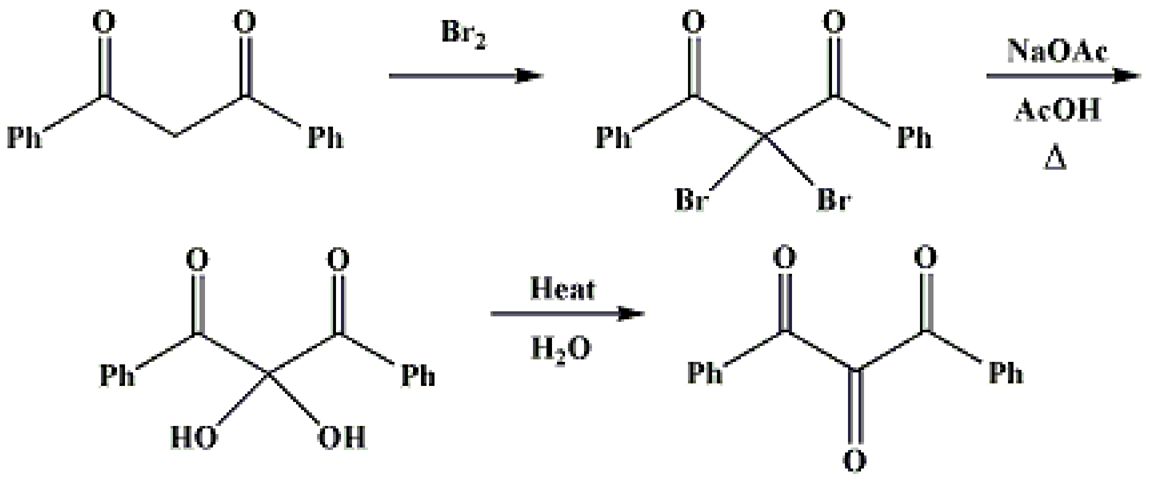
DIPHENYL TRIKETONE

[Propanetrione, diphenyl-]



Submitted by Lucius A. Bigelow and Roy S. Hanslick.
Checked by W. W. Hartman and Lloyd A. Smith.

1. Procedure

(*A*) *Dibenzoyldibromomethane*.—In a 1-l. three-necked flask, equipped with a mechanical stirrer, a dropping funnel, and a thermometer, are placed 56 g. (0.25 mole) of dibenzoylmethane (Org. Syn. Coll. Vol. I, **1941**, 205; Org. Syn. **20**, 32) and 14 cc. of chloroform. The flask is surrounded by an ice bath, the stirrer is started, and a solution of 28.5 cc. (88 g., 0.55 mole) of dry bromine (Note 1) in 230 cc. of chloroform is added slowly from the dropping funnel during a period of about thirty minutes. The temperature of the mixture should not exceed 15° during the bromination; the hydrogen bromide evolved is continuously removed by aspirating a gentle stream of air over the surface of the solution. After all the bromine has been added, stirring is continued for about fifteen minutes. The solution is then transferred to a distilling flask, and the solvent is completely removed under diminished pressure at room temperature (Note 2). The slightly colored residue is crystallized from 125 cc. of hot 95 per cent ethyl alcohol. The dibenzoyldibromomethane is obtained in the form of white crystals melting at 94–95°. The yield is 72.4 g. (76 per cent of the theoretical amount) (Note 3).

(*B*) *Diphenyl Triketone Hydrate*.—A solution of 34.3 g. (0.42 mole) of fused sodium acetate in 142 cc. of hot glacial acetic acid is prepared in a 1-l. round-bottomed flask; 72.4 g. (0.19 mole) of dibenzoyldibromomethane is added, and the mixture is refluxed until the precipitation of sodium bromide ceases (one and one-half to two hours). The mixture is then cooled to room temperature and diluted with 150–200 cc. of water with constant shaking to dissolve the inorganic salt and to precipitate the triketone hydrate,

which separates as a white, curdy mass (Note 4). This is separated by filtration, washed well with water, and dried in an oven at 60°. The melting point varies from 65 to 90°, depending upon the extent of dehydration that occurs during the drying operation. The yield is 41.5 g. (86 per cent of the theoretical amount based on the dibenzoyldibromomethane).

(*C*) *Diphenyl Triketone*.—The 41.5 g. (0.16 mole) of triketone hydrate is distilled in vacuum from a Claisen flask heated by means of a sand bath. A distilling flask is used as a receiver, and no condenser is necessary. The neck of the receiving flask must be warmed, however, to prevent clogging of the apparatus by crystallization of the distillate. The anhydrous triketone distils at 174–176°/2 mm. as a reddish oil that solidifies to a light yellow, crystalline mass. This is dissolved in 70 cc. of hot ligroin (b. p. 90–120°); it separates on cooling in light yellow needles which melt at 68–70°. The yield is 35 g. (91 per cent of the theoretical amount based on the triketone hydrate; 59 per cent based on the dibenzoylmethane) (Note 5).

2. Notes

1. The bromine should be dried by washing it with concentrated sulfuric acid.
2. If the solvent is removed by heat at ordinary pressure, there is a decrease both in the yield and the purity of the product.
3. If the recrystallization is omitted, a lower yield of the triketone hydrate is obtained.
4. If the hydrate separates in part in an oily condition, it may be dissolved in a small amount of glacial acetic acid and reprecipitated with an equal volume of water.
5. The triketone is hygroscopic and must be kept in a vacuum desiccator or sealed tube.

3. Discussion

The two general methods for the preparation of diphenyltriketone involve the treatment of dibenzoylmethane with bromine[1] and with oxides of nitrogen.[2] De Neufville and v. Pechmann, who originated the first method, recommended[1] conversion of the diketone to dibenzoylbromomethane and transformation of this to the acetate and then to dibenzoylbromocarbinol acetate which was split to the triketone. This sequence has been used with success by Kohler and Erickson[3] to prepare the triketone in good yields, but the present method, mentioned but not described by De Neufville and v. Pechmann,[1] is simpler and more direct.

References and Notes

1. De Neufville and v. Pechmann, Ber. **23**, 3375, 3379 (1890).
2. Wieland and Bloch, ibid. **37**, 1524, 1531 (1904).
3. Kohler and Erickson, J. Am. Chem. Soc. **53**, 2308 (1931).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

oxides of nitrogen

ligroin

ethyl alcohol (64-17-5)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

sodium acetate (127-09-3)

chloroform (67-66-3)

hydrogen bromide (10035-10-6)

bromine (7726-95-6)

sodium bromide (7647-15-6)

Dibenzoylmethane (120-46-7)

DIPHENYL TRIKETONE, Propanetrione, diphenyl-, Diphenyltriketone (643-75-4)

Dibenzoyldibromomethane (16619-55-9)

Diphenyl Triketone Hydrate

triketone hydrate

dibenzoylbromomethane

dibenzoylbromocarbinol acetate

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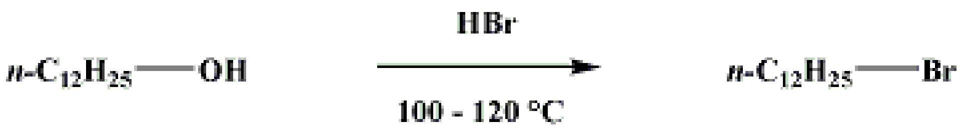
n-DODECYL BROMIDE

[Dodecane, 1-bromo-]



Submitted by E. Emmet Reid, John R. Ruhoff, and Robert E. Burnett.
Checked by W. H. Carothers and W. L. McEwen.

1. Procedure

In a 500-cc. distilling flask, fitted with a thermometer and an inlet tube leading to the bottom (Note 1), is placed 186 g. (1 mole) of *n*-dodecyl alcohol (Note 2). An adapter, one end of which is immersed in about 75 cc. of water contained in a 125-cc. Erlenmeyer flask, is attached to the side arm of the flask. All connections are of rubber. The alcohol is heated to 100°, and dry hydrogen bromide (Note 3) is passed in at 100–120° (Note 4) until no more absorption occurs (Note 5). The crude bromide, together with any of the product that has been carried over into the receiving flask, is transferred to a separatory funnel, separated from the aqueous hydrobromic acid formed during the reaction, and shaken with one-third its volume of concentrated sulfuric acid (Note 6). The lower acid layer is drawn off and discarded (Note 7). The residual bromide is mixed with an equal volume of 50 per cent methyl alcohol (Note 8), and aqueous ammonia is added with intermittent shaking until the solution is alkaline to phenolphthalein. The lower bromide layer is drawn off and washed once with an equal volume of 50 per cent methyl alcohol. It is then dried with calcium chloride, filtered, and distilled. The yield of product boiling at 199.5–201.5°/100 mm. or 134–135°/6 mm. is 220 g. (88 per cent of the theoretical amount) (Note 9).

2. Notes

1. In order to obtain more efficient absorption of the hydrogen bromide, a small bulb is blown on the end of the inlet tube, and a number of pin holes are made in it by means of a small, white-hot tungsten wire.
2. The dodecyl alcohol used was obtained by the fractionation of "Lorol"; its boiling point was 192.5–193.5°/100 mm. or 151–152°/21 mm. If the alcohol is not of good quality, the yield is somewhat lower. Dodecyl alcohol may also be prepared according to the procedure given on p. 372.
3. The hydrogen bromide is conveniently prepared by the direct combination of hydrogen and bromine (p. 338). An excess of hydrogen is to be avoided since it causes loss of product by volatilization.
4. The heat of the reaction maintains the alcohol at this temperature until the preparation is nearly completed.

5. For each mole of alcohol about 1.5 moles of hydrogen bromide is required, of which 1 mole is used to convert the alcohol to the bromide and approximately 0.5 mole to saturate the water formed in the reaction. The rate of addition should be regulated so as to require not less than an hour and a half. The Erlenmeyer flask that serves as a receiver should be weighed with the water in it before it is put in place. When the reaction is complete, the receiver gains weight rapidly and becomes warm owing to the heat of solution of the hydrogen bromide in the water.

6. The crude bromide must be shaken well with the sulfuric acid. The function of the sulfuric acid appears to be to convert any free alcohol to the acid sulfates, which is then soluble in 50 per cent methyl alcohol and ammonia.

7. Care must be taken that the separation of the two layers in this and subsequent washings is complete. Failure to observe this precaution is usually the cause of a low yield.

8. The use of methyl alcohol prevents, to a large extent, the formation of troublesome emulsions. Less than 0.1 g. of dodecyl bromide dissolves in 100 cc. of 50 per cent methyl alcohol at room temperature.

9. The authors have prepared other bromides by this method with the yields indicated below:

Bromide	Yield, %	Solubility of Bromides in Methyl Alcohol
Cyclohexyl	72–75	Less than 1 g. in 100 cc. of 65% methyl alcohol
n-Heptyl	87–90	Less than 0.5 g. in 100 cc. of 50% methyl alcohol
Tetradecyl	88–89	Less than 0.1 g. in 100 cc. of 50% methyl alcohol
Octadecyl	90–91	Practically insoluble in 90% methyl alcohol

Obviously for the lower bromides it is desirable to use no more methyl alcohol than is necessary to prevent the formation of an emulsion. A convenient method is to place the water, phenolphthalein, and crude bromide in a separatory funnel, and add ammonia until the mixture becomes pink. Methyl alcohol is then added in small portions until the emulsion is broken and two layers separate with a distinct boundary after the mixture has been agitated.

3. Discussion

The above method for preparing *n*-dodecyl (lauryl) bromide is an adaptation of that of Ruzicka[1] and has been published.[2] It is thought to present some advantages in ease of manipulation and quality of product over the older method involving the action of aqueous hydrobromic acid on the alcohol in the presence of sulfuric acid.[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 292
- Org. Syn. Coll. Vol. 2, 474
- Org. Syn. Coll. Vol. 3, 363

References and Notes

1. Ruzicka, Stoll, and Schinz, Helv. Chim. Acta **11**, 685 (1928).
2. Ruhoff, Burnett, and Reid, J. Am. Chem. Soc. **56**, 2784 (1934).
3. Kamm and Marvel, ibid. **42**, 299 (1920); Org. Syn. Coll. Vol I, **1941**, 29.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

ammonia (7664-41-7)

methyl alcohol (67-56-1)

hydrogen (1333-74-0)

HYDROBROMIC ACID, hydrogen bromide (10035-10-6)

bromine (7726-95-6)

Dodecane, 1-bromo-, Dodecyl bromide, n-DODECYL BROMIDE (143-15-7)

dodecyl alcohol, n-dodecyl alcohol (112-53-8)

Cyclohexyl bromide (108-85-0)

phenolphthalein (77-09-8)

n-heptyl bromide (629-04-9)

Tetradecyl bromide (112-71-0)

Octadecyl bromide (112-89-0)

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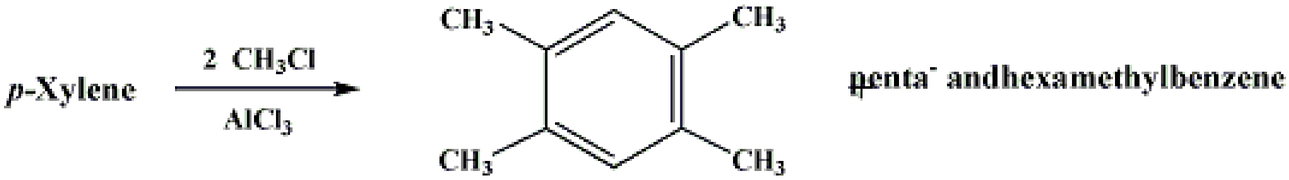
DURENE

[By-products, penta- and hexamethylbenzene]



Submitted by Lee Irvin Smith
Checked by Frank C. Whitmore and Thos E. Hollingshead.

1. Procedure

A 5-l. flask, mounted on a steam bath, is fitted with a wide (Note 1) inlet tube reaching to the bottom of the flask, a reflux condenser, and a delivery tube running from the top of the reflux condenser and reaching to the bottom of a heavy glass cylinder containing a column of mercury about 10 cm. high. All stoppers and joints of the apparatus must fit tightly and be wired, as the reaction is carried out under a slight pressure. In the flask are placed 3180 g. (3.7 l., 30 moles) of xylene (Note 2) and 1 kg. of anhydrous aluminum chloride (Note 2). The inlet tube of the flask is then connected to a tank of methyl chloride or to a methyl chloride generator (Note 3), the steam is turned on in the bath, and a fairly rapid stream of methyl chloride is passed into the mixture (Note 4). At first there will be a rapid absorption, and the stream of gas must be regulated so that the mercury in the pressure tube does not suck back. The hydrogen chloride formed may be conveniently disposed of by a trap. As the reaction slows down, the pressure increases until both hydrogen chloride and methyl chloride begin to escape through the mercury. At this point the current of incoming gas should be cut down so that undue loss of methyl chloride is avoided. About one hundred hours is required for the completion of the reaction (Note 5).

When the reaction is completed, the steam is turned off and the flask is disconnected and loosely stoppered. After standing overnight the reaction mixture is decomposed by pouring it slowly onto 5 kg. of chopped ice. The greenish oil which separates from the aqueous layer is removed, dried over calcium chloride, filtered and fractionated twice, using a round-bottomed flask fitted with an efficient column and an air condenser (Note 6).

The fractions are cut as follows:

Fraction	Temp. Range	Distillate	Yield, g.
I and II	Up to 150°	Benzene, xylene	Little
III	150 to 180	Trimethyl benzenes	570
IV	180 to 205	Tetramethyl benzenes	2075
V	Above 205	Mostly pentamethylbenzene	815

Typical yields of the various fractions are given in the table; they may vary 10 to 20 per cent from these figures, owing to slight differences in procedure and materials, and especially to differences in the quality of the aluminum chloride employed. The more efficient the aluminum chloride, the greater is the percentage of the higher-boiling fractions.

The tetramethylbenzene fraction (IV) is rich in durene, which may be frozen out and filtered

because of its relatively high melting point (80°). To isolate the durene, fraction IV is thoroughly chilled in an ice-calcium chloride pack, and filtered through a cold filter (Note 7), using good suction and pressing down the solid compactly. When no more liquid drips through the cold filter, the filtration apparatus is allowed to come gradually to room temperature (Note 7) and the suction is continued as long as any liquid drips through, after which the solid is removed and bottled. The yield is 540 to 610 g.

Fraction III may be methylated to the tetramethylbenzene stage by heating on the steam bath with 100 g. of anhydrous aluminum chloride and passing in 225 g. of methyl chloride. The filtrates from the durene likewise yield more durene when heated on the steam bath with 50 g. of aluminum chloride. The products are worked up in the usual way; that is, they are decomposed by pouring onto twice their weight of chopped ice, separated from the aqueous layer, fractionated twice, and the durene frozen out as before. By conducting one methylation of the trimethylbenzene fraction, and one treatment of the durene filtrates, the combined yield of crude durene will average 1 to 1.4 kg. (25–35 per cent of the theoretical amount based on the original 30 moles of xylene).

To purify the durene, 200 g. of the crude product is placed in a 1-l. round-bottomed flask fitted with a reflux condenser, and melted in a water bath at 95°; 200 cc. of warm (50°) 95 per cent ethyl alcohol is then added through the top of the condenser, and the mixture is carefully heated until homogeneous. The solution is filtered on a hot-water funnel, allowed to stand tightly covered (Note 8) in a fairly warm place (35°) overnight, cooled to about 0°, and filtered on a suction filter. The product (about 169 g.) melts at 74–78°. A second recrystallization yields 149 g. melting at 77–79°. A third recrystallization yields 140 g. having a melting point of 79–80°. The alcoholic filtrates are fractionated, and the crude durene obtained is worked over with the isomers of durene.

Pentamethylbenzene.—Fraction V, and xylene which is methylated beyond the tetramethylbenzene stage, may be worked up for pentamethylbenzene. If xylene is to be methylated to obtain pentamethylbenzene, one more mole of methyl chloride should be used, and the mixture of xylene and anhydrous aluminum chloride should be methylated for one hundred and ten hours instead of the one hundred used for durene. Otherwise the procedure is exactly the same as for durene. The reaction mixture is decomposed and fractionated in the usual way, and the material boiling above 205° (fraction V) is separated into three fractions:

Fraction	Temperature Range	
VI	205–215°	Tetra- and pentamethylbenzene
VII	215–235	Mostly pentamethylbenzene
VIII	Residue above 235	Hexamethylbenzene and tars

The pentamethylbenzene obtained in this way is nearly pure, and one recrystallization from 95 per cent alcohol or from a mixture of equal volumes of alcohol and benzene gives a snow-white product, but the product generally melts over too wide a range for practical purposes. However, if fraction VII is refractionated under diminished pressure and the fraction boiling at 123–133°/22 mm. (practically all at 127–129°) is collected and recrystallized as in the following paragraph, a product melting quite sharply at 52° (true m.p. 53°) is obtained.

Six hundred grams of crude pentamethylbenzene is heated to 100° and poured slowly with stirring into 1 l. of 95 per cent ethyl alcohol heated to 70° in a 2-l. beaker, and allowed to stand overnight at a temperature of approximately 30°. The crystals formed are collected on a suction filter and dried at room temperature overnight on a porous plate. The yield is about 250 g. (Note 9).

Hexamethylbenzene.—Fraction VIII is fractionated in 250-cc. batches in a Claisen flask at 20 mm. pressure, the following fractions being collected:

Fraction	Temperature Range	
IX	80–110°	Mostly tetra- and pentamethyl benzenes
X	110–135	Mostly pentamethylbenzene
XI	135–170	Hexamethylbenzene
XII	Residue above 170	Hexamethylbenzene and tars

This fractionation may be carried out in an ordinary Claisen flask, but there is some difficulty in maintaining the desired pressure owing to the solvent action of the hydrocarbons on the rubber stopper. This difficulty may be avoided by the use of a Claisen flask with very long necks and a wide side tube. The material should be distilled fast enough to prevent it from solidifying in the column and side tube. Prolonged heating of hexamethylbenzene also causes a considerable amount of decomposition to tars.

The method for the production of large amounts of hexamethylbenzene is the rapid methylation of pentamethylbenzene or the durene filtrates. A mixture of 378 g. of pentamethylbenzene and 200 g. of anhydrous aluminum chloride is heated on an oil bath at 190–200° and a rapid stream of dry methyl chloride is bubbled through for three to four hours, using the same apparatus as for the preparation of durene. The mixture is allowed to stand overnight at room temperature. One liter of hot xylene is added to dissolve the solidified material, and the reaction mixture is decomposed by pouring it onto 3 kg. of chopped ice. The resulting oil is separated, and the xylene and other low-boiling material are removed by distillation under reduced pressure (Note 10). The fractions are divided as above. Two refractionations and two recrystallizations (Note 11) give 98–121 g. of white crystals, melting at 157–161° (Note 12).

2. Notes

1. The inner tube of a condenser makes a good inlet tube. It should be placed so that the wide end is inside the large flask.
2. The xylene should be a good, colorless laboratory grade, b.p. 135–140°. Any moisture present may be removed by distilling and discarding the first 10 per cent of the distillate. The best aluminum chloride available should be used, for the methylation is very unsatisfactory if the catalyst is of an inferior grade. It should be in small pieces but need not be powdered.
3. The methyl chloride generator consists of a 5-l. flask resting on a sand bath and fitted with a reflux condenser, with a delivery tube running from the top of the condenser to a train of wash bottles, two containing water and two containing concentrated sulfuric acid, with three safety bottles, one at each end of the train, and one between the water and sulfuric acid bottles. To charge for about 45 moles (theoretical) of methyl chloride: 200 g. of water and 2.2 kg. (1.2 l.) of concentrated sulfuric acid are placed in the flask, and 1.4 kg. (1760 cc.) of methyl alcohol is added, with cooling, at such a rate that the temperature does not rise above 70°. Then 2.4 kg. of sodium chloride is added, the apparatus is tightly connected, and the flask is heated on the sand bath so that the gas is evolved at a fairly rapid rate. It has been found in practice that, using materials of the commercial grade, the yield of methyl chloride is about 55 to 65 per cent of the theoretical amount, so that about double the calculated quantities must be used. This means that the generator has to be charged three times in order to convert 30 moles of xylene to tetramethylbenzene. If a tank of methyl chloride is available, 65–70 moles of methyl chloride should be used for this same amount of xylene. The tank should be weighed before starting and the reaction stopped when the tank has lost the proper

amount in weight.
4. Experiments have shown that the rapid current of methyl chloride furnishes sufficient stirring.
5. The normal time of one hundred hours can be shortened by increasing the amount of aluminum chloride. The product is then very viscous, however, and rather difficult to handle in large amounts.
6. Two systematic fractionations (not redistillations) with a good column are absolutely necessary in order to obtain good separations. The more efficient the column the better.
7. The material should be filtered through a large Büchner funnel, which is immersed in a freezing mixture as long as any liquid drips through. It is stated in the literature that the first filtrate obtained in this way is mostly isodurene (1,2,3,5-), whereas the second filtrate, obtained as the material warms slowly to room temperature, is pseudodurene or prehnitene (1,2,3,4-), m.p. –4°.
8. Durene, being quite volatile, should not be allowed to remain exposed to the air any longer than necessary. It is also quite volatile with alcohol, and the mother liquors resulting from the recrystallizations should be distilled: the alcoholic distillate is used for further recrystallizations, and the residues may be worked up for durene by heating with aluminum chloride.
9. The melting point of pentamethylbenzene is only slightly affected by recrystallization, because most of the impurity is hexamethylbenzene, which can be removed only by fractionation.
10. Hexamethylbenzene decomposes when heated very strongly for any length of time. Therefore better results are obtained if the distillations are carried out under reduced pressure.
11. Small amounts of impurities greatly influence the melting point of hexamethylbenzene, and several recrystallizations of a fraction of close boiling range are necessary in order to prepare a sharply melting product.
12. Small amounts (25 g. or less) of hexamethylbenzene which is nearly pure are best recrystallized from ethyl alcohol. It requires about 600 cc. of boiling alcohol to dissolve 25 g., but on cooling 20 g. of pure product will result. Ether and benzene dissolve the substance much more readily, and larger amounts of materials are best recrystallized from either of these solvents, or from a mixture of one of them with alcohol. One hundred and twenty-five grams of the hexamethylbenzene distillate which has been refractionated is melted and poured slowly with stirring into 1.5 l. of 95 per cent alcohol. A small amount which remains undissolved may be brought into solution by adding about 300 cc. of hot benzene, the beaker being heated on a steam bath and the mixture stirred constantly until all is dissolved. The solution is allowed to stand overnight at approximately 25°. The crystals are filtered by suction and washed with enough 95 per cent alcohol to moisten thoroughly (about 25 cc.). After drying, the crystals weigh approximately 112 g. and melt at 155–159°.

3. Discussion

Durene, pentamethylbenzene and hexamethylbenzene have usually been prepared from benzene or one of its methylated derivatives by the Friedel-Crafts synthesis.[1] Durene has been made from bromine derivatives of methylated benzenes by the Fittig reaction.[2] It has been obtained in 20 per cent yield by passing methyl alcohol and acetone vapors over heated aluminum oxide[3] and in 45 per cent yield by the chloromethylation of xylene and reduction of the chloromethylated products.[4] Hexamethylbenzene has been obtained by the action of zinc chloride on methyl alcohol[5] or on acetone.[6] The method described in the procedure above has been published.[7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 254
- Org. Syn. Coll. Vol. 2, 360
- Org. Syn. Coll. Vol. 6, 700

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

penta- and hexamethylbenzene

Tetra- and pentamethylbenzene

tetra- and pentamethyl benzenes

isodurene (1,2,3,5-)

pseudodurene or prehnitene (1,2,3,4-)

benzene or one of its methylated derivatives

ethyl alcohol, alcohol (64-17-5)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrogen chloride (7647-01-0)

Benzene (71-43-2)

methyl alcohol (67-56-1)

ether (60-29-7)

sodium chloride (7647-14-5)

mercury (7439-97-6)

methyl chloride (74-87-3)

acetone (67-64-1)

aluminum chloride (3495-54-3)

zinc chloride (7646-85-7)

xylene (106-42-3)

Durene (95-93-2)

Hexamethylbenzene (87-85-4)

Pentamethylbenzene (700-12-9)

tetramethylbenzene (488-23-3)

trimethylbenzene (526-73-8)

aluminum oxide (1344-28-1)

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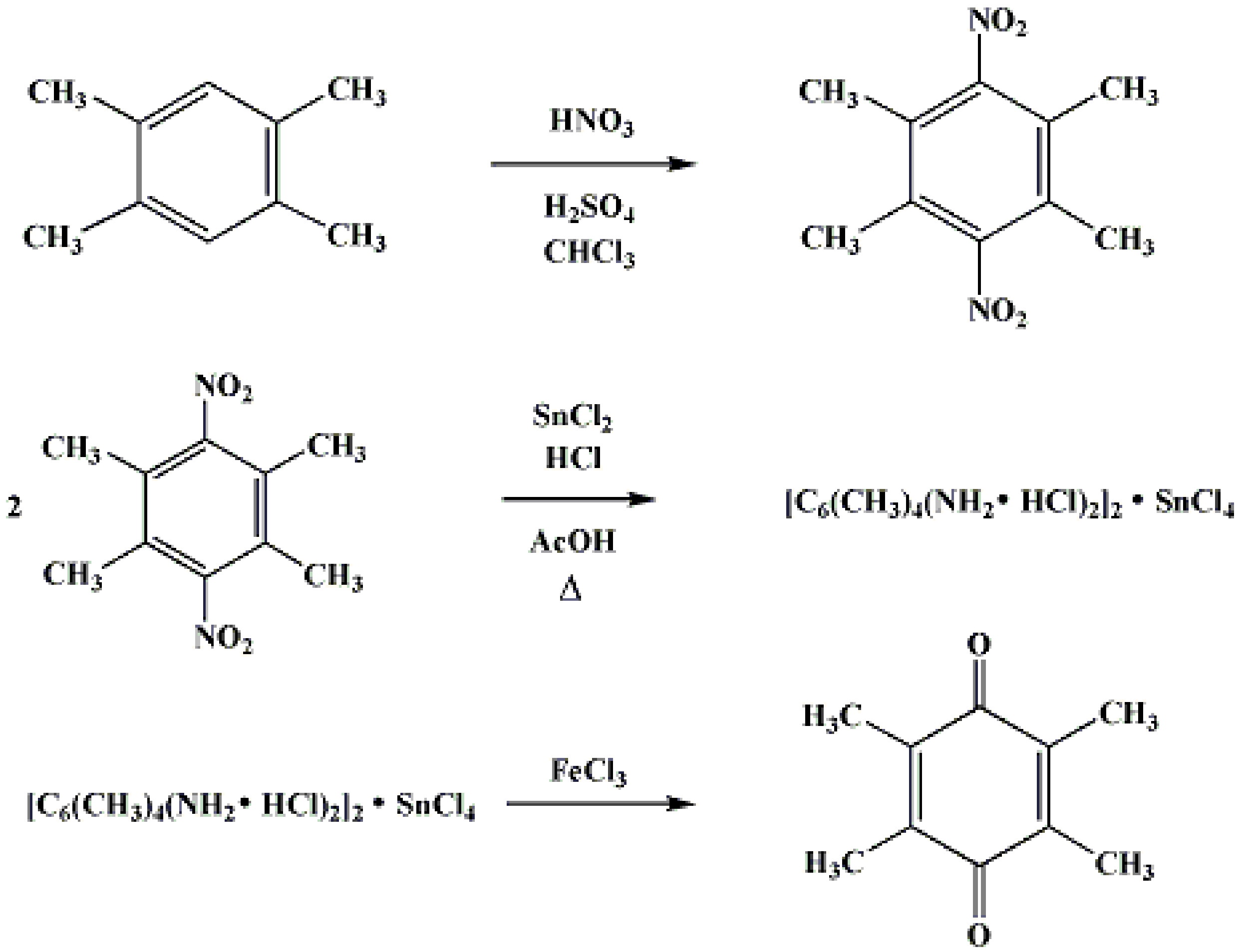
Organic Syntheses, *CV 2*, *254*

DUROQUINONE



Submitted by Lee Irvin Smith
Checked by Frank C. Whitmore and Thos. E. Hollingshead.

1. Procedure

(*A*) *Dinitrodurene*.—A solution of 13.4 g. (0.1 mole) (Note 1) and (Note 2) of durene (p. 248) in 100 cc. of chloroform is added to 75 cc. of concentrated sulfuric acid in an 800-cc. beaker provided with a thermometer and an efficient mechanical stirrer. The mixture is cooled to 10°, and 16 g. (10.7 cc.) of fuming nitric acid (sp. gr. 1.5) (Note 3) is added drop by drop, with stirring, from a 125-cc. separatory funnel, the mixture being cooled in an ice-salt bath and the nitric acid added at such a rate that the temperature does not rise above 50° (about fifteen minutes is required for the addition). As soon as all the acid has been added the mixture is poured into a separatory funnel, the sulfuric acid layer is removed, and the upper chloroform layer is immediately (Note 4) run into 500 cc. of 10 per cent sodium carbonate solution. The sulfuric acid layer is discarded because it contains very little dinitrodurene. Four portions are nitrated, and the combined chloroform solutions are washed twice with 2.5 per cent sodium carbonate solution, dried overnight with 30 g. of anhydrous

calcium chloride, filtered, and the chloroform distilled until crystals of dinitrodurene begin to appear. At this point four times the volume of hot 95 per cent ethyl alcohol is added (about 500 cc.), and the resulting mixture is cooled to 10°. The solid is filtered and washed twice with 50 cc. of cold (10°) 95 per cent ethyl alcohol. The yield from four nitrations is 82.5–84 g. (92–94 per cent of the theoretical amount) of a product melting at 207–208° (Note 5).

(*B*) *Reduction of Dinitrodurene*.—A solution of 90 g. of dinitrodurene in 1 l. of glacial acetic acid is boiled in a 12-l. flask (Note 6); 700 g. of stannous chloride is dissolved in 800 cc. of concentrated hydrochloric acid and heated to boiling. The heat is removed from the acetic acid solution of the nitro compound, and the stannous chloride solution is poured very carefully (during about ten minutes) into the dinitrodurene solution. The reaction is complete in fifteen minutes, and, as the solution cools, the stannic chloride compound of the diamine begins to crystallize. The reaction mixture is cooled to 10° in an ice-water bath, and the solid is filtered by suction, washed twice with 50 cc. of 95 per cent ethyl alcohol and twice with 50 cc. of ether, and dried. The filtrates from the tin compound contain very little of the reduction product and may be discarded. The composition of this compound is $[C_6(CH_3)_4(NH_2\cdot HCl)_2]_2\cdot SnCl_4$, and it crystallizes from the reaction mixture in fine, glistening plates which are almost colorless. The yield is 145 g. (97 per cent of the theoretical amount).

(*C*) *Duroquinone*.—A suspension of 100 g. of the tin compound in a solution of 300 g. of ferric chloride crystals in a mixture of 150 cc. of water and 20 cc. of concentrated hydrochloric acid is allowed to stand overnight at about 30°, and is then filtered. The product is dissolved in 150 cc. of hot 95 per cent ethyl alcohol. The solution is filtered and allowed to stand overnight at 30°. The yield is 40 g. of duroquinone (90 per cent of the theoretical amount) melting at 109–110°.

2. Notes

1. It is better to nitrate the durene in small batches, for a high yield and pure product are obtained only with a minimal contact of the reaction mixture and the nitric acid.
2. Pure durene is absolutely essential for good results. Durene should be recrystallized from methyl alcohol until the melting point is 79–80°.
3. A large excess of nitric acid is undesirable, since it lowers the yield. The concentration of the nitric acid is also of importance, and, to obtain the best results, it should have a specific gravity of 1.5 or more.
4. It is important that the chloroform layer be run into the carbonate solution as quickly as possible, for continued standing in contact with even small amounts of acid leads to the formation of considerable amounts of red, tarry material. This renders the subsequent purification of the nitro compound much more difficult.
5. No mononitrodurene is ever obtained in this process. Either the dinitro

compound results, or else unchanged material and oxidation products.
6. A large flask is necessary because the reduction is vigorous and the reaction mixture will boil up and practically fill the flask of the size recommended.

3. Discussion

Duroquinone has been prepared by the action of alkalies on 2,3-diketopentane[1] or 3,3-dichloro-2-pentanone;[2] from durenol by coupling with diazotized sulfanilic acid, reducing the azo dye, and oxidizing the resulting aminophenol to the quinone;[3] and from durene by the series of reactions used above,[4] which is due originally to Nef.[5] The method of nitration used in preparing dinitrodurene is a modification of a method introduced by Willstätter and Kubli.[6]

References and Notes

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6. Willstätter and Kubli, Ber. **42**, 4151 (1909).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

tin compound

ethyl alcohol (64-17-5)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

methyl alcohol (67-56-1)

ether (60-29-7)

chloroform (67-66-3)

nitric acid (7697-37-2)

sodium carbonate (497-19-8)

aminophenol (95-55-6)

stannous chloride

ferric chloride (7705-08-0)

Quinone (106-51-4)

stannic chloride (7646-78-8)

sulfanilic acid (121-57-3)

Durene (95-93-2)

Duroquinone (527-17-3)

Dinitrodurene (5465-13-4)

mononitrodurene

2,3-diketopentane (600-14-6)

3,3-dichloro-2-pentanone (57856-10-7)

durenol

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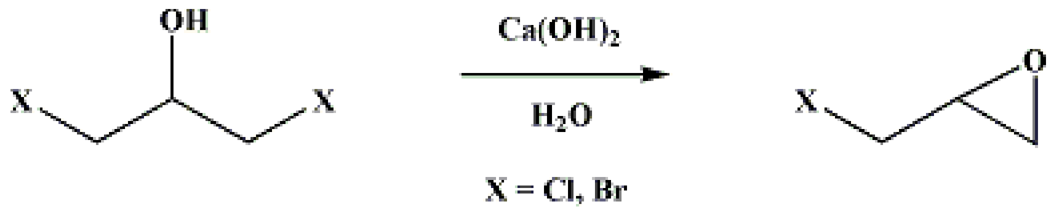
Organic Syntheses, *CV 2, 256*

EPICHLOROHYDRIN AND EPIBROMOHYDRIN



Submitted by Géza Braun
Checked by W. W. Hartman and G. L. Boomer.

1. Procedure

(*A*) *Epichlorohydrin*.—In a 5-l. round-bottomed flask, 1350 g. (988 cc., 10.5 moles) of glycerol α,γ-dichlorohydrin (Org. Syn. Coll. Vol. I, **1941**, 292), 840 g. (10 moles) of technical, finely powdered calcium hydroxide (88 per cent), and 840 cc. of water (20°) are shaken vigorously for fifteen minutes (Note 1). The mixture forms a thick paste at the beginning, but the epichlorohydrin soon separates from the calcium salts as a mobile liquid. The flask is fitted with a rubber stopper carrying a wide delivery tube, and the mixture is distilled from a water bath, at first under 40–50 mm. pressure. The pressure is then lowered to 10 mm. and the temperature raised gradually to 95–100° (Note 2). The receiver must be cooled effectively in an ice-salt mixture to –5° or below, to ensure a maximum yield. The distillate is transferred to a separatory funnel, the upper, aqueous, layer returned to the reaction flask, and the distillation repeated. A third distillation in a similar manner gives a small additional amount of epichlorohydrin (Note 3). The lower layers from the successive distillations are combined and distilled through a fractionating column, under reduced pressure. The epichlorohydrin fraction is collected up to 75°/50 mm., and the residue (about 160–180 cc.), which contains a large percentage of dichlorohydrin, is returned to the original reaction flask, together with 150 cc. of water. This material is distilled once under reduced pressure as described above, and the lower layer of the distillate is combined with the main fraction of epichlorohydrin. The crude product is distilled at ordinary pressure until the temperature of the vapor reaches 115°; at this point the distillation is stopped and the water layer removed from the distillate. The lower layer of the distillate is dried over anhydrous sodium sulfate and returned to the distilling flask. After a small fore-run, the epichlorohydrin distils at 115–117°. The yield is 650–700 g. (67–72 per cent of the theoretical amount).

(*B*) *Epibromohydrin*.—In a 5-l. round-bottomed flask, 2140 g. (1 l., 9.8 moles) of glycerol α,γ-dibromohydrin (p. 308) is suspended in 1.5 l. of water, and 400 g. of technical, powdered calcium hydroxide (88 per cent) is added gradually, with shaking, in the course of about fifteen minutes. A further 400 g. of calcium hydroxide (total, 9.5 moles) is added at once, and the epibromohydrin is distilled at reduced pressure in the manner described for epichlorohydrin (Note 2). The combined lower layers from two

such distillations (about 750 cc.) are dried over anhydrous sodium sulfate and fractionated at atmospheric or reduced pressure. The yield of epibromohydrin, b.p. 134–136° or 61–62°/50 mm., is 1130–1200 g. (84–89 per cent of the theoretical amount).

2. Notes

1. The prescribed amount of water should be used; more water causes frothing. The reaction is not exothermic.
2. Epichlorohydrin boils at 30–32°/10 mm., epibromohydrin at 61–62°/50 mm. Both these liquids are quite volatile with water vapor under reduced pressure.
3. The volume of the epichlorohydrin layer obtained in the successive distillations is roughly: (1) 500 cc., (2) 200 cc., (3) 20 cc.

3. Discussion

Epichlorohydrin[1] and epibromohydrin[2] have been prepared by treatment of glycerol dichloro- and dibromohydrins with alkalies in various ways. The procedures described here represent a laboratory application of the Griesheim process.[3]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Glycerol α,γ-dichlorohydrin

Glycerol α,γ-dibromohydrin

glycerol dichloro- and dibromohydrins

Epichlorohydrin (106-89-8)

sodium sulfate (7757-82-6)

calcium hydroxide

Epibromohydrin (3132-64-7)

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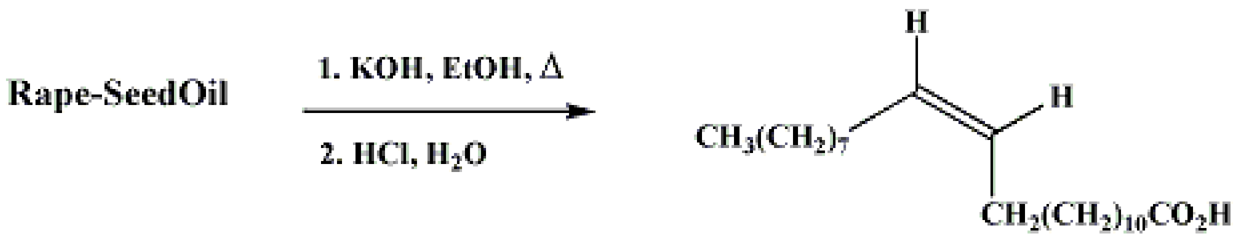
Organic Syntheses, CV 2, 258

ERUCIC ACID

[Hydrolysis of Rape-Seed Oil]



Submitted by C. R. Noller and R. H. Talbot.
Checked by H. T. Clarke and E. R. Taylor.

1. Procedure

In a 5-l. flask fitted with a reflux condenser are placed 2.5 l. of 95 per cent ethyl alcohol and 340 g. (4.5 moles) of commercial (73–75 per cent) potassium hydroxide. The mixture is gently shaken until the hydroxide is dissolved, 1330 g. (1.5 l., approximately 4 equivalents) of rape-seed oil is added with shaking (Note 1), and the mixture is refluxed on a steam bath for twenty-five to thirty hours.

The hot mixture is poured, with stirring, into 15 l. of warm water (50–60°), and is followed by 700 cc. (8.2 moles) of concentrated (36 per cent) hydrochloric acid (Note 2). After standing until the layers are distinct (ten to fifteen minutes), the lower layer is siphoned off as completely as possible and the oil is washed with two 1-l. portions of warm water.

The oil thus obtained, which should amount to 1460–1600 cc., is dissolved in three times its volume of 95 per cent ethyl alcohol and the mixture cooled to −10 to 0°, when the erucic acid crystallizes (Note 3). After six to eight hours at this temperature, the crude erucic acid is collected on a basket centrifuge (Note 4). The mother liquor, on chilling, yields a second crop of erucic acid. The combined product (800–1100 g.) melts either partially or wholly at room temperature, owing to the presence of oleic acid. It is dissolved in an equal volume of alcohol, chilled for six hours at 0°, and centrifuged as before, when it is obtained in well-defined crystalline form. The second crop of this recrystallization resembles that of the first crystallization and must again be recrystallized. The product is finally recrystallized once again from an equal volume of 95 per cent alcohol. The recrystallized acid contains alcohol, which is removed by heating to constant weight on the steam bath under diminished pressure. The yield of acid is 260–360 g. (Note 5); the acid melts at 31–32° (Note 6).

2. Notes

1. If the solution is mixed in this manner, the rape-seed oil emulsifies on being

poured into the alkali and refluxing begins more smoothly.

2. If the acid is added before the water, esterification occurs to an appreciable extent, and the yield may fall to less than 200 g.

3. The crystallization is best accomplished by cooling for several hours at 0°. Cooling in an ice-salt mixture is much quicker but the erucic acid so obtained contains more oleic acid.

4. The centrifuge affords an easy way of filtering the erucic acid, since if the acid is not quickly separated from the mother liquor it melts and makes separation impossible. If a centrifuge is not available, the acid must be filtered at 0°, which is inconvenient except during cold weather.

5. The mother liquors from the recrystallizations may be combined, evaporated, and distilled under reduced pressure, taking two equal fractions. The lower (b.p. 200–220°/5 mm.) consists mainly of oleic acid; the higher (b.p. 220–230°/5 mm.) is solid at 20° and yields a further quantity of erucic acid on recrystallization.

6. The acid obtained contains a small percentage of arachidic acid and other higher saturated fatty acids, and has an iodine number of 66.9 (instead of about 75). If not entirely colorless, the product may be distilled under reduced pressure, when it boils at 241–243°/5 mm. or 252–254°/12 mm.; there is practically no loss, only a minute amount of higher-boiling material remaining in the flask.

3. Discussion

Erucic acid is a constituent of various natural oils but is most conveniently obtained from rape-seed oil. The process described above is essentially that of Reimer and Will.[1] Methods have been developed for obtaining pure erucic acid free from saturated acids,[2] but these involve time-consuming procedures of fractional precipitation and crystallization, and necessarily give poor yields. The product obtained above is satisfactory for most purposes.

References and Notes

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2. Holde and Wilke, Z. angew. Chem. **35**, 105, 186, 289 (1922); Täufel and Bauschinger, ibid. **41**, 157 (1928).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethyl alcohol, alcohol (64-17-5)

hydrochloric acid (7647-01-0)

potassium hydroxide (1310-58-3)

oleic acid (112-80-1)

Erucic acid (112-86-7)

arachidic acid (506-30-9)

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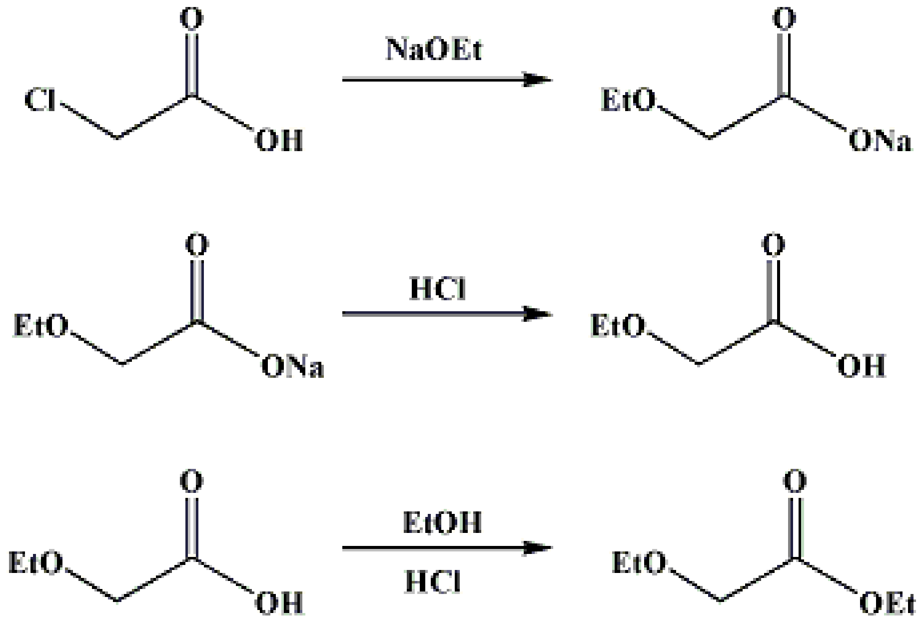
Organic Syntheses, *CV 2*, 260

ETHOXYACETIC ACID AND ETHYL ETHOXYACETATE

[Acetic acid, ethoxy-, and ethyl ester]



Submitted by Reynold C. Fuson and Bruno H. Wojcik.
Checked by C. R. Noller and J. J. Gordon.

1. Procedure

(*A*) *Ethoxyacetic Acid*.—In a 2-l. round-bottomed flask, provided with a reflux condenser 70 to 80 cm. long, is placed 1250 cc. of absolute ethyl alcohol (Note 1). Through the condenser tube 69 g. (3 gram atoms) of metallic sodium is added rapidly enough to keep the alcohol refluxing gently. When the sodium has completely dissolved, a solution of 142 g. (1.5 moles) of chloroacetic acid in 180 cc. of absolute alcohol is added slowly in 20-cc. portions to the sodium ethoxide solution (Note 2). After all the acid has been added, the mixture is heated gently for ten minutes. The excess alcohol is removed as completely as possible by distilling from a steam bath and finally by passing steam into the residue. The aqueous solution is cooled, and 140 cc. (1.7 moles) of concentrated hydrochloric acid (sp. gr. 1.19) is added. The sodium chloride is removed by filtration with suction and is washed with two 50-cc. portions of ether. The original filtrate is saturated with dry sodium sulfate (30–35 g.) and is then extracted with the ether which was used for washing the precipitate, together with an additional 100 cc. of ether. The ether is separated from the aqueous layer, and the latter is extracted four times with 100-cc. portions of fresh ether. The ether is removed by distillation from a steam bath, and the residue is distilled under reduced pressure, using a 500-cc. Claisen flask equipped with a 500-cc. receiver. The acid boils at 109–111°/17–18 mm. and weighs 115–116 g. (74 per cent of the theoretical amount). By

redistilling the low-boiling fraction and collecting the portion boiling at 150–210°, there is obtained an additional 7–10 g. of material which is chiefly ethoxyacetic acid and may be combined with the main fraction for conversion to the ester.

(*B*) *Ethyl Ethoxyacetate*.—The ethoxyacetic acid, which should amount to about 125 g. (1.2 moles), is placed in a 750-cc. Erlenmeyer flask containing 230 cc. (3.9 moles) of absolute ethyl alcohol. The flask is set in a pan filled with cold water (Note 3), and dry hydrogen chloride is passed into the mixture. After the mixture becomes saturated (Note 4) it is allowed to stand twenty-four hours to ensure the completion of the reaction at room temperature (Note 5). The solution is cooled, and a saturated solution of sodium carbonate is added cautiously and with stirring to avoid excessive foaming. The addition is continued until the mixture is faintly alkaline to litmus; an excess of sodium carbonate lowers the yield and should be avoided. The ester is extracted with four 100-cc. portions of ether; the extract is dried with 25 g. of anhydrous potassium carbonate, and the ether is distilled from a steam bath. The residue is distilled at ordinary pressure. The yield of ester boiling at 153–155° is 110–115 g. (55–58 per cent of the theoretical amount based on the chloroacetic acid, or 69–72 per cent based on the ethoxyacetic acid).

2. Notes

1. Alcohol dried over quicklime is satisfactory.
2. The chloroacetic acid should be added fast enough to keep the solution boiling.
3. Heat is evolved during the reaction, and, unless the flask is kept in cold water, an insufficient amount of hydrogen chloride will be absorbed. This lowers the yield.
4. A considerable quantity of dry hydrogen chloride is required. The gas should be allowed to bubble through the mixture for at least five hours.
5. The yield seems to be limited by the equilibrium between the acid and ester. At least twenty-four hours is required to reach this equilibrium.

3. Discussion

Ethoxyacetic acid was first prepared by Heintz[1] by the reaction of chloroacetic acid with sodium ethoxide. The procedure described above is essentially that of Sommelet.[2] Ethoxyacetic acid has also been prepared by hydrolysis of ethoxyacetonitrile with concentrated hydrochloric acid[3] and by the action of excess sodium ethoxide on 1,1,1,2-tetrachlorethane and on α,β-dichlorovinyl ethyl ether.[4] A patent reports the synthesis from diethyl ether and carbon dioxide[5] at high pressure.

Ethyl ethoxyacetate has been prepared by the action of ethyl iodide on sodium ethoxyacetate,[6] of sodium ethoxide on ethyl chloroacetate,[7] of alcohol on crude

diazoacetic ester,[8] and by the alcoholysis of ethoxyacetonitrile using alcoholic hydrogen chloride.[3, 9]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

quicklime

Acetic acid, ethoxy-, and ethyl ester

ethyl alcohol, alcohol (64-17-5)

potassium carbonate (584-08-7)

hydrogen chloride, hydrochloric acid (7647-01-0)

ether, diethyl ether (60-29-7)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

carbon dioxide (124-38-9)

chloroacetic acid (79-11-8)

sodium, metallic sodium (13966-32-0)

sodium ethoxide (141-52-6)

Ethyl chloroacetate (105-39-5)

1,1,1,2-tetrachlorethane (630-20-6)

Ethyl iodide (75-03-6)

Ethoxyacetic acid (627-03-2)

Ethyl ethoxyacetate (817-95-8)

ethoxyacetonitrile (62957-60-2)

α,β-dichlorovinyl ethyl ether

sodium ethoxyacetate

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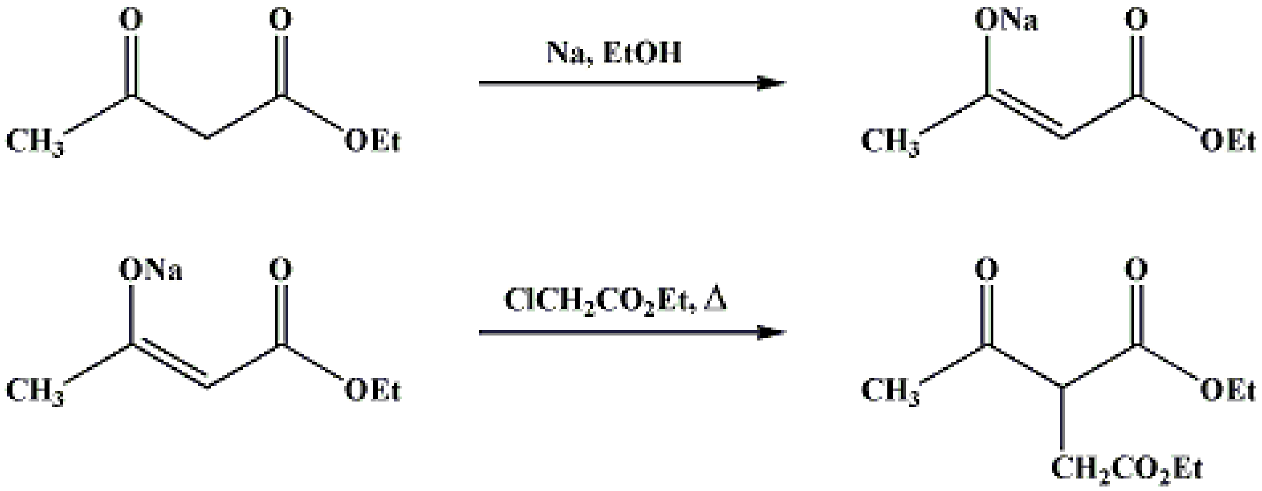
Organic Syntheses, CV 2, 262

ETHYL ACETOSUCCINATE

[Succinic acid, acetyl-, diethyl ester]



Submitted by Homer Adkins, Neville Isbell, and Bruno Wojcik.
Checked by John R. Johnson and H. R. Snyder.

1. Procedure

In a 3-l. three-necked, round-bottomed flask, fitted with a mechanical stirrer, reflux condenser, and separatory funnel, is placed 400 cc. of absolute alcohol (Note 1). Through the condenser tube is added slowly 23 g. (1 gram atom) of clean sodium cut into thin slices. The completion of the reaction is hastened by heating the flask on a steam bath. When the sodium has dissolved completely, 143 g. (1.1 moles) of ethyl acetoacetate (Org. Syn. Coll. Vol. I, **1941**, 235) is introduced slowly. After the mechanical stirrer is started, 123 g. (1 mole) of ethyl chloroacetate (Note 2) is added slowly over a period of an hour, and the reaction mixture is refluxed for five to six hours. At this point the reaction mixture should no longer give an alkaline reaction with moist litmus.

After cooling, the precipitated sodium chloride is removed by filtering with suction and is washed with two 50-cc. portions of absolute alcohol. The alcohol is removed by distilling through a short column from a steam bath. The residue is filtered and transferred to a round-bottomed flask and is fractionated under reduced pressure through a Widmer column containing an 8-cm. spiral (Note 3). The fraction boiling at 121–124°/5 mm. is collected. The yield is 121–134 g. (56–62 per cent of the theoretical amount) (Note 4).

2. Notes

1. A good grade of absolute alcohol is required. For this purpose ordinary absolute alcohol may be dried by treating with a little sodium, adding a few cubic

centimeters of ethyl succinate, and distilling directly into the reaction flask (see Note 1, p. 155, and Org. Syn. Coll. Vol. I, **1941**, 259).

2. Ethyl chloroacetate boiling at 142–145° was used. This ester can be prepared readily by refluxing for six hours a mixture of 200 g. of chloroacetic acid, 120 g. ofabsolute alcohol, and 25 g. of concentrated sulfuric acid.[1] The product is purified in the conventional way, and the yield is 185 g. (70 per cent of the theoretical amount).

3. It is advantageous to use an electrically heated column for this fractionation. The principal by-product of the reaction is ethyl β-acetotricarballylate[2] (b.p. 190°/16 mm.), formed by further action of ethyl chloroacetate upon the initial product.

4. Ethyl α-acetoglutarate may be prepared in a similar way by using 181 g. (1 mole) of ethyl β-bromopropionate (Org. Syn. Coll. Vol. I, **1941**, 246) instead of ethyl chloroacetate. The product is collected at 132–134°/4 mm. and weighs 120 g. (52 per cent of the theoretical amount).

3. Discussion

Ethyl acetosuccinate has been prepared by the interaction of ethyl sodioacetoacetate and ethyl chloroacetate[1] or bromoacetate.[2] The method given above is a modification[3] of that given by Conrad.[1]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 85

References and Notes

1. Conrad, Ann. **188**, 218 (1877).
2. Emery, Ber. **23**, 3755 (1890); Fichter and Pfister, ibid. **37**, 1997 (1904).
3. Isbell, Wojcik, and Adkins, J. Am. Chem. Soc. **54**, 3685 (1932).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alcohol (64-17-5)

sulfuric acid (7664-93-9)

ethyl succinate

sodium chloride (7647-14-5)

chloroacetic acid (79-11-8)

sodium (13966-32-0)

Ethyl chloroacetate (105-39-5)

Ethyl acetoacetate (141-97-9)

Ethyl β-bromopropionate (539-74-2)

Ethyl acetosuccinate

Succinic acid, acetyl-, diethyl ester (1115-30-6)

ethyl β-acetotricarballylate

Ethyl α-acetoglutarate

ethyl sodioacetoacetate

bromoacetate (79-08-3)

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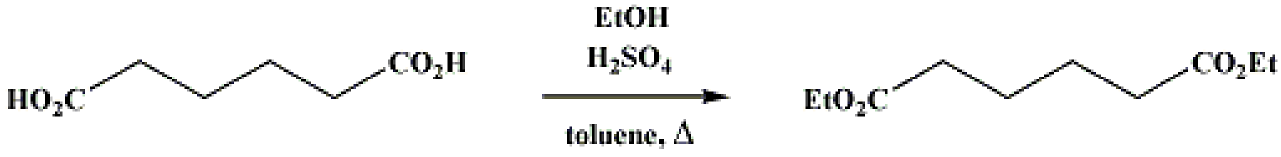
Organic Syntheses, CV 2, 264

ETHYL ADIPATE

[Adipic acid, diethyl ester]



Submitted by V. M. Micovic
Checked by Reynold C. Fuson and E. A. Cleveland.

1. Procedure

Four hundred thirty-eight grams (3 moles) of adipic acid, 1080 cc. (9 moles) of absolute alcohol, 540 cc. of toluene, and 2.5 cc. of concentrated sulfuric acid (Note 1) are placed in a 3-l. distilling flask. The flask is connected with a downward condenser and heated on an oil bath (Note 2). An azeotropic mixture of alcohol, toluene, and water begins to distil at 75°. Distillation is continued until the thermometer in the neck of the flask rises to 78°, when further heating is suspended.

The distillate is collected in a 2-l. flask containing 450 g. of anhydrous potassium carbonate (Note 3). It is well shaken, filtered through a Büchner funnel, and returned to the distilling flask (Note 4). The flask is again heated until the temperature rises to 78–80°, when distillation is discontinued (Note 5). The residual liquid (Note 6) is emptied into a 1-l. flask, the large flask being rinsed with a little alcohol, and distilled under vacuum. Alcohol and toluene distil first; then the temperature rises and ethyl adipate distils at 138°/20 mm. (Note 7). The yield is 580 to 588 g. (95–97 per cent of the theoretical amount) (Note 8) and (Note 9).

2. Notes

1. For esterification by this method, three times the theoretical quantity of absolute alcohol is taken. If only twice the theoretical amount is used, esterification is not complete. The quantity of sulfuric acid required is 1 per cent of the weight of adipic acid used. For smaller quantities of organic acid, a few drops of sulfuric acid are sufficient.
2. It is necessary to maintain the temperature of the bath at about 115° until the mixture dissolves and distillation begins. Later a temperature of 100–110° is sufficient.
3. For each mole of adipic acid to be esterified, 150 g. of anhydrous potassium carbonate is required.
4. Filtering through a fluted filter paper directly into a distillation flask is entirely satisfactory when smaller quantities are used.
5. The distillate, which contains alcohol, toluene, and water, can be dried, distilled, and used again for esterification after the addition of the necessary quantity of absolute alcohol; or, by the addition of water, toluene alone may be separated, dried over calcium chloride, and distilled.
6. If the solution is allowed to cool, small crystals of unesterified acid separate. The quantity is negligible.
7. Towards the end of the distillation, the temperature rises several degrees; but

distillation should be continued, for when redistilled the ester does not leave a residue.
8. According to the submitter, ethyl esters of the dibasic acids from oxalic through sebacic have been prepared in yields of 94–98 per cent by this same procedure.
9. Ethyl adipate can also be prepared[1] by refluxing 175 g. (1.2 moles) of adipic acid, 175 g. (222 cc.) of ethyl alcohol, 450 cc. of benzene, and 80 g. (43.5 cc.) of concentrated sulfuric acid for five hours on the steam bath. The yield of ester boiling at 136–137/19 mm. is 218 g. (90 per cent of the theoretical amount). (Private communication from P. S. Pinkney. Checked by Louis F. Fieser and T. L. Jacobs.)

3. Discussion

Ethyl adipate is obtained by boiling adipic acid, alcohol, benzene, and sulfuric acid;[1] from adipic acid, alcohol, and hydrogen chloride;[2] from adipic acid, absolute alcohol, and sulfuric acid;[3] by distilling a mixture of ethyl alcohol, toluene, and adipic acid with the addition of some hydrochloric acid which acts as a catalyst;[4] and by the procedure described above.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 116
- Org. Syn. Coll. Vol. 2, 276
- Org. Syn. Coll. Vol. 2, 325
- Org. Syn. Coll. Vol. 4, 819

References and Notes

1. Van Rysselberge, Bull. soc. chim. Belg. **35**, 312 (1926).
2. Arppe, J. prakt. Chem. (1) **95**, 208 (1865).
3. Curtius, ibid. (2) **91**, 4 (1915); Bouveault and Locquin, Bull. soc. chim. (4) **3**, 439 (1908).
4. Locquin and Elghozy, ibid. (4) **41**, 445 (1927).
5. Micovic, ibid. (5) **4**, 1661 (1937).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethyl alcohol, alcohol (64-17-5)

calcium chloride (10043-52-4)

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

hydrogen chloride, hydrochloric acid (7647-01-0)

Benzene (71-43-2)

Adipic acid (124-04-9)

Ethyl adipate (626-86-8)

toluene (108-88-3)

Adipic acid, diethyl ester (141-28-6)

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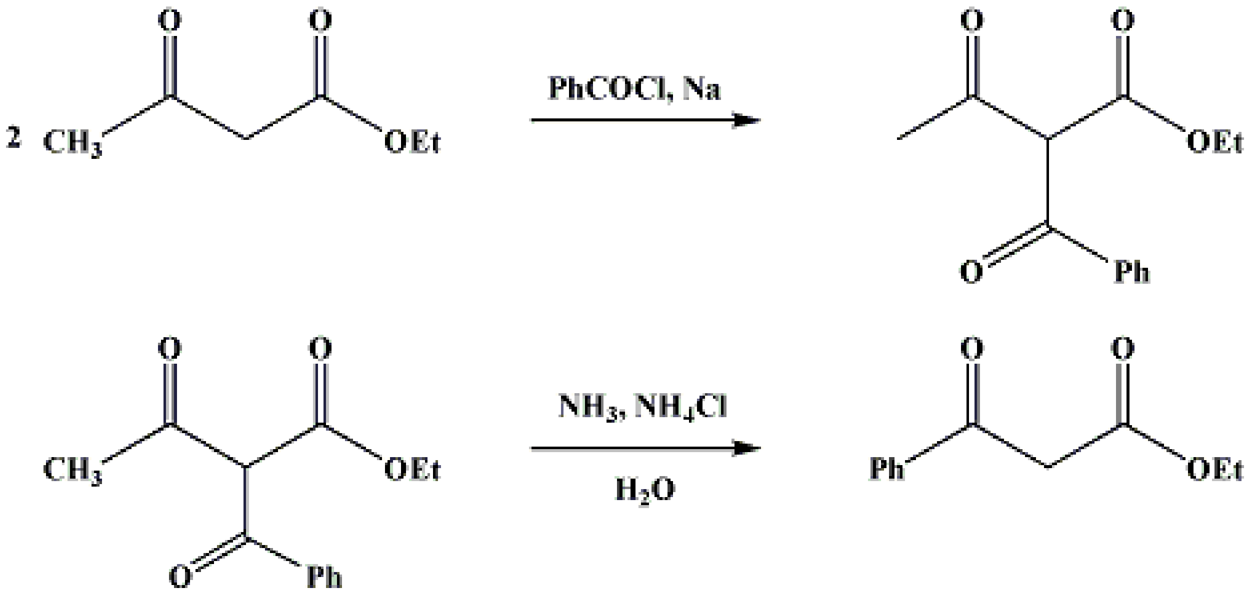
ETHYL BENZOYLACETATE

[Acetic acid, benzoyl-, ethyl ester]



Submitted by R. L. Shriner, A. G. Schmidt, and L. J. Roll.
Checked by C. R. Noller and I. Bergsteinsson.

1. Procedure

(*A*) *Preparation of Ethyl Benzoylacetoacetate*.—In a 5-l. three-necked flask, fitted with a liquid-sealed mechanical stirrer and a reflux condenser, are placed 3.4 l. of dry benzene (Note 1), 195 g. (1.5 moles) of ethyl acetoacetate (Org. Syn. Coll. Vol. I, **1941**, 235), and 34.5 g. (1.5 gram atoms) of clean sodium. The mixture is heated on a steam cone with stirring and allowed to reflux gently for twenty-four hours. After the suspension of the sodioacetoacetic ester has been cooled slightly, 263 g. (218 cc., 1.9 moles) of benzoyl chloride is added over a period of three hours. The mixture is refluxed with stirring for an additional eight hours. It is then cooled to room temperature, and 375 g. of cracked ice is added. After thorough shaking, the benzene layer, which contains the ethyl benzoylacetoacetate, is separated, washed with 75 cc. of 5 per cent sodium bicarbonate solution, dried with sodium sulfate, and the benzene distilled (Note 2). The residue is distilled *in vacuo* from a 500-cc. Claisen flask with a 50-cm. fractionating side arm. After a small fore-run of benzoyl chloride, the fraction boiling at 142–148°/6 mm., or 177–181°/20 mm., is collected. The yield is 223–263 g. (63–75 per cent of the theoretical amount).

(*B*) *Hydrolysis of Ethyl Benzoylacetoacetate*.—Thirty-two grams (0.6 mole) of ammonium chloride is dissolved in 150 cc. (8.3 moles) of water in a 500-cc. Erlenmeyer flask, and 10 cc. (0.15 mole) of ammonia (sp. gr. 0.9) is added. The solution is warmed to 42°, 58.5 g. (0.25 mole) of ethyl benzoylacetoacetate at 20° is

added quickly, and the mixture is shaken (Note 3). The flask is placed in a water bath at 42° for exactly ten minutes and then cooled rapidly by placing it in an ice bath. The solution is extracted twice with 100-cc. portions of ether, and the ether solution is dried with anhydrous magnesium sulfate. The ether is distilled, and the residue distilled *in vacuo*; the yield is 37.0–37.5 g. (77–78 per cent of the theoretical amount) of ethyl benzoylacetate boiling at 132–137°/4 mm., or 165–169°/20 mm.

2. Notes

1. The benzene was dried by distillation, the first portion of the distillate being discarded.
2. It is essential that these steps in the isolation be carried through as rapidly as possible.
3. Larger amounts gave lower yields. The exact procedure must be followed as to time, temperature, and amounts of reagents, and the procedure must be completed without interruption.

3. Discussion

Ethyl benzoylacetate has been prepared by the condensation (by means of sodium ethoxide) of ethyl acetate with ethyl benzoate,[1] acetophenone with ethyl carbonate,[2] and acetophenone with ethyl oxalate, with subsequent heating;[3] by treatment of ethyl phenylpropiolate[4] or α-bromocinnamic acid[5] with concentrated sulfuric acid, and of ethyl diazoacetate with benzaldehyde;[6] by the condensation of benzene with the monoethyl ester of malonyl monoacid chloride and aluminum chloride,[7] of benzoyl chloride with the product of the reaction of magnesium and ethyl chloroacetate in ether;[8] by the action of alcohol on benzoylacetimino ethyl ether hydrochloride;[9] and by the hydrolysis of ethyl benzoylacetoacetate.[10]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 379
- Org. Syn. Coll. Vol. 4, 415
- Org. Syn. Coll. Vol. 7, 359

References and Notes

1. Claisen and Lowman, Ber. **20**, 651 (1887).
2. Claisen, ibid. **20**, 655 (1887).
3. Wislicenus, ibid. **28**, 811 (1895).
4. Baeyer, ibid. **15**, 2705 (1882).
5. Michael and Browne, ibid. **19**, 1392 (1886).
6. Buchner and Curtius, ibid. **18**, 2371 (1885).

7. Marguery, Bull. soc. chim. (3) **33**, 549 (1905).
8. Meyer and Tögel, Ann. **347**, 76 (1906).
9. Haller, Bull. soc. chim. (2) **48**, 23 (1887).
10. Claisen, Ann. **291**, 71 (1896); Shriner and Schmidt, J. Am. Chem. Soc. **51**, 3636 (1929).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodioacetoacetic ester

monoethyl ester of malonyl monoacid chloride

sulfuric acid (7664-93-9)

ammonia (7664-41-7)

Benzene (71-43-2)

ethyl acetate (141-78-6)

ether (60-29-7)

ammonium chloride (12125-02-9)

sodium bicarbonate (144-55-8)

magnesium (7439-95-4)

sodium sulfate (7757-82-6)

benzaldehyde (100-52-7)

Acetophenone (98-86-2)

benzoyl chloride (98-88-4)

aluminum chloride (3495-54-3)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

Ethyl chloroacetate (105-39-5)

ethyl benzoate (93-89-0)

Ethyl acetoacetate (141-97-9)

Ethyl oxalate

magnesium sulfate (7487-88-9)

Ethyl benzoylacetate, Acetic acid, benzoyl-, ethyl ester (94-02-0)

Ethyl benzoylacetoacetate (569-37-9)

ethyl carbonate

ethyl phenylpropiolate (2216-94-6)

α-bromocinnamic acid

ethyl diazoacetate (623-73-4)

benzoylacetimino ethyl ether hydrochloride

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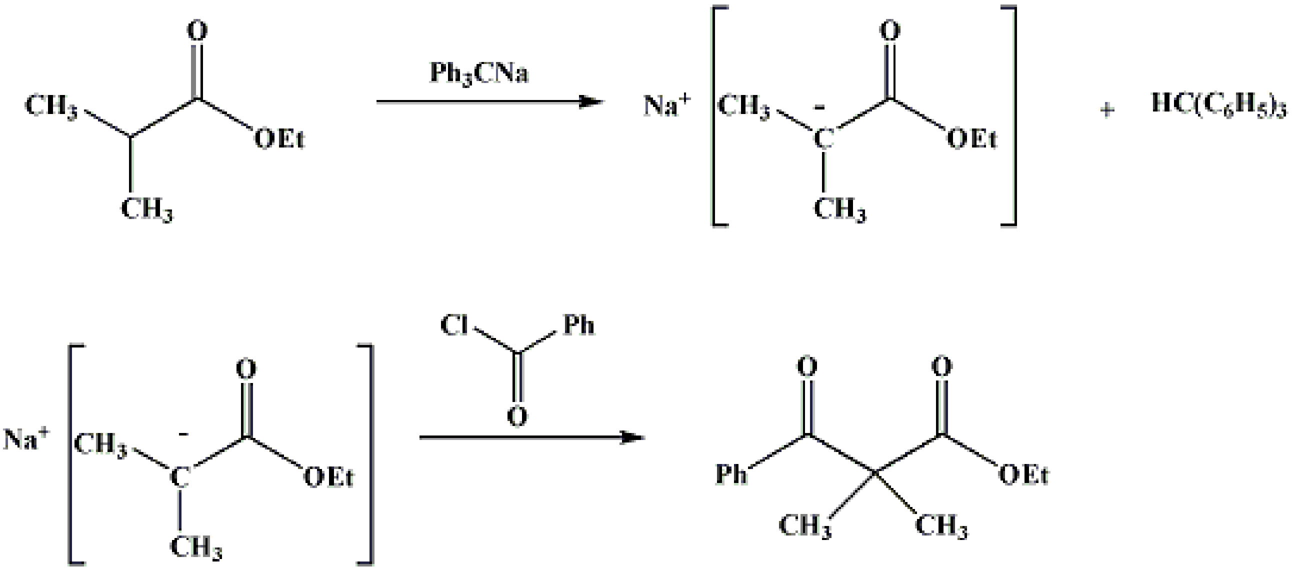
ETHYL BENZOYLDIMETHYLACETATE

[Isobutyric acid, α-benzoyl-, ethyl ester]



Submitted by C. R. Hauser and W. B. Renfrow, Jr.
Checked by Lee Irvin Smith and E. C. Ballard.

1. Procedure

To a freshly prepared solution of 0.187 mole of triphenylmethylsodium (p. 607), contained in the flask into which it was transferred after preparation, is added 21.7 g. (25 cc., 0.187 mole) of pure ethyl isobutyrate (Note 1). The mixture is shaken, and, after it has stood at room temperature for ten minutes, a solution of 26 g. (21.5 cc., 0.186 mole) of pure benzoyl chloride in 50 cc. of dry ether is added, with shaking. The mixture becomes warm, and a white precipitate of sodium chloride separates immediately. After standing at room temperature for several hours the mixture is heated on a water bath and ether is distilled until the volume is reduced to 300–400 cc. A solution of 5 cc. of acetic acid in 300 cc. of water is added, and the mixture is shaken in a separatory funnel until two homogeneous layers separate on standing. The aqueous layer is drawn off and discarded; the ethereal layer is shaken with 10 per cent sodium carbonate solution and dried over calcium chloride or Drierite. The solution is filtered from the drying agent and distilled on a water bath until most of the ether is removed. The residue is cooled in a refrigerator, and the triphenylmethane which crystallizes is filtered with suction and washed with several small portions of dry ether. The filtrate, after removal of ether, is distilled under reduced pressure and all material boiling up to 180° at 15 mm. collected. The distillate is redistilled and the fraction boiling up to 160° at 15 mm. is subjected to a final redistillation. There is obtained 20.5–22.5 g. (50–55 per cent of the theoretical amount) of ethyl benzoyldimethylacetate, b.p. 146–148° at 15 mm. or 133–135° at 9 mm (Note 2) and (Note 3).

2. Notes

1. It is essential to use pure reagents. Commercial ethyl isobutyrate may be purified satisfactorily by washing with 10 per cent sodium carbonate solution, drying over Drierite for several days, and fractionating through an effective column; material boiling over a one-degree range (110–111°) is recommended for this preparation. Benzoyl chloride was purified by

distillation under reduced pressure, and a fraction collected over less than a two-degree range was used.

2. If the more concentrated solution of triphenylmethylsodium, prepared as described in Note 3, p. 609, is employed, approximately 120 g. of ethyl benzoyldimethylacetate can be prepared in a single experiment.

The bottle containing an ether solution of 0.85 mole of triphenylmethylsodium is immersed to two-thirds of its depth in an ice bath. When the bottle is thoroughly cold, the stopper is removed while a tube delivering a rapid stream of dry nitrogen is held at the mouth of the bottle. The bottle is quickly fitted with a three-holed rubber stopper carrying a mechanical stirrer (with open shaft), a dropping funnel, and a bent tube which extends into the bottle for a distance of 1 cm. below the neck. A slow stream of dry nitrogen passes through the bent tube; the nitrogen supply is also connected to the top of the dropping funnel. One hundred two grams (0.875 mole) of ethyl isobutyrate is added rapidly to the vigorously stirred contents of the bottle. After five minutes, 123 g. (101 cc., 0.875 mole) of benzoyl chloride is added through the dropping funnel at such a rate that the mixture does not reflux too vigorously (the addition takes about five minutes). Stirring is continued for two or three minutes after the addition is complete. The bottle is then removed from the ice bath, stoppered, shaken, and allowed to stand for half an hour. The reaction mixture is transferred to a 2.5-l. separatory funnel and the mercury drained off. The remaining mixture is extracted with 300 cc. of water, any sludge formed being collected separately. The sludge is extracted with a little ether, the extract being added to the ether layer in the funnel. The ether solution is washed with two 100-cc. portions of 10 per cent sodium carbonate solution, and dried by shaking with 50 g. of anhydrous sodium or magnesium sulfate and by standing with 50 g. of Drierite in a stoppered 2-l. Erlenmeyer flask. The solution is filtered into a 2-l. round-bottomed flask and the ether removed by distillation. The residue is transferred to a 1-l. Claisen flask and distilled in vacuum, using a metal or oil bath and collecting all the material boiling below 175° at 15 mm. The distillate is transferred to a 200-cc. round-bottomed flask fitted with a 6-inch Widmer fractionating column and redistilled from a metal bath. The ethyl benzoyldimethylacetate boils at 146–148°/15 mm. and weighs 115–125 g. (61–67 per cent of the theoretical amount based on the quantity of triphenylmethylsodium used). (Charles R. Hauser and Boyd E. Hudson, Jr., private communication.)

3. The submitters report that ethyl isobutyrylisobutyrate (ethyl α,α,γ,γ-tetramethylacetoacetate) may be prepared in a similar manner, using isobutyryl chloride instead of benzoyl chloride. The yield of this ester, b.p. 94.5–95.5°/18 mm., is about 55 per cent of the theoretical amount. Several other examples of the acylation of esters by this procedure are given by Hudson, Jr., and Hauser.[1]

3. Discussion

Ethyl benzoyldimethylacetate has been prepared by the condensation of ethyl isobutyrate with ethyl benzoate,[2] phenyl benzoate, benzoic anhydride, or benzoyl chloride.[3] The procedure described above[3] is a modification of the method of Scheibler and Stein.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 607

References and Notes

1. Hudson, Jr., and Hauser, J. Am. Chem. Soc. **63**, 3159 (1941).

2. Renfrow, Jr., and Hauser, ibid. **60**, 464 (1938).
3. Hudson, Jr., Dick, and Hauser, ibid. **60**, 1961 (1938).
4. Scheibler and Stein, J. prakt. Chem. (2) **139**, 111 (1934).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Drierite

sodium or magnesium sulfate

calcium chloride (10043-52-4)

acetic acid (64-19-7)

ether (60-29-7)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

nitrogen (7727-37-9)

mercury (7439-97-6)

benzoyl chloride (98-88-4)

Benzoic anhydride (93-97-0)

ethyl benzoate (93-89-0)

Triphenylmethane (519-73-3)

Ethyl benzoyldimethylacetate (25491-42-3)

Isobutyric acid, α-benzoyl-, ethyl ester

Triphenylmethylsodium (4303-71-3)

ethyl isobutyrate (97-62-1)

Ethyl isobutyrylisobutyrate

isobutyryl chloride (79-30-1)

phenyl benzoate (93-99-2)

ethyl α,α,γ,γ-tetramethylacetoacetate

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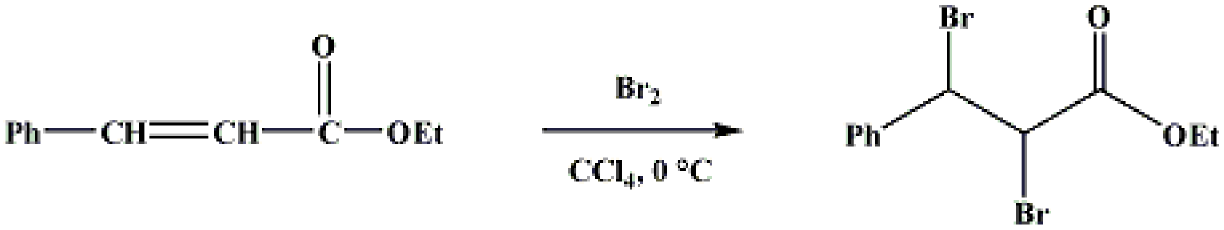
ETHYL α,β-DIBROMO-β-PHENYLPROPIONATE

[Hydrocinnamic acid, α,β-dibromo-, ethyl ester]



Submitted by T. W. Abbott and Darrell Althousen.
Checked by Henry Gilman and G. F. Wright.

1. Procedure

In a 1-l. round-bottomed flask, provided with a two-holed stopper fitted with a dropping funnel and air-vent, is placed 176.2 g. (1 mole) of ethyl cinnamate (Org. Syn. Coll. Vol. I, **1941**, 252) dissolved in 100 cc. of carbon tetrachloride (Note 1). The flask is placed in ice, and 159.8 g. (51.2 cc., 1 mole) of bromine is added in small quantities with frequent stirring (Note 2).

After standing for one hour, the solution is poured into a large dish and the carbon tetrachloride and unused bromine allowed to evaporate spontaneously (Note 3). The dibromo ester separates in large crystals which form a solid cake in the bottom of the dish (Note 4). This cake is broken up and spread in a thin layer on a large Büchner funnel and subjected to suction until all traces of bromine have disappeared. The white crystals are then dried by pressing between large filter papers. The yield of crude dibromo ester is 280–285 g. (83–85 per cent of the theoretical amount). It melts at 65–71°.

If pure ester is desired, it may be obtained by recrystallizing from petroleum ether (b.p. 70–90°); the yield is 80–85 g. of ester melting at 74–75° from 100 g. of crude product.

2. Notes

1. Carbon tetrachloride is used instead of ether, which produces a very disagreeable lachrymator.
2. The bromine disappears rapidly at first, but more slowly at the end of the reaction. No hydrogen bromide is evolved. The time of addition is about twenty to twenty-five minutes.
3. This process is rather slow; it may be accelerated by inverting over the dish a large funnel which is connected to a suction pump. In this manner the crystalline cake separates in about two hours.
4. If the reaction is carried out carefully, practically no mother liquor is left.

However, if such liquor should remain it will yield, on evaporation, crystals which are impure and must be recrystallized before use.

3. Discussion

Ethyl α,β-dibromo-β-phenylpropionate is prepared by adding bromine to ethyl cinnamate.[1]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 515
- Org. Syn. Coll. Vol. 7, 172

References and Notes

1. Anschütz and Kinnicutt, Ber. **11**, 1220 (1878); Aronstein and Hollemann, ibid. **22**, 1181 (1889); Leighton, Am. Chem. J. **20**, 136 (1898); Sudborough and Thompson, J. Chem. Soc. **83**, 671 (1903).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

ether (60-29-7)

hydrogen bromide (10035-10-6)

bromine (7726-95-6)

carbon tetrachloride (56-23-5)

Ethyl cinnamate (103-36-6)

Ethyl α,β-dibromo-β-phenylpropionate, Hydrocinnamic acid, α,β-dibromo-, ethyl ester (5464-70-0)

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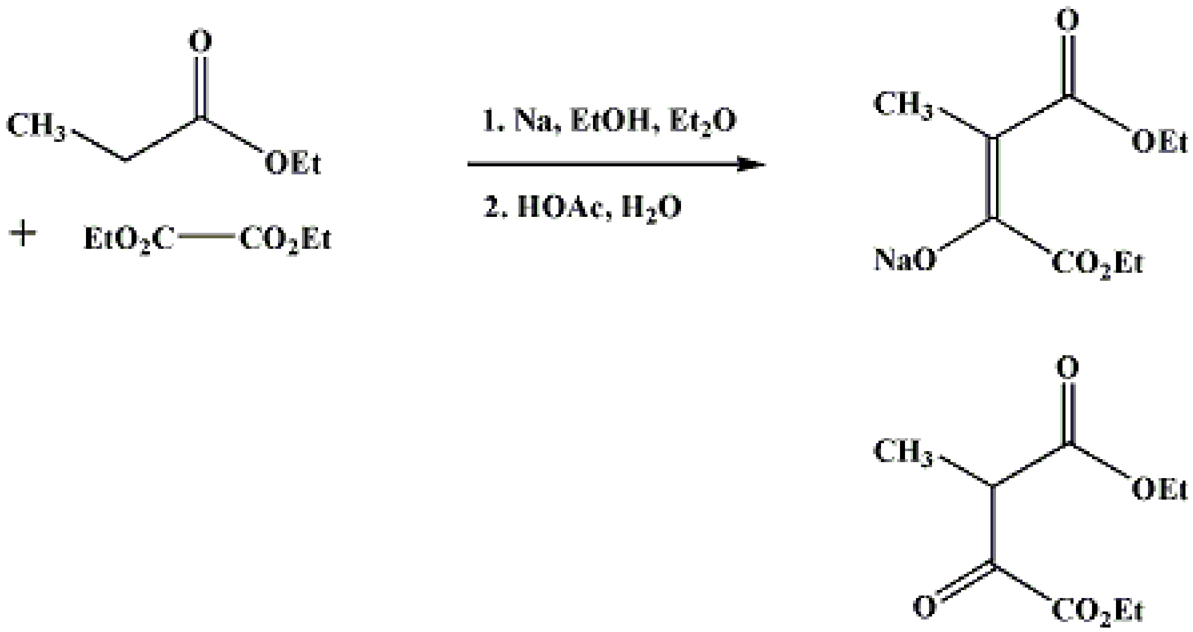
ETHYL ETHOXALYLPROPIONATE

[Oxalacetic acid, methyl-, diethyl ester]



Submitted by Richard F. B. Cox and S. M. McElvain.
Checked by Reynold C. Fuson and William E. Ross.

1. Procedure

Sixty-nine grams (3 gram atoms) of sodium is powdered under xylene in a 3-l. three-necked flask. The mixture is cooled, the xylene is decanted, and the sodium is washed twice with small portions of dry ether. One liter of absolute ether is then added to the powdered sodium. The flask is fitted with a mercury-sealed stirrer, an efficient reflux condenser, and a dropping funnel, the condenser and the funnel being protected from moisture with calcium chloride tubes. One hundred and thirty-eight grams (175 cc., 3 moles) of absolute ethyl alcohol is added drop by drop through the funnel (Note 1). After the alcohol has been added and there is no unchanged sodium (as evidenced by cessation of boiling) the flask is immersed in an ice-water bath, and a mixture of 306 g. (3 moles) of ethyl propionate and 438 g. (3 moles) of ethyl oxalate (Org. Syn. Coll. Vol. I, **1941**, 261) is added slowly through the dropping funnel (Note 2).

After the ester mixture has been added, the stirrer is removed and the condenser set for downward distillation. The ether and the alcohol formed in the reaction are removed by heating on a water bath (Note 3). The residue, which usually solidifies upon cooling, is treated with 600 cc. of cold, 33 per cent acetic acid solution. The mixture is allowed to stand for several hours with occasional shaking in order to decompose the sodium derivative completely, and the product is extracted with four 500-cc. portions of ether. The ether solution is washed with 1 l. of water, with two 500-cc. portions of

10 per cent sodium bicarbonate solution, and finally with 1 l. of water. The ether is then removed by distillation, using a steam bath. The residue is fractionated through an efficient column (Note 4). The portion boiling at 114–116°/10 mm. is collected. The yield is 363–425 g. (60–70 per cent of the theoretical amount).

2. Notes

1. The addition of the alcohol takes from four to six hours, depending on the efficiency of the condenser and stirrer.
2. The addition of the ester mixture should be slow enough so that the ether does not reflux. This addition takes two to three hours.
3. When most of the alcohol has distilled, a yellow scum forms on the surface of the red, viscous liquid. The distillation is stopped at this point. When the solution is cooled, the sodium derivative crystallizes with considerable expansion in volume.
4. No appreciable decomposition of the ethoxalyl ester into ethyl methylmalonate takes place when the distillation is carried out at 10 mm. To prevent overheating, the use of an oil bath and a heated column is recommended.

3. Discussion

Ethyl ethoxalylpropionate has been prepared by the Claisen condensation of ethyl oxalate with ethyl propionate[1] as above, and by the alkylation of ethyl ethoxalylacetate.[1]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 279

References and Notes

1. Wislicenus and Arnold, Ann. **246**, 329, 336 (1888).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ETHYL ETHOXALYLPROPIONATE

ethyl ethoxalylacetate

ethyl alcohol (64-17-5)

acetic acid (64-19-7)

ether (60-29-7)

sodium bicarbonate (144-55-8)

sodium (13966-32-0)

xylene (106-42-3)

Ethyl oxalate

Oxalacetic acid, methyl-, diethyl ester

ethyl propionate (105-37-3)

Ethyl methylmalonate

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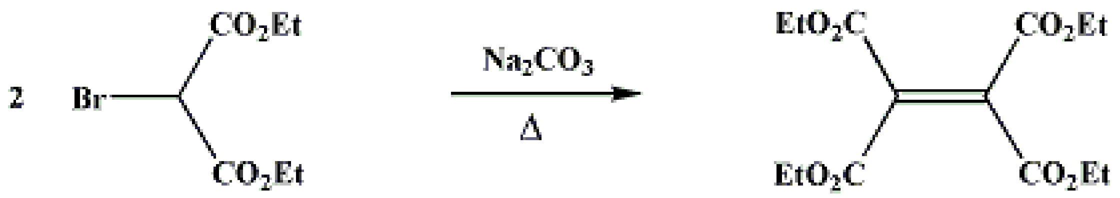
ETHYL ETHYLENETETRACARBOXYLATE

[Ethylenetetracarboxylic acid, tetraethyl ester]



Submitted by B. B. Corson and W. L. Benson.
Checked by C. S. Marvel and H. E. Munro.

1. Procedure

A mixture of 200 g. (1.9 moles) of anhydrous sodium carbonate (Note 1) and 300 g. (1.25 moles) of ethyl bromomalonate (Org. Syn. Coll. Vol. I, **1941**, 245) is heated for three hours in a 1-l. flask (Note 2) immersed in an oil bath at 150–160° (Note 3). After the heating period, 300 cc. of xylene (Note 4) is added while the contents of the flask are still hot (Note 5). The solid is broken up carefully with a rod, and the mixture is transferred to a 2-l. beaker. The reaction flask is then rinsed with a mixture of 100 cc. of xylene and 100 cc. of water. This washing is poured into the 2-l. beaker, and an additional 600 cc. of water is added. The solid readily dissolves upon stirring. The liquid mixture is transferred to a separatory funnel, shaken well, and allowed to settle (Note 6). The lower aqueous layer is discarded (Note 7). The xylene layer is transferred to a 1-l. distilling flask and distilled until the temperature of the liquid itself is 170°. The liquid residue is then transferred to a 500-cc. Claisen flask and distilled under reduced pressure. The fore-run up to 170°/15 mm. is discarded. The product, which is collected at 170–230°/15 mm. (Note 8) and (Note 9), solidifies within about fifteen minutes. The yield is 150–160 g. (75–80 per cent of the theoretical amount).

The crude product is dissolved in 75 cc. of 95 per cent alcohol at a temperature of 40°, which is sufficient to ensure complete solution. The alcoholic solution is cooled to 12° (Note 10) and (Note 11) and filtered. The yield of air-dried, colorless product melting at 52.5–53.5° is 95–110 g. (47–55 per cent of the theoretical amount). By evaporation of the alcohol, distillation of the residue under reduced pressure, and recrystallization of the solidified distillate, the yield may be increased to 110–115 g. (55–57 per cent of the theoretical amount).

2. Notes

1. The sodium carbonate should be fine enough to pass through a 100-mesh sieve.
2. The mixture is heated in an open flask. Owing to the high boiling points of ethyl bromomalonate and ethyl ethylenetetracarboxylate, there is but little loss

by volatilization. The yield is lowered by the use of a condenser, presumably because the water formed by the reaction is kept in the reaction mixture with resultant hydrolysis of one or both of the esters.
3. The flask is placed in the cold bath. The three hours are counted from the time the temperature of the bath reaches 150°.
4. Toluene or benzene can be substituted for xylene, but xylene is preferable because of its higher boiling point.
5. If the mixture is allowed to cool, it solidifies and is difficult to remove.
6. A good separation is obtained in ten minutes.
7. Experiment has shown that the amount of product in the aqueous layer is negligible.
8. Ethyl ethylenetetracarboxylate boils at 197°/8 mm.; 203°/13 mm.; 210°/22 mm.; 221°/33 mm.; 234°/48 mm.
9. There is very little residue left in the flask. Distillation should be stopped as soon as dark yellow drops of distillate begin to come over.
10. The crystallization mixture is a thick slush with low heat conductivity, hence a rather long cooling period is necessary to lower the temperature to 12°. A thermometer should be used because it is important that the mixture be cooled to 12°, since the solubility curve begins to rise above 12°. There is no advantage in cooling below 12°.
11. The solubility of ethyl ethylenetetracarboxylate in 100 cc. of 95 per cent ethyl alcohol is as follows:

2.0 g. at 0°	16.0 g. at 30°
2.5 g. at 11°	19.0 g. at 31°
4.0 g. at 16°	28.0 g. at 33°
8.0 g. at 23°	35.0 g. at 34°
9.7 g. at 26°	61.0 g. at 36.5°

3. Discussion

Ethyl ethylenetetracarboxylate has been prepared from monochloro-and monobromomalonic ester through removal of halogen acid with sodium,[1] sodium ethoxide,[2] potassium acetate,[3] potassium carbonate,[4] sodium urethane,[5] sodium formanilide and sodium acetanilide.[6] It has also been prepared by treating the disodium derivative of ethyl ethane-1,1,2,2-tetracarboxylate with bromine,[7] or iodine;[8] by treating dibromomalonic ester with sodium,[9] or sodium ethoxide,[10] or sodium malonic ester followed by potash;[11] and by treating the disodium derivative of malonic ester with iodine.[12] It is reported that the use of moist benzene as the medium in the reaction between bromomalonic ester and potassium carbonate increases the yield of ethylenetetracarboxylic ester to 80 per cent.[13]

References and Notes

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2. Conrad and Guthzeit, Ann. **214**, 76 (1882).
3. Conrad and Brückner, Ber. **24**, 2998 (1891).
4. Blank and Samson, ibid. **32**, 860 (1899).
5. Diels and Heintzel, ibid. **38**, 303 (1905).
6. Paal and Otten, ibid. **23**, 2591 (1890).
7. Kötz and Stalmann, J. prakt. Chem. (2) **68**, 163 (1903).
8. Bischoff and Hausdörfer, Ann. **239**, 130 (1887).
9. Conrad and Brückner, Ber. **24**, 3004 (1891).
10. Curtiss, Am. Chem. J. **19**, 699 (1897).
11. Adickes, J. prakt. Chem. (2) **145**, 236 (1936).
12. Bischoff and Rach, Ber. **17**, 2781 (1884).
13. Malachowski and Sienkiewiczowa, ibid. **68**, 33 (1935).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium malonic ester

potash

monochloro-and monobromomalonic ester

sodium urethane

disodium derivative of ethyl ethane-1,1,2,2-tetracarboxylate

dibromomalonic ester

disodium derivative of malonic ester

ethylenetetracarboxylic ester

ethyl alcohol, alcohol (64-17-5)

potassium carbonate (584-08-7)

Benzene (71-43-2)

sodium carbonate (497-19-8)

bromine (7726-95-6)

iodine (7553-56-2)

toluene (108-88-3)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

xylene (106-42-3)

Ethyl bromomalonate

potassium acetate (127-08-2)

Ethyl ethylenetetracarboxylate

Ethylenetetracarboxylic acid, tetraethyl ester

sodium formanilide

sodium acetanilide

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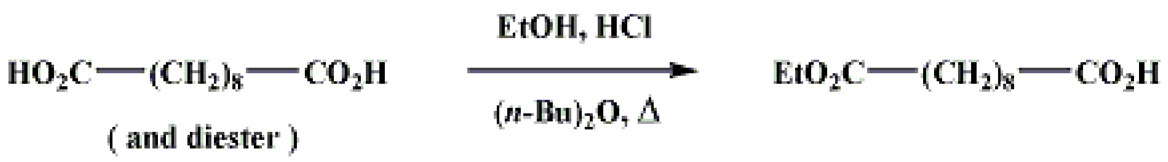
Organic Syntheses, *CV 2*, *276*

ETHYL HYDROGEN SEBACATE

[Sebacic acid, ethyl acid ester]



Submitted by Sherlock Swann, Jr, René Oehler, and R. J. Buswell.
Checked by Lee Irvin Smith and J. W. Clegg.

1. Procedure

In a 1-l. modified Claisen flask (Note 1), the side arm of which is corked, is placed a mixture of 202 g. (1 mole) of sebacic acid, 150 g. (0.58 mole) of diethyl sebacate (Note 2), 50 cc. of di-*n*-butyl ether (Note 3), and 30 g. (25 cc.) of concentrated hydrochloric acid (sp. gr. 1.19). A reflux condenser is connected to the top of the distilling flask.

The flask is heated in a Wood's metal bath at 160–170° until the mixture is completely homogeneous. The temperature of the bath is then lowered to 120–130°, and 60 cc. (1 mole) of 95 per cent ethyl alcohol is added to the solution through the condenser. The mixture is allowed to reflux for two hours. At the end of this period an additional 20-cc. portion of ethyl alcohol is poured into the solution and refluxing is continued for two hours longer.

The Wood's metal bath is allowed to cool to about 75° and the reaction mixture is subjected to distillation under reduced pressure, using a water pump (Note 4). The temperature of the bath is increased slowly and distillation is continued, with a water pump, until the bath reaches a temperature of about 125°. The bath is again cooled to 75–80° and the distillation is continued at lower pressure, using an oil pump.

The first fractions consist of a little alcohol, water, and *n*-butyl ether (Note 5). The next fraction is ethyl sebacate, b.p. 156–158° at 6 mm. (Note 6). Ethyl hydrogen sebacate is collected at 183–187° at 6 mm. The product melts at 34–36° and weighs 114–124 g. (50–54 per cent of the calculated amount, based on the sebacic acid used). Refractionation of the fore-run (b.p. 175–183°/6 mm.) and after-run (b.p. 187–195°/6 mm.) gives an additional 24–26 g. of pure monoester. The total yield is 138–150 g. (60–65 per cent of the theoretical amount) (Note 7) and (Note 8).

2. Notes

1. The column of the flask should be at least 35 cm. in length and well insulated. Wrapping the column with 10-mm. asbestos rope is satisfactory.

2. The addition of diester at the beginning of the reaction decreases its formation from the reactants so that the monoester becomes the main product.
Ethyl sebacate is prepared conveniently by refluxing 130 g. (0.65 mole) of sebacic acid with 250 g. of ethyl alcohol and 25 cc. of concentrated sulfuric acid. The yield is about 90 per cent, and the product boils at 156–158° at 6 mm. See, also, Note 8, p. 265.

3. *n*-Butyl ether is used in preference to other possible compounds because it permits the formation of a homogeneous reaction mixture.

4. At the beginning of the distillation the liquid in the flask foams excessively. It is advisable, therefore, to reduce the pressure gradually and not to use low pressures until the foaming subsides.

5. The *n*-butyl ether may be recovered in pure condition by a simple distillation after the water has been separated from it.

6. After the ethyl sebacate has distilled, it is well to drain the cooling water from the condenser in order to prevent the monoester from solidifying before reaching the receiver. The recovered ethyl sebacate weighs 150–175 g. and may be used directly in a subsequent preparation.

7. In subsequent runs the distillation residue is allowed to remain in the flask. In this way the yield is increased to 70–77 per cent for runs of one and two moles.

8. The submitters report that ethyl hydrogen adipate, b.p. 155–157°/7 mm., has been prepared in 71–75 per cent yields on a one-mole scale by the same procedure.

3. Discussion

Ethyl hydrogen sebacate has been prepared by the direct esterification of sebacic acid with ethyl alcohol,[1] by the half-saponification of ethyl sebacate,[2] and by heating equimolecular quantities of sebacic acid and diethyl sebacate for several hours.[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 154
- Org. Syn. Coll. Vol. 3, 401
- Org. Syn. Coll. Vol. 3, 613
- Org. Syn. Coll. Vol. 4, 635
- Org. Syn. Coll. Vol. 5, 463

References and Notes

1. Neison, J. Chem. Soc. **29**, 319 (1876).
2. Walker, ibid. **61**, 713 (1892).
3. Fourneau and Sabetay, Bull. soc. chim. (4) **43**, 859 (1928); (4) **45**, 834 (1929).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Sebacic acid, ethyl acid ester

ethyl alcohol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

Ethyl hydrogen adipate (626-86-8)

di-n-butyl ether, n-butyl ether (142-96-1)

Ethyl sebacate, Ethyl hydrogen sebacate (693-55-0)

sebacic acid (111-20-6)

diethyl sebacate (110-40-7)

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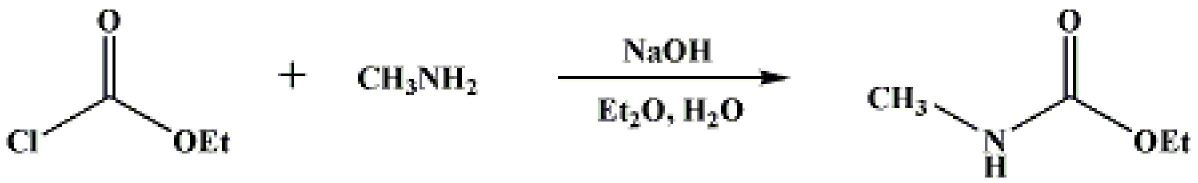
ETHYL N-METHYLCARBAMATE

[Carbamic acid, methyl-, ethyl ester]



Submitted by W. W. Hartman and M. R. Brethen.
Checked by J. B. Conant and C. F. Bailey.

1. Procedure

In a 2-l. flask, provided with a mechanical stirrer and cooled by an ice-salt mixture, are placed 300 cc. of ether and 186 g. (2 moles) of a 33 per cent aqueous methylamine solution. When the stirred mixture has cooled to 5°, 217 g. (2 moles) of ethyl chloroformate (Note 1) is added without allowing the temperature to rise above 5°. When almost half of the chloroformate has been added a cold solution of 80 g. (2 moles) of pure sodium hydroxide in 120 cc. of water is added gradually along with the rest of the chloroformate at such a rate that the last portions of the two solutions are added simultaneously. Constant mechanical stirring throughout the addition is essential (Note 2). After standing for fifteen minutes, the ether layer is separated and the aqueous solution is extracted with 100 cc. of ether. The combined ether layers are rapidly dried by shaking for a short time with about 8 g. of potassium carbonate in two portions. The ether is then distilled and the residue distilled under reduced pressure, the distillate being collected at 55–60°/12 mm. The yield of colorless oil is 182–185 g. (88–90 per cent of the theoretical amount).

2. Notes

1. Technical ethyl chloroformate (chlorocarbonate) is manufactured by the U. S. Industrial Chemicals Company.
2. The rate of addition is determined by the efficiency with which the heat is removed from the reaction mixture. Five hours was required, using an ice-salt mixture outside.

3. Discussion

Ethyl N-methylcarbamate has been prepared by adding aqueous methylamine to ethyl chloroformate;[1] and from methylcarbamyl chloride and ethyl alcohol.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 464
- Org. Syn. Coll. Vol. 4, 780

References and Notes

1. Schreiner, J. prakt. Chem. (2) **21**, 124 (1880); Pechmann, Ber. **28**, 855 (1895); Eistert, Angew. Chem. **54**, 124 (1941).
2. Gattermann, Ann. **244**, 35 (1888).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethyl alcohol (64-17-5)

potassium carbonate (584-08-7)

ether (60-29-7)

sodium hydroxide (1310-73-2)

methylamine (74-89-5)

ethyl chloroformate (541-41-3)

Ethyl N-methylcarbamate, Carbamic acid, methyl-, ethyl ester (105-40-8)

methylcarbamyl chloride

chlorocarbonate

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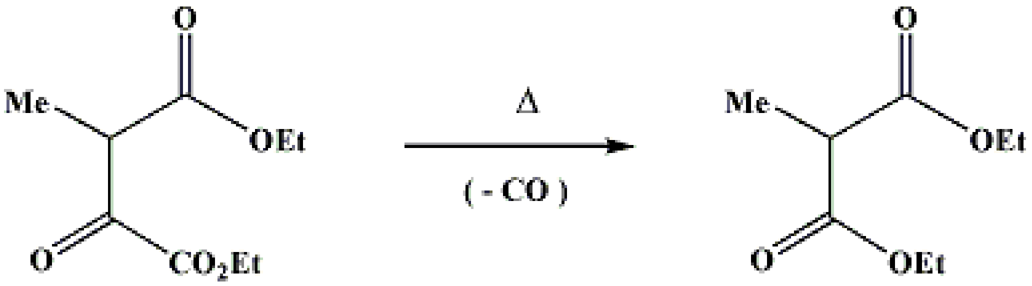
ETHYL METHYLMALONATE

[Malonic acid, methyl-, diethyl ester]

[(*A*) (*From Ethoxalylpropionic Ester*)]

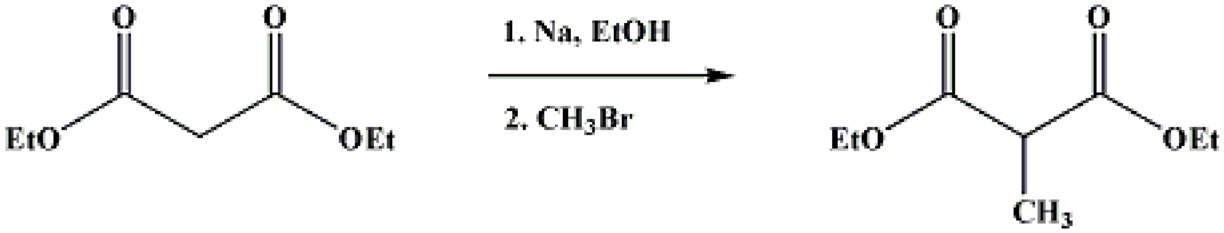


Submitted by Richard F. B. Cox and S. M. McElvain.
Checked by Reynold C. Fuson and William E. Ross.

1. Procedure

Three hundred forty-five grams (1.7 moles) of ethyl ethoxalylpropionate, b.p. 114–116°/10 mm. (p. 272), is placed in a round-bottomed flask of suitable size carrying a reflux condenser, and a thermometer is suspended from the top of the condenser into the liquid. The ethyl ethoxalylpropionate is then heated until a vigorous evolution of carbon monoxide begins (130–150°). The temperature of the liquid is gradually raised as the gas evolution diminishes, and finally the liquid is refluxed until no more gas comes off. The ethyl methylmalonate is then distilled. It boils at 194–196°/745 mm., and the yield is 288 g. (97 per cent of the theoretical amount).

[(*B*) (*From Malonic Ester*)]



Submitted by Nathan Weiner
Checked by Reynold C. Fuson and E. A. Cleveland.

1. Procedure

Forty-six grams (2 gram atoms) of sodium, cut into small pieces, is added to 1 l. of absolute ethyl alcohol (Note 1) in a 2-l. three-necked flask equipped with a mechanical stirrer and a reflux condenser with a calcium chloride tube. When all the sodium is in

solution, 320 g. (2 moles) of ethyl malonate (Note 2) is added. Then 200 g. (2.1 moles) of methyl bromide (Note 3) is bubbled into the stirred solution through a tube (at least 4 mm. in diameter) in the third neck of the flask which dips to the bottom of the solution.

The addition of the methyl bromide consumes about four hours. The reaction proceeds smoothly and with evolution of heat, occasionally reaching the boiling point of the mixture. During the course of the reaction sodium bromide separates. When the addition of methyl bromide is complete, the solution is pale orange and faintly alkaline. It is boiled for an additional half-hour then neutralized with glacial acetic acid and cooled. The sodium bromide is filtered with suction and washed on the funnel with a little cold alcohol. The major part of the alcohol is then removed by distillation at atmospheric pressure (Note 4). The sodium bromide is dissolved in 600–700 cc. of water containing 10 cc. of concentrated hydrochloric acid. The resulting solution (Note 5) is added to the residue from the distillation and the mixture shaken well. The aqueous lower layer is separated from the ester and extracted twice with ether. The ester and ether extracts are combined and dried by shaking quickly with calcium chloride and filtering immediately. The ether is removed, and the ester is shaken for exactly one minute with a cold solution of 10 g. of sodium hydroxide in 30 cc. of water (Note 6). The alkali is drawn off; the ester is washed with dilute acid and dried as before with calcium chloride. It is then distilled *in vacuo*, and the fraction boiling at 96°/16 mm. is taken. There is almost no fore-run or residue. The yield is 275–290 g. (79–83 per cent of the theoretical amount).

2. Notes

1. The quality of the alcohol is very important, traces of water depressing the yield considerably. Absolute alcohol, as ordinarily supplied, is best dried by distillation from a 2–3 per cent solution of sodium, a fore-run and the last 25 per cent being rejected.
2. Even the better grades of malonic ester have been found to contain sufficient impurities to decrease the yield. However, one distillation, at reduced pressure, of even the technical grade of malonic ester makes it sufficiently pure for this synthesis.
3. Vials of methyl bromide may be conveniently used by cooling in an ice bath, breaking the seal, and attaching to the delivery tube by means of ordinary rubber tubing. The vial is then allowed to come to room temperature, and the evaporation of the liquid keeps it sufficiently cool so that it enters the solution at the desired rate. It is best to dry the gas by passage through a tower of potassium hydroxide pellets.
If methyl bromide is not available, it may be generated as follows: 500 g. of 95 per cent sulfuric acid is added slowly, with shaking, to 400 g. of ordinary methyl alcohol, cooled by an ice bath. Six hundred grams of sodium bromide is suspended in one half of this mixture in a 1-l. round-bottomed flask, fitted with a two-holed stopper holding a dropping funnel and a delivery tube. The

evolution of methyl bromide is started by heating the flask with a water bath at 50°, and the remainder of the methyl alcohol-acid mixture is added slowly from the funnel as the volume of the mixture in the flask decreases. As the rate of evolution of the gas falls off the temperature is slowly raised until no more methyl bromide is generated and the contents of the flask have become completely solid. The flask is shaken from time to time during the generation to mix the components more thoroughly. The evolved gas is dried by passage through a tower of potassium hydroxide pellets.

4. The removal of the alcohol at atmospheric pressure is best carried out by returning the filtrate to the original reaction flask, in which the mechanical stirrer is retained but the reflux condenser is replaced by a goose-neck and a condenser for downward distillation. The solution is stirred as the alcohol is distilled, thus eliminating the violent bumping that would otherwise occur at the separation of sodium bromide from the concentrated solution.

5. The use of the sodium bromide in this way serves the multiple purpose of releasing any ester that may be adsorbed on it, of depressing the solubility of the ester in the water, and of making the water layer sufficiently dense for the ester to float on it.

6. The ester is treated in this manner to remove any unchanged ethyl malonate. Michael[1] has shown that this treatment will completely remove unchanged ethyl malonate while hardly attacking ethyl methylmalonate. No ethyl dimethylmalonate is formed when methyl bromide is used as the methylating agent.

3. Discussion

The most widely used method of preparing ethyl methylmalonate is by the alkylation of ethyl malonate with methyl iodide,[2], [1] methyl bromide,[3] or methyl sulfate.[4] A separation of the desired product from traces of unchanged starting material and from ethyl dimethylmalonate cannot be accomplished by distillation as the boiling points of the three esters lie within three and one-half degrees of one another. Michael[1] found that unchanged malonic ester can be removed completely by taking advantage of the greater ease with which it is hydrolyzed by alkali, while Gane and Ingold[5] obtained a pure product by hydrolysis, crystallization of the methylmalonic acid, and re-esterification. It can be inferred from the results of Salkowski, Jr.,[6] with acetoacetic ester that no disubstitution occurs when methyl bromide is employed as the alkylating agent. Procedure *B* above, which is based on the work of Michael,[1] has been published.[7]

Pure ethyl methylmalonate can also be prepared by the reduction of methylidenemalonic ester with Raney nickel;[8] from ethyl α-bromopropionate through the nitrile,[9] an expensive process because of the cost of the materials and the poor yields; and by the pyrolysis of ethyl ethoxalylpropionate. This last method, which

forms the basis for Procedure *A* above, was first described by Wislicenus.[10]

References and Notes

1. Michael, J. prakt. Chem. (2) **72**, 537 (1905).
2. Züblin, Ber. **12**, 1112 (1879); Conrad and Bischoff, Ann. **204**, 146 (1880); Herzig and Wenzel, Monatsh. **24**, 115 (1903).
3. Lucas and Young, J. Am. Chem. Soc. **51**, 2536 (1929).
4. Nef, Ann. **309**, 188 (1899).
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6. Salkowski, Jr., J. prakt. Chem. (2) **106**, 256 (1923).
7. Fieser and Novello, J. Am. Chem. Soc. **62**, 1856 (1940).
8. Wojcik and Adkins, ibid. **56**, 2424 (1934).
9. Zelinsky, Ber. **21**, 3162 (1888); Steele, J. Am. Chem. Soc. **53**, 286 (1931).
10. Wislicenus, Ber. **27**, 796 (1894).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

acetoacetic ester

ETHYL ETHOXALYLPROPIONATE

Ethoxalylpropionic Ester

Malonic Ester

methylidenemalonic ester

ethyl alcohol, alcohol (64-17-5)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

methyl alcohol (67-56-1)

ether (60-29-7)

sodium hydroxide (1310-73-2)

carbon monoxide (630-08-0)

sodium bromide (7647-15-6)

Raney nickel (7440-02-0)

sodium (13966-32-0)

methyl bromide (74-83-9)

Methyl iodide (74-88-4)

methyl sulfate (75-93-4)

ethyl malonate (1071-46-1)

Ethyl methylmalonate

Malonic acid, methyl-, diethyl ester (609-08-5)

ethyl dimethylmalonate

methylmalonic acid (516-05-2)

ethyl α-bromopropionate (535-11-5)

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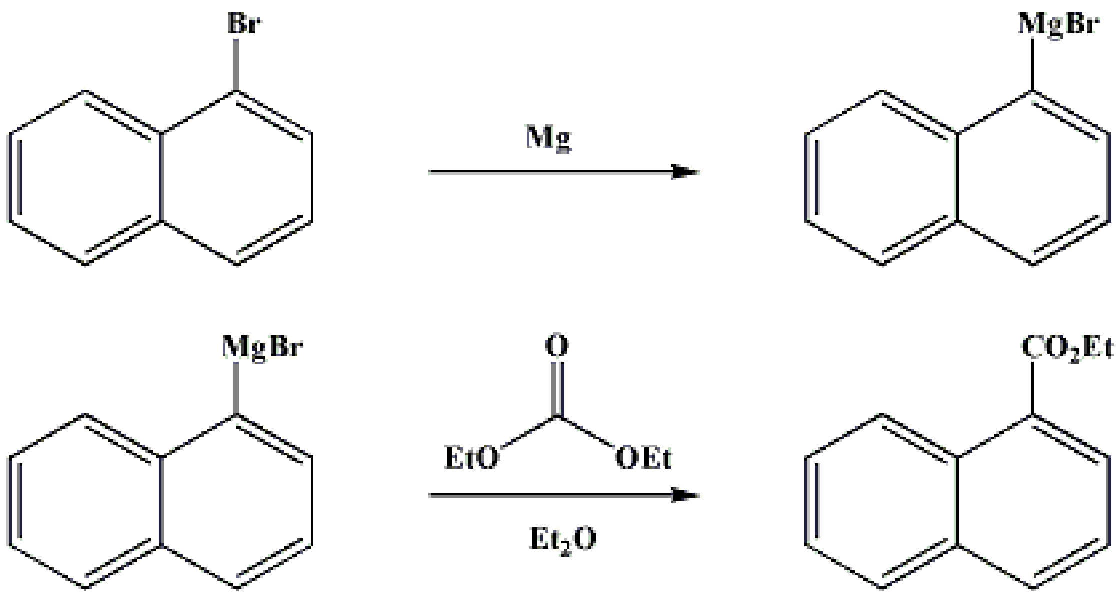
ETHYL α-NAPHTHOATE

[1-Naphthoic acid, ethyl ester]



Submitted by Frank C. Whitmore and D. J. Loder.
Checked by Reynold C. Fuson and Charles F. Woodward.

1. Procedure

A solution of α-naphthylmagnesium bromide is prepared from 24.3 g. (1 gram atom) of magnesium and 207 g. (1 mole) of α-bromonaphthalene by the procedure given on p. 425 (Note 1), but using a large separatory funnel and a 3-l. three-necked flask. The Grignard reagent is transferred to the separatory funnel, and 177 g. (1.5 moles) of ethyl carbonate (Note 2) and 100 cc. of absolute ether are placed in the flask. Stirring is begun, and the α-naphthylmagnesium bromide is added as rapidly as the refluxing of the solution permits. Stirring is continued for a half hour after the addition is finished, and the reaction mixture is then left to stand overnight.

Hydrolysis is effected by pouring the reaction mixture, with shaking, into a 5-l. flask containing 1.2–1.5 kg. of cracked ice. The basic magnesium bromide is dissolved by adding gradually 145 cc. of cold 30 per cent sulfuric acid (30 cc. of concentrated acid and 120 cc. of water). The organic layer is separated and the aqueous layer extracted with 100 cc. of ether. The combined ether solutions are concentrated by distilling the solvent from a steam bath until the volume of the residue is about 400 cc. The residue is washed with two 40-cc. portions of 5 per cent sodium carbonate solution (Note 3) and dried with 20 g. of anhydrous calcium chloride. The calcium chloride is removed by filtration and the ether is distilled from a steam bath. The residue is then transferred to a 500-cc. distilling flask and distilled; the fraction boiling from 287° to 307° is collected as crude ethyl α-naphthoate. The crude product is redistilled from a 250-cc.

modified Claisen flask. The yield of pure ester, boiling at 143–144.5°/3 mm., is 136–147 g. (68–73 per cent of the theoretical amount) (Note 4).

2. Notes

1. If benzene is not added to the reagent, α-naphthylmagnesium bromide precipitates and a separatory funnel of wide bore must be used to prevent clogging during the addition of the reagent to the ester.
2. Two hundred cubic centimeters of commercial ethyl carbonate is washed with 40 cc. of 10 per cent sodium carbonate solution, then with 40 cc. of saturated calcium chloride, and finally with 60 cc. of water. After standing for two hours over 10 g. of calcium chloride, the ester is distilled and the fraction boiling at 125–126° is collected. Ethyl carbonate should not be allowed to stand over anhydrous calcium chloride for more than a day, for the ester combines with the salt.
3. By acidification of the sodium carbonate solution there is obtained 2–3 g. of α-naphthoic acid.
4. This preparation has been run satisfactorily using five times the amounts of materials specified above.

3. Discussion

Ethyl α-naphthoate has been prepared by treating α-naphthoyl chloride with absolute ethyl alcohol,[1] by heating a mixture of α-naphthoic acid and ethyl alcohol in the presence of sulfuric acid,[2] and by the procedure described above.[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 602

References and Notes

1. Hofmann, Ber. **1**, 42 (1868).
2. Perkin, J. Chem. Soc. **69**, 1178 (1896).
3. Loder and Whitmore, J. Am. Chem. Soc. **57**, 2727 (1935).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethyl alcohol (64-17-5)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

Benzene (71-43-2)

ether (60-29-7)

magnesium (7439-95-4)

sodium carbonate (497-19-8)

α-Bromonaphthalene (90-11-9)

ethyl carbonate

Ethyl α-naphthoate, 1-Naphthoic acid, ethyl ester (3007-97-4)

α-naphthylmagnesium bromide

α-Naphthoic acid (86-55-5)

α-naphthoyl chloride (879-18-5)

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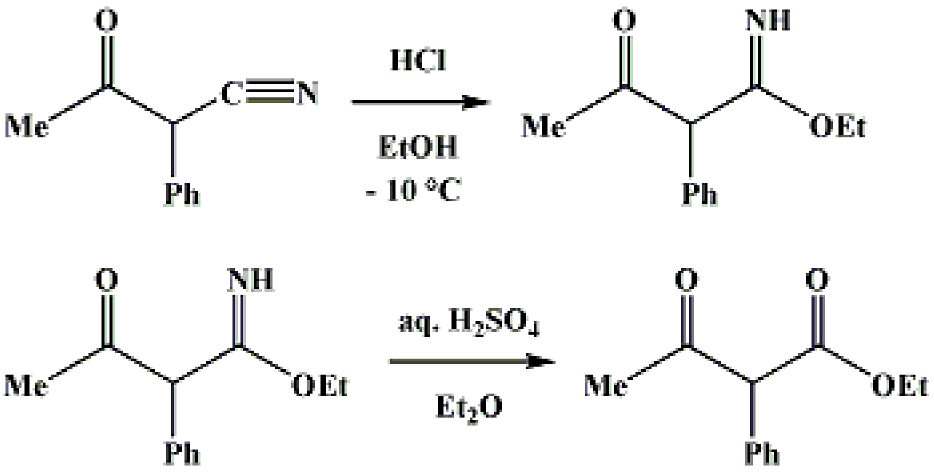
ETHYL α-PHENYLACETOACETATE

[α-Toluic acid, α-acetyl-, ethyl ester]



Submitted by R. H. Kimball, George D. Jefferson, and Arthur B. Pike.
Checked by C. R. Noller

1. Procedure

The apparatus consists of a 1-l. three-necked flask with a mercury-sealed mechanical stirrer and a 6-mm. inlet tube reaching to the bottom of the flask. In the third neck is a cork bearing a low-temperature thermometer and a tube containing phosphorus pentoxide on glass wool, and calcium chloride. The inlet tube is connected to three 20-cm. drying towers, two containing phosphorus pentoxide on glass wool, and one containing calcium chloride. To the last tower is connected a 2-l. Florence flask fitted as a wash bottle with a safety tube and containing 1 l. of concentrated sulfuric acid. The Florence flask is connected to the hydrogen chloride generator described in Org. Syn. Coll. Vol. I, **1941**, 293, in which a single charge of 1.5 l. of concentrated sulfuric acid and 800 cc. of hydrochloric acid is sufficient for this preparation. A pressure equalizer should be provided between the generating flask and the funnel.

After the inlet tube is removed from the reaction flask, 400 cc. of absolute alcohol (Note 1) and 161 g. (1 mole) of dry α-phenylacetoacetonitrile (m.p. 88.5–89.5°) (p. 487) are added. The neck is temporarily closed by a cork, and the nitrile is dissolved by warming with stirring. The flask is then surrounded by a freezing mixture, and the solution vigorously stirred, so that any nitrile which crystallizes will be finely divided. When the temperature reaches –10°, the inlet tube is inserted and a stream of dry hydrogen chloride passed through, with moderate stirring, at such a rate that the bubbles rising from the 6-mm. tubing in the sulfuric acid wash bottle can just be counted. This is continued for five to eight hours until the mixture is saturated (Note 2). The ice bath is then removed, stirring continued until all the solid has dissolved (about one hour), and the flask allowed to stand overnight (Note 3).

Most of the excess hydrogen chloride is removed by adding porous tile and evacuating the flask with a water pump for a half hour, while it is surrounded by a water bath maintained at about 40°. Two hundred grams of sodium carbonate is dissolved in 1.2 l. of water in a 5-l. flask, and 2 l. of cracked ice added. Into this solution the reaction mixture is poured in a thin stream with vigorous shaking, and the solution is extracted at once with three 500-cc. portions of ether. The ether extracts are washed countercurrently with four 250-cc. portions of ice-cold 5 per cent sodium chloride solution to remove the alcohol and then combined in a 3-l. flask placed in an ice bath.

A solution of 100 g. of c.p. concentrated sulfuric acid in 700 cc. of water is prepared in a 5-l. flask, 1.5 l. of cracked ice added, and the mixture shaken until ice forms on the outside of the flask. After about half of this solution has been poured into the cold ether solution of the imino ether, using a funnel to remove the excess ice, the mixture is shaken for exactly fifteen seconds (Note 4), allowed to settle, and the layers separated. The remaining acid is added to the ether layer in two portions, the mixture each time being shaken for fifteen seconds, and separated. Since the ether solution, although now free of the imino ether, still contains a small amount of ethyl phenylacetoacetate, it is saved to be combined with the main portion later.

The sulfuric acid solution of the imino ether sulfate quickly turns cloudy because of the separation of ethyl α-phenylacetoacetate. To complete the hydrolysis, the mixture is heated on the steam bath for one-half hour at the temperature at which the ether just boils (about 50°) (Note 5). It is then cooled, the ester layer separated, and the acid extracted once with 250 cc. of ether. The ether solution is washed once with 100 cc. of water which is recombined with the acid. The acid solution is replaced on the steam bath and heated for forty-five minutes after the temperature reaches 80–90°. After the solution is cooled and extracted as before, all ether extracts, including the original from which the imino ether was removed, are combined and washed once with 250 cc. of 5 per cent sodium bicarbonate solution, once with 250 cc. of water, and then dried over 20 g. of anhydrous sodium sulfate (Note 6). The sodium sulfate is removed by filtration and washed with ether, the ether removed from the filtrates, and the residue fractionated *in vacuo* from a 250-cc. Claisen flask having a 25-cm. fractionating side arm. The main fraction boils at 139–143°/12 mm., or 130–134°/5 mm., and weighs 103–167 g. (50–81 per cent of the theoretical amount). By fractional distillation of the fore-run, main fraction, and residue, a product boiling over a one- to two-degree range may be obtained with no change in the yield (Note 7).

2. Notes

1. The alcohol was dried once with lime, and once with sodium, according to Note 1, Org. Syn. Coll. Vol. I, **1941**, 251.
2. More rapid saturation lowers the yield appreciably.
3. A fine precipitate, probably ammonium chloride, settles. The most successful runs showed little or none of this precipitate.
4. Any delay at this point results in hydrolysis of some of the imino ether to the

product, which stays in the ether layer.

5. Care should be taken in lifting the flask from the bath, since any mixing may cause the ether to boil out of the flask.

6. Removal of product from time to time during the course of the hydrolysis seems to improve the yield.

7. The liquid ester is an equilibrium mixture, the enol content of which is increased by distillation and falls slowly, on standing, to 30 per cent.[1] The boiling point of 145–147°/11 mm., recorded in the literature, is higher than any noted in the present work.

3. Discussion

Ethyl α-phenylacetoacetate can be prepared by the hydrolysis of α-phenylacetoacetonitrile in absolute alcohol with dry hydrogen chloride.[1] The present method differs in specifying neutralization of the hydrogen chloride with sodium carbonate and hydrolysis of the imino ether in aqueous sulfuric acid, so that the product separates as fast as it forms. This protects the ester from further decomposition, and a considerably increased yield results.

References and Notes

1. Beckh, Ber. **31**, 3160 (1898); Post and Michalek, J. Am. Chem. Soc. **52**, 4358 (1930).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

α-Toluic acid, α-acetyl-, ethyl ester

alcohol (64-17-5)

sulfuric acid (7664-93-9)

hydrogen chloride, hydrochloric acid (7647-01-0)

ether (60-29-7)

ammonium chloride (12125-02-9)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

sodium (13966-32-0)

Ethyl α-phenylacetoacetate (5413-05-8)

α-phenylacetoacetonitrile (4468-48-8)

ethyl phenylacetoacetate

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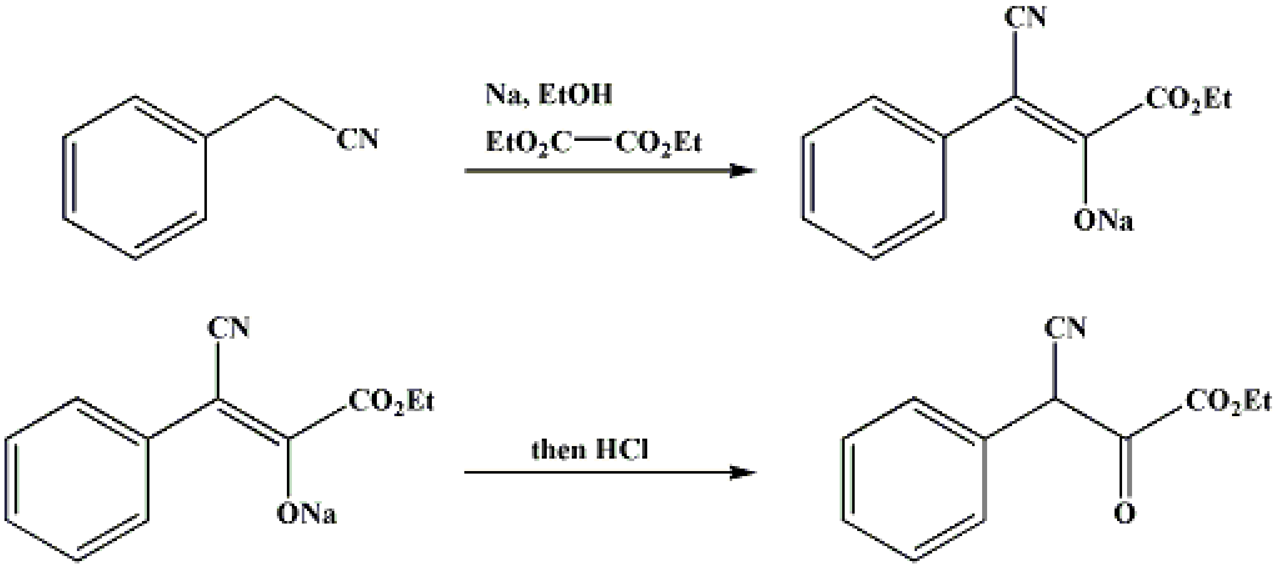
Organic Syntheses, *CV 2, 287*

ETHYL PHENYLCYANOPYRUVATE

[Pyruvic acid, cyanophenyl-, ethyl ester]



Submitted by Roger Adams and H. O. Calvery.
Checked by J. B. Conant and Doris Blumenthal.

1. Procedure

In a 3-l. round-bottomed flask, fitted with a reflux condenser, is placed 650 cc. of absolute alcohol (Note 1), and to it 46 g. (2 gram atoms) of sodium is added as rapidly as possible without loss of material through the condenser. If the sodium does not entirely dissolve, heat is applied. To the hot sodium ethoxide solution 312 g. (2.1 moles) of ethyl oxalate (Org. Syn. Coll. Vol. I, **1941**, 261) is added as rapidly as possible. Then, immediately, 234 g. (2 moles) of benzyl cyanide (Org. Syn. Coll. Vol. I, **1941**, 107) is added, and the reaction mixture is allowed to stand overnight. The solution is transferred to a 3-l. beaker and treated with 250–300 cc. of water (Note 2). It is then warmed to 35° and made strongly acid to litmus with concentrated hydrochloric acid. Mechanical stirring is used during the acidification. On cooling to ordinary temperatures the ester crystallizes. The yield is 360–385 g. of lemon-yellow crystals melting at 126–128°. On recrystallization from 60 per cent alcohol, the ester melts at 130°. The final yield is 300–325 g. (69–75 per cent of the theoretical amount).

2. Notes

1. Absolute alcohol, prepared according to the directions in Org. Syn. Coll. Vol. I, **1941**, 259, is satisfactory.
2. This amount of water dilutes the alcohol so that the ester crystallizes well. If more water is used an oily product separates and then solidifies.

3. Discussion

The only method of preparation mentioned in the literature is that given above.[1]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 531

References and Notes

1. Erlenmeyer, Ann. **271**, 173 (1892).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alcohol (64-17-5)

hydrochloric acid (7647-01-0)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

Benzyl cyanide (140-29-4)

Ethyl oxalate

Ethyl phenylcyanopyruvate, Pyruvic acid, cyanophenyl-, ethyl ester (6362-63-6)

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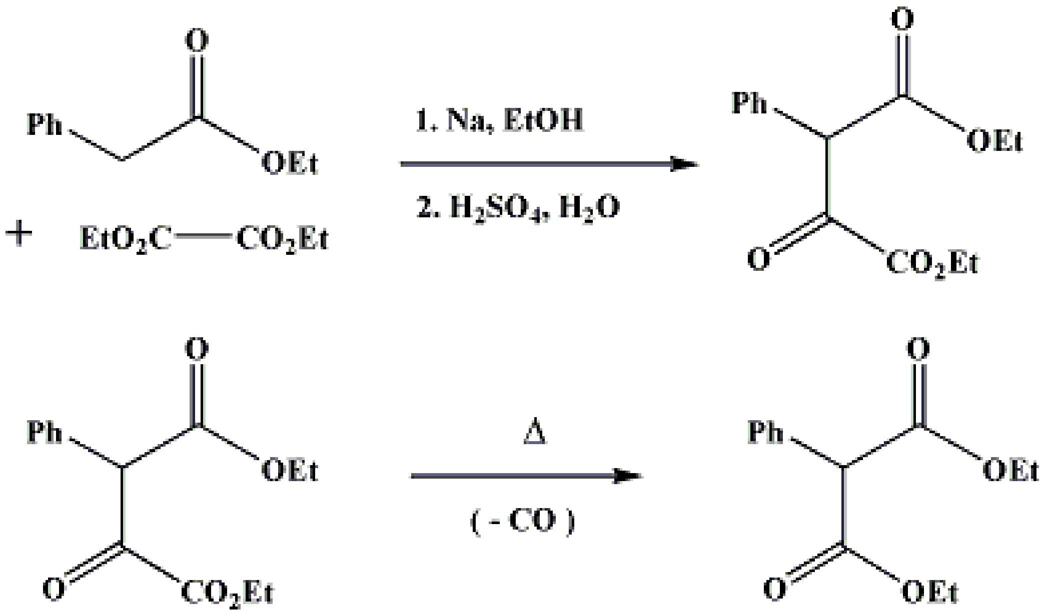
Organic Syntheses, CV 2, 288

ETHYL PHENYLMALONATE

[Malonic acid, phenyl-, diethyl ester]



Submitted by P. A. Levene and G. M. Meyer.
Checked by Louis F. Fieser and C. H. Fisher.

1. Procedure

In a 2-l. three-necked flask, fitted with a mercury-sealed stirrer, reflux condenser, and dropping funnel, is placed 500 cc. of absolute ethyl alcohol (Note 1), and 23 g. (1 gram atom) of cleanly cut sodium is added in portions. When the sodium has dissolved the solution is cooled to 60°, and 146 g. (1 mole) of ethyl oxalate (Note 2) is added in a rapid stream through the funnel with vigorous stirring. This is washed down with a small quantity of absolute alcohol and is followed immediately by the addition of 175 g. (1.06 moles) of ethyl phenylacetate. Stirring is discontinued at once, the reaction flask is lowered from the stirrer, and a 2-l. beaker is made ready. Within four to six minutes after the ethyl phenylacetate has been added crystallization sets in. The contents of the flask are transferred immediately to the beaker at the first sign of crystallization, which is nearly instantaneous.

The nearly solid paste of the sodium derivative is allowed to cool to room temperature and then stirred thoroughly with 800 cc. of dry ether. The solid is collected by suction and washed repeatedly with dry ether. The phenyloxaloacetic ester is liberated from the sodium salt with dilute sulfuric acid (29 cc. of concentrated sulfuric acid in 500 cc. of water). The almost colorless oil is separated, and the aqueous layer is extracted with three 100-cc. portions of ether, which are combined with the oil. The ethereal solution is dried over anhydrous sodium sulfate, and the ether is distilled. The residual oil, contained in a modified Claisen flask having a fractionating side arm, is heated under a

pressure of about 15 mm. in a bath of Wood's metal. The temperature of the bath is brought gradually to 175° and kept there until the evolution of carbon monoxide is complete. During this process the heating is momentarily discontinued in the event of a temporary increase in pressure. At the end of the reaction (five to six hours) the oil which has distilled is returned to the flask, and the ethyl phenylmalonate is distilled at reduced pressure. The fraction boiling at 158–162°/10 mm. weighs 189–201 g. (80–85 per cent of the theoretical amount).

2. Notes

1. A high grade of absolute alcohol is essential. Ordinary "absolute" alcohol may be treated with about 5 per cent of its weight of sodium and distilled directly into the reaction flask.
2. To ensure absolutely dry and neutral reagents the ethyl oxalate (Org. Syn. Coll. Vol. I, **1941**, 261) and ethyl phenylacetate (Org. Syn. Coll. Vol. I, **1941**, 270) were shaken with anhydrous potassium carbonate and distilled carefully under reduced pressure, after a preliminary heating under atmospheric pressure until their boiling points were reached.

3. Discussion

The procedure is based upon the standard method of Wislicenus.[1] Ethyl phenylmalonate has also been obtained from benzyl cyanide and ethyl carbonate.[2] Phenylmalonic acid has been prepared by carbonation of the enolate of phenylacetic acid.[3]

References and Notes

1. Wislicenus, Ber. **27**, 1091 (1894); Ruhemann, J. Chem. Soc. **81**, 1214 (1902); Pickard and Yates, ibid. **95**, 1015 (1909); Forster and Müller, ibid. **97**, 135 (1910); Baker and Ingold, ibid. **1927**, 835; Blum-Bergmann, Ber. **65**, 115 (1932).
2. Nelson and Cretcher, J. Am. Chem. Soc. **50**, 2760 (1928).
3. Ivanoff and Spassoff, Bull. soc. chim. (4) **49**, 20 (1931).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

phenyloxaloacetic ester

ethyl alcohol, alcohol (64-17-5)

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

ether (60-29-7)

carbon monoxide (630-08-0)

sodium sulfate (7757-82-6)

sodium (13966-32-0)

Benzyl cyanide (140-29-4)

Phenylacetic acid (103-82-2)

Ethyl oxalate

Ethyl phenylacetate (101-97-3)

ethyl carbonate

Ethyl phenylmalonate (83-13-6)

Malonic acid, phenyl-, diethyl ester (83-13-6)

Phenylmalonic acid (2613-89-0)

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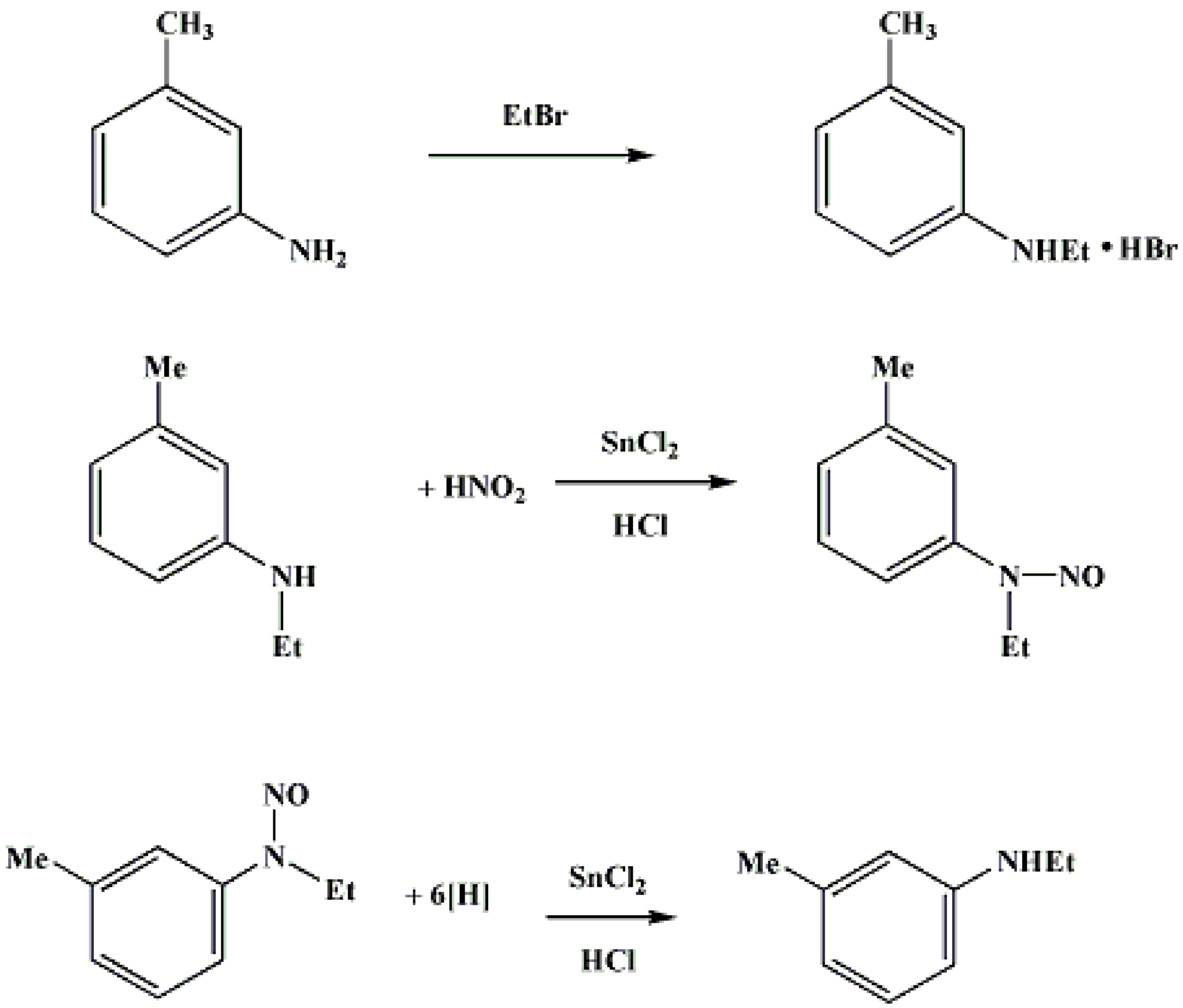
N-ETHYL-*m*TOLUIDINE

[*m*-Toluidine, N-ethyl-]



Submitted by Johannes S. Buck and Clayton W. Ferry.
Checked by John R. Johnson and P. L. Barrick.

1. Procedure

In each of two ordinary 250-cc. (8-oz.) narrow-mouthed bottles are placed 32.1 g. (0.3 mole) of *m*-toluidine and 33 g. (23 cc., 0.3 mole) of ethyl bromide (Note 1). The bottles are sealed with rubber stoppers wired tightly in place and then allowed to stand for twenty-four hours in a 2-l. beaker filled with water at room temperature (Note 2). The white crystalline mass in each bottle is broken up and the amine is liberated by shaking with 150 cc. of 10 per cent sodium hydroxide solution and 50 cc. of ether. The contents of the two flasks are combined, the lower aqueous layer is separated and discarded, and the ether solution of the amine is washed with 150 cc. of water. When the ether is distilled from a steam bath, the crude amine (90–92 g.) is obtained.

This crude amine is added, with cooling, to a solution of 100 cc. of concentrated hydrochloric acid (sp. gr. 1.18) in 350 cc. of water. The solution of the hydrochloride is cooled in an ice bath, and stirred rapidly, while a solution of 41.5 g. (0.6 mole) of sodium nitrite in 150 cc. of water is added slowly. During this addition the temperature should not be allowed to rise above 12°. After all the nitrite has been added, the mixture is allowed to stand for ten minutes and is then extracted with three 100-cc. portions of ether. The ether is evaporated from the extract by warming gently on a steam bath and blowing a stream of air over the surface. Care must be taken to keep the temperature as low as possible during the evaporation (Note 3).

The crude nitroso compound is added gradually, with continuous shaking, to a solution of 407 g. (1.8 moles) of stannous chloride dihydrate in 420 cc. (4.8 moles) of concentrated hydrochloric acid (sp. gr. 1.18) contained in a 3-l. flask. The reaction is exothermic, and cooling is applied, if necessary, to keep the temperature below 60°. After standing for at least an hour (Note 4), the mixture is made strongly alkaline by the cautious addition of a cold solution of 520 g. (13 moles) of sodium hydroxide in about 800 cc. of water. During the addition of the alkali the mixture is agitated vigorously and cooled in running water.

The resulting milky suspension is distilled with steam until about 2 l. of distillate has collected. The distillate is saturated with sodium chloride and extracted with three 100-cc. portions of benzene. The extract is dried thoroughly overnight with flaked potassium hydroxide and decanted from the spent drying agent. After removal of the solvent by distillation, the amine is distilled under reduced pressure. Practically all the material distils at 111–112°/20 mm., or 115.5–117°/26 mm. The pure amine forms a practically colorless, highly refringent liquid and weighs 51–53 g. (63–66 per cent of the theoretical amount) (Note 5). It develops color rapidly on standing.

2. Notes

1. A pure grade of *m*-toluidine was used. A "practical" grade of ethyl bromide gave satisfactory results.
2. If the initial reaction is allowed to proceed too rapidly, considerable pressure may be developed in the bottles. As a safeguard against explosions it is advisable to enclose the bottles in wire mesh shields.
3. The nitroso compound decomposes on warming or on standing. It should not be stored but treated at once with the reducing agent.
4. The mixture may be allowed to stand for a longer period (overnight) without harm. Frequently a granular precipitate of a tin complex of the amine separates.
5. Other N-alkyl-*m*-toluidines may be prepared by practically the same procedure. The submitters report that *n*-propyl, isopropyl, and *n*-butyl derivatives are obtained readily from *m*-toluidine and the appropriate alkyl iodides (rather than the bromides). With these halides the alkylation is effected by placing the sealed bottle in a beaker of water which is warmed gradually to 70–80° and kept in a warm place until the reaction is completed; usually several days are required.

3. Discussion

N-Ethyl-*m*-toluidine has been obtained by passing *m*-toluidine and ethyl alcohol over a catalyst at high temperatures,[1] and by the use of ethyl *p*-toluenesulfonate[2] as an alkylating agent. The present method of purification is a modification of a general procedure for secondary amines developed by Diepolder.[3]

References and Notes

1. Mailhe and de Godon, Compt. rend. **172**, 1417 (1921); Mailhe, Fr. pat. 23,891 (Chem. Zentr. **1922**, IV, 760).
2. Finzi, Ann. chim. applicata **15**, 41 (1925) [C. A. **19**, 2647 (1925)].
3. Diepolder, Ber. **32**, 3514 (1899).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

amine

ethyl alcohol (64-17-5)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

Ethyl bromide (74-96-4)

sodium nitrite (7632-00-0)

potassium hydroxide (1310-58-3)

stannous chloride dihydrate (10025-69-1)

m-toluidine (108-44-1)

ethyl p-toluenesulfonate (80-40-0)

N-ETHYL-mTOLUIDINE, m-Toluidine, N-ethyl-, N-Ethyl-m-toluidine (102-27-2)

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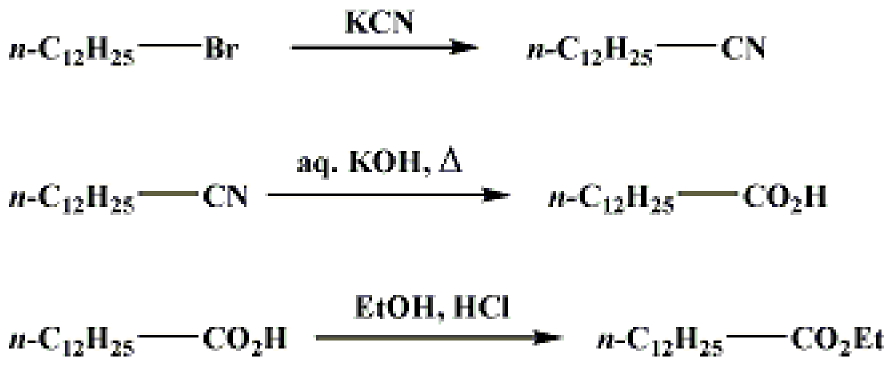
ETHYL *n*-TRIDECYLATE

[*n*-Tridecanoic acid, ethyl ester]



Submitted by John R. Ruhoff
Checked by W. H. Carothers and W. L. McEwen.

1. Procedure

In a 12-l. flask fitted with a reflux condenser and an efficient, liquid-sealed mechanical stirrer (Note 1) are placed 2.5 l. of 95 per cent ethyl alcohol, 872 g. (3.5 moles) of pure *n*-dodecyl bromide (Org. Syn. Coll. Vol. I, **1941**, 29, and p. 246 above), and 278 g. (3.85 moles) of powdered 90 per cent potassium cyanide (Note 2). The mixture is refluxed for fifteen hours, with stirring, in a water bath (Note 3). At the end of this time another 278-g. portion of potassium cyanide is added and the mixture refluxed, with stirring, for fifteen hours longer.

The flask is allowed to cool, and a solution of 670 g. of 90 per cent potassium hydroxide in 1 l. of water is added (Note 4). The solution is refluxed and stirred for thirty hours. The flask is fitted with a head for steam distillation (Note 5), and steam is passed in until foaming prevents further distillation. When the flask has cooled somewhat, the steam inlet is replaced by a separatory funnel with a stem reaching to the bottom of the flask, and 1.5 l. of concentrated hydrochloric acid (sp. gr. 1.18) or the equivalent amount of more dilute acid is added. The flask is shaken occasionally to prevent stratification of the hydrochloric acid. The dropping funnel is then replaced by the steam inlet, and steam is passed through for about one-half hour. At the end of this time the water layer is siphoned off and discarded (Note 6).

The crude acid while still warm and fluid is treated with 815 cc. (14 moles) of 95 per cent ethyl alcohol containing 20–30 g. (3–5 per cent by weight) of anhydrous hydrogen chloride, and the solution is filtered from insoluble impurities. The filtrate is placed in a 3-l. flask fitted with a reflux condenser, 160 g. of anhydrous calcium chloride is added, and the mixture is refluxed for twenty-four hours (Note 7). The lower layer is siphoned off and diluted with twice its volume of water to recover any

dissolved ester. The recovered ester is combined with the main portion, 408 cc. of alcohol containing 3–5 per cent of anhydrous hydrogen chloride and 80 g. of calcium chloride are added, and the mixture is refluxed for another twenty-four hours. The lower layer is siphoned off and the dissolved ester recovered as before. The upper layer is washed twice with an equal volume of warm water (30–40°) and transferred to a 2-l. separatory funnel; the volume of the oil is approximately 1 l. About 500 cc. of warm water and a few drops of phenolphthalein are also placed in the funnel, and very dilute aqueous ammonia (concentrated aqueous ammonia diluted with twenty volumes of water) is added, with shaking, until the resulting emulsion has a distinctly pink color (50–100 cc. is required). Alcohol is added in portions of about 100 cc. until the emulsion is broken and the layers begin to separate quite rapidly; usually two or three additions of alcohol suffice. The lower layer is drawn off and set aside (Note 8). The oil is washed three times with warm water; if necessary, alcohol is added to break the emulsion. The ester is dried with anhydrous calcium chloride, filtered, and distilled under reduced pressure. The yield of ethyl tridecylate, b.p. 163–165°/5 mm. (178–180°/20 mm.; 197–198°/60 mm.) is 615–660 g. (73–78 per cent of the theoretical amount). By refractionating the fore- and after-runs, an additional 50–70 g. of product is obtained; 15–30 g. of ester and acid are recovered from the ammoniacal washings and from the calcium chloride used to dry the main portion. The total yield is 685–710 g. (81–84 per cent of the theoretical amount) (Note 9) and (Note 10).

2. Notes

1. A mercury-sealed stirrer may be used, but a "vaseline seal" is very satisfactory.
2. Potassium cyanide gives better results than sodium cyanide. It is essential that the material be finely powdered.
3. The entire operation should be carried out in a hood. A small wash tub placed on the bench and heated from the side with a Bunsen burner is a convenient water bath.
4. This corresponds to 3.85 moles of potassium hydroxide plus a quantity sufficient so that, after the hydrolysis is completed, the solution will contain 10 per cent of alkali. When less alkali is used the quantity of unhydrolyzed nitrile is greater.
5. The condenser should lead to a 2-l. suction flask the side arm of which is connected directly to the vent of the hood. The alcohol has the odor of hydrocyanic acid and should be discarded.
6. The crude acid may be used for some purposes, but it contains a small quantity of unhydrolyzed nitrile, some material of very disagreeable odor (possibly isocyanide), and usually a small amount of a blue precipitate (an iron-cyanide complex salt). In the preparation of the ester, the precipitate is removed by filtering the alcohol solution of the acid as its presence will interfere with the removal of the free tridecylic acid after esterification.
7. A few pieces of porous plate should be added to prevent bumping.
8. By addition of acid to the washings a small amount (15–30 g.) of ester and acid may be recovered.

9. For larger runs, the procedure is the same and the percentage yields are somewhat higher. Thus, in runs by the author using twice the above quantities, yields of 88–89 per cent were obtained.
10. Pentadecylic acid and ethyl pentadecylate have been prepared by the same procedure from *n*-tetradecyl bromide (p. 247) with approximately the same yield.

3. Discussion

Tridecylic acid has been prepared by the malonic ester synthesis from undecyl iodide,[1] by the oxidation of α-hydroxymyristic acid in acetone with potassium permanganate,[2] by the action of dodecyl bromide on potassium cyanide and subsequent hydrolysis,[3] and from undecyl iodide and ethyl cyanoacetate.[4] The present method is an adaptation of that of Ruzicka, Stoll, and Schinz.[3]

References and Notes

1. Levene, West, Allen, and van der Scheer, J. Biol. Chem. **23**, 73 (1915).
2. Levene and West, ibid. **18**, 465 (1914).
3. Ruzicka, Stoll, and Schinz, Helv. Chim. Acta **11**, 685 (1928).
4. Robinson, J. Chem. Soc. **125**, 230 (1924).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethyl alcohol, alcohol (64-17-5)

calcium chloride (10043-52-4)

hydrogen chloride, hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

potassium permanganate (7722-64-7)

sodium cyanide (143-33-9)

hydrocyanic acid (74-90-8)

Dodecyl bromide, n-DODECYL BROMIDE (143-15-7)

potassium cyanide (151-50-8)

acetone (67-64-1)

potassium hydroxide (1310-58-3)

Ethyl cyanoacetate (105-56-6)

phenolphthalein (77-09-8)

Ethyl tridecylate, Ethyl N-tridecylate, n-Tridecanoic acid, ethyl ester (28267-29-0)

tridecylic acid (638-53-9)

Pentadecylic acid (1002-84-2)

ethyl pentadecylate (41114-00-5)

undecyl iodide (4282-44-4)

α-hydroxymyristic acid (2507-55-3)

n-tetradecyl bromide (112-71-0)

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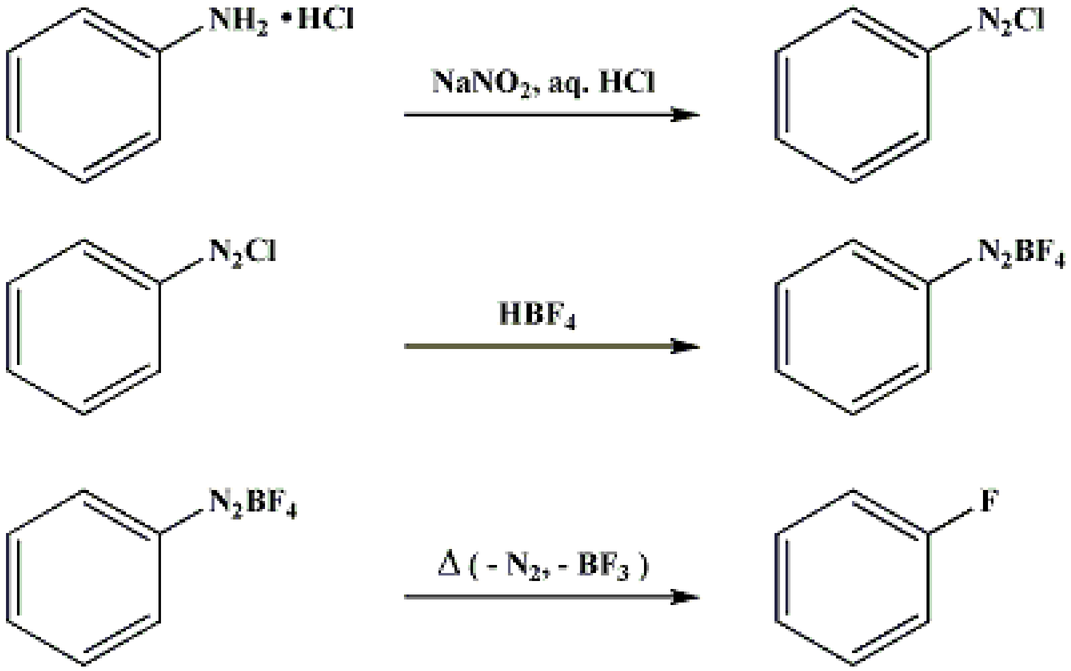
FLUOROBENZENE

[Benzene, fluoro-]



Submitted by D. T. Flood
Checked by W. W. Hartman and J. R. Byers.

1. Procedure

A mixture of 1350 cc. of water and 1650 cc. (20 moles) of concentrated hydrochloric acid (sp. gr. 1.19) is placed in a 30 by 30 cm. glass jar or a 40-l. crock and stirred mechanically (Note 1) while strongly cooled by an ice-salt mixture. Two thousand and seventy-five grams (16 moles) of aniline hydrochloride (Note 2) and a solution of 1.2 kg. (17 moles) of sodium nitrite in 1.5 l. of water are made ready. When the temperature of the acid has reached 5° or below, about one-third of the aniline hydrochloride is added to it, and diazotization is begun by the slow addition of the nitrite solution, the temperature being held below 7°. Additional aniline hydrochloride is added from time to time in such amounts that an excess of crystals is always present. The entire amount may be added by the time that half of the nitrite has been added. The diazotization is stopped when a positive test for free nitrous acid is obtained with potassium iodide starch paper. This should require nearly all the nitrite solution.

Fluoboric acid is made concurrently with the diazotization by the addition, in small amounts, of 1 kg. (16.2 moles) of boric acid (u.s.p. crystals) to 2150 g. (65 moles) of 60 per cent hydrofluoric acid (Note 3). The addition is carried out in two 3-l. flasks coated with wax (Note 4) which are shaken and kept cold by immersion in iced water.

The temperature of the acid should not be allowed to rise above 20–25°.

The ice-cold solution of fluoboric acid is then poured into the diazonium solution, which has been cooled below 0°. The temperature should remain under 10° during the addition, which is carried out fairly rapidly. Powerful stirring is required to agitate the thick magma at this stage (Note 1). After twenty to thirty minutes' stirring, the brown-colored mass is filtered with suction, using two 24-cm. Büchner funnels. The yellowish crystalline solid is washed with about 800 cc. of iced water, with the same volume of methyl alcohol, and with about 900 cc. of commercial ethyl ether. The solid should be sucked as free as possible from liquid after each washing. This washing is important, since it improves the stability of the product (Note 5).

The light-brown, fluffy salt is spread out on absorbent paper overnight in a current of air (a table placed near a hood is effective), and is then placed in a 12-l. flask (Note 6). This is connected by a wide bent tube through a long, wide condenser to three 2-l. Erlenmeyer flasks arranged in series and immersed in ice-salt mixtures. The last flask is fitted with an exit tube leading to a good hood, to carry off the voluminous fumes of boron fluoride, or to an absorption system containing ice and water or soda solution (Note 7). The solid is heated gently at one point near its surface with a small flame until decomposition begins. The flame is then withdrawn and the reaction allowed to continue spontaneously as long as it will. If the reaction becomes too vigorous, it may be necessary to cool the flask by rubbing it with a piece of ice (Note 8). The mixture is heated cautiously from time to time, as may be necessary to keep the reaction going. At the last it should be heated vigorously until no more fumes of boron fluoride are evolved. The last traces of fluorobenzene may be removed from the reaction flask by applying a slight suction to the receiving flask.

The combined distillate is separated from any phenol which may have settled out. It is washed four or five times with 10 per cent sodium hydroxide solution until the washings are almost colorless and then once with water (Note 9). It is dried by shaking with crushed calcium chloride, and then distilled from a 2-l. flask through a short column at a fairly rapid rate. The first runnings may contain a little water and can be further dried. The product is a colorless liquid with an odor resembling that of benzene. The yield of fluorobenzene boiling at 84–85° is 780–870 g. (51–57 per cent of the theoretical amount) (Note 10).

2. Notes

1. A slow-speed, paddle stirrer with several blades is preferable because of the large amount of suspended matter present at several times in the process. A stirrer of wood or metal protected with acid-proof paint is satisfactory, although the paint does not last well. Rubber-covered stirrers may also be used.
2. A technical grade of aniline hydrochloride is used. Technical sodium nitrite, hydrochloric acid, and hydrofluoric acid are also employed.
Aniline (1485 g.) and hydrochloric acid (3 l.) without any added water can be used in place of the aniline hydrochloride, water, and acid. The separation of

aniline hydrochloride in a hard cake on the side of the jar, however, leads to difficulty in cooling and stirring.

3. A corresponding amount of 48 per cent or of 52 per cent hydrofluoric acid may also be used. The quantities given represent an excess of fluoboric acid. A larger excess may be taken but does not appreciably influence the yield. Fluoboric acid (40 per cent) is now a commercial product. Hydrofluoric acid in contact with the skin produces extremely painful burns. It is therefore necessary to use every precaution to protect exposed parts of the body, especially the hands and eyes. Long acid-resisting rubber gloves and rubber goggles should be worn. If one is burned by the acid, the burned surface, which has become white, is held under running water until the natural color returns. Prompt application of a paste made from magnesium oxide and glycerin is said to be helpful in preventing burns from becoming serious [Fredenhagen and Wellmann, Angew. Chem. **45**, 537 (1932)].

4. The fluoboric acid may be more conveniently prepared in a lead jar with mechanical stirring. Such a jar can be readily made from sheet lead by bending to shape and soldering. A piece of iron rod fitted into some narrow lead pipe and having a strip of lead soldered on at the bottom makes an effective stirrer, and a wooden lid covered on the under side with a sheet of lead may serve as a cover. The solder is slowly attacked by the acid and can be protected with an acid-proof grease. The fluoboric acid is siphoned from the jar by means of a rubber tube.

5. The presence of moisture affects the stability of benzenediazonium fluoborate. The moist product, if allowed to stand packed together, may undergo spontaneous decomposition. In damp weather, when spread out on paper, it becomes dark and slowly decomposes. The same result is observed if it is not sufficiently washed.

6. The decomposition may also be carried out in two batches from 5-l. flasks. It is more easily controlled in this way.

7. On account of the large volume of gas evolved, all connections should be made with wide tubing.

8. Normally the decomposition proceeds smoothly under the intermittent heating. If the salt is moist, however, the reaction proceeds more rapidly, and, unless the flask is cooled, it may pass beyond control (see (Note 5)).

9. Since the density of fluorobenzene is about 1.025, it is important that the right strength of caustic soda solution be used in order to effect clean separation of the two layers. Before washing with water, the caustic soda should be completely removed.

10. Preparations have been successfully carried out with two times and three times the quantities here stated and with almost proportionate yields. A large stoneware filter in addition to the lead pot (Note 4) is then desirable to handle the larger quantities of material.

3. Discussion

The method for the preparation of fluorobenzene described above is adapted from that

of Balz and Schiemann.[1] It is recommended that benzenediazonium fluoborate be precipitated from a solution whose total hydrogen-ion concentration does not exceed 1 mole per liter.[2] The diazonium fluoborate has also been prepared from aniline hydrochloride and nitrosyl borofluoride.[3]

Fluorobenzene has also been prepared in 50 per cent yield from benzene diazopiperidide and hydrofluoric acid,[4] although the reaction is said to proceed violently and cannot be used with quantities greater than 10–15 g. of piperidide. Other methods depend on the formation of benzenediazonium fluoride and its decomposition into fluorobenzene when heated.[5], [6], [7] The claim of Valentiner and Schwarz[5] that this reaction proceeds in aqueous solution could not be substantiated by the submitter.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 188
- Org. Syn. Coll. Vol. 2, 225
- Org. Syn. Coll. Vol. 2, 299
- Org. Syn. Coll. Vol. 5, 133
- Org. Syn. Coll. Vol. 5, 1135

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7. Swarts, ibid. **27**, 120 (1908).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

caustic soda

nitrosyl borofluoride

fluoboric acid

large stoneware filter

benzene diazopiperidide

piperidide

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

methyl alcohol (67-56-1)

ethyl ether (60-29-7)

aniline (62-53-3)

sodium hydroxide (1310-73-2)

glycerin (56-81-5)

phenol (108-95-2)

potassium iodide (7681-11-0)

aniline hydrochloride (142-04-1)

sodium nitrite (7632-00-0)

nitrous acid (7782-77-6)

hydrofluoric acid (7664-39-3)

boric acid (10043-35-3)

Fluorobenzene, Benzene, fluoro- (462-06-6)

magnesium oxide

benzenediazonium fluoborate

benzenediazonium fluoride

boron fluoride (7637-07-2)

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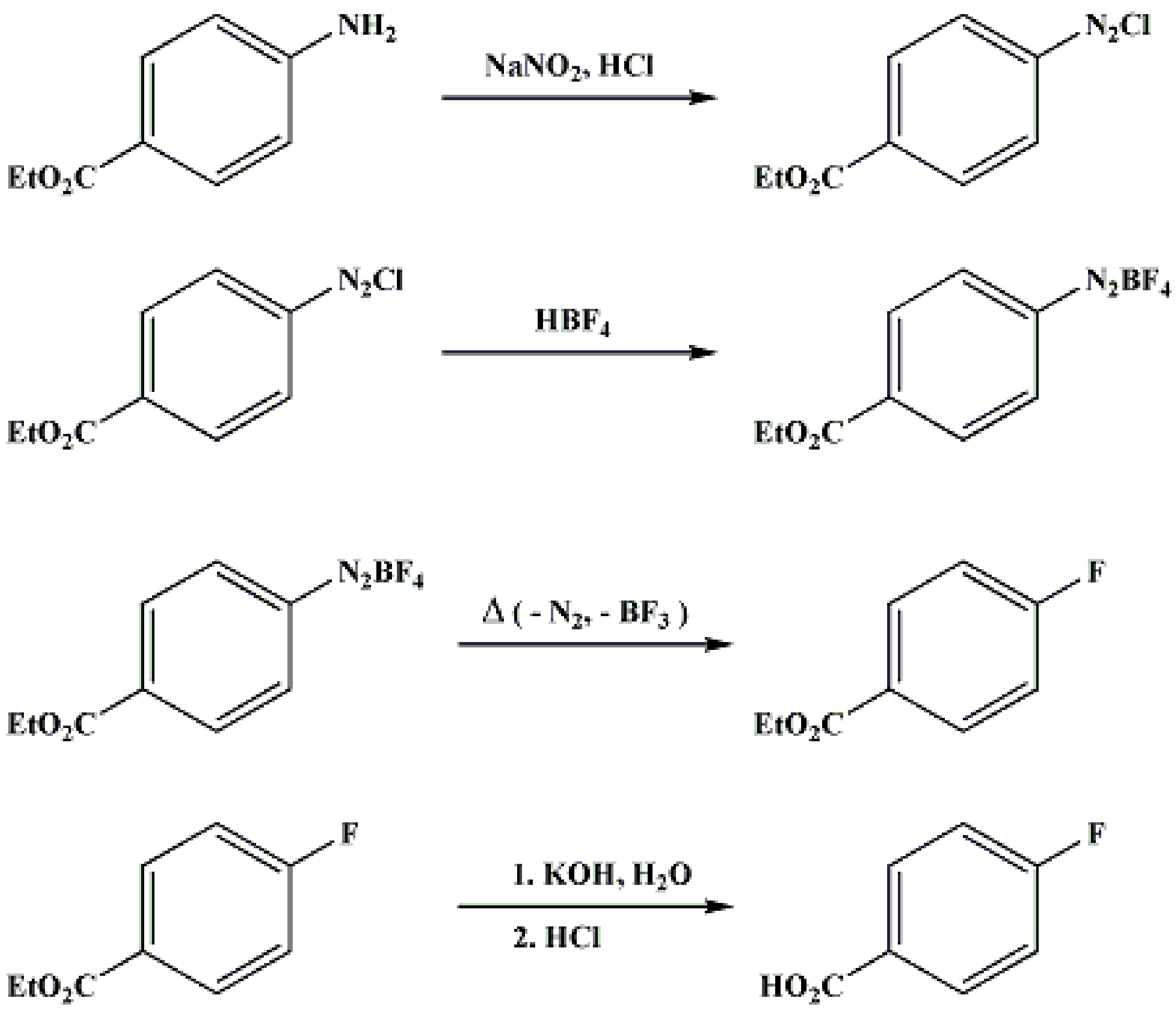
p-FLUOROBENZOIC ACID

[Benzoic acid, *p*-fluoro-]



Submitted by G. Schiemann and W. Winkelmüller.
Checked by W. W. Hartman, J. R. Byers, and J. B. Dickey.

1. Procedure

In a 5-l. round-bottomed flask are placed 165 g. (1 mole) of ethyl *p*-aminobenzoate (Note 1), 300 cc. of water, and 204 cc. (2.5 moles) of concentrated hydrochloric acid (sp. gr. 1.19). This mixture is warmed on a steam bath for an hour with occasional shaking. The flask containing the resulting white paste of *p*-carbethoxyaniline hydrochloride is placed in an ice-salt bath and cooled to 0°. The mixture is stirred mechanically, and a solution of 72.6 g. (1 mole) of 95 per cent sodium nitrite in a minimum quantity of water is run in slowly while the temperature is kept below 7°. The diazotization is complete when a faint positive test for nitrous acid with starch-iodide paper persists for ten minutes.

While the diazotization is in process, 68 g. (1.1 moles) of boric acid is dissolved in 133 g. (4 moles) of 60 per cent hydrofluoric acid (Note 2) in a beaker coated with paraffin-wax. The temperature is kept below 25° during the addition to avoid melting the paraffin-wax, and, after the addition, the solution is chilled in an ice-water bath.

The ice-cold fluoboric acid solution is added rather rapidly, with stirring, to the diazonium solution while the temperature is kept below 10°. A thick paste of *p*-carbethoxybenzenediazonium fluoborate precipitates; stirring is continued for twenty to thirty minutes. The solid is filtered on an 18.5-cm. Büchner funnel and washed consecutively with 300 cc. of cold water, 300 cc. of commercial methyl alcohol, and 200 cc. of commercial ether; it is sucked as dry as possible between washings. The fluoborate is then dried over concentrated sulfuric acid (sp. gr. 1.84) in a vacuum desiccator (Note 3). The yield of the dried fluoborate is 198–205 g. (75–78 per cent of the theoretical amount); the decomposition point is 93–94°.

The thermal decomposition may be conveniently carried out in a 2-l. distilling flask. A second distilling flask of 1-l. capacity is connected directly to the side arm of the first to serve as a receiver. Attached to the side arm of the receiver is a rubber tube arranged to lead the escaping gases over 2 l. of water in a 5-l. round-bottomed flask. The boron trifluoride dissolves in the water, and the other gases are led into a good hood (Note 4). The *p*-carbethoxybenzenediazonium fluoborate is placed in the decomposition flask and heated at its upper edge with a Bunsen flame. When the white fumes of boron trifluoride commence to appear, the flame is removed and the decomposition is permitted to proceed spontaneously. The heat is applied as necessary, and finally the flask is strongly heated to complete the decomposition and melt the solid. Some of the ethyl ester, b.p. 105–106°/25 mm., of *p*-fluorobenzoic acid is collected in the receiver, where it is carried by the gases, but the larger part is left in the decomposition flask. The ester is washed from the decomposition flask and the receiver with ether, and the ether is distilled from a steam bath. The residue is refluxed for one hour on a steam bath with a solution of 56 g. (1 mole) of potassium hydroxide in 80 cc. of 95 per cent ethyl alcohol and 120 cc. of water. The solution is then filtered while still hot. The *p*-fluorobenzoic acid is precipitated by adding concentrated hydrochloric acid to the hot filtrate until the mixture is acid to Congo paper. After the mixture has cooled, the solid is filtered and allowed to dry. For purification, the *p*-fluorobenzoic acid is dissolved in a hot solution of 40 g. of potassium carbonate in 400 cc. of water; the solution is treated with Norite and filtered hot. Hydrochloric acid is added with stirring to precipitate the fluorobenzoic acid, which is then cooled, filtered, and dried.

When 85 g. (0.32 mole) of *p*-carbethoxybenzenediazonium fluoborate is thus decomposed, there is obtained 38–40 g. of *p*-fluorobenzoic acid (84–89 per cent of the theoretical amount based on the fluoborate; 63–69 per cent based on the ester of *p*-aminobenzoic acid). The melting point of the purified acid is 186°. The crude acid melts at 183–184°.

2. Notes

1. Ethyl *p*-aminobenzoate can be prepared by reduction of the corresponding nitro compound as described in Org. Syn. Coll. Vol. I, **1941**, 240, or by esterification of *p*-aminobenzoic acid: 274 g. (2 moles) of *p*-aminobenzoic acid is added to 1.4 kg. of ethyl alcohol which has been saturated with dry hydrogen chloride. The reaction mixture is refluxed for twenty-four hours, poured into water, neutralized with sodium carbonate, and the insoluble ester is separated by filtration. The yield is 80 per cent of the theoretical amount.
2. *Hydrofluoric acid causes extremely painful burns. Exposed parts of the body must be protected when working with this material. Compare Note 3, p. 297.*
For preparing the fluoboric acid a lead jar may be conveniently used instead of the beaker lined with paraffin-wax. By using a lead stirrer of the usual shape, mechanical stirring may be substituted. The stirrer should be thrust through a hole in a lead cover of sufficient size to prevent spattering of the hydrofluoric acid.
Forty per cent fluoboric acid is now available commercially; 200 g. of the commercial product may be used in the procedure above.
3. It is very important that the fluoborate be dry. If this solid is wet, the decomposition is very violent, tar is formed, and the yield is lowered.
4. A simpler apparatus for the decomposition is a 2-l. round-bottomed short-necked flask connected by means of a wide (2-cm.) bent tube to a 1-l. flask containing 500 cc. of water. The gases from the second flask are led to a good hood.

3. Discussion

p-Fluorobenzoic acid has been prepared by the oxidation of *p*-fluorotoluene with chromic acid in dilute sulfuric acid at 160°;[1] by the oxidation of *p*-fluorotoluene with potassium permanganate;[2] by the electrolytic oxidation of *p*-fluorotoluene;[3] by heating *p*-carboxybenzenediazonium chloride with fuming hydrofluoric acid;[4] by the oxidation of *p*-fluorobenzaldehyde;[5] by the oxidation of *p,p'*-difluorostilbene with potassium permanganate;[6] by the oxidation of 4,4'-difluorobiphenyl with nitric acid;[7] and by the oxidation of 4,4'-difluorobiphenyl with chromic acid.[8] The above method is adapted from that of Balz and Schiemann.[9]

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9. Balz and Schiemann, ibid. **60**, 1186 (1927).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

fluoboric acid

ethyl alcohol (64-17-5)

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

hydrogen chloride, hydrochloric acid (7647-01-0)

methyl alcohol (67-56-1)

ether (60-29-7)

nitric acid (7697-37-2)

potassium permanganate (7722-64-7)

sodium carbonate (497-19-8)

sodium nitrite (7632-00-0)

nitrous acid (7782-77-6)

hydrofluoric acid (7664-39-3)

Norite (7782-42-5)

potassium hydroxide (1310-58-3)

chromic acid (7738-94-5)

boric acid (10043-35-3)

boron trifluoride (7637-07-2)

fluorobenzoic acid (445-29-4)

Ethyl p-aminobenzoate (94-09-7)

4,4'-DIFLUOROBIPHENYL (398-23-2)

p-aminobenzoic acid, ester of p-aminobenzoic acid (150-13-0)

p-Fluorobenzoic acid, Benzoic acid, p-fluoro- (456-22-4)

p-carbethoxyaniline hydrochloride

p-Carbethoxybenzenediazonium fluoborate

p-fluorotoluene (352-32-9)

p-carboxybenzenediazonium chloride

p-fluorobenzaldehyde (459-57-4)

p,p'-difluorostilbene

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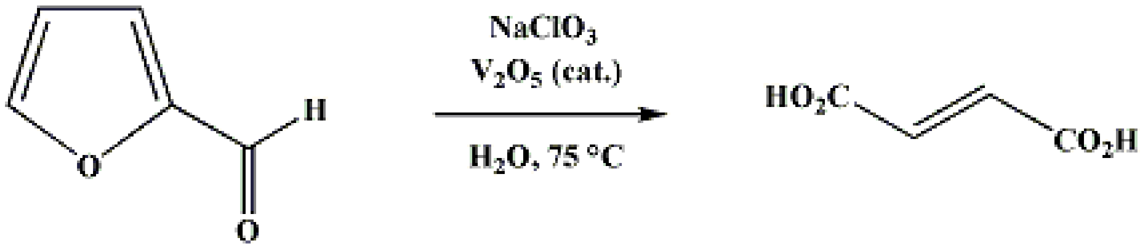
Organic Syntheses, CV 2, 302

FUMARIC ACID



Submitted by Nicholas A. Milas
Checked by Roger Adams and K. L. Amstutz.

1. Procedure

A 5-l. flat-bottomed flask, equipped with a long (80–90 cm.) widebore condenser, a separatory funnel, and a mechanical stirrer (Note 1), is supported 10 cm. above an electric hot plate. Two grams of vanadium pentoxide (Note 2), 450 g. (4.2 moles) of sodium chlorate, and 1 l. of water are placed in the flask; the stirrer is started, the mixture is heated to 70–75° (Note 3), and about 5–10 cc. of 200 g. (2.06 moles) of furfural (Note 4) is added. As soon as a vigorous reaction starts the balance of the furfural is added rapidly enough to maintain it (Note 5). The entire addition requires seventy to eighty minutes. Then the mixture is heated at 70–75°, with stirring, for ten to eleven hours and allowed to stand overnight at room temperature. The crude fumaric acid is filtered with suction and dried in the air. It weighs 155–170 g. (65–72 per cent of the theoretical amount) (Note 6).

More fumaric acid may be obtained from the filtrate by heating it on the water bath with 50 cc. of concentrated hydrochloric acid; the solution usually turns blue at the end of the reaction. The solution is concentrated to about 700 cc. and then cooled with running water. The fumaric acid which separates is collected on a filter and dried in the air. It weighs 10–15 g. and melts at 282–284° in a sealed tube.

The crude product is purified by recrystallization from about 1250 cc. of 1 *N* hydrochloric acid. This gives 100–110 g. of pure fumaric acid, melting at 282–284° in a sealed tube. An additional amount of the acid may be obtained by concentrating the filtrate to a small volume on a water bath. The total yield of pure fumaric acid is 120–138 g. (50–58 per cent of the theoretical amount).

2. Notes

1. The yields were lower when mechanical stirring was not used.
2. The catalyst is prepared by suspending 20 g. of c.p. ammonium metavanadate in 200 cc. of water and adding slowly 30 cc. of concentrated hydrochloric acid (sp. gr. 1.19). The reddish brown semicolloidal precipitate is washed several

times with water by decantation and finally suspended in 300 cc. of water and allowed to stand at room temperature for three days. This treatment makes the precipitate granular and easy to filter. The precipitate is collected on a filter using a pump and washed several times with water to free it from hydrochloric acid. It is then dried at 120° for twelve hours, finely powdered, and again dried for twelve hours at 120°.

3. To observe the temperature, a thermometer may be suspended in the flask through the inner tube of the condenser. The mixture may be heated first to 70–75° over a free flame.

4. The furfural used was the technical grade furnished by the Miner Laboratories, Chicago. According to these laboratories the furfural was "about 99 per cent pure." The crude furfural obtained as described in Org. Syn. Coll. Vol. I, **1941**, 280 may be used.

5. The reaction does not seem to start immediately upon the addition of the first few cubic centimeters of furfural. When the vigorous reaction commences, the temperature rises to about 105° and remains there for some time. The yield of fumaric acid seems to depend somewhat upon the rapidity of this stage of the reaction. It is therefore necessary to regulate the addition of furfural so that a vigorous reaction is maintained.

6. The crude fumaric acid is from 74 to 78 per cent pure as found by titration with standard alkali. The only impurity present besides inorganic salts is a little sodium hydrogen maleate which is decomposed by the hydrochloric acid during the purification process.

3. Discussion

Fumaric acid has been prepared from bromosuccinic acid by heating with water,[1] or dilute hydrobromic acid,[2] and by heating the acid above its melting point.[3] It has also been prepared by heating malic acid,[4] by isomerization of maleic acid;[5] and by the reduction of tartaric acid with phosphorus and iodine.[6] The procedure described is the most satisfactory for laboratory use, and is a slight modification of one described in the literature.[7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 177
- Org. Syn. Coll. Vol. 2, 553

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

ammonium metavanadate (7803-55-6)

HYDROBROMIC ACID (10035-10-6)

PHOSPHORUS (7723-14-0)

vanadium pentoxide

maleic acid (110-16-7)

iodine (7553-56-2)

sodium chlorate (7775-09-9)

tartaric acid (87-69-4)

Fumaric acid (110-17-8)

Furfural (98-01-1)

sodium hydrogen maleate (3105-55-3)

bromosuccinic acid (923-06-8)

malic acid (617-48-1)

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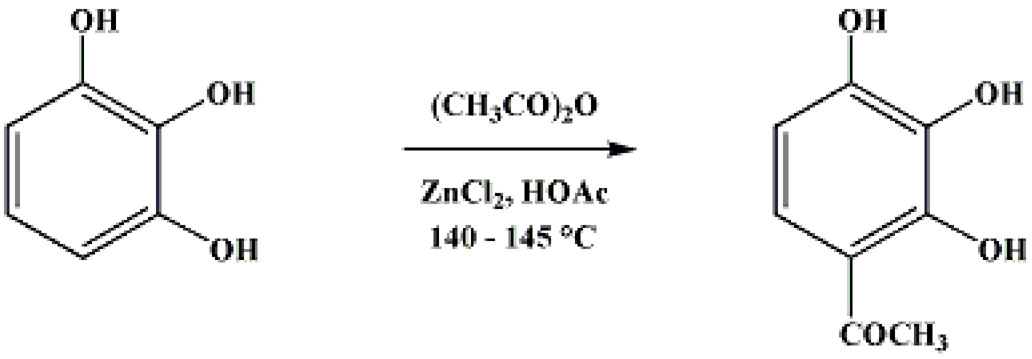
Organic Syntheses, CV 2, 304

GALLACETOPHENONE



Submitted by I. C. Badhwar and K. Venkataraman.
Checked by W. W. Hartman and L. J. Roll.

1. Procedure

In a 250-cc. round-bottomed flask, fitted with a reflux condenser to which is attached a calcium chloride tube, 28 g. (0.21 mole) of freshly fused and finely powdered zinc chloride (Note 1) is dissolved in 38 cc. of glacial acetic acid by heating in an oil bath at 135–140°. Forty grams (0.37 mole) of 95 per cent acetic anhydride is then added to the clear, pale brown liquid, followed by the addition in one lot of 50 g. (0.4 mole) of distilled pyrogallol (Note 2). The mixture is heated at 140–145° (Note 3) for forty-five minutes with frequent and vigorous shaking. The unused acetic anhydride and acetic acid are removed by distilling under reduced pressure. The red-brown cake is broken up by the addition of 300 cc. of water with mechanical stirring for a few minutes. The mixture is cooled in ice water, filtered with suction, and washed with cold water. The crude material, 45–50 g., is crystallized from 500 cc. of boiling water saturated with sulfur dioxide. The yield of straw-colored needles melting at 171–172° is 36–38 g. (54–57 per cent of the theoretical amount). On saturating the mother liquor with salt and cooling to 10°, 4–5 g. of crude material is obtained, which on recrystallization yields 3–4 g. of pure material (Note 4).

2. Notes

1. A good quality of zinc chloride must be used, and it is an advantage to fuse it immediately before use.
2. Variations in the proportions of acetic acid, acetic anhydride, and zinc chloride did not result in increased yields.
3. The temperature must be carefully regulated and must not exceed 150°. In this preparation, as well as in the preparation of other ketones by the Nencki reaction, higher temperatures lead to the formation of a highly colored and resinous product which probably contains a little diketone.
4. This method has been used for the preparation of other phenolic ketones such

as resacetophenone, 2-acetyl-1-naphthol,[1] 2-phenylacetyl-1-naphthol, and 2-phenylpropionyl-1-naphthol.[2]

3. Discussion

The method described above is a modification of the process of Nencki and Sieber.[3] Gallacetophenone has also been prepared by treating pyrogallol with acetyl chloride,[4] and from 2-formyl-4-acetylresorcinol by treatment with hydrogen peroxide and alkali.[5]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Resacetophenone

acetic acid (64-19-7)

acetic anhydride (108-24-7)

acetyl chloride (75-36-5)

sulfur dioxide (7446-09-5)

zinc chloride (7646-85-7)

hydrogen peroxide (7722-84-1)

Gallacetophenone (528-21-2)

pyrogallol (87-66-1)

2-acetyl-1-naphthol (711-79-5)

2-phenylacetyl-1-naphthol

2-phenylpropionyl-1-naphthol

2-formyl-4-acetylresorcinol

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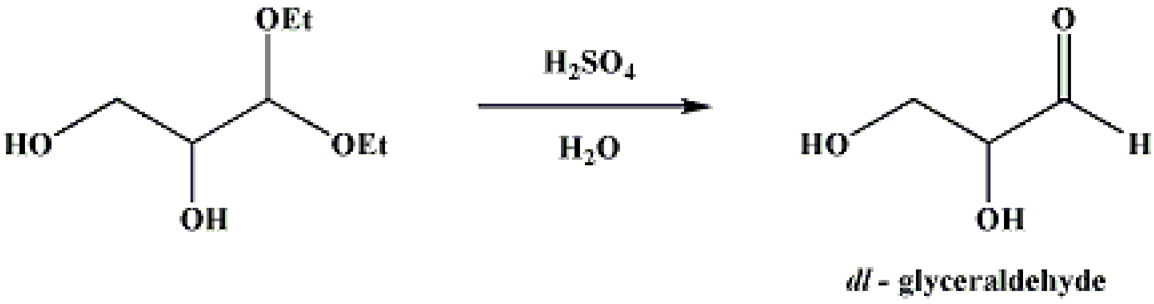
Organic Syntheses, CV 2, 305

dl-GLYCERALDEHYDE



Submitted by E. J. Witzemann, Wm. Llloyd Evans, Henry Hass, and E. F. Schroeder.
Checked by Frank C. Whitmore and Harry T. Neher.

1. Procedure

A mixture of 50 g. (0.3 mole) of *dl*-glyceraldehyde acetal (p. 307) and 500 cc. of 0.1 *N* sulfuric acid is allowed to stand for one week at about 20° (Note 1). Thirty cubic centimeters of glacial acetic acid is added; the mixture is neutralized carefully with barium hydroxide solution (Note 2), stirred with 5 g. of decolorizing carbon, and filtered. The filtrate is evaporated at 10 mm. pressure (Note 3). When no more water can be removed, the residue is treated with an equal volume of absolute alcohol to hasten crystallization. The crystals are collected on a filter and dried in a vacuum desiccator over soda-lime and calcium chloride. The yield of product melting at 137–139° is 22 g. (80 per cent of the theoretical amount).

2. Notes

1. During the entire preparation, including the evaporation, the temperature should be kept below 30°. If this precaution is rigidly observed, the glyceraldehyde crystallizes readily.
2. Samples of the filtered solution should give only a very slight opalescence when tested with barium hydroxide and with sulfuric acid.
3. The use of 10 mm. instead of 20 mm. pressure for the evaporation improves the quality of the glyceric aldehyde, making the difference between a syrup which may or may not crystallize and a product which crystallizes even from the concentrated solution.

3. Discussion

dl-Glyceraldehyde has been obtained by the oxidation of glycerol with nitric acid,[1] with bromine and sodium carbonate,[2] and with hydrogen peroxide in the presence of ferrous salts;[3] by the action of ultraviolet light on glycerol in neutral solution;[4] by the

action of sunlight on glycerol in the presence of uranium sulfate;[5] by electrolysis of *dl*-erythronic acid;[6] by the hydrolysis of *dl*-glyceraldehyde acetal;[7] by the oxidation of acrolein;[8] by the oxidation of benzal-1,3-propenediol followed by hydrolysis;[9] and by the alkaline condensation of formaldehyde.[10]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 919

References and Notes

1. Kiliani, Ber. **54**, 467 (1921); Fischer and Tafel, ibid. **20**, 3385 (1887).
2. Fischer and Tafel, ibid. **20**, 3385 (1887).
3. Fenton and Jackson, Chem. News **78**, 187 (1898); J. Chem. Soc. **75**, 5 (1899); Witzemann, J. Am. Chem. Soc. **36**, 2227 (1914).
4. Bierry, Henri, and Ranc, Compt. rend. **152**, 535 (1911).
5. Neuberg, Biochem. Z. **13**, 307 (1908).
6. Neuberg, Scott, and Lachmann, ibid. **24**, 157 (1910).
7. Wohl, Ber. **31**, 1800, 2395 (1898); Wohl and Neuberg, ibid. **33**, 3100 (1900); Evans and Hass, J. Am. Chem. Soc. **48**, 2706 (1926); Witzemann, ibid. **36**, 1913 (1914); Spoehr and Young, Carnegie Inst. Washington Yearbook, **25**, 177 (1925–1926); Exp. Sta. Record, **57**, 817 (1927) [C. A. **22**, 2368 (1928)].
8. Neuberg, Biochem. Z. **221**, 492 (1930); **255**, 1 (1932).
9. Fischer, Ahlström, and Richter, Ber. **64**, 611 (1931).
10. Kuzin, J. Gen. Chem. (U.S.S.R.) **8**, 592 (1938) [C. A. **33**, 1271 (1939)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

soda-lime

alcohol (64-17-5)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

formaldehyde (630-08-0)

Acrolein (107-02-8)

glycerol (56-81-5)

nitric acid (7697-37-2)

sodium carbonate (497-19-8)

bromine (7726-95-6)

decolorizing carbon (7782-42-5)

hydrogen peroxide (7722-84-1)

barium hydroxide (17194-00-2)

glyceraldehyde, glyceric aldehyde, DL-Glyceraldehyde (56-82-6)

uranium sulfate

benzal-1,3-propenediol

DL-Glyceraldehyde acetal

dl-erythronic acid

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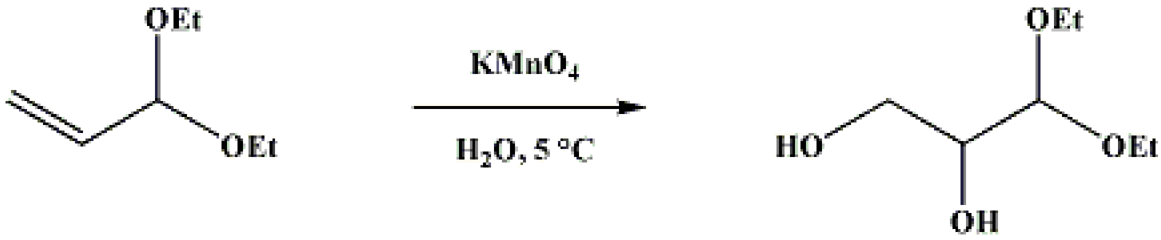
Organic Syntheses, CV 2, 307

dl-GLYCERALDEHYDE ETHYL ACETAL



dl - glyceraldehyde acetal

Submitted by E. J. Witzemann, Wm. Lloyd Evans, Henry Hass, and E. F. Schroeder.
Checked by Frank C. Whitmore and Harry T. Neher.

1. Procedure

In a 3-l. open flask, equipped with a mechanical stirrer and a thermometer and cooled in an ice bath, is placed a suspension of 65 g. (0.5 mole) of acrolein acetal (p. 17) in 600 cc. of water. The suspension is cooled to 5° (Note 1), and a solution of 80 g. (0.5 mole) of potassium permanganate in 1.5 l. of water is added, with stirring, at the rate of about 25 cc. per minute. The temperature is kept as near 5° as possible during the addition. Soon after the stirring is stopped, the mixture sets to a gel (Note 2). After standing for two hours, the mixture is heated for one hour on the steam bath and then filtered by suction on a 30-cm. Büchner funnel. The residual manganese dioxide is pressed thoroughly and washed with 150 cc. of cold water. The filtrate (about 2.3 l.) is kept cool and treated with 1.2 kg. of freshly dehydrated commercial potassium carbonate. The layers are separated and the water layer is extracted with four 100-cc. portions of ether. The ether extracts are added to the crude acetal layer, and the mixture, which may consist of two layers (Note 3), is dried over 10 g. of potassium carbonate. After removal of the ether, the residue is distilled under reduced pressure. The yield of product boiling at 120–121°/8 mm. is 55 g. (67 per cent of the theoretical amount).

2. Notes

1. The oxidation is very sensitive to changes in temperature. The best results are obtained at 5°; a slight variation causes a marked decrease in the yield.
2. If the mixture does not set to a gel, the yield is likely to be poor. This is usually due to poor temperature control.
3. Sometimes two layers appear at first, but these disappear when the potassium carbonate is added.

3. Discussion

dl-Glyceraldehyde acetal has been prepared by heating hydroxychloropropionaldehyde acetal with potassium carbonate solution;[1] by treating glyceraldehyde with alcoholic hydrogen chloride;[2] and by oxidation of acrolein acetal with potassium permanganate.[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 305

References and Notes

1. Wohl, Ber. **31**, 1799 (1898).
2. Wohl and Neuberg, ibid. **33**, 3103 (1900); Witzemann, J. Am. Chem. Soc. **36**, 2229 (1914).
3. Wohl, Ber. **31**, 1799 (1898); Evans and Hass, J. Am. Chem. Soc. **48**, 2706 (1926); Witzemann, ibid. **36**, 1912 (1914); Spoehr and Young, Carnegie Inst. Washington Yearbook, **25**, 177 (1925–1926); Expt. Sta. Record, **57**, 817 (1927) [C. A. **22**, 2368 (1928)]; Fischer and Baer, Helv. Chim. Acta **18**, 516 (1935).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

potassium carbonate (584-08-7)

hydrogen chloride (7647-01-0)

ether (60-29-7)

potassium permanganate (7722-64-7)

manganese dioxide (1313-13-9)

Acrolein acetal

glyceraldehyde (56-82-6)

hydroxychloropropionaldehyde acetal

DL-Glyceraldehyde acetal

dl-GLYCERALDEHYDE ETHYL ACETAL

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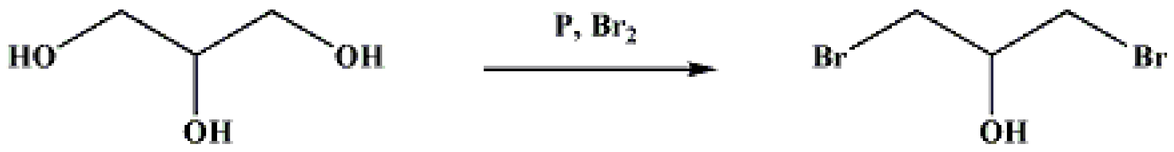
Organic Syntheses, CV 2, 308

GLYCEROL α,γ-DIBROMOHYDRIN

[2-Propanol, 1,3-dibromo-]



Submitted by Géza Braun
Checked by Reynold C. Fuson and S. H. Babcock.

1. Procedure

In a 3-l. three-necked, round-bottomed flask, fitted with a powerful glycerol-sealed stirrer, a dropping funnel, and an outlet tube for escaping gases, 1.6 kg. (17.4 moles) of glycerol is thoroughly mixed with 200 g. (6.5 gram atoms) of red phosphorus (Note 1). Nine hundred cubic centimeters (2808 g., 17.5 moles) of bromine (Note 2) is then gradually added, with effective stirring (Note 3), through the dropping funnel in the course of about eight hours. To minimize the escape of bromine, the end of the dropping funnel should reach almost to the bottom of the flask. The by-product gases, consisting mainly of hydrogen bromide and some bromine, are led over concentrated sodium hydroxide solution or to a gas trap. The reaction is exothermic, and the temperature quickly rises to 80–100°; then the addition of bromine is so regulated that this temperature is maintained. Toward the end of the period of addition of bromine, the flask is placed in a water bath at 70–75°. After all the bromine has been added, the mixture is allowed to stand overnight and is then warmed on the water bath until all the bromine is consumed (one to two hours).

The reaction mixture is transferred to a 3-l. round-bottomed flask provided with a two-holed rubber stopper carrying a wide delivery tube and a capillary tube. The flask is heated in an oil bath, and distillation is begun under the reduced pressure of a water pump. The receiver is cooled with water. At first a mixture of hydrobromic acid and water passes over; later the dibromohydrin distils. The temperature of the bath is raised as fast as the boiling of the mass permits, and is eventually brought to 180°. The distillation is carefully watched at the end and immediately interrupted at the first sign of decomposition. This is clearly indicated by gas formation, in consequence of which the vacuum cannot be maintained at the previous level. To the straw-yellow distillate a slight excess of solid sodium bicarbonate is added with continuous shaking until effervescence ceases. The inorganic salts are removed by filtration, and the aqueous layer of the filtrate is separated from the crude dibromohydrin. The latter is purified by fractional distillation under reduced pressure from a 2-l. Claisen flask. The distillation is continued until no more water passes over and the inside temperature reaches 100°. Then the dibromohydrin is separated from the water in the distillate, dried with anhydrous sodium sulfate, filtered, and poured back into the distilling flask. By this

operation the water is largely removed (Note 4). Then the distillation is continued as before and, after a small fore-run, the dibromohydrin boils at 110–112° under 20 mm. pressure (Note 5). The yield is 2000–2050 g. (52–54 per cent of the theoretical amount) of a colorless product.

The dibromohydrin is a heavy, colorless liquid with a characteristic odor. On standing it gradually becomes yellow. Its specific gravity at 20° is about 2.14.

2. Notes

1. The red phosphorus should be thoroughly mixed with the glycerol before the addition of the bromine. The bromine should not come into contact with the dry phosphorus or a violent reaction will occur.
2. Commercial 98 per cent glycerol and u.s.p. bromine may be used in the preparation.
3. A powerful stirrer is necessary because of the viscous nature of the reaction mixture.
4. The water derives from the chemical interaction of phosphorous acid with the glycerol or with the bromohydrins. Better yields are obtained when the theoretical amount of bromine is used, although on account of this secondary reaction a smaller amount should suffice.
5. The crude dibromohydrin distils without any decomposition at 10–15 mm. pressure if the temperature of the oil bath is not raised over 190°. Above this temperature, formation of acrolein derivatives makes the dibromohydrin lachrymatory.

3. Discussion

Glycerol α,γ-dibromohydrin has been prepared from glycerol and phosphorus tribromide;[1] from glycerol and bromine;[2] and from glycerol, phosphorus, and bromine.[3], [4], [5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 256

References and Notes

1. Berthelot and de Luca, Ann. chim. phys. (3) **48**, 306 (1856).
2. Barth, Ann. **124**, 349 (1862).
3. Aschan, Ber. **23**, 1826 (1890).
4. Lespieau, Ann. chim. phys. (7) **11**, 236 (1897).
5. Braun, J. Am. Chem. Soc. **52**, 3172 (1930).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

red phosphorus

Glycerol α,γ-dibromohydrin

sodium hydroxide (1310-73-2)

glycerol (56-81-5)

sodium bicarbonate (144-55-8)

HYDROBROMIC ACID, hydrogen bromide (10035-10-6)

bromine (7726-95-6)

PHOSPHORUS (7723-14-0)

sodium sulfate (7757-82-6)

phosphorus tribromide (7789-60-8)

2-Propanol, 1,3-dibromo- (96-21-9)

phosphorous acid (13598-36-2)

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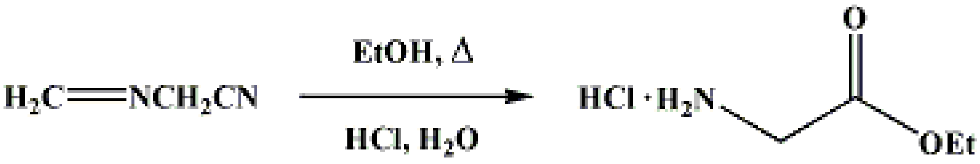
GLYCINE ETHYL ESTER HYDROCHLORIDE



Submitted by C. S. Marvel
Checked by Louis F. Fieser and S. L. Judkins.

1. Procedure

In a 3-l. round-bottomed flask are placed 500 cc. (400 g., 8.7 moles) of absolute alcohol which has been saturated in the cold with hydrochloric acid gas (Note 1), 870 cc. (680 g., 14.8 moles) of 96 per cent alcohol (Note 2), and 70 g. (1.03 moles) of methyleneaminoacetonitrile (Note 3). This mixture is refluxed on a steam bath for three hours (Note 4). During the refluxing, ammonium chloride separates. After the reaction is complete, the hot alcohol solution is filtered with suction and the filtrate cooled, thus allowing the glycine ester hydrochloride to separate in fine white needles. The product is filtered with suction, sucked as dry as possible on the filter, and then allowed to dry in the air. The yield is about 110 g. The alcohol from the filtrate is distilled (Note 5) until about one-third of its volume is left; it is cooled again, when a second crop of crystals is obtained. The total yield of product, m.p. 142–143°, varies from 125 to 129 g. (87–90 per cent of the theoretical amount). If a very pure product is desired, the material may be re-crystallized from absolute alcohol.

2. Notes

1. The 500 cc. of absolute alcohol is cooled in an ice bath and treated with dry hydrogen chloride until 163 g. has been added, an amount sufficient for saturation. The solution should be protected from the moisture of the air with a calcium chloride tube.
2. It is important to use the strengths of alcohol specified in the directions if the best yields are to be obtained, and it is advisable to test the alcohol with a hydrometer just before using. The 870 cc. of 96 per cent alcohol contains just enough water for the hydrolysis. If, therefore, a less concentrated alcohol is used, the glycine ester hydrochloride does not form so readily and does not separate so easily from solution. Experiments using 96 per cent alcohol saturated with hydrochloric acid and 870 cc. of 96 per cent alcohol gave about 8 to 10 g. less product. A more dilute alcohol than 96 per cent gives a much poorer grade and yield of the glycine ester hydrochloride.
3. The crude material as described in Org. Syn. Coll. Vol. I, **1941**, 355, is satisfactory.
4. A cork and not a rubber stopper should be used during the refluxing, as rubber

stoppers will cause the product to be colored.
5. It is important that no water get into the alcohol, as glycine ester hydrochloride is quite soluble in water. Concentration of the filtrate on the steam bath should not be done in an open vessel because the solution will take up moisture and the product will not crystallize.

3. Discussion

Glycine ethyl ester hydrochloride has been prepared by the action of absolute alcohol and hydrogen chloride on glycine;[1] from glycyl chloride and alcohol;[2] by the action of ammonia[3] or hexamethylenetetramine[4] on chloroacetic acid, and subsequent hydrolysis with alcoholic hydrochloric acid; by the action of hydrogen chloride and alcohol on methyleneaminoacetonitrile;[5] and by the reduction of ethyl cyanoformate[6] or the corresponding imido ester hydrochloride.[7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 424

References and Notes

1. Curtius and Goebel, J. prakt. Chem. (2) **37**, 159 (1888); Harries and Weiss, Ann. **327**, 365 (1903).
2. Fischer, Ber. **38**, 2916 (1905).
3. Hantzsch and Silberrad, ibid. **33**, 70 (1900); Hantzsch and Metcalf, ibid. **29**, 1681 (1896).
4. Auger, Bull. soc. chim. (3) **21**, 6 (1899); Locquin, ibid. **23**, 662 (1900).
5. Jay and Curtius, Ber. **27**, 60 (1894); Klages, ibid. **36**, 1508 (1903).
6. Ges. für Kohlentechnik m.b. H., Ger. pat. 594,219 [C. A. **28**, 3417 (1934)]; 638,577 [C. A. **31**, 3066 (1937)]; E. Merck, Ger. pat. 597,305 [C. A. **28**, 5078 (1934)].
7. Ges. für Kohlentechnik m.b. H., Ger. pat. 604,277 [C. A. **29**, 812 (1935)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

glycine ester hydrochloride

alcohol (64-17-5)

hydrogen chloride, hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ammonium chloride (12125-02-9)

chloroacetic acid (79-11-8)

Glycine (513-29-1)

Methyleneaminoacetonitrile (109-82-0)

hexamethylenetetramine (100-97-0)

Glycine ethyl ester hydrochloride (623-33-6)

glycyl chloride

ethyl cyanoformate (623-49-4)

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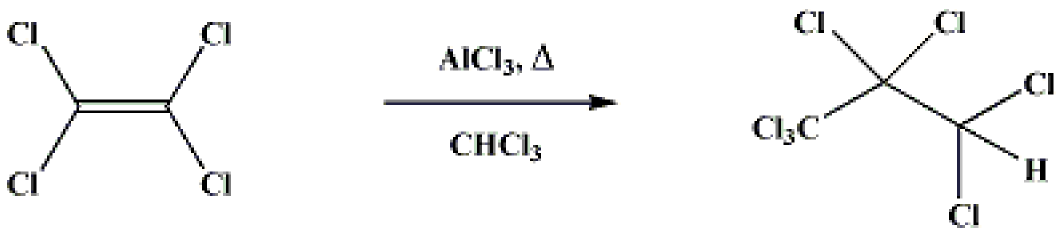
Organic Syntheses, CV 2, 312

unsym.-HEPTACHLOROPROPANE

[Propane, 1,1,1,2,2,3,3-heptachloro-]



Submitted by Mark W. Farlow
Checked by Frank C. Whitmore and F. W. Breuer.

1. Procedure

In a 1-l. round-bottomed flask, equipped with a reflux condenser carrying a calcium chloride tube, are placed 166 g. (103 cc., 1 mole) of technical tetrachloroethylene, 300 g. (200 cc., 2.5 moles) of dry chloroform, and 27 g. (0.2 mole) of anhydrous aluminum chloride. The mixture is refluxed gently on the steam bath for fifteen hours (Note 1), cooled to room temperature, and poured into a 1-l. separatory funnel half filled with crushed ice. The organic layer is washed several times with water and dried over calcium chloride or soluble anhydrite. By fractionation at atmospheric pressure through an efficient column, 160–165 g. of chloroform is recovered. Distillation of the *unsym*.-heptachloropropane fraction at diminished pressure gives material boiling at 110–113°/10 mm., or 137–140°/32 mm., and melting at 29–30°. The yield is 250–266 g. (88–93 per cent of the theoretical amount) (Note 2).

2. Notes

1. A small amount of hydrogen chloride is evolved in the initial stages of the reaction.
2. According to Prins[1] the heptachloropropane can be isolated easily by pouring the reaction mixture into water and removing the unreacted materials by steam distillation. The process is stopped when the product begins to distil, and on cooling the residue is obtained as a colorless solid of the correct melting point.

3. Discussion

The method is essentially that discovered by Böeseken and Prins[2] and studied further by Prins.[1], [3] Pentachloroethane can be used in place of tetrachloroethylene, as it is converted into the unsaturated compound in the presence of aluminum chloride. *unsym*.-Heptachloropropane has been obtained also by the action of phosphorus pentachloride on pentachloroacetone,[4] and by treating dichloroacetyl chloride with

aluminum chloride.[5]

References and Notes

1. Prins, Rec. trav. chim. **54**, 249 (1935).
2. Böeseken and Prins, Chem. Zentr. **1911**, I, 466.
3. Prins, J. prakt. Chem. (2) **89**, 414 (1914).
4. Fritsch, Ann. **297**, 312 (1897).
5. Böeseken, Rec. trav. chim. **29**, 109 (1910).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

unsym.-HEPTACHLOROPROPANE

calcium chloride (10043-52-4)

hydrogen chloride (7647-01-0)

phosphorus pentachloride (10026-13-8)

chloroform (67-66-3)

aluminum chloride (3495-54-3)

pentachloroethane (76-01-7)

HEPTACHLOROPROPANE, Propane, 1,1,1,2,2,3,3-heptachloro- (594-89-8)

tetrachloroethylene (127-18-4)

pentachloroacetone (1768-31-6)

dichloroacetyl chloride (79-36-7)

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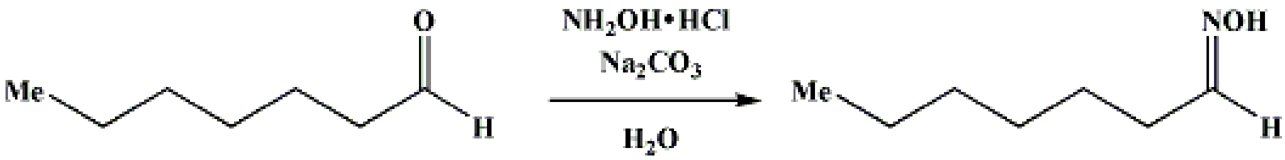
HEPTALDOXIME

[Enanthaldehyde oxime]



Submitted by E. W. Bousquet
Checked by W. H. Carothers and W. L. McEwen.

1. Procedure

In a 5-l. two-necked flask, fitted with a mechanical stirrer, a reflux condenser, a thermometer, and a separatory funnel, are placed an aqueous solution of 348 g. (5 moles) of hydroxylamine hydrochloride (Org. Syn. Coll. Vol. I, **1941**, 318) in 600 cc. of cold water and 460 g. (4 moles) of heptaldehyde (Note 1). Stirring (Note 2) is started, and a solution of 265 g. (2.5 moles) of anhydrous c.p. sodium carbonate in 500 cc. of water is added at such a rate that the temperature of the reaction mixture does not rise above 45°. Stirring is continued at room temperature for an hour after the addition of the sodium carbonate solution is complete.

The oily layer on top of the reaction mixture is separated and washed with two 100-cc. portions of water (Note 3). The washed product is transferred to a 1.5-l. modified Claisen flask and distilled under reduced pressure from an oil bath. The first fraction contains a very small amount of water along with a mixture of heptanonitrile and heptaldoxime. The product is collected at 103–107°/6 mm. (temperature of the oil bath, 140–147°) (Note 4). The yield is 420–480 g. (81–93 per cent of the theoretical amount). The product solidifies slowly on cooling and melts at 44–46°. It can be used for reduction to *n*-heptylamine (p. 318) without further purification.

The product can be purified by recrystallization from 60 per cent ethyl alcohol, using approximately 70 cc. of the solvent to 25 g. of the distilled product. One such recrystallization (Note 5) gives white leaflets melting at 53–55° (Note 6) and (Note 7). The yield of recrystallized material from a single run is 315–320 g.

2. Notes

1. The heptaldehyde used boiled at 54–59°/16 mm.
2. Since the heptaldehyde and the aqueous solution of hydroxylamine hydrochloride form a heterogeneous mixture, it is necessary to provide rapid, efficient stirring in order to obtain good results.
Ethyl alcohol can be used to provide a homogeneous solution, but the yield seems to be diminished slightly owing to the presence of more high-boiling material.
3. The product is so insoluble in water that an ether extraction is hardly necessary to obtain all the product from the water solution if sufficient time is allowed for the separation of the two layers.
4. The temperature of the oil bath during distillation is important. The first fraction is cut as soon as a constant boiling point is reached, and this constancy of boiling point is obtained sooner if the temperature of the oil bath is regulated to a constant temperature before

distillation is started. No more than 50 cc. (of which approximately 10 cc. is water) should come over in the first fraction. If the temperature of the bath is regulated carefully, practically all the product will distil at a constant temperature.
5. The product is dissolved by gentle heating and the solution is then cooled to 0° or below for several hours. The material remaining in the mother liquor (about 30 per cent of the total) may be recovered as impure, oily oxime by evaporation of the alcohol.
6. The melting point given was determined by the capillary-tube method and depended on the rate of heating. The melting point as given in the literature varies from 50° to 58°.
7. Cyclohexanone oxime can be prepared in the same percentage yields by a procedure which differs from the above only in that the reaction mixture becomes solid before the addition of the sodium carbonate is complete. After all the sodium carbonate has been added, steam is passed in until the oxime is melted, and the mixture is shaken vigorously for fifteen minutes at five-minutes intervals. Cyclohexanone oxime boils at 100–105°/10–12 mm. and melts at 87–88°.

3. Discussion

Heptaldoxime has been prepared only by the action of the aldehyde on an aqueous solution of hydroxylamine hydrochloride in the presence of alkali;[1] the method described above is a modification of that given by Westenberger.[1]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 76
- Org. Syn. Coll. Vol. 2, 318
- Org. Syn. Coll. Vol. 2, 371
- Org. Syn. Coll. Vol. 8, 568

References and Notes

1. Westenberger, Ber. **16**, 2992 (1883); Goldschmidt and Zanoli, ibid. **25**, 2593 (1892); Bourgeois and Dambmann, ibid. **26**, 2860 (1893).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Heptaldoxime

ethyl alcohol (64-17-5)

sodium carbonate (497-19-8)

Hydroxylamine hydrochloride (5470-11-1)

Cyclohexanone oxime (100-64-1)

Enanthaldehyde oxime (629-31-2)

heptanonitrile (629-08-3)

heptaldehyde (111-71-7)

n-heptylamine (111-68-2)

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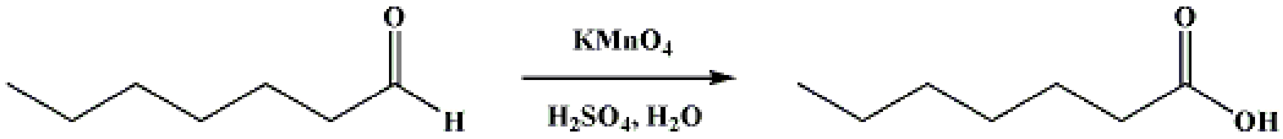
Organic Syntheses, CV 2, 315

n-HEPTANOIC ACID

[Enanthic acid]



Submitted by John R. Ruhoff
Checked by C. R. Noller and M. Patt.

1. Procedure

In a 5-l. flask, fitted with a mechanical stirrer and cooled in an ice bath, are placed 2.7 l. of water and 350 cc. (644 g.) of concentrated sulfuric acid (sp. gr. 1.84). When the temperature has fallen to 15°, 342 g. (403 cc., 3 moles) of heptaldehyde (Note 1) is added, followed by 340 g. (2.15 moles) of potassium permanganate in 15-g. portions. The permanganate is added at such a rate that the temperature does not rise above 20° (Note 2). When the addition of the permanganate is complete, sulfur dioxide is passed through the solution until it becomes clear (Note 3). The oily layer is separated, washed once with water, and distilled from a modified Claisen flask having a 30-cm. fractionating side arm. The fore-runs are separated from any water and distilled again; this is followed by a redistillation of the high-boiling fractions. The yield of material boiling at 159–161°/100 mm. is 296–305 g. (76–78 per cent of the theoretical amount) (Note 4). This product is sufficiently pure for many purposes; titration indicates a purity of 95–97 per cent.

For further purification the product is dissolved in a solution of 140 g. (3.5 moles) of sodium hydroxide in 700 cc. of water and steam-distilled from a 2-l. flask until a test portion of the distillate is free of oil. The solution remaining in the flask is cooled to room temperature and acidified with 375 cc. (4.5 moles) of concentrated hydrochloric acid. The heptanoic acid is separated and distilled from a Claisen flask with fractionating side arm. The recovery of acid boiling at 155–157°/80 mm. is 85–90 per cent of the weight of impure material used. Titration indicates it to be 100 per cent pure.

2. Notes

1. Freshly distilled heptaldehyde boiling at 85.5–87.5°/90 mm. was used.
2. The stirring must be vigorous. About two hours is required for the addition of the permanganate.
3. Sulfur dioxide, in the presence of sulfuric acid, reduces the precipitated manganese dioxide to the soluble sulfate; the removal of this large quantity of flocculent material greatly facilitates separation of the heptanoic acid. The addition of sulfur dioxide requires about two hours; an excess is to be avoided. Sodium bisulfite may be used if sulfur dioxide is not available.
4. Occasionally the heptanoic acid has a yellow color which cannot be removed by fractionation.

3. Discussion

Heptanoic acid has been prepared by the oxidation of heptaldehyde with nitric acid,[1] with potassium permanganate in alkaline aqueous solution[2] or in acetone solution,[3] or with potassium dichromate and sulfuric acid;[4] and by carbonating the reaction product of sodium and 1-chlorohexane.[5]

References and Notes

1. Tilley, Ann. **67**, 107 (1848); Mehlis, ibid. **185**, 360 (1877); Krafft, Ber. **15**, 1717 (1882).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

sodium hydroxide (1310-73-2)

nitric acid (7697-37-2)

potassium permanganate (7722-64-7)

sulfur dioxide (7446-09-5)

sodium bisulfite (7631-90-5)

acetone (67-64-1)

sodium (13966-32-0)

manganese dioxide (1313-13-9)

potassium dichromate (7778-50-9)

Enanthic acid, Heptanoic acid, n-HEPTANOIC ACID (111-14-8)

1-chlorohexane (544-10-5)

heptaldehyde (111-71-7)

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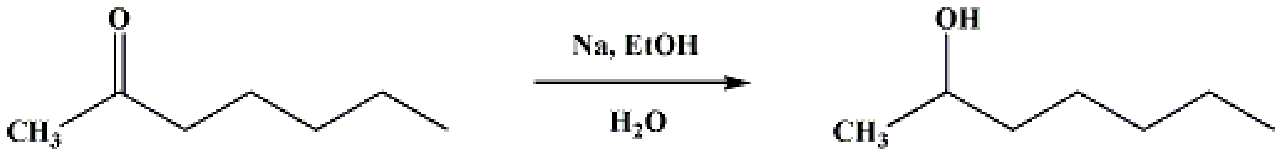
2-HEPTANOL



Submitted by Frank C. Whitmore and T. Otterbacher.
Checked by Henry Gilman and H. J. Harwood.

1. Procedure

In a 3-l. round-bottomed flask, fitted with an efficient Liebig condenser (100 by 1 cm.), 228 g. (2 moles) of methyl *n*-amyl ketone (Org. Syn. Coll. Vol. I, **1941**, 351) is dissolved in a mixture of 600 cc. of 95 per cent alcohol and 200 cc. of water. One hundred thirty grams (5.6 gram atoms) of sodium in the form of wire is gradually added through the condenser. During the addition of the sodium the flask is cooled with running water (Note 1) so that the reaction does not become unduly violent (Note 2).

When the sodium has dissolved (Note 3), 2 l. of water is added and the mixture is cooled to 15°. The upper oily layer is then separated, washed with 50 cc. of 1:1 hydrochloric acid and then with 50 cc. of water, dried over 20 g. of anhydrous sodium sulfate, and distilled with a fractionating column (Note 4). After a small fore-run of low-boiling liquid, the pure heptanol distils at 155–157.5°. The yield is 145–150 g. (62–65 per cent of the theoretical amount).

2. Notes

1. If no cooling is used, condensation products are formed and the yield of heptanol is reduced considerably.
2. The temperature can be held conveniently below 30° by cooling with ice. Such cooling when accompanied by stirring is particularly helpful during the early addition of the sodium (either as wire or in small pieces). With cooling and stirring, very little refluxing takes place and after the addition of about 60 g. of sodium the reaction slows down to such an extent that large amounts of sodium can be added at once without danger of excessive heating.
3. The time required for addition of the sodium may be significantly decreased by the use of mechanical stirring. Although the yield is not increased appreciably by stirring, frothing is prevented and for this reason the sodium may be added more rapidly.
4. The submitters used a Young column with 20 disks 3 cm. apart. The checkers used a Glinsky three-bulbed column.

3. Discussion

2-Heptanol has been prepared by the action of *n*-amylmagnesium bromide on acetaldehyde,[1] and by the reduction of methyl *n*-amyl ketone in alcoholic solution by means of sodium.[2]

References and Notes

1. Henry, Rec. trav. chim. **28**, 446 (1909).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alcohol (64-17-5)

acetaldehyde (75-07-0)

hydrochloric acid (7647-01-0)

sodium sulfate (7757-82-6)

sodium (13966-32-0)

heptanol (111-70-6)

n-amylmagnesium bromide (693-25-4)

METHYL n-AMYL KETONE (110-43-0)

2-Heptanol (543-49-7)

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n-HEPTYLAMINE

Submitted by W. H. Lycan, S. V. Puntambeker, and C. S. Marvel.
Checked by W. H. Carothers and W. L. McEwen.

1. Procedure

A solution of 258 g. (2 moles) of heptaldoxime (p. 313) in 4 l. of absolute alcohol (Note 1) is heated to boiling in a 12-l. round-bottomed flask on a steam bath. The flask is equipped with a 150-cm. reflux condenser in which the inner tube is very wide (2.5 cm.). As soon as the alcohol begins to boil, the steam is shut off and the temperature is maintained by introducing strips of sodium through the top of the condenser. The total amount of sodium added is 500 g., and it should be added as rapidly as is possible without loss of alcohol (Note 2). The last 150 g. of sodium melts in the hot mixture and may be added very rapidly without loss of alcohol or amine.

As soon as the sodium has dissolved, the contents of the flask are cooled and diluted with 5 l. of water. The flask is equipped at once with a condenser set for distillation, and the distillate is carried below the surface of a solution of 300 cc. of concentrated hydrochloric acid in 300 cc. of water in a 12-l. flask. The distillation is continued as long as any basic material passes over. When frothing interferes toward the end of the distillation an additional 3 l. of water is added to the distillation flask. The total distillate is 8–9 l.

The alcohol, water, and unreacted oxime are removed by heating the acid distillate on the steam cone under reduced pressure (about 20–30 mm.); the amine hydrochloride crystallizes in the flask. The flask is then cooled and equipped with a reflux condenser through which 1 l. of 40 per cent potassium hydroxide solution is introduced. The hydrochloride is washed down from the sides of the flask, and the resulting mixture is cooled and transferred to a separatory funnel. The lower alkaline layer is removed and solid potassium hydroxide is added to the amine in the funnel. The aqueous layer is removed and fresh sticks of potassium hydroxide are added from time to time until no further separation of an aqueous alkaline solution occurs. Twenty-four to thirty hours is required for complete drying. The amine is then decanted through the top of the funnel into a 250-cc. modified Claisen flask and distilled. The *n*-heptylamine is collected at 152–157°. The yield is 140–170 g. (60–73 per cent of the theoretical amount) (Note 3).

2. Notes

1. The yields are poor if the alcohol is not completely dehydrated. A very satisfactory grade of alcohol is obtained by distilling ordinary absolute alcohol from magnesium methoxide (Org. Syn. Coll. Vol. I, **1941**, 249).
2. The best yields are obtained when the reduction is carried out rapidly.
3. Using essentially the same method the following amines have been prepared in 50–60 per cent yields: *n*-butylamine, b. p. 75–80°, from butyraldoxime; *sec.*-butylamine, b. p.

59–65°, from ethyl methyl ketoxime; cyclohexylamine, b. p. 133–135°, from cyclohexanone oxime. Greater care must be observed in drying the butylamines.

3. Discussion

n-Heptylamine can be prepared by the reduction of heptaldoxime with sodium amalgam and acetic acid,[1] with ammonium amalgam,[2] with sodium and an alcohol,[3] and catalytically;[4] by the reduction of 1-nitroheptane with iron and acetic acid;[5] by the reduction of heptanonitrile with sodium and an alcohol[3, 6] or catalytically;[7] by the reduction of heptanoamide with sodium and an alcohol[8] or catalytically;[9] by the reduction of heptaldehyde phenylhydrazone with sodium amalgam and acetic acid;[10] and by the catalytic reduction of heptaldehyde and ammonia in alcohol.[11 12] The formation of a secondary amine, which is a serious limitation in the catalytic reduction of heptanonitrile, can be almost completely suppressed by reducing in the presence of a large amount of ammonia.[12]

Other methods which also lead to *n*-heptylamine are the reaction between 1-bromoheptane and ammonia;[13] the Hofmann rearrangement of the amide of caprylic acid;[14] and the Beckmann rearrangement of methyl *n*-heptyl ketoxime, followed by hydrolysis.[15]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 313

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Heptaldoxime

heptaldehyde phenylhydrazone

amide of caprylic acid

alcohol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ammonia (7664-41-7)

iron (7439-89-6)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

magnesium methoxide

Cyclohexanone oxime (100-64-1)

Ammonium (14798-03-9)

heptanonitrile (629-08-3)

butyraldoxime

ethyl methyl ketoxime

cyclohexylamine (108-91-8)

1-nitroheptane

heptanoamide

1-bromoheptane (629-04-9)

n-butylamine (109-73-9)

heptaldehyde (111-71-7)

n-heptylamine (111-68-2)

sec.-butylamine (13952-84-6)

methyl n-heptyl ketoxime

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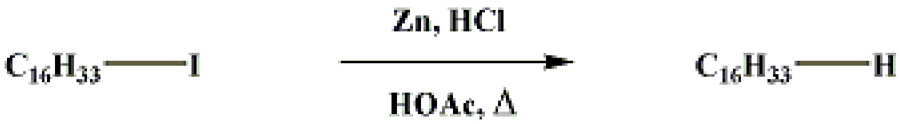
n-HEXADECANE



Submitted by P. A. Levene
Checked by W. W. Hartman, L. A. Smith, and J. B. Dickey.

1. Procedure

In a 2-l. round-bottomed flask, fitted with a liquid-sealed mechanical stirrer, a gas inlet tube, and a tube to carry off hydrogen chloride and acetic acid vapors (Note 1), are placed 915 cc. of glacial acetic acid, 327 g. (5 gram atoms) of zinc dust, and 352 g. (1 mole) of cetyl iodide (m.p. 20–22°) (p. 322). The mixture is saturated with dry hydrogen chloride and then stirred and heated on a steam bath. At the end of every five hours of heating, the mixture is again saturated with hydrogen chloride. After the reaction has proceeded for twenty-five hours, the mixture is allowed to cool, and the layer of hexadecane, which rises to the top of the reaction mixture, is separated. The residue is poured into 3 l. of water and filtered on a Büchner funnel to remove the zinc dust. The zinc dust is washed with 500 cc. of water and then with 250 cc. of ether. The combined water layers are extracted with two 500-cc. portions of ether. The ether extracts are combined and added to the hexadecane, and the resulting solution is washed with two 250-cc. portions of 20 per cent sodium hydroxide and then with water until free of alkali. The ether solution is dried with 150 g. of anhydrous sodium sulfate, filtered, and distilled from a 500-cc. modified Claisen flask with a fractionating side arm. The yield of *n*-hexadecane boiling at 156–158°/14 mm. and melting at 16–17° is 192 g. (85 per cent of the theoretical amount).

2. Notes

1. If the reaction is run in a hood, an open flask may be used.

3. Discussion

n-Hexadecane has been prepared by the reduction of cetyl iodide with zinc and hydrochloric acid in alcohol[1] or acetic acid,[2, 3] with the zinc-copper couple,[3] and with hydrogen and a palladium catalyst.[3] The hydrocarbon has also been prepared by treating octyl iodide with sodium;[4] by heating mercury dioctyl alone or with zinc dust;[5] by heating palmitic acid with hydriodic acid and red phosphorus;[6] and by reducing 1-hexadecene.[7]

n-Hexadecane has been obtained as a by-product from the preparation of octylmagnesium bromide[8] and from the action of sodium on a mixture of octyl bromide and ethyl bromide,[9] and it is one of the products formed on heating sodium stearate[10] or cetyl ether.[11]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

red phosphorus

zinc-copper couple

mercury dioctyl

hydrogen chloride, hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

Ethyl bromide (74-96-4)

Octyl bromide (111-83-1)

sodium sulfate (7757-82-6)

zinc (7440-66-6)

sodium (13966-32-0)

palladium (7440-05-3)

hydriodic acid (10034-85-2)

cetyl iodide (544-77-4)

Hexadecane, n-HEXADECANE (544-76-3)

octyl iodide (629-27-6)

palmitic acid (57-10-3)

1-hexadecene (629-73-2)

octylmagnesium bromide (17049-49-9)

sodium stearate (822-16-2)

cetyl ether (4113-12-6)

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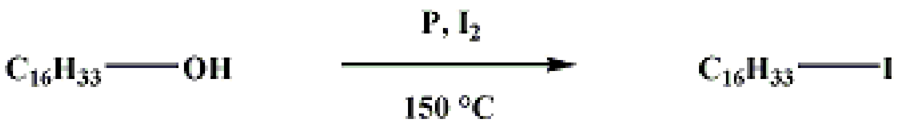
n-HEXADECYL IODIDE

[Hexadecane, 1-iodo-]



Submitted by W. W. Hartman, J. R. Byers, and J. B. Dickey.
Checked by W. H. Carothers and W. L. McEwen.

1. Procedure

Two hundred forty-two grams (1 mole) of cetyl alcohol (Note 1), 10 g. (0.32 gram atom) of red phosphorus, and 134 g. (1.06 gram atoms) of resublimed iodine are placed in a 3-l. round-bottomed flask and heated in an oil bath until the alcohol has melted. The flask is then fitted with a reflux condenser and a liquid-sealed mechanical stirrer. With stirring, the mixture is heated at 145–150° (temperature of the oil bath) for five hours. When the reaction mixture has cooled, the cetyl iodide is removed by extracting once with a 250-cc. portion and twice with 125-cc. portions of commercial ether. The combined ether extracts are filtered free of phosphorus and washed with 500 cc. of cold water, 250 cc. of 5 per cent sodium hydroxide solution, and again with 500 cc. of water. The ether solution is dried over anhydrous calcium chloride. After removal of the ether by distilling on a steam bath, the iodide is distilled under reduced pressure. The main fraction, distilling at 220–225°/22 mm. (210– 215°/12 mm.), weighs 300 g. (85 per cent of the theoretical amount) and melts at 18–20° (Note 2). Redistillation gives 275 g. (78 per cent of the theoretical amount) boiling at 220–223°/22 mm. (203–205°/9 mm.) and melting at 20–22° (Note 3).

2. Notes

1. Cetyl alcohol prepared according to the directions given on p. 374 and melting at 48–49° is satisfactory. If a poorer grade of cetyl alcohol is used, the yield may be reduced to 70 per cent.
2. This material is probably pure enough for most work. Melting points as high as 25° are recorded in the literature.
3. Traces of iodine come over when the distillation starts and the fore-run is therefore strongly colored. When distillation is started again after being interrupted traces of iodine again appear in the first few drops of the main distillate. A more nearly colorless distillate is obtained if the fractions are cut without interrupting the distillation.

3. Discussion

The method described is essentially that of Smith.[1] Several other workers have used a similar method.[2] Cetyl iodide has also been prepared by heating cetyl alcohol with yellow phosphorus and iodine in carbon disulfide solution;[3] by repeatedly passing dry hydrogen iodide into the molten alcohol and permitting the reaction mass to stand between additions;[4] and by heating cetyl alcohol or cetyl stearate with 55 per cent hydriodic acid to a temperature of 120° during two hours.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 320
- Org. Syn. Coll. Vol. 6, 830

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

red phosphorus

calcium chloride (10043-52-4)

ether (60-29-7)

sodium hydroxide (1310-73-2)

PHOSPHORUS (7723-14-0)

iodine (7553-56-2)

carbon disulfide (75-15-0)

hydriodic acid, hydrogen iodide (10034-85-2)

cetyl iodide, Hexadecane, 1-iodo-, n-HEXADECYL IODIDE (544-77-4)

Cetyl alcohol (36653-82-4)

cetyl stearate (1190-63-2)

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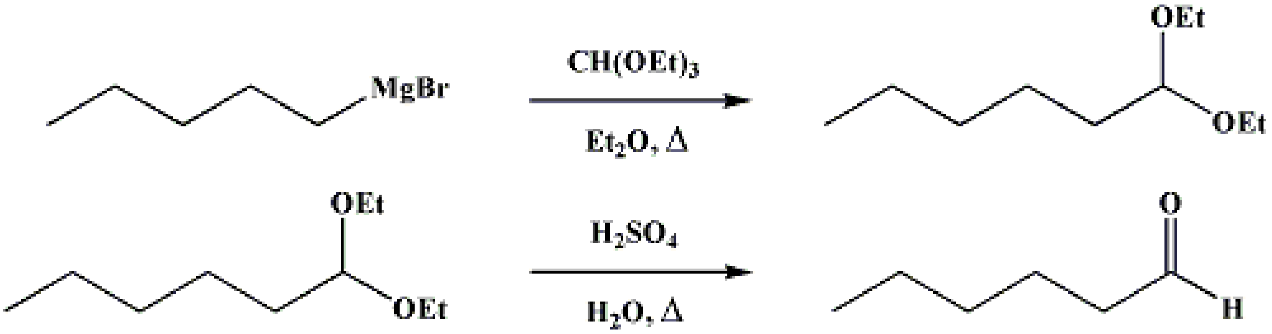
n-HEXALDEHYDE

[Caproaldehyde]



Submitted by G. Bryant Bachman
Checked by C. R. Noller and W. S. Woon.

1. Procedure

In a 2-l. three-necked, round-bottomed flask, fitted with a liquid-sealed mechanical stirrer, a 250-cc. dropping funnel, and a reflux condenser to which is attached a calcium chloride tube, are placed 30 g. (1.25 gram atoms) of magnesium turnings, 50 cc. of dry ether, and a small crystal of iodine. Stirring is started, and 5 cc. (6 g.) of *n*-amyl bromide is added (Note 1). As soon as the reaction has started, 300 cc. of dry ether is added and then, more slowly, a solution of 183 g. (total, 189 g.; 1.25 moles) of *n*-amyl bromide in 150 cc. of dry ether. If external cooling is provided, all the alkyl halide may be added within half an hour; the solution is refluxed gently for another half-hour to complete the reaction. The heat is removed, the flask cooled to 50°, and 148 g. (1 mole) of ethyl orthoformate (Org. Syn. Coll. Vol. I, **1941**, 258) is added during the course of fifteen to twenty minutes. The mixture is refluxed for six hours (Note 2); at the end of this time the condenser is arranged for distillation and the ether is removed completely with the aid of a steam bath.

The reaction mixture is cooled and treated carefully with 750 cc. of chilled 6 per cent hydrochloric acid. The contents of the flask are kept cool by the occasional addition of ice while the acid is being introduced. As soon as all the solid has dissolved (Note 3), the upper oily layer of hexaldehyde acetal is separated. The acetal is hydrolyzed by distilling it with a solution of 100 g. (55 cc.) of concentrated sulfuric acid in 700 cc. of water. The free aldehyde distils rapidly, and the distillation is complete when a sample of fresh distillate contains 5 per cent or less of immiscible oil. The distillate is collected in a solution of 100 g. (1 mole) of sodium bisulfite in 300 cc. of water. The mixture is shaken vigorously for several minutes; the oily layer remaining undissolved in the bisulfite solution is principally *n*-amyl alcohol and is discarded. To remove the remainder of the amyl alcohol and other impurities the bisulfite solution is steam-distilled until 200 cc. of distillate has been collected.

The residual aldehyde-bisulfite solution is cooled to 40–50°, a suspension of 80 g. of sodium bicarbonate in 200 cc. of water is added carefully, and the free aldehyde is removed by steam distillation. The upper layer of the distillate is separated, washed with three 50-cc.

portions of water (Note 4), dried with 20 g. of anhydrous sodium sulfate, and distilled through a 20-cm. column. The yield of *n*-hexaldehyde b.p. 126–129° , is 45–50 g. (45–50 per cent of the theoretical amount).

2. Notes

1. The *n*-amyl bromide was prepared according to the general procedure in Org. Syn. Coll. Vol. I, **1941**, 25, and distilled at 127–129°.
2. Sometimes a white precipitate begins to form immediately, but more often it does not appear until after twenty to thirty minutes of refluxing. If this period of heating is materially decreased, a sudden exothermic reaction occurs when the ether is removed and the yield may be seriously reduced. Longer periods of heating do not increase the yield of hexaldehyde.
3. Solution takes place slowly and is hastened considerably by the use of a mechanical stirrer.
4. The aldehyde dissolved by the wash water may be recovered by steam distillation, but this is scarcely worth while since hexaldehyde is not very soluble in water.

3. Discussion

Hexaldehyde has been prepared from caproic acid by passing it over zinc dust at 300°,[1] by reaction with amylene at 300° in the presence of thorium oxide,[2] by passing it over manganous oxide at 300–360° with two volumes of formic acid,[3] and by distillation of the calcium salt with calcium formate.[4] It has also been prepared by heating α-hydroxyheptoic acid or, better, α-acetoxyheptoic acid,[5] and by the procedure described above.[6]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hexaldehyde acetal

Hexaldehyde

α-hydroxyheptoic acid

α-acetoxyheptoic acid

n-HEXALDEHYDE

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium bicarbonate (144-55-8)

magnesium turnings (7439-95-4)

sodium sulfate (7757-82-6)

formic acid (64-18-6)

sodium bisulfite (7631-90-5)

thorium oxide

iodine (7553-56-2)

zinc (7440-66-6)

Caproic acid (142-62-1)

Ethyl orthoformate

caproaldehyde

amyl alcohol, n-amyl alcohol (71-41-0)

amylene

manganous oxide

calcium formate (544-17-2)

n-amyl bromide (110-53-2)

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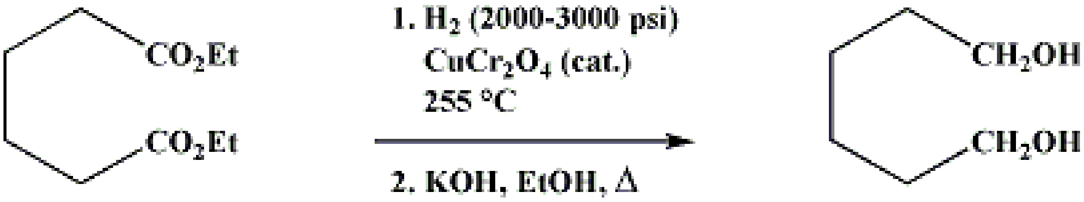
HEXAMETHYLENE GLYCOL

[1,6-Hexanediol]



Submitted by W. A. Lazier, J. W. Hill, and W. J. Amend.
Checked by R. L. Shriner and J. F. Kaplan.

1. Procedure

In a steel reaction vessel (Note 1), capable of withstanding high pressures with an adequate safety factor (Note 2) and having a capacity of 400 cc. or more, are placed 252 g. (1.25 moles) of ethyl adipate (b.p. 144–145°/29 mm.) (p. 264) and 20 g. of copper chromite catalyst, prepared either with or without the addition of barium (p. 142). The reaction vessel is closed, made gas tight, and secured in a suitable agitating device. After connection is made with the hydrogen supply, hydrogen is introduced until a pressure of 2000 to 3000 lb. per sq. in. is reached (Note 2).

Agitation is started, and the reaction system is heated as rapidly as possible to 255°. The temperature is maintained at 255° (Note 3), and hydrogenation is continued until hydrogen absorption is complete (Note 4). The agitation is now stopped, the vessel cooled, and the pressure released. With the aid of four 25-cc. portions of 95 per cent alcohol the reaction mixture is transferred to a 600-cc. beaker. The catalyst is removed by filtering or centrifuging, and is washed with four more 25-cc. portions of alcohol (Note 5). To the reaction product (Note 6), 50 cc. of 40 per cent sodium hydroxide solution is added, and the alcoholic solution is boiled for two hours under a reflux condenser. The mixture is transferred to a 1-l. distilling flask and the alcohol removed by distilling to a vapor temperature of 95°. The hot residue is transferred to an apparatus for the continuous extraction of liquids (p. 615), using 50 cc. of water to rinse the flask, and the solution is exhaustively extracted with ether (Note 7). The ether is distilled, and, after the removal of water and alcohol, the glycol is distilled under reduced pressure in a 250-cc. Claisen flask. The yield is 125–132 g. (85–90 per cent of the theoretical amount). Hexamethylene glycol boils at 143–144° (bath at 160°) under 4 mm. pressure and melts at 41–42°.

2. Notes

1. Suitable reaction vessels and apparatus for agitation of the reaction mixture are commercially available[1], [2] or may be constructed.[3]

2. The pressure of hydrogen to be used is dependent upon the equipment available. Hydrogen in commercial cylinders is sold at a maximum pressure of 2000 lb. per sq. in. Special equipment for compressing hydrogen may be purchased at a reasonable price.[1] The original pressure of hydrogen should not be more than 2000 lb. if the maximum working pressure of the equipment for hydrogenation is 5000 lb. If the working pressure is 10,000 lb. the original pressure in the reaction vessel may be as much as 3000 lb. The full operating pressure is not applied in the beginning since the pressure will rise as the reaction vessel is heated; thus, at 255° the pressure will be 1.8 times as high as it was at 20°. The pressure drops as hydrogenation proceeds; the progress of the reaction may be followed by the change in pressure readings, and completion of the reaction is indicated by the constancy of the pressure readings.
3. The temperature is controlled preferably by an automatic controller operating through a relay which periodically cuts off the supply of electric current.
4. The time (six to twelve hours) required to complete the reaction is a function of the pressure of the hydrogen, activity of the catalyst, and purity of the ethyl adipate. Unless a high pressure of hydrogen is used originally or the reaction vessel is of large capacity (2 l.) it will be necessary to introduce more hydrogen into the reaction vessel; the pressure should never be less than 1500 lb. per sq. in. if the reaction is to run smoothly to completion.
5. The catalyst is most readily removed by centrifuging. If this is not convenient, it may be collected on a sintered glass filter or Büchner funnel.
6. At this point, the amount of ester present may be determined by obtaining the saponification value of the weighed mixture. This procedure is especially desirable when the condition of the apparatus with respect to the possible presence of poisons is unknown, or a new preparation of catalyst is being used. After a batch of catalyst has been tested and the apparatus calibrated so that essentially complete reduction is assured, it is possible to isolate the glycol by fractional distillation at this stage.
According to Burks, Jr., and Adkins [private communication and J. Am. Chem. Soc. **62**, 3300 (1940)] the hydrogenation is reversible and the reaction product always contains esters. In order to obtain hexamethylene glycol free of esters a simpler procedure than that given above is recommended: Thirty grams of crude glycol is dissolved in 50 cc. of water and extracted with four 50-cc. portions of benzene. The water solution is distilled through a modified Widmer column. The recovery of glycol, free of ester, is 93 per cent.
7. The time required for complete extraction varies from twenty-four to fifty hours. It depends on the design of the apparatus and the rate of distillation of the ether. The extraction can be followed by observing the decrease in volume of the aqueous layer containing the glycol. The extraction is complete when the evaporation of a small amount of the supernatant ether on a watch glass leaves no residue. Benzene may be substituted for ether in the extraction.

3. Discussion

Hexamethylene glycol has been prepared by treating hexamethylene iodide with silver

acetate and hydrolyzing the acetate,[4] by hydrolyzing the bromide,[5] by reducing ethyl adipate with sodium and alcohol,[6] and by the method here described.[7] The catalytic hydrogenation over copper-chromium oxide of the carbethoxy group to the carbinol group is a very useful and general method for the preparation of mono- and dihydric alcohols.[3, 8]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 154
- Org. Syn. Coll. Vol. 3, 446
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium and alcohol

alcohol (64-17-5)

Benzene (71-43-2)

ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

Ethyl adipate (626-86-8)

barium (7440-39-3)

COPPER CHROMITE

Copper-Chromium Oxide

Hexamethylene glycol, 1,6-Hexanediol (629-11-8)

hexamethylene iodide (629-09-4)

silver acetate (563-63-3)

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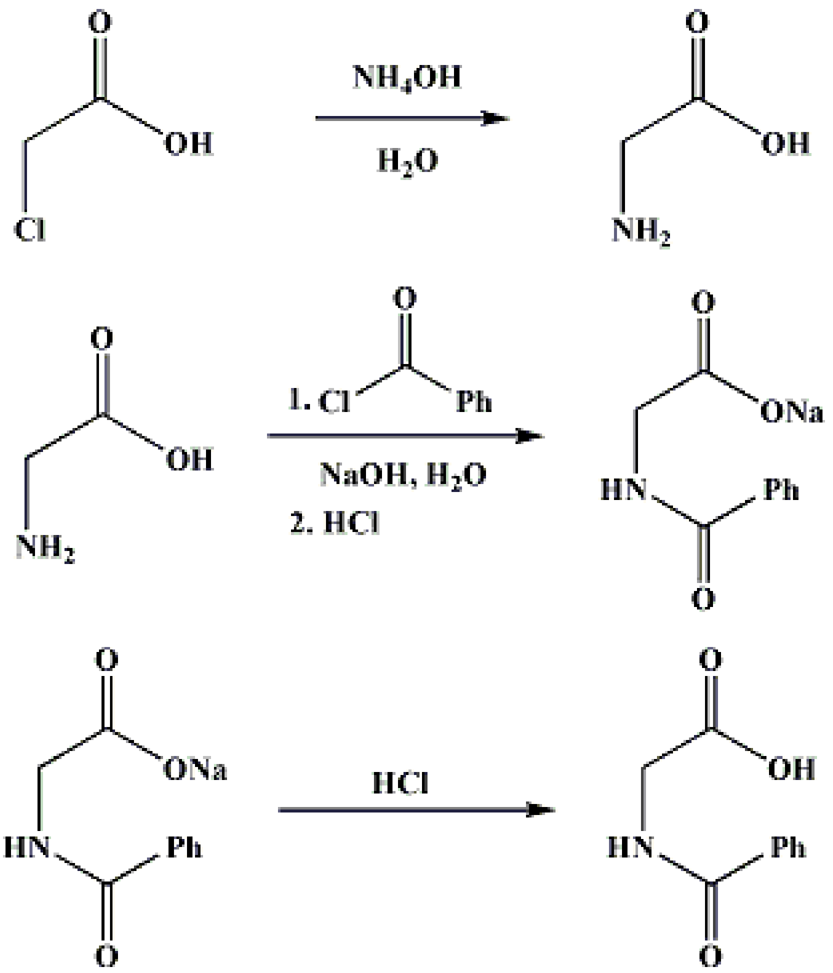
Organic Syntheses, CV 2, 328

HIPPURIC ACID



Submitted by A. W. Ingersoll and S. H. Babcock.
Checked by Roger Adams and B. H. Wojcik.

1. Procedure

To 3 l. (approximately 45 moles) of concentrated ammonium hydroxide (sp. gr. 0.9) (Note 1) in a 5-l. round-bottomed flask is added, with shaking, a solution of 95 g. (1 mole) of chloroacetic acid (Note 2) in 100 cc. of water. The flask is stoppered and allowed to stand for four days (Note 3). It is then attached to a condenser for distillation, and the solution is concentrated to 600–700 cc. The excess ammonia is recovered during this process by connecting the lower end of the condenser to a wide tube leading to the bottom of a 3-l. bottle containing 1.5 l. of distilled water and connecting this in the same way with a smaller bottle containing a little water. The bottles are cooled by running water. About 2 l. of 20–23 per cent ammonium hydroxide is recovered in the first receiver (Note 1).

The residual solution is then transferred to a 2-l. beaker, a solution of 50 g. (1.25 moles) of sodium hydroxide in 100 cc. of water and a little decolorizing carbon are

added, and the mixture is boiled until the odor of ammonia is completely absent (Note 4). The solution is filtered by suction, diluted to 500 cc. with water, and transferred to a 2-l. round-bottomed flask equipped with a mechanical stirrer and cooled by running water. While stirring and cooling below 30°, 150 g. (1.1 moles) of benzoyl chloride (Note 2) and a cold solution of 80 g. (2 moles) of sodium hydroxide in 200 cc. of water are admitted separately from separatory funnels at such rates that the solution is always only slightly alkaline. About an hour is required for adding the reagents, and the mixture is stirred for a half hour longer. It is then poured into 125 cc. of concentrated hydrochloric acid in a 2-l. beaker, and, after cooling, the precipitate is filtered and dried. The weight at this point is 150–160 g. The solid is placed in a beaker with 300 cc. of technical carbon tetrachloride, the beaker is covered with a watch glass, and the mixture is boiled gently for ten minutes. The mixture is then cooled slightly, filtered by gentle suction, and the hippuric acid washed on the filter with 50 cc. of carbon tetrachloride (Note 5). After drying, it weighs 135–140 g. For final purification the acid is dissolved in about 2 l. of boiling water, filtered through a steam-heated funnel and allowed to crystallize without artificial cooling. It then appears in characteristic white needles melting at 186–187°. The yield is 115–122 g. (64–68 per cent of the theoretical amount based on the chloroacetic acid used). Upon concentrating the mother liquor to 200 cc., a further 6–7 g. of slightly brown hippuric acid is obtained.

2. Notes

1. An equivalent amount of recovered ammonium hydroxide (sp. gr. 0.93 or less) was used in a number of runs without reducing the yield.
2. Eastman's "practical" grade reagents were used.
3. The yield was slightly less after two days and no greater after a week.
4. Ammonia must be completely removed to avoid the formation of benzamide.
5. Carbon tetrachloride may be recovered by making the filtrate and washings slightly alkaline with sodium hydroxide, refluxing for a half hour to destroy any benzoyl chloride, and then distilling with steam. Benzoic acid may be recovered by filtering the aqueous residue and acidifying.

3. Discussion

Hippuric acid has been prepared from the urine of herbivorous animals;[1] by heating benzamide with chloroacetic acid;[2] by heating benzoic anhydride and glycine;[3] by heating benzoic acid and glycine;[4] by heating benzoyl chloride with silver glycinate suspended in benzene,[5] or with glycine and zinc oxide;[6] and by the action of benzoyl chloride upon an alkaline solution of glycine.[7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 55

- Org. Syn. Coll. Vol. 2, 489

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

Benzene (71-43-2)

sodium hydroxide (1310-73-2)

carbon tetrachloride (56-23-5)

Benzoic acid (65-85-0)

chloroacetic acid (79-11-8)

decolorizing carbon (7782-42-5)

benzoyl chloride (98-88-4)

Benzoic anhydride (93-97-0)

benzamide (55-21-0)

ammonium hydroxide (1336-21-6)

Glycine (513-29-1)

Hippuric acid (495-69-2)

zinc oxide

silver glycinate

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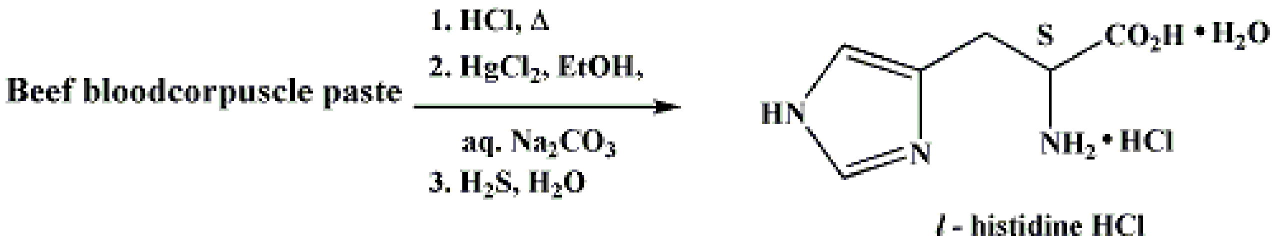
Organic Syntheses, *CV 2, 330*

l-HISTIDINE MONOHYDROCHLORIDE



Submitted by G. L. Foster and D. Shemin.
Checked by John R. Johnson, H. E. Carter, and P. L. Barrick.

1. Procedure

In a large round-bottomed flask are placed 1.4 kg. of dried blood corpuscle paste (Note 1) and 4.5 l. of concentrated hydrochloric acid (sp. gr. 1.18). The flask is warmed on a steam bath until the protein has dissolved, and the mixture is boiled gently under reflux for eighteen to twenty hours. After the hydrolysate has been concentrated under reduced pressure to a thick paste, the distillation is continued with the slow addition of a liter of water, thus eliminating most of the excess hydrochloric acid. The residue is taken up in 8 l. of warm water, cooled, and neutralized to *p*H 4.4–4.6 (methyl orange or bromcresol green) by the addition of concentrated sodium hydroxide solution (Note 2). After the mixture has stood overnight, the precipitated pigment is removed by filtering through a large Büchner funnel fitted with two layers of filter paper and a 2-mm. layer of infusorial earth. The filtrate, which is dull red in color, is decolorized by warming and stirring for ten minutes with 60 g. of Norite.

The pale yellow filtrate and washings from the Norite are diluted to 25 l. with tap water, and a solution of 600 g. of mercuric chloride in 2 l. of hot 95 per cent alcohol is added, with stirring. A concentrated solution of sodium carbonate (corresponding to about 350 g. of anhydrous sodium carbonate) is added slowly, with stirring, until the mixture reaches *p*H 7.0–7.5 (phenol red or litmus). After settling for several hours, preferably overnight, the supernatant liquid is siphoned off, and the crock is refilled with water to the original volume (Note 3). The mixture is allowed to settle, the wash liquid siphoned off, and the precipitate washed twice more in the same fashion. After the third washing, the supernatant liquid is siphoned off and the precipitate collected with suction on a large Büchner funnel fitted with two layers of filter paper and a 2-mm. layer of infusorial earth.

The moist histidine-mercury complex is suspended in 5 l. of water and stirred vigorously while a stream of hydrogen sulfide is introduced. When precipitation of mercuric sulfide is complete, the suspension becomes uniformly black and settles sharply on standing. The filtrate and washings from the mercuric sulfide (Note 4) are concentrated under reduced pressure to a volume of about 1 l. and cleared with 5 g. of Norite. The filtrate and washings from the Norite are concentrated further to a volume of about 250 cc. and mixed with three volumes of 95 per cent alcohol. Crystallization is induced by cooling the solution and scratching the walls of the vessel; the histidine monohydrochloride separates in plates. After

the material has remained in an ice chest for three or four days, the crystals are separated by suction filtration. The yield of crude histidine monohydrochloride is 85–90 g. The filtrate, on standing for several weeks in an ice chest, usually deposits an additional 4–5 g. of material.

The crude product is dissolved in five times its weight of water, and, after clearing with a little Norite, the solution is diluted with one and one-half volumes of 95 per cent alcohol. The product separates in well-formed, snow-white crystals, and after standing for several days in an ice chest is collected with suction on a Büchner funnel. The yield of purified histidine monohydrochloride is 75–80 g. (Note 5). The compound melts at 251–252°, with decomposition. The amino acid is not racemized by the procedure employed, and it shows the characteristic optical activity, $[\alpha]_D^{26°}$ = +8.0°, in the presence of three moles of hydrochloric acid. The recrystallized product is usually analytically pure and shows the correct Van Slyke amino nitrogen content. Occasionally a second recrystallization is necessary to obtain analytically pure material.

2. Notes

1. Commercial "dried blood corpuscle paste" obtained from Armour and Company, Chicago, was used in this preparation. This paste contains about 15 per cent of moisture and ash, and 200 g. contains about the same amount of crude protein as 1 l. of fresh beef blood (170 g. protein per liter).
If fresh blood is used in this preparation, it is convenient to remove much of the water in the following way. Seven liters of beef blood in a 12-l. round-bottomed flask is treated with 50 cc. of glacial acetic acid and heated on a steam bath, with occasional stirring, until a thick, pasty coagulum results. About 4 l. of water is removed by distillation under reduced pressure, using a steam bath, and the residue is hydrolyzed as described above.
2. About 600 cc. of 50 per cent sodium hydroxide is required for neutralization. An excess of alkali should be avoided.
3. If, as occasionally happens, the histidine-mercury complex settles slowly, the supernatant liquid may be siphoned off and filtered. The small amount of material collected on the filter is then returned to the main portion.
4. The mercuric sulfide may be saved and converted to metallic mercury or mercuric chloride by the usual procedures.
5. About 10 g. of crude histidine monohydrochloride may be recovered from the mother liquor by evaporating under reduced pressure to 50–60 cc. and adding one and one-half volumes of 95 per cent alcohol. On recrystallization, 8–9 g. of pure material is obtained.

3. Discussion

The preparation of histidine by the hydrolysis of hemoglobin and precipitation with mercuric chloride in alkaline solution was first carried out by Fränkel.[1], [2], [3] Histidine can also be precipitated as the silver derivative.[4]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

metallic mercury

histidine-mercury complex

alcohol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

sodium hydroxide (1310-73-2)

phenol (108-95-2)

hydrogen sulfide (7783-06-4)

sodium carbonate (497-19-8)

Norite (7782-42-5)

mercuric chloride (7487-94-7)

bromcresol

mercuric sulfide

histidine monohydrochloride, L-Histidine monohydrochloride (1007-42-7)

histidine (71-00-1)

methyl orange (547-58-0)

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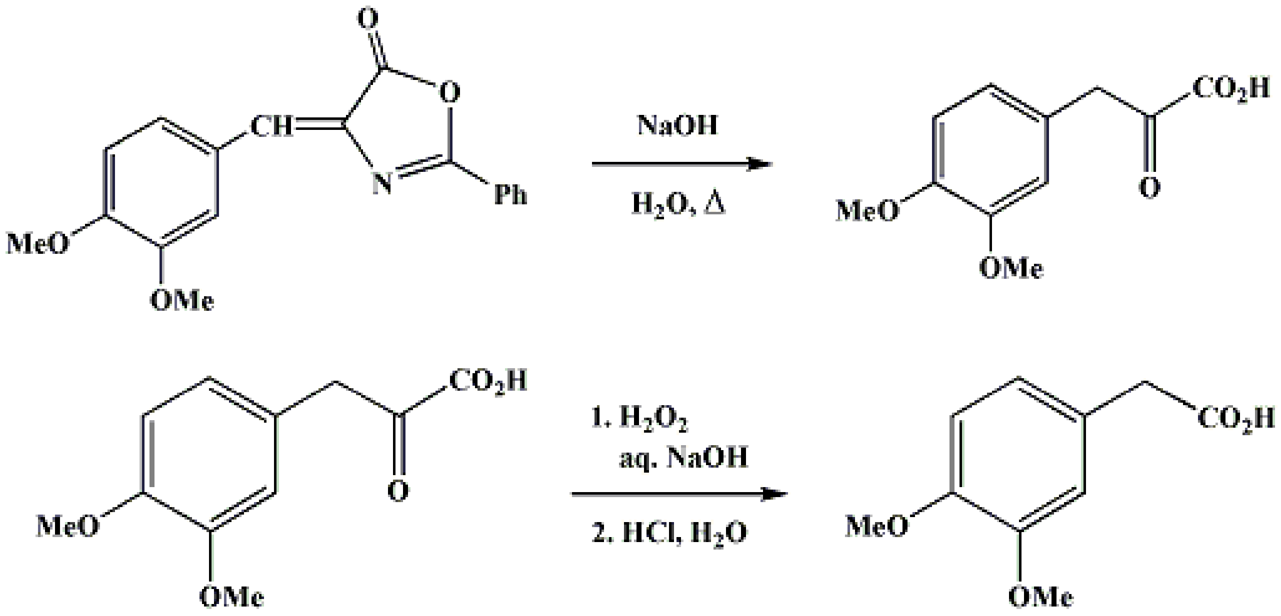
Organic Syntheses, CV 2, 333

HOMOVERATRIC ACID



Submitted by H. R. Snyder, J. S. Buck, and W. S. Ide.
Checked by John R. Johnson and P. W. Vittum.

1. Procedure

(*A*) *Methyl Homoveratrate*.—In a 3-l. round-bottomed flask are placed 1 l. of 10 per cent sodium hydroxide solution and 200 g. (0.65 mole) of the azlactone of α-benzoylamino-β-(3,4-dimethoxyphenyl) acrylic acid (m.p. 149–150°) (p. 55). The flask is fitted with a reflux condenser and immersed in an oil bath so that the inner level is lower than the oil level of the bath (Note 1). The mixture is refluxed gently for six to seven hours, until the evolution of ammonia is complete. The resulting solution contains the sodium salts of 3,4-dimethoxyphenylpyruvic acid (Note 2) and benzoic acid.

To the above aqueous solution, contained in a 2-l. wide-mouthed Erlenmeyer flask, is added 85 cc. of 40 per cent sodium hydroxide solution. The flask is equipped with a mechanical stirrer and is cooled in an ice-salt mixture. With stirring, 75 cc. of 30 per cent hydrogen peroxide (Merck's "Superoxol") diluted with 75 cc. of water is added at such a rate that the temperature does not rise above 15°. After standing for about ten hours at room temperature (preferably overnight) the solution is acidified by the cautious addition (Note 3) of 450 cc. of concentrated hydrochloric acid (sp. gr. 1.19). The warm acid solution is extracted with one 400-cc. portion and two 200-cc. portions of warm benzene. The combined benzene extracts are dried over anhydrous magnesium sulfate and filtered through a cotton plug into a 3-l. round-bottomed flask.

The benzene is removed by distillation, 1 l. of methyl alcohol (Note 4) containing 15 cc. of concentrated sulfuric acid is added, and the flask is fitted with an efficient reflux condenser provided with a drying tube. After refluxing gently for five hours the condenser is set downward for distillation and the methyl alcohol is distilled from a steam bath. The residual liquid is cooled and shaken with 500 cc. of cold water. The mixture is transferred to a

separatory funnel and extracted with one 400-cc. portion and two 200-cc. portions of benzene. The combined extracts are washed twice with 100-cc. portions of 10 per cent sodium carbonate solution and finally with two 100-cc. portions of water. After the benzene solution has been dried over anhydrous magnesium sulfate, it is transferred to a 2-l. flask and the benzene is distilled, using a steam bath. The residual mixture of methyl benzoate and methyl homoveratrate is transferred to a 250-cc. Claisen flask and distilled under reduced pressure. The first fraction, collected up to 100° at 16 mm., is methyl benzoate (b.p. 87°/16 mm.) and weighs about 75 g. (85 per cent of the theoretical amount). After a small intermediate fraction of 2–3 g., pure methyl homoveratrate is collected at 176–178°/16 mm. or 129–131°/1 mm. The yield is 76–82 g. (56–60 per cent of the theoretical amount based on the azlactone).

(*B*) *Homoveratric Acid*.—In a 500-cc. round-bottomed flask are placed 250 cc. of 10 per cent sodium hydroxide solution and 76 g. (0.36 mole) of methyl homoveratrate. The flask is fitted with a reflux condenser and the mixture is boiled gently. The saponification proceeds rapidly, and the ester layer disappears after about ten minutes. The mixture is refluxed gently for twenty minutes longer, after which the solution is cooled in an ice bath and then poured slowly, with stirring, into a mixture of 125 cc. of concentrated hydrochloric acid and 350 g. of ice. Crystals of the hydrate of homoveratric acid separate at once. After standing for about thirty minutes the crystalline product is filtered with suction and washed on the filter with two 25-cc. portions of ice water. The crystals are pressed thoroughly on the filter, pulverized, and allowed to stand overnight in a vacuum desiccator containing soda lime (to remove residual hydrochloric acid) and calcium chloride. The yield in the saponification is almost quantitative and amounts to 70 g. (55 per cent of the theoretical amount based on the original azlactone). This product melts at 96–97° and contains traces of sodium chloride. For purification it is dissolved in 350 cc. of hot benzene and the solution is filtered. To the hot filtrate is added 150 cc. of hot ligroin (b.p. 70–80°), and the solution is covered with a watch glass and allowed to cool slowly. After standing for several hours (preferably overnight) in a cool place, the crystals are filtered with suction and washed with a cold solution of 35 cc. of benzene and 15 cc. of ligroin, followed by 50 cc. of cold petroleum ether. The solvent is removed as completely as possible by pressing on the filter and finally by allowing the product to stand in a vacuum desiccator (Note 5). The purified homoveratric acid weighs 65 g. (51 per cent of the theoretical amount based on the original azlactone) and melts sharply at 98°.

2. Notes

1. The inner level is kept below that of the oil in order to avoid the otherwise uncontrollable bumping of the solution.
2. 3,4-Dimethoxyphenylpyruvic acid can be isolated from this solution in the following way (J. S. Buck and W. S. Ide). The aqueous solution of the sodium salts is saturated with sulfur dioxide, while the temperature is maintained below 40°. The benzoic acid precipitates and is filtered with suction and washed with a small quantity of water. The filtrate and washings are placed in a 3-l. round-bottomed flask provided with a mechanical stirrer and heated to boiling. Concentrated hydrochloric acid is added cautiously, with stirring, until present in excess. The acid must be added carefully since the solution tends to become supersaturated with sulfur dioxide, which is subsequently liberated with violence. A heavy precipitate of 3,4-dimethoxyphenylpyruvic acid separates; after the reaction mixture has cooled, this is filtered with suction, dried, and washed with two 50-cc. portions of ether. The yield of 3,4-dimethoxyphenylpyruvic acid is 110–116 g. (76–80 per cent of the theoretical amount), and the product melts at 181–

184°. It can be purified by crystallization from glacial acetic acid.
An alternative procedure for the preparation of homoveratric acid (J. S. Buck and W. S. Ide) consists in isolating the pyruvic acid and subjecting it to the oxidation given in the second paragraph of part (*A*). This variation obviates the esterification but in the hands of the checkers did not prove so satisfactory as the one described.
3. Large quantities of carbon dioxide are evolved during the addition of the acid.
4. It is unnecessary to use especially dried methyl alcohol. High-grade commercial methanol is quite satisfactory.
5. Since the acid forms a hydrate it is advisable to minimize the exposure of the acid to atmospheric moisture.

3. Discussion

Homoveratric acid has been prepared by the methylation of homoprotocatechuic acid[1] or homovanillic acid[2] with methyl iodide, and from veratric aldehyde through the azlactone and 3,4-dimethoxyphenylpyruvic acid.[3] Homoveratric acid has also been prepared by hydrolysis of its amide or nitrile: the amide was obtained from veratroyl chloride through the diazoketone,[4] or from veratric aldehyde cyanohydrin through α-chlorohomoveratramide;[5] the nitrile was obtained by catalytic reduction of acyl derivatives of veratric aldehyde cyanohydrin.[6]

The procedure given above is adapted from published directions for the preparation of homoveratric acid[3] and *p*-methoxyphenylacetic acid.[7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 471

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ligroin

petroleum ether

azlactone of α-benzoylamino-β-(3,4-dimethoxyphenyl) acrylic acid

sodium salts of 3,4-dimethoxyphenylpyruvic acid

hydrate of homoveratric acid

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ammonia (7664-41-7)

Benzene (71-43-2)

methyl alcohol, methanol (67-56-1)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

sulfur dioxide (7446-09-5)

Benzoic acid (65-85-0)

carbon dioxide (124-38-9)

hydrogen peroxide (7722-84-1)

Methyl iodide (74-88-4)

methyl benzoate (93-58-3)

Pyruvic acid (127-17-3)

magnesium sulfate (7487-88-9)

veratric aldehyde (120-14-9)

Homoveratric acid (93-40-3)

Methyl homoveratrate (15964-79-1)

3,4-Dimethoxyphenylpyruvic acid (2460-33-5)

homoprotocatechuic acid (102-32-9)

homovanillic acid (306-08-1)

veratroyl chloride (3535-37-3)

veratric aldehyde cyanohydrin

α-chlorohomoveratramide

p-methoxyphenylacetic acid (104-01-8)

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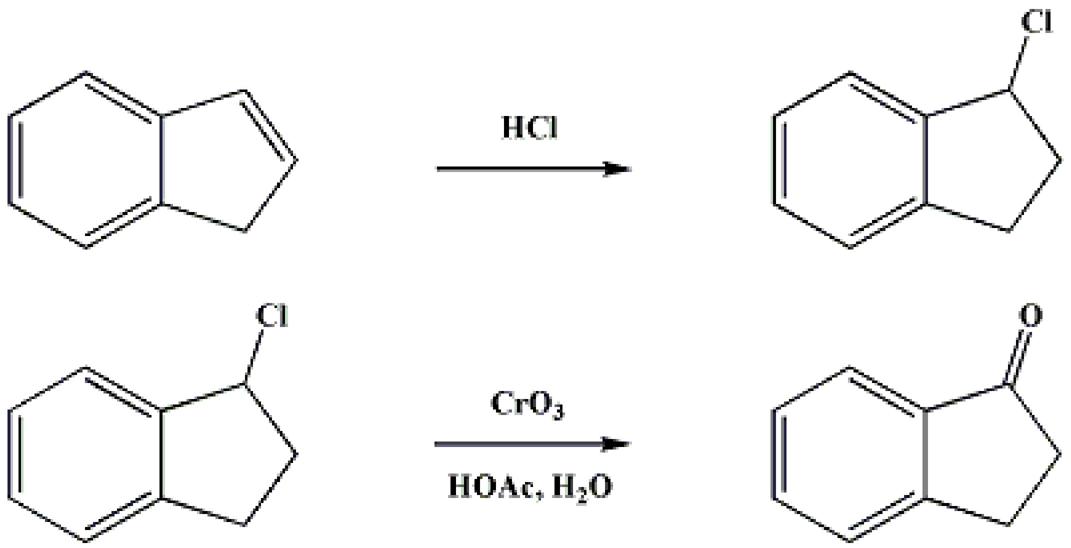
Organic Syntheses, CV 2, 336

α-HYDRINDONE

[1-Indanone]



Submitted by R. A. Pacaud and C. F. H. Allen.
Checked by Louis F. Fieser and W. P. Campbell.

1. Procedure

A 250-cc. flask, fitted with an inlet tube reaching to the bottom, a thermometer, and an exit tube for conducting away unused gas, is immersed in an ice-water bath, and to it is added 80 g. (0.69 mole) of freshly distilled indene (Note 1). While the temperature of the liquid is kept at 5–10°, dry hydrogen chloride is passed in at a moderate rate until 24–27 g. of the gas has been absorbed. The addition takes from eight to ten hours and requires little attention from the operator. The crude α-chlorohydrindene is then transferred to a 250-cc. Claisen flask and distilled at diminished pressure. After a small fore-run (5–10 g.) containing indene, α-chlorohydrindene boiling at 90–103°/15 mm. is collected; the yield is 80–90 g. (Note 2).

In a 500-cc. three-necked flask, fitted with a stirrer, thermometer, and dropping funnel, is placed 100 g. (1 mole) of chromic anhydride dissolved in 100 cc. of water, and 100 cc. of glacial acetic acid is added. The α-chlorohydrindene is then admitted through the funnel at such a rate as to keep the temperature at 35–40°, the flask being cooled externally. This addition takes about one and one-half hours; after it is complete, stirring is continued for fifteen minutes before the mixture is poured into a large beaker and diluted with 300 cc. of water. After the acid present is neutralized by the addition of solid sodium carbonate (Note 3), the α-hydrindone is expelled from the mixture by steam distillation, care being taken to avoid entrainment of froth at the beginning of the process. When about 2.5 l. of distillate has been collected, the solution again begins to froth. The operation is stopped at this point, since further

distillation does not yield an appreciable quantity of product. The α-hydrindone usually solidifies, as soon as the distillate is chilled, to a mixture of colorless crystals and a yellow solid; the product is collected after thorough cooling in an ice bath. This moist solid is dissolved in 200 cc. of benzene, and the solution is subjected to distillation until free from water. After the benzene is removed by vacuum distillation on the steam bath, the α-hydrindone is distilled. It boils at 125–126°/17 mm., and the distillate is a pale yellow solid, m.p. 39–41°. The yield is 46–55 g. (50–60 per cent of the theoretical amount, based on the indene used) (Note 4) and (Note 5).

2. Notes

1. If technical indene is employed, the fraction boiling at 178–182° is suitable for the preparation. The checkers used indene, b.p. 181.6–183.3°, obtained from the Barrett Company, New York City.
2. Most of the material distils at 100–103°/15 mm., but the yield of α-hydrindone is increased by using the material collected over the wider range.
3. An excess of sodium carbonate promotes foaming during the distillation and is to be avoided. Since the neutral point is not easily recognized with test paper, the carbonate is added in decreasing amounts until a fresh portion is no longer decomposed with gas evolution.
4. It is not practicable to dry the steam-distilled product in the air because α-hydrindone has such a high vapor pressure that the loss is appreciable. Drying can be accomplished in a vacuum desiccator, but this takes several days. The distillation specified gives a completely anhydrous product with the loss of no more than 2–5 g.
5. Crystallization is conveniently accomplished by dissolving the α-hydrindone in alcohol (1 cc. per gram) at room temperature, adding water until solid just begins to separate, and cooling to 0°. The substance crystallizes either as long plates or as leaflets.

3. Discussion

α-Hydrindone has been prepared from indene chlorohydrin,[1] the procedure described above; from indene bromohydrin by heating with dilute sulfuric acid;[2] by cyclization of hydrocinnamoyl chloride with ferric chloride[3] or aluminum chloride;[4] by the cyclization of hydrocinnamic acid with hydrogen fluoride[5] or sulfuric acid;[6] and by the interaction of acrylyl chloride with benzene in the presence of aluminum chloride.[7]

References and Notes

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3. Wedekind, Ann. **323**, 255 (1902).
4. Kipping, J. Chem. Soc. **65**, 484 (1894).

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

indene chlorohydrin

indene bromohydrin

sulfuric acid (7664-93-9)

hydrogen chloride (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

sodium carbonate (497-19-8)

hydrogen fluoride (7664-39-3)

aluminum chloride (3495-54-3)

ferric chloride (7705-08-0)

Hydrocinnamic acid (501-52-0)

chromic anhydride

α-Hydrindone, 1-Indanone (83-33-0)

indene (95-13-6)

α-Chlorohydrindene (35275-62-8)

hydrocinnamoyl chloride (645-45-4)

acrylyl chloride (814-68-6)

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Organic Syntheses, CV 2, 338

HYDROGEN BROMIDE (ANHYDROUS)

[Hydrobromic acid]

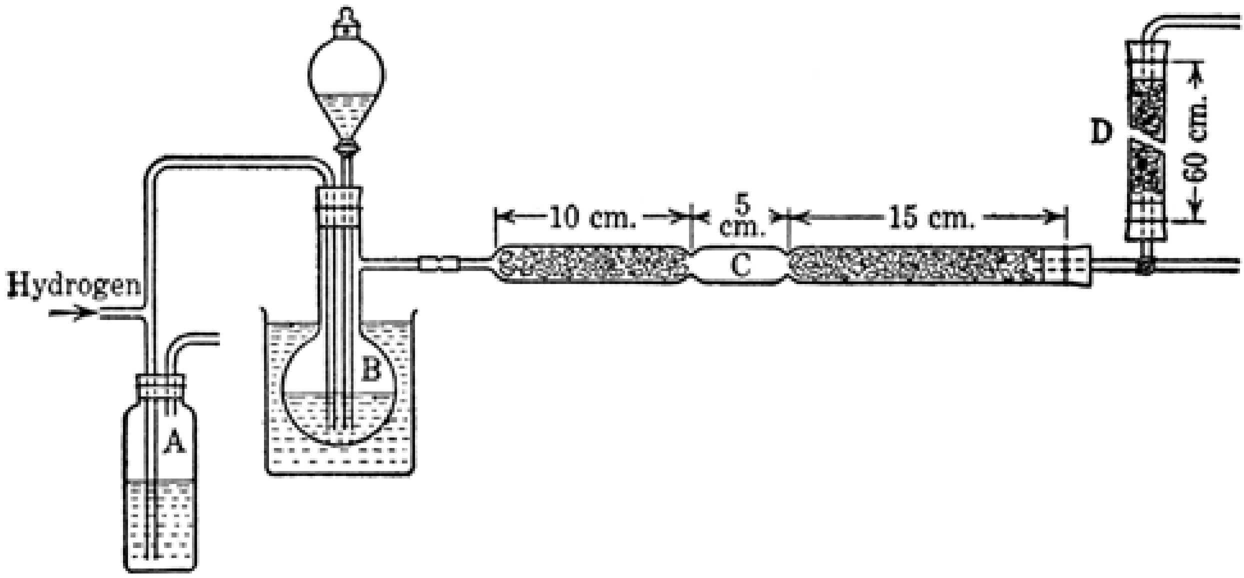
$$H_2 + Br_2 \longrightarrow 2\,HBr$$

Submitted by John R. Ruhoff, Robert E. Burnett, and E. Emmet Reid.
Checked by W. H. Carothers and W. L. McEwen.

1. Procedure

(*A*) *Apparatus*.—A 125-cc. distilling flask (B, f.htmig. 9) (Note 1) is fitted with a two-holed rubber stopper bearing a 50-cc. dropping funnel (Note 2) and an inlet tube about 6 mm. in diameter, both of which reach to the bottom of the flask. The flask is supported in an 800-cc. beaker which serves as a water bath. The side arm of the flask is connected by means of a short piece of rubber tubing to the narrow end (Note 3) of the combustion tube C which is made of Pyrex glass and is 20 mm. in diameter (inside) and 30 cm. in length. It is packed with pieces of porous plate held in place by constrictions as shown in the figure, and it is supported at each end by a small clamp at a sufficient height to give a clearance of 3–4 cm. above a Bunsen burner. The open end of the tube is connected by means of stoppers and a three-way stopcock (Note 4) to the vertical tube D, of the same diameter as C and 60 cm. long. This tube is packed with copper turnings to remove any uncombined bromine which may escape from the combustion tube. A safety bottle A containing water or some other suitable liquid and having a tube leading to the vent of the hood is placed in the train to provide an outlet for the hydrogen in case an obstruction is formed in the apparatus. It also provides a convenient method for determining the hydrogen pressure (Note 5). Hydrogen is obtained from a cylinder fitted with a reducing valve.

Fig. 9



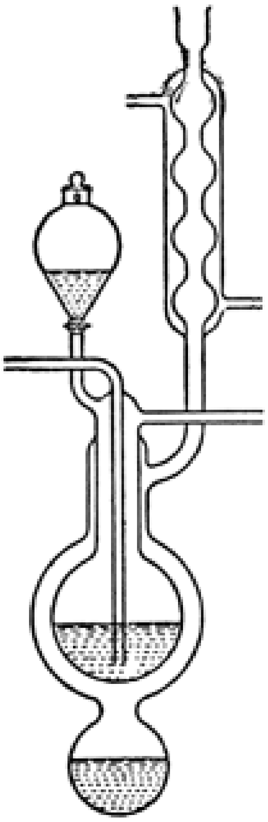
(*B*) *Operation*.—The tube D is disconnected from the combustion tube by turning the

stopcock so that the gases pass directly to the hood. Bromine is placed in flask B; the water bath is heated to 38° and maintained at this temperature (Note 6). A slow stream of hydrogen is started through the apparatus, and, when the combustion tube is completely filled with bromine vapors, a low flame is placed under the empty section of the combustion tube. Soon a small yellow flame appears inside the heated portion of the tube, and, when all bromine vapor has been swept from the combustion tube, the latter is connected to the tube D (Note 7). The flame is adjusted to keep the lower part of the tube at a dull red heat; it may be necessary to raise or lower it, according to the rate of operation. The flow of hydrogen is regulated to give the desired output. The apparatus will conveniently produce 300 g. of hydrogen bromide per hour (Note 8).

2. Notes

1. It is convenient to bend the side arm of the distilling flask so that it is perpendicular to the neck.
2. The stopcock of the dropping funnel should be held in place by means of a rubber band.
3. The distilling flask may be connected to the combustion tube by means of a rubber stopper, but it is preferable to seal a piece of 6-mm. tubing to one end and to use a small piece of rubber tubing for the connection. Even with this arrangement the connection must be inspected from time to time to be sure that the tube is not obstructed. It is still more satisfactory to use a ground-glass joint.
4. The three-way stopcock may be dispensed with, but it facilitates the starting operation and provides a quick method for venting the gas in case combination does not take place properly, thus preventing deterioration of the copper turnings.
5. When operating to produce about 300 g. of hydrogen bromide per hour the water level is depressed approximately 12 cm.
6. The vapor pressure of bromine should be maintained at half an atmosphere. The vapor pressure of bromine is reported as 324 mm. at 35° and 392 mm. at 40°. If the bath becomes too warm, it should be cooled at once with ice; otherwise more bromine will be evaporated than will combine with the hydrogen present.
A more convenient form of apparatus for the vaporization of bromine is shown in .htmFig. 10. This is the same in principle as that described in the above procedure, but the bromine container instead of being heated by warm water is heated by the vapor of boiling ethyl bromide (38.4°). Thus no attention to a water bath is required.
7. The copper turnings remove any trace of bromine that may be present by converting it to black cupric bromide. If the level of blackened copper rises, bromine is being carried over. The presence of a small quantity of moisture, however, will cause a slight darkening of all the copper.

Fig. 10



Alternatively, bromine may be removed by passing the hydrogen bromide through a solution of phenol in carbon tetrachloride (Org. Syn. **20**, 65).
If very dry hydrogen bromide is desired, a small trap surrounded by solid carbon dioxide and placed in the train will condense the water and a small amount of hydrogen bromide. Attention is necessary to prevent clogging of the trap.

8. According to the literature,[1] in the preparation of hydrogen bromide by combination of the elements the chief difficulties are avoiding explosive combination on the one hand and spontaneous extinction of the flame on the other hand. Neither of these difficulties has been encountered in repeated operations extending over many hours with the apparatus described above.

3. Discussion

The very extensive literature on the preparation of hydrogen bromide is completely and concisely reviewed in Gmelin's "Handbuch."[1] The methods most commonly used involve the hydrolysis of certain bromides, particularly the action of bromine on red phosphorus and water; the action of bromine on hydrocarbons, particularly on tetralin; and the direct combination of the elements. The action of bromine on tetralin is a convenient one for small-scale laboratory operation.[2] The direct combination of the elements has certain advantages of simplicity and cleanliness especially when considerable amounts of hydrogen bromide are required. Platinum and charcoal have frequently been used as catalysts but they can be dispensed with at sufficiently high temperatures.[3]

Detailed directions for preparing hydrogen bromide by the bromination of and by the direct combination of hydrogen and bromine are given in Inorganic Syntheses.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 246
- Org. Syn. Coll. Vol. 3, 11
- Org. Syn. Coll. Vol. 3, 576
- Org. Syn. Coll. Vol. 5, 545

References and Notes

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2. For details see Houben, "Die Methoden der organischen Chemie," 3rd ed., Vol. III, p. 1156, Verlag Georg Thieme, Leipzig, 1930.
3. Ruhoff, Burnett, and Reid, J. Am. Chem. Soc. **56**, 2784 (1934).
4. Inorganic Syntheses, **I**, 149, McGraw-Hill, New York, 1939.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

red phosphorus

hydrogen (1333-74-0)

phenol (108-95-2)

HYDROBROMIC ACID, hydrogen bromide (10035-10-6)

bromine (7726-95-6)

Ethyl bromide (74-96-4)

carbon tetrachloride (56-23-5)

carbon dioxide (124-38-9)

platinum (7440-06-4)

copper, copper turnings (7440-50-8)

Tetralin (119-64-2)

cupric bromide (7789-45-9)

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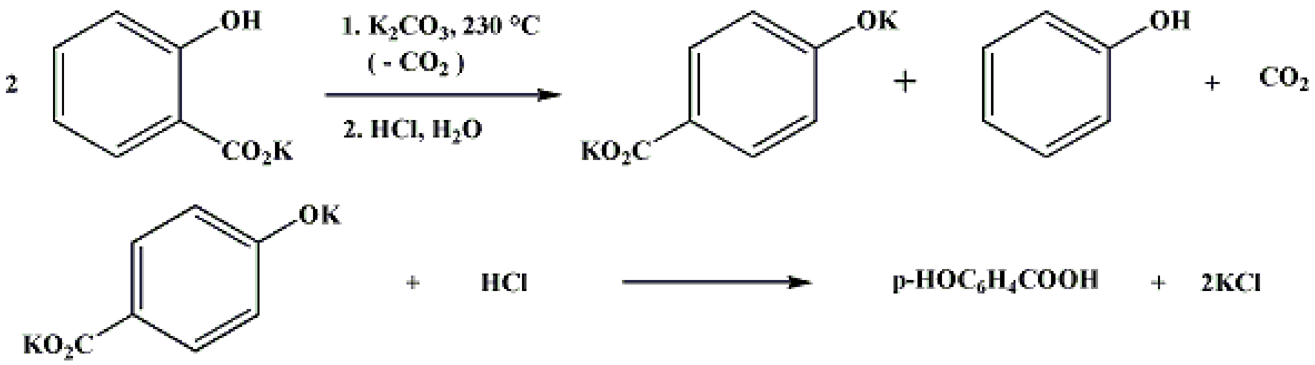
Organic Syntheses, *CV 2, 341*

p-HYDROXYBENZOIC ACID

[Benzoic acid, *p*-hydroxy-]



Submitted by C. A. Buehler and W. E. Cate.
Checked by John R. Johnson and C. P. Nichols.

1. Procedure

Sixty grams (0.43 mole) of potassium carbonate (Note 1) is slowly stirred into a mixture of 100 g. (0.725 mole) of u.s.p. salicylic acid and 150 cc. of water contained in a 20-cm. porcelain dish. The solution is evaporated on a steam bath until a thick, pasty residue is obtained. This is broken up into small pieces and dried in an oven at 105–110° for two hours. The solid is then ground as finely as possible, dried for another two hours at 105–110°, and again ground to a fine powder.

The finely powdered mixture of potassium salicylate and carbonate is placed in a 500-cc. round-bottomed flask which is immersed in an oil bath so that only a small portion of the neck protrudes from the bath (Note 2). The bath is heated to 240° (Note 3) and maintained at this temperature for one and one-half hours. During this time the solid in the flask is stirred occasionally with a curved glass rod flattened at the end.

When the reaction is completed (Note 4), the product is transferred as completely as possible, while hot, to a 2-l. flask containing 1 l. of hot water. The reaction flask is rinsed with several portions of the hot solution. The alkaline solution is acidified with concentrated hydrochloric acid (about 75 cc. is required), heated nearly to boiling, treated with 5–6 g. of decolorizing charcoal, and filtered to remove a small quantity of brown resin. The filtrate is cooled under the tap, and the crude brown crystalline product is filtered with suction. The filtrate is concentrated to a volume of approximately 300 cc. and cooled as before. The second crop of crude acid is filtered with suction and combined with the main portion. The total weight of crude *p*-hydroxybenzoic acid, m. p. 208–211°, is 40–45 g.

The crude acid is dissolved in 300 cc. of hot water, boiled with 4–5 g. of decolorizing charcoal for a few minutes, and the solution filtered. After cooling thoroughly under the tap the purified product is filtered with suction and washed with 10–15 cc. of cold water. The purified acid weighs 35–40 g. (70–80 per cent of the theoretical amount) and melts at 211–212°.

2. Notes

1. An excess of potassium carbonate is used since it prevents the mass from caking during the subsequent heating. Although the original mixture is strongly alkaline a clear solution may not be obtained until the dish is heated.
2. In this way the phenol formed in the reaction is allowed to distil out of the mixture. This operation should be carried out in a hood.
3. The temperature reported is that of the oil bath; the internal temperature is approximately 230°. The temperature should be controlled carefully since pronounced decomposition sets in at higher temperatures.

4. The completeness of the reaction may be determined roughly by treating a small test portion with 3–4 cc. of hot water and acidifying with concentrated hydrochloric acid. Since *p*-hydroxybenzoic acid is relatively soluble and salicylic acid only sparingly so, the absence of a precipitate in the warm solution indicates that the reaction is essentially complete.

3. Discussion

p-Hydroxybenzoic acid has been prepared by heating potassium phenoxide in a stream of carbon dioxide[1] or with carbon tetrachloride,[2] and by heating *p*-cresol with alkalies and various metallic oxides.[3] The procedure described above is similar to one which appears in the early literature.[4] When the dipotassium salt of salicylic acid is dehydrated by heating in vacuum and is then heated in a carbon dioxide atmosphere, essentially complete conversion to *p*-hydroxybenzoic acid is reported.[5]

References and Notes

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4. Kolbe, J. prakt. Chem. (2) **11**, 24 (1875); Heyden, Ger. pat. 48,356 [Frdl. **2**, 132 (1887–90)].
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

phenol (108-95-2)

carbonate (3812-32-6)

carbon tetrachloride (56-23-5)

salicylic acid

carbon dioxide (124-38-9)

potassium salicylate

potassium phenoxide

p-Hydroxybenzoic acid, Benzoic acid, p-hydroxy- (99-96-7)

dipotassium salt of salicylic acid

p-CRESOL (106-44-5)

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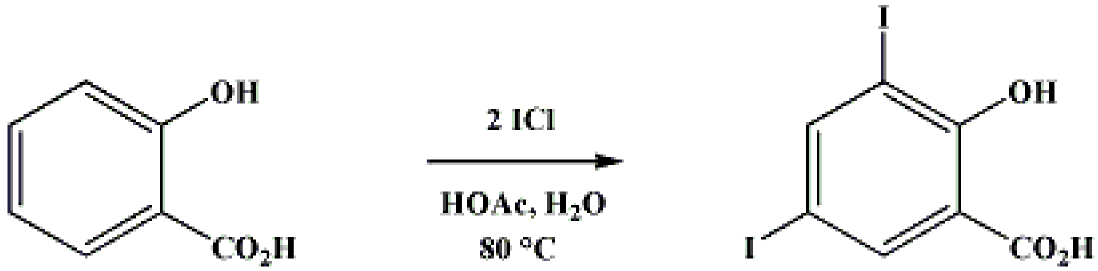
Organic Syntheses, CV 2, 343

2-HYDROXY-3,5-DIIODOBENZOIC ACID

[Salicylic acid, 3,5-diiodo-]



Submitted by G. H. Woollett and W. W. Johnson.
Checked by W. W. Hartman and E. J. Rahrs.

1. Procedure

Twenty-five grams (0.18 mole) of salicylic acid (m.p. 159–160°) is dissolved in 225 cc. of glacial acetic acid in a 2-l. beaker provided with a mechanical stirrer (Note 1). To this is added with stirring a solution of 62 g. (0.38 mole) of iodine monochloride (Note 2) in 165 cc. of glacial acetic acid; then 725 cc. of water is added. A yellow precipitate of diiodosalicylic acid appears. The reaction mixture is gradually heated with stirring on a hot plate to 80° and kept at approximately that temperature for twenty minutes. The entire period of heating should be about forty minutes. Toward the end of the reaction the mixture becomes rather difficult to stir because of the voluminous precipitate. After cooling to room temperature (Note 3), the precipitate is filtered on a Büchner funnel and washed with acetic acid and then with water. When no more water is removed by suction, the solid (75 g.) is dissolved in 100 cc. of warm acetone and filtered by gravity. To the filtrate 400 cc. of water is slowly added with shaking. The fine, flocculent precipitate is filtered by suction, washed with water, and dried. The yield of diiodosalicylic acid melting at 235–236° is 64–64.5 g. (91–92 per cent of the theoretical amount) (Note 4).

2. Notes

1. The amount of glacial acetic acid used may not be sufficient to dissolve the salicylic acid completely. Solution will be completed upon the addition of the iodine chloride solution.
2. Iodine monochloride of sufficient purity for this preparation may be made as follows: Dry chlorine is led in at, or below, the surface of 127 g. (1 mole) of iodine in a 125-cc. distilling flask while the flask is gently shaken. When 34.5 g. (0.97 mole) of chlorine has been introduced, the iodine chloride is distilled in an ordinary distilling apparatus with a filter flask, protected from atmospheric moisture by a calcium chloride tube, as a receiver. The yield of iodine chloride,

boiling between 97° and 105°, is 142 g. (87 per cent of the theoretical amount). The product can be preserved in a dry, glass-stoppered bottle. An excess of iodine is essential in this preparation.

3. Free iodine, if present, is removed by the addition of 5 per cent sodium sulfite solution.

4. The checkers found that 4-hydroxy-3,5-diiodobenzoic acid can be made from 4-hydroxybenzoic acid using the above directions with the exception that the product is not recrystallized from acetone, in which it is only slightly soluble. The yield of 4-hydroxy-3,5-diiodobenzoic acid, melting at 278–279° with decomposition, is 59 g. (84 per cent of the theoretical amount).

3. Discussion

The method given is based on that of Cofman.[1] Diiodosalicylic acid has been prepared by heating salicylic acid with iodine in alcohol;[2] by using the same reagents with the addition of mercuric oxide;[3] by treating salicylic acid with iodine in the presence of alkali;[3], [4] and by treating salicylic acid with iodine and iodic acid.[5] None of these methods, however, appears to give a good yield or a pure product.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 196

References and Notes

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2. Lautemann, Ann. **120**, 300 (1861).
3. Weselsky, ibid. **174**, 103 (1874).
4. Kekulé, ibid. **131**, 226 (1864).
5. Liechti, ibid. Spl. **7**, 133, 141 (1870).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

acetic acid (64-19-7)

sodium sulfite (7757-83-7)

salicylic acid

mercuric oxide (21908-53-2)

iodine (7553-56-2)

acetone (67-64-1)

chlorine (7782-50-5)

iodic acid (7782-68-5)

iodine monochloride, iodine chloride (7790-99-0)

2-Hydroxy-3,5-diiodobenzoic acid, Salicylic acid, 3,5-diiodo- (133-91-5)

diiodosalicylic acid

4-Hydroxy-3,5-diiodobenzoic acid (618-76-8)

4-hydroxybenzoic acid (99-96-7)

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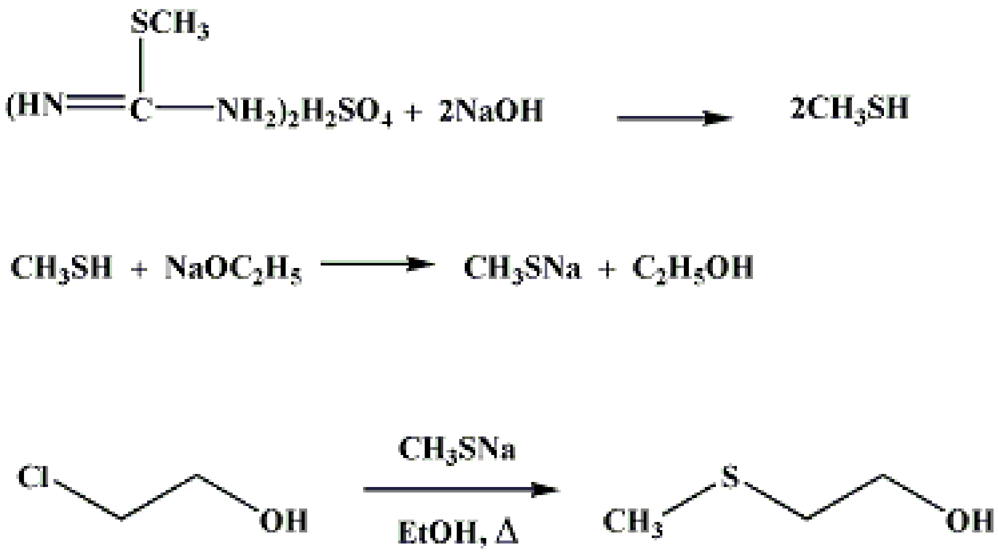
Organic Syntheses, CV 2, 345

β-HYDROXYETHYL METHYL SULFIDE

[Ethanol, 2-methylmercapto-]



Submitted by Wallace Windus and P. R. Shildneck.
Checked by H. T. Clarke and S. Gurin.

1. Procedure

A 2-l. three-necked flask is fitted with a dropping funnel, a stopcock, and a long condenser. The end of the condenser is connected with the following assembly: a safety trap, consisting of an empty gas-washing bottle; a second wash bottle containing 100 cc. of dilute sulfuric acid (1 volume of concentrated sulfuric acid to 2 volumes of water); a tower, about 30 cm. high, containing calcium chloride; an empty 2-l. flask which acts as a trap; a 2-l. flask containing 80.5 g. (3.5 gram atoms) of clean sodium dissolved in 1.5 l. of absolute alcohol; an empty 1-l. flask and a 1-l. flask containing 500 cc. of a saturated solution of lead acetate (Note 1). The exit tube from this last flask leads to a suction pump.

After 556 g. (2 moles) of methyl isothiourea sulfate (p. 411) is placed in the three-necked flask, a very slow current of air is drawn through the apparatus by means of the suction pump while 800 cc. of cold 5 *N* sodium hydroxide is added to the methyl isothiourea sulfate through the dropping funnel. The mixture is warmed very slowly to generate the methyl mercaptan (Note 2). As the reaction nears completion (after about two hours), the mixture is heated strongly for about thirty minutes (Note 3).

The solution of sodium methyl sulfide in absolute alcohol is transferred to a 3-l. three-necked flask, which is placed on a steam bath and fitted with a dropping funnel, a reflux condenser, and a mechanical stirrer. The solution is heated until the alcohol begins to boil. Heating is then discontinued and 302 g. (3.75 moles) of ethylene

chlorohydrin (Note 4) is added dropwise with efficient stirring over a period of about two hours (Note 5). The reaction mixture is concentrated by distilling as much of the alcohol as possible on the steam bath. The mixture is then allowed to cool and the sodium chloride removed by filtration. The flask is rinsed and the sodium chloride washed with three 100-cc. portions of 95 per cent alcohol. The combined filtrate and washings are concentrated on the steam bath under reduced pressure until no further distillate passes over. The residue is then transferred to a modified Claisen flask and fractionally distilled under reduced pressure. The yield is 238–265 g. (74–82 per cent of the theoretical amount based on the sodium used) of a product boiling at 68–70°/20 mm. (Note 6).

2. Notes

1. The lead acetate removes any unreacted methyl mercaptan by precipitating it as the lead salt.
2. The rate of heating controls the rate of evolution of the methyl mercaptan. After the rapid evolution of the gas begins, the reaction mixture should be heated very gently. The slight suction aids in obtaining a regular flow of the gas.
3. The evolution of methyl mercaptan is almost complete after one and one-half to two hours. Prolonged vigorous heating increases the amount of ammonia evolved.
4. The ethylene chlorohydrin should be redistilled and the fraction boiling at 126–128° should be used.
5. The reaction is usually complete immediately after the addition of the ethylene chlorohydrin, obviating the necessity for refluxing the mixture. When the reaction is complete the solution is neutral to litmus paper.
6. Quantities of material five times as large as those called for above may be used without decreasing the percentage yield of product. With the larger amounts of material it is more convenient to filter the sodium chloride before concentrating the solution.

3. Discussion

The methods for preparing methyl mercaptan and β-hydroxyethyl methyl sulfide are essentially those of Arndt[1] and Kirner,[2] respectively.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 136

References and Notes

1. Arndt, Ber. **54**, 2238 (1921).
2. Kirner, J. Am. Chem. Soc. **50**, 2451 (1928).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alcohol (64-17-5)

ammonia (7664-41-7)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

sodium (13966-32-0)

lead acetate

ethylene chlorohydrin (107-07-3)

β-Hydroxyethyl methyl sulfide, Ethanol, 2-methylmercapto- (5271-38-5)

methyl isothiourea sulfate

methyl mercaptan (74-93-1)

methyl sulfide (75-18-3)

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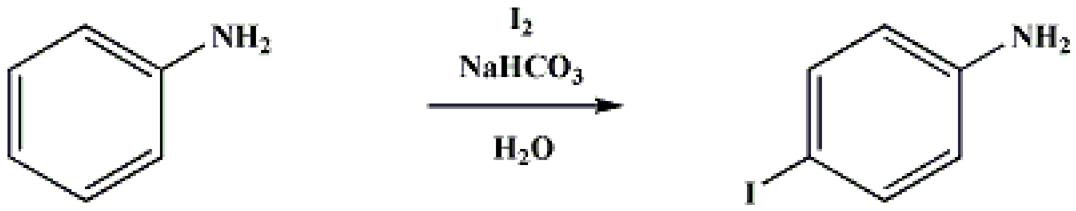
Organic Syntheses, CV 2, 347

p-IODOANILINE

[Aniline, *p*-iodo-]



Submitted by R. Q. Brewster
Checked by W. H. Carothers and W. L. McEwen.

1. Procedure

In a 3-l. beaker are placed 110 g. (1.2 moles) of aniline, 150 g. (1.8 moles) of sodium bicarbonate, and 1 l. of water, and the mixture is cooled to 12–15° by the addition of a small amount of ice. The beaker is then fitted with an efficient mechanical stirrer. The blade of a large porcelain spatula should be inserted into the liquid to overcome the rotary motion and thus obtain better mixing. The stirrer is started and 254 g. (1 mole) of powdered iodine is added in 15–20 g. portions at intervals of two to three minutes so that all the iodine is introduced during one-half hour. Stirring is continued for twenty to thirty minutes. By this time the reaction is complete and the color of the free iodine in the solution has practically disappeared. The crude *p*-iodoaniline, which separates as a dark crystalline mass, is collected on a Büchner funnel, pressed as free from water as possible, and dried in the air. The filtrate may be saved for the recovery of iodine (Note 1).

For the purification of the *p*-iodoaniline, the crude product is placed in a 2-l. flask and 1 l. of gasoline (Note 2) is added. The flask is fitted with an air-cooled reflux condenser and heated in a water bath at a temperature of 75–80° (Note 3). The flask should be shaken frequently, and about fifteen minutes should be allowed for saturation of the solution. The hot gasoline solution is slowly decanted into a beaker set in an ice-salt mixture and stirred constantly. The *p*-iodoaniline crystallizes immediately in practically colorless needles which are filtered and dried in the air (Note 4) and (Note 5). The filtrate is returned to the flask for use in a second extraction (Note 6). The yield is 165–185 g. (75–84 per cent of the theoretical amount) of a product which melts at 62–63°.

2. Notes

1. The sodium iodide which remains in the aqueous solution may be converted into iodine as follows: To the aqueous filtrate from the *p*-iodoaniline are added 100 cc. of concentrated sulfuric acid and 200 g. of sodium dichromate in 200 cc.

of water. The iodine is allowed to settle, washed three times with water by decantation, collected on a filter, and allowed to dry on a watch glass. The yield of crude iodine is 167–179 g.

2. The gasoline used was a fractionated product (b. p. 70–150°). Ordinary gasoline may be used, but it has the disadvantage that the higher-boiling hydrocarbons are removed very slowly from the *p*-iodoaniline.

3. If a higher temperature is used a tarry material is sometimes formed and a diminished yield results.

4. If rapid cooling is not obtained, the product often separates as an oil.

5. For drying purposes, a current of warm air from a commercial hair dryer is advantageous.

6. Two extractions are usually sufficient, but, if much undissolved organic material still remains, a third extraction should be made. The first fraction is practically colorless, but the second and third portions are light brown unless a little charcoal is used for decolorizing the solution.

3. Discussion

p-Iodoaniline has been prepared by the reduction of *p*-nitroiodobenzene;[1] by the hydrolysis of *p*-iodoacetanilide formed by the action of iodine monochloride on acetanilide;[2] and by the direct iodination of aniline.[3] The method described here is an adaptation of the procedure used by Wheeler,[4] and by Hann and Berliner[5] for the iodination of the toluidines.

References and Notes

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2. Michael and Norton, ibid. **11**, 108 (1878); Chattaway and Constable, J. Chem. Soc. **105**, 125 (1914).
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4. Wheeler and Liddle, Am. Chem. J. **42**, 501 (1909); Wheeler, ibid. **44**, 128, 500 (1910).
5. Hann and Berliner, J. Am. Chem. Soc. **47**, 1710 (1925).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

gasoline

sulfuric acid (7664-93-9)

aniline (62-53-3)

Acetanilide (103-84-4)

sodium bicarbonate (144-55-8)

iodine (7553-56-2)

sodium dichromate (7789-12-0)

sodium iodide (7681-82-5)

iodine monochloride (7790-99-0)

p-nitroiodobenzene (636-98-6)

p-IODOANILINE, Aniline, p-iodo- (540-37-4)

p-iodoacetanilide (622-50-4)

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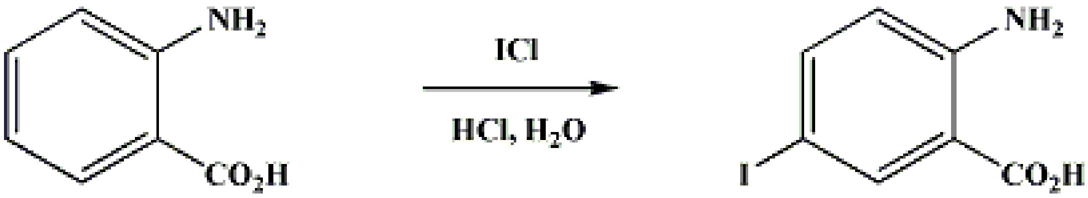
Organic Syntheses, CV 2, 349

5-IODOANTHRANILIC ACID

[Anthranilic acid, 5-iodo-]



Submitted by V. H. Wallingford and Paul A. Krueger.
Checked by Frank C. Whitmore and L. H. Sutherland.

1. Procedure

In a 3-l. beaker, 110 g. (0.8 mole) of anthranilic acid (Note 1) is dissolved in 1 l. of water and 80 cc. of c.p. concentrated hydrochloric acid (sp. gr. 1.19); the solution is cooled to 20°. In a 2-l. beaker a solution of iodine monochloride in hydrochloric acid is prepared by diluting 140 cc. of c.p. concentrated hydrochloric acid with 500 cc. of cold water, adding just sufficient crushed ice to bring the temperature to 5°, and, during about two minutes, stirring in 131 g. (0.8 mole) of iodine monochloride (p. 197).

The iodine monochloride solution at 5° is stirred rapidly into the anthranilic acid solution at 20°. 5-Iodoanthranilic acid separates almost immediately as a granular, tan to violet precipitate, and the reaction temperature rises to 18–22°. The mixture is stirred for an hour, while warming to room temperature, then filtered on a 13-cm. Büchner funnel. The acid is pressed as dry as possible, washed with three 100-cc. portions of cold water, and then dried at 90–100°. There is obtained 185–189 g. (88–90 per cent of the theoretical amount) of brown to purple acid which melts at 185–190°, with decomposition (Note 2).

5-Iodoanthranilic acid is best purified by recrystallization of its ammonium salt, as follows: To 100 g. of the acid in a 400-cc. beaker is added 200 cc. of hot water, and the acid is dissolved by stirring in concentrated ammonia (sp. gr. 0.9) until solution is complete at 60° and there is a slight excess of ammonia. About 40 cc. of concentrated ammonia is required. Sodium hydrosulfite is added in about 1-g. portions until no further bleaching action is observed, about 5 g. of decolorizing charcoal is added, and, after stirring three minutes, the mixture is filtered with suction on a preheated Büchner funnel into a preheated flask. The filter is washed with 10 cc. of boiling water.

The combined filtrate and washings are transferred to a 400-cc. beaker, allowed to cool slowly without agitation until crystal formation appears complete, then cooled to 5°. The crystalline ammonium salt is then removed by suction filtration on a large Büchner funnel, washed with 15 cc. of ice water, sucked as dry as possible, and spread

in a thin layer on an enameled or glass tray and allowed to dry in air at 35–50°. The yield of yellow to violet ammonium salt is 80–89 g., representing a recovery of 76–84 per cent (Note 3) and (Note 4).

The ammonium salt is dissolved in three parts of hot water, ammonia is added if necessary to effect complete solution at 60°, the solution is again treated with sodium hydrosulfite and 3–4 g. of decolorizing charcoal, filtered hot, and the 5-iodoanthranilic acid is precipitated by adding c.p. hydrochloric acid in 3- to 5-cc. portions, stirring thoroughly after each addition, until the reaction mixture is just faintly acid to Congo red. Ice is then added until the temperature is reduced to 20°, and the precipitated acid is removed by suction filtration, washed freely with cold water, and dried at 100–110° (Note 5). 5-Iodoanthranilic acid is almost quantitatively precipitated from its ammonium salt solution and is obtained as a yellow powder, m.p. 190–195° (decomp.) (Note 6).

2. Notes

1. Commercial "Acid Anthranilic Sublimed" is satisfactory.
2. The decomposition point varies with the method of determination. The values given herein were determined by placing the sample in a capillary tube, inserting the tube in the bath at a temperature 25° below the decomposition point, and heating at the rate of 2–3° per minute.
3. The ammonium salt is not stable under the drying conditions. The dry product is a mixture of 5-iodoanthranilic acid and its ammonium salt. Contact with air may change its color from yellow to violet.
4. Crude 5-iodoanthranilic acid is recovered from the mother liquor by carefully making it just acid to Congo red, using a spot plate, with concentrated hydrochloric acid, cooling to 20°, filtering, washing freely with cold water, and drying at 90–110°. This acid can be added to crude acid in further crystallizations or worked up alone.
5. The drying oven must have good air circulation and uniform temperature control; drying at 120° causes the evolution of considerable amounts of free iodine.
6. This product is sufficiently pure for conversion to *m*-iodobenzoic acid (p. 353). If greater purity is desired the ammonium salt can be recrystallized from twice its weight of water, between 45° and 5°, with 85–90 per cent recovery. When the salt remains nearly white after drying, the acid precipitated from it melts with decomposition at a temperature above 210°. Four or five recrystallizations may be required.

3. Discussion

5-Iodoanthranilic acid has been prepared by the reduction of 2-nitro-5-iodobenzoic acid;[1] by treatment of anthranilic acid with iodine in potassium hydroxide solution;[2] by treatment of the anhydride of 5-hydroxymercurianthranilic acid with iodine in

aqueous potassium iodide solution;[3] and by iodination of anthranilic acid in glacial acetic acid solution with iodine monochloride,[4] or in dilute acetic acid solution with iodine.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 353

References and Notes

1. Grothe, J. prakt. Chem. (2) **18**, 326 (1878).
2. Wheeler and Johns, Am. Chem. J. **43**, 403 (1910); Klemme and Hunter, J. Org Chem. **5**, 230 (1940).
3. Schoeller and Hueter, Ber. **47**, 1938 (1914).
4. Borsche, Weussmann, and Fritzsche, ibid. **57**, 1774 (1924).
5. Militzer, Smith, and Evans, J. Am. Chem. Soc. **63**, 436 (1941).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

anhydride of 5-hydroxymercurianthranilic acid

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ammonia (7664-41-7)

potassium iodide (7681-11-0)

sodium hydrosulfite (7775-14-6)

iodine (7553-56-2)

potassium hydroxide (1310-58-3)

Anthranilic Acid (118-92-3)

iodine monochloride (7790-99-0)

5-IODOANTHRANILIC ACID, Anthranilic acid, 5-iodo- (5326-47-6)

2-nitro-5-iodobenzoic acid

m-iodobenzoic acid (618-51-9)

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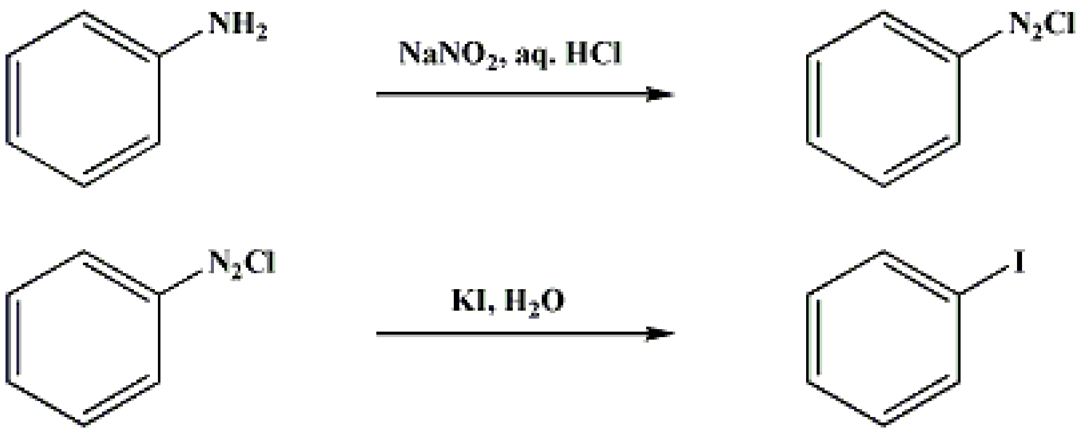
Organic Syntheses, CV 2, 351

IODOBENZENE

[Benzene, iodo-]



Submitted by H. J. Lucas and E. R. Kennedy.
Checked by John R. Johnson and P. L. Barrick.

1. Procedure

In a 3- or 5-gallon stoneware crock are placed 950 cc. (1130 g., 11.7 moles) of concentrated hydrochloric acid (sp. gr. 1.19), 950 cc. of water, 200 g. (196 cc., 2.15 moles) of aniline, and 2 kg. of ice (Note 1). The mixture is agitated by a mechanical stirrer, and, as soon as the temperature drops below 5°, a chilled solution of 156 g. (2.26 moles) of sodium nitrite in a measured volume (700–1000 cc.) of water is introduced fairly rapidly from a separatory funnel, the stem of which projects below the surface of the reaction mixture. The addition should not be fast enough to cause the temperature to rise to 10° or to cause evolution of oxides of nitrogen. The last 5 per cent of the nitrite solution is added more slowly, and the reaction mixture is tested with starch-iodide paper at intervals until an excess of nitrous acid is indicated.

Stirring is continued for ten minutes, and if necessary the solution is filtered rapidly through a loose cotton plug in a large funnel. An aqueous solution of 358 g. (2.16 moles) of potassium iodide is added and the reaction mixture allowed to stand overnight. The mixture is transferred to a large flask (or two smaller flasks) and heated on a steam bath, using an air-cooled reflux condenser, until no more gas is evolved, then allowed to cool and stand undisturbed until the heavy organic layer has settled thoroughly. A large part of the upper aqueous layer is siphoned off, and discarded (Note 2). The residual aqueous and organic layers are made alkaline by the cautious addition of strong sodium hydroxide solution (100–125 g. of solid technical sodium hydroxide is usually required) and steam-distilled at once. The last one-third of the steam distillate is collected separately and combined with the aqueous layer separated from the earlier portions of the distillate. This mixture is acidified with 5–10 cc. of concentrated sulfuric acid and steam-distilled again. The iodobenzene from this

operation is combined with the main portion and dried with 10–15 g. of calcium chloride (Note 3) and (Note 4). Distillation under reduced pressure gives 327–335 g. (74–76 per cent of the theoretical amount) of iodobenzene, b.p. 77–78°/20 mm. or 63–64°/8 mm. (Note 5).

2. Notes

1. If more ice is used a portion remains unmelted after the diazotization is completed.
2. If a good separation has been made not more than 1–2 g. of iodobenzene is lost with the upper layer.
3. An appreciable amount of iodobenzene is retained by the solid calcium chloride. By treating the spent drying agent with water 8–12 g. of iodobenzene can be recovered.
4. The crude iodobenzene weighs 350–355 g. (80 per cent of the theoretical amount) and is pure enough for many purposes without redistillation.
5. If the distillation is carried too far, the distillate will be colored.

3. Discussion

The preparation of iodobenzene by iodination of benzene, with iodine and nitric acid, and a survey of preparative methods have been given in an earlier volume.[1] The present procedure, based upon the method of Gattermann,[2] gives a purer product.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 660
- Org. Syn. Coll. Vol. 5, 665

References and Notes

1. Org. Syn. Coll. Vol. I, **1941**, 323.
2. Gattermann-Wieland, "Laboratory Methods of Organic Chemistry," p. 283. Translated from the twenty-fourth German edition by W. McCartney, The Macmillan Company, New York, 1937.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

oxides of nitrogen

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

aniline (62-53-3)

sodium hydroxide (1310-73-2)

nitric acid (7697-37-2)

potassium iodide (7681-11-0)

sodium nitrite (7632-00-0)

nitrous acid (7782-77-6)

iodine (7553-56-2)

Iodobenzene, Benzene, iodo- (591-50-4)

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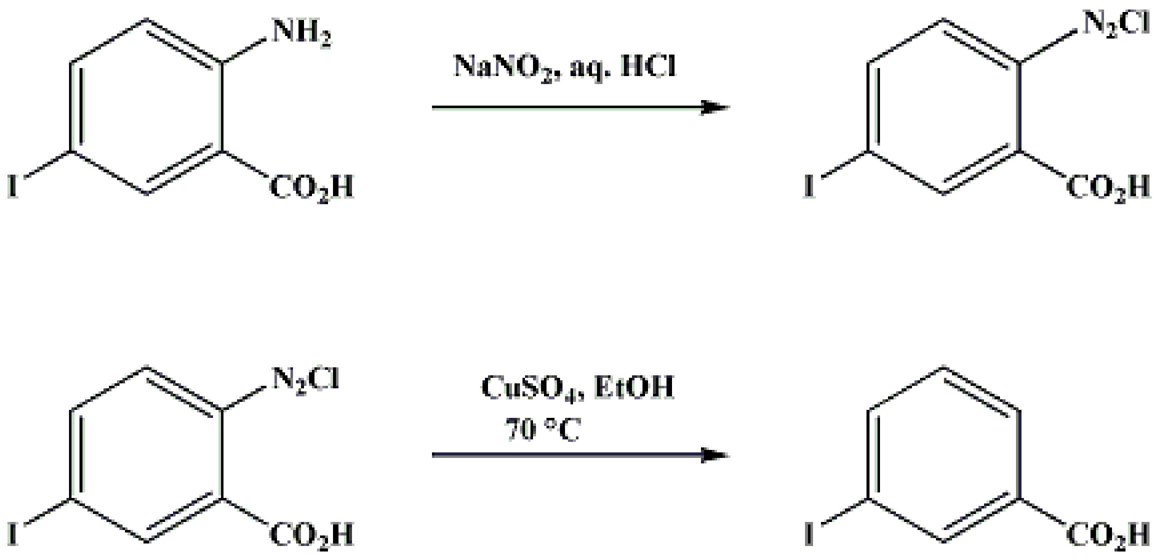
Organic Syntheses, *CV 2*, 353

m-IODOBENZOIC ACID

[Benzoic acid, *m*-iodo-]



Submitted by V. H. Wallingford and Paul A. Krueger.
Checked by Frank C. Whitmore and L. H. Sutherland.

1. Procedure

In a 1-l. flask 132 g. (0.5 mole) of 5-iodoanthranilic acid (p. 349) and 35 g. (0.5 mole) of sodium nitrite are dissolved in a mixture of 500 cc. of warm water and 60 cc. of 30 per cent sodium hydroxide solution. After cooling to 20° the solution is added from a dropping funnel, over a period of fifteen to twenty minutes, to a well-stirred mixture of 250 cc. of concentrated hydrochloric acid (sp. gr. 1.18) and 250 g. of ice in a 2-l. beaker; more ice is added, as required, to keep the temperature below 20°. The insoluble, yellow diazonium compound separates before completion of the diazotization. After all the solution has been added from the dropping funnel, the reaction mixture is stirred for five minutes and tested for excess nitrous acid with starch-iodide paper. If required, small amounts of solid sodium nitrite are added and the test is repeated at three-minute intervals until a slight excess is definitely established. The diazonium compound is allowed to settle and as much as possible of the supernatant liquor is decanted, leaving a slurry of diazonium compound.

In a 3-l. beaker are placed 750 cc. of 95 per cent ethyl alcohol and 1.5 g. of finely ground copper sulfate, and the mixture is heated on a hot plate or steam bath to 70°. The diazonium slurry is added in about 30-cc. portions to the well-stirred alcohol; the temperature is kept between 60° and 70°, and the nitrogen evolution is allowed to subside considerably between additions. The final traces of diazonium slurry are washed into the alcohol with small amounts of the decanted solution, the remainder of which is then added to the alcohol in 100-cc. portions. The reaction mixture is heated

and stirred at 65–70° for half an hour, and then cooled without agitation to 5°. The *m*-iodobenzoic acid which separates is filtered with suction on a Büchner funnel, washed with three 50-cc. portions of cold water, and dried at 90–110°. There is obtained 107–116 g. of crude, brown *m*-iodobenzoic acid (86–93 per cent of the theoretical amount) (Note 1).

The crude *m*-iodobenzoic acid is purified by recrystallization of its ammonium salt. To 100 g. of the acid in a 250-cc. beaker is added 75 cc. of hot water, and the acid is partially neutralized with 24 cc. of concentrated ammonia (sp. gr. 0.9). After stirring at 80° until no more acid dissolves, neutralization is completed by adding 2–5 cc. of ammonia, until the acid is completely dissolved. The solution is heated to 90°, 1 g. of decolorizing charcoal is added, and the mixture is filtered with suction using a preheated Büchner funnel and filter flask. The residue on the filter is washed with 15 cc. of boiling water. The combined washings and filtrate are transferred to a 250-cc. beaker and allowed to cool without agitation to 25–35°, then cooled by any convenient means to 5°. The ammonium *m*-iodobenzoate crystals are filtered and pressed as dry as possible on a Büchner funnel, spread in a thin layer on a glass or enameled tray, and dried at a temperature not above 60°. There is obtained 86–90 g. of faintly yellow to tan prisms of the ammonium salt, a recovery of 80–84 per cent (Note 2).

The ammonium salt thus obtained is recrystallized until white by dissolving it in an equal weight of water at 80° and cooling to 5°. The recovery in this purification averages 75–85 per cent (Note 3).

m-Iodobenzoic acid melting at 187–188° is obtained by dissolving pure ammonium *m*-iodobenzoate in four times its weight of hot water, precipitating the acid by acidifying the solution to Congo red with concentrated hydrochloric acid, adding ice to reduce the temperature to 20°, filtering by suction, washing the acid freely with cold water, and drying at 90–110° (Note 4).

2. Notes

1. Evaporation of the mother liquors to incipient turbidity and cooling the concentrate to 5° will produce a few grams of acid, but this is usually very impure and tarry.
2. Ammonium *m*-iodobenzoate is not stable under these drying conditions. The product at this point contains some free acid.
3. In some runs as many as five recrystallizations failed to furnish white crystals of the ammonium salt, but, in these runs, precipitation of the acid after three or four crystallizations gave a product having the correct melting point.
Mother liquors from the crystallization are best worked up by acidifying to Congo red with concentrated hydrochloric acid, filtering, washing, drying, and reworking the recovered acid.
4. The total overall yield of pure acid from the crude depends on the amount of crude acid taken, the care exercised to avoid material losses, and the number of recrystallizations required to attain the desired purity. Without recoveries from mother liquors, 100 g. of crude acid, after conversion to the ammonium salt, and

three recrystallizations of the latter, gave 40–45 g. of pure acid. Overall recovery of pure acid from 100 g. of the crude gave 50 g. of pure acid melting at 187–188°, 10 g. of less pure acid melting at 184–186°, and about 10 g. of a tarry solid residue.

3. Discussion

m-Iodobenzoic acid has been prepared by diazotization of *m*-aminobenzoic acid and treatment with potassium iodide in acid solution,[1], [2], [3] and by the action of concentrated nitric acid on a glacial acetic acid solution of iodine and benzoic acid.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 349

References and Notes

1. Griess, Ann. **113**, 336 (1860).
2. Cohen and Raper, J. Chem. Soc. **85**, 1273 (1904).
3. Cattelain, Bull. soc. chim. (4) **41**, 1546 (1927).
4. Datta and Chatterjee, J. Am. Chem. Soc. **41**, 294 (1919).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Congo red

ethyl alcohol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ammonia (7664-41-7)

sodium hydroxide (1310-73-2)

nitric acid (7697-37-2)

potassium iodide (7681-11-0)

nitrogen (7727-37-9)

copper sulfate (7758-98-7)

sodium nitrite (7632-00-0)

nitrous acid (7782-77-6)

Benzoic acid (65-85-0)

iodine (7553-56-2)

5-IODOANTHRANILIC ACID (5326-47-6)

m-iodobenzoic acid, Benzoic acid, m-iodo- (618-51-9)

ammonium m-iodobenzoate

m-aminobenzoic acid (99-05-8)

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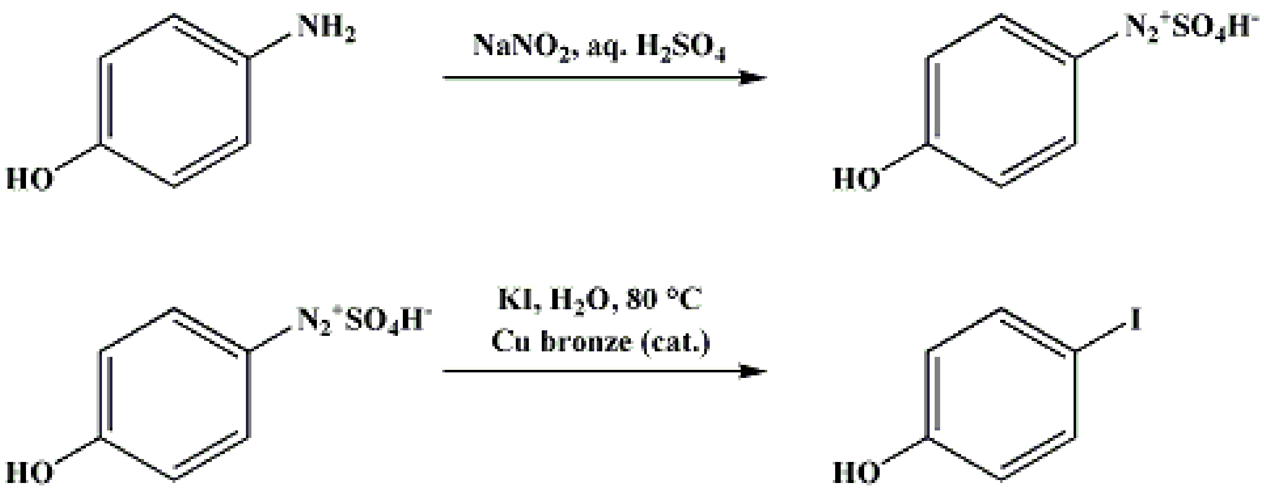
p-IODOPHENOL

[Phenol, *p*-iodo-]



Submitted by F. B. Dains and Floyd Eberly.
Checked by Reynold C. Fuson and H. H. Hully.

1. Procedure

One hundred nine grams (1 mole) of *p*-aminophenol (Note 1) is dissolved in a mixture of 500 g. of ice, 500 cc. of water, and 65 cc. (120 g., 1.2 moles) of concentrated sulfuric acid (sp. gr. 1.84). To this solution, kept in a freezing mixture at 0°, is added, during the course of an hour with constant mechanical stirring, a solution of 72 g. (1 mole) of 95 per cent sodium nitrite in 150 cc. of water. The stirring is continued twenty minutes longer, and then 20 cc. (37 g., 0.37 mole) of concentrated sulfuric acid is added.

This solution is poured into an ice-cold solution of 200 g. (1.2 moles) of potassium iodide in 200 cc. of water. After a few minutes, 1 g. of copper bronze (Note 2) is added, with continued stirring, and the solution is warmed slowly on the water bath. The temperature is kept at 75–80° until the evolution of nitrogen ceases; during this process the iodophenol separates as a heavy dark oil. After cooling to room temperature the reaction mixture is extracted three times with 165-cc. portions of chloroform and the combined extracts are washed with dilute thiosulfate solution. The solvent is removed on the water bath and the residue distilled under reduced pressure, the *p*-iodophenol coming over at 138–140°/5 mm. One crystallization from about 2 l. of ligroin (b.p. 90–110°) gives a colorless product melting sharply at 94°. The yield of recrystallized product is 153–159 g. (69–72 per cent of the theoretical amount).

2. Notes

1. The *p*-aminophenol used was a commercial product melting at 182–183° with decomposition.

2. Some commercial bronzes used for bronze paints are coated with a film of stearic acid. For chemical work an untreated pure copper bronze should be used.

3. Discussion

p-Iodophenol was first obtained as a by-product of the action of iodine on salicylic acid in alkaline solution or by heating iodosalicylic acid.[1] It has also been obtained by the action of iodine on phenol in alkaline solution[2] or in the presence of mercuric oxide,[3] or by the action of iodine monochloride.[4] It is best prepared by the diazotization of *p*-aminophenol and replacement of the diazonium group by iodine[5] although it has also been obtained from *p*-iodoaniline by diazotization and replacement of the diazonium group by hydroxyl.[6]

References and Notes

1. Lautemann, Ann. **120**, 299 (1861); Kekulé, ibid. **131**, 221 (1864).
2. Holleman and Rinkes, Rec. trav. chim. **30**, 96 (1911).
3. Hlasiwetz and Weselsky, Ber. **2**, 523 (1869).
4. Schützenberger and Sengenwald, Jahresb. **1862**, 413.
5. Nölting and Wrzesinski, Ber. **8**, 820 (1875); Nölting and Stricker, ibid. **20**, 3021 (1887); Neumann, Ann. **241**, 74 (1887).
6. Griess, Zeit. für Chem. **1865**, 427; Holleman and Rinkes, Rec. trav. chim. **30**, 95 (1911).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ligroin

copper bronze

sulfuric acid (7664-93-9)

chloroform (67-66-3)

phenol (108-95-2)

potassium iodide (7681-11-0)

nitrogen (7727-37-9)

sodium nitrite (7632-00-0)

salicylic acid

mercuric oxide (21908-53-2)

iodine (7553-56-2)

iodophenol (533-58-4)

iodine monochloride (7790-99-0)

stearic acid (57-11-4)

iodosalicylic acid

p-aminophenol (123-30-8)

p-IODOANILINE (540-37-4)

p-IODOPHENOL, Phenol, p-iodo- (540-38-5)

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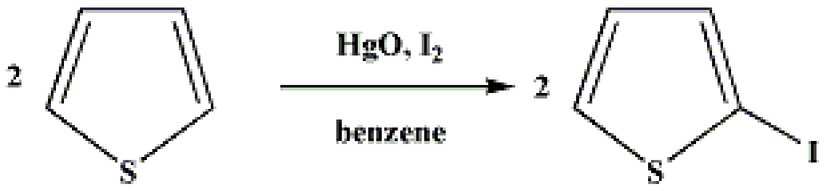
2-IODOTHIOPHENE

[Thiophene, 2-iodo-]



Submitted by Wesley Minnis
Checked by Roger Adams and H. D. Cogan.

1. Procedure

In a glass-stoppered, wide-mouthed bottle cooled by ice water are placed 35 g. (0.42 mole) of thiophene (p. 578) and 50 cc. of benzene (Note 1). With constant shaking (Note 2), and cooling when necessary, 75 g. (0.35 mole) of yellow mercuric oxide and 109 g. (0.43 mole) of iodine are added alternately in small amounts during a period of fifteen to twenty minutes. The yellow mercuric oxide changes to crimson mercuric iodide. The mixture is filtered, and the residue is washed with three 25-cc. portions of ether. The ether-benzene filtrate is shaken with a dilute solution of sodium thiosulfate to remove excess iodine and then dried over 5 g. of calcium chloride and filtered. The ether and benzene are removed by distillation on a steam bath (Note 3), and the residue is fractionally distilled under reduced pressure. 2-Iodothiophene distils at 73°/15 mm.; 80–81°/20 mm.; 90–94°/34–38 mm. (Note 4). The yield is 63–66 g. (72–75 per cent of the theoretical amount) (Note 5). If the iodothiophene is still colored by traces of iodine, the color may be removed by shaking with a small amount of mercuric oxide.

2. Notes

1. Ligroin (b.p. 100–120°) may be substituted for benzene.
2. Better yields are obtained when the mixture is vigorously shaken by hand than when mechanical stirring is used. The ordinary stirrer will not keep the mercuric oxide in suspension.
3. Unreacted thiophene can be recovered from the ether-benzene distillate by treating the latter with mercuric oxide and dilute acetic acid, collecting the white precipitate [$C_4H_2S(HgOCOCH_3)HgOH$] on a Büchner funnel, and decomposing it with concentrated hydrochloric acid.[1] In checking this preparation there was not enough unreacted thiophene to be recovered.
4. A small amount of 2,5-diiodothiophene is formed in the reaction. About 4 g. of crystalline diiodothiophene, m.p. 40–41°, can be isolated from the residue

remaining after distillation of the 2-iodothiophene (b.p. 65.5–66.5°/9 mm.). (O. Ivan Lee, private communication.)
5. 2-Iodothiophene reacts with magnesium to form a Grignard reagent and is hence useful in the preparation of other thiophene derivatives.

3. Discussion

2-Iodothiophene has been prepared only by the action of iodine and mercuric oxide on thiophene.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 545

References and Notes

1. Dimroth, Ber. **32**, 759 (1899).
2. Meyer and Kreis, ibid. **17**, 1558 (1884); Thyssen, J. prakt. Chem. (2) **65**, 5 (1902).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

ether (60-29-7)

magnesium (7439-95-4)

sodium thiosulfate (7772-98-7)

mercuric oxide (21908-53-2)

iodine (7553-56-2)

mercuric iodide (7774-29-0)

Thiophene (110-02-1)

2-IODOTHIOPHENE, Thiophene, 2-iodo-, iodothiophene (3437-95-4)

2,5-diiodothiophene (625-88-7)

diiodothiophene

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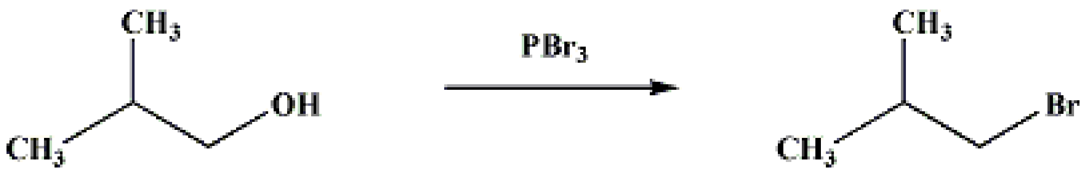
Organic Syntheses, CV 2, 358

ISOBUTYL BROMIDE

[Propane, 1-bromo-2-methyl-]



Submitted by C. R. Noller and R. Dinsmore.
Checked by Frank C. Whitmore, D. E. Badertscher, and A. R. Lux.

1. Procedure

In a 2-l. three-necked flask, fitted with a mechanical stirrer, a thermometer, and a dropping funnel, is placed 518 g. (643 cc., 7 moles) of dry isobutyl alcohol (b.p. 106–108°). The alcohol is cooled to −10° by immersing the flask in an ice-salt bath, and 695 g. (244 cc., 2.56 moles) of phosphorus tribromide (Note 1) is slowly added with stirring at such a rate as to keep the temperature below 0° (about four hours). The cooling bath is removed, and stirring is continued until the mixture reaches room temperature; it is then allowed to stand overnight. The stirrer, funnel, and thermometer are removed, and the flask is fitted with a 30-cm. fractionating column and a condenser. The crude isobutyl bromide is distilled from the reaction mixture under diminished pressure, e.g., at about 50°/200 mm. (Note 2).

The distillate is cooled to about 0° and washed three times with 50-cc. portions of concentrated sulfuric acid cooled to 0°; it is then shaken with 25 g. of anhydrous potassium carbonate until the odor of hydrobromic acid disappears. It is distilled through a 1-m. fractionating column at atmospheric pressure collecting the portion boiling at 91–93° (88.5–90.5°/728 mm.), or under reduced pressure through a 70 by 2-cm. total reflux, adjustable take-off, adiabatic column (Note 3), b.p. 41–43°/135 mm. The product weighs 525–570 g. (55–60 per cent of the theoretical amount) (Note 4).

2. Notes

1. The phosphorus tribromide boiled at 171–173° (168–170°/725 mm.), and was prepared in 90–95 per cent yield by adding bromine to a stirred suspension of red phosphorus in carbon tetrachloride. A good fractionating column is necessary. Old, red phosphorus containing acids of phosphorus gives a poorer yield.
2. In some runs, the crude bromide was successfully distilled at atmospheric pressures; in others it decomposed violently. With reduced pressure no difficulty was experienced. A water pump with an adjustable leak in the vacuum line was used.

3. The column used with reduced pressure was similar to those described by Whitmore and Lux, J. Am. Chem. Soc. **54**, 3451 (1932). The product, fractionated under reduced pressure using a reflux ratio of 5:1, contained less than 1 per cent of tertiary butyl bromide.

4. By similar procedures, the following bromides can be prepared with the yields indicated: *sec*.-butyl, b.p. 90–93°, 80 per cent; *n*-propyl, b.p. 70–73°, 95 per cent; isopropyl, b.p. 60–63°, 68 per cent.

In the preparation of these three bromides and isobutyl bromide as well, the phosphorus tribromide procedure described above gives purer products in better yields than the hydrobromic-sulfuric acid method described in Org. Syn. Coll. Vol. I, **1941**, 25. The phosphorus tribromide method is not convenient for the preparation of tertiary butyl bromide; the product is difficult to purify.

3. Discussion

Isobutyl bromide has been prepared from isobutyl alcohol by the action of bromine and phosphorus,[1] aqueous hydrobromic acid,[2] and gaseous hydrobromic acid;[3] from isobutylene and gaseous hydrogen bromide;[4] or hydrogen bromide in glacial acetic acid;[5] and by the rearrangement of tertiary butyl bromide at 210–220°.[6] A number of bromides, including isobutyl bromide, have been prepared by the action of phosphorus tribromide on alcohols.[7] The procedure described above is a modification of one used for preparing cyclopentyl bromide.[8]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 366
- Org. Syn. Coll. Vol. 2, 406
- Org. Syn. Coll. Vol. 2, 476
- Org. Syn. Coll. Vol. 2, 547

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2. Norris, Am. Chem. J. **38**, 640 (1907).
3. Fournier, Bull. soc. chim. (3) **35**, 623 (1906); Longinov and Lerman, Khim Farm. Prom. **1933**, 14 [C. A. **27**, 3443 (1933)].
4. Brunel, J. Am. Chem. Soc. **39**, 1978 (1917).
5. Ipatiew and Ogonowsky, Ber. **36**, 1988 (1903).
6. Faworsky, Ann. **354**, 343 (1907).
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8. Adams and Noller, J. Am. Chem. Soc. **48**, 1084 (1926).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

red phosphorus

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

HYDROBROMIC ACID, hydrogen bromide (10035-10-6)

bromine (7726-95-6)

PHOSPHORUS (7723-14-0)

Isopropyl bromide (75-26-3)

n-PROPYL BROMIDE (106-94-5)

sec.-BUTYL BROMIDE (78-76-2)

tertiary butyl bromide, t-butyl bromide (507-19-7)

phosphorus tribromide (7789-60-8)

carbon tetrachloride (56-23-5)

isobutyl alcohol (78-83-1)

Isobutyl bromide, Propane, 1-bromo-2-methyl- (78-77-3)

isobutylene (9003-27-4)

cyclopentyl bromide (137-43-9)

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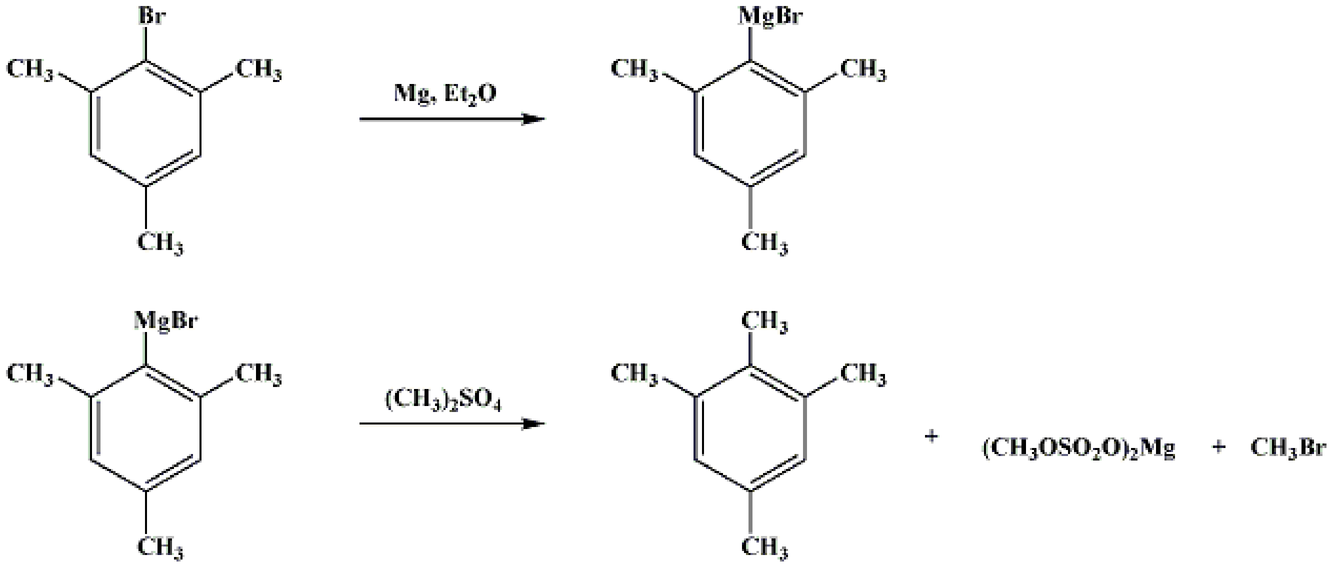
ISODURENE



Submitted by Lee Irvin Smith
Checked by Roger Adams and W. W. Moyer.

1. Procedure

A 3-l. three-necked flask fitted with a reflux condenser protected from the air by a calcium chloride tube, a separatory funnel, and a mechanical stirrer is mounted on a steam bath. In the flask are placed 48 g. (2 moles) of magnesium turnings, 150 cc. of anhydrous ether and 100 g. of bromomesitylene (p. 95). The reaction starts slowly, and sometimes it is necessary to add some iodine or use Gilman's catalyst (Note 1). After the reaction starts, it proceeds smoothly and the remaining 298 g. of bromomesitylene (a total of 2 moles) in about 700 cc. of dry ether is added at such a rate that the ether boils briskly. After the last of this ether solution has been added, the mixture is heated on the steam cone until practically all the magnesium has dissolved (Note 2).

The solution of the Grignard reagent is cooled to about 10°, and to it, while stirring vigorously, is added a solution of 600 g. (4.8 moles) of methyl sulfate (Note 3) in about 500 cc. of dry ether. The reaction is very vigorous, and bumping may occur as the result of the separation of insoluble magnesium compounds. The addition of the methyl sulfate requires two to three hours. The reaction mixture is allowed to stand (Note 4) for about twenty-four hours and is then decomposed by adding dilute hydrochloric acid through the separatory funnel. Stirring is started as soon as the mass is fluid enough. When the mixture is decomposed completely, the ether layer is separated and washed three times with water. After the magnesium salts have been removed, the ether layer is evaporated and the residue is added slowly to a solution of 30 g. of sodium in 500 cc. of absolute alcoholx (Note 5). The mixture is boiled for about one-half hour. Then the solution is cooled, 150–200 cc. of ether is added, and the alkali and alcohol are removed by washing thoroughly with water (Note 6). Finally the ether solution is dried over calcium chloride, the ether is distilled, and the residue is warmed on a water bath for three to four hours with 25–30 g. of metallic sodium (Note 7). The mixture is filtered, and the filtrate is fractionated carefully under reduced pressure in a modified Claisen flask. The fractions collected are: up to 85°/18 mm.; 85–87°/18 mm.; and residue. The low-boiling fraction weighs about 50 g. and is mainly mesitylene. The second fraction is isodurene and has a melting point of −24.2°. The yield is 140–160 g. (52–60 per cent of the theoretical amount).

2. Notes

1. Gilman's catalyst[1] is prepared readily by heating an alloy of magnesium containing 12.75 per cent of copper with about 20 per cent by weight of iodine in an evacuated flask. Only about 0.25 g. of this catalyst is required to bring about a reaction with a halogen compound. When this catalyst is used, the ordinary magnesium turnings are added as soon as the reaction has started. The reaction can also be started by adding a small amount of an ether solution of any Grignard reagent, such as ethylmagnesium bromide.
2. If Gilman's catalyst is used to start the reaction there will always be an excess of magnesium at the end of the

reaction.
3. The methyl sulfate was distilled carefully under reduced pressure, and a fraction boiling within 1° was used. Methyl sulfate is extremely toxic, and great care must be taken to avoid breathing the vapors and spilling the liquid on the hands or clothes. Ammonia is a specific antidote for methyl sulfate.
4. The reaction mixture sometimes becomes almost solid; stirring is then useless.
5. Aqueous alkali is not sufficient to remove the excess methyl sulfate. Sometimes the reaction between the excess methyl sulfate and the sodium ethoxide solution is vigorous; therefore the two solutions should be mixed carefully. If a large excess of methyl sulfate is present, more sodium ethoxide may be needed in order to keep the solution alkaline.
6. Emulsions can be broken by acidifying.
7. The treatment with sodium ensures a halogen-free product.

3. Discussion

Isodurene has been prepared from bromomesitylene, methyl iodide, and sodium;[2] from mesitylene, methyl chloride, and aluminum chloride;[3] from mesitylene, methyl iodide, aluminum chloride, and carbon disulfide;[4] from 1,3,4,5-tetramethylbenzonitrile with hydrogen chloride at 250°;[5] by the action of zinc chloride or iodine on camphor;[6] and in small amounts by the action of concentrated sulfuric acid on acetone.[7] The method of preparation described above has been published.[8]

Methods of preparation in which aluminum chloride is used do not give a pure product; aluminum chloride shifts the methyl groups to give mixtures of the three tetramethylbenzenes from which isodurene cannot be separated efficiently. Compare Note 7, p. 252.

References and Notes

1. Gilman, Peterson, and Schulze, Rec. trav. chim. **47**, 19 (1928)
2. Jannasch, Ber. **8**, 356 (1875); Bielefeldt, Ann. **198**, 380 (1879); Jannasch and Weiler, Ber. **27**, 3442 (1894).
3. Jacobsen, ibid. **14**, 2629 (1881).
4. Claus and Foecking, ibid. **20**, 3097 (1887).
5. Hofmann, ibid. **17**, 1915 (1884).
6. Armstrong and Miller, ibid. **16**, 2259 (1883).
7. Orndorff and Young, Am. Chem. J. **15**, 267 (1893).
8. Smith and MacDougall, J. Am. Chem. Soc. **51**, 3003 (1929).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Gilman's catalyst

alcohol (64-17-5)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrogen chloride, hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ether (60-29-7)

magnesium, magnesium turnings (7439-95-4)

methyl chloride (74-87-3)

copper (7440-50-8)

iodine (7553-56-2)

acetone (67-64-1)

aluminum chloride (3495-54-3)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

carbon disulfide (75-15-0)

zinc chloride (7646-85-7)

Methyl iodide (74-88-4)

methyl sulfate (75-93-4)

Mesitylene (108-67-8)

ethylmagnesium bromide (925-90-6)

Bromomesitylene (27129-86-8)

Isodurene (527-53-7)

1,3,4,5-tetramethylbenzonitrile

camphor (21368-68-3)

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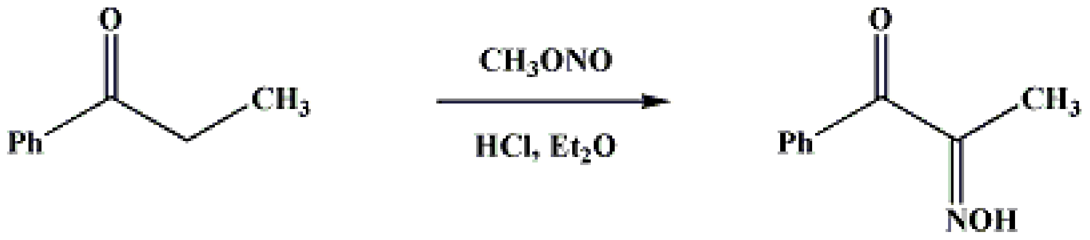
ISONITROSOPROPIOPHENONE

[1,2-Propanedione, 1-phenyl-, 2-oxime]



Submitted by Walter H. Hartung and Frank Crossley.
Checked by Reynold C. Fuson and R. F. Peterson.

1. Procedure

A 3-l. three-necked, round-bottomed flask (A, .htmFig. 11) is provided with a reflux condenser, liquid-sealed mechanical stirrer, and two gas delivery tubes (T_1 and T_2) which extend as far as possible into the flask. Methyl nitrite is generated in a 2-l. Erlenmeyer flask B which is fitted with a 500-cc. dropping funnel C and connected to A by the tube T_1. Dry hydrogen chloride is introduced through $T_{2.}$ The apparatus is assembled preferably in a hood with effective draft.

Fig. 11

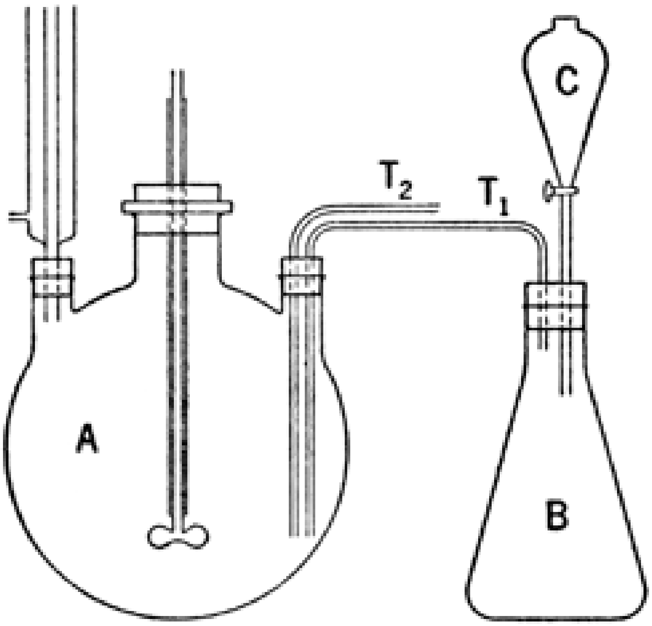


FIG. 11.

In A is placed a solution of 469 g. (3.5 moles) of propiophenone (Note 1) in 2.3 l. of ordinary ethyl ether, and in B a mixture of 290 g. (4 moles) of 95 per cent sodium nitrite, 180 cc. (142 g., 4.5 moles) of methyl alcohol, and 170 cc. of water. In the

dropping funnel C is placed 455 cc. of cold dilute sulfuric acid (prepared by adding one volume of concentrated acid to two volumes of water).

The stirrer is started, and hydrogen chloride is introduced through T_2 at the rate of 6–10 bubbles a second. The acid in C is allowed to drop slowly into B, and the gaseous methyl nitrite (Note 2) is introduced through T_1 into the reaction mixture. The solution in A develops a brown-red color, and after about ten minutes the ether begins to reflux gently (Note 3). The rate of evolution of methyl nitrite is then adjusted so that the ether continues to reflux gently. About four hours is required for addition of the methyl nitrite. Stirring and addition of hydrogen chloride are continued for thirty minutes longer; at the end of this time the solution has ceased boiling and has assumed a clear yellow color.

The reaction mixture is allowed to stand for several hours (preferably overnight) and is then extracted repeatedly with 500-cc. portions of 10 per cent sodium hydroxide solution, until the alkaline extracting medium remains practically colorless when shaken with the ethereal solution (Note 4). Usually five 500-cc. portions of the sodium hydroxide solution are required. The combined alkaline extracts are poured slowly, with stirring, into a mixture of 700–750 cc. of concentrated hydrochloric acid and about 1 kg. of ice. The crystals of isonitrosopropiophenone are filtered with suction and dried. The product weighs 370–390 g. (65–68 per cent of the theoretical amount) and melts at 111–113°. This material can be crystallized from about 550 cc. of toluene and yields 315–335 g. of snow-white crystals, m.p. 112–113° (Note 5).

2. Notes

1. Propiophenone may be prepared in 70–80 per cent yields from benzene and propionyl chloride or propionic anhydride, in the presence of aluminum chloride.
2. For the preparation of small amounts of the isonitrosoketone it is more convenient to employ a higher-boiling alkyl nitrite, such as butyl nitrite (p. 108), which can be added directly to the reaction mixture by substituting a dropping funnel for the tube T_1. Butyl nitrite must be freshly prepared or redistilled shortly before use.
3. The rate of stirring must be kept fairly constant since an abrupt increase in speed may cause the ether to boil at a dangerous rate.
4. The ethereal solution remaining from the alkaline extractions contains unreacted propiophenone which may be recovered by distilling the ether and fractionating the residue. The amount of recovered propiophenone, collected at 210–216°, varies from 80 to 110 g.
5. About 25–30 g. of material may be recovered from the toluene mother liquor by extraction with alkali and reprecipitation with acid.

3. Discussion

Isonitrosopropiophenone has been prepared from esters of α-benzoylpropionic acid by

a process involving saponification, nitrosation, and decarboxylation;[1] from 1-phenyl-1,2-propanedione by the action of hydroxylamine;[2] and from propiophenone by treatment with amyl nitrite,[3] methyl nitrite,[4] or butyl nitrite.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 20
- Org. Syn. Coll. Vol. 3, 191
- Org. Syn. Coll. Vol. 3, 853
- Org. Syn. Coll. Vol. 6, 199

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2. Kolb, Ann. **291**, 292 (1896).
3. Claisen and Manasse, Ber. **22**, 529 (1889).
4. Slater, J. Chem. Soc. **117**, 590 (1920).
5. Hartung and Munch, J. Am. Chem. Soc. **51**, 2264 (1929).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

hydrogen chloride, hydrochloric acid (7647-01-0)

Benzene (71-43-2)

methyl alcohol (67-56-1)

ether, ethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium nitrite (7632-00-0)

aluminum chloride (3495-54-3)

toluene (108-88-3)

Butyl nitrite (544-16-1)

amyl nitrite (463-04-7)

hydroxylamine (7803-49-8)

methyl nitrite (624-91-9)

Propiophenone (93-55-0)

α-benzoylpropionic acid (2051-95-8)

ISONITROSOPROPIOPHENONE

1,2-Propanedione, 1-phenyl-, 2-oxime (119-51-7)

propionyl chloride (79-03-8)

propionic anhydride (123-62-6)

1-phenyl-1,2-propanedione (579-07-7)

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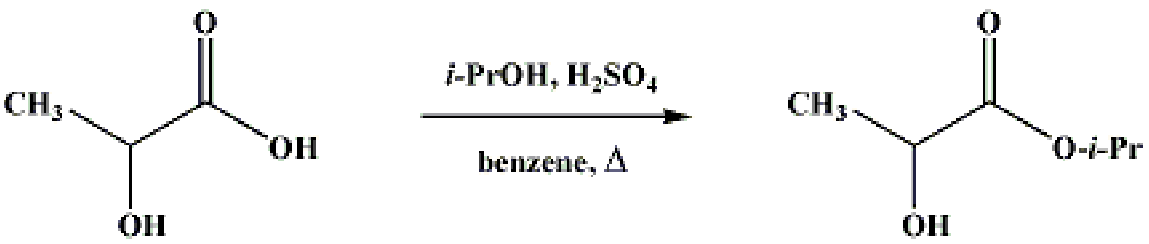
Organic Syntheses, CV 2, 365

ISOPROPYL LACTATE

[Lactic acid, isopropyl ester]



Submitted by F. A. McDermott
Checked by C. R. Noller

1. Procedure

In a 3-l. round-bottomed flask (Note 1) fitted with a 1-meter fractionating column[1] are placed 450 g. (7.5 moles) of anhydrous isopropyl alcohol (Note 2), 212 g. (2 moles) of u.s.p. 85 per cent lactic acid, 1 l. of benzene, and 5 cc. of concentrated sulfuric acid. The flask is placed in an air bath on an electric hot plate (Note 3) and heated until the benzene-isopropyl alcohol-water ternary mixture distils at 66.5°. Distillation is continued slowly (six to seven hours) until the temperature at the head of the column rises to and persists at 71–72° (isopropyl alcohol-benzene binary mixture), and no further separation of water occurs. Ten grams of precipitated calcium carbonate is then added to the mixture, and distillation is continued until the temperature rises to 80° in order to remove most of the benzene and excess isopropyl alcohol (Note 4) and (Note 5). The contents of the flask are then filtered into a modified Claisen flask and distilled under reduced pressure. Cuts are taken to 60°, 60–75°, 75–80°, and 80–100° at 32 mm. The fraction boiling at 75–80°/32 mm. is isopropyl lactate and weighs 130–160 g. By redistilling the high and low fractions an additional 30–60 g. is obtained, bringing the total yield to 160–180 g. (60–68 per cent of the theoretical amount). The ester may be redistilled at atmospheric pressure (with some loss due to decomposition) at 166–168°.

2. Notes

1. With larger amounts of material it is desirable to employ a two-necked flask; the spare neck is used for introducing the calcium carbonate later in the process.
2. Commercial anhydrous alcohol was used in this preparation. Isopropyl alcohol is very difficult to dry satisfactorily. The water binary mixture, boiling at 80.35°, contains 12.1 per cent of water by weight. The ternary mixture with benzene, boiling at 66.5°, contains 73.8 per cent benzene, 18.7 per cent isopropyl alcohol, and 7.5 per cent water. Hence by adding 120 g. of dry benzene to 100 g. of the isopropyl alcohol-water binary mixture, and distilling until the temperature reaches 82°, there will remain 55 to 60 g. of nearly dry

isopropyl alcohol.
3. A water or steam bath or oil bath may be used.
4. The temperature of the vapors should not be allowed to rise above 72° before the addition of the calcium carbonate. If too much alcohol is removed before the acid is neutralized, charring and resinification take place with a decrease in the yield of ester.
5. The recovered benzene and excess isopropyl alcohol may be dried by distillation and used in a subsequent run.

3. Discussion

Isopropyl lactate has been prepared by heating isopropyl alcohol and lactic acid in a sealed tube at 170°,[2] and from silver lactate and isopropyl iodide, together with the isopropyl ester of α-isopropoxypropionic acid.[3] Direct esterification of lactic acid with isopropyl alcohol, using sulfuric acid, has hitherto given less than a 20 per cent yield of impure ester.

References and Notes

1. Clarke and Rahrs, Ind. Eng. Chem. **15**, 349 (1923).
2. Silva, Bull. soc. chim. (2) **17**, 97 (1872).
3. Purdie and Lander, J. Chem. Soc. **73**, 298 (1898).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

Benzene (71-43-2)

calcium carbonate (471-34-1)

isopropyl alcohol (67-63-0)

lactic acid (50-21-5)

Isopropyl lactate, Lactic acid, isopropyl ester (63697-00-7)

silver lactate (128-00-7)

isopropyl iodide (75-30-9)

isopropyl ester of α-isopropoxypropionic acid

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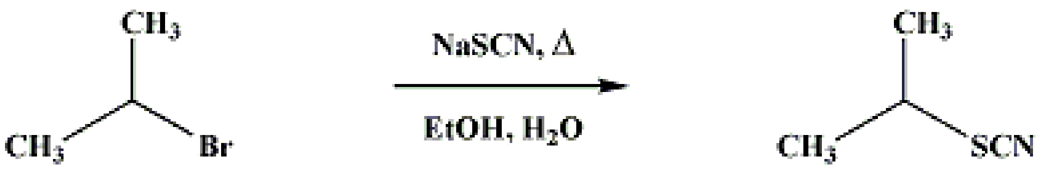
ISOPROPYL THIOCYANATE

[Thiocyanic acid, isopropyl ester]



Submitted by R. L. Shriner
Checked by C. R. Noller

1. Procedure

In a 3-l. round-bottomed flask, fitted with a very efficient mechanical stirrer (Note 1), a reflux condenser, and a 500-cc. separatory funnel, are placed 445 g. (5.5 moles) of sodium thiocyanate (Note 2) and 1250 cc. of 90 per cent ethyl alcohol. The stirrer is started and the mixture is heated to boiling. Then 615 g. (5 moles) of isopropyl bromide (p. 359; Org. Syn. Coll. Vol. I, **1941**, 37) is added slowly during the course of one hour. The mixture is refluxed with stirring for six hours. At the end of this time the precipitated sodium bromide is removed by filtration and washed with 250 cc. of 95 per cent alcohol. As much of the alcohol as possible is then removed by distillation on the steam bath. To the residue in the flask is added 500 cc. of water, and the upper layer of isopropyl thiocyanate is separated. The aqueous layer is extracted with two 100-cc. portions of ether (Note 3). The ether extracts are added to the crude thiocyanate, and the combined product is dried over anhydrous sodium sulfate (Note 4). The dried material is fractionated twice from a modified Claisen flask with a 25-cm. fractionating column. The following fractions are collected: up to 60°; 60–100°; 100–130°; 130–146°; and 146–151°. The last fraction contains the pure product. The yield is 320–345 g. (63–68 per cent of the theoretical amount). By redistilling the alcohol that was removed on the steam bath through an efficient fractionating column (Note 5) until all the alcohol is removed (Note 6), separating the water, and distilling, there is obtained an additional 55–65 g. of product boiling at 146–151°. The total yield is 385–400 g. (76–79 per cent of the theoretical amount). On redistillation of the combined fractions boiling at 146–151°, practically the entire amount distils at 149–151°.

2. Notes

1. A vigorous mechanical stirrer must be used to prevent the precipitated sodium bromide from settling to the bottom and causing bumping.
2. A technical grade of sodium thiocyanate was used. Potassium thiocyanate does not possess any advantages over the sodium salt.
3. If benzene is used to extract the aqueous layer, three fractionations are

necessary to obtain the same yields.
4. The sodium sulfate does not remove the water entirely, and in the subsequent fractionation the water layer should be removed by means of a separatory funnel wherever it appears.
5. An eight-bubbler fractionating column of the type described by Clarke and Rahrs[1] was used.
6. Distillation was continued until water began to appear in the lowest bubbler.

3. Discussion

Isopropyl thiocyanate has been prepared by the action of isopropyl iodide on potassium thiocyanate.[2]

References and Notes

1. Clarke and Rahrs, Ind. Eng. Chem. **18**, 1092 (1926).
2. Henry, Ber. **2**, 496 (1869); Gerlich, Ann. **178**, 80 (1875).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethyl alcohol, alcohol (64-17-5)

Benzene (71-43-2)

ether (60-29-7)

sodium bromide (7647-15-6)

Isopropyl bromide (75-26-3)

sodium sulfate (7757-82-6)

potassium thiocyanate (333-20-0)

isopropyl iodide (75-30-9)

Isopropyl thiocyanate, Thiocyanic acid, isopropyl ester (625-59-2)

sodium thiocyanate (540-72-7)

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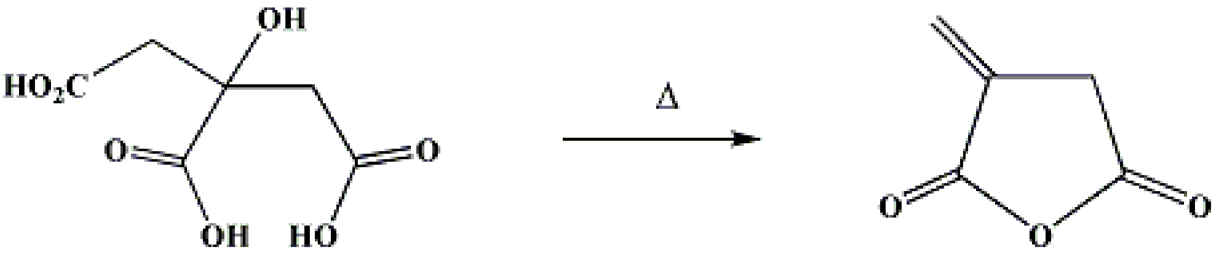
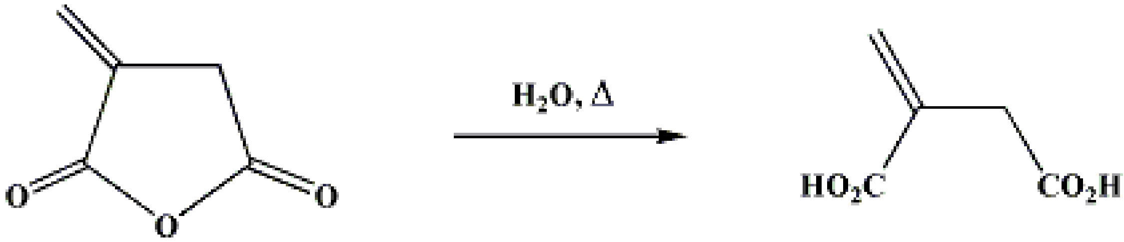
ITACONIC ANHYDRIDE AND ITACONIC ACID





Submitted by R. L. Shriner, S. G. Ford, and L. J. Roll.
Checked by C. R. Noller

1. Procedure

(*A*) *Itaconic Anhydride*.—A 500-cc. Pyrex Kjeldahl flask is fitted with an outlet tube 12 mm. in diameter bent for downward distillation and attached to a 100-cm. water-cooled condenser having an indented Pyrex inner tube (Note 1). Two 250-cc. long-necked distilling flasks, cooled in ice-water baths, are used in series as receivers; the vapors are led to the center of each flask by an adapter and glass tubing.

Two hundred grams (0.95 mole) of u.s.p. citric acid monohydrate is placed in the Kjeldahl flask (Note 2) and heated with a free flame until melted. Then the flask is heated very rapidly with a Meker burner, and the distillation is completed as quickly as possible (ten to twelve minutes). Superheating must be avoided (Note 3). The distillate consists of water and itaconic anhydride, most of which distils at 175–190°. The distillate is immediately poured into a separatory funnel and the lower layer of itaconic anhydride is separated (Note 4). The yield of the anhydride is 40–50 g. (37–47 per cent of the theoretical amount). It is of sufficient purity for use in the preparation of citraconic anhydride (p. 140) (Note 5) and (Note 6).

(*B*) *Itaconic Acid*.—Forty grams of itaconic anhydride is refluxed with 100 cc. of water for one hour. The flask is then set aside to cool, and finally placed in an ice bath. The acid crystallizes and is filtered and dried. The yield is 11–18 g. (24–39 per cent of the theoretical amount) of a product which melts at 162–165°. On concentrating the mother liquor to one-third of the original volume, an additional amount of lower-melting product may be obtained (Note 7) and (Note 8).

2. Notes

1. A Pyrex inner tube is recommended, since the rapid stream of hot vapor often cracks soft glass tubes. A suitable tube may be prepared from a piece of ordinary Pyrex tubing of the proper size by softening it in spots in the blast lamp and applying suction.
2. A clean flask should be used for each run since the presence of residue from a previous run causes excessive foaming during the first part of the decomposition. The flask is cleaned most easily by adding a 25 per cent solution of sodium hydroxide while the residue at the bottom is still molten. Further heating brings about complete solution.
3. Superheating tends to increase the rearrangement to citraconic anhydride. The flask should be heated on all sides over a considerable area, and the distillation should be stopped as soon as the vapors in the reaction flask become yellow.
4. A prompt separation of the anhydride and water layers minimizes hydrolysis of the anhydride. The water layer may be concentrated to give a mixture of itaconic and citraconic acids.
5. The purity of the itaconic anhydride seems to vary greatly with the conditions of the experiment. The crude anhydride always deposits crystals of itaconic acid on standing, probably due to water dissolved or suspended in the anhydride. Some idea of the purity can be obtained by the quantity of itaconic acid that is obtained from it. If the distillation proceeds at exactly the right rate, the anhydride is pure and melts at 67–68°.
6. If larger amounts of itaconic anhydride are desired, it is better to pyrolyze several 200-g. portions of citric acid than a single large portion; the percentage yield of itaconic anhydride usually decreases with larger runs.
7. In some runs no itaconic acid crystallizes. This apparently happens when the distillation of the citric acid has not been carried out rapidly enough and the itaconic anhydride contains a large amount of citraconic anhydride.
8. For preparing considerable amounts of itaconic acid, the following procedure is more convenient than that given above and the yields are much greater. Nine 120-g. portions of citric acid are distilled rapidly (four to six minutes), using 300-cc. Kjeldahl flasks, and all the distillates are collected in the same receiver. The distillate, which generally does not consist of two layers, is placed in an evaporating dish, 50 cc. of water is added, and the mixture is allowed to stand on a steam bath for three hours. On cooling it sets to a semi-solid mass: this is filtered and washed with 150 cc. of water. The residue consists of 138 g. of perfectly white crystals melting at 165°. By concentrating the filtrate an additional 42 g. of product melting at 157–165° is obtained. The total yield is 26–27 per cent of the theoretical amount. (C. V. Wilson and C. F. H. Allen, private communication.)

3. Discussion

Itaconic anhydride has been made by heating itaconic acid and by distillation of citric acid.[1]

Itaconic acid has been prepared by the distillation of citric acid,[2] of aconitic acid,[3] and of itamalic acid;[4] by heating citric acid with dilute sulfuric acid in a closed tube;[5] by treating aconitic acid with water at 180°;[6] by heating citraconic acid with sodium hydroxide;[7] by heating citraconic anhydride with water at 150°;[8] by heating a concentrated solution of citraconic acid at 120–130° in a sealed tube;[9] and by the action of the fungus *Aspergillus itaconicus* on cane sugar.[10]

A mixture of citraconic and itaconic acids is obtained by flowing a concentrated aqueous solution of citric acid into a heated evacuated vessel, distilling under reduced pressure the mixture of anhydrides formed, and allowing the mixture to react with water.[11]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 140
- Org. Syn. Coll. Vol. 4, 554

References and Notes

1. Anschütz, Ber. **13**, 1541 (1880).
2. Baup, Ann. **19**, 29 (1836).
3. Crasso, ibid. **34**, 63 (1840).
4. Swarts, Zeit. für Chem. **1867**, 649.
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7. Delisle, ibid. **269**, 86 (1892).
8. Fittig and Landolt, ibid. **188**, 72 (1877).
9. Wilm, ibid. **141**, 29 (1867).
10. Kinoshita, Acta Phytochim. **5**, 271 (1931) [C. A. **26**, 966 (1932)].
11. Boehringer Sohn A.-G., Brit. pat. 452,460 [C. A. **31**, 1045 (1937)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

citraconic and itaconic acids

itaconic and citraconic acids

sulfuric acid (7664-93-9)

sodium hydroxide (1310-73-2)

citric acid (77-92-9)

Aconitic acid (499-12-7)

citric acid monohydrate (5949-29-1)

Citraconic anhydride (616-02-4)

Citraconic acid (498-23-7)

Itaconic anhydride (2170-03-8)

Itaconic acid (97-65-4)

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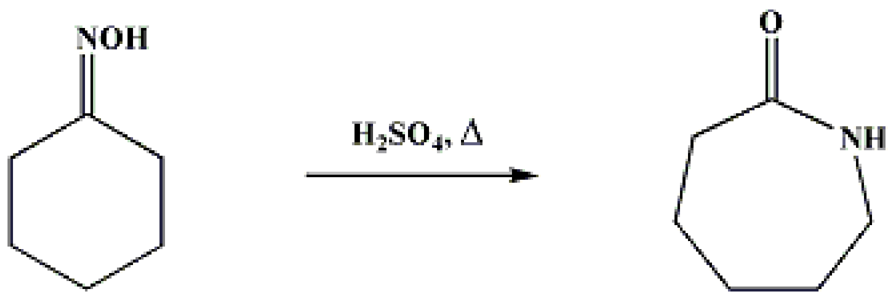
Organic Syntheses, CV 2, 371

2-KETOHEXAMETHYLENIMINE

[Hexamethylenimine, 2-oxo-]



Submitted by C. S. Marvel and J. C. Eck.
Checked by Louis F. Fieser and C. H. Fisher.

1. Procedure

The rearrangement of 120 g. (1.06 moles) of pure cyclohexanone oxime (Note 1) is carried out in twelve 10-g. portions according to the procedure given in the first eight lines of (*B*), p. 77.

The acid solutions of ε-caprolactam from the twelve runs are combined in a 3-l. round-bottomed flask which is fitted with a mechanical stirrer and a separatory funnel and packed in an ice-salt mixture. The solution is cooled to 0° and carefully made faintly alkaline to litmus by the addition of 24 per cent potassium hydroxide solution, added very slowly (five to six hours) with good cooling (Note 2). Usually about 1550 cc. of the alkaline solution is needed. The temperature must be kept below 10° to avoid hydrolysis during this stage of the preparation.

The potassium sulfate which has separated is then removed by filtration and washed with two 100-cc. portions of chloroform. The faintly alkaline aqueous solution is extracted with about five 200-cc. portions (Note 3) of chloroform, and the combined chloroform solutions are washed once with 50 cc. of water to remove any alkali. The chloroform is then distilled and the product fractionated under reduced pressure. The yield of 2-ketohexamethylenimine, boiling at 127–133°/7 mm. and melting at 65–68°, amounts to 71–78 g. (59–65 per cent of the theoretical amount) (Note 4).

2. Notes

1. Pure cyclohexanone oxime, m.p. 86–88° (pp. 76 and 314), must be used since poorer grades char badly when treated with sulfuric acid.
2. Potassium hydroxide gives better results than sodium hydroxide, since the large amount of hydrated sodium sulfate which separates from the solution if sodium hydroxide is used prevents efficient cooling.

3. The extraction is continued until no appreciable amount of product is obtained in the chloroform layer.
4. The boiling point is reported in the literature as 139–140°/12 mm.; the melting point is reported at various temperatures from 65° to 70°.

3. Discussion

2-Ketohexamethylenimine, ε-caprolactam, has been obtained by heating ε-aminocaproic acid or its ethyl ester[1] and by the rearrangement of cyclohexanone oxime.[2, 3, 4] The method[4] described above is Ruzicka's[3] modification of Wallach's[2] original directions for the rearrangement of the oxime. This rearrangement can also be run as a continuous process.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 28
- Org. Syn. Coll. Vol. 2, 76
- Org. Syn. Coll. Vol. 4, 588
- Org. Syn. 79, 165

References and Notes

1. Gabriel and Maass, Ber. **32**, 1271 (1899); von Braun, ibid. **40**, 1840 (1907); Carothers and Berchet, J. Am. Chem. Soc. **52**, 5289 (1930).
2. Wallach, Ann. **312**, 187 (1900); **343**, 43 (1905).
3. Ruzicka, Seidel, and Hugoson, Helv. Chim. Acta **4**, 477 (1921).
4. Eck and Marvel, J. Biol. Chem. **106**, 387 (1934).
5. E. I. du Pont de Nemours and Company, U. S. pat. 2,234,566 [C. A. **35**, 3650 (1941)]; I. G. Farbenind. A.-G., U. S. pat. 2,249,177 [C. A. **35**, 6599 (1941)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

potassium sulfate (37222-66-5)

sodium sulfate (7757-82-6)

potassium hydroxide (1310-58-3)

ε-AMINOCAPROIC ACID (60-32-2)

2-Ketohexamethylenimine, ε-caprolactam, Hexamethylenimine, 2-oxo- (105-60-2)

Cyclohexanone oxime (100-64-1)

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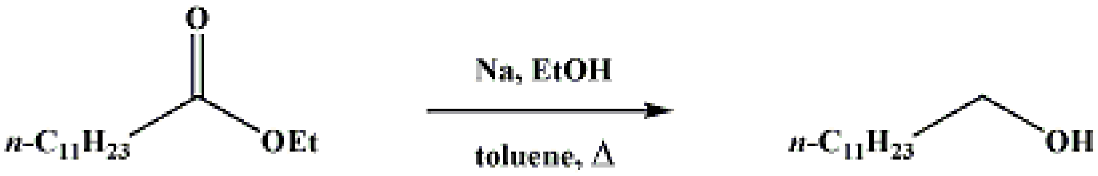
Organic Syntheses, CV 2, 372

LAURYL ALCOHOL

[Dodecyl alcohol]



Submitted by S. G. Ford and C. S. Marvel.
Checked by Frank C. Whitmore and D. J. Loder.

1. Procedure

The central neck of a 5-l. three-necked round-bottomed flask is fitted with a stopper carrying a mercury-sealed mechanical stirrer. One of the side necks is connected by means of a short piece of heavy rubber tubing to a large reflux condenser about 2 m. long, with an inner tube 2.5 cm. in diameter (Note 1). The third neck is fitted with a separatory funnel.

In the flask are placed 70 g. (3 moles) of sodium and 200 cc. of dry toluene (Note 2). The flask is heated in an oil bath until the sodium is melted. The stirrer is then started; when the sodium is finely divided, the oil bath is removed and the mixture allowed to cool. Stirring must be continued during the cooling in order to keep the sodium finely divided.

When the mixture has cooled to about 60°, there are added from the separatory funnel, first, a solution of 114 g. (0.5 mole) of ethyl laurate (Note 3) in 150 cc. of absolute alcohol (Note 4), then 500 cc. more of alcohol, as rapidly as is possible (Note 5) without loss of material through the condenser. The time required for the addition of the ester solution and the alcohol is less than five minutes, usually two or three minutes. When the reaction has subsided, the flask is heated on a steam bath until the sodium is completely dissolved (Note 6). The mixture is then steam-distilled to remove the toluene and ethyl alcohol. The contents of the flask are transferred to a separatory funnel while still hot and washed three times with 200-cc. portions of hot water to remove the sodium laurate (Note 7). The lauryl alcohol is extracted with ether from the cooled mixture and the washings. The combined ether extracts are washed with water, sodium carbonate solution, and again with water, and dried over anhydrous magnesium sulfate. The ether is evaporated and the lauryl alcohol distilled under diminished pressure. The yield is 60–70 g. (65–75 per cent of the theoretical amount) of a product boiling at 143–146°/18 mm. or 198–200°/135 mm. (Note 8).

2. Notes

1. The reaction is very vigorous and, unless the condenser has a wide bore, finely divided sodium may be forced out the top and bad fires may result. The inner tube of the condenser may advantageously be made of brass or copper.
2. The toluene is dried by distillation; the first 10 per cent is discarded and the remainder is stored over sodium until used.
3. The ethyl laurate used was prepared by the alcoholysis of cocoanut oil and fractionation of the resulting esters. The material boiled at 127–132°/5 mm. See Org. Syn. **20**, 69, and Organic Chemical Reagents III, Univ. Illinois Bull. **19** (6) 62 (1921).
4. The grade of absolute alcohol used in the reduction is very important. Alcohol dried with magnesium methoxide (Org. Syn. Coll. Vol. I, **1941**, 249) was used in this preparation. Alcohol dried over lime gives very low yields.
5. The best yields are obtained when the reductions are carried out rapidly. If the reaction seems to be about to get out of control, the stirrer is stopped and the mixture is cooled with an ice pack.
6. When several reductions are being made, time is saved by transferring the mixture at this point to another flask, thus having the original apparatus ready for another reduction.
7. Unless the sodium laurate is carefully removed, it causes trouble some emulsions.
8. Ethyl undecylenate has been reduced to undecylenyl alcohol (b.p. 123–125°/6 mm.) in 70 per cent yields; ethyl myristate to myristyl alcohol (b.p. 170–173°/20 mm.; m.p. 39–39.5°) in 70–80 per cent yields; ethyl palmitate to cetyl alcohol (b.p. 178–182°/12 mm.; m.p. 48.5–49.5°) in 70–78 per cent yields by this same procedure.

3. Discussion

Lauryl alcohol has been prepared by the reduction of the aldehyde;[1] by the reduction of esters of lauric acid with sodium and absolute alcohol[2] or with sodium, liquid ammonia and absolute alcohol,[3] or catalytically;[4] and by the reduction of lauramide with sodium and amyl alcohol.[5] The method in the above procedure is essentially that described by Levene and Allen.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 246
- Org. Syn. Coll. Vol. 2, 468

References and Notes

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3. Chablay, Compt. rend. **156**, 1021 (1913); Ann. chim. (9) **8**, 215 (1917).
4. Adkins and Folkers, J. Am. Chem. Soc. **53**, 1095 (1931); Böhme A.-G., Brit. pat. 356,606 [C. A. **26**, 5573 (1932)].
5. Scheuble and Loebl, Monatsh. **25**, 348 (1904).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethyl alcohol, alcohol (64-17-5)

ammonia (7664-41-7)

ether (60-29-7)

sodium carbonate (497-19-8)

Lauryl alcohol, dodecyl alcohol (112-53-8)

copper (7440-50-8)

toluene (108-88-3)

sodium (13966-32-0)

magnesium methoxide

amyl alcohol (71-41-0)

magnesium sulfate (7487-88-9)

Cetyl alcohol (36653-82-4)

ethyl laurate (106-33-2)

sodium laurate (629-25-4)

Ethyl undecylenate

Undecylenyl alcohol

ethyl myristate (124-06-1)

Myristyl alcohol (112-72-1)

ethyl palmitate (628-97-7)

esters of lauric acid (143-07-7)

lauramide (1120-16-7)

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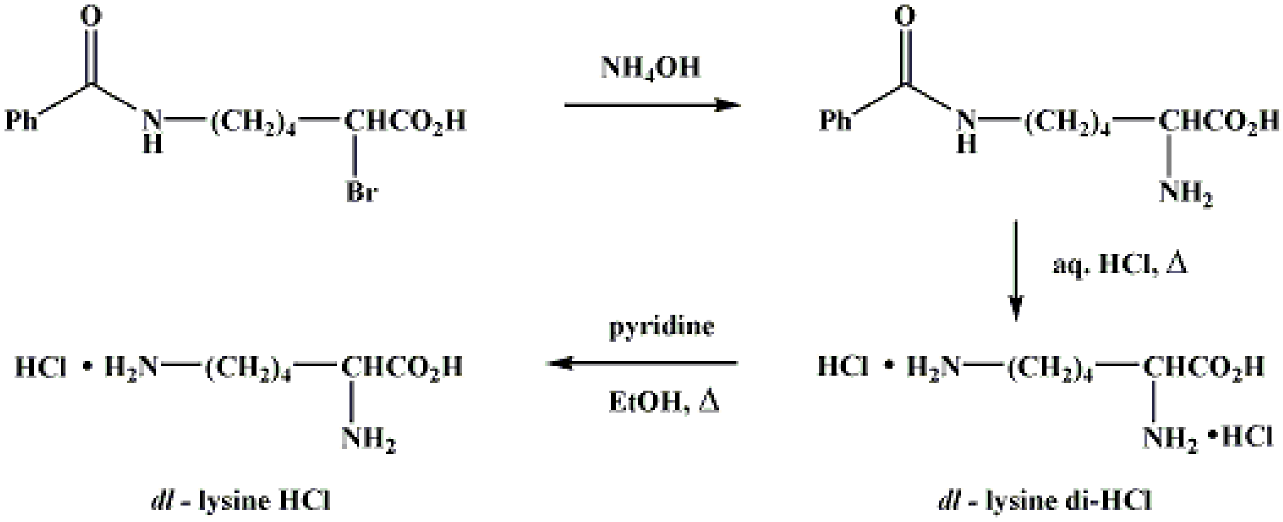
Organic Syntheses, *CV 2*, *374*

dl-LYSINE HYDROCHLORIDES



Submitted by J. C. Eck and C. S. Marvel.
Checked by C. R. Noller and William Munich.

1. Procedure

(*A*) *dl-ε-Benzoyllysine*.—A solution of 180 g. (0.57 mole) of ε-benzoylamino-α-bromocaproic acid (p. 74) in 2 l. of aqueous ammonia (sp. gr. 0.9) is filtered into a 5-l. flask and allowed to stand for two days. Any crystals which have formed at the end of this time are filtered, and the filtrate is evaporated on a steam bath at reduced pressure to about 1 l. The crystals are filtered, combined with the first crop, and washed with 100 cc. of alcohol and finally with 100 cc. of ether. The aqueous filtrate is evaporated under reduced pressure to dryness; the residue is washed with two 100-cc. portions of water to remove the ammonium bromide, and then with 50 cc. of alcohol, followed by 50 cc. of ether. The total yield of ε-benzoyllysine, melting at 265–270°, is 100–116 g. (70–81 per cent of the theoretical amount).

(*B*) *dl-Lysine Dihydrochloride*.—A solution of 100 g. (0.4 mole) of benzoyllysine in a mixture of 600 cc. of hydrochloric acid (sp. gr. 1.18) and 400 cc. of water is boiled under a reflux condenser for ten hours. The mixture is cooled and the benzoic acid removed by filtration. The filtrate is evaporated on a water bath under reduced pressure until a thick syrup remains. The syrup is transferred to a 1.5-l. beaker by means of four volumes (about 400 cc.) of hot absolute alcohol and filtered if necessary. The solution is cooled to 15–20°, and 500 cc. of ether is added slowly with stirring. The precipitate, after filtering and drying, melts at 187–189° and weighs 67–75 g. (76–85 per cent of the theoretical amount); it is analytically pure lysine dihydrochloride (Note 1).

(*C*) *dl-Lysine Monohydrochloride*.—To a solution of 55 g. (0.25 mole) of lysine dihydrochloride in 1 l. of boiling 95 per cent alcohol (Note 2) is added, with stirring, a solution of 25 g. (0.32 mole) of pyridine in 40 cc. of hot 95 per cent alcohol. The white, crystalline monohydrochloride separates immediately. After cooling overnight in a refrigerator the solid is filtered and washed with two 50-cc. portions of cold absolute alcohol. After drying, the product melts at 260–263° and weighs 42–43 g. (91–94 per cent of the theoretical amount).

For further purification to remove any pyridine hydrochloride, the above product is dissolved in

85 cc. boiling water, and 650 cc. of boiling 95 per cent alcohol added with stirring. After cooling overnight in the refrigerator the solid is filtered, and washed with one 20-cc. portion of cold absolute alcohol. There is obtained 40–42 g. (95–97 per cent recovery) of monohydrochloride melting at 263–264° (corr.).

2. Notes

1. If a product of lower melting point is obtained, it may be purified by dissolving in 1 l. of hot 95 per cent alcohol, filtering if necessary, cooling, and, without removing any material that may have crystallized, adding slowly with stirring 1.5 l. of ether. If the product separates as an oil it will soon crystallize on standing. The checkers found that one lot of 75 g. melting at 173–178° when treated in this way gave 67 g. (89 per cent recovery) melting at 187–189°.
2. If the solution is not clear, it should be filtered before the addition of pyridine.

3. Discussion

The above procedure for *dl*-ε-benzoyllysine and *dl*-lysine hydrochloride is a modification[1] of that published by Braun.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 322
- Org. Syn. Coll. Vol. 6, 90

References and Notes

1. Eck and Marvel, J. Biol. Chem. **106**, 387 (1934).
2. Braun, Ber. **42**, 844 (1909).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

dl-LYSINE HYDROCHLORIDES

alcohol (64-17-5)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ether (60-29-7)

ammonium bromide (12124-97-9)

Benzoic acid (65-85-0)

pyridine (110-86-1)

ε-BENZOYLAMINO-α-BROMOCAPROIC ACID (1700-05-6)

pyridine hydrochloride (628-13-7)

DL-ε-Benzoyllysine, ε-benzoyllysine (5107-18-6)

DL-Lysine dihydrochloride (617-68-5)

benzoyllysine

lysine dihydrochloride

dl-Lysine Monohydrochloride, dl-lysine hydrochloride (26124-78-7)

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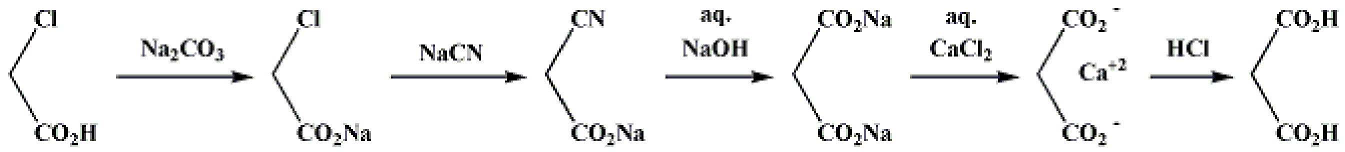
Organic Syntheses, CV 2, 376

MALONIC ACID



Submitted by Nathan Weiner
Checked by C. R. Noller and M. E. Synerholm.

1. Procedure

In a 5-l. round-bottomed flask, 500 g. (5.3 moles) of chloroacetic acid (Note 1) is dissolved in 700 cc. of water. The solution is warmed to 50°, neutralized with 290 g. (2.7 moles) of anhydrous sodium carbonate, and again cooled to room temperature. Meanwhile, 294 g. (6 moles) of sodium cyanide (97 per cent) is dissolved in 750 cc. of water warmed to 55°; the solution is cooled to room temperature and then added to the sodium chloroacetate solution, with rapid mixing of the two solutions and cooling under the water tap. When the solutions are completely mixed, cooling is stopped and the temperature allowed to rise. When it reaches 95°, the solution is cooled by adding 200 cc. of ice water, and this is repeated, if necessary, until the temperature no longer rises (Note 2). The solution is then heated on the steam bath for one hour to ensure completion of the reaction.

At the end of this time, the solution is cooled to room temperature and 240 g. (6 moles) of solid u.s.p. sodium hydroxide is slowly dissolved in it. When solution is complete, the reaction mixture is again heated on the steam bath under a hood. When the temperature reaches 60–70°, evolution of ammonia begins and becomes more vigorous with rise in temperature. Most of the ammonia is evolved in forty-five minutes, but the solution is heated for at least three hours, and the last traces of ammonia are removed by bubbling steam through the hot solution for forty-five to sixty minutes more.

A solution of 600 g. of anhydrous calcium chloride in 1.8 l. of water warmed to 40° is added slowly with rapid mixing to the hot sodium malonate solution. A cheese-like precipitate of calcium malonate is formed immediately and becomes coarsely crystalline on standing for twenty-four hours. After the supernatant solution is decanted, the calcium malonate is washed by decantation four or five times with 500-cc. portions of cold water. It is then transferred to a filter, sucked as dry as possible, and dried in the air, or at 45–50°, to constant weight. The yield is 800–900 g.

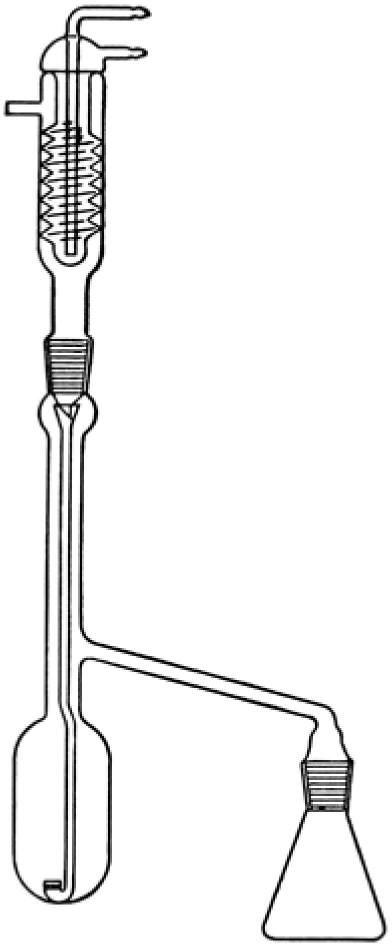
The dry calcium malonate is placed in a 3-l. round-bottomed flask with sufficient (750–1000 cc.) alcohol-free ether (Note 3) to make a paste which can be stirred. The flask is surrounded by an ice bath, and the well-stirred salt is treated with 1 cc. of 12 *N* hydrochloric acid for each gram of salt. After the acid has been added slowly through a dropping funnel, the solution is transferred to a continuous extractor (Note 4) and extracted with ether until no more malonic acid is obtained. The product, as obtained from the undried ether solution by concentration, filtration, and drying in the air, melts at 130° or higher and is sufficiently pure for most purposes. The yield is 415–440 g. (75–80 per cent of the theoretical amount).

2. Notes

1. A freshly distilled product boiling over a 3° range was used.
2. If the reaction between the cyanide and the chloroacetate becomes too vigorous, hydrogen cyanide is liberated and partly changed to a brown material, and a corresponding quantity of glycolate is formed. If the temperature of the reaction mixture is allowed to go above 95° spontaneously, the liquid may boil so vigorously and suddenly as to escape from the flask despite the large extra volume provided.
3. Ether is used to avoid unnecessarily increasing the volume of aqueous solution to be extracted. This ether may be used for further extraction. It is necessary to use alcohol-free ether to avoid esterifying the malonic acid during the protracted extraction period.
4. A convenient type of extractor used in this preparation was made as follows by modifying that described by J. Friedrichs:[1] A 20-cm. calcium chloride tower, or other narrow-necked cylinder with a volume of about 1.3 l., was used as an extraction chamber. The mantle-tube, conducting the ether vapors to an Allihn condenser, was made of 25-mm. tubing and was about 50 cm. long. The goose-neck to the extraction flask, of 14-mm. tubing, was sealed to the mantle-tube about 8 cm. from the bottom end. The inner tube was of 14-mm. tubing, about 65 cm. long, flanged at the top to a diameter of about 20 mm. A Witt filter plate of the proper diameter may be sealed into the bottom of the tube to make the ether pass up through the water in a stream of fine bubbles, or this can also be accomplished by sealing off the bottom of the tube and piercing it with 3–6 pinholes. The mantle-tube was fitted to the chamber by a properly bored rubber stopper, the condenser to the top of the mantle-tube, and the 500-cc. extraction flask to the goose-neck by charred cork stoppers. With this apparatus 395–400 g. of malonic acid was extracted in seventy-two hours, the ether

being changed every twenty-four hours, and the final traces were extracted after an additional twenty-four hours. The extractor as described by Friedrichs is shown in .htmFig. 12.

Fig. 12



3. Discussion

Malonic acid has been prepared by the hydrolysis of malononitrile with concentrated hydrochloric acid;[2] by the hydration of carbon suboxide;[3] and from an alkali cyanide and ethyl bromoacetate,[4] ethyl chloroacetate,[5] or chloroacetic acid[6] followed by hydrolysis. The preparation using sodium cyanide and chloroacetic acid is the most convenient and economical.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 436
- Org. Syn. Coll. Vol. 5, 627

References and Notes

1. Friedrichs, Chem. Fabrik **1**, 91 (1928).
2. Henry, Compt. rend. **102**, 1396 (1886).
3. Diels and Wolf, Ber. **39**, 696 (1906).
4. Franchimont, ibid. **7**, 216 (1874).
5. Kolbe, Ann. **131**, 349 (1864); Müller, ibid. **131**, 352 (1864); Petriev, J. Russ. Phys.-Chem. Soc. **10**, 64 (1878).
6. v. Miller, J. prakt. Chem. (2) **19**, 326 (1879); Grimaux and Tcherniak, Bull. soc. chim. (2) **31**, 338 (1879); Bourgoin, ibid. (2) **33**, 574 (1880); Conrad, Ann. **204**, 126 (1880).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

carbon suboxide

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium cyanide (143-33-9)

hydrogen cyanide (74-90-8)

sodium carbonate (497-19-8)

chloroacetic acid (79-11-8)

sodium chloroacetate (3926-62-3)

Ethyl chloroacetate (105-39-5)

Malonic acid (141-82-2)

sodium malonate (141-95-7)

calcium malonate

Malononitrile (109-77-3)

Ethyl bromoacetate (105-36-2)

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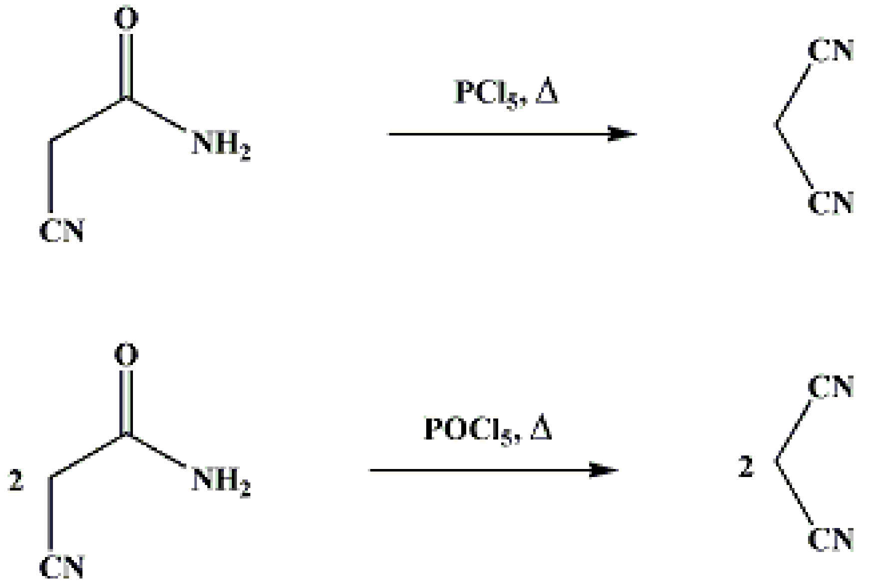
Organic Syntheses, CV 2, 379

MALONONITRILE



Submitted by B. B. Corson, R. W. Scott, and C. E. Vose.
Checked by C. S. Marvel and J. Harmon.

1. Procedure

One hundred fifty grams (1.8 moles) of pure cyanoacetamide (Org. Syn. Coll. Vol. I, **1941**, 179) is thoroughly mixed in a large (20-cm.) mortar with 150 g. (0.7 mole) of phosphorus pentachloride (Note 1). This mixture is transferred (Note 2) as quickly as possible to a 1-l. Claisen flask equipped with a 360° thermometer and an air-intake tube (Note 3). The Claisen flask is connected by means of a double-length air condenser to a 250-cc. filter flask which in turn is connected to a water pump (Note 4) through a manometer.

After the system has been evacuated to about 30 mm. of mercury, the Claisen flask is immersed in a boiling water bath. The mixture melts and its color deepens to orange. Boiling commences in about fifteen minutes, before the solid is completely melted, and the pressure rises to about 150 mm. owing to the liberation of hydrogen chloride and phosphorus oxychloride (Note 5). When the evolution of gas has slackened, as indicated by the fall of pressure and the less vigorous boiling of the reaction mixture (thirty to thirty-five minutes), the receiver is changed. The distilling flask is removed from the boiling water bath, wiped dry, and immersed in an oil bath at 140° (Note 6); the fresh receiver is placed in ice water.

The malononitrile begins to distil at 113°/30 mm. (125°/50 mm.). The temperature of the oil bath is slowly raised over a period of twenty-five minutes to 180° (Note 7) and the nitrile collected between 113° and 125°. When the distillation has almost ceased, the oil bath is removed so as to prevent discoloration of the product (Note 8). The

yield of crude nitrile is 80–95 g. (67–80 per cent of the theoretical amount) (Note 9). The nitrile may be purified by vacuum distillation (Note 10) with about 10 per cent loss; it is collected between 113° and 120°/30 mm. One distillation yields a water-clear liquid, which quickly freezes to an ice-like solid (Note 11) melting at 28–30°. The product has a faint odor resembling that of acetamide.

2. Notes

1. The weights of the reactants correspond to the ratio of 5 molecules of amide to 2 molecules of pentachloride. The use of larger proportions of phosphorus pentachloride leads to lower yields.[1]
The phosphorus pentachloride should be of good quality—a dry solid.
2. This transfer is greatly facilitated by the use of a 15-cm. (6-inch) glass funnel whose stem has been cut off and the hole enlarged to almost the size of the neck of the Claisen flask. The mixture is emptied into the body of the funnel and pushed through the large hole by means of a glass rod. A gas mask should be worn, for any considerable breathing of the fumes brings on a harsh cough which may last for several days.
3. To avoid plugging, the air-intake tube is not drawn out to a capillary.
4. An oil pump cannot be used because of the corrosive acid fumes.
It is reported that a single water pump is usually unable to remove the evolved gases fast enough, with the result that some material is carried over mechanically with the foam. If two water pumps in parallel are used, this difficulty is overcome. (C. F. H. Allen, private communication.)
5. Unless the phosphorus oxychloride is to be recovered, it is advisable to allow it to be carried away by the suction. This is easily accomplished if the receiver is not cooled.
6. If the initial temperature of the oil bath is below 140°, the nitrile distils too slowly (with consequent lowering of yield); if the temperature is above 140°, the nitrile distils too rapidly, some condenses in the rubber tubes leading to the pump and clogs the line.
The flask should be immersed as far as possible in the oil (to within about 100 mm. of the top of the flask). A 1-gal. enamelware coffee-pot makes an excellent oil bath. An ordinary soldered vessel will not stand the temperature.
7. The temperature of the oil bath must not rise much above 180°, else the distillate becomes colored and violent bumping is liable to occur. The distillate should not be allowed to solidify in the condenser. This is most likely to occur during the first part of the distillation. The solid is easily melted by heating with a small flame.
8. The residue in the Claisen flask can be softened by water and broken up with a rod. The small amount remaining is easily removed with concentrated nitric or, preferably, concentrated sulfuric acid.
9. The keynote to success in this preparation is speed. Malononitrile is a sensitive substance and it must be removed from the reaction mixture as rapidly as possible. After experience with one or two runs the yields will consistently be better than 67 per cent.

10. Malononitrile can be distilled in small amounts (50 cc. or so) at ordinary pressure; the boiling point is around 220°. However, the longer heating necessary with larger amounts is likely to cause violent decomposition: the liquid darkens, boils spontaneously, and finally spurts from the flask in a cloud of white fumes and burning liquid; the latter partially solidifies to a brittle red solid.
11. Nitrogen determinations indicate a purity of 99.5 per cent. The product remains colorless for at least one year if stored in brown bottles protected from the light. If kept in ordinary bottles and exposed to the light, the nitrile quickly darkens.
12. This work was aided by a grant from the Cyrus M. Warren Fund of the American Academy of Arts and Sciences.

3. Discussion

Malononitrile has been prepared by the action of phosphorus pentachloride on cyanoacetamide,[1] and by the action of phosphorus pentoxide on malonamide[2] or cyanoacetamide.[3] The preparation using the pentoxide is much less satisfactory than that given above.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 535

References and Notes

1. Hesse, Am. Chem. J. **18**, 726 (1896).
2. Henry, Compt. rend. **102**, 1394 (1886).
3. Henry, ibid. **102**, 1395 (1886).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

hydrogen chloride (7647-01-0)

Acetamide (60-35-5)

phosphorus pentachloride (10026-13-8)

nitrogen (7727-37-9)

mercury (7439-97-6)

Phosphorus Oxychloride (21295-50-1)

CYANOACETAMIDE (107-91-5)

malonamide (108-13-4)

Malononitrile (109-77-3)

phosphorus pentoxide (1314-56-3)

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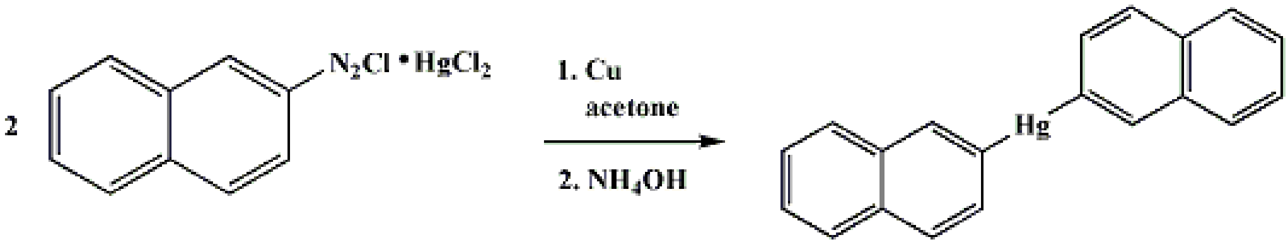
Organic Syntheses, CV 2, 381

MERCURY DI-β-NAPHTHYL

[Mercury, di-2-naphthyl-]



Submitted by A. N. Nesmajanow and E. D. Kohn.
Checked by Frank C. Whitmore and R. W. Beattie.

1. Procedure

In a 2-l. round-bottomed flask, equipped with a stirrer, are placed 231 g. (0.5 mole) of the addition compound of β-naphthalenediazonium chloride and mercuric chloride (p. 432), 700 cc. of acetone (b.p. 55–57°) and 189 g. (3 moles) of copper powder (Note 1). The mixture is quickly cooled to 20° and stirred for one hour. Seven hundred cubic centimeters of concentrated aqueous ammonia solution (sp. gr. 0.9) is added, mixed well, and allowed to stand overnight. The supernatant liquid is decanted; the solid is collected on a Büchner funnel and washed successively with 25-cc. portions of water, acetone, and ether. After air-drying, the crude material is recrystallized from xylene, using decolorizing carbon. The crystals thus obtained are slightly yellow (Note 2) and melt at 241.5–243.5°. The yield is 51–55 g. (45–48 per cent of the theoretical amount based on the addition compound used) (Note 3).

2. Notes

1. The same notes apply as in the preparation of β-naphthylmercuric chloride (p. 432).
2. The product from this reaction is never pure white. Colorless mercury di-β-naphthyl can be prepared in good yield from β-naphthylmercuric chloride (p. 432) and sodium iodide, according to the directions given in Org. Syn. Coll. Vol. I, **1941**, 231, for mercury di-*p*-tolyl.[1]
3. Similar results are obtained with other aromatic amines; aniline and *p*-iodoaniline yield mercury diphenyl and mercury di-*p*-iodophenyl.

3. Discussion

Mercury di-β-naphthyl has been prepared by the action of sodium amalgam on β-bromonaphthalene,[2] and by the action of alcoholic sodium iodide on β-naphthylmercuric chloride.[1]

References and Notes

1. Private communication, Frank C. Whitmore and R. J. Sobatzki.
2. Chattaway, J. Chem. Soc. **65**, 878 (1894); Michaelis, Ber. **27**, 251 (1894).

Appendix

Compounds Referenced (Chemical Abstracts Registry Number)

Mercury di-β-naphthyl

β-Naphthylmercuric chloride

mercury diphenyl

mercury di-p-tolyl

mercury di-p-iodophenyl

ammonia (7664-41-7)

ether (60-29-7)

aniline (62-53-3)

copper powder (7440-50-8)

acetone (67-64-1)

decolorizing carbon (7782-42-5)

sodium (13966-32-0)

β-bromonaphthalene (580-13-2)

mercuric chloride (7487-94-7)

xylene (106-42-3)

sodium iodide (7681-82-5)

Mercury, di-2-naphthyl- (19510-26-0)

β-naphthalenediazonium chloride

p-IODOANILINE (540-37-4)

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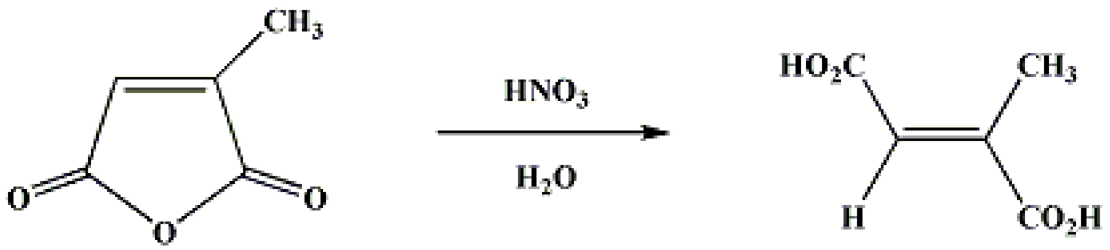
Organic Syntheses, CV 2, 382

MESACONIC ACID



Submitted by R. L. Shriner, S. G. Ford, and L. J. Roll.
Checked by C. R. Noller

1. Procedure

A mixture of 100 g. (0.89 mole) of citraconic anhydride (Note 1) 100 cc. of water, and 150 cc. of dilute nitric acid (1 part of concentrated nitric acid to 4 parts of water by volume) is evaporated in a 500-cc. Erlenmeyer flask until the appearance of red fumes (Note 2). The solution is cooled and the mesaconic acid is collected on a filter. The mother liquor is evaporated to 150 cc., cooled, and the crystalline solid which separates is collected on a filter. Further concentration of the mother liquor to 50 cc. yields more product (Note 3). The entire product is recrystallized from 100 cc. of water. The yield of mesaconic acid melting at 203–205° is 50–60 g. (43–52 per cent of the theoretical amount).

2. Notes

1. An equivalent amount of citraconic acid can be used. Directions for preparing citraconic acid and anhydride are given on p. 140.
2. It is necessary to carry the evaporation to the point where red fumes appear in order for the rearrangement to take place. The volume is usually about 250 cc.
3. The concentration of the mother liquor must be carried out in steps in order to obtain an efficient separation of mesaconic acid.

3. Discussion

Mesaconic acid has been prepared by heating citraconic acid with dilute nitric acid,[1] with hydriodic acid,[2] or with concentrated sodium hydroxide solution;[3] by heating a concentrated water solution of itaconic or citraconic acid at 180–200°;[4] by treating citradibromopyrotartaric acid and mesodibromopyrotartaric acid with potassium iodide and copper at 150°;[5] and by heating citraconic anhydride with nitric acid.[6]

References and Notes

1. Gottlieb, Ann. **77**, 268 (1851).
2. Kekulé, Ann. Spl. **2**, 94 (1862).
3. Delisle, Ann. **269**, 82 (1892).
4. Swarts, Jahresb. **1873**, 579.
5. Swarts, Zeit. für Chem. **1868**, 259.
6. Fittig and Landolt, Ann. **188**, 73 (1877).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

citraconic acid and anhydride

itaconic or citraconic acid

citradibromopyrotartaric acid

sodium hydroxide (1310-73-2)

nitric acid (7697-37-2)

potassium iodide (7681-11-0)

copper (7440-50-8)

hydriodic acid (10034-85-2)

Citraconic anhydride (616-02-4)

Citraconic acid (498-23-7)

Mesaconic acid (498-24-8)

mesodibromopyrotartaric acid

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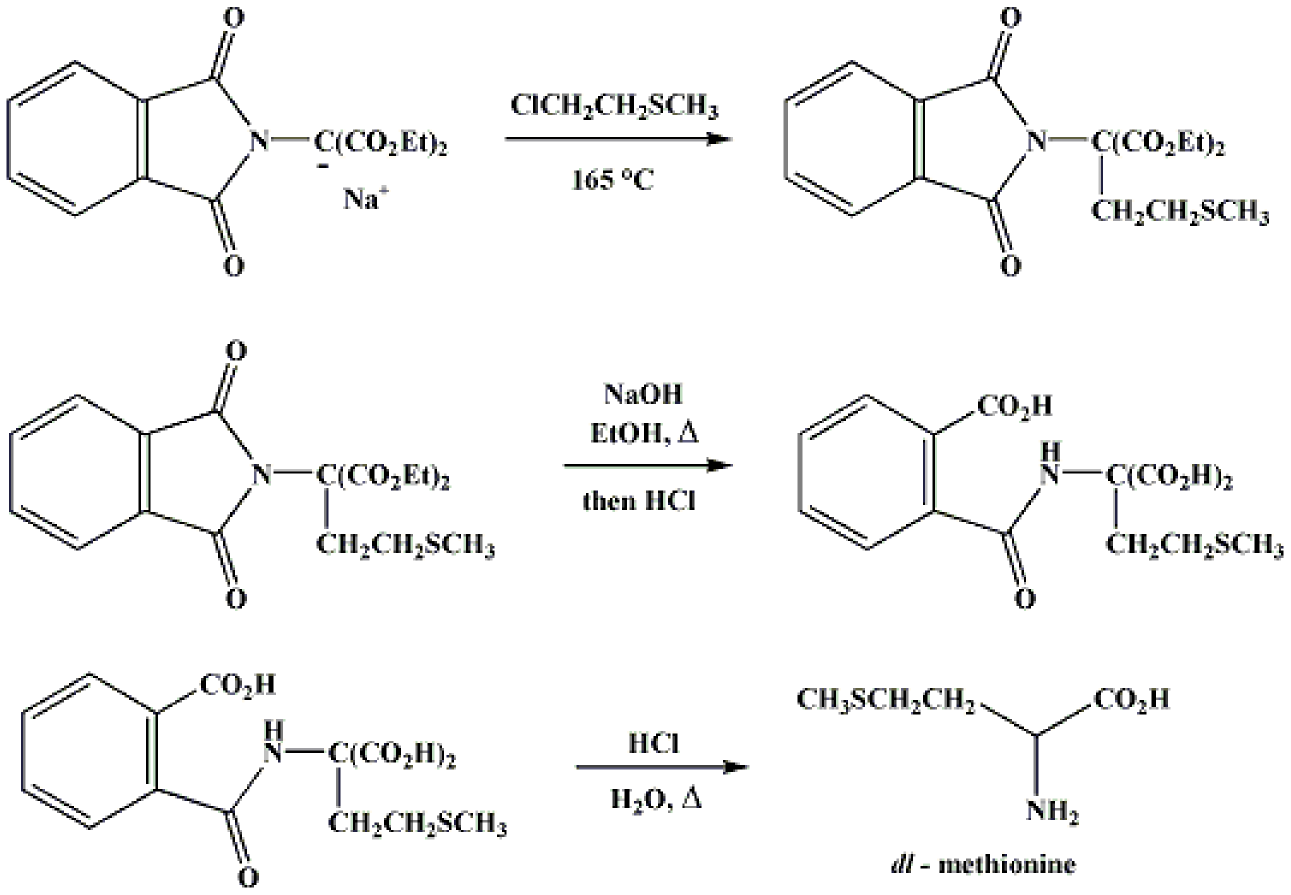
Organic Syntheses, CV 2, 384

dl-METHIONINE



Submitted by G. Barger and T. E. Weichselbaum.
Checked by H. T. Clarke and S. Gurin.

1. Procedure

(*A*) *Ethyl Sodium Phthalimidomalonate*.—To a solution of 9.2 g. (0.4 gram atom) of sodium in 300 cc. of absolute alcohol at 60° is added, with efficient stirring, 126 g. (0.41 mole) of ethyl phthalimidomalonate (Org. Syn. Coll. Vol. I, **1941**, 271). The mixture is rapidly chilled to 0°; the crystalline product is filtered at once by suction and washed successively with two 200-cc. portions of absolute alcohol and two 200-cc. portions of ether. After first drying in a vacuum desiccator and then heating for eight hours under 15 mm. pressure in a flask suspended in an oil bath at 145–155° (Note 1), the product weighs 108–111 g. (82–85 per cent of the theoretical amount).

(*B*) *Ethyl 1-Methylthiol-3-phthalimidopropane-3,3-dicarboxylate*.—A mixture of 85 g. (0.26 mole) of ethyl sodium phthalimidomalonate and 43 g. (0.39 mole) of β-chloroethyl methyl sulfide (p. 136) is heated in an oil bath at 160–165° in a 1-l. three-necked flask, fitted with a condenser, a thermometer, and a stoppered glass tube for sampling. After one and a half to two hours the mixture is no longer alkaline to litmus. The excess chloroethyl methyl sulfide is distilled under reduced pressure (Note 2), the residual oil is treated with 150 cc. of warm water, and the resulting mixture is transferred to a beaker and chilled. The crystalline material is filtered by suction, washed with 100 cc. of cold water, and recrystallized from the smallest possible quantity of warm absolute alcohol. In this way 75–79 g. (76–80 per cent of the theoretical amount) of a pure product, melting at 66–67°, is obtained.

(*C*) *1-Methylthiol-3-phthalamidopropane-3,3-dicarboxylic Acid*.—A solution of 25 g. (0.066 mole) of the above ester in 30 cc. of 95 per cent alcohol is heated on the steam bath in a 200-cc. round-bottomed flask, and 70 cc. of 5*N* sodium hydroxide is added. The cloudy liquid is heated until a sample gives a clear solution on dilution with water; this occurs after about two hours. The solution is then chilled to 0° and cautiously neutralized to Congo red with 0.2 *N* hydrochloric acid, whereupon 75 cc. of 5 *N* hydrochloric acid is slowly added, the temperature being maintained at 0°. The acid separates as colorless crystals. This separation is completed by the slow addition of 60 cc. of concentrated hydrochloric acid (sp. gr. 1.19). The product is filtered by suction and washed free of salt with small quantities of ice-cold water. After drying *in vacuo*, the yield is 21.5–22 g. (95.5–98 per cent of the theoretical amount) of a product melting at 141–143°.

(*D*) *Methionine*.—A suspension of 21.5 g. (0.063 mole) of this tricarboxylic acid in 350 cc. of hot water is heated on the steam bath, and 40 cc. of concentrated hydrochloric acid (sp. gr. 1.19) is added. Carbon dioxide is immediately evolved, and the substance goes into solution. After heating for one and a half hours, 200 cc. more of concentrated hydrochloric acid is added and heating is continued for forty-five minutes longer. The solution, on cooling, deposits phthalic acid; this is filtered and washed with two 50-cc. portions of water (Note 3). The combined filtrate and washings are evaporated to dryness on the steam bath under reduced pressure, and the dry residue is dissolved in 50 cc. of hot water. The resulting solution is treated with 18 cc. of pyridine and poured into 150 cc. of hot absolute alcohol. Methionine rapidly crystallizes; after cooling it is filtered, washed with alcohol, and dried. The first crop weighs about 6.9 g. The mother liquor is evaporated to dryness; the residue is taken up in 15 cc. of hot water and poured into 50 cc. of absolute alcohol, when a further 1.3 g. is obtained. The total 8.2 g. of nearly pure methionine is suspended in 200 cc. of boiling absolute ether, filtered, and dried. In this way, 7.9–8.0 g. of methionine (84–85 per cent of the theoretical amount), melting at 279–280° (corr.), is obtained.

2. Notes

1. The ethyl sodium phthalimidomalonate crystallizes with 1.5 molecules of alcohol, which is removed only on heating above 140° *in vacuo*.
2. About 10–12 g. of a pure product can be recovered by redistilling the distillate.
3. The phthalic acid thus recovered melts at 188° and weighs about 7.8 g. (75 per cent of the theoretical amount). Unless most of the phthalic acid is removed at this point, trouble may be encountered by the separation of pyridine phthalate with the methionine.

3. Discussion

The first synthesis of methionine, by the Strecker method, gave a very low yield.[1] The procedure given above, based on directions published by the submitters,[2] has the advantage over the process of Windus and Marvel[3] of giving a much higher yield (54–60 per cent as against 13–19 per cent, based on the β-chloroethyl methyl sulfide consumed).

Methionine has also been prepared, without using β-chloroethyl methyl sulfide, from α-benzoylamino-γ-butyrolactone[4] and from α-acetyl-γ-butyrolactone.[5] The first of these syntheses proceeds through ethyl α-benzoylamino-γ-chlorobutyrate, its reaction product with methyl mercaptan, and hydrolysis of that product. The second synthesis proceeds through α-oximino-γ-butyrolactone which is reduced to α-amino-γ-butyrolactone and converted to 3,6-*bis*-(β-hydroxyethyl)-2,5-diketopiperazine. The dihydroxydiketopiperazine is converted to the corresponding dichloroethyl compound, and this, after reaction with methyl mercaptan and

subsequent hydrolysis, furnishes methionine.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 55

References and Notes

1. Barger and Coyne, Biochem. J. **22**, 1417 (1928).
2. Barger and Weichselbaum, ibid. **25**, 997 (1931).
3. Windus and Marvel, J. Am. Chem. Soc. **52**, 2575 (1930).
4. Hill and Robson, Biochem. J. **30**, 248 (1936).
5. Snyder, Andreen, Cannon, and Peters, J. Am. Chem. Soc. **64**, 2082 (1942).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ester

Ethyl 1-methylthiol-3-phthalimidopropane-3,3-dicarboxylate

tricarboxylic acid

alcohol (64-17-5)

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium hydroxide (1310-73-2)

carbon dioxide (124-38-9)

pyridine (110-86-1)

sodium (13966-32-0)

Ethyl phthalimidomalonate (5680-61-5)

phthalic acid (88-99-3)

β-Chloroethyl methyl sulfide, chloroethyl methyl sulfide (542-81-4)

methyl mercaptan (74-93-1)

Ethyl Sodium Phthalimidomalonate

Methionine (63-68-3)

pyridine phthalate

α-benzoylamino-γ-butyrolactone

α-acetyl-γ-butyrolactone (517-23-7)

ethyl α-benzoylamino-γ-chlorobutyrate

α-oximino-γ-butyrolactone

α-amino-γ-butyrolactone

dihydroxydiketopiperazine

DL-Methionine (59-51-8)

1-Methylthiol-3-phthalamidopropane-3,3-dicarboxylic Acid

3,6-bis-(β-hydroxyethyl)-2,5-diketopiperazine (50975-79-6)

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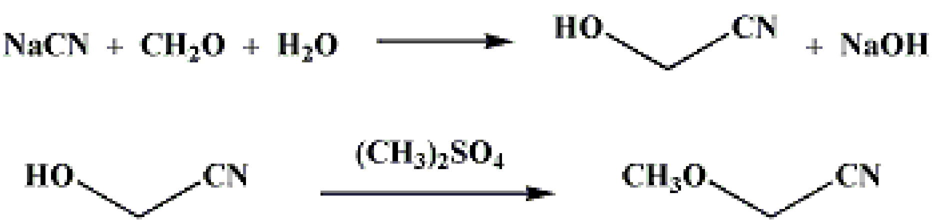
Organic Syntheses, CV 2, 387

METHOXYACETONITRILE

[Acetonitrile, methoxy-]



Submitted by J. A. Scarrow and C. F. H. Allen.
Checked by Reynold C. Fuson and Charles F. Woodward.

1. Procedure

This preparation must be carried out in a hood having good suction. Methyl sulfate has a high vapor pressure in spite of its high boiling point and is very poisonous. Ammonia is a specific antidote and should be kept on hand to destroy any of the ester accidentally spilled. It is advisable to wash the hands in dilute ammonium hydroxide frequently.

In a 1-l. three-necked, round-bottomed flask, fitted with a stirrer, a thermometer for reading low temperatures (Note 1), and a dropping funnel, are placed 98 g. (2 moles) of pulverized sodium cyanide (Note 2) and 200 cc. of water. The stirrer is started, and 60 g. of paraformaldehyde (2 moles) (Note 3) is added in small quantities until the temperature rises to 20–25° and the sodium cyanide has dissolved. The flask is then surrounded by a freezing mixture, and the temperature is kept below 25° during the introduction of the remaining paraformaldehyde.

Two hundred cubic centimeters (270 g., 2.1 moles) of technical methyl sulfate is placed in the dropping funnel, and, when the temperature inside the flask has dropped to 13°, a 20- to 30-cc. portion of the sulfate is added. An exothermic reaction should set in; the ice bath is removed, if necessary, to get the reaction to start (Note 4). When the temperature begins to fall, the remainder of the methyl sulfate is admitted at such a rate as to keep the temperature at 12–15°; this takes at least twenty minutes. When the addition is complete the mixture is stirred an additional forty minutes; during this time the temperature will drop to about 5°. The stirrer is stopped, and the oily, upper layer is separated at once (Note 5). The lower, aqueous layer is returned to the flask and methylated as before with a second 200-cc. portion of methyl sulfate (Note 6).

The oily, upper layer is dried with 10 g. of anhydrous sodium sulfate (Note 7) and is distilled under diminished pressure. For this purpose an efficient fractionating column (Note 8) is used. The portion boiling below 70° at 15 mm. is mainly methoxyacetonitrile and weighs 60–70 g. The upper layer from the second methylation

is treated in a similar manner; the distillate weighs 55–60 g. The residue in the distilling flask is methyl sulfate and is used in a subsequent run (Note 9).

The crude fractions are combined and distilled at atmospheric pressure through a good column; about 95 per cent distils at 118–122° as a colorless liquid. The methoxyacetonitrile so prepared weighs 100–110 g. (70–77 per cent of the theoretical amount).

2. Notes

1. A 30- to 35-cm. thermometer reading from –50 to +50° is most convenient since the graduations used are then outside the flask.
2. Potassium cyanide gives poorer results.
3. An equivalent amount of commercial formalin solution can be used with equally good results, provided that allowance is made for the volume of water—the total volume must not exceed 200 cc.
4. The reaction usually starts immediately; occasionally it does not start until the mixture becomes warm.
5. If the mixture is allowed to stand, the temperature rises to 40–50°, a red color develops, and the yield drops to almost nothing.
6. Recovered methyl sulfate can be used without purification.
7. No drying agent is completely satisfactory; sodium sulfate does the least harm.
8. The authors found a Glinsky column most satisfactory. A capillary tube reaching to the bottom of the flask for the admission of air is essential to prevent bumping. In the redistillation a piece of porous plate is sufficient for this purpose.
9. The density of the residual liquid in two runs was found to be 1.31, 1.32. The pure ester has a density of 1.35.

3. Discussion

Methoxyacetonitrile has been prepared by methylating hydroxyacetonitrile with methyl sulfate;[1] by treating chloromethyl ether with cuprous or mercuric cyanide;[2] and by dehydrating methoxyacetamide with phosphorus pentoxide.[3] The procedure described is a modification of that of Polstorff and Meyer.[1]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 562

References and Notes

1. Polstorff and Meyer, Ber. **45**, 1911 (1912); Slater and Stephen, J. Chem. Soc. **117**, 312 (1920); Malkin and Robinson, ibid. **127**, 372 (1925).
2. Gauthier, Ann. chim. phys. (8) **16**, 302, 306 (1909).

3. Kilpi, Z. physik. Chem. **86**, 671 (1914).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

cuprous or mercuric cyanide

ammonia (7664-41-7)

formalin (630-08-0)

sodium cyanide (143-33-9)

sodium sulfate (7757-82-6)

potassium cyanide (151-50-8)

sulfate (14808-79-8)

ammonium hydroxide (1336-21-6)

methyl sulfate (75-93-4)

chloromethyl ether (542-88-1)

Methoxyacetonitrile, Acetonitrile, methoxy- (1738-36-9)

hydroxyacetonitrile (107-16-4)

methoxyacetamide (16332-06-2)

phosphorus pentoxide (1314-56-3)

paraformaldehyde (30525-89-4)

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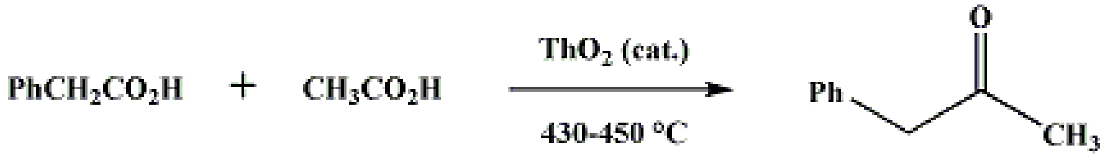
Organic Syntheses, CV 2, 389

METHYL BENZYL KETONE

[2-Propanone, 1-phenyl-]

[(*A*) (*From Phenylacetic and Acetic Acids*)]

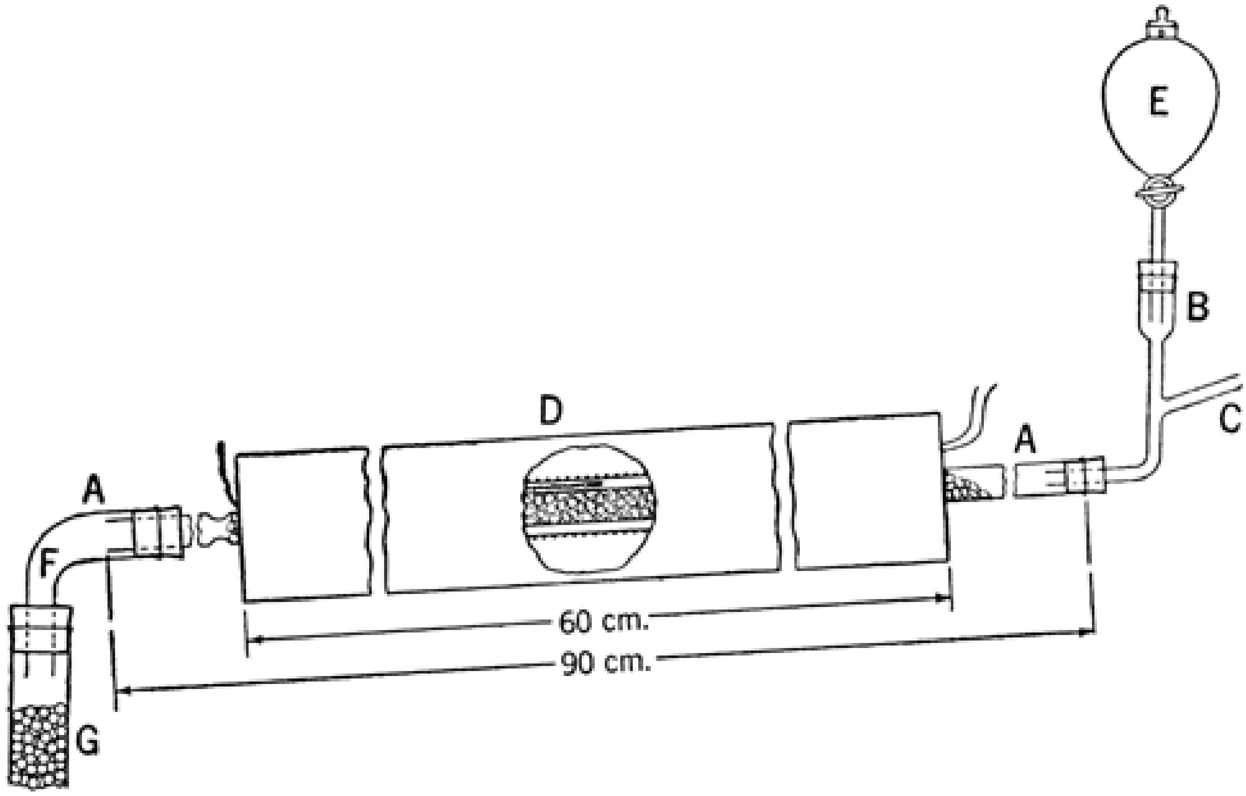


Submitted by R. M. Herbst and R. H. Manske.
Checked by C. R. Noller and C. F. Love.

1. Procedure

The reaction is carried out in the apparatus shown in .htmFig. 13. A-A is a Pyrex combustion tube, 90 cm. long and 2 cm. in diameter, fitted with an inlet chamber B, having a sealed-in side arm C and bearing a separatory funnel E. The center 60 cm. of the tube is filled with thorium oxide catalyst (Note 1) held in place at the lower end by indentations in the combustion tube. The hot junction D of a pyrometer is placed in contact with the glass tube at its center, and the catalyst-filled section of the tube is wrapped with a thin layer of asbestos paper. The tube is supported in an electrically heated cylindrical furnace, 60 cm. in length, which is inclined slightly from the horizontal. The annular space between the tube and the furnace is plugged at the ends with asbestos in order to produce a uniform temperature throughout the tube and to hold the glass tube in place. The lower end of the reaction tube is connected through the adapter F to a vertical glass tube G, 40 cm. long and 2 cm. in diameter, which is filled with glass beads and serves as the condenser. An Erlenmeyer flask or other suitable receiver is placed at the lower end of G.

Fig. 13



The furnace is heated to 430–450°, and simultaneously the tube is swept out thoroughly with a stream of carbon dioxide, introduced through the side arm C. The carbon dioxide is passed through a wash bottle of concentrated sulfuric acid to dry it and to estimate the rate of flow. A solution of 136 g. (1 mole) of phenylacetic acid, m.p. 77–79° (Org. Syn. Coll. Vol. I, **1941**, 436), in 120 cc. (120 g., 2 moles) of glacial acetic acid is placed in the separatory funnel E and is introduced into the inlet chamber B at the rate of twelve to fifteen drops per minute. The entire solution should run through in twelve to fifteen hours. Meanwhile a very slow stream of carbon dioxide (one bubble per second) is passed through the tube C, to keep the gases in motion. After all the solution has been added, the funnel is rinsed with 10 cc. of glacial acetic acid, and this is passed through the reaction tube to facilitate removal of the product. The distillate consists of a slightly fluorescent light brown oil and an aqueous layer; both layers are treated with 300 g. of a mixture of ice and water, and rendered alkaline to litmus with a slight excess of 50 per cent sodium hydroxide solution (Note 2).

The oil is separated (Note 3), and the aqueous layer is extracted with two 50-cc. portions of benzene. The extracts are combined with the oil, and the solvent is removed by distillation. Fractionation of the residue under reduced pressure gives 80–95 g. of a methyl benzyl ketone fraction, boiling at 110–120°/21–22 mm., and a residue of dibenzyl ketone (Note 4). The main fraction on redistillation yields 74–87 g. (55–65 per cent of the theoretical amount) of methyl benzyl ketone boiling at 110–115°/21–22 mm. (Note 5), (Note 6), and (Note 7).

2. Notes

1. The catalyst is prepared as follows: Enough pea-sized pieces of screened pumice to fill the tube is soaked in hot concentrated nitric acid and then washed thoroughly with

hot distilled water. In a porcelain dish the pumice is mixed with a solution of 40 g. of thorium nitrate crystals [$Th(NO_3)_4 + 12H_2O$] in 100 cc. of water and is evaporated to dryness, with frequent stirring to ensure uniform deposition of the salt. The impregnated pumice is ignited over a Bunsen burner until decomposition of the nitrate is complete. The pumice carries about 15 g. of thorium oxide.

2. From the alkaline solution about 10–15 per cent of the phenylacetic acid may be recovered by acidification with sulfuric acid. The acid separates as an oil which crystallizes slowly on cooling.

3. Salt may be added to facilitate the separation.

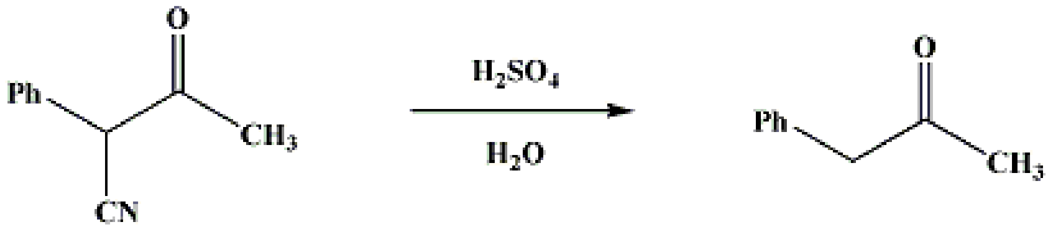
4. When several runs are made, the residues may be combined and distilled under reduced pressure. The fraction boiling at 190–210°/20 mm. amounts to about 19 g. per run and is chiefly dibenzyl ketone.

5. Further purification of the product may be effected by converting the ketone into the bisulfite compound, washing this with ether, decomposing with sodium bicarbonate, and steam-distilling.

6. When several runs are to be made, the catalyst should be regenerated after each run by passing air through the reaction tube for about three hours while the temperature is raised gradually to 550°. The yield in the first run may be low, especially if all the oxides of nitrogen have not been removed from the reaction tube.

7. Using the same procedure the following ketones may be obtained in similar yields: ethyl benzyl ketone from phenylacetic acid and propionic acid, methyl β-phenylethyl ketone from hydrocinnamic acid and acetic acid, and ethyl β-phenylethyl ketone from hydrocinnamic acid and propionic acid.

[(*B*) (*From α-Phenylacetoacetonitrile*)]



Submitted by Percy L. Julian and John J. Oliver.
Checked by C. R. Noller

1. Procedure

Three hundred fifty cubic centimeters of concentrated sulfuric acid is placed in a 3-l. flask and cooled to −10°. The total first crop of moist α-phenylacetoacetonitrile obtained according to the procedure on p. 487 (corresponding to 188–206 g., or 1.2–1.3 moles of dry product) is added slowly, with shaking, the temperature being kept below 20° (Note 1). After all is added the flask is warmed on the steam bath until solution is complete and then for five minutes longer. The solution is cooled to 0°, 1750 cc. of water added rapidly, and the flask placed on a vigorously boiling water bath and heated for two hours, with occasional shaking. The ketone forms a layer and, after cooling, is separated and the acid layer extracted with 600 cc. of ether. The oil and ether layers are washed successively with 100 cc. of water, the ether combined with the oil and dried over 20 g. of anhydrous sodium

sulfate. The sodium sulfate is collected on a filter, washed with ether, and discarded. The ether is removed from the filtrates, and the residue distilled from a modified Claisen flask with a 25-cm. fractionating side arm. The fraction boiling at 109–112°/24 mm. is collected; it weighs 125–150 g. (77–86 per cent of the theoretical amount) (Note 2).

2. Notes

1. If pure dry α-phenylacetoacetonitrile is used, half its weight of water should be added to the sulfuric acid or charring will take place on the steam bath.
2. Usually almost the entire crude product distils in this range with practically no fore-run or residue. Occasionally, however, as much as 30 g. of high-boiling residue, chiefly unchanged nitrile, is obtained. When this happens the yield is correspondingly decreased.

3. Discussion

Methyl benzyl ketone has been prepared by distilling a mixture of the barium[1] or calcium[2] salts of phenylacetic and acetic acids; by passing the vapors of these acids over a heated thorium oxide catalyst;[3], [4] and by heating phenylacetic acid, sodium acetate, and acetic anhydride.[5] Methyl benzyl ketone has also been prepared from phenylacetyl chloride and zinc methyl;[6] from acetyl chloride and cadmium dibenzyl;[7] by rearrangement of α-phenyl-β-methylethylene oxide;[8] by heating α-phenyl-β-methylethylene glycol with dilute sulfuric acid;[9] by heating the addition product of chloroacetone and phenylmagnesium bromide;[9] by treating chloroacetone and benzene with aluminum chloride;[10] and by the hydrolysis of α-phenylacetoacetic ester[11] or phenacylmalonic ester.[12]

The procedure in Part (*A*) above is based on that of Senderens[3] and Pickard and Kenyon.[4] It has been reported that "thoria aërogel" is superior to other forms of thoria catalysts for the preparation of ketones from aliphatic acids or esters.[13]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 487
- Org. Syn. Coll. Vol. 3, 276
- Org. Syn. Coll. Vol. 3, 399

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

oxides of nitrogen

Phenylacetic and Acetic Acids

zinc methyl

cadmium dibenzyl

thoria

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

Benzene (71-43-2)

ether (60-29-7)

acetic anhydride (108-24-7)

sodium acetate (127-09-3)

sodium hydroxide (1310-73-2)

acetyl chloride (75-36-5)

sodium bicarbonate (144-55-8)

nitric acid (7697-37-2)

propionic acid (79-09-4)

sodium sulfate (7757-82-6)

carbon dioxide (124-38-9)

thorium oxide

aluminum chloride (3495-54-3)

Phenylacetic acid (103-82-2)

Phenylmagnesium bromide (100-58-3)

Hydrocinnamic acid (501-52-0)

Methyl benzyl ketone, 2-Propanone, 1-phenyl- (103-79-7)

chloroacetone (78-95-5)

phenylacetyl chloride (103-80-0)

α-phenylacetoacetonitrile (4468-48-8)

dibenzyl ketone (102-04-5)

thorium nitrate (13823-29-5)

ethyl benzyl ketone (1007-32-5)

ethyl β-phenylethyl ketone

α-phenyl-β-methylethylene oxide (14212-54-5)

α-phenyl-β-methylethylene glycol

methyl β-phenylethyl ketone (2550-26-7)

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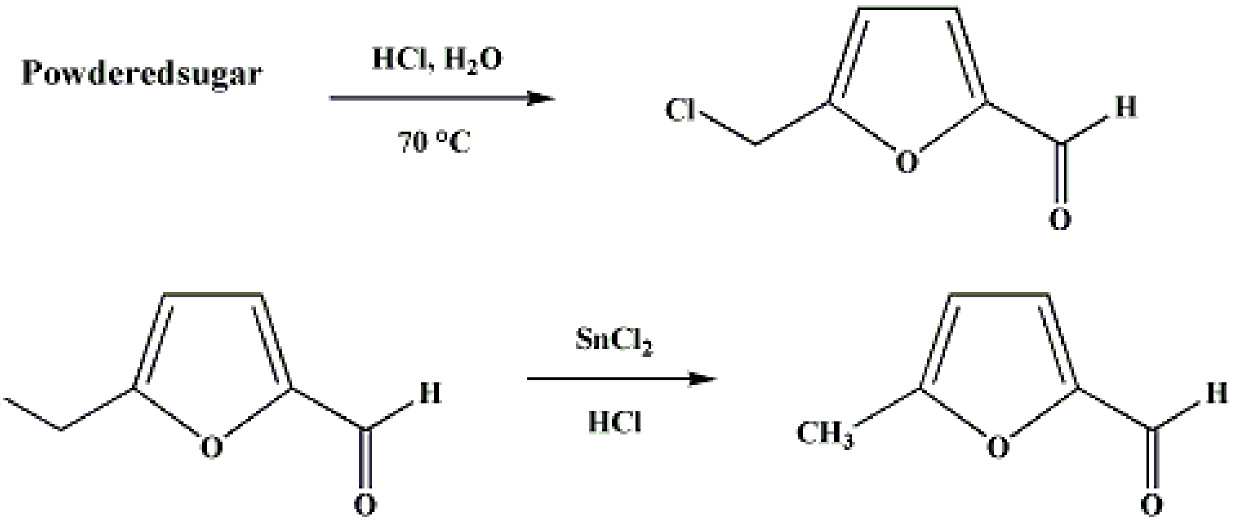
Organic Syntheses, CV 2, 393

5-METHYLFURFURAL

[2-Furaldehyde, 5-methyl-]



Submitted by I. J. Rinkes
Checked by John R. Johnson and A. T. Blomquist.

1. Procedure

In a 12-l. round-bottomed flask, fitted with a cork bearing a thermometer and a large bent glass tube, is placed 6 l. of 32 per cent hydrochloric acid (sp. gr. 1.163) (Note 1). The acid is heated to 50°, and 1 kg. (2.9 moles) of powdered sugar (Note 2) is dissolved in the liquid with shaking. The dark-colored solution is heated rapidly to 70–72°, kept at this temperature for ten minutes, and poured at once onto 3 kg. of cracked ice in a large earthenware crock (preferably in a hood) (Note 3). When the mixture has cooled to room temperature, 600 g. (2.67 moles) of commercial stannous chloride crystals ($SnCl_2 \cdot 2H_2O$) is added. The reaction mixture is stirred thoroughly for ten minutes and then allowed to stand for twenty-four hours.

The following day the acid liquid is filtered with suction through a large Büchner funnel, to remove large quantities of humus which are produced. The humus on the filter is washed with two 350-cc. portions of water and finally with two 300-cc. portions of benzene. The filtered liquid and aqueous washings have a volume of approximately 10 l. The 5-methylfurfural is removed from the aqueous layer by extraction with benzene, using three 300-cc. portions of the solvent for each 2 l. of liquid (Note 4). The combined benzene extracts (about 5 l.) are divided into two or three portions; each is washed with two 150-cc. portions of 5 per cent sodium carbonate solution and two 100-cc. portions of water. The benzene solution is dried with 100–150 g. of anhydrous magnesium or sodium sulfate, and the benzene is removed by distillation from a 1-l. flask provided with a short fractionating column and a separatory funnel for the continuous introduction of the solution. The distillation is stopped when the temperature of the distilling vapor reaches 85°.

The residue is transferred to a 250-cc. Claisen flask; two small portions of benzene (5–10 cc.) are used to rinse the last drops of the residue into the flask. The last traces of benzene are removed by warming gently under reduced pressure, and the 5-methylfurfural is then collected at 83–85°/15 mm. (Note 5). The yield is 63–70 g. (20–22 per cent of the theoretical amount, based upon the levulose portion of the sugar) (Note 6).

2. Notes

1. Commercial hydrochloric acid gives as satisfactory results as the chemically pure grade. The concentration of the hydrochloric acid should not exceed 32 per cent (sp. gr. 1.163) since stronger acid causes frothing during the heating and gives somewhat lower yields (56–57 g.).
2. Ordinary confectioners' sugar (XXXX sugar) was used. The 3 per cent of starch which it contains has no harmful effect.
3. Lengthening the time of heating or raising the temperature above 72° is definitely harmful.
4. The extractions should be carried out immediately after filtration since further quantities of humus are deposited if the liquid is allowed to stand.
5. 5-Methylfurfural discolors rapidly on standing, and after some time becomes quite black. The usual antioxidants do not retard this alteration perceptibly.
6. 5-Methylfurfural may be prepared by a modification of this method, which is more rapid but gives lower yields.[1] A solution of 800 g. of sucrose in 1 l. of hot water is allowed to flow slowly into a boiling solution of 500 g. of stannous chloride crystals, 2 kg. of sodium chloride, and 4 l. of 12 per cent sulfuric acid in a 12-l. flask. The aldehyde distils as rapidly as it is formed and is steam-distilled from the original distillate after being rendered alkaline with sodium carbonate. The product is isolated by benzene extraction of the second distillate and distillation under reduced pressure. The yield is 27–35 g. (10–13 per cent of the theoretical amount).

3. Discussion

5-Methylfurfural has been prepared by the distillation of rhamnose with dilute mineral acids[2] and by the reduction of 5-bromo- and 5-chloromethylfurfural with stannous chloride.[3] The above procedure, starting from sucrose, has been published by Rinkes.[4]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

starch

magnesium or sodium sulfate

5-bromo- and 5-chloromethylfurfural

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

stannous chloride

sucrose

5-Methylfurfural, 2-Furaldehyde, 5-methyl- (620-02-0)

levulose

rhamnose

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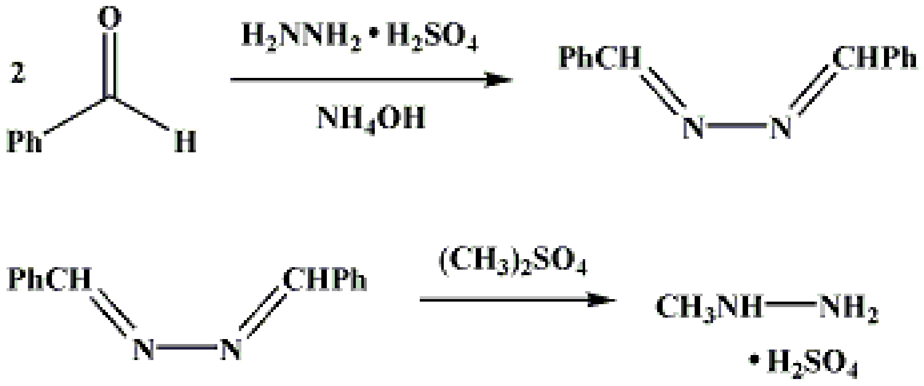
METHYLHYDRAZINE SULFATE

[Hydrazine, methyl-, sulfate]



Submitted by H. H. Hatt
Checked by W. W. Hartman and W. D. Peterson.

1. Procedure

(*A*) *Benzalazine*.—In a 5-l. round-bottomed flask, provided with a stout glass mechanical stirrer, are placed 240 g. (1.85 moles) of powdered hydrazine sulfate (Org. Syn. Coll. Vol. I, **1941**, 309), 1.8 l. of water, and 230 cc. (207 g., 3.4 moles) of 28 per cent aqueous ammonia (sp. gr. 0.90). The mixture is stirred, and, when the hydrazine sulfate has dissolved, 440 cc. (460 g., 4.35 moles) of benzaldehyde (Note 1) is added from a separatory funnel during the course of four to five hours (Note 2). After the mixture has been stirred for a further two hours, the precipitated benzalazine is filtered with suction, washed with water, and pressed thoroughly on a Büchner funnel. The product is dissolved in 800 cc. of boiling 95 per cent ethyl alcohol, and, on cooling, the azine separates in yellow needles melting at 92–93°. The yield is 350–360 g. (91–94 per cent of the theoretical amount); an additional 10–15 g. of less pure material can be isolated from the mother liquors. The azine is freed of ethyl alcohol by drying in a vacuum desiccator over calcium chloride.

(*B*) *Methylhydrazine Sulfate*.—Two hundred grams (0.96 mole) of benzalazine, 350 cc. of dry, thiophene-free benzene, and 100 cc. (133 g., 1.05 moles) of methyl sulfate (Note 3) are mixed in a 3-l. round-bottomed flask, provided with a reflux condenser bearing a calcium chloride tube. The mixture is heated continuously, with occasional shaking, on a water bath to gentle refluxing for five hours. The mixture is cooled, and the solid addition product is decomposed by adding 600 cc. of water and shaking until all the solid material has disappeared. The benzene and benzaldehyde are removed by steam distillation; the residual liquor, after cooling, is treated with 15–20 cc. of benzaldehyde and left overnight. The resin and benzalazine are separated by filtration (Note 4).

The filtrate is evaporated under reduced pressure on a water bath until a semi-crystalline mass remains; this is further desiccated by evaporating twice under reduced pressure with 50-cc. portions of absolute ethyl alcohol. The resulting crystalline cake is crushed with 50 cc. of absolute ethyl alcohol, filtered, and the process repeated. The white, crystalline product is almost pure methylhydrazine sulfate and contains very little hydrazine sulfate. After drying in a vacuum desiccator over calcium chloride, the yield is 105–110 g. (76–80 per cent of the theoretical amount). For purification, the sulfate is dissolved in about 250 cc. of boiling 80 per cent ethyl alcohol, and any undissolved material (chiefly hydrazine sulfate) is filtered. On cooling, the methylhydrazine sulfate separates in white plates, which are filtered with suction and washed with a little absolute alcohol. After drying over calcium chloride, the first fraction, m.p. 141–142°, weighs 70–75 g. (51–54 per cent of the theoretical amount) (Note 5).

2. Notes

1. The benzaldehyde should be freed of benzoic acid by shaking with aqueous sodium carbonate solution.
2. The mixture is stirred vigorously during the reaction, and one or two stout glass rods are clamped in the flask to act as baffles and to break up the lumps of benzalazine.
3. Methyl sulfate is extremely toxic. It should not be spilled; neither should the vapor be inhaled. Ammonia is a specific antidote.
4. Unreacted hydrazine sulfate is removed by conversion to benzalazine. The filtrate should not give an appreciable precipitate when mixed with 5 cc. of benzaldehyde and left for four hours.
5. From the mother liquors about 12 g. of less pure material, m.p. 133–136°, can be recovered.

3. Discussion

The procedure given above is essentially the method of Thiele.[1] Methylhydrazine has also been prepared by reduction and subsequent hydrolysis of nitrosomethylurea,[2] nitromethylurethane,[3] and nitrosomethylamine sulfonic acid;[4] and by methylation of hydrazine hydrate with methyl iodide[5] or diazomethane.[6]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Benzalazine

ethyl alcohol, alcohol (64-17-5)

calcium chloride (10043-52-4)

ammonia (7664-41-7)

Benzene (71-43-2)

sodium carbonate (497-19-8)

Benzoic acid (65-85-0)

benzaldehyde (100-52-7)

Methyl iodide (74-88-4)

methyl sulfate (75-93-4)

hydrazine hydrate (7803-57-8)

Hydrazine sulfate (10034-93-2)

Diazomethane (334-88-3)

Nitrosomethylurea

Methylhydrazine sulfate, Hydrazine, methyl-, sulfate (302-15-8)

Methylhydrazine (60-34-4)

nitromethylurethane

nitrosomethylamine sulfonic acid

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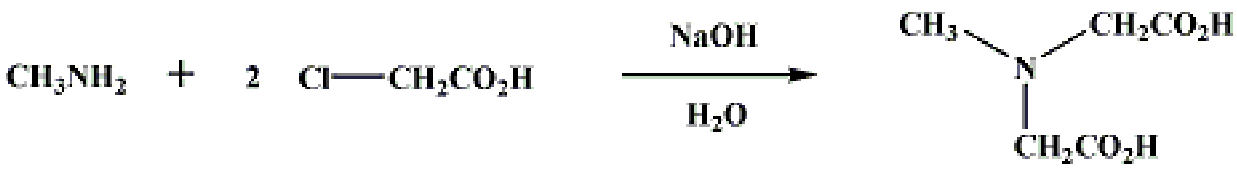
Organic Syntheses, CV 2, 397

METHYLIMINODIACETIC ACID

[Acetic acid, methyliminodi-]



Submitted by G. J. Berchet
Checked by John R. Johnson and P. L. Barrick.

1. Procedure

In a 2-l. flask, provided with a mechanical stirrer, separatory funnel, and thermometer, are placed 189 g. (2 moles) of chloroacetic acid and 150 cc. of water. The flask is cooled in ice water, and a cold solution of 160 g. (4 moles) of sodium hydroxide in 500 cc. of water is added, with stirring, at such a rate that the temperature does not exceed 30° (Note 1). After all the alkali has been added, the cooling bath is removed and an aqueous solution (Note 2) containing 31 g. (1 mole) of methylamine is added slowly. The reaction is exothermic, and the temperature is kept below 50° by occasional immersion of the flask in ice water. After all the methylamine has been added, the solution is allowed to stand for two hours to complete the reaction.

A solution of 257 g. (1.05 moles) of barium chloride dihydrate in about 500 cc. of hot water is added to the reaction mixture, with vigorous shaking, and the mixture is heated on a steam bath for one-half hour. A heavy precipitate of the barium salt of the amino acid separates at once. After cooling to room temperature, the barium salt is collected on a suction filter, transferred to a beaker, and washed with two 250-cc. portions of hot water (80°). After drying at 100°, the barium salt weighs 225–230 g. (80–82 per cent of the theoretical amount).

The dry barium salt is placed in a 2-l. flask provided with a mechanical stirrer, 600 cc. of water is added, and the mixture heated to boiling. The calculated quantity of 5 *N* sulfuric acid (Note 3) is introduced gradually from a separatory funnel into the well-stirred mixture over a period of about one hour. The mixture is then centrifuged or filtered with suction (Note 4) through a thin layer of fuller's earth. The barium sulfate precipitate is transferred to a beaker and extracted with two 250-cc. portions of boiling water. The filtrate and washings are transferred to a distilling flask placed in a water bath and concentrated under reduced pressure to a volume of 175–200 cc. (Note 5). The syrupy residue is poured into a large beaker and treated with 500 cc. of absolute methyl alcohol. Crystals of the acid begin to appear at once. The mixture is allowed to stand for three or four hours in an ice bath to complete the precipitation, and the crystalline solid is separated by filtration with suction. After being washed with two 75-cc. portions of methyl alcohol, the product is dried at 100°. The

methyliminodiacetic acid forms fine, white crystals, m.p. 215°, and weighs 92–105 g. (63–71 per cent of the theoretical amount).

If an especially pure product is desired, the acid may be reprecipitated by dissolving in an equal weight of warm water and adding three volumes of methyl alcohol. The loss in purification is 4–5 per cent.

2. Notes

1. The temperature must be controlled to avoid formation of glycolic acid. One-half of the alkali is sufficient to neutralize the acid, and the remainder may be added rapidly without danger of raising the temperature.
2. Technical aqueous methylamine solution (28–33 per cent) may be used. The amine content should be determined by titration with standard acid.
3. The barium salt requires 1.416 cc. of 5 *N* sulfuric acid per gram. The acid should be titrated before use.
4. If unchanged barium methyliminodiacetate remains in solution, it peptizes the barium sulfate and the filtration is likely to be trouble-some. If colloidal barium sulfate is encountered, it is advisable to add a slight excess (less than 1 per cent) of sulfuric acid and continue the heating for twenty minutes longer. Traces of sulfate in the final product may be removed, if necessary, by reprecipitation of the acid with methyl alcohol.
5. The residue should have a syrupy consistency but should be fluid enough to be poured freely from the flask.

3. Discussion

Methyliminodiacetic acid has hitherto been prepared by the action of methylamine on formaldehyde cyanohydrin with subsequent hydrolysis of the resulting dinitrile.[1] This method was found by the submitter to be much less satisfactory than the procedure given above.

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

barium salt of the amino acid

sulfuric acid (7664-93-9)

methyl alcohol (67-56-1)

sodium hydroxide (1310-73-2)

chloroacetic acid (79-11-8)

barium sulfate (7727-43-7)

methylamine (74-89-5)

formaldehyde cyanohydrin (107-16-4)

Methyliminodiacetic acid, Acetic acid, methyliminodi- (4408-64-4)

barium chloride dihydrate (10326-27-9)

glycolic acid (79-14-1)

barium methyliminodiacetate

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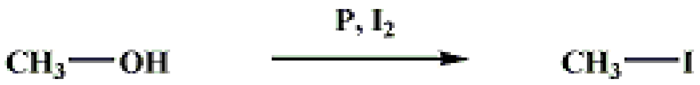
Organic Syntheses, CV 2, 399

METHYL IODIDE

[Methane, iodo-]

[(*A*) (*From Methyl Alcohol*)]



Submitted by Harold S. King
Checked by Louis F. Fieser

1. Procedure

Iodine is slowly washed by means of condensed liquid into a mixture of methyl alcohol and phosphorus. The apparatus employed by the submitter, .htmFig. 14, is rendered more flexible by the use of a three-necked flask, as shown in .htmFig. 15, and a further improvement is in the provision of a side tube for the addition of iodine to the separatory funnel, A (Note 1). In the following description reference is made to the simpler apparatus, .htmFig. 14; the changes required for the modified assembly will be obvious.

Fig. 14

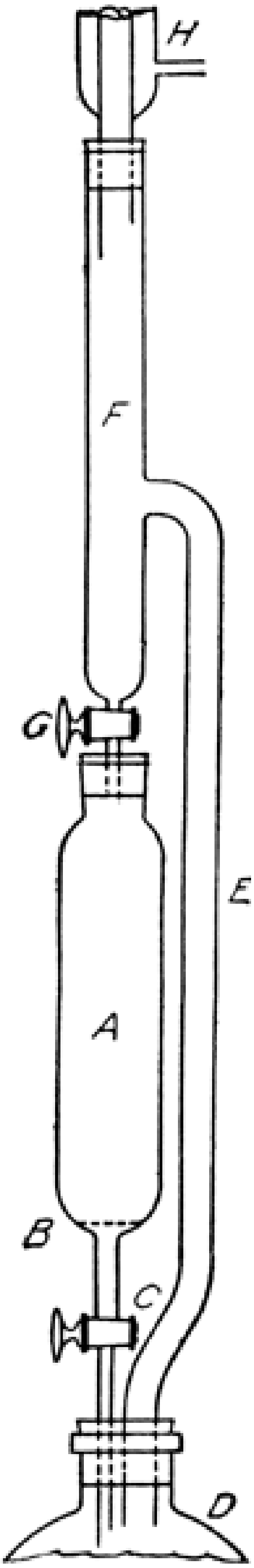
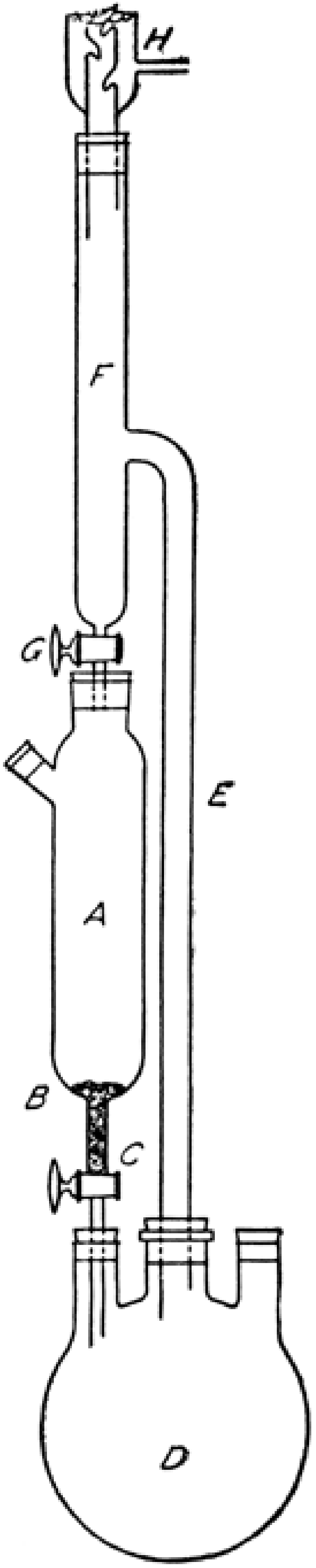


Fig. 15



The cylindrical separatory funnel A has a volume of 1.2 l. and holds 2 kg. (15.75 gram atoms) of iodine crystals (Note 2). A piece of perforated platinum foil B, or a loose

plug of glass wool, is placed in the bottom to prevent clogging of the stopcock by iodine crystals or solid impurities. Stopcock C is as large as 5 mm. in bore as a further precaution. For producing up to 4 kg. of methyl iodide, a 5-l. round-bottomed Pyrex flask D is used (Note 3). It is partly submerged in a water bath. Tube E, fitted into the reaction flask by a rubber stopper, is at least 2.5 cm. in internal diameter in order to allow the vapor to rise without interrupting the return of the excess distillate. Tube F is 4 cm. in diameter to allow for preliminary condensation. A space (13 cm.) is left above stopcock G as a reservoir for the distillate. Stopcock G has a bore of 2 or 3 mm. (Note 4). The bottom of the tube from this stopcock is flush with the bottom of the rubber stopper to the iodine container, so that the liquid will flow down the sides of the container instead of forming a channel through the middle of the iodine. Condenser H, 2.5 cm. in diameter and at least 200 cm. long, is attached by a rubber stopper and is well cooled with a strong stream of water (Note 5) and (Note 6).

In container A is placed 2 kg. of iodine, no crystals being allowed to fall below the platinum foil or glass wool. The iodine is covered with part of 2 l. (50 moles) of methanol (Note 7), the rest of which is added to 200 g. each of red and yellow phosphorus (12.8 gram atoms) in reaction flask D. The apparatus is assembled as illustrated in .htmFig. 14. The water bath is heated to 70–75°; stopcock G is opened wide and stopcock C part way to allow the solution of iodine to flow slowly into the reaction flask. By the time all the alcohol has been added, enough methyl iodide will have been formed to start the refluxing. Stopcock C is then opened wide and stopcock G partly closed so that only a small stream of methyl iodide flows through the iodine container. The temperature is adjusted so that little of the reflux flows back through tube E. This will require the progressive lowering of the temperature of the water bath as the reaction proceeds (Note 8); a temperature of about 55° is sufficient to promote even boiling after the first portion of iodine has been introduced. If for any reason refluxing becomes too violent, both stopcocks are closed. When the reaction has been brought under control, stopcock G is partly opened and then stopcock C part way, until any liquid in A has run out, after which C is opened wide. When all the iodine has been extracted (about two and one-half hours) both stopcocks are closed, the separatory funnel is lowered with a rotary motion, filled with a second charge of 2 kg. (15.75 gram atoms) of iodine, and raised to its former position. Stopcock C is opened wide and stopcock G part way as before.

After the extraction of this second charge of iodine, the flask is cooled, and a condenser arranged for downward distillation is fitted in place of the special apparatus. To the lower end of the condenser is tightly attached an adapter dipping under a slush of ice and water. When all the methyl iodide has distilled (b.p. 40–42.5°) (Note 9), it is separated from the water, dried by shaking with anhydrous calcium chloride, filtered through glass wool, stored for use in a sealed flask or tubes, and kept in the dark (Note 10). The yield is 4150–4250 g. (93–95 per cent of the theoretical amount based on iodine), and the crude product is colorless and sufficiently pure for many purposes. Redistillation gives, with a 95 per cent recovery, a product boiling at 41.0–42.0°. Because of the high vapor pressure of methyl iodide, special precautions should be taken to prevent loss of material. Two different devices that have been found

satisfactory are described in (Note 11) and (Note 12).

The discoloration of purified methyl iodide is greatly retarded by the addition of a drop of mercury, and traces of iodine in an old sample may be removed by shaking with mercury (Note 13). A very highly colored product is best washed with very dilute sodium thiosulfate, then with water, before drying.

With minor modifications, this method is suitable for the preparation of ethyl, *n*-propyl, *n*-butyl, *n*-amyl, isobutyl, and isoamyl iodides with yields of more than 90 per cent. A somewhat lower yield is obtained in the preparation of *sec*.-butyl iodide owing to the formation of hydrogen iodide.

2. Notes

1. The upper opening of the funnel A .htm(Fig. 15) should be the same size as that of tube F, so that the funnel may be used as a receiver in the distillation described below (Note 12).
2. A funnel of this volume and shape is not essential but has been found convenient. Even if a globular separatory funnel is used, the liquid flowing through it has been found to wet the walls.
3. For larger quantities a flask up to 12 l. in capacity may be substituted.
4. The stopcock from a small, broken, separatory funnel serves the purpose.
5. In hot weather there is usually some loss of methyl iodide through the condenser. This can be recovered by a trap made by bending the mouth end of a 50-cc. pipet into a U, which is stoppered into the end of the condenser, the delivery end being just below the surface of a slush of ice and water.
6. In place of the very long condenser, the checker used a modified West condenser with staggered indentures, as shown in .htmFig. 15. The jacket was 90 cm. in length, the inner tube was 2.2 cm. i.d., the opening at the top was 3.3 cm. i.d. At the top of this condenser was attached a 30-cm. bulb condenser which could be cooled with ice water. With the tap water at 5°, there was no difficulty in effecting complete condensation, and the trap described in (Note 5) was not required. In warm weather it will probably be necessary to run the water to each condenser through a large bottle of ice.
7. The methanol need not be absolute. In one experiment it was diluted with 10 per cent of its weight of water. The yield of methyl iodide was identical with that of a check run in which absolute methanol was used.
The refluxing starts more smoothly if the iodine crystals are covered with methanol. The alcoholic solution of iodine forms sufficient methyl iodide to start the refluxing at a lower temperature than would otherwise be necessary.
8. The increased speed of the reaction is largely due to the fact that iodine is more soluble in methyl iodide than in methanol and is therefore more rapidly introduced as the reaction progresses. The reaction is exothermic.
9. It has been pointed out that this distillate is probably the constant-boiling mixture of methyl iodide and methyl alcohol which is composed of 93 per cent by weight of methyl iodide and boils at 39°. The procedure given for recovering

the methyl iodide from the water-ice mixture is adequate. (Robert A. Dinerstein, private communication.)

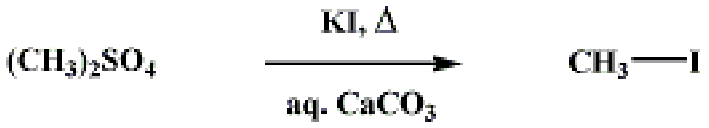
10. Caution is necessary in disposing of the residues left in the reaction flask because they contain yellow phosphorus. They should be covered at once with water.

11. One end of a coil of 2-mm. glass tubing is sealed to the end of the inner tube of the condenser. The other end of the coil is sealed to a tube leading through the stopper of the collecting vessel, which also carries a Bunsen valve to prevent the entrance of moisture from the air. Both the coil and the collecting vessel are cooled with ice and salt, or with carbon dioxide snow.

12. Another convenient assembly for the distillation is furnished by using the condenser shown in .htmFig. 15, together with the separatory funnel, A. The methyl iodide is distilled from a 3-l. flask through an inverted U-tube (22 mm.); this brings the vapor down into the condenser, which is also clamped in a vertical position. The separatory funnel serves as the receiver and permits the easy removal of fractions. The side opening is equipped with a small condenser carrying a calcium chloride tube. A simple and adequate method of recording the boiling temperature is to insert in the U-tube in an inverted position a long thermometer with its head imbedded in a small cork, which rests on the bottom of the flask.

13. *Caution*. Methyl iodide in contact with mercury when exposed to the sunlight readily forms methylmercuric iodide, which is exceedingly poisonous.

[(*B*) (*From Methyl Sulfate*)]



Submitted by W. W. Hartman
Checked by John R. Johnson and H. J. Passino.

1. Procedure

A 3-l. three-necked flask is fitted with a thermometer, a separatory funnel, a liquid-sealed mechanical stirrer, and a small fractionating column connected with an efficient condenser set for downward distillation. The condenser leads to a receiving vessel cooled in ice water (Note 1). A solution of 800 g. (4.8 moles) of u.s.p. potassium iodide in 430 cc. of water is placed in the flask, 60 g. of calcium carbonate is added, and the mixture is heated to 60–65°, with stirring.

The temperature is kept at 60–65°, and 630 g. (473 cc., 5 moles) of "practical" methyl sulfate (Note 2) is added gradually through the separatory funnel. The rate of addition is such that the methyl iodide distils briskly; the addition requires about two hours.

After all the methyl sulfate has been added, the temperature is raised to 65–70° for about forty minutes to complete the distillation of the methyl iodide. The product is

separated from a small amount of water, dried thoroughly over anhydrous calcium chloride, and decanted into a dry distilling flask. A few crystals of potassium iodide are added, and the material is distilled from a water bath. The yield of methyl iodide, boiling at 41–43°, is 615–640 g. (90–94 per cent of the theoretical amount) (Note 3).

2. Notes

1. It is important to avoid loss of the volatile methyl iodide. The notes to Procedure (*A*) can be read with profit on this point.
2. Methyl sulfate is extremely toxic. Contact with the liquid or inhaling the vapor should be avoided. Ammonia is a specific antidote.
3. Similar percentage yields are obtained with quantities of material up to ten times as large as those specified in the procedure.

3. Discussion

Methyl iodide has been prepared by the action of methyl sulfate on an aqueous solution of potassium iodide;[1] by the slow distillation of a mixture of methanol with a large excess of constant-boiling hydriodic acid;[2] by the electrolysis of an aqueous solution of potassium acetate in the presence of iodine or potassium iodide;[3] by the action of an aqueous solution of potassium iodide on methyl *p*-toluenesulfonate;[4] and by the action of methanol on a solution of phosphorus pentaiodide in methyl iodide.[5] The most generally employed method of preparing methyl iodide has been the interaction of methanol and phosphorus triiodide (or a mixture of iodine and phosphorus, red, yellow, or both).[6] Many modifications of this method have been proposed and certain variants have been suggested for the preparation of the higher alkyl iodides which are applicable to the preparation of methyl iodide.[7]

The procedure described in (*A*) is a modification of Walker's method.[8] The method of introducing a soluble substance gradually into a reaction flask, described above, is applicable to other reactions, such as the preparation of mercury dialkyls.[9]

The procedure described in (*B*) can also be employed successfully with iodoform as the iodine-containing starting material, if the iodoform is first heated with alcoholic alkali.[10]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 325
- Org. Syn. Coll. Vol. 6, 830

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

yellow phosphorus

methyl alcohol and phosphorus

red and yellow phosphorus

ethyl, n-propyl, n-butyl, n-amyl, isobutyl, and isoamyl iodides

calcium chloride (10043-52-4)

ammonia (7664-41-7)

methyl alcohol, methanol (67-56-1)

PHOSPHORUS (7723-14-0)

potassium iodide (7681-11-0)

sodium thiosulfate (7772-98-7)

mercury (7439-97-6)

calcium carbonate (471-34-1)

iodine (7553-56-2)

hydriodic acid, hydrogen iodide (10034-85-2)

Methyl iodide, Methane, iodo- (74-88-4)

methyl sulfate (75-93-4)

iodoform (75-47-8)

potassium acetate (127-08-2)

methylmercuric iodide

phosphorus pentaiodide

phosphorus triiodide (13455-01-1)

Methyl p-toluenesulfonate (80-48-8)

sec.-butyl iodide (513-48-4)

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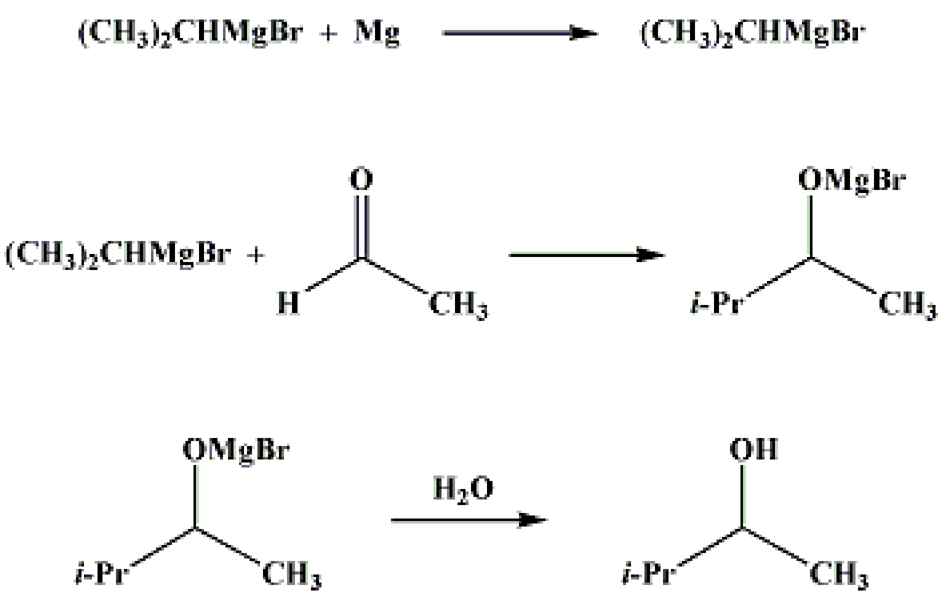
Organic Syntheses, CV 2, 406

METHYL ISOPROPYL CARBINOL

[2-Butanol, 3-methyl-]



Submitted by Nathan L. Drake and Giles B. Cooke.
Checked by C. S. Marvel and B. H. Wojcik.

1. Procedure

In a 3-l. three-necked flask, fitted with a mechanical stirrer, a separatory funnel, and a reflux condenser the upper end of which is protected by a calcium chloride tube, are placed 146 g. (6 gram atoms) of dry magnesium turnings (Note 1) and about 250 cc. of dry ether (Note 2).

A solution of 600 g. (4.9 moles) of isopropyl bromide (Note 3) in 300 cc. of dry ether is then added through the separatory funnel. The reaction begins after about 15 cc. of the solution has been added (Note 4). The solution is added at such a rate that the reaction mixture refluxes gently. It is well to arrange to cool the flask with running water if the refluxing becomes too vigorous. The addition of the isopropyl bromide solution should require from three and one-half to four hours. The reaction mixture is refluxed on the water bath for forty minutes after addition of the isopropyl bromide solution is complete.

The flask is then cooled to –5° (Note 5), and a solution of 200 g. (4.5 moles) of acetaldehyde (Note 6) in 250 cc. of dry ether is added at this temperature over a period of one hour.

After addition of the acetaldehyde solution is complete, the product is decomposed by pouring the reaction mixture onto 2 kg. of cracked ice. The excess magnesium may be removed conveniently by decantation at this point. The basic magnesium halide is

dissolved by addition of about 1 l. of 15 per cent sulfuric acid. The ether solution is separated, and the aqueous layer is extracted with four 150-cc. portions of ether. The ether solutions are combined, dried over 25 g. of calcined potassium carbonate, filtered, and fractionally distilled, using a short column. The methyl isopropyl carbinol distils at 110–111.5°. The fraction boiling at 37–109° should be dried and refractionated. The total yield is 210–215 g. (53–54 per cent of the theoretical amount).

2. Notes

1. The excess of magnesium is used to increase the yield of Grignard reagent.
2. More ether may be added during the preparation to replace any which may be lost. The ether used should be dried over bright sodium wire.
3. The isopropyl bromide (b.p. 59–60°) was obtained from the Eastman Kodak Company and was used without further treatment. Directions for preparing isopropyl bromide are given in Org. Syn. Coll. Vol. I, **1941**, 37, and on p. 359 above.
4. Heating on the water bath to start the reaction should be unnecessary if all the apparatus and reagents are completely dry.
5. The temperature must not be allowed to rise above –5°.
6. The acetaldehyde may be prepared conveniently by depolymerizing pure, dry paraldehyde with toluenesulfonic acid as a catalyst. Acetaldehyde boiling at 20.5–21° must be used for this preparation. There is no advantage in using gaseous acetaldehyde.

3. Discussion

Methyl isopropyl carbinol has been prepared by reduction of methyl isopropyl ketone with sodium amalgam,[1] and with sodium;[2] by treatment of chloroacetyl chloride with zinc methyl;[3] by treatment of bromoacetyl bromide with zinc methyl;[4] by treatment of isobutyraldehyde with methylmagnesium bromide;[5] and as a by-product of the reaction between chloroacetone and methylmagnesium iodide.[6]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 200

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

zinc methyl

acetaldehyde (75-07-0)

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

ether (60-29-7)

magnesium, magnesium turnings (7439-95-4)

Isopropyl bromide (75-26-3)

sodium, sodium wire (13966-32-0)

chloroacetyl chloride (79-04-9)

methylmagnesium iodide (917-64-6)

bromoacetyl bromide (598-21-0)

chloroacetone (78-95-5)

Methyl isopropyl carbinol, 2-Butanol, 3-methyl- (598-75-4)

toluenesulfonic acid (88-20-0)

Methyl isopropyl ketone (563-80-4)

isobutyraldehyde (78-84-2)

methylmagnesium bromide (75-16-1)

paraldehyde (123-53-7)

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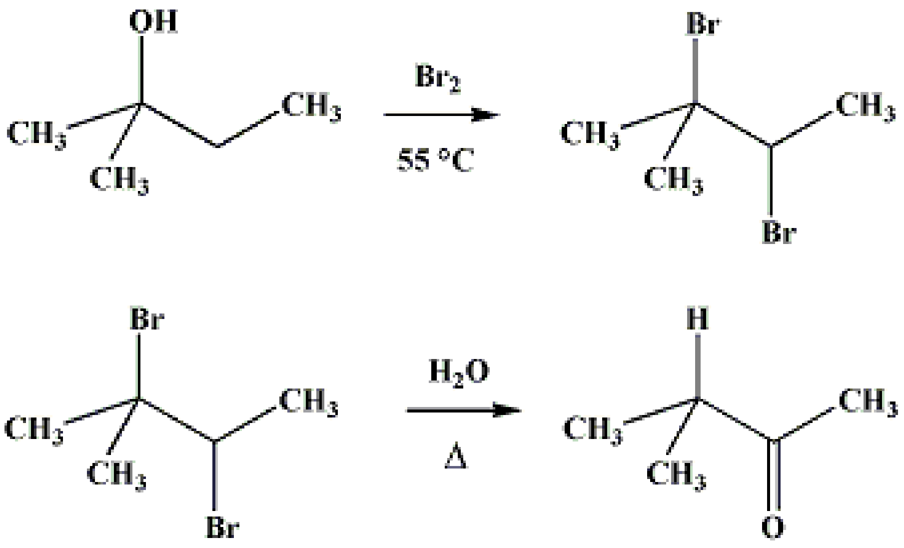
Organic Syntheses, CV 2, 408

METHYL ISOPROPYL KETONE

[2-Butanone, 3-methyl-]



Submitted by Frank C. Whitmore, W. L. Evers, and H. S. Rothrock.
Checked by W. W. Hartman and L. J. Roll.

1. Procedure

In a 1.5-l. round-bottomed Pyrex flask, fitted with a dropping funnel, an efficient mechanical stirrer, and a thermometer, is placed 176 g. (2 moles) of *tert.*-amyl alcohol (redistilled, b.p. range 0.5°). The flask is surrounded by a water bath, and the temperature of the alcohol is held at 50–60° while 320 g. (103 cc., 2 moles) of bromine is slowly added with stirring during about two hours (Note 1). The stirring is continued for a few minutes until the bromine color has disappeared (Note 2).

To the reaction flask containing the crude trimethylethylene dibromide is added 540 cc. of water, and the flask is fitted with a long reflux condenser and a mercury-sealed stirrer (Note 3). The mixture is refluxed with stirring for three to five hours until hydrolysis is practically complete (Note 4). The reflux condenser is then replaced by a condenser for distillation, and the crude methyl isopropyl ketone is removed from the reaction mixture by direct distillation, with stirring, until the temperature rises (Note 5) and the oil nearly stops coming over (about one and one-half hours), or until the oil coming over is heavier than water. The residue in the flask can be distilled to yield about 380 cc. of constant-boiling hydrobromic acid.

To the distillate, consisting of a yellow oil with a small lower water layer, powdered sodium carbonate (about 10 g.) is added, and the mixture is shaken until the water layer is alkaline and nearly saturated (Note 6). The layers are separated, and the oil is refluxed for about sixteen hours with 20 g. of powdered potassium carbonate and 5 cc.

of water (Note 7). The oily layer is again separated and dried over about 6 g. of anhydrous calcium chloride or potassium carbonate (Note 8). It is then placed in a flask containing 2 g. of dry sodium carbonate and distilled through an efficient column. The yield of methyl isopropyl ketone boiling at 92–94° (Note 9) is about 102 g. (59 per cent of the theoretical amount). The product is slightly yellow.

2. Notes

1. The bromine is added at such a rate that only a small amount is present at any time, as shown by an orange-red color. The speed of the reaction depends on the temperature and efficiency of stirring. The temperature of the reaction mixture remains a few degrees above that of the water bath.
After about half the bromine has been added, the mixture becomes cloudy owing to the separation of water, and a somewhat lower temperature (40–45°) suffices to prevent the accumulation of unreacted bromine.
2. The crude trimethylethylene dibromide can be purified by washing with sodium carbonate solution and water, drying, and distilling under reduced pressure; b.p. 49–51°/11 mm.; 60–70 per cent yield. Hydrolysis of the purified dibromide gives a 78 per cent yield of methyl isopropyl ketone. However, the losses in purifying the dibromide result in a slightly decreased over-all yield of ketone so that the purification of the dibromide is not recommended.
3. The quantity of water used is 50 per cent more than the theoretical amount for hydrolyzing the dibromide and converting all the bromine to constant-boiling (47.3 per cent) hydrobromic acid. Less water can be used, but more darkening of the reaction mixture occurs, and the yield of ketone is slightly decreased.
4. Efficient stirring lessens the time required for hydrolysis and avoids loss of material by intermittent sudden boiling. To be sure of complete hydrolysis, refluxing should be continued for at least an hour after the specific gravity of the oily layer becomes less than that of the water layer.
5. The distillate and residue contain a very powerful lachrymator and should be handled under a good hood.
6. The ketone is somewhat soluble in water, and the sodium carbonate serves to salt it out as well as to remove any hydrobromic acid.
7. The crude ketone contains small amounts of bromides, and it darkens even after repeated distillation unless first refluxed over potassium carbonate.
8. It is necessary to dry the ketone thoroughly since water distils with it at about 78°. This fraction can be dried again to recover the ketone.
9. A column 55 cm. high packed with glass tubes 6 mm. in length and diameter was employed with good results. A few grams of trimethylethylene, b.p. 34–36°/735 mm., is always obtained if adequate condensers have been used throughout the preparation. The presence of a little sodium carbonate during the final distillation hinders decomposition.

3. Discussion

Trimethylethylene dibromide has been obtained by the reaction between bromine and

trimethylethylene[1] or tertiary amyl alcohol.[2]

Methyl isopropyl ketone has been obtained by the hydration of isopropylacetylene;[3] from isopropylmagnesium bromide and acetic anhydride;[4] from isopropylmagnesium chloride and ethyl acetate;[5] by the hydrolysis of ethyl dimethylacetoacetate;[6] by passing a mixture of the vapors of isobutyric and acetic acids over a thoria catalyst;[7] and from butane or isobutane, aluminum chloride, and carbon monoxide.[8] Methyl isopropyl ketone can also be obtained by rearrangement of methyl isopropenyl carbinol[9] or trimethylethylene oxide;[10] by heating trimethylethylene glycol with dilute hydrochloric acid;[11] by heating trimethylethylene chlorohydrin (2-methyl-2-hydroxy-3-chlorobutane) with water;[12] and by the hydrolysis of trimethylethylene dibromide.[13]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

thoria

isobutyric and acetic acids

calcium chloride (10043-52-4)

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

acetic anhydride (108-24-7)

carbon monoxide (630-08-0)

HYDROBROMIC ACID (10035-10-6)

sodium carbonate (497-19-8)

bromine (7726-95-6)

aluminum chloride (3495-54-3)

Methyl isopropyl ketone, 2-Butanone, 3-methyl- (563-80-4)

Trimethylethylene dibromide (594-51-4)

trimethylethylene (513-35-9)

tertiary amyl alcohol, tert.-amyl alcohol (75-85-4)

isopropylacetylene (598-23-2)

isopropylmagnesium bromide (920-39-8)

isopropylmagnesium chloride (1068-55-9)

ethyl dimethylacetoacetate

butane (106-97-8)

methyl isopropenyl carbinol (10473-14-0)

trimethylethylene oxide

trimethylethylene glycol (7778-85-0)

trimethylethylene chlorohydrin

2-methyl-2-hydroxy-3-chlorobutane

isobutane (75-28-5)

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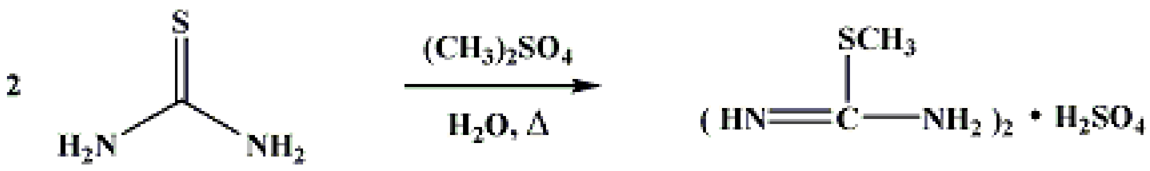
Organic Syntheses, CV 2, 411

S-METHYL ISOTHIOUREA SULFATE

[Pseudourea, 2-methyl-2-thio-, sulfate]



Submitted by P. R. Shildneck and Wallace Windus.
Checked by Henry Gilman and W. F. Schulz.

1. Procedure

In a 2-l. round-bottomed flask are mixed 152 g. (2 moles) of finely divided thiourea and 70 cc. of water. To this is added 138 g. (1.1 moles) of technical methyl sulfate (Note 1). The flask is immediately attached to a long reflux condenser carrying a trap. The reaction is allowed to progress spontaneously (Note 2), with occasional cooling as the reaction becomes more rapid and the flask becomes filled with vapor. After the initial vigorous reaction is completed, the mixture is refluxed for one hour, during which time crystallization takes place (Note 3). The mixture is then allowed to cool, the flask is removed, 200 cc. of 95 per cent ethyl alcohol is added, and the contents of the flask are then filtered with suction. The residue is washed twice with 100-cc. portions of 95 per cent alcohol and allowed to dry in air. The yield is 190 g. of a product which melts with decomposition at 235°. Another crop of crystals weighing 43 g. and melting at 230° can be obtained from the alcoholic filtrate by concentrating it to a paste to which, after cooling, is added 120 cc. of 95 per cent alcohol. The total yield is 220–233 g. (79–84 per cent of the theoretical amount).

2. Notes

1. Technical methyl sulfate, if it has not turned dark brown, need not be distilled before using.
2. If the mixture is cooled too much with ice water, the spontaneous reaction almost ceases and gentle heating is required to start the reaction again. If the mixture is not cooled, the initial vigorous reaction is so violent that material is likely to be lost through the condenser. Since methyl sulfate is poisonous, this must be avoided. Ammonia, which is a specific antidote for methyl sulfate, should be kept at hand.
The checkers observed no spontaneous reaction, and in order to initiate reaction the flask and contents were gently heated with a moving low flame. When reaction sets in, the flame is removed. A container with ice water is kept handy to moderate any unduly vigorous reaction, particularly if the water condenser is less than 125 cm. in length.

3. The completion of the vigorous reaction indicates that half of the thiourea is methylated and that the methyl sulfate has been converted to methylhydrogen sulfate. Vigorous heating is necessary to complete the methylation.

3. Discussion

The procedure described is essentially that of Arndt.[1]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 345
- Org. Syn. Coll. Vol. 3, 73

References and Notes

1. Arndt, Ber. **54**, 2236 (1921).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethyl alcohol, alcohol (64-17-5)

ammonia (7664-41-7)

methyl sulfate, methylhydrogen sulfate (75-93-4)

thiourea (62-56-6)

S-Methyl isothiourea sulfate, Pseudourea, 2-methyl-2-thio-, sulfate (867-44-7)

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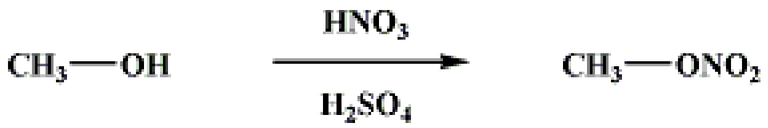
Organic Syntheses, CV 2, 412

METHYL NITRATE



Submitted by Alvin P. Black and Frank H. Babers.
Checked by John R. Johnson and H. B. Stevenson.

1. Procedure

In a flask cooled in an ice bath are mixed 425 g. (300 cc., 4.7 moles) of c.p. nitrous-free, concentrated nitric acid (sp. gr. 1.42) (Note 1) and 550 g. (300 cc.) of c.p. concentrated sulfuric acid (sp. gr. 1.84). In a second flask, also cooled in an ice bath, 92 g. (50 cc.) of c.p. concentrated sulfuric acid is added to 119 g. (150 cc., 3.7 moles) of pure methyl alcohol (Note 2) while the temperature is maintained below 10°.

One-third of the cold nitric-sulfuric mixture is placed in each of three 500-cc. Erlenmeyer flasks (Note 3), and each portion is treated separately with one-third of the methyl alcohol-sulfuric acid mixture, with constant shaking and thorough mixing (Note 4). The temperature is allowed to rise fairly rapidly to 40° and kept at this point by external cooling. During the addition of the methyl alcohol-sulfuric acid, most of the ester separates as an almost colorless oily layer above the acid. The time required for completion of the reaction is two to three minutes for each flask. The reaction mixtures are allowed to stand in the cold for an additional fifteen minutes but not longer. The lower layer of spent acid is separated promptly and poured at once into a large volume of cold water (about 1 l. for each portion) to avoid decomposition which quickly ensues with copious evolution of nitrous fumes.

The combined ester layers are washed with two 25-cc. portions of ice-cold salt solution (sp. gr. 1.17) (Note 5). A small quantity (8–10 drops) of concentrated sodium hydroxide solution is added to the second wash liquid until it has a faintly alkaline reaction to litmus. The ester is washed free of alkali with ice-cold salt solution and finally washed with two 15-cc. portions of ice water (Note 6). The product is treated with 10–15 g. of anhydrous calcium chloride and allowed to stand with occasional shaking for an hour at 0°. It is then decanted onto a fresh 5-g. portion of the drying agent and after standing for one-half hour is filtered. The crude ester without further purification (Note 7) may be used directly for most synthetic purposes, such as the preparation of phenylnitromethane (p. 512). The yield is 190–230 g. (66–80 per cent of the theoretical amount). *The crude ester should be used promptly and not stored.*

2. Notes

1. Colored specimens of nitric acid may be treated with a small quantity of urea (about 1–2 g. per 100 cc.), but this is unnecessary unless the acid is appreciably

colored.
2. Commercial synthetic methanol of high grade was used without further purification. This material is believed to be superior to wood alcohol for this preparation.
3. It should be noted that volume contractions occur in mixing the reagents. The total volume of the mixed acids is about 585 cc. (instead of 600 cc.), and that of the methyl alcohol-sulfuric acid is about 182 cc. (instead of 200 cc.).
4. *The treatment of methyl alcohol with a mixture of concentrated nitric and sulfuric acids is not without elements of danger, and adequate precautionary measures should be taken.* However, the submitters report that more than one hundred preparations were carried out without a single explosion or violent decomposition.
5. This corresponds to a 22 per cent solution of sodium chloride. This particular solution was found to give satisfactory separations and obviate emulsions.
6. Traces of acid remaining in the ester facilitate decomposition, and violent explosions may occur if such specimens are heated.
7. Methyl nitrate may be distilled if adequate precautions are taken. The ester must not be heated suddenly and must not contain any free acid. *Distillation is not recommended*, as the crude ester (after washing and drying) gives as good yields as the distilled product in most synthetic reactions. The loss in distillation is small, and the pure material distils at 64.5–65°. *The residue in the distilling flask must not be superheated*.

3. Discussion

Methyl nitrate has been prepared by distilling a methyl alcohol-nitric acid mixture to which methyl alcohol-sulfuric acid is added dropwise,[1] and by the use of dilute nitric acid in a procedure otherwise similar to that given above.[2] Neither of these methods is satisfactory, and explosions occur frequently.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 512

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

methyl alcohol, methanol (67-56-1)

sodium hydroxide (1310-73-2)

nitric acid (7697-37-2)

sodium chloride (7647-14-5)

urea (57-13-6)

Methyl nitrate (598-58-3)

Phenylnitromethane (622-42-4)

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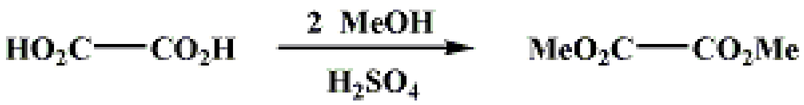
Organic Syntheses, CV 2, 414

METHYL OXALATE

[Oxalic acid, dimethyl ester]



Submitted by Everett Bowden
Checked by C. S. Marvel and A. T. Koide.

1. Procedure

In a 500-cc. Pyrex flask, fitted with a cork which loosely carries a glass mechanical stirrer and a separatory funnel, are placed 90 g. (1 mole) of anhydrous oxalic acid (Org. Syn. Coll. Vol. I, **1941**, 421) and 100 cc. (79 g., 2.5 moles) of methanol (Note 1). Then, while the mixture is rapidly stirred, 35 cc. of pure concentrated sulfuric acid (Note 2) is slowly added through the separatory funnel. The mixture is heated, if necessary (Note 3), nearly to boiling, then filtered as rapidly as possible through a 15-cm. filter paper placed in a slightly heated glass funnel, the filtrate being collected in a 500-cc. wide-mouthed Erlenmeyer flask. The first flask is rinsed with 40 cc. of hot methanol, which is poured through the filter paper. After twenty-four hours at 15° (Note 4) the crystals are filtered with suction, sucked as dry as possible, pressed between filter paper, and air-dried for a few minutes. The filtrate, after cooling to about –10°, is filtered rapidly and the product dried as before. A total of 100–115 g. of material, slightly moist with sulfuric acid and melting at 50–52°, is obtained.

For purification, the crude product is dissolved in 100 cc. of redistilled methanol, filtered through a warm funnel, and allowed to crystallize. After several hours the crystals are filtered, and the filtrate is chilled and filtered as before. A total of 80–90 g. (68–76 per cent of the theoretical amount) of methyl oxalate, melting at 52.5–53.5° (Note 5), is obtained.

2. Notes

1. The methanol used is the commercial (almost acetone-free) grade known as Columbian Spirits. This material is redistilled for recrystallizing the methyl oxalate.
2. Less sulfuric acid than that employed gives a smaller yield; larger quantities sometimes result in a product that causes difficulty in filtration. It is essential that the acid be added slowly and with vigorous stirring to prevent local superheating and darkening of the solution and product. Some commercial grades of methanol become quite dark in contact with sulfuric acid. The grade of methanol used here does not discolor, the filtrates being only light yellow.

3. Solution of the oxalic acid causes a sharp drop in temperature whereas solution of the sulfuric acid raises the temperature.
4. The major portion of the reaction is complete within a few minutes, but several hours are necessary for complete crystallization.
5. Larger batches give the same percentage yield as the one described. When several batches are to be run, the alcohol from the first recrystallization becomes the starting alcohol for the second batch, etc. This increases the yield somewhat.

3. Discussion

Methyl oxalate has been prepared by distilling a mixture of oxalic acid, methyl alcohol, and sulfuric acid;[1] by dissolving anhydrous oxalic acid in hot methyl alcohol;[2] by esterifying oxalic acid with methyl alcohol, using anhydrous hydrogen chloride as a catalyst;[3] by methanolysis of ethyl oxalate;[4] by passing vapors of dry methanol through hydrated oxalic acid until the water has been removed;[5] and by a process in which the methyl alcohol-water mixture evolved from hydrated oxalic acid and methanol is dried over potassium carbonate and returned to the reaction flask.[6] The method described in the procedure is simpler than any of these and gives very satisfactory yields.

References and Notes

1. Dumas and Peligot, Ann. chim. phys. (2) **58**, 44 (1835); Ann. **15**, 32 (1835); Wöhler, ibid. **81**, 376 (1852).
2. Erlenmeyer, Jahresb. **1874**, 572.
3. Rising and Stieglitz, J. Am. Chem. Soc. **40**, 726 (1918).
4. Pfannl, Monatsh. **31**, 316 (1910); Reimer and Downes, J. Am. Chem. Soc. **43**, 950 (1921).
5. Dutt, J. Chem. Soc. **123**, 2714 (1923).
6. Kenyon, Org. Syn. Coll. Vol. I, **1941**, 264.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

hydrogen chloride (7647-01-0)

methyl alcohol, methanol (67-56-1)

Oxalic acid (144-62-7)

Ethyl oxalate

Methyl oxalate

Oxalic acid, dimethyl ester (553-90-2)

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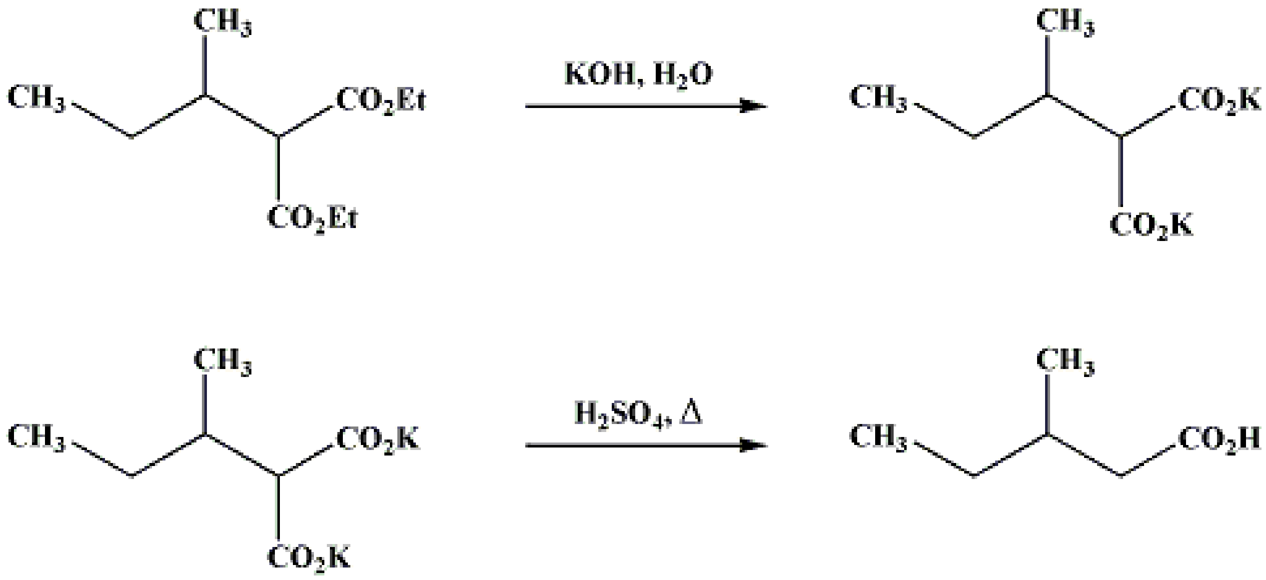
Organic Syntheses, CV 2, 416

3-METHYLPENTANOIC ACID

[Valeric acid, β-methyl-]



Submitted by E. B. Vliet, C. S. Marvel, and C. M. Hsueh.
Checked by Henry Gilman and R. E. Brown.

1. Procedure

A solution of 200 g. (3.6 moles) of potassium hydroxide (Note 1) in 200 cc. of water is placed in a 2-l. round-bottomed flask fitted with a reflux condenser, a mechanical stirrer, and a separatory funnel. The stirrer is started, and to the hot solution 200 g. (0.92 mole) of ethyl *sec.*-butylmalonate (Note 2) is added slowly. The solution refluxes quietly owing to the heat of saponification. After all the *sec.*-butylmalonic ester has been added, the solution is boiled gently for two hours. It is then diluted with 200 cc. of water, and 200 cc. of liquid is distilled from the solution in order to remove all the alcohol formed during the saponification (Note 3).

The residual liquid in the flask is allowed to cool, and a cold solution of 320 g. (3.3 moles) of concentrated sulfuric acid (Note 4) in 450 cc. of water is added through the separatory funnel. This should be done slowly and with stirring in order to prevent foaming. The solution becomes hot and may reflux spontaneously. After all the sulfuric acid has been added the solution is refluxed for about three hours. A layer of organic acid appears and the reflux condenser is replaced by an automatic separator (Note 5). The solution is distilled with the separator attached, and the aqueous portion is returned to the distilling flask. This operation is continued until practically all the organic acid has been driven over; from ten to fifteen hours is required. At the end, about 100 cc. of water is collected in the separator and extracted with ether in order to remove the dissolved acid (Note 6). The ether is distilled; the crude acid is mixed with an equal volume of dry benzene (Note 7) and distilled from a modified Claisen flask with a fractionating side

arm. Benzene and water distil first and then 3-methylpentanoic acid distils at 193–196°/743 mm. The yield is 66–69 g. (62–65 per cent of the theoretical amount) (Note 8).

2. Notes

1. Sodium hydroxide is unsatisfactory for this saponification because an organic sodium salt separates, yielding a semi-solid mass.
2. The ethyl *sec.*-butylmalonate was prepared from *sec.*-butyl bromide and malonic ester according to the general method described in Org. Syn. Coll. Vol. I, **1941**, 250. The yield of ester boiling at 124–132°/28 mm. was 80–81 per cent of the theoretical amount. The yields of 3-methylpentanoic acid given in this procedure were obtained with this grade of ester.
3. It is necessary that all the alcohol be eliminated after the saponification. If some is allowed to remain, ethyl 3-methylpentanoate is formed and a considerable amount of low-boiling material is present in the final product.
4. If hydrochloric acid is used, it distils and complicates the purification of the product.
5. The apparatus shown in Org. Syn. Coll. Vol. I, **1941**, 422, Fig. 22, was found to be very effective. Other methods of isolating the acid were not so satisfactory. When extraction with a solvent was used, the yield was about 10 per cent less and the product was contaminated with tarry impurities.
6. The amount of acid recovered by the ether extraction is only 1–2 g.
7. The acid may be dried by other means, but this method was found most convenient.
8. Other acids may be prepared by this general procedure; thus *n*-caproic acid may be obtained from ethyl *n*-butylmalonate in 75 per cent yield.

3. Discussion

3-Methylpentanoic acid has been prepared by heating *sec.*-butylmalonic acid,[1] and by the addition of ethylmagnesium bromide to the N-methylanilide of crotonic acid, followed by hydrolysis.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 474

References and Notes

1. Van Romburgh, Rec. trav. chim. **6**, 153 (1887); Kulisch, Monatsh. **14**, 559 (1893); Bentley, J. Chem. Soc. **67**, 267 (1895); Olivier, Rec. trav. chim. **55**, 1032 (1936).
2. Maxim and Ioanid, Bul. Soc. Chim. România **12**, (1930) [C. A. **25**, 488 (1931)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Malonic Ester

N-methylanilide of crotonic acid

sec.-butylmalonic ester

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sec.-BUTYL BROMIDE (78-76-2)

potassium hydroxide (1310-58-3)

n-caproic acid (142-62-1)

ETHYL n-BUTYLMALONATE

ethylmagnesium bromide (925-90-6)

3-Methylpentanoic acid, Valeric acid, β-methyl- (105-43-1)

ethyl 3-methylpentanoate (5870-68-8)

ethyl sec.-butylmalonate

sec.-butylmalonic acid

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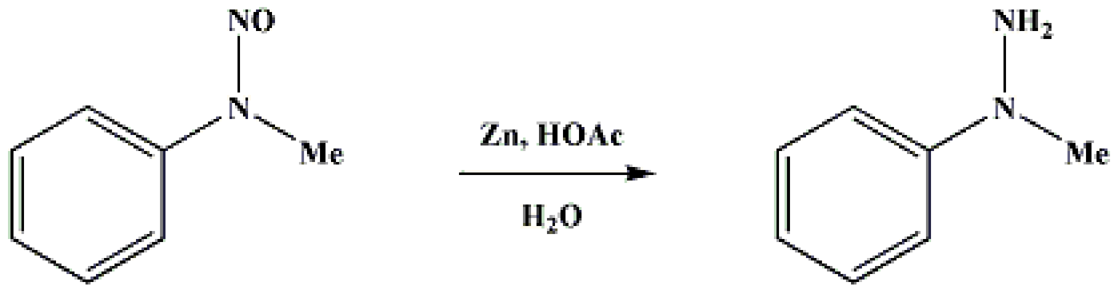
Organic Syntheses, CV 2, 418

α-METHYL-α-PHENYLHYDRAZINE

[Hydrazine, 1-methyl-1-phenyl-]



Submitted by W. W. Hartman and L. J. Roll.
Checked by Louis F. Fieser and J. T. Walker.

1. Procedure

A mixture of 200 g. (3.1 gram atoms) of zinc dust and 300 cc. of water is placed in a 2-l. three-necked flask equipped with an efficient mechanical stirrer, a thermometer, and a dropping funnel. The suspension is then stirred vigorously while a solution of 100 g. (0.73 mole) of N-nitrosomethylaniline (p. 460) in 200 cc. (210 g., 3.5 moles) of glacial acetic acid is added in a slow stream. The temperature is maintained between 10° and 20° by external cooling or by the addition of finely crushed ice. When all the acid solution has been added (about one and one-half to two hours is required, depending upon the rate of cooling) the mixture is stirred for an hour longer at room temperature and then warmed to 80° on the steam bath. The hot solution is filtered from the unreacted zinc, which is washed with three 100-cc. portions of a warm 5 per cent hydrochloric acid solution. The combined filtrate and washings are cooled and treated with sufficient 40 per cent sodium hydroxide solution to redissolve the zinc hydroxide precipitated. (About 1.2 l. is required.) The oily layer is separated and the aqueous layer extracted with two or three 100-cc. portions of ether. The combined oil and extracts are distilled from a steam bath until the ether is removed; the residue is then distilled under reduced pressure. The yield of colorless (Note 1) α-methyl-α-phenylhydrazine boiling at 106–109° 13 mm. is 46–50 g. (52–56 per cent of the theoretical amount).

2. Notes

1. α-Methyl-α-phenylhydrazine darkens on standing.

3. Discussion

α-Methyl-α-phenylhydrazine has been obtained by reducing nitrosomethylaniline with zinc and acetic acid[1] or electrolytically;[2] by reducing N-methylnitroformaldehyde

phenylhydrazone with zinc and acetic acid;[3] by heating methylbenzoylphenylhydrazine with concentrated hydrochloric acid;[4] and by methylating phenylhydrazine with sodamide and methyl iodide.[5]

References and Notes

1. Fischer, Ann. **190**, 152 (1878); **236**, 198 (1886).
2. Wells, Babcock, and France, J. Am. Chem. Soc. **58**, 2630 (1936).
3. Bamberger and Schmidt, Ber. **34**, 591 (1901).
4. Tafel, ibid. **18**, 1744 (1885).
5. Grammaticakis, Compt. rend. **210**, 303 (1940).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

α-Methyl-α-phenylhydrazine

N-methylnitroformaldehyde phenylhydrazone

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ether (60-29-7)

sodium hydroxide (1310-73-2)

Phenylhydrazine (100-63-0)

zinc (7440-66-6)

Methyl iodide (74-88-4)

Hydrazine, 1-methyl-1-phenyl- (618-40-6)

N-Nitrosomethylaniline, nitrosomethylaniline

zinc hydroxide (20427-58-1)

methylbenzoylphenylhydrazine

sodamide (7782-92-5)

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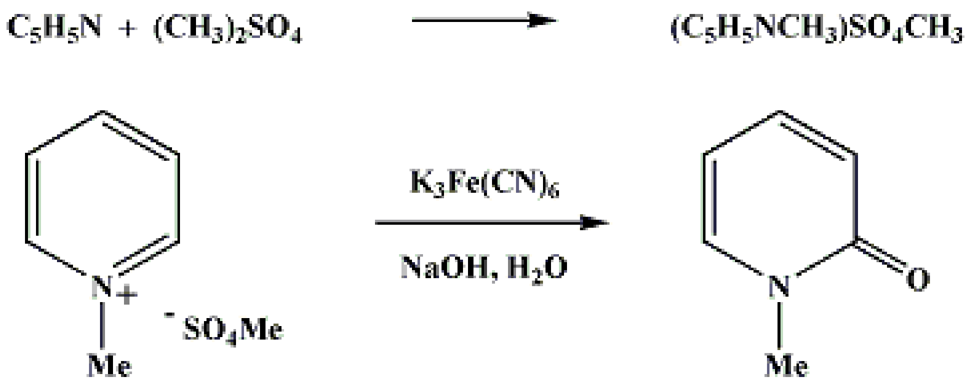
1-METHYL-2-PYRIDONE

[[2(1)-Pyridone, 1-methyl-]]



Submitted by E. A. Prill and S. M. McElvain.
Checked by C. S. Marvel and Sidney H. Babcock.

1. Procedure

In a 5-l. round-bottomed flask, fitted with a separatory funnel and a reflux condenser, is placed 145 g. (1.83 moles) of dry pyridine (Note 1); 231 g. (1.83 moles) of methyl sulfate is added dropwise through the separatory funnel. After the addition of the methyl sulfate the flask is heated in a boiling water bath for two hours to complete the reaction.

The flask containing the crude pyridinium salt is removed from the condenser, and the salt is dissolved by adding 400 cc. of water. The flask is fitted with a mechanical stirrer which will stir efficiently any volume of liquid which may be in the flask, and the solution is cooled to 0° in an ice-salt bath. Separate solutions of 1.2 kg. (3.65 moles) of potassium ferricyanide in 2.4 l. of water and of 300 g. (7.5 moles) of sodium hydroxide in 500 cc. of water are prepared and added dropwise from two separatory funnels to the well-stirred solution of the pyridinium salt at such a rate that the temperature of the reaction mixture does not rise above 10°. The rate of addition of these two solutions is regulated so that all the sodium hydroxide solution has been introduced into the reaction mixture when one-half of the potassium ferricyanide solution has been added. This usually requires about one hour. The remaining half of the potassium ferricyanide is then added during another hour. The reaction mixture is allowed to stand five hours, during which time it comes to room temperature.

The 1-methyl-2-pyridone is salted out of the reaction mixture by the addition of 400–500 g. of anhydrous sodium carbonate to the well-stirred solution. When no more sodium carbonate dissolves, stirring is discontinued and the yellow or brown oily layer containing most of the desired pyridone, together with some of the unreacted pyridinium salt, water, and inorganic salts, is separated from the aqueous mixture. The aqueous mixture is filtered (Note 2) to remove the excess sodium carbonate and the

precipitated potassium or sodium ferrocyanide. The filtrate is divided into three portions, each of which is extracted twice with 200-cc. portions of technical isoamyl alcohol (Note 3). The alcohol used for the second extraction of the first aqueous portion is satisfactory for the first extraction of a second aqueous portion, et cetera, so that a total volume of 800 cc. is used. The isoamyl alcohol extracts are combined and added to the oily layer which was first separated from the reaction mixture. An aqueous layer usually appears and is separated and extracted with another 100-cc. portion of amyl alcohol.

The combined alcohol extract is distilled under reduced pressure from a modified Claisen flask by heating on a water bath. All the solvent is thus recovered for use in a subsequent preparation.

The residue is transferred to a 250-cc. modified Claisen flask and distilled under diminished pressure from an oil bath. There is almost no low-boiling fraction if the alcohol has been carefully removed. The yield of product boiling at 122–124°/11 mm. is 130–140 g. (65–70 per cent of the theoretical amount) (Note 4) and (Note 5). A small amount of black solid remains in the distillation flask after the pyridone has distilled.

2. Notes

1. A commercial medicinal grade of pyridine was used without further purification.
2. This operation is most satisfactory when a glass-wool plug placed in a glass funnel is used as the filter. The liquid in this funnel should be stirred to prevent the heavy precipitate from settling and clogging the filter.
3. The extraction of the pyridone from the aqueous solution is difficult when benzene or ether is used as a solvent. 1-Methyl-2-pyridone, when dry, is very soluble in ethyl ether, benzene, and most organic solvents. It is, however, practically insoluble in petroleum ether or ligroin. When a mixture of water, benzene, and a little pyridone is shaken together all the pyridone is found in the water layer. When the pyridone is salted out from water by adding a sufficient quantity of potassium carbonate, the oily layer does not dissolve when benzene or ethyl ether is added, but three layers are formed. The pyridone seems to be extracted by ether or benzene only when the aqueous solution is strongly saturated with sodium hydroxide or potassium hydroxide, and then the tendency to form an emulsion is so great that separation of the layers is extremely difficult. When equal volumes of water, technical isoamyl alcohol, and a little pyridone are shaken together, the pyridone is found to be about equally distributed between the two solvents. Chloroform is also satisfactory for the extraction of pyridone from water.
4. The 1-methyl-2-pyridone when pure is odorless and colorless. It turns dark on standing unless it is kept in a sealed tube.
5. The boiling points at other pressures are given by Fisher and Chur[1] as 250°/740 mm., 130°/14.5 mm., 126°/12.5 mm., and 121°/10 mm.

3. Discussion

1-Methyl-2-pyridone has been prepared by the methylation of 2-pyridone,[2] by the oxidation of 1-methylpyridinium iodide[3] and of 1-methylpyridinium methyl sulfate[4] with a ferricyanide, and by the electrolytic oxidation of 1-methylpyridinium methyl sulfate.[1]

References and Notes

1. Fisher and Neundlinger, Ber. **46**, 2544 (1913); Neundlinger and Chur, J. prakt. Chem. (2) **89**, 466 (1914); Fisher and Chur, ibid. (2) **93**, 363 (1916).
2. v. Pechmann and Baltzer, Ber. **24**, 3144 (1891).
3. Decker, J. prakt. Chem. (2) **47**, 28 (1893).
4. Decker and Kaufmann, ibid. (2) **84**, 435 (1911); Fargher and Furness, J. Chem. Soc. **107**, 690 (1915).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

2(1)-Pyridone, 1-methyl-

pyridinium salt

potassium or sodium ferrocyanide

petroleum ether or ligroin

alcohol (64-17-5)

potassium carbonate (584-08-7)

Benzene (71-43-2)

ether, ethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium carbonate (497-19-8)

pyridine (110-86-1)

potassium hydroxide (1310-58-3)

methyl sulfate (75-93-4)

isoamyl alcohol (123-51-3)

amyl alcohol (71-41-0)

potassium ferricyanide (13746-66-2)

1-Methyl-2-pyridone (694-85-9)

2-pyridone

1-methylpyridinium iodide (930-73-4)

1-methylpyridinium methyl sulfate

ferricyanide

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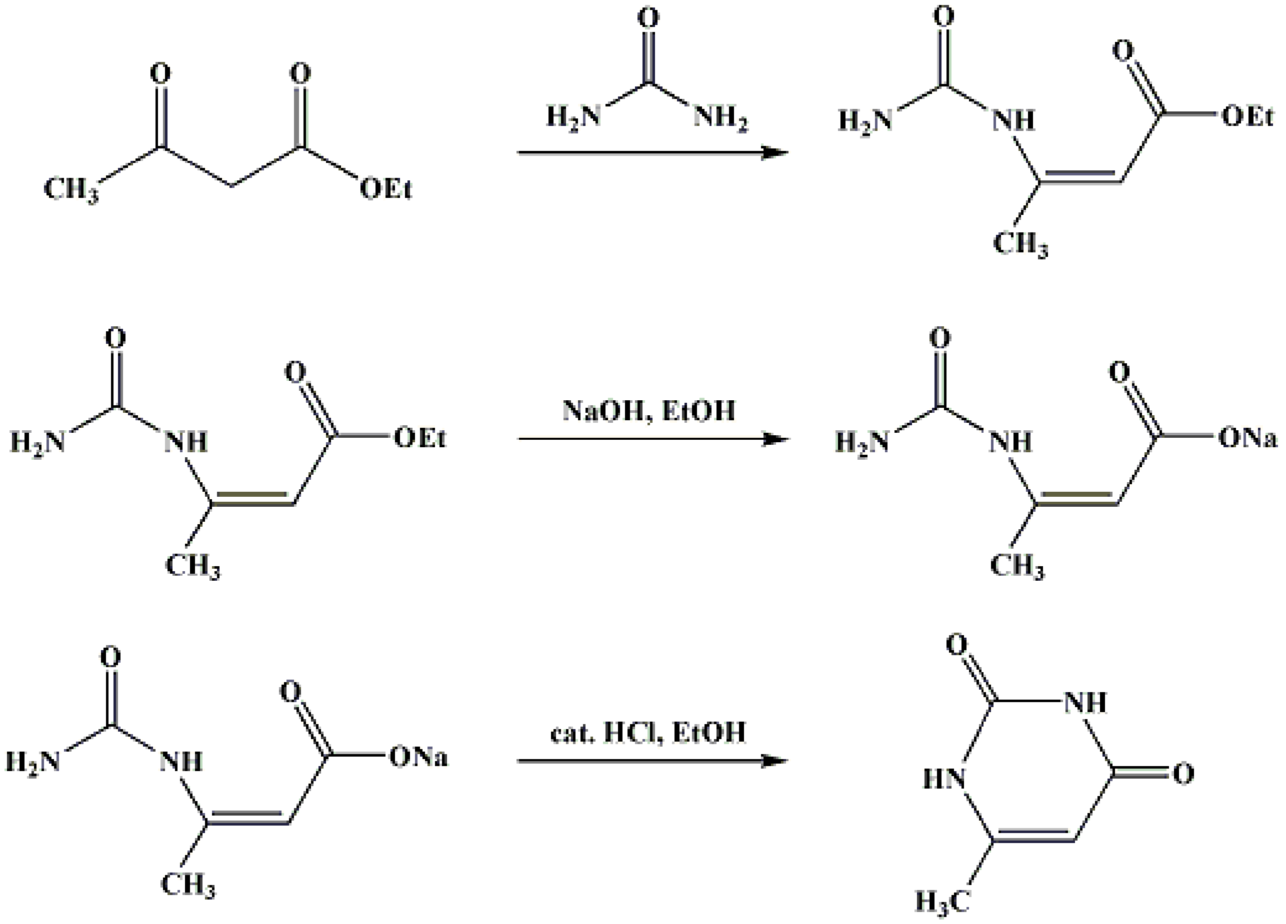
6-METHYLURACIL

[Uracil, 6-methyl-]



Submitted by John J. Donleavy and Mearl A. Kise.
Checked by Reynold C. Fuson and William E. Ross.

1. Procedure

Eighty grams (1.33 moles) of finely powdered urea is stirred into a mixture of 160 g. (155 cc., 1.23 moles) of ethyl acetoacetate (Note 1), 25 cc. of absolute alcohol (Note 2), and ten drops of concentrated hydrochloric acid in a 5-in. crystallizing dish. The reagents are mixed well, and the dish is covered loosely with a watch glass and placed in a vacuum desiccator over concentrated sulfuric acid. The desiccator is evacuated continuously with a water pump until the mixture has gone to dryness (Note 3), which usually requires from five to seven days (Note 4). The crude β-uraminocrotonic ester when thoroughly dry weighs 200–205 g.

The dry, finely powdered, crude β-uraminocrotonic ester is stirred into a solution of 80 g. (2 moles) of sodium hydroxide in 1.2 l. of water at 95°. The clear solution is then cooled to 65° and carefully acidified, while stirring, by the slow addition of concentrated hydrochloric acid. The 6-methyluracil precipitates almost immediately, and after the mixture is cooled the product is collected on a filter, washed with cold water, alcohol, and ether, and air-dried. The substance is obtained as a colorless powder of a high degree of purity, and the yield is 110–120 g. (71–77

per cent of the theoretical amount). For further purification the pyrimidine may be crystallized from glacial acetic acid. 6-Methyluracil decomposes above 300°.

2. Notes

1. Commercial ethyl acetoacetate can be used with satisfactory results. Directions for preparing this ester are given in Org. Syn. Coll. Vol. I, **1941**, 235.
2. Larger amounts of alcohol increase the period of drying without improving the yield. When no alcohol is used, the condensation proceeds slowly and the yields are low.
3. If the condensation product is used before it is dry, a large amount of carbon dioxide is evolved later in the acidification, indicating incomplete utilization of the ethyl acetoacetate.
4. It is usually advisable to change the sulfuric acid at least daily. Any lumps should be disintegrated occasionally to aid in the drying process.

3. Discussion

The synthesis of 6-methyluracil from ethyl acetoacetate and urea was described first by Behrend.[1] The substance has been obtained also by the action of lead hydroxide on methylthiouracil in an alkaline medium;[2] by boiling benzal-2-(4-hydroxy-6-methyl) pyrimidylhydrazine with hydrochloric acid;[3] and from urea and diketene.[4]

References and Notes

1. Behrend, Ann. **229**, 5 (1885); Behrend and Roosen, ibid. **251**, 238 (1889) Biltz and Heyn, ibid. **413**, 109 (1917).
2. List, ibid. **236**, 23 (1886).
3. Thiele and Bihan, ibid. **302**, 308 (1898).
4. Carbide and Carbon Chemicals Corporation, U. S. pat. 2,138,756 [C. A. **33**, 2152 (1939)]; Standard Oil Development Company, U. S. pat. 2,174,239 [C. A. **34**, 450 (1940)]; Boese, Ind. Eng. Chem. **32**, 16 (1940).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

β-uraminocrotonic ester

benzal-2-(4-hydroxy-6-methyl) pyrimidylhydrazine

alcohol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ether (60-29-7)

sodium hydroxide (1310-73-2)

lead hydroxide

carbon dioxide (124-38-9)

diketene (674-82-8)

urea (57-13-6)

Ethyl acetoacetate (141-97-9)

6-Methyluracil, Uracil, 6-methyl- (626-48-2)

pyrimidine (289-95-2)

methylthiouracil

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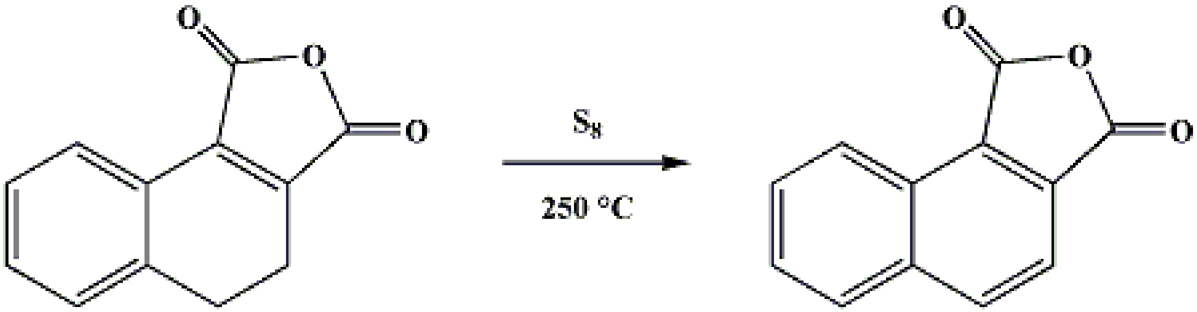
1,2-NAPHTHALIC ANHYDRIDE

[1,2-Naphthalenedicarboxylic anhydride]



Submitted by E. B. Hershberg and Louis F. Fieser.
Checked by C. R. Noller and S. Kinsman.

1. Procedure

In a 50-cc. Claisen distilling flask with a 50-cc. sealed-on distilling flask as a receiver are placed 20 g. (0.1 mole) of 3,4-dihydro-1,2-naphthalic anhydride (p. 194) and 3.2 g. (0.1 gram atom) of sulfur. After the flask is immersed in a bath (Note 1) previously heated to 230–235° and shaken until the globule of sulfur has dissolved (fifteen to twenty minutes), the temperature is raised to 250° for thirty minutes (Note 2). The residue is distilled under reduced pressure (Note 3), and the distillate is crystallized from 150 cc. of benzene to which 50 cc. of ligroin (b.p. 60–80°) has been added at the boiling point. The yield is 15–18 g. (76–91 per cent of the theoretical amount) of light yellow needles melting at 166–167°.

2. Notes

1. A Wood's metal bath or a mixture (m.p. about 150°) of ten parts of potassium nitrate and seven and one-half parts of sodium nitrite may be used.
2. If the heating at 250° is continued until hydrogen sulfide is no longer evolved (about ten hours), the product, after recrystallization, is lighter in color and shrinks less before melting.
3. The material comes over between 210° and 215° at 12–13 mm. with the bath at 260°.

3. Discussion

1,2-Naphthalic anhydride has been prepared by the hydrolysis of the dinitrile of 1,2-naphthalic acid;[1] by the oxidation of suitably substituted hydrocarbons or ketones;[2] and by the dehydrogenation of the 3,4-dihydro compound with bromine[3] or with sulfur.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 300

References and Notes

1. Cleve, Ber. **25**, 2475 (1892); Waldmann, J. prakt. Chem. (2) **127**, 197 (1930); Cook, J. Chem. Soc. **1932**, 462.
2. Freund and Fleischer, Ann. **399**, 186, 210 (1913); Kruber and Schade, Ber. **68**, 11 (1935).
3. von Auwers and Möller, J. prakt. Chem. (2) **109**, 141 (1925).
4. Fieser and Hershberg, J. Am. Chem. Soc. **57**, 1853 (1935).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ligroin

dinitrile of 1,2-naphthalic acid

Benzene (71-43-2)

hydrogen sulfide (7783-06-4)

bromine (7726-95-6)

sodium nitrite (7632-00-0)

sulfur (7704-34-9)

potassium nitrate (7757-79-1)

3,4-Dihydro-1,2-naphthalic anhydride (37845-14-0)

1,2-Naphthalic anhydride, 1,2-Naphthalenedicarboxylic anhydride (5343-99-7)

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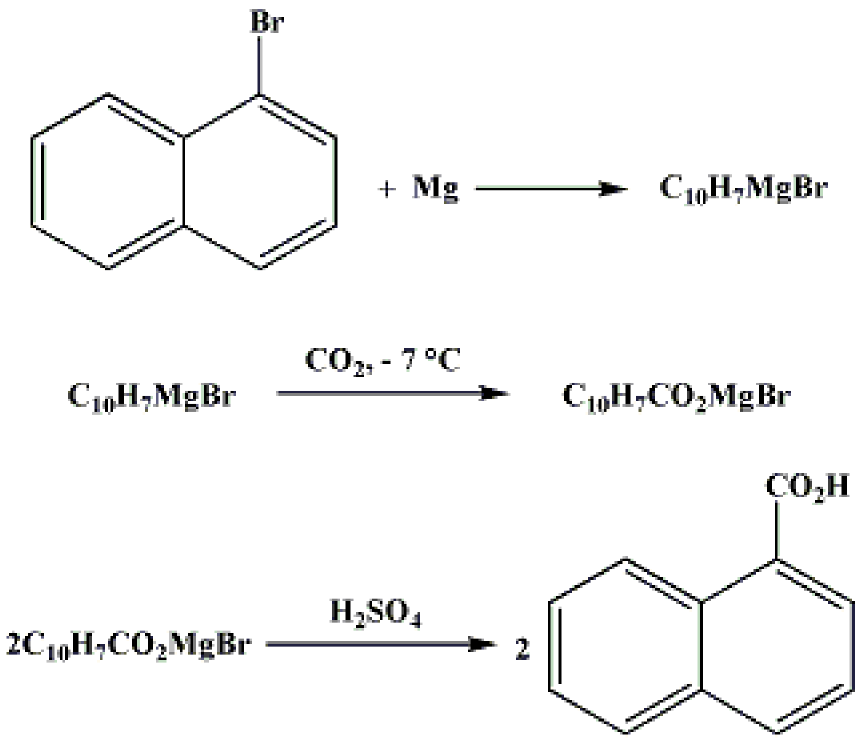
α-NAPHTHOIC ACID

[1-Naphthoic acid]



Submitted by Henry Gilman, Nina B. St. John, and F. Schulze.
Checked by C. R. Noller

1. Procedure

In a 2-l. three-necked flask, fitted with a mechanical stirrer, a reflux condenser, and a separatory funnel, is placed 24.3 g. (1 gram atom) of magnesium turnings (Note 1). The magnesium is covered with 100 cc. of anhydrous ether, and 10 cc. (15 g., 0.07 mole) of α-bromonaphthalene (Note 2) (with a crystal or two of iodine) (Note 3) is added to start the reaction. A warm water bath (45° or higher) is placed under the flask until the reaction starts. The stirrer is started, and a solution of 192 g. (0.93 mole) of α-bromonaphthalene in 500 cc. of anhydrous ether is added to the magnesium at such a rate that the reaction is vigorous but not violent. The addition requires from one and one-half to three hours. The water bath is again placed under the flask, and stirring and refluxing are continued for one-half hour after the addition of the halide is complete. The Grignard reagent which collects as a heavy oil in the bottom of the flask is dissolved by the addition of 533 cc. of dry benzene (Note 4).

The reaction mixture is then cooled by an ice-salt mixture. The separatory funnel is replaced by a two-holed rubber stopper containing a thermometer (bulb immersed in the reaction mixture) and a glass tube drawn out to make a fine capillary (Note 5). When the temperature of the reaction mixture has reached –7°, the condenser is

replaced by an entry tube, 10 mm. in diameter and adjusted so that the end is about 50 mm. above the surface of the reaction mixture (Note 6). The reaction mixture is stirred, and dry carbon dioxide is added through this tube (Note 7). The rate of flow of the carbon dioxide is regulated so that the temperature of the reaction mixture does not rise above −2°. The time required for the completion of the reaction varies from one and one-fourth to one and one-half hours. When the reaction is complete, the temperature falls below −7° and does not rise on increasing the rate of flow of carbon dioxide.

The flask is placed in an ice bath, and 25 per cent sulfuric acid is added slowly, with stirring, until no further reaction takes place and all the excess magnesium has dissolved (Note 8). The oily layer is separated, and the water layer is extracted with two 100-cc. portions of ether. The combined ether-benzene extracts (Note 9) are shaken with three 100-cc. portions of 25 per cent sodium hydroxide. Each alkaline layer is extracted successively with a 100-cc. portion of ether, and the combined alkaline extracts are then heated to 100° to drive off volatile impurities.

The solution is cooled and acidified strongly with 50 per cent sulfuric acid. The crude α-naphthoic acid is collected on a Büchner funnel, washed until free from sulfate, and dried. The yield of crude material melting at 142–155° is 130–135 g. This is dissolved in 400 cc. of hot toluene, a small amount of Filter-Cel is added, and the solution is filtered through a hot Büchner funnel. The filtrate is cooled in an ice bath, filtered with suction, and the filter cake washed with cold toluene until the filtrate is practically colorless. A light-colored product melting at 159–161° is obtained. The yield is 118–121 g. (68–70 per cent of the theoretical amount) (Note 10).

2. Notes

1. The finer commercial grade of turnings was used. After the reaction had once started, it proceeded smoothly with any grade of commercial turnings.
2. The α-bromonaphthalene (Org. Syn. Coll. Vol. I, **1941**, 121) was purified by distillation under reduced pressure. The fraction boiling at 144–147°/16 mm. was collected.
3. The checker was more successful in starting the reaction within a reasonable length of time when as much as 0.5 g. of iodine was added.
4. It is necessary to dissolve the Grignard reagent in benzene to prevent it from solidifying when the solution is cooled. The benzene should be added to the solution before it cools, as the hardened mass is difficult to redissolve.
5. This is to allow the carbon dioxide which does not react to escape slowly in order that the pressure in the flask does not become too great.
6. The inlet tube is placed at this distance above the surface of the reaction mixture in order to prevent clogging.
7. The carbon dioxide from an ordinary commercial cylinder was dried by passing it through two wash bottles containing sulfuric acid.
8. Cooling the solution externally with ice permits rapid hydrolysis without

danger of loss of material through refluxing (cf. Org. Syn. Coll. Vol. I, **1941**, 361).
9. If the ether-benzene solution is not entirely clear, it should be filtered before extraction with sodium hydroxide.
10. A second recrystallization from toluene gives an almost white product melting at 160.5–162°.

3. Discussion

α-Naphthoic acid has been prepared from α-naphthylmagnesium bromide and carbon dioxide, gaseous[1] or solid;[2] by hydrolysis of ethyl α-naphthoate, prepared in turn from α-naphthylmagnesium bromide;[3] by hydrolysis of α-naphthyl cyanide;[4] and from methyl α-naphthyl ketone and potassium hypochlorite.[2] The acid has been obtained by fusing sodium formate and sodium α-naphthalenesulfonate,[5] and by passing carbamyl chloride into naphthalene and aluminum chloride and hydrolyzing the α-naphthamide thus formed.[6] The methods for preparing α-naphthoic acid have been discussed by Wahl, Goedkoop, and Heberlein.[7]

The procedure described above[8] was developed from the methods of Acree,[1] of Blicke,[1] and of Whitmore and Fox.[1]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 282

References and Notes

1. Acree, Ber. **37**, 625 (1904); Blicke, J. Am. Chem. Soc. **49**, 2846 (1927); Whitmore and Fox, ibid. **51**, 3363 (1929).
2. Fieser, Holmes, and Newman, ibid. **58**, 1055 (1936).
3. Loder and Whitmore, ibid. **57**, 2727 (1935), and p. 282, above.
4. Merz and Mühlhaüser, Ber. **3**, 712 (1870).
5. Meyer, ibid. **3**, 364 (1870).
6. Gattermann and Schmidt, ibid. **20**, 860 (1887).
7. Wahl, Goedkoop, and Heberlein, Bull. soc. chim. (5) **6**, 533 (1939).
8. Gilman, St. John, and St. John, Rec. trav. chim. **48**, 594 (1929).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

Benzene (71-43-2)

ether (60-29-7)

sodium hydroxide (1310-73-2)

magnesium, magnesium turnings (7439-95-4)

carbon dioxide (124-38-9)

iodine (7553-56-2)

aluminum chloride (3495-54-3)

toluene (108-88-3)

α-Bromonaphthalene (90-11-9)

Naphthalene (91-20-3)

sodium formate

potassium hypochlorite

Ethyl α-naphthoate (3007-97-4)

α-naphthylmagnesium bromide

α-Naphthoic acid, 1-Naphthoic acid (86-55-5)

α-naphthyl cyanide (86-53-3)

methyl α-naphthyl ketone (941-98-0)

sodium α-naphthalenesulfonate (130-14-3)

carbamyl chloride

α-naphthamide (2243-81-4)

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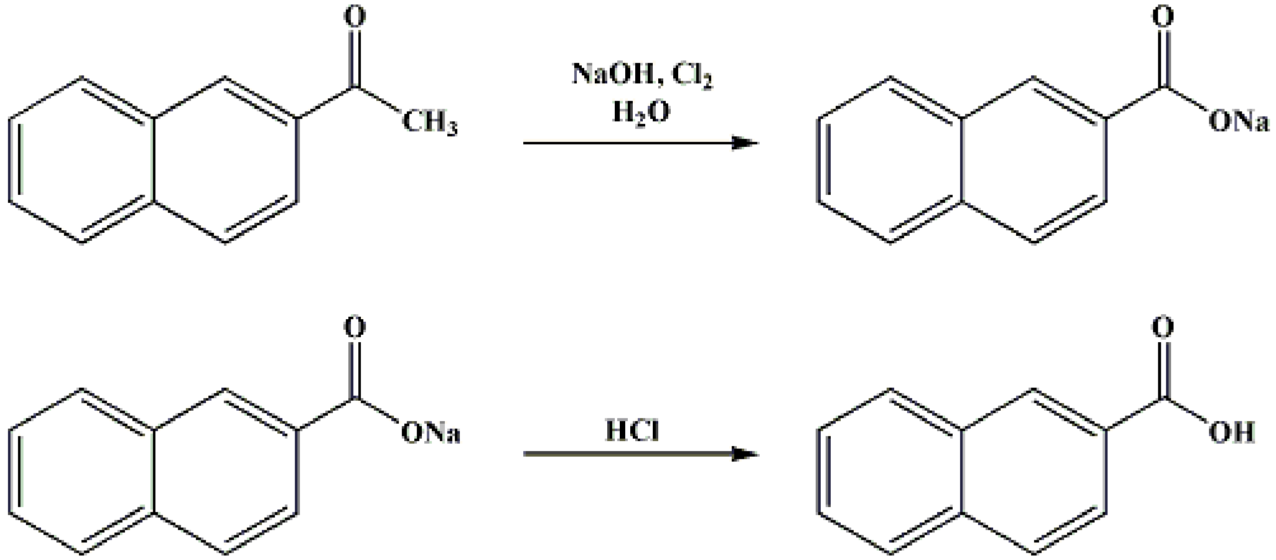
Organic Syntheses, *CV 2, 428*

β-NAPHTHOIC ACID

[2-Naphthoic acid]



Submitted by M. S. Newman and H. L. Holmes.
Checked by W. W. Hartman and F. W. Jones.

1. Procedure

In a 3-l. flask is placed a solution of 184 g. (4.6 moles) of sodium hydroxide in 300–400 cc. of water; sufficient ice is added to make the total volume about 1.5 l. Chlorine is passed into the solution, the temperature being kept below 0° by means of a salt-ice bath, until the solution is neutral to litmus, then a solution of 34 g. of sodium hydroxide in 50 cc. of water is added (Note 1) and (Note 2). The flask is now supported by a clamp and equipped with a thermometer and an efficient stirrer. The solution is warmed to 55°, and 85 g. (0.5 mole) of methyl β-naphthyl ketone (Note 3) is added. The mixture is vigorously stirred, and, after the exothermic reaction commences, the temperature is kept at 60–70° (Note 4) by frequent cooling in an ice bath until the temperature no longer tends to rise. This requires thirty to forty minutes. The solution is stirred for thirty minutes longer and then the excess hypochlorite is destroyed by adding a solution of 50 g. of sodium bisulfite in 200 cc. of water (Note 5). After cooling to room temperature, the reaction mixture is transferred to a 4-l. beaker and carefully acidified with 200 cc. of concentrated hydrochloric acid. The crude colorless acid is collected on a Büchner funnel, washed with water, and sucked as dry as possible with a rubber dam. After drying, the acid is crystallized (Note 6) from 600 cc. of 95 per cent alcohol, giving 75–76 g. (87–88 per cent of the theoretical amount) of β-naphthoic acid melting at 184–185° (corr.). By distilling 450 cc. of solvent from the mother liquor, an additional 9 g. (10 per cent of the theoretical amount) of acid, m.p. 181–183° (corr.), is obtained (Note 7).

2. Notes

1. It is reported that, in preparing a sodium hypochlorite solution by passing chlorine into sodium hydroxide, it is very difficult to determine the neutral point because of the instant bleaching of the indicator. If too much chlorine is added, even though the final solution may react alkaline because of the additional sodium hydroxide added later, oxidation of methyl β-naphthyl ketone to β-naphthoic acid does not take place. Consequently the following modified procedure for preparing the hypochlorite solution is recommended.

A solution of 218 g. (5.45 moles) of sodium hydroxide in 300 cc. of water in a 3-l. flask is cooled to room temperature with tap water. Next, 1250 g. of ice is added and chlorine is passed in rapidly until 161 g. (4.5 moles) has been taken up. External cooling is unnecessary. With the amount of ice specified, the solution will be at 0° when the addition of chlorine has been completed. From this point on the procedure is the same as that on p. 428. (Private communication from Edward C. Sterling.)

2. The hypochlorite solution also may be prepared conveniently from the calcium hypochlorite sold by the Mathieson Alkali Works under the trade name "HTH" and specified to contain not less than 65 per cent of available calcium hypochlorite.

In a 3-l. round-bottomed flask 250 g. of commercial calcium hypochlorite is dissolved in 1 l. of warm water, and a warm solution of 175 g. of potassium carbonate and 50 g. of potassium hydroxide in 500 cc. of water is added. The flask is stoppered and shaken vigorously until the semi-solid gel which first forms becomes quite fluid. The suspended solid is removed by filtration on a large Büchner funnel, washed with 200 cc. of water, and sucked as dry as possible with the aid of a rubber dam and an efficient suction pump. The filtrate of approximately 1.5 l. is placed in a 3-l. round-bottomed flask and is ready for the addition of methyl β-naphthyl ketone.

Such a solution contains approximately 200 g. (2.3 moles) of potassium hypochlorite. Sodium or potassium hypochlorite may be used, but the calcium salt is not satisfactory because the calcium salt of β-naphthoic acid is sparingly soluble.

3. The Eastman product, m.p. 53–55°, was used.

4. If the mixture is not cooled, the reaction will get out of control because of the rapid evolution of chloroform, and some ketone may steam-distil.

5. It is advisable to test the solution after the addition of the sodium bisulfite with acidified potassium iodide solution to be sure that all the hypochlorite has been destroyed. If hypochlorite is present, the chlorine liberated when the solution is acidified forms a high-melting impurity.

6. The moist acid may be crsytallized without drying, but more alcohol must be used to get the product into solution.

7. This method may be used for the preparation of larger quantities, a batch twenty times this size giving a yield of 87 per cent. It may be used also for the preparation of other aromatic acids where suitable ketones are available.

3. Discussion

β-Naphthoic acid has been prepared principally by the hydrolysis of β-naphthonitrile,[1] the over-all yields from β-naphthylamine, from sodium β-naphthalenesulfonate, and from calcium β-naphthalenesulfonate being given as (approximately) 20 per cent, 21 per cent, and 50 per cent, respectively.[2] The acid has been prepared also by the carbonation of the

Grignard reagent from the less accessible β-bromo derivative;[3] by chlorination of β-methylnaphthalene followed by hydrolysis and oxidation;[4] and by the procedure described above.[5] The various methods for preparing β-naphthoic acid have been discussed by Wahl, Goedkoop, and Heberlein.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 302
- Org. Syn. Coll. Vol. 4, 484
- Org. Syn. Coll. Vol. 6, 78
- Org. Syn. Coll. Vol. 8, 26

References and Notes

1. Baeyer and Besemfelder, Ann. **266**, 187 (1891).
2. Derick and Kamm, J. Am. Chem. Soc. **38**, 408 (1916).
3. Gilman and St. John, Rec. trav. chim. **48**, 743 (1929).
4. Wahl, Goedkoop, and Heberlein, Bull. soc. chim. (5) **6**, 533 (1939).
5. Fieser, Newman, and Holmes, J. Am. Chem. Soc. **58**, 1055 (1936).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Sodium or potassium hypochlorite

alcohol (64-17-5)

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

potassium iodide (7681-11-0)

sodium bisulfite (7631-90-5)

chlorine (7782-50-5)

potassium hydroxide (1310-58-3)

sodium hypochlorite (7681-52-9)

potassium hypochlorite

β-Naphthoic acid, 2-Naphthoic acid (93-09-4)

methyl β-naphthyl ketone

calcium hypochlorite (7778-54-3)

β-naphthonitrile (613-46-7)

sodium β-naphthalenesulfonate (532-02-5)

calcium β-naphthalenesulfonate

β-methylnaphthalene (91-57-6)

calcium salt of β-naphthoic acid

β-naphthylamine (91-59-8)

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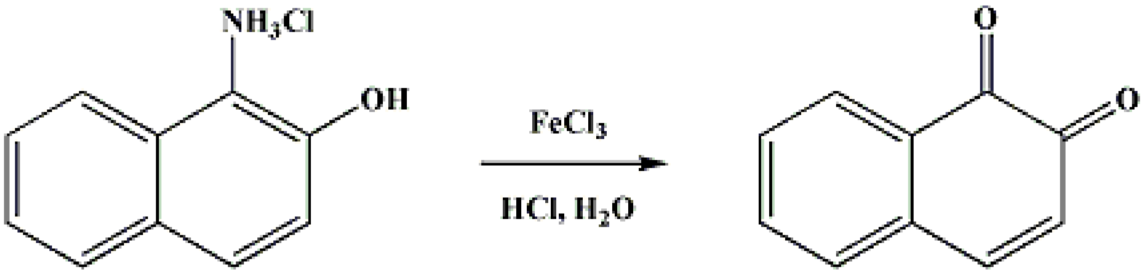
Organic Syntheses, CV 2, 430

1,2-NAPHTHOQUINONE



Submitted by Louis F. Fieser
Checked by C. R. Noller and W. R. White.

1. Procedure

For the best results this preparation must be carried out rapidly. The vessels and reagents required should be made ready in advance. The oxidizing solution is prepared by dissolving 240 g. (0.89 mole) of ferric chloride hexahydrate in a mixture of 90 cc. of concentrated hydrochloric acid and 200 cc. of water with heating, cooling to room temperature by the addition of 200–300 g. of ice, and filtering the solution by suction.

Eighty grams (0.41 mole) of 1,2-aminonaphthol hydrochloride of a high degree of purity (Note 1) is placed in a 5-l. round-bottomed flask and covered with a solution of 5 cc. of hydrochloric acid in 3 l. of water which has been heated to 35°. The material is dissolved quickly by shaking (one to two minutes), and the solution is filtered rapidly by suction from a trace of residue and transferred to a clean 5-l. flask (Note 2). The oxidizing solution is added all at once while rotating the flask vigorously in order to mix the two solutions thoroughly. The quinone separates at once as a voluminous, microcrystalline, yellow precipitate. The product is collected on a Büchner funnel, washed well with water (Note 3), and then for more thorough washing it is transferred to a large beaker, stirred for a few minutes with 2 l. of water (at 30°), and again collected. The filter cake is cut into slices and dried on filter paper at room temperature in an atmosphere free from acid fumes. The yield is 60–61 g. (93–94 per cent of the theoretical amount).

The material is pure golden yellow in color and melts with decomposition at 145–147°, with some softening at about 140°. It contains none of the black, sparingly soluble dinaphthyldiquinhydrone and dissolves without residue in alcohol or benzene. Under the microscope it is seen to consist of a mass of well-formed, fine needles. By crystallization from alcohol or benzene it may be obtained as orange-red needles of good appearance, but the process is unreliable, it involves much loss of material, and the point of decomposition is lowered by 10–20°. It is thus best to use or to preserve the quinone in the form originally obtained; in this condition it is essentially pure and it will keep indefinitely. The material should not be pulverized, for it then becomes highly electrified.

2. Notes

1. The quality of the naphthoquinone is closely dependent upon the purity of the starting material. The crystalline product described on p. 36 may be used without recrystallization and, indeed, without being dried. The excess of oxidizing agent specified is sufficient to allow for a yield of aminonaphthol slightly higher than that given; if the yield is lower the larger excess of ferric chloride does no harm.
2. The solution at this point should be clear, but it may acquire a rather pronounced orange-yellow color when viewed in bulk. It should not, however, turn purple.
3. The yellow color of the wash water is due to a slight solubility of the quinone.

3. Discussion

The only satisfactory method of preparing 1,2-naphthoquinone (β-naphthoquinone) is by the oxidation of 1,2-aminonaphthol in acid solution, and the chief problem involved is the preparation of this intermediate in suitable yield and purity. This problem and the literature pertaining to it are discussed on p. 38. Most reports of the preparation of the aminonaphthol include some description of its oxidation, but the only particularly helpful comment on the reaction is that ferric chloride is a better oxidizing agent than chromic acid because at a low temperature it does not attack the quinone, even when present in excess.[1]

One other method of preparing β-naphthoquinone is from 1,2-bromonaphthol through the ketonitrobromide.[2] Though the parent quinone itself is such a sensitive compound that the material so obtained decomposes within a few hours, the method is of considerable value for the preparation of certain substituted β-naphthoquinones.[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 465

References and Notes

1. Groves, J. Chem. Soc. **45**, 298 (1884).
2. Fries, Ann. **389**, 315 (1912).
3. Fries and Schimmelschmidt, ibid. **484**, 245 (1930).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

1,2-Aminonaphthol hydrochloride

1,2-aminonaphthol

dinaphthyldiquinhydrone

1,2-bromonaphthol

ketonitrobromide

alcohol (64-17-5)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

aminonaphthol

chromic acid (7738-94-5)

ferric chloride (7705-08-0)

naphthoquinone (130-15-4)

1,2-Naphthoquinone, β-naphthoquinone (524-42-5)

ferric chloride hexahydrate (10025-77-1)

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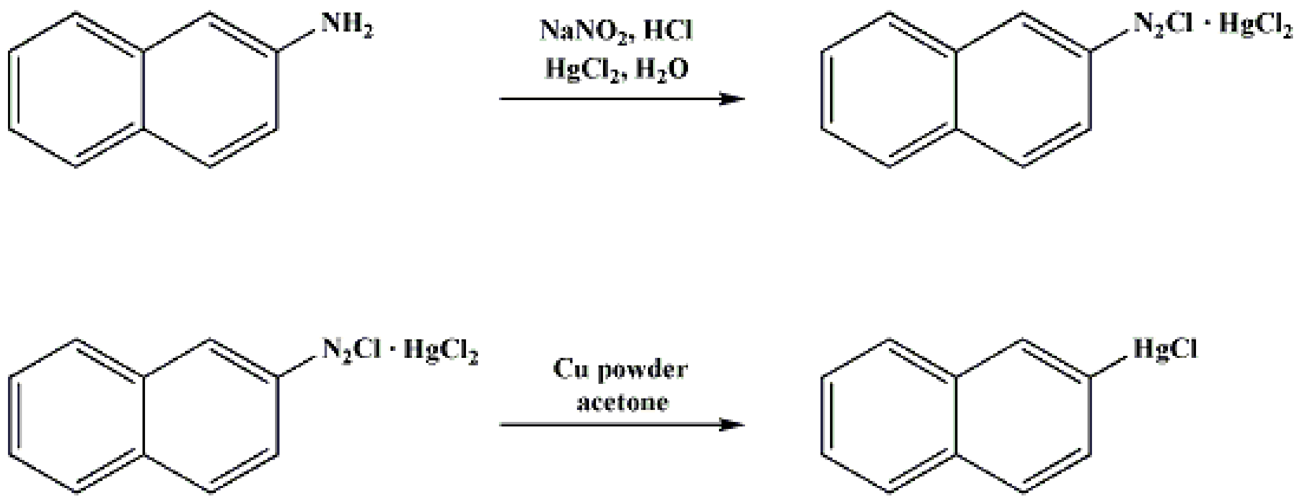
β-NAPHTHYLMERCURIC CHLORIDE

[[Naphthalene, 2-(chloromercuri)-]]



Submitted by A. N. Nesmajanow
Checked by Frank C. Whitmore and R. W. Beattie.

1. Procedure

To 450 cc. of concentrated hydrochloric acid (sp. gr. 1.19) and 500 cc. of water, in a 4-l. (1-gal.) earthenware crock equipped with an efficient stirrer, is added 143 g. (1 mole) of β-naphthylamine. The suspension of the amine hydrochloride is cooled by the addition of 500 g. of cracked ice. When the temperature reaches 5°, solid sodium nitrite (about 69 g.) is added until starch-iodide paper shows an excess. During the diazotization about 600 g. of cracked ice is introduced at such a rate as to keep the temperature at 5°. The cold solution of the diazonium salt is filtered to remove a small amount of precipitate and returned to the crock. A solution of 271 g. (1 mole) of mercuric chloride in 300 cc. of concentrated hydrochloric acid is mixed with 300 g. of ice and added slowly to the rapidly stirred solution. A heavy precipitate of the yellow addition compound of β-naphthalenediazonium chloride and mercuric chloride separates. Stirring is continued for a half hour, after which the precipitate is collected on a 20-cm. Büchner funnel, sucked as dry as possible, and washed with two 400-cc. portions of water and two 150-cc. portions of acetone (Note 1). The solid is air-dried at about 20° (Note 2) to constant weight. The yield is 380–390 g. (82–84 per cent of the theoretical amount) (Note 3).

In a 2-l. round-bottomed Pyrex flask equipped with a stirrer are placed 139 g. (0.3 mole) of the addition compound, 700 cc. of acetone (Note 4), and 38 g. (0.6 gram atom) of copper powder (Note 5). The mixture is cooled at once to about 20°, stirred for one hour, and then allowed to stand overnight. The insoluble material is collected on a Büchner funnel (Note 6). The solid mixture is extracted with about 3 l. of boiling commercial xylene and filtered through a hot funnel. On cooling the filtrate, crystals of β-naphthylmercuric chloride separate (Note 7). The yield of product which melts at 266–267° is 52–64 g. (40–49 per cent of the theoretical amount based on the amine used) (Note 8) and (Note 9).

2. Notes

1. The washing with large amounts of solvents is necessary to remove small amounts of highly

colored impurities. The product is practically insoluble in the cold wash liquids.
2. The double salt *explodes violently* if heated. For preparation of the organic mercury compounds the double salt need not be completely dry.
3. It is unsafe to store the addition complexes of mercuric chloride and diazonium chlorides in a closed vessel. The complex salt should be used as soon as possible and, if it is to be kept for any length of time, should be placed in a large open dish or a loosely covered container.
In one of a number of preparations, a batch of about 960 g. of the addition compound from benzenediazonium chloride was air-dried and placed in a large bottle with a screw cap. About four hours later the entire complex decomposed with considerable violence. At the time no heat or strong light was near the bottle. (Henry Gilman, private communication.)
4. The acetone employed boiled at 55–57°. The use of methyl or ethyl alcohol decreases the yield slightly.
5. The copper powder is prepared from zinc dust and an excess of copper sulfate solution maintained below 70°.
6. The acetone filtrate contains only a trace of the product.
7. The mother liquor from these crystals may be used again to extract the original crude residue, since the product is practically insoluble in cold xylene.
8. If hydrobromic acid and mercuric bromide are used, the product is β-naphthylmercuric bromide.
9. In a similar way, aniline, the three toluidinmnmes, and the aminophenols can be converted into the corresponding chloromercuric compounds in about 40 per cent yields.

3. Discussion

β-Naphthylmercuric chloride has been prepared by the action of mercuric chloride in amyl alcohol on mercury di-β-naphthyl;[1] from β-naphthalenesulfinic acid and mercuric chloride;[2] from β-naphthylboric acid and mercuric chloride;[3] and by the procedure described above.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 381

References and Notes

1. Michaelis, Ber. **27**, 251 (1894).
2. Whitmore and Howe, "Organic Compounds of Mercury," by Frank C. Whitmore, The Chemical Catalog Company, New York, 1921, p. 203.
3. König and Scharrnbeck, J. prakt. Chem. (2) **128**, 168 (1930).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

mercury compounds

aminophenols

Mercury di-β-naphthyl

β-Naphthylmercuric chloride

methyl or ethyl alcohol

β-naphthylmercuric bromide

toluidinmnmes

β-naphthylboric acid

hydrochloric acid (7647-01-0)

aniline (62-53-3)

HYDROBROMIC ACID (10035-10-6)

copper sulfate (7758-98-7)

benzenediazonium chloride

sodium nitrite (7632-00-0)

copper powder (7440-50-8)

acetone (67-64-1)

zinc (7440-66-6)

mercuric chloride (7487-94-7)

xylene (106-42-3)

amyl alcohol (71-41-0)

β-naphthalenediazonium chloride

Naphthalene, 2-(chloromercuri)- (39966-41-1)

mercuric bromide (7789-47-1)

β-naphthalenesulfinic acid

β-naphthylamine (91-59-8)

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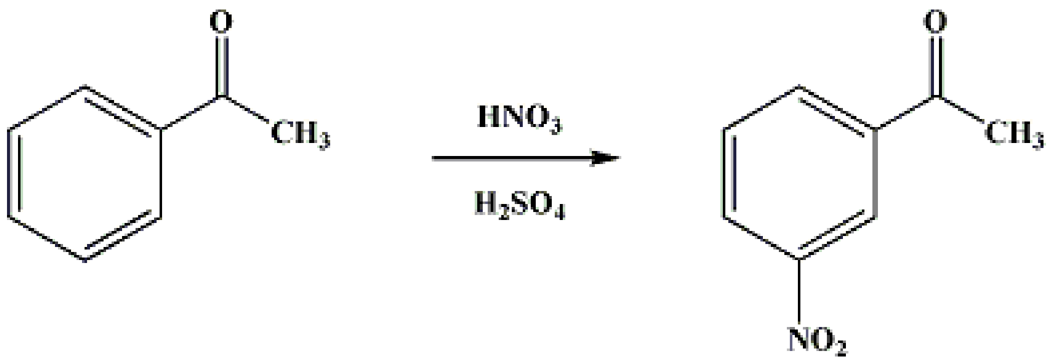
Organic Syntheses, CV 2, 434

m-NITROACETOPHENONE

[Acetophenone, *m*-nitro-]



Submitted by B. B. Corson and R. K. Hazen.
Checked by Roger Adams and W. W. Moyer.

1. Procedure

In a 1-l. wide-mouthed Erlenmeyer flask, immersed in an ice-salt bath contained in a 2-gal. earthenware crock, is placed 150 cc. of concentrated sulfuric acid. The flask is equipped with an efficient mechanical stirrer, a small dropping funnel, and a thermometer reaching almost to the bottom of the flask (Note 1). The stirrer is started, and, when the sulfuric acid has cooled to ice temperature or below, 60 g. (0.5 mole) of pure acetophenone is slowly dropped in from the dropping funnel at such a rate (about ten minutes for the addition) that the temperature does not rise above 5° (Note 2). After the reaction mixture has cooled, this time to about –7°, the cooled (15–20°) nitrating mixture, consisting of 40 cc. (0.65 mole) of nitric acid (sp. gr. 1.42 at 15.5°) (Note 3) and 60 cc. of concentrated sulfuric acid, is added through the dropping funnel at such a rate (100–120 drops per minute) that the temperature of the reaction mixture remains at 0° or lower (Note 4). After the nitrating acid has been added, stirring is continued for ten minutes longer and the contents of the flask are poured (Note 5), with vigorous manual stirring, into a mixture of 750 g. of cracked ice and 1.5 l. of water. The product separates as a yellow flocculent solid.

After the ice has melted, the product is filtered by suction and the somewhat sticky mass pressed as dry as possible. It is transferred to a mortar and triturated with three successive 300-cc. portions of cold water (to remove acid); it is then stirred to a mush with two successive 25-cc. portions of ice-cold ethyl alcohol (to remove adhering oil); the solid is pressed dry on the suction filter after each of the five washings. The product is pressed on a porous plate and, when fairly dry (about one hour), is dissolved in 100–120 cc. of hot ethyl alcohol (Note 6). The dark solution is filtered quickly through a small suction funnel (Note 7), and the hot filtrate is poured slowly into 1 l. of cold water which is stirred vigorously (Note 8) with a stirring rod during the addition and for several minutes afterward. After standing a few minutes the yellow

solid is filtered by suction, washed with 200 cc. of cold water, sucked dry, and pressed out on a porous clay plate.

When the reprecipitated *m*-nitroacetophenone (50–55 g.) is dry it is dissolved in 100 cc. of hot alcohol in a 300-cc. Erlenmeyer flask. The flask is then immersed in an ice bath and shaken vigorously while crystallization is taking place. Because of the great change in solubility between 60° and 50° the agitation of the liquid must be vigorous during this temperature interval, or large clumps of crystals will be formed instead of the purer and more easily dried mush. After the temperature has reached 20° (about one hour) the mixture is filtered by suction (Note 9). The solid (Note 10) is washed with 10 cc. of ice-cold alcohol and pressed dry on a clay plate. The product is light yellow; it softens at 74° and melts at 76–78°. The total yield is 45 g. (55 per cent of the theoretical amount) (Note 11).

2. Notes

1. The only flask found suitable for this preparation is the 1-l. wide-mouthed Erlenmeyer. A large flask is necessary to ensure rapid cooling. A propeller with long, wide blades agitates the viscous liquid much more efficiently than a stirrer of the centrifugal type. The blades should be as long as allowed by the wide mouth of the flask. The thermometer which is to record the temperature of the reaction mixture should enter at an angle and reach almost to the bottom of the flask, since the amount of liquid is small. The thermometer should have the zero point at least 15 cm. from the bulb in order to facilitate reading the temperature. It is essential that the temperature be watched throughout the experiment. A smaller ice-salt bath than that contained in a 2-gal. earthenware crock is inadequate.

2. The same dropping funnel can be used, without washing, for the addition of the concentrated sulfuric acid, the acetophenone, and the nitrating mixture. With rapid stirring the acetophenone can be easily added in seven minutes without raising the temperature of the reaction mixture above 3°.

3. Nitric acid of lower specific gravity than 1.42 at 15.5° yields an impure product. Ordinary concentrated nitric acid usually has to be strengthened by the addition of fuming nitric acid.

4. Two conditions are necessary for a good nitration: low temperature (0° or below) and rapidity of addition of the nitrating mixture (not longer than forty-five minutes). With efficient cooling the temperature can be held between –5 and 0°. If the temperature should rise once or twice to 3° no harm is done provided that the reaction mixture is quickly cooled back to the correct temperature. In order to avoid local heating the delivery tube of the dropping funnel should be so directed as to deliver the nitrating acid near the site of greatest agitation.

The rate of stirring must be rapid. The optimum speed will be different for different stirrers, depending on the shape and size of the blades. For the stirrer described the speed is 1600 r.p.m. During the addition of acetophenone this high speed is not necessary; in fact, it cannot be maintained on account of excessive splashing. However, during the addition of the nitrating acid the reaction

mixture thickens and high-speed stirring becomes possible. The ice-salt mixture must be stirred repeatedly with a stick, and fresh ice and salt must be added from time to time. The temperature of the bath should be around –16°. Enough liquid should be present in the cooling bath so that the lower half of the flask is immersed in brine. If no especial care is exercised, the addition of the nitrating acid requires from two to three hours in order to maintain the temperature at 0° or below. This long exposure to the mixture of sulfuric and nitric acids is as harmful as a rise of temperature; the product is of poor quality and the yield drops from 55 to 15 per cent or less.
By using solid carbon dioxide as the cooling medium and also adding it directly to the reaction mixture, a temperature of –20° can be maintained during the nitration.[1] According to W. W. Hartman, private communication, the use of solid carbon dioxide in this way permits larger runs of *m*-nitroacetophenone to be made.
5. The experiment should not be stopped until the product has been poured into ice water.
6. Although 55° suffices to dissolve the *m*-nitroacetophenone it is desirable to bring the alcoholic solution to a boil to avoid crystallization during filtration.
7. Excessive frothing in the filter flask is easily checked by pinching off the suction tube from time to time.
8. Vigorous stirring and slow pouring are absolutely necessary. In the absence of either, the product will be lumpy rather than flocculent.
9. Since the solubility curve is so flat in the vicinity of room temperature it is not necessary to cool very low before filtering. The difference in solubility between 20° and 10° amounts to only 1 g. per 100 cc. of solution. The solubility of *m*-nitroacetophenone in 96 per cent alcohol is as follows:

Temperature	Weight in 10 cc.	Temperature	Weight in 10 cc.
8°	0.16	48°	1.88
17	0.25	50	2.38
22	0.31	52	3.08
23	0.34	53.5	4.05
27	0.41	56	5.46
28	0.45	57	8.05
32	0.64	59	11.00
39	0.97	60	15.60
42	1.22		

10. A small additional yield (about 5 g.) may be obtained from the mother liquor by concentrating to 20 cc. and then cooling in ice.
11. This work was aided by a grant from the Cyrus M. Warren Fund of the American Academy of Arts and Sciences.

3. Discussion

m-Nitroacetophenone has usually been prepared by the nitration of acetophenone;[1], [2] it

has been made also by the hydrolysis of *m*-nitrobenzoylacetoacetic ester.[3] The procedure given above has been modified by Morgan and Watson; the modified procedure is reported to increase the yield of *m*-nitroacetophenone to 83 per cent of the theoretical amount.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 393

References and Notes

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3. Gevekoht, Ann. **221**, 334 (1883).
4. Morgan and Watson, J. Soc. Chem. Ind. **55**, 29T (1936).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric and nitric acids

m-nitrobenzoylacetoacetic ester

ethyl alcohol, alcohol (64-17-5)

sulfuric acid (7664-93-9)

nitric acid (7697-37-2)

carbon dioxide (124-38-9)

Acetophenone (98-86-2)

m-Nitroacetophenone, Acetophenone, m-nitro- (121-89-1)

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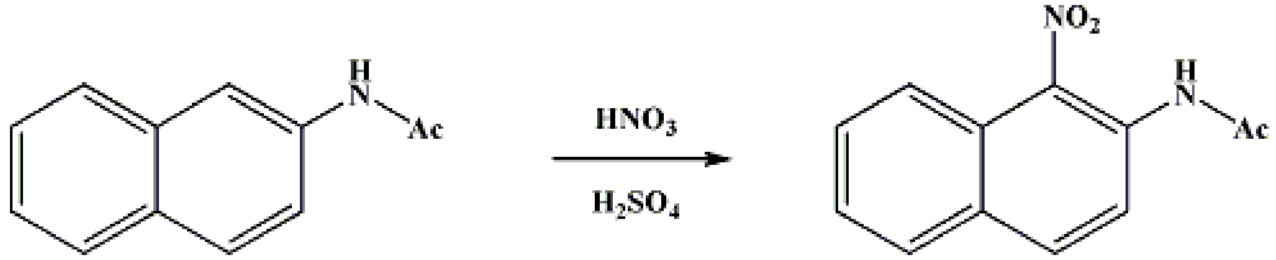
Organic Syntheses, *CV 2*, *438*

1-NITRO-2-ACETYLAMINONAPHTHALENE

[Acetamide, N-(1-nitro-2-naphthyl)-]



Submitted by W. W. Hartman and Lloyd A. Smith.
Checked by Louis F. Fieser and J. T. Walker.

1. Procedure

In a 2-l. round-bottomed flask equipped with a mechanical stirrer, a thermometer, and a dropping funnel, and clamped in a position such that it may be surrounded by a bath of water and ice when desired, are placed 300 g. (1.62 moles) of β-acetylaminonaphthalene (m.p. 131–132°) and 500 cc. of glacial acetic acid. With the mixture at room temperature, the stirrer is set in motion, and 200 g. (143 cc., 2.1 moles) of concentrated nitric acid (sp. gr. 1.4) is added dropwise over a period of forty-five minutes; the temperature is kept below 40° by occasionally immersing the flask in the cooling bath. When about one-tenth of the nitric acid has been added, the reaction mixture sets to a mass that is stirred with difficulty. The addition of nitric acid is stopped at this point. After three to five minutes the mass becomes fluid, and the addition of nitric acid is resumed. When about one-fourth of the nitric acid has been added, all the solid material dissolves. Considerable heat is evolved at this point, and good cooling is required to keep the temperature from rising above 40°; the mixture must be cooled during the addition of the remainder of the acid. After the addition is complete, stirring is continued for ten minutes longer.

The flask is stoppered and cooled in a bath of ice and water for three hours; the reaction product should then separate in the form of a yellow, crystalline paste (Note 1) and (Note 2). The crystals are collected on a 19-cm. Büchner funnel and washed, first with 200 cc. of 50 per cent acetic acid, and next with 400 cc. of ordinary ether. This crude, dry product, weighing 270–290 g., is placed in a 3-l. flask and heated under a reflux condenser with 1.7 l. of benzene for twenty minutes. The mixture is then allowed to cool to 40–45° and filtered through a 19-cm. Büchner funnel. The residue is a mixture of sparingly soluble isomers, chiefly 5- and 8-nitro-2-acetylaminonaphthalene. On further cooling of the filtered solution, there is obtained 190–200 g. of 1-nitro-2-acetylaminonaphthalene melting at 117–119°. This material is recrystallized from about 500 cc. of hot 95 per cent ethyl alcohol. Fine yellow crystals melting at 123–124° are obtained. The yield is 175–182 g. (47–49 per cent of the theoretical amount).

2. Notes

1. The material is sometimes slow in crystallizing, and it is then advisable to scratch the walls of the container with a stirring rod. If this fails to induce crystallization, seed may be obtained by diluting a small portion of the solution with water.
2. Crystallization is nearly, but not entirely, complete after this period of time. When the mother liquor was allowed to stand for five days, an additional quantity of material separated. From this material only 3 g. of pure 1-nitro-2-acetylaminonaphthalene was obtained.

3. Discussion

This procedure is based upon previous studies of the nitration of 2-acetylaminonaphthalene.[1]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 451

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

5- and 8-nitro-2-acetylaminonaphthalene

ethyl alcohol (64-17-5)

acetic acid (64-19-7)

Benzene (71-43-2)

ether (60-29-7)

nitric acid (7697-37-2)

1-Nitro-2-acetylaminonaphthalene, Acetamide, N-(1-nitro-2-naphthyl)- (5419-82-9)

β-acetylaminonaphthalene, 2-acetylaminonaphthalene (581-97-5)

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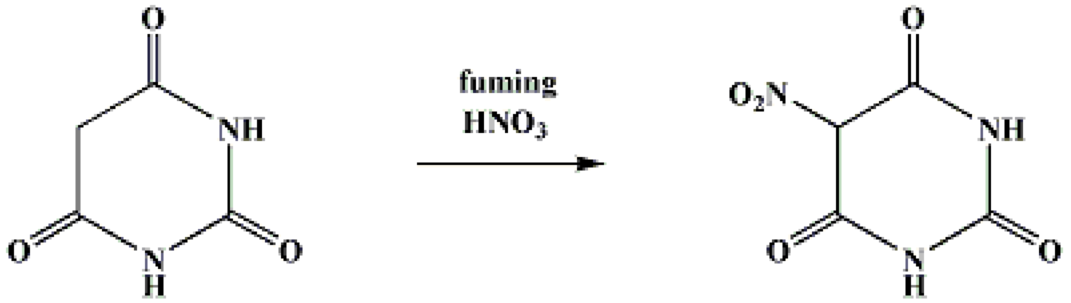
Organic Syntheses, CV 2, 440

NITROBARBITURIC ACID

[Barbituric acid, 5-nitro-]



Submitted by W. W. Hartman and O. E. Sheppard.
Checked by C. S. Marvel and B. H. Wojcik.

1. Procedure

In a 2-l. flask, equipped with a mechanical stirrer and surrounded by an ice bath, is placed 143 cc. of fuming nitric acid (sp. gr. 1.52). Stirring is started, and 100 g. (0.61 mole) of barbituric acid (p. 60) is added over a period of two hours; the temperature is kept below 40° during the addition. The mixture is stirred for one hour after the barbituric acid has been added, and stirring is continued while 430 cc. of water is added and the solution is cooled to 10°. The mixture is filtered, and the residue is washed with cold water and dried on a glass tray at 60–80° (Note 1). The nitrobarbituric acid is dissolved by adding it to 860 cc. of boiling water in a 2-l. flask and heating the mixture on a boiling water bath while steam is blown in until solution is complete (Note 2). After filtration and cooling overnight, the crystals are removed, washed with cold water, and dried in trays in an oven at 90–95° for two to three hours. The product melts with decomposition at 181–183° when heated rapidly. The yield is 139–141 g. (Note 3). On drying the product at 110–115° for two to three hours, the yield is 90–94 g. (85–90 per cent of the theoretical amount) of an anhydrous compound which melts with decomposition at 176°.

2. Notes

1. Unless the product is dried before recrystallization it is difficult to remove all the nitric acid, and the final product will have a strong odor of nitric acid.
2. If a clear yellow solution is not obtained, Norite should be added before filtering.
3. This yield is slightly above the theoretical yield of 139 g., but this is probably due to a greater degree of hydration than is indicated in the formula.

3. Discussion

Nitrobarbituric acid has been prepared by oxidation of violuric acid,[1] and by treatment of barbituric acid with fuming nitric acid[2] or concentrated nitric acid.[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 617

References and Notes

1. Ceresole, Ber. **16**, 1134 (1883).
2. Baeyer, Ann. **130**, 140 (1864).
3. Fredholm, Z. anal. Chem. **104**, 400 (1936).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

nitric acid (7697-37-2)

Barbituric acid (67-52-7)

Nitrobarbituric acid, Barbituric acid, 5-nitro- (480-68-2)

violuric acid (87-39-8)

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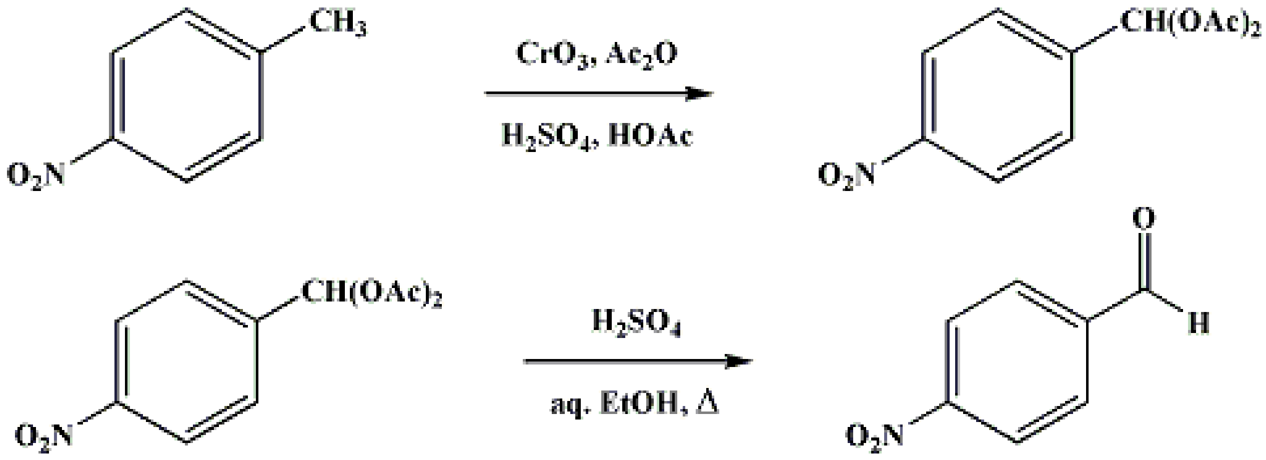
Organic Syntheses, CV 2, 441

p-NITROBENZALDEHYDE

[Benzaldehyde, *p*-nitro-]



Submitted by S. V. Lieberman and Ralph Connor.
Checked by John R. Johnson and E. A. Cleveland.

1. Procedure

(*A*) *p-Nitrobenzaldiacetate*.—In a 2-l. three-necked, round-bottomed flask equipped with a mechanical stirrer and a thermometer, and surrounded by an ice-salt bath, are placed 570 cc. (600 g.) of glacial acetic acid, 565 cc. (612 g., 6 moles) of acetic anhydride (Note 1), and 50 g. (0.36 mole) of *p*-nitrotoluene (Note 2). To this solution is added slowly, with stirring, 85 cc. (1.5 moles) of concentrated sulfuric acid (Note 3). When the mixture has cooled to 5°, 100 g. (1 mole) of chromium trioxide (Note 2) is added in small portions at such a rate that the temperature does not rise above 10° (Note 4), and stirring is continued for ten minutes after the chromium trioxide has been added. The contents of the flask are poured into two 3-l. beakers two-thirds filled with chipped ice, and cold water is added until the total volume is 5–6 l. The solid is separated by suction filtration and washed with cold water until the washings are colorless. The product is suspended in 500 cc. of cold 2 per cent sodium carbonate solution and stirred mechanically. After thorough mixing, the solid is collected on a filter (Note 5) and washed with cold water and finally with 20 cc. of cold alcohol. The product, after drying in a vacuum desiccator, weighs 44–49 g. (48–54 per cent of the theoretical amount), m.p. 120–122° (Note 6).

The crude material is suitable for hydrolysis, and for other reactions, without further purification. The pure diacetate may be obtained by recrystallizing from 150 cc. of hot alcohol. The hot solution is filtered through a fluted filter to remove insoluble impurities. The yield of pure *p*-nitrobenzaldiacetate is 43–46 g. (47–50 per cent of the theoretical amount), m.p. 125–126°.

(*B*) *p-Nitrobenzaldehyde*.—A mixture of 45 g. (0.18 mole) of crude *p*-nitrobenzaldiacetate, 100 cc. of water, 100 cc. of alcohol, and 10 cc. of concentrated

sulfuric acid is refluxed for thirty minutes and filtered through a fluted filter, and the filtrate is chilled in an ice bath. The crystals are separated by suction filtration, washed with cold water, and dried in a vacuum desiccator. The first crop weighs 22–24 g. (82–89 per cent of the theoretical amount), m.p. 106–106.5°. A second crop amounting to 2–3 g. is obtained by diluting the filtrate with about 300 cc. of water. The total yield is 24–25.5 g. (89–94 per cent of the theoretical amount) (Note 6).

2. Notes

1. The "practical" grade of acetic anhydride (95 per cent) gave yields as high as those obtained with 99–100 per cent acetic anhydride.
2. The *p*-nitrotoluene used was a "practical" grade, m.p. 50–51°. The chromium trioxide was a u.s.p. grade of 98 per cent purity.
3. If the sulfuric acid is added too rapidly, charring occurs.
4. It is essential that the temperature of the reaction mixture be maintained below 10°. If the oxidant is added so rapidly that this temperature is exceeded, the yield is lowered considerably. With a good ice-salt bath, the time required for the addition is forty-five to sixty minutes.
5. By acidification of the sodium carbonate washings, 7–10 g. of *p*-nitrobenzoic acid, m.p. 242–243°, is obtained.
6. This procedure appears to be generally applicable to the preparation of those substituted benzaldehydes in which the substituent is not attacked in the oxidation reaction. Thus, the submitters report that *p*-bromobenzaldehyde may be prepared by the same procedure, substituting 62 g. (0.37 mole) of *p*-bromotoluene for the *p*-nitrotoluene and carrying out the oxidation and isolation in the same manner. The yield of crude *p*-bromobenzaldiacetate is 51–64 g. (48–60 per cent of the theoretical amount), m.p. 90–92°. The pure diacetate is obtained by dissolving the crude product in 150 cc. of hot alcohol, filtering through a fluted filter, and cooling. Filtration gives 39–52 g. of pure material, m.p. 94–95°. A second crop is obtained by diluting the filtrate. The total yield is 47–56 g. (46–54 per cent of the theoretical amount, based on the bromotoluene). The crude product is hydrolyzed to *p*-bromobenzaldehyde by refluxing 45 g. (0.157 mole) with 100 cc. of water, 150 cc. of alcohol, and 10 cc. of concentrated sulfuric acid, filtering through a fluted filter, cooling, and filtering with suction. A second crop is obtained by diluting the filtrate with about 300 cc. of water. The product weighs 24–28 g. (83–96 per cent of the theoretical amount), m.p. 55–57°.
It is further reported that *p*-cyanotoluene furnishes *p*-cyanobenzaldehyde, the yield being about the same as that in the preparation of *p*-nitrobenzaldehyde. (Leonard Weisler, private communication.)

3. Discussion

p-Nitrobenzaldehyde has been prepared from *p*-nitrotoluene by treatment with isoamyl nitrite in the presence of sodium methoxide[1] or by oxidation with chromyl chloride,[2] cerium dioxide,[3] or chromium trioxide in the presence of acetic anhydride.[4] It can also

be prepared by the oxidation of *p*-nitrobenzyl chloride,[5] *p*-nitrobenzyl alcohol,[6] or the esters of *p*-nitrocinnamic acid.[7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 89
- Org. Syn. Coll. Vol. 3, 200
- Org. Syn. Coll. Vol. 4, 713

References and Notes

1. Angeli and Angelico, Atti accad. Lincei (5) **8**, II, 28 (1899) (Chem. Zentr. **1899**, II, 371).
2. Richter, Ber. **19**, 1060 (1886); Law and Perkin, J. Chem. Soc. **93**, 1635 (1908).
3. Farbw. vorm. Meister, Lucius, and Brüning, Ger. pat. 174,238 [Frdl. **8**, 150 (1905–07)].
4. Thiele and Winter, Ann. **311**, 353 (1900).
5. Fischer and Greiff, Ber. **13**, 669 (1880); Schmidt, Ger. pat. 15,881 [Frdl. **1**, 60 (1877–87)].
6. Cohen and Harrison, J. Chem. Soc. **71**, 1057 (1897); Walter, Ger. pat. 118,567 [Frdl. **6**, 131 (1900–02)].
7. Baeyer, Ger. pat. 15,743 [Frdl. **1**, 60 (1877–87)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alcohol (64-17-5)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

acetic anhydride (108-24-7)

sodium carbonate (497-19-8)

sodium methoxide (124-41-4)

p-cyanotoluene (104-85-8)

chromyl chloride

chromium trioxide (1333-82-0)

Isoamyl nitrite (110-46-3)

p-Nitrobenzaldiacetate (2929-91-1)

p-Nitrobenzaldehyde, Benzaldehyde, p-nitro- (555-16-8)

bromotoluene (95-46-5)

cerium dioxide

p-NITROBENZOIC ACID (62-23-7)

p-Bromotoluene (106-38-7)

p-Nitrobenzyl alcohol (619-73-8)

p-Bromobenzaldehyde (1122-91-4)

p-nitrotoluene (99-99-0)

p-bromobenzaldiacetate (55605-27-1)

p-cyanobenzaldehyde (105-07-7)

p-nitrobenzyl chloride (100-14-1)

esters of p-nitrocinnamic acid (619-89-6)

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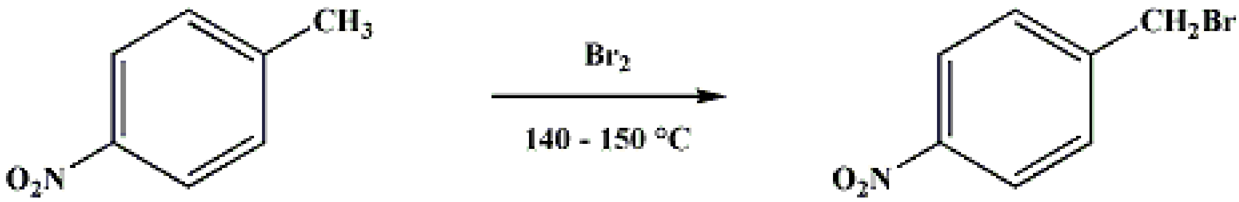
Organic Syntheses, CV 2, 443

p-NITROBENZYL BROMIDE

[Toluene, α-bromo-*p*-nitro-]



Submitted by G. H. Coleman and G. E. Honeywell.
Checked by W. H. Carothers and W. L. McEwen.

1. Procedure

In a 1-l. three-necked flask is placed 300 g. (2.2 moles) of technical *p*-nitrotoluene (m. p. 51–52°). The flask is fitted with a liquid-sealed stirrer, reflux condenser, and a separatory funnel arranged so that the stem reaches nearly to the bottom of the flask. The condenser is attached to a gas trap. The flask is heated in an oil bath at 145–150° (Note 1), and 368 g. (118 cc., 2.3 moles) of bromine is added dropwise over a period of two hours (Note 2).

After all the bromine has been added, the heating and stirring are continued for ten minutes. While still liquid, the contents of the flask (Note 3) are poured into a 5-l. round-bottomed flask containing 4 l. of hot ligroin (b.p. 90–100°), and 15 g. of Norite is added. The material is brought into solution by heating on an electric hot plate, and, after boiling for ten minutes, the solution is filtered rapidly with suction (Note 4). After cooling to 20°, the crystals are filtered with suction, pressed thoroughly, and washed with two 50-cc. portions of cold ligroin. The crude product, m.p. 94–97°, weighs 280–315 g. (59–66 per cent of the theoretical amount) and is sufficiently pure for some purposes.

For purification, this material is dissolved in 3–3.5 l. of hot ligroin, boiled with 10–15 g. of decolorizing carbon, and filtered with suction (Note 4). After cooling in an ice bath the crystals are collected on a Büchner funnel, pressed, and washed with two 25-cc. portions of cold ligroin. The pale yellow product melts at 97.5–99° and weighs 250–280 g. (53–59 per cent of the theoretical amount) (Note 5) and (Note 6).

2. Notes

1. The temperature should be kept within the limits mentioned to obtain the best results.
2. The bromine should be added within two hours even though a small amount may be lost through the condenser.
3. *p*-Nitrobenzyl bromide and its solution should be handled with caution. If the

substance comes in contact with the skin, bathing the affected parts in alcohol will give relief.

4. The inverted filtration method of Bost and Constable (p. 610) is particularly advantageous for filtering hot solutions of nitrobenzyl bromide, since it reduces the fire hazard and the manipulation of the lachrymatory solutions. To avoid clogging, a tube of 8- to 10-mm. bore must be used for connecting the filtering flasks. About 3.5 l. of ligroin may be recovered from the mother liquors.

5. *p*-Nitrobenzyl bromide has been used as a reagent for the identification of many acids[1] and phenols[2] by conversion into their *p*-nitrobenzyl esters and ethers.

6. It is reported that the bromination procedure described by Brewster[3] is simpler and more convenient than that given above if tungsten lamps are employed as a source of artificial light. The light from two 300-watt tungsten lamps is satisfactory for the bromination of 300 g. of *p*-nitrotoluene. The yield of *p*-nitrobenzyl bromide is 60–70 per cent of the theoretical amount. (Leonard Weisler and Donald Pearlman, private communication.)

3. Discussion

p-Nitrobenzyl bromide has usually been prepared by brominating *p*-nitrotoluene.[1], [3] It has also been prepared by treating *p*-nitrobenzyl alcohol with hydrobromic acid,[4] and by nitrating benzyl bromide.[5]

References and Notes

1. Reid, J. Am. Chem. Soc. **39**, 126 (1917); Lyons and Reid, ibid. **39**, 1728 (1917).
2. Reid, ibid. **39**, 304 (1917); Lyman and Reid, ibid. **42**, 615 (1920).
3. Brewster, ibid. **40**, 406 (1918).
4. Norris, Watt, and Thomas, ibid. **38**, 1077 (1916).
5. Moureu and Brown, Bull. soc. chim. (4) **29**, 1008 (1921).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ligroin

phenols

p-nitrobenzyl esters and ethers

HYDROBROMIC ACID (10035-10-6)

bromine (7726-95-6)

Norite, carbon (7782-42-5)

nitrobenzyl bromide

benzyl bromide (100-39-0)

p-Nitrobenzyl alcohol (619-73-8)

p-Nitrobenzyl bromide, Toluene, α-bromo-p-nitro- (100-11-8)

p-nitrotoluene (99-99-0)

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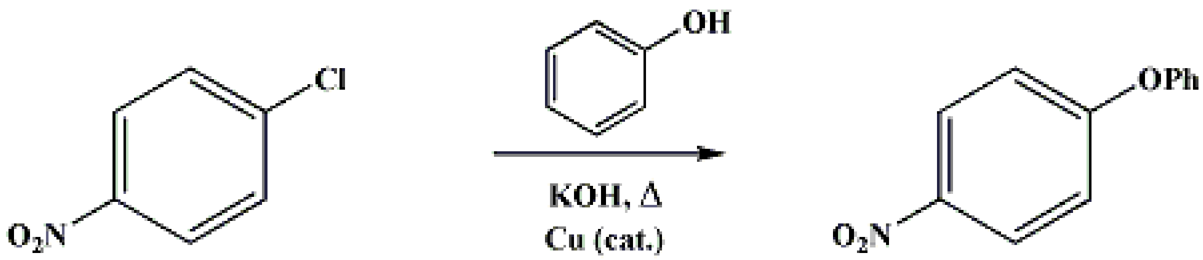
Organic Syntheses, CV 2, 445

p-NITRODIPHENYL ETHER

[Ether, *p*-nitrophenyl phenyl,]



Submitted by Ray Q. Brewster and Theodore Groening.
Checked by W. W. Hartman and J. B. Dickey.

1. Procedure

One hundred sixty grams (1.7 moles) of a good grade of phenol and 80 g. (1.43 moles) of potassium hydroxide are placed in a 2-l. flask, and the mixture is heated to 130–140° until all the alkali has dissolved. The potassium phenoxide is cooled to 100–110°, and 0.5 g. of copper catalyst (Note 1) and 78.8 g. (0.5 mole) of *p*-nitrochlorobenzene are added. The flask is then fitted with a mechanical stirrer, thermometer, and a reflux condenser. The stirrer is started, and the contents of the flask are warmed with a Bunsen burner to 150–160°, at which temperature a spontaneous reaction begins with ebullition and the separation of potassium chloride. The flame should be removed during this stage of the reaction. Boiling nearly ceases within five to seven minutes, and another 78.8 g. (0.5 mole) of *p*-nitrochlorobenzene is added. The mixture is again heated as before until a second spontaneous reaction begins. This also proceeds for about five minutes without the application of heat. When boiling due to the exothermic reaction has ceased, heat is applied and a temperature of 150–160° is maintained for an additional thirty minutes. The dark-colored melt is then poured into 1.5 l. of ice water containing 50 g. of sodium hydroxide and stirred well to remove excess phenol. The crude *p*-nitrodiphenyl ether separates as a dark brown crystalline mass which is allowed to settle. The product is filtered on a Büchner funnel, washed with 2 l. of water, and pressed as free from water as possible. After drying in the air it is distilled from a 500-cc. Claisen flask. The small fraction boiling up to 170°/8 mm., which contains *p*-nitrochlorobenzene, is discarded. A fraction boiling at 170–188°/8 mm. and weighing 14 g. is collected (Note 2). The main fraction boiling at 188–193°/8 mm. boils at 188–190°/8 mm. on redistillation with no fore-run and practically no residue. *p*-Nitrodiphenyl ether solidifies on cooling to diamond-shaped crystals melting at 56–58°. The yield is 173–177 g. (80–82 per cent of the theoretical amount) (Note 3).

2. Notes

1. An active copper powder can be prepared from copper sulfate. One hundred

grams (0.4 mole) of copper sulfate ($CuSO_4 \cdot 5H_2O$) is dissolved in 350 cc. of hot water in a 1-l. beaker. After cooling to room temperature 35 g. (0.53 gram atom) of zinc dust (more if necessary) is gradually added until the solution is decolorized. The precipitated copper is washed by decantation with water. Dilute hydrochloric acid (5 per cent) is added to the precipitate to remove the excess of the zinc, and agitation is continued until the escape of hydrogen ceases. The copper powder is filtered, washed with water, and kept in a moist condition in a carefully stoppered bottle.
2. This fraction on redistillation yields 4 g. of *p*-nitrodiphenyl ether.
3. A yield of 84 per cent of *o*-nitrodiphenyl ether boiling at 183–185°/8 mm. is obtained when *o*-nitrochlorobenzene is used. For the preparation of *m*-nitrodiphenyl ether, the method of Ullmann and Sponagel,[1] using *m*-bromonitrobenzene, seems to be the best, since *m*-chloronitrobenzene gives large amounts of tarry matter.

3. Discussion

p-Nitrodiphenyl ether has been prepared by the nitration of diphenyl ether[2] and by heating *p*-nitrochlorobenzene[3] or *p*-nitrofluorobenzene[4] with potassium phenoxide and phenol.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 62
- Org. Syn. Coll. Vol. 3, 566

References and Notes

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2. Suter, J. Am. Chem. Soc. **51**, 2583 (1929).
3. Haeussermann and Teichmann, Ber. **29**, 1446 (1896).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

phenol (108-95-2)

copper sulfate (7758-98-7)

copper, copper powder (7440-50-8)

potassium hydroxide (1310-58-3)

zinc (7440-66-6)

m-Bromonitrobenzene (585-79-5)

m-Chloronitrobenzene (121-73-3)

o-nitrochlorobenzene (88-73-3)

potassium chloride (7447-40-7)

potassium phenoxide

diphenyl ether (101-84-8)

p-nitrochlorobenzene (100-00-5)

p-Nitrodiphenyl ether, Ether, p-nitrophenyl phenyl (620-88-2)

o-Nitrodiphenyl ether (2216-12-8)

m-nitrodiphenyl ether (620-55-3)

p-nitrofluorobenzene (350-46-9)

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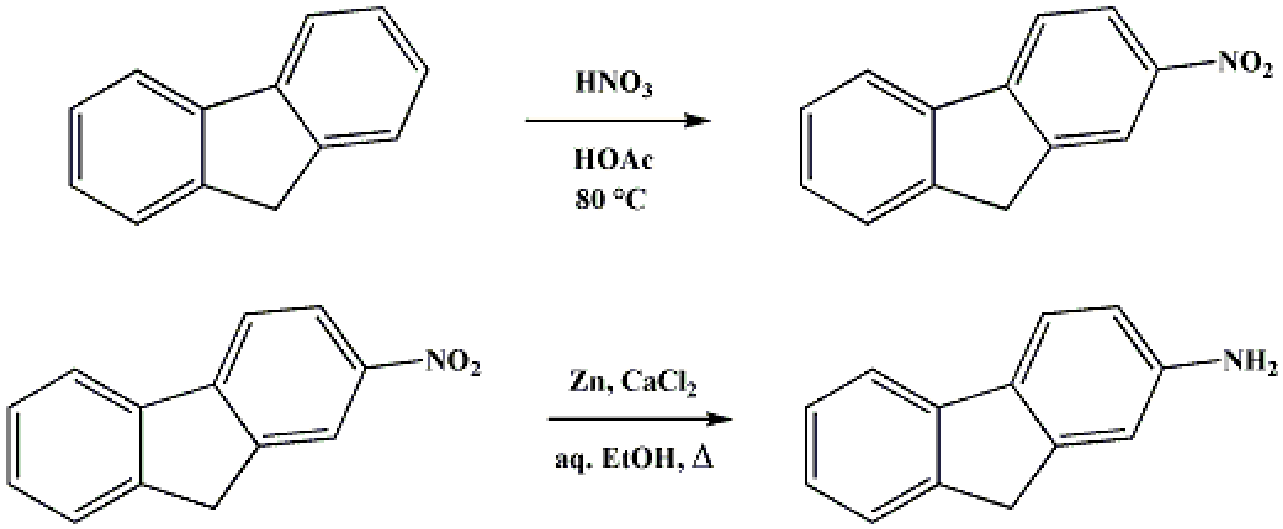
Organic Syntheses, CV 2, 447

2-NITROFLUORENE AND 2-AMINOFLUORENE

[Fluorene, 2-nitro-, and 2-Fluorenylamine]



Submitted by W. E. Kuhn
Checked by Louis F. Fieser and J. T. Walker.

1. Procedure

(*A*) *2-Nitrofluorene*.—Sixty grams (0.36 mole) of fluorene (Note 1) is dissolved in 500 cc. of warm glacial acetic acid in a 1-l. three-necked flask fitted with a thermometer, a mechanical stirrer, and a dropping funnel, and supported in a water bath. The temperature is brought to 50°, and 80 cc. (1.3 moles) of concentrated nitric acid (sp. gr. 1.42) is added with stirring in the course of fifteen minutes. During the addition, the solution becomes slightly yellow, and a small amount of material precipitates. The water bath is slowly brought to 60–65°, when the precipitate dissolves and the color of the solution deepens. Stirring is continued, and heat is applied continuously until the temperature of the mixture reaches 80° (Note 2). After five minutes, the water bath is removed, and the mixture, which now consists of a semi-solid paste of fine, yellow needles, is allowed to cool to room temperature during two hours. The product is collected on a Büchner funnel, sucked as dry as possible, and washed with two 25-cc. portions of cold glacial acetic acid containing 0.5 g. of potassium acetate. It is then washed several times with water and dried. The 2-nitrofluorene so obtained melts at 155–156° and is sufficiently pure for most purposes. The yield is 60 g. (79 per cent of the theoretical amount).

If a purer product is desired, the above material may be crystallized from 200 cc. of glacial acetic acid. The purified product melts at 157° and weighs 56 g.

(*B*) *2-Aminofluorene*.—In a 2-l. round-bottomed flask, 30 g. (0.14 mole) of dried and powdered 2-nitrofluorene is made into a thin paste with 1 l. of 78 per cent alcohol (820 cc. of 95 per cent alcohol and 180 cc. of water). A solution of 10 g. of calcium chloride in 15 cc. of water, together with 300 g. of zinc dust, is added to the suspension, and the whole is thoroughly mixed. The flask is fitted with an effective reflux condenser, and the mixture is refluxed for two hours.

The sludge of zinc dust and zinc oxide is filtered from the boiling solution and extracted (Note

3) with 50 cc. of boiling 78 per cent alcohol. The combined filtrates are then poured into 2 l. of water, whereupon a white, flocculent precipitate is obtained. This is filtered with suction and recrystallized from 400 cc. of hot 50 per cent alcohol. The purified 2-aminofluorene crystallizes in needles melting at 127.5°. The yield is 20–21 g. (78–82 per cent of the theoretical amount).

2. Notes

1. The fluorene used had a melting point of 113–114° and was obtained from the Gesellschaft für Teerverwertung, Duisberg-Meiderich.
2. The reaction is exothermic at this point, and the temperature of the reaction mixture may be expected to rise ten to fifteen degrees above that of the surrounding bath. If the temperature is allowed to rise above 85°, the 2-nitrofluorene will be highly colored and impure.
3. The sludge of zinc dust and zinc oxide is filtered while hot, through a previously warmed filter. Unless the solution is kept near the boiling point, some of the compound will crystallize during the filtration. If a small amount of zinc dust runs through the filter paper, it is advisable to heat the filtrate to the boiling point and refilter without suction through a folded filter paper in a hot water or steam jacket.

3. Discussion

The procedures given are essentially those of Diels.[1] 2-Nitrofluorene has also been prepared by passing nitrous vapors into a benzene solution of fluorene.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 30

References and Notes

1. Diels, Ber. **34**, 1758 (1901).
2. Monti, Martello, and Valente, Gazz. chim. ital. **66**, 31 (1936).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alcohol (64-17-5)

calcium chloride (10043-52-4)

acetic acid (64-19-7)

Benzene (71-43-2)

nitric acid (7697-37-2)

zinc (7440-66-6)

zinc oxide

potassium acetate (127-08-2)

2-Nitrofluorene, Fluorene, 2-nitro- (607-57-8)

2-Aminofluorene, 2-Fluorenylamine (153-78-6)

fluorene (86-73-7)

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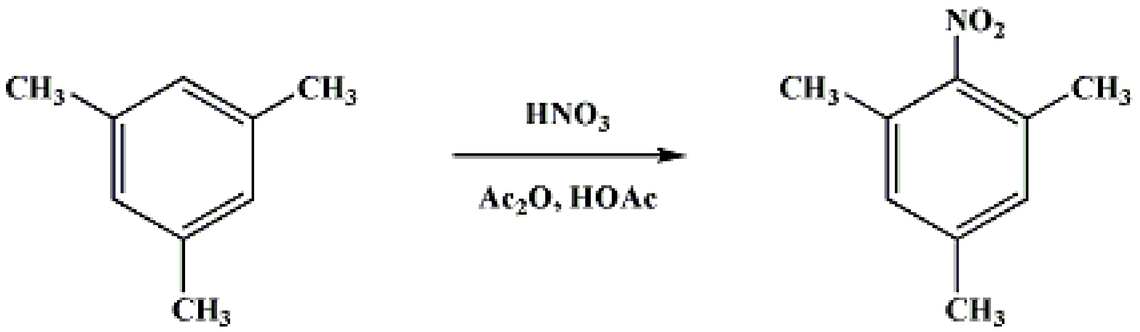
Organic Syntheses, CV 2, 449

NITROMESITYLENE

[Mesitylene, 2-nitro-]



Submitted by Garfield Powell and F. R. Johnson.
Checked by W. W. Hartman and J. B. Dickey.

1. Procedure

In a 500-cc. three-necked, round-bottomed flask, provided with a mechanical stirrer, a dropping funnel, and a thermometer well, are placed 40 g. (0.333 mole) of mesitylene (Org. Syn. Coll. Vol. I, **1941**, 341) and 60 g. (55.5 cc.) of acetic anhydride (Note 1). The flask is placed in a bath of ice and water, and the reaction mixture is cooled below 10°. A solution of 31.5 g. (20.8 cc., 0.5 mole) of fuming nitric acid (sp. gr. 1.51) in 20 g. (19.1 cc.) of glacial acetic acid and 20 g. (18.5 cc.) of acetic anhydride (Note 2) is added, with stirring, over a period of forty minutes, the temperature being kept between 15° and 20°.

When the addition of the nitric acid solution is complete, the reaction mixture is removed from the ice bath and allowed to stand at room temperature for two hours. The flask is then warmed, with shaking, to 50° on a water bath (Note 3) and maintained at that temperature for ten minutes. The cooled reactants are then poured slowly into 800 cc. of ice water and well stirred. About 40 g. of sodium chloride is added, and the aqueous layer is decanted and extracted with 200–250 cc. of a commercial grade of ether. The ethereal extract is added to the residual nitromesitylene, and this ethereal solution is washed with three or four 30-cc. portions of a 10–15 per cent sodium hydroxide solution until the water extract is distinctly alkaline. The ether is then distilled from a steam bath. The residue, after the addition of about 150 cc. of 10 per cent sodium hydroxide solution, is steam-distilled until a test sample of the distillate is clear and free of oil drops. The steam distillation requires about three hours, during which time 1.5 l. of distillate is collected. The nitromesitylene settles to the bottom of the distillate. The water is decanted through a filter paper, and the residue is dissolved in 30 cc. of ether. The filter paper, if it contains any solid particles, is washed with 10 cc. of ether, and the two fractions are combined and placed in a 150-cc. distilling flask with a water-cooled receiver. After

removal of the ether on a steam bath, the yellow residue is distilled with a free flame. All but 0.5 to 1.5 g. of material distils at 243–250°, and the distillate, which weighs 47 g., solidifies on cooling. The yellow crystalline product is purified by dissolving in 25 cc. of commercial methyl alcohol and cooling with stirring in a bath of ice and salt. The crystals are then filtered on a small Büchner funnel and washed twice with 5-cc. portions of cold methyl alcohol. From the wash alcohol, by exactly the same procedure, there is obtained 6–8 g. of crude crystals boiling at 243–249°. This material yields on crystallization 4 g. of pure nitromesitylene. The pure nitromesitylene, which has a light yellow color, melts at 43–44°. The yield is 41–42 g. (74–76 per cent of the theoretical amount).

2. Notes

1. A commercial grade of 85 per cent acetic anhydride is of sufficient purity.
2. The nitric acid is added with care to the acetic acid-acetic anhydride solution, the temperature being kept below 20° by means of a bath of ice and salt. An **explosive** reaction will take place if the nitric acid is added too rapidly.
3. A higher temperature is not advisable.

3. Discussion

Nitromesitylene has been prepared by the direct nitration of mesitylene with concentrated nitric acid;[1] by the action of benzoyl nitrate on mesitylene in carbon tetrachloride at low temperature;[2] and from dinitromesitylene by reduction of one nitro group and replacement of the resulting amino group by hydrogen.[3]

References and Notes

1. Fittig and Storer, Ann. **147**, 1 (1868); Biedermann and Ledoux, Ber. **8**, 58 (1875); Schultz, ibid. **17**, 477 (1884); Bamberger and Rising, ibid. **33**, 3625 (1900).
2. Francis, ibid. **39**, 3801 (1906).
3. Ladenburg, ibid. **7**, 1135 (1874).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

acetic acid (64-19-7)

methyl alcohol (67-56-1)

ether (60-29-7)

acetic anhydride (108-24-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

nitric acid (7697-37-2)

sodium chloride (7647-14-5)

carbon tetrachloride (56-23-5)

Mesitylene (108-67-8)

Nitromesitylene

Mesitylene, 2-nitro- (603-71-4)

benzoyl nitrate

dinitromesitylene

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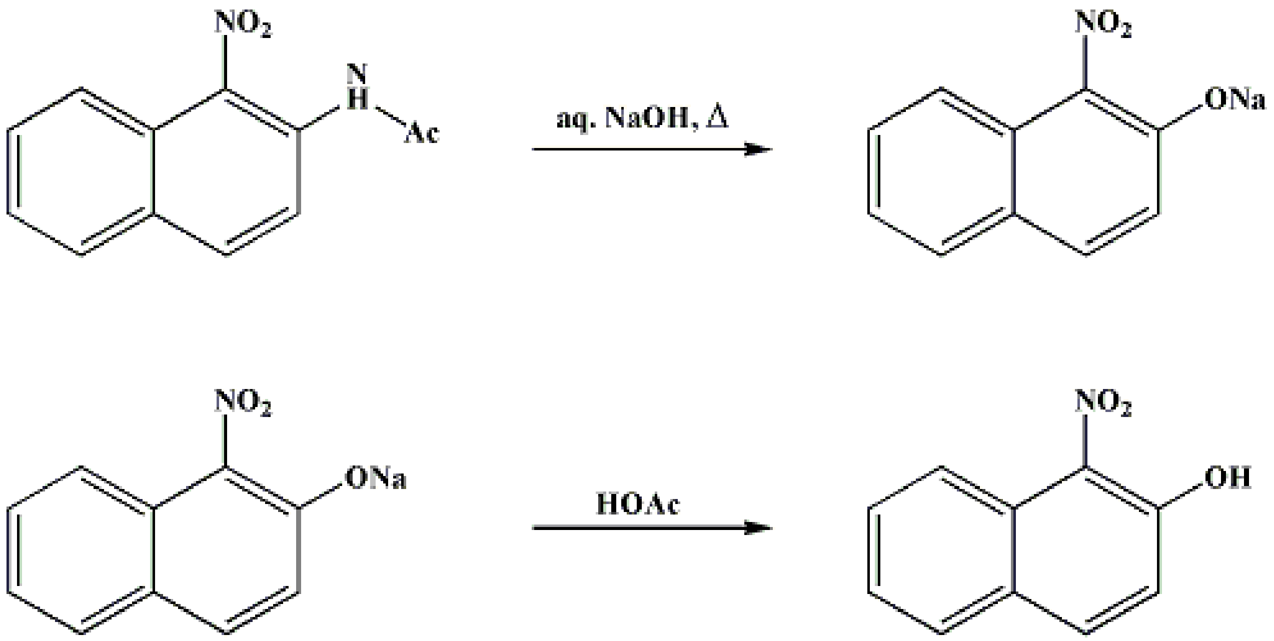
Organic Syntheses, CV 2, 451

1-NITRO-2-NAPHTHOL

[2-Naphthol, 1-nitro-]



Submitted by W. W. Hartman, J. R. Byers, and J. B. Dickey.
Checked by Louis F. Fieser and J. T. Walker.

1. Procedure

In a 3-l. round-bottomed flask, fitted with a reflux condenser, are placed 100 g. (0.435 mole) of 1-nitro-2-acetylaminonaphthalene (p. 438) and a solution of 112 g. (2.8 moles) of sodium hydroxide in 2.7 l. of water (Note 1). The mixture is boiled until ammonia is no longer evolved (six to seven hours). The solution becomes deep red in color. It contains suspended crystals of sodium nitronaphthoxide; these are dissolved by the addition of 1 l. of hot water. The small amount of insoluble material is removed by filtration, washed with hot water until the washings are colorless, and then discarded although it contains a little nitronaphthylamine. The combined washings and filtrate are made acid by adding 500 cc. of glacial acetic acid. The nitronaphthol precipitates as small, bright yellow crystals which are filtered on a 10-cm. Büchner funnel, washed with water, and dried. The yield of material melting at 101–103° is 76–81 g. (92–98 per cent of the theoretical amount).

The product is purified by recrystallization from 500 cc. of methyl alcohol containing 5 cc. of concentrated hydrochloric acid. The first crop of crystals amounts to 60 g. and melts at 103–104°. The mother liquors are concentrated to 150 cc., and a second crop weighing 12–13 g. is collected. The total yield of recrystallized material is 72–73 g. (88–89 per cent of the theoretical amount).

2. Notes

1. This concentration of alkali was found to be very satisfactory. The hydrolysis takes

place rather rapidly at first when stronger alkali is used, with the precipitation of the sodium salt which forms a thick paste and causes bumping. When more dilute alkali is used, much more time is required to complete the hydrolysis.

3. Discussion

1-Nitro-2-naphthol has been prepared by the nitration of β-naphthyl ethyl ether;[1, 2] by the oxidation of 1-nitroso-2-naphthol;[3] and by the treatment of β-naphthol with diacetylnitric acid.[4] It has also been prepared by the treatment of β-naphthylamine with three moles of sodium nitrite in the presence of an excess of acid;[5] by the decomposition of benzeneazo-β-naphthol with nitric acid;[6] by heating the nitrate of pseudocumeneazo-β-naphthol under reduced pressure;[6] by the treatment of 1-bromo-2-naphthol in acetic acid with nitric acid;[7] and by the reaction of nitrogen dioxide with β-naphthol.[7] It has been prepared from 1-nitro-1-bromo-2-ketodihydronaphthalene by treatment with caustic alkali,[8] and by the fusion of α-nitronaphthalene with sodium hydroxide.[9]

The method on which this procedure is based has been described by Andreoni and Biedermann and by others.[10]

References and Notes

1. Wittkampf, Ber. **17**, 393 (1884).
2. Gaess, J. prakt. Chem. (2) **43**, 22 (1891).
3. Stenhouse and Groves, Ann. **189**, 151 (1877); Fierz-David and Ischer, Helv. Chim. Acta **21**, 680 (1938).
4. Pictet and Krijanowski, Arch. sci. phys. nat. Genève (4) **16**, 191 (1903) (Chem. Zentr. **1903**, II, 1109).
5. Deninger, J. prakt. Chem. (2) **40**, 300 (1889).
6. Charrier and Ferreri, Gazz. chim. ital. **44** (I) 176 (1914).
7. Armstrong and Rossiter, Ber. **24** (R), 720 (1891); J. Chem. Soc. Proc. **1891**, 87, 89.
8. Fries, Ann. **389**, 317 (1912).
9. Wohl, Ger. pat. 116,790 [Frdl. **6**, 114 (1900–02)].
10. Andreoni and Biedermann, Ber. **6**, 342 (1873); Jacobson, ibid. **14**, 806 (1881); Liebermann and Jacobson, Ann. **211**, 46 (1882).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

diacetylnitric acid

sodium nitronaphthoxide

nitrate of pseudocumeneazo-β-naphthol

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ammonia (7664-41-7)

methyl alcohol (67-56-1)

sodium hydroxide (1310-73-2)

nitric acid (7697-37-2)

sodium nitrite (7632-00-0)

β-naphthol (135-19-3)

nitrogen dioxide (10102-44-0)

α-nitronaphthalene (86-57-7)

1-nitroso-2-naphthol (131-91-9)

1-Nitro-2-acetylaminonaphthalene (5419-82-9)

1-Nitro-2-naphthol, 2-Naphthol, 1-nitro- (550-60-7)

nitronaphthylamine

nitronaphthol (607-24-9)

β-naphthyl ethyl ether (93-18-5)

benzeneazo-β-naphthol

1-bromo-2-naphthol (573-97-7)

1-nitro-1-bromo-2-ketodihydronaphthalene

β-naphthylamine (91-59-8)

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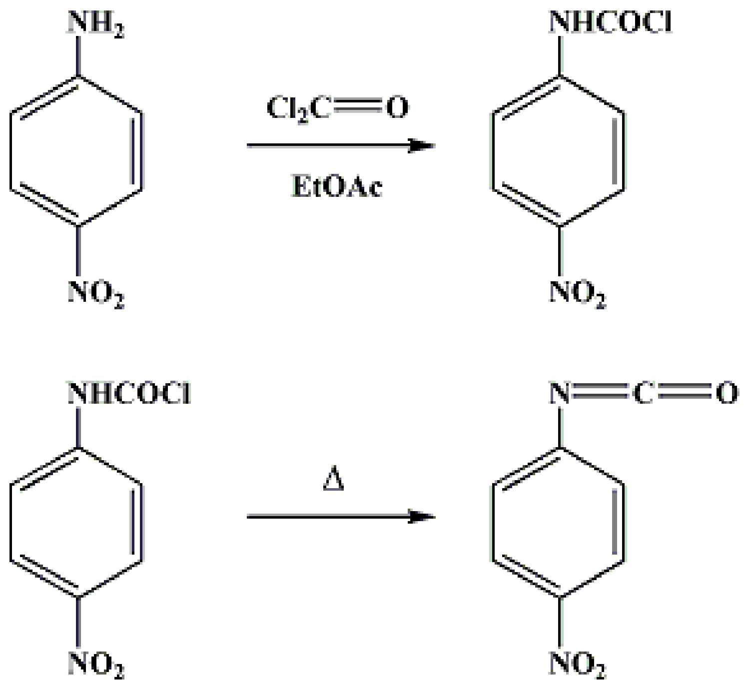
Organic Syntheses, *CV 2*, 453

p-NITROPHENYL ISOCYANATE

[Isocyanic acid, *p*-nitrophenyl ester]

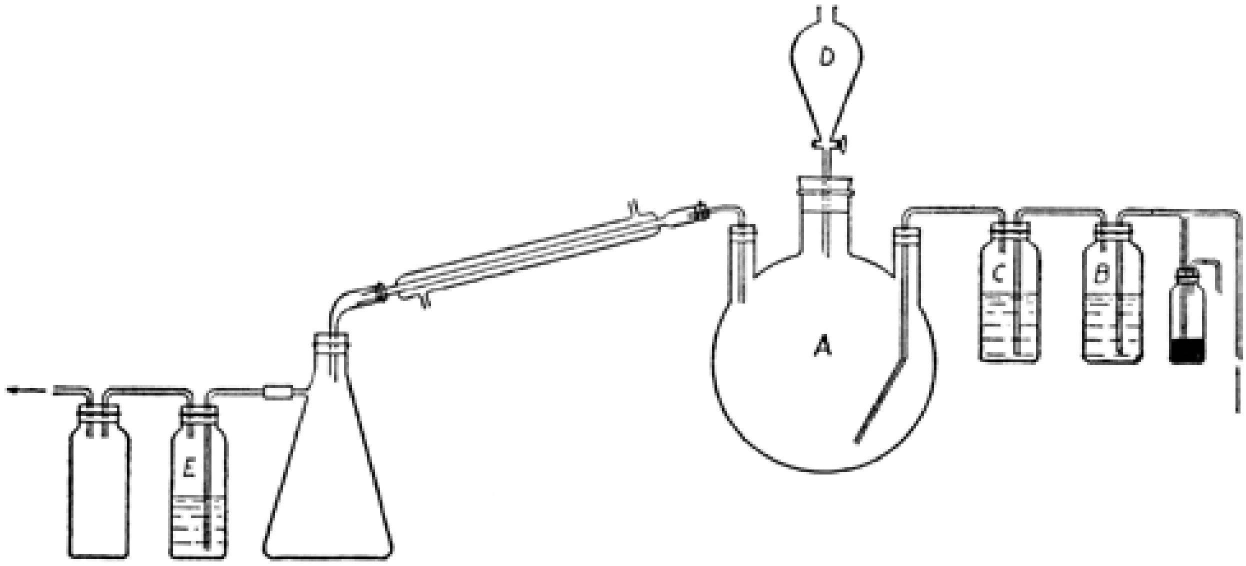


Submitted by R. L. Shriner, W. H. Horne, and R. F. B. Cox.
Checked by W. W. Hartman and J. B. Dickey.

1. Procedure

The apparatus is shown in .htmFig. 16. Phosgene is introduced at one end of the apparatus, and gentle suction is applied at the other. In the 5-l. flask, A, 500 cc. of dry ethyl acetate (Note 1) is saturated with phosgene at room temperature. The phosgene is purified by bubbling it through cottonseed oil, B, to remove chlorine, and then through concentrated sulfuric acid, C, as shown in the figure (Note 2). A solution of 150 g. (1.09 moles) of *p*-nitroaniline in 1.5 l. of dry ethyl acetate is run in slowly from the separatory funnel, D, over a period of three to four hours. The addition of the *p*-nitroaniline solution must be at such a rate that the precipitate of *p*-nitroaniline hydrochloride that is formed at first is allowed to dissolve and not accumulate (Note 3). During this time a steady stream of phosgene is passed through the solution to ensure an excess (Note 4). Towards the end of the reaction, the solution must be boiled gently with a Bunsen flame to break up the lumps of *p*-nitroaniline hydrochloride which otherwise dissolve very slowly.

Fig. 16



After the addition of the last of the *p*-nitroaniline, the stream of phosgene is continued for five minutes and then shut off. The flame under the flask is then turned up and the ethyl acetate distilled. Care must be taken at the end not to overheat the residue. The brown residue (Note 5) is treated with 800 cc. of hot dry carbon tetrachloride, and the insoluble residue (the disubstituted urea) is removed by filtration.

About two-thirds of the carbon tetrachloride is distilled. The solution is cooled, and the crystals of *p*-nitrophenyl isocyanate are filtered as quickly as possible in order to avoid prolonged exposure of the compound to the moisture of the air. By concentration of the mother liquor a further crop is obtained. The product is recrystallized from dry carbon tetrachloride and is obtained in the form of light yellow needles melting at 56–57° (Note 6). The yield after one recrystallization is 152–170 g. (85–95 per cent of the theoretical amount) (Note 7).

2. Notes

1. The ethyl acetate, free from ethyl alcohol, is dried with anhydrous magnesium sulfate.
2. This arrangement permits the phosgene reaction to be carried out conveniently and without danger, provided that a good hood and an exhaust fan are available. A slight vacuum is maintained in the system. The excess phosgene is absorbed in 20 per cent sodium hydroxide solution, E.
Although phosgene can be shipped only in steel cylinders in the United States, in some other countries it is available in glass ampoules. If an ampoule of phosgene is used in this preparation, only one-third the weight of *p*-nitroaniline necessary to react with the phosgene should be taken. In this way an excess of phosgene is assured; compare (Note 4). Because of the danger involved, the use of glass ampoules of phosgene is not recommended.
3. The mixture may be warmed if necessary to dissolve the *p*-nitroaniline hydrochloride.
4. The excess of phosgene retards the following reaction: *p*-$NO_2C_6H_4NHCOCl$ + *p*-

$NO_2C_6H_4NH_2$ → *p*-$NO_2C_6H_4NHCONHC_6H_4NO_2$-*p* + HCl

5. The crude residue is a mixture of *p*-nitroaniline hydrochloride, *p*-nitrophenyl carbamyl chloride, *p*-nitrophenyl isocyanate, and *p,p'*-dinitrodiphenylurea. The *p*-nitrophenyl carbamyl chloride is converted to *p*-nitrophenyl isocyanate during recrystallization from the hot carbon tetrachloride.

6. The freshly prepared material melts at 56–57° but after storage soon starts to melt at 54°, particularly if the bottle in which it is stored is opened occasionally. In contact with the moisture of the air, *p,p'*-dinitrodiphenylurea is formed (m.p. 360°). This reaction with water is avoided if the material is sealed in a glass container.

7. *p*-Nitrophenyl isocyanate distils undecomposed at 160–162°/18 mm.

3. Discussion

p-Nitrophenyl isocyanate has been prepared by heating *p*-nitrophenyl carbamyl chloride. The latter has been obtained by the action of phosgene on *p*-nitroaniline in benzene-toluene solutions,[1] and by the action of phosphorus pentachloride on methyl *p*-nitrophenylcarbamate.[2] The preparation given above is based upon directions published by the submitters.[3]

References and Notes

1. Vittenet, Bull. soc. chim. (3) **21**, 586 (1899); Van Hoogstraten, Rec. trav. chim. **51**, 418 (1932).
2. Swartz, Am. Chem. J. **19**, 318 (1897).
3. Shriner and Cox, J. Am. Chem. Soc. **53**, 1603 (1931); Horne and Shriner, ibid **53**, 3186 (1931).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethyl alcohol (64-17-5)

sulfuric acid (7664-93-9)

Benzene (71-43-2)

ethyl acetate (141-78-6)

sodium hydroxide (1310-73-2)

phosphorus pentachloride (10026-13-8)

carbon tetrachloride (56-23-5)

chlorine (7782-50-5)

toluene (108-88-3)

phosgene (75-44-5)

magnesium sulfate (7487-88-9)

p-NITROPHENYL ISOCYANATE, Isocyanic acid, p-nitrophenyl ester (100-28-7)

p-nitroaniline (100-01-6)

p-nitroaniline hydrochloride (15873-51-5)

p-nitrophenyl carbamyl chloride

p,p'-dinitrodiphenylurea

methyl p-nitrophenylcarbamate (1943-87-9)

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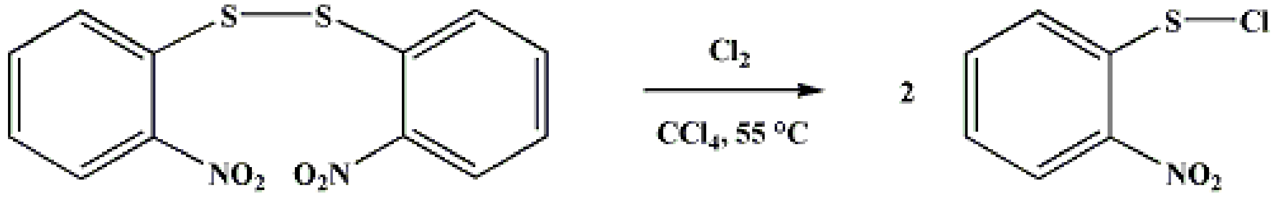
o-NITROPHENYLSULFUR CHLORIDE

[Benzenesulfenyl chloride, *o*-nitro-]



Submitted by Max H. Hubacher
Checked by Louis F. Fieser and D. J. Potter.

1. Procedure

In a 1-l. three-necked flask, fitted with a thermometer, a reflux condenser, and an inlet tube extending to the bottom of the flask and drawn out to a small opening, are placed 600 cc. of dry carbon tetrachloride, 154 g. (0.5 mole) of di-*o*-nitrophenyl disulfide, m.p. 193–195° (Org. Syn. Coll. Vol. I, **1941**, 220), and 0.25 g. of iodine. To the upper end of the condenser is attached a glass tube which dips below the surface of a little carbon tetrachloride contained in a test tube. A current of chlorine, dried with sulfuric acid, is passed into the reaction mixture, the temperature of which is maintained at 50–60°. The rate of flow of the chlorine (about 16–17 g. per hour) is regulated so that little or no gas escapes through the carbon tetrachloride trap. The yellow di-*o*-nitrophenyl disulfide gradually disappears, and after two to two and one-half hours a homogeneous, dark yellow solution is obtained (Note 1). The warm solution is filtered from a small amount of dark residue through a warm Büchner funnel, the flask and filter being rinsed with 30 cc. of warm carbon tetrachloride. The yellow filtrate (Note 2) is cooled to 5° and the product allowed to crystallize. The cake of crystals is broken with a rod, collected on a Büchner funnel, and drained well. The product is dried rapidly (two hours) at 50° and bottled (Note 3). This material melts at 73–74.5° and weighs 126–135 g. (66–71 per cent of the theoretical amount). A further crop is obtained by removing the solvent from the mother liquor by distillation from a water bath (Note 4), the dark, residual oil being poured into an evaporating dish. The last traces of carbon tetrachloride are removed by drying at 50°, during which process the oil crystallizes. This material melts at 67–72° and weighs 48–58 g. It is pure enough for most purposes (Note 5). The total yield is 183–184 g. (96–97 per cent of the theoretical amount) (Note 6) and (Note 7).

2. Notes

1. An excess of chlorine will do no harm.

2. For many purposes this filtered solution can be used without purification after distilling about 100 cc. of the solvent to remove the excess chlorine. The yield of material in solution is considered as 98 per cent of the theoretical amount.

3. The pure material melts at 74.5–75°. When in contact with moist air, *o*-nitrophenylsulfur chloride decomposes within a few days, giving off hydrogen

chloride. Stored in a brown, glass-stoppered bottle and sealed well, the material can be kept for many months.

4. Since *o*-nitrophenylsulfur chloride decomposes spontaneously when heated to about 170°, it is advisable to use a water bath when removing the solvent.

5. This material may be crystallized from hot carbon tetrachloride (2 cc. per gram), the filtered solution being cooled to 5°. The recovery of a product melting at 70–73° is 75 per cent.

6. Practically the same method can be used for the preparation of *o*-nitro-*p*-chlorophenylsulfur chloride (m.p. 95–97°); the chlorination of the disulfide (m.p. 212–213°) in this case proceeds much more slowly. 2,4-Dinitrophenylsulfur chloride can be prepared by the chlorination of the corresponding disulfide in nitrobenzene suspension at 120–130°. As the chloride is explosive the solvent must be removed by distillation in vacuum at 130°. The crude material melts at 89–92°. After crystallization from carbon tetrachloride it melts at 94–95°.

7. The arylsulfur chlorides are used for the introduction of the ArS- group, their reactions being analogous to those of acid chlorides.

3. Discussion

o-Nitrophenylsulfur chloride has always been prepared by the chlorination of the disulfide.[1]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 843

References and Notes

1. Zincke, Ber. **44**, 770 (1911); Zincke and Farr, Ann. **391**, 63 (1912).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

hydrogen chloride (7647-01-0)

carbon tetrachloride (56-23-5)

iodine (7553-56-2)

chlorine (7782-50-5)

Nitrobenzene (98-95-3)

2,4-Dinitrophenylsulfur chloride (528-76-7)

Di-o-nitrophenyl disulfide (1155-00-6)

o-Nitrophenylsulfur chloride, Benzenesulfenyl chloride, o-nitro- (7669-54-7)

o-Nitro-p-chlorophenylsulfur chloride (4153-06-4)

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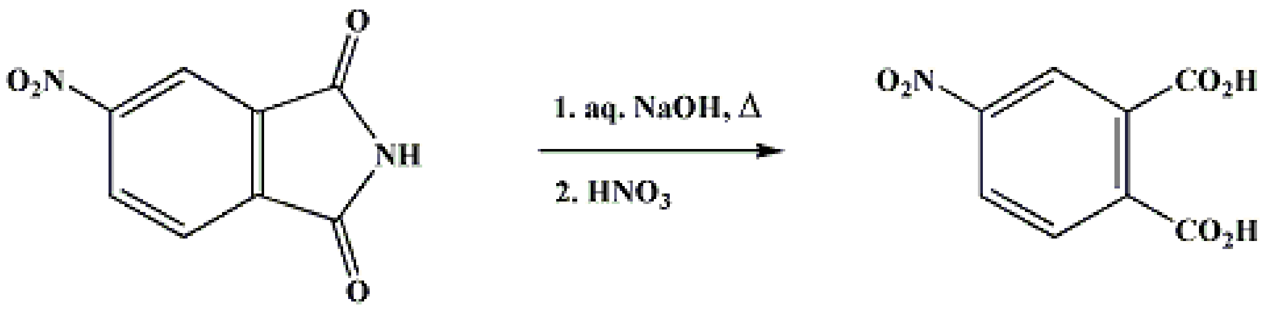
Organic Syntheses, CV 2, 457

4-NITROPHTHALIC ACID

[Phthalic acid, 4-nitro-]



Submitted by E. H. Huntress, E. L. Shloss, Jr, and P. Ehrlich.
Checked by W. W. Hartman and G. W. Sawdey.

1. Procedure

To a solution of 26.6 g. (0.66 mole) of sodium hydroxide in 240 cc. of water is added 80 g. (0.416 mole) of 4-nitrophthalimide (p. 459) (Note 1). The mixture is heated rapidly to boiling and boiled gently for ten minutes. The solution is made barely acid to litmus with concentrated nitric acid (sp. gr. 1.42); after the neutral point is reached, an additional 70 cc. (100 g., 1.1 moles) of nitric acid is added (Note 2). The solution is again boiled for three minutes, then cooled below room temperature, transferred to a 1-l. separatory funnel, and extracted with two 300-cc. portions of alcohol-free ether (Note 3). Care is taken to ensure thorough mixing before separation of the layers. After the extract is dried over anhydrous sodium sulfate, the ether is distilled until solid begins to separate. The concentrated ether solution is poured into a porcelain dish and the residual solvent allowed to evaporate in a hood (Note 4). The practically white crystals of 4-nitrophthalic acid which separate melt at 163–164° and have a neutralization equivalent of 105.5 (theoretical, 105.5). The yield is 85–87 g. (96–99 per cent of the theoretical quantity).

2. Notes

1. If a large amount of 4-nitrophthalimide is to be hydrolyzed, it will generally be found convenient to carry out a series of small runs of the size given here.
2. The quantity of alkali used at the start is sufficient to neutralize the nitroimide and leave the resulting alkaline solution approximately 1 *N*. When the solution is neutralized the red color changes to a dirty brown, which turns to a pale yellow on acidification. The 70-cc. portion of concentrated nitric acid suffices to set free all the 4-nitrophthalic acid but avoids the presence of a large excess during the ether extraction.
Nitric acid appears to be preferable to hydrochloric or sulfuric acid. The yields are similar, but the product obtained using nitric acid is pure white and in better

physical condition.
3. The simultaneous presence of nitric acid and alcohol in the ether extract must be avoided as explosive oxidation might occur during evaporation of the ether. Furthermore, the presence of alcohol may lead to contamination of the product with traces of the acid ester.
4. Evaporation of the last portion of ether proceeds slowly; the rather soft, fluffy crystals of acid which separate at first gradually become hard and dense. No trouble was experienced from nitric acid remaining with the ether extract, if the ether was free from alcohol and the specified amount of nitric acid was used.

3. Discussion

4-Nitrophthalic acid has usually been prepared by nitration of phthalic acid[1] or phthalic anhydride,[2], [3] followed by separation from the accompanying 3-nitrophthalic acid.[4], [5], [6] It has also been prepared from 6-nitro-2-naphthol-4-sulfonic acid (obtained from the technical diazoanhydride of 6-nitro-1-amino-2-naphthol-4-sulfonic acid).[7] The present procedure is more convenient than any of the earlier methods.

References and Notes

1. Miller, Ann. **208**, 223 (1881); Huisinga, Rec. trav. chim. **27**, 261 (1908).
2. Levy and Stephen, J. Chem. Soc. **1931**, 79.
3. Culhane and Woodward, Org. Syn. Coll. Vol. I, **1941**, 408.
4. Bogert and Boroschek, J. Am. Chem. Soc. **23**, 752 (1901).
5. Cohen, Woodroffe, and Anderson, J. Chem. Soc. **109**, 232 (1916).
6. Lawrance, J. Am. Chem. Soc. **42**, 1872 (1920).
7. Ruggli, Knapp, Merz, and Zimmerman, Helv. Chim. Acta **12**, 1043 (1929).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alcohol-free ether

hydrochloric or sulfuric acid

diazoanhydride of 6-nitro-1-amino-2-naphthol-4-sulfonic acid

ether (60-29-7)

sodium hydroxide (1310-73-2)

nitric acid (7697-37-2)

sodium sulfate (7757-82-6)

3-Nitrophthalic acid (603-11-2)

phthalic anhydride (85-44-9)

4-nitrophthalic acid, Phthalic acid, 4-nitro- (610-27-5)

phthalic acid (88-99-3)

4-Nitrophthalimide (89-40-7)

6-nitro-2-naphthol-4-sulfonic acid

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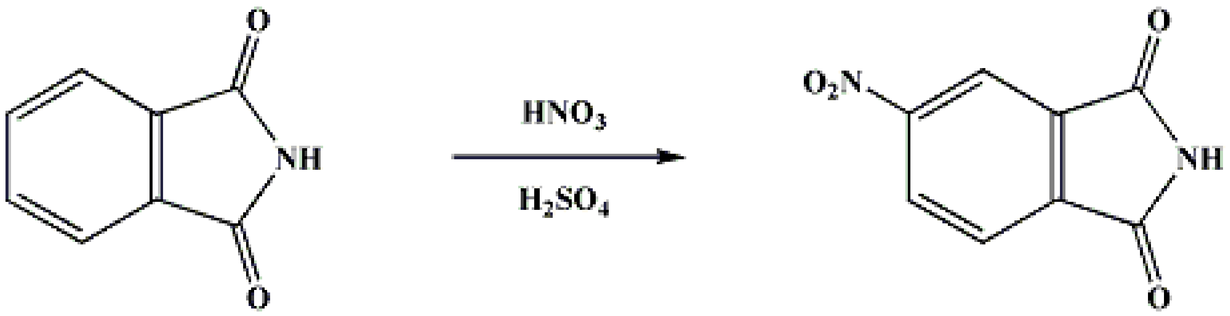
Organic Syntheses, CV 2, 459

4-NITROPHTHALIMIDE

[Phthalimide, 4-nitro-]



Submitted by E. H. Huntress and R. L. Shriner.
Checked by Frank C. Whitmore and C. P. Krimmel.

1. Procedure

Two hundred forty cubic centimeters (5.7 moles) of c.p. fuming nitric acid (sp. gr. 1.50) is added to 1.4 l. of concentrated c.p. sulfuric acid (sp. gr. 1.84) in a 3-l. beaker, and the mixture is cooled in an ice bath. As soon as the temperature of the mixed acids reaches 12°, 200 g. (1.36 moles) of commercial phthalimide is stirred in as rapidly as possible while the temperature of the nitrating mixture is kept between 10° and 15°. The reaction mixture is allowed to warm to room temperature in the ice bath as the ice melts, and left overnight.

The clear, pale yellow solution is poured slowly with vigorous stirring onto 4.5 kg. of cracked ice; the temperature of this mixture must not rise above 20°. The crude nitration product is filtered through cloth on a 20-cm. Büchner funnel, using suction, and the mass is pressed as dry as possible. The cake is removed and stirred vigorously with 2 l. of *ice water*. The solid is filtered; the cake is removed and stirred again with 2 l. of *ice water*. This washing is repeated four times. The crude product, after drying in the air, melts at 185–190° and weighs 165–174 g. (63–66 per cent of the theoretical amount). This material is purified by crystallization from 3 to 3.2 l. of 95 per cent ethyl alcohol. This furnishes 136–140 g. (52–53 per cent of the theoretical amount) of 4-nitrophthalimide melting at 198°.

3. Discussion

4-Nitrophthalimide has been prepared from 4-nitrophthalic acid[1] and by nitrating phthalimide.[2] The procedure described is a modification of the method of Levy and Stephen.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 457

References and Notes

1. Seidel, Ber. **34**, 4351 (1901); Seidel and Bittner, Monatsh. **23**, 420 (1902); Bogert and Renshaw, J. Am. Chem. Soc. **30**, 1137 (1908).
2. Levy and Stephen, J. Chem. Soc. **1931**, 79.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethyl alcohol (64-17-5)

sulfuric acid (7664-93-9)

nitric acid (7697-37-2)

Phthalimide (85-41-6)

4-nitrophthalic acid (610-27-5)

4-Nitrophthalimide, Phthalimide, 4-nitro- (89-40-7)

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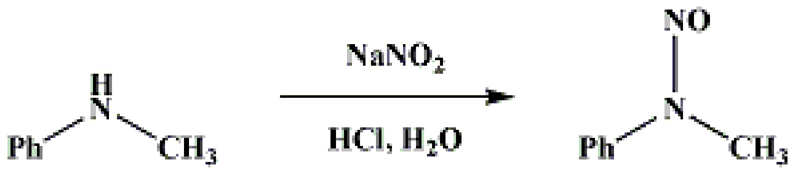
N-NITROSOMETHYLANILINE

[Aniline, N-methyl-N-nitroso-]



Submitted by W. W. Hartman and L. J. Roll.
Checked by Louis F. Fieser and J. T. Walker.

1. Procedure

A mixture of 107 g. (1 mole) of methylaniline (Note 1), 145 cc. of concentrated hydrochloric acid, and 400 g. of ice is placed in a 3-l. flask equipped with a mechanical stirrer. The mixture is stirred vigorously, and the temperature is maintained at 10° or below by the addition of more ice as required, while a solution of 70 g. (1 mole) of sodium nitrite in 250 cc. of water is added during the course of five or ten minutes. Stirring is then continued for one hour more. The oily layer is separated, and the aqueous portion is extracted with two 100-cc. portions of benzene. The benzene is removed by distillation at ordinary pressure, and the residue is fractionated under reduced pressure. The main fraction of the nitrosomethylaniline distils as a light yellow liquid boiling at 135–137°/13 mm. The yield (Note 1) is 118–127 g. (87–93 per cent of the theoretical amount).

2. Notes

1. The yield is dependent upon the quality of the methylaniline used. The higher yield reported was obtained with pure material, b.p. 81–82°/14 mm.

3. Discussion

N-Nitrosomethylaniline was first prepared by the action of nitrous acid on methylaniline.[1] It has been obtained also by the action of methyl iodide on the sodium salt of benzene diazoic acid followed by reduction;[2] by treating dimethylaniline with tetranitromethane,[3] or with phenylnitrocarbinol;[4] by the acid hydrolysis of nitrosophenylglycine;[5] and by oxidizing dimethyldiphenylhydrazine with nitric oxide.[6]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 418

References and Notes

1. Hepp, Ber. **10**, 329 (1877).
2. Bamberger, ibid. **27**, 373 (1894).
3. Schmidt and Fischer, ibid. **53**, 1538 (1920).
4. Cohen and Calvert, J. Chem. Soc. **73**, 164 (1898).
5. Fischer, Ber. **32**, 249 (1899).
6. Wieland and Fressel, Ann. **392**, 148 (1912).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium salt of benzene diazoic acid

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

sodium nitrite (7632-00-0)

nitrous acid (7782-77-6)

dimethylaniline (121-69-7)

Methyl iodide (74-88-4)

nitric oxide

N-Nitrosomethylaniline, nitrosomethylaniline

Aniline, N-methyl-N-nitroso- (614-00-6)

methylaniline (100-61-8)

tetranitromethane (509-14-8)

phenylnitrocarbinol

nitrosophenylglycine (6415-68-5)

dimethyldiphenylhydrazine

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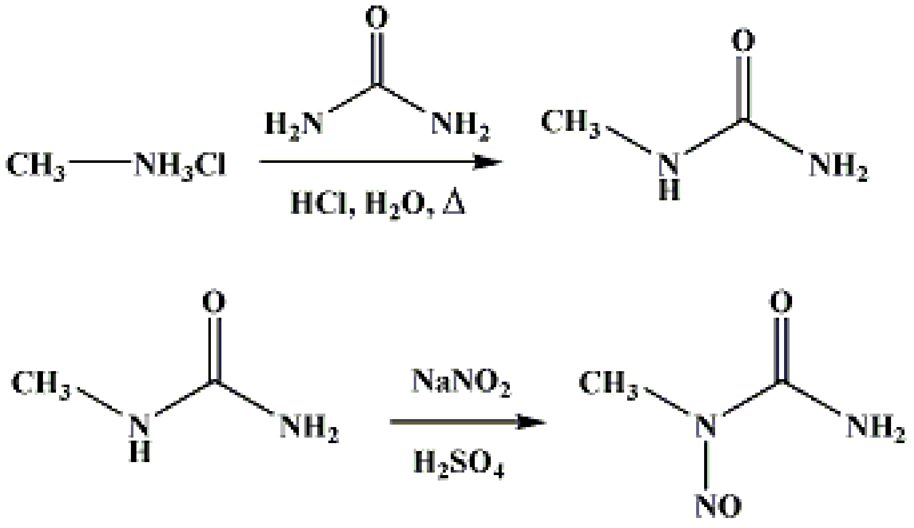
Organic Syntheses, CV 2, 461

NITROSOMETHYLUREA

[Urea, α-methyl-α-nitroso-]

[*I.* (*From Methylamine Hydrochloride*)]



Submitted by F. Arndt
Checked by C. R. Noller and S. Lieberman.

1. Procedure

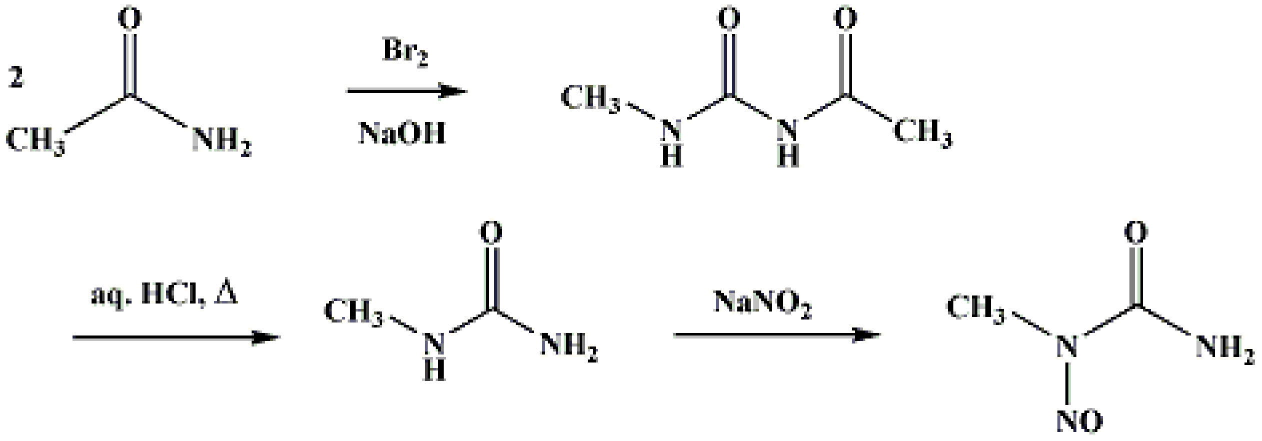
In a tared 1-l. flask is placed 200 g. (1.5 moles) of 24 per cent aqueous methylamine solution (Note 1), and concentrated hydrochloric acid is added until the solution is acid to methyl red; about 155 cc. of acid is required. Water is added to bring the total weight to 500 g., 300 g. (5 moles) of urea is added, and the solution is boiled gently under reflux for two and three-quarters hours and then vigorously for one-quarter hour. The solution is cooled to room temperature, 110 g. (1.5 moles) of 95 per cent sodium nitrite is dissolved in it, and the whole is cooled to 0°. A mixture of 600 g. of ice and 100 g. (1 mole) of concentrated sulfuric acid in a 3-l. beaker is surrounded by an efficient freezing mixture, and the cold methylurea-nitrite solution is run in slowly with mechanical stirring at such a rate that the temperature does not rise above 0° (Note 2).

The nitrosomethylurea rises to the surface as a crystalline foamy precipitate which is filtered at once with suction and pressed well on the filter. The crystals are stirred to a paste with about 50 cc. of cold water, sucked as dry as possible (Note 3), and dried in a vacuum desiccator to constant weight. The yield is 105–115 g. (66–72 per cent of the theoretical amount) (Note 4).

2. Notes

1. The methylamine content of the commercial aqueous solution (Röhm and Haas) was determined by titration with standard acid using methyl red as indicator. If the methylamine content is found to be different an equivalent quantity is used.
2. It is convenient to keep the methylurea-nitrite solution in an ice-salt bath and to siphon it into the acid solution, the end of the siphon dipping below the surface. About one hour is required for the addition.
3. A sample of the moist product should dissolve completely in boiling methyl alcohol. If an appreciable residue remains, which is not usually the case, the washing process is repeated. Each successive washing decreases the yield somewhat.
4. The preparation obtained in this way may be kept indefinitely in a refrigerator. It should not be kept above 20° for more than a few hours. At temperatures in the neighborhood of 30° it may undergo a sudden decomposition without explosion but with the evolution of irritating fumes. It has been reported that the stability is increased by the addition of a few drops of acetic acid.

[*II*. (*From Acetamide*)]



Submitted by E. D. Amstutz and R. R. Myers.
Checked by C. F. H. Allen and J. Dec.

1. Procedure

(*A*) *Acetyl Methylurea*.—To a solution (Note 1) of 59 g. (1 mole) of acetamide in 88 g. (0.55 mole) of bromine in a 4-l. beaker is added, dropwise and with hand stirring, a solution of 40 g. (1 mole) of sodium hydroxide in 160 cc. of water. The resulting yellow reaction mixture is heated on a steam bath until effervescence sets in (Note 2), after which heating is continued for an additional two to three minutes. Crystallization of the product from the yellow to red colored solution usually commences immediately (Note 3) and is completed by cooling in an ice bath for one hour. The weight of the white crystalline acetyl methylurea obtained by filtration and air drying is 49–52 g. (84–90 per cent of the theoretical amount) (Note 4)(Note 5). It melts at 169–170°.

(*B*) *Nitrosomethylurea*.—A mixture of 49 g. (0.42 mole) of acetyl methylurea (Note 6) and 50 cc. of concentrated hydrochloric acid is heated, with hand stirring, on a steam bath until it is apparent that no more solid (Note 5) is dissolving. Heating is continued for three or four minutes longer (total time on steam bath—eight to twelve minutes), after which the solution is diluted with an equal volume of water and cooled below 10° in an ice bath. A cold saturated solution of 38 g. (0.55 mole) of sodium nitrite in 55 cc. of water is then run in slowly with stirring. The mixture is allowed to remain in the ice bath for several minutes, after which the nitrosomethylurea is filtered and washed with about 8–10 cc. of ice-cold water. Air drying gives 33–36 g. (76–82 per cent of the theoretical amount) of nitrosomethylurea as pale yellow crystals melting at 123–124°.

2. Notes

1. Gentle heating on a steam bath assists in dissolving the acetamide. Care is necessary, however, to see that only the minimum amount of bromine is lost during the heating.
2. Occasionally this effervescence becomes quite brisk, and for this reason a large container is used.
3. If the solution at this point is perfectly colorless, the product is usually slower in crystallizing, it contains more sodium bromide, and the yield is somewhat lower. For these reasons, the slight excess of bromine used is necessary.
4. When the crude yield is the lower figure given, the remainder of the product can be secured by long cooling of the filtrate in ice.
5. The crude acetyl methylurea contains some sodium bromide, which appears as a white crystalline material insoluble in concentrated hydrochloric acid in Part (*B*). The sodium bromide dissolves when the solution is diluted and has no effect upon the subsequent treatment with sodium nitrite.
6. The acetyl methylurea prepared in Part (*A*) may be used without drying.

3. Discussion

Nitrosomethylurea is always prepared by the nitrosation of methylurea. Methylurea, in turn, can be prepared from (*a*) methylamine hydrochloride and potassium cyanate;[1] (*b*) methyl sulfate, ammonia, and potassium cyanate;[1] (*c*) methylamine hydrochloride and urea;[2] and (*d*) acetamide, bromine, and alkali.[3] Checked directions for preparing methylurea, and for its subsequent nitrosation, according to (*a*) and (*b*) are described on p. 48 of Volume 15 of Organic Syntheses. The preparation of methylurea, and its subsequent nitrosation, according to (*c*) and (*d*) are given in procedures I and II, above. The preparations using potassium cyanate suffer because of the difficulty and the expense of obtaining that reagent. Arndt, Loewe, and Avan[2] have discussed the merits of the different methods of preparing nitrosomethylurea.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 165

References and Notes

1. Arndt and Amende, Z. angew. Chem. **43**, 444 (1930); Arndt and Scholz, ibid. **46**, 47 (1933).
2. Arndt, Loewe, and Avan, Ber. **73**, 606 (1940); Eistert, Angew. Chem. **54**, 124 (1941).
3. Owen, Ramage, and Simonsen, J. Chem. Soc. **1938**, 1213.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Methyl Red

Urea, α-methyl-α-nitroso-

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

Acetamide (60-35-5)

acetic acid (64-19-7)

ammonia (7664-41-7)

methyl alcohol (67-56-1)

sodium hydroxide (1310-73-2)

bromine (7726-95-6)

sodium bromide (7647-15-6)

sodium nitrite (7632-00-0)

urea (57-13-6)

methyl sulfate (75-93-4)

Methylamine hydrochloride (593-51-1)

methylamine (74-89-5)

potassium cyanate (590-28-3)

Nitrosomethylurea

methylurea-nitrite

Acetyl methylurea (623-59-6)

methylurea (598-50-5)

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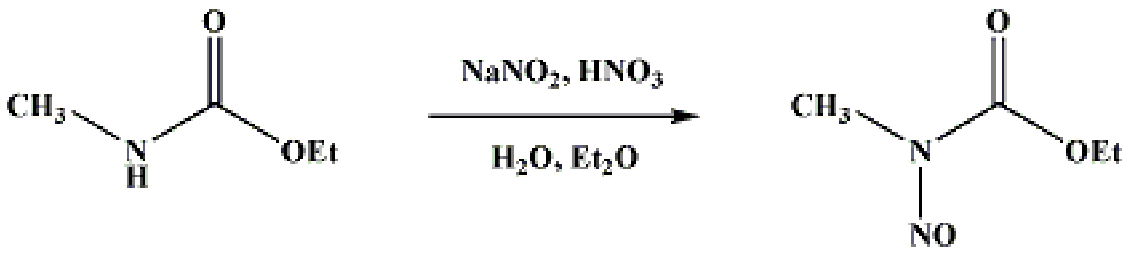
NITROSOMETHYLURETHANE

[Carbamic acid, methylnitroso-, ethyl ester]



Submitted by W. W. Hartman and Ross Phillips.
Checked by Louis F. Fieser and J. T. Walker.

1. Procedure

To 206 g. (2 moles) of ethyl N-methylcarbamate (p. 278) and 600 cc. of ordinary ethyl ether in a 5-l. flask is added, along with 200 g. of ice, 650 g. (9 moles) of 96 per cent sodium nitrite (Note 1) dissolved in 1 l. of cold water. The flask is provided with a stopper carrying a thermometer, a tube to lead off evolved nitric oxide, and a separatory funnel with an extension tube reaching to the bottom of the flask. A solution of 1.2 kg. (6.7 moles) of cold 35 per cent nitric acid, prepared by pouring 600 g. (426 cc.) of concentrated acid onto 600 g. of ice, is then cautiously added through the funnel in the course of one and one-half hours. The flask is given an occasional swirl to ensure some mixing, but most of the stirring is done by the evolved gases. Ice is added as required to keep the temperature below 15°. The ether layer first becomes pale red and gradually changes to a blue-green. As soon as the color has changed to green, the ether layer is separated (Note 2), washed twice with cold water, and then with cold potassium carbonate solution until carbon dioxide is no longer evolved. The solution is dried with solid potassium carbonate, and the ether is distilled from a water bath using a 1-l. flask with a 30-cm. column arranged for vacuum distillation. The vacuum is applied as soon as most of the ether has been removed, and the flask is heated gently so that the temperature of the liquid does not exceed 45–50° (Note 3) until the pressure has been reduced below 20 mm. The yield of nitrosomethylurethane boiling at 59–61/10 mm. is 200 g. (76 per cent of the theoretical amount). The density is 1.133 at 20°.

2. Notes

1. A large excess of sodium nitrite is required to give a satisfactory yield. This may be due to reaction according to the following equations: Nitric oxide (NO) is lost during the reaction. It is not thought advisable to use this by passing in oxygen because of the danger of an explosion, or by passing in air because of the loss of material by evaporation.

2. Nitrosomethylurethane irritates the skin.
3. According to the literature, nitrosomethylurethane explodes when attempts are made to distil it at normal pressure.

3. Discussion

Nitrosomethylurethane has been prepared by treating ethyl methylcarbamate with sodium nitrite and sulfuric acid,[1] and by passing the gases generated from arsenious oxide and nitric acid into an ethereal solution of ethyl methylcarbamate.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 119
- Org. Syn. Coll. Vol. 4, 780
- Org. Syn. Coll. Vol. 5, 842

References and Notes

1. Klobbie, Rec. trav. chim. **9**, 139 (1890).
2. v. Pechmann, Ber. **28**, 856 (1895); Schmidt, ibid. **36**, 2477 (1903); Brühl, ibid. **36**, 3635 (1903).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

arsenious oxide

Nitric oxide (NO)

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

ether, ethyl ether (60-29-7)

nitric acid (7697-37-2)

oxygen (7782-44-7)

sodium nitrite (7632-00-0)

carbon dioxide (124-38-9)

nitric oxide

Nitrosomethylurethane

Ethyl N-methylcarbamate, ethyl methylcarbamate (105-40-8)

Carbamic acid, methylnitroso-, ethyl ester (615-53-2)

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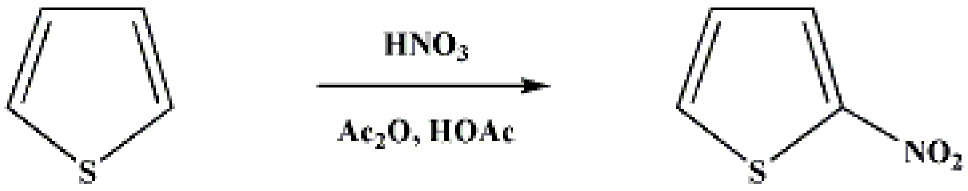
2-NITROTHIOPHENE

[Thiophene, 2-nitro-]



Submitted by V. S. Babasinian
Checked by Roger Adams and A. E. Knauf.

1. Procedure

Eighty-four grams (1 mole) of thiophene (p. 578) is dissolved in 340 cc. of acetic anhydride, and 80 g. (1.2 moles) of fuming nitric acid (sp. gr. 1.51) is dissolved in 600 cc. of glacial acetic acid (Note 1). Each solution is divided into two equal parts. One-half of the nitric acid solution is introduced into a 2-l. three-necked, round-bottomed flask, provided with a thermometer, a motor stirrer, and a separatory funnel. The mixture is cooled to 10°. Then with moderate stirring one-half of the thiophene solution is introduced, drop by drop, and at such a rate as to prevent the heating of the reaction mixture above room temperature. A rapid rise of temperature will occur during the addition of the first fraction of the thiophene solution. In cool weather the temperature is controlled by dipping the nitrating flask into a bath of cold tap water. Cooling to a very low temperature is not necessary, but it is important to avoid superheating the reaction mixture (Note 2). After the addition of the first half of the thiophene, the temperature of the reaction mixture is reduced to 10° and the remainder of the nitric acid solution is rapidly introduced into the flask. Nitration is continued by the gradual addition of thiophene. Throughout the nitration the solution should show a permanent light brown color. The appearance of a pink or dark red color indicates oxidation. The product is allowed to remain at room temperature for two hours. It is then treated with an equal weight of finely crushed ice with rapid shaking. Mononitrothiophene separates in pale yellow crystals. More crystals form if the mixture is allowed to remain in the ice chest for twenty-four hours or longer. The solid is filtered (Note 3) on a Büchner funnel or a Jena glass filter plate at a low temperature, washed thoroughly with ice water, pressed, and dried in a brown desiccator or in the absence of light (Note 4).

The filtrate and the washings contain in solution a small quantity of the product. This is recovered by distillation with steam. The acid distillate consists of snow-white crystals (if it is protected from light) and a solution of the compound. The solid is removed by filtration and washed. The filtrate is made neutral with sodium carbonate and extracted with ether. Upon drying and evaporating, the ethereal layer yields

mononitrothiophene contaminated with dinitrothiophene (Note 5).

The total yield is 90–110 g. (70–85 per cent of the theoretical amount) of a product which melts at 44–45°. If this material is steam-distilled and then repeatedly crystallized from petroleum ether (b.p. 20–40°) it is obtained as colorless crystals melting at 45.5° (Note 6) and (Note 7).

2. Notes

1. The two acids should be mixed gradually, the nitric acid being added to the acetic with shaking. Cooling is often necessary.
2. Success will depend largely upon the proper control of temperature. No trouble may be anticipated if the reaction mixture responds readily to the cooling effect of a cold water bath.
3. Mononitrothiophene is an active poison.[1] The accidental contact of an ethereal solution with the skin has produced painful blisters. In case of accident the compound should be removed from the exposed surface by washing with alcohol.
4. Earlier workers[2] have noted that the compound is sensitive toward light.
5. The yellow color of the nitrothiophene is due to the presence of traces of dinitrothiophene and other impurities.
In order to detect the presence of dinitrothiophene, a few crystals of the solid are dissolved in alcohol and treated with a drop of a weak solution of alcoholic potassium hydroxide. A pink or deep red color will develop at once. An excess of potassium hydroxide will destroy the color.[3]
6. Meyer and Stadler[2] state that nitrothiophene distils without decomposition at 224–225°.
7. Mononitrothiophene has been crystallized from ether, alcohol, benzene, and other solvents. As a rule these solvents fail to yield a snow-white product. It has been found in this work that petroleum ether (b.p. 20–40°) possesses decided advantages in that by prolonged refluxing it extracts mononitrothiophene but does not readily dissolve the impurities. With petroleum ether, snow-white crystals have been obtained in needles 10 to 20 cm. in length.

3. Discussion

Nitrothiophene has been obtained along with dinitrothiophene by drawing a vigorous stream of air charged with thiophene through red fuming nitric acid.[2] It has also been prepared by nitrating thiophene between 0° and 5° with a mixture of acetic anhydride and fuming nitric acid.[4]

References and Notes

1. Meyer, Ber. **18**, 1772 (1885).

2. Meyer and Stadler, ibid. **17**, 2648 (1884).
3. Meyer and Stadler, ibid. **17**, 2780 (1884).
4. Steinkopf and Lützkendorf, Ann. **403**, 27 (1914); Ger. pat. 255,394 [Frdl. **11**, 144 (1912-14)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

alcohol (64-17-5)

acetic acid (64-19-7)

Benzene (71-43-2)

ether (60-29-7)

acetic anhydride (108-24-7)

nitric acid (7697-37-2)

sodium carbonate (497-19-8)

potassium hydroxide (1310-58-3)

Thiophene (110-02-1)

2-Nitrothiophene, Thiophene, 2-nitro-, Mononitrothiophene, nitrothiophene (609-40-5)

dinitrothiophene

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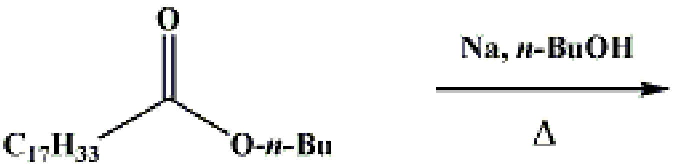
OLEYL ALCOHOL



Submitted by E. E. Reid, F. O. Cockerille, J. D. Meyer, W. M. Cox Jr, and J. R. Ruhoff.
Checked by C. R. Noller and R. Bannerot.

1. Procedure

A 5-l. round-bottomed flask is fitted with a wide-bore Y adapter and two wide-bore reflux condensers. Three liters of anhydrous butyl alcohol (Note 1) and 507 g. (1.5 moles) of butyl oleate (Note 2) are placed in the flask, and 180 g. (7.8 gram atoms) of clean sodium, cut in approximately 2.5-cm. cubes, is added in one lot and the flask connected to the condensers. The reaction is rather sluggish at first, requiring about one-half hour to reach the boiling point of the butyl alcohol (Note 3), but then becomes quite vigorous. With two condensers no difficulty is encountered in taking care of the reflux, but, if the reaction becomes too vigorous or excessive foaming occurs, wet towels should be placed on the flask until the reaction is again under control (Note 4). Toward the end of the reaction the flask is placed on a heated sand bath and gentle refluxing maintained until all the sodium has reacted. The heating is stopped temporarily, 160 cc. of water is added gradually through the condenser, and the solution is again refluxed gently for one hour (Note 5). At the end of this time the heating is stopped and 1.2 l. of water is added. The flask is well shaken and the mixture allowed to separate into two layers. The lower aqueous layer of sodium hydroxide is siphoned off and discarded (Note 6) and (Note 11).

About 200 g. of solid sodium chloride (Note 7) is added to the flask, and the butyl alcohol is removed by steam distillation (Note 8). The alcohol layer is separated while still hot (Note 9), transferred to a 1-l. beaker, and heated on a hot plate with stirring until the temperature reaches about 160°. By this time all the water is removed and foaming has stopped (Note 10). The hot liquid is transferred to a 1-l. Claisen flask having a 25-cm. fractionating side arm, and distilled at 3 mm. After a small fore-run of 5–10 g., the main fraction boils at 177–183°/3 mm. and amounts to 330–340 g. (82–84 per cent of the theoretical amount) (Note 11).

2. Notes

1. Commercial butyl alcohol is dried by distillation through a 1-m. column, and the portion boiling at 117.5–118.5° is used. The ordinary commercial alcohol is usually sufficiently pure so that the bulk of the alcohol remaining in the flask

after the temperature at the top of the column reaches 117° need not be distilled but may be used directly for the reduction.

2. The butyl oleate was prepared by the alcoholysis of 3 kg. of cold-pressed olive oil by refluxing with 7 l. of butyl alcohol and 150 g. of concentrated sulfuric acid for 20 hours. The mixture was washed three times with 2.5-l. portions of saturated sodium chloride solution. During the last washing methyl orange was added to the solution and enough sodium carbonate was added to neutralize any acid remaining. The excess butyl alcohol was distilled and the residue carefully fractionated from a 2-l. Claisen flask having a 25-cm. fractionating side arm. A total of 3075 g. of distilled esters was obtained, of which 2422 g. (about 70 per cent based on the olive oil used) distilled at 204–208°/3 mm. and had approximately the theoretical iodine number. This product contains a small amount of saturated esters, but it is considerably purer than can be obtained from commercial oleic acid and is satisfactory for most purposes.

3. If one wishes to reduce this time, external heat may be applied until the boiling point is reached. In a run in which the butyl alcohol was heated to boiling before the addition of the sodium, the reaction began more vigorously but the yield was practically unchanged.

4. The reaction mixture should not be cooled below the boiling point of the butyl alcohol as a continuously vigorous reaction is essential for good yields.

5. This saponifies any unreacted ester.

6. The procedure up to this point requires about three and one-half hours and should be continuous.

7. The sodium chloride prevents the formation of an emulsion during the steam distillation.

8. The butyl alcohol is readily recovered and dried with very little loss.

9. The soap, and possibly a high-boiling by-product, causes even the liquid alcohols to set to a jelly on cooling.

10. This procedure largely eliminates the difficulty caused by foaming at the start of the vacuum distillation.

11. The procedure as given is generally applicable for the reduction of esters to alcohols in excellent yields. When preparing the solid normal saturated alcohols, the procedure may be modified, if desired, to permit the recovery of the acid from the unreduced ester. After the alkali is removed the alcohol layer is washed with two successive portions of 20 per cent salt solution which are discarded. Neither the strong alkali nor the salt solution removes an appreciable amount of organic acid. A solution of 50 g. of calcium chloride in 150 cc. of water is added to the butyl alcohol solution, the mixture is steam-distilled until the butyl alcohol is removed, and the flask and contents are allowed to cool. A hole is made in the cake of solid alcohol and the water layer removed. Two liters of toluene is added, and the flask is warmed and shaken until the alcohol dissolves and only fine crystals of the calcium salt of the unreduced acid remain. The solution is cooled to 35° and filtered with suction. The calcium soap is removed from the filter, warmed with about 500 cc. of toluene, cooled, filtered, and washed with a little more toluene. The combined toluene solutions may be concentrated and the alcohol crystallized, or the toluene may be completely

distilled and the residue vacuum distilled. The insoluble calcium soap may be decomposed, re-esterified, and used in a subsequent reduction.

3. Discussion

Oleyl alcohol has been prepared by the reduction of ethyl oleate with hydrogen and a zinc-chromium oxide catalyst[1] or with sodium and absolute ethyl alcohol.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 671

References and Notes

1. Sauer and Adkins, J. Am. Chem. Soc. **59**, 1 (1937).
2. Bouveault and Blanc, Bull. soc. chim. (3) **31**, 1210 (1904). See the preparation of lauryl alcohol on p. 372 above.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethyl alcohol (64-17-5)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

butyl alcohol (71-36-3)

toluene (108-88-3)

sodium (13966-32-0)

oleic acid (112-80-1)

Oleyl alcohol (143-28-2)

butyl oleate (142-77-8)

ethyl oleate (111-62-6)

zinc-chromium oxide

methyl orange (547-58-0)

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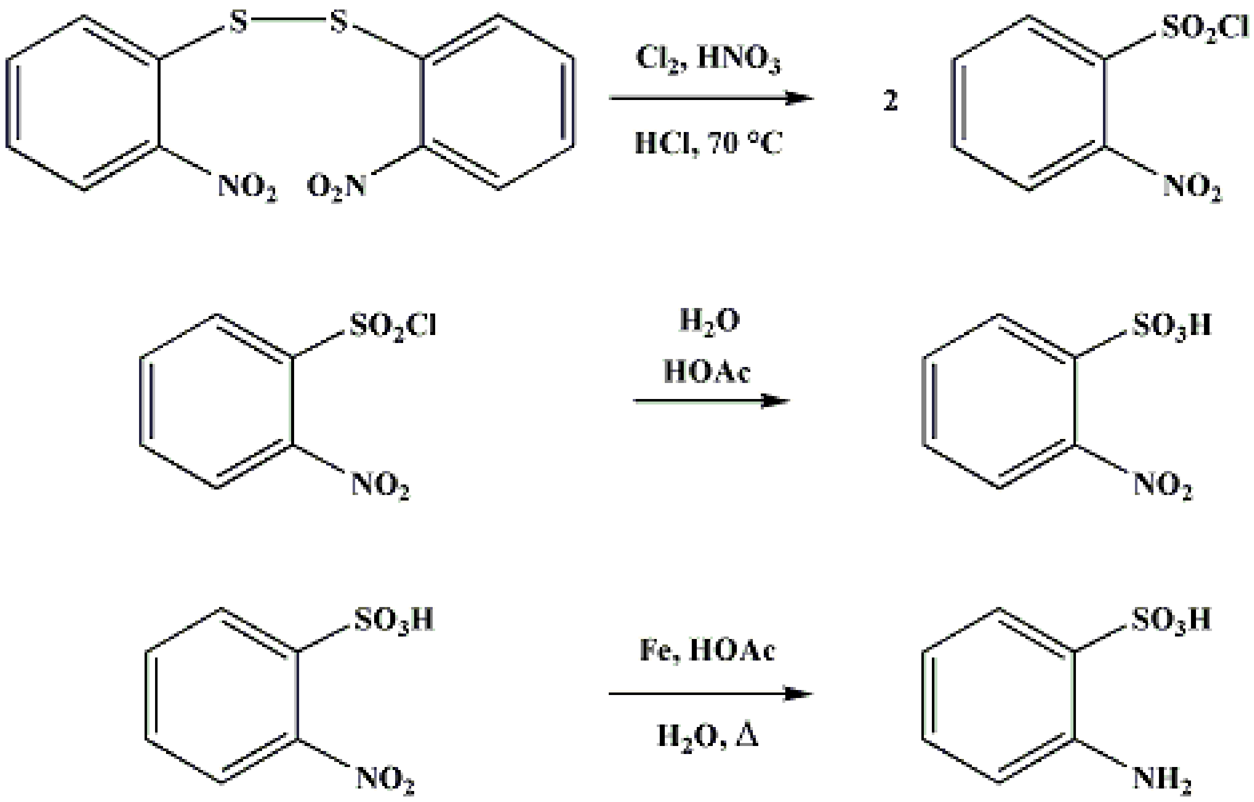
Organic Syntheses, CV 2, 471

ORTHANILIC ACID

[Benzenesulfonic acid, *o*-amino-]



Submitted by E. Wertheim
Checked by Reynold C. Fuson and R. S. Schreiber.

1. Procedure

(*A*) *o-Nitrobenzenesulfonyl Chloride*.—A 3-l. three-necked, round-bottomed flask is fitted with an efficient liquid-sealed stirrer, a reflux condenser, and an inlet tube for introducing chlorine well beneath the surface of the liquid. A glass outlet tube leads from the reflux condenser to the hood. In the flask are placed 200 g. (0.65 mole) of di-*o*-nitrophenyl disulfide (Org. Syn. Coll. Vol. I, **1941**, 220), 1 l. of concentrated hydrochloric acid (sp. gr. 1.18), and 200 cc. of concentrated nitric acid (sp. gr. 1.42). A stream of chlorine is passed into the mixture at the rate of about two bubbles per second, and the solution is warmed on a steam bath to 70°. In about thirty minutes the disulfide melts and the solution becomes orange-red in color. After the disulfide has melted, the heating and addition of chlorine are continued for one hour. The sulfonyl chloride is separated immediately from the supernatant liquid by decantation, washed with two 300-cc. portions of warm water (70°), and allowed to solidify. The water is drained from the solid mass as completely as possible.

The washed chloride is dissolved in 140 cc. of glacial acetic acid at 50–60°, and the

solution is quickly filtered by suction. The filtrate is chilled by immersing the flask in cold water and is vigorously stirred in order to cause the sulfonyl chloride to separate in fine crystals. The mixture is now triturated thoroughly with a liter of cold water which is then decanted into a large Büchner funnel. The process is repeated twice. Finally, a liter of cold water is added to the mixture, and then 10 cc. of concentrated ammonium hydroxide (sp. gr. 0.90) is added, with stirring. The crystals are collected at once on the filter, washed with 200 cc. of water, and allowed to dry in the air. The yield is 240 g. (84 per cent of the theoretical amount) of a light yellow product, melting at 64–65°. This material may be used without further purification (and without being dried) for the preparation of orthanilic acid.

(*B*) *Orthanilic Acid*.—A 3-l. flask, fitted with a reflux condenser and a liquid-sealed stirrer, is placed on a hot plate. In the flask is placed a mixture of 200 g. (0.90 mole) of *o*-nitrobenzenesulfonyl chloride, 100 g. of anhydrous sodium carbonate, and 600 cc. of water. The mixture is heated to boiling and stirred in order to promote the hydrolysis, which is complete within forty-five minutes after the compound has melted. The orange-red solution is filtered, and the filtrate is made just acid to litmus by the addition of acetic acid, about 25 cc. being required. The solution is transferred to a 3-l. three-necked flask which is provided with a reflux condenser and an efficient liquid-sealed stirrer. The solution is heated to boiling on the hot plate, and iron filings (about 20-mesh) are added, with vigorous stirring, at the rate of about 25 g. every fifteen minutes. A total of 350 g. of iron is used. In a few minutes the mixture becomes very deep brown in color and has a tendency to foam. After stirring for four hours, a sample when filtered should yield an almost colorless filtrate; if the filtrate is red or orange, stirring and heating must be continued. When a light-colored filtrate is obtained, 2 g. of decolorizing carbon is added, the hot mixture is filtered by suction, and the residue is washed several times with small amounts of hot water which are added to the main solution. The filtrate is chilled to about 15°, and 95 cc. of concentrated hydrochloric acid is slowly added. The orthanilic acid separates in fine colorless crystals which appear as hexagonal plates under the microscope (Note 1). When the temperature has again fallen to about 15°, the mass is filtered and the precipitate is washed with water and then with ethyl alcohol. If about 20 cc. of concentrated hydrochloric acid is added to the filtrate, an additional deposit of about 1 g. will be obtained after a few hours' standing. The yield is 89 g. (57 per cent of the theoretical amount). The compound is 97–100 per cent pure and for many purposes will not require recrystallization. Material of analytical purity may be obtained by one recrystallization from hot water. The decomposition point is about 325° (bloc Maquenne).

2. Notes

1. Solutions of orthanilic acid, when chilled below 13.5°, yield the hydrated form of the acid, which crystallizes as needles (see photographs in the paper by Fierz-David and others).[1]

3. Discussion

Orthanilic acid was first made by the reduction of nitrobenzenesulfonic acid by ammonium sulfide.[2] This reduction has also been carried out electrolytically, and by the use of iron or zinc.[3] The acid has also been made by the rearrangement of phenylsulfamic acid;[4] by the action of sodium hypobromite upon potassium *o*-carbaminebenzenesulfonate;[5] by the reduction of the mixed nitrobenzenesulfonic acids followed by separation of the isomers;[6] by the action of methyl alcohol upon *o*-nitrophenylsulfur chloride;[7] by the action of acid upon diacetyl diphenylsulfamide;[8] by the debromination of *p*-bromoaniline-*o*-sulfonic acid;[9] by the reduction of 1,2,6-aminothiophenolsulfonic acid;[10] and by the hydrolysis and reduction of *o*-nitrobenzenesulfonyl chloride, which was obtained from di-*o*-nitrophenyl disulfide.[11]

References and Notes

1. Fierz-David, Schlittler, and Waldemann, Helv. Chim. Acta **12**, 663 (1929).
2. Limpricht, Ann. **177**, 79, 98 (1875).
3. Wohlfahrt, J. prakt. Chem. (2) **66**, 556 (1902); Goldschmidt and Eckardt, Z. physik. Chem. **56**, 411 (1906); Holleman and Polak, Rec. trav. chim. **29**, 419 (1910); Sharvin, Arbuzov, and Varshavskii, J. Chem. Ind. (Moscow) **6**, 1409 (1929) [C. A. **25**, 501 (1931)].
4. Bamberger and Hindermann, Ber. **30**, 654 (1897); Bamberger and Kunz, ibid. **30**, 2276 (1897); Bretschneider, J. prakt. Chem. (2) **55**, 286 (1897); Bamberger and Rising, Ber. **34**, 249 (1901); Baumgarten, ibid. **59**, 1976 (1926).
5. Bradshaw, Am. Chem. J. **35**, 339 (1906).
6. Bahlmann, Ann. **186**, 307 (1877); Franklin, Am. Chem. J. **20**, 457 (1898); Obermiller, Ger. pat. 281,176 [Frdl. **12**, 125 (1914-16)].
7. Zincke and Farr, Ann. **391**, 59, 66 (1912).
8. Wohl and Koch, Ber. **43**, 3301 (1910).
9. Thomas, Ann. **186**, 128 (1877); Baseler Chem. Fabrik Bindschedler, Ger. pat. 84,141 [Frdl. **4**, 90 (1894-97)]; Kreis, Ann. **286**, 377 (1895); Bradshaw, Am. Chem. J. **35**, 340 (1906); Boyle, J. Chem. Soc. **95**, 1698 (1909); Scott and Cohen, ibid. **121**, 2042 (1922).
10. Rassow and Döhle, J. prakt. Chem. (2) **93**, 188, 203 (1916).
11. Elgersma, Rec. trav. chim. **48**, 752 (1929).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

nitrobenzenesulfonic acids

1,2,6-aminothiophenolsulfonic acid

potassium o-carbaminebenzenesulfonate

ethyl alcohol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

methyl alcohol (67-56-1)

iron, iron filings (7439-89-6)

nitric acid (7697-37-2)

sodium carbonate (497-19-8)

decolorizing carbon (7782-42-5)

chlorine (7782-50-5)

zinc (7440-66-6)

ammonium hydroxide (1336-21-6)

ammonium sulfide

sodium hypobromite

Orthanilic acid, Benzenesulfonic acid, o-amino- (88-21-1)

o-Nitrobenzenesulfonyl chloride (1694-92-4)

nitrobenzenesulfonic acid (80-82-0)

phenylsulfamic acid

diacetyl diphenylsulfamide

Di-o-nitrophenyl disulfide (1155-00-6)

o-Nitrophenylsulfur chloride (7669-54-7)

p-bromoaniline-o-sulfonic acid

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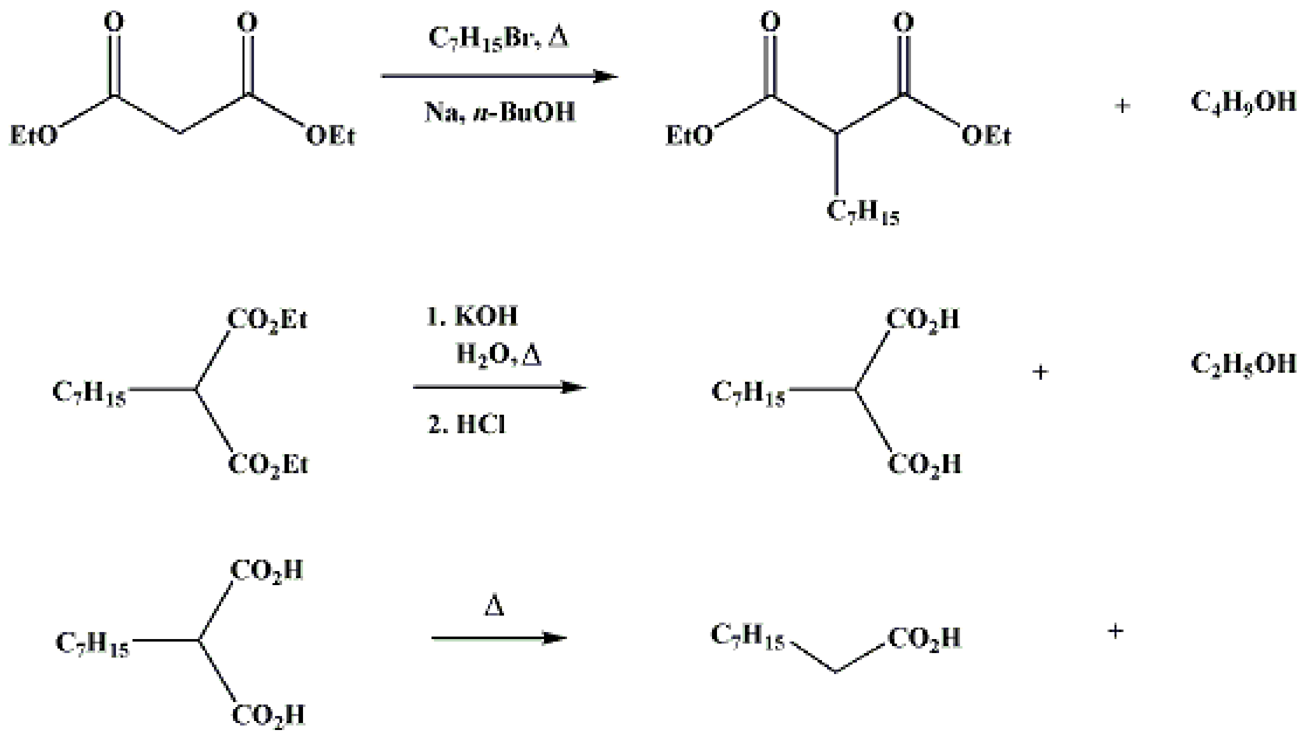
Organic Syntheses, CV 2, 474

PELARGONIC ACID



Submitted by E. Emmet Reid and John R. Ruhoff.
Checked by W. W. Hartman and G. W. Sawdey.

1. Procedure

A 5-l. three-necked flask is fitted with a liquid-sealed mechanical stirrer, reflux condenser, dropping funnel, and thermometer. In the flask is placed 2.5 l. of anhydrous butyl alcohol (Note 1), and 115 g. (5 gram atoms) of clean, bright sodium cut in small pieces is added at one time. Solution of the sodium may be facilitated by stirring, but heating is unnecessary. After the sodium has dissolved completely, the solution is allowed to cool to 70–80°, and then 800 g. (5 moles) of redistilled ethyl malonate (b.p. 135–136°/100 mm.) is added rapidly with stirring. After heating the reaction solution to 80–90°, 913 g. (5.1 moles) of pure heptyl bromide (p. 247, b.p. 179–180°) is added. The bromide should be added rather slowly at first, until precipitation of sodium bromide begins; it may then be added at such a rate that the butyl alcohol refluxes gently. Usually about one hour is required for the introduction of the heptyl bromide. The mixture is refluxed gently until it is neutral to litmus (about one hour).

The entire mixture, including the precipitated sodium bromide, is transferred to a 12-l. flask together with a small amount of water used to rinse the reaction flask. A solution of 775 g. (12.5 moles) of 90 per cent potassium hydroxide in an equal weight of water is added slowly with shaking. The mixture is heated cautiously, with occasional shaking, until refluxing starts (Note 2), and refluxing is continued until saponification is complete (about four or five hours). The flask is fitted at once for steam distillation (Org. Syn. Coll. Vol. I, **1941**, 479), and the mixture is distilled until no more butyl alcohol passes over (Note 3). To the residue 1350 cc. (15.5 moles) of concentrated hydrochloric acid (sp. gr. 1.18) is added carefully, with shaking, and the mixture is refluxed for about one hour (Note 4). After cooling, the water layer is siphoned off and discarded (Note 5).

The oil obtained in the preceding step is transferred to a 3-l. round-bottomed flask and heated under an air-cooled reflux condenser in an oil bath at about 180°. When the evolution of carbon dioxide has

ceased (about two hours), the oil is decanted from a small amount of solid material. The solid residue on treatment with 200–300 cc. of concentrated hydrochloric acid gives an additional small quantity of oil which is added to the main portion.

The crude pelargonic acid is distilled in a modified Claisen flask having a fractionating side arm, and the material boiling at 140–142°/12 mm. (188–190°/100 mm.) is collected. The yield is 525–590 g. (66–75 per cent of the theoretical amount). The melting point of the pure acid is 12–12.5° (Note 6).

2. Notes

1. Commercial butyl alcohol was dried over solid potassium carbonate and distilled through a 90-cm. indented column. The portion boiling at 117–118° was used.
2. Two layers are formed at first, but the solution becomes homogeneous as saponification occurs. Boiling chips should be placed in the flask, and heating should be done carefully at first, with occasional shaking, or the reaction may get beyond control.
3. The flask should not be allowed to cool between saponification and distillation. It is advisable to heat the flask to prevent the volume of distillate from becoming too large. Usually about 7 l. of distillate is collected, from which the butyl alcohol can be recovered.
4. When the oily layer ceases to increase, decomposition of the potassium heptylmalonate is complete. A layer of salt sometimes accumulates at the bottom of the flask. Care must be taken in heating to prevent cracking the flask.
5. It is unnecessary to extract the aqueous layer with an organic solvent.
6. *n*-Caproic acid may be prepared by this method from *n*-butyl bromide in similar yields (see also p. 417). In this preparation a partial decomposition of the substituted malonic acid is brought about by refluxing the aqueous solution in the 12-l. flask after the addition of the hydrochloric acid. Butylmalonic acid is appreciably soluble in water, and separation of the oily layer does not occur until the malonic acid has been largely decomposed to caproic acid. The time required is about eight to ten hours. It is advisable to heat the acid layer under air reflux as in the preparation of pelargonic acid.

3. Discussion

Pelargonic acid has been prepared by the oxidation of oleic acid[1] and by hydrolysis of octyl cyanide[2] or heptylacetoacetic ester.[3]

References and Notes

1. Redtenbacher, Ann. **59**, 52 (1846); Harries and Thieme, ibid. **343**, 355 (1905); Harries and Türk, Ber. **39**, 3737 (1906); Molinari and Soncini, ibid. **39**, 2739 (1906); Molinari and Barozi, ibid. **41**, 2795 (1908); Jegorow, J. prakt. Chem. (2) **86**, 531 (1912).
2. Zincke and Franchimont, Ann. **164**, 333 (1872).
3. Jourdan, ibid. **200**, 107 (1880).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

heptylacetoacetic ester

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

n-butyl bromide (109-65-9)

sodium bromide (7647-15-6)

carbon dioxide (124-38-9)

butyl alcohol (71-36-3)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

Caproic acid, n-caproic acid (142-62-1)

ethyl malonate (1071-46-1)

Malonic acid (141-82-2)

oleic acid (112-80-1)

Heptyl bromide (629-04-9)

Pelargonic acid (112-05-0)

potassium heptylmalonate

Butylmalonic acid (534-59-8)

octyl cyanide (2243-27-8)

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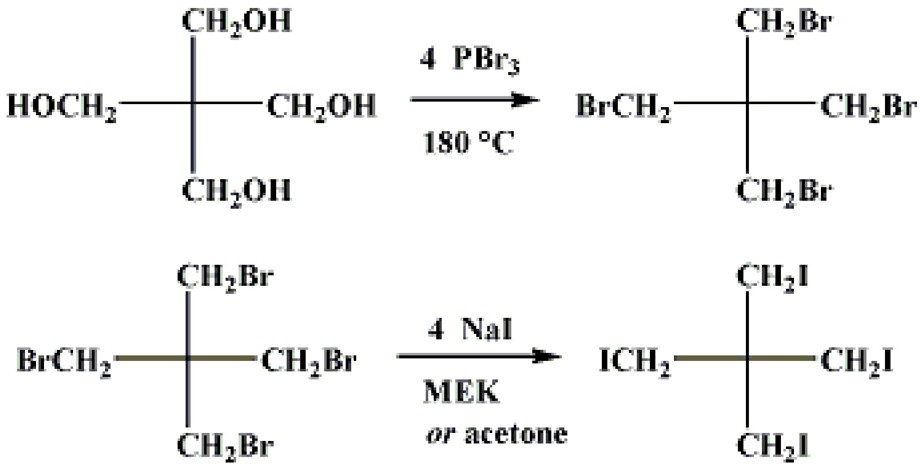
Organic Syntheses, *CV 2, 476*

PENTAERYTHRITYL BROMIDE AND IODIDE

[[Methane, tetrakis(bromomethyl)- and (iodomethyl)-]]



Submitted by H. B. Schurink
Checked by W. H. Carothers and W. L. McEwen.

1. Procedure

(*A*) *Pentaerythrityl Bromide*.—One hundred twenty-five grams (0.92 mole) of dry pentaerythritol (Org. Syn. Coll. Vol. I, **1941**, 425) is placed in a 500-cc. round-bottomed flask provided with an air-cooled reflux condenser bearing at the upper end a long-stemmed dropping funnel and a bent glass tube. The tube is connected to a suitable trap for absorbing the large quantity of hydrogen bromide which is evolved. The flask is heated on a steam bath, and 500 g. (175 cc., 1.85 moles) of freshly distilled phosphorus tribromide (p. 359) is added cautiously from the dropping funnel. When this addition has been completed the steam bath is replaced by an oil bath and the temperature is raised gradually to 170–180° (Note 1). After heating at this temperature for twenty hours, the orange-red reaction mixture is transferred to a beaker containing 1 l. of cold water and stirred thoroughly to reduce the lumps to a small size. The red, flocculent material is filtered with suction and washed several times with hot water; finally it is washed thoroughly with two 200-cc. portions of cold 95 per cent ethyl alcohol (Note 2). After drying, the material is transferred to a large Soxhlet extractor and extracted exhaustively with 95 per cent alcohol (Note 3). The pentaerythrityl bromide separates from the alcohol and after cooling is collected with suction. The yield of crude product melting at 158–160° is 245–270 g. (69–76 per cent of the theoretical amount); this material is sufficiently pure for conversion to the iodide (Note 4). For purification, the crude product may be recrystallized from 95 per cent alcohol, using 30 cc. of solvent per gram; the melting point is raised to 163°, and the recovery is about 85 per cent.

(*B*) *Pentaerythrityl Iodide*.—In a 500-cc. round-bottomed flask fitted with a reflux

condenser, a mixture of 100 g. (0.67 mole) of sodium iodide (dried at 120°), 300 cc. (240 g.) of ethyl methyl ketone (Note 5), and 50 g. (0.13 mole) of crude pentaerythrityl bromide (m.p. 158–160°) is refluxed on a steam bath for forty-eight hours. The condenser is set for distillation, the solvent is distilled, and the residue is washed into a hot Büchner funnel with hot water. The product is washed thoroughly on the funnel with boiling water, pressed well, and transferred to a large Soxhlet extractor. To remove impurities the material is extracted with boiling 95 per cent alcohol until a sample removed from the extraction thimble melts at 233° (Note 6). The product is then removed from the thimble and dried; the yield is 66–73 g. (89–98 per cent of the theoretical amount). The crude product may be recrystallized from hot benzene, using about 18 cc. of solvent per gram. The recovery is about 80 per cent, and the melting point is not changed.

2. Notes

1. The temperature must be raised slowly to avoid formation of spontaneously inflammable hydrides of phosphorus which will ignite and destroy the preparation. A similar result occurs if the phosphorus tribromide is added at 170°.
2. This washing eliminates intermediate bromohydrins.
3. Since the extraction is slow, it is advisable to divide the material into several portions and carry out a number of simultaneous extractions. The extractor used was a modified Soxhlet, arranged so that the extractor tube is heated by the vapor of the solvent (p. 524, Note 3).
4. The crude product has a disagreeable odor, probably due to the presence of a compound of phosphorus. The odor may be eliminated by heating at 120°, followed by several recrystallizations.
5. Acetone may be used as solvent in place of ethyl methyl ketone, but the reaction must then be carried out in a sealed vessel at 95–100° for thirty to thirty-six hours.
6. The extraction requires twelve to sixteen hours, depending upon the rate of refluxing of the alcohol.

3. Discussion

Pentaerythrityl bromide has been prepared by the action of phosphorus tribromide on pentaerythritol,[1], [2] and of an acetic acid solution of hydrobromic acid on pentaerythrityl tetracetate.[3] The iodide has been prepared by the action of red phosphorus and hydriodic acid on pentaerythritol[4] and by treating the bromide with sodium iodide in acetone.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 753

References and Notes

1. Rave and Tollens, Ann. **276**, 61 (1893); Gustavson, J. prakt. Chem. (2) **54**, 98 (1896).
2. Backer and Schurink, Rec. trav. chim. **50**, 924 (1931).
3. Perkin and Simonsen, J. Chem. Soc. **87**, 860 (1905).
4. Tollens and Wigand, Ann. **265**, 331 (1891).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

red phosphorus

Methane, tetrakis(bromomethyl)- and (iodomethyl)-

ethyl alcohol, alcohol (64-17-5)

acetic acid (64-19-7)

Benzene (71-43-2)

HYDROBROMIC ACID, hydrogen bromide (10035-10-6)

phosphorus tribromide (7789-60-8)

acetone (67-64-1)

hydriodic acid (10034-85-2)

sodium iodide (7681-82-5)

Pentaerythritol (115-77-5)

iodide (20461-54-5)

ethyl methyl ketone (78-93-3)

Pentaerythrityl bromide (3229-00-3)

Pentaerythrityl iodide (1522-88-9)

pentaerythrityl tetracetate (597-71-7)

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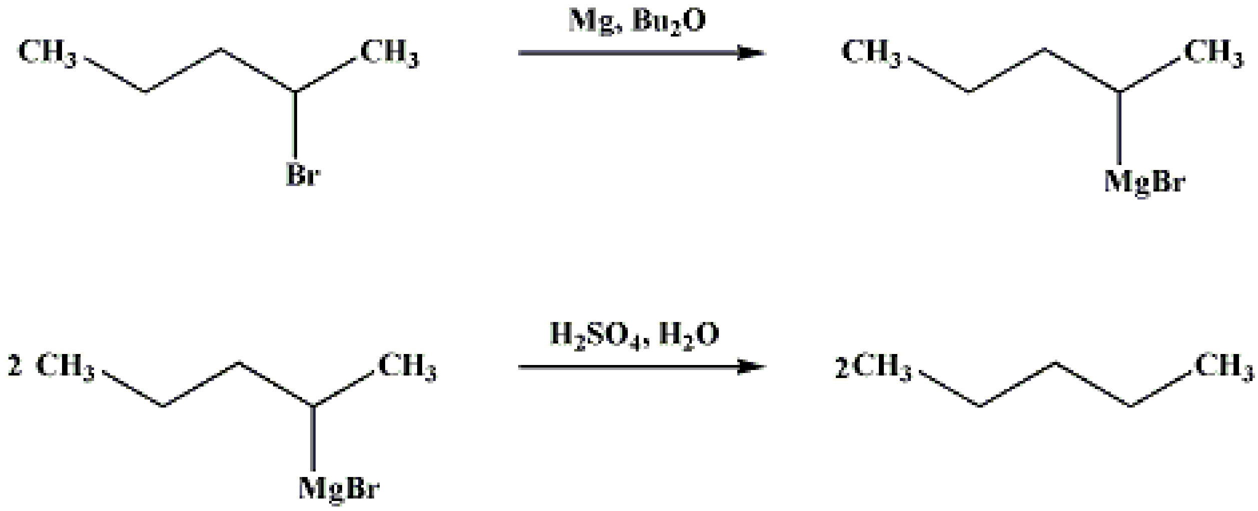
Organic Syntheses, CV 2, 478

n-PENTANE



Submitted by C. R. Noller
Checked by Roger Adams and L. J. Roll.

1. Procedure

In a 5-l. flask, placed on a steam bath and fitted with a mechanical stirrer, a separatory funnel, a thermometer well (Note 1), and a calcium chloride tube, is placed 182 g. (7.5 gram atoms) of magnesium turnings. To this are added a crystal of iodine and 100 cc. of a solution of 1133 g. (7.5 moles) of 2-bromopentane (Note 2) in 750 g. of *n*-butyl ether (Note 3). The stirrer is started, and the flask is heated with steam until the reaction starts. This may take from fifteen minutes to one hour; the flask must be watched quite closely because the reaction, when once started, is very vigorous and evolves a large amount of heat. As soon as the reaction has started, 750 g. of *n*-butyl ether is added and then the balance of the solution of 2-bromopentane in *n*-butyl ether is added at such a rate that the temperature is kept at 50–60°. External cooling is used in order to allow more rapid addition of the 2-bromopentane. After addition is complete (about three hours), the mixture is heated on a steam bath for one hour.

In the meantime, a 12-l. flask containing a solution of 450 cc. of concentrated sulfuric acid in 3 l. of water is placed on a steam bath and fitted with a stirrer, a separatory funnel, and an efficient ice-cooled condenser set for distillation. The stirrer is started, and the solution of the Grignard reagent, prepared above, is added. The acid solution is allowed to become warm but is kept below the boiling point by external cooling. After all the Grignard reagent has been added, the mixture is heated on the steam bath until no more pentane distils. The reaction flask is allowed to cool, and the *n*-butyl ether layer is separated, transferred to a 5-l. flask connected with the condenser, and heated with a free flame until the boiling point of the *n*-butyl ether is reached (Note 4). The combined distillate is separated from a small amount of water, washed twice with 125-cc. portions of cold, concentrated sulfuric acid, and allowed to stand overnight with

anhydrous potassium carbonate. After removing the potassium carbonate, the *n*-pentane is fractionated twice through an efficient 100-cm. fractionating column. The yield is 270–290 g. (50–53 per cent of the theoretical amount) of a product which boils at 35.5–36.5°.

2. Notes

1. A closed glass tube containing mercury was used as a thermometer well. It was inserted with the end in the reaction mixture. The thermometer was placed in the well with the bulb in the mercury.
2. The 2-bromopentane used in this preparation was prepared by the action of hydrobromic acid on secondary amyl alcohol (methyl *n*-propyl carbinol) obtained from Stanco Distributors, Inc. Other commercial straight-chain amyl alcohols when converted to the bromides gave a pentane boiling at 33–35°, showing that a considerable quantity of isopentane was present.
3. The use of *n*-butyl ether allows the ready separation of the pentane by distillation. The butyl ether used in this preparation boiled at 142–144°.
4. About 70 per cent of the *n*-butyl ether is recovered readily and may be purified by distillation.

3. Discussion

n-Pentane has been obtained in many ways, but the reactions which are of preparative interest are few. They include the reduction of 2-bromopentane with zinc and hydrochloric acid;[1] the reduction of 3-iodopentane with zinc and hydriodic acid;[2] the catalytic reduction of pyridine at 50°;[3] the reduction of *n*-amylene;[4] and the decomposition of *sec*.-amylmagnesium bromide with ammonium chloride.[5] The use of *n*-butyl ether in the procedure described above, which eliminates the problem of separating *n*-pentane and ethyl ether,[5] was suggested by a paper of Marvel, Blomquist, and Vaughn.[6]

References and Notes

1. Clarke and Talbot, unpublished results.
2. Karvonen, Acta Chem. Fennica, **3**, 101 (1930) [C. A. **25**, 2412 (1931)].
3. Skita and Brunner, Ber. **49**, 1598 (1916).
4. Fettindustrieges. m. b. H., Ger. pat. 329,471 [Frdl. **13**, 178 (1916-21)]; Wibaut and collaborators, Rec. trav. chim. **58**, 337 (1939).
5. Fischer and Klemm, Z. physik. Chem. A **147**, 275 (1930).
6. Marvel, Blomquist, and Vaughn, J. Am. Chem. Soc. **50**, 2810 (1928).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

secondary amyl alcohol

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ethyl ether (60-29-7)

ammonium chloride (12125-02-9)

magnesium turnings (7439-95-4)

HYDROBROMIC ACID (10035-10-6)

mercury (7439-97-6)

iodine (7553-56-2)

pyridine (110-86-1)

zinc (7440-66-6)

hydriodic acid (10034-85-2)

butyl ether, n-butyl ether (142-96-1)

Pentane, n-PENTANE (109-66-0)

methyl n-propyl carbinol (6032-29-7)

3-iodopentane (1809-05-8)

n-amylene

2-bromopentane (107-81-3)

isopentane (78-78-4)

sec.-amylmagnesium bromide

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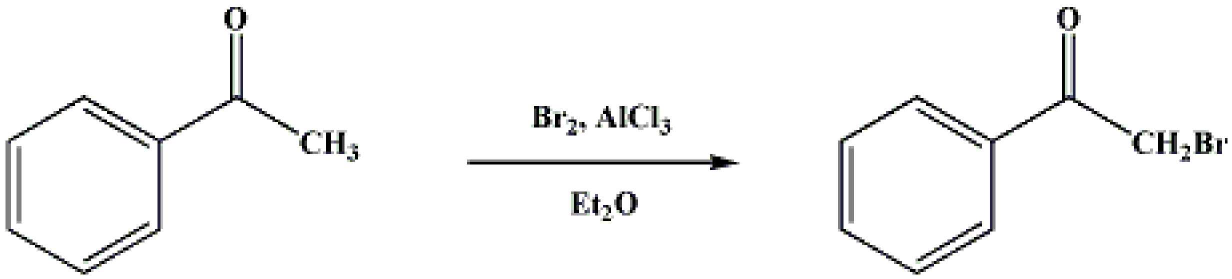
Organic Syntheses, CV 2, 480

PHENACYL BROMIDE

[Acetophenone, α-bromo-]



Submitted by R. M. Cowper and L. H. Davidson.
Checked by Lee Irvin Smith and E. W. Kaiser.

1. Procedure

A solution of 50 g. (0.42 mole) of acetophenone (Org. Syn. Coll. Vol. I, **1941**, 111) in 50 cc. of pure anhydrous ether (Note 1) is placed in a dry three-necked flask fitted with a separatory funnel, mechanical stirrer, and reflux condenser (Note 2). The solution is cooled in an ice bath, 0.5 g. of anhydrous aluminum chloride is introduced (Note 3), and 67 g. (21.5 cc., 0.42 mole) of bromine is added gradually from the separatory funnel, with stirring, at the rate of about 1 cc. per minute. The bromine color disappears rapidly although very little hydrogen bromide is evolved; towards the end of the reaction the solution becomes pink.

After the bromine has been added the ether and dissolved hydrogen bromide are removed at once (Note 4) under reduced pressure with a slight current of air. The phenacyl bromide remains as a solid mass of brownish yellow crystals (Note 5); the color is removed by shaking with a mixture of 10 cc. of water and 10 cc. of petroleum ether. The crystals are filtered with suction and washed several times with fresh portions of the solvent mixture, if necessary, until a white product is obtained (Note 6). The crude phenacyl bromide weighs 74–80 g. (88–96 per cent of the theoretical amount) and melts at 45–48°. This material is sufficiently pure for many purposes. If higher purity is desired the crude product may be recrystallized from 25–30 cc. of methanol, yielding 54–55 g. (64–66 per cent of the theoretical amount) of white crystals melting at 49–51° (Note 7).

2. Notes

1. Dry carbon tetrachloride may be used as a solvent but is less favorable than dry ether.
2. Quantities up to 200 g. of acetophenone may be brominated in a single operation with equally good yields but this is not generally advisable unless the

product is to be used at once, since it becomes discolored on standing.
3. Without aluminum chloride the reaction is slow and incomplete.
4. If the ether and hydrogen bromide are not removed immediately the solution blackens on standing and a lower yield of less pure product results.
5. Phenacyl bromide is a lachrymator and should be manipulated carefully, to avoid contact with the skin and inhalation of the vapor.
6. The water removes yellow color due to residual hydrogen bromide, and the petroleum ether removes unchanged acetophenone or oily by-product. Since the product is quite insoluble in water and only slightly soluble in cold petroleum ether, it may be washed several times with little loss.
7. The checkers observed that all specimens of the product, even after recrystallization, although white at first, became dark and discolored on standing in a vacuum desiccator over calcium chloride.

3. Discussion

Phenacyl bromide has been prepared by the bromination of acetophenone without a solvent,[1] in carbon disulfide,[2, 3] in acetic acid,[3, 4, 5] and in other organic solvents.[5] The quantitative aspects of the bromination in various solvents have been investigated by Kröhnke.[3] The use of ether in the method described is based on the use of this solvent in the bromination of desoxybenzoin.[6]

Phenacyl bromide is a useful reagent for the identification of organic acids by conversion to crystalline phenacyl esters.[4, 7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 117

References and Notes

1. Emmerling and Engler, Ber. **4**, 148 (1871).
2. Hunnius, ibid. **10**, 2007 (1877); Staedel and Kleinschmidt, ibid. **13**, 837 (1880); Staedel, ibid. **16**, 22 (1883).
3. Kröhnke, ibid. **69**, 921 (1936).
4. Rather and Reid, J. Am. Chem. Soc. **41**, 77 (1919).
5. Möhlau, Ber. **15**, 2465 (1882); Lazennec, Bull. soc. chim. (4) **5**, 501 (1909).
6. Limpricht and Schwanert, Ann. **155**, 68 (1870).
7. Shriner and Fuson, "The Systematic Identification of Organic Compounds," pp 130 and 132, John Wiley & Sons, New York, 2nd Ed., 1940.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Desoxybenzoin

petroleum ether

calcium chloride (10043-52-4)

acetic acid (64-19-7)

methanol (67-56-1)

ether (60-29-7)

hydrogen bromide (10035-10-6)

bromine (7726-95-6)

carbon tetrachloride (56-23-5)

Acetophenone (98-86-2)

aluminum chloride (3495-54-3)

carbon disulfide (75-15-0)

Phenacyl bromide, Acetophenone, α-bromo- (70-11-1)

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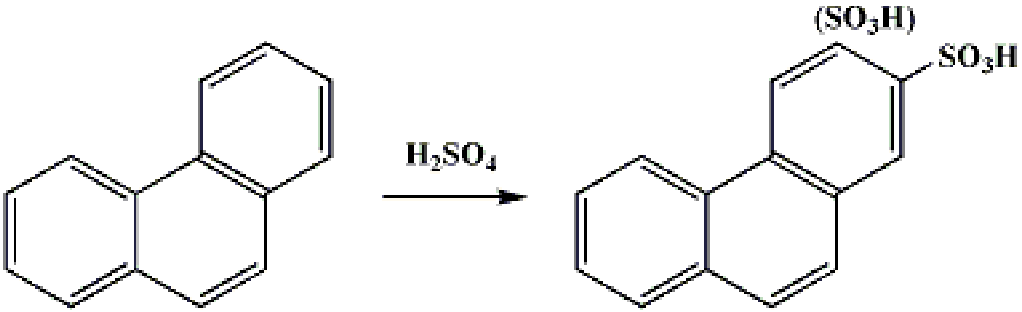
Organic Syntheses, CV 2, 482

2- AND 3-PHENANTHRENESULFONIC ACIDS



Submitted by Louis F. Fieser
Checked by W. W. Hartman and G. L. Boomer.

1. Procedure

The sulfonation is carried out in a 2-l. round-bottomed, three-necked flask fitted with a thermometer, a dropping funnel, and a stirrer (Note 1). Five hundred grams (2.8 moles) of pure phenanthrene (Note 2) is melted in the flask, which is clamped in an oil bath heated to 110°. Mechanical stirring is started, and 327 cc. (600 g., 5.8 moles) of concentrated sulfuric acid is run in at such a rate that the internal temperature does not rise above 120° (ten to fifteen minutes). The reaction mixture is stirred and maintained at a temperature of 120–125° for three and one-half hours, when a test portion should give a nearly clear solution in water. The reaction is exothermic, and the bath must be kept at a temperature 5–10° below that of the mixture. Some sulfur dioxide is given off, and the mixture becomes green.

The viscous solution, while still hot, is dissolved in 4 l. of water, and a solution of 400 g. of sodium hydroxide in 600–800 cc. of water is added. After thorough cooling in an ice bath, the precipitated sodium salt is collected on a large funnel, pressed well, and washed thoroughly with 1 l. of half-saturated sodium chloride solution (about 180 g. per liter). The precipitate contains chiefly the sodium 2- and 3-sulfonates. The filtrate contains a mixture of disulfonates and is discarded (Note 3). In order to effect a preliminary concentration of the less-soluble 2-isomer, the sodium salt mixture is dissolved in 7–8 l. of boiling water containing 100 cc. of concentrated hydrochloric acid (Note 4), and the filtered solution is then neutralized with sodium hydroxide and allowed to crystallize. After separating the mother liquor (A), which is saved, the crystals (consisting largely of the sodium 2-sulfonate) are dissolved in about 8 l. of boiling water (Note 5), and 100 g. of solid barium chloride dihydrate is added to the hot solution. The fine white precipitate of barium 2-phenanthrenesulfonate which forms is digested at the boiling point for a short time and then brought onto a 20-cm. Büchner funnel, preheated on the steam bath. The mother liquor (B) is saved.

The precipitated barium 2-sulfonate always retains a certain quantity of the 3-sulfonate, which must be extracted with hot water. The precipitate is digested at the

boiling point with 6-l. portions of boiling water until the residual salt is found to be free from isomers. The purity is determined from the melting point of the *p*-toluidine salt, in the manner described below. Usually two or three such washings are required. The mother liquor (B) from the barium 2-sulfonate is combined with the various washings, and the whole is boiled down to a volume of about 6 l. Sulfuric acid (25–30 cc. of concentrated acid, diluted with water) is then added to precipitate the barium; the filtered solution (Note 6) is concentrated to about 2 l. and neutralized with potassium hydroxide to bring down a mixture of potassium sulfonates (C). The filtrate from the potassium salts may be boiled down further and treated with potassium chloride to ensure complete recovery of the potassium sulfonates, and then discarded. The potassium salt mixture collected in these operations is set aside. (C).

The mother liquor (A) from the sodium salt crystallization is boiled down to a volume of about 2–3 l., and 200 g. of potassium chloride is added to the hot solution. The potassium salt mixture which separates on cooling is collected and combined with the potassium salts (C) described in the preceding paragraph; the filtrate is discarded. The combined material is dissolved in the minimum amount of hot water, and the filtered solution is heated to boiling and allowed to cool without disturbance. It deposits a large crop of the potassium 3-sulfonate in a very pure condition (180–210 g.). The mother liquor, containing more of the 3-sulfonate together with some of the 2-sulfonate, is concentrated to a small volume; the product is salted out with potassium chloride and washed free of sulfate ion with potassium chloride solution. A hot aqueous solution of this material is then treated with 10 g. of barium chloride dihydrate, and the precipitated barium 2-sulfonate (5–10 g.) is washed free of isomers. The original filtrate is reserved, but the washings are discarded. From the original filtrate, by evaporation, precipitation of the barium with sulfuric acid, neutralization with potassium hydroxide, and crystallization of the product, there is obtained an additional quantity of the pure potassium 3-sulfonate (50–70 g.).

The yields are: barium 2-phenanthrenesulfonate, 150–200 g. (17–21 per cent); potassium 3-phenanthrenesulfonate, 200–220 g. (24–26 per cent) (Note 7)and(Note 8).

Identification and Test of Purity.—The method[1] consists in the preparation and examination of a test sample of the *p*-toluidine salt of the sulfonic acid (Note 9). An aqueous solution of the free sulfonic acid (or of the sodium or potassium salt) is treated with an excess of *p*-toluidine and hydrochloric acid, enough water is added to bring all the material into solution at the boiling point, and crystallization is allowed to take place. The crystals should be washed well with water. A barium salt should be boiled with dilute sulfuric acid, a little decolorizing carbon added, and the filtered solution treated with *p*-toluidine. If the amine salt separates in an oily condition, the walls of the vessel should be scratched, for the *p*-toluidine salt, particularly that of the 3-acid, may remain as an oil for a short time, even when nearly pure. On the other hand, a rather impure acid gives a *p*-toluidine salt which remains as an oil almost indefinitely. This property characterizes a mixture of isomers nearly as definitely as the depression in the melting point, though this is large. In determining the melting point of an amine salt, the sample may be dried by pressing the material on a filter

paper, but the capillary should be placed in the bath when the temperature is below 130°. The preliminary heating gives ample provision for thorough drying, without which the material may melt twenty to thirty degrees below the true melting point.

The *p*-toluidine salt of 2-phenanthrenesulfonic acid forms flat needles or plates melting at 282° (291° corr.); that of the 3-acid forms thick needles melting at 217° (222° corr.).

2. Notes

1. A convenient form of stirrer is made by bending a glass rod to an angle of 45° about 4 cm. from the end. This type of stirrer can be used to dislodge material adhering to the walls of the flask.
2. A pure grade of phenanthrene should be used. Technical 70 per cent phenanthrene may be purified by the method of Cohen and Cormier.[2] It is important to note that the presence of more than about 2 per cent of anthracene in phenanthrene raises the melting point.
3. It is estimated that no less than twelve isomeric disulfonates are present. No useful products have been obtained from the mixture.
4. The solubility of the sulfonates is increased appreciably by the presence of a mineral acid.
5. A 10-l. enameled pail heated with a ring burner serves as a convenient, if not very durable, vessel for boiling and evaporating the large volumes of solution involved. The contents may be ladled out with a casserole.
6. The addition of a little decolorizing carbon greatly facilitates the coagulation of barium sulfate and aids in retaining it on the filter.
7. The low yield of the monosulfonates is due in large part to the fact that disulfonic acids are invariably formed along with the mono acids.
8. For some reactions, such as alkali fusion, the barium salt of the 2-phenanthrenesulfonic acid is suitable. For conversion into the potassium salt, it is highly advisable to use the barium salt in the moist and finely divided condition in which it is first obtained. Since the reaction is slow at best, several fresh portions of sulfuric acid should be employed for precipitating the barium.
9. This is recommended as a general method of identifying sulfonates. In economy of time and material it is superior to the preparation of the free acid, the acid chloride, the ester, the amide, or the phenol. By this method one can identify quickly a few milligrams of an acid or of any of its metal salts, whether it is in the solid state or in solution.

3. Discussion

The sulfonation of phenanthrene has been studied by Werner and his students,[3] by Sandqvist,[4] by Fieser,[1] and by Ioffe.[5]

References and Notes

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2. Cohen and Cormier, ibid. **52**, 4363 (1930).
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4. Sandqvist, ibid. **392**, 76 (1912).
5. Ioffe, J. Gen. Chem. (U.S.S.R.) **3**, 448 (1933) [C. A. **28**, 1694 (1934)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

2- AND 3-PHENANTHRENESULFONIC ACIDS

barium salt of the 2-phenanthrenesulfonic acid

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

sulfur dioxide (7446-09-5)

barium sulfate (7727-43-7)

decolorizing carbon (7782-42-5)

potassium hydroxide (1310-58-3)

anthracene (120-12-7)

barium (7440-39-3)

potassium chloride (7447-40-7)

barium chloride dihydrate (10326-27-9)

phenanthrene (85-01-8)

Barium 2-phenanthrenesulfonate

Potassium 3-phenanthrenesulfonate

p-toluidine (106-49-0)

p-toluidine salt of 2-phenanthrenesulfonic acid

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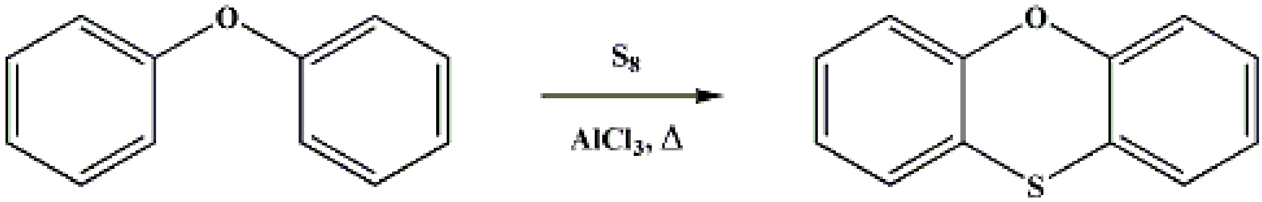
PHENOXTHIN

[Phenoxathiin]



Submitted by C. M. Suter and Charles E. Maxwell.
Checked by Reynold C. Fuson and E. A. Cleveland.

1. Procedure

In a 5-l. flask are placed 1886 g. (11 moles) of phenyl ether (Note 1), 256 g. (8 gram atoms) of sulfur (flowers), and 510 g. (3.8 moles) of anhydrous aluminum chloride. The reactants are mixed well by shaking the flask vigorously; the mixture becomes purple. The flask is fitted with a water-cooled reflux condenser (Note 2) and heated on the steam bath in an efficient hood. The evolution of hydrogen sulfide, vigorous at first, becomes slow after one and one-half hours. After the heating has been continued for a total of four hours, with occasional shaking, the reaction mixture is poured slowly, with stirring, into a 4-l. beaker half filled with ice to which 250 cc. of concentrated hydrochloric acid has been added. More ice is added if necessary. The flask is rinsed with water and the rinsings added to the main product. After the two layers are separated the water layer is discarded and the phenyl ether-phenoxthin layer dried overnight with calcium chloride. This mixture is then distilled at 5 mm. pressure from a 3-l. special Claisen flask having a well-lagged 18-in. column. After removal of the phenyl ether the fraction boiling at 140–160°/5 mm., practically all of which comes over at 150–152°, is collected as phenoxthin (Note 3). The yield is 700 g. (87 per cent of the theoretical amount). This material, which is somewhat colored and has a strong odor, is purified by crystallization from 1.2–1.5 l. of boiling methyl alcohol; the solution should be chilled rapidly and stirred well to prevent the product from separating as an oil. The loss on crystallization is about 3 per cent and the dried material melts at 56–57° (Note 4). A second crystallization gives a product melting about one degree higher.

2. Notes

1. The commercial "diphenyl oxide" is satisfactory.
2. The condenser returns to the flask a small amount of phenyl ether, which would otherwise be carried away by the hydrogen sulfide.
3. The fore-run of phenyl ether, b.p. 98–101°/5 mm., may be used in subsequent runs. Other boiling points are: phenyl ether, 134–137°/15 mm., 259–262°/745 mm.; and phenoxthin, 180–183°/15 mm., 311°/745 mm. Fractionation at 15 mm. gives a lower yield with a larger amount of tarry residue remaining in the flask than fractionation at 5 mm.

4. A pure sample melts at 57.5–58°.

3. Discussion

Phenoxthin has been obtained by a series of reactions utilizing thiocatechol and 3,5-dinitro-4-chlorobenzoic acid[1] as the starting materials, from phenoxtellurin and sulfur,[2] and by the action of sulfur and aluminum chloride upon phenyl ether.[3]

References and Notes

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2. Drew, J. Chem. Soc. **1928**, 519.
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Phenoxthin

phenyl ether-phenoxthin

phenoxtellurin

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

methyl alcohol (67-56-1)

hydrogen sulfide (7783-06-4)

sulfur (7704-34-9)

aluminum chloride (3495-54-3)

phenyl ether, diphenyl oxide (101-84-8)

Phenoxathiin (262-20-4)

thiocatechol (1121-24-0)

3,5-dinitro-4-chlorobenzoic acid (118-97-8)

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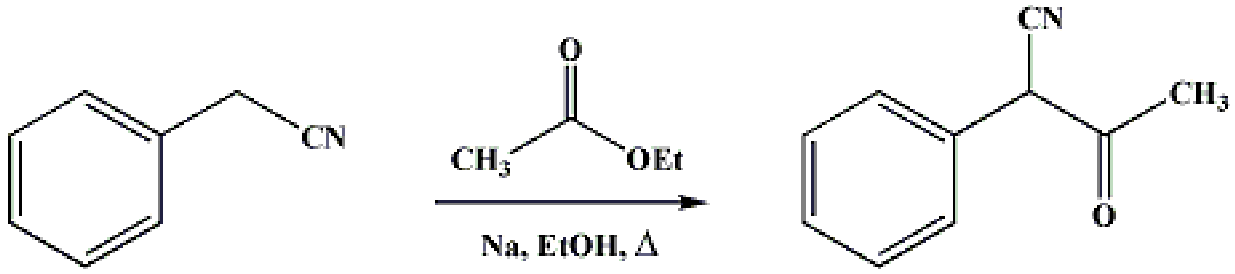
α-PHENYLACETOACETONITRILE

[α-Tolunitrile, α-acetyl-]



Submitted by Percy L. Julian, John J. Oliver, R. H. Kimball, Arthur B. Pike, and George D. Jefferson.
Checked by C. R. Noller and Martin Synerholm.

1. Procedure

A solution of sodium ethoxide is prepared from 60 g. (2.6 gram atoms) of clean sodium and 700 cc. of absolute alcohol (Note 1) in a 2-l. round-bottomed flask equipped with a reflux condenser. To the hot solution is added a mixture of 234 g. (2 moles) of pure benzyl cyanide (Note 2) and 264 g. (3 moles) of dry ethyl acetate (Note 3). The mixture is thoroughly shaken, the condenser closed with a calcium chloride tube, and the solution heated on the steam bath for two hours before standing overnight (Note 4). The next morning the mixture is stirred with a wooden rod to break lumps, cooled in a freezing mixture to −10°, and kept at this temperature for two hours. The sodium salt is collected on a 6-in. Büchner funnel and washed four times on the funnel with 250-cc. portions of ether. The filter cake is practically colorless and corresponds to 250–275 g. of dry sodium salt, or 69–76 per cent of the calculated amount. The combined filtrates are placed in the freezing mixture until they can be worked up as indicated below.

The sodium salt still wet with ether is dissolved in 1.3 l. of distilled water at room temperature, the solution cooled to 0°, and the nitrile precipitated by adding slowly, with vigorous shaking, 90 cc. of glacial acetic acid, while the temperature is kept below 10°. The precipitate is separated by suction filtration and washed four times on the funnel with 250-cc. portions of water. The moist cake weighing about 300 g. (Note 5) corresponds to 188–206 g. (59–64 per cent) of dry colorless α-phenylacetoacetonitrile, m.p. 87–89°, which is suitable for most purposes.

If it is desired to recrystallize the crude product, the moist cake is dissolved in 100 cc. of hot methyl alcohol and the solution filtered and cooled, with stirring, to −10°. The crystals are separated by suction filtration and washed once on the filter with 40 cc. of methyl alcohol cooled to −10°. When dry, the product weighs 173–191 g. (54–60 per cent) and melts at 88.5–89.5°.

The filtrates and washings from the separation of the sodium salt are placed in a 5-l. flask and diluted with ice-cold water until the flask is full; the lower layer is removed almost completely by siphoning, most of the ether removed by decantation, and the remainder separated in a separatory funnel. The aqueous layer is extracted twice in a similar manner with 500-cc. portions of ether, and the ether extracts are discarded. The ether remaining in the aqueous layer is removed under diminished pressure by drawing air through the solution for one hour with a suction pump, and the α-phenylacetoacetonitrile is precipitated by adding 60 cc. of glacial acetic acid. If an oil is thrown out, the flask is placed in an ice bath until the precipitate is crystalline. The crystals are separated by suction filtration and washed four times on the funnel with 50-cc. portions of water. When dry the tan-colored product weighs 50–55 g. and melts at 83–86°. It is dissolved in the methyl alcohol mother liquors from the crystallization of the first lot. The solution is boiled with a little Norite, filtered, and cooled to −10°. The crystals which form are collected on a filter, washed with 10 cc. of cold methyl alcohol, and dried. There is obtained 43–48 g. of pale straw-colored material, m.p. 87–89°. The product is recrystallized from 25 cc. of pure methyl alcohol and washed with 10 cc. of cold methyl alcohol; there is obtained 37–41 g., m.p. 88.5–89.5°, making a total yield of material of this purity of 210–232 g. (66–73 per cent of the theoretical amount) (Note 6) and (Note 7).

2. Notes

1. The absolute alcohol may be prepared by drying 95 per cent alcohol twice with lime, or once with lime and once with sodium according to Note 1, Org. Syn. Coll. Vol. I, **1941**, 251, or commercial absolute alcohol may be dried once with lime or sodium just before use.
2. Benzyl cyanide was prepared according to Org. Syn. Coll. Vol. I, **1941**, 107, including the purification with concentrated sulfuric acid.
3. Commercial absolute ethyl acetate was refluxed for one-half hour over phosphorus pentoxide and distilled just before use.
4. If time permits, the procedure may be continued without allowing the mixture to stand overnight. If the drying of the alcohol and ethyl acetate is begun in the morning, however, this is a convenient point at which to interrupt the procedure.
5. If used for the preparation of methyl benzyl ketone (p. 391), the product should not be dried.
6. It does not pay to attempt to recover more pure material by concentration of the mother liquors.
7. The number of steps may be decreased by omitting the isolation of the sodium salt. If this procedure is followed, the reaction mixture, after standing overnight, is diluted in a 5-l. flask with 2 l. of water and shaken until the sodium salt dissolves. A liter of cracked ice is added and the mixture extracted with one 1-l. and two 500-cc. portions of ether. The extracted aqueous solution is freed of ether as above and precipitated with a solution of 150 cc. of glacial acetic acid in 400 cc. of water, filtered, and washed with water. The product is colored and of

lower melting point than that obtained from the purified sodium salt, and must be recrystallized twice from methyl alcohol to reach a melting point of 88.5–89.5°. The total yield of material of this melting point is somewhat less than that given above.

3. Discussion

α-Phenylacetoacetonitrile has been prepared by the condensation of ethyl acetate with the sodium derivative of benzyl cyanide prepared from benzyl cyanide and sodium amide in ether,[1] and by condensation of ethyl acetate and benzyl cyanide by means of dry[2] or alcoholic[3] sodium ethoxide.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 284
- Org. Syn. Coll. Vol. 2, 389

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3. Beckh, Ber. **31**, 3160 (1898); Post and Michalek, J. Am. Chem. Soc. **52**, 4358 (1930).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium derivative of benzyl cyanide

alcohol (64-17-5)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

ethyl acetate (141-78-6)

methyl alcohol (67-56-1)

ether (60-29-7)

Norite (7782-42-5)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

Benzyl cyanide (140-29-4)

Methyl benzyl ketone (103-79-7)

α-phenylacetoacetonitrile, α-Tolunitrile, α-acetyl- (4468-48-8)

sodium amide (7782-92-5)

phosphorus pentoxide (1314-56-3)

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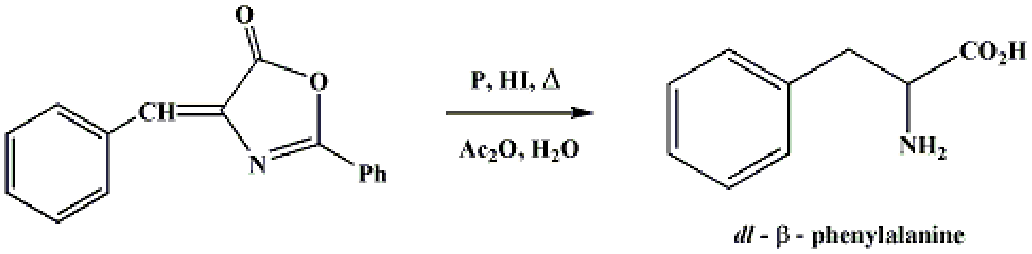
dl-β-PHENYLALANINE

[Alanine, β-phenyl-, *dl*-]

[(*A*) (*From the Azlactone of* α-*Benzoylaminocinnamic Acid*)]



Submitted by H. B. Gillespie and H. R. Snyder.
Checked by W. W. Hartman and J. B. Dickey.

1. Procedure

In a 1-l. three-necked, round-bottomed flask fitted with a reflux condenser, a mechanical stirrer, and a dropping funnel (Note 1) are placed 25 g. (0.1 mole) of the azlactone of α-benzoylaminocinnamic acid (Note 2) and (Note 3), 20 g. (0.64 gram atom) of red phosphorus, and 135 g. (125 cc.) of acetic anhydride. During a period of about one hour 195 g. (125 cc., 0.76 mole) of 50 per cent hydriodic acid (sp. gr. 1.56) is added with stirring (Note 4). The mixture is refluxed for three to four hours and, after cooling, is filtered with suction. The unreacted phosphorus is washed on the filter with two 5-cc. portions of glacial acetic acid, and discarded. The filtrate and washings are evaporated to dryness, under reduced pressure, in a 500-cc. Claisen flask heated in a water bath. A 250-cc. distilling flask cooled in ice is used as a receiver, and the distillate is reserved for a second reduction (Note 5).

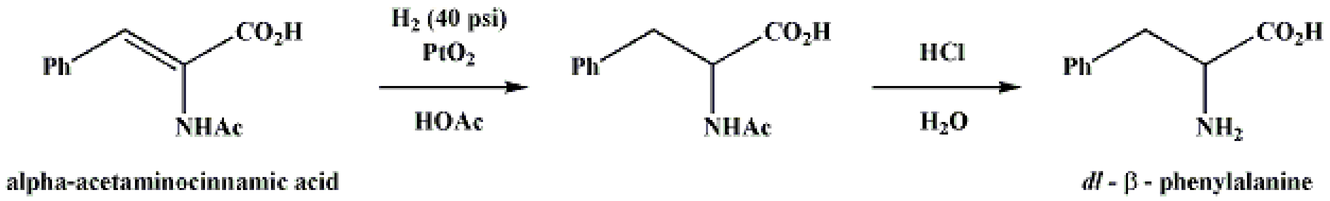
To the dry residue in the Claisen flask 100 cc. of water is added, and the evaporation to dryness is repeated. The second distillate is discarded. To the residue in the flask 150 cc. of water and 150 cc. of ether are added, and the mixture is shaken until solution is complete. The aqueous layer is separated and extracted three times with 100-cc. portions of ether. The ether extracts are discarded; the water solution is heated on a steam bath with 2–3 g. of Norite and a trace of sodium sulfite until all dissolved ether has been removed. The solution is filtered, and the filtrate is heated to boiling and neutralized to Congo red with 15 per cent ammonia (sp. gr. 0.94). Usually about 25 cc. of ammonia is required. The phenylalanine separates in colorless plates which, when cold, are filtered and washed thoroughly on the filter with two 30-cc. portions of cold water. The yield is 10.5–11 g. (63.6–67 per cent of the theoretical amount) of a product which decomposes at 284–288°(corr.) (Note 6).

2. Notes

1. Clean corks protected by tin foil should be used.
2. This azlactone is prepared readily from benzaldehyde according to the procedure given for the azlactone of α-benzoylamino-β-(3,4-dimethoxyphenyl) acrylic acid (p. 55). From 53 g. (0.5 mole) of benzaldehyde, 89.5 g. (0.5 mole) of hippuric acid (p. 328), 41 g. of fused sodium acetate, and 153 g. of acetic anhydride there is obtained 78–80 g. (62–64 per cent yield) of an almost pure product melting at 165–166° (corr.). This material is sufficiently pure for use in the preparation of phenylalanine. By crystallization from 150 cc. of benzene a product melting at 167–168° (corr.) is obtained.
3. The reduction may be carried out by the same procedure starting from α-benzoylaminocinnamic acid, and in this way slightly higher yields are obtained. The azlactone may be converted into the free acid in the following way.
In a 12-l. flask fitted with a mechanical stirrer, 62.3 g. (0.25 mole) of the azlactone is suspended in 6 l. of water, and 11 g. (0.275 mole) of sodium hydroxide is added as a 10 per cent solution. The mixture is heated on the steam bath with stirring until solution is complete. This requires three to four hours. The hot solution is filtered and acidified with hydrochloric acid. The α-benzoylaminocinnamic acid separates as white prisms in the hot solution, and when cold it is filtered. The yield is 55.5–64.5 g. (83–96.5 per cent) of almost pure product melting with decomposition over a two-degree range between the limits 224° and 236° (corr.). The

crude acid can be recrystallized from alcohol, but its melting point remains unchanged.
4. During the addition the reaction mixture may solidify. If this occurs the stirrer is stopped and one or two portions of about 5 cc. of the hydriodic acid solution are stirred into the cake with a glass rod. The mass then becomes sufficiently fluid to permit use of the mechanical stirrer.
5. For a second run the distillate is placed in a 1-l. flask with 4 cc. of water, 25 g. of the azlactone, and 20 g. of red phosphorus. The mixture is refluxed for three to four hours and treated according to the above procedure. The yield is practically the same as in the first run.
6. The decomposition temperature is extremely variable and depends upon the rate of heating. The temperatures reported here were obtained by immersing the melting-point tube in a bath preheated to 200°, and then heating rapidly.

[(*B*) (*From α-Acetaminocinnamic Acid*)]



Submitted by R. M. Herbst and D. Shemin.
Checked by Reynold C. Fuson and E. A. Cleveland.

1. Procedure

A solution of 20.5 g. (0.1 mole) of α-acetaminocinnamic acid (p. 1) in 150 cc. of glacial acetic acid (Note 1) is placed in the bottle of a Burgess-Parr reduction apparatus, 0.5 g. of platinum oxide catalyst (Org. Syn. Coll. Vol. I, **1941**, 463) is added, and the mixture is shaken in an atmosphere of hydrogen under an initial pressure of 40 lb. per sq. in. until the calculated amount of gas is taken up; usually about two hours is required (Note 2) and (Note 3). When the reduction is complete, the catalyst is removed by suction filtration and washed with a little water. The combined filtrate and washings are evaporated to dryness under diminished pressure on a water bath.

The crystalline residue (Note 4) is taken up in 400 cc. of 1 *N* hydrochloric acid, transferred to a 1-l. flask fitted with a reflux condenser, and boiled for ten hours (Note 5). The resulting solution is evaporated to dryness under diminished pressure on the water bath; to the residue 100 cc. of water is added slowly through a dropping funnel at about the same rate as that at which it distils, in order to remove the excess hydrochloric acid as completely as possible. The residue is then taken up in 30–40 cc. of boiling water, and the *p*H of the solution is adjusted until it is basic to Congo red, but still acid to litmus, by careful addition of concentrated ammonia and acetic acid (Note 6). Then two volumes of 95 per cent alcohol is added to aid in the separation of the phenylalanine. The mixture is placed in the refrigerator for a day, after which the product is transferred to a Büchner funnel, and washed first with three 25-cc. portions of ice-cold water and then with alcohol. The yield is 14.5 g. The filtrate is evaporated to dryness under reduced pressure on the water bath, and the residue is extracted with about 70 cc. of ice-cold water in three or four portions. The insoluble material, after washing with 95 per cent alcohol, is added to the main fraction of phenylalanine. The total yield is 16 g. (Note 7).

The combined fractions weighing about 16 g. are dissolved in a minimum amount of boiling water (Note 8), two volumes of 95 per cent alcohol is added, and the flask is placed in a refrigerator overnight to complete crystallization. The phenylalanine is transferred to a Büchner funnel, washed with several small portions of ice-cold water, and finally with alcohol. The yield is 10.5–11 g. By concentrating the filtrate and washings further, 3–3.5 g. of product can be obtained conveniently. The total yield is 14–14.3 g. (85–86 per cent of the theoretical amount) of analytically pure phenylalanine.

2. Notes

1. It may be necessary to warm the mixture in order to dissolve the acetaminocinnamic acid completely in this amount of acetic acid. If so the solution should be allowed to cool to room temperature before it is placed in the reduction apparatus.
2. When the calculated amount of hydrogen is taken up, the catalyst is no longer colloidal and the rate of hydrogen uptake becomes very slow.

3. With freshly prepared and moist catalyst the benzene ring may also be reduced and N-acetylhexahydrophenylalanine formed. When this occurs, the hydrogen uptake continues at a rapid rate even after the amount required for hydrogenation of the side chain has been taken up. After recrystallization from water or dilute alcohol, the hexahydro compound forms needles melting at 178°.
4. Pure N-acetylphenylalanine can be obtained by recrystallizing the residue from hot water or from hot dilute alcohol; it forms colorless needles melting at 150–151°.
5. Hydrolysis with 1 *N* hydrochloric acid is not complete if less than ten hours is allowed. With higher acid concentrations the hydrolysis can be completed more rapidly.
6. When the solution is made just basic to Congo red, the product separates in an almost solid mass; addition of alcohol facilitates the testing of the *p*H by disintegrating the mass and also decreases the solubility of the product.
7. This product contains about 2.5 per cent of ammonium chloride; allowing for this the yield of phenylalanine is 94 per cent. Unless absolutely pure phenylalanine is required, the subsequent recrystallization can be omitted.
8. Phenylalanine dissolves rather slowly in boiling water. It is therefore convenient to start with an excess of water and to concentrate the solution over a free flame until crystals begin to separate from the hot solution.

3. Discussion

dl-Phenylalanine has been prepared by the action of ammonia and hydrogen cyanide on phenylacetaldehyde;[1] by the reduction of the oxime[2] or the phenylhydrazone[3] of phenylpyruvic acid; by the reduction of phenylpyruvic acid in alcoholic-ammoniacal solution;[4] by the reduction of α-aminocinnamic acid or its derivatives;[5] and by the action of ammonia on α-bromo-β-phenylpyruvic acid[6]—a procedure for which detailed directions are given in Org. Syn. **21**, 99.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 705
- Org. Syn. Coll. Vol. 4, 80

References and Notes

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2. Erlenmeyer, ibid. **271**, 169 (1892); Knoop and Hoessli, Ber. **39**, 1479 (1906); Shemin and Herbst, J. Am. Chem. Soc. **60**, 1951 (1938).
3. Feofilaktov and Vinogradova, Compt. rend. acad. sci. U.R.S.S. **24**, 759 (1939) [C. A. **34**, 1971 (1940)]; J. Gen. Chem. (U. S.S.R.) **10**, 255 (1940) [C. A. **34**, 7283 (1940)].
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

red phosphorus

Congo red

azlactone of α-benzoylamino-β-(3,4-dimethoxyphenyl) acrylic acid

Azlactone of α-Benzoylaminocinnamic acid

alcohol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ammonia (7664-41-7)

Benzene (71-43-2)

ether (60-29-7)

acetic anhydride (108-24-7)

ammonium chloride (12125-02-9)

sodium acetate (127-09-3)

hydrogen (1333-74-0)

sodium sulfite (7757-83-7)

sodium hydroxide (1310-73-2)

hydrogen cyanide (74-90-8)

PHOSPHORUS (7723-14-0)

platinum oxide

benzaldehyde (100-52-7)

Norite (7782-42-5)

hydriodic acid (10034-85-2)

Hippuric acid (495-69-2)

α-Acetaminocinnamic acid, acetaminocinnamic acid (5469-45-4)

Phenylpyruvic acid (156-06-9)

α-Benzoylaminocinnamic acid (1155-48-2)

phenylalanine (63-91-2)

N-Acetylhexahydrophenylalanine

N-Acetylphenylalanine (2018-61-3)

phenylacetaldehyde (122-78-1)

α-aminocinnamic acid

α-bromo-β-phenylpyruvic acid (42990-49-8)

DL-β-Phenylalanine, Alanine, β-phenyl-, dl-, DL-Phenylalanine (150-30-1)

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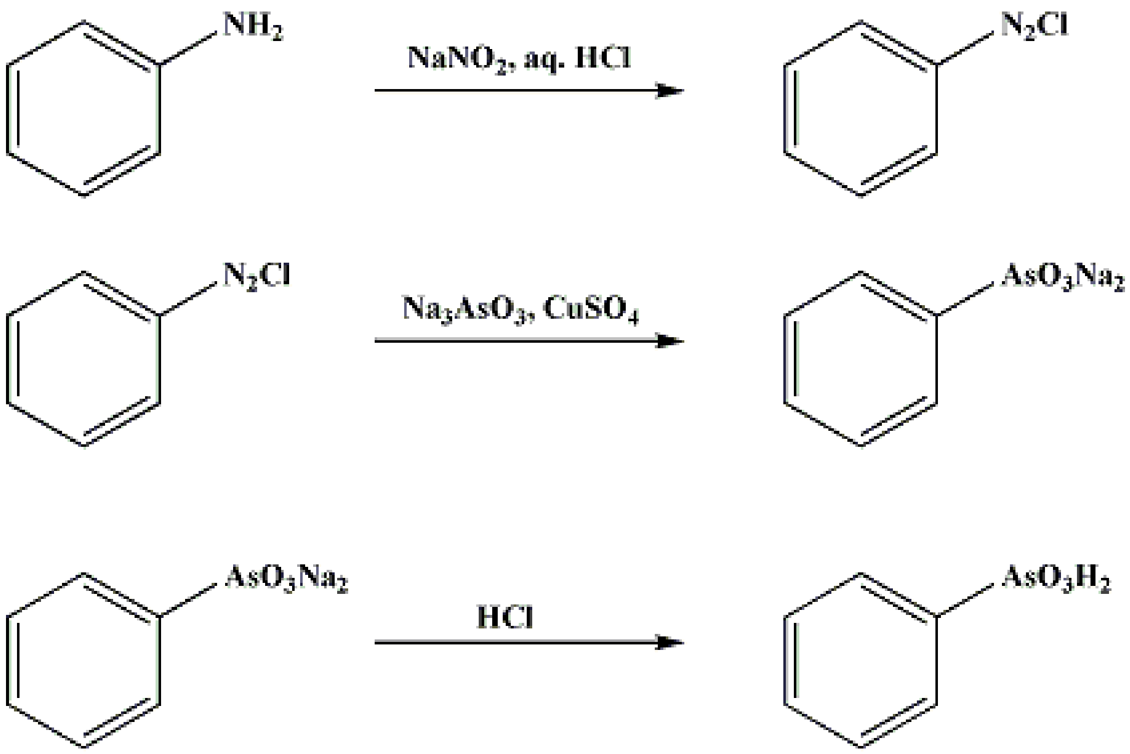
Organic Syntheses, *CV 2, 494*

PHENYLARSONIC ACID

[Benzenearsonic acid]



Submitted by R. H. Bullard and J. B. Dickey.
Checked by W. H. Carothers and W. L. McEwen.

1. Procedure

In a 12-l. round-bottomed flask fitted with a mechanical stirrer is placed 1 l. of water. The water is heated to boiling, and 500 g. (4.7 moles) of anhydrous sodium carbonate is added. As soon as the carbonate has dissolved, 250 g. (1.26 moles) of arsenious oxide and 11 g. of crystalline copper sulfate are added with stirring. When all the solids have dissolved the solution is cooled with stirring under a stream of tap water until the temperature falls to 15°.

Concurrently with the preparation of the sodium arsenite solution, a solution of benzenediazonium chloride is prepared. To a well-stirred mixture of 186 g. (2 moles) of technical aniline, 400 cc. (4.8 moles) of concentrated hydrochloric acid (sp. gr. 1.19), 1 l. of water, and enough crushed ice to make a volume of about 3 l., is added slowly a solution of 145 g. (2 moles) of 95 per cent sodium nitrite in 500 cc. of water. This requires about thirty to forty minutes.

The benezenediazonium chloride solution is then added with stirring during a period of one hour to the suspension of sodium arsenite, cooled in an ice and salt bath to 0°. The temperature during the reaction is held below 5° (Note 1). Frothing takes place

owing to the escape of nitrogen, but this is easily controlled by the occasional addition of a small quantity of benzene. Stirring is continued for one hour after the addition of the diazonium chloride solution, and the mixture is filtered to remove the solid material which separates. This is washed with 500 cc. of cold water, and the combined liquors are concentrated over a free flame to a volume of about 1.5 l. (Note 2).

To the hot concentrated solution, which is deep brown in color, concentrated hydrochloric acid is added until no more tarry material separates (Note 3). The tar is filtered and more hydrochloric acid is added until, after filtering, a clear pale yellow solution results. It is important to remove all the tar at this time; otherwise, subsequent recrystallizations will not free the product from color. The phenylarsonic acid is then precipitated by the addition of 250 cc. of concentrated hydrochloric acid (sp. gr. 1.19) (Note 4). When the mixture has cooled (preferably by standing overnight) the phenylarsonic acid is filtered on a Büchner funnel and washed with 200 cc. of cold water. The light yellow crystals are dissolved in 500 cc. of boiling water, 20 g. of Norite is added, the solution filtered hot, and the filtrate allowed to cool. After filtering and drying, the white crystals melt with decomposition at 154–158°, passing into the anhydride, $C_6H_5AsO_2$. The yield is 160–182 g. (39–45 per cent of the theoretical amount) (Note 5).

2. Notes

1. This temperature is advised because it appears to be near the optimum with regard to yield and ease of purifying the product. However, a reaction temperature as high as 15° may be used with good results.
2. The solution is concentrated at atmospheric pressure since frothing occurs if reduced pressure is used.
3. About 100 cc. of hydrochloric acid is required. Care must be exercised not to precipitate any of the phenylarsonic acid.
4. Too large an excess of hydrochloric acid will dissolve some of the product and lower the yield.
5. In occasional runs by this procedure yields as high as 57 per cent have been obtained, but the reasons for this are not known.

3. Discussion

Phenylarsonic acid has been prepared by oxidizing phenyldichloroarsine[1] or phenyldiiodoarsine[2] with chlorine in water; by the oxidation of phenylarsine with nitric acid or air;[3] by decomposing phenylarsinetetrachloride or phenylarsineoxychloride with water;[4] by heating iodobenzene or bromobenzene with potassium arsenite;[5] by diazotizing *p*-arsanilic acid and decomposing in a solution of sodium hydrosulfite and hydrochloric acid;[6] by the action of potassium arsenite on potassium benzeneisodiazo oxide;[7] by the action of benzenediazonium chloride on

sodium arsenite in the presence of a copper compound[8] or of magnesium chloride and copper powder;[9] and by the action of a neutral or alkaline mixture containing arsenious oxide, a copper salt, and a reducing agent on benzenediazonium chloride.[10]

The preparation given here in detail is essentially that described by Palmer and Adams.[8] It has been reported that the use of buffers to ensure constant *p*H increases the yield of phenylarsonic acid in this reaction.[11]

References and Notes

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5. Dehn, Am. Chem. J. **33**, 140 (1905); Rosenmund, Ber. **54**, 438 (1921).
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8. Chem. Fabrik von Heyden A.-G., Ger. pat. 264,924 [Frdl. **11**, 1030 (1912-14)]; Palmer and Adams, J. Am. Chem. Soc. **44**, 1361 (1922); Norris, J. Ind. Eng. Chem. **11**, 825 (1919); Schmidt, Ann. **421**, 169 (1920).
9. Bart, Ger. pat. 254,092 [Frdl. **11**, 1030 (1912-14)].
10. Mouneyrat, Brit. pat. 142,947 [C. A. **14**, 2802 (1920)].
11. Blas, Génie civil **115**, 448 (1939) [C. A. **34**, 2342 (1940)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

arsenious oxide

potassium benzeneisodiazo oxide

copper compound

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

aniline (62-53-3)

nitric acid (7697-37-2)

sodium carbonate (497-19-8)

nitrogen (7727-37-9)

copper sulfate (7758-98-7)

benzenediazonium chloride, benezenediazonium chloride

sodium nitrite (7632-00-0)

sodium hydrosulfite (7775-14-6)

copper powder (7440-50-8)

p-Arsanilic acid (98-50-0)

sodium arsenite

Norite (7782-42-5)

chlorine (7782-50-5)

bromobenzene (108-86-1)

Iodobenzene (591-50-4)

Phenylarsonic acid, Benzenearsonic acid (98-05-5)

phenyldichloroarsine (696-28-6)

phenyldiiodoarsine (6380-34-3)

phenylarsine

phenylarsinetetrachloride

phenylarsineoxychloride

potassium arsenite

magnesium chloride

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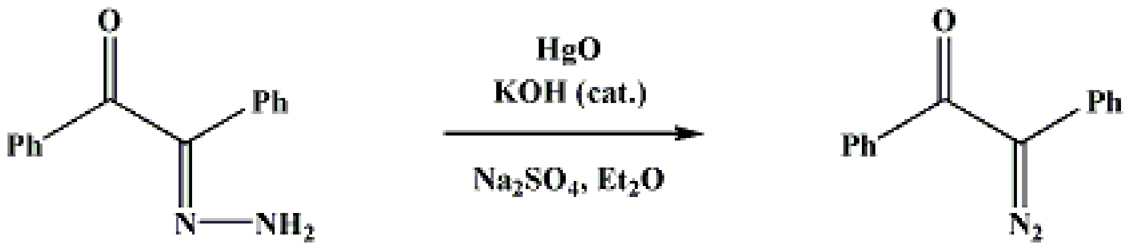
Organic Syntheses, CV 2, 496

PHENYLBENZOYLDIAZOMETHANE

[Acetophenone, α-diazo-α-phenyl-]



Submitted by Costin D. Nenitzescu and Eugen Solomonica.
Checked by Louis F. Fieser and Ralph S. Temple.

1. Procedure

Thirty grams (0.134 mole) of benzil hydrazone (Note 1) is mixed in a mortar with 60 g. (0.28 mole) of yellow mercuric oxide and 15 g. of anhydrous sodium sulfate (Note 2). The mixture is introduced into a 500-cc. glass-stoppered bottle and covered with 200 cc. of absolute ether (Note 3). Four cubic centimeters of a cold, saturated solution of alcoholic potassium hydroxide is added to catalyze the reaction (Note 4), and the mixture is shaken for ten to fifteen minutes. The solution is filtered by gravity through a fine paper, and the residue is washed several times with ether until the liquid is only slightly colored. The combined ethereal extracts are evaporated to dryness at the pressure of the water pump by heating the flask in a water bath to a temperature not greater than 40° (Note 5). The yellow, crystalline material is dried on a porous plate and recrystallized from anhydrous ether. The yield of azibenzil which melts at about 79° with decomposition is 26–28 g. (87–94 per cent of the theoretical amount) (Note 6).

2. Notes

1. Benzil hydrazone[1] may be prepared as follows:[2] A mixture of 52 g. (0.4 mole) of hydrazine sulfate (Org. Syn. Coll. Vol. I, **1941**, 309), 110 g. (0.8 mole) of sodium acetate, and 250 g. of water is boiled five minutes, cooled to about 50°, and 225 cc. of methyl alcohol added. The precipitated sodium sulfate is filtered and washed with a little alcohol.
A hot solution of 50 g. (0.24 mole) of benzil (Org. Syn. Coll. Vol. I, **1941**, 87) in 75 cc. of methyl alcohol is prepared, and the above solution, heated to 60°, is added. Most of the benzil hydrazone separates immediately, but the yield is increased by refluxing for half an hour. The hydrazone is filtered from the cold solution and washed with a little ether to remove the yellow color. The yield is 50.5 g. (94 per cent of the theoretical amount), melting at 147–151° with

decomposition.
Directions for preparing benzil hydrazone from benzil and hydrazine hydrate are given in Org. Syn. **20**, 48.

2. The sodium sulfate absorbs the water formed during the reaction.

3. By using ether, instead of benzene or petroleum ether as specified in the older methods, the evaporation of the solvent after the reaction is facilitated.

4. Without this catalyst the oxidation may require several hours and the results may vary considerably, depending largely upon the quality of the mercuric oxide.

5. The material may explode if the evaporation is carried out at atmospheric pressure on the steam bath.

6. This procedure may be used also for the preparation of diazofluorene.[3]

3. Discussion

Phenylbenzoyldiazomethane, azibenzil, has been prepared by the oxidation of benzil hydrazone with mercuric oxide,[4] using benzene or petroleum ether as the solvent, and without the catalyst here specified.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 356
- Org. Syn. Coll. Vol. 6, 392
- Org. Syn. Coll. Vol. 6, 840

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

azibenzil

Benzene (71-43-2)

methyl alcohol (67-56-1)

ether (60-29-7)

sodium acetate (127-09-3)

sodium sulfate (7757-82-6)

mercuric oxide (21908-53-2)

Benzil (134-81-6)

potassium hydroxide (1310-58-3)

hydrazine hydrate (7803-57-8)

Hydrazine sulfate (10034-93-2)

Phenylbenzoyldiazomethane, Acetophenone, α-diazo-α-phenyl- (3469-17-8)

Benzil hydrazone (5344-88-7)

diazofluorene

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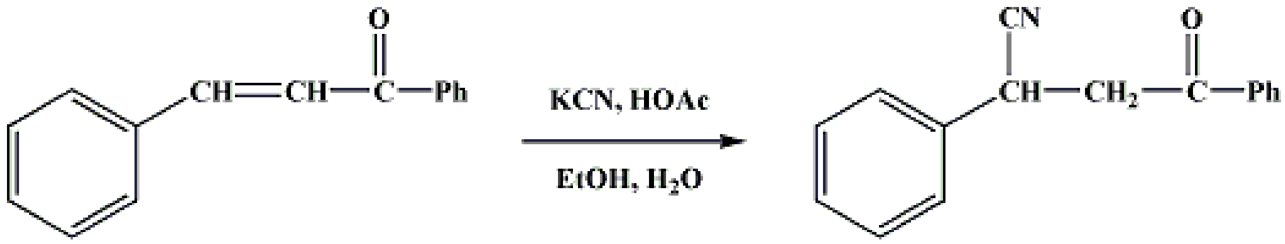
α-PHENYL-β-BENZOYLPROPIONITRILE

[α-Tolunitrile, α-phenacyl-]



Submitted by C. F. H. Allen and R. K. Kimball.
Checked by J. B. Conant and Helen O'Brien.

1. Procedure

The following preparation, through the filtration of the crude solid and washing with water, should be carried out in a hood with a good draft.

Into a 5-l. flask or bottle, set in a water bath and fitted with a stirrer, thermometer, and separatory funnel, are placed 208 g. (1 mole) of benzalacetophenone (Note 1), 3.5 l. of 95 per cent ethyl alcohol (Note 2), and 60 g. (1 mole) of glacial acetic acid (Note 3). The mixture is warmed with stirring to 35°, and a solution of 130 g. (2 moles) of potassium cyanide in 375 cc. of water is added from the separatory funnel over a period of about fifteen minutes. The initial greenish color changes to yellow after all the acetic acid has reacted and the solution has become alkaline (Note 3). Stirring is continued for three hours, the temperature being maintained at 35°. During this time about half of the nitrile crystallizes. The flask is then loosely stoppered and left in a cool place for about fifty hours (conveniently out-of-doors in cold weather, but out of direct sunlight), after which the solid is filtered and washed, first with 500 cc. of cold 50 per cent alcohol, and then with water until free from potassium cyanide (silver nitrate test). The yield of air-dried material melting at 125° is 220–227 g. (93–96 per cent of the theoretical amount). This product is sufficiently pure for most purposes, although it contains traces of a high-melting substance. If a product of higher melting point is desired, it may be recrystallized from 1 l. of 95 per cent alcohol or 375 cc. of acetone. Pure phenylbenzoylpropionitrile melts at 127°.

2. Notes

1. Crude alkali-free, air-dried benzalacetophenone is used (Org. Syn. Coll. Vol. I, **1941**, 78).
2. The preparation may be carried out in a more concentrated solution (1 l. of alcohol) with the same yield, but an inferior product is obtained. If this is done, it is best to stir for fifteen minutes at 50° after all the cyanide has been added and then cool in tap water. Since the product separates as an oil from a solution of this concentration, it is best to inoculate with a crystal of the nitrile.
3. If the solution becomes too alkaline, the nitrile formed will add to a second molecule of unsaturated ketone so readily that the product will consist almost entirely of a high-melting (284–286°) substance. For this reason it is essential to measure the acetic acid accurately; if too much is used, addition of hydrocyanic acid will not take place.

3. Discussion

α-Phenyl-β-benzoylpropionitrile has been prepared by the action of sodium or potassium cyanide on β-chlorobenzylacetophenone[1] or benzalacetophenone dibromide;[2] and by the addition of hydrocyanic acid to benzalacetophenone in the presence of sodium or potassium cyanide.[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 358

References and Notes

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2. Dodwadmath and Wheeler, Proc. Indian Acad. Sci. **2A**, 438 (1935) [C. A. **30**, 1771 (1936)].
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethyl alcohol, alcohol (64-17-5)

acetic acid (64-19-7)

hydrocyanic acid (74-90-8)

silver nitrate (7761-88-8)

potassium cyanide (151-50-8)

Benzalacetophenone (94-41-7)

acetone (67-64-1)

sodium (13966-32-0)

Benzalacetophenone dibromide (611-91-6)

α-Phenyl-β-benzoylpropionitrile, α-Tolunitrile, α-phenacyl-, phenylbenzoylpropionitrile (6268-00-4)

β-chlorobenzylacetophenone

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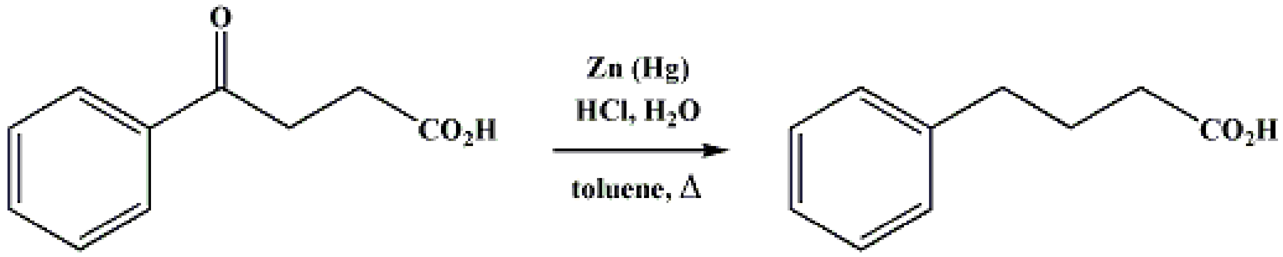
Organic Syntheses, CV 2, 499

γ-PHENYLBUTYRIC ACID

[Butyric acid, γ-phenyl-]



Submitted by E. L. Martin
Checked by C. R. Noller and F. M. McMillan.

1. Procedure

Amalgamated zinc is prepared by shaking for five minutes a mixture of 120 g. of mossy zinc, 12 g. of mercuric chloride, 200 cc. of water, and 5–6 cc. of concentrated hydrochloric acid contained in a 1-l. round-bottomed flask. The solution is decanted and the following reagents are added, in the order named, to the zinc: 75 cc. of water, 175 cc. of concentrated hydrochloric acid, 100 cc. of toluene, and 50 g. (0.28 mole) of β-benzoylpropionic acid (p. 81). The flask is fitted with a vertical condenser connected to a gas absorption trap (Note 1), and the reaction mixture is boiled vigorously for twenty-five to thirty hours (Note 2). Three 50-cc. portions of concentrated hydrochloric acid are added at approximately six-hour intervals during the refluxing period.

After cooling to room temperature the layers are separated. The aqueous layer is diluted with 200 cc. of water and extracted with three 75-cc. portions of ether. The toluene layer and the ether extracts are combined, washed with water, and dried over calcium chloride. The solvents are removed by distillation under reduced pressure on the steam bath, after which the γ-phenylbutyric acid is distilled at 178–181°/19 mm. (148–154°/8–10 mm., 125–130°/3 mm.). The yield of acid, which melts at 46–48° (Note 3), is 38–41 g. (82–89 per cent of the theoretical amount) (Note 4).

2. Notes

1. Considerable hydrogen chloride is driven off during the initial heating, and it might appear that it would be advantageous to use constant-boiling instead of concentrated hydrochloric acid. If this is done, however, the product has a melting point of 40–44° and the yield is somewhat lower.
2. If the refluxing is interrupted for any reason, great care must be exercised to avoid frothing on heating again. The upper part of the flask may be occasionally brushed with a free flame. Once the two layers are well mixed, boiling proceeds smoothly.
3. The recorded melting points vary from 47° to 51°. The acid may be crystallized from hot water (75 cc. per g.) but the recovery is only about 50 per cent. No other suitable solvent or combination of solvents was discovered. Redistillation raises the melting point to 47–48° with only mechanical losses.

4. The procedure described differs from that published in Org. Syn. **15**, 64, by the addition of toluene to the reaction mixture. In the presence of toluene the concentration of organic material in the aqueous layer is extremely small and polymolecular reactions take place to a smaller extent than in the original procedure. As a result the yield of pure product is greater.
When the modified procedure is applied to the preparation of higher-melting compounds, for example the γ-naphthylbutyric acids, the layers are separated after cooling to 50–60°, benzene is used for the extraction, and the combined benzene-toluene solution is clarified with Norite while still wet; it is then concentrated somewhat and allowed to cool for crystallization. In preparing methoxylated acids, such as γ-anisyl- or γ-veratrylbutyric acid, some demethylation occurs. When this happens the toluene layer and extracts are mixed with an excess of dilute sodium hydroxide solution and the organic solvents are removed by steam distillation. The alkaline solution is treated at 80° with an excess of methyl sulfate, the solution is clarified with Norite, cooled, and acidified, whereupon the product separates in good condition.

3. Discussion

Of the several methods by which γ-phenylbutyric acid has been obtained, those of preparative value are the decarboxylation of γ-phenylethylmalonic acid;[1] the carbonation of γ-phenylpropylmagnesium bromide;[2] and the reduction of β-benzoylpropionic acid with amalgamated zinc and hydrochloric acid[3] or of its hydrazone with sodium ethoxide.[4] The use of toluene in the Clemmensen reduction of β-benzoylpropionic acid and almost a score of related compounds has been described by Martin.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 194
- Org. Syn. Coll. Vol. 2, 569
- Org. Syn. Coll. Vol. 3, 300
- Org. Syn. Coll. Vol. 4, 898

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3. Krollpfeiffer and Schäfer, ibid. **56**, 620 (1923).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

amalgamated zinc

benzene-toluene

γ-naphthylbutyric acids

γ-anisyl- or γ-veratrylbutyric acid

γ-phenylethylmalonic acid

calcium chloride (10043-52-4)

hydrogen chloride, hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether (60-29-7)

sodium hydroxide (1310-73-2)

Norite (7782-42-5)

toluene (108-88-3)

zinc (7440-66-6)

sodium ethoxide (141-52-6)

mercuric chloride (7487-94-7)

methyl sulfate (75-93-4)

β-Benzoylpropionic acid (2051-95-8)

γ-Phenylbutyric acid, Butyric acid, γ-phenyl- (1821-12-1)

γ-phenylpropylmagnesium bromide

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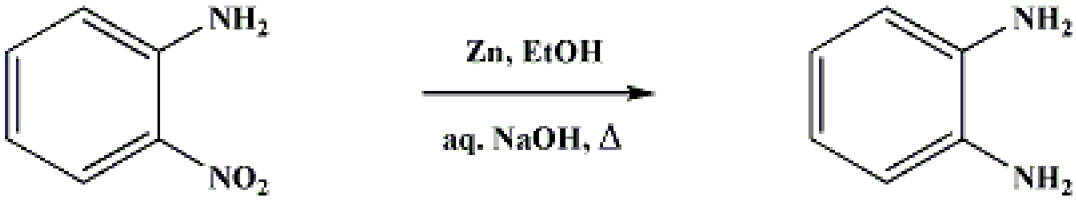
Organic Syntheses, CV 2, 501

o-PHENYLENEDIAMINE



Submitted by E. L. Martin
Checked by W. W. Hartman and S. S. Fierke.

1. Procedure

In a 1-l. three-necked, round-bottomed flask, fitted with a liquid-sealed mechanical stirrer and reflux condenser, are placed 69 g. (0.5 mole) of *o*-nitroaniline (Org. Syn. Coll. Vol. I, **1941**, 388), 40 cc. of a 20 per cent solution of sodium hydroxide, and 200 cc. of 95 per cent ethanol. The mixture is stirred vigorously and heated on a steam bath until the solution boils gently. The steam is turned off, and 10-g. portions of 130 g. (2 gram atoms) of zinc dust (Note 1) are added frequently enough to keep the solution boiling (Note 2) and (Note 3). After the addition of zinc dust has been completed the mixture is refluxed with continued stirring for one hour; the color of the solution changes from a deep red to nearly colorless. The hot mixture is filtered by suction, and the zinc residue is returned to the flask and extracted with two 150-cc. portions of hot alcohol. To the combined filtrates is added 2–3 g. of sodium hydrosulfite, and the solution is concentrated under reduced pressure (using a water pump), on a steam bath, to a volume of 125–150 cc. After cooling thoroughly in an ice-salt bath, the faintly yellow crystals are collected, washed once with a small amount of ice water, and dried in a vacuum desiccator. The yield of crude *o*-phenylenediamine melting at 97–100° is 46–50 g. (85–93 per cent of the theoretical amount). If a purer product is desired, the material is dissolved in 150–175 cc. of hot water containing 1–2 g. of sodium hydrosulfite and treated with decolorizing charcoal. After cooling thoroughly in an ice-salt mixture, the colorless crystals are filtered by suction and washed with 10–15 cc. of ice water. The purified *o*-phenylenediamine weighs 40–46 g. (74–85 per cent of the theoretical amount) and melts at 99–101° (Note 4) and (Note 5).

2. Notes

1. The zinc dust should be at least 80 per cent pure, and the amount used should be equivalent to 130 g. of 100 per cent material. A large excess of zinc dust has been used without changing the yield.
2. Great care must be taken not to add too much zinc dust at first as the reaction becomes very vigorous. It is well to have a bath of ice and wet towels at hand in order to control the reaction if it should become too violent.
3. Occasionally the reaction suddenly stops and it is necessary to add an

additional 10 cc. of 20 per cent sodium hydroxide solution, which causes the reaction to proceed.
4. The product can also be purified by distillation under reduced pressure in an inert atmosphere, but, unless the material is very nearly pure, considerable decomposition occurs and the distilled product darkens rapidly in contact with air.
5. The free diamine may also be converted into the dihydrochloride, and the salt purified as follows: The crude *o*-phenylenediamine is dissolved in a mixture of 90–100 cc. of concentrated hydrochloric acid (sp. gr. 1.19) and 50–60 cc. of water containing 2–3 g. of stannous chloride, and the hot solution is treated with decolorizing charcoal. To the hot, colorless filtrate is added 150 cc. of concentrated hydrochloric acid, and the mixture is cooled thoroughly in an ice-salt bath. The colorless crystals are filtered by suction, washed with a small amount of cold concentrated hydrochloric acid, and dried in vacuum over solid sodium hydroxide. The yield of *o*-phenylenediamine dihydrochloride is 77–81 g. (85–90 per cent of the theoretical amount based on the weight of *o*-nitroaniline used).

3. Discussion

o-Phenylenediamine has been prepared by the reduction of *o*-nitroaniline by means of tin and hydrochloric acid,[1] stannous chloride and hydrochloric acid,[2] sodium stannite,[3] zinc dust and water,[4] sodium hydrosulfite and sodium hydroxide,[5] and zinc dust and alcoholic alkali;[6] by electrolytic reduction in aqueous alcohol in the presence of sodium acetate;[7] and from *o*-dichlorobenzene or *o*-chloroaniline by treatment with aqueous ammonia at 150° under pressure in the presence of copper.[8] The procedure described above is a modification of the method of Hinsberg and König.[6]

o-Phenylenediamine has been proposed as a reagent for the identification of aliphatic acids, by conversion to crystalline 2-alkylbenzimidazoles (p. 65).

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 65
- Org. Syn. Coll. Vol. 4, 569
- Org. Syn. Coll. Vol. 4, 824

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alcohol, ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

sodium acetate (127-09-3)

sodium hydroxide (1310-73-2)

sodium hydrosulfite (7775-14-6)

tin (7440-31-5)

stannous chloride

copper (7440-50-8)

zinc (7440-66-6)

sodium stannite

o-Phenylenediamine (95-54-5)

o-NITROANILINE (88-74-4)

o-chloroaniline (95-51-2)

o-dichlorobenzene (95-50-1)

o-phenylenediamine dihydrochloride (615-28-1)

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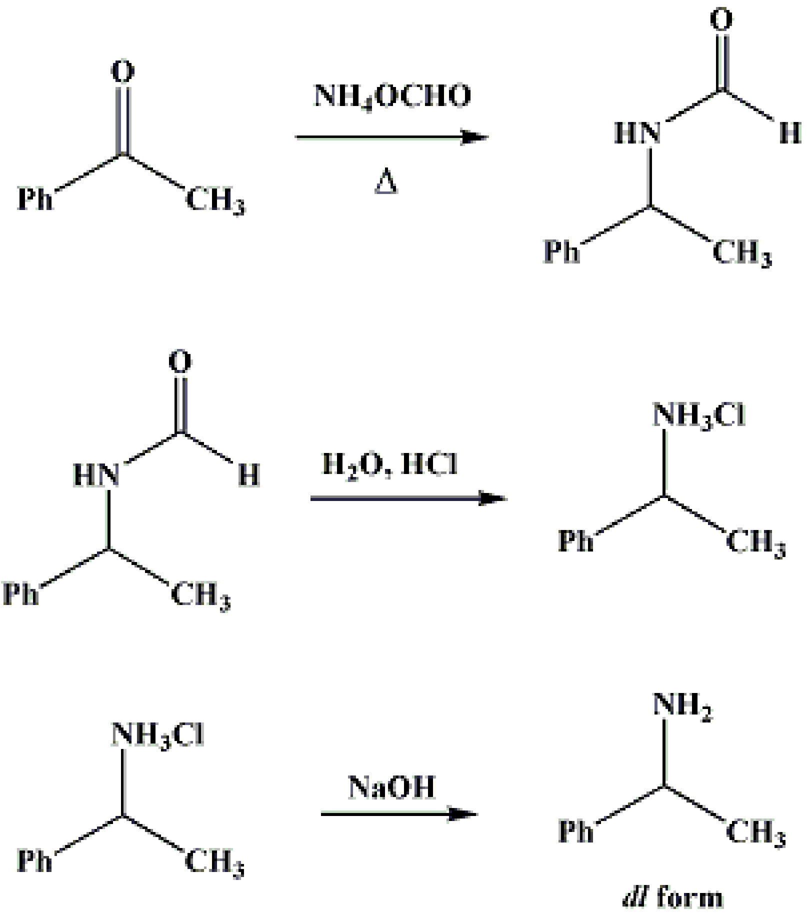
Organic Syntheses, CV 2, 503

α-PHENYLETHYLAMINE

[Benzylamine, α-methyl-]



Submitted by A. W. Ingersoll
Checked by Reynold C. Fuson and William E. Ross.

1. Procedure

In a 500-cc. modified Claisen flask are placed 250 g. (4 moles) of ammonium formate (Note 1), 150 g. (1.25 moles) of acetophenone (Note 2), and a few chips of porous plate. The flask is fitted with a cork carrying a thermometer extending nearly to the bottom, and the side arm is connected to a small condenser set for distillation. On heating the flask with a small flame the mixture first melts to two layers and distillation occurs; at 150–155° it becomes homogeneous and reaction takes place with moderate foaming. The heating is continued, more slowly if necessary, until the temperature reaches 185°. During this process water, acetophenone, and ammonium carbonate distil; about three hours is required and little attention is necessary. At 185° the heating is stopped and the upper layer of acetophenone is separated from the distillate and returned, without drying, to the reaction flask. The mixture is then heated for three hours at 180–185°. The distillate is extracted with 25–30 cc. of benzene to

recover acetophenone (Note 3), and the aqueous portion is discarded.

The reaction mixture is cooled and then shaken in a 500-cc. separatory funnel with 150–200 cc. of water to remove ammonium formate and formamide. The crude α-phenylethylformamide is drawn off into the original flask, and the water layer is extracted with two 30-cc. portions of benzene and discarded. The benzene extracts are united with the main portion, and 150 cc. of concentrated hydrochloric acid is added, together with a few pieces of porous plate. The mixture is cautiously heated until the benzene has distilled and then boiled gently for forty to fifty minutes longer. Hydrolysis proceeds rapidly, and the mixture becomes homogeneous except for a small layer of acetophenone and other neutral substances. The mixture is cooled and extracted first with 50 cc. of benzene and then with three or four 25-cc. portions of the solvent. The extracts are saved for the recovery of acetophenone (Note 3).

The aqueous acid solution is transferred to a 1-l. round-bottomed flask provided with a separatory funnel and equipped for steam distillation. A solution of 125 g. of sodium hydroxide in 250 cc. of water is added through the funnel, and the mixture is distilled with steam (Note 4). The first liter of distillate contains most of the amine, but the distillate should be collected until it is only faintly alkaline. A small residue containing di-(α-phenylethyl)-amine and neutral substances remains in the flask and may be discarded.

The distillate is extracted with five 50-cc. portions of benzene, and the benzene solution is dried thoroughly with powdered sodium hydroxide and distilled (Note 5). Most of the amine distils at 184–186°, but the fraction distilling at 180–190° is sufficiently pure for most purposes (Note 6). The yield of this fraction is 80–88 g. By combining the benzene fore-run with the distillation residue, extracting with dilute acid, and recovering the amine as above, an additional 10–12 g. of material can be obtained (Note 7), making the total yield 90–100 g. (60–66 per cent of the theoretical amount based on the acetophenone taken) (Note 8).

2. Notes

1. Ammonium formate may be made in quantity by treating solid ammonium carbonate with a slight excess of commercial 85 per cent formic acid and concentrating the solution, in stages, on a steam bath under reduced pressure. The slightly moist product obtained by suction filtration is suitable for this preparation.
2. Eastman's "practical" acetophenone, m.p. 16–20°, was used. Directions for preparing acetophenone are given in Org. Syn. Coll. Vol. I, **1941**, 111.
3. The benzene solution is washed with dilute alkali, dried, and distilled, the fraction boiling at 198–207° being collected.
4. In the steam distillation it is advisable to heat the distillation flask directly so that the volume remains nearly constant.
5. The amine attacks cork and rubber and absorbs carbon dioxide from the air. It

is best distilled in a flask having an in-set side arm and collected in a distilling flask protected by a soda-lime tube.

6. If very pure amine is desired the product described above is dissolved with 1.04 parts of crystalline oxalic acid in 8 parts of hot water. After clarification with Norite, the filtered solution on cooling deposits crystals of the acid oxalate. About 5 g. of the salt remains in each 100 cc. of the mother liquor; most of this can be obtained by evaporation and further crystallization. The amine is liberated from the pure oxalate with potassium hydroxide, distilled with steam, and purified as described above. When a known amount of amine is desired in water solution (as for optical resolution), a weighed amount of the (anhydrous) oxalate is decomposed and the amine is distilled quantitatively with steam.

7. When several runs are to be made the acid solution of the amine may be combined with the next run previous to steam distillation.

8. The method described is rather general. With appropriate modifications for the purification of the amine the method yields α-*p*-tolylethylamine (72 per cent), α-*p*-chlorophenylethylamine (65 per cent), α-*p*-bromophenylethylamine (63 per cent), α-*p*-xenylethylamine (66 per cent), and α-(β-naphthyl)-ethylamine (84 per cent) from the corresponding ketones.

3. Discussion

The present procedure was developed from those of Wallach[1] and Freylon,[2] based upon the general method discovered by Leuckart.[3] α-Phenylethylamine also can be prepared satisfactorily by the reduction of acetophenone oxime with sodium and absolute alcohol[4] or sodium amalgam,[5] or with ammonium amalgam,[6] or electrolytically.[7] The amine has been obtained by reducing acetophenone phenylhydrazone with sodium amalgam and acetic acid;[8] from α-phenylethyl bromide and hexamethylenetetramine;[9] by the action of methylmagnesium iodide on hydrobenzamide;[10] and by reducing acetophenone in the presence of ammonia with hydrogen and a nickel catalyst,[11] a method for which detailed directions are given in Volume 23 of this series.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 506
- Org. Syn. Coll. Vol. 3, 717
- Org. Syn. Coll. Vol. 5, 909

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

α-p-Xenylethylamine

alcohol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ammonium carbonate

ammonia (7664-41-7)

Benzene (71-43-2)

formamide (75-12-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

formic acid (64-18-6)

Oxalic acid (144-62-7)

carbon dioxide (124-38-9)

nickel (7440-02-0)

Acetophenone (98-86-2)

Norite (7782-42-5)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

oxalate

methylmagnesium iodide (917-64-6)

hexamethylenetetramine (100-97-0)

Ammonium (14798-03-9)

α-Phenylethylamine, Benzylamine, α-methyl- (3886-69-9)

ammonium formate (540-69-2)

α-phenylethylformamide (6948-01-2)

di-(α-phenylethyl)-amine

α-(β-naphthyl)-ethylamine

acetophenone oxime

acetophenone phenylhydrazone

α-phenylethyl bromide (585-71-7)

hydrobenzamide

α-p-Tolylethylamine

α-p-Chlorophenylethylamine (6299-02-1)

α-p-Bromophenylethylamine (24358-62-1)

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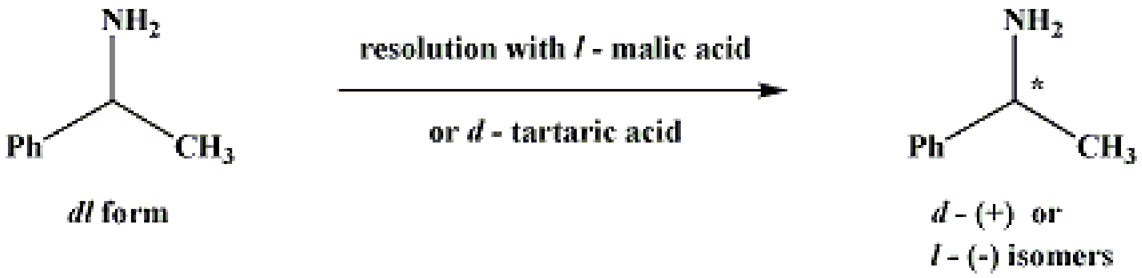
Organic Syntheses, CV 2, 506

d- AND *l*-α-PHENYLETHYLAMINE

[Benzylamine, α-methyl-, *d*- and *l*-]



Submitted by A. W. Ingersoll
Checked by Reynold C. Fuson and William E. Ross.

1. Procedure

d-α-*Phenylethylamine*.—A solution of 100 g. (0.75 mole) (Note 1) of *l*-malic acid in 500 cc. of distilled water is mixed with 120 g. (1 mole) of *dl*-α-phenylethylamine (p. 503); the resulting solution is heated for a short time on the steam bath, filtered into a 1-l. beaker, and allowed to cool slowly. After several hours the crude *d*-α-phenylethylamine-*l*-malate which crystallizes is collected by suction filtration and washed on the filter with 25 cc. of ice water. The filtrate and washings are evaporated on a steam bath to a volume about two-thirds that of the original filtrate, and a second crop of crystals is obtained on cooling (Note 2) and (Note 3). By repeating the process it is possible to obtain a third and usually a fourth crop, after which the mother liquor becomes too viscous to permit satisfactory crystallization. The mother liquor is reserved for later use.

The successive crops of crystals are systematically recrystallized as follows, using Norite if necessary. About two-thirds of the first crop is dissolved in about three parts of water and the hot solution allowed to deposit crystals by slow cooling (Note 3). The liquor is filtered or decanted, the remainder of the first crop is dissolved in it, and the process of crystallization is repeated. The remaining crops are then similarly recrystallized in succession from the same liquor, the solution being evaporated to the appropriate volume before each crystallization. The final mother liquor is evaporated in stages, and the viscous residue is united with that from the original crystallization. The various crops are systematically recrystallized from fresh water until pure (Note 4). It is possible to obtain 80–90 g. (63–70 per cent of the theoretical amount) of the pure *d*-base-*l*-acid (anhydrous acid salt).

The pure malate (mol. wt. 255) is decomposed by warming with very slightly more (Note 5) than two equivalents of approximately 2 *N* sodium hydroxide. The amine is extracted, after cooling, with three or four 25-cc. portions of pure benzene, the solution is dried thoroughly with powdered sodium hydroxide, and the pure amine, b.p. 184–

185°, $[\alpha]_D^{25°}$ + 39.2° to + 39.7° (without solvent), is obtained by distillation (Note 6). A small amount of the amine distils with the benzene. The yield is 35–40 g. (92–94 per cent of the theoretical amount based on the pure malate).

The mother liquors from the original crystallization and recrystallizations are treated in a similar manner, and the sodium malate solutions are united and reserved for the recovery of *l*-malic acid (Note 7). The recovered amine amounts to 75–80 g. and contains 40–50 per cent excess *l*-amine.

l-α-*Phenylethylamine*.—The recovered amine is converted to the acid tartrate in water solution, using for each gram of amine 1.25 g. of *d*-tartaric acid and 4.0 cc. of water. The solution is boiled with decolorizing carbon, if necessary, filtered, and allowed to cool slowly without disturbance (Note 3). A dense mass of coarse crystals of crude *l*-α-phenylethylamine-*d*-tartrate is deposited. The solution is decanted and evaporated to about two-thirds its original volume, and a second crop of crystals is obtained as before. These operations are repeated once or twice more, after which usually no more coarse crystals, but only a mass of needle-like crystals (mixed salts), can be obtained (Note 8). Meanwhile the first crop is recrystallized from about twice its weight of water. About two-thirds of the weight of crude salt is thus obtained pure; the mother liquor is used as solvent for the second crop, and so forth. The final mother liquor is united with that from the original crystallization and reserved for the recovery of the partially resolved amine. The yield of pure *l*-base-*d*-acid salt (anhydrous acid salt) is 75–100 g., an amount equivalent to somewhat more than the excess of *l*-amine in the mixture taken. The pure salt has a specific rotation of +13.0 to 13.2° in an 8 per cent solution in water.

The pure salt (mol. wt. 271) is dissolved in four parts of water; the amine is liberated with an excess of 20–25 per cent sodium hydroxide solution, extracted with benzene, and purified as described for the *d*-amine. The constants agree closely with those given for the *d*-amine, and the yield is 32–42 g. (94–96 per cent of the theoretical amount based on the pure tartrate, or 53–70 per cent based on the total *l*-amine originally present).

The amine recovered in the same way from the mother liquors amounts to 40–50 g. and contains a slight excess of *d*-amine. It may be used conveniently in the next run in place of the *dl*-amine.

2. Notes

1. The amount of malic acid theoretically is sufficient to convert half of the amine to the acid salt and the remaining half to the neutral salt.
2. Small amounts of the volatile amine are lost by hydrolysis during the evaporation and recrystallization of the salt.
3. Fractional crystallization is facilitated by inoculating the warm solution with a crystal of the species expected to separate and allowing crystallization to proceed slowly without disturbance.
4. The purity of *d*-α-phenylethylamine-*l*-malate is not readily determined by its

melting point or specific rotation, but rather by its massive crystalline form and solubility. The acid and neutral *l*-base-*l*-acid salts are much more soluble, and usually do not crystallize at all.

5. Excess alkali must be avoided if the malic acid is to be recovered, since it is slowly racemized by heating with concentrated alkali.

6. When the amine is to be used in water solution a weighed amount of the pure salt may be decomposed with alkali, the base distilled quantitatively with steam, and the entire distillate used.

7. The solution containing sodium malate is neutralized with acetic acid, diluted to contain about 5 per cent of sodium malate, and treated at the boiling point with 10 per cent lead acetate solution until lead malate no longer precipitates. The lead malate is collected after cooling and washed by trituration with boiling water. The salt is made into a thin paste with distilled water and decomposed with hydrogen sulfide (two days). The lead sulfide is filtered and the malic acid solution evaporated to a convenient volume. After titration of an aliquot, the solution may be used instead of pure acid in another run. The recovery is 70–80 per cent.

8. The *l*-base-*d*-acid salt no longer can be obtained pure when the solution contains about equal proportions of the salts of *d*- and *l*-amines. For this reason, also, an initial resolution of the *dl*-amine with *d*-tartaric acid is not feasible.

3. Discussion

The present method is adapted from that of Lovén.[1] The resolution has been carried out with *d*-α-bromocamphor-π-sulfonic acid (*l*-form);[2], [3] with *l*- and *dl*-malic acids (*d*- and *l*-forms);[4] with *l*-quinic acid and *d*-tartaric acid (*d*- and *l*-forms),[5] and with *d*- and *l*-6, 6'-dinitrodiphenic acids (*d*- and *l*-forms).[6] Methods employing *d*-benzylmethylacetyl chloride,[7] *d*-oxymethylenecamphor,[8] *l*-quinic acid,[9] and *d*-camphoric anhydride[10] are of theoretical interest only. The *dl*-amine is not resolved by the active camphor-10-sulfonic acids[11] or mandelic acids.[12]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 717
- Org. Syn. Coll. Vol. 5, 932

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

camphor-10-sulfonic acids

mandelic acids

D- and L-α-Phenylethylamine

Benzylamine, α-methyl-, d- and l-

acetic acid (64-19-7)

Benzene (71-43-2)

sodium hydroxide (1310-73-2)

hydrogen sulfide (7783-06-4)

lead sulfide

decolorizing carbon, Norite (7782-42-5)

lead acetate

malic acid, l-malic acid (617-48-1)

dl-α-phenylethylamine (3886-69-9)

Phenylethylamine (64-04-0)

sodium malate

D-tartaric acid (147-71-7)

lead malate

d-α-phenylethylamine-l-malate

l-α-phenylethylamine-d-tartrate

d-benzylmethylacetyl chloride

d-oxymethylenecamphor

d-camphoric anhydride

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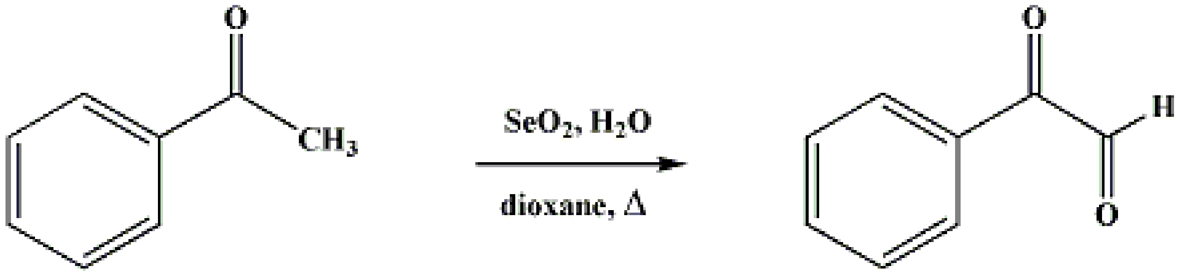
Organic Syntheses, CV 2, 509

PHENYLGLYOXAL

[Glyoxal, phenyl-]



Submitted by H. A. Riley and A. R. Gray.
Checked by Louis F. Fieser and C. H. Fisher.

1. Procedure

In a 1-l. three-necked, round-bottomed flask, fitted with a liquid-sealed stirrer and a reflux condenser, are placed 600 cc. of dioxane(Note 1), 111 g. (1 mole) of selenium dioxide (Note 2), and 20 cc. of water (Note 3). The mixture is heated to 50–55° and stirred until the solid has gone into solution, 120 g. (1 mole) of acetophenone is added in one lot, and the resulting mixture is refluxed with continued stirring for four hours (Note 4). The hot solution is decanted from the precipitated selenium, and the dioxane and water are removed by distillation through a short column. The phenylglyoxal is distilled at diminished pressure from a 250-cc. Claisen flask (Note 5), and the fraction boiling at 95–97°/25 mm. collected (Note 6). The yield is 93–96 g. (69–72 per cent of the theoretical amount) (Note 7).

The aldehyde sets to a stiff gel on standing, probably as the result of polymerization. It may be recovered without appreciable loss by distillation. Phenylglyoxal may be preserved also in the form of the hydrate, which is conveniently prepared by dissolving the yellow liquid in 3.5–4 volumes of hot water and allowing crystallization to take place (Note 8).

2. Notes

1. Ethyl alcohol (95 per cent) can also be used as solvent. The reaction can be carried out with an excess of acetophenone (2 moles) as solvent, but the results are less satisfactory. The dioxane can be recovered and used in later runs.
2. For the preparation of selenium dioxide, 200 g. (141 cc.) of concentrated nitric acid is heated in a 3-l. beaker on a hot plate under a good hood and 100 g. of selenium is added in portions of 5–10 g. A glass mechanical stirrer to break the foam hastens the process of oxidation. The resulting solution is transferred under the hood to a large evaporating dish and heated on a hot plate at a

temperature not exceeding 200° until the selenious acid is completely dehydrated. The crude product is purified by sublimation. A 50-g. portion of the oxide is transferred to a 7-cm. porcelain crucible upon which is placed a 250-cc. filter flask through which a stream of cold water is run from the tap. The crucible is protected with asbestos and heated with a low flame until sublimation is complete (20–30 minutes). When the crucible has cooled, the sublimed selenium dioxide will be found wedged against the condenser. Extreme care should be used when working with selenium dioxide because of its poisonous properties.
An alternative procedure for the oxidation of selenium to the dioxide has been described by Hahn and Schales.[1]
3. Commercial selenious acid (129 g., 1 mole) may be used in place of the mixture of selenium dioxide and water.
4. After about two hours the solution becomes clear and little further precipitation of selenium is observable.
5. Several grams of the hydrate may be obtained by adding the fore-run to an equal volume of warm water and allowing the product to crystallize.
6. Boiling points reported in the literature are 120°/50 mm. and 142°/125 mm.
7. Phenylacetaldehyde may be used in place of acetophenone.
Phenylmethylgloxal is obtained in a similar manner from propiophenone, and many other compounds containing a methylene group adjacent to a carbonyl group may be oxidized by means of selenium dioxide to the corresponding α-ketoaldehyde or α-diketone.[2]
For the oxidation of lepidine and quinaldine to the corresponding quinoline aldehydes, the selenium dioxide should be freshly prepared.[3]
8. The solubility of the hydrate at 20° is given in the literature as one part in about thirty-five parts of water. The melting points recorded range from 73° to 91°; the difference is said to be due to varying degrees of dryness of the samples.[4] The hydrate crystallizes well from water; chloroform, carbon disulfide, alcohol, or ether-ligroin also may be used for the purpose.
Phenylglyoxal can be recovered from the hydrate by distillation in vacuum.

3. Discussion

Phenylglyoxal has been prepared from isonitrosoacetophenone through the bisulfite compound[4, 5] or by treatment with nitrosylsulfuric acid[6] or with nitrous acid.[7] It also has been prepared by the oxidation of benzoylcarbinol with copper acetate,[8] by heating bromophenacyl acetate,[9] and by the oxidation of acetophenone with selenium dioxide.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 438
- Org. Syn. Coll. Vol. 5, 937

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ligroin

ethyl alcohol (64-17-5)

ether (60-29-7)

chloroform (67-66-3)

nitric acid (7697-37-2)

nitrous acid (7782-77-6)

Acetophenone (98-86-2)

selenium dioxide (7446-08-4)

Phenylglyoxal, Glyoxal, phenyl- (1074-12-0)

carbon disulfide (75-15-0)

copper acetate (142-71-2)

Propiophenone (93-55-0)

nitrosylsulfuric acid (7782-78-7)

dioxane (5703-46-8)

selenium

phenylacetaldehyde (122-78-1)

selenious acid (7783-00-8)

Lepidine (491-35-0)

quinaldine (91-63-4)

isonitrosoacetophenone

benzoylcarbinol (582-24-1)

bromophenacyl acetate

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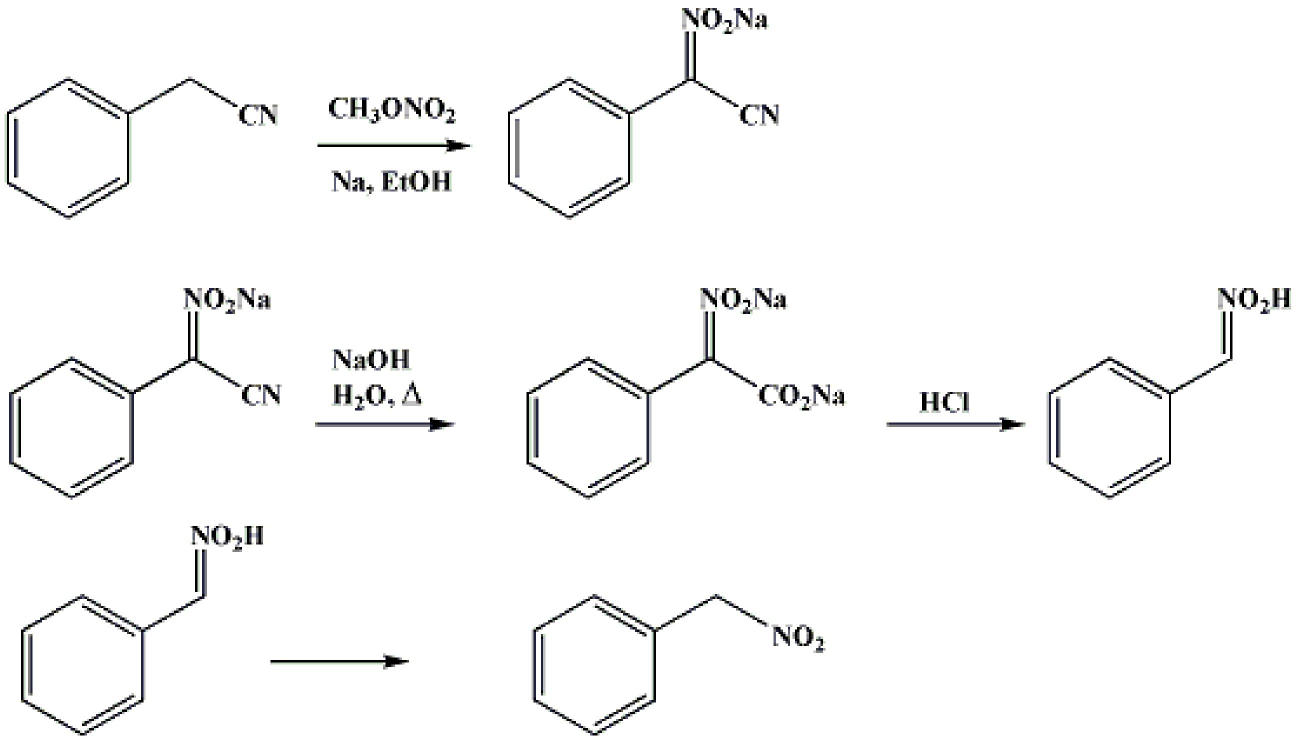
Organic Syntheses, CV 2, 512

PHENYLNITROMETHANE

[Toluene, α-nitro-]



Submitted by Alvin P. Black and Frank H. Babers.
Checked by John R. Johnson and H. B. Stevenson.

1. Procedure

(*A*) *Sodium Phenyl-aci-nitroacetonitrile*.—In a 2-l. round-bottomed flask fitted with an efficient reflux condenser is placed 400 cc. of absolute ethyl alcohol. Through the condenser tube 46 g. (2 gram atoms) of freshly cut metallic sodium is added as rapidly as possible, and the flask is heated in an oil bath after all the sodium has been added. After about one-half hour only a small globule of molten sodium (0.5–1.0 g.) remains and sodium ethoxide begins to precipitate. At this point 100 cc. of absolute alcohol is added and the mixture is cooled to 0°. A second 100-cc. portion of cold absolute alcohol is then poured on top of the solid cake of sodium ethoxide in the flask (Note 1). The reflux condenser is replaced by a stopper carrying a separatory funnel and a calcium chloride tube. An ice-cold mixture of 234 g. (2 moles) of freshly distilled benzyl cyanide (Org. Syn. Coll. Vol. I, **1941**, 107) and 216 g. (180 cc., 2.8 moles) of methyl nitrate (Note 2) is added with constant shaking, at such a rate that the temperature is kept between 4° and 8°. After this addition is completed (about one hour is required), the reaction mixture is allowed to remain at 4–8° and shaken intermittently for one hour. The flask is then provided with a stopper fitted with a Bunsen valve and placed in a freezing mixture for twenty-four hours. The sodium salt of the *aci*-nitro compound which precipitates is filtered with suction on a Büchner funnel, washed thoroughly with dry ether (Note 3), and air dried. The first crop of material weighs 215–275 g. (58–75 per cent of the theoretical amount). The mother liquor and ether washings are combined and concentrated stepwise to about 150 cc. under reduced pressure. Successive crops of the sodium salt which separate are filtered with suction and washed with dry ether. The total weight of the crude sodium salt is 275–300 g. (75–82 per cent yield). This material is used directly without purification.

(*B*) *Phenylnitromethane*.—In a 4-l. beaker 300 g. of sodium hydroxide is dissolved in 1.2 l. of water. The beaker is placed in an enameled pan (as a precaution against breakage), and the solution is heated to boiling. Over a period of one hour the air-dried, crude sodium salt of phenylnitroacetonitrile (275–300 g.) is added in small portions to the boiling alkali. Boiling is continued until the evolution of ammonia ceases (about three hours); hot water is added from time to time to keep the volume of the solution fairly constant (Note 4). The hot alkaline solution is poured into a shallow porcelain dish and on cooling solidifies to a waxy mass.

The cake of crude sodium salt of phenylnitroacetic acid is broken up with a spoon, transferred to a 4-l. beaker, and stirred with 500 g. of ice. The beaker is placed in a large crock packed with ice-salt mixture, and is provided with a mechanical stirrer. When the solution in the beaker has cooled to −5°, concentrated hydrochloric acid is added slowly from a separatory funnel, with vigorous stirring, until the solution is faintly acid to Congo red. During the addition of acid the temperature is not allowed to rise above −5° (Note 5). Usually about 900 cc. of acid is needed and the addition requires about two hours. The cold solution is extracted with one 500-cc. portion of ether, followed by two 250-cc. portions. The combined ether extracts are washed with ice-cold portions of saturated sodium bicarbonate solution until the wash liquid is colorless or only faintly yellow (usually two 100-cc. portions suffice). The ether solution is then washed with 250 cc. of ice water containing two drops of hydrochloric acid, and finally with three 50-cc. portions of ice water. The ether solution is dried over anhydrous sodium sulfate and allowed to stand for three or four days to complete the isomerization of the labile *aci*-form. The solution is filtered and the ether removed at 15–20° under reduced pressure. The residual oil is distilled at 3 mm. pressure in an ordinary Claisen flask, and the phenylnitromethane is obtained as a light yellow oil, b.p. 90–92°/3 mm. (Note 6). The yield is 135–150 g. (50–55 per cent of the theoretical amount, based upon the benzyl cyanide) (Note 7).

2. Notes

1. The supernatant layer of alcohol prevents the reactants dropping directly onto the sodium ethoxide and causing local overheating.
2. The large excess of methyl nitrate increases the yield appreciably. Freshly prepared methyl nitrate (p. 412) was dried and used directly without distillation. It is convenient to use the entire product (usually 210–230 g.) obtained from 120 g. of methyl alcohol.
3. Ordinary ether that has been allowed to stand for several days over anhydrous calcium chloride may be used.
4. The reaction must be watched carefully. Vigorous foaming sometimes occurs, necessitating the addition of small quantities of cold water from a wash bottle.
5. At −5° the *aci*-nitro compound separates as a gray, pasty solid. When the solution becomes acid the colloidal precipitate tends to undergo coagulation.
6. In the distillation of the crude product it is essential to maintain a low pressure and to avoid overheating. If the distillation is pushed too far, decomposition occurs and the distillate discolors rapidly on standing. If the distillation is not carried out carefully violent decomposition may occur which will blow out all connections.
The distilled product decomposes on standing and should be used promptly. Phenylnitromethane should not be stored in a glass-stoppered bottle, as the stopper is likely to become frozen and explosions may occur in attempting to remove it.
7. The procedure outlined can be shortened and simplified considerably by operating at somewhat higher temperatures than those specified. Thus it was found advantageous to add the benzyl cyanide-methyl nitrate solution to the sodium ethoxide with shaking at 5–15°, at which temperature the reaction proceeds smoothly and at a steady rate. The total yield of satisfactory sodium salt is 300–320 g.
The hydrolysis of the nitrile and the acidification operation are best carried out in the same 4-l. beaker, thus avoiding the necessity for making a transfer. In dissolving the sodium hydroxide

required for hydrolysis, 1.5 l. of water is used. As soon as no more ammonia is liberated (litmus) the beaker is placed in an ice-salt bath and the mixture stirred vigorously with a mechanically driven glass stirrer. When the temperature has dropped to 30°, 500 g. of ice is added. The acidification with hydrochloric acid (800–850 cc.) is conducted at 0–10° with continued stirring. The reaction mixture is allowed to stand overnight and is extracted the next day. The ethereal solution of the product need be allowed to stand over sodium sulfate for only twenty to twenty-four hours before distillation. The yield is then 153–163 g. of very light-colored product boiling at 92–94°/4 mm. (bath at 135°). Some 10–15 g. of darker material can be distilled from the residue at a slightly higher temperature. (Louis F. Fieser and E. Berliner, private communication.)

3. Discussion

Phenylnitromethane has been prepared by the nitration of toluene with dilute nitric acid in a sealed tube,[1] by the interaction of benzenediazonium chloride and nitromethane in alkaline solution,[2] by the action of silver nitrite on benzyl chloride[3] or iodide,[4] and by the condensation of ethyl nitrate with benzyl cyanide and subsequent hydrolysis.[5] The use of methyl nitrate, which can be prepared with less danger and difficulty than ethyl nitrate, is advantageous.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 412

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Congo red

Sodium Phenyl-aci-nitroacetonitrile

sodium salt of phenylnitroacetonitrile

benzyl cyanide-methyl nitrate

ethyl alcohol, alcohol (64-17-5)

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

methyl alcohol (67-56-1)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

nitric acid (7697-37-2)

sodium sulfate (7757-82-6)

benzenediazonium chloride

toluene (108-88-3)

sodium, metallic sodium (13966-32-0)

sodium ethoxide (141-52-6)

benzyl chloride (100-44-7)

Benzyl cyanide (140-29-4)

Nitromethane (75-52-5)

silver nitrite (7783-99-5)

Methyl nitrate (598-58-3)

Phenylnitromethane, Toluene, α-nitro- (622-42-4)

ethyl nitrate (625-58-1)

sodium salt of phenylnitroacetic acid

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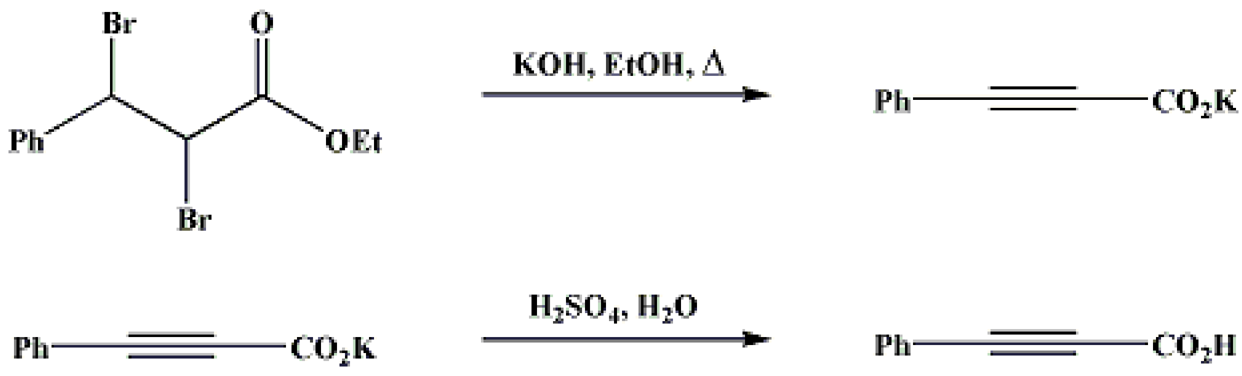
Organic Syntheses, CV 2, 515

PHENYLPROPIOLIC ACID

[Propiolic acid, phenyl-]



Submitted by T. W. Abbott
Checked by Henry Gilman and G. F. Wright.

1. Procedure

A solution of potassium hydroxide is prepared by dissolving 252.5 g. (4.5 moles) of potassium hydroxide (Note 1) in 1.2 l. of 95 per cent alcohol contained in a 3-l. round-bottomed flask provided with a reflux condenser and heated on a steam bath. To the alkaline solution, cooled to 40–50°, is added 336 g. (1 mole) of crude ethyl α,β-dibromo-β-phenylpropionate (p. 270). When the initial reaction has subsided, the contents of the flask are refluxed for five hours on the steam bath.

The reaction mixture is cooled, and the salts which separate are filtered by suction. The filtrate is treated with concentrated hydrochloric acid until neutral to litmus (Note 2), and the salts which precipitate are separated by filtration. The filtrate is then distilled until the vapor reaches 95°. The residue and the precipitated salts, previously separated by filtration, are combined, dissolved in 800 cc. of water, and chilled by the addition of cracked ice to make a volume of 1.8 l. (Note 3). The cooled solution is immersed in an ice-water bath and stirred mechanically while a 20 per cent sulfuric acid solution is added until the solution is strongly acid to litmus. After stirring for twenty minutes the phenylpropiolic acid is filtered by suction and washed with four 30-cc. portions of a 2 per cent sulfuric acid solution.

The acid thus obtained as a light brown, granular product is dissolved in 1 l. of 5 per cent sodium carbonate solution, treated with 20 g. of Norite, and heated on a steam bath for thirty minutes with occasional stirring. The mixture is then filtered and cooled externally, and about 200 g. of cracked ice is added. The solution is stirred mechanically while a 20 per cent solution of sulfuric acid is added slowly. The precipitated acid is filtered by suction, washed first with 50 cc. of a 2 per cent sulfuric acid solution and then with a little water, and air-dried. The yield of acid melting

between 115° and 125° is 112–118 g. (77–81 per cent of the theoretical amount).

One hundred grams of the crude acid can be purified by crystallization from 200–300 cc. of carbon tetrachloride, yielding 70 g. of phenylpropiolic acid melting at 135–136°.

2. Notes

1. The best yields are obtained when a 50 per cent excess of potassium hydroxide is used. The concentration of alkali has little or no effect on the yield.
2. The alcohol is best distilled from neutral rather than from alkaline solution.
3. In order to prevent decarboxylation, the temperature should be kept as low as possible. If this precaution is not observed, the yield is lowered and the product is less pure.

3. Discussion

The procedure described is essentially that of Perkin.[1] Phenylpropiolic acid can also be prepared from ether solutions of β-bromostyrene[2] and β-chlorostyrene[3] with sodium and carbon dioxide; from β-bromostyrene and butyllithium in ether;[4] by the action of alcoholic alkali on α-bromocinnamic acid,[2] β-bromocinnamic acid,[5] or ethyl α-bromocinnamate;[6] and by the action of carbon dioxide on sodium phenylacetylide.[2, 7]

The preparation of phenylpropiolic acid by the action of alkali on α,β-dibromocinnamic acid, a more direct synthesis than that involving the ester, has not been much used because of the difficulty of preparing the dibromo acid. It has been reported, however, that α,β-dibromocinnamic acid can be prepared easily and in a 95 per cent yield by the addition of bromine to cinnamic acid in boiling carbon tetrachloride, and that the crude product can be used for the preparation of phenylpropiolic acid.[8] A simplified procedure for the preparation of small amounts of phenylpropiolic acid from α,β-dibromocinnamic acid is described in the same article.

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alcohol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium carbonate (497-19-8)

bromine (7726-95-6)

carbon tetrachloride (56-23-5)

carbon dioxide (124-38-9)

Norite (7782-42-5)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

cinnamic acid (621-82-9)

β-bromostyrene (103-64-0)

Phenylpropiolic acid, Propiolic acid, phenyl- (637-44-5)

β-Chlorostyrene (622-25-3)

α-bromocinnamic acid

Ethyl α,β-dibromo-β-phenylpropionate (5464-70-0)

butyllithium (109-72-8)

β-bromocinnamic acid

ethyl α-bromocinnamate

sodium phenylacetylide

α,β-dibromocinnamic acid

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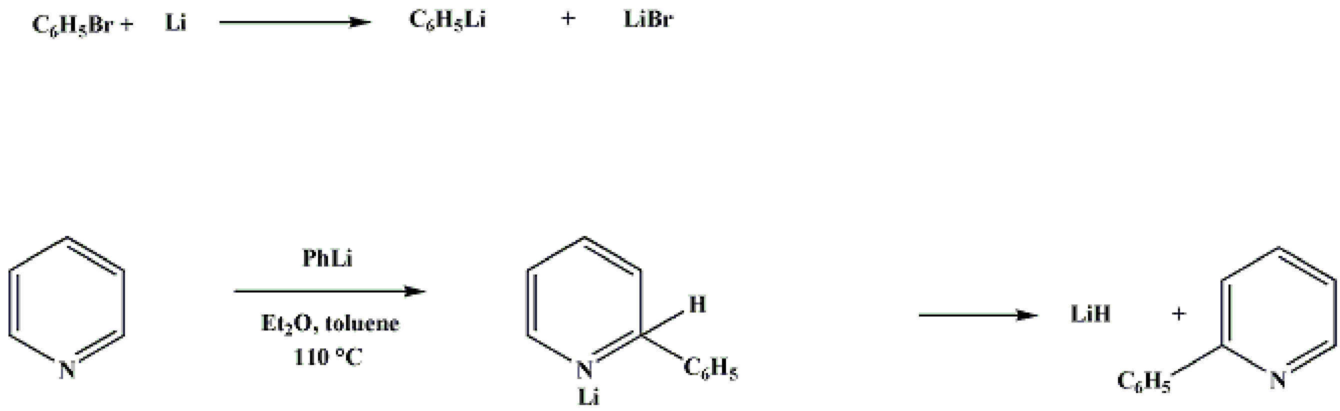
Organic Syntheses, CV 2, 517

2-PHENYLPYRIDINE

[Pyridine, 2-phenyl-]



Submitted by J. C. W. Evans and C. F. H. Allen.
Checked by Reynold C. Fuson, W. E. Ross, and E. A. Cleveland.

1. Procedure

In a 1-l. three-necked flask, fitted with a dropping funnel, a thermometer, mechanical stirrer, and reflux condenser protected from moisture (Note 1), the whole being swept with dry nitrogen, are placed 3.5 g. (0.5 gram atom) of lithium, cut into pieces the size of a pea, and 100 cc. of dry ether. The stirrer is started, and about 10 cc. of a mixture of 40 g. of bromobenzene (0.25 mole) in 50 cc. of dry ether is admitted from the dropping funnel; a vigorous reaction usually takes place (Note 2). The remainder of the mixture is added gradually over a half-hour period, when the metal should have largely disappeared (Note 3).

From the dropping funnel is next slowly introduced, with stirring, 40 g. (0.5 mole) of dry pyridine (Note 4) in 100 cc. of dry toluene. The ether is then distilled (Note 5) and the residual suspension stirred at 110° (inside temperature) for eight hours. It is then cooled to about 40°, 35 cc. of water cautiously added, and the liquids filtered if necessary (Note 6). The lower layer is separated and discarded. The toluene layer is dried for an hour with 20 g. of pulverized potassium hydroxide and carefully distilled, using a modified Claisen flask with a fractionating column attached. The material boiling up to 150° is removed at ordinary pressure and the residue distilled *in vacuo*; after two fractional distillations, the yield of 2-phenylpyridine, b.p. 140°/12 mm., is 15.5–19 g. (40–49 per cent of the theoretical amount).

2. Notes

1. The apparatus and reagents must be dried as for the Grignard reaction.
2. Occasionally the reaction will not start without the application of heat; as soon as the reaction begins, however, the source of heat is removed.
3. The yield of phenyllithium is approximately 75 per cent. It can be determined by allowing the phenyllithium to react with an excess of benzophenone and weighing the triphenylcarbinol formed. It is assumed that the carbinol is formed quantitatively.[1]
4. The success of the preparation depends on the dryness of the pyridine. The pyridine was refluxed for eight hours over fresh quicklime and distilled, and then a similar treatment with pulverized potassium hydroxide followed. None of the available barium oxide gave as good results. Merck's medicinal pyridine gave the highest yields.
5. This is easily accomplished by running the water out of the condenser, while heating to 110°.
6. The small particles of unused metal that usually remain hinder the separation into layers.

3. Discussion

2-Phenylpyridine has been prepared from pyridine and phenyllithium[2] or benzenediazonium chloride.[3] In the procedure described above, replacing ether as a solvent by toluene avoids the necessity of using a sealed tube.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 757

References and Notes

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2. Ziegler and Zeiser, Ber. **63**, 1847 (1930).
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4. Walters and McElvain, J. Am. Chem. Soc. **55**, 4625 (1933).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

quicklime

ether (60-29-7)

barium oxide

nitrogen (7727-37-9)

benzenediazonium chloride

pyridine (110-86-1)

potassium hydroxide (1310-58-3)

toluene (108-88-3)

Benzophenone (119-61-9)

bromobenzene (108-86-1)

Triphenylcarbinol (76-84-6)

Phenyllithium (591-51-5)

lithium (7439-93-2)

2-Phenylpyridine, Pyridine, 2-phenyl- (1008-89-5)

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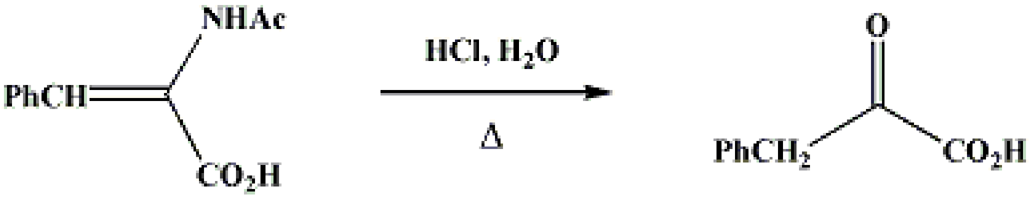
Organic Syntheses, CV 2, 519

PHENYLPYRUVIC ACID

[Pyruvic acid, phenyl-]



Submitted by R. M. Herbst and D. Shemin.
Checked by Reynold C. Fuson and E. A. Cleveland.

1. Procedure

Ten grams (0.05 mole) of α-acetaminocinnamic acid (p. 1) and 200 cc. of 1 *N* hydrochloric acid (Note 1) are placed in a 500-cc. flask fitted to an upright condenser with a ground-glass joint. Hydrolysis is completed by boiling for three hours. A few droplets of pale green oil may separate from the boiling solution; these are removed by filtration. The crystals of phenylpyruvic acid which separate from the filtrate on cooling (Note 2) are transferred to a Büchner funnel and washed with a little ice-cold water. The combined filtrate and washings are extracted with four 50-cc. portions of ether. The solvent is removed from the ether solution by evaporation at room temperature, finally in a vacuum desiccator (Note 3). The residue is combined with the first crop of crystals and dried in a vacuum desiccator over calcium chloride and potassium hydroxide. The yield is 7.2–7.7 g. (88–94 per cent of the theoretical amount), and the product melts at 150–154° (Note 4) and (Note 5).

2. Notes

1. Larger quantities of phenlypyruvic acid may be prepared by increasing the amounts of reactants proportionately. However, this is advisable only when the product is to be used immediately since phenylpyruvic acid begins to decompose after standing only a few days.
2. The amount of phenylpyruvic acid which separates from the filtrate is increased if the solution is allowed to stand in the refrigerator several days before filtration. No decomposition was noted when the product was kept suspended in cold, dilute acid.
3. The evaporation may be carried out conveniently at room temperature by passing a stream of dry air or inert gas over the surface of the solution under a glass bell.
4. The melting point varies considerably with the rate of heating.
5. Phenylpyruvic acid may be recrystallized from ethylene chloride, benzene, or chloroform, but losses due to instability of the compound are quite large.

3. Discussion

Phenylpyruvic acid has been prepared by the hydrolysis of α-benzoylaminocinnamic acid with alkalies or acids;[1, 2] by the acid hydrolysis of ethyl phenyloxalacetate;[3] by the acid hydrolysis of ethyl phenylcyanopyruvate;[2, 4] by dehydration of β-phenylglyceric acid with sulfuric acid;[5] and by the alkaline hydrolysis of α-acetaminocinnamic acid.[6]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

phenlypyruvic acid

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether (60-29-7)

chloroform (67-66-3)

ethylene chloride (107-06-2)

potassium hydroxide (1310-58-3)

α-Acetaminocinnamic acid (5469-45-4)

Phenylpyruvic acid, Pyruvic acid, phenyl- (156-06-9)

Ethyl phenylcyanopyruvate (6362-63-6)

α-Benzoylaminocinnamic acid (1155-48-2)

ethyl phenyloxalacetate

β-phenylglyceric acid

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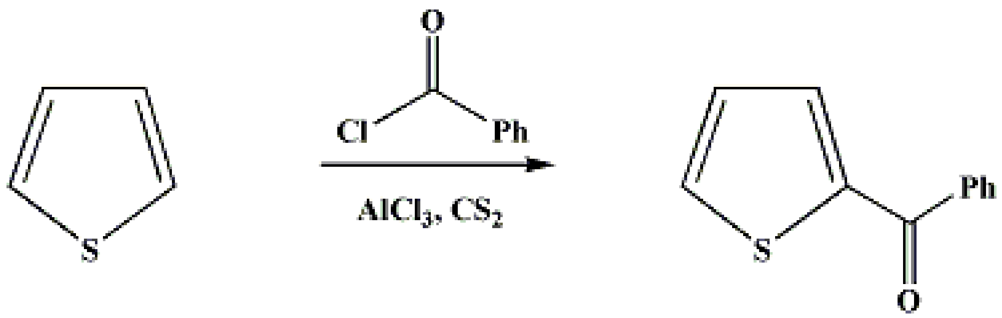
Organic Syntheses, CV 2, 520

PHENYL THIENYL KETONE

[Ketone, phenyl 2-thienyl]



Submitted by Wesley Minnis
Checked by Roger Adams and H. D. Cogan.

1. Procedure

In a 1-l. three-necked flask, equipped with a mechanical stirrer, a reflux condenser, and a thermometer (with bulb immersed in the liquid), are placed 100 g. (0.75 mole) of anhydrous aluminum chloride and 300 g. of carbon disulfide (Note 1). The suspension is cooled to 15–25°, and a solution of 60 g. (0.71 mole) of thiophene (p. 578) and 105 g. (0.75 mole) of benzoyl chloride in 225 g. of carbon disulfide is added through the condenser, with stirring, over a period of three and one-half hours (Note 2). The solution is allowed to warm up to room temperature, and stirring is continued for three more hours; the reaction mixture is then allowed to stand overnight. The mixture is refluxed on the water bath for three and one-half hours, cooled, poured on ice, and extracted with ether. The ether extract is washed successively with sodium carbonate solution and water, and then dried over calcium chloride. The ether is removed by distillation on the water bath, and the residue is distilled under reduced pressure. The yield of product boiling at 200–209°/30–40 mm. is 117–120 g. (88–90 per cent of the theoretical amount). On crystallization from 1 l. of petroleum ether (b.p. 65–110°) there is obtained 110–112 g. of product melting at 52°. Another crystallization from petroleum ether gives a product which melts at 55–56°. The loss on the second crystallization is about 10 per cent.

2. Notes

1. The carbon disulfide was dried over calcium chloride.
2. Thiophene and aluminum chloride react vigorously in carbon disulfide suspension. Subsequent addition of a carbon disulfide solution of benzoyl chloride produces a tar, and a low yield of ketone results.

3. Discussion

Phenyl thienyl ketone has been prepared by treatment of benzoyl chloride with thienylmercuric chloride;[1] by treatment of thiophene with benzoyl chloride in the presence of thienylmercuric chloride,[2] phosphorus pentoxide,[3] stannic chloride,[4] and aluminum chloride.[5] It has also been prepared from thienylmagnesium iodide and benzonitrile.[6]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

calcium chloride (10043-52-4)

ether (60-29-7)

benzonitrile (100-47-0)

sodium carbonate (497-19-8)

benzoyl chloride (98-88-4)

aluminum chloride (3495-54-3)

carbon disulfide (75-15-0)

Thiophene (110-02-1)

stannic chloride (7646-78-8)

Phenyl thienyl ketone, Ketone, phenyl 2-thienyl (135-00-2)

thienylmercuric chloride

thienylmagnesium iodide

phosphorus pentoxide (1314-56-3)

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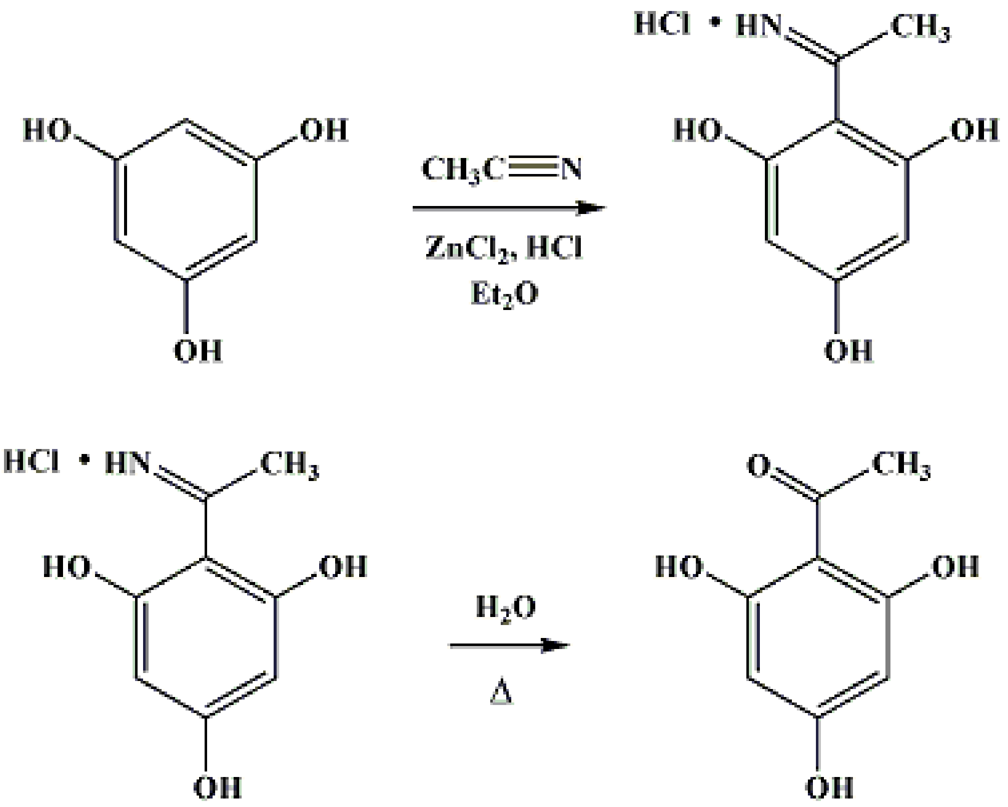
Organic Syntheses, CV 2, 522

PHLOROACETOPHENONE



Submitted by K. C. Gulati, S. R. Seth, and K. Venkataraman.
Checked by John R. Johnson and M. T. Bush.

1. Procedure

In a 250-cc. filtering flask, fitted with a calcium chloride tube and a rubber stopper carrying an inverted thistle tube (Note 1) for the introduction of hydrogen chloride, are placed 20 g. (0.16 mole) of well-dried phloroglucinol (Note 2), 13 g. (0.32 mole) of anhydrous acetonitrile, 80 cc. of anhydrous ether, and 4 g. of finely powdered, fused zinc chloride. The flask is cooled in an ice-salt mixture and shaken occasionally while a rapid stream of dry hydrogen chloride is passed through the solution for two hours. The flask is allowed to stand in an ice chest for twenty-four hours, and hydrogen chloride is again passed into the mixture, now pale orange in color, for two hours. The flask is stoppered and allowed to stand in an ice chest for three days.

The bulky orange-yellow precipitate of the ketimine hydrochloride is separated by decanting the ether and washed twice with 20-cc. portions of dry ether. The solid is transferred to a 2-l. round-bottomed flask with 1 l. of hot water. The flask is provided with a reflux condenser, and the yellow solution is boiled vigorously over a wire gauze for two hours. About 3 to 4 g. of Norite is added; the solution is boiled for five minutes longer and filtered with suction while hot. The decolorizing carbon is

extracted with two 100-cc. portions of boiling water and this filtrate added to the main portion.

After standing overnight the colorless or pale yellow needles of phloroacetophenone are filtered with suction and dried in an oven at 120° (Note 3). The yield is 20–23.5 g. (74–87 per cent of the theoretical amount) of a product which melts at 217–219° (corr.). This product is quite pure and may be used directly for many purposes. It may be recrystallized from thirty-five times its weight of hot water, with a loss of about 5 per cent. The recrystallized material melts at 218–219° (corr.).

2. Notes

1. A wide-mouthed entry tube for hydrogen chloride is necessary to avoid clogging due to separation of the solid ketimine hydrochloride.
2. All the reagents must be dried carefully. Phloroglucinol (Org. Syn. Coll. Vol. I, **1941**, 455) contains two molecules of water of hydration which is removed by drying overnight at 120°. The acetonitrile and ether used were freshly distilled from phosphorus pentoxide.
3. Phloroacetophenone crystallizes from aqueous solutions with one molecule of water of hydration.[1] The oven-dried crystals take up water readily on exposure to the air. Phloroacetophenone gives a wine-red color with ferric chloride in contrast to the violet color given by phloroglucinol.[2]

3. Discussion

The Hoesch reaction is the most satisfactory method for preparing phloroacetophenone.[3] The procedure described above is that of Robinson and Venkataraman.[4] Phloroacetophenone has been obtained also by the action of acetyl chloride on phloroglucinol in the presence of aluminum chloride.[2]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Phloroacetophenone

hydrogen chloride (7647-01-0)

ether (60-29-7)

acetonitrile (75-05-8)

acetyl chloride (75-36-5)

decolorizing carbon, Norite (7782-42-5)

aluminum chloride (3495-54-3)

zinc chloride (7646-85-7)

ferric chloride (7705-08-0)

Phloroglucinol (108-73-6)

phosphorus pentoxide (1314-56-3)

ketimine hydrochloride

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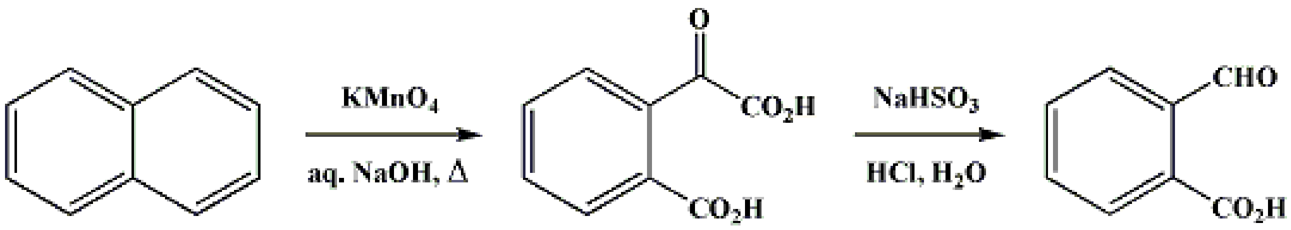
Organic Syntheses, CV 2, 523

PHTHALALDEHYDIC ACID



Submitted by J. H. Gardner and C. A. Naylor Jr.
Checked by C. R. Noller and Carl Linn.

1. Procedure

In a 3-l. three-necked flask, provided with a liquid-sealed mechanical stirrer, a reflux condenser, and a dropping funnel, are placed 500 cc. of 0.5 *N* sodium hydroxide solution and 32 g. (0.25 mole) of pure naphthalene. The mixture is heated to boiling, and a boiling solution of 212 g. (1.34 moles) of potassium permanganate in 1.5 l. of water is added in small portions during one and one-half hours with vigorous stirring (Note 1). After the last addition, the mixture is boiled for thirty to forty-five minutes to complete the oxidation. Any unchanged permanganate is reduced by the addition of 20 cc. of alcohol, the flask is cooled to solidify the residual naphthalene, and the mixture is filtered.

The filtrate is acidified with 150 cc. (1.8 moles) of concentrated hydrochloric acid (sp. gr. 1.18), evaporated to 500 cc., cooled, and filtered. The filtrate is neutralized with 30 per cent sodium hydroxide solution (150–160 cc.), 50 g. (0.48 mole) of sodium bisulfite is added, and the mixture is evaporated to dryness on a steam bath. The residue is stirred with 100 cc. of concentrated hydrochloric acid and evaporated to dryness on a steam bath. The hydrochloric acid treatment and evaporation are repeated (Note 2).

The residue is extracted thoroughly with benzene in a large Soxhlet extractor (Note 3), and the benzene extract is evaporated to dryness. The crude product is dissolved in 50 cc. of hot water, the solution filtered, and the filtrate cooled in an ice bath with stirring (Note 4). The crystals are filtered with suction and dried in the air. The yield of slightly colored product melting at 94–95° 15–15.5 g. (40–41 per cent of the theoretical amount).

When this material is recrystallized from 40 cc. of water with 1 g. of decolorizing carbon, and the filtrate cooled to 0°, there is obtained 14–14.5 g. of white crystals melting at 96–96.5°.

2. Notes

1. During the addition of the hot permanganate solution no external heat is applied. From time to time steam is passed through the condenser jacket to return the sublimed naphthalene to the reaction flask.
2. The treatment with hydrochloric acid and the evaporation are repeated in order to decompose completely the phthalaldehydic acid bisulfite compound. Wegscheider and Bondi[1] state that it is necessary to heat the bisulfite compound on the water bath several days with a large excess of hydrochloric acid, but the treatment described above has been found adequate.
3. The material requires two extraction thimbles of the 45 by 125 mm. size, or four of the 30 by 75 mm. size. It is advantageous to use a modified Soxhlet extractor of the Clausnitzer type,[2] which allows the vapor of the boiling solvent to surround the extractor tube.

4. It is essential to control carefully the volume of water used in recrystallization. The crude acid contains considerable amounts of phthalic acid; too small a volume of water results in a contaminated product, and too large an amount causes a decided decrease in yield.

3. Discussion

Phthalaldehydic acid has been prepared by the hydrolysis of 2-bromo- or 2-chlorophthalide,[3] of *o*-trichloromethylbenzal chloride,[4] of *o*-cyanobenzal chloride,[5] and of *o*-dichloromethylbenzoyl chloride;[6] by the ozonization of naphthalene;[7] by the alkaline oxidation of naphthalene,[8] or α-nitronaphthalene[9] followed by the preparation and decomposition of the aniline condensation product[10] or the bisulfite compound[1, 11] of phthalonic acid; and by carbonating the reaction product of *o*-chlorobenzaldehyde and sodium.[12] Detailed directions for the preparation of phthalaldehydic acid by bromination of phthalide and hydrolysis of the bromination product are given in Volume 23 of this series.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 476
- Org. Syn. Coll. Vol. 3, 737

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

2-bromo- or 2-chlorophthalide

phthalonic acid

alcohol (64-17-5)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

sodium hydroxide (1310-73-2)

potassium permanganate (7722-64-7)

sodium bisulfite (7631-90-5)

decolorizing carbon (7782-42-5)

sodium (13966-32-0)

Naphthalene (91-20-3)

α-nitronaphthalene (86-57-7)

phthalic acid (88-99-3)

Phthalaldehydic acid (119-67-5)

phthalaldehydic acid bisulfite

Phthalide (87-41-2)

o-chlorobenzaldehyde (89-98-5)

o-trichloromethylbenzal chloride

o-cyanobenzal chloride

o-dichloromethylbenzoyl chloride

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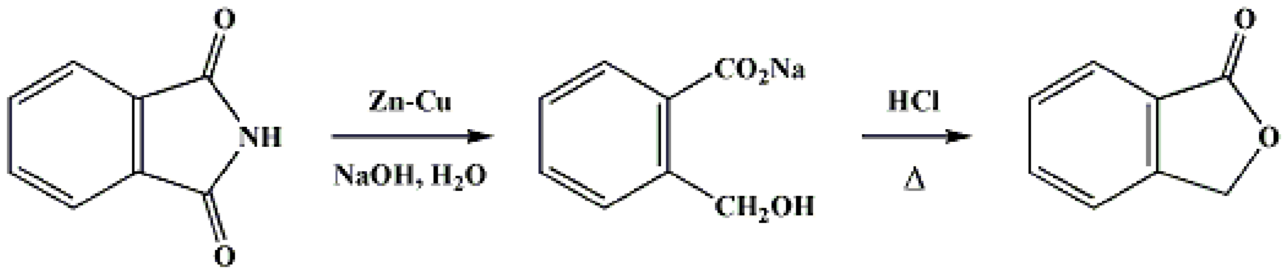
PHTHALIDE



Submitted by J. H. Gardner and C. A. Naylor Jr.
Checked by H. T. Clarke and D. Blumenthal.

1. Procedure

In a 2-l. round-bottomed flask, 180 g. (2.75 gram atoms) of zinc dust is stirred to a thick paste with a solution of 1 g. of copper sulfate in about 35 cc. of water (Note 1), and 400 g. (327 cc.) of 20 per cent aqueous sodium hydroxide is added. The flask is equipped with a mechanical stirrer, the contents are cooled to 5° by means of an ice bath, and 147 g. (1 mole) of phthalimide (Org. Syn. Coll. Vol. I, **1941**, 457) is added in small portions at such a rate that the temperature does not rise above 8° (about thirty minutes is required). After all the phthalimide has been added, stirring is continued for one-half hour. The mixture is diluted with 400 cc. of water, warmed on a steam bath until evolution of ammonia has ceased (about three hours), and concentrated to a volume of about 400 cc. by distillation under reduced pressure. The material is filtered and the filtrate made acid to Congo red with concentrated hydrochloric acid (about 150 cc. is required). The mixture, in which the phthalide has separated as an oil, is boiled for one hour in order to complete the lactonization of the hydroxymethylbenzoic acid, and transferred while hot to a beaker. On cooling, the oily product solidifies to a hard red-brown cake. After chilling overnight in a refrigerator, when a further quantity of crystalline solid separates from the aqueous layer, the cold mixture is filtered with suction (Note 2). The crude phthalide, which contains a considerable quantity of sodium chloride, is recrystallized in 20-g. portions from 1.5 l. of water; the mother liquor from the first crop is employed for recrystallization of the subsequent portions. Each portion is filtered hot and cooled below 5° before collecting the crystals, which are finally washed with small quantities of ice-cold water (Note 3). The phthalide crystallizes in transparent plates which melt at 72–73°. The yield is 90–95 g. (67–71 per cent of the theoretical amount) (Note 4).

2. Notes

1. In checking these directions complete failure was repeatedly encountered with good commercial grades of zinc dust, and only when the metal was activated with copper sulfate did reduction proceed at all.
2. The mother liquor, on concentrating to less than half its volume, yields no further crystals on chilling.
3. On cooling, a minute amount of a yellow impurity separates with the phthalide at the beginning of crystallization. This impurity apparently cannot be eliminated by boiling with charcoal but is present in too small amount to affect the melting point of the product.
4. Concentration of the final mother liquor to a volume of 500 cc. yields a further small

quantity of phthalide, but this operation is scarcely worth while.

3. Discussion

Phthalide has been prepared by the bromination of *o*-toluic acid followed by hydrolysis;[1] by the reduction of phthalic anhydride,[2] ammonium phthalate,[3] or ethyl acid phthalate;[4] and by the method described in the procedure above.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 174
- Org. Syn. Coll. Vol. 3, 737
- Org. Syn. Coll. Vol. 4, 810
- Org. Syn. Coll. Vol. 5, 145

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Congo red

ethyl acid phthalate

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

copper sulfate (7758-98-7)

phthalic anhydride (85-44-9)

zinc (7440-66-6)

Phthalimide (85-41-6)

ammonium phthalate (523-24-0)

Phthalide (87-41-2)

hydroxymethylbenzoic acid (612-20-4)

o-Toluic acid (118-90-1)

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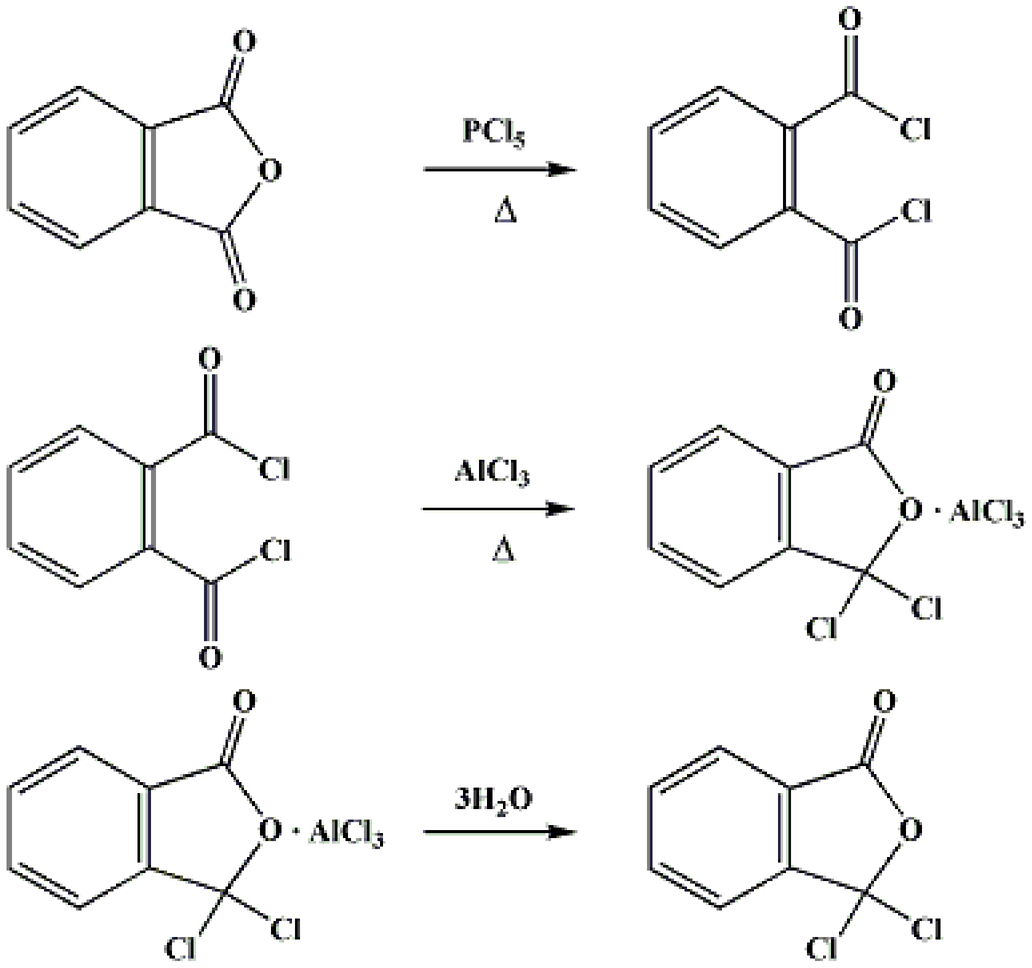
Organic Syntheses, CV 2, 528

SYMMETRICAL AND UNSYMMETRICAL *o*-PHTHALYL CHLORIDES



Submitted by Erwin Ott
Checked by Henry Gilman and F. J. Prochaska.

1. Procedure

(*A*) *Symmetrical o-Phthalyl Chloride*.—A mixture of 148 g. (1 mole) of phthalic anhydride (Note 1) and 220 g. (1.06 moles) of phosphorus pentachloride (Note 2) is placed in a 500-cc. Claisen flask. The flask is equipped with a reflux condenser, the upper end of which is provided with a calcium chloride tube, and the side arm of the flask is closed with a cork. The flask is inclined slightly so that any phosphorus oxychloride which collects in the stoppered side arm will run back into the flask. After heating in an oil bath at 150° for twelve hours, the air condenser and the stopper in the end of the side arm are removed, and the flask is connected to a water-cooled condenser. The temperature is then raised gradually to 250°, during which time most of the phosphorus oxychloride distils into a receiver. The liquid residue is distilled under reduced pressure; at first a small quantity of phosphorus oxychloride distils, and then the *sym. o*-phthalyl chloride distils at 131–133°/9–10 mm. The product thus

obtained contains a small amount of phthalic anhydride; it solidifies on cooling in an ice-salt mixture and melts at 11–12° (Note 3). The yield is 187 g. (92 per cent of the theoretical amount).

(*B*) *Unsymmetrical o-Phthalyl Chloride*.—A mixture of 105 g. of the symmetrical *o*-phthalyl chloride and 75 g. of finely ground aluminum chloride (Note 4) is heated on a steam bath for eight to ten hours, with exclusion of moisture. The mixture should be stirred frequently until all the powder has dissolved. Upon cooling there is formed a hard mass which is broken into small pieces while still warm. When thoroughly cool, it is triturated with pieces of ice in a mortar, working with small amounts at a time. The white sediment which results is collected on a Büchner funnel and dissolved immediately in about 300 cc. of warm benzene (40–50°). The benzene solution is separated from the small aqueous layer, dried over calcium chloride for eight hours, and filtered. The benzene is distilled under reduced pressure by heating in a water bath at 30–40°. The crystalline residue is extracted in a Soxhlet apparatus with petroleum ether (b.p. 20–40°) until the residue in the thimble consists of practically pure phthalic anhydride (Note 5). The petroleum ether is distilled from the extract, and the crude unsymmetrical phthalyl chloride is purified by fractional crystallization from petroleum ether (b.p. 20–50°). The purified chloride melts at 87–89°. The melting point is not sharp because the unsymmetrical compound begins to revert to the symmetrical isomer. The yield of pure unsymmetrical phthalyl chloride is about 76 g. (72 per cent of the theoretical amount) and is dependent on the quality of the aluminum chloride used.

2. Notes

1. A good grade of sublimed phthalic anhydride should be used (m.p. 128–129°). If this cannot be obtained the ordinary phthalic anhydride can be purified by sublimation.
2. The phosphorus pentachloride should be freed of any phosphorus trichloride or oxychloride present. This may be done by placing the pentachloride in a flask connected to an ice-cooled receiver and heating on a water bath. The pressure in the apparatus is reduced as much as possible by means of a water pump. A calcium chloride tube should be inserted between the pump and the receiver.
3. Pure symmetrical *o*-phthalyl chloride cannot be obtained, even by recrystallization from carbon tetrachloride. A product melting at 16° may be obtained by distilling the unsymmetrical phthalyl chloride at atmospheric pressure.
4. A good quality of aluminum chloride must be used. If this is not available, it may be prepared by heating dried aluminum granules in a current of pure, dry hydrogen chloride. The gas is dried thoroughly by passing it through a tube containing phosphorus pentoxide spread on glass wool. Access of moisture to the aluminum chloride while weighing and pulverizing should be avoided as far as possible.
5. The extraction requires from eight to ten hours. The residue should be practically pure phthalic anhydride (m.p. 126°).

3. Discussion

Symmetrical *o*-phthalyl chloride has been prepared by heating phthalic anhydride with phosphorus pentachloride,[1] thionyl chloride, or benzotrichloride. With the last two reagents a small amount of zinc chloride is used as a catalyst.[2]

Attempts have been made to prepare pure symmetrical *o*-phthalyl chloride by repeatedly heating the crude chloride, still containing phthalic acid, with small amounts of phosphorus pentachloride.[3]

Conversion of the symmetrical chloride into the unsymmetrical isomer can also be effected by heating with tin tetrachloride.[4] The yield, however, is not satisfactory.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

unsymmetrical phthalyl chloride

o-PHTHALYL CHLORIDES

SYMMETRICAL AND UNSYMMETRICAL o-PHTHALYL CHLORIDES

Symmetrical o-Phthalyl Chloride

sym. o-phthalyl chloride

Unsymmetrical o-Phthalyl Chloride

calcium chloride (10043-52-4)

hydrogen chloride (7647-01-0)

Benzene (71-43-2)

phosphorus pentachloride (10026-13-8)

thionyl chloride (7719-09-7)

carbon tetrachloride (56-23-5)

aluminum (7429-90-5)

phthalic anhydride (85-44-9)

Phosphorus Oxychloride (21295-50-1)

aluminum chloride (3495-54-3)

benzotrichloride (98-07-7)

phosphorus trichloride (7719-12-2)

zinc chloride (7646-85-7)

phthalic acid (88-99-3)

tin tetrachloride (7646-78-8)

phosphorus pentoxide (1314-56-3)

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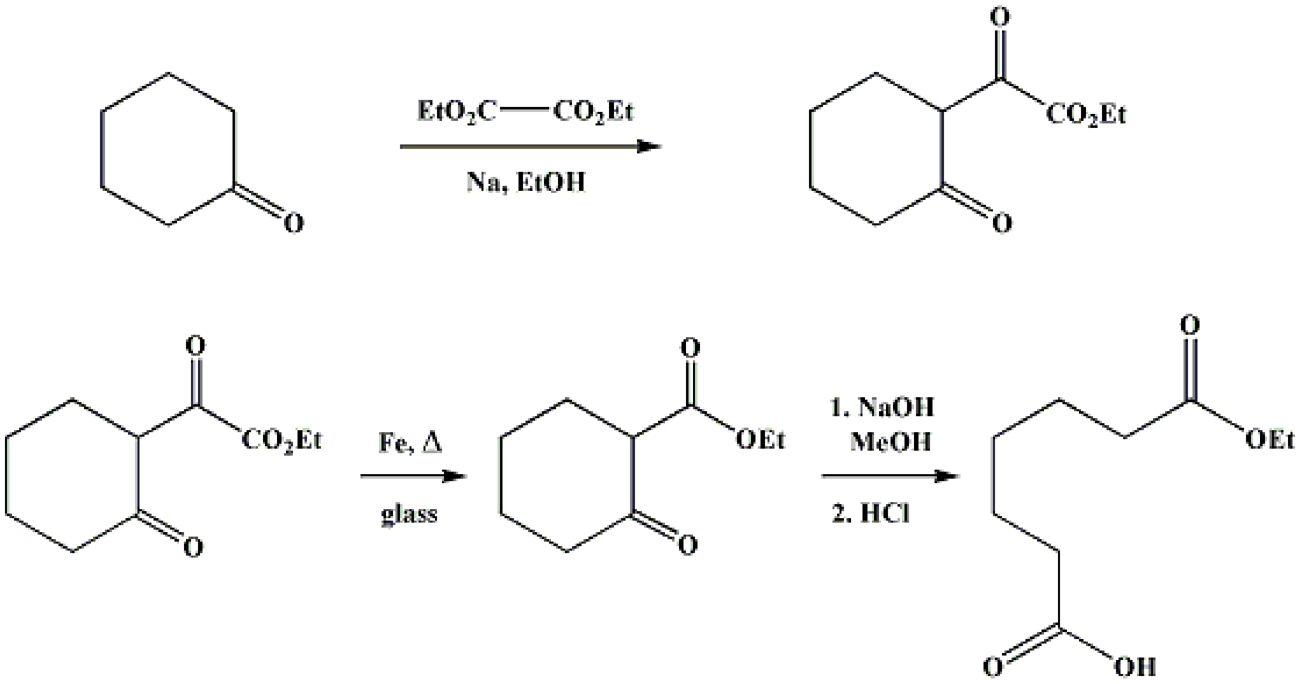
Organic Syntheses, CV 2, 531

PIMELIC ACID

[(*A*) (*From Cyclohexanone*)]



Submitted by H. R. Snyder, L. A. Brooks, and S. H. Shapiro.
Checked by Lee Irvin Smith, R. T. Arnold, and John Moran.

1. Procedure

A solution of sodium ethoxide is prepared by the cautious addition of 46 g. (2 gram atoms) of clean sodium to 600 cc. of anhydrous ethyl alcohol (Note 1) in a 2-l. three-necked flask equipped with a dropping funnel, a mercury-sealed stirrer, and a reflux condenser carrying a calcium chloride tube. The flask is then immersed in an ice-salt bath and the stirrer is started. When the temperature of the solution has reached 10° (Note 2) an ice-cold solution of 196 g. (2 moles) of cyclohexanone (Note 3) in 292 g. (2 moles) of ethyl oxalate (Note 4) is added from the dropping funnel over a period of about fifteen minutes. Vigorous stirring is required to prevent complete solidification of the reaction mixture (Note 5). When the addition is complete, the ice bath is retained for an hour, and then the mixture is stirred at room temperature for about six hours.

The reaction mixture is then decomposed by the careful addition of ice-cold dilute sulfuric acid prepared by adding 56 cc. of concentrated acid (sp. gr. 1.84) to 435 g. of ice. During this neutralization the temperature of the mixture is maintained at about 5–10° by means of an ice-salt bath. The solution, which should now be acid to Congo red paper, is diluted with cold water to a volume of about 4 l. The ethyl 2-ketocyclohexylglyoxalate separates as a heavy oil and is removed. The aqueous solution is extracted with four 500-cc. portions of benzene. The crude product is combined with the extracts, and the resulting solution is washed with two 200-cc. portions of water. The benzene solution is then allowed to stand in a separatory funnel for a few minutes until it is free from suspended water.

The benzene solution, without drying, is transferred in portions of about 500 cc. to a 1-l. Claisen flask connected to a water-cooled condenser. The flask is heated on the steam bath until the benzene no longer distils. The steam bath is then replaced by an oil bath and the system is gradually evacuated to a pressure of 10–12 mm. while the oil bath is held at about 90°. When all the benzene, unchanged ester,

and ketone have distilled (Note 6) the temperature of the oil bath is increased. When the temperature of the distillate reaches 105°/10–12 mm. the receiver is changed. The bath temperature is immediately raised to 175° and all material distilling between 105° and 165° at 10–15 mm. is collected. This requires one-half to one hour. During this time the bath temperature is slowly increased to 200° to obtain the last portions. The yield is 250–265 g. (63–67 per cent of the theoretical amount). The distillate is transferred to a 500-cc. modified Claisen flask, and a trace of iron powder and some finely ground soft glass are added (Note 7). The mixture is distilled at 40 mm. with the bath temperature maintained at 165–175° (Note 8). Carbon monoxide is evolved and the distillate is collected between 125° and 140°. About one and a half to two hours is required for the pyrolysis. The yield of ethyl 2-ketohexahydrobenzoate is 200–210 g. (59–62 per cent of the theoretical amount based on cyclohexanone). This product, whose refractive index at 25° varies from 1.476 to 1.479, is sufficiently pure for use in the next step without redistillation.

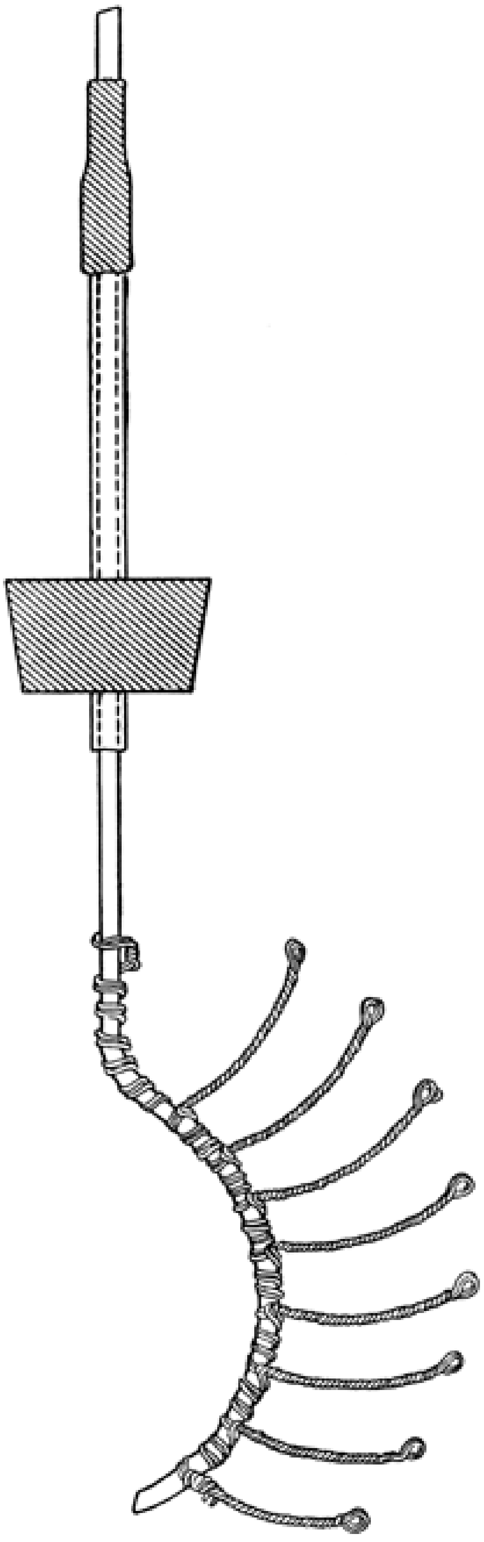
In a 2-l. three-necked flask equipped with a dropping funnel, a reflux condenser, and a special stirrer (Note 9) is placed 100 g. (2.5 moles) of sodium hydroxide and 300 cc. of anhydrous methyl alcohol. The stirred mixture is heated for one hour in an oil bath held at 120° in order to effect solution of most of the sodium hydroxide. Stirring and heating are continued while 100 g. (0.59 mole) of ethyl 2-ketohexahydrobenzoate is added over a period of two hours. The resulting mixture is heated for one hour longer with the bath temperature at 120°. It is then diluted with 600 cc. of water and the condenser is arranged for distillation. The methyl alcohol is removed by distillation until a thermometer immersed in the boiling solution reads 98–100°. The residual aqueous solution is vigorously stirred, and exactly 210 cc. of concentrated hydrochloric acid (sp. gr. 1.18) is carefully added drop by drop from a dropping funnel (Note 10). The hot acid solution is treated with 2–4 g. of Darco and is filtered through a heated Büchner funnel. The filtrate is cooled in an ice bath. The pimelic acid is collected on a Büchner funnel and is crystallized from 100 cc. of boiling water for each 45 g. of acid. After drying in the air the acid melts at 103.5–104° and weighs 65–73 g. The mother liquors from the hydrolysis and recrystallization are combined and evaporated to dryness on a steam bath. The resulting solid is extracted with two 500-cc. portions of acetone. The acetone is distilled from a steam bath, and the residual crude pimelic acid is recrystallized from the minimum quantity of benzene, yielding an additional 10–12 g. of pure material. The total yield is 75–83 g. (80–88 per cent of the theoretical amount based on ethyl 2-ketohexahydrobenzoate; 47–54 per cent based on cyclohexanone).

2. Notes

1. Dry sodium methoxide can be used with good results. One hundred eight grams (2 moles) of sodium methoxide (Matheson Alkali Company) and 400 cc. of anhydrous ethyl alcohol are used instead of the sodium ethoxide solution.
2. The dropping funnel may be replaced with a cork carrying a thermometer during this part of the procedure.
3. Commercial cyclohexanone was redistilled through a 20-in. column packed with Carborundum. The fraction boiling at 154°/746 mm. is of sufficient purity.
4. Commercial ethyl oxalate was redistilled from a modified Claisen flask, and the fraction boiling at 83–86°/25 mm. was used.
5. A precipitate usually appears within an hour or two after addition of the reagents. If the solution is orange in color and no precipitate forms, it may still be worked up with fair results.
6. The last portions of this distillate are tested with ferric chloride. A red or violet color indicates ethyl 2-ketohexahydrobenzoate.
7. More than a milligram of iron, although increasing the rate of pyrolysis, leaves behind a hard residue difficult to remove. Ordinary soft glass is ground in a mortar; from 0.5 to 1 g. is sufficient.
8. If the bath temperature is too high, the unpyrolyzed ester will distil. A high refractive index indicates the presence of unchanged ester.
9. The stirrer .htm(Fig. 17) is constructed by wrapping a double strand of copper magnet wire around a semicircular glass stirring rod. At intervals a loop of the wire is twisted to make a

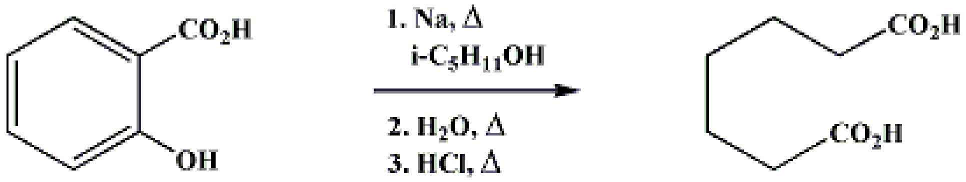
projection which extends about 2" in. from the glass rod. The stirrer is introduced into the center neck of the three-necked flask. The projections are arranged so that they touch the sides of the flask when the stirrer is in use. This adjustment is made by a steel or glass rod introduced through one of the side necks. The scraping of the sides of the flask by the copper wire prevents the deposition of the salt on the walls, with consequent moderation of bumping. With an ordinary stirrer the yield in this step is at least 10 per cent less.

Fig. 17



10. The solution becomes almost clear when sufficient acid has been added.

[(*B*) (*From Salicylic Acid*)]



Submitted by Adolf Müller
Checked by Reynold C. Fuson, J. R. Little, and Wesley Fugate.

1. Procedure

Four hundred cubic centimeters of freshly distilled isoamyl alcohol (b.p. 128–132°) is heated to 90–100° on an oil bath in a 5-l. two-necked flask fitted with a dropping funnel and reflux condenser. Two hundred forty grams (10.4 gram atoms) of clean sodium is then added, and the temperature of the oil bath is raised rapidly until the alcohol is brought to vigorous boiling (Note 1). A solution of 100 g. (0.73 mole) of salicylic acid in 2 l. of isoamyl alcohol is allowed to flow into the flask at the rate of 100 cc. every four minutes, so that the entire amount is added over a period of eighty minutes. The dropping funnel is then rinsed with 100 cc. of isoamyl alcohol. The solution in the flask is clear at first, then becomes cloudy with the addition of the salicylic acid. The temperature of the oil bath is regulated so that the alcohol refluxes rapidly throughout the course of the experiment. The sodium goes completely into solution in seven to eight hours.

The flask is then allowed to cool to 100°, and 800 cc. of hot water is added with vigorous shaking (Note 2). The hot mixture is transferred to a 5-l. separatory funnel, the flask being rinsed with 200 cc. of hot water (Note 3). The mixture is shaken well and the layers separated. The isoamyl alcohol layer is extracted with four or five 200-cc. portions of nearly boiling water (Note 4). The combined aqueous extracts are then steam-distilled in order to remove any isoamyl alcohol from the aqueous solution of the sodium salt. About 500 cc. of distillate is collected (Note 5).

The flask is allowed to cool, and 920 cc. of hydrochloric acid (sp. gr. 1.19) is added. The unchanged salicylic acid is then steam-distilled from the mixture. The flask is strongly heated, so that its contents are concentrated and, towards the end of the distillation, sodium chloride begins to precipitate. The removal of salicylic acid is practically complete when about 10–12 l. of distillate has come over, although the distillate still gives a ferric chloride test for salicylic acid. The solution in the flask is allowed to cool overnight and is finally chilled in an ice bath.

The crystalline precipitate, which is a mixture of sodium chloride and pimelic acid, is then collected on a suction filter without washing. The product is dried in an evaporating dish on the water bath for several hours, with frequent stirring, whereby the brown mass is partially melted. The mass, after cooling, is transferred to a 500-cc. Soxhlet thimble. The Soxhlet apparatus is mounted over a hot plate and the solid extracted with about 650 cc. of benzene. Complete extraction is indicated when the liquid in the siphon is no longer turbid (Note 6). The extraction is complete when evaporation of a small quantity of the solution in the extractor leaves no residue (two to three hours). After the extraction is complete, the benzene solution is concentrated to about 300 cc. and the pimelic acid allowed to crystallize. The crystals are collected on a filter, washed with cold benzene, and dried in the air. The product melts at 104–105° and weighs 50–58 g. (43–50 per cent of the theoretical amount).

2. Notes

1. The yield of pimelic acid is materially reduced if the alcohol is not refluxing rapidly at this point.
2. The water must be added slowly and with thorough shaking at first, since traces of unchanged sodium may still be present.

3. Unless hot water (85–90°) is used for the extractions troublesome emulsions are likely to form. If such emulsions do form they may be broken by passing steam into the solution while in the separatory funnel.

4. A large portion of the isoamyl alcohol may be recovered for use in subsequent preparations. The moist alcohol from the water extractions is directly distilled, and a fraction boiling at 128–135° collected. The alcohol layer in the fore-run may be separated from the water layer and redistilled with the moist alcohol from the following run.

5. Ethyl pimelate may be prepared by proceeding as follows: The combined aqueous extracts, instead of being subjected to steam distillation, are evaporated on a steam bath until the thick crystalline magma which forms has only a faint odor of isoamyl alcohol. The magma is dissolved in 600 cc. of water, and 800 cc. of concentrated hydrochloric acid is added. The mixture is cooled to room temperature and filtered, and 170 cc. of concentrated hydrochloric acid is added to the filtrate. The acid mixture is extracted with three 400-cc. portions of ether—a continuous extractor such as that shown in Org. Syn. Coll. Vol. I, **1941**, 277, can be used to advantage—and the ether is removed from the extract by distillation. Upon cooling the residue in an ice bath, crystals separate; they are cooled thoroughly, collected on a Büchner funnel, and pressed on a porous plate. The filtrate, after the addition of a few pieces of porous plate, is left overnight in a vacuum desiccator over concentrated sulfuric acid. The crystals which separate are collected on a filter, pressed on a porous plate, and added to the rest of the product. The total weight is 60–70 g.

The crude material, which is a mixture of pimelic and salicylic acids, is esterified by boiling for four hours with 520 cc. of absolute ethyl alcohol and 6 cc. of concentrated sulfuric acid. Two-thirds of the alcohol is then removed by distillation. To the residue, 600 cc. of water and 400 cc. of ether are added, the mixture is shaken, and the aqueous layer is drawn off. The ether solution is shaken with two 200-cc. portions of 2 *N* sodium hydroxide solution to remove ethyl salicylate, and then with water until the disappearance of an alkaline reaction. The ether is evaporated and the residue is distilled under reduced pressure. Ethyl pimelate boils at 153–156°/24 mm.; 148–152°/22 mm. The yield is 54–60 g. (35–38 per cent of the theoretical amount based upon the salicylic acid).

In this procedure it is important to remove the brown sludge formed by partial acidification of the alkaline solution of the sodium salts. If all the hydrochloric acid is added at once, ether extraction of the entire precipitate is tedious because of the slow separation of the aqueous and ether layers. It is also important to wash the ether solution of ethyl pimelate and ethyl salicylate carefully with sodium hydroxide solution in order to avoid loss of product by hydrolysis. (Private communication by Adolf Müller and Erich Rölz. Checked by W. H. Carothers and W. L. McEwen.)

6. During some runs the pimelic acid begins to crystallize in the siphon. This difficulty may be minimized by fashioning an asbestos jacket around the extraction chamber. Occasionally it is necessary to pass steam over the siphon.

3. Discussion

Pimelic acid has been obtained as a by-product of the reaction between trimethylene bromide and sodium cyanoacetic ester;[1] by the action of carbon dioxide upon pentamethylene-1,5-dimagnesium bromide;[2] by hydrolysis of pentamethylene cyanide;[3] by the action of sodium and amyl alcohol upon salicylic acid, guaiacol carboxylic acid,[4] or anthranilic acid;[5] and from 2-cyanocyclohexanone.[6]

The preparation of pimelic acid from cyclohexanone, described in Part (*A*) above, and from salicylic acid, described in Part (*B*) above,[7] are new procedures in Organic Syntheses. The older directions for preparing ethyl pimelate[8] are given as Note 5 on p. 536.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Ethyl 2-ketocyclohexylglyoxalate

pimelic and salicylic acids

sodium cyanoacetic ester

pentamethylene-1,5-dimagnesium bromide

ethyl alcohol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

methyl alcohol (67-56-1)

ether (60-29-7)

sodium hydroxide (1310-73-2)

carbon monoxide (630-08-0)

iron, iron powder (7439-89-6)

Cyclohexanone (108-94-1)

sodium chloride (7647-14-5)

Trimethylene bromide (109-64-8)

salicylic acid

carbon dioxide (124-38-9)

acetone (67-64-1)

sodium methoxide (124-41-4)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

ferric chloride (7705-08-0)

Anthranilic Acid (118-92-3)

Ethyl oxalate

isoamyl alcohol (123-51-3)

amyl alcohol (71-41-0)

Pimelic acid (111-16-0)

Ethyl 2-ketohexahydrobenzoate (1655-07-8)

Ethyl pimelate (33018-91-6)

ethyl salicylate (118-61-6)

pentamethylene cyanide (646-20-8)

2-cyanocyclohexanone

guaiacol carboxylic acid (6324-11-4)

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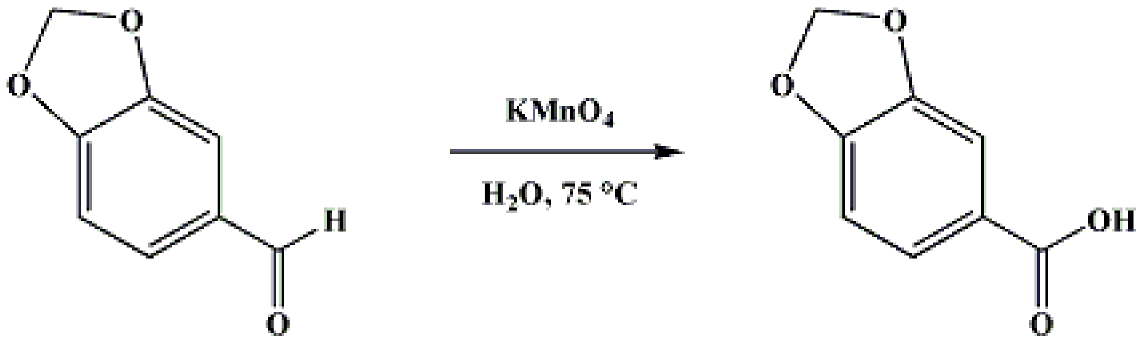
Organic Syntheses, CV 2, 538

PIPERONYLIC ACID



Submitted by R. L. Shriner and E. C. Kleiderer.
Checked by H. T. Clarke and S. Graff.

1. Procedure

Sixty grams (0.4 mole) of piperonal (Note 1) and 1.5 l. of water are placed in a 5-l. flask fitted with an efficient mechanical stirrer. The flask is placed on a steam bath, heated to 70–80°, and the stirrer started (Note 2). A solution of 90 g. (0.56 mole) of potassium permanganate in 1.8 l. of water is allowed to flow into the emulsion of piperonal and water over a period of forty to forty-five minutes (Note 3). The stirring and heating are continued for an hour longer, at the end of which time the permanganate is reduced. Enough 10 per cent potassium hydroxide solution is added to make the solution alkaline. The mixture is filtered while hot, and the manganese dioxide is washed with three 200-cc. portions of hot water. The combined filtrate and washings are cooled. At this point any unreacted piperonal that separates must be filtered (Note 4). The solution is now acidified with hydrochloric acid, the acid being added until no further precipitate forms. The resulting piperonylic acid is filtered, washed with cold water until free of chlorides, and dried. The yield is 60–64 g. (90–96 per cent of the theoretical amount) of a colorless product melting at 224–225° (corr.). For most purposes the crude material is pure enough, but it may be crystallized from ten times its weight of 95 per cent ethyl alcohol, yielding 52–56 g. (78–84 per cent of the theoretical amount) of needles melting at 227–228° (corr.).

2. Notes

1. The commercial grade of piperonal, m.p. 36°, may be used without purification.
2. The stirring must be sufficiently vigorous to emulsify the molten piperonal thoroughly with the water.
3. Addition of the piperonal to the permanganate lowers the yield to 50 per cent.
4. If the temperature of the reaction mixture is kept between 70° and 80° and the permanganate is added at the rate stated, the piperonal will be entirely oxidized.

3. Discussion

Piperonylic acid has been made by the oxidation of piperic acid,[1] piperonal,[1] safrole,[2] and isosafrole[2] with potassium permanganate. It has also been prepared by the action of methylene iodide on protocatechuic acid[3] in the presence of alkali.

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

piperic acid

ethyl alcohol (64-17-5)

hydrochloric acid (7647-01-0)

potassium permanganate (7722-64-7)

potassium hydroxide (1310-58-3)

safrole (94-59-7)

manganese dioxide (1313-13-9)

Methylene iodide (75-11-6)

Piperonylic acid (94-53-1)

piperonal (120-57-0)

isosafrole (120-58-1)

protocatechuic acid (99-50-3)

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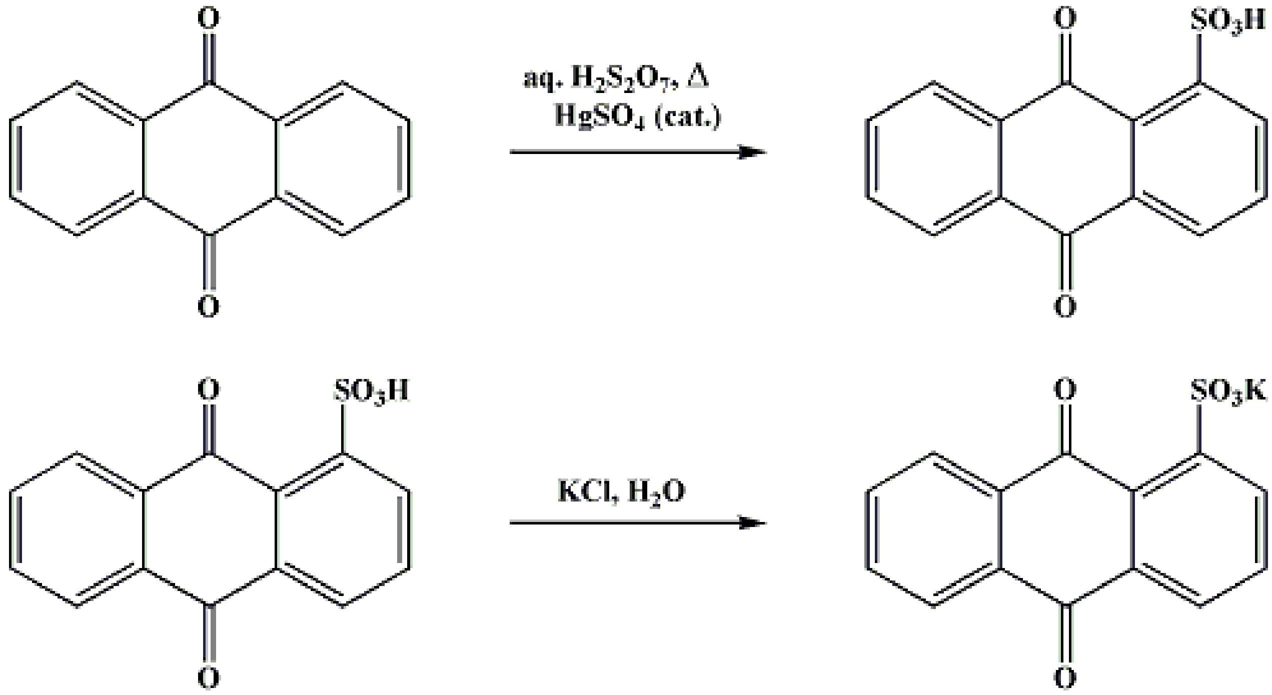
Organic Syntheses, *CV 2*, *539*

POTASSIUM ANTHRAQUINONE-α-SULFONATE

[1-Anthraquinonesulfonic acid, potassium salt]



Submitted by W. J. Scott and C. F. H. Allen.
Checked by Louis F. Fieser and E. B. Hershberg.

1. Procedure

A 500-cc. three-necked flask fitted with a mechanical stirrer (Note 1) and a thermometer is half immersed in an oil bath mounted in a hood. In the flask are placed 120 g. of 19–22 per cent oleum and 1 g. of yellow mercuric oxide, the bath is warmed to 100°, and 100 g. (0.48 mole) of anthraquinone (Note 2) is added through a powder funnel attached by a piece of wide rubber tubing. The mixture is stirred vigorously and heated at 147–152° for forty-five to sixty minutes, after which the bath is removed and the flask is lowered from the stirrer and replaced by a 2-l. beaker containing 1 l. of hot water. While the water is being stirred, the hot acid solution is poured cautiously down the inner wall of the beaker; the mixture is then boiled for five minutes longer with stirring. After the unchanged anthraquinone (53–59 g.) (Note 3) is collected by suction on a 20-cm. Büchner funnel provided with a cotton filter cloth, it is washed with 200 cc. of hot water. The light brown filtrate, together with the wash water, is heated to 90°, and a solution of 32 g. of potassium chloride in 250 cc. of water is added. After cooling to room temperature (Note 4), the potassium salt, which crystallizes in the form of pale yellow leaflets, is collected on a large Büchner funnel (filter paper) and washed with 200 cc. of cold water. The yield of product, dried at 100° *in vacuo*, is 57–55 g. (Note 5) (77–86 per cent of the theoretical amount based on the anthraquinone converted) (Note 6) and (Note 7).

2. Notes

1. It is necessary to provide an efficient stirrer driven by a powerful motor. The yields reported were obtained using a Hershberg Chromel wire stirrer (p. 117); with other stirrers the yields were about 10 per cent lower.
2. The anthraquinone employed melted at 284.5–285.5° (corr.). It may be prepared conveniently by oxidation of anthracene (p. 554).
3. The recovered material contains mercury and other impurities and melts at 265–275°. When this is used as such in a second run, there is considerably more disulfonation than with pure anthraquinone.
4. Under the conditions specified very little disulfonation occurs, so that the crystallizing mixture may be allowed to cool to 25° without danger of contamination of the product with disulfonates. When recovered anthraquinone is employed, it is advisable to collect the product when the mixture has cooled to 60°, for the disulfonates present are then retained in the mother liquor. The solubilities of the 1,5- and 1,8-disulfonates increase more rapidly with increasing temperature than does the solubility of the α-monosulfonate.
5. The 57-g. yield refers to the experiment in which 53 g. of starting material was recovered; the percentage yield improves with increase in the amount of anthraquinone recovered.
6. The purity of the product may be checked by converting a sample to α-chloroanthraquinone (p. 128) and taking the melting point; that from the above salt melted at 158–160° (corr.).
7. The conditions adopted in this procedure favor the production of the α-monosulfonate in a state of high purity at the expense of a high conversion of anthraquinone. A better conversion can be achieved by conducting the sulfonation at a higher temperature, or by using more oleum, but in either case there is a considerable increase in the amount of disulfonic acids formed. The extent of β-sulfonation is not influenced greatly by the temperature but is dependent chiefly on the amount of mercuric salt present in the solution. The amount specified corresponds approximately to the limit of solubility of the salt in the acid employed, and very little of the β-acid is formed. As the potassium β-sulfonate is more soluble than the α-salt, traces of this isomer are easily eliminated by crystallization.

3. Discussion

The only practical method for the preparation of anthraquinone-α-sulfonates is based upon the discovery[1] that in the presence of a small amount of mercuric salt anthraquinone is sulfonated chiefly in the α-rather than in the β-position. Detailed procedures are described by Fierz-David,[2] by Lauer,[3] and by Groggins;[4] the above directions are based largely upon the observations of Lauer.[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 128
- Org. Syn. Coll. Vol. 3, 573

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

oleum

anthraquinone-α-sulfonates

mercury (7439-97-6)

mercuric oxide (21908-53-2)

Anthraquinone (84-65-1)

anthracene (120-12-7)

potassium chloride (7447-40-7)

α-Chloroanthraquinone (82-44-0)

Potassium anthraquinone-α-sulfonate, 1-Anthraquinonesulfonic acid, potassium salt (30845-78-4)

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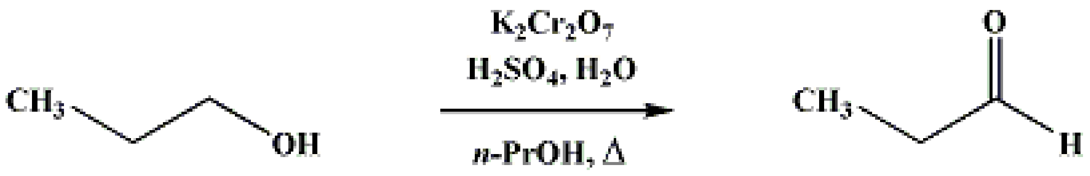
Organic Syntheses, CV 2, 541

PROPIONALDEHYDE



Submitted by Charles D. Hurd and R. N. Meinert.
Checked by W. L. McEwen and W. H. Carothers.

1. Procedure

One hundred grams (125 cc., 1.7 moles) of *n*-propyl alcohol, b.p. 96–96.6°, is placed in a 2-l. three-necked, round-bottomed flask fitted with a mercury-sealed stirrer (Note 1), a dropping funnel, and a 60-cm. bulb condenser (Note 2) set at an angle of 45°. Water at 60° is kept circulating through this condenser. A condenser set for downward distillation is connected to the top of the first condenser. Cold water circulates through the second condenser. By means of an adapter, the lower end of the second condenser is fitted to a receiver which is cooled with ice water.

The alcohol in the flask is heated to boiling, stirred, and a mixture of 164 g. (0.56 mole) of potassium dichromate, 120 cc. of concentrated sulfuric acid (2.2 moles), and 1 l. of water is added through the dropping funnel. The addition takes about thirty minutes, and during this time the contents of the flask are kept vigorously boiling. After all the oxidizing mixture has been added, the contents of the flask are boiled for fifteen minutes to distil the last of the aldehyde. The propionaldehyde which collects in the receiver is dried with 5 g. of anhydrous sodium sulfate and fractionally distilled. The yield of propionaldehyde boiling at 48–55°, and having a refractive index of 1.364 (Note 3), is 44–47 g. (45–49 per cent of the calculated amount).

2. Notes

1. The yield of propionaldehyde depends largely upon the efficiency of the stirrer.
2. The purpose of the first condenser is to condense and return to the flask any propyl alcohol which escapes.
3. The recorded value for the index of refraction ($N_D^{20°}$) is 1.3636.

3. Discussion

Propionaldehyde has been prepared by passing propyl alcohol over finely powdered reduced copper;[1] by passing a mixture of propyl alcohol and air over a hot platinum spiral[2] or a silver catalyst containing a small amount of samarium oxide;[3] by passing a

mixture of steam and propylene oxide over silica gel at 300°;[4] by adding propyl alcohol to a dichromate oxidizing mixture[5] or adding a dichromate oxidizing mixture to propyl alcohol;[6] by heating propylene glycol to 500°;[7] by heating a mixture of calcium formate and calcium propionate;[8] by the action of ethylmagnesium iodide on amyl formate;[9] by catalytic hydrogenation of acrolein;[10] by electrolysis of calcium chloride or dilute sulfuric acid solutions of propyl alcohol;[11] by passing vapors of propyl alcohol over cadmium oxide at 325°;[12] by passing vapors of propionic acid and formic acid over titanium oxide at 250–300°;[13] by oxidizing propyl alcohol with a stream of air in the presence of copper bronze, nitrobenzene, and quinoline;[14] and by treating ethyl orthoformate with ethylmagnesium bromide.[15]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

copper bronze

platinum spiral

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

Acrolein (107-02-8)

propionic acid (79-09-4)

sodium sulfate (7757-82-6)

formic acid (64-18-6)

Propionaldehyde (123-38-6)

propylene oxide (75-56-9)

copper (7440-50-8)

Nitrobenzene (98-95-3)

propyl alcohol, n-propyl alcohol (71-23-8)

Ethyl orthoformate

Quinoline (91-22-5)

potassium dichromate (7778-50-9)

ethylmagnesium bromide (925-90-6)

propylene glycol (57-55-6)

silver (7440-22-4)

calcium formate (544-17-2)

samarium oxide (12060-58-1)

calcium propionate (4075-81-4)

ethylmagnesium iodide

amyl formate (638-49-3)

cadmium oxide

titanium oxide

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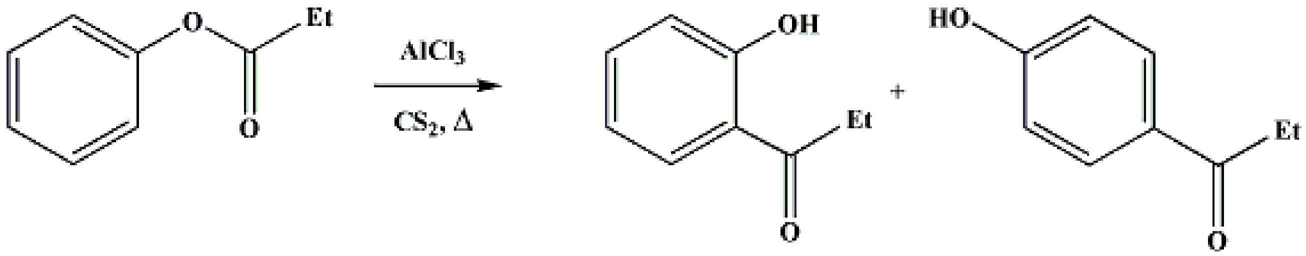
Organic Syntheses, CV 2, 543

o-PROPIOPHENOL AND *p*-PROPIOPHENOL

[Propiophenone, *o*- and *p*-hydroxy-]



Submitted by Ellis Miller and Walter H. Hartung.
Checked by W. W. Hartman and L. J. Roll.

1. Procedure

In a 2-l. three-necked, round-bottomed flask, fitted with a reflux condenser, a mechanical stirrer (Note 1), and a 100-cc. dropping funnel, are placed 374 g. (2.8 moles) of anhydrous aluminum chloride and 400 cc. of carbon bisulfide (Note 2). To the stirred suspension is added slowly through the dropping funnel 375 g. (2.5 moles) of phenyl propionate (Note 3). Reaction sets in almost at once with the evolution of hydrogen chloride (Note 4), and the carbon bisulfide begins to reflux from the heat of reaction (Note 5). When all the propionate is in (one and one-half hours is required), the mixture is further heated to gentle refluxing on a steam bath until the evolution of hydrogen chloride has practically ceased (about two hours). The reflux condenser is then turned downward, and the carbon bisulfide is distilled. The steam bath is replaced by an oil bath which is heated to 140° and maintained at 140–150° for three hours (Note 6). During this period a fresh evolution of hydrogen chloride takes place. The mixture thickens and finally congeals to a brown resinous mass. Stirring is continued as long as possible (Note 7).

The solid is then allowed to cool, and the aluminum complex is decomposed by slowly adding first a mixture of 300 cc. of concentrated hydrochloric acid with 300 cc. of water and then 500 cc. of water (Note 8), whereupon a black oil collects at the surface. After standing overnight in the ice box, a large portion of this layer solidifies and can be separated by filtration. This solid (*p*-propiophenol) is recrystallized from 400 cc. of methyl alcohol. The yield is 129–148 g. (34–39 per cent of the theoretical amount) of a light yellow product melting at 145–147°. A second recrystallization raises the melting point to 147–148°.

The oily filtrate combined with the concentrated mother liquors of the above recrystallization is dissolved in 500 cc. of 10 per cent sodium hydroxide and extracted with two 100-cc. portions of ether to remove non-phenolic products. The alkaline solution is acidified with hydrochloric acid and the oily layer is separated, dried over anhydrous magnesium sulfate, and distilled. The *o*-propiophenol boils at 110–115°/6 mm. The yield is 120–132 g. (32–35 per cent of the theoretical amount). About 40 g. of *p*-propiophenol boiling at 135–150°/11 mm. is obtained. The total yield of crude *p*-propiophenol is thus 169–188 g. (45–50 per cent of the theoretical amount) (Note 9).

2. Notes

1. The stirrer should be made of sturdy glass rod, bent preferably in the shape of a golf-club head, to provide for heavy duty when the reaction mass becomes thick.
2. When nitrobenzene was used as a solvent the products were always tarry.
3. Crude, undistilled phenyl propionate, made by gently heating a mixture of equivalent quantities of phenol and propionyl chloride until hydrogen chloride evolution ceases, is satisfactory for rearrangement. The ester can also be made conveniently by slowly adding one mole of thionyl

chloride to a mixture of 1.05 moles each of phenol and propionic acid, driving off all the hydrogen chloride and sulfur dioxide, and distilling.

4. Because of the large volume of hydrogen chloride evolved, it is desirable to work under a good hood. If this is not available, the gas-trap described on p. 4 may be used.

5. The addition of the phenyl propionate is regulated so as to maintain gentle refluxing.

6. The temperature of the reaction mixture is about ten degrees lower than the bath temperature, or 130–135°. The reaction temperature determines the yield ratio of the two isomers. In general, higher temperature (above 160–170°) favors the formation of the ortho isomer.

7. It is necessary to stir the thickening mass continuously to permit the escape of hydrogen chloride formed during the heating; otherwise it may swell rapidly and choke the outlets of the flask.

8. This decomposition is strongly exothermic, and the dilute acid should be added slowly.

9. The above procedure has been found satisfactory for the preparation of a number of the homologs of *o*- and *p*-propiophenol, such as aceto-, butyro-, and caprophenol.

3. Discussion

Ortho and para propiophenols have been previously prepared by condensing propionic acid and phenol in the presence of zinc chloride,[1] and from phenol and propionyl chloride.[2] The procedure described above is an adaptation of one described by Cox[3] and by Hartung, Munch, Miller, and Crossley.[4] In an alternative procedure phenyl propionate is added directly to aluminum chloride; no solvent is used.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 387
- Org. Syn. Coll. Vol. 3, 444

References and Notes

1. Goldzweig and Kaiser, J. prakt. Chem. (2) **43**, 86 (1891).
2. Perkin, J. Chem. Soc. **55**, 547 (1889).
3. Cox, J. Am. Chem. Soc. **49**, 1028 (1927).
4. Hartung, Munch, Miller, and Crossley, ibid. **53**, 4153 (1931).
5. Farinholt, Harden, and Twiss, ibid. **55**, 3386 (1933).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

aceto-, butyro-, and caprophenol

Ortho and para propiophenols

o-PROPIOPHENOL

p-PROPIOPHENOL

Propiophenone, o- and p-hydroxy-

o- and p-Propiophenol

hydrogen chloride, hydrochloric acid (7647-01-0)

methyl alcohol (67-56-1)

ether (60-29-7)

sodium hydroxide (1310-73-2)

thionyl chloride (7719-09-7)

phenol (108-95-2)

propionic acid (79-09-4)

sulfur dioxide (7446-09-5)

aluminum chloride (3495-54-3)

Nitrobenzene (98-95-3)

zinc chloride (7646-85-7)

magnesium sulfate (7487-88-9)

propionyl chloride (79-03-8)

carbon bisulfide

phenyl propionate (637-27-4)

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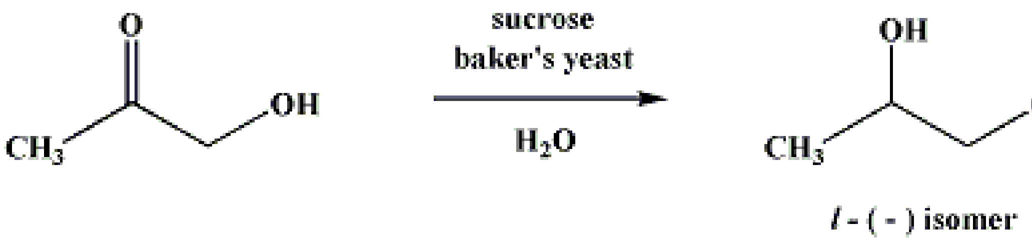
Organic Syntheses, CV 2, 545

l-PROPYLENE GLYCOL

[1,2-Propanediol, *l*-]



Submitted by P. A. Levene and A. Walti.
Checked by Frank C. Whitmore and J. Pauline Hollingshead.

1. Procedure

A solution of 1 kg. of sucrose in 9 l. of water is placed in a 20-l. bottle provided with a gas trap. A paste of baker's yeast (Note 1) is made by breaking up 1 kg. of yeast and gradually stirring in 1 l. of water. This is then added to the sugar solution and the mixture is allowed to stand at room temperature until a lively evolution of gas starts (from one to three hours). To the vigorously fermenting solution 100 g. (1.35 moles) of freshly prepared acetol (p. 5) is added, and the mixture is allowed to stand at room temperature until the reaction subsides (Note 2). The bottle is then transferred to an incubator at 32°, when the fermentation recommences. At the end of three days the reaction is generally completed, and the solution when tested with Fehling's reagent gives a negligible test for reducing sugars.

At this point 20–30 g. of short glass fiber or asbestos is added and the yeast is filtered by suction. The filtrate is concentrated to a thick syrup under diminished pressure on a water bath, the temperature being kept below 40° (Note 3). The residue (about 200 cc.) is taken up in a mixture of 400 cc. of absolute alcohol and 100 cc. of dry ether (Note 4). The precipitate formed is removed by centrifuging, the supernatant liquid is decanted, and the residue is extracted with a mixture of 200 cc. of 98.5 per cent alcohol and 100 cc. of dry ether (Note 5). The combined alcohol-ether solutions are concentrated under diminished pressure at 35–40° to a thick syrup. The residue is again taken up in a mixture of 400 cc. of 98.5 per cent alcohol and 100 cc. of dry ether and centrifuged (Note 5). The supernatant liquid is concentrated under diminished pressure and distilled from a modified Claisen flask. The yield of the crude product boiling at 86–91°/12 mm. is approximately 100 g. The crude material is refractionated and collected at 88–90°/12 mm. or 187–189°/760 mm. The final product (Note 4) is a colorless liquid having a density 1.04 and specific rotation $[\alpha]_D^{20} = -15.0°$. The yield is 50–60 g. (49–58 per cent of the theoretical amount) (Note 6).

2. Notes

1. Fleischmann's yeast is satisfactory.
2. The addition of the acetol may cause the reaction to slacken for a time.
3. The evaporation must be carried out at as low a temperature as is practicable. A suitable device for this evaporation is given in Org. Syn. Coll. Vol. I, **1941**, 427.
4. The product reacts slightly acid. If an entirely neutral *l*-propylene glycol is desired, the syrup first obtained should be made neutral with a solution of sodium methoxide in methyl alcohol, and again concentrated and extracted as indicated.
5. If a centrifuge is not available the same result may be obtained by adding about 15 g. of short glass fiber or asbestos to the solution, stirring the solution mechanically or shaking it vigorously for five minutes, and filtering with suction.
6. The optically active glycols are convenient starting materials for the preparation of optically active carbinols, hydroxyacids, etc. The biological method of asymmetric reduction is perhaps the only convenient method for the preparation of these glycols. The steps in the preparation of other optically active glycols are identical with those in the preparation of *l*-propylene glycol from acetone. In the synthesis of certain glycols it is convenient to prepare the chloroketone by oxidizing the corresponding chlorohydrin, the succeeding steps being the same as those in the synthesis of *l*-propylene glycol.

3. Discussion

l-Propylene glycol has been obtained from the optically inactive glycol by the action of bacteria,[1] and by means of strychnine compounds.[2] The present method is based on that of Färber, Nord, and Neuberg.[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 478
- Org. Syn. Coll. Vol. 7, 356
- Org. Syn. Coll. Vol. 8, 332

References and Notes

1. LeBel, Jahresb. **1881**, 512.
2. Grün, Ber. **52**, 260 (1919).
3. Färber, Nord, and Neuberg, Biochem. Z. **112**, 313 (1920).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Fehling's reagent

glycol

alcohol (64-17-5)

Acetol (64-19-7)

methyl alcohol (67-56-1)

ether (60-29-7)

sucrose

acetone (67-64-1)

sodium methoxide (124-41-4)

L-Propylene glycol, 1,2-Propanediol, l- (57-55-6)

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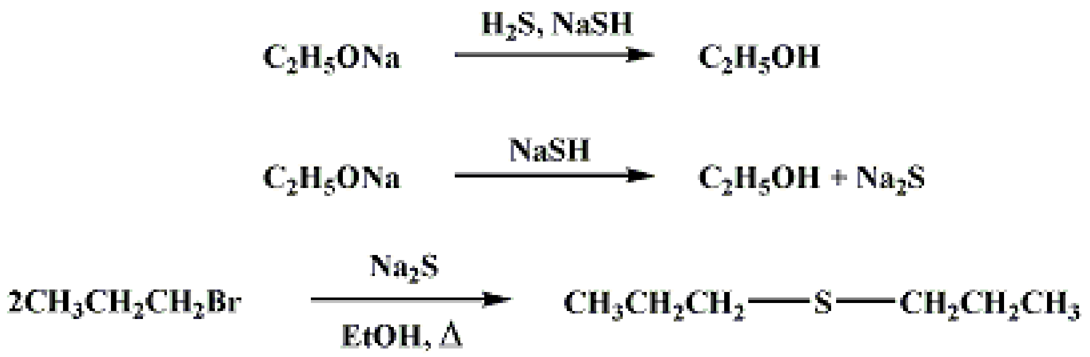
Organic Syntheses, CV 2, 547

n-PROPYL SULFIDE



Submitted by R. W. Bost and M. W. Conn.
Checked by Reynold C. Fuson and Charles F. Woodward.

1. Procedure

In a 2-l. round-bottomed flask, fitted with a reflux condenser and a 6-mm. glass tube closed at the upper end with a rubber tube and pinch-cock and reaching to the bottom of the flask, are placed 800 cc. of absolute alcohol and 50.6 g. (2.2 gram atoms) of clean sodium cut in small pieces. When the sodium is completely dissolved, one half of the solution is transferred to a 2-l. three-necked, round-bottomed flask fitted with a dropping funnel, a liquid-sealed mechanical stirrer, and a reflux condenser closed by a calcium chloride tube. The flask containing the remainder of the solution is connected again to the reflux condenser, and hydrogen sulfide from a cylinder is introduced by means of the glass tube at the rate of about two bubbles per second until the solution is saturated (about six hours is required). This solution of sodium hydrogen sulfide is added to the sodium ethoxide solution in the three-necked flask, and the mixture is refluxed for one hour. After cooling to room temperature, sufficient absolute alcohol (about 200 cc.) is added to dissolve all the sodium sulfide (Note 1).

To this solution of sodium sulfide is added dropwise with stirring 246 g. (2 moles) of *n*-propyl bromide (Org. Syn. Coll. Vol. I, **1941**, 37 and p. 359 above). After all the bromide has been added the flask is heated on a steam cone for eight hours (Note 2), during which time the mixture should not be stirred too vigorously. It is then cooled and added to 2 l. of 25 per cent aqueous sodium chloride solution contained in a separatory funnel. The mixture is shaken to ensure thorough mixing, allowed to stand until the layers have separated, and the upper oily layer of propyl sulfide removed and dried with anhydrous sodium sulfate. The lower layer is extracted with five 200-cc. portions of petroleum ether (b.p. 25–45°) (Note 3), the extract dried with 20 g. of sodium sulfate, and the petroleum ether distilled through a 60-cm. fractionating column until the temperature of the vapors passing over reaches 60°. The residue is added to the crude propyl sulfide previously separated and the combined portions distilled. The yield of product boiling at 140–143° is 80–100 g. (68–85 per cent of the

theoretical amount) (Note 4).

2. Notes

1. It is best to have the sodium sulfide completely dissolved before it is added to the bromide; subsequent extraction is facilitated, however, if the solution is kept at a minimum volume.
2. In order to be certain that no propyl sulfide is being lost during the refluxing, the condenser should be connected to a trap containing an aqueous solution of mercuric chloride. Condenser water cooled to 5–10° is recommended.
3. To avoid contamination of the product the petroleum ether should be distilled before being used. Ethyl ether is not suitable for this extraction.
4. *n*-Butyl and *sec*.-amyl sulfides can be prepared by procedures essentially the same as that given here.

3. Discussion

n-Propyl sulfide has always been prepared by the action of an alcoholic solution of an alkali sulfide on a *n*-propyl halide.[1]

References and Notes

1. Cahours, Compt. rend. **76**, 133 (1973); Winssinger, Bull. soc. chim. (2) **48**, 109 (1887).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

alcohol (64-17-5)

ethyl ether (60-29-7)

sodium chloride (7647-14-5)

hydrogen sulfide (7783-06-4)

bromide (24959-67-9)

n-PROPYL BROMIDE (106-94-5)

sodium sulfate (7757-82-6)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

mercuric chloride (7487-94-7)

sodium sulfide (1313-82-2)

sodium hydrogen sulfide

Propyl sulfide, n-PROPYL SULFIDE (111-47-7)

n-butyl sulfide (544-40-1)

n-amyl sulfide

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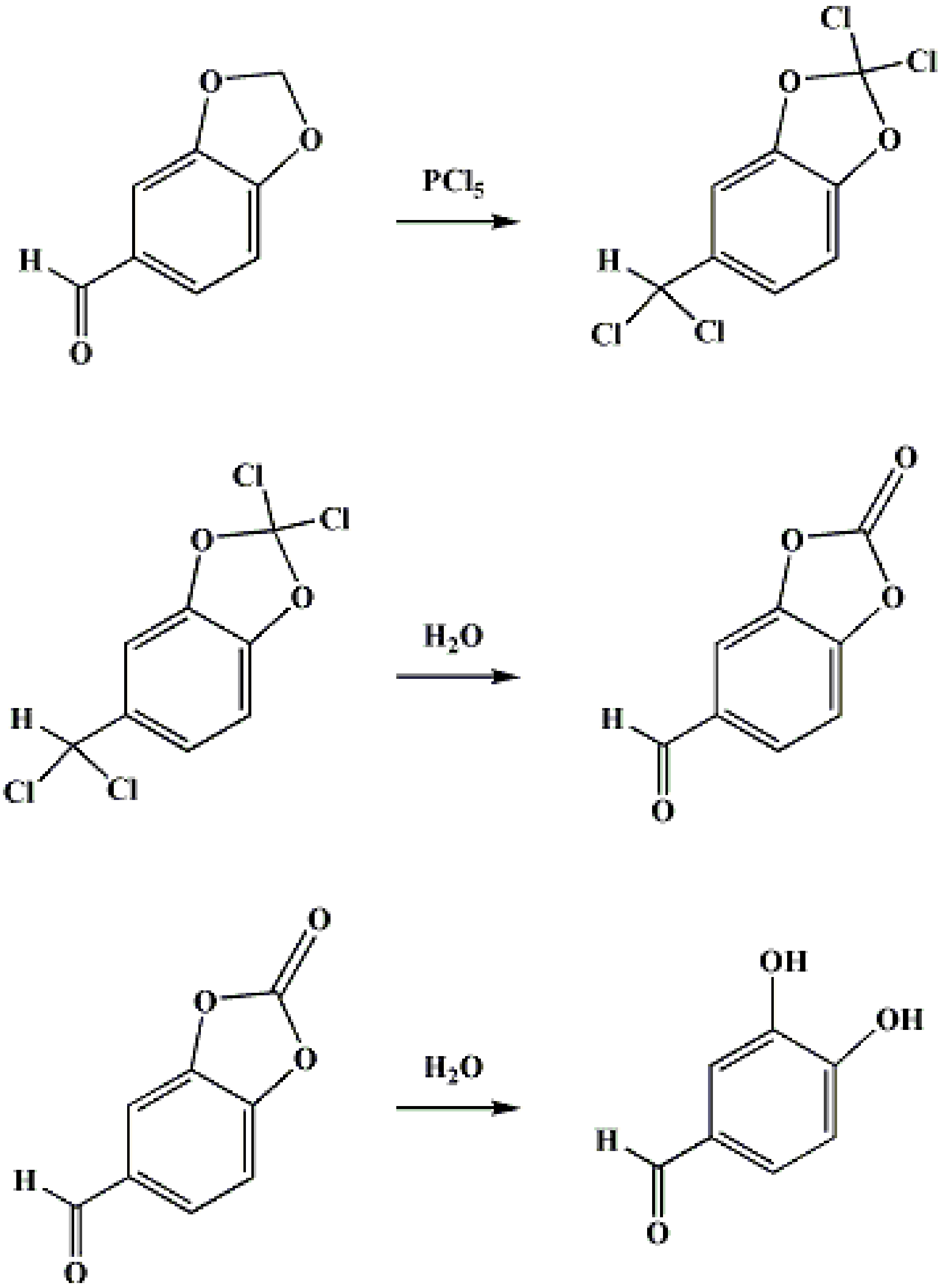
Organic Syntheses, CV 2, 549

PROTOCATECHUALDEHYDE



Submitted by Johannes S. Buck and F. J. Zimmermann.
Checked by Reynold C. Fuson and W. E. Ross.

1. Procedure

To 108 g. (0.72 mole) of piperonal in a 3-l. round-bottomed flask is added, in portions of 20 to 30 g., 454 g. (2.18 moles) of fresh phosphorus pentachloride. The reaction is vigorous at first, and the flask is kept cold with ice; moisture must be excluded. After about half of the pentachloride has been added the reaction becomes sluggish and cooling is unnecessary. The entire addition requires about thirty minutes. The resulting green or blue liquid containing undissolved pentachloride is heated very gently over a

flame for about sixty minutes to expel hydrogen chloride. From the turbid, light brown liquid thus formed, volatile material is removed on a steam bath under the reduced pressure of a water pump. This operation takes about thirty minutes. The contents of the flask are then poured into 5 l. of cold water contained in a 12-l. round-bottomed flask (Note 1). A milky oil is formed which rises and sinks in the water and, after about thirty minutes, becomes solid. After standing overnight, the mixture is boiled gently for three hours. The brown solution, containing a little tar, is cleared with charcoal and evaporated under reduced pressure to about 700 cc., when the aldehyde begins to separate. The solution is allowed to stand overnight at about 0°; a large crop of crystals separates, is collected on a filter, and washed with a little water. The product is purified by recrystallization from three times its weight of water. It melts at 153–154°, with decomposition, and weighs 61 g. (61 per cent of the theoretical amount).

2. Notes

1. This must be done cautiously because the residual phosphorus pentachloride reacts vigorously with water.

3. Discussion

Protocatechualdehyde has been made by a variety of methods, but is usually prepared from catechol by the Reimer-Tiemann method;[1] from vanillin[2] or veratric aldehyde[3] by demethylation; and from piperonal by the action of aluminum chloride[4] or phosphorus pentachloride followed by hydrolysis.[5]

References and Notes

1. Reimer and Tiemann, Ber. **9**, 1268 (1876); Tiemann and Koppe, ibid. **14**, 2015 (1881).
2. Tiemann and Haarmann, ibid. **7**, 620 (1874).
3. Dreyfus, Ger. pat. 193,958 [Frdl. **9**, 161 (1908–10)].
4. Givaudan-Delawanna, Inc., U. S. pat. 2,027,148 [C. A. **30**, 1395 (1936)].
5. Fittig and Remsen, Ann. **159**, 144 (1871); Pauly, Ber. **40**, 3096 (1907); Barger, J. Chem. Soc. **93**, 563 (1908); Hoering and Baum, Ber. **41**, 1914 (1908).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrogen chloride (7647-01-0)

phosphorus pentachloride (10026-13-8)

aluminum chloride (3495-54-3)

Catechol (120-80-9)

veratric aldehyde (120-14-9)

vanillin (121-33-5)

piperonal (120-57-0)

PROTOCATECHUALDEHYDE (139-85-5)

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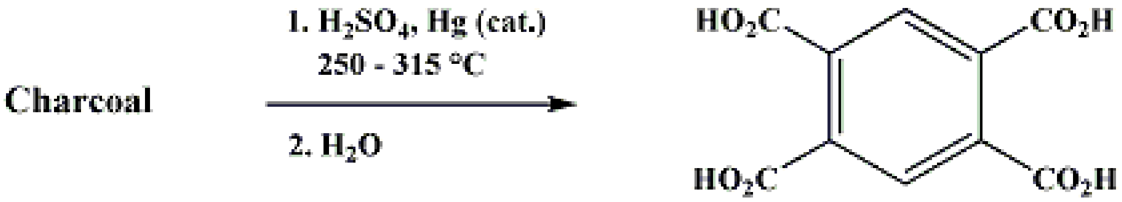
Organic Syntheses, CV 2, 551

PYROMELLITIC ACID



Submitted by E. Philippi and R. Thelen.
Checked by H. T. Clarke and S. Graff.

1. Procedure

In a 5-l. round-bottomed flask, set on a wire gauze in a hood and provided with a thermometer, are placed 100 g. of finely powdered pine or spruce charcoal (Note 1), 650 cc. of 82–88 per cent sulfuric acid (sp. gr. 1.76–1.80) (Note 2), and a small drop of mercury (Note 3). The mixture is heated with a small flame so that the temperature is raised to 250° during four hours. During another half hour the temperature is raised to 290°, when the acid begins to volatilize and the reaction mixture froths and expands greatly (Note 4). During the next hour the temperature is raised to 300°, and during the following hour to 315°. The mixture thickens somewhat, then much bubbling and spurting take place and fine white needles of pyromellitic anhydride begin to collect in the neck of the flask (Note 5). Fifty cubic centimeters of sulfuric acid is now added—the acid being poured in so as to rinse the walls of the flask; the syrupy reaction mixture is again heated to 250° for a few minutes and is transferred while still hot to a 1-l. tubulated retort (Note 6). The flask is rinsed with the minimum amount of water and the washings are added to the retort.

The material in the retort is heated with a free flame until the water present has distilled, then 30 g. of acid potassium sulfate is added and the distillation is continued. At first almost colorless sulfuric acid distils. As soon as crystals of pyromellitic anhydride appear, the receiver is replaced by one containing 50 cc. of water and the distillation is continued until nothing more passes over. The retort is then rinsed with 100 cc. of water and the rinsings are filtered and evaporated on the steam bath to 25 cc. (Note 7). The last distillate is also evaporated to 25 cc. On cooling, pyromellitic acid crystallizes. The product from both portions is collected on a suction funnel, using hardened filter paper, washed with two 10-cc. portions of ice water (Note 8), and recrystallized from four parts of boiling water. After drying at 105° the product (containing 2 moles of water of crystallization) melts at 271° (262° uncorr.). The yield is 6–8 g. (Note 9).

2. Notes

1. The yield of pyromellitic acid depends considerably on the kind of charcoal

used. An experiment with ordinary willow charcoal gave none of the desired product.
2. The specific gravity of the acid used should not vary from the limits indicated.
3. A series of experiments has proved the helpful action of mercuric sulfate.
4. If the time for the first stage (temperature below 250°) is shortened, the frothing is greater at this point, and the final yield is lowered.
5. The end of the reaction can be readily detected by the bubbling and spurting which take the place of the quiet boiling. If the mixture is not fairly thick, less sulfuric acid should be used in the next run. If it is solid, more acid should be used.
6. The transfer to the retort must be made before the mixture solidifies. The best method of closing the tubulure of the retort (unless this consists of Pyrex glass) is by means of a glass stopper too small for the hole and wrapped with asbestos paper moistened with sodium silicate solution.
7. If much pyromellitic anhydride collects in the neck of the retort, it should be rinsed into a clean dish rather than into the receiver for the receiver contains considerable sulfuric acid.
8. In recovering pyromellitic acid from the mother liquor it is advisable first to remove the sulfuric acid by adding a slight excess of barium hydroxide and acidifying to Congo red with hydrochloric acid.
9. The anhydride of pyromellitic acid may be obtained by boiling the dry anhydrous acid with acetic anhydride.

3. Discussion

Pyromellitic acid may be obtained by the oxidation of benzene derivatives containing organic substituents in the 1-, 2-, 4-, and 5-positions: by the oxidation of durene with nitric acid;[1] by condensing benzene with diethylmalonyl chloride, reducing to the hydrocarbon, again condensing in the same way, and finally oxidizing the resulting tetraethylbenzodihydrindenedione; [2] by an analogous synthesis from *m*-xylene, involving condensation with acetyl chloride, reduction, and oxidation;[3] and by the oxidation of tetrahydro-5,6-benzindan-1-one.[4]

Mellitic acid can be decarboxylated to yield pyromellitic acid, either by the action of heat alone[5] or in the presence of sulfuric acid.[6]

The oxidation of wood charcoal by means of sulfuric acid leads to mellitic acid and its decarboxylation products;[7] nitric acid may also be employed.[8] Pyromellitic acid has also been obtained by the electrolytic oxidation of graphite in an alkaline medium.[9]

References and Notes

1. Jacobsen, Ber. **17**, 2516 (1884).

2. Freund, Fleischer, and Gofferjé, Ann. **414**, 26 (1918).
3. Philippi, Seka, and Froeschl, ibid. **428**, 300 (1922).
4. Darzens and Levy, Compt. rend. **201**, 904 (1935).
5. Erdmann, Ann. **80**, 281 (1851); Baeyer, Ann. Suppl. **7**, 36 (1870).
6. Erdmann, Ann. **80**, 282 (1851); Silberrad, J. Chem. Soc. **89**, 1795 (1906).
7. Verneuil, Compt. rend. **118**, 195 (1894); **132**, 1340 (1901); Philippi and Thelen, Ann. **428**, 296 (1922).
8. Silberrad, Ger. pat. 214,252 [Frdl. **9**, 173 (1908–10)]; Philippi and Rie, Ann. **428**, 287 (1922).
9. Bartoli and Papasogli, Gazz. chim. ital. **12**, 113 (1882); **13**, 37 (1883).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Congo red

tetraethylbenzodihydrindenedione

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

acetic anhydride (108-24-7)

acetyl chloride (75-36-5)

sodium silicate

nitric acid (7697-37-2)

mercury (7439-97-6)

barium hydroxide (17194-00-2)

mercuric sulfate (7783-35-9)

Durene (95-93-2)

Pyromellitic acid (89-05-4)

pyromellitic anhydride (89-32-7)

diethylmalonyl chloride (54505-72-5)

tetrahydro-5,6-benzindan-1-one

Mellitic acid (517-60-2)

m-xylene (108-38-3)

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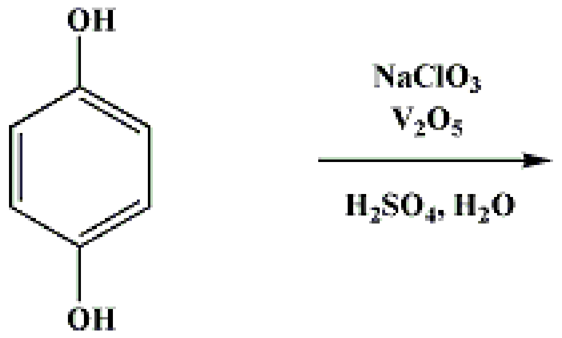
Organic Syntheses, CV 2, 553

QUINONE



Submitted by H. W. Underwood, Jr. and W. L. Walsh.
Checked by Louis F. Fieser and D. J. Potter.

1. Procedure

In a 2-l. round-bottomed flask equipped with a mechanical stirrer are placed 1 l. of 2 per cent sulfuric acid, 0.5 g. of vanadium pentoxide (Note 1), 110 g. (1 mole) of hydroquinone, and 60 g. (0.56 mole) of sodium chlorate. The mixture is vigorously stirred for about three hours, when the green quinhydrone first formed is converted to yellow quinone. The temperature of the reaction mixture rises to about 40° (Note 2). The reaction is usually complete in three and one-half to four hours. The flask is then disconnected and cooled under the tap, the mixture is filtered with suction, and the quinone is washed once with about 100 cc. of cold water. After drying in a desiccator over calcium chloride, the product weighs 86–90 g. and melts at 110–112°. This material is pure enough for most purposes. Extraction of the filtrate and washings with four 100-cc. portions of benzene yields a further 12–14 g. of quinone and brings the total amount to 99–104 g. (92–96 per cent of the theoretical yield) (Note 3).

Very pure quinone can be obtained either by vacuum sublimation or recrystallization from boiling ligroin (b.p. 90–120°). One hundred grams of the crude quinone requires about 1.2 l. of ligroin for recrystallization and yields 92–97 g. of bright yellow quinone, m.p. 111–113°.

2. Notes

1. Vanadium pentoxide may be obtained from the Vanadium Corporation of America or prepared from ammonium metavanadate as described in Note 2, p. 302.
2. If quantities larger than one mole of hydroquinone are used the temperature should not be allowed to rise above 40°.
3. By the use of a suitable organic solvent the same oxidizing agent can be employed for the preparation of anthraquinone. A mixture of 90 g. (0.51 mole) of finely powdered pure anthracene, 0.5 g. of vanadium pentoxide, 76 g. of

sodium chlorate, 1 l. of glacial acetic acid, and 200 cc. of 2 per cent sulfuric acid is warmed under reflux until a vigorous reaction commences. The source of heat is removed, and the reaction allowed to proceed for about twenty minutes. The mixture is refluxed for one hour longer and then cooled in ice. The light yellow solid is filtered with suction, washed well with water, and dried at 110°. The yield is 92–96 g. (88–91 per cent of the theoretical amount) of a product melting at 273–275°.

The sodium chlorate-vanadium pentoxide mixture is not very powerful, and, although it attacks easily the particularly reactive anthracene, it is not suitable for the conversion of hydrocarbons of the naphthalene and phenanthrene series into the corresponding quinones or for the oxidation of acenaphthene or fluorene (observation of the checkers).

3. Discussion

The oxidation of hydroquinone by means of sodium dichromate in sulfuric acid solution and references to other methods of preparation are given in an earlier volume of this series.[1]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 62
- Org. Syn. Coll. Vol. 2, 539

References and Notes

1. Org. Syn. Coll. Vol. I, **1941**, 482.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ligroin

quinhydrone

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

Benzene (71-43-2)

hydroquinone (123-31-9)

ammonium metavanadate (7803-55-6)

vanadium pentoxide

Anthraquinone (84-65-1)

Naphthalene (91-20-3)

sodium dichromate (7789-12-0)

sodium chlorate (7775-09-9)

anthracene (120-12-7)

Quinone (106-51-4)

fluorene (86-73-7)

phenanthrene (85-01-8)

sodium chlorate-vanadium pentoxide

acenaphthene (83-32-9)

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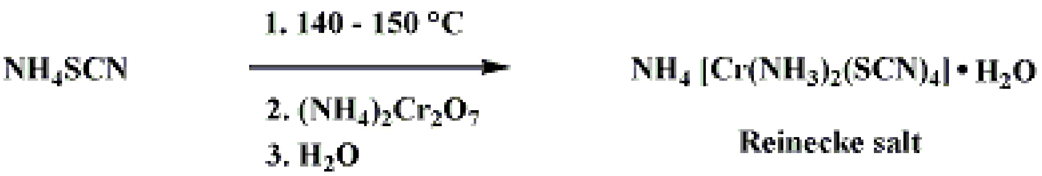
Organic Syntheses, CV 2, 555

REINECKE SALT



Submitted by H. D. Dakin
Checked by H. T. Clarke and R. S. Ingols.

1. Procedure

Eight hundred grams (10.5 moles) of ammonium thiocyanate is gently heated, by means of three small flames (Note 1), in a white enameled cooking pot of about 4-l. capacity. The mass is stirred with a thermometer enclosed in a glass tube until the solid has partially melted and the temperature has reached 145–150°. At this point an intimate mixture of 170 g. (0.675 mole) of finely powdered ammonium dichromate and 200 g. (2.6 moles) of ammonium thiocyanate is added in portions of 10–12 g. with constant stirring. After about ten such portions have been added a fairly vigorous reaction takes place with evolution of ammonia and the temperature rises to 160°. The flames are extinguished, and the remainder of the mixture is added at such a rate that the heat of reaction maintains the temperature at 160° (Note 2). Stirring is continued while the mass cools, and any lumps of solid which form around the sides of the vessel are broken loose (Note 3).

The product, while still warm (Note 4), is finely powdered and stirred with 750 cc. of ice water in a large beaker. After fifteen minutes the insoluble portion is filtered by suction, freed as completely as possible from mother liquor without washing (Note 5), and stirred into 2.5 l. of water previously warmed to 65°. The temperature is then rapidly raised to 60° (Note 6), the solution is filtered at once through a hot-water funnel, and the filtrate is placed in a refrigerator overnight.

The resulting crystals are collected and the mother liquor employed for a second similar extraction of the residue at 60°. This yields a further crop of crystalline Reinecke salt. The mother liquor is finally concentrated to 250–300 cc. by evaporation at 40–50° under reduced pressure, when a small third crop (12–13 g.) is obtained. The total yield of air-dried crystals is 250–275 g. (52–57 per cent of the theoretical amount) (Note 7).

The undissolved residue from the second extraction consists chiefly of Morland salt (the guanidine salt of the Reinecke acid) and amounts to 130–135 g. (33–34 per cent of the theoretical amount) (Note 8).

2. Notes

1. Heat must be applied as uniformly as possible.
2. The addition of the mixture requires five to seven minutes.
3. The product is detached from the walls during cooling as it is difficult to remove when cold.
4. The material should be pulverized while warm before it has had an opportunity to attract moisture from the air.
5. The filtrate, which consists largely of unchanged ammonium thiocyanate and its decomposition products, contains too little Reinecke salt to repay further treatment.
6. Reinecke salt decomposes in aqueous solution with formation of a blue color and free hydrogen cyanide. At room temperature this decomposition occurs in about two weeks, and above 65° it takes place quite rapidly. A similar decomposition takes place in boiling alcohol.
7. Reinecke salt is of value as a precipitant for primary and secondary amines, proline and hydroxyproline, and certain amino acids.[1]
8. The Morland salt, which is soluble in acetone, contains a small proportion of a colorless sulfur compound insoluble in hot water. It can be partially converted into Reinecke salt by treatment in dilute ammonia solution with a large excess of ammonium chloride, but the amounts so obtainable are unprofitably small.

3. Discussion

Reinecke salt has been prepared by adding either potassium dichromate[2] or ammonium dichromate[1], [3] to fused ammonium thiocyanate.

References and Notes

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3. Werner, Z. anorg. Chem. **15**, 260 (1897); Ann. **406**, 276 (1914).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

REINECKE SALT

Morland salt (the guanidine salt of the Reinecke acid)

alcohol (64-17-5)

ammonia (7664-41-7)

ammonium chloride (12125-02-9)

ammonium thiocyanate (1762-95-4)

hydrogen cyanide (74-90-8)

acetone (67-64-1)

potassium dichromate (7778-50-9)

ammonium dichromate

proline (147-85-3)

hydroxyproline

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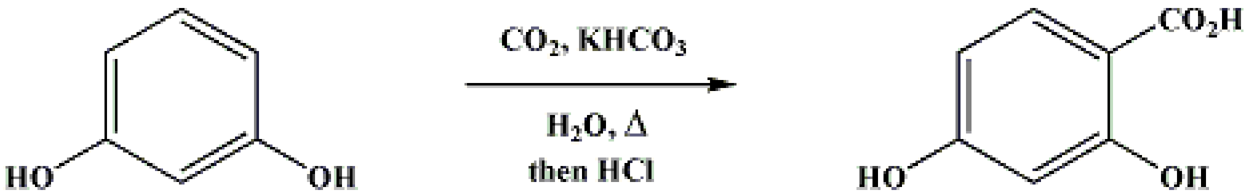
β-RESORCYLIC ACID



Submitted by M. Nierenstein and D. A. Clibbens.
Checked by Roger Adams and F. E. Kendall.

1. Procedure

In a 5-l. flask fitted with a reflux condenser, a solution containing 200 g. (1.8 moles) of resorcinol, 1 kg. (9.9 moles) of potassium acid carbonate (Note 1), and 2 l. of water (Note 2) is heated slowly on a steam bath for four hours. The flask is then placed over a flame and refluxed vigorously for thirty minutes; a rapid stream of carbon dioxide is passed through the solution during this heating process.

While still hot the solution is acidified by adding 900 cc. of concentrated hydrochloric acid (sp. gr. 1.19) from a separatory funnel with a tube delivering the acid to the bottom of the flask; this prevents the formation of a layer of acid over the unneutralized solution. The flask is allowed to cool to room temperature and is then chilled in an ice bath. The resorcyclic acid crystallizes in prisms which are almost colorless but which, on exposure to air, turn pink owing to contamination with a small amount of resorcinol. The yield of crude acid is 225 g. By extracting the mother liquor with ether several times, 35 g. of resorcylic acid and some unchanged resorcinol can be recovered. The resorcylic acid is extracted from the ether by shaking with an aqueous solution of sodium bicarbonate. The aqueous solution is acidified with hydrochloric acid and again extracted withether. The ether is then evaporated, leaving the resorcylic acid, which is usually highly colored and must be recrystallized several times from boiling water and charcoal to remove the color.

The combined yield of crude acid (260–270 g.) is dissolved in 1 l. of water, boiled with about 25 g. of Norite, filtered through a heated filter, and crystallized by placing in an ice-salt freezing mixture and stirring vigorously. A finely crystalline, colorless product is obtained in this way. If the acid is allowed to crystallize slowly the crystals are somewhat colored. The yield of pure resorcylic acid melting at 216–217° is 160–170 g. (57–60 per cent of the theoretical amount) (Note 3).

2. Notes

1. Instead of potassium acid carbonate, the sodium salt in corresponding quantity may be used.
2. If less than ten parts of water to one of resorcinol is used, the yield is

diminished.
3. The air-dried crystals lose at 110° a quantity of water corresponding to a half mole of water of crystallization.

3. Discussion

The method of preparing β-resorcylic acid described above is a modification[1] of the procedure given by Bistrzycki and Kostanecki.[2] A more rapid but less efficient variant of this procedure has been described.[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 100

References and Notes

1. Clibbens and Nierenstein, J. Chem. Soc. **107**, 1494 (1915).
2. Bistrzycki and Kostanecki, Ber. **18**, 1984 (1885).
3. Couturier, Ann. chim. (11) **10**, 570 (1938).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

potassium acid carbonate

resorcyclic acid

resorcylic acid

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium bicarbonate (144-55-8)

carbon dioxide (124-38-9)

Norite (7782-42-5)

resorcinol (108-46-3)

β-Resorcylic acid (89-86-1)

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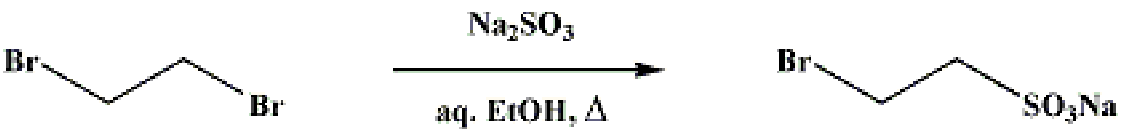
Organic Syntheses, CV 2, 558

SODIUM 2-BROMOETHANESULFONATE

[Ethanesulfonic acid, 2-bromo-, sodium salt]



Submitted by C. S. Marvel and M. S. Sparberg.
Checked by Frank C. Whitmore and D. J. Loder.

1. Procedure

In a 5-l. round-bottomed flask, fitted with a reflux condenser, a mechanical stirrer, and a separatory funnel, are placed 615 g. (3.3 moles) of ethylene dibromide (Note 1), 1250 cc. of 95 per cent alcohol, and 450 cc. of water (Note 2). The stirrer is started and the mixture heated to boiling. To the well-stirred boiling mixture a solution of 125 g. (1 mole) of anhydrous sodium sulfite in 450 cc. of water is added through the separatory funnel over a period of about two hours. The solution is boiled under a reflux condenser for two hours after all the sulfite solution has been added. The condenser is then set for distillation, and the alcohol and the ethylene bromide are distilled (Note 3). The remaining water solution is poured into a large evaporating dish and evaporated to dryness on the water bath. The sodium 2-bromoethanesulfonate is extracted from the sodium bromide and unchanged sodium sulfite with 2 l. of boiling 95 per cent alcohol. On cooling the solution, most of the salt crystallizes; the mother liquor is used for a second extraction of the residue. The yield is 165–190 g. (78–90 per cent of the theoretical amount). The product (Note 4) may be further purified by recrystallizing from alcohol and drying in an oven at 110° (Note 5). The recovery on recrystallization is 75–80 per cent.

2. Notes

1. The large excess of ethylene dibromide is necessary to reduce the formation of the disulfonic acid.
2. The concentration of the alcohol seems to be important; poorer yields were obtained when it was changed in either direction.
3. By diluting the alcoholic distillate from the reaction mixture with 10 l. of water, it is possible to recover about 400 g. of ethylene dibromide.
4. This product may contain as much as 2 to 5 per cent of sodium bromide, but it is pure enough for the preparation of taurine (p. 563). A very pure product can be obtained by a second crystallization from alcohol.
5. The salt is slightly hygroscopic.

3. Discussion

The directions given in the procedure are based on those of Kohler.[1] Sodium 2-bromoethanesulfonate has also been prepared by treating ethylene oxide with sodium bisulfite and converting the isethionic acid thus obtained to the bromo acid with hydrobromic acid.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 563

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

disulfonic acid

alcohol (64-17-5)

sodium sulfite (7757-83-7)

HYDROBROMIC ACID (10035-10-6)

sodium bromide (7647-15-6)

sodium bisulfite (7631-90-5)

Ethylene oxide (75-21-8)

ethylene dibromide, ethylene bromide (106-93-4)

Taurine (107-35-7)

Sodium 2-bromoethanesulfonate, Ethanesulfonic acid, 2-bromo-, sodium salt (4263-52-9)

isethionic acid (107-36-8)

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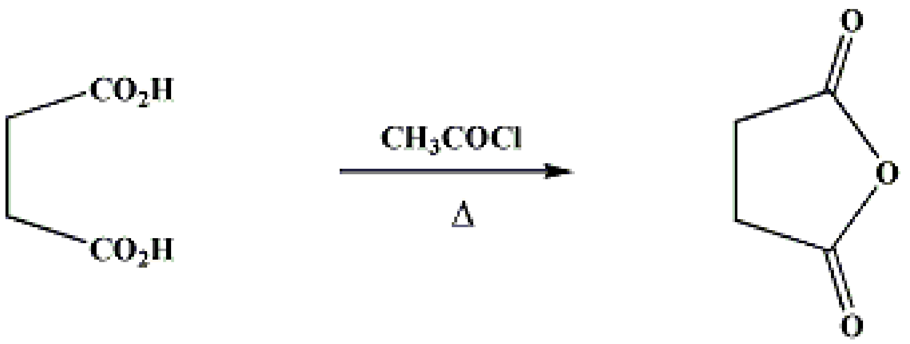
Organic Syntheses, CV 2, 560

SUCCINIC ANHYDRIDE

[I]

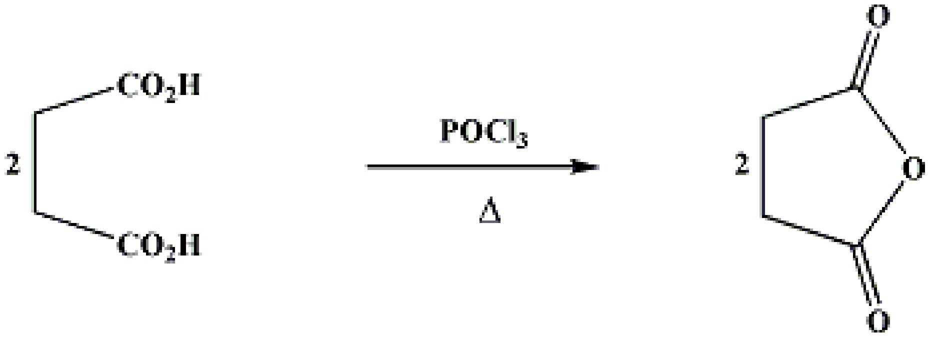


Submitted by Louis F. Fieser and E. L. Martin.
Checked by C. R. Noller

1. Procedure

In a 1-l. round-bottomed flask, fitted with a reflux condenser attached to a gas trap, are placed 118 g. (1 mole) of succinic acid and 215 cc. (235 g., 3 moles) of acetyl chloride. The mixture is gently refluxed on the steam bath until all the acid dissolves; this requires one and a half to two hours. The solution is allowed to cool undisturbed and is finally chilled in an ice bath. The succinic anhydride, which separates in beautiful crystals, is collected on a Büchner funnel, washed with two 75-cc. portions of ether, and dried in a vacuum desiccator. The yield of material melting at 118–119° is 93–95 g. (93–95 per cent of the theoretical amount).

[II]



Submitted by R. L. Shriner and H. C. Struck.
Checked by C. R. Noller, F. B. Hilmer, and J. D. Pickens.

1. Procedure

Two hundred thirty-six grams (2 moles) of succinic acid (Note 1) and 153.5 g. (1 mole) of phosphorus oxychloride are placed in a 1-l. Claisen flask. One neck of the

flask is equipped with a reflux condenser connected to a gas trap; the other neck and the side arm of the flask are closed with corks. The mixture is heated (Note 2) with a free flame for about fifty minutes until no more hydrogen chloride is evolved. The condenser is removed and the flask is arranged for distillation, with a tube leading from the side arm of the receiver to the drain in order to carry off the vapors. A few cubic centimeters of distillate is collected below 255°, at which temperature the receiver is changed and succinic anhydride is collected from 255–260° (Note 3). The product melts at 118–120° and weighs 164–192 g. (82–96 per cent of the theoretical amount).

The succinic anhydride may be purified by dissolving 50 g. of the crude material in 35 cc. of acetic anhydride. The hot solution is cooled in an ice bath. The crystals are filtered with suction, washed with two 20-cc. portions of cold, absolute ether, and air-dried quickly at 40°. The yield of the pure anhydride, which melts at 119–120°, is 43.5 g.

2. Notes

1. Succinic acid having a melting point of 189–190° was used. Less pure material gives a lower-melting product.
2. The reaction foams considerably at the start, hence slow and careful heating is necessary. It is best to heat the flask directly with the flame, making certain that all parts of the mixture are heated about equally.
3. The tarry mass left in the distilling flask may be easily removed by warm dilute sodium hydroxide.

3. Discussion

Succinic anhydride has been prepared from succinic acid with phosphorus pentachloride,[1, 2] phosphorus oxychloride,[2, 3] phosphorus pentoxide,[4] thionyl chloride,[5] acetyl chloride,[3, 6, 7] or succinyl chloride;[8] from barium or sodium succinate with benzoyl chloride,[1] acetyl chloride,[9] acetic anhydride,[10] or benzophenone dichloride;[11] from succinyl chloride and oxalic acid[6] or sodium acetate;[9] and from ethyl succinate and benzoyl chloride.[12]

The procedure in Org. Syn. Coll. Vol. I, **1941**, 91, for preparing benzoic anhydride when applied to succinic acid and acetic anhydride gives a 72 per cent yield of succinic anhydride. Procedure I above has the advantage of convenience; Procedure II is more economical.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 81

References and Notes

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3. Verkade and Hartman, Rec. trav. chim. **52**, 947 (1933).
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5. Meyer, Monatsh. **22**, 420 (1901).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

barium or sodium succinate

hydrogen chloride (7647-01-0)

ether (60-29-7)

acetic anhydride (108-24-7)

sodium acetate (127-09-3)

sodium hydroxide (1310-73-2)

phosphorus pentachloride (10026-13-8)

acetyl chloride (75-36-5)

thionyl chloride (7719-09-7)

ethyl succinate

Oxalic acid (144-62-7)

Succinic acid (110-15-6)

benzoyl chloride (98-88-4)

Benzoic anhydride (93-97-0)

Phosphorus Oxychloride (21295-50-1)

benzophenone dichloride

Succinic anhydride (108-30-5)

succinyl chloride (543-20-4)

phosphorus pentoxide (1314-56-3)

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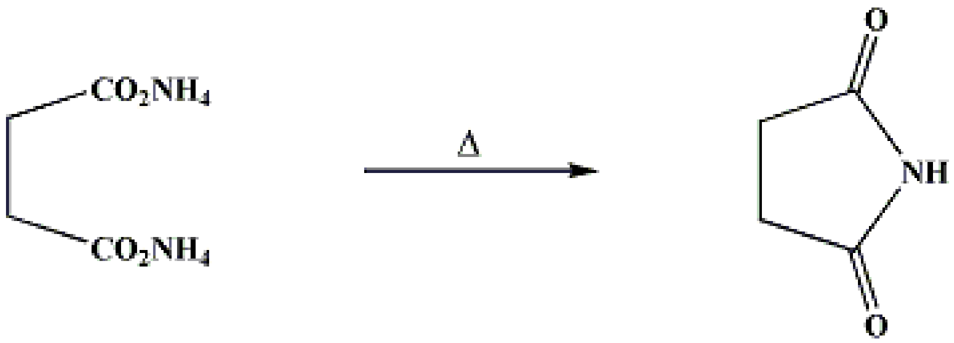
SUCCINIMIDE



Submitted by H. T. Clarke and Letha Davies Behr.
Checked by W. H. Carothers and W. L. McEwen.

1. Procedure

In a 1-l. distilling flask, fitted with a side arm 40 cm. in length and not less than 10 mm. in internal diameter (Note 1), is placed 236 g. (2 moles) of succinic acid. To this is added slowly, with cooling and shaking, 270 cc. (243 g., 4 moles) of 28 per cent aqueous ammonia (sp. gr. 0.90). Most of the acid dissolves, forming a clear solution. The flask is set for downward distillation, and a water-cooled 500-cc. distilling flask is attached to the side arm. Provision may be made for removal of ammonia from the side tube of the receiver. The mixture is heated gently over a free flame; solution takes place rapidly, and a small amount of uncombined ammonia passes over with the first portions of the distillate. The temperature of the vapor rises to 100° and remains at this point until about 200 cc. of water has distilled. The flame is then increased, and the ammonium succinate begins to decompose with evolution of ammonia; the temperature of the vapor falls to 97° during the distillation of the next 30 cc. When the vapor temperature has risen to 102°, the receiver is changed and an intermediate fraction collected from 102° to 275°. Succinimide then distils and is collected over the range 275–289°, largely at 285–289°. Decomposition takes place to a small extent with formation of a black tar; the distillation is stopped when the tarry residue begins to decompose with evolution of yellow fumes.

The crude succinimide, which solidifies completely, amounts to about 168 g. The intermediate fraction is redistilled from a smaller flask and furnishes about 10 g. more of crude succinimide boiling between 275° and 289°. The two portions of crude succinimide are combined and crystallized from 95 per cent ethyl alcohol, employing 1 cc. of solvent for every gram of product. If the mixture is chilled to 0° for some hours before filtration and about 25 cc. of cold alcohol is employed for washing the crystals, the first crop amounts to 163–164 g. (82–83 per cent of the theoretical amount). On concentrating the mother liquor to one-third of its volume, a second crop of 4–5 g. can be secured (Note 2). The product melts at 123–125° and contains no water of crystallization.

2. Notes

1. It is essential to employ a side arm of at least this diameter in order to avoid clogging by crystals of succinimide when this first passes over.
2. A further small quantity of a less pure product can be obtained by evaporating the dark mother liquor to dryness and recrystallizing the residue from fresh 95 per cent alcohol.

3. Discussion

Succinimide has usually been prepared by heating succinic acid in a current of ammonia[1], [2] or by distilling ammonium succinate.[1], [3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 19

References and Notes

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2. Franchimont and Friedmann, Rec. trav. chim. **25**, 79 (1906).
3. Bunge, Ann. Suppl. **7**, 118 (1870); Menschutkin, Ann. **162**, 166 (1872).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethyl alcohol, alcohol (64-17-5)

ammonia (7664-41-7)

Succinic acid (110-15-6)

Succinimide (123-56-8)

ammonium succinate

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Organic Syntheses, CV 2, 563

TAURINE

[I]

Submitted by C. S. Marvel and C. F. Bailey.
Checked by Frank C. Whitmore and D. J. Loder.

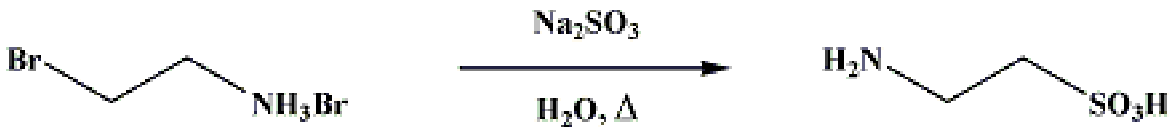
1. Procedure

A solution of 110 g. (0.52 mole) of sodium 2-bromoethanesulfonate (p. 558) in about 2 l. (28 moles) of concentrated aqueous ammonia (sp. gr. 0.9) is allowed to stand for five to seven days (Note 1) and is then evaporated to dryness. The last of the water is removed by heating on a steam bath. The residue is dissolved in the minimum quantity of hot water (about 500 cc.) and, if necessary, treated with 5 g. of Norite. The colorless solution is concentrated to 65–70 cc., and 250 cc. of 95 per cent alcohol is added. In a short time taurine mixed with some sodium bromide separates. When crystallization is complete, the crude taurine is collected on a filter and recrystallized by dissolving in 100 cc. of hot water and then adding to the solution enough 95 per cent ethyl alcohol (about 500 cc.) to give a final concentration of 80 per cent of alcohol. The taurine which separates is usually free from bromides. However, occasional runs must be recrystallized four or five times to remove all the sodium bromide. The yield of pure taurine (Note 2) is 31–36 g. (48–55 per cent of the theoretical amount).

2. Notes

1. The reaction is about 25 per cent complete in five hours, 60 per cent complete in thirty hours, and 90 per cent complete in five days, as indicated by titration of the bromide ion.
2. The purity of the taurine prepared by this method was established by analysis.

[II]



Submitted by Frank Cortese
Checked by C. S. Marvel and C. L. Fleming.

1. Procedure

A solution of 615 g. (3 moles) of β-bromoethylamine hydrobromide (p. 91) and 416 g. (3.3 moles) of anhydrous u.s.p. sodium sulfite (Note 1) in 2.4 l. of water is concentrated on the steam bath to a minimum volume; thirty-six to forty-eight hours is required for this operation. After the mixture has cooled, the cold, moist cake is triturated with 1.5 l. of concentrated hydrochloric acid and collected on an asbestos mat in a Büchner funnel. The precipitate is washed ten times with 150-cc. portions of concentrated hydrochloric acid. The filtrate is mixed well, decanted from precipitated salts if necessary, and concentrated over a free flame to a volume of 600 cc.

Two and four-tenths liters of 95 per cent ethyl alcohol is added, with vigorous stirring, to the hot mixture. After fifteen minutes, the product is collected on a filter, washed with 95 per cent ethyl alcohol until it is colorless, and air-dried. The crude material is purified by dissolving it in four times its weight of hot water, adding Norite, filtering, and adding to the hot filtrate five volumes of 95 per cent ethyl alcohol.

This product is practically pure taurine; it decomposes at 305–310° (Maquenne block). The yield is 255–275 g. (68–73 per cent of the theoretical amount).

2. Notes

1. An equivalent quantity (831 g.) of the more expensive crystalline sodium sulfite may be used.

3. Discussion

Taurine is generally prepared from ox bile[1] or the large muscle of the abalone.[2] It has been obtained from the oxidation of cystamine[3] and the decarboxylation of cysteic acid;[4] from ethyleneimine and sulfur dioxide;[5] from chloroethanesulfonic acid and ammonia;[6] from 2-mercaptothiazoline by oxidation with bromine water;[7] and from acetaldehyde by a complex set of reactions involving sulfonation, formation of the aldehyde ammonia and the imidosulfonic acid, and finally reduction.[8] Taurine is usually synthesized either from bromoethanesulfonic acid and ammonia[9]—Procedure I, or from β-bromoethylamine hydrobromide and sodium sulfite[10]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 91
- Org. Syn. Coll. Vol. 2, 558

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

bromine water

ethyl alcohol (64-17-5)

acetaldehyde (75-07-0)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

sodium sulfite (7757-83-7)

sulfur dioxide (7446-09-5)

sodium bromide (7647-15-6)

Norite (7782-42-5)

β-Bromoethylamine hydrobromide (2576-47-8)

Taurine (107-35-7)

ethyleneimine (9002-98-6)

Sodium 2-bromoethanesulfonate (4263-52-9)

cystamine

cysteic acid

chloroethanesulfonic acid

2-mercaptothiazoline

bromoethanesulfonic acid

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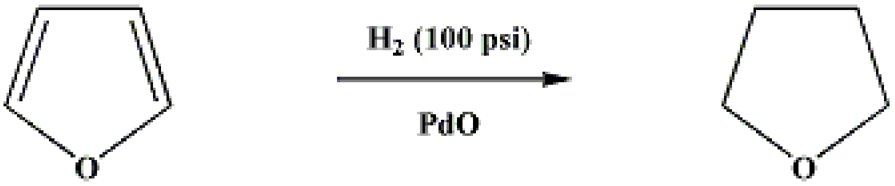
Organic Syntheses, CV 2, 566

TETRAHYDROFURAN

[Furan, tetrahydro-]



Submitted by Donald Starr and R. M. Hixon.
Checked by John R. Johnson and H. B. Stevenson.

1. Procedure

(*A*) *Preparation of Palladous Oxide*.—In a 350-cc. casserole, 2.2 g. (0.02 gram atom) of palladium metal is dissolved in a small amount of aqua regia, and the solution (Note 1) is treated with 55 g. of c. p. sodium nitrate and enough distilled water to make a thick paste. The substances are thoroughly mixed and then heated gently to drive off the water. The heating is increased until the mixture melts (about 270–280°) and continued cautiously. Just above the melting point the mixture must be stirred and heated carefully as oxides of nitrogen are evolved and foaming occurs. After the evolution of gases is nearly complete (about five minutes) the full flame of a Bunsen burner is applied for about ten minutes. The entire time of heating should be about one-half hour. As the mass cools, the casserole is rotated to allow the melt to solidify on the sides of the dish. After digestion with about 200 cc. of distilled water until the sodium salts are completely dissolved, the dark brown precipitate of palladous oxide is filtered and washed thoroughly with 1 per cent sodium nitrate solution (Note 2). The oxide must not be washed with pure water since it shows a marked tendency to become colloidal. After drying in a vacuum desiccator the palladous oxide weighs 2.3–2.4 g. (91–95 per cent of the theoretical amount) (Note 3).

(*B*) *Tetrahydrofuran*.—In the pressure bottle of an apparatus for catalytic reduction (Note 4) are placed 10 g. of pure furan (Note 5) and 0.2 g. of palladous oxide. The bottle is swept out with hydrogen (Note 6), and an initial hydrogen pressure of about 7 atm. (100 lb.) is applied (Note 7). After a lag of about ten minutes the reduction proceeds smoothly, and in an hour the theoretical amount of hydrogen is absorbed; the reaction is noticeably exothermic. After the reaction has ceased 20 g. of furan and 0.2 g. of palladous oxide are added (Note 6), the bottle swept out with hydrogen, and the hydrogen pressure raised to 7 atm. After this addition the lag is short and the reaction proceeds somewhat more rapidly than before; the temperature rises to 40–50°. When the reaction nears completion, 30 g. of furan and 0.2 g. of palladous oxide are added, and the reduction is continued. Successive portions of 30 g. of furan and 0.2 g. of palladous oxide are added in the same manner, until the bottle is about two-thirds

filled. To ensure complete reduction, another portion of palladous oxide is added and the mixture shaken until no more hydrogen is taken up. The catalyst is allowed to settle (Note 8), and the tetrahydrofuran is decanted through a filter into a flask for distillation. The reduction product distils completely at 64–66°.

The reduction of 120 g. (128 cc., 1.76 moles) of furan requires about fifteen to twenty hours, depending upon the purity of the furan and the activity of the catalyst (Note 9). The yield of redistilled tetrahydrofuran is 114–118 g. (90–93 per cent of the theoretical amount). Since reduction is practically quantitative, the yield is determined largely by the care exercised in handling the volatile furan and tetrahydrofuran.

2. Notes

1. An aqueous solution of the equivalent quantity of Eimer and Amend's c.p. or Merck's reagent palladium chloride may be used.
2. The filtrates should be clear and colorless; if they show a yellow-orange opalescence, some of the oxide has become colloidal. The palladium may be recovered[1] as the oxide by evaporating the filtrates to dryness and re-fusing, or as palladium black by rendering the filtrates slightly alkaline with sodium carbonate and heating with formaldehyde.
3. A small amount of palladous oxide adheres to the casserole and cannot be removed by the ordinary means. The oxide is not dissolved readily by aqua regia but is easily removed by boiling with 48 per cent hydrobromic acid.
4. If initial pressures of 6–7 atm. are to be applied, the ordinary apparatus for catalytic reduction (Org. Syn. Coll. Vol. I, **1941**, 61) must be modified by using a flexible coil of copper tubing instead of rubber tubing for the connection between the hydrogen tank and the reduction bottle. To avoid dangerous accidents and loss of materials, it is advisable to cover the reduction bottle at all times with a screen of wire mesh and to test the bottle at the higher pressures before use. Brass fittings are used to hold the mouth of the bottle against a rubber gasket; before use the gasket is treated with alkali, washed thoroughly, and dried.
5. As in all catalytic reductions, the purity of the starting material is of great importance. Redistilled furan, b.p. 31–32°, prepared by the method of Wilson (Org. Syn. Coll. Vol. I, **1941**, 274) is quite satisfactory. It has been reported that furan prepared by the method of Gilman and Louisinian[2] should be dried over calcium chloride and fractionated carefully.[3] It is advisable to redistil the furan shortly before use and to avoid contact with rubber stoppers.
6. Owing to the high volatility of furan and tetrahydrofuran the bottle is not evacuated, as is customary, before the hydrogen pressure is applied; instead, the air is displaced by hydrogen. For the same reason, appreciable losses will occur if the reduction bottle is not cooled before the hydrogen pressure is released for the introduction of fresh portions of furan and catalyst. Effective and rapid cooling may be obtained by directing a jet of ether, from a wash bottle, over the surface of the reduction bottle while the shaking motor is in operation.

7. The hydrogenation of furan may be carried out with initial pressures of only 3 atm. (45 lb.), but the reduction is slower.
8. The catalyst may be removed, dried in a vacuum desiccator over sulfuric acid, and used again. The second reduction usually proceeds much more slowly, and it is advantageous to use one or two portions of fresh oxide along with the recovered material. Spent catalyst may be regenerated by conversion to the oxide as described in Part (*A*).
9. In the high-pressure apparatus of Adkins, 120 g. of furan can be hydrogenated with 10 g. of Raney nickel catalyst[4] in a single run. Using pressures of 100–150 atm. and a temperature range of 100–150° the reduction is extremely rapid and is strongly exothermic. Platinum oxide-platinum black is not a satisfactory catalyst for the reduction of furan.[3]

3. Discussion

The preparation of palladous oxide-palladium black and its use as a catalyst in the reduction of organic compounds have been studied by Shriner and Adams.[1] Palladium black and colloidal palladium have been widely used as hydrogenation catalysts.[5]

Tetrahydrofuran has been prepared by the reduction of furan in the vapor phase with a nickel catalyst at 170°,[6] in butyl alcohol at 50° with Raney nickel catalyst,[7] with palladous oxide-palladium black in the absence of a solvent,[3] and with an osmium-asbestos catalyst;[8] by the reduction of an alkyl succinate over a copper chromite catalyst;[9] and by the dehydration of 1,4-butyleneglycol.[10]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 571
- Org. Syn. Coll. Vol. 5, 60

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

oxides of nitrogen

palladium black

platinum oxide-platinum black

Palladous oxide-palladium black

aqua regia

Eimer and Amend's c.p. or Merck's reagent palladium chloride

colloidal palladium

osmium-asbestos

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

ether (60-29-7)

hydrogen (1333-74-0)

formaldehyde (630-08-0)

HYDROBROMIC ACID (10035-10-6)

sodium carbonate (497-19-8)

butyl alcohol (71-36-3)

nickel, Raney nickel (7440-02-0)

palladium (7440-05-3)

Furan (110-00-9)

sodium nitrate

Palladous oxide

COPPER CHROMITE

Tetrahydrofuran, Furan, tetrahydro- (109-99-9)

1,4-butyleneglycol

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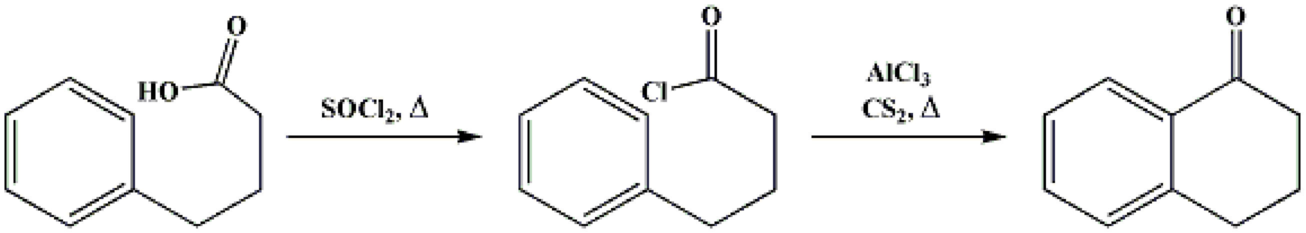
Organic Syntheses, CV 2, 569

α-TETRALONE

[1(2)-Naphthalenone, 3,4-dihydro-]



Submitted by E. L. Martin and Louis F. Fieser.
Checked by C. R. Noller

1. Procedure

In a 500-cc. round-bottomed flask, fitted with a reflux condenser carrying at the top a tube leading to a gas absorption trap, are placed 32.8 g. (0.2 mole) of γ-phenylbutyric acid (p. 499) and 20 cc. (32 g., 0.27 mole) of thionyl chloride (Note 1). The mixture is carefully heated on a steam bath until the acid is melted, and then the reaction is allowed to proceed without the application of external heat. After twenty-five to thirty minutes hydrogen chloride is no longer evolved and the mixture is warmed on the steam bath for ten minutes. The flask is then connected to the water pump, evacuated, and heated for ten minutes on the steam bath and finally for two or three minutes over a small flame in order to remove the excess thionyl chloride. The acid chloride thus obtained is a nearly colorless liquid and needs no further purification. The flask is cooled, 175 cc. of carbon disulfide is added, and the solution cooled in an ice bath. Thirty grams (0.23 mole) of aluminum chloride is added rapidly in one lot, and the flask is immediately connected to the reflux condenser. After a few minutes, the rapid evolution of hydrogen chloride ceases and the mixture is slowly warmed to the boiling point on the steam bath. After heating and shaking the mixture for ten minutes the reaction is complete. The reaction mixture is cooled to 0°, and the aluminum chloride complex is decomposed by the careful addition, with shaking, of 100 g. of ice. Twenty-five cubic centimeters of concentrated hydrochloric acid is added and the mixture transferred to a 2-l. round-bottomed flask and steam-distilled (Note 2). The carbon disulfide distils first (Note 3), then there is a definite break in the distillation, after which the reaction product comes over completely in about 2 l. of the next distillate. The oil is separated, and the water is extracted three times with 100-cc. portions of benzene. The oil and extracts are combined, the solvent is removed, and the residue is distilled at reduced pressure. The yield of α-tetralone boiling at 105–107°/2 mm. is 21.5–26.5 g. (74–91 per cent of the theoretical amount based on the γ-phenylbutyric acid).

2. Notes

1. The thionyl chloride was purified by distilling 50 g. of commercial thionyl chloride from 10 cc. of quinoline and then from 20 cc. of boiled linseed oil in a system protected from moisture.
2. It is advisable to use an efficient condenser system, such as that described in Org. Syn. Coll. Vol. I, **1941**, 479, as α-tetralone is only moderately volatile with steam.
3. On recovery of the carbon disulfide there is not more than a trace of residue.

3. Discussion

α-Tetralone has been obtained from the catalytic hydrogenation of α-naphthol;[1] from γ-phenylbutyryl chloride and aluminum chloride;[2] from γ-phenylbutyric acid and concentrated sulfuric acid;[3] and by the oxidation of tetralin with chromic anhydride[4] or with atmospheric oxygen.[5] Detailed directions for preparing

α-tetralone by this last-named method are given in Org. Syn. **20**, 94.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 798
- Org. Syn. Coll. Vol. 4, 898

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

1(2)-Naphthalenone, 3,4-dihydro-

sulfuric acid (7664-93-9)

hydrogen chloride, hydrochloric acid (7647-01-0)

Benzene (71-43-2)

thionyl chloride (7719-09-7)

α-naphthol (90-15-3)

aluminum chloride (3495-54-3)

carbon disulfide (75-15-0)

Quinoline (91-22-5)

chromic anhydride

Tetralin (119-64-2)

γ-Phenylbutyric acid (1821-12-1)

α-Tetralone (529-34-0)

γ-phenylbutyryl chloride

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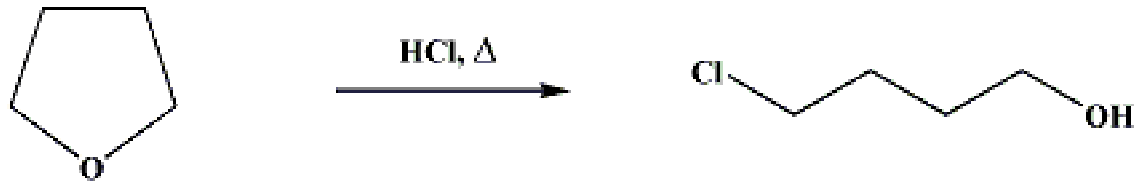
TETRAMETHYLENE CHLOROHYDRIN

[1-Butanol, 4-chloro-]



Submitted by Donald Starr and R. M. Hixon.
Checked by John R. Johnson and H. B. Stevenson.

1. Procedure

A 500-cc. three-necked flask containing 114 g. (1.58 moles) of tetrahydrofuran (p. 566) is fitted with a reflux condenser, a thermometer dipping into the liquid, and a bent glass tube arranged to introduce gaseous hydrogen chloride (Note 1) near the bottom of the flask. The upper end of the reflux condenser is connected to a 150-cc. distilling flask cooled in an ice-salt mixture to trap material entrained by the hydrogen chloride.

The tetrahydrofuran is heated to the boiling point (64–65°), and a slow stream of hydrogen chloride is bubbled into the liquid. As the reaction proceeds the temperature of the boiling liquid increases, slowly at first and then more rapidly, until it is above 100° (after about four hours' heating). At the end of about five hours the temperature remains practically constant in the range 103.5–105.5°, and the reaction is stopped. The light brown liquid is cooled, transferred to a 250-cc. Claisen flask having a 20-cm. fractionating side arm, and fractionated at reduced pressure, using a water aspirator. A large quantity of hydrogen chloride is evolved at the start of the distillation and a low pressure cannot be obtained until this has been removed. Throughout the fractionation a trap cooled to −15° in an ice-salt mixture is used to collect the recovered tetrahydrofuran.

After removal of a small amount of low-boiling material the main fraction distils in the range 80–90°/14 mm. or 65–75°/7 mm. (Note 2) and weighs 95–100 g. A small amount (5–10 g.) of high-boiling material remains. The crude product on refractionation yields 93–98 g. (54–57 per cent of the theoretical amount) of pure tetramethylene chlorohydrin boiling over a one-degree interval, 81–82°/14 mm. or 70–71°/7 mm. (Note 3) and (Note 4).

2. Notes

1. Hydrogen chloride prepared by dropping concentrated sulfuric acid into a mixture of sodium chloride and concentrated hydrochloric acid may be used directly without drying.

2. It has been reported[1] that tetramethylene chlorohydrin undergoes loss of hydrogen chloride when distilled at pressures appreciably above 15 mm. If an oil pump is used for the distillation of the main fraction, it should be protected from hydrogen chloride by means of soda-lime towers.

3. For recovery of tetrahydrofuran, the condensate from the cooling traps and the low-boiling material from the fractionations are combined, cooled in an ice bath, and treated carefully with 15–20 cc. of 40 per cent alkali. The upper layer is separated, dried with a little calcium chloride, and distilled. The recovered tetrahydrofuran, b.p. 64–67°, weighs 20–22 g. (17–19 per cent of the original material). The residue (12–14 g.) remaining after distillation of the tetrahydrofuran distils at 43–45°/10 mm. and is tetramethylene dichloride.

4. Tetramethylene chlorohydrin may be converted to the chlorobromide in excellent yields by the action of phosphorus tribromide.[2]

3. Discussion

Tetramethylene chlorohydrin has been prepared by the action of thionyl chloride on tetramethylene glycol in the presence of pyridine,[1] and by the method described above.[2]

References and Notes

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2. Starr and Hixon, ibid. **56**, 1595 (1934).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrogen chloride, hydrochloric acid (7647-01-0)

thionyl chloride (7719-09-7)

sodium chloride (7647-14-5)

phosphorus tribromide (7789-60-8)

pyridine (110-86-1)

Tetrahydrofuran (109-99-9)

tetramethylene glycol

TETRAMETHYLENE CHLOROHYDRIN, 1-Butanol, 4-chloro- (928-51-8)

tetramethylene dichloride (110-56-5)

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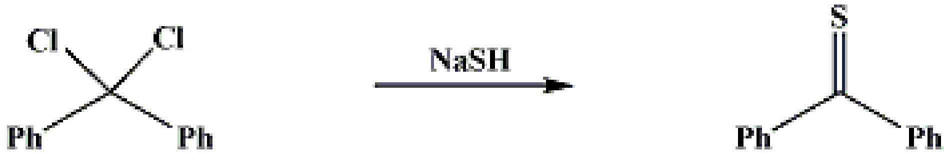
THIOBENZOPHENONE

[Benzophenone, thio-]

$$CH_3CH_2ONa + H_2S \longrightarrow C_2H_5OH + NaSH$$



Submitted by H. Staudinger and H. Freudenberger.
Checked by Roger Adams and E. H. Woodruff.

1. Procedure

An alcoholic solution of sodium hydrosulfide is prepared by dissolving 4.6 g. (0.2 gram atom) of sodium in 150 cc. of absolute alcohol and saturating the solution with dry hydrogen sulfide.

A 3-l. three-necked flask is equipped with a reflux condenser, a mechanical stirrer, a dropping funnel, and a tube for introducing dry carbon dioxide. Twenty-five grams (0.11 mole) of benzophenone dichloride (Note 1) is put into the flask, the air in the flask is displaced by a stream of carbon dioxide, and the sodium hydrosulfide solution is added slowly (Note 2). A vigorous reaction, which must be controlled by cooling, takes place, and the reaction mixture becomes deep blue in color.

After the reaction mixture has stood for one-half hour, water is added and the solution is extracted with ether. The ether solution is dried over calcium chloride and the ether is distilled. The residue is distilled under reduced pressure in an atmosphere of carbon dioxide (Note 3). Thiobenzophenone boils at 174°/14 mm.; it distils as a blue oil which, if pure and dry, forms beautiful blue crystals on cooling. The yield of crude product is 10–12.5 g. (50–63 per cent of the theoretical amount) (Note 4).

This product is approximately 75 per cent pure and is purified further by recrystallization from petroleum ether (b.p. 70–90°). The yield of purified product melting at 53–54° is 8.4–9.9 g. (42–50 per cent of the theoretical amount).

For preservation, the thiobenzophenone is sealed in a glass tube with dry carbon dioxide and placed in the dark.

2. Notes

1. The benzophenone dichloride was prepared by heating equivalent molecular

quantities of benzophenone and phosphorus pentachloride to 145–150° for two hours and then fractionating the mixture under reduced pressure. The product used for this preparation boiled at 201–202°/35 mm.
2. It is necessary to have an excess of the chloride present at all times in order to prevent the formation of dibenzohydryldisulfide, due to reduction of the thioketone with the hydrosulfide. If the chloride is added to the sodium hydrosulfide solution, a 70 per cent yield of the pure disulfide is obtained and no thioketone is formed.
3. All the operations in the purification should be done very quickly and out of contact with the air as much as possible.
4. Larger runs using 100 g. of benzophenone dichloride gave the same percentage yields of product.

3. Discussion

Thiobenzophenone has been prepared by the action of thiophosgene on benzene in the presence of aluminum chloride;[1] by the action of phosphorus pentasulfide[2] or ethyl thioacetoacetate[3] on benzophenone; and by treating benzophenone dichloride with alcoholic potassium sulfide,[4] alcoholic sodium hydrosulfide,[5] or thioacetic acid.[6]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 914
- Org. Syn. Coll. Vol. 4, 927

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

dibenzohydryldisulfide

alcohol (64-17-5)

calcium chloride (10043-52-4)

Benzene (71-43-2)

ether (60-29-7)

phosphorus pentachloride (10026-13-8)

hydrogen sulfide (7783-06-4)

carbon dioxide (124-38-9)

aluminum chloride (3495-54-3)

Benzophenone (119-61-9)

sodium (13966-32-0)

benzophenone dichloride

Thiophosgene (463-71-8)

potassium sulfide (1312-73-8)

sodium hydrosulfide

Thiobenzophenone, Benzophenone, thio- (1450-31-3)

phosphorus pentasulfide

ethyl thioacetoacetate

thioacetic acid (507-09-5)

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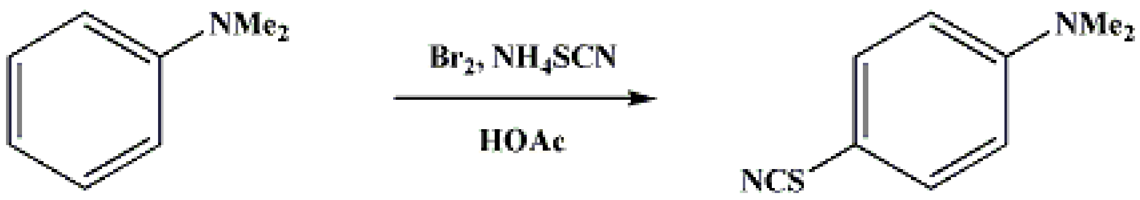
p-THIOCYANODIMETHYLANILINE

[Aniline, N,N-dimethyl-*p*-thiocyano-]



Submitted by R. Q. Brewster and Wesley Schroeder.
Checked by W. H. Carothers

1. Procedure

A solution of 60.5 g. (0.5 mole) of dimethylaniline and 80 g. (1.05 moles) of ammonium thiocyanate in 250 cc. of glacial acetic acid, contained in a 1-l. beaker, is cooled to 10–20° in a bath of ice and water. The solution is stirred mechanically while a solution of 80 g. (25.7 cc., 0.5 mole) of bromine in 100 cc. of glacial acetic acid is added dropwise, over a period of twenty to thirty minutes, and the temperature is kept below 20° (Note 1) and (Note 2). After all the bromine has been added the reaction mixture is removed from the cooling bath and, after standing at room temperature for ten minutes, is poured into 5–6 l. of water. Most of the *p*-thiocyanodimethylaniline separates as a pale yellow solid (Note 3), which is collected on a suction filter and washed with water. After drying in air it weighs 50–55 g. and melts at 71–73°. An additional 10–15 g. of less pure product is obtained by making the filtrate alkaline to litmus; this requires about 1250 cc. of 20 per cent sodium hydroxide. The two fractions are combined, dissolved in about 1.2 l. of boiling ligroin (b.p. 90–100°), and filtered rapidly through a large fluted filter in a heated funnel. The product separates from the filtrate in the form of long yellow needles, and crystallization is completed by thorough chilling. The melting point of the purified product is 73–74°, and the total yield is 56–60 g. (63–67 per cent of the theoretical amount) (Note 4).

2. Notes

1. At higher temperatures a considerable quantity of a yellow thiocyanogen polymer is formed which contaminates the product.
2. Toward the end of the addition a heavy precipitate begins to accumulate on the walls of the beaker; this should be dislodged occasionally with a spatula.
3. *p*-Thiocyanodimethylaniline is a weak base, and its salts are easily hydrolyzed.
4. An additional 4–5 g. of low-melting product may be recovered by evaporation of the mother liquor.

3. Discussion

p-Thiocyanodimethylaniline has been prepared from dimethylaniline and thiocyanogen,[1] chlorothiocyanogen,[2] ammonium thiocyanate and bromine,[3, 4] or lead thiocyanate and iodobenzene dichloride.[5] Thiocyanation of aromatic amines and phenols has also been accomplished electrolytically.[4, 6]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ligroin

thiocyanogen

acetic acid (64-19-7)

ammonium thiocyanate (1762-95-4)

sodium hydroxide (1310-73-2)

bromine (7726-95-6)

dimethylaniline (121-69-7)

chlorothiocyanogen

iodobenzene dichloride (2401-21-0)

lead thiocyanate

p-THIOCYANODIMETHYLANILINE, Aniline, N,N-dimethyl-p-thiocyano- (7152-80-9)

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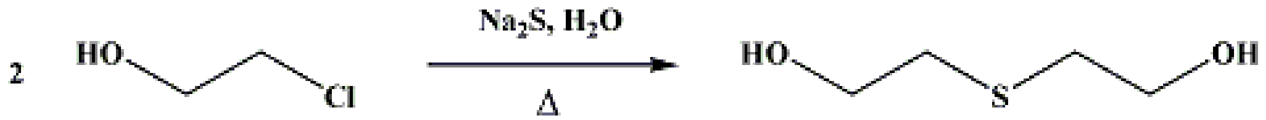
Organic Syntheses, CV 2, 576

β-THIODIGLYCOL

[Ethanol, 2,2'-thiodi-]



Submitted by E. M. Faber and G. E. Miller.
Checked by W. L. McEwen and W. H. Carothers.

1. Procedure

In a 3-l. round-bottomed flask equipped with a mechanical stirrer are placed 1.5 kg. (3.7 moles) of 20 per cent ethylene chlorohydrin solution (Note 1) and 750 g. of water. The flask is set in an empty pan of suitable size to serve as a bath in case cooling becomes necessary. With the stirrer in operation, 493 g. (2.05 moles) of crystalline sodium sulfide containing nine molecules of water of crystallization is added to the chlorohydrin solution at a rate which will maintain the temperature at 30–35°. This will require from forty to sixty minutes. After all the sodium sulfide has been added the solution is stirred for thirty minutes.

The stirrer is removed, and the flask is fitted with a reflux condenser and a thermometer which dips into the liquid. The flask is then heated on a steam bath until the temperature of the liquid is 90°, and for a period of forty-five minutes the temperature is held at 90–95°. The solution is then cooled to 25° and neutralized to turmeric paper by adding concentrated hydrochloric acid drop by drop (Note 2). After filtering, the solution is returned to the flask for concentration at reduced pressure.

The flask is equipped with a short column attached to a condenser set for distillation. A capillary is provided to prevent bumping. The water is then distilled at a pressure of 30–40 mm. by heating the flask in a water bath which is raised to the boiling point as rapidly as is consistent with smooth distillation. The residue in the flask, which consists of sodium chloride and thiodiglycol, is extracted twice with 500-cc. portions of hot absolute alcohol in order to dissolve the sulfide. After the second extraction, the salt is transferred to a Büchner funnel and is washed with a little hot alcohol (Note 3).

The extract and washings are returned to the distilling flask, and the alcohol is removed under reduced pressure. When practically all the alcohol has distilled, the temperature of the bath is raised to 100° and the residue is heated for three hours under 30-mm. pressure (Note 4).

The crude product, which is colorless or very pale yellow, weighs 200–215 g. It boils at 164–166°/20 mm. and may be purified by vacuum distillation (Note 5). The yield of pure material is 180–195 g. (79–86 per cent of the theoretical amount).

2. Notes

1. Aqueous solutions of ethylene chlorohydrin of 18–40 per cent are suitable for the preparation of thiodiglycol; a 20 per cent solution is convenient because the reaction proceeds very smoothly and is easy to control.
If the chlorohydrin is available in the form of a solution weaker than 20 per cent, it may be concentrated by distillation. Chlorohydrin and water form a constant-boiling-point mixture of 42.5 per cent chlorohydrin which boils at 95.8°/735 mm.
2. At the end of the reaction the liquid is alkaline and must be neutralized; otherwise considerable decomposition occurs during distillation. Care must be taken not to pass the neutral point, as a small amount of mustard gas may be formed. Furthermore, if much acid is present, the heat necessary for vacuum distillation causes resinification and the yield of distilled material falls to about 50 per cent. The use of litmus paper for the neutralization is not satisfactory.
3. If 95 per cent alcohol is used for this extraction, some salt is dissolved with the thiodiglycol. This salt may be filtered easily after the alcohol has been removed from the product.
4. The time of drying is dependent upon the pressure used. At 20 mm. the water and alcohol are removed in one hour. If the water has not been completely removed before the alcohol extraction, there may be a small amount of salt left in the material after the alcohol is removed. This may be removed by decanting the product or by pouring it through a glass-wool filter.
5. If chemicals of good quality are used in the preparation the crude product is practically water-white and is sufficiently pure for many purposes. A completely pure product can be obtained by vacuum distillation.

3. Discussion

The method described in the procedure is a modification of the one originally described by Meyer.[1] Irvine[2] showed that this general method could be adapted to works-scale production. β-Thiodiglycol can also be prepared from ethylene oxide and hydrogen sulfide, a process that works well only if some of the product is used as a solvent for the reactants.[3]

References and Notes

1. Meyer, Ber. **19**, 3260 (1886); Clarke, J. Chem. Soc. **101**, 1583 (1912); Gomberg, J. Am. Chem. Soc. **41**, 1414 (1919).
2. Irvine, British War Report.
3. Chichibabin, Fr. pat. 769,216 [C. A. **29**, 481 (1935)]; Chichibabin and Bestuzhev, Compt. rend. **200**, 242 (1935); Nenitzescu and Scarlatescu, Ber. **68**, 587 (1935); Othmer and Kern, Ind. Eng. Chem. **32**, 160 (1940).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

β-Thiodiglycol

alcohol (64-17-5)

hydrochloric acid (7647-01-0)

sodium chloride (7647-14-5)

hydrogen sulfide (7783-06-4)

Ethylene oxide (75-21-8)

sodium sulfide (1313-82-2)

ethylene chlorohydrin (107-07-3)

thiodiglycol

Ethanol, 2,2'-thiodi- (111-48-8)

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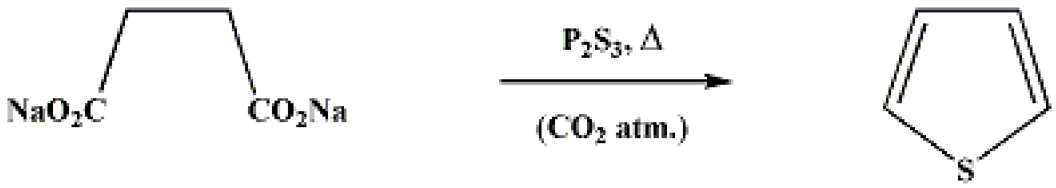
Organic Syntheses, CV 2, 578

THIOPHENE



Submitted by Ross Phillips
Checked by Roger Adams and H. D. Cogan.

1. Procedure

In a 3-l. round-bottomed flask is placed an intimate mixture of 486 g. (3 moles) of finely powdered anhydrous sodium succinate (Note 1) and 648 g. (4.1 moles) of finely ground phosphorus trisulfide (Note 2). The flask is fitted to a 100-cm. (40-in.) condenser set for distillation (Note 3), and a tube for introduction of carbon dioxide is extended through the stopper to the center of the flask. The condenser is connected to a 2-l. flask cooled in an ice-salt mixture. The uncondensed gases are bubbled through two 2-l. flasks connected in series with the receiving flask; each flask is cooled by an ice-salt mixture and contains 1 kg. of cracked ice and 200 cc. of 40 per cent sodium hydroxide solution.

The reaction flask is thoroughly swept out with carbon dioxide (Note 4) while the flask is rotated to remove any air that is trapped by the solid. The flask is then connected to the condenser, and a slow stream of carbon dioxide is passed through the system while the mixture is heated moderately for thirty minutes with a low Bunsen flame (Note 5), and then with the full force of the Bunsen burner until no more yellow vapors are produced (about thirty minutes). Carbon dioxide is passed through more rapidly during the latter heating period to ensure complete removal of the thiophene (Note 6). The contents of the receiver and the two absorption flasks are combined and steam-distilled from a 5-l. flask until no more oily drops are formed in the distillate. The thiophene layer in the distillate is separated, dried successively over solid sodium hydroxide and sodium, and fractionated. The yield of product boiling at 83–86° is 63–75 g. (25–30 per cent of the theoretical amount) (Note 7) and (Note 8).

2. Notes

1. The sodium succinate, prepared from succinic acid, was dried in shallow pans on a water bath for several days.
2. If phosphorus trisulfide is not obtainable, it may be prepared by the following method developed by A. M. Griswold: An intimate mixture of the calculated amounts of finely powdered sulfur and red phosphorus is placed in an earthenware flower pot, sealed at the bottom with a cork. The pot is imbedded in a bucket of sand, and a heavily weighted cover is held in readiness over the top.

A lighted match is dropped into the mixture, the lid is quickly put in place, and the crevices are sealed with sand. The reaction should be carried on out-of-doors as it is extremely vigorous and often gives an excellent display of fireworks. When thoroughly cool, the flower pot is broken and the contents are removed and kept in a tightly stoppered bottle. It is desirable to keep this material for some time before grinding, as the freshly prepared product is not completely crystallized and is difficult to grind.

3. Because of the rapid evolution of a large volume of gas, the tube connecting the flask to the condenser should be about 2 cm. in diameter and all stoppers should fit tightly.

4. If the air is not completely removed before heating the flask, the reaction may take place with explosive violence.

5. The checkers found that continual heating was necessary during this part of the preparation.

6. The stopper should not be removed from the reaction flask until the flask is quite cool, in order to prevent ignition of the excess phosphorus trisulfide on contact with the air. The hard mass remaining may be softened by treatment with hot water, after which it may be broken up and shaken out.

7. The freshly prepared product often deposits a small amount of a brown precipitate on standing for some time. If this is removed by filtration, no further precipitate is formed.

8. Larger runs have been made successfully, but there is greater danger of a violent reaction.

3. Discussion

Thiophene is found in small amounts in coal gas and benzene.[1] It has been prepared by passing ethylene or acetylene into boiling sulfur;[2] by passing ethyl sulfide through a hot tube;[3] by passing ethylene or illuminating gas over hot pyrites;[4] by heating succinic anhydride with phosphorus pentasulfide;[5] by treatment of erythritol with phosphorus pentasulfide;[6] by treatment of succinic aldehyde with phosphorus trisulfide;[7] by passing acetylene over pyrites at 300°;[8] by treatment of sodium succinate with phosphorus trisulfide;[9] by passing acetylene and hydrogen sulfide over bauxite at 320°, or over nickel hydroxide at 300°;[10] and by passing furan and hydrogen sulfide over heated alumina.[11]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 8
- Org. Syn. Coll. Vol. 2, 357
- Org. Syn. Coll. Vol. 2, 466
- Org. Syn. Coll. Vol. 2, 520
- Org. Syn. Coll. Vol. 4, 671

References and Notes

1. Meyer, Ber. **16**, 1471 (1883); **17**, 2642 (1884).
2. Meyer and Sandmeyer, ibid. **16**, 2176 (1883).
3. Kekulé, ibid. **18**, 217 (1885).
4. Nahnsen, ibid. **18**, 217 (1885).
5. Volhard and Erdmann, ibid. **18**, 454 (1885).
6. Paal and Tafel, ibid. **18**, 689 (1885).
7. Harris, ibid. **34**, 1496 (1901).
8. Steinkopf and Kirchoff, Ann. **403**, 5 (1914); Ger. pat. 252,375 [C. A. **7**, 538 (1913)]; Steinkopf, Chem. Ztg. **35**, 1098 (1911).
9. Volhard and Erdmann, Ber. **18**, 454 (1885); Friedburg, J. Am. Chem. Soc. **12**, 85 (1890).
10. Stuer and Grob, U. S. pat. 1,421,743 [C. A. **16**, 3093 (1922)].
11. Yur'ev, Ber. **69**, 440 (1936).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

red phosphorus

alumina

phosphorus trisulfide

bauxite

acetylene (74-86-2)

Benzene (71-43-2)

sodium hydroxide (1310-73-2)

hydrogen sulfide (7783-06-4)

sulfur (7704-34-9)

carbon dioxide (124-38-9)

Succinic acid (110-15-6)

sodium (13966-32-0)

ethylene (9002-88-4)

Furan (110-00-9)

Thiophene (110-02-1)

Succinic anhydride (108-30-5)

sodium succinate (150-90-3)

phosphorus pentasulfide

ethyl sulfide (352-93-2)

erythritol

succinic aldehyde (638-87-9)

nickel hydroxide (12054-48-7)

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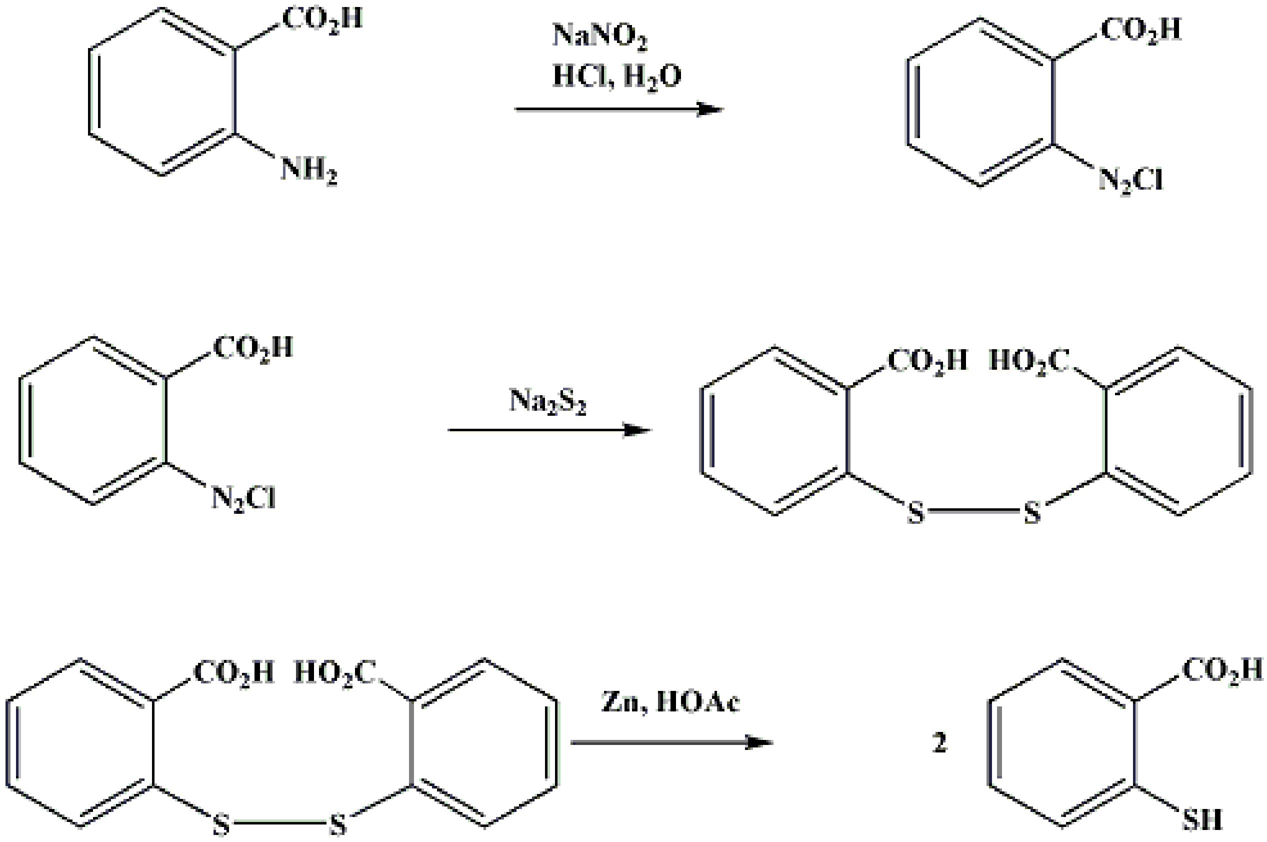
Organic Syntheses, CV 2, 580

THIOSALICYLIC ACID

[Benzoic acid, *o*-mercapto-]



Submitted by C. F. H. Allen and D. D. MacKay.
Checked by Roger Adams and A. E. Knauf.

1. Procedure

In a 4-l. beaker, 290 cc. of water is heated to boiling, and 260 g. (1.1 moles) of crystallized sodium sulfide ($Na_2S{\cdot}9H_2O$) and 34 g. of powdered sulfur are dissolved by heating and stirring. A solution of 40 g. of sodium hydroxide in 100 cc. of water is then added and the mixture cooled, first in cold water, and finally by a freezing mixture of ice and salt.

In a 2-l. beaker, set in a freezing mixture and provided with a stirrer and a thermometer for reading temperatures to 0°, are placed 500 cc. of water, 137 g. (1 mole) of anthranilic acid, and 200 cc. of concentrated hydrochloric acid; the stirrer is started and the mixture cooled to about 6°. Meanwhile 69 g. (1 mole) of sodium nitrite is dissolved in 280 cc. of hot water and the solution cooled in ice; portions are then placed in a separatory funnel of convenient size, supported in such a way that the lower end of the stem extends beneath the surface of the anthranilic acid solution. When the temperature has fallen to 5°, the nitrite solution is run in; about 500 g. of cracked ice is added at such a rate as to keep the temperature below 5°. This takes about ten minutes (Note 1). A drop of the solution should give an immediate blue color with starch-iodide paper.

The stirrer and thermometer are now transferred to the alkaline sulfide solution, the temperature of which must be below 5°. The diazo solution is added over a period of twenty to thirty minutes along with 950 g. of ice to prevent the temperature from rising above 5°. When addition is complete, the water bath is removed and the mixture allowed to warm up to room temperature; after two hours the evolution of nitrogen ceases (Note 2). About 180 cc. of concentrated hydrochloric acid is added until the solution is acid to Congo red paper, and the precipitate of dithiosalicylic acid is filtered and washed with water.

To remove the excess sulfur, the precipitate is dissolved by boiling with a solution of 60 g. of anhydrous sodium carbonate (soda ash) in 2 l. of water, and the mixture is filtered while hot. It is divided into five equal parts (Note 3), and the dithiosalicylic acid is reprecipitated as before with concentrated hydrochloric acid. The solid is filtered, the cake being sucked as dry as possible.

The moist cake is mixed with 27 g. of zinc dust and 300 cc. of glacial acetic acid in a 1-l. round-bottomed flask, and the mixture is refluxed vigorously for about four hours (Note 4). When the reduction is complete, the mixture is cooled and filtered with suction. The filter cake is washed once with water and then transferred to a 1-l. beaker. The cake is suspended in 200 cc. of water, and the suspension is heated to boiling. The hot solution is made strongly alkaline by the addition of about 40 cc. of 33 per cent aqueous sodium hydroxide solution. The alkaline solution is boiled for about twenty minutes to ensure complete extraction of the product from the filter cake, filtered from the insoluble material (Note 5), and the thiosalicylic acid is then precipitated by the addition of sufficient concentrated hydrochloric acid to make the solution acid to Congo red paper. The product is filtered with suction, washed once with water, and dried in an oven at 100–110°. The yield of a product which melts at 162–163° is 110–130 g. (71–84 per cent of the theoretical amount based on the anthranilic acid).

This product is sufficiently pure for most purposes (Note 6).

For recrystallization 5 g. of this material is dissolved in 20 cc. of hot 95 per cent alcohol, and 40 cc. of water is added. The solution is boiled with a little decolorizing carbon, filtered hot, and then allowed to cool. The product crystallizes in yellow flakes. The yield of recrystallized material is 4.7 g.; the melting point of the material is 163–164°.

2. Notes

1. This method is much more rapid than when external cooling alone is used (Org. Syn. Coll. Vol. I, **1941**, 374). The total volume of the solution is not important since the insoluble dithiosalicylic acid is readily filtered.
2. Foaming sometimes becomes very during the evolution of nitrogen. The addition of a few cubic centimeters of ether from time to time helps to keep this foaming under control.
3. The dithiosalicylic acid may be precipitated all at once if desired and the entire amount reduced in one operation. If this is done, the reduction must be carried out in a 5-l. flask fitted with a good stirrer. The mixture needs to be refluxed about ten hours over a ring burner. In the laboratory, this is much less convenient than it is to

divide the material and reduce in smaller amounts. The yield is not materially lowered by making the reduction in one portion.

4. The reduction does not always run smoothly. If the zinc lumps and becomes inactive more must be added. To determine whether reduction is complete, a sample is removed, cooled, and filtered. The precipitate is boiled with strong sodium hydroxide solution, filtered, and then acidified with hydrochloric acid. If the reduction is complete, the precipitated material will melt at 164° or lower. If the reduction is not complete, the precipitated material will melt above 164°. If the reduction is not complete, the refluxing of the main portion must be continued (and perhaps more zinc must be added) until a test portion shows that the reaction is complete.

In determining the melting point of the material, the capillary tube containing the test sample should be inserted in a bath previously heated to 163–164°.

5. When the reduction is carried out in five portions, one extraction with sodium hydroxide is usually sufficient for each portion. If the reduction is carried out in one operation, several extractions are usually required. When the material is to be extracted more than once, it is best to boil the residue from the first alkaline treatment with hydrochloric acid, filter, and then treat again with the alkali.

6. Thiosalicylic acid is used for the preparation of oxythionaphthene and many thioindigoid dyes.

3. Discussion

Of the several methods described for the production of thiosalicylic acid, only the following are of preparative interest: heating *o*-halogenated benzoic acids with an alkaline hydrosulfide at 150–200° in the presence of copper or copper salts,[1, 2] or with sodium sulfide at 200°;[3] and reduction of dithiosalicylic acid with glucose,[4] or metals[5, 2] in alkaline solution. The dithiosalicylic acid is prepared by treating diazotized anthranilic acid with sodium disulfide in alkaline solution.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 809

References and Notes

1. (*a*) Cassella and Company, Ger. pat. 189,200 [C. A. **2**, 607 (1908)]; (*b*) Cain, "Intermediate Products for Dyes," p. 151.
2. Chem. Age **21**, Dyestuffs Suppl. p. 11 (1929).
3. Cassella and Company, Ger. pat. 193,290 [C. A. **2**, 1514 (1908)]; Ref. 1(*b*).
4. Claasz, Ber. **45**, 2427 (1912).
5. Kalle and Company, Ger. pat. 204,450 [C. A. **3**, 1695 (1909)]; Ref. 1(*b*).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium sulfide ($Na_2S \cdot 9H_2O$)

dithiosalicylic acid

sodium carbonate (soda ash)

copper or copper salts

o-halogenated benzoic acids

alcohol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ether (60-29-7)

sodium hydroxide (1310-73-2)

nitrogen (7727-37-9)

sodium nitrite (7632-00-0)

sulfur (7704-34-9)

decolorizing carbon (7782-42-5)

zinc (7440-66-6)

sodium sulfide (1313-82-2)

sodium disulfide

Anthranilic Acid (118-92-3)

glucose (492-62-6)

hydrosulfide

Thiosalicylic acid, Benzoic acid, o-mercapto- (147-93-3)

oxythionaphthene

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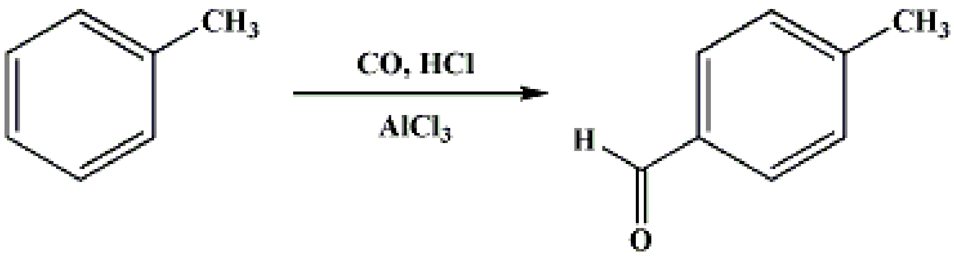
Organic Syntheses, CV 2, 583

p-TOLUALDEHYDE

$$CO + HCl \xrightarrow{(CuCl)} HCOCl$$

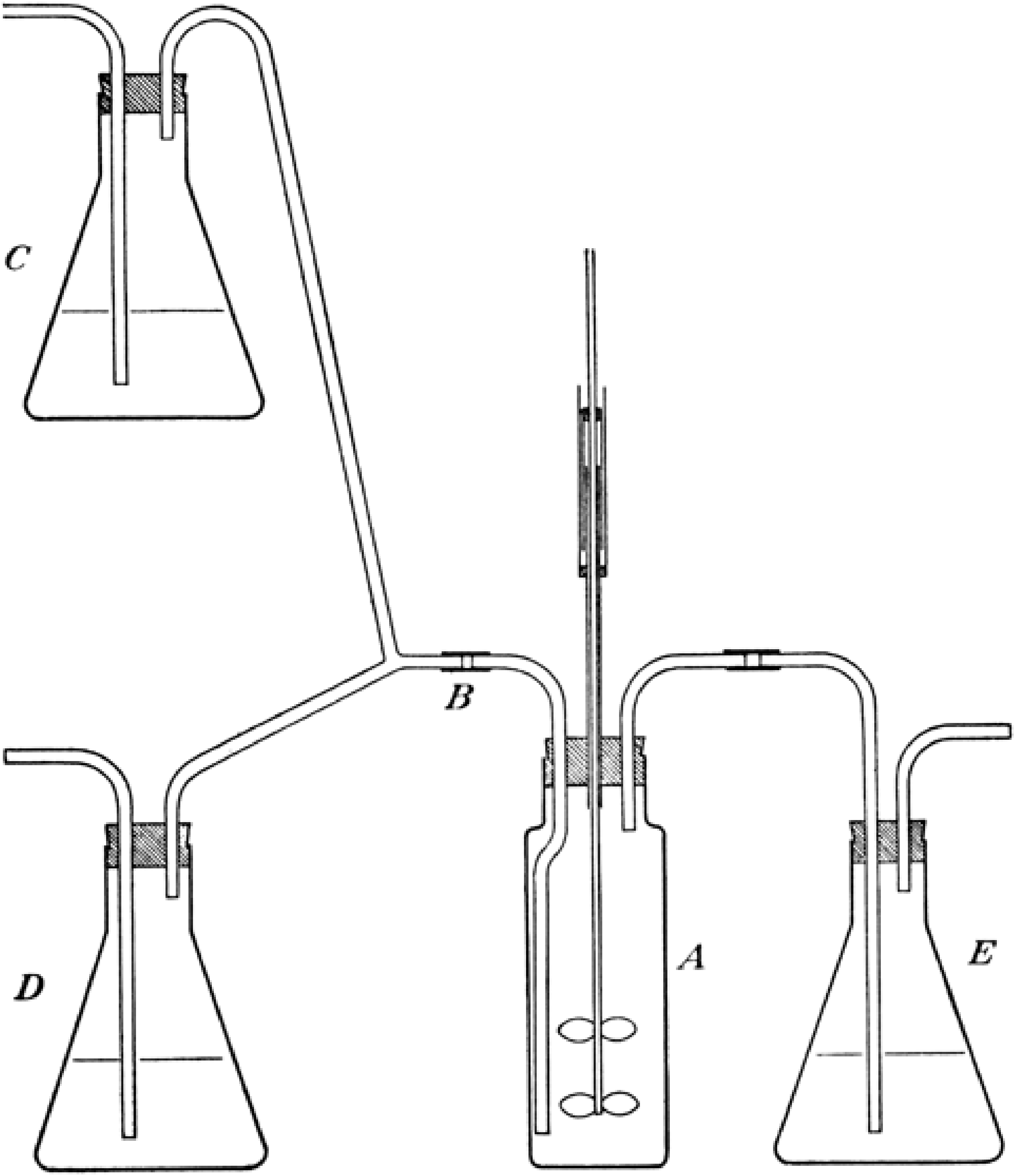


Submitted by G. H. Coleman and David Craig.
Checked by Henry Gilman and J. B. Dickey.

1. Procedure

The apparatus shown in .htmFig. 18 is set up in a hood. The narrow reaction bottle A, of about 500-cc. capacity and having a wide mouth, is provided with an efficient mercury-sealed mechanical stirrer, an inlet tube B for admitting the mixture of gases, and an outlet tube connected with the wash bottle E. Into A, contained in a water bath at 20°, is placed 200 g. (2.17 moles) of dry toluene; then 30 g. (0.3 mole CuCl) of cuprous chloride (Note 1) and 267 g. (2 moles) of finely powdered anhydrous aluminum chloride are added rapidly with active stirring.

Fig. 18



A mixture of hydrogen chloride and carbon monoxide (Note 2) is led to the bottom of the reaction bottle through tube B at such rates that the carbon monoxide is admitted uniformly during seven hours and the hydrogen chloride at about one-half this rate. The rates of flow of the two gases may be compared by the bubbling in wash bottles C and D. The extent of absorption can be estimated from the bubbling of the effluent gases in wash bottle E. The carbon monoxide is absorbed almost quantitatively at the beginning, and as the mixture thickens the absorption becomes less complete.

The mixture is hydrolyzed by adding it (Note 3) slowly and with shaking to 1.5 kg. of cracked ice in a 3-l. flask. The resulting mixture is then steam-distilled until all the aldehyde and unchanged toluene are driven over. Fifty cubic centimeters of ether is added

to the distillate, the two layers are separated, and the aqueous layer is washed with 150 cc. of ether which is then added to the first non-aqueous layer (Note 4). After drying with calcium chloride, the aldehyde is obtained by distilling from a 500-cc. flask provided with a short fractionating column (Note 5). The yield of *p*-tolualdehyde distilling at 201–205° is 121–132 g. (46–51 per cent of the theoretical amount based on the toluene). Redistillation involves but a slight loss and gives an almost colorless product which distils at 203–205° (Note 6).

2. Notes

1. The cuprous chloride may be prepared according to Org. Syn. Coll. Vol. I, **1941**, 170. The precipitate is washed several times by decantation with sulfurous acid, collected on a large Büchner funnel, washed with glacial acetic acid, and dried in an evaporating dish until the odor of acetic acid has disappeared. The cuprous chloride obtained is pure white and should not be exposed unnecessarily to the air.
An alternative procedure for preparing cuprous chloride is given on p. 131.
2. The carbon monoxide may be forced by water from a 75-l. container, after which it is dried by bubbling through two wash bottles containing concentrated sulfuric acid.
In place of this large container for carbon monoxide it is possible to generate the gas more conveniently by adding 170 g. (141 cc., 3.69 moles) of pure formic acid (sp. gr. 1.2) to 250 g. (135.8 cc.) of concentrated sulfuric acid contained in a 1-l. distilling flask heated on an oil bath to 70–80°. The side arm of the flask is connected to the sulfuric acid wash bottles. In order to ensure a smooth and constant flow of carbon monoxide, the formic acid is placed in a dropping funnel which extends through a two-holed rubber stopper in the neck of the distilling flask. The other hole of this stopper is connected by rubber tubing to a one-holed stopper in the dropping funnel. No frothing was evident under these conditions, but should frothing occur it is recommended that a small quantity of paraffin be added to the sulfuric acid in the generating flask.
3. The mixture frequently is too thick to be poured, and a spatula must be used to remove it.
4. The extraction of the aldehyde from the unchanged toluene with sodium bisulfite at this point in the preparation does not appreciably increase the purity of the product.
5. It is necessary to use a water-condenser until the temperature reaches 150°, after which an air-condenser is used.
6. The use of a few crystals of hydroquinone has been recommended for the storage of *p*-tolualdehyde.

3. Discussion

The method described is that of Gattermann and Koch.[1] *p*-Tolualdehyde has also been prepared from toluene, hydrogen cyanide, hydrogen chloride, and aluminum chloride;[2] from toluene, nickel carbonyl, and aluminum chloride;[3] from *p*-tolunitrile by reduction with stannous chloride followed by hydrolysis of the aldimine;[4] from *p*-xylene by

oxidation, particularly with chromyl chloride;[5] and from *p*-tolylmagnesium bromide with formaldehyde phenylhydrazone,[6] ethyl orthoformate, methylformanilide, ethoxymethyleneaniline, or carbon disulfide. The syntheses involving the Grignard reagent, except the first mentioned, have been examined and evaluated by Smith and Bayliss[7] and Smith and Nichols:[7] the use of ethoxymethyleneaniline or of ethyl orthoformate is recommended.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 590

References and Notes

1. Gattermann and Koch, Ber. **30**, 1622 (1897).
2. Bayer and Company, Ger. pat. 99,568 [Frdl. **5**, 98 (1897–1900)]; Hinkel, Ayling, and Morgan, J. Chem. Soc. **1932**, 2796; Hinkel, Ayling, and Beynon, ibid. **1935**, 677.
3. Dewar and Jones, J. Chem. Soc. **85**, 216 (1904).
4. Stephen, ibid. **127**, 1874 (1925); Williams, J. Am. Chem. Soc. **61**, 2248 (1939).
5. Law and Perkin, J. Chem. Soc. **91**, 258 (1907).
6. Grammaticakis, Compt. rend. **210**, 303 (1940).
7. Smith and Bayliss, J. Org. Chem. **6**, 437 (1941); Smith and Nichols, ibid. **6**, 489 (1941).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrogen chloride (7647-01-0)

acetic acid (64-19-7)

ether (60-29-7)

methylformanilide (103-84-4)

carbon monoxide (630-08-0)

hydroquinone (123-31-9)

hydrogen cyanide (74-90-8)

formic acid (64-18-6)

stannous chloride

sodium bisulfite (7631-90-5)

aluminum chloride (3495-54-3)

toluene (108-88-3)

carbon disulfide (75-15-0)

cuprous chloride (7758-89-6)

p-xylene (106-42-3)

Ethyl orthoformate

p-Tolunitrile (104-85-8)

sulfurous acid (7782-99-2)

chromyl chloride

nickel carbonyl

formaldehyde phenylhydrazone

ethoxymethyleneaniline (6780-49-0)

p-tolylmagnesium bromide (4294-57-9)

p-Tolualdehyde (104-87-0)

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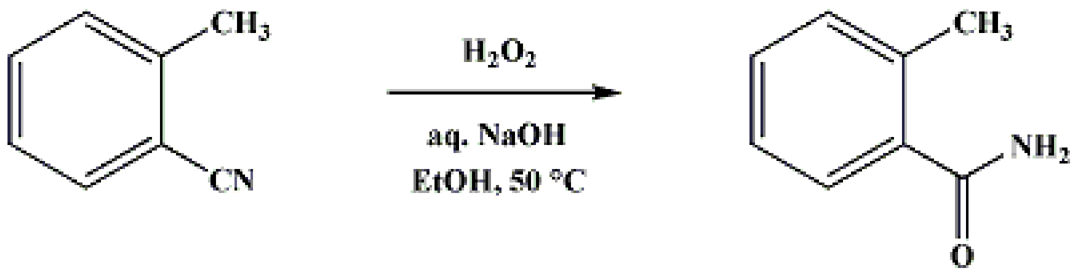
Organic Syntheses, *CV 2*, *586*

o-TOLUAMIDE



Submitted by C. R. Noller
Checked by W. W. Hartman and L. A. Smith.

1. Procedure

In a 2-l. round-bottomed flask are placed 88 g. (0.75 mole) of *o*-tolunitrile (Org. Syn. Coll. Vol. I, **1941**, 514), 300 cc. (2.6 moles) of 30 per cent hydrogen peroxide, 400 cc. of 95 per cent alcohol, and 30 cc. of 6 *N* sodium hydroxide solution (Note 1). The mixture evolves oxygen and soon warms up owing to the heat of reaction; the temperature is kept at 40–50° by external cooling (Note 2). After about one hour, heat is no longer evolved; the temperature is then maintained at 50° by external heating for an additional three hours. The mixture, while still warm, is made exactly neutral to litmus with 5 per cent sulfuric acid and distilled with steam until 1 l. of distillate is collected. The residue, which has a volume of about 600 cc. (Note 3), is poured while hot into a 1-l. beaker and cooled to 20°. The crystals which form are filtered with suction. They are transferred to a mortar and ground to a paste with 100 cc. of cold water, filtered again, and then washed on the filter with an additional 100 cc. of cold water. The *o*-toluamide is obtained in the form of white crystals melting at 141–141.5°. The yield of air-dried product is 91–93 g. (90–92 per cent of the theoretical amount) (Note 4). The product may be recrystallized from water (10 g. per 100 cc.). The recovery is 92 per cent, and the melting point is not changed (Note 5).

2. Notes

1. This amount of alcohol is sufficient to provide a homogeneous solution.
2. If the temperature is allowed to rise much above 50° the evolution of oxygen will be sufficiently rapid to cause the mixture to foam out of the flask.
3. The volume of the solution in the flask is kept down by applying a small flame to the flask after most of the alcohol has been distilled.
4. An additional 3–4 g. of low-melting material may be obtained by concentrating the filtrate, but this is hardly worth while.
5. In general, amides may be prepared by this method from aliphatic nitriles in yields of 50–60 per cent and from aromatic nitriles in yields of 80–95 per cent. Slight variations in the above procedure may be necessary for carrying out the reaction and for isolating the amide, depending on the solubility of the nitriles

and amides. Except for difficulty hydrolyzable nitriles such as the *o*-substituted aromatic nitriles, an equivalent amount of 6 to 12 per cent hydrogen peroxide gives better yields than the 30 per cent reagent.[1]

3. Discussion

o-Toluamide has been prepared by the action of ammonia on *o*-toluyl chloride,[2] and by the action of alcoholic potassium hydroxide[3] or of an alkaline solution of hydrogen peroxide[4], [1] on *o*-tolunitrile.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 1054

References and Notes

1. McMaster and Noller, Wash. Univ. Studies **13**, 23 (1925); J. Indian Chem. Soc. **12**, 652 (1935) [C. A. **30**, 1736 (1936)].
2. Remsen and Reid, Am. Chem. J. **21**, 289 (1899).
3. Weith, Ber. **6**, 419 (1873).
4. Kattwinkel and Wolffenstein, ibid. **37**, 3224 (1904); Dubsky, J. prakt. Chem. (2) **93**, 137 (1916).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

ammonia (7664-41-7)

sodium hydroxide (1310-73-2)

oxygen (7782-44-7)

potassium hydroxide (1310-58-3)

hydrogen peroxide (7722-84-1)

o-toluyl chloride (95-49-8)

o-Tolunitrile (529-19-1)

o-Toluamide (527-85-5)

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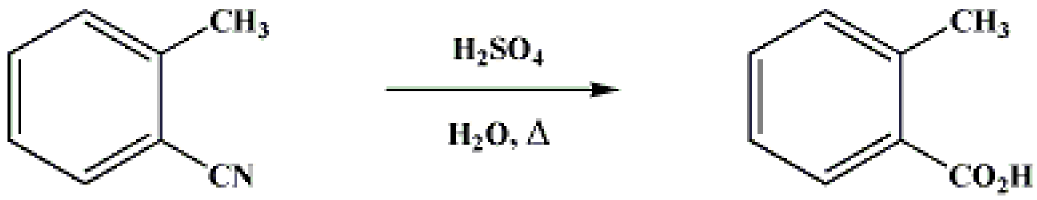
Organic Syntheses, CV 2, 588

o-TOLUIC ACID



Submitted by H. T. Clarke and E. R. Taylor.
Checked by C. S. Marvel and W. W. Moyer.

1. Procedure

In a 5-l. flask, equipped with a mechanical stirrer, a reflux condenser, and a separatory funnel, is placed 3 kg. of 75 per cent sulfuric acid (sp. gr. 1.67). The solution is heated to about 150°, the stirrer is started, and 1 kg. (8.54 moles) of *o*-tolunitrile (Org. Syn. Coll. Vol. I, **1941**, 514) is added during two hours. The temperature is maintained at 150–160° and the mixture is stirred for two hours after the addition of the nitrile is complete. The temperature is then raised to 190° and stirring is continued for another hour. Usually some crystalline material appears in the condenser at this stage. The reaction mixture is cooled, poured into ice water, and filtered. The crude material is dissolved in an excess of 10 per cent sodium hydroxide solution (Note 1), filtered hot, and the filtrate acidified with dilute sulfuric acid. The product is collected on a Büchner funnel, dried, and recrystallized from about 3 l. of benzene (Note 2). The yield is 930–1030 g. (80–89 per cent of the theoretical amount) of *o*-toluic acid which melts at 102–103° (Note 3).

2. Notes

1. Any insoluble material which separates on conversion into the sodium salt is toluamide, which may be isolated. The appearance of this substance indicates too short a period of heating or too low a temperature.
The reaction can be stopped readily so that a considerable quantity of the amide is produced. The amide purified by recrystallization from water, melts at 139–140°.
2. An additional amount of pure *o*-toluic acid may be obtained by distilling the benzene mother liquor to a small volume and allowing to cool.
3. *p*-Toluic acid (m.p. 178°) may be obtained from *p*-tolunitrile by the same process and in the same yields. This acid is less soluble in benzene, and about 9 l. is needed for recrystallization.

3. Discussion

o-Toluic acid has been prepared by heating 1,3-naphthalenedisulfonic acid, 1,3-

dihydroxynaphthalene, 1-naphthol-3-sulfonic acid, or 1-naphthylamine-3-sulfonic acid with sodium hydroxide;[1] by reduction of phthalide with hydriodic acid and phosphorus;[2] by electrolytic oxidation of *o*-xylene;[3] by oxidation of *o*-xylene with dilute nitric acid;[4] by catalytic hydrogenation of phthalic anhydride;[5] by hydrolysis of *o*-tolunitrile with 75 per cent sulfuric acid;[6] and by carbonating the ether solution of the reaction product from butyl lithium and *o*-bromotoluene.[7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 820
- Org. Syn. Coll. Vol. 3, 822

References and Notes

1. Kalle and Company, Ger. pat. 79,028 [Frdl. **4**, 147 (1894-97)]; Friedlaender and Rüdt, Ber. **29**, 1611 (1896).
2. Hessert, ibid. **11**, 238 (1878); Racine, Ann. **239**, 72 (1887).
3. Fichter and Rinderspacher, Helv. Chim. Acta **10**, 41 (1927).
4. Fittig and Bieber, Ann. **156**, 242 (1870).
5. Willstätter and Jaquet, Ber. **51**, 771 (1918).
6. Cahn, Ann. **240**, 280 (1887).
7. Gilman, Langham, and Moore, J. Am. Chem. Soc. **62**, 2330 (1940).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

Benzene (71-43-2)

ether (60-29-7)

sodium hydroxide (1310-73-2)

nitric acid (7697-37-2)

PHOSPHORUS (7723-14-0)

phthalic anhydride (85-44-9)

toluamide (55-21-0)

hydriodic acid (10034-85-2)

o-Tolunitrile (529-19-1)

p-Tolunitrile (104-85-8)

o-Bromotoluene (95-46-5)

butyl lithium (109-72-8)

Phthalide (87-41-2)

1-naphthylamine-3-sulfonic acid

1,3-dihydroxynaphthalene (132-86-5)

1-naphthol-3-sulfonic acid (3771-14-0)

1,3-naphthalenedisulfonic acid

p-Toluic acid (99-94-5)

o-Toluic acid (118-90-1)

o-Xylene (95-47-6)

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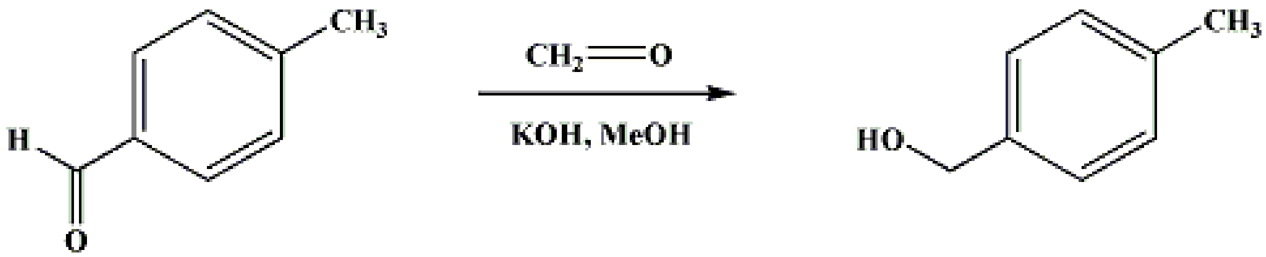
Organic Syntheses, CV 2, 590

p-TOLYL CARBINOL

[Benzyl alcohol, *p*-methyl-]



Submitted by David Davidson and Marvin Weiss.
Checked by Reynold C. Fuson and E. A. Cleveland.

1. Procedure

The apparatus consists of a 3-l. three-necked flask fitted with a mercury-sealed mechanical stirrer, a reflux condenser, a dropping funnel, and a thermometer which reaches almost to the bottom of the flask. Five hundred grams of potassium hydroxide pellets (85 per cent potassium hydroxide) (7.6 moles) and 750 cc. of commercial absolute methyl alcohol (free from acetone) are placed in the flask, and stirring is begun. The bulk of the alkali dissolves in a few minutes, with the evolution of heat. The flask is now surrounded by an ample cold-water bath, and, when the internal temperature drops to 60°, addition of a mixture of 360 g. (353 cc., 3 moles) of *p*-tolualdehyde (Note 1), 300 cc. of formalin (3.9 moles) (Note 2), and 300 cc. of absolute methyl alcohol is begun at such a rate that the internal temperature remains at 60–70°. This addition requires about fifteen minutes. The internal temperature is then maintained at 60–70° for three hours, after which the reflux condenser is replaced by a downward condenser and the methyl alcohol distilled with the aid of a brine bath until the internal temperature reaches 101°. Nine hundred cubic centimeters of cold water is then added to the warm residue, and the mixture is cooled. The resulting two layers are separated at once (Note 3), and the aqueous layer is extracted with three 200-cc. portions of benzene. The combined oil and extracts are washed with five or six 50-cc. portions of water (Note 4), and the combined washings extracted with 50 cc. of benzene, the benzene layer being added to the washed extract. The benzene solution is cleared by shaking it with a few grams of anhydrous sodium sulfate and is then distilled under diminished pressure. After removal of the benzene, 331 g. (90 per cent of the theoretical amount) of *p*-tolyl carbinol (b.p. 116–118°/20 mm.) is obtained; the product solidifies in the receiver to a mass of oil-drenched crystals melting at 54–55°. Recrystallization from an equal weight of commercial heptane (b.p. 90–100°) gives an 80 per cent recovery of long needles which melt at 61°. A further 8 per cent is recoverable by concentration of the mother liquor (Note 5) and (Note 6).

2. Notes

1. A technical grade of *p*-tolualdehyde, obtained from Fritzsche Brothers, New York, New York, was found satisfactory. Directions for preparing *p*-tolualdehyde are given on p. 583.
2. The formaldehyde content of the solution is determined by analysis (p. 611).
3. The upper layer solidifies if allowed to stand.
4. This washing removes potassium *p*-toluate, which causes difficulty in the distillation of the product if allowed to remain.
5. The final residue from the mother liquor is an oil which does not solidify in a freezing mixture and which appears to be a mixture of *p*- and *m*-tolyl carbinols. Only a trace of phthalic acid (phenolphthalein test) was obtained by oxidizing this oil with permanganate; the portion of the oil which was more readily soluble in water yielded a phenylurethan which depressed the melting point of the phenylurethan of either *p*-tolyl carbinol or benzyl alcohol.
6. Under the same conditions, benzaldehyde yielded 80 per cent of benzyl alcohol and piperonal 86 per cent of piperonyl alcohol.

3. Discussion

p-Tolyl carbinol has been prepared from *p*-tolualdehyde by the action of alcoholic potassium hydroxide,[1] by electrolytic reduction,[2] and by the reducing action of the Grignard reagent,[3] as well as from *p*-toluic acid by electrolytic reduction.[4] The procedure described is an adaptation of a general method for reducing aromatic aldehydes to the corresponding alcohols.[5]

References and Notes

1. Cannizzaro, Ann. **124**, 252 (1862).
2. Law, J. Chem. Soc. **91**, 755 (1907).
3. Oddo, Gazz. chim. ital. **41** (I) 285 (1911).
4. Mettler, Ber. **39**, 2933 (1906).
5. Davidson and Bogert, J. Am. Chem. Soc. **57**, 905 (1935).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

p- and m-tolyl carbinols

Benzene (71-43-2)

methyl alcohol (67-56-1)

formaldehyde, formalin (630-08-0)

sodium sulfate (7757-82-6)

benzaldehyde (100-52-7)

acetone (67-64-1)

potassium hydroxide (1310-58-3)

Benzyl alcohol (100-51-6)

phthalic acid (88-99-3)

piperonal (120-57-0)

heptane (142-82-5)

phenylurethan (101-99-5)

Piperonyl alcohol (495-76-1)

p-Toluic acid (99-94-5)

p-Tolualdehyde (104-87-0)

p-TOLYL CARBINOL, Benzyl alcohol, p-methyl- (589-18-4)

potassium p-toluate

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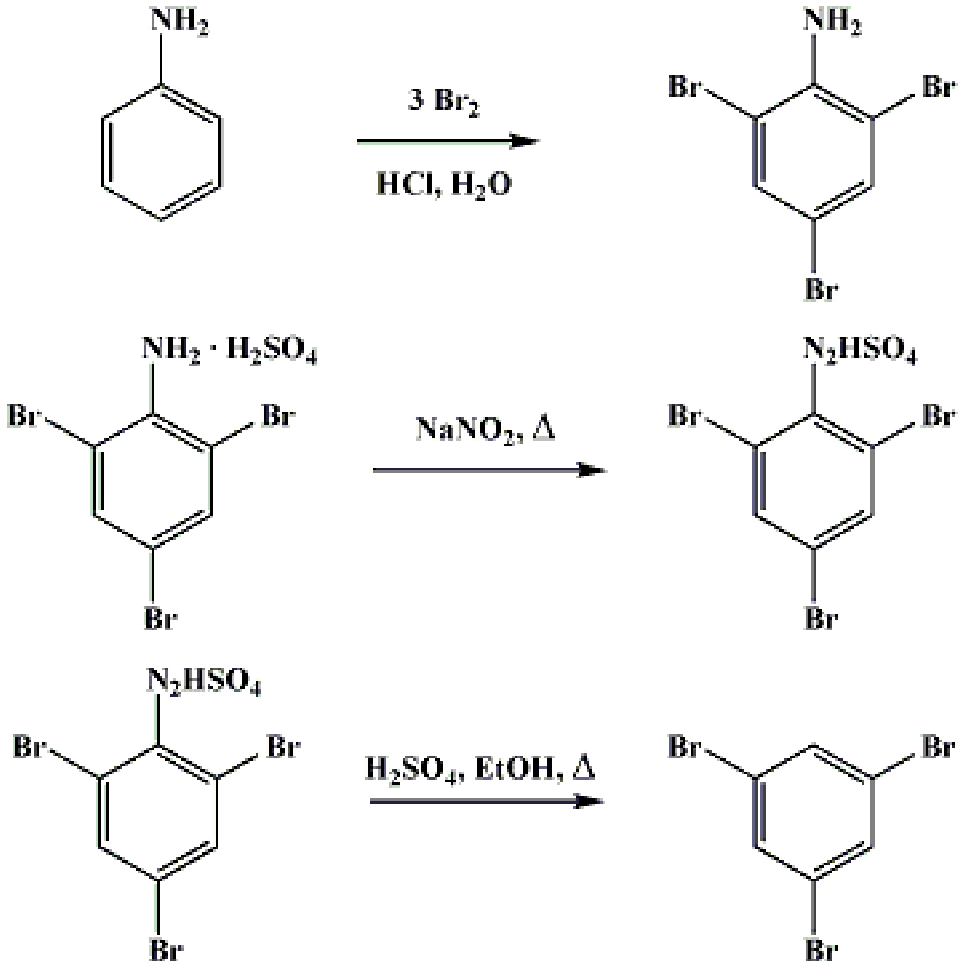
Organic Syntheses, CV 2, 592

sym.-TRIBROMOBENZENE

[Benzene, 1,3,5-tribromo-]

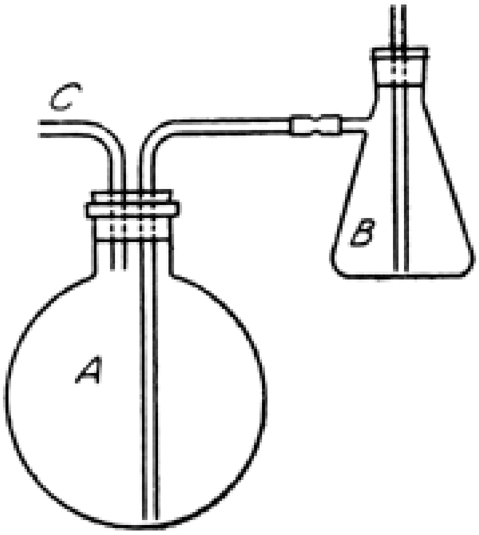


Submitted by G. H. Coleman and William F. Talbot.
Checked by Reynold C. Fuson and Charles F. Woodward.

1. Procedure

The apparatus consists of a 12-l. round-bottomed flask and a 250-cc. suction flask provided with stoppers and glass tubes as shown in .htmFig. 19. After the flasks have been charged, A is surrounded by an ice bath and B by a water bath heated to 40–50°. In flask A are placed 100 g. (1.1 moles) of aniline, 1 l. of water, and 100 cc. (1.2 moles) of concentrated hydrochloric acid; when the aniline has dissolved, sufficient water is added to bring the volume of the solution to 5 l. Flask B is charged with 577 g. (185 cc., 3.6 moles) of bromine; the baths are adjusted, and a rapid stream of air saturated with bromine vapor is drawn into A by applying suction at C (Note 1) and (Note 2).

Fig. 19



The introduction of bromine is continued until the solution assumes a distinctly yellow color; approximately three to four hours is required, and the reaction is then complete. The tribromoaniline is filtered on a Büchner funnel, thoroughly washed with water to remove hydrobromic acid, sucked as dry as possible, and taken without further drying to the next step.

The moist tribromoaniline, together with 2.1 l. of 95 per cent alcohol and 525 cc. of benzene, is placed in a 5-l. two-necked flask. One neck of the flask bears a reflux condenser; the other is closed with a stopper that can be removed momentarily for the addition of reagents. The tribromoaniline is brought into solution by heating the flask on a steam bath. To this solution is added 140 cc. of concentrated sulfuric acid, and then 140 g. (2.03 moles) of powdered sodium nitrite as rapidly as the violence of the reaction will permit. When the reaction has moderated, the solution is brought to boiling and maintained there as long as gas is evolved. It is then allowed to stand in a warm place for three hours more.

After the mixture has been cooled (preferably in an ice bath), the mother liquor is removed from the solid by decantation through a Büchner funnel; if necessary, a wire gauze is used to retain the solid in the flask. To the solid is then added a solution of 150 cc. of concentrated sulfuric acid in 1.5 l. of water. When the excess sodium nitrite has been decomposed, the solid is transferred to a Büchner funnel and washed first with water and then with a small amount of alcohol. The yield of crude, dry tribromobenzene is 250–260 g. (74–77 per cent of the theoretical amount). The product is reddish brown and melts at 112–116°.

For further purification, 100 g. of the crude product is dissolved in a boiling mixture of 1560 cc. of glacial acetic acid and 350 cc. of water; the solution is boiled for a few minutes with 25 g. of decolorizing carbon, filtered hot, and allowed to cool. The crystals are washed on a Büchner funnel with a small amount of chilled 95 per cent alcohol to remove the acetic acid. The whole of the crude product crystallized in this way furnishes 216–240 g. (64–71 per cent of the theoretical amount) of slightly colored tribromobenzene, melting at 121.5–122.5° (corr.).

The yield of crude product may be increased 50–60 g.—making a total of 300–320 g. (89–95 per cent of the theoretical amount)—by working up the mother liquors. The alcoholic liquors and washings are diluted to 6 l., and the aqueous layer is separated from the heavy oil at the bottom. The benzene is then distilled from the oil in a distilling flask, care being taken not to overheat the product after the benzene has been removed. The residual tribromobenzene may be recrystallized in the manner described above.

2. Notes

1. Considerable heat is generated by the reaction, and it is necessary to cool A to prevent the loss of bromine. Flask B must be kept at 40–50° to ensure a high concentration of bromine vapor in the air stream; the violent agitation produced by air saturated at lower temperatures whips the reaction mixture into a light foam that is likely to overflow the flask.
2. It is well to interpose a safety flask between the reaction flask and the aspirator. The safety flask is partially filled with water through which the air stream passes after the bromine vapor has been removed. This device has a double purpose; it enables one to gauge the rate of aspiration by the rate at which the air current bubbles through the water, and it serves to detect the escape of bromine vapors from the reaction flask. A small amount of bromine will impart to the water a distinctly yellow color. In case bromine does escape into this trap a momentary release of the suction will cause the wash water to be drawn into the reaction flask, thus returning the bromine to the reaction mixture.

3. Discussion

Sym.-tribromobenzene has been prepared from 3,5-dibromoaniline by the replacement of the amino group by bromine;[1] from bromoacetylene by the action of light;[2] by the decomposition of 2,4,6-tribromophenylhydrazine;[3] by the reduction of 2,4,6-tribromobenzenediazonium sulfate;[4], [5] and as a by-product in the preparation of 2,4,6-tribromobenzonitrile.[6]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 947

References and Notes

1. Körner, Gazz. chim. ital. **4**, 410 (1874).
2. Sabanejew, J. Russ. Phys.-Chem. Soc. **17**, I, 176 (1885) [Ber. **18**, 374 (R) (1885)].
3. Chattaway and Vonderwahl, J. Chem. Soc. **107**, 1508 (1915).
4. Jackson and Moore, Am. Chem. J. **12**, 167 (1890).
5. Jackson and Bentley, ibid. **14**, 335 (1892).

6. Montagne, Rec. trav. chim. **27**, 347 (1908).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sym.-TRIBROMOBENZENE

alcohol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

aniline (62-53-3)

HYDROBROMIC ACID (10035-10-6)

bromine (7726-95-6)

sodium nitrite (7632-00-0)

carbon (7782-42-5)

TRIBROMOBENZENE

Benzene, 1,3,5-tribromo- (626-39-1)

tribromoaniline

3,5-dibromoaniline

bromoacetylene (593-61-3)

2,4,6-tribromophenylhydrazine

2,4,6-tribromobenzenediazonium sulfate

2,4,6-tribromobenzonitrile

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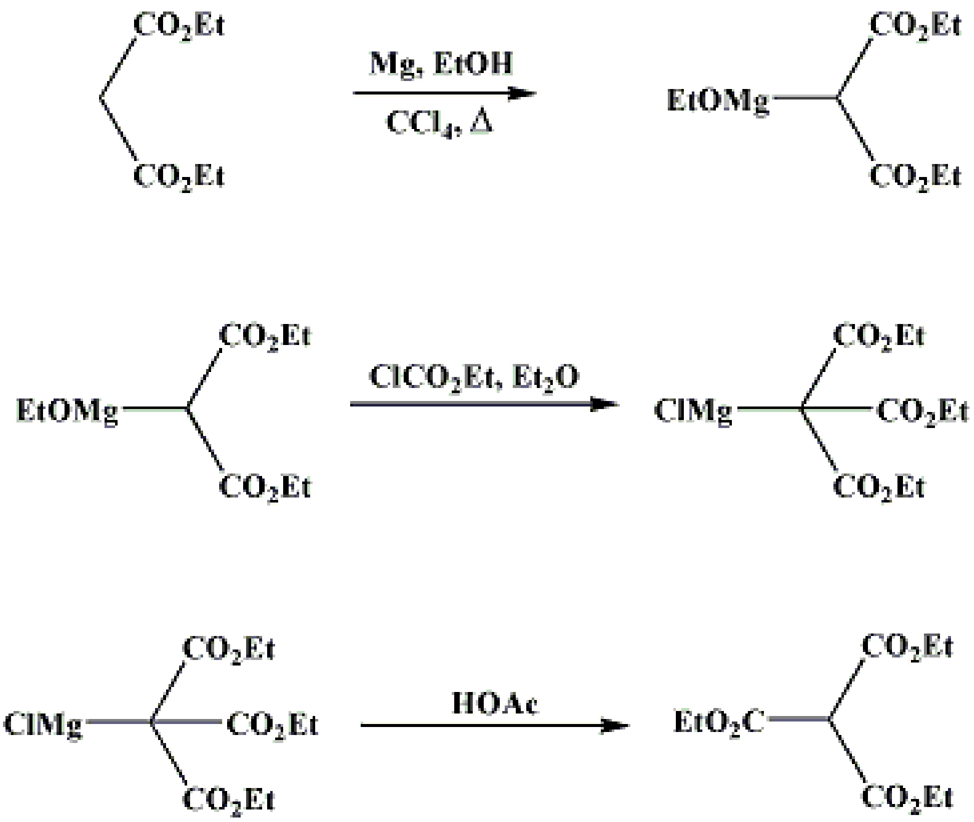
Organic Syntheses, CV 2, 594

TRICARBETHOXYMETHANE

[Methanetricarboxylic acid, triethyl ester]



Submitted by Hakon Lund and Axel Voigt.
Checked by W. H. Carothers and W. L. McEwen.

1. Procedure

In a 1-l. round-bottomed flask, provided with an efficient and not too narrow reflux condenser, are placed 25 g. (1.03 gram atoms) of magnesium turnings (Grignard), 25 cc. of absolute alcohol (Note 1), 1 cc. of carbon tetrachloride (Note 2), and 30 cc. of a mixture of 160 g. (151 cc., 1 mole) of ethyl malonate and 80 cc. of absolute alcohol. Provision is made for cooling the flask when necessary in cold water, and the mixture is gently heated until hydrogen is evolved. The reaction may become so violent that external cooling is necessary. The ethyl malonate is gradually added through the condenser at such a rate that the reaction proceeds vigorously but not beyond control. When the reaction moderates the flask is cooled and 300 cc. of ether, dried twenty-four hours with calcium chloride, is added through the condenser. On gentle heating the crystals which have separated are dissolved, and hydrogen is again evolved for some time without further heating. The reaction is brought to completion on the steam bath. The flask is then removed from the steam bath, and a mixture of 100 cc. of ethyl chloroformate (1.05 moles) and 100 cc. of dry ether is added through the condenser from a dropping funnel at such a rate that vigorous boiling is maintained throughout

the addition (Note 3). The reaction is complete after heating for fifteen minutes on the steam bath.

The viscous magnesium compound formed is cautiously decomposed with dilute acetic acid (75 cc. in 300 cc. of water), the flask being cooled under the tap. Two clear layers are formed, and, after separation, the aqueous layer is extracted with 100 cc. of ether, the combined ethereal solution is washed with water and dried with sodium sulfate, and the ether is distilled on the steam bath. The residue is distilled under reduced pressure. After a small fore-run the temperature rapidly rises to 130° at 10 mm. when the pure tricarbethoxymethane begins to distil. The yield of material collected over a five-degree interval is 204–215 g. (88–93 per cent of the theoretical amount). The product solidifies at 25°. The melting point of the pure substance is 28–29°.

2. Notes

1. Anhydrous alcohol is preferable, but a good grade of commercial absolute alcohol may be used without appreciably lowering the yield. The submitters used alcohol dehydrated by means of magnesium.[1]
2. Carbon tetrachloride (as well as a number of other halogen compounds) greatly accelerates the reaction between magnesium and alcohol. If anhydrous alcohol is used the reaction will start after some time without heating, whereas 99.5 per cent alcohol has to be heated nearly to boiling before the evolution of hydrogen becomes rapid.
3. Towards the end of the reaction the magnesium compound of ethyl methanetricarboxylate separates as a viscous mass which tends to prevent the remaining magnesium malonic ester and ethyl chloroformate from reacting. Vigorous boiling keeps the material from forming a compact mass. If larger runs are made it may be necessary to stir during this part of the process.

3. Discussion

Tricarbethoxymethane has been prepared by the action of ethyl chloroformate upon sodiomalonic ester suspended in benzene,[2] toluene, or xylene;[3] by the distillation of ethyl ethoxalylmalonate;[4] from ethyl carbonate and malonic ester;[5] and by the procedure described above.[6]

According to Backer and Lolkelma,[3] the aromatic esters of methanetricarboxylic acid and the ethyl ester of that acid are best prepared by the Lund procedure using magnesium; the other aliphatic esters of methanetricarboxylic acid are best prepared using sodium—compare the preparation of the trimethyl ester below—with toluene or xylene as the reaction medium.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 379
- Org. Syn. Coll. Vol. 4, 285

References and Notes

1. Lund and Bjerrum, Ber. **64**, 210 (1931).
2. Conrad and Guthzeit, Ann. **214**, 32 (1882).
3. Backer and Lolkelma, Rec. trav. chim. **57**, 1237 (1938).
4. Bouveault, Bull. soc. chim. (3) **19**, 79 (1898); Scholl and Egerer, Ann. **397**, 353 (1913).
5. Wallingford, Homeyer, and Jones, J. Am. Chem Soc. **63**, 2056 (1941).
6. Lund, Ber. **67**, 938 (1934).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

magnesium compound of ethyl methanetricarboxylate

magnesium malonic ester

ethyl ethoxalylmalonate

aromatic esters of methanetricarboxylic acid

aliphatic esters of methanetricarboxylic acid

alcohol (64-17-5)

calcium chloride (10043-52-4)

acetic acid (64-19-7)

Benzene (71-43-2)

ether (60-29-7)

hydrogen (1333-74-0)

magnesium, magnesium turnings (7439-95-4)

sodium sulfate (7757-82-6)

carbon tetrachloride (56-23-5)

toluene (108-88-3)

sodium (13966-32-0)

xylene (106-42-3)

ethyl malonate (1071-46-1)

ethyl chloroformate (541-41-3)

ethyl carbonate

Tricarbethoxymethane, Methanetricarboxylic acid, triethyl ester (6279-86-3)

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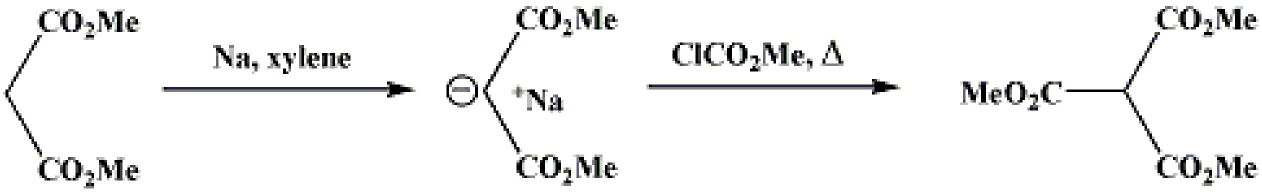
TRICARBOMETHOXYMETHANE

[Methanetricarboxylic acid, trimethyl ester]



Submitted by B. B. Corson and J. L. Sayre.
Checked by Roger Adams and A. E. Knauf.

1. Procedure

In a 2-l. three-necked flask, fitted with an upright condenser, a separatory funnel, and a mercury-sealed stirrer, are placed 400 cc. of dry xylene and 13 g. (0.56 gram atom) of sodium. The flask is heated in an oil bath until the sodium melts, and the mixture is stirred until the sodium is broken up into fine globules. Then 69 g. (0.57 mole) of methyl malonate is added over a period of five to ten minutes (Note 1).

The mixture is cooled while being well stirred, and, when the temperature reaches about 65°, 57 g. (0.6 mole) of methyl chloroformate is added during five to ten minutes. The mixture is then warmed slowly so that the boiling point is reached in about fifteen to twenty minutes. Boiling and stirring are maintained for five hours.

The mixture is cooled to room temperature, the flask is filled two-thirds full with water, and stirring is continued for five minutes. The xylene solution is separated, washed with water, dried over calcium chloride, filtered, and distilled under reduced pressure. After removal of the solvent, the tricarbomethoxymethane distils at 128–142°/18 mm. The yield of crude product is 50–51 g. (50–51 per cent of the theoretical amount). This material becomes semi-solid on cooling.

The crude product is purified by dissolving it in an equal volume of methyl alcohol and then cooling the solution in a freezing mixture until crystallization is complete. The crystals are filtered with suction, and the mother liquors are again cooled in a freezing mixture. If necessary this process is repeated a third time or until no further crop of crystals separates on chilling the mother liquors. The crystals are transferred from the funnel to a beaker, stirred with about 70 cc. of petroleum ether (b.p. 32–45°), filtered, pressed dry, and washed with a little petroleum ether. The yield of fine, snow-white crystals melting at 43–45° is about 40–42 g. (40–42 per cent of the theoretical amount) (Note 2).

2. Notes

1. A brisk evolution of hydrogen occurs, and sodium methyl malonate settles as a pasty mass. Stirring should be vigorous during the addition of the malonic ester and

also during the subsequent heating, to avoid caking of the sodium salt.
2. Tricarbomethoxymethane is very soluble, and only by repeated cooling and filtration can a good recovery be obtained. Owing to this excessive solubility the apparent loss on crystallization is high. However, a considerable portion of this material can be recovered from the alcoholic mother liquors.

3. Discussion

The method described is very similar to one published by Adickes, Brunnert, and Lücker[1] for the preparation of the ethyl ester. In other procedures the sodium derivative of methyl malonate was isolated.[2] Compare the "Methods of Preparation" for tricarbethoxymethane on p. 596 above.

References and Notes

1. Adickes, Brunnert, and Lücker, J. prakt. Chem. (2) **130**, 163 (1931).
2. Scholl and Egerer, Ann. **397**, 355 (1913); Philippi, Hanusch, and von Wacek, Ber. **54**, 901 (1921); Backer and Lolkelma, Rec. trav. chim. **57**, 1237 (1938).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

sodium derivative of methyl malonate

calcium chloride (10043-52-4)

methyl alcohol (67-56-1)

hydrogen (1333-74-0)

sodium (13966-32-0)

xylene (106-42-3)

Tricarbethoxymethane (6279-86-3)

Tricarbomethoxymethane, Methanetricarboxylic acid, trimethyl ester (1186-73-8)

methyl malonate

methyl chloroformate (79-22-1)

sodium methyl malonate

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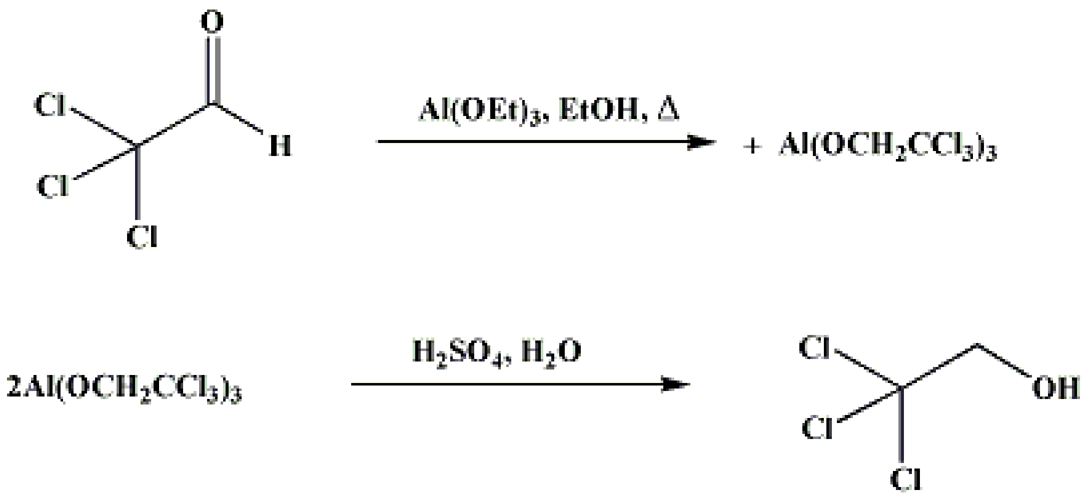
TRICHLOROETHYL ALCOHOL

[Ethanol, 2-trichloro-]



Submitted by William Chalmers
Checked by Reynold C. Fuson and H. H. Hully.

1. Procedure

In a 2-l. three-necked flask immersed in an oil bath are placed 250 g. (1.7 moles) of anhydrous chloral, 650 cc. of anhydrous alcohol (Note 1), and 75 g. (0.46 mole) of pure aluminum ethoxide (Note 2). An efficient fractionating column (Note 3) is attached to the flask through a cork in the central neck, and through one of the side necks is passed a tube leading to the bottom of the flask for the introduction of dry nitrogen (Note 4). The remaining neck is tightly stoppered. It is used to withdraw portions of liquid for testing.

To the outlet of the column is attached a U-tube and a Peligot tube each of about 100-cc. capacity. The U-tube is immersed in a freezing mixture, and the Peligot tube is filled with saturated sodium bisulfite solution. The oil bath is then heated to 135° and a slow current of gas is admitted. The mixture boils vigorously, but the alcohol is returned by the refluxing device whereas the acetaldehyde formed by the reaction is allowed to pass through and is caught in the freezing mixture and the Peligot tube.

The end of the reaction is easily determined by removing a few drops of the reaction mixture and treating with water in a test tube. After the aluminum hydroxide settles, the clear liquid is decanted and a few drops of yellow ammonium sulfide are added to it. So long as chloral is present, even in traces, a dark brown coloration will be produced on heating to incipient boiling. If the liquid collecting in the U-tube is removed every few hours, the completion of the reaction will be readily noticed by the diminishing quantity of acetaldehyde coming over. After twenty-three or twenty-four hours of heating (over a period of two or three days) the reaction is complete. The

temperature of the bath is then allowed to fall to 120° and the alcohol is distilled through an ordinary condenser which replaces the fractionating column. When the residue of aluminum trichloroethoxide is nearly dry (Note 5), the flask is removed from the oil bath and the solid is treated with 250 cc. of 20 per cent sulfuric acid and stirred thoroughly to ensure complete decomposition.

The mixture is then subjected to steam distillation until no more trichloroethyl alcohol passes over. About 4 l. of distillate is obtained (Note 6). The oil is separated from the aqueous layer, which is saturated with sodium sulfate and extracted with three 200-cc. portions of ether. The ether solution is added to the main portion of the alcohol, and the whole is dried over anhydrous sodium sulfate.

The ether is removed by distillation and the product distilled under reduced pressure (Note 7). There is obtained 215 g. (84 per cent of the theoretical amount) of trichloroethyl alcohol boiling at 94–97°/125 mm. and melting at 16–17° (Note 8). A purer compound can be obtained by refractionating under reduced pressure and pressing the crystals on a cooled porous plate. Pure trichloroethyl alcohol has a melting point of 19° (Note 9).

2. Notes

1. The action of a small proportion of aluminum ethoxide on pure chloral or chloral diluted with benzene leads to the formation of trichloroethyl trichloroacetate in the same manner that ethyl acetate is formed from acetaldehyde by aluminum ethoxide, but the yields are small. A slightly better yield is obtained when molecular proportions are employed, but it is only in the presence of a large amount of an alcohol that good yields are obtained.
2. Aluminum ethoxide is now obtainable commercially. The submitter recommends the following method of preparation,[1] which has been checked:
In a flask fitted with a reflux condenser is placed 27 parts of aluminum filings or groats. This is treated with 276 parts of absolute alcohol, 0.1 to 0.25 part of mercuric chloride, and several crystals of iodine. After a few minutes a violent evolution of hydrogen takes place, and by heating on the water bath for several hours the ethoxide is produced in the form of a grayish powder.
Unchanged alcohol is removed by distillation from an oil bath until the residual material melts to a dark-colored liquid. It is then poured into a Claisen flask and distilled under reduced pressure, using a short air condenser and a Pyrex suction flask as a receiver. Since aluminum ethoxide tends to sublime, a glass-wool filter is inserted between the receiving flask and the vacuum line to prevent clogging. A free flame is necessary, and distillation should be rapid. While the distillate is still liquid it is poured into a Pyrex flask and allowed to cool. It forms a tough, white mass which must be preserved in a well-stoppered flask to prevent adsorption of water vapor. A yield of 90 per cent of the theoretical amount may be obtained.
For the present reaction, where a trace of water does no harm, some of the

ethoxide may be fused and poured into a mortar and covered with a watch glass until cool, when it can be powdered and weighed.

The submitter has found that it is possible to make a large quantity of the ethoxide by the above method with 95 per cent alcohol, but that success is more certain if the alcohol is refluxed and distilled twice over quicklime.

3. This column must be capable of separating acetaldehyde from ethyl alcohol with the greatest completeness. A very efficient type is that of Hahn,[2] in which the column is kept at a constant temperature by means of boiling methyl alcohol in a central tube, the vapors passing up an outer annular space. It is necessary that the lower part of the condenser employed be sufficiently broad (say 2 cm. in diameter) so that when in operation there will be no tendency for liquid to collect in the column.

A column involving the same principle can be made from two reflux condensers. The lower outlet of the outer jacket of the condenser connected to the flask is closed, and the jacket is filled to about two-thirds its height with methyl alcohol. A few small pieces of pumice are introduced to prevent bumping of the alcohol. The upper outlet of this jacket is joined to a second condenser to prevent loss of the methanol vapors. The inner tube of the fractionating column is filled with glass beads which are held in place by indentations made in the lower part of the tube. The outlet of this tube is connected to the U-tube immersed in the freezing mixture.

Care is essential to ensure the complete separation of aldehyde and alcohol, because any slight continual loss of solvent is multiplied into a serious loss in the long period of heating necessary. The boiling point of chloral is only twenty degrees above that of ethyl alcohol, and any loss of the latter would lead to some loss of the reagent.

4. The nitrogen is supplied from a cylinder and is dried by passing through a calcium chloride tube and a tube containing phosphorus pentoxide mixed with glass wool or beads. A tube filled with glass wool is placed between the phosphorus pentoxide tube and the flask to prevent the pentoxide from being blown into the reaction mixture if the nitrogen is turned on too rapidly.

5. The residue must not be heated too strongly as it becomes compact and some tarry material is formed which makes the action of the acid upon it very slow.

6. A small amount of trichloroaldol, $CCl_3CHOHCH_2CHO$, can be extracted from the residue of the steam distillation by means of ether.

7. The product can be distilled at ordinary pressure at a temperature of 151°, but the distillate has a brown color due to slight decomposition.

8. Even by simple refluxing of the mixture without separation of the aldehyde, a yield of 65 per cent may be obtained.[3] The reaction between the aluminum ethoxide and the chloral is in equilibrium with that between the aluminum trichloroethoxide and the acetaldehyde. A certain amount of the acetaldehyde is removed from the reaction by condensation to ethyl acetate under the catalytic influence of aluminum ethoxide, but the change takes place only slowly in this mixture. A great deal of the aldehyde is converted into paraldehyde and acetal, but these changes are reversible.

9. The use of aluminum ethoxide in the presence of alcohol offers a means of reducing many compounds which could not be reduced in the desired manner by the more customary methods. Meerwein and his students have used the method to convert bromal into tribromoethyl alcohol and have also prepared cinnamyl alcohol and various halogenated cinnamyl and crotyl alcohols from the corresponding aldehyes.[4], [5] Excellent yields are obtained.

3. Discussion

The method given here is essentially that of Meerwein and his pupils Schmidt[5] and von Bock.[3] The theory of the reaction and applications are also discussed by Dworzak[4] and by Verley.[6] A number of patents have appeared covering this reaction, in some of which a secondary alcohol such as isopropyl alcohol[7] is used in place of ethyl alcohol. Trichloroethyl alcohol is one of the chlorination products of alcohol and is found in the high-boiling fractions in the production of chloral.[8] It was prepared by Garzarolli-Thurnlackh[9] and by Delacre[10] by the action of diethylzinc on chloral.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 48

References and Notes

1. Meister, Lucius, and Brüning, Ger. pat. 286,596 [Frdl. **12**, 29 (1914-16)].
2. Hahn, Ber. **43**, 419 (1910). A modified form of this apparatus is described in Org. Syn. **20**, 27.
3. v. Bock, Dissertation, Albertus-Universität, Königsberg i. Pr., Germany, 1926.
4. Dworzak, Monatsh. **47**, 11 (1926).
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8. Altschul and Meyer, Ber. **26**, 2758 (1893).
9. Garzarolli-Thurnlackh, Ann. **210**, 63 (1881).
10. Delacre, Bull. soc. chim. (2) **48**, 784 (1887).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ACETAL (105-57-7)

ethyl alcohol, alcohol (64-17-5)

calcium chloride (10043-52-4)

acetaldehyde (75-07-0)

sulfuric acid (7664-93-9)

Benzene (71-43-2)

ethyl acetate (141-78-6)

methyl alcohol, methanol (67-56-1)

ether (60-29-7)

hydrogen (1333-74-0)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

aluminum filings or groats (7429-90-5)

sodium bisulfite (7631-90-5)

iodine (7553-56-2)

isopropyl alcohol (67-63-0)

mercuric chloride (7487-94-7)

ammonium sulfide

diethylzinc (557-20-0)

aluminum hydroxide

Bromal (115-17-3)

chloral (75-87-6)

ethoxide

Trichloroethyl alcohol (115-20-8)

Ethanol, 2-trichloro-

aluminum ethoxide

aluminum trichloroethoxide

trichloroethyl trichloroacetate

tribromoethyl alcohol (75-80-9)

cinnamyl alcohol (104-54-1)

phosphorus pentoxide (1314-56-3)

paraldehyde (123-53-7)

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Organic Syntheses, CV 2, 602

TRIETHYL CARBINOL

[3-Pentanol, 3-ethyl-]

$$C_2H_5Br + Mg \longrightarrow C_2H_5MgBr$$

$$3C_2H_5MgBr + (C_2H_5O)_2CO \longrightarrow (C_2H_5)_3COMgBr + 2C_2H_5OMgBr$$

$$(C_2H_5)_3COMgBr + H_2O \longrightarrow (C_2H_5)_3COH + Mg(OH)Br$$

Submitted by W. W. Moyer and C. S. Marvel.
Checked by Frank C. Whitmore and D. J. Loder.

1. Procedure

In a 3-l. three-necked flask, fitted with a mechanical stirrer, a 500-cc. separatory funnel, and an efficient reflux condenser to which a calcium chloride tube is attached, are placed 107 g. (4.4 gram atoms) of magnesium turnings and 800 cc. of anhydrous ether. The reaction is started by adding 5 cc. (7 g., 0.06 mole) of ethyl bromide (Note 1) without stirring. The stirrer is started, and a solution of 480 g. (4.4 moles) of ethyl bromide in 1 l. of anhydrous ether is added as rapidly as the refluxing of the ether allows. The addition requires about two hours (Note 2). The reaction is practically complete when all the halide has been added, but stirring should be continued for fifteen minutes longer.

A solution of 156 g. (1.32 moles) of ethyl carbonate (Note 3) in 200 cc. of ether is added to the Grignard reagent, with rapid stirring, over a period of approximately three hours. The reaction is vigorous, and the ether refluxes continually. After all the diethyl carbonate has been added, the flask is heated on a water bath and stirring is continued for another hour.

The reaction mixture is hydrolyzed by pouring it, with frequent shaking, into a 5-l. round-bottomed flask containing 1.5 kg. of cracked ice and a solution of 300 g. of ammonium chloride in 600 cc. of water. The ether layer is separated in a large separatory funnel, and the aqueous residue is extracted with two 500-cc. portions of ether (Note 4).

The ether is distilled from the combined extracts, and the crude triethyl carbinol is dried with 10 g. of anhydrous potassium carbonate. The alcohol is then distilled at atmospheric pressure, and the portion (80–90 g.) boiling at 139–142° is collected. The low-boiling distillate is treated with 5 g. of anhydrous potassium carbonate, filtered, and redistilled, whereby another portion (about 25 g.) of triethyl carbinol boiling at 139–142° is obtained. The process is repeated once, or twice if necessary, and an additional 20 g. is collected (Note 5). The total yield is 125–135 g. (82–88 per cent of

the theoretical amount) (Note 6). Triethyl carbinol is a viscous liquid with a penetrating, camphor-like odor.

2. Notes

1. The ethyl bromide used in this preparation was dried over calcium chloride and then distilled from phosphorus pentoxide. The fraction boiling at 38–39° was collected. Directions for preparing ethyl bromide are given in Org. Syn. Coll. Vol. I, **1941**, 29, 36.
2. The time of addition may be decreased by cooling the flask externally. A towel is folded in a narrow strip and wrapped about the flask above the ether line, and cracked ice is packed on top of the flask. This arrangement allows the ether vapor to be condensed without appreciable cooling of the reaction mixture.
3. The commercial "99 per cent" ester was used. It was purified according to the description given in Note 2 on p. 283 above.
4. The ether used for extraction may be obtained by distilling the ether from the triethyl carbinol solution.
5. In checking this preparation the first drying was allowed to continue for fifteen hours. The first fractionation of the carbinol yielded 122 g., the second 10 g., and the third yielded none.
6. The preparation of homologous trialkyl carbinols by use of the Grignard reagent and ethyl carbonate was found to be very satisfactory. The following compounds were prepared: tri-*n*-propyl carbinol (b.p. 89–92°/20 mm.) in 75 per cent yield; tri-*n*-butyl carbinol (b.p. 129–131/20 mm.) in 84 per cent yield; tri-*n*-amyl carbinol (b.p. 160–164°/19 mm.) in 75 per cent yield; and tri-*n*-heptyl carbinol (b.p. 195–200°/6 mm.) in 72 per cent yield.

3. Discussion

Triethyl carbinol has been prepared by the action of zinc on a mixture of ethyl iodide and diethyl ketone;[1] by the action of magnesium on ethyl bromide in diethyl ketone solution;[2] by the action of sodium and ethyl bromide on diethyl ketone or ethyl propionate;[3] as a by-product in the reaction between ethylmagnesium bromide and carbon oxysulfide;[4] and by the action of ethylmagnesium bromide on ethyl propionate,[5] ethyl chloroformate, [6] ethyl cyanoformate, [7] or ethyl carbonate.[8]

References and Notes

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2. Davies and Kipping, J. Chem. Soc. **99**, 298 (1911).
3. Morton and Stevens J. Am. Chem. Soc. **53**, 2247 (1931).
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5. Schreiner, J. prakt. Chem. (2) **82**, 295 (1910); Böeseken and Wildschut, Rec. trav. chim. **51**, 169 (1932).

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

carbon oxysulfide

Grignard reagent

calcium chloride (10043-52-4)

potassium carbonate (584-08-7)

ether (60-29-7)

ammonium chloride (12125-02-9)

magnesium, magnesium turnings (7439-95-4)

Ethyl bromide (74-96-4)

zinc (7440-66-6)

sodium (13966-32-0)

ethyl chloroformate (541-41-3)

ethylmagnesium bromide (925-90-6)

Ethyl iodide (75-03-6)

ethyl carbonate

ethyl propionate (105-37-3)

ethyl cyanoformate (623-49-4)

TRIETHYL CARBINOL, 3-Pentanol, 3-ethyl- (597-49-9)

diethyl carbonate (105-58-8)

diethyl ketone (96-22-0)

phosphorus pentoxide (1314-56-3)

tri-n-propyl carbinol (2198-72-3)

tri-n-butyl carbinol (597-93-3)

tri-n-amyl carbinol

tri-n-heptyl carbinol

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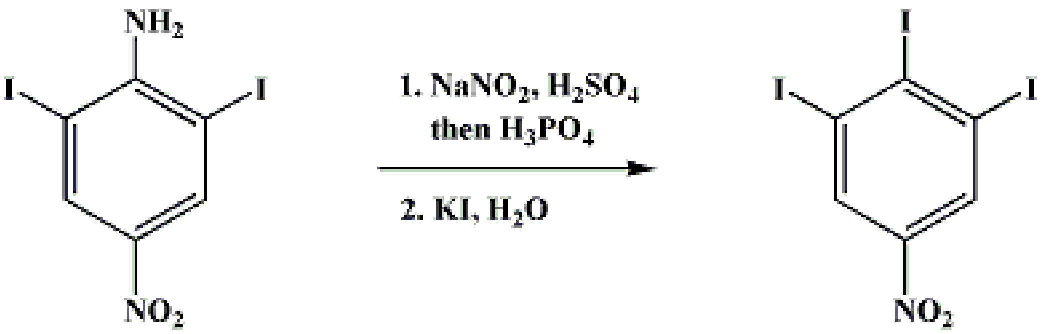
Organic Syntheses, CV 2, 604

1,2,3-TRIIODO-5-NITROBENZENE

[Benzene, 1,2,3-triiodo-5-nitro-]



Submitted by R. B. Sandin and T. L. Cairns.
Checked by Frank C. Whitmore and L. H. Sutherland.

1. Procedure

Fifty grams (0.13 mole) of 2,6-diiodo-4-nitroaniline (p. 196) is dissolved in 200 cc. of concentrated sulfuric acid (sp. gr. 1.84) in a 1-l. two-or three-necked flask provided with a mechanical stirrer. The solution is cooled to 5° in an ice-salt mixture, and to it is added with stirring a mixture of 100 cc. of concentrated sulfuric acid and 12 g. (0.17 mole) of sodium nitrite, also cooled to 5° (Note 1). To liberate nitrous acid from the nitrosylsulfuric acid, there is then added slowly from a separatory funnel, with rapid stirring, 200 cc. of 85 per cent phosphoric acid (151 cc. of u.s.p. phosphoric acid diluted to 200 cc.). During the addition the temperature is kept below 10°. The mixture is removed from the ice-salt bath and stirred until diazotization is complete (one to two hours) (Note 2). At the end of this time the solution is poured, with stirring, into 2 l. of a mixture of cracked ice and water in a 4-l. beaker. To destroy excess nitrous acid about 15 g. of urea is added in small portions, with stirring, as long as gas is produced. The mixture is filtered if it is not clear and is then treated gradually with a solution of 30 g. (0.18 mole) of potassium iodide in 200 cc. of water. To complete the reaction the mixture is heated until no more gas is evolved. Any free iodine is removed by sodium bisulfite, and the mixture is then filtered on a Büchner funnel, washed free from sulfuric acid and inorganic salts, pressed, and sucked as dry as possible. The product is then air dried to constant weight. The yield of light brown, crude material, m.p. 160–162°, is 60–61 g. (94–95 per cent of the theoretical amount). The pure product can be obtained by dissolving the crude material in 200 cc. of boiling benzene, filtering, and cooling the filtrate to 10°. The yield of yellow crystals melting at 161–162° is 40–42 g. (65–70 per cent recovery) (Note 3).

2. Notes

1. The sodium nitrite must be finely powdered and added slowly with vigorous

stirring to the sulfuric acid, which is kept at 5° in an ice-salt mixture. The evolution of oxides of nitrogen during the addition of the nitrite must be avoided.

2. During this time the temperature of the mixture gradually rises to that of the room. When diazotization is complete a drop of the mixture will form a clear yellow solution if added to 10 cc. of cold water.

3. It has been reported that the procedure of Hodgson and Walker[1] is preferable to that described above, and that crude triiodonitrobenzene is best purified by crystallization from cellosolve. [Carl Niemann and C. E. Redemann, private communication, and J. Am. Chem. Soc. **63**, 1550 (1941).]

3. Discussion

1,2,3-Triiodo-5-nitrobenzene has been prepared by the diazotization of 2,6-diiodo-4-nitroaniline (without the use of phosphoric acid) and subsequent treatment with potassium iodide.[1] The present procedure is an example of a general method developed by Schoutissen[2] for diazotization of weakly basic amines, such as the 2,6-dihalogen derivatives of *p*-nitroaniline.

References and Notes

1. Willgerodt and Arnold, Ber. **34**, 3343 (1901); Kalb, Schweizer, Zellner, and Berthold, ibid. **59**, 1866 (1926); Harington and Barger, Biochem. J. **21**, 175 (1927); Hodgson and Walker, J. Chem. Soc. **1933**, 1620.
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

oxides of nitrogen

2,6-dihalogen derivatives of p-nitroaniline

sulfuric acid (7664-93-9)

Benzene (71-43-2)

potassium iodide (7681-11-0)

sodium nitrite (7632-00-0)

nitrous acid (7782-77-6)

sodium bisulfite (7631-90-5)

iodine (7553-56-2)

phosphoric acid (7664-38-2)

cellosolve (107-21-1)

urea (57-13-6)

nitrosylsulfuric acid (7782-78-7)

2,6-Diiodo-4-nitroaniline (5398-27-6)

1,2,3-TRIIODO-5-NITROBENZENE, Benzene, 1,2,3-triiodo-5-nitro- (53663-23-3)

triiodonitrobenzene

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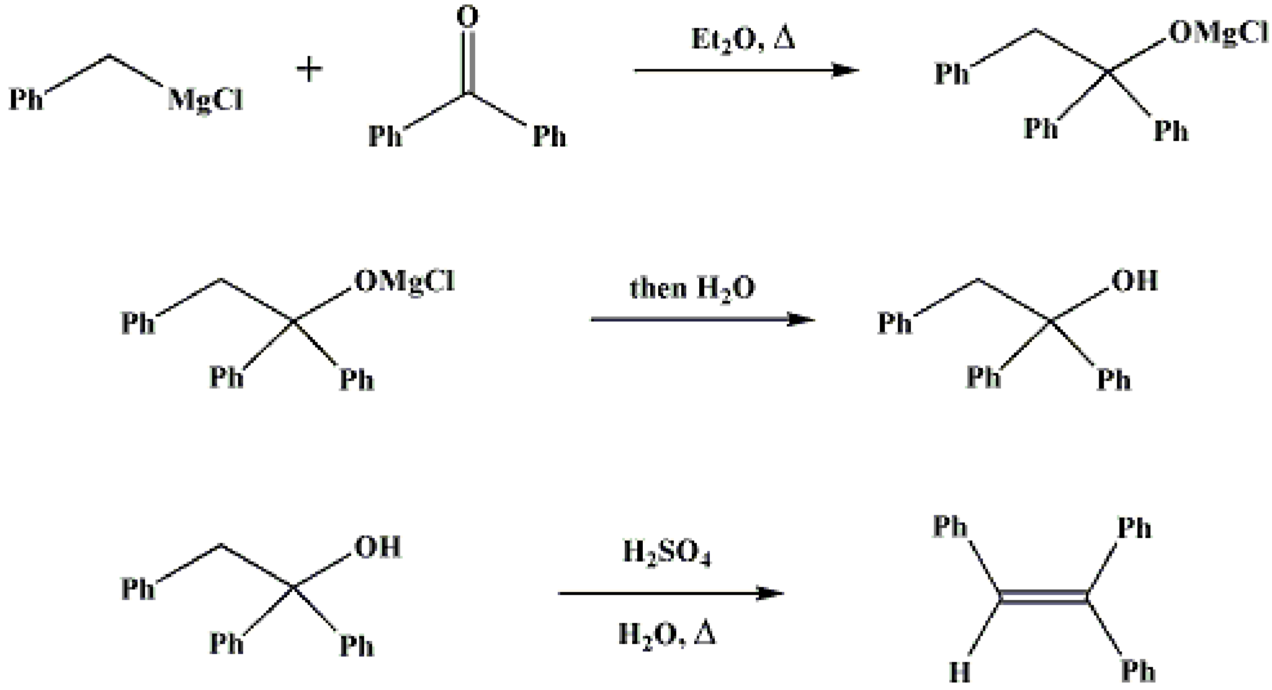
Organic Syntheses, CV 2, 606

TRIPHENYLETHYLENE

[Ethylene, triphenyl-]



Submitted by Homer Adkins and Walter Zartman.
Checked by C. R. Noller and F. M. McMillan.

1. Procedure

In a 3-l. three-necked flask, fitted with a mechanical stirrer, a reflux condenser, and a separatory funnel, are placed 24.3 g. (1 gram atom) of magnesium turnings, 500 cc. of absolute ether, a crystal of iodine, and a 5- to 10-cc. portion of 126.5 g. (115 cc., 1 mole) of freshly distilled benzyl chloride (b.p. 177–179°). In a few minutes the reaction starts (Note 1) and is controlled if necessary by cooling with a wet towel. The stirrer is started, and the balance of the benzyl chloride is run in as fast as the refluxing will permit. The addition requires from one to two hours, and when completed the mixture is refluxed on the steam bath with stirring for three hours. With the stirrer still running, 182 g. (1 mole) of benzophenone (Org. Syn. Coll. Vol. I, **1941**, 95) dissolved in 500 cc. of absolute ether is added at such a rate that the mixture refluxes rapidly. This requires about twenty minutes, and then the reaction mixture is allowed to stand for two hours (Note 2).

The flask is placed in an ice bath, 700 g. of cracked ice is added, and the magnesium hydroxide is dissolved by adding 500 cc. of cold 20 per cent sulfuric acid. The ether layer is separated, and the water layer extracted with two 200-cc. portions of ether. The ether is distilled from the combined extracts, and the residual liquid is refluxed for two hours with 100 cc. of 20 per cent sulfuric acid to dehydrate the carbinol. The layers are separated and the product vacuum-distilled (Note 3). The fraction boiling at 215–225°/15 mm. weighs 160–170 g. and melts at 60–68° (Note 4). Crystallization from 900 cc. of hot 95 per cent

alcohol and cooling to 0° gives 140–150 g. of the hydrocarbon melting at 68–69° (54–59 per cent of the theoretical amount). Concentration of the mother liquor to 150 cc. and cooling gives 5–10 g., m.p. 65–67.5° (Note 5).

2. Notes

1. If the reaction does not start within thirty minutes, the mixture is warmed on a water bath with the stirrer running.
2. Slightly better yields are obtained if the reaction mixture is allowed to stand overnight.
3. The product should not be washed with water as the presence of a trace of sulfuric acid during the distillation seems to be necessary to complete the dehydration.
4. Seeding is usually necessary to induce crystallization.
5. By the same procedure, stilbene may be prepared from benzaldehyde and benzylmagnesium chloride in 25–35 per cent yield.

3. Discussion

Triphenylethylene has been prepared by the reaction between phenylmagnesium bromide and desoxybenzoin or ethyl phenylacetate;[1] and by the reaction between diphenylketene-quinoline and benzaldehyde.[2] The procedure given above is an adaptation of that published by Hell and Wiegandt.[3] The intermediate diphenylbenzylcarbinol can be dehydrated very effectively by heating with potassium bisulfate or by boiling its solution in glacial acetic acid.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 952

References and Notes

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2. Staudinger and Kon, Ann. **384**, 89 (1911).
3. Hell and Wiegandt, Ber. **37**, 1429 (1904).
4. Van de Kamp and Sletzinger, J. Am. Chem. Soc. **63**, 1880 (1941).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Desoxybenzoin

diphenylketene-quinoline

alcohol (64-17-5)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

ether (60-29-7)

magnesium turnings (7439-95-4)

potassium bisulfate (7646-93-7)

benzaldehyde (100-52-7)

iodine (7553-56-2)

Benzophenone (119-61-9)

benzyl chloride (100-44-7)

benzylmagnesium chloride (6921-34-2)

magnesium hydroxide

Phenylmagnesium bromide (100-58-3)

Ethyl phenylacetate (101-97-3)

Triphenylethylene, Ethylene, triphenyl- (58-72-0)

stilbene

diphenylbenzylcarbinol (4428-13-1)

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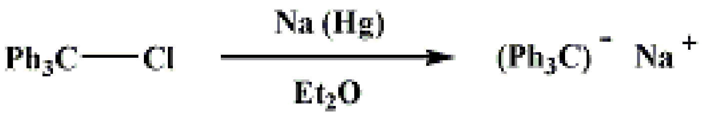
TRIPHENYLMETHYLSODIUM

[Sodium, triphenylmethyl-]



Submitted by W. B. Renfrow Jr and C. R. Hauser.
Checked by Lee Irvin Smith and E. C. Ballard.

1. Procedure

A solution of 63 g. (0.226 mole) of pure triphenylchloromethane (Note 1) in 1.5 l. of pure anhydrous ether is prepared in a 2-l. bottle provided with a tight ground-glass stopper, and 1150 g. of freshly prepared 1 per cent sodium amalgam (0.5 gram atom of sodium) is added (Note 2). The stopper is greased with a small amount of Lubriseal and the bottle is stoppered tightly. The bottle is clamped firmly in a mechanical shaker and shaken vigorously. The reaction is strongly exothermic, and the bottle should be cooled with wet towels during the shaking operation. A persistent blood-red color develops rapidly, generally within ten minutes. After shaking for three hours *the bottle is cooled to room temperature*, removed from the shaker, and allowed to stand undisturbed until the sodium chloride has settled (Note 3).

The ether solution of triphenylmethylsodium is separated from the sodium chloride and amalgan by the following procedure. The stopper of the reaction bottle is removed and replaced immediately by a closely fitting two-holed cork carrying a short glass tube that protrudes about 1 cm. into the bottle, and a long glass tube bent into an inverted U-shape. The short tube is connected through a drying train to a cylinder of nitrogen. One arm of the U-tube reaches to within about 4 cm. of the bottom of the bottle, and the other end extends just below the bottom of a two-holed cork that is fitted tightly into a 2-l. Erlenmeyer flask. The flask is filled with nitrogen and serves as receiver for the decanted solution. The cork of the Erlenmeyer flask is provided with a short-stemmed separatory funnel which serves to release nitrogen during the decantation and may be used subsequently to introduce reactants (Note 4). The corks are sealed by a coating of paraffin-wax. The stopcock of the dropping funnel is opened slightly, and the ether solution of triphenylmethylsodium is forced slowly and steadily into the nitrogen-filled flask by means of a small pressure of nitrogen from the cylinder. With proper adjustment of the height of the glass tube above the surface of the sodium chloride and amalgam, it is possible to remove all but 50 to 75 cc. of the ether solution.

If a good grade of triphenylchloromethane and freshly prepared amalgam are used the yield of triphenylmethylsodium is almost quantitative. The solution may be analyzed approximately, as follows: A 50-cc. aliquot portion is allowed to flow into 25 cc. of

water in a separatory funnel. The aqueous layer is drawn off and the ether solution washed with three 25-cc. portions of water. The aqueous solutions are combined, boiled to expel ether, and titrated with 0.2 *N* sulfuric acid, methyl red being used as indicator.

2. Notes

1. A good grade of triphenylchloromethane, m.p. 112–113°, should be used. The commercial product may be recrystallized conveniently from a mixture of five parts of ligroin (b.p. 90–110°) and one part of acetyl chloride, using about 1.8 g. of solvent per gram of material. Directions for preparing triphenylchloromethane are given in Volume 23 of this series.
2. A 1 per cent sodium amalgam is prepared by cutting 11.5 g. (0.5 gram atom) of sodium into pieces about 5 mm. square and dissolving them, one at a time, in 1150 g. of purified mercury. A piece of sodium is speared on the sharpened end of a long glass rod and thrust quickly beneath the surface of the mercury, in a 500-cc. wide-mouthed Erlenmeyer flask. To avoid damage from flying pieces of sodium resulting from the vigorous reaction, the glass rod is inserted through a piece of heavy cardboard which serves to cover the mouth of the flask during the reaction.
3. If solid 3 per cent sodium amalgam is used, solutions containing almost 0.67 mole of triphenylmethylsodium per liter—about five times as concentrated as the solution described in the procedure above—can be prepared.
One and seven-tenths kilograms of 3 per cent sodium amalgam (2.2 gram atoms of sodium) is prepared by adding 1649 g. of mercury to 51 g. of molten sodium under mineral oil—compare Org. Syn. Coll. Vol. I, **1941**, 554, Note 1. The amalgam while still hot is poured into a large evaporating dish and left to cool. It is then transferred to a large iron mortar, broken into pieces about 1 mm. on a side, washed free from oil with ligroin, and placed in a 2-l. glass-stoppered bottle. One and one-half liters of dry ether and 278 g. (1 mole) of triphenylchloromethane are added, and the glass stopper, greased with Lubriseal, is inserted. The bottle is shaken in a mechanical shaker until no solid amalgam remains, and then for two hours longer. If the shaker has a 4- to a 5-in. stroke and makes three to four strokes per second, the total time on the shaker is from five to eight hours. With less effective shaking, more time is required. The reaction is sufficiently slow so that cooling with towels is unnecessary. The rest of the procedure is the same as that on p. 608. (Private communication from Charles R. Hauser and Boyd E. Hudson, Jr. Checked by Lee Irvin Smith and R. W. Liggett.)
4. Triphenylmethylsodium is a useful reagent for the preparation of the sodium derivatives of very weak acids (aliphatic esters, acid anhydrides, etc.). An example of this procedure, using ethyl isobutyrate, is given on p. 268.

3. Discussion

The procedure described above is a modification of the method of Schlenk and Ochs.[1]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 268
- Org. Syn. Coll. Vol. 6, 461

References and Notes

1. Schlenk and Ochs, Ber. **49**, 608 (1916).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ligroin

Methyl Red

sulfuric acid (7664-93-9)

ether (60-29-7)

acetyl chloride (75-36-5)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

mercury (7439-97-6)

sodium (13966-32-0)

Triphenylchloromethane (76-83-5)

Triphenylmethylsodium, Sodium, triphenylmethyl- (4303-71-3)

ethyl isobutyrate (97-62-1)

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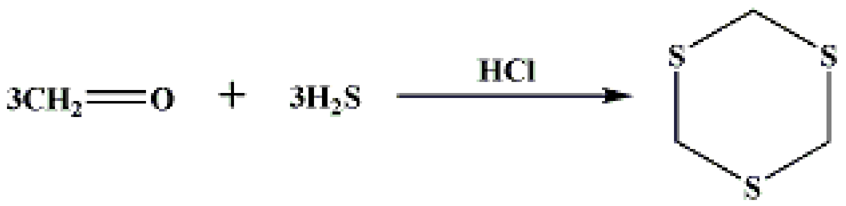
Organic Syntheses, CV 2, 610

sym.-TRITHIANE



Submitted by R. W. Bost and E. W. Constable.
Checked by Reynold C. Fuson and C. F. Woodward.

1. Procedure

A mixture of 326 g. (3.9 moles) of a 36 per cent formaldehyde solution (Note 1) and 700 cc. of concentrated hydrochloric acid (sp. gr. 1.18) is placed in a tall glass cylinder (Note 2), and hydrogen sulfide is passed through the solution until no more precipitate is formed. In order to facilitate the process, the accumulated mass of crystals is removed from time to time by filtration. The time required for completion of the reaction varies from twelve to twenty-four hours. A crude yield of 176 g. (98 per cent of the theoretical amount) of fine, nearly colorless needles melting at 210–213° is obtained.

The product is purified by the inverted filtration method. The apparatus used is shown in .htmFig. 20. A 2-l. round-bottomed flask is equipped with a reflux condenser and a bent glass tube, 8–10 mm. in diameter (Note 3). To the lower end of this tube is attached, by means of a cork, a 25-mm. tip prepared from a paper Soxhlet thimble and packed with glass wool. A 2-l. conical flask serves as a receiver for the hot filtrate.

Fig. 20

Fig. 20

The crude product is placed in the round-bottomed flask, 1 l. of benzene is added, and heat is applied until the solvent boils vigorously. After a few minutes the source of heat is withdrawn and the mixture is allowed to become quiet. The filtering thimble, which up to this point is kept at the top of the flask (see .htmFig. 20), is now lowered to its normal position and the conical flask is attached. Gentle suction is applied, and the liquid is drawn over into the conical flask. The hot solution is removed, allowed to cool, and filtered. In the meantime, the extraction process is repeated with a second 1-l. portion of benzene. The two portions of benzene are used alternately over and over in the manner described until all the crude product has been recrystallized. This requires about ten separate extractions, using each 1-l. portion of benzene five times.

The yield of pure product, melting at 214–215°, is 165–169 g. (92–94 per cent of the theoretical amount).

2. Notes

1. The formaldehyde content of the solution is determined by analysis, for which the iodimetric method of Borgstrom and Horsch[1] is recommended. The yield is calculated upon the basis of the amount of formaldehyde actually present, as shown by analysis. Since commercial solutions of formaldehyde contain methyl alcohol, the formaldehyde present cannot be estimated accurately by reference to specific-gravity tables—compare Org. Syn. Coll. Vol. I, **1941**, 378, Note 1.
2. A tall cylindrical vessel ensures good contact between the solution and the gas bubbling through it. Hydrogen sulfide from a commercial cylinder was used.
3. Successful use of the inverted filtration method requires attention to these details: (*a*) use of a sufficiently wide transfer tube; (*b*) minimum exposure of tubing between the flasks; (*c*) rapid transfer of the hot solution; (*d*) avoidance of too strong an application of suction.

The inverted filtration device is convenient for simple recrystallizations as well as repeated extractions. It is of particular advantage for the manipulation of volatile, inflammable solvents and of lachrymatory solutions.

3. Discussion

sym.-Trithiane has been prepared by treating carbon bisulfide,[2] ethyl isothiocyanate,[3] or potassium thiocyanate[3] with zinc and hydrochloric acid; by heating methylene iodide with alcoholic sodium hydrosulfide;[4] and by treating aqueous formaldehyde with hydrogen sulfide and concentrated hydrochloric acid.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 443
- Org. Syn. Coll. Vol. 2, 590
- Org. Syn. Coll. Vol. 4, 560

References and Notes

1. Borgstrom and Horsch, J. Am. Chem. Soc. **45**, 1493 (1923).
2. Girard, Compt. rend. **43**, 396 (1856); Ann. **100**, 306 (1856).
3. Hofmann, Ber. **1**, 176, 179 (1868).
4. Husemann, Ann. **126**, 293 (1863).
5. Hofmann, ibid. **145**, 360 (1868); Baumann, Ber. **23**, 67 (1890).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

methyl alcohol (67-56-1)

formaldehyde (630-08-0)

hydrogen sulfide (7783-06-4)

zinc (7440-66-6)

potassium thiocyanate (333-20-0)

Methylene iodide (75-11-6)

carbon bisulfide

sodium hydrosulfide

ethyl isothiocyanate (542-85-8)

sym.-TRITHIANE (291-21-4)

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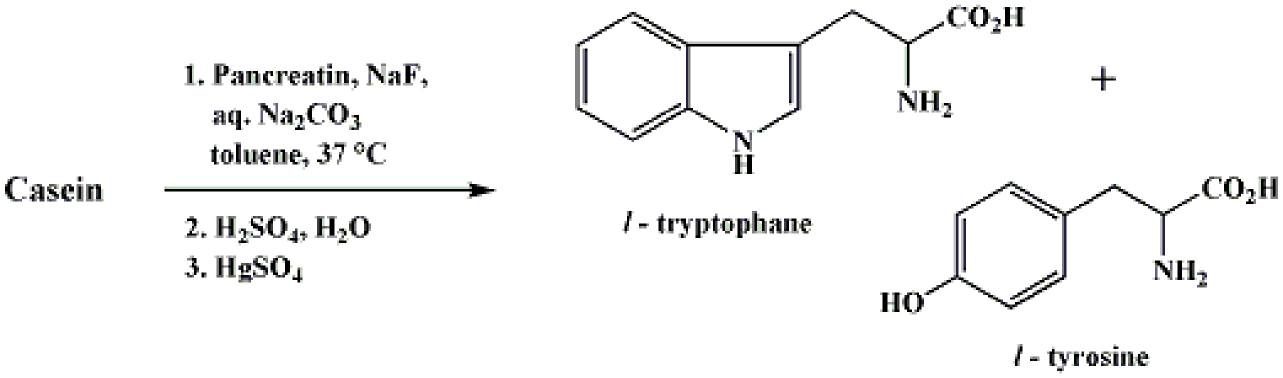
Organic Syntheses, CV 2, 612

l-TRYPTOPHANE

[By-product, *l*-Tyrosine]



Submitted by Gerald J. Cox and Harriette King.
Checked by H. T. Clarke and Jessica P. Leland.

1. Procedure

(*A*) *Tryptophane*.—In an 8-l. (2-gal.) bottle is placed 600 g. of commercial casein (coarse powder), which is then covered with about 3.2 l. of tap water at 37° (Note 1). The bottle is shaken until all the casein is moistened. A solution of 60 g. of anhydrous sodium carbonate (Note 2) and 6 g. of sodium fluoride (Note 3) in 1 l. of water at 37° is added. A thin paste of 20 g. of commercial pancreatin in 100 cc. of water (37°) is poured in. The mixture is covered with a layer of toluene (80 cc.), diluted to 6 l., stoppered, shaken thoroughly, and placed in a warm room or bath at 37°.

After four or five days, with daily shakings, most of the casein is in solution and chalky masses of tyrosine begin to separate. After five days, a second 20-g. portion of pancreatin in 100 cc. of water is added. After twelve days, the bottle is cooled in an icebox overnight and the undissolved material is filtered (Note 4) and reserved for the preparation of tyrosine.

The filtrate (6.9–7 l.) is measured into a 16-l. (4-gal.) stone jar, and for every liter there is added 163 cc. of dilute sulfuric acid (one volume of 95 per cent sulfuric acid and one volume of water, cooled to room temperature). The first part of the acid must be added cautiously on account of the liberation of carbon dioxide.

The tryptophane is precipitated by adding a solution of 200 g. of mercuric sulfate (Note 5) in a mixture of 1860 cc. of water and 140 cc. of 95 per cent sulfuric acid. After standing for twenty-four to forty-eight hours, the clear liquid is siphoned out and the yellow precipitate is filtered and washed (Note 6) with a solution of 100 cc. of concentrated sulfuric acid in 1.9 l. of distilled water containing 20 g. of mercuric sulfate, until the filtrate is colorless and Millon's test is atypical (Note 7); about 1.5 l. is necessary. The precipitate is washed with three successive 500-cc. portions of distilled water to remove most of the sulfuric acid.

The moist precipitate (120–130 g.) is suspended with mechanical stirring in 1.2–1.3 l. of distilled water, and a hot, 20 per cent aqueous solution of barium hydroxide is added until the mixture is permanently alkaline to phenolphthalein (about 120 cc. is required). A rapid stream of hydrogen

sulfide is passed in with stirring until the mercury is completely precipitated (Note 8). The precipitate is filtered and washed with water until a sample of the washings gives a negative test for tryptophane with bromine water (Note 9). The barium is removed from the combined filtrate and washings by adding the exact amount of dilute sulfuric acid (Note 10) and filtering. The filtrate is concentrated under reduced pressure to about 80 cc.

The tryptophane is extracted from the aqueous solution by repeated shaking in a separatory funnel with 25-cc. quantities of *n*-butyl alcohol; water is added from time to time to keep the volume approximately constant (Note 11). The butyl alcohol extract is distilled under reduced pressure. After the water present has distilled, the tryptophane precipitates in the distilling flask and may cause bumping. When all the water has been removed, as is indicated by non-formation of drops on the side of the condenser, the distillation is stopped and, after cooling, the tryptophane is filtered and washed with a little fresh butyl alcohol. Such extractions and distillations are continued until the quantities of tryptophane obtained are negligibly small (Note 11).

The tryptophane so produced (7–8 g.) varies somewhat in quality in different runs. It is purified by recrystallization from 60 cc. of dilute alcohol (two volumes of 95 per cent alcohol to one volume of water), filtering from the hot solution an appreciable quantity of insoluble matter, and subjecting this to a second extraction with an additional 10 cc. of aqueous alcohol. The solution is decolorized by the addition of 1 g. of Norite and allowed to stand in the icebox; the silvery leaflets of tryptophane are filtered and washed successively with cold 70 per cent, 80 per cent, 95 per cent alcohol, and, finally, with a little ether. Less than half the tryptophane is obtained in each crystallization (Note 12). The yield of pure (Note 13) tryptophane is 4.0–4.1 g., together with under 0.1 g. of less pure product.

(*B*) *Tyrosine*.—The insoluble material (160–170 g.) obtained on filtering the digestion mixture (p. 612) is suspended in 320 cc. of water and 80 cc. of 36 per cent hydrochloric acid, and the mixture is boiled gently for thirty minutes (Note 14). After straining through cheesecloth, decolorizing with 6 g. of Norite (Note 15), and filtering hot (Note 16), the warm (60–70°) solution is shaken with three 20-cc. portions of benzene (Note 17) and heated to boiling (Note 18). A slight excess (120–150 cc.) of 28 per cent ammonia is cautiously added, and the mixture is allowed to stand overnight in the icebox. The crystalline product is then filtered and washed with three 40-cc. portions of ice-water. After drying, it weighs about 23 g. The mother liquor and washings are evaporated to about 200 cc., when a second crop is obtained, weighing slightly under 1 g.

The combined product is suspended in 400 cc. of water and dissolved by adding 8 g. of sodium hydroxide in 20–30 cc. of water (Note 19); 2 g. of Norite is added, and the solution filtered. The residue is washed on the funnel with 20–30 cc. of hot distilled water. The filtrate is heated to boiling (Note 18) and treated with 13 cc. of hydrochloric acid (Note 20), when crystallization usually begins. The mixture is then acidified to litmus with acetic acid (Note 21) and allowed to stand overnight in the refrigerator. The resulting tyrosine is filtered and washed with ice-cold distilled water (130–150 cc. is necessary) until the washings are free of chloride. The product is dried in air or in a vacuum oven. The yield is 17.0–18.2 g. of pure white, silky needles of tyrosine. A second crop (about 0.5 g.) of a slightly less pure product may be obtained on concentrating the mother liquor to about 120 cc.

2. Notes

1. Tryptic action is more rapid if all water used is at 37°. Distilled water is not necessary at this stage.
2. This is a considerable excess of sodium carbonate. Smaller quantities might be satisfactory.
3. The sodium fluoride probably inhibits the action of the oxidases.
4. This filtration may be slow. Büchner funnels of 20-cm. diameter are best used; the material from a single filling is allowed to suck dry and the filter paper then changed.
5. Approximately this quantity of mercuric sulfate is necessary to precipitate the tryptophane completely, as judged by the Hopkins-Cole glyoxylic acid test.
6. This washing is to remove tyrosine, which is precipitated as a mercury compound somewhat more soluble than the tryptophane precipitate. The mercuric sulfate addition tends to reduce the tryptophane solubility.
7. A persistent red color is always obtained in the filtrates, but the final color is distinctly different from that due to tyrosine.
8. Excess hydrogen sulfide must remain in the solution after standing. A sample of the filtrate, after acidifying with acetic acid, should give a copious black preciptate with lead acetate.
9. The bromine water test is somewhat more satisfactory for pure tryptophane than the glyoxylic acid test. Hydrogen sulfide may interfere (owing to sulfur formation) and must be boiled out first. The solution to be tested must be acid with acetic acid.
10. This amount is best determined in a 20-cc. aliquot sample, employing 2 per cent sulfuric acid in a buret.
11. In checking, it was found satisfactory to extract in a continuous apparatus .htm(Fig. 21). Extraction is continued until the liquid in the flask begins to bump on account of the separation of solid; a new charge of butyl alcohol is then employed, about five charges being necessary. This process is repeated until the residue after a three-hour period of extraction fails to give the red color, characteristic of tryptophane, with bromine water. The time necessary, of course, depends upon the rate of boiling; in checking, it was found to be twenty-eight to thirty hours.

Fig. 21

Fig. 21

12. The recrystallization of the crude tryptophane is an extremely troublesome process. Not only must a less soluble by-product be removed, but the mother liquors contain a more soluble, gummy impurity in considerable proportion. After collecting each crop, the mother liquor must be evaporated to a small volume on the steam bath and treated with a double volume of alcohol. This process is repeated until no further crystals are obtained, but only a gum.
13. The purity of the tryptophane has been checked by the optical rotation ($[\alpha]_D$ = –28 to –33°) and by analysis for amino nitrogen (6.8–6.9 per cent) by Van Slyke's method.
14. The boiling acid solution hydrolyzes protein material that otherwise greatly retards filtration.
15. The Norite used in this preparation is insufficient to decolorize the solutions completely but gives a white final product.
16. All the filtrations in the purification of tyrosine, except possibly the last, are best done on a 20-cm. Büchner funnel. Whenever charcoal is used, kieselguhr may be employed to obtain a clear filtrate.
17. Benzene extracts traces of substances, probably fatty acid, that retard filtration and

greatly alter the quality of the final product.
18. The tyrosine crystallizes in long, silky needles, easy to filter, if the solution is neutralized at the boiling point.
19. A small amount of flocculent impurity remains undissolved.
20. The hydrochloric acid is added to provide chloride ion as an index of complete washing.
21. Tyrosine is very slightly soluble in all concentrations of acetic acid. Therefore any excess of acetic acid does not redissolve the tyrosine.

3. Discussion

The above procedure for preparing tryptophane is an adaptation from the methods of Hopkins and Cole,[1] Dakin,[2] and Onslow.[3]

Tyrosine, as a primary product, may be readily prepared by hydrolyzing silk with hydrochloric acid, neutralizing the acid with sodium hydroxide, and finally acidifying with acetic acid.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 325

References and Notes

1. Hopkins and Cole, J. Physiol. **27**, 418 (1902).
2. Dakin, Biochem. J. **12**, 302 (1918).
3. Onslow, ibid. **15**, 392 (1921).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

bromine water

dilute alcohol

aqueous alcohol

alcohol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ammonia (7664-41-7)

Benzene (71-43-2)

ether (60-29-7)

sodium hydroxide (1310-73-2)

hydrogen sulfide (7783-06-4)

sodium carbonate (497-19-8)

sulfur (7704-34-9)

mercury (7439-97-6)

carbon dioxide (124-38-9)

butyl alcohol, n-butyl alcohol (71-36-3)

Norite (7782-42-5)

toluene (108-88-3)

lead acetate

barium hydroxide (17194-00-2)

tyrosine, L-Tyrosine (60-18-4)

mercuric sulfate (7783-35-9)

barium (7440-39-3)

phenolphthalein (77-09-8)

glyoxylic acid (298-12-4)

Tryptophane, l-TRYPTOPHANE (73-22-3)

sodium fluoride (7681-49-4)

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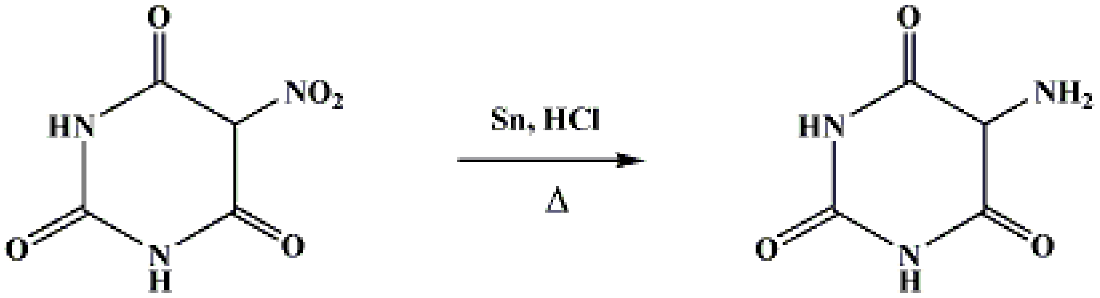
Organic Syntheses, CV 2, 617

URAMIL



Submitted by W. W. Hartman and O. E. Sheppard.
Checked by C. S. Marvel and B. H. Wojcik.

1. Procedure

In a 5-l. flask are placed 100 g. (0.44 mole) of nitrobarbituric acid (p. 440) and 600 cc. of concentrated hydrochloric acid, and the mixture is heated on a boiling water bath. To the hot mixture are added 250 g. (2.1 gram atoms) of mossy tin and 400 cc. of hydrochloric acid over a period of about thirty minutes; heating is continued until there is no yellow color in the liquid (Note 1). The solution is treated with about 3 l. more of concentrated hydrochloric acid and heated until all the white solid is in solution. Norite is added, and the hot mixture is filtered through a sintered-glass funnel (Note 2). The filtrate is allowed to stand in an icebox overnight, and then the precipitate (Note 3) of uramil is collected on a filter and washed with liberal quantities of dilute hydrochloric acid and finally with water (Note 4). The filtrate is concentrated under reduced pressure to about 1 l. and cooled overnight. The additional uramil thus obtained is collected on a Büchner funnel and added to the first product (Note 5). The uramil is dried in a desiccator over concentrated sulfuric acid, and finally over 40 per cent sodium hydroxide to remove hydrochloric acid (Note 6).

Uramil is a fine, white powder which becomes pink to red on standing. The yield of a product which does not melt below 400° is 40–46 g. (63–73 per cent of the theoretical amount).

2. Notes

1. Nitrobarbituric acid forms a yellow aqueous solution, but, as the color is weak in concentrated hydrochloric acid solution, no trace of it should show at the end of the reaction.
2. If a sintered-glass funnel is not available, the solution may be filtered through a half-inch layer of decolorizing carbon on a double filter paper. After the uramil is once dissolved in the concentrated hydrochloric acid it comes out of solution very slowly, and, if filtered promptly, the solution may be cooled to 60–

80° with little loss of product.
3. If, as happens occasionally, the uramil does not crystallize, the solution must be concentrated and cooled again.
4. Unless the product is washed thoroughly it will contain tin salts.
5. To test for uramil an ammoniacal solution is boiled in the air. A positive test is the appearance of a pink color which gradually grows deeper. The reaction proceeds more rapidly in the presence of mercuric oxide.
6. If the material is dried in the air or in an oven, a pink product is almost always obtained. The pink color is produced more rapidly if ammonia or amines are present in the air.

3. Discussion

Uramil has been obtained by boiling alloxantin with ammonium chloride;[1] by reduction of nitrosobarbituric acid or nitrobarbituric acid with hydrogen iodide;[2] and by reduction of alloxan phenylhydrazone with tin and hydrochloric acid.[3]

References and Notes

1. Wöhler and Liebig, Ann. **26**, 309 (1838).
2. Baeyer, ibid. **127**, 223 (1863).
3. Kühling, Ber. **31**, 1973 (1898).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

dilute hydrochloric acid

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ammonium chloride (12125-02-9)

sodium hydroxide (1310-73-2)

tin (7440-31-5)

mercuric oxide (21908-53-2)

decolorizing carbon, Norite (7782-42-5)

hydrogen iodide (10034-85-2)

Nitrobarbituric acid (480-68-2)

Uramil (118-78-5)

alloxantin (76-24-4)

nitrosobarbituric acid

alloxan phenylhydrazone

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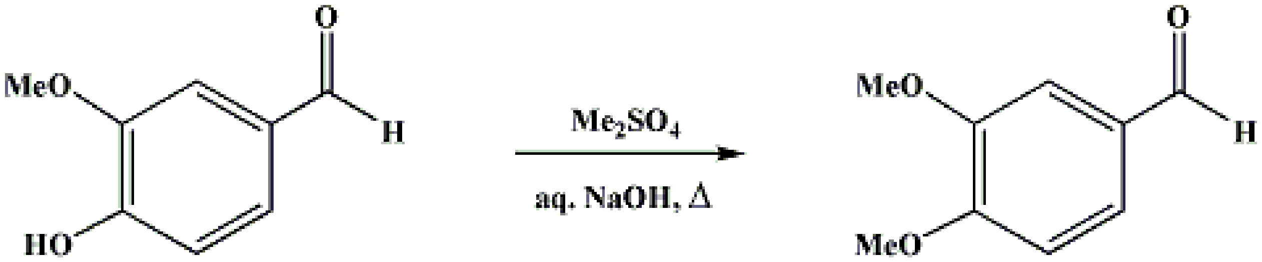
Organic Syntheses, CV 2, 619

VERATRALDEHYDE



Submitted by Johannes S. Buck
Checked by John R. Johnson and H. R. Snyder.

1. Procedure

In a 3-l. three-necked flask a mixture of 182 g. (1.2 moles) of vanillin (Note 1) and 450 cc. of boiling water is heated on a steam bath. A solution of sodium hydroxide is prepared by dissolving 150 g. of u.s.p. sodium hydroxide in 200–300 cc. of water and diluting to 750 cc. A 360-cc. portion of this solution is heated to about 100° and added in one lot to the hot mixture of vanillin and water (Note 2). The flask is now fitted with a reflux condenser, mechanical stirrer, and 250-cc. separatory funnel.

Heating is continued on a steam bath, and 189 g. (142 cc.) of methyl sulfate (Note 3) is added through the separatory funnel just rapidly enough to maintain the gentle ebullition which starts after the addition of the first 10–15 cc. (Note 4). After the addition of all the methyl sulfate, which requires about one hour, the reaction mixture is heated for forty-five minutes longer and an additional portion of 39 g. (30 cc.) of methyl sulfate is added at the same rate as the first portion. At the end of this addition the reaction mixture should show an acid reaction to litmus (Note 5). After ten minutes' heating the reaction mixture is rendered slightly alkaline by the addition of about 60 cc. of the sodium hydroxide solution (prepared above), and another 39-g. portion of methyl sulfate is added. The alternate addition of sodium hydroxide solution and of methyl sulfate (39-g. portions) is repeated twice more, so that a total of 345 g. (2.7 moles) of methyl sulfate is added. The reaction mixture is then made strongly alkaline by the addition of 150 cc. of the sodium hydroxide solution and is heated for twenty minutes after the last addition of methyl sulfate. The reaction mixture is cooled rapidly to 25° (Note 6) with continued stirring, and the veratraldehyde is extracted with three 300-cc. portions of ether.

The combined ether extracts are dried over anhydrous magnesium sulfate, and the ether is distilled. There remains a slightly yellow oil which soon solidifies. The yield is 164–173 g. (82–87 per cent of the theoretical amount) of veratraldehyde melting at 43–44.5°. This product is sufficiently pure for many purposes, but it can be purified further with slight loss by distillation under diminished pressure. From 164 g. of the above product there is obtained 156 g. of pure veratraldehyde, boiling at 153°/8 mm. and melting at 46° (Note 7). Since this aldehyde is easily oxidized in the air it should be stored in a tightly

corked or sealed container.

2. Notes

1. A good grade of vanillin (m.p. 81–82°) should be used.
2. The reactants are mixed while hot in order to avoid precipitation of the sodium salt of vanillin.
3. A practical grade of methyl sulfate gives satisfactory results. Methyl sulfate is very toxic; the vapor must not be inhaled or the liquid spilled. Ammonia is a specific antidote. The preparation is preferably carried out under a good hood.
4. The yield is usually lowered if this ebullition does not occur.
5. In order to obtain a good yield the reaction mixture must be allowed to become acid at several times. For this reason the last 156 g. of methyl sulfate is added in four small portions, and the reaction mixture is allowed to become acid after each portion is added. It is convenient to test the reaction of the solution by lowering through the condenser tube a glass tube with a piece of litmus paper attached at the end.
6. If the reaction mixture is cooled too slowly or below 25°, the veratraldehyde may solidify at this stage. If this occurs it is advisable to remelt the product before extracting with ether.
7. Veratraldehyde of sufficient purity for most synthetic purposes may be prepared rapidly and conveniently by the method of Barger and Silberschmidt, J. Chem. Soc. **133**, 2924 (1928). In a 1-l. three-necked, round-bottomed flask (or a wide-mouthed bottle), fitted with a mechanical stirrer, a reflux condenser, and two separatory funnels, 152 g. (1 mole) of vanillin is melted by warming on a steam bath. With vigorous stirring, a solution of 92 g. (1.5 moles) of 90 per cent potassium hydroxide in 150 cc. of water is run in at the rate of two or three drops a second; twenty seconds after this is started, the addition of 160 g. (120 cc., 1.25 moles) of methyl sulfate is begun at about the same rate. (Just before use, the methyl sulfate is washed with an equal volume of ice-water, followed by one-third its volume of cold, saturated sodium bicarbonate solution.) The external heating is stopped after a few minutes, and the mixture continues to reflux from the heat of reaction. A turbidity soon develops, and separation into two layers occurs after about one-half of the methyl sulfate has been added. The addition of both reagents should be completed in about twenty minutes.
The color of the reaction mixture, which is purplish brown at the beginning, changes abruptly to yellow towards the end. A temporary greenish yellow during the earlier part of the reaction indicates that the solution has become acid, and this condition should be corrected by increasing the rate of addition of the alkali. The final yellow color is permanent, and at the end the reaction mixture is alkaline to litmus.
The reaction mixture is transferred at once to a large beaker covered with a watch glass and allowed to cool without disturbance, preferably overnight. The hard, crystalline mass of veratraldehyde is removed, ground in a mortar with 300 cc. of ice-water, filtered with suction, and dried in a vacuum desiccator. The yield is 152–158 g. (92–95 per cent of the theoretical amount) of a product melting at 42.5–43.5°. This material gives a 90 per cent yield of the oxime (m.p. 89–90°) and

an overall yield of 68–70 per cent of veratronitrile (m.p. 65–66°)—compare p. 622, below. The nitrile thus produced is satisfactory for the preparation of aminoveratrole (p. 44). (John R. Johnson and H. B. Stevenson, private communication.)

3. Discussion

Veratraldehyde has been prepared by treatment of veratrole with hydrogen cyanide in the presence of aluminum chloride;[1] by condensing veratrole with formylpiperidine and hydrolyzing the product;[2] and by methylating vanillin with methyl iodide,[3] methyl sulfate,[4] methyl *p*-toluenesulfonate,[5] or trimethylphenylammonium hydroxide.[6]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 55
- Org. Syn. Coll. Vol. 2, 622
- Org. Syn. Coll. Vol. 4, 735

References and Notes

1. Gattermann, Ann. **357**, 367 (1907).
2. Akabori and Senoh, Bull. Chem. Soc. Japan **14**, 166 (1939) [C. A. **33**, 6270 (1939)].
3. Tiemann, Ber. **8**, 1135 (1875); **11**, 663 (1878); Juliusberg, ibid. **40**, 119 (1907).
4. v. Kostanecki and Tambor, ibid. **39**, 4022 (1906).
5. Kanevska, Arch. Pharm. **271**, 462 (1933).
6. Rodionow, Bull. soc. chim. (4) **45**, 116 (1929).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

oxime

ammonia (7664-41-7)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

hydrogen cyanide (74-90-8)

aluminum chloride (3495-54-3)

potassium hydroxide (1310-58-3)

Methyl iodide (74-88-4)

methyl sulfate (75-93-4)

Veratronitrile (2024-83-1)

aminoveratrole

magnesium sulfate (7487-88-9)

Veratraldehyde (120-14-9)

vanillin (121-33-5)

veratrole (91-16-7)

formylpiperidine (2591-86-8)

trimethylphenylammonium hydroxide (1899-02-1)

sodium salt of vanillin

Methyl p-toluenesulfonate (80-48-8)

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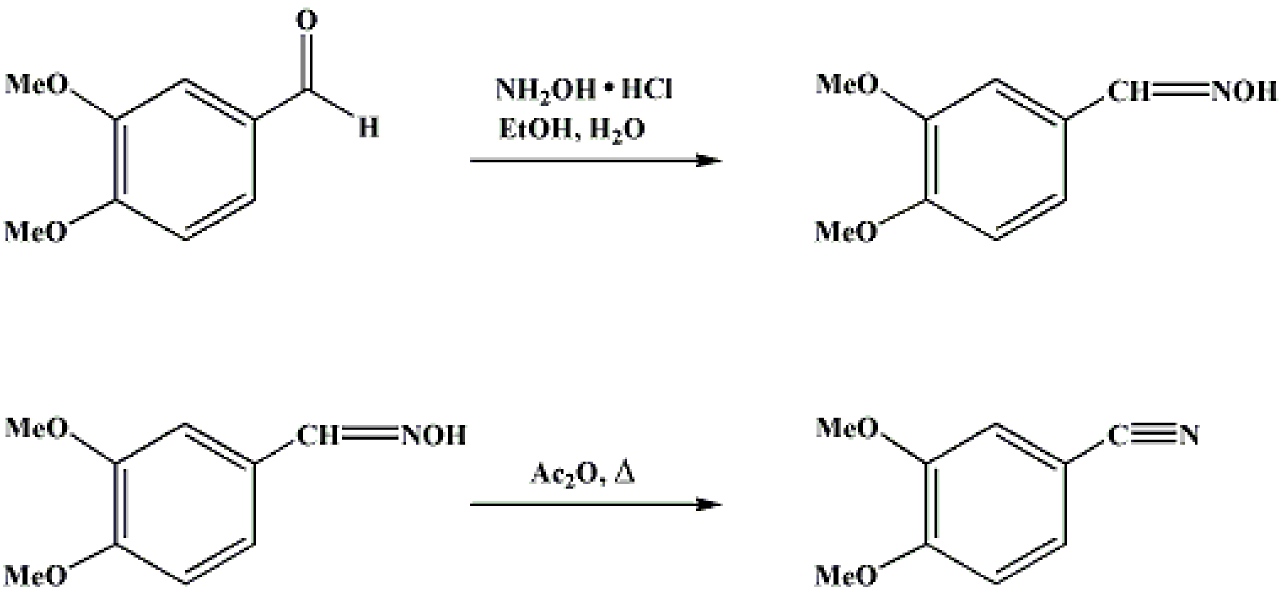
Organic Syntheses, CV 2, 622

VERATRONITRILE



Submitted by J. S. Buck and W. S. Ide.
Checked by John R. Johnson and E. Amstutz.

1. Procedure

In a 1-l. round-bottomed flask, 83 g. (0.5 mole) of veratraldehyde (p. 619) is dissolved in 200 cc. of warm 95 per cent alcohol, and a warm solution of 42 g. (0.6 mole) of hydroxylamine hydrochloride (Org. Syn. Coll. Vol. I, **1941**, 318) in 50 cc. of water is added. The two solutions are mixed thoroughly, and a solution of 30 g. (0.75 mole) of sodium hydroxide in 40 cc. of water is introduced. After the mixture has stood for two and one-half hours at room temperature, 250 g. of crushed ice is added and the solution is saturated with carbon dioxide. This causes the separation of the aldoxime as an oil which solidifies on standing overnight in an ice chest (Note 1). The crystalline oxime is filtered with suction, washed thoroughly with water, and allowed to dry in the air. The yield of oxime is 88–89 g. (97–98 per cent of the theoretical amount).

The veratraldoxime is placed with 100 g. of acetic anhydride (94–96 per cent) in a 300-cc. round-bottomed flask provided with a ground-glass air condenser (Note 2), and heated cautiously. A vigorous reaction takes place, and when this occurs the flame is removed. After the reaction has subsided the solution is boiled gently for twenty minutes and then poured carefully, with stirring, into 300 cc. of cold water. The stirring is continued, and on cooling the nitrile separates in small, almost colorless crystals, which are filtered and dried in the air. The veratronitrile thus obtained is quite pure; it weighs 57–62 g. (70–76 per cent of the theoretical amount, based upon the veratraldehyde), and melts at 66–67°.

2. Notes

1. Occasionally the oxime does not solidify after standing overnight. If this happens it is advisable to separate the oily layer, treat with crushed ice, and induce crystallization by scratching. If a seed crystal of the oxime is available no difficulty is experienced.
2. If a cork or rubber stopper is used the product is likely to be colored.

3. Discussion

Veratronitrile has been obtained from 4-aminoveratrole by diazotization and treatment with cuprous cyanide,[1] and by heating veratrylglyoxylic acid with hydroxylamine.[2] The general method employed above has been used for the preparation of a variety of substituted aromatic nitriles.[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 44
- Org. Syn. Coll. Vol. 2, 619

References and Notes

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2. Garelli, Gazz. chim. ital. **20**, 700 (1890).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alcohol (64-17-5)

acetic anhydride (108-24-7)

sodium hydroxide (1310-73-2)

Cuprous Cyanide (544-92-3)

carbon dioxide (124-38-9)

Hydroxylamine hydrochloride (5470-11-1)

hydroxylamine (7803-49-8)

4-Aminoveratrole (6315-89-5)

Veratronitrile (2024-83-1)

Veratraldehyde (120-14-9)

veratrylglyoxylic acid (2460-33-5)

veratraldoxime

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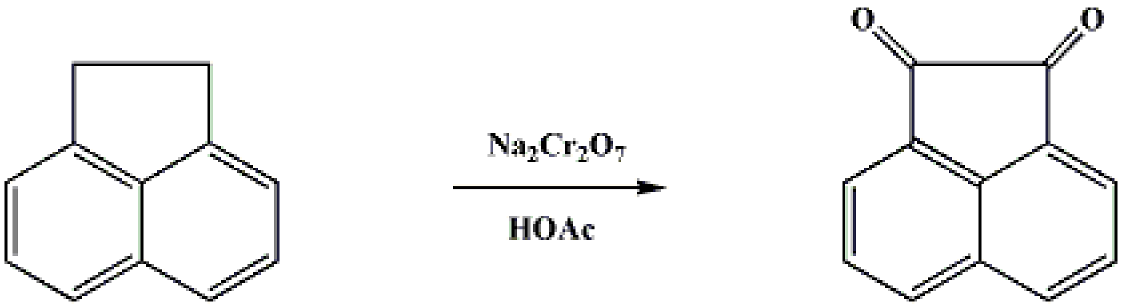
Organic Syntheses, CV 3, 1

ACENAPHTHENEQUINONE



Submitted by C. F. H. Allen and J. A. VanAllan.
Checked by L. Matternas, H. Lloyd, and E. C. Horning.

1. Procedure

A mixture of 100 g. (0.65 mole) of a technical grade of acenaphthene, 5 g. of ceric acetate (Note 1), and 800 ml. of glacial acetic acid is placed in a 4-l. stainless-steel beaker arranged for external cooling with cold water (Note 2). A thermometer and a powerful stirrer are inserted, and 325 g. (1.1 mole) of sodium bichromate dihydrate is added over a period of 2 hours, the temperature being kept at 40° (Note 3). Stirring is then continued at room temperature for an additional 8 hours; during this time the reaction mixture becomes quite thick, owing to the separation of the quinone and chromium salts. The suspension is diluted with 1.5 l. of cold water, and the solid is collected on a 10-in. Büchner funnel and washed free from acid.

The solid is next digested on the steam bath for 30 minutes with 500 ml. of a 10% sodium carbonate solution, and is filtered and washed. The solid is then extracted for 30 minutes at 80° with 1 l. of 4% sodium bisulfite solution; at the end of this period 15 g. each of Filtercel and Norit are added, and the suspension is filtered. The extraction is repeated, and the combined filtrates are acidified at 80° with constant stirring (Note 4), to Congo red paper, with concentrated hydrochloric acid (50–60 ml.). The temperature is maintained at 80° for 1 hour with constant stirring. The acenaphthenequinone separates as a bright yellow crystalline solid; it is collected on a Büchner funnel and washed with water until free from acid. The yield is 45–70 g. (38–60%); m.p. 256–260°.

The crude quinone (50 g.) is recrystallized from 250 ml. of *o*-dichlorobenzene without filtering (Note 5); the crystals are rinsed with methanol. The recovery is 45 g., m.p. 259–260° (Note 6), (Note 7).

2. Notes

1. The checkers used Eastman Kodak white label acenaphthene. Cerium salts appear to have a beneficial effect. Probably any cerous salt will be satisfactory,

it being oxidized in the reaction. The submitters have used cerous chloride, ceric carbonate, and ceric acetate; the last can be obtained in the form of a 50% mixture with other rare-earth acetates from the Lindsay Light and Chemical Company, West Chicago, Illinois. The checkers used cerous chloride.

2. The checkers found no need to cool the reaction; instead the bath was used to heat the reaction to 40°. With technical grade acenaphthene, cooling is necessary.

3. If the oxidation temperature has been allowed to rise to 50°, tar formation makes it necessary to do five or six treatments with sodium bisulfite. The extractions should be continued as long as the filtrate gives a precipitate on acidification.

4. The acidification should be performed in a hood; much sulfur dioxide is evolved.

5. The quinone crystallizes so rapidly that filtration is impossible; however, there is no insoluble material if mechanical dirt has been excluded.

6. This oxidation has been run using 80 times these amounts; the yield of recrystallized material drops to 38–40%.

7. The red color of acenaphthenequinone[1] is due to biacenaphthylidenedione, m. p. 295°. It is an appreciable contaminant in a hot oxidation; the product may also contain appreciable amounts of naphthalic anhydride.

3. Discussion

Acenaphthenequinone has been prepared by oxidation of acenaphthene with chromic acid,[1,2,3,4,5,6,7,8,9,10] with calcium permanganate,[11] with air in the presence of catalysts in various solvents,[12,13,14,15] with 30% hydrogen peroxide in acetic acid,[16] by the formation of an oxime with an alkyl nitrite followed by hydrolysis,[17,18,19] and from oxalyl chloride and naphthalene.[20,21] This procedure is based on the disclosure in a P. B. report.[10]

References and Notes

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16. Charrier and Moggi, *Gazz. chim. ital.*, **57**, 740 (1927).
17. Reissert, *Ber.*, **44**, 1750 (1911).
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20. Lesser and Gad, *Ber.*, **60**, 243 (1927).
21. Lesser and Gad, Ger. pat. 470,277 (1928) [*Frdl.*, **16**, 518 (1931)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

chromium salts

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

methanol (67-56-1)

sodium carbonate (497-19-8)

sulfur dioxide (7446-09-5)

sodium bisulfite (7631-90-5)

Norit (7782-42-5)

chromic acid (7738-94-5)

Naphthalene (91-20-3)

hydrogen peroxide (7722-84-1)

naphthalic anhydride (5343-99-7)

acenaphthene (83-32-9)

Acenaphthenequinone (82-86-0)

ceric acetate

sodium bichromate dihydrate (10588-01-9)

cerous chloride (7790-86-5)

biacenaphthylidenedione

calcium permanganate

oxalyl chloride (79-37-8)

o-dichlorobenzene (95-50-1)

ceric carbonate

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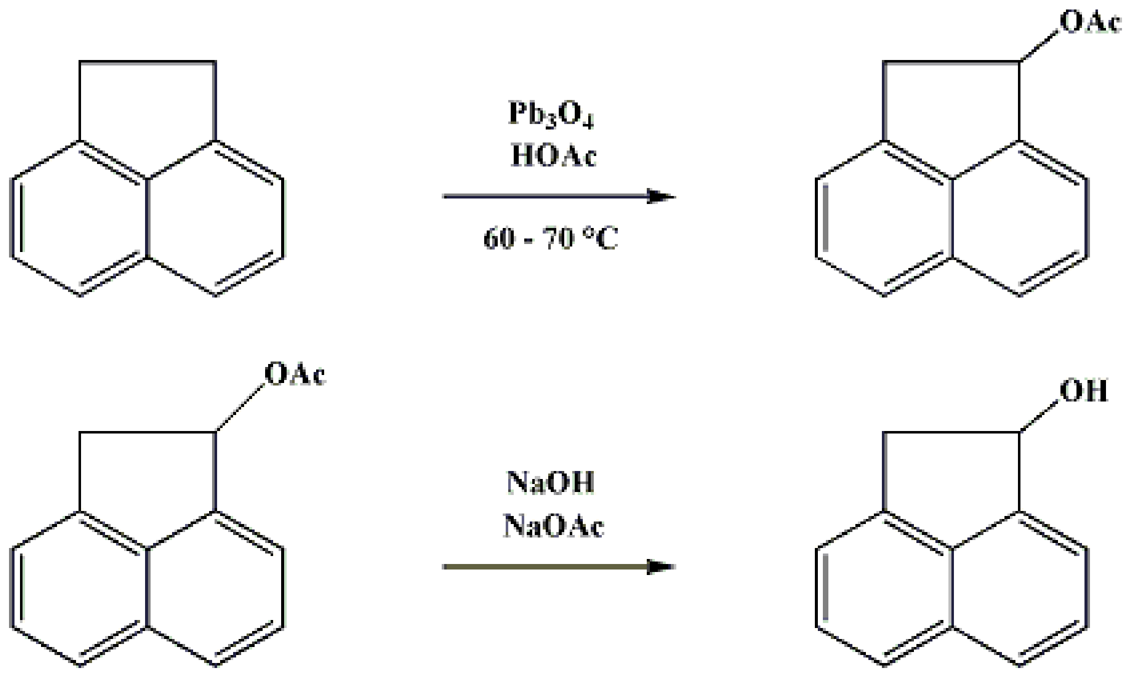
Organic Syntheses, CV 3, 3

ACENAPHTHENOL-7

[1-Acenaphthenol]



Submitted by James Cason
Checked by R. L. Shriner and Elmer H. Dobratz.

1. Procedure

A. *Acenaphthenol acetate*. In a 2-l. round-bottomed flask are placed 154 g. (1 mole) of acenaphthene (Note 1) and 1.1 l. of glacial acetic acid (Note 2). The flask is fitted with a tantalum or Nichrome wire stirrer[1] and a thermometer extending below the surface of the liquid. The solution is stirred and heated to 60°, at which point the source of heat is removed and 820 g. of red lead (Note 3) is added in portions of about 50 g., each portion being added as soon as the color due to the previous portion has been discharged. During this operation, which requires 30–40 minutes, the temperature is maintained at 60–70 (Note 4) by external cooling. The reaction is complete when a portion of the solution gives no test for lead tetraacetate (Note 5). The dark red syrupy solution (which may contain a few suspended particles of red lead and lead dioxide) is poured into 2 l. of water contained in a 4-l. separatory funnel. The acetate is extracted with a 350-ml. portion of ether and then with a 250-ml. portion. The total extract is washed first with 100 ml. of water, then with 300 ml. of saturated sodium chloride solution and is finally dried over 50 g. of anhydrous sodium sulfate. The sodium sulfate is removed by filtration and washed colorless with three 50-ml. portions of dry ether. The combined filtrate and washings are placed in a 500-ml. Claisen flask with an inset side arm, and, after distillation of the solvent, the acetate is distilled under reduced pressure. The acetate distils almost entirely at 166–168°/5 mm. (bath

temperature 180–185°, raised to 220° at the end) as a mobile yellow oil. The yield is 170–175 g. (80–82%) (Note 6).

B. *Acenaphthenol*. The acetate obtained as above is dissolved in 275 ml. of methanol in a 2-l. round-bottomed flask, and a solution of 40 g. (1.2 equiv.) of sodium hydroxide in 400 ml. of water is added (Note 7). This mixture is refluxed for 2 hours (Note 7) and then cooled below 20°. The yellow crystalline acenaphthenol is collected on a filter and washed well with about 1.5 l. of water. The crude product is air-dried (138–143 g.) and then dissolved in 2 l. of boiling benzene. The solution is treated with 6–8 g. of decolorizing carbon (Note 8) and filtered through a heated funnel. The orange-red filtrate is concentrated to about 1 l., and the acenaphthenol is allowed to crystallize. After filtering with suction and washing with cold benzene (about 500 ml.) until the wash solvent is colorless, the acenaphthenol is obtained as practically colorless needles, m.p. 144.5–145.5° (cor.) (Note 9). It weighs 117–121 g. From the filtrate may be obtained an additional quantity of material which on one recrystallization gives only 3–5 g. of pure acenaphthenol. The total yield amounts to 120–126 g. (70–74% based on the acenaphthene).

2. Notes

1. The "95% acenaphthene" sold by Reilly Tar and Chemical Corporation melts at 92.5–93.5° (cor.) and is quite satisfactory for use in this reaction. A recrystallized sample of this acenaphthene (m.p. 93–93.5°) or acenaphthene from the Gesellschaft für Teerverwertung (m.p. 93–93.5°) gives no better yield of pure acenaphthenol.
2. The glacial acetic acid should be purified by distillation from potassium permanganate. About 30–50 g. of potassium permanganate for each 1.5 l. of acetic acid should be used.
3. Mallinckrodt's analytical reagent red lead (assay 85–90%) was used. Merck's and Baker's N.F. V red lead are also quite satisfactory. Previously prepared lead tetraacetate is in no way preferable to red lead for this oxidation.
4. If the oxidation is carried out at 50° the yield is unaffected, but several hours are required to complete the addition. At 40°, the reaction is very slow and the yield is lowered.
5. A drop of the reaction mixture is placed on a moist piece of starch-iodide paper. The development of a blue color shows the presence of lead tetraacetate.
6. The acenaphthenol acetate contains small amounts of acenaphthene and acenaphthenone but is pure enough for the next step.
7. The dark violet color appearing on addition of the alkali is probably due to the presence of acenaphthenone. Crystalline acenaphthenol begins to separate almost immediately after the alkali has been added. Care must be taken in heating to refluxing because when heated too rapidly the acenaphthenol crystallizes suddenly from solution and the heat evolved may blow part of it out through the condenser.
8. If the charcoal treatment is omitted, the acenaphthenol obtained is light

yellow but practically pure.

9. Marquis[2] reported the melting point as 148°; von Braun and Bayer[3] reported it as 146°.

3. Discussion

Acenaphthenol has been prepared in poor yield by the oxidation of acenaphthene with lead dioxide;[2] and it is among the products obtained by hydrogenation of acenaphthene quinone.[3] The above procedure is essentially that described more briefly in the literature.[4]

References and Notes

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4. Fieser and Cason, *J. Am. Chem. Soc.*, **62**, 432 (1940).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

red lead

acetic acid (64-19-7)

Benzene (71-43-2)

methanol (67-56-1)

ether (60-29-7)

sodium hydroxide (1310-73-2)

potassium permanganate (7722-64-7)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

carbon (7782-42-5)

acenaphthene (83-32-9)

acenaphthene quinone (82-86-0)

ACENAPHTHENOL-7

1-Acenaphthenol, acenaphthenol (6306-07-6)

Acenaphthenol acetate (14966-36-0)

acenaphthenone (2235-15-6)

lead dioxide

lead tetraacetate

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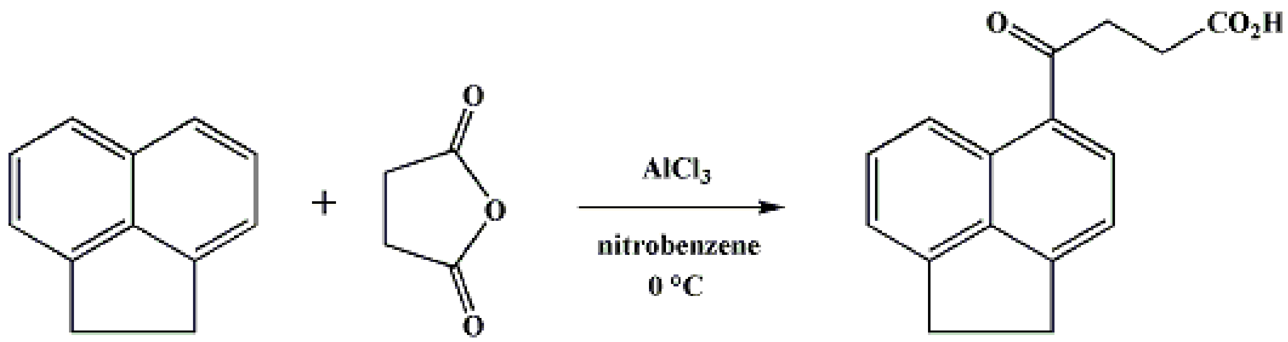
Organic Syntheses, CV 3, 6

β-(3-ACENAPHTHOYL)PROPIONIC ACID

[Acenaphthenebutyric acid, γ-oxo]



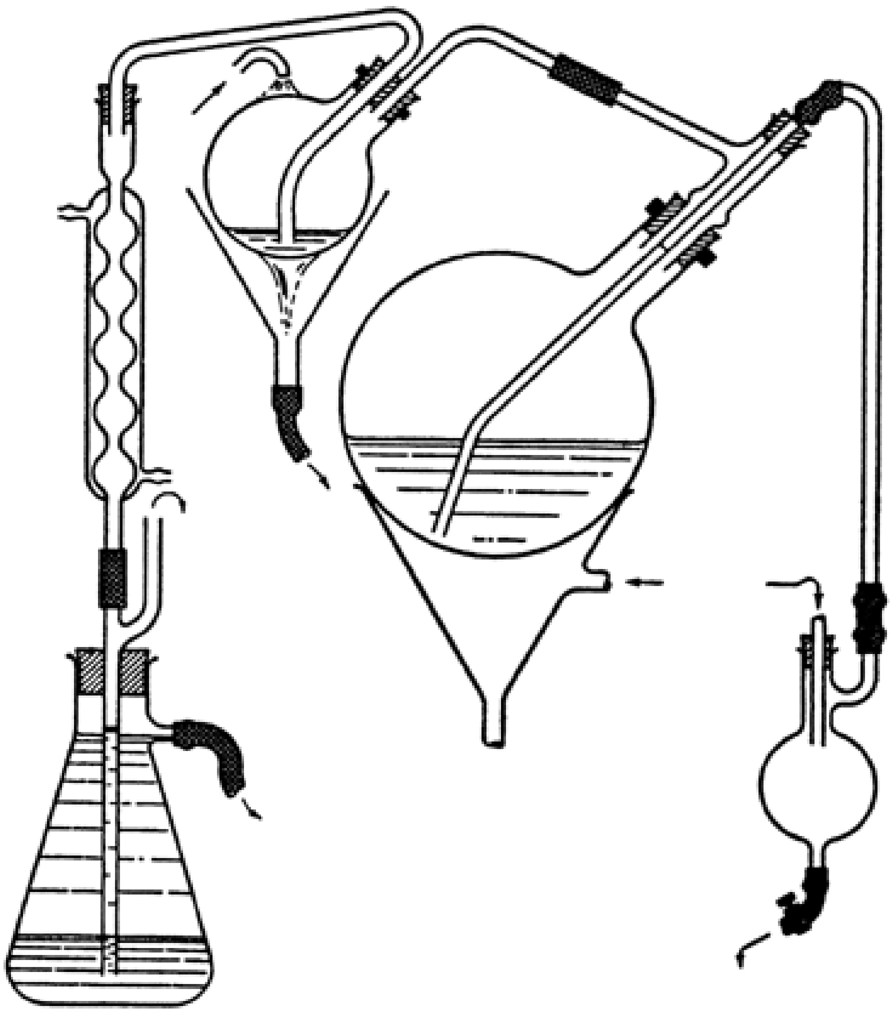
Submitted by L. F. Fieser
Checked by W. W. Hartman and A. Weissberger.

1. Procedure

In a 3-l. round-bottomed three-necked flask (Note 1), 100 g. (0.65 mole) of pure acenaphthene (Note 2) and 72 g. (0.72 mole) of succinic anhydride are dissolved by warming in 600 ml. of nitrobenzene. The flask is clamped in a large ice bath. Through the central opening is inserted a mercury-sealed mechanical stirrer. A second opening is connected to a gas trap and also carries a thermometer; the third is for the introduction of aluminum chloride. After the mixture has been cooled to about 0°, 195 g. (1.46 moles) of aluminum chloride is added in small portions in the course of 1 hour, the temperature being kept below 5°. Stirring is continued at 0° for 4 more hours, after which time the mixture is allowed to stand for at least 12 hours so that the ice melts and the clear red solution gradually comes to room temperature.

The flask is cooled by immersion in a slush of ice and water, and the addition compound is decomposed by adding gradually 200 g. of ice, 100 ml. of water, and 100 ml. of concentrated hydrochloric acid (this is best done under a hood). The keto acid separates in the form of a stiff, grayish white paste. The solvent is removed by steam distillation, in which operation it is advisable to use a very rapid flow of steam together with an efficient condensing system, such as that illustrated (.htmFig. 1). The condensing flask shown need be no more than 1 l. in capacity, and the exit tube should be centered at the bottom of this flask so that it can drain the contents completely. Some condensate ordinarily remains in the flask to serve as a vapor seal, a factor which adds greatly to the efficiency of condensation. For purposes of inspection, the flask can be emptied by diverting for a moment the stream of water to one side of the flask. The stoppers which are under pressure should be secured with wire. The distilling flask is heated to prevent too much condensation of steam (Note 3).

Fig. 1.



The bulk of the nitrobenzene comes over in about 1.5 hours, and the product then separates as a pasty mass which slowly disintegrates to a powder. During this process the elimination of nitrobenzene is very slow, but the steaming should be continued until only a few small lumps remain (4–5 hours), although it is not necessary to remove every trace of solvent (Note 4). The mixture is cooled with tap water, the crude acid is filtered and returned to the flask, and 115 g. of sodium carbonate decahydrate is added, together with sufficient water to make the flask a little less than half full. The mixture is heated with shaking over a free flame until most of the solid has dissolved and the frothing has diminished. A few drops of capryl alcohol may be added to dissipate the froth. The dark brown solution is steam-distilled to eliminate the last traces of nitrobenzene (about 30 minutes) and then filtered by suction from a very light residue. One hundred grams of sodium chloride is dissolved in the hot solution (volume, about 1.5 l.), which is then allowed to cool without disturbance. The sodium salt of β-(3-acenaphthoyl) propionic acid separates as colorless, fibrous needles, while the isomeric 1-acid largely remains in solution (Note 5). The product is collected on a large Büchner funnel and washed free of the dark mother liquor with half-saturated sodium chloride solution (about 150 ml.), the combined filtrates (A) being set aside. The sodium salt is crystallized once more from boiling water (1–1.5 l.) (Note 6), using Norit if required, and adding 50 g. of sodium chloride to the hot filtered solution. The mother liquor (B) is again saved. The purified salt is dissolved in 1.2 l. of hot water and the solution is acidified. The free acid separates as a white powder in a very pure condition. The yield of β-(3-acenaphthoyl) propionic acid melting at 206–208° with decomposition is 133 g. (81%) (Note 7).

2. Notes

1. By using a flask suitable for steam distillation, the loss in time and material attending a transfer is avoided.
2. Suitable material is supplied by Reilly Tar and Chemical Corporation, New York, or Gesellschaft für Teerverwertung, Duisburg-Meiderich, Germany.
3. As compared with the apparatus shown in Fig. 24 of *Org. Syntheses* Coll. Vol. **1**, 479, this arrangement requires a much smaller flask and yet offers unlimited capacity. It also enables the operator to observe more closely the nature of the distillate.
4. If the flask fills up with condensed steam, it should be cooled, the contents filtered, and the product returned to the flask. The process of disintegration can be hastened by breaking up the lumps with a flattened stirring rod.
5. The small amount of isomeric 1-acid may be obtained from the mother liquors, A and B. The first of these on acidification gives a product which is dark and tarry, but which soon solidifies on being cooled and stirred. The material is dissolved in 1 l. of water containing 25–30 g. of sodium carbonate decahydrate, and the solution is boiled for 30 minutes with Norit, filtered, cooled, and acidified. The product, which now solidifies at once and is lighter in color, is dried and combined with the material obtained by acidifying the second mother liquor, B (total amount, 23.9 g.). The crude mixture of acids is suspended in 170 ml. of cold methanol, 8.5 ml. of concentrated sulfuric acid is added, and the mixture is heated on the steam bath for about 10 minutes, after which dissolution and esterification are complete. The dark product that crystallizes when the solution cools is largely the 1-ester, which is very much less soluble than the 3-ester. The 1-ester (13.1 g.) is washed free of acid; it crystallizes from ethanol with the use of decolorizing carbon in long needles melting at 126°; yield, 9 g. (Note 8). The ester is hydrolyzed by heating with 100 ml. of alcohol and 30 ml. of 25% sodium hydroxide solution until dissolved; the solution is then diluted with water and acidified. The β-(1-acenaphthoyl)propionic acid melts at 180° (crystallized from dilute alcohol, 181°) and weighs 8.4 g. (5%) (Note 9).
6. If, owing to hydrolysis, the sodium salt fails to dissolve completely, alkali should be added as required.
7. The 3-acid crystallizes well from glacial acetic acid, alcohol, or xylene, but large volumes of solvent are required and there is no change in the melting point.
8. The 3-ester melts at 89°.
9. Ordinarily the mother liquors from the preparation and purification of 1-ester will be discarded, but a small additional quantity of the 3-acid may be obtained by concentrating these solutions, adding alkali to hydrolyze the ester, adding water, and acidifying. The precipitated material is purified by crystallizing the sodium salt twice, and from this 8 g. (5%) of the pure 3-acid is obtained.
The ratio of 3-acid to 1-acid is dependent on the temperature, lower temperatures favoring the production of 3-acid. At −15° the yield of 3-acid is 87%, and of 1-acid, 5%. At room temperature there is some increase in the proportion of the 1-acid formed, but the product is very dark and difficult to work up, and the total yield is lower even though the aluminum chloride is added in nitrobenzene solution.

3. Discussion

This procedure is based upon a study[1] of the method outlined in the patent literature.[2] The procedure is a general one and may be used for the condensation of succinic anhydride with naphthalene and with the mono- and dimethylnaphthalenes, although in no other case are the purification and separation of isomers so easily accomplished. In this particular type of condensation, as well as in certain other types of Friedel-Crafts reactions, nitrobenzene is far superior to the solvents that are more frequently employed. This is partly because of its great solvent power and partly because it forms a molecular compound with aluminum chloride, and so

decreases the activity of the catalyst in promoting side reactions.

References and Notes

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2. Fr. pat. 636,065 (*Chem. Zentr.*, **1928**, I, 2751); Swiss pat. 131,959 (*Chem. Zentr.*, **1930**, I, 1539); U. S. pat. 1,759,111 (*Chem. Zentr.*, **1930**, II, 806); Ger. pat. 376,635 [*Frdl.*, **14**, 285 (1926)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alcohol, ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

methanol (67-56-1)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

Norit (7782-42-5)

aluminum chloride (3495-54-3)

Nitrobenzene (98-95-3)

Naphthalene (91-20-3)

sodium carbonate decahydrate (6132-02-1)

xylene (106-42-3)

Succinic anhydride (108-30-5)

capryl alcohol (111-87-5)

acenaphthene (83-32-9)

β-(3-Acenaphthoyl)propionic acid, β-(3-acenaphthoyl) propionic acid (16294-60-3)

Acenaphthenebutyric acid, γ-oxo, β-(1-acenaphthoyl)propionic acid

sodium salt of β-(3-acenaphthoyl) propionic acid

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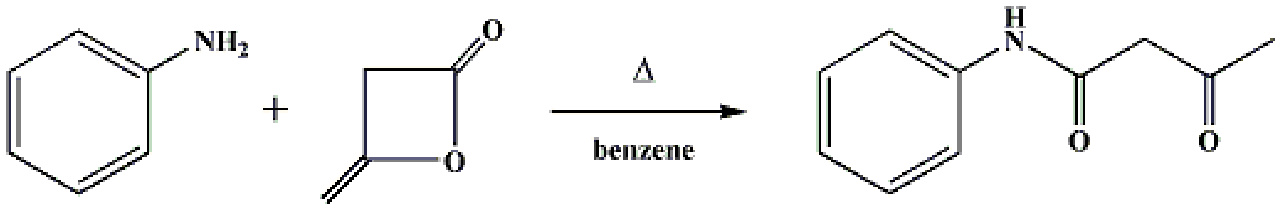
Organic Syntheses, *CV 3, 10*

ACETOACETANILIDE



Submitted by Jonathan W. Williams and John A. Krynitsky.
Checked by Nathan L. Drake and Joseph Lann.

1. Procedure

In a 500-ml. round-bottomed three-necked flask fitted with a reflux condenser, a dropping funnel, and a mercury-sealed stirrer (Note 1) is placed a solution of 46 g. (0.5 mole) of dry aniline in 125 ml. of pure dry benzene. Stirring is started, and a solution of 42 g. (0.5 mole) of ketene dimer (p. 508) in 75 ml. of pure dry benzene is added dropwise over a period of 30 minutes. The reaction mixture is then heated under reflux on the steam bath for 1 hour. After the major portion of the benzene has been removed by distillation from the steam bath, the remainder is removed under reduced pressure. The residue is dissolved in 500 ml. of hot 50% aqueous ethanol from which the acetoacetanilide separates on cooling. The mixture is cooled to 0° before filtration. A second crop of crystals can be obtained by adding 250 ml. of water to the mother liquor and cooling again (Note 2). The total yield of product, m.p. 82–83.5°, is 65 g. (74%). Further purification by recrystallization from 300 ml. of 50% ethanol yields 55 g. of a product that melts at 84–85°.

2. Notes

1. A seal of rubber tubing lubricated by glycerol is satisfactory.
2. If the second mother liquor is evaporated to about half of its original volume, a small third crop of very impure crystals may be obtained.

3. Discussion

Acetoacetanilide has been prepared by the reaction of aniline with ethyl acetoacetate[1,2,3,4,5] or acetoacetyl chloride,[6] and by the reaction of ketene dimer with aniline.[7,8]

References and Notes

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8. Boese, *Ind. Eng. Chem.*, **32**, 16 (1940).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Ketene dimer

ethanol (64-17-5)

Benzene (71-43-2)

aniline (62-53-3)

glycerol (56-81-5)

Ethyl acetoacetate (141-97-9)

Acetoacetanilide (102-01-2)

acetoacetyl chloride

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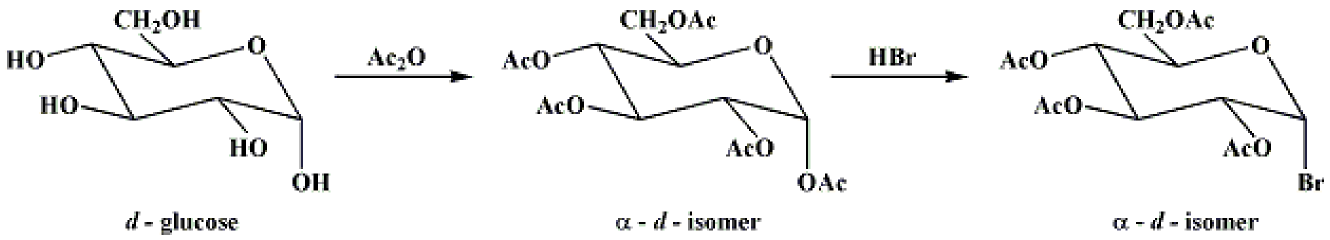
Organic Syntheses, CV 3, 11

ACETOBROMOGLUCOSE

[2,3,4,6-Tetraacetyl-α-*d*-glucopyranosyl bromide]



Submitted by C. Ernst Redemann and Carl Niemann.
Checked by Lee Irvin Smith, R. T. Arnold, and Iver Lerohl.

1. Procedure

In a 1-l. round-bottomed flask are placed 66 g. (0.33 mole) of *d*-glucose monohydrate (Note 1) and 302 g. of 95% acetic anhydride (280 ml., 2.81 moles). To this mixture 3 small drops of concentrated sulfuric acid are added *from a medicine dropper* (Note 2). The glucose is kept in partial suspension by shaking the flask with a swirling motion; the reaction starts almost immediately. If the temperature of the mixture approaches the boiling point, the flask is momentarily immersed in a pan of cold water. Within 10–15 minutes nearly all the glucose will have dissolved and the temperature of the reaction mixture will have risen nearly to 100°. The flask is loosely stoppered and is heated on a steam bath for 2 hours. Then about 200 ml. of mixed acetic acid and acetic anhydride is removed by distillation under reduced pressure (Note 3).

Sixty-five grams (60 ml., 0.64 mole) of acetic anhydride is added to the warm, viscous, light-yellow syrup; the mixture is warmed slightly and is mixed by imparting a swirling motion to the flask until the solution is homogeneous. The flask is then fitted with a two-holed rubber stopper bearing an inlet tube and an exit tube, the former reaching within 5 mm. of the bottom. Dry hydrogen bromide is passed into the mixture, while it is cooled in an ice bath, until the gain in weight is 140–160 g. (Note 4). The flask is then sealed with a rubber stopper and allowed to stand at 5° overnight.

The hydrogen bromide, acetic acid, and acetic anhydride are then removed from the straw-yellow solution by distillation under reduced pressure; a water bath whose temperature does not exceed 60° should be used to heat the mixture (Note 5). During the distillation the solution becomes slightly darker. When no further distillate comes over, or when the residue crystallizes, distillation is stopped, 250–300 ml. of dry isopropyl ether is added (Note 6), and the flask is warmed carefully on a water bath to hasten solution of the product (Note 7). The hot solution is transferred to a 1-l. Erlenmeyer flask and is cooled rapidly, with cold water, to about 45°. The mixture is then allowed to cool slowly to room temperature and is finally placed in a refrigerator at 5° for 2 or more hours. The acetobromoglucose is collected on a Büchner funnel, pressed into a firm cake, and washed with about 50 ml. of dry isopropyl ether. The white crystalline material, after being dried under reduced pressure over calcium (or sodium) hydroxide, weighs 110–120 g. (80–87%) (Note 8).

2. Notes

1. Ordinary commercial glucose monohydrate (Cerelose, Clintose, etc.) was used.
2. If any uncertainty exists about the size of the drops, it is better to add 2 drops at first and then to wait at least 10 minutes before adding the third drop. If too much sulfuric acid is added the reaction may become so vigorous that it cannot be controlled.
3. The lowest pressure attainable with a good aspirator is satisfactory. The acetic acid may be removed rapidly at bath temperatures up to 100°. Two hundred milliliters of distillate is collected in about 35 minutes. Complete removal of the acetic acid is not necessary; the only purpose of removing it is to decrease the amount of hydrogen bromide required.
4. Hydrogen bromide may be generated by dropping liquid bromine into boiling tetrahydronaphthalene, or catalytically from hydrogen and bromine (*Org. Syntheses*, **15**, 35). Free bromine should be removed from the gas by passing it over red phosphorus. The hydrogen bromide may be passed in very rapidly at first, but as the

solution becomes more concentrated the rate of introduction of the gas must be decreased. The absorption of 140 g. of hydrogen bromide requires about 2 hours if the solution is well stirred; otherwise a longer time is required.

5. This distillation is best conducted in the following manner: The hydrogen bromide is removed as completely as possible at a bath temperature of 40–50° under the pressure attainable with a good aspirator; this requires about 1 hour. The bath temperature is then slowly increased to 50–60° over a period of about 30 minutes, during which time considerable acetic acid and acetic anhydride are removed. The receiver is then emptied and the system is connected to a mechanical pump capable of maintaining a pressure of less than 5 mm. By keeping the temperature of the bath at 55–60°, sufficient acetic acid and anhydride are removed in 30–45 minutes. The mechanical pump must be adequately protected; the vapors should be passed through a trap cooled in carbon dioxide-ethanol, then through a 12- to 16-in. tower of flake sodium hydroxide, before they enter the pump. A somewhat higher bath temperature can be used with a good aspirator alone, but this will produce much darkening of the reaction mixture and will give a less desirable product.

6. Isopropyl ether which has been in contact with air for some time will contain peroxides. They should be removed by washing the ether, first with sodium bisulfite solution, then with sodium hydroxide solution, and finally with water. The ether is dried (24 hours over calcium chloride, then 24 hours over phosphorus pentoxide) and distilled.

7. Heating to effect solution should be as brief as possible. The water bath should be at a temperature near the boiling point, and the flask should be immersed for only short periods of time. The flask should be shaken continuously during this process.

8. The product, m.p. 87–88°, is satisfactory for most purposes. A single recrystallization from isopropyl ether gives a product having a melting point of 88–89°.

The product is best stored in a vacuum desiccator.

3. Discussion

α-Acetobromoglucose has been prepared by the action of acetyl bromide on anhydrous glucose;[1,2,3,4] by the action of hydrogen bromide in acetic acid upon β-pentaacetylglucose;[5,6,7,8] by the action of hydrogen bromide in acetic anhydride upon anhydrous glucose;[9,10] and by the action of hydrogen bromide in acetic anhydride upon starch or maltose.[11]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 434
- Org. Syn. Coll. Vol. 8, 148
- Org. Syn. Coll. Vol. 8, 583

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

red phosphorus

calcium (or sodium) hydroxide

acetic acid and anhydride

α-Acetobromoglucose

β-pentaacetylglucose;

ethanol (64-17-5)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

ether (60-29-7)

acetic anhydride (108-24-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

hydrogen bromide (10035-10-6)

bromine (7726-95-6)

sodium bisulfite (7631-90-5)

carbon dioxide (124-38-9)

glucose (492-62-6)

tetrahydronaphthalene (119-64-2)

Acetobromoglucose (572-09-8)

isopropyl ether (108-20-3)

glucose monohydrate, d-glucose monohydrate (14431-43-7)

acetyl bromide (506-96-7)

maltose

phosphorus pentoxide (1314-56-3)

2,3,4,6-Tetraacetyl-α-d-glucopyranosyl bromide

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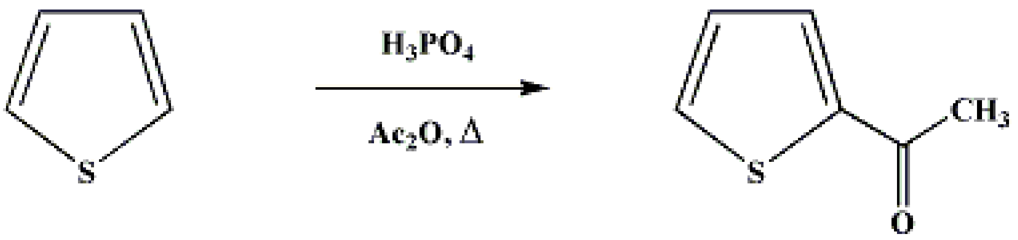
Organic Syntheses, CV 3, 14

2-ACETOTHIENONE

[Ketone, methyl 2-thienyl]



Submitted by Alvin I. Kosak and Howard D. Hartough.
Checked by George T. Gmitter, F. Lee Benton, and Charles C. Price.

1. Procedure

In a 1-l. three-necked flask fitted with a mechanical stirrer, a thermometer, and a reflux condenser are placed 168 g. (2 moles) (Note 1) of thiophene (Note 2) and 107 g. (1 mole) of 95% acetic anhydride (Note 3). The solution is heated to 70–75°, the source of heat is removed, and 10 g. (6 ml.) of 85% phosphoric acid is added with stirring. After 2–3 minutes an exothermic reaction occurs, and it is necessary to immerse the flask in a cold water bath to control the reaction. The boiling subsides in a few minutes; heat is again applied, and the mixture is refluxed for a total of 2 hours. The cooled mixture is washed successively with one 250-ml. portion of water and two 100-ml. portions of 5% sodium carbonate and is dried over anhydrous sodium sulfate. The orange-red liquid is distilled through a short fractionating column. After the removal of 76–80 g. of unchanged thiophene (b.p. 83–84°) by distillation at atmospheric pressure the residue is distilled under reduced pressure. The yield of 2-acetothienone, b.p. 89–90°/10 mm. (m.p. 9.2–10.5°; n_D^{20} 1.5662), is 93–100 g. (74–79%).

2. Notes

1. Acetic anhydride rather than thiophene may be used in excess, but the unchanged reagent cannot be recovered by the procedure given. With a 3:1 mole ratio of thiophene to anhydride the yield is of the order of 85%.
2. Commercial 99+% thiophene was employed.
3. The use of an equivalent amount of freshly distilled 100% acetic anhydride does not improve the yield.

3. Discussion

In addition to the methods of preparation given in connection with the procedure[1] for the acetylation of thiophene with acetyl chloride in the presence of stannic chloride, 2-acetothienone has been prepared from thiophene and either acetyl chloride or acetic

anhydride in the presence of iodine,[2] hydriodic acid,[2] silica-metal oxides,[3] zinc chloride,[4] inorganic oxyacids,[5,6] and boron trifluoride.[7,8,9] It has also been prepared from thiophene and acetic acid in the presence of hydrogen fluoride[5] or phosphorus pentoxide.[10] The acylation in the presence of phosphorus pentoxide is particularly useful with higher aliphatic acids.[10]

Procedures using acetic anhydride and stannic chloride or ferric chloride have been described.[11]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica-metal oxides

acetic acid (64-19-7)

acetic anhydride (108-24-7)

acetyl chloride (75-36-5)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

hydrogen fluoride (7664-39-3)

iodine (7553-56-2)

phosphoric acid (7664-38-2)

zinc chloride (7646-85-7)

hydriodic acid (10034-85-2)

ferric chloride (7705-08-0)

Ketone, methyl 2-thienyl (88-15-3)

Thiophene (110-02-1)

stannic chloride (7646-78-8)

boron trifluoride (7637-07-2)

phosphorus pentoxide (1314-56-3)

2-Acetothienone (88-15-3)

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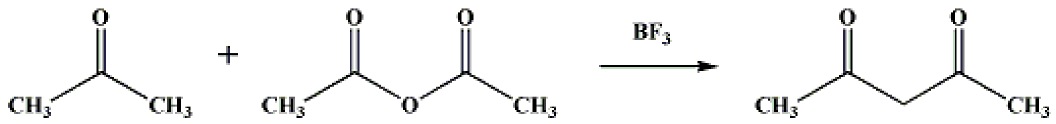
Organic Syntheses, CV 3, 16

ACETYLACETONE

[Diacetylmethane; 2,4-pentanedione]

[I. BORON TRIFLUORIDE METHOD]



Submitted by C. E. Denoon, Jr.
Checked by Homer Adkins and Ivan A. Wolff.

1. Procedure

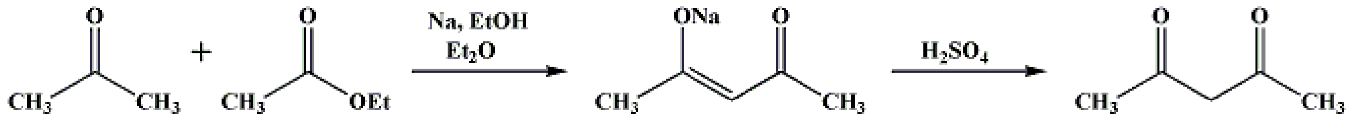
One hundred and sixteen grams (2 moles) of acetone (Note 1) and 510 g. (5 moles) of reagent grade acetic anhydride are placed in a 2-l. three-necked flask and cooled in an ice-salt bath. One neck of the flask is stoppered; the second neck contains a tube for admitting boron trifluoride; and the third neck contains an outlet tube leading to an alkali trap to catch any unabsorbed boron trifluoride. Commercial grade boron trifluoride (Note 2) is passed through a Kjeldahl bulb, to prevent the reaction mixture from sucking back into the cylinder, and is then bubbled into the reaction mixture at such a rate that 500 g. is absorbed in about 5 hours (2 bubbles per second). The reaction mixture is poured into a solution of 800 g. of hydrated sodium acetate in 1.6 l. of water contained in a 5-l. flask. The mixture is then steam-distilled and the distillate collected in the following portions: 1 l., 500 ml., 500 ml., 400 ml.

A solution of reagent grade hydrated copper acetate is made by dissolving 240 g. of the salt in 3 l. of water at about 85° and filtering from any basic acetate. The copper salt of acetylacetone is then precipitated by adding 1.4 l. of the hot copper acetate solution to the first fraction of the acetylacetone, 700 ml. to the second, 500 ml. to the third, and 400 ml. to the fourth fraction. After standing for 3 hours, or better overnight, in a refrigerator the salt is filtered, washed once with water, and sucked dry. The salt is shaken in a separatory funnel with 800 ml. of 20% sulfuric acid and 800 ml. of ether, and the ether layer is removed. The aqueous layer is extracted with 400 ml. and then 200 ml. of ether. The combined extracts are dried with 250 g. of anhydrous sodium sulfate, and the ether is removed by distillation. The residue is distilled through a Widmer column (Note 3) and yields 160–170 g. of acetylacetone boiling at 134–136° (80–85% based on acetone).

2. Notes

1. Acetone is preferably dried over anhydrous potassium carbonate or anhydrous calcium sulfate, followed by phosphorus pentoxide if a very dry product is required. Calcium chloride is commonly used (100–150 g. per liter), but this is less satisfactory since it combines chemically with acetone.[1] For this preparation the checkers used acetone that had been dried over calcium chloride, followed by distillation from phosphorus pentoxide.
2. Boron trifluoride may be purchased in cylinders from Harshaw Chemical Company, Cleveland, Ohio.
3. The Widmer column used contained a spiral 15 cm. in length, 13 mm. in diameter, with 15 turns of the helix.

[II. SODIUM ETHOXIDE METHOD]



Submitted by Homer Adkins and James L. Rainey.
Checked by R. L. Shriner and Neil S. Moon.

1. Procedure

Sixty-nine grams (3 gram atoms) of sodium, from which all the oxide coating has been cut away, and 400 ml. of dry xylene (Note 1) are placed in a 1-l. round-bottomed flask and heated until the sodium is melted. The flask is closed with a rubber stopper (Note 2), and the sodium is finely powdered by vigorous shaking. The contents of the flask are transferred to a 3-l. three-necked flask, and the xylene decanted. The sodium is washed with two 100-ml. portions of anhydrous ether (Note 3) by decantation. One liter of anhydrous ether is added, and the flask is placed on a steam bath and fitted with a condenser, Hershberg stirrer (*Org. Syntheses*, **17**, 31), and a 250-ml. dropping funnel. The condenser and dropping funnel are protected by drying tubes containing absorbent cotton (Note 4). One hundred and thirty-eight grams (175 ml., 3 moles) of anhydrous ethanol is placed in the dropping

funnel, and the stirrer is started. The alcohol is dropped in over a period of 2–3 hours with gentle refluxing. The reaction mixture is refluxed with stirring for 6 hours (Note 5) after the addition of the alcohol. The stirrer is stopped, the condenser turned downward, and the ether distilled as completely as possible from the steam bath (Note 6).

The condenser is again arranged for refluxing, and 1.2 l. of ethyl acetate(Note 7) is added to the warm sodium ethoxide through the separatory funnel as rapidly as possible. The stirrer is started immediately, and 174 g. (220 ml., 3 moles) of acetone (Note 1, p. 17) is dropped in over a period of 15–20 minutes, refluxing being maintained by heating if necessary. Addition of the acetone must be started as soon as the ethyl acetate has been added. During the addition the solution becomes quite red, and then the mixture turns brown (Note 8). The mixture is refluxed for 1 hour; the stirrer is then stopped and the contents of the flask are allowed to stand at room temperature for 12 hours, during which time crystals of the sodium salt separate.

The liquid layer is decanted into a 5-l. flask, and the sodium salt of the diketone is dissolved and washed into the flask with 2.5 l. of ice water. After the salt is dissolved, the ester layer is separated as soon as possible (Note 9). The water layer is extracted twice with 300-ml. portions of ether, and the ether extract is discarded. To the water solution is added ice-cold dilute sulfuric acid (150 g. of concentrated sulfuric acid and 400 g. of cracked ice) until the solution is just acid to litmus. The diketone is extracted from the solution with four 300-ml. portions of ether. The combined ether extracts are dried for 24 hours over 60 g. of anhydrous sodium sulfate in the icebox. The ether solution is decanted into a 2-l. round-bottomed flask, and the sodium sulfate is extracted with 100 ml. of anhydrous ether. This extract is added to the ether solution, and the ether is distilled by means of a steam bath. The residue is transferred to a 500-ml. flask, rinsing with a little ether, and distilled through a Widmer column, the portion boiling between 130° and 139° being collected. This fraction is dried over 5 g. of anhydrous potassium carbonate for 1 hour and, after the carbonate has been removed, is redistilled through the Widmer column. The portion boiling at 134–136° is collected; it amounts to 115–136 g. (38–45% based on acetone).

2. Notes

1. The xylene is dried by distillation from sodium.
2. Rubber stoppers should be used throughout, including the drying of reagents, as corks contain some moisture. The stoppers should be boiled in 10% sodium hydroxide solution for 2 hours, thoroughly washed with dilute acetic acid, and dried.
3. Commercial anhydrous ethyl ether and ethanol are satisfactory. If these are unavailable, the ether should be purified as for use in the Grignard reaction and the ethanol as described in *Org. Syntheses* Coll. Vol. **1**, 249 (1941).
4. Absorbent cotton is an excellent drying agent and more convenient for drying tubes than anhydrous calcium chloride.[2] It is possible to keep maleic anhydride in a flask, closed only by a plug of absorbent cotton, for 3 weeks without appreciable change in the titration value (F. P. Pingert, private communication).
5. The period of heating varies somewhat with the size of the powdered sodium. Almost all the sodium should be used up before removal of the ether. However, a few small pieces do no harm.
6. The success of the reaction depends upon the quality of the sodium ethoxide used. The product at this point should be white and very finely divided. All moisture must be excluded during its preparation in order to avoid the formation of sodium hydroxide, which markedly lowers the yield.
7. The ethyl acetate is allowed to stand over calcium chloride for 2 days, with occasional shaking. The calcium chloride is removed by filtration, and the ester is allowed to stand over phosphorus pentoxide several hours. It is then distilled directly from the phosphorus pentoxide.
8. After about half of the acetone has been added, the mixture usually sets to a solid mass. The stirrer is turned by hand and the addition of acetone continued. In a few minutes the mass can again be stirred.
9. The ethyl acetate layer is washed with water, sodium bisulfite solution, saturated calcium chloride solution, and again with water. It is further purified as in (Note 6), giving 316–400 g. of recovered ester. The amount of recovered ester depends somewhat upon the length of time the two layers are allowed to remain in contact before separating.

3. Discussion

Acetylacetone has been prepared by the reaction of acetyl chloride with aluminum chloride, followed by hydrolysis;[3] by the condensation of acetone with ethyl acetate in the presence of sodium,[4] sodium amide,[5,6] sodium ethoxide,[5,7,8] and alkali or alkaline-earth hydrides;[9] by the reaction of acetone and acetic anhydride in the presence of boron trifluoride;[10] by the pyrolysis of isopropenyl acetate;[11,12,13] by the reaction of ethyl acetoacetate and acetic anhydride in the presence of magnesium at 140°;[11] from methyl or ethyl diacetylacetate by treatment with acids;[14] and by the dehydrogenation of 4-pentanol-2-one in the presence of Raney nickel.[15]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 251

- Org. Syn. Coll. Vol. 3, 829

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

copper salt of acetylacetone

condenser

Hershberg stirrer

methyl or ethyl diacetylacetate

ethanol (64-17-5)

calcium chloride (10043-52-4)

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

ethyl acetate (141-78-6)

ether, ethyl ether (60-29-7)

acetic anhydride (108-24-7)

sodium acetate (127-09-3)

sodium hydroxide (1310-73-2)

acetyl chloride (75-36-5)

magnesium (7439-95-4)

carbonate (3812-32-6)

sodium sulfate (7757-82-6)

sodium bisulfite (7631-90-5)

calcium sulfate (7778-18-9)

Raney nickel (7440-02-0)

acetone (67-64-1)

aluminum chloride (3495-54-3)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

copper acetate (142-71-2)

xylene (106-42-3)

Ethyl acetoacetate (141-97-9)

boron trifluoride (7637-07-2)

Acetylacetone, Diacetylmethane, 2,4-pentanedione (123-54-6)

maleic anhydride (108-31-6)

isopropenyl acetate (108-22-5)

4-pentanol-2-one

phosphorus pentoxide (1314-56-3)

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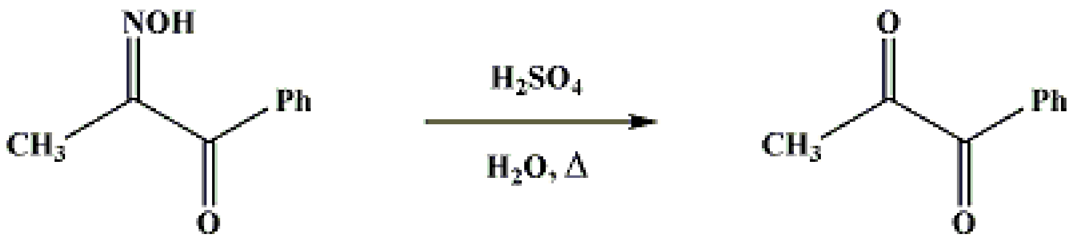
Organic Syntheses, CV 3, 20

ACETYLBENZOYL

[1,2-Propanedione, 1-phenyl-]



Submitted by W. W. Hartman and L. J. Roll.
Checked by A. H. Blatt and Lewis Rothstein.

1. Procedure

In a 1-l. flask arranged for steam distillation (Note 1), 50 g. (0.31 mole) of isonitrosopropiophenone (*Org. Syntheses*, **16**, 44; Coll. Vol. **2**, 363) and 500 g. of 10% sulfuric acid are mixed, and the mixture is distilled with steam until about 2 l. of distillate is collected. During the distillation the flask is heated so that the volume of the reaction mixture is kept roughly constant. The distillation requires about 6 hours, and at the end of this time the liquid in the flask is clear (Note 2).

The lower, yellow layer of diketone in the distillate is separated; the water layer is then saturated with salt and extracted with ether, one 80-ml. and two 25-ml. portions being used for each liter of the aqueous solution. The ether extracts are combined with the diketone proper and dried over sodium sulfate. The ether is removed on the steam bath, and the residual material is distilled from a Claisen flask under reduced pressure. Acetylbenzoyl is collected at 114–116°/20 mm. (Note 3). The yield is 30–32 g. (66–70% of the theoretical amount) (Note 4).

2. Notes

1. A spray trap should be placed between the flask and the condenser; otherwise some isonitrosoketone will be carried over. The checkers used a "Kjeldahl Connecting Bulb, Cylindrical Type," illustrated as item 2020 in the Pyrex Catalog, LP–34, for 1954.
2. On being cooled, the reaction mixture deposits 3–7 g. of the dioxime of acetylbenzoyl, m.p. 234–236° dec.[1]
3. Other boiling points reported for acetylbenzoyl are 216–218°, 164–165°/116 mm., and 102–103°/12 mm.
4. According to the submitters the reaction can be carried out with about the same percentage yields using five times the amounts of material specified above.

3. Discussion

Acetylbenzoyl has been prepared by dehydrogenation of acetylphenylcarbinol over copper at 350°;[2] by oxidation of 1-methyl-2-phenylethylene glycol;[3] by action of amyl nitrite on isonitrosopropiophenone;[4] and by acid hydrolysis of isonitrosopropiophenone[5] or of isonitrosobenzyl methyl ketone.[6] The last-named reaction is reported to furnish quantitative yields of acetylbenzoyl, but the starting material is not easily accessible. Treatment of propiophenone with amyl nitrite (2 moles) without isolating the isonitroso compound has been mentioned as a method of preparing acetylbenzoyl,[4] but the yield of diketone is much better when the isonitroso compound is isolated.[7] Acetylbenzoyl also has been prepared by the oxidation of phenyl acetone with selenium dioxide.[8]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

dioxime of acetylbenzoyl

sulfuric acid (7664-93-9)

ether (60-29-7)

sodium sulfate (7757-82-6)

copper (7440-50-8)

selenium dioxide (7446-08-4)

amyl nitrite (463-04-7)

Propiophenone (93-55-0)

phenyl acetone (103-79-7)

ISONITROSOPROPIOPHENONE

1,2-Propanedione, 1-phenyl- (579-07-7)

1-methyl-2-phenylethylene glycol

Acetylbenzoyl (579-07-7)

acetylphenylcarbinol

isonitrosobenzyl methyl ketone

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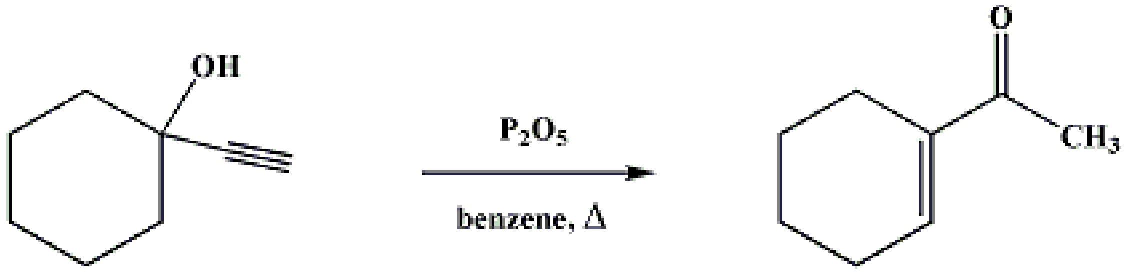
1-ACETYLCYCLOHEXENE

[Ketone, 1-cyclohexenyl methyl]



Submitted by J. H. Saunders[1]
Checked by E. L. Jenner and R. S. Schreiber.

1. Procedure

In a 500-ml. round-bottomed flask are placed 40 g. (0.32 mole) of 1-ethynylcyclohexanol (p. 416), 250 ml. of dry benzene, 10 g. of phosphorus pentoxide, and a boiling chip. A reflux condenser is attached to the flask, and the benzene solution is refluxed gently on a steam cone for 2.5 hours. At the end of that time the contents of the flask are cooled and the benzene is decanted from the phosphorus pentoxide, washed once with 100 ml. of 5% sodium bicarbonate solution, and dried over 15 g. of anhydrous sodium sulfate. The benzene is removed by distillation at atmospheric pressure, and the acetylcyclohexene is carefully fractionated at reduced pressure, through a 15-cm. helix-packed column. The yield of material boiling at 85–88°/22 mm., n_D^{20} 1.4892, is 22.5–28 g. (56–70%).

3. Discussion

1-Acetylcyclohexene has been prepared by treating cyclohexene with acetyl chloride and aluminum chloride,[2,3,4,5] by treating 1-ethynylcyclohexanol with oxalic acid[6] or 85% aqueous formic acid,[5,7,8,9] and by the dehydrohalogenation and hydrolysis of ethylidenecyclohexane nitrosochloride.[10] 1-Acetylcyclohexene and its homologs also have been prepared by the addition of a suitable diene to vinylacetylene in the presence of water and a mercury salt.[11]

References and Notes

1. This investigation was carried out under the sponsorship of the Office of Rubber Reserve, Reconstruction Finance Corporation, in connection with the Government Synthetic Rubber Program.

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11. U. S. pat. 2,301,515 [*C. A.*, **37**, 2015 (1943)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethylidenecyclohexane nitrosochloride

Benzene (71-43-2)

acetyl chloride (75-36-5)

sodium bicarbonate (144-55-8)

Cyclohexene (110-83-8)

sodium sulfate (7757-82-6)

formic acid (64-18-6)

Oxalic acid (144-62-7)

mercury (7439-97-6)

aluminum chloride (3495-54-3)

1-Acetylcyclohexene, Ketone, 1-cyclohexenyl methyl, acetylcyclohexene (932-66-1)

1-Ethynylcyclohexanol (78-27-3)

vinylacetylene (689-97-4)

phosphorus pentoxide (1314-56-3)

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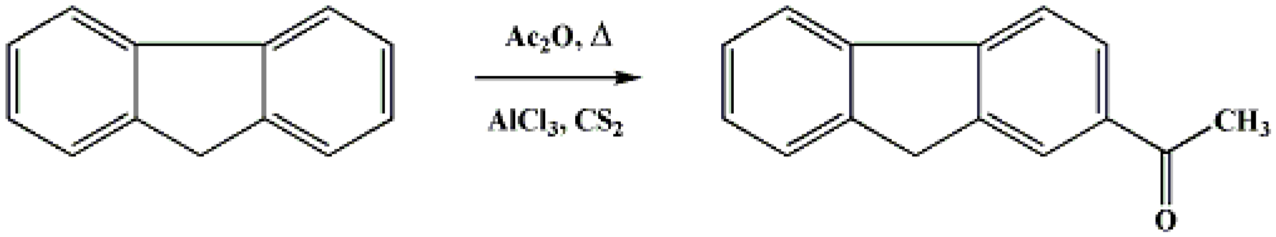
2-ACETYLFLUORENE

[Ketone, 2-fluorenyl methyl]



Submitted by F. E. Ray and George Rieveschl, Jr..
Checked by R. L. Shriner and Arne Langsjoen.

1. Procedure

Caution! Carbon disulfide, used as a solvent in this preparation, is highly inflammable; its vapor may ignite on contact with a hot laboratory steam line.

A 1-l. three-necked round-bottomed flask is fitted with a dropping funnel, a reflux condenser attached to a hydrogen chloride absorption trap,[1] and a very sturdy mechanical stirrer (Note 1), which may be of the mercury-sealed or rubber-sleeve type. In the flask are placed 350 ml. of dry carbon disulfide and 80 g. (0.48 mole) of fluorene (Note 2). The stirrer is started, and, after the fluorene has dissolved, 128 g. (0.96 mole) of anhydrous aluminum chloride is added in one portion. In the dropping funnel is placed 49.4 g. (0.48 mole) of redistilled acetic anhydride, and about 1 ml. of it is added dropwise to the vigorously stirred dark red reaction mixture. If the reaction does not start immediately it is initiated by warming the reaction flask in a water bath (Note 3). After the reaction has started, the balance of the acetic anhydride is added at such a rate that the carbon disulfide refluxes gently; about 45–55 minutes is required. When approximately one-half of the acetic anhydride has been added an addition complex separates as a heavy mass which makes stirring very difficult. However, stirring must be maintained to prevent excessive local reaction at the point of introduction of the acetic anhydride. The mixture is stirred and refluxed on the water bath for an hour after the addition of the acetic anhydride is complete.

The dark green mass is collected on a large Büchner funnel and transferred as quickly as possible (Note 4) to a 1-l. beaker in which it is stirred mechanically for 10 minutes with 300 ml. of carbon disulfide (Note 5). The solid is again collected and washed on the filter with two 50-ml. portions of carbon disulfide (Note 6) and with one 100-ml. portion of petroleum ether (b.p. 28–35°). The resulting granular aluminum chloride complex is decomposed by portionwise addition to a well-stirred mixture of 800 ml. of water and 30 ml. of concentrated hydrochloric acid in a 2-l. beaker under a hood. Each portion is allowed to hydrolyze before the next is added. The hydrolysis mixture should not be cooled. The crude 2-acetylfluorene is collected on a filter and washed three times with 100-ml. portions of water. After drying in an oven at 100° for 3 hours the light-orange ketone weighs 83–95 g. (83–95%) and melts over the range 113–117° (Note 7). This crude product is transferred to a 2-l. round-bottomed flask containing 800 ml. of 95% ethanol and 5 g. of decolorizing carbon. The mixture is refluxed

for 1 hour and filtered hot. On cooling the filtrate deposits 71–83 g. of light-tan solid melting at 120–123°. A second recrystallization from 800 ml. of ethanol yields 55–63 g. (55–63%) of a light-cream-colored powder which melts at 124–126° and which is pure enough for most purposes (Note 8).

2. Notes

1. The stirrer, which may be of either the half-round or the propeller type, must be of heavy construction and must be driven by one of the more powerful laboratory stirring motors. Agitation must be maintained throughout the reaction period.
2. If technical fluorene (m.p. 103–107°) from Eastman Kodak Company or the Barrett Company is used, much difficulty is experienced in the purification of the product. Technical fluorene can be rendered suitable for the preparation by recrystallization from hot 95% ethanol (1 l. for 150 g.). The once-recrystallized material melts at 114–115° (lit. 116°).
3. It is necessary to make sure that the reaction has started before the addition of more acetic anhydride in order to prevent a violent reaction.
4. Exposure to the air causes the addition product to become sticky and difficult to handle.
5. Unless this operation can be conducted at a point remote from flames, hot plates, and other sources of heat, a flask should be substituted for the open beaker.
6. The carbon disulfide extracts unchanged fluorene and other impurities. Any lumps in the crude material should be crushed during the first washing. The rinsing with petroleum ether removes the last of the carbon disulfide.
7. This crude 2-acetylfluorene is completely soluble in carbon disulfide and thus is free of the insoluble 2,7-diacetylfluorene. It may be used directly for the oxidation to fluorenone-2-carboxylic acid (p. 420).
8. The pure product[2] melting at 128–129° (cor.) can be obtained in 42–45% yield by two more recrystallizations from 400-ml. portions of acetone. Pure 2-acetylfluorene has also been reported[3] as melting at 132°, but this value has not been checked.

3. Discussion

2-Acetylfluorene has been prepared by the reaction of fluorene with acetic anhydride[2,4] or with acetyl chloride[3,5] in the presence of aluminum chloride in carbon disulfide or in nitrobenzene. When nitrobenzene is employed as the solvent it must be removed by a time-consuming steam distillation, and the use of acetyl chloride as a reagent agent leads to the formation of considerable amounts of 2,7-diacetylfluorene.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 420

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

aluminum chloride complex

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

acetic anhydride (108-24-7)

acetyl chloride (75-36-5)

acetone (67-64-1)

decolorizing carbon (7782-42-5)

aluminum chloride (3495-54-3)

Nitrobenzene (98-95-3)

carbon disulfide (75-15-0)

fluorene (86-73-7)

2-Acetylfluorene, Ketone, 2-fluorenyl methyl (781-73-7)

2,7-diacetylfluorene (39665-89-9)

Fluorenone-2-carboxylic acid (784-50-9)

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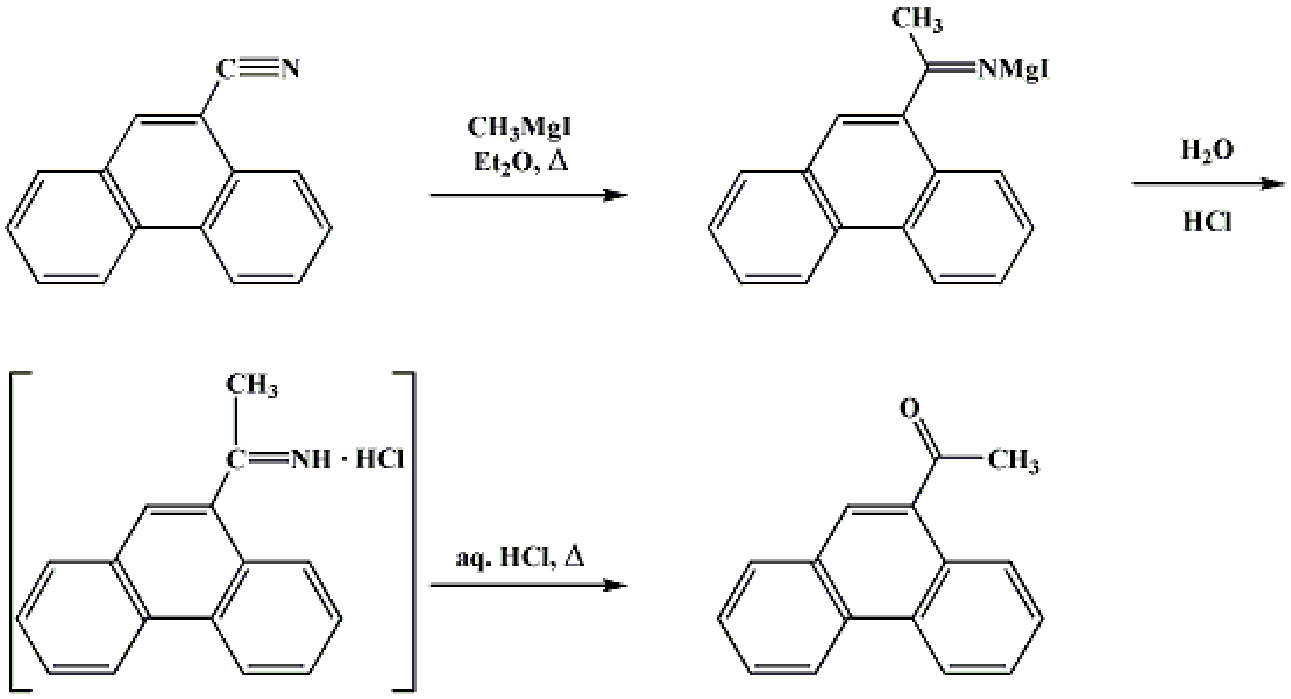
9-ACETYLPHENANTHRENE

[Ketone, methyl 9-phenanthryl]



Submitted by Joseph E. Callen, Clinton A. Dornfeld, and George H. Coleman[1].
Checked by Robert E. Carnahan and Homer Adkins.

1. Procedure

A dry 12-l. three-necked flask is equipped with an efficient motor-driven stirrer (Note 1), a nitrogen inlet tube, a large Allihn condenser, and a 1-l. separatory funnel. Both the condenser and the funnel are provided with calcium chloride drying tubes. To the flask is added 146 g. (6 gram atoms) of magnesium turnings (Note 2), and nitrogen gas, first bubbled through concentrated sulfuric acid, is passed in to displace the air. During the reaction the nitrogen atmosphere is maintained. The magnesium is covered with 200 ml. of anhydrous ether, and a few milliliters of a solution of 852 g. (6 moles) of methyl iodide in 1 l. of anhydrous ether is added from the separatory funnel. The reaction starts spontaneously, and then the remainder of the methyl iodide solution is added slowly. When the reaction is complete (Note 3), 4 l. of dry benzene is added, a condenser is arranged for downward distillation, and about 1.2 l. of solvent is distilled (Note 4). The condenser is changed to a reflux position, 609 g. (3 moles) of 9-cyanophenanthrene (p. 212) is added quickly through a powder funnel, and the mixture is heated and stirred under reflux for 3 hours. It is then cooled in an ice bath to 0°, 3 l. of cold 6 *N* hydrochloric acid is slowly added (*Caution!*) from a separatory funnel with stirring, and the mixture is refluxed for 6 to 8 hours (Note 5).

After cooling, the layers are separated, the organic layer is washed with dilute sodium bicarbonate solution and placed in a flask equipped for distillation, and the solvent is distilled The oily residue is transferred while still warm to a 1-l. Claisen flask, and the product is distilled under reduced pressure; b. p. 190–200°/2.5 mm. (168–170°/1 mm.). The yield is 400–430 g. (61–65%). The distilled ketone is recrystallized once from ethanol (1.5–2 l.) to yield 345–390 g. (52–59%) of 9-acetylphenanthrene of m. p. 73–74°.

2. Notes

1. If a 12-l. three-necked flask is not available, a three-way adapter tube may be used in making the necessary connections. Although a mercury seal may be used, a glycerol-rubber tube seal is adequate.
2. The checkers operated on one-tenth the scale specified.
3. In several runs the Grignard reagent was filtered at this point, but the improvement in yield was not appreciable.
4. The addition of benzene and distillation of part of the solvent raises the reaction temperature.
5. The oily layer of ketimine hydrochloride usually dissolves during 6 hours' refluxing.

3. Discussion

The method described above is a modification of that of Bachmann and Boatner.[2] 9-Acetylphenanthrene has also been obtained by a Claisen condensation of methyl phenanthrene-9-carboxylate with ethyl acetate followed by scission of the resulting phenanthroylacetic ester,[3] by the reaction of 9-phenanthrylmagnesium bromide with acetyl chloride,[4] and by dehydrogenation of 9-acetyl-1,2,3,4-tetrahydrophenanthrene by heating with sulfur.[5]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ethyl acetate (141-78-6)

ether (60-29-7)

acetyl chloride (75-36-5)

sodium bicarbonate (144-55-8)

magnesium, magnesium turnings (7439-95-4)

nitrogen (7727-37-9)

sulfur (7704-34-9)

Methyl iodide (74-88-4)

9-Acetylphenanthrene, Ketone, methyl 9-phenanthryl (2039-77-2)

9-Cyanophenanthrene (2510-55-6)

methyl phenanthrene-9-carboxylate

9-phenanthrylmagnesium bromide

9-acetyl-1,2,3,4-tetrahydrophenanthrene

ketimine hydrochloride

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ACID ANHYDRIDES

$$RCOCl + C_5H_5N \longrightarrow RCOCl \cdot C_5H_5N$$

$$\text{(A)}\quad RCOCl \cdot C_5H_5N + RCOOH \longrightarrow (RCO)_2O + C_5H_5N \cdot HCl$$

$$\text{(B)}\quad 2RCOCl \cdot C_5H_5N + H_2O \longrightarrow (RCO)_2O + 2C_5H_5N \cdot HCl$$

Submitted by C. F. H. Allen, C. J. Kibler, D. M. McLachlin, and C. V. Wilson.
Checked by Cliff S. Hamilton, Dexter Sharp, and R. Kretzinger.

1. Procedure

A. *Heptoic anhydride (enanthic anhydride)*. In a 250-ml. round-bottomed three-necked flask, equipped with a stirrer, dropping funnel, and thermometer, are placed 15.8 g. (16.1 ml., 0.2 mole) of dry pyridine (Note 1) and 25 ml. of dry benzene (Note 2). Then 14.8 g. (15.5 ml., 0.1 mole) of heptoyl chloride (Note 3) is added rapidly to the stirred solution. The temperature rises only slightly, and a pyridinium complex separates. While stirring is continued, 13.0 g. (14.1 ml., 0.1 mole) of heptoic acid (Note 3) is added from the dropping funnel over a period of 5 minutes. The temperature rises rapidly to 60–65° (Note 4), and pyridine hydrochloride is formed. After stirring for 10 minutes, the solid is collected on a chilled Büchner funnel and washed twice with 25-ml. portions of dry benzene (Note 5).

The filtrate is concentrated under reduced pressure on the steam bath, and the residue is distilled using a 200-ml. modified Claisen flask.[1] The fraction boiling up to 155°/12 mm. is discarded; the anhydride is collected at 155–162°/12 mm. (170–173°/15 mm.). It amounts to 19–20 g. (78–83%).

B. *p-Chlorobenzoic anhydride* (*benzoic anhydride, p,p'-dichloro-*). A mixture of 17.5 g. (0.1 mole) of *p*-chlorobenzoyl chloride (Note 6) and 50 ml. (0.6 mole) of pyridine in a loosely stoppered 200-ml. flask is warmed on the steam bath for 5 minutes and poured upon 100 g. of cracked ice and 50 ml. of concentrated hydrochloric acid (sp. gr. 1.18). The anhydride separates at once; as soon as the ice has melted sufficiently the mixture is filtered by suction. The solid is washed once with 15 ml. of methanol, then with 15 ml. of dry benzene. The yield is 14.2–14.6 g. (96–98%). Though suitable for most purposes, the crude product can be purified by recrystallization from 250 ml. of dry benzene; the recovery is 90%; it melts at 192–193°.

2. Notes

1. The pyridine was Eastman grade which was dried by long standing over

potassium hydroxide for A but used without further drying in B. Adkins' studies on the mechanism of this reaction indicate that the intermediate complex may react with water or with a molar quantity of the acid to form an anhydride.[2]

2. The benzene is dried by distilling the fist 10% and using the residue directly.

3. The heptoyl chloride, b.p. 173–175°, and the heptoic acid, b.p. 108–109°/9 mm., were obtained from the Eastman Kodak Company.

4. When preparing larger amounts, it would probably be better to control the temperature by external cooling as well as by the rate of addition of the acid.

5. Pyridine hydrochloride is hygroscopic; the filtration should be done rapidly, using a Büchner funnel.

6. *p*-Chlorobenzoyl chloride (m.p. 14–15°) is readily obtained by refluxing and stirring 156 g. (1.0 mole) of *p*-chlorobenzoic acid (obtained by the procedure for the *o*-isomer[3]) and 200 g. (1.7 moles) of thionyl chloride until solution is complete. The unused thionyl chloride is distilled, under slightly reduced pressure, and the product at 10 to 25 mm.; the yield of *p*-chlorobenzoyl chloride, b.p. 119–120°/22 mm., is 131–142 g. (75–81%). An additional amount can be secured by working up the fore-run and residue.

3. Discussion

These procedures are generally applicable to both aliphatic and aromatic compounds. They are reported to fail for furoic anhydride and to give poor results for *p*-nitrobenzoic anhydride (W. W. Prichard, private communication). They are superior to the common interchange method[4] in that they avoid the fractional distillation which is very troublesome in the aliphatic series. They have been used in numerous instances[2,5,6,7,8,9,10,11,12] and can be adapted to give mixed anhydrides.[13] Benzoic anhydride has been obtained, by closely related procedures, from benzoic acid and benzoyl chloride by heating under reduced pressure[14] or in the presence of zinc chloride.[15] Benzoic, acetic, and propionic anhydrides have been conveniently prepared by the action of bromine on the sodium salts of the acids in the presence of sulfur.[16]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Heptoic anhydride (enanthic anhydride

heptoyl chloride

heptoic acid

p-Chlorobenzoic anhydride (benzoic anhydride, p,p'-dichloro-

Benzoic, acetic, and propionic anhydrides

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

methanol (67-56-1)

thionyl chloride (7719-09-7)

bromine (7726-95-6)

Benzoic acid (65-85-0)

sulfur (7704-34-9)

benzoyl chloride (98-88-4)

Benzoic anhydride (93-97-0)

pyridine (110-86-1)

potassium hydroxide (1310-58-3)

zinc chloride (7646-85-7)

pyridine hydrochloride (628-13-7)

furoic anhydride

p-chlorobenzoic acid (74-11-3)

p-chlorobenzoyl chloride (122-01-0)

p-nitrobenzoic anhydride

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Organic Syntheses, CV 3, 30

ACRYLIC ACID

[I. PYROLYSIS METHOD]

Submitted by W. P. Ratchford
Checked by Arthur C. Cope, William R. Armstrong, and James J. Ryan.

1. Procedure

A 90-cm. length of 28-mm. (outside diameter) Pyrex tubing packed with pieces of Pyrex tubing (Note 1) is mounted vertically in an electric furnace (Note 2) capable of maintaining a temperature of 585–595°. A 250-ml. long-stemmed separatory funnel is connected to the upper end of the tubing with a stopper (Note 3), and the lower end is connected to a 500-ml. three-necked flask immersed in ice water. The flask, which serves as a receiver, is attached to a 50-cm. water-cooled reflux condenser, which in turn is connected by short lengths of rubber tubing to two traps in series which are immersed in a Dry Icetrichloroethylene mixture. The exit tube of the second trap is vented to a hood. From 0.2 to 0.3 g. of hydroquinone is placed in the receiver, together with a few pieces of Dry Ice which serve to displace air from the entire apparatus. The third neck of the receiver is stoppered.

The furnace is heated to 590° (Note 4), and after the air has been displaced 200 g. (216 ml., 2 moles) of ethyl acrylate (Note 5) is placed in the separatory funnel and admitted to the reaction tube at a rate of about 90 drops a minute (Note 3), so that the addition requires about 2 hours. At the end of the addition the contents of the receiver and the small amount of liquid in the traps are combined. The total weight of crude acrylic acid containing some ethyl acrylate is 126–136 g.

The crude product is placed in a 250-ml. flask containing a capillary inlet tube through which carbon dioxide is admitted. Ten grams of hydroquinone and 15 g. of diphenyl ether are added, and the flask is attached to a suitable fractionating column (Note 6). The product is fractionated carefully (Note 7) at 135 mm. pressure. The pressure is lowered gradually when most of the ethyl acrylate has distilled, and at about 70°/90 mm. the receiver is changed. The first fraction (mostly ethyl acrylate) amounts to 9–10 g. The pressure is lowered further to 50 mm., and the acrylic acid is distilled fairly rapidly, without reflux, at 69–71°/50 mm. The acrylic acid fraction weighs 108–116 g. and is 95–97% pure according to acidimetric titration. The yield is 68–75% based upon 100% acrylic acid content (Note 8) and (Note 9).

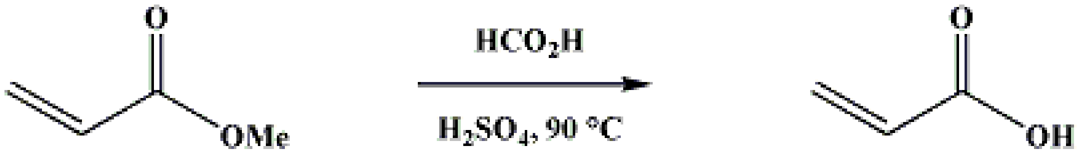
If the acrylic acid is not to be used at once, it is stabilized by the addition of

hydroquinone and is stored in a refrigerator.

2. Notes

1. The middle third of the Pyrex tube should be packed with 20-mm. lengths of fire-polished 7-mm. Pyrex tubing. The lower end of the tube is drawn out to a size that permits attachment to the receiver with a rubber stopper.
2. A type FD303 combustion furnace (made and sold by the Hoskins Manufacturing Company, Detroit, Michigan) or any similar furnace is satisfactory.
3. A groove filed in the stopcock of the separatory funnel aids in controlling the rate of addition. If available, a small constant-feed pump may be used to introduce the ester into the pyrolysis tube. The rate of addition of the ester is not critical, but at high rates cracking is incomplete and at low rates the yield is reduced. A stream of nitrogen (100 bubbles per minute) flowing through the tube reduces refluxing and makes the feed rate easier to observe. The nitrogen may be introduced through a tube in the stopper holding the separatory funnel or through a side arm sealed near the upper end of the pyrolysis tube.
4. The temperature is measured by a movable Chromel-Alumel thermocouple located in the furnace by the side of the tube and connected to a potentiometer or millivoltmeter. The thermocouple junction is adjusted so that during the run it is at the hottest point in the furnace. For the Hoskins Company furnace this point is about 9 in. from the top of the furnace. The temperature is controlled manually to 590 ± 5° by means of an autotransformer (Variac) rated at 5 amperes, 110 volts.
5. Commercial ethyl acrylate, containing hydroquinone inhibitor, may be used directly if it is of good quality.
6. The submitter used an insulated column with a 38 by 1.1 cm. section packed with 1/8-in. copper helices made of No. 26 B & S gauge copper wire. He states that a column packed with glass helices is unsatisfactory. The checkers used a 100 by 1.7 cm. Vigreux column. Either type of column should be equipped with a total-condensation partial take-off head.
7. Ethyl acrylate and acrylic acid polymerize easily, and overheating must be avoided in the distillation. The flask is heated in an oil bath which is not permitted to rise above 115°. The diphenyl ether that is added serves to expel the acrylic acid at the end of the distillation.
8. The submitter states that the product may be purified by freezing and decanting the supernatant liquid several times. The acrylic acid may be obtained in 97% purity by this method, but it has a faint yellow color. The yield is 50–60%.
9. The submitter states that methacrylic acid may be prepared in a similar manner by pyrolyzing ethyl methacrylate. Under the same conditions of temperature and feed rate, the conversion is slightly higher and the yield is about the same.

[II. ACIDOLYSIS METHOD]



Submitted by C. E. Rehberg
Checked by Arthur C. Cope and Elbert C. Herrick.

1. Procedure

One hundred and eighty-four grams (151 ml., 4 moles) of formic acid (Note 1), 1032 g. (1060 ml., 12 moles) of methyl acrylate (Note 2), 30 g. of hydroquinone, and 2 ml. of sulfuric acid are mixed in a 2-l. two-necked round-bottomed flask fitted with a capillary inlet tube. The flask is attached to a 100 by 1.7 cm. Vigreux column (Note 3) and is heated in an oil bath at 85–95°. The mixture is heated under total reflux until the temperature of the vapor at the still head falls to 32° (after 1–3 hours). Methyl formate then is distilled slowly at 32–35° as long as it is formed (8–10 hours). A reflux ratio of about 5 to 1 is maintained during the first part of the distillation, which is decreased to total take-off at the end. When no more methyl formate is produced, the excess methyl acrylate is distilled at 32–35°/140 mm. with the bath temperature at 60–65°. During the distillation, a slow stream of carbon dioxide is admitted through the capillary inlet. When all the methyl acrylate has been removed, the acrylic acid is distilled at 53–56°/25 mm. Upon redistillation through the same column (Note 4) acrylic acid of 97% purity (by acidimetric titration) is obtained in a yield of 220–230 g. (74–78% based upon 100% acrylic acid content), b.p. 54–56°/25 mm.

2. Notes

1. Acetic acid may be used, but it reacts much less rapidly and less completely, and fractionation of the reaction mixture is more difficult. Pure formic acid (98–100%) is preferred.
2. Commercial methyl acrylate may be used without purification if it is of good quality.
3. Either a Vigreux column or a column containing an open spiral of copper or Nichrome wire is satisfactory. The column should be jacketed and fitted with a total-condensation variable take-off head.
4. Hydroquinone or another polymerization inhibitor should be added before distillation of acrylic acid or its esters.

3. Discussion

Acrylic acid free of water has been prepared by treating lead acrylate with hydrogen sulfide;[1,2] by heating α,β-dibromopropionic acid with copper;[3] by dry distillation of a mixture of equivalent amounts of sodium acrylate and β-chloropropionic acid;[4] by pyrolysis of the polymer of β-propiolactone;[5] by heating β-chloropropionic acid with

potassium fluoride;[6] by heating β-acetoxypropionic acid in the presence of hydroquinone;[7] by heating lactic acid with metal chlorosulfonates;[8] and by the two methods described here.[9] It also has been prepared by dehydration of hydracrylic acid in the presence of copper and concentrated acids,[10] by acid exchange of acrylates in the presence of polymerization inhibitors,[11] and by the reaction of β-hydroxypropionitrile with 100% sulfuric acid, followed by addition of water and distillation.[12]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 746

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

hydroquinone (123-31-9)

hydrogen sulfide (7783-06-4)

formic acid (64-18-6)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

copper (7440-50-8)

β-hydroxypropionitrile (109-78-4)

Acrylic acid (9003-01-4)

hydracrylic acid (503-66-2)

β-Chloropropionic acid (107-94-8)

ethyl acrylate (140-88-5)

methyl formate (107-31-3)

methyl acrylate (96-33-3)

lactic acid (50-21-5)

diphenyl ether (101-84-8)

methacrylic acid (79-41-4)

ethyl methacrylate (97-63-2)

α,β-dibromopropionic acid (600-05-5)

sodium acrylate (7446-81-3)

β-propiolactone (57-57-8)

potassium fluoride (7789-23-3)

β-acetoxypropionic acid

lead acrylate

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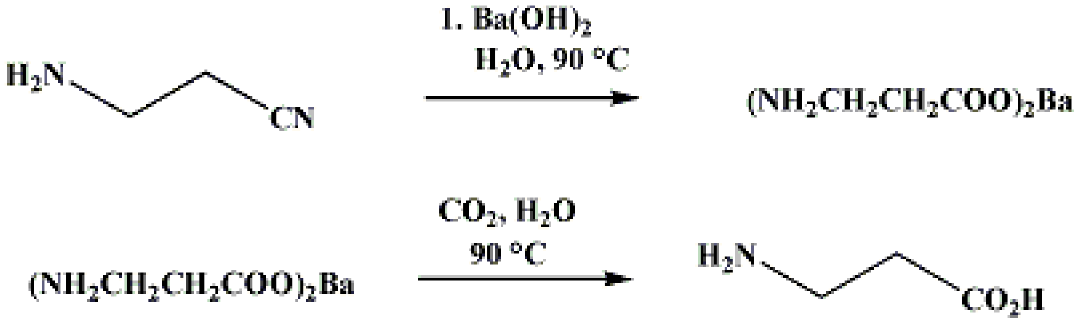
Organic Syntheses, CV 3, 34

β-ALANINE



Submitted by Jared H. Ford
Checked by Homer Adkins and James M. Caffrey.

1. Procedure

In a 2-l. three-necked flask equipped with a mechanical stirrer, a thermometer, and a dropping funnel is placed 185 g. (0.55 mole) of technical barium hydroxide octahydrate. The flask is heated on a steam bath in a hood. When the barium hydroxide has dissolved in its water of crystallization, the stirrer is started and 70.1 g. (1.00 mole) of β-aminopropionitrile (p. 93) is added dropwise over a period of 40 minutes. The temperature is maintained at 90–95° during the addition and for 40 minutes thereafter. Forty grams of asbestos filter aid (Note 1) and 1 l. of hot water are added, and the mixture is saturated with carbon dioxide (Note 2) while the temperature is held at 85–90°. The mixture is filtered with suction, the precipitate is returned to the flask with 500 ml. of hot water, and the mixture is heated and stirred for 20 minutes. After the barium carbonate has been filtered the washing procedure is again repeated with a second 500 ml. of hot water. The combined filtrates and washings are concentrated under reduced pressure on the steam bath (Note 3) until solid material separates. To the residue are added 200 ml. of hot water and 0.5 g. of decolorizing carbon (Note 4). The resulting solution is warmed on the steam bath for a few minutes and then filtered into a weighed 500-ml. Erlenmeyer flask. The flask is heated on a steam bath, and a jet of clean compressed air is directed at the surface of the solution. When the total weight of the solution is 130 g., it is cooled to 15–20° and diluted slowly with 400 ml. of methanol. After the solution has stood for several hours in the refrigerator, the product is filtered with suction and washed with two 100-ml. portions of methanol. The yield of β-alanine melting at 197–198° (dec.) is 75–80 g. (85–90%).

2. Notes

1. Standard Super-Cel (Johns-Manville, Inc.) was used.
2. Either carbon dioxide gas or Dry Ice may be used, and the saturation may be completed in 15–20 minutes by either method. The *p*H of the saturated solution is about 8–9 when tested with a universal indicator paper, such as Alkacid or

Hydrion.
3. The submitter used a special apparatus suitable for the rapid evaporation of water under reduced pressure. The checkers used standard flasks.
4. The solution is nearly colorless at this point, but the carbon aids in the removal of finely divided insoluble material.

3. Discussion

β-Alanine has been prepared by the catalytic reduction of cyanoacetic acid,[1] esters,[2] or salts;[3] by heating acrylonitrile,[4] β-aminopropionitrile,[5] bis-(β-cyanoethyl) amine,[6] β-hydroxypropionitrile,[7] β-alkoxypropionitriles,[8] bis-(β-cyanoethyl) ether,[9] or bis-(β-cyanoethyl) sulfide[9] with aqueous ammonia at 150–225°; by the hydrolysis of β-aminopropionitrile with concentrated hydrochloric acid and subsequent removal of the acid with anion-exchange resins;[10] by hydrolysis of β-phthalimidopropionitrile prepared from phthalimide and acrylonitrile;[11] from β,β'-iminodipropionic acid, β,β'-iminopropionitrile, or diethyl-β,β'-iminopropionate through preliminary conversion with phthalic anhydride at 200° to the corresponding phthalimide and subsequent hydrolysis.[12] The method as described above has been published.[13] Additional references to methods of preparation are given in connection with a procedure for making β-alanine from succinimide through the action of potassium hypobromite.[14,15]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

β,β'-iminopropionitrile

diethyl-β,β'-iminopropionate

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

methanol (67-56-1)

carbon dioxide (124-38-9)

phthalic anhydride (85-44-9)

carbon (7782-42-5)

Phthalimide (85-41-6)

β-hydroxypropionitrile (109-78-4)

cyanoacetic acid (372-09-8)

barium hydroxide (17194-00-2)

barium carbonate (513-77-9)

barium hydroxide octahydrate (12230-71-6)

β-Alanine (107-95-9)

Succinimide (123-56-8)

β-Aminopropionitrile (151-18-8)

acrylonitrile (107-13-1)

bis-(β-cyanoethyl) amine (111-94-4)

bis-(β-cyanoethyl) ether (1656-48-0)

bis-(β-cyanoethyl) sulfide (111-97-7)

β-phthalimidopropionitrile

potassium hypobromite

β,β'-iminodipropionic acid

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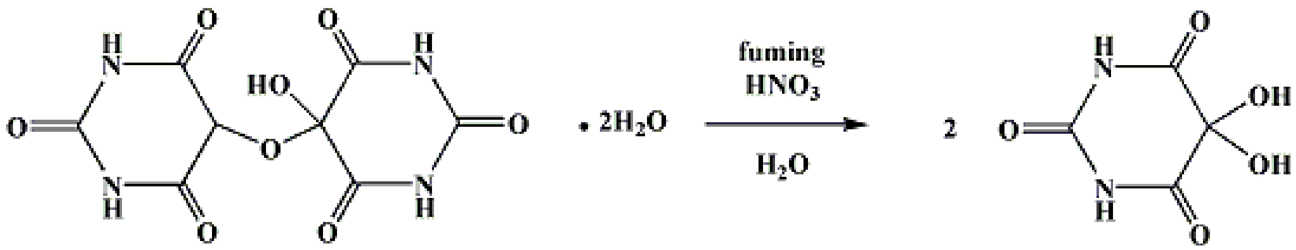
Organic Syntheses, CV 3, 37

ALLOXAN MONOHYDRATE

[Alloxan]

[I. METHOD A]



Submitted by W. W. Hartman and O. E. Sheppard.
Checked by C. S. Marvel and B. H. Wojcik.

1. Procedure

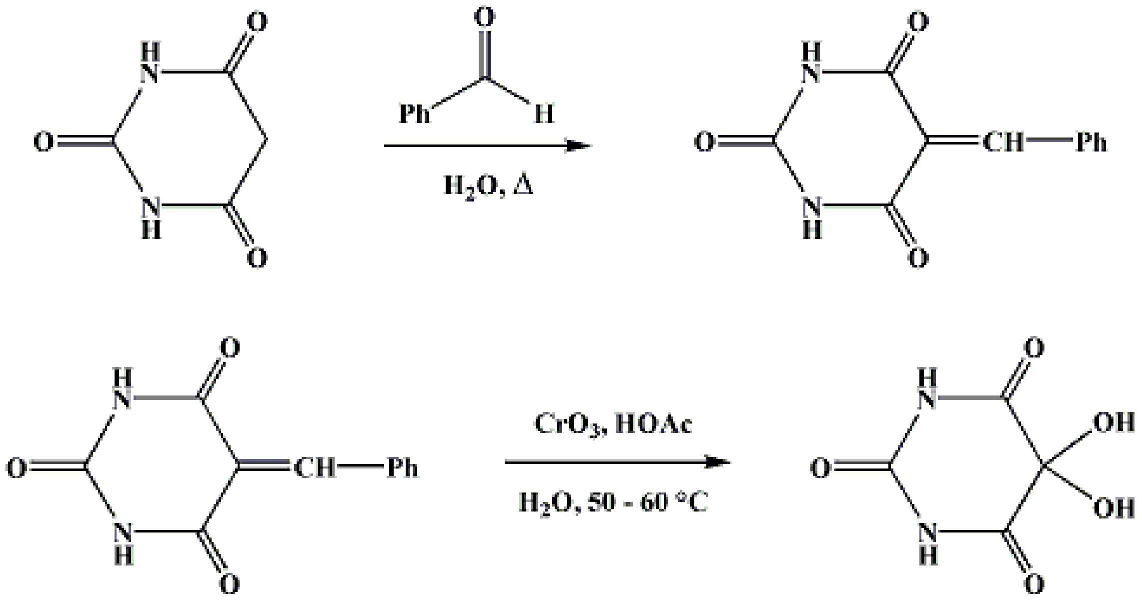
In a 500-ml. flask (Note 1), fitted with a mechanical stirrer, are placed 36 ml. of water and 25 g. (0.078 mole) of finely crystalline alloxantin dihydrate (p. 42). The flask and contents are heated on a steam bath to 50°, and 3.6 ml. of fuming nitric acid (sp. gr. 1.62) is added in a fine stream while vigorous stirring is maintained and the temperature is not allowed to rise above 60° (Note 2). After all the fuming nitric acid has been added, the temperature is brought to 55° and the stirrer is stopped. In a few minutes a vigorous reaction begins, and large quantities of oxides of nitrogen are evolved. The stirrer is again started, and, if the reaction becomes too violent, the mixture is cooled somewhat; otherwise, the reaction is allowed to take its course. The reaction is complete when a current of air, introduced into the flask above the mixture, does not produce much color due to formation of nitrogen tetroxide (Note 3). The mixture is then heated to 60–65° for 10–15 minutes, whereupon practically all the solid dissolves. The reaction mixture is poured into a glass (Pyrex) tray and cooled overnight at 0° or below. The large triclinic, colorless crystals of alloxan tetrahydrate are broken up, filtered with suction, washed with ice water, and pressed as dry as possible. The crystals are then added to 25–26 ml. of *hot* water (Note 4), and the mixture is shaken until solution is complete. The solution is filtered immediately, and the filtrate is cooled overnight in a tray at 0°. The crystals are broken up, filtered, washed with ice water, and pressed as dry as possible. These moist crystals of the tetrahydrate, which weigh 22–24 g., are dried to constant weight in a glass tray over concentrated sulfuric acid. The resulting product is a fine white powder (Note 5) which weighs 16 g.

The mother liquor from the recrystallization is placed in a 250-ml. flask and is concentrated to a volume of 8–10 ml. under reduced pressure at not over 30–40° (Note 6). The concentrate, when cooled overnight at 0°, deposits a solid which is filtered, recrystallized from its own weight of boiling water, and dried over sulfuric acid. This solid weighs about 2 g. The mother liquors from the two crystallizations are combined with the original mother liquor from the oxidation, and the whole is evaporated to dryness under diminished pressure at not above 30–40°. This solid residue is somewhat yellow and possesses a strong odor of nitric acid. It is kept on a tray for several days until the odor of nitric acid disappears, and then it is dissolved in its own weight (2–3 g.) of boiling water, and the solution is cooled for several days below 0° (Note 7). The solid is removed, recrystallized from water, and dried over sulfuric acid (Note 8). This crop weighs about 0.5 g. The total yield of alloxan monohydrate is 18–19 g. (72–76%) (Note 9).

2. Notes

1. The large flask is necessary because the mixture foams greatly during the reaction.
2. Very little reaction occurs during the addition of the nitric acid, and consequently there is very little rise in temperature. The acid is added during a few minutes.
3. The reaction is complete in about 30 minutes.
4. The water must not be boiled during the addition of the crystals or afterwards as this will cause decomposition of the alloxan to carbon dioxide, parabanic acid, and alloxantin.
5. The tetrahydrate effloresces readily, gradually loses part of its water, and becomes moist when allowed to stand at room temperature. For this reason it is not suitable for storage. The monohydrate results when the material is dried over sulfuric acid. Drying in an oven is likely to result in local overheating and decomposition, which starts slightly above 100°; it is also likely to result in reddening if even a trace of ammonia or amines is present in the air.
6. A higher temperature is likely to cause oxidation and to result in a violent reaction which may become explosive as the nitric acid becomes concentrated.
7. Alloxan tetrahydrate crystallizes from solution much more slowly when it is nearly free of nitric acid and when other soluble substances are present; it is, however, less soluble in nitric acid solution than in water.
8. A little alloxan still remains in solution. The mother liquor still slowly colors the skin red and on standing deposits alloxantin. The alloxantin can be removed and used in another oxidation. About 0.3–0.5 g. of it may deposit after the filtrate has stood for some time.
9. The submitters obtained the same yields (per cent) when approximately 65 times these amounts of materials were used. Thus, carrying out the oxidation of 1610 g. (5 moles) of alloxantin dihydrate in a 22-l. flask, the submitters obtained 1085 g. of the first crop, 160 g. of the second, and 28 g. of the third, a total of 1273 g.

[II. METHOD B]



Submitted by John H. Speer and Thomas C. Dabovich.
Checked by W. E. Bachmann and R. O. Edgerton.

1. Procedure

A. *Benzalbarbituric acid*. A mixture of 128 g. (1 mole) of barbituric acid and 1250 ml. of water in a 2-l. three-necked round-bottomed flask equipped with an efficient stirrer and a reflux condenser is heated on a steam bath to effect solution (Note 1). When the acid has dissolved, 115 g. (110 ml., 1.08

moles) of benzaldehyde is added while heating and stirring are continued. The solution rapidly fills with the insoluble benzalbarbituric acid. The mixture is heated for 1 hour on the steam bath to complete the reaction, and then is filtered by suction (Note 2). The filter cake is washed with several portions of hot water and dried at 100°. The yield is 190–205 g. (88–95%) of product possessing a very pale yellow color. The substance melts at 254–256° and needs no further purification.

B. *Alloxan monohydrate*. A mixture of 730 ml. of acetic acid, 95 ml. of water, and 162 g. (1.62 moles) of chromium trioxide (Note 3) is placed in a 2-l. three-necked round-bottomed flask fitted with a stirrer and a thermometer; the stirrer is started, and the mixture is warmed to 50°. To the solution 180 g. (0.83 mole) of benzalbarbituric acid is added in small portions during the course of 30 minutes, a cold water bath being used to maintain the temperature at 50–60°. After all the acid has been added, stirring is continued and the temperature maintained at 50–60° by a warm water bath for another 30 minutes to complete the reaction. Alloxan monohydrate generally starts to crystallize from the warm solution. The mixture is cooled to 15° and filtered. The product is washed on the filter with cold glacial acetic acid until the washings are no longer green, and then is dried by washing with ether. The yield is 105–112 g. (79–84%) of yellow crystals which melt at about 254° (Note 4) with decomposition and are sufficiently pure for most purposes.

In order to obtain practically colorless alloxan monohydrate (Note 5), 25 g. of the yellow crystals is dissolved in 37 ml. of hot water, the solution is boiled with Norit, and the hot solution is filtered into a 500-ml. round-bottomed flask. About 15–20 ml. of water is removed by distillation under reduced pressure on a water bath. The colorless crystalline residue is dissolved in the minimal volume of hot water, the solution is cooled somewhat, and to it is added 250 ml. of glacial acetic acid. After the mixture has been kept cold (5–10°) for 4–6 hours, the alloxan monohydrate is filtered. The yield is 20–21 g. (80–84% recovery) (Note 6) of practically colorless crystals which melt at about 254° (Note 7) with decomposition.

2. Notes

1. The submitters report that a single attempt to use the aqueous-ethanolic solution of barbituric acid obtained in *Org. Syntheses*, **18**, 8, before recrystallization of the product gave an excellent yield of an apparently isomeric product unsuited for the preparation of alloxan.
2. This filtration may be done hot or cold at the convenience of the operator.
3. The technical grade (flakes) was found quite satisfactory.
4. This value is obtained in a Pyrex capillary tube; the solid remains yellow until about 254°, when it suddenly decomposes to a red melt with vigorous evolution of gas. When a soft-glass capillary tube is used, the solid assumes a red color at about 180–200° and melts between 240° and 250°.
5. By recrystallization of the yellow product from glacial acetic acid (12 ml. per g.), using Norit, the checkers invariably obtained yellow crystals (75–80% recovery) instead of the practically colorless crystals reported by the submitters. By adding a volume of water equal to the weight of crystals to the hot acetic acid solution, the checkers obtained a pale yellow product.
6. This represents the first crop of crystals.
7. This value is obtained in a Pyrex capillary tube. The colorless solid begins to turn yellow at about 180° and melts at about 254° (occasionally 258–260°) to a red liquid with vigorous evolution of gas.

3. Discussion

Alloxan monohydrate has been prepared by the oxidation of uric acid with chlorine,[1,2] or potassium chlorate and hydrochloric acid;[3] by the oxidation of alloxantin,[4] xanthine,[5] uramil,[4] and thiouramil;[6]

and by the hydrolysis of dibromobarbituric acid.[7] The method here described is originally due to Biilmann and Berg.[8]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 23

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ammonia (7664-41-7)

ether (60-29-7)

nitric acid (7697-37-2)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

benzaldehyde (100-52-7)

Norit (7782-42-5)

chlorine (7782-50-5)

potassium chlorate (3811-04-9)

nitrogen tetroxide

uric acid

Barbituric acid (67-52-7)

chromium trioxide (1333-82-0)

Uramil (118-78-5)

alloxantin (76-24-4)

Alloxan monohydrate (2244-11-3)

Alloxan (50-71-5)

Alloxantin dihydrate (6011-27-4)

alloxan tetrahydrate

Benzalbarbituric acid (27402-47-7)

xanthine

thiouramil

dibromobarbituric acid (511-67-1)

Parabanic acid (120-89-8)

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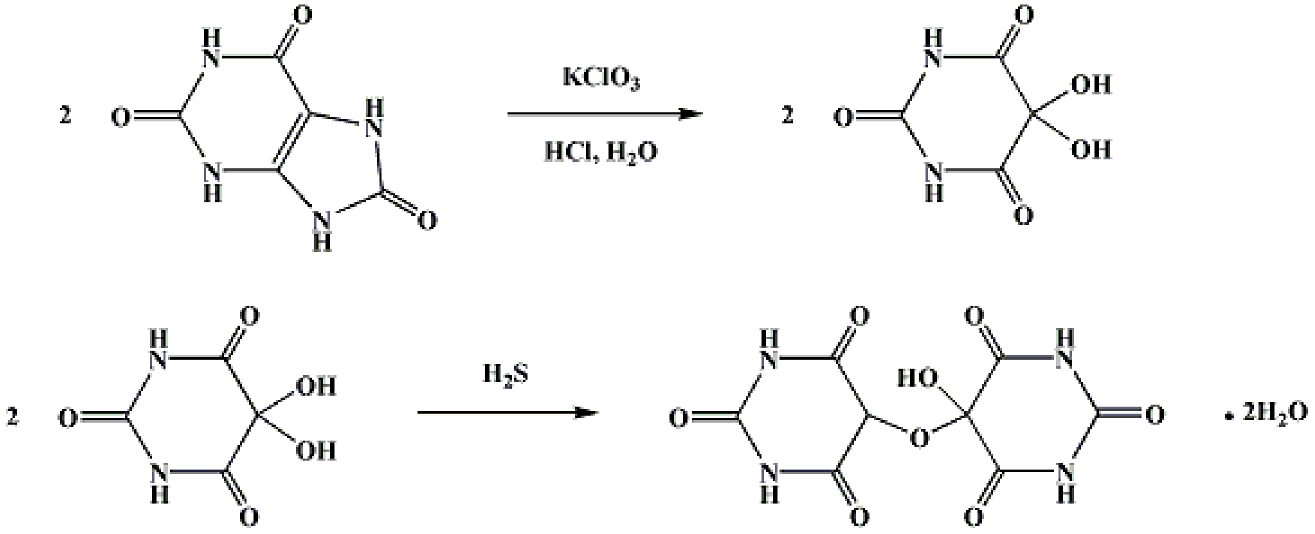
ALLOXANTIN DIHYDRATE



Submitted by Dorothy Nightingale
Checked by R. L. Shriner and C. H. Tilford.

1. Procedure

In a 500-ml. three-necked flask, provided with a stirrer, are placed 15 g. (0.09 mole) of finely powdered uric acid, 30 g. (25.2 ml.) of concentrated hydrochloric acid, and 40 ml. of water. The mixture is warmed to 30°, the stirrer is started, and 4 g. (0.014 mole) of finely powdered potassium chlorate is added in small portions during a period of not less than 45 minutes (Note 1). Most of the uric acid dissolves; any undissolved material is removed by filtration through a fritted-glass filter. The clear filtrate is diluted with 30 ml. of water, and a rapid stream of hydrogen sulfide is led into it until it is saturated (about 10–15 minutes). Sulfur and alloxantin separate, and the mixture is cooled for 2–3 hours in an ice bath until the separation is complete.

The solid is collected on a Büchner funnel and washed with three 30-ml. portions of cold water. The alloxantin is dissolved by boiling the wet solid for 15 minutes with 250 ml. of water, and the *hot* solution is filtered to remove the sulfur (Note 2). Alloxantin dihydrate crystallizes from the filtrate in glistening plates which should be pressed as dry as possible on a Büchner filter, washed with about 30 ml. of ether, and dried in a vacuum desiccator (Note 3). The yield is 8–10 g. (55–69%) (Note 4). The product melts with decomposition at 234–238° (Note 5), and is pure enough for most purposes.

2. Notes

1. It is important that the temperature of the reaction mixture be kept near 30°. The potassium chlorate must be added slowly.
2. Since alloxantin is difficulty soluble, it is desirable to make a second extraction of the sulfur to be certain that all the alloxantin has been removed.
3. The compound gradually turns pink on standing in the air. It should be stored in a tightly stoppered bottle or kept in a vacuum desiccator over calcium chloride.
4. If larger amounts of material are desired it is best to oxidize several 15-g. portions of uric acid and to combine the sulfur-alloxantin mixtures for the extraction.
5. The water of crystallization may be removed by heating the dihydrate at 120–150° under reduced pressure for 2 hours. The melting points reported in the literature vary considerably. The anhydrous material turns yellow at about 225–230° and decomposes at temperatures ranging from 238–242° to 253–255°, depending on the rate of heating. The instantaneous decomposition temperatures determined on the Maquenne block were 270–275°.

3. Discussion

This procedure is essentially that described in the laboratory manual by Fischer and Helferich.[1]

Alloxantin has been obtained by the oxidation of uric acid with nitric acid, followed by reduction with hydrogen sulfide;[2] by oxidation of uric acid with potassium chlorate, followed by reduction with stannous chloride;[3] by condensation of alloxan with dialuric acid in aqueous solution;[4] and by oxidation of dialuric acid.[5] A preparation from alloxan has been published.[6]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 37
- Org. Syn. Coll. Vol. 3, 46
- Org. Syn. Coll. Vol. 4, 25

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6. *Org. Syntheses*, **33**, 3 (1953).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

ether (60-29-7)

nitric acid (7697-37-2)

hydrogen sulfide (7783-06-4)

stannous chloride

sulfur (7704-34-9)

potassium chlorate (3811-04-9)

uric acid

alloxantin (76-24-4)

Alloxan (50-71-5)

Alloxantin dihydrate (6011-27-4)

dialuric acid (444-15-5)

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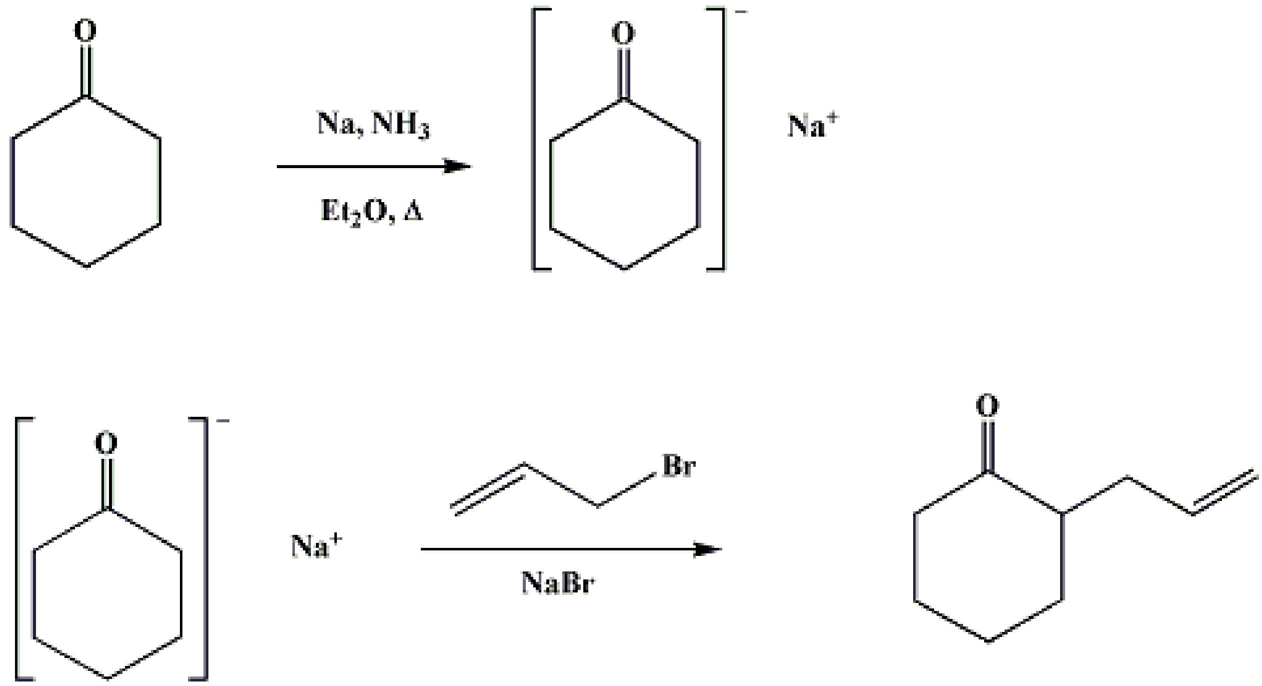
Organic Syntheses, *CV 3*, *44*

2-ALLYLCYCLOHEXANONE

[Cyclohexanone, 2-allyl-]



Submitted by Calvin A. Vanderwerf and Leo V. Lemmerman.
Checked by Arthur C. Cope and Theodore T. Foster.

1. Procedure

Approximately 1.5 l. of anhydrous liquid ammonia is introduced into a dry 5-l. three-necked flask fitted with a sealed mechanical stirrer and an efficient reflux condenser which is connected through a sodalime tube to a gas-absorption trap. Freshly cut sodium (47.2 g., 2.05 gram atoms) is converted to sodium amide by addition to the liquid ammonia in the presence of a small amount of ferric nitrate, according to p. 219. A 1-l. dropping funnel and a gas inlet tube connected to a source of dry nitrogen are attached to the third neck of the flask, and, after the blue color of the solution has disappeared and a gray suspension of sodium amide remains (Note 1), 1.2 l. of dry ether is added as rapidly as the rate of vaporization of ammonia will permit. The ammonia is removed by warming the flask on a steam bath until refluxing of the ether occurs. Cyclohexanone (Note 2) (220 g., 2.24 moles) is added through the dropping funnel (Note 3), and the mixture is stirred and heated under reflux on a steam bath for 3 hours. Nitrogen is then introduced through the gas inlet tube to maintain an inert atmosphere (Note 4), and the mixture is cooled in an ice bath. A solution of 246 g. (2.03 moles) of allyl bromide (Note 5) in 1 l. of anhydrous ether is added rapidly through the dropping funnel with stirring. If the reaction does not start soon after the completion of this addition the mixture is warmed cautiously on the steam bath. When the exothermic reaction has started it is controlled by cooling in the ice bath while refluxing continues for 20–30 minutes. The

mixture is finally heated under reflux on the steam bath for 3 hours.

The mixture is cooled in an ice bath, any sodium or sodium amide which may remain in the necks of the flask is scraped into the reaction mixture with a spatula, and enough water is added to dissolve the sodium bromide. The ether layer is separated and combined with five 100-ml. ether extracts of the aqueous phase, washed with 150 ml. of saturated sodium chloride solution, and dried over anhydrous sodium sulfate. The ether is removed by distillation, and the residue is fractionated carefully under reduced pressure through a 4-ft. heated column packed with glass helices and fitted with a total-condensation variable take-off head. The yield of 2-allylcyclohexanone boiling at 90–92°/17 mm. is 153–174 g. (54–62%). In addition, 28–38 g. of unchanged cyclohexanone boiling at 51–52°/17 mm., 15–35 g. of diallylcyclohexanone boiling at 123–124°/17 mm., and small intermediate fractions are obtained.

2. Notes

1. The conversion of the sodium to sodium amide requires 30–90 minutes. More liquid ammonia may be added if too much is lost by vaporization before the conversion is complete.
2. Redistilled cyclohexanone, b.p. 154–156°, was used.
3. The submitters obtained equally good results by adding 80 g. (2.05 moles) of freshly prepared finely powdered sodium amide in portions to a solution of the cyclohexanone in 1.2 l. of dry ether, heating under reflux for 3 hours, and continuing the preparation in the manner described.
4. The submitters state that the yield is increased appreciably if a nitrogen atmosphere is maintained after this point. Loss of ether may be avoided by stopping the flow of nitrogen when refluxing begins.
5. Allyl bromide was dried over calcium chloride and redistilled, b.p. 70–71.5°.

3. Discussion

2-Allylcyclohexanone has been prepared by the direct alkylation of the sodium derivative of cyclohexanone with allyl iodide, sodium amide having been used in the preparation of the sodium enolate,[1] and by ketonic hydrolysis of ethyl 1-allyl-2-ketocyclohexanecarboxylate, prepared by alkylation of ethyl 2-ketocyclohexanecarboxylate.[2,3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 25

References and Notes

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3. Grewe, *Ber.*, **76**, 1075 (1943).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium enolate

calcium chloride (10043-52-4)

ammonia (7664-41-7)

ether (60-29-7)

Cyclohexanone (108-94-1)

sodium chloride (7647-14-5)

Allyl bromide (106-95-6)

sodium bromide (7647-15-6)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

allyl iodide (556-56-9)

sodium (13966-32-0)

sodium amide (7782-92-5)

ethyl 2-ketocyclohexanecarboxylate (1655-07-8)

2-Allylcyclohexanone, Cyclohexanone, 2-allyl- (94-66-6)

ferric nitrate

diallylcyclohexanone

ethyl 1-allyl-2-ketocyclohexanecarboxylate

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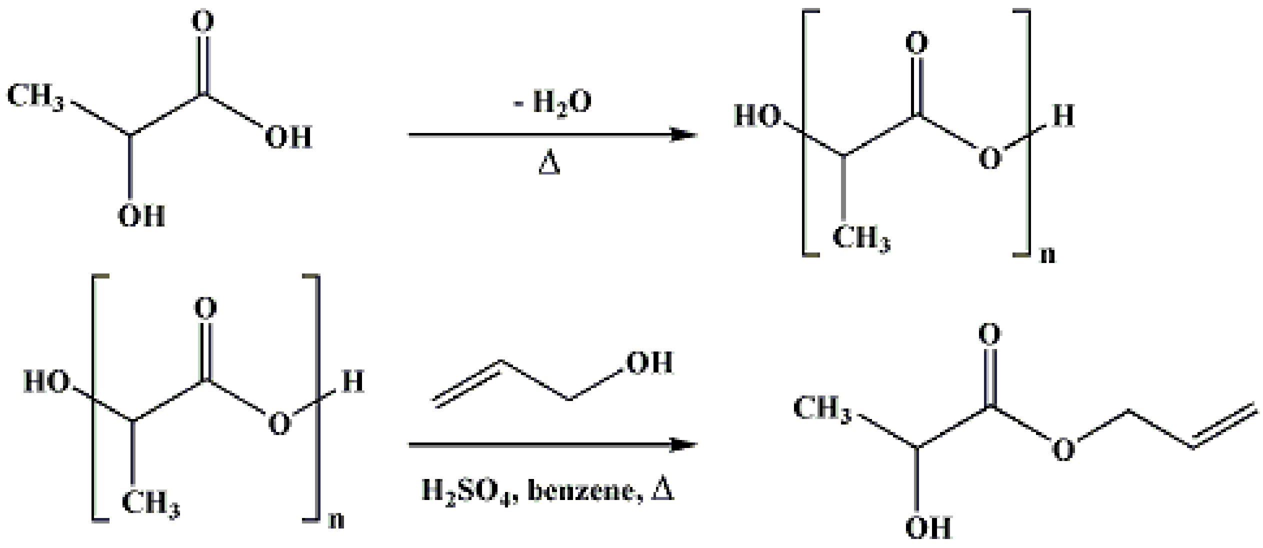
Organic Syntheses, CV 3, 46

ALLYL LACTATE

[Lactic acid, allyl ester]



Submitted by Chessie E. Rehberg
Checked by H. R. Snyder and Fred E. Boettner.

1. Procedure

Six hundred and seventy-five grams (6 moles) of 80% lactic acid (Note 1), 300 ml. of benzene, and 5 ml. of concentrated sulfuric acid are placed in a 3-l. three-necked round-bottomed flask having a capillary ebullition tube in one neck. The flask is attached to a Vigreux column 75 cm. in length, having at its top a trap of the Dean and Stark type, preferably the Barrett modification carrying a stopcock (Note 2), and a reflux condenser. The mixture is refluxed, and the aqueous layer is withdrawn from the trap until liberation of water becomes slow or until noticeable darkening of the material begins (Note 3). Then 1394 g. (1635 ml. or 24 moles) of allyl alcohol is added (Note 4), and refluxing and removal of water are continued until production of water ceases (Note 5). The acid catalyst is then neutralized with anhydrous sodium acetate (18 g.) (Note 6), and the fractionating column is replaced by a short distillation head leading to a 3-l. round-bottomed receiving flask cooled in salt and ice. The liquid is distilled rapidly under diminished pressure, first at the water pump and finally at a pressure of about 5 mm. A viscous residue (about 130 g.) containing inorganic salts is discarded. The distillate is fractionated through the column used in the first steps. The trap at the reflux condenser is replaced with a still head arranged for controlled partial take-off. The first fraction is the benzene-allyl alcohol binary azeotrope, which distils at 76.8° and contains 17.4% of the alcohol. Frequently a small amount of allyl ether is obtained at 94–95°. Allyl alcohol is then distilled at 97° until most of it is removed and the temperature of the residue in the pot reaches about 120°. The pressure is reduced to about 50 mm. while the remainder of the alcohol is removed. Finally the allyl lactate is distilled at 56–60°/8 mm. (Note 7). It amounts to 693–710 g. (89–91%) (Note 8).

2. Notes

1. The lactic acid used was the commercial edible grade and was almost colorless. The checkers used 635.6 g. of 85% lactic acid, U.S.P. The lower grades of commercial acid probably would give somewhat lower yields.
2. A suitable piece of apparatus is listed in Catalog LP-34, p. 43, of the Corning Glass Works.
3. Generally, about 35 ml. of water per mole of 80% lactic acid is obtained at this stage, and 4–6 hours of refluxing is required for its removal. The linear lactic acid polymer thus produced contains approximately 3 lactic acid units.
4. A large excess of alcohol is essential for a high yield of ester. Thus, when the ratio of alcohol to acid is 4:1, the yield is 90%; when it is 3:1, the yield is 85–88%; when it is 2:1, the yield is about 65%; and when it is 5:3, the yield is 58–60%.
5. The checkers found this distillation to require about 16 hours. The distillate is the ternary azeotrope. It consists of 8.6% water,[1] 9.2% allyl alcohol, and 82.2% benzene, and boils at 68.2°. The aqueous layer contains some allyl alcohol, though this loss is insignificant, since only about 15 ml. of the aqueous layer is obtained from each mole of lactic acid used.
6. It is essential to neutralize any strong acid present before distilling lactic ester; otherwise, condensation by ester interchange occurs, with liberation of alcohol and production of "polylactic acid," a linear polyester. Other neutralizing agents, such as alkali or alkaline-earth hydroxides or carbonates, doubtless could be used satisfactorily instead of sodium acetate.
7. Allyl lactate is a clear, colorless, mobile liquid boiling at 60°/8 mm., 79°/25 mm., and 175–176°/740 mm. Other properties are d_4^{20} 1.0452; n_D^{20} 1.4369.
8. This method of preparation is suitable for producing primary alkyl lactates but is unsatisfactory for β-methallyl lactate because the strong mineral acid catalyzes the rearrangement of methallyl alcohol to isobutyraldehyde. Methyl lactate[2] can be made conveniently (80–85% yield) by heating 1 mole of lactic acid condensation polymer with 2.5–5 moles of methanol and a small quantity of sulfuric acid at 100° for 1–4 hours in a heavy-walled bottle, such as is used for catalytic hydrogenation with a platinum catalyst.

3. Discussion

Allyl lactate has been prepared by the repeated treatment of lactic acid or its polymer with allyl alcohol in the presence of mineral acid.[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 350

References and Notes

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3. Fisher, Rehberg, and Smith, *J. Am. Chem. Soc.*, **65**, 763 (1945).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ester

benzene-allyl alcohol binary azeotrope

lactic ester

sulfuric acid (7664-93-9)

Benzene (71-43-2)

methanol (67-56-1)

sodium acetate (127-09-3)

Allyl alcohol (107-18-6)

platinum (7440-06-4)

lactic acid (50-21-5)

isobutyraldehyde (78-84-2)

Allyl lactate, Lactic acid, allyl ester (5349-55-3)

allyl ether (557-40-4)

β-methallyl lactate

methallyl alcohol (513-42-8)

Methyl lactate (547-64-8)

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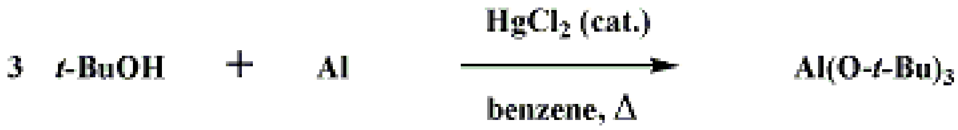
ALUMINUM *tert*-BUTOXIDE



Submitted by Winston Wayne and Homer Adkins.
Checked by Nathan L. Drake, Wm. H. Souder, Jr., and Ralph Mozingo.

1. Procedure

In a 2-l. round-bottomed flask, bearing a reflux condenser protected by a calcium chloride tube, are placed 64 g. (2.37 gram atoms) of aluminum shavings, 200 g. (254 ml., 2.7 moles) of dry *tert*-butyl alcohol, and 5–10 g. of aluminum *tert*-butoxide (Note 1). After the mixture is heated to boiling on a steam bath, approximately 0.4 g. of mercuric chloride is added followed by vigorous shaking (Note 2). As the heating is continued the color of the reaction mixture gradually changes from clear to milky to black, and hydrogen is evolved. When the mixture has become black, the heating is interrupted.

After the reaction has been allowed to proceed for an hour without heating, an additional 244 g. (309 ml., 3.3 moles) of dry *tert*-butyl alcohol (total quantity, 6 moles) and 200 ml. of dry benzene are added. The reaction will again set in upon gentle heating and will continue vigorously without further heating. After about 2 hours the reaction subsides and the mixture is refluxed for about 10 hours.

The benzene and unchanged *tert*-butyl alcohol are removed by distillation from the steam bath, the final traces being removed under 10–30 mm. pressure. A liter of *dry* ether is added, and the solid aluminum *tert*-butoxide is dissolved by refluxing for a short period. After cooling, 35 ml. of *undried* ether is added, followed immediately by vigorous shaking (Note 3). After standing for 2 hours the solution is centrifuged for 30 minutes to remove unused aluminum, aluminum hydroxide, and mercury (Note 4).

The solvent is removed by distillation from the steam bath, the final traces under 10–30 mm. pressure. The flask is allowed to cool with a calcium chloride tube attached, and the product is crushed with a spatula and transferred to bottles sealed against moisture. The yield is 394–418 g. (80–85%) of a white or slightly gray solid.

2. Notes

1. Commercial *tert*-butyl alcohol dried over calcium oxide is suitable for this preparation. Aluminum isopropoxide or ethoxide[1,2] may be used in place of the aluminum *tert*-butoxide to remove traces of water. The grade of metal known as "fast cutting rods" has proved most satisfactory. The checkers used turnings

made from aluminum cast from melted-down kitchen utensils. Aluminum *tert*-butoxide has also been prepared successfully in another laboratory from commercially pure aluminum (2S) and from rods of the alloy 17ST (communication from L. F. Fieser). The checkers were able to obtain considerably higher yields of the butoxide from pure aluminum than from a copper-bearing alloy.

2. The use of larger amounts of mercuric chloride increases the difficulty of getting the final product free from color. This difficulty may be avoided by previously amalgamating the aluminum.[3,4] The mixture is shaken to distribute the mercuric chloride and thus aid in an even amalgamation of the aluminum.

3. The small amount of water introduced with the undried ether forms aluminum hydroxide which aids in the precipitation of the black suspended material. Shaking is essential to obtain the hydroxide formation throughout the solution.

4. The centrifuging may be carried out in 250-ml. stoppered bottles at 2000 r.p.m. After centrifuging, the solution should be colorless or light tan. If it is still dark in color another 25-ml. portion of undried ether should be added and the centrifuging repeated.

3. Discussion

Aluminum *tert*-butoxide can be prepared by refluxing dry *tert*-butyl alcohol with amalgamated aluminum[1,5,6] or aluminum plus mercuric chloride.[6] The method described is that of Adkins and Cox.[6] The preparation of amalgamated aluminum has been described.[3,4] Aluminum isopropoxide can be prepared from dry isopropyl alcohol and aluminum,[1,2] the method being essentially that described for aluminum ethoxide.[7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 207
- Org. Syn. Coll. Vol. 3, 367

References and Notes

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Appendix

Compounds Referenced (Chemical Abstracts Registry Number)

copper-bearing

Benzene (71-43-2)

ether (60-29-7)

hydrogen (1333-74-0)

aluminum (7429-90-5)

mercury (7439-97-6)

isopropyl alcohol (67-63-0)

aluminum isopropoxide

mercuric chloride (7487-94-7)

calcium oxide

aluminum hydroxide

ethoxide

aluminum ethoxide

butoxide

tert-butyl alcohol (75-65-0)

ALUMINUM tert-BUTOXIDE

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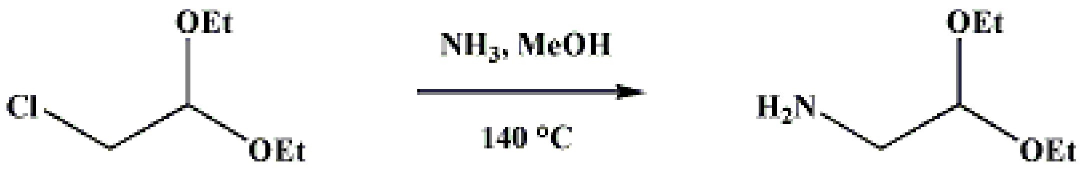
Organic Syntheses, CV 3, 50

AMINOACETAL

[Acetaldehyde, amino-, diethyl acetal]



Submitted by R. B. Woodward and W. E. Doering.
Checked by C. F. H. Allen and J. A. VanAllan.

1. Procedure

To a solution of 38.2 g. (0.25 mole) of chloroacetal (b.p. 62–64°/20 mm.) in 800 ml. of absolute methanol, cooled in a hydrogenation bomb of about 1.1-l. capacity to the temperature of a Dry Ice-acetone bath, is added approximately 300 g. (290 ml.; about 18 moles) of liquid ammonia (Note 1). The bomb is closed, connected with a pressure gauge, and heated at 140° with shaking for 10 hours.

After the bomb has cooled, the ammonia is allowed to escape (Note 2) and the solution is poured out. The bomb is rinsed with two 200-ml. portions of dry methanol (Note 3), and the combined solution and washings are filtered. The colored solution is concentrated on the steam bath to about 500 ml., 100 ml. of 5% aqueous potassium hydroxide is added, and concentration is continued until the vapors no longer burn (about 2 hours). The solution is saturated with salt (Note 4) and placed in the bulb of an automatic extractor (Note 5); 100 ml. of 50% aqueous potassium hydroxide is added, and the solution is extracted continuously with 350 ml. of ether overnight. The oil that remains after concentration of the ether extract gives on fractionation under reduced pressure (Note 6) 23–24 g. (71–74%) of aminoacetal, b.p. 99–103°/100 mm. (Note 7), (Note 8), and (Note 9).

2. Notes

1. The bomb is cooled by placing it in an iron pot of about two-thirds the height of the bomb. The pot is half filled with acetone, and pieces of Dry Ice are added until the vigorous evolution of carbon dioxide accompanying the addition of each new piece is no longer observed. If liquid ammonia is added to an insufficiently cooled solution of chloroacetal and alcohol, the ammonia is volatilized so vigorously that much of the starting material is lost. It is possible to force the ammonia from a small bomb into the bomb containing the alcohol and chloroacetal, at room temperature, by the aid of compressed hydrogen.[1]

2. Some of the reaction mixture may be carried from the bomb by the escaping ammonia. If the ammonia is allowed to escape through a tube leading into a

beaker or flask, this material can be collected.
3. An appreciable amount of a slimy solid collects on the walls of the bomb. It appears to consist of ammonium chloride together with a small amount of iron salts dissolved from the walls of the bomb by the action of the ammonia. The amount of product recovered by careful working of this material is less than 2 g.
4. About 70 g. is required.
5. An automatic extraction apparatus supplied by Ace Glass, Inc., Vineland, New Jersey, was used; see their catalog 40, p. 90, No. 6835 (500-ml. extraction chamber).
6. An ordinary Claisen flask having a modified side arm was used.
7. Yields of 56–70% were obtained by using larger quantities (76–100 g.) of chloroacetal but the same amounts of methanol and ammonia.
8. The residue contains diacetalylamine (b.p. 124–127°/7 mm.; 189°/100 mm.). It can be isolated by combining the residues from several runs and fractionating through an efficient column. The residues from 14 runs of double the size given above gave 83 g. of diacetalylamine.
9. The main difference between this procedure and the one published earlier[2] is that a much smaller amount of haloacetal is used in the same total volume.

3. Discussion

The most useful and general method for preparing aminoacetal consists of the action of ammonia upon the haloacetals.[3,4,5,6,7,8,9,10] It has also been prepared by the reduction of nitroacetal using sodium in alcohol,[11] and by the reduction of glycine ester hydrochloride with sodium amalgam.[12] The haloacetal-ammonia reaction has been patented.[13]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

glycine ester hydrochloride

Aminoacetal

chloroacetal

iron pot

iron salts

diacetalylamine

nitroacetal

ammonia (7664-41-7)

methanol (67-56-1)

ether (60-29-7)

ammonium chloride (12125-02-9)

hydrogen (1333-74-0)

carbon dioxide (124-38-9)

acetone (67-64-1)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

Acetaldehyde, amino-, diethyl acetal

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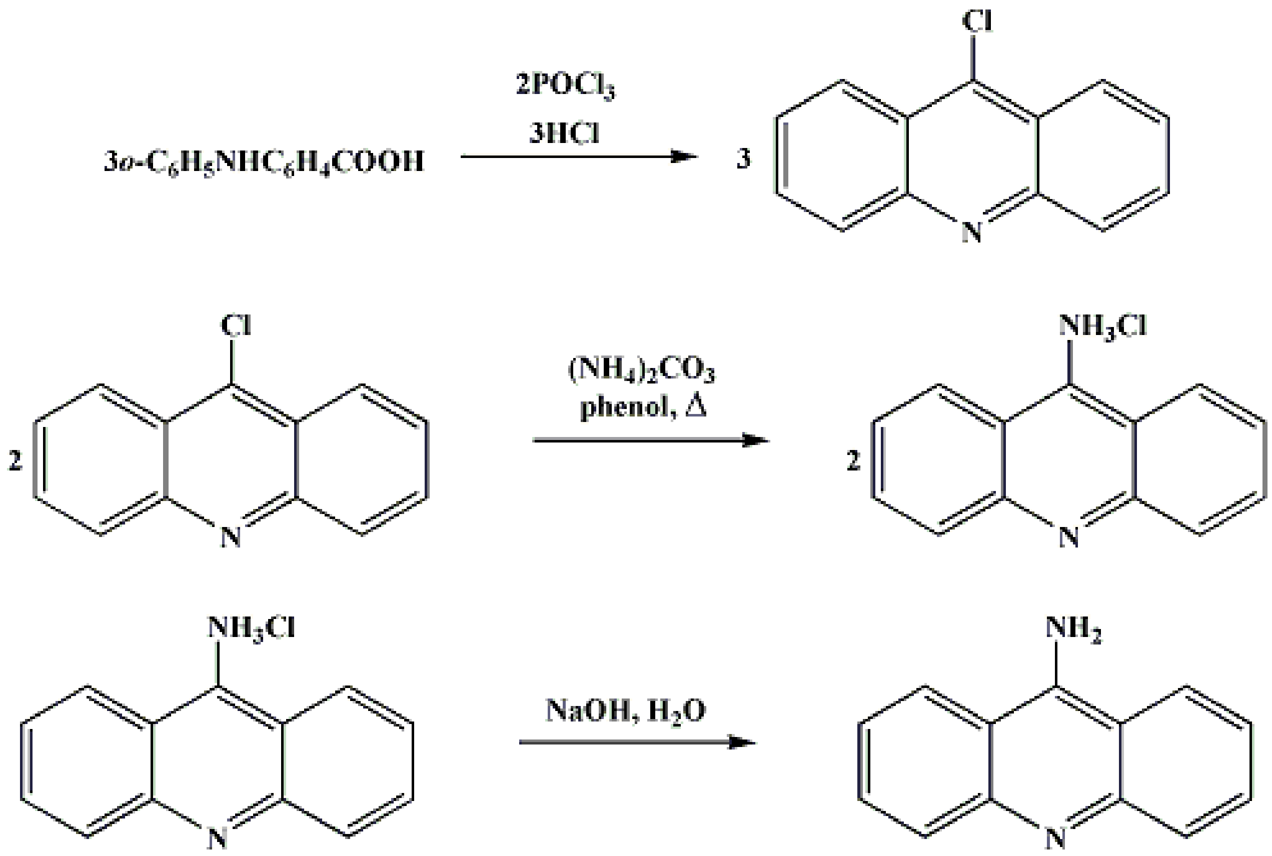
9-AMINOACRIDINE

[Acridine, 9-amino-]



Submitted by Adrien Albert and Bruce Ritchie.
Checked by R. L. Shriner and John C. Robinson, Jr..

1. Procedure

In a 500-ml. round-bottomed flask fitted with a water-cooled condenser, 50 g. (0.23 mole) of N-phenylanthranilic acid (or 46 g. of acridone) is mixed with 160 ml. (270 g., 1.76 moles) of phosphorus oxychloride (Note 1). The mixture is slowly heated (about 15 minutes) to 85–90° on a water bath. A vigorous reaction sets in, and the flask is removed at once from the hot bath. If the reaction becomes too violent, the flask is immersed in a beaker of cold water for a moment. After 5–10 minutes, when the boiling subsides somewhat, the flask is immersed in an oil bath. The temperature of the bath is then raised to 135–140°, where it is maintained for 2 hours. The excess phosphorus oxychloride is removed by distillation from an oil bath at 140–150° under a vacuum of about 50 mm. The residue, after cooling, is poured into a well-stirred mixture of 200 ml. of concentrated ammonia solution, 500 g. of ice, and 200 ml. of chloroform. The flask is rinsed by shaking with a little chloroform-ammonia mixture (about 25–30 ml.). When no more undissolved solid remains (about 30 minutes is required), the chloroform layer is separated and the aqueous layer is extracted with an additional 40 ml. of chloroform. The united chloroform extracts are dried over 10 g. of calcium chloride and filtered, and the solvent is removed by

distillation. The resultant greenish gray powder is dried at 70° for 20 minutes (Note 2) and (Note 3). The yield of crude 9-chloroacridine is 50 g. (practically theoretical), m.p. 117–118° (Note 4).

In a 1-l. beaker are placed 50 g. (0.23 mole) of crude 9-chloroacridine and 250 g. (2.7 moles) of phenol (Note 5). The mixture is stirred mechanically while it is heated to 70° (internal temperature) in an oil bath. Stirring is continued, and 30 g. (0.38 mole) of powdered ammonium carbonate (Note 6) is added as rapidly as the vigorous effervescence permits. The internal temperature is quickly raised to 120° and maintained there while the mixture is stirred for 45 minutes. The mixture is cooled to 30° and poured into 600 ml. of acetone in a beaker surrounded by ice. After about an hour, precipitation of 9-aminoacridine hydrochloride is complete and the product is filtered and washed free from phenol with 250 ml. of acetone (Note 7). The cake is extracted by boiling it with water three times, using successively 800, 200, and 100 ml., the last portion containing 2 ml. of concentrated hydrochloric acid. The hot solutions are filtered to remove the small amount of carbonaceous matter, and the filtrates are combined. Any precipitate is redissolved by heating, and then a solution of 60 g. of sodium hydroxide in 300 ml. of water is added. The mixture is cooled and filtered; the solid is washed with 300 ml. of cold water and dried at 120°. The yield is 34–38 g. (76–85% based on phenylanthranilic acid or acridone) of bright yellow powder, m.p. 230°. This product is pure enough for most purposes, but the crude material may be purified by boiling 38 g. of it with 1.2 l. of acetone. The mixture is filtered by suction, and the filtrate is chilled in an ice-salt bath. The first crop weighs 26–27 g., and concentration of the mother liquor to 500 ml. yields an additional 6–7 g. of crystals. Both crops melt at 232–233°, and the recovery is 32–34 g. (84–89%) (Note 8).

2. Notes

1. The phosphorus oxychloride should be freshly distilled.
2. 9-Chloroacridine is readily hydrolyzed in neutral and acid solutions; hence it must not be exposed to the air after removal of the phosphorus oxychloride and before treatment with ammonia. If the drying is carried out at a higher temperature, loss results through sublimation. Care should be taken to keep 9-chloroacridine from entering the eyes, as it is distinctly irritating.
3. It was found convenient to dry the chloroacridine by pouring the concentrated chloroform extract directly into the 1-l. beaker to be used for the next step, and heating the oil bath to 70° for the required 20 minutes.
4. If pure 9-chloroacridine is desired, the crude product is dissolved in a little boiling alcohol, and 0.5% ammonia is added until the solution becomes milky. About 0.5 g. of Norit is then added; the solution is quickly filtered and at once cooled in an ice bath. White crystals, melting at 119–120°, are obtained. The product keeps best in a desiccator over potassium carbonate. By warming 9-chloroacridine with various primary and secondary amines, many substituted 9-aminoacridines are readily obtained.
5. 9-Phenoxyacridine appears to be an intermediate in this reaction.
6. The ammonium carbonate should analyze for 30% ammonia. Baker's analyzed ammonium carbonate (lump) is suitable.
7. The acetone and the phenol, recovered from the filtrate by simple distillation and

by vacuum distillation, respectively, may be used again.
8. 9-Aminoacridine hydrochloride is one of the most highly fluorescent of substances. The 1:1000 aqueous solution is pale yellow with only a faint green fluorescence, but the 1:100,000 solution is colorless with an intense blue fluorescence.9-Aminoacridine is a moderately strong base;[1] the dissociation constant is 3×10^{-5} (aniline = 5×10^{-10}).

3. Discussion

9-Chloroacridine has been prepared by heating thioacridone,[1] acridone,[2] or N-phenylanthranilic acid[3,4,5] with phosphorus pentachloride, phosphorus oxychloride, or a mixture of the two phosphorus halides, with and without the addition of hydrocarbon solvents. The present method is essentially that of Magidson,[3] but the troublesome filtration of the glutinous and easily hydrolyzed 9-chloroacridine has been avoided by the use of chloroform.

The method described for converting 9-chloroacridine to 9-aminoacridine was developed after experience with the methods given in the literature, namely: conversion of 9-chloroacridine, through 9,9-diphenoxyacridan, to 9-phenoxyacridine, which is then heated with ammonium chloride;[6] heating 9-chloro-, 9-ethoxy-, or 9-phenoxyacridine with ammonia and a copper compound under pressure,[7] or with phenylhydrazine followed by acid reduction.[8] 9-Aminoacridine has also been prepared by hydrolyzing 9-cyanoacridine (from acridine or 9-chloroacridine) to the corresponding acid amide, and subsequent degradation to the required amine;[9] and by the decomposition of the acid azide.[10] Some methods developed for preparing aminoethoxyacridines[11] are also of interest. 9-Aminoacridine has also been obtained by the reaction of acridine with sodium amide.[12]

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9. Lehrnstedt, *Ber.*, **64**, 1232 (1931).
10. Meister, Lucius, and Bruning, Ger. pat. 364,035–6 [*Frdl.*, **14**, 805–806 (1921–1925); *C. A.*, **18**, 1131 (1924)].
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12. Bauer, *Chem. Ber.*, **83**, 10 (1950).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

9-chloro-, 9-ethoxy-, or 9-phenoxyacridine

calcium chloride (10043-52-4)

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

ammonium carbonate

ammonia (7664-41-7)

ammonium chloride (12125-02-9)

aniline (62-53-3)

sodium hydroxide (1310-73-2)

phosphorus pentachloride (10026-13-8)

chloroform (67-66-3)

phenol (108-95-2)

Phenylhydrazine (100-63-0)

copper (7440-50-8)

acetone (67-64-1)

Norit (7782-42-5)

Phosphorus Oxychloride (21295-50-1)

Acridone (578-95-0)

N-Phenylanthranilic acid, phenylanthranilic acid (91-40-7)

azide

sodium amide (7782-92-5)

9-Aminoacridine, Acridine, 9-amino- (90-45-9)

chloroform-ammonia

9-Chloroacridine (1207-69-8)

9-aminoacridine hydrochloride

chloroacridine

9-Phenoxyacridine

thioacridone

9,9-diphenoxyacridan

9-cyanoacridine

acridine (260-94-6)

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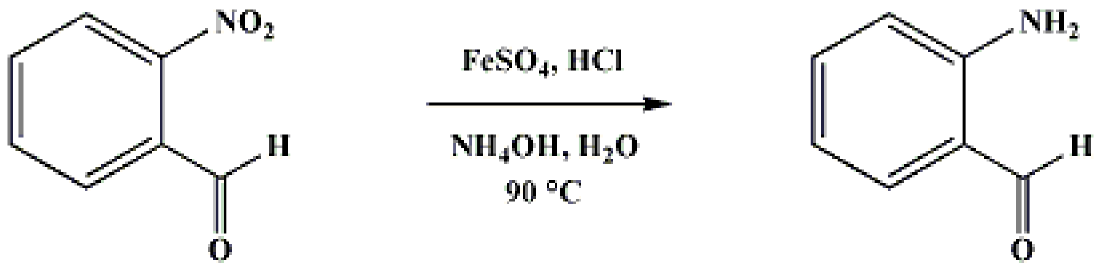
Organic Syntheses, CV 3, 56

o-AMINOBENZALDEHYDE

[Anthranilaldehyde]



Submitted by Lee Irvin Smith and J. W. Opie[1].
Checked by Cliff S. Hamilton, C. W. Winter, and Harry M. Walker.

1. Procedure

A 1-l. three-necked flask is employed as a reaction vessel from which the product can be steam-distilled *immediately* after completion of the reaction (Note 1). It is convenient to arrange the apparatus for the reaction and that for the steam distillation on the same steam bath, with provision for the rapid connection of the flask to the distillation assembly at the desired time. For use as a reaction vessel the flask is mounted on a steam bath and fitted with a mechanical stirrer and a reflux condenser; the third neck is closed by a cork.

In the steam-distillation assembly (Note 1) one of the small necks of the flask is fitted with a steam-inlet tube, connected through a water trap to a steam line; the other small neck is closed by a cork. The central neck is fitted to a Kjeldahl trap leading to a 50-cm. Allihn condenser set downward and connected in series to a 50-cm. Liebig condenser. The second condenser leads to a 500-ml. three-necked flask used as the receiver. The receiving flask is immersed in an ice bath and fitted with an Allihn reflux condenser.

When all the apparatus has been set up and tested the flask is connected to the reaction assembly, and 175 ml. of water, 105 g. (0.38 mole) of ferrous sulfate heptahydrate, 0.5 ml. of concentrated hydrochloric acid, and 6 g. (0.04 mole) of *o*-nitrobenzaldehyde (see p. 641) are introduced in the order given. The stirrer is then started, and the flask is heated by means of the steam bath. When the temperature of the mixture reaches 90°, 25 ml. of concentrated ammonium hydroxide is added in one portion, and at 2-minute intervals three 10-ml. portions of ammonium hydroxide are added. Stirring and heating are continued throughout. The total reaction time is 8–10 minutes.

Immediately after the addition of the last portion of ammonium hydroxide, the reflux condenser and stirrer are removed and the flask is connected to the steam-distillation assembly. The mixture is steam-distilled as rapidly as possible, and two 250-ml. fractions of distillate are collected during a period of 10–13 minutes (Note 2). The first

fraction is saturated with sodium chloride, and the solution is stirred at 5° until precipitation appears to be complete. The solid is collected on a Büchner funnel and dried in the air. The product weighs 2.72–3.11 g. (57–65%) and melts at 38–39°. The second fraction of the distillate is saturated with sodium chloride and combined with the filtrate remaining from the first fraction. The combined solution is extracted with two 45-ml. portions of ether. The combined ether extract is filtered, dried over anhydrous sodium sulfate, and concentrated by distillation, finally under reduced pressure. The residue solidifies on cooling and weighs 0.6–1.0 g.; it can be purified by steam distillation from 40–50 ml. of saturated sodium chloride solution until 100 ml. of distillate is collected, saturation of the distillate with sodium chloride, cooling, and filtration. The pure product so obtained weighs 0.42–0.87 g. The total yield (Note 3) is 3.3–3.6 g. (69–75%).

2. Notes

1. Rapid removal of the product from the reaction mixture is essential to the success of this preparation. The steam-distillation assembly should be sturdily constructed, with all parts except the distilling flask in place at the time the reaction is started. To ensure the proper fitting of the distilling flask it is convenient to construct the distillation apparatus with the flask in place and, after testing of the apparatus, to remove the flask and incorporate it into the reaction assembly.
2. The first fraction is drawn into a round-bottomed flask through a tube inserted into the third neck of the receiver (by the use of a water pump or a suction line) without interruption of the distillation.
3. The submitters have obtained yields of about 70% in runs eight times as large as that described. This amino aldehyde undergoes self-condensation on standing, especially in a desiccator, and so the product should be used immediately.

3. Discussion

o-Aminobenzaldehyde has been obtained from its oxime by the action of ferric chloride;[2] the oxime was obtained by reduction of *o*-nitrobenzaldoxime.[3] *o*-Aminobenzaldehyde has also been obtained from *o*-aminobenzyl alcohol by the action of sodium sulfide[4] or by the action of zinc dust and alkali;[5] and from *o*-nitrobenzylaniline or N-(2-nitrobenzyl) sulfanilic acid by the action of alkali sulfides and sulfur.[6] The aldehyde results in small amounts from the action of alkali alone upon *o*-nitrobenzyl alcohol[7] and from the action of ferrous sulfate and ammonia upon anthranil.[8] The only preparative methods involve the reduction of *o*-nitrobenzaldehyde with ferrous sulfate and ammonia.[8], [9] Catalytic reduction of *o*-nitrobenzaldehyde has been reported to yield *o*-aminobenzaldehyde,[10,11] but the method was not successful in the hands of the submitters.

References and Notes

1. Work done under contract with the Office of Scientific Research and Development.
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3. Gabriel and Meyer, *Ber.*, **14**, 2339 (1881); **36**, 803 (1903).
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7. Freundler, *Bull. soc. chim. France*, [3] **31**, 879 (1904); Carré, *Compt. rend.*, **140**, 664 (1905); *Bull. soc. chim. France*, [3] **33**, 1162, 1165 (1905); *Ann. chim.*, [8] **6**, 409, 413 (1905).
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9. Friedländer and Göhring, *Ber.*, **17**, 456 (1884); Bamberger, *Ber.*, **60**, 319 (1927).
10. Ruggli and Schmidt, *Helv. Chim. Acta*, **18**, 1235 (1935); Nord, *Ber.*, **52**, 1711 (1919).
11. Borsche and Ried, *Ber.*, **76B**, 1015 (1943).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ether (60-29-7)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

sulfur (7704-34-9)

ferrous sulfate (13463-43-9)

zinc (7440-66-6)

ferric chloride (7705-08-0)

ammonium hydroxide (1336-21-6)

sodium sulfide (1313-82-2)

o-Nitrobenzaldehyde (552-89-6)

Anthranilaldehyde, o-Aminobenzaldehyde (529-23-7)

ferrous sulfate heptahydrate (7782-63-0)

N-(2-nitrobenzyl) sulfanilic acid

anthranil (271-58-9)

o-nitrobenzaldoxime

o-Aminobenzyl alcohol (5344-90-1)

o-nitrobenzylaniline

o-nitrobenzyl alcohol (612-25-9)

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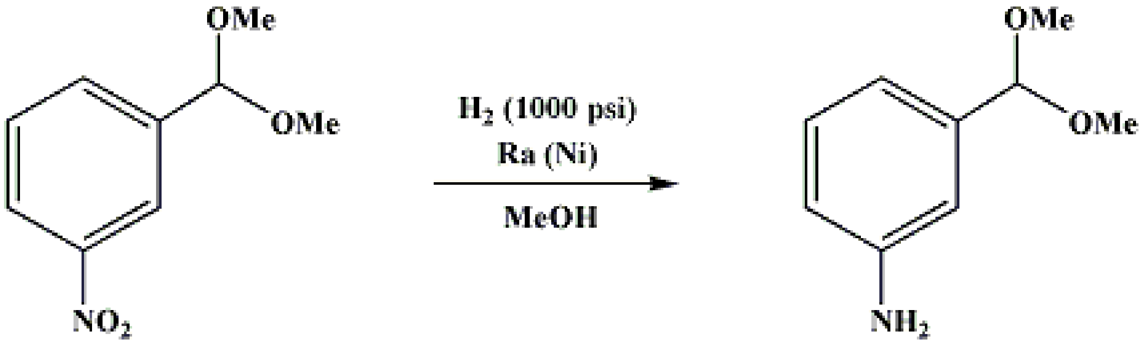
Organic Syntheses, CV 3, 59

m-AMINOBENZALDEHYDE DIMETHYLACETAL

[Benzaldehyde, *m*-amino-, dimethylacetal]



Submitted by Roland N. Icke, C. Ernst Redemann, Burnett B. Wisegarver, and Gordon A. Alles.
Checked by H. R. Snyder and Frank X. Werber.

1. Procedure

In a 1-l. steel bomb are placed 295 g. (1.5 moles) of *m*-nitrobenzaldehyde dimethylacetal (p. 644), 250 ml. of technical anhydrous methanol, and 1 tablespoon of Raney nickel catalyst. Hydrogen is introduced until the pressure is about 1000 lb. (Note 1). The bomb is heated to about 40°, at which point the heating is discontinued and the shaker is started. The hydrogenation soon becomes rapid as the temperature rises to about 70° (Note 2). The bomb is refilled with hydrogen as many times as necessary (Note 3). The theoretical amount of hydrogen (4.5 moles) is absorbed in about 1.5 hours.

The bomb is cooled, the remaining hydrogen is discharged, and the bomb is opened. The solution is transferred to a beaker, and the bomb is rinsed with a little methanol which is added to the solution. The catalyst is removed by filtration *(Caution! The catalyst may be pyrophoric)*, and most of the filtrate is transferred to a 500-ml. Claisen flask set on a steam bath for distillation of the methanol; the remainder of the filtrate is introduced into the Claisen flask when the volume of the first portion has been reduced sufficiently by distillation. After all the methanol has been removed the aminoacetal is distilled under diminished pressure. The yield of *m*-aminobenzaldehyde dimethylacetal, a light-yellow liquid boiling at 123–124°/4 mm. or 110–112°/1.5 mm., is 168–196 g. (67–78%).

2. Notes

1. The hydrogenation is similar to one described on p. 63. As the bomb does not contain enough hydrogen to complete the reduction, more hydrogen should be admitted whenever the pressure drops below 300 lb.

2. Because of the high heat capacity of the bomb the internal temperature continues to rise (to about 70°) after the heater is turned off. As the exothermic hydrogenation begins the temperature rises to about 80°. The temperature should be kept below 85° to prevent hydrogenolysis of the acetal.

3. If the hydrogenation is started at a pressure of about 1500 lb. in a 2.5-l. bomb it will not be necessary to introduce more hydrogen. However, it may be necessary to stop the shaker occasionally to prevent a temperature rise beyond 85°.

3. Discussion

This acetal has not been described previously. The corresponding diethylacetal has been prepared by the reduction of *m*-nitrobenzaldehyde diethylacetal with sodium sulfide[1] and by the reaction of the anhydro compound of *m*-aminobenzaldehyde with ethanolic hydrogen chloride and ethyl orthoformate.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 564

References and Notes

1. Haworth and Lapworth, *J. Chem. Soc.*, **121**, 76 (1922).
2. Bottomley, Cocker, and Nanney, *J. Chem. Soc.*, **1937**, 1891.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Aminoacetal

diethylacetal

ACETAL (105-57-7)

hydrogen chloride (7647-01-0)

methanol (67-56-1)

hydrogen (1333-74-0)

nickel (7440-02-0)

sodium sulfide (1313-82-2)

Ethyl orthoformate

m-aminobenzaldehyde (1709-44-0)

m-Aminobenzaldehyde dimethylacetal (53663-37-9)

m-nitrobenzaldehyde dimethylacetal (3395-79-7)

m-nitrobenzaldehyde diethylacetal

Benzaldehyde, m-amino-, dimethylacetal

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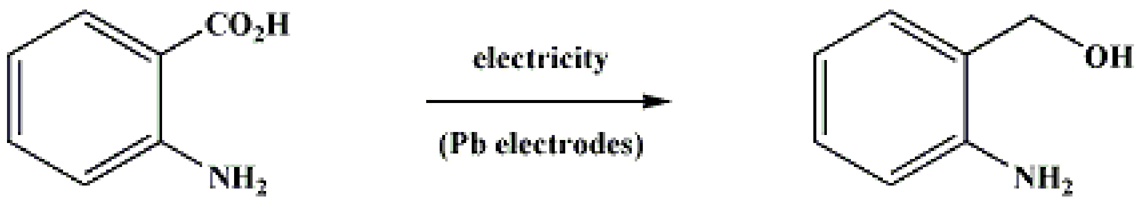
o-AMINOBENZYL ALCOHOL

[Benzyl alcohol, *o*-amino-]

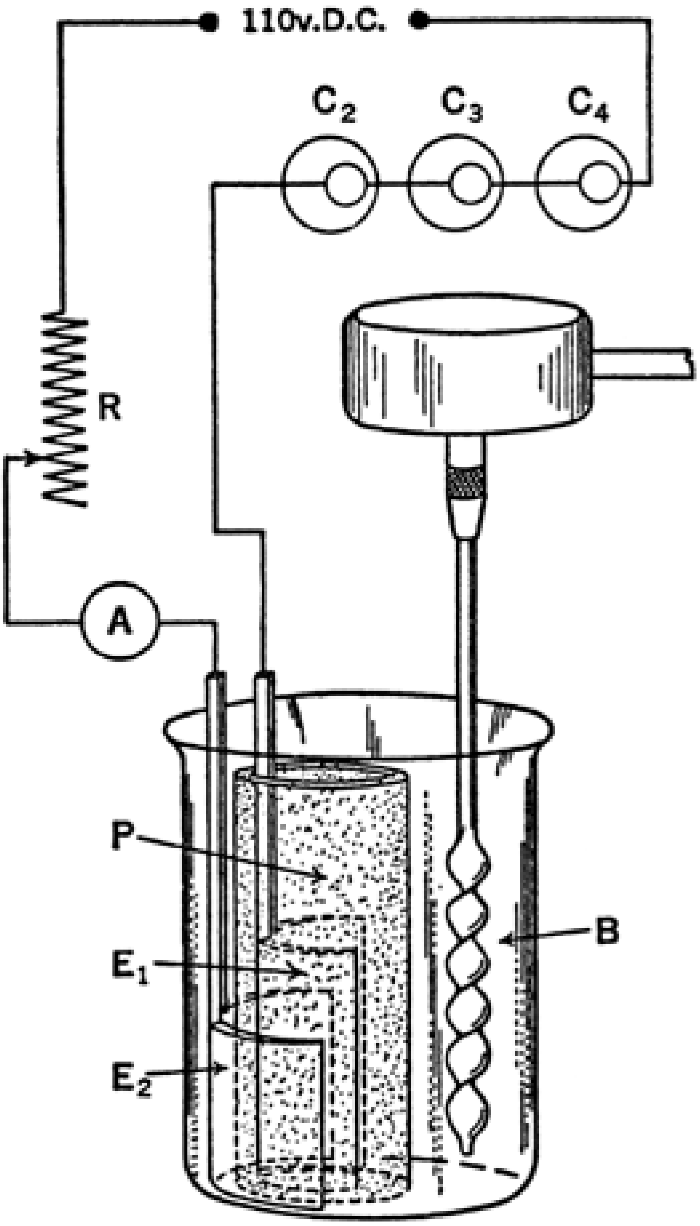


Submitted by George H. Coleman and Herbert L. Johnson.
Checked by Reynold C. Fuson and E. A. Cleveland.

1. Procedure

The reduction is carried out in four cells of the type shown in f.htmig. 2. Each cell consists of a 1-l. beaker (*B*), a porous cup (*P*), a mechanical stirrer, and sheet lead electrodes (E_1 and E_2) each having a total surface area of 100 sq. cm. (Note 1). In the cathode space of each cell are placed 25 g. (0.18 mole) of anthranilic acid (Note 2) and 400 ml. of 15% sulfuric acid. In each porous cup is placed 200 ml. of 15% sulfuric acid. The cells are connected in series as shown in Fig. 5 with an ammeter (*A*) and suitable resistance (*R*) (Note 3) also in the circuit.

Fig. 2.



The stirrers are started, the current (110 volt d.c.) is turned on, and the resistance is so adjusted that the ammeter records 10–12 amperes. The temperature of the solution in the cells is maintained at 20–30° by surrounding them with a bath of cool water (Note 4). The reduction is complete after 60–70 ampere-hours. This fact is indicated by the increased evolution of hydrogen and the complete solution of the anthranilic acid.

The cathode liquid is removed from the cells and neutralized with solid ammonium carbonate or concentrated aqueous ammonia. The solution is filtered to remove any resinous material, then saturated with ammonium sulfate and extracted with five 80-ml. portions of chloroform (Note 5). The chloroform solution is dried with 20 g. of anhydrous sodium or magnesium sulfate and filtered, and the chloroform is removed by evaporation on a steam bath (Note 6). The yield of *o*-aminobenzyl alcohol obtained from the four cells is 62–70 g. (69–78%).

This product is light brown and melts at 75–80°. After one recrystallization from petroleum ether the melting point is 80–81° (Note 7).

2. Notes

1. Ordinary sheet lead of 99.9% purity is satisfactory.
2. The anthranilic acid melted at 143–144°.
3. A resistance of 10–12 ohms is required for the apparatus described. It may be necessary to adjust the rheostat several times during the course of the reaction.
4. The checkers found it necessary to cool the cells by frequent addition of ice to the water bath surrounding them.
5. Ethyl ether may be used in place of chloroform but is not so satisfactory since several more extractions are necessary to remove the same amount of product from the aqueous solution.
6. The evaporation may be carried out in an apparatus that permits recovery of the solvent.
7. Petroleum ether boiling at 65–75° is used for recrystallization. The product has a limited solubility even in the hot solvent, and a relatively large volume is therefore required.

3. Discussion

o-Aminobenzyl alcohol has been prepared by the reduction of *o*-nitrobenzaldehyde[1,2] or *o*-nitrobenzyl alcohol[3,4] with zinc and hydrochloric acid in alcoholic solution, and by the reduction of anthranilic acid with lithium aluminum hydride.[5,6] The present method of preparing *o*-aminobenzyl alcohol is a modification of that described by Mettler.[7] Other substituted benzyl alcohols have been obtained by the same method.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 276

References and Notes

1. Friedländer and Henriques, *Ber.*, **15**, 2109 (1882).
2. Paal and Senniger, *Ber.*, **27**, 1084 (1894).
3. Gabriel and Posner, *Ber.*, **27**, 3512 (1894).
4. Auwers, *Ber.*, **37**, 2260 (1904).
5. Nystrom and Brown, *J. Am. Chem. Soc.*, **69**, 2548 (1947).
6. Conover and Tarbell, *J. Am. Chem. Soc.*, **72**, 3586 (1950).
7. Mettler, *Ber.*, **38**, 1751 (1905).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

sodium or magnesium sulfate

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ammonium carbonate

ammonia (7664-41-7)

ethyl ether (60-29-7)

hydrogen (1333-74-0)

chloroform (67-66-3)

zinc (7440-66-6)

Anthranilic Acid (118-92-3)

ammonium sulfate (7783-20-2)

o-Nitrobenzaldehyde (552-89-6)

lithium aluminum hydride (16853-85-3)

o-Aminobenzyl alcohol, Benzyl alcohol, o-amino- (5344-90-1)

o-nitrobenzyl alcohol (612-25-9)

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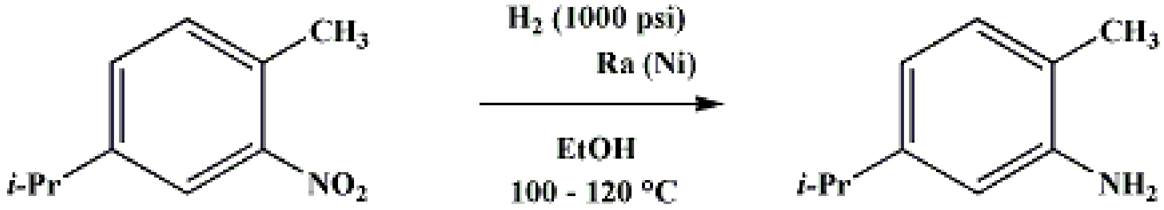
Organic Syntheses, CV 3, 63

2-AMINO-*p*-CYMENE

[Carvacrylamine]



Submitted by C. F. H. Allen and James VanAllan.
Checked by Homer Adkins

1. Procedure

A mixture of 179 g. (167 ml., 1 mole) of 2-nitro-*p*-cymene (p. 653), 300 ml. of absolute ethanol, and 3–5 g. of Raney nickel (p. 181) is placed in the steel reaction vessel of a high-pressure hydrogenation apparatus.[1] The bomb is then closed, and hydrogen is admitted until the pressure, at 25°, is about 1000 lb. While the bomb is shaken, the temperature is rapidly raised to 80–90°, and then the heater is shut off (Note 1). Owing to the strong exothermic reaction, the temperature continues to rise, reaching about 120°, while the pressure drops rapidly. The pressure in the reaction vessel is maintained at 700–1500 lb., by the introduction of hydrogen from a tank, until the rapid reaction is over (15 minutes). The reaction mixture is kept at 100–120° for 30 minutes after there is no further drop in the pressure of hydrogen. After the bomb has cooled, the hydrogen is slowly released and the catalyst is separated from the reaction mixture by centrifuging, or by filtration through a sintered-glass or Büchner funnel (Note 2). The alcohol and water are removed by distillation, and the product is fractionated in a suitable apparatus (Note 3), (Note 4), (Note 5), (Note 6), (Note 7).

The amine distils at 239–240°/740 mm., 242° (cor.)/760 mm., 110°/10 mm., or 92–94°/2 mm. In the first distillation the portion boiling below 225°/740 mm. (or below 100°/9 mm.) is discarded. The yield is 130–135 g. (87–90%).

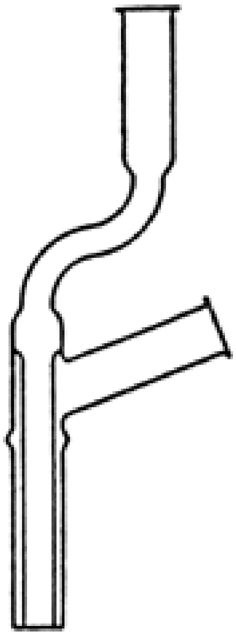
2. Notes

1. The hydrogenation of nitro compounds liberates so much heat, and the reaction may proceed so rapidly, that precautions must be taken against excessive reaction temperatures. Temperatures of 150–200° may bring about the formation of secondary amines, and at higher temperatures decomposition reactions may occur with explosive violence. These dangers may be avoided by the use of small amounts of catalyst and by having an insufficient amount of hydrogen in the reaction vessel at the beginning of the reaction. After sufficient

hydrogen for the hydrogenation of half of the nitro compound has been taken up there need be no fear that the reaction will proceed too rapidly. It is always desirable, however, to complete the hydrogenation as rapidly as possible while avoiding temperatures above about 120°. The use of ethanol as a solvent prevents the separation of a water layer, which would cover most of the catalyst and thus give rise to a slow and perhaps incomplete hydrogenation.

2. If the sample of nitrocymene is impure, or if the catalyst is of poor quality, the hydrogenation may not proceed to completion and a solution of the product in hydrochloric acid will be turbid. In this event, the mixture of products (after separation of the spent catalyst) may again be submitted to hydrogenation. An alternative procedure involves removal of the non-basic material by steam distillation of a mixture of the product with 350 ml. of water and 90 ml. of concentrated hydrochloric acid. The amine is then liberated from its salt by the addition of 45 g. of sodium hydroxide and is extracted with 500 ml. of ether. The ether layer may be siphoned from the water layer. The ether is removed by distillation, and the residue is fractionated as described in the procedure. For steam distillations, the submitters employ the adapter shown in f.htmig. 3. With this adapter the apparatus is much more compact than in the usual arrangement, for the receiver may serve as a partial condenser, as in distillation under reduced pressure.

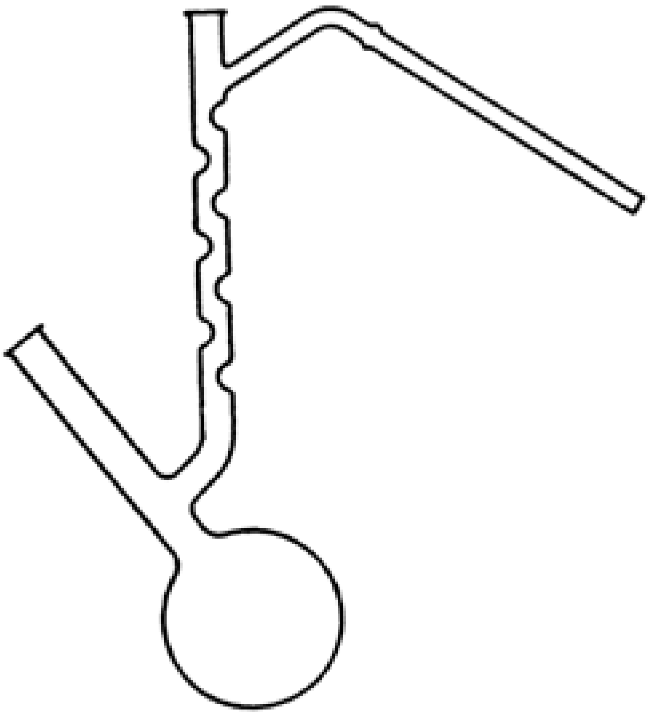
Fig. 3.



3. The apparatus may consist of a modified Claisen flask, or of an ordinary flask connected to a Vigreux, Widmer, modified Widmer, or other column. The checker used a modified Widmer column and a distillation at 9 mm. pressure. The submitters conducted the distillation at atmospheric pressure, in the type of flask shown in f.htmig. 4. This type of flask, as well as the adapter described in (Note 2), has been used in the laboratories of the Eastman Kodak Company for some time. In comparison with the standard Claisen flask, this flask has several advantages. It has a longer column; liquids seldom bump over, and consequently

more material may be handled in a flask of given size; and material that has come into contact with the rubber stopper cannot contaminate the distillate. No dimensions are given for the flask, or for the adapter described in (Note 2) above; these pieces may be constructed in various sizes to suit individual needs.

Fig. 4.



4. Nitrocymene usually contains about 8% of *p*-nitrotoluene. The complete separation of the resulting *p*-toluidine from the 2-amino-*p*-cymene requires a rather careful fractionation.
5. If air comes in contact with the hot amine vapor, the product will be colored. However, a product distilled at 9 mm. with a capillary ebullition tube was only faintly yellow.
6. The reduction may also be carried out at lower pressures in the usual laboratory apparatus [*Org. Syntheses* Coll. Vol. **1**, 53 (1932); 63 (1941)]. A mixture of 50 g. of nitrocymene, 200 ml. of 95% ethanol, and 5 g. of Raney nickel is reduced at 85–90°, at an initial pressure of 55–60 lb.; the time required is 6 hours. The product is processed as described above. The yield is 33–36 g. (80–85%).
7. Nitrocymene may also be reduced by the use of iron powder, essentially as described under 2,4-diaminotoluene (*Org. Syntheses,* **11**, 32; Coll. Vol. **2**, 160) (Kenneth A. Kobe, private communication).[2]

3. Discussion

Because of the accessibility of *p*-cymene, reduction of the nitroderivative constitutes the only practical method for preparation of 2-aminocymene. Tin[3,4,5,6] and iron,[7,8] together with hydrochloric acid, have been used for this purpose. A patent[7] mentions

the use of hydrogen in the presence of a nickel catalyst.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 59
- Org. Syn. Coll. Vol. 3, 140
- Org. Syn. Coll. Vol. 3, 159
- Org. Syn. Coll. Vol. 3, 438

References and Notes

1. American Instrument Company, Silver Springs, Maryland, or Parr Instrument Company, Moline, Illinois.
2. Doumani and Kobe, *J. Am. Chem. Soc.*, **62**, 563 (1940).
3. Soderbaum and Widman, *Ber.*, **21**, 2127 (1888).
4. Wheeler and Smithey, *J. Am. Chem. Soc.*, **43**, 2613 (1921).
5. Demonbreun and Kremers, *J. Am. Pharm. Assoc.*, **12**, 296 (1923) [*C. A.*, **17**, 3906 (1923)].
6. Straneo, *Ann. chim. appl.*, **31**, 116 (1941).
7. U. S. pat. 1,314,920 [*C. A.*, **13**, 2765 (1919)].
8. Doumani and Kobe, *Ind. Eng. Chem.*, **31**, 264 (1939).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

iron (7439-89-6)

tin (7440-31-5)

nickel (7440-02-0)

p-cymene (99-87-6)

2,4-Diaminotoluene (95-80-7)

Carvacrylamine, 2-aminocymene, 2-Amino-p-cymene (2051-53-8)

nitrocymene

p-toluidine (106-49-0)

p-nitrotoluene (99-99-0)

2-Nitro-p-cymene (943-15-7)

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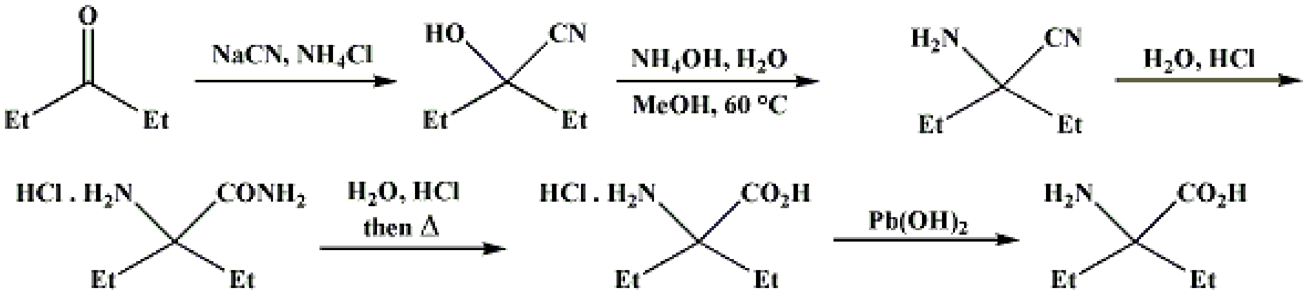
α-AMINODIETHYLACETIC ACID

[Butyric acid, α-amino-α-ethyl-]



Submitted by Robert E. Steiger
Checked by W. E. Bachmann and Yun-Tsung Chao.

1. Procedure

A solution of 50 g. (1 mole) of sodium cyanide (98% purity) in 100 ml. of water is placed in a 2-l. round-bottomed flask (Note 1) fitted with a ground-glass stopper. A solution of 58.9 g. (1.1 moles) of ammonium chloride in 140 ml. of lukewarm water is added, followed by 67 ml. (1 mole) of concentrated ammonium hydroxide (sp. gr. 0.9). This mixture is stirred mechanically and is cooled by a stream of water while a solution of 86.1 g. (1 mole) of diethyl ketone in 160 ml. of methanol (Note 2) is added. The flask is then stoppered (Note 3) and half immersed for 5 hours in a water bath, the temperature of which is kept at 55–60°. The reaction mixture is then cooled in an ice bath and poured (with precautions, i.e., under a properly ventilated hood) into 800 ml. of concentrated hydrochloric acid (sp. gr. 1.18) contained in a 5-l. round-bottomed flask which is surrounded up to the neck by ice and water. The reaction flask is rinsed with two 25-ml. portions of water. The mixture is now saturated at 0–5° with hydrogen chloride gas. After standing overnight under a hood, the mixture is refluxed for 2.5 hours (Note 4).

The solution is evaporated to dryness under reduced pressure on a water bath. In order to remove as much hydrochloric acid as possible, the temperature of the bath is raised to 100° toward the end of the distillation. The residue of amino acid hydrochloride and inorganic salts is suspended in 500 ml. of absolute ethanol. The suspension is boiled on a steam bath for a short time, then cooled to room temperature and filtered on a Büchner funnel. The residue of inorganic salts is washed with 500 ml. of absolute ethanol. To the combined filtrates is added 400 ml. of ethyl ether (U. S. P. quality) in order to precipitate inorganic material. After several hours the mixture is filtered, and the residue is washed with a 5:2 mixture of absolute ethanol and ether. The filtrate is transferred to a 5-l. round-bottomed flask, about 200 ml. of water is added, and the liquids are removed by distillation under reduced pressure. The nearly dry residue is dissolved in 2 l. of water, and the solution is treated with an excess of freshly prepared lead hydroxide (Note 5). The suspension is diluted with water to a volume of about 3.5 l. and is then concentrated under reduced pressure, at as low a temperature as possible, to a volume of about 2 l. The suspension is then filtered with suction (Note 6), and the residue of lead salts is washed thoroughly with water. The cloudy filtrate, which still contains some free ammonia, is concentrated by distillation under reduced pressure to a volume of about 300–400 ml. The mixture is filtered, the filtrate is saturated with hydrogen sulfide gas, and the precipitate of lead sulfide is removed by filtration with suction (Note 6). The solution is now concentrated by distillation under reduced pressure on a water bath, and 1 l. of 95% ethanol is added to the nearly dry residue of the amino acid. The suspension is boiled under a reflux condenser until nearly all the amino acid is dissolved, and the mixture is then allowed to cool to room temperature. The amino acid, which separates in the form of fine needles, is collected on a Büchner funnel and washed with a little 95% ethanol. A second crop of crystals is obtained by evaporating the combined filtrates to dryness, dissolving the residue in the minimum amount of hot water, and treating the solution with 95% ethanol. The amino acid is dried in the air and then in a vacuum desiccator over phosphorus pentoxide. The total yield of product is 58.8–65 g. (39–43%, assuming that the product contains exactly one molecule of water

of crystallization) (Note 7).

2. Notes

1. The checkers used a 1-l. Erlenmeyer flask fitted with a ground-glass stopper.
2. The methanol must be free from acetone since this ketone would give rise to α-aminoisobutyric acid.
3. The ground-glass stopper should be lubricated slightly with stop-cock grease. It must be secured firmly by means of adhesive tape, as some pressure develops when the flask is heated.
4. The hydrolysis must be carried out under a hood. The top of the reflux condenser should be connected with the ventilation pipe by means of a piece of glass tubing. The methanol contained in the reaction mixture escapes in the form of methyl chloride, along with some hydrogen chloride.
5. The lead hydroxide is prepared by adding 1.5 l. of a 2 *N* solution of sodium hydroxide (3 moles) through a dropping funnel to a continuously stirred solution of 569 g. (1.5 moles) of lead acetate, $(CH_3CO_2)_2Pb \cdot 3H_2O$, in 1.35 l. of water. The precipitate is collected on a 13-cm. Büchner funnel and washed well with water in order to remove water-soluble impurities. The paste of lead hydroxide is transferred to the solution that is to be freed of chloride ions.
6. A Büchner funnel of adequate size is fitted with two pieces of hardened filter paper covered with a thin layer of moistened Norit.
7. The checkers obtained 65 g. of pure amino acid in the first crop; the second crop of 5 g. contained chloride ion. When heated in an open tube, the pure product sublimed at 255° without melting.

3. Discussion

α-Aminodiethylacetic acid has been prepared from α-bromodiethylacetic acid and ammonia;[1] and by hydrolysis of α-aminodiethylacetonitrile with hydrochloric acid.[1,2,3,4] The required nitrile was obtained by heating diethyl ketone cyanohydrin with one equivalent of ethanolic ammonia;[2] by heating diethyl ketone with an ethanolic solution of ammonium cyanide;[3] and by heating diethyl ketone with a solution of potassium cyanide and ammonium chloride.[1, 4] α-Aminodiethylacetic acid has also been obtained from ethyl α-cyanodiethylacetate by partial hydrolysis to ethyl diethylmalonamate and subsequent degradation in alkaline hypobromite.[5]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

amino acid hydrochloride

ethanol (64-17-5)

hydrogen chloride, hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

methanol (67-56-1)

ether, ethyl ether (60-29-7)

ammonium chloride (12125-02-9)

sodium hydroxide (1310-73-2)

sodium cyanide (143-33-9)

lead hydroxide

hydrogen sulfide (7783-06-4)

lead sulfide

ammonium cyanide

potassium cyanide (151-50-8)

methyl chloride (74-87-3)

acetone (67-64-1)

lead acetate

ammonium hydroxide (1336-21-6)

α-Aminoisobutyric acid (62-57-7)

diethyl ketone (96-22-0)

α-Aminodiethylacetic acid, Butyric acid, α-amino-α-ethyl- (2566-29-2)

α-bromodiethylacetic acid (5456-23-5)

α-aminodiethylacetonitrile

diethyl ketone cyanohydrin

ethyl α-cyanodiethylacetate

ethyl diethylmalonamate

phosphorus pentoxide (1314-56-3)

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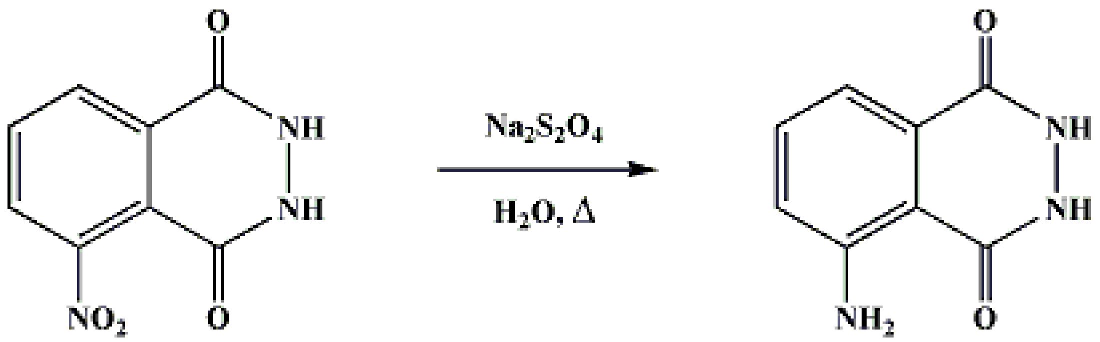
5-AMINO-2,3-DIHYDRO-1,4-PHTHALAZINEDIONE

[1,4-Phthalazinedione, 5-amino-2,3-dihydro-]



Submitted by Carl T. Redemann and C. Ernst Redemann.
Checked by Cliff S. Hamilton and C. W. Winter.

1. Procedure

In a 1-l. conical flask are placed 52 g. (about 0.15 mole) of the equimolecular mixture of 5-nitro-2,3-dihydro-1,4-phthalazinedione (p. 656) and sodium sulfate (Note 1), 200 ml. of water, and 75 ml. of 15 *N* ammonium hydroxide solution (sp. gr. 0.90). The flask is stoppered and shaken until all, or very nearly all, of the solid has dissolved, and 84 g. (0.4 mole) of sodium hydrosulfite dihydrate (Note 2) is added in three portions. The solution becomes hot, the temperature sometimes reaching the boiling point, and the dark orange-red color begins to fade. After the spontaneous reaction has subsided the solution is boiled gently for a few minutes and filtered to remove insoluble impurities. The filtrate is heated on a steam bath or over a small flame for 30 minutes. During this time the 5-amino-2,3-dihydro-1,4-phthalazinedione begins to separate as a light-yellow flocculent precipitate or as a crust adhering to the walls of the flask. The hot solution is made distinctly acid to litmus paper with glacial acetic acid and allowed to stand overnight. The yellow precipitate is separated by filtration, washed well with cold water, and dried in a hot-air oven at 110° or below. The dry material weighs 25–27 g. and melts with decomposition at 301–305° (Note 3).

This material is sufficiently pure for most purposes. The chief impurities are small amounts of inorganic salts and a trace of the unreduced nitro compound. If a purer product is desired the crude material (5 g. per 100 ml.) is dissolved in hot 3 *N* hydrochloric acid, decolorizing carbon is added, the solution is filtered promptly (Note 4), and the filtrate is made just faintly acid to Congo red paper with concentrated ammonium hydroxide. After the mixture has cooled to room temperature the pale yellow flocculent precipitate is separated by filtration, washed well with cold water, and dried in the oven at 100° or below. The recovery in the crystallization is 70–75% (Note 5), and the product melts at 329–332° (Note 4).

2. Notes

1. No advantage is gained by using the purified nitro compound.
2. The success of this reduction depends upon the quality of the sodium hydrosulfite. The reagent should be taken from a fresh bottle; material which has stood in the laboratory for a long time probably has undergone oxidation.
3. The submitters used a Kullmann copper block for the melting-point determinations. The melting point of the pure material has been reported in the literature at various values between 319° and 333°.
4. The 5-amino-2,3-dihydro-1,4-phthalazinedione should not be exposed to hot hydrochloric acid longer than necessary, since some hydrolysis appears to take place.
5. The percentage yield cannot be calculated with precision, since the exact quantity of nitro compound in the mixture taken for the reduction is unknown. The quantity of sodium hydrosulfite dihydrate employed is sufficient for the reduction of only 0.133 mole of nitro compound; the weight of the purified amino compound corresponds to about 80% of the theoretical yield calculated on the assumption that the hydrosulfite is the limiting reagent.

3. Discussion

5-Amino-2,3-dihydro-1,4-phthalazinedione, also called luminol and 3-aminophthalhydrazide, has been prepared from 5-nitro-2,3-dihydro-1,4-phthalazinedione by reduction with ammonium sulfide[1] or stannous chloride[2] and by catalytic hydrogenation over palladium on charcoal in alkaline solution[3] and by the reaction of 3-aminophthalimide[2] with hydrazine hydrate.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 656

References and Notes

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3. Wegler, *J. prakt. Chem.*, **148**, 135 (1937).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

luminol

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

sodium sulfate (7757-82-6)

sodium hydrosulfite (7775-14-6)

stannous chloride

decolorizing carbon (7782-42-5)

palladium (7440-05-3)

ammonium hydroxide (1336-21-6)

hydrazine hydrate (7803-57-8)

ammonium sulfide

5-Amino-2,3-dihydro-1,4-phthalazinedione, 1,4-Phthalazinedione, 5-amino-2,3-dihydro-, 3-aminophthalhydrazide (521-31-3)

5-Nitro-2,3-dihydro-1,4-phthalazinedione (3682-15-3)

sodium hydrosulfite dihydrate

3-aminophthalimide (2518-24-3)

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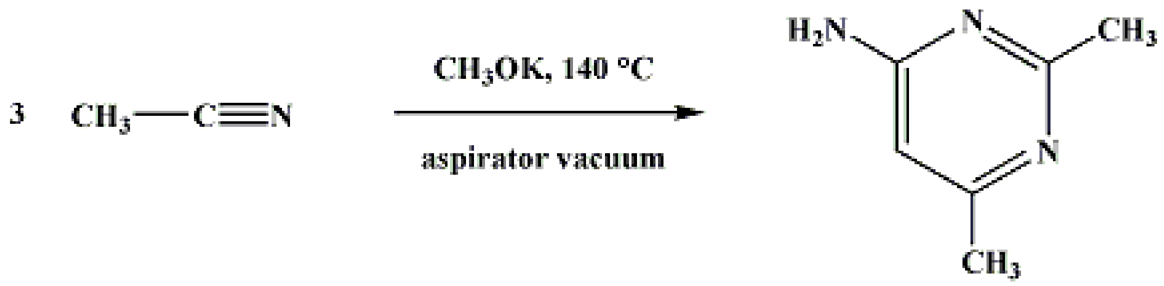
4-AMINO-2,6-DIMETHYLPYRIMIDINE

[Pyrimidine, 4-amino-2,6-dimethyl-]



Submitted by Anthony R. Ronzio and William B. Cook.
Checked by C. G. Stuckwisch and Henry Gilman.

1. Procedure

Seventy grams (1 mole) of freshly prepared potassium methoxide (Note 1) and 41 g. (1 mole) of freshly purified acetonitrile (Note 2) are placed in a 500-ml. distilling flask. A cold-finger condenser which extends into the bulb of the flask is inserted through a rubber stopper in the neck of the flask, and a short piece of rubber tubing carrying a Hofmann clamp is connected to the side arm of the flask. The tubing is connected to an aspirator, and suction is applied until the acetonitrile begins to boil, whereupon the tubing is closed by means of the clamp and the flask is heated for 5 hours in an oil bath maintained at 140°.

At the end of the heating period the contents of the flask will have solidified. To the cold mixture 40 ml. of water is added to hydrolyze the potassium methoxide and precipitate the pyrimidine; the fine crystals are filtered and dried. The crude product is placed in a 500-ml. distilling flask with 250 ml. of purified kerosene (Note 3). On distilling the kerosene, the pyrimidine codistils and solidifies in the receiving flask to a snow-white mass of crystals. These are filtered, washed well with petroleum ether, and dried in an oven at 100°. The yield of pure material, melting at 182–183°, is 27.5–28.7 g. (67–70%) (Note 4).

2. Notes

1. To prepare the potassium methoxide 39 g. (1 gram atom) of metallic potassium, cut *under toluene* (*Caution!*) in 1-cm. cubes, is placed in a 1-l. three-necked flask which has been swept with nitrogen. The flask, fitted with a reflux condenser, mechanical stirrer, and dropping funnel, is immersed in a cooling bath at –30°, and absolute methanol is added through the funnel until all the potassium has dissolved. The excess methanol is removed by heating on the steam bath, finally under reduced pressure, and the potassium methoxide is dried

overnight in a vacuum desiccator over sulfuric acid.

2. Commercial acetonitrile is treated with solid sodium carbonate until no more carbon dioxide is evolved. The nitrile is then distilled over phosphorus pentoxide and stored in tightly stoppered bottles. Before use, the nitrile is redistilled over phosphorus pentoxide.

3. Kerosene is purified by shaking for 24 hours with concentrated sulfuric acid. The kerosene is separated from the acid, washed several times with dilute sodium hydroxide then with water, and finally dried over calcium chloride and distilled using an air condenser. Purified kerosene is a water-white, sweet-smelling liquid.

4. The percentage yield decreases when larger or smaller quantities of material are used.

3. Discussion

4-Amino-2,6-dimethylpyrimidine has been prepared by heating the reaction product obtained from acetic anhydride and acetamidine;[1] by treating 4-chloro-2,6-dimethylpyrimidine with ammonia;[2] and by heating acetonitrile either with sodium ethoxide in a sealed tube[3] or with sodium.[4,5]

It has been reported that this trimerization may be carried out with equally good results through the use of a small amount of sodium methoxide in place of a large amount of potassium methoxide.[6]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

kerosene

metallic potassium

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

ammonia (7664-41-7)

methanol (67-56-1)

acetic anhydride (108-24-7)

acetonitrile (75-05-8)

sodium hydroxide (1310-73-2)

sodium carbonate (497-19-8)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

sodium methoxide (124-41-4)

toluene (108-88-3)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

potassium (7440-09-7)

pyrimidine (289-95-2)

4-Amino-2,6-dimethylpyrimidine, Pyrimidine, 4-amino-2,6-dimethyl- (461-98-3)

potassium methoxide (865-33-8)

acetamidine (143-37-3)

4-chloro-2,6-dimethylpyrimidine

phosphorus pentoxide (1314-56-3)

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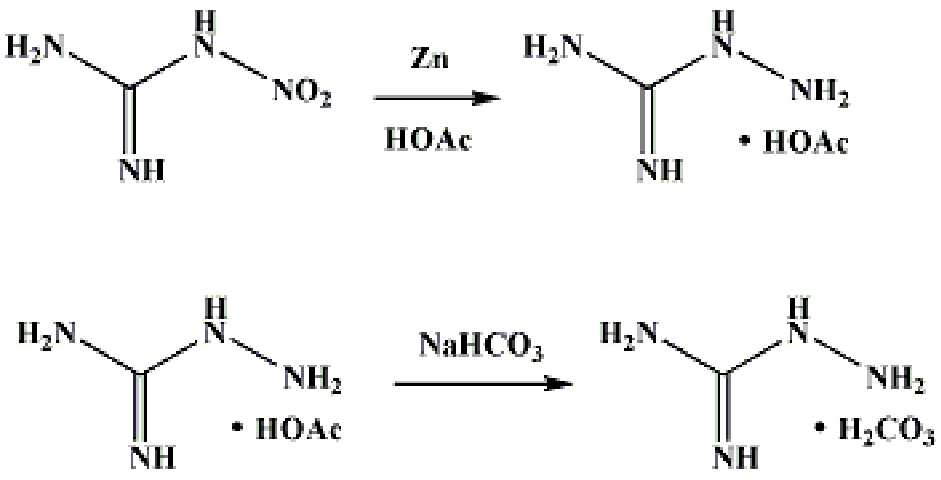
AMINOGUANIDINE BICARBONATE

[Guanidine, amino-, bicarbonate]



Submitted by R. L. Shriner and Fred W. Neumann.
Checked by Homer Adkins and M. J. Curry.

1. Procedure

Two hundred and sixteen grams (2.07 moles) of nitroguanidine[1] and 740 g. (11.3 moles) of purified zinc dust (Note 1) are thoroughly ground together in a mortar, and then enough water (about 400 ml.) is added with stirring with the pestle to form a thick paste. The paste is transferred to a 3-l. enameled can or beaker surrounded by an ice bath. A solution of 128 g. (2.14 moles) of glacial acetic acid in 130 ml. of water is cooled to 5° in another 3-l. beaker, which is fitted with a strong mechanical stirrer and surrounded by an ice bath. The paste of nitroguanidine and zinc dust, cooled to 5°, is added slowly with mechanical stirring, the temperature of the reaction mixture being kept between 5° and 15°. A total of about 1 kg. of cracked ice is added to the mixture from time to time as the mixture becomes too warm or too thick to stir. The addition of the paste takes about 8 hours, and the final volume of the mixture is about 1.5 l. (Note 2). The mixture is then slowly warmed to 40° on a water bath with continued stirring, and this temperature is maintained for 1–5 minutes, until reduction is complete (Note 3).

The solution is immediately separated from the insoluble material by filtration on a 20-cm. Büchner funnel, and the cake is sucked as dry as possible. The residue is transferred to the 3-l. beaker, triturated well with 1 l. of water, and then separated from the liquid by filtration. In the same manner, the residue is washed twice more with two 600-ml. portions of water. The filtrates are combined and placed in a 5-l. round-bottomed flask. Two hundred grams of ammonium chloride is added, and the solution is mechanically stirred until solution is complete (Note 4). The stirring is continued, and 220 g. (2.62 moles) of sodium bicarbonate is added during a period of about 10

minutes. The aminoguanidine bicarbonate begins to precipitate after a few minutes, and the solution is then placed in a refrigerator overnight. The precipitate is collected by filtration on a Büchner funnel. The cake is removed to a 1-l. beaker and mixed with a 400-ml. portion of a 5% solution of ammonium chloride and filtered. It is again washed with two 400-ml. portions of distilled water, the wash solution being removed each time by filtration. Finally the solid is pressed down on the Büchner funnel; the mat is broken up with a spatula and washed while on the funnel with two 400-ml. portions of 95% ethanol and then with one 400-ml. portion of ether. After air drying, the aminoguanidine bicarbonate amounts to 180–182 g. (63–64%) of a white solid, melting at 172° with decomposition (Note 5) and (Note 6).

2. Notes

1. The zinc is purified by stirring 1.2 kg. of commercial zinc dust with 3 l. of 2% hydrochloric acid for 1 minute. The acid is removed by filtration, and the zinc is washed in a 4-l. beaker with one 3-l. portion of 2% hydrochloric acid, three 3-l. portions of distilled water, two 2-l. portions of 95% ethanol, and finally with one 2-l. portion of absolute ether, the wash solutions being removed each time by filtration. Then the material is thoroughly dried and any lumps are broken up in a mortar.
2. The solution becomes basic to litmus after one-half to three-fourths of the paste has been added. Lower yields are obtained if a larger excess of acetic acid is employed.
3. The state of reduction can be determined by placing 3 drops of the reaction mixture in a test tube containing 5 ml. of a 10% solution of sodium hydroxide and then adding 5 ml. of a freshly prepared saturated solution of ferrous ammonium sulfate. A red coloration indicates incomplete reduction; when the reduction is complete, only a greenish precipitate is observed. The mixture should not be heated after this test shows that reduction is complete.
4. The presence of the ammonium chloride prevents the coprecipitation of zinc salts when sodium bicarbonate is added to the solution to precipitate the aminoguanidine as the bicarbonate. If the solution is not clear at this step, it should be filtered.
5. The aminoguanidine bicarbonate is pure enough for most purposes. It should not be recrystallized from hot water, since decomposition will occur.
6. W. W. Hartman and Ross Philips have submitted a procedure suitable for the preparation of aminoguanidine bicarbonate on a larger scale. The sulfates of methylisothiourea and of hydrazine are allowed to react with the evolution of methyl mercaptan. In a 30-gal. crock are placed 10 l. of water and 5760 g. (20 moles) of methylisothiourea sulfate.[2] In a 22-l. flask, 5.2 kg. (40 moles) of hydrazine sulfate[3] is stirred with 12 l. of water, and 40% sodium hydroxide is added until all the hydrazine sulfate has dissolved and the solution is just neutral to Congo paper. The exact amount of alkali is noted and a duplicate amount added. The hydrazine solution is then added to the 30-gal. crock with stirring, as

fast as possible, without allowing the foam to overflow the crock. The mixing is done out-of-doors, or in an efficient hood, since large volumes of methyl mercaptan are evolved. If the reaction is carried out on a smaller scale in 12- or 22-l. flasks, using appropriate amounts of material, the methyl mercaptan evolved may be absorbed in cold sodium hydroxide solution and isolated if desired. The solution is stirred until evolution of mercaptan stops, and then a few liters of water are distilled off under reduced pressure to free the solution entirely from mercaptan. The residual liquor is chilled in a crock, and a crop of hydrated sodium sulfate is filtered off, washed with ice water, and discarded. The filtrate is warmed to 20–25°, 25 ml. of glacial acetic acid is added, then 4 kg. of sodium bicarbonate, and the solution is stirred vigorously for 5 minutes and thereafter occasionally during an hour, or until the precipitate no longer increases. The precipitate is filtered with suction and washed with ice water and then with methanol, and is dried at a temperature not above 60–70°. The yield is 3760 g. (69% of the theoretical amount). Hydrazine sulfate may be recovered from the final filtrate, if the filtrate is strongly acidified with sulfuric acid and allowed to cool.

3. Discussion

Numerous references for the preparation of aminoguanidine bicarbonate and other salts can be found in an excellent review article by Lieber and Smith.[4] It has also been prepared by treating a cyanamide solution at 20–50° with hydrazine and carbon dioxide,[5] and by the electrolytic reduction of nitroguanidine.[6]

References and Notes

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4. Lieber and Smith, *Chem. Revs.*, **25**, 213 (1939)
5. Ger. pat. 689,191 [*C. A.*, **35**, 3650 (1941)].
6. Shreve and Carter, *Ind. Eng. Chem.*, **36**, 423 (1944).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

methanol (67-56-1)

ether (60-29-7)

ammonium chloride (12125-02-9)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

carbon dioxide (124-38-9)

zinc (7440-66-6)

Nitroguanidine (556-88-7)

Hydrazine sulfate (10034-93-2)

hydrazine (302-01-2)

methyl mercaptan (74-93-1)

Aminoguanidine bicarbonate, Guanidine, amino-, bicarbonate (2582-30-1)

ferrous ammonium sulfate (10045-89-3)

aminoguanidine

bicarbonate (71-52-3)

methylisothiourea

methylisothiourea sulfate

cyanamide (420-04-2)

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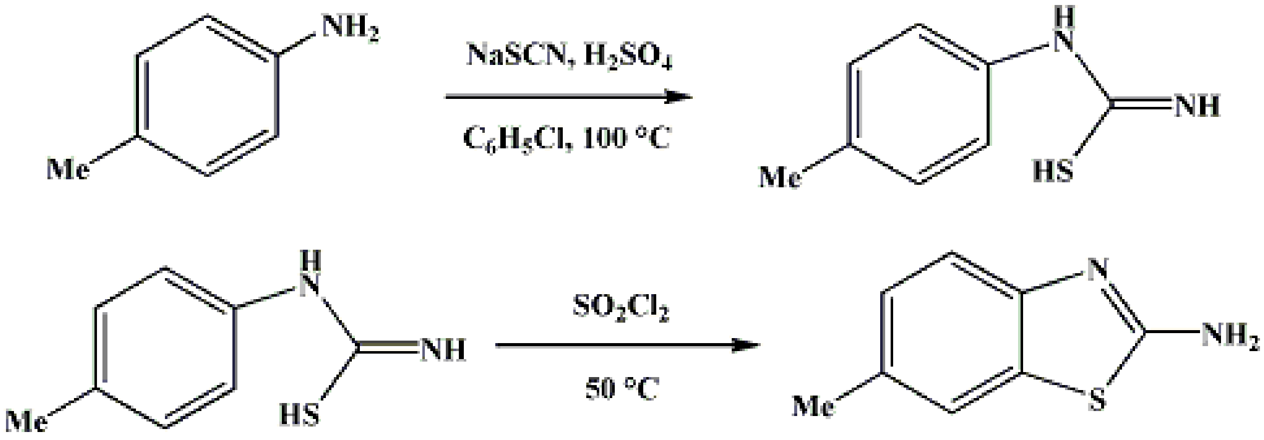
2-AMINO-6-METHYLBENZOTHIAZOLE

[Benzothiazole, 2-amino-6-methyl-]



Submitted by C. F. H. Allen and James VanAllan.
Checked by W. E. Bachmann and N. W. MacNaughton.

1. Procedure

A solution of 107 g. (1 mole) of *p*-toluidine (Note 1) in 700 ml. of chlorobenzene is prepared in a 3-l. three-necked, round-bottom flask fitted with a stirrer, reflux condenser, thermometer, and dropping funnel. Over a period of 5 minutes, 54 g. (29.3 ml., 0.55 mole) of concentrated sulfuric acid is added dropwise. To the finely divided suspension of *p*-toluidine sulfate is added 90 g. (1.1 moles) of sodium thiocyanate, and the mixture is heated for 3 hours at 100° (inside temperature) in an oil bath (Note 2). The solution, which now contains the thiourea, is cooled to 30°, and 180 g. (108 ml., 1.34 moles) of sulfuryl chloride is added over a period of 15 minutes, with care that the temperature does not exceed 50°. The mixture is kept at 50° for 2 hours (no further evolution of hydrogen chloride), after which the chlorobenzene is removed by filtration (Note 3).

The solid residue is then dissolved in 1 l. of hot water, and the remainder of the solvent is removed by a current of steam (Note 4). The solution is filtered from a little solid and is then made alkaline to litmus by the addition of 200 ml. of concentrated ammonium hydroxide (sp. gr. 0.90). The precipitated aminomethylbenzothiazole is filtered and washed with 200 ml. of water. The solid, which melts over the range 123–128°, is dissolved in 300 ml. of hot ethanol (Note 5), 10 g. of Norit is added, and the hot suspension is filtered. The filtrate is diluted with 500 ml. of hot water, and the mixture is vigorously stirred and quickly chilled. After 30 minutes, the pale yellow granular product is filtered and washed with 150 ml. of 30% ethanol. After drying to constant weight, the product weighs 100–105 g. and melts at 135–136°, with preliminary shrinking at 130–131° (Note 6). On the addition of 200 ml. of water to the filtrate, a further 5–8 g. of product is recovered, making the total yield 105–110 g. (64–67%).

2. Notes

1. All the chemicals used were from the Eastman Kodak Company. The checkers used the practical grade of *p*-toluidine, which was distilled just before use.
2. The *p*-tolylthiourea may be isolated at this point, if desired, by filtering and washing the solid residue with ether. The dried solid (172 g.) is a mixture of the urea and sodium sulfate. It is extracted with 250 ml. of warm (50–60°) water; the residual urea, m.p. 188–189°, is completely soluble in ethanol. The yield is 139 g. (84%).
3. The recovery is about 600 ml.; it may be used again without purification.
4. Treatment of the solution with Norit at this point does not give a product of any better quality.
5. If less ethanol is used, crystallization takes place during filtration.
6. The literature gives melting points ranging from 128° to 142°, the higher value being for aminomethylbenzothiazole prepared via the hydrochloride (m.p. 250–253°). The submitters report that the product obtained above is unchanged in melting point after regeneration from the hydrochloride. By this treatment, however, the color is removed.

3. Discussion

2-Amino-6-methylbenzothiazole has been prepared by the action of cupric thiocyanate,[1,2,3] or of chloramine and ammonium thiocyanate,[4] on *p*-toluidine; by the action of chlorine on di-*p*-tolylthiourea;[5] or of bromine on acetyldi-*p*-tolylthiourea;[6] by treatment of *p*-tolylthiourea with halogens[7] or acid halides.[8,9,10,11,12] 2-Aminobenzothiazole has been prepared in excellent yield by the action of hydroxylamine upon benzothiazole,[13] and has also been obtained from 2-mercaptobenzothiazole by the action of ammonium bisulfite at 150°.[14] It has been prepared by the electrolysis of *p*-toluidine in the presence of ammonium thiocyanate.[15] Two German patents report a general method for the preparation of 2-aminobenzothiazoles[16] and 2-aminonaphthothiazoles[17] consisting of the treatment of an aromatic amine with potassium thiocyanate and acetic acid and subsequently with bromine in acetic acid.

Nearly quantitative yields are reported for a process using a modified cupric thiocyanate method.[18]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

2-aminobenzothiazoles

2-aminonaphthothiazoles

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrogen chloride (7647-01-0)

acetic acid (64-19-7)

ether (60-29-7)

ammonium thiocyanate (1762-95-4)

bromine (7726-95-6)

sodium sulfate (7757-82-6)

Norit (7782-42-5)

chlorobenzene (108-90-7)

sulfuryl chloride (7791-25-5)

chlorine (7782-50-5)

urea (57-13-6)

ammonium hydroxide (1336-21-6)

potassium thiocyanate (333-20-0)

hydroxylamine (7803-49-8)

thiourea (62-56-6)

sodium thiocyanate (540-72-7)

2-Amino-6-methylbenzothiazole, Benzothiazole, 2-amino-6-methyl- (2536-91-6)

aminomethylbenzothiazole

cupric thiocyanate (18223-42-2)

chloramine (10599-90-3)

2-Aminobenzothiazole (136-95-8)

benzothiazole (95-16-9)

2-mercaptobenzothiazole (149-30-4)

ammonium bisulfite (10192-30-0)

p-toluidine (106-49-0)

p-toluidine sulfate

p-tolylthiourea (622-52-6)

di-p-tolylthiourea

acetyldi-p-tolylthiourea

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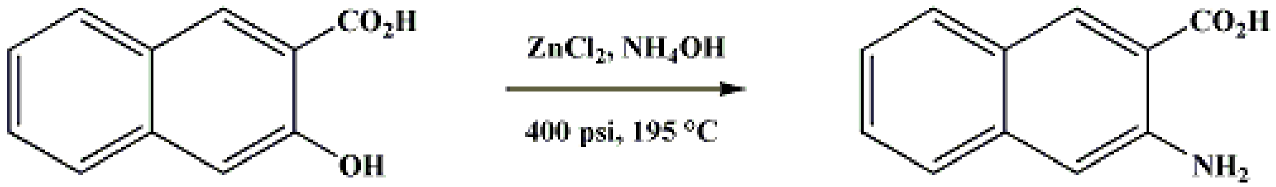
3-AMINO-2-NAPHTHOIC ACID

[2-Naphthoic acid, 3-amino-]



Submitted by C. F. H. Allen and Alan Bell.
Checked by Nathan L. Drake, E. W. Reeve, and J. Van Hook.

1. Procedure

An autoclave (Note 1) is charged *successively* with 600 ml. (9.5 moles) of approximately 28% aqueous ammonia, 78 g. of zinc chloride (0.57 mole) (Note 2) and (Note 3), and 167 g. of 3-hydroxy-2-naphthoic acid (0.89 mole) (Note 4). The autoclave is closed, and then, with continuous stirring or shaking (Note 5), it is gradually heated, so that, at the end of 3 hours, the temperature is 195°. This temperature is maintained for 36 hours; the pressure is about 400 lb. (Note 6). The autoclave is allowed to cool to room temperature, with continuous stirring or shaking. The cover is removed, the solid is scraped off the walls, and the reaction mixture is transferred to a 5-l. flask. The autoclave is rinsed with two 700-ml. portions of water, which are added to the reaction mixture.

To the reaction mixture is added 660 g. of concentrated hydrochloric acid (sp. gr. 1.18), and the suspension is boiled for 30 minutes. It is then filtered, while hot, through a Büchner funnel. The residual cake is boiled again, for the same length of time, with a mixture of 500 ml. of water and 30 ml. of concentrated hydrochloric acid, and then filtered as before.

The combined filtrates, on cooling, deposit the hydrochloride of the aminonaphthoic acid; this is filtered with suction and is pressed as dry as possible. To obtain a second crop of the hydrochloride, the filtrate is heated to 85°, 500 g. of salt is added, and the solution is cooled.

The combined moist filter cakes are placed in a 5-l. flask with 1.3 l. of water, and, with stirring, sufficient 40% sodium hydroxide solution is added to make the solution just alkaline to Clayton yellow paper (Note 7); about 110 ml. is required. The mixture is heated to 85° and is filtered to remove a small amount of insoluble material. The filtrate is then made acid to Congo red by the addition of concentrated hydrochloric acid (about 100 ml. of acid is required). The mixture is stirred for 15 minutes, and then enough 10% sodium acetate solution is added so that Congo red paper is no longer turned blue; the amount needed depends on the acidity; usually about 15 ml. is sufficient.

The hot mixture is filtered; the aminonaphthoic acid is washed on the Büchner funnel with 400 ml. of hot water and is pressed as dry as possible. The product is dried at 50° to constant weight (24–36 hours). 3-Amino-2-naphthoic acid is a yellow, powdery substance, which melts at 214–215° (Note 8); the yield is 110–115 g. (66–70%) (Note 6). The quantities of starting materials are limited only by the size of the autoclave available; the yield (per cent)

in large runs is the same as that obtained above.

2. Notes

1. An autoclave fitted for stirring or shaking is essential. An example of the former is the one furnished by the Will Corporation, catalog No. 1735. This is large enough so that three times the amounts specified may be handled. A hydrogenation autoclave of the type supplied by the American Instrument Company, catalog No. 406–21, having a capacity of about 1.4 l., may also be used. This type of autoclave is not fitted with a stirrer but is shaken by means of a "Bomb Shaker" in which the autoclave is placed. In using the hydrogenation autoclave, the long hydrogen inlet tube, which extends half way into the chamber of the autoclave, is unscrewed and removed. The inlet for hydrogen, on the outside of the autoclave, is closed by means of a solid steel rod, the end of which is finished and held in place in the same manner as the ordinary steel pressure tubing.

After making a run, the hydrogenation autoclave is poisoned for hydrogenations. It may be cleaned by filling it with 5% hydrochloric acid and rubbing the inside walls with a cloth or brush. It should then be washed with water and dried; any solid matter adhering to the walls is removed by rubbing with emery paper. Care must be taken not to scratch either the copper gasket or the groove into which the gasket fits. All parts of the hydrogenation autoclave, including the head, must be thoroughly cleaned. Traces of the reaction product will cause pitting in a few hours if they are allowed to remain in contact with the steel while the bomb is exposed to the air.

After the hydrogenation autoclave is cleaned it is best to carry out one or two ester hydrogenolyses with copper chromite in order to remove the last traces of "poison." The bomb may then be used for hydrogenations.

2. The zinc chloride should not contain appreciable amounts of the oxychloride.

3. Since zinc chloride and aqueous ammonia react with evolution of heat, the solid must be added gradually and with hand stirring. It is best to carry out this operation under a hood.

4. A technical grade of 3-hydroxy-2-naphthoic acid, m.p. 211–214°, was used.

5. Continued stirring or shaking is required throughout, i.e., from the time heating is begun until the reaction product has again attained room temperature. With a hydrogenation autoclave there will be no trouble due to leaks, but with the stirrer type of autoclave the packing around the stirrer shaft may leak. In this event the pressure will fall and a longer period of time will be required. If a large quantity of ammonia escapes, the yield will be diminished, but the run should be finished and the unused hydroxynaphthoic acid should be recovered and used in another run.

6. In a run in which the gaskets leaked, the pressure never exceeded 200 lb. In this run, the (stirrer-type) autoclave was operated for 5 days; the yield was 67%.

7. Clayton yellow paper (thiazole paper) is paper impregnated with the dye formed by coupling diazotized primuline sulfonic acid with primuline sulfonic acid. The color change occurs at *p*H 11–12. If this paper is not available, a little less than the estimated amount of alkali should be used. The mixture is warmed to 85°, and a small test portion is removed and warmed with more alkali. If any appreciable amount of the insoluble matter dissolves, more alkali is needed.

8. This product is pure enough for most purposes. It can be recrystallized from ethanol (10 g. dissolves in 100 ml. of hot ethanol); the recovery is 78% (7.8 g.), and the purified product melts at 216–217°.

3. Discussion

3-Amino-2-naphthoic acid has been prepared by heating 3-hydroxy-2-naphthoic acid with ammonia under pressure, in the presence of catalysts. These catalysts include zinc (or calcium) chloride;[1,2,3,4] alone or with the addition of aluminum chloride.[5] Zinc oxide or carbonate and ammonium chloride,[6,7,8] or ferrous ammonium salts,[9,10] have also been used. When sodium hydroxynaphthoate is heated with 35% ammonia at 260–280°, the product is contaminated with considerable amounts of β-naphthol and β-naphthylamine.[11] Modifications of Henle's procedure[4] have been described.[12]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 573

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloride of the aminonaphthoic acid

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ammonium chloride (12125-02-9)

sodium acetate (127-09-3)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

β-naphthol (135-19-3)

copper (7440-50-8)

aluminum chloride (3495-54-3)

zinc chloride (7646-85-7)

zinc oxide

COPPER CHROMITE

3-Amino-2-naphthoic acid, 2-Naphthoic acid, 3-amino- (5959-52-4)

3-hydroxy-2-naphthoic acid (92-70-6)

aminonaphthoic acid

hydroxynaphthoic acid (2283-08-1)

ferrous ammonium

sodium hydroxynaphthoate

β-naphthylamine (91-59-8)

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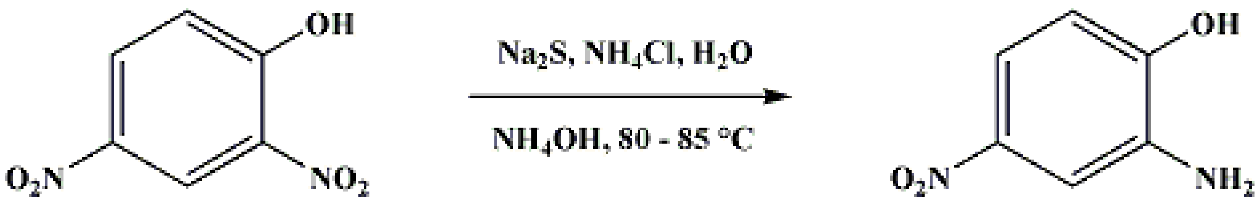
2-AMINO-4-NITROPHENOL

[Phenol, 2-amino-4-nitro-]



Submitted by W. W. Hartman and H. L. Silloway.
Checked by H. R. Snyder and J. Wayne Kneisley.

1. Procedure

In a 5-l. three-necked flask, suspended over a steam bath, are placed 300 g. (1.63 moles) of technical 2,4-dinitrophenol and 2.5 l. of water. The flask is fitted with an efficient stirrer, a reflux condenser, and a thermometer which dips below the surface of the mixture. After the stirrer has been started, 600 g. (11.6 moles) of ammonium chloride and 100 ml. of concentrated aqueous ammonia (about 28%) are added, and the mixture is heated to 85°. The steam is turned off, and the mixture is allowed to cool. When the temperature reaches 70° (Note 1), 700 g. (5.4 moles) of 60% fused sodium sulfide is added in portions of about 100 g. at 5-minute intervals. After two or three such additions the temperature of the reaction mixture reaches 80–85°; it is kept in this range either by adding the remaining portions of sodium sulfide at 10-minute intervals or by wrapping the flask with a wet cloth and continuing the additions at 5-minute intervals. After all the sodium sulfide has been added, the reaction mixture is heated at 85° for 15 minutes and then filtered through a heated 6-in. Büchner funnel (Note 2).

The hot filtrate is transferred to a 5-l. round-bottomed flask and cooled overnight by a stream of cold water. The mixture is filtered, and the crystals are pressed nearly dry. The solid is dissolved in 1.5 l. of boiling water, and the solution is acidified with glacial acetic acid (about 100 ml. is required, (Note 3)). The solution is heated with 10 g. of Norit, filtered hot, and cooled to 20°. The brown crystals are collected and dried for several hours in an oven at 65° or in a vacuum desiccator (Note 4). The yield of 2-amino-4-nitrophenol melting at 140–142° is 160–167 g. (64–67%). If a purer product is desired, the crude substance is recrystallized from 1.5 l. of hot water; 147–153 g. (58–61%) of material melting at 142–143° is obtained.

2. Notes

1. If the reaction is run at temperatures below 70° it is impossible to obtain a pure product even after several recrystallizations.
2. The Büchner funnel is preheated by inverting it over a steam bath and passing a lively current of steam through it for at least 10 minutes. During the filtration,

suction is applied gently and at intervals to avoid excessive cooling by evaporation in the lower part of the funnel. If the filtration is not performed rapidly and carefully, the crude product will crystallize in the funnel. The filtration can be omitted, but the presence of insoluble materials complicates the next step by making it difficult to determine when solution of the crude product is complete.

3. The amount of acid required varies with dryness of the filter cake. The acidification can be followed by observing the color of a thin layer of the solution splashed against the side of the container. The color changes from dark red to olive brown at the end point. Both colors are so deep that they are not easily distinguished except when thin layers are viewed. After the end point is observed, an additional 10 ml. of acetic acid is added.

4. Unless properly dried the substance will melt at 80–90°, owing to the presence of water of crystalliaztion.

3. Discussion

2-Amino-4-nitrophenol has been prepared by the partial reduction of 2,4-dinitrophenol chemically[1,2,3,4,5] and electrolytically,[6] and by the action of sulfuric acid on 3-nitroazidobenzene.[7]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

ammonia (7664-41-7)

ammonium chloride (12125-02-9)

Norit (7782-42-5)

sodium sulfide (1313-82-2)

2,4-dinitrophenol (51-28-5)

2-Amino-4-nitrophenol, Phenol, 2-amino-4-nitro- (99-57-0)

3-nitroazidobenzene

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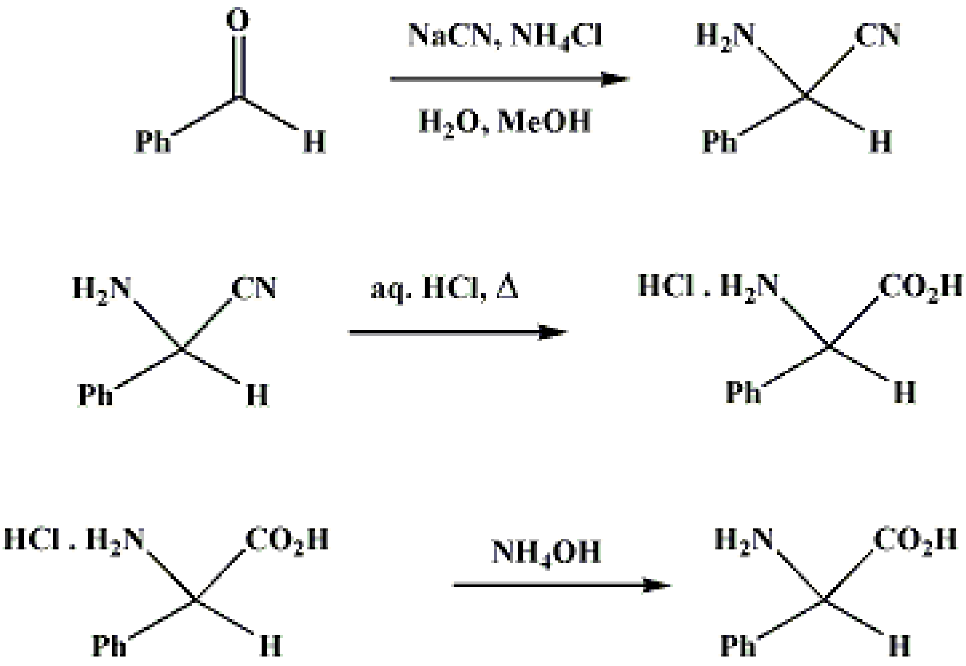
dl-α-AMINOPHENYLACETIC ACID

[Glycine, α-phenyl-]



Submitted by Robert E. Steiger
Checked by R. L. Shriner, S. P. Rowland, and C. H. Tilford.

1. Procedure

To a solution of 100 g. (2.0 moles) of 98% sodium cyanide in 400 ml. of water, contained in a 3-l. round-bottomed flask fitted with a Hershberg stirrer, is added 118 g. (2.2 moles) of ammonium chloride. The mixture is stirred at room temperature under a properly ventilated hood. When the ammonium chloride has dissolved, a solution of 212 g. (2.0 moles) of benzaldehyde in 400 ml. methanol is added in one portion. The reaction begins rapidly, the temperature rising to about 45°. Stirring is continued for 2 hours. The heterogeneous mixture, after dilution with 1 l. of water, is extracted with 1 l. of benzene, and the aqueous layer is discarded. The benzene layer is washed with three 50-ml. portions of water, and the aminonitrile is extracted, in the form of its hydrochloride, by shaking the benzene solution with 6 *N* hydrochloric acid, first with one 600-ml. portion and then with two 300-ml. portions.

The combined acid extracts are placed in a 3-l. round-bottomed flask and refluxed for 2 hours (Note 1). The hydrolysate is diluted with water to bring its volume to about 2 l. and is then subjected to distillation under reduced pressure (20–30 mm.) to remove all benzaldehyde and other volatile substances (Note 2). To remove some resinous matter deposited in the course of the hydrolysis, the mixture is treated with 10 g. of Norit and filtered through a Büchner funnel. The yellow filtrate is transferred to a 3-l. beaker. It

is stirred by hand with a thick glass rod while ammonium hydroxide (sp. gr. 0.90) is added through a dropping funnel until the liquid is faintly alkaline to litmus (Note 3). The mixture becomes quite hot and acquires a strong odor of benzaldehyde. The amino acid separates in the form of yellow crystals. The mixture is cooled to room temperature, and the crystals are collected on a 15-cm. Büchner funnel. After washing with about 1 l. of water in small portions to remove the ammonium chloride, the solid is washed successively with 150 ml. of ethyl ether, three 50-ml. portions of hot 95% ethanol, and finally with about 500 ml. of water. The crystals, when dried by suction, weigh 220 to 240 g. (Note 4). Drying is completed in a vacuum desiccator over phosphorus pentoxide. The yield of crude amino acid is 102–116 g. (34–39%).

For purification, the product is dissolved in 800 ml. of 1 *N* sodium hydroxide, 500 ml. of ethanol is added, and the solution is filtered. The filtrate is transferred to a 2-l. beaker and is heated to the boiling point. Then 160 ml. of 5 *N* hydrochloric acid is slowly added, through a dropping funnel, while stirring by hand. The mixture is cooled to room temperature and is filtered with suction. The product is washed with 100 ml. of ethanol, then with 200 ml. of water, and is dried in a vacuum desiccator over phosphorus pentoxide. The nearly white, lustrous platelets have no definite melting point (Note 5). The yield of pure amino acid is 98–112 g. (33–37%) (Note 6).

2. Notes

1. The hydrolysis of the aminonitrile should be carried out under a hood, since some hydrocyanic acid is liberated.
2. During this process, the volume of the solution must be maintained at about 2 l. by the frequent addition of water through a dropping funnel. Otherwise the hydrochloride of *dl*-phenylglycine, which is sparingly soluble in concentrated hydrochloric acid, may separate.
3. From 375 to 425 ml. of ammonium hydroxide of sp. gr. 0.90 is required.
4. This crude product is hydrated.
5. The decomposition range was about 270–280° with sintering at 258°. A new sample, when placed in the melting-point bath at 280–300°, sintered, and then decomposed at 300–302°.
6. Increasing the quantities of cyanide and ammonium chloride to 3 moles does not markedly improve the yields.

3. Discussion

dl-Phenylglycine has been prepared by heating α-bromophenylacetic acid with three times its weight of ammonium hydroxide (sp. gr. 0.90) to 100–110°;[1] by hydrolysis of α-aminophenylacetonitrile with dilute hydrochloric acid;[2,3] and by reduction of benzoylformic acid phenylhydrazone with sodium amalgam in dilute sodium hydroxide.[4] The method described above is, with some modifications and additions, the procedure used by Marvel and Noyes.[3,5]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloride of dl-phenylglycine

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

methanol (67-56-1)

ethyl ether (60-29-7)

ammonium chloride (12125-02-9)

sodium hydroxide (1310-73-2)

sodium cyanide (143-33-9)

hydrocyanic acid (74-90-8)

aminonitrile (7727-37-9)

benzaldehyde (100-52-7)

Norit (7782-42-5)

sodium (13966-32-0)

ammonium hydroxide (1336-21-6)

Glycine, α-phenyl- (2935-35-5)

α-Bromophenylacetic acid (4870-65-9)

α-aminophenylacetonitrile

benzoylformic acid phenylhydrazone

dl-phenylglycine (103-01-5)

phosphorus pentoxide (1314-56-3)

DL-α-Aminophenylacetic acid (2835-06-5)

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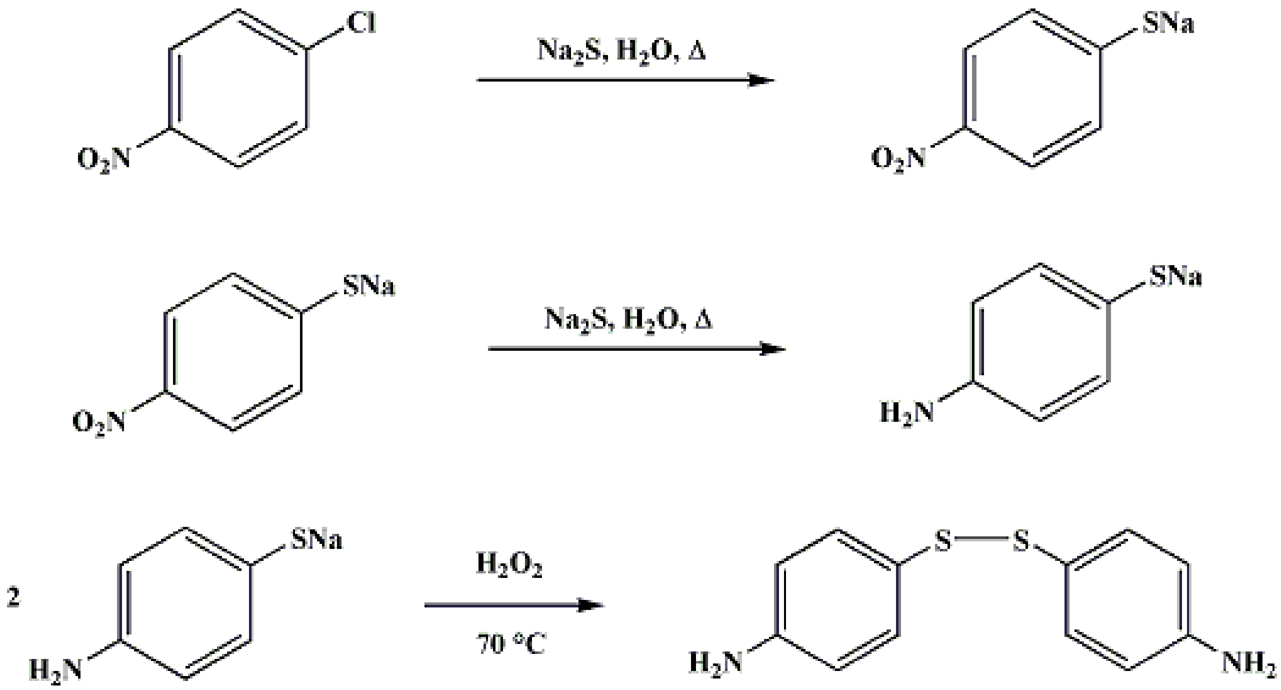
p-AMINOPHENYL DISULFIDE

[Aniline, *p,p*'-dithiodi-]



Submitted by Charles C. Price and Gardner W. Stacy.
Checked by Cliff S. Hamilton and Theo Brown.

1. Procedure

In a 5-l. round-bottomed flask equipped with a reflux condenser and a mechanical stirrer are placed 236 g. (1.5 moles) of *p*-chloronitrobenzene, 960 g. (4 moles) of sodium sulfide nonahydrate, and 2.5 l. of water. With rapid agitation, the reaction mixture is slowly heated to the reflux temperature (Note 1). Heating is continued over a period of 20 hours.

The mixture is cooled to about 15° and filtered on a large Büchner funnel to remove insoluble material, chiefly *p*-chloroaniline. The filtrate is placed in a 5-l. three-necked flask, equipped with a dropping funnel, a mechanical stirrer, and a downward condenser; it is concentrated by distillation over a flame to a volume of 1.5 l. (Note 2). The condenser is replaced by a thermometer, the stirrer is started, and the dropping funnel is charged with 230 ml. of 30% hydrogen peroxide. The temperature of the reaction mixture is maintained at 65–70° while the hydrogen peroxide is added dropwise over a period of about 2 hours (Note 3).

The reaction mixture is cooled, and the crude *p*-aminophenyl disulfide, obtained as spherical lumps amounting to 125–150 g. and melting at 73°, is collected on a Büchner funnel. It is dissolved in 1 l. of hot ethanol, and the small amount of insoluble material is removed by filtration. To the hot solution is then added 800 ml. of water containing several grams of sodium hydrosulfite to prevent discoloration of the solution by oxidation. The solution is cooled, and an additional 700 ml. of water is added with stirring to reduce the solubility of the product. The crystalline precipitate is removed by filtration and dried in a vacuum desiccator. The yield of pure product melting at 75–76° is 108–120 g. (58–64%).

2. Notes

1. The reaction mixture should not be heated too strongly as the temperature nears the boiling point, since the initial reaction is quite vigorous.
2. Some *p*-chloroaniline is removed by steam distillation during the concentration.
3. At first the solution becomes cloudy, and later large yellow globules begin to accumulate. Frequent cooling is required to maintain the temperature within the specified range.

3. Discussion

The procedure outlined is essentially that of Lantz[1] except for the use of hydrogen peroxide rather than air in the final oxidation. *p*-Aminophenyl disulfide has also been prepared by heating a mixture of aniline, aniline hydrochloride, and sulfur,[2] by the reduction of *p*-nitrophenyl disulfide with stannous chloride,[3,4] and by the action of potassium hydroxide upon *p*-acetamidobenzenesulfinic acid (autoclave) followed by hydrolysis.[5]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

aniline (62-53-3)

aniline hydrochloride (142-04-1)

sodium hydrosulfite (7775-14-6)

stannous chloride

sulfur (7704-34-9)

potassium hydroxide (1310-58-3)

hydrogen peroxide (7722-84-1)

sodium sulfide nonahydrate (1313-84-4)

p-chloronitrobenzene (100-00-5)

p-chloroaniline (106-47-8)

p-acetamidobenzenesulfinic acid (710-24-7)

p-Aminophenyl disulfide, Aniline, p,p'-dithiodi- (722-27-0)

p-nitrophenyl disulfide (100-32-3)

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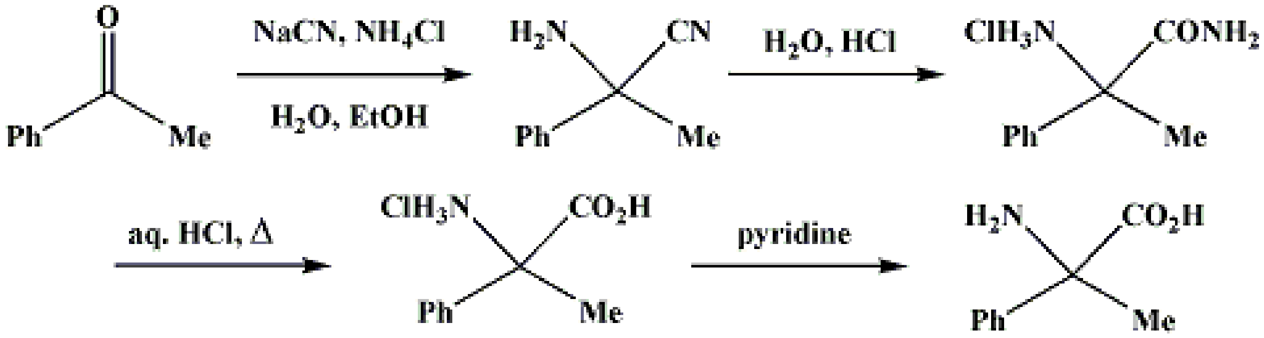
Organic Syntheses, CV 3, 88

dl-α-AMINO-α-PHENYLPROPIONIC ACID

[Alanine, α-phenyl-, *dl*-]



Submitted by Robert E. Steiger
Checked by R. L. Shriner and S. P. Rowland.

1. Procedure

In a 2-l. round-bottomed flask are placed, in the order mentioned, 50 g. (1 mole) of 98% sodium cyanide in 100 ml. of water, 58.9 g. (1.1 moles) of ammonium chloride in 140 ml. of lukewarm water (about 35°), and 134 ml. (2 moles) of aqueous ammonia (sp. gr. 0.90). The mixture is shaken while 120 g. (1 mole) of acetophenone in 300 ml. of 95% ethanol is added. The flask is stoppered with a rubber stopper, which is wired in place (Note 1), and is then immersed in a water bath maintained at 60°. The flask is shaken from time to time, and a homogeneous solution results within 30 minutes. The reaction mixture is heated for 5 hours at 60°, then well cooled in an ice-water mixture, and poured, with precautions (under a well-ventilated hood), into a 5-l. round-bottomed flask which is immersed up to the neck in an ice-water mixture and which contains 800 ml. of concentrated hydrochloric acid (sp. gr. 1.18–1.19). The reaction flask is rinsed with two 25-ml. portions of water, which are added to the hydrochloric acid solution. The solution of the aminonitrile is saturated at 0–5° with dry hydrogen chloride (Note 2) and is then set aside overnight in the ice-water bath, which is allowed to melt and come to the temperature of the room. The mixture of solid and liquid material is diluted with 1 l. of water and boiled vigorously for 2.5 hours under a reflux condenser in a well-ventilated hood (Note 3). The dark hydrolysate is concentrated under reduced pressure to remove the acetophenone and other volatile impurities. The solution is finally transferred to a 10-in. evaporating dish and is stirred occasionally while it is evaporated almost to dryness. Once a heavy deposit of inorganic salts has formed, very little bumping occurs. The solid residue is evaporated on a water bath twice with 100-ml. portions of water in order to remove as much hydrochloric acid as possible. The residue is crushed, and 600 ml. of absolute ethanol is added. The suspension is warmed for a short time on a steam bath; it is shaken thoroughly and then chilled in an ice-water mixture. The inorganic salts are removed by filtration through a 15-cm. Büchner funnel, and the cake is washed with small portions of absolute ethanol until 600 ml. has been used. The combined filtrates

and washings are placed in a 3-l. beaker, and pyridine is added while the mixture is stirred by hand with a thick glass rod. The addition of pyridine is continued until the solution is nearly neutral to Congo red paper, and then an additional 50 ml. is added; the total amount of pyridine required is 80–100 ml. (Note 4).

The resulting rather stiff paste is chilled in an ice-water mixture for 1 hour. The solid is collected on a 15-cm. Büchner funnel and washed with 25-ml. portions of absolute ethanol until it is white and until the filtrate becomes colorless (100–200 ml. of ethanol is required). The fluffy material, after it is dried in a vacuum desiccator over flake sodium hydroxide, weighs 66 g. (40%).

The amino acid contains a small amount of ammonium chloride, which can be removed by dissolving the product in 21 times its weight of water and precipitating it by the addition of 42 times its weight of absolute ethanol (Note 5). The mixture is allowed to stand overnight in a refrigerator. The amino acid is collected on a Büchner funnel and washed with an ethanol-water mixture containing 80% by weight of ethanol. The amino acid is dried in a vacuum desiccator over flake sodium hydroxide. The recovery is about 70% (Note 6).

2. Notes

1. A flask fitted with a ground-glass stopper is convenient for carrying out this step. The ground-glass stopper should be slightly lubricated with stopcock grease. It must be firmly secured in place by means of adhesive tape, as some pressure develops when the reaction mixture is heated.
2. From 500 to 600 g. of dry hydrogen chloride gas is required. Since this gas is very rapidly absorbed, a high-speed generator can be used.
3. The hydrolysis of the aminonitrile must be carried out under a good hood. The top of the reflux condenser should be connected with the ventilating pipe by means of a piece of glass tubing.
4. The minimum amount of pyridine necessary is determined by the amount of hydrochloric acid remaining in the residue.
5. The material does not readily become wet in contact with water, and it dissolves very slowly. The finely powdered material is best suspended in a large excess of water, e.g., about 30 times its weight. The suspension is boiled under a reflux condenser and frequently shaken until the solid is dissolved. The excess water is then boiled off at atmospheric pressure until a solution of the amino acid in 21 times its weight of water is obtained. The solution is then cooled and treated with absolute ethanol.
6. The amino acid does not have a sharp melting point. It sublimes with decomposition at about 265–270°.

3. Discussion

α-Amino-α-phenylpropionitrile has been prepared by heating acetophenone cyanohydrin for 6–8 hours in a closed vessel with 1 equivalent of ethanolic ammonia at 70°;[1,2] and by heating acetophenone for 4 hours in a closed vessel with an ethanolic

solution of ammonium cyanide to 80°.[3] α-Amino-α-phenylpropionitrile has been hydrolyzed by the action of, first, fuming hydrochloric acid at room temperature, and then dilute hydrochloric acid at boiling temperature, in the presence of some ethanol. This procedure gives a good yield of the amino acid hydrochloride. The amino acid has usually been liberated from its hydrochloride by means of ammonium hydroxide.[1,2,3] The process of isolating the amino acid by treating an ethanolic solution of its hydrochloride with pyridine is essentially the same as that developed for the preparation of glycine[4] and of α-aminoisobutyric acid.[5]

References and Notes

1. Tiemann and Köhler, *Ber.*, **14**, 1981 (1881).
2. McKenzie and Clough, *J. Chem. Soc.*, **101**, 395 (1912).
3. Jawelow, *Ber.*, **39**, 1195, 1197 (1906).
4. Clarke and Taylor, *Org. Syntheses*, **4**, 31 (1925); Coll. Vol. **1**, 298 (1941).
5. Clarke and Bean, *Org. Syntheses*, **11**, 4 (1931); Coll. Vol. **2**, 29 (1943).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanolic ammonia

ethanol (64-17-5)

hydrogen chloride, hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ammonium chloride (12125-02-9)

sodium hydroxide (1310-73-2)

sodium cyanide (143-33-9)

ammonium cyanide

aminonitrile (7727-37-9)

Acetophenone (98-86-2)

pyridine (110-86-1)

ammonium hydroxide (1336-21-6)

Glycine (513-29-1)

α-Aminoisobutyric acid (62-57-7)

α-Amino-α-phenylpropionitrile

acetophenone cyanohydrin

DL-α-Amino-α-phenylpropionic acid (6945-32-0)

Alanine, α-phenyl-, dl-

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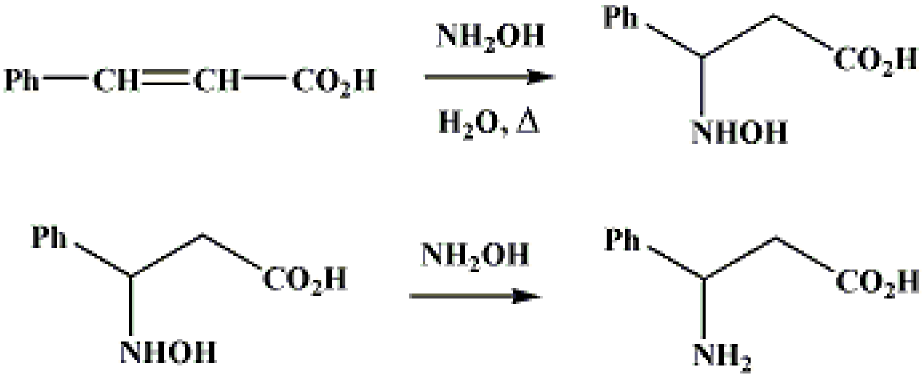
dl-β-AMINO-β-PHENYLPROPIONIC ACID

[Hydrocinnamic acid, β-amino-*dl*-]



Submitted by Robert E. Steiger
Checked by W. E. Bachmann and Yun-Tsung Chao.

1. Procedure

A hot solution of sodium ethoxide is prepared, in a 3-l. round-bottomed flask, from 46 g. (2 gram atoms) of sodium and 1.6 l. of absolute ethanol. With shaking, a solution of 139 g. (2 moles) of hydroxylamine hydrochloride in 100 ml. of hot water is added. The resulting suspension is cooled quickly by placing the flask in an ice-water mixture and is then filtered with suction through a Büchner funnel. The residue of sodium chloride is washed with small portions (total 200 ml.) of absolute ethanol. The filtrate is returned to the 3-l. flask, and to it is added 148 g. (1 mole) of cinnamic acid, whereupon a voluminous precipitate forms. The mixture is refluxed on a steam bath for 9 hours (Note 1). The amino acid begins to separate after 5–6 hours; the suspended solid causes the mixture to bump (Note 2). The suspension is allowed to remain overnight at room temperature, and the crystals are then collected on a Büchner funnel (Note 3). The product is washed with 300 ml. of absolute ethanol, then with some ice-cold water to remove all the sodium chloride, and finally with 300 ml. of absolute ethanol, always in small portions. The colorless crystals of amino acid are dried in a vacuum desiccator over flake sodium hydroxide. The yield is 56 g. (34%).

If a purer product is desired, the amino acid is dissolved in 16 times its weight of boiling water, and to the solution is added absolute ethanol (46 ml. per g. of acid). The solution is stirred mechanically while it is cooled in an ice-water mixture. After 3 hours, the snow-white crystals are collected on a Büchner funnel and are washed with 300 ml. of 95% ethanol, in small portions, and dried as before. The recovery of amino acid, melting at 221° with decomposition (Note 4), is 81%.

2. Notes

1. The solution becomes clear when the boiling point is reached. It is important that the mixture be boiled for the specified time in order to ensure complete conversion of the hydroxylamino acid into the amino acid. The solubilities of these two acids are nearly the same.
2. It may happen that the hot solution remains supersaturated, and crystallization does not take place, until the solution is cooled. The checkers obtained a poor yield when this occurred. They, therefore, seeded other runs during the boiling process in order to bring about crystallization. Posner[1] had to concentrate the solution to about half its volume in order to bring about crystallization.
3. The mother liquors from the crystallization appear to be free of amino acid if the yield mentioned is obtained. Among other products they contain at least 19 g. of acetophenoneoxime (14%), which is formed by the secondary reaction:

The acetophenoneoxime may be isolated by evaporating the mother liquors almost to dryness, adding water repeatedly to remove the alcohol, and then treating the oily residue with 1 *N* sodium carbonate solution.
4. The melting point varies considerably with the rate and duration of heating. Values ranging from 215° to 231° have been reported in the literature. The product obtained appears to be perfectly stable and shows no tendency to assume the pink coloration reported by Posner.[1]

3. Discussion

The procedure described is that given by Posner,[1] with some modifications and additions. The amino acid has also been prepared by boiling the oxime hydrate of β-hydroxylaminohydrocinnamohydroxamic acid with water;[2] by decarboxylation of β-amino-β-phenylethane-α,α-dicarboxylic acid;[3] and by the reaction of cinnamic acid with ammonia under pressure in the presence of anhydrous stannic chloride.[4]

References and Notes

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2. Posner, *Ber.*, **40**, 227 (1904).
3. Rodionow and Malewinskaja, *Ber.*, **59**, 2956 (1926); Rodionow, *J. Am. Chem. Soc.*, **51**, 851 (1929); Evans and Johnson, *J. Am. Chem. Soc.*, **52**, 5001 (1930); Johnson and Livak, *J. Am. Chem. Soc.*, **58**, 301 (1936).
4. Enkvist, Monoven, and Soderlund, *Finska Kemistsamfundets Medd.*, **53**, No. , 66 (1944); [*C. A.*, **41**, 4103 (1947)].

Appendix

Compounds Referenced (Chemical Abstracts Registry Number)

oxime hydrate of β-hydroxylaminohydrocinnamohydroxamic acid

ethanol (64-17-5)

ammonia (7664-41-7)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

Hydroxylamine hydrochloride (5470-11-1)

cinnamic acid (621-82-9)

stannic chloride (7646-78-8)

acetophenoneoxime

β-amino-β-phenylethane-α,α-dicarboxylic acid

DL-β-Amino-β-phenylpropionic acid, Hydrocinnamic acid, β-amino-dl- (614-19-7)

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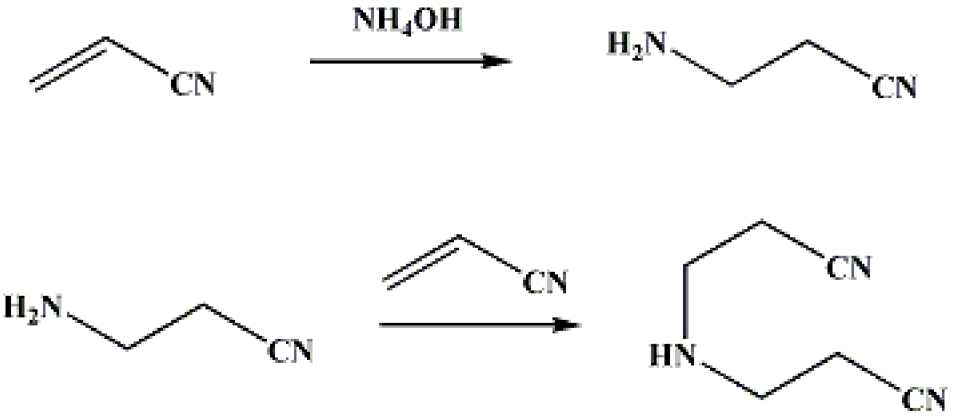
β-AMINOPROPIONITRILE and *bis*-(β-CYANOETHYL)-AMINE

[Propionitrile, β-amino-, and propionitrile, β,β'-iminodi-]



Submitted by Saul R. Buc
Checked by Homer Adkins and James M. Caffrey.

1. Procedure

Acrylonitrile is a poisonous compound. All steps in the procedure up to the distillation of the products should be carried out in a hood.

The reactions are carried out in 1-l. heavy-walled bottles provided with rubber stoppers which must be wired securely in place (Note 1). In each of four bottles are placed 400 ml. of concentrated ammonium hydroxide (28–30% ammonia) and 100 ml. (80 g., 1.5 moles) of cold acrylonitrile (Note 2). The rubber stoppers are immediately wired in place (Note 3). Each bottle is then shaken intermittently until after about 5 minutes the reaction mixture becomes homogeneous. Thereupon, the bottle, wrapped in a towel, is immediately set away under a hood (Note 4).

The reaction mixtures are allowed to stand a few hours or overnight and then are transferred to a 3-l. flask. The water and ammonia are distilled under reduced pressure as rapidly as possible until the boiling point is about 50°/20 mm. (Note 5). The higher-boiling products (395 g.) are then transferred to a 1-l. Claisen flask and fractionated under reduced pressure.

The crude primary amine (138–149 g.) is distilled over the range 75–110°/21 mm. (Note 6), and the crude secondary amine (213–226 g.) in the range 130–150°/1 mm. The primary amine, b.p. 79–81°/16 mm. or 87–89°/20 mm. (n_D^{20} 1.3496), after refractionation, is obtained in a yield of 130–140 g. (31–33%) (Note 7). The secondary amine, b.p. 134–135°/1 mm. (n_D^{20} 1.4640), is obtained in a yield of about 210 g.

(57%) (Note 8).

2. Notes

1. The 1-l. centrifuge bottles (Corning No. 1280) carrying No. 6 rubber stoppers, as used for catalytic hydrogenation, are suitable for carrying out reactions under pressures up to at least 3 atm. The submitter used a heavy, selected 2-l. round-bottomed flask instead of the four bottles specified in the procedure above.
2. The acrylonitrile should be free of polymer. If there is uncertainty as to its quality, the acrylonitrile should be redistilled.
3. The temperature of the mixture does not rise during the period of solution of the acrylonitrile in the ammonium hydroxide. However, almost immediately thereafter the temperature of the solution begins to rise slowly, reaching a value of about 65° after an interval of perhaps 10 minutes. There is no significant rise in pressure within the bottle until the temperature of the reaction mixture begins to rise. The maximum pressure reached is apparently less than 2 atm.
4. The checkers placed the wrapped bottles within a 10-gal crock located under a hood. There is no danger that the bottles will be broken by the pressure developed. However, if a stopper is not firmly held, it may be pushed out, in which event a portion of the reaction mixture will foam out of the bottle.
5. The submitter used a special apparatus suitable for the rapid evaporation of water under reduced pressure. The checkers used standard flasks. Better yields result from the rapid removal of water.
6. It is not necessary to purify the crude primary amine by redistillation if it is to be used immediately for the preparation of β-alanine. However, the moist nitrile is not stable in storage, pressure being developed in a container stored at room temperature.
7. Yields of 60–80% of the primary amine[1] have been obtained by introducing the acrylonitrile below the surface of the aqueous ammonia preheated at 110° in a steel reactor suitable for pressure reactions.
8. Yields of 88.5% of the secondary amine, as well as 6% *tris*-(β-cyanoethyl) amine, have been obtained by adding the acrylonitrile dropwise to aqueous ammonia whose amount was to the amount of acrylonitrile as 0.53 mole:1 mole.[2]

3. Discussion

β-Aminopropionitrile and *bis*-(β-cyanoethyl) amine have been made by the addition of anhydrous[3] or aqueous ammonia[4] to acrylonitrile. β-Aminopropionitrile has been made from β-chloropropionitrile and liquid ammonia (90% yield).[5] *bis*-(β-Cyanoethyl) amine may be converted to β-aminopropionitrile by distillation at atmospheric pressure.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 34

References and Notes

1. Ford, Buc, and Greiner, *J. Am. Chem. Soc.*, **69**, 844 (1947).
2. Wiedeman and Montgomery, *J. Am. Chem. Soc.*, **67**, 1994 (1945).
3. Whitmore, Mosher, Adams, Taylor, Chapin, Weisel, and Yanko, *J. Am. Chem. Soc.*, **66**, 725 (1944).
4. Buc, Ford, and Wise, *J. Am. Chem. Soc.*, **67**, 92 (1945).
5. U. S. pat. 2,443,292 [*C. A.*, **42**, 7322 (1948)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ammonia (7664-41-7)

ammonium hydroxide (1336-21-6)

β-Alanine (107-95-9)

β-Aminopropionitrile, Propionitrile, β-amino- (151-18-8)

acrylonitrile (107-13-1)

bis-(β-cyanoethyl) amine, bis-(β-CYANOETHYL)-AMINE, propionitrile, β,β'-iminodi- (111-94-4)

β-chloropropionitrile (542-76-7)

tris-(β-cyanoethyl) amine

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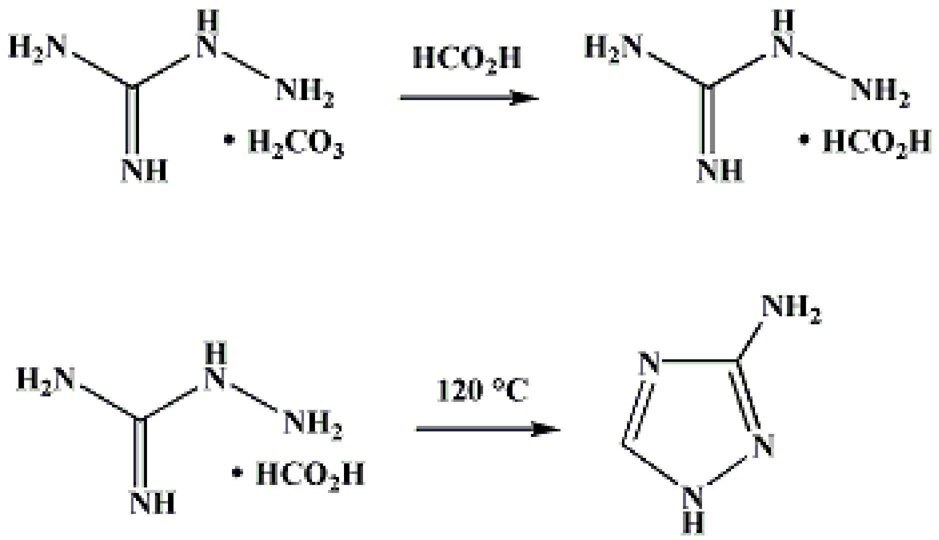
3-AMINO-1H-1,2,4-TRIAZOLE

[1H-1,2,4-Triazole, 3-amino-]



Submitted by Georg Sjostedt and Leopold Gringas.
Checked by E. C. Horning, H. Lloyd, and L. Matternas.

1. Procedure

To 136 g. (1 mole) of finely powdered aminoguanidine bicarbonate in a 500-ml. two-necked round-bottomed flask fitted with a thermometer is added 48 g. (40 ml., 1.05 moles) of 98–100% formic acid (Note 1). The foaming mixture is heated cautiously, with gentle rotation of the flask to avoid local overheating, until gas evolution ceases and the whole mass is dissolved. The solution of aminoguanidine formate is held at a temperature of 120° for 5 hours (Note 2). After the solution is cooled, 500 ml. of 95% ethanol is added, the product is dissolved by heating, and the solution is filtered while hot. The product, obtained by evaporating the ethanol solution to dryness on the steam bath, and oven-drying at 100°, is 80–81.6 g. (95–97%) of colorless crystalline 3-amino-1,2,4-triazole melting at 152–156° (Note 3). The 3-amino-1,2,4-triazole can be recrystallized from ethanol (Note 4).

2. Notes

1. The submitters report that aminoguanidine bicarbonate of practical grade is satisfactory. The checkers used Eastman Kodak white label quality.
2. The submitters and checkers used an infrared heater.
3. The main part of the ethanol can be removed by distillation. From the remaining ethanolic solution yellow crystals precipitate, which are collected on a Büchner funnel. When melted and dried they lose water and give 3-amino-1,2,4-triazole in its pure form.

4. The 3-amino-1,2,4-triazole may be crystallized from ethanol or ethanol-ether.[1] The checkers preferred ethanol (200 ml. for 40 g.). The recovery is 70–73%, m.p. 152–153°.

3. Discussion

3-Amino-1,2,4-triazole has been prepared by evaporating formylguanidine nitrate with sodium carbonate,[2] and from 5(3)-amino-1,2,4-triazolecarboxylic acid-3(5) by heating above its melting point,[3,4,5] or by a long digestion with acetic acid.[2] It has been prepared from the sulfate in essentially the same yield and purity.[1]

References and Notes

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2. Thiele and Manchot, *Ann.*, **303**, 45, 54 (1898).
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4. Hantzsch and Silberrad, *Ber.*, **33**, 79 (1900).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

5(3)-amino-1,2,4-triazolecarboxylic acid-3(5)

ethanol (64-17-5)

acetic acid (64-19-7)

ether (60-29-7)

sodium carbonate (497-19-8)

formic acid (64-18-6)

Aminoguanidine bicarbonate (2582-30-1)

3-Amino-1H-1,2,4-triazole, 1H-1,2,4-Triazole, 3-amino-, 3-amino-1,2,4-triazole (61-82-5)

aminoguanidine formate

formylguanidine nitrate

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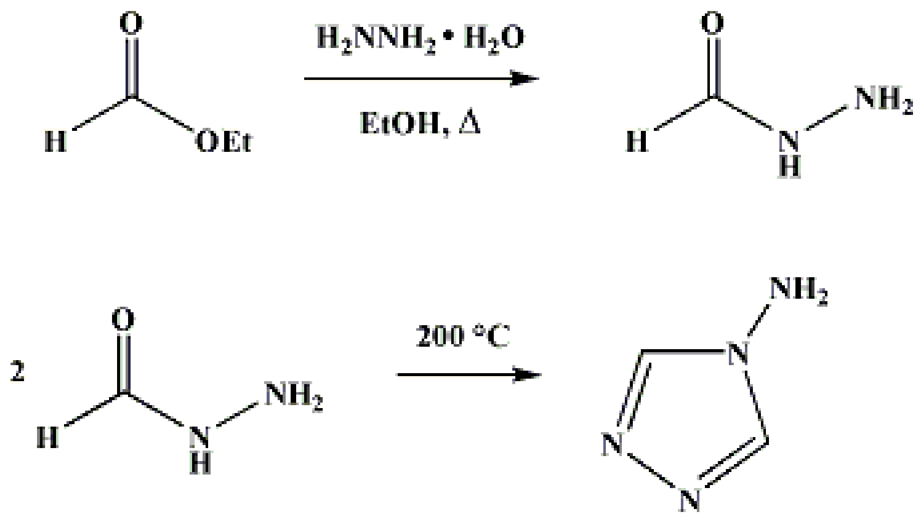
4-AMINO-4H-1,2,4-TRIAZOLE

[4H-1,2,4-Triazole, 4-amino-]



Submitted by C. F. H. Allen and Alan Bell.
Checked by W. E. Bachmann and G. Dana Johnson.

1. Procedure

In a 1-l. round-bottomed flask equipped with an efficient water condenser are placed 148 g. (2 moles) of ethyl formate (b.p. 52–53°) and 150 ml. of 95% ethanol. One hundred and twenty grams (2 moles) of 85% hydrazine hydrate is added cautiously to this solution (Note 1) with shaking over a period of 10 minutes. After the reaction has subsided, the solution is refluxed on a steam bath for 18 hours. The bulk of the water and ethanol is now removed by evaporation under reduced pressure until the volume in the flask is about 150 ml. The resulting syrup, crude formhydrazide, is heated under atmospheric pressure for 3 hours, during which time the temperature of the bath is raised from 150° to 200°. After cooling to about 100°, the oil is taken up in 50 ml. of 95% ethanol, and 5 g. of Norite is added. The filtered solution is then diluted with 75 ml. of ether and placed in an icebox to cool. The crystalline product is filtered, washed with 50 ml. of 1:2 ethanol-ether, and dried. The yield of aminotriazole, melting at 77–78°, is 55–60 g. (65–71%) (Note 2). If a purer product is desired, the crude, washed material may be recrystallized, using 2 ml. of warm 95% ethanol per gram of compound followed by the addition of 2.5 ml. of ether, and chilling. The melting point of the purified product is 81–82°.

The residual amine in the filtrate may be isolated in the form of the hydrochloride. The combined solutions are evaporated on a steam bath, 50 ml. of concentrated hydrochloric acid is added, and heating is continued for 2 hours. On cooling, the syrupy solution crystallizes. It is triturated with 50 ml. of ethanol, and the 4-amino-

1,2,4-triazole hydrochloride is filtered, washed with a little ethanol, and dried. The yield of the hydrochloride is 10–18 g. (8–15%); the salt melts at 147–148° and may be recrystallized from 95% ethanol, using 10 ml. per gram; the melting point is thus raised to 151–152°.

2. Notes

1. The reaction is very vigorous, but if the hydrazine hydrate is added carefully no difficulty of control is encountered.
2. The combined yield of base and hydrochloride is always about 80–81%. When the amount of base is low, that of the hydrochloride is high.

3. Discussion

4-Amino-1,2,4-triazole has been obtained from orthoformic ester and hydrazine hydrate in a sealed tube at 120°;[1] by heating formylhydrazine at 150–210°;[2,3,4] by heating N,N'-diformylhydrazine at 160°;[5] by decarboxylation of 4-amino-1,2,4-triazoldicarboxylic acid;[6] by fusion of 1,2-dihydro-1,2,4,5-tetrazine;[6] and by heating 1,2-dihydro-1,2,4,5-tetrazinedicarboxylic acid above its melting point.[4,6,7]

A process in which hydrazine and carbon monoxide are heated under pressure has been patented.[8]

References and Notes

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2. Ruhemann and Stapleton, *J. Chem. Soc.*, **75**, 1132 (1899).
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5. Pellizzari, *Atti accad. Lincei*, (5) **8** (I), 331 (*Chem. Zentr.*, **1899**, I, 1240); *Gazz. chim. ital.*, **39** (I), 530 (1909).
6. Curtius, Darapsky, and Müller, *Ber.*, **40**, 835, 1194 (1907).
7. Curtius and Lang, *J. prakt. Chem.*, (2) **38**, 549 (1888).
8. Brit. pat. 649,445 [*C. A.*, **45**, 8560 (1951)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ether (60-29-7)

carbon monoxide (630-08-0)

Norite (7782-42-5)

hydrazine hydrate (7803-57-8)

ethyl formate (109-94-4)

hydrazine (302-01-2)

4-Amino-4H-1,2,4-triazole, 4H-1,2,4-Triazole, 4-amino-, 4-Amino-1,2,4-triazole (584-13-4)

formhydrazide, formylhydrazine (624-84-0)

aminotriazole

4-amino-1,2,4-triazole hydrochloride

4-amino-1,2,4-triazoldicarboxylic acid

1,2-dihydro-1,2,4,5-tetrazine

1,2-dihydro-1,2,4,5-tetrazinedicarboxylic acid (3787-09-5)

N,N'-diformylhydrazine

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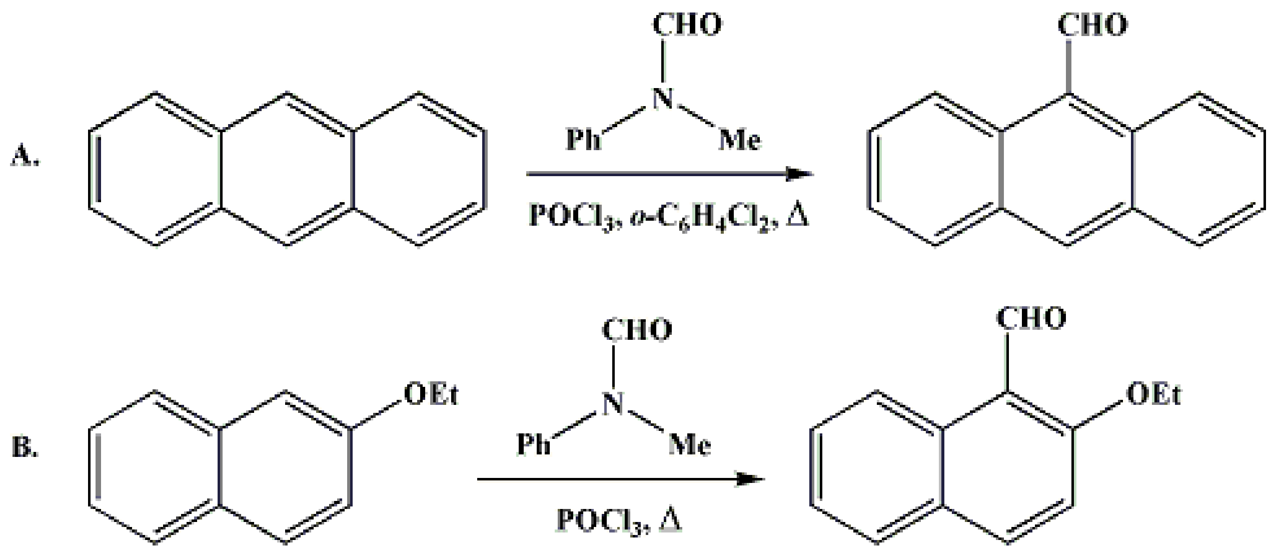
Organic Syntheses, CV 3, 98

9-ANTHRALDEHYDE; 2-ETHOXY-1-NAPHTHALDEHYDE



Submitted by (A) L. F. Fieser, J. L. Hartwell, J. E. Jones, (B) J. H. Wood, and R. W. Bost.
Checked by C. F. H. Allen and J. VanAllan.

1. Procedure

A. *9-Anthraldehyde*. In a 2-l. round-bottomed flask fitted with a mechanical stirrer and reflux condenser are placed 35 g. (32 ml., 0.26 mole) of N-methylformanilide (p. 590), 35 g. (21 ml., 0.23 mole) of phosphorus oxychloride, 20 ml. of *o*-dichlorobenzene, and 22.5 g. (0.13 mole) of anthracene (Note 1). The flask is heated on the steam bath, with stirring, to 90–95° over a period of 20 minutes; the anthracene dissolves during this time to give a deep red solution, and hydrogen chloride is evolved (Note 2). The heating is continued for 1 hour (Note 3), after which a solution of 140 g. of crystalline sodium acetate in 250 ml. of water (Note 4) is added to the cooled mixture, and the *o*-dichlorobenzene and most of the methylaniline are rapidly distilled with steam (15–20 minutes). The residual reddish oil solidifies on cooling. The solid residue is broken up, and, after the aqueous liquor has been decanted through a Büchner funnel, it is washed by decantation with two 100-ml. portions of 6 *N* hydrochloric acid to remove amine, and then thoroughly with water (1–1.2 l.). The crude solid (22–24 g., m.p. 97–101°) is recrystallized from 50 ml. of hot glacial acetic acid; when cold, the bright yellow aldehyde is filtered by suction and washed on the filter with 30 ml. of methanol (Note 5). The yield is 20–22 g. (77–84%), and the melting point is 104.5–105° (Note 6).

B. *2-Ethoxy-1-naphthaldehyde*. A mixture of 45 g. (0.33 mole) of N-methylformanilide (p. 590), 51 g. (0.33 mole) of phosphorus oxychloride, and 43 g. (0.25 mole) of β-naphthyl ethyl ether in a 500-ml. round-bottomed flask provided with an air condenser (Note 2) is heated on a steam bath for 6 hours. The hot mixture is then poured in a thin

stream into 700 ml. of cold water with very vigorous stirring to avoid the formation of large lumps (Note 7); the aldehyde separates in a granular condition. It is filtered by suction and washed thoroughly, using 1 l. of water. Without drying, the crude aldehyde is dissolved in 450 ml. of ethanol and decolorized by the addition of 4 g. of Norit, boiling for 15 minutes, and filtering hot (Note 8), using a double filter paper. The filtrate is cooled, and the product is collected on a filter and washed with 40 ml. of cold ethanol; it crystallizes in pale yellow needles, m.p. 111–112°. The yield is 37–42 g. (74–84%).

2. Notes

1. The yield and purity of the anthraldehyde depend on the quality of the hydrocarbon. The figures given are attained only if the anthracene melts at 213° or higher. With anthracene, m.p. 208–210°, the yield is 19–20 g., m.p. 103–104° (Note 6).
2. The reaction may be carried on in a hood, or a gas trap may be used.
3. When run on a fourfold scale, the time of heating should be extended to 2 hours. Prolonged heating leads to the formation of tars.
4. Sodium acetate appears to decompose a product of the condensation of methylaniline with phosphorus oxyhalides; substances other than the aldehyde are largely retained in the sodium acetate solution.
5. A brighter-colored product is secured by this wash.
6. The aldehyde also exists in a low-melting form, m.p. 98.5–99.5°, and occasionally this form is obtained from the reaction. It is less stable than the high-melting form, into which it is easily converted by seeding.
7. Care must be exercised to prevent the reaction product from lumping upon being poured into water. If this happens, decomposition by the water is slow and subsequent purification is more difficult. Any lumps that are formed should be broken up, and the reaction mixture should then be permitted to stand overnight in contact with the water. The flask in which the reaction is carried out is also filled with water to decompose the product adhering to the walls. This is purified with the rest.
8. A heated funnel is desirable. Some of the product usually crystallizes during the filtration.

3. Discussion

This aldehyde synthesis is applicable to compounds of the aromatic series having a labile hydrogen atom (phenyl ethers,[1] naphthols,[2] dialkylanilines,[3,4] naphthostyril,[2] anthrones[2]) and to certain hydrocarbons of requisite reactivity (anthracene,[5,6] 1,2-benzanthracene,[6] 3,4-benzpyrene,[3,7] pyrene,[8] styrene,[9] and α,α-diarylethylenes[9]). With polynuclear hydrocarbons the best results are secured by the use of a solvent such as *o*-dichlorobenzene. 9-Anthraldehyde has also been prepared by the action of hydrogen cyanide and aluminum chloride on anthracene in chlorobenzene.[10]

With liquid or low-melting ethers no solvent is required. 2-Ethoxy-1-naphthaldehyde has also been prepared by ethylation of the hydroxy compound,[11] and from β-naphthyl ethyl

ether by the Gattermann reaction.[12]

It is possible to employ N,N-dimethylformamide in place of N-methylformanilide in some cases. A general method, applied to 9-anthraldehyde, has been described by Campaigne and Archer.[13]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

naphthostyril

3,4-benzpyrene

ethanol (64-17-5)

hydrogen chloride, hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

methanol (67-56-1)

sodium acetate (127-09-3)

hydrogen cyanide (74-90-8)

Norit (7782-42-5)

chlorobenzene (108-90-7)

Phosphorus Oxychloride (21295-50-1)

aluminum chloride (3495-54-3)

anthracene (120-12-7)

styrene (100-42-5)

β-naphthyl ethyl ether (93-18-5)

methylaniline (100-61-8)

9-ANTHRALDEHYDE (642-31-9)

2-ETHOXY-1-NAPHTHALDEHYDE (19523-57-0)

N-methylformanilide (93-61-8)

anthraldehyde

1,2-benzanthracene (56-55-3)

pyrene (129-00-0)

N,N-dimethylformamide (68-12-2)

o-dichlorobenzene (95-50-1)

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D-ARABINOSE

Submitted by Géza Braun
Checked by H. T. Clarke and S. M. Nagy.

1. Procedure

A solution of 100 g. (0.26 mole) of pentaacetyl gluconbooitrile (p. 690) in 150 ml. of chloroform in a 1-l. Erlenmeyer flask is chilled to −12°. A chilled (−12°) solution of 16 g. (0.7 gram atom) of sodium in 250 ml. of anhydrous methanol is added with continual shaking and chilling to the chloroform solution of the nitrile. The mixture soon solidifies to a pale yellow gelatinous mass. After 10 minutes at −12° this is broken up with a heavy glass rod and dissolved in 600 ml. of a suspension of ice in water. The resulting solution is acidified with an ice-cold mixture of 33 g. (18 ml., 0.32 mole) of 95% sulfuric acid, 5 ml. of acetic acid, and 45 g. of ice. The aqueous layer is separated, washed once with 50 ml. of chloroform, and evaporated without delay (Note 1) under reduced pressure. The residual heavy syrup is dissolved in 300 ml. of water and again evaporated as completely as possible under reduced pressure, in order to remove residual hydrogen cyanide (Note 2). The highly viscous residue, which contains some crystals of sodium sulfate, is dissolved in 500 ml. of hot methanol. After about 10 minutes the sodium sulfate is filtered with suction and washed with two 25-ml. portions of methanol. The filtrate is concentrated under reduced pressure at 40° to a heavy syrup which is poured while warm into a 200-ml. Erlenmeyer flask. The distilling flask is rinsed twice with 20-ml. portions of hot ethanol, and this rinse is added to the filtrate. The resulting ethanol solution soon begins to deposit crystals of arabinose; it is stirred by hand during the crystallization and gradually diluted with more ethanol until 100 ml. in all has been added during the course of an hour. The mixture is allowed to stand for 4–5 hours; the crystals are then filtered, washed with two 25-ml. portions of ethanol, and dried at 40°. The yield of colorless D-arabinose, m.p. 158–158.5°, $[\alpha]_D^{20}$ −105° (final value), is 23.5–26.3 g. (61–68%) (Note 3).

2. Notes

1. After the reaction mixture has been dissolved in water and acidified, the hydrogen cyanide should be removed as soon as possible, for the arabinose tends to react with it even in dilute solution.
2. A slightly higher yield of crystalline arabinose is obtainable by removing the hydrogen cyanide with silver acetate. The procedure then consists in acidifying with acetic acid in place of sulfuric acid, adding an excess of silver acetate,

shaking for an hour, filtering, saturating with hydrogen sulfide, again filtering, and adding sulfuric acid as indicated above. The rest of the procedure is the same. The yield of crystalline arabinose so obtained is 27.1 g. (70%).
3. A further quantity of arabinose may be isolated from the mother liquors by the use of diphenylhydrazine: to a solution of 22 g. of diphenylhydrazine hydrochloride in 100 ml. of absolute methanol is added a solution of 3.3 g. of sodium in 50 ml. of methanol. After 15 minutes' standing the sodium chloride is removed by filtration and washed with methanol. The filtrate, which contains approximately 18 g. of free diphenylhydrazine, is added to the alcoholic mother liquor from the arabinose, and the mixture is inoculated with diphenylhydrazone prepared from some of the crystalline arabinose. The mixture is allowed to stand overnight, and the crystalline diphenylhydrazone is filtered, washed with 95% ethanol, and dried in a vacuum desiccator. In a preparation in which the yield of crystalline arabinose had been 23.5 g., the yield of diphenylhydrazone was 16.5 g., corresponding to 7.8 g. of the sugar. Arabinose can be recovered from the diphenylhydrazone by treatment with formaldehyde in aqueous solution. In view of the high cost of diphenylhydrazine, however, it is doubtful whether its use for this purpose is profitable.

3. Discussion

D-Arabinose was first prepared by Wohl,[1] by treating pentaacetyl gluconpremitrile with ammoniacal silver nitrate. It has also been obtained from *d*-gluconic acid in various ways: by oxidation of the calcium salt by means of hydrogen peroxide in the presence of ferric acetate;[2,3,4,5] by boiling an aqueous solution of the mercuric salt;[6] by electrolysis;[7] by the action of sodium hypochlorite upon the amide.[8] It has also been obtained by the electrolytic reduction of D-arabonic acid lactone.[9] The present method, developed by Zemplén and Kiss,[10] furnishes better yields than that of Wohl.

A modification of the Ruff method,[2] using ion-exchange resins for the removal of salts, has been published.[11]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

diphenylhydrazone

ammoniacal silver nitrate

ethanol (64-17-5)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

methanol (67-56-1)

formaldehyde (630-08-0)

chloroform (67-66-3)

sodium chloride (7647-14-5)

hydrogen sulfide (7783-06-4)

hydrogen cyanide (74-90-8)

sodium sulfate (7757-82-6)

arabinose, d-ARABINOSE (28697-53-2)

sodium (13966-32-0)

hydrogen peroxide (7722-84-1)

sodium hypochlorite (7681-52-9)

silver acetate (563-63-3)

pentaacetyl gluconitrile

diphenylhydrazine (530-50-7)

diphenylhydrazine hydrochloride (530-47-2)

ferric acetate

d-arabonic acid lactone

d-gluconic acid (526-95-4)

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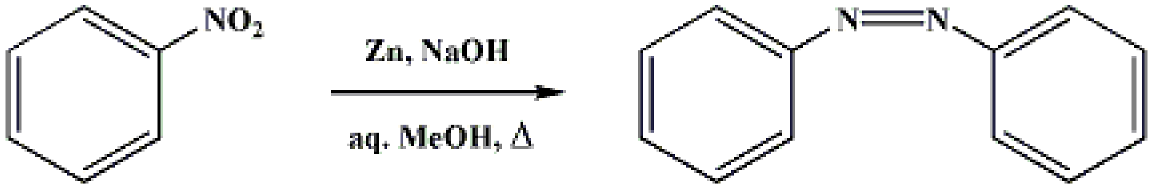
AZOBENZENE



Submitted by H. E. Bigelow and D. B. Robinson.
Checked by W. E. Bachmann and W. S. Struve.

1. Procedure

A 5-l. three-necked round-bottomed flask, fitted with a mercury-sealed stirrer and a reflux condenser, is placed on a steam cone. In the flask are placed 250 g. (208 ml., 2 moles) of nitrobenzene, 2.5 l. of methanol, and a solution of 325 g. (8.1 moles) of sodium hydroxide (Note 1) in 750 ml. of distilled water. To the mixture is added 265 g. (4.1 moles) of zinc dust (Note 2), the stirrer is started, and the mixture is refluxed for 10 hours (Note 3). The mixture is filtered while hot, and the precipitate of sodium zincate is washed on the filter with a little warm methanol. All the methanol is distilled from the filtrate, the residue is chilled, and the crystalline azobenzene is filtered.

In order to remove zinc salts from the crude azobenzene, the latter is added to 500 ml. of 2% hydrochloric acid, the mixture is warmed to about 70° in order to melt the azobenzene and is stirred rapidly for about 5 minutes. Stirring is continued while the mixture is chilled to solidify the azobenzene. The product is filtered, washed well with water, and recrystallized from a mixture of 720 ml. of 95% ethanol and 60 ml. of water. The yield of azobenzene melting at 66–67.5° is 156–160 g. (84–86%).

2. Notes

1. This amount assumes 100% purity. The checkers used 342 g. of 95% sodium hydroxide.
2. This amount assumes 100% purity. The checkers used 288 g. of 92% zinc dust.
3. At the end of this time, the reddish mixture should be free from the odor of nitrobenzene. If it is not, refluxing is continued for 2–3 hours longer.

3. Discussion

Azobenzene has been prepared by many different methods, of which the following are representative. It may be obtained by the reduction of nitrobenzene with iron and acetic acid;[1] with sodium amalgam;[2] with alkali sulfides;[3] with cellulose,[4] molasses,[5]

or dextrose[5] in alkaline solution; and by catalytic reduction.[6] The reduction with zinc and sodium hydroxide described here is a modification of Alexejew's method.[7] Azobenzene also results from the reduction of diazotized aniline with cuprous salts.[8] Aniline has been oxidized to azobenzene by air[9] and by potassium permanganate.[10] The condensation of nitrobenzene and aniline acetate also yields azobenzene.[11]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium zincate

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

methanol (67-56-1)

aniline (62-53-3)

sodium hydroxide (1310-73-2)

iron (7439-89-6)

potassium permanganate (7722-64-7)

zinc (7440-66-6)

sodium (13966-32-0)

Nitrobenzene (98-95-3)

dextrose (492-62-6)

Azobenzene (103-33-3)

aniline acetate

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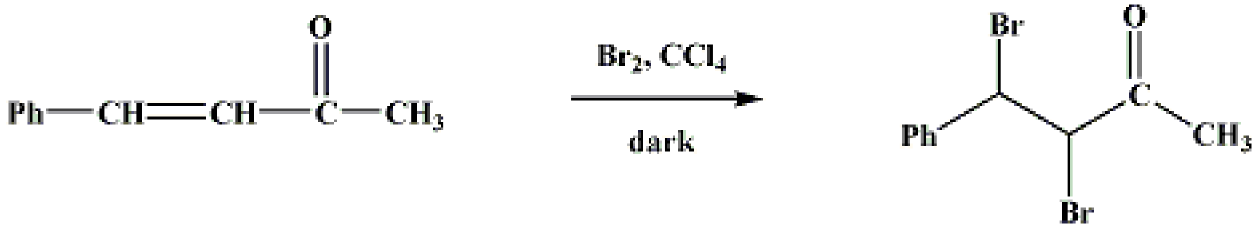
BENZALACETONE DIBROMIDE

[2-Butanone, 3,4-dibromo-4-phenyl-]



Submitted by Norman H. Cromwell and Richard Benson.
Checked by R. L. Shriner and William O. Foye.

1. Procedure

In a 1-l. three-necked round-bottomed flask fitted with an efficient mechanical stirrer, a thermometer, and a 125-ml. dropping funnel are placed 100 g. (0.68 mole) of pure, redistilled benzalacetone[1] and 300 ml. of carbon tetrachloride. The reaction flask is immersed in an ice-water bath to maintain the reaction mixture between 10° and 20°. With stirring, a cooled solution of 109.5 g. (34.2 ml., 0.68 mole) of bromine in 60 ml. of carbon tetrachloride is run through the dropping funnel as rapidly as the color is destroyed (Note 1). During this addition the reaction flask should be shielded from direct sunlight (Note 2).

After all the bromine has been added, stirring is continued for 4–5 minutes longer and the dibromide is collected by filtration on an 11-cm. Büchner funnel, using suction. The product is washed with 100 ml. of warm 75% ethanol (Note 3). The crude product is purified by dissolving in the minimum amount of boiling methanol (800–1000 ml.) and cooling the solution in an ice bath for 4 hours. The product is collected by filtration and dried in a vacuum desiccator in the absence of light for 24 hours. The yield amounts to 110–120 g. (52–57%) of white needles which melt at 124–125° (Note 4).

2. Notes

1. Until a considerable amount of the dibromide has precipitated, the bromine solution may be run into the reaction mixture as fast as the color is discharged, within the temperature limits of 10–20°. As the mixture becomes thick with the precipitated bromide it is necessary to reduce the speed of the addition of the bromine solution considerably.

2. Strong sunlight seems to favor the substitution of the available α-hydrogen as evidenced by the strong evolution of hydrogen bromide.

3. If the crude product is dried it is found to melt at 114–117° and to weigh 138–

144 g. This is probably a mixture of the two racemic forms.
4. Evaporation and subsequent cooling of the filtrate give a second crop of white crystals, about 15 g., melting at 112–115°. This may be the lower-melting racemate.

3. Discussion

Benzalacetone dibromide has been prepared by the addition of bromine to a solution of benzalacetone in chloroform,[2] in carbon disulfide,[3] and in carbon tetrachloride;[4] and by the reaction of benzalacetone with N-bromosuccinimide.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 125

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

α-hydrogen

ethanol (64-17-5)

methanol (67-56-1)

chloroform (67-66-3)

hydrogen bromide (10035-10-6)

bromine (7726-95-6)

carbon tetrachloride (56-23-5)

Benzalacetone (122-57-6)

carbon disulfide (75-15-0)

Benzalacetone dibromide, 2-Butanone, 3,4-dibromo-4-phenyl- (6310-44-7)

N-bromosuccinimide (128-08-5)

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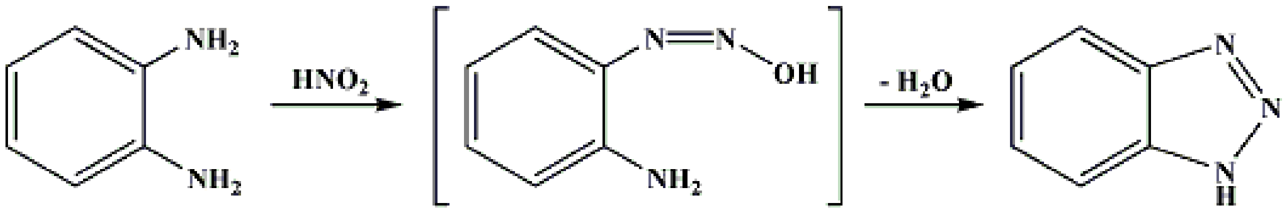
1,2,3-BENZOTRIAZOLE

[1H-Benzotriazole]



Submitted by R. E. Damschroder and W. D. Peterson.
Checked by W. E. Bachmann and W. S. Struve.

1. Procedure

In a 1-l. beaker are placed 108 g. (1 mole) of *o*-phenylenediamine, 120 g. (115 ml., 2 moles) of glacial acetic acid, and 300 ml. of water. By warming the mixture slightly a clear solution is obtained. The beaker is placed in ice water, and the contents are cooled to 5°. As soon as this temperature is reached, a cold solution of 75 g. (1.09 moles) of sodium nitrite in 120 ml. of water is added all at once, the mixture being stirred with a glass rod or by a slow mechanical stirrer. The reaction mixture turns dark green, and the temperature rises rapidly to 70–80° (Note 1). The color of the solution changes to a clear orange-red. The beaker is now removed from the cooling bath, and the contents are allowed to stand for 1 hour; as the solution cools, the benzotriazole separates as an oil. The beaker is then packed in ice, and the mixture is stirred until it sets to a solid mass. After being kept cold for 3 hours, the solid is collected on a Büchner funnel, washed with 200 ml. of ice water, and sucked as dry as possible under a rubber dam. The tan-colored product, after drying at 45–50° overnight, weighs 110–116 g.

The crude benzotriazole is placed in a 200-ml. modified Claisen flask and distilled under reduced pressure (Note 2). The yield of white solid (yellow cast) boiling at 201–204° at 15 mm. or 156–159° at 2 mm. is 92–99 g. The product in the receiver is melted over a luminous flame and poured into 250 ml. of benzene. The clear solution is stirred until crystallization sets in; after being chilled for 2 hours, the product is filtered on a Büchner funnel. The colorless benzotriazole weighs 90–97 g. (75–81%) (Note 3) and melts at 96–97°.

2. Notes

1. Too efficient cooling and stirring are to be avoided. It is essential that the temperature rise to 80°. Too rapid cooling after this temperature has been reached results in lower yields. With runs one-tenth this size it is advisable to remove the mixture from the cooling bath as soon as the sodium nitrite has been added in order to ensure the rise in temperature.
2. The crude product can be purified by repeated crystallizations from benzene or water. Greater losses accompany this tedious method of purification than a single distillation.
3. The submitters report that runs of double this size can be made with equally good results.

3. Discussion

1,2,3-Benzotriazole has been prepared directly by the action of nitrous acid on *o*-

phenylenediamine[1] and by the hydrolysis of an acylated or aroylated benzotriazole which has been previously prepared by the action of nitrous acid on the corresponding mono acylated or aroylated *o*-phenylenediamine.[2,3,4] The above procedure is the direct method and gives better over-all yields than the methods involving several intermediate steps. Most methods described in the literature employ mineral acid. Acetic acid is much more satisfactory.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

acetic acid (64-19-7)

Benzene (71-43-2)

sodium nitrite (7632-00-0)

nitrous acid (7782-77-6)

1,2,3-Benzotriazole, 1H-Benzotriazole, benzotriazole (95-14-7)

o-Phenylenediamine (95-54-5)

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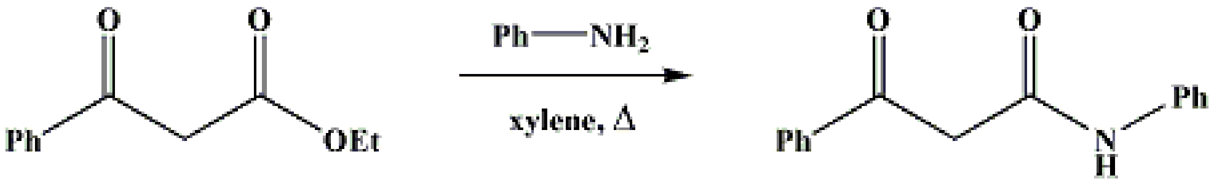
BENZOYLACETANILIDE

[Acetanilide, α-benzoyl-]



Submitted by Charles J. Kibler and A. Weissberger.
Checked by R. L. Shriner and Fred W. Neumann.

1. Procedure

A 250-ml. three-necked round-bottomed flask is fitted with a dropping funnel, a mechanical stirrer, and a steam-jacketed column (15–20 cm. long) terminating in a still head. The still head carries a thermometer and is connected to a condenser set for downward distillation. In the flask are placed 42.2 g. (0.22 mole) of ethyl benzoylacetate (Note 1) and 50 ml. of dry xylene, and the flask is immersed in an oil bath. The bath is heated to 145–150°, stirring is begun, and 18.2 ml. (18.6 g., 0.20 mole) of aniline is added dropwise during 30 minutes. About 5 minutes after the addition has begun, the temperature in the still head rises to 75–78° as ethanol begins to distil. Approximately 12–14 ml. of distillate (Note 2) is collected in a 25-ml. graduate in about 1 hour; the end of the reaction is indicated by the fall of the temperature in the still head.

The reaction flask is removed from the oil bath, and the solution is poured into a 250-ml. beaker to crystallize; 10 ml. of benzene is used to rinse out the flask. When crystallization sets in, 50 ml. of petroleum ether (b.p. 35–55°) is added to the warm mixture with manual stirring. After the mixture has been chilled in an ice bath, the product is filtered by suction and washed with 100 ml. of a 1:1 petroleum ether-benzene mixture. It is then removed from the funnel, stirred into a slurry with 100 ml. of the mixed solvent, filtered, and again washed with 50 ml. of the solvent. These washings remove the bulk of the color, and a powdery white product remains. After standing overnight in a warm place, the product weighs 35.5–36.5 g. (74–76%) and melts at 104–105°. It may be purified further by recrystallization from benzene (3.7 ml. per g.). The yield of colorless benzoylacetanilide melting at 106–106.5° cor, is 32–34 g.

2. Notes

1. The ethyl benzoylacetate, aniline, and xylene should be redistilled before use. It is necessary that the flask and reagents be free from moisture. Impure starting materials and particularly traces of acids lower the yields. The submitters

obtained 82–83% yields of benzoylacetanilide by using Eastman xylene (histological).
2. The distillate consists of a mixture of xylene and ethanol. By adding 100 ml. of water, the xylene layer can be separated and measured. Of 14 ml. of distillate, about 3.5 ml. is xylene and the balance, 10.5 ml. (89% of the theoretical amount), is ethanol.

3. Discussion

Benzoylacetanilide has been made by heating aniline and methyl benzoylacetate in an autoclave at 150°[1] and by heating the anil $C_6H_5NHCOCH_2(C{=}NC_6H_5)C_6H_5$ with dilute acid.[1]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 80

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

ethanol (64-17-5)

Benzene (71-43-2)

aniline (62-53-3)

xylene (106-42-3)

Ethyl benzoylacetate (94-02-0)

Benzoylacetanilide, Acetanilide, α-benzoyl- (85-99-4)

methyl benzoylacetate

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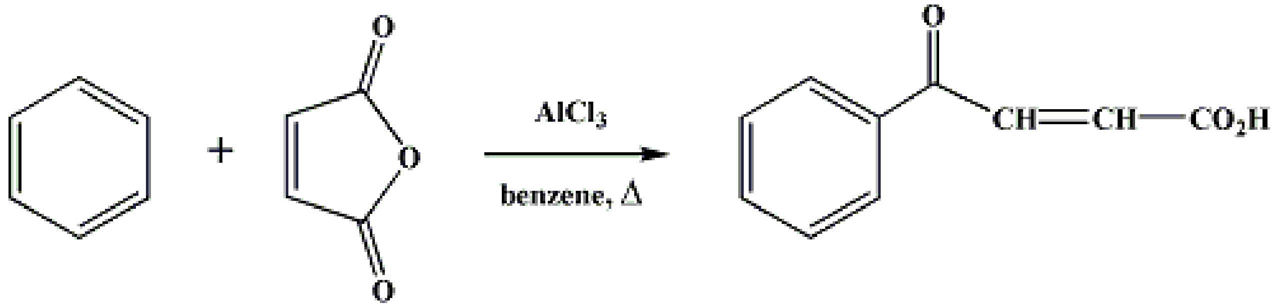
β-BENZOYLACRYLIC ACID

[Acrylic acid, β-benzoyl-]



Submitted by Oliver Grummitt, E. I. Becker, and C. Miesse.
Checked by Arthur C. Cope and Claude F. Spencer.

1. Procedure

In a 1-l. three-necked round-bottomed flask fitted with a mercury-sealed stirrer and a reflux condenser are placed 34 g. (0.347 mole) of maleic anhydride (Note 1) and 175 g. (200 ml., 2.24 moles) of dry, thiophene-free benzene. Stirring is started, and, when the maleic anhydride has dissolved, 100 g. (0.75 mole) of anhydrous reagent grade aluminum chloride powder is added in 6–8 portions through the third neck of the flask at a rate so that the benzene refluxes moderately. The addition requires about 20 minutes. The mixture is then heated under reflux on a steam bath and stirred for 1 hour. The reaction flask is cooled thoroughly in an ice bath, a 250-ml. dropping funnel is attached to the third neck, and the mixture is hydrolyzed by adding 200 ml. of water with stirring and cooling (the first 50 ml. during 15–20 minutes and the balance in about 10 minutes), followed by 50 ml. of concentrated hydrochloric acid (Note 2). Stirring is continued for an additional 40 minutes, during which time it may be necessary to use a spatula to scrape adhering particles of the red-brown aluminum chloride addition compound from the walls of the flask.

The hydrolyzed mixture is transferred to a 1-l. Claisen flask, the transfer of material being completed by rinsing with about 50 ml. of warm water. The flask is heated in a water bath at 50–60°, and the benzene and some water are distilled at 20–30 mm. pressure (Note 3). While the residue is still molten, it is transferred to a 1-l. beaker, and the flask is rinsed with 50 ml. of warm water. After standing at 0–5° for 1 hour, the yellow solid is collected on a suction filter and washed with a solution of 25 ml. of concentrated hydrochloric acid in 100 ml. of water and then with 100 ml. of water. The washing is done most efficiently by suspending the solid in the wash liquid, cooling to 0–5° with stirring, and then filtering with suction. The preparation should not be interrupted before this point (Note 3), at which stage the crude acid may be air-dried overnight at room temperature if desired. The crude product is dissolved in a solution of 40 g. of anhydrous sodium carbonate in 250 ml. of water by warming to 40–50° (Note 4), 2 g. of Celite or other filter aid is added, and the solution is filtered with suction while warm. After the filter has been washed with two 30-ml. portions of warm water, 2 g. of Norit is added to the combined filtrates and the mixture is heated at 40–50° for 10–15 minutes with frequent stirring, then filtered with suction. The clear,

yellow filtrate is transferred to a 1-l. beaker and cooled to 5–10°, and 70 ml. of concentrated hydrochloric acid is added dropwise with stirring. Efficient cooling and stirring are necessary to avoid the precipitation of the acid as an oil. After being cooled to 0–5°, the mixture is filtered with suction; the solid is washed with two 50-ml. portions of cold water and then is dried at 50° for 12–36 hours to give 56–63 g. of light-yellow anhydrous β-benzoylacrylic acid, m.p. 90–93° (Note 5). The crude acid may be crystallized from benzene, using 12–15 ml. of benzene per 5 g. of acid and cooling at 5–10° (Note 6) to give 44–47 g. of β-benzoylacrylic acid, m.p. 94–96° (Note 7). Concentration of the filtrate to one-fourth to one-fifth of its original volume gives an additional 3–6 g., melting in the range 92–96°. The total yield is 49–52 g. (80–85%) (Note 8).

2. Notes

1. A good grade of commercial maleic anhydride was used, m.p. 52–54°.
2. When β-benzoylacrylic acid is heated with dilute hydrochloric acid, β-benzoyllactic acid is formed, which makes the purification of the product very difficult.[1] For this reason the mixture is well cooled during hydrolysis and the hydrochloric acid is not added until the heat of the exothermic hydrolysis has been dissipated.
3. The benzene solution of β-benzoylacrylic acid is concentrated under reduced pressure to avoid overheating, and the crude product is separated from aqueous hydrochloric acid without long standing in order to minimize the possibility of forming β-benzoyllactic acid (Note 2).
4. Heating a mixture of β-benzoylacrylic acid and excess sodium carbonate causes hydrolysis to acetophenone and other products, which decreases the yield and interferes with purification of the product.[2,3]
5. Before drying, the product is the monohydrate, m.p. 64–65° when pure. It is dried until it reaches constant weight and has the melting point of the anhydrous acid.
6. The benzene solution should not be boiled longer than necessary to dissolve the acid, because prolonged heating discolors the product.
7. The evidence indicates that this is the *trans* form of β-benzoylacrylic acid.[4,5,6] Inhalation of β-benzoylacrylic acid dust should be avoided because of its sternutatory action.
8. It has been reported (E. L. Ringwald, private communication) that this reaction may be carried out on a large scale (170 g. of maleic anhydride, 1 kg. of dry benzene, and 1 kg. of aluminum chloride). After the first addition of 500 g. of aluminum chloride, the remaining material is added in 100-g. portions. The mixture is heated with stirring at 55–60° for 1 hour. The complex is decomposed by pouring into ice and concentrated hydrochloric acid. The crude air-dried product, separated by filtration, is combined with the residue obtained by removal of the solvent. The combined crude products are recrystallized from benzene-hexane. The yield is 252 g. (m.p. 95–96°) of first crop, and 15 g. (m.p. 90–94°) of second crop, a total yield of 87%.

3. Discussion

β-Benzoylacrylic acid has been prepared by the condensation of acetophenone and chloral to 1,1,1-trichloro-2-hydroxy-3-benzoylpropane, followed by hydrolysis to the corresponding

acid and dehydration;[7] by the action of iodine, potassium iodide, and sodium carbonate on γ-phenylisocrotonic acid;[8] by bromination of β-benzoylpropionic acid and subsequent dehydrohalogenation;[1] by the action of phenylzinc chloride on maleic anhydride;[9] and by the condensation of the acid chloride of ethyl hydrogen maleate with benzene in the presence of aluminum chloride, followed by hydrolysis.[10] The present method is based on the work of von Pechmann and others.[2,11,12]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

acid chloride of ethyl hydrogen maleate

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

sodium carbonate (497-19-8)

potassium iodide (7681-11-0)

iodine (7553-56-2)

Acetophenone (98-86-2)

aluminum chloride (3495-54-3)

β-Benzoylpropionic acid (2051-95-8)

β-Benzoylacrylic acid, Acrylic acid, β-benzoyl- (583-06-2)

chloral (75-87-6)

maleic anhydride (108-31-6)

β-benzoyllactic acid

1,1,1-trichloro-2-hydroxy-3-benzoylpropane

γ-phenylisocrotonic acid

phenylzinc chloride

hexane (110-54-3)

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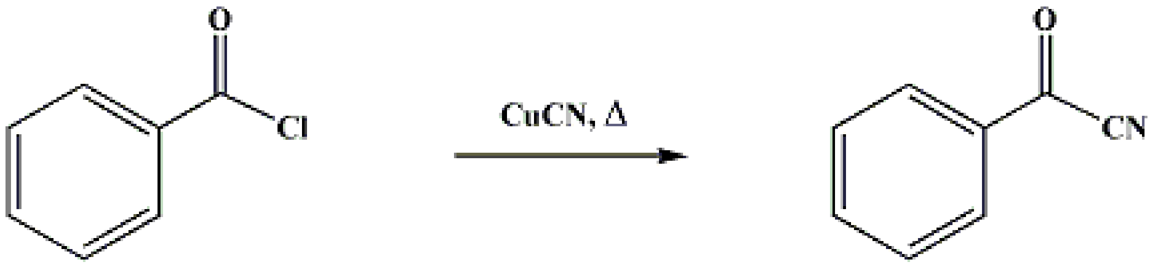
BENZOYL CYANIDE

[Glyoxylonitrile, phenyl-]



Submitted by T. S. Oakwood and C. A. Weisgerber.
Checked by R. L. Shriner and Charles R. Russell.

1. Procedure

In a 500-ml. distilling flask (Note 1) fitted with a thermometer extending to within 0.5 in. of the bottom are placed 110 g. (1.2 moles) of cuprous cyanide (Note 2) and 143 g. (118 ml., 1.02 moles) of purified benzoyl chloride (Note 3). The flask is shaken to moisten almost all the cuprous cyanide and is placed in an oil bath (Note 4) which has been previously heated to 145–150°. The temperature of the bath is raised to 220–230° and maintained between these limits for 1.5 hours. During the heating the flask is frequently removed from the bath (about every 15 minutes) and the contents are thoroughly mixed by vigorous shaking (Note 5). At the end of the 1.5 hours the flask is connected with an air-cooled condenser set for downward distillation. The temperature of the bath is slowly raised to 305–310°, and distillation is continued until no more product comes over (Note 6). About 100–112 g. of crude benzoyl cyanide boiling at 207–218°/745 mm. is obtained.

The crude benzoyl cyanide is purified by fractional distillation through a column (Note 7). The low-boiling material is taken off at a reflux ratio of 25–30 to 1 until the temperature reaches 208°; about 15 g. is collected. The benzoyl cyanide is collected at a reflux ratio of 1 to 1 at a temperature of 208–209°/745 mm. (bath temperature 260–280°). The distillate solidifies to colorless crystals which melt at 32–33°; the product weighs 80–86 g. (60–65%).

2. Notes

1. It is advisable to wrap the neck of the flask with asbestos paper or asbestos tape.
2. The cuprous cyanide is dried at 110° for 3 hours before use.
3. The commercial grade of benzoyl chloride may be purified as follows: 300 ml. (363 g.) of benzoyl chloride in 200 ml. of benzene is washed with two 100-ml. portions of cold 5% sodium bicarbonate solution. The benzene layer is

separated, dried over calcium chloride, and distilled. After all the benzene has distilled, pure benzoyl chloride boiling at 196.8°(cor.)/745 mm. is collected. The recovery is 225 g.

4. Hydrogenated cottonseed oil, "Coto Flakes," obtainable from the Procter and Gamble Company, Cincinnati, Ohio, is suitable for the bath. A Wood's metal bath may also be used.

5. Upon addition of the benzoyl chloride to the cuprous cyanide thorough mixing by shaking is impossible. After the mixture is heated for about 30 minutes, the solid becomes granular and mixing is easily effected.

6. The distillate should be collected in the 200-ml. round-bottomed flask which is used in the subsequent fractionation. The distillation takes about an hour. The cake of copper salts in the flask is best removed by digestion with concentrated ammonium hydroxide solution.

7. The fractionating column was of the Whitmore-Lux type[1] and had about 14 theoretical plates. The packed section was 37 by 1.1 cm. (o.d.) and was packed with 3/32-in. single-turn glass helices. The distilling flask was a 200-ml. round-bottomed flask. A metal bath or the oil bath described in (Note 4) may be used for heating.

3. Discussion

Benzoyl cyanide can be prepared by the thermal decomposition of ω-isonitrosoacetophenone,[2] from silver cyanide and benzoyl chloride,[3] from anhydrous hydrogen cyanide and benzoyl chloride in the presence of pyridine,[4] and by the thermal decomposition of phenylchloronitrocyanomethane.[5,6] It has been prepared by the vapor-phase reaction between hydrogen cyanide and benzoic anhydride in the presence of a granular catalyst (activated charcoal, alumina, or silica gel).[7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 114

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

calcium chloride (10043-52-4)

Benzene (71-43-2)

sodium bicarbonate (144-55-8)

hydrogen cyanide (74-90-8)

Cuprous Cyanide (544-92-3)

benzoyl chloride (98-88-4)

Benzoic anhydride (93-97-0)

pyridine (110-86-1)

ammonium hydroxide (1336-21-6)

Benzoyl cyanide, Glyoxylonitrile, phenyl- (613-90-1)

ω-isonitrosoacetophenone

silver cyanide (506-64-9)

phenylchloronitrocyanomethane

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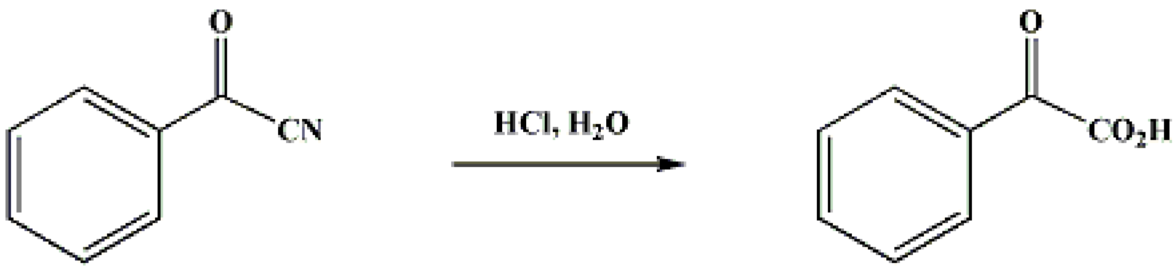
Organic Syntheses, CV 3, 114

BENZOYLFORMIC ACID

[Glyoxylic acid, phenyl-]



Submitted by T. S. Oakwood and C. A. Weisgerber.
Checked by R. L. Shriner and Charles R. Russell.

1. Procedure

In a 1-l. flask are placed 50 g. (0.38 mole) of benzoyl cyanide (p. 112) and 500 ml. of concentrated hydrochloric acid (sp. gr. 1.18). The mixture is shaken occasionally until the solid is dissolved completely and is then allowed to stand at room temperature for 5 days (Note 1). At the end of this time the clear yellow solution is poured into 2 l. of water and extracted with one 400-ml. portion and three 250-ml. portions of ether. The ether is removed by distillation from a steam bath, and the residual oil is placed in a vacuum desiccator containing phosphorus pentoxide and solid sodium hydroxide and allowed to remain there until dry (Note 2). The yield of crude solid acid melting from 57° to 64° is about 55–56 g. (96–98%). The crude acid is dissolved in 750 ml. of hot carbon tetrachloride, and 2 g. of Norit is added (Note 3). The solution is filtered and allowed to cool to room temperature and then cooled in an ice-water mixture until crystallization is complete. The solid acid is filtered with suction, and the solvent remaining on the crystals is removed by placing the product in a vacuum desiccator for about 2 days. The yield of slightly yellow benzoylformic acid melting at 64–66° is 42–44 g. (73–77%) (Note 4).

2. Notes

1. With occasional shaking about a day is necessary for complete solution of the solid benzoyl cyanide. A yellow oil separates which dissolves on shaking. At the end of this time some ammonium chloride occasionally separates.
2. If the oil does not crystallize it is cooled in an ice-water mixture until solidification is complete. The solid is returned to the desiccator for complete drying. The desiccator must be evacuated slowly or spattering will take place.
3. If decolorizing carbon is not used, the acid tends to separate as an oil which solidifies on cooling.
4. Titration with standard sodium hydroxide solution showed the acid to be

about 99% pure.

3. Discussion

Benzoylformic acid can be prepared by the oxidation of acetophenone with potassium permanganate in alkaline solution,[1] by the oxidation of mandelic acid with potassium permanganate in alkaline solution,[2,3] and by the hydrolysis of benzoyl cyanide with concentrated hydrochloric acid.[4]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

ether (60-29-7)

ammonium chloride (12125-02-9)

sodium hydroxide (1310-73-2)

Mandelic acid (90-64-2)

potassium permanganate (7722-64-7)

carbon tetrachloride (56-23-5)

Acetophenone (98-86-2)

decolorizing carbon, Norit (7782-42-5)

Benzoylformic acid, Glyoxylic acid, phenyl- (611-73-4)

Benzoyl cyanide (613-90-1)

phosphorus pentoxide (1314-56-3)

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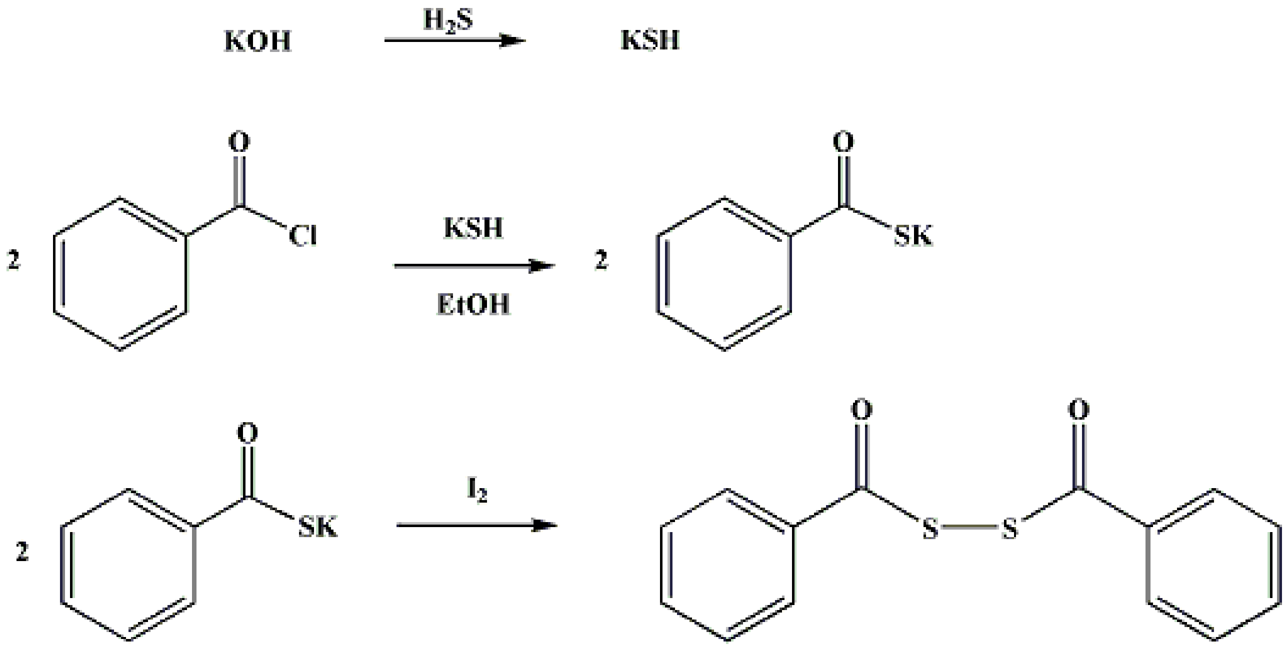
Organic Syntheses, CV 3, 116

BENZOYL DISULFIDE



Submitted by Robert L. Frank and James R. Blegen[1].
Checked by Arthur C. Cope and Frank S. Fawcett.

1. Procedure

A solution of 315 g. (4.76 moles) of potassium hydroxide in 3150 ml. of commercial absolute ethanol is prepared with mechanical stirring in a 5-l. three-necked round-bottomed flask. The flask is fitted with a 500-ml. dropping funnel and a gas inlet tube extending to the bottom of the flask, and hydrogen sulfide is passed in through the inlet tube with stirring until the solution is saturated and no longer gives an alkaline reaction with phenolphthalein (Note 1), (Note 2). The mixture is cooled to 10–15° by means of an ice bath, and 346.5 g. (2.46 moles) of redistilled benzoyl chloride is introduced dropwise with stirring while the temperature is kept below 15°. The potassium chloride which precipitates during the addition (Note 3) is separated by filtration with suction through a Büchner funnel and is washed with about 200 ml. of ethanol (Note 4). The filtrate and washings are cooled to 10–15°, and solid iodine is added slowly, with constant agitation, until a slight excess is present, as shown by a faint permanent coloration of the solution. The amount of iodine required varies from 336 g. to 407 g. (1.32–1.61 moles) (Note 5). Benzoyl disulfide precipitates during the addition. It is collected on a filter and washed with 750 ml. of 95% ethanol followed by 3 l. of water. The crude product, after drying at room temperature, or in an oven at a temperature which does not exceed 60° (Note 6), weighs 325–333 g.

The crude material is dissolved with stirring in 910 ml. of ethylene chloride heated to 60° in a water bath (Note 6). The solution is allowed to cool to room temperature, 122 ml. of a saturated aqueous solution of sodium bicarbonate is added to the resulting slurry, and the mixture is stirred for 1 hours (Note 7). The layers are then separated in a separatory funnel, and the ethylene chloride slurry is heated to 60° in a water bath. The resulting solution is filtered through a small cotton plug in a preheated funnel. Absolute ethanol (313 ml.) is added to the filtrate, and the mixture is stored in an icebox overnight while the product crystallizes. The crystals are collected

on a filter and washed with 40 ml. of ether. The product is recrystallized by dissolving it in ethylene chloride (3.0 ml. per g. of product) heated to 60° in a water bath (Note 6) and cooling. The yield of white to light pink plates, m.p. 129–130°, is 230–246 g. (68–73%).

2. Notes

1. It is convenient during this step to use the dropping funnel as an exhaust tube by attaching its upper end to a gas-absorption trap. If this is not done, the preparation should be conducted in a well-ventilated hood.
2. The gas inlet tube should be of moderately large diameter or it may become plugged with crystals during the later stages of the saturation with hydrogen sulfide.
3. Stirring is discontinued after the benzoyl chloride has been added. The precipitate of potassium chloride can be separated more easily if the mixture is allowed to stand overnight before filtration.
4. After the filtration and washing, the application of suction is continued until bubbles of hydrogen sulfide no longer form in the filtrate. Much of the excess hydrogen sulfide is removed during the filtration.
5. The amount of iodine required is presumed to vary according to the presence of variable amounts of hydrogen sulfide and to the extent of oxidation by atmospheric oxygen. In one unsatisfactory preparation in which a relatively large amount of hydrogen sulfide must have remained in the solution a total of 493 g. (1.94 moles) of iodine was required and the final product contained free sulfur.
6. If the temperature exceeds 60°, discoloration occurs and the product cannot be decolorized by recrystallization or treatment with activated charcoal.
7. This operation is carried out at room temperature because heating in the presence of alkalies decomposes benzoyl disulfide.

3. Discussion

Benzoyl disulfide has been obtained by the reaction of benzoyl chloride with hydrogen sulfide,[2] hydrogen disulfide,[3] hydrogen trisulfide,[3,4] potassium sulfide,[5] sodium disulfide,[6] lead sulfide,[7 8] sodium hydrosulfite,[9] sodium thiosulfate,[10] sulfhydrylmagnesium bromide,[11] and thiobenzamide.[12] It is also formed by reaction of benzoic anhydride with hydrogen sulfide.[13] The better preparative methods involve the oxidation of thiobenzoic acid by means of air,[7,8,14,15] hydrogen peroxide,[16,17] or sulfur monochloride,[18] or of the sodium or potassium salt by means of air,[17,19] chlorine,[20] iodine,[7,15,16,21,22] copper sulfate,[7,8,17] potassium ferricyanide,[7,8,17,23] or ferric chloride.[7,8,17]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfhydrylmagnesium bromide

ethanol (64-17-5)

ether (60-29-7)

sodium bicarbonate (144-55-8)

hydrogen sulfide (7783-06-4)

lead sulfide

oxygen (7782-44-7)

sodium thiosulfate (7772-98-7)

ethylene chloride (107-06-2)

copper sulfate (7758-98-7)

sodium hydrosulfite (7775-14-6)

sulfur (7704-34-9)

iodine (7553-56-2)

benzoyl chloride (98-88-4)

Benzoic anhydride (93-97-0)

chlorine (7782-50-5)

potassium hydroxide (1310-58-3)

hydrogen peroxide (7722-84-1)

ferric chloride (7705-08-0)

sulfur monochloride

sodium disulfide

potassium sulfide (1312-73-8)

phenolphthalein (77-09-8)

potassium ferricyanide (13746-66-2)

potassium chloride (7447-40-7)

Benzoyl disulfide (644-32-6)

hydrogen disulfide

hydrogen trisulfide

thiobenzamide (2227-79-4)

Thiobenzoic acid (98-91-9)

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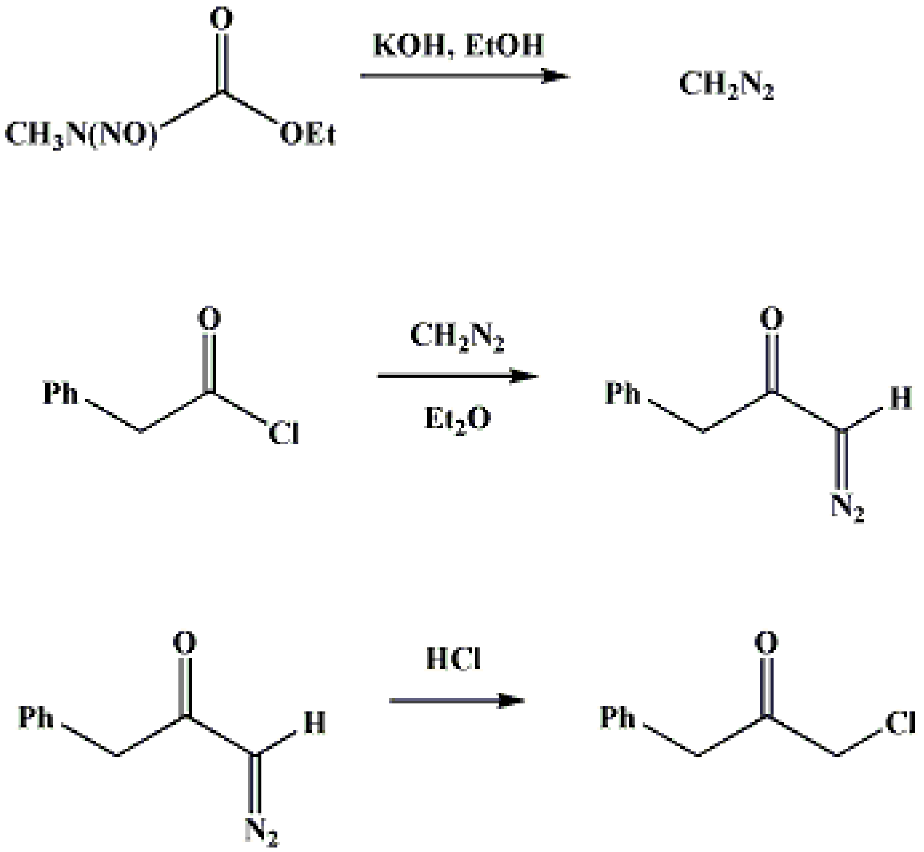
Organic Syntheses, CV 3, 119

BENZYL CHLOROMETHYL KETONE

[2-Propanone, 1-chloro-3-phenyl-]



Submitted by Warren D. McPhee and Erwin Klingsberg.
Checked by Nathan L. Drake and Marvin Schwartz.

1. Procedure

Warning: Diazomethane is poisonous and explosive.

Twelve grams (0.18 mole) of ground potassium hydroxide is dissolved in 45 ml. of *n*-propyl alcohol in a three-necked 500-ml. flask set on a steam bath so that the mixture can be warmed. Two necks of the flask are fitted with dropping funnels. A Vigreux fractionating column (25 cm. in length and 12 mm. in diameter) is inserted in the third neck of the flask. The column is connected, through a condenser and adapter, to a filter flask set in ice as the receiver. The side arm of the receiver is fitted with a drying tube. About 1.5 hours is required to dissolve the hydroxide, whereupon an additional amount of alcohol is added to bring the total volume to 50 ml. The solution is then cooled, and 100 ml. of absolute ether is added. Through one dropping funnel is added dropwise 20 ml. of nitrosomethylurethan[1] (equivalent to 0.10 mole of diazomethane; (Note 1)). The flask is warmed on a steam bath so that diazomethane distils over with ether while the nitrosomethylurethan is being added. The addition requires about 20

minutes. During this operation more dry ether is added as needed, through the second dropping funnel, until the total volume of ether distillate is 250 ml. When the ether distilling over is colorless, the distillate is transferred to another three-necked 500-ml. flask, equipped with a mechanical stirrer, a dropping funnel, and a condenser. To the stirred solution is added, over a period of 15 minutes, a solution of 6.6 ml. (7.7 g., 0.050 mole) of phenylacetyl chloride in 10 ml. of absolute ether. A copious evolution of nitrogen accompanies this operation.

After standing for 2 hours, the solution of diazoketone is cooled in ice and treated with dry gaseous hydrogen chloride until the passage of the gas no longer causes evolution of nitrogen (Note 2). At the end of this time, the original yellow color of the solution has changed to an orange-red. About 100 ml. of water is slowly and cautiously added to the ether solution in order to cause a separation into two layers. An additional 50 ml. of water is then added to give a more complete separation. The ether layer is then washed with two 50-ml. portions of a 5% solution of sodium carbonate in water. The ether solution is dried with anhydrous calcium chloride or calcium sulfate, the solvent evaporated, and the product distilled. The yield of benzyl chloromethyl ketone, b.p. 133–135°/19 mm. or 96–98°/1 mm., is 7.0–7.1 g. (83–85%) (Note 3) and (Note 4).

2. Notes

1. The yield of diazomethane from nitrosomethylurethan is usually given as 0.005 mole per ml.[2] Another method for the preparation of diazomethane has been described.[3]
2. This usually requires about 25 minutes. In certain runs, the hydrogen chloride caused the deposition of a dark red flocculent solid, which was removed by filtration. The yield was then 5–10% lower. This can apparently be avoided by waiting 2 hours, as directed, and by cooling the solution before the hydrogen chloride treatment.
3. This method is general for chloromethyl ketones. Yields of 75–85% may be obtained using hydrocinnamoyl chloride or diphenylacetyl chloride.
4. *Diazomethane is poisonous and explosive.*[4] *The preparation should be carried out in a good hood.*

3. Discussion

Benzyl chloromethyl ketone has been prepared by the reaction of diazomethane with phenylacetyl chloride. The method of Clibbens and Nierenstein,[5] in which one equivalent of diazomethane is added to the acyl chloride and the chloromethyl ketone obtained directly, could not be duplicated by Bradley and Schwarzenbach[6] or by the submitters.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 250
- Org. Syn. Coll. Vol. 5, 351

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

calcium chloride (10043-52-4)

hydrogen chloride (7647-01-0)

ether (60-29-7)

sodium carbonate (497-19-8)

nitrogen (7727-37-9)

calcium sulfate (7778-18-9)

potassium hydroxide (1310-58-3)

n-propyl alcohol (71-23-8)

phenylacetyl chloride (103-80-0)

Diazomethane (334-88-3)

nitrosomethylurethan

hydrocinnamoyl chloride (645-45-4)

BENZYL CHLOROMETHYL KETONE, 2-Propanone, 1-chloro-3-phenyl- (937-38-2)

Diphenylacetyl chloride (1871-76-7)

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Organic Syntheses, CV 3, 121

BIALLYL

[1,5-Hexadiene]

Submitted by Amos Turk and Henry Chanan.
Checked by Arthur C. Cope and Frank S. Fawcett.

1. Procedure

In a 5-l. three-necked flask fitted with a mercury-sealed stirrer (Note 1), a dropping funnel, and an efficient reflux condenser protected by a calcium chloride drying tube is placed 82 g. (3.5 gram atoms) of magnesium turnings. A solution of 459 g. (6 moles) of dry, freshly distilled allyl chloride in 2.4 l. of anhydrous ether is added to the flask through the dropping funnel in the following manner: A 100- to 200-ml. portion of the solution and a small crystal of iodine are added, and the mixture is warmed, if necessary, until the reaction starts. The remainder of the solution is added with stirring and cooling in an ice bath as rapidly as possible without loss of material through the condenser (Note 2). By sponging the upper part of the flask with ice water from the cooling bath, the addition can be completed in 1–1.5 hours. When the addition is complete, the thick slurry is allowed to stand at room temperature for 5 hours with stirring for as much of that period as is practicable (Note 1). The flask is again cooled in an ice bath, and a cold 5% solution of hydrochloric acid is added through the dropping funnel until the evolution of heat has practically ceased (Note 2) and the magnesium chloride is in solution. The mechanical stirrer is started again when the mixture becomes sufficiently fluid (Note 1).

The contents of the flask are transferred to a separatory funnel; the ether layer is separated and distilled without washing or drying through a small packed column (Note 3) until the distillation temperature begins to rise (38–40°). The residue is transferred to a separatory funnel, washed with two 500-ml. portions of water, dried over 10 g. of calcium chloride, and fractionated through the small packed column. After distillation of ether and some allyl chloride (b.p. 45°) biallyl is collected as a colorless liquid in a yield of 135–160 g. (55–65%), b.p. 59–60°/760 mm.; n_D^{20} 1.4040; n_D^{25} 1.4012.

2. Notes

1. Efficient stirring is essential during the early part of the reaction. The submitters used a double-loop-type Hershberg wire (Nichrome, Chromel, or tantalum) stirrer[1] and a motor[2] powerful enough to stir the mixture during the entire preparation. The checkers used the simpler Hershberg wire (No. 16 B and

S gauge Chromel or stainless-steel) stirrer[3] and an ordinary good laboratory motor. Although the slurry became so thick that it could not be stirred with this equipment, the yield of pure biallyl obtained equaled that reported by the submitters.

2. Care must be taken to avoid loss of material (and reduction in yield) through evaporation of allyl chloride or biallyl, both of which are very volatile.

3. A simple total-condensation partial take-off column with a 2.2 by 25 cm. section packed with 3/32-in. single-turn glass helices was used with a reflux ratio of 7 or 8 to 1.

3. Discussion

This procedure is a modification of one described by Cortese.[4] Allyl chloride is employed rather than allyl bromide because of its low cost. Biallyl has been prepared by the action of sodium[5] or aluminum[6] on allyl iodide; from allyl mercuric iodide by dry distillation[7] or by the action of potassium cyanide solution;[8] by the action of magnesium on allyl bromide,[4,9] allyl chloride,[4,10] allyl iodide,[11] or 1,2,3-tribromopropane;[12] and from diallyl ether by the action of sodium.[13]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

ether (60-29-7)

magnesium, magnesium turnings (7439-95-4)

Allyl bromide (106-95-6)

potassium cyanide (151-50-8)

allyl chloride (107-05-1)

allyl iodide (556-56-9)

aluminum (7429-90-5)

iodine (7553-56-2)

sodium (13966-32-0)

1,2,3-Tribromopropane (96-11-7)

magnesium chloride

diallyl ether (557-40-4)

Biallyl, 1,5-Hexadiene (592-42-7)

allyl mercuric iodide

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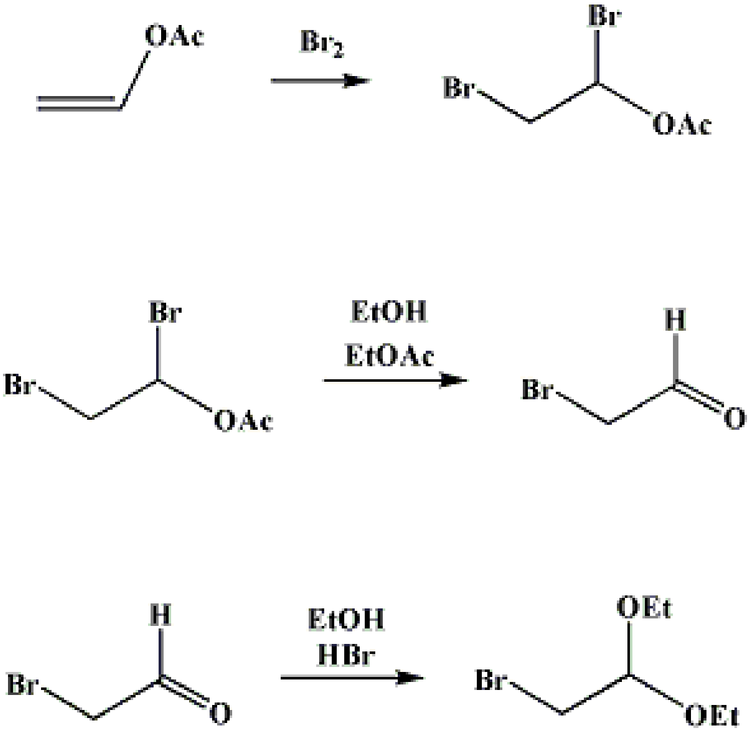
Organic Syntheses, *CV 3, 123*

BROMOACETAL

[Acetaldehyde, bromo-, diethyl acetal]

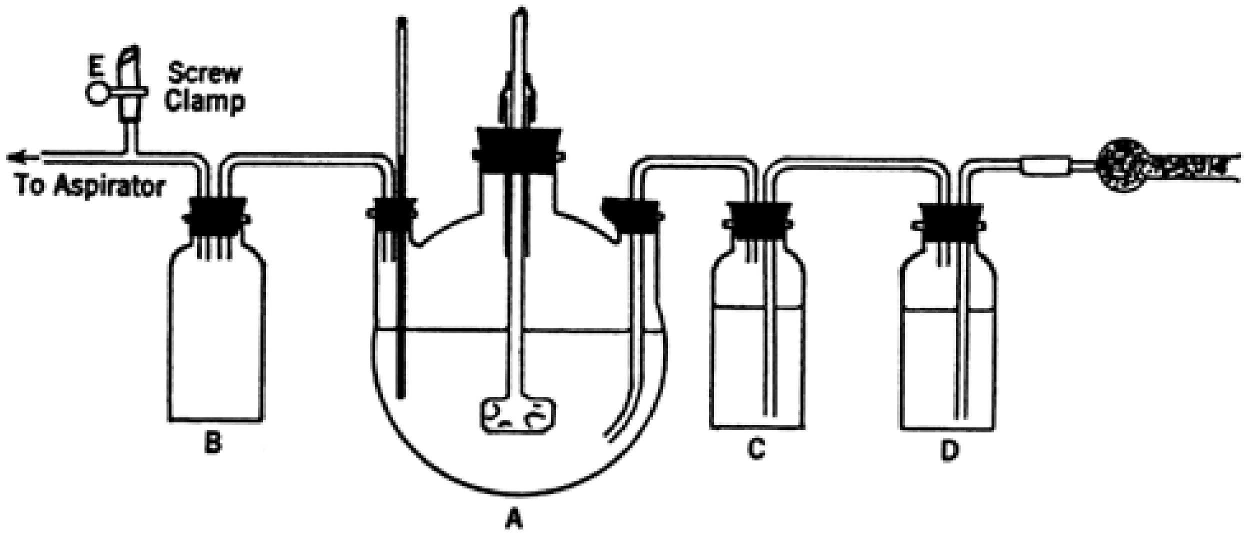


Submitted by S. M. McElvain and D. Kundiger.
Checked by R. L. Shriner and C. H. Tilford.

1. Procedure

An apparatus is assembled as shown in f.htmig. 5. The 3-l. three-necked round-bottomed flask *A* is equipped with a mechanical stirrer sealed with a well-lubricated rubber sleeve. In one neck of the flask are fitted a thermometer and a glass tube leading through a safety trap *B* to a water pump. In the other neck a 7-mm. glass tube, extending to the bottom of the flask, is attached to a 500-ml. bottle *C* in which is placed 255 ml. (5 moles) of bromine (Note 1). This bottle is connected to a 500-ml. wash bottle *D* containing 250 ml. of sulfuric acid. The inlet tube of *D* is connected to a calcium chloride tube.

Fig. 5.



A solution of 430 g. (5 moles) of vinyl acetate (Note 2) in 1.5 l. (26 moles) of absolute ethanol is placed in flask *A*. The solution is cooled to about −10° by an ice-salt mixture, and stirring is started. Gentle suction is applied at the outlet tube of *B*, and the bromine is introduced into *A* by a rapid current of air. The rate of introduction of the bromine, controlled by adjustment of the clamp *E*, should be regulated so that 8–10 hours is required to volatilize all the bromine. Stirring is stopped, and the reaction mixture is allowed to stand overnight and to come to the temperature of the room. The mixture is poured into 1.7 l. of ice water (Note 3); the lower layer of bromoacetal and ethyl acetate is separated (Note 4), washed twice with 300-ml. portions of cold water and once with 300 ml. of cold 10% sodium carbonate solution, and dried over two successive 25-g. portions of anhydrous calcium chloride for 30 minutes. The crude product weighs 990–1010 g.; it is purified by distillation under diminished pressure (water pump) through a 6-in. Widmer column or a 20-cm. Vigreux column. The first fraction consists of ethyl acetate; this is followed by the pure bromoacetal which boils at 62–63°/15 mm. (84–85°/30 mm.) and which amounts to 610–625 g. (62–64%) (Note 5).

2. Notes

1. The bromine is previously washed with 100 ml. of concentrated sulfuric acid.
2. The vinyl acetate (Eastman Kodak Company) is distilled from the added preservative; the first turbid portion containing water is discarded, and the fraction boiling at 69–71°/740 mm. is used.
3. If an emulsion forms at this point, 320 g. of hydrated sodium sulfate is added.
4. Bromoacetal is a fairly strong lachrymator and is best handled under a hood.
5. A yield of 78% of bromoacetal has been obtained by a slight modification of the procedure described above. One-half of the amounts of materials specified above were used, and, after the bromination was complete, the reaction mixture was allowed to stand for 64 hours before it was processed. The yield of bromoacetal was 380 g.[1]

3. Discussion

The procedure given above is essentially a large-scale adaptation of that of Filachione.[2] Bromoacetal has been prepared by the bromination of acetal directly,[3] or in the presence of

calcium carbonate;[4] by action of sodium ethoxide on α,β-dibromodiethyl ether;[5] by bromination of paraldehyde followed by action of ethanol;[6,7] by the action of ethanol on bromoacetaldehyde;[8,9] and by bromination of acetal with N-bromosuccinimide.[10]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 60
- Org. Syn. Coll. Vol. 3, 623
- Org. Syn. Coll. Vol. 6, 448

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Bromoacetal

ACETAL (105-57-7)

ethanol (64-17-5)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

ethyl acetate (141-78-6)

sodium carbonate (497-19-8)

bromine (7726-95-6)

sodium sulfate (7757-82-6)

calcium carbonate (471-34-1)

sodium ethoxide (141-52-6)

N-bromosuccinimide (128-08-5)

Acetaldehyde, bromo-, diethyl acetal

vinyl acetate (108-05-4)

α,β-dibromodiethyl ether (2983-26-8)

bromoacetaldehyde (17157-48-1)

paraldehyde (123-53-7)

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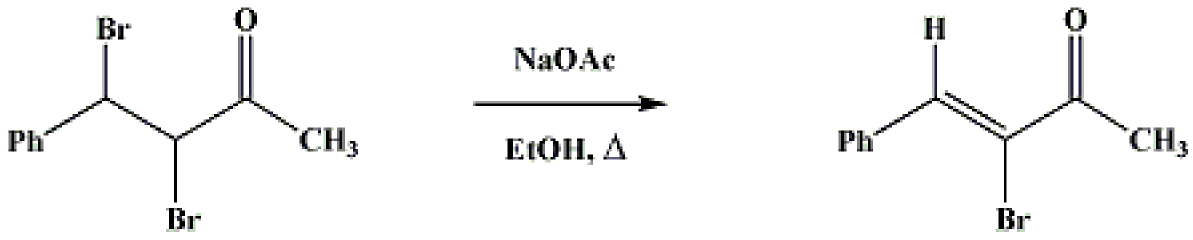
Organic Syntheses, CV 3, 125

α-BROMOBENZALACETONE

[3-Buten-2-one, 3-bromo-4-phenyl-]



Submitted by Norman H. Cromwell, Donald J. Cram, and Chas. E. Harris.
Checked by R. L. Shriner and William O. Foye.

1. Procedure

Warning: Precautions must be taken to avoid contact with α-bromobenzalacetone since it is a skin irritant (Note 1).

In a 500-ml. round-bottomed flask fitted with a reflux condenser are placed 100 g. (0.33 mole) of benzalacetone dibromide (p. 105), 30 g. (0.37 mole) of anhydrous sodium acetate, and 250 ml. of 95% ethanol, and the mixture is refluxed vigorously for 4 hours in the absence of direct sunlight. The precipitate of sodium bromide is removed by filtration, and the alcohol is removed from the filtrate by distillation under reduced pressure (Note 2). The residual salt-oil mixture is extracted with two 50-ml. portions of ether, and the ether solution is transferred to a 250-ml. separatory funnel *(Caution! (Note 1))*.

The ether solution is washed thoroughly six times with 25-ml. portions of saturated sodium chloride solution and twice with 25-ml. portions of 5% sodium bicarbonate solution (Note 3). The ether layer is allowed to dry over anhydrous sodium sulfate at room temperature for 24 hours. The ether is removed by distillation, and the residual oil is distilled from a Claisen flask under reduced pressure, using an oil bath. A yield of 47–54 g. (64–73%) of a pale yellow oil, boiling at 114–117°/1 mm. (Note 4), is obtained. On cooling, the oil crystallizes; m.p. 30–31°. The product is stored in a dark bottle in the ice chest (Note 5) and (Note 6).

2. Notes

1. α-Bromobenzalacetone or its solutions cause the formation of red spots on the skin. After several days these form large red blisters that are painful and take several days to heal. The affected parts should be treated with a mixture of peanut-oil and glycerol containing a little ammonia.
2. The reduced pressure produced by a water pump is satisfactory. The flask is

warmed with a hot water bath (40–50°).
3. It is necessary that the product be entirely free from acetic acid before it is distilled in order to obtain the yields stated.
4. Boiling points at other pressures are: 136–138°/4 mm.; 150–151°/10 mm.
5. When stored in this manner the product is quite stable and darkens only slightly after 9 months.
6. The analogous α-bromobenzalacetophenone may be prepared by a similar procedure. In a 1-l. three-necked round-bottomed flask fitted with a mercury-sealed stirrer and a reflux condenser are placed 150 g. (0.41 mole) of benzalacetophenone dibromide,[1] 41 g. (0.50 mole) of anhydrous sodium acetate, and 250 ml. of 95% ethanol. The mixture is stirred and refluxed for 5 hours and then worked up in the same manner as described above for α-bromobenzalacetone. Distillation gives a yield of 100–110 g. (85–94%) of a pale yellow oil, boiling at 170–173°/1 mm. On cooling, the oil crystallizes and melts at 42–44°. This product should also be stored in a dark bottle in the ice chest, but it is more stable and darkens less on standing than the analogous α-bromobenzalacetone. This product is less irritating to the skin than α-bromobenzalacetone (Note 1).

3. Discussion

α-Bromobenzalacetone has been prepared from benzalacetone dibromide by heating with alcoholic potassium hydroxide[2] or with sodium acetate[3] solutions. α-Bromobenzalacetophenone is prepared by a similar procedure from benzalacetophenone dibromide.[4]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

acetic acid (64-19-7)

ammonia (7664-41-7)

ether (60-29-7)

sodium acetate (127-09-3)

glycerol (56-81-5)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

sodium bromide (7647-15-6)

sodium sulfate (7757-82-6)

potassium hydroxide (1310-58-3)

Benzalacetophenone dibromide (611-91-6)

Benzalacetone dibromide (6310-44-7)

α-Bromobenzalacetone

3-Buten-2-one, 3-bromo-4-phenyl- (31207-17-7)

α-bromobenzalacetophenone (6935-75-7)

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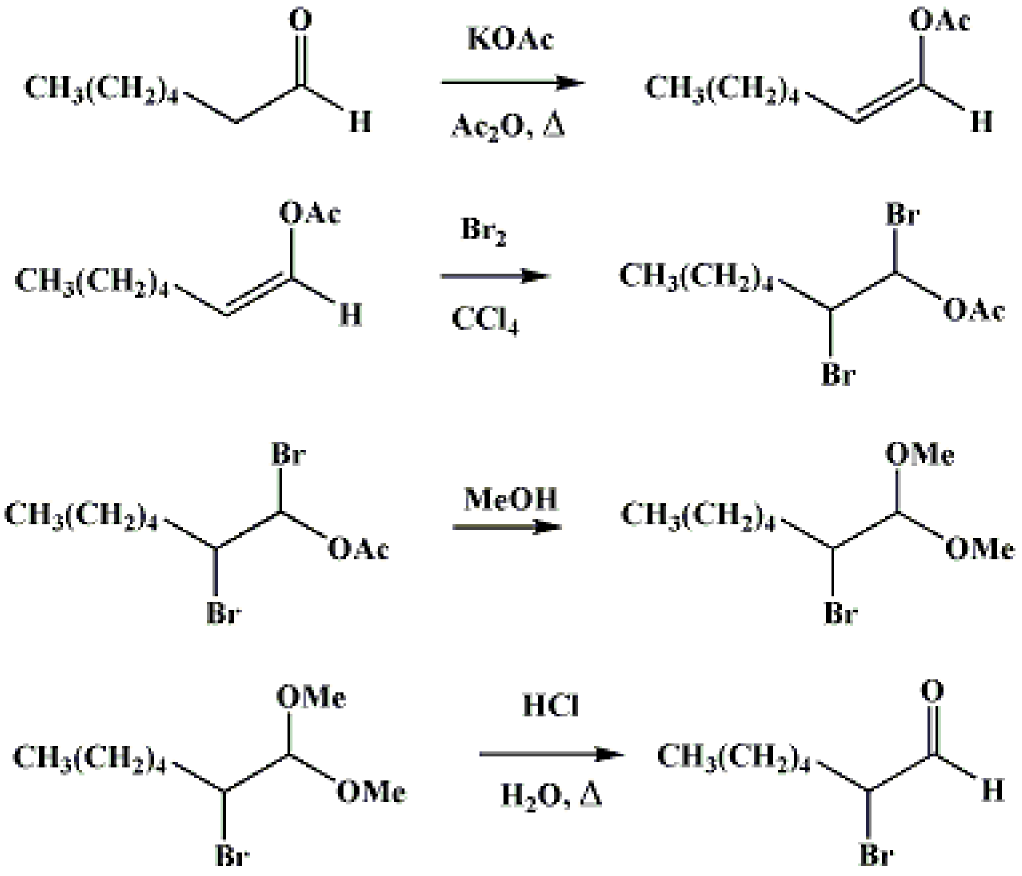
Organic Syntheses, CV 3, 127

α-BROMOHEPTALDEHYDE

[Enanthaldehyde, α-bromo-]



Submitted by Paul Z. Bedoukian
Checked by Joseph A. Pappalardo and Charles C. Price.

1. Procedure

Caution! Since most of the reactants are of unpleasant odor or have lachrymatory effects it is best to use a good hood.

A. *Heptaldehyde enol acetate*. A mixture of 285 g. (335 ml., 2.5 moles) of heptaldehyde (Note 1), 612 g. (566 ml., 6 moles) of acetic anhydride, and 49 g. (0.5 mole) of powdered potassium acetate is placed in a 2-l. flask fitted with a reflux condenser. The flask is heated in an oil bath kept at 155–160° for 1 hour. The mixture is then allowed to cool, placed in a 2-l. separatory funnel, washed several times with warm water (Note 2) to remove the excess acetic anhydride, and finally washed with 5% sodium carbonate solution (Note 3). The resultant oil is fractionated under reduced pressure through an efficient column (Note 4). The initial fraction consists of pure heptaldehyde followed by heptaldehyde containing heptaldehyde enol acetate. The fraction boiling at 88–90°/17 mm. is pure enol acetate, n_D^{25} 1.4295–1.4305; d_4^{25}

0.880–0.884. The yield is 175–195 g. (45–50%) (Note 5).

B. α-*Bromoheptaldehyde dimethyl acetal*. A solution of 156 g. (177 ml., 1 mole) of the enol acetate and 200 ml. of carbon tetrachloride is placed in a 1-l. flask and cooled in an ice-water bath. A mixture of 160 g. (51 ml., 1 mole) of bromine and 50 ml. of carbon tetrachloride is added slowly through a buret, the flask being constantly shaken and the rate of addition so controlled as not to allow the temperature of the brominated mixture to rise above 10° (Note 6). The addition of bromine takes from 20 minutes to 1 hour, and the end point is reached when the calculated amount is absorbed and the bromine is no longer decolorized. The brominated mixture is added to 600 ml. of anhydrous methanol (Note 7) and allowed to stand for 48 hours or longer. At the end of this period the mixture is diluted with 2 l. of water and the separated oil (lower layer) is washed with 1 l. of water and finally with 1 l. of 5% sodium carbonate (Note 8). The carbon tetrachloride and methyl acetate are removed by distillation at atmospheric pressure. The residual oil is then distilled under reduced pressure in the presence of a small amount of sodium carbonate. The fraction boiling at 117–119°/17 mm. is collected as pure α-bromoheptaldehyde dimethyl acetal, n_D^{25} 1.4510–1.4520; d_4^{25} 1.180–1.195. The yield is 191–203 g. (80–85%) (Note 9).

C. α-*Bromoheptaldehyde*. A mixture of 119.5 g. (100 ml., 0.5 mole) of α-bromoheptaldehyde dimethyl acetal and 80 ml. of concentrated hydrochloric acid is boiled gently in a 250-ml. distilling flask, and the methanol liberated is removed by distillation, which is continued slowly until the vapor temperature reaches 90°, at which point the heating is stopped and the residue and distillate are combined and diluted with 200 ml. of water. The somewhat brownish oil which separates is distilled under reduced pressure from a 250-ml. Claisen flask. The yield of pure α-bromoheptaldehyde, boiling at 87–92°/17 mm., n_D^{25} 1.4580–1.4600, d_4^{25} 1.210–1.230, is 87–92.5 g. (90–95%).

2. Notes

1. The heptaldehyde should be a freshly distilled product boiling at 151.5–153.5°.
2. Decomposition of the excess acetic anhydride takes place very slowly and with difficulty unless warm water is used. The checkers used three portions of wash water at 40–50°, totaling 1.3 l.
3. The checkers found that five or six portions of 5% sodium carbonate totaling 5 l. were required before rapid carbon dioxide evolution ceased.
4. The reaction mixture consists of unchanged heptaldehyde, heptaldehyde enol acetate, heptaldehyde diacetate, and a small amount of polymerized material. The proportion of free heptaldehyde and heptaldehyde diacetate depends upon the time of heating, longer periods of heating favoring the formation of the diacetate. An efficient fractionating column, preferably of the Whitmore-Fenske type, should be used in order to obtain the enol acetate free of the heptaldehyde and heptaldehyde diacetate impurities. The checkers used a Whitmore-Fenske

type column of about six theoretical plates.
5. The residue consists largely of heptaldehyde diacetate, which when slowly distilled at atmospheric pressure partially decomposes to acetic anhydride and heptaldehyde. In this manner, 50–60% of the available heptaldehyde is recovered from the residue.
6. The checkers recommend a mechanical stirrer to avoid danger of contact with bromine.
7. Commercial methanol (99.5–100%) was used in all experiments.
8. The acetal must be free of acid; otherwise decomposition takes place during distillation.
9. The pure bromoacetal is a stable, colorless liquid, of mild odor. It may be kept indefinitely when stored in a dark bottle over a small amount of anhydrous sodium carbonate.

3. Discussion

The procedure described is an example of a general method of preparation of α-bromoaldehydes.[1] α-bromoheptaldehyde has been prepared by the bromination of heptaldehyde diethyl acetal with phosphorus trichlorodibromide[2] and by direct bromination of heptaldehyde trimer with subsequent treatment with alcohol.[3]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

α-Bromoheptaldehyde

Heptaldehyde enol acetate

α-Bromoheptaldehyde dimethyl acetal

heptaldehyde diacetate

heptaldehyde diethyl acetal

phosphorus trichlorodibromide

hydrochloric acid (7647-01-0)

methanol (67-56-1)

acetic anhydride (108-24-7)

sodium carbonate (497-19-8)

bromine (7726-95-6)

carbon tetrachloride (56-23-5)

carbon dioxide (124-38-9)

potassium acetate (127-08-2)

Enanthaldehyde, α-bromo- (16486-84-3)

methyl acetate (79-20-9)

heptaldehyde (111-71-7)

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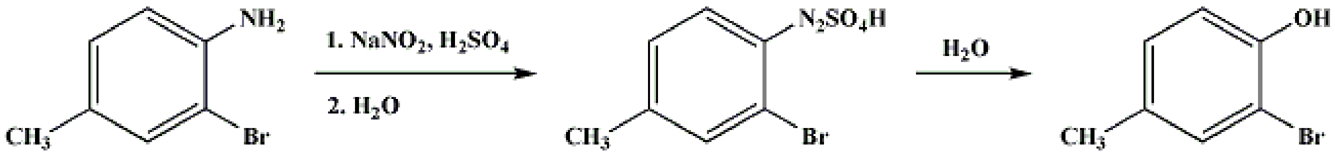
Organic Syntheses, CV 3, 130

3-BROMO-4-HYDROXYTOLUENE

[*p*-Cresol, 2-bromo-]



Submitted by H. E. Ungnade and E. F. Orwoll.
Checked by C. F. H. Allen and Alan Bell.

1. Procedure

In a 2-l. beaker is placed 75 g. (0.4 mole) of 3-bromo-4-aminotoluene (Note 1), and to it is added the hot diluted acid obtained by adding 72 ml. of concentrated sulfuric acid to 200 ml. of water. The clear solution is stirred and cooled to about 15°, after which 180 g. of ice is added; the amine sulfate usually separates. As soon as the temperature has dropped below +5°, a solution of 32.2 g. (0.47 mole) of sodium nitrite in 88 ml. of water is added from a dropping funnel, the stem of which extends below the surface of the liquid. The temperature of the solution is kept below +5° during the addition, which requires about 15 minutes. The solution is stirred for 5 minutes after the addition of all the sodium nitrite, and 300 g. of cold water, 3 g. of urea, and 300 g. of cracked ice are then added successively. The solution is kept in an ice bath until used.

A 1-l. Claisen flask fitted with a dropping funnel and a thermometer dipping into the liquid is attached to a condenser set for downward distillation. In the flask are placed 150 g. of anhydrous sodium sulfate, 200 g. (108 ml.) of concentrated sulfuric acid, and 100 ml. of water. The flask is heated over a wire gauze, and while the internal temperature is maintained at 130–135°, the diazonium solution, in 25-ml. portions, is added at the same rate as the distillate is collected (Note 2). When this operation has been completed, 200 ml. of water, in 25-ml. portions, is introduced and the distillation is continued until an additional 200 ml. of distillate has been collected. The complete distillation requires 3–3.5 hours.

The distillate is extracted with two 150-ml. portions of ether, and the combined extracts are washed successively with 100 ml. of water and 150 ml. of 10% sodium bicarbonate solution. The phenol is then extracted from the ether layer by use of one 200-ml. and two 50-ml. portions of 10% sodium hydroxide solution. The combined alkaline solutions are acidified, with cooling, by the addition of 100 ml. of concentrated hydrochloric acid. The phenol is extracted with one 200-ml. and two 100-ml. portions of ether, and the combined extracts are washed with 100 ml. of water and dried over 50 g. of anhydrous sodium sulfate. The mixture is filtered, and the ether is removed from the filtrate by distillation on a water bath. The residue, 65–72 g. of a brown oil (Note 3), is then distilled from a Claisen flask with modified side arm; b.p. 102–104°/20 mm. The yield is 60–69 g. (80–92%) (Note 4).

2. Notes

1. The 3-bromo-4-aminotoluene may be purchased, or prepared according to *Org. Syntheses* Coll. Vol. **1**, 111 (1941). The material used melted at 12–13°.
2. If the diazonium solution is added too rapidly, and the temperature of the liquid falls, the addition is interrupted until the temperature again exceeds 130°.
3. This crude product serves for most purposes, e.g., conversion to *o*-bromo-*p*-methylanisole.
4. The procedure has been used by the submitters for the conversion of *m*-bromoaniline into *m*-bromophenol, b.p. 234–237°/742 mm.; 105–107°/11 mm. The yield was 66%.

3. Discussion

o-Bromo-*p*-cresol has been prepared by the direct bromination of *p*-cresol in chloroform solution;[1,2] by bromination of dry sodium *p*-cresoxide;[3] and by decomposition of the diazonium sulfate of 3-bromo-4-aminotoluene;[4] the last is a general method.[5,6]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium p-cresoxide

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

sodium nitrite (7632-00-0)

3-Bromo-4-aminotoluene (583-68-6)

urea (57-13-6)

3-Bromo-4-hydroxytoluene, o-Bromo-p-cresol, p-Cresol, 2-bromo- (6627-55-0)

o-bromo-p-methylanisole (22002-45-5)

m-bromoaniline (591-19-5)

p-CRESOL (106-44-5)

m-bromophenol (591-20-8)

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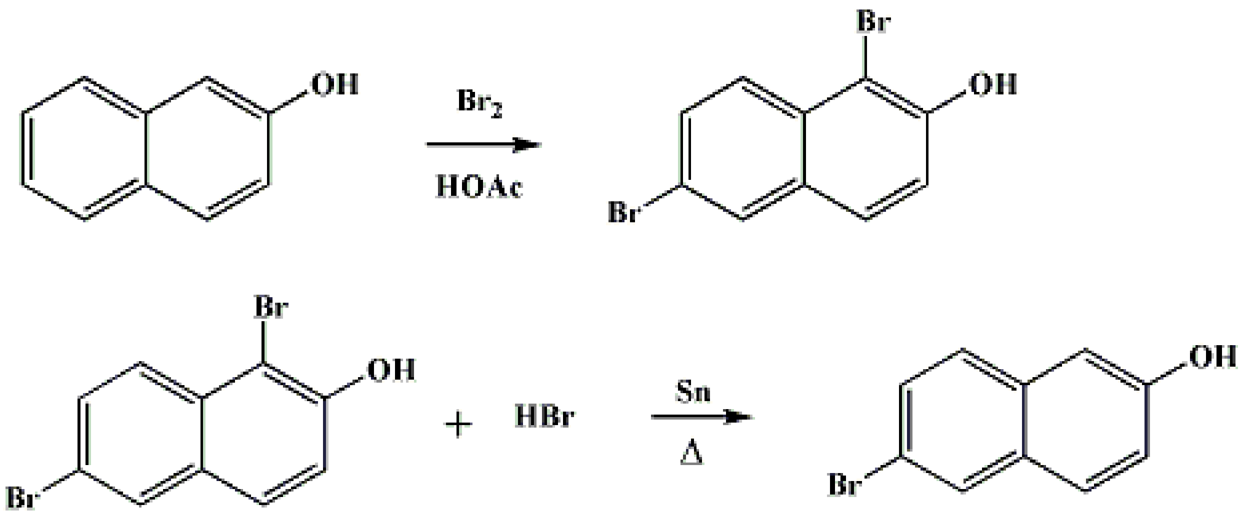
Organic Syntheses, CV 3, 132

6-BROMO-2-NAPHTHOL

[2-Naphthol, 6-bromo-]



Submitted by C. Frederick Koelsch
Checked by W. E. Bachmann and S. Kushner.

1. Procedure

In a 3-l. round-bottomed flask fitted with a dropping funnel and a reflux condenser (Note 1) are placed 144 g. (1 mole) of β-naphthol and 400 ml. of glacial acetic acid. Through the dropping funnel is then added a solution of 320 g. (2 moles) of bromine in 100 ml. of acetic acid. The flask is shaken gently during the addition, which requires 15–30 minutes. The β-naphthol dissolves during this period, and heat is evolved; the mixture is cooled somewhat towards the end of the addition to avoid excessive loss of hydrogen bromide. One hundred milliliters of water is then added, and the mixture is heated to boiling. It is then cooled to 100°, 25 g. of mossy tin is added (Note 2), and boiling is continued until the metal is dissolved. A second portion of 25 g. of tin is then added and dissolved by boiling, and finally a third portion of 100 g. (a total of 150 g., 1.27 gram atoms) of tin is introduced. The mixture is boiled for 3 hours, cooled to 50°, and filtered with suction. The crystalline tin salts which are thus removed are washed on the funnel with 100 ml. of cold acetic acid, the washings being added to the main portion of the filtrate.

This filtrate is stirred into 3 l. of cold water; the 6-bromo-2-naphthol which is precipitated is filtered with suction, removed from the funnel, and washed by stirring with 1 l. of cold water. After filtering again and drying at 100° there is obtained 214–223 g. (96–100%) of 6-bromo-2-naphthol. This crude product, which is pink and melts at 123–127°, contains some tin but is pure enough for most purposes.

A white product is obtained by vacuum distillation followed by crystallization of the

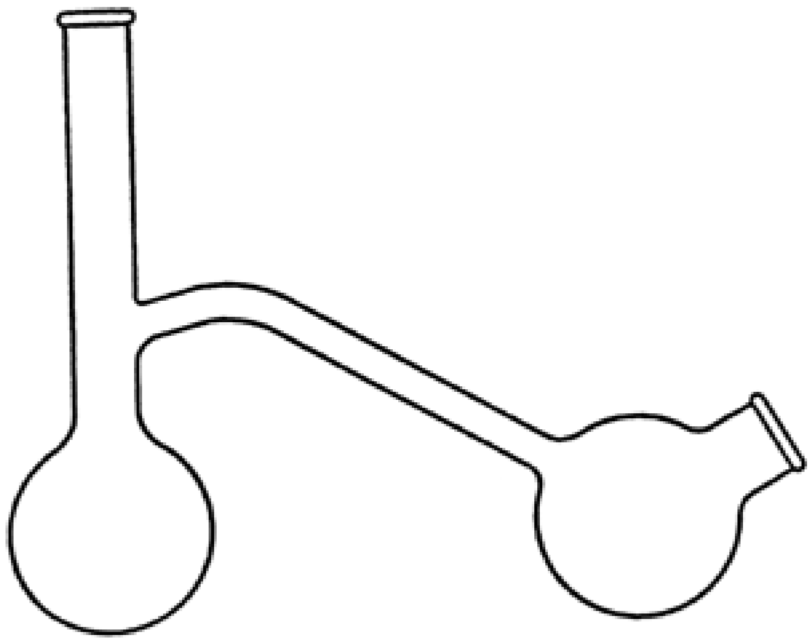
crude product. Twenty-five grams of the crude substance on distillation (Note 3) gives 20 to 24 g. of distillate boiling at 200–205°/20 mm., and when this is crystallized from a mixture of 75 ml. of acetic acid and 150 ml. of water it gives 17.5 to 22.5 g. of 6-bromo-2-naphthol which melts at 127–129°.

2. Notes

1. An all-glass apparatus is of considerable advantage. If this is not available, the cork is covered with lead foil.
2. The reflux condenser is removed in order to add the tin, but it should be held in readiness so that it can be replaced quickly. The first two portions of tin react vigorously, and solution of the metal is accompanied by the evolution of hydrogen and the loss of some hydrogen bromide.

3. For the distillation a sausage flask or two-bulb flask[1] (.htmFig. 6) is employed.

Fig. 6.



3. Discussion

6-Bromo-2-naphthol has been prepared by the reduction of 1,6-dibromo-2-naphthol with hydriodic acid,[2] with tin and hydrochloric acid,[3] or with stannous chloride and hydrochloric acid in aqueous alcohol[3] or in aqueous acetic acid.[4] It has also been obtained by the bromination of 2-naphthol with pyridinium bromide perbromide.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 828
- Org. Syn. Coll. Vol. 5, 918
- Org. Syn. Coll. Vol. 6, 34

References and Notes

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3. Franzen and Staubel, *J. prakt. Chem.*, (2) **103**, 369 (1922); Fries and Schimmelschmidt, *Ber.*, **58**, 2840 (1925).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

pyridinium bromide perbromide

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

hydrogen (1333-74-0)

hydrogen bromide (10035-10-6)

bromine (7726-95-6)

β-naphthol, 2-naphthol (135-19-3)

tin (7440-31-5)

stannous chloride

hydriodic acid (10034-85-2)

6-Bromo-2-naphthol, 2-Naphthol, 6-bromo- (15231-91-1)

1,6-dibromo-2-naphthol (16239-18-2)

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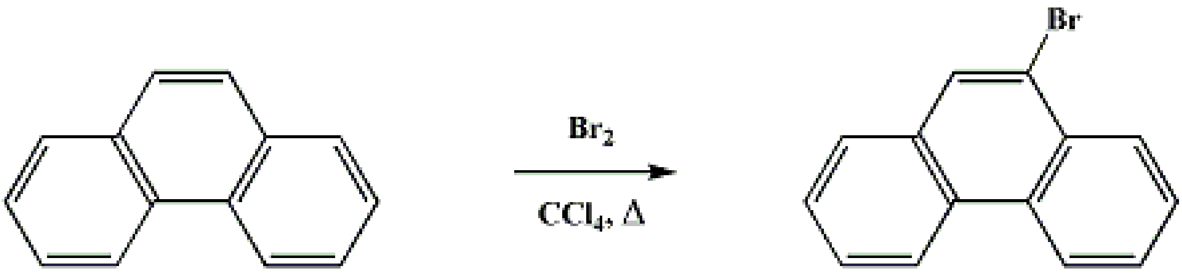
Organic Syntheses, CV 3, 134

9-BROMOPHENANTHRENE

[Phenanthrene, 9-bromo-]



Submitted by Clinton A. Dornfeld, Joseph E. Callen, and George H. Coleman[1].
Checked by Robert E. Carnahan and Homer Adkins.

1. Procedure

A. *Purification of technical phenanthrene*. One and one-half kilograms of technical 90% phenanthrene is dissolved in 9 l. of ethanol in a 12-l. flask on a steam bath, and the hot solution is decanted from any insoluble material. The product crystallizes upon cooling of the solution. One kilogram of the crystallized product is dissolved in 2.2 l. of hot glacial acetic acid in a 5-l. three-necked flask provided with an efficient reflux condenser and a dropping funnel. To the boiling solution is gradually added 72 ml. of an aqueous solution containing 60 g. of chromic anhydride, and then 30 ml. of concentrated sulfuric acid is added slowly from the dropping funnel. The solution is refluxed for 15 minutes. The hot solution is then poured with vigorous stirring into 4.5 l. of water in a 12-l. round-bottomed flask. After cooling, the mixture is filtered, and the product is washed with water and air-dried. The product is distilled (Note 1) at 148–149°/1 mm. The distillate is recrystallized from ethanol to give 800–900 g. of nearly white phenanthrene, m.p. 98.7–99°.

B. *9-Bromophenanthrene*. One kilogram (5.6 moles) of pure phenanthrene (Note 2) is dissolved in 1 l. of dry carbon tetrachloride in a 5-l. three-necked flask. A 500-ml. dropping funnel, a reflux condenser (with tube to conduct evolved hydrogen bromide to the hood), and an efficient motor-driven sealed stirrer (Note 3) are attached. The mixture is heated at gentle reflux with stirring, and 900 g. (5.64 moles) of bromine is added from the dropping funnel over a period of about 3 hours. After stirring at gentle reflux for 2 additional hours, during which most of the remaining hydrogen bromide is evolved, the reaction mixture is placed in a Claisen flask and the solvent is distilled at a pressure of 10–30 mm. The flask containing the residue is then provided with a fine capillary inlet tube, a thermometer, and a 2-l. distilling flask as receiver. The impure 9-bromophenanthrene is distilled (Note 4), and the material boiling at 177–190°/2 mm. is collected. The yield is 1300–1360 g. (90–94%), m.p. 54–56° (Note 5) and (Note 6).

2. Notes

1. Since the melting point of phenanthrene is relatively close to its boiling point under the pressure of the distillation, it is necessary to employ an apparatus so constructed that the solidified distillate will not clog the outlet tube. The submitters used a 2-l. modified Claisen flask attached directly, with a 14-mm. glass tube, to a 2-l. round-bottomed flask. The checkers used a similar all-glass apparatus.
2. The checkers used from 100 to 250 g. of phenanthrene with corresponding reductions of other quantities specified in the procedure.
3. A glycerol-rubber tube seal made with Neoprene rather than natural rubber is very satisfactory.
4. The flask may be supported on a wire gauze and heated directly with a Fisher or Meker burner. A modified Claisen flask equipped with a short column is desirable, but an ordinary Claisen flask can be used if the heating is carefully controlled to prevent impure bromophenanthrene from splashing over. The oil pump should be protected with the usual Dry Ice trap and with a potassium hydroxide tower to absorb hydrogen bromide. Even in runs in which the carbon tetrachloride solution was washed successively with sodium bisulfite, sodium carbonate, and water, much hydrogen bromide was evolved during distillation.
5. If the distillation is performed carefully the product is probably sufficiently pure for most purposes without recrystallization. 9-Bromophenanthrene may be recrystallized from ethanol (about 10 ml. per g.).
6. In runs of one-tenth the scale specified, the product obtained by the checkers had a melting point of 50–55° when yields above 90% were obtained. The yields were about 10% lower when 9-bromophenanthrene of melting point 54–56° was produced. The yield of recrystallized compound, melting at 65–66°, as obtained by the checkers, was 60% of the theoretical.

3. Discussion

The procedure for the purification of technical phenanthrene is that of W. E. Bachmann[2] with slight modification.

The procedure described for the preparation of 9-bromophenanthrene is an adaptation of that described by Henstock,[3] who effected the bromination at various temperatures and in different solvents but gave little experimental detail. Other methods[4] of preparation involve the formation and isolation of phenanthrene dibromide and its subsequent conversion to 9-bromophenanthrene by heating.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 212
- Org. Syn. Coll. Vol. 3, 701

References and Notes

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3. Henstock, *J. Chem. Soc.*, **123**, 3097 (1923).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

hydrogen bromide (10035-10-6)

sodium carbonate (497-19-8)

bromine (7726-95-6)

carbon tetrachloride (56-23-5)

sodium bisulfite (7631-90-5)

chromic anhydride

phenanthrene (85-01-8)

9-Bromophenanthrene, Phenanthrene, 9-bromo- (573-17-1)

bromophenanthrene

phenanthrene dibromide

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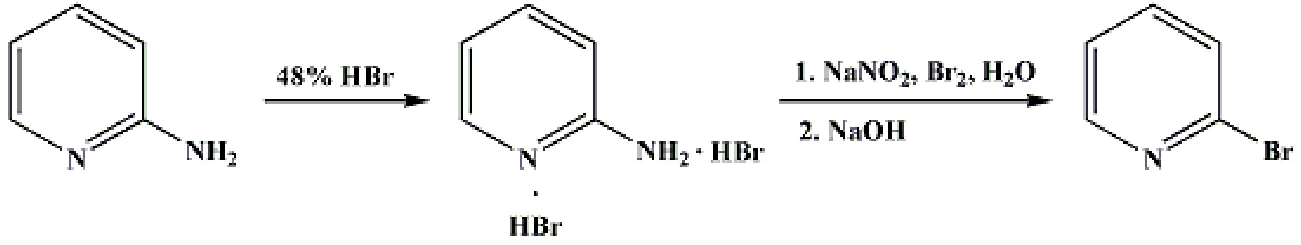
Organic Syntheses, CV 3, 136

2-BROMOPYRIDINE

[Pyridine, 2-bromo-]



Submitted by C. F. H. Allen and John R. Thirtle.
Checked by Cliff S. Hamilton and Carol K. Ikeda.

1. Procedure

In a 5-l. three-necked flask fitted with a mechanical stirrer (Note 1), a dropping funnel, and a thermometer for reading low temperatures is placed 790 ml. (7 moles) of 48% hydrobromic acid. The flask and contents are cooled to 10–20° in an ice-salt bath, and 150 g. (1.59 moles) of 2-aminopyridine (Note 2) is added over a period of about 10 minutes. While the temperature is kept at 0° or lower, 240 ml. (4.7 moles) of bromine is added dropwise (Note 3). A solution of 275 g. (4 moles) of sodium nitrite in 400 ml. of water is added dropwise over a period of 2 hours, the temperature being carefully maintained at 0° or lower (Note 4). After an additional 30 minutes of stirring, a solution of 600 g. (15 moles) of sodium hydroxide in 600 ml. of water is added at such a rate that the temperature does not rise above 20–25° (Note 5). The nearly colorless reaction mixture is extracted with four 250-ml. portions of ether (Note 6). The extract is dried for 1 hour over 100 g. of solid potassium hydroxide and is then distilled through a Vigreux column 15 cm. in length. 2-Bromopyridine distils at 74–75°/13 mm., and the yield is 216–230 g. (86–92%) (Note 7).

2. Notes

1. A stirrer which gives efficient stirring near the walls of the flask is advisable. The fittings should not be gas tight since oxides of nitrogen and bromine are evolved during the reaction. It is advisable to work in a hood or out-of-doors.
2. The checkers used Eastman Kodak Company's practical grade of 2-aminopyridine.
3. The reaction mixture thickens, owing to formation of a yellow-orange perbromide during the addition of about one-half of the bromine; the first half of the bromine is added over a period of 30 minutes; the second half, over a period of 15 minutes.
4. The ice-salt bath is renewed before the sodium nitrite is added and once during the addition.
5. The color of the reaction mixture darkens during the addition of the alkali but becomes light yellow toward the end.
6. The separation into layers may not take place readily. The use of a "lily" may be helpful in separating the ether layer. A "lily"[1] is essentially a U-tube having unequal legs, the shorter of which has a flared top. It is easily prepared from a thistle or funnel tube by making a U bend just below the funnel. In use, a suction flask to act as a receiver is attached by means of rubber tubing. With this device it is a simple matter to draw off the upper layer when making separations, in any wide-mouth bottle or open jar. It may be necessary to filter the intermediate layer before attempting the separation.
7. This procedure can be used with 7 times the above amounts in a 22-l. flask, cooled in a half-

barrel. A "Lightnin" stirrer is required (Model C-2).

3. Discussion

2-Bromopyridine has been made by direct bromination of pyridine;[2] from N-methyl-2-pyridone with phosphorus pentabromide and phosphorus oxybromide;[3] from 2-aminopyridine by diazotization with amyl nitrite in 20% hydrobromic acid;[4] from sodium 2-pyridinediazotate by solution in concentrated hydrobromic acid;[5] from 2-aminopyridine by diazotization in the presence of bromine and concentrated hydrobromic acid;[6] and from 2-aminopyridine by diazotization with nitrogen trioxide in 40% hydrobromic acid.[7] The method described here is essentially that of Craig.[6]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

oxides of nitrogen

sodium 2-pyridinediazotate

ether (60-29-7)

sodium hydroxide (1310-73-2)

HYDROBROMIC ACID (10035-10-6)

bromine (7726-95-6)

sodium nitrite (7632-00-0)

pyridine (110-86-1)

potassium hydroxide (1310-58-3)

amyl nitrite (463-04-7)

phosphorus oxybromide

phosphorus pentabromide (7789-69-7)

2-aminopyridine (504-29-0)

N-methyl-2-pyridone (694-85-9)

2-Bromopyridine, Pyridine, 2-bromo- (109-04-6)

nitrogen trioxide

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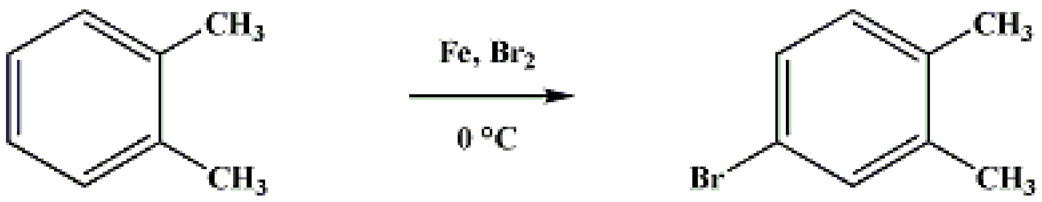
Organic Syntheses, CV 3, 138

4-BROMO-*o*-XYLENE

[*o*-Xylene, 4-bromo-]



Submitted by W. A. Wisansky and S. Ansbacher.
Checked by N. L. Drake, Wilkins Reeve, and John Sterling, Jr..

1. Procedure

In a 1-l. three-necked flask having ground-glass joints are placed 500 g. (569 ml., 4.72 moles) of *o*-xylene, 12 g. of clean iron filings, and a crystal of iodine (Note 1). The flask is fitted with a dropping funnel, a stirrer (Note 2), and a condenser; a thermometer is suspended through the condenser on a platinum or Nichrome wire and arranged so that the bulb extends beneath the surface of the liquid. The top of the condenser is connected to a gas-absorption trap. The mixture is stirred and cooled in an ice-salt mixture, preferably under a hood. Six hundred and sixty grams (4.13 moles) of bromine is added drop-wise over a 3-hour period; during this time the internal temperature is maintained at 0° to −5° (Note 3). After all the bromine has been added the reaction mixture is allowed to stand overnight. It is poured into water and washed successively with a 500-ml. portion of water, two 500-ml. portions of 3% sodium hydroxide solution (Note 4), and one 500-ml. portion of water. The product is then steam-distilled; about 8 l. of distillate is collected (Note 5). The organic layer is separated from the water and dried over calcium chloride. The 4-bromo-*o*-xylene is distilled through a short column under reduced pressure, and the fraction boiling at 92–94°/14–15 mm. (n_D^{22} 1.5558) is collected. The yield is 720–745 g. (94–97%, based on bromine) (Note 6).

2. Notes

1. Essentially the same yield results if only one of the catalysts (iron or iodine) is used.
2. The checkers used a glycerol-sealed stirrer.
3. In experiments in which the temperature of the reaction mixture was allowed to rise as high as +10°, the submitters noted a slight increase in the amount of dibromo-*o*-xylene formed.
4. A dilute sodium bisulfite solution may be used instead of the alkali in this washing.
5. Near the end of the steam distillation a white waxy product begins to collect

in the condenser. This is apparently a dibromo-*o*-xylene.
6. This material is of sufficient purity for most uses, including the conversion to 3,4-dimethylaniline (p. 307). It is reported[1] that the boiling point of the product can be raised slightly (from 211–212° to 214–215°/760 mm.) by sulfonation, recrystallization of the barium sulfonate, and regeneration of the bromo compound by acid hydrolysis.

3. Discussion

The procedure given was developed by Ghigi[1] from an earlier preparation by Jacobsen.[2] 4-Bromo-*o*-xylene has also been prepared from 3,4-dimethylaniline by the Sandmeyer reaction.[3,4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 307

References and Notes

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2. Jacobsen, *Ber.*, **17**, 2372 (1884).
3. Brand, Ludwig, and Berlin, *J. prakt. Chem.*, [2] **110**, 34 (1925).
4. Kohlrausch and Pongratz, *Monatsh.*, **64**, 361 (1934).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

calcium chloride (10043-52-4)

sodium hydroxide (1310-73-2)

iron (7439-89-6)

bromine (7726-95-6)

sodium bisulfite (7631-90-5)

iodine (7553-56-2)

3,4-Dimethylaniline (95-64-7)

barium sulfonate

4-Bromo-o-xylene (583-71-1)

o-Xylene (95-47-6)

dibromo-o-xylene

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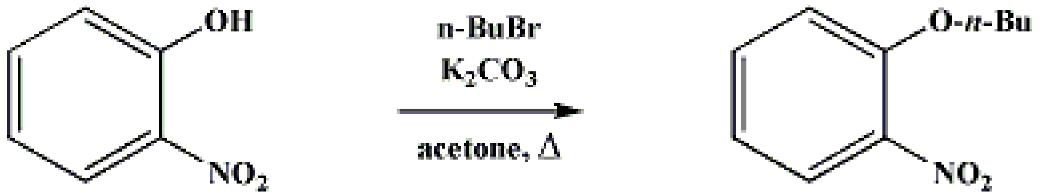
Organic Syntheses, CV 3, 140

o-n-BUTOXYNITROBENZENE

[Ether, butyl *o*-nitrophenyl]



Submitted by C. F. H. Allen and J. W. Gates, Jr..
Checked by W. E. Bachmann and G. Dana Johnson.

1. Procedure

A mixture of 28 g. (0.2 mole) of *o*-nitrophenol (Note 1), 30 g. (0.22 mole) of *n*-butyl bromide, 28 g. (0.2 mole) of anhydrous potassium carbonate, and 200 ml. of dry acetone in a 1-l. round-bottomed flask is refluxed on a steam bath for 48 hours (Note 2). At the end of this time the acetone is distilled from the mixture, 200 ml. of water is added to the residue, and the product is extracted with two 100-ml. portions of benzene. The combined benzene extracts are washed with three 100-ml. portions of 10% sodium hydroxide, the benzene is removed by distillation at ordinary pressure, and the residual oil is distilled under reduced pressure. The yield of product boiling at 118–121°/1 mm. (Note 3) is 29–31 g. (75–80%) (Note 4) and (Note 5).

2. Notes

1. A technical grade of *o*-nitrophenol was used; the yield is no better with the pure material. In place of *n*-butyl bromide, a corresponding amount (36.8 g.) of the iodide can be used with no change in yield.
2. The checkers shook the flask occasionally during the first 1.5 hours in order to prevent caking of the contents.
3. The boiling point is 126–129°/2 mm. and 171–172°/19 mm.
4. Other nitrophenyl ethers can be prepared in a similar manner and in essentially the same yields. When the size of the run was increased to 2 moles, the yields were increased to 85–90%. The hexyl derivatives require 72 hours for reaction.
The boiling points of some ethers prepared by the present procedure are as follows: *m-n*-butoxynitrobenzene, 120–124°/2 mm.; *p-n*-butoxynitrobenzene, 150–154°/5 mm.; *p*-isopropoxynitrobenzene, 283–286°/760 mm.; *o-n*-hexyloxynitrobenzene, 145–148°/1 mm.; *p-n*-hexyloxynitrobenzene, 170–174°/5 mm.
5. The alkoxyanilines are obtained readily by reduction of the alkoxynitrobenzenes in alcohol in the presence of Raney nickel catalyst (see p.

63). The boiling points of some of these are as follows: *m-n*-butoxyaniline, 120–124°/2 mm.; *p-n*-butoxyaniline, 135–138°/5 mm.; *p*-isopropoxyaniline, 145–147°/20 mm.; *p-n*-hexoxyaniline, 155–158°/5 mm.

3. Discussion

The present procedure, which avoids the preparation of the salts of the phenols, is of general utility. It was first used by Claisen[1] for allyl ethers. *o-n*-Butoxynitrobenzene has been prepared in a similar manner previously.[2] The *m*-nitro- and *p*-nitrobutoxybenzenes have been obtained by alkylation of the phenol salts.[3,4,5] The corresponding amines have been prepared previously by reduction of the nitro compounds by means of iron and water[2] and by stannous chloride and hydrochloric acid.[4]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

p-n-hexoxyaniline

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

sodium hydroxide (1310-73-2)

iron (7439-89-6)

n-butyl bromide (109-65-9)

stannous chloride

Raney nickel (7440-02-0)

acetone (67-64-1)

o-nitrophenol (88-75-5)

iodide (20461-54-5)

o-n-hexyloxynitrobenzene

o-n-BUTOXYNITROBENZENE, Ether, butyl o-nitrophenyl (7252-51-9)

m-n-butoxynitrobenzene

p-n-butoxynitrobenzene (7244-78-2)

p-isopropoxynitrobenzene (26455-31-2)

m-n-butoxyaniline

p-n-butoxyaniline (4344-55-2)

p-isopropoxyaniline (7664-66-6)

m-nitrobutoxybenzene, p-nitrobutoxybenzene

p-n-hexyloxynitrobenzene

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Organic Syntheses, *CV 3*, *141*

tert-BUTYL ACETATE

[Acetic acid, *tert*-butyl ester]

[I. ACETIC ANHYDRIDE METHOD]

Submitted by Robert H. Baker and Frederick G. Bordwell.
Checked by R. L. Shriner and Fred W. Neumann.

1. Procedure

In a 1-l. flask equipped with a reflux condenser and drying tube are placed 200 ml. (2.1 moles) of *tert*-butyl alcohol (Note 1), 200 ml. (2.1 moles) of acetic anhydride, and 0.5 g. of anhydrous zinc chloride. After thorough shaking, the mixture is slowly heated to reflux temperature, maintained at gentle refluxing for 2 hours, and then cooled. The reflux condenser is replaced by a 20-cm. Vigreux column through which the mixture is distilled up to a temperature of 110°. The crude distillate, weighing 200–250 g., is washed with two 50-ml. portions of water, then with 50-ml. portions of 10% potassium carbonate until the ester layer is neutral to litmus; the product is finally dried over anhydrous potassium carbonate (about 20 g.).

After removal of the drying agent, the ester is fractionally distilled through an efficient fractionating column (Note 2). A fore-run of 21–37 g. is collected up to a temperature of 95°. The pure ester distils between 95° and 96° and amounts to 129–148 g. (53–60%) (Note 3).

2. Notes

1. Eastman Kodak Company's best grade of *tert*-butyl alcohol and the practical grade of acetic anhydride are satisfactory. If these are not available, the alcohol should be dried over quicklime and distilled, and the acetic anhydride should be redistilled also.
2. The fractionating column may be a 16-plate Stedman column or a 30-cm. Carborundum-packed column.
3. The corrected boiling point of the ester is given as 97.9°.[1]

[II. ACETYL CHLORIDE METHOD]

Submitted by C. R. Hauser, B. E. Hudson, B. Abramovitch, and J. C. Shivers.
Checked by R. L. Shriner and Fred W. Neumann.

1. Procedure

In a 2-l. flask equipped with a reflux condenser, mercury-sealed stirrer, and a dropping funnel are placed 147 ml. (114 g., 1.5 moles) of *tert*-butyl alcohol (Note 1), 212 ml. (202 g., 1.67 moles) of dimethylaniline, and 200 ml. of dry ether. The solution is heated to refluxing, and 113 ml. (124 g., 1.58 moles) of acetyl chloride is run into the stirred solution at such a rate that moderate refluxing continues after the source of heat is removed. When approximately two-thirds of the acetyl chloride has been added, dimethylaniline hydrochloride begins to crystallize and the mixture refluxes very vigorously. An ice bath is applied immediately, and, after refluxing ceases, the remainder of the acetyl chloride is added. Finally, the mixture is heated for 1 hour on a water bath. The mixture is cooled to room temperature, approximately 200 ml. of water is added, and stirring is continued until all the solid material dissolves. The ether layer is separated and extracted with 50-ml. portions of cold 10% sulfuric acid until the extract does not become cloudy when made alkaline with sodium hydroxide. After a final washing with 25 ml. of saturated sodium bicarbonate solution, the ether solution is dried by shaking it with 10 g. of anhydrous sodium sulfate. The solution is decanted and allowed to stand over 10 g. of Drierite overnight. The solution is filtered, and the ether is removed by distillation through a good fractionating column (Note 2). The residue is fractionally distilled, and 110–119 g. (63–68%) of *tert*-butyl acetate boiling at 95–98° is obtained (Note 2). Most of the ester boils at 97.0–97.5° (Note 3).

2. Notes

1. All reactants should be pure and anhydrous. The *tert*-butyl alcohol should be dried over quicklime and the dimethylaniline redistilled. Reagent grade acetyl chloride should be employed.
2. Either a 30-cm. Carborundum-packed column or a 30-cm. Widmer column may be used. The pure ester was collected over a range of 94.5–95.5°.
3. The submitters report that the following *tert*-butyl esters have been prepared in a similar manner. Eastman Kodak Company chemicals were used.
(*a*) *tert*-Butyl propionate. From 221 ml. (171 g., 2.31 moles) of *tert*-butyl alcohol, 318 ml. (303 g., 2.5 moles) of dimethylaniline, and 206 ml. (220 g., 2.38 moles) of propionyl chloride, refluxed for 3 hours, there was obtained 184 g. (61.4%) of *tert*-butyl propionate, b.p. 117–118.5°; most of the product boiled at 118.0–118.5°.
(*b*) *tert*-Butyl isobutyrate. From 94.5 ml. (73.4 g., 0.99 mole) of *tert*-butyl alcohol, 127 ml. (121 g., 1 mole) of dimethylaniline in 200 ml. of ether, and 105

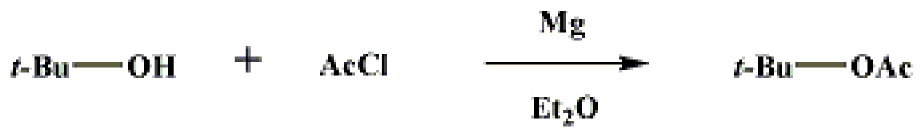
ml. (108 g., 1 mole) of isobutyryl chloride in 50 ml. of ether, after standing for 15 hours at room temperature, the ether being distilled, and the residue heated for 5 hours on a water bath, there was obtained 102 g. (71%) of the ester boiling at 127–128.3°.

(*c*) *tert*-Butyl isovalerate. From 121.4 g. (1.64 moles) of *tert*-butyl alcohol, 198.5 g. (1.64 moles) of dimethylaniline, and 200.7 g. (1.66 moles) of isovaleryl chloride, after standing overnight, the ether being distilled, and the residue heated for 5 hours on a water bath, there was obtained 67.3 g. (26%) of *tert*-butyl isovalerate boiling at 154–157°.

(*d*) *tert*-Butyl cinnamate. The cinnamoyl chloride from 100 g. (0.675 mole) of cinnamic acid and 400 g. (3.37 moles) of thionyl chloride was treated with 64 ml. (49.5 g., 0.67 mole) of *tert*-butyl alcohol and 90 ml. (86.0 g., 0.71 mole) of dimethylaniline. The mixture was refluxed 12 hours and then allowed to stand 12 hours at room temperature. Distillation furnished 78.8 g. (58%) of *tert*-butyl cinnamate boiling at 144°/8 mm.

(*e*) *tert*-Butyl chloroacetate (submitted by Robert H. Baker). Thirty-five and four-tenths milliliters (0.4 mole) of *tert*-butyl alcohol was added over a period of 10 minutes to a mixture of 30.6 ml. (0.4 mole) of chloroacetyl chloride and 50 ml. (0.4 mole) of dimethylaniline, care being taken to keep the temperature below 30°. After standing 45 minutes at room temperature, the mixture was poured into water and worked up in the usual way. The ester was fractionated in a 6-in. Widmer column. The yield was 38 g. (63%) of ester which boiled at 48–49°/11 mm.; n_D^{20} 1.4259–1.4260.

[III. ACETYL CHLORIDE-MAGNESIUM METHOD]



Submitted by A. Spassow
Checked by W. E. Bachmann and J. Korman.

1. Procedure

In a 1-l. round-bottomed flask are placed 12 g. (0.5 gram atom) of magnesium powder, 37 g. (0.5 mole) of *tert*-butyl alcohol, and 100 g. of anhydrous ether (Note 1). The flask is fitted with an addition tube, one arm of which bears a reflux condenser and the other arm a dropping funnel. While the mixture is being shaken by hand, a solution of 55 g. (0.7 mole) of acetyl chloride (Note 2) in 50 g. of anhydrous ether is added dropwise (Note 3). A lively reaction gradually ensues with evolution of hydrogen, mixed with ether vapor and a little hydrogen chloride (Note 4). After all the acetyl chloride has been added, the reaction mixture is allowed to stand in a pan of cold water for 1 hour (Note 5). After another hour at room temperature the mixture is warmed in a water bath at 40–45° for 30 minutes in order to complete the reaction.

The solid reaction product is cooled in ice water and decomposed by addition of an ice-cold solution of 20 g. of potassium carbonate in 250 ml. of water, cooling being continued throughout (Note 6). The mixture is extracted three times with 35-ml. portions of ether; the ether extract is dried over calcium chloride and then distilled (Note 7). The ester is obtained from the fraction boiling at 85–98° by fractional distillation by means of a good column (Note 8). The purified ester boils at 95–97°/740 mm. and weighs 37–45 g. (45–55%).

2. Notes

1. The *tert*-butyl alcohol must be completely anhydrous. It was dried over sodium and distilled from sodium just before use. The ether was likewise dried over sodium.
2. The acetyl chloride was distilled before use.
3. The addition of the acetyl chloride requires about 15 minutes. After the addition of about two-thirds of the acid chloride, the reaction mixture rapidly becomes semisolid.
4. The course of the esterification is best followed by the evolution of the hydrogen, the hydrogen being led by means of a tube from the top of the condenser through a wash bottle containing a small amount of water. A moderate rate of reaction is obtained throughout by judicious immersion of the reaction flask in a pan of cold water.
5. After 30 minutes the reaction becomes more lively and the mixture more fluid.
6. The potassium carbonate solution is added all at once. The carbon dioxide which is evolved does not interfere with the extraction of the ester.
7. Since the ester is quite volatile, the ether is distilled through a 60-cm. Vigreux column. The distillation is interrupted at 40°, and a 40-cm. column is employed. A fraction boiling up to 85° and one boiling from 85° to 98° are collected. The first fraction, which contains considerable amounts of the ester, is redistilled, and the portion boiling above 85° is added to the second fraction. The fraction boiling from 85° to 98° weighs 43–48 g.
8. A 40-cm. Vigreux or Widmer column is used for this distillation. The fore-run is redistilled from the same flask.

3. Discussion

tert-Butyl acetate has been prepared from the alcohol and acetyl chloride in the presence of pyridine,[1] dimethylaniline,[2] or magnesium. Acetic anhydride has been used with zinc chloride,[2] a small amount of zinc dust,[2] or anhydrous sodium acetate.[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 171
- Org. Syn. Coll. Vol. 5, 586

- Org. Syn. Coll. Vol. 6, 259

References and Notes

1. Bryant and Smith, *J. Am. Chem. Soc.*, **58**, 1016 (1936).
2. Norris and Rigby, *J. Am. Chem. Soc.*, **54**, 2097 (1932).
3. Tronow and Ssibgatullin, *Ber.*, **62**, 2850 (1929).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Drierite

calcium chloride (10043-52-4)

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

hydrogen chloride (7647-01-0)

ether (60-29-7)

acetic anhydride (108-24-7)

sodium acetate (127-09-3)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

acetyl chloride (75-36-5)

thionyl chloride (7719-09-7)

sodium bicarbonate (144-55-8)

magnesium, magnesium powder (7439-95-4)

sodium sulfate (7757-82-6)

carbon dioxide (124-38-9)

pyridine (110-86-1)

zinc (7440-66-6)

sodium (13966-32-0)

zinc chloride (7646-85-7)

chloroacetyl chloride (79-04-9)

dimethylaniline (121-69-7)

cinnamic acid (621-82-9)

isobutyryl chloride (79-30-1)

propionyl chloride (79-03-8)

dimethylaniline hydrochloride (5882-44-0)

isovaleryl chloride (108-12-3)

cinnamoyl chloride

tert-butyl alcohol (75-65-0)

tert-Butyl acetate, Acetic acid, tert-butyl ester (540-88-5)

tert-Butyl propionate (20487-40-5)

tert-Butyl isobutyrate (16889-72-8)

tert-Butyl isovalerate (16792-03-3)

tert-Butyl cinnamate (14990-09-1)

tert-Butyl chloroacetate (107-59-5)

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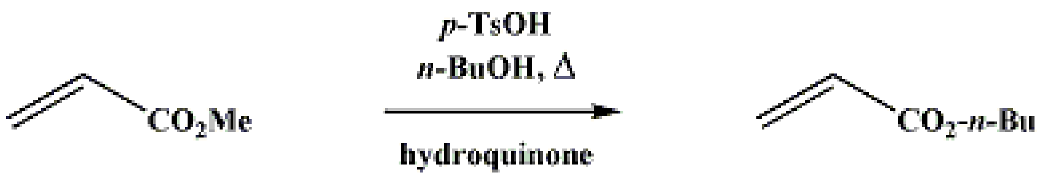
Organic Syntheses, CV 3, 146

n-BUTYL ACRYLATE

[Acrylic acid, *n*-butyl ester]



Submitted by Chessie E. Rehberg
Checked by H. R. Snyder and Fred E. Boettner.

1. Procedure

In a 2-l. two-necked round-bottomed flask having a capillary ebullator tube in one neck (Note 1) are placed 371 g. (5 moles) of *n*-butyl alcohol, 861 g. (10 moles) of methyl acrylate, 20 g. of hydroquinone, and 10 g. of *p*-toluenesulfonic acid (Note 2). The flask is attached to an all-glass fractionating column, preferably one without packing such as the Vigreux type (Note 3), and the solution is heated to boiling in an oil bath. The column is operated under total reflux until the temperature of the vapors at the still head falls to 62–63°, which is the boiling point of the methanol-methyl acrylate azeotrope (Note 4). This azeotrope is then distilled as rapidly as it is formed, the temperature at the still head not being allowed to exceed 65°. When the production of methanol has become very slow (6–10 hours), the excess methyl acrylate is distilled, and the butyl acrylate is then distilled, preferably at 10–20 mm. It boils at 39°/10 mm., 84–86°/101–102 mm., and at about 145° at atmospheric pressure. The yield is 500–600 g. (78–94%) (Note 5).

2. Notes

1. The capillary is used to introduce a gas to prevent bumping and superheating during the vacuum distillation of the product. As air has some tendency to catalyze polymerization of the acrylic ester, if it is introduced through the capillary the amount must be as small as possible. The gas introduced should be an inert one, such as carbon dioxide or nitrogen. If polymeriaztion is troublesome, it may be advantageous to pass in a slow stream of carbon dioxide through the capillary during the entire reaction period.
2. Sulfuric acid is also a very satisfactory catalyst; aluminum alkoxides also are useful, especially when the alcohols would be adversely affected by strong acids. Sodium alkoxides produce undesirable side reactions and give lower yields. When alkaline catalysts are employed, an alkaline polymerization inhibitor, such as *p*-phenylenediamine or phenyl-β-naphthylamine, should be used instead of hydroquinone.
3. The fractionating column should be one that can be cleaned readily if a

polymer is formed in it. A large number of plates is not required, though the column should be capable of separating the methanol-methyl acrylate azeotrope (b.p. 62–63°) from methyl acrylate (b.p. 80°), and butanol (b.p. 117°) from butyl acrylate (b.p. 145°). The necessity of effecting the latter separation can be practically eliminated by allowing the reaction to go virtually to completion, all the butanol thus being consumed. This can be done by extending the reaction period as long as reaction occurs and by adding a considerable excess of methyl acrylate. Instead of the twofold excess specified, three or four times the theoretical amount may be used with benefit. The larger amount is especially desirable when the acrylate of a relatively unreactive alcohol is being prepared.
4. The methanol-methyl acrylate azeotrope contains about 45% methyl acrylate, which can be recovered by washing out the methanol with a large volume of water or brine; the acrylate is purified by drying and distilling. An inhibitor, such as hydroquinone, should always be added to any acrylic ester before attempting to distil it, and, unless it is stored in a refrigerator, the distilled ester should not be kept more than a few hours without the addition of a small amount (0.1–1.0%) of an inhibitor.
5. Yields of the primary alkyl acrylates vary somewhat, owing to occasional losses through formation of polymer, but are usually in the range of 85–99%. Some secondary alcohols react very slowly, others readily. The method has been applied to more than fifty alcohols, some of which (with percentage yields) are listed below: ethyl, 99%; isopropyl, 37%; *n*-amyl, 87%; isoamyl, 95%; *n*-hexyl, 99%; 4-methyl-2-pentyl, 95%; 2-ethylhexyl, 95%; capryl, 80%; lauryl, 92%; myristyl, 90%; allyl, 70%; furfuryl, 86%; citronellyl, 91%; cyclohexyl, 93%; benzyl, 81%; β-ethoxyethyl, 99%; β-(β-phenoxyethoxy) ethyl (from diethylene glycol monophenyl ether), 88%.

3. Discussion

n-Butyl acrylate has been prepared by direct esterification,[1] by debromination of *n*-butyl α,β-dibromopropionate with zinc,[2] by treatment of either butyl β-chloropropionate[1] or butyl β-bromopropionate[1] with diethylaniline, and by the pyrolysis of butyl β-acetoxypropionate.[3] Direct esterification and alcoholysis of methyl or ethyl acrylate have been recommended for the preparation of the higher alkyl acrylates.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 350

References and Notes

1. Moureau, Murat, and Tampier, *Ann. chim.*, **15**, 245 (1921) [*C. A.*, **16**, 55 (1922)].

2. Kobeko, Koton, and Florinskii, *J. Applied Chem. U.S.S.R.*, **12**, 313 (1939) [*C. A.*, **33**, 6795 (1939)].
3. Burns, Jones, and Ritchie, *J. Chem. Soc.*, **1935**, 400.
4. Neher, *Ind. Eng. Chem.*, **28**, 267 (1936).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

phenyl-β-naphthylamine

methyl or ethyl acrylate

ß-ethoxyethyl alcohol

ß-(ß-phenoxyethoxy) ethyl alcohol

ethyl alcohol (64-17-5)

sulfuric acid (7664-93-9)

methanol (67-56-1)

hydroquinone (123-31-9)

Cyclohexanol (108-93-0)

Allyl alcohol (107-18-6)

Lauryl alcohol (112-53-8)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

butanol, n-butyl alcohol (71-36-3)

zinc (7440-66-6)

isopropyl alcohol (67-63-0)

Benzyl alcohol (100-51-6)

Furfuryl alcohol (98-00-0)

n-HEXYL ALCOHOL (111-27-3)

isoamyl alcohol (123-51-3)

n-amyl alcohol (71-41-0)

methyl acrylate (96-33-3)

capryl alcohol (111-87-5)

diethylaniline (91-66-7)

Myristyl alcohol (112-72-1)

Butyl acrylate, n-BUTYL ACRYLATE, Acrylic acid, n-butyl ester (141-32-2)

diethylene glycol monophenyl ether

butyl β-chloropropionate (27387-79-7)

butyl β-bromopropionate

butyl β-acetoxypropionate

p-toluenesulfonic acid (104-15-4)

citronellyl alcohol (106-22-9)

p-phenylenediamine (106-50-3)

n-butyl α,β-dibromopropionate

4-methyl-2-pentanol

2-ethylhexanol

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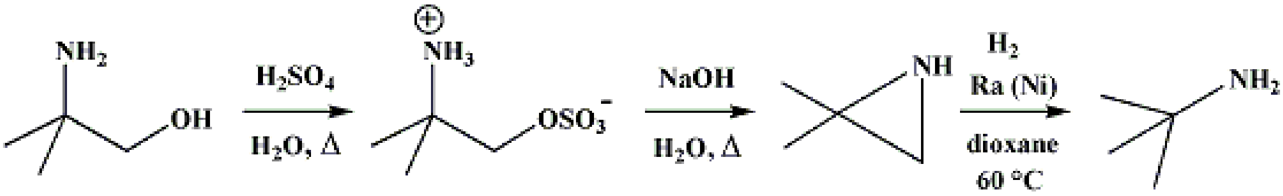
Organic Syntheses, *CV 3, 148*

tert-BUTYLAMINE

[I. HYDROGENOLYSIS OF 2,2-DIMETHYLETHYLENIMINE]



Submitted by Kenneth N. Campbell, Armiger H. Sommers, and Barbara K. Campbell.
Checked by Nathan L. Drake and Sidney Melamed.

1. Procedure

A. *2,2-Dimethylethylenimine*. A cold mixture of 110 g. (60 ml., 1.06 moles) of concentrated sulfuric acid and 200 ml. of water is added in portions, with shaking, to a solution of 100 g. (107 ml., 1.12 moles) of 2-amino-2-methyl-1-propanol in 200 ml. of water contained in a 1-l. round-bottomed flask (Note 1). The flask is fitted with a thermometer extending into the liquid and a short still head carrying a downward condenser.

Water is distilled from the mixture at atmospheric pressure until the temperature of the solution reaches 115° (Note 2) and (Note 3), whereupon the liquid is transferred to a 500-ml. round-bottomed flask. This flask is connected to the distillation apparatus used previously except that the thermometer is replaced by a capillary tube. Distillation is then continued under the reduced pressure obtainable from a water aspirator. The bath temperature is raised to 175° over a period of about an hour and is held there until the mixture solidifies (usually 30–60 minutes longer), and for 1 hour thereafter. The flask is cooled and broken to remove the product.

The brown solid from the above operations is ground in a mortar and placed in a 500-ml. distilling flask equipped with a downward condenser and a receiver. A cold solution of 100 g. (2.5 moles) of technical sodium hydroxide in 150 ml. of water is added to the solid in the flask, and heat is applied by means of an oil bath whose temperature is slowly raised to 125° From 70 to 75 g. of distillate is collected; the head temperature ranges from about 70° to 101° (Note 2). The distillate is cooled in ice and saturated with technical potassium hydroxide; the organic layer that forms is separated and dried over potassium hydroxide pellets in a refrigerator for about 15 hours.

The organic layer is separated from the drying agent and distilled from a few fresh pellets of potassium hydroxide through a column of the Whitmore-Fenske type. After a 3- to 5-g. fore-run, the product distils at 71–72°; the yield is 36–41 g. (45–51%) (Note 4) and (Note 5).

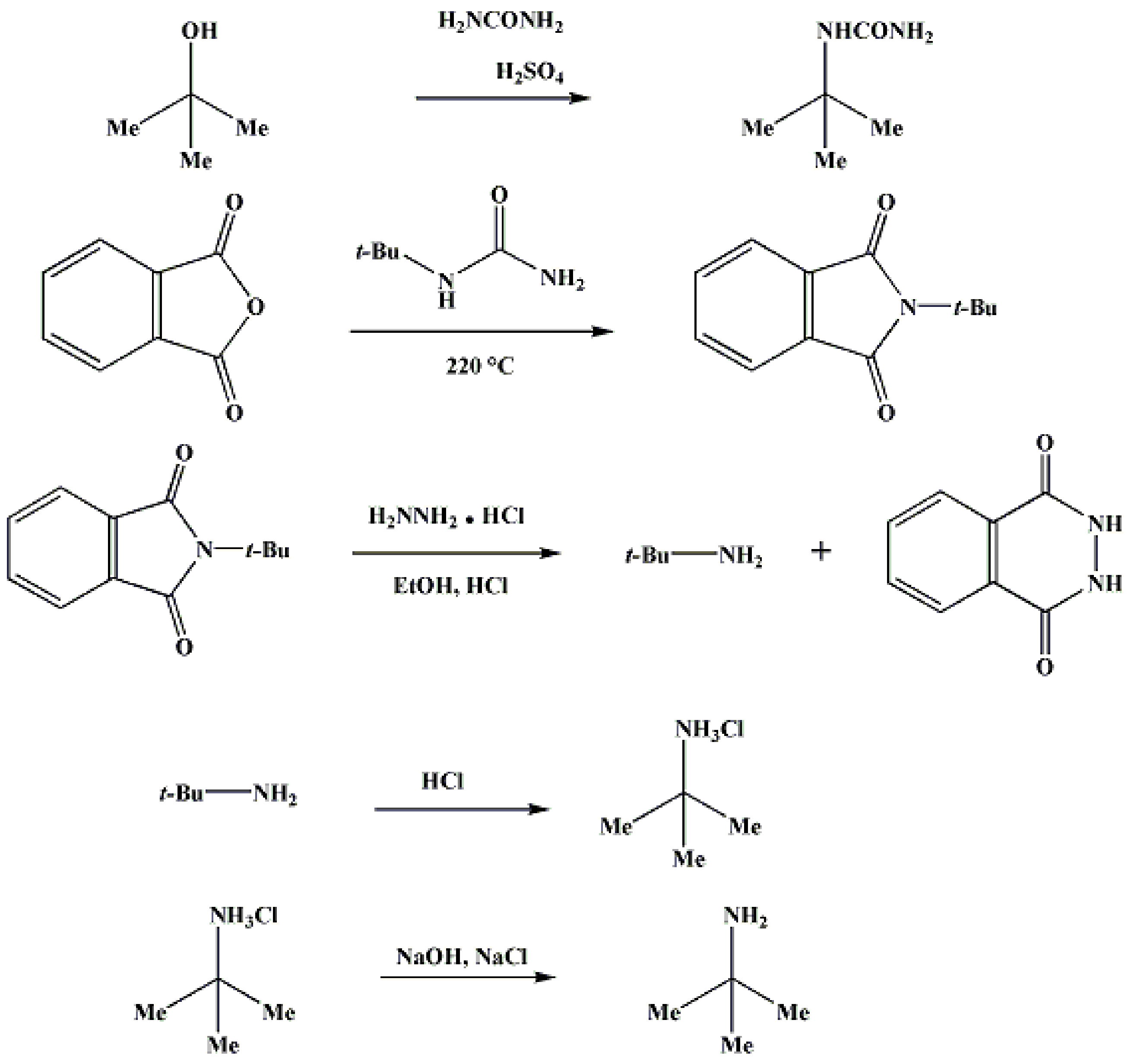
B. *tert-Butylamine*. A hydrogenation bomb or bottle (Note 6) is charged with 100 ml. of purified dioxane,[1] 35.5 g. (0.5 mole) of freshly distilled 2,2-dimethylethylenimine, and about 9 g. (alcohol-wet weight) of Raney nickel.[2] The apparatus is filled with hydrogen, warmed to 60°, and shaken until hydrogenation is complete (Note 7). The contents of the bomb are removed and filtered to separate the catalyst, which is washed on the funnel with a little dioxane.

The filtrates from two such runs are combined and distilled through a Whitmore-Fenske column of 10–15 theoretical plates at a 5:1 reflux ratio. The yield of *tert*-butylamine is 55–60 g. (75–82%); the product boils at 44–44.5°, and its refractive index is n_D^{20} 1.3770 (Note 8).

2. Notes

1. The 2-amino-2-methyl-1-propanol used was the practical grade obtained from the Eastman Kodak Company. This aminoalcohol can also be secured from the Commercial Solvents Corporation.
2. An electric heating mantle may conveniently be substituted for the oil bath specified.
3. Approximately 285 ml. of water must be collected before the temperature of the reaction mixture reaches 115°.
4. 2,2-Dimethylethylenimine polymerizes on standing; the product should be hydrogenated within a few hours after preparation.
5. The checkers have followed the same procedure successfully using tenfold quantities; the yield of the imine was 42%.
6. The hydrogenation can be carried out equally well in metal or glass equipment. If a hydrogenator of the Parr low-pressure type is used, the bottle can be wound for electrical heating. Five turns of 24-gauge asbestos-covered Nichrome or Chromel A wire is satisfactory for the heating element. In use, current is supplied from a variable transformer, and the voltage necessary to heat the contents of the bottle to 60° is determined by experiment. The checkers used hydrogenation equipment supplied by the American Instrument Company.
7. If the hydrogenation is carried out in a Parr hydrogenation apparatus at 40–60 lb. pressure, about 2 hours is required to complete the hydrogenation as described. The low boiling point of the ethylenimine makes it impossible to remove the air from the bottle by evacuation in the usual way before hydrogenation. Instead the bottle is filled with hydrogen to 15–20 lb. pressure, the pressure is released, and the process repeated.
8. The checkers used high-pressure equipment and found that the hydrogenation of 336 g. of 2,2-dimethylethylenimine in 250 ml. of purified dioxane in the presence of 3 teaspoonfuls of Raney nickel under 3000 lb. hydrogen pressure was complete in 10–15 minutes; the temperature rise during the hydrogenation was about 50°. The yield of product was 283 g. (82%).

[II. VIA *tert*-BUTYLPHTHALIMIDE]



Submitted by Lee Irvin Smith and Oliver H. Emerson[3].
Checked by R. L. Shriner and Arne Langsjoen.

1. Procedure

A. *tert-Butylurea* (Note 1). In a 500-ml. three-necked flask equipped with a fast mechanical stirrer, a 200-ml. dropping funnel, and a thermometer is placed 193 g. (105 ml., 1.98 moles) of concentrated sulfuric acid (sp. gr. 1.84). The flask is surrounded by an ice bath, and 60 g. (1 mole) of finely powdered urea is added slowly at such a rate that the temperature remains between 20° and 25°. Then 148 g. (188 ml., 2 moles) of *tert*-butyl alcohol is added dropwise from the funnel at such a rate that the temperature is maintained between 20° and 25° (Note 2). After the addition is completed the mixture is stirred for an additional 30 minutes, allowed to stand at room temperature overnight (about 16 hours) (Note 3), and then poured with stirring on 1.5 kg. of cracked ice and water in a 4-l. beaker. Without removal of the precipitate, the mixture is made alkaline to Congo red indicator by adding slowly with stirring a solution of sodium hydroxide (160 g. in 750 ml. of water). The mixture is cooled with an ice bath to keep the temperature below 25°. The mixture is stirred in the ice bath until the temperature falls to about 15° (Note 4), at which point the precipitate is collected on a 15-cm. Büchner funnel, washed with two 100-ml. portions of cold water, and pressed and sucked as dry as possible. The cake is transferred to a 2-l. beaker, and 500 ml. of water is added. The mixture is heated to boiling and quickly filtered while hot through an

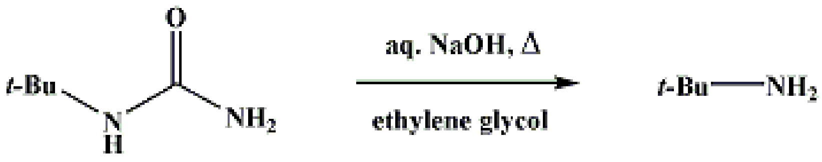
8-cm. steam-heated Büchner funnel (Note 5) with the aid of suction. The filtrate is cooled to 0–5° with occasional stirring, and the white precipitate of *tert*-butylurea is collected on a 15-cm. Büchner funnel with suction and pressed as dry as possible. After the product has been spread out on absorbent paper and air-dried overnight (Note 6) there is obtained 36–39 g. (31–33%) of *tert*-butylurea melting at 180–182° (Note 7).

B. *tert-Butylphthalimide*. Thirty-five grams (0.3 mole) of *tert*-butylurea and 100 g. (0.675 mole) of phthalic anhydride are ground together in a mortar. The mixture is placed in a 1-l. Erlenmeyer flask which is then immersed in a metal bath previously heated to 200°. The mixture melts and effervesces vigorously; after 10 minutes the temperature of the bath is raised to 240° (internal temperature 200°) and held there for 5 minutes (Note 8). The flask is removed and cooled to 60–70°, and 100 ml. of 95% ethanol is added to dissolve the contents partially. A 20% solution of sodium carbonate is added until the solution is alkaline to litmus paper, and the mixture is diluted with water to 1 l. The solid is collected on a Büchner funnel with the aid of suction and pressed as dry as possible. The filter cake is warmed on a steam bath with 500 ml. of petroleum ether (b.p. 60–70°) in a 1 l. flask, and the hot mixture is filtered. Any water layer that may separate from the filtrate is removed, and the filtrate is cooled to 25° and again filtered. The clear filtrate is concentrated by distillation to about one-third of its original volume and placed in a refrigerator overnight. The crystalline material is collected on a filter, and as much as possible of the solvent is removed by suction. After air drying, this first crop weighs 40–43 g. and melts at 58–59°. By concentration of the filtrate an additional 2–4 g. may be obtained. The total yield of *tert*-butylphthalimide is 43–46.5 g. (72–76%).

C. *tert-Butylamine hydrochloride*. In a 2-l. flask fitted with an efficient bulb-type reflux condenser are placed 203 g. (1 mole) of *tert*-butylphthalimide, 1 l. of 95% ethanol, and 59 g. (1 mole) of 85% hydrazine hydrate. The solution is refluxed for 2 hours and cooled, and concentrated hydrochloric acid (about 100 ml.) is added until the solution is strongly acid to Congo red paper, though a large excess of acid is avoided. The voluminous precipitate of phthalhydrazide is collected on a 15-cm. Büchner funnel with the aid of suction and washed with four 100-ml. portions of 95% ethanol. The combined filtrate and washings are concentrated under reduced pressure to a volume of 200 ml. About 1 l. of water is added, any insoluble material is removed by filtration, and the filtrate is concentrated to about 300–350 ml. If any additional insoluble material separates it is removed by filtration, and the solvent is completely removed by evaporation under reduced pressure. This crude amine hydrochloride may be converted to the free amine as described below, or it may be purified by solution in 500 ml. of absolute ethanol, the solution being filtered and 500 ml. of dry ether being added to the filtrate. The crude amine hydrochloride is collected on a filter; the solvent is removed by suction, and the residue is dissolved in hot absolute ethanol using 5 ml. per gram of material; absolute ether (50% of the volume of ethanol) is added, and the solution is cooled in a refrigerator for several hours. All the *tert*-butylamine hydrochloride is collected on a Büchner funnel and dried in a vacuum desiccator. It weighs 79–97 g. (72–88%) and melts with sublimation at 270–290°.

D. *tert-Butylamine*. To 150 ml. of cold 40% solution of sodium hydroxide is added 109.5 g. (1 mole) of *tert*-butylamine hydrochloride with stirring. The solution is saturated with potassium carbonate (about 100–150 g.); the layer of amine is separated and dried over 20 g. of sodium hydroxide pellets. The product is distilled using an ice-cooled receiver, and the fraction boiling at 44–46° is collected. If the purified amine hydrochloride is the starting material for this step the yield ranges from 65 g. to 69 g. (89–94%). When the crude amine salt is employed, the yield is 46–60 g. (64–83%) (Note 9).

[III. HYDROLYSIS OF *tert*-BUTYLUREA]



Submitted by D. E. Pearson, J. F. Baxter, and K. N. Carter.
Checked by R. L. Shriner and Calvin N. Wolf.

1. Procedure

A 1-l. round-bottomed flask is charged with 60 g. (1.5 moles) of sodium hydroxide pellets dissolved in 75 ml. of water, 70 g. (0.6 mole) of *tert*-butylurea, and 225 ml. of commercial ethylene glycol. The flask is fitted with an efficient reflux condenser, and a glass tube is led from the top of the condenser to a small flask immersed in ice water (Note 10).

The mixture is refluxed gently for 4 hours (Note 11). The flask is cooled and equipped for distillation, and the fraction boiling at 40–60° is collected in an ice-cooled receiver. The crude amine, including any collected in the trap, weighs 37–39 g. It is dried overnight with 5–7 g. of sodium hydroxide pellets (Note 12) and then distilled, a 12- to 15-cm. fractionating column (Note 13) and an ice-cooled receiver equipped with a soda-lime tube being used. The fraction boiling at 44–46° amounts to 31–34 g. (71–78%) of *tert*-butylamine; d_4^{20} 0.699; n_D^{20} 1.3800.

2. Notes

1. This step may be omitted if a practical grade of *tert*-butylurea is purchased from the Eastman Kodak Company. Since the commercial product may contain sodium sulfate and di-*tert*-butylurea it should be recrystallized from hot water, about 1 l. of solvent being used for 100 g. of the urea.
2. The temperature of the mixture should be kept in the range 20–25°. Higher temperatures lead to the formation of diisobutylene, and at lower temperatures (15°) the urea does not dissolve readily. Even at 25° the urea is usually not completely in solution. It has been found convenient to warm the *tert*-butyl alcohol to about 30–35° before placing it in the dropping funnel. This avoids solidification in the stem (the melting point of *tert*-butyl alcohol is 25.5°).
3. Longer standing does not improve the yield.
4. If the temperature is allowed to fall below 15°, large amounts of sodium sulfate decahydrate crystallize with the product. If this happens it may be necessary to recrystallize the *tert*-butylurea several times.
5. The insoluble residue weighs 10–22 g. and consists of di-*tert*-butylurea, which sublimes above 200° but melts in a sealed tube at 243°. If several runs are being made, the di-*tert*-butylurea should be saved and dried. It may be converted to *tert*-butylphthalimide in 63% yields by heating with four equivalents of phthalic anhydride under the same conditions as specified for mono-*tert*-butylurea.
6. The product should not be dried in an oven at elevated temperatures, as it sublimes.
7. This material is pure enough for the next step. Melting points of 172° (dec.) and 183° are given in the literature.[4,5] Recrystallization from dilute ethanol gives long, white needles melting at 182° (cor.), whereas use of 95% ethanol gives plates melting at the same temperature. The temperature of the melting-point bath should be raised more rapidly than usual since the product sublimes slowly above 100°.
8. Less rapid heating results in a diminished yield. The reaction is usually completed after a total time of 15 minutes, no further evolution of carbon dioxide or ammonia occurring. Prolonged heating causes the formation of a colored product and reduces the yield.
9. A similar series of reactions may be used to prepare *tert*-amylamine. The *tert*-amylurea is produced in yields of 50–58%, *tert*-amylphthalimide in yields of 63–72%, and *tert*-amylamine, b.p. 77–78°, in 87% yields (N. L. Drake and John Garman, private communication).
10. If the water in the condenser is cold enough to prevent loss of the amine the extra trap is unnecessary.
11. The *tert*-butylurea gradually dissolves, and a gelatinous mass of sodium carbonate forms.
12. If an aqueous layer forms it is separated and the amine is dried with a fresh portion of 5 g. of sodium hydroxide pellets.
13. The submitters and checkers used a Vigreux column.

3. Discussion

tert-Butylurea has been prepared by the action of *tert*-butyl bromide upon a mixture of urea and white lead;[4] by the action of *tert*-butylamine upon potassium cyanate;[5] in small amounts by heating N-*tert*-butylurethan with alcoholic ammonia.[4] The method given above is a modification of a general method for preparation of alkyl ureas, described by Harvey and Caplan in a patent.[6]

The direct hydrolysis of *tert*-butylurea is perhaps the simplest and most convenient method for preparing *tert*-butylamine.[7] In addition to the ethylene glycol method described here, it is possible to carry out the hydrolysis in a pressure vessel with aqueous sodium hydroxide (40%) at 130° (A. H. Sommers, private communication).

tert-Butylphthalimide is a new compound. The procedure given here is a modification[8] of a general procedure for the cleavage of alkylphthalimides, as developed by Ing and Manske[9] and Manske.[10]

2,2-Dimethylethylenimine has been prepared by the dehydration of 2-amino-2-methyl-1-propanol. The method described here is essentially that of Cairns.[11]

Methods for the hydrogenolysis of 2,2-dimethylethylenimine have been published.[12,13]

tert-Butylamine has also been obtained from trimethylacetamide by the Hofmann rearrangement,[14] from trimethylacetic acid by the Schmidt reaction,[15] from trimethylacetazide,[16] by the reduction of *tert*-butylhydrazide,[17] and by the reaction of *tert*-butylmagnesium chloride with O-methylhydroxylamine[18] or with monochloramine.[19]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 801

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

trimethylacetazide

ethanol (64-17-5)

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

lead (7439-92-1)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

tert-Butyl bromide (507-19-7)

carbon dioxide (124-38-9)

phthalic anhydride (85-44-9)

nickel (7440-02-0)

potassium hydroxide (1310-58-3)

ethylene glycol (107-21-1)

urea (57-13-6)

hydrazine hydrate (7803-57-8)

potassium cyanate (590-28-3)

Trimethylacetic acid (75-98-9)

dioxane (5703-46-8)

monochloramine (10599-90-3)

2,2-Dimethylethylenimine (2658-24-4)

2-amino-2-methyl-1-propanol (124-68-5)

Phthalhydrazide (1445-69-8)

sodium sulfate decahydrate (7727-73-3)

trimethylacetamide (758-96-3)

O-methylhydroxylamine (67-62-9)

tert-butyl alcohol (75-65-0)

tert-Butylamine (75-64-9)

tert-butylmagnesium chloride (677-22-5)

tert-Butylphthalimide (2141-99-3)

tert-Butylurea, mono-tert-butylurea (1118-12-3)

tert-Butylamine hydrochloride (10017-37-5)

di-tert-butylurea

tert-amylamine (594-39-8)

tert-amylurea

tert-amylphthalimide

N-tert-butylurethan

tert-butylhydrazide (3619-17-8)

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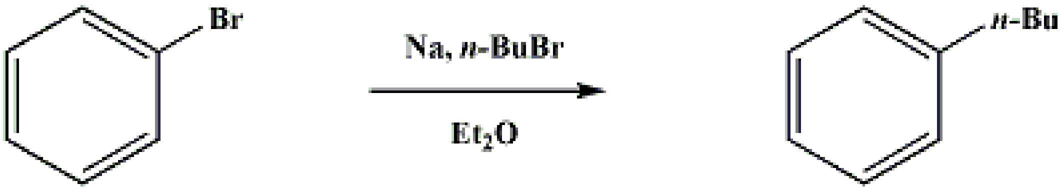
Organic Syntheses, *CV 3, 157*

n-BUTYLBENZENE

[Benzene, butyl-]



Submitted by R. R. Read, L. S. Foster, Alfred Russell, and V. L. Simril.
Checked by C. F. H. Allen and James VanAllan.

1. Procedure

A dry, 3-l., three-necked, round-bottomed flask (Note 1) and (Note 2) is fitted with an efficient reflux condenser (Note 3) protected by a drying tube, a dropping funnel, and a thermometer which extends well into the reaction mixture (Note 4); the flask is arranged so that it can be cooled externally (Note 5). In the flask is placed 161 g. (7 gram atoms) of sodium cut into shavings 1–2 mm. in thickness (Note 6) and (Note 7); the sodium is just covered with dry ether (about 300 ml.) (Note 8). A mixture of 411 g. (321 ml., 3 moles) of *n*-butyl bromide and 471 g. (315 ml., 3 moles) of bromobenzene (Note 9) is added slowly from the dropping funnel over a period of about 2.5 hours, the temperature being kept as near 20° as possible; the mass acquires a bluish color.

After the flask and contents have been allowed to stand at room temperature for 2 days with occasional shaking, the liquid is decanted (Note 10). Three hundred milliliters of methanol> is then added carefully, and the mixture is refluxed on a steam bath for 4 hours. Then 800 ml. of water is added to dissolve the salt, and the hydrocarbon layer is separated and added to the decanted liquid. The aqueous layer is extracted once with 250 ml. of ether (Note 11), and the combined hydrocarbon fraction, decanted solution, and ether extract are dried over 40 g. of calcium chloride. Most of the ether is removed on a steam bath, and the residual liquid is distilled through an electrically heated, jacketed column (Note 12). The fraction that boils at 180–182.5°/750 mm. is collected as *n*-butylbenzene (Note 13) and (Note 14); the yield is 261–281 g. (65–70%) (Note 15).

2. Notes

1. The size of the pieces of sodium, the control of temperature, and the use of an electrically heated, jacketed fractionating column are important factors in the successful preparation of the compound.
2. A copper flask and copper condenser reduce the hazard from breakage but are not essential and are less convenient with the quantities indicated.

3. Unless the reaction gets out of hand, the only function of the condenser is to prevent loss of ether. If the temperature gets above 30°, the reaction becomes violent and cannot be controlled by a single condenser.
4. A thermometer on which the scale is well above the surface of the reaction mixture is advisable; one reading from –50° to 50° is convenient.
5. The temperature range is critical. Below 15° reaction is extremely slow, but in time a vigorous reaction suddenly sets in and blows a good part of the reactants out through the condenser. Above 30° the reaction gets out of hand (Note 3).
6. This is a very tedious task. It is best accomplished by flattening the usual bars of sodium with a hammer and cutting the flattened strips with scissors. Alternatively the sodium, in 1-lb. lots, can be rolled under a heavy lawn roller (Read and Foster).
7. If the sodium is too thick, much of it fails to react, whereas sodium "sand" reacts very vigorously but gives poor yields of the desired product.
8. Larger runs require more ether. The ether may be dried over calcium chloride and used directly.
9. The *n*-butyl bromide and bromobenzene need not be redistilled.
10. Read and Foster recommend extracting the residue with benzene, using an automatic extractor.
11. Although this extract contains but 2–3 g. of hydrocarbon, its use facilitates drying later on and reduces loss through an occasional imperfect separation of layers.
12. A column such as the Whitmore-Lux or Fenske column provided with an electrically heated jacket is essential.
13. Alternatively, a crude fraction boiling at 160–185° is collected; on redistillation, the product that boils at 181–184° is collected (Read and Foster).
14. The fore-run amounts to about 45 g. The residue is largely biphenyl. Small additional amounts of product can be secured by combining these fractions from several runs and refractionating.
15. Without a heated column, the yield drops to 221 g. (54%).

3. Discussion

n-Butylbenzene has been prepared by the action of sodium (*a*) on benzyl chloride or bromide and *n*-propyl bromide without diluents,[1] or (*b*) on *n*-butyl bromide and bromobenzene without a solvent[2] or in benzene;[3] by Clemmensen[4] or Wolff-Kishner[5] reduction of *n*-butyrophenone; by the action of benzylmagnesium chloride on *n*-propyl *p*-toluenesulfonate;[6] and by the action of phenylmagnesium bromide on *n*-butyl bromide or of benzylmagnesium bromide on *n*-propyl bromide in the presence of a trace of ferric chloride.[7] It has also been prepared from benzylsodium and *n*-propyl bromide.[8]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

calcium chloride (10043-52-4)

Benzene (71-43-2)

methanol (67-56-1)

ether (60-29-7)

bromide (24959-67-9)

n-butyl bromide (109-65-9)

n-PROPYL BROMIDE (106-94-5)

sodium (13966-32-0)

benzyl chloride (100-44-7)

bromobenzene (108-86-1)

Biphenyl (92-52-4)

ferric chloride (7705-08-0)

benzylmagnesium chloride (6921-34-2)

Phenylmagnesium bromide (100-58-3)

benzylsodium

Benzene, butyl-, n-BUTYLBENZENE (104-51-8)

benzylmagnesium bromide (1589-82-8)

n-butyrophenone (495-40-9)

n-propyl p-toluenesulfonate (599-91-7)

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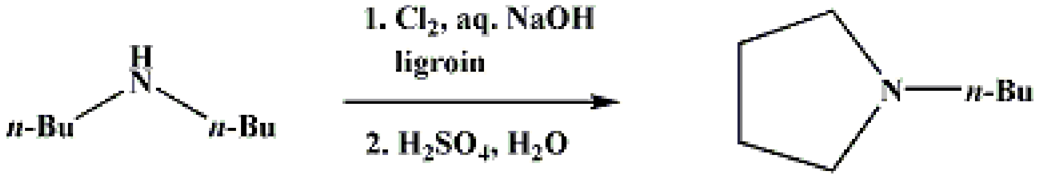
Organic Syntheses, *CV 3, 159*

1-*n*-BUTYLPYRROLIDINE

[Pyrrolidine, 1-butyl-]



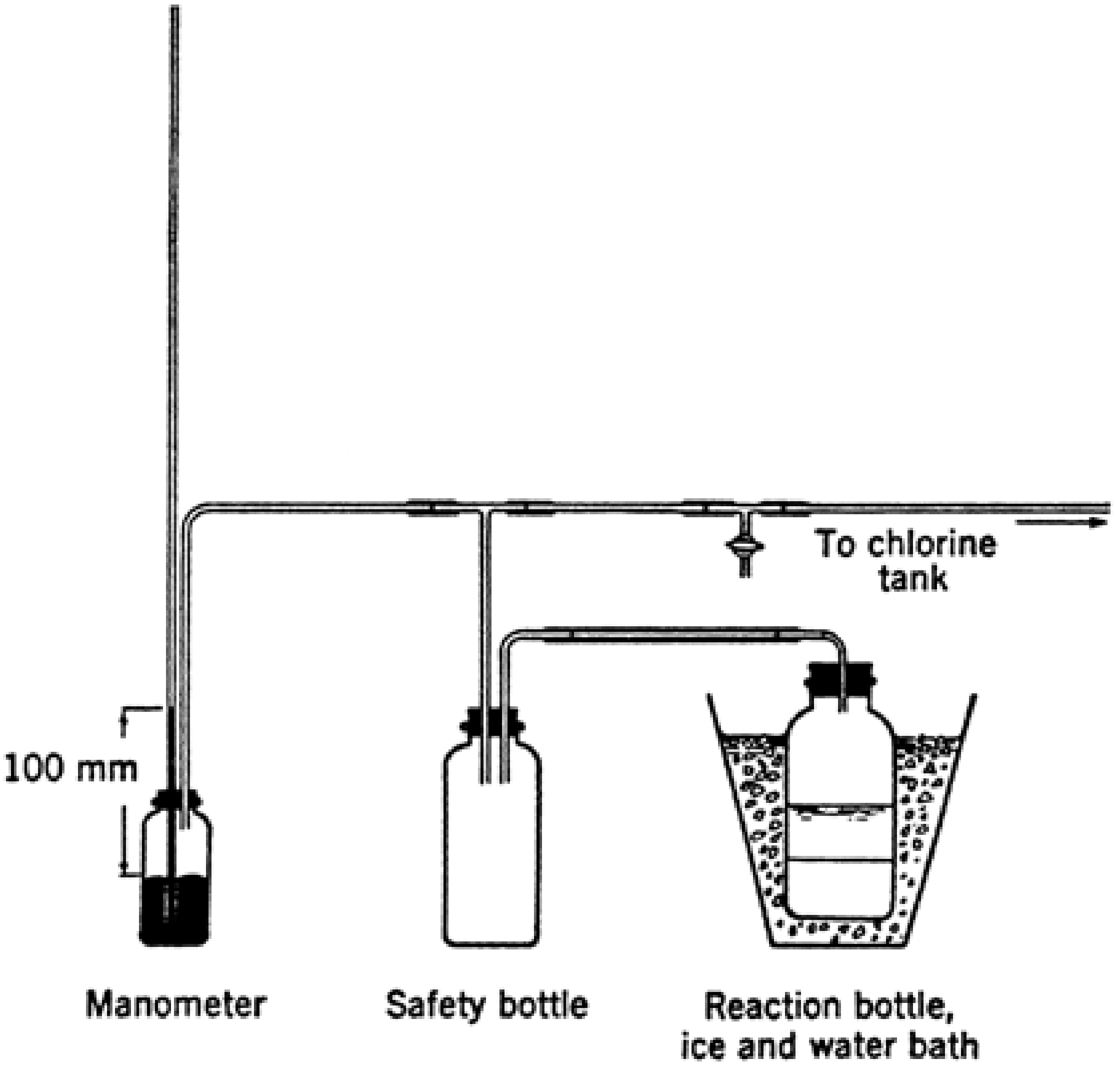
Submitted by George H. Coleman, Gust Nichols, and Ted F. Martens.
Checked by C. F. H. Allen and J. VanAllan.

1. Procedure

This preparation must be carried through the ring closure without interruption.

The apparatus is arranged as in f.htmig. 7. In a bottle of about 1.5-l. capacity are placed 64.5 g. (0.5 mole) of di-*n*-butylamine,[1] 350 ml. of ligroin (Note 1), and 350 ml. of 3 *N* sodium hydroxide (Note 2). The bottle is fitted with an inlet tube which passes only 1 in. through the stopper. The mixture is cooled in an ice bath (Note 3), and chlorine from a cylinder is passed in under pressure (Note 4). The bottle is kept in the ice bath and is shaken during the addition to aid in absorption of the gas. The rate of shaking and the valve on the chlorine cylinder are so regulated that the pressure as indicated on the manometer is maintained between 100 and 150 mm. (Note 5). The addition of the chlorine is continued until the white fumes of the hydrochloride, which form when chlorine comes in contact with the amine vapor, disappear, and the non-aqueous layer takes on a greenish yellow color, due to a slight excess of chlorine. This indicates that chlorination is complete (Note 6).

Fig. 7.



The ligroin solution of the chloramine is separated from the aqueous layer in a chilled, short-stemmed 1-l. separatory funnel and washed successively with 50 ml. of ice-cold 3 *N* sodium hydroxide (Note 7), 50 ml. of ice water, and 50 ml. of cold 2 *N* sulfuric acid. The ligroin solution becomes nearly colorless. The chloramine is extracted from the solution with sulfuric acid in the following manner. An ice-cold mixture of 200 ml. of concentrated sulfuric acid (sp. gr. 1.84) and 80 ml. of water is allowed to stand in contact with the ligroin solution for 10 minutes *without* shaking, then for 20 minutes *with* occasional shaking; the mixture is kept cool by immersion in an ice bath. After separation from the acid layer, the ligroin is extracted with two 60-ml. portions of cold concentrated sulfuric acid. The combined sulfuric acid extracts are used for ring closure (Note 8). The ligroin, which contains not more than a trace of chloramine, is discarded.

A 1-l. wide-mouthed Erlenmeyer flask, fitted with a propeller-type stirrer and a thermometer, is set in an oil bath. A mixture of 40 ml. of concentrated sulfuric acid and 10 ml. of water is placed in the flask, the oil bath is heated to 120°, and the cold sulfuric acid solution of the chloramine is allowed to flow into the heated acid from the short-stemmed separatory funnel (Note 9). The addition, which requires 30–40 minutes (Note 10), is carried out at such a rate that the temperature of the reaction

mixture in the flask is dropped from 120° rapidly to 95° by the addition of the cold chloramine solution, and thereafter at such a rate that the temperature of the reaction mixture remains at 90–100°, preferably at 95°. The reaction is exothermic, and the rise in temperature is controlled by the addition of the cold chloramine solution. To avoid an undue rise in temperature after the last addition of the chloramine, the oil bath is removed, and the flask and contents are allowed to come to room temperature.

A 5-l. flask is fitted with a separatory funnel and arranged for steam distillation (p. 64). Two liters of crushed ice is placed in the flask, and the sulfuric acid solution, cooled to 0°, is slowly added. The amines are then liberated (Note 11) by adding cold concentrated sodium hydroxide solution (650 g. in 1.5 l. of water) through the separatory funnel. The amines are steam-distilled and collected in a solution of 100 ml. of concentrated hydrochloric acid (sp. gr. 1.19) and 200 ml. of water (Note 12). Distillation is continued until all amine has passed over, as indicated by a negative test with litmus paper. About 2 l. of distillate is usually required.

The amine hydrochloride solution is evaporated nearly to dryness on a steam bath (Note 13) and transferred with about 300 ml. of water to a 1-l. three-necked flask equipped with a stirrer,[2] separatory funnel, and condenser. The stirrer is started, and the acid solution is cooled to 0° by immersing the flask in an ice bath. The amines are liberated by adding slowly 100 g. of sodium hydroxide dissolved in 250 ml. of water.

Hinsberg separation. To this solution, which should be cold (5–8°), is now added 23 g. of benzenesulfonyl chloride,[3] and the mixture is stirred vigorously for 30 minutes. The separatory funnel is replaced by a stopper bearing a thermometer, and the contents of the flask are warmed to 40° and stirred until the odor of the acid chloride is no longer noticeable. This usually requires about 30 minutes. The 1-*n*-butylpyrrolidine is separated (Note 14) from the non-volatile di-*n*-butylbenzenesulfonamide by steam distillation, the amine being collected in dilute acid (Note 12) as before. The acid solution is then evaporated to dryness, and the amine is liberated by adding 20% sodium hydroxide solution until the aqueous layer turns red litmus blue. The amine is extracted by one 200-ml. portion of ether, and the ethereal solution is dried over 15–20 pellets of potassium hydroxide. After the ether has been distilled from the decanted solution, the residue is distilled from an oil bath. The yield of 1-*n*-butylpyrrolidine boiling at 154–155°/758 mm. is 44–51 g. (70–80%); n_D^{27} 1.437 (Note 15).

2. Notes

1. Any fraction boiling within the range 60–90° may be used.
2. This is obtained by dissolving 42 g. of sodium hydroxide in 350 ml. of water.
3. All equipment, the solutions, and the chloramine solution should be kept ice-cold to prevent decomposition during the preparation. Apparatus may be stored in a refrigerator.
4. As the addition of chlorine is started, the stopper in the reaction bottle is loosened momentarily and the chlorine is allowed to replace most of the air in

the system.
5. As the chlorine passes initially into the bottle, the pressure rises rapidly. Shaking greatly increases the rate of absorption, and the pressure drops. The chlorine valve is then regulated so as to maintain the proper pressure with shaking. One hundred millimeters was selected as the approximate pressure, since the rate of chlorination under this pressure is satisfactory.
6. A large excess of chlorine is undesirable and may result in greatly decreased yields. The time required varies widely, being dependent upon the chlorine pressure maintained and the vigor of the shaking. The checkers found that 20 minutes was ample under their conditions; the submitters reported that 1–1.5 hours was required.
7. If the green color, due to excess chlorine, is not removed by one washing, the operation is repeated as many times as may be necessary.
8. The sulfuric acid layers are transferred directly into the 500-ml. short-stemmed separatory funnel to be used in the next step. The solution, which usually has a light brown color, should be cold and well mixed before the ring-closure operation. The ratio of acid to water is important, and only the amounts specified should be used.
9. The funnel and contents may be supported over the reaction flask during the addition without cooling.
10. The rate of addition should be as rapid as possible provided that the proper temperature is maintained. Deviation of more than 5° from the optimum reaction temperature of 95° results in reduced yields.
11. This reaction is vigorous, and the solution of alkali should be added slowly while the flask is shaken gently with a rotary motion.
12. An adapter (rubber connector and glass tube) from the lower end of the condenser should extend below the surface of the absorbing acid in the receiver. To reduce fuming, a 3- to 4-mm. layer of ligroin is placed over the acid solution. The acid solution may be stirred occasionally.
13. Use of reduced pressure considerably diminishes the time required.
14. The amine can be separated from the sulfonamide by extracting both with ether, drying this extract over solid potassium hydroxide, and fractionating. The pyrrolidine distils smoothly, but the yield is slightly lower.
15. Several other pyrrolidines of this series can be prepared by the same general method. The temperature required for ring closure and the percentage yield of pyrrolidine vary with the different amines used. The tabulated temperatures are given as approximately correct for the ring closure of the N-chloro-derivatives of the amines listed. With lower-boiling pyrrolidines, incomplete separation from the ether may result in lower yields.

Amine	*Optimum Temperature, °C*	*Pyrrolidine Formed*
Methyl-*n*-butyl	100–110	1-Methylpyrrolidine
Ethyl-*n*-butyl	110–115	1-Ethylpyrrolidine

n-Propyl-*n*-butyl	80–85	1-*n*-Propylpyrrolidine
Methyl-*n*-amyl	90–100	1,2-Dimethylpyrrolidine
Ethyl-*n*-amyl	80–90	1-Ethyl-2-methylpyrrolidine
Methyl-*n*-octyl	60–70	1-Methyl-2-*n*-butylpyrrolidine

3. Discussion

1-*n*-Butylpyrrolidine has been prepared by heating the corresponding N-bromoamine in concentrated sulfuric acid;[4] by catalytic reduction of N-butylpyrrole;[5] from furan and *n*-butylamine in the presence of aluminum oxide at 350–450°;[6] from 1,4-dichlorobutane and *n*-butylamine with potassium carbonate.[7] The procedure described is adapted from a preparation reported earlier.[8]

References and Notes

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4. Britton, U. S. pat. 1,607,605 [*C. A.*, **21**, 249 (1927)].
5. Ochiai, Tsude, and Yokoyama, *Ber.*, **68**, 2293 (1935).
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7. Elderfield and Hageman, *J. Org. Chem.*, **14**, 605 (1949).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ligroin

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium hydroxide (1310-73-2)

Benzenesulfonyl chloride (98-09-9)

chlorine (7782-50-5)

potassium hydroxide (1310-58-3)

Furan (110-00-9)

aluminum oxide (1344-28-1)

1,4-dichlorobutane (110-56-5)

Pyrrolidine, 1-butyl-, 1-n-BUTYLPYRROLIDINE (767-10-2)

pyrrolidine (123-75-1)

1-Methylpyrrolidine (120-94-5)

1-Ethylpyrrolidine (7335-06-0)

1,2-Dimethylpyrrolidine

1-Ethyl-2-methylpyrrolidine

N-bromoamine

N-butylpyrrole (589-33-3)

n-Propyl-n-butylamine (20193-21-9)

n-butylamine (109-73-9)

di-n-butylamine (111-92-2)

Methyl-n-butylamine (110-68-9)

Methyl-n-amylamine (25419-06-1)

Ethyl-n-butylamine (13360-63-9)

Ethyl-n-amylamine

di-n-butylbenzenesulfonamide (5339-59-3)

1-n-Propylpyrrolidine

1-Methyl-2-n-butylpyrrolidine

di-n-butylchloramine

Methyl-n-octylamine

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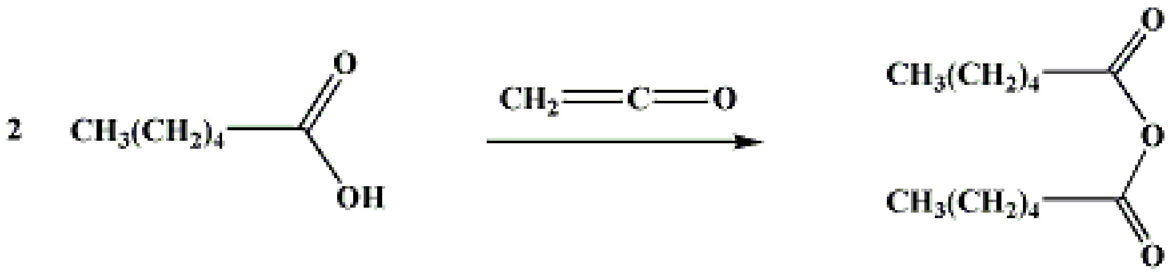
Organic Syntheses, CV 3, 164

n-CAPROIC ANHYDRIDE



Submitted by Jonathan W. Williams and John A. Krynitsky.
Checked by Nathan L. Drake and Joseph Lann.

1. Procedure

One hundred and sixteen grams (126 ml., 1 mole) of *n*-caproic acid is placed in a 250-ml. gas-washing bottle. The bottle is supported in an ice bath, and 0.50 to 0.55 mole of ketene is passed into the acid at a rate of approximately 0.45 mole per hour (Note 1) and (Note 2).

The resulting mixture is transferred to an apparatus for fractional distillation, and carefully fractionated, an oil bath being used for heating (Note 3). A low-boiling fraction, consisting of acetone containing some ketene, acetic acid, and a small quantity of acetic anhydride, is removed at atmospheric pressure. As the distillation progresses the temperature of the oil bath is raised to 220° over a period of about 1 hour and held there until 3 hours has elapsed from the time distillation started (Note 4).

The distillation at atmospheric pressure is then discontinued, the liquid is allowed to cool somewhat, and distillation is continued at a pressure of 3–10 mm. After a fore-run of less than 20 g., *n*-caproic anhydride is collected (b.p. 109–112°/3 mm., 118–121°/6 mm.). The yield is 86–95 g. (80–87%) (Note 5).

2. Notes

1. Ketene may be generated conveniently, at the proper rate, in the apparatus described by Williams and Hurd.[1]
2. Addition of 1 mole of ketene per mole of acid does not increase the yield. Under these conditions more acetic anhydride is found in the low-boiling fraction.
3. Submitters and checkers used a column of the Whitmore-Lux type,[2] 12 mm. in diameter, 50 cm. long, packed with glass helices, and provided with the usual jackets for heating. A less efficient column will serve in the preparation of caproic anhydride but not in the preparation of propionic anhydride or butyric anhydride by the same method.

4. It is imperative to continue the distillation at atmospheric pressure until conversion of any mixed anhydride to caproic anhydride is complete. The acetic acid formed by this conversion comes off very slowly, and approximately 3 hours is necessary to complete the distillation at atmospheric pressure.
5. According to the submitters, equally good yields can be obtained in the preparation of propionic anhydride and *n*-butyric anhydride.

3. Discussion

n-Caproic anhydride has been prepared by heating caproic acid with acetic anhydride,[3] by heating sodium caproate and acetic anhydride in a sealed tube,[4] by the action of phosphorus oxychloride on barium caproate,[5] by the action of acetyl chloride on caproic acid,[6] and by treating a mixture of sodium caproate and sulfur with chlorine.[7] The method used in the present synthesis was first described by Hurd and Dull.[8]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 176
- Org. Syn. Coll. Vol. 3, 181

References and Notes

1. Williams and Hurd, *J. Org. Chem.*, **5**, 122 (1940).
2. Whitmore and Lux, *J. Am. Chem Soc.*, **54**, 3451 (1932).
3. Autenrieth, *Ber.*, **34**, 168 (1901).
4. Michael, *Ber.*, **34**, 918 (1901).
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6. Fournier, *Bull. soc. chim. France*, (4), **5**, 920 (1909).
7. Brit. pat. 24,842 (1908) [*C. A.*, **4**, 2190, 2719 (1910)].
8. Hurd and Dull, *J. Am. Chem. Soc.*, **54**, 3427 (1932).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

acetic acid (64-19-7)

acetic anhydride (108-24-7)

acetyl chloride (75-36-5)

sulfur (7704-34-9)

acetone (67-64-1)

Phosphorus Oxychloride (21295-50-1)

chlorine (7782-50-5)

Caproic acid, n-caproic acid (142-62-1)

butyric anhydride, n-butyric anhydride (106-31-0)

Ketene (463-51-4)

propionic anhydride (123-62-6)

caproic anhydride, n-CAPROIC ANHYDRIDE (2051-49-2)

sodium caproate (10051-44-2)

barium caproate

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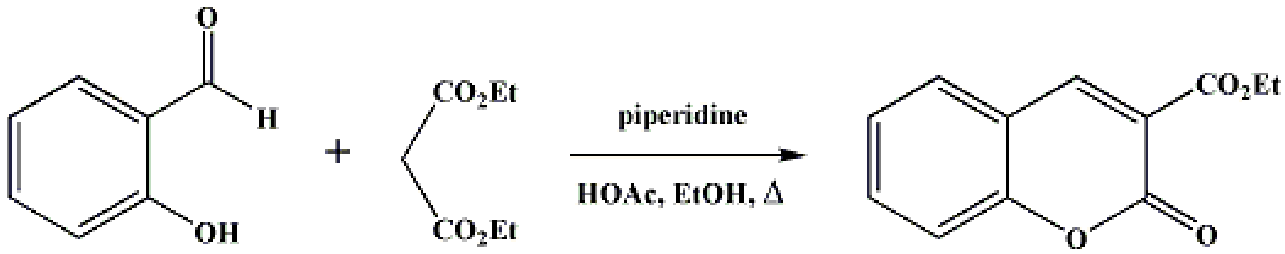
Organic Syntheses, CV 3, 165

3-CARBETHOXYCOUMARIN

[2H-1-Benzopyran-3-carboxylic acid, 2-oxo-, ethyl ester]



Submitted by E. C. Horning, M. G. Horning, and D. A. Dimmig.
Checked by Richard T. Arnold and Marshall Freerks.

1. Procedure

In a 500-ml. round-bottomed flask equipped with a reflux condenser are placed 61 g. (0.50 mole) of salicylaldehyde (Note 1), 88 g. (0.55 mole) of ethyl malonate, and 200 ml. of absolute ethanol. To this mixture are added 5 ml. of piperidine (Note 2) and 0.5 ml. of glacial acetic acid, and the solution is heated under reflux for 3 hours. The hot solution is transferred to a 1-l. Erlenmeyer flask, the reaction flask is rinsed with 20 ml. of ethanol, and the ethanol rinse and 330 ml. of hot water (Note 3) are added to the solution. The product crystallizes readily as the solution cools; the mixture is stirred from time to time as crystallization proceeds and is finally stored overnight in a refrigerator. The crystalline product is collected by filtration and washed with a solution made from 80 ml. of 95% ethanol and 120 ml. of water. The material is dried in the air. The yield is 85–91 g. (78–83%) of product melting at 91–93°.

The product may be recrystallized by dissolving it in 200 ml. of hot ethanol (95%), filtering, and adding 315 ml. of hot water. The recrystallized product is washed on the filter with 200 ml. of aqueous ethanol, as before, and air-dried. The yield of white 3-carbethoxycoumarin is 79–85 g. (73–78%); m.p. 92–94°.

2. Notes

1. The yield of the final product (m.p. 92–94°) may be increased to 80–84% by the use of salicylaldehyde purified in the following manner.

Preparation of pure salicylaldehyde.[1] Two hundred and fifty grams (1 mole) of copper sulfate pentahydrate is dissolved in 500 ml. of hot water in a 1-l. Erlenmeyer flask, and 244 g. (2 moles) of salicylaldehyde (Eastman practical grade) is added. A solution of 80 g. (2 moles) of sodium hydroxide in 100 ml. of water is added slowly in small portions with intermittent vigorous shaking. The mixture is permitted to cool slowly to room temperature with intermittent shaking and is finally allowed to stand overnight. The solid is collected and washed with 200 ml. of ethanol (95%), digested with 400 ml. of ether, and again collected on a filter. Without drying, the product is treated with 1 l. of water containing 108.5 g. (59 ml., 105 moles) of 95% sulfuric acid. The mixture is shaken vigorously, and 200 ml. of ether is added to break up the oily mass that forms. The aldehyde is collected in ether and recovered by distillation of the dried (over calcium sulfate) solution. It distils at 96–97°/35 mm.; the recovery is 90%.

2. Eastman practical grade is satisfactory.
3. The water should be heated to about 60°.

3. Discussion

This compound has been prepared only by the Knoevenagel[2] condensation, with a secondary amine as a catalytic agent. The corresponding methyl ester and free acid have also been prepared by using methyl malonate[3] and malonic acid,[4] respectively, in the condensation with salicylaldehyde.

References and Notes

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2. Knoevenagel, *Ber.*, **31**, 2593 (1898).
3. Werder, *Jahresber.*, **50**, 88 (1936).
4. U. S. pat. 2,338,569 [*C. A.*, **38**, 3671 (1944)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

ether (60-29-7)

sodium hydroxide (1310-73-2)

calcium sulfate (7778-18-9)

piperidine (110-89-4)

Salicylaldehyde (90-02-8)

ethyl malonate (1071-46-1)

Malonic acid (141-82-2)

methyl malonate

3-Carbethoxycoumarin, 2H-1-Benzopyran-3-carboxylic acid, 2-oxo-, ethyl ester (1846-76-0)

copper sulfate pentahydrate (7758-99-8)

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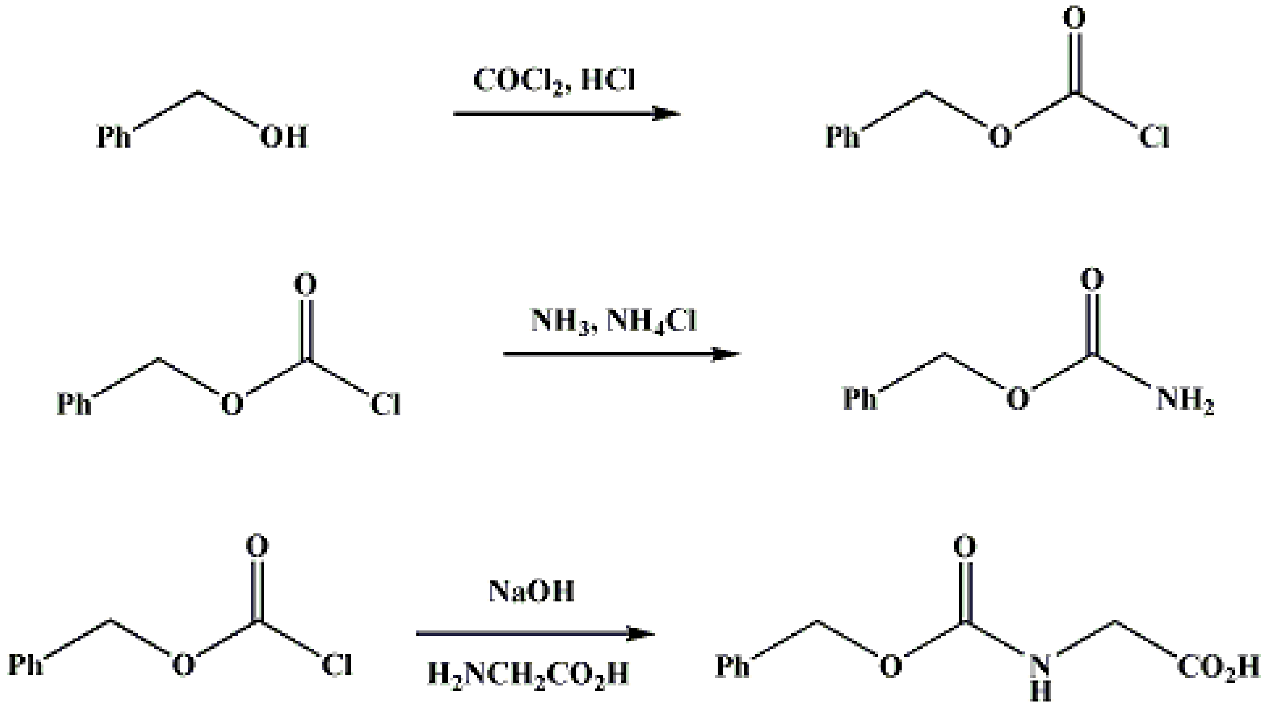
CARBOBENZOXY CHLORIDE AND DERIVATIVES

[Formic acid, chloro-, benzyl ester]



Submitted by H. E. Carter, R. L. Frank, and H. W. Johnston.
Checked by Nathan L. Drake and Charles M. Eaker.

1. Procedure

Caution! This procedure should be carried out in a hood.

A. *Benzyl chloroformate*. A 3-l. round-bottomed flask is fitted with a rubber stopper carrying an exit tube and a delivery tube extending to the bottom of the flask. The tubes are equipped with stopcocks so that the reaction flask may be disconnected. In the flask is placed 500 g. of dry toluene (Note 1), and the apparatus is weighed. The flask is then cooled in an ice bath, and phosgene (Note 2) is bubbled into the toluene until 109 g. (1.1 moles) has been absorbed (Note 3). The exit gases are passed through a flask containing toluene to remove any phosgene and then through a calcium chloride tube to a gas trap.

After the absorption of phosgene is completed the connection to the phosgene tank is replaced by a separatory funnel. The reaction flask is gently shaken while 108 g. (104 ml., 1 mole) of redistilled benzyl alcohol is added rapidly through the separatory funnel. The flask is allowed to stand in the ice bath for 30 minutes and at room temperature for 2 hours. The solution is then concentrated under reduced pressure, at a temperature not exceeding 60°, in order to remove hydrogen chloride, excess phosgene (Note 4), and the major portion of the toluene. The residue weighs 200–220 g. and contains 155–160 g. of benzyl chloroformate (91–94% based on the benzyl alcohol) (Note 5). The amount of

benzyl chloroformate present in this solution may be estimated by preparing the amide from a small aliquot portion, or it may be safely calculated by assuming a minimum yield of 90% based on the benzyl alcohol used.

B. *Benzyl carbamate*. A measured aliquot (suitably 10 ml.) of the solution of benzyl chloroformate, prepared as described above, is added slowly and with vigorous stirring to 5 volumes of cold concentrated ammonium hydroxide (sp. gr. 0.90), and the reaction mixture is allowed to stand at room temperature for 30 minutes. The precipitate is filtered with suction, washed with cold water, and dried in a vacuum desiccator. The yield of practically pure benzyl carbamate, melting at 85–86°, is 7.0–7.2 g. (91–94% based on the benzyl alcohol used in A). Pure benzyl carbamate melting at 87° is obtained by recrystallizing the slightly impure material from 2 volumes of toluene.

C. *Carbobenzoxyglycine*. A solution of 7.5 g. (0.1 mole) of glycine in 50 ml. of 2 *N* sodium hydroxide is placed in a 200-ml. three-necked flask fitted with a mechanical stirrer and two dropping funnels. The flask is cooled in an, ice bath, and 17 g. (0.1 mole) of benzyl chloroformate (21–24 g. of the solution obtained in A) and 25 ml. of 4 *N* sodium hydroxide are added simultaneously to the vigorously stirred solution over a period of 20–25 minutes. The mixture is stirred for an additional 10 minutes. The toluene layer is separated, and the aqueous layer is extracted once with ether. The aqueous solution is cooled in an ice bath and acidified to Congo red with concentrated hydrochloric acid (Note 6). The precipitate is filtered, washed with small portions of cold water, and dried in the air. It is practically pure carbobenzoxyglycine; it weighs 18–19 g. (86–91%) and melts at 119–120°. The material may be recrystallized from chloroform; it then melts at 120° (Note 7).

2. Notes

1. The toluene may be dried by distillation.
2. Commercial phosgene was used; it was obtained in a tank from the Ohio Chemical Company.
3. The phosgene is absorbed rapidly for some time, then more slowly as the concentration increases. About 1 hour is required for this step. The amount of phosgene absorbed is checked by weighing the flask and delivery tubes occasionally.
4. In order to prevent the escape of phosgene, a toluene trap is inserted between the apparatus and the water pump. For this purpose it is convenient to use a 2-l. flask immersed in an ice bath and containing about 1 l. of toluene. The flask is fitted with an inlet tube reaching almost to the bottom.
5. It is not practical to remove the toluene completely; moreover, toluene does not interfere in the preparation of the derivatives.
6. The derivative may precipitate as an oil. However, crystallization is readily induced by cooling and scratching.
7. Carbobenzoxyalanine (m.p. 114–115°) is obtained in 80–90% yield from alanine and benzyl chloroformate by the same procedure.

3. Discussion

Benzyl chloroformate has been prepared by action of phosgene on benzyl alcohol.[1,2,3] The methods described here for the preparation of benzyl chloroformate and the carbobenzoxy derivatives of glycine and alanine are essentially those of Bergmann and Zervas.[2] The carbobenzoxy derivatives of other amino acids are conveniently prepared in the same way. Benzyl carbamate has been prepared by the action of ammonia on benzyl chloroformate.[1,4] The present method is that of Martell and Herbst.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 788

References and Notes

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2. Bergmann and Zervas, *Ber.*, **65**, 1192 (1932).
3. Farthing, *J. Chem. Soc.*, **1950**, 3213.
4. Martell and Herbst, *J. Org. Chem.*, **6**, 882 (1941).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

carbobenzoxy derivatives of glycine

hydrogen chloride, hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ether (60-29-7)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

alanine (56-41-7)

toluene (108-88-3)

phosgene (75-44-5)

Benzyl alcohol (100-51-6)

ammonium hydroxide (1336-21-6)

Glycine (513-29-1)

Carbobenzoxy chloride, Formic acid, chloro-, benzyl ester, benzyl chloroformate (501-53-1)

Benzyl carbamate (621-84-1)

carbobenzoxyglycine (1138-80-3)

Carbobenzoxyalanine

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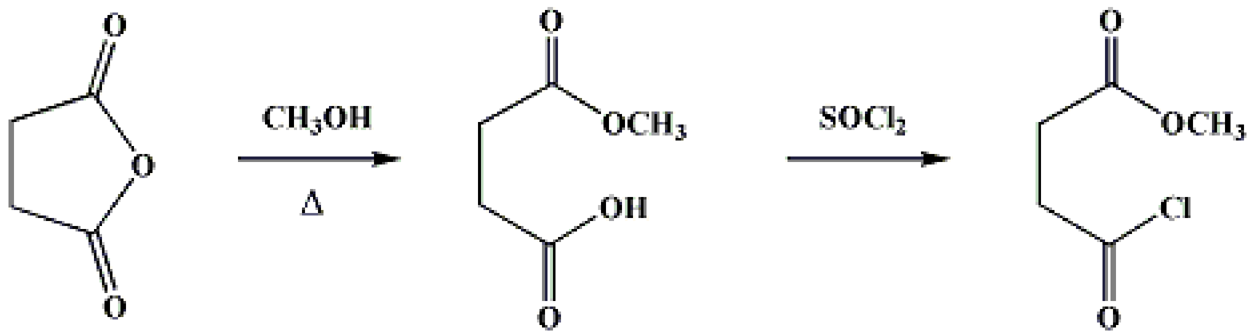
β-CARBOMETHOXYPROPIONYL CHLORIDE

[Propionic acid, β-(chloroformyl)-, methyl ester]



Submitted by James Cason
Checked by C. F. H. Allen and C. V. Wilson.

1. Procedure

A. *Methyl hydrogen succinate*. A mixture of 400 g. (4 moles) of succinic anhydride (Note 1) and 194 ml. (4.8 moles) of methanol (Note 2) in a 1-l. round-bottomed flask is refluxed on a steam bath. After about 35 minutes the mixture is swirled frequently until it becomes homogeneous (this requires 15–30 minutes); the flask is then half immersed in the steam bath for an additional 30–25 minutes (Note 3).

The excess methanol is removed by distillation under reduced pressure (water pump) from a steam bath, and the residual liquid is poured into an 18- to 25-cm. evaporating dish which is cooled in a shallow pan of cold water. As the half ester crystallizes, it is stirred and scraped off the dish in order to prevent formation of a solid cake. After being dried to constant weight in a vacuum desiccator (5–8 days), the product weighs 502–507 g. (95–96%) and melts at 57–58° (Note 4) and (Note 5).

B. *β-Carbomethoxypropionyl chloride*. In a 1-l. flask (Note 6) bearing a reflux condenser are placed 264 g. (2 moles) of methyl hydrogen succinate and 290 ml. (4 moles) of thionyl chloride (Note 7), and the solution is warmed in a bath at 30–40° for 3 hours (Note 8). The condenser is replaced by a modified Claisen still head, the excess thionyl chloride is removed on a steam bath under reduced pressure, and the β-carbomethoxypropionyl chloride is distilled (Note 9) and (Note 10). The yield of colorless product is 270–278 g. (90–93%), b.p. 92–93°/18 mm. (Note 11) and (Note 12).

2. Notes

1. Eastman's succinic anhydride (m.p. 115–116°) was used.
2. Synthetic methanol was used. Since this anhydrous alcohol is hygroscopic,

partly filled bottles that have been opened intermittently in the laboratory should be rejected.

3. Thirty minutes is allowed if solution resulted after 15 minutes of swirling; 25 minutes if 30 minutes was needed for homogeneity.

The time factor is very important. In one run in which the mixture was heated for a total of 55 minutes, a product was obtained which was shown by titration to contain about 6% of anhydride. Longer heating than that specified increases the yield of diester. Any change in quantity of materials used may necessitate a new set of conditions in order to obtain the maximum yield.

4. The checkers prefer the following procedure, which can be carried through in one day. A suspension of approximately one-half of the crude product in 750 ml. of carbon disulfide is warmed on a steam bath; two layers form, in which some solid remains in suspension. This is dissolved by the addition of 350 ml. of ether. The whole is chilled to 0°, and the solid is filtered by suction. The other half of the crude product is now dissolved in this filtrate, the solution is again chilled to 0°, and the solid is filtered. The combined yield of acid ester, m.p. 57–58°, is 438–449 g. (83–85%). A further 32–37 g. (6–7%) of less pure material (m.p. 56–57°) can be obtained by concentrating the filtrate to half its volume and chilling to 0°.

5. The product, which is sufficiently pure for the next step, contains at least 98% methyl hydrogen succinate as shown by titration or distillation through an 18-in. Podbielniak-type column.

6. Equipment with ground-glass joints is used throughout.

7. Eastman's thionyl chloride (b.p. 75–76°) was used. The checkers obtained equivalent yields of the chloride by using only 20% excess of thionyl chloride. The mixture was heated for 1 hour at 40°, allowed to stand overnight, and heated again for 2 hours at 40°.

8. Since hydrogen chloride is evolved, it is advisable to work in a hood or employ a gas trap.

9. An electric heating mantle is convenient.

10. Other boiling points are 85.5–87°/13 mm. and 89–90°/15 mm. The use of as low a pressure as possible is advisable, since the substance tends to lose methyl chloride and form succinic anhydride.

11. The submitter obtained the same yield when phosphorus pentachloride was used instead of thionyl chloride. Consistent results were obtained with the former reagent only when the acid chloride was distilled at pressures below 3 mm. (b.p. 58–59°/2.5 mm.).

12. Methyl hydrogen glutarate, ethyl hydrogen adipate, and ethyl hydrogen sebacate may be converted to the corresponding ester acid chlorides by this procedure in about the same yields. Distillation should be carried out rapidly at a pressure of 4 mm. or lower.

3. Discussion

Methyl hydrogen succinate has been prepared by heating succinic acid with methyl succinate,[1] by treating ethyl succinate with sodium methoxide,[2] and by heating

succinic anhydride with methanol.[3,4,5,6]

β-Carbomethoxypropionyl chloride has been prepared from methyl hydrogen succinate by the use of thionyl chloride[4,6] or phosphorus pentachloride.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 601
- Org. Syn. Coll. Vol. 3, 613

References and Notes

1. Fourneau and Sabetay, *Bull. soc. chim. France*, (4) **45**, 841 (1929).
2. Komnenos, *Monatsh.*, **32**, 77 (1911).
3. Bone, Sudborough, and Sprankling, *J. Chem. Soc.*, **85**, 539 (1904).
4. Nenitzescu, Cioranescu, and Przemetsky, *Ber.*, **73B**, 313 (1940).
5. Cason, *J. Am. Chem. Soc.*, **64**, 1106 (1942).
6. Ruggli and Maeder, *Helv. Chim. Acta*, **25**, 936 (1942).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrogen chloride (7647-01-0)

methanol (67-56-1)

ether (60-29-7)

phosphorus pentachloride (10026-13-8)

thionyl chloride (7719-09-7)

ethyl succinate

Ethyl hydrogen adipate (626-86-8)

methyl chloride (74-87-3)

Succinic acid (110-15-6)

sodium methoxide (124-41-4)

carbon disulfide (75-15-0)

Succinic anhydride (108-30-5)

Ethyl hydrogen sebacate (693-55-0)

β-Carbomethoxypropionyl chloride, Propionic acid, β-(chloroformyl)-, methyl ester (1490-25-1)

Methyl hydrogen succinate, methyl succinate (3878-55-5)

Methyl hydrogen glutarate (1501-27-5)

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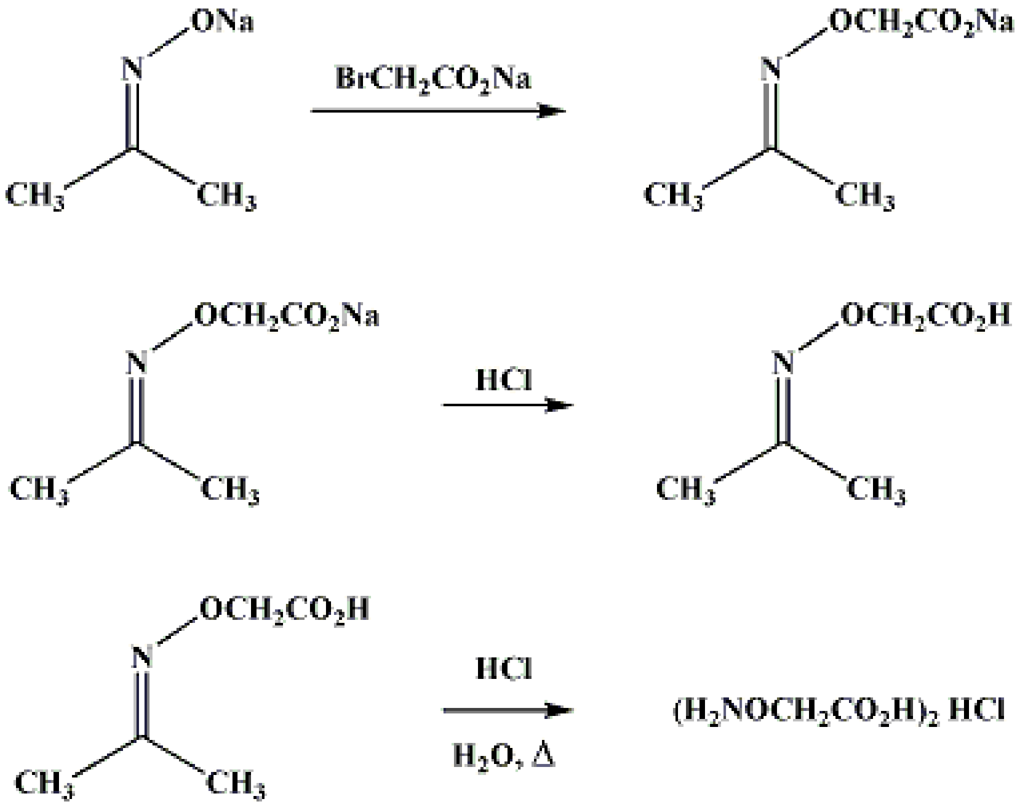
CARBOXYMETHOXYLAMINE HEMIHYDROCHLORIDE

[Acetic acid, aminoöxy-, hydrochloride]



Submitted by H. S. Anker and H. T. Clarke.
Checked by H. R. Snyder and Peter Kovacic.

1. Procedure

A. *Acetone carboxymethoxime*. A mixture of 612 g. (4.4 moles) of bromoacetic acid (Note 1) and 500 g. of crushed ice is chilled in an ice-salt bath and made distinctly alkaline to litmus with sodium hydroxide (about 440 g. of a 40% solution). During the neutralization an additional 500 g. of ice is added. To the solution are then added 292 g. (4.0 moles) of acetoxime[1] and 440 g. of 40% sodium hydroxide (4.4 moles), the temperature being held below 20° during the addition of the alkali. The mixture is then allowed to flow dropwise, during 3–4 hours, through the inner tube of a steam-heated Liebig condenser (jacket 75 cm. long; inner tube 10-mm. diameter; angle of inclination about 20°) into a 5-l. round-bottomed flask cooled with running water (Note 2). The resulting solution is extracted three times with 500-ml. quantities of freshly distilled peroxide-free ether (Note 3), and the aqueous solution is then cooled and made strongly acid by the addition of 500 ml. of concentrated hydrochloric acid (6 moles). During the acidification the temperature should not rise above 15°. The solution is saturated with sodium chloride and immediately extracted with six

successive 1.5-l. portions of peroxide-free ether. The ether is distilled from the combined ethereal extracts, and the residue, consisting of the crude acetone carboxymethoxime (333–345 g.), is used for the next step. The acetone carboxymethoxime may be purified by distillation under reduced pressure, the fraction boiling at 95–97°/1 mm. (Note 4) being collected (Note 5). The yield is 300 g. (57%) of a colorless product melting at 76°.

B. *Carboxymethoxylamine hemihydrochloride*. The crude acetone carboxymethoxime is dissolved in about twice its weight of benzene; the solution is filtered and freed of benzene by distillation under reduced pressure from a steam bath. To a solution of 200 g. (1.52 moles) of the residue in 1 l. of water, in a 5-l. flask, are added 2 mg. of hydroquinone and 1 l. of concentrated hydrochloric acid. The flask is connected with a condenser, and steam is passed through the solution until acetone no longer comes over (30–40 minutes). The solution is concentrated under reduced pressure to a volume of 180–220 ml., and 400 ml. of isopropyl alcohol is added. The solution is then stored for 12 hours in the icebox, and the crystals that separate are collected on a Büchner funnel and washed with cold isopropyl alcohol. Further crops are obtained by concentrating the mother liquors and adding isopropyl alcohol. The crude product (120–135 g.) may be recrystallized (Note 6) with very little loss by dissolving it in twice its weight of warm (50°) water (Note 7), adding 2 volumes of isopropyl alcohol, and again chilling in an icebox. Further small quantities can be recovered from the mother liquors by systematic repetition of the process described. The yield is 110–120 g. (66–72%) of white crystals which melt with decomposition at 152–153° (Note 8) and (Note 9).

2. Notes

1. Chloroacetic acid gives a poorer yield (46–49%) of acetone carboxymethoxime, and the crude product is more difficult to purify.[2]
2. By this procedure, the reaction takes place in a few seconds, and the formation of by-products is minimized. If the solution of the reactants is heated in bulk, the reaction temperature cannot be controlled, and a lower yield is obtained of a dark product which, however, can be purified by distillation under reduced pressure.
3. The unchanged acetoxime extracted by the ether amounts to 14–24 g. (5–8%).
4. The temperature of the vapor, during distillation under apparently comparable conditions, may differ from run to run by as much as 20°. The temperature range of 95–97° is the lowest observed for 1-mm. pressure. Boiling ranges of 110–118°/1 mm. have been reported.
5. No carbonization and only slight formation of hydrogen cyanide, which occurs extensively during the distillation of preparations from chloroacetic acid,[2] are observed.
6. The use of decolorizing carbon should be avoided, as some brands appear to contain impurities that catalyze decomposition to ammonium chloride.
7. If the resulting aqueous solution is cooled to 0° before the addition of

isopropyl alcohol, about one-third of the product crystallizes in very pure form.
8. The melting point depends on the rate at which the sample is heated. When the temperature is raised in the ordinary way the material melts (with evolution of gas) at 152–153°; when the bath is heated to 150° before the sample is inserted, the melting point is 159°. On the other hand, when a sample is held between 140° and 145° it melts after about 6 minutes. Decomposition evidently plays a large part in the matter.
9. The hydrolysis of acetone carboxymethoxime may also be accomplished on a smaller scale (10 g.) by a simplified procedure as described by Lott.[3]

3. Discussion

Carboxymethoxylamine (also called hydroxylamine-O-acetic acid), which is of value for the isolation of ketones,[4] has been prepared by the hydrolysis of ethylbenzhydroximinoacetic acid[5] and of ethyl benzhydroximinoacetate.[6] The present method is a modification of that described by Borek and Clarke.[2]

References and Notes

1. *Org. Syntheses* Coll. Vol. **1**, 318 (1941).
2. Borek and Clarke, *J. Am. Chem. Soc.*, **58**, 2020 (1936).
3. Lott, *J. Am. Chem. Soc.*, **70**, 1972 (1948).
4. Anchel and Schoenheimer, *J. Biol. Chem.*, **114**, 539 (1936).
5. Werner, *Ber.*, **26**, 1567 (1893); Werner and Sounenfeld, *Ber.*, **27**, 3350 (1894).
6. Kitagawa and Takani, *J. Biochem. Japan*, **23**, 181 (1936).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Carboxymethoxylamine hemihydrochloride

Acetone carboxymethoxime

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether (60-29-7)

ammonium chloride (12125-02-9)

sodium hydroxide (1310-73-2)

hydroquinone (123-31-9)

sodium chloride (7647-14-5)

hydrogen cyanide (74-90-8)

chloroacetic acid (79-11-8)

acetone (67-64-1)

decolorizing carbon (7782-42-5)

isopropyl alcohol (67-63-0)

ACETOXIME

Bromoacetic acid (79-08-3)

CARBOXYMETHOXYLAMINE, hydroxylamine-O-acetic acid (645-88-5)

ethylbenzhydroximinoacetic acid

ethyl benzhydroximinoacetate

Acetic acid, aminooxy-, hydrochloride (2921-14-4)

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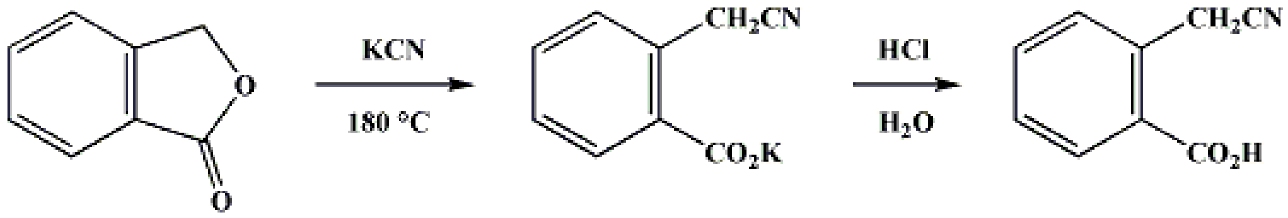
Organic Syntheses, *CV 3*, *174*

o-CARBOXYPHENYLACETONITRILE

[*o*-Toluic acid, α-cyano-]



Submitted by Charles C. Price and Richard G. Rogers.
Checked by W. E. Bachmann and Richard D. Morin.

1. Procedure

A mixture of 100 g. of phthalide (Note 1) and 100 g. of powdered potassium cyanide is placed in a 2-l. round-bottomed flask fitted with a stirrer and a thermometer. The stirred mixture is heated to 180–190° (internal temperature) for 4–5 hours in an oil bath (Note 2). One liter of water is added to the cooled mass, and the mixture is stirred until the solid salts are dissolved (Note 3). Any insoluble material that separates is removed by filtration (Note 4). Under a hood, 6 *N* hydrochloric acid (20–60 ml.) is added to the dark aqueous solution until it becomes turbid (Note 5). The solution is carefully neutralized with sodium bicarbonate (Note 6), a few grams of Norit is added, and the mixture is stirred for several minutes and filtered. The nearly colorless filtrate is acidified with 40–50 ml. of concentrated hydrochloric acid and, after cooling in an ice bath, is filtered with suction. The yield is 80–100 g. (67–83%) of white crystals which melt at 113–115° (Note 7).

2. Notes

1. The submitters used phthalide obtained from E. I. du Pont de Nemours and Company, Wilmington, Delaware. The checkers prepared it according to *Org. Syntheses* Coll. Vol. **2**, 526 (1943).
2. At the end of the reaction, the mixture should be dark brown and nearly solid. The temperature must not rise above 200°; the checkers kept it at 180°.
3. About 1 hour is required to disintegrate the mass.
4. In some runs 5–15 g. of phthalide is recovered at this point.
5. Occasionally a small amount of crystalline homophthalimide separated from the alkaline solution at this point; m.p. 235°.[1]
6. The checkers found it advisable to acidify the solution slightly at this stage in order to precipitate dark impurities.
7. This material is satisfactory for most purposes. It can be purified by recrystallization from benzene or acetic acid, though with considerable loss.

3. Discussion

o-Carboxyphenylacetonitrile has been prepared by the reaction of phthalide with potassium cyanide.[2,3,4] The above procedure is essentially that of Wislicenus.[2,3]

References and Notes

1. Gabriel, *Ber.*, **19**, 1655 (1886).
2. Wislicenus, *Ann.*, **233**, 102 (1886).
3. Price, Lewis, and Meister, *J. Am. Chem. Soc.*, **61**, 2760 (1939).
4. Johnston, Kaslow, Langsjoen, and Shriner, *J. Org. Chem.*, **13**, 477 (1948).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

sodium bicarbonate (144-55-8)

potassium cyanide (151-50-8)

Norit (7782-42-5)

Phthalide (87-41-2)

homophthalimide

o-CARBOXYPHENYLACETONITRILE, o-Toluic acid, α-cyano- (6627-91-4)

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Organic Syntheses, CV 3, 176

CATALYST, RANEY NICKEL, W-6

[With high contents of aluminum and adsorbed hydrogen]

Submitted by Harry R. Billica and Homer Adkins.
Checked by Arthur C. Cope and Harold R. Nace.

1. Procedure

Caution! The Raney nickel catalysts described below cannot be used safely under all conditions of temperature, pressure, and ratio of catalyst to hydrogen acceptor which are employed with less active nickel catalysts. They are particularly effective for low-pressure hydrogenations. No difficulty has been encountered in their use of temperatures below 100°, or above 100° if the ratio of catalyst to possible hydrogen acceptor is 5% or less. Outside these limits their use sometimes has led to reactions proceeding with violence. In one case a hydrogenation proceeding at 125° and 5000 lb. showed a pressure rise to considerably more than 10,000 lb. before the reaction could be stopped or the pressure released. Several instances of sudden increases in pressure have been noted when 10–15 g. of catalyst was used with a similar amount of hydrogen acceptor in 100 ml. of ethanol in the temperature range of 100–150° under 5000 lb. of hydrogen in a bomb of 270 ml. void. Accordingly the catalysts should be used with caution for high-pressure hydrogenations.

W-6 *Raney nickel catalyst*. In a 2-l. Erlenmeyer flask equipped with a thermometer and a stainless-steel stirrer are placed 600 ml. of distilled water and 160 g. of c.p. sodium hydroxide pellets. The solution is stirred rapidly and allowed to cool to 50° in an ice bath equipped with an overflow siphon. Then 125 g. of Raney nickel-aluminum alloy powder is added in small portions during a period of 25–30 minutes. The temperature is maintained at 50 ± 2° by controlling the rate of addition of the alloy to the sodium hydroxide solution and the addition of ice to the cooling bath. When all the alloy has been added, the suspension is digested at 50 ± 2° for 50 minutes with gentle stirring. It is usually necessary to remove the ice bath and replace it with a hot-water bath to keep the temperature constant. After this period of digestion the catalyst is washed with three 1-l. portions of distilled water by decantation (Note 1).

A glass test tube approximately 5.1 cm. in diameter and 38 cm. in length with a side arm sealed 6 cm. from the top is used as the container for washing the catalyst. The tube is closed with a rubber stopper clamped or wired in place tightly enough to withstand a gas pressure of 0.5 atm. The stopper contains three holes through which extend: (1) a tube 10 mm. in diameter reaching to the bottom of the test tube, for admitting distilled water; (2) a T-tube for equalizing gas pressures; (3) a gas-tight

bushing through which the [ ]-in. shaft of a stainless-steel stirrer projects to the bottom of the washing tube. A 5-l. aspirator bottle containing distilled water is so placed that water will flow from it through a stopcock to the. bottom of the washing tube. The side arm of the test tube is connected by pressure tubing to a 5-l. aspirator bottle that serves as an overflow from which the water may be allowed to flow through a stopcock to a drain. A source of distilled water is connected to the reservoir. Other connections and the general arrangement of the apparatus are shown in f.htmig. 8, and details of the construction of the gas-tight brass bushing are given in f.htmig. 9. Rubber pressure tubing and stoppers used in making the connections should be boiled with 5% sodium hydroxide and rinsed with water to remove sulfur. All connections should be wired in place to withstand a pressure of 0.5 atm. (7.5 lb.).

Fig. 8. Apparatus for washing catalyst. It is convenient to have the inlet tube for wash water sealed into the bottom of the chamber rather than introduced through the stopper as shown.

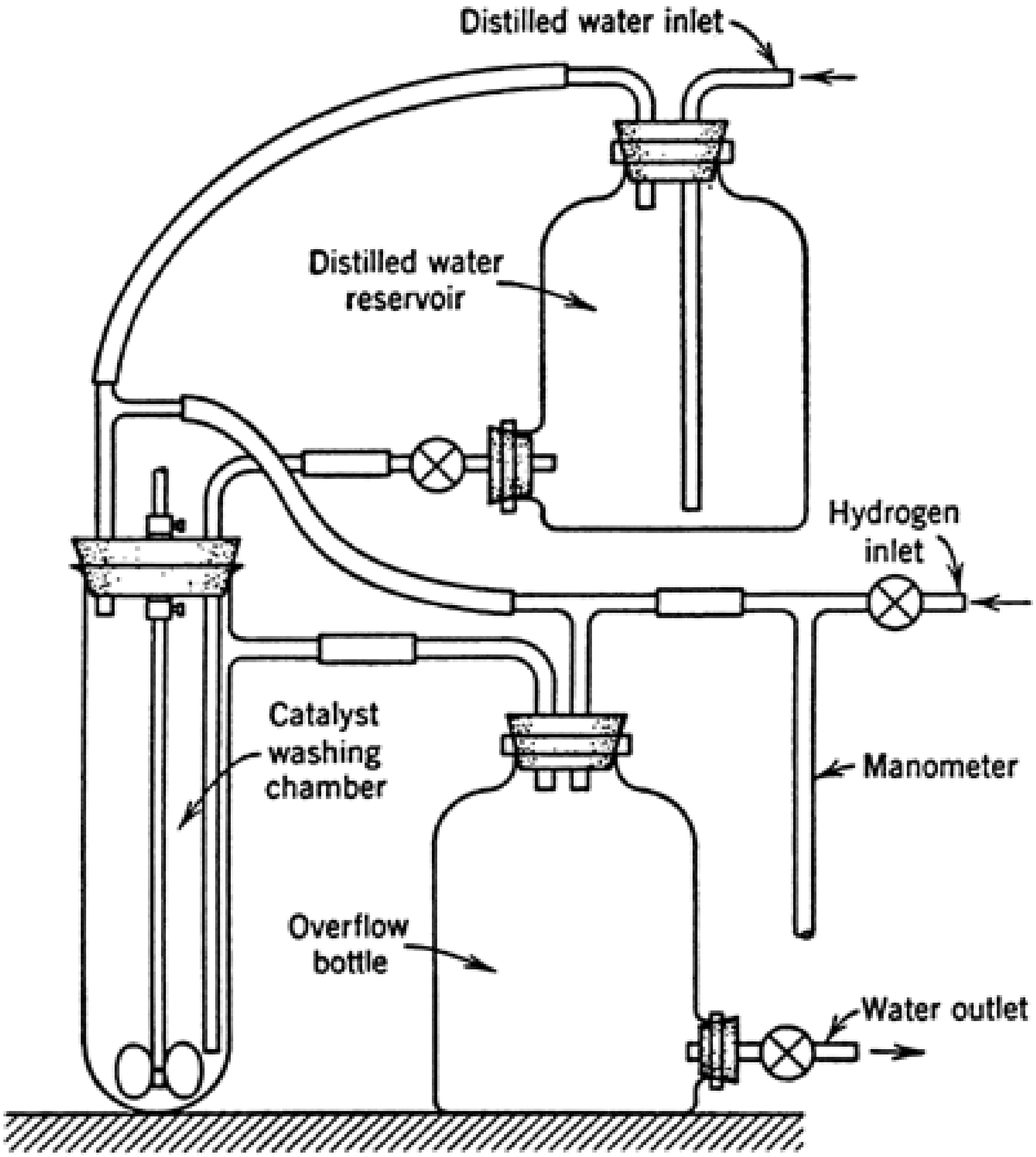
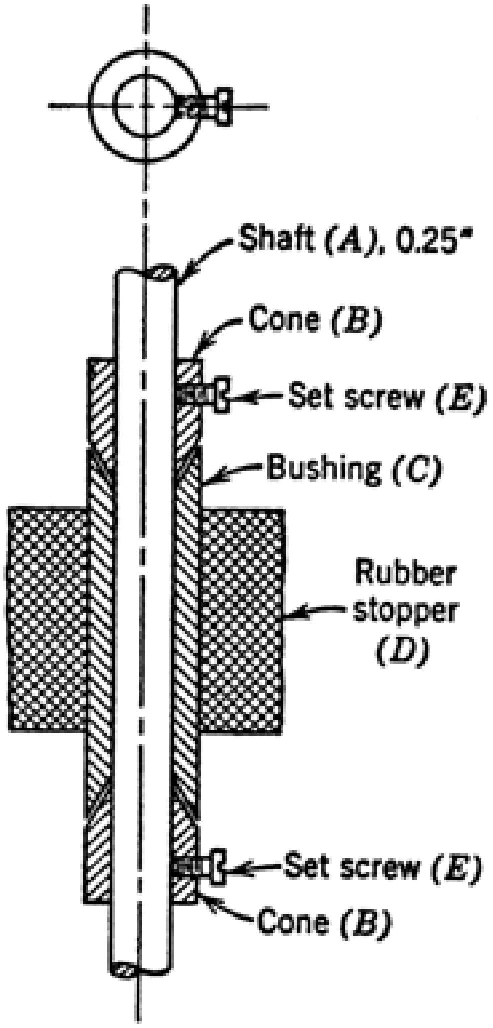


Fig. 9. Gas-tight brass bushing. The gas-tight bushing for the shaft of the stirrer

consists of three parts: two cones (*B*) which fit the shaft snugly and are attached to it by set screws (*E*); and a bushing (*C*) so cut that the cones fit into it at top and bottom. The two cones are placed on shaft *A* of the stirrer, above and below the bushing and attached to the shaft so that they fit snugly against the bushing. A gas-tight seal is obtained by placing a drop or two of heavy lubricating oil between each cone and the bushing. The over-all dimensions of the bushing are approximately 13 by 65 mm., and it is held in a rubber stopper (*D*).



The catalyst sludge is transferred to the washing tube immediately after its third washing by decantation. The last portions are rinsed from the flask into the washing tube with distilled water, and the tube, reservoir, and overflow bottle are nearly filled with distilled water. The apparatus is assembled rapidly, and hydrogen is introduced through the inlet while most of the water in the overflow bottle is displaced through the outlet. The outlet then is closed, and hydrogen is admitted until the water in the reservoir, washing tube, and overflow bottle is under a pressure about 0.5 atm. above that of the outside atmosphere. The stirrer is operated at such a speed that the catalyst is suspended to a height of 18–20 cm. Distilled water from the reservoir is allowed to flow through the suspended catalyst at a rate of about 250 ml. per minute. When the reservoir is nearly empty and the overflow bottle full, the drain cock and distilled-water inlet are opened simultaneously to an equal rate of flow such that, as the overflow bottle empties, the reservoir is filled, while the pressure in the system

remains constant.

After about 15 l. of water has passed through the catalyst, the stirrer and the flow of water are stopped, the pressure is released, and the apparatus disassembled. The water is decanted from the settled sludge, which is then transferred to a 250-ml. centrifuge bottle with 95% ethanol. The catalyst is washed three times by stirring, not shaking, with 150-ml. portions of 95% ethanol, each addition being followed by centrifuging. In the same manner the catalyst is washed three times with absolute ethanol. One to two minutes' centrifugation at 1500–2000 r.p.m. is sufficient to separate the catalyst. All operations should be carried out as rapidly as possible if a catalyst of the maximum activity is desired. The catalyst should be kept in a closed bottle filled with absolute ethanol and should be stored at once in a refrigerator. The total elapsed time from the beginning of the addition of the alloy to the completion of the preparation should be not more than about 3 hours (Note 2), (Note 3), and (Note 4).

2. Notes

1. The procedure in the preparation of W-7 Raney nickel, after the digestion and the three decantations, is to transfer the catalyst to a 250-ml. centrifuge bottle with 95% ethanol. It is then washed three times by stirring, not shaking, with 150-ml. portions of 95% ethanol, with centrifuging after each addition. In the same manner, the catalyst is washed three times with absolute ethanol and is at once stored in a refrigerator in a closed bottle filled with absolute ethanol. The catalyst so prepared contains alkali. This may be advantageous for various reasons in the hydrogenation of ketones, phenols, and nitriles. In certain cases the alkali may have a harmful effect upon a hydrogenation.

2. The volume of the settled catalyst (W-6) in ethanol is about 75–80 ml. containing about 62 g. of nickel and 7–8 g. of aluminum. The catalyst is extremely pyrophoric when exposed to the air in a dry condition, and it should be kept wet with solvent at all times. It amounts to about 28 "half teaspoonfuls" if it is so measured. The catalyst loses some of its special activity upon standing but seems to be quite active for about 2 weeks when stored in a refrigerator. After this period it is similar in activity to the Raney nickel made by an earlier procedure.[1] The W-3 to W-7 catalysts all lose their special activity rather rapidly when stored under water.

3. A somewhat less active but nevertheless excellent catalyst, referred to as W-5, is made by the procedure described above for W-6 except that it is washed at atmospheric pressure without the addition of hydrogen to the system. The W-5 catalyst is similar in method of preparation and activity to the W-4 Raney nickel catalyst as prepared by Pavlic.[2]

4. Raney nickel prepared by the procedure described for W-6 will bring about the hydrogenation of alkyne and alkene linkages, of aldehydes, ketones, oximes, nitriles, nitro compounds, and benzenoid and pyridinoid nuclei under the conditions of temperature and pressure normally employed with platinum and palladium catalysts.[3] At higher pressures W-6 Raney nickel brings about

reactions at a more rapid rate and at lower temperatures than Raney nickel prepared by the older procedures.

3. Discussion

The various procedures for the preparation of Raney nickel[4] from the nickel-aluminum alloy differ from one another in the method of adding the alloy, in the concentration of sodium hydroxide, in the temperature and duration of digestion, and in the method of washing the catalyst free of sodium aluminate and alkali. For convenience in reference, the Raney nickel catalysts prepared by various procedures have been designated W-1,[5] W-2,[1] W-3,[2,6] W-4,[2,6] W-5,[3] W-6,[3] and W-7.[3] They have been compared as to activity against β-naphthol.[7] A Raney nickel catalyst is available commercially from the Gilman Paint and Varnish Company, Chattanooga, Tennessee.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 181
- Org. Syn. Coll. Vol. 3, 358
- Org. Syn. Coll. Vol. 4, 603
- Org. Syn. Coll. Vol. 5, 102

References and Notes

1. *Org. Syntheses*, **21**, 15 (1941).
2. Pavlic and Adkins, *J. Am. Chem. Soc.*, **68**, 1471 (1946).
3. Adkins and Billica, *J. Am. Chem. Soc.*, **70**, 695 (1948).
4. Murray Raney, U. S. pat. 1,628,190 [*C. A.*, **21**, 2116 (1927)].
5. Covert and Adkins, *J. Am. Chem. Soc.*, **54**, 4116 (1932).
6. Adkins and Pavlic, *J. Am. Chem. Soc.*, **69**, 3039 (1947).
7. Adkins and Krsek, *J. Am. Chem. Soc.*, **70**, 412 (1948).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

W-6 Raney nickel

Raney nickel-aluminum alloy powder

W-7 Raney nickel

W-4 Raney nickel

ethanol (64-17-5)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

β-naphthol (135-19-3)

sulfur (7704-34-9)

aluminum (7429-90-5)

platinum (7440-06-4)

nickel, Raney nickel (7440-02-0)

palladium (7440-05-3)

nickel-aluminum

sodium aluminate (1302-42-7)

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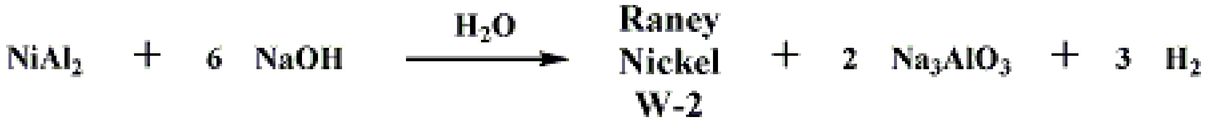
Organic Syntheses, CV 3, 181

CATALYST, RANEY NICKEL, W-2



Submitted by Ralph Mozingo
Checked by Homer Adkins and Lawrence Richards.

1. Procedure

A solution of 380 g. of sodium hydroxide in 1.5 l. of distilled water, contained in a 4-l. beaker (Note 1) equipped with an efficient stirrer (Note 2), is cooled in an ice bath to 10°, and 300 g. of nickel-aluminum alloy (Note 3) is added to the solution in small portions, with stirring, at such a rate that the temperature does not rise above 25° (Note 4), the beaker being allowed to remain in the ice bath. When all the alloy has been added (about 2 hours is required) the stirrer is stopped, the beaker is removed from the ice bath, and the contents are allowed to come to room temperature. After the evolution of hydrogen becomes slow, the reaction mixture is allowed to stand on a steam bath until the evolution of hydrogen again becomes slow (about 8–12 hours). The heating should not be too rapid at the beginning or the solution may foam over. During this time the volume of the solution is maintained constant by adding distilled water if necessary. After heating, the nickel is allowed to settle and most of the liquid is decanted. Distilled water is then added to bring the solution to the original volume; the nickel is suspended by stirring, again allowed to settle, and the solution is decanted. The nickel is then transferred to a 2-l. beaker (Note 5) with the aid of distilled water, and the water is again decanted. A solution of 50 g. of sodium hydroxide in 500 ml. of distilled water is added; the catalyst is suspended and allowed to settle; and the alkali is decanted. The nickel is washed by suspension in distilled water and decantation until the washings are neutral to litmus and then ten times more to remove the alkali completely (twenty to forty washings are required) (Note 6). The washing process is repeated three times with 200 ml. of 95% ethanol and three times with absolute ethanol; the catalyst is then stored under absolute ethanol in bottles which are completely filled with absolute ethanol and tightly closed (Note 7). The product is highly pyrophoric and must be kept under a liquid at all times. The Raney nickel contained in the suspension weighs about 150 g. (Note 8).

To prepare the catalyst under methylcyclohexane (Note 9), the catalyst, which has been prepared as above and washed free of alkali with water, but to which no ethanol has been added, is covered with 1 l. of methylcyclohexane which is distilled from an oil bath until all the water has been codistilled with the hydrocarbon, more of the methylcyclohexane being added from time to time so that the nickel always remains covered. When the catalyst is free from water it becomes freely suspended in the liquid.

To prepare nickel under dioxane, dioxane (Note 10) is used in place of the methylcyclohexane above and the distillation is continued until the temperature of the vapor reaches 101°. (*Caution. Do not use nickel in dioxane above 210°; the dioxane may react almost explosively with hydrogen and Raney nickel above this temperature*.)

2. Notes

1. A Pyrex battery jar of about 10-l. capacity is also suitable and is sufficiently large for the preparation of a batch of catalyst of two to three times the size given here.
2. The stirrer should be provided with a motor which will not ignite the hydrogen. Either an induction motor or an air stirrer may be used. The stirrer blades may be made of glass, Monel, or stainless steel.
3. The alloy used is "Raney Nickel Aluminum Catalyst Powder" from the Gilman Paint and Varnish Company, Chattanooga, Tenn. It contains about 50% nickel.
4. The thermometer should not be left in the alkali or the bulb may be eaten away. The catalyst is inactivated by mercury. If the mixture foams badly at this point, 2 ml. of *n*-octyl alcohol may be added to prevent excessive foaming; however, this is not usually necessary.
5. A stoppered graduate of 2-l. capacity is somewhat more convenient than a 2-l. beaker.
6. The number of washings required may be materially reduced by allowing time for diffusion of base from the surface of the catalyst into the surrounding wash water. To this end the catalyst is stirred well with 1.5 l. of water for each washing. Diffusion is allowed to proceed for 3–10 minutes, and the mixture is then stirred again and the wash water decanted as soon as the catalyst settles to the bottom. By this method twenty washings should be sufficient to remove all traces of the alkali adsorbed on the catalyst surface.
7. The quantity of catalyst prepared should not be larger than necessary for a 6 months' supply as the catalyst may deteriorate on standing.
8. It is more convenient to measure the catalyst than to weigh it. Raney nickel in alcohol contains about 0.6 g. of the catalyst per milliliter of the settled material. The half and quarter teaspoons used in kitchens are convenient for measuring the catalyst. A level teaspoonful is about 3 g. of nickel.
9. It is necessary that the catalyst be freely suspended in the reaction mixture during a reduction. Therefore, the liquid under which the nickel is placed must be soluble in the reduction mixture at all times, i.e., in both the reactants and products.
10. The dioxane used should be dry, halogen-free, and distilled from sodium.

3. Discussion

These are summarized in the preceding procedure (p. 176). The previously published procedure [*Org. Syntheses*, **21**, 15 (1941)] which is included here results in the catalyst now known as W-2.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 63
- Org. Syn. Coll. Vol. 3, 148
- Org. Syn. Coll. Vol. 3, 278
- Org. Syn. Coll. Vol. 3, 328
- Org. Syn. Coll. Vol. 3, 358
- Org. Syn. Coll. Vol. 3, 717
- Org. Syn. Coll. Vol. 3, 720
- Org. Syn. Coll. Vol. 3, 794
- Org. Syn. Coll. Vol. 3, 827
- Org. Syn. Coll. Vol. 4, 283
- Org. Syn. Coll. Vol. 4, 298
- Org. Syn. Coll. Vol. 4, 603
- Org. Syn. Coll. Vol. 4, 660
- Org. Syn. Coll. Vol. 5, 743
- Org. Syn. Coll. Vol. 6, 468
- Org. Syn. Coll. Vol. 6, 581
- Org. Syn. Coll. Vol. 6, 601

References and Notes

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

nickel-aluminum alloy

Raney Nickel Aluminum Catalyst Powder

ethanol (64-17-5)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

mercury (7439-97-6)

nickel, Raney nickel (7440-02-0)

sodium (13966-32-0)

methylcyclohexane (108-87-2)

dioxane (5703-46-8)

n-octyl alcohol (111-87-5)

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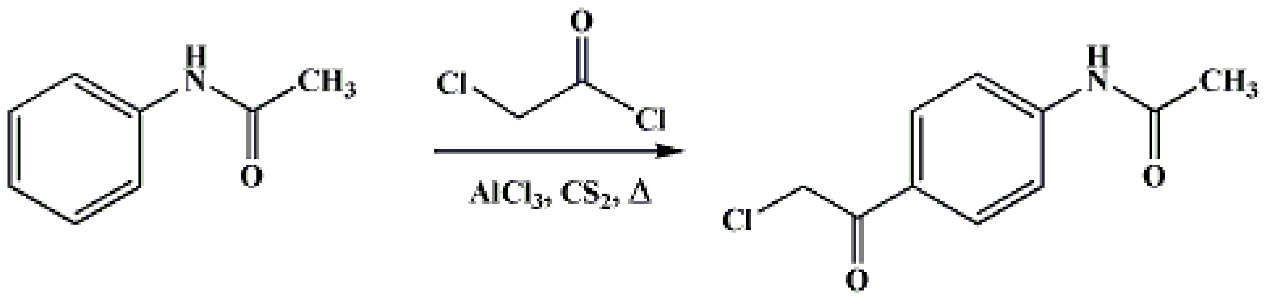
p-CHLOROACETYLACETANILIDE

[Acetanilide, *p*-chloroacetyl-]



Submitted by J. L. Leiserson and A. Weissberger.
Checked by Cliff S. Hamilton and Yao-Hua Wu.

1. Procedure

Caution! Carbon disulfide, used as a solvent in this preparation, is highly inflammable; its vapor may ignite on contact with a hot laboratory steam line.

In a 5-l. three-necked flask mounted on a steam bath in the hood and equipped with a mechanical stirrer (Note 1) and a wide-bore condenser (Note 1) is placed 1.4 kg. (1.1 l.) of carbon disulfide. Through the open neck of the flask 202 g. (1.5 moles) of acetanilide and 300 g. (2.66 moles) of chloroacetyl chloride (Note 2) are introduced. The mixture is vigorously stirred while 600 g. (4.5 moles) of aluminum chloride is added in 25–50 g. portions over a period of 20–30 minutes; the neck of the flask is stoppered between additions (Note 3). After the addition of the last portion of aluminum chloride, the mixture is heated at reflux temperature for 30 minutes while stirring is continued. Heating and stirring are discontinued and the mixture is allowed to stand for 3 hours, during which time it separates into layers. The upper layer (carbon disulfide) is decanted, and the viscous red-brown lower layer is poured cautiously with stirring into about 1 kg. of finely crushed ice to which 100 ml. of concentrated hydrochloric acid has been added. After the hydrolysis of the aluminum chloride, the product crystallizes as a white solid, which is collected on a Büchner funnel and washed well with water. It is then transferred to a beaker where it is thoroughly washed by stirring with sufficient 95% ethanol to give a fluid slurry. The solid is again collected on the funnel. After drying in the air it melts at 213–214° and weighs 250–265 g. (79–83%). It can be recrystallized from 95% ethanol (about 1 l. of the solvent being required for 40 g. of the solid) as fine white crystals melting at 216°; the recovery in the recrystallization, without reworking of the mother liquor, is about 70%.

2. Notes

1. Unless a well-ventilated hood is available the stirrer should be provided with a seal and the condenser should be connected to a gas-absorption trap.

2. The chloroacetyl chloride should be weighed in the hood; it is strongly lachrymatory.
3. The addition of each portion of aluminum chloride causes vigorous boiling.

3. Discussion

The method of preparation given, devised by Kunckell,[1] is the only one reported.

References and Notes

1. Kunckell, *Ber.*, **33**, 2644 (1900).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

Acetanilide (103-84-4)

aluminum chloride (3495-54-3)

carbon disulfide (75-15-0)

chloroacetyl chloride (79-04-9)

p-Chloroacetylacetanilide, Acetanilide, p-chloroacetyl- (140-49-8)

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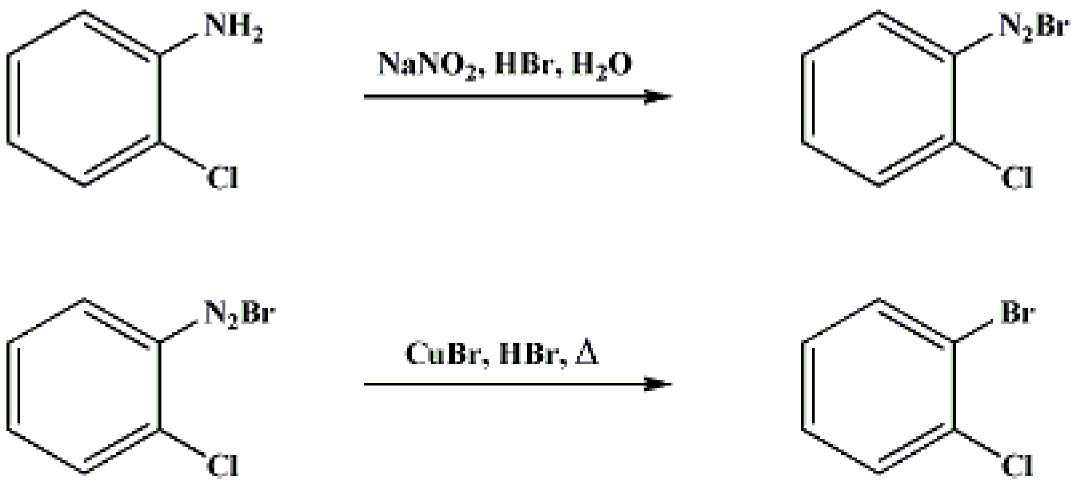
Organic Syntheses, CV 3, 185

o-CHLOROBROMOBENZENE

[Benzene, 1-bromo-2-chloro-]



Submitted by Jonathan L. Hartwell
Checked by H. R. Snyder and Zeno Wicks, Jr..

1. Procedure

A mixture of 127.5 g. (1 mole) of a good commercial grade of *o*-chloroaniline and 300 ml. (2.5 moles) of 48% hydrobromic acid (Note 1) in a 2-l. flask set in an ice bath is cooled to 0° by the addition of ice. A solution of 70 g. (1 mole) of sodium nitrite in 125 ml. of water is added rapidly, with stirring, the temperature being kept below 10° by the addition of small pieces of ice. When only about 5 ml. of the sodium nitrite solution remains, further additions are made cautiously until an excess of nitrous acid remains after the last addition (Note 2).

In the meantime, a mixture of 79 g. (0.55 mole) of cuprous bromide (Note 3) and 80 ml. (0.6 mole) of 48% hydrobromic acid (Note 1) is heated to boiling in a 5-l. round-bottomed three-necked flask, equipped with a condenser set for distillation and provided with a 2-l. receiving flask, a steam inlet tube closed by a screw clamp, and a separatory funnel. About one-fourth of the diazonium solution is transferred to the separatory funnel, without filtration, and immediately run into the cuprous bromide-hydrobromic acid solution, which is kept boiling over a free flame, at such a rate that boiling is continuous. When the separatory funnel is nearly empty a further portion of the cold diazonium solution is transferred to it without interrupting the addition. All the diazonium solution is added in this way over a period of about 30 minutes, during which time much of the product steam-distils. When the addition is complete, the stopcock in the separatory funnel is closed, the screw clamp in the steam line is opened, and a vigorous current of steam is passed through the mixture until no more organic material distils. About 1–1.5 l. of distillate is collected.

The heavy organic layer is separated from the distillate and washed with 10-ml. portions of concentrated sulfuric acid until the acid becomes only slightly colored during the washings; four washings usually suffice. The oil is then washed with one 100-ml. portion of water, two 50-ml. portions of 5% aqueous sodium hydroxide, and finally with one 100-ml. portion of water. The product is dried over about 3 g. of calcium chloride and distilled from a 250-ml. distilling flask. The yield of pure, colorless *o*-chlorobromobenzene, boiling at 199–201°/742 mm., is 170–183 g. (89–95%) (Note 4) and (Note 5).

2. Notes

1. When 40% hydrobromic acid is used in both the diazotization and Sandmeyer reaction the yield is only about 75%.
2. Free nitrous acid causes an *immediate* blue color at the point of contact with starch-iodide test paper. A delayed color or a color around the periphery of the wetted area is of no significance. At all times there must be an excess of mineral acid (blue color on Congo paper).
3. The submitter used commercial cuprous bromide. The checkers prepared cuprous bromide by dissolving 600 g. (2.4 moles) of commercial copper sulfate crystals and 350 g. (3.4 moles) of sodium bromide in 2 l. of warm water; the solution was stirred while 151 g. (1.2 moles) of solid sodium sulfite was added over a period of 10 minutes. Occasionally a little more sodium sulfite was required to discharge the blue color. The mixture was cooled, and the solid collected on an 8-in. Büchner funnel, washed once with water, pressed nearly dry, and then dried in the air overnight. The yield of cuprous bromide was 320 g. (93%).
4. Runs 3 times this size give proportional yields.
5. The checkers have prepared the following bromides by the same procedure: *m*-chlorobromobenzene (b.p. 191–194°) from *m*-chloroaniline in 91–94% yields; *m*-dibromobenzene (b.p. 215–217°) from *m*-bromoaniline in 80–87% yields; and *o*-bromoanisole (b.p. 114–116°/29 mm.) from *o*-anisidine in 88–93% yields. In the preparation of *o*-bromoanisole the washing with sulfuric acid was omitted.

3. Discussion

o-Chlorobromobenzene has been prepared by the diazotization of *o*-bromoaniline followed by replacement of the diazonium group by chlorine;[1] by the elimination of the amino group from 3-chloro-4-bromoaniline;[2] by the chlorination of bromobenzene in the presence of thallous chloride,[3] aluminum chloride,[4] or ferric chloride;[4] by the bromination of chlorobenzene without a catalyst[5] or in the presence of aluminum,[4] iron,[4] ferric bromide,[4] or aluminum-mercury couple;[6] by the diazotization of *o*-chloroaniline followed by replacement of the diazonium group with bromine;[4,7] from *o*-chlorophenylmercuric chloride by the action of bromine;[8] and by treatment of silver

o-chlorobenzoate with bromine.[9]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 200
- Org. Syn. Coll. Vol. 6, 36

References and Notes

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8. Hanke, *J. Am. Chem. Soc.*, **45**, 1321 (1923).
9. Dauben and Tilles, *J. Am. Chem. Soc.*, **72**, 3185 (1950).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

cuprous bromide-hydrobromic acid

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

sodium sulfite (7757-83-7)

sodium hydroxide (1310-73-2)

iron (7439-89-6)

HYDROBROMIC ACID (10035-10-6)

bromine (7726-95-6)

sodium bromide (7647-15-6)

copper sulfate (7758-98-7)

sodium nitrite (7632-00-0)

nitrous acid (7782-77-6)

aluminum (7429-90-5)

chlorobenzene (108-90-7)

aluminum chloride (3495-54-3)

chlorine (7782-50-5)

bromobenzene (108-86-1)

cuprous bromide (7787-70-4)

ferric chloride (7705-08-0)

Benzene, 1-bromo-2-chloro-, o-Chlorobromobenzene (694-80-4)

3-chloro-4-bromoaniline (21402-26-6)

thallous chloride

ferric bromide (10031-26-2)

aluminum-mercury

m-chloroaniline (108-42-9)

o-chloroaniline (95-51-2)

o-bromoaniline (615-36-1)

m-bromoaniline (591-19-5)

o-bromoanisole (578-57-4)

m-chlorobromobenzene (108-37-2)

m-dibromobenzene (108-36-1)

o-anisidine (90-04-0)

o-chlorophenylmercuric chloride

silver o-chlorobenzoate

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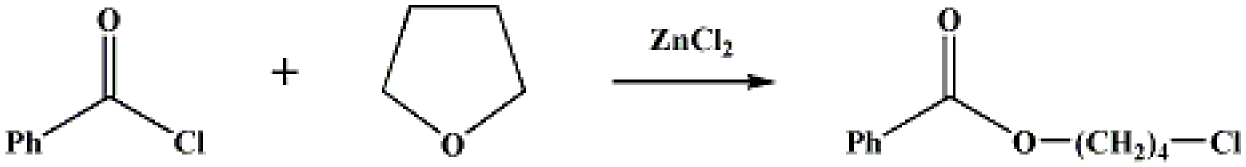
Organic Syntheses, CV 3, 187

4-CHLOROBUTYL BENZOATE

[1-Butanol, 4-chloro-, benzoate]



Submitted by Martin E. Synerholm
Checked by Arthur C. Cope and James J. Ryan.

1. Procedure

In a 200-ml. round-bottomed flask fitted with an efficient reflux condenser are mixed 31.4 ml. (38 g., 0.27 mole) of freshly distilled benzoyl chloride, 28.2 ml. (25 g., 0.35 mole) of tetrahydrofuran (Note 1), and 5 g. of freshly fused zinc chloride. A vigorous reaction begins immediately, and after a few seconds, when the mixture starts to boil, external cooling is applied with an ice bath. After the initial reaction has subsided, the mixture is heated on a steam bath for 15 minutes, cooled, and dissolved in 100 ml. of benzene. The benzene solution is washed with 100 ml. of a 5% solution of sodium chloride and then with 100 ml. of a saturated solution of sodium bicarbonate. The benzene layer is dried over anhydrous sodium sulfate and fractionally distilled from a modified Claisen flask.

The product is collected at 140–143°/5 mm., 132–135°/2.5 mm.; n_D^{25} 1.5176 (Note 2). The yield is 45–48 g. (78–83%).

2. Notes

1. Good-quality commercial tetrahydrofuran may be used as received, or redistilled; b.p. 65–66°.
2. The product develops a slight yellow tint on standing.

3. Discussion

4-Chlorobutyl benzoate has been prepared by the action of benzoyl chloride on tetrahydrofuran in the presence of titanium chloride, stannic chloride,[1] or zinc chloride.[2]

References and Notes

1. Gol'dfarb and Smorgonskii, *J. Gen. Chem. U.S.S.R.*, **8**, 1516 (1938) [*C. A.*, **33**, 4593 (1939)].

2. Cloke and Pilgrim, *J. Am. Chem. Soc.*, **61**, 2667 (1939).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Benzene (71-43-2)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

benzoyl chloride (98-88-4)

zinc chloride (7646-85-7)

stannic chloride (7646-78-8)

Tetrahydrofuran (109-99-9)

4-CHLOROBUTYL BENZOATE, 1-Butanol, 4-chloro-, benzoate (946-02-1)

titanium chloride (7550-45-0)

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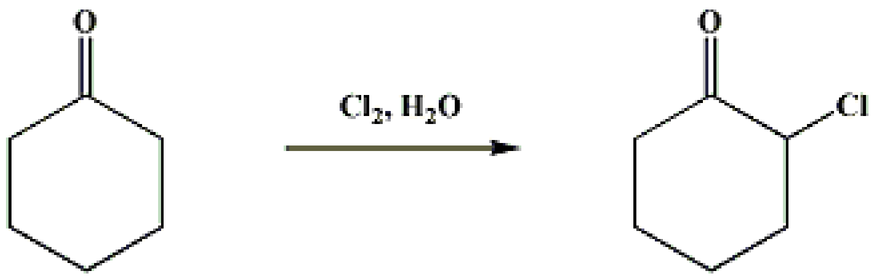
2-CHLOROCYCLOHEXANONE

[Cyclohexanone, 2-chloro-]



Submitted by M. S. Newman, M. D. Farbman, and H. Hipsher.
Checked by C. S. Hamilton and C. W. Whitehead.

1. Procedure

In a 3-l. three-necked round-bottomed flask, fitted with a gas inlet tube reaching almost to the bottom, a sealed mechanical stirrer (Note 1), and a gas outlet tube connected to a mercury valve (Note 2), are placed 294 g. (3 moles) of cyclohexanone (Note 3) and 900 ml. of water. After the reaction vessel has been swept out with chlorine, the gas outlet tube is connected to the mercury valve, the flask is cooled in an ice bath, the stirrer is started, and 215 g. (slightly more than 3 moles) of chlorine is bubbled in as rapidly as the gas is absorbed (about 45 minutes) (Note 4).

The heavier chlorocyclohexanone layer is separated and combined with three 150-ml. ether extracts of the aqueous phase, and washed with 150 ml. of water and then with 200 ml. of saturated sodium chloride solution. After filtration (gravity) through anhydrous sodium sulfate the ether is removed and the residue vacuum-distilled in a modified Claisen flask. The fraction (300–340 g.) boiling below 100° at 10 mm. (Note 5) is collected (Note 6). This material is then fractionated carefully under reduced pressure by means of a 42-in. modified Vigreux column (heated) with a total-condensation variable take-off head (Note 7). The yield of 2-chlorocyclohexanone boiling at 90–91°/14–15 mm. is 240–265 g. (61–66%) (Note 8) and (Note 9).

2. Notes

1. A large propeller-type stirrer is satisfactory. The blades should be pitched to drive the liquid upwards, and the propeller should be located just below the surface of the liquid to provide splashing. The checkers used a glycerol-lubricated rubber-tube seal.[1]
2. The mercury valve consists of a tube dipping about 0.5 in. into some mercury in a vented test tube. This allows the reaction to be carried out under a slight pressure of chlorine. The checkers found a water valve to be more satisfactory.

The outlet tube was made to dip about 7 in. into water in a vented glass tube. A trap (125-ml. suction flask) was placed between the water valve and the reaction flask to prevent water from being sucked into the reaction mixture.
3. The checkers used Eastman's cyclohexanone boiling at 154–156°. The submitters report that the practical grade gives just as good yields.
4. Careful control of the temperature is unnecessary as approximately the same results are obtained when the temperature is allowed to rise to about 50° or is kept below 20°. However, at the lower temperature a greater amount of cyclohexanone is recovered.
5. Or below 110°/13 mm., or 92°/4 mm.
6. This preliminary purification is advisable before careful fractionation.
7. The head used was similar to that described by Turk and Matuszak[2] except for the stopcock, which was of the variety described by Newman.[3]
8. This material shows a long flat at 23.2° cor. in a time-temperature cooling curve. It can be stored in a refrigerator in paraffin-covered stoppered bottles for long periods of time without discoloration.
9. About 15–40 g. (5–13%) of cyclohexanone, b.p. 52°/14–15 mm., is recovered.

3. Discussion

2-Chlorocyclohexanone can be prepared by chlorinating cyclohexanone in glacial acetic acid as the solvent,[4] by passing chlorine into a mixture of cyclohexanone[5] or cyclohexanol[6] and water in the presence of powdered calcium carbonate, by the electrochemical chlorination of cyclohexanone in hydrochloric acid,[7] by the action of monochlorourea in acetic acid on the ketone,[8] by the oxidation of 2-chlorocyclohexanol,[9] and by the chlorination of the sodio derivative of cyclohexanone with ethyl hypochlorite.[10]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 928
- Org. Syn. Coll. Vol. 7, 456
- Org. Syn. 78, 212

References and Notes

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4. Bartlett and Rosenwald, *J. Am. Chem. Soc.*, **56**, 1992 (1934).
5. Kotz and Grethe, *J. prakt. Chem.*, (2) **188**, 487 (1909).
6. Ebel, *Helv. Chim. Acta*, **12**, 9 (1929); Bouveault and Chereau, *Compt. rend.*, **142**, 1086 (1906); Meyer, *Helv. Chim. Acta*, **16**, 1291 (1933); Vavon and Mitchovitch, *Bull. soc.*

chim. France, (4) **45**, 961 (1929).

7. Szper, *Bull. soc. chim. France*, (4) **51**, 653 (1932).
8. Godchot and Mousseron, *Bull. soc. chim. France*, (4) **51**, 361 (1932).
9. Detoeuf, *Bull. soc. chim. France*, (4) **31**, 178 (1922).
10. Mousseron and Froger, *Bull. soc. chim. France*, **12**, 69 (1945).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ether (60-29-7)

Cyclohexanol (108-93-0)

Cyclohexanone (108-94-1)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

mercury (7439-97-6)

calcium carbonate (471-34-1)

chlorine (7782-50-5)

2-Chlorocyclohexanol (1561-86-0)

2-Chlorocyclohexanone, Cyclohexanone, 2-chloro-, chlorocyclohexanone (822-87-7)

monochlorourea

ethyl hypochlorite (624-85-1)

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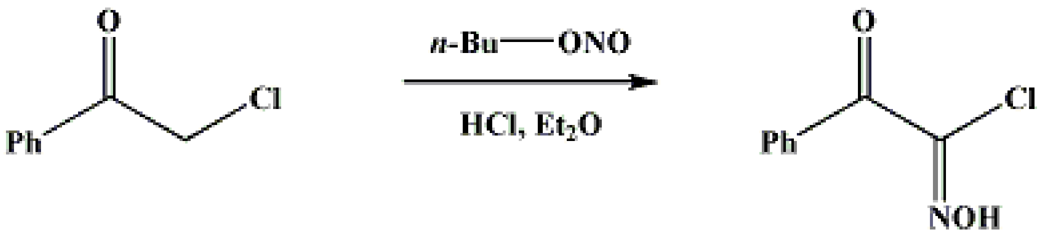
ω-CHLOROISONITROSOACETOPHENONE

[Glyoxylyl chloride, phenyl-, oxime]



Submitted by Nathan Levin and Walter H. Hartung.
Checked by C. F. H. Allen and J. VanAllan.

1. Procedure

A 500-ml. three-necked round-bottomed flask is provided with a small dropping funnel, a sealed mechanical stirrer, a reflux condenser connected to a gas-absorption trap, and a hydrogen chloride delivery tube which extends to the bottom of the flask.

In the reaction flask are placed 15.4 g. (0.1 mole) of phenacyl chloride (Note 1) and 100 ml. of dry ether. The stirrer is started, and, after the solid has dissolved, anhydrous hydrogen chloride (Note 2) is introduced at the rate of 2–3 bubbles per second. Ten and three-tenths grams (11.8 ml., 0.1 mole) of freshly distilled *n*-butyl nitrite[1] (Note 3) is then admitted from the dropping funnel in 0.5- to 1-ml. portions. After addition of the first portion of nitrite the reaction mixture becomes orange-brown, and after several minutes, light yellow; at this point a second portion of nitrite is added and a similar color change takes place, whereupon a third portion is added; further additions are made until all the butyl nitrite has been added. The reaction mixture warms up, and the ether begins to reflux gently (Note 4). After all the nitrite has been added (about 30 minutes is required), stirring and addition of hydrogen chloride are continued an additional 15 minutes. At this point, the solution will have practically ceased boiling and will have assumed an orange color.

The reaction mixture is allowed to stand for 1–2 hours (or overnight, if more convenient); after this interval the solution will have assumed a clear, pale yellow color. The condenser is then set for downward distillation, stirring is resumed, and the solvent is removed by distillation from a steam bath (Note 5). After nearly all the ether has been removed, the distillation is continued under reduced pressure (40–50 mm.) until no further appearance of crystals is noted. The residue, which consists of yellow crystals of the crude product, is then allowed to stand until dry in a vacuum desiccator which contains concentrated sulfuric acid, soda lime, and anhydrous calcium chloride (Note 6).

The dried product is then recrystallized from 30–35 ml. of a 1:3 mixture of boiling

benzene and carbon tetrachloride (Note 7). The yield of snow-white crystals is 15–15.7 g. (82–86%); the recrystallized product melts at 131–132° and is sufficiently pure for synthetic purposes. A second recrystallization gives a product which melts at 132–133° (Note 8) and (Note 9).

2. Notes

1. Commercial phenacyl chloride may be used; if unavailable the chloride may be prepared in 85–88% yield by a Friedel-Crafts reaction, using 234 g. (265 ml., 3 moles) of dry benzene and 79.5 g. (53 ml., 0.70 mole) of chloroacetyl chloride, in the presence of 103 g. (0.77 mole) of powdered anhydrous aluminum chloride; the product distils at 120–125°/4 mm. and melts at 56–57°. *Phenacyl chloride is a strong lachrymator and vesicant; it should be handled with care*.
2. Hydrogen chloride is now available in cylinders.
3. Any alkyl nitrite may be employed. The submitters preferred the use of isopropyl nitrite, since the low boiling point of the isopropyl alcohol formed facilitates its removal.
Isopropyl nitrite may be prepared according to the procedure given for *n*-butyl nitrite.[1]
A mixture of 147 g. (80 ml., 1.5 moles) of concentrated sulfuric acid (sp. gr. 1.84), 60 ml. of water, and 180 g. (230 ml., 3 moles) of 97% isopropyl alcohol, previously cooled to 0°, is added to a solution of 227.7 g. (3.3 moles) of 97% sodium nitrite in 1 l. of water, cooled to −5°. About 2 hours is required for the addition of the alcohol solution, during which time the temperature of the reaction mixture is maintained at −2° to 0°. The product may be isolated and purified as described under butyl nitrite. After drying over 15–20 g. of anhydrous sodium sulfate, the nitrite is distilled from a steam bath using a 20-cm. column. Practically all the isopropyl nitrite distils at 39–40°/745 mm. as a pale yellow oil; the yield of product is 191 g. (71.4%). Isopropyl nitrite, when stored in a refrigerator, has been found to be much more stable than butyl nitrite. The checkers used commercially available *n*-butyl nitrite and experienced no difficulty in removing the *n*-butyl alcohol.
4. The rate of stirring must be kept fairly constant since an abrupt increase in speed may cause the ether to reflux at an undesirably rapid rate. The rate of addition of the nitrite is also governed by the rate of the refluxing.
5. The recovered ether may be employed without purification as the solvent in a subsequent run.
6. ω-Chloroisonitrosoacetophenone is extremely soluble in butanol, hence the alcohol should be removed as completely as possible before the crude product is recrystallized.
7. This is most conveniently done by dissolving the chloride in the benzene and then diluting.
8. This procedure works equally well in 0.5-mole runs.

9. This procedure, with minor changes, may be applied to various nuclear-substituted phenacyl chlorides. The yields vary from 74% to 92%.[2,3]

3. Discussion

The above procedure[2] is modeled after that described for the nitrosation of arylethyl ketones.[4,5] ω-Chloroisonitrosoacetophenone has been prepared by the chlorination of isonitrosoacetophenone;[6,7,8] by treating the ammonium salt of ω-nitroacetophenone with anhydrous hydrogen chloride,[9] or by refluxing ω-nitroacetophenone with dilute alcoholic hydrogen chloride;[10] and by the nitrosochlorination of acetophenone with nitrosyl chloride.[11] The isolation of small quantities of ω-chloroisonitrosoacetophenone from the reaction product obtained by nitrosating acetophenone in the presence of hydrogen chloride has been reported.[12,13]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

soda lime

ammonium salt of ω-nitroacetophenone

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrogen chloride (7647-01-0)

Benzene (71-43-2)

ether (60-29-7)

sodium sulfate (7757-82-6)

carbon tetrachloride (56-23-5)

sodium nitrite (7632-00-0)

butanol, n-butyl alcohol (71-36-3)

Acetophenone (98-86-2)

aluminum chloride (3495-54-3)

isopropyl alcohol (67-63-0)

chloroacetyl chloride (79-04-9)

Butyl nitrite, n-butyl nitrite (544-16-1)

nitrosyl chloride (2696-92-6)

isonitrosoacetophenone

ω-Chloroisonitrosoacetophenone (4937-87-5)

Glyoxylyl chloride, phenyl-, oxime

phenacyl chloride (532-27-4)

isopropyl nitrite (541-42-4)

ω-nitroacetophenone (614-21-1)

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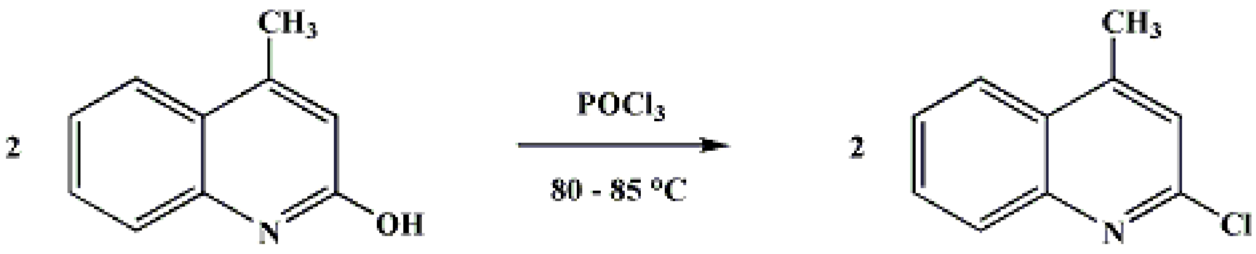
2-CHLOROLEPIDINE

[Lepidine, 2-chloro-]



Submitted by C. E. Kaslow and W. M. Lauer.
Checked by C. F. H. Allen and H. W. J. Cressman.

1. Procedure

In a 500-ml. flask, to which is attached an air condenser whose open end is protected by absorbent cotton or calcium chloride in a drying tube, are mixed 119 g. (0.75 mole) of 4-methylcarbostyril (p. 580) and 138 g. (82.5 ml., 0.9 mole) of freshly distilled phosphorus oxychloride. The mixture is maintained at 80–85° in a water bath for about 15 minutes until most of the solid has dissolved, and then it is warmed carefully for an additional 15 minutes on a wire gauze until solution is complete. The hot reaction mixture is poured into 1 l. of water containing 1 kg. of cracked ice.

The 2-chlorolepidine is extracted, using two 750-ml. portions of ether (Note 1). The extract is shaken with two 200-ml. portions of water and then dried over 50 g. of potassium carbonate. After removal of the ether, the residual oil is distilled from a 200-ml. modified Claisen flask. The colorless distillate boils at 132–135°/3 mm. and weighs 118–122 g. (89–92%). The distillate is melted if necessary and poured into 250 ml. of petroleum ether (b.p. 40–50°); the solution is then chilled in a freezing mixture; the crystals are filtered by suction and dried in a vacuum desiccator over paraffin. The snow-white 2-chlorolepidine melts at 58–59° and weighs 114–118 g. (86–89%).

2. Notes

1. An additional 5–8 g. of slightly colored material can be secured by neutralizing the aqueous solution with 200 g. of sodium carbonate, extracting with 500 ml. of ether, and distilling. The total yield of distilled product then amounts to 125–130 g. (95–97%).

3. Discussion

The preparation described is based on the method of Knorr[1] and has been used by Mikhailov,[2] Krahler and Burger,[3] and Mizuno.[4] 2-Chlorolepidine has also been

prepared by the action of benzoyl chloride on 4-methylcarbostyril.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 519
- Org. Syn. Coll. Vol. 3, 580

References and Notes

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2. Mikhailov, *J. Gen. Chem. U.S.S.R.*, **6**, 511 (1936) [*C. A.*, **30**, 6372 (1936)].
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

potassium carbonate (584-08-7)

ether (60-29-7)

sodium carbonate (497-19-8)

benzoyl chloride (98-88-4)

Phosphorus Oxychloride (21295-50-1)

2-Chlorolepidine, Lepidine, 2-chloro- (634-47-9)

4-Methylcarbostyril (607-66-9)

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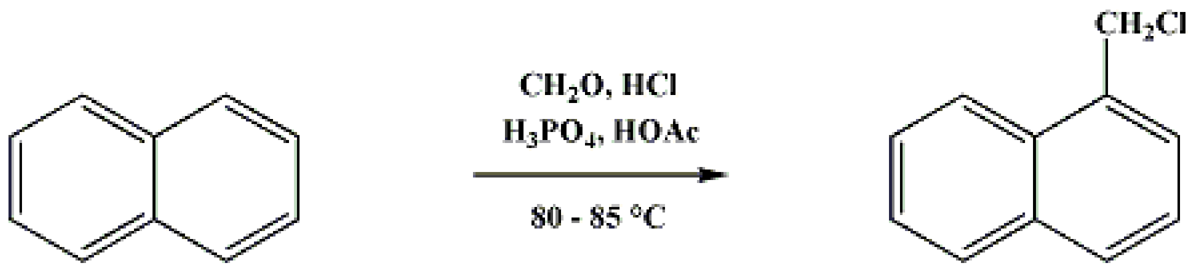
1-CHLOROMETHYLNAPHTHALENE

[Naphthalene, 1-chloromethyl-]



Submitted by Oliver Grummitt and Allen Buck.
Checked by C. F. H. Allen and J. VanAllan.

1. Procedure

Caution! Both chloromethylnaphthalene and the by-products are lachrymators and vesicants. Although it is not necessary to work in a hood, precautions should be taken during the handling of the substance and apparatus.

In a 3-l. three-necked flask, fitted with a reflux condenser and Hershberg stirrer, are placed 256 g. (2 moles) of naphthalene, 110 g. of paraformaldehyde (Note 1), 260 ml. of glacial acetic acid, 165 ml. of 85% phosphoric acid, and 428 g. (362 ml., 4.2 moles) of concentrated hydrochloric acid. This mixture is heated in a water bath at 80–85° and vigorously stirred for 6 hours (Note 2).

After the mixture has been cooled to 15–20° it is transferred to a 2-l. separatory funnel and the crude product is washed first with two 1-l. portions of water cooled to 5–15°, then with 500 ml. of cold 10% potassium carbonate solution, and finally with 500 ml. of cold water. The product is the lower layer in all the washings. After the addition of 200 ml. of ether, the solution is given a preliminary drying by being allowed to stand over 10 g. of anhydrous potassium carbonate, with frequent shaking, for 1 hour. The lower aqueous layer which forms is separated, and the ether solution is again dried over 20 g. of potassium carbonate for 8–10 hours (Note 3) and (Note 4).

The dried solution is distilled, first at atmospheric pressure to remove most of the solvent, and then under reduced pressure (Note 5). A fore-run of unused naphthalene amounting to 35–40 g. is collected at 90–110°/5 mm. (Note 6). This is followed by 195–204 g. of 1-chloromethylnaphthalene which boils at 128–133°/5 mm. or at 148–153°/14 mm. (74–77% based on naphthalene consumed) (Note 7) and (Note 8).

2. Notes

1. "Trioxymethylene" from the Eastman Kodak Company was used.
2. The level of the water bath should be maintained at the same height as that of the stirred reaction mixture.
3. Both the washing and drying operations must be done very carefully, because the presence of small amounts of water or acid is liable to cause the product to resinify during the final distillation.
4. The checkers added 50 ml. of dry benzene before distilling the solvent to remove traces of water by azeotropic distillation.
5. A clean, dry flask and a moderate rate of distillation help to overcome the tendency of the product to resinify.
6. Care should be taken to prevent clogging of the line by the naphthalene.
7. The oil pump should be protected from acid fumes by means of a trap containing alkali.
8. The residue left after distillation consists mainly of *bis*-(chloromethyl) naphthalene and di-1-naphthylmethane.

3. Discussion

1-Chloromethylnaphthalene has been made from naphthalene and a variety of reagents: methyl chloromethyl ether;[1] aqueous formaldehyde and hydrogen chloride with or without sulfuric acid as a condensing agent;[2,3,4,5,6,7,8] and paraformaldehyde with hydrogen chloride or hydrochloric acid.[9,10,11] Catalysts employed have been zinc chloride,[2,12,13,14] aluminum chloride,[13] phosphoric acid,[15,16,17] and *p*-toluenesulfonyl chloride.[18] Petroleum ether and glacial acetic acid have been used as solvents. The present method is a modification of that described by Cambron.[15]

The chloromethylation of aromatic hydrocarbons has been discussed by Fuson and McKeever.[19] It is reported that arsenic salts are helpful in the chloromethylation process.[20]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 690

References and Notes

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19. Fuson and McKeever, *Organic Reactions*, **1**, 63 (1942); John Wiley & Sons.
20. U. S. pat. 2,541,408 [*C. A.*, **45**, 6662 (1951)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

trioxymethylene

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

hydrogen chloride, hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

ether (60-29-7)

formaldehyde (630-08-0)

aluminum chloride (3495-54-3)

phosphoric acid (7664-38-2)

Naphthalene (91-20-3)

zinc chloride (7646-85-7)

methyl chloromethyl ether (107-30-2)

1-Chloromethylnaphthalene, Naphthalene, 1-chloromethyl-, chloromethylnaphthalene (86-52-2)

di-1-naphthylmethane

p-Toluenesulfonyl chloride (98-59-9)

bis-(chloromethyl) naphthalene

paraformaldehyde (30525-89-4)

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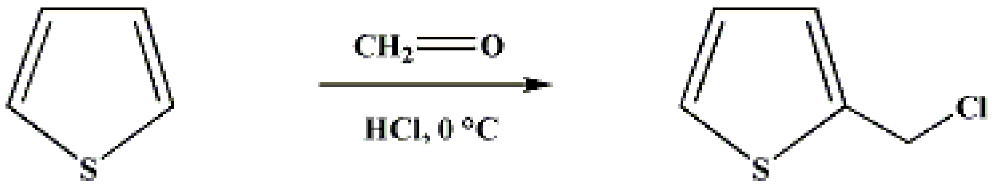
Organic Syntheses, CV 3, 197

2-CHLOROMETHYLTHIOPHENE

[Thiophene, 2-chloromethyl-]



Submitted by K. B. Wiberg and H. F. McShane.
Checked by Cliff S. Hamilton and J. L. Pauley.

1. Procedure

Caution! Suitable precautions should be observed in the preparation, purification, and storage of 2-chloromethylthiophene. The product is lachrymatory, and the procedure should be carried out in an efficient hood. The distillation and storage of the material are described in (Note 6) and (Note 7).

In a 2-l. beaker surrounded by an ice-salt bath (Note 1), and fitted with a mechanical stirrer and a thermometer, are placed 420 g. (392 ml., 5 moles) of thiophene (Note 2) and 200 ml. of concentrated hydrochloric acid. A rapid stream of hydrogen chloride (Note 3) is passed continuously into the mixture with vigorous stirring. When the temperature reaches 0°, 500 ml. of 37% formaldehyde solution (Note 4) is added at a rate that will permit the temperature to remain below 5°. The addition requires about 4 hours. When all the formaldehyde solution has been added, the mixture is extracted with three 500-ml. portions of ether. The ether extracts are combined, washed successively with water and saturated sodium bicarbonate solution, and then dried over anhydrous calcium chloride. The solvent is removed by distillation, and the product is distilled under reduced pressure through a 50-cm. fractionating column (Note 5). The product boiling at 73–75°/17 mm. is collected. The yield is 257–267 g. (40–41%) of a colorless oily liquid (Note 6) and (Note 7).

2. Notes

1. The checkers preferred to use a Dry Ice bath or to add Dry Ice to the reaction mixture as needed.
2. The thiophene used by the submitters was that supplied by the Socony-Vacuum Oil Company. It was used without any additional purification.
3. A satisfactory hydrogen chloride generator has been described earlier.[1]
4. The apparatus should be set up in a hood, for, although nearly all the hydrogen chloride is absorbed, a small amount does escape. The rate of addition

of hydrogen chloride should be such that nearly complete absorption is maintained at all times.

According to the submitters, paraformaldehyde (165 g., 5.5 moles) may be substituted for the formaldehyde solution. This modification affords an easier control of the temperature. However, paraformaldehyde does not react to any appreciable extent below 0°, and so the temperature should be kept between 0° and 5°. The reaction time is 6–8 hours, and the yield is unchanged.

5. A Vigreux column was used by both the submitters and checkers.

6. Some *bis*-(2-thienyl) methane may be obtained from the residue at 125–126°/9 mm. When recrystallized from methanol it melts at 46–47°.

7. It is advisable not to store chloromethylthiophene for any length of time or in sealed containers, since it has a tendency to decompose, often with explosive violence, even when kept cold and in the dark. If the product is to be used for the preparation of 2-thiophenaldehyde it is convenient to convert it to the more stable hexamethylenetetrammonium salt, for storage.

Instances of explosion of the product on storage have been reported; these are apparently due to generation of hydrogen chloride within a closed container.

The following procedure for distillation and storage is recomended (F. C. Myer, private communication). The crude product is stabilized by the addition of 2% by weight of dicyclohexylamine and purified by rapid distillation under reduced pressure. The pot temperature should not rise above 100° during the main part of the distillation, or above 125° at the end of the distillation. The distillate is stabilized immediately with 1–2% by weight of dicyclohexylamine and stored in a glass bottle plugged loosely with a stopper wrapped with glass wool. The bottle is placed in a large beaker and stored in a refrigerator. A small amount of gelatinous salt separates on standing; this has no deleterious effect.

When stabilized properly and stored in the cold, decomposition is slow. The material should be inspected regularly to observe excessive darkening and liberation of hydrogen chloride. Restabilization and distillation may permit recovery of pure material if the decomposition is not too far advanced. Complete decomposition results in frothing, resinification, and liberation of hydrogen chloride.

3. Discussion

2-Chloromethylthiophene has been prepared by the action of hydrogen chloride on 2-thienylcarbinol[2] and by the action of hydrogen chloride and formaldehyde on thiophene.[3] The above procedure is essentially that of Blicke and Burckhalter.[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 811

References and Notes

1. *Org. Syntheses* Coll. Vol. **1**, 534 (1941).
2. Biedermann, *Ber.*, **19**, 636 (1886).
3. Blicke and Burckhalter, *J. Am. Chem. Soc.*, **64**, 477 (1942).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

calcium chloride (10043-52-4)

hydrogen chloride, hydrochloric acid (7647-01-0)

methanol (67-56-1)

ether (60-29-7)

formaldehyde (630-08-0)

sodium bicarbonate (144-55-8)

Thiophene (110-02-1)

2-Chloromethylthiophene, Thiophene, 2-chloromethyl-, chloromethylthiophene (765-50-4)

2-thiophenaldehyde

dicyclohexylamine (101-83-7)

2-thienylcarbinol (636-72-6)

bis-(2-thienyl) methane (4341-34-8)

paraformaldehyde (30525-89-4)

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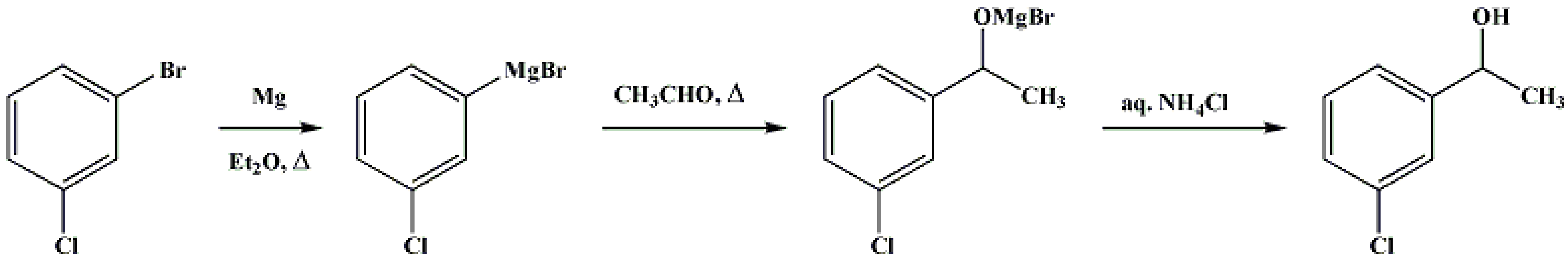
Organic Syntheses, CV 3, 200

m-CHLOROPHENYLMETHYLCARBINOL

[Benzyl alcohol, *m*-chloro-α-methyl-]



Submitted by C. G. Overberger, J. H. Saunders, R. E. Allen, and Robert Gander.
Checked by Arthur C. Cope and Theodore T. Foster.

1. Procedure

A dry 2-l. three-necked round-bottomed flask is equipped with a sealed stirrer, a 500-ml. dropping funnel (Note 1), and an efficient reflux condenser attached to a calcium chloride tube. In the flask are placed 29.1 g. (1.2 gram atoms) of magnesium turnings, a crystal of iodine, and about 50 ml. of dry ether. A solution of 229 g. (1.2 moles) of *m*-bromochlorobenzene (Note 2) in 850 ml. of dry ether is added with stirring at a rate which maintains rapid refluxing. The reaction begins after 20–50 ml. of the ether solution is added (Note 3), and the addition requires 1–3 hours. The mixture is stirred and heated on the steam bath under reflux for 1 hour after all the *m*-bromochlorobenzene has been added.

A cooled solution of 60 g. (1.365 moles) of freshly distilled acetaldehyde in 200 ml. of dry ether (Note 4) is added through the dropping funnel during 2–3.5 hours, as rapidly as the condenser capacity permits. The mixture is stirred and heated under reflux for 1 hour after the addition is completed.

The reaction mixture is cooled in ice, and the addition compound is decomposed by adding dropwise with stirring 185 ml. of a 25% solution of ammonium chloride in water (Note 5). The ether solution becomes clear, and the salts separate as a cake. The ether solution is decanted, combined with 150 ml. of ether that has been used to rinse the salt cake, and dried over anhydrous magnesium sulfate. After removal of the ether the product is distilled under reduced pressure to give 154.5–164.5 g. (82.5–88%) of *m*-chlorophenylmethylcarbinol boiling at 99–104°/4 mm.; n_D^{25} 1.5405 (Note 6).

2. Notes

1. It is convenient to use a Hershberg stirrer with a rubber slip seal protected from ether vapor with a short water-cooled condenser. The dropping funnel may be connected to the flask through an extension tube to prevent clogging, which occurs if the Grignard reagent comes in contact with the acetaldehyde in the tip of the funnel.

2. *m*-Bromochlorobenzene was prepared according to p. 185. It may be purchased from the Eastman Kodak Company.

3. If the reaction does not begin spontaneously, the mixture should be heated under reflux until the reaction starts before more than 50 ml. of the *m*-bromochlorobenzene solution is added.

4. The solution is cooled to prevent loss of acetaldehyde by vaporization. Commercial acetaldehyde may be redistilled just before it is used, or acetaldehyde may be prepared by depolymerization of paraldehyde.[1]

5. The submitters state that the complex may be decomposed by pouring the reaction mixture onto 1 kg. of crushed ice to which 50 ml. of concentrated sulfuric acid has been added. The ether layer is separated, combined with two 100-ml. ether extracts of the aqueous layer, and washed with three 250-ml. portions of water, one 250-ml. portion of 10% sodium carbonate solution, and finally with 250 ml. of water.

6. The same general method (including the procedure of (Note 5)) has been used by the submitters to prepare the following substituted phenylmethylcarbinols:

Carbinol	*Boiling Point*	*% Yield*
m-Trifluoromethylphenylmethylcarbinol	100–102°/17 mm.	83
m-Methylphenylmethylcarbinol	103–105°/6 mm.	71
m-*tert*-Butylphenylmethylcarbinol	130–134°/17 mm.	56

An alternative preparation of similar carbinols, consisting in the reaction of methylmagnesium iodide with a substituted benzaldehyde, is advantageous when the aromatic aldehyde is available. The following carbinols have been prepared by the submitters in that way:

Aldehyde	*Carbinol*	*Boiling Point*	*% Yield*
p-Chlorobenzaldehyde [Heyden Chemical Corporation; *Org. Syntheses* Coll. Vol. **2**, 133 (1943)]	*p*-Chlorophenylmethylcarbinol	98–100°/4.5 mm.	59
o-Chlorobenzaldehyde (Heyden Chemical Corporation)	*o*-Chlorophenylmethylcarbinol	94°/4 mm.	69
o-Bromobenzaldehyde	*o*-Bromophenylmethylcarbinol	102–105°/2–3 mm.	73
m-Bromobenzaldehyde	*m*-Bromophenylmethylcarbinol	105–110°/2–3 mm.	74
p-Bromobenzaldehyde [*Org. Syntheses* Coll. Vol. **2**, 89, 442 (1943)]	*p*-Bromophenylmethylcarbinol	90°/1 mm.	64

2,3-Dichlorobenzaldehyde	2,3-Dichlorophenylmethylcarbinol	112–113°/2 mm. m.p. 55–57°	76
2,4-Dichlorobenzaldehyde (Heyden Chemical Corporation)	2,4-Dichlorophenylmethylcarbinol	125–126°/7 mm.	62
2,6-Dichlorobenzaldehyde (Eastman Kodak Company)	2,6-Dichlorophenylmethylcarbinol	104–107°/2.5 mm.	89
3,5-Dichlorobenzaldehyde	3,5-Dichlorophenylmethylcarbinol	126°/4 mm.	69
3,4-Dichlorobenzaldehyde (Heyden Chemical Corporation)	3,4-Dichlorophenylmethylcarbinol	125–130°/3–4 mm.	73

3. Discussion

This procedure is adapted from the preparation described by Marvel and Schertz.[2] *m*-Chlorophenylmethylcarbinol also has been prepared from *m*-chlorobenzaldehyde and methylmagnesium iodide,[3,4,5] and by the reduction of *m*-chloroacetophenone in the presence of copper chromite.[6]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 204

References and Notes

1. *Org. Syntheses* Coll. Vol. **2**, 407 (1943).
2. Marvel and Schertz, *J. Am. Chem. Soc.*, **65**, 2054 (1943).
3. Lock and Bock, *Ber.*, **70**, 916 (1937).
4. Brooks, *J. Am. Chem. Soc.*, **66**, 1295 (1944).
5. Ushakov and Matuzov, *J. Gen. Chem. U.S.S.R.*, **14**, 120 (1944) [*C. A.*, **39**, 916 (1945)].
6. Emerson and Lucas, *J. Am. Chem. Soc.*, **70**, 1180 (1948).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

acetaldehyde (75-07-0)

sulfuric acid (7664-93-9)

ether (60-29-7)

ammonium chloride (12125-02-9)

magnesium turnings (7439-95-4)

sodium carbonate (497-19-8)

benzaldehyde (100-52-7)

iodine (7553-56-2)

methylmagnesium iodide (917-64-6)

magnesium sulfate (7487-88-9)

COPPER CHROMITE

2,3-Dichlorobenzaldehyde (6334-18-5)

2,3-Dichlorophenylmethylcarbinol

2,4-Dichlorobenzaldehyde (874-42-0)

2,4-Dichlorophenylmethylcarbinol (81156-68-5)

2,6-Dichlorobenzaldehyde (83-38-5)

2,6-Dichlorophenylmethylcarbinol

3,5-Dichlorobenzaldehyde (10203-08-4)

3,5-Dichlorophenylmethylcarbinol

3,4-Dichlorobenzaldehyde (6287-38-3)

3,4-Dichlorophenylmethylcarbinol

m-Bromobenzaldehyde (3132-99-8)

m-Chlorobenzaldehyde (587-04-2)

p-Chlorobenzaldehyde (104-88-1)

p-Bromobenzaldehyde (1122-91-4)

o-chlorobenzaldehyde (89-98-5)

m-bromochlorobenzene (108-37-2)

m-Chlorophenylmethylcarbinol (5182-44-5)

Benzyl alcohol, m-chloro-α-methyl- (6939-95-3)

m-Trifluoromethylphenylmethylcarbinol (455-01-6)

m-Methylphenylmethylcarbinol (1875-89-4)

m-tert-Butylphenylmethylcarbinol

p-Chlorophenylmethylcarbinol (1875-88-3)

o-Chlorophenylmethylcarbinol (19819-95-5)

o-Bromobenzaldehyde (6630-33-7)

o-Bromophenylmethylcarbinol (1074-16-4)

m-Bromophenylmethylcarbinol (28229-69-8)

p-Bromophenylmethylcarbinol (4654-39-1)

m-chloroacetophenone (99-02-5)

paraldehyde (123-53-7)

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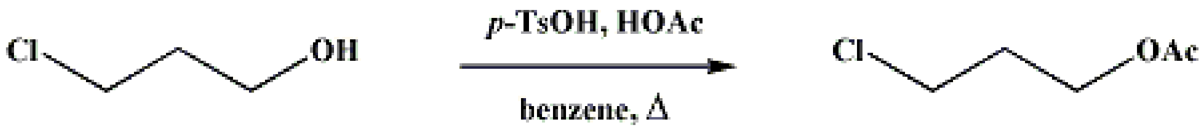
Organic Syntheses, *CV 3*, *203*

γ-CHLOROPROPYL ACETATE

[1-Propanol, 3-chloro-, acetate]



Submitted by C. F. H. Allen and F. W. Spangler.
Checked by Millard Seeley and C. R. Noller.

1. Procedure

A 1-l. round-bottomed flask is fitted with a 30-cm. Vigreux column (Note 1) connected to a condenser. The condenser leads to an automatic separator arranged so that the lighter liquid is returned to the flask.[1] In the flask is placed a mixture of 189 g. (167 ml., 2 moles) of trimethylene chlorohydrin,[2] 180 g. (172 ml., 3 moles) of glacial acetic acid, 300 ml. of benzene, and 2 g. of *p*-toluenesulfonic acid monohydrate. The mixture is refluxed at such a rate that the temperature at the top of the column remains at 69° (boiling point of benzene-water azeotrope) during the time the greatest amount of water is distilling, and rises gradually to 80° (boiling point of benzene-acetic acid azeotrope) as the last of the water is removed. The volume of the aqueous layer collected varies with the temperature of the vapors and the length of time required for distillation, but it is approximately 50 ml. at the end of the reaction; the time required is 7–9 hours (Note 2).

The solution is cooled, then washed successively with two 500-ml. portions of 10% sodium carbonate solution, one 500-ml. portion of water, and one 100-ml. portion of saturated sodium chloride solution. The wash solutions are extracted successively with one 100-ml. portion of benzene, which is added to the main benzene solution. After removal of the benzene the ester is distilled at atmospheric pressure through a 30-cm. asbestos-wrapped Vigreux column, the fraction boiling at 166–170°, n_D^2 1.4295, being collected. The yield of colorless product is 257–260 g. (93–95%).

2. Notes

1. The submitters prefer to use the Clarke-Rahrs ester column,[3] for which they claim two distinct advantages: (1) dehydration requires no attention beyond occasionally noting the amount of distillate—when no more aqueous layer separates the reaction is over; (2) reagents do not need to be dry—any water present is removed during the heating.
2. Titration of an aliquot portion of the aqueous layer with standard alkali will give the amount of acetic acid carried over, from which the amount of water can be determined. The expected amount of water is 36 ml.

3. Discussion

γ-Chloropropyl acetate has been prepared by heating 1-bromo-3-chloropropane and potassium acetate in glacial acetic acid,[4] and by the action of acetyl chloride on trimethylene chlorohydrin.[5,6]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 835

References and Notes

1. *Org. Syntheses* Coll. Vol. **1**, 422 (1941).
2. *Org. Syntheses* Coll. Vol. **1**, 533 (1941).
3. *Synthetic Org. Chemicals*, **9**, No. 3 (May, 1936), Eastman Kodak Company.
4. Henry, *Bull. acad. roy. Belg.*, **1906**, 738 [*C. A.*, **1**, 1969 (1907)].
5. Derick and Bissel, *J. Am. Chem. Soc.*, **38**, 2483 (1916).
6. Lespieau, *Bull. soc. chim. France*, **7**, 254 (1940).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

benzene-acetic acid azeotrope

acetic acid (64-19-7)

Benzene (71-43-2)

acetyl chloride (75-36-5)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

1-bromo-3-chloropropane (109-70-6)

Trimethylene chlorohydrin (627-30-5)

γ-Chloropropyl acetate, 1-Propanol, 3-chloro-, acetate (628-09-1)

potassium acetate (127-08-2)

p-toluenesulfonic acid monohydrate (6192-52-5)

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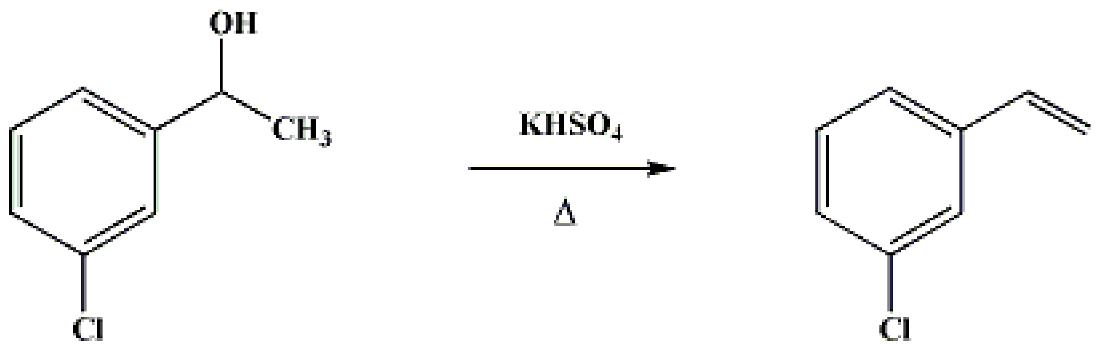
Organic Syntheses, CV 3, 204

m-CHLOROSTYRENE

[Styrene, *m*-chloro-]



Submitted by C. G. Overberger and J. H. Saunders.
Checked by Arthur C. Cope and Theodore T. Foster.

1. Procedure

A 500-ml. three-necked round-bottomed flask is attached to a 250-ml. dropping funnel and a total-condensation variable take-off fractionating column with a 20 by 1.2 cm. section packed with glass helices (Note 1). The fractionating column is fitted to a 500-ml. receiving flask. In the reaction flask are placed 12.5 g. of powdered fused potassium acid sulfate and 0.05 g. of *p-tert*-butylcatechol. The flask is immersed in an oil bath maintained at 220–230°, and 145 g. (0.925 mole) of *m*-chlorophenylmethylcarbinol (p. 200) and 0.05 g. of *p-tert*-butylcatechol (Note 2) are placed in the dropping funnel. The system is evacuated to a pressure of 125 mm., maintained by a manostat, and the *m*-chlorophenylmethylcarbinol is added dropwise at a rate (15–20 drops per minute) which maintains a vapor temperature at 110–120° at the top of the column. The *m*-chlorostyrene and water formed are collected in a receiver. When the addition is completed (5.5–8.5 hours) the pressure is held constant until distillation stops, and it is then reduced to 20 mm. until no more liquid distils.

The distillate is rinsed into a separatory funnel with 25 ml. of ether, and the organic layer is separated and dried over 10 g. of anhydrous magnesium sulfate. The drying agent is separated and rinsed with 25 ml. of ether, and 0.1 g. of *p-tert*-butylcatechol is added to the solution. The ether is removed, and the product is distilled under reduced pressure. *m*-Chlorostyrene is obtained in a yield of 102–106 g. (80–82.5%), boiling at 55–57°/3 mm.; n_D^{20} 1.5625 (Note 3) and (Note 4). A small amount (3–8 g.) of *m*-chlorophenylmethylcarbinol can be recovered as a higher-boiling fraction.

2. Notes

1. Effective separation of *m*-chlorostyrene from *m*-chlorophenylmethylcarbinol is possible with the short column specified. If a fractionating column is not used,

lower conversions result and the crude product contains *m*-chlorophenylmethylcarbinol, which can be separated by fractional distillation and used in a subsequent preparation.

2. The submitters state that hydroquinone is not a satisfactory polymerization inhibitor for use in this preparation but that picric acid is very effective (less than 0.01 g. is required).

3. The submitters have used a similar procedure to prepare the following substituted styrenes from arylmethylcarbinols. The reactions were conducted more rapidly (addition rate about 2 drops per second), and no fractionating column was used in the initial distillation. A lower pressure (100 mm.) was used in dehydration of the dichlorophenylmethylcarbinols. The yields cited are based on the weights of arylmethylcarbinols which reacted; varying amounts of the carbinols were recovered in the distillation of the products.

	Boiling Point	*% Yield*
o-Chlorostyrene	67–69°/3–3.5 mm.	64–66.5
p-Chlorostyrene	65°/4 mm.	57
o-Bromostyrene	64–65°/3 mm.	64.5
m-Bromostyrene	74–75°/3 mm.	56
p-Bromostyrene	87–88°/12 mm.	50
m-Fluorostyrene	30–32°/2 mm.	45
2,3-Dichlorostyrene	92–94°/4–5 mm.	44
2,4-Dichlorostyrene	81°/6 mm.	33
3,4-Dichlorostyrene	95°/5 mm.	63.5
2,6-Dichlorostyrene	64–65°/3 mm.	31.5
3,5-Dichlorostyrene	59°/1 mm.	43.5

The dehydration procedure of this preparation is stated to be unsatisfactory for substituted phenylmethylcarbinols which have a strongly electronegative group, such as the nitro or trifluoromethyl group, in the *meta* position.

4. Some color due to small amounts of iodine may be present in substituted styrenes prepared by this procedure from arylmethylcarbinols synthesized from the corresponding aldehyde and methylmagnesium iodide. If present, iodine may be removed by shaking the crude product with 1 g. of powdered zinc and 25 ml. of water.

3. Discussion

m-Chlorostyrene has been prepared by dehydration of *m*-chlorophenylmethylcarbinol by modifications of this procedure,[1,2,3] and by the vapor-phase dehydration in the presence of alumina at reduced pressure.[4]

References and Notes

1. Marvel and Schertz, *J. Am. Chem. Soc.*, **65**, 2054 (1943).
2. Brooks, *J. Am. Chem. Soc.*, **66**, 1295 (1944).
3. Ushakov and Matuzov, *J. Gen. Chem. U.S.S.R.*, **14**, 120 (1944) [*C. A.*, **39**, 916 (1945)].
4. Emerson and Lucas, *J. Am. Chem. Soc.*, **70**, 1180 (1948).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alumina

potassium acid sulfate

ether (60-29-7)

hydroquinone (123-31-9)

iodine (7553-56-2)

zinc (7440-66-6)

picric acid (88-89-1)

methylmagnesium iodide (917-64-6)

magnesium sulfate (7487-88-9)

2,3-Dichlorostyrene

2,4-Dichlorostyrene

3,4-Dichlorostyrene (2039-83-0)

2,6-Dichlorostyrene (28469-92-3)

3,5-Dichlorostyrene

p-tert-butylcatechol (98-29-3)

o-Bromostyrene (2039-88-5)

m-Chlorophenylmethylcarbinol (5182-44-5)

m-Chlorostyrene, Styrene, m-chloro- (2039-85-2)

o-Chlorostyrene (2039-87-4)

p-Chlorostyrene (1073-67-2)

m-Bromostyrene (2039-86-3)

p-Bromostyrene (2039-82-9)

m-Fluorostyrene (350-51-6)

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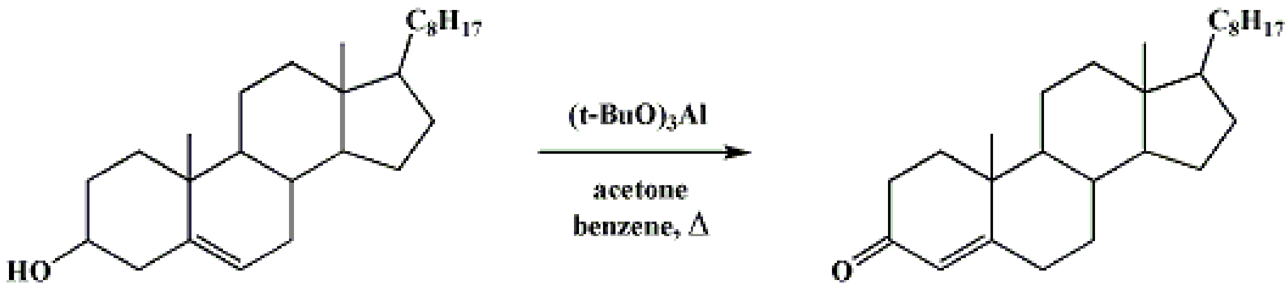
Organic Syntheses, CV 3, 207

CHOLESTENONE



Submitted by R. V. Oppenauer
Checked by J. Cason and L. F. Fieser.

1. Procedure

A carefully dried 5-l. round-bottomed flask equipped with a reflux condenser carrying a calcium chloride tube is charged with 100 g. of cholesterol (Note 1), 750 ml. of acetone (Note 2), and 1 l. of benzene (Note 3). A boiling tube is introduced to prevent bumping (Note 4), and the mixture is heated to boiling in an oil bath which is maintained at 75–85° during the reaction. A solution of 80 g. of aluminum *tert*-butoxide (p. 48) in 500 ml. of dry benzene is added in one portion to the boiling solution. The mixture turns cloudy and in 10–15 minutes develops a yellow color. Gentle boiling is continued at a bath temperature of 75–85° for a total of 8 hours. The mixture is then cooled, treated with 200 ml. of water and then 500 ml. of 10% sulfuric acid, shaken vigorously, and transferred to a 5-l. separatory funnel. The mixture is diluted with 1.5 l. of water and shaken for several minutes, after which the yellow aqueous layer is drawn off into a second separatory funnel and shaken out with a small amount of benzene (Note 5). The combined benzene extracts are washed thoroughly with water and dried by filtration through a layer of sodium sulfate; the solvent is evaporated, the last traces being removed by heating the residue at 60° at the water pump vacuum. The oily yellow residue solidifies when it is cooled in an ice-salt bath and scratched. For crystallization the material is dissolved in a mixture of 70 ml. of acetone and 100 ml. of methanol; the solution is allowed to cool very slowly and is seeded, for otherwise the product tends to separate as an oil. After the bulk of the material has crystallized, the mixture is allowed to stand for 1 day at 0°; the product is then collected, washed with 100 ml. of ice-cold methanol, and dried in vacuum at room temperature. The yield of almost colorless cholestenone, m.p. 77–79°, is 70–81 g. (70–81%). Recrystallization by the same method gives material melting at 78.5–80.5° with 90% recovery (Note 6) and (Note 7).

2. Notes

1. The material should be dried to constant weight at 80–100° in vacuum. Commercial cholesterol, m.p. 146–148.5°, gives satisfactory results; the yield is raised 5–10% by using cholesterol that has been purified by regeneration from the dibromide.

2. The acetone is distilled once from permanganate and twice from freshly fused potassium hydroxide.

3. The benzene is distilled over sodium.

4. If boiling stones are employed, fresh ones must be added at intervals; the boiling tube promotes smooth boiling at the bath temperature specified.

5. The troublesome emulsions sometimes encountered are easily broken by filtration from a trace of suspended solid.

6. For recovery of material in the mother liquors, the solutions are subjected to steam distillation to remove solvents and condensation products from the acetone. The process is continued until the distillate is odorless (1–2 hours), and the residual oil is dried by heating it under reduced pressure on the steam bath. From a solution in acetone-methanol (20 ml. and 50 ml., respectively) there is obtained after some manipulation (slow cooling, scratching) 3.3 g. of crude cholestenone, m.p. 72–80° (cloudy melt).

7. The yield is reduced by about 5% by halving the amounts of acetone and benzene specified and using only 50 g. of aluminum *tert*-butoxide.

3. Discussion

Cholestenone has been prepared by oxidation of cholesterol dibromide with chromic acid[1,2] or potassium permanganate[3] and subsequent debromination; by dehydrogenation of cholesterol over copper oxide;[4,5] and by the method described above.[6,7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 192
- Org. Syn. Coll. Vol. 4, 195

References and Notes

1. Windaus, *Ber.*, **39**, 518 (1906).
2. Bretschneider and Ajtai, *Monatsh.*, **74**, 57 (1943).
3. Schoenheimer, *J. Biol. Chem.*, **110**, 461 (1935).
4. Diels and Abderhalden, *Ber.*, **37**, 3099 (1904).
5. Diels, Gädke, and Körding, *Ann.*, **459**, 21 (1927).
6. Oppenauer, *Rec. trav. chim.*, **56**, 137 (1937).
7. Brit. pat. 487,360 [*C. A.*, **33**, 323 (1939)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

Benzene (71-43-2)

methanol (67-56-1)

potassium permanganate (7722-64-7)

sodium sulfate (7757-82-6)

acetone (67-64-1)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

chromic acid (7738-94-5)

copper oxide (1317-38-0)

Cholesterol (57-88-5)

Cholestenone

acetone-methanol (590-90-9)

Cholesterol dibromide (1857-80-3)

ALUMINUM tert-BUTOXIDE

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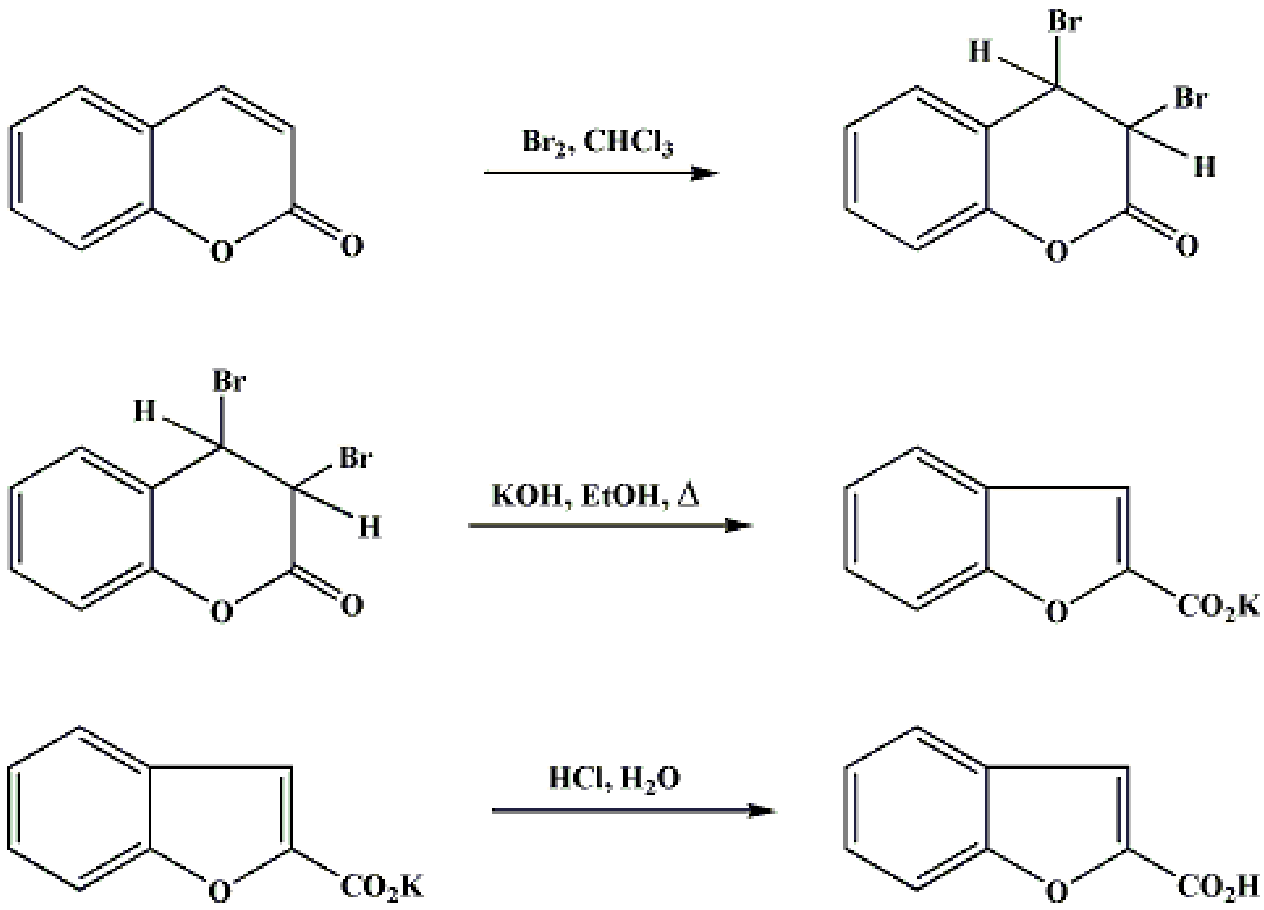
Organic Syntheses, *CV 3, 209*

COUMARILIC ACID



Submitted by R. C. Fuson, J. Wayne Kneisley, and E. W. Kaiser.
Checked by W. E. Bachmann and G. Dana Johnson.

1. Procedure

A. *Coumarin dibromide*. In a 1-l. three-necked flask, equipped with a mechanical stirrer, a dropping funnel, and a condenser fitted with a trap for hydrogen bromide, are placed 146 g. (1 mole) of coumarin and 200 ml. of chloroform. A solution of 160 g. (1 mole) of bromine in 85 ml. of chloroform is added dropwise to the well-stirred solution of coumarin at room temperature over a period of 3 hours (Note 1). Excess bromine is removed by adding approximately 200 ml. of a 20% solution of sodium sulfite through the dropping funnel. The colorless chloroform layer is separated, washed with two 200-ml. portions of water, and dried over magnesium sulfate (Note 2). After the mixture has stood for only a few minutes (Note 3), the magnesium sulfate is removed by filtration and the solution of the dibromide is evaporated to 100 ml. in a rapid stream of dry air (Note 4). The coumarin dibromide is collected on a filter, and the mother liquor is evaporated nearly to dryness by an air blast. This mixture is filtered, and the slightly yellow mother liquor is evaporated to dryness. The product of the third evaporation is slightly discolored, and it is washed with two 15-ml. portions of ether (Note 5). The combined precipitates weigh 215 g. (70%) and melt at 102–105° (Note 6).

B. *Coumarilic acid*. In a 5-l. three-necked flask fitted with a mechanical stirrer and reflux condenser, 450 g. (8 moles) of solid potassium hydroxide is dissolved in 700 ml. of absolute ethanol. The solution is cooled to 15° by immersing the flask in an ice bath, and 215 g. (0.7 mole) of finely divided coumarin dibromide is added in 10- to 15-g. portions to the well-stirred basic solution. The rate of addition is controlled so that the temperature never rises above 20°; the addition requires about 30 minutes. After all the dibromide has been added, the reaction mixture is refluxed, with stirring, for 30 minutes (Note 7). One and a half liters of water is added, and the resulting solution is steam-distilled until 2.5 l. of distillate has been collected (Note 8). The residue is cooled to room temperature by the addition of 1 kg. of cracked ice (Note 9) and is then acidified by the addition of 1.2 l. of 6 *N* hydrochloric acid. The crude coumarilic acid is collected on a filter and stirred with 600 ml. of cold water. The acid is separated from the water by filtration, sucked as dry as possible on the filter, and then crystallized from a mixture of 250 ml. of ethanol and 250 ml. of water (Note 10). The recrystallized coumarilic acid is colorless, weighs 93–100 g. (82–88%) (Note 11), and melts at 190–193°.

2. Notes

1. Occasional use of an ice bath is necessary to keep the temperature from rising.
2. If any coumarin dibromide separates before the magnesium sulfate is removed, enough chloroform should be added to dissolve the dibromide.
3. The mixture should be worked up immediately in order to avoid decomposition of the dibromide.
4. The checkers found that considerable decomposition occurred when this procedure was employed, perhaps because it happened to be carried out on a warm, humid day; they found it preferable to remove the chloroform by distillation under reduced pressure from a water bath at this step and the succeeding ones. Because of the instability of the dibromide, it is advisable to convert it to coumarilic acid on the day it is made.
5. The first evaporation produces 136 g. of colorless crystals; the second, 63 g.; and the third, 16 g. of ether-washed product.
6. The first crop of crystals melts at 102–105°. The succeeeding products melt somewhat lower but are sufficiently pure for the next reaction.
7. The suspension of potassium bromide must be stirred vigorously to avoid bumping.
8. The steam distillation is carried out conveniently by fitting the reaction vessel with a steam inlet tube and a condenser set for downward distillation. The flask should be heated so that the final volume of the distilland is not more than 3 l.
9. A heavy precipitate composed of potassium coumarilate and potassium bromide may appear if the steam distillation has been very efficient. The precipitate dissolves during the addition of hydrochloric acid.
10. The crude acid is dissolved in 250 ml. of boiling absolute ethanol to which has been added 3 g. of Norit; 250 ml. of water, previously heated to 85°, is then added to the filtered solution.
11. The over-all yield, based on the amount of coumarin, is 57–62%.

3. Discussion

Coumarilic acid has been prepared by treating coumarin dibromide with alcoholic potassium hydroxide and acidifying with hydrochloric acid, a method due essentially to Perkin.[1] Coumarilic acid has also been prepared by Perkin from 3-chlorocoumarin and from 3-bromocoumarin by the action of alcoholic potassium hydroxide.[2]

Coumarilic acid has also been prepared from 2-bromobenzofuran by reaction with *n*-butyllithium and subsequent carbonation[3] and by the oxidation (NaOCl) of 2-acetylbenzofuran.[4]

Coumarin dibromide has been prepared by the addition of bromine to coumarin in chloroform solution.[1,2]

References and Notes

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2. Perkin, *J. Chem. Soc.*, **24**, 37 (1871).
3. Gilman and Melstrom, *J. Am. Chem. Soc.*, **70**, 1655 (1948).
4. Farrar and Levine, *J. Am. Chem. Soc.*, **72**, 4433 (1950).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium sulfite (7757-83-7)

chloroform (67-66-3)

hydrogen bromide (10035-10-6)

bromine (7726-95-6)

potassium hydroxide (1310-58-3)

potassium bromide (7758-02-3)

NaOCl (7681-52-9)

magnesium sulfate (7487-88-9)

n-butyllithium (109-72-8)

coumarin

Coumarin dibromide (55077-11-7)

3-chlorocoumarin

3-bromocoumarin

2-bromobenzofuran

2-acetylbenzofuran (1646-26-0)

Coumarilic acid (496-41-3)

potassium coumarilate

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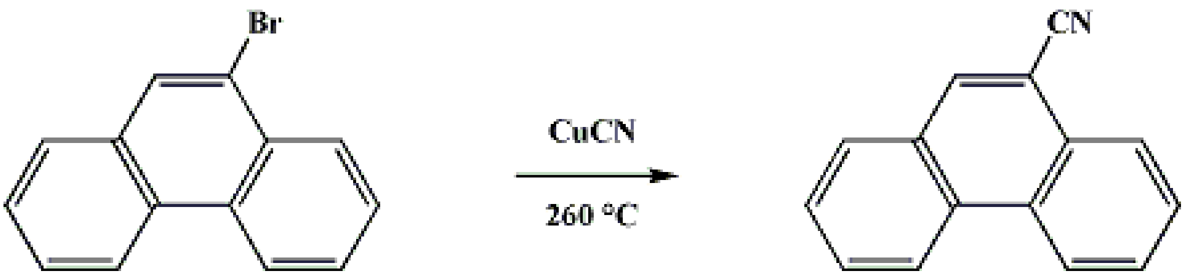
9-CYANOPHENANTHRENE

[9-Phenanthrenecarbonitrile]



Submitted by Joseph E. Callen, Clinton A. Dornfeld, and George H. Coleman[1].
Checked by Robert E. Carnahan and Homer Adkins.

1. Procedure

In a 2-l. Claisen flask (Note 1) are mixed 1 kg. (3.90 moles) of 9-bromophenanthrene (p. 134) (Note 2) and 400 g. (4.46 moles) of cuprous cyanide. A small motor-driven spiral stirrer is inserted, and the flask is heated (Note 3) at 260° for 6 hours (Note 4). The flask is then provided with a fine capillary inlet tube, a thermometer, and a 2-l. distilling flask attached to the side arm of the Claisen flask as receiver. The 9-cyanophenanthrene is distilled at 190–195°/2 mm. The yield of crude product is 740 g. (93%), m.p. 94–98°. One recrystallization from about 2 l. of dry ethanol yields 690 g. (87%) of material melting at 105–107° (Note 5), (Note 6), and (Note 7).

2. Notes

1. It is necessary to sacrifice the flask after the distillation, since the inorganic residue cannot be removed easily.
2. The 9-bromophenanthrene need not be recrystallized if it has been purified by distillation.
3. The heating may be readily controlled by the use of an electric heating mantle and variable transformer.
4. Increasing the heating period beyond 6 hours has no effect on the yield.
5. The melting point can be raised to 110° by further recrystallization from ethanol. The unrecrystallized product is probably pure enough for most purposes.
6. The checkers operated on one-tenth the scale and duplicated the percentage yields obtained on the larger scale. Material melting at 109–110° was obtained in a 75–77% yield.
7. It has been reported (W. R. Vaughan, private communication) that this reaction is highly exothermic, and that the flask contents may erupt when the mixture is heated to the prescribed temperature. Better control of the reaction may result if the cuprous cyanide is added in portions after the reaction has been

initiated at 260–280° with about one-third or less of the total amount of cuprous cyanide.

3. Discussion

The procedure described above is an adaptation of methods of Mosettig and van de Kamp[2] and of Bachmann and Boatner.[3] 9-Cyanophenanthrene has also been prepared from 9-phenanthrenesulfonic acid[4] and from phenanthrene-9-aldoxime.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 26

References and Notes

1. Work done under contract with the Office of Scientific Research and Development.
2. Mosettig and van de Kamp, *J. Am. Chem. Soc.*, **54**, 3355 (1932).
3. Bachmann and Boatner, *J. Am. Chem. Soc.*, **58**, 2098 (1936); Goldberg, Ordas, and Carsh, *J. Am. Chem. Soc.*, **69**, 260 (1947).
4. Werner and Kunz, *Ann.*, **321**, 327 (1902).
5. Shoppee, *J. Chem. Soc.*, **1933**, 40.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

Cuprous Cyanide (544-92-3)

9-Cyanophenanthrene, 9-Phenanthrenecarbonitrile (2510-55-6)

9-Bromophenanthrene (573-17-1)

9-phenanthrenesulfonic acid

phenanthrene-9-aldoxime

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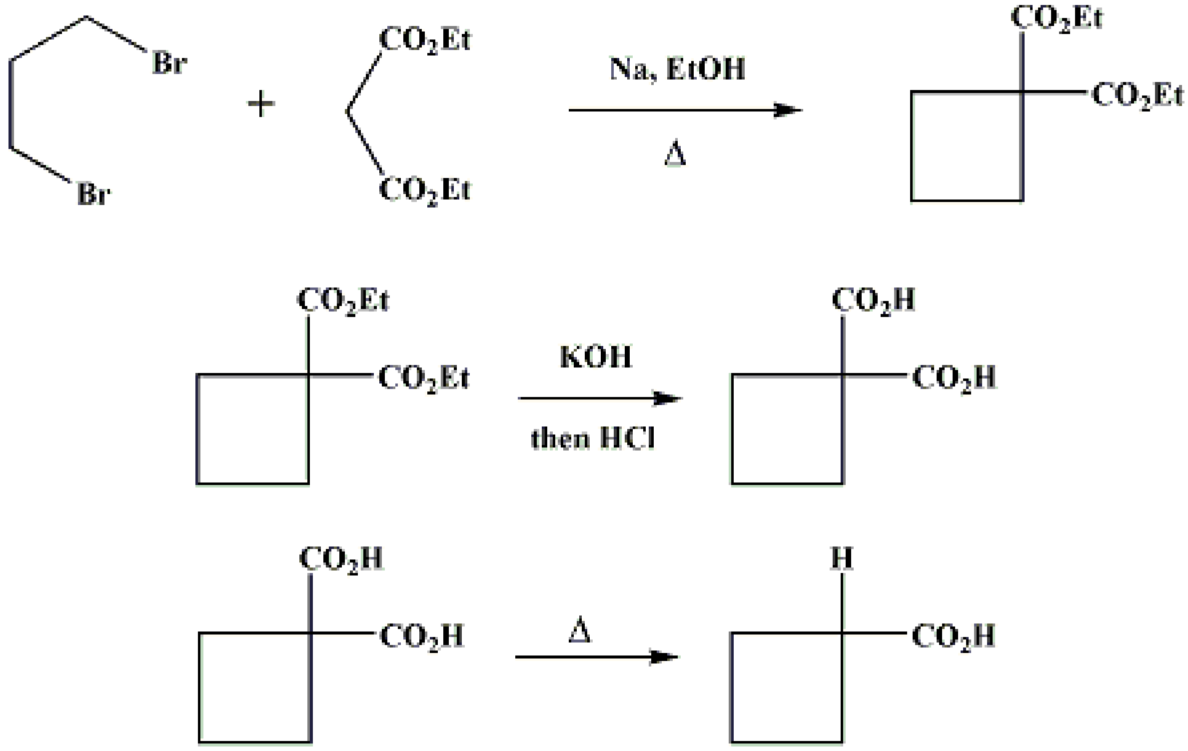
1,1-CYCLOBUTANEDICARBOXYLIC ACID AND CYCLOBUTANECARBOXYLIC ACID



Submitted by G. B. Heisig and F. H. Stodola.
Checked by F. C. Whitmore, T. S. Oakwood, and D. L. Green.

1. Procedure

A. *1,1-Cyclobutanedicarboxylic acid.* In a 3-l. three-necked round-bottomed flask, carrying a separatory funnel, a mechanical stirrer, a reflux condenser fitted with a calcium chloride tube, and a thermometer, are placed 160 g. (1 mole) of ethyl malonate and 212 g. (1.05 moles) of trimethylene bromide. The thermometer is adjusted so that the bulb is immersed in the liquid in the flask; the stirrer is started, and a solution of 46 g. (2 gram atoms) of sodium in 800 ml. of absolute ethanol is added through the separatory funnel while the temperature of the reaction mixture is kept at 60–65° (Note 1). During the addition of the first quarter of the ethoxide solution (20 minutes) it is necessary to cool the reaction mixture occasionally in order to maintain the proper temperature, but after this point the remainder of the ethoxide solution is added just rapidly enough to keep the reaction mixture at 60–65°; this part of the addition requires about 30 minutes.

The reaction mixture is allowed to stand until the temperature drops to 50–55°, after which it is heated on a steam bath until a sample added to water is neutral to phenolphthalein (about 2 hours). Water is added to dissolve the precipitate of sodium bromide, and the ethanol is removed by distillation. The flask is now arranged for

steam distillation, and the ethyl 1,1-cyclobutanedicarboxylate and unchanged malonic ester are removed by steam distillation (Note 2); about 4 l. of distillate is collected. The ester layer in the distillate is separated, and the aqueous layer is extracted once with 1 l. of ether. The extract and the ester layer are combined, and the ether is removed on the steam bath (Note 3).

The esters are hydrolyzed by refluxing them for 2 hours with a solution of 112 g. of potassium hydroxide in 200 ml. of ethanol. Most of the ethanol is removed by distillation, and the mixture is then evaporated to dryness on a steam bath. The residue is dissolved in the minimum amount of hot water (100 to 125 ml.), and concentrated hydrochloric acid (about 90–95 ml.) is added until the solution is slightly acid (Note 4). After the solution has been boiled for a few minutes to removed carbon dioxide, it is made slightly alkaline with ammonia. To the boiling solution there is added a slight excess of barium chloride. The hot solution is filtered to remove barium malonate, the filtrate is cooled, and to it is added 100 ml. of 12 *N* hydrochloric acid. The solution is then extracted with four 250-ml. portions of ether. The extracts are combined and dried over calcium chloride, and the ether is removed by distillation on a steam bath. The residual pasty mass (about 38 g.) is pressed on a porous plate to remove adherent oil and then dissolved in 30–50 ml. of hot ethyl acetate. The solution, when cooled in an ice-salt bath, deposits the pure dicarboxylic acid. This is filtered; the filtrate, when evaporated, yields a pasty mass of acid which, in turn, is crystallized from ethyl acetate. The yield of pure 1,1-cyclobutanedicarboxylic acid melting at 156–158° is 30–34 g. (21–23%).

B. *Cyclobutanecarboxylic acid.* The above dibasic acid is placed in a 75-ml. distilling flask carrying a thermometer and attached to a 75-ml. Claisen flask as a receiver. The receiver is cooled with running water while the flask containing the dibasic acid is heated in a metal or oil bath (bath temperature, 160–170°) until no more carbon dioxide is evolved. Then the temperature of the bath is raised to 210–220°, and the material that boils at 189–195° is collected. The crude cyclobutanecarboxylic acid (19–22 g.) is redistilled from the Claisen flask in which it was collected. The pure acid boils at 191.5–193.5°/740 mm. (Note 5) and weighs 18–21 g. (18–21% based on malonic ester). There is a small higher-boiling fraction, which comes over at 193.5–196°/740 mm.

2. Notes

1. The submitters and the checkers prepared the sodium ethoxide in the conventional manner. However, sodium ethoxide and sodium methoxide are very conveniently prepared by the "inverse" procedure, as described by Tishler in Fieser, *Experiments in Organic Chemistry*, 2nd ed., 1941, D. C. Heath and Company, Boston, p. 385 (bottom). The metal is placed in the flask, and the alcohol is added through the condenser at such a rate that rapid refluxing is maintained. It is necessary, as a precautionary measure, to clamp the flask and not to trust to the friction between a rubber stopper and the flask to hold the flask in place. When this precaution is taken, a cooling bath may be used with

safety. It is necessary to cool the flask; the metal must not be allowed to melt, as this will result in the formation of one large mass with a greatly decreased metallic surface. (Private communication, C. F. H. Allen.)

2. The steam distillation separates ethyl malonate and ethyl 1,1-cyclobutanedicarboxylate from ethyl pentane-1,1,5,5-tetracarboxylate, formed in a side reaction between malonic ester (2 moles) and trimethylene bromide (1 mole). The tetraethyl ester remains in the residue from the steam distillation. In several test experiments, in which about two-thirds of the amounts specified above were used, the yield of tetraethyl ester was 30–40% of the theoretical amount, based upon the sodium ethoxide used.

3. If this extraction with ether is omitted the yield of 1,1-cyclobutanedicarboxylic acid is 3–4 g. less.

4. The submitters used 55 ml. of hydrochloric acid at this point; the checkers stated that this amount was insufficient to neutralize the mixture. The purpose of acidification at this point is not to liberate the cyclobutanedicarboxylic acid, but merely to remove carbonates and excess potassium hydroxide. After the carbon dioxide has been expelled, the solution is made alkaline with ammonia; hence a great excess of hydrochloric acid should be avoided. The submitters used only enough hydrochloric acid to make the solution acid to litmus. After the solution has been made basic with ammonia, barium chloride solution is added until there is no further precipitation of barium malonate.

5. This acid is quite pure. The checkers distilled 52.5 g. of it through an analytical column; except for a fore-run of 1.5–2.0 g., all the material had a constant boiling point and index of refraction.

3. Discussion

1,1-Cyclobutanedicarboxylic acid has been prepared by hydrolysis of the ethyl ester,[1] or of the half nitrile, 1-cyano-1-carboxycyclobutane.[2] The ethyl ester has been prepared by condensation of ethyl malonate with trimethylene bromide[1,3] or chlorobromide,[4] and by the action of sodium ethoxide on diethyl γ-bromopropylmalonate.[5] The half nitrile has been prepared by condensation of trimethylene bromide with ethyl cyanoacetate followed by hydrolysis of the ester to the acid.[2]

Cyclobutanecarboxylic acid has been prepared by decarboxylation of the 1,1-dibasic acid,[1,6] and by decarboxylation of 1-cyano-1-carboxycyclobutane followed by hydrolysis of the cyano group.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 733
- Org. Syn. Coll. Vol. 4, 288

- Org. Syn. Coll. Vol. 5, 273
- Org. Syn. Coll. Vol. 5, 909
- Org. Syn. Coll. Vol. 6, 271
- Org. Syn. Coll. Vol. 6, 312
- Org. Syn. Coll. Vol. 7, 117

References and Notes

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2. Carpenter and Perkin, *J. Chem. Soc.*, **75**, 930 (1899).
3. Cason and Allen, *J. Org. Chem.*, **14**, 1036 (1949).
4. Kishner, *J. Russ. Phys. Chem. Soc.*, **37**, 507 (1905) (*Chem. Zentr.*, **1905**, II, 761).
5. Walborsky, *J. Am. Chem. Soc.*, **71**, 2941 (1949).
6. Perkin and Sinclair, *J. Chem. Soc.*, **61**, 40 (1892).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

chlorobromide

ethanol (64-17-5)

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ethyl acetate (141-78-6)

ether (60-29-7)

sodium bromide (7647-15-6)

Trimethylene bromide (109-64-8)

carbon dioxide (124-38-9)

barium chloride (10361-37-2)

sodium methoxide (124-41-4)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

Ethyl cyanoacetate (105-56-6)

ethyl malonate (1071-46-1)

phenolphthalein (77-09-8)

1,1-Cyclobutanedicarboxylic acid, cyclobutanedicarboxylic acid (5445-51-2)

Cyclobutanecarboxylic acid (3721-95-7)

ethyl 1,1-cyclobutanedicarboxylate

barium malonate

ethyl pentane-1,1,5,5-tetracarboxylate

diethyl γ-bromopropylmalonate

1-cyano-1-carboxycyclobutane

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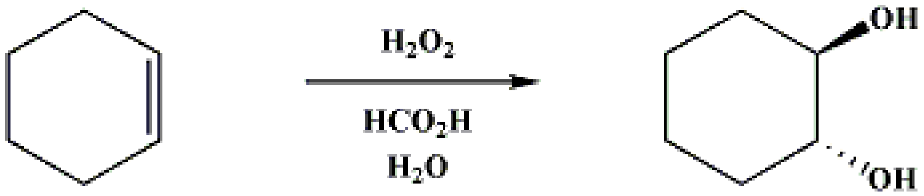
trans-1,2-CYCLOHEXANEDIOL

[1,2-Cyclohexanediol, *trans*-]



Submitted by Alan Roebuck and Homer Adkins.
Checked by Arthur C. Cope and Claude F. Spencer.

1. Procedure

One hundred and forty milliliters of 30% hydrogen peroxide (1.4 moles) (Note 1) is added to 600 ml. of 88% formic acid (13.7 moles) (Note 2) in a 1-l. three-necked flask equipped with a thermometer and a motor-driven stirrer. Freshly distilled cyclohexene (82 g., 1.0 mole) (Note 3) is added slowly from a dropping funnel over a period of 20–30 minutes while the temperature of the reaction mixture is maintained between 40° and 45° by cooling with an ice bath and by controlling the rate of addition (Note 4). The reaction mixture is kept at 40° for 1 hour after all the cyclohexene has been added, and then it is allowed to stand overnight at room temperature.

The formic acid and water are removed by distillation from a steam bath under reduced pressure. An ice-cold solution of 80 g. of sodium hydroxide in 150 ml. of water is added in small portions to the residual viscous mixture of the diol and its formates, with care that the temperature of the mixture does not exceed 45°. The alkaline solution is warmed to 45°, and an equal volume (350 ml.) or more of ethyl acetate is added. After thorough extraction, the lower layer is separated and extracted at 45° six times with equal volumes of ethyl acetate. The seven ethyl acetate solutions (Note 5) are combined (total volume about 2.1 l.), and the solvent is distilled from a steam bath until the residual volume is 300–350 ml. and the solid product begins to crystallize. The mixture is cooled to 0°, and the product is separated by filtration (77–90 g., melting in the range of 90–98°). The mother liquor is concentrated on a steam bath to a volume of 65–75 ml., and more solid crystallizes. The mixture is cooled and filtered as before and yields an additional 4–15 g. of crude product melting in the range of 80–89°. *trans*-1,2-Cyclohexanediol, b.p. 120–125°/4 mm., is obtained by distillation of the combined crude products, with the use of an oil bath and a flask having a side arm and an air condenser sufficiently wide that they will not become plugged as the product solidifies (Note 6). The yield of product of m.p. 101.5–103° is 75–85 g. (65–73%) (Note 7).

2. Notes

1. The concentration of the hydrogen peroxide may be determined by titration with 0.2 *N* potassium permanganate in acid solution.
2. Less formic acid than is specified may be used, but the yields are lower and the reaction is not so easily controlled.
3. The cyclohexene used may be the commercial product or it may be prepared from cyclohexanol.[1]
4. If the temperature rises above 45°, the reaction may be stopped by discontinuing the stirring.
5. The total quantity of ethyl acetate required is less if the first three extractions are combined and the solvent required for successive extractions is distilled at a steam bath from this solution.
6. If there is an appreciable quantity of solid residue in the flask, it may be dissolved in hot water and crystallized by cooling in ice. The crystals of cyclohexanediol, after being dried, may be distilled as described above.
7. The product can be recrystallized from ethyl acetate.

3. Discussion

The method described is essentially that of Swern, Billen, Findley, and Scanlan.[2] In addition to the performic acid method,[3] *trans*-1,2-cyclohexanediol may be obtained through hydrolysis of the monoacetate[4,5] or cyclohexene oxide.[4] It has also been obtained by a peracetic acid oxidation of cyclohexene with tungsten trioxide,[6] and as a by-product in several instances.[7,8] *cis*-1,2-Cyclohexanediol has been prepared by reaction of cyclohexene with hydrogen peroxide in *tert*-butyl alcohol with osmium tetroxide as a catalyst.[6,9] Mixtures of *cis* and *trans* isomers have resulted from the hydrogenation (Raney nickel) of catechol,[10,11] and the sodium-alcohol[12] or catalytic[13] reduction of adipoin.

References and Notes

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13. U. S. pat. 2,467,451 [*C. A.*, **43**, 6229 (1949)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

adipoin

alcohol (64-17-5)

ethyl acetate (141-78-6)

sodium hydroxide (1310-73-2)

Cyclohexanol (108-93-0)

potassium permanganate (7722-64-7)

Cyclohexene (110-83-8)

formic acid (64-18-6)

Raney nickel (7440-02-0)

sodium (13966-32-0)

Catechol (120-80-9)

hydrogen peroxide (7722-84-1)

Cyclohexene oxide (286-20-4)

cyclohexanediol

peracetic acid (79-21-0)

tungsten trioxide

osmium tetroxide (20816-12-0)

tert-butyl alcohol (75-65-0)

trans-1,2-Cyclohexanediol, 1,2-Cyclohexanediol, trans- (1460-57-7)

cis-1,2-Cyclohexanediol (1792-81-0)

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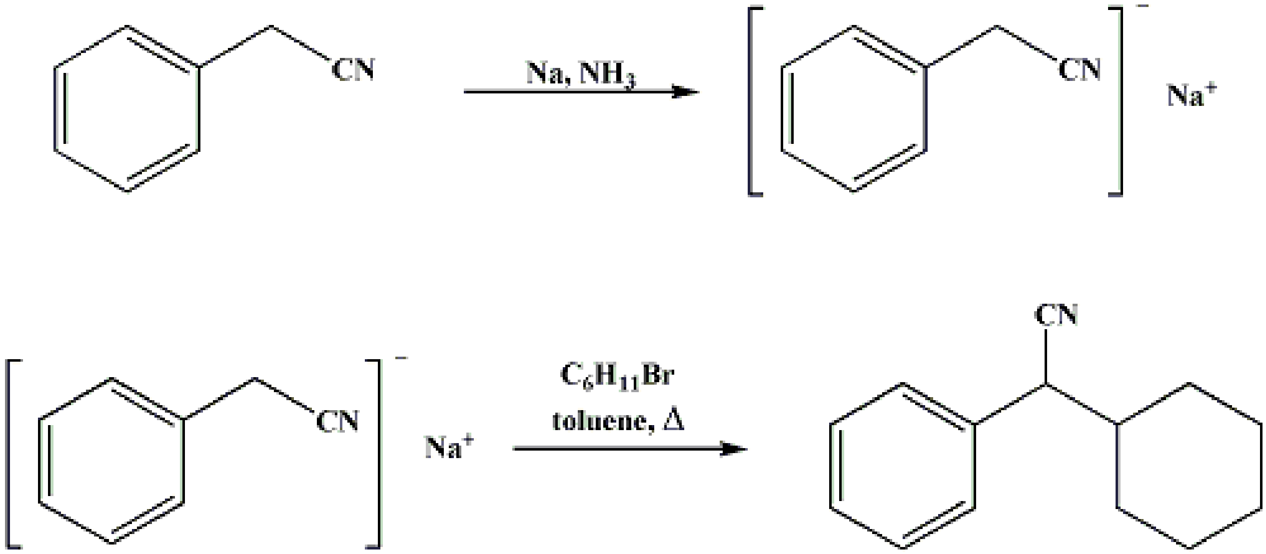
Organic Syntheses, CV 3, 219

α-CYCLOHEXYLPHENYLACETONITRILE

[Cyclohexaneacetonitrile, α-phenyl-]



Submitted by Evelyn M. Hancock and Arthur C. Cope.
Checked by Nathan L. Drake and W. Mayo Smith.

1. Procedure

A 1-l. three-necked flask is equipped with a mercury-sealed stirrer, an inlet tube, and a reflux condenser which is connected through a sodalime tube to a gas-absorption trap. The apparatus is dried in an oven and assembled rapidly to exclude moisture; it is advisable to set up the apparatus in a hood to vent ammonia that may escape by accident. The flask is cooled in a Dry Ice-trichloroethylene bath, and 200 ml. of anhydrous (refrigeration grade) ammonia is introduced through the inlet tube from an ammonia cylinder which is either inverted or equipped with a siphon tube. Just before the apparatus is assembled, 8.1 g. (0.35 gram atom) of sodium is cut, weighed, and kept under kerosene in a small beaker. The Dry Ice bath is removed, the inlet tube is replaced by a rubber stopper, and a crystal of hydrated ferric nitrate (about 0.2 g.) is added. A small (about 5-mm.) cube of the sodium is cut, blotted rapidly with filter paper, and added quickly to the liquid ammonia. The solution is stirred until the blue color disappears, after which the remainder of the sodium is added in narrow, thin strips about as rapidly as it can be cut and blotted, while the solution is stirred vigorously (Note 1). After the solution has turned from blue to gray, the flask is swirled by hand until the blue flecks of sodium that have spattered onto the upper part of the flask are washed into the solution.

The flask is again cooled in the Dry Ice bath, and 41 g. (0.35 mole) of benzyl cyanide (Note 2) is added during about 10 minutes through a dry dropping funnel. The Dry Ice bath is removed, and the clear solution is stirred for about 15 minutes, after which 200 ml. of dry sulfur-free toluene (Note 3) and 25 ml. of anhydrous ether are added dropwise through the funnel while the ammonia evaporates. The solution is allowed to stand or is warmed in a

water bath until it comes to room temperature; the ammonia may be vaporized at any rate that does not cause gas to escape through the mercury seal on the stirrer. The remainder of the ammonia is removed by turning off the water in the reflux condenser, warming the flask in a hot water bath, and distilling most of the ether (and ammonia) through the reflux condenser.

A fresh drying tube is attached to the reflux condenser, the cooling water is turned on, and to the warm solution is added 65.2 g. (0.4 mole) of bromocyclohexane (Note 4) during approximately 20 minutes. The reaction is vigorous and may require cooling. Refluxing is continued by heating the mixture in an oil bath for 2 hours. The reaction mixture is cooled and washed with 300 ml. of water. The aqueous layer is extracted with two 50-ml. portions of benzene, and the combined benzene and toluene solutions are washed with two 50-ml. portions of water and distilled from a 500-ml. modified Claisen flask under reduced pressure. The yield of α-cyclohexylphenylacetonitrile boiling at 174–176°/13 mm. (Note 5) is 45–53 g. (65–77%); the distillate solidifies to a crystalline mass which has a melting point of 50–53.5°. The nitrile can be recrystallized from commercial pentane with approximately 15% loss; it then melts at 56–58°.

2. Notes

1. Vigorous stirring and addition of the sodium in small pieces decrease the time required for complete conversion of the sodium into sodamide.
2. Redistilled benzyl cyanide was used, b.p. 108–110°/13 mm.
3. The toluene (Merck reagent grade) was kept dry by storage over sodium wire. Dry thiophene-free benzene may be used instead but is less convenient because it freezes when added to the liquid ammonia solution.
4. Bromocyclohexane obtained from the Eastman Kodak Company was dried over calcium chloride and redistilled.
5. Another boiling point is 165–167°/9 mm.

3. Discussion

α-Cyclohexylphenylacetonitrile has been prepared by treating the sodium derivative obtained from benzyl cyanide and sodamide with bromocyclohexane in benzene,[1] in ether,[2] and in xylene.[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 44
- Org. Syn. Coll. Vol. 4, 387
- Org. Syn. Coll. Vol. 4, 404
- Org. Syn. Coll. Vol. 4, 755

References and Notes

1. Venus-Danilova and Bol'shukon, *J. Gen. Chem. U.S.S.R.*, **7**, 2823 (1937) [*C. A.*, **32**, 2925

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2. Vasiliu, *Bul. Soc. Chim. România*, **19A**, 75 (1937) [*C. A.*, **33**, 4207 (1939)].
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfur-free toluene

calcium chloride (10043-52-4)

ammonia (7664-41-7)

Benzene (71-43-2)

ether (60-29-7)

toluene (108-88-3)

sodium, sodium wire (13966-32-0)

Benzyl cyanide (140-29-4)

bromocyclohexane (108-85-0)

xylene (106-42-3)

Pentane (109-66-0)

sodamide (7782-92-5)

ferric nitrate

α-Cyclohexylphenylacetonitrile, Cyclohexaneacetonitrile, α-phenyl- (3893-23-0)

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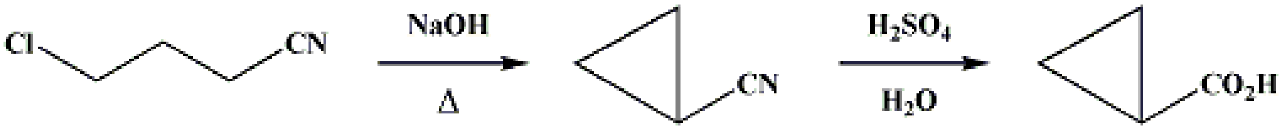
Organic Syntheses, CV 3, 221

CYCLOPROPANECARBOXYLIC ACID



Submitted by Chester M. McCloskey and George H. Coleman.
Checked by C. F. H. Allen and Homer W. J. Cressman.

1. Procedure

In a 2-l. three-necked round-bottomed flask surmounted by two large condensers (Note 1) and (Note 2) are placed 150 g. (3.75 moles) of powdered sodium hydroxide (Note 3) and 103.5 g. (1 mole) of γ-chlorobutyronitrile.[1] The contents of the flask are well mixed by shaking, after which the mixture is heated on a steam bath; a rather vigorous reaction sets in (Note 4). The water formed in the reaction hydrolyzes some of the cyclopropyl cyanide, so that after 1 hour's heating very little liquid is apparent. The hydrolysis of the cyanide is completed by the addition of water in small portions over a period of about 2 hours and subsequent heating; 15–20 ml. of water is added at first, and portions of 60–75 ml. later at intervals of 10–15 minutes until 500 ml. in all has been added. The mixture is then heated for an additional 1.5 hours with occasional stirring; at the end of this time the oily layer will have disappeared.

The solution is then cooled in an ice bath and acidified by 200 g. of concentrated sulfuric acid (sp. gr. 1.84) previously mixed with 300 g. of cracked ice. The solution is again cooled in an ice bath. The thick floating layer of cyclopropanecarboxylic acid and various polymers is separated and the cold aqueous solution extracted once with 1 l. of ether, using a stirrer instead of shaking (Note 5). The extract and crude acid are combined and dried over 50 g. of Drierite, and the solvent is removed in a 500-ml. modified Claisen flask on a steam bath. The residue is then distilled under reduced pressure. The yield of acid boiling at 94–95°/26 mm. or 117–118°/75 mm. is 63.5–68 g. (74–79%) (Note 6).

2. Notes

1. It is advisable to set up the apparatus in a hood, as small amounts of isocyanide are evolved.
2. The yield is slightly higher if the first vigorous reaction is allowed to take place without external cooling.
3. The commercial flakes are ground in a mortar if powder is not available. The powdered potassium hydroxide on the market can be used equally well.
4. The reaction sets in after about 15 minutes. If potassium hydroxide is used, there is only a 5-minute interval.
5. Since troublesome emulsions tend to form, it is advisable to avoid all vigorous shaking. If the mixture is stirred mechanically for 15 minutes, emulsions are avoided; if formed, they can be broken by treatment with anhydrous sodium sulfate.
6. The submitters have made runs twice this size; the yields were proportional to those given above.

3. Discussion

Cyclopropanecarboxylic acid has been prepared by the hydrolysis of cyclopropyl cyanide, although it is unnecessary to isolate the nitrile;[2,3,4] by heating cyclopropanedicarboxylic acid;[5,6] and by the action of alkali on ethyl γ-chlorobutyrate.[7] The last two methods do not appear to be of practical importance. The oxidation of cyclopropyl methyl ketone with sodium hypobromite is reported to be an excellent preparative method for this acid.[8]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 126
- Org. Syn. Coll. Vol. 7, 117

References and Notes

1. *Org. Syntheses* Coll. Vol. **1**, 156 (1941).
2. Henry, *Bull. sci. acad. roy. Belg.*, (3) **36**, 34 (1898) (*Chem. Zentr.*, **1899**, I, 975).
3. Kishner, *J. Russ. phys. chem. Ges.*, **37**, 304 (*Chem. Zentr.*, **1905**, I, 1703).
4. Bruylants and Stassen, *Bull. sci. acad. roy. Belg.*, (5) **7**, 702 (1921) [*Chem. Zentr.*, **1922**, I, 1229; *C. A.*, **17**, 2872 (1923)].
5. Perkin, *J. Chem. Soc.*, **47**, 815 (1885).
6. Skraup and Binder, *Ber.*, **62**, 1132 (1929).
7. Rambaud, *Bull. soc. chim. France*, (5) **5**, 1564 (1938).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Drierite

sulfuric acid (7664-93-9)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium sulfate (7757-82-6)

potassium hydroxide (1310-58-3)

γ-Chlorobutyronitrile (628-20-6)

sodium hypobromite

Cyclopropanecarboxylic acid (1759-53-1)

Cyclopropyl cyanide (5500-21-0)

cyclopropanedicarboxylic acid (598-10-7)

ethyl γ-chlorobutyrate (3153-36-4)

cyclopropyl methyl ketone (765-43-5)

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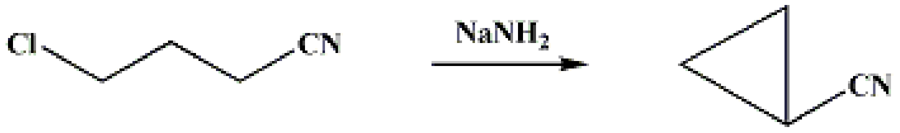
Organic Syntheses, *CV 3, 223*

CYCLOPROPYL CYANIDE

[Cyclopropane, cyano-]

$$2Na + 2NH_3 \longrightarrow 2NaNH_2 + H_2$$

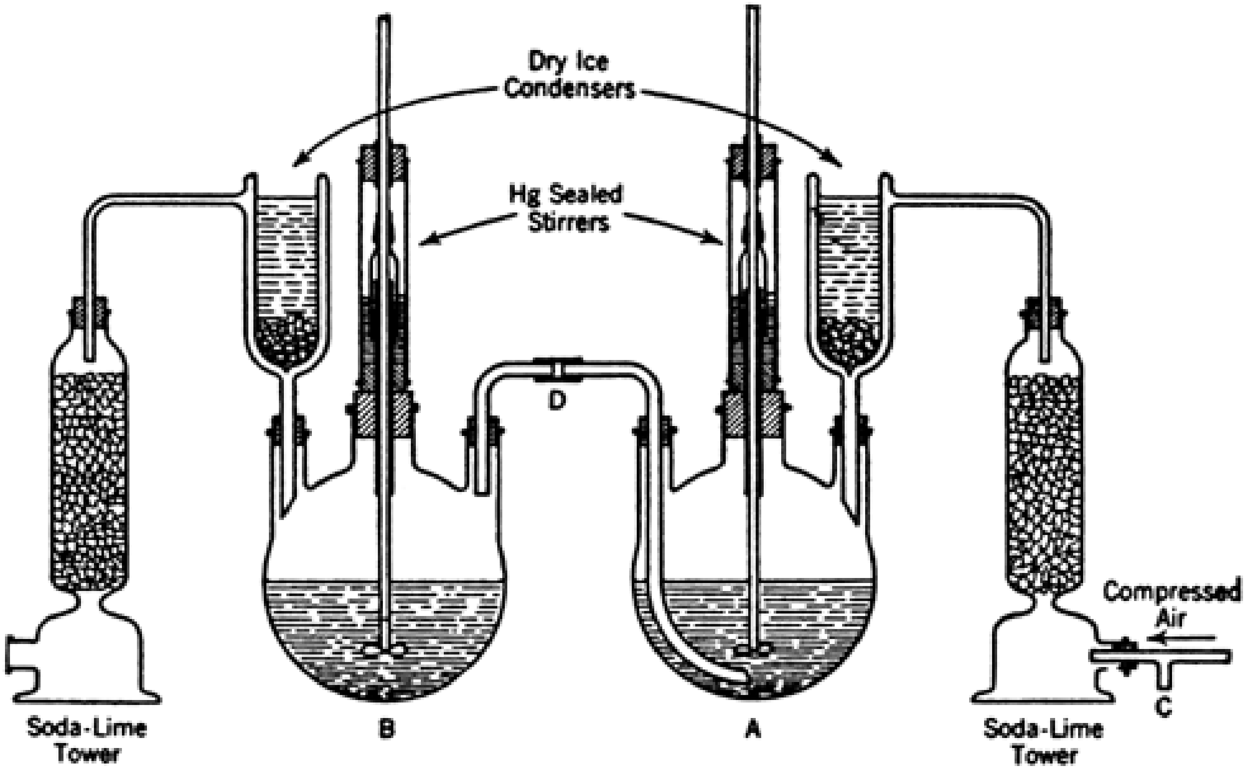


Submitted by M. J. Schlatter
Checked by R. L. Shriner and Chris Best.

1. Procedure

The apparatus shown in .htmFig. 10 is assembled in a good hood. One liter of liquid ammonia and 0.5 g. of hydrated ferric nitrate are placed in the 2-l. three-necked flask *A*, which is equipped with a stirrer and a special reflux condenser cooled with Dry Ice. This condenser is attached to a soda-lime tower which is connected to a source of compressed air through the T-tube *C*. Over a period of about 45 minutes, 92 g. (4 gram atoms) of clean sodium shavings is added to the liquid ammonia, and the mixture is stirred until the blue color disappears (1–2 hours).

Fig. 10.



In the similarly equipped 5-l. three-necked flask *B* are placed 1.5 l. of liquid ammonia and 440 g. (4.25 moles) of γ-chlorobutyronitrile [*Org. Syntheses* Coll. Vol. **1**, 156 (1941)]. The

flasks are connected by means of the 12-mm. glass tube *D* reaching to the bottom of the sodamide flask *A* and extending 1 cm. through the rubber stopper in one neck of flask *B*. Vigorous stirring is maintained in both flasks while the sodamide suspension is slowly forced over into the reaction flask in small portions *(Caution! (Note 1))* by means of air pressure applied through *C*; the rate of addition is controlled by placing the finger over the by-pass in the T-tube. At first the reaction is violent, and only small amounts of the sodamide solution should be added. The addition is continued at such a rate that the total time required for addition of all the sodamide solution is 1–1.5 hours. The sodamide flask is rinsed with 300 ml. of liquid ammonia, and the washings are added to the reaction mixture, after which stirring is continued for 2 hours. During the second hour, addition of Dry Ice to the reflux condenser is discontinued, and the ammonia is permitted to evaporate slowly. At the end of the 2-hour stirring period, the inlet tube is replaced by a dropping funnel and 1 l. of dry ether is slowly added (Note 2). The reaction mixture is quickly filtered through a sintered-glass funnel, and the filter cake is washed with two 200-ml. portions of dry ether (Note 3). The ammonia and ether are removed by distillation on a water bath through a packed column (Note 4). The residue is then distilled through the column under the pressure of a water pump (Note 5). The yield of cyclopropyl cyanide boiling at 69–70°/80 mm. (75–76°/95 mm.) is 149–152 g. (52–53% based upon γ-chlorobutyronitrile) (Note 6) and (Note 7). The pressure is then reduced, and the unchanged γ-chlorobutyronitrile is collected at 93–96°/26 mm. It amounts to 52–62 g.

2. Notes

1. The reaction is very vigorous, and addition of the sodamide solutions in large portions must be avoided. The use of stopcocks or pinch clamps to regulate the addition is not recommended.
2. Very little cyclopropyl cyanide is obtained unless the ether is added *before* complete evaporation of the ammonia.
3. The mixture may be permitted to stand at this point and the ammonia allowed to evaporate spontaneously under a hood.
4. The Carborundum column described in *Org. Syntheses*, **20**, 96, is quite satisfactory.
5. It is desirable to interpose a Dry Ice trap between the receiver and the pump in order to prevent loss of the nitrile, and too low a pressure should not be used.
6. The submitter reports that an equivalent number of moles of γ-bromobutyronitrile or a mixture of γ-chloro- and γ-bromobutyronitrile may be substituted for γ-chlorobutyronitrile. If the bromo compound is used the reaction mixture should be refluxed 6 hours and it is necessary to filter off the sodium bromide just before the final vacuum distillation.
7. This yield is based upon the γ-chlorobutyronitrile taken. When the recovered γ-chlorobutyronitrile (52–62 g.) is taken into account, the yield of cyclopropyl cyanide is about 60%.

3. Discussion

Cyclopropyl cyanide has been prepared by the repeated distillation of γ-chlorobutyronitrile over powdered potassium hydroxide,[1,2,3,4,5] or over a mixture of sodium hydroxide and

alumina.[6] The preparation, on a small scale, of cyclopropyl cyanide from γ-chlorobutyronitrile by action of sodium in liquid ammonia, or of sodium suspended in ether, has been described.[7] The present directions are based upon those given by Schlatter.[8]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 12

References and Notes

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2. Dalle, *Bull. acad. roy. Belg.*, **1902**, 36–79 (*Chem. Zentr.*, **1902**, I, 913).
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4. von Braun, Fussgänger, and Kühn, *Ann.*, **485**, 210 (1925).
5. Nicolet and Sattler, *J. Am. Chem. Soc.*, **49**, 2068 (1927).
6. Cloke, *J. Am. Chem. Soc.*, **51**, 1180 (1929).
7. Cloke, Anderson, Lachman, and Smith, *J. Am. Chem. Soc.*, **53**, 2791 (1931).
8. Schlatter, *J. Am. Chem. Soc.*, **63**, 1733 (1941).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alumina

γ-chloro- and γ-bromobutyronitrile

ammonia (7664-41-7)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium bromide (7647-15-6)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

γ-Chlorobutyronitrile (628-20-6)

sodamide (7782-92-5)

ferric nitrate

Cyclopropyl cyanide, Cyclopropane, cyano- (5500-21-0)

γ-bromobutyronitrile (5332-06-9)

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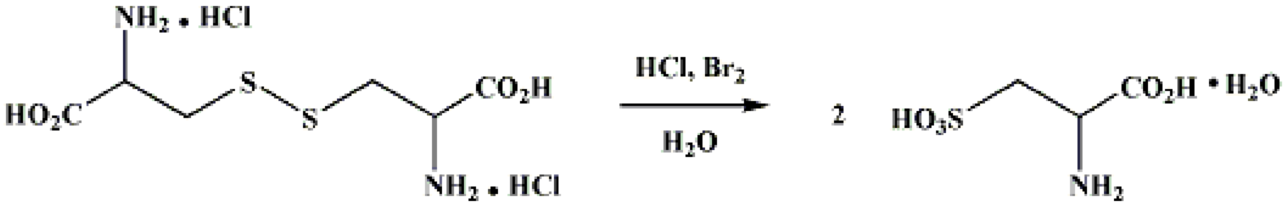
Organic Syntheses, CV 3, 226

CYSTEIC ACID MONOHYDRATE



Submitted by H. T. Clarke
Checked by Henry Gilman and H. J. Harwood.

1. Procedure

To a solution of 24 g. (0.1 mole) of cystine in a cold mixture of 150 ml. of water and 50 ml. of concentrated hydrochloric acid is added, dropwise, 80 g. (25 ml., 0.5 mole) of commercial bromine, with occasional stirring, during 40 minutes. The temperature of the mixture rises to about 60°. The resulting solution, which contains a little unreduced bromine, is then evaporated under reduced pressure on a steam bath. The dark-colored crystalline residue is dissolved in 100 ml. of distilled water and filtered from a small quantity of amorphous insoluble matter. The filtrate is concentrated by evaporation on a water bath to 65 ml. and allowed to crystallize by standing overnight in a refrigerator. The crystals are filtered with suction and washed well with about 100 ml. of 95% ethanol in several portions, the washings being collected separately. The crystals are dried under reduced pressure over phosphorus pentoxide. A second crop is obtained by diluting the washings with an equal volume of water, evaporating until free of ethanol (Note 1), adding the residue to the mother liquor, and evaporating the combined solution to dryness on the water bath. The residue is dissolved in 30–40 ml. of water, decolorized with 0.5–1.0 g. of charcoal, concentrated to 15 ml., and, when cold, treated with 30 ml. of 95% ethanol. The crystals so formed are collected, washed with ethanol, and dried as before (Note 2). The total yield is 30.5–33.5 g. of pure cysteic acid monohydrate (81–90%). It melts, with vigorous evolution of gas, at 278° (289° cor.) (Note 3), and shows the rotation $[\alpha]_{54}^{246}$ + 9.36° (6% in water).

2. Notes

1. Cysteic acid appears to esterify readily on warming with ethanol, but the resulting ester is rapidly hydrolyzed by warming with dilute mineral acid.
2. The final mother liquors, on evaporation to dryness, yield 2–3 g. of a light-brown amorphous product which is readily soluble in water but insoluble in 95% ethanol. In concentrated hydrobromic acid this by-product forms a dark solution, the color of which is discharged on dilution with water.
3. The decomposition point of 278° is obtained by placing the capillary in a bath already heated to 260–270°. If the sample is slowly heated, starting at room temperature, a decomposition point of 257–258° is observed.

3. Discussion

The most convenient oxidant for the preparation of cysteic acid from cystine is aqueous bromine.[1] Iodine[2] and hydrogen peroxide[3] also bring about the reaction, but with both substances some of

the sulfur is split off as sulfuric acid.

References and Notes

1. Friedmann, *Beitr. Chem. Physiol. u. Pathol.*, **3**, 1 (1903).
2. Yamazaki, *J. Biochem. Japan*, **12**, 207 (1930); Shinohara, *J. Biol. Chem.*, **96**, 285 (1932).
3. Schöberl, *Z. physiol. Chem.*, **216**, 193 (1933).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

HYDROBROMIC ACID (10035-10-6)

bromine (7726-95-6)

sulfur (7704-34-9)

iodine (7553-56-2)

hydrogen peroxide (7722-84-1)

cystine (56-89-3)

cysteic acid

Cysteic acid monohydrate (23537-25-9)

phosphorus pentoxide (1314-56-3)

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Organic Syntheses, *CV 3, 227*

DECAMETHYLENE BROMIDE

[Decane, 1,10-dibromo-]

Submitted by W. L. McEwen
Checked by Reynold C. Fuson and E. A. Cleveland.

1. Procedure

A 2-l. three-necked flask, supported in an oil bath, is fitted with a mechanical stirrer and an inlet tube which reaches almost to the bottom of the flask. In it is placed 696 g. (4 moles) of decamethylene glycol, and, after the oil bath is heated to 95–100°, a rapid stream of dry hydrogen bromide is introduced, with stirring. When the mixture becomes saturated with the gas, as shown by vigorous fuming at the open neck of the flask (Note 1), the temperature of the oil bath is raised to 135° and a slow current of hydrogen bromide is passed in for 6 hours (Note 2).

After cooling, the crude product is transferred to a separatory funnel and the lower aqueous layer is drawn off and discarded. The upper layer is washed once with an equal volume of warm water, and then with successive portions of 10% sodium carbonate solution until all acid has been removed. It is then washed once with warm water, which is separated as completely as possible (Note 3). The product thus washed is distilled from a Claisen flask under reduced pressure. The first few drops of distillate containing some water are discarded: the main fraction distils at 139–142°/2 mm. The yield is 1080 g. (90%) (Note 4).

2. Notes

1. In larger runs it is advantageous to stop the stirrer and gas stream at this point and allow the lower aqueous layer to separate, after which it is siphoned out.
2. The total quantity of bromine used is about 950 g.
3. If difficulty is encountered with separation of layers in washing, the substance may be dissolved in an equal volume of ether.
4. This yield was almost invariably obtained by the submitter, who used quantities of glycol varying from 150 g. to 2 kg.
By the same procedure the following dibromides have been prepared.

	% Yield	*Boiling Point*
Trimethylene bromide	75	165–167°

Hexamethylene bromide	90	108–112°/8 mm.
Nonamethylene bromide	93	128–130°/2 mm.

3. Discussion

Decamethylene bromide was first prepared by heating the glycol in a sealed tube with fuming hydrobromic acid.[1] Later it was prepared in the manner here described,[2,3] and by treating the glycol with hydrobromic acid in the presence of sulfuric acid.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 598

References and Notes

1. Franke and Hankam, *Monatsh.*, **31**, 181 (1910).
2. Chuit, *Helv. Chim. Acta*, **9**, 264 (1926).
3. Carothers, Hill, Kirby, and Jacobson, *J. Am. Chem. Soc.*, **52**, 5279 (1930).
4. Price, Guthrie, Herbrandson, and Peel, *J. Org. Chem.*, **11**, 281 (1946).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

ether (60-29-7)

HYDROBROMIC ACID, hydrogen bromide (10035-10-6)

sodium carbonate (497-19-8)

bromine (7726-95-6)

Trimethylene bromide (109-64-8)

Decamethylene glycol (112-47-0)

Decamethylene bromide, Decane, 1,10-dibromo- (4101-68-2)

Hexamethylene bromide (629-03-8)

Nonamethylene bromide (4549-33-1)

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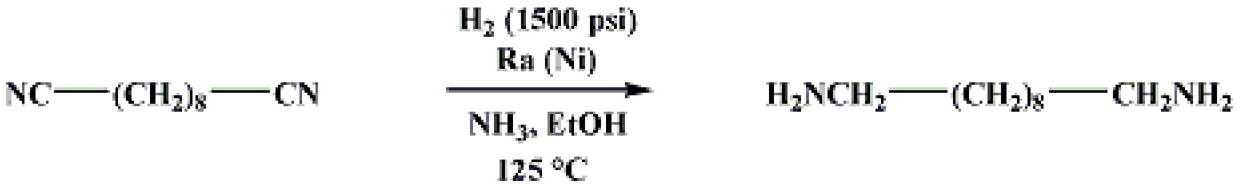
DECAMETHYLENEDIAMINE

[1,10-Decanediamine]



Submitted by B. S. Biggs and W. S. Bishop.
Checked by C. F. H. Allen and John R. Byers, Jr..

1. Procedure

A high-pressure bomb of about 1.1-l. capacity is charged with 82 g. (0.50 mole) of sebaconitrile and about 6 g. of Raney nickel catalyst (Note 1) suspended in 25 ml. of 95% ethanol, an additional 25 ml. of ethanol being used to rinse in the catalyst. The bomb is closed (Note 2), and about 68 g. (4 moles) of liquid ammonia is introduced from a tared 5-lb. commercial cylinder (Note 3). Hydrogen is then admitted at tank pressure (1500 lb.), and the temperature is raised to 125°. The reaction starts at about 90° and proceeds rapidly at 110–125°. When hydrogen is no longer absorbed (1–2 hours) the heater is shut off and the bomb allowed to cool. The hydrogen and ammonia are allowed to escape, and the contents of the bomb are rinsed out with two 100-ml. portions of 95% ethanol. The ethanolic solution is filtered quickly through a layer of decolorizing carbon (Note 4) to remove the catalyst and transferred to a 500-ml. Claisen flask having a modified side arm and connected by ground-glass joints to a receiver (Note 5). The ethanol is removed by distillation at atmospheric pressure, the receiver is changed, and the decamethylenediamine is distilled under reduced pressure. It boils at 143–146°/14 mm. (Note 6) and solidifies, on cooling, to a white solid, freezing point 60°. The yield is 68–69 g. (79–80%) (Note 7), (Note 8), and (Note 9).

2. Notes

1. Raney nickel catalyst, already prepared and suspended in water, can be obtained from the Gilman Paint and Varnish Company, Chattanooga, Tennessee.
2. The safety disk should be made of steel, nickel, or other suitable material. It must not be of copper, which is readily attacked by ammonia under pressure.
3. The ammonia may be introduced by a number of methods. A suitable one is given under α-phenylethylamine (p. 717). The amount of ammonia is not critical, but maximum yields are obtained when 6–8 moles is used per mole of dinitrile. The purpose of the ammonia is to suppress secondary amine formation.[1,2]

4. A 9-cm. Büchner funnel is used. The decolorizing carbon is deposited from a slurry in ethanol.
5. As decamethylenediamine combines with atmospheric carbon dioxide rapidly, any solutions left standing should be protected by a drying tube containing solid potassium hydroxide. When air is admitted to the apparatus at the end of the distillation it should be through such a tube.
6. Decamethylenediamine should not be allowed to solidify in a bottle or Erlenmeyer flask, since it will probably break such a container. A tared round-bottomed flask less than half filled is advisable.
7. A dermatitis is induced in susceptible individuals by decamethylenediamine.
8. The submitters reported yields of 85–90% on runs four times this size.
9. Other boiling points are 139–140°/12 mm.; 126–127°/5 mm.

3. Discussion

Decamethylenediamine has been obtained by reduction of sebaconitrile either catalytically[2] or by sodium and ethanol,[3] or by lithium aluminum hydride.[4] It has also been obtained by hydrolysis of the condensation product from decamethylene iodide and phthalimide,[5] and from decamethylene glycol in the presence of Raney nickel and ammonia at 220–260°.[6]

References and Notes

1. Brit. pat. 490,922 [*C. A.*, **33**, 993 (1939)].
2. Schwoegler and Adkins, *J. Am. Chem. Soc.*, **61**, 3499 (1939).
3. Phookan and Krafft, *Ber.*, **25**, 2253 (1892).
4. Nystrom and Brown, *J. Am. Chem. Soc.*, **70**, 3738 (1948).
5. von Braun, *Ber.*, **42**, 4551 (1909).
6. U. S. pat. 2,412,209 [*C. A.*, **41**, 1237 (1947)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

ammonia (7664-41-7)

hydrogen (1333-74-0)

carbon dioxide (124-38-9)

Raney nickel (7440-02-0)

decolorizing carbon (7782-42-5)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

Phthalimide (85-41-6)

Decamethylene glycol (112-47-0)

α-Phenylethylamine (3886-69-9)

lithium aluminum hydride (16853-85-3)

Decamethylenediamine, 1,10-Decanediamine (646-25-3)

Sebaconitrile (1871-96-1)

decamethylene iodide (16355-92-3)

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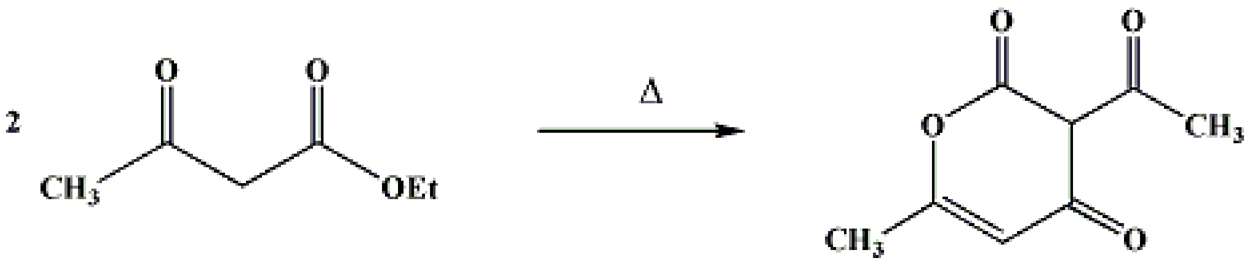
DEHYDROACETIC ACID

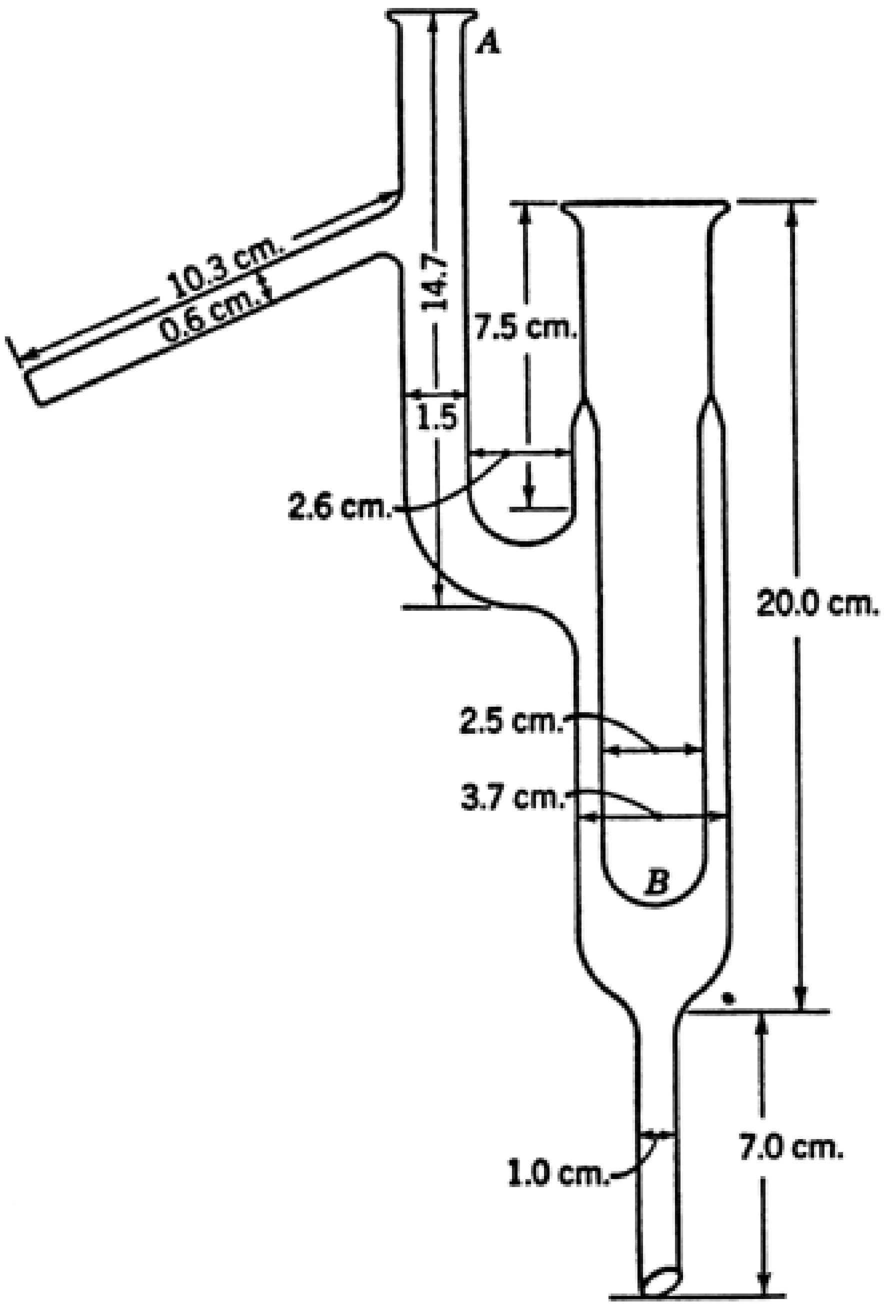


Submitted by F. Arndt
Checked by W. W. Hartman and A. Weissberger.

1. Procedure

A 250-ml. round-bottomed flask is fitted with a thermometer reaching nearly to the bottom (Note 1) and a three- or four-bulb fractionating column without a side arm, at the upper end of which is attached a partial condenser .htm(Fig. 11) (Note 2). The side arm (*A*) of the partial condenser carries a 110° thermometer and is connected to a condenser set for downward distillation. The inside container (*B*) of the partial condenser is filled halfway with toluene, a chip of porous plate is added, and the top is attached to a reflux condenser.

Fig. 11.



In the 250-ml. flask 100 g. (0.78 mole) of freshly vacuum-distilled ethyl acetoacetate and 0.05 g. of sodium bicarbonate (Note 3) are placed and heated so that the toluene is kept just boiling until the liquid in the flask has reached 200–210° (Note 4). The time for heating is usually 7–8 hours, during which period 27 g. of distillate boiling at 72° (mostly ethanol) is collected, and the color of the reaction mixture becomes dark brown. The dehydroacetic acid, while still hot (Note 5), is transferred to a 200-ml. distilling flask (Note 6) and distilled under reduced pressure. After a fore-run boiling up to 128° at 12 mm., consisting of ethyl acetoacetate, has been collected, the receiver is changed and dehydroacetic acid is collected up to 140°/12 mm. The yield of dehydroacetic acid melting at 104–110° is 34 g. (53%) (Note 7). A purer product, m.p. 108°, may be secured in 80% yield by recrystallization from ethanol, using 2 ml. per gram of material (Note 8).

2. Notes

1. The bulb of the thermometer must be immersed in the liquid.

2. This partial condenser, which is a modification of one described by Hahn,[1] is very effective in reducing the time required for fractional distillation of many mixtures. It is best constructed of Pyrex. The dimensions given are approximate and may be varied to suit individual needs. The inside container is a 30 by 140 mm. Pyrex test tube sealed at the top to standard Pyrex tubing. It is very effective in the purification of cyclohexene [*Org. Syntheses* Coll. Vol. **1**, 183 (1941)].[2] The crude hydrocarbon mixture is first put into the flask with ethanol in the partial condenser, and the whole heated as long as a distillate is obtained. The ethanol is then replaced by ethylene chloride and the cyclohexene is collected.

3. It is essential to use sodium bicarbonate to secure consistent results.

4. Above this temperature extensive decomposition sets in. The time required varies with the size of the run, being less with smaller quantities.

5. The residue solidifies on cooling. The dehydroacetic acid may be filtered and washed at this stage, but the yield is lower, owing to its solubility in the reaction mixture.

6. An ordinary 200-ml. distilling flask with a large-diameter side arm placed well down on the neck gave the best results. There was no foaming, frothing, or spattering.

7. The yield falls off with larger amounts; e.g., 500 g. of ester gave only 35% of the calculated quantity of acid.

8. The acid may be isolated through the sodium salt, but the quality is poorer and the yield less.

3. Discussion

Dehydroacetic acid has been prepared by the action of acetic anhydride on acetonedicarboxylic acid,[3] as a by-product in the pyrolysis of acetone to give ketene,[4] by treatment of ketene dimer with pyridine[5] or sodium phenoxide,[6] and by removal of ethanol from acetoacetic ester.[7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 238

References and Notes

1. Hahn, *Ber.*, **43**, 419 (1910).
2. A. W. Hutchison, private communication.
3. von Pechmann, *Ber.*, **24**, 3600 (1891); von Pechmann and Neger, *Ann.*, **273**, 194 (1893).
4. Hurd, Sweet, and Thomas, *J. Am. Chem. Soc.*, **55**, 336 (1933).
5. Chick and Wilsmore, *J. Chem. Soc.*, **93**, 946 (1908); **97**, 1987 (1910).

6. Steele, Boese, and Dull, *J. Org. Chem.*, **14**, 460 (1949).
7. Arndt and Nachtwey, *Ber.*, **57**, 1489 (1924); Arndt, Eistert, Scholz, and Aron, *Ber.*, **69**, 2373 (1936).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

acetoacetic ester

ethanol (64-17-5)

acetic anhydride (108-24-7)

Acetonedicarboxylic acid

sodium bicarbonate (144-55-8)

Cyclohexene (110-83-8)

ethylene chloride (107-06-2)

acetone (67-64-1)

pyridine (110-86-1)

toluene (108-88-3)

Ethyl acetoacetate (141-97-9)

sodium phenoxide

Ketene (463-51-4)

Dehydroacetic acid (520-45-6)

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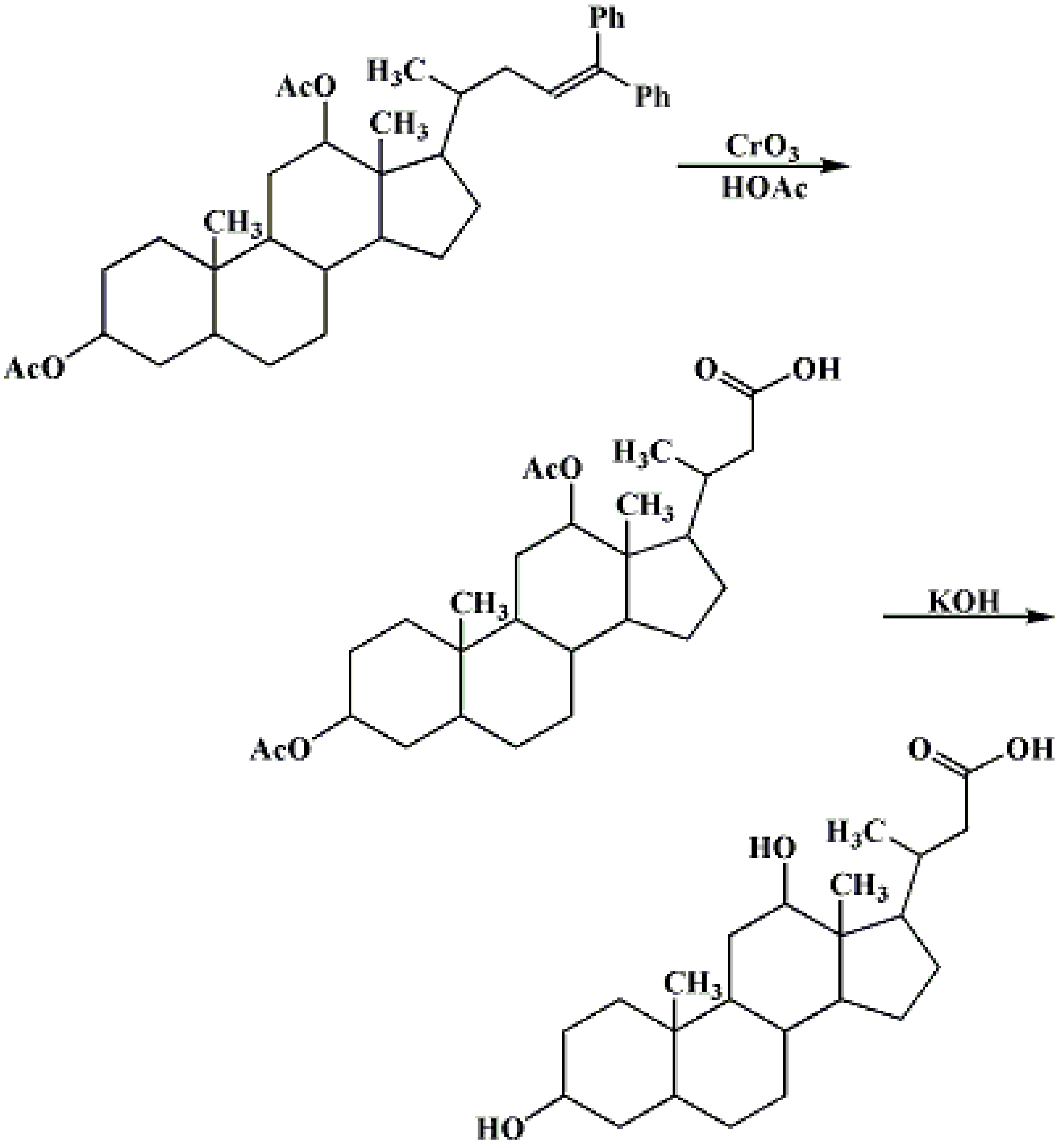
Organic Syntheses, CV 3, 234

nor-DESOXYCHOLIC ACID

[3,12-Dihydroxy-*nor*-cholanic acid]



Submitted by Byron Riegel, R. B. Moffett, and A. V. McIntosh.
Checked by Richard B. Turner and Louis F. Fieser.

1. Procedure

A solution of 59.6 g. (0.1 mole) of 3,12-diacetoxy-*bisnor*-cholanyldiphenylethylene (p. 237) in 60 ml. of chloroform is prepared by warming and poured into a 1-l. round-bottomed flask containing 300 ml. of glacial acetic acid at about 40°. The flask is provided with a stirrer, a thermometer dipping below the surface of the solution, and a dropping funnel, and is surrounded by a water bath through which cold water can be circulated. A solution of 37 g. of chromium trioxide in 30 ml. of water and 200 ml. of acetic acid is added from the dropping funnel at such a rate that the temperature is kept

at about 50°; the mixture is stirred and cooled. This operation should require about 10 minutes. When the temperature starts to drop, the water bath is warmed and the temperature is maintained at about 50° for an additional 20 minutes. The solution is then cooled, and the excess chromic acid is destroyed by adding carefully about 30 ml. of methanol, the temperature being kept below 50° (Note 1).

The reaction mixture is concentrated by distillation under reduced pressure. At first the solvent may be distilled rapidly, but, after the mixture becomes syrupy, the distillation should be carried out below 30° until the residue is almost solid. At a pressure of 10 mm. the concentration requires about 2 hours. The residue is diluted with 500 ml. of cold water, which should be added in several portions with thorough shaking to break up all the lumps. The product is collected on a filter and washed with dilute hydrochloric acid until the filtrate comes through colorless.

The solid crystalline cake (Note 2) is dissolved in about 400 ml. of ether and extracted with 500 ml. of 2.5% potassium hydroxide solution (Note 3). The alkaline solution is immediately acidified with 200 ml. of 10% hydrochloric acid, and the crude 3,12-diacetoxy-*nor*-cholanic acid (Note 4) is collected on a filter.

The crude diacetate is hydrolyzed by dissolving it in 350 ml. of 10% aqueous potassium hydroxide and refluxing the solution for 2 hours. The alkaline solution is diluted to about 700 ml., cooled, and filtered. The filtrate is poured into 300 ml. of 10% hydrochloric acid, and the *nor*-desoxycholic acid is separated by filtration and dried. The crude product is dissolved in about 600 ml. of acetone and filtered, while hot, to remove small amounts of salt. On cooling, 25–30 g. (57–68%) of white crystals which melt at 209–211° is obtained in two crops (Note 5). This material contains 1 molecule of acetone of crystallization. The fully purified substance softens at about 160° (loss of acetone) and melts at 213.5–214.5°.

2. Notes

1. Solid chromic acid and methanol will ignite spontaneously; care should be taken that the methanol does not come in contact with any of the chromic acid solution that may have dried around the edges of the dropping funnel.
2. If the cake is not nearly colorless it should be stirred with 250 ml. of 10% hydrochloric acid and the mixture extracted with 400 ml. of ether. The ether solution is then extracted with the 2.5%potassium hydroxide as described.
3. Vigorous mixing should be avoided in order to prevent the formation of an emulsion.
4. The 3,12-diacetoxy-*nor*-cholanic acid may be purified by crystallization from acetone. It melts at 207–208°.
5. This procedure, coupled with the procedure described on p. 237, illustrates the Barbier-Wieland method for systematically degrading carboxylic acids. *bisnor*-Desoxycholic acid may be prepared from *nor*-desoxycholic acid by repetition of this procedure. If the chromic acid oxidation product is not sufficiently solid to filter after dilution with water, the mixture must be extracted

with ether and washed with dilute hydrochloric acid before the alkaline extraction. *bisnor*-Desoxycholic acid may be crystallized from ethyl alcohol. It melts at 239–241.°

3. Discussion

nor-Desoxycholic acid has been prepared from desoxycholic acid by modification of the Barbier-Wieland degradation.[1]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 237

References and Notes

1. Hoehn and Mason, *J. Am. Chem. Soc.*, **60**, 1493 (1938); Sawlewicz, *Roczniki Chem.*, **18**, 250, 755 (1938); Kazuno and Simizu, *J. Biochem. Japan*, **29**, 421 (1939); Reichstein and Arx, *Helv. Chim. Acta*, **23**, 747 (1940).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

nor-Desoxycholic acid

3,12-Dihydroxy-nor-cholanic acid

3,12-Diacetoxy-bisnor-cholanyldiphenylethylene

3,12-Diacetoxy-nor-cholanic acid

bisnor-Desoxycholic acid

ethyl alcohol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

methanol (67-56-1)

ether (60-29-7)

chloroform (67-66-3)

acetone (67-64-1)

potassium hydroxide (1310-58-3)

chromic acid (7738-94-5)

chromium trioxide (1333-82-0)

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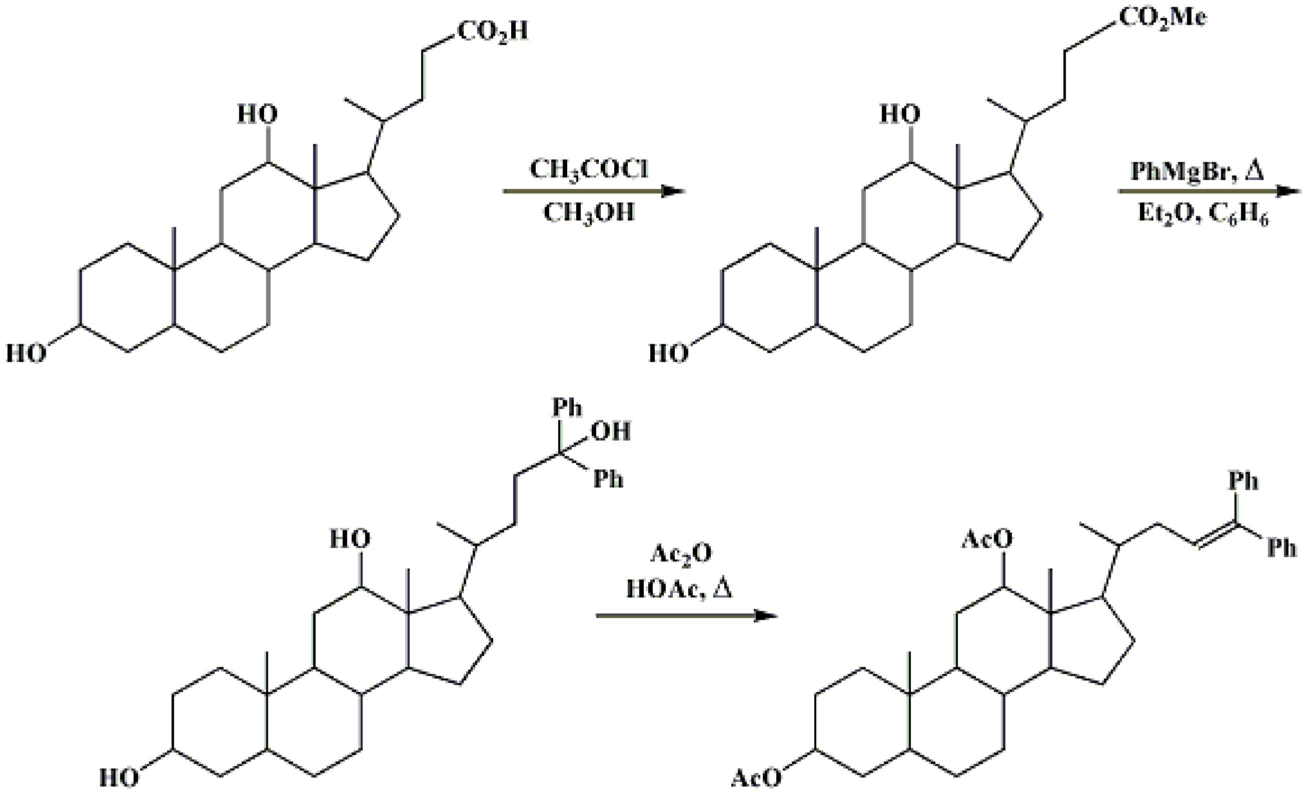
Organic Syntheses, CV 3, 237

3,12-DIACETOXY-*bisnor*-CHOLANYLDIPHENYLETHYLENE

[Bisnorcholanyldiphenylethylene, 3,12-diacetoxy-]



Submitted by Byron Riegel, R. B. Moffett, and A. V. McIntosh.
Checked by Richard B. Turner and Louis F. Fieser.

1. Procedure

A. *Methyl desoxycholate*. To a cooled solution of 100 g. (0.255 mole) of desoxycholic acid (Note 1) in 1 l. of methanol is added carefully 50 ml. of acetyl chloride. The solution is allowed to stand overnight at room temperature (Note 2) and is then diluted with cold water until just turbid. Crystallization is induced by scratching and seeding, if necessary. When much of the ester has crystallized, the mixture is further diluted to about 2.5 l. and allowed to stand for 30 minutes until crystallization is complete. The ester is collected on a filter, washed with water, and dried. The yield is 100–103 g. (97–100%) of material which melts at 95–100° (Note 3).

B. 3,12-*Diacetoxy-bisnor-cholanyldiphenylethylene*. A solution of phenylmagnesium bromide is prepared in a 5-l. three-necked flask, fitted with a dropping funnel, an efficient reflux condenser, and a mechanical stirrer, from 97.2 g. (4 gram atoms) of magnesium, 675 g. (450 ml., 4.3 moles) of bromobenzene, and 1250 ml. of dry ether.

To the solution of the Grignard reagent is added a solution of 102 g. (0.25 mole) of methyl desoxycholate in 700 ml. of dry benzene (Note 4). The desoxycholate is washed into the flask with 500 ml. of dry benzene, and the mixture is refluxed with stirring for 3 hours. After cooling, the complex is decomposed by pouring its benzene solution into a mixture of about 4 l. of ice and 700 ml. of concentrated hydrochloric acid. After thorough shaking, the layers are separated, and the aqueous layer is extracted twice with ether. The combined ether solution is washed with dilute hydrochloric acid, water, 5% sodium hydroxide solution, and finally with water. The solvent and some biphenyl are removed by steam distillation; approximately 5 hours is required to remove the biphenyl formed during the preparation of the Grignard reagent. The lumps should be broken up from time to time, if necessary. After cooling, the residue of crude 3,12-dihydroxy-*nor*-

cholanyldiphenylcarbinol is collected and dried.

The crude carbinol is acetylated and dehydrated by refluxing its solution in 1 l. of glacial acetic acid and 500 ml. of acetic anhydride for 1 hour. The solution is then concentrated to about 500 ml. by distillation. After cooling overnight, the crystalline 3,12-diacetoxy-*bisnor*-cholanyldiphenylethylene is collected on a filter and washed with acetic acid. The yield is 95–105 g. (63.5–70.0%) of material melting at 154–157° (Note 5). This product is sufficiently pure to be used for the preparation of *nor*-desoxycholic acid (p. 234); one crystallization from acetone gives white crystals which melt at 156–157.5°; fully purified material melts at 159.5–160.5°.

2. Notes

1. A good grade of desoxycholic acid should be used. The product from Wilson Laboratories has been found to be satisfactory.
2. At this point the solution should be filtered if any insoluble material is present.
3. This methyl desoxycholate is pure enough for most purposes, but if desired it may be recrystallized from methanol or from a mixture of ether and petroleum ether.
4. The solution of methyl desoxycholate in dry benzene is conveniently prepared by dissolving the ester in 900 ml. of ordinary benzene and distilling the excess solvent.
5. An additional 5–7 g. of product may be obtained by concentrating the filtrate and recrystallizing the product from acetone. If the material is to be used for the preparation of *nor*-desoxycholic acid (p. 234), it is more convenient to oxidize the filtrate directly with chromic acid and isolate the product as the acid.

3. Discussion

The literature on methods of preparation is the same as that given for *nor*-desoxycholic acid (p. 234).

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 234

References and Notes

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

nor-Desoxycholic acid

3,12-Diacetoxy-bisnor-cholanyldiphenylethylene

Bisnorcholanyldiphenylethylene, 3,12-diacetoxy-

Methyl desoxycholate

desoxycholic acid

3,12-dihydroxy-nor-cholanyldiphenylcarbinol

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

methanol (67-56-1)

ether (60-29-7)

acetic anhydride (108-24-7)

sodium hydroxide (1310-73-2)

acetyl chloride (75-36-5)

magnesium (7439-95-4)

acetone (67-64-1)

chromic acid (7738-94-5)

bromobenzene (108-86-1)

Phenylmagnesium bromide (100-58-3)

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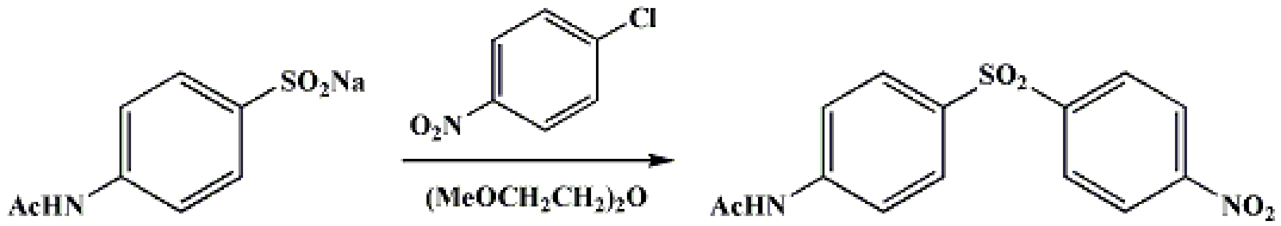
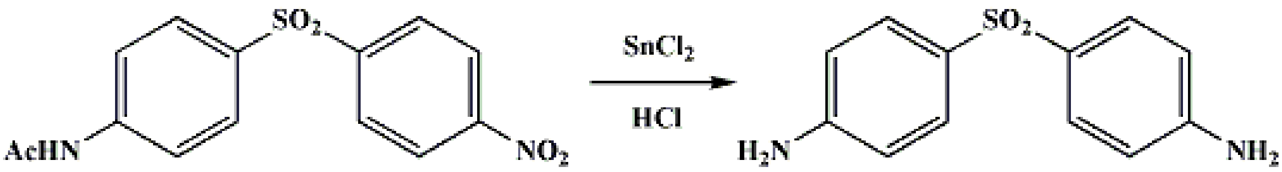
Organic Syntheses, CV 3, 239

4,4'-DIAMINODIPHENYLSULFONE

[Aniline, 4,4'-sulfonylbis-]





Submitted by C. W. Ferry, J. S. Buck, and R. Baltzly.
Checked by C. F. H. Allen and James VanAllan.

1. Procedure

In a 1-l. beaker on a steam bath, 155 g. (0.78 mole) of *p*-acetaminobenzenesulfinic acid is suspended in 310 ml. of water. The suspension is stirred by hand and warmed gently while it is neutralized by the addition of a solution of 31.5 g. of sodium hydroxide in 125 ml. of water (Note 1). The solution is then transferred to a 2-l. flask and the bulk of the water is removed under the vacuum of a good water pump; 330–350 ml. of water is removed during 1.5 hours. During this time, the solid salt begins to separate. When bumping becomes severe, the flask is cooled by immersion in an ice bath for 30 minutes, and the salt is filtered with suction. The filtrate is concentrated as before, the product being added to the first crop. The second filtrate, on concentration, yields a less pure salt which may be worked up separately. The yields are 107–124 g. (63–73%) of the first crop, 25–34 g. (15–20%) of the second crop, and 12–17 g. (7–10%) of material of inferior grade.

In a 500-ml. three-necked round-bottomed flask fitted with a reflux condenser, a mechanical stirrer, and a thermometer are placed 48.5 g. (0.22 mole) of the sodium sulfinate and 60 ml. of a mixture of 75 ml. of ethylene glycol and 120 ml. of carbitol or methyl carbitol. The mixture is stirred and heated in an oil bath until solution is complete, after which 31.5 g. (0.2 mole) of 4-chloronitrobenzene (m.p. 76–78°) is added. The mixture is heated for 3.5 hours at 141–143° (thermometer in the mixture), with continued stirring, and then is allowed to cool overnight. After the addition of 20 ml. of water, the pasty lumps are broken up, and the solid is filtered with suction and washed with 50–75 ml. of hot water. The solid is then transferred to a 1-l. flask and refluxed with 250 ml. of 95% ethanol for 15 minutes. After cooling, the *p*-nitro-*p*'-acetylaminodiphenylsulfone is filtered with suction and washed on the funnel, first with 25 ml. of ethanol and then with 25 ml. of ether. After drying in the air, the tan-colored solid weighs 32–33 g. (50–52%) and melts at 226–228° (Note 2).

To a solution of 300 g. of stannous chloride dihydrate in 300 ml. of concentrated hydrochloric acid (sp. gr. 1.19) in a 1-l. beaker there is added 96 g. of the sulfone, and the mixture is stirred occasionally. Evolution of heat is sufficiently great so that, after 10–15 minutes, external cooling is necessary to prevent violent boiling with possible loss of material (Note 3). After nearly all the solid

has dissolved, the mixture is heated on the steam bath for 2 hours. The solution is then cooled and added to 1.35 l. of 40% sodium hydroxide solution contained in a 3-l. beaker; it is necessary to stir mechanically and to add about 1.5 kg. of ice during the operation. The final temperature should be about 10°. After standing for 30 minutes the crude amine is filtered with suction (Note 4) and washed with water (200–250 ml.) until free from alkali.

The amine is recrystallized by dissolving it in 250 ml. of 95% ethanol, boiling a few minutes with 5 g. of Norit, and filtering. The clear filtrate is either concentrated to a small volume or is diluted by the addition of 200–250 ml. of water (Note 5) and allowed to stand overnight in the icebox. The crystalline amine (m.p. 176°) is then filtered and air-dried. The yield is 55–57 g. (74–77%) (Note 6).

2. Notes

1. Frequently the solution develops a blue color. If this persists, a little additional sodium hydroxide solution is required.
2. The yield (per cent) is the same if twice the amounts given are used. It is convenient to combine several runs for the reduction.
3. Sometimes the reduction does not start readily. In this event the beaker may be cautiously heated, but provision for rapid cooling should be made.
4. Filtration is facilitated by use of a Pyrex glass or Vinyon filter fabric; a 30-cm. funnel is advisable.
5. A part of the amine usually crystallizes during the filtration. It is dissolved by warming, after which water is added until the solution is just cloudy.
6. If the melting point is low, a second recrystallization is needed.

3. Discussion

4,4'-Diaminodiphenylsulfone and/or 4,4'-diacetylaminodiphenylsulfone have been prepared by various procedures, starting with 4,4'-dinitrodiphenylsulfide;[1] or 4,4'-dichlorodiphenylsulfone.[2,3] It has also been made from a sulfinate and a halonitrobenzene;[4] from 4-acetylaminobenzenesulfonyl chloride and acetanilide;[5] from acetanilide and thionyl chloride;[6] from 4-nitro-4'-aminodiphenylsulfide;[7] and by acetylation of thioaniline (4,4'-diaminodiphenylsulfide) followed by hydrogen peroxide oxidation.[8] The 4,4'-diacetylaminodiphenylsulfone obtained by any of these procedures is readily deacetylated.[7,8] A method somewhat similar to the one described above has been patented.[9]

References and Notes

1. Fromm and Wittmann, *Ber.*, **41**, 2270 (1908).
2. I. G. Farbenind. A-G., Brit. pat. 506,227 [*C. A.*, **33**, 9328 (1939)].
3. I. G. Farbenind. A-G., Fr. pat. 829,926 [*C. A.*, **33**, 1760 (1939)].
4. Schering A-G., Brit. pat. 510,127 [*C. A.*, **34**, 4079 (1940)].
5. Kereszty and Wolf, Hung. pat. 120,021 [*C. A.*, **33**, 4600 (1939)].
6. Sugasawa and Sakurai, *J. Pharm. Soc. Japan*, **60**, 22 (1940 [*C. A.*, **34**, 3704 (1940)].
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9. Roblyn and Williams, U. S. pat. 2,227,400 [*C. A.*, **35**, 2531 (1941)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

carbitol or methyl carbitol

4,4'-diacetylaminodiphenylsulfone

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ether (60-29-7)

Acetanilide (103-84-4)

sodium hydroxide (1310-73-2)

4-acetylaminobenzenesulfonyl chloride (121-60-8)

thionyl chloride (7719-09-7)

sulfone (7446-09-5)

ethylene glycol (107-21-1)

hydrogen peroxide (7722-84-1)

stannous chloride dihydrate (10025-69-1)

sodium sulfinate

4-chloronitrobenzene (100-00-5)

thioaniline

p-Acetaminobenzenesulfinic acid (710-24-7)

4,4'-dinitrodiphenylsulfide (1223-31-0)

4,4'-DIAMINODIPHENYLSULFONE, Aniline, 4,4'-sulfonylbis- (80-08-0)

p-nitro-p'-acetylaminodiphenylsulfone (1775-37-7)

4,4'-dichlorodiphenylsulfone

4-nitro-4'-aminodiphenylsulfide

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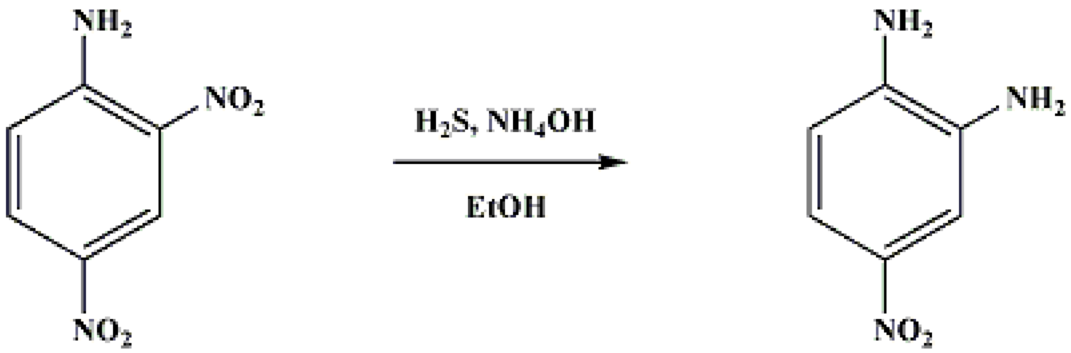
Organic Syntheses, *CV 3, 242*

1,2-DIAMINO-4-NITROBENZENE

[*o*-Phenylenediamine, 4-nitro-]



Submitted by K. P. Griffin and W. D. Peterson.
Checked by Nathan L. Drake, Ralph Mozingo, and Jonathan Williams.

1. Procedure

A 5-l. three-necked flask is fitted with a mechanical stirrer, a reflux condenser, a thermometer, and an inlet tube extending to the bottom of the flask (Note 1). In the flask is placed a mixture of 238 g. (1.3 moles) of 2,4-dinitroaniline, 2.4 l. of 95% ethanol, and 1.2 l. of concentrated ammonium hydroxide (sp. gr. 0.90).

The mixture is heated to 45°, and with good stirring hydrogen sulfide is passed into the reaction mixture while its temperature is maintained between 45° and 55° (Note 2) and (Note 3). The yellow suspended particles of 2,4-dinitroaniline dissolve slowly to form an intensely red-colored solution. The reaction is complete when all the *yellow* particles have disappeared; reduction should be complete in 30–60 minutes (Note 4).

The reaction mixture is allowed to stand in an icebox for 16–18 hours to complete the separation of the product, which forms small, well-defined, deeply red-colored crystals. The 1,2-diamino-4-nitrobenzene is filtered by suction, washed with 150–250 ml. of cold water, and sucked dry on the funnel (Note 5).

The crude product is purified by dissolving it in a boiling mixture of 900 ml. of water and 110 ml. of concentrated hydrochloric acid (sp. gr. 1.19), and filtering the hot solution through a Norit bed using suction. The filter bed is washed with a boiling mixture of 90 ml. of water and 10 ml. of concentrated hydrochloric acid, and the washings are added to the main body of the solution. The filtered solution, while still hot, is treated with 100 ml. of concentrated ammonia (sp. gr. 0.90). The precipitated 1,2-diamino-4-nitrobenzene is filtered hot on a Büchner funnel, washed on the funnel with 150 ml. of water, and dried in an oven at 40–50°.

The purified material melts at 197–198° and weighs 105–115 g. (52–58%).

2. Notes

1. The inlet tube should have a diameter of about 15 mm.
2. Enough heat is generated so that it is necessary to play a stream of cold water on the flask from time to time to maintain this temperature.
3. The rate of the gas stream should be as rapid as is consistent with complete absorption.
4. The product may begin to separate during the last few minutes.
5. Concentration of the mother liquor yields only a few grams of material (8–10 g.), a mixture of 1,4-diamino-2-nitrobenzene and 1,2-diamino-4-nitrobenzene.

3. Discussion

1,2-Diamino-4-nitrobenzene can be prepared by the partial reduction of 2,4-dinitroaniline in alcohol solution using sodium hydrosulfide[1] or ammonium sulfide.[2,3] The method described here is a modification of that given by Kehrmann.[3] 2-N,N-Dialkyl derivatives of 1,2-diamino-4-nitrobenzene have been prepared by acylation, nitration, and hydrolysis of substituted phenylenediamines.[4]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

hydrogen sulfide (7783-06-4)

ammonium hydroxide (1336-21-6)

ammonium sulfide

2,4-Dinitroaniline (97-02-9)

sodium hydrosulfide

1,2-Diamino-4-nitrobenzene, o-Phenylenediamine, 4-nitro- (99-56-9)

1,4-diamino-2-nitrobenzene (5307-14-2)

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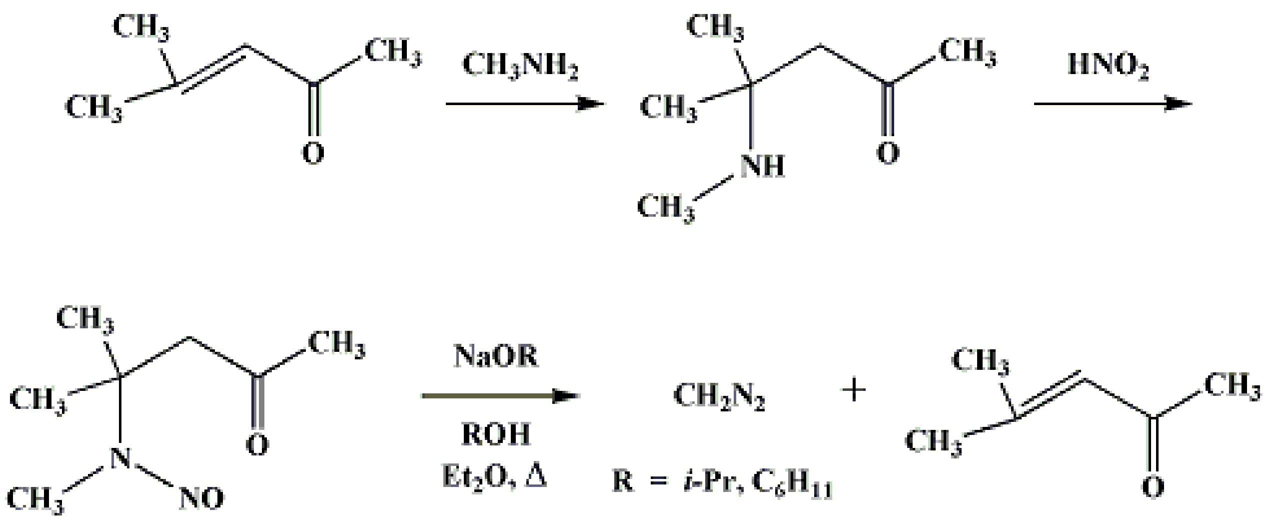
Organic Syntheses, *CV 3, 244*

DIAZOMETHANE

[Methane, diazo-]



Submitted by C. Ernst Redemann, F. O. Rice, R. Roberts, and H. P. Ward.
Checked by Nathan L. Drake, Charles M. Eaker, Robert K. Preston, and W. Mayo Smith.

1. Procedure

A. *N-Nitroso-β-methylaminoisobutyl methyl ketone*. In a 2-l. three-necked flask, fitted with a mechanical stirrer, a thermometer, and a dropping funnel, is placed 250 ml. (2.1 moles) of 30% aqueous methylamine (Note 1). The flask is surrounded by an ice bath, and the stirrer is started. When the temperature of the solution has dropped to 5°, 196 g. (2 moles) of mesityl oxide is added through the dropping funnel at such a rate that the temperature remains below 20° (Note 2) and (Note 3). After the mesityl oxide has been added, the mixture is allowed to stand without cooling for 30 minutes.

The solution is then cooled to 10° by means of the ice bath, and 125 ml. of glacial acetic acid is added through the dropping funnel at such a rate that the temperature remains below 15°; then an additional 75 ml. of the acid is added rapidly.

The ice bath is removed, and 300 ml. of 8 *N* sodium nitrite (Note 4) is added in 20–30 minutes to the stirred solution, which is kept at 25–35° by intermittent cooling with the ice bath. Stirring is then discontinued, and the mixture is allowed to stand for 6 hours or longer (Note 5).

The oily layer is separated from the aqueous layer, the aqueous layer is extracted with two 200-ml. portions of ether, and the combined extracts and oil are dried over calcium chloride. The drying agent is removed by filtration, and the ether is distilled on a water bath; finally, all low-boiling material is removed from the mixture on a boiling water bath under the lowest pressure obtainable with a water pump (Note 6). The nitrosoaminoketone

which remains in the flask is sufficiently pure for the preparation of diazomethane (Note 7). The yield is 221–257 g. (70–80% based on mesityl oxide).

If a purer product is desired for other purposes, the nitrosoaminoketone is distilled at low pressure (see *Caution*). The substance boils at 119°/5 mm., at 111°/3 mm., or at 101°/1.5 mm.

Caution! Only a small quantity of the nitrosoaminoketone should be distilled at a time. It is reported that the substance occasionally undergoes violent decomposition. If the distillation is carried out, the operator should be protected by a suitable screen or plate of safety glass (Note 8).

B. *Diazomethane. Sodium isopropoxide method* (Note 9).

Caution! Diazomethane is very toxic; its preparation should be carried out only in a well-ventilated hood. Individuals differ in their susceptibility; some develop symptoms similar to asthma from very small concentrations, whereas others notice no ill effects from much larger quantities. The use of a safety screen is also recommended.

Thirty milliliters of a solution of sodium isopropoxide, prepared from 1 g. of sodium and 100 ml. of isopropyl alcohol, is placed in a 250-ml. Claisen flask arranged for heating in a water bath. The flask is provided with a dropping funnel, a condenser, and a receiver cooled in a Dry Ice bath; this receiver is connected to a second one containing 20 ml. of anhydrous ether; the inlet tube of the second receiver should dip below the surface of the ether.

The water bath is heated to 70–75°, and one-half of a solution prepared by dissolving 15.8 g. (0.1 mole) of N-nitroso-β-methylaminoisobutyl methyl ketone in a mixture of 80 ml. of anhydrous ether and 12 ml. of isopropyl alcohol is added through the dropping funnel at a rate slightly greater than that of distillation. When the separatory funnel is empty, an additional 15 ml. of the solution of sodium isopropoxide is added; the remainder of the solution of nitroso compound is then added as before. Anhydrous ether is then added gradually through the dropping funnel until the condensing ether becomes colorless. The diazomethane comes over with the ether as a golden yellow distillate. The process can be continued until all the nitrosoaminoketone has been decomposed. The yield of diazomethane, which varies with the purity of the nitrosoaminoketone, is 1.9–2.5 g (45–60%).

C. *Diazomethane. Sodium cyclohexoxide method* (Note 10). A solution of sodium cyclohexoxide is prepared from 4 g. of sodium and 100 ml. of cyclohexanol (Note 11) in a 2-l. flask; the cyclohexanol is heated to boiling under reflux to speed up the formation of the alkoxide. As soon as the sodium has disappeared, heating is discontinued and the condenser is removed. When solid begins to separate from the solution, the mixture is stirred with a stout rod to prevent the formation of a hard cake. The flask is surrounded by an ice bath, and, when the temperature of the mixture has dropped to 10°, 300 ml. of dry ether and a solution of 49 g. (0.33 mole) of N-nitroso-β-methylaminoisobutyl methyl ketone dissolved in 600 ml. of dry ether are added. The flask is connected to a 25-cm.

fractionating column and an efficient water-cooled condenser (Note 12). The delivery end of the condenser should be connected to an adapter which dips below the surface of 50 ml. of ether contained in a 1-l. Erlenmeyer flask immersed in an ice bath. The mixture is heated by a water bath whose temperature is maintained at 50–55°. Distillation is continued until the condensing ether is colorless; usually 700–750 ml. of distillate containing 10–11 g. (77–84% yield) (Note 13) of diazomethane is collected (Note 14) and (Note 15). The diazomethane-ether solution may be purified further with only slight loss by drying over potassium hydroxide pellets (Note 16) and redistillation through a fractionating column.

2. Notes

1. Methylamine is available from several manufacturers. The Commercial Solvents Corporation and Rohm and Haas Company offer an aqueous solution containing 30% to 33% of amine. Solutions of other strengths are satisfactory if appropriate quantities are employed. The amine solution may be prepared from the hydrochloride by adding slowly 210 ml. of 10 *N* sodium hydroxide solution to an ice-cold solution of 142 g. (2.1 moles) of methylamine hydrochloride in 250 ml. of water. The resulting solution is used without further treatment.
2. The mesityl oxide should be freshly distilled.
3. The length of time needed for this addition varies with the efficiency of the cooling bath; a period of 30 minutes to 1 hour is usually required.
4. The nitrite solution is very nearly saturated. The sodium nitrite need not be of c. p. grade; if it is less pure, appropriate allowance must be made when the solution is prepared.
5. It is preferable to allow the mixture to stand overnight; care should be taken, however, that its temperature does not exceed 35° at any time.
6. The pressure should not be above 30 mm.; a pressure of 20 mm. is desirable.
7. Because of the low cost of the starting materials and the stability in storage of the nitrosoaminoketone, this substance is an excellent intermediate for preparing diazomethane. One of the submitters (Redemann) reports that a sample of the crude material was kept in the laboratory in a brown bottle for more than 2 years without evident decomposition; the trace of acetic acid remaining in the ketone tends to stabilize it.
8. One of the submitters (Redemann) reports that he has never experienced difficulty during distillation of this ketone.
9. Submitted by F. O. Rice, R. Roberts, and H. P. Ward.
10. Submitted by C. Ernst Redemann.
11. The cyclohexanol may be replaced by benzyl alcohol. Benzyl alcohol is reported to give a slightly increased rate of formation of diazomethane and a slightly more concentrated ethereal solution; however, the over-all yield is somewhat lower. If only a small amount of diazomethane is wanted, concentrated aqueous sodium hydroxide may replace the solution of the alkoxide of cyclohexanol. The yield under these conditions is 40–50%.
12. A column with smooth packing or smooth inner surface should be used; rough surfaces catalyze the decomposition of diazomethane. A column helps to remove mesityl oxide.

13. The diazomethane content of the ethereal solution may be determined by the method described previously.[1]
14. A solution of diazomethane in dry ether may be stored in a smooth flask or bottle in a refrigerator for several weeks. Since slow decomposition of the diazomethane occurs, the concentration of the solution should be checked before use.
15. Other alkyl diazo compounds can be prepared readily by the same general method with some alterations because of the lower volatility of the higher homologs.[2]
16. Pellets are recommended because their smooth surface causes little decomposition of diazomethane.

3. Discussion

Diazomethane has been prepared from nitrosomethylurea,[1,3] from nitrosomethylurethane,[4,5] from a mixture of chloroform and hydrazine hydrate by reaction with potassium hydroxide,[6] and from N-methyl-N-nitroso-N'-nitroguanidine with potassium hydroxide.[7] The methods described above are adapted from the work of Kenner.[8,9] Two reviews of the reactions and use of diazomethane have appeared.[10,11]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 119
- Org. Syn. Coll. Vol. 4, 250
- Org. Syn. Coll. Vol. 5, 351

References and Notes

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10. Smith, *Chem. Revs.*, **23**, 193 (1938).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium cyclohexoxide

calcium chloride (10043-52-4)

acetic acid (64-19-7)

ether (60-29-7)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

Cyclohexanol (108-93-0)

sodium nitrite (7632-00-0)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

isopropyl alcohol (67-63-0)

sodium isopropoxide (683-60-3)

Benzyl alcohol (100-51-6)

Mesityl oxide (141-79-7)

hydrazine hydrate (7803-57-8)

Methylamine hydrochloride (593-51-1)

methylamine (74-89-5)

Diazomethane, Methane, diazo- (334-88-3)

Nitrosomethylurea

Nitrosomethylurethane

N-Nitroso-β-methylaminoisobutyl methyl ketone (16339-21-2)

N-methyl-N-nitroso-N'-nitroguanidine (674-81-7)

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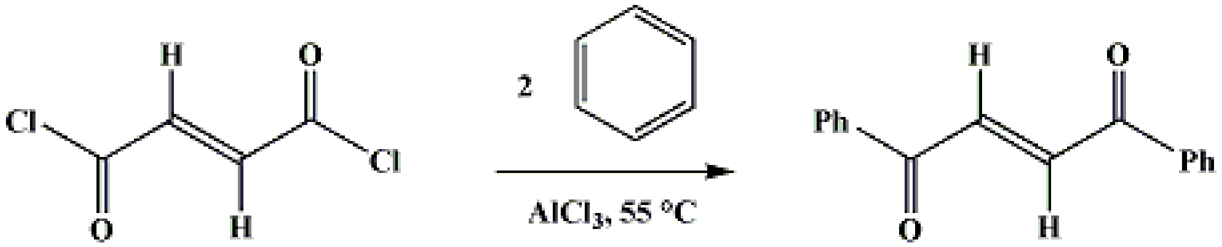
Organic Syntheses, CV 3, 248

trans-DIBENZOYLETHYLENE

[2-Butene-1,4-dione, 1,4-diphenyl-]



Submitted by R. E. Lutz
Checked by C. F. H. Allen and F. P. Pingert.

1. Procedure

Eighteen hundred milliliters of benzene (Note 1) and 350 g. of finely ground anhydrous aluminum chloride (2.6 moles) (Note 2) are placed in a 3-l. three-necked flask, fitted with a mechanical stirrer, a dropping funnel (Note 3) containing 153 g. (1 mole) of fumaryl chloride (p. 422), and a reflux condenser (Note 4). A trap for absorbing hydrogen chloride is attached to the condenser.

The mixture is well stirred and heated externally by hot water (50–60°) (Note 5), the water removed, and the fumaryl chloride admitted at a *brisk* rate, moderated only enough to avoid a too rapid evolution of hydrogen chloride; this requires 15–25 minutes (Note 6) and (Note 7). The mixture turns dark red and soon reaches the boiling point; hydrogen chloride is rapidly given off. The mixture is then refluxed gently for 10 minutes with stirring.

The pasty red mixture is then poured portionwise upon 4 kg. of cracked ice to which has been added 75 ml. of concentrated hydrochloric acid, the reaction mixture being thoroughly stirred before each pouring so that the aluminum chloride complex does not settle out and become concentrated at the bottom of the flask. The residue in the flask is decomposed by adding some of the ice and water. After standing 20–30 minutes, very hot water (Note 8) is added to melt any ice or frozen benzene and raise the temperature generally. The bulk of the aqueous layer is discarded by drawing it off with a glass tube connected to a suction flask. The benzene layer is next washed at least four times with hot water (Note 8) and (Note 9). Finally the warm benzene layer is transferred to a large separatory funnel, any crusts of dibenzoylethylene adhering to the various pieces of apparatus are dissolved in hot benzene, and the solutions combined; the small water layer is separated and discarded (Note 10). The hot benzene layer is then filtered, either by gravity using a large glass funnel or by suction on a Büchner funnel, into a 3-l. round-bottomed flask. After a few porcelain chips have been added, the bulk of the solvent is distilled, using a steam or boiling water bath.

Most of the residual solvent is removed under diminished pressure, using a water pump, and heating until the syrupy liquid begins to crystallize suddenly (Note 11). At this point, the heating and suction are discontinued and 125 ml. of 95% ethanol is added rapidly, stirring with a wooden paddle to break up any lumps. The flask is cooled a few minutes under the tap, and the bright yellow product is collected on a 127-mm. Büchner funnel. The solid is triturated on the funnel with cold ethanol for 10 minutes to remove adhering mother liquor, and sucked as dry as possible. The yield is 186–197 g. (78–83%) (Note 11), and the melting point is 109–110° (Note 12) and (Note 13).

2. Notes

1. The checkers used thiophene-free benzene, m.p. 5°; it gave a product of better quality than the commercial hydrocarbon. A large excess is used to facilitate stirring.
2. Resublimed aluminum chloride is suitable; it requires no further grinding. The excess over the required 2 moles assures a complete reaction and a product of good color.
3. A dropping funnel is preferred to the ordinary separatory funnel, since the rate of addition of the fumaryl chloride is important.
4. A wide-bore condenser permits a more rapid reaction, favoring an increased yield and better product.
5. If the mixture is not heated before the fumaryl chloride is added the reaction is slow, and when the temperature finally rises the accumulated chloride and intermediates react so vigorously that frothing and boiling over occur.
6. If for any reason stirring is interrupted, the *addition* of fumaryl chloride *must be stopped immediately*, and the stirrer started again *very cautiously*.
7. The product and yield are better with the shorter time of addition.
8. Very hot water is desirable; unless the benzene layer is really warm (50–60°), the separation into layers is poor and the product does not readily dissolve. For the same reasons, hot water is used in the subsequent washings.
9. The first and second wash waters should be acidulated with 25 ml. of concentrated hydrochloric acid; this facilitates the formation of layers.
10. If the water used has been hot enough to keep the benzene really warm (50–60°), there are no crusty deposits.
11. Ordinarily there is but 8 g. in the second crop; however, in the event that not enough solvent has been removed, there may be a larger amount, with a correspondingly smaller first crop. The total yield is 194–205 g. (82–86%). If the first crop weighs over 190 g., it is not economical to work up the mother liquor.
12. In some runs, the product sinters slightly at 106°, but the melting point is unaltered.
13. Lower-melting material, whatever its source, can be recrystallized from 95% ethanol, using 3 ml. per gram.

3. Discussion

trans-Dibenzoylethylene has been prepared by the present method,[1] by heating dibenzoylmalic acid,[2] by condensing benzoylformaldehyde and acetophenone,[3] and by the Friedel-Crafts reaction on benzoylacrylyl chloride.[4] Analogs may be prepared using other aromatics such as mesitylene,[1,4,5,6] with carbon disulfide as the solvent, and also using other acid chlorides such as mesaconyl chloride,[7] dibromofumaryl chloride,[8] and dimethylfumaryl chloride.[9]

A mixture of stereoisomers has been prepared by the action of alcoholic potassium hydroxide on phenacyl chloride.[10]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

aluminum chloride complex

ethanol (64-17-5)

hydrogen chloride, hydrochloric acid (7647-01-0)

Benzene (71-43-2)

Acetophenone (98-86-2)

aluminum chloride (3495-54-3)

potassium hydroxide (1310-58-3)

benzoylformaldehyde (1074-12-0)

carbon disulfide (75-15-0)

Mesitylene (108-67-8)

phenacyl chloride (532-27-4)

2-Butene-1,4-dione, 1,4-diphenyl-

Fumaryl chloride (627-63-4)

dibenzoylethylene, trans-Dibenzoylethylene

dibenzoylmalic acid

benzoylacrylyl chloride

mesaconyl chloride

dibromofumaryl chloride

dimethylfumaryl chloride

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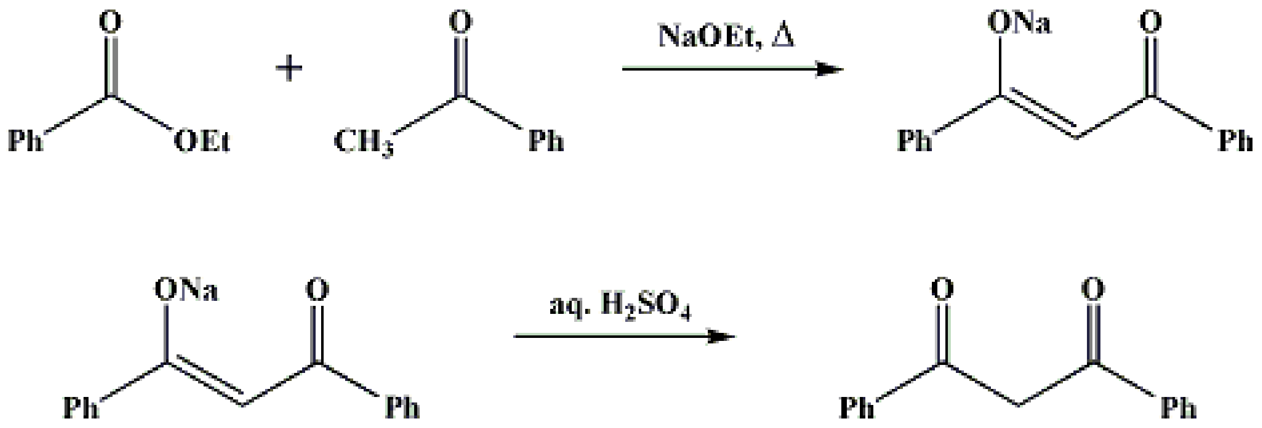
Organic Syntheses, CV 3, 251

DIBENZOYLMETHANE

[1,3-Propanedione, 1,3-diphenyl-]



Submitted by Arthur Magnani and S. M. McElvain.
Checked by R. L. Shriner and F. J. Wolf.

1. Procedure

In a dry 2-l. three-necked flask are placed 600 g. (4 moles) of freshly distilled ethyl benzoate and 60 g. (0.5 mole) of freshly distilled acetophenone (Note 1). The flask is fitted with a mercury-sealed stirrer which must be rugged enough to stir the reaction mixture even after it becomes very viscous (Note 2). A condenser for downward distillation is attached to one of the necks, and a 500-ml. filter flask is used as the receiver. This receiver is connected to a water pump through a suction flask carrying a two-holed rubber stopper, one hole of which is left open. The reaction flask is heated in an oil bath kept at 150–160°, and, after the mixture is hot, 44 g. (0.65 mole) of sodium ethoxide (Note 3) is added through the third arm of the flask in 1- to 2-g. portions. The ethoxide addition can be conveniently accomplished with a spoon shaped to enter the arm of the flask or by placing a very short-stemmed large funnel in the third neck and pushing the ethoxide through the funnel with a small glass rod or wire spatula. The reaction mixture becomes orange immediately; ethanol distils after the first few additions, and thereafter the evolution of ethanol is quite vigorous. The additions are made as rapidly as evolution of the ethanol permits. During the ethoxide addition a gentle stream of air is kept passing through the flask by means of a water pump attached to the receiver in order to prevent the ethanol vapor from rising in the third arm of the flask and interfering with the addition (Note 4).

After all the ethoxide has been added (20–30 minutes) the gelatinous reaction mixture is stirred until no more distillate comes over (15–30 minutes). The weight of this distillate amounts to 38–45 g. (Note 5).

The oil bath is removed, and, with the stirring maintained, the reaction mixture is cooled to room temperature by running cold water over the flask. Then 150 ml. of

water is added to dissolve the reaction mass, and both layers of the mixture are transferred to a separatory funnel. An ice-cold solution of 25 ml. of concentrated sulfuric acid in 200 ml. of water is added, and the mixture is shaken vigorously. The ester layer is separated and washed with 200 ml. of water; it is then shaken with successive 200-ml. portions of 5% sodium bicarbonate solution until the evolution of carbon dioxide ceases, after which it is washed with 200 ml. of water. The bicarbonate solution is separated and extracted with 100 ml. of ether (Note 6). The ether extract, after washing with 50 ml. of water, is combined with the ester layer and the resulting ethereal solution dried with 40 g. of calcium chloride. The ether is removed by distillation from a water bath, and the excess ethyl benzoate is removed by distillation under reduced pressure. The recovered ester, b.p. 80–83°/8 mm., amounts to 475–490 g. After the ester is removed the temperature of the oil bath is slowly raised to 180–185° while the system is maintained under 8 mm. pressure. A small amount of liquid distilling higher than the ester is thus removed. When no more distillate comes over at this temperature, the remaining oil, while still warm, is poured into a 500-ml. Erlenmeyer flask and allowed to crystallize. This crude dibenzoylmethane weighs 92–108 g. and is usually brown. It is recrystallized by dissolving in 150 ml. of hot methanol, adding 1 g. of Norit, filtering, and cooling the filtrate to 0° (Note 7). The yield of yellow crystals of dibenzoylmethane, m.p. 77–78° (Note 8), thus obtained is 70–80 g. (62–71% based on the acetophenone).

2. Notes

1. The apparatus and all reagents must be carefully dried.
2. A thick glass rod stirrer bent to fit around the inside of the flask works well. The mixture is too viscous to be stirred with a Hershberg stirrer.
3. The sodium ethoxide should be freshly prepared according to the directions under acetylacetone (p. 16). It must be kept in a tightly stoppered bottle and handled quickly.
4. The water flow through the pump is so regulated that no appreciable vacuum is allowed to build up in the reaction flask when the side arm through which the ethoxide is added is closed.
5. The amount of this distillate depends somewhat upon the rate of flow of air through the apparatus. If an appreciable vacuum builds up, this distillate may contain some acetophenone.
6. By acidification of the aqueous bicarbonate layer, 20–25 g. of benzoic acid may be obtained.
7. If the product is still dark colored, it may be purified by recrystallization from 400 ml. of 90% methanol and the color removed with Norit. In either method of crystallization 4–6 g. of inferior product may be obtained from the mother liquor.
8. Occasionally crystals melting at 71–72° may be obtained which upon standing change to the higher-melting form.

3. Discussion

In addition to the methods listed in *Org. Syntheses* Coll. Vol. **1**, 205 (1941),

dibenzoylmethane has been prepared by the action of sodium amide[1] and lithium amide[2] on acetophenone and ethyl benzoate, by the action of sodium ethoxide on certain alkyl benzoates,[3] by the reaction of ethyl benzoate and sodium acetylbenzoylmethane,[4] and by the hydrolysis of N-(1,3-dimethylbutyl) acetophenone imide.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 244

References and Notes

1. Levine, Conroy, Adams, and Hauser, *J. Am. Chem. Soc.*, **67**, 1510 (1945).
2. Zellars and Levine, *J. Org. Chem.*, **13**, 160 (1948).
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4. McElvain and Weber, *J. Am. Chem. Soc.*, **63**, 2192 (1941).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium acetylbenzoylmethane

ethanol (64-17-5)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

methanol (67-56-1)

ether (60-29-7)

sodium bicarbonate (144-55-8)

Benzoic acid (65-85-0)

carbon dioxide (124-38-9)

Acetophenone (98-86-2)

sodium ethoxide (141-52-6)

Dibenzoylmethane, 1,3-Propanedione, 1,3-diphenyl- (120-46-7)

ethyl benzoate (93-89-0)

sodium amide (7782-92-5)

Acetylacetone (123-54-6)

lithium amide (7782-89-0)

N-(1,3-dimethylbutyl) acetophenone imide

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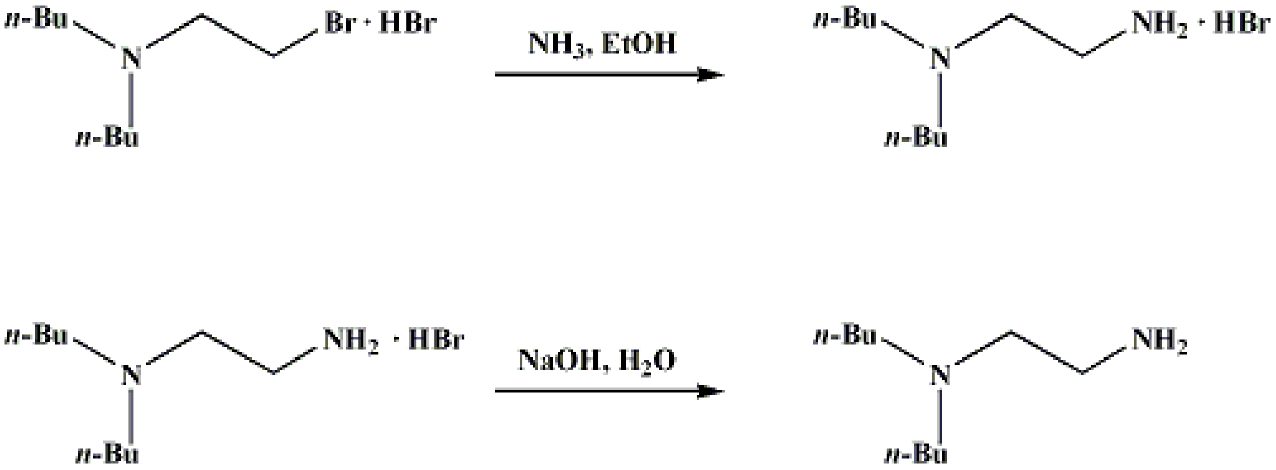
Organic Syntheses, *CV 3, 254*

β-DI-*n*-BUTYLAMINOETHYLAMINE

[Ethylenediamine, N,N-dibutyl-]



Submitted by Lawrence H. Amundsen, Karl W. Krantz, and James J. Sanderson.
Checked by R. L. Shriner and John L. Rendall.

1. Procedure

A rubber tube from an inverted cylinder of liquid ammonia is attached to a glass tube which extends beneath the surface of 325 ml. of 90% ethanol in a 500-ml. Erlenmeyer flask. Ammonia is passed into the ethanol until the weight increases by 41 g. (2.4 moles). The flask is cooled in ice water occasionally in order to hasten the absorption of the ammonia.

The ethanolic ammonia is added to 49 g. (0.16 mole) of di-*n*-butylaminoethyl bromide hydrobromide [*Org. Syntheses* Coll. Vol. **2**, 92 (1943)] (Note 1) in a 1-l. round-bottomed flask. The flask is stoppered tightly and allowed to stand for 6 days at room temperature. The solution is then transferred to an evaporating dish and stirred while it is evaporated to a crystalline paste under a hood. The crystalline paste is transferred to a 400-ml. beaker, and to it is added a solution of 16 g. of sodium hydroxide in 18 ml. of water. The solution separates into an upper layer of brown oil and a lower layer which contains a considerable amount of undissolved sodium bromide. About 10 ml. of water is added to dissolve most of the precipitate. The whole is then extracted with three 50-ml. portions of benzene. The combined extracts are placed in a 250-ml. flask over 15 g. of potassium carbonate and set aside to dry overnight.

The dried benzene extract is placed in a 250-ml. flask fitted with a 30-cm. fractionating column, and the benzene is removed by distillation at atmospheric pressure. Fractionation of the residue is carried out under reduced pressure using a 50-ml. Claisen flask with a built-in 12- to 15-cm. Vigreux column. The fraction boiling at 100–103°/13 mm. is collected; it weighs 11 to 14.7 g. (41–55%) (Note 2).

2. Notes

1. It is not necessary to isolate the di-*n*-butylaminoethyl bromide hydrobromide. The crude di-*n*-butylaminoethyl bromide hydrobromide prepared from 405 g. (2.34 moles) of di-*n*-butylaminoethanol is taken up in 600 ml. of water, and the tarry impurities are removed by extraction with three 200-ml. portions of benzene. About 400 ml. of water is evaporated from this solution, and to it is then added 2.8 l. of ethanolic ammonia prepared from absolute ethanol; the concentration of the ethanol in the reaction mixture should be 90% with respect to water. The yield is 114 g. (28% based on 405 g. of the aminoethanol). The over-all yield obtained by the procedure described above is 27% based on the aminoethanol.
2. The submitter reports that diethylaminoethylamine and di-*n*-propylaminoethylamine have also been prepared by this method.

3. Discussion

Di-*n*-butylaminoethylamine has been prepared by the action of ethanolic ammonia on di-*n*-butylaminoethyl bromide hydrobromide,[1] and by the reduction of di-*n*-butylaminoacetonitrile with sodium in butanol.[2]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

potassium carbonate (584-08-7)

ammonia (7664-41-7)

Benzene (71-43-2)

sodium hydroxide (1310-73-2)

sodium bromide (7647-15-6)

butanol (71-36-3)

sodium (13966-32-0)

aminoethanol (141-43-5)

Ethylenediamine, N,N-dibutyl-, β-DI-n-BUTYLAMINOETHYLAMINE, Di-n-butylaminoethylamine (3529-09-7)

diethylaminoethylamine (100-36-7)

di-n-butylaminoethyl bromide hydrobromide

di-n-butylaminoethanol (102-81-8)

di-n-propylaminoethylamine

di-n-butylaminoacetonitrile

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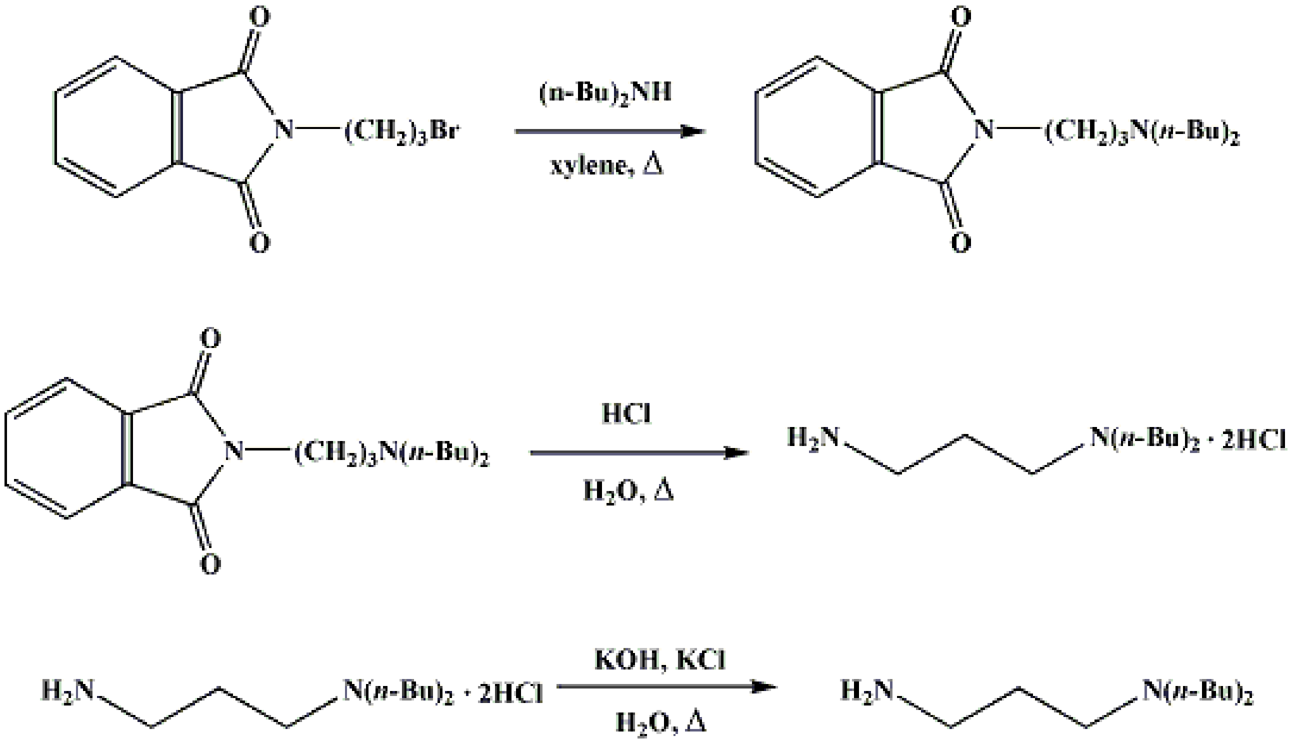
Organic Syntheses, *CV 3, 256*

γ-DI-*n*-BUTYLAMINOPROPYLAMINE

[1,3-Propanediamine, N,N-di-*n*-butyl-]



Submitted by Lawrence H. Amundsen and James J. Sanderson.
Checked by R. L. Shriner and John L. Rendall.

1. Procedure

In a 500-ml. distilling flask are placed 107 g. (0.40 mole) of γ-bromopropylphthalimide (Note 1) and 240 ml. of xylene. Solution is effected by heating, and 24 ml. of xylene is distilled to remove traces of moisture. After cooling, the solution is transferred to a 1-l. round-bottomed flask with a ground-glass joint and treated with 107 g. (140 ml., 0.83 mole) of di-*n*-butylamine. The flask is fitted with a reflux condenser and heated with occasional shaking for 10 hours in an oil bath maintained at 140–150°.

The solution is allowed to cool, and the di-*n*-butylamine hydrobromide, which separates in the course of the reaction, is removed by means of a suction filter (Note 2). The filtrate is transferred to a 500-ml. distilling flask, and the xylene is removed by distillation. The crude γ-di-*n*-butylaminopropylphthalimide, a brown oil, is transferred to a 500-ml. round-bottomed flask with a ground-glass joint and treated with 20 ml. of water and 120 ml. of 12 *N* hydrochloric acid. The flask is fitted with a reflux condenser, and the solution is heated for 6 hours in an oil bath maintained at 140–150°. After the solution has cooled to room temperature, the precipitated phthalic acid is removed by filtration and washed with four 25-ml. portions of cold water. The combined filtrates are transferred to a 600-ml. beaker and heated on a steam bath to evaporate the water and hydrochloric acid.

The residue, a thick brown oil, which is crude γ-di-*n*-butylaminopropylamine dihydrochloride, is treated with a solution of 80 g. of potassium hydroxide in 80 ml. of water. A brown oil separates

above the aqueous layer, which contains a considerable amount of solid potassium chloride. The whole is extracted with one 200-ml. portion and two 50-ml. portions of benzene (Note 3). The combined extracts are then placed in a 500-ml. Erlenmeyer flask over 50 g. of potassium hydroxide and allowed to dry overnight.

The dried benzene extract is placed in a 500-ml. round-bottomed flask with a ground-glass joint. The flask is fitted with a Vigreux column, and the benzene is distilled from the solution at atmospheric pressure, an oil bath maintained at 100–110° being the source of heat. The crude γ-di-*n*-butylaminopropylamine is fractionated under reduced pressure from a 250-ml. Claisen flask; heat is supplied by an oil bath maintained at 170–180°. The yield of product boiling at 108–110.5°/5–6 mm. or 98–100°/2 mm. amounts to 57–60 g. (77–80%) (Note 4).

2. Notes

1. The γ-bromopropylphthalimide was prepared from potassium phthalimide and trimethylene bromide in 78% yield, using the conditions and molar quantities specified for the preparation of β-bromoethylphthalimide.[1] γ-Bromopropylphthalimide can also be prepared from phthalimide, potassium carbonate, and trimethylene bromide.[2]
2. About 55–58 g. of di-*n*-butylamine hydrobromide is recovered.
3. The increase in volume of the first portion is about 75 ml. There is no noticeable increase in the volumes of the two 50-ml. portions.
4. This same procedure has been followed in the preparation of γ-diethylaminopropylamine and γ-di-*n*-propylaminopropylamine. When these substances are prepared by the method described, yields of 60% and 67% respectively are obtained.

3. Discussion

The above procedure is based on the directions of Sanderson.[3] γ-Di-*n*-butylaminopropylamine has also been prepared from β-di-*n*-butylaminopropionitrile by the action of sodium and alcohol[4] and by catalytic reduction.[5] (β-Di-*n*-butylaminopropionitrile has been prepared from di-*n*-butylamine and acrylonitrile.)

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

Trimethylene bromide (109-64-8)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

β-Bromoethylphthalimide

Potassium Phthalimide (1074-82-4)

xylene (106-42-3)

phthalic acid (88-99-3)

potassium chloride (7447-40-7)

γ-bromopropylphthalimide

acrylonitrile (107-13-1)

γ-diethylaminopropylamine (104-78-9)

di-n-butylamine (111-92-2)

γ-DI-n-BUTYLAMINOPROPYLAMINE, 1,3-Propanediamine, N,N-di-n-butyl- (102-83-0)

di-n-butylamine hydrobromide

γ-di-n-butylaminopropylphthalimide

γ-di-n-butylaminopropylamine dihydrochloride

γ-di-n-propylaminopropylamine (34155-34-5)

β-di-n-butylaminopropionitrile (25726-99-2)

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DI-β-CARBETHOXYETHYLMETHYLAMINE

[Propionic acid, β,β'-(methylimino)di-, diethyl ester]

Submitted by Ralph Mozingo and J. H. McCracken.
Checked by C. F. H. Allen and Joseph Dec.

1. Procedure

In a 2-l. flask, fitted with a rubber stopper carrying a soda-lime drying tube and a glass tube reaching almost to the bottom, is placed 325 g. (420 ml.) of absolute ethanol. The whole is then tared and placed in an ice bath, and the inlet tube is connected to a source of dry methylamine.

The methylamine generator consists of a 1-l. flask fitted with a dropping funnel and outlet tube, which in turn is connected to a 25-cm. drying tower containing soda-lime, followed by a 1-l. safety trap (Note 1). In the flask is placed 200 g. of technical sodium hydroxide flakes, and 263 g. of a 33–35% solution of methylamine in water (Note 2) is dropped in slowly at such a rate that an even current of gas is evolved. When the addition has been completed and the gas bubbles very slowly into the ethanol, the flask and contents are removed and weighed; the increase should be 84–86 g. (2.71–2.77 moles) (Note 3).

The flask is reimmersed in the ice bath, and 900–925 g. (5.4–5.5 moles), depending upon the weight of methylamine, of a 60% solution of ethyl acrylate in ethanol (Note 4) is added in portions of about 100 ml. at such a rate that the temperature of the mixture does not rise above 40°; this requires about 10 minutes. After each addition the flask is stoppered to exclude moisture. When all the ester has been added the flask is closed by a rubber stopper and allowed to stand 6 days (Note 5).

Most of the ethanol is removed by distillation (1.5 hours) on a steam bath, and the residue is transferred to a modified Claisen flask and distilled. The fraction boiling below 50°/20 mm. (Note 6) is removed with the aid of a water pump, and the residue is distilled using an oil pump (at 3 mm. pressure) (Note 7). The portion boiling at 105–108°/3 mm. (Note 8) is collected as di-β-carbethoxyethylmethylamine (Note 9); it amounts to 519–550 g. (83–86%) (Note 10).

2. Notes

1. The safety trap is important, since the ethanol tends to suck back easily.
2. Solutions of methylamine in water are obtainable from Eastman Kodak Company (33%) and Rohm and Haas Company (35%).

3. It is much more convenient to use the amount of methylamine secured than to try to collect a predetermined weight.
4. The ethyl acrylate (60% solution in ethanol) is available from the Rohm and Haas Company. The solution, containing a polymerization inhibitor, is used without treatment. The inhibitor must not be removed.
5. If the time is shortened, the yield is correspondingly decreased.
6. Most of this distillate comes over with the oil-bath temperature at 75°; the temperature is finally raised to 150°. The fractionating arm of the Claisen flask used was wrapped with asbestos cord.
7. Any ethyl N-methyl-β-aminopropionate formed comes over in the first or middle fraction (6–8 ml.). The middle fraction is obtained as the fraction boiling up to 105°/3 mm., on changing from the water pump to an oil pump. The oil bath is cooled to 100° before applying the higher vacuum.
8. The observed boiling points vary with the particular apparatus used.
9. Since the ester decomposes very slightly during distillation, the oil pump should be protected from ethyl acrylate and methylamine by a Dry Ice trap. The distillation should not be interrupted.
10. Di-β-carbomethoxyethylmethylamine may be prepared in a similar yield by substituting an equivalent quantity of methyl acrylate in methanol in the above procedure.

3. Discussion

This ester has been prepared by the action of ethyl β-bromopropionate on methylamine hydrochloride in the presence of silver oxide,[1] by the addition of methylamine to ethyl acrylate,[2] and by heating ethyl β-chlπropropionate, methylamine, and benzene in an autoclave.[3]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethyl β-chlπropropionate

ethanol (64-17-5)

Benzene (71-43-2)

methanol (67-56-1)

sodium hydroxide (1310-73-2)

silver oxide (20667-12-3)

Ethyl β-bromopropionate (539-74-2)

ethyl acrylate (140-88-5)

Methylamine hydrochloride (593-51-1)

methylamine (74-89-5)

methyl acrylate (96-33-3)

DI-β-CARBETHOXYETHYLMETHYLAMINE, Propionic acid, β,β'-(methylimino)di-, diethyl ester (6315-60-2)

ethyl N-methyl-β-aminopropionate

Di-β-carbomethoxyethylmethylamine

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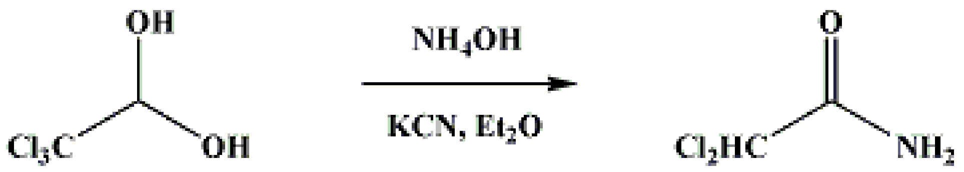
α,α-DICHLOROACETAMIDE

[Acetamide, α,α-dichloro-]



Submitted by John R. Clark, W. J. Shibe, and Ralph Connor.
Checked by R. L. Shriner and Neil S. Moon.

1. Procedure

A solution of 134 g. (0.81 mole) of chloral hydrate (Note 1) in 400 ml. of ether (Note 2) is placed in a 2-l. round-bottomed three-necked flask equipped with a dropping funnel, a reflux condenser, and an efficient mercury-sealed stirrer (Note 3). A solution of 12 g. of potassium cyanide (Note 4) in 220 ml. of concentrated ammonium hydroxide (sp. gr. 0.9) is added through the dropping funnel over the course of 15 minutes at a rate sufficient to cause the ether to reflux vigorously. Stirring is continued for an additional 20 minutes (Note 5). The layers are separated, and the ether layer is washed once with 75 ml. of water and once with 75 ml. of 10% aqueous sulfuric acid solution (Note 6). (These washings are retained and used again later.) The aqueous layer from the reaction mixture is extracted with three 75-ml. portions of ether, and each ether extract is washed successively with the same water and sulfuric acid solutions used previously. The combined ether extracts are dried with 40 g. of sodium sulfate, the ether is removed by distillation, and the residue is recrystallized from 200 ml. of benzene. The solid is removed by filtration with suction and washed with two 25-ml. portions of cold benzene. The yield is 66–76 g. melting at 97.5–99.5° (cor.). Concentration of the filtrate gives 1–5 g. of material with a slightly lower (96–97° cor.) melting point, making the total yield 67–81 g. (65–78%).

2. Notes

1. The chloral hydrate was of U.S.P. XI quality.
2. Ether decreases the amount of charring, presumably by controlling the temperature of the reaction mixture.
3. It is very difficult to prevent the escape of ammonia and ether. The reaction should be carried out in a hood.
4. Baker's potassium cyanide, 94–96%, was used.
5. A decided increase in reaction time will cause charring and give a product that is difficult to purify. The reaction should not be interrupted until the ethereal extracts have been washed as described.

6. The ethereal extracts of the reaction mixture contain impurities that cause charring when the solvent is removed. The water and acid treatments remove these impurities. Equally good yields may be obtained by omitting these washings, but then it is necessary to decolorize with Norit in the recrystallization from benzene, and a second recrystallization may be necessary to obtain a white product.

3. Discussion

Dichloroacetamide has been prepared from ethyl dichloroacetate with alcoholic ammonia[1] or aqueous ammonium hydroxide;[2] from ethyl dichloromalonate and ethanolic ammonia;[3] by the action of ammonia on pentachloroacetone,[4] chloral cyanohydrin,[5] and hexachloro-1,3,5-cyclohexanetrione;[6] from chloral ammonia and potassium cyanide;[7] by the action of hydrogen chloride on dichloroacetonitrile;[8] from the reaction of asparagine with the sodium salt of N-chloro-*p*-toluenesulfonamide;[9] and by the action of an alkali cyanide and ammonia on chloral hydrate.[10]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium salt of N-chloro-p-toluenesulfonamide

sulfuric acid (7664-93-9)

hydrogen chloride (7647-01-0)

ammonia (7664-41-7)

Benzene (71-43-2)

ether (60-29-7)

sodium sulfate (7757-82-6)

potassium cyanide (151-50-8)

ammonium hydroxide (1336-21-6)

chloral hydrate (302-17-0)

pentachloroacetone (1768-31-6)

α,α-DICHLOROACETAMIDE, Dichloroacetamide, Acetamide, α,α-dichloro- (683-72-7)

ethyl dichloroacetate (535-15-9)

ethyl dichloromalonate

chloral cyanohydrin

hexachloro-1,3,5-cyclohexanetrione

chloral ammonia (594-65-0)

dichloroacetonitrile (3018-12-0)

asparagine (70-47-3)

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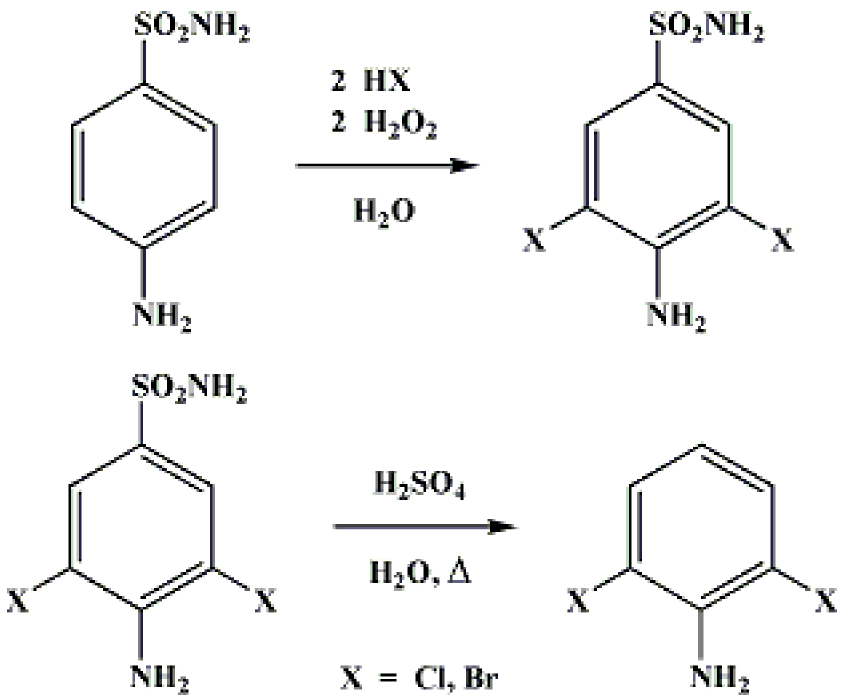
2,6-DICHLOROANILINE AND 2,6-DIBROMOANILINE

[Aniline, 2,6-dichloro- and 2,6-dibromo-]



Submitted by Margaret K. Seikel
Checked by H. R. Snyder and A. B. Spradling.

1. Procedure

A. *3,5-Dichlorosulfanilamide*. In a 2-l. round-bottomed flask, fitted with a two-holed stopper carrying a mechanical stirrer and a thermometer, are placed 50 g. (0.29 mole) of sulfanilamide and 500 ml. of water. About 50 ml. of a 500-ml. portion (approximately 6 moles) of pure concentrated hydrochloric acid is added, and the mixture is stirred until a clear solution results (Note 1). The remainder of the 500 ml. of hydrochloric acid is then added. If the internal temperature does not rise to 45°, the stirred solution should be warmed gently with a free flame until this temperature is reached. At this point 65 g. (59 ml., 0.58 mole) of 30% hydrogen peroxide (sp. gr. 1.108) is added and rapid stirring is initiated (Note 2). The heat of reaction causes a progressively faster rise in temperature. After 5 minutes the solution fills with a white precipitate which increases rapidly in amount and becomes delicately colored. When the temperature has reached 60°, about 10 minutes after adding the peroxide (Note 3), any further rise is preferably prevented by judicious cooling (Note 4). The reaction is allowed to proceed for 15 minutes more at 60°, and then an ice bath is raised about the flask while stirring is continued. When the temperature has fallen to 25–30°, the mixture is filtered at once. The yield of 3,5-dichlorosulfanilamide is 45–50 g. (65–71%), and the crude dusky pink product melts over a range of 1–2° in the region 200–205° (Note 5).

B. *2,6-Dichloroaniline*. The crude 3,5-dichlorosulfanilamide is added to 200–250 ml. (5 ml./g.) of 70% sulfuric acid (50 ml. of concentrated acid diluted with 31 ml. of water) in a 500-ml. flask, and the mixture is boiled gently for 2 hours; heat is supplied by an oil bath kept at 165–195° (Note 6). The dark mixture is then poured into 1 l. of water in a 2-l. round-bottomed flask, whereupon partial separation of a suspension of black oil occurs. The flask is attached to a condenser by a gooseneck of glass tubing; the tubing entering the flask is bent at a slight angle and cut so that its opening is at right angles to the level of the solution (Note 7). The product is steam-distilled by boiling the mixture with a free flame; the collecting vessel should be immersed in an ice bath. The solid product is separated from the distillate and dried in the air (Note 8); the white 2,6-dichloroaniline weighs 23.5–26 g. (75–80% based on 3,5-dichlorosulfanilamide or 50–55% based on sulfanilamide) and melts at 39–40°. If the product is colored it can be purified by a second steam distillation; recovery is over 90%.

C. *3,5-Dibromosulfanilamide*. The bromination of sulfanilamide is carried out in much the same way as the chlorination. The stirrer must be more efficient (Note 9); a glass stirrer with two sets of blades is satisfactory if run at high speed. Fifty grams (0.29 mole) of sulfanilamide is dissolved in a mixture of 850 ml. of water (Note 9) and 100 ml. (0.68 mole) of 40% hydrobromic acid (Note 10). The solution is heated as above, but to 70–75°, and 65 g. (59 ml., 0.58 mole) of 30% hydrogen peroxide is added (Note 2) and (Note 11). A precipitate settles in 2–3 minutes, and the solution becomes yellow. The heat of reaction causes the internal temperature to rise without further application of heat to a maximum of 85–90° after 10 minutes; by the end of the reaction time the temperature will have fallen to about 70° (Note 12). After a total reaction time of 30 minutes (Note 13), during which the mixture has become almost solid and is very difficult to stir, the material is filtered hot (Note 14). The yield of 3,5-dibromosulfanilamide is 85–90 g. (90–94%), and the crude tan product (Note 15) melts over a range of 1–2° in the region 230–237° (Note 16).

D. *2,6-Dibromoaniline*. In a 2-l. flask, equipped with a two-holed stopper carrying an exit tube to a condenser and an entrance tube for steam, 50 g. of crude 3,5-dibromosulfanilamide (Note 17) and (Note 18) and 250 ml. (5 ml./g.) of 70% sulfuric acid are heated in an oil bath; when the temperature of the bath reaches 175–180°, steam is passed rapidly through the mixture (Note 19). The hydrolysis is continued in this way for 2 hours; small amounts of the dibromoaniline distil (Note 20). The bath is then allowed to cool to 105–110°. At this temperature the main mass of the product is steam-distilled. The slightly colored 2,6-dibromoaniline melts at 84–86° and weighs 25–30 g. (66–79% based on 3,5-dibromosulfanilamide) (Note 21). It may be purified by recrystallization from 70% alcohol (7 ml./g.); after recrystallization the product is obtained as long colorless needles which melt at 87–88°. The recovery is 85–90%.

2. Notes

1. Solution of sulfanilamide is more readily obtained in this way than by treating the amide at once with 6 *N* acid for, in the latter case, the salt precipitates at first and redissolves only slowly. If acid stronger than 6 *N* is used, a larger volume is required to dissolve the sulfanilamide hydrochloride, and the product is partly held in solution as dichlorosulfanilamide hydrochloride unless the solution is diluted. If 4 *N* acid is used, the reaction is much slower without any worthwhile decrease in the color of the product.
2. Equivalent quantities of sulfanilamide and hydrogen peroxide are used in order to minimize the cost since no better yields are obtained with either in excess. If sulfanilamide is in excess, the product is tinged more orange-tan than pink and never becomes red from subsequent oxidation. If hydrogen peroxide is in excess, the reaction is faster but rapid oxidation giving dark-colored materials occurs toward the end.
3. When smaller amounts of reactants are employed, it is necessary to apply heat to reach and maintain a temperature of 60°.
4. Without cooling, the temperature rises above 70° and the precipitate becomes deep rose from oxidation by-products. The color, however, does not seem to affect the yield or purity of the dichloroaniline to any great extent.
5. The color of the product varies; higher temperatures, larger excesses of peroxide, longer reaction times, higher acidity, and higher concentrations of the reactants lead to the formation of more deeply colored materials. The color may be removed by several recrystallizations from glacial acetic acid with decolorizing carbon. As a preparative method for dichlorosulfanilamide, when a pure product is desired, the following procedure is recommended. For each 10 g. (0.058 mole) of sulfanilamide, 200 ml. of water, 200 ml. of concentrated hydrochloric acid, and 24 ml. (0.23 mole or 2 equivalents) of 30% hydrogen peroxide are used and the reaction is run at 25° for not more than 2 hours. A practically white product is obtained in 45–60% yield. It may be recrystallized from a very large volume of water, from 95% ethanol, or from glacial acetic acid; the recrystallized product melts at 205–205.5°.
6. Desulfonamidation is brought about faster by 75% sulfuric acid, but the yield is lower. The reaction is inconveniently slow with 65% sulfuric acid.
7. This bend prevents the mechanical carry-over of dark materials from the spray rising from the boiling dark solution. A distilling flask is not employed because dark oil creeps out the side arm.
8. It is difficult to measure the yield accurately; the material must be air-dried on account of its low melting point; the substance volatilizes to a significant extent on standing.
9. The larger amount of product obtained requires a more dilute initial solution coupled with violent stirring to maintain sufficient agitation.
10. Speedier reactions can be run at lower temperatures, producing lighter-colored crude materials if the amount of hydrobromic acid is doubled (30 minutes at 45°) or quadrupled (20 minutes at 25°); the use of the minimum quantity recommended above (approximately 1.15 times the required amount) produces as high yields of as high-melting materials with an attendant reduction in cost.

The 100 ml. of 40% hydrobromic acid can be replaced by 75 ml. of 48% hydrobromic acid.

11. The use of excess peroxide in the bromination also causes the formation of tribromoaniline.[1,2,3,4] If only 0.29 mole of hydrogen peroxide is used, the monobromo derivative is obtained.

12. When small runs are made, it is necessary to use a bath to attain and maintain an internal temperature of 80–85° during the reaction time of 30 minutes.

13. The reaction is considered complete when a sudden increase in or appearance of the brownish yellow color of free bromine is noted. This may or may not be evident under the above conditions, for the solution is deeply colored because of the high temperature and a very slight excess of hydrobromic acid is used; it is clearly evident whenever the excess is greater or the temperature lower.

14. Hot filtration removes traces of the monobromo compound, which is soluble in water and acids.

15. When the reaction is run at lower temperature with excess hydrobromic acid, the crude product is lighter colored. However, it melts no higher and is purified with no greater ease and with only slightly better recovery.

16. The purification of the crude material is effected by recrystallization from glacial acetic acid or, preferably, 95% ethanol (25 ml./g.), using decolorizing carbon; colorless needles, which melt at 239–240°, are obtained after two recrystallizations.

17. The crude material to be used for desulfonamidation should be tested for absence of *sym*-tribromoaniline by ascertaining its solubility in 1 *N* alkali. A clear, though colored, solution should result. If the solution is cloudy, purification of the impure material by dissolving it in alkali, filtering the solution, and reprecipitating the amide is essential.

18. Fifty-gram lots seem to be the maximum size if consistently high-melting pure material is to be obtained under the conditions employed. If a very pure product is desired, less starting material should be used.

19. The use of a current of steam in the desulfonamidation of the dibromo compound as recommended by earlier investigators[1,3,5] was found to be absolutely necessary in this instance. Without the steam, considerable amounts of *sym*-tribromoaniline are formed;[6] superheated steam is not necessary. The purity of the crude product varies directly with the ratio of the amount of steam to the size of the reaction mixture; the current of steam should be very rapid or the amount of material in a single operation should be small.

20. One and a half liters of distillate was collected in the time given.

21. If the crude product melts lower, it contains too much tribromoaniline to permit satisfactory purification. Recrystallization effects no separation; repeated fractional steam distillation is very slowly effective.

3. Discussion

2,6-Dichloroaniline was prepared by Beilstein[7] and by Körner[8] by reduction of 2,6-dichloronitrobenzene. A better method, more recently reported,[9] involves the chlorination of sulfanilic acid in 1% solution with free chlorine, subsequent evaporation of the solution, and desulfonation as above. The present method (reported earlier in slightly different form and for small amounts[10]), although requiring more expensive raw materials, is more convenient and gives higher yields.

2,6-Dibromoaniline has been prepared many times[1,3,5,6,11] by bromination of sulfanilic acid and desulfonation of the product or its salts. Fuchs[12] brominated sulfanilamide with free bromine and desulfonamidated it in the usual manner. Reduction of the corresponding nitro compound[13] and other methods[14] also have been employed.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sym-tribromoaniline

Aniline, 2,6-dichloro- and 2,6-dibromo-

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

HYDROBROMIC ACID (10035-10-6)

bromine (7726-95-6)

decolorizing carbon (7782-42-5)

chlorine (7782-50-5)

hydrogen peroxide (7722-84-1)

sulfanilic acid (121-57-3)

tribromoaniline

2,6-Dichloroaniline (608-31-1)

2,6-Dibromoaniline (608-30-0)

sulfanilamide (63-74-1)

3,5-Dichlorosulfanilamide (22134-75-4)

3,5-Dibromosulfanilamide (39150-45-3)

dibromoaniline

sulfanilamide hydrochloride

dichlorosulfanilamide hydrochloride

dichloroaniline

dichlorosulfanilamide

2,6-Dichloronitrobenzene (601-88-7)

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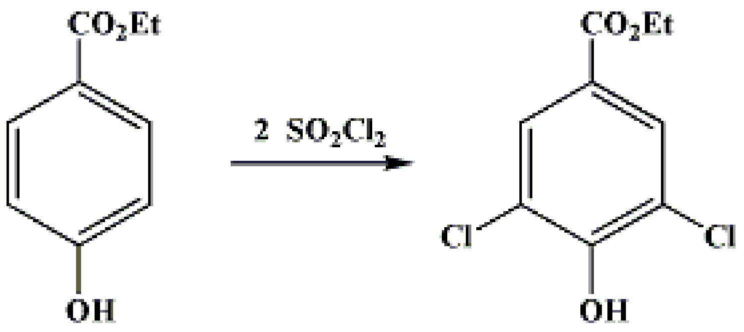
2,6-DICHLOROPHENOL

[Phenol, 2,6-dichloro-]

A.



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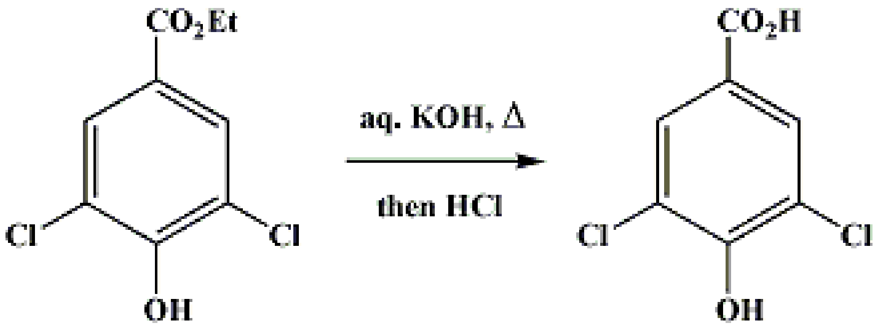

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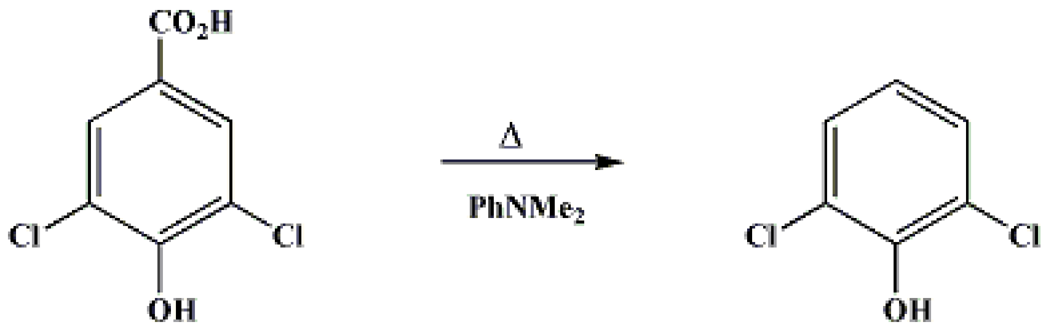

Submitted by D. S. Tarbell, J. W. Wilson, and Paul E. Fanta.
Checked by R. L. Shriner and Arne Langsjoen.

1. Procedure

A. *Ethyl 3,5-dichloro-4-hydroxybenzoate*. A tared 2-l. round-bottomed flask is equipped with an efficient reflux condenser connected through a calcium chloride drying tube to a gas-absorption trap, and is set up on a steam bath in a hood. In the flask are placed 250 g. (1.5 moles) of ethyl 4-hydroxybenzoate (Note 1) and 444 g. (266 ml., 3.3 moles) of sulfuryl chloride. The mixture is warmed on the steam bath (gently at first) until gas is no longer evolved (about 1 hour). Then 50 ml. of sulfuryl

chloride is added to the reaction flask, and the warming is continued until gas is no longer evolved. This entire chlorination procedure requires about 1.5 hours. The excess sulfuryl chloride is then removed by attaching a water pump through an empty safety flask to the reaction flask and warming on the steam bath until no evidence of vapor can be detected above the white solid in the reaction flask. The residue in the flask should weigh about 350 g. (Note 2). Recrystallization from a mixture of 600 ml. of ethanol and 140 ml. of water gives 315–334 g. (83–88%) of ethyl 3,5-dichloro-4-hydroxybenzoate hydrate (Note 3) melting at 110–114° with decomposition.

B. 3,5-*Dichloro*-4-*hydroxybenzoic acid*. In a 2-l. round-bottomed flask equipped with a reflux condenser and set upon a steam bath are placed 315 g. (1.25 moles) of ethyl 3,5-dichloro-4-hydroxybenzoate hydrate and 600 ml. of Claisen's alkali (Note 4). Saponification is brought to completion by heating on the steam bath for 1 hour. A yellow homogeneous solution results which is diluted with 400 ml. of water and acidified to Congo red paper by pouring it into a rapidly stirred solution of 320 ml. of concentrated hydrochloric acid and 380 ml. of water in a 4-l. beaker. The thick white slurry is then cooled to 0–10°; the acid is collected on a 20-cm. Büchner funnel and washed with two 250-ml. portions of cold water (Note 5). After being freed from as much water as possible by suction, the filter cake is broken up and dissolved in a boiling mixture of 1 l. of ethanol and 350 ml. of water. Cooling to 0° gives the first crop of crystals, weighing about 200 g. Concentration of the mother liquors to 750 ml. and cooling to 0° yields an additional 40–50 g. of product of equal purity. After drying in an oven at 85–95° for 8 hours, the white crystalline acid weighs 240–250 g. (93–97%) and melts at 266–268°.

C. 2,6-*Dichlorophenol*. A mixture of 250 g. (1.2 moles) of dry 3,5-dichloro-4-hydroxybenzoic acid and 575 g. (600 ml., 4.8 moles) of redistilled dimethylaniline is placed in a 2-l. round-bottomed flask provided with a thermometer and a short air-cooled condenser and is heated slowly in an oil bath. Evolution of gas commences at 130° and is vigorous at 150°. The solution is heated at 190–200° for 2 hours or until the evolution of gas has ceased. After cooling, the solution is poured by portions into 600 ml. of concentrated hydrochloric acid in a 3-l. separatory funnel, with cooling from time to time by holding the funnel under a stream of cold water. When the solution is thoroughly cooled and acid to Congo red paper, the phenol is extracted with three 250-ml. portions and three 100-ml. portions of ether (Note 6). The combined ether extracts are washed with 15 ml. of 6 *N* hydrochloric acid, dried overnight over 20 g. of anhydrous sodium sulfate, and filtered into a 2-l. Claisen flask, and the ether is removed by distillation. After cooling, the residue begins to solidify, and 500 ml. of petroleum ether (40–60°) is added. After the phenol has been brought into solution by refluxing gently on the steam bath it is poured into a 1-l. beaker and cooled to 0°. A crop of white crystals (130–140 g.) is collected, having a melting point of 64.5–65.5°. By concentration of the mother liquor to 200 ml., a second crop (25–40 g.) melting at 64–65° can be collected. The total yield amounts to 157–180 g. (80–91%) (Note 7).

2. Notes

1. The ethyl 4-hydroxybenzoate was obtained from the Eastman Kodak Company and melted at 115.5–116°.
2. If the product weighs much less than 350 g. at this point, an additional 50 ml. of sulfuryl chloride should be added and the heating continued until gas is no longer evolved.
3. The ester crystallizes from dilute ethanol as the monohydrate; after long drying in a vacuum desiccator over phosphorus pentoxide, it melts at 111–112°.
4. Claisen's alkali is prepared by dissolving 350 g. of potassium hydroxide in 250 ml. of water, cooling, and diluting to 1 l. with methanol.
5. If the acid is dried completely at this point it contains about 5% potassium chloride. The submitters state that recrystallization is unnecessary if the acid is to be used in Part C.
6. The aqueous layer should be saved. Low yields are due to incomplete extraction of the 2,6-dichlorophenol. If the final yield is low, the aqueous layer should be extracted with three 100-ml. portions of ether and the product recovered by following the procedure outlined.
7. If the product is colored or low melting it may be purified further by recrystallization from 600 ml. of petroleum ether (40–60°) containing about 4 g. of Norit. By cooling and concentrating, 170–175 g. may be recovered (m.p. 65–66°) from 180 g. of crude product.

3. Discussion

2,6-Dichlorophenol has been prepared by the chlorination of phenol with chlorine gas in the presence of nitrobenzene and fuming sulfuric acid,[1] by the decomposition of the diazotate of 2,6-dichloro-4-aminophenol,[2] and by the decarboxylation of 3,5-dichloro-4-hydroxybenzoic acid in quinoline[3] or dimethylaniline.[4]

References and Notes

1. Huston and Neeley, *J. Am. Chem. Soc.*, **57**, 2177 (1935).
2. Seifart, *Ann.*, *Spl.*, **7**, 203 (1870).
3. Blicke, Smith, and Powers, *J. Am. Chem. Soc.*, **54**, 1467 (1932).
4. Tarbell and Wilson, *J. Am. Chem. Soc.*, **64**, 1066 (1942).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

Claisen's alkali

diazotate of 2,6-dichloro-4-aminophenol

ethanol (64-17-5)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

methanol (67-56-1)

ether (60-29-7)

phenol (108-95-2)

sodium sulfate (7757-82-6)

Norit (7782-42-5)

sulfuryl chloride (7791-25-5)

chlorine (7782-50-5)

potassium hydroxide (1310-58-3)

Nitrobenzene (98-95-3)

dimethylaniline (121-69-7)

Quinoline (91-22-5)

potassium chloride (7447-40-7)

2,6-Dichlorophenol, Phenol, 2,6-dichloro- (87-65-0)

ethyl 4-hydroxybenzoate (120-47-8)

ethyl 3,5-dichloro-4-hydroxybenzoate hydrate

3,5-dichloro-4-hydroxybenzoic acid (3336-41-2)

phosphorus pentoxide (1314-56-3)

Ethyl 3,5-dichloro-4-hydroxybenzoate (17302-82-8)

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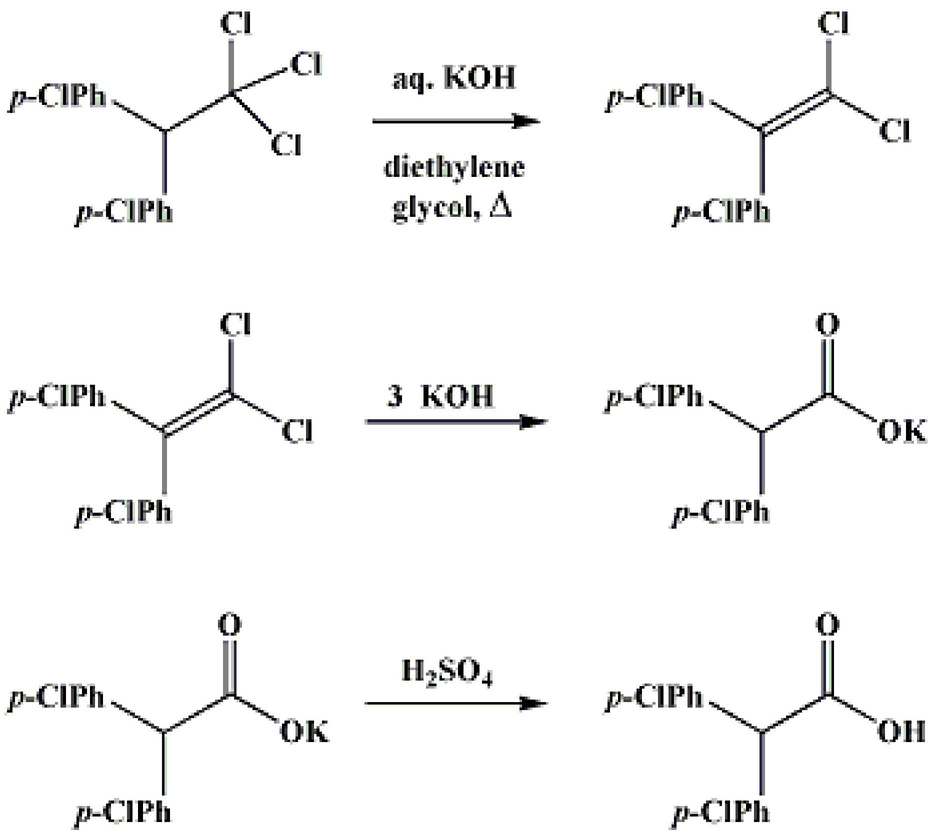
DI-(*p*-CHLOROPHENYL)ACETIC ACID

[Acetic acid, di-(*p*-chlorophenyl)]



Submitted by Oliver Grummitt, Allen Buck, and Richard Egan.
Checked by Lee Irvin Smith, R. T. Arnold, and Paul N. Craig.

1. Procedure

A mixture of 400 ml. of diethylene glycol (Note 1) and 49.5 g. (0.14 mole) of 1,1-di-(*p*-chlorophenyl)-2,2,2-trichloroethane (Note 2) is placed in a 1-l. three-necked flask fitted with a stirrer, a reflux condenser, and a thermometer. To this is added a solution of 63 g. (1.12 mole) of potassium hydroxide in 35 ml. of water. The mixture is stirred and refluxed for 6 hours at such a rate that the temperature is maintained at 134–137° (Note 3) and (Note 4). The mixture is allowed to cool and, with vigorous stirring, is poured into 1 l. of cold water. The insoluble material is filtered and washed twice with 50-ml. portions of warm water (Note 5). The filtrate is then boiled gently for 5 minutes with 2 g. of Norit; the carbon is removed, the filtrate is acidified to litmus with 20% sulfuric acid (approximately 120 ml.), and then an additional 30 ml. of acid is added. The mixture is cooled to 0–5°; the precipitate is collected by filtration under suction, washed free of sulfate ions with water, and dried at 100–110°. The product is di-(*p*-chlorophenyl) acetic acid melting at 163–165°; it weighs 27–28.5 g. (69–73%). For purification, this material is dissolved in 100 ml. of boiling 95% ethanol, the solution

is filtered, and approximately 45 ml. of water is added to the boiling filtrate until it just becomes turbid. The solution is then cooled to 0–5°, and the solid is removed by suction filtration. The material weighs 25–26 g. and melts at 164–166°.

2. Notes

1. Diethylene glycol with a boiling range of 230–270°, from Carbide and Carbon Chemicals Corporation, is satisfactory.
2. A purified grade of 1,1-di-(*p*-chlorophenyl)-2,2,2-trichloroethane (DDT) melting at 105–106° should be used. It can be obtained by crystallizing the technical material from ethanol. Thus, 100 g. of technical DDT melting at 81–96°, when crystallized from 550 ml. of 95% ethanol, gave about 70 g. of material melting at 105–106°.
3. The intermediate product, 1,1-di-(*p*-chlorophenyl)-2,2-dichloroethylene,[1,2] can be isolated readily. The mixture is gradually (7–8 minutes) heated to reflux temperature and is then refluxed 2 minutes. The mixture is cooled and poured into 1 l. of cold water, and the product is removed by suction filtration, washed well with water, and dried. The yield of crude product melting at 83–86° is 43.5 g. (97%). This may be purified by crystallization from 200 ml. of 95% ethanol; the product weighs 39.5 g. and melts at 86.5–88°.
4. Longer reaction times or higher temperatures favor the formation of di-(*p*-chlorophenyl) methane; see Note 5.
5. The insoluble material consists of silica, 1,1-di-(*p*-chlorophenyl)-2,2-dichloroethylene and a small amount of di-(*p*-chlorophenyl) methane[3] (melting at 54–55° when purified), formed by decarboxylation of the acid.

3. Discussion

Di-(*p*-chlorophenyl) acetic acid has been made by the action of alcoholic potassium hydroxide on 1,1-di-(*p*-chlorophenyl)-2,2-dichloroethane;[2,4] by the action of barium hydroxide on DDT in ethylene glycol;[4] and by the condensation of chlorobenzene with glyoxylic acid.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 130
- Org. Syn. Coll. Vol. 5, 370

References and Notes

1. Zeidler, *Ber.*, **7**, 1181 (1874).
2. Grummitt, Buck, and Stearns, *J. Am. Chem. Soc.*, **67**, 156 (1945).
3. Montagne, *Rec. trav. chim.*, **25**, 379 (1906).
4. White and Sweeney, *Public Health Repts. U. S.*, **60**, 66 (1945).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica

1,1-di-(p-chlorophenyl)-2,2,2-trichloroethane (DDT)

alcoholic potassium hydroxide

ethanol (64-17-5)

sulfuric acid (7664-93-9)

carbon, Norit (7782-42-5)

chlorobenzene (108-90-7)

potassium hydroxide (1310-58-3)

ethylene glycol (107-21-1)

barium hydroxide (17194-00-2)

glyoxylic acid (298-12-4)

diethylene glycol (111-46-6)

Di-(p-chlorophenyl)acetic acid, Acetic acid, di-(p-chlorophenyl) (83-05-6)

1,1-di-(p-chlorophenyl)-2,2,2-trichloroethane (50-29-3)

1,1-Di-(p-chlorophenyl)-2,2-dichloroethylene (72-55-9)

di-(p-chlorophenyl) methane (101-76-8)

Di-(p-chlorophenyl) acetic acid

1,1-di-(p-chlorophenyl)-2,2-dichloroethane (72-54-8)

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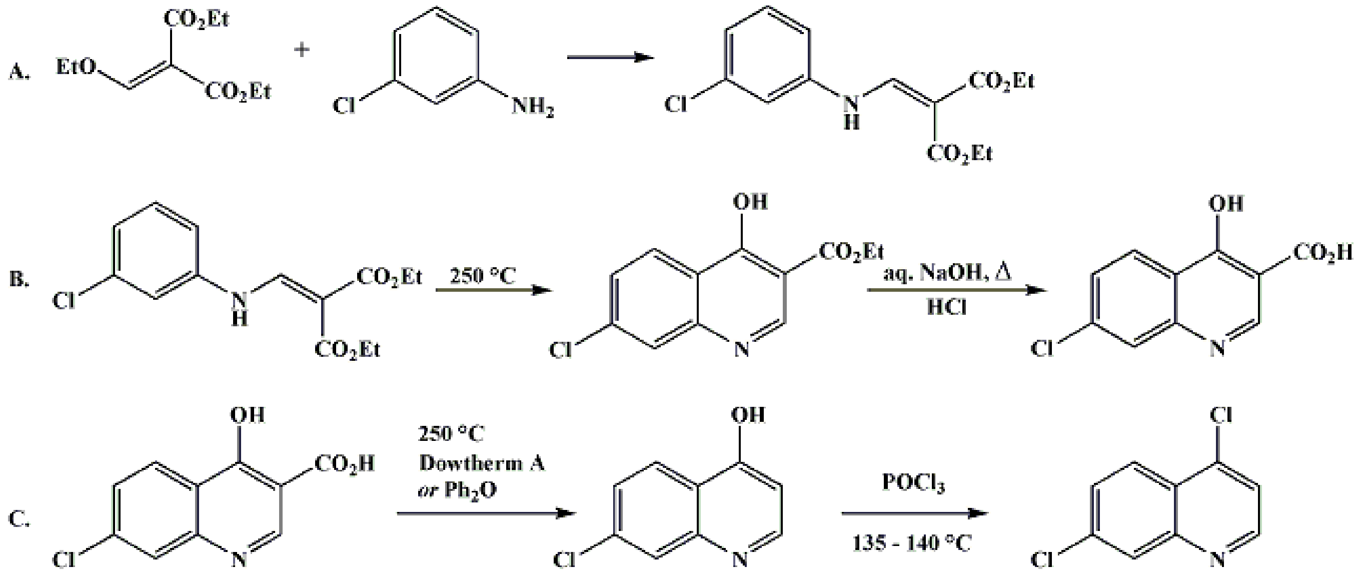
4,7-DICHLOROQUINOLINE

[Quinoline, 4,7-dichloro-]



Submitted by Charles C. Price and Royston M. Roberts[1].
Checked by J. R. Roland and R. S. Schreiber.

1. Procedure

A. *Ethyl α-carbethoxy-β-m-chloroanilinoacrylate*. A few boiling chips are added to a mixture of 127.5 g. (1.0 mole) of *m*-chloroaniline (Note 1) and 233 g. (1.1 moles) of ethyl ethoxymethylenemalonate (p. 395) (Note 2) in an open 500-ml. round-bottomed flask. The mixture is heated on a steam bath for 1 hour, the evolved ethanol being allowed to escape. The warm product is used directly in the next step (Note 3).

B. *7-Chloro-4-hydroxy-3-quinolinecarboxylic acid*. In a 5-l. round-bottomed flask equipped with an air condenser 1 l. of Dowtherm A (Note 4) is heated to vigorous boiling, and the product of the above step is poured in through the condenser. Heating is continued for 1 hour, during which time a large proportion of the cyclization product crystallizes. The mixture is cooled, filtered, and washed with two 400-ml. portions of Skellysolve B (b.p. 61–70°) to remove the major portion of colored impurities. The air-dried filter cake (Note 5) is mixed with 1 l. of 10% aqueous sodium hydroxide, and the mixture is refluxed vigorously until all the solid ester dissolves (about 1 hour). The saponification mixture is cooled, and the aqueous solution is separated from any oil that may be present. The solution is acidified to Congo red paper with concentrated hydrochloric acid (ca. 270 ml. of the 38% acid, sp. gr. 1.19) or 10% sulfuric acid. The 7-chloro-4-hydroxy-3-quinolinecarboxylic acid, weight 190–220 g. (85–98%), is collected by filtration and washed thoroughly with water. The dry acid melts at about 266° with effervescence (Note 6).

C. *7-Chloro-4-quinolinol and 4,7-dichloroquinoline*. The above air-dried acid (Note 7) is suspended in 1 l. of Dowtherm A in a 2-l. flask equipped with a stirrer and a reflux condenser. The mixture is boiled for 1 hour under a stream of nitrogen to assist in the removal of the water (Note 8). The clear, light-brown solution is cooled to room temperature, and 90 ml. (150 g., 0.98 mole) of phosphorus oxychloride is added. The temperature is raised to 135–140°, and the mixture is stirred for 1 hour. The reaction mixture is cooled and poured into a separatory funnel. The portion of the mixture adhering to the flask is rinsed into the funnel with ether, and the solution is washed with three 500-ml. portions of 10% hydrochloric acid. The combined acid extracts are cooled in ice and neutralized with 10% sodium hydroxide to precipitate the 4,7-dichloroquinoline. The solid is collected, washed thoroughly with water, and dried; it weighs 130–145 g. (66–73%) and melts at 80–82°. The pure product is obtained by one recrystallization from Skellysolve B (b.p. 61–70°); weight 110–120 g. (55–60%), m.p. 84–85°.

2. Notes

1. The checkers found it desirable to distil the *m*-chloroaniline through a 20-plate column, the fraction boiling at 64–66°/18 mm. being collected for use in this preparation.
2. A good criterion of the purity of the ethyl ethoxymethylenemalonate is the refractive index; material of n_D^{2} > 1.4600 is satisfactory. The checkers redistilled the ethyl ethoxymethylenemalonate through a 1 by 12 in. bead-packed column just before use and employed the fraction boiling at 112–115°/0.1 mm., n_D^{25} 1.4604.
3. The anilinoacrylate can be recrystallized from low-boiling petroleum ether as slender white needles, m.p. 55–56°.
4. Dowtherm A, a mixture of biphenyl and diphenyl ether, may be replaced by diphenyl ether. The high-boiling solvent is most

conveniently heated to its boiling point (ca. 250°) by an electric heating mantle.
5. The yield of ester isolated at this point is 215–240 g. (85–95%), m.p. 295–297°.
6. The acid can be recrystallized from ethanol as fine white needles melting with decomposition at 273–274°.
7. The acid need not be dry if care is taken to remove water during the decarboxylation in boiling Dowtherm.
8. If the 7-chloro-4-quinolinol is desired, it is more convenient to effect the decarboxylation without a solvent.[2]

3. Discussion

4,7-Dichloroquinoline has been prepared through a somewhat similar scheme from *m*-chloroaniline and oxaloacetic ester[3] or formylacetic ester.[4] The synthesis outlined above can be modified in various ways.[2,5,6,7]

The procedure has been utilized on a large scale in the preparation of several thousand pounds of 4,7-dichloroquinoline, essentially as described above. It has also been applied successfully to many other aromatic amines, including aniline,[8] *o*-,[9] and *m*-,[9] and *p*-anisidine,[3] 3,4-dimethylaniline,[3] *o*-nitroaniline,[8] *p*-chloroaniline,[8] *m*- and *p*-phenoxyaniline,[8] *p*-dimethylaminoaniline,[8] 3,4-dimethoxyaniline,[8] 3-aminopyridine,[3] *o*-phenylenediamine,[10] and 8-aminoquinoline.[10]

References and Notes

1. Work done under contract with the Office of Scientific Research and Development.
2. Price and Roberts, *J. Am. Chem. Soc.*, **68**, 1206 (1946).
3. Surrey and Hammer, *J. Am. Chem. Soc.*, **68**, 115 (1946).
4. Price, Leonard, and Reitsema, *J. Am. Chem. Soc.*, **68**, 1256 (1946).
5. Snyder and Jones, *J. Am. Chem. Soc.*, **68**, 1253 (1946).
6. Price and Roberts, *J. Am. Chem. Soc.*, **68**, 1255 (1946).
7. Price, Leonard, and Herbrandson, *J. Am. Chem. Soc.*, **68**, 1251 (1946); Price, Roberts, and Herbrandson, Brit. pat. 627,297 [*C. A.*, **44**, 2572 (1950)].
8. Riegel, Lappin, Adelson, Jackson, Albisetti, Dodson, and Baker, *J. Am. Chem. Soc.*, **68**, 1264 (1946).
9. Lauer, Arnold, Tiffany, and Tinker, *J. Am. Chem. Soc.*, **68**, 1268 (1946).
10. Snyder and Freier, *J. Am. Chem. Soc.*, **68**, 1320 (1946).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

Dowtherm A

Skellysolve B

formylacetic ester

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ether (60-29-7)

aniline (62-53-3)

sodium hydroxide (1310-73-2)

nitrogen (7727-37-9)

Phosphorus Oxychloride (21295-50-1)

Biphenyl (92-52-4)

3,4-dimethoxyaniline (6315-89-5)

diphenyl ether (101-84-8)

3,4-Dimethylaniline (95-64-7)

4,7-Dichloroquinoline, Quinoline, 4,7-dichloro- (86-98-6)

ethyl ethoxymethylenemalonate

7-Chloro-4-hydroxy-3-quinolinecarboxylic acid (86-47-5)

anilinoacrylate

7-chloro-4-quinolinol (86-99-7)

3-Aminopyridine (462-08-8)

8-aminoquinoline (578-66-5)

o-Phenylenediamine (95-54-5)

o-NITROANILINE (88-74-4)

m-chloroaniline (108-42-9)

p-chloroaniline (106-47-8)

p-anisidine (104-94-9)

p-dimethylaminoaniline (99-98-9)

Ethyl α-carbethoxy-β-m-chloroanilinoacrylate (3412-99-5)

p-phenoxyaniline (139-59-3)

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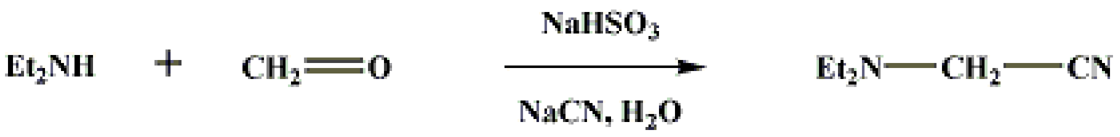
DIETHYLAMINOACETONITRILE

[Acetonitrile, diethylamino-]



Submitted by C. F. H. Allen and J. A. VanAllan.
Checked by Cliff S. Hamilton, A. F. Harris, and C. W. Winter.

1. Procedure

This preparation should be carried out under a good hood since poisonous hydrogen cyanide may be evolved.

To a solution of 312 g. (3 moles) of sodium bisulfite in 750 ml. of water in a 3-l. beaker is added 225 ml. of a 37–40% formaldehyde solution, and the mixture is warmed to 60°. After cooling to 35°, 219 g. (309 ml., 3 moles) of diethylamine is added with hand stirring, and the mixture is allowed to stand for 2 hours. The beaker containing the reaction mixture is placed under a good hood, and to it is added a solution of 147 g. (3 moles) of sodium cyanide dissolved in 400 ml. of water with efficient stirring so that the two layers are thoroughly mixed. After 1.5 hours the upper nitrile layer is separated and dried over 25 g. of Drierite; it weighs 299–309 g. (90–92%). The crude product is purified by distillation; the portion boiling at 61–63°/14 mm., n_D^{25} 1.4230, amounts to 298–302 g. (88–90%) (Note 1).

2. Notes

1. Higher homologs have been prepared from other aldehydes.

3. Discussion

This procedure is essentially that recorded in the literature.[1]

References and Notes

1. Knoevenagel and Mercklin, *Ber.*, **37**, 4089 (1904).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Drierite

formaldehyde (630-08-0)

sodium cyanide (143-33-9)

hydrogen cyanide (74-90-8)

sodium bisulfite (7631-90-5)

diethylamine (109-89-7)

Diethylaminoacetonitrile, Acetonitrile, diethylamino- (3010-02-4)

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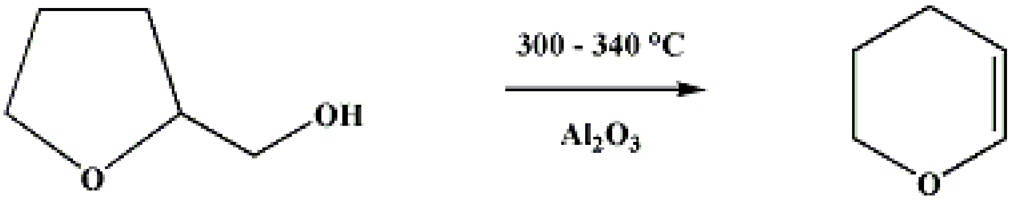
2,3-DIHYDROPYRAN

[Pyran, dihydro-]



Submitted by R. L. Sawyer and D. W. Andrus.
Checked by Nathan L. Drake and Charles M. Eaker.

1. Procedure

The reaction is carried out in a heated tube similar to that described by Herbst and Manske [*Org. Syntheses* Coll. Vol. **2**, 389 (1943)] except that the receiving chamber B (*loc. cit.*, Fig. 2) does not have a side arm, and that a 10-cm. water-cooled condenser is attached to the exit end of the tube leading directly to the receiver. The tube is packed with activated alumina (Note 1) held in place at the ends by plugs of glass wool.

The furnace is heated to 300–340° (Note 2), and 204 g. (195 ml., 2 moles) of tetrahydrofurfuryl alcohol (Note 3) is introduced from the dropping funnel at the rate of 50 ml. per hour. The product, collected in an Erlenmeyer flask which contains 30 g. of anhydrous potassium carbonate, consists of a light-brown oil and a lower aqueous layer. When the reaction tube has drained, the lower aqueous layer is separated and discarded. The upper layer is fractionated through a short column, and a fraction boiling at 70–86° is collected. This consists of a mixture of water and dihydropyran, most of which distils at 83–86°. The residue (25–35 g.) is mainly unchanged tetrahydrofurfuryl alcohol (Note 4).

The water-dihydropyran fraction separates into two layers. The lower aqueous layer is separated and discarded. The upper layer, consisting of fairly pure dihydropyran, is dried over 5–6 g. of anhydrous potassium carbonate, decanted, refluxed for 1 hour with 2–3 g. of metallic sodium, and then distilled from sodium (Note 5). The yield is 110–118 g. of dihydropyran, boiling at 84–86° (66–70%).

2. Notes

1. Several varieties of technical activated alumina were used. After three or four runs the catalyst becomes covered with a brown tar and the yield of dihydropyran decreases. The catalyst may be regenerated by igniting it at red heat until the tar is burned off. The checkers used 8–14 mesh activated alumina from the Aluminum Ore Company of America. The catalyst was reactivated at 450° by drawing a slow stream of air through it until the tar was burned off.

2. The temperature of the furnace is measured by a thermometer placed alongside the glass tube inside the furnace. The temperature should be 330–340° except in the regions about 10 cm. from each end of the furnace; here the temperatures will be 300–340°, depending on the construction of the furnace.
3. According to the submitters, Eastman's practical grade of tetrahydrofurfuryl alcohol must be purified by distillation; the fraction boiling at 79–80°/20 mm. was used. The checkers used, without purification, tetrahydrofurfuryl alcohol obtained from the Quaker Oats Company. The yields were equally good.
4. The recovered tetrahydrofurfuryl alcohol turns yellow on standing and is unsuitable for further runs. If it is used, the yield of dihydropyran drops to 36–38%, and the catalyst must be regenerated after each run.
5. Dihydropyran is very difficult to dry. Even after this treatment the product often contains traces of water.

3. Discussion

The procedure given above is essentially that of Paul.[1,2] Aluminum silicate, titanium oxide, and basic aluminum phosphate have also been used as catalysts in this rearrangement.[3] The action of sodium amide upon tetrahydrofurfuryl bromide gives chiefly 1,4-epoxy-4-pentene and a small amount of dihydropyran. 1,4-Epoxy-4-pentene undergoes rearrangement at 380° in the presence of alumina to yield dihydropyran.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 470
- Org. Syn. Coll. Vol. 3, 794
- Org. Syn. Coll. Vol. 4, 354
- Org. Syn. Coll. Vol. 4, 496

References and Notes

1. Paul, *Bull. soc. chim. France,* (4) **53**, 1489 (1933).
2. Schniepp and Geller, *J. Am. Chem. Soc.*, **68**, 1646 (1946).
3. Wilson, *J. Am. Chem. Soc.*, **69**, 3004 (1947).
4. Paul, *Bull. soc. chim. France,* (5) **2**, 745 (1935).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

activated alumina

basic aluminum phosphate

potassium carbonate (584-08-7)

sodium (13966-32-0)

tetrahydrofurfuryl alcohol (97-99-4)

sodium amide (7782-92-5)

titanium oxide

2,3-Dihydropyran, Pyran, dihydro-, dihydropyran

Tetrahydrofurfuryl bromide (1192-30-9)

1,4-epoxy-4-pentene

Aluminum silicate

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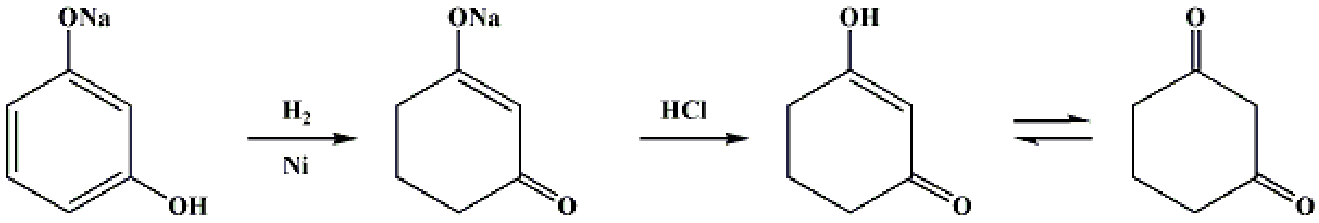
Organic Syntheses, CV 3, 278

DIHYDRORESORCINOL

[1,3-Cyclohexanedione]



Submitted by R. B. Thompson
Checked by Nathan L. Drake, G. Forrest Woods, and I. W. Tucker.

1. Procedure

A solution of 24 g. (0.6 mole) of sodium hydroxide, 100 ml. of water, and 55 g. (0.5 mole) of resorcinol is placed in an apparatus for high-pressure hydrogenation together with 10 g. of reduced Universal Oil Products hydrogenation catalyst (Note 1) or Raney nickel (see p. 181). The pressure in the bomb is raised to 1000–1500 lb. with hydrogen, and the temperature is adjusted to 50° (Note 2). The bomb is shaken and the reaction allowed to proceed for 10 to 12 hours, during which time 0.5 mole of hydrogen is absorbed (Note 3).

The apparatus is allowed to cool to room temperature, the pressure is released, and the catalyst is removed by filtration. The filtrate is made acid to Congo red with concentrated hydrochloric acid, and the solution is cooled to 0° in an ice-salt bath and held at that temperature for 30 minutes before filtration. The dihydroresorcinol which crystallizes is separated by filtration and dried; 50–60 g. of crude dry product containing sodium chloride is obtained.

The crude dihydroresorcinol is dissolved in 125–150 ml. of hot benzene, filtered to remove the sodium chloride, and allowed to crystallize. The solid is separated by filtration and dried overnight in a vacuum desiccator. The product melts at 103–104° and weighs 48–53 g. (85–95%) (Note 4).

2. Notes

1. The Universal Oil Products hydrogenation catalyst consists of a mixture of nickel, nickel oxides, and kieselguhr compressed into pills containing 50–55% nickel. Before use in a liquid-phase hydrogenation of this sort, the catalyst must be reduced in a stream of hydrogen at 430°. The reduced catalyst is cooled in the stream of hydrogen and may be kept under alcohol. It also may be saturated with carbon dioxide and kept in a sealed bottle. The pilled material should be pulverized before use in this preparation. The pelleted Universal Oil Products hydrogenation catalyst may be purchased from Universal Oil Products Company, 310 S. Michigan Ave., Chicago 4, Illinois.
2. It is particularly important that the temperature should not rise above 50°; at higher temperatures complex condensation products result.
3. It is important that hydrogenation be complete; incompletely hydrogenated material yields an oily product which is exceedingly difficult to crystallize. The usual time of hydrogen absorption is 4 to 5 hours with Universal Oil Products catalyst and about 4 hours with Raney nickel. The extra time mentioned in the procedure avoids any chance of incomplete reduction.
4. Dihydroresorcinol is unstable; it can be stored only a short time. If it is not used immediately, it should be stored under an inert gas in a brown bottle in a refrigerator.

3. Discussion

Dihydroresorcinol has been prepared by the reduction of resorcinol with sodium amalgam,[1] by reduction of hydroxyhydroquinone or its carboxylic acid with sodium amalgam,[2] by hydrolysis of its dioxime,[3] or by cyclization of ethyl γ-acetylbutyrate.[4] The present method of preparation is essentially that of Klingenfuss.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 539
- Org. Syn. Coll. Vol. 5, 743

References and Notes

1. Merling, *Ann.*, **278**, 28 (1894).
2. Thiele and Jaeger, *Ber.*, **34**, 2841 (1901).
3. Kötz and Grethe, *J. prakt. Chem.*, (2) **80**, 502 (1909).
4. Vorländer, *Ann.*, **294**, 270 (1897); Schilling, *Ann.*, **308**, 190 (1899).
5. Klingenfuss (to Hoffmann-La Roche, Inc.), U. S. pat. 1,965,499 [*C. A.*, **28**, 5476 (1934)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

nickel oxides

kieselguhr

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

carbon dioxide (124-38-9)

nickel, Raney nickel (7440-02-0)

sodium (13966-32-0)

hydroxyhydroquinone (533-73-3)

resorcinol (108-46-3)

Dihydroresorcinol

1,3-Cyclohexanedione (504-02-9)

ethyl γ-acetylbutyrate (13984-57-1)

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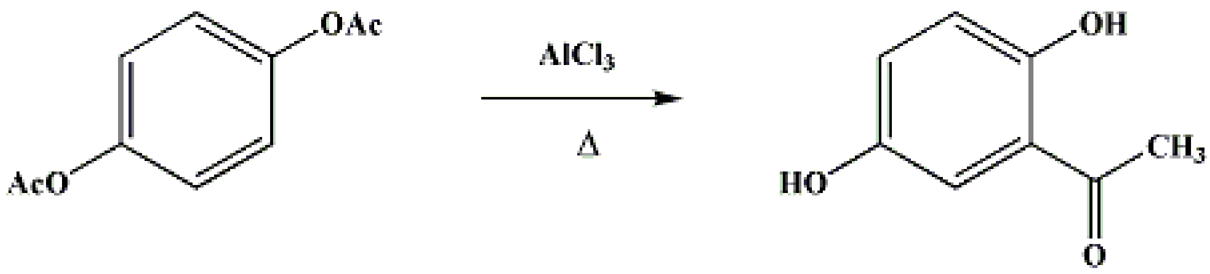
Organic Syntheses, *CV 3*, *280*

2,5-DIHYDROXYACETOPHENONE

[Acetophenone, 2,5-dihydroxy-; quinacetophenone]



Submitted by G. C. Amin and N. M. Shah.
Checked by R. S. Schreiber and W. W. Prichard.

1. Procedure

A mixture of 50 g. (0.257 mole) of dry hydroquinone diacetate (p. 452) and 116 g. (0.87 mole) (Note 1) of anhydrous aluminum chloride is finely powdered in a mortar and introduced into a dry 500-ml. round-bottomed flask fitted with an air condenser protected by a calcium chloride tube and connected to a gas-absorption trap. The flask is placed in an oil bath (Note 2) which is heated slowly from room temperature so that at the end of about 30 minutes the temperature of the oil reaches 110–120°, at which point the evolution of hydrogen chloride begins. The temperature is then raised slowly to 160–165° and maintained at that point for about 3 hours (Note 3); at the end of about 2 hours the evolution of hydrogen chloride becomes very slow and the mass assumes a green color and becomes pasty in consistency (Note 4).

The flask is removed from the oil bath and allowed to cool to room temperature. The excess aluminum chloride is decomposed by treating the reaction mixture with 350 g. of crushed ice followed by 25 ml. of concentrated hydrochloric acid. The solid obtained is collected on a Büchner funnel and washed with two 100-ml. portions of cold water. The crude product weighs about 35 g. (89–90%). Recrystallization from 4 l. of water yields 25–30 g. (64–77%) of green, silky needles melting at 202–203° (Note 5).

2. Notes

1. Ordinary commercial aluminum chloride can be used. If the amount of this reagent is less than 3 moles per mole of the ester the yield diminishes. To compensate for any inert ingredients in the commercial aluminum chloride, the reagent is employed in an excess of about 10% over 3 moles.
2. The flask should not touch the bottom of the oil bath; if it does, the lower portion of the mixture may char.
3. If the evolution of the hydrogen chloride becomes vigorous, the calcium

chloride tube may be removed temporarily and the top of the condenser connected directly to the gas-absorption trap. When the gas evolution slackens and there is no longer any danger that the calcium chloride tube will be blown off, the guard tube is reinserted.
4. The reaction requires about 2 hours, but the heating is continued another hour to ensure its completion.
5. The product may be recrystallized from 250 ml. of 95% ethanol rather than from the much larger quantity of water.

3. Discussion

2,5-Dihydroxyacetophenone has been prepared in 54% yield[1] by heating hydroquinone diacetate, hydroquinone, and anhydrous aluminum chloride. It has also been prepared[2] by the reaction of hydroquinone with acetic acid in the presence of zinc chloride.

The procedure given has also been applied in the Fries rearrangement of hydroquinone dipropionate, with the production of 2,5-dihydroxypropiophenone in good yields.[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 836

References and Notes

1. Rosenmund and Lohfert, *Ber.*, **61**, 2606 (1928).
2. Nencki and Schmid, *J. prakt. Chem.*, **23**, 546 (1881).
3. Amin and Shah, *J. Indian Chem. Soc.*, **25**, 377 (1948).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

2,5-Dihydroxyacetophenone

2,5-dihydroxypropiophenone

ethanol (64-17-5)

calcium chloride (10043-52-4)

hydrogen chloride, hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

hydroquinone (123-31-9)

Acetophenone (98-86-2)

aluminum chloride (3495-54-3)

zinc chloride (7646-85-7)

Hydroquinone diacetate (1205-91-0)

hydroquinone dipropionate (7402-28-0)

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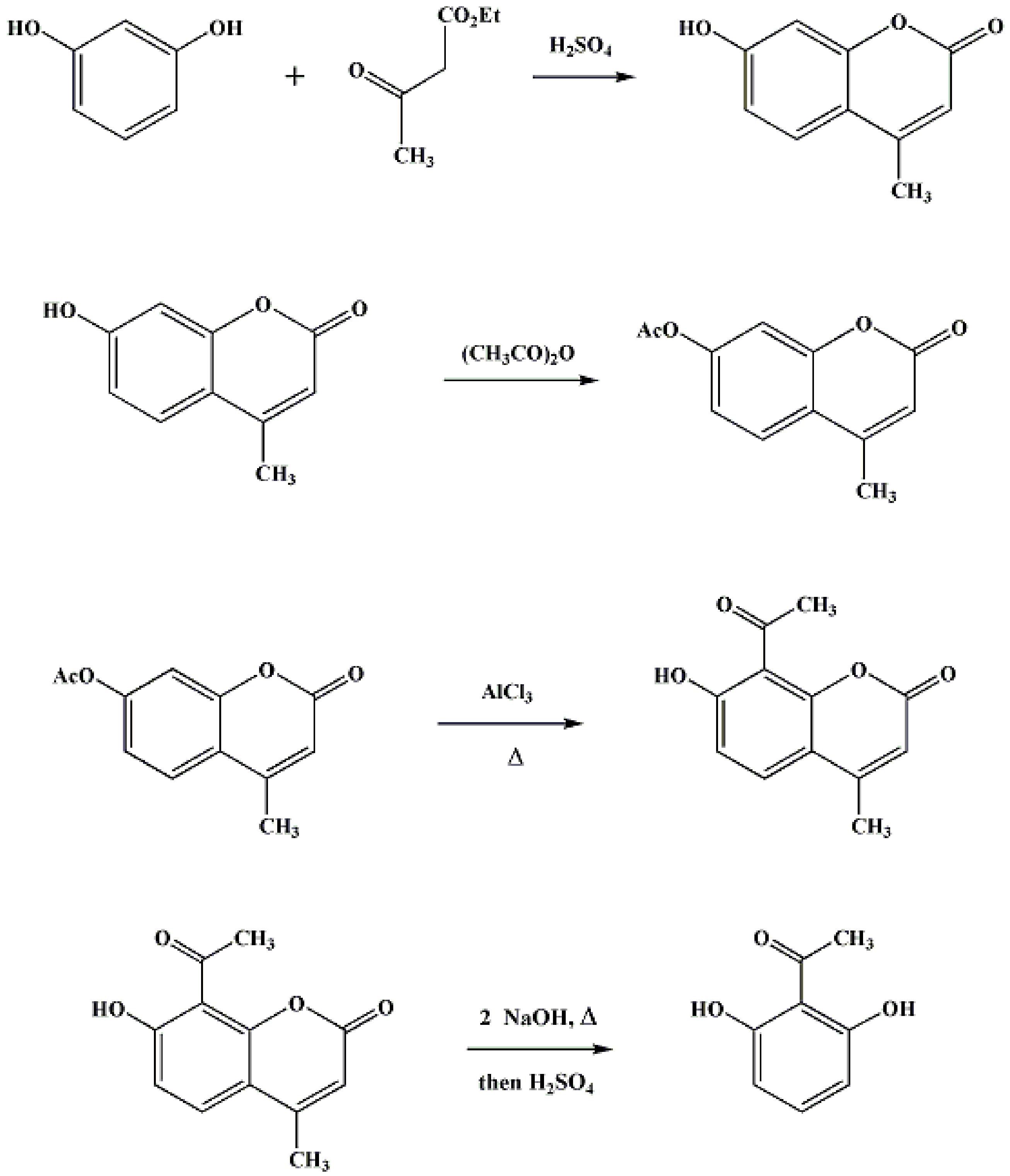
2,6-DIHYDROXYACETOPHENONE

[Acetophenone, 2,6-dihydroxy-]



Submitted by Alfred Russell and John R. Frye.
Checked by R. L. Shriner and Michael Witte.

1. Procedure

A. *4-Methyl-7-hydroxycoumarin* (I). In a 5-l. three-necked round-bottomed flask, fitted with a

mechanical stirrer, a thermometer reaching to the bottom, and a dropping funnel, is placed 2 l. of concentrated sulfuric acid (sp. gr. 1.84). The flask is surrounded by an ice bath, and when the temperature falls below 10° a solution of 220 g. (2 moles) of resorcinol in 260 g. (2 moles) of freshly distilled ethyl acetoacetate is added dropwise. The mixture is stirred, and the temperature is kept below 10° by means of ice and salt. After all the solution has been added (about 2 hours) the reaction mixture is set aside for 12–24 hours without further cooling. The reaction mixture is now poured with vigorous stirring into a mixture of 4 kg. of ice and 6 l. of water. The precipitate is collected on a filter and washed with three 50-ml. portions of cold water. The crude product is then dissolved in 3 l. of 5% aqueous sodium hydroxide solution, the solution is filtered, and the substituted coumarin is reprecipitated from the filtrate by the slow addition of dilute (1:10) sulfuric acid until the solution is acid to litmus. About 1.1 l. of dilute sulfuric acid is required. During the neutralization, the reaction mixture must be well stirred. The product is collected on a Büchner funnel, washed with four 50-ml. portions of cold water, and dried. The yield of 4-methyl-7-hydroxycoumarin is 290–320 g. (82–90%). It is sufficiently pure for use in the next step but may be purified by recrystallization from 95% ethanol using about 15 ml. of ethanol for 5 g. of product. The recrystallized material forms stout almost colorless needles melting at 185°.

B. 4-*Methyl*-7-*acetoxycoumarin* (II). A mixture of 286 g. (1.6 moles) of crude, dry 4-methyl-7-hydroxycoumarin and 572 g. (5.6 moles) of acetic anhydride is placed in a 2-l. round-bottomed flask fitted to a reflux condenser by a ground-glass joint. The mixture is refluxed for 1.5 hours, cooled to about 50°, and poured with vigorous stirring into a mixture of 4 kg. of cracked ice and 4 l. of water. The precipitate is collected on a Büchner funnel, washed with five 50-ml. portions of cold water, and spread on absorbent paper to dry. The drying is completed by placing the product in a steam oven for 10 hours. The yield of crude 4-methyl-7-acetoxycoumarin is 320–340 g. (90–96%). It may be purified by recrystallization from 95% ethanol (5 g. of compound to 20 ml. of solvent) and forms fibrous needles melting at 150–151°. The crude oven-dried product is finely powdered and used in the next step.

C. 4-*Methyl*-7-*hydroxy*-8-*acetylcoumarin* (III). In a clean, dry, 5-l. round-bottomed flask are placed 200 g. (0.92 mole) of dry, powdered 4-methyl-7-acetoxycoumarin and 453 g. (3.4 moles) of technical anhydrous aluminum chloride. The flask is stoppered and shaken vigorously for 3–5 minutes in order to mix the ingredients thoroughly. The stopper is removed and the flask attached to a reflux condenser fitted with a gas-absorption tube. The flask is placed in an oil bath the temperature of which is raised quickly to 125° and then slowly over a period of 2 hours to 170°. At the end of this time the flask is removed from the oil bath, allowed to cool, and immersed in an ice bath. About 1 kg. of cracked ice is added, and then 2.4 l. of dilute (1:7) hydrochloric acid is added over a period of about 2 hours. The mixture is then heated on a steam bath for 30 minutes with vigorous stirring in order to effect complete decomposition. The mixture is filtered and the precipitate washed with four 50-ml. portions of cold water and sucked dry. This crude product is recrystallized by dissolving it in 4 l. of hot 95% ethanol, filtering the hot solution through a warm funnel, and chilling the filtrate. The crystals are collected on a funnel and air-dried. The product melts at 162–163°, and the yield is 145–155 g. (72.5–77.0%) (Note 1).

D. 2,6-*Dihydroxyacetophenone* (IV). A 5-l. three-necked round-bottomed flask is fitted with a reflux condenser, a dropping funnel, and a glass tube, extending to the bottom of the flask, connected to a cylinder of nitrogen (Note 2). In the flask are placed 148 g. (0.68 mole) of 4-methyl-7-hydroxy-8-acetylcoumarin and 500 ml. of distilled water. A rapid stream of nitrogen is bubbled through the water suspension until all the air in the apparatus is displaced, and then a slow stream of the gas is kept passing through the solution (Note 3). A solution of 129 g. (3.23 moles) of sodium hydroxide in 580 ml. of water is added through the dropping funnel, and the mixture is heated on a steam bath for 5 hours. The solution is then cooled and acidified by the addition of about 1 l. of dilute (1:3) hydrochloric acid. The stream of nitrogen gas is continued throughout the period of heating and while the solution is cooling. It may be stopped after the solution is acid. The crude 2,6-

dihydroxyacetophenone which separates on acidification is collected on a filter, washed three times with 50-ml. portions of cold water, and air-dried. A yield of 90–95 g. (87–92% based on the 4-methyl-7-hydroxy-8-acetylcoumarin) of light-yellow solid is obtained.

The purification is accomplished by dissolving the crude product in 1 l. of 95% ethanol, adding 20 g. of Norit, and heating the mixture on a steam cone for 15 minutes with occasional shaking. After this time, 800 ml. of warm water is added, and the solution is heated 5 more minutes and filtered through a hot funnel. The greenish filtrate is chilled in an ice-salt bath, and the first crop (about 65 g.) of lemon-yellow needles of 2,6-dihydroxyacetophenone is removed by filtration. The filtrate is then concentrated under reduced pressure to a volume of 800 ml., again chilled, and the second crop of product (about 15 g.) collected on a filter. The total yield of purified 2,6-dihydroxyacetophenone, melting at 154–155°, is 75–85 g. (a recovery of 83–89%) (Note 4).

2. Notes

1. The mother liquor from this crystallization contains the isomeric acetyl derivative, 4-methyl-6-acetyl-7-hydroxycoumarin.
2. Hydrogen or illuminating gas may be used in place of nitrogen, provided that proper precautions are taken to conduct the gas from the condenser to a flue.
3. It is important to prevent oxygen from coming in contact with the alkaline solution of the 2,6-dihydroxyacetophenone since it causes the formation of oxidation products which materially lower the yield and cause difficulty in purification. The inert atmosphere must be maintained until after the mixture is acidified.
4. The first two steps in this preparation have been carried out using four times the quantities stated with no reduction in the yields. The third step, involving the Fries rearrangement, usually gives lower yields when larger amounts are used. The amounts of materials in the fourth step may be doubled.

3. Discussion

2,6-Dihydroxyacetophenone has been prepared by the action of methylmagnesium iodide on 2,6-dimethoxybenzonitrile[1] followed by cleavage of the ether linkages with aluminum chloride. The present method is based on the procedures described by Limaye[2] and by Baker.[3]

References and Notes

1. Mauthner, *J. prakt. Chem.*, **139**, 290 (1934).
2. Limaye, *Ber.*, **67**, 12 (1934).
3. Baker, *J. Chem. Soc.*, **1934**, 1953.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

2,6-DIHYDROXYACETOPHENONE

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic anhydride (108-24-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

oxygen (7782-44-7)

nitrogen (7727-37-9)

Acetophenone (98-86-2)

Norit (7782-42-5)

aluminum chloride (3495-54-3)

methylmagnesium iodide (917-64-6)

Ethyl acetoacetate (141-97-9)

resorcinol (108-46-3)

coumarin

4-Methyl-7-hydroxycoumarin (90-33-5)

4-Methyl-7-acetoxycoumarin (2747-05-9)

4-Methyl-7-hydroxy-8-acetylcoumarin (2555-29-5)

4-methyl-6-acetyl-7-hydroxycoumarin

2,6-Dimethoxybenzonitrile (16932-49-3)

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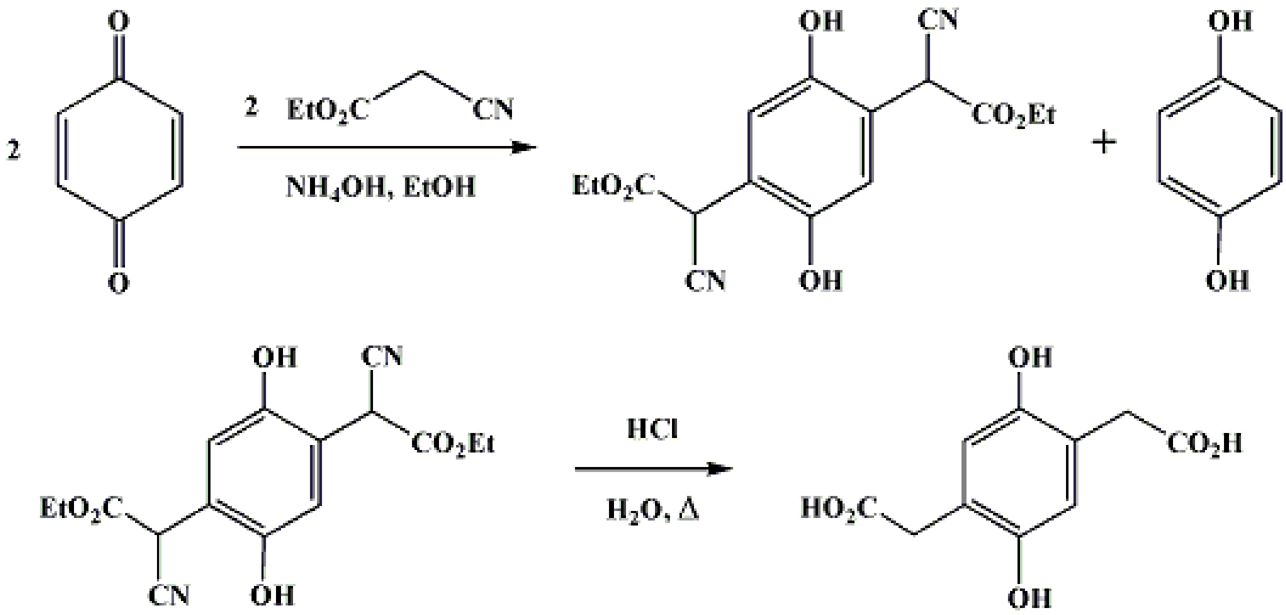
2,5-DIHYDROXY-*p*-BENZENEDIACETIC ACID

[*p*-Benzenediacetic acid, 2,5-dihydroxy-]



Submitted by J. H. Wood and Lucile Cox.
Checked by Lee Irvin Smith, Scott Searles, and R. T. Arnold.

1. Procedure

A 3-l. round-bottomed three-necked flask is equipped with a mechanical stirrer, a 500-ml. dropping funnel, and a 250-ml. dropping funnel. The flask is contained in a pneumatic trough through which water at room temperature is circulated. A mixture of 30 ml. of ethyl cyanoacetate and 100 ml. of ethanol is placed in the flask. Meanwhile 54 g. (0.5 mole) of *p*-benzoquinone in a 1-l. flask is heated to 40° with 500 ml. of 95% ethanol, and, when practically all the quinone is dissolved, 56 g. (0.5 mole) of ethyl cyanoacetate is added and the mixture is stirred until solution is complete (Note 1). Most of this solution is placed in the 500-ml. dropping funnel, the remainder being added when the funnel becomes sufficiently emptied after the reaction has started.

Twenty-five milliliters of concentrated ammonium hydroxide (Note 2) is introduced into the 3-l. flask. A solution of 100 ml. of concentrated ammonium hydroxide in 150 ml. of water is placed in the 250-ml. dropping funnel, which is loosely stoppered. Stirring is started, and the stopcocks of the two dropping funnels are adjusted so that the solutions will be delivered into the flask at a uniform rate in a period of about 45 minutes (Note 3). Stirring is continued for an additional 10 minutes. The mixture is then permitted to stand for 1 hour, after which the purplish red precipitate is filtered with suction. Any solid material adhering to the walls of the flask is washed onto the funnel with ethanol. The solid is then washed three times on the funnel with ethanol (Note 4). The filtrate and washings are discarded. The product is slightly impure diethyl α,α'-dicyano-2,5-dihydroxy-*p*-benzenediacetate and weighs 36–41 g. (43–49%) (Note 5).

For the hydrolysis, 36 g. (0.11 mole) of the residue is transferred to a 1-l. round-bottomed flask equipped with a reflux condenser, and 210 ml. of concentrated hydrochloric acid in 190 ml. of water is added. The mixture is refluxed gently at first, then vigorously (Note 6), until hydrolysis is

essentially complete (about 20 hours). Then 180 ml. of water and 4 g. of Norit A are added and the mixture is stirred and boiled for 3 minutes, after which it is rapidly filtered with suction through two layers of hardened filter paper in a Büchner funnel (Note 7). The filtrate, upon cooling to 20° or below, deposits 18 g. (72%) of lightly colored 2,5-dihydroxy-*p*-benzenediacetic acid (Note 8). A snow-white product is obtained by dissolving 18 g. of this material in 375 ml. of boiling water, treating with 2 g. of Norit A, and filtering. Upon cooling, there is deposited 15 g. (61%) of the acid which melts at 233° (Note 9).

2. Notes

1. Precautions must be taken to prevent ammonia from coming in contact with the quinone before the desired time. The dropping funnel is loosely stoppered, and the flask containing the remainder of the solution is well stoppered.
2. Concentrated ammonium hydroxide (28% NH_3) must be used to obtain a good yield. The ammonium hydroxide may be introduced through either the central opening or the 250-ml. dropping funnel with the precaution given in (Note 1).
3. Preferably, all the ammonium hydroxide solution should be added by the time 90% of the quinone solution has been added.
4. This product is insoluble in ethanol, and there is no loss in washing.
5. Slightly lower yields were obtained by the checkers at this point. The yields in three experiments were respectively 32.5, 32.0, and 31.5 g. (39, 38.5, and 38%).
6. In the early stages, considerable foaming usually occurs, and care must be exercised that the foam does not carry part of the insoluble product into the condenser. The insoluble material accumulating on the walls of the flask is occasionally returned to the liquid portion by whirling the flask.
7. Rapid filtration is essential to avoid crystallization in the funnel and to decrease the time the filter paper is in contact with the concentrated acid.
8. The checkers obtained, in two experiments, yields of 71 and 86% of material melting respectively at 232–238° (cor.) and 235–239° (cor.).
9. The checkers obtained, in two experiments, yields of 63 and 73% at this point. The product was white and melted at 233° (cor.).

3. Discussion

The method described above is a modification of that described by Wood, Colburn, Cox, and Garland.[1]

References and Notes

1. Wood, Colburn, Cox, and Garland, *J. Am. Chem. Soc.*, **66**, 1540 (1944).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

Norit A (7782-42-5)

ammonium hydroxide (1336-21-6)

Ethyl cyanoacetate (105-56-6)

Quinone, p-benzoquinone (106-51-4)

2,5-Dihydroxy-p-benzenediacetic acid, p-Benzenediacetic acid, 2,5-dihydroxy- (5488-16-4)

diethyl α,α'-dicyano-2,5-dihydroxy-p-benzenediacetate

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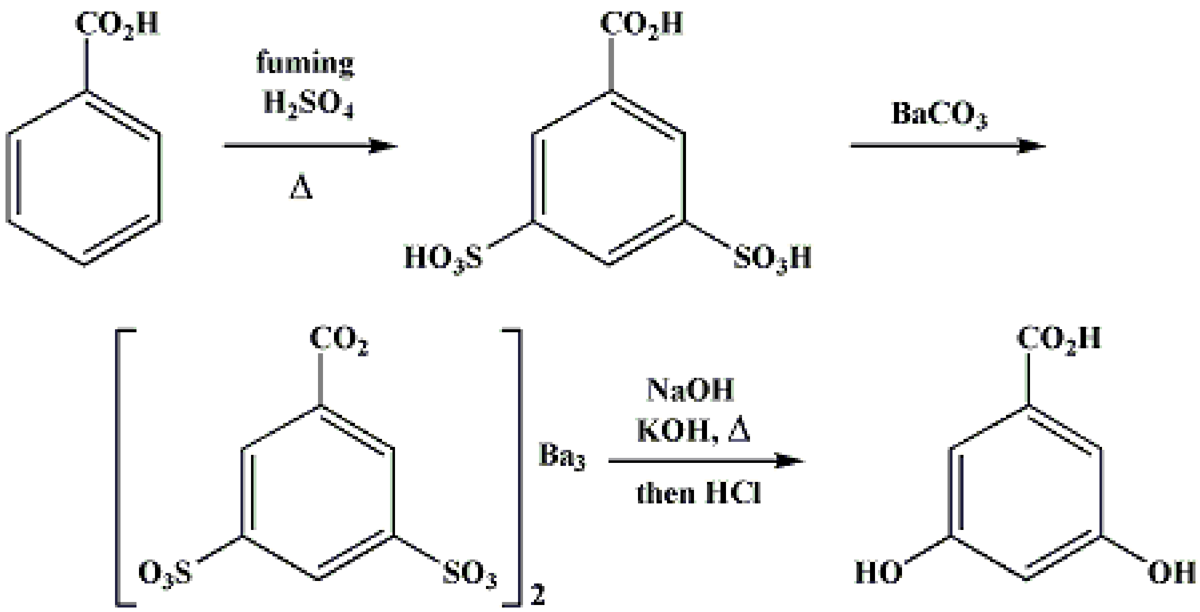
3,5-DIHYDROXYBENZOIC ACID

[α-Resorcylic acid]



Submitted by Arthur W. Weston and C. M. Suter.
Checked by C. F. H. Allen and John W. Gates, Jr..

1. Procedure

To 200 g. (1.64 moles) of benzoic acid in a 1-l. Kjeldahl flask, in the top of which is inserted a loosely fitting cold finger (Note 1), is added 500 ml. of fuming sulfuric acid (Note 2). The mixture is heated in an oil bath for 5 hours at 240–250° (bath temperature).

After standing overnight the syrupy liquid is poured slowly with stirring into 3 kg. of ice in a 3-gal. crock (Note 3). The solution is then neutralized by adding barium carbonate in 100-g. portions, stirring occasionally until the gas evolution slackens before each addition: 2.4–2.5 kg. is required. The pasty mass is filtered by suction on a 30-cm. Büchner funnel, and the barium sulfate is washed with five 300-ml. portions of water. The combined filtrates are evaporated nearly to dryness on a steam bath and finally dried in an oven at 125–140° (Note 4). The yield of crude barium salt is 640–800 g.

The operator should wear goggles and long-sleeved gloves during the next two operations. The dried, pulverized barium salt is introduced in 200-g. portions into a melt of 600 g. each of sodium and potassium hydroxides contained in a 14 by 20 cm. copper beaker. The mixture is stirred with a copper stirrer and the temperature determined with a thermometer in a copper well. (Note 5). Each portion is well stirred in before the next is added. The temperature is then slowly raised to 250–260°, at

which point a vigorous reaction occurs with copious evolution of gas. After this has slackened (about 30 minutes) the temperature is raised to 280–310° and maintained there for 1 hour, then allowed to drop to 200°. The melt is ladled into 6 l. of water (Note 6) and (Note 7). The barium sulfite is filtered by suction, and the filtrate is acidified with concentrated hydrochloric acid (about 2.5 l. is required).

The resulting solution (about 9 l.) is divided into two portions and each is extracted three times, 600 ml. of ether being used each time (Note 8). The combined extracts are concentrated to about 1 l. and dried overnight over 150 g. of anhydrous sodium sulfate. After filtration and evaporation of the ether, there remains 137–160 g. (58–65%) of a slightly colored product, melting with decomposition at 227–229°. It is sufficiently pure for most purposes (Note 9) and (Note 10).

2. Notes

1. An ordinary glass funnel suspended in the neck serves less satisfactorily, whereas with a water condenser solidification of the sulfur trioxide causes difficulty.
2. This acid, approximately 30% sulfur trioxide, is made by mixing 500 g. each of fuming sulfuric acid containing 60% free sulfur trioxide and concentrated sulfuric acid (sp. gr. 1.84); 500 ml. of this mixture is used.
3. The reaction product may solidify at first, but it dissolves later.
4. The evaporation of the solution is most conveniently done overnight. The final drying is best done in flat metal trays; the length of time required depends upon the temperature. The checkers left trays on a steam coil over a week end.
5. An 18-cm. piece of 10- to 12-mm. copper tubing, pounded together at the lower end, is used. The stirrer can be made of the same tubing.
6. The addition of the hot melt causes some spattering.
7. Alternatively, the melt may be poured into shallow metal trays and allowed to cool and solidify. It is then pulverized and dissolved. Grinding is difficult and unpleasant. The melt should not be allowed to solidify in the reaction vessel.
8. A large automatic extraction apparatus may be used if available.
9. The color can be removed by recrystallization from hot acetic acid, using a decolorizing carbon. A solution of 16 g. of the crude acid in 85 ml. of hot acetic acid deposits 13.4 g. of white needles after filtration through a 2-mm. layer of Darco in a hot funnel and cooling. These are anhydrous after drying at 100° at 35 mm. for 2 hours; m.p. 234–235° with decomposition (cor.). The melting point varies with the rate of heating.
10. This material is partially hydrated.[1] The melting point is unchanged after recrystallization from water.

3. Discussion

3,5-Dihydroxybenzoic acid is most conveniently prepared by alkaline fusion of the disulfonic acid obtained by sulfonation of benzoic acid.[1,2,3] It has also been prepared

by alkaline fusion of the 3,5-dihalobenzoic acids[4,5] or of 3-bromo-5-sulfobenzoic acid.[6] Benzoic acid has been sulfonated using various strengths of sulfuric acid with or without catalysts.[7,8]

References and Notes

1. Barth and Senhoefer, *Ann.*, **159**, 222 (1871); **164**, 109 (1872).
2. Graves and Adams, *J. Am. Chem. Soc.*, **45**, 2439 (1923).
3. Hohenemser, *Ber.*, **35**, 2305 (1902).
4. Ger. pat. 286,266 [*Frdl.*, **12**, 158 (1914–1916)].
5. U. S. pat. 1,321,271 [*C. A.*, **14**, 186 (1920)].
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7. Herzig and Epstein, *Monatsh.*, **29**, 661 (1901); Brunner, *Monatsh.*, **50**, 216 (1928); Lock and Nottes, *Monatsh.*, **68**, 51 (1936); Suter and Weston, *J. Am. Chem. Soc.*, **61**, 232 (1939).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

barium salt

potassium hydroxides

3,5-dihalobenzoic acids

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ether (60-29-7)

sulfur trioxide (7446-11-9)

sodium sulfate (7757-82-6)

Benzoic acid (65-85-0)

barium sulfate (7727-43-7)

decolorizing carbon (7782-42-5)

sodium (13966-32-0)

barium carbonate (513-77-9)

3,5-Dihydroxybenzoic acid, α-Resorcylic acid (99-10-5)

barium sulfite

3-bromo-5-sulfobenzoic acid

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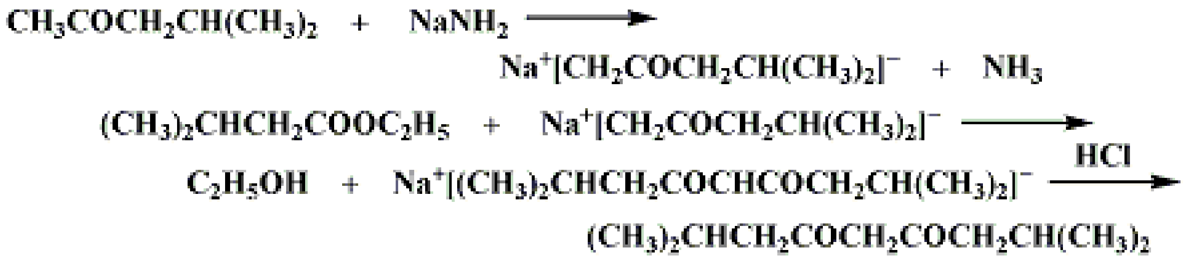
Organic Syntheses, CV 3, 291

DIISOVALERYLMETHANE

[4,6-Nonanedione, 2,8-dimethyl-]



Submitted by C. R. Hauser, J. T. Adams, and R. Levine.
Checked by Arthur C. Cope and Frank S. Fawcett.

1. Procedure

Approximately 300 ml. of commercial anhydrous liquid ammonia is added to a 500-ml. three-necked round-bottomed flask equipped with a mercury-sealed stirrer and a reflux condenser connected to a soda-lime drying tube (Note 1). The drying tube is attached to a gas-absorption trap, or the apparatus is assembled in a well-ventilated hood. The third neck of the flask is closed with a stopper. Freshly cut sodium (13.8 g., 0.6 gram atom) is weighed under xylene or kerosene, and a small amount is added to the liquid ammonia, with stirring, until a permanent blue color is produced. A few small crystals of ferric nitrate are added to catalyze the conversion of sodium to sodium amide (Note 2), and when the blue color has disappeared the remainder of the sodium is added in small pieces. When the sodium is converted completely to sodium amide, as indicated by change of the blue solution to a gray suspension, the ammonia is evaporated by warming the flask on a steam bath. During this operation sufficient dry ether is added through a dropping funnel (attached to the third neck of the flask) so that the volume of the liquid remains approximately 300 ml. After practically all the ammonia has been evaporated, as indicated by refluxing of the ether, the sodium amide suspension is stirred and heated under reflux for a few minutes and then cooled to room temperature. The procedure to this point requires approximately 1 hour.

A solution of 30 g. (0.3 mole) of redistilled methyl isobutyl ketone in 50 ml. of absolute ether is added to the stirred suspension of sodium amide during 5–10 minutes. After an additional 5 minutes, a solution of 78 g. (0.6 mole) of redistilled ethyl isovalerate in 50 ml. of dry ether is added during about 15 minutes. Stirring is continued for 2 hours while the mixture is heated under reflux on the steam bath. The gelatinous suspension of the sodium salt of diisovalerylmethane is poured into 300 ml. of water, made neutral to litmus by dilute hydrochloric acid, and extracted with three 100-ml. portions of ether. The solvent is removed by distillation under reduced pressure, and the residue is dissolved in an equal volume of methanol. A solution

prepared from 44 g. of cupric acetate monohydrate and 350 ml. of water is heated nearly to the boiling point, filtered, and added to the methanol solution. The resulting mixture is allowed to stand until it has cooled to room temperature. The blue copper salt of diisovalerylmethane is collected on a Büchner funnel, pressed as dry as possible, washed on the funnel with 100 ml. of petroleum ether (b.p. 30–60°), and again sucked dry. The yield of the copper salt after air drying is 44–51 g. (69–79%); it melts in the range 150–155° (Note 3).

The diisovalerylmethane is regenerated by shaking the copper salt vigorously with 500 ml. of 10% sulfuric acid and 200 ml. of ether until all the salt has dissolved. The aqueous acid layer is extracted with two 100-ml. portions of ether, and the combined ether solutions are dried over anhydrous sodium sulfate. The solvent is removed, and the residue is distilled under reduced pressure. The yield of diisovalerylmethane is 32–42 g. (58–76%, based on methyl isobutyl ketone), b.p. 115–116°/20 mm., n_D^{25} 1.4565 (Note 4) and (Note 5).

2. Notes

1. Apparatus fitted with standard-taper ground-glass joints is convenient for this preparation.
2. It may be helpful to provide additional catalysis of the conversion to sodium amide of the small amount of sodium added initially by bubbling dry air through the solution.[1]
3. After recrystallization from methanol or 95% ethanol the fluffy light blue copper salt melts at 157–158°.
4. The submitters state that the reaction may be conducted with equal success by using 0.6 mole each of sodium amide and methyl isobutyl ketone, and 0.3 mole of ethyl isovalerate (yield 75% based on the ester).[2,3]
5. Acetone may be acylated with ethyl laurate by either procedure (with excess ester or excess ketone). Lauroylacetone (m.p. 31.5–32°) is obtained in 75% yield[3] by either procedure.

3. Discussion

Diisovalerylmethane has been prepared by the method described[2,3] and by the use of sodium hydride[4] as the condensing agent.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

kerosene

sodium salt of diisovalerylmethane

copper salt of diisovalerylmethane

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

methanol (67-56-1)

ether (60-29-7)

sodium sulfate (7757-82-6)

acetone (67-64-1)

sodium (13966-32-0)

xylene (106-42-3)

Methyl isobutyl ketone (108-10-1)

ethyl laurate (106-33-2)

sodium amide (7782-92-5)

ferric nitrate

Diisovalerylmethane, 4,6-Nonanedione, 2,8-dimethyl- (7307-08-6)

ethyl isovalerate (108-64-5)

cupric acetate monohydrate (6046-93-1)

Lauroylacetone

sodium hydride (7646-69-7)

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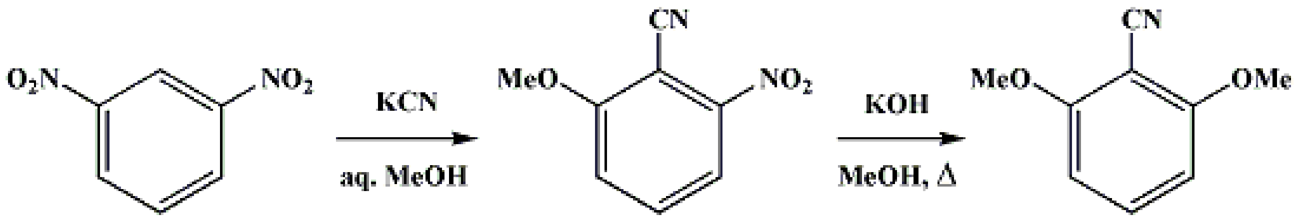
Organic Syntheses, CV 3, 293

2,6-DIMETHOXYBENZONITRILE

[Benzonitrile, 2,6-dimethoxy-]



Submitted by Alfred Russell and W. G. Tebbens.
Checked by R. L. Shriner and Robert S. Voris.

1. Procedure

A. 2-*Nitro*-6-*methoxybenzonitrile*. Five hundred grams (2.97 moles) of technical *m*-dinitrobenzene (m.p. 88–89°) is dissolved in 7.5 l. of absolute methanol in a 12-l. round-bottomed flask fitted with an efficient mechanical stirrer. The temperature is raised to 40° by means of a water bath and maintained there while a solution of 230 g. of potassium cyanide in 400 ml. of water is added with stirring. The dark purple mixture is stirred for 2 hours and then is allowed to stand at room temperature for 2–3 days. The black precipitate is collected with suction on a Büchner funnel, pressed as dry as possible, and then spread out in the air to dry. It weighs about 185–188 g.

The filtrate is diluted with 60 l. of cold water (Note 1) and allowed to stand overnight. The brown sludge is filtered with suction (Note 2) and pressed as dry as possible on the funnel. After drying, it weighs about 164 g. The combined precipitates are refluxed for 30 minutes each with successive 650-, 500-, and 500-ml. portions of chloroform. The chloroform extracts are filtered while hot, and the bright red filtrates are combined and concentrated to a volume of 500 ml. by distillation. One liter of petroleum ether (b.p. 60–90°) is added, whereupon the crude 2-nitro-6-methoxybenzonitrile separates as a red powder. It is removed by filtration and air-dried. It weighs 120–125 g. (22–23%) and melts at 148–157° (Note 3). It is used without purification (Note 4).

B. 2,6-*Dimethoxybenzonitrile*. The crude nitrile is placed in a 3-l. flask and is refluxed for 2 hours with a solution of 75 g. of potassium hydroxide in 1.9 l. of methanol. The solution is concentrated by distillation to a volume of 400 ml. and then is poured into 4 l. of cold water. The brownish solid is filtered, washed thoroughly with cold water, and dried. The crude product (85–95 g.) is dissolved in 300 ml. of chloroform and refluxed with 8 g. of Darco for 30 minutes. The hot mixture is filtered, and 500 ml. of hot petroleum ether (b.p. 60–90°) is added to the filtrate. The solution is cooled, and the light-tan-colored needles of 2,6-dimethoxybenzonitrile are removed by filtration. The product weighs 75–86 g. (15–17%) and melts at 116–117° (Note 5).

2. Notes

1. The dilution is conveniently carried out by dividing the mixture among seven 3-gal. earthenware crocks.
2. The filtration can be performed by siphoning the mixture from the crocks through an 18.5 cm. Büchner funnel fitted to a 12-l. flask attached to a suction pump.
3. A fourth extraction with 500 ml. of chloroform gives only an additional 4 g. of product.
4. Dioxane is an excellent solvent for cleaning the flasks and crocks used in this first step.
5. This product is pure enough for most purposes. Pure white needles, melting at 117–118°, may

be obtained by repeating the crystallization from the chloroform-petroleum ether mixture. The recovery is about 89–90%.

3. Discussion

The action of alcoholic potassium cyanide on *m*-dinitrobenzene was first studied by Lobry de Bruyn.[1] The present method is a modification of the procedure described by Mauthner.[2]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

chloroform-petroleum ether

alcoholic potassium cyanide

methanol (67-56-1)

chloroform (67-66-3)

potassium cyanide (151-50-8)

potassium hydroxide (1310-58-3)

dioxane (5703-46-8)

2,6-Dimethoxybenzonitrile, Benzonitrile, 2,6-dimethoxy- (16932-49-3)

2-Nitro-6-methoxybenzonitrile (38469-85-1)

m-dinitrobenzene (99-65-0)

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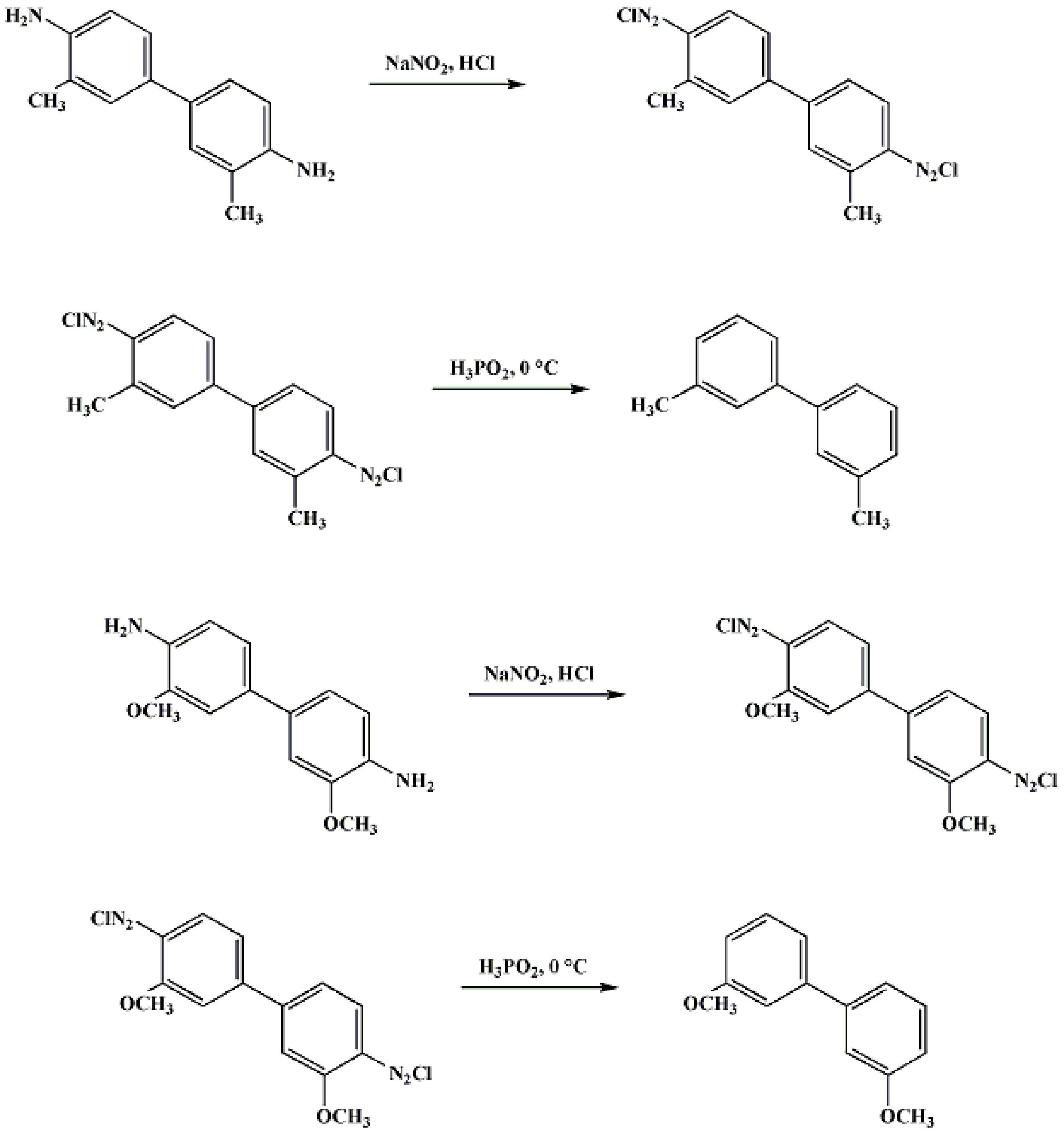
3,3'-DIMETHOXYBIPHENYL AND 3,3'-DIMETHYLBIPHENYL

[Biphenyl, 3,3'-dimethyl-, and biphenyl, 3,3'-dimethoxy-]



Submitted by Nathan Kornblum
Checked by W. E. Bachmann and S. Kushner.

1. Procedure

A. 3,3'-*Dimethoxybiphenyl*. In a 1.5-l. beaker are placed 400 ml. of water and 31 ml. of concentrated hydrochloric acid (sp. gr. 1.19). This solution is heated to boiling, the flame is removed, and 40 g. (0.16 mole) of *o*-dianisidine (Note 1) is added. The hot mixture is stirred for about 3 minutes, until only a small amount of solid remains. The beaker is then placed in an ice-salt mixture and its contents are stirred mechanically until the temperature has dropped to about 15°. At this point 35 ml. more of concentrated hydrochloric acid is added. When the temperature of

the mixture has fallen to 10–13°, a solution of 23.3 g. (0.33 mole) of 97% sodium nitrite (or an equivalent amount of sodium nitrite of higher or lower purity) in 50 ml. of water is added from a dropping funnel in the course of 10–15 minutes. The contents of the beaker are then stirred for 15–20 minutes at 5–10°, and finally filtered rapidly with suction from an appreciable amount of dark material (Note 2).

The cold, clear red filtrate is now poured rapidly into a 2-l. flask containing 325 ml. of ice-cold 30% hypophosphorous acid solution (Note 3). Immediate evolution of nitrogen occurs. The flask is stoppered loosely, placed in a refrigerator for 8–10 hours, and then allowed to stand at room temperature for another 8–10 hours (Note 4). The reaction product is transferred to a 2-l. separatory funnel, and the lower dark brown layer is separated from the aqueous phase. The aqueous layer is extracted with two 125-ml. portions of ether (Note 5). The brown oil combined with the ether extracts is washed in a separatory funnel with two 30-ml. portions of 20% sodium hydroxide solution (Note 6). Separation into two layers occurs rapidly, but occasionally the aqueous phase will remain turbid for some time. The loss by discarding the turbid sodium hydroxide washings is negligible. The ether solution is dried with a minimal amount of anhydrous potassium carbonate, 5 g. usually being sufficient (Note 7).

After filtration of the ether solution from the mixture of solid potassium carbonate and dark solids which have settled out, the ether is removed by distillation on a steam cone from a 50-ml. modified Claisen flask having a 15-cm. column. Usually suction must be applied to remove the last traces of ether. The residue is distilled at 4 mm. and a bath temperature of 200°. There is a small fore-run of 1–1.5 g. of a very pale yellow liquid which distils at 155–157°. The main fraction, boiling at 157–159°, is practically colorless and weighs 19–22 g. When the temperature of the thermometer in the flask starts to drop, the bath temperature is gradually raised to 240°. In this way, 3–4 g. more of light orange-yellow dianisyl is obtained. The yield based on the three fractions is 23–27.5 g. (66–78%). The fractions usually crystallize spontaneously; if they do not crystallize, they are cooled and scratched.

The main fraction melts at 41–43° (Note 8), and the other two fractions usually melt about a degree or two lower. The product is pure enough for most purposes; it may be recrystallized from the minimal volume of ethanol necessary for solution at 45–50°. The solution is cooled to about 35°; any oil that precipitates is brought back into solution by cautious addition of ethanol. The saturated solution is seeded, allowed to cool to room temperature, and then kept in a refrigerator for at least 4 hours. In this manner, 20–21 g. of flat, colorless needles is obtained; the product melts at 42–43.5°.

B. *3,3'-Dimethylbiphenyl*. Twenty-seven grams (0.13 mole) of *o*-tolidine (Note 9) is tetrazotized according to *Org. Syntheses* Coll. Vol. **2**, 145 (1943). It is not necessary to take the indicated precautions against a slight excess of nitrous acid. The clear orange tetrazonium solution is added to 290 ml. of 30% hypophosphorous acid (Note 10), and the mixture is allowed to stand, loosely stoppered, at room temperature for 16–18 hours (Note 11).

The reaction product is transferred to a 2-l. separatory funnel, and the red oily layer is separated from the aqueous phase. The aqueous layer is extracted once with 60 ml. of benzene. The combined red oil and benzene extract are dried with 1–5 g. of anhydrous sodium sulfate (Note 12). The benzene is removed by distillation from a 50-ml. modified Claisen flask having a 15-cm. column. The flask is heated in an oil bath to a final temperature of about 150° to ensure removal of the last traces of benzene. The residue is distilled at 3 mm. and a bath temperature of 155°. A practically colorless fore-run of 1–1.5 g. comes over from 109° to 114°. This is followed by 15.5–16 g. of a very pale lemon-yellow liquid which boils at 114–115°. When the temperature of the thermometer in the flask starts to fall the bath temperature is raised to 170°, and an additional 1–1.5 g. of light lemon-yellow material is obtained (Note 13). The total yield is 17.5–19 g. (76–82%) (Note 14) and (Note 15).

2. Notes

1. Eastman Kodak Company's technical grade, melting at 133–135°, was used.
2. Usually the pores of the filter paper become partially clogged after about half of the mixture has been filtered so that the rate of filtration is cut down considerably. In this event a fresh funnel and filter should be employed.
3. When less hypophosphorous acid solution is used, the yields are slightly lower, the product more highly colored than that obtained here, and the reaction time appreciably greater. When large amounts of a cheap amine are to be deaminated, it might be worth while to investigate the use of less hypophosphorous acid. In one run, 645 ml. of hypophosphorous acid solution was used for 40 g. of dianisidine. The yield was 29 g. (83%). With valuable amines it is probably best to use more hypophosphorous acid than is called for in these directions. Thus, in deaminating 33 g. of 2,2'-dimethyl-4,4'-diamino-5,5'-dimethoxybiphenyl, 1.2 l. of 30% hypophosphorous acid was used. There was obtained 24.5 g. (83%) of purified 2,2'-dimethyl-5,5'-

dimethoxybiphenyl.

4. If the flask is permitted to stand at room temperature directly after the two solutions are mixed, the yield is a little lower than that obtained with these directions and the product is somewhat more highly colored. The entire reaction may be run at refrigerator temperature, in which event 25–30 hours should elapse before the product is worked up.

When this reaction is applied to aniline derivatives, it appears advisable to conduct it entirely at refrigerator temperature owing to lowered thermal stability of the diazonium compounds as compared to the tetrazonium salts obtained from the benzidine type.

5. If the entire reaction is carried out at refrigerator temperatures the crude product is a light-brown solid, which is best worked up by filtering with suction, dissolving in ether, and proceeding as in the regular directions.

6. When this washing is omitted, the product contains a white, alkali-soluble solid and rapidly becomes orange-brown.

7. The potassium carbonate usually retains some dianisyl. It should be washed with a little of the ether which has been removed by distillation, and these washings should be redistilled.

8. In agreement with others, the checkers obtained a product melting at 31.5–33.5°. After recrystallization from ethanol, the 3,3'-dimethoxybiphenyl melted at 33.5–35°. This low-melting form changed rapidly to the form melting at 42–43.5° when a solution or melt of the former or even the solid came in contact with a crystal of the high-melting form (obtained from the submitter).

9. Eastman Kodak Company's *o*-tolidine, m.p. 128–129°, was used.

10. Use of 175 ml. of hypophosphorous acid gave a yield of 17.8 g. (77%). The first and last fractions were turbid.

11. The yield and quality of the product are identical with those obtained by conducting the reaction at refrigerator temperature.

12. Washing the benzene solution with aqueous alkali was found to be unnecessary.

13. In spite of the slight differences in color, the three fractions have almost identical refractive indices (n_D^{20} 1.5945).

14. One run was made using 27 g. of Eastman's practical *o*-tolidine, m.p. 121–125°. The procedure employed differed from the above only in that the benzene solution was washed once with 40 ml. of 10% aqueous alkali. There was obtained 18.9 g. (82%) of a light orange-yellow liquid possessing essentially the same refractive index as the product obtained from the better grade of *o*-tolidine.

15. This method of deaminating aromatic amines appears to be of general applicability, particularly to benzidine and its derivatives. Benzidine itself has been deaminated in 60% yield. The use of hypophosphorous acid in preference to ethanol for these deaminations arises from the fact that this procedure is much simpler, the yields are higher, and the products are of better quality.

This use of hypophosphorous acid for the deamination of aromatic amines appears to have originated with Mai.[1] It has also been used for this purpose by Raiford and Oberst.[2]

3. Discussion

3,3'-Dimethoxybiphenyl has been prepared by methylating 3,3'-dihydroxybiphenyl with methyl iodide[3] or dimethyl sulfate;[4] and by deaminating tetrazotized *o*-dianisidine with alcohol.[5,6,7] The present procedure is a slight modification of Mai's directions.

3,3'-Dimethylbiphenyl can be prepared from *m*-bromotoluene[8] or *m*-iodotoluene[9] and sodium; by the action of copper powder on *m*-iodotoluene;[10] by treating 4,4'-dihydroxy-3,3'-dimethylbiphenyl with zinc dust;[11] by heating 4,4'-dichloro-3,3'-dimethylbiphenyl with hydriodic acid and phosphorus;[11] by treating *o*-toluidine with nitrous acid in alcoholic solution;[12] by the decomposition of tetrazotized *o*-toluidine with methanol or ethanol in the presence of zinc dust.[13,14] It has been prepared by reduction of *m*-bromotoluene with hydrazine hydrate, using a palladium-calcium carbonate catalyst.[15] Upon treatment of *m*-tolyllithium with oxygen, a small amount of 3,3'-dimethylbiphenyl is formed.[16]

3,3'-Dimethylbiphenyl, prepared by the general method described here, may be purified further.[17]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 412

References and Notes

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16. Müller and Töpel, *Ber.*, **72**, 273 (1939).
17. Mills, *Nature*, **167**, 726 (1951).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hypophosphorous acid

dianisyl

ethanol (64-17-5)

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

methanol (67-56-1)

ether (60-29-7)

aniline (62-53-3)

sodium hydroxide (1310-73-2)

PHOSPHORUS (7723-14-0)

sodium sulfate (7757-82-6)

oxygen (7782-44-7)

nitrogen (7727-37-9)

sodium nitrite (7632-00-0)

nitrous acid (7782-77-6)

dimethyl sulfate (77-78-1)

copper powder (7440-50-8)

calcium carbonate (471-34-1)

zinc (7440-66-6)

sodium (13966-32-0)

palladium (7440-05-3)

hydriodic acid (10034-85-2)

Methyl iodide (74-88-4)

hydrazine hydrate (7803-57-8)

benzidine (92-87-5)

o-toluidine (95-53-4)

m-Bromotoluene (591-17-3)

m-iodotoluene (625-95-6)

3,3'-DIMETHOXYBIPHENYL, biphenyl, 3,3'-dimethoxy- (6161-50-8)

3,3'-DIMETHYLBIPHENYL, Biphenyl, 3,3'-dimethyl- (612-75-9)

2,2'-dimethyl-4,4'-diamino-5,5'-dimethoxybiphenyl

2,2'-dimethyl-5,5'-dimethoxybiphenyl

3,3'-dihydroxybiphenyl (612-76-0)

4,4'-dihydroxy-3,3'-dimethylbiphenyl

4,4'-dichloro-3,3'-dimethylbiphenyl

m-tolyllithium

o-TOLIDINE (119-93-7)

dianisidine, o-dianisidine (119-90-4)

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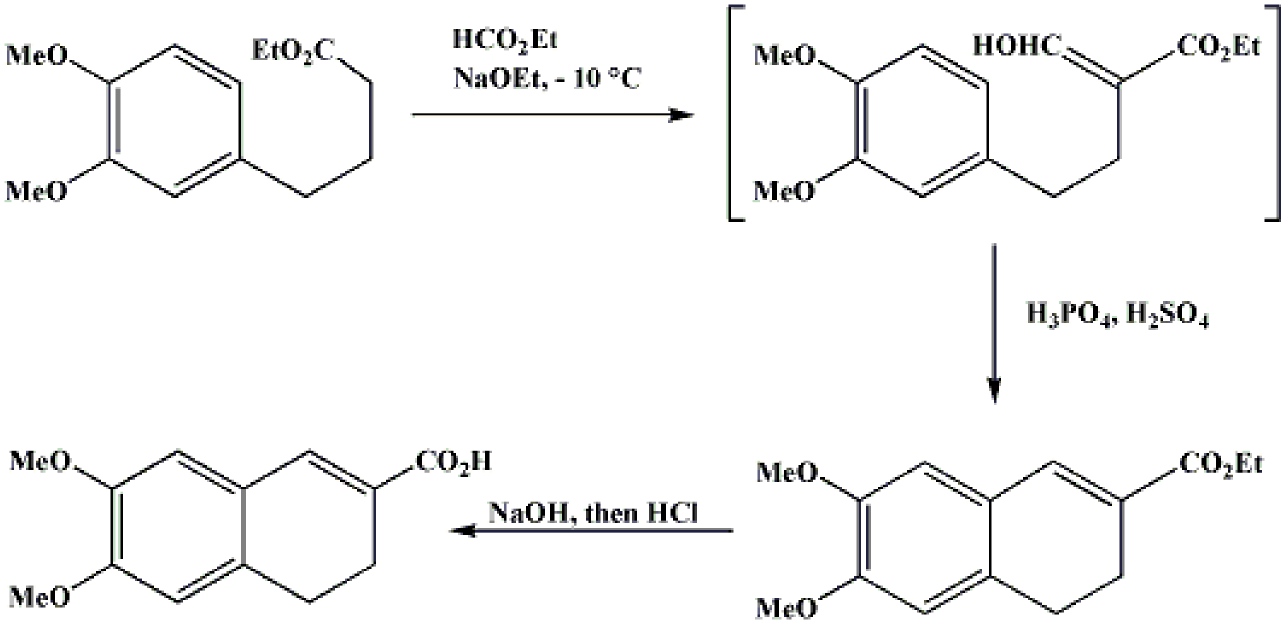
6,7-DIMETHOXY-3,4-DIHYDRO-2-NAPHTHOIC ACID

[2-Naphthoic acid, 3,4-dihydro-6,7-dimethoxy-]



Submitted by H. L. Holmes and L. W. Trevoy.
Checked by Cliff S. Hamilton and Carol K. Ikeda.

1. Procedure

A. *Ester condensation*. A suspension of 9.40 g. (0.41 gram atom) of powdered sodium[1] in 100 ml. of absolute ether is placed in a 1-l. three-necked flask (Note 1) fitted with a reflux condenser, dropping funnel, and a calcium chloride tube. A solution of 23.8 ml. (0.41 mole) of absolute ethanol (Note 2) in 50 ml. of absolute ether is added through the dropping funnel, and the mixture is refluxed on a steam bath for 10–11 hours. The reflux condenser is replaced by a mercury-seal stirrer. A thermometer and a calcium chloride tube are fitted into the third neck of the flask. The suspension of sodium ethoxide in absolute ether is cooled to –10° to –15° in an ice-hydrochloric acid bath, and a solution of 47.85 g. (0.19 mole) of ethyl γ-veratrylbutyrate (Note 3) and 29.6 g. (0.40 mole) of ethyl formate in 100 ml. of absolute ether is added dropwise through the dropping funnel with vigorous stirring (Note 4). The mixture is kept at –10° for 4 hours, and then the thermometer and calcium chloride tube are removed and the stirrer is replaced by a reflux condenser equipped with a calcium chloride tube. The mixture is allowed to come to room temperature and stand for 72 hours. During this time a gas is evolved and a pale yellow solid separates.

On digestion of this solid mass with 1 l. of ice and water, the sodium salt of the enol dissolves in the water, and the unreacted ester is removed by extracting the aqueous layer with two 200-ml. portions of ether (Note 5). The formyl derivative settles out as an oil upon acidification of the aqueous layer with dilute sulfuric acid. The oil is extracted with three 200-ml. portions of ether, and the ethereal extract is washed several times with water and dried over anhydrous sodium sulfate. The ether is distilled, and, to remove traces of ethyl formate, the oil is heated on a steam bath under a pressure of 20–30 mm. for 1 hour. The remaining yellow formyl derivative weighs 27–

29 g. (Note 6).

B. *Cyclization*. The above oil is poured dropwise into a well-stirred mixture of 110 ml. of 90% phosphoric acid (sp. gr. 1.75) and 23.4 ml. of sulfuric acid (sp. gr. 1.83) which is kept at –10°. The temperature is allowed to rise to 0–10°, and the stirring is continued for 2 hours. The viscous reaction mixture is poured into 500 ml. of ice and water, and the acid is partially neutralized with 300 ml. of 40% sodium hydroxide solution with efficient cooling. The viscous cream-colored oil is extracted with three 150-ml. portions of ether; the ether extract is washed well with water and sodium bicarbonate solution to remove the last traces of acid and then dried over anhydrous sodium sulfate. The cyclized ester, after removal of the ether, is a red oil which solidifies upon cooling. The yield is 23–24 g.

C. *Saponification*. The ester is saponified by refluxing for 5 hours with 75 ml. of a 10% sodium hydroxide solution containing 3 ml. of ethanol; it is then poured into 150 ml. of water and decolorized with Norit. Upon acidification of the alkaline solution with dilute hydrochloric acid, 18–19 g. (40–43%) (Note 7) and (Note 8) of acid is obtained, melting at 191–193° (cor.).

2. Notes

1. It is suggested that a flask with a ground-glass joint be employed for the condensation as it leads to less discoloration of the formylation product.
2. The absolute ethanol employed in the condensation was refluxed over calcium oxide for 20 hours and finally distilled from magnesium ethoxide.
3. The ethyl γ-veratrylbutyrate, b.p. 203–207°/20 mm., is obtained in 80% yield by esterification of γ-veratrylbutyric acid by the Fischer-Speier method. The γ-veratrylbutyric acid is prepared by the method of E. L. Martin[2] from β-(3,4-dimethoxybenzoyl) propionic acid.
4. The ethereal solution of the two esters should be added at such a rate that the addition is complete in about 1 hour.
5. On distillation, after removal of the ether, 18–20 g. of the ethyl γ-veratrylbutyrate is recovered.
6. The formylation product is too sensitive to purify by distillation even at pressures of 1–2 mm. of mercury.
7. In a similar manner, 3,4-dihydro-2-naphthoic acid, m.p. 111–114° (cor.), and 7-methoxy-3,4-dihydro-2-naphthoic acid, m.p. 149–150.5° (cor.), have been obtained in 35% yields.
8. 6,7-Dimethoxy-3,4-dihydro-2-naphthoic acid can be dehydrogenated[3] to give 6,7-dimethoxy-2-naphthoic acid. The yield of the latter was 85% after distillation and crystallization from ethanol.

3. Discussion

This method of preparation is essentially that used by Robinson and Crowley[4] for the preparation of 6-methoxy-3,4-dihydro-2-naphthoic acid. They first used concentrated sulfuric acid but found that this reagent caused sulfonation.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

mercury (7439-97-6)

Norit (7782-42-5)

sodium (13966-32-0)

phosphoric acid (7664-38-2)

sodium ethoxide (141-52-6)

calcium oxide

ethyl formate (109-94-4)

γ-veratrylbutyric acid

6,7-Dimethoxy-3,4-dihydro-2-naphthoic acid, 2-Naphthoic acid, 3,4-dihydro-6,7-dimethoxy- (53684-50-7)

ethyl γ-veratrylbutyrate

magnesium ethoxide (2414-98-4)

β-(3,4-dimethoxybenzoyl) propionic acid

3,4-dihydro-2-naphthoic acid

7-methoxy-3,4-dihydro-2-naphthoic acid

6,7-dimethoxy-2-naphthoic acid

6-methoxy-3,4-dihydro-2-naphthoic acid

sodium salt (824-79-3)

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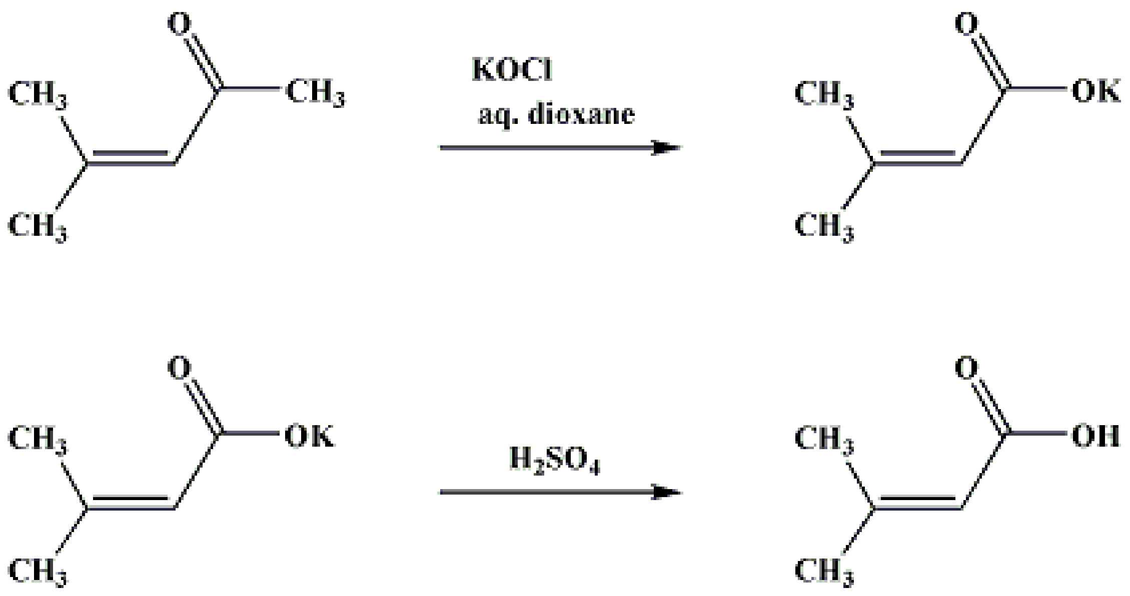
Organic Syntheses, CV 3, 302

β,β-DIMETHYLACRYLIC ACID

[Senecioic acid]



Submitted by Lee Irvin Smith, W. W. Prichard, and Leo J. Spillane.
Checked by Nathan L. Drake and Harry D. Anspon.

1. Procedure

A 5-l. round-bottomed three-necked flask is equipped with a Kyrides sealed stirrer and two long condensers, and the apparatus is so arranged that, if necessary, the exit water from the condensers may be quickly used to cool the flask.

In the flask are placed 200 ml. of dioxane, 100 g. (1.02 moles) of mesityl oxide, and a solution of 4.6 moles of potassium hypochlorite in 3 l. of water (Note 1), and the stirrer is started. The mixture becomes warm immediately, and within 5 minutes chloroform begins to reflux. When the reaction becomes very vigorous the stirrer is stopped and the flask is cooled with running water (Note 2). The stirring is resumed as soon as feasible and is continued for 3–4 hours, when the temperature of the mixture will have dropped to that of the room. Sodium bisulfite (about 5 g.) is then added to react with the excess hypochlorite (Note 3).

One of the condensers is then replaced by a dropping funnel, and enough 50% sulfuric acid (about 200 ml.) is added, with stirring and cooling, to make the solution acid to Congo red paper. When the solution has cooled, it is extracted with eight 400-ml. portions of ether (Note 4). The ether extract is *carefully* distilled on a steam bath until the ether and chloroform are removed.

The residue is then placed in a modified Claisen flask and distilled under reduced pressure. Dimethylacrylic acid distils at 100–106°/20 mm. The yield of white solid is

49–53 g. (49–53%). This product melts at 60–65°. It may be further purified by recrystallization from petroleum ether (b.p., 60–70°) or water (Note 5).

2. Notes

1. The hypochlorite is prepared according to *Org. Syntheses*, **17**, 66; Coll. Vol. **2**, 429 (1943), Note 2. It is cooled to 10° before it is placed in the flask.
2. The flask is cooled only as much as is necessary to keep the chloroform refluxing gently. After 30 minutes the reaction will have subsided enough so that no further cooling is necessary.
3. When a few milliliters of the solution no longer liberate iodine from a slightly acid potassium iodide solution, enough sodium bisulfite has been added.
4. It is important that the ether be *well shaken* with the solution during the extractions.
5. For recrystallization from water, 48–50 g. of the acid is dissolved in 450 ml. of hot water. The solution is cooled in ice for several hours, and the crystalline precipitate is filtered with suction and dried overnight in a desiccator. The yield of pure dimethylacrylic acid melting at 66–67.5° is 35–40 g., a recovery of 70–83%.

3. Discussion

This acid has been prepared from various α-haloisovaleric acid derivatives by elimination of the halogen together with one of the β-hydrogen atoms;[1,2,3,4] from β-hydroxyisovaleric acid derivatives by elimination of water;[5,6,7] by action of sodium isobutoxide on iodoform;[8] by the condensation of malonic acid with acetone;[9,10,11] by the reaction of acetone and ketene;[12] by condensation of acetoacetic ester with acetone and action of barium hydroxide on the product, isopropylidene acetoacetic ester;[13] by the action of alkali upon 2,4-dibromo-2-methyl-butanone;[14] by the incomplete ozonolysis of phorone;[15] by the action of alcoholic potassium hydroxide upon 2,5,5,7-tetramethylocta-2,6-diene-4-one;[16] by the action of potassium hydroxide on isopropenylacetic acid;[17] by the action of aluminum chloride on α,α-dimethylsuccinic anhydride;[18] by metallating isobutylene with amylsodium, carbonating, and acidifying;[19] by the action of hypohalites on mesityl oxide;[20,21,22] and by the action of sulfuric acid on 3-methyl-3-butenoic acid.[23]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

isopropylidene acetoacetic ester

phorone

sulfuric acid (7664-93-9)

ether (60-29-7)

chloroform (67-66-3)

potassium iodide (7681-11-0)

sodium bisulfite (7631-90-5)

iodine (7553-56-2)

acetone (67-64-1)

aluminum chloride (3495-54-3)

potassium hydroxide (1310-58-3)

barium hydroxide (17194-00-2)

Mesityl oxide (141-79-7)

Ketene (463-51-4)

iodoform (75-47-8)

Malonic acid (141-82-2)

potassium hypochlorite

hypochlorite (14380-61-1)

dioxane (5703-46-8)

isobutylene (9003-27-4)

β,β-Dimethylacrylic acid, Senecioic acid (541-47-9)

Dimethylacrylic acid

β-hydroxyisovaleric acid (625-08-1)

sodium isobutoxide

2,4-dibromo-2-methyl-butanone

2,5,5,7-tetramethylocta-2,6-diene-4-one

isopropenylacetic acid, 3-methyl-3-butenoic acid (53774-20-2)

α,α-dimethylsuccinic anhydride (17347-61-4)

amylsodium

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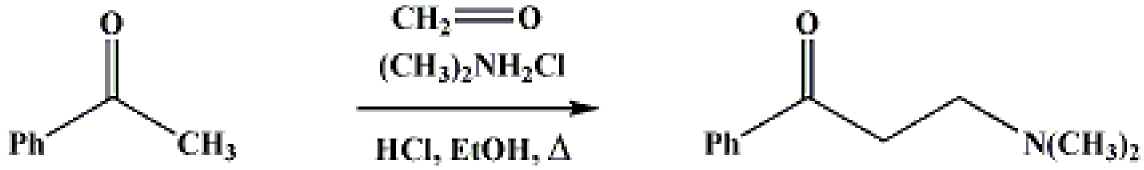
Organic Syntheses, CV 3, 305

β-DIMETHYLAMINOPROPIOPHENONE HYDROCHLORIDE

[Propiophenone, β-dimethylamino-]



Submitted by Charles E. Maxwell
Checked by C. F. H. Allen and J. VanAllan.

1. Procedure

In a 500-ml. round-bottomed flask attached to a reflux condenser are placed 60 g. (58.5 ml., 0.5 mole) of acetophenone (Note 1), 52.7 g. (0.65 mole) of dimethylamine hydrochloride, and 19.8 g. (0.22 mole) of paraformaldehyde. After the addition of 1 ml. of concentrated hydrochloric acid (sp. gr. 1.19) in 80 ml. of 95% ethanol, the mixture is refluxed on a steam bath for 2 hours (Note 2). The yellowish solution is filtered, if it is not clear (Note 3) and (Note 4), and is transferred to a 1-l. wide-mouthed Erlenmeyer flask. While still warm, it is diluted by the addition of 400 ml. of acetone (Note 5), allowed to cool slowly to room temperature, and then chilled overnight in the refrigerator. The large crystals are filtered and washed with 25 ml. of acetone. After it has been dried for 2.5 hours at 40–50°, this crude product weighs 72–77 g. (68–72%) and melts at 138–141° (Note 6) and (Note 7); it is suitable for many reactions.

It may be recrystallized by dissolving it in 85–90 ml. of hot 95% ethanol and slowly adding 450 ml. of acetone to the solution. The recovery is about 90%. The purified material, dried at 70°, melts at 155–156° (Note 8) and (Note 9).

2. Notes

1. Acetophenone, m.p. 19–20°, and a practical grade of dimethylamine hydrochloride were used.
2. The reaction mixture, which at first forms two layers, soon becomes homogeneous, and the paraformaldehyde dissolves.
3. The filtration must be done rapidly, preferably through a preheated funnel. Any material that crystallizes in the receiver is brought into solution again by warming on the steam bath.
4. Alternatively, the reaction mixture may be cooled at once and the solid product removed. The filtrate is successively concentrated and chilled three

times, each crop of crystals being rinsed with acetone. For example, in a run using 480 g. of acetophenone, the amounts obtained were 297, 92, 53, and 16 g. respectively, and 42 g. from the acetone washings, making a total of 500 g., or 66% of the theoretical amount.
5. The excess dimethylamine hydrochloride is held in solution by the acetone.
6. The material is somewhat hygroscopic and holds traces of water tenaciously. The melting point is lowered by the presence of moisture; a preliminary shrinking is usually observed.
7. After it has been dried for an additional 4 hours, the product melts at 152–153°. The product melts at this same temperature after it has been kept for 60 hours in a vacuum desiccator, except that then there is no preliminary shrinking.
8. These directions are applicable equally well for runs of larger size.
9. The diethylamino homolog results when diethylamine hydrochloride is used.

3. Discussion

The procedure described is an example of a general reaction,[1,2] the Mannich reaction, a review of which, from the experimental point of view, has been published.[3]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

acetone (67-64-1)

Acetophenone (98-86-2)

dimethylamine hydrochloride (506-59-2)

β-Dimethylaminopropiophenone hydrochloride (879-72-1)

Propiophenone, β-dimethylamino- (3506-36-3)

diethylamine hydrochloride (660-68-4)

paraformaldehyde (30525-89-4)

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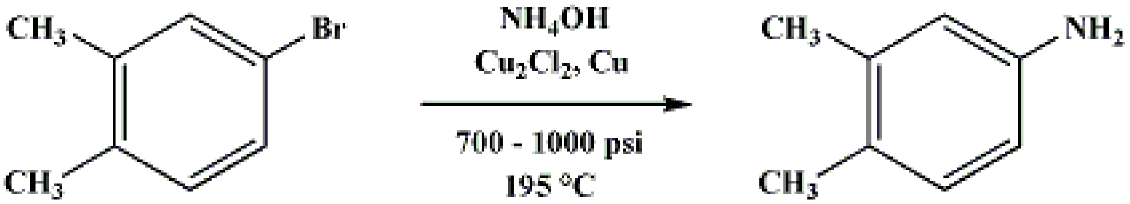
3,4-DIMETHYLANILINE

[Xylidine, 3,4-]



Submitted by W. A. Wisansky and S. Ansbacher.
Checked by N. L. Drake, Wilkins Reeve, and John Sterling, Jr..

1. Procedure

In a 1.1-l. steel reaction vessel (Note 1) are placed 200 g. (1.08 moles) of 4-bromo-*o*-xylene (p. 138), 14 g. copper wire, and 600 ml. (540 g., 9.0 moles) of 28% ammonia containing 12 g. of cuprous chloride. The steel reaction vessel is heated and rocked at 195° (thermostatic control) (Note 2) for 14 hours (Note 3); the pressure rises to 700–1000 lb. After cooling, the bomb is emptied and the two layers are separated; 40 ml. of 40% sodium hydroxide is added to the organic layer, and the mixture is steam-distilled. The amine distils and crystallizes when the distillate is cooled. It is separated from the water and dissolved in 500 ml. of 8% hydrochloric acid; the acid solution is extracted with two 100-ml. portions of ether (Note 4). The ether extracts are discarded, and the acid solution is made alkaline with 160 ml. of 40% sodium hydroxide. The resulting mixture is steam-distilled (Note 5). The distillate is cooled, most of the water is decanted, and the crystalline xylidine is dissolved by shaking with two 250-ml. portions of ether. The combined ether solutions are dried over calcium chloride and concentrated by distillation at a steam bath. The residue is distilled under reduced pressure from a Claisen flask. The yield of 3,4-dimethylaniline, boiling at 116–118°/22–25 mm., is 103 g. (79%). This crude product is recrystallized from 200 ml. of petroleum ether (b.p. 60–80°); the hot solution is placed in a refrigerator, and the crystallization is allowed to proceed overnight. The yield of recrystallized 3,4-dimethylaniline is 86 g. (66%) (Note 6); it melts at 47.3–49.2° (Note 7).

2. Notes

1. A hydrogenation vessel supplied by the American Instrument Company is satisfactory. A certain amount of copper plates out on the walls of the bomb during the reaction, but most of it is removed when the apparatus is cleaned.
2. The heating and rocking are carried out in a hydrogenation assembly. The temperature must not be allowed to exceed 200°; at higher temperatures decomposition occurs and the yield suffers.
3. The optimum reaction time may vary slightly with apparatus of different

types.

4. The crude product contains a small amount of unchanged 4-bromo-*o*-xylene which is removed by the ether extraction.

5. Caution must be exercised because a considerable amount of ether is present; it distils first and may be only partially condensed. A preliminary heating of the mixture on a steam bath does not remove the ether completely.

6. In an alternative method of purification the submitters collected the amine from the second steam distillation on a suction filter, pressed out the oily materials on the filter, and distilled the resulting crystalline product under diminished pressure; the distillate was not recrystallized. The checkers found it difficult to effect complete removal of oils by filtration; they preferred to omit this step and to recrystallize the distilled amine.

7. The reported melting point of 3,4-dimethylaniline varies from 47–48°[1] to 48.5–49°.[2]

3. Discussion

3,4-Dimethylaniline has been prepared by reduction of the corresponding nitro compound, either chemically[2,3] or catalytically using platinum,[4] Raney nickel,[5] or molybdenum[6,7] or tungsten sulfide[6] catalysts. It has been prepared from 3,4-dimethylphenol by heating with ammonia, ammonium bromide, and zinc bromide;[8] from *m*-toluidine hydrochloride by alkylation with methanol at high temperature,[1,9] from anhydro-4-amino-2-methylbenzyl alcohol by dry distillation from calcium hydroxide;[10] from 2-methyl-5-aminobenzyl alcohol by reduction with sodium; from 2-methyl-5-nitrobenzyl acetate by catalytic reduction;[11] from 2-methyl-5-nitrobenzyl or -benzal chloride (prepared from dichloromethyl ethyl ether[12] or *bis*-chloromethyl ether[13] and *p*-nitrotoluene) by catalytic,[12,13] chemical,[13] or electrochemical[12,14] reduction; from *o*-xylene by direct amination with hydroxylamine hydrochloride in the presence of aluminum chloride;[15] and from 3,4-dimethylacetophenone by Beckmann rearrangement of the oxime[16,17] or by reaction with hydrazoic acid in the presence of concentrated sulfuric acid.[18] The present method has been published.[19]

This preparation is referenced from:

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

oxime

anhydro-4-amino-2-methylbenzyl alcohol

3,4-dimethylacetophenone

hydrazoic acid

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

methanol (67-56-1)

ether (60-29-7)

sodium hydroxide (1310-73-2)

ammonium bromide (12124-97-9)

platinum (7440-06-4)

Raney nickel (7440-02-0)

aluminum chloride (3495-54-3)

sodium (13966-32-0)

cuprous chloride (7758-89-6)

calcium hydroxide

Hydroxylamine hydrochloride (5470-11-1)

3,4-Dimethylaniline, Xylidine, 3,4- (95-64-7)

xylidine (95-68-1)

molybdenum (7439-98-7)

tungsten sulfide

3,4-dimethylphenol (95-65-8)

zinc bromide (7699-45-8)

2-methyl-5-aminobenzyl alcohol

2-methyl-5-nitrobenzyl acetate

dichloromethyl ethyl ether

bis-chloromethyl ether

4-Bromo-o-xylene (583-71-1)

o-Xylene (95-47-6)

p-nitrotoluene (99-99-0)

m-toluidine hydrochloride (638-03-9)

2-methyl-5-nitrobenzyl chloride

2-methyl-5-nitrobenzal chloride

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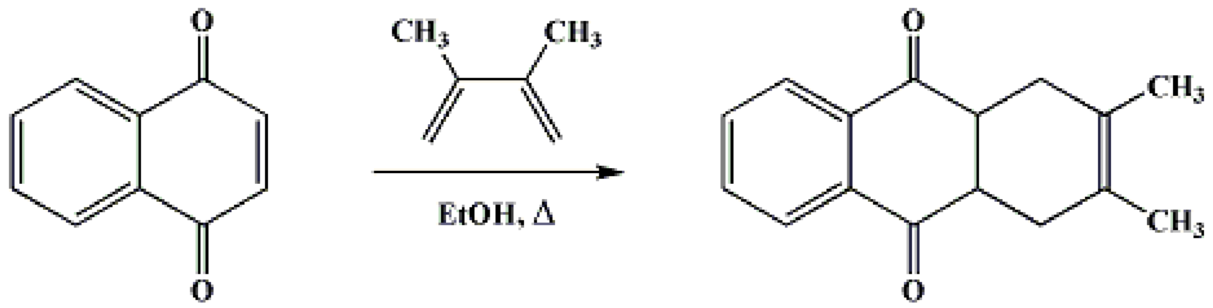
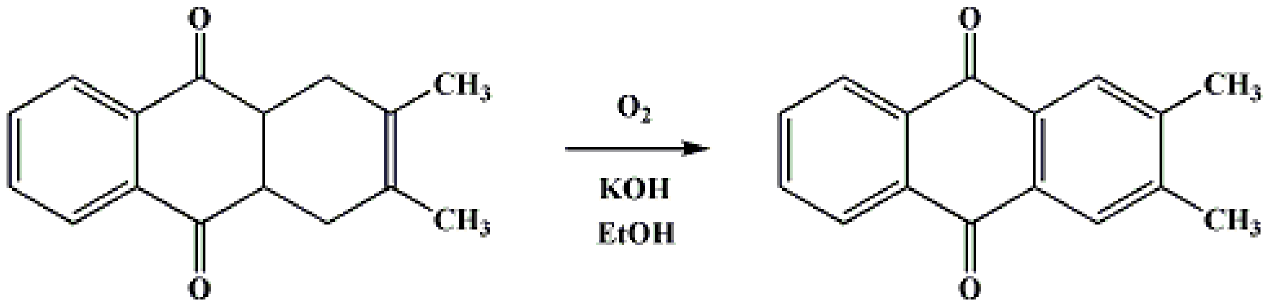
2,3-DIMETHYLANTHRAQUINONE

[Anthraquinone, 2,3-dimethyl-]





Submitted by C. F. H. Allen and Alan Bell.
Checked by R. L. Shriner and John C. Robinson, Jr..

1. Procedure

A solution of 80 g. (0.5 mole) of 1,4-naphthoquinone [*Org. Syntheses* Coll. Vol. **1**, 375 (1932), 383 (1941)] and 80 g. (1 mole) of 2,3-dimethylbutadiene-1,3 (p. 312) in 300 ml. of alcohol is refluxed for 5 hours, using a 1-l. round-bottomed flask and an efficient reflux condenser. The solution is cooled and placed in a refrigerator for 10–12 hours. The crystalline mass is then broken up with a spatula, and the addition product is filtered and washed with 50 ml. of cold ethanol. The product forms white, feathery crystals melting at 147–149° (Note 1). The yield is 116 g. (96% based on the 1,4-naphthoquinone).

For the dehydrogenation, 40 g. of the addition product is dissolved in 600 ml. of 5% ethanolic potassium hydroxide solution (Note 2) in a 1-l. three-necked flask equipped with a reflux condenser and inlet tube. A current of air is bubbled through the solution for 24 hours; considerable heat is generated, and the initial green color soon changes to yellow. The yellow quinone that has separated is then filtered with suction and is washed, first with 200 ml. of water, then with 100 ml. of ethanol, and finally with 50 ml. of ether. The yield of air-dried product (m.p. 209–210°) is 36.5–37.5 g. (94–96%) (Note 3). The over-all yield for both steps is 90% (Note 4).

2. Notes

1. The addition product is usually pure enough for the next step. It may be purified

by recrystallization from acetone, ethanol, or methanol, and then it melts sharply at 150°. If the crude product is deeply colored, it should be recrystallized, using a decolorizing carbon.

2. This is prepared by dissolving 30 g. of potassium hydroxide in 570 g. of 95% ethanol.

3. The melting points given in the literature vary from 183°[1] to 208°.[2]

4. Essentially the same percentage yield has been obtained using three times the amounts given.

3. Discussion

2,3-Dimethylanthraquinone has been obtained by ring closure of the corresponding *o*-benzoylbenzoic acid;[1,2,3] by oxidation of the corresponding anthrone;[4] by decarboxylation of 2,3-dimethylanthraquinone-5-carboxylic acid;[5] from 2-chloro- and 2,3-dichloro-1,4-naphthoquinone and 2,3-dimethylbutadiene-1,3 by the action of sodium hydroxide;[6] and from 2-methyl-1,4-naphthoquinone and 2,3-dimethylbutadiene-1,3 with subsequent dehydrogenation by sulfur.[7] The addition product employed in the present procedure has been described.[8]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

2-chloro- and 2,3-dichloro-1,4-naphthoquinone

ethanol (64-17-5)

methanol (67-56-1)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sulfur (7704-34-9)

Anthrone (90-44-8)

acetone (67-64-1)

decolorizing carbon (7782-42-5)

potassium hydroxide (1310-58-3)

Quinone (106-51-4)

1,4-Naphthoquinone (130-15-4)

2,3-Dimethylanthraquinone, Anthraquinone, 2,3-dimethyl- (6531-35-7)

2,3-dimethylbutadiene-1,3 (513-81-5)

2,3-dimethylanthraquinone-5-carboxylic acid

2-methyl-1,4-naphthoquinone

o-benzoylbenzoic acid (85-52-9)

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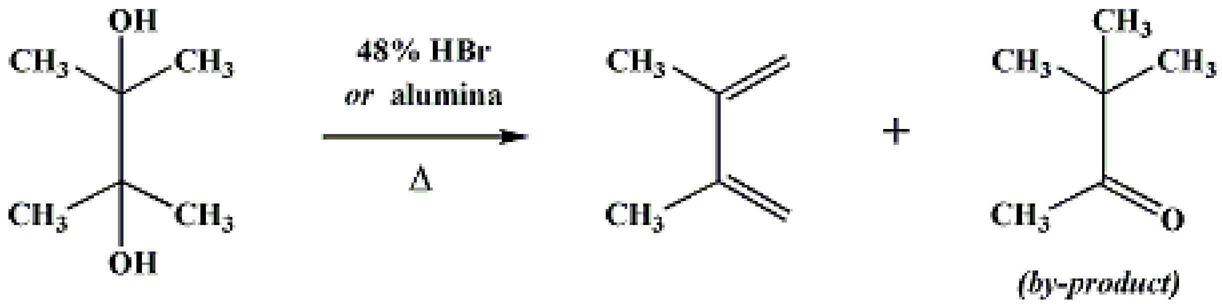
2,3-DIMETHYL-1,3-BUTADIENE

[1,3-Butadiene, 2,3-dimethyl- I. HYDROBROMIC ACID METHOD]



Submitted by C. F. H. Allen and Alan Bell.
Checked by R. L. Shriner and John C. Robinson, Jr..

1. Procedure

In a 2-l. round-bottomed flask, surmounted by a packed fractionating column (Note 1), is placed a mixture of 354 g. (3 moles) of pinacol (Note 2) and 10 ml. of commercial 48% hydrobromic acid. A few boiling chips are added, and the flask is then heated slowly with a colorless flame about 3 in. high (Note 3). The distillate is collected until the thermometer reads 95°; this requires about 2 hours when the rate of distillation is approximately 20–30 drops per minute. The upper, non-aqueous layer is washed twice with 100-ml. portions of water, 0.5 g. of hydroquinone is added, and the liquid is dried overnight with 15 g. of anhydrous calcium chloride. It is then fractionated as below, using the same column but a 1-l. flask (Note 4).

Fraction	*B.P.*	*Grams*	*Yield Per Cent*
2,3-Dimethylbutadiene	69–70.5°	135–147	55–60
Intermediate	70.5–105°	10–15	
Pinacolone	105–106°	66–75	22–25
Residue		7–8	

2. Notes

1. The column described in *Organic Syntheses*, **20**, 96, filled with glass helices, and wrapped with asbestos paper, is satisfactory. Carborundum may also be used as the filling, but a longer time is required for the distillation. Cold water is circulated through the cold finger.
2. The pinacol used was the commercially available material, or that obtained by dehydration of pinacol hydrate. This dehydration may be accomplished by

adding 2 l. of benzene to 1 kg. of pinacol hydrate [*Org. Syntheses* Coll. Vol. **1**, 448 (1932), 459 (1941)], and distilling the water-benzene mixture. The lower layer is separated, and the upper benzene layer is returned to the distilling flask. This is repeated until the benzene distillate is clear. The anhydrous pinacol is then distilled, and the fraction boiling from 168° to 173° is collected. Depending upon the quality of the material used, 1 kg. of pinacol hydrate yields about 500 g. of anhydrous pinacol.

3. If too large a flame is used the column floods.

4. 2,3-Dimethylbutadiene can be kept, without appreciable change, for a limited time in a refrigerator. If it is not to be used reasonably soon, a little hydroquinone should be added as an inhibitor.

[II. ALUMINUM OXIDE METHOD]

Submitted by L. W. Newton and E. R. Coburn.
Checked by Nathan L. Drake and Richard Tollefson.

1. Procedure

A Claisen flask, provided with the usual capillary inlet for air, is connected to a Pyrex tube (Note 1) which is drawn out at one end and packed with 8-mesh alumina (Note 2). The tube is inserted in an electric furnace (Note 3) capable of maintaining a temperature of 420–470°; the temperature is measured by a thermometer placed alongside the tube in the furnace. The drawn-out end of the tube is connected by a rubber stopper to an efficient Pyrex coil-condenser, which is in turn connected by a rubber stopper to the first of two receivers, arranged in series and connected by a short length of rubber tubing. Each receiver consists of a 500-ml. filter flask, which carries an inlet tube (Note 4) extending somewhat more than halfway to the bottom of the flask. The first receiver is immersed in an ice-salt mixture (Note 5); the second is immersed in a Dry Ice-methanol mixture contained in a Dewar flask. The exit tube of the second receiver is connected to a manometer (Note 6) and to a water pump.

Pinacol (Note 7) or pinacolone is placed in the Claisen flask and is distilled, under the vacuum of a water pump, through the Pyrex tube, which is maintained at a temperature of 420–470°. About 100 g. of pinacol is distilled in 15 minutes, and then the apparatus is swept out by maintaining the reduced pressure for 15 minutes longer. The water and resinous material collected in the ice-cooled receiver are discarded (Note 8). The second receiver is removed from the cooling bath, and the product is allowed to melt. Two layers are formed; these are allowed to separate, and then the receiver is replaced in the cooling bath until the lower water layer is frozen. The crude dimethylbutadiene is then decanted. The yellow product is dried over anhydrous calcium sulfate and is fractionated (Note 9) through a Widmer or other column; the portion boiling at 67–70° is collected. The yield from 100 g. of pinacol is 55–60 g. (79–86%) (Note 10). The diene is best stored over a small amount of hydroquinone in a refrigerator.

2. Notes

1. The Pyrex tube should have a diameter of 3 cm. and a length of 70 cm.
2. The grade of alumina is important. With an ordinary grade of desiccator alumina, the checkers were unable to obtain the yields stated. The alumina employed successfully was Alorco activated alumina, from the Aluminum Ore Company, East St. Louis, Illinois. The catalyst darkens in use, but it can be kept in a clean and active condition by the following treatment: after each run, or at least after two or three runs, the tube is heated to 420–470°, and a slow stream of air is drawn through it until the alumina is white (2–5 hours).
3. A very convenient furnace can be constructed by wrapping a 3-ft. length of 1 -in. iron pipe with asbestos paper and winding a suitable heating element over this paper (about 47.5 ft. of No. 18 B. & S. gauge Nichrome wire). The whole is enclosed in a length of steam-pipe insulation. The temperature is controlled by a properly chosen Variac (variable transformer).
4. The inlet tube should have a diameter of 10 mm.
5. This receiver serves to collect most of the water and polymer formed.
6. Another receiver, consisting of a 3 by 30 cm. side-arm test tube, may be used. It is immersed in a Dewar flask and cooled with Dry Ice-methanol. Only a small amount of material is collected in this receiver.
7. Anhydrous pinacol can be prepared from pinacol hydrate [*Org. Syntheses* Coll. Vol. **1**, 448 (1932), 459 (1941)] by distillation. The material that boils at 172–178° is collected, and the distillate should be refractionated. It is more convenient, however, to prepare anhydrous pinacol from the hydrate by the method described in (Note 2) under part I (p. 313). Pinacol hydrate may be used as starting material; the yield will be slightly less than that obtained when the anhydrous material is used.
8. The contents of this receiver should be examined carefully for the presence of 2,3-dimethylbutadiene; the checkers usually found appreciable amounts present.
9. If the dehydration has been inefficient, some pinacolone (b.p. 107°) may be present in this product. The pinacolone may be distilled over the alumina again.
10. According to the submitters, the yield from 100 g. of pinacolone is 57–63 g. (70–77%).

3. Discussion

The most convenient method for preparation of 2,3-dimethylbutadiene involves the dehydration of pinacol. Many catalysts have been used, among them hydrobromic,[1] hydriodic,[1] and sulfuric acids;[2,3,4] sulfonic acids of the benzene[5] and naphthalene[6,7,8] series; acid potassium sulfate;[9] alum;[10] aniline hydrobromide;[1] iodine;[11] hot copper at 450–480°;[1] and alumina at 400°.[12,13,14] The diene has also been obtained by distillation of the product from the reaction between methylmagnesium iodide and ethyl α-methacrylate;[15] by treatment of tetramethylethylene dichloride with alcoholic potash;[4] from pinacol hydrochloride and sodium carbonate;[16] by the action of sodium or pyridine on α,α,β-trimethyl-βγ-dibromobutyric acid;[17] by passing 1,2,4-trimethyl-4-

isopropenylcyclohexene over hot copper;[18] and by dehydration of dimethylisopropenylcarbinol with hydrochloric[19] or sulfuric acid.[17]

A patent reports the preparation of 2,3-dimethylbutadiene from trimethylethylene and formaldehyde in the presence of aqueous sulfuric acid.[20]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 310
- Org. Syn. Coll. Vol. 4, 795

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

α,α,β-trimethyl-βγ-dibromobutyric acid

sulfonic acids

ethyl α-methacrylate

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

Benzene (71-43-2)

formaldehyde (630-08-0)

potassium sulfate (37222-66-5)

hydroquinone (123-31-9)

HYDROBROMIC ACID (10035-10-6)

sodium carbonate (497-19-8)

copper (7440-50-8)

calcium sulfate (7778-18-9)

iodine (7553-56-2)

Pinacolone (75-97-8)

pyridine (110-86-1)

sodium (13966-32-0)

Naphthalene (91-20-3)

methylmagnesium iodide (917-64-6)

Pinacol hydrate (6091-58-3)

pinacol (76-09-5)

trimethylethylene (513-35-9)

2,3-DIMETHYL-1,3-BUTADIENE, 1,3-Butadiene, 2,3-dimethyl-, 2,3-Dimethylbutadiene (513-81-5)

dimethylbutadiene (926-56-7)

tetramethylethylene dichloride

pinacol hydrochloride

1,2,4-trimethyl-4-isopropenylcyclohexene

dimethylisopropenylcarbinol

aniline hydrobromide

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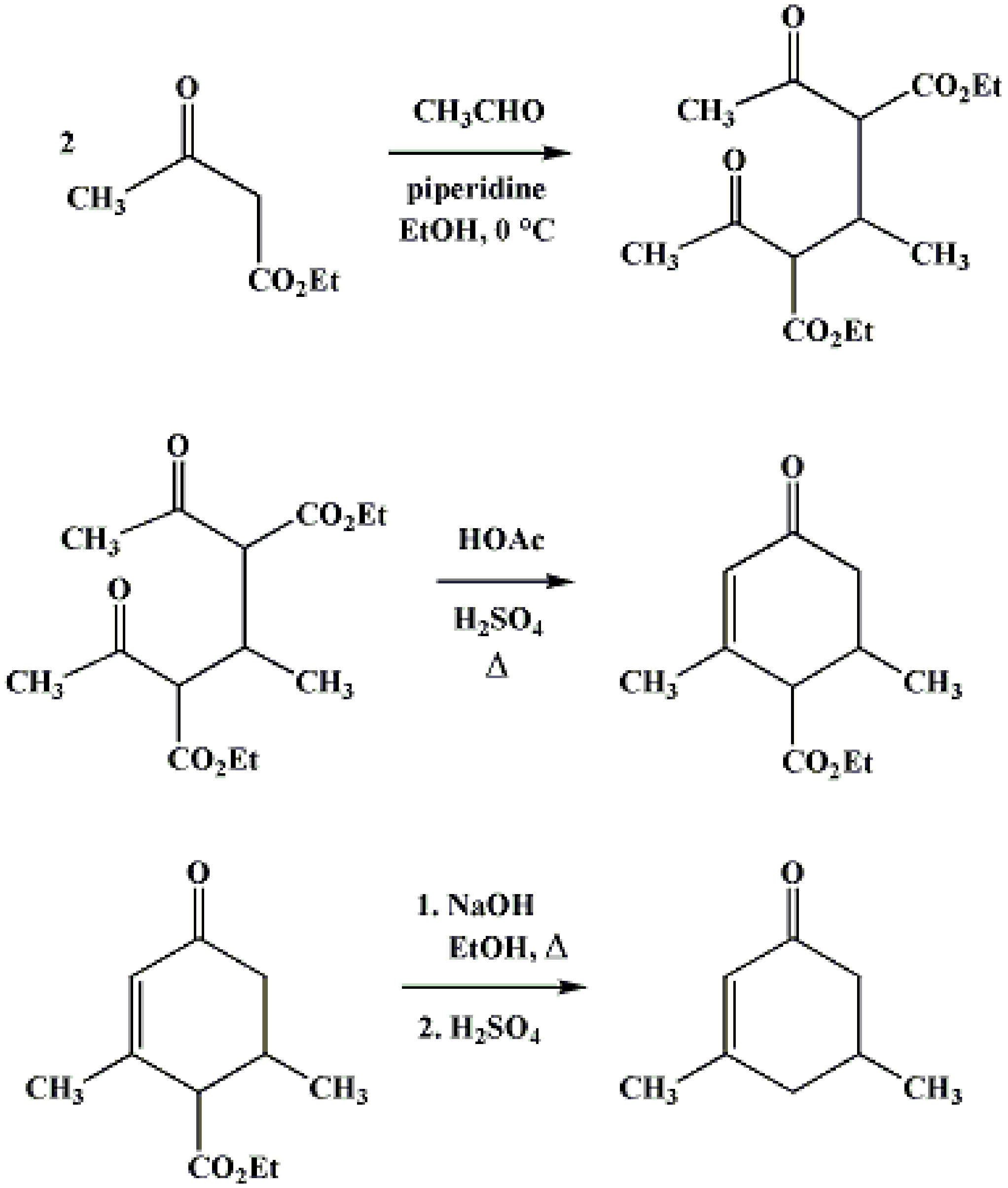
3,5-DIMETHYL-4-CARBETHOXY-2-CYCLOHEXEN-1-ONE and 3,5-DIMETHYL-2-CYCLOHEXEN-1-ONE

[2-Cyclohexen-1-one, 4-carbethoxy-3,5-dimethyl-, and 2-cyclohexen-1-one, 3,5-dimethyl-]



Submitted by E. C. Horning, M. O. Denekas, and R. E. Field.
Checked by Cliff S. Hamilton and Robert F. Coles.

1. Procedure

A. *3,5-Dimethyl-4-carbethoxy-2-cyclohexen-1-one*. In each of three 500-ml. Erlenmeyer flasks (Note 1) is placed 210 ml. (210 g., 1.61 mole) of ethyl acetoacetate (Note 2). The flasks are placed in an ice-salt bath and chilled to 0°; to each flask there

is then added 45 ml. (35.2 g., 0.78 mole) of acetaldehyde. When the contents of the flasks have cooled to –5° to 0° there is added to each flask, with shaking, a solution of 2 ml. of piperidine in 5 ml. of absolute ethanol. The flasks, the contents of which become cloudy in a short time because of the separation of water, are kept in the ice-salt bath for 6 hours. The reaction mixtures are then combined in a 1-l. flask and placed in an icebox. About 24 hours later, 3 ml. of piperidine in 5 ml. of absolute ethanol is added with shaking, and the flask is replaced in an icebox until the next day. The addition of 3 ml. of piperidine in 5 ml. of absolute ethanol is repeated once more, and the mixture is again returned to the icebox for 24 hours. The mixture is then allowed to stand for at least 1 day at room temperature. At some point during this reaction period the mixture should crystallize as a mass of yellow-white needles (Note 3). This product is crude ethyl ethylidenebisacetoacetate.

The crude bis ester is melted on a steam cone and poured into a 3-l. round-bottomed flask containing 600 ml. of glacial acetic acid, 40 ml. of concentrated sulfuric acid, and approximately 10 g. of small chips of porous plate (Note 4). The mixture is heated under reflux for 1 hour. There is a copious evolution of carbon dioxide which should be directed to a gas-absorption trap since it is accompanied by acetic acid vapors. The mixture is poured, with mechanical stirring, into 2 l. of ice water in a 4-l. beaker. Enough ether is added to allow separation of the layers (Note 5), and the organic layer is returned to the beaker with 1.2–1.3 l. of water. With the aid of good stirring the mixture is neutralized by slow addition of solid sodium carbonate until the effervescence ceases. The layers are separated, and the material so obtained may be used immediately for the preparation of 3,5-dimethyl-2-cyclohexen-1-one. To obtain 3,5-dimethyl-4-carbethoxy-2-cyclohexen-1-one, the ether solution is washed with 100 ml. of 5% sodium hydroxide solution and then with 100 ml. of water containing 2 ml. of acetic acid, is dried over anhydrous magnesium sulfate, and distilled through a short column under reduced pressure. After a very slight fore-run the main fraction is collected at 135–155°/10 mm. This is redistilled through a moderately good column, preferably of the Widmer or Vigreux type. The product is 3,5-dimethyl-4-carbethoxy-2-cyclohexen-1-one, b.p. 136–138°/9 mm. The yield is 220–234 g. (47–50%).

B. 3,5-*Dimethyl*-2-*cyclohexen*-1-*one*. The ether solution of crude 3,5-dimethyl-4-carbethoxy-2-cyclohexen-1-one obtained as described above is transferred to a 3-l. round-bottomed flask. The ether is removed on a steam cone, perferably with the aid of an aspirator, and there are added 1140 ml. of water, 60 ml. of ethanol (95%), and 130 g. of sodium hydroxide. The mixture is shaken continuously and heated on a steam cone until the alkali dissolves, and heating is continued on a steam cone with frequent shaking until the ester dissolves (Note 6). The solution is then refluxed for 15 minutes.

The flask is cooled with a stream of water while a solution of 100 ml. of concentrated sulfuric acid in 200 ml. of water is added slowly and cautiously (Note 7). The acidified mixture is heated under reflux for 15 minutes, allowed to cool, and the layers are separated. The crude product is diluted with 100 ml. of ether and washed successively

with two 100-ml. portions of 5% sodium hydroxide solution and with 100 ml. of water containing 5 ml. of acetic acid. The ethereal solution, after drying over anhydrous magnesium sulfate, is distilled through a short column under reduced pressure. The product boiling at 84–86°/9 mm. is 3,5-dimethyl-2-cyclohexen-1-one; the yield is 155–165 g. (52–55%) (Note 8).

2. Notes

1. The checkers found it more convenient to use a 1-l. Erlenmeyer flask instead of three 500-ml. flasks.
2. The ethyl acetoacetate was obtained from the Carbide and Carbon Chemicals Company. The acetaldehyde was obtained from the Niacet Chemicals Corporation. The piperidine was the Practical grade of the Eastman Kodak Company.
3. Crystals may appear before the addition of all the piperidine has been completed. In this even the time of standing as described is followed, but no more catalyst need be added.
4. Ordinary boiling chips are convenient.
5. Usually 150–200 ml. of ether is ample. The layers may be separated in a separatory funnel, or the lower aqueous layer may be removed with a siphon.
6. The solution of the ester is an exothermic process. No attempt should be made to heat the mixture to reflux temperature until the ester has been dissolved.
7. It is important that this step be carried out slowly and with a hot solution. A satisfactory method is to place the flask in a sink while the contents are still hot and to cool with a stream of water directed over the entire flask. The sulfuric acid solution should be poured slowly down the wall of the flask, the rate of addition being regulated by the vigor of the decarboxylation. It is possible to carry out part of the decarboxylation in the alkaline solution by prolonging the reflux period, but this procedure offers no advantage over that described.
8. This general procedure can also be applied to compounds derived from other aliphatic aldehydes.[1]

3. Discussion

3,5-Dimethyl-4-carbethoxy-2-cyclohexen-1-one and 3,5-dimethyl-2-cyclohexen-1-one are usually prepared from acetaldehyde and acetoacetic ester through the Knoevenagel condensation.[2] The keto ester has been obtained previously by selective saponification and decarboxylation methods which have involved heating the crude condensation product with water at 140°[2,3] or with sodium ethoxide in ethanol.[3] The ketone has also been obtained from the same condensation product by prolonged refluxing in 20% sulfuric acid.[2,4,5] 3,5-Dimethyl-2-cyclohexen-1-one has also been obtained by the reduction of 2,4,6-trimethylpyridine with sodium and ethanol in liquid amomnia, followed by hydrolysis and cyclization.[6]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

acetaldehyde (75-07-0)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium carbonate (497-19-8)

carbon dioxide (124-38-9)

sodium (13966-32-0)

piperidine (110-89-4)

sodium ethoxide (141-52-6)

Ethyl acetoacetate (141-97-9)

magnesium sulfate (7487-88-9)

3,5-Dimethyl-4-carbethoxy-2-cyclohexen-1-one, 2-Cyclohexen-1-one, 4-carbethoxy-3,5-dimethyl- (6102-15-4)

3,5-Dimethyl-2-cyclohexen-1-one, 2-cyclohexen-1-one, 3,5-dimethyl- (1123-09-7)

ethyl ethylidenebisacetoacetate

2,4,6-trimethylpyridine (108-75-8)

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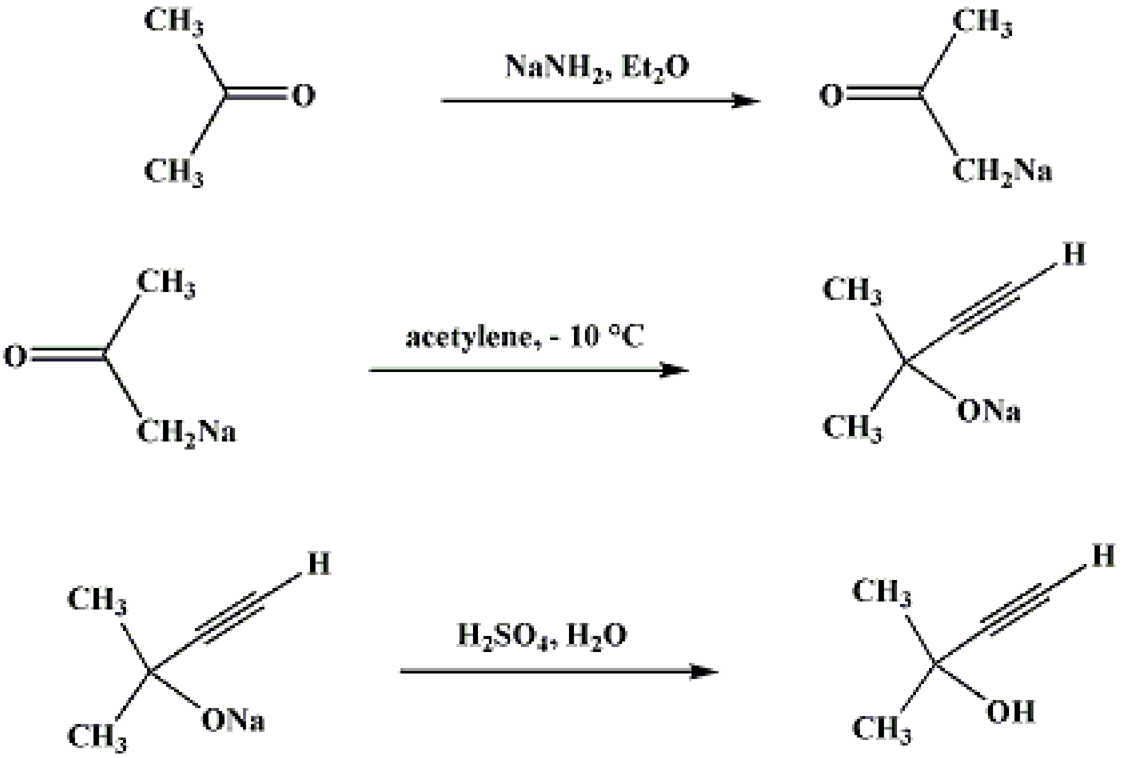
DIMETHYLETHYNYLCARBINOL

[3-Butyn-2-ol, 2-methyl-]



Submitted by Donald D. Coffman
Checked by C. F. H. Allen and Alan Bell.

1. Procedure

In a 2-l. round-bottomed flask fitted with a three-holed stopper bearing a mechanical stirrer, a separatory funnel, and a gas outlet tube leading to a hood (Note 1) are placed 1 l. of anhydrous ether (Note 2) and 156 g. (4 moles) of finely ground sodium amide (p. 778) (Note 3). The flask is surrounded by a well-packed ice-salt bath. To the vigorously stirred mixture 232 g. (4 moles) of dry acetone (Note 4) is added, dropwise, during a period of 3 hours. With the flask cooled to −10° (Note 5), a slow current of acetylene (Note 6) is passed through the reaction mixture for 2 hours to sweep out the ammonia. The three-holed stopper is then replaced by a two-holed stopper having a stopcock and an inlet tube reaching to the bottom of the flask and connected with a cylinder of acetylene. The stopper is wired in. The mixture is placed in an ice-salt mixture (Note 5), the whole being mounted on a shaking machine and agitated vigorously for 10 hours; the mixture is kept under a pressure of 10 lb. of acetylene. Every 30 minutes the pressure is released by means of the stopcock, to sweep out ammonia formed from small amounts of previously unreacted sodium amide.

The reaction mixture is poured cautiously into 800 g. of crushed ice and acidified in

the cold by the addition of 400 ml. of 10 *N* sulfuric acid (Note 7). The ether layer is separated and the aqueous layer extracted twice with 100-ml. portions of ether. The combined ethereal solutions are dried over 100 g. of anhydrous potassium carbonate, and the filtered solution is fractionated (Note 8). The portion boiling at 103–107° is collected; any low-boiling fraction is dried and redistilled. The total yield is 135–155 g. (40–46%) of a colorless product that boils at 103–107° (Note 9), (Note 10), and (Note 11).

2. Notes

1. In cold weather, it is convenient to carry out the reaction out-of-doors. This minimizes the attention needed to replace the ice. The outlet tube then opens to the air.
2. A commercial grade of anhydrous ether was dried over sodium.
3. The sodium amide, moistened by the heptane, was rapidly ground and the solvent allowed to evaporate.
4. An Eastman grade of acetone was used, after standing over anhydrous potassium carbonate.
5. It was found convenient to add Dry Ice to the freezing mixture, thus decreasing the frequency of packing. The temperature never rose above –10° and was usually considerably less.
6. Commercial acetylene used for welding was dried by passing over anhydrous calcium chloride.
7. This is prepared by adding 110 ml. of concentrated sulfuric acid to 290 ml. of water.
8. The checkers used a modified Widmer column.
9. There is a considerable quantity of high-boiling material; the quantity and boiling-point range are greater when the shaking is insufficient.
10. The reaction may be interrupted at several points. After the ammonia has been swept out by acetylene, it is usually convenient to place the mixture in a refrigerator overnight and start the shaking the next day. The shaking period need not be continuous; in this event the chilled mixture is placed in the icebox.
11. By the same procedure the submitter obtained methylethylethynylcarbinol, b. p. 119–123° (33% yield), using methyl ethyl ketone,[1,2] and 1-ethynylcyclohexanol-1, b.p. 53–55°/2 mm. (50% yield), using cyclohexanone and double the amount of ether.

3. Discussion

Dimethylethynylcarbinol has usually been prepared by the addition of acetylene to the sodium derivative of acetone,[3,4,5,6,7,8] but potassium metal[9] and sodium ethoxide[10] have also been used. The above method is based upon that described by Sung Wouseng.[3] Other methods use potassium hydroxide with calcium carbide,[11] or with acetylene and an immiscible alcohol such as butanol[12] or amyl alcohol.[13]

Dimethylethynylcarbinol has also been prepared by the action of sodium acetylide on the bisulfite addition compound of acetone.[14]

A modified procedure, involving the addition of acetone to sodium acetylide in liquid ammonia, has been reported to give a 67% yield.[15]

The general procedure of Campbell, Campbell, and Eby[16] gives excellent yields of ethynylcarbinols.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 416

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

calcium carbide

calcium chloride (10043-52-4)

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

acetylene (74-86-2)

ammonia (7664-41-7)

ether (60-29-7)

Cyclohexanone (108-94-1)

butanol (71-36-3)

acetone (67-64-1)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

potassium (7440-09-7)

amyl alcohol (71-41-0)

bisulfite (7782-99-2)

methyl ethyl ketone (78-93-3)

sodium amide (7782-92-5)

heptane (142-82-5)

1-ethynylcyclohexanol-1 (78-27-3)

Dimethylethynylcarbinol, 3-Butyn-2-ol, 2-methyl- (115-19-5)

methylethylethynylcarbinol (77-75-8)

sodium acetylide

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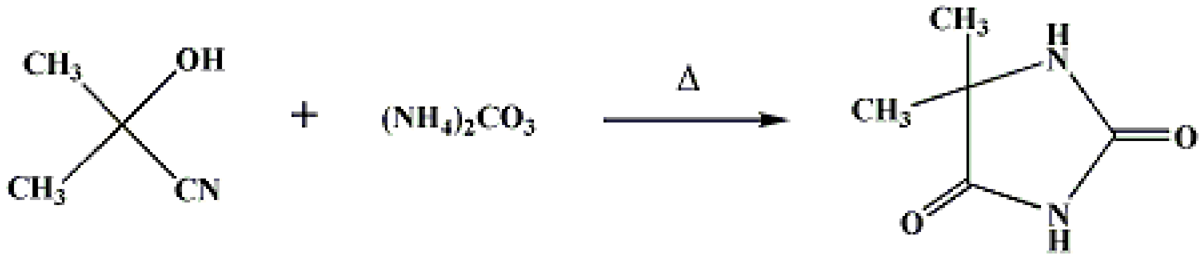
5,5-DIMETHYLHYDANTOIN

[Hydantoin, 5,5-dimethyl-]



Submitted by E. C. Wagner and Manuel Baizer.
Checked by C. F. H. Allen and G. F. Frame.

1. Procedure

In a 600-ml. beaker are mixed 85 g. (1 mole) of acetone cyanohydrin (Note 1) and 150 g. (1.31 moles) of freshly powdered ammonium carbonate. The mixture is warmed on a steam bath, preferably in a hood (Note 2), and stirred with a thermometer (Note 3). Gentle action begins around 50° and continues during about 3 hours at 68–80°. To complete the reaction and to decompose excess ammonium carbonate, the temperature is finally raised to 90° and maintained at this point until the liquid mixture is quiescent (30 minutes). The residue is colorless or pale yellow (Note 1) and solidifies on cooling. It is dissolved in 100 ml. of hot water, digested with Norit, and filtered rapidly through a heated filter. The filtrate is evaporated on a hot plate until crystals appear at the surface of the liquid, which is then chilled in an ice bath. The white crystals are filtered with suction; the filter cake is pressed and sucked dry and then washed twice with small portions (5–7 ml.) of ether, each portion being well incorporated with the crystals and then drawn through with suction. The mother liquor is concentrated as before to a volume of 25 ml. or less and chilled, and a further crop of crystals is obtained by repetition of the operations outlined (Note 4). The yield is 65–72 g. (51–56%). The first crop is nearly pure and melts at 173°; the second crop melts at about 164°.

The dimethylhydantoin is dissolved in the least boiling water (about 65 ml.) and digested with charcoal, and the hot solution is filtered through a heated filter. The filtrate is chilled, and the separated crystals are filtered with suction and washed sparingly with cold water. The recovery is about 80–85% of the crude weight. The recrystallized product melts at 174–175° (178° cor.). A further crop of less pure material (m.p. 171–172°) may be obtained by concentration of the mother liquor to small volume (Note 5).

2. Notes

1. Acetone cyanohydrin [*Org. Syntheses* Coll. Vol. **2**, 7 (1943)] is entirely satisfactory. For immediate use, a less pure cyanohydrin will serve; this is readily made as follows.[1] A solution of 165 g. (pure basis) of sodium bisulfite in 300 ml. of cold water is transferred to a 1-l. flask, which is cooled in an ice bath, while 87 g. of acetone is dropped in slowly with rotation of the flask. A solution of 100 g. (pure basis) of potassium or 75 g. of sodium cyanide in 300 ml. of cold water is then added gradually. The cyanohydrin separates as an upper layer; when sodium cyanide is used, this separation is slower and is not complete until the mixture has come to room temperature. It is drawn off and dried for several hours over sodium sulfate in a stoppered flask kept in the dark. The yield is about 90 g. (70%); it may be somewhat increased by ether extraction of the aqueous liquid. Acetone cyanohydrin so prepared is colorless, or nearly so, and if used promptly is satisfactory for the preparation of dimethylhydantoin. If it is kept more than a day or two, the cyanohydrin may become deep red and will then impart a red color to the dimethylhydantoin which is difficult to remove.

2. The reaction mixture evolves ammonia slowly in amounts which are unpleasant though tolerable in a well-ventilated room.

3. During most of the reaction, the mixture is partly solid or very viscous and cannot be stirred properly by a mechanically operated stirrer of the usual type. A Hershberg stirrer is unsatisfactory.

4. Dimethylhydantoin is highly soluble in hot water, and its solubility in cold water is considerable. Several crops may be removed by successive concentrations of the mother liquors, taken finally to very small volume. The conversion of acetone cyanohydrin to dimethylhydantoin is said to be practically quantitative.[2]

5. The method described serves for the preparation of various 5-substituted or 5,5-disubstituted hydantoins, using appropriate cyanohydrins. With methylethylketone cyanohydrin there was obtained a 75% yield of 5-methyl-5-ethylhydantoin, m.p. 141.5°.

3. Discussion

Hydantoins with one or two substituents in the 5 position have been prepared by heating cyanohydrins with urea and treating this reaction mixture with moderately concentrated hydrochloric acid;[3] by heating alanine sulfate with potassium cyanate;[4] by the action of phosgene or oxalyl chloride[5] or carbonic esters[6] on C-substituted aminoacetamides; by the fusion of amino acids with urea;[7] by the action of potassium cyanate on α-aminonitrile hydrochlorides, and heating the resulting ureido-nitriles with dilute hydrochloric acid;[8] by heating aldehydes or ketones with alkali cyanide and ammonium carbonate under pressure of several atmospheres of carbon dioxide;[9] by warming cyanohydrins with ammonium carbonate;[2] by the interaction of ketone or aldehyde and ammonium carbonate with hydrogen cyanide or alkali cyanide, in ligroin

or in 50% ethanol, at room temperature or at 50–80°;[10] or by the interaction of ketone or aldehyde bisulfite compounds with cyanide and ammonium carbonate.[10] The procedure described[11] is that of Bucherer and Steiner.[2] In a more recent method, an equimolecular mixture of acetone and hydrogen cyanide is treated with ammonia and carbon dioxide.[12]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 7

References and Notes

1. Houben, *Die Methoden der organischen Chemie*, 3rd Ed., Vol. III, p. 568, Verlag Georg Thieme, Leipzig, 1930.
2. Bucherer and Steiner, *J. prakt. Chem.*, **140**, 291 (1934).
3. Pinner, *Ber.*, **20**, 2355 (1887); **21**, 2320 (1888).
4. Urech, *Ann.*, **165**, 99 (1873).
5. Ger. pat. 310,427 [*Frdl.*, **13**, 803 (1923–1924)].
6. Read, *J. Am. Chem. Soc.*, **44**, 1749 (1922).
7. Griess, *Ber.*, **2**, 47 (1869); Halpern, *Monatsh.*, **17**, 243 (1896).
8. Herbst and Johnson, *J. Am. Chem. Soc.*, **54**, 2465 (1932).
9. Bergs, Ger. pat. 566,094 (1929) [*C. A.*, **27**, 1001 (1933)].
10. Bucherer and Lieb, *J. prakt. Chem.*, **141**, 5 (1934).
11. Wagner and Simons, *J. Chem. Education*, **13**, 266 (1936).
12. U. S. pat. 2,391,799 [*C. A.*, **40**, 1876 (1946)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

cyanohydrin

cyanohydrins

α-aminonitrile hydrochlorides

ureido-nitriles

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ammonium carbonate

ammonia (7664-41-7)

ether (60-29-7)

sodium cyanide (143-33-9)

hydrogen cyanide (74-90-8)

sodium sulfate (7757-82-6)

cyanide (57-12-5)

sodium bisulfite (7631-90-5)

carbon dioxide (124-38-9)

acetone (67-64-1)

Norit, charcoal (7782-42-5)

phosgene (75-44-5)

urea (57-13-6)

potassium (7440-09-7)

potassium cyanate (590-28-3)

Acetone cyanohydrin (75-86-5)

oxalyl chloride (79-37-8)

5,5-Dimethylhydantoin, Hydantoin, 5,5-dimethyl-, dimethylhydantoin (77-71-4)

methylethylketone cyanohydrin

5-methyl-5-ethylhydantoin (16820-12-5)

alanine sulfate

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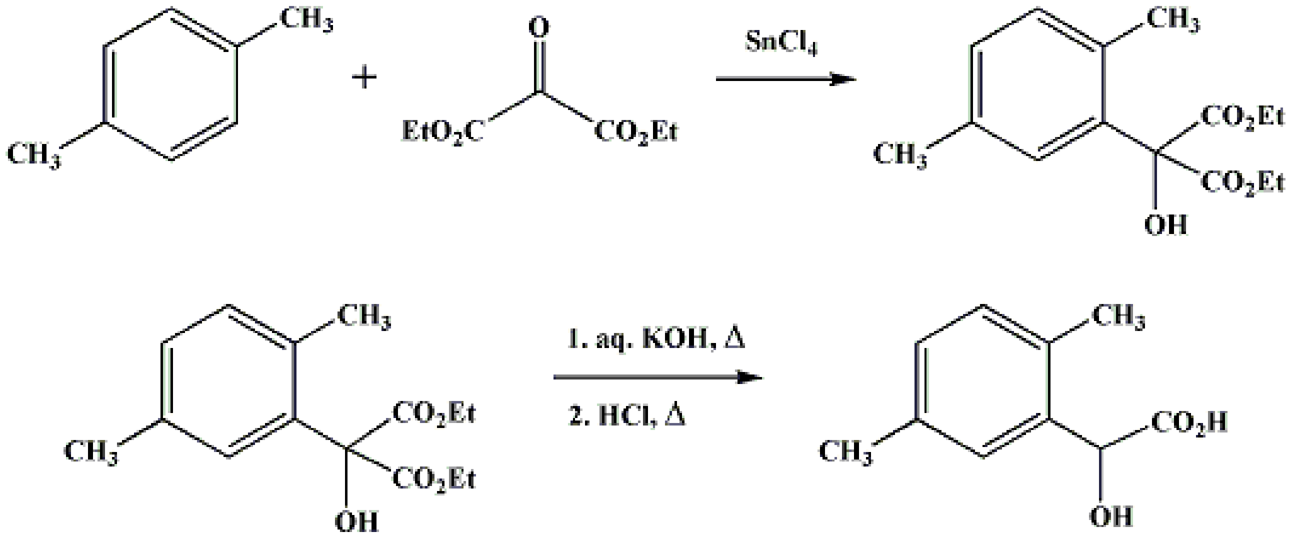
2,5-DIMETHYLMANDELIC ACID

[Mandelic acid, 2,5-dimethyl-]



Submitted by J. L. Riebsomer and James Irvine.
Checked by H. R. Snyder and R. L. Rowland.

1. Procedure

A. *Ethyl 2,5-dimethylphenylhydroxymalonate*. One hundred and seventy-four grams (1 mole) of ethyl oxomalonate (Note 1) and 265 g. (2.5 moles) of *p*-xylene are mixed in a 1-l. three-necked flask equipped with a good stirrer, a dropping funnel, and a calcium chloride drying tube. Suitable precautions are taken to exclude moisture from the reaction mixture. While the mixture is cooled in an ice-water bath and stirred vigorously, 325 g. (1.25 moles) of anhydrous stannic chloride is added dropwise from the funnel. After the addition is complete, the cooling bath is removed and stirring is continued for 3 hours. The reaction mixture is poured with stirring into about 300 g. of cracked ice containing 50 ml. of concentrated hydrochloric acid. On standing this mixture separates into two layers. Two hundred milliliters of ether is added, and the ether layer is washed with 100-ml. portions of water until the wash water is free from chlorides. The ether solution is dried with anhydrous sodium sulfate and distilled. After removal of the ether and the excess of reagents (Note 2), the fraction boiling at 154–156°/5 mm. is collected. The yield of 2,5-dimethylphenylhydroxymalonic ester is 144.5–160 g. (51.5–57%).

B. 2,5-*Dimethylmandelic acid*. A mixture prepared from 140 g. (0.5 mole) of 2,5-dimethylphenylhydroxymalonic ester and a cold solution of 140 g. of potassium hydroxide in 560 ml. of water in a 1-l. round-bottomed flask is warmed on a steam bath for 5 hours. The alkaline solution is cooled and extracted with one 100-ml. portion of ether to remove any material not soluble in alkali. The alkaline solution is acidified with 300 ml. of concentrated hydrochloric acid and then warmed on a steam bath and stirred for 2 hours (or until there is no further evidence that carbon dioxide is escaping). The mixture is cooled, the oily layer is extracted with ether, the ethereal solution is dried with anhydrous sodium sulfate, and the ether is distilled under partial vacuum (Note 3). The oily residue is crystallized from benzene. The yield of 2,5-dimethylmandelic acid melting at 116.5–117° is 55–63 g. (63–70%) (Note 4).

2. Notes

1. The ethyl oxomalonate must be of good quality. It has been found possible to use nitrogen peroxide (now available in cylinders from the du Pont Company) in the preparation of this reagent. The general conditions are the same as in the previous method in *Organic Syntheses*[1] except that the generating flask containing arsenious oxide and nitric acid is replaced with a cylinder of nitrogen peroxide. This method is much more satisfactory.
2. The excess *p*-xylene can be recovered easily.
3. It is important to avoid long heating after removal of the ether. The mandelic acid tends to react with itself.
4. This general method has been applied to the synthesis of a variety of alkyl-substituted mandelic acids.[2]

3. Discussion

2,5-Dimethylmandelic acid has been prepared by the procedure described above;[2] and by the reaction between 2,5-dimethyphenylmagnesium bromide and chloral, followed by alkaline hydrolysis.[3]

References and Notes

1. *Org. Syntheses* Coll. Vol. **1**, 266 (1941).
2. Ando, *J. Chem. Soc. Japan*, **56**, 745 (1935) [*C. A.*, **29**, 7960 (1935)]; Riebsomer, Irvine, and Andrews, *J. Am. Chem. Soc.*, **60**, 1015 (1938); *Proc. Indiana Acad. Sci.*, **47**, 139 (1938); Riebsomer, Baldwin, Buchanan, and Burkett, *J. Am. Chem. Soc.*, **60**, 2974 (1938); Riebsomer, Stauffer, Glick, and Lambert, *J. Am. Chem. Soc.*, **64**, 2080 (1942).
3. Savarian, *Compt. rend.*, **146**, 297 (1908) [*C. A.*, **2**, 1443 (1908)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

arsenious oxide

2,5-dimethylphenylhydroxymalonic ester

2,5-dimethyphenylmagnesium bromide

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether (60-29-7)

Mandelic acid (90-64-2)

nitric acid (7697-37-2)

sodium sulfate (7757-82-6)

carbon dioxide (124-38-9)

potassium hydroxide (1310-58-3)

p-xylene (106-42-3)

Ethyl oxomalonate

stannic chloride (7646-78-8)

chloral (75-87-6)

2,5-Dimethylmandelic acid, Mandelic acid, 2,5-dimethyl-

nitrogen peroxide

Ethyl 2,5-dimethylphenylhydroxymalonate

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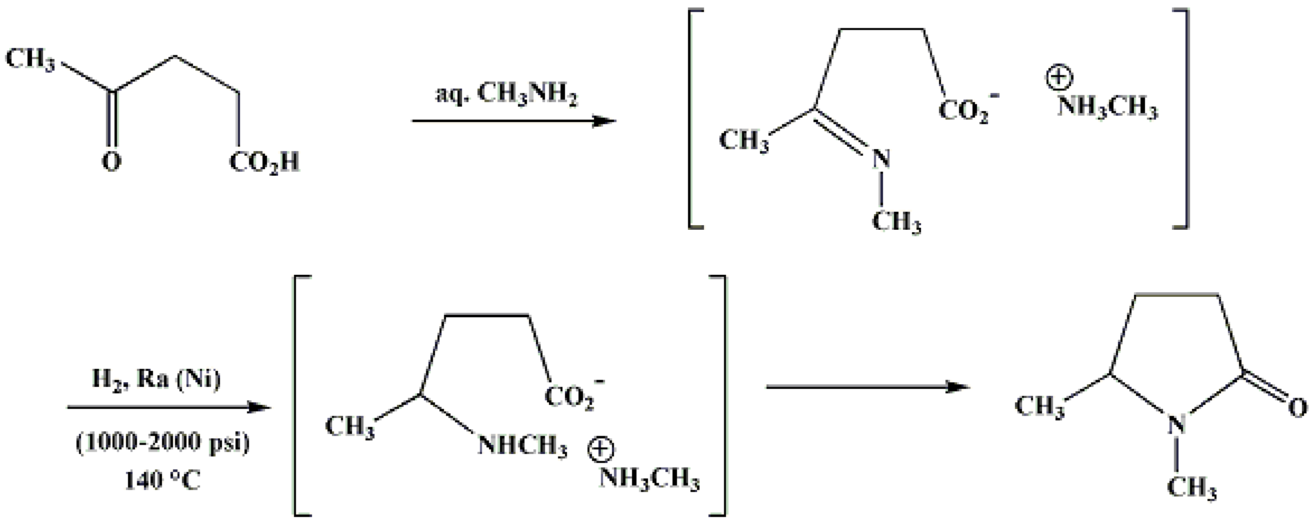
1,5-DIMETHYL-2-PYRROLIDONE

[2-Pyrrolidone, 1,5-dimethyl-]



Submitted by Robert L. Frank, William R. Schmitz, and Blossom Zeidman.
Checked by Arthur C. Cope and W. H. Jones.

1. Procedure

One hundred and ninety-four grams (170 ml., 1.67 moles) of levulinic acid (Note 1) and 500 ml. of 35% aqueous methylamine (sp. gr., 0.89; 3.94 moles of methylamine) (Note 2) are placed in a 2-l. steel reaction vessel of a high-pressure hydrogenation apparatus. Ten grams of Raney nickel catalyst[1] is added, the vessel is closed, and hydrogen is admitted to a pressure of 1000–2000 lb. The bomb is then heated with continuous agitation to 140° and maintained at that temperature for 5 hours (Note 3). The contents are removed, and the bomb is washed with two 100-ml. portions of water. After removal of the catalyst by filtration (Note 4), the filtrate is distilled under reduced pressure using a good column. A low-boiling fore-run of water and methylamine distils first, followed by the product, a colorless liquid boiling at 84–86°/13 mm.; 102–104°/27 mm.; n_D^{25} 1.4611 (Note 5). The yield is 140–146 g. (74–77%).

2. Notes

1. A. E. Staley Manufacturing Company's Grade A levulinic acid was used.
2. Commercial 35% aqueous methylamine solution was used.
3. The course of the reaction may be followed by the drop in hydrogen pressure, the decrease depending upon the size of the bomb employed.
4. Because of its pyrophoric nature, the nickel catalyst should not be allowed to dry on the filter. A convenient alternative procedure for removing catalyst is to centrifuge the reaction mixture.
5. The product of some runs has a light yellow tint, but the color appears to cause no complications in subsequent reactions of the material.

3. Discussion

1,5-Dimethyl-2-pyrrolidone has been prepared by the reaction of 5-methyl-2-pyrrolidone with excess methyl iodide[2] and by the catalytic hydrogenation of a mixture of levulinic acid and methylamine.[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 615

References and Notes

1. *Org. Syntheses* Coll. Vol. **3**, 181 (1954).
2. Senfter and Tagel, *Ber.*, **27**, 2313 (1894).
3. Hoffman-LaRoche and Co., Ger. pat. 609,244 [*C. A.*, **29**, 3116 (1935)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrogen (1333-74-0)

nickel, Raney nickel (7440-02-0)

Methyl iodide (74-88-4)

LEVULINIC ACID (123-76-2)

methylamine (74-89-5)

1,5-Dimethyl-2-pyrrolidone, 2-Pyrrolidone, 1,5-dimethyl- (5075-92-3)

5-methyl-2-pyrrolidone (108-27-0)

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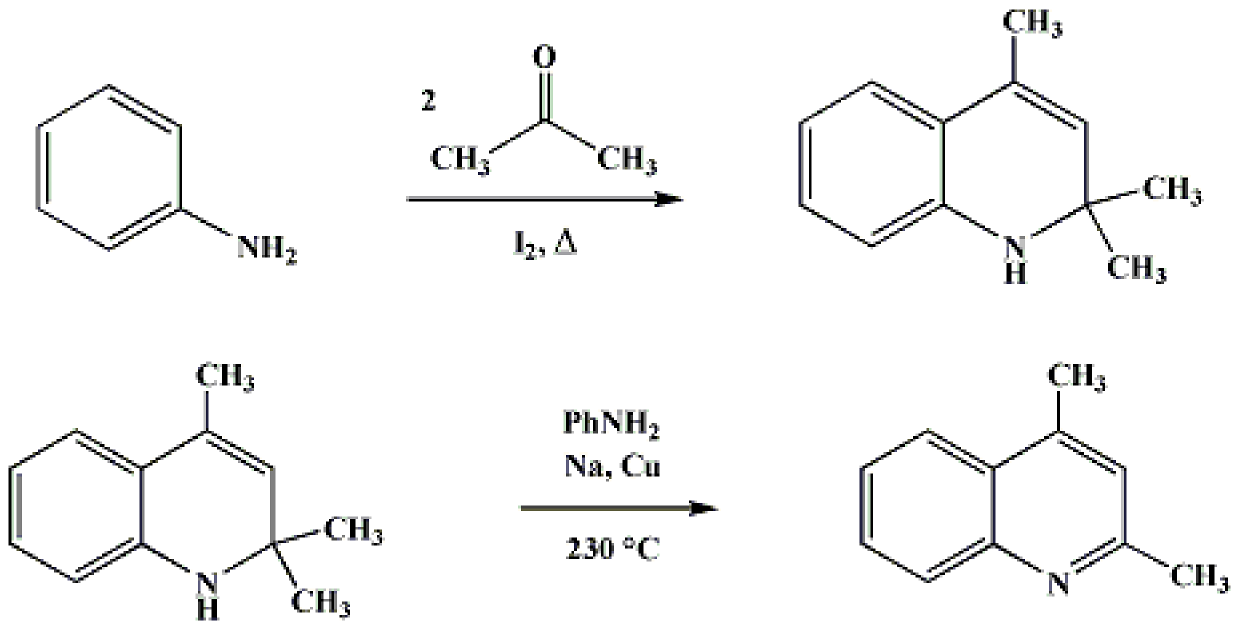
2,4-DIMETHYLQUINOLINE

[Quinoline, 2,4-dimethyl-]



Submitted by W. R. Vaughan[1]
Checked by Richard T. Arnold and Horace R. Davis, Jr..

1. Procedure

A. *"Acetone-anil"* (Note 1). A mixture of 279 g. (3 moles) of aniline and 9 g. of iodine is placed in a 1-l. three-necked round-bottomed flask. The flask is fitted with a dropping funnel (the delivery tube of which extends below the liquid surface), a mercury-sealed stirrer (Note 2), and an adapter carrying a thermometer which extends into the liquid and a condenser system such that most of the aniline will return and all the water produced (as well as excess acetone) will distil (Note 3). The flask is now heated in an oil bath (Note 4) and (Note 5), and the reaction mixture is maintained at 170–175° while acetone is passed in through the dropping funnel at such a rate that no more than 2 drops of liquid distils per second. During the addition the mixture is vigorously stirred. A total volume of 850 ml. (670 g., 11.6 moles) of acetone is added over a 4-hour period, and about 610 ml. of distillate is collected. At the end of this period the reaction mixture is cooled and distilled in vacuum, three fractions being collected (up to 136°/15 mm., 136–141°/15 mm., and 141–146°/15 mm.). The acetone-water distillate is now distilled through a simple column at atmospheric pressure until essentially all the acetone has come over. There remains a mixture of oil and water which is separated after being cooled. The oil is then used as the first fraction for a fractional distillation in vacuum of the reaction product, each of the previous fractions being added in succession. Three new fractions are collected: 78–82°/13 mm. (a little aniline); 82–133°/13 mm. (a small intermediate fraction); and 133–138°/13 mm.

(acetone-anil). An appreciable quantity of tarry residue remains in the distillation flask. The yield based upon aniline actually consumed in the reaction is 61–68% (Note 5).

B. *2,4-Dimethylquinoline*. A small quantity of copper powder (Note 6) is added to 4.6 g. (0.2 gram atom) of sodium metal (small pieces) and 56 g. (0.6 mole) of dry aniline (Note 7) contained in a 1-l. round-bottomed flask. The mixture is warmed carefully over a low flame until the evolution of hydrogen ceases, at which time the mixture is usually black. A few boiling chips and 346 g. (2 moles) of acetone-anil are then added. The resulting mixture is heated at the reflux temperature (220–230°) until the evolution of gas (methane) ceases (Note 8). At the end of the reaction the mixture is cooled and then distilled in vacuum. The fraction boiling at 135–140°/12 mm. weighs 252–283 g. (80–90%) (Note 9).

2. Notes

1. The so-called acetone-anil has been assigned the structure indicated in accordance with the work of Craig.[2]
2. A convenient stirrer may be made from tantalum wire as described by Hershberg.[3]
3. A Liebig condenser in reflux position is heated with steam and connected at the top to a water-cooled downward condenser.
4. For a reaction temperature of 170–175° the oil is best maintained at about 200° during the addition of the acetone.
5. The reaction may be carried out at any temperature from 70° to 175°. At lower temperature it is much slower and is best carried out by refluxing the theoretical quantities of acetone and aniline with iodine catalyst for an extended time. Regardless of the time or reaction temperature, if due allowance is made for aniline reclaimed at the end of the reaction the yield falls between the limits indicated. At the higher temperature, equilibrium is attained more rapidly, as would be expected, and relatively little aniline is recovered. (A typical run may yield 40 g. of aniline and 297 g. of "anil," with 11 g. of middle fraction.)
6. The exact amount of copper powder used as a catalyst in the preparation of the sodium salt of aniline is not important. Approximately 0.2 g. has been found to be satisfactory in runs of the size described.
7. Aniline which has been recently distilled is satisfactory. An excess of aniline over the sodium is used to minimize decomposition of the 2,4-dimethylquinoline.[2]
8. The time required for the decomposition of the acetone-anil varies from 3 to 6 hours. The checkers, however, found that essentially all the methane is eliminated after 2 hours.
9. Fractionation of 245 g. of this product through a 14-plate Lecky-Ewell[4] column yielded 6 g. of aniline, 3 g. of an intermediate fraction, and 218 g. (89%) of 2,4-dimethylquinoline, b.p. 149–150°/20 mm. (controlled). If the material is

to be nitrated, the crude product is quite satisfactory.

3. Discussion

The present procedure for the preparation of acetone-anil is described by Reddelien.[5] A reaction at lower temperature is reported by Craig,[2] who also describes the alkaline decomposition of the anil to 2,4-dimethylquinoline and methane and gives a method of purification of the final product. Other methods for the preparation of 2,4-dimethylquinoline involve the Beyer[6] synthesis from aniline hydrochloride and ethylidene acetone, a modification of this synthesis,[7] a synthesis using 2-chloro-2-pentenone-4,[8] and the Combes synthesis from acetylacetone and aniline.[9]

References and Notes

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2. Craig, *J. Am. Chem. Soc.*, **60**, 1458 (1938).
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4. Lecky and Ewell, *Ind. Eng. Chem., Anal. Ed.*, **12**, 544 (1940).
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7. Mikeska, Stewart, and Wise, *Ind. Eng. Chem.*, **11**, 456 (1919).
8. Julia, *Compt. rend.*, **228**, 1807 (1949).
9. Combes, *Bull. soc. chim. France*, **49**, 89 (1888).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

acetone-anil

aniline (62-53-3)

hydrogen (1333-74-0)

aniline hydrochloride (142-04-1)

copper powder (7440-50-8)

iodine (7553-56-2)

acetone (67-64-1)

methane (7782-42-5)

sodium (13966-32-0)

Acetylacetone (123-54-6)

2,4-DIMETHYLQUINOLINE, Quinoline, 2,4-dimethyl- (1198-37-4)

ethylidene acetone (625-33-2)

2-chloro-2-pentenone-4

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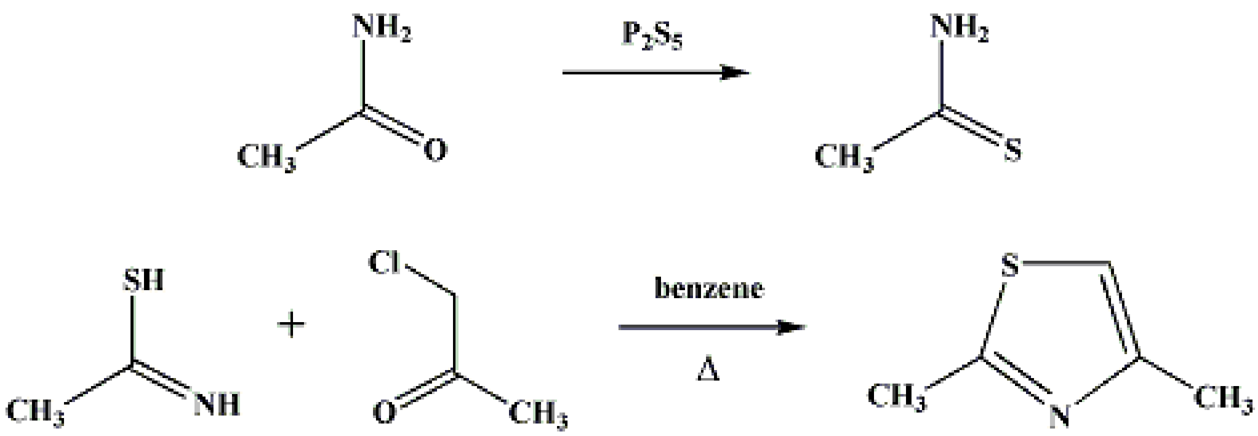
2,4-DIMETHYLTHIAZOLE

[Thiazole, 2,4-dimethyl-]



Submitted by George Schwarz
Checked by C. S. Hamilton and Edward J. Cragoe, Jr..

1. Procedure

In a 2-l. round-bottomed flask provided with a reflux condenser is placed 200 ml. of dry benzene (Note 1). A mixture of 300 g. (5.08 moles) of finely divided acetamide and 200 g. (0.9 mole) of powdered phosphorus pentasulfide is prepared quickly and transferred immediately to the flask. To this is added 20 ml. of a mixture of 400 ml. (4.97 moles) of chloroacetone (Note 2) and 150 ml. of dry benzene. The exothermic reaction is started by careful heating in a water bath. The water bath is removed, and the remainder of the chloroacetonebenzene mixture is introduced gradually through the reflux condenser (Note 3) and (Note 4). When all the chloroacetone has been added and reaction is no longer apparent, the mixture is refluxed on the water bath for 30 minutes.

About 750 ml. of water is added to the mixture with shaking. After 30 minutes the mixture is poured into a separatory funnel, and the reddish upper layer containing the benzene with some impurities is discarded. The lower layer is made alkaline (Note 5) by the addition of 5 *N* sodium hydroxide or potassium hydroxide, and the crude thiazole, which separates as a black upper layer, is removed with ether, and the aqueous lower layer is extracted with five 120-ml. portions of ether. The combined ethereal extracts are dried over anhydrous sodium sulfate and filtered through glass wool. The ether is removed by distillation from a steam bath (Note 6), and the residual oil is fractionated at atmospheric pressure; the fraction boiling at 140–150° is collected and redistilled. The yield of 2,4-dimethylthiazole boiling at 143–145° (Note 7) is 210–230 g. (41–45% based on the phosphorus pentasulfide).

2. Notes

1. Commercial benzene is satisfactory after being dried over calcium chloride and distilled.
2. Commercial chloroacetone is distilled, and the fraction boiling at 116–122° is used.
3. The progress of the reaction is controlled by the portions of chloroacetone added. If too much is added at once the reaction may become too vigorous. Portions of 20 ml. are safe. Toward the end of the reaction, larger portions may be added.
4. As soon as the reaction has begun, the mixture becomes a gray-black oily liquid.
5. The alkalinity of the deeply colored solution can be tested with phenolphthalein paper. The edges of the wetted paper become visibly red. One should be sure to test the aqueous solution and not the separated thiazole floating on top of the liquid.
6. The thiazole is hygroscopic and should be protected from moisture.
7. Reported boiling points are 144–145.5°/719 mm.[1] and 143°.[1] No 2,4-dimethyloxazole (b.p. 108°) was obtained during the distillation.

3. Discussion

2,4-Dimethylthiazole has been prepared from chloroacetone and thioacetamide,[2] but forming the required thioacetamide in the reaction mixture is to be preferred since no additional manipulation is involved. The method here described is substantially that of E. Merck.[1] Other substituted thiazoles can be prepared by practically the same method.[1] 2,4-Dimethylthiazole has been obtained by dry distillation of 2-methylthiazyl-4-acetic acid,[3] and also by heating 2,4-dimethylthiazole-5-carboxylic acid with calcium oxide.[4]

References and Notes

1. E. Merck, Ger. pat. 670,131 [*C. A.*, **33**, 2909 (1939)].
2. Hantzsch, *Ann.*, **250**, 265 (1889).
3. Steude, *Ann.*, **261**, 41 (1891).
4. Rubleff, *Ann.*, **259**, 266 (1890).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

chloroacetonebenzene

2-methylthiazyl-4-acetic acid

calcium chloride (10043-52-4)

Acetamide (60-35-5)

Benzene (71-43-2)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium sulfate (7757-82-6)

potassium hydroxide (1310-58-3)

calcium oxide

phenolphthalein (77-09-8)

chloroacetone (78-95-5)

phosphorus pentasulfide

thiazole (288-47-1)

2,4-Dimethylthiazole, Thiazole, 2,4-dimethyl- (541-58-2)

2,4-dimethyloxazole (7208-05-1)

thioacetamide (62-55-5)

2,4-dimethylthiazole-5-carboxylic acid

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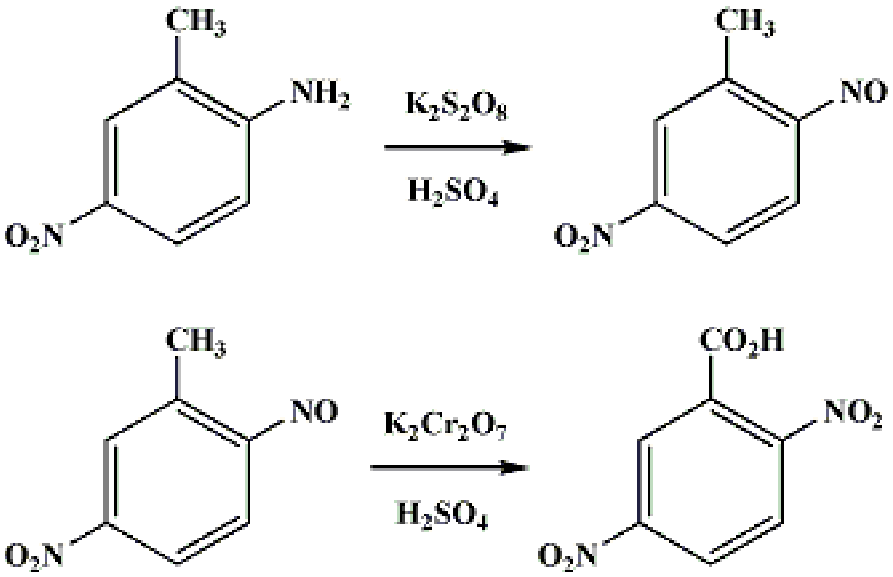
2,5-DINITROBENZOIC ACID

[Benzoic acid, 2,5-dinitro-]



Submitted by Wilson D. Langley
Checked by W. E. Bachmann and D. W. Holmes.

1. Procedure

A. 2-*Nitroso*-5-*nitrotoluene.* In a 5-l. round-bottomed flask fitted with a mechanical stirrer is placed 50 g. (0.33 mole) of pulverized 5-nitro-2-aminotoluene (Note 1). To this is added an ice-cold solution of 200 ml. of concentrated sulfuric acid in 50 ml. of water. While the suspension is stirred at room temperature, a solution of Caro's acid is prepared, as follows: to 175 ml. of ice-cold sulfuric acid (sp. gr. 1.84) in a 2-l. beaker is added 300 g. (1.11 moles) of pulverized potassium persulfate. The mixture is thoroughly stirred with a glass rod, and to it is added 900 g. of crushed ice and 300 ml. of water.

The well-stirred solution of Caro's acid is poured into the suspension of nitroaminotoluene. The mixture is stirred and warmed, but as soon as the temperature reaches 40°, heating is discontinued. After the solution has been stirred for 2 hours longer, an additional 100 g. (0.37 mole) of powdered potassium persulfate is added in one portion. The heat of reaction is sufficient to maintain the temperature at 40°. Stirring is continued for 2 hours more, and the suspension is then diluted with water to 4 l. The solid is filtered with suction (Note 2) and washed with 400 ml. of water. The wet material is transferred to a 5-l. round-bottomed flask, about 700 ml. of water is added, and the mixture is steam-distilled. The 2-nitroso-5-nitrotoluene is filtered from the distillate (Note 3). The total yield of air-dried product is 30–39 g. (55–71%) (Note 4).

B. 2,5-*Dinitrobenzoic acid*. A suspension of 20 g. (0.12 mole) of the air-dried 2-nitroso-5-nitrotoluene in 100 ml. of water is prepared in a 500-ml. Erlenmeyer flask, and to it is added 50 g. (0.17 mole) of powdered potassium dichromate (Note 5). The flask is placed in an ice-salt bath, and the mixture is stirred vigorously by means of an efficient stirrer. When the temperature has dropped to 5°, 175 ml. of concentrated sulfuric acid is added in a thin stream (Note 6) while the temperature is not allowed to exceed 35°. After all the sulfuric acid has been added the mixture is stirred and heated to 50°. The source of heat is removed, and the temperature is maintained between 50° and 55° by cooling in an ice bath as the exothermic reaction takes place (Note 7). After 20 minutes the temperature is raised to 65° ± 3° and held there for 1 hour longer.

The solution is cooled to 20°, and 250 g. of ice is added. The mixture is stirred for a few minutes, then is filtered with suction (hardened filter paper), and the solid is washed with 35 ml. of ice water. The solid is suspended in 25 ml. of water in a 600-ml. beaker and is slowly dissolved by gradual addition of 55–65 ml. of a 10% solution of sodium carbonate. The solution is filtered (Note 8), and the filtrate is made strongly acidic to Congo red by addition of 1:1 hydrochloric acid. The mixture is chilled in ice for an hour and is then filtered. The product is washed with 12 ml. of ice water and air-dried. The acid melts at 174–176° and weighs 14–17 g. (55–66%). The acid may be recrystallized by dissolving 10 g. of it in 250 ml. of boiling 5% hydrochloric acid (Note 9). The solution, when chilled in ice, deposits 9.4 g. of 2,5-dinitrobenzoic acid as nearly colorless crystals which melt at 177–178° (Note 10).

2. Notes

1. Eastman Kodak Company's practical grade was used.
2. The filtrates, on standing overnight, deposit 5–5.6 g. of crude 2-nitroso-5-nitrotoluene, which is not included in the weights recorded. It may be added to the product obtained by steam distillation.
3. The submitters reported that successive 2.5-l. portions of distillate were filtered, and the following weights of product were obtained: 14.5, 10.7, 9.0, and 2 g., or 36.2 g. in 10 l. From one run the checkers obtained 19, 12, 6, and 2 g., or 39 g. In some runs it was necessary to collect 15–30 l. of distillate in order to obtain a 30-g. yield. The submitters report that unchanged amine, if present during the steam distillation, condenses with the nitroso compound, giving tarry products, and the yield of nitroso compound is reduced.
4. In favorable cases, the product is white and melts at 135–136°.
5. The procedures given in *Org. Syntheses* Coll. Vol. **1**, 385, 528 (1932), 392, 543 (1941), are not suitable for the oxidation of nitrosonitrotoluenes. Using the procedure given on p. 385 (1932) and p. 392 (1941) the yield of dinitro acid is low, and using the procedure given on p. 528 (1932) and p. 543 (1941) the dinitro acid is deeply colored.
6. This requires 20–25 minutes.
7. In a run twice this size the checkers observed that at this stage some of the semi-solid material on the top of the stirred solution burned. The burning ceased after a few minutes. The yield of final product was slightly lower. It must be

emphasized that careful control of the temperature is necessary during the oxidation with dichromate in order to prevent the reaction from becoming too vigorous.

8. The undissolved residue is largely 2,5-dinitrotoluene, which may be used in subsequent oxidations. Larger yields of this compound may be obtained by shortening the time of stirring during the oxidation process.

9. Additional data on the recrystallization of 2,5-dinitrobenzoic acid are: a solution of 6.83 g. in 200 ml. of boiling toluene, when filtered and chilled, furnished 5.9 g.; a solution of 10 g. in 110 ml. of boiling water, when filtered and chilled, furnished 9.18 g.

10. When 3-nitro-4-aminotoluene was used, 3,4-dinitrobenzoic acid was obtained in approximately the same yields as those recorded for 2,5-dinitrobenzoic acid. The submitter reports: "3-nitro-4-aminotoluene dissolves readily in the sulfuric acid when the Caro's acid is added, and the 3-nitro-4-nitrosotoluene which separates is practically free of the amine. Therefore, the steam distillation may be omitted and the nitroso compound may be oxidized directly to the dinitro acid, which is obtained as a light-colored product. From 100 g. of 3-nitro-4-aminotoluene there was obtained 102 g. of yellow nitrosonitrotoluene which, when oxidized, gave 85 g. of 3,4-dinitrobenzoic acid melting at 158–162°. One crystallization gave the pure acid. A solution of 10 g. of the acid in 210 ml. of boiling water gave, after cooling, 9.1 g. of the acid. Similarly, a solution of 10 g. of the acid in 280 ml. of hot 5% hydrochloric acid was filtered quickly and then cooled. The filtrate deposited 9.4 g. of the acid."

3. Discussion

2,5-Dinitrobenzoic acid has been prepared by nitration of *o*-nitrobenzoic acid and fractional crystallization of the acids as the barium salts;[1] and by oxidation of 2,5-dinitrotoluene.[2]

References and Notes

1. Griess, *Ber.*, **7**, 1223 (1874).
2. Grell, *Ber.*, **28**, 2564 (1895).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Caro's acid

nitrosonitrotoluenes

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

dichromate

sodium carbonate (497-19-8)

toluene (108-88-3)

barium (7440-39-3)

potassium dichromate (7778-50-9)

potassium persulfate (7727-21-1)

o-nitrobenzoic acid (552-16-9)

3-nitro-4-aminotoluene (89-62-3)

5-nitro-2-aminotoluene (99-52-5)

2,5-Dinitrobenzoic acid, Benzoic acid, 2,5-dinitro- (610-28-6)

nitroaminotoluene

2-Nitroso-5-nitrotoluene (57610-10-3)

2,5-dinitrotoluene (619-15-8)

3,4-dinitrobenzoic acid (528-45-0)

3-nitro-4-nitrosotoluene

nitrosonitrotoluene

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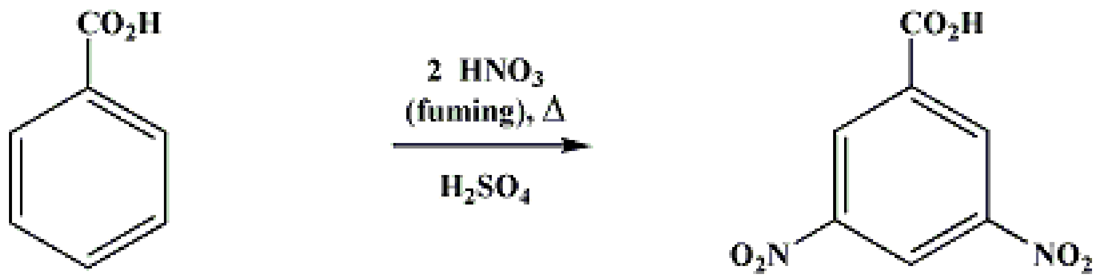
3,5-DINITROBENZOIC ACID

[Benzoic acid, 3,5-dinitro-]



Submitted by (A) R. Q. Brewster, Bill Williams, and (B) Ross Phillips.
Checked by Homer Adkins and James Ruhoff.

1. Procedure

A. In a 2-l. round-bottomed flask are placed 61 g. (0.5 mole) of benzoic acid and 300 ml. of concentrated sulfuric acid (sp. gr. 1.84). To this mixture is added 100 ml. of fuming nitric acid (sp. gr. 1.54) in portions of 2 or 3 ml. The temperature during the addition of the acid is kept between 70° and 90° by means of external cooling with cold water (Note 1), and the addition should be carried out in a good hood. The flask is covered with a watch glass and allowed to stand for an hour, or overnight, in the hood. The flask is then heated on a steam bath in the hood for 4 hours, during which time considerable amounts of brown fumes are evolved. The reaction mixture is then allowed to cool to room temperature (Note 2), whereupon yellow crystals separate from the solution. An additional 75 ml. of fuming nitric acid is added, and the mixture is heated on the steam bath for 3 hours and then in an oil bath at 135–145° for 3 hours (hood). Brown fumes are evolved continuously, especially during the heating in the oil bath. The color of the reaction mixture is light to reddish yellow.

The mixture is allowed to cool and is poured into 800 g. of ice and 800 ml. of water. After standing for 30 minutes the 3,5-dinitrobenzoic acid is filtered with suction and washed with water until free of sulfates. The crude product weighs 62–65 g. and melts at 200–202°. This product is recrystallized from 275 ml. of hot 50% ethanol. The purified 3,5-dinitrobenzoic acid weighs 57–61 g. (54–58%) and melts at 205–207° (Note 3).

B. Two hundred grams of benzoic acid (1.6 moles) is stirred into 1 l. of concentrated sulfuric acid contained in a 3-l. round-bottomed flask. The flask is surrounded by cold water, and the temperature is maintained below 45° while 80 ml. of fuming nitric acid is added. When the temperature of the reaction mixture has fallen to 30°, 240 ml. of fuming nitric acid is added, a beaker is inverted over the neck of the flask, and the mixture is allowed to stand for 6 weeks.

The flask is heated on a steam bath for 4 hours and then in an oil bath at 145° until all

the crystals are dissolved. A mush of crystals separates when the mixture is cooled to room temperature. These are filtered on a Büchner funnel without any filtering medium. After the crystals are pressed dry, they are placed in 1.5 l. of cold water, washed thoroughly, filtered through paper, and dried in the air. The yield is 200–213 g. (60%), and the product melts at 205–207° (cor.) (Note 4) and (Note 5).

2. Notes

1. The temperature is so controlled that evolution of brown fumes, in other than small quantities, is avoided.
2. Mechanical stirring is advantageous but not necessary.
3. The melting points were taken with a short-stem total-immersion thermometer.
4. Procedure B has been carried out on ten times the scale specified, with yields a few per cent higher than those given above.
5. A purification procedure which gives material suitable for use in the determination of creatinine has been reported.[1]

3. Discussion

3,5-Dinitrobenzoic acid has been prepared by nitration of benzoic acid with sulfuric acid and fuming nitric acid;[2] by nitration of 3-nitrobenzoic acid;[3] and by oxidation of 3,5-dinitrotoluene.[2,4,5] It has been obtained as a product of the action of nitric acid on 1,5-dinitronaphthalene.[6]

References and Notes

1. Jansen, Sombrock, and Noyons, *Chem. Weekblad*, **43**, 731 (1947).
2. Cahours, *Jahresber. Fortsch. Chem.*, **1847–1848**, 533; Voit, *Ann.*, **99**, 104 (1856); Michler, *Ann.*, **175**, 152 (1875); Hübner, *Ann.*, **222**, 72 (1884); Saunders, Stacey, and Wilding, *Biochem. J.*, **36**, 368 (1942)
3. Tiemann and Judson, *Ber.*, **3**, 224 (1870).
4. Staedel, *Ann.*, **217**, 194 (1883).
5. Goldstein and Voegeli, *Helv. Chim. Acta*, **26**, 475 (1943)
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

fuming nitric acid

ethanol (64-17-5)

sulfuric acid (7664-93-9)

nitric acid (7697-37-2)

Benzoic acid (65-85-0)

Creatinine (60-27-5)

3,5-Dinitrobenzoic acid, Benzoic acid, 3,5-dinitro- (99-34-3)

3-nitrobenzoic acid (121-92-6)

3,5-dinitrotoluene (618-85-9)

1,5-dinitronaphthalene (605-71-0)

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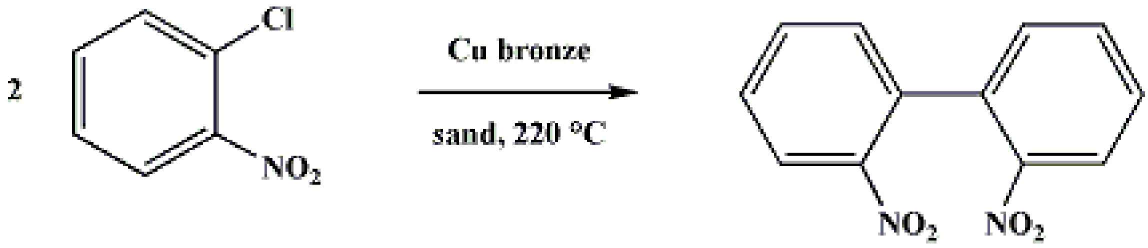
2,2'-DINITROBIPHENYL

[Biphenyl, 2,2'-dinitro-]



Submitted by Reynold C. Fuson and E. A. Cleveland.
Checked by W. E. Bachmann, A. L. Wilds, and J. Korman.

1. Procedure

In a 1-l. flask equipped with a mechanical stirrer are placed 200 g. (1.27 moles) of *o*-chloronitrobenzene and 300 g. of clean dry sand. The mixture is heated in an oil bath to 215–225°, and then 200 g. of copper bronze (Note 1) is slowly added, the addition requiring about 1.2 hours (Note 2). The temperature is kept at 215–225° for 1.5 hours longer, the stirring being continued throughout. The mixture is poured while hot into a beaker containing 300–500 g. of sand and is then stirred until small clumps are formed; upon cooling, these are broken up in a mortar (Note 3). The mixture is boiled 10 minutes with two 1.5-l. portions of ethanol and removed by filtration each time. The filtrates are cooled in an ice bath, and the 2,2'-dinitrobiphenyl is collected on a filter (Note 4). A second crop is obtained by concentrating the filtrate. The product is dissolved in hot ethanol (Note 5), and the solution is treated with Norit, filtered, and cooled in an ice bath. The solid is recrystallized from hot ethanol and is obtained as pure, yellow crystals melting at 123.5–124.5° (cor). The yield is 80–95 g. (52–61%).

2. Notes

1. Ordinary copper bronze does not always give satisfactory results in the Ullmann reaction. More uniform results are obtained if the copper bronze is prepared as suggested by Kleiderer and Adams.[1] The copper bronze is treated with 2 l. of a 2% solution of iodine in acetone for 5–10 minutes. The product is then collected on a Büchner funnel, removed, washed by stirring into a slurry with 1 l. of a 1:1 solution of concentrated hydrochloric acid in acetone, and again filtered. The copper iodide dissolves, and the copper bronze remaining is separated by filtration and washed with acetone. It is then dried in a vacuum desiccator. It should be used immediately.
2. The temperature of the mixture must not be allowed to rise much above 240° or reduction of the nitro groups will occur and carbazole will be formed.
3. The reaction mixture should not be allowed to cool in the flask, as it will set

to a hard mass; it is almost impossible to remove this from the flask.
4. If the first two extractions with ethanol do not yield about 90 g. of crude product, a third extraction of the sand and residue is well worth while (the yield of impure product was never less than 90 g. when this procedure was carried out).
5. If the impure material is recrystallized from the minimum amount of ethanol, the suction funnel will become rapidly plugged during filtration with consequent loss of time and material. Two liters of alcohol per 100 g. of 2,2'-dinitrobiphenyl is preferable. All filtrates were reduced to a small volume, and the crude material obtained was recrystallized twice, using Norit. (This amounted to about 10% of the total yield.)

3. Discussion

2,2'-Dinitrobiphenyl has been prepared by the action of copper on *o*-chloronitrobenzene, on *o*-bromonitrobenzene,[2,3] and on diazotized *o*-nitroaniline.[4]

References and Notes

1. Kleiderer and Adams, *J. Am. Chem. Soc.*, **55**, 4225 (1933).
2. Ullman and Bielecki, *Ber.*, **34**, 2174 (1901).
3. Mascarelli and Gatti, *Gazz. chim. ital.*, **67**, 807 (1937)
4. Niementowski, *Ber.*, **34**, 3325 (1901).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

copper bronze

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

copper (7440-50-8)

iodine (7553-56-2)

acetone (67-64-1)

Norit (7782-42-5)

Biphenyl (92-52-4)

o-bromonitrobenzene (577-19-5)

o-chloronitrobenzene (88-73-3)

carbazole (86-74-8)

copper iodide (7681-65-4)

o-NITROANILINE (88-74-4)

2,2'-DINITROBIPHENYL (2436-96-6)

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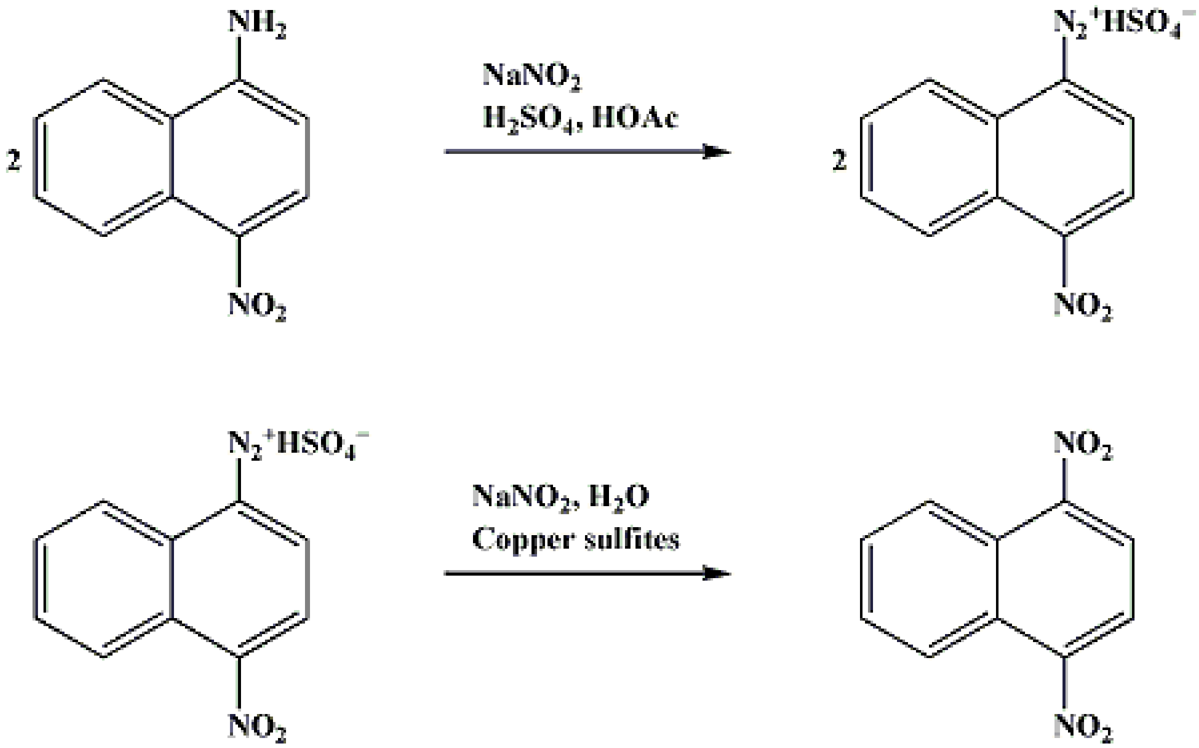
1,4-DINITRONAPHTHALENE

[Naphthalene, 1,4-dinitro-]



Submitted by H. H. Hodgson, A. P. Mahadevan, and E. R. Ward.
Checked by C. C. Price and Sing-Tuh Voong.

1. Procedure

Ten grams (0.14 mole) of powdered sodium nitrite is dissolved in 50 ml. of concentrated sulfuric acid (sp. gr. 1.84) contained in a 1-l. beaker placed in an ice bath. A solution of 10 g. of 4-nitro-1-naphthylamine (0.053 mole) (p. 664) in 100 ml. of glacial acetic acid is prepared by heating, and the well-stirred solution is cooled below 20°. Some crystals separate. The resulting thin slurry is dropped slowly into the cold solution of nitrosylsulfuric acid with mechanical stirring. Throughout the addition, and for 30 minutes thereafter, the temperature is kept below 20°. Seven hundred milliliters of dry ether is added slowly with stirring, and the temperature of the mixture is kept at 0° for 1 hour. At the end of this period, the precipitation (aided by scratching) of the crystalline 4-nitronaphthalene-1-diazonium sulfate is complete (Note 1). This precipitate is collected, washed with ether and then with 95% ethanol until all the acid is removed, and finally dissolved in 100 ml. of iced water.

A saturated aqueous solution containing 50 g. of crystalline copper sulfate is treated with a similar solution of 50 g. of crystallized sodium sulfite. The greenish brown precipitate is collected, washed with water (Note 2), and then stirred into a solution of

100 g. (1.45 moles) of sodium nitrite in 400 ml. of water contained in a 2-l. beaker provided with an efficient mechanical stirrer.

The cold aqueous solution of the diazonium salt is then added slowly to the decomposition mixture. Considerable frothing occurs, and 4–5 ml. of ether is added from time to time to break the foam. After stirring for 1 hour (Note 3), the mixture is filtered and the crude dark brown precipitate of the 1,4-dinitronaphthalene is washed several times with water, then with 2% aqueous sodium hydroxide, and again with water. The precipitate is dried and extracted three times with boiling 95% ethanol (450 ml. in all). The extract is concentrated to 75 ml.; most of the 1,4-dinitronaphthalene separates and is collected. Additional amounts can be obtained by further concentration. The resulting product melts at 130–132° and weighs 6.0–7.0 g. (52–60%). The product can be purified either by steam distillation (Note 4) or by recrystallization from aqueous ethanol. Pale yellow needles melting at 134° are obtained (Note 5) and (Note 6).

2. Notes

1. This precipitate is sometimes sticky. It can be made granular by treating it with a small amount of 95% ethanol (after the removal of the supernatant liquid). Alternatively, it may suffice to keep the ethereal diazotized solution cold and scratch the sides of the beaker with a glass rod.
2. The cupro-cupri sulfite of this variety is more efficient as a decomposition reagent than the red-violet precipitate obtained by treating a hot solution of copper sulfate with a solution of ammonium sulfite saturated with sulfur dioxide and subsequently heating the mixture for 10 minutes at 90°.
3. The decomposition appears to be immediate, and at the end of 1 hour most of the inorganic material has passed into solution.
4. Steam distillation of 1,4-dinitronaphthalene is very slow. However, the cupro-cupri sulfite method[1] is a general one for the replacement of the diazonium group by the nitro group, and steam distillation is preferable whenever the product is readily volatile.
5. The solution is decolorized with charcoal in the course of the recrystallization. The checkers obtained 5 g. (43%) of golden needles after three recrystallizations.
6. 1,2-Dinitronaphthalene may be obtained similarly from 2-nitro-1-naphthylamine, or less satisfactorily from 1-nitro-2-naphthylamine; 1,6- and 2,6-dinitronaphthalenes can be prepared from the 5-nitro- and 6-nitro-2-naphthylamines, respectively, by a modification of the process. Since the solubility of these amines in glacial acetic acid is slight, it is preferable to prepare the diazonium sulfate as follows: Ten grams of the amine is dissolved in 50 ml. of sulfuric acid (sp. gr. 1.84), and the solution is mixed with one of 10 g. of sodium nitrite in 50 ml. of sulfuric acid (sp. gr. 1.84). This mixture is stirred into 200 ml. of glacial acetic acid. The temperature is maintained below 20° throughout these operations. After 30 minutes, the diazonium sulfate is

precipitated at 0° by the addition of 200–500 ml. of ether as previously described.

3. Discussion

1,4-Dinitronaphthalene has been prepared previously from diazotized 4-nitro-1-naphthylamine by a modified Sandmeyer procedure,[2,3] from 5,8-dinitrotetralin by dehydrogenation,[4] by the deamination of 1,4-dinitro-2-naphthylamine,[5] and by the decomposition of 4-nitro-1-naphthalenediazonium cobaltinitrite.[6] The method described above has been published.[1]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

diazonium sulfate

cupro-cupri sulfite

1,6- and 2,6-dinitronaphthalenes

5-nitro- and 6-nitro-2-naphthylamines

4-nitro-1-naphthalenediazonium cobaltinitrite

ethanol (64-17-5)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

ether (60-29-7)

sodium sulfite (7757-83-7)

sodium hydroxide (1310-73-2)

sulfur dioxide (7446-09-5)

copper sulfate (7758-98-7)

sodium nitrite (7632-00-0)

charcoal (7782-42-5)

nitrosylsulfuric acid (7782-78-7)

1,4-Dinitronaphthalene, Naphthalene, 1,4-dinitro- (6921-26-2)

4-nitro-1-naphthylamine (776-34-1)

4-nitronaphthalene-1-diazonium sulfate

ammonium sulfite (10196-04-0)

1,2-Dinitronaphthalene

2-nitro-1-naphthylamine (607-23-8)

1-nitro-2-naphthylamine

5,8-dinitrotetralin

1,4-dinitro-2-naphthylamine

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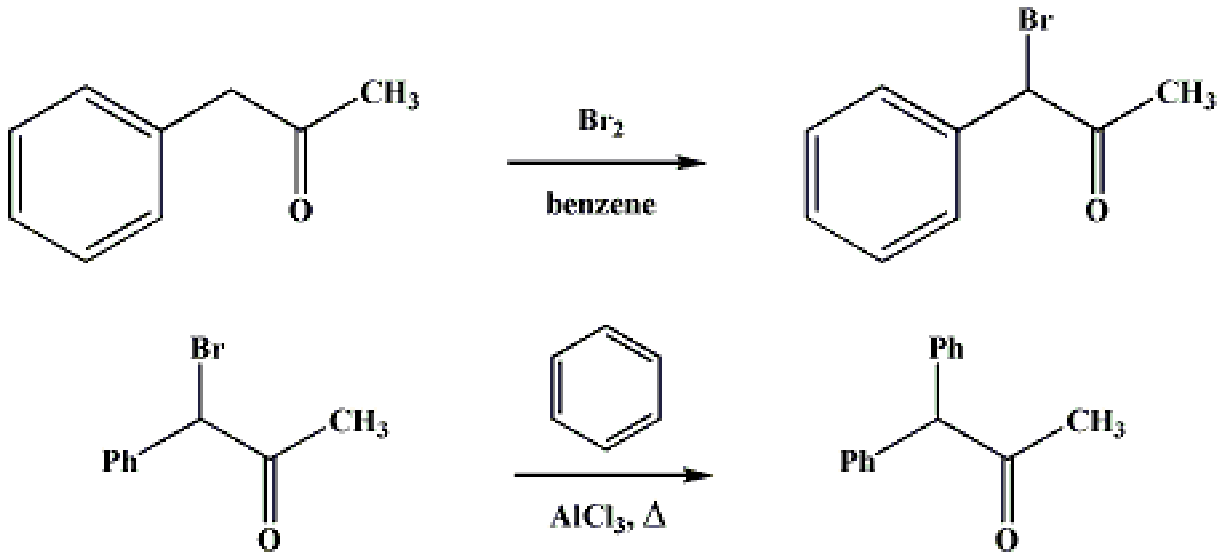
α,α-DIPHENYLACETONE

[2-Propanone, 1,1-diphenyl-]



Submitted by Everett M. Schultz and Sally Mickey.
Checked by Edward T. Cline and R. S. Schreiber.

1. Procedure

A. *α-Bromo-α-phenylacetone*. A 1-l. three-necked flask is equipped with a sealed stirrer (Note 1), a dropping funnel, and a water-cooled reflux condenser provided with a short inverted U-tube on the open end; the equipment is assembled in the hood. In the flask are placed 200 ml. of dry, thiophene-free benzene (Note 2) and 37 g. (36.89 ml., 0.276 mole) of phenylacetone (Note 3). The stirrer is started, and 45 g. (14.42 ml., 0.28 mole) of reagent bromine is added dropwise during a period of 1 hour. The reaction mixture first becomes cloudy but changes to a clear orange-red solution by the time all the bromine is added. After the addition of bromine is complete, a rapid stream of dry nitrogen or carbon dioxide is passed through the solution by means of an inlet tube which now replaces the dropping funnel. The hydrogen bromide issuing from the inverted U-tube at the top of the condenser may be trapped in water in an Erlenmeyer flask or other container adjusted so that the water surface is about 1 cm. below the outlet of the tube. The reaction is complete when no more hydrogen bromide fumes can be detected in the gas issuing from the condenser. This operation requires 3–6 hours. During this period the reaction mixture becomes yellow to green. The benzene solution of α-bromo-α-phenylacetone is then transferred to a dry 500-ml. separatory funnel (Note 4).

B. *α,α-Diphenylacetone* (Note 5). The reaction flask used in A is again equipped as it was originally, and in it are placed 75 g. (0.56 mole) of anhydrous aluminum chloride

(Note 6) and 150 ml. of dry benzene (Note 2). The stirrer is started, and the flask is heated by means of a steam bath so that the benzene boils gently. The benzene solution of α-bromo-α-phenylacetone (Part A) is added dropwise from the separatory funnel to the boiling mixture over a period of 1 hour. After the addition is complete, the almost black reaction mixture is heated to boiling for an additional hour, then cooled and poured with stirring onto 500 g. of crushed ice and 100 ml. of concentrated hydrochloric acid contained in a 2-l. beaker. The deeply colored benzene solution gradually becomes orange-yellow. When the ice has melted, the benzene layer is separated and the aqueous layer is extracted with three 50-ml. portions of ether. The combined ether and benzene solution is washed with 100 ml. of water and then with 100 ml. of saturated sodium bicarbonate solution. After the solution has been dried for at least 1 hour over 60 g. of anhydrous sodium sulfate, the solvents are evaporated on a steam bath until the solution no longer boils. The dark residue is transferred to a 250-ml. Claisen flask equipped for reduced-pressure distillation and having a receiver fused to the side arm (Note 7). The residual benzene is first distilled at 19–20 mm. while the flask is being heated on a steam bath. The steam bath is replaced by an oil or metal bath which is gradually heated to 190°. A small fore-run of yellow oil which darkens rapidly is collected. It is removed from the receiver by siponing and rinsing with acetone. The bath is allowed to cool to 100–120°, the system is evacuated with an oil pump (Note 8), and the diphenylacetone is distilled. The bulk of the material boils at 142–148°/2–3 mm. The distillate may solidify in the receiver (Note 9). The crude product is triturated with just sufficient petroleum ether (b.p. 35–60°) to moisten it, cooled in an ice-water bath, collected on a filter, and washed on the filter with small amounts of petroleum ether at 0–5° until nearly colorless. The amount of petroleum ether used up to this point should not exceed 50 ml. The product is then crystallized from petroleum ether using 8 ml. of solvent per gram of crude, dry solid. The hot solution is allowed to stand at room temperature until crystallization begins, and then at 0–5° for 16 hours (Note 10). The crystals are collected by filtration and dried in air at room temperature. The yield of nearly colorless product melting at 60–61° (Note 11) is 31–33 g. (53–57%).

2. Notes

1. A rubber tubing seal is satisfactory. The submitters used an all-glass seal made from a 5-ml. glass syringe.
2. The benzene was reagent grade and was dried by distilling until no more water collected in the condenser. The undistilled portion was used directly.
3. Phenylacetone was obtained from the Swope Oil Company, Philadelphia, Pennsylvania. On attempted distillation of this material as received, the checkers observed considerable water in the forerun. The distillation was interrupted, the material was dried over anhydrous sodium sulfate and redistilled at atmospheric pressure, but small amounts of water still appeared in the condensate, indicating possible decomposition. The fraction boiling at 214–214.8° (uncor.)/ 756 mm. was used.
4. The transfer may be carried out easily by admitting dry nitrogen or air under

pressure continuously to the flask and allowing the benzene solution to be blown out of the flask through the glass tube previously used for introducing nitrogen or carbon dioxide.

5. Once Part B is started, it should be continued without interruption until the Friedel-Crafts reaction product is decomposed.

6. Baker and Adamson reagent grade powdered aluminum chloride was used.

7. Diphenylacetone may solidify in the side arm, in which event it may become necessary to melt it by heating with a small flame.

8. It is necessary to protect the pump by means of a sodium hydroxide tower since hydrogen halide may be evolved during the distillation. The checkers, in addition, used a Dry Ice trap.

9. The checkers transferred the distillate to another container before solidification occurred.

10. The checkers found that the small additional amount (approximately 5 g.) of product obtained by cooling to –25° is more highly colored and considerably less pure than that obtained at 0–5°.

11. A labile form of α,α-diphenylacetone, melting at 46°, is described in the literature.[1,2]

3. Discussion

α,α-Diphenylacetone has been prepared by the oxidation of 1,1-diphenyl-2-propanol;[1] by the action of dilute mineral acid on 1,1-diphenyl-1,2-propanediol,[1,2] 1,1-diphenyl-1-hydroxy-2-ethoxypropane,[3] 1,1-diphenyl-1-hydroxy-2-aminopropane,[4] 1,1-diphenyl-2-ethoxy-1-propene,[5] and 2,2-diphenyl-3-methylethylenimine;[6] by the distillation at atmospheric pressure of 1,1-diphenyl-2-methylethylene oxide;[7] by the reaction of benzene with α-phenyl-α-chloro- (or bromo-) acetone;[8,9] by acetylation of potassium *t*-butyl diphenylacetate, followed by hydrolysis[10] and by the rearrangement of α-methyldesoxybenzoin in the presence of zinc chloride.[11] The present method is adapted from the procedure of Ruggli, Dahn, and Wegmann.[8]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

α-phenyl-α-chloro- (or bromo-) acetone

α-methyldesoxybenzoin

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

hydrogen bromide (10035-10-6)

bromine (7726-95-6)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

acetone (67-64-1)

aluminum chloride (3495-54-3)

zinc chloride (7646-85-7)

phenylacetone (103-79-7)

α,α-Diphenylacetone, 2-Propanone, 1,1-diphenyl-, diphenylacetone (781-35-1)

α-bromo-α-phenylacetone (23022-83-5)

1,1-diphenyl-2-propanol (29338-49-6)

1,1-diphenyl-1,2-propanediol

1,1-diphenyl-1-hydroxy-2-ethoxypropane

1,1-diphenyl-1-hydroxy-2-aminopropane

1,1-diphenyl-2-ethoxy-1-propene

2,2-diphenyl-3-methylethylenimine

1,1-diphenyl-2-methylethylene oxide

potassium t-butyl diphenylacetate

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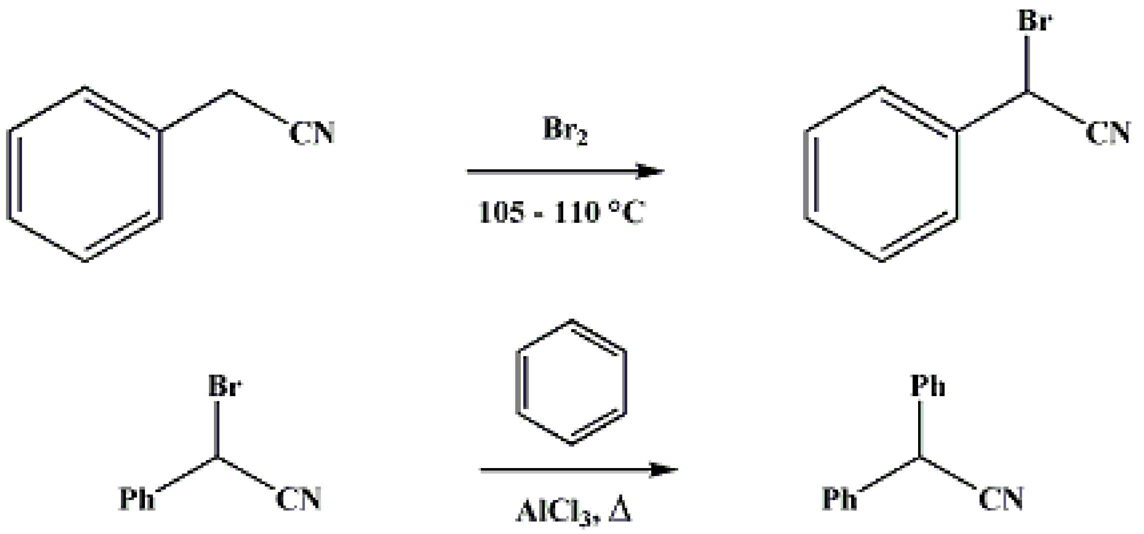
Organic Syntheses, CV 3, 347

DIPHENYLACETONITRILE

[Acetonitrile, diphenyl-]



Submitted by C. M. Robb and E. M. Schultz.
Checked by Richard T. Arnold and J. W. Britain.

1. Procedure

A. *α-Bromo-α-phenylacetonitrile*. In a well-ventilated hood (Note 1), a dry 500-ml. round-bottomed three-necked flask is equipped with a sealed stirrer, an air condenser (Note 2), and a cork carrying a dropping funnel and a thermometer. In the flask is placed 117 g. (1 mole) of benzyl cyanide (Note 3). The thermometer is adjusted so that the bulb is immersed in the benzyl cyanide. The flask is placed in a bath and heated to 105–110° (inside temperature). With good stirring, 176 g. (1.1 moles) of bromine (Note 4) is added over a period of 1 hour; during the addition and for 15 minutes thereafter the temperature of the liquid is maintained at 105–110°. At the end of the heating period the evolution of hydrogen bromide gas has practically ceased. The dropping funnel is replaced by a cork carrying a glass tube reaching to within 2–3 cm. of the surface of the reaction mixture. Dry nitrogen is then led through the apparatus for 30 minutes. The hot mixture is poured into the 500-ml. addition funnel fitted to the apparatus to be used in the next step (see part B). The reaction flask is rinsed with 100 g. (1.3 moles) of dry benzene (Note 5), and this is added to the bromonitrile. The benzene solution thus obtained is used immediately in the next step (Note 6).

B. *Diphenylacetonitrile*. A dry 2-l. round-bottomed three-necked flask, equipped with a sealed stirrer, a 500-ml. dropping funnel, and a dry reflux condenser (Note 2), is mounted on a steam bath. In the flask are placed 368 g. (4.7 moles) of dry benzene (Note 5) and 133.5 g. (1 mole) of powdered anhydrous aluminum chloride. The stirrer is started, and the benzene is heated to vigorous refluxing. The α-bromo-α-

phenylacetonitrile solution is added to the boiling mixture over a period of 2 hours in small portions (Note 7). After the addition is complete, the reaction mixture is refluxed for an additional hour. The flask is cooled, and the mixture is poured into a stirred mixture of 1 kg. of crushed ice and 100 ml. of concentrated hydrochloric acid in a 3-l. beaker.

The benzene layer is separated. The aqueous layer is extracted with 500 ml. of ether in two equal portions. The ether and benzene solutions are combined and washed successively with 500 ml. of water, 250 ml. of saturated sodium bicarbonate solution, and 500 ml. of water. The organic layer is dried over 100 g. of anhydrous sodium sulfate. The drying agent is separated from the solution, and the solvents are removed by heating on a steam bath. The last traces of benzene are removed by vacuum distillation from a 250-ml. Claisen flask heated on a steam bath. The residue weighs about 190 g. A receiver is connected directly to the side arm (Note 8) of the Claisen flask, and the product is distilled under reduced pressure. It boils at 122–125°/1–2 mm. and crystallizes to a yellow solid which melts at 68–70°. The solid is recrystallized from isopropyl alochol (1 ml. per g.); the flask containing the filtered hot solution is placed on an asbestos mat, and the solution is allowed to cool only to room temperature without shaking or stirring. The crystals are then collected and washed on the funnel with chilled isopropyl alcohol (one-fifth the volume used in the recrystallization). The product is dried in a vacuum desiccator over concentrated sulfuric acid or phosphorus pentoxide. The yield of pure white product, melting at 74–75°, is 97–116 g. (50–60% based on benzyl cyanide) (Note 9).

2. Notes

1. α-Bromo-α-phenylacetonitrile is a lachrymator.
2. The mouth of the condenser is fitted with a cork carrying a short U-tube, to prevent condensed moisture from running back into the flask.
3. The benzyl cyanide used was a redistilled grade obtained from the Benzol Products Company.
4. Reagent grade bromine was used.
5. Reagent grade benzene was subjected to distillation until no droplets of water formed in the distillate. The residual benzene was used directly without further distillation or drying.
6. The checkers found that the work could be interrupted for as much as 1 day after the preparation of α-bromo-α-phenylacetonitrile without appreciable effect on the yield.
7. The reaction is vigorous, but it can be readily controlled by adding the bromonitrile frequently in small portions.
8. The flask must be of such a type that the side arm can be heated to prevent plugging by the solidified distillate.
9. A second crop, amounting to 10–15 g. and melting at 68–70°, can be obtained by chilling the mother liquor, but recrystallization of this fraction from isopropyl alcohol does not raise the melting point.

3. Discussion

Diphenylacetonitrile has been prepared by the dehydration of diphenylacetamide,[1,2,3,4,5,6,7,8,9] by the reaction of diphenylbromomethane and mercuric cyanide,[10] by the reaction of diphenylaectic acid and lead thiocyanate,[11] by the removal of ammonia from diphenylacetamidine,[12] by phenylation of potassium acetonitrile with chlorobenzene in liquid ammonia,[13] by the action of benzene on benzaldehyde cyanohydrin in the presence of aluminum chloride,[14] and from diphenylmethane and cyanogen chloride.[15] The present method is a modification of that of Hoch.[16,17]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

isopropyl alochol

diphenylaectic acid

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

Benzene (71-43-2)

ether (60-29-7)

sodium bicarbonate (144-55-8)

hydrogen bromide (10035-10-6)

bromine (7726-95-6)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

chlorobenzene (108-90-7)

aluminum chloride (3495-54-3)

isopropyl alcohol (67-63-0)

Diphenylmethane (101-81-5)

Benzyl cyanide (140-29-4)

benzaldehyde cyanohydrin (532-28-5)

mercuric cyanide (592-04-1)

cyanogen chloride (506-77-4)

Diphenylacetonitrile, Acetonitrile, diphenyl- (86-29-3)

bromonitrile

α-bromo-α-phenylacetonitrile (5798-79-8)

diphenylacetamide (519-87-9)

diphenylbromomethane (776-74-9)

diphenylacetamidine

potassium acetonitrile

phosphorus pentoxide (1314-56-3)

lead thiocyanate

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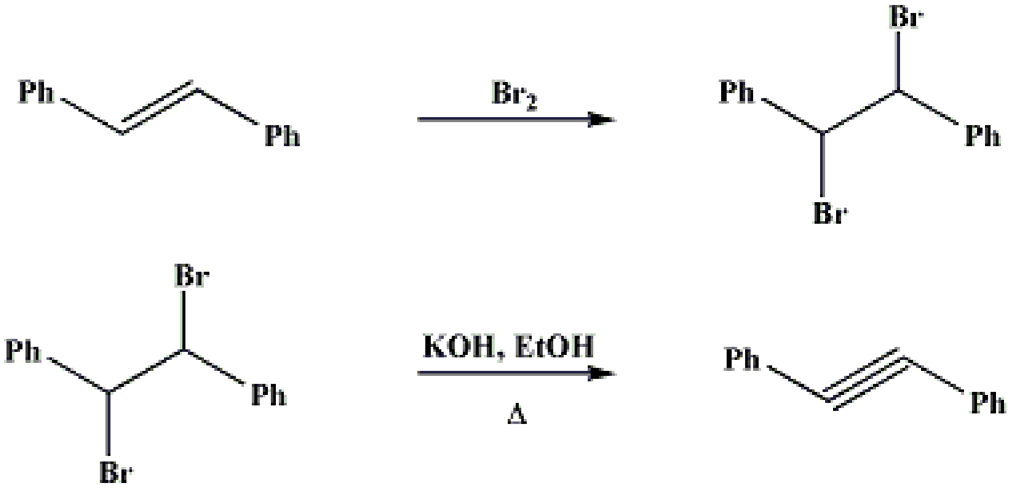
Organic Syntheses, CV 3, 350

DIPHENYLACETYLENE

[Tolan]



Submitted by Lee Irvin Smith and M. M. Falkof.
Checked by W. E. Bachmann and Charles E. Maxwell.

1. Procedure

A solution of 45 g. (0.25 mole) of *trans*-stilbene in 750 ml. of ether is prepared in a 1-l. three-necked round-bottomed flask fitted with a reflux condenser, an efficient mechanical stirrer, and a dropping funnel. To the well-stirred solution there is added 13.8 ml. (43 g.; 0.27 mole) of bromine, during the course of 10 minutes. A solid begins to separate in 5 minutes, but stirring is continued for 1 hour. The product is collected on a Büchner funnel and washed with ether until it is white. The yield of stilbene dibromide, melting at 235–237°, is 65.8–69.1 g. (77–81%).

A solution of 90 g. of potassium hydroxide in 150 ml. of absolute ethanol is prepared in a 500-ml. round-bottomed flask fitted with a reflux condenser (Note 1). The solution is cooled somewhat, and the stilbene dibromide is added in several portions (Note 2). The mixture is then refluxed for 24 hours in an oil bath (Note 3). The hot mixture is poured into 750 ml. of cold water, and the product is removed by filtration and washed with 50 ml. of water. The crude diphenylacetylene is dried over calcium chloride in a vacuum desiccator for 18 hours at room temperature. The chunky, pale yellow crystals melt at 58–60° and weight 33.7–37.8 g. By recrystallization of this product from 50 ml. of 95% ethanol there is obtained 29.2–30.5 g. (66–69% based on the stilbene) of pure diphenylacetylene, which forms white needles melting at 60–61° (Note 4).

2. Notes

1. Complete solution of the alkali in the alcohol is effected by placing the flask in an oil bath at 130–140°.
2. The addition of the stilbene dibromide causes an immediate, vigorous reaction, with the evolution of heat. It is necessary to replace the reflux condenser after each addition, until boiling has ceased.
3. An electrically heated oil bath is used to maintain a constant bath temperature of 130–140°.
4. The submitters obtained the same percentage yield on runs four times this size; the time employed was the same as that described here, except for the addition of bromine, which required 30 minutes.

3. Discussion

Diphenylacetylene has been prepared by the present method;[1] by the action of sodium amide on monochlorostilbene;[2] by the action of potassium amide on stilbene dichloride;[3] by heating 1,1-diphenyl-2-chloroethane with sodium ethoxide in a sealed tube;[4] and from benzil via the hydrazone.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 377
- Org. Syn. Coll. Vol. 5, 604
- Org. Syn. Coll. Vol. 6, 531

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrazone

ethanol (64-17-5)

calcium chloride (10043-52-4)

ether (60-29-7)

bromine (7726-95-6)

Benzil (134-81-6)

potassium hydroxide (1310-58-3)

Tolan (108-88-3)

sodium ethoxide (141-52-6)

1,1-diphenyl-2-chloroethane

sodium amide (7782-92-5)

stilbene

Diphenylacetylene (501-65-5)

Stilbene dibromide (5789-30-0)

monochlorostilbene

potassium amide

stilbene dichloride

trans-Stilbene (103-30-0)

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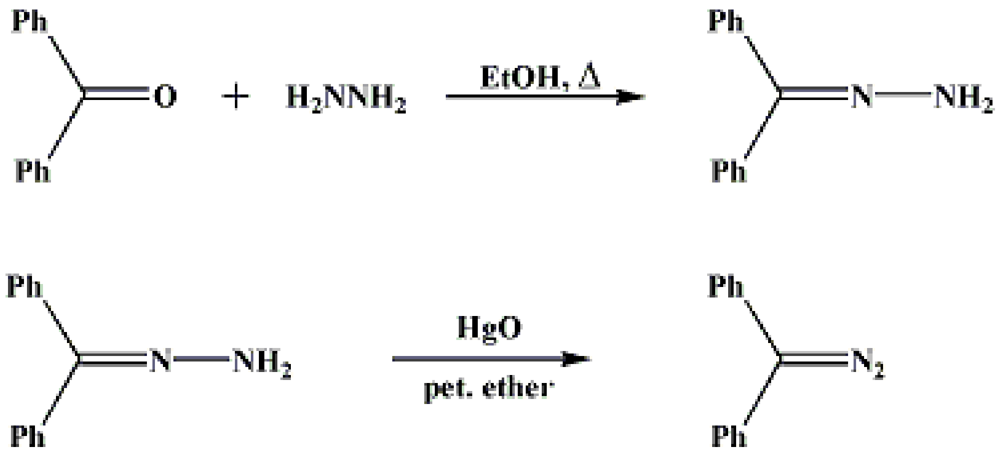
Organic Syntheses, *CV 3, 351*

DIPHENYLDIAZOMETHANE

[Methane, diazodiphenyl-]



Submitted by Lee Irvin Smith and Kenneth L. Howard.
Checked by H. R. Snyder, R. L. Rowland, and H. J. Sampson, Jr..

1. Procedure

In a pressure bottle are placed 19.6 g. (0.1 mole) of benzophenone hydrazone (Note 1), 22 g. (0.1 mole) of yellow oxide of mercury, and 100 ml. of petroleum ether (b.p. 30–60°). The bottle is closed, wrapped in a wet towel, and shaken mechanically at room temperature for 6 hours. The mixture is then filtered to remove mercury and any benzophenone azine (Note 2), and the filtrate is evaporated to dryness under reduced pressure at room temperature. The crystalline residue of diphenyldiazomethane melts when its temperature reaches that of the room (Note 3), but it is difficult to purify and this product is pure enough for all practical purposes. The material weighs 17.3–18.6 g. (89–96%). The product should be used immediately (Note 4).

2. Notes

1. Benzophenone hydrazone is most readily prepared from benzophenone (40 g., 0.22 mole) in 150 ml. of absolute ethanol with 41.2 g. (0.824 mole) of 100% hydrazine; the mixture is heated under reflux for 10 hours. On cooling in ice, colorless benzophenone hydrazone separates. The yield is 37.5 g. (87%), m.p. 97–98°. If anhydrous hydrazine is not available, it may be prepared by the method described in *Org. Syntheses*, **24**, 53 (1944).
2. This ketazine is insoluble in petroleum ether.
3. The reported melting point of diphenyldiazomethane is 29–30°, but this melting point is shown only after the substance has been recrystallized from petroleum ether.
4. On standing, diphenyldiazomethane decomposes to yield benzophenone

azine. In one of the checkers' runs the product was stored at room temperature; after 2 days, crystals of the azine were visible. The product at this stage was assayed by treatment with benzoic acid; addition of 6.8 g. of the diazo compound in a thin stream to a solution of 17 g. of benzoic acid in 90 ml. of ether, and, after 30 minutes, extraction of the excess benzoic acid with dilute sodium hydroxide followed by distillation of the ether gave 7.4 g. (75%) of crude benzohydryl benzoate melting at 83–85°. In the same procedure the freshly prepared diazo compound gave a quantitative yield of the crude ester.

3. Discussion

Diphenyldiazomethane has been prepared only by oxidation of benzophenone hydrazone.[1] The procedure given above is that of Staudinger, Anthes, and Pfenninger, with minor changes.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 392
- Org. Syn. Coll. Vol. 7, 438

References and Notes

1. Staudinger, Anthes, and Pfenninger, *Ber.*, **49**, 1932 (1916)

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

oxide of mercury

benzohydryl benzoate

ethanol (64-17-5)

ether (60-29-7)

sodium hydroxide (1310-73-2)

Benzoic acid (65-85-0)

mercury (7439-97-6)

Benzophenone (119-61-9)

hydrazine (302-01-2)

Diphenyldiazomethane (883-40-9)

Methane, diazodiphenyl-

benzophenone hydrazone (5350-57-2)

benzophenone azine (983-79-9)

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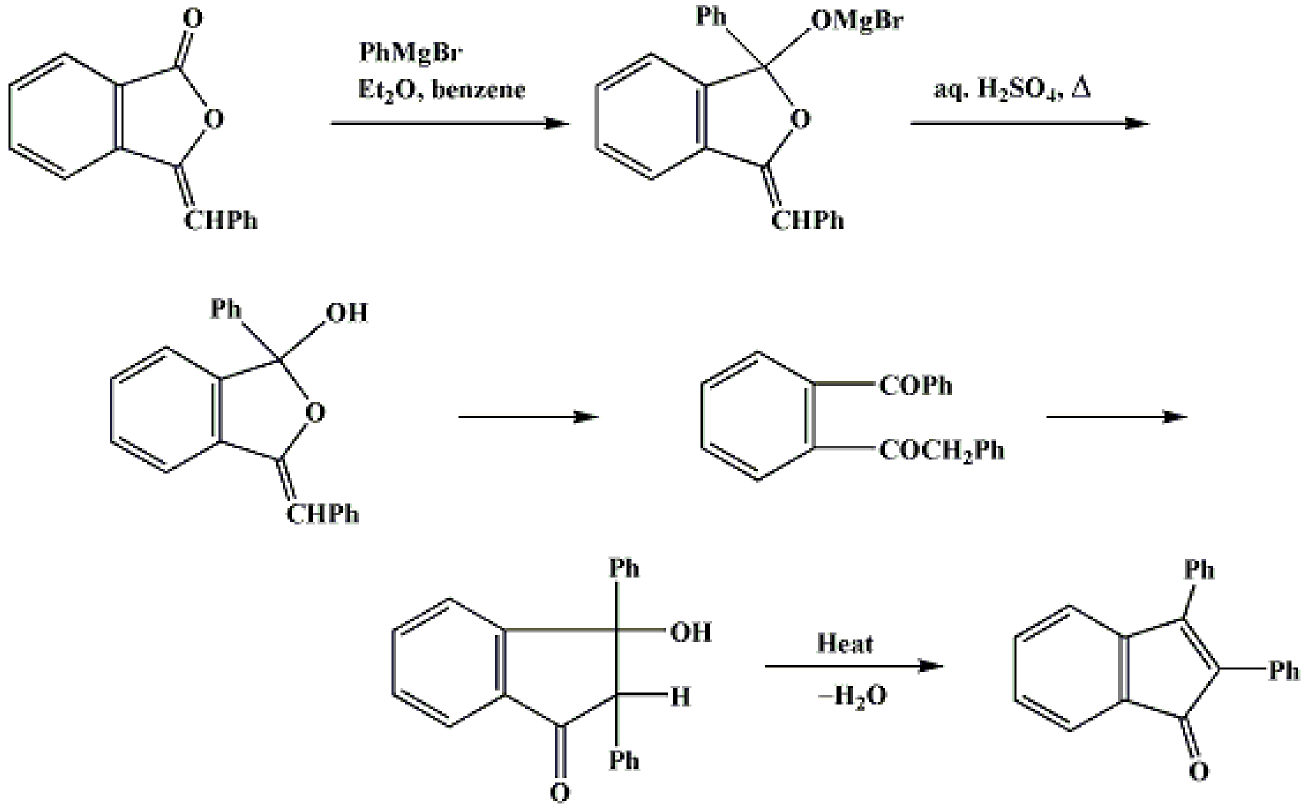
Organic Syntheses, CV 3, 353

2,3-DIPHENYLINDONE (2,3-DIPHENYL-1-INDENONE)

[Indone, 2,3-diphenyl-]



Submitted by C. F. H. Allen, J. W. Gates, Jr., and J. A. VanAllan.
Checked by R. L. Shriner and H. W. Johnston.

1. Procedure

A solution of phenylmagnesium bromide is prepared in the usual manner[1] using 12.2 g. (0.5 gram atom) of magnesium, 78.5 g. (52 ml., 0.5 mole) of bromobenzene, and 500 ml. of absolute ether in a 2-l. round-bottomed three-necked flask fitted with a reflux condenser, a mechanical stirrer, and a dropping funnel. No unreacted magnesium should remain; if any does, an additional 1–2 ml. of bromobenzene should be added.

To this vigorously stirred solution is added slowly a solution of 44.5 g. (0.20 mole) of benzalphthalide[2] in 400 ml. of dry benzene. After about half of this solution has been added, the magnesium complex begins to separate; it hinders the stirring somewhat. When all the phthalide solution has been admitted (about 1 hour), the reflux condenser is replaced by a still head carrying a thermometer and attached to a condenser set for downward distillation. The bulk of the solvent is then removed; this requires about 30 minutes, the temperature of the vapor remaining at 50° for about half this time and rising to about 65° toward the end. About 220–230 ml. of distillate is obtained. The flask and contents are then immersed in an ice bath, and the magnesium complex is decomposed by the slow addition of a cold solution of 15 ml. of concentrated sulfuric acid in 300 ml. of water (Note 1) with rapid stirring. The upper benzene layer is separated and transferred to a 1-l. Claisen flask, and the solvent is removed by distillation from a steam bath; this requires about 4 hours. The residual thick red syrup is transferred to a 125-ml. Claisen flask with a wide side arm set up for vacuum distillation. The residue is heated under a pressure of about 10 mm. to remove all low-boiling material (Note 2) and then is distilled under reduced pressure. The fraction boiling at 215–255°/6 mm. (195–220°/1 mm.) is collected, most of the distillate coming over at

235–240°/6 mm. The distillate is dissolved in 50 ml. of boiling benzene, 200 ml. of hot 95% ethanol is added, and the solution is chilled in an ice bath for 2 hours. The red, crystalline 2,3-diphenylindone is collected on a filter, washed with 50 ml. of cold 95% ethanol, and air-dried. The yield is 34–40 g. (60–71%) of red crystals melting at 149–151° (Note 3) and (Note 4).

2. Notes

1. The decomposition is vigorous, and the acid must be admitted slowly at first but may be added more rapidly toward the end.
2. During this heating any carbinol present is dehydrated. Low and erratic yields usually indicate incomplete dehydration.
3. The product may be recrystallized by dissolving it in 50 ml. of boiling benzene and diluting with 200 ml. of hot ethanol. The recovery of material, m.p. 150–151°, is about 90%.
4. This procedure is capable of considerable variation, by which other indenones may be secured. For example, the benzalphthalide may be replaced by other phthalides made from (*a*) other aldehydes, or (*b*) other anhydrides; the phenylmagnesium bromide can be replaced by other Grignard reagents.

3. Discussion

2,3-Diphenylindone has been prepared by the action of phenylmagnesium bromide upon benzalphthalide[3,4] and by ring closure from α,β-diphenylcinnamic acid[5,6] or from 2,3,3-triphenyl-3-hydroxypropionic acid.[7,8]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Indone, 2,3-diphenyl-

magnesium complex

2,3-Diphenylindone

ethanol (64-17-5)

sulfuric acid (7664-93-9)

Benzene (71-43-2)

ether (60-29-7)

magnesium (7439-95-4)

bromobenzene (108-86-1)

Phenylmagnesium bromide (100-58-3)

Benzalphthalide (575-61-1)

2,3-DIPHENYL-1-INDENONE (1801-42-9)

α,β-diphenylcinnamic acid

2,3,3-triphenyl-3-hydroxypropionic acid

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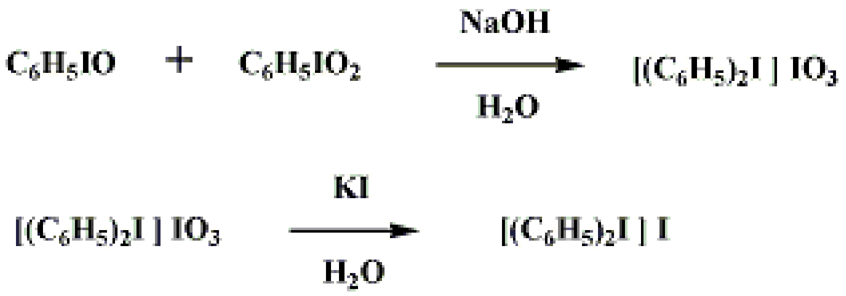
DIPHENYLIODONIUM IODIDE

[Iodonium compounds, diphenyl—iodide]



Submitted by H. J. Lucas and E. R. Kennedy.
Checked by John R. Johnson and M. W. Formo.

1. Procedure

A mixture of 22 g. (0.1 mole) of iodosobenzene (p. 483), 24 g. (0.1 mole) of iodoxybenzene (p. 485), and 200 ml. of 1 *N* sodium hydroxide (Note 1) is gently stirred for 24 hours. The resulting brown slurry is thoroughly stirred with 1 l. of cold water, and, after the mixture settles, the supernatant solution of diphenyliodonium iodate is decanted through a filter. The solid residue is extracted twice with 500-ml. portions of water, and the extracts are separated, by decantation through a filter, from the small amount of tarry residue. An aqueous solution of 20 g. (0.12 mole) of potassium iodide is added to the combined filtrates. After the bulky white precipitate of diphenyliodonium iodide has stood for an hour or two, with occasional shaking, it is filtered with suction, washed with water, and dried on porous tile at room temperature. The product weighs 29–30 g. (70–72%) and melts at 172–175° with vigorous decomposition.

2. Notes

1. Since the reaction is catalyzed by hydroxide ions, the amount of base may be varied within wide limits. It is advantageous to grind the solid reactants with 50 ml. of water before the alkali is added.

3. Discussion

Diphenyliodonium iodide is obtained when sulfur dioxide or aqueous potassium iodide is added to a solution containing diphenyliodonium iodate.[1,2] Such solutions have been prepared by the action of moist silver oxide, or of aqueous sodium or potassium hydroxide, on an equimolar mixture of iodosobenzene and iodoxybenzene;[1,2] by shaking iodosobenzene with moist silver oxide;[3] by shaking iodoxybenzene with

sodium hydroxide;[2] and by steam distillation of a mixture of iodosobenzene and iodoxybenzene.[2] Diphenyliodonium iodide has been prepared by heating iodoxybenzene with aqueous potassium iodide and barium hydroxide.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 483
- Org. Syn. Coll. Vol. 3, 485
- Org. Syn. Coll. Vol. 6, 928

References and Notes

1. Hartmann and Meyer, *Ber.*, **27**, 504, 506 (1894).
2. Hartmann and Meyer, *Ber.*, **27**, 1598 (1894).
3. Hartmann and Meyer, *Ber.*, **27**, 503 (1894).
4. Willgerodt, *Ber.*, **29**, 2009 (1896).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium or potassium hydroxide

sodium hydroxide (1310-73-2)

silver oxide (20667-12-3)

sulfur dioxide (7446-09-5)

potassium iodide (7681-11-0)

barium hydroxide (17194-00-2)

DIPHENYLIODONIUM IODIDE (2217-79-0)

Iodosobenzene (536-80-1)

Iodoxybenzene (696-33-3)

diphenyliodonium iodate

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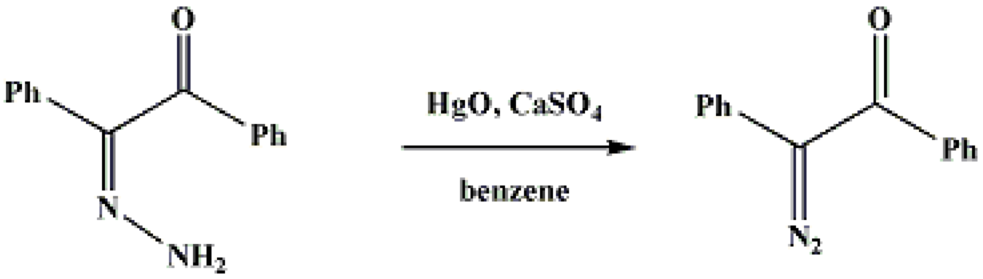
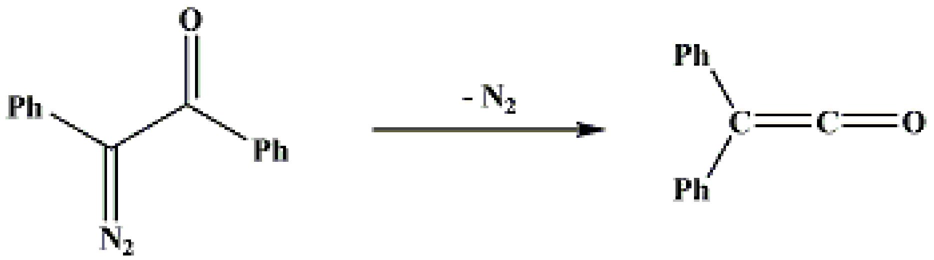
Organic Syntheses, CV 3, 356

DIPHENYLKETENE

[Ketene, diphenyl-]





Submitted by Lee Irvin Smith and H. H. Hoehn.
Checked by Nathan L. Drake and Jonathan Williams.

1. Procedure

Fifty-six grams (0.25 mole) of benzil monohydrazone [*Org. Syntheses*, **15**, 62 (1935)] (Note 1) is mixed in a mortar with 81 g. (0.38 mole) of yellow mercuric oxide and 35 g. of anhydrous calcium sulfate (Note 2). The mixture is introduced into a 1-l. three-necked flask fitted with a stirrer, a condenser, and a thermometer. The flask is placed in a water bath, 200 ml. of dry thiophene-free benzene is added, and the suspension is stirred at 25–35° (thermometer in solution) for 4 hours (Note 3) and (Note 4). The reaction mixture is filtered through a fine-grained filter paper, with slight suction, and the residue is washed with dry benzene until the washings are colorless.

The benzene solution of the diazo compound is poured into a separatory funnel protected with a drying tube and connected to a 125-ml. Claisen distilling flask provided with a condenser set for downward distillation and arranged so that it can be heated in a bath of Wood's metal. The temperature of the metal bath being maintained at 100–110°, the benzene solution is dropped slowly into the hot flask. Under these conditions, the benzene is removed by distillation and the diazo compound is transformed into diphenylketene. The residue is distilled under reduced pressure in an atmosphere of nitrogen, and the fraction boiling at 115–125° at 3–4 mm. (Note 5) is collected. The yield is 31 g. (64%) of a product which, on redistillation, yields 28 g. of diphenylketene boiling at 119–121° at 3.5 mm. (58%).

Diphenylketene is best stored in an atmosphere of nitrogen; the addition of a small crystal of hydroquinone serves to inhibit polymerization (Note 6).

2. Notes

1. Benzil monohydrazone can also be obtained in practically quantitative yield using hydrazine hydrate, a method first suggested by Curtius and Thun.[1] Hydrazine hydrate (45 g., 0.75 mole, of an 85% solution of hydrazine hydrate in water) is slowly dropped into a hot solution of benzil (158 g., 0.75 mole) in alcohol (300 ml.) with stirring. The product begins to separate from the hot solution after three-fourths of the hydrazine hydrate has been added. The solution is heated under reflux for 5 minutes after all the hydrazine hydrate has been added. The flask is then cooled to 0°, and the hydrazone is filtered off and washed twice on the funnel with 100-ml. portions of cold ethanol. The product melts at 149–151° with decomposition.
2. Anhydrous calcium sulfate removes the water formed in the oxidation.
3. Considerable heat is generated at the beginning of the reaction, and ice must be used in the water bath to keep the temperature within the prescribed limits. After 10–15 minutes the ice is removed, and the temperature is maintained at 25–35° by the water bath.
4. Best results are obtained when the reaction mixture is stirred for 4 hours.
5. A viscous red residue always remains in the distilling flask, necessitating superheating to remove the last traces of diphenylketene.
6. According to the submitters, the preparation has been carried out using twice the quantities of material throughout with no loss in yield of diphenylketene.

3. Discussion

Diphenylketene has been prepared by action of tripropylamine on diphenylacetyl chloride,[2] by treating diphenylchloroacetyl chloride with granulated zinc,[3] and by the action of quinoline on diphenylacetyl chloride.[4] It is most conveniently prepared by heating phenylbenzoyldiazomethane—a method first described by Schroeter[5] and later used by Staudinger.[6]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 496
- Org. Syn. Coll. Vol. 6, 392
- Org. Syn. Coll. Vol. 6, 549

References and Notes

1. Curtius and Thun, *J. prakt. Chem.*, (2) **44**, 176 (1891).

2. Staudinger, *Ber.*, **44**, 1619 (1911).
3. Staudinger, *Ber.*, **38**, 1735 (1905).
4. Staudinger, *Ber.*, **40**, 1148 (1907).
5. Schroeter, *Ber.*, **42**, 2346 (1909).
6. Staudinger, *Ber.*, **44**, 1623 (1911).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

Benzene (71-43-2)

hydroquinone (123-31-9)

nitrogen (7727-37-9)

mercuric oxide (21908-53-2)

calcium sulfate (7778-18-9)

Benzil (134-81-6)

zinc (7440-66-6)

hydrazine hydrate (7803-57-8)

Quinoline (91-22-5)

Benzil monohydrazone (5344-88-7)

Diphenylacetyl chloride (1871-76-7)

Diphenylketene, Ketene, diphenyl- (525-06-4)

tripropylamine (102-69-2)

diphenylchloroacetyl chloride (2902-98-9)

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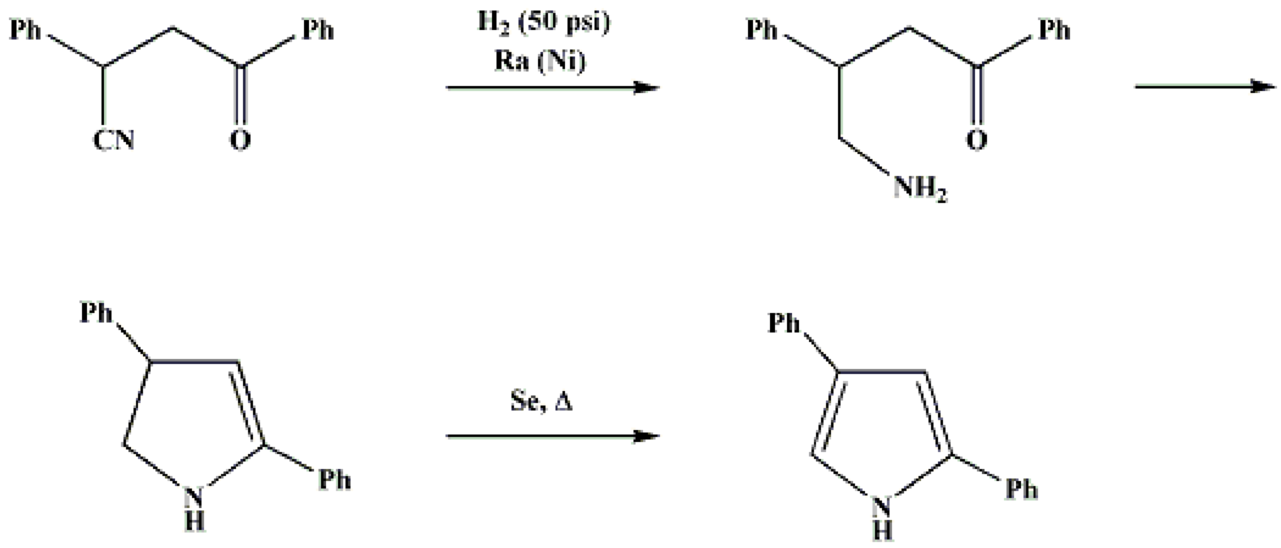
Organic Syntheses, CV 3, 358

2,4-DIPHENYLPYRROLE

[Pyrrole, 2,4-diphenyl-]



Submitted by C. F. H. Allen and C. V. Wilson.
Checked by Arthur C. Cope, Frank S. Fawcett, and Harold R. Nace.

1. Procedure

A suspension of 61 g. (0.26 mole) of α-phenyl-β-benzoylpropionitrile[1] (Note 1) in 150 ml. of methanol and 1 level teaspoonful of Raney nickel catalyst[2,3] (Note 2) are placed in a 400–500 ml. pressure bottle (Note 3) connected to a low-pressure reduction apparatus. The bottle is alternatively evacuated and filled with hydrogen twice, and the reduction is conducted at 80–90° by shaking with hydrogen at an initial pressure of 50 lb. After 2 moles of hydrogen is absorbed the reduction is discontinued, the solution is filtered to separate the catalyst, and the solvent is removed from the green filtrate by distillation under reduced pressure. The crude 2,4-diphenyl-2-pyrroline (Note 4) is rinsed into a 300-ml. Kjeldahl flask with a little methanol, which is removed by distillation at reduced pressure (water pump) while the flask is immersed in a bath at 100°. Selenium (10 g.) is added, and the mixture is heated in a metal bath at 245–265° for 5 hours while a slow stream of nitrogen is passed over the surface of the liquid. This operation is conducted in a well-ventilated hood. The molten mass is poured from the reaction flask into a beaker (Note 5), and the product is extracted with 300 ml. of boiling toluene. The green toluene solution is filtered through a cotton plug to remove a small amount of suspended selenium, and the filtrate is cooled. The 2,4-diphenylpyrrole separates as light green crystals which melt at 174–176° and weigh 24–26 g. (42–46%) (Note 6). A second crop of 2–3 g. (4–5%), m.p. 160–170°, can be obtained by concentrating the filtrate and cooling.

2. Notes

1. The α-phenyl-β-benzoylpropionitrile[1] was used without recrystallization (m.p. 123–125°).
2. The time required for the hydrogenation was 2.5 hours with a very active nickel catalyst,

and longer with a less active catalyst. Raney nickel prepared according to [2] is a particularly active catalyst and gives excellent results in this preparation.
3. A 500-ml. Pyrex centrifuge bottle is satisfactory.
4. The submitters state that distillation yields pure 2,4-diphenyl-2-pyrroline, b.p. 170–172°/3 mm., 203–205°/8 mm., which solidifies on cooling (yield 80–90%).
5. If the contents of the flask are not poured into a beaker while molten, it is difficult to remove the cake of selenium. If more than one preparation is to be made, the contents of the flask are allowed to cool and the product is extracted with hot toluene. The selenium can be reused.
6. The product is sufficiently pure for most purposes. Recrystallization from toluene gives a 90–93% recovery of a very light-green product, m.p. 179–180° (cor.). The submitters state that the product obtained in the first crystallization has this melting point if the 2,4-diphenyl-2-pyrroline is purified by distillation before dehydrogenation.

3. Discussion

2,4-Diphenylpyrrole has been prepared only by dehydrogenation of 2,4-diphenyl-2-pyrroline with selenium, Raney nickel, and nickel supported on pumice.[4]

References and Notes

1. *Org. Syntheses* Coll. Vol. **2**, 498 (1943)
2. Pavlic and Adkins, *J. Am. Chem. Soc.*, **68**, 1471 (1946).
3. *Org. Syntheses* Coll. Vol. **3**, 176, 181 (1954).
4. Rogers, *J. Chem. Soc.*, **1943**, 594.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

methanol (67-56-1)

hydrogen (1333-74-0)

nitrogen (7727-37-9)

nickel, Raney nickel (7440-02-0)

toluene (108-88-3)

selenium

α-Phenyl-β-benzoylpropionitrile (6268-00-4)

2,4-Diphenylpyrrole, Pyrrole, 2,4-diphenyl- (3274-56-4)

2,4-Diphenyl-2-pyrroline

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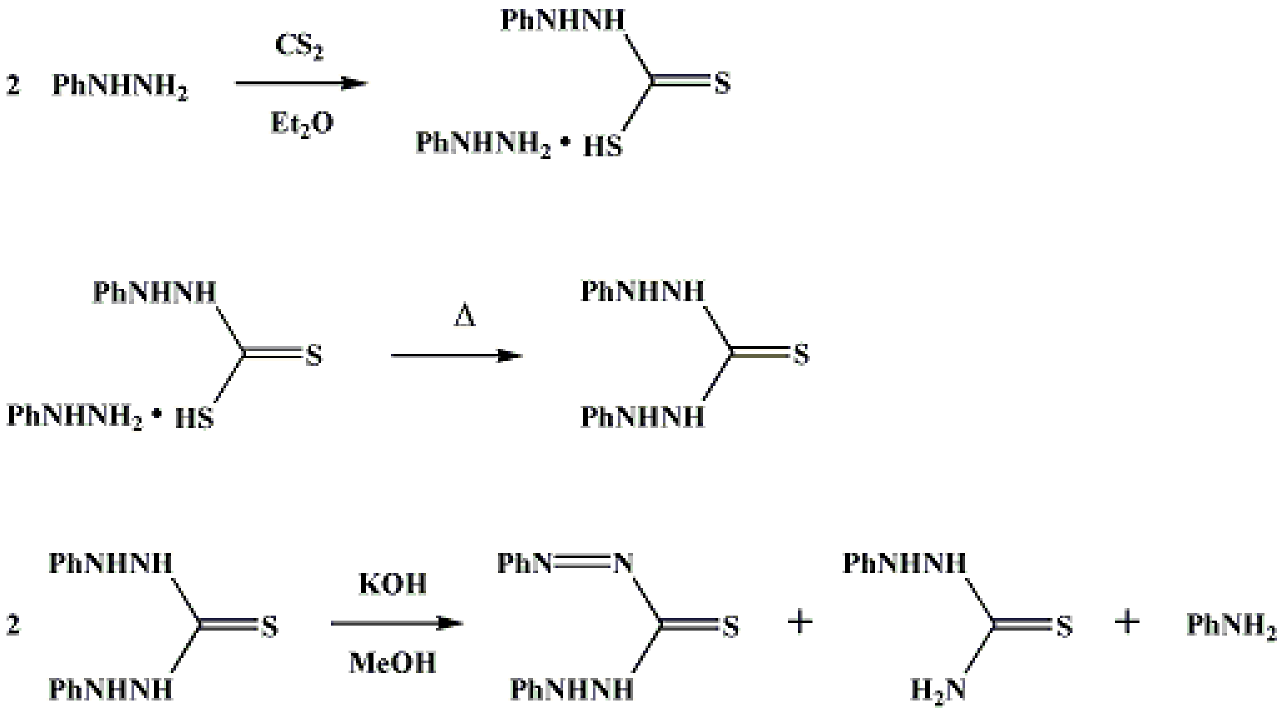
Organic Syntheses, *CV 3, 360*

DITHIZONE



Submitted by John H. Billman and Elizabeth S. Cleland.
Checked by Lee Irvin Smith and Burris D. Tiffany.

1. Procedure

A. *Phenylhydrazine salt of β-phenyldithiocarbazic acid*. In a 1-l. three-necked flask, fitted with a mechanical stirrer, a condenser, and a dropping funnel, is placed a solution of 128 ml. (1.3 moles) of pure redistilled phenylhydrazine in 600 ml. of ordinary ether. To the vigorously stirred mixture, 52 ml. (0.86 mole) of carbon disulfide is added in the course of 30 minutes (Note 1). After the mixture has been stirred for an additional 30 minutes, the precipitate is filtered with suction, washed with 50 ml. of ether, and spread on filter paper for 15–20 minutes to allow evaporation of the ether. The yield of the salt is 181–185 g. (96–98%).

B. *Diphenylthiocarbazide*. The above salt is transferred to a 1-l. beaker, and, while it is continuously stirred by hand (Note 2), it is heated (hood) in a water bath maintained at 96–98° (Note 3). After about 10–15 minutes the material softens to a taffylike mass, becomes yellow, foams, and evolves hydrogen sulfide. After about 20–30 minutes ammonia is evolved. When a distinct odor of ammonia is *first detected* (Note 4), the beaker is removed from the bath, placed in a pan of cold water for 1 minute (Note 5), and then surrounded immediately by cracked ice. About 150 ml. of absolute ethanol is added, the mixture is warmed slightly to loosen the mass, and the taffylike material is stirred until it is transformed into a granular precipitate. After the mixture has stood at room temperature for 1 hour, the precipitate is collected on a Büchner funnel and washed with 50 ml. of absolute ethanol (Note 6). The yield of crude diphenylthiocarbazide is 100–125 g. (60–75% based on phenylhydrazine) (Note 7).

C. *Dithizone*. The crude diphenylthiocarbazide is added to a solution of 60 g. of potassium

hydroxide in 600 ml. of methanol in a 1-l. round-bottomed flask. The flask is immersed in a boiling water bath, and the mixture is *refluxed* for exactly 5 minutes (Note 8). The red solution is cooled with ice water and filtered by gravity. Ice-cold 1 *N* sulfuric acid (900–1100 ml.) is added to the filtrate, which is stirred vigorously by means of a mechanical stirrer, until the solution is just acid to Congo red paper (Note 9). The blue-black precipitate is filtered with suction and washed with 50 ml. of cold water (Note 10). The crude carbazone is dissolved in 500 ml. of 5% sodium hydroxide solution, the mixture is filtered with suction, and the filtrate is cooled in an ice bath and acidified immediately with ice-cold 1 *N* sulfuric acid (about 650 ml. is required) until it is just acid to Congo red paper. The precipitate is filtered with suction and then washed by transferring it to a 2-l. beaker and stirring it thoroughly with 1.6–1.8 l. of cold water. The mixture is filtered, and the process of washing is repeated until there is no trace of sulfate in the washings (Note 11). After air has been drawn through the precipitate on the Büchner funnel for 20–30 minutes, the solid is dried in an oven at 40°. The product at this stage weighs 63–85 g. For purification, a portion of 5–10 g. of the carbazone is placed in the thimble of a Soxhlet extractor (Note 12), covered with ether, allowed to stand for 1 hour, and then extracted for 1.5 hours. The material in the thimble is transferred immediately to a beaker, stirred with 50 ml. of ether, and the mixture is filtered with suction until most, but not all, of the liquid is removed. The wet product is then dried by pressing it between filter papers. The yield of pure dithizone (diphenylthiocarbazone) which decomposes sharply at a temperature between 165° and 169° is 43–54.8 g. (50–64% based on phenylhydrazine) (Note 13).

2. Notes

1. A precipitate is formed immediately upon addition of the carbon disulfide; the mixture becomes warm, and the temperature soon approaches the boiling point. The temperature is maintained just below the boiling point; cooling with ice water may be necessary to keep it there. As the carbon disulfide is added, the mixture soon becomes pasty, then more fluid, and finally pasty again.
2. A heavy glass rod, bent or flattened at the bottom, serves as an efficient stirrer.
3. Care must be taken that the temperature of the bath does not exceed 98°. If the material remains above 98° for a long period of time and/or if it is not immediately cooled after removal from the water bath, the product decomposes violently after standing for 10–15 minutes.
4. Ammonia can be detected by means of litmus paper before the odor is noticeable, but the heating should be continued until there is a *distinct* odor of ammonia (but no longer). The yield depends upon the rapidity with which the heating is stopped after the first sign of ammonia is detected.
5. The mass may be olive-green or brown while hot, but it becomes light brown on cooling.
6. The precipitate is almost pure white. More diphenylthiocarbazide crystallizes from the red alcoholic filtrate and washings, if they are allowed to evaporate slowly. When the mixture is allowed to stand for some time before it is filtered, the amount of precipitate is increased and that of the material left in the filtrate is decreased.
7. Diphenylthiocarbazide does not have a sharp melting point. The compound is reported to become green at 130° and melt at 150° to a dark green liquid which decomposes on further heating.
8. The solution is heated until it is definitely boiling; then it is allowed to boil for 5 minutes only. If the solution is boiled for a longer time, the yield of product is decreased.
9. When the end point is reached, the mother liquor is no longer red but colorless.

10. Care should be exercised in handling this precipitate or suspensions of it. If any of it is spilled or splashed, it should be removed at once, for it dries to a light, fine powder which is readily scattered; it dyes the skin black and other material pink.
11. Four or five washings are usually necessary.
12. The Soxhlet extractor used by the submitters had a capacity of 85 ml. to the top of the siphon tube. The size of the thimble was 33 by 80 mm.
13. The pure compound is completely soluble in chloroform.

3. Discussion

This method of preparation is a modification of the method used by Emil Fischer.[1] Similar methods have been described by H. Fischer,[2] Wertheim,[3] and Grummitt and Stickle.[4]

References and Notes

1. E. Fischer, *Ann.*, **190**, 118 (1878); **212**, 316 (1882).
2. H. Fischer and Leopoldi, *Wiss. Veröffentl. Siemens-Konzern*, **12**, 44 (1933) [*C. A.*, **27**, 3418 (1933)].
3. Wertheim, *Organic Chemistry Laboratory Guide*, 2nd ed., p. 504, P. Blakiston's Son & Co.
4. Grummitt and Stickle, *Ind. Eng. Chem., Anal. Ed.*, **14**, 953 (1942).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

sulfuric acid (7664-93-9)

ammonia (7664-41-7)

methanol (67-56-1)

ether (60-29-7)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

hydrogen sulfide (7783-06-4)

Phenylhydrazine (100-63-0)

potassium hydroxide (1310-58-3)

carbon disulfide (75-15-0)

Dithizone (60-10-6)

diphenylthiocarbazide (622-03-7)

diphenylthiocarbazone

Phenylhydrazine salt of β-phenyldithiocarbazic acid

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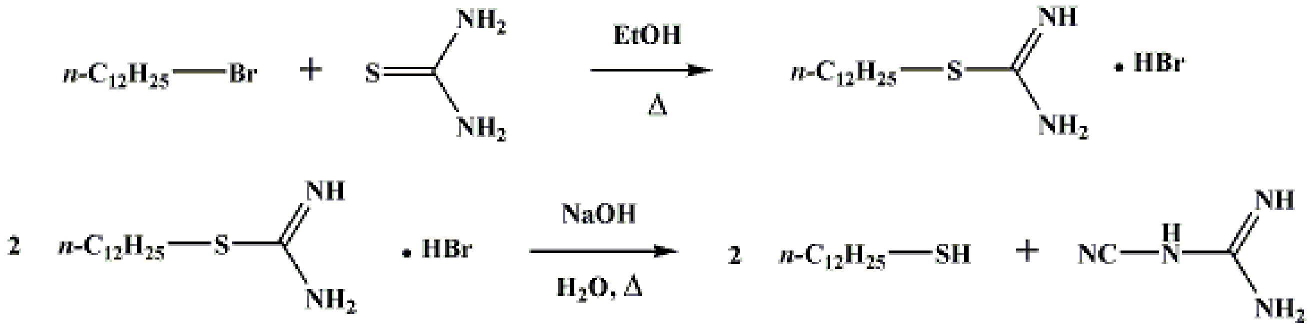
Organic Syntheses, CV 3, 363

n-DODECYL (LAURYL) MERCAPTAN



Submitted by G. G. Urquhart, J. W. Gates, Jr., and Ralph Connor.
Checked by Lee Irvin Smith, R. T. Arnold, and Kenneth Stevenson.

1. Procedure

A mixture of 125 g. (0.5 mole) of *n*-dodecyl bromide (Note 1), 38 g. (0.5 mole) of thiourea, and 250 ml. of 95% ethanol is refluxed on a steam cone for 3 hours (Note 2), (Note 3), and (Note 4). A solution of 30 g. (0.75 mole) of sodium hydroxide in 300 ml. of water is added, and the mixture is refluxed for 2 hours. During this period the mercaptan separates as a pink to red oil. The layers are separated, and the aqueous layer is acidified with dilute sulfuric acid (7 ml. of concentrated acid to 50 ml. of water) and then extracted with one 75-ml. portion of benzene (Note 5). The extract is added to the crude mercaptan layer, and the whole is washed twice with 200-ml. portions of water and then dried over 20 g. of anhydrous sodium sulfate (Note 6). The solvent is removed and the residual oil distilled from a modified Claisen flask. There is no appreciable fore-run (Note 6). The yield of *n*-dodecyl mercaptan, b.p. 165–169°/39 mm., is 80–84 g. (79–83%) (Note 7) and (Note 8).

2. Notes

1. The preparation of lauryl bromide has been described [*Org. Syntheses* Coll. Vol. **1**, 29 (1941)], but the following modification avoids the emulsion formed in washing lauryl bromide with sulfuric acid. The crude bromide from the reaction mixture is washed thoroughly with water and then with potassium carbonate solution. The washing with water must be thorough enough to remove most of the acid in order to prevent the formation of heavy foam by the carbonate. The bromide is then dried over calcium chloride and distilled. The distillate is washed with concentrated sulfuric acid and treated as described (*loc. cit.*). The checkers, however, found the method using anhydrous hydrogen bromide [*Org. Syntheses* Coll. Vol. **2**, 246 (1943)] to be preferable.
2. The intermediate laurylisothiourea hydrobromide may be obtained by cooling the ethanol solution in ice and filtering the precipitate. It may be further purified by washing with ether. An alternative method gives more satisfactory results. The ethanol solution is diluted with 150 ml. of water and heated until the solution is homogeneous, and then, after cooling slightly, 200 ml. of concentrated hydrochloric acid is added; the laurylisothiourea hydrochloride separates quantitatively as a waxy white solid.
3. The reflux period required for complete reaction varies considerably with the structure of the halide. Some alkyl bromides require more than 3 hours. Alkyl chlorides frequently require 16 hours and occasionally as much as 24 hours.
4. This procedure is useful for the preparation of other mercaptans. The yields are of the same order. The boiling points are as follows:

n-Heptyl	174–176°
n-Octyl	198–200°; 98–100°/22 mm.

n-Nonyl	220–222°;	98–100°/15 mm.
n-Decyl	88–91°/2 mm.;	96–97°/5 mm.
n-Undecyl		103–104°/3 mm.
n-Octadecyl		170–175°/4 mm.

5. Although benzene is the most satisfactory solvent for this extraction, emulsions are sometime produced when it is used for the extraction of other mercaptans. To obviate this difficulty the same amount of ether may be used, provided that the ethanol is first removed by distillation on a steam bath.
6. If the ether extracts are not thoroughly dry, the mercaptan appears slightly cloudy on subsequent distillation. The checkers found that this cloudiness was frequently due to colloidal sulfur. The sulfur can be removed by shaking an ether solution of the cloudy product with bone black, then filtering and distilling.
7. The odor of lauryl mercaptan is not disagreeable, and no unusual precautions need be taken in working with it. With lower-molecular-weight mercaptans a trap containing alkaline potassium permanganate solution will prevent the escape of unpleasant odors.
8. Other boiling points: 107–109°/2 mm.; 133–135°/7 mm.; 145–147°/15 mm.; 150–152°/20 mm.; 158–160°/28 mm.; 168–170°/38 mm.

3. Discussion

n-Dodecyl mercaptan has been prepared by the action of alkali on the salts of S-*n*-dodecyl thiourea[1] and by reduction of di-*n*-dodecyl disulfide.[2,3]

It has also been prepared from lauryl alcohol by the action of thiourea in the presence of hydrobromic acid, followed by alkaline hydrolysis.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 491

References and Notes

1. Backer, Terpstra, and Dijkstra, *Rec. trav. chim.*, **51**, 1166 (1932).
2. Noller and Gordon, *J. Am. Chem. Soc.*, **55**, 1090 (1933).
3. Henkel et Cie., Fr. pat. 751,117; U. S. pat. 2,031,529 [*C. A.*, **30**, 2202 (1936)].
4. Frank and Smith, *J. Am. Chem. Soc.*, **68**, 2104 (1946).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

calcium chloride (10043-52-4)

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether (60-29-7)

sodium hydroxide (1310-73-2)

HYDROBROMIC ACID, hydrogen bromide (10035-10-6)

Lauryl Bromide, n-DODECYL BROMIDE (143-15-7)

Lauryl alcohol (112-53-8)

sodium sulfate (7757-82-6)

sulfur (7704-34-9)

thiourea (62-56-6)

laurylisothiourea hydrobromide

laurylisothiourea hydrochloride

lauryl mercaptan, n-dodecyl mercaptan (112-55-0)

n-DODECYL (LAURYL) MERCAPTAN

S-n-dodecyl thiourea

di-n-dodecyl disulfide

n-Heptyl mercaptan

n-Nonyl mercaptan

n-Decyl mercaptan

n-Undecyl mercaptan

n-Octadecyl mercaptan

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Organic Syntheses, CV 3, 366

n-DODECYL (LAURYL) *p*-TOLUENESULFONATE

$$p\text{-}CH_3C_6H_4SO_2Cl + CH_3(CH_2)_{10}CH_2OH + C_5H_5N \longrightarrow p\text{-}CH_3C_6H_4SO_3CH_2(CH_2)_{10}CH_3 + C_5H_5NH^+Cl^-$$

Submitted by C. S. Marvel and V. C. Sekera.
Checked by C. F. H. Allen and C. V. Wilson.

1. Procedure

In a 1-l. three-necked flask fitted with a stirrer and thermometer are placed 93 g. (0.5 mole) of dodecanol (Note 1) and 158 g. (2 moles) of pyridine. The flask is surrounded by a water bath sufficiently cold to lower the temperature of the mixture to 10°. At this temperature 105 g. (0.55 mole) of *p*-toluenesulfonyl chloride is added in portions over a 20- to 30-minute period, or at such a rate that the temperature does not exceed 20° at any time. The mixture is then stirred for 3 hours at a temperature below 20°, after which it is diluted with 300 ml. of hydrochloric acid (sp. gr. 1.19) in 1 l. of ice water. The ester which crystallizes is collected on a chilled Büchner funnel and sucked as dry as possible. The solid is transferred to a 600-ml. beaker, 250–300 ml. of methanol is added, and the mixture is warmed on the steam bath until the ester melts. It is then cooled in a freezing mixture while being stirred continuously; the ester separates in a fairly fine state. It is then collected on a chilled funnel and allowed to dry in the air, preferably at a temperature below 20°. The yield of ester is 152–156 g. (88–90% based upon the dodecanol used). It melts at 20–25° (Note 2) and is sufficiently pure for most purposes.

If a purer product is desired, it is recrystallized from petroleum ether (b.p. 30–60°), using 4 ml. per 3 g., and drying over anhydrous sodium sulfate. The solution is chilled to 0° and the ester filtered on a chilled funnel; the recovery is 90%, and the melting point is 28–30°. Evaporation of the solvent to a small volume deposits an additional amount (Note 3).

2. Notes

1. Dodecanol (lauryl alcohol), m.p. 20–22°; pyridine, b.p. 113–115°; and *p*-toluenesulfonyl chloride, m.p. 66–68°, are used.
2. The ester contains traces of water, which makes the melting point unreliable; the freezing point is 24–25°.
3. The following esters have been made in essentially the same yields; butyl *p*-toluenesulfonate [*Org. Syntheses* Coll. Vol. **1**, 145 (1941)]; *n*-tetradecyl *p*-toluenesulfonate, m.p. 35°; *n*-hexadecyl *p*-toluenesulfonate, m.p. 49°; *n*-octadecyl *p*-toluenesulfonate, m.p. 56°; *n*-decyl *p*-bromobenzenesulfonate, m.p. 43–44°; *n*-dodecyl *p*-bromobenzenesulfonate, m.p. 49°; *n*-tetradecyl *p*-bromobenzenesulfonate, m.p. 51.5°; *n*-hexadecyl *p*-bromobenzenesulfonate, m.

p. 60°; *n*-octadecyl *p*-bromobenzenesulfonate, m.p. 64–65°.

3. Discussion

n-Dodecyl *p*-toluenesulfonate has been prepared only by the action of *p*-toluenesulfonyl chloride on dodecanol-1 in the presence of pyridine[1] according to the general procedure developed by Patterson and Frew[2] for making esters of sulfonic acids.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 376
- Org. Syn. Coll. Vol. 6, 652

References and Notes

1. Sekera and Marvel, *J. Am. Chem. Soc.*, **55**, 345 (1933).
2. Patterson and Frew, *J. Chem. Soc.*, **89**, 332 (1906).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

hydrochloric acid (7647-01-0)

methanol (67-56-1)

Lauryl alcohol, dodecanol, dodecanol-1 (112-53-8)

sodium sulfate (7757-82-6)

pyridine (110-86-1)

p-Toluenesulfonyl chloride (98-59-9)

n-Dodecyl p-toluenesulfonate (10157-76-3)

Butyl p-toluenesulfonate (778-28-9)

n-DODECYL (LAURYL) p-TOLUENESULFONATE

n-tetradecyl p-toluenesulfonate

n-hexadecyl p-toluenesulfonate

n-octadecyl p-toluenesulfonate (3386-32-1)

n-decyl p-bromobenzenesulfonate

n-dodecyl p-bromobenzenesulfonate

n-tetradecyl p-bromobenzenesulfonate

n-hexadecyl p-bromobenzenesulfonate

n-octadecyl p-bromobenzenesulfonate

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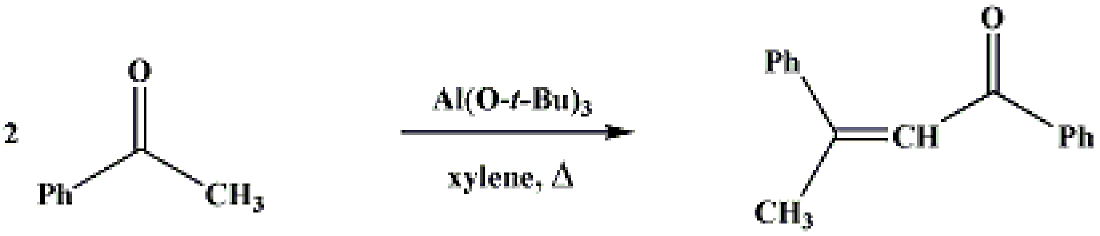
Organic Syntheses, CV 3, 367

DYPNONE



Submitted by Winston Wayne and Homer Adkins.
Checked by Nathan L. Drake, Wm. H. Souder, Jr., and Ralph Mozingo.

1. Procedure

In a 1-l. round-bottomed three-necked flask, equipped with a thermometer, an efficient mechanical stirrer (Note 1), and a 35-cm. Vigreux column fitted to a condenser and receiver protected by a calcium chloride tube, are placed 345 g. (400 ml.) of dry xylene, 120 g. (117 ml., 1 mole) of dry acetophenone, and 135 g. (0.55 mole) of aluminum *tert*-butoxide (p. 48) (Note 2). The stirrer is started and the flask heated in an oil bath so that the temperature of the reaction mixture is held between 133° and 137°. *tert*-Butyl alcohol slowly distils at a temperature in the vapor of 80–85°. The distillation of the alcohol can be accomplished by maintaining the temperature of the heating bath between 150° and 155° for 2 hours after distillation has commenced (Note 3) and (Note 4).

The reaction mixture is cooled to 100°, and 40 ml. of water is added cautiously in small portions with continued stirring. As the water is added the mixture sets to a gel, and then, upon the addition of the remainder of the water and gentle tapping of the reaction flask, the stiff mass breaks up and boiling begins. Refluxing is continued by heating the oil bath for another 15 minutes to ensure the complete hydrolysis of the aluminum *tert*-butoxide.

After cooling, the reaction mixture is transferred in nearly equal portions to four centrifuge bottles and the aluminum hydroxide is centrifuged out (Note 5). The upper liquid layer is removed, and the aluminum hydroxide is worked up to a smooth paste, by means of a spatula, with a total of approximately 250 ml. of ether for the four portions. The aluminum hydroxide is again centrifuged out and the ether extract poured off. The centrifuging is repeated three more times so that approximately a liter of ether is used to separate the product from the aluminum hydroxide (Note 6).

Ether and *tert*-butyl alcohol are removed by distillation at atmospheric pressure without a column, and the xylene is removed by distillation through a 35-cm. Vigreux column at 25–50 mm. The residue is transferred to a smaller flask, and the acetophenone is first distilled at about 80°/10 mm., and finally the dypnone is distilled at 150–155°/1 mm. (Note 7) and (Note 8). The yield is 85–91 g. (77–82%) of a yellow

liquid.

2. Notes

1. Instead of the customary mercury seal, a simple rubber tube seal suggested by Dr. L. P. Kyrides is recommended. The upper end of an 8-cm. length of 10-mm. glass tubing, projecting through a stopper, is fitted with a 2-cm. piece of 6-mm. rubber tubing so that it projects 5 mm. beyond the end of the glass tube. This projecting portion fits snugly to form a seal round an 8-mm. stirrer shaft running through the glass tubing. Glycerol is applied at the point of contact of glass and rubber to act as a lubricant and sealing medium. This type of seal can be conveniently used with reduced pressure down to 10 mm.
2. Slightly more than a mole of aluminum *tert*-butoxide is used for each mole of water split out as the alkoxide loses its effectiveness after the replacement of one alkoxyl by an hydroxyl group.
3. The reaction may proceed so vigorously at first that the distillation temperature will rise to 100° or above. This is not detrimental and the temperature will soon fall.
4. As the reaction proceeds the color changes from yellow to deep orange and the mixture becomes viscous. After about 45 minutes the distillation temperature begins to fall and eventually reaches 70° owing to the formation of butylene from the aluminum *tert*-butoxide which decomposes slightly at this temperature.
5. Ordinary undried ether is used in balancing the centrifuge bottles, in removing any aluminum hydroxide and product remaining in the flask, and in the subsequent extraction of the aluminum hydroxide.
6. This method eliminates the washing and drying of the customary extraction. procedure. The small amount of water present distils off with the solvent. The extraction should be done carefully and thoroughly. If it has been carried out properly the aluminum hydroxide will be white or faintly yellow and at least 95% of the original acetophenone can be accounted for after the final distillation.
7. The acetophenone and dypnone are easily separated in any of the common types of fractionating columns. The column should be short (12–18 cm.) and electrically heated because of the high boiling point of the product. An undistillable residue of 5–10 g. remains.
8. The boiling point varies greatly with the rate of distillation and the amount of ebullition.

3. Discussion

Dypnone has been prepared by the action of sodium ethoxide,[1] aluminum bromide,[2] phosphorus pentachloride,[3] aluminum triphenyl,[4] zinc diethyl,[5] calcium hydroxide,[6] anhydrous hydrogen chloride,[5,7] anhydrous hydrogen bromide,[8] aluminum chloride,[4] aluminum *tert*-butoxide,[9] and hydrogen fluoride[10] on acetophenone. It has been obtained by the action of aniline hydrochloride on acetophenone anil followed by

treatment with hydrochloric acid.[11] The preparation of aluminum *tert*-butoxide has been described.[9,12,13] The procedure described is a modification of that by Adkins and Cox.[9]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 188
- Org. Syn. Coll. Vol. 3, 387
- Org. Syn. Coll. Vol. 4, 291
- Org. Syn. Coll. Vol. 4, 427
- Org. Syn. Coll. Vol. 4, 881

References and Notes

1. Eijkman, *Chem. Weekblad*, **1**, 349 (1904).
2. Konowalow and Finogejew, *J. Russ. Phys. Chem. Soc.*, **34**, 944 (1902) [*Chem. Zentr.*, **74**, I, 521 (1903)].
3. Taylor, *J. Chem. Soc.*, **1937**, 304.
4. Calloway and Green, *J. Am. Chem. Soc.*, **59**, 809 (1937).
5. Henrich and Wirth, *Monatsh.*, **25**, 423 (1904).
6. Porlezza and Gatti, *Gazz. chim. ital.*, **56**, 265 (1926).
7. Delacre, *Bull. classe sci. Acad. roy. Belg.*, (3) **20**, 467 (1898); Colonge, *Bull. soc. chim. France*, (4) **49**, 426 (1931); Kohler, *Am. Chem. J.*, **31**, 642 (1904).
8. Müller and Spinosa-Stöckel, *Österr. Chem. Ztg.*, **49**, 130 (1948).
9. Adkins and Cox, *J. Am. Chem. Soc.*, **60**, 1151 (1938).
10. Simons and Ramler, *J. Am. Chem. Soc.*, **65**, 1390 (1943).
11. Reddelien, *Ber.*, **46**, 2712 (1913).
12. Oppenauer, *Rec. trav. chim.*, **56**, 137 (1937).
13. *Org. Syntheses* Coll. Vol. **3**, 48 (1954).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

aluminum triphenyl

zinc diethyl

acetophenone anil

hydrogen chloride, hydrochloric acid (7647-01-0)

ether (60-29-7)

phosphorus pentachloride (10026-13-8)

glycerol (56-81-5)

hydrogen bromide (10035-10-6)

aniline hydrochloride (142-04-1)

hydrogen fluoride (7664-39-3)

Acetophenone (98-86-2)

aluminum chloride (3495-54-3)

sodium ethoxide (141-52-6)

calcium hydroxide

xylene (106-42-3)

aluminum bromide

aluminum hydroxide

butylene

tert-butyl alcohol (75-65-0)

ALUMINUM tert-BUTOXIDE

Dypnone (495-45-4)

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Organic Syntheses, CV 3, 370

β-ETHOXYETHYL BROMIDE

[Ethane, 1-bromo-2-ethoxy-]

Submitted by George C. Harrison and Harvey Diehl.
Checked by R. L. Shriner and C. H. Tilford.

1. Procedure

In a 2-l. three-necked flask, fitted with a mechanical stirrer (Note 1), a reflux condenser, and a dropping funnel, is placed 630 g. (670 ml., 7 moles) of β-ethoxyethyl alcohol (Note 2). The stirrer is started, and 600 g. (210 ml., 2.2 moles) (Note 3) of phosphorus tribromide is added from the dropping funnel over a period of 1.5–2 hours. The temperature is permitted to rise until the reaction mixture refluxes gently.

The mixture is then distilled, and the distillate boiling below 150° is collected in a 2-l. flask containing 1 l. of water. The lower layer of crude β-ethoxyethyl bromide is separated and dried over 10 g. of calcium chloride. The liquid is decanted and distilled through a 25-cm. fractionating column, and the fraction boiling at 125–127°/760 mm. is collected (Note 4). The yield of pure product is 660–670 g. (65–66% based on the phosphorus tribromide).

2. Notes

1. A rubber sleeve lubricated with a drop of oil provides an effective seal for the stirrer.
2. Technical β-ethoxyethyl alcohol is marketed commercially as Cellosolve; it should be dried over calcium oxide and distilled.
3. A slight excess of β-ethoxyethyl alcohol gives the best results.
4. The first fraction, boiling at 38–40°, is ethyl bromide, and it weighs 120–130 g. Lower yields (56–59%) of β-ethoxyethyl bromide are obtained by distillation without a fractionating column. The residue, however, should not be overheated, for at high temperatures phosphorous acid decomposes to give phosphine and perhaps even elementary phosphorus, and then, when air is admitted to the apparatus an explosion may occur. A minor explosion in connection with this preparation has been reported (N. L. Drake, private communication) and a similar situation has been observed in reactions with phosphorus trichloride.[1]

3. Discussion

β-Ethoxyethyl bromide has been prepared by the action of sodium ethoxide upon ethylene bromide;[2] by the action of bromine upon β-ethoxyethyl iodide;[3] and by the procedure adopted here, which was first used by Chalmers.[4] The action of sodium bromide and sulfuric acid on β-ethoxyethyl alcohol cleaves the ether linkage.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 372

References and Notes

1. Coghill, *J. Am. Chem. Soc.*, **60**, 488 (1938).
2. Foran, *J. Soc. Chem. Ind.*, **44**, 173 (1925).
3. Henry, *Jahresb.*, **1885**, 1163.
4. Chalmers, *Can. J. Research*, **7**, 464 (1932).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

ether (60-29-7)

bromine (7726-95-6)

sodium bromide (7647-15-6)

PHOSPHORUS (7723-14-0)

phosphorus tribromide (7789-60-8)

sodium ethoxide (141-52-6)

phosphorus trichloride (7719-12-2)

ethylene bromide (106-93-4)

calcium oxide

phosphorous acid (13598-36-2)

β-Ethoxyethyl bromide, Ethane, 1-bromo-2-ethoxy- (592-55-2)

β-ethoxyethyl alcohol (110-80-5)

phosphine (7723-14-0)

β-ethoxyethyl iodide

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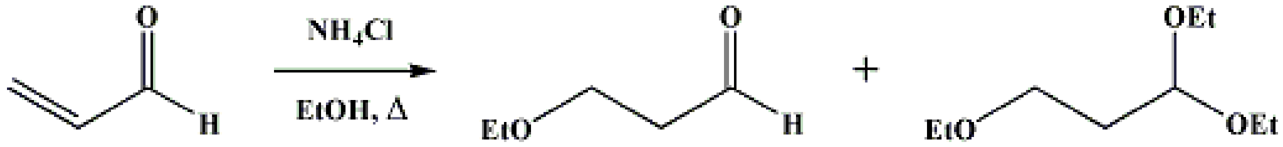
Organic Syntheses, CV 3, 371

β-ETHOXYPROPIONALDEHYDE ACETAL

[Propionaldehyde, β-ethoxy-, diethyl acetal]



Submitted by C. G. Alberti and R. Sollazzo.
Checked by Miriam Sharp, V. L. Stromberg, and E. C. Horning.

1. Procedure

In a 1-l. three-necked round-bottomed flask fitted with a reflux condenser, a mechanical stirrer, and a thermometer dipping below the surface of the mixture are placed 158 g. (2.8 moles) of acrolein (Note 1), 500 ml. of absolute ethanol, and 10 g. of ammonium chloride (Note 2). The material is stirred for 1 hour without external heating; the temperature of the mixture should rise to about 30°. Over a 3-hour period the temperature is raised to 80°, and the mixture is maintained at this temperature for an additional hour. The flask is then cooled, and anhydrous sodium or magnesium sulfate is added as a drying agent.

After 24 hours the mixture is filtered and distilled under reduced pressure through a good column (Note 3). The following fractions are collected (Note 4):

Below 23°/20 mm.	Acrolein and alcohol
38–42°/16 mm.	β-Ethoxypropionaldehyde
75–78°/16 mm.	β-Ethoxypropionaldehyde acetal

The yield of β-ethoxypropionaldehyde is 22–24 g. (7–8%) and of β-ethoxypropionaldehyde acetal is 166–193 g. (31–39%), n_D^{20} 1.4067, d_4^{15} 0.898.

2. Notes

1. Commercial acrolein may be employed. It should be dried over anhydrous sodium sulfate.
2. Reagent grade ammonium chloride is used. It should be washed several times with absolute ethanol.
3. A 1-m. Fenske column packed with 3/32-in. glass helices was employed by the submitters.
4. Ammonium chloride separates during the distillation. It is advisable to decant the liquid into a clean flask for distillation of the last two fractions.

3. Discussion

β-Ethoxypropionaldehyde acetal is best prepared from acrolein by reaction with ethanol.[1,2]

References and Notes

1. Hall and Stern, *Chemistry & Industry*, **1950**, 775.
2. *Org. Syntheses*, **25**, 1 (1945).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

ammonium chloride (12125-02-9)

Acrolein (107-02-8)

sodium sulfate (7757-82-6)

magnesium sulfate (7487-88-9)

β-Ethoxypropionaldehyde acetal (7789-92-6)

Propionaldehyde, β-ethoxy-, diethyl acetal

β-Ethoxypropionaldehyde (2806-85-1)

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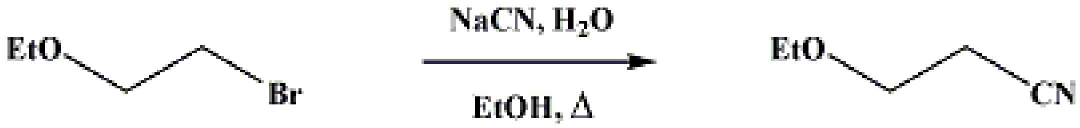
Organic Syntheses, CV 3, 372

β-ETHOXYPROPIONITRILE

[Propionitrile, β-ethoxy-]



Submitted by George C. Harrison and Harvey Diehl.
Checked by R. L. Shriner and C. H. Tilford.

1. Procedure

In a 3-l. three-necked flask, equipped with a Hershberg stirrer, a reflux condenser, and a dropping funnel, are placed 175 g. (3.6 moles) of sodium cyanide and 125 ml. of distilled water (Note 1). The mixture is stirred until the sodium cyanide is dissolved, and then, while vigorous stirring is continued, 535 g. (360 ml., 3.5 moles) of β-ethoxyethyl bromide (p. 370) in 260 ml. of 95% ethanol is added over a period of 15 minutes. The separatory funnel is replaced by a 360° thermometer, and the mixture is stirred and gently refluxed for 10 hours.

The mixture is then fractionally distilled until the temperature reaches 140°. The first fraction boiling at 75–95° consists mostly of ethanol and water, and is discarded. The fraction boiling between 95° and 140° contains water and 25–30 g. of β-ethoxypropionitrile. This is extracted twice with 50-ml. portions of benzene, and the benzene extracts are added to the cooled residue in the distilling flask. The mixture is filtered (Note 2), the solid material is washed with 75 ml. of benzene, which is added to the filtrate, and the whole is distilled. The fraction boiling at 169–174° is collected; it weighs 178–200 g. (52–58%).

2. Notes

1. The reaction should be carried out under the hood.
2. Direct distillation without filtration may result in clogging the condenser by ammonium bromide.

3. Discussion

β-Ethoxypropionitrile has been prepared by the action of potassium cyanide on β-ethoxyethyl bromide.[1] The addition of ethanol to acrylonitrile with sodium ethoxide,[2,3] sodium hydroxide,[3] or benzyltrimethylammonium hydroxide[4] is reported to be a superior procedure. The action of sodium ethoxide on a mixture of β-hydroxypropionitrile and ethyl formate, ethyl benzoate, ethyl bromide, or ethyl sulfate

also results in the formation of β-ethoxypropionitrile.[5]

References and Notes

1. Henry, *Bull. soc. chim. France*, (2) **44**, 458 (1885).
2. Koelsch, *J. Am. Chem. Soc.*, **65**, 437 (1943).
3. MacGregor and Pugh, *J. Chem. Soc.*, **1945**, 535.
4. Utermohlen, *J. Am. Chem. Soc.*, **67**, 1505 (1945).
5. Chelintsev, Benevolenskaya, and Dubinin, *J. Gen. Chem. U.S.S.R.*, **17**, 269 (1947).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

Benzene (71-43-2)

sodium hydroxide (1310-73-2)

sodium cyanide (143-33-9)

ammonium bromide (12124-97-9)

Ethyl bromide (74-96-4)

potassium cyanide (151-50-8)

sodium ethoxide (141-52-6)

β-hydroxypropionitrile (109-78-4)

ethyl benzoate (93-89-0)

ethyl formate (109-94-4)

ethyl sulfate

acrylonitrile (107-13-1)

β-Ethoxyethyl bromide (592-55-2)

β-Ethoxypropionitrile, Propionitrile, β-ethoxy- (2141-62-0)

benzyltrimethylammonium hydroxide (100-85-6)

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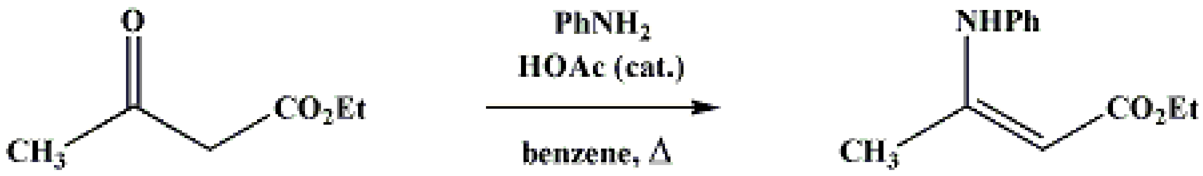
Organic Syntheses, *CV 3, 374*

ETHYL β-ANILINOCROTONATE

[Crotonic acid, β-anilino-, ethyl ester]



Submitted by George A. Reynolds and Charles R. Hauser.
Checked by Arthur C. Cope and William R. Armstrong.

1. Procedure

In a 1-l. round-bottomed flask attached to a Dean and Stark constant water separator (Note 1) which is connected to a reflux condenser are placed 46.5 g. (45.5 ml., 0.5 mole) of redistilled aniline, 65 g. (63.5 ml., 0.5 mole) of commercial ethyl acetoacetate, 100 ml. of benzene, and 1 ml. of glacial acetic acid. The flask is heated in an oil bath at about 125°, and the water which distils out of the mixture with the refluxing benzene is removed at intervals. Refluxing is continued until no more water separates (9 ml. collects in about 3 hours) and then for an additional 30 minutes. The benzene is then distilled under reduced pressure, and the residue is transferred to a 125-ml. modified Claisen flask with an insulated column. The flask is heated in an oil or metal bath maintained at a temperature not higher than 120° while the fore-run of aniline and ethyl acetoacetate is removed by distillation under reduced pressure, and at 140–160° during distillation of the product (Note 2). The yield of ethyl β-anilinocrotonate boiling at 128–130° /2 mm., n_D^{25} 1.5770, is 78–82 g. (76–80%).

2. Notes

1. A Dean and Stark separator made with a stopcock for removal of water[1] or any continuous water separator which will return the benzene to the reaction mixture may be used.
2. The submitters state that if the temperature of the bath rises much above 120° during distillation of the fore-run, or much above 160° during distillation of the product, the ethyl β-anilinocrotonate may be contaminated with diphenylurea, part of which may precipitate from the distillate on standing. Such a precipitate can be removed by adding an equal volume of 30–60° petroleum ether to the distillate and filtering. The petroleum ether is distilled from the filtrate, and the residue is placed in a vacuum desiccator over mineral oil or is redistilled.

3. Discussion

The procedure described is a modification of procedures employed previously. Ethyl β-anilinocrotonate is obtained when the reactants are allowed to stand at room temperature for several days without a catalyst,[2,3,4] or are heated on a steam bath,[4] or are allowed to stand for 12 hours in the presence of a catalytic amount of aniline hydrochloride.[5] Iodine also is a catalyst.[5] Properties of the ester are reported by Coffey, Thomson, and Wilson.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 593

References and Notes

1. Cope, Hofmann, Wyckoff, and Hardenbergh, *J. Am. Chem. Soc.*, **63**, 3452 (1941).
2. Knorr, *Ber.*, **16**, 2593 (1883).
3. Limpach, *Ber.*, **64**, 969 (1931).
4. Conrad and Limpach, *Ber.*, **20**, 944 (1887).
5. Coffey, Thomson, and Wilson, *J. Chem. Soc.*, **1936**, 856.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

acetic acid (64-19-7)

Benzene (71-43-2)

aniline (62-53-3)

aniline hydrochloride (142-04-1)

iodine (7553-56-2)

Ethyl acetoacetate (141-97-9)

diphenylurea (603-54-3)

ETHYL β-ANILINOCROTONATE, Crotonic acid, β-anilino-, ethyl ester (6287-35-0)

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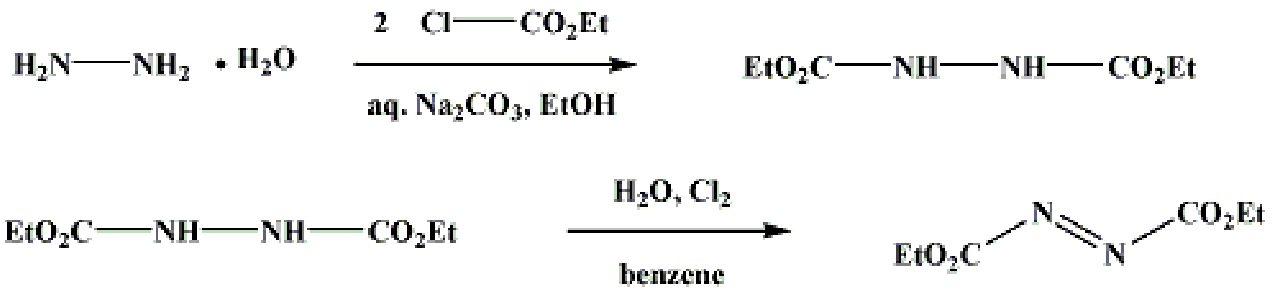
Organic Syntheses, CV 3, 375

ETHYL AZODICARBOXYLATE

[Formic acid, azodi-, diethyl ester]



Submitted by Norman Rabjohn
Checked by H. J. Sampson and R. S. Schreiber.

1. Procedure

A report has been received that a sample of ethyl azodicarboxylate decomposed upon attempted distillation with sufficient violence to shatter the distillation apparatus. It is possible that the explosion may have been due to over chlorination or to insufficient washing of the product with sodium bicarbonate solution. It is recommended that ethyl azodicarboxylate be distilled only behind a safety shield, and protected from direct sources of light.

A. *Ethyl hydrazodicarboxylate.* In a 2-l. three-necked flask, equipped with a mechanical stirrer, two 500-ml. dropping funnels, and a thermometer (Note 1), is placed a solution of 59 g. (1 mole) of 85% hydrazine hydrate in 500 ml. of 95% ethanol. The reaction flask is cooled by means of an ice bath. When the temperature of the solution has dropped to 10°, 217 g. (2 moles) of ethyl chloroformate is added dropwise with stirring at a rate sufficient to maintain the temperature between 15° and 20°. After one-half of the ethyl chloroformate has been introduced, a solution of 106 g. (1 mole) of sodium carbonate in 500 ml. of water is added dropwise simultaneously with the remaining ethyl chloroformate. The addition of these two reactants is regulated so that the temperature does not rise above 20° and so that the addition of the chloroformate is completed slightly in advance of the sodium carbonate in order to ensure a slight excess of ethyl chloroformate in the reaction mixture at all times.

After all the reactants have been added, the precipitate on the upper walls of the flask is washed down with 200 ml. of water and the reaction mixture is allowed to stir for an additional 30-minute period. The precipitate is then collected on a Büchner funnel, washed well with a total of 800 ml. of water, and dried in an oven at 80°. There is obtained 145–150 g. (82–85%) of ethyl hydrazodicarboxylate which melts at 131–133°. It is sufficiently pure (Note 2) for the preparation of ethyl azodicarboxylate.

B. *Ethyl azodicarboxylate.* A mixture of 100 g. (0.57 mole) of ethyl hydrazodicarboxylate, 500 ml. of benzene, and 500 ml. of water is placed in a 2-l. three-necked flask equipped with a mechanical stirrer and a gas inlet tube. The flask and contents are tared, the flask is

placed in an ice bath, and a slow stream of chlorine is bubbled into the mixture with stirring. The temperature is maintained below 15°, and chlorine is introduced until the increase in weight amounts to 50–55 g. (Note 3). The flow of chlorine is stopped, and the reaction mixture is stirred until a clear, orange-colored benzene layer forms when the mixture is allowed to settle.

The layers are separated, and the water layer is extracted once with benzene. The benzene solutions are combined and washed twice with 100-ml. portions of water, then with 100-ml. portions of 10% sodium bicarbonate solution until neutral (usually four to six washes are required), and twice more with water, and then are dried over anhydrous sodium sulfate. The benzene is removed under reduced pressure on a steam bath, and the residue is distilled in vacuum through a short indented column. After a small fore-run, the main fraction is collected at 107–111° /15 mm. There is obtained 80–82 g. (81–83%) of ethyl azodicarboxylate.

2. Notes

1. The thermometer and one of the funnels are fitted to a two-necked adapter; the thermometer scale must be such that the range between 10° and 20° is easily visible, preferably outside the flask, when the bulb is inserted in the liquid.
2. Ethyl hydrazodicarboxylate may be purified by crystallization from dilute ethanol; m.p. 134–135°
3. A larger excess of chlorine causes the formation of higher-boiling materials and lowers the yield of ethyl azodicarboxylate.

3. Discussion

Ethyl hydrazodicarboxylate can be prepared by the reaction of ethyl chloroformate with hydrazine hydrate[1] or hydrazine sulfate in the presence of potassium hydroxide.[2] It can be prepared also by the treatment of symmetrical hydrazinedicarboxylic acid diazide with ethanol.[3]

Ethyl azodicarboxylate can be prepared by treating ethyl hydrazodicarboxylate with concentrated nitric acid[2] or a mixture of concentrated and fuming nitric acid.[4,5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 411
- Org. Syn. Coll. Vol. 5, 96
- Org. Syn. Coll. Vol. 3, 58
- Org. Syn. Coll. Vol. 5, 544

References and Notes

1. Curtius and Heidenreich, *J. prakt. Chem.*, **52**, 476 (1895); Vogelesang, *Rec. trav. chim.*, **65**, 789 (1946).

2. Ingold and Weaver, *J. Chem. Soc.*, **127**, 381 (1925).
3. Stolle, *Ber.*, **43**, 2470 (1910).
4. Curtius and Heidenreich, *Ber.*, **27**, 774 (1894).
5. Diels and Fritzsche, *Ber.*, **44**, 3018 (1911).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

symmetrical hydrazinedicarboxylic acid diazide

ethanol (64-17-5)

Benzene (71-43-2)

sodium bicarbonate (144-55-8)

nitric acid (7697-37-2)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

chlorine (7782-50-5)

potassium hydroxide (1310-58-3)

hydrazine hydrate (7803-57-8)

Hydrazine sulfate (10034-93-2)

ethyl chloroformate (541-41-3)

Ethyl azodicarboxylate

Formic acid, azodi-, diethyl ester (1972-28-7)

Ethyl hydrazodicarboxylate

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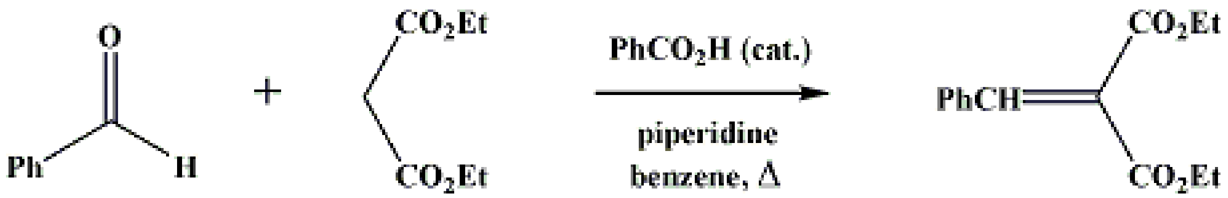
Organic Syntheses, CV 3, 377

ETHYL BENZALMALONATE

[Malonic acid, benzal-, diethyl ester]



Submitted by C. F. H. Allen and F. W. Spangler.
Checked by R. L. Shriner and Fred W. Neumann.

1. Procedure

In a 1-l. round-bottomed flask, which is fitted with a Clarke-Rahrs column[1] with a unit for removing water and surmounted by a reflux condenser, are placed 100 g. (0.63 mole) of ethyl malonate (Note 1), about 72–76 g. of commercial benzaldehyde (Note 2), 2–7 ml. of piperidine (Note 3), and 200 ml. of benzene. The mixture is refluxed vigorously in an oil bath at 130–140° until no more water (total, 12–13 ml.) is collected; this operation requires 11–18 hours. After the mixture has been cooled, 100 ml. of benzene is added and the solution is washed with two 100-ml. portions of water, with two 100-ml. portions of 1 *N* hydrochloric acid, and then with 100 ml. of a saturated solution of sodium bicarbonate. The aqueous wash solutions are shaken with a single 50-ml. portion of benzene, the benzene extract is added to the original organic layer, and the organic solution is dried with 30 g. of anhydrous sodium sulfate. After the benzene has been removed under reduced pressure on a steam bath, the residue is distilled under reduced pressure from a 250-ml. modified Claisen flask well wrapped with asbestos. The yield of colorless ethyl benzalmalonate boiling at 140–142° /4 mm. (Note 4) is 137–142 g. (89–91%) (Note 5).

2. Notes

1. B.p. 94–96° /16mm. The checkers used redistilled ethyl malonate.
2. Commercial benzaldehyde which contains 2–8% of benzoic acid is eminently satisfactory. The acid content is determined (conveniently by titration of a sample in neutral ethanol with standard alkali), and a quantity of aldehyde containing 70 g. (0.66 mole) of benzaldehyde is used. The checkers used 76 g. of commercial benzaldehyde which contained 8% of benzoic acid. If pure benzaldehyde is employed, then 2 g. of benzoic acid should be added. It has been shown[2] that piperidine salts and not the free base act as the catalyst in the Knoevenagel reaction. The checkers obtained only a 71% yield with benzaldehyde containing less than 0.2% of benzoic acid.

3. The amount of piperidine that is employed depends on the benzoic acid content of the aldehyde; it should be slightly in excess of that required to neutralize the benzoic acid. About 1.2 ml. of piperidine per gram of acid is satisfactory.
4. Another boiling point is 179–181° /10 mm. The boiling points reported for ethyl benzalmalonate vary widely. The temperature observed depends on the degree of superheating and the rapidity of distillation.
5. Methyl benzalmalonate (b.p. 143–146° /2 mm., 169–171° /10 mm.) can be prepared in the same manner and in the same apparatus in yields of 90–94%.

3. Discussion

Ethyl benzalmalonate has been prepared by the esterification of benzalmalonic acid in the presence of concentrated sulfuric acid;[3] by the action of benzal chloride on sodiomalonic ester;[4] by the condensation of benzaldehyde and malonic ester in the presence of hydrogen chloride,[5,6] acetic anhydride,[7] alcoholic piperidine or ammonia,[8] or aluminum chloride,[9] and by the action of phenylmagnesium bromide on hydroxymethylene malonic ester.[10]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 80
- Org. Syn. Coll. Vol. 4, 804
- Org. Syn. Coll. Vol. 9, 314

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodiomalonic ester

hydroxymethylene malonic ester

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrogen chloride, hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

Benzene (71-43-2)

acetic anhydride (108-24-7)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

Benzoic acid (65-85-0)

benzaldehyde (100-52-7)

aluminum chloride (3495-54-3)

piperidine (110-89-4)

Phenylmagnesium bromide (100-58-3)

ethyl malonate (1071-46-1)

Ethyl benzalmalonate

benzal chloride (98-87-3)

Malonic acid, benzal-, diethyl ester (5292-53-5)

Methyl benzalmalonate

benzalmalonic acid (584-45-2)

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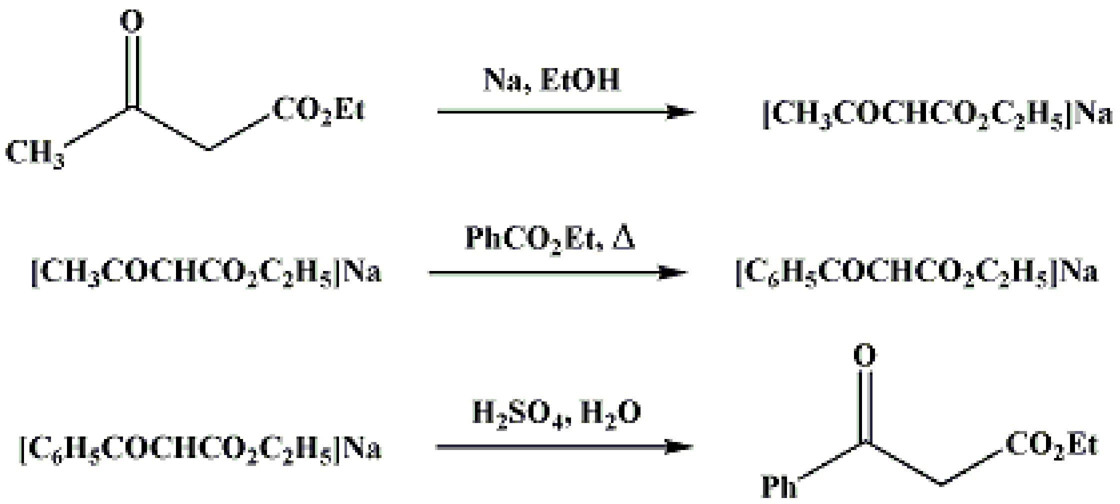
Organic Syntheses, CV 3, 379

ETHYL BENZOYLACETATE

[Acetic acid, benzoyl-, ethyl ester]



Submitted by S. M. McElvain and K. H. Weber.
Checked by R. L. Shriner and C. H. Tilford.

1. Procedure

A 2-l. three-necked flask is mounted on a steam bath and fitted with a reflux condenser, a separatory funnel, and an efficient sealed stirrer. In the flask is placed 600 ml. of absolute ethanol, and to this is added gradually 46 g. (2 gram atoms) of clean sodium cut into small pieces. The sodium ethoxide solution is stirred and cooled to room temperature, after which 267 g. (260 ml., 2.05 moles) of ethyl acetoacetate (Note 1) is added slowly through the separatory funnel. The reflux condenser is then replaced by a short still head, and the ethanol is removed by distillation at approximately room temperature and under the pressure of a water pump. When approximately half the ethanol has been removed, sufficient sodium enolate precipitates so that stirring has to be discontinued. When the residue appears dry (after about 2 hours) the last traces of ethanol are removed by heating for an hour on the steam bath under a pressure of 2 mm. The flask is allowed to cool to room temperature under reduced pressure.

To the cooled residue of sodium enolate is added 600 g. (570 ml., 4 moles) of ethyl benzoate. The steam bath is replaced by an oil bath, and the temperature of the bath is raised to 140–150° and maintained there for 6 hours. Then, over a period of another hour, the temperature of the bath is gradually raised to 180° (Note 2). The distillate that is collected during this period of heating amounts to 200–210 g. and consists chiefly of ethyl acetate and ethanol.

The reaction mixture is cooled, 250 ml. of water is added, and the mixture is made

acid to litmus by addition of a cooled solution of 100 g. of concentrated sulfuric acid in 200 ml. of water. Chipped ice is added if necessary to keep the mixture cool. The upper ester layer is separated, and the aqueous layer is extracted with 200 ml. of ether. The combined ether and ester layers are shaken with 350 ml. of a saturated sodium bicarbonate solution until no more carbon dioxide is evolved, and then the organic layer is washed with 200 ml. of water. The water layer is combined with the sodium bicarbonate solution and extracted with 400 ml. of ether. The combined ether and ester layers are dried over sodium sulfate. The ether is removed by distillation on the steam bath, and the excess ethyl benzoate and acetoacetic ester (Note 3) are then removed by distillation under reduced pressure through a 15-cm. fractionating column. Finally, the ethyl benzoylactetate is distilled (Note 3) at 101–106° /1 mm. (130–135° /3 mm.). The yield of ester boiling over a 5° range is 190–210 g. (50–55% based on the ethyl acetoacetate).

2. Notes

1. Commercial ethyl acetoacetate was distilled, and the fraction boiling at 68–69° /11 mm. was used.
2. During the last hour of heating about 20 g. of the ethyl acetate-ethanol mixture distilled.
3. A mixture of ethyl acetoacetate and ethyl benzoate (100–150 g.) was collected at 75–90° /12 mm., after which 250–300 g. of pure ethyl benzoate, b.p. 90–93° /12 mm., was recovered. These products were removed through a 15-cm. fractionating column. The remaining ethyl benzoylacetate was distilled through a short still head without a fractionating column.

3. Discussion

Methods of preparation are listed in an earlier volume.[1] In addition ethyl benzoylacetate has been prepared by the reaction of benzoyl chloride with the magnesium enolate of malonic ester[2] and subsequent decomposition with β-naphthalenesulfonic acid,[3] and by the condensation of acetophenone with ethyl carbonate in the presence of sodium hydride.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 415

References and Notes

1. *Org. Syntheses* Coll. Vol.**2**, 266 (1943).
2. *Org. Syntheses* Coll. Vol.**2**, 594 (1943).
3. Riegel and Lilienfeld, *J. Am. Chem. Soc.*, **67**, 1273 (1945).

4. Swamer and Hauser, *J. Am. Chem. Soc.*, **72**, 1352 (1950).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethyl benzoylactetate

ethanol (64-17-5)

sulfuric acid (7664-93-9)

ethyl acetate (141-78-6)

ether (60-29-7)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

carbon dioxide (124-38-9)

β-naphthalenesulfonic acid (120-18-3)

Acetophenone (98-86-2)

benzoyl chloride (98-88-4)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

ethyl benzoate (93-89-0)

Ethyl acetoacetate (141-97-9)

Ethyl benzoylacetate, Acetic acid, benzoyl-, ethyl ester (94-02-0)

ethyl carbonate

sodium hydride (7646-69-7)

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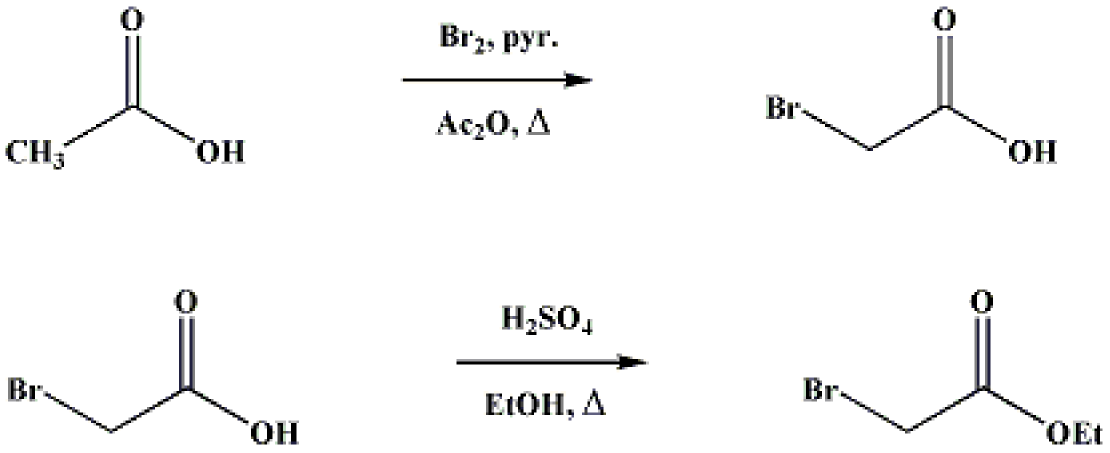
Organic Syntheses, *CV 3, 381*

ETHYL BROMOACETATE

[Acetic acid, bromo-, ethyl ester]



Submitted by Samuel Natelson and Sidney Gottfried.
Checked by Nathan L. Drake and Stuart Haywood..

1. Procedure

A. *Bromoacetic acid.* (Note 1). A mixture of 1 l. (17.5 moles, excess) of glacial acetic acid, 200ml. of acetic anhydride, and 1 ml. of pyridine is placed in a 3-l. flask fitted with a dropping funnel and a reflux condenser, the end of which is protected with a drying tube (Note 2); the tip of the dropping funnel should reach below the level of the liquid. Some glass beads are added, and the mixture is heated to boiling. The flame is then removed, approximately 1 ml. of bromine is added, and the reaction is allowed to proceed until the liquid becomes colorless (Note 3). Then the remainder of 1124 g. (360 ml., 7.03 moles) of bromine (Note 4) is added as rapidly as it will *react* (Note 5); during this period (about 2.5 hours), the acid is kept boiling *gently* by means of a flame. After about half the bromine has been added, the liquid assumes a cherry color which is retained throughout the remainder of the bromination. After all the bromine has been added, the mixture is heated until it becomes colorless.

The mixture is allowed to cool, and 75 ml. of water is added slowly to destroy the acetic anhydride. Excess acetic acid and water are now removed on a boiling water bath under a pressure of approximately 35 mm. When the evaporation is complete, the residue will crystallize on cooling; this residue, which is almost pure bromoacetic acid, weighs 845–895 g. (Note 6).

B. *Ethyl bromoacetate.* For the esterification, an apparatus similar to that used in the preparation of anhydrous oxalic acid [*Org. Syntheses*, Coll. Vol. 1, 422 (1941)] may be used, but with the outlets from the trap reversed so that the lighter liquid returns to the mixture and the heavier liquid (water) is drawn off at the bottom. A somewhat simpler apparatus may be built using the water trap shown in .htmFig. 12 (Note 7).

The crude bromoacetic acid is placed in a 3-l. flask, together with 610 ml. of ethanol (9.9 moles, excess) and 950 ml. of benzene. About 1.5 ml. of concentrated sulfuric acid is added to hasten the reaction (Note 8), and the mixture is refluxed on a boiling water bath while the water is separated and measured. Approximately 296 ml. of liquid (whose composition is approximately 50% ethanol and water) separates from the benzene; this includes all the water formed in the reaction, together with the excess ethanol. When no more water separates from the benzene, 75 ml. of ethanol is added to the reaction mixture and heating is continued for 30 minutes. If the reaction has been completed, there will not be a second phase in the distillate. The end of the reaction is also indicated when the benzene flowing through the side tube becomes clear and the rate of refluxing decreases considerably. At this point, 150 ml. of benzene is condensed and removed through the trap.

Fig. 12.

Fig. 12.

The mixture is transferred to a separatory funnel and washed once with 1.5 l. of water, once with 1.5 l. of 1% sodium bicarbonate solution, and finally with 1.5 l. of water. It is then dried over anhydrous sodium sulfate and fractionated at atmospheric pressure from an oil bath using a Vigreux column 1 ft. in length (Note 9). The fraction boiling at 154–155°/759 mm. is collected (Note 10). The yield is approximately 818 g. (65–70%).

2. Notes

1. The vapors of ethyl bromoacetate are extremely irritating to the eyes. Care should be taken to keep the material in closed containers and to manipulate it in open vessels only in a good hood.
2. An all-glass apparatus is advisable. If it is not available, one-holed asbestos stoppers may be made by soaking strips of asbestos in water, wrapping them around pieces of glass tubing of suitable size until the desired diameter has been reached, and then allowing them to dry at 110°.
3. At the beginning there is a lag of about 10 minutes before the reaction starts and the color of the bromine disappears.
4. If C.P. bromine is available it may be used directly. Technical bromine should be dried with concentrated sulfuric acid.
5. The bromine should not be added so rapidly that loss occurs through the condenser.
6. Pure bromoacetic acid may be obtained by distillation of this crude product from a Claisen flask immersed in an oil bath and fitted with an 8-in. insulated Vigreux column. The fraction boiling at 108–110°/30 mm. is collected. The yield is 775–825 g. (80–85%).
7. The trap shown in .htmFig. 12 is a modification of the moisture trap designed by Dean and Stark.[1] The dimensions may be varied to suit individual purposes,

for the size is largely a matter of convenience. The trap may be used without the inner funnel, but with this funnel (C. F. Koelsch, private communication) the condensate separates into two layers rapidly and completely, and the liquid falling from the condenser does not agitate the two phases in the trap. The funnel tube must be of such a length that the top of the funnel is above the side arm of the trap. The tube of the trap may be graduated, but this is not necessary.

8. In the absence of a catalyst the reaction proceeds more slowly and smaller yields are obtained. Phosphoric acid may be substituted for sulfuric acid, but the use of sulfuric acid results in the best yield in the shortest time.

9. If a fractionating column is not used, as much as 15–20% of the product may be lost in the fore-run.

10. The fraction boiling over a 1-degree range is collected. The boiling point has been observed to range from 154–155° to 158–159° on different days.

3. Discussion

Bromoacetic acid has been prepared by direct bromination of acetic acid at elevated temperatures and pressures,[2,3,4] or with dry hydrogen chloride as a catalyst;[5] and with red phosphorus as a catalyst with the formation of bromoacetyl bromide.[6,7,8,9,10] Bromoacetic acid has also been prepared from chloroacetic acid and hydrogen bromide at elevated temperatures;[6] by oxidation of ethylene bromide with fuming nitric acid;[7] by oxidation of an ethanolic solution of bromoacetylene by air;[8] and from ethyl α,β-dibromovinyl ether by hydrolysis.[9] Acetic acid has been converted into bromoacetyl bromide by action of bromine in the presence of red phosphorus, and ethyl bromoacetate has been obtained by action of ethanol upon the acid bromide.[10,11,12,13,14] Ethyl bromoacetate has also been prepared by direct bromination of ethyl acetate at elevated temperatures;[15,16] by action of ethanol upon bromoacetic anhydride;[17] by action of phosphorus tribromide upon ethyl glycollate;[18] and by action of hydrogen bromide upon ethyl diazoacetate.[19] The method described above is based upon the procedure of Natelson and Gottfried.[20]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 408
- Org. Syn. Coll. Vol. 4, 573
- Org. Syn. Coll. Vol. 4, 605
- Org. Syn. Coll. Vol. 5, 277
- Org. Syn. Coll. Vol. 5, 303
- Org. Syn. Coll. Vol. 5, 762
- Org. Syn. Coll. Vol. 5, 808
- Org. Syn. Coll. Vol. 5, 883
- Org. Syn. Coll. Vol. 5, 1060

- Org. Syn. Coll. Vol. 6, 520
- Org. Syn. Coll. Vol. 7, 135

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16. Schutzenberger, *Ber.*, **6**, 71 (1873).
17. Gal, *Compt. rend.*, **71**, 274 (1870).
18. Henry, *Ann.*, **156**, 176 (1870).
19. Curtius, *J. Prakt. Chem.*, (2) **38**, 430 (1888).
20. Natelson and Gottfried, *J. Am. Chem. Soc.*, **61**, 970 (1939).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

red phosphorus

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrogen chloride (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

ethyl acetate (141-78-6)

acetic anhydride (108-24-7)

sodium bicarbonate (144-55-8)

nitric acid (7697-37-2)

hydrogen bromide (10035-10-6)

bromine (7726-95-6)

sodium sulfate (7757-82-6)

phosphorus tribromide (7789-60-8)

Oxalic acid (144-62-7)

chloroacetic acid (79-11-8)

pyridine (110-86-1)

phosphoric acid (7664-38-2)

ethylene bromide (106-93-4)

bromoacetyl bromide (598-21-0)

Bromoacetic acid (79-08-3)

ethyl diazoacetate (623-73-4)

Ethyl bromoacetate, Acetic acid, bromo-, ethyl ester (105-36-2)

bromoacetylene (593-61-3)

ethyl α,β-dibromovinyl ether

bromoacetic anhydride (13094-51-4)

ethyl glycollate (623-50-7)

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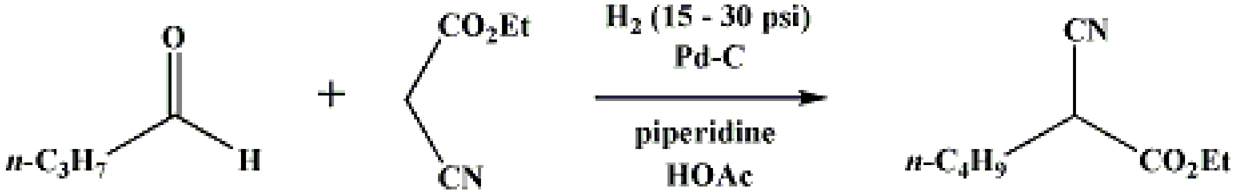
Organic Syntheses, CV 3, 385

ETHYL *n*-BUTYLCYANOACETATE

[Caproic acid, α-cyano-, ethyl ester]



Submitted by Elliot R. Alexander and Arthur C. Cope.
Checked by Cliff S. Hamilton and Robert F. Coles.

1. Procedure

A mixture of ethyl cyanoacetate (Note 1) (56.6 g., 0.5 mole), freshly distilled butyraldehyde (43.2 g., 0.6 mole), 1 g. of palladium on carbon (Note 2), and 80 ml. of glacial acetic acid is placed in a 500-ml. bottle suitable for attachment to a low-pressure reduction apparatus. A solution of piperidine (2.0 ml., 0.02 mole) in 20 ml. of glacial acetic acid is added, and the bottle is connected to the reduction apparatus.

The bottle is alternately evacuated and filled with hydrogen twice, and the mixture is reduced by shaking with hydrogen at 1 to 2 atm. (15–30 lb.) pressure. The reduction is rapid and exothermic. In 1–2 hours the theoretical amount of hydrogen (0.5 mole) is taken up and absorption ceases (Note 3).

The reaction mixture is filtered through a Hirsch or Büchner funnel, and the bottle is rinsed with 50 ml. of benzene, which is also poured through the funnel. The filtrate is washed with two 50-ml. portions of 10% sodium chloride solution and three 25-ml. portions of water (Note 4). The washings are extracted with three 10-ml. portions of benzene, and the combined benzene solutions are distilled under reduced pressure from a 250-ml. modified Claisen flask. The yield of ethyl *n*-butylcyanoacetate, b.p. 108–109°/9 mm., is 79–81 g. (94–96%, based on the ethyl cyanoacetate used) (Note 5).

2. Notes

1. Ethyl cyanoacetate was purchased from the Dow Chemical Company, Midland, Michigan, and redistilled before using.
2. The palladium on carbon catalyst was prepared by the following method, developed by Walter H. Hartung, School of Pharmacy, University of Maryland, Baltimore. Ten milliliters of a commercial palladium chloride solution containing 0.1 g. of palladium and approximately 0.05 g. of hydrogen chloride per milliliter (obtained from the J. Bishop Company, Malvern, Pennsylvania) is added to a solution of 27 g. of sodium acetate trihydrate in 100 ml. of water.

Norit (9 g.) is added, and the mixture is hydrogenated until absorption ceases. The catalyst (10 g.) is filtered on a Büchner funnel, washed with water, dried by drawing air through the funnel for about 30 minutes, and stored in a desiccator over calcium chloride. The palladium catalysts, prepared as described elsewhere in this volume, are presumably also satisfactory for the reductive alkylation described above (p. 685).

3. It is advisable to start the reduction as soon as the reactants are mixed. The yield dropped to 87% when the reaction mixture was allowed to stand for 3 hours before hydrogenating.

4. If an emulsion is formed, it can be broken by adding a few drops of ethanol or several milliliters of ether.

5. Ethyl ethylcyanoacetate and ethyl propylcyanoacetate have been prepared by the same method in yields of 85 and 94%, respectively. Other aldehydes and ketones have been used under slightly different conditions to prepare other ethyl monoalkylcyanoacetates.[1]

3. Discussion

Ethyl *n*-butylcyanoacetate has been prepared by alkylation of the sodium enolate of ethyl cyanoacetate with butyl bromide [2] and by condensation of capronitrile with ethyl carbonate,[3] in addition to the method given above.[1]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 685
- Org. Syn. Coll. Vol. 4, 304

References and Notes

1. Alexander and Cope, *J. Am. Chem. Soc.*, **66**, 886 (1944).
2. Hessler and Henderson, *J. Am. Chem. Soc.*, **43**, 674 (1921).
3. Wallingford, Jones, and Homeyer, *J. Am. Chem. Soc.*, **64**, 577 (1942).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium enolate of ethyl cyanoacetate

ethanol (64-17-5)

calcium chloride (10043-52-4)

hydrogen chloride (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

ether (60-29-7)

hydrogen (1333-74-0)

sodium chloride (7647-14-5)

Butyl bromide (109-65-9)

carbon, Norit (7782-42-5)

piperidine (110-89-4)

palladium (7440-05-3)

butyraldehyde (123-72-8)

Ethyl cyanoacetate (105-56-6)

palladium chloride

ethyl carbonate

Caproic acid, α-cyano-, ethyl ester, ETHYL n-BUTYLCYANOACETATE (7391-39-1)

sodium acetate trihydrate (6131-90-4)

Ethyl ethylcyanoacetate

ethyl propylcyanoacetate

capronitrile (628-73-9)

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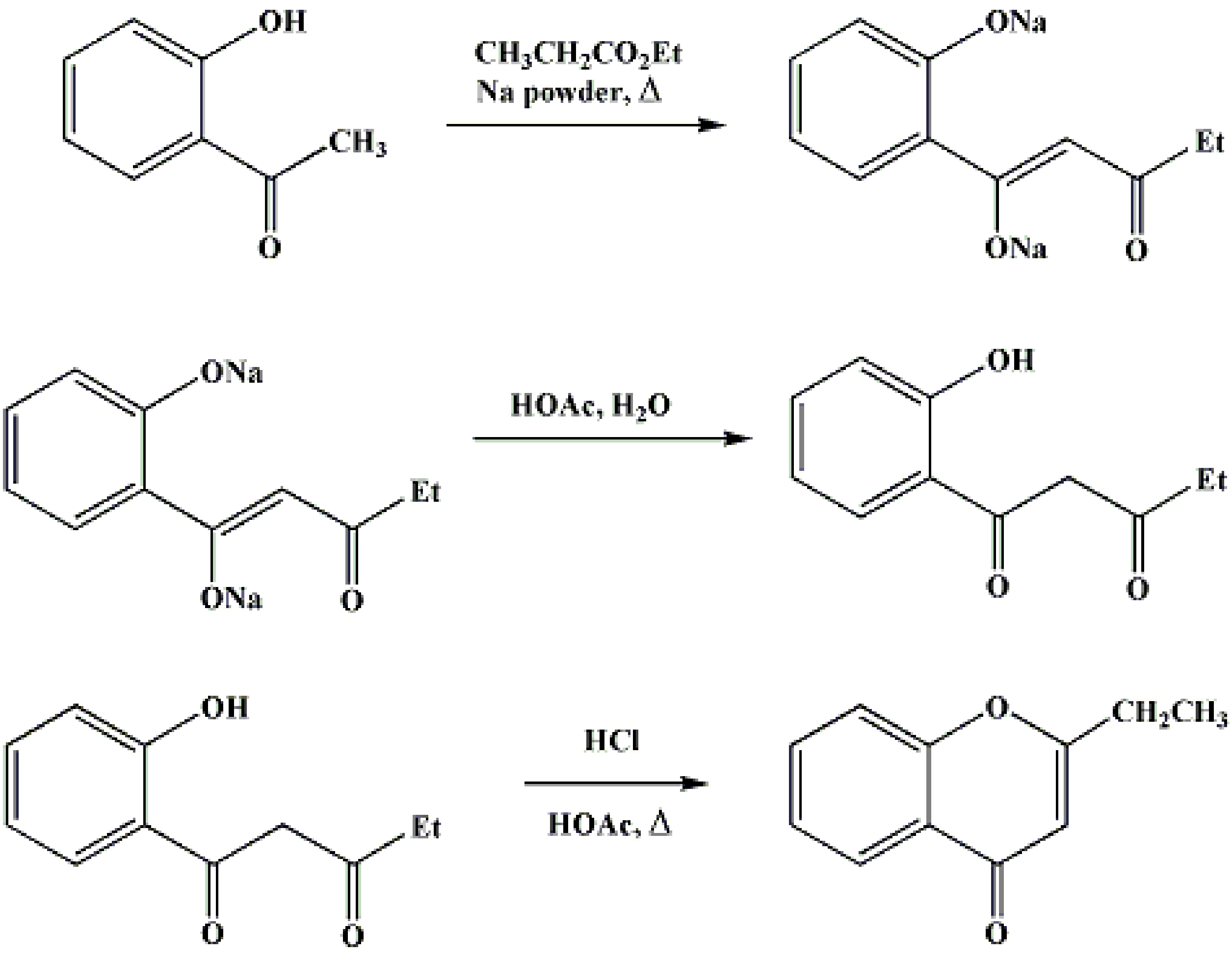
Organic Syntheses, CV 3, 387

2-ETHYLCHROMONE

[Chromone, 2-ethyl-]



Submitted by Ralph Mozingo
Checked by Homer Adkins and Robert J. Gander.

1. Procedure

In a 1-l. three-necked flask fitted (Note 1) with a reflux condenser, a dropping funnel, and a stirrer (Note 2) are placed 24 g. (1.05 gram atoms) of oxide-free sodium and 200 ml. of xylene (Note 3). The condenser is protected by a drying tube containing soda-lime. The flask is surrounded by an oil bath which is heated until the sodium is melted. The stirrer is started, and, after the sodium is powdered, the oil bath is removed. When the contents of the flask have cooled to room temperature, the stirrer is stopped, the xylene decanted, and the sodium washed with 100 ml. of dry ether to remove traces of xylene.

The flask is replaced and completely surrounded by an ice bath (Note 4). A current of nitrogen is passed through the flask for 5 minutes by means of a rubber tube attached to

the dropping funnel. The nitrogen inlet tube is removed, and a mixture of 60 g. (0.44 mole) of *o*-hydroxyacetophenone (Note 5) and 125 g. (140 ml., 1.2 moles) of ethyl propionate (Note 3) is placed in the dropping funnel and protected by a soda-lime tube. The ester-ketone mixture is dropped very slowly onto the powdered sodium. After a small amount (2–5 ml.) of the mixture has been added, the ice bath is removed and the flask warmed with the hand to make sure that the reaction has started (Note 6). When the reaction has started, the funnel is adjusted so that one-half of the ester-ketone mixture is added over a period of 1.5–2 hours. After half of the mixture has been added, the rate of addition is again regulated so that the remainder is added in 30 minutes.

After all the ester-ketone mixture has been added and the reaction has subsided, the ice bath is removed and replaced by a steam bath. The crust on the mixture is broken up and the mixture heated on a steam bath until all the sodium has reacted (30–60 minutes). The reaction mixture is allowed to cool and is poured with stirring onto 300 g. of crushed ice. Ninety-five milliliters of glacial acetic acid in 350 ml. of water is added, and the mixture is stirred for 30 minutes. The organic layer which separates is removed by means of a separatory funnel, and the water layer is extracted three times with 200-ml. portions of ether. The extracts are combined with the original organic material, and the ether is distilled from a steam bath. To the residue are added 150 ml. of glacial acetic acid and 10 ml. of concentrated hydrochloric acid, and the solution is refluxed for 30 minutes, after which it is allowed to cool to room temperature (Note 7).

The entire reaction mixture is then subjected to fractional distillation through a Widmer column (Note 8). The material boiling up to 120° is removed at atmospheric pressure and discarded. The contents of the flask are cooled and the pressure reduced to 7 mm. The fraction up to 80°/7 mm. is removed and discarded. The material boiling at 80–90°/7 mm. is collected, and, after the contents of the flask have been cooled, the pressure is reduced to 2 mm. and all the material boiling up to 110°/2 mm. is collected and combined with the 80–90°/7 mm. fraction. The next fraction, boiling at 110–138°/2 mm., is collected separately. On refractionation of the lower fraction (b.p. 80°/7 mm.–110°/2 mm.) there is obtained 13–15 g. of *o*-hydroxyacetophenone (b.p. 87–88°/7 mm.). To the residue after recovery of the *o*-hydroxyacetophenone is added the fraction boiling at 110–138°/2 mm. The pressure is again reduced to 2 mm. and the fraction boiling at 124–126°/2 mm. collected. This fraction is pure 2-ethylchromone and weighs 42–45 g. (70–75% based on the ketone not recovered) (Note 9).

2. Notes

1. All the stoppers used should be rubber ones that have been boiled for 2 hours in 10% sodium hydroxide and thoroughly washed and dried before use.

2. A convenient stirrer may be made by fitting a -in brass rod with a disk 1 in. in diameter. Four holes are drilled through the disk, and through each hole is placed a loop of 18-gauge Nichrome wire. The loops are each turned so that the twisted end is next to the stirrer shaft and each is twisted in the middle to give a double loop. The stirrer shaft is then passed through a 4-in. length of glass tubing which fits tightly about the shaft. A rubber seal is made by slipping a piece of rubber tubing over the brass rod and glass tubing. The rubber tubing extends

about 3 mm. up onto the stirrer shaft, over which it fits rather tightly. A drop of glycerol placed on the stirrer shaft just above the rubber sleeve serves as a lubricant for the seal. The seal is similar to that described for the preparation of dypnone (p. 368, Note 1).

3. The xylene is dried over sodium and distilled from it. The ethyl propionate is dried over phosphorus pentoxide, more of the drying agent being added from time to time until some solid phosphorus pentoxide remains. The ester is then decanted into a flask containing fresh phosphorus pentoxide and fractionated. The fraction boiling at 98–99°/745 mm. is collected.

4. An ice bath is used to keep the reaction from becoming too violent. An ice-salt bath must not be used or the reaction may be delayed in starting.

5. The *o*-hydroxyacetophenone was made as described by Miller and Hartung [*Org. Syntheses* Coll. Vol. **2**, 543 (1943)] for *o*- and *p*-hydroxypropiophenone except that the procedure for isolating the product was modified as follows. The cold, partly solidified oil, separating after acidification, was diluted with benzene and the water layer extracted with benzene. After distillation of the benzene, the residue was distilled at 17 mm. until the solid *p*-isomer began to collect in the condenser. The distillate was then fractionated through a Widmer column, and the fraction boiling at 90–110°/17 mm. was saved. Refractionation gave *o*-hydroxyacetophenone boiling at 105–106°/20 mm. or 87–88°/7 mm. in a yield of 30% based upon the phenyl acetate.

6. It is *very important* that the operator assure himself that the reaction has started before more of the ester-ketone mixture is added, and that the first half of the mixture be added slowly, or the reaction may proceed with *explosive violence*. It is usually possible to tell when the reaction has started by the local evolution of heat when the ice bath is removed and by the appearance of the yellow salt of the diketone.

7. The preparation should be carried as far as this point without interruption.

8. The Widmer column had a spiral 15 cm. in length, and had an electrically heated jacket.[1]

9. The submitter carried out this preparation with twice the quantities recommended here. The yield was 68–77 g. (56–64%).

3. Discussion

This chromone has been prepared by the condensation of ethyl propionate with *o*-hydroxyacetophenone using sodium.[2,3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 478

References and Notes

1. Smith and Adkins, *J. Am. Chem. Soc.*, **60**, 662 (1938).

2. Heilbron, Hey, and Lowe, *J. Chem. Soc.*, **1934**, 1312.
3. Mozingo and Adkins, *J. Am. Chem. Soc.*, **60**, 669 (1938).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

oxide-free sodium

o- and p-hydroxypropiophenone

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

ether (60-29-7)

sodium hydroxide (1310-73-2)

glycerol (56-81-5)

nitrogen (7727-37-9)

sodium (13966-32-0)

xylene (106-42-3)

ethyl propionate (105-37-3)

2-Ethylchromone, Chromone, 2-ethyl- (14736-30-2)

phenyl acetate (122-79-2)

phosphorus pentoxide (1314-56-3)

o-Hydroxyacetophenone (118-93-4)

Dypnone (495-45-4)

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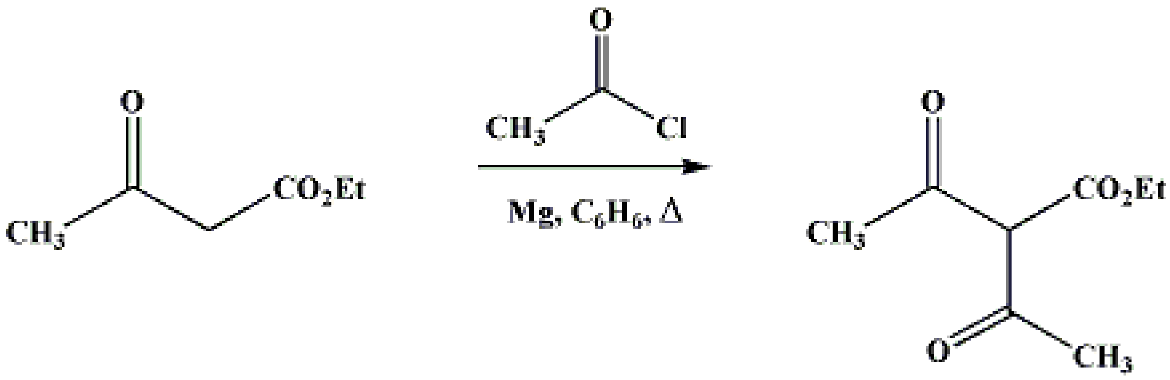
Organic Syntheses, CV 3, 390

ETHYL DIACETYLACETATE



Submitted by A. Spassow
Checked by Nathan L. Drake, Leonard Smith, and Jonathan W. Williams.

1. Procedure

A mixture of 12 g. (0.50 gram atom) of magnesium turnings, 130 g. (1.0 mole) of ethyl acetoacetate, 200 g. of benzene (dried over sodium), and 120 g. (1.50 moles) of acetyl chloride is heated under reflux for 2 hours in a 1-l. round-bottomed flask provided with a condenser closed by a calcium chloride tube and supported in an oil bath (85–90°) (Note 1). The yellow reaction mixture is cooled in an ice bath, and the liquid portion is decanted into a separatory funnel. The residue in the flask is washed twice with 50-ml. portions of ether, and the ethereal solution is poured over ice. The ether-water mixture is then added to the benzene solution in the separatory funnel, and the mixture is shaken thoroughly (Note 2); the aqueous layer is drawn off and discarded. The benzene-ether solution is washed once with 500 ml. of 5% sodium bicarbonate solution and once with 50 ml. of water, and finally is dried over calcium chloride. The ether and most of the benzene are removed by distillation from a water bath, and the remainder of the benzene is driven off at 50°/50 mm. The ethyl diacetylacetate is then precipitated from the residue as the copper derivative by the addition of 1.2 l. of a saturated aqueous solution of copper acetate (Note 3). After addition of the copper acetate solution, the contents of the flask are shaken vigorously now and then and allowed to stand for an hour to ensure complete precipitation of the copper derivative. The blue copper derivative is filtered on a Büchner funnel, washed with two 50-ml. portions of water, and transferred directly to a separatory funnel where it is mixed with 600 ml. of ether.

Four hundred milliliters of 25% sulfuric acid is added, and the contents of the funnel are shaken continually until the copper derivative has disappeared (5–10 minutes). After separation of the ethereal layer, the aqueous layer is extracted twice with 100-ml. portions of ether, and the combined ethereal extracts are dried over calcium chloride. The ether is removed on the steam bath and the residual ester distilled under diminished pressure. A few drops come over up to 90°, but the bulk of the material

distils at 92–98°/12 mm. Redistillation yields pure ethyl diacetylacetate boiling at 95–97°/12 mm. The yield is 80–90 g. (46–52%).

2. Notes

1. Hydrogen and hydrogen chloride are evolved; this operation must be conducted in a hood.
2. The greater part of the magnesium remains unchanged. It should be removed by filtering the solution through a plug of *fine* glass wool in an ordinary funnel.
3. The saturated solution of copper acetate is prepared by dissolving 100 g. of finely pulverized copper acetate in 1.2 l. of boiling water. If the preparation contains basic salt, a few milliliters of acetic acid is added, and the solution is filtered. The solution is cooled to 35° before use.

3. Discussion

Ethyl diacetylacetate has been prepared by Claisen from the sodium derivative of acetylacetone and ethyl chloroformate.[1] It has also been prepared from the sodium derivative of ethyl acetoacetate and acetyl chloride,[2,3,4] from ethyl acetoacetate and acetyl chloride in the presence of magnesium,[5] and from ethyl acetoacetate and ketene.[6]

References and Notes

1. Claisen, *Ann.*, **277**, 171 (1893).
2. James, *Ann.*, **226**, 211 (1884).
3. Elion, *Rec. trav. chim.*, **3**, 250 (1884).
4. Michael, *Ber.*, **38**, 2088 (1905).
5. Ogata, Nosaki, and Takagi, *J. Pharm. Soc. Japan*, **59**, 105 (1939) [*C. A.*, **33**, 4230 (1939)].
6. U. S. pat. 2,417,381 [*C. A.*, **41**, 4169 (1947)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium derivative of ethyl acetoacetate

sodium derivative of acetylacetone

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrogen chloride (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

ether (60-29-7)

hydrogen (1333-74-0)

acetyl chloride (75-36-5)

sodium bicarbonate (144-55-8)

magnesium, magnesium turnings (7439-95-4)

sodium (13966-32-0)

copper acetate (142-71-2)

Ethyl acetoacetate (141-97-9)

Ketene (463-51-4)

ethyl chloroformate (541-41-3)

Ethyl diacetylacetate (603-69-0)

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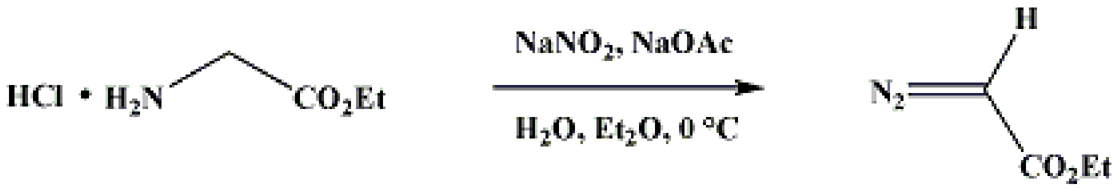
Organic Syntheses, CV 3, 392

ETHYL DIAZOACETATE

[Acetic acid, diazo-, ethyl ester]



Submitted by Ennis B. Womack and A. B. Nelson.
Checked by R. L. Shriner and C. H. Tilford.

1. Procedure

A 1-l. three-necked round-bottomed flask is fitted with a 50-ml. separatory funnel and a mechanical stirrer sealed with a well-lubricated rubber collar. A stopper in the third neck of the flask carries a glass tube that reaches to the bottom of the flask, enters the top of a 1-l. separatory funnel, and extends down to the stopcock.

A solution of 140 g. (1 mole) of glycine ethyl ester hydrochloride and 3 g. of sodium acetate in 150 ml. of water is added to the flask and cooled to 2° by means of an ice-salt bath. A cold solution of 80 g. (1.15 moles) of sodium nitrite in 100 ml. of water is added, and the mixture is stirred until the temperature has fallen to 0°. The temperature is maintained below 2°, and stirring is continued throughout all the following operations. To the cold mixture are added 80 ml. of cold, ethanol-free ethyl ether (Note 1) and 3 ml. of cold 10% sulfuric acid. After 5 minutes, the reaction mixture is blown over into the 1-l. separatory funnel by application of air pressure. The lower aqueous layer is *quickly* sucked back into the reaction flask. The ether layer is removed and immediately washed with 50 ml. of cold 10% sodium carbonate solution. This ether solution should be neutral to moist litmus paper; if not, the washing with sodium carbonate is repeated. The ether solution is finally dried over 10 g. of anhydrous sodium sulfate.

A second portion of 80 ml. of ethanol-free ether is then added to the reaction mixture with stirring, followed by 15 ml. of cold 10% sulfuric acid over a period of 5 minutes. After 3 minutes' contact (Note 2), the ether layer is removed as before, washed immediately with 50 ml. of fresh 10% sodium carbonate solution, and dried over 10 g. of sodium sulfate. This procedure is repeated (about 6 or 7 times) until the ether layer is no longer yellow.

The combined ether solutions are then subjected to distillation at 20°or below under the vacuum obtainable from a water pump until all the ether is removed. Prolonged distillation results in decomposition of the diazo ester and in a decreased yield. The yellow residual oil is practically pure ethyl diazoacetate and is satisfactory for most

synthetic purposes (Note 3). The yield is about 98 g. (85%) (Note 4) and (Note 5).

2. Notes

1. The ethanol is removed from 600 ml. of commercial ethyl ether by thorough washing with 75 ml. of a saturated calcium chloride solution.
2. The ether layer should be removed as rapidly as possible from the aqueous layer, because ethyl diazoacetate is rapidly decomposed by acid.
3. Ethyl diazoacetate may be purified, but with considerable loss, by steam distillation under reduced pressure.[1]
4. The submitters have carried out preparations using twice the amounts stated.
5. The product should be placed in dark brown bottles and kept in a cool place. It should be used as soon as possible. *Distillation, even under reduced pressure, is dangerous, for the substance is explosive.*

3. Discussion

Ethyl diazoacetate has been prepared by the action of sodium nitrite on glycine ethyl ester hydrochloride.[1,2,3] A modification of this method, which is reported to give better yields than those described here, has been published.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 424
- Org. Syn. Coll. Vol. 5, 258

References and Notes

1. Gattermann, *Laboratory Methods of Organic Chemistry*, p. 277, The Macmillan Company, New York, 1948.
2. Curtius, *J. prakt. Chem.*, (2) **38**, 396 (1888); Silberrad, *J. Chem. Soc.*, 81, 600 (1902).
3. U. S. pat. 2,490,714 [*C. A.*, **44**, 3519 (1950)].
4. La Forge, Gersdorff, Green, and Schechter, *J. Org. Chem.*, **17**, 381 (1952).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

ether, ethyl ether (60-29-7)

sodium acetate (127-09-3)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

sodium nitrite (7632-00-0)

ethyl diazoacetate, Acetic acid, diazo-, ethyl ester (623-73-4)

Glycine ethyl ester hydrochloride (623-33-6)

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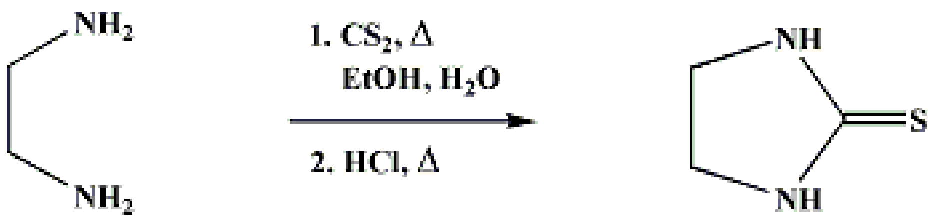
Organic Syntheses, CV 3, 394

ETHYLENE THIOUREA

[2-Imidazolidinethione]



Submitted by C. F. H. Allen, C. O. Edens, and James VanAllan.
Checked by R. L. Shriner and Curtis D. Snow.

1. Procedure

In a 2-l. round-bottomed flask are placed 120 g. (1.83 moles) of 92% ethylenediamine (Note 1), 300 ml. of 95% ethanol, and 300 ml. of water. The flask is attached to an efficient reflux condenser, and 121 ml. of carbon disulfide is placed in a separatory funnel attached to the top of the condenser by means of a notched cork. About 15 to 20 ml. of the carbon disulfide is added, and the flask is shaken to mix the contents. A vigorous reaction takes place (Note 2), and it may be necessary to cool the flask. After the reaction has started, a water bath at 60° is placed under the flask and the balance of the carbon disulfide is added at such a rate that the vapors reflux about one-third the way up the condenser. About 2 hours is required for the addition of the carbon disulfide. At this time the bath temperature is raised to about 100°, and the mixture is allowed to reflux for 1 hour. Then 15 ml. of concentrated hydrochloric acid is added, and the mixture is refluxed under a good hood (bath at 100°) for 9–10 hours. The mixture is cooled in an ice bath, and the product is filtered by suction on a Büchner funnel and washed with 200–300 ml. of cold acetone (Note 3). A yield of 156–167 g. (83–89%) of white crystals is obtained melting at 197–198° (Note 4) and (Note 5).

2. Notes

1. If commercial ethylenediamine is used, it should be redistilled. The concentration of the ethylenediamine may be determined by titration with standard acid and the proper amount taken.
2. Care should be exercised to make certain that the reaction starts, before an additional quantity of carbon disulfide is added. In one experiment in which the carbon disulfide was added all at once, a very violent reaction occurred.
3. Since all the likely contaminants are readily volatile, extensive washing is unnecessary.
4. This product is pure enough for most purposes. It gives no precipitate with copper sulfate solution, indicating the absence of the open-chain acid.[1].

5. It has been reported (J. VanAllan) that this procedure may also be used for the preparation of 2-thio-3,4,5,6-tetrahydropyrimidine; in this case 130 g. (150 ml., 1.76 moles) of propylenediamine is used in place of ethylenediamine. The yield is 160 g. (80%) of colorless product, m.p. 207–208°, after recrystallization from water.

3. Discussion

The only practical method for preparing alkylene thioureas is by the action of the diamines upon carbon disulfide in aqueous alcohol.[1,2,3,4,5] The final heating is essential to convert the thiocarbamic acid into the cyclic compound, the addition of hydrochloric acid being beneficial. Alkylene thioureas have also been prepared by heating N-formylalkylenediamines with sulfur.[6]

References and Notes

1. Ruiz and Libenson, *Anales asoc. quím. argentina*, **18**, 37 (1930) [*C. A.*, **24**, 5726 (1930)].
2. Hofmann, *Ber.*, **5**, 242 (1872).
3. Johnson and Edens, *J. Am. Chem. Soc.*, **64**, 2707 (1942).
4. Schackt, *Arch. Pharm.*, **235**, 442 (1897).
5. Klut, *Arch. Pharm.*, **240**, 675 (1902).
6. Zienty, *J. Am. Chem. Soc.*, **68**, 1388 (1946).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

copper sulfate (7758-98-7)

sulfur (7704-34-9)

acetone (67-64-1)

carbon disulfide (75-15-0)

Ethylene thiourea, 2-Imidazolidinethione (96-45-7)

ethylenediamine (107-15-3)

2-thio-3,4,5,6-tetrahydropyrimidine (2055-46-1)

propylenediamine (78-90-0)

thiocarbamic acid

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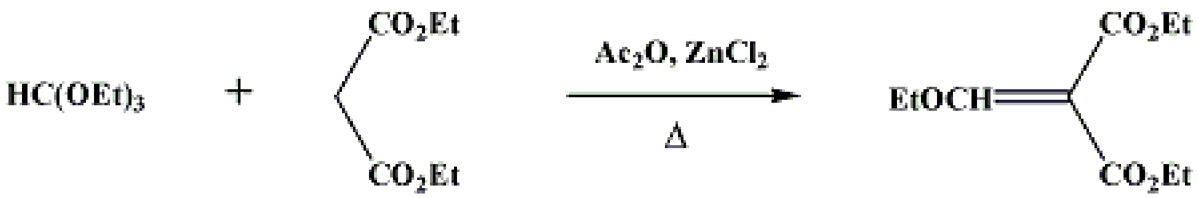
ETHYL ETHOXYMETHYLENEMALONATE

[Malonic acid, ethoxymethylene-, diethyl ester]



Submitted by W. E. Parham and L. J. Reed[1].
Checked by J. R. Roland, C. W. Todd, and R. S. Schreiber.

1. Procedure

A mixture of 1000 g. (6.75 moles) of ethyl orthoformate, 1260 g. (12.3 moles) of acetic anhydride, 960 g. (6.0 moles) of ethyl malonate, and 0.5 g. of anhydrous zinc chloride is prepared in a 5-l. three-necked flask equipped with a thermometer, a gas inlet tube, and a 12-in. column packed with Berl Saddles (Note 1). The column is attached to a still head and condenser. The contents of the flask are well agitated for 5 minutes by a stream of dry air and then heated (Note 2) as follows: 102–115° for 2.5 hours, 115–127° for 7 hours [after the eighth hour of heating, 250 g. (2.45 moles) of acetic anhydride and 200 g. (1.35 moles) of ethyl orthoformate are added], 127–145° for 2 hours, and 145–155° for 2 hours (Note 3). At the end of 13.5 hours of heating the mixture is cooled to room temperature and filtered (Note 4). The filtrate is distilled under reduced pressure (15–20 mm.) until the temperature at the still head reaches 100° (Note 5). The distillation is then continued under lower pressure (0.25 mm.). The yield of ethyl ethoxymethylenemalonate, b.p. 108–110°/0.25 mm. (Note 6), is 650–780 g. (50–60% based on the ethyl malonate used).

2. Notes

1. The use of this column prevents loss of acetic anhydride during the heating process and permits volatile products formed during the reaction to be removed by distillation. The checkers used a 1 by 12 in. column packed with 6 by 6 mm. glass rings.
2. The zinc chloride dissolves, and a chlorine-free crystalline precipitate soon separates. The checkers observed only traces of this precipitate.
3. The final heating is necessary to convert unchanged ethyl diethoxymethylmalonate, an intermediate in the reaction, into ethyl ethoxymethylenemalonate. This intermediate is difficult to separate from ethyl ethoxymethylenemalonate by distillation, and it is important that it be converted as completely as possible during the heating process.
4. The mixture is filtered through a fluted filter paper to remove suspended zinc

salts.
5. Unchanged ethyl malonate (as much as 15% of the amount used) can be obtained by redistillation of the fraction boiling at 70–100°/17 mm.
6. Since ethyl diethoxymethylmalonate is difficult to separate from ethyl ethoxymethylenemalonate by distillation, it is necessary to follow the course of the distillation by observation of the change in refractive index instead of the change in boiling point. After a low-boiling fraction is collected, there is obtained an intermediate fraction (n_D^{20} 1.4142–1.4580), the size of which depends upon the amount of ethyl diethoxymethylmalonate present. Under the best of conditions it amounts to 15 g. In each of three runs, the checkers obtained about 300–400 g. of material having a refractive index in this range. The ethyl ethoxymethylenemalonate was collected at n_D^{20} 1.4580–1.4623. The checkers used a 5-in. Vigreux column and observed that at the low pressures the boiling point of the distillate in several runs was about 10° lower than that reported by the submitters. For example, in one run at 0.25 mm. (gauge pressure) the boiling point of the distillate never rose above 97.2°; however, the refractive indices of twelve 50-ml. fractions taken in the course of this distillation were all in the proper range, n_D^{20} 1.4612–1.4623. Interruption of the heating during the reaction period should be avoided. In an experiment in which the heating was discontinued after about 8 hours and resumed the next day the yield was about 50%.

3. Discussion

Ethyl ethoxymethylenemalonate has been prepared by heating ethyl orthoformate, ethyl malonate, and acetic anhydride in the presence of zinc chloride.[2,3] A higher yield of purer product is obtained by the method described above,[4] which is a modification of the Claisen procedure.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 272
- Org. Syn. Coll. Vol. 4, 298

References and Notes

1. Work done under contract with the Office of Scientific Research and Development.
2. Claisen, *Ber.*, **26**, 2729 (1893); *Ann.*, **297**, 76 (1897).
3. Wheeler and Johns, *Am. Chem. J.*, **40**, 237 (1908).
4. Fuson, Parham, and Reed, *J. Org. Chem.*, **11**, 194 (1946).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

acetic anhydride (108-24-7)

zinc chloride (7646-85-7)

Ethyl orthoformate

ethyl malonate (1071-46-1)

ethyl ethoxymethylenemalonate

Malonic acid, ethoxymethylene-, diethyl ester (87-13-8)

ethyl diethoxymethylmalonate

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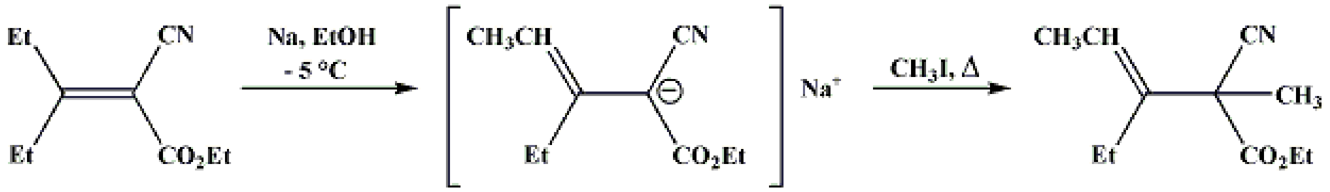
ETHYL (1-ETHYLPROPENYL)METHYLCYANOACETATE

[3-Pentenoic acid, 2-cyano-3-ethyl-2-methyl-, ethyl ester]



Submitted by Evelyn M. Hancock and Arthur C. Cope.
Checked by H. R. Snyder and J. H. Saunders.

1. Procedure

A solution of sodium ethoxide is prepared from 9.2 g. (0.40 mole) of freshly cut sodium and 400 ml. of absolute ethanol (Note 1) in a 1-l. three-necked flask fitted with a dropping funnel, a thermometer, a mercury-sealed stirrer, and a condenser protected by a drying tube (Note 2). To the stirred solution, which is kept at –5° (conveniently by partially immersing the flask in a Dry Ice bath), 72.4 g. (0.40 mole) of ethyl (1-ethylpropylidene) cyanoacetate (p. 399) is added dropwise from the funnel during 8–10 minutes. After the mixture has been stirred for an additional 20 minutes at –5°, 62.5 g. (0.44 mole) of methyl iodide is added from the dropping funnel as rapidly as possible. The flask is heated immediately with a strong flame which is withdrawn just as the solution reaches the boiling point. The alkylation is vigorous, but the flask is not cooled unless loss of material through the reflux condenser appears imminent (Note 3). After the spontaneous reaction has subsided, the solution is refluxed until a piece of red litmus paper dipped into the liquid and subsequently moistened shows a neutral reaction (15–30 minutes).

The solution is cooled and diluted with 1 l. of water, and the ester layer is separated. The aqueous layer is extracted with four 50-ml. portions of benzene, and the combined ester and benzene extracts are washed with two 25-ml. portions of water and then distilled from a 500-ml. modified Claisen flask. The fraction (above 75 g.) which is collected at 95–118°/10 mm. is shaken mechanically for 4 hours with 100 ml. of 20% sodium bisulfite solution (Note 4). The ester layer is separated, the aqueous layer is extracted with three 25-ml. portions of benzene, and the combined ester and benzene extracts are washed with 25 ml. of water. The product remaining after removal of the benzene is distilled under reduced pressure from a 250-ml. modified Claisen flask or through a Widmer column. The yield of ester boiling at 112–113°/8 mm. is 63.5–68 g. (81–87%).

2. Notes

1. Commercial absolute ethanol is dried with sodium and ethyl phthalate[1] and redistilled. The checkers obtained a considerably lower yield in a run employing ethanol dried over magnesium methoxide.
2. The various pieces of apparatus are dried in an oven and assembled rapidly in order to exclude moisture.
3. Excessive cleavage (alcoholysis) of the product is avoided by carrying out the alkylation rapidly. This procedure minimizes the time during which the product is in contact with sodium ethoxide.
4. This treatment removes ethyl (1-ethylpropylidene) cyanoacetate as a water-soluble sodium bisulfite addition product (p. 399).

3. Discussion

The above procedure illustrates a general method for preparing homologous ethyl (dialkylvinyl) alkylcyanoacetates by the alkylation of ethyl alkylidenecyanoacetates.[2]

References and Notes

1. *Org. Syntheses* Coll. Vol. **2**, 155 (1943).
2. Cope and Hancock, *J. Am. Chem. Soc.*, **60**, 2903 (1938).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

Benzene (71-43-2)

sodium bisulfite (7631-90-5)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

Methyl iodide (74-88-4)

magnesium methoxide

ethyl phthalate

ETHYL (1-ETHYLPROPENYL)METHYLCYANOACETATE, 3-Pentenoic acid, 2-cyano-3-ethyl-2-methyl-, ethyl ester (53608-83-6)

ethyl (1-ethylpropylidene) cyanoacetate (868-04-2)

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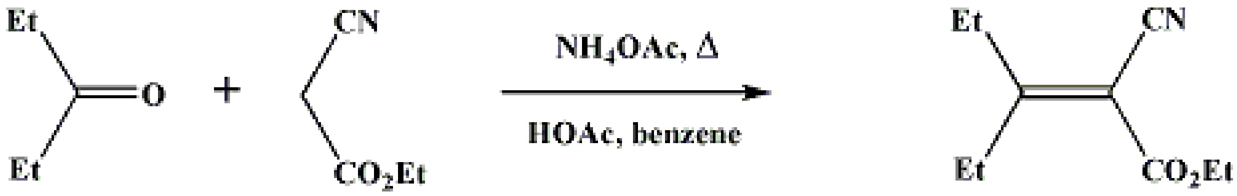
Organic Syntheses, CV 3, 399

ETHYL (1-ETHYLPROPYLIDENE)CYANOACETATE

[2-Pentenoic acid, 2-cyano-3-ethyl-, ethyl ester]



Submitted by Arthur C. Cope and Evelyn M. Hancock.
Checked by H. R. Snyder and J. H. Saunders.

1. Procedure

In a 500-ml. round-bottomed flask attached to a modified Dean and Stark constant water separator[1] (Note 1) which is connected to a reflux condenser are placed 67.8 g. (0.60 mole) of ethyl cyanoacetate (Note 2), 56.8 g. (0.66 mole) of diethyl ketone (Note 3), 9.2 g. (0.12 mole) of ammonium acetate, 30 g. (0.48 mole) of glacial acetic acid, and 100 ml. of benzene. The flask is heated in an oil bath at 160–165°, and the water that distils out of the mixture with the refluxing benzene is removed from the separator at intervals. Refluxing is continued for 24 hours (several hours after the separation of water has ceased) (Note 4).

The solution is cooled and washed with three 25-ml. portions of 10% sodium chloride solution, after which the benzene is removed by distillation under reduced pressure. The residue is transferred to a 1-l. bottle, a solution of 78 g. (0.75 mole) of commercial sodium bisulfite in 310 ml. of water is added, and the mixture is shaken on a mechanical shaker for 2 hours. The turbid solution is diluted with 500 ml. of water and extracted with three 50-ml. portions of benzene. The extracts are discarded (Note 5). The bisulfite solution is then cooled in an ice bath, and an ice-cold solution of 32 g. (0.8 mole) of sodium hydroxide in 130 ml. of water is added dropwise with mechanical stirring. The ester which separates is extracted at once with four 25-ml. portions of benzene (Note 6). The benzene solution is washed with 50 ml. of 1% hydrochloric acid, dried for a short time over 20 g. of anhydrous sodium sulfate, filtered into a 250-ml. modified Claisen flask, and distilled under reduced pressure. The yield of ester boiling at 123–125°/12 mm. (Note 7) is 65.4–75 g. (60.5–68%) (Note 8), (Note 9), and (Note 10).

2. Notes

1. Any continuous water separator that will return the benzene to the reaction mixture may be used.
2. Commercial ethyl cyanoacetate (Dow Chemical Company) was redistilled

before use; b.p. 93–94°/12 mm.
3. Diethyl ketone was either purchased from the Eastman Kodak Company and redistilled, or prepared by passing propionic acid slowly over a mixture of manganous oxide and clay plate chips in a tube furnace at 420–440°;[2] the apparatus was similar to one described in *Organic Syntheses*.[3] When prepared by this method the ketone was distilled, dried over potassium carbonate, and redistilled; b.p. 100–101°.
4. The water layer (20–25 ml.) contains some acetic acid and acetamide, the acetamide being formed from the ammonium acetate catalyst.
5. Extraction of the aqueous solution removes ethyl cyanoacetate from the aqueous solution of the sodium bisulfite addition product of ethyl (1-ethylpropylidene)cyanoacetate.
6. The unsaturated ester is regenerated when the bisulfite is neutralized with sodium hydroxide. The solution is kept cold during neutralization and extraction, and but little excess sodium hydroxide is used in order to prevent hydrolytic cleavage of the ester to diethyl ketone and ethyl cyanoacetate.
7. Other boiling points are 135–137°/25 mm. and 88–89°/1 mm.
8. A number of ketones have been condensed with ethyl cyanoacetate by this procedure. Reactive ketones such as aliphatic methyl ketones and cyclohexanone condense with ethyl cyanoacetate much more rapidly and give better yields of alkylidene esters. It is advantageous with such ketones to use a lower ratio of ammonium acetate-acetic acid catalyst.[1]
9. The sodium bisulfite purification step may be omitted, and the alkylidene ester purified directly by distillation. Care must be taken to separate the product from ethyl cyanoacetate by fractionation through a moderately efficient column. Purification through the bisulfite addition compound is recommended for alkylidene cyanoacetic esters derived from ketones containing four and five carbon atoms, but not for the higher homologs. The checkers obtained a slightly higher yield by the method employing fractional distillation (64% vs. 60.5%) but the quality of the product appeared to be slightly inferior (n_D^{25} 1.4645 vs. 1.4649).
10. A trace of a water-soluble white solid may cause the distillate to be slightly turbid. It may be removed by washing the product with water and redistilling.

3. Discussion

The above procedure is a very slight modification of a general method[1] for condensing ketones with ethyl cyanoacetate. Ethyl (1-ethylpropylidene)cyanoacetate also has been prepared by condensing diethyl ketone with ethyl cyanoacetate in the presence of piperidine or acetic anhydride and zinc chloride,[4] or piperidine and anhydrous sodium sulfate in a pressure bottle at 100°.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 397
- Org. Syn. Coll. Vol. 4, 234

References and Notes

1. Cope, Hofmann, Wyckoff, and Hardenbergh, *J. Am. Chem. Soc.*, **63**, 3452 (1941).
2. Sabatier and Mailhe, *Compt. rend.*, **158**, 831 (1914).
3. *Org. Syntheses* Coll. Vol. **2**, 389 (1943).
4. Birch and Kon, *J. Chem. Soc.*, **1923**, 2448.
5. Cowan and Vogel, *J. Chem. Soc.*, **1940**, 1528.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

METHYL KETONES

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

Acetamide (60-35-5)

acetic acid (64-19-7)

Benzene (71-43-2)

ammonium acetate (631-61-8)

acetic anhydride (108-24-7)

sodium hydroxide (1310-73-2)

Cyclohexanone (108-94-1)

sodium chloride (7647-14-5)

propionic acid (79-09-4)

sodium sulfate (7757-82-6)

sodium bisulfite (7631-90-5)

carbon (7782-42-5)

piperidine (110-89-4)

zinc chloride (7646-85-7)

Ethyl cyanoacetate (105-56-6)

manganous oxide

diethyl ketone (96-22-0)

Ethyl (1-ethylpropylidene)cyanoacetate, 2-Pentenoic acid, 2-cyano-3-ethyl-, ethyl ester (868-04-2)

ammonium acetate-acetic acid

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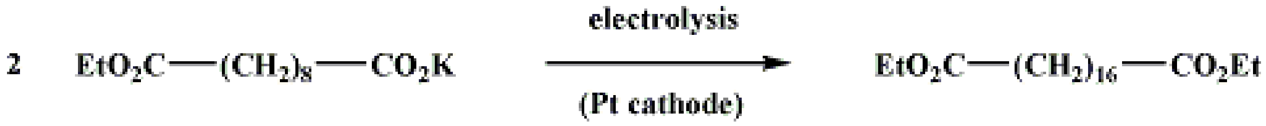
Organic Syntheses, CV 3, 401

ETHYL 1,16-HEXADECANEDICARBOXYLATE

[Octadecanedioic acid, diethyl ester]



Submitted by Sherlock Swann, Jr., René Oehler, and P. S. Pinkney.
Checked by Lee Irvin Smith, James W. Horner, Jr., and J. W. Clegg.

1. Procedure

To 86.5 g. (0.38 mole) of ethyl hydrogen sebacate [*Org. Syntheses* Coll. Vol. 2, 276 (1943)] is added slowly and with cooling 125–130 ml. of approximately 3 *N* potassium hydroxide. The solution is then diluted to approximately 250 ml., yielding a 1.5 *N* solution of potassium ethyl sebacate.

The solution of potassium ethyl sebacate (Note 1) is poured into a 500-ml. tall beaker provided with a cooling coil (Note 2), a thermometer, a stirrer, a platinum sheet anode 45–55 sq. cm. in area (Note 3), and two platinum wire cathodes (Note 4). To the solution 10 g. of monoethyl sebacate (Note 5) is added.

The electrodes are connected to a suitable source of direct current, 10 amperes of which is allowed to pass through the cell. To the solution there is now added 40 g. more of monoethyl sebacate in portions of 10 g. each over a period of 10 minutes (Note 6). The temperature of the cell is held below 50° by running cold water through the cooling coil (Note 7).

The run is finished in 60–70 minutes. The reaction will have reached completion when a few drops of the electrolyte removed with a pipet show an alkaline reaction to phenolphthalein. The alkalinity should be tested every 10 minutes after the first 45.

When the electrolyte has become alkaline, the oily product floating on the top is removed by means of a pipet (Note 8). The oil is washed with an equal volume of 10% potassium carbonate (Note 9), then with an equal volume of 3.5% hydrochloric acid, and finally twice with half its volume of water (a little ether effectively breaks up any emulsions which may form at this point). It is then crystallized from methanol, filtered by suction, and washed twice while in the funnel with ice-cold methanol (Note 10). The product, snow-white and waxy in appearance, is dried in a desiccator over sulfuric acid. The yield is 16–22 g. (40–55%) of material melting at 41–42°. These figures for the percentage yields, however, are based only upon the 50 g. of ethyl hydrogen sebacate used in the second part and no account is taken of the 86.5 g. used in preparing the electrolyte solutions. This preparation becomes practicable, therefore, only when several consecutive runs are made (Note 8).

2. Notes

1. The reaction mixture may require slight warming on the water bath to make a homogeneous solution.
2. The checkers used a copper cooling coil. This was slightly attacked during the electrolysis: the solution became blue, and copper deposited on the cathodes.
3. Convenient dimensions for the anode are 3.75 by 6.0 cm. (the area of the anode [both sides] used by the checkers was 52 sq. cm.). Care should be taken to submerge it in the solution to a depth such that the oil that gathers on the top of the solution during the electrolysis will not insulate it, thus increasing the current density. The wire tab of the platinum sheet may be sealed into a glass tube so that only the sheet is exposed to the solution.
4. The cathodes should be equidistant from the anode to ensure uniform current density on both sides of the anode.
5. As the potassium salt of monoethyl sebacate is decomposed during the electrolysis, the free acid forms new salt. The alkalinity of the solution may, therefore, be used as the end point of the electrolysis.
6. If the 50 g. of monoethyl sebacate is added all at once, excessive foaming will occur.
7. Addition of more water (50 ml.) makes possible a much better control of the temperature.
8. If it is desired to prepare larger amounts of product, more free acid may be added to the solution without turning off the current after the product has been drawn off by the pipet. Between ten and fifteen batches of monoethyl sebacate may be converted in this way. The length of time for a run will gradually increase with the number of runs. After ten to fifteen runs, the time required to convert a 50-g. batch is 3.5–4 hours. The electrolyte should then be renewed.
9. Unchanged mono ester may be recovered by acidification of the carbonate washings, followed by extraction with ether.
10. About the same amount of by-product as main product is in solution in the methanol. The first material that crystallizes is pure main product.

3. Discussion

Diethyl 1,16-hexadecanedicarboxylate has been prepared by the electrolysis of potassium ethyl sebacate[1] and by the electrolysis of a mixture of sodium and hydrogen sebacates.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 463

References and Notes

1. Brown and Walker, *Proc. Roy. Soc. Edinburgh*, **17**, 297 (1890); *Trans. Roy. Soc. Edinburgh*, **36**, 222 (1890); *Ann.*, **261**, 125 (1891); Fairweather, *Proc. Roy. Soc.*

Edinburgh, **45**, 283 (1925); Shiina, *J. Soc. Chem. Ind. Japan*, **40**, Suppl. binding 324 (1937) [*C. A.*, **32**, 499 (1938)].

2. Drake, Carhart, and Mozingo, *J. Am. Chem. Soc.*, **63**, 617 (1941).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium and hydrogen sebacates

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

methanol (67-56-1)

ether (60-29-7)

platinum (7440-06-4)

copper (7440-50-8)

potassium hydroxide (1310-58-3)

phenolphthalein (77-09-8)

Ethyl hydrogen sebacate, monoethyl sebacate (693-55-0)

ETHYL 1,16-HEXADECANEDICARBOXYLATE

Octadecanedioic acid, diethyl ester, Diethyl 1,16-hexadecanedicarboxylate (1472-90-8)

potassium ethyl sebacate, potassium salt of monoethyl sebacate

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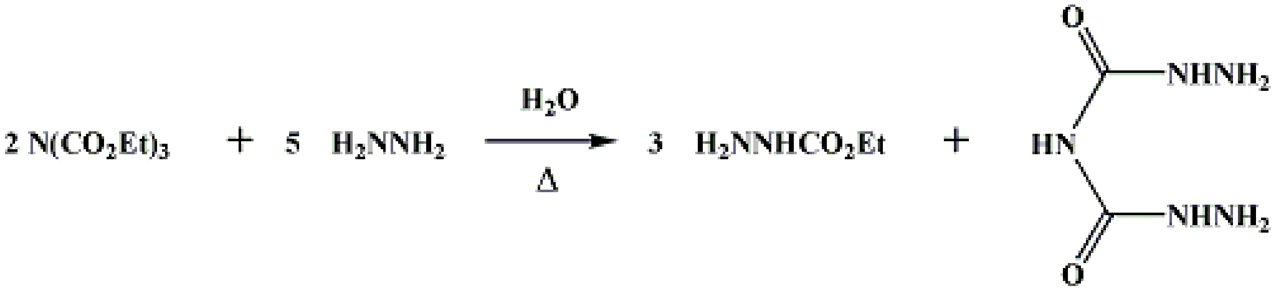
Organic Syntheses, CV 3, 404

ETHYL HYDRAZINECARBOXYLATE AND DIAMINOBIURET

[Carbazic acid, ethyl ester]

[Imidodicarboxylic acid dihydrazide]



Submitted by C. F. H. Allen and Alan Bell.
Checked by Nathan L. Drake and Carl Blumenstein.

1. Procedure

In a 3-l. round-bottomed flask equipped with a reflux condenser are placed 582 g. (2.5 moles) of N-tricarboxylic ester (p. 415) and 800 g. (6.7 moles) of 42% hydrazine hydrate (Note 1). The flask is shaken by hand to mix the two layers. After a short time, reaction begins with considerable evolution of heat, and all the N-tricarboxylic ester goes into solution (Note 2). After the reaction subsides, the solution is heated for 1 hour on a steam bath and then evaporated under reduced pressure until the mixture becomes a thick slurry of diaminobiuret crystals (Note 3). The mixture is cooled, 2 l. of 95% ethanol is added, and the diaminobiuret which has crystallized is filtered, washed with 250 ml. of ethanol, and dried. The substance melts at 205° with decomposition. The yield is 115–125 g. (69–75%).

The filtrate is now evaporated at atmospheric pressure to remove the ethanol, and the residual oil is distilled using a Vigreux column. Ethyl hydrazinecarboxylate boils at 92–95° /13 mm. The yield is 350–370 g. (90–95%). After distillation in vacuum, the ester may crystallize; the crystals melt at 51–52°.

2. Notes

1. This reaction can be carried out successfully with these amounts, but, if larger quantities of starting materials were to be used, it would be advisable to dilute the ester with ethanol and run in the hydrazine slowly. Several hours of refluxing on a steam bath would serve to complete the reaction. In smaller runs no difficulty is encountered.
2. It is advisable to keep an ice bath at hand in case the reaction becomes too violent and it is necessary to cool the mixture rapidly.
3. If insufficient water is removed by evaporation, too much diaminobiuret will remain in solution and will interfere during the distillation of the ethyl hydrazinecarboxylate.

3. Discussion

Diaminobiuret has been prepared only from N-tricarboxylic ester and hydrazine hydrate.[1] Ethyl hydrazinecarboxylate has been prepared by reduction of nitrourethan electrolytically[2] or with zinc dust and acetic acid,[3] and by the action of hydrazine hydrate on diethyl carbonate,[4,5] ethyl chlorocarbonate,[6] and N-tricarboxylic ester.[1]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 936

References and Notes

1. Diels, *Ber.*, **36**, 736 (1903).
2. Backer, *Rec. trav. chim.*, **31**, 20 (1912).
3. Thiele and Lachmann, *Ann.*, **288**, 293 (1895).
4. Diels, *Ber.*, **47**, 2186 (1914).
5. Merck, Ger. pat. 285,800 [*Frdl.*, **12**, 94 (1914–1916)].
6. Stollé and Benrath, *J. prakt. Chem.*, (2) **70**, 276 (1904).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Imidodicarboxylic acid dihydrazide

N-tricarboxylic ester

ethanol (64-17-5)

acetic acid (64-19-7)

zinc (7440-66-6)

hydrazine hydrate (7803-57-8)

hydrazine (302-01-2)

ethyl chlorocarbonate (541-41-3)

diethyl carbonate (105-58-8)

Ethyl hydrazinecarboxylate, Carbazic acid, ethyl ester (4114-31-2)

diaminobiuret (4375-11-5)

nitrourethan

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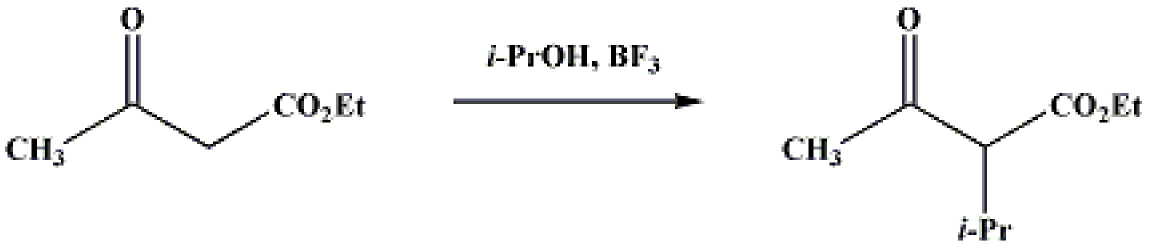
Organic Syntheses, CV 3, 405

ETHYL α-ISOPROPYLACETOACETATE

[Isovaleric acid, α-acetyl, ethyl ester]



Submitted by Joe T. Adams, Robert Levine, and Charles R. Hauser.
Checked by H. R. Snyder and John Mirza.

1. Procedure

This reaction should be carried out under a well-ventilated hood (Note 1).

A mixture of 30.0 g. (0.5 mole) of anhydrous isopropyl alcohol and 65.0 g. (0.5 mole) of freshly distilled ethyl acetoacetate is placed in a 500-ml. round-bottomed three-necked flask equipped with a mercury-sealed stirrer, a gas inlet tube terminating about 1 cm. above the surface of the liquid, a gas outlet tube connected with a calcium chloride drying tube, and a thermometer (Note 2). The gas inlet tube is connected to a source of boron fluorides (Note 3), and an ice bath is applied to the reaction flask; when the temperature of the stirred mixture has fallen to approximately 0° the stream of boron fluoride is started and adjusted so that the temperature of the mixture does not exceed 7°. The addition of boron fluoride is continued until the mixture is saturated and for 15 minutes thereafter (Note 4). The reaction mixture then is stirred at 28° for 2.5 hours (Note 5), at the end of which period it is poured slowly into a stirred mixture of 130 g. of hydrated sodium acetate, 100 ml. of water, and 200 g. of crushed ice. The beaker containing the resulting mixture is allowed to stand in an ice bath for 2 hours with occasional stirring.

The mixture is poured into a 1-l. separatory funnel. The beaker is rinsed with 300 ml. of ether, and this portion of solvent is shaken with the mixture in the separatory funnel. The phases are separated, and the aqueous solution is extracted twice with 100-ml. portions of ether. The combined ether solutions are washed with saturated aqueous bicarbonate solution until carbon dioxide no longer forms. The solution is transferred to an Erlenmeyer flask and dried over about 25 g. of anhydrous sodium sulfate for 12 hours, after which it is decanted into another Erlenmeyer flask and dried over about 10 g. of Drierite for 6 hours.

A 125-ml. modified Claisen flask is arranged for distillation, but with a dropping funnel fitted in the neck intended for the ebullator tube. Portions of the dried ether

solution are introduced into the flask through the funnel while the flask is heated on the steam bath for continuous removal of the solvent. After all the ether solution and the ether washings from the last drying agent have been concentrated, the dropping funnel is replaced by an ebullator tube and distillation under diminished pressure is begun cautiously. Fractions are collected at 60–96°/20 mm. and at 96–98°/20 mm. The first fraction is redistilled to give an additional quantity of material boiling at 96–98°/20 mm. (Note 6). The combined product weighs 52–58 g. (60–67%) (Note 7).

2. Notes

1. Although no definite data are available concerning the toxicity of boron fluoride, users should exercise caution and avoid breathing the fumes. The toxic effects of hydrogen fluoride and alkali fluorides are well known. Boron fluoride reacts with moisture in the air, forming white fumes of fluoboric acid and boric acid which cause a choking sensation when breathed.
2. The entire apparatus is dried in an oven at about 100° just before use.
3. Commercial boron fluoride from a tank is passed through a saturated solution of boric oxide in concentrated sulfuric acid.
4. The time required for saturation varies from 1 to 2 hours, depending upon the rate of addition. As the saturation point is approached, the fuming at the end of the exit tube increases rather sharply; the mixture is considered to be saturated when the fuming appears to have become constant.
5. The temperature and time at this point are critical and must be controlled carefully.
6. If the fractionation is conducted with a 30-cm. Vigreux column the redistillation of the fore-run is unnecessary.
7. By the same method ethyl α-cyclohexylacetoacetate (b.p. 146–148°/20 mm.) has been prepared in 34% yield from cyclohexanol and acetoacetic ester, and ethyl α-*tert*-butylacetoacetate (b.p. 101–102°/20 mm.) In 10–14% yield from *tert*-butyl alcohol and acetoacetic ester.

3. Discussion

The above procedure is based on that described by Adams, Abramovitch, and Hauser.[1] Ethyl α-isopropylacetoacetate has also been prepared by Hauser and Breslow[2] by the reaction of ethyl acetoacetate with isopropyl ether in the presence of boron trifluoride, by Bischoff[3] by the alkylation of the sodium derivative of ethyl acetoacetate with isopropyl bromide, and by Renfrow[4] by the alkylation of ethyl acetoacetate with isopropyl bromide using potassium *tert*-amyloxide as the condensing agent.

References and Notes

1. Adams, Abramovitch, and Hauser, *J. Am. Chem. Soc.*, **65**, 552 (1943).
2. Hauser and Breslow, *J. Am. Chem. Soc.*, **62**, 2389 (1940).

3. Bischoff, *Ber.*, **28**, 2620 (1895).
4. Renfrow, *J. Am. Chem. Soc.*, **66**, 144 (1944).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

acetoacetic ester

sodium derivative of ethyl acetoacetate

fluoboric acid

Drierite

potassium tert-amyloxide

boric oxide

sulfuric acid (7664-93-9)

ether (60-29-7)

sodium acetate (127-09-3)

Cyclohexanol (108-93-0)

Isopropyl bromide (75-26-3)

sodium sulfate (7757-82-6)

carbon dioxide (124-38-9)

hydrogen fluoride (7664-39-3)

isopropyl alcohol (67-63-0)

Ethyl acetoacetate (141-97-9)

boric acid (10043-35-3)

boron fluoride, boron trifluoride (7637-07-2)

isopropyl ether (108-20-3)

Ethyl α-isopropylacetoacetate, Isovaleric acid, α-acetyl, ethyl ester (1522-46-9)

ethyl α-cyclohexylacetoacetate

tert-butyl alcohol (75-65-0)

ethyl α-tert-butylacetoacetate

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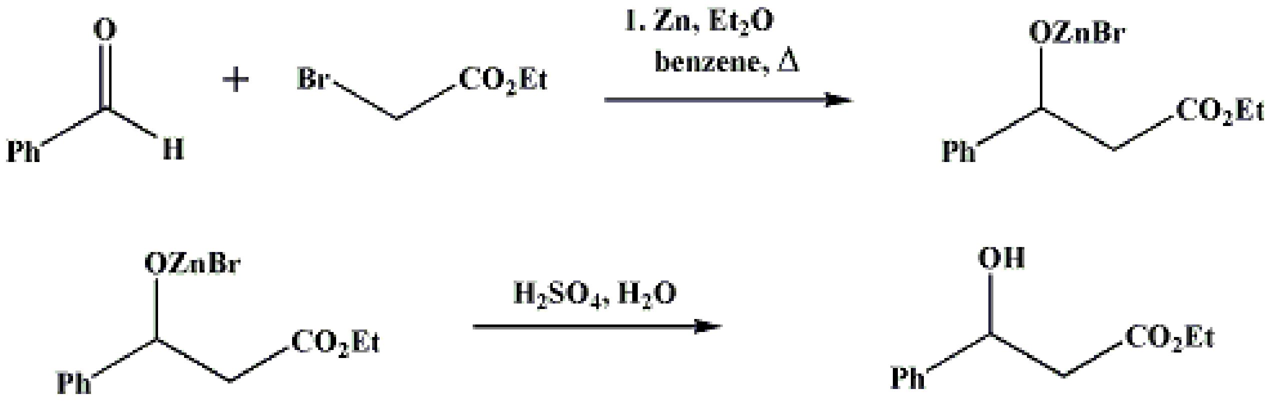
Organic Syntheses, CV 3, 408

ETHYL β-PHENYL-β-HYDROXYPROPIONATE

[Hydracrylic acid, β-phenyl-, ethyl ester]



Submitted by Charles R. Hauser and David S. Breslow.
Checked by R. L. Shriner, W. M. Hoehn, and Vera A Patterson..

1. Procedure

In a clean, dry, 500-ml. three-necked flask, fitted with a mechanical stirrer, a 250-ml. separatory funnel, and a reflux condenser (Note 1), the upper end of which is protected by a calcium chloride drying tube, is placed 40 g. (0.62 gram atom) of powdered zinc (Note 2).

A solution of 83.5 g. (0.50 mole) of ethyl bromoacetate (Note 3) and 65 g. (0.61 mole) of benzaldehyde (Note 4) in 80 ml. of dry benzene and 20 ml. of absolute ether is placed in the separatory funnel. About 10 ml. of this solution is added to the zinc, and the flask is warmed until the reaction starts (Note 5). The mixture is then stirred and the rest of the solution added at such a rate that the reaction mixture refluxes, care being taken that the reaction does not become too vigorous. The addition should take about an hour. The reaction mixture is refluxed for 30 minutes on a water bath after the addition of the solution is complete.

The flask is then cooled in an ice bath and the reaction mixture hydrolyzed by the addition of 200 ml. of cold 10% sulfuric acid with vigorous stirring during the addition. The acid layer is drawn off and the benzene solution extracted twice with 50-ml. portions of 5% sulfuric acid. The benzene solution is washed once with 25 ml. of 10% sodium carbonate solution, then with 25 ml. of 5% sulfuric acid (Note 6), and finally with two 25-ml. portions of water. The combined acid solutions are extracted with two 50-ml. portions of ether, and the combined ether and benzene solutions are dried with 5 g. of magnesium sulfate or Drierite. The solution is filtered, the solvent removed by distillation at atmospheric pressure from a steam bath, and the residue fractionated under reduced pressure. The ester is collected at 151–154°/11–12 mm. (128–132°/5–7 mm.). The total yield is 59–62 g. (61–64%) (Note 7).

2. Notes

1. An efficient reflux condenser is necessary to prevent loss of solvent. The same precautions as to cleanliness of apparatus and absence of moisture should be observed in carrying out Reformatsky reactions as in reactions involving the Grignard reagent.
2. The zinc dust is purified by washing it rapidly with dilute sodium hydroxide solution, water, dilute acetic acid, water, ethanol, acetone, and ether. It is then dried in a vacuum oven at 100°.
3. Ethyl bromoacetate is a powerful lachrymator, and care should be exercised in handling it. A 10% solution of ammonium hydroxide should be kept available to neutralize any of the bromo ester which may be spilled.
4. The benzaldehyde should be washed with two 50-ml. portions of 10% sodium bicarbonate solution, dried, and distilled.
5. It is essential that the reaction start before any additional ethyl bromoacetate and benzaldehyde are added.
6. The acid extraction should be continued until no white precipitate of zinc hydroxide is formed on extraction with sodium carbonate. This step is important, since the zinc complex hydrolyzes much less readily than the corresponding magnesium complex. A small amount of unhydrolyzed complex forms at the interface of the benzene and acid solutions. It is most readily separated during the first alkaline extraction.
7. Ethyl α,α-dimethyl-β-phenyl-β-hydroxypropionate may be prepared in a similar manner. For instance, from 100 g. of ethyl α-bromoisobutyrate and 65 g. of benzaldehyde, 82.5 g. (73%) of ethyl α,α-dimethyl-β-phenyl-β-hydroxypropionate, boiling at 153–158°/11 mm., is obtained. It may be recrystallized by dissolving it at 30° in 100 ml. of ligroin (30–60°), chilling the solution for several days, and decanting the clear liquid from the precipitate; m.p. 38.5–39°.

3. Discussion

Ethyl β-phenyl-β-hydroxypropionate has been prepared by esterification of β-phenyl-β-hydroxypropionic acid[1,2] obtained in turn by the addition of hydrogen bromide to cinnamic acid and hydrolysis; by catalytic reduction of ethyl benzoylacetate in aqueous acetic acid or aqueous ethanol;[3] by catalytic reduction of ethyl α-anilino-β-phenyl-β-hydroxypropionate;[4] and by the procedure described.[5,6,7]

References and Notes

1. Findlay and Hickmans, *J. Chem. Soc.*, **1909**, 1004.
2. Fittig and Binder, *Ann.*, **195**, 131 (1877).
3. Kindler and Blaas, *Ber.*, **76B**, 1211 (1943).
4. Fourneau and Billeter, *Bull. soc. chim. France*, **7**, 593 (1940).
5. Andrijewski, *J. Russ. Phys. Chem. Soc.*, **40**, 1635 (1908).
6. Blaise and Herman, *Ann. chim. phys.*, [8] **23**, 532 (1911).
7. Gaudini, *Gazz. chim. ital.*, **73**, 263 (1943).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ligroin

Drierite

ethanol (64-17-5)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

Benzene (71-43-2)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

hydrogen bromide (10035-10-6)

sodium carbonate (497-19-8)

benzaldehyde (100-52-7)

acetone (67-64-1)

zinc (7440-66-6)

ammonium hydroxide (1336-21-6)

cinnamic acid (621-82-9)

magnesium sulfate (7487-88-9)

Ethyl benzoylacetate (94-02-0)

Ethyl bromoacetate (105-36-2)

zinc hydroxide (20427-58-1)

Ethyl β-phenyl-β-hydroxypropionate, Hydracrylic acid, β-phenyl-, ethyl ester (5764-85-2)

Ethyl α,α-dimethyl-β-phenyl-β-hydroxypropionate

β-phenyl-β-hydroxypropionic acid

ethyl α-anilino-β-phenyl-β-hydroxypropionate

ethyl α-bromoisobutyrate (600-00-0)

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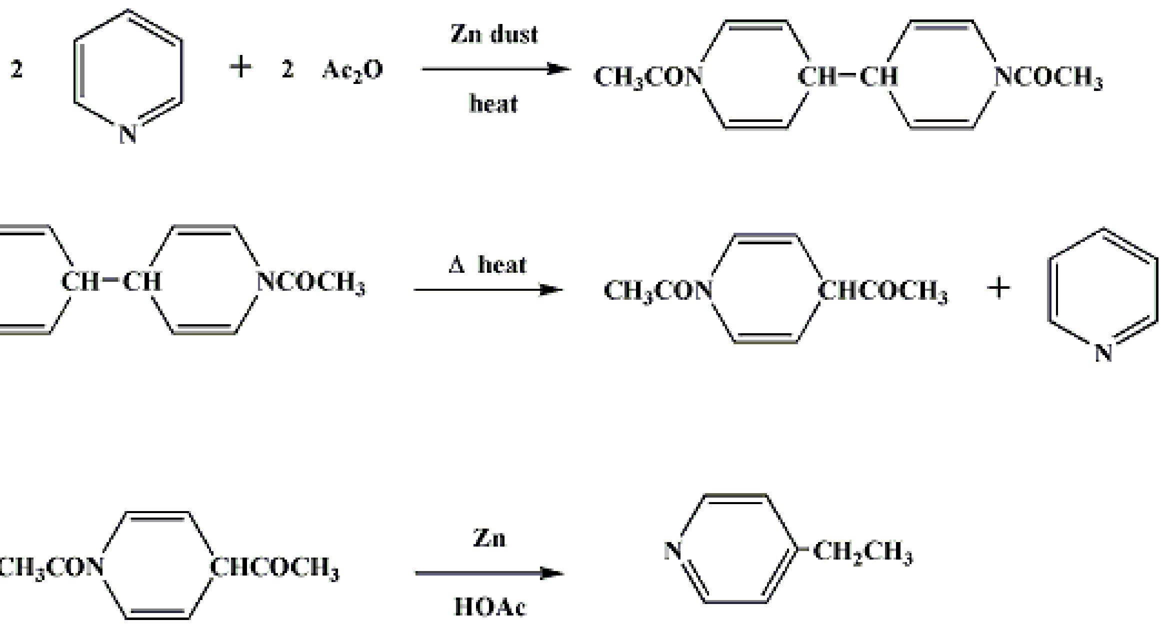
Organic Syntheses, CV 3, 410

4-ETHYLPYRIDINE

[Pyridine, 4-ethyl-]



Submitted by Robert L. Frank and Paul V. Smith[1].
Checked by Homer Adkins and Robert H. Jones.

1. Procedure

In a 3-l. three-necked round-bottomed flask fitted with a Hershberg stirrer and a thermometer are placed 1500 ml. of acetic anhydride and 300 g. (306 ml., 3.80 moles) of dry pyridine (Note 1). Three hundred grams (4.6 gram atoms) of zinc dust (Note 2), in amounts of 5–10 g., is added with stirring over a period of 3 hours. Heat is evolved almost immediately, and a cooling bath of water may be necessary. The reaction mixture becomes green after about 20 minutes. The temperature of the contents of the flask should be maintained between 25° and 30°. After the addition of the first 300-g. portion of zinc, 300 ml. of acetic acid is added to the reaction mixture and a reflux condenser is attached to the flask. Then 120 g. (1.83 gram atoms) of zinc dust is added in small portions. Heat is evolved during the addition, and the reaction may become rather violent. The mixture is refluxed with stirring for 30 minutes. A third portion of 180 g. (2.75 gram atoms) of zinc dust is added all at once, and refluxing is continued for an additional half hour. The solution is now orange-brown.

The flask is allowed to cool, and the contents are transferred to a 5-l. round-bottomed flask. The mixture is cautiously neutralized with 2 l. of a 40% aqueous solution of sodium hydroxide. The mixture is steam-distilled until 3 l. of distillate is collected, after which the residue is discarded. The distillate, which separates into two layers, is saturated with 1.5–1.8 kg. of solid potassium carbonate (Note 3). The organic layer is removed by decantation; the remaining water layer is divided into two portions, and each is extracted once with 150 ml. of chloroform. The chloroform extracts are combined with the organic layer.

The mixture is distilled using an efficient fractionating column (Note 4). There is a large fore-run of chloroform, pyridine, and water (Note 5), after which the temperature rises and 145–167 g. of material, b.p. 145–165°/760 mm., is collected. This is refractionated, and 135–155 g. (33–38%) of 4-ethylpyridine, b.p. 163–165°/760 mm., n_D^{20} 1.5010, is obtained (Note 6).

2. Notes

1. The pyridine is dried over calcium oxide and redistilled.

2. The zinc is activated before use by stirring 830 g. of zinc dust in 300 ml. of 10% hydrochloric acid for 2 minutes, filtering, and washing the zinc with 600 ml. of water, then with 200 ml. of acetone.

3. An equal weight of sodium chloride may be used instead of potassium carbonate.

4. A Fenske-type column 30 cm. in length and 18 mm. in diameter packed with glass helices gave satisfactory separations.

5. It does not appear feasible to recover the pyridine from the mixture of chloroform, water, and pyridine.

6. This procedure has been employed by Arens and Wibaut[2] to prepare other 4-alkyl derivatives of pyridine. The yields tend to decrease as the molecular weight of the anhydride increases. The boiling points are as given below: 4-propylpyridine 189°, 4-*n*-butylpyridine 207–209°, 4-isobutylpyridine 197–199°, 4-isoamylpyridine 222–223°, and 4-*n*-octylpyridine 265–268°.

3. Discussion

4-Ethylpyridine has been prepared by heating N-ethylpyridinium iodide in a sealed tube at 300°;[3] by heating pyridine with ethyl iodide;[4] from 4-ethylpyridinecarboxylic acid through distillation from lime;[5] and in small amounts by distilling brucine with potassium hydroxide.[6] Pyridine when heated with ferric chloride in an autoclave gives a mixture of alkylated pyridines from which 4-ethylpyridine can be isolated.[7] A general method for 4-alkylpyridines involves heating 5-(γ-pyridyl)-5-alkylbarbituric acids with alkali followed by an acid cleavage to remove the carbon dioxide.[8] 4-Ethylpyridine has been isolated from California petroleum.[9] The most useful method involves the treatment of pyridine with acetic anhydride and zinc.[10,11]

References and Notes

1. Work done under contract with the Office of Rubber Reserve, Reconstruction Finance Corporation.
2. Arens and Wibaut, *Rec. trav. chim.*, **61**, 59 (1942).
3. Ladenburg, *Ber.*, **16**, 2059 (1883); **18**, 2961 (1885); *Ann.*, **247**, 1 (1888).
4. Ladenburg, *Ber.*, **32**, 42 (1899).
5. Gabriel and Colman, *Ber.*, **35**, 1358 (1902).
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7. Morgan and Burstall, *J. Chem. Soc.*, **1932**, 20.
8. Gebauer (Chemische Fabrik von Heyden, A.-G.), Ger. pat. 638,596 [*C. A.*, **31**, 3067 (1937)].
9. Hackmann, Wibaut, and Gitsels, *Rec. trav. chim.*, **62**, 229 (1943).
10. Dohrn and Horsters (Chemische Fabrik auf Actien vorm. E. Schering), Ger. pat. 390,333 [*Chem. Zentr.*, **1924**, II, 891].
11. Wibaut and Arens, *Rec. trav. chim.*, **60**, 119 (1941).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

acetic anhydride (108-24-7)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium chloride (7647-14-5)

carbon dioxide (124-38-9)

acetone (67-64-1)

pyridine (110-86-1)

potassium hydroxide (1310-58-3)

zinc (7440-66-6)

ferric chloride (7705-08-0)

calcium oxide

brucine

Ethyl iodide (75-03-6)

Pyridine, 4-ethyl-, 4-ethylpyridine (536-75-4)

4-propylpyridine (1122-81-2)

4-isobutylpyridine (4810-79-1)

4-isoamylpyridine

N-ethylpyridinium iodide

4-ethylpyridinecarboxylic acid (4021-13-0)

4-n-butylpyridine (5335-75-1)

4-n-octylpyridine

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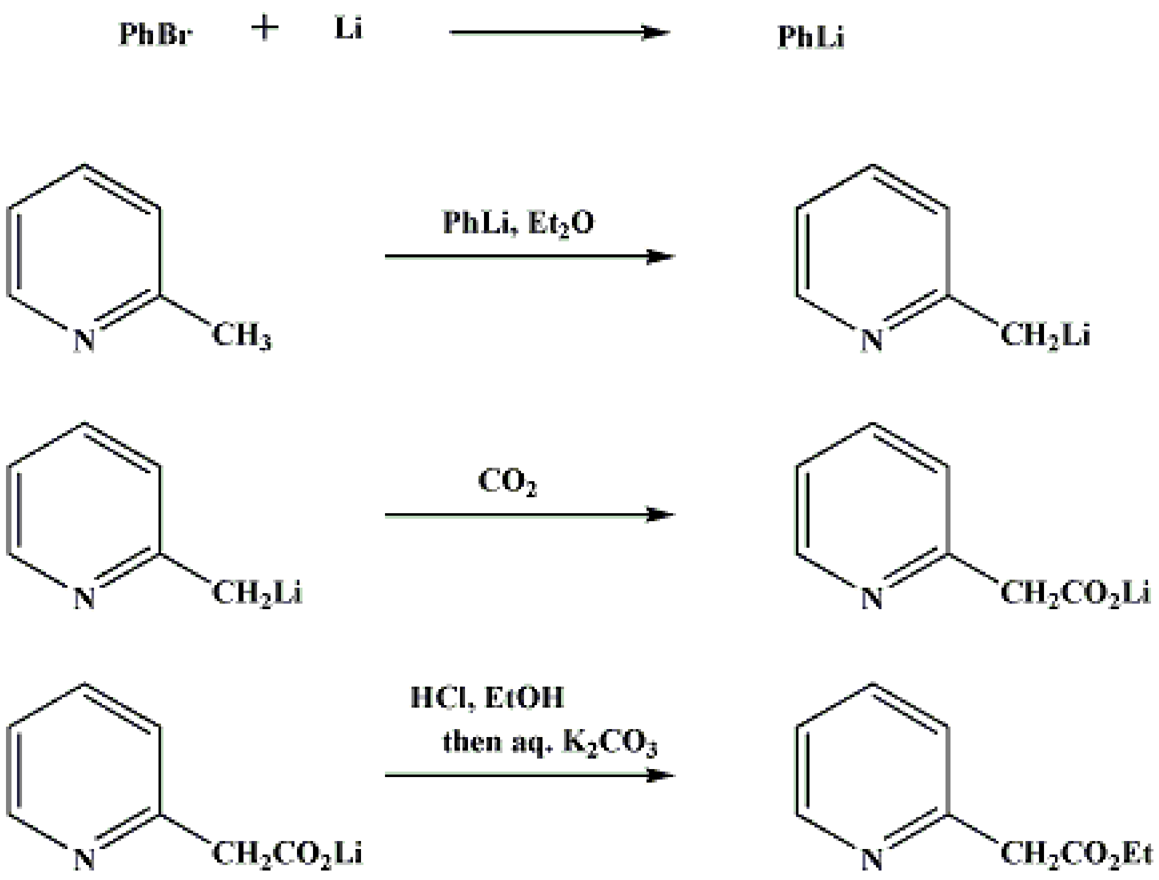
Organic Syntheses, CV 3, 413

ETHYL 2-PYRIDYLACETATE

[2-Pyridineacetic acid, ethyl ester]



Submitted by R. B. Woodward and E. C. Kornfeld.
Checked by Arthur C. Cope and William R. Armstrong.

1. Procedure

A 2-l. round-bottomed three-necked flask is fitted with a reflux condenser, a dropping funnel, and an efficient mechanical stirrer. A calcium chloride tube is attached to the condenser to protect the apparatus from moisture. To the flask are added 800 ml. of absolute ether and 13.9 g. (2 gram atoms) of lithium chips or shavings (Note 1). The stirrer is started, and 105 ml. (157 g., 1 mole) of dry bromobenzene is placed in the dropping funnel. About 5–15 ml. of the bromobenzene is added to initiate the reaction; when the ether begins to reflux, the balance is added at such a rate that the solvent refluxes continuously (1 hour) (Note 2). The mixture is then stirred and refluxed until most of the lithium disappears (45–90 min.). While stirring is continued, 97 ml. (93.1 g., 1 mole) of α-picoline is added dropwise in about 5–10 minutes. The dark red-brown solution of picolyllithium is stirred for an additional 30 minutes and is then poured slowly and with shaking onto 500–750 g. of crushed Dry Ice contained in a 3-l. round-bottomed flask (Note 3). The mixture is stirred well until the dark color of the

picolyllithium is discharged, and the excess of Dry Ice is allowed to evaporate. The ether is removed by distillation under reduced pressure at room temperature. The lumpy residue of lithium salts is broken up, and to it is added 750 ml. of commercial absolute ethanol. The solution is saturated with dry hydrogen chloride while cooling in an ice bath. The esterification mixture is allowed to stand overnight, after which the solvent is removed as completely as possible by distillation under reduced pressure on a steam bath. The syrupy residue is dissolved in 750 ml. of chloroform, and a paste prepared from 225 g. of potassium carbonate and 135 ml. of water is slowly added to the solution with mechanical stirring. After the paste has been added, the solution is stirred vigorously and is kept just below the boiling point for 1 hour. The chloroform solution is decanted from the inorganic salts, and the chloroform is removed by distillation. The residue is fractionated under reduced pressure from a modified Claisen flask with a fractionating side arm. About 40 g. of α-picoline is recovered in the fore-run, and the ethyl 2-pyridylacetate is obtained as a light yellow liquid, b.p. 135–137° /28 mm., 142–144° /40 mm., 109–112° /6 mm.; n_{D}^{25} 1.4979. The yield is 58–66 g. (35–40% based on lithium) (Note 4) and (Note 5).

2. Notes

1. The most convenient method of preparing the lithium chips is as follows. Pieces of lithium several grams each in size and slightly moist with paraffin oil are pounded with a hammer into thin sheets on a dry surface. The sheets are quickly cut into small chips by means of a pair of scissors and are added immediately to the absolute ether.
2. The use of a nitrogen atmosphere is not essential if the solution is kept protected from oxygen by an atmosphere of ether vapor. For this purpose the solution is kept at the reflux point throughout.
3. Rapid filtration of the picolyllithium solution onto the Dry Ice through a thin layer of glass wool is useful in removing unreacted lithium at this point.
4. Runs twice the size of the one described give comparable yields.
5. Methyl 2-pyridylacetate, b.p. 122–125° /21 mm., can be obtained in similar yield by use of methanol in the esterification.

3. Discussion

2-Pyridylacetic esters have been obtained by the alcoholysis of 2-pyridylacetanilide, in turn prepared by Beckmann rearrangement of the oxime of 2-phenacylpyridine,[1] and by the carbethoxylation of α-picoline in the presence of potassium amide.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 611

References and Notes

1. Oparina and Smirnov, *Khim. Farm. Prom.*, **1934**, No. 4, 15 [*C. A.*, **29**, 1820 (1935)]; *J. Gen. Chem.* U.S.S.R., **5**, 1699 (1935) [*C. A.*, **30**, 2567 (1936)].
2. Weiss and Hauser, *J. Am. Chem. Soc.*, **71**, 2023 (1949).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

oxime of 2-phenacylpyridine

ethanol (64-17-5)

potassium carbonate (584-08-7)

hydrogen chloride (7647-01-0)

methanol (67-56-1)

ether (60-29-7)

chloroform (67-66-3)

oxygen (7782-44-7)

nitrogen (7727-37-9)

bromobenzene (108-86-1)

lithium (7439-93-2)

potassium amide

Ethyl 2-pyridylacetate, 2-Pyridineacetic acid, ethyl ester (2739-98-2)

picolyllithium

Methyl 2-pyridylacetate (1658-42-0)

2-pyridylacetanilide

α-picoline (109-06-8)

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Organic Syntheses, CV 3, 415

ETHYL N-TRICARBOXYLATE

[N-Tricarboxylic ester]

Submitted by C. F. H. Allen and Alan Bell.
Checked by Nathan L. Drake and Carl Blumenstein.

1. Procedure

In a 12-l. round-bottomed flask equipped with stirrer, dropping funnel, and efficient reflux condenser are placed 450 g. (5 moles) of urethan (m.p. 46–48°), 7.5 l. of dry ether, and 218 g. of sodium wire (Note 1) and (Note 2). The mixture is warmed, and evolution of hydrogen accompanied by formation of sodium compound soon begins; after 2–3 hours the greater part of the metal will have been replaced by a gelatinous white precipitate. The stirrer is now started and the mixture warmed under reflux for an additional 2 hours. The flask is then cooled externally with running water, and 1050 g. (9.6 moles) of ethyl chlorocarbonate is added slowly over a period of 2 hours. The gelatinous precipitate becomes powdery, and the remainder of the sodium dissolves. After all the ester has been added, the mixture is stirred overnight at room temperature and then filtered (Note 3). The white residue is washed with 1 l. of ether, and the ether is removed from the combined solutions by evaporation on a steam bath (Note 4). The residual oil is distilled; after a fore-run containing some urethan, the product distils at 143–147° /12 mm. The yield is 575–640 g. (51–57%). On redistillation, all the product boils at 146–147° /12 mm.

2. Notes

1. Since water is usually present, it is advisable to distil the urethan before use, discarding the first 10%.
2. Sodium wire is not essential. The reaction will proceed just as well with sodium cut into pieces the size of a small pea. It is important that the sodium be cut into *small* pieces; otherwise a protective coating forms on the surface of the metal, preventing further reaction.
3. The sodium chloride is very finely divided and quickly clogs the pores of the filter paper. The mixture should be allowed to stand for a time before filtration to allow the salt to settle; the clear supernatant liquor can then be filtered rapidly.
4. Care should be taken in disposing of this residue; it invariably contains some unreacted sodium.

3. Discussion

Ethyl N-tricarboxylate has been prepared from urethan by reaction with sodium and chlorocarbonic ester[1] as well as from the potassium salt of ethyl imidodicarboxylate.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 404

References and Notes

1. Diels, *Ber.*, **36**, 740 (1903).
2. Diels, *Ber.*, **36**, 742 (1903).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Ethyl N-tricarboxylate

chlorocarbonic ester

ether (60-29-7)

hydrogen (1333-74-0)

sodium chloride (7647-14-5)

sodium (13966-32-0)

ethyl chlorocarbonate (541-41-3)

urethan (51-79-6)

potassium salt of ethyl imidodicarboxylate

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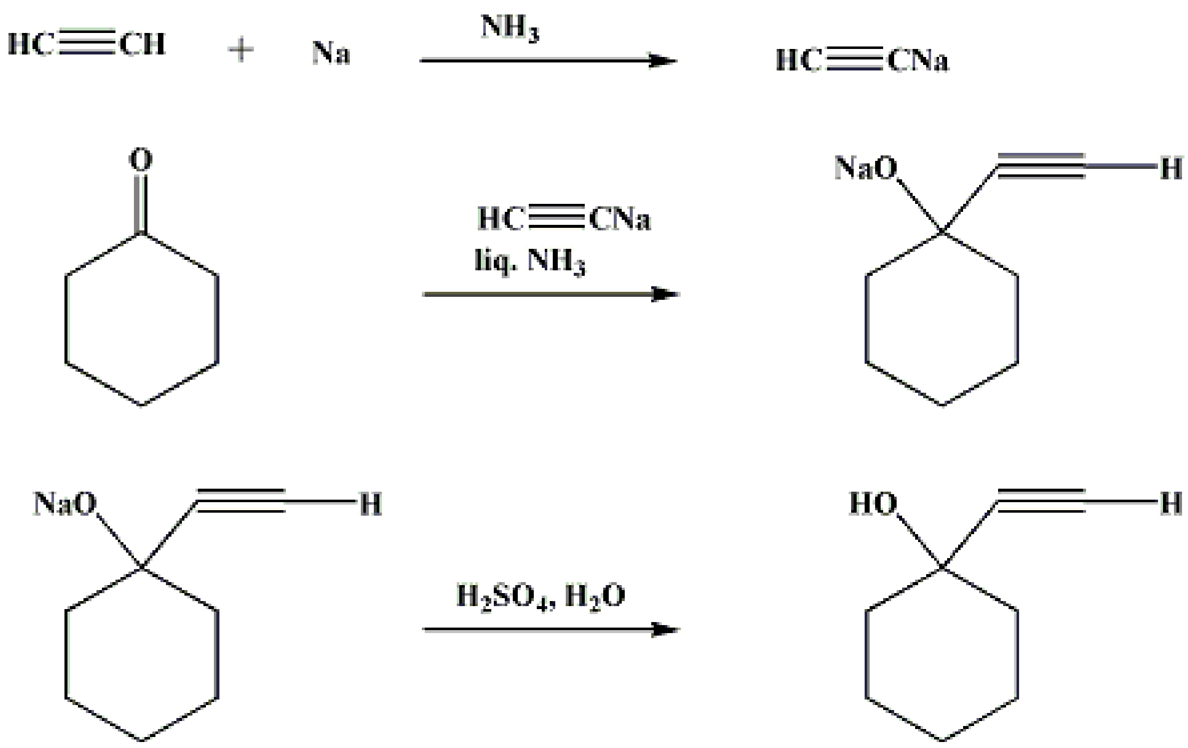
Organic Syntheses, CV 3, 416

1-ETHYNYLCYCLOHEXANOL

[Cyclohexanol, 1-ethynyl-]



Submitted by J. H. Saunders[1]
Checked by R. S. Schreiber and E. L. Jenner..

1. Procedure

A rapid stream of dry acetylene is passed into approximately 1 l. of liquid ammonia in a 2-l. three-necked flask equipped with a gas inlet tube and a mechanical stirrer while 23 g. (1 gram atom) of sodium is added over a period of 30 minutes (Note 1) and (Note 2). The flow of acetylene is then reduced (Note 3), and 98 g. (1 mole) of cyclohexanone is added dropwise. When this addition, which requires about an hour, is completed, the reaction mixture is allowed to stand for about 20 hours to permit the evaporation of nearly all the ammonia (Note 4).

The solid residue is decomposed by adding approximately 400 ml. of ice and water, and the resulting mixture is carefully acidified with 50% sulfuric acid (Note 5). The organic layer is dissolved in 100 ml. of ether and washed with 50 ml. of brine. The original aqueous phase and the brine wash are then extracted with two 50-ml. portions of ether. The combined ethereal solutions are dried over anhydrous magnesium sulfate and filtered, and the ether is distilled. The product is then distilled under reduced pressure through a good column (Note 6). The yield of 1-ethynylcyclohexanol is 81–93 g. (65–75%), b.p. 74°/14 mm.; n_D^{20} 1.4822 (Note 7).

2. Notes

1. The preparation of sodium acetylide is based on the procedure of Vaughn, Hennion, Vogt, and Nieuwland.[2]
2. The blue color of dissolved sodium is discharged so rapidly by the acetylene that it seldom spreads through the entire mixture.
3. The flow of acetylene may be terminated before the cyclohexanone is added. This operation, however, is alleged to increase the formation of glycol.[3]
4. If all the ammonia is allowed to evaporate and the residual solid is exposed to the air the yields may be decreased.
5. Upwards of 70 ml. is required. The amount depends upon the quantity of ammonia remaining.
6. The submitters and the checkers used a 15-cm. Vigreux column.
7. The product may solidify to a colorless solid, m.p. 30°.

3. Discussion

An attractive alternative procedure for the preparation of 1-ethynylcyclohexanol which gives yields of 80–90% employs the potassium salt of *tert*-amyl alcohol to effect the addition of acetylene to cyclohexanone.[4,5,6] This condensation has been brought about by a suspension of sodium amide in ether[7,8,9,10,11] and by potassium hydroxide in ether.[12] 1-Ethynylcyclohexanol has also been prepared by the action of acetylene on the sodium enolate of cyclohexanone[13] and by the action of sodium acetylide on cyclohexanone in liquid ammonia.[14] The procedure described here is essentially that of Campbell, Campbell, and Eby.[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 22
- Org. Syn. Coll. Vol. 4, 13

References and Notes

1. This investigation was carried out under the sponsorship of the Office of Rubber Reserve, Reconstruction Finance Corporation, in connection with the Government Synthetic Rubber Program.
2. Vaughn, Hennion, Vogt, and Nieuwland, *J. Org. Chem.*, **2**, 1 (1937).
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4. Pinkney, Nesty, Wiley, and Marvel, *J. Am. Chem. Soc.*, **58**, 972 (1936).
5. Dimroth, *Ber.*, **71B**, 1333 (1938).
6. Backer and van der Bij, *Rec. trav. chim.*, **62**, 561 (1943).
7. Ger. pat. 289,800 [*Frdl.*, **12**, 55 (1914–1916)].
8. Locquin and Sung, *Bull. soc. chim. France*, **35**, 597 (1924).

9. Rupe, Messner, and Kambli, *Helv. Chim. Acta*, **11**, 449 (1928).
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11. *Org. Syntheses*, **20**, 41 (1940), Note 11.
12. Azerbaev, *J. Gen. Chem. U.S.S.R.*, **15**, 415 (1945) [*C. A.*, **40**, 4683 (1946)].
13. Hurd and Jones, *J. Am. Chem. Soc.*, **56**, 1924 (1934).
14. Milas, MacDonald, and Black, *J. Am. Chem. Soc.*, **70**, 1831 (1948).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

brine

sodium enolate of cyclohexanone

sulfuric acid (7664-93-9)

acetylene (74-86-2)

ammonia (7664-41-7)

ether (60-29-7)

Cyclohexanone (108-94-1)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

magnesium sulfate (7487-88-9)

sodium amide (7782-92-5)

1-Ethynylcyclohexanol, Cyclohexanol, 1-ethynyl- (78-27-3)

sodium acetylide

potassium salt of tert-amyl alcohol (41233-93-6)

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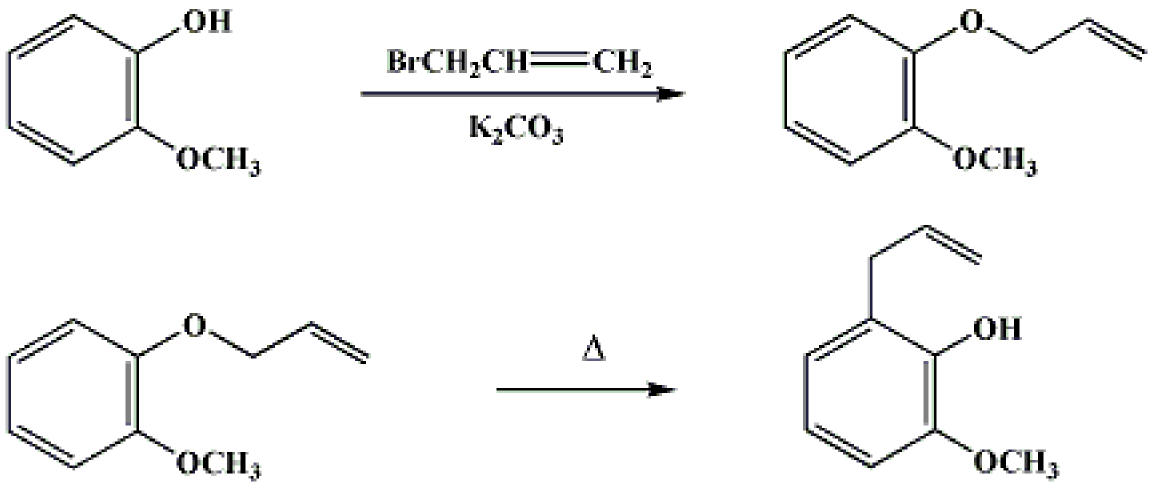
o-EUGENOL



Submitted by C. F. H. Allen and J. W. Gates, Jr..
Checked by W. E. Bachmann and N. C. Deno..

1. Procedure

A. *Guaiacol allyl ether*. A mixture of 63 g. (0.5 mole) of guaiacol, 66 g. (0.55 mole) of allyl bromide, 70 g. of anhydrous potassium carbonate (0.5 mole), and 100 ml. of dry acetone in a 500-ml. round-bottomed flask is refluxed on a steam bath for 8 hours and cooled. The mixture is diluted with 200 ml. of water and extracted with two 100-ml. portions of ether. The combined extracts are washed with two 100-ml. portions of 10% sodium hydroxide (Note 1) and dried with 50 g. of anhydrous potassium carbonate. After removal of the solvent, the residual oil (Note 2) is distilled under reduced pressure. The yield of guaiacol allyl ether boiling at 110–113°/12 mm. is 66–75 g. (80–90%).

B. *o-Eugenol*. The allyl ether (70 g.) is cautiously (Note 3) brought to boiling in a 500-ml. round-bottomed flask, refluxed for 1 hour, and cooled. The oil is dissolved in 100 ml. of ether (Note 4), and the solution is extracted with three 100-ml. portions of 10% sodium hydroxide. The combined alkaline extracts are then acidified with 100 ml. of concentrated hydrochloric acid diluted with 100 ml. of water, and the mixture is extracted with three 100-ml. portions of ether. The combined ether extracts are dried with 50 g. of anhydrous sodium sulfate and evaporated, and the residual oil is distilled under reduced pressure. The yield of *o*-eugenol boiling at 120–122°/12 mm. (Note 5) is 56–63 g. (80–90%).

2. Notes

1. A small amount of guaiacol may be recovered by acidifying the alkaline wash and extracting with ether.

2. When this crude guaiacol allyl ether was rearranged without prior distillation, the yields of *o*-eugenol were about 10% lower than those obtained with the distilled ether.
3. This rearrangement is sometimes quite vigorous and needs little heat once it is started. Dimethylaniline is said to be a good solvent for use in this type of rearrangement.[1]
4. Benzene may be substituted for ether throughout.
5. Other boiling points are 250–251°/760 mm., 125°/14 mm., and 115°/9 mm.

3. Discussion

Guaiacol allyl ether has been prepared from guaiacol, ethanolic potassium hydroxide, and allyl iodide;[2] or from guaiacol, allyl bromide, and potassium carbonate in acetone.[3,4] *o*-Eugenol has been prepared by the rearrangement of guaiacol allyl ether;[3,4] from 3-methoxy-2-allyloxybenzaldehyde by heating to 210°;[5] and from 3-methoxy-2-allyloxybenzoic acid by heating above 110°.[6]

References and Notes

1. Tarbell, *Org. Reactions*, **2**, 24 (1944).
2. Marfori *Annali di chimica e di farmacologia*, (5), **12**, 115; *Jahresb*., **1890**, 1196.
3. Claisen and Eisleb, *Ann.*, **401**, 52 (1913).
4. Claisen, *Ber.*, **45**, 3161 (1912); Ger. pat. 268,099 [*Chem. Zentr.*, **1914**, I, 308; *Frdl.*, **11**, 181 (1912–1914)].
5. Claisen and Eisleb, *Ann.*, **401**, 112, 114 (1913).
6. Claisen, *Ann.*, **418**, 117 (1919).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanolic potassium hydroxide

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether (60-29-7)

sodium hydroxide (1310-73-2)

Allyl bromide (106-95-6)

sodium sulfate (7757-82-6)

allyl iodide (556-56-9)

acetone (67-64-1)

Guaiacol (90-05-1)

dimethylaniline (121-69-7)

Guaiacol allyl ether (4125-43-3)

3-methoxy-2-allyloxybenzaldehyde

3-methoxy-2-allyloxybenzoic acid

o-Eugenol (579-60-2)

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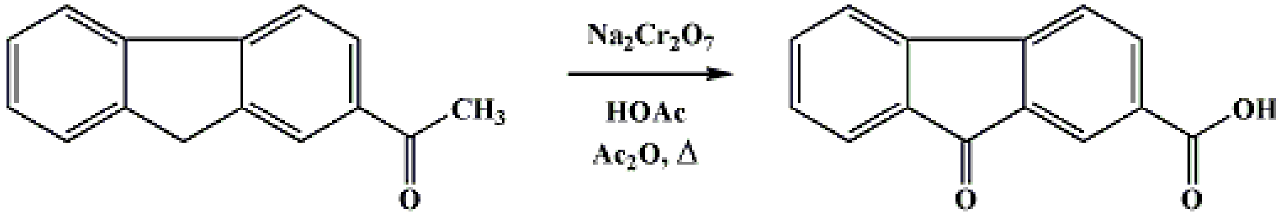
FLUORENONE-2-CARBOXYLIC ACID

[2-Fluorenecarboxylic acid, 9-oxo-]



Submitted by George Rieveschl, Jr. and F. E. Ray.
Checked by R. L. Shriner and Arne Langsjoen.

1. Procedure

A 5-l. three-necked round-bottomed flask (Note 1) equipped with a mercury-sealed stirrer, a reflux condenser, and a dropping funnel is set up on a steam bath. In the flask are placed 50 g. (0.24 mole) of 2-acetylfluorene (p. 23) (Note 2) and 650 ml. of glacial acetic acid. After the ketone has been brought into solution by heating and stirring, 450 g. (1.5 moles) of sodium dichromate dihydrate, previously ground to a coarse powder, is added carefully in small portions (about 10 g. each) (Note 3). Heating and stirring are continued throughout the addition, which requires about 45 minutes. The reaction flask is then removed from the steam bath, and the solution is brought to gentle reflux over a flame. During a period of 1.5 hours, 200 ml. of acetic anhydride is added through the dropping funnel. The mixture is refluxed and stirred during this addition and for 8 hours longer (Note 4).

The hot mixture is stirred into 9 l. of hot water in a 5-gal. crock. The suspension is agitated for 15 minutes and is then filtered on a 24-cm. Büchner funnel. The filter cake is washed with four 400-ml. portions of 2% sulfuric acid. The wet filter cake is transferred to a 2-l. beaker containing 700 ml. of a 5% solution of potassium hydroxide (Note 5). The mixture is stirred and heated to about 80°, and the hot solution is filtered. The alkali-insoluble material (Note 6) is washed with 50 ml. of hot 5% potassium hydroxide solution, and the combined alkaline filtrates are placed in a beaker, stirred with 5 g. of decolorizing carbon for 20 minutes, and again filtered. The solution of the potassium salt is heated with vigorous mechanical stirring to 70°, and 200 ml. of 18% hydrochloric acid is added dropwise, the heating being continued so that the temperature rises to about 85°. The fluorenone-2-carboxylic acid separates as a thick yellow mass. It is allowed to digest for 10 minutes with stirring, and the hot mixture is filtered on a 24-cm. Büchner funnel. The acid is washed free of potassium chloride by five or six 200-ml. portions of hot water. The product is pressed as dry as possible and then dried for 3 hours in an oven at 150°. It is a bright canary-yellow, weighs 36–40 g. (67–74%), and melts on an aluminum block at 339–341° (uncor.) with partial sublimation (Note 7).

2. Notes

1. A relatively large flask is used so that the sodium dichromate may be added without the escape of much acetic acid vapor.
2. 2-Acetylfluorene melting at 124–126° has been found to give as good results as the

pure compound of melting point 128–129°. The submitters report that the over-all yield from fluorene to fluorenone-2-carboxylic acid can be improved by the use of the crude product of the acylation (m.p. 113–117°) without purification (p. 23).

3. The acetic acid solution of 2-acetylfluorene is conveniently and safely heated to the maximum temperature attainable on the steam bath, and then small portions of sodium dichromate are added as the speed of the reaction permits. To prevent a violent reaction, not more than 10 g. of dichromate is added until the oxidation has begun (as indicated by the appearance of a green color).

4. Small yellow crystals usually appear after the mixture has refluxed for about 7 hours; their quantity does not increase much during the remaining heating period.

5. Sodium hydroxide should not be substituted here because of the lower solubility of the sodium salt.

6. The alkali-insoluble material (3–9 g.) can be washed with water, dried, and recrystallized from 95% ethanol to yield from 1 to 5 g. of pure 2-acetylfluorenone melting at 154–155°. Alternatively, it can be added to the next lot of 2-acetylfluorene if another oxidation is to be carried out.

7. This melting point corresponds to that given in the literature.[1,2] The submitters report that the product can be recrystallized from acetic anhydride or Cellosolve.

3. Discussion

The method described is a modification of the method of Dziewonski and Schnayder[1] and is described in a patent by the submitters.[2] Fluorenone-2-carboxylic acid has also been obtained by the oxidation of 2-fluorenealdehyde[3] and by the reaction of 2-acetylfluorene with potassium hypochlorite.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 23

References and Notes

1. Dziewonski and Schnayder, *Bull. intern. acad. polon. sci.*, **1930A**, 529 [*C. A.*, **25**, 5416 (1931)].
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3. Hinkel, Ayling, and Beynon, *J. Chem. Soc.*, **1936**, 345.
4. Schiessler and Eldred, *J. Am. Chem. Soc.*, **70**, 3958 (1948).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

acetic anhydride (108-24-7)

sodium hydroxide (1310-73-2)

decolorizing carbon (7782-42-5)

potassium hydroxide (1310-58-3)

cellosolve (107-21-1)

sodium dichromate (7789-12-0)

potassium hypochlorite

potassium chloride (7447-40-7)

fluorene (86-73-7)

sodium dichromate dihydrate (10588-01-9)

2-Acetylfluorene (781-73-7)

Fluorenone-2-carboxylic acid, 2-Fluorenecarboxylic acid, 9-oxo- (784-50-9)

2-acetylfluorenone (42136-05-0)

2-fluorenealdehyde (30084-90-3)

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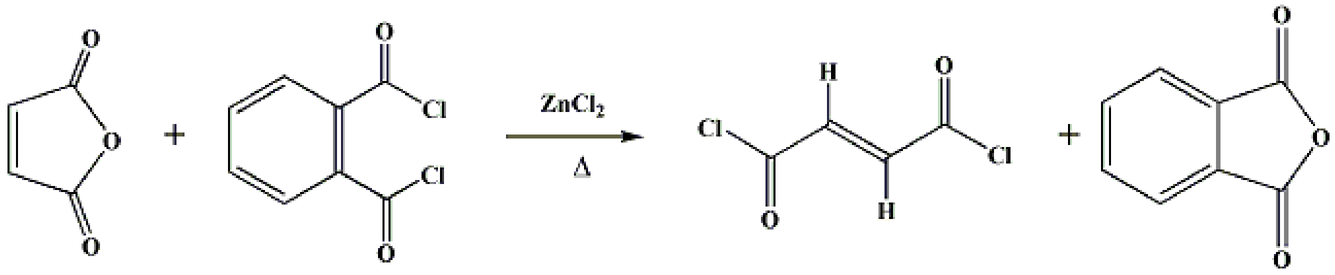
Organic Syntheses, CV 3, 422

FUMARYL CHLORIDE



Submitted by L. P. Kyrides
Checked by C. F. H. Allen and F. P. Pingert.

1. Procedure

A mixture of 98 g. (1 mole) of maleic anhydride, m.p. 52–54°, 230 g. of commercial phthaloyl chloride (Note 1), and 2 g. of anhydrous zinc chloride is placed in a 500-ml. three-necked round-bottomed flask. The flask is provided with a thermometer, the bulb of which extends into the liquid nearly to the bottom, and an efficient fractionating column (Note 2), (Note 3), and (Note 4). A 500-ml. water-cooled distilling flask is connected to the side arm of the column to serve as a receiving vessel.

The reaction mixture is heated by means of an oil bath (inside temperature 130–135°) for 2 hours, care being taken to avoid overheating (Note 5), and then allowed to cool to 90–95°. The fumaryl chloride is distilled as rapidly as possible (20 minutes), and the portion boiling over a 25° range (60–85°/13–14 mm.) is collected. It is then redistilled slowly (1 hour), and the portion boiling over a 2° range (62–64°/13 mm.) is collected (Note 6). The yield is 125–143 g. (82–95%) (Note 7) and (Note 8).

2. Notes

1. Commercial phthaloyl chloride contains about 94% of halide and some phthalic anhydride. The amount of chloride specified corresponds to a slight molar excess.

2. The checkers employed a modified Widmer column[1] .htm(Fig. 13) that has been used in many organic laboratories, but not officially described. They also used a Vigreux column (50 cm. effective length, 2.7 cm. inside diameter); the first distillation then required 1.5 hours, and the yield was 82–83%. The final temperature of the reaction mixture and observed boiling point will depend upon the type of apparatus used.

Fig. 13.

Fig. 13.

3. This procedure has also been checked using a fractionating column 30 cm. in length and 1.5 cm. in inside diameter packed with glass Wilson rings[2] and provided with the usual jackets for electrical heating. The distillation requires 3 hours. If this column is used, a single distillation gives a product pure enough for most purposes. An unpacked, indented column of about the same dimensions was unsatisfactory (checked by N. L. Drake).

4. Rubber stoppers are used throughout. Tightly fitting ground-glass connections are convenient but unnecessary. The third neck of the flask is used when acid chlorides are prepared from the corresponding acids (Note 9).

5. Above 135° the reaction is likely to get out of control; the ensuing decomposition seriously reduces the yield. For this reason the flask should be immersed only slightly in the oil bath (about one-third of the depth of the liquid layer).

6. With some lots of phthaloyl chloride, owing to the presence of an unknown impurity, the first few drops of the distillate have a reddish color. If the distillation is interrupted and air admitted to the system, the same phenomenon is observed on resuming the distillation.

7. The yield obtained is usually nearer the higher figure. The checkers carried out this preparation using five times these amounts and a 3-l. flask. The distillation times were 1 hour for the first and 3 hours for the final distillation.

8. Fumaryl chloride is best preserved in sealed glass containers. Bottles, closed by rubber stoppers free from sulfur, can be used for short periods. Ground-glass-stoppered bottles are unsuitable, the joints readily becoming "frozen," owing to hydrolysis of the chloride.

9. According to the submitters, yields of the order of 95% of other acid chlorides can be obtained by the use of phthaloyl chloride (1 mole of chloride to 1 mole of a monobasic acid, 2 moles of chloride to 1 mole of a dibasic

acid). Zinc chloride, as catalyst, is not necessary in the reaction of most acids and their anhydrides with phthaloyl chloride. When acids are used, it is best to add one of the components slowly, in order to avoid a too violent evolution of hydrogen chloride on warming.

3. Discussion

Fumaryl chloride has been prepared from fumaric acid and phthaloyl chloride,[3] from maleic acid by the action of thionyl chloride in the presence of zinc chloride, and from maleic anhydride by the use of phthaloyl chloride in the presence of zinc chloride.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 47
- Org. Syn. Coll. Vol. 3, 248

References and Notes

1. Widmer, *Helv. Chim. Acta*, **7**, 59 (1927).
2. Wilson, Parker, and Laughlin, *J. Am. Chem. Soc.*, **55**, 2795 (1933).
3. Van Dorp and Van Dorp, *Rec. trav. chim.*, **25**, 96 (1906).
4. Kyrides, *J. Am. Chem. Soc.*, **59**, 207 (1937).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrogen chloride (7647-01-0)

thionyl chloride (7719-09-7)

sulfur (7704-34-9)

phthalic anhydride (85-44-9)

maleic acid (110-16-7)

zinc chloride (7646-85-7)

phthaloyl chloride (88-95-9)

Fumaric acid (110-17-8)

maleic anhydride (108-31-6)

Fumaryl chloride (627-63-4)

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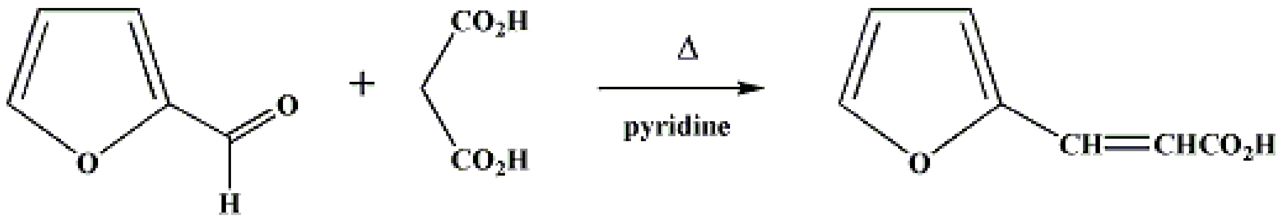
Organic Syntheses, CV 3, 425

FURYLACRYLIC ACID

[2-Furanacrylic acid]

[I. METHOD A]



Submitted by S. Rajagopalan and P. V. A. Raman.
Checked by C. S. Hamilton and R. A. Alberty.

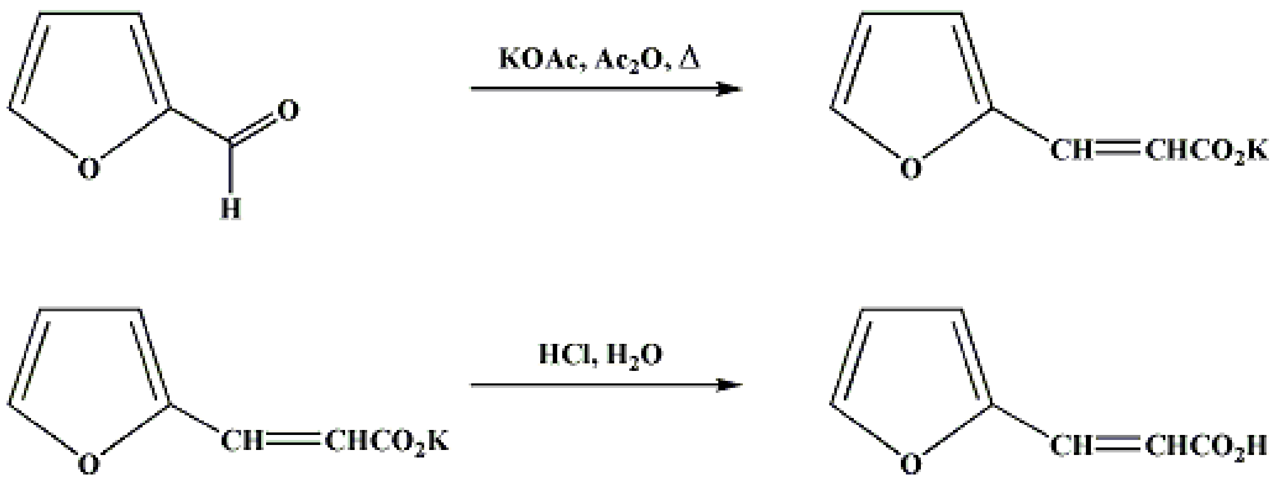
1. Procedure

In a 1-l. round-bottomed flask fitted with a reflux condenser are placed 192 g. (166 ml., 2 moles) of freshly distilled furfural (Note 1), 208 g. (2 moles) of malonic acid (Note 2), and 96 ml. (1.2 moles) of pyridine (Note 3). The flask is heated on a boiling water bath for 2 hours, and the reaction mixture is cooled and diluted with 200 ml. of water. The acid is dissolved by the addition of concentrated aqueous ammonia, the solution is filtered through a fluted filter paper, and the paper is washed with three 80-ml. portions of water. The combined filtrates are acidified with an excess of diluted (1:1) hydrochloric acid with stirring. The mixture is cooled by running water and then allowed to stand in an ice bath for at least 1 hour. The furylacrylic acid is filtered, washed with four 100-ml portions of water, and dried. The yield of practically colorless needles melting at 141° is 252–254 g. (91–92%). If a purer product is desired, recrystallization is best effected from dilute alcohol (Note 4). On slow cooling of the solution, needles melting at 141° separate.

2. Notes

1. Commercial furfural is subjected to a single distillation; b.p. 160–161°.
2. Commercial malonic acid is dried at 100° for 2 hours and stored in a stoppered bottle.
3. The pyridine, which may be a commercial grade, is dried over sticks of potassium hydroxide for a few hours and filtered.
4. A convenient procedure is to dissolve the acid in a slight excess of 50% ethanol, reflux the solution with charcoal (5 g. per 100 g. of acid) for 5–10 minutes, and filter through a fluted filter in a preheated funnel. Any solid material that separates toward the later stages is redissolved by the addition of a few drops of ethanol. The residue is thoroughly washed with boiling water. The hot solution is then diluted with cold water until crystals separate, heated to boiling, cooled slowly, and allowed to stand in a refrigerator for several hours. When the mother liquors are used for subsequent batches, the usual loss (2–3%) by recrystallization is more than halved.

[II. METHOD B]



Submitted by John R. Johnson
Checked by R. L. Shriner and C. M. Stevens.

1. Procedure

In a 3-l. round-bottomed flask provided with a mechanical stirrer and a 90-cm. air-cooled condenser are placed 288 g. (3 moles) of freshly distilled furfural, 460 g. (425 ml., 4.5 moles) of acetic anhydride, and 294 g. (3 moles) of dry, pulverized, freshly fused potassium acetate (Note 1). The ingredients are mixed thoroughly, stirring is started, and the flask is heated in an oil bath at 150° (bath temperature) for 4 hours, without interruption (Note 2). It is well to make provision for acetic acid vapor which escapes through the air condenser.

After cooling slightly, the reaction mixture is transferred to a large flask and treated with 3.5 l. of water. Part of this is used to rinse out the reaction flask. The mixture is boiled with 30 g. of Norit for about 10 minutes and is filtered while still *hot* with suction, using a preheated Büchner funnel. Furylacrylic acid tends to separate quickly and sometimes offers trouble in clogging the funnel. The filtrate is acidified to Congo red by the addition of a 1:1 solution of concentrated hydrochloric acid in water. After being cooled to 20° or below, preferably with stirring, and being allowed to stand for at least 1 hour, the acid is filtered with suction and washed with a small quantity of ice water. The yield is 270–290 g. (65–70%). The light tan crude acid melts at 138–139° (Note 3)

2. Notes

1. If fused sodium acetate is used the reaction is slower and 6–8 hours' heating is required.
2. When the temperature of the bath approaches 145–150° a rapid exothermic reaction sets in. This must be controlled (by application of cold, wet towels to the flask) to avoid too vigorous ebullition.
3. Furylacrylic acid melting at 138–139° is sufficiently pure for most purposes. The acid is perfectly white when pure, but many recrystallizations are required to attain that state. It may be recrystallized from benzene or ligroin (90–100°) with the addition of Norit. The loss is about 20–25%, and the product melts at 139–140° (sometimes 140–141°).

3. Discussion

This acid is usually prepared by the condensation of furfural with malonic acid in the presence

of pyridine.[1] It may also be prepared from furfural by the Perkin reaction.[2] The use of potassium acetate is advantageous since it allows the reaction to proceed rapidly at relatively lower temperatures. A preparation from furfuralacetone by oxidation has also been reported.[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 742
- Org. Syn. Coll. Vol. 4, 302

References and Notes

1. Dutt, *J. Indian Chem. Soc.*, **1**, 297 (1925); Kurien, Pandya, and Surange; *J. Indian Chem. Soc.*, **11**, 824 (1934) [*C. A.*, **29**, 3325 (1935)].
2. Marckwald, *Ber.*, **10**, 357 (1877); Gibson and Kahnweiler, *Am. Chem. J.*, **12**, 314 (1890).
3. Hurd and Thomas, *J. Am. Chem. Soc.*, **55**, 1646 (1933).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ligroin

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ammonia (7664-41-7)

Benzene (71-43-2)

acetic anhydride (108-24-7)

sodium acetate (127-09-3)

Norit (7782-42-5)

pyridine (110-86-1)

potassium hydroxide (1310-58-3)

Furfural (98-01-1)

furfuralacetone

Furylacrylic acid, 2-Furanacrylic acid (539-47-9)

Malonic acid (141-82-2)

potassium acetate (127-08-2)

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Organic Syntheses, CV 3, 428

β-GENTIOBIOSE OCTAACETATE

[Gentiobiose, β-octaacetyl-]

$$2C_6H_{12}O_6 \xrightarrow{\text{Emulsin}} C_{12}H_{22}O_{11} + H_2O$$

$$C_{12}H_{22}O_{11} + 8(CH_3CO)_2O \longrightarrow C_{12}H_{14}O_3(OCOCH_3)_8 + 8CH_3CO_2H$$

Submitted by B. Helferich and J. F. Leete.
Checked by Homer Adkins and E. E. Bowden.

1. Procedure

A solution of 1.65 kg. of crystallized glucose or 1.5 kg. of anhydrous glucose (8.3 moles) is prepared by heating the solid on a steam bath with 1.35 l. of distilled water. The solution is cooled and placed in a 2.5-1. glass-stoppered bottle. Fifteen grams of emulsin (Note 1) is added, then 20 ml. of toluene, and the flask is closed and allowed to stand at room temperature, with occasional shaking, for 5 weeks. The solution is then boiled, diluted with 8.5 l. of water, and filtered. To the filtrate is added 56 g. of baker's yeast in 650 ml. of water, and the temperature of the mixture is maintained at 28–32° for 12–14 days (Note 2). The mixture is then boiled for 30 minutes with an excess of powdered calcium carbonate and filtered.

The filtrate is evaporated under a pressure of 20–30 mm. to as thick a syrup as possible. For this operation the solution is placed in a 12-l. flask set in a steam bath and connected by a goose-neck to a condenser, which in turn is connected to a suction or distilling flask. A very fine capillary inlet tube into the 12-l. flask prevents any violent ebullition (Note 3) and (Note 4).

To the thick syrup (170–185 g.) are added 100 g. of anhydrous sodium acetate and 1.125 l. of acetic anhydride. The mixture is carefully heated to the boiling point with provision for cooling the flask with wet cloths should the acetylation become too violent. When the reaction is complete (about 20 minutes is required) the solution is poured into 10 l. of ice water. The water is decanted and renewed twice at 24-hour intervals in order to render the acetylated sugar filterable.

The dark brown product is filtered and, after drying in the air, is extracted with ether in a Soxhlet apparatus. The ether is removed by evaporation, and the light-colored residue (170 g.) is recrystallized from 1.65 l. of hot methanol. The crystals are washed on a Büchner funnel with methanol until free from colored impurities. The yield is 77–87 g. of material which melts at 187–190°. A second recrystallization from methanol (1.25 ml. per g. of product) gives pure βoctaacetylgentiobiose, with about 10% loss. The pure substance melts at 196° (cor.).

2. Notes

1. A commercial sample of emulsin was purchased from Merck and Company. If freshly prepared emulsin of good quality is available, the quantity may be reduced to one-tenth or less of the specified amount.
2. The yeast, by fermentation, removes the glucose which has not been transformed into gentiobiose. Fleischmann's and "Red Star" yeast have been used. The flask should be stoppered and protected with the conventional trap for the escape of carbon dioxide.
3. The submitters suggest a more complicated apparatus (Note 4) for this operation. However, the checkers have had no trouble with foaming or bumping when using the simple apparatus described above. Very little water condenses in the receiver, which serves as a safety trap in case foaming or bumping should occur.
4. The submitters used quantities four times as large as those stated above. They give the following directions for the distillation:
"The solution is drawn slowly through a glass tube provided with a stopcock into a 3-l. distillation flask standing in a bath of rapidly boiling water. The small portion which foams over is collected and evaporated in a second 3-l. distillation flask, likewise standing in rapidly boiling water. The distillate is passed through an efficient condenser and is collected in a thick-walled bottle or flask to which the vacuum pump or water pump is connected. A high vacuum is essential. The tube connecting the condenser and the receiver is provided with a stopcock so that the distillate may be poured out without interrupting the vacuum to any extent."

3. Discussion

The chief methods for the preparation of gentiobiose and its octa-acetate are discussed in a paper by Reynolds and Evans.[1,2] These methods involve isolation of the substance from gentian root;[3,4] the action of emulsin on glucose;[5,6] the catalytic hydrogenolysis of amygdalin;[7] separation from the mother liquors ("Hydrol") obtained in the manufacture of glucose;[8] and the condensation of acetobromoglucose with β-*d*-glucose-1,2,3,4-tetraacetate.[1,9,10] Reynolds and Evans recommend the last-mentioned method.

The method given above is a modification of those originally described by Bourguelot[3] and Zemplén.[11]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 332

References and Notes

1. Reynolds and Evans, *J. Am. Chem. Soc.*, **60**, 2559 (1938).
2. Haworth and Wylam, *J. Chem. Soc.*, **1923**, 123.
3. Bourquelot and Hérissey, *Compt. rend.*, **132**, 571 (1901).
4. Bourquelot and Hérissey, *Bull. soc. chim. France*, (3) **29**, 363 (1903).
5. Bourquelot and Hérissey, *Compt. rend.*, **157**, 732 (1913).
6. J. F. Leete, Ph.D. dissertation, Univ. of Greifswald, 1929.
7. Bergmann and Freudenberg, *Ber.*, **62**, 2783 (1929).
8. Berlin, *J. Am. Chem. Soc.*, **48**, 2627 (1926).
9. Helferich and Klein, *Ann.*, **450**, 219 (1926).
10. Gilbert, Smith, and Stacey, *J. Chem. Soc.*, **1946**, 622.
11. Zemplén, *Ber.*, **48**, 232 (1915).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

amygdalin

Gentiobiose, β-octaacetyl-

gentiobiose and its octa-acetate

methanol (67-56-1)

ether (60-29-7)

acetic anhydride (108-24-7)

sodium acetate (127-09-3)

carbon dioxide (124-38-9)

calcium carbonate (471-34-1)

toluene (108-88-3)

glucose (492-62-6)

Acetobromoglucose (572-09-8)

β-Gentiobiose octaacetate (4613-78-9)

Gentiobiose (554-91-6)

β-D-Glucose-1,2,3,4-tetraacetate (13100-46-4)

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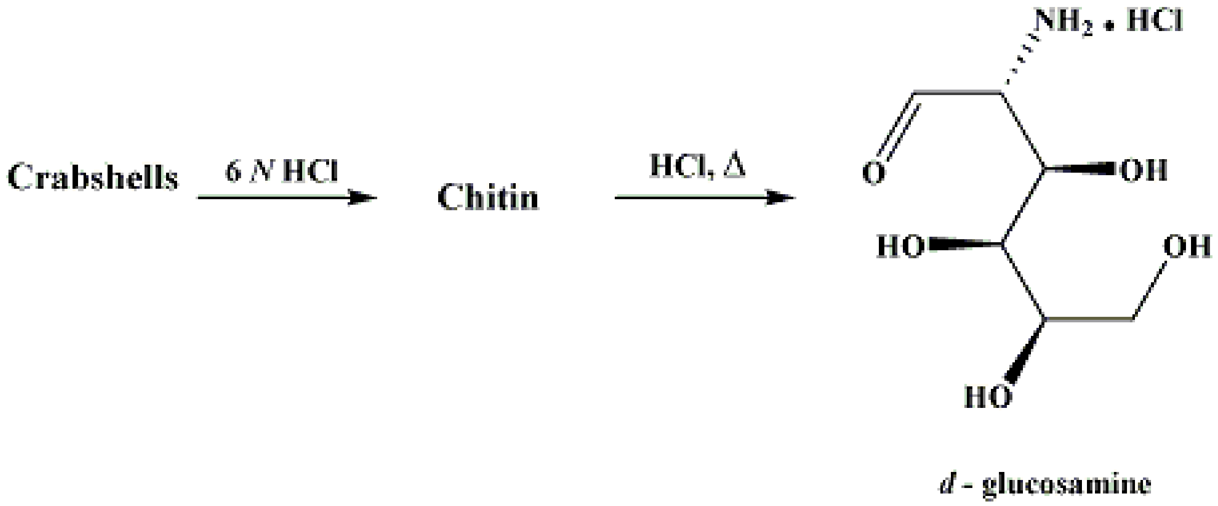
d-GLUCOSAMINE HYDROCHLORIDE



Submitted by Earl R. Purchase and Charles E. Braun.
Checked by H. R. Snyder and Nelson R. Easton.

1. Procedure

Two hundred grams of cleaned and dried crab shells (Note 1) ground to a fine powder is placed in a 2-l. beaker, and an excess of dilute (approximately 6 *N*) commercial hydrochloric acid is added slowly to the powdered material until no further action is evident. Much frothing occurs during the addition of the acid, and care must be exercised to avoid loss of material due to foaming over the sides of the beaker. After the reaction has subsided, the reaction mixture is allowed to stand from 4 to 6 hours to ensure complete removal of calcium carbonate. The residue is then filtered, washed with water until neutral to litmus, and dried in an oven at 50–60°. The weight of dried chitin is usually about 70 g., but with some lots of crab shells it may be as low as 40 g.

To 40 g. of dry chitin in a 500-ml. beaker is added 200 ml. of concentrated hydrochloric acid (C.P., sp. gr. 1.18), and the mixture is heated on a boiling water bath for 2.5 hours with continuous mechanical agitation. At the end of this time solution is complete, and 200 ml. of water and 4 g. of Norit are added. The beaker is transferred to a hot plate, and the solution is maintained at a temperature of about 60° and is stirred continuously during the process of decolorization. After an hour the solution is filtered through a layer of a filter aid such as Filter-Cel. The filtrate is usually a pale straw color; however, if an excessive color persists, the decolorization may be repeated until the solution becomes almost colorless. The filtrate is concentrated under diminished pressure at 50° until the volume of the solution is 10–15 ml. The white crystals of glucosamine hydrochloride are washed onto a sintered-glass filter with 95% ethanol. The white crystalline product, after being washed with 95% ethanol and dried, weighs 24–28 g. (60–70% of the weight of the chitin used). The optical rotation of a stable solution of the product containing the α- and β-isomers at equilibrium, $[\alpha]^{25.5}_{D}$,

varies from +68.8° to +70.1° (*c* = 4.75 in water).

The product is pure enough for most uses. If a purer product is desired, the crystals may be dissolved in the minimum amount of boiling water and treated with Norit. The resulting solution is filtered and added to a large excess of 95% ethanol and stirred vigorously for several hours. The product is collected after 4–6 hours. An appreciable amount of the β-form of the amino sugar remains dissolved in the alcohol and may be precipitated by adding ether.

2. Notes

1. The cleaned and dried crab shells were obtained from Carter and Lanhardt Company, Eleventh and Maine Avenue, S.W., Washington, D. C.

3. Discussion

The preparation of glucosamine hydrochloride from lobster shells and crab shells by essentially this method has been reported by Irvine, McNicoll, and Hynd[1] and Hudson and Dale.[2] Other methods involving the use of cicad larvae shells[3] and shrimp shells[4,5] also have been reported.

References and Notes

1. Irvine, McNicoll, and Hynd, *J. Chem. Soc.*, **99**, 256 (1911).
2. Hudson and Dale, *J. Am. Chem. Soc.*, **38**, 1434 (1916).
3. Komori, *J. Biochem. Japan*, **6**, 1–20 (1926) [*C. A.*, **21**, 372 (1927)].
4. van Alphen, *Chem. Weekblad*, **26**, 602 (1929) [*C. A.*, **24**, 2113 (1930)].
5. Rigby, U. S. pat. 2,040,879 [*C. A.*, **30**, 4598 (1936)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ether (60-29-7)

calcium carbonate (471-34-1)

glucosamine hydrochloride, D-Glucosamine hydrochloride (66-84-2)

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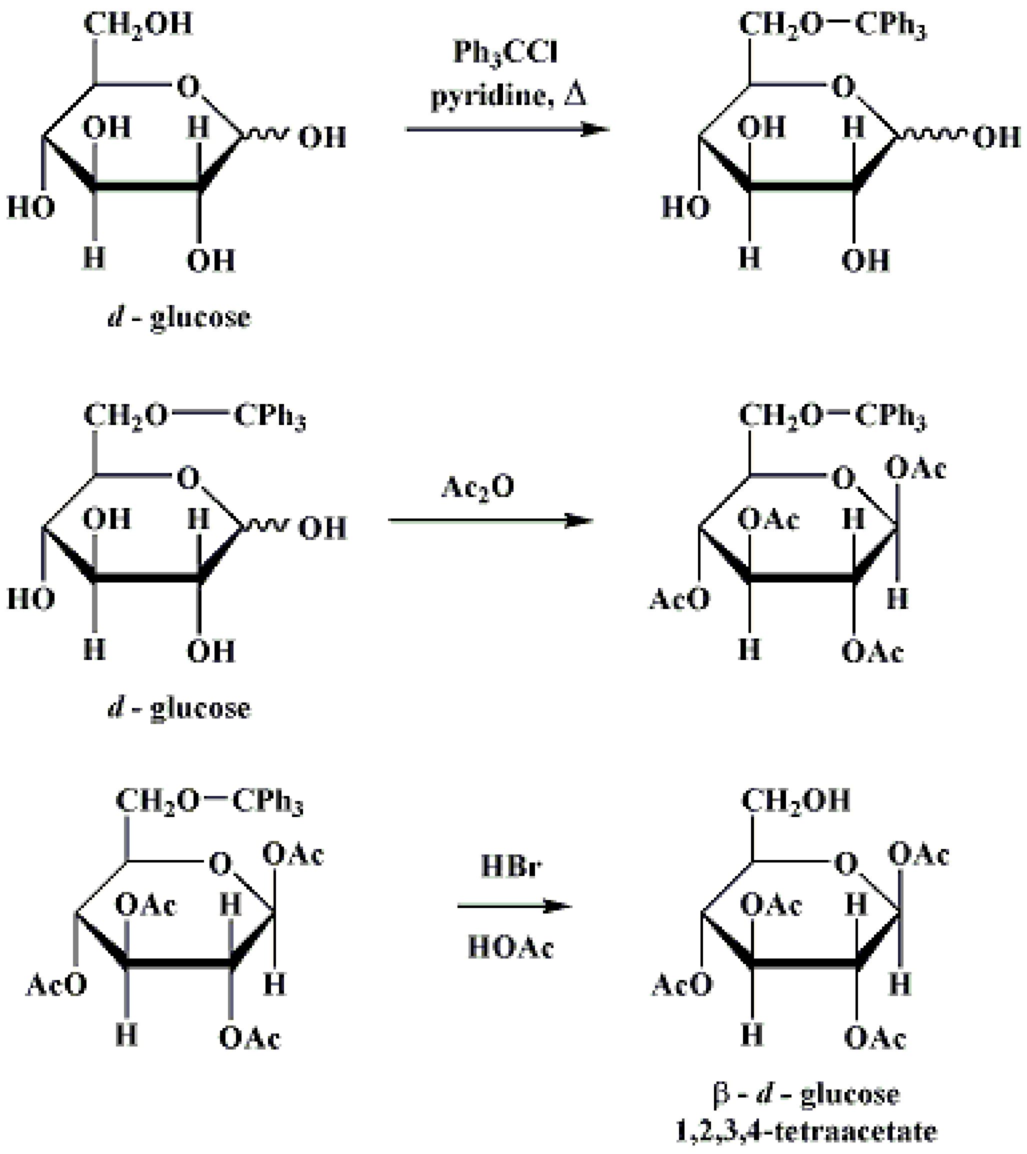
Organic Syntheses, CV 3, 432

β-*d*-GLUCOSE-1,2,3,4-TETRAACETATE

[D-Glucose, β-1,2,3,4-tetraacetyl-]



Submitted by Delbert D. Reynolds and William Lloyd Evans.
Checked by Lee Irvin, Smith R. T. Arnold, Newman Bortnick, Aaron Lerner, and Everett Schultz.

1. Procedure

A. *6-Trityl-β-d-glucose-1,2,3,4-tetraacetate.* A mixture containing 120 g. (0.67 mole) of anhydrous glucose, 193.2 g. (0.7 mole) of trityl chloride, and 500 ml. of anhydrous pyridine [*Org. Syntheses* Coll. Vol. **1**, 100 (1941)], is heated on the steam cone until solution is complete (Note 1). Without cooling, 360 ml. of acetic anhydride is added in one portion (Note 2). After standing for 12 hours, the reaction mixture is poured slowly into 10 l. of ice water, to which 500 ml. of acetic acid has been added, and the

resulting mixture is vigorously stirred mechanically for 2 hours (Note 3). The precipitate is filtered and is immediately stirred for a short time with 10 l. of ice water. The white, granular precipitate is filtered, washed well with cold water, and then air-dried (Note 4). The dried solid is digested with 500 ml. of ether (Note 5). The insoluble portion is dissolved in hot 95% ethanol (approximately 3 l.), and the solution is decolorized and filtered while hot. The filtrate, upon cooling, deposits fine needles of 6-trityl-β-*d*-glucose-1,2,3,4-tetraacetate of sufficient purity for further use. The yield at this point is about 169 g. (43%). Recrystallization from 95% ethanol gives the pure compound which melts at 166–166.5°. In pyridine, $[\alpha]_D^{19}$ is + 44.8°; $[\alpha]_D^{28}$, +45.3°. The yield of purified material is 137 g. (35%) (Note 6).

B. *β-d-Glucose-1,2,3,4-tetraacetate*. A solution of 46 g. (0.078 mole) of 6-trityl-β-*d*-glucose-1,2,3,4-tetraacetate in 200 ml. of acetic acid is prepared by warming on the steam bath. The solution is then cooled to approximately 10°, 18 ml. of a saturated solution of dry hydrogen bromide in acetic acid is added, and the reaction mixture is shaken for about 45 seconds. The trityl bromide formed during the reaction is removed *at once* by filtration, and the filtrate is poured *immediately* into 1 l. of cold water. The tetraacetate is extracted with 250 ml. of chloroform; the chloroform extract is washed four times with ice water and dried over anhydrous sodium sulfate. The drying agent is removed, and the chloroform is evaporated, under reduced pressure at room temperature. The remaining syrup is covered with 100 ml. of anhydrous ether and is rubbed with a glass rod. Crystallization takes place immediately. The product is removed and is purified by dissolving it in the minimum amount of chloroform and adding anhydrous ether until crystallization begins. The purified product melts at 128–129°. In chloroform, $[\alpha]_D^{20}$ is +12.1°. The yield is 15 g. (55%).

2. Notes

1. The materials and apparatus used for this reaction must be strictly anhydrous in order to prevent hydrolysis of the trityl chloride.
2. Higher temperatures favor formation of the β-isomer.
3. The stirring must be unusually rapid, and the solution must be added to the water slowly and in a fine stream. If this is not done, the precipitate will not be granular and will be extremely difficult to filter.
4. If the material warms up to room temperature during the time required for drying, it becomes exceedingly sticky, and mechanical difficulties in manipulation result. This behavior appears to be due to the presence of traces of pyridine. The checkers found that the pure product, m.p., 166–166.5°, when recrystallized from pyridine, gave a sticky material.
5. The α-isomer is soluble in ether, whereas the β-isomer is insoluble. In some cases the entire product dissolves, but the β-isomer separates when the solution is allowed to stand.
6. The submitters state that the yield of purified product varies from 148 g. to 180 g.

3. Discussion

These directions are modifications of the methods used by Helferich and Klein for the original preparation of the substance,[1] although it had apparently previously been obtained by Oldham by hydrolysis of tetraacetylglucose-6-mononitrate.[2]

References and Notes

1. Helferich and Klein, *Ann.*, **450**, 219 (1926); Helferich, Moog, and Junger, *Ber.*, **58**, 877 (1925).
2. Oldham, *J. Chem. Soc.*, **127**, 2840 (1925).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

D-Glucose, β-1,2,3,4-tetraacetyl-

ethanol (64-17-5)

acetic acid (64-19-7)

ether (60-29-7)

acetic anhydride (108-24-7)

chloroform (67-66-3)

hydrogen bromide (10035-10-6)

sodium sulfate (7757-82-6)

pyridine (110-86-1)

glucose (492-62-6)

trityl chloride (76-83-5)

trityl bromide (596-43-0)

tetraacetylglucose-6-mononitrate

β-D-Glucose-1,2,3,4-tetraacetate (13100-46-4)

6-trityl-β-d-glucose-1,2,3,4-tetraacetate

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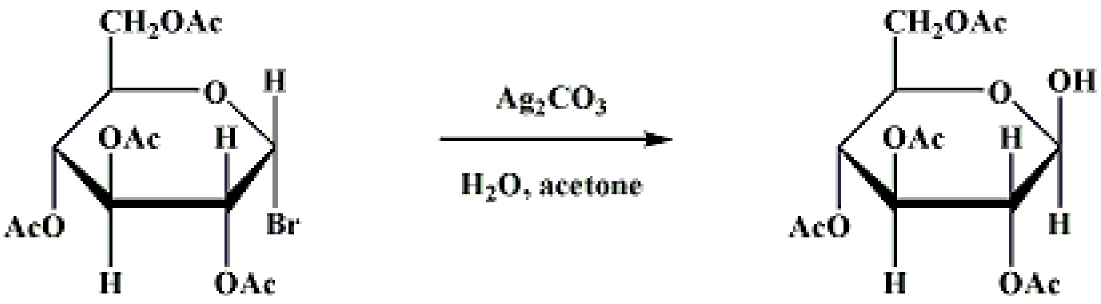
Organic Syntheses, CV 3, 434

β-*d*-GLUCOSE-2,3,4,6-TETRAACETATE

[D-Glucose, β-2,3,4,6-tetraacetyl-]



β - *d* - glucose
2,3,4,6-tetraacetate

Submitted by Chester M. McCloskey and George H. Coleman.
Checked by C. S. Hamilton, Robert Angier, and Ivan Baumgart.

1. Procedure

A solution of 82.2 g. (0.2 mole) of acetobromoglucose (p. 11) (Note 1) in 125 ml. of dry acetone (Note 2) in a 250-ml. flask is cooled to 0° in an ice bath. To the cold solution is added 2.3 ml. of water and then 46.5 g. (0.17 mole) of silver carbonate (Note 3) in small portions in the course of 15 minutes. The mixture is shaken well during the addition and for 30 minutes longer (Note 4). The mixture is then warmed to 50–60° and filtered. The mass of silver salts is washed with 65 ml. of dry acetone (Note 5), removed from the funnel, warmed in a flask with 65 ml. more of acetone, filtered, and washed again on the funnel.

The combined filtrates are concentrated under reduced pressure in a 500-ml. filter flask (Note 6) until most of the solution is filled with crystals. The mixture is warmed to dissolve the crystals, the solution is poured into a 600-ml. beaker, and an equal volume of absolute ether and a similar volume of ligroin are added. The resulting solution is cooled in a freezing mixture with gentle stirring. The crystals of the tetraacetate form quickly and after about 10 minutes are filtered and air-dried. The crystals so obtained melt at 132–134° (Note 7). If a purer product is required, the product is dissolved in acetone, and ether and ligroin are added to the solution in the manner described. The yield of once-crystallized product melting at 132–134° is 52–56 g. (75–80%).

2. Notes

1. The acetobromoglucose that was used had a melting point of 87–88°.
2. The acetone was dried over calcium chloride.

3. The silver carbonate should be freshly prepared and finely ground. Silver carbonate can be prepared by the addition of a solution of sodium carbonate (53 g. in 600 ml. of water) to one of silver nitrate (172 g. in 2 l. of water). This is a very slight excess of the silver nitrate. The sodium carbonate solution is added slowly (10 minutes), and the reaction mixture is stirred vigorously with a mechanical stirrer. The silver carbonate is filtered, washed with a little acetone to facilitate drying, and then air-dried. All operations are carried out in dim light.
4. At the end of this time, evolution of carbon dioxide should no longer be appreciable. The time required for the reaction depends largely on the agitation of the silver carbonate. In large runs mechanical stirring is required.
5. Anhydrous chemicals are used throughout as the presence of any appreciable amount of water interferes with the crystallization of the tetraacetate.
6. The solution is not heated during the concentration, and thus the temperature is maintained below that of the room by the evaporation of the solvent. If a capillary is used it should be equipped with a drying tube.
7. β-*d*-Glucose-2,3,4,6-tetraacetate (2,3,4,6-tetraacetyl-β-*d*-glucose) decomposes slightly on prolonged standing and after 1–2 months has a melting range of 5–8 degrees. Such material can be purified by recrystallization.

3. Discussion

β-*d*-Glucose-2,3,4,6-tetraacetate has been prepared usually by the hydrolysis of acetobromoglucose.[1]

References and Notes

1. Fischer and Delbruck, *Ber.*, **42**, 2776 (1909); Georg, *Helv. Chim. Acta*, **15**, 924 (1932); Hendricks, Wulf, and Liddel, *J. Am. Chem. Soc.*, **58**, 1998 (1936); McCloskey, Pyle, and Coleman, *J. Am. Chem. Soc.*, **66**, 349 (1944).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ligroin

calcium chloride (10043-52-4)

ether (60-29-7)

silver nitrate (7761-88-8)

sodium carbonate (497-19-8)

carbon dioxide (124-38-9)

acetone (67-64-1)

d-Glucose (492-62-6)

Acetobromoglucose (572-09-8)

β-D-Glucose-2,3,4,6-tetraacetate

silver carbonate (534-16-7)

2,3,4,6-tetraacetyl-β-d-glucose

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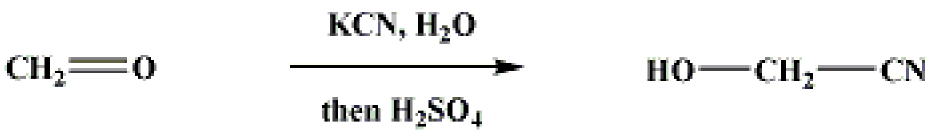
Organic Syntheses, CV 3, 436

Glycolonitrile



Submitted by Roger Gaudry
Checked by C. F. H. Allen and J. A. VanAllan.

1. Procedure

This preparation should be carried out under a good hood since poisonous hydrogen cyanide may be evolved.

In a 1-l. three-necked flask, fitted with a stirrer, thermometer for reading low temperatures, and a dropping funnel, and surrounded by an ice-salt bath, is placed a solution of 130 g. (2.0 moles) of potassium cyanide in 250 ml. of water. With stirring, a solution of 170 ml. (2.0 moles) of commercial 37% formaldehyde solution[1] and 130 ml. of water is admitted slowly from the dropping funnel at such a rate that the temperature never rises above 10° (about 40 minutes is required). After 10 minutes' standing, 230 ml. of dilute sulfuric acid (57 ml. of concentrated sulfuric acid, sp. gr. 1.84, in 173 ml. of water) is added with stirring, the same low temperature being maintained. A copious precipitate of potassium sulfate is formed. The *p*H of the solution is then about 1.9. A 5% potassium hydroxide solution is then added, dropwise, and with cooling, until the *p*H is about 3.0 (determined either by means of a *p*H meter or tropaeolin 00 paper); about 4 ml. of the solution is required. The flask is then removed from the cooling bath, 30 ml. of ether is added, and the mixture is well shaken. The salt is removed by filtration, using a 14-cm. Büchner funnel, and washed with 30 ml. of ether. The filtrate is poured into a 1-l. continuous ether extractor[2] and extracted for 48 hours with 300 ml. of ether (Note 1). The ether extract is dried for 3–4 hours over 15 g. of anhydrous calcium sulfate (Drierite) (Note 2) and filtered. Ten milliliters of absolute ethanol is added to the filtrate, and the ether is removed on a steam bath (Note 3). The residue is distilled under reduced pressure using a flask having a Vigreux side arm. After a small (2–3 ml.) fore-run, the glycolonitrile distils smoothly at 86–88°/8 mm. (102–104°/16 mm.). The yield of pure glycolonitrile (Note 4) amounts to 86.5–91 g. (76–80%).

2. Notes

1. It is impractical to extract more than 40–45% of the nitrile without using a continuous ether extractor. A slightly lower yield is obtained if the extraction is continued for only 24 hours. The reaction mixture may be extracted in portions if the available flask is smaller than that specified.

2. Anhydrous sodium sulfate can be used equally well, but its drying action is slower, at least 24 hours being advisable.
3. If the ethanol is omitted, the nitrile shows a strong tendency to polymerize during the removal of the ether, especially when most of the ether has distilled.
4. The ethanol serves as a preservative before and after the distillation. Glycolonitrile obtained without the use of ethanol usually cannot be kept more than a few days; it sometimes turns brown within 24 hours. Some samples of ethanol-stabilized glycolonitrile have been preserved in sealed bottles for 2 years, whereas other samples polymerized in a few months.

3. Discussion

Glycolonitrile has usually been prepared by the interaction of formaldehyde and an alkali cyanide in aqueous solution[3] of which the procedure outlined is a modification. A more recent development is the cyanohydrin interchange method.[4,5] Glycolonitrile has also been prepared by a catalytic oxidation of methanol and ammonia in the vapor phase.[6]

References and Notes

1. *Org. Syntheses* Coll. Vol **1**, 378, Note 1 (1941).
2. *Org. Syntheses* Coll. Vol. **2**, 378 (1943).
3. Polstorff and Meyer, *Ber.*, **45**, 1911 (1912).
4. Kung, U. S. pat. 2,259,167 [*C. A.*, **36**, 494 (1942)].
5. Mowry, *J. Am. Chem. Soc.*, **66**, 372 (1944).
6. U. S. pat. 2,405,963 [*C. A.*, **40**, 7231 (1946)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

sulfuric acid (7664-93-9)

ammonia (7664-41-7)

methanol (67-56-1)

ether (60-29-7)

formaldehyde (630-08-0)

potassium sulfate (37222-66-5)

hydrogen cyanide (74-90-8)

sodium sulfate (7757-82-6)

potassium cyanide (151-50-8)

calcium sulfate (7778-18-9)

potassium hydroxide (1310-58-3)

Glycolonitrile (107-16-4)

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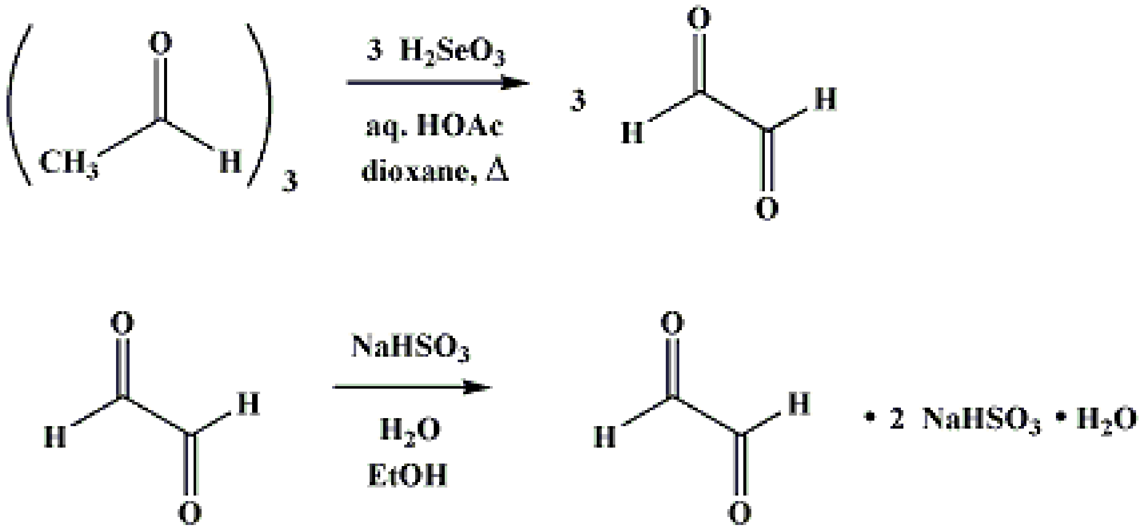
Organic Syntheses, CV 3, 438

GLYOXAL BISULFITE



Submitted by Anthony R. Ronzio and T. D. Waugh.
Checked by C. F. H. Allen and J. Vanallan.

1. Procedure

In a 2-l. round-bottomed flask, attached to an efficient reflux condenser (Note 1) and set in a hot water bath, are placed 222 g. (1.72 moles) of selenious acid (Note 2), 270 ml. of paraldehyde (Note 3), 540 ml. of dioxane, and 40 ml. of 50% acetic acid (Note 4), and the mixture is refluxed for 6 hours (Note 5). The solution is then decanted from the inorganic material (Note 6), which is washed with two 150-ml. portions of water. The combined solutions are steam-distilled through a still head (p. 65) until the paraldehyde and dioxane have been removed; this requires about 3.5 hours (Note 7). The mixture is decanted from a little selenium (Note 6), and to the solution, without filtration, is added a slight excess of 25% lead acetate solution (Note 8) and (Note 9). The lead selenite is removed by filtration, and the filtrate is saturated with hydrogen sulfide in a hood (Note 8). Then 20 g. of Norit is added; the whole is warmed to 40° in a hood and filtered with suction. The water-clear solution is concentrated on a hot water bath under reduced pressure to about 150 ml. in the usual apparatus (Note 10).

This concentrate is added to a previously prepared and filtered solution of sodium bisulfite in 40% ethanol (Note 11) contained in a 4-l. beaker provided with a mechanical stirrer (Note 12). The mixture is stirred for 3 hours, and the addition product then is filtered with suction on an 18-cm. Büchner funnel and washed, first with two 150-ml. portions of ethanol and then with 150 ml. of ether. The yield of air-dried product is 350–360 g. (72–74%, based on the selenious acid used) (Note 13).

2. Notes

1. The loss of large quantities of acetaldehyde is avoided by use of a spiral condenser, with sufficient heating so that a vapor lock is formed–the entrapped liquid should fill about two-thirds of the spiral. In cold weather, the tap water is usually cold enough so that any efficient long condenser, or two in series, is sufficient.
2. The selenious acid does not need to be freshly prepared. A larger amount does not increase the yield. The submitters specified selenium dioxide as the oxidizing agent, but the checkers prepared their material by evaporating an aqueous solution to dryness on the water bath. They, therefore, have considered the oxidizing agent to be selenious acid and have calculated the yield on this basis. If this product is in reality selenium dioxide, then the yield is 62–64%, and 222 g. is 2.0 moles.
3. This amount of paraldehyde represents a considerable excess over the theoretical but was found to be most satisfactory.
4. Acetic acid appears to function both as an accelerator for the oxidation and an inhibitor of the rearrangement to glycolic acid.
5. This is regulated by the temperature of the water bath, 65–80° being the required range.
6. This material, impure selenium, may be reoxidized,[1] and then it is suitable for a subsequent preparation. About 130 g. is recovered at this point, and 8–10 g. after the concentration.
7. Alternatively, direct distillation may be employed; this requires only 2.5 hours but demands more attention. The volume is reduced to 200–300 ml., and then 800 ml. of water is added.
8. A test sample is filtered, and the clear filtrate is treated with more of the reagent to determine the end point.
9. Lead acetate is more satisfactory than sulfur dioxide for the removal of selenious acid, provided that the solution is kept cool and a large excess is avoided.
10. This volume of solution is most easily handled. Should glyoxal itself be desired, the solution may be evaporated to dryness in a desiccator. The product thus obtained is identical with that sold as "polyglyoxal."
11. The solution is prepared by dissolving 312 g. of technical sodium bisulfite in 2.1 l. of warm (about 40°) water, and adding 1.4 l. of 95% ethanol.
12. Alternatively, this may be done in a flask, which is shaken by hand frequently to prevent formation of a solid cake. The use of a stirrer results in a granular product. The mother liquor retains about 7 g. of glyoxal bisulfite per liter.
13. This product is pure enough for most purposes. It can be recrystallized by dissolving it in water and adding enough alcohol to make a 40% solution. The recovery is 90–92%.

3. Discussion

Glyoxal has been obtained by several methods, only a few of which are of preparative

value. The most feasible are the oxidation of acetaldehyde by nitric[2,3,4] or selenious[5] acid; the hydrolysis of dichlorodioxane;[6] and the hydrolysis of the product resulting from the action of fuming sulfuric acid upon tetrahaloethanes.[7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 824

References and Notes

1. *Org. Syntheses* Coll. Vol. **2**, 510, Note 2 (1943).
2. Lubawin, *Ber.*, **8**, 768 (1875).
3. Wyss, *Ber.*, **10**, 1366 (1877).
4. Behrend and Kölln, *Ann.*, **416**, 230 (1918).
5. Riley, Morley, and Friend, *J. Chem. Soc.*, **1932**, 1881.
6. Butler and Cretcher, *J. Am. Chem. Soc.*, **54**, 2988 (1932).
7. Ott, Ger. pat. 362,743 [*C. A.*, **18**, 991 (1924)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

acetaldehyde (75-07-0)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

ether (60-29-7)

glyoxal (107-22-2)

hydrogen sulfide (7783-06-4)

sulfur dioxide (7446-09-5)

sodium bisulfite (7631-90-5)

Norit (7782-42-5)

selenium dioxide (7446-08-4)

lead acetate

dioxane (5703-46-8)

selenium

glycolic acid (79-14-1)

selenious acid (7783-00-8)

Glyoxal bisulfite (18381-20-9)

dichlorodioxane

lead selenite

paraldehyde (123-53-7)

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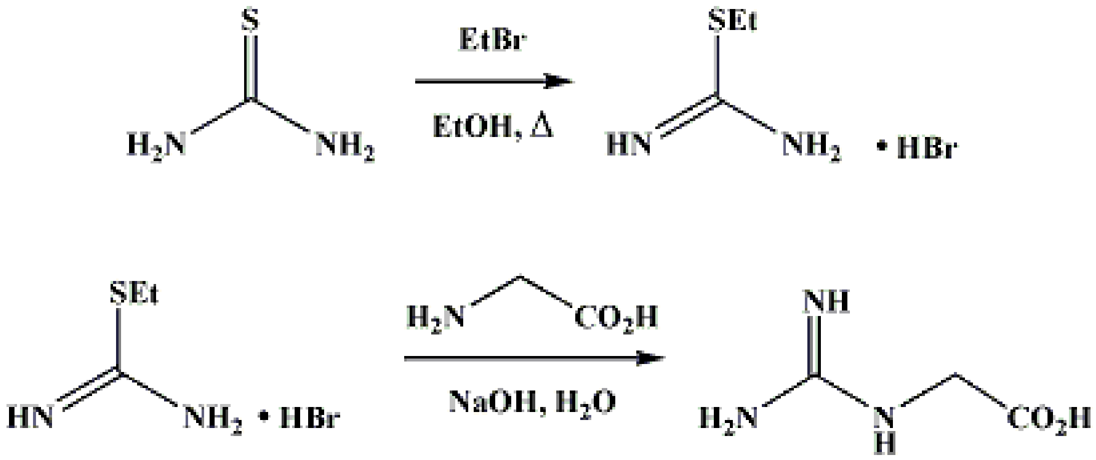
Organic Syntheses, CV 3, 440

GUANIDOACETIC ACID

[Glycocyamine]



Submitted by E. Brand and F. C. Brand.
Checked by C. F. H. Allen and John W. Gates, Jr..

1. Procedure

A. *S-Ethylthiourea hydrobromide.* A mixture of 150 g. of powdered thiourea (1.97 moles) (Note 1), 250 g. of ethyl bromide (2.29 moles), and 200 ml. of absolute ethanol is placed in a 1-l. round-bottomed flask equipped with an efficient condenser. The mixture is warmed on a water bath (bath temperature 55–65°) for 3 hours, with occasional shaking. During this time all the thiourea dissolves. The reflux condenser is replaced by one set for downward distillation, and the ethanol and excess ethyl bromide are removed under the vacuum of a water pump. During the distillation, the temperature of the bath is slowly raised to the boiling point (Note 2). The residual oil is poured into a 500-ml. beaker and allowed to crystallize (Note 3). The solid is pulverized and dried in a desiccator (Note 4) and (Note 5). The yield is 340–360 g. (93–99%).

B. *Guanidoacetic acid.* This reaction should be carried out in a well-ventilated hood, as considerable amounts of ethyl mercaptan are evolved. In a 1-l. Erlenmeyer flask is placed 92.5 g. (0.50) mole of S-ethylthiourea hydrobromide. The flask is immersed in an ice bath, and 252 ml. of 2 *N* sodium hydroxide solution is added. A hot (80+°) solution of 41 g. of glycine in 90 ml. of water is added rapidly. When the temperature reaches 25° (Note 6), the flask is removed from the ice water. After about 30 minutes crystallization begins; then approximately 100 ml. of ether is added, and the mixture is left in the hood overnight (Note 7). The mixture is then chilled for 2 hours in an ice bath, the ether layer is decanted, and the solid is filtered with suction. The crystals are washed on the funnel successively with two 20-ml. portions of ice water (Note 8), two 150-ml. portions of 95% ethanol, and two 150-ml. portions of ether. The yield of air-

dried guanidoacetic acid is 47–53 g. (80–90%). This product is pure enough for most purposes (Note 9); it melts with decomposition at 280–284°.

2. Notes

1. Commercial thiourea is usually sufficiently finely divided so that it may be used directly.
2. The last traces are more quickly removed if the vacuum line is attached directly to the flask.
3. If the product is inoculated, the liquid solidifies at once.
4. The crude product is sufficiently pure for the subsequent reaction. If kept in a cool place in the absence of air, it is stable for several months.
5. This is a general method for preparing S-alkylthiourea hydrobromides and hydriodides. The yields are always over 90%. The hydrochlorides are not so readily prepared; it is necessary to determine, by experiment, the optimum conditions for each hydrochloride.
6. The temperature may rise or fall to 25°, depending upon the temperatures of the component solutions.
7. The yield is slightly lower (45 g.) if the mixture is filtered after standing for only 3 hours.
8. The product is appreciably soluble in water.
9. Further purification of this product may be accomplished by (a) recrystallizing it from hot water (125 ml. per 5 g.), or (b) dissolving it in slightly more than the calculated amount of 2 *N* hydrochloric acid and reprecipitating by adding an equivalent quantity of 2 *N* sodium hydroxide. Analytical values for nitrogen (Dumas) given by the crude and purified products were as follows: Calculated: 35.9%. Found: acid as prepared, 35.4%; once recrystallized, 35.9%; reprecipitated, 35.7%.

3. Discussion

S-Ethylthiourea has been prepared as the hydrobromide[1,2,3] and hydriodide.[2,4] Guanidoacetic acid has previously been made from S-ethylthiourea hydriodide[2] and from S-methylthiourea.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 449
- Org. Syn. Coll. Vol. 5, 612

References and Notes

1. Claus, *Ber.*, **7**, 236 (1874).
2. Wheeler and Merriam, *Am. Chem. J.*, **29**, 483 (1903).
3. Schotte, Priewe, and Roescheisen, *Z. physiol. Chem.*, **174**, 119 (1928).

4. Claus, *Ber.*, **8**, 41 (1875).
5. Mourgue, *Bull. soc. chim. France*, **1948**, 181.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium hydroxide (1310-73-2)

Ethyl bromide (74-96-4)

Glycine (513-29-1)

thiourea (62-56-6)

Guanidoacetic acid (352-97-6)

ethyl mercaptan (75-08-1)

S-ethylthiourea hydrobromide (1071-37-0)

S-Ethylthiourea

S-ethylthiourea hydriodide

S-methylthiourea

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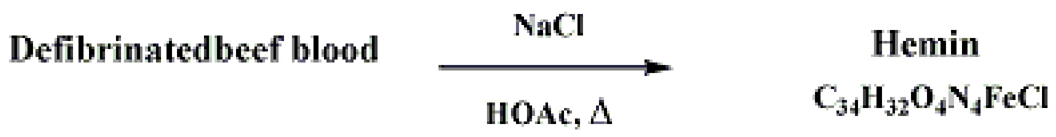
Organic Syntheses, CV 3, 442

HEMIN



Submitted by Hans Fischer
Checked by C. R. Noller and G. A. Smith.

1. Procedure

In a 5-l. round-bottomed flask equipped with a thermometer, reflux condenser, and dropping funnel are placed 4 l. of glacial acetic acid and 1 g. of sodium chloride. The acid is heated to boiling on a sand bath until the sodium chloride is in solution, and then 1 l. of defibrinated blood (Note 1) is added in a thin stream from the dropping funnel over a period of about 30 minutes. The blood should not touch the sides of the flask. During this time the temperature is kept at 100–105°, and heating is continued for 10 minutes after all the blood has been added. The flame is then removed and the mixture allowed to cool and stand overnight.

The precipitated hemin is removed by centrifuging (Note 2). If the centrifuging is carried out in 100-ml. tubes, each lot of tubes is centrifuged 10 minutes, the supernatant liquid is decanted, more of the mixture added, and the centrifuging repeated. The hemin is allowed to accumulate in the tubes until all the mixture has been centrifuged, after which it is stirred with a glass rod and washed from the several tubes into one with 75 ml. of 50% aqueous acetic acid. After centrifuging and decanting, the hemin is washed successively in the same manner with two 75-ml. portions of distilled water, one 50-ml. portion of 95% ethanol, and one 50-ml. portion of ether. After the ether has been decanted the hemin is transferred to a watch glass by means of a rubber policeman and about 5 ml. of ether. After evaporation to dryness 3.5–4.5 g. of crude product is obtained.

For recrystallization, 5 g. of the crude hemin is placed in a 100-ml. Erlenmeyer flask, 25 ml. of pyridine is added, and the flask is shaken until the hemin has dissolved. Forty milliliters of chloroform is added, and the flask is stoppered with a cork and shaken for 15 minutes; the cork is carefully removed from time to time to release the pressure. The solution is then filtered with slight suction through a small Büchner funnel, and the Erlenmeyer flask and filter are washed with 15 ml. of chloroform.

During the shaking 350 ml. of glacial acetic acid is heated to boiling in a 600-ml. beaker under a hood, and 5 ml. of a saturated sodium chloride solution and 4 ml. of concentrated hydrochloric acid are added. The flame is extinguished, and the filtered hemin solution poured in a steady stream with stirring into the hot mixture; the suction flask is rinsed with 15 ml. of chloroform. After the mixture has stood for 12 hours, the crystals are filtered with suction on a small Büchner funnel and washed with 50 ml. of

50% aqueous acetic acid, 100 ml. of distilled water, 25 ml. of ethanol, and 25 ml. of ether. Suction is continued until the crystals are dry, when they can be readily removed. The recovery is 75–85%.

2. Notes

1. Fresh blood obtained from a slaughter house is defibrinated by whipping it with a stiff vegetable-fiber brush followed by filtration with suction through a large Büchner funnel. The blood is stirred during the filtration to prevent settling of the erythrocytes. Beef blood was used for checking this preparation.
2. The hemin may be removed by filtration but it is usually so finely divided that centrifuging is easier and less loss results.

3. Discussion

Hemin has been synthesized,[1] but it is always prepared from blood.[2]

References and Notes

1. Fischer and Zeile, *Ann.*, **468**, 98 (1929).
2. Nencki and Zaleski, *Z. physiol. Chem.*, **30**, 390 (1900); Piloty, *Ann.*, **377**, 358 (1910).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

HEMIN

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ether (60-29-7)

chloroform (67-66-3)

sodium chloride (7647-14-5)

pyridine (110-86-1)

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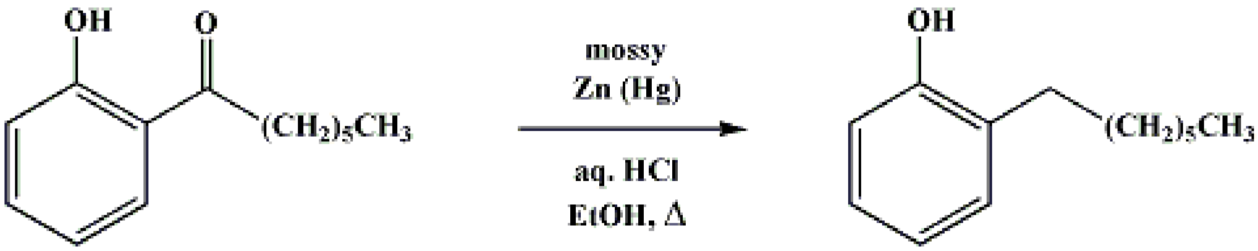
Organic Syntheses, *CV 3*, *444*

o-*n*-HEPTYLPHENOL

[Phenol, *o*-*n*-heptyl-]



Submitted by R. R. Read and John Wood, Jr..
Checked by W. E. Bachmann and M. C. Kloetzel.

1. Procedure

In a 1-l. three-necked flask fitted with a stirrer (Note 1) and a reflux condenser is placed 200 g. of amalgamated mossy zinc (Note 2). A mixture of 200 ml. of water and 200 ml. of concentrated hydrochloric acid is added and then a solution of 60 g. of *o*-heptanoyl phenol (Note 3) in 100 ml. of ethanol. The mixture is agitated vigorously and refluxed until reduction is complete (Note 4).

To the mixture is added 120 ml. of toluene, stirring being continued for a few minutes. The toluene solution is separated from the aqueous solution and washed three times with water. The solution is filtered from suspended matter, and the toluene is distilled from a Claisen flask until a thermometer in the liquid reads 170° (Note 5). The residue is then distilled under reduced pressure, the portion boiling at 118–123° at 1 mm. being collected (Note 6). The yield of colorless *o*-*n*-heptylphenol is 45–47 g. (81–86%) (Note 7).

2. Notes

1. The stirrer should be as large and substantial as the flask will accommodate, since the rate of reduction depends greatly on complete emulsification of the oil.
2. The zinc is amalgamated in the reaction flask by covering it with a solution of 4 g. of mercuric chloride in 300 ml. of water. Occasional agitation during 30 minutes is sufficient for amalgamation. The solution is poured off, and the zinc is rinsed once with water.
3. *o*-Heptanoyl phenol may be prepared by the method of Miller and Hartung [*Org. Syntheses* Coll. Vol. **2**, 543 (1943)]. The checkers found that, by keeping the mixture of *ortho* and *para* isomers in a cool place overnight, most of the *para* isomer crystallized and could be separated by filtration. The *ortho* isomer is then obtained by fractional vacuum distillation, repeated two or three times. *o*-Heptanoylphenol boils at 135–140°/3 mm.; *p*-heptanoyl phenol boils at 200–

207°/4 mm.

4. The reduction requires at least 8 hours and may take twice that long. For testing completeness of reduction, 0.1 ml. of the oil is withdrawn and dissolved in 2 ml. of ethanol; to the solution is added 2–4 drops of a 10% solution of ferric chloride in ethanol. A deep red or reddish brown color is produced by the ketone; a light brownish yellow color indicates completion of the reduction. A standard solution containing 0.5 g. of the ketone per liter of ethanol is used for comparison, 2 ml. of this being treated with a few drops of the ferric chloride solution. Since the *para* acylphenols usually do not give a pronounced color with ferric chloride, at least 8 hours should be allowed for their reduction.

5. Drying of the toluene extract is unnecessary, since the water is carried over during the removal of the toluene. If necessary, the toluene may be returned once to the flask to effect complete removal of the water.

6. The residue from the distillation is usually less than 5 g. and may be discarded.

7. Other ketones may be reduced by this same procedure. The submitters report that the following have been reduced with yields of 70–90%: *o*- and *p*-butyryl phenols, *o*- and *p*-valeryl phenols, *o*- and *p*-caproyl phenols, *o*- and *p*-heptanoyl phenols, *o*- and *p*-octanoyl phenols, *o*- and *p*-pelargonyl phenols, *o*- and *p*-undecylyl phenols. The same procedure applies to acyl resorcinols and acyl chlororesorcinols. Caproyl and octanoyl resorcinols reduce to the corresponding alkyl derivatives in yields of 70–80%. Butyryl, valeryl, caproyl, heptanoyl, and octanoyl chlororesorcinols reduce to the corresponding alkyl chlororesorcinols in yields of 60–75%.

3. Discussion

Primary alkyl phenols have been prepared by the reduction of acyl phenols;[1] by the demethylation of the corresponding ethers;[1,2] by the diazotization of the corresponding amines;[3] and by the alkali fusion of sulfonates.[4] Alkyl resorcinols have been prepared by the reduction of acyl resorcinols.[1,5,6] Alkyl chlororesorcinols have been prepared from the corresponding acyl chlororesorcinols by reduction.[7]

References and Notes

1. Johnson and Hodge, *J. Am. Chem. Soc.*, **35**, 1014 (1913); Coulthard, Marshall, and Pyman, *J. Chem. Soc.*, **1930**, 280.
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

butyryl phenols

o- and p-valeryl phenols

o- and p-caproyl phenols

o- and p-heptanoyl phenols

o- and p-octanoyl phenols

o- and p-pelargonyl phenols

o- and p-undecylyl phenols

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

toluene (108-88-3)

zinc (7440-66-6)

mercuric chloride (7487-94-7)

ferric chloride (7705-08-0)

o-n-HEPTYLPHENOL, Phenol, o-n-heptyl- (5284-22-0)

o-heptanoyl phenol, o-Heptanoylphenol

p-heptanoyl phenol

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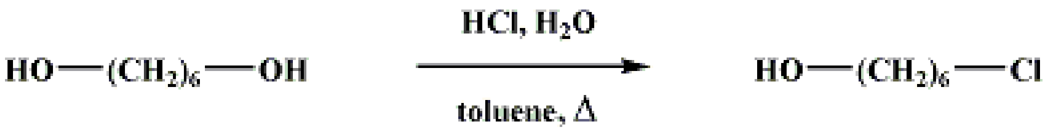
HEXAMETHYLENE CHLOROHYDRIN

[1-Hexanol, 6-chloro-]



Submitted by Kenneth N. Campbell and Armiger H. Sommers[1].
Checked by Richard T. Arnold and Roger Amidon.

1. Procedure

The apparatus shown in .htmFig. 14 is constructed from a 1-l. distilling flask (*A*) and a 500-ml. distilling flask (*B*) the side arm of which has been replaced by 10-mm. Pyrex tubing sealed at an upward angle to the side arm of the larger flask (*A*). Charred cork stoppers are used, and a hydrogen chloride trap[2] is connected to the water-cooled reflux condenser. The bent side arm (*C*) is insulated by a wrapping of cloth. Reaction flask *A* is charged with 105 g. (0.89 mole) of hexamethyleneglycol,[3] 785 ml. (9.5 moles) of concentrated hydrochloric acid, 130 ml. of water (Note 1), and 55 ml. of toluene (Note 2) and (Note 3). In flask *B* are put 350 ml. toluene and a few boiling chips. The apparatus is assembled, and the flasks are heated in oil baths. The bath covering about two-thirds of flask *A* is kept at 95°; the one surrounding most of flask *B* is kept between 160° and 165° (Note 4). As the reaction proceeds and the products are removed by the continuous flow of toluene through the mixture, the organic-aqueous interface in *A* falls steadily. After 9 hours the heating baths and condensers are removed, and water is added to *A* to force the upper layer of toluene into *B*. The aqueous solution is siphoned out of *A*, and then the toluene extract in *B* is poured into a dropping funnel inserted through a stopper in the neck of a 500-ml. Claisen flask. Some of the extract is run into the flask, and most of the toluene is removed by distillation at atmospheric pressure while the remainder of the solution is slowly run into the flask. To remove the last of the solvent, the pressure is lowered to 65 mm. while the bath temperature is kept at 100°.

Fig. 14.

Fig. 14.

The material obtained from two such runs is combined and fractionated through a Fenske-Whitmore column[4] packed with glass helices. Distillation is carried out at a pressure of 8–12 mm., with a reflux ratio of 5:1. After a fore-run of 5–15 g., about 45 g. (16%) of hexamethylene dichloride distils at 80–84°/9 mm., n_D^{20} 1.4585–1.4565. An intermediate fraction of 10–20 g. distils at 84–100° /9 mm., and then 108–122 g.

(45–50%) of hexamethylene chlorohydrin boiling at 100–104° /9 mm., n_D^{20} 1.4551–1.4557, is collected. If several runs are made the residues may be distilled from a Claisen flask and the distillate combined with the intermediate fractions for refractionation. In this way the average yield may be raised to 50–55%.

2. Notes

1. The use of concentrated hydrochloric acid without dilution results in violent bubbling during the reaction.

2. In the original work of Bennett and Turner[5] a petroleum fraction of b.p. 90–120° was used. When the submitters used Skellysolve L, b.p. 90–100°, the hexamethylene chlorohydrin was not sufficiently soluble in it to be removed from the reaction mixture. A study of the solubility of hexamethylene chlorohydrin in various commonly available solvents was made, and toluene was found to be the most satisfactory.

3. The exact volume of free space below the side arm of *A* will vary somewhat according to the exact dimensions of the flask and the adapter tube, and it may be desirable to make corresponding changes in the volumes of hydrochloric acid and water used. In the apparatus constructed by the checkers the aqueous phase expanded during the heating to such an extent that only about 5 ml. of toluene remained in the neck below the side arm; this apparatus operated satisfactorily when the volumes of hydrochloric acid and water were reduced to 720 ml. and 115 ml., respectively.

4. The bath temperature may be controlled by heating with an immersed loop of Nichrome resistance coil, such as the heating element from an electrical appliance. The coil is connected to a 110-volt line in series with a 27-ohm 5-ampere variable resistor and a 600-watt heater element, which may be cut out of the circuit to lower the fixed resistance. An ammeter in the circuit helps to determine the proper adjustment of the sliding contact of the resistor. To avoid an excessive load on the coil, the bath about *B* should be heated in addition by a hot plate adjusted to give a temperature somewhat below 160°.

3. Discussion

Hexamethylene chlorohydrin has been prepared by the reaction of hydrochloric acid with hexamethylene glycol, without a catalyst[5,6,7] or in the presence of cuprous chloride.[8]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

toluene (108-88-3)

cuprous chloride (7758-89-6)

Hexamethylene glycol, hexamethyleneglycol (629-11-8)

Hexamethylene chlorohydrin, 1-Hexanol, 6-chloro- (2009-83-8)

hexamethylene dichloride (2163-00-0)

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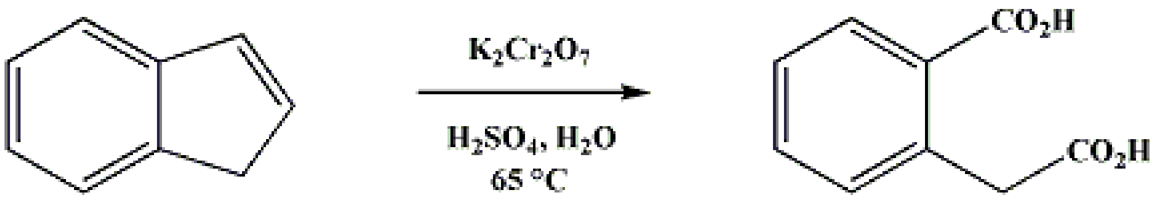
Organic Syntheses, CV 3, 449

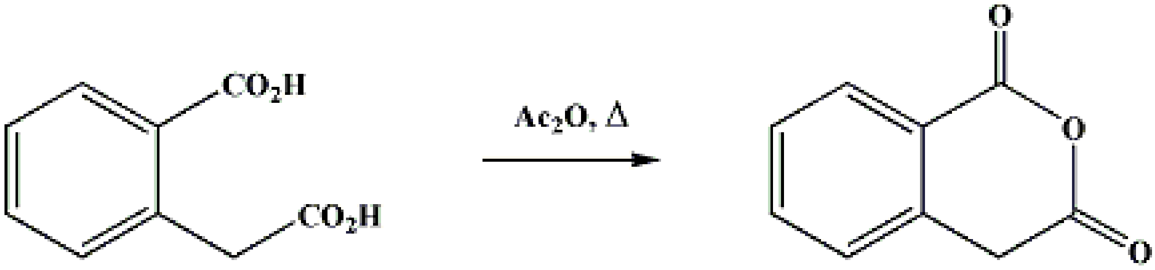
HOMOPHTHALIC ACID AND ANHYDRIDE

[Phenylacetic acid, *o*-carboxy-, and 1,3-Isochromandione]

A.



B.



Submitted by Oliver Grummitt, Richard Egan, and Allen Buck.
Checked by R. L. Shriner and Walter R. Knox.

1. Procedure

A. *Homophthalic acid.* A solution of 243 g. (0.83 mole) of technical potassium dichromate in 3.6 l. of water and 1330 g. (725 ml., 13 moles) of concentrated sulfuric acid is prepared in a 5-l. three-necked flask fitted with a sealed mechanical stirrer, a thermometer, a 100-ml. dropping funnel, and a reflux condenser. The mixture is warmed to 65°, and 72 g. (72 ml., 0.56 mole) of technical 90% indene (Note 1) is added dropwise from the dropping funnel. The temperature must be kept at 65 ± 2°, and cooling by a water bath is necessary during the addition. After the addition is complete the mixture is stirred for 2 hours at 65 ± 2° (Note 2). At the end of this period the mixture is cooled with stirring to 20–25° and then further cooled in an ice-salt bath for 5 hours at 0°. The homophthalic acid which separates is collected on a 10-cm. Büchner funnel with the aid of suction, then washed with two 75-ml. portions of ice-cold 1% sulfuric acid and once with 75 ml. of ice water (Note 3). The precipitate is then dissolved in 215 ml. of 10% sodium hydroxide solution, and the resulting solution is extracted with two 50-ml. portions of benzene (Note 4), which are discarded. The aqueous solution is added to 160 ml. of 33% sulfuric acid with vigorous stirring, and the mixture is chilled in an ice-salt bath for 2–3 hours. The homophthalic acid is collected on a 10-cm. Büchner funnel with the aid of suction, washed with three 25-ml. portions of ice water, and pressed and sucked as dry as possible. The acid is transferred to a 500-ml. distilling flask, 300 ml. of benzene is added, and the mixture is distilled from a steam bath until about 250 ml. of distillate (benzene and water) has been collected (Note 5). The slurry of acid and benzene is filtered with the aid of suction through a 10-cm. Büchner funnel, and the product is spread out on a porous

plate to allow the last traces of benzene to evaporate. The yield of white crystals of homophthalic acid, melting at 180–181° (Note 6), amounts to 67–77 g. (66–77% calculated on the basis of 90% indene content of the commercial indene) (Note 7).

B. *Homophthalic anhydride.* A mixture of 60 g. (0.33 mole) of dry homophthalic acid and 33.7 g. (31 ml., 0.33 mole) of acetic anhydride in a 200-ml. round-bottomed flask fitted to a reflux condenser by a ground-glass joint is refluxed for 2 hours. The mixture is cooled to about 10° for 30 minutes, and the solid anhydride is collected on a Büchner funnel with the aid of suction. It is washed with 10 ml. of glacial acetic acid and pressed, and as much of the solvent as possible is removed by suction. The product is spread out on a porous plate for several hours (Note 8); it amounts to 46–47.5 g (85–88%) of white crystals melting at 140–141° (Note 9).

2. Notes

1. Indene of approximately 90% purity may be obtained from the Koppers Company, Pittsburgh, Pennsylvania, or United Gas Improvement Company, Philadelphia, Pennsylvania. The practical grade of the same purity from the Eastman Kodak Company may also be used. If the material is dark colored, it should be redistilled and the fraction boiling from 180° to 182° should be used.
2. It is important to control the temperature of this oxidation. If the oxidation is carried out at the reflux temperature, the yield of purified acid drops to about 52–54%.
3. Homophthalic acid possesses an appreciable solubility in water (about 1.6 g. per 100 ml. at 20°); hence it is necessary to cool the solutions and wash liquids to obtain good yields.
4. This extraction removes about 7–8 g. of oily alkali-insoluble products.
5. This azeotropic distillation is the quickest method for drying homophthalic acid. The acid turns dark colored if dried in an oven at 110°. It may be dried over anhydrous calcium chloride in a vacuum desiccator for 24–36 hours; it melts at 180–181°.
6. The melting point depends on the rate of heating. When the melting-point tube was placed in the bath preheated to 170°, the acid melted at 180–181°. When the heating was started at room temperature, the observed melting point was 172–174°.
7. If phthalide is available, an alternative procedure via *o*-carboxyphenylacetonitrile may be preferred for the preparation of homophthalic acid [*Org. Syntheses*, **22**, 61 (1942)].
8. Drying in an oven causes some loss because the anhydride sublimes.
9. If all the acetic acid is not removed the product melts lower, *ca.* 138–139°.

3. Discussion

Homophthalic acid has been prepared from naphthalene[1] or tetralin[2] via phthalonic acid; by hydrolysis of *o*-cyanobenzylcyanide;[3] by oxidation of β-indanone with

alkaline permanganate solution;[4] from α-indanone by chromic acid oxidation,[5] by nitrosation, Beckmann rearrangement, and hydrolysis,[6] or by nitrosation, hydrolysis, and hydrogen peroxide oxidation;[7] from *o*-toluic acid by bromination of the acid chloride followed by treatment with ethanol and sodium cyanide and hydrolysis with 50% sulfuric acid;[8] from indene by oxidation with chromic and sulfuric acid;[9] and from *o*-acetylbenzoic acid by Willgerodt reaction with morpholine and sulfur followed by hydrolysis of the dimorpholide.[10] The oxidation of indene by alkaline permanganate produces homophthalic acid[11] and phthalic acid;[12] oxidation with chromic acid leads to a purer product.[13] The hydrolysis of *o*-carboxyphenylacetonitrile yields homophthalic acid.[14]

The procedure described here is a modification of that described by Meyer and Vittenet[9] and Whitmore and Cooney.[15]

Homophthalic anhydride has been obtained by heating the acid alone,[1] and by refluxing with acetyl chloride[14] or with acetic anhydride.[16]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 612

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

phthalonic acid

HOMOPHTHALIC ACID AND ANHYDRIDE

chromic and sulfuric acid

ethanol (64-17-5)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

Benzene (71-43-2)

acetic anhydride (108-24-7)

sodium hydroxide (1310-73-2)

acetyl chloride (75-36-5)

sodium cyanide (143-33-9)

sulfur (7704-34-9)

chromic acid (7738-94-5)

Naphthalene (91-20-3)

hydrogen peroxide (7722-84-1)

permanganate

potassium dichromate (7778-50-9)

phthalic acid (88-99-3)

Tetralin (119-64-2)

α-indanone (83-33-0)

indene (95-13-6)

Phthalide (87-41-2)

Homophthalic acid, Phenylacetic acid, o-carboxy- (89-51-0)

1,3-Isochromandione, Homophthalic anhydride (703-59-3)

β-indanone (615-13-4)

morpholine (110-91-8)

o-Toluic acid (118-90-1)

o-CARBOXYPHENYLACETONITRILE (6627-91-4)

o-cyanobenzylcyanide (3759-28-2)

o-acetylbenzoic acid (577-56-0)

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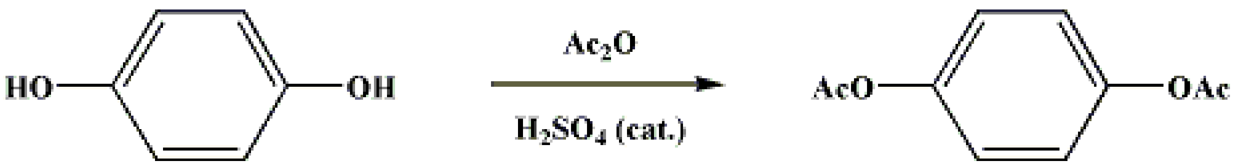
HYDROQUINONE DIACETATE

[Hydroquinone, diacetate]



Submitted by W. W. Prichard
Checked by Homer Adkins and Maynette Vernsten.

1. Procedure

One drop of concentrated sulfuric acid is added to a mixture of 110 g. (1.0 mole) of hydroquinone and 206 g. (190.3 ml., 2.02 moles) of acetic anhydride (Note 1) in a 1-l. Erlenmeyer flask. The mixture is stirred gently by hand; it warms up very rapidly, and the hydroquinone dissolves. After 5 minutes the clear solution is poured onto about 800 ml. of crushed ice. The white crystalline solid which separates is collected on a Büchner filter and washed with 1 l. of water. The filter cake is pressed occasionally to facilitate the removal of water; the solid is dried to constant weight over phosphorus pentoxide in a vacuum desiccator. The nearly pure product weighs 186–190 g. (96–98%) and melts at 121–122° (Note 2); it can be recrystallized from dilute ethanol (Note 3).

2. Notes

1. The use of commercial acetic anhydride in this preparation sometimes results in appreciably lower yields. The checkers used the freshly redistilled reagent.
2. The melting point is recorded in the literature[1,2] as 121° and as 123–124°.
3. Recrystallization from 50% ethanol (by weight) permits a 93–94% recovery of material melting at 121.5–122.5°; about 365 g. (400 ml.) of the solvent is required for 100 g. of the crude product.

3. Discussion

Hydroquinone diacetate has been prepared by the treatment of hydroquinone with acetic anhydride, both in the presence[1,3,4] and in the absence[5,6,7] of strong acid catalysts, by the treatment of the sodium salt of hydroquinone with acetic anhydride, and by the reaction of hydroquinone with acetic anhydride in the presence of sodium acetate.[8,9] It has also been prepared from hydroquinone and acetyl chloride;[10] the acetylation with acetyl chloride is reported to be improved by the addition of metallic

magnesium.[11]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 280

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

sulfuric acid (7664-93-9)

acetic anhydride (108-24-7)

sodium acetate (127-09-3)

acetyl chloride (75-36-5)

hydroquinone (123-31-9)

magnesium (7439-95-4)

Hydroquinone diacetate, Hydroquinone, diacetate (1205-91-0)

phosphorus pentoxide (1314-56-3)

sodium salt of hydroquinone

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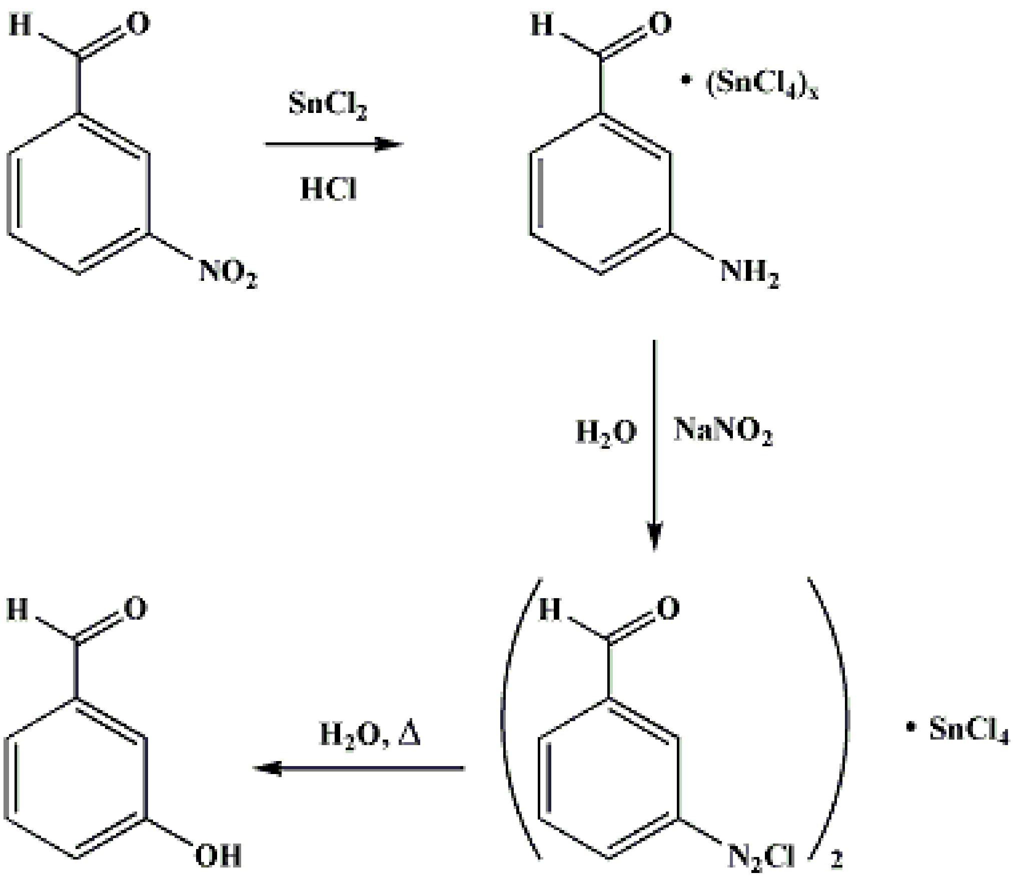
m-HYDROXYBENZALDEHYDE

[Benzaldehyde, *m*-hydroxy-]



Submitted by R. B. Woodward
Checked by C. S. Hamilton and Raymond J. Andres.

1. Procedure

A solution of 450 g. (2 moles) of powdered stannous chloride dihydrate (Note 1) in 600 ml. of concentrated hydrochloric acid in a 3-l. beaker provided with an efficient mechanical stirrer is cooled in an ice-salt bath. When the temperature of the solution has fallen to 5°, the ice bath is removed, and 100 g. (0.66 mole) of *m*-nitrobenzaldehyde (Note 2) is added in one portion. The temperature rises slowly at first, reaching 25–30° in about 5 minutes. As it then rises rapidly to about 100° the ice-salt bath is again placed around the beaker. Stirring must be vigorous or the reaction mixture may be forced out of the beaker (Note 3). During the reaction the *m*-nitrobenzaldehyde dissolves, and an almost clear red solution is obtained. The solution is cooled with very slow stirring (Note 4) in an ice-salt mixture for 2.5 hours. The orange-red paste of the stannichloride of *m*-aminobenzaldehyde (Note 5) is filtered on a sintered-glass funnel (Note 6).

A suspension of the material in 600 ml. of concentrated hydrochloric acid is stirred mechanically in a 3-l. beaker which is set in an ice-salt bath. A solution of 46 g. of sodium nitrite in 150 ml. of water in a 250-ml. dropping funnel fixed with its stem below the surface of the suspension is added slowly while the temperature of the mixture is kept at 4–5° (Note 7). After the addition is completed (in approximately 80 minutes), stirring in the ice-salt bath is continued for 1 hour to crystallize completely the stannichloride of the diazonium salt. The reddish brown salt is filtered on a sintered glass funnel (Note 6).

The damp salt is added cautiously in small portions to 1.7 l. of boiling water in a 4-l. beaker in the course of 40 minutes. During the reaction, the water lost by vaporization is replaced (Note 8). The solution is treated with 4 g. of Norit, boiled a few minutes, and filtered hot. The red filtrate is kept in an icebox for 12–16 hours; during this time scratching is employed occasionally to induce crystallization (Note 9). The yield of orange crystals melting at 99–101° is 48–52 g. (59–64%). A solution of this product in about 1 l. of boiling benzene is treated with Norit, filtered, and concentrated to 300 ml. On cooling, 41–45 g. (51–56%) of light-tan crystals melting at 101–102° is obtained (Note 10).

2. Notes

1. A chemically pure grade of stannous chloride ($SnCl_2 \cdot 2H_2O$) should be used. Lower yields are obtained with technical stannous chloride.
2. A practical grade of *m*-nitrobenzaldehyde (m.p. 52–55°) was used by the submitter. The checkers used Eastman's *m*-nitrobenzaldehyde (m.p. 57–58°).
3. Less satisfactory yields are obtained when the reaction is moderated by the addition of the *m*-nitrobenzaldehyde in several portions.
4. Stirring must be very slow since gradual cooling is necessary in order to obtain particles large enough to permit fairly rapid filtration.
5. The exact formula of the *m*-aminobenzaldehyde stannichloride is not known.
6. As a substitute for the sintered-glass funnel, a large Büchner funnel provided with an asbestos fiber mat under the filter paper will serve. The asbestos mat can be washed and used repeatedly.
7. Best results are obtained by keeping the temperature during diazotization at 4–5°. Below 0° the speed of diazotization is greatly decreased, and above 5° the diazonium salt begins to decompose.
8. Concentrating the solution below 1.7 l. results in markedly decreased purity.
9. If scratching does not succeed in inducing crystallization, a small portion of the solution may be removed and evaporated for seed.
10. According to the submitter, further purification can be effected by sublimation: the material is placed in the bottom of a Pyrex desiccator which is then evacuated and placed on a steam bath overnight. The mat of interwoven needles can be removed easily. One crystallization from benzene gives 37–40 g. (47–49%) of needles melting at 103–104°.

3. Discussion

m-Hydroxybenzaldehyde has been made by reduction of *m*-hydroxybenzoic acid with sodium amalgam in weak acid solution;[1] by oxidation of the arylsulfonic ester $ArSO_2OC_6H_4CH_3$ with manganese dioxide and sulfuric acid to the corresponding derivative of *m*-hydroxybenzaldehyde $ArSO_2OC_6H_4CHO$ and hydrolysis of the latter with concentrated sulfuric acid;[2] from *m*-dichloromethylphenyl benzoate by heating with water and calcium carbonate under a pressure of 4–5 atm.[3] The present method is derived from that of Tiemann and Ludwig[4] and is similar to the procedure for the preparation of *m*-chlorobenzaldehyde.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 564

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

sodium nitrite (7632-00-0)

stannous chloride

calcium carbonate (471-34-1)

Norit (7782-42-5)

sodium (13966-32-0)

manganese dioxide (1313-13-9)

stannous chloride dihydrate (10025-69-1)

Benzaldehyde, m-hydroxy-, m-Hydroxybenzaldehyde (100-83-4)

m-Chlorobenzaldehyde (587-04-2)

m-hydroxybenzoic acid (99-06-9)

m-Nitrobenzaldehyde (99-61-6)

m-aminobenzaldehyde (1709-44-0)

m-dichloromethylphenyl benzoate

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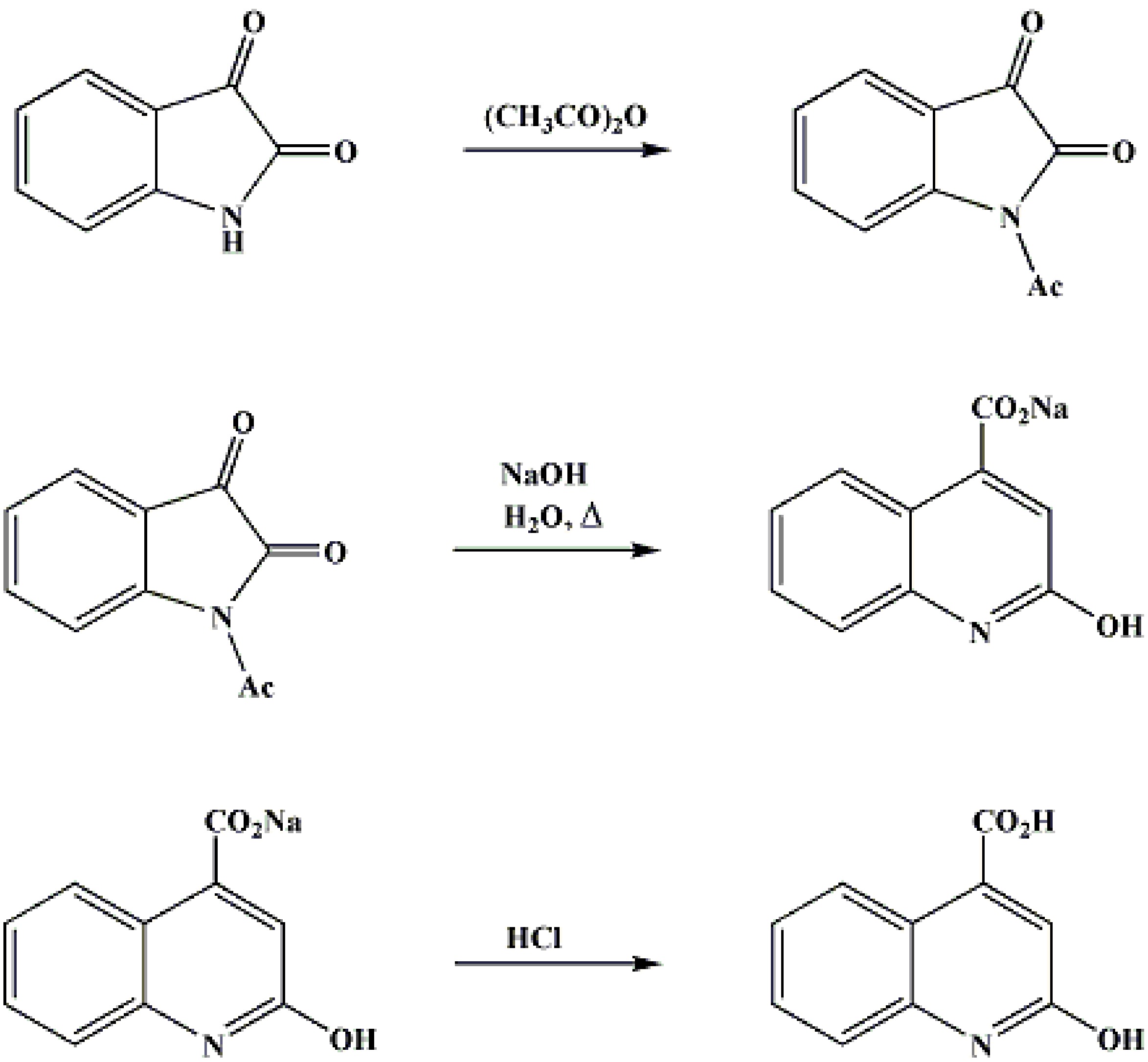
2-HYDROXYCINCHONINIC ACID

[Cinchoninic acid, 2-hydroxy-]



Submitted by Thomas L. Jacobs, S. Winstein, Gustave B. Linden, Jean H. Robson, Edward F. Levy, and Dexter Seymour[1].
Checked by R. T. Arnold and F. M. Robinson.

1. Procedure

A. *N-Acetylisatin.* In a 3-l. three-necked flask equipped with a mercury-sealed stirrer and reflux condenser are placed 600 g. (4.1 moles) of isatin (Note 1) and 1390 ml. (14.7 moles) of acetic anhydride (Note 2). This mixture is refluxed for 4 hours over a free flame with constant stirring. The solution is allowed to cool slowly to room temperature with stirring and is then cooled to about 10° (Note 3). The slurry of crystals is collected on a 12-in. Büchner funnel and washed with five 175-ml. portions of ether or until the washings are light red. The yield of crude air-dried N-acetylisatin,

m.p. 141–142° (cor.), is 635 to 643 g. (82–83%) (Note 4).

B. *2-Hydroxycinchoninic acid.* To a solution of 160 g. (about 3.8 moles) of U.S.P. sodium hydroxide in 9.6 l. of water in a 12-l. flask is added 310 g. (1.64 moles) of crude N-acetylisatin. The mixture is stirred mechanically and heated to boiling; the flame is adjusted to maintain gentle boiling. After the mixture has boiled 1 hour (Note 5) the flame is removed, 50 g. of decolorizing carbon is added cautiously (vigorous boiling and frothing may occur if the solution is too hot), and the suspension is stirred for 30 minutes. The charcoal is allowed to settle for a few minutes, and the solution is siphoned into a filter funnel containing a layer of Supercel. The filtrate is allowed to cool overnight in a 5-gal. crock. The solution is stirred with a hook-type stirrer driven by a powerful motor (Note 6), and 6 *N* hydrochloric acid is added until the mixture is neutral to Congo red. The suspension is filtered immediately (Note 7) through a 12-in. Büchner funnel, and the solid is washed with 2 l. of water. The filtrate is made distinctly acid to Congo red and set aside for a few hours. The solid acid is dried at 90° for 2 days; the anhydrous acid, m.p. 346–347° (cor.), so obtained has the correct neutral equivalent (Note 8) and weighs 200 to 205 g. (70–73% over-all yield, based on isatin consumed). From the acidified filtrate, after precipitation is complete, about 60 g. of isatin is recovered.

2. Notes

1. Commercial isatin, m.p. 199.0–200.5° (cor.), was obtained from the National Aniline and Chemical Company.
2. Acetic anhydride obtained from the Carbide and Carbon Chemicals Corporation was employed. Redistillation of this reagent did not increase the yield.
3. If the solution is not stirred during the cooling, the product crystallizes as a solid cake which is difficult to remove from the flask.
4. Recrystallization from benzene, unnecessary for the present purpose, gives a yellow crystalline product of m.p. 142.0–143.5° (cor.).
5. It is convenient to make two of these runs simultaneously. A reflux condenser is unnecessary, but if none is used the stopper holding the stirrer must be provided with a vent to permit steam to escape.
6. The ordinary small laboratory stirring motor is insufficiently powerful to maintain rapid agitation after most of the cinchoninic acid has precipitated.
7. If the mixture is not filtered immediately after acidification, or if the first end point is overrun, isatin is precipitated along with the cinchoninic acid and the product has a deep red color. Such material can be freed of isatin by dissolving it in sodium bicarbonate solution, filtering, and reprecipitating.
8. This crude acid, which is satisfactory for most purposes, can be recrystallized from glacial acetic acid to yield a product melting at 352–353° (cor.).

3. Discussion

2-Hydroxycinchoninic acid has been prepared by the rearangement of N-acetylisatin in

alkali,[2,3,4] by the treatment of isatin with malonic acid in glacial acetic acid,[5] by heating cinchoninic acid with concentrated potassium hydroxide,[6] and by the treatment of ethyl 2-chlorocinchoninate with 30% sodium hydroxide.[7]

References and Notes

1. Work done under contract with the Office of Scientific Research and Development.
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5. Borsche and Jacobs, *Ber.*, **47**, 354 (1914).
6. Koenigs and Koerner, *Ber.*, **16**, 2152 (1883).
7. Thielpape, *Ber.*, **71B**, 387 (1938); Ger. pat 670,582 [*C. A.*, **33**, 6348 (1939)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

ether (60-29-7)

acetic anhydride (108-24-7)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

decolorizing carbon (7782-42-5)

potassium hydroxide (1310-58-3)

Isatin (91-56-5)

Malonic acid (141-82-2)

2-Hydroxycinchoninic acid, Cinchoninic acid, 2-hydroxy- (15733-89-8)

N-Acetylisatin (574-17-4)

cinchoninic acid (486-74-8)

ethyl 2-chlorocinchoninate

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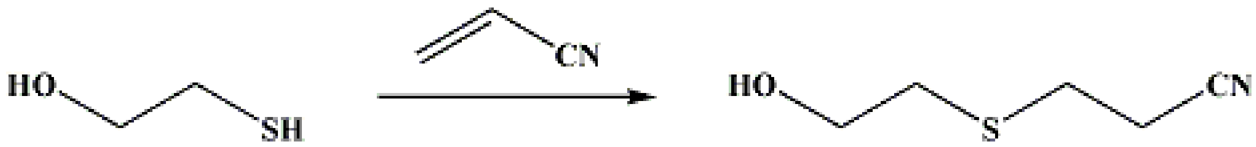
Organic Syntheses, *CV 3*, *458*

β-(2-HYDROXYETHYLMERCAPTO)PROPIONITRILE

[Propionitrile, β-(2-hydroxyethylmercapto)-]



Submitted by Leon L. Gershbein
Checked by Charles D. Hurd, Cliff S. Hamilton, and John A. Stephens.

1. Procedure

In a 500-ml. three-necked round-bottomed flask equipped with a sealed stirrer, a reflux condenser, a dropping funnel, and a thermometer is placed 78 g. (70 ml., 1 mole) of 2-mercaptoethanol (Note 1). Into the dropping funnel is poured 67 ml. (54.3 g., 1 mole) of acrylonitrile (Note 2), and after the addition of about 3 ml. of the nitrile, with stirring, the contents are warmed with a water bath to about 35–40° for 5 minutes. The remainder of the acrylonitrile is then added dropwise during 10 minutes. The temperature soon mounts to about 65° and is kept between 55° and 60° by intermittent short cooling with water until it only slowly increases or remains stationary at 55–60° (Note 3). Forty milliliters of acrylonitrile is then added all at once, cooling being applied if necessary, and the contents are stirred for 16 hours at room temperature. The product is distilled from a 250-ml. Claisen flask after removal of excess acrylonitrile under reduced pressure. The yield of nitrile distilling at 178–180°/14 mm., n_D^{25} 1.5101, as a colorless viscous liquid is 121–123 g. (92–94%) (Note 4).

2. Notes

1. The 2-mercaptoethanol was obtained from Carbide and Carbon Chemicals Corporation.
2. Commercial acrylonitrile may be used without further purification.
3. This requires about 30 minutes. As an inhibition period generally occurs, care must be taken in the initiation of the reaction and subsequent moderation of the heat evolved, but this operation can easily be controlled.
4. In the presence of alcoholic sodium hydroxide, either 2-mercaptoethanol or β-(2-hydroxyethylmercapto) propionitrile is converted to the dicyanoethylated product, 4-oxa-7-thiadecanedinitrile, $NCCH_2$-$CH_2OCH_2CH_2SCH_2CH_2CN$. This basic agent can also be applied to the general reaction of thiophenols or mercaptans with acrylonitrile.

3. Discussion

This method is a modification of the directions of Hurd and Gershbein.[1] The compound has been made also[2] with piperidine as the basic catalyst.

References and Notes

1. Hurd and Gershbein, *J. Am. Chem. Soc.*, **69**, 2331 (1947).
2. Gribbins, Miller, and O'Leary, U. S. pat. 2,397,960 [*C. A.*, **40**, 3542 (1946)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium hydroxide (1310-73-2)

piperidine (110-89-4)

acrylonitrile (107-13-1)

β-(2-Hydroxyethylmercapto)propionitrile, Propionitrile, β-(2-hydroxyethylmercapto)-, β-(2-hydroxyethylmercapto) propionitrile (15771-37-6)

2-mercaptoethanol (60-24-2)

4-oxa-7-thiadecanedinitrile

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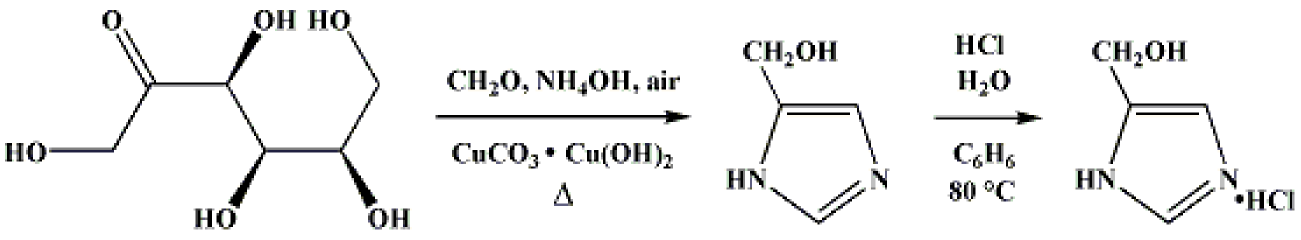
Organic Syntheses, CV 3, 460

4(5)-HYDROXYMETHYLIMIDAZOLE HYDROCHLORIDE

[4-Imidazolemethanol, hydrochloride]



d - fructose

Submitted by John R. Totter and William J. Darby.
Checked by H. R. Snyder and R. L. Rowland.

1. Procedure

A. *Hydroxymethylimidazole picrate.* To 222 g. (1 mole) of basic cupric carbonate (Note 1) in a 5-l. flask are added 1.5 l. of distilled water and 720 g. (800 ml., 12 moles) of 28% ammonia. The bulk of the copper carbonate is brought into solution by swirling; 112 g. (100 ml., 1.3–1.4 moles) of 37–40% formaldehyde and 90 g. (0.475 mole) of commercial 95% fructose are added. The solution is well mixed and placed on a steam bath under a hood. After 30 minutes of heating with occasional shaking, a moderate current of air is bubbled through the solution (500–600 ml. per minute) (Note 2), with continued heating, for 2 hours longer (Note 3).

The mixture is then chilled in an ice bath for at least 3 hours, and the olive-brown precipitate of the sparingly soluble copper complex of imidazole derivatives is filtered. The product is washed with about 500 ml. of cold water, suspended while moist (Note 4) in 1 l. of water, and rendered just acid to litmus by the addition of concentrated hydrochloric acid (about 40 ml.). Hydrogen sulfide is then passed into the suspension, with frequent shaking, until precipitation of the copper is complete (2–3 hours). The precipitate is filtered and extracted with 500 ml. of hot water in two or three portions. The clear, light-brown to reddish brown filtrate and washings are boiled for 15 minutes, and then 60 g. (0.26 mole) of picric acid is added with stirring; heating is continued until solution is complete.

The greenish yellow plates, which separate as the solution is cooled to room temperature, are filtered, washed 3 times with 150- to 200-ml. portions of water, and air-dried. The filtrate and first washings are combined and heated, 10 g. of picric acid is added, and the mixture is cooled and filtered. This process is repeated, using 10-g. portions of picric acid, until the air-dried picrate fraction so obtained melts below 195° (Note 5).

All fractions melting above 200° (Note 5) are combined and recrystallized from water by adding 700 ml. of water for each 30 g. of crystals, heating the mixture in a covered beaker until solution occurs, treating with charcoal, and filtering through a warm funnel. The crystals deposit upon the slightest cooling. After cooling, the yellow needles (occasionally plates) are filtered, washed, and air-dried; their melting point is 204° or higher, with decomposition (Note 5). The fractions melting at 195–200° (Note 5) are recrystallized in like manner until the melting point is raised to 203°. The yield of crude picrate is 95–100 g. (61–64%); of recrystallized picrate, 84–94 g. (54–60%) (Note 6). The melting point varies slightly with the rate of heating between 203.5° and 206° with decomposition (Note 5).

B. *Hydroxymethylimidazole hydrochloride.* One hundred and twenty grams (100 ml., 1.2 moles) of 37%

hydrochloric acid, 250 ml. of water, and 500 ml. of benzene are placed in a 2-l. round-bottomed flask, which is then immersed in a water bath maintained at 80°. One hundred grams of the pure picrate (0.306 mole) is added to this mixture, and the flask is shaken thoroughly until the picrate dissolves. The benzene layer is decanted. The aqueous layer is then extracted 5 times with 330-ml. portions of benzene, treated with about 3 g. of Norit, and filtered through a wet filter paper. The clear, pale yellow filtrate is evaporated to dryness at 60–70° under reduced pressure. The resulting pale yellow to slightly brown crystals are taken up in the minimum quantity (30–35 ml.) of hot absolute ethanol. Colorless needles deposit on cooling. Three to four volumes of ethyl ether are added, and the mixture is kept in the refrigerator overnight. The almost colorless needles are filtered and, after being washed with a small amount of ether, are dried in a vacuum desiccator. The yield amounts to 37–39 g. (90–95%) of a product which melts at 107–109° after sintering a few degrees lower (Note 6).

2. Notes

1. Equally good results are obtained with technical or pure grades of basic copper carbonate, $CuCO_3 \cdot Cu(OH)_2$. Satisfactory results are obtained also when the reagent is prepared by adding an equivalent amount of a solution of sodium carbonate to a solution of copper sulfate and washing the resulting precipitate until it is nearly free of sulfate ion. When the reagent is prepared in this way, 4 moles of copper sulfate are used for each mole of fructose, and the wet basic cupric carbonate is used without drying or weighing.
2. If the aeration is omitted, the yield is about 10% lower.
3. No attempt is made to recover ammonia which escapes during the aeration.
4. The copper precipitate can be dried unchanged but is then difficult to decompose with hydrogen sulfide.
5. One to three such additions usually are necessary. The melting points given are those of the submitters and were observed by immersing the capillary melting-point tubes containing the samples in a bath preheated to a temperature 20° to 50° below the expected melting point and heating rather rapidly. The checkers determined the melting points in the ordinary manner, starting with the bath at room temperature, and observed melting points about 5° lower than those of the submitters. In one of the checkers' preparations the main fraction of crude picrate weighed 86 g. and melted at 193–194°; the second fraction weighed 12 g. and melted at 191–193°; the third fraction, which melted at 186–188°, was rejected. One recrystallization raised the melting point of the first fraction to 199° (75 g. recovered) and that of the second fraction to 197° (9.5 g. recovered). The once-recrystallized products were combined and employed in the preparation of the hydrochloride, which was obtained in the yield described and with a melting point of 107–108°.
6. Equally good yields are obtainable with double the quantities indicated.

3. Discussion

4(5)-Hydroxymethylimidazole has been synthesized in a long series of steps from citric acid.[1] Weidenhagen and Herrmann prepared it from dihydroxyacetone.[2] The reaction which provides the basis of the procedure here described[3] was discovered by Parrod[4] and developed by Weidenhagen, Herrmann, and Wegner.[5] The method developed by these last-named investigators, however, provides considerably smaller yields than that described above.

References and Notes

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2. Weidenhagen and Herrmann, *Ber.*, **68**, 1953 (1935).
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4. Parrod, *Bull. soc. chim. France*, (4) **51**, 1424 (1932).

5. Weidenhagen, Herrmann, and Wegner, *Ber.*, **70**, 570 (1937).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

4(5)-Hydroxymethylimidazole hydrochloride

copper complex of imidazole

copper carbonate, $CuCO_3 \cdot Cu(OH)_2$

4(5)-Hydroxymethylimidazole

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

Benzene (71-43-2)

ether, ethyl ether (60-29-7)

citric acid (77-92-9)

formaldehyde (630-08-0)

hydrogen sulfide (7783-06-4)

sodium carbonate (497-19-8)

copper sulfate (7758-98-7)

Norit (7782-42-5)

picric acid, picrate (88-89-1)

dihydroxyacetone

fructose

4-Imidazolemethanol, hydrochloride (32673-41-9)

cupric carbonate, copper carbonate

Hydroxymethylimidazole picrate

Hydroxymethylimidazole hydrochloride

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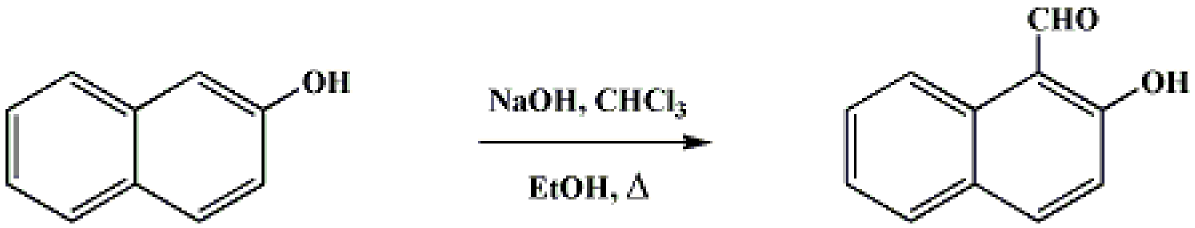
Organic Syntheses, CV 3, 463

2-HYDROXY-1-NAPHTHALDEHYDE

[1-Naphthaldehyde, 2-hydroxy-]



Submitted by Alfred Russell and Luther B. Lockhart.
Checked by W. E. Bachmann and Charles E. Maxwell.

1. Procedure

In a 2-l. three-necked round-bottomed flask (Note 1) fitted with a 40-in. reflux condenser, a mercury-sealed stirrer, and a dropping funnel are placed 100 g. (0.69 mole) of β-naphthol and 300 g. of 95% ethanol. The stirrer is started, and a solution of 200 g. (5 moles) of sodium hydroxide in 415 g. of water is rapidly added.

The resulting solution is heated to 70–80° on a steam bath, and the dropwise addition of chloroform is started. After the reaction begins (Note 2), further heating is unnecessary. A total of 131 g. (1.1 moles) of chloroform is added at such a rate that gentle refluxing is maintained (Note 3). Near the end of the addition the sodium salt of the phenolic aldehyde separates. Stirring is continued for 1 hour after all the chloroform has been added.

The ethanol and excess chloroform are removed by distillation from a steam bath. Hydrochloric acid (sp. gr. 1.18) is added dropwise to the residue, with good stirring, until the contents of the flask are acid to Congo red paper (Note 4). The dark oil that separates is mixed with a considerable amount of sodium chloride. Sufficient water to dissolve the salt is added, and the oil is separated and washed several times with hot water. By distillation of the oil under reduced pressure there is obtained 87.5–93.7 g. of a slightly colored distillate which boils at 163–166° at 8 mm. (Note 5) and which solidifies on cooling. Recrystallization of the solid from 75 ml. of ethanol yields 45.2–57.5 g. (38–48%) of pure 2-hydroxy-1-naphthaldehyde, melting at 79–80°.

2. Notes

1. The submitters employed a 5-l. flask for a run four times this size. They obtained the same percentage yield of product.
2. The beginning of the reaction is indicated by the formation of a deep blue color.
3. The chloroform is added over a period of 1 to 1.5 hours.

4. About 175 ml. of hydrochloric acid is required to neutralize the excess sodium hydroxide and to liberate the phenolic aldehyde from its sodium salt.
5. The boiling range of the aldehyde is 177–180°/20 mm. The lower pressure is preferable to avoid decomposition. The checkers found a boiling point of 139–142°/4 mm. The color of the distillate varies in different runs; it may be green, pink, or amber.

3. Discussion

2-Hydroxy-1-naphthaldehyde has been prepared from β-naphthol, zinc chloride, and hydrogen cyanide;[1] from β-naphthol, zinc cyanide, and anhydrous hydrogen chloride;[2] from β-naphthol, chloroform, and sodium hydroxide (Reimer-Tiemann reaction);[3],[4] from β-naphthol and hexamethylene tetramine in glycerin-boric acid, followed by hydrolysis;[5] and by hydrolysis of 2-hydroxynaphthaldehyde anil,[6] prepared in turn from 2-hydroxydithionaphthoic acid.[7].

References and Notes

1. Gattermann and von Horlacher, *Ber.*, **32**, 285 (1899).
2. Adams and Levine, *J. Am. Chem. Soc.*, **45**, 2373 (1923).
3. Fosse, *Bull. soc. chim. France*, (3) **25**, 373 (1901).
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5. Duff, *J. Chem. Soc.*, **1941**, 547.
6. Brit. pat. 563,747 [*C. A.*, **40**, 3141 (1946)].
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium salt of the phenolic aldehyde

2-hydroxynaphthaldehyde anil

ethanol (64-17-5)

hydrogen chloride, hydrochloric acid (7647-01-0)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium chloride (7647-14-5)

hydrogen cyanide (74-90-8)

β-naphthol (135-19-3)

zinc chloride (7646-85-7)

phenolic aldehyde (90-02-8)

hexamethylene tetramine (100-97-0)

2-Hydroxy-1-naphthaldehyde, 1-Naphthaldehyde, 2-hydroxy- (708-06-5)

glycerin-boric acid

2-hydroxydithionaphthoic acid

zinc cyanide (557-21-1)

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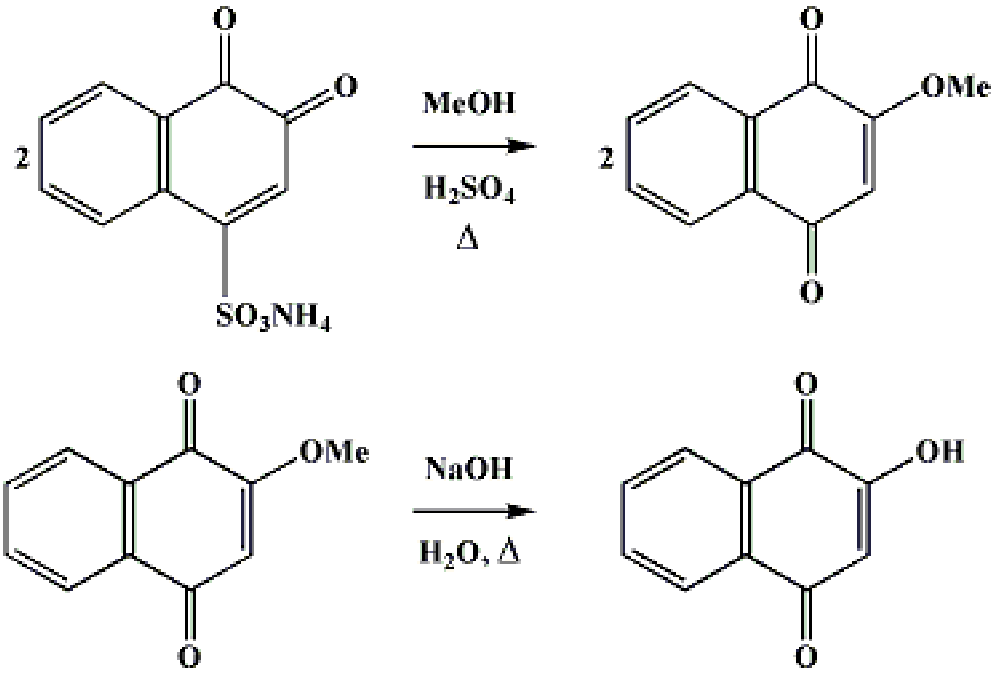
2-HYDROXY-1,4-NAPHTHOQUINONE

[1,4-Naphthoquinone, 2-hydroxy-]



Submitted by L. F. Fieser and E. L. Martin.
Checked by Reynold C. Fuson and E. A. Cleveland.

1. Procedure

One liter of absolute methanol is cooled in a 3-l. round-bottomed flask to 0° in an ice-salt bath, and 80 ml. of concentrated sulfuric acid is slowly added, with good shaking, the temperature being kept at 0°. The flask is removed from the freezing mixture, and 255 g. (1 mole) of ammonium 1,2-naphthoquinone-4-sulfonate (p. 633) is added and made into an even paste by thorough shaking. After standing for 30 minutes, during which time the temperature rises to 15–20°, the flask is heated gradually on the steam bath with continuous shaking and rotating so that the solution reaches its boiling point in about 15 minutes. The solution becomes red, sulfur dioxide is evolved, and methoxynaphthoquinone begins to separate. The mixture is kept boiling very gently, with continued shaking, for 15 minutes, when the paste of separated material becomes very stiff. Two hundred and fifty milliliters of methanol is added, and the heating and rotating continued for an additional 15–20 minutes. The reaction mixture is cooled to 20–25°, water and ice are added until the flask is nearly filled, and the methoxynaphthoquinone is collected on a 15-cm. Büchner funnel and washed with cold water until the filtrate is nearly colorless; about 2–2.5 l. of water is required (Note 1).

The moist material is washed into a solution of 30 g. of sodium hydroxide in 1.5 l. of

water, and the mixture is heated rapidly nearly to the boiling point. In about 10 minutes all the ether is hydrolyzed and a deep red solution results (Note 2). The hot solution is filtered by suction from a trace of residue, transferred to a 2-l. beaker, and acidified while still hot by adding 130 ml. of 6 *N* hydrochloric acid slowly, and with good stirring. The yellow suspension of hydroxynaphthoquinone thus obtained is cooled to 0° and allowed to stand for 2 hours (Note 3). The hydroxynaphthoquinone is collected, washed with 2 l. of cold water, dried overnight at room temperature, and finally to constant weight at 60–80°. The yield is 101–112 g. (58–65% based on ammonium 1,2-naphthoquinone-4-sulfonate; 99%, based on methoxynaphthoquinone) (Note 4). The hydroxynaphthoquinone thus obtained is bright yellow, is granular, and melts, with decomposition, at about 188–189° (Note 5). It is of high quality and for ordinary uses requires no further purification (Note 6).

2. Notes

1. The methoxynaphthoquinone weighs 111–122 g. (59–65%). It melts at 181–182° and can be further purified by crystallization from ethanol. The pure substance forms pale yellow needles, m.p. 183.5°.
2. Should the sodium salt separate during the heating or filtration, it is brought into solution by adding about 1 l. of water and heating.
3. By allowing the precipitate to stand for the indicated period, the final product is granular, and the filtration is rapid.
4. Numerous modifications have been tried without improving the yield. The loss is probably due to a partial reduction of the quinone sulfonate by the sulfur dioxide liberated, but this was not prevented by adding manganese dioxide to the reaction mixture and no pure product could be obtained from the mother liquor.
5. The temperature of decomposition varies with the rate of heating and with the nature of the glass capillary.
6. Crystallization from ethanol containing a trace of acetic acid gives glistening yellow needles, melting with decomposition at about 191–192°. The red samples of hydroxynaphthoquinone often mentioned in the literature are not completely pure. Such material, or crude material of any kind, is best purified through either the sodium salt or the methyl ether.

3. Discussion

Of the many reactions by which hydroxynaphthoquinone has been obtained,[1,2] two have been developed into practical preparative methods, and both utilize the inexpensive β-naphthol as the primary starting material. In the first method, this is converted into β-naphthoquinone [*Org. Syntheses* Coll. Vol. 2, 430 (1943)], which reacts with acetic anhydride-sulfuric acid to give 1,2,4-trihydroxynaphthalene triacetate, which is then hydrolyzed and oxidized to the desired product. The yield of the acetylation reaction is about 75%; that in the final step can be brought to 93% of the theoretical amount by hydrolyzing with ethanolic alkali in an atmosphere of

nitrogen and with a trace of sodium hydrosulfite present, then diluting with water, acidifying, and adding ferric chloride. The overall yield from β-naphthol can thus be brought to 54%. The method is a good one, and it can be used to advantage for the preparation of many similar hydroxyquinones. With ordinary laboratory equipment, however, one is limited to 0.5 mole runs, and not more than about 50 g. of hydroxynaphthoquinone can be prepared at a time.

The second method is that described above: β-naphthol is converted through the nitroso derivative and 1-amino-2-naphthol-4-sulfonic acid into naphthoquinone sulfonate, and this is subjected to acid hydrolysis. The sulfonate can be converted directly into hydroxynaphthoquinone by the action of concentrated sulfuric acid,[3,4] but the process is not so easily controlled as when the quinone is etherified as it is formed and the ether subsequently hydrolyzed.[4] The overall yield from β-naphthol is 46% of the theoretical amount, but all the reagents are inexpensive, and with ordinary apparatus, 150 g. of hydroxynaphthoquinone can be made conveniently in one run (from 300 g. of β-naphthol).

The compound has also been prepared in good yield by air oxidation of 1,3-dihydroxynaphthalene,[5] which in turn was obtained from ethyl γ-phenylacetoacetate.[6]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

methanol (67-56-1)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sulfur dioxide (7446-09-5)

nitrogen (7727-37-9)

sodium hydrosulfite (7775-14-6)

β-naphthol (135-19-3)

methyl ether (115-10-6)

manganese dioxide (1313-13-9)

ferric chloride (7705-08-0)

1-AMINO-2-NAPHTHOL-4-SULFONIC ACID (116-63-2)

ethyl γ-phenylacetoacetate

β-naphthoquinone (524-42-5)

2-Hydroxy-1,4-naphthoquinone, 1,4-Naphthoquinone, 2-hydroxy-, hydroxynaphthoquinone (83-72-7)

ammonium 1,2-naphthoquinone-4-sulfonate (53684-60-9)

methoxynaphthoquinone (2348-82-5)

acetic anhydride-sulfuric acid

1,2,4-trihydroxynaphthalene triacetate

naphthoquinone sulfonate

1,3-dihydroxynaphthalene (132-86-5)

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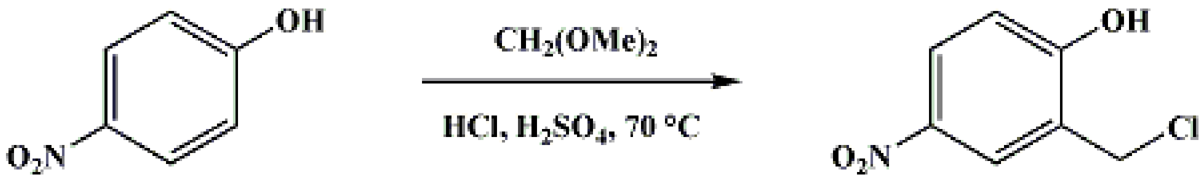
2-HYDROXY-5-NITROBENZYL CHLORIDE

[Toluene, α-chloro-2-hydroxy-5-nitro-]



Submitted by C. A. Buehler, Fred K. Kirchner, and George F. Deebel.
Checked by C. F. H. Allen and Alan Bell.

1. Procedure

In a 1-l. three-necked round-bottomed flask equipped with a mechanical stirrer, short reflux condenser, and bent glass tube reaching below the surface of the liquid for the introduction of hydrogen chloride, are placed 50 g. (0.36 mole) of *p*-nitrophenol (Note 1), 650 ml. of concentrated hydrochloric acid, 5 ml. of concentrated sulfuric acid (Note 2), and 76 g. (1 mole) of methylal (Note 3). The mixture is stirred while the temperature is maintained at 70 ± 2° for 4–5 hours by means of a water bath (Note 4). During this time hydrogen chloride is bubbled into the reaction mixture through the bent glass tube, and the excess gas is carried away through the reflux condenser to a hood or gas-absorption trap (Note 5).

The 2-hydroxy-5-nitrobenzyl chloride begins to separate as a solid about 1 hour after the beginning of the reaction. At the end the mixture is cooled in ice for 1 hour whereby more crystals separate, after which the acid liquors are either filtered or decanted from the crystals (Note 6). The 2-hydroxy-5-nitrobenzyl chloride is purified by recrystallization from 125 ml. of hot benzene (Note 7). The yield is 46 g. (69% based on *p*-nitrophenol) of a white product melting at 129–130°.

2. Notes

1. Best results are obtained by using *p*-nitrophenol of a grade melting above 112°.
2. The reaction will proceed in the absence of sulfuric acid, but in its presence a greater reaction velocity results.
3. Methylal, used in excess, is prepared according to the method given by Houben.[1] Twelve hundred grams of methanol is added to 800 g. of anhydrous calcium chloride in a 5-l. round-bottomed flask equipped with a reflux condenser. Twenty-four grams of concentrated hydrochloric acid is added, and then, with cooling, 800 g. of technical 35–40% formaldehyde is slowly dropped in through a dropping funnel. The reaction is strongly exothermic, requiring

about 2 hours for complete addition of the formaldehyde. When all the formaldehyde has been added, the mixture is heated with a Bunsen flame for a few minutes until the liquid boils vigorously. The methylal forms quickly as an upper layer and, after 6 hours' standing, is fractionally distilled, preferably using a Clarke and Rahrs column.[2] The 42–46° fraction is sufficiently pure for use.

4. Temperatures higher than 72° may result in the formation of oily-resinous material with a corresponding decrease in chloride. The reaction is nearly complete at the end of 4 hours, but additional time will result in a slightly increased yield.

5. Rubber joints should be used sparingly as the hydrogen chloride causes an internal swelling of the rubber with subsequent blocking of the lines.

6. The high acid concentration makes ordinary filtration difficult. By allowing the reaction mixture to stand in an ice bath for 1 hour, the solid clings together, and filtration with gentle suction or decantation can be used with ease.

7. The solid material should be air-dried for several hours or, better, overnight to remove all water before recrystallizing from hot benzene. The chlorine atom is very labile and hydrolyzes easily to form 2-hydroxy-5-nitrobenzyl alcohol.

3. Discussion

2-Hydroxy-5-nitrobenzyl chloride can also be prepared from 2-hydroxy-5-nitrobenzyl alcohol by passing hydrogen chloride into an ethanolic solution at 70 ± 2° for 2 hours. In this case the yield of chloride is almost quantitative. The foregoing detailed procedure has been arrived at from that given in German Patent 132,475.[3]

References and Notes

1. Houben, *Die Methoden der organischen Chemie*, 3rd Ed., Vol. III, p. 193, Verlag Georg Thieme, Leipzig, 1930.
2. Clarke and Rahrs, *Ind. Eng. Chem.*, **18**, 1092 (1926).
3. *Frdl.*, **6**, 142 (1904).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrogen chloride, hydrochloric acid (7647-01-0)

Benzene (71-43-2)

methanol (67-56-1)

formaldehyde (630-08-0)

chlorine (7782-50-5)

methylal (109-87-5)

2-Hydroxy-5-nitrobenzyl chloride, Toluene, α-chloro-2-hydroxy-5-nitro- (2973-19-5)

2-hydroxy-5-nitrobenzyl alcohol

p-nitrophenol (100-02-7)

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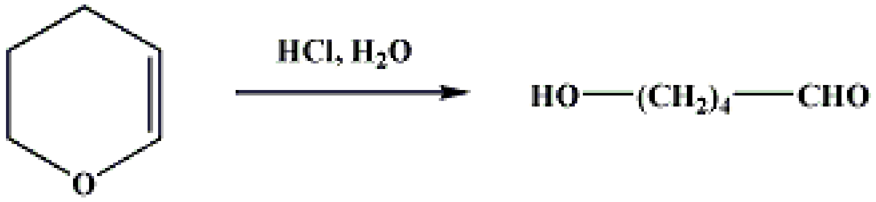
Organic Syntheses, CV 3, 470

5-HYDROXYPENTANAL

[Valeraldehyde, δ-hydroxy-]



Submitted by G. Forrest Woods, Jr.
Checked by Cliff S. Hamilton and Wm. V. Ruyle.

1. Procedure

In a 1-l. three-necked flask provided with a Hershberg stirrer are mixed 300 ml. of water, 25 ml. of concentrated hydrochloric acid (Note 1), and 100 g. of 2,3-dihydropyran (p. 276). The mixture is stirred until the solution has become homogeneous and then for an additional 20 minutes (Note 2). After the addition of a few drops of phenolphthalein indicator to the mixture, the acid is neutralized with 20% sodium hydroxide; enough alkali is added so that a faint pink color just persists.

The solution is then transferred to a continuous extractor and extracted with ether for about 16 hours. The ether extract is added in convenient portions to a 250-ml. modified Claisen flask fitted with a condenser and a suitable fraction-cutter for distillation under reduced pressure. The ether is removed by distillation under the diminished pressure of a water pump, and the residue is then distilled at about 10 mm. pressure. After a small fore-run which weighs 2–5 g., the product distils as a clear, colorless, viscous oil at 62–66°/9–10 mm.; n_D^{25} 1.4513. The yield is 90–95 g. (74–79%) (Note 3) and (Note 4).

2. Notes

1. The quantity of acid is arbitrary. This amount was chosen to minimize the time of hydration. The order of addition of the reactants should be that stated above. Less acid may be used with increased reaction time; more should not be used.
2. About 5–10 minutes is required before the solution becomes homogeneous. Some heat is evolved during the hydration. The submitter has found that the amount of 2,3-dihydropyran may be increased up to 300 g. without using more water or acid; however, if larger quantities of the pyran are used, the pyran must be added dropwise to the acid solution with cooling.
3. A convenient apparatus for the distillation is a modified Claisen flask whose side arm is provided with a short water-cooled condenser. A fraction-cutter of the "pig" type is satisfactory.

4. According to the submitter the product can be converted smoothly to pentamethylene glycol by hydrogenation over Raney nickel at 90° and 2000 lb. pressure. It will also undergo reductive alkylamination by a procedure similar to that described for 2-isopropylaminoethanol (p. 501).

3. Discussion

5-Hydroxypentanal has been prepared only by the method of Paul,[1] of which the above is an adaptation.

References and Notes

1. Paul, *Bull. soc. chim. France*, (5), **1**, 976 (1934).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium hydroxide (1310-73-2)

Raney nickel (7440-02-0)

pentamethylene glycol (111-29-5)

phenolphthalein (77-09-8)

2,3-Dihydropyran

5-Hydroxypentanal, Valeraldehyde, δ-hydroxy- (4221-03-8)

2-isopropylaminoethanol (109-56-8)

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Organic Syntheses, CV 3, 471

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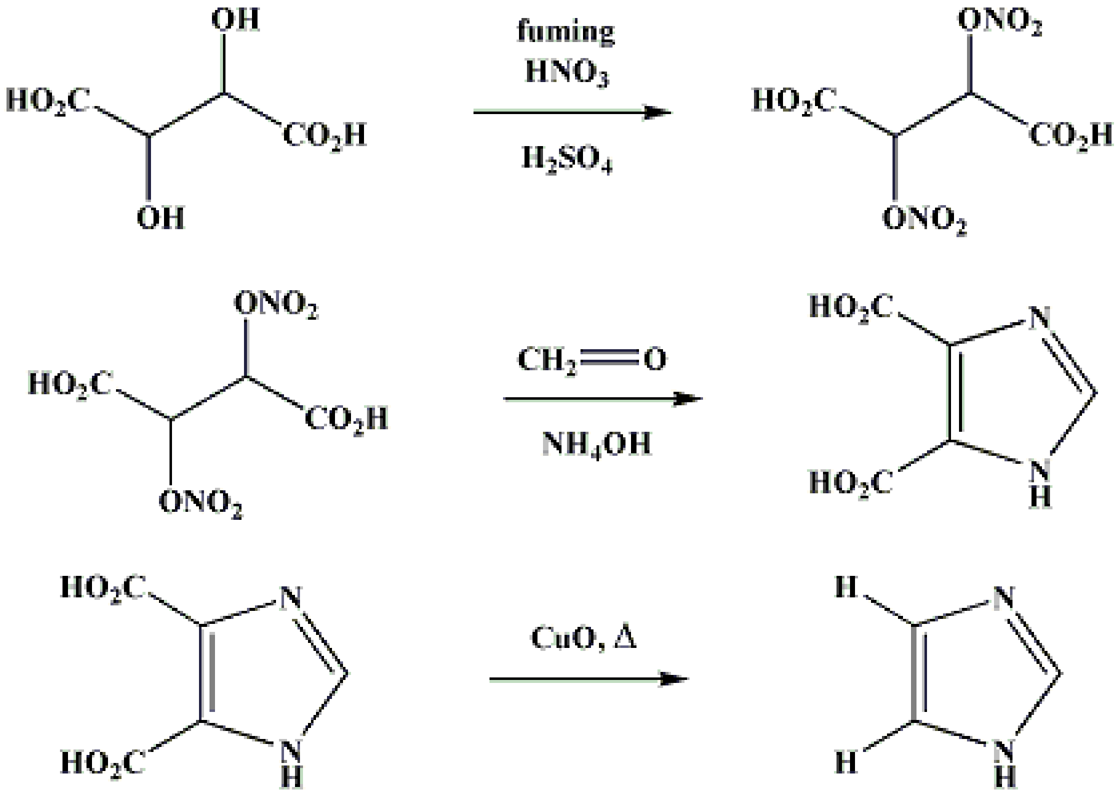

Submitted by H. R. Snyder, R. G. Handrick, and L. A. Brooks.
Checked by C. F. H. Allen, C. J. Kibler, and James VanAllan.

1. Procedure

In a 2-l. three-necked round-bottomed flask fitted with a thermometer, mechanical stirrer, and 1-l. dropping funnel is placed 200 g. (1.33 moles) of powdered *d*-tartaric acid (Note 1). To this are added, successively, 432 ml. of nitric acid (sp. gr. 1.42) and 432 ml. of fuming nitric acid (sp. gr. 1.50). The mixture is stirred until the tartaric acid is all, or nearly all, in solution (5–10 minutes) (Note 2). Then 800 ml. of concentrated sulfuric acid (sp. gr. 1.84) is slowly added from the dropping funnel. As soon as the temperature of the reaction mixture reaches 38°, the flask is surrounded by a vessel of ice water, and the rate of addition of acid is regulated so that the temperature is maintained at 38–43° (Note 3). Near the end of the addition (about 15 minutes), tartaric acid dinitrate sometimes begins to crystallize. After all the sulfuric acid has been added the mixture is allowed to stand in a cool (20–25°) place for 3 hours.

The crystalline mass is broken up with a glass rod and collected on a glass filter cloth (Note 4) in an 18-cm. Büchner funnel. The resulting cake is pressed nearly dry by means of a large flat glass stopper or the bottom of a 125-ml. Erlenmeyer flask. After most of the mother liquor has been removed (Note 5), the solid is transferred in portions to a 4-l. beaker containing about 3 l. of *finely cracked ice* The ice is stirred to effect solution of each portion of the solid as it is added; a wooden stirring rod with a

flat end is advisable. Not more than 10 minutes should be required.

The cold solution is poured *immediately* into a previously assembled apparatus, consisting of a 5-l. three-necked flask, immersed in a 20-in. tub of ice-salt mixture (Note 6), and provided with a stirrer, dropping funnel, and thermometer for reading low temperatures. The solution is neutralized by the addition of 600–700 ml. of concentrated ammonium hydroxide (sp. gr. 0.90) at such a rate that the temperature *never* exceeds −5°(Note 7); the tip of the dropping funnel should be placed directly over the vortex created by the stirrer. After 500 ml. of ammonium hydroxide has been added, the solution is tested with Congo red paper at intervals corresponding to the addition of 50 ml. of ammonium hydroxide; 3–4 hours is required for the neutralization. An additional 100 ml. of ammonium hydroxide is then added.

While the neutralization is in progress, a solution of hexamethylenetetramine (Note 8) is prepared by the cautious addition of 520 ml. of formalin (sp. gr. 1.08; approximately 7 moles) to 500 ml. of ammonium hydroxide (sp. gr. 0.90; approximately 7.5 moles). The temperature must be maintained below 20° by external cooling with ice water. The solution is finally chilled to 0° and added dropwise to the cold ammoniacal solution of tartaric acid dinitrate; the temperature should not exceed 2°. The addition requires 30 minutes. Stirring is then discontinued, and the mixture is allowed to stand overnight. During this period the cooling bath and the reaction mixture come to room temperature.

The solution is now filtered, and 100 ml. of ethanol is added to the filtrate, which is then acidified (hood) to Congo red paper by the slow (30 minutes) addition of about 400 ml. of concentrated hydrochloric acid (sp. gr. 1.19). The acidified mixture is cooled in an icebox for 4–5 hours, and the imidazole-4,5-dicarboxylic acid is collected on an 18-cm. Büchner funnel. The solid is transferred to a 1-l. beaker, stirred with 400–500 ml. of water, and again filtered. It is washed on the funnel successively with three 150-ml. portions of water, two 75-ml. portions of methanol, and finally with 75 ml. of ether. After drying in the air, it weighs 90–100 g. (43–48%) and melts with decomposition at about 280°.

The imidazole-4,5-dicarboxylic acid is divided into two portions. Each portion is intimately mixed with about 0.5 g. of copper-chromium oxide catalyst [*Org. Syntheses* Coll. Vol. **2**, 142 (1943)] or powdered copper oxide (Note 9), and the resulting mixture is transferred to a 250-ml. Claisen flask having a modified side arm; the receiving flask is loosely placed over the side arm. The flask is heated gently with a free flame. After a small fore-run at 95–100°, the temperature rises sharply to 260° (Note 10), and the imidazole distils at 262–264°. The product is purified by dissolving it in 60–70 ml. of benzene, boiling the solution for a few minutes with 2–3 g. of decolorizing carbon (Note 11), filtering the mixture through a preheated Büchner funnel, and cooling the filtrate to 10° for 2 hours. The yield is 13–14.5 g. (68–76%) of a pure white product, m. p. 88–90° (Note 12).

2. Notes

1. The submitters used u.s.p. tartaric acid. The checkers used the Eastman Kodak Company acid, m.p. 169–171°.
2. It is possible to carry out the preparation without mechanical stirring, merely using a single-necked flask and shaking by hand. Temperature control is not so satisfactory under these conditions.
3. At lower temperatures tartaric acid dinitrate separates during the addition of the sulfuric acid. Under these conditions, it forms very fine crystals that are not easily filtered.
4. Vinyon fabric serves equally well. If a filter cloth is not available, a layer of glass wool is prepared on the funnel; the mixed wool and solid are then added to the cracked ice.
5. A fairly dry cake is obtained in about 45 minutes. Since the substance decomposes in the air, it is advisable not to leave it for a longer period.
6. Efficient cooling is extremely important; a small ice bath will not suffice.
7. The decomposition temperature is about 0°. A centrifugal-type stirrer is advisable.
8. No product was obtained when solid hexamethylenetetramine was substituted at this point.
9. Copper oxide gives a slightly lower yield.
10. If an ordinary 250-ml. distilling flask is used, the fraction boiling from 200° to 270° is collected as crude imidazole. The fore-run contains about 1 g. of imidazole, which can be recovered by boiling this fraction of the distillate with benzene, until the water is removed, and then evaporating to crystallization.
11. If a flask and fractionating column are used, the crude product is white; otherwise it is colored.
12. The benzene filtrate from the recrystallization contains about 0.5 g. of imidazole.

3. Discussion

Imidazole has been prepared from glyoxal and ammonia, with[1] or without[2] the addition of formaldehyde; from imidazolthione-2 and nitric acid;[3] and by decarboxylation of imidazole-4,5-dicarboxylic acid.[4,5,6] The procedure described is essentially that of Fargher and Pyman.[6]

References and Notes

1. Wallach, *Ber.*, **15**, 645 (1882).
2. Behrend and Schmitz, *Ann.*, **277**, 338 (1893).
3. Marckwald, *Ber.*, **25**, 2361 (1892).
4. Maquenne, *Ann. chim.*, (6) **24**, 525 (1891).
5. Dedichen, *Ber.*, **39**, 1835 (1906).
6. Fargher and Pyman, *J. Chem. Soc.*, **115**, 227 (1919).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

Benzene (71-43-2)

methanol (67-56-1)

ether (60-29-7)

glyoxal (107-22-2)

formaldehyde, formalin (630-08-0)

nitric acid (7697-37-2)

decolorizing carbon (7782-42-5)

tartaric acid (87-69-4)

ammonium hydroxide (1336-21-6)

copper oxide (1317-38-0)

hexamethylenetetramine (100-97-0)

Copper-Chromium Oxide

Imidazole (288-32-4)

tartaric acid dinitrate

Imidazole-4,5-dicarboxylic acid (570-22-9)

imidazolthione-2

D-tartaric acid (147-71-7)

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Organic Syntheses, CV 3, 475

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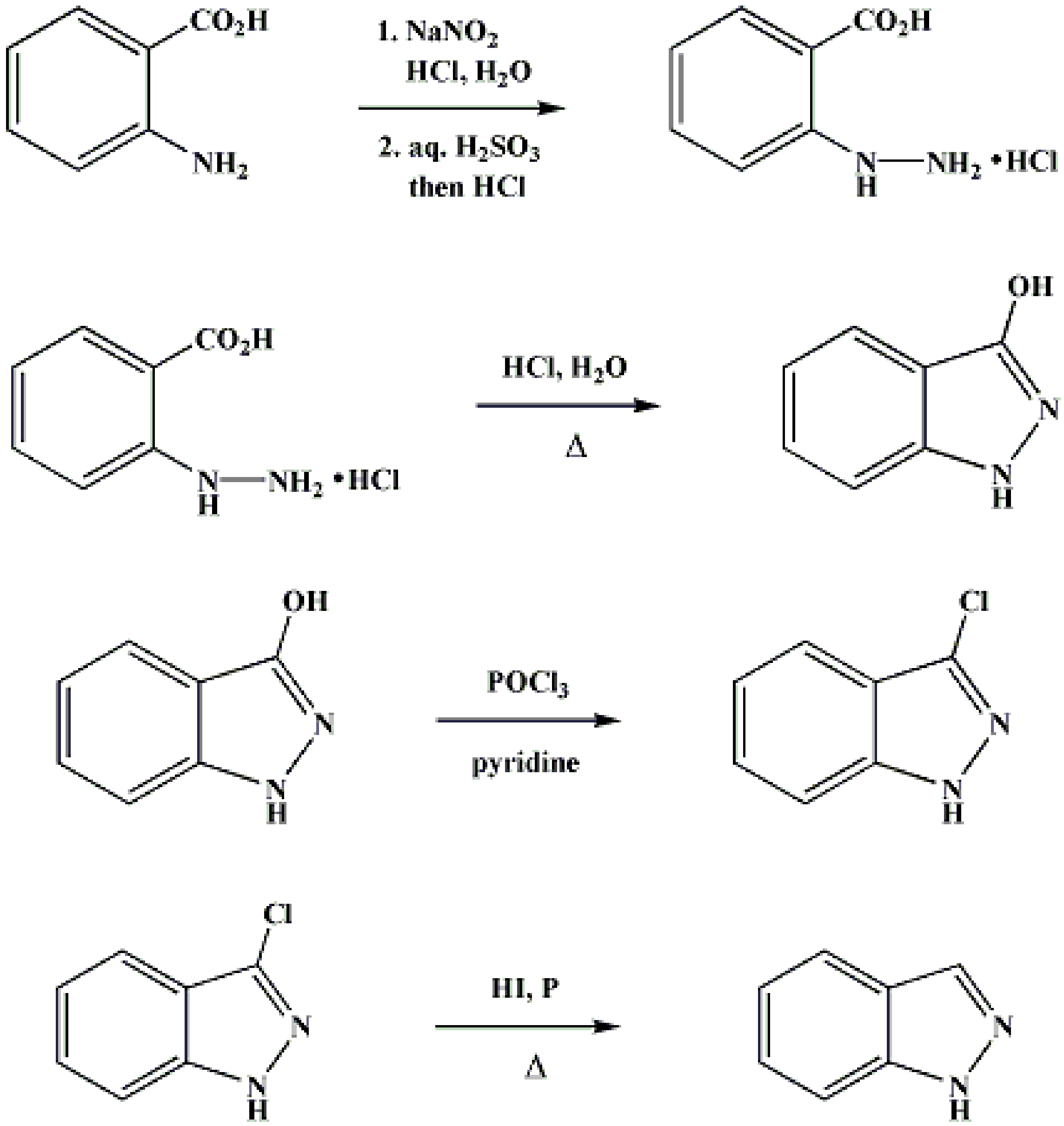

Submitted by Emily F. M. Stephenson
Checked by C. F. H. Allen, C. V. Wilson, and Jean V. Crawford.

1. Procedure

A. *o-Hydrazinobenzoic acid hydrochloride*. In a 2-l. beaker, provided with a stirrer and a low-temperature thermometer, and cooled in an ice-salt bath, are placed 42 g. (0.31 mole) of anthranilic acid and 300 ml. of water. The stirrer is started, and 340 ml. of concentrated hydrochloric acid (sp. gr. 1.18) is added in one portion; the anthranilic acid dissolves, and its hydrochloride begins to separate almost immediately. After the mixture has been cooled to 0°, a solution of 21.6 g. (0.31 mole) of technical sodium nitrite in 210 ml. of water is added from a dropping funnel, the tip of which extends

below the surface of the suspension, at such a rate that the temperature never rises above 3°. The addition requires about 30 minutes; stirring is continued for 15 minutes longer, and at the end of this period a positive test with starch-iodide paper should be obtained (Note 1). The clear brown solution is then diluted with 150 ml. of ice water.

In a 12-l. flask, equipped with a low-temperature thermometer and surrounded by an ice-salt bath, a solution of sulfurous acid is prepared by saturating 2.4 l. of water at 0–5° with sulfur dioxide from a cylinder. A brisk stream of the gas is continued (Note 2) while the cold diazonium salt solution is added in about 150-ml. portions over a 30-minute period and the temperature is maintained at 5–10°; the reaction mixture assumes a dark orange color (Note 3). The cooling bath is removed, but sulfur dioxide is passed into the mixture for an additional 30 minutes. After the mixture has been allowed to stand for 12 hours at room temperature, 3 l. of concentrated hydrochloric acid (sp. gr. 1.18) is added; the *o*-hydrazinobenzoic acid hydrochloride separates at once. The mixture is chilled to 0–5° and filtered through a precooled Büchner funnel; the product is washed with two 50-ml. portions of ice-cold dilute (1:1) hydrochloric acid. The yield is 50–51 g. (86–88%); the salt melts at 194–195° with decomposition (Note 4) and is suitable for the next step without further purification (Note 5).

B. *Indazolone*. In a 2-l. round-bottomed flask to which a reflux condenser is attached are placed 47.1 g. (0.25 mole) of *o*-hydrazinobenzoic acid hydrochloride, 1.25 l. of water, and 12.5 ml. of concentrated hydrochloric acid (sp. gr. 1.18). The mixture is refluxed for 30 minutes. The resulting pale yellow solution is transferred in two portions to a 23-cm. evaporating dish and concentrated on the steam bath to about one-fourth its original volume. The indazolone separates at an early stage of the evaporation but redissolves as the concentration of acid increases. Sodium carbonate is added to the warm solution in small portions until the acid is neutralized (Note 6), and the suspension is allowed to stand for 2 hours. The nearly colorless indazolone is removed by filtration, washed with two 25-ml. portions of cold water, and air-dried. The yield of product, m.p. 246–249°, is 30–33 g. (90–98%) (Note 7).

C. *3-Chloroindazole*. In a 200-ml. flask connected by a glass joint to an air condenser protected by a drying tube are placed 26.8 g. (0.2 mole) of dry indazolone and 15.8 g. (16 ml., 0.2 mole) of dry pyridine (Note 8); 46.1 g. (27.6 ml., 0.3 mole) of phosphorus oxychloride is then added, with shaking, over a 10-minute period. Heat is evolved, and acid fumes are generated. The mixture is heated with occasional shaking in an oil bath, which is maintained at 128–130° for 1 hour and at 130–140° for 4 hours. The clear brown solution is then cooled to 70° and poured, with hand stirring, upon 500 g. of cracked ice. This mixture is allowed to stand for 24 hours. The pale buff solid is removed, washed on the filter, first with 100 ml. of 0.5 *N* hydrochloric acid and then with 40 ml. of cold water, and air-dried (Note 9). The 3-chloroindazole is crystallized from 3 l. of 20% ethanol. The yield is 21–22.5 g. (68–74%) of material melting at 148–148.5° (Note 10).

D. *Indazole*. In a 300-ml. flask are placed 15.3 g. (0.1 mole) of 3-chloroindazole, 18.6

g. (0.15 mole) of red phosphorus, and 100 ml. of constant-boiling hydriodic acid (sp. gr. 1.7) (Note 11). The mixture is refluxed for 24 hours (Note 12), cooled, and filtered through a sintered-glass funnel (Note 13) to remove the phosphorus; the flask and the solid are washed with two 20-ml. portions of water. The clear filtrate is transferred to a 300-ml. Claisen flask and concentrated to about 40 ml. by heating in a water bath at a reduced pressure. The residue is washed into a 250-ml. beaker with 70–80 ml. of hot water, and the clear solution is cooled in an ice bath and made strongly alkaline with concentrated ammonium hydroxide (about 80 ml. is required). The next day, the indazole is collected and dried; the white solid melts at 143–145° (Note 14).

The product is added to 75 ml. of benzene, and the suspension is boiled until the frothing has ceased, the benzene lost being replaced (Note 15); the resulting suspension is filtered to remove the insoluble material. The clear filtrate is heated to boiling, diluted with 25 ml. of petroleum ether (b.p. 70–90°), and allowed to cool slowly. The yield of white product, m.p. 145–146.5°, is 9.7–10.2 g. (82–86%). The over-all yield from anthranilic acid is 43–55%.

2. Notes

1. If the starch-iodide test is negative at this point a little solid sodium nitrite may be added.
2. This operation should be carried out in a hood or out-of-doors.
3. Small amounts of a red crystalline solid were obtained at this point by the checkers in several runs. This substance can be converted to *o*-hydrazinobenzoic acid by the addition of 5 ml. of concentrated hydrochloric acid to a suspension of 1 g. of the solid in 25 ml. of dilute (1:1) hydrochloric acid. The red solid changes to the white *o*-hydrazinobenzoic acid hydrochloride without apparent solution.
4. The melting point varies with the rate of heating. The values given were obtained with a bath preheated to 180°.
5. The free acid may be obtained by treatment of a solution of the hydrochloride with a concentrated aqueous solution of sodium acetate. The powdered hydrochloride (18.9 g., 0.1 mole) is dissolved in 567 ml. of water, and sodium acetate solution (8.2 g. [0.1 mole] of anhydrous sodium acetate in 30 ml. of water) is added. *o*-Hydrazinobenzoic acid separates at once; the mixture is chilled, and the light-tan acid is removed by filtration, washed with two 25-ml. portions of water, and air-dried. The yield is 13.1 g. (86%); m.p. 248–250°. If a purer acid is required, the crude material may be recrystallized from ethanol (50 ml. per g.); the pale tan product then melts at 250–251.5°.
6. About 20 g. of sodium carbonate is required.
7. The indazolone may be purified further by recrystallization from methanol (24 ml. per g.), with filtration of the hot solution through a layer of Norit. It separates as white needles, m.p. 250–252°; the recovery is about 50%. An additional 10% of material (m.p. 246–248°) may be obtained by dilution of the filtrate with 2 volumes of water.
The submitter reports that the described method of purification gives a better

product than is obtained by solution in dilute sodium hydroxide and reprecipitation with acid.
8. The submitter reports that dimethylaniline can be used but that it is less desirable because a small amount of a green by-product is formed.
9. The crude chloroindazole, m.p. 143–145°, is difficult to dry. Small quantities may be crystallized satisfactorily from water (250 ml. per g.). The submitter reports that a good product can be obtained by steam distillation but that even with superheated steam the distillation is very slow.
10. In a run 2.5 times this size, the checkers dissolved the crude product in 190 ml. of ethanol and diluted the hot filtrate with 260 ml. of water; the chloroindazole was obtained in 80% yield.
11. It is essential to use acid of this concentration.
12. This reaction time ensures complete conversion of the chloroindazole.
13. As an alternative procedure, the mixture may be diluted with 70 ml. of water and filtered through S & S No. 596 filter paper.
14. The crude indazole is so difficult to dry that the weight at this stage is not significant.
15. This operation is carried out in an open flask in the hood and at a point remote from flames; the indazole is dried by the steam distillation of the water with the benzene.

3. Discussion

The preparations of *o*-hydrazinobenzoic acid hydrochloride and indazolone are essentially those given by Pfannstiel and Janecke.[1] The procedure for the conversion of indazolone to indazole is a modification of that of Fischer and Seuffert.[2] A procedure involving the decarboxylation of indazole-3-carboxylic acid is described by Schad.[3]

Indazole has been obtained in a variety of ways which are of no preparative value. The elimination of the amino group from aminoindazoles, first utilized by Witt,[4] by the action of ethanol or sodium stannite on the diazonium compounds appears to be the only other useful procedure.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 536
- Org. Syn. Coll. Vol. 5, 650

References and Notes

1. Pfannstiel and Janecke, *Ber.*, **75**, 1104 (1942).
2. Fischer and Seuffert, *Ber.*, **34**, 796 (1901).
3. Schad, *Ber.*, **26**, 217 (1893).

4. Witt, Nölting, and Grandmougin, *Ber.*, **23**, 3642 (1890).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

red phosphorus

petroleum ether

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

methanol (67-56-1)

sodium acetate (127-09-3)

sodium hydroxide (1310-73-2)

sodium carbonate (497-19-8)

sulfur dioxide (7446-09-5)

PHOSPHORUS (7723-14-0)

sodium nitrite (7632-00-0)

Phosphorus Oxychloride (21295-50-1)

pyridine (110-86-1)

hydriodic acid (10034-85-2)

ammonium hydroxide (1336-21-6)

dimethylaniline (121-69-7)

Anthranilic Acid (118-92-3)

sodium stannite

sulfurous acid (7782-99-2)

Indazole (271-44-3)

Indazolone (5686-93-1)

3-Chloroindazole, chloroindazole (29110-74-5)

indazole-3-carboxylic acid (4498-67-3)

o-Hydrazinobenzoic acid hydrochloride (52356-01-1)

o-hydrazinobenzoic acid (5326-27-2)

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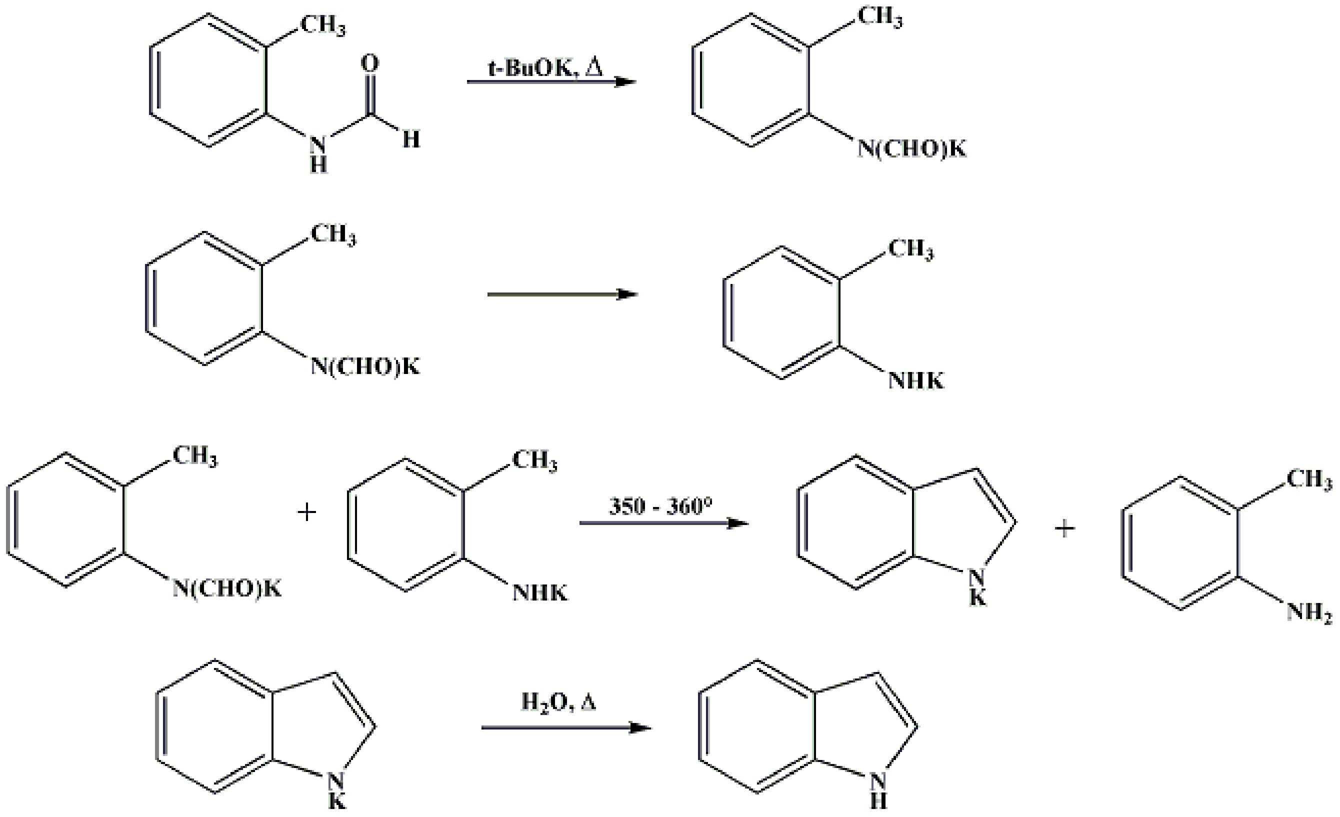

Submitted by F. T. Tyson
Checked by R. L. Shriner and C. H. Tilford.

1. Procedure

A 2-l. three-necked round-bottomed flask is fitted with a reflux condenser and a glass inlet tube connected to a cylinder of nitrogen. The third opening of the flask is closed by a stopper. The top of the condenser is connected to an air trap which consists of two 500-ml. suction flasks joined in series. The first suction flask is empty; the second contains 100 ml. of paraffin oil, and the inlet tube of this flask extends slightly below the surface of the oil.

In the reaction flask is placed 600 ml. of commercial *tert*-butyl alcohol (Note 1), and the air in the flask is displaced by dry nitrogen gas. Then 29 g. (0.75 gram atom) of metallic potassium is added, in portions, to the alcohol. The mixture is heated on a water bath until all the potassium has dissolved, and then 68 g. (0.5 mole) of *o*-formotoluide (Note 2) is added and brought into solution. The condenser is set for distillation with a filter flask as the receiver; this flask is protected from the air by connecting it to the trap used in the initial operation. The reaction flask is surrounded by a metal bath, and the excess alcohol is removed by distillation. The residue is heated to 350–360° for about 20 minutes (Note 3) and then is allowed to cool in a stream of nitrogen. The residue is decomposed by addition of 300 ml. of water, and the mixture is steam-distilled to remove the indole. The distillate is extracted successively with 300 ml. and 100 ml. of ether, and the combined ether extracts are shaken with cold dilute 5% hydrochloric acid to remove small amounts of *o*-toluidine. The ether extract is washed with 100 ml. of water, followed by 100 ml. of 5% sodium carbonate solution, and is dried over 20 g. of sodium sulfate. The ether is removed by distillation, and the residue is distilled under reduced pressure. Indole distils at 142–144°/27 mm. (128°/10 mm.; 121°/5 mm.) as a pale yellow oil which solidifies and then melts at 52–53°. The yield is 23 g. (79%) (Note 4).

2. Notes

1. Alcohols other than *tert*-butyl alcohol, such as methyl, ethyl, butyl, or isobutyl alcohol, may be used, but with a decrease in yield. If methyl or ethyl alcohol is substituted for *tert*-butyl alcohol, the potassium should be added in smaller portions and the more vigorous reaction must be controlled by external cooling. Furthermore, if methyl alcohol is used the amount of potassium should be decreased from 0.75 gram atom to 0.5 gram atom.
2. *o*-Formotoluide can be prepared by heating a mixture of 856 g. (8 moles) of *o*-toluidine and 403 g. (8.4 moles) of

90% formic acid on a steam bath for about 3 hours and allowing the reaction mixture to stand overnight. The mixture is fractionated under reduced pressure; there is obtained 920–963 g. (85–89%) of *o*-formotoluide, b.p. 173–5°/25 mm., m.p. 55–58°. This product is a pale yellow solid which contains traces of toluidine and possesses an odor indicating the presence of traces of an isocyanide. However, the material is sufficiently pure for conversion to indole. By use of 99% formic acid, a quantitative yield may be obtained. If a purer product is desired, the original reaction mixture is mixed with about a liter of water, the crude formotoluide is filtered, then washed with 1% hydrochloric acid and with water. After drying, the crude formotoluide is recrystallized from benzene-petroleum ether. The yield is practically the same as that obtained by direct distillation, and the product melts at 61°. In order to assure freedom from moisture, the recrystallized product may be distilled under reduced pressure; the loss in this distillation is negligible.

3. During this interval combustible gases, chiefly carbon monoxide and hydrogen, are evolved, and a liquid, which is principally *o*-toluidine, distils.

4. The product is pale yellow. The color may be removed by crystallizing the material from a mixture of 100 ml. of petroleum ether and about 10 ml. of ethyl ether. The recovery is 21 g. (91%).

3. Discussion

Indole has been obtained through many syntheses which have little value as methods of preparation. In addition to these syntheses it has been prepared by heating 2-amino-ω-chlorostyrene with sodium methoxide;[1] by pyrolysis of 2,2'-diaminostilbene hydrochloride under reduced pressure;[2] by reduction of indoxyl with zinc dust and alkali;[3] by reduction of 2-aminoindole with sodium and alcohol;[4] by reduction of methyl *o*-nitrostyrylcarbamate,[5] by heating *o*-formylphenylglycine with acetic anhydride and sodium acetate;[6] by passing a mixture of acetylene and aniline through an iron tube at 700°;[7] and by reduction of ω,2-dinitrostyrene with iron and acetic acid.[8] The method described above is related to the Madelung synthesis of 2-alkylindoles[9] and has been published.[10] The methods for preparation of indole have been examined experimentally.[11] The authors recommend the method of Reissert,[12] which involves condensation of *o*-nitrotoluene with ethyl oxalate, followed by reduction to indole-2-carboxylic acid and decarboxylation of the latter. A patent reports the preparation of indole by catalytic dehydrogenation of *o*-ethylaniline at 650° in the presence of titania gel.[13] The cyclization of N-formyl-*o*-toluidine with sodium in methanol has been described and is recommended as a safer and less expensive method than that involving the use of potassium metal.[14]

The reaction of carbon monoxide with *o*-toluidine, as the sodium salt, under pressure, at an elevated temperature, has been patented.[15]

References and Notes

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8. Nenitzescu, *Ber.*, **58**, 1063 (1925).
9. Madelung, *Ber.*, **45**, 1128 (1912); cf. Verley, *Bull. soc. chim. France*, (4) **35**, 1039 (1924).
10. Tyson, *J. Am. Chem. Soc.*, **63**, 2024 (1941).
11. Shorygin and Polyakova, *Khim. Referat. Zhur.*, **1940**, No. 4, 114 [*C. A.*, **36**, 3802 (1942)].
12. Reissert, *Ber.*, **30**, 1045 (1897).
13. U. S. pat. 2,409,676 [*C. A.*, **41**, 998 (1947)].
14. Galat and Friedman, *J. Am. Chem. Soc.*, **70**, 1280 (1948).
15. Tyson, *J. Am. Chem. Soc.*, **72**, 2801 (1950); U. S. pat. 2,537,609 [*C. A.*, **45**, 5190 (1951)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

benzene-petroleum ether

methyl or ethyl alcohol

methyl, ethyl, butyl, or isobutyl alcohol

indoxyl

ω,2-dinitrostyrene

titania gel

acetylene (74-86-2)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

methyl alcohol, methanol (67-56-1)

ether, ethyl ether (60-29-7)

acetic anhydride (108-24-7)

sodium acetate (127-09-3)

aniline (62-53-3)

hydrogen (1333-74-0)

carbon monoxide (630-08-0)

iron (7439-89-6)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

formic acid (64-18-6)

nitrogen (7727-37-9)

isocyanide (57-12-5)

sodium methoxide (124-41-4)

zinc (7440-66-6)

sodium (13966-32-0)

potassium (7440-09-7)

Ethyl oxalate

o-nitrotoluene (88-72-2)

Indole (120-72-9)

toluidine (106-49-0)

formotoluide (3085-54-9)

2-amino-ω-chlorostyrene

2-aminoindole

indole-2-carboxylic acid (1477-50-5)

tert-butyl alcohol (75-65-0)

o-toluidine (95-53-4)

o-formotoluide, N-formyl-o-toluidine (94-69-9)

methyl o-nitrostyrylcarbamate

o-formylphenylglycine

o-ethylaniline (578-54-1)

2,2'-diaminostilbene hydrochloride

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Organic Syntheses, CV 3, 482

IODOBENZENE DICHLORIDE

[Benzene, iodo-, dichloride-]

$$C_6H_5I + Cl_2 \xrightarrow{CHCl_3} C_6H_5ICl_2$$

Submitted by H. J. Lucas and E. R. Kennedy.
Checked by John R. Johnson and M. W. Formo.

1. Procedure

In a 1-l. three-necked flask, protected from the light and equipped with a mechanical stirrer, an inlet tube for the introduction of chlorine (Note 1), and an exit tube carrying a calcium chloride drying tube, are placed 150 ml. of dry chloroform (Note 2) and 102 g. (0.5 mole) of iodobenzene. The flask is cooled in an ice-salt mixture, and dry chlorine (Note 3) is introduced, as rapidly as the solution will absorb it, until an excess is present (usually about 3 hours is required). The yellow, crystalline iodobenzene dichloride is filtered with suction, washed sparingly with chloroform, and dried in the air on filter paper. The yield is 120–134 g. (87–94%) (Note 4) and (Note 5). The product is quite pure and may be used directly for the preparation of iodosobenzene and iodoxybenzene. Since iodobenzene dichloride decomposes slowly on standing, it should not be stored indefinitely.

2. Notes

1. The delivery tube should be at least 10 mm. in diameter and should terminate about 5 mm. above the surface of the liquid.
2. Chloroform was dried and rendered free of ethanol by allowing it to stand over anhydrous calcium chloride for 24 hours. It was then decanted through a filter and distilled through dry apparatus. The initial low-boiling fraction was rejected.
3. Chlorine was dried by passing it through at least two wash bottles containing sulfuric acid. Spray was removed by passing the gas through a plug of glass wool. The yields are reduced appreciably if the reactants are not dry.
4. In some runs an additional quantity of the product may be obtained by evaporating the chloroform filtrate to a small volume under reduced pressure. The solvent must not be evaporated completely if a pure product is desired.
5. The submitters report that the three isomeric iodotoluene dichlorides may be prepared in good yields by a similar procedure, but in these cases the chloroform solution must be concentrated by evaporation under reduced pressure (Note 4), since the tolyl homologs are more soluble in chloroform.

3. Discussion

The best preparative method for iodobenzene dichloride is the direct combination of iodobenzene and chlorine in chloroform.[1]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 483
- Org. Syn. Coll. Vol. 3, 485

References and Notes

1. Willgerodt, *J. prakt. Chem.*, (2) **33**, 155 (1886).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Benzene, iodo-, dichloride-

ethanol (64-17-5)

calcium chloride (10043-52-4)

chloroform (67-66-3)

chlorine (7782-50-5)

Iodobenzene (591-50-4)

iodobenzene dichloride (2401-21-0)

Iodosobenzene (536-80-1)

Iodoxybenzene (696-33-3)

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Organic Syntheses, CV 3, 483

IODOSOBENZENE

[Benzene, iodoso-]

$$C_6H_5ICl_2 \xrightarrow[Na_2CO_3]{NaOH,\ H_2O} C_6H_5IO$$

Submitted by H. J. Lucas, E. R. Kennedy, and M. W. Formo.
Checked by Lee Irvin Smith, R. T. Arnold, and R. A. Matthews.

1. Procedure

In a large mortar chilled in an ice bath are placed 55 g. (0.2 mole) of iodobenzene dichloride (p. 482), 50 g. of anhydrous sodium carbonate, and 100 g. of finely crushed ice. The mixture is ground thoroughly (Note 1) until all the ice has melted and a thick paste results. To this suspension 140 ml. of 5 *N* sodium hydroxide is added, in 20-ml. portions, with repeated trituration after each addition. Finally, 100 ml. of water is added to render the mixture more fluid and the material is allowed to stand overnight. The product is collected with suction, pressed thoroughly on the filter, transferred to a beaker, and washed thoroughly with 300 ml. of water (Note 2). The material is filtered with suction, washed again in a beaker with 300 ml. of water, collected with suction, and washed with about 250 ml. of water on the filter. After thorough drying in the air, the product is stirred to a thin mush with a little chloroform (Note 3), freed of solvent by suction, and spread on filter paper to dry in the air. The yield is 26–27 g. (60–62%) of a product having a purity of about 99%, as determined by titration (Note 4) and (Note 5).

2. Notes

1. The solid forms a caked mass, which is disintegrated by trituration.
2. The filtrate contains some diphenyliodonium salts, which may be recovered in the form of the sparingly soluble iodide by the addition of potassium iodide (p. 355). Usually 7–9 g. of diphenyliodonium iodide is obtained.
3. The chloroform removes iodobenzene, which may be recovered.
4. The following procedure is used in the analysis of iodoso and iodoxy compounds. In a 200-ml. iodine flask are placed 100 ml. of water, 10 ml. of 6 *N* sulfuric acid, 2 g. of iodate-free potassium iodide, 10 ml. of chloroform, and finally the sample, about 0.25 g. The flask is shaken for 15 minutes (or longer, if the reaction is not complete), and then the mixture is titrated with 0.1 *N* sodium thiosulfate. If the sample is pure the change of color in the chloroform layer may be taken as the end point, but if impurities are present starch must be used, for the impurities impart a brownish color to the chloroform. This solvent is desirable, as it facilitates the reaction with potassium iodide by dissolving the

reaction products. Iodosobenzene may be differentiated from iodoxybenzene, for the former reduces iodide ion in a saturated sodium borate solution, whereas the latter does not.[1] The reactions involved are: $C_6H_5IO + 2HI \square C_6H_5I + H_2O + I_2$ $C_6H_5IO_2 + 4HI \square C_6H_5I + 2H_2O + 2I_2$

5. For use in the preparation of iodoxybenzene by the disproportionation method (p. 485) it is superfluous to dry the crude product and to wash it with chloroform to remove iodobenzene. The crude wet iodosobenzene may also be used directly for the preparation of diphenyliodonium iodide (p. 355), but it is desirable to assay the wet product by titration to determine the quantity of iodoxybenzene needed.

3. Discussion

Iodosobenzene has been prepared by the action of aqueous sodium or potassium hydroxide upon iodobenzene dichloride;[2] and by repeated additions of water to iodobenzene dichloride.[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 355
- Org. Syn. Coll. Vol. 3, 485
- Org. Syn. Coll. Vol. 5, 658
- Org. Syn. Coll. Vol. 5, 660

References and Notes

1. Masson, Race, and Pounder, *J. Chem. Soc.*, **1935**, 1678.
2. Willgerodt, *Ber.*, **25**, 3495 (1892); **26**, 357, 1807 (1893); Askenasy and Meyer, *Ber.*, **26**, 1356 (1893); Hartmann and Meyer, *Ber.*, **27**, 505 (1894).
3. Willgerodt, *Ber.*, **26**, 357 (1893); Ortoleva, *Chem. Zentr.*, **1900**, I, 722.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium or potassium hydroxide

sulfuric acid (7664-93-9)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium carbonate (497-19-8)

potassium iodide (7681-11-0)

sodium thiosulfate (7772-98-7)

Iodobenzene (591-50-4)

iodobenzene dichloride (2401-21-0)

DIPHENYLIODONIUM IODIDE (2217-79-0)

Iodosobenzene, Benzene, iodoso- (536-80-1)

Iodoxybenzene (696-33-3)

sodium borate

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Organic Syntheses, CV 3, 485

IODOXYBENZENE

[Benzene, iodoxy-]

[A. DISPROPORTIONATION OF IODOSOBENZENE]

Submitted by H. J. Lucas and E. R. Kennedy.
Checked by John R. Johnson and M. W. Formo.

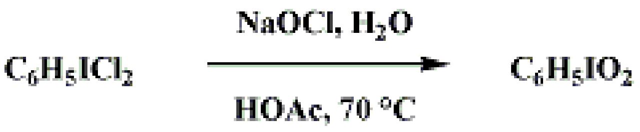
1. Procedure

In a 5-l. flask (Note 1), 110 g. (0.5 mole) of iodosobenzene (p. 483) is made into a thin paste with water, and the mixture is rapidly steam-distilled (Note 2) until almost all the iodobenzene (Note 3) is removed. The distillation should not be continued any longer than necessary, and the contents of the flask should be cooled at once. The white solid is filtered with suction and dried in the air at room temperature. It is then washed with chloroform, again dried, and the resulting cake is ground lightly in a mortar to facilitate removal of moisture in a final drying. The yield is 54–56 g. (92–95%). The product has a purity of about 99%, as determined by iodimetry (Note 4). The solid may be crystallized from hot water (Note 5).

2. Notes

1. Because of a tendency to froth, a large flask should be used.
2. Direct heating must be avoided, as the solid reactant and product may decompose with explosive violence on heating, especially when dry.
3. The recovered iodobenzene is quite pure and may be used for the preparation of iodobenzene dichloride. The recovery is about 46 g. (90%).
4. The iodimetric method described under iodosobenzene (p. 484) is applicable here. The main impurity in the iodoxybenzene is iodosobenzene.
5. The solubility of iodoxybenzene, per liter of water, is 2.8 g. at 12°, and about 12 g. at 100°.

[B. HYPOCHLORITE OXIDATION OF IODOBENZENE DICHLORIDE]



Submitted by M. W. Formo and John R. Johnson.
Checked by Lee Irvin Smith, R. T. Arnold, and Louis E. Demytt.

1. Procedure

In a 2-l. round-bottomed flask equipped with an efficient mechanical stirrer (Note 1) are placed 110 g. (0.4 mole) of freshly prepared, pulverized iodobenzene dichloride (p. 482) (Note 2), 1.0 mole of sodium hypochlorite solution (Note 3), and 2 ml. of glacial acetic acid. The vigorously stirred mixture is heated on a water bath maintained at 65–75°. After 10–15 minutes the heated mixture becomes frothy and the yellow color of iodobenzene dichloride is displaced by the white color of iodoxybenzene. The stirring is stopped after 1 hour, and the flask is cooled in an ice bath. The product is filtered with suction, pressed with a glass stopper, and transferred to an 800-ml. beaker. The material is stirred thoroughly with 300 ml. of water, filtered with suction, washed on the filter with 100 ml. of water, pressed, and dried in the air. The crude product weighs 85–89 g. (90–94%) and has a purity, as determined iodimetrically, of 97–99% (Note 4). The air-dried material may be washed with 50–60 ml. of chloroform, air-dried, and finally dried in a vacuum desiccator. This product weighs 82–87g. (87–92%) and has a purity of 99.0–99.9% as determined by iodimetry (Note 5).

2. Notes

1. A Hershberg stirrer is well suited for stirring the pasty suspension.
2. Any lumps of iodobenzene dichloride should be broken up by pressing with a spatula; otherwise the reaction may be incomplete.
3. Stabilized hypochlorite solutions, commercially available, are satisfactory. The submitters used 1.15 l. of "Clorox" solution, containing 5.25% sodium hypochlorite by weight.
4. The iodimetric method as described under iodosobenzene (p. 484) is applicable here. The crude product is satisfactory for the preparation of diphenyliodonium iodide (p. 355).
5. The checkers obtained the yields claimed, but the purity of the product was 90% before, and 95.7% after, washing with chloroform.

3. Discussion

Iodoxybenzene has been prepared by oxidizing iodobenzene with Caro's acid;[1,2] by treating iodobenzene with hypochlorous acid or with aqueous sodium hydroxide and bromine;[3] by action of chlorine upon iodobenzene dissolved in pyridine;[4] by oxidation of iodosobenzene with hypochlorous acid or bleaching powder;[5] by heating iodosobenzene;[6] by steam distillation of iodosobenzene;[7] by heating iodobenzene dichloride with aqueous sodium hypochlorite containing some acetic acid;[8] and by oxidation of iodobenzene with concentrated chloric acid solution.[9]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 355
- Org. Syn. Coll. Vol. 3, 483
- Org. Syn. Coll. Vol. 5, 665

References and Notes

1. Bamberger and Hill, *Ber.*, **33**, 534 (1900).
2. Masson, Race, and Pounder, *J. Chem. Soc.*, **1935**, 1678.
3. Willgerodt, *Ber.*, **29**, 1571, 1572 (1896).
4. Ortoleva, *Chem. Zentr.*, **1900**, I, 723.
5. Willgerodt, *Ber.*, **29**, 1568, 1569 (1896).
6. Willgerodt, *Ber.*, **25**, 3500 (1892); **26**, 1806 (1893); Askenasy and Meyer, *Ber.*, **26**, 1356 (1893).
7. Willgerodt, *Ber.*, **26**, 358, 1307 (1893).
8. Willgerodt and Wiegand, *Ber.*, **42**, 3765 (1909).
9. Datta and Choudhury, *J. Am. Chem. Soc.*, **38**, 1085 (1916).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

acetic acid (64-19-7)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

bromine (7726-95-6)

pyridine (110-86-1)

chlorine (7782-50-5)

hypochlorous acid (7790-92-3)

sodium hypochlorite (7681-52-9)

Iodobenzene (591-50-4)

iodobenzene dichloride (2401-21-0)

DIPHENYLIODONIUM IODIDE (2217-79-0)

Iodosobenzene (536-80-1)

Iodoxybenzene, Benzene, iodoxy- (696-33-3)

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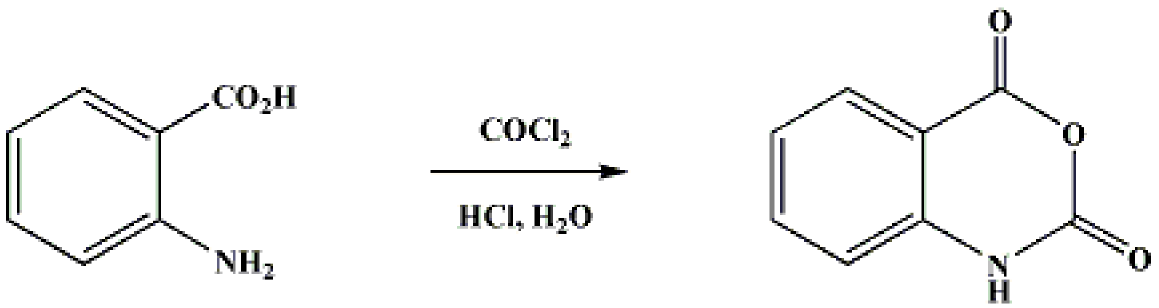
Organic Syntheses, CV 3, 488

ISATOIC ANHYDRIDE



Submitted by E. C. Wagner and Marion F. Fegley.
Checked by R. L. Shriner and R. M. Hedrick.

1. Procedure

Phosgene is toxic. The apparatus should be set up in a good hood.

One hundred and thirty-seven grams (1 mole) of anthranilic acid is dissolved, with the aid of gentle warming, in a mixture of 1 l. of water and 126 ml. of concentrated hydrochloric acid (sp. gr. 1.19). The solution is filtered into a 2-l. three-necked flask fitted with a gas-tight, mechanically driven Hershberg stirrer. Through one of the side necks extends an inlet tube which ends in a coarse sintered-glass gas-dispersing tip extending well into the liquid into the liquid in the flask. The inlet tube is connected with a cylinder of phosgene through an empty safety flask. In the third neck of the flask is mounted an addition tube, through the vertical arm of which a thermometer (Note 1) is mounted so that the bulb is immersed in the reaction liquid. The outlet is attached to the lateral arm of the addition tube and is connected to an empty safety flask which in turn is connected to a Drechsel bottle charged with ammonium hydroxide.

With the stirrer in rapid motion (Note 2) phosgene is passed into the solution of anthranilic acid at such a rate that bubbles of gas escape slowly into the ammonia scrubber (about two bubbles per second). Isatoic anhydride appears as a precipitate soon after the stream of phosgene is started. The temperature rises but is prevented from exceeding 50° (Note 3) by regulation of the rate at which phosgene is introduced. The stream of phosgene is continued for 2–4 hours, or until the rate of absorption is clearly much decreased (Note 4). The flask is disconnected, and residual phosgene is blown out by passing a current of air through the mixture. The product is collected on a Büchner funnel and is washed with three 500-ml. portions of cold water. The first crop amounts to 54–56 g.

The mother liquor is returned to the reaction flask, the apparatus reassembled, and the passage of phosgene resumed (Note 5). When the rate of absorption has noticeably

decreased (1–1.5 hours) the precipitated isatoic anhydride is collected on a filter and washed. The second crop amounts to 34–54 g. A third passage of phosgene at a considerably reduced rate will often yield a small additional crop (10–24 g.) of isatoic anhydride (Note 6).

The product is dried in air and then at 100°. The total yield is 118–123 g. (72–75%) of a white or nearly white product which decomposes at 237–240° cor.; this material is pure enough for most purposes. It may be recrystallized from 95% ethanol (about 30 ml. per gram) or from dioxane (about 10 ml. per gram). The former solvent permits the higher recovery (89–90%) and, except for the large volume required, is to be preferred. The mother liquor may be used for recrystallization of several successive lots of isatoic anhydride. The purified compound decomposes at 243° cor. (Note 7).

2. Notes

1. A thermometer with the graduation marks on the upper half of the stem is convenient.
2. The rate of absorption of phosgene is dependent upon the speed and efficiency of the stirring. This also determines the amount of product obtained in each treatment with phosgene.
3. Operation below room temperature is without advantage. At 60° or above the yield of isatoic anhydride is decreased, or the process may yield precipitated material from which little or no isatoic anhydride can be obtained. Cooling of the mixture might become advisable during operation on a scale larger than specified.
4. It is advisable to precipitate the isatoic anhydride in several successive crops as directed, rather than to attempt to complete the reaction in one step, because the accumulation of precipitated isatoic anhydride slows the rate of absorption of phosgene to such an extent that prolonged passage of the gas at a decreasing and eventually very low rate would be necessary.
5. It is important to clean the glass gas-dispersing tip with hot dioxane before reassembling the apparatus.
6. A small (usually trifling) final crop of isatoic anhydride can be obtained by addition of 40 g. (1 mole) of sodium hydroxide to the liquid and by introducing phosgene slowly.
7. The method is capable of extension to other *o*-aminocarboxylic acids,[1] e.g., to 3-amino-2-naphthoic acid, 4,4'-diaminobiphenyl-3,3'-dicarboxylic acid, and 2-amino-*p*-toluic acid. With some acids other than anthranilic, difficulty may be encountered owing to the readiness with which their hydrochlorides are salted out of solution by hydrochloric acid.

3. Discussion

Isatoic anhydride has been prepared by prolonged refluxing of a mixture of anthranilic acid and ethyl chlorocarbonate,[2] a reaction usually accompanied by formation of

considerable monoethyl or/and diethyl isatoate; or by action of phosgene upon anthranilic acid in a solution the acidity of which is moderated by occasional addition of sodium carbonate.[2] The method described is based upon a patented procedure[1] in which, under conditions not fully specified, phosgene is passed into a solution of anthranilic acid hydrochloride with no subsequent adjustment of the acidity.

References and Notes

1. Ger. pat. 500,916 [*Frdl.*, **17**, 500 (1930)]; Clark and Wagner, *J. Org. Chem.*, **9**, 60 (1944).
2. Erdmann, *Ber.*, **32**, 2159 (1899).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

sodium hydroxide (1310-73-2)

sodium carbonate (497-19-8)

phosgene (75-44-5)

ammonium hydroxide (1336-21-6)

Anthranilic Acid (118-92-3)

ethyl chlorocarbonate (541-41-3)

dioxane (5703-46-8)

3-Amino-2-naphthoic acid (5959-52-4)

Isatoic anhydride (118-48-9)

diethyl isatoate

anthranilic acid hydrochloride

2-amino-p-toluic acid

4,4'-diaminobiphenyl-3,3'-dicarboxylic acid

monoethyl isatoate

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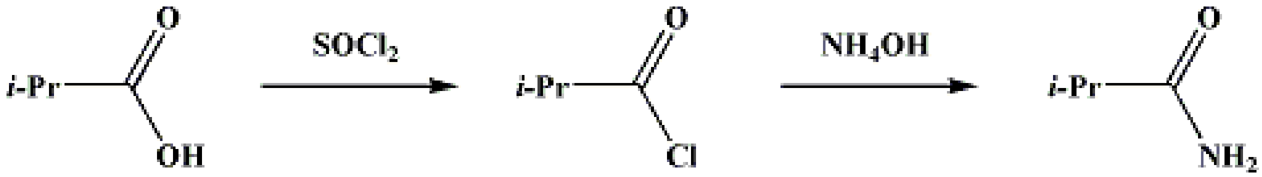
Organic Syntheses, CV 3, 490

ISOBUTYRAMIDE



Submitted by R. E. Kent and S. M. McElvain.
Checked by C. R. Noller and D. Frazier.

1. Procedure

A. *Isobutyryl chloride*. A 1-l. three-necked flask is equipped with a 250-ml. dropping funnel, an efficient stirrer sealed with a glycerol-lubricated rubber tube, and an efficient condenser (Note 1). The water supplied to the condenser is cooled to 0°, and the flask is cooled in a large water bath. The apparatus is set up in a hood, and a gas-absorption trap is attached to the top of the condenser.

In the flask is placed 542 g. (4.55 moles) of thonyl chloride; to this is added dropwise, and with rapid stirring, 352 g. (4 moles) of isobutyric acid (Note 2). A vigorous evolution of hydrogen chloride and sulfur dioxide takes place. When all the acid has been added, the water bath is heated to 80° and is kept at this temperature for 30 minutes. Stirring is continued throughout the heating. The reaction mixture is then distilled through a 30-cm. Vigreux column by means of an oil bath heated on a hot plate (Note 3). The fore-run boiling up to 89° weighs 44 g. The isobutyryl chloride which is collected at 89–93° weighs 351 g. The residue weighs 49 g. On combining the fore-run and residue and redistilling slowly, an additional 33 g. of isobutyryl chloride is obtained; the total yield is 384 g. (90%). Redistillation gives a faintly yellow product boiling at 90–92° (Note 4) and (Note 5).

B. *Isobutyramide*. In a 3-l. flask, equipped with an efficient stirrer and a 500-ml. dropping funnel, and surrounded by an ice-salt freezing mixture, is placed 1.25 l. of cold concentrated aqueous ammonia (about 28%). To this 318 g. (3 moles) of isobutyryl chloride is added dropwise with rapid stirring at such a rate that the temperature of the reaction mixture does not rise above 15°, and the evolution of white fumes (mostly ammonium chloride) does not become vigorous. Stirring is continued for 1 hour after the addition of the acid chloride is finished.

The flask is heated by steam in a large can, and the reaction mixture is evaporated to dryness under reduced pressure (Note 6). The dry residue of ammonium chloride and isobutyramide is boiled 10 minutes with 2 l. of dry ethyl acetate, and the boiling solution is filtered quickly through a fluted filter paper on a large hot funnel. The residue on the filter is extracted in the same way with two 1-l. portions of ethyl acetate. The combined ethyl acetate extracts are cooled to 0°, and the crystalline amide which separates is removed by filtration. The filtrate is concentrated to about 300 ml. and

chilled, and a second crop of amide is collected (Note 7) and (Note 8). The two crops of isobutyramide are combined and dried, first in an oven at 70° for 3 hours and then in a vacuum desiccator. The yield of glistening white needles melting at 127–129° is 203–215 g. (78–83%) (Note 9). This material is suitable for the preparation of isobutyronitrile.

2. Notes

1. A Friedrichs condenser is recommended. This efficient condenser has an inner cooling coil around which the vapors pass and condense. The submitters used rubber stoppers throughout.
2. Eastman's technical grade of isobutyric acid was distilled, and the fraction boiling at 151–153° was used.
3. The submitters used an electrically heated oil bath.
4. When 5 moles of thionyl chloride and 4 moles of isobutyric acid were used, the yield on the first distillation was 83%, and redistillation of the fore-run gave an additional 7%. There was practically no high-boiling material.
5. The submitters obtained the same percentage yields in runs four times as large.
6. The steam can should be large enough to contain the entire reaction flask; otherwise the evaporation is very slow.
7. If the mixture of amide and ammonium chloride is not thoroughly dry, the ethyl acetate removed at this point will contain water and must be dried and redistilled before further use.
8. The filtrate from the second crop of amide may be evaporated to dryness and the residue crystallized from a mixture of ethyl acetate and ligroin (60–68°). It is profitable to work up this third crop of amide only when the mother liquors from several runs are combined.
9. The submitters obtained the same percentage yield in runs twice as large.

3. Discussion

Isobutyramide has been prepared by the action of concentrated aqueous ammonia on isobutyryl chloride [1] or methyl isobutyrate; [2] by the action of liquid ammonia on ethyl isobutyrate; [3] by the Willgerodt reaction with aqueous ammonium polysulfide; [4] by distillation of ammonium isobutyrate [5] or a mixture of isobutyric acid and potassium thiocyanate; [6] by hydrolysis of isobutyronitrile; [7] and from the ozonolysis of 2,3-dimethyl-6-isopropylpyridine. [8]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 436

References and Notes

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2. Meyer, *Monatsh.*, **27**, 43 (1906).
3. Hauser, Levine, and Kibler, *J. Am. Chem. Soc.*, **68**, 26 (1946).
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6. Letts, *Ber.*, **5**, 671 (1872).
7. Hoffmann and Barbier, *Bull. soc. chim. Belg.*, **45**, 565 (1936) [*C. A.*, **31**, 919 (1937)].
8. Lochte, Barton, Roberts, and Bailey, *J. Am. Chem. Soc.*, **72**, 3007 (1950).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ligroin

thonyl chloride

ammonium polysulfide

hydrogen chloride (7647-01-0)

ammonia (7664-41-7)

ethyl acetate (141-78-6)

ammonium chloride (12125-02-9)

thionyl chloride (7719-09-7)

sulfur dioxide (7446-09-5)

potassium thiocyanate (333-20-0)

ethyl isobutyrate (97-62-1)

isobutyryl chloride (79-30-1)

Isobutyramide (563-83-7)

isobutyric acid (79-31-2)

Isobutyronitrile (78-82-0)

methyl isobutyrate (547-63-7)

ammonium isobutyrate (22228-82-6)

2,3-dimethyl-6-isopropylpyridine

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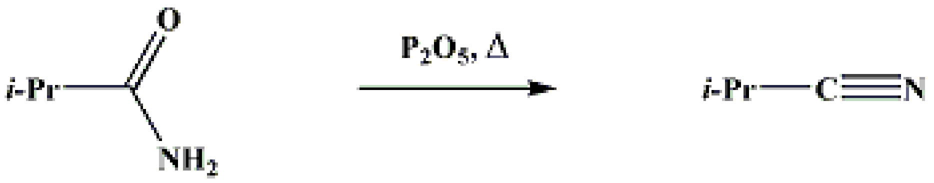
Organic Syntheses, CV 3, 493

ISOBUTYRONITRILE



Submitted by R. E. Kent and S. M. McElvain.
Checked by C. R. Noller and D. Frazier.

1. Procedure

To 308 g. (2.1 moles) of phosphorus pentoxide (reagent grade) in a 3-l. round-bottomed flask is added 174 g. (2 moles) of finely powdered, dry isobutyramide (Note 1). The flask is tightly stoppered, and the two dry solids are thoroughly mixed by shaking. The flask then is attached to a water-cooled condenser set for downward distillation; a 500-ml. suction flask connected to the condenser by a rubber stopper is a convenient receiver. A calcium chloride tube is attached to the side arm of the receiver, and the receiver is surrounded by crushed ice. The reaction flask is heated for 8–10 hours in an electrically heated oil bath maintained at 200–220°. The nitrile starts to distil almost at once. The reaction mixture becomes a thick, brown syrup which foams considerably toward the end of the distillation. The time of reaction may be cut to 1–2 hours by connecting the distillation system to an aspirator and intermittently removing the nitrile under reduced pressure (Note 2). Very little additional nitrile can be obtained by further heating of the reaction mixture.

The contents of the receiver are transferred to a 500-ml. modified Claisen flask, 10–15 g. of phosphorus pentoxide is added (Note 3), and the product is distilled from an oil bath held at 145–155°. After only a few drops of fore-run, the main fraction distils at 99–102°/740 mm. The yield is 96–120 g. (69–86%). The product is colorless when first distilled but acquires a yellow tint after standing a few days. If it is again distilled from phosphorus pentoxide or Drierite, it boils at 101–103° and remains colorless; n_D^{25} 1.3713.

2. Notes

1. The amide must be thoroughly dry or immediate reaction will take place with considerable generation of heat, and the yield will be lowered owing to the failure to obtain proper mixing of the reactants. If the amide is not finely powdered the yield of nitrile falls off sharply.
2. The yield is not altered by this procedure if care is taken not to evaporate the nitrile in the receiver. Keeping the flask surrounded by crushed ice and using a Dry Ice-acetone safety trap between the receiver and aspirator will guard against such loss.
3. When phosphorus pentoxide is added to isobutyronitrile, the liquid sets to a

semisolid gel which is difficult to transfer from a flask. Hence, the addition of one to the other should be made only in the flask from which the distillation is to be made.

3. Discussion

Isobutyronitrile has been prepared by a number of catalytic vapor-phase reactions at elevated temperatures: isobutylamine over copper[1] or nickel,[2] isobutyramide over alumina,[3] a mixture of ammonia and isobutyraldehyde over thorium dioxide[4] or other catalysts,[5] a mixture of ammonia and isobutyl alcohol over copper,[6] and a mixture of isobutylene oxide and ammonia over alumina and copper.[7] It has also been prepared by decarboxylation of 2-methyl-2-cyanopropanoic acid,[8] and by the reaction of isobutyric acid with potassium thiocyanate.[9] The above procedure is a modification of the method used by Walter and McElvain.[10]

References and Notes

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2. Mailhe and de Godon, *Bull. soc. chim. France,* (4) **21**, 288 (1917).
3. Boehmer and Andrews, *J. Am. Chem. Soc.*, **38**, 2503 (1916).
4. Mailhe, *Compt. rend.*, **166**, 215 (1918).
5. U. S. pat. 2,535,818 [*C. A.*, **45**, 2015 (1951)].
6. Hara and Komatsu, *Mem. Coll. Sci. Kyoto Imp. Univ.*, **8A**, 241 (1925) [*C. A.*, **19**, 3248 (1925)].
7. U. S. pat. 2,500,256 [*C. A.*, **44**, 7342 (1950)].
8. Hoffmann and Barbier, *Bull. soc. chim. Belg.*, **45**, 565 (1936) [*C. A.*, **31**, 919 (1937)].
9. Letts, *Ber.*, **5**, 671 (1872).
10. Walter and McElvain, *J. Am. Chem. Soc.*, **56**, 1614 (1934).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alumina

Drierite

ammonia (7664-41-7)

thorium dioxide

copper (7440-50-8)

nickel (7440-02-0)

potassium thiocyanate (333-20-0)

isobutyl alcohol (78-83-1)

isobutyraldehyde (78-84-2)

Isobutyramide (563-83-7)

isobutyric acid (79-31-2)

Isobutyronitrile (78-82-0)

isobutylamine (78-81-9)

isobutylene oxide (558-30-5)

2-methyl-2-cyanopropanoic acid

phosphorus pentoxide (1314-56-3)

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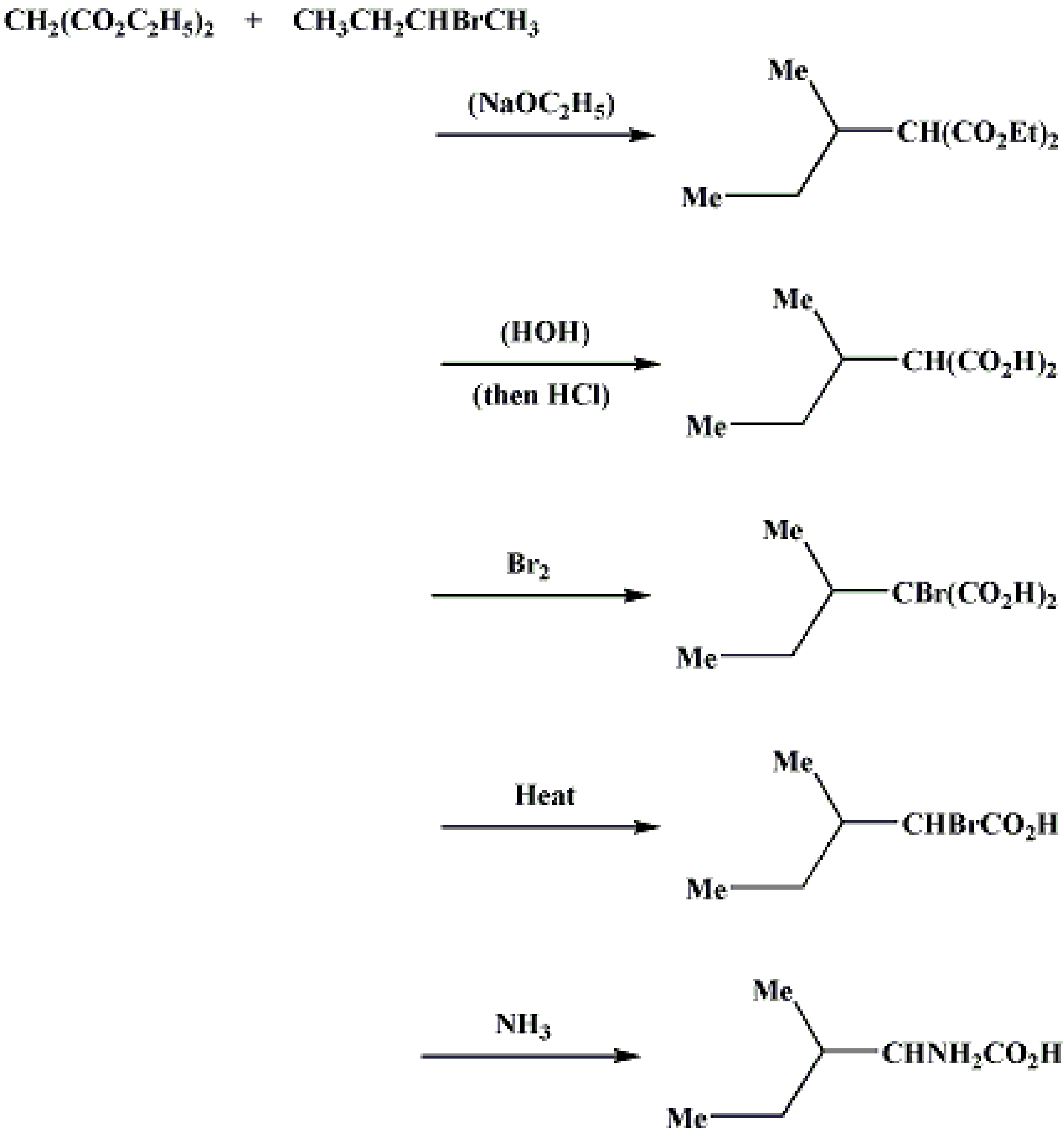
Organic Syntheses, CV 3, 495

dl-ISOLEUCINE

[α-Amino-β-methylvaleric acid]



Submitted by C. S. Marvel[1]
Checked by W. E. Bachmann and D. W. Holmes.

1. Procedure

A. *Diethyl sec.-butylmalonate*. To 700 ml. of absolute ethanol in a 2-l. three-necked round-bottomed flask equipped with a long, wide-bore reflux condenser is added 35 g. (1.52 gram atoms) of sodium cut in pieces of suitable size. When all the sodium has reacted, the flask is placed on a steam cone and fitted with a mercury-sealed stirrer, a dropping funnel, and a reflux condenser bearing a calcium chloride tube (Note 1). The

flask is heated, and 250 g. (1.56 moles) of diethyl malonate is added in a steady stream with stirring. After the ester addition, 210 g. (1.53 moles) of *sec*-butyl bromide is added at such a rate that the heat of reaction causes refluxing. The mixture is then stirred and refluxed for 48 hours. At the end of this time, the reflux condenser is exchanged for a downward condenser and the ethanol is removed by distillation (Note 2). The residue is treated with 200 ml. of water, shaken, and allowed to stand until the ester layer separates. The ester layer is separated from the aqueous layer and distilled from a 500-ml. two-necked flask fitted with a well-wrapped 18-in. Vigreux column. The fraction boiling at 110–120°/18–20 mm. is diethyl *sec*-butylmalonate, and it amounts to 274–278 g. (83–84%).

B. *α-Bromo-β-methylvaleric acid*. In a 2-l. three-necked round-bottomed flask equipped with a stirrer and dropping funnel and placed on a steam cone, 250 g. of technical potassium hydroxide is dissolved in 200 ml. of water. To the hot solution, 250 g. (1.16 moles) of diethyl *sec*-butylmalonate is added in a steady stream with vigorous stirring (Note 3). A tube connected to a vacuum line assists in the removal of ethanol. The mixture is stirred and heated for 5 hours (Note 4), and then the contents of the flask are transferred to a beaker fitted with a stirrer and surrounded by an ice bath. The cooling is hastened by the addition of 50 g. of ice, and, when the temperature reaches 15°, technical hydrochloric acid is added at such a rate that the temperature does not rise above 20°. After the addition of about 250 ml. of acid, the monopotassium salt separates, necessitating stirring by hand until solution again occurs. When the solution is acid to Congo red (Note 5) it is transferred to a separatory funnel (Note 6).

The *sec*-butylmalonic acid is extracted with three 200-ml. portions of ether, and the combined extracts are dried over calcium chloride overnight. The ether solution is then decanted into a 2-l. three-necked flask fitted with a mercury-sealed stirrer, reflux condenser, and dropping funnel. Five milliliters of bromine is added at one time, and the solution is stirred until decolorized (Note 7). Then 50 ml. more bromine is added dropwise at such a rate that the ether refluxes gently. When all the bromine has been added, 200 ml. of water is added through the dropping funnel dropwise so as to produce no foaming or violent reaction.

The ether layer containing the bromomalonic acid is separated from the aqueous layer, and the ether is removed by distillation from a steam cone. The residual liquid is decarboxylated by refluxing for 5 hours in a 500-ml. round-bottomed flask on an oil bath heated to 130°. The bromo acid is then separated from the small amount of water and distilled. The material distilling at 125–140°/18–20 mm. is α-bromo-β-methylvaleric acid (Note 8). The yield is 150.5 g. (66.7%).

C. *dl-Isoleucine*. One hundred and fifty grams (0.77 mole) of α-bromo-β-methylvaleric acid is added to 645 ml. of technical ammonium hydroxide (sp. gr. 0.90) in a 1.5-l. round-bottomed flask. A stopper is wired in, and the flask is allowed to stand at room temperature for a week (Note 9). The stopper is removed and the

mixture heated on a steam cone overnight to remove ammonia. The aqueous solution is concentrated under reduced pressure until bumping becomes violent (about 300 ml.). The mixture is then cooled to 15° and the crystals are collected on a filter. The crystals are washed with 40 ml. of ethanol and dried. The filtrate is again concentrated to about 150 ml., and a second crop of crystals is obtained. This second crop is washed with 25 ml. of water and then with 25 ml. of 95% ethanol. The yield of crude product is 65 g.

The isoleucine is recrystallized by dissolving it in 850 ml. of water heated to 95° on a steam cone. The solution is decolorized by treatment with a gram of Norit for 30 minutes and is then filtered hot. To the hot solution is added 425 ml. of 95% ethanol. and the flask is placed in an ice chest overnight. The yield of pure product is 38 g. An additional crop of 12 g. may be obtained by concentrating the mother liquors from the recrystallization to about 100 ml. and adding an equal volume of ethanol. This second crop is washed with 10 ml. of cold water and 10 ml. of cold ethanol. The total yield is 50 g. (49%). The product decomposes at 278–280° in a sealed evacuated capillary (Note 10).

2. Notes

1. The submitters carried out the preparation on a run ten times this size, using a 12-l. round-bottomed flask. After the sodium had reacted, the flask was fitted with a stopper containing the stirrer and two angle tubes connected respectively to a reflux condenser and a dropping funnel. The time allowed for the various reactions to take place was the same as for the smaller run. The percentage yields of the various products were practically identical.
2. On a run ten times this size, the submitters distilled the ethanol into another 12-l. flask connected by means of an adapter and fitted with the wide-bore reflux condenser originally used. The sodium necessary for a second run was added to the second flask as the ethanol distilled into it; on the large run this took 4–6 hours.
3. The ester is added quite slowly at first, until the reaction gets under way, and then more rapidly.
4. Water is added if necessary to keep the mass from solidifying.
5. About 400 ml. of acid is required.
6. For a run ten times this size, the solution is transferred to a 12-l. round-bottomed flask fitted with a stopper containing a large stop-cock which barely pierces the stopper and a glass tube which reaches to the bottom of the flask. A flask so fitted can be used as a large separatory funnel. The stopper is wired when the flask is upturned.
7. It is important that the first 5-ml. portion react completely; otherwise the bromination will not go smoothly and the solution may foam out of the condenser.
8. .If the decarboxylation was not complete it will be finished here. Occasionally it is some time before a good water pump will maintain constant pressure.
9. On a larger run, the submitters allowed 350 g. of the bromoacid and 1.5 l. of

ammonium hydroxide in a 3-l. flask to stand for a week. The contents of four such flasks, including any solid material, were combined in a 12-l. round-bottomed flask and heated on a steam cone overnight.
10. The product obtained in this manner has the calculated amount of amino nitrogen.

3. Discussion

dl-Isoleucine has been prepared by the reduction and subsequent hydrolysis of ethyl α-oximino-β-methyl-*n*-valerate;[2] by the action of aqueous ammonia on α-bromo-β-methyl-*n*-valeric acid;[3] and from ethyl *sec*-butylbromomalonate by saponification, decarboxylation, and amination.[4] The procedure described above is a combination of these last two methods.

References and Notes

1. These directions are the result of the efforts of many men who have worked on the preparation of isoleucine at the University of Illinois.
2. Bouveault and Locquin, *Compt. rend.*, **141**, 115 (1905); *Bull. soc. chim. France*, (3), **35**, 965 (1906).
3. Ehrlich, *Ber.*, **41**, 1453 (1908); Brasch and Friedmann, *Beitr. Chem. Physiol. Path.*, (2) 376 (1908).
4. Romburgh, *Rec. trav. chim.*, **6**, 150 (1887).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ether (60-29-7)

bromine (7726-95-6)

sec-Butyl bromide (78-76-2)

Norit (7782-42-5)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

ammonium hydroxide (1336-21-6)

diethyl malonate (105-53-3)

α-Bromo-β-methylvaleric acid, α-bromo-β-methyl-n-valeric acid (42880-22-8)

α-Amino-β-methylvaleric acid

isoleucine, DL-Isoleucine (73-32-5)

bromomalonic acid

sec-butylmalonic acid

Diethyl sec-butylmalonate, Diethyl sec.-butylmalonate (83-27-2)

ethyl α-oximino-β-methyl-n-valerate

ethyl sec-butylbromomalonate

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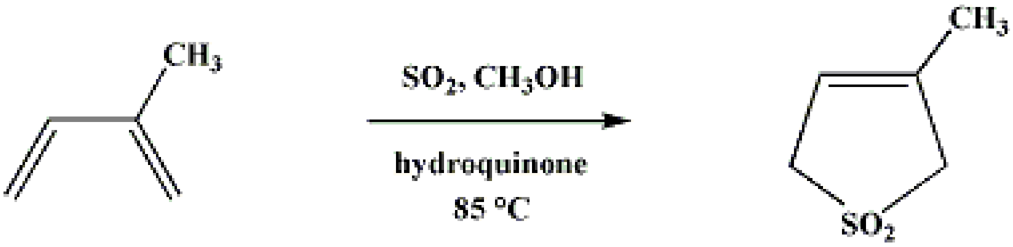
Organic Syntheses, *CV 3*, *499*

ISOPRENE CYCLIC SULFONE

[Thiophene, 2,5-dihydro-3-methyl-, 1-dioxide]



Submitted by Robert L. Frank and Raymond P. Seven[1].
Checked by A. E. Barkdoll and R. S. Schreiber.

1. Procedure

Caution! If peroxides are present in the isoprene, they should be destroyed by washing with 10% acidified ferrous ammonium sulfate before distillation.

A 600-ml. steel reaction vessel (Note 1) is precooled before loading by filling it between one-fourth and one-half full of methanol and Dry Ice. After removal of the methanol and Dry Ice, the autoclave is charged with 120 g. (176 ml., 1.76 moles) of isoprene (Note 2), 113 g. (80 ml., 1.76 moles) of liquid sulfur dioxide, 88 ml. of methanol, and 4 g. of hydroquinone. The vessel is sealed, heated slowly to 85°, and maintained at that temperature for 4 hours. It is then cooled, the sulfone removed, the bomb rinsed with methanol, and the combined product and washings are treated hot with 5 g. of Norite. The filtered solution is concentrated to a volume of 250–300 ml., and the sulfone is allowed to crystallize. The material is filtered and washed with 50 ml. of cold methanol. Recrystallization from methanol (20 ml. per 25 g. of sulfone) yields 140–150 g. of thick, colorless plates. Concentration of the mother liquors raises the total yield to 182–191 g. (78–82%) (Note 3), melting at 63.5–64° (Note 4).

2. Notes

1. A steel reaction vessel of the type used for high-pressure catalytic hydrogenations is satisfactory. The pressure generated is less than 200 lb. For smaller quantities a heavy glass tube can also be used with proper precautions.
2. Commercial isoprene, obtained from Phillips Petroleum Company, should be freshly distilled before use, in order to eliminate isoprene dimers and polymers which are likely to accumulate in storage. If peroxides are present, they should be destroyed before distillation of the isoprene by washing with 10% acidified ferrous ammonium sulfate. As an added precaution, the distillation flask should not be permitted to go dry.

3. The yield of the cyclic sulfone depends upon the purity of isoprene. In one experiment, the checkers obtained the sulfone in 86% yield, using freshly distilled isoprene of 99 mole per cent purity, while the yield fell to 77% with commercial isoprene which had been distilled and stored at 5° for 1 week before use.

4. The checkers consistently obtained a slightly higher melting point (uncor.) in the range 64.4–65.4°. The purified cyclic sulfone serves as an ideal intermediate for the preparation of extremely pure isoprene, since isoprene can be regenerated nearly quantitatively at 135–140°[2] Other sulfones that can be prepared by this method and that are useful in the purification of dienes are those of butadiene, m.p. 65.5°,[3] and 2,3-dimethylbutadiene, m.p. 135°[3] The sulfone of piperylene is a liquid.[4]

3. Discussion

Isoprene cyclic sulfone has been prepared only from isoprene and sulfur dioxide.[2,3,5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 454

References and Notes

1. Work done under contract with the Office of Rubber Reserve, Reconstruction Finance Corporation.
2. Frank, Adams, Blegen, Deanin, and Smith, *Ind. Eng. Chem.*, **39**, 887 (1947).
3. Staudinger and Ritzenthaler, *Ber.*, **68**, 455 (1935).
4. Craig, *J. Am. Chem. Soc.*, **65**, 1006 (1943); Frank, Emmick, and Johnson, *J. Am. Chem. Soc.*, 69, 2313 (1947).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Isoprene cyclic sulfone

sulfone of piperylene

methanol (67-56-1)

hydroquinone (123-31-9)

sulfur dioxide (7446-09-5)

Norite (7782-42-5)

butadiene (106-99-0)

ferrous ammonium sulfate (10045-89-3)

2,3-Dimethylbutadiene (513-81-5)

ISOPRENE (78-79-5)

Thiophene, 2,5-dihydro-3-methyl-, 1-dioxide (1193-10-8)

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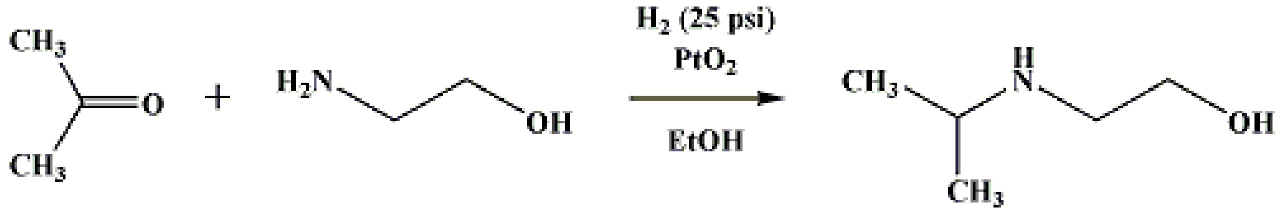
Organic Syntheses, CV 3, 501

2-ISOPROPYLAMINOETHANOL

[Ethanol, 2-isopropylamino-]



Submitted by Evelyn M. Hancock and Arthur C. Cope.
Checked by Nathan L. Drake and Larry Green.

1. Procedure

The reaction is carried out in a catalytic hydrogenation apparatus similar to the one described by Adams and Voorhees.[1] In a 1-l. reduction bottle are placed 0.5 g. of platinum oxide catalyst[1] and 50 ml. of commercial absolute ethanol. The bottle is connected to a calibrated low-pressure hydrogen tank and alternately evacuated and filled with hydrogen twice. Hydrogen is then admitted to the system until the pressure is 1–2 atm. (15–30 lb.), and the bottle is shaken for 20–30 minutes to reduce the platinum oxide (Note 1). The shaker is stopped, air is admitted to the bottle, and a solution of 61.0 g. (1.0 mole) of ethanolamine (Note 2), 75.4 g. (94 ml., 1.3 moles) of acetone, and 100 ml. of absolute ethanol is rinsed into the reduction bottle with 50 ml. of absolute ethanol. The bottle is alternately evacuated and filled with hydrogen twice. Hydrogen is admitted to the system until the pressure is approximately 25 lb., and the bottle is shaken until the pressure drop indicates that the theoretical amount (1 mole) of hydrogen has been taken up and absorption ceases (6–10 hours). Air is admitted to the bottle, and the catalyst is removed by filtration through a Hirsch funnel with a filter plate of small diameter (Note 3). The bottle is rinsed with a total of 75ml. of benzene, which is also poured through the funnel. The filtrate is rinsed into a 500-ml. modified Claisen flask with 25 ml. of benzene, and most of the solvent is distilled at atmospheric pressure. Distillation of the residue under reduced pressure yields 97–98 g. of 2-isopropylaminoethanol, b.p. 86–87°/23 mm. (94–95%, based on the ethanolamine used) (Note 4).

2. Notes

1. If hydrogenation of the reaction mixture is begun in the presence of platinum oxide, a long induction period or lag occurs before the catalyst is reduced.
2. Commercial ethanolamine (Carbide and Carbon Chemicals Corporation) was dried by distillation with a small amount of benzene and redistilled; b.p. 70–72°/12 mm.
3. The usual precaution was observed of keeping the catalyst wet with the solution being filtered to prevent ignition of the filter paper.
4. Similar procedures have been used in preparing other 2-alkylaminoethanols[2] and N-alkyl derivatives of 1-amino-2-propanol, 2-amino-1-propanol, 3-amino-1-propanol, 2-

amino-1-butanol, and 1-amino-2-methyl-2-propanol.[3]

3. Discussion

2-Isopropylaminoethanol has been prepared by the reaction of isopropylamine with ethylene oxide,[4,5] and by the method given above.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 470

References and Notes

1. *Org. Syntheses* Coll. Vol. **1**, 61, 463 (1941).
2. Cope and Hancock, *J. Am. Chem. Soc.*, **64**, 1503 (1942).
3. Cope and Hancock, *J. Am. Chem. Soc.*, **66**, 1453 (1944); Hancock and Cope, *J. Am. Chem. Soc.*, **66**, 1738 (1944); Hancock, Hardy, Heyl, Wright, and Cope, *J. Am. Chem. Soc.*, **66**, 1747 (1944).
4. Matthes, *Ann.*, **315**, 104 (1901).
5. Biel, *J. Am. Chem. Soc.*, **71**, 1306 (1949).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

Benzene (71-43-2)

hydrogen (1333-74-0)

platinum oxide

acetone (67-64-1)

Ethylene oxide (75-21-8)

ethanolamine (141-43-5)

2-isopropylaminoethanol, Ethanol, 2-isopropylamino- (109-56-8)

1-amino-2-methyl-2-propanol (2854-16-2)

isopropylamine (75-31-0)

3-amino-1-propanol (156-87-6)

2-amino-1-butanol (13054-87-0)

1-amino-2-propanol (78-96-6)

2-amino-1-propanol (6168-72-5)

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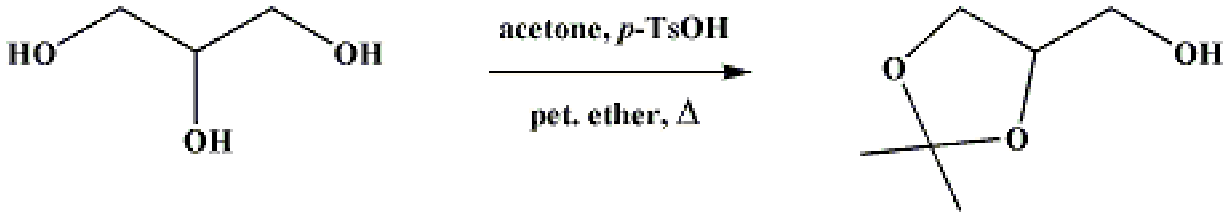
dl-ISOPROPYLIDENEGLYCEROL

[Glycerol, isopropylidene-; also 1,3-dioxolane-4-methanol, 2,2-dimethyl-]



Submitted by Mary Renoll and Melvin S. Newman.
Checked by R. L. Shriner and Arne Langsjoen.

1. Procedure

In a 1-l. three-necked flask, fitted with a sealed mechanical stirrer and a fractionating column (about 2 by 45 cm., packed with glass helices) attached to a total reflux phase-separating head .htm(Fig. 15) (Note 1), are placed 237 g. (300 ml., 4.09 moles) of acetone (Note 2), 100 g. (1.09 moles) of glycerol (Note 3), 300 ml. of low-boiling petroleum ether (Note 4), and 3.0 g. of *p*-toluenesulfonic acid monohydrate. The third neck is closed with a cork or a ground-glass stopper, and the mixture is heated (Note 5) with stirring so that the petroleum ether refluxes as rapidly as the column permits. The stirring and refluxing are continued until no more water collects in the trap of the separating head; the time required varies between 21 and 36 hours (Note 6).

The mixture is cooled to room temperature, and 3.0 g. of powdered, freshly fused sodium acetate is added. Stirring is continued for 30 minutes; the mixture is then filtered, and the petroleum ether and excess acetone are removed by distillation under reduced pressure (water pump). The residual liquid is distilled from a modified Claisen flask. The fraction boiling at 80–81°/11 mm. is collected. The yield of colorless isopropylideneglycerol (n_D^{25} 1.4339, d_4^{25} 1.062) is 125–129 g. (87–90%).

Fig. 15.

Fig. 15.

2. Notes

1. During operation, the apparatus shown in .htmFig. 15 requires no attention beyond occasional draining of the water trap. It is suitable for a number of preparations in which water is removed by distillation with an immiscible solvent; it functions only when the condensate separates into two phases, of which water is the more dense.

2. The acetone was the 99.5% grade obtained from the Carbide and Carbon Chemicals Company.
3. The glycerol should be of U.S.P. grade; if it has absorbed moisture, it may be dehydrated by heating at 170° in an open dish under a hood for 3 hours.[1]
4. Skellysolve F, b.p. 35–55°, obtainable from the Skelly Oil Company, is suitable.
5. The mixture may be heated by means of a steam or water bath, but in view of the long reflux period it is better to use a hemispherical electric heating mantle controlled by a variable transformer.
6. The period of refluxing need not be continuous. A longer reflux time, up to 70 hours, does not increase the yield. The volume of the aqueous phase collected in the separating head varies from 32 to 42 ml., depending on the quality of the glycerol.

3. Discussion

Isopropylideneglycerol has been prepared from acetone and glycerol in the presence of the following acidic catalyst: hydrogen chloride,[2,3] hydrogen chloride and anhydrous sodium sulfate,[4] phosphorus pentoxide,[5] and anhydrous copper sulfate.[6] It has also been prepared from acetone and glycerol in the presence of calcium carbide and a neutral surface-active agent.[7] The two optically active isomers of isopropylideneglycerol have been prepared from 1,2,5,6-diacetone-D-mannitol and 1,2,5,6-diacetone-L-mannitol.[8] The procedure given is based on the method of Newman and Renoll.[9]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 496

References and Notes

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2. Fischer, *Ber.*, **28**, 1167 (1895).
3. Irvine, Macdonald, and Soutar, *J. Chem. Soc.*, **107**, 343 (1915).
4. Fischer and Pfähler, *Ber.*, **53**, 1607 (1920).
5. Smith and Lindberg, *Ber.*, **64**, 510 (1931).
6. Hibbert and Morazain, *Can. J. Research*, **2**, 38 (1930).
7. Maglio and Burger, *J. Am. Chem. Soc.*, **68**, 529 (1946).
8. Baer and Fischer, *J. Biol. Chem.*, **128**, 468 (1939); *J. Am. Chem. Soc.*, **67**, 2035 (1945).
9. Newman and Renoll, *J. Am. Chem. Soc.*, **67**, 1621 (1945).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

calcium carbide

1,2,5,6-diacetone-D-mannitol

1,2,5,6-diacetone-L-mannitol

hydrogen chloride (7647-01-0)

sodium acetate (127-09-3)

glycerol (56-81-5)

sodium sulfate (7757-82-6)

copper sulfate (7758-98-7)

acetone (67-64-1)

isopropylideneglycerol, dl-ISOPROPYLIDENEGLYCEROL, Glycerol, isopropylidene-

1,3-dioxolane-4-methanol, 2,2-dimethyl- (100-79-8)

phosphorus pentoxide (1314-56-3)

p-toluenesulfonic acid monohydrate (6192-52-5)

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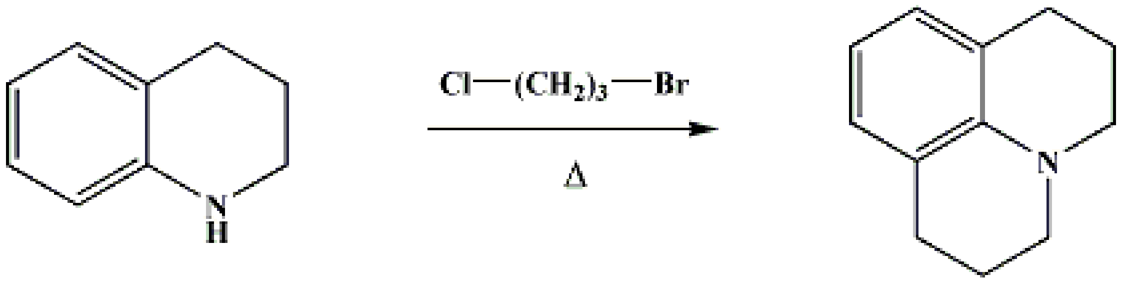
Organic Syntheses, CV 3, 504

JULOLIDINE

[Benzo[*ij*]quinolizine, 1,2,3,5,6,7-hexahydro-]



Submitted by D. B. Glass and A. Weissberger.
Checked by Cliff S. Hamilton and Carol K. Ikeda.

1. Procedure

A mixture of 66.5 g (0.5 mole) of tetrahydroquinoline and 400 g. of trimethylene chlorobromide (Note 1) is placed in a 1-l. round-bottomed flask attached to a reflux condenser, and heated in an oil bath held at 150–160° for 20 hours (Note 2). The reaction mixture is cooled, a solution of 50 ml. of concentrated hydrochloric acid in 500 ml. of water is added, and the excess trimethylene chlorobromide is removed by distillation with steam (Note 3). The acid residue from the steam distillation is made alkaline with a 40% solution of sodium hydroxide (about 75 ml.), and the julolidine is extracted with two 150-ml. portions of ether. The ethereal solution is washed with 150 ml. of water and dried over sodium hydroxide pellets. The ether is evaporated and the residue distilled under reduced pressure. The portion that boils at 105–110°/1 mm. is collected (Note 4) and (Note 5). The yield is 67–70 g. (77–81%).

2. Notes

1. The tetrahydroquinoline and trimethylene chlorobromide were Eastman grade materials of the Eastman Kodak Company.
2. The heating should be carried out in a hood, or a gas trap should be used to remove the hydrogen halides that are evolved.
3. The trimethylene chlorobromide recovered may be dried over calcium chloride and used in a subsequent run.
4. The julolidine solidifies in the receiver, m.p. 39–40°.
5. After standing in contact with air for several weeks, the julolidine may become colored by the formation of a red compound. This red compound may be removed by distillation or by dissolving the amine in 2 or 3 volumes of hexane, treating the hexane solution with Norit or Darco, and filtering. The julolidine is crystallized from the hexane solution by cooling in an acetone-Dry Ice bath. The resulting product melts at 39–40° and amounts to 85–90% of the

original.

3. Discussion

Julolidine has been prepared by the reaction of trimethylene chlorobromide with formanilide,[1] aniline,[1] methylaniline,[1] and tetrahydroquinoline;[1,2] by the reduction of 8,10-diketojulolidine;[1] by the intra-molecular condensation of N-(γ-bromopropyl) tetrahydroquinoline;[3] and by dehydration of N-(γ-hydroxypropyl) tetrahydroquinoline or di-(γ-hydroxypropyl) aniline with phosphorus pentoxide.[4]

References and Notes

1. Pinkus, *Ber.*, **25**, 2802 (1892).
2. von Braun, Heider, and *Wyczatkowska*, *Ber.*, **51**, 1219 (1918).
3. Jones and Dunlop, *J. Chem. Soc.*, **101**, 1752 (1912).
4. Rindfusz and Harnack, *J. Am. Chem. Soc.*, **42**, 1724 (1920).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Darco

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

ether (60-29-7)

aniline (62-53-3)

sodium hydroxide, sodium hydroxide pellets (1310-73-2)

Norit (7782-42-5)

Trimethylene chlorobromide (109-70-6)

methylaniline (100-61-8)

Julolidine, Benzo[ij]quinolizine, 1,2,3,5,6,7-hexahydro- (479-59-4)

tetrahydroquinoline (635-46-1)

hexane (110-54-3)

formanilide (103-70-8)

8,10-diketojulolidine

N-(γ-bromopropyl) tetrahydroquinoline

N-(γ-hydroxypropyl) tetrahydroquinoline

di-(γ-hydroxypropyl) aniline

phosphorus pentoxide (1314-56-3)

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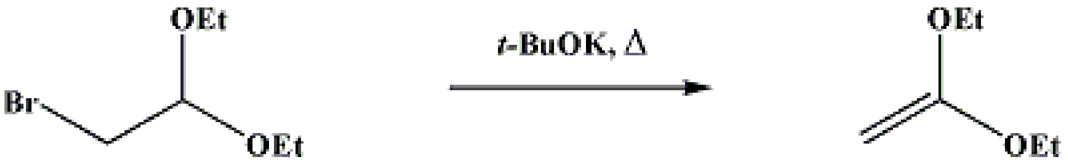
Organic Syntheses, CV 3, 506

KETENE DIETHYLACETAL

[Ketene, diethyl ketal]



Submitted by S. M. McElvain and D. Kundiger.
Checked by R. L. Shriner and C. H. Tilford.

1. Procedure

In a 2-l. round-bottomed flask, preferably fitted with an interchangeable ground-glass joint, are placed 650 g. (820 ml.) of absolute *tert*-butyl alcohol (Note 1) and 39.1 g. (1 gram atom) of potassium (Note 2). A reflux condenser is attached to the flask and the mixture is refluxed until all the potassium is dissolved (about 8 hours). The solution is allowed to cool slightly, and 198 g. (1 mole) of bromoacetal, together with some boiling chips (Note 3) is quickly added. A cream-colored precipitate of potassium bromide begins to deposit immediately. The flask is attached at once to a closely indented 46-cm. Vigreux column, equipped with a glass insulating jacket and a total-reflux partial take-off still head[1] (Note 4), and the *tert*-butyl alcohol is distilled from an oil bath (about 120–130°) at the rate of 25 drops per minute with a reflux ratio at the still head of about 6:1. This operation requires 16–18 hours (Note 5), and at the end of this time the temperature of the oil bath is raised to 160° and maintained there until no more alcohol comes over. The bath is then lowered and allowed to cool while the pressure within the fractionating system is very gradually reduced to 200 mm. and held there by a barostat (Note 6).

A small amount of the alcohol comes over at 51–52° /200 mm., and then, after the heating bath is replaced, 4–6 ml. of an intermediate fraction distils. This is followed by a fraction which boils at 83–86°/200 mm. and which is collected as pure ketene acetal. A total of 78–87 g. is obtained (67–75%). The major portion is collected while the temperature of the bath is 120–140°, and the remainder is obtained by raising the bath temperature to 170–180°.

Ketene acetal is best stored in a bottle made of alkaline glass which is preferably new and dusted with sodium *tert*-butoxide (Note 7). The glass stopper should be very well greased. Even with these precautions a small amount of a voluminous precipitate of the white polymer will develop.

2. Notes

1. The *tert*-butyl alcohol is refluxed over quicklime, distilled, and then redistilled over 1 g. of potassium per 100 g. of the alcohol. Improved yields of ketene acetal are obtained from *tert*-butyl alcohol that has been recovered from a previous preparation of the acetal.
2. The potassium should be cut into pieces sufficiently small to pass through the neck of the flask. Sodium in *tert*-butyl alcohol can be used, but it is necessary to carry out the subsequent reaction at 125° in sealed tubes. The amount of *tert*-butyl alcohol specified is sufficient to provide for complete solution of the potassium as the *tert*-butoxide.
3. An ebullator tube through which dry nitrogen was drawn has been used for the subsequent distillation under reduced pressure, but it is far more advantageous to use about six boiling chips. Because of its rapid reaction with water, ketene acetal must be protected from moisture of the air.

4. The still head described by Whitmore and Lux[1] is most satisfactory for controlling this distillation. The tube leading from the take-off of the column is attached to the receiver through a fraction cutter protected from moisture by a large tube of calcium chloride. The checkers replaced the Vigreux column by a 50-cm. column filled with glass helices and surrounded by a heating jacket. With this column the removal of the *tert*-butyl alcohol was complete in 5–6 hours.
5. A slower rate of fractionation does not result in an increased yield, but interrupted fractionation results in a decreased yield.
6. A good barostat is necessary. Control of the reduced pressure by adjusting a "leak" in the system is entirely unsatisfactory, for, as a result of a small increase in pressure, the liquid ceases to boil, the column drains, and the boiling chips are rendered ineffective. The barostat used by the submitters is essentially that described by Ellis[2] in which the relay is replaced by the thermionic relay described by Waddle and Saeman.[3]
7. The column and apparatus should not be washed with acid cleaning solution because the glass surface is left acidic and it then catalyzes the polymerization of ketene acetal.[4] A thin coating of the polymer on the walls of the apparatus is not detrimental. If polymer must be removed, it is best done by dissolving it in a 10% solution of hydrochloric acid in acetone; a deep red solution results.

3. Discussion

Ketene acetal may be prepared by the action of potassium *tert*-butoxide on iodoacetal[5] or bromoacetal.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 684

References and Notes

1. Whitmore and Lux, *J. Am. Chem. Soc.*, **54**, 3451 (1932).
2. Ellis, *Ind. Eng. Chem., Anal. Ed.*, **4**, 318 (1932).
3. Waddle and Saeman, *Ind. Eng. Chem., Anal. Ed.*, **12**, 225 (1940); Ferry, *Ind. Eng. Chem., Anal. Ed.*, **10**, 647 (1938).
4. Johnson, Barnes, and McElvain, *J. Am. Chem. Soc.*, **62**, 964 (1940).
5. Beyerstedt and McElvain, *J. Am. Chem. Soc.*, **58**, 529 (1936).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Bromoacetal

absolute tert-butyl alcohol

iodoacetal

hydrochloric acid (7647-01-0)

nitrogen (7727-37-9)

acetone (67-64-1)

sodium (13966-32-0)

potassium bromide (7758-02-3)

potassium (7440-09-7)

Ketene diethylacetal (2678-54-8)

Ketene, diethyl ketal

ketene acetal

tert-butyl alcohol (75-65-0)

potassium tert-butoxide (865-47-4)

tert-butoxide

sodium tert-butoxide (865-48-5)

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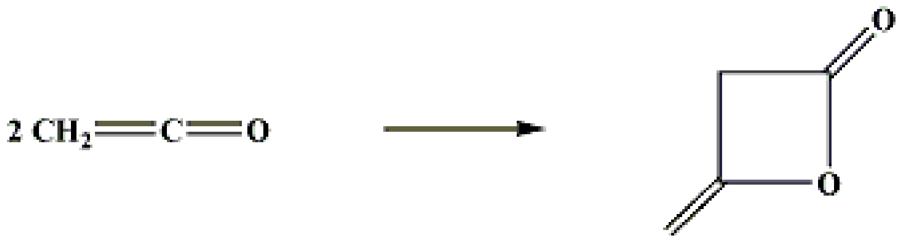
Organic Syntheses, CV 3, 508

KETENE DIMER

[Acetylketene]



Submitted by Jonathan W. Williams and John A. Krynitsky.
Checked by Nathan L. Drake and Joseph Lann.

1. Procedure

Three 300-ml. gas-washing cylinders (Note 1) are connected in series, and the second and third cylinders are charged with 150 ml. each of dry acetone. Each of the three cylinders is immersed, in a thermos bottle, in sufficient Dry Ice-acetone cooling mixture to cover half of the cylinder. Ketene gas, prepared by the pyrolysis of acetone (Note 2), is passed through the system (Note 3) until a quantity of 2 moles has been introduced. This process requires 4–4.5 hours. During this time, after the ketene has been passing through the system for 1.5 hours, the Dry Ice-acetone cooling mixture is removed from the thermos bottle around the first cylinder. The cold thermos bottle is then replaced around the cylinder. Two hours after the completion of the ketene passage, the cooling mixture is removed from the second thermos bottle, and 6 hours later the third thermos bottle is emptied, both bottles being immediately restored to position. The entire system should be at room temperature 24 hours after the beginning of the run.

The liquids from all three cylinders are combined and fractionally distilled (Note 4). Most of the acetone is removed at room temperature under a pressure of 20 mm.; the last small portion is removed under atmospheric pressure. When the distillation temperature reaches 120°, the system is evacuated to a pressure of 80–100 mm. (Note 5), and the ketene dimer is collected within the boiling range 67–69°/92 mm. The yield of pure product is 42–46 g. (50–55%) (Note 6) and (Note 7).

2. Notes

1. The gas-washing cylinders are preferably without flanges. Those used by the submitters were prepared from 45-mm. Pyrex tubing, measured 28 cm. in length, and were fitted with 29/42 standard taper ground-glass joints. The inlet tubes extended two-thirds of the way into the cylinders.
2. Ketene may be generated conveniently from acetone by means of a "ketene lamp."[1] This apparatus was used by submitters and checkers. Other apparatus

[*Org. Syntheses* Coll. Vol. 1, 331 (1941)] might also be used.

3. The effluent gases from the third cylinder should be conducted to an efficient hood, or passed through a washing bottle containing a 10% aqueous solution of sodium hydroxide.

4. The submitters and checkers used a column of the Whitmore-Lux type.

5. Pressure between these limits is the optimum for this distillation. At higher pressure too much polymerization to dehydroacetic acid occurs, and at a lower pressure special cooling methods are necessary to prevent loss of distillate by evaporation.

6. A viscous dark red residue remains in the distillation flask. This material is mostly dehydroacetic acid.

7. The Ketene dimer may be kept in a tightly stoppered bottle in the dark without appreciable further polymerization for about a week.[2]

3. Discussion

The procedure described is a modification of the method of Chick and Wilsmore,[3] which has been studied by several other workers.[4 5 2]

Homologous diketenes have been prepared by the action of tertiary amines on the corresponding acid chlorides.[6]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 10

References and Notes

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2. Boese, *Ind. Eng. Chem.*, **32**, 16 (1940).
3. Chick and Wilsmore, *J. Chem. Soc.*, **1908**, 946; **1910**, 1978.
4. Hurd, Sweet, and Thomas, *J. Am. Chem. Soc.*, **55**, 335 (1933);
5. Hurd and Williams, *J. Am. Chem. Soc.*, **58**, 962 (1936);
6. Sauer, *J. Am. Chem. Soc.*, **69**, 2444 (1947).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Ketene dimer

sodium hydroxide (1310-73-2)

acetone (67-64-1)

Ketene (463-51-4)

Dehydroacetic acid (520-45-6)

Acetylketene

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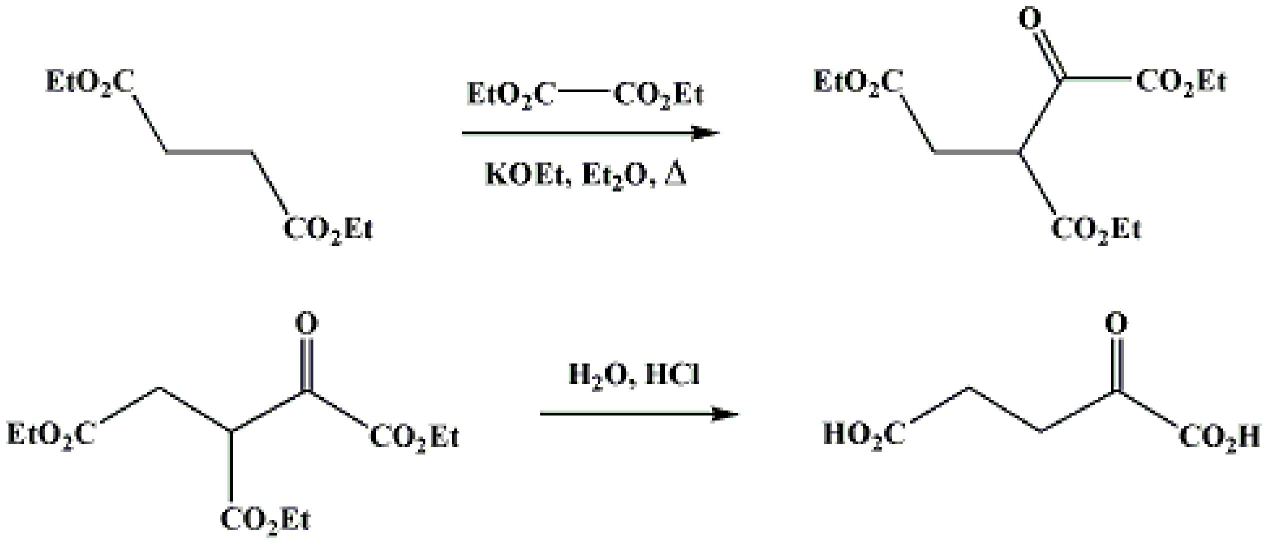
Organic Syntheses, CV 3, 510

α-KETOGLUTARIC ACID

[Glutaric acid, α-oxo-]



Submitted by Lester Friedman and Edward Kosower.
Checked by Reynold C. Fuson and Elliott N. Marvell.

1. Procedure

A. *Ethyl oxalylsuccinate*. Potassium (39.5 g., 1 gram atom) is cut into pieces under xylene (Note 1) in a wide evaporating dish. The xylene is poured off, and the metal is washed with three 50-ml. portions of absolute ether. The potassium is then transferred quickly to a 2-l. three-necked flask containing 650 ml. of anhydrous ether and fitted with a reflux condenser, a mercury-sealed mechanical stirrer (Note 2), and a dropping funnel containing 150 ml. of anhydrous ethanol. The ethanol is added over a period of about 1.5 hours; stirring is unnecessary. After most of the ethanol has been added, the flask is heated on a water bath to ensure complete solution of the potassium. This usually takes from 3 to 4 hours. After the reaction is completed, the flask is cooled to room temperature, and 146 g. (1 mole) of ethyl oxalate is added rapidly through the dropping funnel, with stirring, to the solution of potassium ethoxide in ether. A yellow color develops at this point. The stirring is continued for an additional 10 minutes. Then 174 g. (1 mole) of ethyl succinate is added rapidly, with vigorous stirring (Note 3). After a few minutes, the potassium salt crystallizes, making further stirring impracticable. It is collected on a filter and washed with ether until the salt is colorless.

The salt is dissolved in 270 ml. of water, and 100 ml. of concentrated hydrochloric acid is added. The ethyl oxalylsuccinate separates as an oil and rises to the surface. It is removed by extracting the mixture with 100-ml. portions of ether until the aqueous solution is almost colorless. The extracts are dried over sodium sulfate, and the ether is distilled under reduced pressure. The ethyl oxalylsuccinate remains in the flask as a yellow oil.

The yield is 225–227 g. (82–83%) (Note 4).

B. *α-Ketoglutaric acid*. The ester obtained by the foregoing procedure is mixed with 600 ml. of concentrated hydrochloric acid and left overnight. The mixture is concentrated by distillation (Note 5) until the temperature of the liquid reaches 140°. It is poured into an evaporating dish and allowed to cool. The solid mass, weighing 110–112 g., is then pulverized. The yield of α-ketoglutaric acid is 92–93% of the theoretical for the last step, or 75–77% based upon diethyl succinate. The light-tan product, obtained as described above, is suitable for most purposes, but a purer acid, m.p. 109–110° (cor.), may be obtained by recrystallization from an acetone-benzene mixture.

2. Notes

1. All containers must be absolutely dry, and anhydrous xylene must be used. Important! Destroy with anhydrous ethanol all potassium remaining in the xylene and waste ether.
2. The stirrer is not necessary until the ethyl oxalate is added. The submitters found the use of a nitrogen atmosphere to be unnecessary.
3. The ethyl oxalate was redistilled, and the fraction boiling at 106–107°/25 mm. was used. The ethyl succinate was c.p. material obtained from Eimer and Amend and was used without further purification.
4. For further purification, the product can be distilled at about 115°/1 mm.
5. This should be done in a hood, or a trap should be used to remove the hydrochloric acid.

The submitters wish to thank Mr. Andrew Streitweiser for his invaluable assistance.

3. Discussion

Ethyl oxalylsuccinate has been prepared by the condensation of ethyl oxalate with ethyl succinate in the presence of sodium ethoxide[1] or of potassium ethoxide.[2 3] The method described above is somewhat more convenient, and has given a higher yield of a better product, than one based upon sodium ethoxide, submitted by A. E. Martell and R. M. Herbst.

α-Ketoglutaric acid has been prepared by the hydrolysis of ethyl oxalylsuccinate with concentrated hydrochloric acid;[4] by the distillation of ethyl oxalylsuccinate with concentrated hydrochloric acid;[5] by treating α,β-dibromoglutaric acid with 2 *N* sodium carbonate solution;[6] by treatment of ethyl α-bromoglutaconate with alkalies;[7] and by treating ethyl α,α'-dibromoglutarate with alcoholic potash.[8]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 687

References and Notes

1. Wislicenus, *Ber.*, **22**, 885 (1889); *Ann.*, **285**, 1 (1895).
2. Wislicenus, *Ber.*, **44**, 1567 (1911);
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4. Blaise and Gault, *Compt. rend.*, **147**, 199 (1908); Gabriel, *Ber.*, **42**, 655 (1909).
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6. Ingold, *J. Chem. Soc.*, **119**, 2014 (1921).
7. Ingold, *J. Chem. Soc.*, **119**, 2019 (1921).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alcoholic potash

acetone-benzene

ethyl α,α'-dibromoglutarate

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ether (60-29-7)

ethyl succinate

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

sodium ethoxide (141-52-6)

potassium (7440-09-7)

xylene (106-42-3)

Ethyl oxalate

potassium ethoxide (917-58-8)

α-Ketoglutaric acid, Glutaric acid, α-oxo- (328-50-7)

Ethyl oxalylsuccinate

Diethyl succinate (123-25-1)

α,β-dibromoglutaric acid

ethyl α-bromoglutaconate

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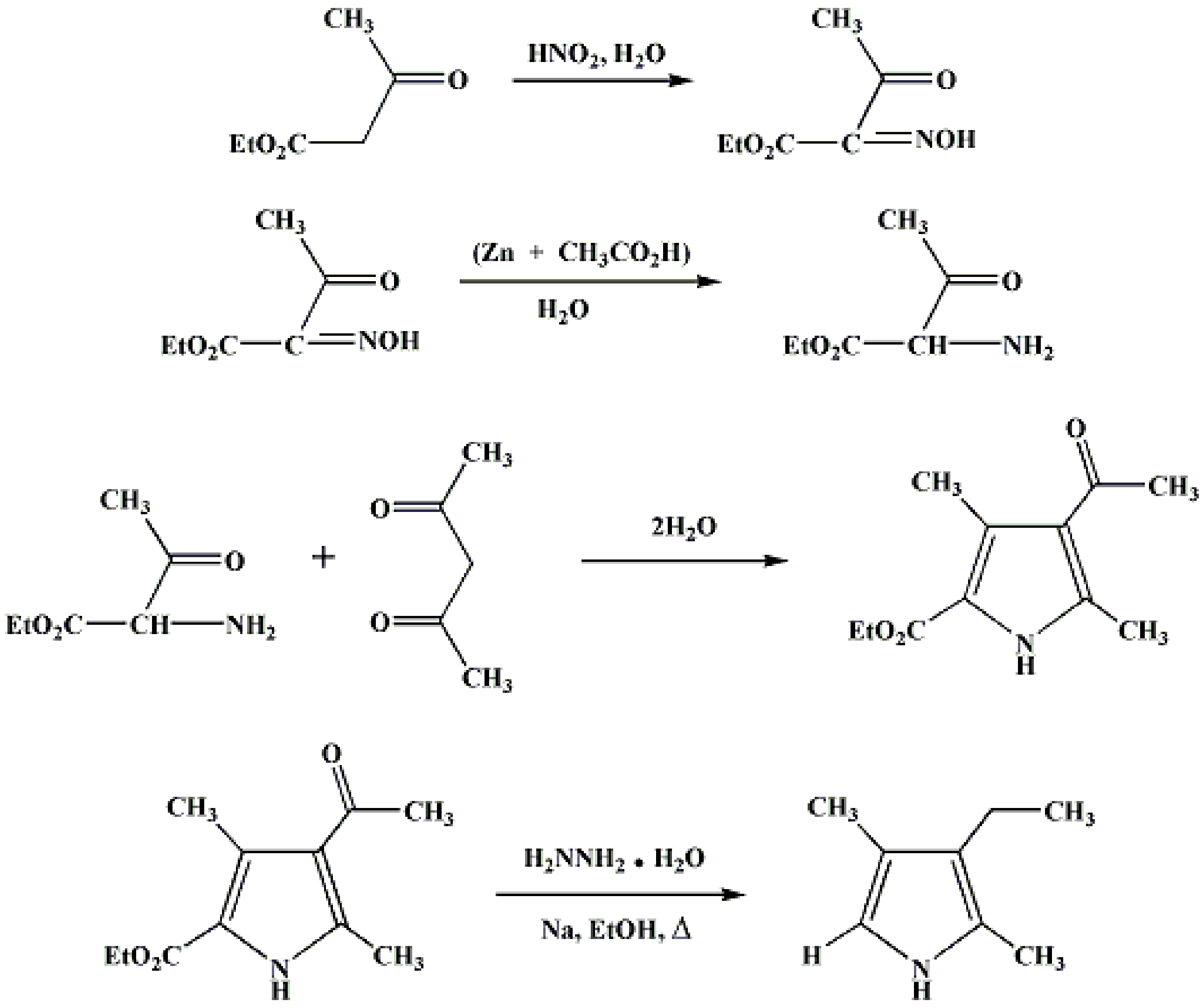
Organic Syntheses, CV 3, 513

KRYPTOPYRROLE

[Pyrrole, 2,4-dimethyl-3-ethyl]



Submitted by Hans Fischer
Checked by Homer Adkins and Ivan A. Wolff.

1. Procedure

In a 3-l. three-necked flask provided with a stirrer and surrounded by an ice bath are placed 402 g. (3.09 moles) of ethyl acetoacetate (Note 1) and 1.2 1. of glacial acetic acid. To this solution is then added dropwise with stirring a solution of 246 g. (3.55 moles) of sodium nitrite in 400 ml. of water. The rate of addition is controlled so that the temperature does not rise above 12°. After the sodium nitrite solution has been added, the mixture is stirred an additional 2–3 hours. It is then allowed to warm up to room temperature and stand about 12 hours, after which 348 g. (3.48 moles) of acetylacetone is added at one time.

To the reaction mixture 450 g. of zinc dust (Note 2) is added in portions of about 10 g. with vigorous stirring. The rate of addition is regulated so that the temperature never rises above 60°. After the addition is complete (Note 3), the mixture is refluxed for 2–3 hours on a hot plate until the unreacted zinc dust collects in balls. The hot solution is then poured through a fine copper

sieve, with stirring, into 30 l. of ice water. The crude product which separates is contaminated with zinc (Note 4). On recrystallization from 1.5 l. of 95% ethanol, 360–390 g. of 2,4-dimethyl-3-acetyl-5-carbethoxypyrrole (m.p. 143–144°) is obtained (55–60% based on the ethyl acetoacetate used) (Note 5). A second recrystallization may be necessary to secure a perfectly white product, but the product of the first recrystallization is sufficiently pure for conversion to kryptopyrrole.

Thirty grams of sodium is dissolved in 430 ml. of absolute ethanol, the last protions by heating under reflux. The hot ethanolic solution is poured into an autoclave (Note 6), 75 g. (0.36 mole) of 2,4-dimethyl-3-acetyl-5-carbethoxypyrrole is stirred in, and 36 ml. of hydrazine hydrate (Note 7) is added. The autoclave is then heated and the mixture kept at 165–170° for 12 hours. After being cooled, the contents of the autoclave are emptied into a 2-l. round-bottomed flask. The autoclave is rinsed with a small amount of absolute ethanol, and these washings are added to the 2-l. flask. Then 50 ml. of water is added, and the ethanol is distilled from a steam bath, followed by steam distillation of the kryptopyrrole. The ethanolic distillate is collected separately. A glass condenser should be used for the steam distillation, as in some runs a white solid which melts around room temperature begins to appear after about 1 l. has distilled. The condenser water is turned off periodically to allow the solid in the condenser to melt. Steam distillation is continued until the drops of distillate are no longer cloudy, that is, after about 1.7 l. has distilled. A slow stream of nitrogen is passed over the surface of the distillate during the steam distillation (Note 8).

The ethanolic distillate is diluted to 2 l. with distilled water and extracted with a 500-ml. and then a 300-ml. portion of ether. The steam distillate is extracted twice with this ether extract, and twice more with 250-ml. portions of fresh ether. The ether extracts are combined and dried with 150 g. of anhydrous sodium sulfate. The space above the solution is filled with nitrogen. The ether solution is decanted, and the sodium sulfate is washed three times with distilled ether. The ether is then distilled, the temperature of the bath about the flask being raised finally to 130°. The kryptopyrrole is then fractionated under reduced pressure (Note 9). The yield of water-white product boiling within a 1.5° range (85.5–87°/12.5 mm.; 92.5–94° /18 mm.) is 22–25.5 g. (50–58%).

2. Notes

1. The ester used was a commercial product and was not further purified.
2. The zinc dust should be at least 80% pure.
3. Before the reaction mixture is refluxed, enough time should be allowed for the zinc dust to react completely; otherwise considerable trouble with foaming may be encountered.
4. The crude pyrrole darkens on exposure to light, especially when exposed to direct sunlight. The recrystallized product is unaffected by light.
5. The preparation can be carried out in larger or smaller quantities with proportionate amounts of materials and volumes of containers without affecting the yield. The amounts specified here are 60% of those used by the submitter.
6. The checkers used a steel hydrogenation bomb with a void of 650 ml. from which the inside bent steel tube leading to the gauge assembly was removed. A steel plug was inserted in the opening which usually carries a gauge. The temperature was controlled by an automatic regulator, and the reaction mixture was not shaken or stirred.
7. Hydrazine hydrate may be prepared by the ammonolysis of hydrazine sulfate,[1] followed by the addition of water.
Liquid ammonia is placed in a 1-pint thermos bottle, and 60 g. of Eastman's hydrazine sulfate is added in small portions while the liquid is stirred mechanically. After the addition is complete, stirring is continued for 30 minutes. The mixture is filtered into another thermos bottle through a fluted filter paper, and the remaining solid is washed twice with liquid

ammonia by transferring it back to the original flask, stirring, and again filtering. On evaporation of the liquid ammonia 7.5–10 g. of colorless liquid is left, 51–68% calculated as anhydrous hydrazine. Five milliliters of water is then added. Three to four such runs are required to obtain the hydrazine hydrate needed in this preparation.

8. Kryptopyrrole is very sensitive to oxidation and should be handled with a minimum amount of exposure to the air. It is best stored in sealed glass tubes. If a capillary ebullition tube is used during distillation under reduced pressure, the tube should be connected to a supply of nitrogen.

9. A Vigreux, a modified Widmer, or other column may be used for this separation.

3. Discussion

Kryptopyrrole has been obtained by the degradation of bilirubin, hemin, rhodoporphyrin, etc.[2] The synthesis given above is based upon the work of Knorr and Hess.[3]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

HEMIN

Kryptopyrrole

bilirubin

rhodoporphyrin

ethanol (64-17-5)

acetic acid (64-19-7)

ammonia (7664-41-7)

ether (60-29-7)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

sodium nitrite (7632-00-0)

zinc (7440-66-6)

sodium (13966-32-0)

hydrazine hydrate (7803-57-8)

Ethyl acetoacetate (141-97-9)

Hydrazine sulfate (10034-93-2)

hydrazine (302-01-2)

Acetylacetone (123-54-6)

Pyrrole, 2,4-dimethyl-3-ethyl (517-22-6)

2,4-Dimethyl-3-acetyl-5-carbethoxypyrrole (2386-26-7)

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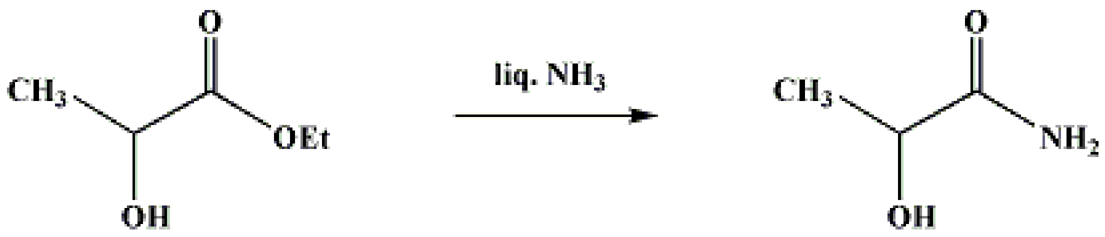
Organic Syntheses, CV 3, 516

LACTAMIDE



Submitted by J. Kleinberg and L. F. Audrieth.
Checked by Homer Adkins and William H. Bateman.

1. Procedure

One hundred and twenty-five grams (1.06 moles) of ethyl lactate is placed in a suitable Pyrex container which is subsequently cooled in a Dry Ice-acetone bath. When the ester has been cooled below the boiling point of ammonia (Note 1), 125 ml. of liquid ammonia (Note 2) is added. The mixture is then placed in a specially constructed steel pressure apparatus (Note 3) and permitted to come to room temperature. After 24 hours (Note 4) the excess of ammonia is allowed to escape slowly through the gas outlet of the bomb. The last traces of ammonia are removed under reduced pressure. The reaction product is stirred with 200 ml. of absolute ether to dissolve unchanged ester and ethanol. The residue is filtered, washed with ether, and air-dried. The yield of lactamide melting at 74–75° amounts to 65–70 g. (70–74%) (Note 5).

2. Notes

1. Care must be taken to cool the ester below the boiling point of ammonia before addition of the ammonia, to avoid loss of ester by spattering.
2. For manipulative procedures employing liquid ammonia see Franklin, *The Nitrogen System of Compounds*, A.C.S. Monograph 68, Appendix, Reinhold Publishing Corporation, New York, 1935; also, Fernelius and Johnson, *J. Chem. Education*, 6, 441 (1929).
3. The steel bomb in which the reaction is carried out is depicted in .htmFig. 16. It consists of a cylindrical tube (A) of ordinary steel to which a steel bottom (B) has been welded. A 1-in. flange (C) is welded to the top of the container extending about 3/16 in. above the top of the bomb. The lead gasket (D) is pressed into the groove (E) when the cover of stainless steel is tightened by means of six steel bolts (G). The top (F) is machined to make a tight seal on the gasket (D). A -in. steel Hoke ammonia valve serves as the gas outlet. The cross-sectional dimensions are noted in the diagram. The checkers carried out the reaction in a glass beaker which was set in a steel reaction vessel such as is used for hydrogenations at pressures of 50–500 atm.[1]

Fig. 16.

Fig. 16.

4. Increase in reaction time causes no appreciable increase in yield of amide.

5. This method has been used for the preparation of numerous amides.[2] However, with many esters it is necessary to heat the reaction mixture to 200–250° for a few hours. Ethyl mandelate is like ethyl lactate in that it gives a good yield (75–80%) of mandelamide at room temperatures.

3. Discussion

Lactamide has been prepared by the action of ammonia on ethyl lactate,[3] methyl lactate,[4] lactic anhydride,[5] lactide,[6] and the condensation product of lactic acid with acetone.[7] In general, amides have been prepared by the reaction of liquid ammonia with esters at temperatures varying from –33° to 250°.[2,8,9]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 85

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

ammonia (7664-41-7)

ether (60-29-7)

acetone (67-64-1)

ethyl lactate (687-47-8)

lactic acid (50-21-5)

Methyl lactate (547-64-8)

Lactamide (2043-43-8)

Ethyl mandelate (4358-88-7)

Mandelamide (4410-31-5)

lactic anhydride

lactide (95-96-5)

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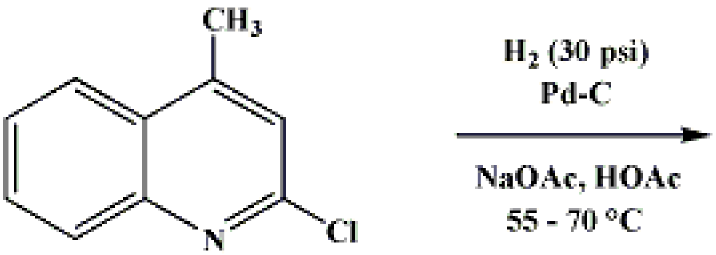
Organic Syntheses, CV 3, 519

LEPIDINE



Submitted by Fred W. Neumann, Nolan B. Sommer, C. E. Kaslow, and R. L. Shriner.
Checked by Cliff S. Hamilton and Robert F. Coles.

1. Procedure

In a 500-ml. Erlenmeyer flask are placed 20 g. (0.11 mole) of pure 2-chlorolepidine[1] (Note 1), 9.3. g. (0.11 mole) of powdered anhydrous sodium acetate, and 200 ml. of glacial acetic acid. The mixture is heated to about 70° and shaken until solution is complete. The solution is transferred to a pressure bottle of an apparatus for catalytic reduction,[2] equipped with a heating element and a variable resistance. The flask is rinsed with two 10-ml. portions of hot glacial acetic acid. Then 3 g. of palladium on carbon is added (Note 2), the bottle is attached to the shaking machine, and the variable resistance is adjusted until the temperature of the liquid is between 55° and 70° (Note 3). The bottle is swept out with hydrogen, an initial pressure of about 1.8–2.2 atm. (26–33 lb.) is applied, and the shaking is started. Hydrogen absorption is rapid during the first 15 minutes and then gradually slackens; the theoretical amount is absorbed in 1.5–2 hours. To ensure complete reduction, shaking is continued an additional 30 minutes. The warm acid solution is separated from the catalyst by filtration through a 1- to 2-mm. layer of Norit on a Büchner funnel. The bottle and funnel are washed with three 30-ml. portions of glacial acetic acid. The acetic acid is removed from the combined filtrates by heating to 70° under reduced pressure (water pump, 25 mm.). The residue is dissolved in 50 ml. of water and transferred to a 500-ml. separatory funnel, an additional 25 ml. of water being used for washing. The water solution is made basic to litmus with 30% sodium hydroxide (about 40–100 ml.) and extracted with one 100-ml. portion of ether and then with two 50-ml. portions. The ether extracts are combined and dried overnight with about 30 g. of solid potassium hydroxide. The ether is removed by distillation from a 250-ml. flask, and the residue is transferred to a modified 50-ml. distilling flask (Note 4), three 5-ml. portions of anhydrous ether being used to ensure complete transference. After the ether is removed, the residue distils at 126–127°/14–15 mm. The product is colorless, water clear, and weighs 13–14 g. (81–87%) (Note 5) and (Note 6).

2. Notes

1. Pure 2-chlorolepidine, m.p. 58–59°, should be used.
2. The catalyst is previously prepared in an apparatus for catalytic hydrogenation,[2] in which are placed 0.5 g. of palladous chloride, 3.0 g. of Norit, and 20 ml. of distilled water. The bottle is swept out with hydrogen and then shaken with hydrogen for 2–3 hours at 2–3 atm. (40 lb.) pressure. The palladium on carbon is collected on a Büchner funnel, washed with five 50-ml. portions of distilled water, then with five 50-ml. portions of 95% ethanol, and finally twice with ether. Upon drying, about 3 g. of the catalyst is obtained. It is stored in a vacuum desiccator over solid sodium hydroxide. If the reduction of the chlorolepidine does not proceed normally, the used catalyst should be removed by suction filtration and a fresh 3-g. portion of catalyst added. Failure of the reduction step is usually due to an inactive catalyst or to impurities in the acetic acid or chlorolepidine. The palladium catalysts, prepared as described elsewhere in this volume, are also satisfactory for the reduction of 2-chlorolepidine.
3. The reduction does not proceed smoothly at room temperature with the palladium catalyst. Raney nickel may be used as a catalyst with ethanol containing potassium hydroxide at room temperature, but about 15 hours is required for reduction.
4. The submitters used a special flask having the shape and dimensions shown in .htmFig. 17. The two necks were wrapped with asbestos cord. The checkers used an ordinary Claisen flask (50 ml.).

Fig. 17.

Fig. 17.

5. By distillation of the crude product from four runs, a yield of 92% was obtained.
6. The submitters have followed the same procedure in preparing the compounds listed below from the corresponding 2-chloro derivatives. The ether extractions and distillation steps were omitted when solid products were obtained.

	Product		
	%	%	
Compound	*Crude*	*Purified*	*B.P. or M.P.*
6-Methyllepidine	100	87	B.p. 137°/12 mm.
8-Methyllepidine	94	90	M.p. 54–55°
5,8-Dimethyllepidine	96	86	B.p. 154–56°/13 mm.
6,8-Dimethyllepidine	100	91	M.p. 55–56°

6-Methoxylepidine monohydrate	100	80	M.p. 50–52°
5,8-Dimethoxylepidine	98	90	M.p. 94–95°
2-Methyl-6-methoxyquinoline *	96	..	M.p. 62–65°

* From 2-methyl-4-chloro-6-methoxyquinoline.

3. Discussion

The process described above is essentially that of Ainley and King,[3] who prepared 6-methoxylepidine. Lepidine has also been prepared by the reduction of 2-chlorolepidine with hydrogen and Raney nickel,[4] with tin[5,6,7 8] or zinc[7] and hydrochloric acid, and with concentrated hydriodic acid and red phosphorus;[9] by the reduction of 2-iodolepidine with iron and dilute sulfuric acid;[10] by the zinc dust distillation of 2-hydroxy-4-methylquinoline under reduced pressure[11] or of 2-hydroxy-3-cyano-4-methylquinoline;[12] by the reduction of 2-hydroxy-4-methylquinoline with concentrated hydriodic acid and red phosphorus;[13] by the distillation of 1,2,3,4-tetrahydroquinoline-4-carboxylic acid with zinc dust in a stream of hydrogen;[14] by decarboxylation of 4-methylquinoline-2-carboxylic acid;[15] by leading vapors of aniline and crotonaldehyde over a contact catalyst at above 500°;[16] by heating aniline and vinyl methyl ketone with sulfuric acid and nitrobenzene;[17] by heating aniline and β-hydroxyethyl methyl ketone in the presence of concentrated sulfuric acid and nitrobenzene[18] or aniline hydrochloride and ethanol;[19] by heating aniline and β-chloroethyl methyl ketone in the presence of concentrated hydrochloric acid and nitrobenzene or arsenic acid[20,21] or in the presence of aniline hydrochloride, ethanol, and nitrobenzene;[22] by heating a mixture of acetone, formaldehyde, and aniline hydrochloride;[23,24] by passing vapors of acetylene and aniline over aluminum oxide at 360–420°;[25] and by passing vapors of aniline and acetaldehyde or paraldehyde over aluminum oxide in a copper tube at 480°.[26] Campbell and Schaffner[27] have described the preparation of lepidine in 70–73% yields by the reaction of aniline hydrochloride with methyl vinyl ketone, 1,3,3,-trimethoxybutane, or 1-methoxybutanone-3 in ethanol in the presence of ferric and zinc chloride.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

red phosphorus

ferric and zinc chloride

ethanol (64-17-5)

acetaldehyde (75-07-0)

sulfuric acid (7664-93-9)

acetylene (74-86-2)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ether (60-29-7)

sodium acetate (127-09-3)

aniline (62-53-3)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

formaldehyde (630-08-0)

iron (7439-89-6)

aniline hydrochloride (142-04-1)

tin (7440-31-5)

arsenic acid (1327-52-2)

Raney nickel (7440-02-0)

acetone (67-64-1)

carbon, Norit (7782-42-5)

potassium hydroxide (1310-58-3)

zinc (7440-66-6)

palladium (7440-05-3)

Nitrobenzene (98-95-3)

hydriodic acid (10034-85-2)

palladous chloride

aluminum oxide (1344-28-1)

Lepidine (491-35-0)

2-Chlorolepidine, chlorolepidine (634-47-9)

2-hydroxy-4-methylquinoline (607-66-9)

β-hydroxyethyl methyl ketone (590-90-9)

2-methyl-4-chloro-6-methoxyquinoline (50593-73-2)

6-Methyllepidine (826-77-7)

8-Methyllepidine (13362-80-6)

5,8-Dimethyllepidine

6,8-Dimethyllepidine

6-Methoxylepidine monohydrate

5,8-Dimethoxylepidine

2-Methyl-6-methoxyquinoline (1078-28-0)

6-methoxylepidine (41037-26-7)

2-iodolepidine

2-hydroxy-3-cyano-4-methylquinoline

1,2,3,4-tetrahydroquinoline-4-carboxylic acid

4-methylquinoline-2-carboxylic acid

crotonaldehyde (123-73-9)

vinyl methyl ketone, methyl vinyl ketone (78-94-4)

β-chloroethyl methyl ketone (6322-49-2)

1,3,3,-trimethoxybutane (6607-66-5)

1-methoxybutanone-3 (6975-85-5)

paraldehyde (123-53-7)

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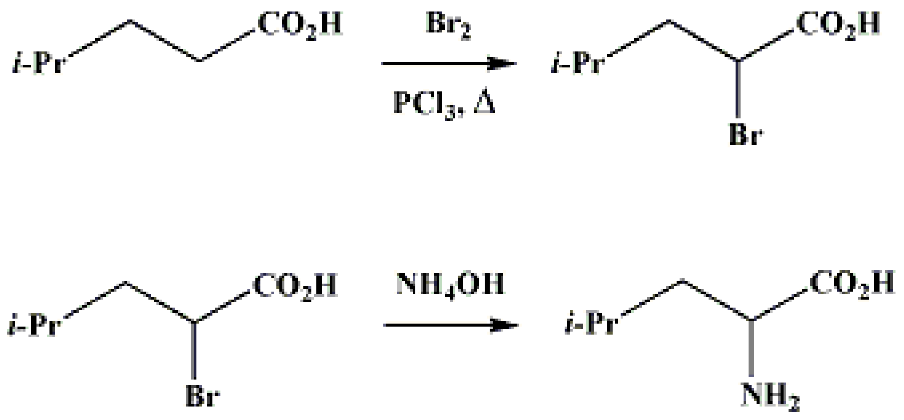
dl-LEUCINE

[Isocaproic acid, α-amino]



Submitted by C. S. Marvel[1]
Checked by Homer Adkins and Robert Gander.

1. Procedure

A. *α-Bromoisocaproic acid.* Five hundred grams (4.3 moles) of commercial isocaproic acid is mixed with 250 ml. of benzene in a 2-l. round-bottomed flask, and the water and benzene are removed by distillation through a short column until the temperature of the vapors reaches 100°. The temperature rises rapidly as soon as the last of the benzene is removed. The residual acid is cooled to room temperature, 743 g. (4.65 moles, 243 ml.) of dry bromine (Note 1) is added, and the flask is fitted with a long condenser and placed in an oil bath. The top of the condenser is connected to an empty 500-ml. Erlenmeyer flask which acts as a safety flask, and this in turn leads to a gas-absorption trap (Note 2). Ten milliliters of phosphorus trichloride is added to the mixture through the top of the condenser, and the flask is heated to 80–85°. The bromination proceeds smoothly at this temperature and is allowed to continue for 8–15 hours until the dark red color of bromine disappears from the condenser. When it has, the temperature is raised to 100–105° and kept there 2 hours. The contents of the flask are transferred to a 1-l. modified Claisen flask or a flask attached to a Widmer column and distilled. The fraction boiling at 125–131°/12 mm. is collected. The yield amounts to 530–550 g. (63–66%). The low-boiling fraction is mainly isocaproic acid (Note 3).

B. *dl-Leucine*. To 1.5 l. of technical ammonium hydroxide (sp. gr. 0.90) in a 3-l. round-bottomed flask is added 300 g. (1.56 moles) of α-bromoisocaproic acid. A rubber stopper is wired in, and the flask is allowed to stand for a week at room temperature. The crude leucine from four such flasks is collected on a filter and washed with 400 ml. of ethanol. This crop amounts to about 300 g. The ammonia is removed from the filtrate by heating the solution in a 12-l. flask on a steam cone overnight. The solution is concentrated under reduced pressure until vigorous bumping occurs (about 2.5 l.).

The mixture is then cooled to about 15° and filtered. The precipitate is washed with 250 ml. of cold water and 250 ml. of 95% ethanol. The total yield of crude leucine in the two fractions is 440–460 g.

The amino acid is recrystallized by dissolving all the crude material in 12.5 l. of water heated to 95° on a steam cone. The hot solution is treated with 20 g. of Norit for 30 minutes and filtered hot. An equal volume of 95% ethanol is added immediately, and the flask is placed in the ice chest overnight. The crystalline material is collected on a filter and washed with 200 ml. of 95% ethanol. The yield of pure leucine in this fraction is 290–300 g. An additional crop is obtained by evaporating the mother liquors under reduced pressure until considerable solid separates (liquid volume about 1 l.), adding an equal volume of ethanol, and cooling. This crop is washed with 100 ml. of cold water and then with 200 ml. of ethanol; it amounts to 60–65 g. The total yield of pure leucine is 350–365 g. (43–45%). It decomposes at 290–292° (uncor.) in a sealed capillary (Note 4).

2. Notes

1. The bromine is dried by shaking with 500 ml. of C.P. concentrated sulfuric acid.
2. The hydrogen bromide may be collected in water and distilled to give constant-boiling hydrobromic acid. See *Org. Syntheses* Coll. Vol. **1**, 26 (1941).
3. The low-boiling fractions (105–115 g.) may be combined with the next portion of acid to be brominated, or several such fractions may be collected and brominated together. If this last is done only two-thirds as much bromine is used as in the original run.
4. The amino nitrogen content of leucine prepared in this way checks with the theoretical value.

3. Discussion

dl-Leucine has been prepared by the hydrolysis of isobutylhydantoin with barium hydroxide;[2] by reduction and hydrolysis of α-oximinoisocaproate; [3] by racemization of *l*-leucine;[4] by the action of ammonia and hydrogen cyanide on isovaleraldehyde followed by hydrolysis;[5] by the action of heat on isobutylmalonylazidic acid followed by hydrolysis; [6] by the action of ammonia on α-bromoisocaproic acid;[7] by the condensation of isobutyl halides and sodio aminomalonic ester[8] or sodio benzoylaminomalonic ester[9] followed by hydrolysis; by the condensation of isobutyraldehyde and hippuric acid followed by reduction and hydrolysis,[10] by reduction of α-ketoisocaproic acid phenylhydrazone;[11] by the action of sodium hypobromite on ethyl isobutylmalonamate;[12] by the action of hexamethylene tetramine on α-chloro and α-bromoisocaproic acids;[13] and by hydrogenation and

subsequent hydrolysis of methallyl acetamidomalonic ester.[14] The method described above is essentially that of Fischer[7] and is the cheapest and best procedure for the synthesis of large amounts of this amino acid.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

sulfuric acid (7664-93-9)

ammonia (7664-41-7)

Benzene (71-43-2)

hydrogen cyanide (74-90-8)

HYDROBROMIC ACID, hydrogen bromide (10035-10-6)

bromine (7726-95-6)

Norit (7782-42-5)

phosphorus trichloride (7719-12-2)

ammonium hydroxide (1336-21-6)

barium hydroxide (17194-00-2)

Hippuric acid (495-69-2)

hexamethylene tetramine (100-97-0)

sodium hypobromite

α-Bromoisocaproic acid (49628-52-6)

isobutyraldehyde (78-84-2)

Isocaproic acid, α-amino, DL-Leucine (328-39-2)

leucine, l-leucine (61-90-5)

isocaproic acid (646-07-1)

isobutylhydantoin

α-oximinoisocaproate

isovaleraldehyde (590-86-3)

isobutylmalonylazidic acid

α-ketoisocaproic acid phenylhydrazone

ethyl isobutylmalonamate

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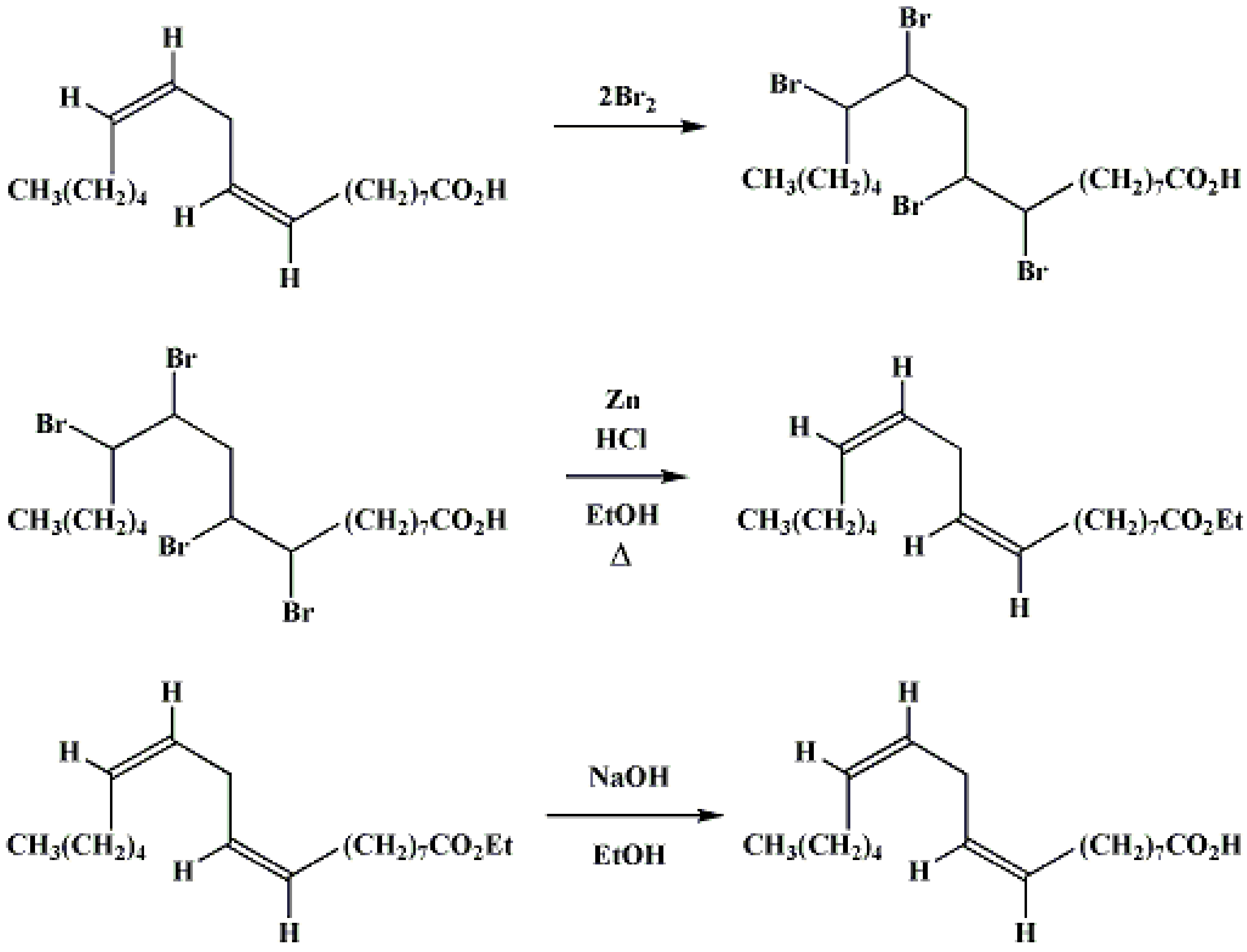
Organic Syntheses, *CV 3, 526*

LINOLEIC ACID



Submitted by J. W. McCutcheon
Checked by R. L. Shriner and S. P. Rowland.

1. Procedure

A. *Fatty acids*. In a 1-l. Erlenmeyer flask are placed 250 ml. of dynamite-grade glycerin (Note 1) and 40 g. (0.71 mole) of potassium hydroxide. The mixture is heated to 120–140° and is shaken by hand until the alkali is dissolved. To the hot solution there is added, in one portion (Note 2), 110 ml. (100 g., 0.11 mole) of sunflower-seed oil (Note 3) and (Note 4) which has been preheated to 110–115°. The hot solution is swirled vigorously until saponification is complete (Note 5). This is indicated by the formation of a permanent lather. After the mixture has cooled somewhat, 150 ml. of sulfuric acid (25% by volume) is added cautiously (Note 6) while the flask is swirled. Then 200 ml. of hot water is added, and, if necessary, the mixture is heated until the layer of fatty acid is clear. The water layer is removed, the acid layer is washed with two 500-ml. portions of hot water, and then it is filtered with the aid of suction through a large Hirsch funnel which is heated by a steam or hot-water jacket. The acids (90–95 g.) (Note 7) are dried thoroughly by heating them rapidly to 130°, with stirring.

B. *Tetrabromostearic acid*. In a 4-l. beaker equipped with a mechanical stirrer the above fatty acids are dissolved in 2 l. of petroleum ether (Note 8), and the solution is chilled to 0–10°.

After 20–25 minutes, the solution deposits about 10 g. of solid saturated fatty acids, which are removed by rapid filtration with gentle suction. The filtrate is transferred to the 4-l. beaker and cooled to 0–10°. Then, with stirring, 30.7 ml. (90 g., 0.56 mole) of bromine (Note 9) is slowly introduced from a dropping funnel (Note 10). The bromine is added at such a rate that the temperature remains between 10° and 15°; about 20 minutes is usually required. Tetrabromostearic acid begins to separate toward the end of the addition. The solution, which should contain a slight excess of bromine (reddish color), is allowed to remain in the ice bath for 15–20 minutes (Note 11). The precipitate settles rapidly, and a large portion of the liquid is removed by decantation, after which the precipitate is finally collected with suction on a 12.5-cm. Büchner funnel and is washed with 200 ml. of petroleum ether. The solid is then thoroughly stirred with 300 ml. of petroleum ether (Note 12) in a 600-ml. beaker and is filtered as before. The gray-white tetrabromide, after being dried at 50°, is transferred to a 2-l. beaker and dissolved in 90–100 ml. of hot ethylene dichloride (Note 13). The solution is filtered through filter paper and allowed to crystallize at room temperature. The solid is removed by filtration and is washed on the funnel with 200 ml. of fresh petroleum ether. The tetrabromide is transferred to a *glass plate* and is worked to a powder (Note 14) with a spatula. The needle-shaped crystals are snow-white, with a silvery sheen, and have a melting point of 114.7–115.2°. The yield (Note 15) is 35–40 g. (32–36%) (Note 16). The product should be stored in brown screw-top bottles and kept away from sunlight.

C. *Ethyl linoleate*. In a 300-ml. Erlenmeyer flask are placed 26–30 g. of recrystallized tetrabromostearic acid, 85 ml. of absolute ethanol, and 30 g. of granulated zinc (20 mesh). This mixture is warmed gently until the debromination reaction begins. Since the reaction is exothermic, it is usually necessary to moderate it from time to time by dipping the flask into a basin of cold water. The vigorous reaction subsides in about 5 minutes, after which the flask is fitted with a reflux condenser and the mixture is refluxed for 30 minutes. In order to esterify the linoleic acid, 10 ml. of a 4 *N* solution of hydrochloric acid in ethanol (Note 17) is poured into the refluxing mixture through the top of the condenser, and successive 5-ml. portions are then added every 30 minutes for 2 hours. At the end of this time the solution is removed from the unchanged zinc by decantation into another flask. The zinc is washed with 15 ml. of absolute ethanol to complete the transfer of the solution. A 10-ml. portion of 4 *N* ethanolic hydrochloric acid is added and the solution is refluxed for an hour, with addition of a second 10-ml. portion of ethanolic acid after 30 minutes. The mixture is poured into 300 ml. of hot, saturated brine solution in a 500-ml. separatory funnel, and the crude ester is allowed to settle for 10–20 minutes. The brine layer is removed, and the ester is washed (Note 18) at room temperature with 300 ml. of 0.5% sodium carbonate solution. The rather stable emulsion is broken by centrifuging the solution, in 100-ml. tubes, for 5 minutes at 3300 r.p.m. The ester and any remaining emulsion are washed with 80 ml. of warm water, and the emulsion is again broken by centrifuging. Washing is continued (Note 19) until the wash water is neutral to methyl orange. The neutral ester is then transferred to a 50-ml. distilling flask and is distilled under reduced pressure; boiling point, 175°/2.5 mm., 193°/6 mm. The product is water-white (Note 20), gives a negative Beilstein test, has an iodine value (Wijs, 30-minute exposure) of 162.3–162.5, an n_D^{48} of 1.4489, and a true specific gravity of 0.8846 at 15.5/4°. The yield (Note 15) is 12–15 g.

D. *Linoleic acid*. The ester is dissolved in 200 ml. of a 5% ethanolic (Note 21) solution of sodium hydroxide in a 400-ml. beaker and is allowed to saponify overnight at room temperature. The resulting jelly is dissolved in 200 ml. of warm water, and a slow stream of carbon dioxide is introduced, beneath the surface of the liquid, while it is acidified with 50 ml.

of dilute sulfuric acid (1:1 by volume). The stream of carbon dioxide is maintained throughout the subsequent operations. The linoleic acid rises to the surface as a clear layer. The water layer is siphoned off; the acid is washed once with hot water and then dried over anhydrous sodium sulfate and preserved under carbon dioxide. The yield is 10–12 g. of material having a melting point of –8° to –9° (Note 22).

2. Notes

1. Dynamite-grade glycerin is specified, because of its high glycerol content (99 plus per cent). Water interferes with the ease of saponification.
2. The oil must not be allowed to run down the side of the flask, as this interferes with complete saponification.
3. The following oils are recommended in decreasing order of preference, the numbers in parentheses indicating the approximate linoleic acid content: sunflower-seed oil (60), poppy-seed oil (60), cotton-seed oil (45).
4. The sample used must have a negative hexabromide test, indicating the absence of acids more highly unsaturated than linoleic. The test is carried out as follows: 2 ml. of the oil and 25 ml. of a 4:1 ethyl ether-glacial acetic acid mixture are chilled to 0° for 15–20 minutes; the mixture is filtered if it is not clear. To this solution is added sufficient bromine to give a deep red color, and the whole is allowed to stand for 15 minutes. The absence of a precipitate constitutes a negative test.
5. Usually 4–6 minutes of vigorous swirling is sufficient, but it may be necessary to reheat the mixture to 150° if difficulty is encountered. Saponification, once started, proceeds to completion within a few seconds. The emulsion thickens to a viscous paste which is transformed into a clear, limpid solution on continued swirling.
6. By adding the acid to the *hot* solution, with vigorous agitation, delay in clearing the fatty acid layer is avoided.
7. When large quantities of the fatty acids are desired, the following method is more economical: In a 5-l. round-bottomed flask, fitted with a mechanical stirrer and a reflux condenser, are placed 1.5 l. of methanol and 350 g. of potassium hydroxide. After solution is complete, 1.1 l. (1 kg.) of cotton-seed oil is added. The solution is stirred and refluxed for 1–2 hours, and then the methanol is removed by distillation. To the residue are added 1 l. of water and (slowly) 1.5 l. of cold 20% sulfuric acid. The fatty acid layer is separated from the water layer, washed with two 1.5-l. portions of hot water, and then filtered with the aid of a hot-water funnel. The acids are dried as described above. The yield is 950–975 g. of crude acids.
8. The petroleum ether used throughout had a boiling range of 40–60°.
9. The weight of bromine is independent of the amount (per cent) of linoleic acid in the sample, but it varies with the iodine value.[1] For the purpose of this preparation, the amount of bromine (grams) may be calculated as 0.7 times the iodine value of the oil. This allows an excess of 10–11%.
10. The tip of the dropping funnel should be just above the fatty acid solution.
11. Tetrabromostearic acid has a decided tendency to form a supersaturated solution in petroleum ether.
12. The solubility of the tetrabromide[2] is about 2–3 g. per l. of petroleum ether at room temperature, hence there is little danger of losing appreciable quantities by solution during the washing.
13. As an alternative but less satisfactory method of purification, the crude tetrabromide may be dissolved in 800 ml. of ethyl ether, filtered, and reprecipitated by stirring the

solution into 800 ml. of petroleum ether. This solution is cooled below 20° and allowed to stand overnight. Ninety per cent of the precipitate will be deposited in 2 hours. The solid is removed by filtration and is washed on the funnel as described above.

14. The ease with which the product dries and powders is an indication of its purity. Usually the material falls apart to a fine white powder at the mere touch of the spatula. A glass spatula should be used in the transfer of the crude material before the recrystallization.

15. These figures are based on the use of sunflower-seed oil containing 57% linoleic acid. With other oils, the yield will be proportionally larger or smaller, depending on the analysis of the oil. Approximate values for three oils may be calculated from the values given in Note 3 above. The yield from cotton-seed oil is 26–30 g. The checkers have brominated about nine times the amounts stated in these directions and have obtained proportionate yields.

16. Two isomers, a solid and a liquid, are formed during the bromination.

17. The 4 *N* ethanolic hydrochloric acid is prepared by passing dry hydrogen chloride gas into slightly warmed absolute ethanol until the calculated increase in weight is obtained.

18. The ester contains about 0.5% of free fatty acid, and for some purposes this is not objectionable, particularly if the acid itself is desired. It is recommended, therefore, that this step be omitted where possible since the yields, particularly from the small batches, may be as low as 80% of the crude ester used. In the absence of an alkaline wash, centrifuging is not necessary, as water alone causes no emulsions to form.

19. Usually three washings are sufficient.

20. A small amount of decolorizing carbon may be added before distillation, but it is usually unnecessary and is to be avoided if possible, for it is likely to cause priming in the still.

21. Ordinary 95% denatured ethanol is satisfactory here.

22. The ester is much more stable toward oxidation than the acid; it is recommended that the material be stored as the ester, and that the acid be prepared only for immediate use. The acid oxidizes to some extent under the best of conditions and, unlike the ester, cannot be distilled without some decomposition. It is for this reason that the constants are determined on the ester rather than on the acid.

3. Discussion

Ethyl linoleate is prepared by debromination of the tetrabromide by action of zinc, or nascent hydrogen from zinc and glacial acetic acid;[3] by zinc and ethanolic-hydrochloric acid;[2,4] and by zinc and ethanolic-sulfuric acid.[5] The pure acid can be obtained by saponification of the ester, by hydrolysis of the hydroxamic acid,[6] and directly by the action of zinc and pyridine (or quinoline, aniline, piperidine) on tetrabromostearic acid.[7] It has also been prepared from 1-iodohexadecadiene-7,10 by condensation with malonic ester and subsequent hydrolysis.[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 531

8

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

brine

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrogen chloride, hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

methanol (67-56-1)

ethyl ether (60-29-7)

aniline (62-53-3)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

glycerol, glycerin (56-81-5)

sodium carbonate (497-19-8)

bromine (7726-95-6)

sodium sulfate (7757-82-6)

ethylene dichloride (107-06-2)

carbon dioxide (124-38-9)

pyridine (110-86-1)

potassium hydroxide (1310-58-3)

zinc (7440-66-6)

piperidine (110-89-4)

Quinoline (91-22-5)

Linoleic acid (60-33-3)

Tetrabromostearic acid (18464-04-5)

Ethyl linoleate (544-35-4)

1-iodohexadecadiene-7,10

methyl orange (547-58-0)

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LINOLENIC ACID

$$CH_3CH_2CH{=}CHCH_2CH{=}CHCH_2CH{=}CH(CH_2)_7CO_2H + 3Br_2 \longrightarrow CH_3CH_2CHBrCHBrCH_2CHBrCHBrCH_2CHBrCHBr(CH_2)_7CO_2H$$

$$CH_3CH_2CHBrCHBrCH_2CHBrCHBrCH_2CHBrCHBr(CH_2)_7CO_2H + 3Zn \xrightarrow[HCl]{EtOH} CH_3CH_2CH{=}CHCH_2CH{=}CHCH_2CH{=}CH(CH_2)_7CO_2Et + 3ZnBr_2$$

$$CH_3CH_2CH{=}CHCH_2CH{=}CHCH_2CH{=}CH(CH_2)_7CO_2Et + NaOH \xrightarrow{H_2SO_4} CH_3CH_2CH{=}CHCH_2CH{=}CHCH_2CH{=}CH(CH_2)_7CO_2H + NaHSO_4 + C_2H_5OH$$

Submitted by J. W. McCutcheon
Checked by R. L. Shriner and S. P. Rowland.

1. Procedure

A. *Fatty acids* .The procedure outlined for linoleic acid (p. 526) is followed, omitting (Note 3) and (Note 4). Linseed oil is used as the raw material.

B. *Hexabromostearic acid*. In a 4-l. beaker equipped with a mechanical stirrer (Note 1), 90–95 g. of the fatty acids is dissolved in 2.5 l. of ethyl ether, and the solution is chilled to 0–10°. Then, with stirring, 35 ml. of bromine (Note 2) and (Note 3) is introduced slowly, from a dropping funnel (Note 4), at such a rate that the temperature does not exceed 20°; about 50 minutes is usually required. The solution, which must contain an excess of bromine (deep red color), is allowed to stand in an ice bath at 0–10° overnight. The excess bromine is removed by addition of a small amount of amylene, and then the white precipitate is collected with suction on a 12.5-cm. Büchner funnel and is washed with 200 ml. of ethyl ether. The hexabromide is thoroughly stirred with 300 ml. of ethyl ether in a 600-ml. beaker and is filtered as before. The yield is 20–22 g. of gray-white hexabromostearic acid (Note 5). It is recommended that 100 g. of the crude hexabromide (Note 6) be accumulated before proceeding to the next step.

In a 1-l. beaker 100 g. of crude hexabromostearic acid is heated to 70–80° with 600 ml. of dioxane (Note 7). The mixture is filtered, and the filtrate is set aside at 15–20° for several hours or preferably overnight. The precipitate is collected on a Büchner funnel with gentle suction and is washed thoroughly on the funnel with several 300-ml. portions of ethyl ether. The hexabromide is then transferred to a glass plate and spread out with a glass spatula to dry in the air. The fine snow-white crystals weigh 80 g. and melt at 181.5–181.9° (Note 8).

C. *Ethyl linolenate*. In a 1-l. Erlenmeyer flask 80 g. of the pure hexabromide is dissolved

in 190 ml. of absolute ethanol, and 40 g. of granulated zinc (20 mesh) is added. The mixture is refluxed for 1 hour, at the end of which time the solution should be clear. About 10 g. of zinc dust is added, refluxing is continued for a short time, and then 10 ml. of 4 *N* ethanol-hydrochloric acid (p. 530) is added. Refluxing is continued for 6 hours, and during this time 5 ml. of the ethanolic hydrochloric acid is added every 30 minutes. At the end of 6 hours, the solution is removed from the unchanged zinc by decantation into another flask, and the zinc is washed with 15 ml. of absolute ethanol to complete the transfer of the solution. A 10-ml. portion of ethanolic hydrochloric acid is added, and the solution is refluxed for a period of 3 hours, with addition of 5-ml. portions of ethanolic hydrochloric acid at 30-minute intervals. The mixture is poured into 500 ml. of hot saturated brine solution in a 1-l. separatory funnel, and the crude ester is allowed to settle for 10–20 minutes. The brine is removed, and the ester is washed (Note 9) at room temperature with 500 ml. of 0.5% sodium carbonate solution. The rather stable emulsion is broken by centrifuging the mixture for 5 minutes at 3300 r.p.m The ester and any remaining emulsion are washed with 150 ml. of warm water, and the emulsion is broken by centrifuging. Washing (Note 10) is continued until the wash water is neutral to methyl orange. The neutral ester is distilled under reduced pressure. It boils at 174°/2.5 mm. and 198°/6.5 mm.

D. *Linolenic acid*. The ester is dissolved in 400 ml. of a 5% ethanolic solution of sodium hydroxide in a 1-l. beaker, and the solution is allowed to stand overnight at room temperature. The resulting jelly is dissolved in 400 ml. of warm water, and a slow stream of carbon dioxide is introduced beneath the surface of the liquid while it is acidified with 50 ml. of dilute sulfuric acid (1:1 by volume). The stream of carbon dioxide is maintained throughout the subsequent operations. The linolenic acid rises to the surface as a clear layer, which is washed once with hot water. The acid is dried over anhydrous sodium sulfate and is preserved under carbon dioxide. The yield of acid is 22–24 g., and the product has a melting point of −17° to −16° (Note 11).

2. Notes

1. In order to guard against fire hazard it is advisable to use hand stirring when proper safety equipment is not available.
2. Care must be observed that the stopcock does not slip out of place.
3. The weight of bromine is independent of the amount (per cent) of linolenic acid in the sample, but it varies with the iodine value. For the purposes of this experiment the amount of bromine (grams) may be calculated as 0.7 times the iodine value of the oil. This allows an excess of 10–11%.
4. The tip of the dropping funnel should be just above the fatty acid solution in order to avoid plugging the exit.
5. The yield is based on a linseed oil containing approximately 45% of linolenic acid. Because of the formation of stereoisomers, only 25% of the bromoacid is precipitated in the solid form. By using water-white distilled linseed fatty acids, obtained from Archer-Daniels-Midland Company, Minneapolis, Minnesota, the yield of solid bromoacid may be increased to 48–53 g.
6. The theoretical yield of the ethyl ester from 20 g. of pure hexabromide is 8 g. Losses through recrystallization, distillation, etc., amount to approximately 50%;

hence the actual yield is about 4 g. of ester.
7. The by-product, insoluble in dioxane, is heptabromostearic acid. If the solution is yellow at this point, a small amount of decolorizing charcoal should be added.
8. The melting point varies with the rate of heating. Any uniform method of taking the melting point may be adopted. It has been found convenient to insert the capillary tube in the bath when the temperature is 5° below the expected melting point, and then to raise the temperature 1° per minute.
9. The ester contains about 0.5% of free fatty acid, and for some purposes this is not objectionable, particularly if the acid itself is desired. It is recommended, therefore, that this step be omitted where possible, since the yields, particularly from small batches, may be as low as 80% of the crude ester used. In the absence of an alkaline wash centrifuging is not necessary, as water alone causes no emulsions to form.
10. Usually three washings are sufficient.
11. The ester is much more stable toward oxidation than the acid; it is recommended that the material be stored as the ester, and that the acid be prepared only for immediate use. The acid oxidizes to some extent under the best of conditions and, unlike the ester, cannot be distilled without some decomposition. It is for this reason that the constants are determined on the ester rather than on the acid.

3. Discussion

Linolenic acid is always obtained from natural sources, chiefly from the oils of various seeds, such as hemp seed,[1] walnut,[2] poppy seed,[2] cotton seed,[2] and, best of all, linseed.[3,4] The crude acid has been purified via the solid hexabromide, either directly,[5,6,7] or by the hydrolysis of the methyl or ethyl ester, obtained by simultaneous debromination and esterification of hexabromostearic acid.[5,8] The method described above is a modification[9,10] of the procedure of Rollett.[8] The acid has also been obtained from soy oil and has been purified via the hydroxamic acid.[11]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

brine

ethanolic solution of sodium hydroxide

hydroxamic acid

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ethyl ether (60-29-7)

sodium carbonate (497-19-8)

bromine (7726-95-6)

sodium sulfate (7757-82-6)

carbon dioxide (124-38-9)

zinc (7440-66-6)

dioxane (5703-46-8)

amylene

Linoleic acid (60-33-3)

Linolenic acid (463-40-1)

Hexabromostearic acid

heptabromostearic acid

methyl orange (547-58-0)

Ethyl linolenate (1191-41-9)

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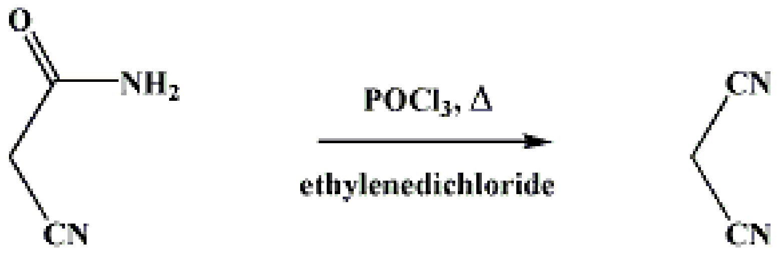
MALONONITRILE



Submitted by Alexander R. Surrey
Checked by C. F. H. Allen and J. VanAllan.

1. Procedure

In a 12-l. three-necked round-bottomed flask, fitted with a powerful stirrer (Note 1) and a reflux condenser, are placed 1260 g. (15 moles) of cyanoacetamide, 1 kg. of salt (Note 2), and 5 l. of ethylene dichloride. After the mixture has been stirred rapidly for 15 minutes, 800 ml. (8.75 moles) of phosphorus oxychloride is added and the mixture is refluxed for 8 hours in an oil bath (Note 3). After the mixture has been cooled to room temperature, it is filtered and the solid is washed with 500 ml. of ethylene dichloride. The solvent is distilled from the combined filtrates in a 12-l. flask, and the residual crude nitrile is decanted into a 1-l. flask (Note 4) from any solid that may have separated. A fractionating column, condenser, and fractionating receiver are attached, and the malononitrile is distilled under reduced pressure. The fraction boiling at 113–118°/25 mm. weighs 570–654 g. (57–66%) (Note 5). This material may be freed from a small amount of phosphorus oxychloride which is present by redistillation. After a fore-run of about 5 ml., the malononitrile distils smoothly at 92–94°/8 mm.

2. Notes

1. A heavy motor-driven stirrer is advisable, because frequently the solid that separates contains some viscous material that makes stirring difficult.
2. The addition of salt gives a lighter-colored, granular solid that can be easily removed by filtration and washed.
3. The reaction can be done in a hood, or the hydrogen chloride that is evolved can be absorbed in a gas trap.
4. Ground-glass equipment is advisable. The fractionating column is the standard modified Claisen type.
5. The submitter obtained a 70–72% yield at this point in a run of this size and 80% yields in small runs. He also obtained yields of the same order by using a mixture of phosphorus oxychloride and a small amount of phosphorus pentachloride.

3. Discussion

In addition to the methods cited previously,[1] malononitrile has been prepared by the dehydration of cyanoacetamide by phosphorus oxychloride either with salt,[2] as in the above procedure, or with sodium metabisulfite.[3] The vapor-phase reaction of cyanogen chloride and acetonitrile has been patented.[4]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium metabisulfite

hydrogen chloride (7647-01-0)

acetonitrile (75-05-8)

phosphorus pentachloride (10026-13-8)

ethylene dichloride (107-06-2)

Phosphorus Oxychloride (21295-50-1)

CYANOACETAMIDE (107-91-5)

cyanogen chloride (506-77-4)

Malononitrile (109-77-3)

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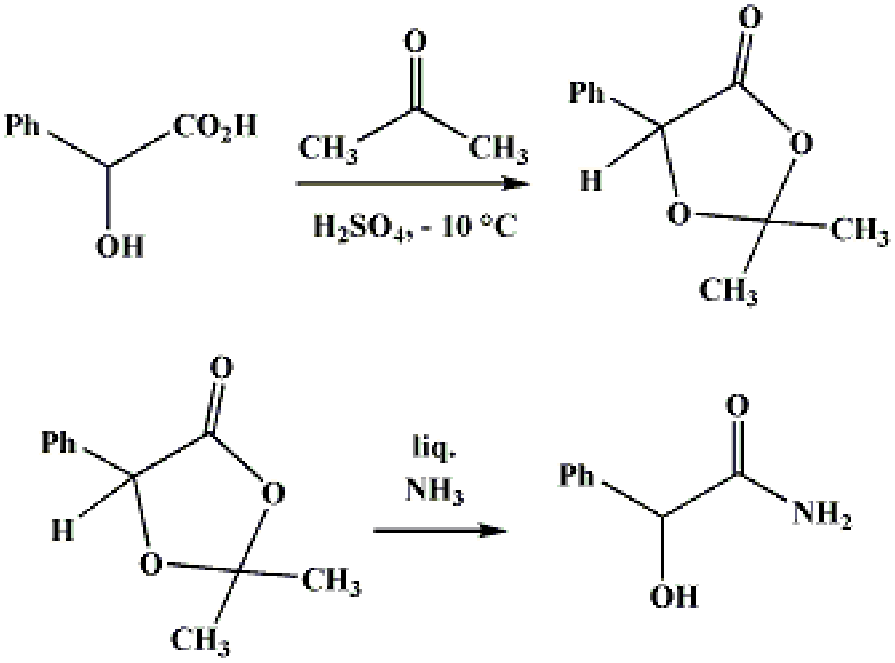
Organic Syntheses, CV 3, 536

MANDELAMIDE



Submitted by L. F. Audrieth and M. Sveda.
Checked by Homer Adkins and William H. Bateman.

1. Procedure

One hundred and forty-six grams (0.96 mole) of mandelic acid is dissolved in 440 ml. (6.2 moles) of acetone, and the resulting solution is placed in a 2-l. three-necked flask fitted with an efficient stirrer, a dropping funnel, and a thermometer. The reaction flask is placed in an ice-salt bath, and 98 g. of concentrated sulfuric acid (sp. gr. 1.84) is added through the dropping funnel at such a rate that the temperature does not exceed −10°. The reaction mixture is then poured into an ice-cold solution of sodium carbonate containing 200 g. of the anhydrous salt in 1800 ml. of water. The mandelic acid-acetone condensation product precipitates from the solution. The curdy product is washed by grinding with ice water (200 ml.) and is then filtered and dried over calcium chloride under reduced pressure. The crude product weighs 181 g. (Note 1).

The mandelic acid-acetone condensation product is added in small portions to about 1.8 l. of liquid ammonia (Note 2) contained in two silvered 1-l. Dewar flasks. Each flask is fitted with a stopper containing a capillary tube to serve as an ammonia outlet. The ammonolysis is allowed to proceed overnight, after which the contents of the flasks are poured into open beakers to facilitate rapid evaporation of the liquid ammonia.

After the ammonia has been removed to a point where a pulverulent mass remains, the product is treated with 475 ml. of hot absolute ethanol and the resulting solution is filtered through a hot funnel to remove insoluble impurities. The filtrate is cooled in an

ice bath to give about 90 g. of glistening white crystals of mandelamide melting at 132° (62% based upon the mandelic acid) (Note 3) and (Note 4).

2. Notes

1. The crude product contains varying quantities of sodium carbonate and sodium sulfate, which are difficult to remove. These impurities are insoluble in liquid ammonia; consequently the crude compound can be ammonolyzed without further purification. The mandelic acid-acetone condensation product may be purified by recrystallization from absolute ethanol; it then melts at 45°.
2. The solubility of the mandelic acid-acetone condensation compound in liquid ammonia at its boiling point is approximately 10 g. per 100 ml.
3. Additional quantities of mandelamide may be obtained by concentrating the ethanolic mother liquor carefully.
4. This method is generally applicable to the preparation of the amides of α-hydroxy acids.

3. Discussion

Mandelamide has been prepared by treating the ethyl ester with concentrated aqueous ammonia,[1,2] and a saturated ethanolic solution of ammonia has been used to effect ammonolysis of the methyl ester.[3] Esters of mandelic acid were treated with liquid ammonia at its boiling point;[4] this procedure was improved by use of ammonia at superatmospheric pressures and higher temperatures.[5] The procedure described in this synthesis was first used by Ôeda.[6]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanolic solution of ammonia

ethanol (64-17-5)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

ammonia (7664-41-7)

Mandelic acid (90-64-2)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

acetone (67-64-1)

Mandelamide (4410-31-5)

mandelic acid-acetone

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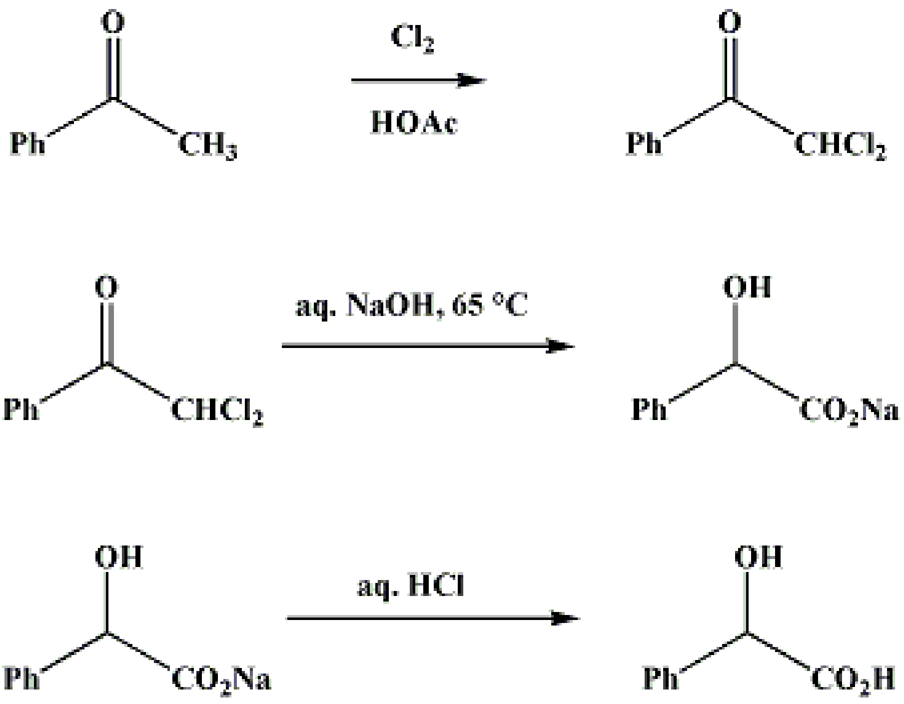
Organic Syntheses, CV 3, 538

MANDELIC ACID



Submitted by J. G. Aston, J. D. Newkirk, D. M. Jenkins, and Julian Dorsky.
Checked by R. L. Shriner and C. H. Tilford.

1. Procedure

A. *Dichloroacetophenone*. A 3-l. round-bottomed flask is fitted with a three-holed rubber stopper through which are passed an inlet tube extending to the bottom of the flask, an outlet tube, and a thermometer. The inlet tube is connected to a cylinder of chlorine through a bubble counter consisting of a 500-ml. wash bottle which contains about 200 ml. of concentrated sulfuric acid. The outlet tube is connected with a gas trap in which the evolved hydrochloric acid is absorbed by running water. It is best to set up the apparatus under a good hood.

In the flask are placed 240 g. (2 moles) of acetophenone and 1 l. of glacial acetic acid. The thermometer is adjusted so that it extends considerably below the surface of the solution, and chlorine is admitted at such a rate that the temperature does not exceed 60° (Note 1). Chlorination is continued until an excess of the halogen has been absorbed. This requires about 5 hours; completion of the reaction is indicated by the development of a yellow color. The reaction mixture is poured over 6 l. of crushed ice in a 2-gal. jar. The mixture is stirred several times (Note 2) and allowed to stand until the ice has melted. The dichloroacetophenone, which separates as a heavy lachrymatory oil, is removed. The yield is 340–370 g. (90–97%). This product, containing only a few per cent of water and acetic acid, is pure enough for the preparation of mandelic acid. It may be purified by adding about 100 ml. of benzene, removing the water and benzene by distillation, and fractionally distilling the residual

oil under reduced pressure. There is obtained 302–356 g. (80–94%) of a colorless oil boiling at 132–134°/13 mm. (142–144°/25 mm.).

B. *Mandelic acid*. In a 2-l. three-necked round-bottomed flask, fitted with an efficient mechanical stirrer, a dropping funnel, and a thermometer, is placed 156 g. (3.9 moles) of sodium hydroxide dissolved in 1.4 l. of water. The solution is warmed to 60° (Note 3), vigorous stirring is begun, and 200 g. (1.06 moles) of dichloroacetophenone (either crude or distilled) is added from the dropping funnel. The dichloroacetophenone is added slowly at first so that the temperature does not exceed 65°. The addition requires about 2 hours (Note 4). Stirring is continued for 1 hour longer while the temperature is maintained at 65° by means of a water or steam bath. After addition of 170 ml. of 12 *M* hydrochloric acid (Note 5), the solution is extracted with ether. The continuous extractor shown in .htmFig. 18 is very useful for this purpose. About 250–300 ml. of ether is used, and the extraction is continued until no more material is obtained. With this apparatus, about 130 g. of crude mandelic acid is recovered after 24 hours, and 150 g. after 48 hours. The volume of liquid in the larger flask must be great enough so that, when 250–300 ml. of ether is used for the extraction, there will be a continuous overflow from the larger to the smaller flask; the latter serves as the "boiler."

Fig. 18.

Fig. 18.

The ether extracts are transferred to a 1-l. round-bottomed flask, the ether is removed by distillation, and the residue of crude mandelic acid is dried by warming it on a steam bath under the vacuum of a water pump. About 400 ml. of benzene is added, and the mixture is distilled until 100 ml. of distillate is collected. The acid in the residual mixture is brought completely into solution by the addition of 6–10 ml. of ethanol. The hot solution is then filtered through a warm Büchner funnel, and the filtrate is cooled overnight at 6°. The first crop of pure mandelic acid weighs 100–120 g. A second crop is obtained by evaporation of the mother liquor to about one-fourth its volume; this weighs 20–40 g. The total yield is 136–144 g. (85–90% based on the dichloroacetophenone, or 76–87% based on the acetophenone). The white crystalline product melts at 115–117° (Note 6).

2. Notes

1. According to Beilstein (**VII**, 283) trichloroacetophenone is obtained by chlorination of acetophenone at elevated temperatures.[1] However, at 60° less than 1% of trichloroacetophenone is formed.
2. Stirring results in a better separation of acetic acid from the oil and prevents the formation of an emulsion.
3. At lower temperatures, hydrolysis is slow.
4. If the temperature becomes much higher, side reactions occur and loss in yield and purity results. The heat of reaction is sufficient to maintain the

required temperature.

5. If the reaction mixture is cooled at this point, some of the mandelic acid may crystallize. If this happens, the precipitate should not be filtered, as it is contaminated with sodium chloride.

6. The submitters report that when 1 kg. of acetophenone is used yields of 0.98–1.06 kg. of mandelic acid are obtained.

3. Discussion

Dichloroacetophenone has been prepared by chlorination of acetophenone with and without aluminum chloride;[2] by action of dichloroacetyl chloride upon benzene and aluminum chloride;[2] by action of hypochlorous acid upon phenylacetylene;[1] by heating trichloromethylphenylcarbinol;[3] and by chlorination of phenylacetylene in alcohol.[4]

Mandelic acid has been prepared by hydrolysis of mandelonitrile (prepared in turn from benzaldehyde and hydrogen cyanide or from benzaldehyde, sodium bisulfite, and sodium cyanide);[5] by action of water at 180° upon trichloromethylphenylcarbinol;[6] by action of potassium carbonate upon a heated mixture of benzaldehyde and chloroform;[7] by action of warm, dilute alkali upon dibromoacetophenone;[8] by the action of warm, dilute sodium hydroxide upon phenylglyoxal;[9] by the hydrolysis of α-bromophenylacetic acid[10] or dimethyl α-cyano-α-hydroxybenzylphosphonate;[11] and by the hydrolysis of ethyl mandelate, prepared in turn by the catalytic reduction of phenylglyoxalate.[12]

α-C^{14}-Mandelic acid has been prepared from α-C^{14}-phenylglyoxal, and from α-C^{14}-α,α-dibromoacetophenone.[13] α-C^{13}-Mandelic acid has been prepared from α-C^{13}-α,α-dibromoacetophenone.[14]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 572

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

α-C^{14}-Mandelic acid

α-C^{14}-phenylglyoxal

α-C^{14}-α,α-dibromoacetophenone

α-C^{13}-Mandelic acid

α-C^{13}-α,α-dibromoacetophenone

ethanol (64-17-5)

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

ether (60-29-7)

sodium hydroxide (1310-73-2)

Mandelic acid (90-64-2)

chloroform (67-66-3)

sodium cyanide (143-33-9)

sodium chloride (7647-14-5)

hydrogen cyanide (74-90-8)

sodium bisulfite (7631-90-5)

benzaldehyde (100-52-7)

Acetophenone (98-86-2)

aluminum chloride (3495-54-3)

chlorine (7782-50-5)

Phenylglyoxal (1074-12-0)

mandelonitrile (532-28-5)

hypochlorous acid (7790-92-3)

Phenylacetylene (536-74-3)

dichloroacetyl chloride (79-36-7)

α-Bromophenylacetic acid (4870-65-9)

Ethyl mandelate (4358-88-7)

dichloroacetophenone (2648-61-5)

trichloroacetophenone (2902-69-4)

trichloromethylphenylcarbinol (2000-43-3)

dibromoacetophenone

dimethyl α-cyano-α-hydroxybenzylphosphonate

phenylglyoxalate

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Organic Syntheses, *CV 3, 541*

D-MANNOSE

$$C_6H_{11}O_5OCH_3 + H_2O \longrightarrow C_6H_{12}O_6 + CH_3OH$$

Submitted by J. T. Sheehan and W. Freudenberg.
Checked by Homer Adkins, Winston Wayne, and Richard Juday.

1. Procedure

A solution of 200 g. (1.03 moles) of α-methyl-*d*-mannoside [*Org. Syntheses* Coll. Vol. **1**, 362 (1932), 371 (1941)] in 3.2 l. of 2 *N* sulfuric acid (178 ml. concentrated sulfuric acid diluted to 3.2 l.) is steamdistilled from a 5-l. flask for 1 hour. The flask is heated externally during this time so that the volume of the solution remains constant. The mixture is transferred to a 2- or 3-gal. crock, 10 g. of decolorizing charcoal (Norit) is added, and the solution is rapidly stirred while it is neutralized (litmus) by the addition of barium carbonate (Note 1).

The mixture is filtered with suction through an asbestos mat supported on a filter paper in a 25-cm. Büchner funnel, and the barium sulfate is washed with two 100-ml. portions of water. The filtrate and washings are combined, and the clear colorless solution of the sugar is concentrated to about 300 ml. under reduced pressure (water pump) on a water bath whose temperature does not exceed 60°. The mixture is filtered, and the solid is washed on the filter with a little water. The combined filtrate and washings are then concentrated to a volume of 100 ml. under the conditions described above. The warm, slightly tan-colored syrup is poured into a 500-ml. Erlenmeyer flask. The transfer is completed by rinsing the distilling flask five times with 40-ml. portions of glacial acetic acid, each portion of the acetic acid being warmed to 50° in the bath before it is transferred. The acetic acid solution of the sugar is seeded with crystalline D-mannose (Note 2), and, after standing overnight at room temperature, the solution is placed in a refrigerator for a day or two.

The crystalline D-mannose is filtered and washed successively with two 20-ml. portions of cold glacial acetic acid, two 20-ml. portions of cold dry ethanol, and three 30-ml. portions of cold, dry ether (Note 3). After drying in the air for 3 days, the product weighs 112 to 115 g. (60%) (Note 4) and melts at 126.5–127.5° (Note 5).

2. Notes

1. The calculated quantity of pure barium carbonate required to neutralize the sulfuric acid is 630 g. However, the checkers found that the mixture was still acid after stirring it for 2–3 hours with 780 g. of carbonate. An additional 100 g. of carbonate was required to bring the mixture to the neutral point. The checkers found that it was preferable to add 975 g. of barium hydroxide [$Ba(OH)_2$·

$8H_2O$], stir for 30 minutes, and then to complete the neutralization by stirring with 75 g. of barium carbonate.

2. Crystallization may be induced by scratching with a glass rod if crystalline D-mannose is not available.

3. The sugar should be ground with each portion of the wash liquid, if the maximum purification with the minimum amount of solvent is to be obtained.

4. The submitters obtained 18–19 g. of crystalline D-mannose from the mother liquors, which increased the yield to about 70% of the theoretical amount.

5. The sugar so prepared is said to be predominately α-D-mannose. If a purer product is desired, the substance may be recrystallized from 80% ethanol. This procedure gives a product which melts at 131–132°; α_D^{23} + 15°. The recovery in this crystallization is about 80%.

3. Discussion

D-Mannose has been prepared by hydrolysis of the mannan in vegetable ivory,[1,2,3] but the crystalline sugar is apparently best obtained from mannan through the isolation of α-methyl-*d*-mannoside.[4] The method described above is similar to that of Hudson and Jackson[4] except that sulfuric acid, rather than hydrochloric acid, is used for hydrolysis of the α-methyl-*d*-mannoside. Levene[5] has described what is probably the best method for the conversion of mannan to D-mannose without the isolation of α-methyl mannoside. The D-mannose obtained by Levene was predominately the β-isomer.

The electrolytic reduction of D-mannonic lactone to D-mannose has been described.[6]

References and Notes

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4. Hudson and Jackson, *J. Am. Chem. Soc.*, **56**, 958 (1934).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

α-METHYL MANNOSIDE

α-methyl-d-mannoside

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ether (60-29-7)

barium sulfate (7727-43-7)

decolorizing charcoal (Norit) (7782-42-5)

barium hydroxide (17194-00-2)

barium carbonate (513-77-9)

D-Mannose

α-d-mannose

d-mannonic lactone

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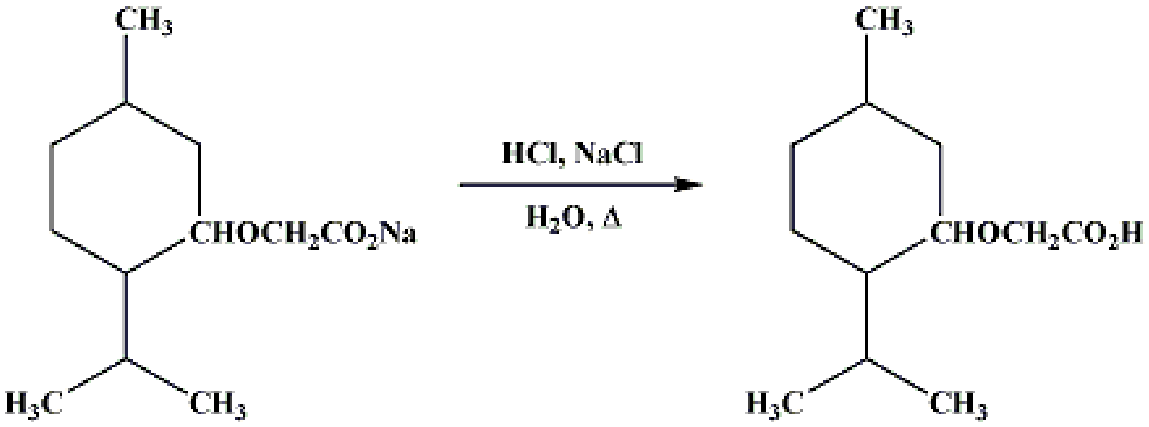
Organic Syntheses, CV 3, 544

l-MENTHOXYACETIC ACID

[Acetic acid, (menthyloxy)-, *l*-]

$$2C_{10}H_{19}OH + 2Na \longrightarrow 2C_{10}H_{19}ONa + H_2$$

$$2C_{10}H_{19}ONa + ClCH_2CO_2H \longrightarrow C_{10}H_{19}OCH_2CO_2Na + C_{10}H_{19}OH + NaCl$$



Submitted by M. T. Leffler and A. E. Calkins.
Checked by R. L. Shriner and C. H. Tilford.

1. Procedure

A 5-l. three-necked round-bottomed flask is fitted with a mechanical stirrer (Note 1) and a reflux condenser bearing a calcium chloride tube. A solution of 400 g. (2.56 moles) of *l*-menthol (crystals, m.p. 41–42°) in 1 l. of dry toluene (Note 2) is placed in the flask, and to it is added 70 g. (3.04 gram atoms) of clean sodium. The third neck of the flask is then tightly closed with a cork stopper, and the flask is heated in an oil bath until the toluene refluxes gently. As soon as the sodium has melted, stirring is begun and is maintained at such a rate that the sodium is broken into fine globules.

After the reaction mixture has been refluxed for 15 hours, the stirrer is stopped, the reaction mixture is allowed to cool, and the excess sodium (Note 3) is carefully removed. The apparatus is then assembled as before (Note 1), but with a 1-l. separatory funnel fitted into the third neck of the flask (Note 4). The temperature of the oil bath is raised to 85–90°, and with continued stirring, a solution of 95 g. (1.01 moles) of monochloroacetic acid (Note 5) in 800 ml. of warm dry toluene is added from the separatory funnel at such a rate that refluxing is not too vigorous. A heavy precipitate of sodium chloroacetate forms immediately. After all the chloroacetic acid has been added, the mixture is refluxed and stirred for 48 hours. During this period, the stirring must be as thorough as possible; it is necessary to add 1–1.5 l. of dry toluene, and the stirrer must be stopped at

frequent intervals while the solid material is removed from the side of the flask.

When the reaction is complete, the flask is removed from the oil bath and the cooled reaction mixture is transferred to a 5-l. separatory funnel and extracted with three 1-l. portions of water (Note 6). The water extract is carefully acidified with 20% hydrochloric acid, and the crude menthoxyacetic acid, which collects on top as a brown oil, is extracted with three 200-ml. portions of benzene. The benzene extracts are combined, and the solvent is removed by distillation on a steam cone. The residue is then fractionally distilled under reduced pressure. The fraction boiling below 100°/20 mm. is mainly water and toluene. The second fraction boiling at 100–115°/8–10 mm. is impure *l*-menthol and may be saved for redistillation (Note 6). The yield of *l*-menthoxyacetic acid, boiling at 134–137°/2 mm. (150–155°/4 mm.), $[\alpha]_D^{2}$ –92.4°, amounts to 166–180 g. (78–84%).

2. Notes

1. The success of the reaction depends largely on the type of agitation used. A stainless-steel stirrer of the anchor type with a gas-tight rubber or metal-graphite bearing serves well because of its strength. It should be operated at high speed in the first part of the reaction in order to powder the sodium; in the second stage vigorous stirring is not so essential, but the solid and liquid phases should be mixed efficiently.
2. The toluene may be dried by refluxing it over metallic sodium for several hours. It is distilled from the sodium into a receiver protected from the air by a calcium chloride tube.
3. The excess sodium should amount to about 11 g. If the sodium remains divided, it is removed by filtering the hot mixture through glass wool.
4. It is not advisable to leave the separatory funnel attached to the flask during the long period of stirring which follows, as the constant, heavy vibration tends to loosen the connection. As soon as it has been used, the funnel should be replaced by a tightly fitting cork stopper.
5. The commercial grade (m.p. 61–63°) of monochloroacetic acid should be ground and thoroughly dried over concentrated sulfuric acid in a vacuum desiccator for 2 days. The yield was lowered by about 10% when the chloroacetic acid was used without previous drying.
6. The toluene layer, containing the menthol formed in the reaction, is saved for the recovery of both the toluene and the menthol, which are separated by distillation under atmospheric pressure. The *l*-menthol collected at 210–212° (cor.) amounts to 150–225 g.

3. Discussion

l-Menthoxyacetic acid has been prepared only by the action of sodium menthoxide upon monochloroacetic acid.[1]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 547

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium menthoxide

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

chloroacetic acid, monochloroacetic acid (79-11-8)

sodium chloroacetate (3926-62-3)

toluene (108-88-3)

sodium (13966-32-0)

menthol, l-menthol (15356-60-2)

menthoxyacetic acid, l-MENTHOXYACETIC ACID, Acetic acid, (menthyloxy)-, l- (40248-63-3)

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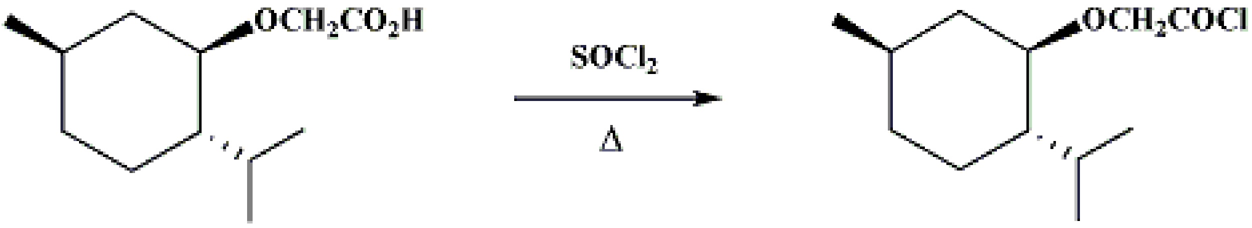
Organic Syntheses, CV 3, 547

l-MENTHOXYACETYL CHLORIDE

[Acetyl chloride, (menthyloxy)-, *l*-]



l - isomer *l* - isomer

Submitted by M. T. Leffler and A. E. Calkins.
Checked by R. L. Shriner and C. H. Tilford.

1. Procedure

A 1-l. three-necked round-bottomed flask is mounted on a steam cone and is fitted with a 250-ml. separatory funnel and a reflux condenser connected to a trap (Note 1) for absorbing gases. In the flask is placed 325 g. (198 ml., 2.73 moles) of thionyl chloride (Note 2), and to it is added, during the course of 1 hour, 125 g. (0.58 mole) of *l*-menthoxyacetic acid (p. 544). The flask is shaken frequently during the addition of the acid and, if necessary, is warmed to start the reaction. When all the acid has been added (Note 3), the reaction mixture is refluxed gently for 5 hours. After the reaction is complete, the excess of thionyl chloride is removed by distillation on the steam bath (Note 4) and the residue is distilled under reduced pressure. The yield of *l*-menthoxyacetyl chloride boiling at 117–120° /3 mm. (120–125° /5 mm.), $[\alpha]_D^{25}$ –89.6°, amounts to 115–118 g. (Note 5) (85–87%). The product turns dark on standing; it should be stored in a glass-stoppered amber bottle.

2. Notes

1. The gas-absorption trap shown in *Org. Syntheses* Coll. Vol. **1**, 97 (1941) may be used.
2. The commercial grade (b.p. 74–78°) of thionyl chloride was used.
3. Owing to the high viscosity of the acid, it is desirable to rinse the separatory funnel with a little thionyl chloride which is then added to the reaction mixture.
4. The recovered thionyl chloride may be redistilled for future runs. It is best to remove the last traces of thionyl chloride by heating the crude product to about 140° under the vacuum of the water pump.
5. The submitters report the same yields (per cent) when twice the amounts of materials are used.

3. Discussion

The procedure given above is adapted from that described by Read and Grubb.[1] No other methods for the preparation of *l*-menthoxyacetyl chloride have been described.

References and Notes

1. Read and Grubb, *J. Soc. Chem. Ind.*, **51**, 330T (1932).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

thionyl chloride (7719-09-7)

l-MENTHOXYACETIC ACID (40248-63-3)

L-Menthoxyacetyl chloride, Acetyl chloride, (menthyloxy)-, l- (15356-62-4)

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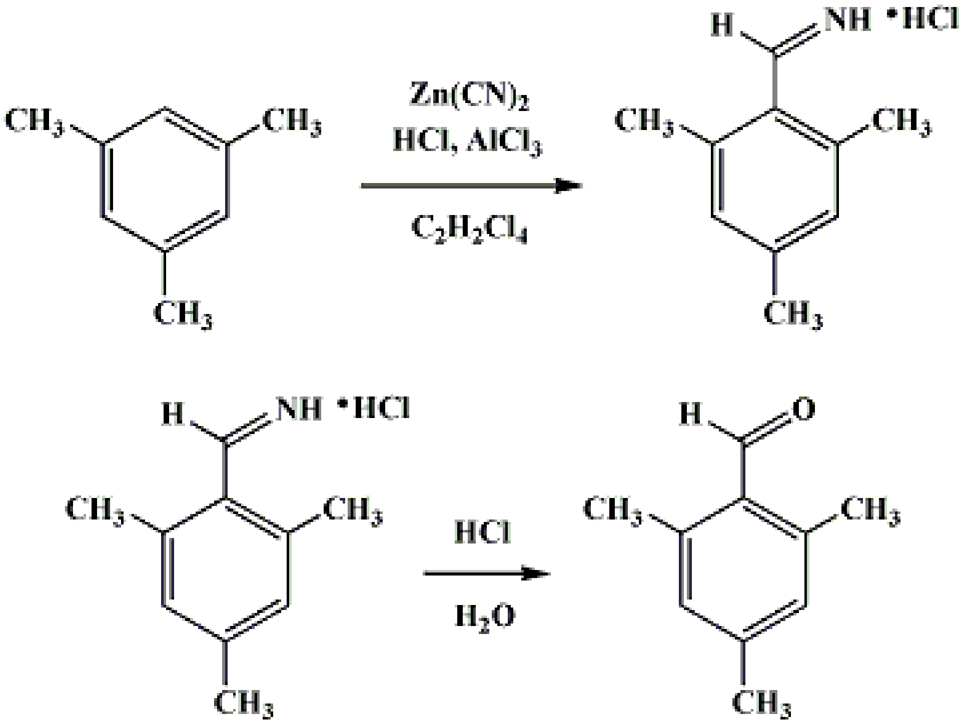
Organic Syntheses, CV 3, 549

MESITALDEHYDE

[Benzaldehyde, 2,4,6-trimethyl-]

[I. METHOD A]



Submitted by R. C. Fuson, E. C. Horning, S. P. Rowland, and M. L. Ward.
Checked by C. F. H. Allen and J. VanAllan.

1. Procedure

In a 1-l. three-necked round-bottomed flask, fitted with an efficient stirrer, a reflux condenser, an inlet tube, and a thermometer (Note 1) and (Note 2), are placed 102 g. (118 ml., 0.85 mole) of mesitylene, 147 g. (1.25 moles) of zinc cyanide (Note 3), and 400 ml. of tetrachloroethane (Note 4). The inlet tube is connected to a source of hydrogen chloride (Note 5), and the mixture is stirred at room temperature while a rapid stream of dry hydrogen chloride is passed through it. This is continued until the zinc cyanide is decomposed; usually about 3 hours is required. The flask is then immersed in an ice bath, the inlet tube is removed, and 293 g. (2.2 moles) of finely ground anhydrous aluminum chloride is added to the mixture (Note 6) and (Note 7), with *very vigorous* stirring. The ice bath is then removed, and the passage of hydrogen chloride is resumed for the remainder of the reaction period. The heat of reaction is sufficient to warm the mixture slowly, and a temperature of about 70° is reached at the end of an hour. A temperature of 67–72° is maintained for an additional 2.5 hours. The cooled mixture is decomposed by pouring it cautiously, with stirring by hand, into a 4-

l. container about half full of crushed ice, to which has been added 100 ml. of concentrated hydrochloric acid. After the mixture has stood overnight, it is transferred to a 3-l. round-bottomed flask and refluxed for 3 hours. The organic layer is then separated, and the aqueous layer is extracted once with 50 ml. of tetrachloroethane. The combined tetrachloroethane solutions are washed with 150 ml. of a 10% solution of sodium carbonate and distilled with steam. The first 800–900 ml. of distillate is set aside for recovery of the solvent (Note 8) and (Note 9), and the second portion is collected as long as oily drops are observed (Note 10). This distillate is extracted with 500 ml. of benzene, the solvent is removed on the steam bath, and the residue is distilled from a 250-ml. modified Claisen flask. After a small fore-run, the mesitaldehyde distils at 118–121°/16 mm. The yield is 95–102 g. (75–81%) (Note 11) and (Note 12).

2. Notes

1. Because of the toxic nature of tetrachloroethane and hydrogen cyanide, *all operations* as far as the final distillation should be carried out in a *good* hood.
2. It is convenient to place the thermometer in the gas inlet tube. The bulb should be immersed in the liquid, but the inlet tube need extend only just below the liquid surface.
3. The zinc cyanide may be commercial material, or it may be prepared as directed by Adams and Levine.[1] However, the zinc cyanide does not react well if it is too carefully purified.[2]
4. Tetrachloroethane is a toxic substance; it should be handled with due care.
5. Commercial cylinders of hydrogen chloride, now available, are most convenient.
6. Although it is more convenient to add the zinc cyanide and aluminum chloride together, the procedure results in lower yields.
7. The apparatus shown in .htmFig. 19 is most convenient. A 250-ml. Erlenmeyer flask is connected to the side neck of the flask by a 13-cm. length of 20-mm. thin-walled rubber tubing.[3]

Fig. 19.

Fig. 19.

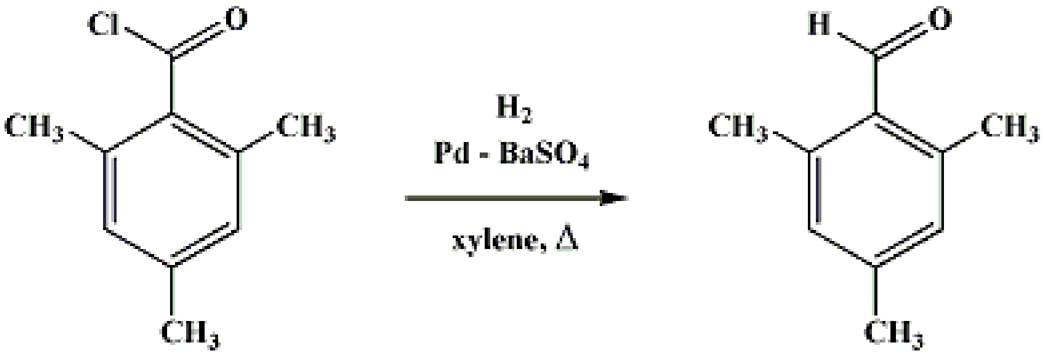
8. If difficulty is experienced in separating the organic layer, the entire solution may be subjected to steam distillation.
9. The first portion of the distillate consists almost entirely of tetrachloroethane and water. The solvent may be recovered by separating the organic layer, drying it with calcium chloride, and distilling.
10. About 9 l. of water is obtained; the time required is about 4 hours.
11. If a smaller yield of mesitaldehyde is acceptable and time is of importance, the preparation may be carried out without a solvent, and with other changes as follows: The zinc cyanide and aluminum chloride are mixed by shaking, the

mesitylene is added, and the flask is immersed in an oil bath at 100°. The stirrer is started, and a fairly rapid current of dry hydrogen chloride is passed into the mixture, below the surface of the liquid, for 4 hours; at the end of this time, the current of gas is discontinued, but stirring and heating are maintained for 2 hours longer. The reaction mixture is decomposed and processed as already described. The fraction which boils at 110–120°/9–10 mm. is taken as mesitaldehyde; the yield is 73% (private communication, D. B. Glass).

12. 2,4,6-Triethylbenzaldehyde and 2,4,6-triisopropylbenzaldehyde may be prepared in yields of 69 and 65%, respectively, by the procedure described above, with a reaction time of 8 hours and the following modifications:

	Triethylbenzaldehyde	*Triisopropylbenzaldehyde*
Hydrocarbon	100 g. (0.62 mole)	100 g. (0.49 mole)
Zinc cyanide	115 g. (0.97 mole)	102 g. (0.74 mole)
Aluminum chloride	215 g. (1.60 moles)	134 g. (1.0 mole)
Boiling point	146–149°/21 mm.	123–126°/4 mm.

[II. METHOD B]



Submitted by R. P. Barnes
Checked by Nathan L. Drake, Harry D. Anspon, and Ralph Mozingo.

1. Procedure

A 1-l. three-necked flask *with ground-glass joints* is fitted with a mercury-sealed stirrer (Note 1) and (Note 2), a glass tube of 6-mm. internal diameter which runs to the bottom of the flask, and a Friedrich condenser, protected by a drying tube. A solution of 90 g. (0.49 mole) of mesitoyl chloride (p. 555) in 270 g. of carefully dried xylene is placed in the flask together with 20 g. of palladium-barium sulfate (Note 3). The contents of the flask are refluxed while a stream of hydrogen (Note 4), which has been freed from oxygen by passage through Fieser's solution,[4] and dried by passage through concentrated sulfuric acid followed by a drying tube of Drierite (Note 5), is bubbled through the suspension until hydrogen chloride ceases to be evolved (Note 2). The catalyst is then removed by filtration and the xylene distilled. The residual liquid is transferred to a 125-ml. modified Claisen flask and distilled. The product boils at 96–

98°/6 mm., and weighs 53–60 g. (70–80%) (Note 6).

2. Notes

1. The stirrer is not essential, but without it the time required for the reduction is increased about threefold.
2. The course of the reaction may be followed conveniently by passing the exit gases into water and titrating with approximately 1 *N* sodium hydroxide. The time for complete reduction is about 6–7 hours with stirring, and about 18 hours with no stirrer.
3. The palladium-barium sulfate is prepared by the method described by Houben.[5] The barium sulfate should be freshly precipitated material.
4. The checkers found that electrolytic hydrogen directly from the cylinder without purification gives only a slightly decreased yield.
5. Dehydrite or Anhydrone should not be used because of the danger of sulfuric acid spraying into it. Drierite is much more efficient than calcium chloride.
6. This preparation illustrates Rosenmund's method of synthesizing aldehydes without use of a poisoned catalyst. See p. 629 for the more general form of the method.

3. Discussion

Mesitaldehyde has been prepared from mesitylglyoxylic acid;[6,7] from mesitylmagnesium bromide and ethoxymethyleneaniline,[8] ethyl orthoformate,[8] or N-methylformanilide;[9] from mesitylene, hydrogen cyanide, and hydrogen chloride[10] or mesitylene, carbon monoxide, and hydrogen chloride[11] in the presence of aluminum and cuprous chlorides; and from mesitylene, zinc cyanide, and hydrogen chloride in the presence of aluminum chloride.[12,13,14]

The procedures described here are based on the method applied to the preparation of other aldehydes by Rosenmund and Zetzsche;[15] and by Nencki, as adapted for mesitaldehyde.[12,13,14]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 771
- Org. Syn. Coll. Vol. 3, 841
- Org. Syn. Coll. Vol. 4, 649
- Org. Syn. Coll. Vol. 5, 49
- Org. Syn. Coll. Vol. 5, 959

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Drierite

Dehydrite

Anhydrone

aluminum and cuprous chlorides

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrogen chloride, hydrochloric acid (7647-01-0)

Benzene (71-43-2)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

carbon monoxide (630-08-0)

hydrogen cyanide (74-90-8)

sodium carbonate (497-19-8)

oxygen (7782-44-7)

barium sulfate (7727-43-7)

aluminum chloride (3495-54-3)

xylene (106-42-3)

Mesitylene (108-67-8)

Ethyl orthoformate

tetrachloroethane (630-20-6)

ethoxymethyleneaniline (6780-49-0)

N-methylformanilide (93-61-8)

Mesitaldehyde, Benzaldehyde, 2,4,6-trimethyl- (487-68-3)

zinc cyanide (557-21-1)

2,4,6-Triethylbenzaldehyde

2,4,6-triisopropylbenzaldehyde

Mesitoyl chloride (938-18-1)

palladium-barium sulfate

mesitylglyoxylic acid (3112-46-7)

mesitylmagnesium bromide

Triethylbenzaldehyde

Triisopropylbenzaldehyde

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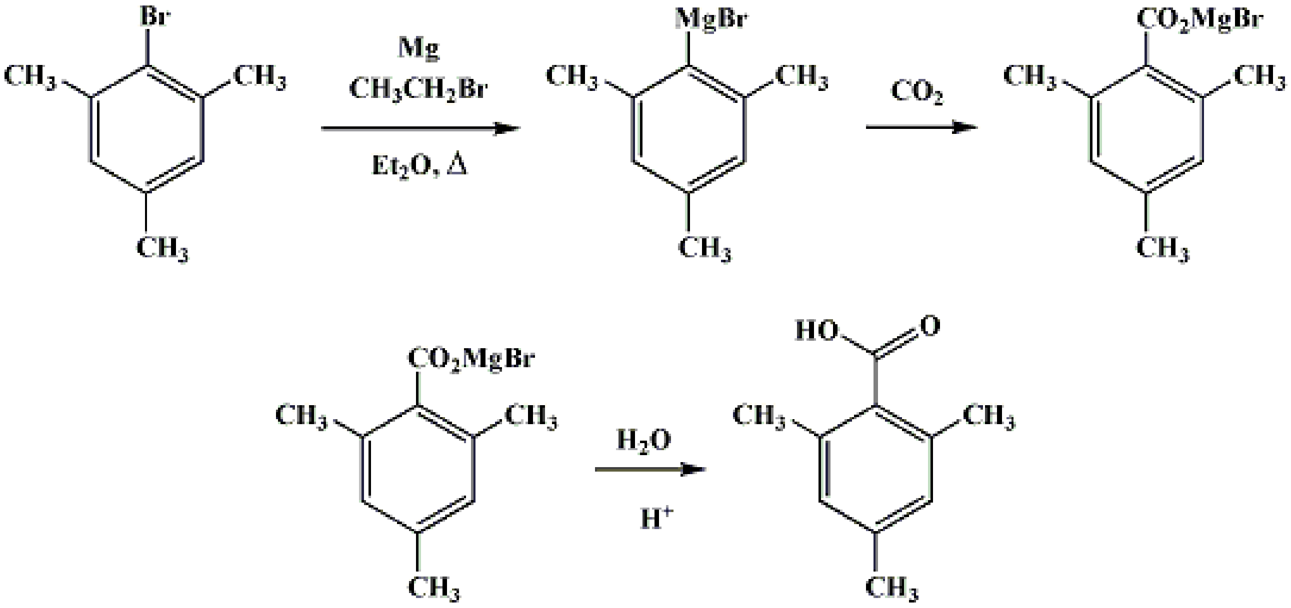
Organic Syntheses, *CV 3, 553*

MESITOIC ACID

[β-Isodurylic acid]

[I. METHOD A]



Submitted by Douglas M. Bowen
Checked by H. R. Snyder and John R. Demuth.

1. Procedure

In a dry 2-l. three-necked flask, equipped with a sealed wire stirrer, a condenser protected by a drying tube, and a dropping funnel, are placed 85.0 g. (3.5 gram atoms) of magnesium turnings and 150 ml. of dry ether (Note 1). A solution of 199 g. (1 mole) of carefully fractionated bromomesitylene and 218 g. (2 moles) of ethyl bromide (Note 2) in 1 l. of dry ether (Note 1) is placed in the funnel. Stirring is commenced, and about 25 ml. of the ether solution is added; the reaction begins almost at once. The rest of the solution of halides is added during the course of 1.25–1.5 hours to the vigorously refluxing mixture; moderate cooling is necessary to permit addition within the specified period. After completion of the addition, refluxing is maintained by external heating for 30 minutes. The reaction mixture is then cooled, and the solution of alkyl magnesium bromides is decanted slowly from the excess magnesium onto 600 g. of Dry Ice which is stirred manually in a 4-l. beaker. The Dry Ice should be in the form of small lumps, and the addition must be slow enough to avoid spattering. The flask is rinsed with two 200-ml. portions of dry ether, which are added to the carbonation mixture. When most of the Dry Ice has evaporated, an additional 200-g. portion is added along with 250 ml. of dry ether. The viscous is stirred until it becomes largely granular.

When the bulk of the Dry Ice has evaporated, 800 ml. of 20% hydrochloric acid and enough ice to keep the mixture cold are added with stirring. After most of the solid has dissolved, the mixture is transferred to a separatory funnel with the addition of ordinary ether if the volume of the organic layer is much less than 1 l. After agitation until both layers are clear, the aqueous layer is rejected, and the ethereal layer is washed with three 1-l. portions of cold water to remove hydrochloric acid and most of the propionic acid formed in the carbonation. The product is extracted by shaking first

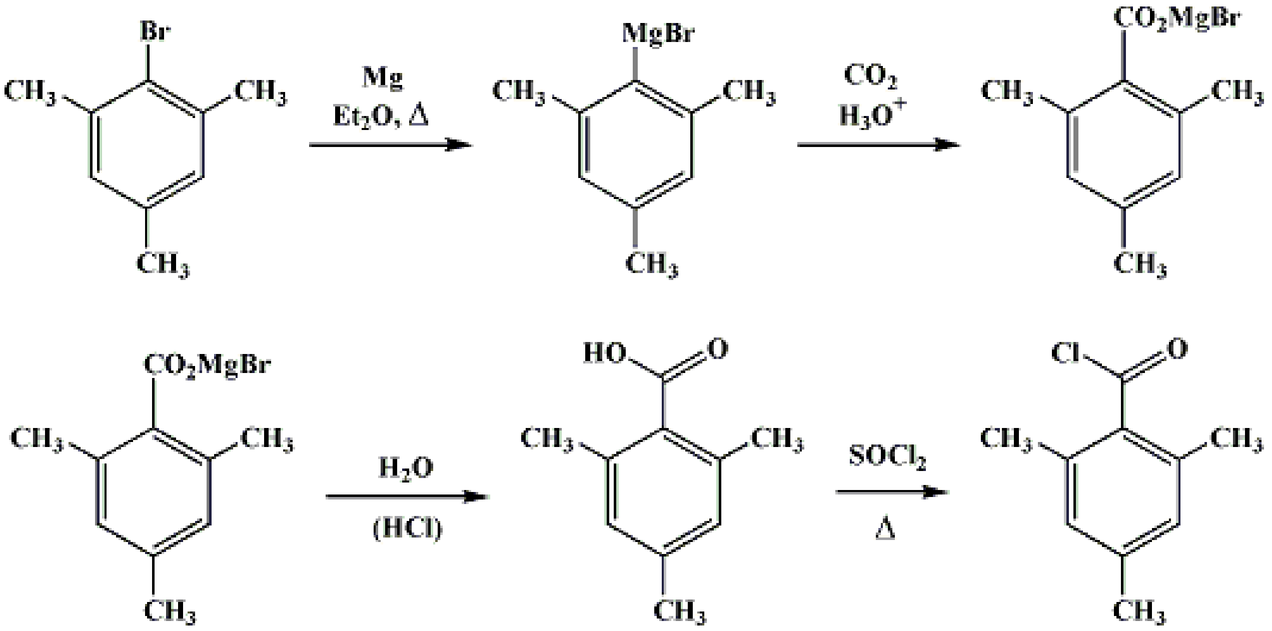
gently and then vigorously with a 540-ml. (600-g.) portion of *ice-cold* 10% sodium hydroxide solution. After agitation for several minutes the aqueous solution should still be strongly basic as shown by testing with a suitable indicator paper. The aqueous layer is separated and acidified with stirring by the slow addition of 250 ml. of 20% hydrochloric acid. The suspension is cooled, and the nearly colorless product, consisting of small granules, is collected and washed well with water. The crude acid, amounting to 141–143 g. (86–87%) (Note 3), melting at 152–154° (cor.), is satisfactory for most purposes. A purer product may be obtained as large, nearly colorless crystals, m.p. 153.4–154.4° (cor.), by crystallization from a solution, saturated at the boiling point, in 45% methanol. The yield of the recrystallized acid is 138–141.5 g. (84–86%) (Note 4).

2. Notes

1. The checkers used commercial anhydrous ether which had been stored over sodium wire, and they dried the various pieces of apparatus in an oven before assembly. If the redrying of the ether over sodium was omitted, the yield was lowered appreciably.
2. When 1 mole of ethyl bromide is used with 1 mole of bromomesitylene, the yield of crude acid is 81–82%. No appreciable improvement in yield is effected by use of more than 2 equivalents of ethyl bromide. If the ethyl bromide is omitted entirely, bromomesitylene reacts with magnesium very slowly and the Grignard reagent obtained affords mesitoic acid in 61–66% overall yield. Except in the absence of ethyl bromide there is no advantage in the use of an atmosphere of nitrogen.
3. This procedure may be conducted on one-fifth the scale without alteration in yield.
4. The checkers employed 20 ml. of a solvent mixture containing 45% of methanol by weight for each 10 g. of the crude acid. To avoid the loss of methanol from the hot solution the operation was carried out under a reflux condenser, and the clear, nearly colorless solution was cooled rapidly without transferral. If filtration of the hot solution should be desirable a higher concentration of methanol would be more convenient.

[II. METHOD B]

[MESITOIC ACID AND MESITOYL CHLORIDE]



Submitted by R. P. Barnes
Checked by Nathan L. Drake and Ralph Mozingo.

1. Procedure

In a 2-l. three-necked flask, fitted with a condenser protected by a drying tube, a dropping funnel, and a sealed stirrer, are placed 24.3 g. (1 gram atom) of magnesium turnings, a small crystal of iodine, enough absolute ether to cover the magnesium, and 10 g. (0.05 mole) of bromomesitylene. The bottom of the flask is warmed with the hand or a warm cloth until the reaction begins. The mixture is then stirred gently during the gradual addition of 190 g. (0.95 mole) of bromomesitylene dissolved in 500 g. (700 ml.) of absolute ether. When all the ethereal solution has been added, the reaction mixture is refluxed for about 2 hours, or until all the magnesium has dissolved. A large excess of solid carbon dioxide is now added slowly in small pieces with rapid stirring (Note 1). The resulting tough addition product is decomposed by pouring, with stirring, into a large volume of finely crushed ice to which has been added 100 ml. (1.2 moles) of concentrated hydrochloric acid. The ether is removed by evaporation, and the resulting oily solid is filtered, dissolved in 200–400 ml. of hot methanol, filtered, and thrown out by dilution with 1 l. of ice water. The crude mesitoic acid melts between 135° and 148° and weighs 110–120 g. The acid is recrystallized from petroleum ether (b.p. 90–100°), about 10 ml. of petroleum ether being used per gram of the crude acid. The product, melting at 150–152° after one recrystallization, weighs 90–100 g. (55–61%) (Note 2).

A mixture of 90 g. (0.55 mole) of mesitoic acid and 100 g. (63 ml., 0.84 mole) of thionyl chloride in a 500-ml. large-mouthed Claisen flask, with the side arm and adjacent neck closed, and with the other neck fitted with a condenser protected by a drying tube, is refluxed gently until the evolution of sulfur dioxide and hydrogen chloride ceases (Note 3). The excess thionyl chloride is removed by distillation at atmospheric pressure, and the residual acid chloride is distilled at 143–146°/60 mm. (Note 4). The yield is 90–97 g. (90–97%).

2. Notes

1. The Grignard reagent may be carbonated by pouring it slowly over Dry Ice contained in a 2-l. beaker. The yield is unchanged.
2. A small amount of mesitoic acid can be recovered by concentrating the filtrate to a small volume and cooling it.
3. This requires from 1 to 2 hours. The reaction mixture may also be allowed to stand overnight at room temperature, in which case no heating is necessary.
4. The boiling point varies with the rate of distillation.

3. Discussion

Mesitoic acid has been obtained by hydrolysis of its amide which was prepared from mesitylene, carbamyl chloride, and aluminum chloride in carbon disulfide.[1] It has been prepared by heating isodurene with dilute nitric acid,[2,3] in small yields by the distillation of 2,4,6-trimethylmandelic acid,[4] by dry distillation of 2,4,6-trimethylphenylglyoxylic acid,[4,5] by oxidation of 2,4,6-trimethylphenylglyoxylic acid with potassium permanganate,[6] and by treating 2,4,6-trimethylphenylglyoxylic acid with concentrated sulfuric acid either with heating[7] or in the cold.[8] The preparation of the acid from 2,4,6-trimethylphenylmagnesium bromide and a stream of carbon dioxide has been described.[9]

The method for the preparation of the chloride is the general method for preparing aromatic acid chlorides with thionyl chloride,[10] which has been applied to the preparation of mesitoyl chloride.[9]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 549
- Org. Syn. Coll. Vol. 5, 706

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

β-Isodurylic acid

sulfuric acid (7664-93-9)

hydrogen chloride, hydrochloric acid (7647-01-0)

methanol (67-56-1)

ether (60-29-7)

sodium hydroxide (1310-73-2)

thionyl chloride (7719-09-7)

magnesium, magnesium turnings (7439-95-4)

nitric acid (7697-37-2)

potassium permanganate (7722-64-7)

propionic acid (79-09-4)

sulfur dioxide (7446-09-5)

Ethyl bromide (74-96-4)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

iodine (7553-56-2)

aluminum chloride (3495-54-3)

sodium (13966-32-0)

carbon disulfide (75-15-0)

Mesitylene (108-67-8)

Bromomesitylene (27129-86-8)

Isodurene (527-53-7)

carbamyl chloride

Mesitoyl chloride (938-18-1)

2,4,6-trimethylphenylglyoxylic acid (3112-46-7)

2,4,6-trimethylphenylmagnesium bromide

Mesitoic acid (480-63-7)

2,4,6-trimethylmandelic acid

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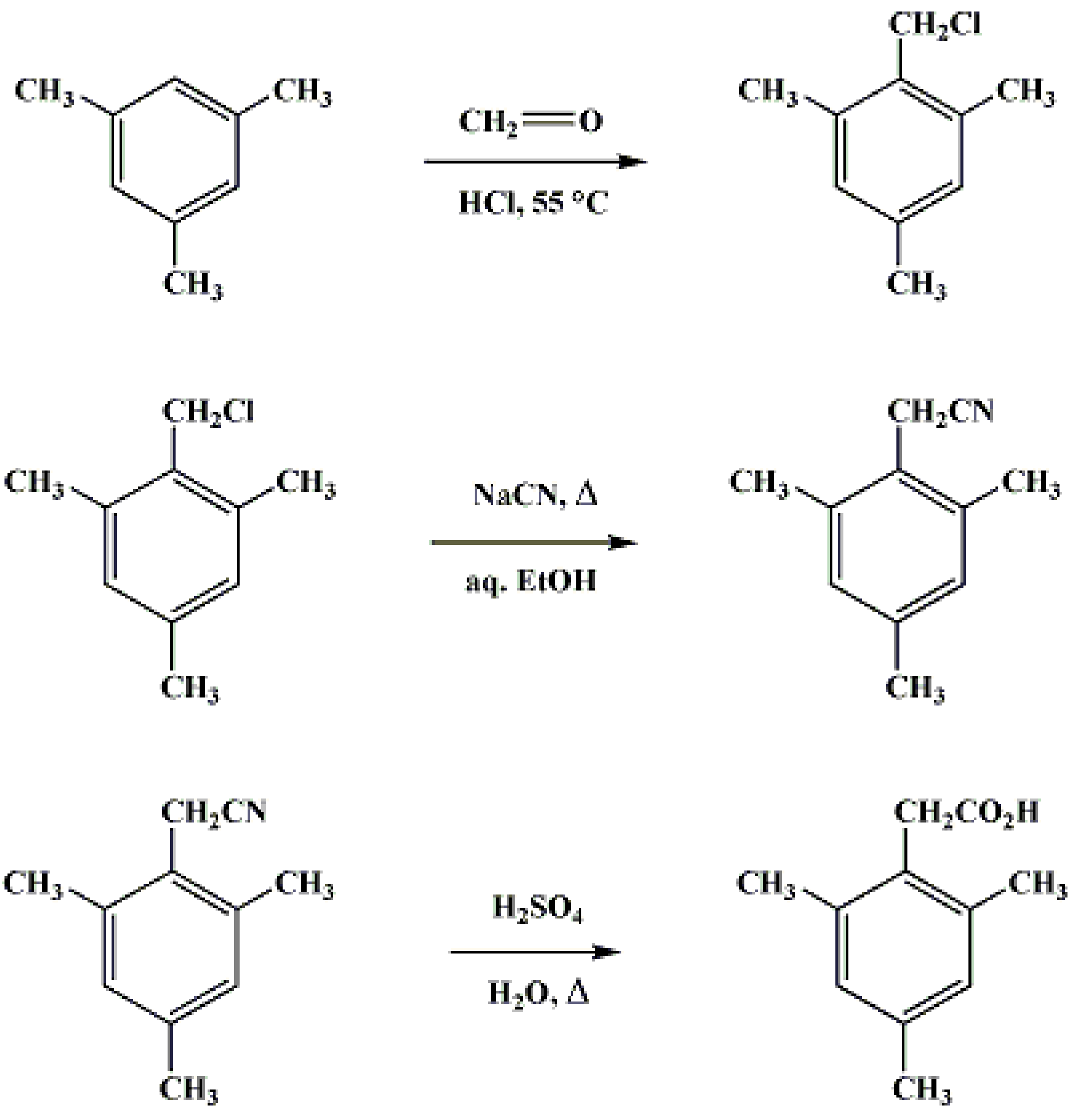
Organic Syntheses, CV 3, 557

MESITYLACETIC ACID

[Acetic acid, mesityl-]



Submitted by Reynold C. Fuson and Norman Rabjohn.
Checked by W. E. Bachmann, E. L. Jenner, and G. Dana Johnson.

1. Procedure

A. α[1]-*Chloroisodurene*. In a 2-l. round-bottomed flask, equipped with a sealed mechanical stirrer (Note 1), a gas inlet tube, and a reflux condenser, are placed 200 g. (1.66 moles) of mesitylene, 1 l. of concentrated hydrochloric acid, and 63 ml. (0.84 mole) of formaldehyde solution (concentration, 37%) (Note 2). Hydrogen chloride is introduced below the surface of the mixture (Note 3), which is stirred vigorously and heated in a water bath kept at 55°. These conditions are maintained throughout the reaction, which requires a total of 5.5 hours. At the halfway point, an additional 63 ml. (0.84 mole) of formaldehyde solution is added (Note 4).

After the mixture has been cooled to room temperature (Note 5), it is extracted with three 300-ml. portions of benzene. The combined benzene extracts are washed successively with water, dilute sodium hydroxide, and water, dried over calcium chloride, and filtered. The mixture is distilled through a still head under reduced pressure; the pressure is reduced only slightly while the benzene is distilling. The yield of α^1-chloroisodurene boiling at 130–131°/22 mm. is 155–170 g. (55–61%) (Note 6); the distillate solidifies to a crystalline mass which melts at 37°.

B. *Mesitylacetonitrile*. In a 1-l. three-necked flask, fitted with a mechanical stirrer, a reflux condenser, and a dropping funnel, are placed 77 g. (1.57 moles) of sodium cyanide, 110 ml. of water, and 160 ml. of ethanol. The flask is heated in a boiling water bath, and the contents are stirred until all the sodium cyanide is dissolved. Then 152 g. (0.90 mole) of α^1-chloroisodurene is added slowly, and stirring and heating are continued for 3 hours.

The reaction mixture is allowed to cool to about 40° (Note 7) and extracted with three 300-ml. portions of benzene. The benzene solution is washed well with water, dried over calcium chloride, filtered, and distilled under slightly reduced pressure to remove all the benzene. The residue is then distilled under reduced pressure from a Claisen flask with a wide-bore side arm. The yield of mesitylacetonitrile boiling at 160–165°/22 mm. is 128–133 g. (89–93%) (Note 8). This product is sufficiently pure for the next step. When recrystallized from petroleum ether, it melts at 79–80°.

C. *Mesitylacetic acid*. To 900 ml. of water in a 3-l. three-necked flask is added 750 ml. of concentrated sulfuric acid. When the mixture has cooled to about 50°, 127 g. (0.80 mole) of mesitylacetonitrile is added (Note 9), and the mixture is refluxed and stirred mechanically for 6 hours. At the end of this period, a large amount of mesitylacetic acid has precipitated from the solution. The contents of the flask are cooled and poured into 3 l. of ice water. The acid is collected on a Büchner funnel and washed well with water. A solution of the acid in dilute alkali is boiled with Norit, and the acid is precipitated from the filtered solution by acidifying with dilute hydrochloric acid. The mesitylacetic acid is collected on a filter, washed well with water, and dried in an oven at about 80°. The yield of mesitylacetic acid melting at 163–166° is 123 g. (87%). After recrystallization from dilute alcohol or ligroin, the acid melts at 167–168°.

2. Notes

1. The checkers used an Ace Tru-bore stirrer. This convenient sealed stirrer, which owes its seal to the snug fit between a ground-glass section of the stirrer shaft and a ground-glass bearing, can be obtained from the Ace Glass Company, Vineland, New Jersey.
2. Commercial formalin was used. This aqueous-methanolic solution contains 37% formaldehyde by weight. It is sometimes called "40% formalin" because 100 ml. of the solution contains 40 g. of formaldehyde.

3. The hydrogen chloride is introduced at such a rate that the bubbles form a little faster than they can be counted.
4. The yield of monochloromethyl compound seems to be improved slightly by adding the formalin in two portions instead of introducing the entire amount at the beginning of the reaction.
5. If the reaction mixture is cooled to too low a temperature, the chloromethyl derivatives will solidify. It is much easier to carry out the extractions while the mixture is still liquid.
6. The residue consists chiefly of α^1,α^2-dichloropentamethylbenzene. The fraction boiling at 131–200°/22 mm. is collected and recrystallized from petroleum ether; m.p. 105°.
7. If the reaction mixture is allowed to cool much below this temperature, it will solidify in the flask.
8. This method has been applied successfully to the preparation of 2,4,6-triethylphenylacetonitrile (b.p. 127°/3–4 mm.; yield, 72%); durylacetonitrile (m.p. 80–81°; yield, 75%); and isodurylacetonitrile (m.p. 74–75°; yield, 74%).
9. If the mesitylacetonitrile has not been purified by distillation, or if it is added to a boiling solution of sulfuric acid, the reaction mixture has a tendency to become very dark.

3. Discussion

α^1-Chloroisodurene can be prepared by the action of chloromethyl ether on mesitylene in the presence of stannic chloride[3] or acetic acid.[1] The procedure described is based on that of Nauta and Dienske.[4]

Mesitylacetonitrile can be prepared by the action of potassium cyanide on α^1-chloroisodurene[2] or by treating α^1-chloroisodurene with cuprous cyanide in the presence of pyridine.[5] The procedure described is based upon the method for the preparation of benzyl cyanide from benzyl chloride.

Mesitylacetic acid has been prepared from 2,4,6-trimethylacetophenone by treatment with yellow ammonium sulfide and hydrolyzing the resulting amide with alkali,[6] by the dry distillation of 2,4,6-trimethylmandelic acid,[7] by heating 2,4,6-trimethylphenylglyoxylic acid with hydriodic acid and red phosphorus[8] or with hydrazine hydrate,[9] by the action of boiling water on mesitoyldiazomethane[10] (prepared in turn from mesitylglyoxal monohydrazone), and by treating mesitylacetonitrile with potassium hydroxide.[2]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

red phosphorus

ligroin

petroleum ether

durylacetonitrile

isodurylacetonitrile

2,4,6-trimethylacetophenone

ethanol (64-17-5)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrogen chloride, hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

sodium hydroxide (1310-73-2)

formaldehyde, formalin (630-08-0)

sodium cyanide (143-33-9)

Cuprous Cyanide (544-92-3)

potassium cyanide (151-50-8)

Norit (7782-42-5)

pyridine (110-86-1)

potassium hydroxide (1310-58-3)

benzyl chloride (100-44-7)

Benzyl cyanide (140-29-4)

hydriodic acid (10034-85-2)

Mesitylene (108-67-8)

hydrazine hydrate (7803-57-8)

ammonium sulfide

chloromethyl ether (542-88-1)

stannic chloride (7646-78-8)

2,4,6-trimethylphenylglyoxylic acid (3112-46-7)

2,4,6-trimethylmandelic acid

Mesitylacetic acid, Acetic acid, mesityl- (4408-60-0)

mesitylacetonitrile (34688-71-6)

2,4,6-triethylphenylacetonitrile

mesitoyldiazomethane

mesitylglyoxal monohydrazone

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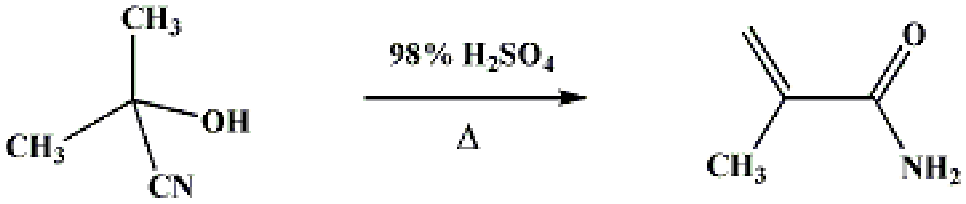
Organic Syntheses, CV 3, 560

METHACRYLAMIDE



Submitted by Richard H. Wiley and Walter E. Waddey.
Checked by R. L. Shriner and Arne Langsjoen.

1. Procedure

In a 1-l. three-necked round-bottomed flask fitted with an efficient stirrer, a dropping funnel, and a thermometer, are placed 150 g. (82 ml., 1.5 moles) of 98% sulfuric acid (Note 1) and 1 g. of flowers of sulfur. To this is added, with rapid stirring, 85 g. (91 ml., 1 mole) of acetone cyanohydrin[1] (Note 2) over a period of 25 minutes, the temperature of the contents of the flask being kept at 75–80° by cooling in a water bath. At the end of this period, the water bath is replaced with an oil bath preheated to 160°. With continued stirring, the temperature of the reaction mixture is raised to 150° within 5 minutes and maintained at 150° for 15 minutes (Note 3). The reaction mixture is quickly cooled to room temperature by replacing the oil bath with an ice bath and is then poured into 300 ml. of cold water, and the flask is rinsed with 75 ml. of water. The diluted mixture is filtered (Note 4) through a 10-cm. Büchner funnel with the aid of suction. The filtrate is placed in a 1-l. beaker, cooled with an ice bath and 180–190 g. of anhydrous sodium carbonate sifted in with vigorous stirring (*Caution! foaming*) (Note 5). The precipitate is collected on a 20-cm. Büchner funnel and pressed and sucked as dry as possible. The crude product is dried in a vacuum desiccator over anhydrous calcium chloride for 36–48 hours (Note 6). The light cream- or tan-colored crude product weighs 300–400g.

The crude dried soild is crushed to break up lumps and is placed in a 2-l. flask and heated and stirred mechanically with 500 ml. of boiling benzene. The solution is decanted, and the extraction is repeated four times using 200-ml. portions of benzene. The combined benzene solutions are heated to boiling, treated with 2–4 g. of Norit, and filtered. On cooling, 48–52 g. of methacrylamide separates; m.p. 105–107° (Note 7). An additional 5–8 g., m.p. 103–105°, is obtained when the mother liquor is concentrated to 150 ml. and cooled. The yield of methacrylamide is 52–60 g. (61–70%) after storing in a vacuum desiccator over paraffin wax and anhydrous calcium chloride.

2. Notes

1. Acid of 98% strength may be prepared by the addition of 33.5 ml. of fuming

sulfuric acid (15% SO_3) to 48 ml. of concentrated sulfuric acid of sp. gr. 1.84.

2. Acetone cyanohydrin of 98% purity may be purchased from the Rohm and Haas Company, Philadelphia, Pennsylvania.

3. This heating converts the intermediate compounds into methacrylamide sulfate. Longer periods of heating decrease the yield.

4. A small amount of dark polymeric material, which may form, is separated at this point.

5. Care is taken to crush lumps of sodium carbonate formed during the addition. The final reaction mixture should be slightly alkaline to litmus paper, and the temperature of the mixture should not rise above 25–30°.

6. The precipitated methacrylamide contains varying amounts of sodium sulfate. It is essential to obtain a dry product for the benzene extraction. The desiccator should be evacuated with an oil pump to about 5 mm. several times during 24–36 hours in order to obtain a sufficiently dry material.

7. The methacrylamide tends to retain some solvent. By placing the product in a vacuum desiccator containing paraffin wax shavings and anhydrous calcium chloride for 36–48 hours material with a melting point of 109–110° may be obtained.

3. Discussion

Methacrylamide has been prepared by the reaction of acetone cyanohydrin with concentrated sulfuric acid[2,3,4,5,6,7] and sulfuric acid with ammonium sulfate,[8] and by the hydrolysis of methacrylonitrile.[9] The method described is an adaptation of that of Crawford and McGrath.[4]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

SO_3

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

Benzene (71-43-2)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

sulfur (7704-34-9)

Norit (7782-42-5)

ammonium sulfate (7783-20-2)

Acetone cyanohydrin (75-86-5)

Methacrylamide (79-39-0)

methacrylamide sulfate

methacrylonitrile (126-98-7)

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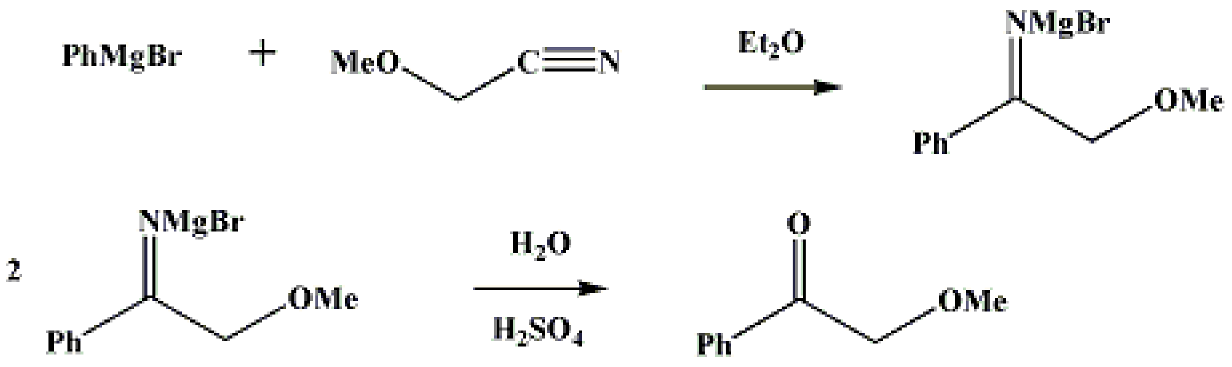
Organic Syntheses, CV 3, 562

ω-METHOXYACETOPHENONE

[Acetophenone, ω-methoxy-]



Submitted by R. B. Moffett and R. L. Shriner.
Checked by W. E. Bachmann and W. S. Struve.

1. Procedure

A solution of phenylmagnesium bromide is prepared in a 2-l. three-necked flask, fitted with a separatory funnel, reflux condenser, and a mercury-sealed stirrer, from 8.8 g. (0.36 gram atom) of magnesium, 56.5 g. (38 ml., 0.36 mole) of bromobenzene, and a total of 350 ml. of dry ether by the procedure described in *Org. Syntheses* Coll. Vol. **1**, 226 (1941).

To the solution of the Grignard reagent, cooled by an ice-salt bath, a mixture of 21.3 g. (0.3 mole) of methoxyacetonitrile [*Org. Syntheses* Coll. Vol. **2**, 387 (1943)] and 50 ml. of dry ether is slowly added with stirring. The colorless addition product separates at once. After standing at room temperature for 2 hours, the mixture is again cooled and then decomposed by adding, with stirring, 500 ml. of water and cracked ice, and then 100 ml. of cold dilute sulfuric acid (Note 1). When the decomposition is complete (Note 2), the ether layer is separated and the aqueous layer is extracted with a little ether. This ether extract is combined with the ether layer, and the whole is washed with 5% aqueous sodium carbonate solution and then with water. The solution is dried with anhydrous sodium sulfate.

The ether is removed by distillation from a steam bath, and the residue is distilled under diminished pressure. ω-Methoxyacetophenone is a colorless liquid which boils at 118–120° /15 mm. or 228–230° /760 mm. (Note 3). The yield is 32–35 g. (71–78% based on the methoxyacetonitrile).

2. Notes

1. One volume of concentrated sulfuric acid is added to 2 volumes of water, and

the mixture is cooled in an ice-salt bath.
2. The two layers should be light yellow in color with only a small amount of solid or tarry material present.
3. The checkers observed a boiling point of 110–112° /9 mm.

3. Discussion

The method described is essentially that of Pratt and Robinson.[1] ω-Methoxyacetophenone has also been prepared by chromic acid oxidation of α-phenyl-β-methoxyethanol, which in turn was prepared from styrene oxide.[2]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

ether (60-29-7)

magnesium (7439-95-4)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

chromic acid (7738-94-5)

bromobenzene (108-86-1)

Phenylmagnesium bromide (100-58-3)

Styrene oxide (96-09-3)

Methoxyacetonitrile (1738-36-9)

ω-Methoxyacetophenone, Acetophenone, ω-methoxy- (4079-52-1)

α-phenyl-β-methoxyethanol

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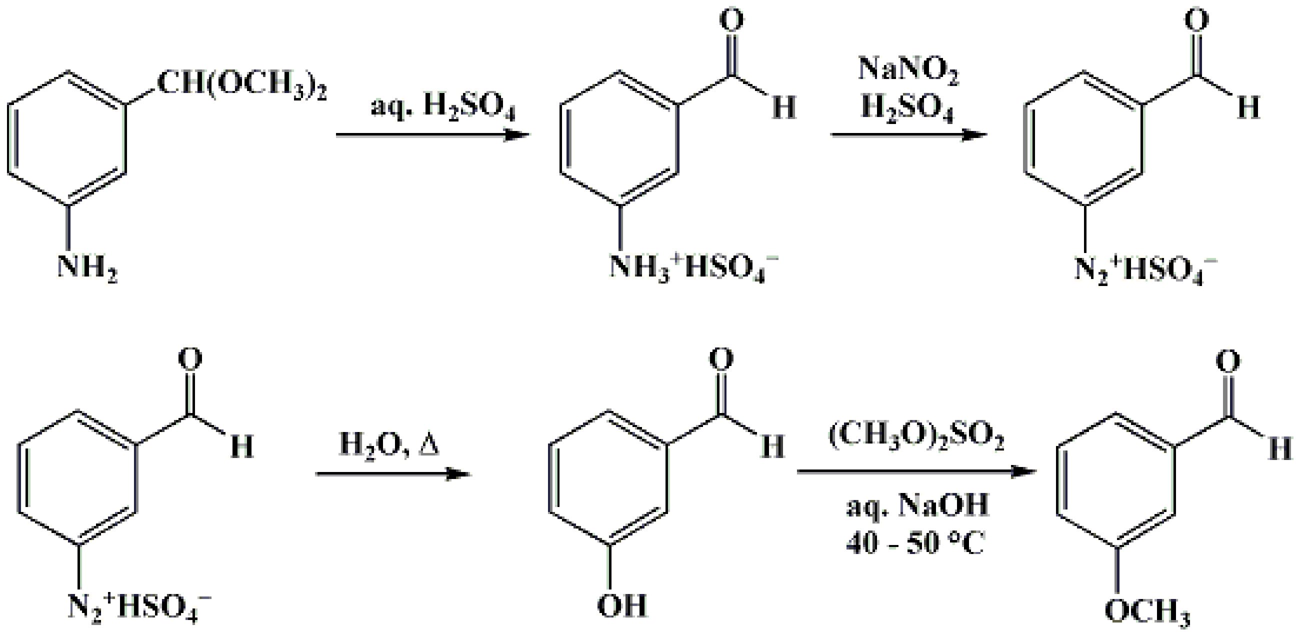
Organic Syntheses, *CV 3*, *564*

m-METHOXYBENZALDEHYDE

[Benzaldehyde, *m*-methoxy-]



Submitted by Roland N. Icke, C. Ernst Redemann, Burnett B. Wisegarver, and Gordon A. Alles.
Checked by H. R. Snyder and Frank X. Werber.

1. Procedure

A. *m-Hydroxybenzaldehyde*. In a 2-l. three-necked flask, equipped with a mechanical stirrer, a thermometer, and a 250-ml. dropping funnel, 575 ml. of 6 *N* sulfuric acid is cooled to 0° by means of a salt-ice bath. The acid is stirred and maintained at 0° or below while 167 g. (1 mole) of *m*-aminobenzaldehyde dimethylacetal (p. 59) is added dropwise. The solution becomes deep orange or red. When the addition of the amino compound is complete, a solution of 71 g. (1 mole) of 97% sodium nitrite in about 175 ml. of water is introduced slowly while the temperature of the acid solution is maintained at 5°. Stirring at 5° is continued for 1 hour to complete the reaction.

In each of two 4-l. beakers are placed 450 ml. of water and 50 ml. of concentrated sulfuric acid, and the solutions are heated to boiling with large burners. The cold diazonium solution is divided into two approximately equal portions which are placed in 500-ml. separatory funnels suspended above the beakers containing the boiling acid. The two portions of the diazonium solution are run dropwise into the strongly heated acid at such a rate that boiling continues. The solutions are boiled for 5 minutes after the additions are complete. They are then allowed to cool to room temperature and are finally stored overnight in a refrigerator. The crude product separates as a dark oil which crystallizes (Note 1) and becomes lighter in color upon standing. It is collected on a Büchner funnel and used in part B without purification (Note 2).

Methyl sulfate is quite toxic. Caution! The methylation should be carried out in a good hood.

B. *m-Methoxybenzaldehyde*. The crude *m*-hydroxybenzaldehyde is dissolved in about 550 ml. of 2 *N* sodium hydroxide in a 2-l. three-necked flask equipped with a mechanical stirrer, a thermometer, and a 125-ml. dropping funnel. The dark-colored solution is stirred while 126 g. (95 ml., 1 mole) of methyl sulfate (Note 3) is added dropwise and the temperature is maintained at 40–45°. When the addition is

complete the mixture is stirred for 5 minutes. A 275-ml. portion of 2 *N* sodium hydroxide (Note 4) is added in one lot, and then 63 g. (47.5 ml.) of methyl sulfate is added as before, except that the temperature is allowed to rise to 50°. Stirring at 50° is continued for 30 minutes, the mixture is cooled, and the organic layer is extracted with ether (Note 5). The ether solution is dried over anhydrous sodium sulfate for 8 hours, then filtered and concentrated by distillation. The residue is distilled under reduced pressure. The yield of *m*-methoxybenzaldehyde, a pale yellow liquid boiling at 88–90° /3 mm., is 86–98 g. (63–72%) (Note 6).

2. Notes

1. Seeding the mixture helps to initiate crystallization.
2. If *m*-hydroxybenzaldehyde is desired, the crude product may be purified as described elsewhere (p. 453).
3. A good technical grade of methyl sulfate was used.
4. The optimum amount of sodium hydroxide solution apparently varies according to the amount of acid remaining in the crude, wet hydroxybenzaldehyde employed in the methylation. The checkers found it advisable to increase the amount added at this point to 345 ml. It is wise to test the reaction mixture with litmus paper occasionally during the final heating period and to add alkali as necessary to keep the solution from becoming acid.
5. If the methylation is not complete, some *m*-hydroxybenzaldehyde will remain dissolved in the aqueous phase. This may be recovered by acidifying the alkaline solution and collecting any crystalline solid which separates.
6. As with other aromatic aldehydes, *m*-methoxybenzaldehyde is susceptible to air oxidation and should be stored in a bottle which will just hold the product, so that air space above the liquid is minimized.

3. Discussion

m-Methoxybenzaldehyde has been prepared by the reduction of *m*-methoxybenzoic acid,[1] by the reaction of diazotized *m*-aminobenzaldehyde with methanol,[2] by an acid hydrolysis of the phenylhydrazone which was obtained by oxidation of the hydrazine analog,[3] and by the methylation of *m*-hydroxybenzaldehyde, with methyl iodide,[4,5,6,7] and with methyl sulfate.[2,7,8,9]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

phenylhydrazone

sulfuric acid (7664-93-9)

methanol (67-56-1)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium sulfate (7757-82-6)

sodium nitrite (7632-00-0)

hydroxybenzaldehyde (90-02-8)

Methyl iodide (74-88-4)

methyl sulfate (75-93-4)

m-Hydroxybenzaldehyde (100-83-4)

m-aminobenzaldehyde (1709-44-0)

m-Aminobenzaldehyde dimethylacetal (53663-37-9)

m-Methoxybenzaldehyde, Benzaldehyde, m-methoxy- (591-31-1)

m-methoxybenzoic acid (586-38-9)

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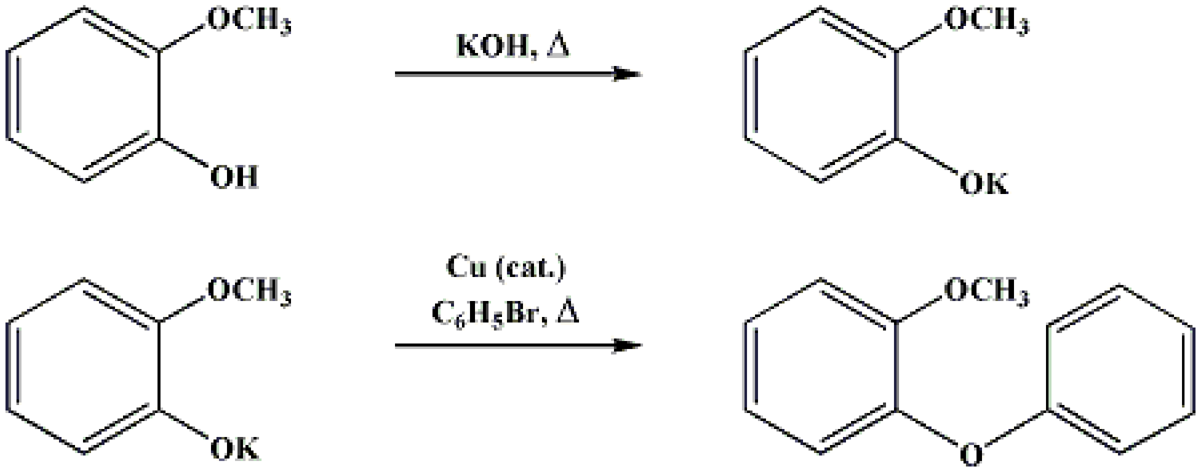
Organic Syntheses, CV 3, 566

2-METHOXYDIPHENYL ETHER

[Benzene, 1-methoxy-2-phenoxy-]



Submitted by H. E. Ungnade and E. F. Orwoll.
Checked by Homer Adkins and E. E. Burgoyne.

1. Procedure

Powdered potassium hydroxide (29.4 g., 0.43 mole) is placed in a 500-ml. round-bottomed flask. Guaiacol (75 g., 0.60 mole) is added, and the mixture is allowed to react exothermically. After the reaction is complete, the mixture is stirred with a glass rod and then heated under reduced pressure for 3 hours at 150° in an oil bath (Note 1).

To the dry salt is added 0.3 g. of copper powder (Note 2), 81 g. (0.51 mole) of bromobenzene, and a few drops of guaiacol (Note 3). The mixture is stirred thoroughly with a glass rod; the flask is fitted with an air condenser and heated in a metal bath (Note 4). A reaction becomes evident at a bath temperature of 160–180°, liquefaction occurs, and the color of the mixture changes to red or purple. The temperature is gradually raised to 200° and maintained at 200° for 2 hours.

After cooling, the products are extracted from the reaction mixture with successive portions of water and ether. Extraction is facilitated by breaking up the solid material with a glass rod. The total amounts. of solvents required are approximately 750 ml. of water and 150 ml. of ether. The combined ether and water solutions are transferred to a 3-l. round-bottomed flask and steam-distilled with superheated steam maintained at 180–200°. After removal of the ether, 300 ml. of distillate is collected. This distillate contains the unreacted starting materials. Continued distillation gives 64–69 g. (62–67%) of crude solid 2-methoxydiphenyl ether in 14 l. of distillate. The product is filtered with suction and dried. Crystallization from a mixture of 600 ml. of low-boiling petroleum ether (b.p. 30–60°) and 435 ml. of higher-boiling petroleum ether (b. p. 60–70°) yields 54–61 g. of 2-methoxydiphenyl ether melting at 77–78°. Other 2-

methoxydiphenyl ethers have been prepared by this procedure (Note 5).

2. Notes

1. The salt of guaiacol is heated under reduced pressure, in order to remove water, which is a negative catalyst in the Ullmann reaction.[1]
2. The copper catalyst may be prepared by the method of Brewster and Groening.[2]
3. An excess of guaiacol is essential. Weston and Adkins[1] have found that the phenol, copper, and air form the active catalyst in the Ullmann reaction.
4. The checkers used an electrically heated oil bath.
5. Yields of 54% of 2-methoxy-4'-methyldiphenyl ether from *p*-bromotoluene and guaiacol, and 60% of 2-methoxy-5-methyldiphenyl ether from 3-bromo-4-methoxytoluene and phenol, have been obtained by the same method in the laboratory of the submitters.

3. Discussion

The procedure above is a modification of the method of Ullmann and Stein[3] for the same compound. Sartoretto and Sowa[4] used the same general method. The need for a catalyst can be avoided by heating a mixture of guaiacol potassium, guaiacol, and chlorobenzene at 200° under pressure.[5] Ullmann and Stein[6] have prepared the compound by using phenol, *o*-bromoanisole, copper powder, and potassium hydroxide. 2-Hydroxydiphenyl ether can be converted to the methoxy derivative by treating it with methanol, methyl iodide, and potassium hydroxide.[7]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

methanol (67-56-1)

ether (60-29-7)

phenol (108-95-2)

copper, copper powder (7440-50-8)

chlorobenzene (108-90-7)

potassium hydroxide (1310-58-3)

bromobenzene (108-86-1)

Guaiacol (90-05-1)

Methyl iodide (74-88-4)

2-Methoxydiphenyl ether, Benzene, 1-methoxy-2-phenoxy- (1695-04-1)

2-methoxy-5-methyldiphenyl ether

3-bromo-4-methoxytoluene (22002-45-5)

guaiacol potassium

2-Hydroxydiphenyl ether

p-Bromotoluene (106-38-7)

o-bromoanisole (578-57-4)

2-methoxy-4'-methyldiphenyl ether

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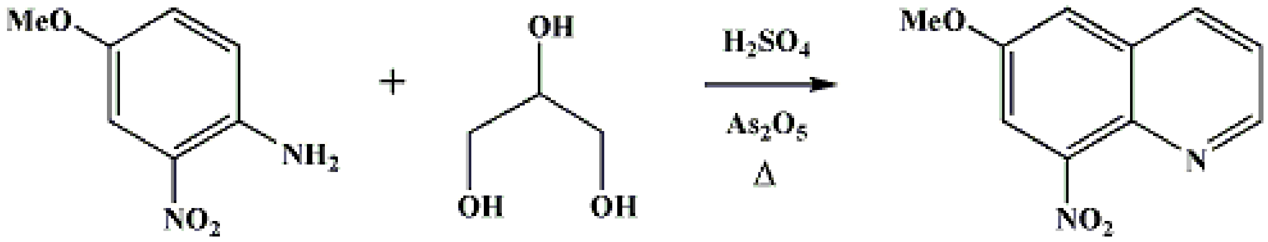
Organic Syntheses, CV 3, 568

6-METHOXY-8-NITROQUINOLINE

[Quinoline, 6-methoxy-8-nitro-]



Submitted by Harry S. Mosher, William H. Yanko, and Frank C. Whitmore.
Checked by R. L. Shriner, C. E. Kaslow, and Mason Hayek.

1. Procedure

This preparation must be carried out with careful attention to the times and temperatures specified, since Skraup reactions are likely to become violent. The operator should wear goggles, and there should be a safety shower close at hand.

In a 5-l. three-necked round-bottomed flask, a homogeneous slurry of the following compounds is made by mixing in the order given (Note 1): 588 g. (2.45 moles) of powdered arsenic oxide (Note 2), 588 g. (3.5 moles) of 3-nitro-4-aminoanisole (Note 3), and 1.2 kg. (950 ml., 13 moles) of u.s.p. glycerol. The flask is fitted with an efficient mechanical stirrer and a 500-ml. dropping funnel in which is placed 315 ml. (579 g., 5.9 moles) of concentrated sulfuric acid (sp. gr. 1.84). With good mechanical stirring the sulfuric acid is dropped into the orange reaction mixture over a period of 30–45 minutes. During this addition, the temperature spontaneously rises to 65–70°.

The stirrer and dropping funnel are removed, and a thermometer is inserted in one neck of the flask by means of a stopper so that the bulb is well below the surface of the reaction mixture. A 10-mm. bent glass tube is attached to the second neck by a rubber stopper and attached through a trap to a water aspirator (Note 4). The third neck is closed with a stopper, and the flask and its contents are weighed. The flask, clamped in place in an oil bath which rests on a hot plate (Note 5), is evacuated, and heat is carefully applied at such a rate that the internal temperature slowly rises to 105° (Note 6). The mixture is kept between 105° and 110° until the loss in weight amounts to 235–285 g. (Note 7), which requires approximately 2–3 hours, depending on the efficiency of the aspirator. If the temperature shows any tendency to rise above 110°, the oil bath should be lowered and the mixture cooled.

When the removal of the water is complete, the suction tube is removed and the stirrer and dropping funnel are replaced. The internal temperature is raised with extreme care to 118° and is held rigidly between 117° and 119° during the subsequent addition of 438 g. (236 ml.) of concentrated sulfuric acid (sp. gr. 1.84) from the dropping funnel. The sulfuric acid must be added dropwise over a period of 2.5–3.5 hours, and the temperature *must not* vary

from 117–119° (Note 8). After the addition is complete the temperature is maintained at 120° for 4 hours (Note 9) and finally at 123° for 3 hours. The reaction mixture is cooled below 100°, diluted with 1.5 l. of water, and allowed to cool overnight, preferably with stirring (Note 10). The diluted reaction mixture is poured with stirring into a mixture of 1.8 l. (1580 g.) of concentrated ammonium hydroxide (sp. gr. 0.9) and 3.5 kg. of ice in a 12-l. enameled pail. The resultant thick slurry is filtered through a large Büchner funnel (24–30 cm.), and the filtrate is discarded. The earth-colored precipitate is washed with four 700-ml. portions of water and then transferred to a 3-l. beaker and stirred with 1 l. of methanol for 15 minutes. The slurry is filtered and this process repeated (Note 11). The crude product at this point is a light chocolate brown and weighs about 800 g. when dried. It is purified by boiling for 30 minutes with 4.5 l. of chloroform (Note 12) to which has been added 30 g. of decolorizing carbon. The carbon and other humus-like material are removed by filtration from the hot chloroform solution by means of a 24-cm. warm Büchner funnel. The insoluble material is boiled with 500 ml. of chloroform, the resultant mixture filtered, and the combined filtrates concentrated by distillation from a steam bath to a volume of 1.5–2.5 l., at which point crystals of the 6-methoxy-8-nitroquinoline separate. The solution is then cooled to 5°, and the first crop of crystals is obtained by collection on a 24-cm. Büchner funnel. The crystals are transferred to a 1-l. beaker, stirred with 400 ml. of methanol for 15 minutes, and again collected on a Büchner funnel and washed with 200 ml. of methanol. The product consists of light-tan crystals which weigh 435–500 g. and melt at 158–160° (Note 13). By concentrating the filtrate to 400–500 ml., a second crop of crystals weighing 25–65 g. is obtained which, after washing with methanol in the same way as above, melts at 158–159°. The total yield is 460–540 g. (65–76%) (Note 14), (Note 15).

2. Notes

1. It is desirable to carry out the reaction without interruption. In order to do this, it is best to set up the apparatus and mix the arsenic oxide, 3-nitro-4-aminoanisole, and glycerol on one day and start the sulfuric acid addition the first thing in the morning of the following day. If the reaction must be interrupted, the mixture can be allowed to cool after it has been heated under reduced pressure. The yield is not affected, but great care must be exercised in reheating the reaction mixture since it sets to a glass, and it is very easy to superheat the outer portions while the center is still cold. If this happens, vigorous decomposition is very likely to occur.
2. Although powdered arsenic oxide was used, probably an equivalent amount of any form of the oxide, such as syrupy arsenic acid, would be suitable since the excess water would be removed when heated under reduced pressure.
3. The 3-nitro-4-aminoanisole was the technical commercial product, m.p. 124–126°, obtained from E. I. du Pont de Nemours and Company.
4. It is desirable to have a manometer in the system. The pressure should drop to approximately 30 mm. as the temperature approaches 105°. If, during the initial evacuation, foaming occurs, it will be necessary to loosen the stopper on the reaction flask or trap and let in air until foaming subsides and steady bubbling commences.
5. The oil bath can be heated by a hot plate which is connected in series to a variable resistance for temperature control. It may be heated with a Bunsen burner, but the temperature of the reaction must then be watched continually. The flask should be clamped in place in such a manner that the source of heat can be removed quickly if necessary.

6. The external temperature may be kept at about 110–115° but should not be raised above this, particularly after the internal temperature has reached 105°. If the temperature rises uncontrolled at this point, complete decomposition of the reaction mixture will result.
7. The loss in weight is dependent upon the quality of the arsenic oxide and glycerol used. If these are dry, the weight loss should be as indicated. The lower figure is equivalent to 1 mole of water for each mole of glycerol.
8. The success of the reaction depends upon the temperature control at this and subsequent points. Since the temperature is dependent upon at least four variables—the rate of addition of sulfuric acid, the rate of stirring, the heat of reaction which decreases as the reaction proceeds, and the heat applied—the temperature must be watched very closely. Too rapid addition of the sulfuric acid during the initial stages of the addition will result in an uncontrolled rise in temperature, terminating in the complete oxidation of the reaction mixture by the sulfuric acid. A large volume of sulfur dioxide is evolved, and the reaction mixture is converted into a voluminous, porous, carbon mass. *The progress of the reaction must be watched throughout its complete course and cannot be left unattended.*
9. The reaction is complete when a drop of the mixture on a piece of wet filter paper does not give an orange ring due to the presence of unreacted 3-nitro-4-aminoanisole. If the test is still positive at the end of the heating period, the temperature should be cautiously raised to 125° and heating continued until the test is negative. If the reaction does not go to completion, it is very difficult to remove this unused starting material from the product and it must be repeatedly decolorized and recrystallized.
10. On cooling, the sulfate salt of the 6-methoxy-8-nitroquinoline partially crystallizes from the reaction mixture. By stirring the mixture, the product comes down as a fine tan, microcrystalline precipitate. This can be isolated and crystallized, but it is more convenient to work it up in the form of the base.
11. These methanol washings remove much of the impurities, especially small amounts of unreacted nitroanisidine, with a minimum loss of product. The solubility of 6-methoxy-8-nitroquinoline in methanol at room temperature is 0.8 g. per 100 g. of solvent and at the boiling point is 4.1 g. per 100 g. of solvent. The solubility in chloroform, on the other hand, is 3.9 g. per 100 g. of solvent at room temperature and 14.2 g. at the boiling point. It is possible to obtain about 12 g. of product by working up these washings, but it is usually not worth the trouble.
12. The 4.5 l. of chloroform used is more than is necessary to dissolve the product, but this amount prevents the difficulties arising from crystallization in the Büchner funnel during filtration.
13. If, during the reaction, the temperature has not been properly regulated, the crystals may require another treatment with decolorizing carbon and crystallization from chloroform.
14. The product may also be recrystallized from hot ethylene dichloride using 300 ml. of solvent for each 100 g. The recovery is 80–90% of 6-methoxy-8-nitroquinoline melting at 160–161°.
15. By the same procedure the submitters have prepared 6-ethoxy-8-nitroquinoline in 70% yield, 8-methoxy-6-nitroquinoline in 68% yield, 6-chloro-8-nitroquinoline in 75% yield, and 6-methoxy-5-bromo-8-nitroquinoline in 69% yield from the properly substituted aromatic amines.

3. Discussion

6-Methoxy-8-nitroquinoline was first obtained by Schulemann and coworkers[1] by a modification of the Skraup reaction. Various other modifications of this reaction have been used.[2,3,4,5,6,7,8,9] The modification given here was the best of several tried and is taken from the procedure of Strukov.[10] It has been reported that 85% phosphoric acid may be used in place of sulfuric acid in certain Skraup reactions; thus with 3-nitro-4-aminoanisole, acrolein, and arsenic trioxide, with 85% phosphoric acid, a 60% yield of 6-methoxy-8-nitroquinoline was obtained.[11] A preparation from α-bromoacrolein has been reported.[12]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfate salt of the 6-methoxy-8-nitroquinoline

sulfuric acid (7664-93-9)

methanol (67-56-1)

chloroform (67-66-3)

Acrolein (107-02-8)

glycerol (56-81-5)

sulfur dioxide (7446-09-5)

ethylene dichloride (107-06-2)

arsenic acid (1327-52-2)

decolorizing carbon, carbon (7782-42-5)

phosphoric acid (7664-38-2)

ammonium hydroxide (1336-21-6)

6-Methoxy-8-nitroquinoline, Quinoline, 6-methoxy-8-nitro- (85-81-4)

arsenic oxide

3-nitro-4-aminoanisole (96-96-8)

nitroanisidine

6-ethoxy-8-nitroquinoline

8-methoxy-6-nitroquinoline

6-chloro-8-nitroquinoline

6-methoxy-5-bromo-8-nitroquinoline

arsenic trioxide

α-bromoacrolein

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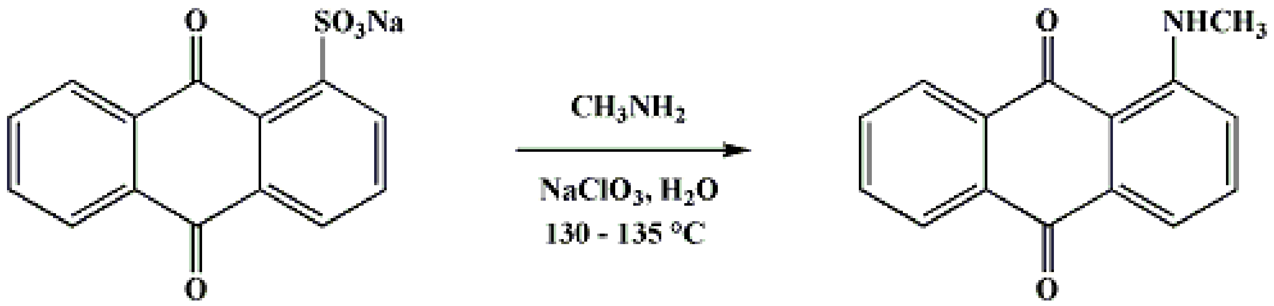
Organic Syntheses, CV 3, 573

1-METHYLAMINOANTHRAQUINONE

[Anthraquinone, 1-methylamino-]



Submitted by C. V. Wilson, J. B. Dickey, and C. F. H. Allen.
Checked by George L. Evans and R. S. Schreiber.

1. Procedure

A 1-gal. autoclave (p. 80) (Note 1) is charged with 399 g. (1.29 moles) of technical sodium anthraquinone-α-sulfonate (Note 2), 45 g. (0.43 mole) of sodium chlorate, 780 g. (6.25 moles) of a 25% aqueous solution of methylamine, and 1.2 l. of water. The mixture is heated, with stirring, for 12 hours at 130–135° (Note 3). The heat is then shut off, but stirring is continued so that the product separates in an easily removable form. When cold, the autoclave is opened and the contents are removed; the material adhering to the walls is removed by water. The solid is filtered on a 13-cm. Büchner funnel. The red product is washed with two 500-ml. portions of hot water (70°) and dried in the air. The yield of 1-methylaminoanthraquinone, melting at 166–171° (Note 4), is 180–199 g. (59–65%) (Note 5) and (Note 6).

2. Notes

1. A shaking autoclave employed for high-pressure hydrogenations may be used equally well, but the quantities taken must be reduced to 155 g. (0.5 mole) of sodium anthraquinone-α-sulfonate, 17.5 g. of sodium chlorate, 300 g. of a 25% aqueous methylamine solution, and 600 ml. of water. The checkers used a 2-gal. stirred autoclave (stainless steel).

2. A corresponding quantity of the potassium salt[1] can be utilized.

3. According to the checkers the heating time may be decreased to 8 hours if desirable.

4. The melting point varies slightly with the method of heating; if the bath is preheated to 160° before the sample is inserted, the melting point is 168–169.5° When taken in the ordinary way, the melting point is 166–171°. This product is sufficiently pure for most purposes. One recrystallization from toluene raises the melting point 1°.

5. The yield depends upon the purity of the sodium anthraquinone-α-sulfonate. Apparent yields of as high as 87% have been obtained. The checkers employed

technical-grade material, which apparently resulted in an appreciable decrease in the yields of 76–80% reported by the submitters.

6. α-Chloroanthraquinone[2] can be used as a starting material. In this case, 433 g. (1.79 moles) is taken, together with 1.5 l. of pyridine, 600 ml. of 25% aqueous methylamine, and 2.5 g. of a copper salt. The product is washed with dilute (2%) hydrochloric acid. The yield is 380–400 g. (90–95%).

3. Discussion

1-Methylaminoanthraquinone has been prepared from 1-chloro-, 1-bromo-, and 1-nitroanthraquinone by treatment with alcoholic methylamine under pressure,[3] from 1-methoxy- and 1-phenoxyanthraquinone with methylamine in pyridine solution at 150°;[4] from potassium anthraquinone-1-sulfonate with aqueous methylamine at 150–160°;[5,6] from 1-aminoanthraquinone by treatment with formaldehyde,[7] or methanol[8] in sulfuric acid or oleum; and by hydrolysis of *p*-toluenesulfonylmethylaminoanthraquinone with sulfuric acid.[9]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 575

References and Notes

1. *Org. Syntheses* Coll. Vol. **2**, 539 (1943).
2. *Org. Syntheses* Coll. Vol. **2**, 128 (1943).
3. Ger. pat. 144,634 [*Frdl.*, **7**, 201 (1902–1904)].
4. Ger. pat. 165,728 [*Frdl.*, **8**, 289 (1905–1907)].
5. Ger. pat. 175,024 [*Frdl.*, **8**, 283 (1905–1907)].
6. Ger. pat. 256,515 [*Frdl.*, **11**, 551 (1912–1914)].
7. Ger. pat. 156,056 [*Frdl.*, **8**, 288 (1905–1907)].
8. Ger. pat. 288,825 [*Frdl.*, **12**, 414 (1914–1916)].
9. Ullmann and Fodor, *Ann.*, **380**, 320 (1911).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

copper salt

1-chloro-, 1-bromo-, and 1-nitroanthraquinone

1-methoxy- and 1-phenoxyanthraquinone

sulfuric acid or oleum

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

methanol (67-56-1)

formaldehyde (630-08-0)

pyridine (110-86-1)

toluene (108-88-3)

sodium chlorate (7775-09-9)

methylamine (74-89-5)

α-Chloroanthraquinone (82-44-0)

potassium anthraquinone-1-sulfonate (30845-78-4)

1-aminoanthraquinone (82-45-1)

1-METHYLAMINOANTHRAQUINONE, Anthraquinone, 1-methylamino- (82-38-2)

sodium anthraquinone-α-sulfonate (128-56-3)

p-toluenesulfonylmethylaminoanthraquinone

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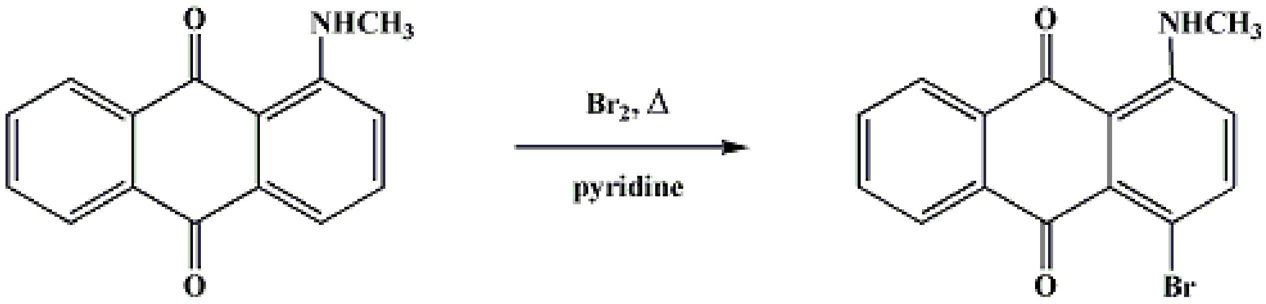
Organic Syntheses, CV 3, 575

1-METHYLAMINO-4-BROMOANTHRAQUINONE

[Anthraquinone, 1-methylamino-4-bromo-]



Submitted by C. V. Wilson
Checked by G. L. Evans and R. S. Schreiber.

1. Procedure

In a 2-l. three-necked flask having ground-glass joints and equipped with a mechanical stirrer, a condenser (Note 1), and a dropping funnel are placed 119 g. (0.5 mole) of 1-methylaminoanthraquinone (p. 573) and 600 ml. of pyridine (Note 2) and (Note 3). The stirrer is started, and 90 g. (29 ml., 0.56 mole) of bromine is added over a period of 9–10 minutes. The flask and contents are now heated on the steam bath for 6 hours with continuous stirring. At the end of this period the hot mixture is transferred from the flask to a beaker and allowed to cool. The solid that separates (Note 4) is collected on a Büchner funnel and is washed thoroughly with hot water to remove a considerable portion of pyridine hydrobromide which is precipitated along with the desired product. The resulting deep red 1-methylamino-4-bromoanthraquinone, after thorough drying, weighs 111–117 g. (70–74%). It melts at 193–195° and is pure enough for most purposes (Note 5).

2. Notes

1. An air condenser of any type is sufficient.
2. A good grade of pyridine is essential. Very poor results are obtained with the practical or technical grades.
3. Larger volumes of pyridine have been used, but the yield drops progressively with increasing amounts.
4. Some of the solid separates during the heating on the steam bath.
5. It may be recrystallized, if desired, from pyridine, by the use of 3.5 ml. per g.; the melting point is raised to 195–196°.

3. Discussion

4-Bromo-1-methylaminoanthraquinone has been prepared from 4-bromo-1-nitroanthraquinone and methylamine at 60°,[1] and from 1-methylaminoanthraquinone in pyridine solution by treatment with two moles of bromine.[2] This procedure is based on the

latter method.

References and Notes

1. Ger. pat. 144,634 [*Frdl.*, **7**, 201 (1902–1904)].
2. Ger. pat. 164,791 [*Frdl.*, **8**, 280 (1905–1907)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

bromine (7726-95-6)

pyridine hydrobromide (18820-82-1)

pyridine (110-86-1)

methylamine (74-89-5)

1-METHYLAMINOANTHRAQUINONE (82-38-2)

1-Methylamino-4-bromoanthraquinone, Anthraquinone, 1-methylamino-4-bromo-, 4-Bromo-1-methylaminoanthraquinone (128-93-8)

4-bromo-1-nitroanthraquinone

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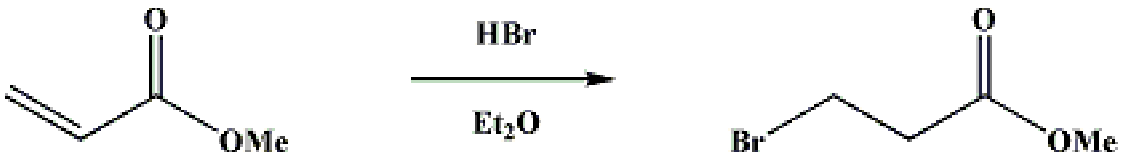
Organic Syntheses, CV 3, 576

METHYL β-BROMOPROPIONATE

[Propionic acid, β-bromo-, methyl ester]



Submitted by Ralph Mozingo and L. A. Patterson.
Checked by Nathan L. Drake and Homer Carhart.

1. Procedure

Six hundred and fifty grams of a 60% solution of methyl acrylate in methanol to which has been added 4 g. of hydroquinone (Note 1) is washed, successively, with 800-ml., 400-ml., and 200-ml. portions of a 7% sodium sulfate solution. The methyl acrylate layer is dried by shaking with 45 g. of anhydrous sodium sulfate for 20–30 minutes. The ester is then removed from the sodium sulfate by filtration and used without distillation. The yield is 280–325 g.

A solution of 258 g. (3 moles) of washed and dried methyl acrylate in 500 ml. of anhydrous ether is placed in a 1-l. round-bottomed flask. The flask is fitted with a rubber stopper carrying a drying tube and an 8-mm. glass inlet tube for hydrogen bromide. The inlet tube, which extends almost to the bottom of the flask, is connected through a 1-l. safety trap to a hydrogen bromide generator (Note 2). The flask with its contents is placed in an ice bath, and 245 g. (3.03 moles) of anhydrous hydrogen bromide is passed into the solution (Note 3). After the hydrogen bromide has been added, the flask is stoppered and allowed to stand for about 20 hours at room temperature.

The ether is removed by distillation (Note 4) from a hot-water bath. At the end of the distillation, the water bath is heated to 80–85°, and when no more liquid comes over at this temperature the residue is transferred to a 500-ml. modified Claisen distilling flask and distilled under reduced pressure. The methyl β-bromopropionate distils at 64–66°/18 mm. and weighs 410–428 g. (80–84%) (Note 5) and (Note 6).

2. Notes

1. Methyl acrylate in methanol is available from Rohm and Haas Company, Philadelphia, Pennsylvania. Since the ester polymerizes in the presence of peroxides, it is necessary to add some hydroquinone as an inhibitor. The ester should not be stored for long periods of time, even when it contains hydroquinone. Storage should be in a refrigerator.

2. The hydrogen bromide [*Org. Syntheses* Coll. Vol. 2, 338 (1943)] may be completely freed from bromine by bubbling it through a solution of phenol in carbon tetrachloride.
3. The addition may be as rapid as is convenient without the loss of ether due to the exothermic reaction.
4. The ether may be removed under anhydrous conditions and used for a subsequent preparation of the ester without further treatment.
5. Ethyl β-bromopropionate may be prepared in the same manner in about 90% yield. The boiling point of the ethyl ester is 77–79°/19 mm.
6. The residue consists largely of β-bromopropionic acid which may be recovered by distillation, b.p. 115–120°/18 mm., followed by recrystallization from carbon tetrachloride. The yield of this acid has never been more than 5% of the theoretical amount.

3. Discussion

Methyl β-bromopropionate has been prepared by the esterification of β-bromopropionic acid with methyl alcohol alone[1] and through the use of hydrogen bromide as a catalyst,[2] and by the direct addition of hydrogen bromide to methyl acrylate.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 338

References and Notes

1. Le Mer and Kamner, *J. Am. Chem. Soc.*, **53**, 2833 (1931).
2. Moureu, Murat, and Tampier, *Ann. chim.*, **15**, 221 (1921).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

methyl alcohol, methanol (67-56-1)

ether (60-29-7)

hydroquinone (123-31-9)

phenol (108-95-2)

hydrogen bromide (10035-10-6)

bromine (7726-95-6)

sodium sulfate (7757-82-6)

carbon tetrachloride (56-23-5)

β-Bromopropionic acid (590-92-1)

Ethyl β-bromopropionate (539-74-2)

methyl acrylate (96-33-3)

METHYL β-BROMOPROPIONATE, Propionic acid, β-bromo-, methyl ester (3395-91-3)

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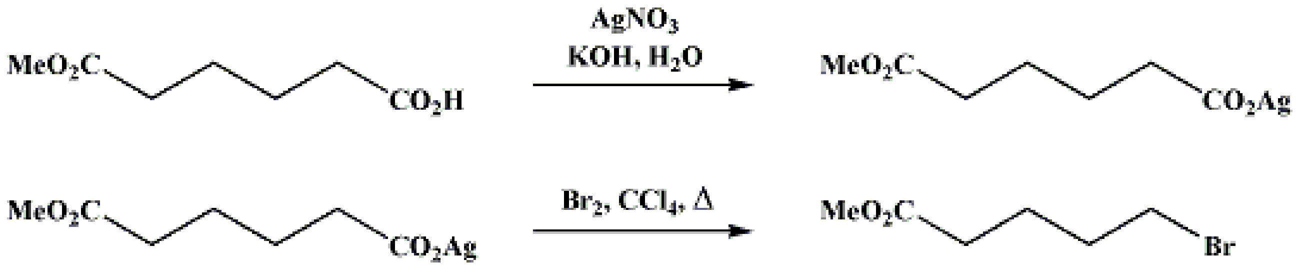
Organic Syntheses, CV 3, 578

METHYL 5-BROMOVALERATE

[Valeric acid, δ-bromo-, methyl ester]



Submitted by C. F. H. Allen and C. V. Wilson.
Checked by Cliff S. Hamilton and Noboru Tosaya.

1. Procedure

To a solution of 33 g. (0.5 mole) of potassium hydroxide (Note 1) in 1.5 l. of distilled water in a 5-l. flask or other appropriate container fitted with a mechanical stirrer is added 80 g. (0.5 mole) of methyl hydrogen adipate (Note 2). With continuous stirring a solution of 85 g. (0.5 mole) of silver nitrate in 1 l. of distilled water is added rapidly (about 15 minutes). The precipitated methyl silver adipate is collected on a Büchner funnel, washed with methanol, and dried in an oven at 50–60°. For the next step the dried silver salt is finely powdered and sieved through a 40-mesh screen. The combined yield from two such runs is 213 g. (80%).

The 213 g. (0.8 mole) of finely powdered silver salt is placed in a 1-l. three-necked flask (Note 3); two necks of the flask are stoppered, and the third is connected to a water pump through a U-tube or flask containing Drierite. The flask is then placed in an oil bath and evacuated to a pressure of about 15 mm. The temperature of the oil bath is maintained at 100–110° for 36 hours (Note 4) and (Note 5).

The pressure in the flask is restored to that of the atmosphere. The flask is removed from the oil bath and equipped with a dropping funnel, condenser, and mechanical stirrer (Note 6). To the salt is added 350 ml. of dry carbon tetrachloride (Note 7); the stirrer is started, and 117 g. (40 ml., 0.73 mole) of dry bromine (p. 790, Note 2) is added through the dropping funnel over a 30- to 40-minute period. Occasional cooling may be necessary as the reaction is quite vigorous at first. When all the bromine has been added, the mixture is heated for 1 hour on a steam bath. It is then filtered and the silver bromide washed thoroughly on the filter with 100 ml. of warm carbon tetrachloride. The filtrate is washed once with 100 ml. of 10% sodium carbonate solution and dried over 30–40 g. of Drierite. The solvent is removed and the residue distilled under reduced pressure. The yield of product boiling at 75–80°/4 mm. is 101–106 g. The yield is 65–68% based on the weight of the methyl silver adipate before drying under reduced pressure, or 52–54% based upon methyl hydrogen adipate.

2. Notes

1. Reagent grade potassium hydroxide containing 85% potassium hydroxide is used.
2. The methyl hydrogen adipate was Eastman Kodak grade.
3. Drying is carried out in the flask in which the final reaction is to be run in order to avoid a transfer. The success of this preparation depends upon the exclusion of moisture. The silver salt retains traces of water tenaciously.
4. If the indicated pressure is maintained the water pump may be disconnected, but owing to

leaks it will usually be found necessary to re-evacuate several times over the 36-hour period.
5. A good vacuum oven would serve for drying just as well, but the temperature of the salt should not exceed 110°.
6. For best results all equipment should be thoroughly dried.
7. The carbon tetrachloride is dried over phosphorus pentoxide or some other drying agent.

3. Discussion

This method with some slight modifications is applied in the synthesis of ω-bromo esters from C_5 to C_{17}.[1] Methyl 5-bromovalerate has been prepared by treating the silver salt of methyl hydrogen adipate with bromine.[1] The ethyl ester has been prepared from the acid by esterification[2,3] or through the acid chloride.[3]

References and Notes

1. Hunsdiecker and Hunsdiecker, *Ber.*, **75**, 296 (1942).
2. Cloves, *Ann.*, **319**, 367 (1901).
3. Merchant, Wickert, and Marvel, *J. Am. Chem. Soc.*, **49**, 1829 (1927).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Drierite

silver salt of methyl hydrogen adipate

methanol (67-56-1)

silver nitrate (7761-88-8)

sodium carbonate (497-19-8)

bromine (7726-95-6)

carbon tetrachloride (56-23-5)

potassium hydroxide (1310-58-3)

Methyl 5-bromovalerate, Valeric acid, δ-bromo-, methyl ester (5454-83-1)

methyl hydrogen adipate (627-91-8)

methyl silver adipate

silver bromide (7785-23-1)

phosphorus pentoxide (1314-56-3)

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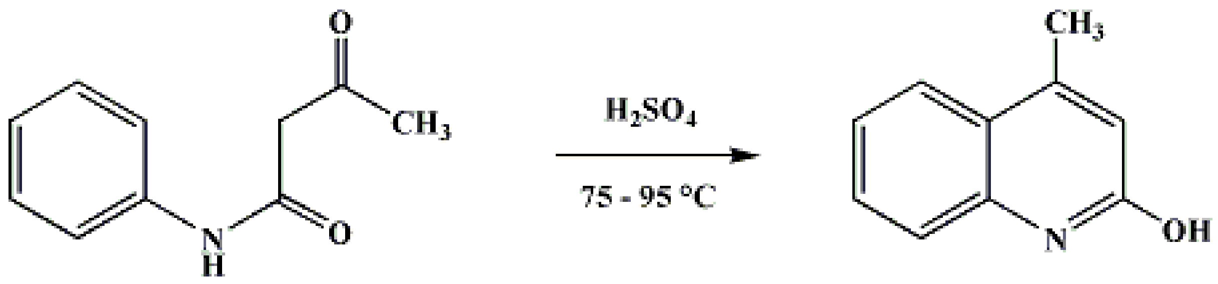
Organic Syntheses, CV 3, 580

4-METHYLCARBOSTYRIL

[Carbostyril, 4-methyl-]



Submitted by W. M. Lauer and C. E. Kaslow.
Checked by C. F. H. Allen and H. W. J. Cressman.

1. Procedure

One hundred seventy-seven grams (1 mole) of acetoacetanilide is added in small portions by means of a spatula to 185 ml. of concentrated sulfuric acid which has been heated previously to 75° (Note 1) in a 1-l. three-necked flask provided with a mechanical stirrer and a thermometer which extends into the liquid. The temperature of the mixture is maintained at 70–75° by intermittent cooling until nearly all the acetoacetanilide has been added. The last 10–15 g. is added without cooling, and the temperature rises to 95°; the addition requires 20–30 minutes. The heat of reaction maintains the temperature at 95° for about 15 minutes; the reaction mixture is then kept an additional 15 minutes at 95° by external heating. After the solution has cooled to 65°, it is poured into 5 l. of water with vigorous stirring.

After cooling, the product is filtered by suction, washed with four 500-ml. portions of water and two 250-ml. portions of methanol, and air-dried. The yield of 4-methylcarbostyril is 138–144 g. (86–91%). This material, which melts at 219–221°, is suitable for preparing 2-chlorolepidine (p. 194). It may be purified further by recrystallization from 95% ethanol. For recrystallization 39 g. is dissolved in 650 ml. of solvent; the recovery is 33–33.5 g., and the melting point of the product is 222–224°.

2. Notes

1. The reaction flask must be so situated that it can be cooled rapidly. The submitter reports that the yield was reduced to 72% in one run in which the temperature reached 120°.

3. Discussion

The only useful method for preparing 4-methylcarbostyril is that of Knorr,[1] described

by Mikhailov.[2] Two modifications include the use of aniline and ethyl acetoacetate, without isolation of acetoacetanilide,[3] and the use of boron trifluoride as a cyclization agent.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 194

References and Notes

1. Knorr, *Ann.*, **236**, 83 (1886).
2. Mikhailov, *J. Gen. Chem. U.S.S.R.*, **6**, 511 (1936) [*C. A.*, **30**, 6372 (1936)].
3. Hauser and Reynolds, *J. Am. Chem. Soc.*, **70**, 2402 (1948).
4. Killelea, *J. Am. Chem. Soc.*, **70**, 1971 (1948).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

sulfuric acid (7664-93-9)

methanol (67-56-1)

aniline (62-53-3)

Ethyl acetoacetate (141-97-9)

boron trifluoride (7637-07-2)

Acetoacetanilide (102-01-2)

2-Chlorolepidine (634-47-9)

4-Methylcarbostyril, Carbostyril, 4-methyl- (607-66-9)

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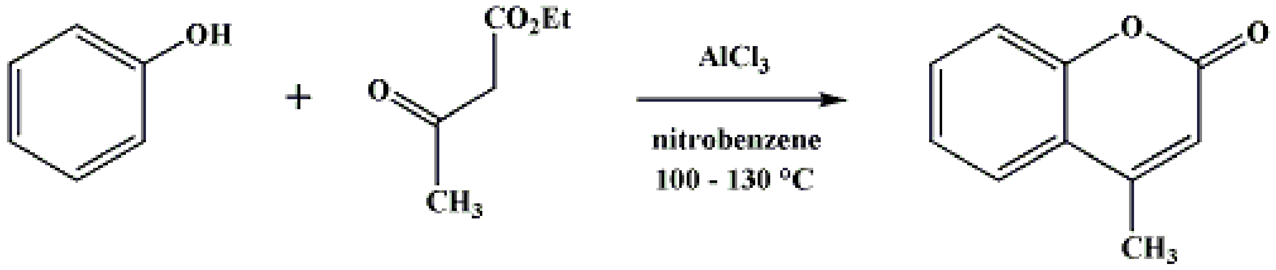
Organic Syntheses, CV 3, 581

4-METHYLCOUMARIN

[Coumarin, 4-methyl-]



Submitted by Eugene H. Woodruff
Checked by Nathan L. Drake and Carl Blumenstein.

1. Procedure

In a 5-l. three-necked round-bottomed flask, fitted with a sealed stirrer, dropping funnel, and air condenser, the open end of which is connected to a gas-absorption trap, are placed 188 g. (2 moles) of phenol and 268 g. (2 moles) of ethyl acetoacetate in 300 ml. of dry nitrobenzene (Note 1) and (Note 2). The mixture is heated to 100° by means of an oil bath, stirring is started, and 532 g. (4 moles) of anhydrous aluminum chloride dissolved in 2.1 l. of dry nitrobenzene is added over a period of 30–45 minutes (Note 3). The dropping funnel is then replaced by a thermometer, and the temperature of the solution is raised to 130° and held there 3 hours (Note 4). By this time the evolution of hydrogen chloride will have practically ceased.

The solution is cooled until its temperature is approximately that of the room, and 500 ml. of a mixture of equal parts of concentrated hydrochloric acid and water is added with stirring. The flask is then arranged for steam distillation and heated with a free flame while steam is passed into the reaction mixture until about 200 ml. of distillate is collected (Note 5). While hot, the mixture is placed in a large separatory funnel and the lower aqueous layer removed; the nitrobenzene layer is filtered through a Büchner funnel (Note 6) and (Note 7).

The nitrobenzene is then removed by vacuum distillation using a 2-l. Claisen flask, and the residue in the flask is distilled under diminished pressure; the fraction boiling at 180–195°/15 mm. is collected (Note 8) and (Note 9). The red-yellow oil, which solidifies on cooling, amounts to 128–176 g. (40–55%) and is sufficiently pure for some purposes (Note 10). A nearly white product can be obtained by dissolving the crude product in ether, shaking the ether solution with portions of 5% sodium hydroxide solution until no color appears in the aqueous layer, evaporating the ether, and recrystallizing the residue from a mixture of petroleum ether (b.p. 60–90°, Skellysolve B) and benzene (Note 11). The recrystallized product melts at 83–84°; the recovery is 80–85%.

2. Notes

1. Methyl acetoacetate has been used but insufficient data have been obtained as to the

yield produced.
2. Commercial nitrobenzene is dried by distillation under reduced pressure until the distillate is clear. The residue is suitable for use without other treatment.
3. The aluminum chloride is added in 25- to 50-g. portions to the 2.1 l. of dry nitrobenzene contained in a 5-l. round-bottomed flask with stirring after each addition. The temperature may rise to 80–90° during the addition; occasional cooling of the flask under running water is necessary. After all the aluminum chloride has been added, the solution is cooled to room temperature. A small amount of aluminum chloride may settle to the bottom.
In one instance when the final cooling was omitted the temperature continued to rise and a large amount of hydrogen chloride was evolved. The residue in the flask was a thick paste. Addition of a portion of the paste to water caused nitrobenzene to separate. However, this batch was not suitable for condensation.
4. Below 100° the condensation does not take place; at 150° tar is formed and no coumarin can be isolated.
5. Some unchanged ester distils before the nitrobenzene; its removal aids in the subsequent separation of the two layers.
6. If a sufficiently large funnel is not available the separation may be done by dividing the solution in portions to suit the funnel available. If too much steam has condensed during the distillation, the aqueous layer may appear on top.
7. The tarry by-products clog filter paper immediately; a small quantity of filter aid may be used to promote the filtration. If the condensation has been satisfactory only a small amount of material will be retained, and this step may be omitted. Occasionally a considerable amount of lumpy, tarry material is removed; filtration is then more difficult, and the yield is lower. The tar, on distillation, yields no coumarin.
8. The recovered nitrobenzene, after being washed with water and dried as in (Note 2), may be used again. The loss is from 400 to 700 ml.
9. Considerable tar remains in the distillation flask. The tar is best poured immediately into a flat pan of water or a sink, where it solidifies to a hard brittle mass; that adhering to the walls of the flask is easily removed by adding 100–200 ml. of nitrobenzene to the flask and heating the solvent to boiling under atmospheric pressure.
10. According to the submitter, when quantities 3 times this size are used, the yield of distilled material is 38–50%.
11. The ratio of petroleum ether to benzene should be 8 to 2.

3. Discussion

4-Methylcoumarin is prepared by the condensation of phenol and acetoacetic ester. Concentrated sulfuric acid[1,2] and 73% sulfuric acid have been used.[3,4] The method given here was mentioned by Sethna, Shah, and Shah,[5] and the procedure is adapted from that of the same authors[6] for another coumarin derivative.

References and Notes

1. Von Pechmann and Duisberg, *Ber.*, **16**, 2127 (1883).
2. Von Pechmann and Kraft, *Ber.*, **34**, 421 (1901).
3. Peters and Simonis, *Ber.*, **41**, 831 (1908).
4. Fries and Volk, *Ann.*, **379**, 94, footnote 1 (1911).

5. Sethna, Shah, and Shah, *Current Sci.*, **6**, 93 (1937) [*C. A.*, **32**, 549 (1938)].

6. Sethna, Shah, and Shah, *J. Chem. Soc.*, **1938**, 228.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

acetoacetic ester

sulfuric acid (7664-93-9)

hydrogen chloride, hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether (60-29-7)

sodium hydroxide (1310-73-2)

phenol (108-95-2)

aluminum chloride (3495-54-3)

Nitrobenzene (98-95-3)

Ethyl acetoacetate (141-97-9)

4-Methylcoumarin, Coumarin, 4-methyl- (607-71-6)

Methyl acetoacetate (105-45-3)

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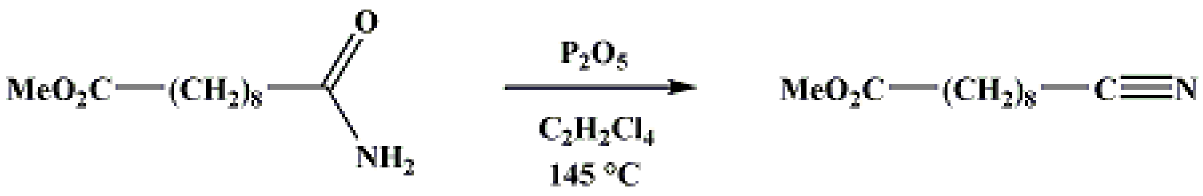
Organic Syntheses, *CV 3*, 584

METHYL ω-CYANOPELARGONATE

[Pelargonic acid, θ-cyano-, methyl ester]



Submitted by W. S. Bishop
Checked by C. F. H. Allen and J. VanAllan.

1. Procedure

Caution! Tetrachloroethane is toxic; the operations should be conducted in a hood.

In a 1.5-l. Erlenmeyer flask to which is attached a reflux condenser, 190 g. (0.88 mole) of methyl sebacamate (p. 613) is dissolved in 200 ml. of boiling tetrachloroethane. The solution is allowed to cool to 40–50° (Note 1), 95 g. (0.67 mole) of phosphorus pentoxide is added (Note 2), and the mixture is stirred well by means of a glass rod. The mixture is heated in an oil bath to 120° (thermometer in oil), and a second 95-g. portion of phosphorus pentoxide is added. After the mixture has been heated at 145° for 30 minutes with occasional hand stirring, the liquid is decanted. The residue is heated at 145° with 200 ml. of tetrachloroethane for 30 minutes with occasional stirring, and the liquid is decanted. This process is repeated once. The combined extracts are placed in a 1-l. flask, and most of the solvent is distilled under the reduced pressure of a water pump. The residue is transferred to a 300-ml. flask, and the remainder of the solvent is removed (Note 3). When no more distillate comes over, the receiver is changed, the water pump is replaced by an oil pump, and the residue is fractionated (Note 4). The yield of methyl ω-cyanopelargonate boiling at 121–124°/1 mm. (Note 5) is 119–124 g. (69–71%).

2. Notes

1. The slush that results on cooling is easily mixed with the phosphorus pentoxide.
2. The phosphorus pentoxide is weighed rapidly on a piece of paper, from which it can be slid quickly into the flask.
3. About 550–560 ml. of tetrachloroethane is recovered. Ground-glass equipment is preferable for the distillations.
4. There is no fore-run. At 1 mm., the thermometer reads about 118° when the first drop appears at the end of the side tube of the distilling flask. There is a 5- to 6-g. fraction, b.p. 124–135°/1 mm., and some residue.

5. Other boiling points are 154°/5 mm. and 170°/14 mm.

3. Discussion

Methyl ω-cyanopelargonate has also been prepared by esterification of ω-cyanopelargonic acid with methyl sulfate[1] or methanol,[2] and by dehydration of methyl sebacamate with phosphorus pentoxide[3] or thionyl chloride.[4] The procedure described appears in the literature.[1,3]

References and Notes

1. Biggs and Bishop, *J. Am. Chem. Soc.*, **63**, 944 (1941).
2. Biggs, U. S. pat. 2,339,672 [*C. A.*, **38**, 3990 (1944)].
3. Bishop, U. S. pat. 2,277,033 [*C. A.*, **36**, 4636 (1942)].
4. Soffer, Strauss, Trail, and Sherk, *J. Am. Chem. Soc.*, **69**, 1884 (1947).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Pelargonic acid, θ-cyano-, methyl ester

methanol (67-56-1)

thionyl chloride (7719-09-7)

methyl sulfate (75-93-4)

tetrachloroethane (630-20-6)

Methyl ω-cyanopelargonate (53663-26-6)

Methyl sebacamate (53663-35-7)

ω-CYANOPELARGONIC ACID (5810-19-5)

phosphorus pentoxide (1314-56-3)

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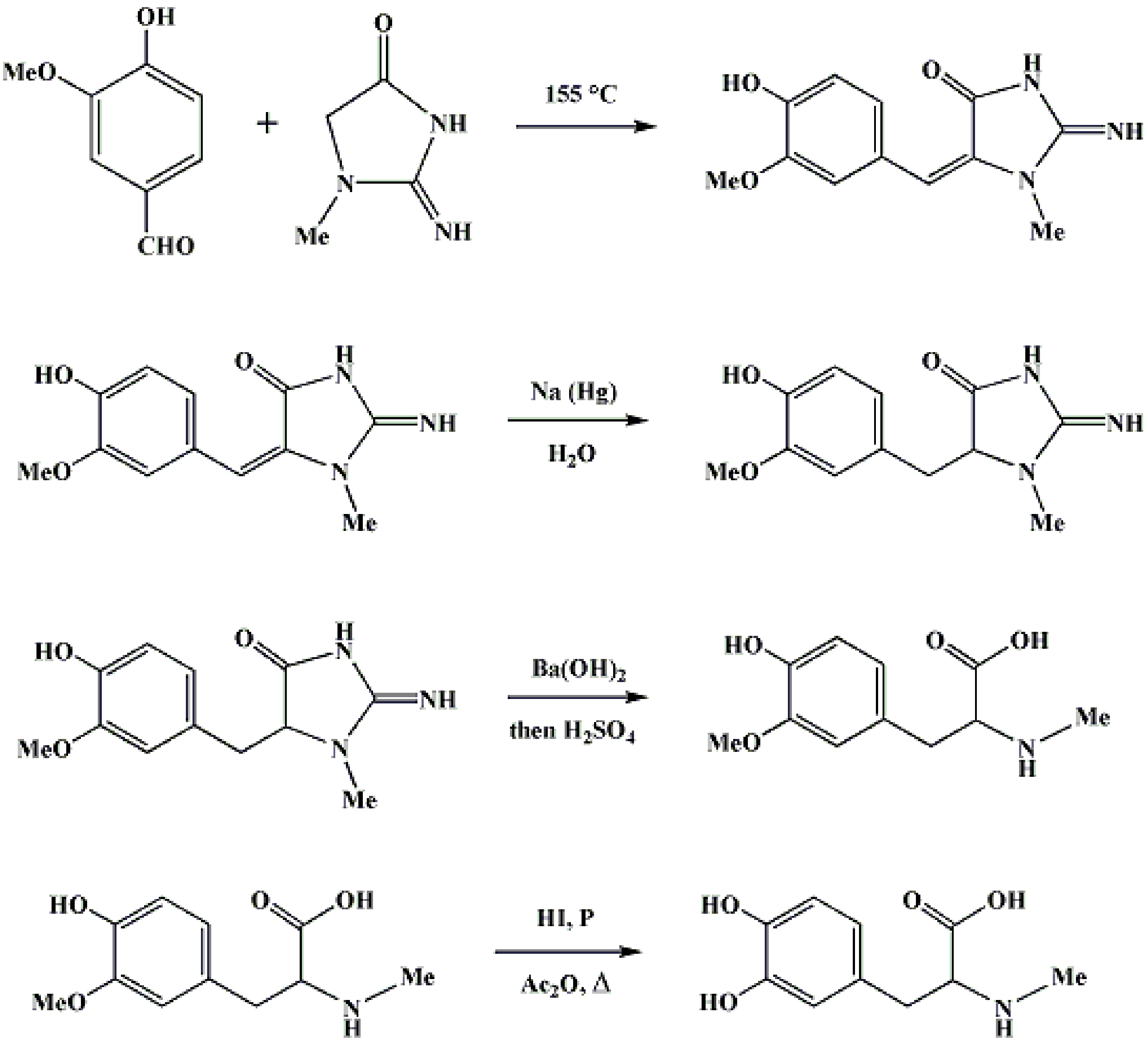
Organic Syntheses, CV 3, 586

N-METHYL-3,4-DIHYDROXYPHENYLALANINE

[Alanine, β-(3,4-dihydroxyphenyl)-N-methyl-]



Submitted by V. Deulofeu and T. J. Guerrero.
Checked by Homer Adkins, Harold H. Geller, and Everett E. Bowden.

1. Procedure

A. 5-(3-*Methoxy*-4-*hydroxybenzal*)*creatinine* (I). In a large Pyrex test tube (51 mm. outside diameter and 200 mm. long) is placed an intimate mixture of 11.3 g. (0.1 mole) of creatinine [*Org. Syntheses* Coll. Vol. **1**, 172 (1941)] and 24 g. (0.16 mole) of vanillin. The tube is placed in an oil bath, which is then heated to 170°, and the mixture is melted while it is constantly agitated (Note 1). The temperature of the mixture reaches 155° in about 10 minutes; reaction then begins, and water is evolved. After 3–5 minutes longer, evolution of water ceases, and the mixture solidifies. The tube is heated for 3 minutes more, and then it is removed from the bath and allowed to cool.

When the temperature has fallen to 50–60°, 50 ml. of ethanol is added and the mixture is heated gently by occasional immersion in the warm oil bath. The solid partially disintegrates and forms a

suspension. The suspension is filtered, and the solid remaining in the tube is warmed with a second 50-ml. portion of ethanol. This operation is repeated until all the orange-colored condensation product has been transferred to the filter. The material on the filter is then washed with three successive 30-ml. portions of water at 60°.

After drying, the crude product weighs 24 g. (95%), melts at 261–263°, and is suitable for use in the next step. A pure product, which melts at 273°, may be obtained by recrystallizing the crude material from acetic acid.

B. *5-(3-Methoxy-4-hydroxybenzyl)creatinine* (II). To a suspension of 24 g. (0.1 mole) of the crude condensation product in 150 ml. of water, contained in a 500-ml. beaker, there is added, with continuous agitation, 180 g. of 3% sodium amalgam (Note 2). The amalgam is added in six portion, at intervals of 5 minutes. The solid dissolves, and the initial orange-red color of the solution slowly fades as the reduction proceeds. With good agitation, decolorization is complete in 45–60 minutes, if the starting material is pure. When the crude condensation product is used, the color of the solution fades to a faint, but permanent, yellow tint, which should mark the end point of the reduction.

The solution is decanted from the mercury and filtered from suspended impurities. The filtrate is stirred and is acidified with hydrochloric acid to *p*H 6.6, phenol red being used as the indicator (Note 3). After standing for 2 hours at 0°, the mixture is filtered and the solid is washed with a little cold water and dried. The product (free base) is microcrystalline, weighs 17.5–18 g. (72–74%), and usually melts at 167–169° (Note 4). After solidification from fusion, the substance melts at 226–228°. When recrystallized from water, the substance melts at 231–233°. The crude product may be used for the subsequent hydrolysis.

C. *N-Methyl-(3-methoxy-4-hydroxyphenyl)alanine* (III). In a 2-l. round-bottomed flask (Note 5), 18 g. (0.07 mole) of the crude reduction product is refluxed for 12 hours with a solution of 180 g. of crystalline barium hydroxide in 270 ml. of water. The hot solution is diluted with 1.2 l. of water, and the barium is precipitated by addition of 250–270 ml. of 6 *N* sulfuric acid (Note 6). The precipitated barium sulfate is separated by centrifuging and washed with two 100-ml. portions of water; the combined water; solutions are evaporated under reduced pressure at 50° to a volume of about 50 ml. The acid solution is made alkaline to litmus by addition of about 10 ml. of a 12% solution of ammonium hydroxide in water. After standing for 24 hours at 0°, the mixture is filtered, and the solid is washed with cold water and dried. The yield is 12 g. (74%) (Note 7). On rapid heating, the solid melts at 273–275°. When recrystallized from water, the substance melts at 276–278°. The crude product may be used for the next step.

D. *N-Methyl-3,4-dihydroxyphenylalanine* (IV). In a carbon dioxide atmosphere, 12 g. (0.05 mole) of the methoxy compound is boiled gently for 3 hours with 24 g. of red phosphorus and a mixture of 60 ml. of acetic anhydride and 60 ml. of hydriodic acid (sp. gr. 1.7). The phosphorus is then removed by filtration and washed with 25 ml. of 50% acetic acid. The filtrates are combined and, in a current of carbon dioxide, are evaporated to a syrup at 50° under 35 mm. pressure. A 60-ml. portion of warm water is then added, and the solution is evaporated as before. The residue is dissolved in 100 ml. of water, and dilute ammonia (10% by volume) is added until the solution does not change Congo red paper to blue (Note 8). The mixture is allowed to stand for 2 hours at 0°, and then the white crystalline precipitate is filtered. The precipitate is washed on the funnel with a little water containing sulfur dioxide, and is dried by washing with ethanol and ether. The product weighs 9.5 g. (82%). When slowly heated it becomes slightly brown at 230° and melts at 282–283°; when rapidly heated it becomes slightly brown at 255–260° and melts at 290–292°.

This material may be purified by boiling 1 g. of it with 50 ml. of water containing sulfur dioxide, filtering the solution, and keeping the filtrate at 0° for 24 hours. The purified product (0.74 g.), when slowly heated, becomes slightly brown at 245° and melts at 287°; when rapidly heated it becomes

slightly brown at 260° and melts at 298–300°.

2. Notes

1. Sometimes the evolution of water is too rapid, and there is excessive foaming. The reaction may be moderated by removing the tube from the oil bath.
2. The amalgam may be made by adding 5-mm. cubes of sodium (5.4 g.) to 175 g. of mercury, warmed to 30–40°, and contained in a mortar or Erlenmeyer flask. The mortar is covered with an asbestos board having a small hole in the center. The cubes of sodium are fixed on the end of a pointed glass rod and are quickly pushed through this hole beneath the surface of the mercury. A more convenient method is described in Fieser, *Experiments in Organic Chemistry*, 2nd Ed., 1941, D. C. Heath and Company, Boston, p. 419.
3. The solution becomes dark in color if allowed to stand overnight.
4. In some cases the melting point may be as low as 98°; but after melting and solidifying, the substance melts at 226–228°.
5. A large flask should be used, since the mixture foams during the hydrolysis.
6. An excess of acid must be added to make certain that all the amino acid is in solution.
7. The yield can be increased slightly by evaporation of the mother liquor.
8. If the solution is made too alkaline, colored impurities precipitate. Neutralization must be performed carefully since the end point to Congo red is reached just before the colored impurities precipitate.

3. Discussion

5-(3-Methoxy-4-hydroxybenzal)creatinine was first prepared by a similar method by Richardson, Welch, and Calvert.[1]

N-Methyl-3,4-dihydroxyphenylalanine has been prepared by methylation of α-acetamino-3,4-methylenedioxycinnamic acid, followed by reduction and hydrolysis of the product;[2] and by a method similar to that outlined above.[3]

N-Methylaminoaromatic acids have been prepared by a variety of methods: by the reaction between methylamine and an α-bromo acid;[4] by condensing methylhydantoin with aromatic aldehydes;[5] by condensation of creatinine[6] or benzoyl sarcosine with aromatic aldehydes;[7] by methylation of the toluenesulfonyl derivative of the amino acid;[8] and by substituting methylamine for ammonia in the Strecker synthesis.[9]

References and Notes

1. Richardson, Welch, and Calvert, *J. Am. Chem. Soc.*, **51**, 3074 (1929).
2. Heard, *Biochem. J.*, **27**, 54 (1933).
3. Guerrero and Deulofeu, *Ber.*, **70**, 947 (1937).
4. Friedmann and Gutmann, *Biochem. Z.*, **27**, 491 (1910).
5. Johnson and Nicolet, *Am. Chem. J.*, **47**, 459 (1912).
6. Nicolet and Campbell, *J. Am. Chem. Soc.*, **50**, 1155 (1928); Deulofeu and Mendivelzua, *Ber.*, **68**, 783 (1935).
7. Deulofeu, *Ber.*, **67**, 1542 (1934).
8. Fischer and Lipschitz, *Ber.*, **48**, 360 (1915).
9. Kanewskaja, *J. prakt. Chem.*, (2) **124**, 48 (1929).

Appendix

Compounds Referenced (Chemical Abstracts Registry Number)

N-Methylaminoaromatic acids

α-bromo acid

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ammonia (7664-41-7)

ether (60-29-7)

acetic anhydride (108-24-7)

phenol (108-95-2)

sulfur dioxide (7446-09-5)

PHOSPHORUS (7723-14-0)

mercury (7439-97-6)

carbon dioxide (124-38-9)

barium sulfate (7727-43-7)

sodium (13966-32-0)

hydriodic acid (10034-85-2)

Creatinine (60-27-5)

ammonium hydroxide (1336-21-6)

barium hydroxide (17194-00-2)

barium (7440-39-3)

methylamine (74-89-5)

vanillin (121-33-5)

N-Methyl-3,4-dihydroxyphenylalanine, Alanine, β-(3,4-dihydroxyphenyl)-N-methyl- (53663-27-7)

α-acetamino-3,4-methylenedioxycinnamic acid

methylhydantoin (616-04-6)

benzoyl sarcosine (2568-34-5)

N-Methyl-(3-methoxy-4-hydroxyphenyl)alanine

5-(3-Methoxy-4-hydroxybenzal)creatinine (29974-40-1)

5-(3-Methoxy-4-hydroxybenzyl)creatinine

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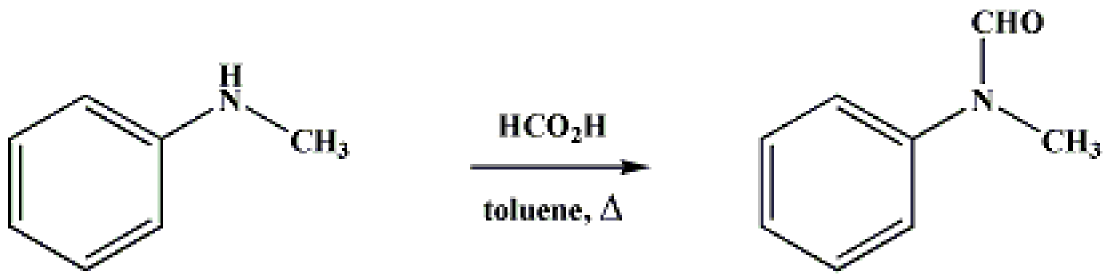
Organic Syntheses, CV 3, 590

N-METHYLFORMANILIDE

[Formanilide, N-methyl-]



Submitted by L. F. Fieser and J. E. Jones.
Checked by C. F. H. Allen and J. VanAllan.

1. Procedure

In a 3-l. round-bottomed flask fitted with a 3-ft. indented column to which is attached a condenser set for downward distillation are placed 321 g. (3 moles) of methylaniline, 300 g. of formic acid (85–90%), and 1.8 l. of toluene (Note 1). The solution is distilled slowly. As long as the azeotrope containing water is present, the temperature of the vapor is 87–88°; when the water has been removed, the temperature rises to 108–110° (Note 2). The distillation is continued until approximately 1.5 l. of toluene has been collected (5–6 hours). The residue is then transferred to a modified Claisen flask and distilled under reduced pressure, the portion boiling at 114–121°/8 mm. being collected. This has a freezing point of 13.6–13.7°; n_D^{29} 1.553–1.555. The yield is 380–393 g. (93–97%). This product is satisfactory for the preparation of aldehydes. Upon redistillation it boils at 117–121°/8 mm., 130–132°/22 mm. The freezing point and refractive index are unchanged (Note 3).

2. Notes

1. The toluene serves to remove the water and minimize side reactions.
2. The water layer of the distillate is separated; it amounts to 140–150 ml.
3. If a water separator with a stopcock is employed, in such a way that the organic solvent is returned to the reaction flask, it is possible to use 200 ml. of benzene in place of the 1.8 l. of toluene (J. Meek, private communication).

3. Discussion

N-Methylformanilide has been obtained in a yield of 67.5% by heating methylaniline with formamide in glacial acetic acid solution.[1] The method above is a modification of that of Morgan and Grist,[2] who heated the amine and formic acid in the absence of a solvent or water-carrier (the present authors obtained a yield of only 40–50% by that

procedure).

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 98
- Org. Syn. Coll. Vol. 4, 915

References and Notes

1. Hirst and Cohen, *J. Chem. Soc.*, **67**, 830 (1895).
2. Morgan and Grist, *J. Chem. Soc.*, **113**, 690 (1918).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

acetic acid (64-19-7)

Benzene (71-43-2)

formamide (75-12-7)

formic acid (64-18-6)

toluene (108-88-3)

methylaniline (100-61-8)

N-methylformanilide, Formanilide, N-methyl- (93-61-8)

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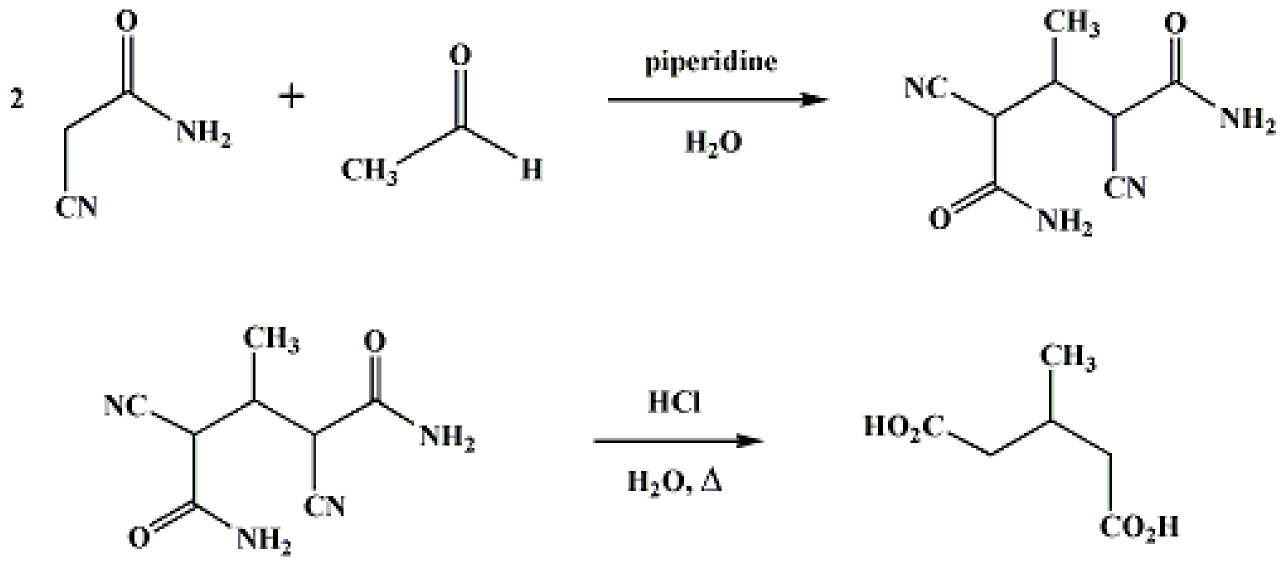
β-METHYLGLUTARIC ACID

[Glutaric acid, β-methyl-]



Submitted by Robert E. Kent and S. M. McElvain.
Checked by Lee Irvin Smith and G. A. Boyack.

1. Procedure

A. *α,α'-Dicyano-β-methylglutaramide*. In a 6-l. flask, 520 g. (6.2 moles) of recrystallized cyanoacetamide (Note 1) is dissolved in 3.4 l. of water, and the solution is cooled to 10° and filtered if it is not clear (Note 2). While the flask is shaken constantly, 137.5 g. (3.1 moles) of freshly distilled acetaldehyde and 20 ml. of piperidine are added *successively* to the solution. After the mixture has stood at room temperature for 2 hours, the flask is transferred to an ice-salt bath and the mixture is partially frozen. During this operation, the flask should be shaken frequently. After 30 minutes, α,α'-dicyano-β-methylglutaramide begins to deposit, and when the precipitation is complete (about 1 hour), the mixture is allowed to come to room temperature in order to melt the ice that is present. The precipitate is then filtered with suction and washed thoroughly with cold distilled water. The yield is 420–425 g. (71%) of a white, powdery solid which melts at 152–157° (Note 3).

B. *β-Methylglutaric acid.* In a 5-l. flask are placed 400 g. of the amide and 1 l. of concentrated hydrochloric acid; the mixture is warmed on a steam bath until solution is complete, after which it is diluted with 1 l. of water and refluxed for 8 hours. The amber-colored solution is saturated with sodium chloride and extracted with five 600-ml. portions of ether. The combined ether extracts are dried for 1 hour over phosphorus pentoxide, and the solvent is removed by distillation. The residue, crude β-methylglutaric acid, weighs 238–240 g. (80%) and melts at 79–82° with previous softening. This product is recrystallized from about 250 ml. of 10% hydrochloric acid. The recovery is about 90% (Note 4), and the purified product melts at 85–86°.

2. Notes

1. Ammonia exerts a hindering effect on this condensation, and the yield is greatly reduced when crude cyanoacetamide is used.
2. At 10°, cyanoacetamide sometimes crystallizes. The mixture should not be filtered until it is certain that the precipitate contains no cyanoacetamide. Any cyanoacetamide that separates redissolves quickly after the acetaldehyde and piperidine have been added.
3. This amide is insoluble in the usual solvents, but it may be further purified, if desired, by trituration with dilute hydrochloric acid, followed by washing with hot absolute ethanol. It then melts sharply at 160–161°.
4. The checkers used one-tenth of the specified amounts of reagents. They obtained, in two runs, the following average yields of products: crude α,α'-dicyano-β-methylglutaramide, m.p. 152–157°, 75%; crude β-methylglutaric acid, m.p. 79–82°, 78%; purified β-methylglutaric acid, m.p. 84–85°, 80% (recovery). In the second run, however, the yields (except for the recovery in the recrystallization) were slightly higher than those given for the larger runs.

3. Discussion

The above method is adapted from the procedure of Day and Thorpe.[1] β-Methylglutaric acid has been prepared by hydrolysis of β-methylglutaronitrile;[2] by condensation of crotonic ester with ethyl sodiocyanoacetate,[3] and with sodiomalonic ester;[4,5] and by condensation of acetaldehyde with malonic ester.[6]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 630

References and Notes

1. Day and Thorpe, *J. Chem. Soc.*, **117**, 1465 (1920).
2. Blaise and Gault, *Bull. soc. chim. France*, (4) **1**, 88 (1907).
3. Howles, Thorpe, and Udall, *J. Chem. Soc.*, **77**, 948 (1900); Darbishire and Thorpe, *J. Chem. Soc.*, **87**, 1716 (1905).
4. Hunsdiecker, *Ber.*, **75B**, 1199 (1942).
5. Auwers, Kobner, and Meyenberg, *Ber.*, **24**, 2887 (1891).
6. Knoevenagel, *Ber.*, **31**, 2585 (1899).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodiomalonic ester

Malonic Ester

ethanol (64-17-5)

acetaldehyde (75-07-0)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ether (60-29-7)

sodium chloride (7647-14-5)

piperidine (110-89-4)

CYANOACETAMIDE (107-91-5)

β-Methylglutaric acid, Glutaric acid, β-methyl- (626-51-7)

β-methylglutaronitrile

ethyl sodiocyanoacetate

phosphorus pentoxide (1314-56-3)

α,α'-Dicyano-β-methylglutaramide

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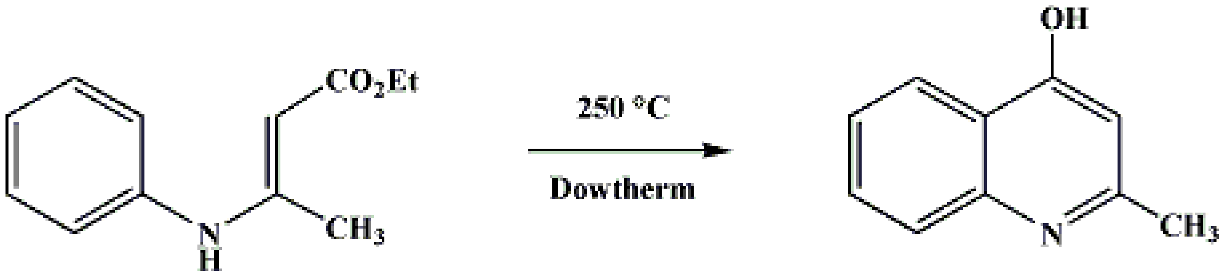
Organic Syntheses, CV 3, 593

2-METHYL-4-HYDROXYQUINOLINE

[4-Quinolinol, 2-methyl-]



Submitted by George A. Reynolds and Charles R. Hauser.
Checked by Arthur C. Cope and William R. Armstrong.

1. Procedure

In a 500-ml. three-necked round-bottomed flask equipped with a dropping funnel, a sealed mechanical stirrer, and an air condenser is placed 150 ml. of Dowtherm (Note 1). The Dowtherm is stirred and heated at the reflux temperature while 65 g. (0.32 mole) of ethyl β-anilinocrotonate (p. 374) is added rapidly through the dropping funnel. Stirring and refluxing are continued for 10–15 minutes after the addition is completed. The ethanol formed in the condensation reaction may be allowed to escape from the condenser through a tube leading to a drain, or it may be collected by attaching a water-cooled condenser set for distillation to the top of the air condenser. The mixture is allowed to cool to room temperature, at which stage a yellow solid separates. Approximately 200 ml. of petroleum ether (b.p. 60–70°) is added; the solid is collected on a Büchner funnel and washed with 100 ml. of petroleum ether (b.p. 60–70°). After air drying, the crude product is treated with 10 g. of Darco or Norit in 1 l. of boiling water (Note 2). The hot solution is filtered and allowed to cool. The white, hairlike needles of 2-methyl-4-hydroxyquinoline are separated by filtration. The yield of product, melting at 235–236° (cor.), is 43–46 g. (85–90%).

2. Notes

1. Dowtherm is a mixture of diphenyl and diphenyl ether, obtainable from the Dow Chemical Company.
2. If the treatment with decolorizing carbon is omitted, the product has a low melting point after several crystallizations.

3. Discussion

The present procedure is a modification of preparations described previously.[1,2,3] The cyclization has been effected by allowing a solution of ethyl β-anilinocrotonate in

concentrated sulfuric acid to stand at room temperature for several hours; by rapidly heating the ester to 240–250° without a solvent;[2] or by adding the ester to paraffin oil at 250°[3] or to refluxing diphenyl ether.[4] The procedure described has been applied to the preparation of other 2-substituted 4-hydroxyquinolines.[5]

References and Notes

1. Knorr, *Ber.*, **16**, 2593 (1883).
2. Conrad and Limpach, *Ber.*, **20**, 944 (1887).
3. Cavalito and Haskell, *J. Am. Chem. Soc.*, **66**, 1166 (1944).
4. Kaslow and Marsh, *J. Org. Chem.*, **12**, 456 (1947).
5. Hauser and Reynolds, *J. Am. Chem. Soc.*, **70**, 2402 (1948).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

Dowtherm

diphenyl

ethanol (64-17-5)

sulfuric acid (7664-93-9)

decolorizing carbon, Norit (7782-42-5)

diphenyl ether (101-84-8)

ETHYL β-ANILINOCROTONATE (6287-35-0)

2-Methyl-4-hydroxyquinoline, 4-Quinolinol, 2-methyl- (607-67-0)

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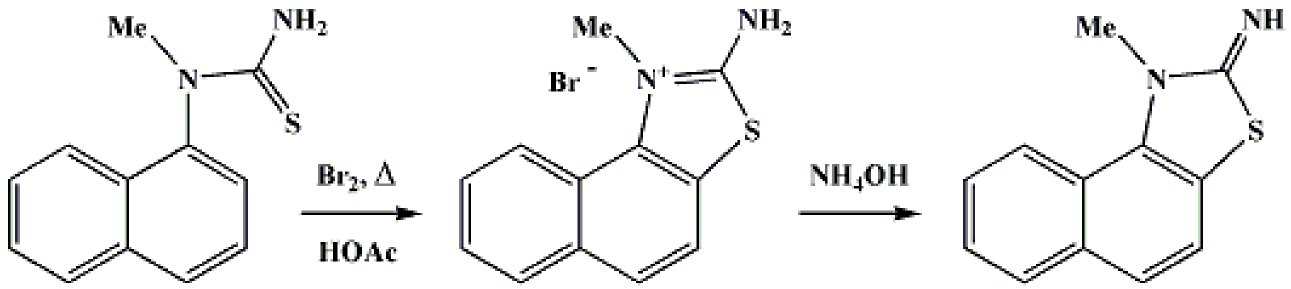
1-METHYL-2-IMINO-β-NAPHTHOTHIAZOLINE

[Naphtho[1,2]thiazole, 1-methyl-1,2-dihydro-2-imino-]



Submitted by Homer W. J. Cressman
Checked by Nathan L. Drake and Werner R. Boehme.

1. Procedure

In a 1-l. three-necked flask fitted with a thermometer, a dropping funnel, and a mechanical stirrer are placed 65 g. (0.3 mole) of 1-methyl-1-(1-naphthyl)-2-thiourea (p. 609) (Note 1) and 400 ml. of glacial acetic acid (Note 2). To the mechanically stirred suspension, maintained at 18–20° by cooling in a water bath, is added dropwise over a 30-minute period 48 g. (0.3 mole) of bromine in 50 ml. of glacial acetic acid. The light-yellow addition product is stirred an additional 15 minutes at 18–20°. After the thermometer is replaced by an outlet tube (Note 3), the mixture is heated in a water bath maintained at 80–85° (Note 4) for 3 hours. Hydrogen bromide is evolved copiously with the formation of a white, crystalline hydrobromide. When the mixture is cool, it is filtered and the precipitate is washed on the filter with 50 ml. of acetone and then with two 250- to 300-ml. portions of dry ether. One hundred milliliters of concentrated ammonia is then added with stirring to the salt suspended in 700 ml. of warm water (60–65°). The imine base first separates as an oil (Note 5); after the mixture has been stirred and warmed on the steam bath for 10 minutes, it is extracted with 500 ml. of chloroform and filtered by suction through a Norit filter pad 5–6 mm. thick. The bottom layer is separated, washed with 350 ml. of water, and dried by stirring with 40 g. of potassium carbonate. The residual oil, after removal of the solvent on the steam bath under reduced pressure, is poured into an evaporating dish and stirred while cooling. The brownish-colored crystals (Note 6) are dried at 80–85°; they melt at 97–99° and weigh 58–62 g. (90–97%). If desired, the naphthothiazoline (Note 7) can be crystallized from petroleum ether (60–90°) using 75 ml. per gram of product. The recovery of the almost colorless (cream) crystals is 85%. The recrystallized thiazoline melts at 97–99°.

2. Notes

1. The thiazoline was obtained in the best yields and with the lightest color from freshly prepared 1-methyl-1-(1-naphthyl)-2-thiourea. The air-dried thiourea loses hydrogen sulfide and ammonia after several days' storage.
2. The use of glacial acetic acid for cyclization is essential; in chloroform, the bromo-addition product does not lose hydrogen bromide.
3. A gas-absorption trap can be used to absorb the hydrogen bromide evolved.
4. The temperature of the water bath is easily maintained at 80–85° by heating it on a steam bath.

5. The oil solidifies on cooling. The crystalline product can be separated by filtration and recrystallized from 50% aqueous ethanol or petroleum ether (60–90°).
6. This product is satisfactory for synthetic purposes.
7. This type of reaction can be used successfully for the preparation of other naphthothiazolines and naphthoselenazolines. The submitter has prepared 2-imino-1-methylnaphtho [1,2] selenazoline, m.p. 94–95°, and 2-imino-1-ethylnaphtho [1,2] selenazoline, m.p. 82–84°, by similar methods.

3. Discussion

The preparation of this compound is not described in the literature.

References and Notes

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

1-Methyl-2-imino-β-naphthothiazoline

Naphtho[1,2]thiazole, 1-methyl-1,2-dihydro-2-imino-

naphthothiazoline

naphthothiazolines

naphthoselenazolines

2-imino-1-methylnaphtho [1,2] selenazoline

2-imino-1-ethylnaphtho [1,2] selenazoline

ethanol (64-17-5)

potassium carbonate (584-08-7)

acetic acid (64-19-7)

ammonia (7664-41-7)

ether (60-29-7)

chloroform (67-66-3)

hydrogen sulfide (7783-06-4)

hydrogen bromide, hydrobromide (10035-10-6)

bromine (7726-95-6)

acetone (67-64-1)

thiourea (62-56-6)

1-methyl-1-(1-naphthyl)-2-thiourea (53663-34-6)

thiazoline

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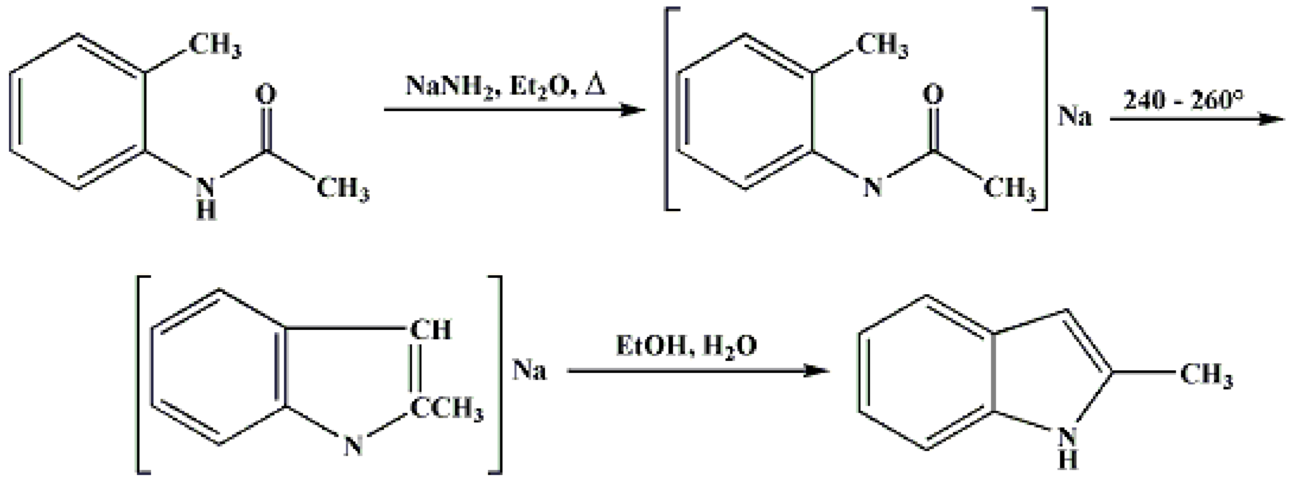
Organic Syntheses, *CV 3, 597*

2-METHYLINDOLE

[Indole, 2-methyl-]



Submitted by C. F. H. Allen and James VanAllan.
Checked by Nathan L. Drake and Richard Tollefson.

1. Procedure

In a 1-l. Claisen flask is placed a mixture of 64 g. of finely divided sodium amide (Note 1) and 100 g. of acetyl-*o*-toluidine (Note 2). About 50 ml. of dry ether is added (Note 3), and the apparatus is swept out with dry nitrogen. Then, with a slow current of nitrogen passing through the mixture, the reaction flask (Note 4) is heated in a metal bath (Note 5). The temperature is raised to 240–260° over a 30-minute period and is maintained in this range for 10 minutes. A vigorous evolution of gas occurs, the cessation of which indicates that the reaction is complete (Note 6). The metal bath is removed, the flask is allowed to cool, and 50 ml. of 95% ethanol and 250 ml. of warm (about 50°) water are added, successively, to the reaction mixture. The decomposition of the sodium derivative of 2-methylindole, and of any excess sodium amide, is completed by warming the mixture gently with a Bunsen burner. The cooled reaction mixture is extracted with two 200-ml. portions of ether (Note 7). The combined ether extracts are filtered, and the filtrate is concentrated to about 125 ml. The solution is then transferred to a 250-ml. modified Claisen flask and distilled. The 2-methylindole distils at 119–126° /3–4 mm. as a water-white liquid, which rapidly solidifies in the receiver to a white crystalline mass. This product melts at 56–57°. The yield is 70–72 g. (80–83%) (Note 8).

The product may be further purified by dissolving it in 100 ml. of methanol, adding 30 ml. of water, and allowing the solution to stand in the ice chest for 5 hours. The pure white plates (52 g.) melt at 59°. An additional 10 g. may be recovered by cooling the filtrate after it has been diluted with about 20 ml. of water.

2. Notes

1. The sodium amide was ground in an open mortar, and at no time was difficulty experienced. As a precautionary measure, the grinding could be carried out under ether.
2. Acetyl-*o*-toluidine, m.p. 110–111°, obtained from the Eastman Kodak Company, was used. After the reactants are introduced into the flask, they should be mixed thoroughly with a long spatula.

3. The ether is added to facilitate the formation of the sodium salt of the amide.
4. It is advisable to cover the bottom of the reaction flask with soot, to prevent the metal from adhering to the glass.
5. Sand and salt baths are not satisfactory.
6. Reaction begins when the bath temperature has risen to approximately 200°. Frothing occurs, and the froth solidifies. The checkers found it necessary to stir the solidified froth into the reaction mixture, so that heating of the whole mass could be uniform. This stirring is necessary throughout—i.e., from the beginning of vigorous gas evolution until completion of the period of heating.
7. The indole may be isolated, less conveniently, by steam distillation; the crystalline product (m.p. about 56–57°) can be filtered from the cold distillate.
8. The method described here is of general application to substituted acetyl- and benzoyl-*o*-toluidines.

3. Discussion

The method described here is a modification of Verley's procedure.[1] 2-Methylindole may also be prepared by the treatment of acetone phenylhydrazone with zinc chloride at 180°.[2]

The cyclization of acetyl-*o*-toluidine has been reported to occur in low yield on distillation with zinc dust.[3] Better yields have been obtained by heating the toluidide with sodium ethoxide or with barium oxide in a current of hydrogen at 360–380°.[4] A vapor-phase cyclization over a silica-alumina catalyst has also been reported.[5]

References and Notes

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3. Mauthner and Suida, *Monatsh.*, **7**, 230, 237 (1886).
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5. Ger. pat. 458,383 [*Frdl.*, **16**, 709 (1931)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium derivative of 2-methylindole

acetyl- and benzoyl-o-toluidines

toluidide

silica-alumina

ethanol (64-17-5)

methanol (67-56-1)

ether (60-29-7)

hydrogen (1333-74-0)

barium oxide

nitrogen (7727-37-9)

zinc (7440-66-6)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

zinc chloride (7646-85-7)

sodium amide (7782-92-5)

Indole (120-72-9)

2-Methylindole, Indole, 2-methyl- (95-20-5)

acetone phenylhydrazone (103-02-6)

acetyl-o-toluidine (120-66-1)

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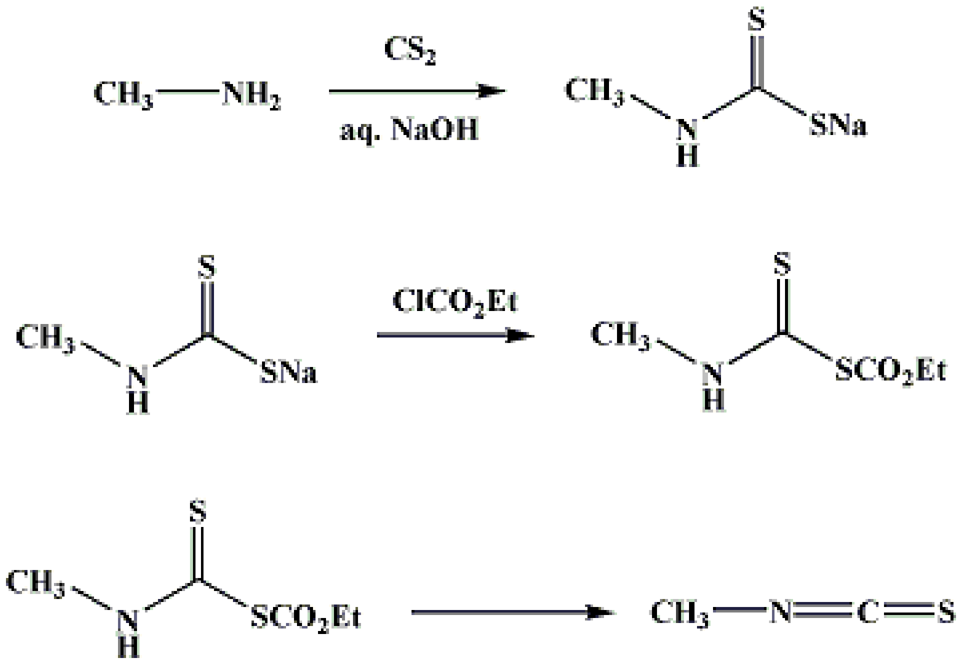
Organic Syntheses, CV 3, 599

METHYL ISOTHIOCYANATE

[Isothiocyanic acid, methyl ester)]



Submitted by Maurice L. Moore and Frank S. Crossley.
Checked by Nathan L. Drake and Ralph Mozingo.

1. Procedure

In a 1-l. round-bottomed three-necked flask, surrounded by an ice bath and fitted with a mechanical stirrer, a reflux condenser, thermometer, and a 250-ml. dropping funnel, are placed 137 g. (110 ml., 1.8 moles) of carbon disulfide and a cold solution of 72 g. (1.8 moles) of sodium hydroxide in 160 ml. of water. To this mixture, cooled to 10–15°, is added, with stirring, 180 ml. (56 g., 1.8 moles of methylamine) of 35% aqueous methylamine solution (Note 1) and (Note 2) over a period of 30 minutes. Stirring is continued, and the mixture is warmed gently on a steam bath for 1–2 hours to ensure complete reaction (Note 3). The bright red solution is cooled to 35–40°, and to it is added over a period of 1 hour, with stirring, 196 g. (175 ml., 1.8 moles) of ethyl chlorocarbonate (Note 4). The stirring is continued for 30 minutes after all the ethyl chlorocarbonate has been added, at which time the temperature should have fallen to 30–40°. The methyl isothiocyanate, which separates on top, is removed from the reaction mixture and weighs 170–190 g.

The product is dried over 10 g. of sodium sulfate and distilled under atmospheric pressure through a short Vigreux column; the fraction which boils at 115–121° is collected. The yield is 85–100 g. (65–76%) (Note 5) and (Note 6). The product may be further purified by refractionation. The portion which boils at 117–119° is collected.

2. Notes

1. The monomethylamine used in this preparation was a "Commercial Special 35% Solution" obtained from Rohm and Haas Company.
2. Methylamine hydrochloride can be used in place of the commercial aqueous methylamine solution by a slight modification of the above procedure. The carbon disulfide and a solution of 122 g. (1.8 moles) of methylamine hydrochloride in 200 ml. of water are mixed together in the flask, and a cold solution of 144 g. (3.6 moles) of sodium hydroxide in 320 ml. of water is added, with stirring, over a period of 30 minutes. Two equivalents of sodium hydroxide must be used in this case. The remainder of the procedure is the same as with the free base.
3. The temperature gradually rises from 25°, which is that noted at the end of the addition of the methylamine solution, to 75–85°.
4. The temperature may rise rather rapidly during this addition; it is advisable to maintain the rate of addition constant so that the reaction does not become too vigorous.
5. Larger runs, up to 5.4 moles of carbon disulfide, have been made with only a slight reduction in yield.
6. This reaction is general for the preparation of alkyl isothiocyanates in good yields; thus, according to the submitters, ethyl isothiocyanate is obtained in yields of 60–70% from ethylamine hydrochloride.

3. Discussion

Methyl isothiocyanate has been prepared from methyl thiocyanate by rearrangement with heat[1] and from N,N'-dimethylthiuramdisulfide by the action of iodine[2] or by heating with water or methanol.[3] The most useful method of preparation has been the reaction of methylamine with carbon disulfide to form methyldithiocarbamic acid which is decomposed by steam distillation of the lead salt,[4] or by reaction with ethyl chlorocarbonate.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 617

References and Notes

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5. Slotta and Dressler, *Ber.*, **63**, 888 (1930).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

lead salt

methanol (67-56-1)

sodium hydroxide (1310-73-2)

sodium sulfate (7757-82-6)

iodine (7553-56-2)

carbon disulfide (75-15-0)

Methylamine hydrochloride (593-51-1)

methylamine, monomethylamine (74-89-5)

ethyl chlorocarbonate (541-41-3)

ethyl isothiocyanate (542-85-8)

Methyl isothiocyanate, Isothiocyanic acid, methyl ester (556-61-6)

ethylamine hydrochloride (557-66-4)

methyl thiocyanate (556-64-9)

methyldithiocarbamic acid

N,N'-dimethylthiuramdisulfide

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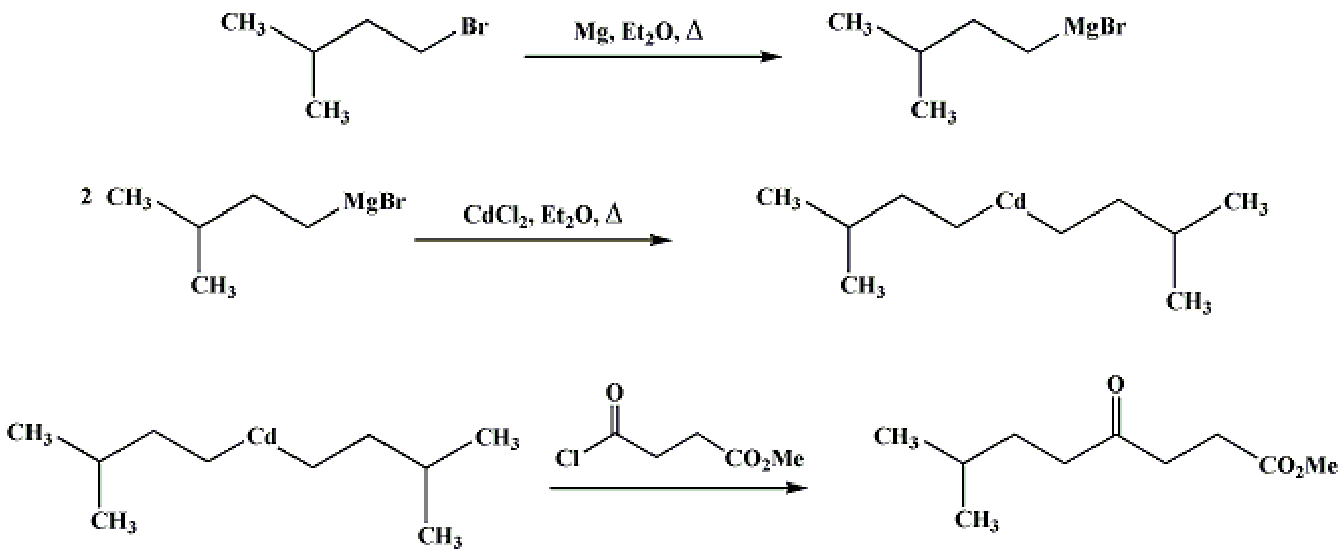
Organic Syntheses, CV 3, 601

METHYL 4-KETO-7-METHYLOCTANOATE

[Caprylic acid, ζ-methyl-γ-oxo-, methyl ester]



Submitted by James Cason and Franklin S. Prout.
Checked by Homer Adkins and Robert Turner.

1. Procedure

A 2-l. three-necked flask (Note 1) is fitted with a reflux condenser having a take-off attachment,[1] a mercury-sealed Hershberg stirrer (Note 2), and a 500-ml. dropping funnel (Note 1). A nitrogen inlet tube is connected to the top of the condenser, and a branch of the tube, connected by means of a T-tube, is connected to a mercury valve[1] consisting of a U-tube, the bend of which is just filled with mercury. Unless the dropping funnel is equipped with a pressure-equalizing side tube,[1] a second branch of the nitrogen line is arranged for connection to its mouth. In the flask is placed 24.3 g. (1.0 gram atom) of magnesium turnings, and the entire flask is warmed with a soft flame while a slow stream of nitrogen is passed through and permitted to escape by way of the dropping funnel. The flask is allowed to cool, the dropping funnel is closed, and the nitrogen flow is reduced until the gas bubbles very slowly through the mercury valve. The magnesium is covered with 150 ml. of dry ether, introduced from the dropping funnel, and a solution of 151 g. (1.0 mole) of pure isoamyl bromide (Note 3) in 350 ml. of dry ether is placed in the dropping funnel. A few milliliters of the bromide solution is added to the flask, and the stirrer is started. The flask is warmed gently if the reaction does not start spontaneously. The remainder of the bromide is added during 1–2 hours, and the mixture is refluxed for 15 minutes longer. The flask is then cooled in an ice bath, the dropping funnel is removed, and 98 g. (0.535 mole) of anhydrous C.P. cadmium chloride (Note 4) is added over a period of 5–10 minutes. After all the cadmium chloride has been added, the ice bath is removed and the mixture is stirred for 5 minutes and then heated under reflux with stirring for an additional 45 minutes (Note 5).

Ether is now rapidly distilled from the reaction mixture (Note 6) by heating on a steam bath. Distillation is continued with stirring until it becomes very slow and a dark viscous residue remains. The distillate amounts to 250–325 ml. At this point, 350 ml. of dry thiophene-free benzene is added to the flask and the distillation is continued until an additional 100 ml. of distillate has been collected. A second 350-ml. portion of dry benzene is added to the flask, and the mixture is refluxed with vigorous stirring for a few minutes in order to break up the cake in the flask and disperse it through the mixture. The heating bath is then removed, and 120 g. (0.8 mole) (Note 7) of β-carbomethoxypropionyl chloride (p. 169) in 150 ml. of dry benzene is added from the dropping funnel. This addition, which causes vigorous refluxing, requires 10–20 minutes. During this time the heavy precipitate changes in appearance and stirring becomes more difficult. After the addition of the acid chloride is complete and spontaneous refluxing has stopped, the mixture is stirred and heated under reflux for an additional hour.

The reaction mixture is cooled in an ice bath and decomposed in the usual way by the careful addition of about 600 g. of ice and water, followed by sufficient 20% sulfuric acid to give two clear phases (Note 2). The aqueous phase is separated in a 2-l. separatory funnel and extracted with two 100-ml. portions of benzene. The two benzene extracts are placed in two 500-ml. separatory funnels. The original benzene layer and each extract are washed successively (Note 8) with 200 ml. of water, 200 ml. of 5% sodium carbonate solution, 200 ml. of water, and 100 ml. of saturated sodium chloride solution, and then each is

filtered through a layer of anhydrous sodium sulfate. A little fresh solvent is used to rinse the separatory funnels and the filter.

A fractionating column (Note 9) is connected to a 250-ml. flask carrying a dropping funnel and heated in an oil bath at 150–160°. The combined benzene solutions are run into the flask from the dropping funnel so that the benzene is removed by flask distillation at atmospheric pressure. The pressure is then lowered, and after the distillation of the last of the solvent and a little 2,7-dimethyloctane (from coupling of the Grignard reagent) the vapor temperature rises to about 100°/20 mm. About 5 g. of methyl ethyl succinate (Note 10) and (Note 11) is collected at 100–106°/20 mm., and after an intermediate fraction (about 3 g.) the keto ester is collected at 136–137°/20 mm. (Note 11) and (Note 12). The yield of methyl 4-keto-7-methyloctanoate is 108.5–111.5 g. (73–75%, based on β-carbomethoxypropionyl chloride) (Note 13) and (Note 14).

2. Notes

1. Connections may be made with rubber stoppers, but ground-glass joints are preferable.
2. The heavy sludges encountered in this preparation make a strong and efficient stirrer essential. A stirrer of the Hershberg type of tantalum wire is preferable, but new, unetched Nichrome is quite satisfactory. If a Nichrome stirrer is used it should be removed before acid is added to complete the decomposition of the organometallic complex.
3. Isoamyl bromide, b.p. 120–120.5°, was prepared as previously described.[2] The product was fractionated through a packed column, such as that referred to in (Note 9) below, to remove small quantities of *tert*-amyl bromide arising from *sec*-butyl carbinol present in the isoamyl alcohol.
4. The cadmium chloride is dried to constant weight at 110° in an oven, ground thoroughly, and stored in a desiccator. If stored in a screw-cap bottle in the laboratory it may absorb moisture slowly.
5. It is best to continue stirring at this point until the mixture gives a negative Gilman test for the Grignard reagent.[3] One-half milliliter of the reaction mixture is added to an equal volume of a 1% solution of Michler's ketone in dry benzene. After this mixture is shaken briefly, 1 ml. of water is added, followed by a few drops of a 0.2% solution of iodine in glacial acetic acid and 0.5 ml. of glacial acetic acid. If any Grignard reagent is still present, a greenish blue color is observed.
6. If the reaction with the acid chloride is carried out in ether solution larger amounts of methyl ethyl succinate are formed, and the yield of keto ester is only 42–59%.
7. The use of β-carbomethoxypropionyl chloride of poor quality frequently resulted in poor yields of the desired keto ester. It is most important that the methyl hydrogen succinate, m.p. 56–57°, from which the acyl chloride is prepared, be of high quality and that it be ground thoroughly before drying. The melting point of a sample of methyl hydrogen succinate is not a sufficient criterion of purity, so that the neutral equivalent of the sample of ester should be determined. If the neutral equivalent is not in the range 130–134, the reagent should be purified by recrystallization.
8. The indicated portion of each wash solution is used to wash each of the benzene solutions in turn. If three separatory funnels are used this process is not laborious and results in very thorough extraction.
9. An efficient column packed with glass helices and provided with a heating jacket and a suitable head[4] should be used. Columns of dimensions 50 cm. by 14 mm. i.d. and 43 cm. by 12 mm. i.d. have been found satisfactory.
10. The methyl ethyl succinate apparently results from the reaction of the acid chloride with ether.
11. The apparent boiling points of the fractions may vary somewhat, depending on the fractionating column.
12. Boiling points of the keto ester at other pressures are as follows: 117°/8 mm., 120–122°/11 mm., 125°/14 mm., 139.5°/22 mm., and 145°/27 mm.
13. In an alternative procedure the fractionating column is removed after the intermediate fraction has been collected, and the residual ester is distilled through a short still head.
14. The procedure described has been used by the submitters for the preparation of the following keto esters:

Keto Ester	*B.P.*	*% Yield*
Ethyl 10-keto-13-methyltetradecanoate	180–182°/3 mm.	85
Ethyl 10-keto-16-methyloctadecanoate	192–195°/2 mm.	76.5
Ethyl 6-ketoheptanoate	143–145°/33 mm.	76
Ethyl 10-ketohendecanoate	137–138°/2 mm.	83
Ethyl 10-keto-14-methyltetracosanoate	242–245°/1 mm.	77

The ester acid chlorides used in these preparations, ω-carbethoxyvaleryl chloride and ω-carbethoxynonanoyl chloride, were obtained from the corresponding half esters in yields of 90–95%. The method described for β-naphthoyl chloride (p.629, Note 2) was used, but since with these acids the reaction is much more vigorous the phosphorus pentachloride was added in small portions and the mixture was not heated until after the exothermic reaction had subsided.
The procedure described failed completely when a secondary bromide, 2-bromopentane, was used; however, when the cadmium derivative was prepared at −5° to −7° and allowed to react in ether at this temperature with β-

carbomethoxypropionyl chloride, methyl 4-keto-5-methyloctanoate was obtained in a yield of 19.3%, b.p. 130.5–130.7°/21 mm.

3. Discussion

Methyl 4-keto-7-methyloctanoate has been prepared by the procedure given, which is based on the method of Cason and Prout.[5] The use of cadmium derivatives for the preparation of simple ketones was introduced by Gilman and Nelson.[6]

A preparation from isobutyl-2-furylcarbinol (obtained by a Grignard reaction from furfural) has also been described.[7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 93
- Org. Syn. Coll. Vol. 5, 813

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Caprylic acid, ζ-methyl-γ-oxo-, methyl ester

acyl chloride

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

Benzene (71-43-2)

ether (60-29-7)

phosphorus pentachloride (10026-13-8)

magnesium, magnesium turnings (7439-95-4)

sodium chloride (7647-14-5)

bromide (24959-67-9)

sodium carbonate (497-19-8)

Isoamyl bromide (107-82-4)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

mercury (7439-97-6)

iodine (7553-56-2)

Furfural (98-01-1)

isoamyl alcohol (123-51-3)

2-bromopentane (107-81-3)

β-Carbomethoxypropionyl chloride (1490-25-1)

Methyl hydrogen succinate (3878-55-5)

Methyl 4-keto-7-methyloctanoate (53663-32-4)

cadmium chloride (10108-64-2)

2,7-dimethyloctane (1072-16-8)

methyl ethyl succinate

Ethyl 10-keto-13-methyltetradecanoate

Ethyl 10-keto-16-methyloctadecanoate

Ethyl 6-ketoheptanoate

Ethyl 10-ketohendecanoate

Ethyl 10-keto-14-methyltetracosanoate

ω-carbethoxyvaleryl chloride

ω-carbethoxynonanoyl chloride

β-naphthoyl chloride (2243-83-6)

isobutyl-2-furylcarbinol

tert-amyl bromide (507-36-8)

sec-butyl carbinol (137-32-6)

methyl 4-keto-5-methyloctanoate

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Organic Syntheses, CV 3, 605

METHYL MYRISTATE AND METHYL PALMITATE AND THE CORRESPONDING ACIDS

Submitted by J. C. Sauer, B. E. Hain, and P. W. Boutwell.
Checked by Homer Adkins and Robert E. Burks, Jr..

1. Procedure

In a 3-l. round-bottomed flask are placed 500 g. of bayberry wax (Note 1), 600 g. of methanol, and 31 g. of sulfuric acid. Boiling chips are added, and the mixture is refluxed for 48 hours on the steam bath. About half of the methanol is removed by distillation, and 500 ml. of water is added to the remaining mixture. The ester layer is separated and washed several times with water. About 500 g. of crude methyl esters is obtained.

The esters are fractionally distilled through a suitable fractionating column (Note 2). A second fractionation is then made so that each successive fraction is added to the distilling flask after the temperature has reached the upper limit for the fraction being collected. There is obtained 170–190 g. of methyl myristate, b.p. 91–94°/0.5 mm., 112–116°/1 mm., or 157–162°/10 mm., and 170–190 g. methyl palmitate, b.p. 115–118°/0.5 mm., 129–133°/1 mm., or 180–183°/10 mm. (Note 3), (Note 4), (Note 5), and (Note 6).

2. Notes

1. Bayberry wax, also known as myrtle or laurel wax, is obtained from the berries of various species of *Myrica*. The commercial wax, prepared from the berries of *Myrica cerifera*, may be obtained from chemical supply houses for about $0.60 per pound. The relative proportion of myristin and palmitin in bayberry wax varies somewhat, but these two compounds constitute about 95% of the wax.
2. Several columns are suitable for this separation. The submitters used a three-ball Snyder column 26 cm. in length (similar to No. 28575 of E. H. Sargent, Chicago), sealed to a 500- or 200-ml. modified Claisen flask. The method of operation was essentially that of Simons and Wagner.[1] The column was not electrically heated but was snugly wrapped with asbestos paper. The rate of distillation was about 20 drops per minute, and the reflux ratio 2 or 3 to 1. Flooding of the column must be carefully avoided. The checkers used a modified Widmer column which carried a spiral, 14 cm. long with eleven turns of the helix, contained in a glass tube 12 mm. in internal diameter. A 500-ml. flask was employed for the first fractionation and a 250-ml. one for the refractionation. The column and the oil bath were heated electrically. A ground-glass joint was used for connecting the flask and column, the design and method of operation being that described by Smith and Adkins.[2] The temperature of the bath and column heater was so adjusted that the rate of distillation was 3–4 drops per minute, the spiral being well covered with returning liquid.
3. Suitable ranges for taking off fractions at various pressures on the first fractionation are as follows: 6 g., 152–157°/10 mm.; 176 g., 157–160°/10 mm.; 119 g., 160–180°/10 mm.; 126 g., 180–183°/10 mm.; 163 g., 115–123°/1 mm.; 115 g., 123–130°/1 mm.; 141 g., 130–

133°/1 mm.; 29 g., below 91.5°/0.5 mm.; 116 g., 91.5–94.5°/0.5 mm.; 71 g., 94.5–115°/0.5 mm.; 170 g., 115–118°/0.5 mm.; 28 g., 118–125°/0.5 mm. Upon refractionation cuts were made as follows: 6 g., 152–157°/10 mm.; 161 g., 157–162°/10 mm.; 81 g., 162–171°/10 mm.; 64 g., 171–180°/10 mm.; 120 g., 180–183°/10 mm.; 198 g., 112–116°/1 mm.; 72 g., 116–129°/1 mm.; 147 g., 129–133°/1 mm.; 8 g., below 91.5°/0.5 mm.; 172 g., 91.5–94.5°/0.5 mm.; 10 g., 94.5–115.2°/0.5 mm.; 200 g., 115.2–118.2°/0.5 mm.; 25 g., 118.2–125°/0.5 mm. The temperature at which the esters distil varies with the rate of distillation and with the details of construction and operation of the column. The figures given above are intended to suggest the approximate ranges for cutting fractions.

4. This procedure has been used successfully for many years in the preparation of ethyl laurate, caprylate, and myristate by the alcoholysis of cocoanut oil (1 kg.) in ethanol (1.9 kg.) with hydrogen chloride (50 g.) as a catalyst.[3] The method differs slightly from the one described above. The alcoholysis is complete after 15 or 20 hours, and the solution is then neutralized to methyl orange with barium carbonate. The mixture is added to an equal volume of a saturated sodium chloride solution, whereupon 1100–1300 g. of the mixture of crude ethyl esters separates. This mixture of esters is washed with water and fractionated as described above. The yields are approximately 50 g. of ethyl caprylate, 350 g. of ethyl laurate, and 60 g. of ethyl myristate from 1 kg. of cocoanut oil.

5. The methyl myristate obtained (n_D^{25} 1.4353) showed a melting point of 19° when at equilibrium with the liquid. The methyl palmitate (n_D^{25} 1.4391 when supercooled) gave a melting point of 29.5°.

6. Myristic and palmitic acids can be obtained from their esters by the procedure in *Org. Syntheses* Coll. Vol. 1, 379 (1941). From 100 g. of methyl myristate is obtained 85–89 g. (90–95%) of colorless myristic acid melting at 52–53°. From 100 g. of methyl palmitate is obtained 84–88 g. (90–95%) of colorless palmitic acid melting at 62–63°.

3. Discussion

Of the early references to the preparation of methyl myristate and methyl palmitate, few are of preparative value. Methyl myristate can be prepared by the fractional distillation of the methyl esters from ucuhuba fat[4] and from cocoanut oil.[5,6] Methyl palmitate can be prepared in a similar manner from cocoanut oil[6] and from bayberry wax.[7,8]

Myristic and related acids may be prepared synthetically by a mixed Kolbe reaction.[9]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 372

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

bayberry wax

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrogen chloride (7647-01-0)

methanol (67-56-1)

sodium chloride (7647-14-5)

barium carbonate (513-77-9)

Myristic acid (544-63-8)

Methyl myristate (124-10-7)

palmitin (544-76-3)

palmitic acid (57-10-3)

ethyl laurate (106-33-2)

ethyl myristate (124-06-1)

Methyl palmitate (112-39-0)

myristin (629-59-4)

myristate

ethyl caprylate (106-32-1)

Caprylate

methyl orange (547-58-0)

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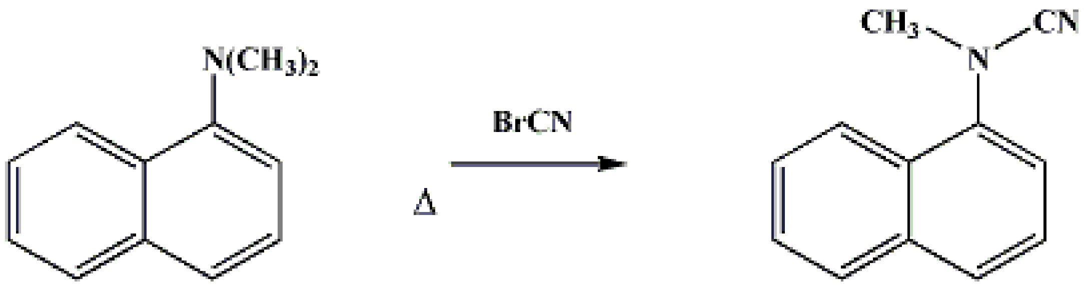
Organic Syntheses, CV 3, 608

N-METHYL-1-NAPHTHYLCYANAMIDE

[Cyanamide, methyl-(1-naphthyl)-]



Submitted by Homer W. J. Cressman
Checked by Nathan L. Drake and Werner R. Boehme..

1. Procedure

Caution! Cyanogen bromide is highly toxic. This preparation should be carried out under a good hood.

A mixture of 171 g. (1 mole) of dimethyl-α-naphthylamine (Note 1) and 125 g. (1.2 moles) of cyanogen bromide[1] in a 1-l. flask (Note 2) is heated under reflux on the steam bath for 16 hours (Note 3). The cooled reaction mixture is added to 2.5 l. of dry ether, and the insoluble quaternary salt (Note 4) is filtered. The ether filtrate is extracted with four 800-ml. portions of approximately 15% hydrochloric acid solution (Note 5) and washed with five 500-ml. portions of water. The ether solution is dried with 30–35 g. of anhydrous calcium sulfate (Drierite). After filtration, the solvent is removed by distillation at atmospheric pressure on the steam bath; the residue is fractionated under reduced pressure. The yield of pale yellow oil, boiling at 170–171°/1 mm. (185–187°/3 mm.), amounts to 115–122 g. (63–67%) (Note 6).

2. Notes

1. Better yields are obtained by dealkylating the tertiary amine in this manner than by starting with the secondary amine. In a similar manner, N-ethyl-1-naphthylcyanamide, b.p. 165–168°/2 mm., is obtained in a 48% yield from diethyl-α-naphthylamine; the yield from the secondary amine is only 25%.
2. Ground-glass equipment is preferable.
3. In order to avoid loss of cyanogen bromide an efficient condenser must be used and the heating should be very gradual at first.
4. About 10 g. of α-naphthyltrimethylammonium bromide, m.p. 160°, is generally obtained.
5. About 25 g. of crystalline dimethyl-α-naphthylamine hydrochloride may be

recovered by efficient chilling of the hydrochloric acid extracts.
6. The N-methyl-1-naphthylcyanamide turns dark green upon standing exposed to the air for several days. It may be preserved in sealed, evacuated ampoules in the absence of light.

3. Discussion

The preparation described is based on the method of von Braun and co-workers.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 609

References and Notes

1. *Org. Syntheses* Coll. Vol. **2**, 150 (1943).
2. Von Braun, Heider, and Muller, *Ber.*, **51**, 281 (1918).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

dimethyl-α-naphthylamine

diethyl-α-naphthylamine

dimethyl-α-naphthylamine hydrochloride

hydrochloric acid (7647-01-0)

ether (60-29-7)

calcium sulfate (7778-18-9)

Cyanogen bromide (506-68-3)

N-Methyl-1-naphthylcyanamide, Cyanamide, methyl-(1-naphthyl)- (53663-33-5)

N-ethyl-1-naphthylcyanamide

α-naphthyltrimethylammonium bromide

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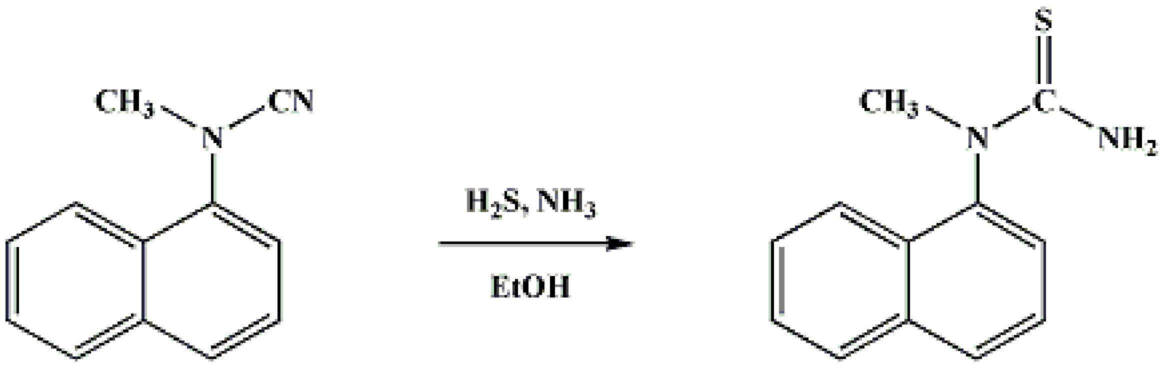
Organic Syntheses, CV 3, 609

1-METHYL-1-(1-NAPHTHYL)-2-THIOUREA

[Urea, 1-methyl-1-(1-naphthyl)-2-thio-]



Submitted by Homer W. J. Cressman
Checked by Nathan L. Drake and Werner R. Boehme.

1. Procedure

The apparatus, consisting of a 1-l. three-necked flask, fitted with a glycerol-sealed mechanical stirrer, two inlet tubes (10-mm. bore) extending nearly to the blades of the stirrer, and an outlet tube (Note 1), is set up in a good hood. Into a solution of 91 g. (0.5 mole) of N-methyl-1-naphthylcyanamide (p. 608) in 350 ml. of absolute ethanol, mechanically stirred and cooled by immersion of the flask in a water bath maintained at 20–25°, ammonia is bubbled at a moderate rate. After 5 minutes, hydrogen sulfide (Note 2) is passed into the solution at about the same rate. The introduction of ammonia is continued for 1.5 hours; hydrogen sulfide is passed into the mixture an additional 30 minutes. A white solid begins to separate soon after the first addition of hydrogen sulfide. After the mixture is chilled in an ice-salt bath, it is filtered. The solid is suspended in 350 ml. of cold water, again separated by filtration, and finally washed with two 100-ml. portions of water, then with two 100-ml. portions of methanol, and dried. The yield of 1-methyl-1-(1-naphthyl)-2-thiourea, m.p. 168–170° (Note 3), amounts to 89–97 g. (82–90%); this material is suitable for most purposes.

2. Notes

1. The use of an alkali trap[1] is recommended.
2. This general reaction can be used for preparing other unsymmetrical thioureas when the desired cyanamides can be obtained. The submitter has also prepared 1-methyl-1-(1-naphthyl)-2-selenourea, m.p. 174–175° with decomposition, and 1-ethyl-1-(1-naphthyl)-2-selenourea, m.p. 168–170° with decomposition, by substitution of hydrogen selenide for hydrogen sulfide.
3. The thiourea can be further purified by recrystallization from ethanol. The recrystallized product melts at 170–171°.

3. Discussion

The preparation of this compound is not reported in the literature.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 595

References and Notes

1. *Org. Syntheses* Coll. Vol. **1**, 266 (1941).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

ammonia (7664-41-7)

methanol (67-56-1)

hydrogen sulfide (7783-06-4)

thiourea (62-56-6)

1-methyl-1-(1-naphthyl)-2-thiourea, Urea, 1-methyl-1-(1-naphthyl)-2-thio- (53663-34-6)

N-Methyl-1-naphthylcyanamide (53663-33-5)

1-methyl-1-(1-naphthyl)-2-selenourea

1-ethyl-1-(1-naphthyl)-2-selenourea

hydrogen selenide (7782-49-2)

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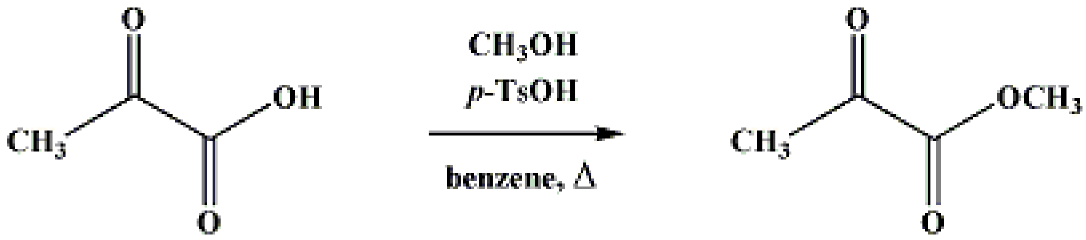
Organic Syntheses, CV 3, 610

METHYL PYRUVATE

[Pyruvic acid, methyl ester]



Submitted by A. Weissberger and C. J. Kibler.
Checked by C. S. Hamilton and R. F. Coles.

1. Procedure

A solution of 88 g. (1 mole) of freshly distilled pyruvic acid,[1] 128 g. (4 moles) of absolute methanol, 350 ml. of benzene, and 0.2 g. of *p*-toluenesulfonic acid is placed in a 1-l. round-bottomed flask connected through a ground-glass joint (Note 1) to a methyl ester column shown in .htmFig. 20[2] (Note 2). The column is fitted at the top with a cold finger, a thermometer, and an efficient condenser. The solution is refluxed vigorously using an oil bath maintained at 150–155°. The temperature at the top of the column is 59–60°. After refluxing overnight, the liquid in the lower bubbler becomes cloudy and separates into two layers. The lower layer is removed as fast as it is formed (i.e., every 20–30 minutes) throughout the day. Refluxing is continued overnight, and the next morning the lower layer is again removed until cloudiness persists in the upper bubblers (Note 3). The ester is then isolated by fractional distillation of the remaining liquid. The fraction boiling at 136–140° at atmospheric pressure is collected (Note 4). It weighs 66–73 g. (65–71%) (Note 5) and (Note 6).

Fig. 20.

Fig. 20.

2. Notes

1. A ground-glass joint is advisable on account of the long reflux period. Benzene attacks a rubber stopper, and pyruvic acid destroys cork.

2. The Clarke-Rahrs methyl ester column[2] is illustrated in .htmFig. 20. *A* is the stopcock, above which the aqueous phase collects and is drawn off as necessary. *B* is a standard-taper ground joint; *C* is a trap whose outside diameter is 12 mm. At *D* the space between the consecutive bubblers is shown. *E* is the thermometer tube, set in at an angle of about 45°; it carries a piece of rubber tubing *H* which holds the thermometer. *F* is a solid spot in the top return tube *only*, where that

tube has been sealed off; the apparatus will not function without this seal. It should be pointed out that the upper ends of all the return tubes should terminate just above the bends, as shown at *J*; otherwise there will be too great a pressure due to the height of the liquid. The overall length as given is not critical.

3. A total of about 300 ml. of liquid will have separated when cloudiness persists in the fourth and fifth bubblers. The liquid collected separates into two layers on cooling. It contains a trace of pyruvic acid.

4. A tarry residue of 10–17 g. is obtained. If an efficient column is not used in the distillation, the fore-runs will contain 5–10 g. of recoverable ester. The yield given is the total yield.

5. The difficulty in the preparation of methyl pyruvate is caused by the fact that this ester is very easily hydrolyzed and that the ester equilibrium is far on the side of the hydrolysis products.

6. Other methyl esters can be made by this procedure.

3. Discussion

Methyl pyruvate has been prepared from the silver salt of pyruvic acid and methyl iodide;[3] from the free acid, by the ethanol-vapor method without a catalyst,[4] by azeotropic removal of the water produced by the reaction of methanol in the presence of *p*-toluenesulfonic acid (the present method), and by refluxing with methanol in ethylene dichloride using ethanesulfonic acid as a catalyst (73% yield).[5] Pyruvic esters have also been prepared by the catalytic dehydrogenation of lactic acid esters[6] and by the oxidation of ethyl lactate with potassium permanganate.[7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 212

References and Notes

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5. Clinton and Laskowski, *J. Am. Chem. Soc.*, **70**, 3135 (1948).
6. U. S. pat. 1,614,195 [*C. A.*, **21**, 746 (1927)].
7. *Org. Syntheses*, **31**, 59 (1951).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Benzene (71-43-2)

methanol (67-56-1)

potassium permanganate (7722-64-7)

ethylene dichloride (107-06-2)

Methyl iodide (74-88-4)

Pyruvic acid (127-17-3)

ethyl lactate (687-47-8)

Methyl pyruvate, Pyruvic acid, methyl ester (600-22-6)

ethanesulfonic acid (594-45-6)

p-toluenesulfonic acid (104-15-4)

silver salt of pyruvic acid

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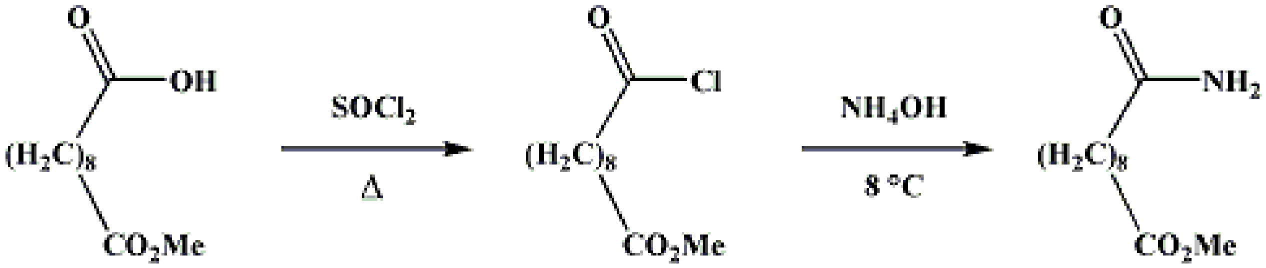
Organic Syntheses, CV 3, 613

METHYL SEBACAMATE

[Sebacamic acid, methyl ester]



Submitted by W. S. Bishop
Checked by C. F. H. Allen and J. VanAllan.

1. Procedure

A. *ω-Carbomethoxypelargonyl chloride*. A mixture of 216 g. (1 mole) of methyl hydrogen sebacate (Note 1) and 147 g. (1.24 moles) of thionyl chloride in a 2-l. round-bottomed flask attached by a standard ground-glass joint to an upright condenser is refluxed on a steam bath for 5 hours. The condenser is then replaced by a still head having a modified side arm, and the unused thionyl chloride is removed. The residual ω-carbomethoxypelargonyl chloride is suitable for the next step. If a purer product is desired it is distilled under reduced pressure. The yield of ester chloride boiling at 158–160°/10 mm. is 194–201 g. (83–86%).

B. *Methyl sebacamate.* Two and one-half liters of concentrated aqueous ammonia (about 28%) in a 4-l. beaker or enameled pot (Note 2) is stirred vigorously with an off-center stirrer and chilled to 8° in a cooling bath. The crude chloride from part A is added slowly from a dropping funnel to the solution, which is kept below 8° throughout the addition. A vigorous reaction takes place, and methyl sebacamate precipitates immediately. After the addition has been completed, the product is filtered by suction and washed with 200 ml. of cold water. After 3 days' drying in a vacuum desiccator, the methyl sebacamate weighs 200–204 g. (93–95%) and melts at 72–74° (Note 3).

2. Notes

1. Methyl hydrogen sebacate (b.p. 168–170°/3 mm.) was prepared by the checkers in yields of 52–61% from sebacic acid and methanol by the procedure described for the ethyl analog.[1] The ethyl ester can be used to obtain ethyl sebacamate. The preparation of the acid chloride from ethyl hydrogen sebacate is mentioned in Note 12, p. 171.
2. A variety of enameled-steel pots known as bain-marie is available from the American Specialty Company, Rochester, New York.
3. The yield is no higher with the distilled chloride.

3. Discussion

These compounds have been described in the literature.[2,3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 584
- Org. Syn. Coll. Vol. 3, 768

References and Notes

1. *Org. Syntheses* Coll. Vol. **2**, 276 (1943).
2. Biggs and Bishop, *J. Am. Chem. Soc.*, **63**, 944 (1941).
3. Bishop, U. S. pat. 2,277,033 [C. A., **36**, 4636 (1942)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ammonia (7664-41-7)

methanol (67-56-1)

thionyl chloride (7719-09-7)

Ethyl hydrogen sebacate (693-55-0)

methyl hydrogen sebacate (818-88-2)

sebacic acid (111-20-6)

Methyl sebacamate, Sebacamic acid, methyl ester (53663-35-7)

ω-Carbomethoxypelargonyl chloride

ethyl sebacamate

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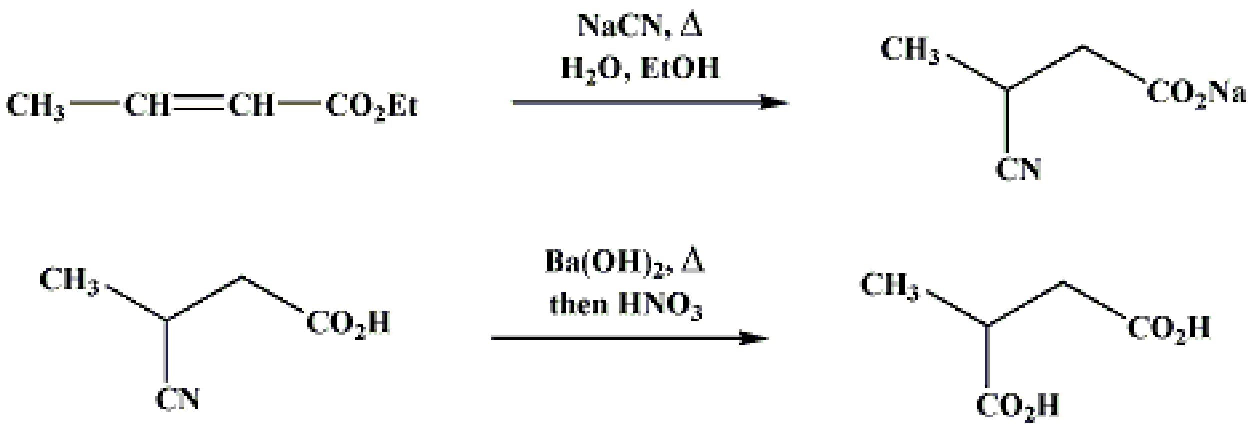
Organic Syntheses, CV 3, 615

METHYLSUCCINIC ACID

[Pyrotartaric acid]



Submitted by George Bosworth Brown
Checked by Lee Irvin Smith and Vincent J. Webers.

1. Procedure

The procedure should be carried out under a hood since the poisonous hydrogen cyanide may be evolved.

In a 3-l. flask provided with a reflux condenser are placed 114 g. (1.0 mole) of ethyl crotonate (Note 1), 460 ml. of 95% ethanol, and a solution of 54 g. (1.06 moles) of 95% sodium cyanide in 128 ml. of water. The solution is refluxed on a steam bath for 5 hours, during which time some ammonia is evolved and the solution becomes dark yellow. A suspension of 150 g. of barium hydroxide octahydrate in 286 ml. of hot water is added to the solution, and the mixture is concentrated under reduced pressure (about 30 mm.) to a volume of about 400 ml. It is again refluxed on the steam bath for 4 hours or until the evolution of ammonia almost ceases (Note 2). The solution is then concentrated to a thick paste under reduced pressure.

The residue is cooled and dissolved in 171 ml. of nitric acid (sp. gr. 1.4) (Note 3), and the solution is warmed for 30 minutes on the steam bath. It is immediately concentrated to complete dryness under reduced pressure (Note 4). The flask is cooled, 300 ml. of benzene is added, and the mixture is refluxed for a short time to render the cake friable. The benzene is removed by decantation, and the cake is pulverized and extracted six times by refluxing it briefly with 300-ml. portions of ether. The combined benzene and ether extracts are filtered and concentrated to a volume of about 225 ml. In the mean-time the residual salts are extracted twice by refluxing them vigorously for a short time with 300-ml. portions of benzene. The benzene solutions are separated by decantation and added to the ether concentrate. The distillation is then

continued until about two-thirds of the benzene has been removed, when the benzene solution is poured into a beaker and allowed to cool. The methylsuccinic acid is collected on a filter and is washed by shaking a suspension of it in 150 ml. of chloroform (Note 5). The yield of air-dried product, melting at 110–111°, amounts to 87–93 g. (66–70%) (Note 6).

2. Notes

1. Ethyl crotonate may be prepared readily from technical crotonic acid by action of sulfuric acid and ethanol. The checkers obtained 72% yield both by the ordinary procedure and by the method of azeotropic distillation.
2. The checkers refluxed the mixture for 8 hours at this point; traces of ammonia were still present. Most of the ammonia was evolved in 4 hours, however.
3. The excess nitric acid is used in order to oxidize unchanged crotonic acid. Since hydrocyanic acid may be evolved the operation should be carried out under a hood.
4. The residue must be dry because methylsuccinic acid is extremely soluble in water.
5. If a series of runs is to be made, the chloroform may be used repeatedly.
6. The submitter states that the same percentage yield is obtained when four times the above quantities of reagents are used.

3. Discussion

Methylsuccinic acid has been prepared by the pyrolysis of tartaric acid;[1] from 1,2-dibromopropane or allyl halides by the action of potassium cyanide followed by hydrolysis;[2] by reduction of itaconic citraconic, and mesaconic acids;[3] by hydrolysis of ketovalerolactonecarboxylic acid;[4] by decarboxylation of 1,1,2-propanetricarboxyl acid;[5] by oxidation of β-methylcyclohexanone;[6] by fusion of gamboge with alkali;[7] by hydrogenation and condensation of sodium lactate over nickel oxide;[8] from acetoacetic ester by successive alkylation with a methyl halide and a monohaloacetic ester;[9] by hydrolysis α-methyl-α'-oxalosuccinic ester[10] or α-methyl-α'-acetosuccinic ester;[11] by action of hot, concentrated potassium hydroxide upon methylsuccinaldehyde dioxime;[12] from the ammonium salt of α-methylbutyric acid by oxidation with hydrogen peroxide;[13] from β-methyllevulinic acid by oxidation with dilute nitric acid[14] or hypobromite;[15] fro, β-methyladipic acid;[16] from the decomposition products of glyceric acid[17] and pyruvic acid;[18] and by the action of methylmagnesium bromide on ethylene tetracarboxylic ester, followed by hydrolysis and decarboxylation.[19] The method described above is a modification of that of Higginbotham and Lapworth.[20]

References and Notes

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2. Simpson, *Ann.*, **121**, 160 (1862); Claus, *Ann.*, **191**, 37 (1878); Pinner, *Ber.*, **12**, 2054 (1879); Euler, *Ber.*, **28**, 2953 (1895).
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19. Hsing and Li, *J. Am. Chem. Soc.*, **71**, 774 (1949).
20. Higginbotham and Lapworth, *J. Chem. Soc.*, **121**, 49 (1922).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

itaconic citraconic, and mesaconic acids

ketovalerolactonecarboxylic acid

1,1,2-propanetricarboxyl acid

α-methyl-α'-oxalosuccinic ester

α-methyl-α'-acetosuccinic ester

ethylene tetracarboxylic ester

ethanol (64-17-5)

sulfuric acid (7664-93-9)

ammonia (7664-41-7)

Benzene (71-43-2)

ether (60-29-7)

chloroform (67-66-3)

nitric acid (7697-37-2)

sodium cyanide (143-33-9)

hydrogen cyanide, hydrocyanic acid (74-90-8)

1,2-dibromopropane (78-75-1)

potassium cyanide (151-50-8)

potassium hydroxide (1310-58-3)

hypobromite

hydrogen peroxide (7722-84-1)

tartaric acid (87-69-4)

barium hydroxide octahydrate (12230-71-6)

Pyruvic acid (127-17-3)

glyceric acid (600-19-1)

methylmagnesium bromide (75-16-1)

crotonic acid (3724-65-0)

Methylsuccinic acid, Pyrotartaric acid (498-21-5)

ethyl crotonate (623-70-1)

β-methylcyclohexanone (583-60-8)

sodium lactate (72-17-3)

nickel oxide

methylsuccinaldehyde dioxime

β-methyllevulinic acid (6628-79-1)

β-methyladipic acid (3058-01-3)

ammonium salt of α-methylbutyric acid

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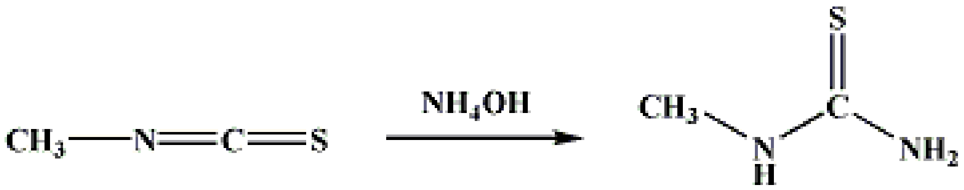
Organic Syntheses, CV 3, 617

METHYLTHIOUREA

[Urea, 1-methyl-2-thio-]



Submitted by Maurice L. Moore and Frank S. Crossley.
Checked by Nathan L. Drake and Ralph Mozingo.

1. Procedure

In a 500-ml. three-necked flask, equipped with a stirrer, a reflux condenser, and a dropping funnel, is placed 140 ml. (34 g.; 2 moles of ammonia) of concentrated ammonium hydroxide solution, and 95 g. (1.3 moles) of methyl isothiocyanate (p. 599), b.p. 115–121°, is added, with stirring, over a period of 1 hour (Note 1). After the addition has been completed, the condenser is removed and the solution is heated on a water bath for 30 minutes to remove excess ammonia. The solution is then boiled with 2 g. of Norit and filtered, and the filtrate is chilled in an ice bath. The methylthiourea crystallizes as a colorless, compact, solid mass, which is collected on a filter, washed three times with 25-ml. portions of ice water, and dried. The first crop of crystals weighs 65–75 g. A second crop amounting to 15–20 g. is obtained by concentrating the mother liquor and washings to a volume of 75 ml. and again chilling in the ice bath. The total yield of methylthiourea, m.p. 119–120.5° (Note 2), is 85–95 g. (74–81%) (Note 3) and (Note 4).

2. Notes

1. The addition of the methyl isothiocyanate should be maintained at a constant rate since the reaction is slow to start; when the mixture has warmed up, the reaction becomes very vigorous and hard to control.
2. Further purification by crystallizing from boiling anhydrous ethanol yields a product melting at 120.5–121°.
3. The yield is only slightly higher if purer methyl isothiocyanate is used.
4. This is a general method for the preparation of alkyl thioureas. Ethylthiourea, m.p. 103–106°, has been prepared from ethyl isothiocyanate in the same manner. Di- and trialkyl thioureas may be prepared from alkyl isothiocyanates in a similar manner by substituting an equivalent amount of an amine solution in place of the ammonium hydroxide. Thus, *sym*-dimethylthiourea is prepared from methyl isothiocyanate and methylamine solution. A solution of dimethylamine and methyl isothiocyanate gives trimethylthiourea.

3. Discussion

Methylthiourea has been prepared from methyl isothiocyanate and ammonia in ethanolic[1] or aqueous[2] solution, from methylammonium thiocyanate,[3] and by heating the methyl or ethyl ester of N-methyldithiocarbamic acid with alcoholic ammonia.[4]

References and Notes

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3. Salkowski, *Ber.*, **26**, 2497 (1893).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sym-dimethylthiourea

methyl or ethyl ester of N-methyldithiocarbamic acid

ethanol (64-17-5)

ammonia (7664-41-7)

Norit (7782-42-5)

ammonium hydroxide (1336-21-6)

methylamine (74-89-5)

dimethylamine (124-40-3)

ethyl isothiocyanate (542-85-8)

Methyl isothiocyanate (556-61-6)

METHYLTHIOUREA, Urea, 1-methyl-2-thio- (598-52-7)

Ethylthiourea (625-53-6)

trimethylthiourea (2489-77-2)

methylammonium thiocyanate

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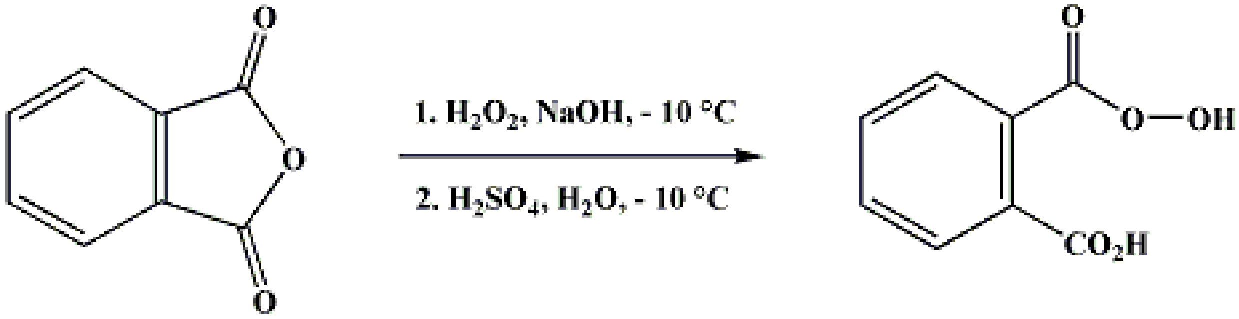
Organic Syntheses, CV 3, 619

MONOPERPHTHALIC ACID

[Phthalic monoperacid]



Submitted by Horst Böhme
Checked by Homer Adkins and E. Leon Foreman.

1. Procedure

In a 1-l. round-bottomed flask, equipped with a mechanical stirrer and cooled in an ice-salt bath, is placed 275 g. (250 ml., approximately 1 mole) of 15% sodium hydroxide solution. This is cooled to −10° (Note 1), and 115 g. (105 ml., approximately 1 mole) of 30% hydrogen peroxide which has been similarly cooled is added in one portion. The heat of reaction causes the temperature to rise markedly. When the temperature has again dropped to −10°, 75 g. (0.5 mole) of phthalic anhydride which has been pulverized to pass a 40-mesh sieve is added as quickly as possible while the contents are stirred vigorously in the freezing mixture (Note 2) and (Note 3). As soon as all the anhydride has dissolved, 250 ml. (0.5 mole) of 20% sulfuric acid which has been previously cooled to −10°, but not frozen (Note 4), is added.

The acid solution is filtered without suction through glass wool into a 2-l. separatory funnel and extracted once with 500 ml. of ether, then three times with 250-ml. portions of the same solvent. The combined ether extracts are shaken out with three 150-ml. portions of 40% ammonium sulfate solution and dried for 24 hours, preferably in a refrigerator, over 50 g. of anhydrous sodium sulfate.

If the ether is evaporated under reduced pressure (Note 5), crystalline monoperphthalic acid is obtained. It is more convenient, however, to use the ether solution directly (Note 6). Its peracid content is determined by adding to 2 ml. of the solution 30 ml. of 20% potassium iodide solution and titrating the iodine after 10 minutes with 0.05 *N* thiosulfate solution. The yield is 60–65 g. (65–70% based on the phthalic anhydride) (Note 7).

2. Notes

1. If the solutions are cooled to –10°, little oxygen is evolved and the yields of peracid are good. If the reaction is carried out at 0°, a large amount of oxygen is evolved and the yields are poor.
2. Commercial phthalic anhydride may be used directly. If excessive decomposition occurs, however, the anhydride should be purified by distillation under reduced pressure.
3. The anhydride is added in large portions or, better, in one portion.
4. The decisive factor in the success of this preparation is the time interval between the addition of the anhydride and the acidification of the reaction mixture. All the anhydride should dissolve, but prolonged stirring results in excessive oxygen evolution. The quicker the anhydride dissolves, and the smaller the oxygen evolution, the better the yield of the peracid. Hence, stirring must be vigorous.
5. If crystalline monoperphthalic acid is desired, it may be prepared conveniently as follows: The dried ether solution is placed in a distilling flask equipped with a capillary tube connected with a drying tube, and the flask is connected with the water pump. The ether is evaporated at the pressure thus obtained without the application of heat (ice will form on the flask) to a thin syrup (approximately 150 ml.). The syrup is transferred to an evaporating dish and the flask rinsed with a small amount of dry ether, the washings being added to the syrup. The remainder of the ether is then evaporated in a vacuum desiccator over concentrated sulfuric acid. For good results in this preparation the drying must be very thorough, for only 1% of water in the ether solution will be more than sufficient to destroy the entire amount of peracid.
6. If ether is not suitable for the oxidation reactions in which the peracid is to be used, the material can be dissolved in another solvent after removal of the ether. An excellent solvent for monoperphthalic acid oxidations is dioxane, and a solution of the peracid in dioxane is readily prepared by adding dioxane to the dried ether extract and then removing the ether under reduced pressure at 15°. The dioxane must be peroxide-free.[1]
7. As originally submitted, this preparation was on one-fifth the scale indicated here. However, the checkers have had no difficulty with the larger-scale preparation.

It has been reported[2] that an 86% yield of monoperphthalic acid results when a single ether extraction is employed. In the modified procedure, 40% alkali was employed, and crushed ice was added directly for cooling.

3. Discussion

Monoperphthalic acid has been prepared by hydrolysis of phthalyl peroxide with sodium hydroxide[3] and by shaking phthalic anhydride with excess alkaline peroxide solution.[3] The method described here is a modification of the latter process.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 805
- Org. Syn. Coll. Vol. 6, 482

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Monoperphthalic acid

Phthalic monoperacid

sulfuric acid (7664-93-9)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium sulfate (7757-82-6)

oxygen (7782-44-7)

potassium iodide (7681-11-0)

phthalic anhydride (85-44-9)

iodine (7553-56-2)

hydrogen peroxide, peroxide (7722-84-1)

thiosulfate

ammonium sulfate (7783-20-2)

dioxane (5703-46-8)

phthalyl peroxide

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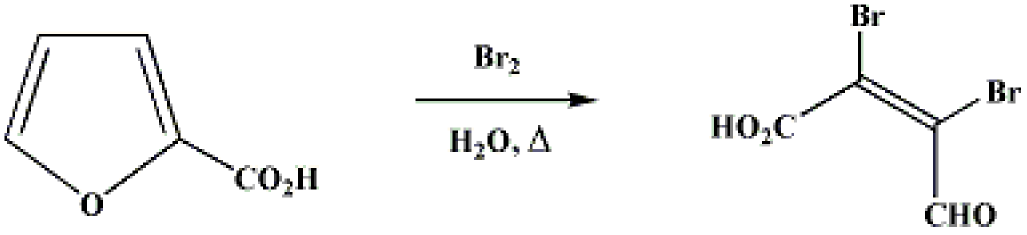
Organic Syntheses, CV 3, 621

MUCOBROMIC ACID

[Acrylic acid, α,β-dibromo-β-formyl-]



Submitted by C. F. H. Allen and F. W. Spangler.
Checked by R. L. Shriner and Nicholas J. Kartinos.

1. Procedure

In a 2-l. three-necked round-bottomed flask, equipped with a reflux condenser attached to a gas trap, a dropping funnel, and a mechanical stirrer, are placed 100 g. (0.9 mole) of furoic acid (Note 1) and 440 ml. of water. The flask is immersed in a pan of crushed ice, and 686 g. (220 ml., 4.3 moles) of bromine is placed in the dropping funnel. The stirrer is started, and the bromine is added over a period of about 1 hour with constant stirring and cooling (Note 2). The bromine is decolorized almost immediately at first and then more slowly as the reaction proceeds. The mixture is then heated to boiling and refluxed for 30 minutes. The condenser is removed and the boiling continued for an additional 30 minutes with one neck of the flask open. The mixture is cooled and chilled thoroughly, whereupon the mucobromic acid separates and is collected on a filter. The filter cake is removed and thoroughly triturated with a solution of 5 g. of sodium bisulfite in 150 ml. of water (Note 3), and the product is again removed by filtration. After drying in the air the crude product weighs 155–170 g. (67–73%) and melts at 120–122° (cor.).

The mucobromic acid may be recrystallized by solution in 250 ml. of boiling water with the addition of 2 g. of Darco. The hot solution is filtered, and the filtrate is thoroughly chilled in an ice bath. After filtration and drying there is obtained 148–155 g. (64–67%) of white crystals melting at 123–124° (cor.).

2. Notes

1. The furoic acid may be obtained from furfural by means of the Cannizzaro reaction[1] or by oxidation with alkaline potassium permanganate.[2] It is important to purify the furoic acid to a melting point of 131–132°.
2. It is essential that the flask and its contents be well cooled; otherwise the yield is materially decreased.
3. The sodium bisulfite solution removes the color produced by the excess

bromine.

3. Discussion

The only practical methods of preparation are the action of bromine on furfuraldehyde[3] or furoic acid[4,5,6] in aqueous solution.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 688

References and Notes

1. *Org. Syntheses* Coll. Vol. **1**, 276 (1941).
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3. Simonis, *Ber.*, **32**, 2085 (1899).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

potassium permanganate (7722-64-7)

bromine (7726-95-6)

sodium bisulfite (7631-90-5)

furoic acid (88-14-2)

Furfural, furfuraldehyde (98-01-1)

Mucobromic acid, Acrylic acid, α,β-dibromo-β-formyl- (488-11-9)

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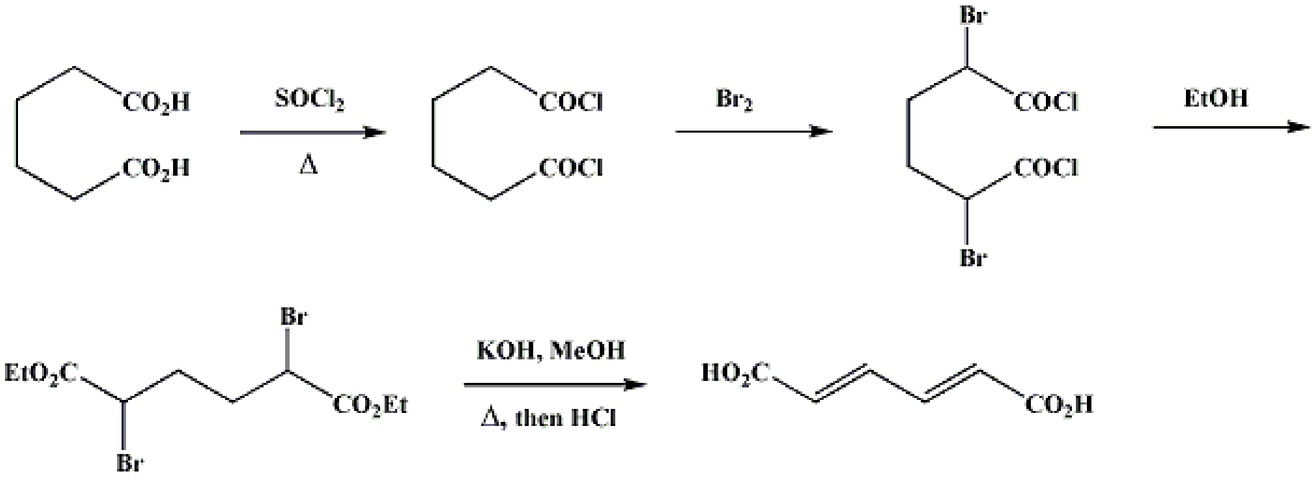
Organic Syntheses, CV 3, 623

MUCONIC ACID



Submitted by P. C. Guha and D. K. Sankaran.
Checked by C. F. H. Allen and H. W. J. Cressman.

1. Procedure

A. *Diethyl α,δ-dibromoadipate.* In a 3-l. three-necked flask (Note 1) fitted with a reflux condenser, a dropping funnel, and a mechanical stirrer are placed 1 kg. (6.85 moles) of adipic acid and 2 kg. (1220 ml., 16.8 moles) of thionyl chloride (Note 2) and (Note 3). The mixture is stirred and heated gently on the steam bath until solution is effected, and the evolution of hydrogen chloride (Note 4) ceases after about 3 hours. The excess thionyl chloride is distilled by heating on a steam bath, the last portion of the reagent being taken off under reduced pressure.

To the acid chloride, mechanically stirred and heated on the steam bath, is added 2.5 kg. (805 ml., 15.6 moles) of dry bromine (p. 124) as rapidly as it will react (Note 5). The addition requires about 12 hours. The contents of the flask are stirred and heated an additional 2 hours, transferred to a dropping funnel (Note 6), and added in a thin stream to 5 l. of absolute ethanol, which has previously been placed in a 12-l. flask provided with a stopper carrying an efficient reflux condenser, a separatory funnel, and a mechanical stirrer. The resulting vigorous reaction is controlled by external cooling. After the dibromoacid chloride has been added, the reaction mixture is allowed to stand at room temperature overnight and is then poured into 5 l. of cold water. The top ethanolic aqueous layer is decanted and extracted once with 8 l. of ether. The oily bottom layer is dissolved in the ether extract and washed first with 1 l. of a 2% sodium bisulfite solution, then with two 1-l. portions of 3% sodium carbonate solution, and finally with several portions of water. The ether solution is dried over 175 g. of potassium carbonate; the solvent is distilled on the steam bath. The yield of residual ester (Note 7) amounts to 2260–2400 g. (91–97%).

B. *Muconic acid.* To a solution of 3 kg. of potassium hydroxide and 5 l. of methanol (Note 8) in a 12-l. flask, equipped as described above, is added in a thin stream from a separatory funnel (Note 6), and with stirring, 1130 g. (3.14 moles) of diethyl α,δ-dibromoadipate. The ester is heated on the steam bath to nearly 100° before it is added. The addition is so regulated as to permit rather vigorous refluxing and requires 45 minutes. Heating on the steam bath and stirring are continued an additional 2 hours. The mixture is allowed to stand at room temperature overnight and is cooled. The potassium muconate and potassium bromide are filtered (Note 9), washed on the funnel with two 350-ml. portions of methanol and 400 ml. of ether, transferred without further drying to an enameled 11- to 12-l. pail, and dissolved in 8 l. of hot water. The aqueous solution, to which is added 30 g. of Norit, is heated to boiling by introduction of steam, filtered through a Norit filter pad by suction, and cooled in an ice-salt bath. The muconic acid is precipitated by the addition of a large excess (1.5 l.) (sp. gr. 1.18) of concentrated hydrochloric acid to the cold solution. The acid is added in a thin stream to the well-stirred solution. After 2 hours the muconic acid is filtered, washed first with two 400-ml. portions of cold water and then with 200 ml. of methanol, and dried at 85°. The yield of nearly colorless product melting at 296–298°, with decomposition, amounts to 165–195 g. (37–43%).

2. Notes

1. Apparatus with ground-glass joints is preferable.
2. The yield obtained in molar-sized runs is also about 40% of the theoretical.
3. The submitters used 1 mole of adipic acid and added 2 moles of phosphorus pentachloride in 20-g. portions over an interval of 30 minutes.
4. The considerable quantities of hydrogen chloride and hydrogen bromide evolved are best handled by means of a gas-absorption trap. The insertion of a calcium chloride tube between the trap and the reflux condenser is recommended.
5. The bromine is added as rapidly as it will react but not so rapidly that loss occurs through the condenser. A photoflood lamp accelerates the rate of bromination.
6. The dibromoacid chloride solidifies at room temperature. It is advisable to heat the funnel by means of a coil of copper tubing through which steam is passed.
7. Two isomers, a solid and a liquid, are formed during the bromination and subsequent esterification.
8. A commercial grade of methanol was used; absolute methanol did not result in an increased yield.
9. A pad of Filter-Cel aids in the slow filtration. About 100 g. is needed with a 30-cm. funnel.

3. Discussion

Muconic acid has been obtained in a variety of ways. The procedures that seem most important from a preparative point of view are by treatment of ethyl α,δ-dibromoadipate with ethanolic potassium hydroxide,[1,2] by condensation of glyoxal (as the sodium bisulfite addition product) with malonic acid,[3,4] by heating ethyl 1-acetoxy-1,4-dihydromuconate (obtained by condensing ethyl oxalate and ethyl crotonate, acetylating, and reducing),[5,6] by oxidation of phenol[7] or catechol[8] with peracetic acid, and by hydrolysis of the half-ester obtained by the condensation of ethyl fumaraldehydate with malonic acid.[9]

Three steroisomeric muconic acids are known.[10]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

dibromoacid chloride

ethyl 1-acetoxy-1,4-dihydromuconate

muconic acids

ethanol (64-17-5)

calcium chloride (10043-52-4)

potassium carbonate (584-08-7)

hydrogen chloride, hydrochloric acid (7647-01-0)

methanol (67-56-1)

ether (60-29-7)

glyoxal (107-22-2)

phosphorus pentachloride (10026-13-8)

thionyl chloride (7719-09-7)

Adipic acid (124-04-9)

phenol (108-95-2)

hydrogen bromide (10035-10-6)

sodium carbonate (497-19-8)

bromine (7726-95-6)

sodium bisulfite (7631-90-5)

copper (7440-50-8)

potassium hydroxide (1310-58-3)

potassium bromide (7758-02-3)

Catechol (120-80-9)

Ethyl oxalate

Malonic acid (141-82-2)

peracetic acid (79-21-0)

ethyl crotonate (623-70-1)

Muconic acid (505-70-4)

Diethyl α,δ-dibromoadipate (869-10-3)

potassium muconate

ethyl α,δ-dibromoadipate

ethyl fumaraldehydate (2960-66-9)

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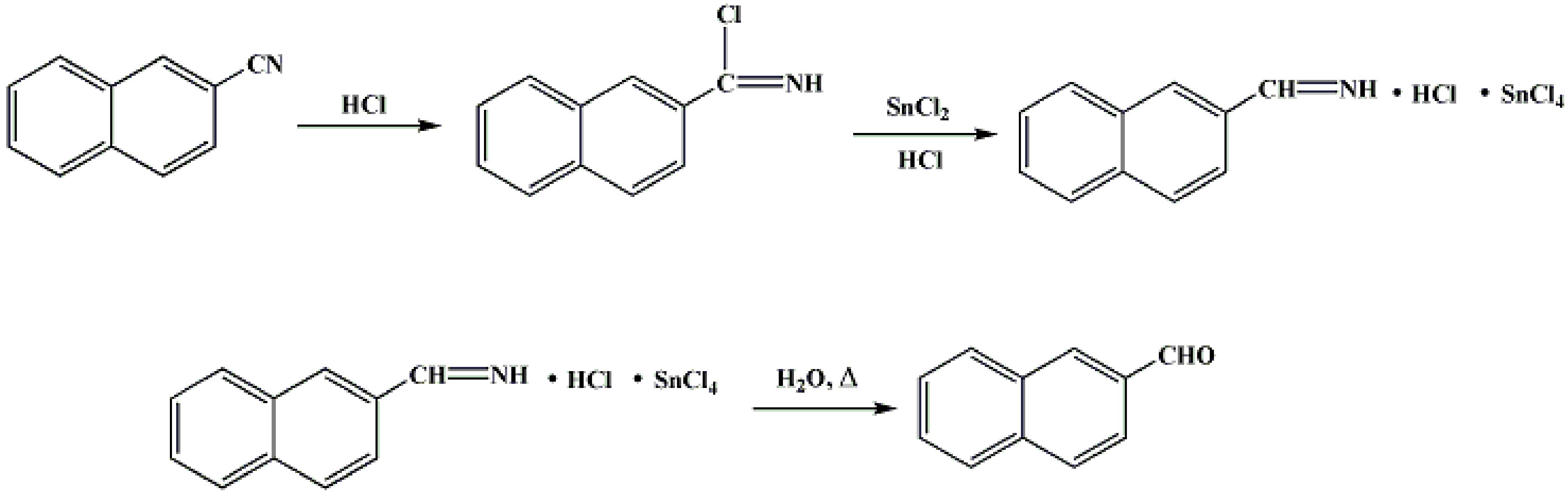
Organic Syntheses, CV 3, 626

β-NAPHTHALDEHYDE

[2-Naphthaldehyde]

[I. METHOD A]



Submitted by Jonathan W. Williams
Checked by C. F. H. Allen and J. VanAllan.

1. Procedure

In a 2-l. three-necked round-bottomed flask, provided with a mechanical stirrer, a reflux condenser carrying a drying tube, and an inlet tube reaching nearly to the bottom of the flask, are placed 76 g. (0.4 mole) of anhydrous stannous chloride (Note 1) and 400 ml. of anhydrous ether. The mixture is then saturated with dry hydrogen chloride, while it is slowly stirred; this requires 2.5–3 hours, during which time the stannous chloride forms a viscous lower layer.

The inlet tube is replaced by a dropping funnel, and a solution of 30.6 g. (0.2 mole) of β-naphthonitrile, m.p. 60–62° (Note 2), in 200 ml. of

dry ether is added rapidly. Hydrogen chloride is again passed into the mixture until it is saturated, and the mixture is then stirred rapidly for 1 hour and allowed to stand overnight while the yellow aldimine-stannichloride separates completely.

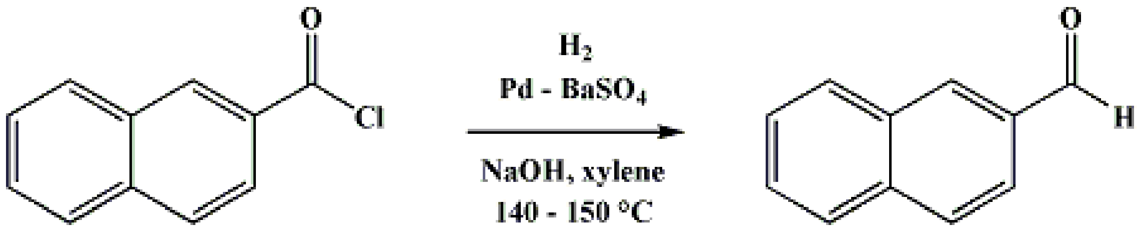
The ethereal solution is decanted, and the solid is rinsed with two 100-ml. portions of ether. The solid is transferred to a 5-l. flask fitted for steam distillation and immersed in an oil bath, the temperature of which is maintained at 110–120° (Note 3). Dry steam is passed through the mixture (Note 4) until the aldehyde is completely removed; this requires 8–10 hours, and 8–10 l. of distillate is collected.

The white solid is filtered and allowed to dry in the air; it amounts to 23–25 g. (73–80%) and melts at 53–54°. For further purification, it is distilled under reduced pressure (Note 5); the water-clear distillate (b.p. 156–158°/15 mm.) is poured into a mortar while hot and is pulverized when cool. The recovery is 93–95%, and the melting point is 57–58°.

2. Notes

1. The success of this type of reaction depends on the quality of the catalyst. The most active and dependable form of anhydrous stannous chloride[1] is prepared as follows: In a 600-ml. beaker is placed 204 g. (189 ml., 2 moles) of acetic anhydride (99–100%) and, while the liquid is stirred by hand, 226 g. (1 mole) of commercial C.P. crystalline stannous chloride dihydrate is added. This operation should be performed in a hood, for the heat of the reaction is sufficient to cause the acetic anhydride to boil. After about 1.5 hours, the anhydrous stannous chloride is filtered on a large Büchner funnel, rinsed with two 50-ml. portions of dry ether, and dried overnight in a vacuum desiccator. The yield is quantitative (189 g.). The product may be kept in a tightly closed bottle until it is wanted. The product secured by dehydrating crystalline stannous chloride in an oil bath at 195–200° is satisfactory in many instances but is not dependable.
2. β-Naphthonitrile is prepared by the procedure described under *o*-Tolunitrile, in *Org. Syntheses* Coll. Vol. 1, 514 (1941).
3. The use of dry, slightly superheated steam reduces the time of distillation but is not essential.
4. A superheater obtained from the Fisher Scientific Company was used. It was preceded by the usual steam trap to remove the condensed water. The thermometer in the superheater recorded 260°.
5. It is convenient to combine the material from several runs.

[II. METHOD B]



Submitted by E. B. Hershberg and James Cason.
Checked by Nathan L. Drake, Harry D. Anspon, and Ralph Mozingo.

1. Procedure

A 500-ml. three-necked flask, *equipped with ground joints*, is fitted with a mercury-sealed stirrer (Note 1), a reflux condenser, and a gas-inlet tube extending to a point just above the stirrer. In the flask are placed 57 g. (0.30 mole) of β-naphthoyl chloride (Note 2), 200 ml. of xylene (Note 3), 6 g. of palladium-barium sulfate catalyst (p. 685), and 0.6 ml. of stock poison solution (Note 4). The top of the condenser is connected by a rubber tube to a 6-mm. glass tube extending to the bottom of a 500-ml. Erlenmeyer flask containing 400 ml. of distilled water and a few drops of phenolphthalein indicator solution. A buret containing approximately 5 *N* sodium hydroxide solution (prepared by dissolving 20.5 g. of analytical reagent sodium hydroxide in water and diluting to 100 ml.) is arranged for delivery into this flask, which for safety should be placed at least 2 ft. away from any flame. Commercial electrolytic hydrogen is passed from a cylinder directly into the reaction flask at such a rate that 100–300 bubbles per minute emerge in the Erlenmeyer flask.

After the air in the reaction flask has been displaced by hydrogen, the flask is heated in an oil bath at 140–150°, the stirrer is started (Note 5), and 1 ml. of alkali is run into the Erlenmeyer flask. The course of the reaction is followed by the rate of hydrogen chloride evolution. The first 5 ml. of alkali should be neutralized in 12–15 minutes, and the reaction should be complete in approximately 3 hours. About 92% of the theoretical amount of hydrogen chloride (equivalent to 55 ml. of 5 *N* sodium hydroxide solution) is recovered. The end of the reaction is evidenced by a rather abrupt cessation of hydrogen chloride evolution, and the reaction is discontinued at this point.

The flask is cooled, 1–2 g. of Norit added with stirring, and the solution filtered with suction through a hardened filter paper (Note 6). The xylene is removed from the nearly colorless filtrate by flash distillation under diminished pressure. For this purpose, a 125-ml. modified Claisen flask is arranged for vacuum distillation, the usual capillary being replaced by a separatory funnel whose stem extends to the bottom of the flask. The flask is heated in an oil bath at 90–100° and the solution added from the funnel as rapidly as possible without causing accumulation of xylene in the distilling flask. After all the solution has been added, the separatory funnel is replaced by a capillary and the bath temperature is raised. After a small fore-run consisting mostly of naphthalene, the β-naphthaldehyde distils at 147–149°/11 mm. (bath temperature 170–180°), leaving a small non-volatile residue. In this way, 34.5–38 g. (74–81%) of white aldehyde, m.p. 59–60°, is obtained

(Note 7).

2. Notes

1. A Hershberg tantalum or platinum wire stirrer whose shaft runs in a ball bearing is convenient, but an ordinary all-glass stirrer may be used. The stirrer must be capable of running at a high speed, for the rate of reaction is dependent to a high degree on the speed of stirring. It is also extremely important that the stirrer be carefully lined up so that there is a minimum of splashing of mercury in the seal. If mercury works down into the flask, the reaction will not proceed properly (Note 5).

2. β-Naphthoyl chloride is conveniently prepared from β-naphthoic acid and phosphorus pentachloride. A mixture of 57.4 g. (0.33 mole) of acid and 69 g. (0.33 mole) of phosphorus pentachloride in a 250-ml. modified Claisen distilling flask is warmed on a steam bath in a hood. As soon as the vigorous reaction sets in, the flask is removed from the steam bath until the rapid evolution of hydrogen chloride has moderated, then warmed on the steam bath for 30 minutes. After removal of the phosphorus oxychloride at diminished pressure, using a water pump, the acid chloride is distilled. The fraction boiling at 160–162°/11 mm. (bath temperature 170–180°) weighs 57–60 g. (90–95%) and melts at 51–52°. The distillation should be carefully conducted, and a quite colorless product should result.

3. One liter of technical xylene is refluxed overnight with 2 g. of sodium, distilled, and stored over sodium.

4. The quinoline-sulfur poison of Rosenmund and Zetzsche[2] is prepared by refluxing 1 g. of sulfur with 6 g. of quinoline for 5 hours and diluting the resultant dark brown liquid to 70 ml. with the purified xylene. The literature on the Rosenmund reduction contains many conflicting reports concerning the necessity for a catalyst poison; however, the work of Zetzsche and collaborators[3,4] indicates that the purity of the solvent is the determining factor. These workers found that by using technical xylene without added poison a good yield of aldehyde could usually be obtained but after the xylene had been purified by distilling over anhydrous aluminum chloride practically no aldehyde was obtained under the same conditions. Instead, products arising from further reduction of the aldehyde were obtained. In view of these results the use of a poison is recommended in order to ensure controlled conditions. The submitters claim that the use of twice the ratio of poison specified has no effect except slowing up the reaction; the yield and quality of the product remain the same.

5. The rapid rate of stirring desirable for maximum reaction rate often causes spraying of fine droplets of mercury from the seal. This can be prevented by a layer of paraffin oil over the mercury. It is important for the gas-inlet tube to extend below the surface of the stirred liquid, for absorption of hydrogen occurs chiefly at the rapidly agitated surface.

6. The palladium may be recovered from used catalyst by ignition and solution in aqua regia.[5]

7. According to the submitters, this reaction is quite satisfactory on a small scale and can be used with other acid chlorides. In a 0.05-mole run carried out in the same manner, an 83% yield of β-naphthaldehyde was obtained. 1-Acetoxy-3-naphthaldehyde, m.p. 112–114°, was obtained in 70% yield from 0.85 g. of the corresponding acid chloride. Methyl β-formylpropionate, b.p. 69–70°/14 mm.,

was also obtained in 65% yield from the acid chloride; reduction proceeds rapidly at 110° in this case.

3. Discussion

β-Naphthaldehyde has been prepared from β-chloromethylnaphthalene by the use of hexamethylenetetramine in ethanol,[6] or by oxidation with lead nitrate;[7] from β-bromomethylnaphthalene by the use of hexamethylenetetramine in ethanol[8] or in acetic acid,[9] or by oxidation with lead nitrate;[7] by distillation of a mixture of calcium formate and calcium β-naphthoate;[10,11] by reduction of β-naphthoic acid with sodium amalgam;[12] from β-naphthylcarbinol by oxidation with chromic acid;[13] from β-naphthylglyoxylic acid anil;[14] from β-naphthylmagnesium iodide and methyl orthoformate;[15] from β-naphthylmagnesium bromide and ethoxymethylaniline[16] or orthoformic ester;[14,17] by treatment of β-naphthylmagnesium bromide with carbon disulfide, followed by conversion of the dithioacid to a semicarbazone and hydrolysis;[18] from β-naphthonitrile by Stephen reduction;[19,20] from β-naphthoyl chloride by Rosenmund reduction;[3,21,22] and from 2-methylnaphthalene by oxidation with selenium dioxide.[23]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 549
- Org. Syn. Coll. Vol. 3, 601
- Org. Syn. Coll. Vol. 3, 818
- Org. Syn. Coll. Vol. 4, 444

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

semicarbazone

aldimine-stannichloride

β-naphthylcarbinol

β-naphthylglyoxylic acid anil

ethanol (64-17-5)

hydrogen chloride (7647-01-0)

acetic acid (64-19-7)

ether (60-29-7)

acetic anhydride (108-24-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

phosphorus pentachloride (10026-13-8)

stannous chloride

sulfur (7704-34-9)

mercury (7439-97-6)

platinum (7440-06-4)

Phosphorus Oxychloride (21295-50-1)

aluminum chloride (3495-54-3)

selenium dioxide (7446-08-4)

sodium (13966-32-0)

lead nitrate (10099-74-8)

palladium (7440-05-3)

chromic acid (7738-94-5)

carbon disulfide (75-15-0)

Naphthalene (91-20-3)

xylene (106-42-3)

Quinoline (91-22-5)

hexamethylenetetramine (100-97-0)

phenolphthalein (77-09-8)

o-Tolunitrile (529-19-1)

chloride

stannous chloride dihydrate (10025-69-1)

tantalum (7440-25-7)

calcium formate (544-17-2)

β-Naphthoic acid (93-09-4)

β-naphthonitrile (613-46-7)

2-methylnaphthalene (91-57-6)

palladium-barium sulfate

β-naphthoyl chloride (2243-83-6)

β-Naphthaldehyde, 2-Naphthaldehyde (66-99-9)

quinoline-sulfur

1-Acetoxy-3-naphthaldehyde

Methyl β-formylpropionate (13865-19-5)

β-chloromethylnaphthalene (2506-41-4)

β-bromomethylnaphthalene (939-26-4)

calcium β-naphthoate

β-naphthylmagnesium iodide

methyl orthoformate

β-naphthylmagnesium bromide

ethoxymethylaniline

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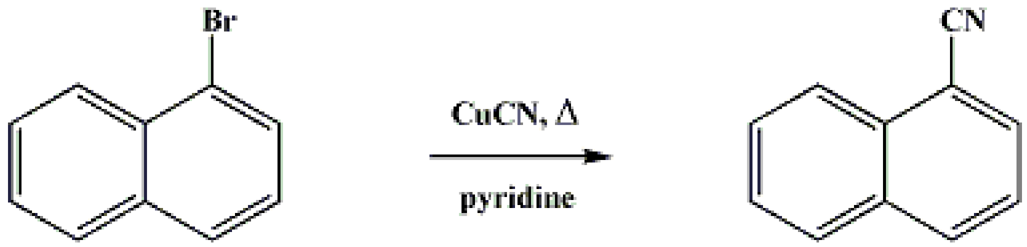
Organic Syntheses, CV 3, 631

α-NAPHTHONITRILE

[1-Naphthonitrile]



Submitted by M. S. Newman
Checked by R. L. Shriner and F. J. Wolf.

1. Procedure

In a dry 200-ml. flask fitted with a ground-joint reflux condenser and protected from moisture by a calcium chloride tube are put 66 g. (0.32 mole) of α-bromonaphthalene (Note 1), 35 g. (0.39 mole) of dry powdered cuprous cyanide (Note 2), and 30 ml. of pyridine (Note 3) in the order mentioned. This mixture is heated in a Wood's metal bath (Note 4) at 215–225° for 15 hours. The resulting dark brown solution is poured while still hot (about 100°) into a flask containing 150 ml. of aqueous ammonia (sp. gr. 0.90) and 150 ml. of water. About 140 ml. of benzene is added, and the flask is stoppered and shaken until all the lumps have disintegrated. After the mixture has cooled to room temperature, 100 ml. of ether is added and the mixture is filtered (Note 5). The filtrate is transferred to a 1-l. separatory funnel, and the aqueous layer is separated (Note 6). The ether-benzene layer is washed successively with (*a*) four 100-ml. portions of dilute aqueous ammonia (Note 7), (*b*) two 100-ml. portions of 6 *N* hydrochloric acid (Note 8), (*c*) two 100-ml. portions of water, and (*d*) two 100-ml. portions of saturated sodium chloride solution. The ether and benzene are removed by distillation from a water bath, and the residue is distilled under reduced pressure from a 125-ml. modified Claisen flask. The temperature rises rapidly, and the yield of colorless α-naphthonitrile, b.p. 173–174°/27 mm. (166–169°/18 mm.), is 40–44 g. (82–90%) (Note 9) and (Note 10).

2. Notes

1. The α-bromonaphthalene was redistilled just before use and the fraction boiling at 153–154°/22 mm. taken.
2. "Baker's Analyzed" cuprous cyanide (powdered) was used. The cuprous cyanide must be dry.
3. Pure pyridine dried over barium oxide was used. A considerable amount of heat is liberated on addition of the pyridine to the mixture.

4. A fused salt bath consisting of 8.5 parts (by weight) of sodium nitrite and 10 parts of potassium nitrate has a melting point of about 140° and may replace the metal bath.
5. The cuprammonium solution attacks filter paper and hence this solution is best filtered through a fritted-glass filter. Two layers of ordinary toweling cloth on a Büchner funnel may also be used.
6. It is occasionally necessary to add an additional 50–100 ml. of ether to facilitate separation.
7. If the final ammoniacal wash solution is not colorless, the ether/benzene solution should be washed with additional 100-ml. portions of dilute aqueous ammonia.
8. If a precipitate separates during this operation it should be removed by filtration.
9. The yields vary with the quality of the cuprous cyanide. One lot of this reagent gave yields of only 60–75%. Larger amounts may be run, but the amount of pyridine used should be reduced to decrease the reflux. For a 2-mole run, 160 ml. of pyridine was satisfactory. The yield of the large runs was 81%.
10. α-Chloronaphthalene (b.p. 144–146.5°/29 mm.) may be used in place of α-bromonaphthalene, but 24 hours' heating at 245–250° is required. The yields are about the same.

3. Discussion

α-Naphthonitrile has been prepared from α-naphthylamine by the Sandmeyer reaction,[1] from α-chloronaphthalene,[2] from α-bromonapth, thalene[3] by heating with cuprous cyanide, by heating the sodium salt of α-naphthalenesulfonic acid with sodium cyanide[4] or with potassium ferrocyanide, iron, and ferric oxide,[5] by heating α-naphthamide with phosphorus pentachloride[6] or with sodium chloroaluminate,[7] and by distilling α-naphthoic acid with dicyandiamide.[8]

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Appendix

Compounds Referenced (Chemical Abstracts Registry Number)

α-naphthylamine

α-bromonapththalene

sodium chloroaluminate

dicyandiamide

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

Benzene (71-43-2)

ether (60-29-7)

phosphorus pentachloride (10026-13-8)

iron (7439-89-6)

sodium cyanide (143-33-9)

sodium chloride (7647-14-5)

barium oxide

Cuprous Cyanide (544-92-3)

sodium nitrite (7632-00-0)

pyridine (110-86-1)

α-Bromonaphthalene (90-11-9)

potassium ferrocyanide

potassium nitrate (7757-79-1)

ferric oxide (1309-37-1)

α-Naphthoic acid (86-55-5)

α-Naphthonitrile, 1-Naphthonitrile (86-53-3)

sodium salt of α-naphthalenesulfonic acid (130-14-3)

α-naphthamide (2243-81-4)

α-Chloronaphthalene (90-13-1)

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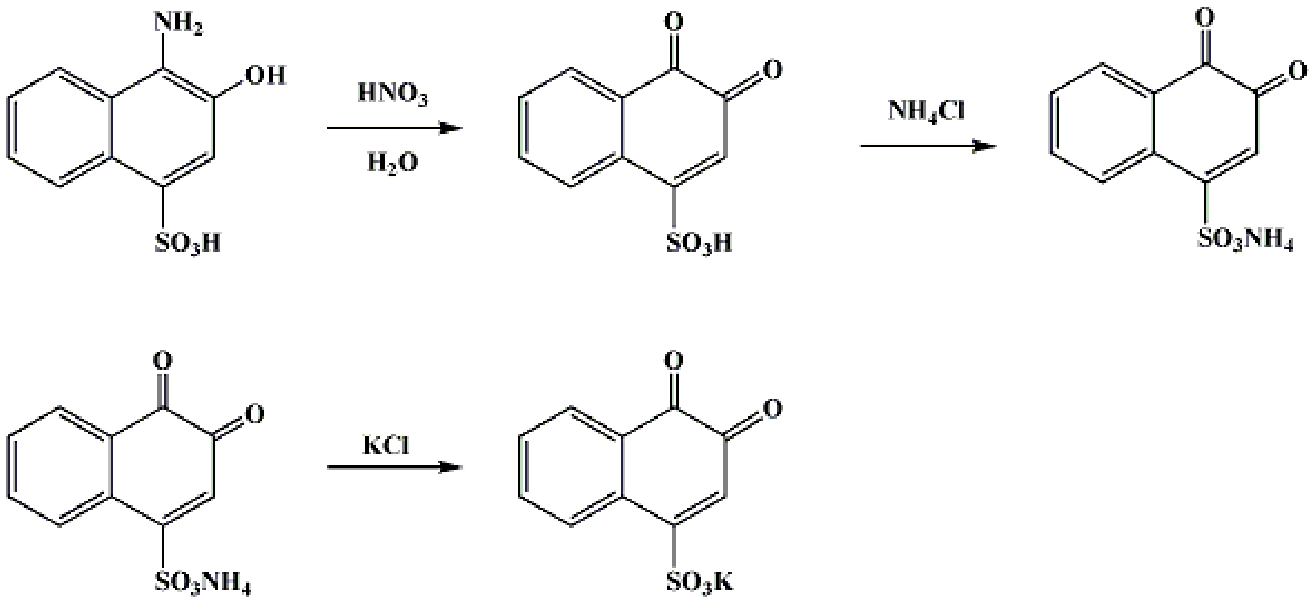
Organic Syntheses, CV 3, 633

1,2-NAPHTHOQUINONE-4-SULFONATE, AMMONIUM AND POTASSIUM

[1-Naphthalenesulfonic acid, 3,4-dihydro-3,4-dioxo, ammonium and potassium salts]



Submitted by E. L. Martin and L. F. Fieser.
Checked by R. L. Shriner and Eldred Welch.

1. Procedure

A mixture of 145 ml. of nitric acid (sp. gr. 1.42) and 400 ml. of water in a 2-l. beaker is cooled to 30° in a slush of ice and water, and 350 g. (1.46 moles) of pure, anhydrous 1-amino-2-naphthol-4-sulfonic acid (Note 1) is weighed into a separate 2-l. beaker. The beaker is removed from the bath; a 10-g. portion of the 1-amino-2-naphthol-4-sulfonic acid is stirred into the solution, and the liquid is then allowed to become entirely motionless. Generally, oxidation starts during this addition; if not, 2 ml. of concentrated nitric acid is poured carefully down the side of the beaker without stirring. Oxidation commences in 1–2 minutes and the mixture turns yellow (Note 2).

The beaker is replaced in the ice bath, and 20–25 g. of 1-amino-2-naphthol-4-sulfonic acid is stirred into the mixture by hand. A second portion of 20–25 g. is added immediately and stirred. The mixture begins to froth and is covered with a layer of 100 ml. of ether which serves as an efficient subsident (Note 3). The remainder of the 1-amino-2-naphthol-4-sulfonic acid is added in 20–25 g. portions during the course of 3–4 minutes, the mixture being stirred well after each addition. Oxides of nitrogen are freely evolved, and a stiff yellow-orange paste is formed. The temperature is maintained between 25° and 30° by vigorous stirring and by controlling the rate of addition of the compound (Note 4). The oxidation is complete within 3–4 minutes after the last addition and gas is then no longer evolved. The thick mass is stirred until the temperature has dropped to 5–10° and then 175 ml. of saturated ammonium chloride solution (30°) is added.

After the mixture has been cooled to 0°, the ammonium 1,2-naphthoquinone-4-sulfonate is collected on a 20-cm. Büchner funnel and as much of the mother liquor is removed as possible by pressing the cake with a porcelain spatula or glass stopper. The product is washed with three equal portions of a cold mixture of 150 ml. of saturated ammonium chloride solution and 100 ml. of water. The wash solution is removed as completely as possible, and the product is washed twice with 50-ml. portions of ethanol, followed by 300 ml. of ether in small portions (Note 5). The ammonium 1,2-naphthoquinone-4-sulfonate is spread out in a thin layer and dried to constant weight at 35–40°. An orange, microcrystalline product of bright appearance is thus obtained. The yield is 350–365 g. (94–98%). The ammonium salt is of good quality and is sufficiently pure for

many purposes. No satisfactory method has been devised for its further purification, but it can be converted into a pure potassium salt as follows.

Seventeen hundred milliliters of water containing 0.3 ml. of liquid bromine is heated in a 2-l. Erlenmeyer flask to 50° on a steam bath (Note 6). The flask is removed, 50 g. of ammonium 1,2-naphthoquinone-4-sulfonate is added, and the mixture is shaken for a few minutes until solution is complete. Three grams of Norit is added, and the solution is stirred for 2–3 minutes. It is then filtered by suction and the clear orange filtrate is transferred to a 4-l. Erlenmeyer flask. Four hundred milliliters of saturated potassium chloride solution (30°) is added rapidly in one portion, and the flask is allowed to stand undisturbed. Orange crystals of potassium salt begin to separate immediately, and after standing for 30 minutes the contents of the flask are cooled to 0° in an ice-salt bath and the potassium 1,2-naphthoquinone-4-sulfonate is collected on a 15-cm. Büchner funnel. The solid is washed with 150 ml. of cold, dilute potassium chloride solution (30 ml. of saturated potassium chloride solution added to 120 ml. of water), and then with 150 ml. of ethanol in small portions followed by 300 ml. of ether. The potassium salt is dried to constant weight at 40–50°. The yield is 48–50 g. (90–92% based on the ammonium salt used). The product consists of orange needles free of colored decomposition products but still containing traces of ammonium salts. An ammonium-free compound is obtained by a second crystallization. Seventeen hundred milliliters of water containing 0.2 ml. of liquid bromine is heated to 60° in a 2-l. Erlenmeyer flask on a steam bath; the flask is removed, and 50 g. of the potassium salt is added. The salt dissolves rapidly; the solution is filtered with suction; and the clear orange filtrate is transferred to a 4-l. Erlenmeyer flask. Three hundred milliliters of saturated potassium chloride solution is added rapidly in one portion, and the flask is allowed to stand undisturbed. Orange needles of potassium salt appear in a moment or two, and after standing for 30 minutes the mixture is cooled to 0° in an ice-salt bath. The crystals are collected, washed, and dried as outlined above. The salt thus obtained weighs 45–49 g. (90–98% based on the potassium 1,2-naphthoquinone-4-sulfonate used). This product compared favorably with the sodium salt prepared by the more elaborate borax process[1] with respect to color, colored decomposition products and ammonia content (Note 7) and (Note 8).

2. Notes

1. The 1-amino-2-naphthol-4-sulfonic acid earlier described [*Org. Syntheses* Coll. Vol. **2**, 42 (1943)] is not quite pure and gives an oxidation product of somewhat inferior quality. The procedure in question yields a gray product containing water of hydration (the percentage yield reported is thus in error). On reinvestigating the matter it has been found that the darkening of the material can be minimized if not prevented entirely, and that the colored impurity can be removed completely by extraction with ethanol. The colorless, anhydrous sulfonic acid required for the present preparation is thus prepared by modifying the earlier procedure in the following respects. By stirring the mixture of nitroso-β-naphthol and sodium bisulfite solution vigorously by hand (wooden paddle), all the soluble product can be dissolved in 3–4 minutes. The solution is then filtered as rapidly as possible, using two 15-cm. Büchner funnels and changing filter papers frequently. The clear, golden-yellow filtrate is acidified immediately on completion of the filtration. The product is then light gray, whereas, if much time elapses before the bisulfite solution is acidified, the solution turns red and the aminonaphtholsulfonic acid may be deep purple-gray. After the product has been collected and washed with water, it is washed with warm ethanol until the filtrate is colorless; 1.5–2 l. of ethanol is required. The product is washed with two 100-ml. portions of ether and dried to constant weight at 60–80° in the absence of light. A pure white, dust-dry product which weighs 370–380 g. (75–78% based on the β-naphthol) is thus obtained. This product is used in the present procedure.
If technical 1-amino-2-naphthol-4-sulfonic acid is used, the yield of ammonium 1,2-naphthoquinone-4-sulfonate is 313 g. (84%) of a rust-colored product. If the technical material is washed with 2 l. of warm 95% ethanol the yield is 337 g. (90%) of an orange-colored ammonium salt.

2. It is important that the oxidation start at this point. Should oxidation not begin, a second 1–2 ml. portion of concentrated nitric acid is added; the acid is introduced along the side of the beaker with as little disturbance as possible.

3. It is necessary to add more ether from time to time to replace that which evaporates.

4. The temperature must be kept within this range. At lower temperatures the oxidation is slow and not satisfactory; at higher temperatures the quinone is slightly decomposed.

5. The ethanol and ether remove the small amount of decomposition products and assist in the rapid drying of the product. It is advisable to dry the preparation as rapidly as possible.
6. Aqueous solutions of 1,2-naphthoquinone-4-sulfonate begin to decompose when heated to this temperature in the absence of bromine.

7. Tests for the purity of the product were devised by Folin and later improved by Danielson.[1] A direct comparison of the two preparations revealed no difference in the degree of purity of the product.
8. This purified salt is suitable for use in the procedures of Folin and of Sullivan for the determination of amino acids.

3. Discussion

Salts of 1,2-naphthoquinone-4-sulfonate have been prepared by the oxidation of 2-amino-1-naphthol-4-sulfonic acid with nitric acid,[2] or by the oxidation of the more readily available 1-amino-2-naphthol-4-sulfonic acid with the same reagent.[3,4,5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 465

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

1-Naphthalenesulfonic acid, 3,4-dihydro-3,4-dioxo, ammonium and potassium salts

ethanol (64-17-5)

ammonia (7664-41-7)

ether (60-29-7)

ammonium chloride (12125-02-9)

nitric acid (7697-37-2)

bromine (7726-95-6)

nitrogen (7727-37-9)

β-naphthol (135-19-3)

sodium bisulfite (7631-90-5)

Norit (7782-42-5)

potassium (7440-09-7)

Quinone (106-51-4)

Nitroso-β-naphthol (131-91-9)

potassium chloride (7447-40-7)

1-AMINO-2-NAPHTHOL-4-SULFONIC ACID (116-63-2)

aminonaphtholsulfonic acid

ammonium 1,2-naphthoquinone-4-sulfonate, 1,2-NAPHTHOQUINONE-4-SULFONATE, AMMONIUM (53684-60-9)

potassium 1,2-naphthoquinone-4-sulfonate (5908-27-0)

1,2-naphthoquinone-4-sulfonate

2-amino-1-naphthol-4-sulfonic acid

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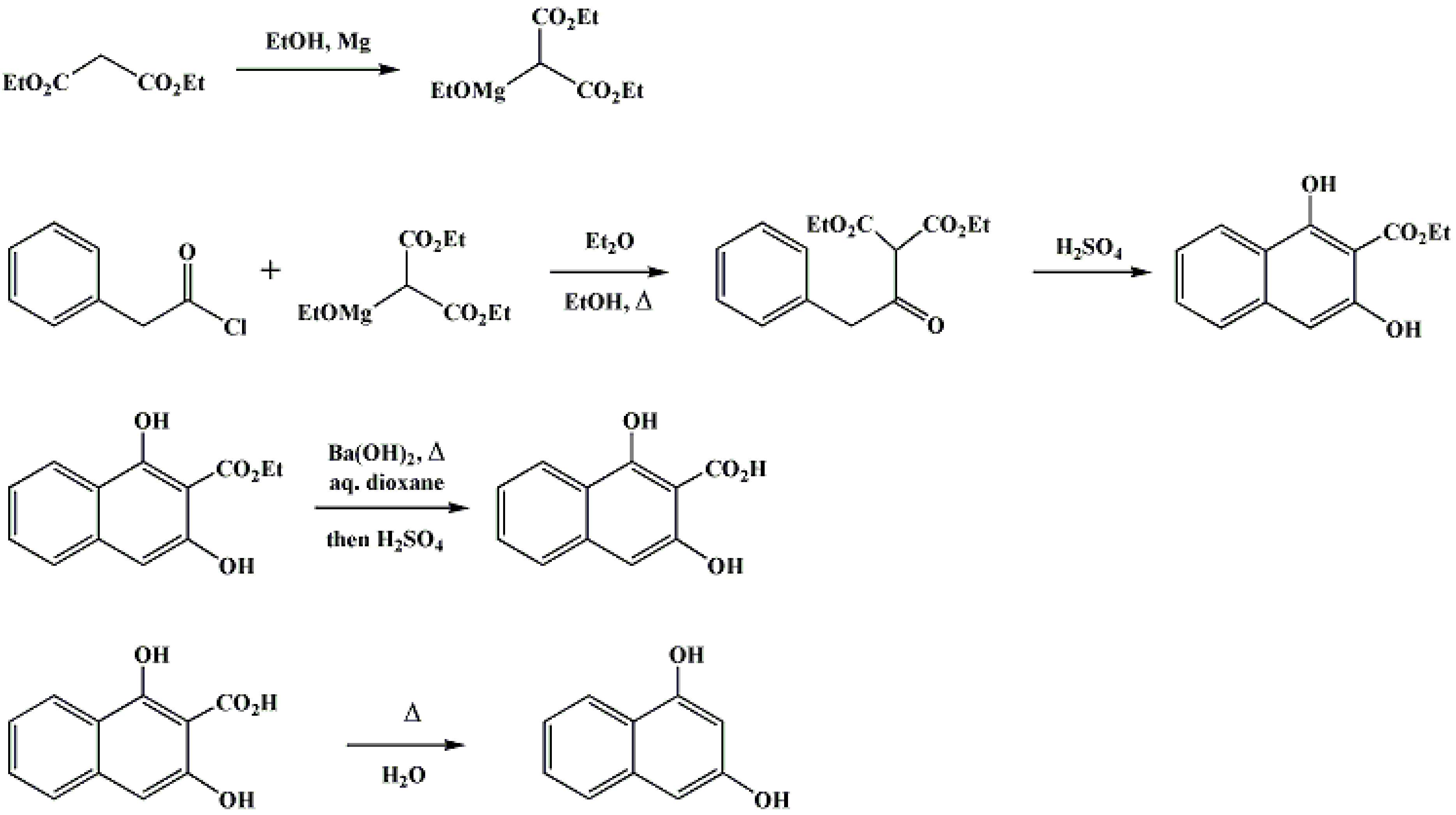
Organic Syntheses, CV 3, 637

NAPHTHORESORCINOL

[1,3-Naphthalenediol]



Submitted by Karl Meyer and Henry S. Bloch.
Checked by H. R. Snyder and Curtis W. Smith.

1. Procedure

A. *Ethyl phenylacetylmalonate.* A 1-l. three-necked round-bottomed flask is equipped with a dropping funnel (Note 1) and a reflux condenser provided with a calcium chloride tube. Before the apparatus is assembled, it is washed in the following manner with absolute ethanol which has been prepared in a distilling flask (Note 2). Ninety milliliters of the anhydrous ethanol is distilled through the dropping funnel into the apparatus, used for rinsing, and discarded. In the reaction flask are placed 12.5 g. (0.52 atom) of magnesium turnings, 1 ml. of carbon tetrachloride (Note 3), and 40 g. (0.25 mole) of malonic ester (Note 3); then 90 ml. of absolute ethanol is distilled into the dropping funnel and transferred to the flask. The reaction is started by heating and is controlled by applying an ice bath when the condenser begins to flood. When the reaction has subsided, 40 g. (0.25 mole) more of malonic ester is added at one time. After this reaction has subsided, the flask is cooled slightly, 180 ml. of dry ether is added, and the reaction mixture is heated on a steam bath for 1 hour. Then 88 g. (74 ml., 0.57 mole) of phenylacetyl chloride, diluted with 90 ml. of dry ether, is added slowly (in about 30 minutes) from the dropping funnel in portions at such a rate that the vigorous reaction subsides between additions. When the addition has been completed, the flask is warmed for 10 minutes on a steam bath. After the mixture has been cooled, 100 ml. of water is added dropwise in about 30 minutes. The oily layer is washed with two 100-ml. portions of water and dried over sodium sulfate, and the ether is removed by distillation under reduced pressure (water pump). The crude phenylacetylmalonic ester (87 ml.) which remains is a reddish, somewhat viscous oil.

B. *Ethyl 1,3-dihydroxy-2-naphthoate.* In a 1-l. flask 1 volume (87 ml.) of the crude ester is added in one lot to 3 volumes (261 ml.) of concentrated sulfuric acid without cooling, and the solution is allowed to stand for about 1 week (Note 4). The whole mixture, including any precipitate which may have formed, is poured slowly with stirring into a mixture of 1 kg. of ice and 500 ml. of water (Note 5); the solid yellow ester is filtered with suction, washed with a small amount of cold water, pressed in the filter for 30 minutes with a rubber dam, and finally dried in a vacuum desiccator. The yield of ester melting at 80° is 58–68 g. (50–59% based on the malonic ester used).

Recrystallization of 50 g. of the ester from 300 ml. of 70% ethanol (Note 6) yields 45 g. of yellow, needle-like crystals melting at 82°.

C. 1,3-*Dihydroxy*-2-*napthoic acid.* In a 1-l. three-necked round-bottomed flask, fitted with a mechanical stirrer, a nitrogen inlet tube, and a condenser carrying a separatory funnel attached by means of a notched cork, is placed 20.9 g. (0.09 mole) of the recrystallized ester dissolved in 300 ml. of dioxane. The apparatus is flushed with nitrogen, the solution is stirred and heated on a steam bath, and a solution of 40 g. (0.13 mole) of barium hydroxide octahydrate in 500 ml. of water is added in the course of 1 hour. Heating and stirring are continued for 3 hours. The precipitated barium salt, which may vary in color from yellow to greenish gray, is filtered from the hot solution and transferred immediately to a cool (25°) solution of 11 ml. of concentrated sulfuric acid in 185 ml. of water in a 500-ml. three-necked round-bottomed flask fitted with a nitrogen inlet tube, a mechanical stirrer, and a condenser. The mixture is stirred in an atmosphere of nitrogen for 5 minutes without heating (Note 7). The precipitate is removed by filtration, washed with a small amount of distilled water, transferred to a beaker, and extracted with two 100-ml. portions of hot absolute ethanol. To the warm filtrate is added 200 ml. of water, and the solution is allowed to

cool in an ice bath for 2 hours. The yield of the crude acid which is obtained by filtration as a fine, yellow powder melting at 135° (Note 8) is 16.5 g. (90%).

D. *Naphthoresorcinol*. In a 200-ml. three-necked round-bottomed flask, equipped with a nitrogen inlet tube, a stirrer, and a condenser, is placed 65 ml. of water; the water is then boiled to expel dissolved oxygen. To the boiling water is added 16.5 g. of the crude acid (Note 9), and the mixture is boiled with stirring for 2 hours in an atmosphere of nitrogen. The water is decanted from any pasty residue; the residue is boiled with 35 ml. of water for 2 hours, and the supernatant liquid is decanted through a filter and combined with the first solution. Just enough sodium hydrosulfite (about 0.3–0.5 g.) is added to decolorize the red solution, 15 g. of sodium chloride is dissolved in the solution, and the mixture is allowed to stand at 5° for 24 hours. The naphthoresorcinol precipitates first as an oil, which solidifies to a reddish solid on further cooling, and then as colorless or slightly yellow plates. The yield is 7.0–7.3 g. (54–56%). After standing over calcium chloride in a vacuum desiccator for 1 day, the white or slightly yellow plates melt at 119–122° and the reddish solid melts at 110–118°.

To 100 ml. of hot water are added 3.5 g. of the reddish solid, just enough sodium hydrosulfite to remove the red coloration, and 0.3 g. of Norit. The mixture is filtered, 7 g. of sodium chloride is dissolved in the filtrate, and the solution is allowed to stand in a closed container at 5° for 24 hours. The yield of naphthoresorcinol, which separates as large, nearly transparent plates melting at 122–124° (Note 10), is 2.6 g. (75% recovery).

2. Notes

1. In order to measure the volume of ethanol to be used, an equal volume of water (90 ml.) is placed in the dropping funnel and a label is pasted at the level of the water. The funnel is then emptied and carefully dried.

2. A liter of commercial absolute ethanol is dried by means of sodium and ethyl phthalate[1] in a 2-l. distilling flask equipped with a reflux condenser. A short section of rubber tubing closed by a screw clamp is attached to the side arm of the flask. In the next step the condenser is set for downward distillation.

3. The carbon tetrachloride, ether, and malonic ester are dried over anhydrous magnesium sulfate. The malonic ester is distilled before use.

4. The yield of ethyl 1,3-dihydroxy-2-naphthoate is decreased to 45% if the sulfuric acid solution is allowed to stand for only 2 days.

5. After about 25 ml. of the sulfuric acid solution has been added, the mixture is stirred until a yellow solid separates. Precipitation of the main portion of the product then occurs very smoothly as the remainder of the sulfuric acid solution is added.

6. The ester may be recrystallized also by solution in dioxane and precipitation by water.

7. An alternative procedure consists in decomposing the barium salt with hydrochloric acid. However, in the checkers' hands this procedure did not yield a barium-free product.

8. The submitters obtained the pure acid as follows: To 0.5 g. of the crude acid was addded 200 ml. of boiling water, and the mixture was heated for an instant to effect solution and filtered immediately. The filtrate was cooled by vigorous shaking in an ice bath.

Addition of 1 ml. of concentrated hydrochloric acid to the solution caused the separation of crystals, which were collected after 30 minutes' additional cooling in ice, washed with ice water, and dried in vacuum over phosphorus pentoxide. The recovery of material melting in the range of 138.5–140.5° to 146.5° was 62%.

9. The solid has a tendency to assume a semi-plastic consistency, but the size of the mass decreases as decarboxylation occurs.

10. If part of the material separates as an oil and solidifies, the appearance of the product may be poor, although the melting point is 122–124°. Separation as an oil may be prevented by slow cooling with shaking and seeding. An alternative procedure for final purification of naphthoresorcinol consists in sublimation at 120–130°/5 × 10^{-4} mm.

3. Discussion

Naphthoresorcinol has been prepared by heating 1-amino-3-hydroxy-4-naphthalenesulfonic acid or its salt in water or slightly acidic solution,[2] by cyclization of ethyl phenylacetylmalonate[3] or of ethyl phenylacetoacetate,[4] and by alkaline fusion of 1,3-naphtholsulfonic acid or 1,3-naphthalenedisulfonic acid.[5] Phenylacetyl malonic ester has been prepared by condensing phenylacetyl chloride and malonic ester with sodium in ether,[3] or with magnesium.[6]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Malonic Ester

Naphthoresorcinol

phenylacetylmalonic ester

sodium and ethyl phthalate

Phenylacetyl malonic ester

ethanol (64-17-5)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ether (60-29-7)

magnesium, magnesium turnings (7439-95-4)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

oxygen (7782-44-7)

carbon tetrachloride (56-23-5)

nitrogen (7727-37-9)

sodium hydrosulfite (7775-14-6)

sodium (13966-32-0)

barium hydroxide octahydrate (12230-71-6)

magnesium sulfate (7487-88-9)

dioxane (5703-46-8)

phenylacetyl chloride (103-80-0)

ethyl phenylacetoacetate

1,3-Naphthalenediol (132-86-5)

Ethyl 1,3-dihydroxy-2-naphthoate (6843-89-6)

1-amino-3-hydroxy-4-naphthalenesulfonic acid

Ethyl phenylacetylmalonate

1,3-naphtholsulfonic acid (3771-14-0)

1,3-naphthalenedisulfonic acid

phosphorus pentoxide (1314-56-3)

1,3-Dihydroxy-2-napthoic acid (3147-58-8)

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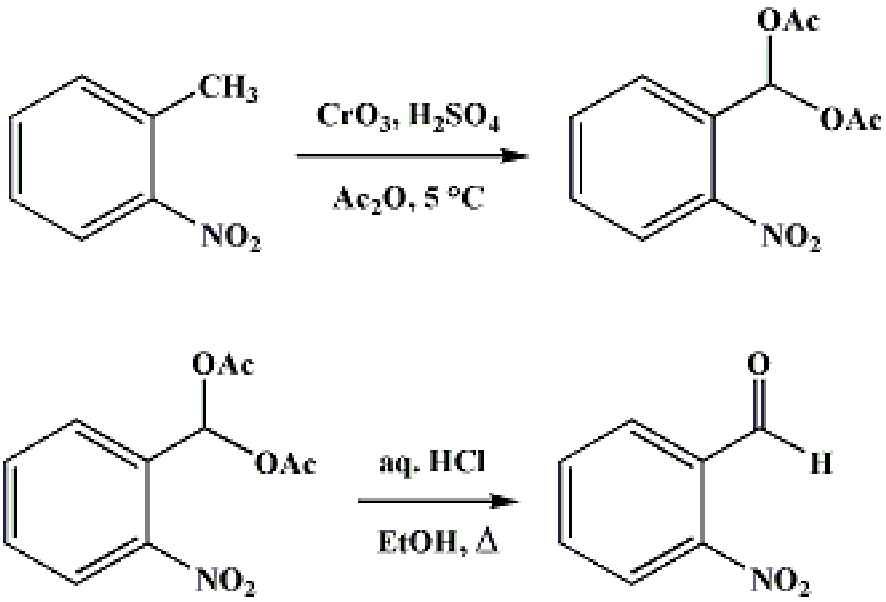
Organic Syntheses, CV 3, 641

o-NITROBENZALDEHYDE

[Benzaldehyde, *o*-nitro-]



Submitted by S. M. Tsang, Ernest H. Wood, and John R. Johnson.
Checked by Lee Irvin Smith and J. W. Opie.

1. Procedure

A. *o-Nitrobenzaldiacetate.* In a 2-l. three-necked round-bottomed flask equipped with an effective mechanical stirrer and a thermometer, and surrounded by an ice bath, are placed 600 g. (570 ml.) of glacial acetic acid, 565 ml. (612 g., 6 moles) of acetic anhydride, and 50 g. (0.36 mole) of *o*-nitrotoluene. To this solution is added slowly, with stirring, 156 g. (85 ml., 1.5 moles) of concentrated sulfuric acid. When the mixture has cooled to 5°, 100 g. (1 mole) of chromium trioxide is added in small portions at such a rate that the temperature does not rise above 10°; about 2 hours is required for the addition (Note 1). Stirring is continued for 5 hours after the chromium trioxide has been added (Note 2). The reaction mixture is poured into a large jar two-thirds filled with chipped ice, and cold water is added until the total volume is about 6 l. The mixture is then stirred vigorously for at least 15 minutes to promote solidification of the oily layer (Note 3). The oily solid is filtered with suction on a Büchner funnel, washed with cold water, and then stirred mechanically with 500 ml. of cold 2% sodium carbonate solution. The solid is then collected on a filter, washed with cold water, and dried in the air. The crude substance is digested with 150 ml. of petroleum ether (b.p. 60–70°) for 30 minutes, cooled, and filtered (Note 4). After having been dried in a vacuum desiccator, the product weighs 21–22 g. (23–24%) and melts at 87–88° (Note 5).

B. *o-Nitrobenzaldehyde.* A suspension of 51.6 g. of the diacetate in a mixture of 500 g.

(272 ml.) of concentrated hydrochloric acid, 450 ml. of water, and 80 ml. of ethanol is stirred and refluxed for 45 minutes. The mixture is then cooled to 0°, and the solid is filtered with suction and washed with water (Note 6) and (Note 7). The crude product is purified by rapid steam distillation through a 100-cm. Allihn condenser into a cooled receiver. About 3.5 l. of distillate is collected during 30 minutes; the cooled distillate is filtered, and the *o*-nitrobenzaldehyde is dried in a desiccator over calcium chloride. It weighs 23.7 g. (74%) and melts at 44–45°.

2. Notes

1. Proper control of the temperature is very important during addition of the chromium trioxide. If the temperature rises very much, the reaction may become violent.
2. A hard, tarry mass forms during the later stages of this oxidation. For this reason stirring becomes increasingly difficult and a rather powerful motor must be used. After decantation of the liquid portion of the reaction mixture, ice and a little water (total volume 1 l. for the amounts of materials specified) are added to the reaction flask, and the mass is broken up with a spatula. The suspension is then combined with the mixture in the large jar.
3. It is essential that the oily layer should be stirred vigorously until it has solidified; otherwise large losses will be incurred during the subsequent filtration.
4. This treatment removes unchanged *o*-nitrotoluene.
5. The checkers have carried out this preparation using three times the amounts of material specified here. The percentage yields were the same.
6. In one run, the submitters substituted an equivalent amount of sulfuric acid for the hydrochloric acid, omitted the filtration, and steam-distilled the mixture directly. The yield of *o*-nitroaldehyde was 74.7%; this product also melted at 44–45°.
7. The crude aldehyde may be dried and then purified by distillation under reduced pressure. For this purpose, an ordinary Claisen flask is used. No fractionation is necessary; the distillation serves only to remove a small amount of tarry material. The boiling range is rather wide (120–144°/3–6 mm.), but the entire distillate (30 g. from 66 g. of the diacetate) solidifies and melts at 44–45°. The aldehyde may also be recrystallized, although with some loss. For this purpose 11 g. of the solid is dissolved in toluene (2–2.5 ml. per gram) at room temperature, the solution is diluted with petroleum ether (b.p. 30–60°; 7 ml. per ml. of solution) and cooled to −10° or below. The pale yellow needles weigh 9 g. and melt at 44–45°.

3. Discussion

o-Nitrobenzaldehyde has been prepared by action of oxides of nitrogen upon *o*-nitrobenzyl alcohol;[1] by oxidation of *o*-nitrocinnamic acid or ester with permanganate or nitrous acid;[2] by oxidation of *o*-nitrophenylpyruvic acid with permanganate;[3] and from *o*-nitrotoluene by a number of methods. These include: action of isoamyl nitrite

and sodium ethoxide, followed by hydrolysis of the resulting *o*-nitrobenz-*anti*-aldoxime with concentrated hydrochloric acid;[4] direct action of a number of oxidizing agents including potassium dichromate and sulfuric acid,[5] manganese dioxide,[6] nickel oxide,[7] and cerium oxide;[8] action of mercury oxide in the presence of alkali, followed by hydrolysis of the resulting *o*-nitrobenzalmercurioxide with nitrous or nitric acid;[9] and action of chromic acid in acetic acid and acetic anhydride, followed by hydrolysis of the resulting *o*-nitrobenzaldiacetate.[10] *o*-Nitrobenzaldehyde is also formed, along with much *m*-nitrobenzaldehyde, by direct nitration of benzaldehyde.[11]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 56
- Org. Syn. Coll. Vol. 4, 713
- Org. Syn. Coll. Vol. 4, 730
- Org. Syn. Coll. Vol. 5, 825

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

o-nitroaldehyde

o-nitrobenzalmercurioxide

ethanol (64-17-5)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

acetic anhydride (108-24-7)

nitric acid (7697-37-2)

sodium carbonate (497-19-8)

nitrogen (7727-37-9)

nitrous acid (7782-77-6)

mercury oxide (21908-53-2)

benzaldehyde (100-52-7)

toluene (108-88-3)

sodium ethoxide (141-52-6)

chromic acid (7738-94-5)

manganese dioxide (1313-13-9)

permanganate

potassium dichromate (7778-50-9)

o-nitrotoluene (88-72-2)

chromium trioxide (1333-82-0)

Isoamyl nitrite (110-46-3)

o-Nitrobenzaldehyde, Benzaldehyde, o-nitro- (552-89-6)

nickel oxide

cerium oxide

o-Nitrobenzaldiacetate (6345-63-7)

m-Nitrobenzaldehyde (99-61-6)

o-nitrobenz-anti-aldoxime

o-nitrobenzyl alcohol (612-25-9)

o-nitrocinnamic acid

o-nitrophenylpyruvic acid (5461-32-5)

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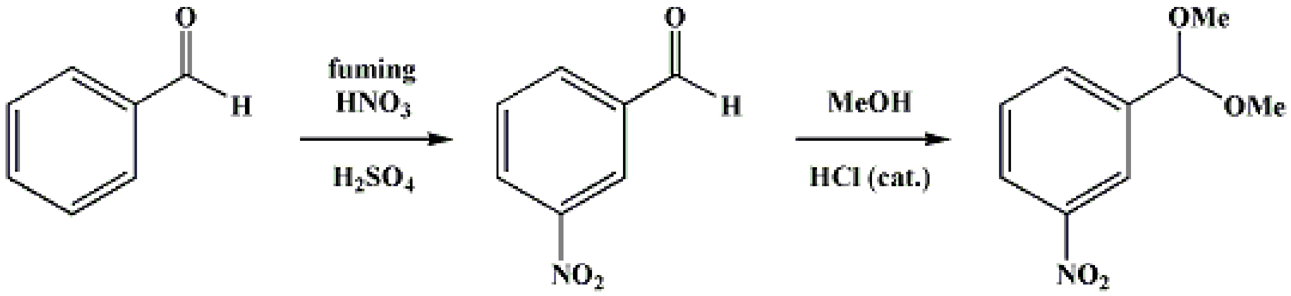
Organic Syntheses, CV 3, 644

m-NITROBENZALDEHYDE DIMETHYLACETAL

[Benzaldehyde, *m*-nitro-, dimethylacetal]



Submitted by Roland N. Icke, C. Ernst Redemann, Burnett B. Wisegarver, and Gordon A. Alles.
Checked by H. R. Snyder and Frank X. Werber.

1. Procedure

A. *m-Nitrobenzaldehyde.* In a 3-l. three-necked flask provided with a dropping funnel, a thermometer, and an efficient mechanical stirrer is placed 1.25 l. of technical concentrated sulfuric acid (sp. gr. 1.84). The acid is stirred during the fairly rapid addition of 167 ml. (250 g., 4 moles) of technical fuming nitric acid (sp. gr. 1.49–1.50), with sufficient cooling by an ice bath so that the temperature of the mixed acids does not exceed 10°. The mixture is maintained at 5–10° while 213 g. (2 moles) of U.S.P. benzaldehyde (Note 1) is added with good stirring over a period of 2–3 hours. At the end of the addition the ice bath is removed and the mixture is allowed to stand overnight at room temperature.

The mixture is poured carefully onto about 3.25 kg. of cracked ice in a 2-gal. crock (Note 2) with manual stirring. The yellow precipitate is collected on a large Büchner funnel, washed with cold water, and pressed as dry as possible (Note 3). Further removal of water is accomplished by dissolving the moist product in about 100 ml. of warm benzene and separating the water layer in a separatory funnel. The benzene solution is filtered (Note 4) into a 1-l. distilling flask and concentrated on a steam bath. Distillation is discontinued when benzene no longer comes over or when nitrous fumes (from incompletely removed nitric acid) appear. The residual *m*-nitrobenzaldehyde is sufficiently pure for use in the next step (Note 5).

B. *m-Nitrobenzaldehyde dimethylacetal.* The above crude product is dissolved in 750 ml. of technical anhydrous methanol, 1 ml. of concentrated hydrochloric acid is added if necessary (Note 6), and the solution is allowed to stand at room temperature for 5 days (Note 7). A solution of sodium methoxide in methanol is added until the solution is just alkaline to moistened litmus paper. The methanol is removed by distillation on a steam bath; the residue is cooled to room temperature and treated with cool water to dissolve the inorganic salts. The aqueous solution is extracted with two 50-ml. portions of ether, and the extracts are added to the crude acetal. The solution is subjected to a preliminary drying over anhydrous magnesium sulfate (or sodium sulfate), filtered, and then dried for at least 12 hours over anhydrous sodium carbonate. After the ether has been removed by distillation on a steam bath the residue is distilled under reduced pressure from a 500-ml. Claisen flask. The yield of the light-yellow liquid acetal, boiling at 141–143°/8 mm. (Note 8), is 300–335 g. (76–85%) (Note 9).

2. Notes

1. Commercial benzaldehyde may contain some benzoic acid. When taken from a previously unopened bottle, U.S.P. benzaldehyde usually is quite satisfactory. If there is any doubt concerning its purity, the aldehyde may be washed with dilute sodium carbonate solution, dried over anhydrous sodium carbonate, and distilled under diminished pressure just before use.
2. Two 4-l. beakers may be used.
3. A small amount of an oily liquid passes through the filter; this material is a mixture of the *ortho* and *meta* isomers. If a very pure product is desired, this oil may be discarded, although some of the *meta* isomer will be lost. It is usually satisfactory to combine it with the solid material, the *m*-nitro acetal being obtained in a state of purity sufficient for most purposes in the final distillation.
4. A small amount of a solid by-product is removed.
5. If pure *m*-nitrobenzaldehyde is desired, the benzene solution is diluted with additional benzene and is washed well with aqueous sodium bicarbonate solution until the washings are alkaline. (*Warning! It has been reported* [*K. Ueno*] *that incomplete washing of the product in solution may result in an explosion during the distillation; all remaining acids must be removed before distillation is attempted*.) The solution is dried (with anhydrous sodium or magnesium sulfate), and the solvent is removed. The aldehyde is distilled under reduced pressure from a Claisen flask connected to an air-cooled condenser. The yield of product boiling at 119–123°/4 mm. is 226–254 g. (75–84%). The product readily crystallizes in the receiver.
6. When nitrous fumes are observed, there usually is enough acid present to catalyze the acetal formation.
7. The yield is not increased by extending the reaction period beyond 5 days.
8. The acetal boils at 116–119°/1 mm., 122–126°/2 mm., 130–132°/3 mm. The boiling range depends somewhat upon the rate of distillation.
9. The submitters obtained yields in the upper part of this range from runs twice the size described. They have stored samples of the product for as long as 4 years without deterioration.

3. Discussion

The only satisfactory method for the preparation of *m*-nitrobenzaldehyde is the direct nitration of benzaldehyde with a mixture of nitric and sulfuric acids. The procedure described is essentially that of Baker and Moffitt.[1].

m-Nitrobenzaldehyde dimethylacetal has been prepared from the aldehyde and methanol in the presence of formiminomethyl ether hydrochloride[2] or Twitchell's reagent[3] as the acid catalyst.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 59

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

m-nitro acetal

ACETAL (105-57-7)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

methanol (67-56-1)

ether (60-29-7)

sodium bicarbonate (144-55-8)

nitric acid (7697-37-2)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

Benzoic acid (65-85-0)

benzaldehyde (100-52-7)

sodium methoxide (124-41-4)

sodium (13966-32-0)

magnesium sulfate (7487-88-9)

formiminomethyl ether hydrochloride

m-Nitrobenzaldehyde (99-61-6)

m-nitrobenzaldehyde dimethylacetal (3395-79-7)

Benzaldehyde, m-nitro-, dimethylacetal

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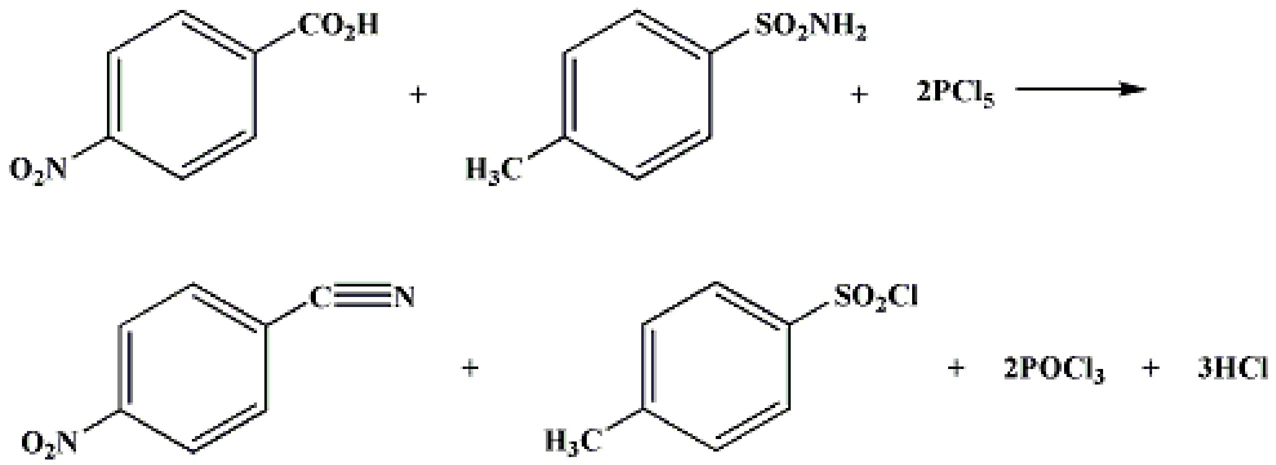
Organic Syntheses, *CV 3, 646*

p-NITROBENZONITRILE

[Benzonitrile, *p*-nitro-]



Submitted by Charles S. Miller
Checked by Arthur C. Cope and James J. Ryan.

1. Procedure

In a 1-l. round-bottomed flask with a ground-glass joint are mixed 100.3 g. (0.6 mole) of *p*-nitrobenzoic acid and 109.9 g. (0.64 mole) of *p*-toluenesulfonamide (Note 1). To this mixture is added 262.2 g. (1.26 moles, 5% excess) of phosphorus pentachloride, which is manually stirred into the mixture while the flask is rotated to facilitate mixing (Note 2). The flask is then attached to a short column fitted with a thermometer and side arm for distillation. The thermometer is adjusted so that the bulb is immersed in the reaction mixture, and the mixture is then warmed gently in a hot-air bath to initiate the reaction (Note 3). In some cases this initial reaction must be controlled by a cold-water bath which temporarily replaces the hot-air bath. After the first reaction has subsided and the contents of the flask have become almost liquid, the temperature is gradually raised to 205° and maintained at 200–205° until no more material distils (Note 4). The cooled reaction mixture is treated with 240 ml. of pyridine and warmed gently with manual stirring until solution is complete. To this solution is added cautiously 1.1 l. of water with manual stirring (Note 5), and the cooled suspension is filtered. The solid is washed with water and suspended in 400 ml. of 5% sodium hydroxide solution. After this mixture has been stirred for 30 minutes, the solid is removed, washed thoroughly with water, and dried. The yield of the light-tan product is 74.5–80 g. (85–90%); m.p. 146–147° (cor.) (Note 6) and (Note 7). This product may be further purified with 91% recovery by recrystallization from 50% acetic acid (6.5 ml. per gram). The recrystallized material melts at 147–148° (cor.).

2. Notes

1. Benzenesulfonamide and *p*-nitrobenzenesulfonamide have also been used in place of *p*-toluenesulfonamide.

2. This preparation is carried out in a hood.
3. The air bath consists of a hemispherical metal pan about 5 in. in diameter fitted to the bottom of the flask so as to leave an air space of 1/8 in. to in. between the metal and the flask. The bath is heated with a small flame.
4. This operation requires about 30 minutes, and the phosphorus halides that distil over weigh 145–155 g.
5. The water should be added about 1 ml. at a time at the beginning. Since this decomposition is very vigorous, the solution is stirred until the reaction subsides before the next addition is made. Later in the addition the water may be poured in slowly.
6. Alternatively, according to the submitter, the cooled reaction mixture may be treated with crushed ice to decompose the remaining phosphorus halides, after which the oily solid is separated from the water by filtration and washed thoroughly with water. The oily solid is added to a mixture of 350 ml. of 14% ammonium hydroxide and 350 ml. of acetone and stirred for 15–30 minutes to ensure complete reaction between the *p*-toluenesulfonyl chloride and ammonia. The acetone is evaporated on a steam bath, and, after cooling, the solid is filtered and ground in a mortar with a pestle. The finely divided solid is then stirred with 300 ml. of 10% sodium hydroxide until all the *p*-toluenesulfonamide is dissolved (0.5 to 1 hour). The solid *p*-nitrobenzonitrile is filtered, washed with water, and dried. The alkaline filtrate is treated with charcoal, filtered and acidified with dilute hydrochloric acid to yield about 75% of the *p*-toluenesulfonamide that was used as a reactant.
7. The submitter states that a number of aromatic mono- and dinitriles have been prepared by this procedure with slight or no modification in the temperature. The reaction mixtures were usually worked up by the acetone-ammonia method described in Note 6. Among the compounds prepared by this method are *o*-nitrobenzonitrile, *o*-bromobenzonitrile, *m*-methoxybenzonitrile, 4,4'-dicyanodiphenylsulfone, 4,4'-dicyanostilbene, α,γ-di-(4-cyanophenoxy) propane. With the last, a temperature of 185–190° for 20 minutes gave the best results. The yields before purification ranged between 75% and 95% and after purification between 63% and 79%. Aliphatic acids give low yields of the corresponding nitriles and, in some cases, chlorinated by-products.

3. Discussion

p-Nitrobenzonitrile has been prepared by the action of phosphorus pentoxide on *p*-nitrobenzamide,[1,2] by the Sandmeyer reaction on *p*-nitroaniline,[3,4] by thermal decomposition of *p*-nitrophenylglyoxylic acid oxime,[5] by the thermal decomposition of *o*-benzoyl-*p*-nitrobenzaldoxime,[6] by the action of acetic anhydride and phosphorus pentoxide on *p*-nitrobenzaldoxime,[7] by the action of fused sodium chloride-aluminum chloride on *p*-nitrobenzamide;[8] by the action of tertiary amines on *syn*-*p*-nitrobenzaldoxime benzoate,[9,10] by heating *p*-nitrobenzoic acid or *p*-nitrobenzoic anhydride with benzenesulfonamide or *p*-toluenesulfonamide,[11] and by heating *p*-nitrobenzamide with sulfamic acid.[12]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium chloride-aluminum chloride

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ammonia (7664-41-7)

acetic anhydride (108-24-7)

sodium hydroxide (1310-73-2)

phosphorus pentachloride (10026-13-8)

acetone (67-64-1)

charcoal (7782-42-5)

pyridine (110-86-1)

ammonium hydroxide (1336-21-6)

acetone-ammonia (298-08-8)

Benzenesulfonamide (98-10-2)

4,4'-dicyanodiphenylsulfone

4,4'-dicyanostilbene

sulfamic acid (5329-14-6)

p-Toluenesulfonyl chloride (98-59-9)

p-NITROBENZOIC ACID (62-23-7)

phosphorus pentoxide (1314-56-3)

p-toluenesulfonamide (70-55-3)

p-nitroaniline (100-01-6)

p-NITROBENZONITRILE, Benzonitrile, p-nitro- (619-72-7)

p-nitrobenzoic anhydride

p-nitrobenzenesulfonamide (6325-93-5)

o-nitrobenzonitrile (612-24-8)

o-bromobenzonitrile (2042-37-7)

m-methoxybenzonitrile (1527-89-5)

p-nitrobenzamide (619-80-7)

p-nitrophenylglyoxylic acid oxime

o-benzoyl-p-nitrobenzaldoxime

p-nitrobenzaldoxime

syn-p-nitrobenzaldoxime benzoate

α,γ-di-(4-cyanophenoxy) propane

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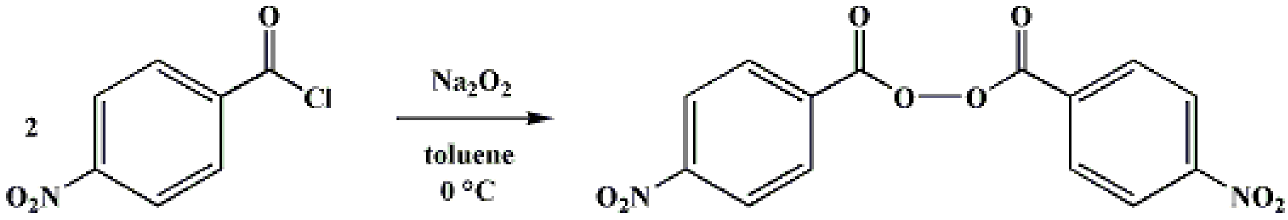
Organic Syntheses, CV 3, 649

p-NITROBENZOYL PEROXIDE

[Peroxide, bis(*p*-nitrobenzoyl)]



Submitted by Charles C. Price and Edwin Krebs.
Checked by R. L. Shriner and C. H. Tilford.

1. Procedure

A 600-ml. beaker containing 100 ml. of water and equipped with an efficient stirrer, a thermometer, and a 200-ml. separatory funnel is immersed in an ice-water bath. When the temperature of the water has fallen to 0–5°, 10 g. (0.13 mole) of sodium peroxide (Note 1) is added. Then, with vigorous stirring, a solution of 37 g. (0.2 mole) of *p*-nitrobenzoyl chloride in 100 ml. of dry toluene is added dropwise over a period of about 30 minutes. After the mixture has been stirred for an additional 1.5 hours, the precipitate is filtered and washed with 200 ml. of cold water (Note 2). The yield of *p*-nitrobenzoyl peroxide is 28.5–29 g. (86–88%). It melts at 155–156°.

The product may be recrystallized most conveniently by dissolving it as rapidly as possible (Note 3) in 500 ml. of dry toluene which has been preheated to 80–85°. As soon as the solid is completely dissolved (2–3 minutes of stirring), the solution is filtered through a warm Büchner funnel and the filtrate is immediately cooled in an ice-water bath. The yield of very pale yellow glistening needles is 25 to 26 g. (86–89% recovery); they melt at 156° with vigorous decomposition (Note 4).

2. Notes

1. In a parallel experiment in which 25 g. of sodium peroxide was used, the precipitate was not the peroxide but evidently consisted of sodium *p*-nitroperbenzoate.
2. *p*-Nitrobenzoic acid may be recovered by acidification of the filtrate.
3. Excessive heating during recrystallization leads to extensive decomposition of the peroxide.
4. By a procedure similar to that described for *p*-nitrobenzoyl peroxide, the following peroxides have been prepared: *m*-nitrobenzoyl peroxide (m.p. 136–137°) in 90% yield; anisoyl peroxide (m.p. 126–127°) in 86–89% yields; *p*-bromobenzoyl peroxide (m.p. 144°) in 73% yield; and 3,4,5-tribromobenzoyl peroxide (m.p. 186°) in 40% yield.[1] The procedure is not satisfactory for preparation of acetylsalicylyl peroxide, which is more conveniently prepared by action of hydrogen peroxide upon an acetone solution of the acid chloride.

3. Discussion

p-Nitrobenzoyl peroxide,[2] as well as *m*-nitrobenzoyl peroxide[2] and anisoyl peroxide,[3] have been prepared in about 50% yields from the acid chlorides and an acetone solution of hydrogen

peroxide, in the presence of a basic substance such as pyridine, sodium acetate, or sodium hydroxide. *m*-Nitrobenzoyl peroxide has also been prepared by nitration of benzoyl peroxide with cold concentrated nitric acid,[4] or with a cold[5] or hot[2] mixture of nitric and sulfuric acids.

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5. Vanino, *Ber.*, **30**, 2004 (1897); Gelissen and Hermans, *Ber.*, **58**, 285 (1925).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium p-nitroperbenzoate

sodium acetate (127-09-3)

sodium hydroxide (1310-73-2)

nitric acid (7697-37-2)

acetone (67-64-1)

pyridine (110-86-1)

toluene (108-88-3)

hydrogen peroxide (7722-84-1)

sodium peroxide

benzoyl peroxide (94-36-0)

anisoyl peroxide

3,4,5-tribromobenzoyl peroxide

acetylsalicylyl peroxide

p-NITROBENZOIC ACID (62-23-7)

p-Nitrobenzoyl chloride (122-04-3)

p-Nitrobenzoyl peroxide, Peroxide, bis(p-nitrobenzoyl) (1712-84-1)

m-nitrobenzoyl peroxide

p-bromobenzoyl peroxide

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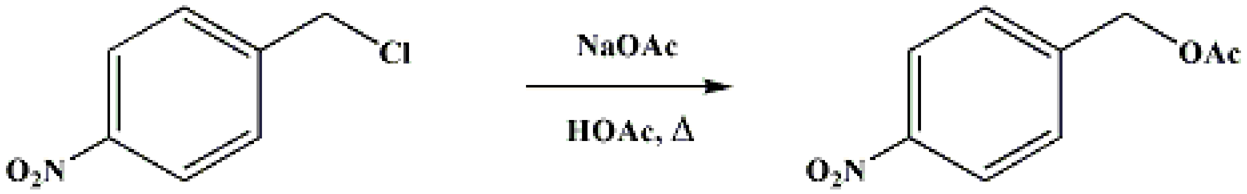
Organic Syntheses, CV 3, 650

p-NITROBENZYL ACETATE

[Acetic acid, *p*-nitrobenzyl ester]



Submitted by W. W. Hartman and E. J. Rahrs.
Checked by R. L. Shriner and Charles Russell.

1. Procedure

A mixture of 250 g. (1.46 moles) of *p*-nitrobenzyl chloride, 225 g. (2.74 moles) of fused sodium acetate, and 375 g. (6.25 moles) of glacial acetic acid is refluxed for 8–10 hours in a 2-l. flask heated by an oil bath, the temperature of which is maintained at 160–170° (Note 1). After this time the bath is allowed to cool to about 125°, and the acetic acid is removed by distillation under reduced pressure. Care must be taken not to reduce the pressure too rapidly in the early stages of the distillation. As the distillation slows down, the pressure is further reduced until it reaches 50 mm. or lower, and the temperature is slowly raised to 160°. From 2.5 to 3 hours is required for the complete removal of the acetic acid. About 500 ml. of water is added, and the hard cake is broken up with a stirring rod (Note 2).

The entire contents of the flask are then transferred to a 1.5-l. beaker and stirred with a mechanical stirrer for about 30 minutes or long enough to break up all the lumps. The finely divided material is filtered on a Büchner funnel and washed with 200 ml. of cold water. The above process of washing, stirring, and filtering is repeated twice. The product is then transferred to a 1.5-l. beaker, and 500 ml. of methanol is added and heated to boiling in order to effect solution. The hot solution is filtered through a heated Büchner funnel and allowed to cool slowly. When the solution has cooled to 20°, the product is collected on a filter and air-dried. This first crop consists of yellow needles which melt at 74–77° and weigh 215–225 g. The filtrate is evaporated to 100 ml. and cooled. An additional 25–30 g. of solid separates. Both crops are again washed with cold water and recrystallized from 500 ml. of hot methanol. The first crop from this second crystallization weighs 210–218 g. and melts at 77–78°. Evaporation of the filtrate to 100 ml. and cooling yield an additional 15–18 g. of acetate which is purified by recrystallization from methanol; about 12 to 15 g. of product is obtained. The combined yield of pale yellow crystals which melt at 77–78° amounts to 222–233 g. (78–82%).

2. Notes

1. *p*-Nitrobenzyl chloride obtained from the Eastman Kodak Company was used.
2. The hard cake may be removed by the addition of 500 ml. of boiling water; the ester melts and forms an oily layer. The molten ester solidifies in small lumps when the flask is cooled rapidly in an ice bath while the molten mixture is stirred vigorously. Purification in this manner by repeating the process two or three times does not seem to produce better results than purification with cold water.

3. Discussion

p-Nitrobenzyl acetate has been prepared by the action of ethanolic potassium acetate on *p*-nitrobenzyl chloride[1] or bromide,[2] and by the nitration of benzyl acetate.[3,4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 652

References and Notes

1. Grimaux, *Zeit. für Chem.*, **1867**, 562.
2. Reid, *J. Am. Chem. Soc.*, **39**, 130 (1917).
3. Beilstein and Kuhlberg, *Ann.*, **147**, 340 (1868).
4. Hurd, Fancher, and Bonner, *J. Org. Chem.*, **12**, 369 (1947).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

acetic acid (64-19-7)

methanol (67-56-1)

sodium acetate (127-09-3)

bromide (24959-67-9)

acetate

potassium acetate (127-08-2)

benzyl acetate (140-11-4)

p-nitrobenzyl chloride (100-14-1)

p-Nitrobenzyl acetate, Acetic acid, p-nitrobenzyl ester (619-90-9)

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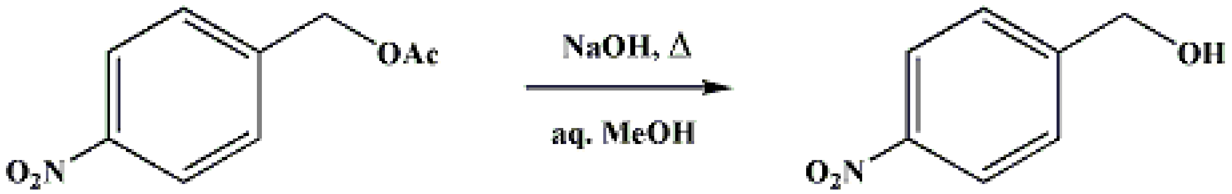
p-NITROBENZYL ALCOHOL

[Benzyl alcohol, *p*-nitro]



Submitted by W. W. Hartman and E. J. Rahrs.
Checked by R. L. Shriner and Charles Russell.

1. Procedure

A solution of 218 g. (1.12 moles) of *p*-nitrobenzyl acetate (p. 650) in 500 ml. of hot methanol is prepared in a 2-l. flask. To the hot solution is added 380 g. (1.43 moles) of a 15% solution of sodium hydroxide. The alkali should be added slowly at first with shaking to prevent too vigorous boiling. After standing for 5 minutes, the mixture is poured with vigorous hand stirring into 4.5 kg. of a mixture of cracked ice and water. The precipitate is collected on a Büchner funnel and recrystallized from 3 to 3.7 l. of hot water with the aid of 15 g. of Norit. The alcohol is dried at 60° to 65° in an oven for several hours and bottled (Note 1). The yield of slender, nearly colorless needles amounts to 110–121 g. (64–71%); the product melts at 92–93° (Note 2).

2. Notes

1. The product turns yellow if it is spread out to dry in the air.
2. The submitters report that *p*-iodobenzyl alcohol can be prepared in a similar manner, and that it is unnecessary to isolate the acetate. A mixture of 148 g. of *p*-iodobenzyl bromide, 52 g. of potassium acetate, and 750 ml. of 95% ethanol is refluxed for 8 hours, cooled, and filtered from the salt. To the filtrate is added 33.6 g. of potassium hydroxide, and the solution is refluxed for 6 hours. It is then diluted with 2 l. of water, and the oil taken up in 500 ml. of chloroform. After concentration to 150 ml. and chilling, *p*-iodobenzyl alcohol crystallizes. It is filtered and the solid rinsed with petroleum ether; the rinse added to the mother liquor causes the separation of an additional amount of *p*-iodobenzyl alcohol. The combined yield is 95–100 g. (81–86%); the product melts at 70–72°.

3. Discussion

p-Nitrobenzyl alcohol has been secured by the oxidation of *p*-nitrotoluene electrolytically[1] or chemically,[2] by the reduction of *p*-nitrobenzaldehyde with

formaldehyde in alkaline solution,[3] and by the hydrolysis of the acetate.[4,5] *p*-Iodobenzyl alcohol has been prepared by hydrolysis of *p*-iodobenzyl bromide and p-iodobenzyl acetate.[6,7]

References and Notes

1. Elbs, *Ber.* (Ref.), **29**, 1122 (1896).
2. Dieffenbach, Ger. pat. 214,949 [*Frdl.*, **9**, 156 (1908–10)].
3. B. M. Bogoslovskii and Z. S. Kazakova, *Zhur. Priklad. Khim.*, **21**, 1183 (1948) [*C. A.*, **43**, 6182 (1949)].
4. Beilstein and Kuhlberg, *Ann.*, **147**, 343 (1868).
5. Basler, *Ber.*, **16**, 2715 (1883).
6. Mabery and Jackson, *Ber.*, **11**, 56 (1878).
7. Jackson and Mabery, *Am. Chem. J.*, **2**, 251 (1880).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

ethanol (64-17-5)

methanol (67-56-1)

sodium hydroxide (1310-73-2)

formaldehyde (630-08-0)

chloroform (67-66-3)

Norit (7782-42-5)

potassium hydroxide (1310-58-3)

potassium acetate (127-08-2)

p-Nitrobenzaldehyde (555-16-8)

p-iodobenzyl acetate

p-Nitrobenzyl alcohol, Benzyl alcohol, p-nitro (619-73-8)

p-nitrotoluene (99-99-0)

p-Nitrobenzyl acetate (619-90-9)

p-iodobenzyl alcohol (18282-51-4)

p-iodobenzyl bromide (16004-15-2)

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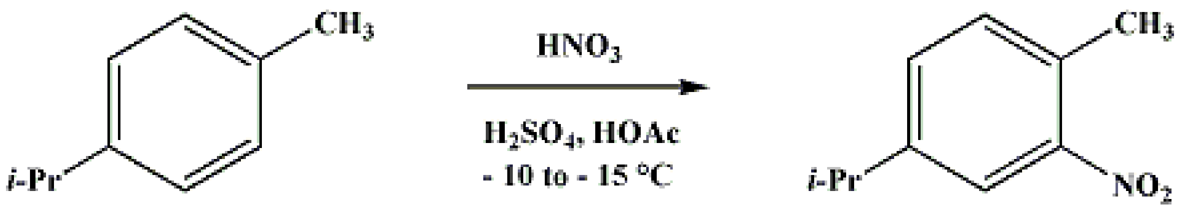
Organic Syntheses, CV 3, 653

2-NITRO-*p*-CYMENE

[*p*-Cymene, 2-nitro-]



Submitted by Kenneth A. Kobe and Thomas F. Doumani.
Checked by C. F. H. Allen and James VanAllan.

1. Procedure

A 5-qt. enamel pail or bain-marie jar is fitted with two mechanical stirrers (Note 1) placed off center, a thermometer for reading low temperatures, and a dropping funnel, the lower end of which is placed just over the vortex created by one of the stirrer blades, so that each drop of added liquid is immediately mixed with and diluted by the chilled reaction mixture.

In the pail are placed 1 kg. (544 ml.) of concentrated sulfuric acid and 300 ml. of glacial acetic acid (Note 2), and this mixture is chilled by Dry Ice until the temperature is 0° to −5°. Next, 500 g. (585 ml.) of *p*-cymene (Note 3) is added from the dropping funnel with vigorous stirring, any rise of temperature being prevented by the addition of Dry Ice (Note 4). Concurrently the nitrating mixture is prepared from 369 g. (262 ml.) of nitric acid (sp. gr. 1.42) and 1 kg. (544 ml.) of concentrated sulfuric acid, and cooled to 0–5° by the direct addition of small pieces of Dry Ice (Note 4).

The hydrocarbon emulsion is then cooled to −15° to −10° and the nitrating mixture is admitted dropwise from the dropping funnel over a period of about 2 hours, avoiding any temperature rise (Note 4) and (Note 5). Stirring is continued for 10 minutes, after which the entire contents of the pail are poured, with adequate stirring, into a mixture of 1 kg. of cracked ice and 1 l. of water. Separation into layers occurs after about 2 hours, whereupon the lower acid layer is drawn off by siphoning or by means of a large separatory funnel (Note 6) and extracted twice, using 50-ml. portions of petroleum ether or 500-ml. portions of ether (Note 7). The extracts and crude nitrocymene are combined and washed three times with 300-ml. portions of water (Note 8), and the ether layer is dried by 50 g. of calcium chloride. After the ether is filtered and distilled, the residual liquid is fractionated under reduced pressure, using a 1-l. modified Claisen flask with indented neck. Fractions are collected at 15–17 mm. as follows: up to 125°, 25–30 g. (Note 9); 125–139°, 520–550 g. (78–82%), n_D^{26} 1.5280; tarry residue, 25–30 g. The product is mainly 2-nitro-*p*-cymene but contains about 8% of *p*-nitrotoluene; it is suitable for reduction[1] to 2-amino-*p*-cymene, from

which the *p*-toluidine is readily removed. Upon refractionation of the mixed nitro compounds, the last half is essentially pure 2-nitro-*p*-cymene, b.p. 137–139°/17 mm.; 128–131°/12 mm.; 108°/3 mm., n_D^{25} 1.5290. The properties of pure 2-nitro-*p*-cymene are as follows: b.p. 126°/10 mm.; 142°/20 mm.; n_D^{20} 1.5287.

2. Notes

1. It is advisable to use more powerful stirring motors than those usually found in the organic laboratory, since the success of the preparation is largely dependent on the production of a good emulsion. The checkers employed two "Lightnin" stirrers (Model L mixers) having shafts and blades of Monel metal.
2. On mixing the acids, the temperature rises to about 60°.
3. The authors recommended that a technical grade of cymene be used, since the terpenic impurities present facilitated emulsification. The checkers used both a technical product and one free from terpenes; They encountered no difficulties with emulsification and secured a slightly higher yield (3–4%) with the purified grade. Cymene from different sources varies considerably in its composition.
4. The amounts of Dry Ice given are approximate. The actual quantities depend on the initial temperature and the rapidity of cooling required. Ordinarily 200 g. is required to cool the nitrating mixture, 500 g. to chill the cymene-sulfuric-acetic acid mixture, and 1.5 kg. during the actual nitration. The nitrating acid will solidify if chilled too far. It is extremely important to keep the temperatures indicated to secure the best yields, and Dry Ice should be used freely. The carbon dioxide evolved aids in mixing.
5. If the mixture is cooled too much, the emulsion is broken.
6. The separation into layers is not sharp; 10–15 g. of product may be lost with the acid layer at this point (Note 7).
7. The extractions can be omitted with a smaller yield of product. Thus from the first extraction there is obtained approximately 15 g. of nitro compound, and 7 g. from the second.
8. Sometimes an emulsion is formed during washing; this can be broken by the addition of a few milliliters of sulfuric acid and shaking.
9. The fore-run, on refractionation at atmospheric pressure, yields 4–6 g. of impure *p*-cymene, b.p. 160–165°, and 10–13 g. of nitro compound. This latter amount is included in the total yields given in the procedure.

3. Discussion

2-Nitro-*p*-cymene has always been secured by the nitration of the hydrocarbon, either by the use of mixed sulfuric and nitric acids with[2] or without[3] the addition of acetic acid, or by fuming nitric acid in acetic acid.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 63

References and Notes

1. Doumani and Kobe, *Ind. Eng. Chem.*, **31**, 264 (1939).
2. Söderbaum and Widman, *Ber.*, **21**, 2126 (1888); Andrews, *J. Ind. Eng. Chem.*, **10**, 453 (1918); Wheeler and Smithey, *J. Am. Chem. Soc.*, **43**, 2613 (1921); Phillips, *J. Am. Chem. Soc.*, **44**, 1777 (1922); Demonbreun and Kremers, *J. Am. Pharm. Assoc.*, **12**, 296 (1926) [*C. A.*, **17**, 3906 (1923)]; Kobe and Doumani, *Ind. Eng. Chem.*, **31**, 257 (1939).
3. Andrews, U. S. pat. 1,314,920 [*C. A.*, **13**, 2765 (1919)]; Selden, Brit. pat. 142,226 [*C. A.*, **14**, 2645 (1920)].
4. Schumow, *J. Russ. Phys. Chem. Soc.*, (1) **19**, 119 (1887); *Ber. Ref.*, **20**, 218 (1887).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

sulfuric and nitric acids

cymene-sulfuric-acetic acid

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

ether (60-29-7)

nitric acid (7697-37-2)

carbon dioxide (124-38-9)

cymene, p-cymene (99-87-6)

2-Amino-p-cymene (2051-53-8)

nitrocymene

p-toluidine (106-49-0)

p-nitrotoluene (99-99-0)

2-Nitro-p-cymene, p-Cymene, 2-nitro- (943-15-7)

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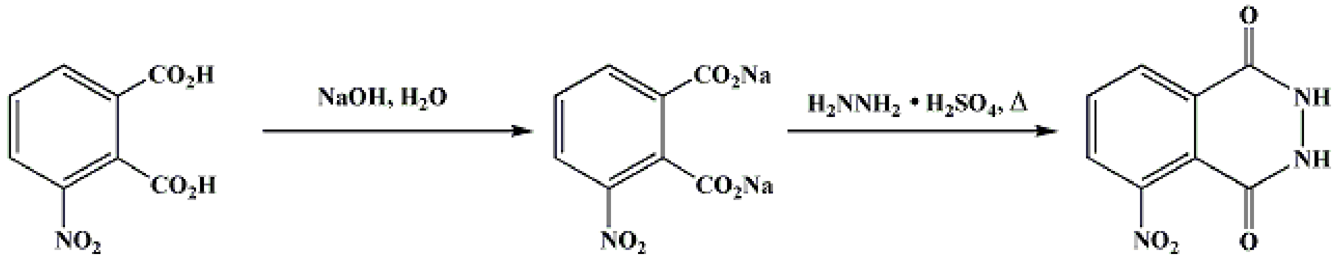
5-NITRO-2,3-DIHYDRO-1,4-PHTHALAZINEDIONE

[1,4-Phthalazinedione, 5-nitro-2,3-dihydro-]



Submitted by Carl T. Redemann and C. Ernst Redemann.
Checked by Cliff S. Hamilton and Carl L. Carlson.

1. Procedure

In a 16-cm. evaporating dish are placed 42.2 g. (0.2 mole) of 3-nitrophthalic acid,[1] 50 ml. of water, and a few drops of phenolphthalein indicator solution. The mixture is made faintly alkaline to phenolphthalein with about 66 ml. (0.4 mole) of 6 *N* sodium hydroxide solution (Note 1), the last portions of which are added slowly with good stirring so that the end point may be observed. The color of the phenolphthalein is discharged by the addition of 0.2–0.3 g. of the 3-nitrophthalic acid, and 26.0 g. (0.2 mole) of hydrazine sulfate[2] is added. The solution is evaporated to dryness over a sand bath, with stirring at the latter part of the evaporation (Note 2), and the residual solid is cooled, ground in a mortar to a fine powder, and placed in a 200-ml. conical flask with 25 ml. of tetralin (Note 3). The mixture is heated at 160–170° for 3 hours and allowed to cool. After the addition of 50 ml. of benzene the solid is collected on a Büchner funnel and pressed down well, and most of the benzene is removed by suction. The solid is then washed with two 25-ml. portions of ether and allowed to stand in the air until the odor of ether is no longer detectable. The resulting material, weight 62–68 g., is an equimolar mixture of sodium sulfate and 5-nitro-2,3-dihydro-1,4-phthalazinedione, and it may be used directly for preparing 5-amino-2,3-dihydro-1,4-phthalazinedione (luminol, p. 69).

For purification, the crude material is suspended in 600–700 ml. of boiling water, and solid sodium carbonate is added in portions until the nitro compound has dissolved. Decolorizing carbon is added cautiously, and the suspension is boiled for a few minutes and filtered. The clear red-brown filtrate is acidified with concentrated hydrochloric acid, and the 5-nitro-2,3-dihydro-1,4-phthalazinedione is precipitated as a cream-colored flocculent solid. The solution is allowed to cool to room temperature, and the solid is separated by filtration and dried. The product thus obtained weighs 31–32 g. (75–78%) and has a melting point of 315–316° (dec.) when determined with the Kullman copper block (Note 4).

2. Notes

1. The strength of the sodium hydroxide solution is not critical; the equivalent amount of a solution of a different concentration may be used.
2. It is wise to cover the hand with a cloth or a glove while stirring, for the hot mixture may spatter if the heating is too rapid. The evaporation may be finished by transferring the evaporating dish to an oven shortly after the solid begins to separate. It is necessary to continue the evaporation until the solid is completely dry.
3. In an optional procedure the dry powder is heated in an oven at 160–170° for 3 hours.
4. No satisfactory solvent has been found for the recrystallization of 5-nitro-2,3-dihydro-1,4-phthalazinedione, but this precipitation gives a satisfactory product, free of sodium sulfate. The melting points given in the literature range from 297° to 320°.

3. Discussion

5-Nitro-2,3-dihydro-1,4-phthalazinedione has been prepared by heating 3-nitrophthalic acid with a large excess of hydrazine hydrate,[3] by heating 3-nitrophthalic acid with hydrazine sulfate[4] and sodium acetate, and by heating the nitro acid with hydrazine hydrate in ethanol at 150°.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 69

References and Notes

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2. *Org. Syntheses* Coll. Vol. **1**, 309 (1941).
3. Bogert and Boroschek, *J. Am. Chem. Soc.*, **23**, 740 (1901).
4. Huntress, Stanley, and Parker, *J. Am. Chem. Soc.*, **56**, 241 (1934).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether (60-29-7)

sodium acetate (127-09-3)

sodium hydroxide (1310-73-2)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

3-Nitrophthalic acid (603-11-2)

decolorizing carbon (7782-42-5)

hydrazine hydrate (7803-57-8)

Hydrazine sulfate (10034-93-2)

phenolphthalein (77-09-8)

Tetralin (119-64-2)

5-Amino-2,3-dihydro-1,4-phthalazinedione (521-31-3)

5-Nitro-2,3-dihydro-1,4-phthalazinedione, 1,4-Phthalazinedione, 5-nitro-2,3-dihydro- (3682-15-3)

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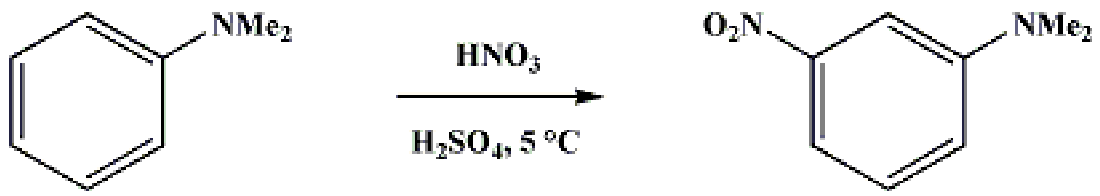
Organic Syntheses, CV 3, 658

m-NITRODIMETHYLANILINE

[Aniline, N,N-dimethyl-*m*-nitro-]



Submitted by Howard M. Fitch
Checked by C. F. H. Allen and J. A. Vanallan.

1. Procedure

In a 3-l. three-necked round-bottomed flask fitted with an effective mechanical stirrer, a dropping funnel, and a thermometer, and surrounded by an ice bath, is placed 1270 ml. (23.0 moles) of concentrated sulfuric acid (sp. gr. 1.84). Then 363 g. (3.0 moles) of dimethylaniline (Note 1) is slowly added with stirring and cooling so that the temperature remains below 25°. Stirring and cooling are continued until the temperature falls to 5°. A nitrating mixture is prepared by adding 366 g. (200 ml., 3.6 moles) of concentrated sulfuric acid (sp. gr. 1.84) to 286 g. (200 ml., 3.15 moles) of concentrated nitric acid (sp. gr. 1.42), with cooling and stirring. This is placed in the dropping funnel and added, drop by drop, the end of the dropping funnel being kept beneath the surface of the solution of dimethylaniline sulfate. The temperature is regulated between 5° and 10°, best by addition of small pieces of Dry Ice (Note 2); about 1.5 hours is required (Note 3). When the addition has been completed, the solution is stirred at 5–10° for 1 hour, and then poured, with stirring (Note 4), into an enameled pail containing 6 l. of ice and water (Note 5). Concentrated ammonium hydroxide is added slowly, with good stirring and using a dropping funnel that extends beneath the surface of the liquid, until the color of the precipitate changes to a light orange (Note 6). During this step the temperature is kept below 25°, using Dry Ice. From 1900 to 2050 ml. of ammonium hydroxide is required. The crude *p*-nitrodimethylaniline is collected on a filter and washed with 200 ml. of water (Note 7). Concentrated ammonium hydroxide (sp. gr. 0.90) is again added to the combined filtrate and washings, with good agitation and cooling to keep the temperature below 25°, until the liquid gives a purple color on Congo red paper (Note 8). From 1500 to 1650 ml. of ammonium hydroxide is required. The product is collected on a Büchner funnel and washed with 500 ml. of water. The crude *m*-nitrodimethylaniline (316–342 g. dry weight) is recrystallized from 400 ml. of hot 95% ethanol and carefully washed on the filter with 100 ml. of cold 95% ethanol. The yield is 280–316 g. (56–63%) of bright orange crystals that melt at 59–60°.

2. Notes

1. The dimethylaniline should be of good quality. Dimethylaniline (free from mono), m.p. 1°, of the Eastman Kodak Company, and dimethylaniline, Merck, are satisfactory.
2. A cooling bath of Dry Ice and acetone can be used, but addition of the solid directly to the mixture is more satisfactory and less is required.
3. The mixture may be left overnight at room temperature. It is advisable to complete the subsequent neutralization in 1 day.
4. A powerful stirrer is required to mix the large volumes.
5. If large equipment is not available, it is convenient to divide the nitration mixture into four parts (about 490 ml. each) and to pour each portion into 1.5 l. of ice and water in a 4-l. beaker. After neutralization, the precipitates from the four lots are combined on the filter.
6. It is essential that all the *para* isomer be precipitated, since it is not easily removed by recrystallization from solvents. The point at which the yellow *p*-nitrodimethylaniline ceases to precipitate and the orange *m*-nitrodimethylaniline begins to precipitate is difficult to judge without experience, since the solution itself has an orange color. If doubt exists, a small sample may be filtered so that the color of the precipitate can be clearly seen. If very much of the *para* isomer remains in solution, a yellow precipitate or turbidity is obtained on diluting the filtrate with several volumes of water.
7. If the *para* isomer is to be recovered, the precipitate should be washed well with water to remove all acid and dried. The solid (143–155 g.) is recrystallized from 400 ml. of benzene and carefully washed on the filter with 125 ml. of cold benzene. The yield is 74–92 g. (14–18%) of bright yellow crystals that melt at 163–164°.
8. Substantially all the *m*-nitrodimethylaniline is precipitated at a *p*H of about 3, while any dimethylaniline present remains in solution.

3. Discussion

The above procedure is a modification of the method of Groll;[1] a more laborious method of purification has been described.[2] *m*-Nitrodimethylaniline can also be prepared by methylation of *m*-nitroaniline using methyl sulfate[3] or methyl *p*-toluenesulfonate.[4]

References and Notes

1. Groll, *Ber.*, **19**, 198 (1886).
2. Bobranskii and Eker, *J. Applied Chem. U.S.S.R.*, **14**, 524 (1941) [*C. A.*, **36**, 3159 (1942)].
3. Ullmann, *Ann.*, **327**, 112 (1903).
4. Simonov, *J. Gen. Chem. U.S.S.R.*, **13**, 51 (1943) [*C. A.*, **38**, 338 (1944)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

sulfuric acid (7664-93-9)

Benzene (71-43-2)

nitric acid (7697-37-2)

acetone (67-64-1)

ammonium hydroxide (1336-21-6)

dimethylaniline (121-69-7)

methyl sulfate (75-93-4)

dimethylaniline sulfate

m-nitroaniline (99-09-2)

Methyl p-toluenesulfonate (80-48-8)

m-Nitrodimethylaniline, Aniline, N,N-dimethyl-m-nitro- (619-31-8)

p-nitrodimethylaniline (100-23-2)

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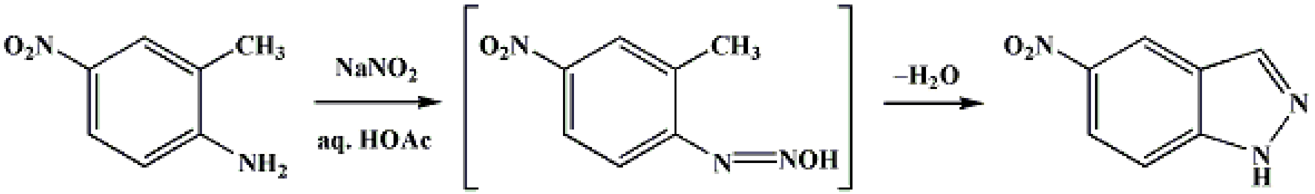
Organic Syntheses, CV 3, 660

5-NITROINDAZOLE

[Indazole, 5-nitro-]



Submitted by H. D. Porter and W. D. Peterson.
Checked by N. L. Drake and A. F. Freeman.

1. Procedure

To a solution of 55 g. (0.36 mole) of 2-amino-5-nitrotoluene (m.p. 129–132°) in 2.5 l. of glacial acetic acid in a 5-l. round-bottomed flask, provided with an efficient mechanical stirrer, is added all at once (Note 1) a solution of 25 g. (0.36 mole) of sodium nitrite in 60 ml. of water. During this addition the temperature is not allowed to rise above 25° (Note 2). After the nitrite solution has been added, stirring is continued for 15 minutes to complete the diazotization. Any yellow precipitate formed during the next few hours is filtered and discarded (Note 3).

The solution is allowed to stand for 3 days at room temperature, and is then concentrated on the steam bath under reduced pressure (water pump) until spattering makes further evaporation impossible. Two hundred milliliters of water is added to the residue, and the contents of the flask are washed into a small beaker where they are stirred to a smooth slurry. The product is filtered, washed thoroughly on the funnel with cold water, and dried in an oven at 80–90°. The crude material melts at 204–206° and weighs 47–57 g. (80–96%). It is purified by recrystallization from 650 ml. of boiling methanol using 5 g. of decolorizing charcoal. The recrystallized, pale yellow needles of 5-nitroindazole melt at 208–209°. The yield is 42–47 g. (72–80%) (Note 4). Further recrystallization does not raise the melting point.

2. Notes

1. If the sodium nitrite solution is added slowly, a considerable quantity of a yellow precipitate, presumably the diazoamino compound, is formed.
2. If the solution is cooled in an ice bath to 15–20° before addition of the nitrite solution, the temperature of the mixture will not rise above 25° during the diazotization.
3. This is presumably the diazoamino compound, insoluble in most organic solvents. It melts at about 200°.[1]
4. The unsubstituted *o*-toluidine gives indazole itself, but the yield is very low (3–5%).

3. Discussion

The procedure is essentially that of Noelting.[2]

References and Notes

1. Meunier, *Bull. soc. chim. France*, (3) **31**, 641 (1904).
2. Noelting, *Ber.*, **37**, 2584 (1904).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

acetic acid (64-19-7)

methanol (67-56-1)

sodium nitrite (7632-00-0)

2-amino-5-nitrotoluene (99-52-5)

5-Nitroindazole, Indazole, 5-nitro- (5401-94-5)

o-toluidine (95-53-4)

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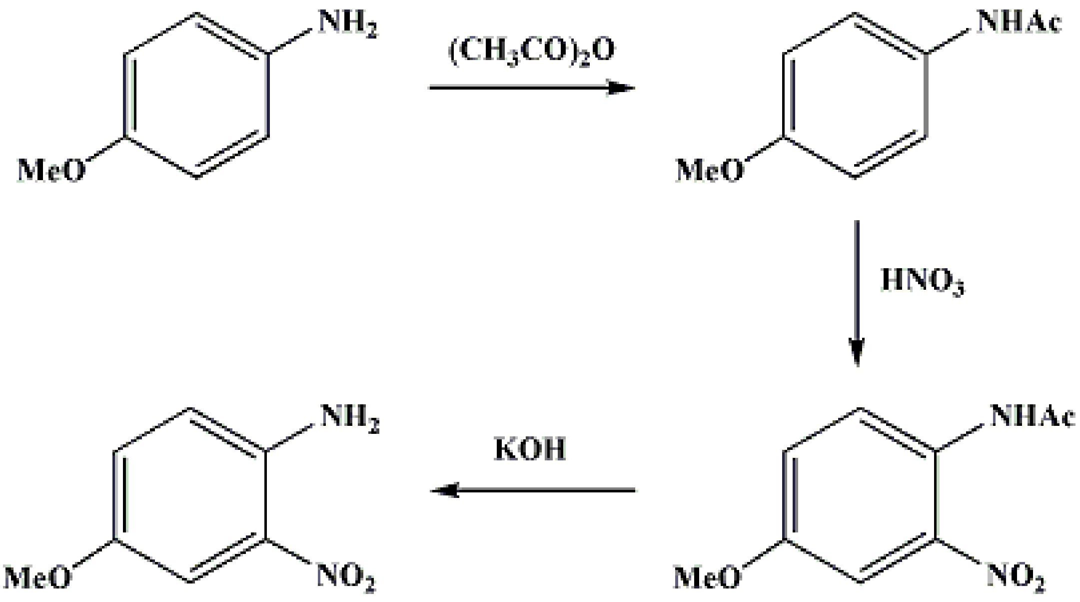
Organic Syntheses, CV 3, 661

2-NITRO-4-METHOXYANILINE

[*p*-Anisidine, 2-nitro-]



Submitted by Paul E. Fanta and D. S. Tarbell.
Checked by W. E. Bachmann and N. C. Deno.

1. Procedure

A. *2-Nitro-4-methoxyacetanilide.* In a 2-l. three-necked, round-bottomed flask equipped with a mechanical stirrer and a thermometer are placed 123 g. (1 mole) of *p*-anisidine (Note 1), 300 ml. of glacial acetic acid, and 217 ml. of water. Stirring is started, and, when the *p*-anisidine has dissolved, 350 g. of ice is added. When the temperature reaches 0–5°, 103 ml. (1.1 moles) of acetic anhydride is added all at once with rapid stirring. Within several seconds the contents of the flask set to a crystalline mass and the temperature rises to 20–25°. The flask is heated on a steam bath until the crystalline material dissolves and is then cooled with stirring to 45°, at which temperature crystals begin to separate. An ice bath is applied, and 100 ml. (55% excess) of concentrated nitric acid (sp. gr. 1.42) is added all at once. The temperature rises rapidly to 70° and soon begins to fall. By suitable adjustment of the cooling bath the temperature is maintained at 60–65° for 10 minutes and then brought down to 25° in the course of 10 minutes (Note 2).

The solution is chilled overnight in an ice chest, and the precipitated yellow crystals are collected on a 19-cm. Büchner funnel. The crystals are washed with 270 ml. of ice-cold water and pressed as dry as possible with a rubber dam. The filter cake can be dried (Note 3) in air or in a vacuum desiccator over calcium chloride and soda lime. The yield of 2-nitro-4-methoxyacetanilide melting at 116–116.5° is 158–168 g. (75–79%).

B. *2-Nitro-4-methoxyaniline.* A mixture of 160 g. of 2-nitro-4-methoxyacetanilide and 250 ml. of cold Claisen's alkali (Note 4) in a 2-l. beaker is stirred and warmed on a steam bath for 15 minutes; it first becomes liquid and then sets to a thick, red paste. After the addition of 250 ml. of hot water the mixture is stirred and digested on a steam bath for an additional 15 minutes and then cooled to 0–5°. The product is collected on a 19-cm. Büchner funnel, washed with three 160-ml. portions of ice-cold water, and pressed as dry as possible with a rubber dam. The yield of vacuum-dried product melting at 122.5–123° is 122–124 g. (95–97%).

2. Notes

1. Eastman Kodak Company's Practical grade of *p*-anisidine was used.
2. In a run in which the mixture was allowed to cool spontaneously from 65° the product became dark.
3. Drying is unnecessary if the 2-nitro-4-methoxyacetanilide is used in step B. The material may be recrystallized with 97% recovery from dilute aqueous ethanol (2 ml. of 95% ethanol and 4 ml. of water per gram). The product so obtained melts at 116.5–117°.
4. Claisen's alkali is prepared by dissolving 88 g. of potassium hydroxide in 63 ml. of water, cooling, and diluting to 250 ml. with methanol.

3. Discussion

2-Nitro-4-methoxyacetanilide has been prepared by the nitration of *p*-acetaniside.[1 2 3 4] The procedure described for the nitration is essentially that used by Lothrop.[4]

2-Nitro-4-methoxyaniline has been prepared by heating nitrohydroquinone dimethyl ether with aqueous ammonia;[5] by heating the tetramethylammonium salt of 3-nitro-4-aminophenol;[6] by the hydrolysis of 2-nitro-4-methoxyacetanilide[1] with alcoholic potassium hydroxide[2,3] or hydrochloric acid;[4] and by the hydrolysis of the *p*-toluenesulfonamide,[7] the 3-nitrobenzenesulfonamide,[8] the 3-nitro-*p*-toluenesulfonamide,[8] the benzenesulfonamide,[9] and the acetyl derivative of the *p*-toluenesulfonamide[10] of 2-nitro-4-methoxyaniline with concentrated sulfuric acid.

References and Notes

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9. Elderfield, Gensler, and Birstein, *J. Org. Chem.*, **11**, 812 (1946).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

soda lime

Nitro-4-methoxyacetanilide

2-Nitro-4-methoxyacetanilide

acetyl derivative of the p-toluenesulfonamide

ethanol (64-17-5)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ammonia (7664-41-7)

methanol (67-56-1)

acetic anhydride (108-24-7)

nitric acid (7697-37-2)

potassium hydroxide (1310-58-3)

2-Nitro-4-methoxyaniline, p-Anisidine, 2-nitro- (96-96-8)

Benzenesulfonamide (98-10-2)

nitrohydroquinone dimethyl ether (89-39-4)

3-nitrobenzenesulfonamide (121-52-8)

p-anisidine (104-94-9)

p-toluenesulfonamide (70-55-3)

p-acetaniside (51-66-1)

3-nitro-p-toluenesulfonamide

tetramethylammonium salt of 3-nitro-4-aminophenol

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Organic Syntheses, CV 3, 664

4-NITRO-1-NAPHTHYLAMINE

[1-Naphthylamine, 4-nitro-]

Submitted by Charles C. Price and Sing-Tuh Voong.
Checked by Richard T. Arnold and Jay S. Buckley, Jr..

1. Procedure

Twenty grams (0.115 mole) of α-nitronaphthalene (Note 1) and 50 g. (0.72 mole) of powdered hydroxylamine hydrochloride are dissolved in 1.2 l. of 95% ethanol contained in a 3-l. flask which is heated in a bath maintained at 50–60°. A filtered solution of 100 g. of potassium hydroxide in 500 g. (630 ml.) of methanol is added gradually with vigorous mechanical stirring (Note 2) over a period of 1 hour. Stirring is continued for an additional hour, and the warm solution is poured slowly into 7 l. of ice water. After the solid has coagulated, it is collected on a filter and washed thoroughly with water. The crude 4-nitro-1-naphthylamine is purified by recrystallization from 500 ml. of 95% ethanol (Note 3). About 12–13 g. (55–60%) of long golden-orange needles, m.p. 190.5–191.5°, is obtained.

2. Notes

1. The α-nitronaphthalene, m.p. 56–57°, was obtained from Eastman Kodak Company.
2. The color changes from yellow to orange, and potassium chloride separates.
3. In some experiments a few milliliters of dilute hydrochloric acid (1:1) or sulfuric acid (1:1) was added to facilitate the crystallization of the 4-nitro-1-naphthylamine.

3. Discussion

This method is essentially that described by Goldhahn.[1] 4-Nitro-1-naphthylamine has also been prepared by the nitration of α-naphthylamine,[2] acetyl-α-naphthylamine,[3,4] and ethyl-1-naphthyloxamate,[5,6] by the oxidation of 4-nitroso-1-naphthylamine,[7] and

by reaction of 4-chloro-1-nitronaphthalene with ammonia.[8]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 341

References and Notes

1. Goldhahn, *J. prakt. Chem.*, **156**, 315 (1940); **157**, 96 (1940).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

α-naphthylamine

acetyl-α-naphthylamine

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

methanol (67-56-1)

potassium hydroxide (1310-58-3)

Hydroxylamine hydrochloride (5470-11-1)

α-nitronaphthalene (86-57-7)

potassium chloride (7447-40-7)

4-nitro-1-naphthylamine, 1-Naphthylamine, 4-nitro- (776-34-1)

ethyl-1-naphthyloxamate

4-nitroso-1-naphthylamine

4-chloro-1-nitronaphthalene

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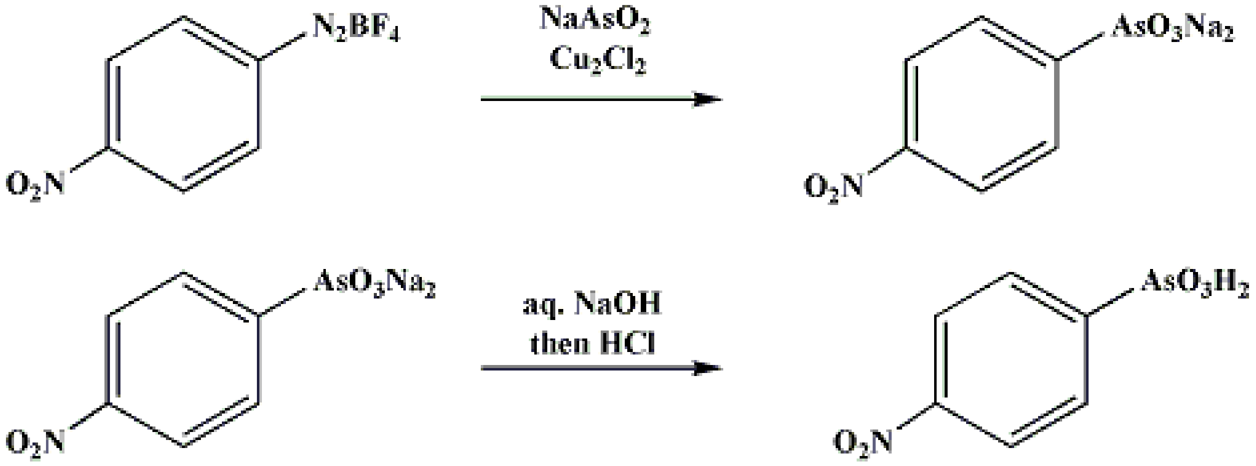
Organic Syntheses, CV 3, 665

p-NITROPHENYLARSONIC ACID

[Benzenearsonic acid, *p*-nitro-]



Submitted by A. Wayne Ruddy and Edgar B. Starkey.
Checked by Cliff S. Hamilton and Richard E. Benson.

1. Procedure

In a 2-l. beaker provided with an efficient mechanical stirrer, 52 g. (0.4 mole) of sodium metaarsenite and 16 g. (0.4 mole) of sodium hydroxide are dissolved in 600 ml. of water (Note 1) and 6 g. of cuprous chloride is suspended in the solution.

A mixture of 300 ml. of water and the *p*-nitrobenzenediazonium borofluoride[1] obtained from 0.25 mole of *p*-nitroaniline (Note 2) is added during a period of 1 hour to the sodium arsenite solution. The foaming that accompanies the evolution of nitrogen is readily controlled by the occasional addition of small amounts of ether or benzene (Note 3). As the reaction proceeds, 100 ml. of 10% sodium hydroxide solution (0.25 mole) is added in 20-ml. portions. Stirring is continued for another hour, and then the mixture is warmed to 60° for 30 minutes and filtered with suction through a sintered-glass funnel. The residue on the funnel is washed with two 50-ml. portions of water. To the combined filtrate and washings is added concentrated hydrochloric acid (sp. gr. 1.19) until the solution is acid to litmus paper. The mixture is filtered, activated charcoal is added to the filtrate, and the solution is concentrated to about 350 ml. After the hot solution has been filtered with suction, concentrated hydrochloric acid is added until the solution is acid to Congo red paper. The solution is placed in a refrigerator overnight, and the crystals are collected on a Büchner funnel and washed twice with 20-ml. portions of ice water. The combined filtrates and washings are concentrated to about 150 ml., chilled, and filtered. The total quantity of crystals is dissolved in 10% ammonium hydroxide solution; the solution is filtered and again made acid to Congo red paper with concentrated hydrochloric acid. After the solution

has been thoroughly chilled (preferably overnight), the *p*-nitrophenylarsonic acid is filtered on a Büchner funnel and washed with small portions of ice water until free of ammonium chloride. After drying, the yellow crystals melt with decomposition at 298–300.° The yield is 44–48.5 g. (71–79%) (Note 4).

2. Notes

1. The sodium arsenite solution may also be prepared by dissolving 39.6 g. (0.2 mole) of arsenious oxide and 32 g. (0.8 mole) of sodium hydroxide in 600 ml. of water.

2. According to the submitters *p*-nitrobenzenediazonium borofluoride may also be prepared as follows:
p-Nitroaniline (34.5 g.) is dissolved in 63 ml. of concentrated hydrochloric acid (sp. gr. 1.19) and 50 ml. of water. The solution is cooled to 0°, and 17.3 g. of sodium nitrite in 40 ml. of water is added slowly with vigorous stirring. After the diazotization is complete, as indicated by a positive test with starch iodide paper, a solution of 55 g. of sodium fluoborate in 110 ml. of water is added. The thick slurry is stirred for 15 minutes and then filtered with suction and washed with ice water, twice with methanol, and twice with ether. The solid should be sucked as free as possible from liquid after each washing. The compound may be kept in an evacuated desiccator until needed.

3. The checkers found that the foaming is more readily controlled by amyl alcohol than by the addition of ether or benzene.

4. This is a general method for preparing arylarsonic acids. The melting points and yields of other arsonic acids prepared by the submitters are as follows: phenyl, 156°, 58%; *o*-nitrophenyl, 232–234° dec., 67%; *m*-nitrophenyl, 182°, 47%; *o*-tolyl, 159–160°, 63%; *m*-tolyl, 150°, 54%; *p*-tolyl, 300° dec., 73%; *o*-chlorophenyl, 182°, 52%; *p*-chlorophenyl, above 300°, 63%; *o*-carboxyphenyl, above 300°, 65%; *p*-carboxyphenyl, 232° dec., 67%; *p*-carbethoxyphenyl, 260°, 60%; *p*-acetophenyl, 175°, 70%.

3. Discussion

p-Nitrophenylarsonic acid has been prepared by heating *p*-nitrobenzenediazonium chloride with arsenious acid in hydrochloric acid,[2] by the action of *p*-nitrobenzenediazonium chloride on sodium arsenite,[3] by the action of sodium arsenite on sodium *p*-nitrobenzeneisodiazo oxide,[4] by the diazotization of *p*-nitroaniline in acetic acid in the presence of arsenic chloride and cuprous chloride,[5] and by the reaction of *p*-nitrobenzenediazonium borofluoride with sodium arsenite in the presence of cuprous chloride.[6]

References and Notes

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3. Bart, *Ann.*, **429**, 95 (1922).
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5. Scheller, U. S. pat. 1,704,106; Fr. pat. 624,028 [*Chem. Zentr.*, **98**, II, 2229 (1927)]; Brit. pat. 261,026; Ger. pat. 624,028 [*Frdl.*, **17**, 2372 (1930)].
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

arsenious acid

arsenious oxide

sodium metaarsenite

sodium p-nitrobenzeneisodiazo oxide

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

methanol (67-56-1)

ether (60-29-7)

ammonium chloride (12125-02-9)

sodium hydroxide (1310-73-2)

nitrogen (7727-37-9)

sodium nitrite (7632-00-0)

sodium arsenite

cuprous chloride (7758-89-6)

ammonium hydroxide (1336-21-6)

amyl alcohol (71-41-0)

Phenylarsonic acid (98-05-5)

sodium fluoborate (13755-29-8)

arsenic chloride

p-Nitrophenylarsonic acid, Benzenearsonic acid, p-nitro- (98-72-6)

p-nitroaniline (100-01-6)

p-nitrobenzenediazonium borofluoride (456-27-9)

p-nitrobenzenediazonium chloride

o-nitrophenylarsonic acid

m-nitrophenylarsonic acid

o-tolylarsonic acid

m-tolylarsonic acid

p-tolylarsonic acid

o-chlorophenylarsonic acid

p-chlorophenylarsonic acid

o-carboxyphenylarsonic acid

p-carboxyphenylarsonic acid

p-carbethoxyphenylarsonic acid

p-acetophenylarsonic acid

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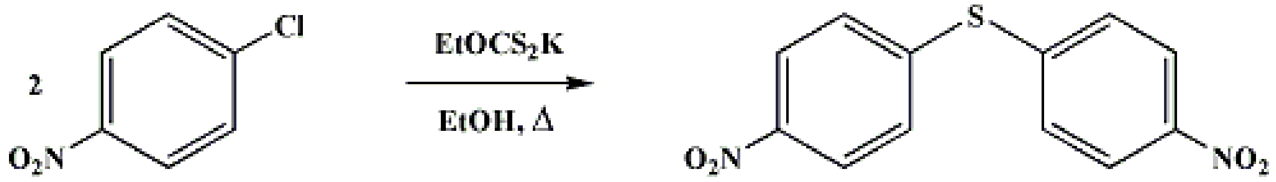
p-NITROPHENYL SULFIDE

[Sulfide, bis-(*p*-nitrophenyl)]



Submitted by Charles C. Price and Gardner W. Stacy.
Checked by Cliff S. Hamilton and Paul D. Berry.

1. Procedure

In a 1-l. round-bottomed flask equipped with a reflux condenser are placed 157.5 g. (1 mole) of *p*-chloronitrobenzene, 160 g. (1 mole) of potassium xanthate (Note 1), and 450 ml. of 95% ethanol. This reaction mixture is heated under reflux on a steam bath for 48 hours. The crystalline product, which deposits from solution during the course of the reaction, is collected by filtration, crushed into small particles in a mortar, and washed twice with hot ethanol and once with hot water. The yield of *p*-nitrophenyl sulfide melting at 158–160° is 105–113 g. (76–82%). This product is pure enough for most purposes. Recrystallization from glacial acetic acid (15 ml. per gram) raises the melting point to 160–161°.

2. Notes

1. Potassium xanthate may be prepared in the following manner: With heating, 300 g. (5.36 moles) of potassium hydroxide is dissolved in 3 l. of absolute ethanol. The solution is then cooled in an ice bath, and the temperature is kept below 10° while carbon disulfide is added in portions with stirring until the solution is no longer alkaline; about 456 g. (360 ml., 5.95 moles) of carbon disulfide is required. The potassium xanthate is collected by suction filtration and air-dried on large sheets of filter paper; yield, 429–472 g. (50–55%).

3. Discussion

p-Nitrophenyl sulfide has been prepared by the reaction between *p*-chloronitrobenzene and sodium sulfide.[1] This is not a practical means of preparation, however, because of the variety of substances formed.[2] The method described has been published.[3] A preparation of pure *p*-nitrophenyl sulfide has been reported from *p*-chloronitrobenzene and sodium thiosulfate.[4]

References and Notes

1. Nietski and Bothof, *Ber.*, **27**, 3261 (1894).
2. Kehrmann and Bauer, *Ber.*, **29**, 2362 (1896).

3. Price and Stacy, *J. Am. Chem. Soc.*, **68**, 498 (1946).
4. Dall'Olio, *Chimica e industria*, **28**, 73 (1946) [*C. A.*, **41**, 380 (1947)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

acetic acid (64-19-7)

sodium thiosulfate (7772-98-7)

potassium hydroxide (1310-58-3)

carbon disulfide (75-15-0)

sodium sulfide (1313-82-2)

p-chloronitrobenzene (100-00-5)

potassium xanthate

p-Nitrophenyl sulfide, Sulfide, bis-(p-nitrophenyl) (1223-31-0)

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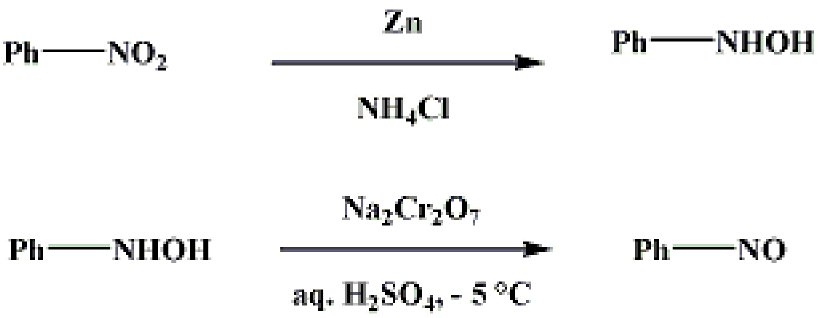
Organic Syntheses, CV 3, 668

NITROSOBENZENE

[Benzene, nitroso-]



Submitted by George H. Coleman, Chester M. McCloskey, and Frank A. Stuart.
Checked by W. E. Bachmann, N. C. Deno, and R. F. Edgerton.

1. Procedure

A mixture of 250 ml. (2.44 moles) of nitrobenzene (Note 1) and (Note 2) and a solution of 150 g. of ammonium chloride in 5 l. of water in a 5-gal. crock (Note 3) is stirred vigorously (Note 4), and 372 g. (5.15 moles) of zinc dust (90% zinc) is added in small portions over a period of 5 minutes. About 5 minutes after the addition of the zinc, the main reaction occurs and the temperature rises. When the temperature reaches about 65°, enough ice is added to the stirred mixture to bring the temperature down to 50–55° (Note 5). Twenty minutes after the addition of zinc was started, the solution is filtered through a 24-cm. Büchner funnel and the zinc oxide residues are washed with 3 l. of boiling water. The filtrate and washings are combined in a 6-gal. crock (Note 6) and cooled immediately (Note 7) by the addition of enough ice to bring the temperature to 0° to –2° and leave at least 1 kg. of ice unmelted.

To this cold solution or suspension of β-phenylhydroxylamine, a cold solution of sulfuric acid (750 ml. of concentrated acid and sufficient ice to bring the temperature down to –5°) is added with stirring. An ice-cold solution of 170 g. of sodium dichromate dihydrate in 500–750 ml. of water is added as rapidly as it can be poured into the mixture, which is stirred or swirled (Note 8). After 2 to 3 minutes, the straw-colored precipitate of nitrosobenzene is collected on a Büchner funnel and washed with 1 l. of water (Note 9).

The crude nitrosobenzene is steam-distilled (Note 10), and the distillate is collected in a receiver cooled by ice (Note 11). The nitrosobenzene is finely ground in a mortar, transferred to a Büchner funnel, and washed with water until the washings are no longer brown. After it has been sucked as dry as possible on the filter the nitrosobenzene is pressed between layers of filter paper (or other porous paper). One or two changes of paper may be necessary. The yield of nitrosobenzene melting at 64–

67° is 128–138 g. (49–53%) (Note 12) and (Note 13). If a purer product is desired, the crude nitrosobenzene can be recrystallized from a small amount of ethanol with good cooling, and the product dried over calcium chloride at atmospheric pressure.

2. Notes

1. Commercial nitrobenzene of good quality is satisfactory.
2. Contact with nitrobenzene, phenylhydroxylamine, and nitrosobenzene or prolonged breathing of the vapors should be avoided.
3. The checkers used a 12-l. round-bottomed flask.
4. Vigorous stirring is necessary in order to prevent the zinc dust from caking on the bottom of the crock. The submitters employed two mechanically driven stirrers in order to keep the zinc dust in suspension. The checkers used a single paddle stirrer successfully.
5. At higher temperatures secondary reactions take place.
6. The checkers used a 22-l. round-bottomed flask.
7. Since β-phenylhydroxylamine decomposes on standing, the filtrate should be cooled as soon as the filtration is completed, and the oxidation to nitrosobenzene should be carried out immediately. An excess of ice should be present since the oxidation reaction is exothermic and the temperature of the solution should still be near 0° after the oxidation. At higher temperatures oxidation products other than nitrosobenzene are produced.
8. It is important to add the dichromate solution rapidly in order to obtain a good yield of easily filterable product. In a run in which the dichromate solution was added over a period of 25 minutes, only a 10% yield of nitrosobenzene was obtained.
9. This product is stable for about a week if kept at 0°.
10. Connections should be of glass since cork and rubber are attacked readily. Since nitrosobenzene decomposes at the elevated temperature, it should be steam-distilled as rapidly as possible. If several runs are made, not more than four or five should be combined for distillation. A Hopkins still head is effective for preventing contamination.
The nitrosobenzene condenses to a green liquid which solidifies to a white solid. Care should be taken that the solid does not clog the condenser. Distillation is stopped when yellow oily material appears in the condenser.
11. Cooling of the receiver is necessary because the nitrosobenzene has a very high vapor pressure at room temperature.
12. Yields as high as 65–70% have been obtained in smaller runs.
13. Nitrosobenzene can be kept at room temperature in a closed container for 1–2 days. Over longer periods it should be stored at 0°.

3. Discussion

Nitrosobenzene can be prepared by the oxidation of aniline with permonosulfuric acid[1] or peracetic acid[2] and by the oxidation of β-phenylhydroxylamine,[3] which is prepared

by the reduction of nitrobenzene. Purification by sublimation has been recommended.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 711

References and Notes

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3. Bamberger, *Ber.*, **27**, 1555 (1894); Parsons and Bailar, *J. Am. Chem. Soc.*, **58**, 268 (1936).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

β-Phenylhydroxylamine

ethanol (64-17-5)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

ammonium chloride (12125-02-9)

aniline (62-53-3)

zinc (7440-66-6)

Nitrobenzene (98-95-3)

Phenylhydroxylamine (100-65-2)

zinc oxide

sodium dichromate dihydrate (10588-01-9)

peracetic acid (79-21-0)

Nitrosobenzene, Benzene, nitroso- (586-96-9)

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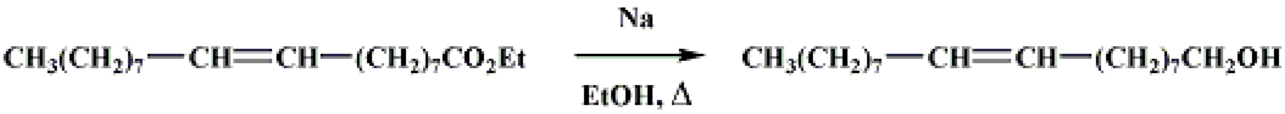
Organic Syntheses, CV 3, 671

OLEYL ALCOHOL

[9-Octadecen-1-ol]



Submitted by Homer Adkins and R. H. Gillespie.
Checked by Cliff S. Hamilton, C. W. Winter, and Alfred Stepan.

1. Procedure

In a 5-l. round-bottomed flask fitted with a large-bore reflux condenser are placed 200 g. (230 ml., 0.65 mole) of ethyl oleate (Note 1) and 1.5 l. of absolute ethanol (Note 2). Through the reflux condenser is added 80 g. (3.5 gram atoms) of sodium rapidly enough to keep up a vigorous reaction. The flask is shaken occasionally. After the initial reaction has subsided, about 200 ml. more of absolute ethanol is added, and the mixture is heated on a steam bath until all the sodium has reacted. Then 500 ml. of water is added, and the mixture is refluxed for 1 hour to saponify the unreacted ester. The mixture is cooled, and 1.2 l. of water is added. The unsaponifiable fraction is extracted with ether, and the extracts are washed with 1% potassium hydroxide solution and then with water till free of alkali when tested externally with phenolphthalein. The ether extract is dried over sodium sulfate, the ether removed by distillation, and the residue disstilled through an efficient column (Note 3). A yield of 84–89 g. (49–51%), b.p. 150–152°/1 mm., is obtained.

Fifty grams of the crude oleyl alcohol is crystallized from 400 ml. of acetone at −20° to −25° (Note 4) in a jacketed sintered-glass funnel (Note 5). The residue, amounting to about 25 g., is then recrystallized from 250 ml. of acetone at −5° (Note 6) to remove saturated alcohols. The oleyl alcohol in the filtrate is recrystallized at −60° to −65° (Note 7) and then distilled from a 25-ml. flask with a thermometer well and a low side arm. The yield is 13–16 g., b.p. 148–150°/less than 1 mm.; n_D^{25} 1.4590.

2. Notes

1. The ethyl oleate used by the submitters was prepared by esterification of commercial U.S.P. grade oleic acid and fractionated through a Widmer column. The fraction boiling at 160–170°/1 mm., n_D^{25} 1.4482–1.4570, iodine value 83.6 (calculated 81.8), was used. The checkers distilled ethyl oleate (technical, Eastman Kodak Company) and used the fraction boiling at 164–166°/1 mm., n_D^{25} 1.4522.
2. The purity of the absolute ethanol is of prime importance. Ethanol dried only by a lime process gives a low yield (20–25%). The ethanol used in this procedure was dried over lime and then over aluminum *tert*-butoxide, after which it was distilled directly into the flask used for the reaction.
3. The submitters used a modified Widmer column; the checkers, a Claisen flask modified with a short Vigreux column.
4. The temperature is controlled by selecting a liquid whose freezing point is approximately the temperature at which one wishes to carry out the crystallization, and crushed Dry Ice is added with stirring to keep just a slush. There must be an intimate mixture of solid and

liquid at all times. Carbon tetrachloride was used for temperatures of −20° to −25°.
5. The apparatus was as follows: A 50-ml. Pyrex sintered-glass funnel, with a sealed-on extension tube, was jacketed with an inverted 500-ml. wide-mouth bottle with the bottom cut off and the edges ground smooth. The jacketed funnel was then placed in a 250-ml. suction flask, the side arm of which was connected to a three-way stopcock. One arm of the stopcock was connected to a water aspirator; the other, to a large test tube (1 1/8 in. by 8 in.) fitted with a two-hole stopper. From the second hole in this stopper was led a tube extending to the bottom of a smaller test tube partly filled with mercury. During crystallization, this large test tube was filled three-quarters full of Dry Ice, the carbon dioxide gas evolved being allowed to bubble up through the bottom of the sintered-glass funnel. This prevents the solution from filtering through and also stirs the solution by the rise of small carbon dioxide bubbles, and hence induces crystallization. The porosity of the sintered-glass funnel is a factor in the size and number of bubbles formed. The mercury trap may be raised or lowered to adjust the pressure, and to act as a vent to prevent the accumulation of carbon dioxide to give excessive pressures. After crystallization had taken place (about 1 hour) the stopcock was turned to the aspirator and the solution immediately filtered. With this apparatus, about 80 ml. of solution may be crystallized at a time, and no transferring from one container to another is necessary. The checkers found it more convenient to use a 500-ml. sintered-glass funnel along with a proportionally larger bottle, flask, etc. The 400 ml. of acetone solution was then poured into the funnel in 50-ml. portions with adequate cooling intervals.
6. A crushed ice-salt bath was used.
7. A Dry Ice-chloroform bath was used.

3. Discussion

Oleyl alcohol has been prepared by the catalytic reduction of ethyl oleate[1] and heavy-metal oleates;[2] by the action of sodium and absolute ethanol on ethyl[3] or butyl[4] oleate; by the action of sodium and absolute butyl alcohol on butyl oleate;[5] and by the action of sodium and *tert*-butyl alcohol on ethyl oleate.[6] The above procedure is essentially that of Kass and Burr,[7] who prepared linoleyl alcohol. The purification step was derived from the low-temperature crystallization technique of Hartsuch.[8]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 630

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

ether (60-29-7)

sodium sulfate (7757-82-6)

carbon tetrachloride (56-23-5)

mercury (7439-97-6)

carbon dioxide (124-38-9)

butyl alcohol (71-36-3)

acetone (67-64-1)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

phenolphthalein (77-09-8)

oleic acid (112-80-1)

Oleyl alcohol (143-28-2)

butyl oleate (142-77-8)

ethyl oleate (111-62-6)

9-Octadecen-1-ol

linoleyl alcohol (506-43-4)

tert-butyl alcohol (75-65-0)

ALUMINUM tert-BUTOXIDE

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Organic Syntheses, CV 3, 673

OZONE

[A laboratory ozonizer]

$$\text{Oxygen} \xrightarrow[\text{discharge}]{\text{silent electrical}} \text{Ozone}$$

Submitted by L. I. Smith, F. L. Greenwood, and O. Hudrlik.
Checked by R. L. Shriner, C. E. Kaslow, and R. D. Stayner.

1. Procedure

A diagrammatic sketch of the complete apparatus for the laboratory production and use of ozone in organic reactions is shown in .htmFig. 21.

Fig. 21.

Fig. 21.

A. *Purification train*. Oxygen from a cylinder (*A*) fitted with a reducing valve (*B*) is led to a pressure release tube (*C*). This is a T-tube, the long arm of which dips into a test tube of mercury. The height of the mercury column should be about 2 to 3 cm. The release tube is connected through a stopcock (1) to a 40-cm. condenser jacket (*D*). This is filled with 4-mesh anhydrous calcium chloride held in place by plugs of glass wool at the ends. A second condenser jacket (*E*) is filled about halfway with 4-mesh soda lime, then a 4- to 6-in. layer of anhydrous calcium chloride, and the remainder of the tube is packed with glass wool. The ends of the condensers are closed with rubber stoppers. Part *F* is a flowmeter, the U-tube of which should be about 20 cm. long. The bore of the capillary should be about 0.5 mm. in diameter. The flowmeter tube is filled about half full with Hyvac pump oil. Part *G* is a condenser jacket (40 cm.) loosely packed with glass wool.

All parts up to the ozonizer may be connected with heavy rubber tubing or, preferably, Tygon tubing. If rubber tubing is used, it is desirable to place this purification train several feet from the ozonizer proper in order to prolong the life of the rubber connectors (Note 1). The sizes of parts *C* through *G* are not critical. After this part of the apparatus has been assembled, a very rapid stream of oxygen should be passed through it for 30 minutes in order to blow out all dust particles.

B. *Ozonizer*. The conversion of oxygen to ozone is accomplished by means of three Berthelot tubes constructed of soft lime glass (Note 2) with the dimensions shown in .htmFig. 22. It is important that the glass be thoroughly cleaned and that the annular space through which the gases pass be as uniform as possible. Each tube has a cooling coil (Note 3) consisting of a long U-shaped piece of 6-mm. Pyrex glass tubing which

fits into the innermost space of the Berthelot tube and reaches nearly to the bottom. The top of the Berthelot tube is closed by a cork with three holes, two for the cooling tubes and one for the inner electrode. The last is a stainless steel rod about 2–4 mm. in diameter. This electrode should extend to about 1 cm. of the bottom of the inner tube. The Berthelot tubes .htm(Fig. 22) are connected by means of mercury-cup seals as shown in .htmFig. 23 (Note 4). The third Berthelot tube is connected to the reaction vessels by means of either mercury-cup seals or ground-glass joints. No rubber connectors can be used for gases containing ozone.

Fig. 22.

Fig. 22.

Fig. 23.

Fig. 23.

The three Berthelot tubes are mounted vertically in a large battery jar about 13 in. by 9 in. by 18 in. (Note 5). They are held in place by a wooden top (see .htmFig. 23) which has holes and slots cut to fit the tubes. A second wooden block with holes and slots to fit the bottom of the Berthelot tubes .htm(Fig. 22) is placed in the bottom of the battery jar. It should be weighted with a few pieces of lead. Both the top and the bottom blocks should be soaked in hot molten paraffin wax. The holes in the top should be directly above those in the bottom so that the Berthelot tubes will be as nearly vertical as possible to facilitate making good connections (Note 6). However, a slight slant of the tubes does not affect the operation of the ozonizer.

C. *Electrical equipment*. A transformer operating on 110 volts alternating current having a secondary capable of producing about 8000–15,000 volts and a capacity of about 400 watts or more is suitable. It is important that provision be made for varying the secondary voltage. This may be done by purchasing a transformer provided with taps on the primary windings or by inserting a variable transformer in series with the primary (Note 7). During the initial test runs for calibration it is desirable to connect an ammeter in the primary circuit in order to make certain the transformer is not overloaded.

The inner electrodes of the Berthelot tubes are connected to one of the secondary terminals of the transformer. *This wire must be grounded* (Note 8); otherwise the cooling tube inside the Berthelot tube will act as a conductor to the water line and the laboratory water line would be charged. The other wire from the secondary is connected to the electrode in the battery jar. This outer electrode consists of a grid of stainless-steel wire (No. 8 or 10 B. and S. gauge). Connecting the inner electrode to the ground results in a charge on the battery jar. *Precautions* must be taken so that the jar is not touched while the current is passing. Also the battery jar must be kept away from any of the plumbing so that it will not be grounded. It is best to arrange a wooden shield so that the operator cannot come in contact with any of the high-voltage connections of the secondary.

D. *Ozone absorption assembly*. One useful combination of reaction flasks is shown in .htmFig. 24. It is best that the parts be connected by ground-glass joints. Tube *H* is the main reaction flask (Note 9), *I* is a condensing tube surrounded by acetone and Dry Ice to trap any volatile compounds, and *J* is an auxiliary analyzing tube for determining the amount of ozone not absorbed by the compound in tube *H*. The tubes should be assembled and clamped high enough above the desk for cooling baths to be placed around tubes *H* and *I* in order that ozonizations may be carried out at temperatures below that of the surroundings.

Fig. 24.

Fig. 24.

E. *Ozone destroyer*. Ozone is a powerful irritant. The maximum possible working concentration has been reported to be 0.15 to 1.0 part per million of air.[1] It is necessary to destroy any excess ozone and to see that the exit tube from the above absorption assembly is connected to a good hood. It is safer to incorporate an ozone destroyer in the set-up. One such destroyer consists of two tall towers (30 in.) filled with broken glass moistened with 5% aqueous sodium hydroxide and connected in series (Note 10). The room in which an ozonizer is used should be well ventilated.

F. *Analysis for ozone*. The analysis is made by passing a definite amount of oxygen through the ozonizer at a selected secondary voltage and then through a neutral 2% solution of potassium iodide. Iodine is liberated, and the resulting solution is acidified with 10% sulfuric acid (about 15 ml.) and titrated with a previously standardized 0.1 *N* sodium thiosulfate solution using soluble starch as the indicator.

G. *Procedure and calibration of apparatus*. For satisfactory use of an ozonizer it is desirable to obtain data relating rate of flow and secondary voltage with the amount of ozone produced.

A wet-type gas meter (Note 11) is connected to the tube *J* as indicated in .htmFig. 24. Enough 2% potassium iodide solution (about 70 ml.) is added to absorption tubes *H* and *J* to fill them to a depth of about one-third to one-half their height, and the tubes are marked at this level (Note 12). The reducing valve of the oxygen tank is opened far enough to show a pressure of 3–4 lb. per sq. in.; stopcocks 2, 3, 4, 5, and 6 are turned so as to by-pass *H*, *I*, and *J* and direct the gases through the ozone destroyer. Stopcock 1 is opened far enough to give a flowmeter reading of about 2–3 mm.; the transformer is turned on and adjusted to a definite voltage (Note 13). After the apparatus has been swept out for 5 minutes, the stopcocks are turned so as to pass the ozonized oxygen successively through tubes *H*, *I*, *J*, and the gas meter. The ozonized oxygen is passed through the potassium iodide solution for 5 minutes (stopwatch), and notes are made of the exact flowmeter reading and the volume of gas passing through the wet meter. At the end of 5 minutes the stopcocks are turned so as to by-pass tubes *H*, *I*, *J*, and the gas meter; and the ozonized oxygen stream is directed through the ozone destroyer.

(Caution: do not pass the ozone through the wet gas meter.) The solutions in *H* and *J* are then combined, acidified, and titrated as described in paragraph F above. Practically all the ozone is absorbed in tube *H*. The second tube *J* is to prevent any damage to the wet gas meter.

The procedure is then repeated, the secondary voltage being kept constant but the rate of flow of oxygen being increased so that the flowmeter readings are about 5 mm. and 10 mm. The voltage is then changed so that the general range of 7000–12,000 volts in steps of about 1000 volts is obtained (Note 13). Determinations of ozone produced are made for each voltage and each rate of flow. These data may be plotted on coordinate paper in order to determine the performance of the ozonizer. A portion of such data is summarized in Table I, which represents the results from two different ozonizers constructed by different workers in different laboratories.

TABLE I VARIATION IN PERCENTAGE (BY VOLUME) OF OZONE (FROM OXYGEN) WITH RATE OF FLOW AND SECONDARY VOLTAGE

Flowmeter Reading, mm.	*Rate of Flow,* l./hr.	*Secondary Voltage* 7000	8000	9000	10,000	11,000	12,000
		Ozonizer 1					
2.0	5.6	1.3%	3.1%	4.5%	6.0%	...	...
6.0	10.6	0.9	2.1	4.2	5.6	...	...
12.0	15.4	0.5	1.7	3.6	4.9	...	...
		Ozonizer 2					
2.0	5.7	6.7%	7.0%	7.1%	7.3%	7.2%	7.1%
5.0	9.8	6.0	6.5	6.7	7.2	6.9	6.8
10.0	14.4	5.5	6.2	6.5	6.7	6.8	6.9

For practical use in ozonolysis of compounds it is convenient to recalculate these data to show the time required to produce 0.1 mole of ozone at a specified rate of flow and voltage. This is illustrated by Table II.

TABLE II HOURS REQUIRED TO PRODUCE 0.1 MOLE OZONE FROM OXYGEN

Flowmeter, mm.	*Rate of Flow,* l./hr.	*Secondary Voltage* 7000	8000	9000	10,000	11,000	12,000
		hr.	hr.	hr.	hr.	hr.	hr.
2.0	5.7	5.97	5.55	5.55	5.48	5.48	5.48
5.0	9.8	3.60	3.55	3.42	3.32	3.33	3.33
10.0	14.4	2.90	2.57	2.43	2.32	2.29	2.26

All ozonizers have individual characteristics since it is difficult if not impossible to build two absolutely identical ozonizers. Variations in the composition of the glass and

the annular space in the Berthelot tubes cause considerable changes in the amount of ozone produced, as shown by Table I. Hence the performances indicated by the data in Table I would be duplicated only under very fortuitous circumstances. The production of ozone from the same ozonizer may vary from time to time; hence it is desirable to check the percentage of ozone occasionally. If the production of ozone drops markedly, the Berthelot tubes should be carefully cleaned with hot nitric acid, thoroughly rinsed, and dried. Higher percentages of ozone may be obtained by having more Berthelot tubes. With six tubes, concentrations of 9–11% may be obtained.

H. *Ozonization of organic compounds*. The ozonization of each unsaturated organic compound is more or less an individual problem, but some general comments may be made. *Organic ozonides are highly explosive,* and hence it is safest to carry out the ozonization in a solvent which dissolves both the original compound and the ozonide. *In all cases, a shatter proof screen* of laminated safety glass should be placed between the operator and the tubes *H*, *I*, and *J*. A second screen should be placed back of the tubes to protect other pieces of the apparatus.

The general procedure consists in dissolving a weighed amount of the compound in a suitable solvent such as glacial acetic acid, methyl chloride, ethyl chloride, or carbon tetrachloride. The solution is placed in tube *H*, and such an amount is used that the same hydrostatic head is obtained as when the 2% potassium iodide solution was used in both tubes *H* and *J*. Usually both tubes *H* and *I* are surrounded by cooling baths. The ozonizer is started and the gases by-passed through the destroyer for about 5 minutes while the apparatus is attaining equilibrium. The ozonized oxygen is then passed through the solution of the compound for the calculated time. Since all organic compounds do not absorb ozone rapidly enough for a quantitative absorption it is frequently necessary to run the ozonization longer. The presence of unsaturation may often be detected by testing a small portion of the reaction mixture with a dilute solution of bromine in carbon tetrachloride. The ozonization is continued until the test with the bromine solution is negative.

It is also possible to place a solution of the compound in tube *H* to the proper height and use a 2% potassium iodide solution in tube *J*. At the end of the calculated time the contents of tube *J* are titrated in order to determine the amount of ozone that failed to react with the compound. From these data the additional time necessary to complete the ozonization is calculated and the apparatus operated accordingly (Note 14) and (Note 15).

The procedures for the decomposition of the ozonide and separation of the reaction products will vary according to the nature of the compounds and must be designed and selected accordingly.

Selective ozonization of compounds containing different types of unsaturated linkages is possible by choosing a proper concentration of ozone and by stopping the ozonization at the right time. It is for this reason that the calibration described above is carried out, since for certain ozonizations it is important to have the correct concentration for best results.

1. *Use of air in place of oxygen*. When air is the source of oxygen the exit gases from the Berthelot tubes contain lower percentages of ozone than when pure oxygen is used. The gases also contain small amounts of nitric anhydride,[2] the presence of which may cause some side reactions to occur. However, a considerable number of compounds may be satisfactorily ozonized with air as the source of oxygen. The above apparatus will operate satisfactorily with compressed air. It is essential to bubble the compressed air through three 5-l. flasks half filled with concentrated sulfuric acid before passing the air into the purification train *B, C, D, E, F, G*. Some data on the production of ozone from air at a secondary potential of 10,000 volts are given in Table III.

TABLE III PRODUCTION OF OZONE FROM AIR AT SECONDARY VOLTAGE OF 10,000

	Rate of Flow	
	15.3 l./hr.	21.8 l./hr.
Ozone, % by volume	3.0	2.9
Hours for production of 0.1 mole ozone	4.8	3.4
N_2O_5, % by volume	0.13	0.08
Moles HNO_3 formed per 0.1 mole ozone	0.009	0.006

At higher secondary voltages the percentage of nitrogen pentoxide rises. A decrease in the rate of flow also increases the amount of nitrogen pentoxide. It is obvious from the data in Table III that the amounts of nitrogen pentoxide are very small and need to be considered only when examining a reaction mixture for small amounts of by-products or when the presence of this oxide of nitrogen would act as a catalyst for the oxidation of the organic compounds by oxygen or ozone.

2. Notes

1. If necessary, the rubber connecting tubes in the purification train may be protected by painting them with molten paraffin wax.
2. Berthelot tubes constructed of Pyrex may fail to produce ozone or may give a low yield.[3] However, Henne and Perilstein[4] have described a satisfactory ozonizer constructed of Pyrex glass.
With Pyrex tubes, voltages of 14,000–18,000 volts are needed. The power consumption is 15–25 watts per tube. The gap should be 1.5–2.00 mm.; this may be obtained through the use of 22-mm. o.d. and 28-mm. o.d. Pyrex tubing. The transformer which is recommended (E. O. Brimm and G. A. Cook, private communication) for use with Pyrex equipment is catalog No. 969-001-395, 15,000 volts, 30 M.A., of the Jefferson Electric Company.
3. Some form of cooling is necessary. The equipment described here involves the use of a cooling coil in the inner tubes. It is also possible to cool the entire unit by means of a copper cooling coil inserted in the outer bath. When the latter

method is used, the inner tubes are not cooled and the outer bath is grounded. This is reported to be a less hazardous method of operation (E. O. Brimm and G. A. Cook).

4. Mercury cup seals have been recommended in the past, but satisfactory results have been obtained with ground joints lubricated with a very small amount of 85% phosphoric acid. It is also possible to use Tygon connections with the tube ends butted together. If ground-glass connections are used the inlet and outlet tubes should be bent to facilitate union. .htmFigure 25 shows top and side views of such Berthelot tubes. The holes in the wooden supports should be large enough to permit the tubes to fit loosely.

Fig. 25.

Fig. 25.

5. Any large commercial laboratory battery jar is suitable. The Exide types F-9 or F-11 are satisfactory.

6. The dimensions of these wooden supports will be determined by the battery jar. The position of the holes and slots should be arranged so that the tubes may be spaced at convenient distances as shown in .htmFig. 23.

7. The submitters used a transformer purchased from the Franklin Transformer Company, Minneapolis, Minnesota. It was provided with taps so that secondary voltages of 5500, 6600, 7700, 8800, 9900, and 11,000 could be obtained. These transformers do not always deliver the rated voltage and hence should be calibrated by actual measurement. The checkers used a luminous tube transformer obtained from the Jefferson Electric Company, Bellwood, Illinois, catalog No. 721-411. Cap. 825 V.A. Primary 115 V.A.C. 60 cycles. Secondary 15,000 volts, 60 M.A. The variable transformer used to regulate the voltage should be rated at 7.5 amperes.

8. It may make a difference which side of the transformer is grounded, depending on the construction of the transformer; the maker of the transformer should be queried on this point.

9. The reaction flask *H* can be made of different sizes depending on the amount of solution being ozonized. The dimensions of the parts in .htmFig. 24 are not critical; any tubes and stopcocks of convenient size are suitable.

10. Many reagents act as contact catalysts for the destruction of ozone; a study of some of them has been made.[5]

11. A wet gas meter such as No. S-39465, E. H. Sargent and Company, is satisfactory. This meter need not be a permanent part of the apparatus. It is used only to calibrate the flowmeter.

12. In order that the flowmeter may be used during an ozonization when tube *J* is empty it is necessary to mark the heights of liquid on both tubes. The same liquid head (height × density) must be present in the absorption tubes during calibration and ozonization. For very accurate work a pressure regulator should be incorporated in the oxygen train and a gas meter made part of the set-up. For ordinary preparative work, however, these are not necessary.

13. If a transformer with taps is used the voltage chosen is determined by each tap. With a luminous tube transformer and Variac, a voltmeter is connected

across the primary of the transformer. Since these transformers have a fixed ratio of primary to secondary windings, the secondary voltage will be nearly proportional to the impressed primary voltage. Thus a transformer designed to deliver 15,000 volts with a primary voltage of 115 volts will deliver approximately 12,000 volts when the primary voltage is 4/5 of 115 or 92 volts.

14. It is evident that for ordinary preparative work the careful calibration given in section G is not essential. It is only necessary to adjust the voltage of the transformer to about 10,000 to 11,000 volts and turn on the flow of oxygen to as rapid a rate as the absorption tubes will handle when surrounded by cooling baths. The amount of ozone produced in 5 minutes at the observed flowmeter reading is determined as in section F. By operating the ozonizer at this rate of flow and voltage the ozonization of organic compounds can be carried out.

15. The ozonizer may be operated at higher rates of flow of oxygen than shown in Tables I and II, provided that the organic compound reacts with ozone at a reasonably rapid rate. Some data on high rates of flow are given in Table IV.

TABLE IV Production ofOzonefromOxygenatHighRates ofFlow andSecondaryVoltage of10,000

Rate, l./hr.	*%* *Ozone* (by volume)	*Hours to Produce 0.1 Mole Ozone*
27	4.7	1.76
32	4.5	1.55
45	4.1	1.23

16. A laboratory ozonizer is manufactured by the Welsbach Corporation, Philadelphia, Pennsylvania.

3. Discussion

Ozone for laboratory use has always been prepared by the action of a silent electric discharge upon a stream of air or oxygen. Although dielectrics other than glass are used in commercial ozonizers, they do not give a percentage of ozone high enough for laboratory use, and practically all laboratory ozonizers employ the Berthelot tube and are modeled after the one originally constructed by Harries.[6] Good ozonizers of this type have been described by Briner, Patry, and de Luserna,[7] and by Church, Whitmore, and McGrew.[8] The ozonizer described above is a modification of the one described by Smith,[9] as improved by Henne,[10] and by Smith and Ullyot[3] and Greenwood.[11] Henne and Perilstein[4] described a modification of their ozonizer in which the inner electrode is a tube filled with mercury; the outer electrode is water-cooled. More recently a 4% concentration of ozone has been prepared using a compressed-air-cooled inner electrode.[12] Ozone has also been produced in good concentrations (over 12%) by electrolysis methods.[13]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 403

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

soda lime

oxide of nitrogen

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

sodium hydroxide (1310-73-2)

nitric acid (7697-37-2)

lead (7439-92-1)

bromine (7726-95-6)

oxygen (7782-44-7)

carbon tetrachloride (56-23-5)

potassium iodide (7681-11-0)

sodium thiosulfate (7772-98-7)

mercury (7439-97-6)

methyl chloride (74-87-3)

iodine (7553-56-2)

acetone (67-64-1)

phosphoric acid (7664-38-2)

ozone (10028-15-6)

nitric anhydride, nitrogen pentoxide

ethyl chloride (75-00-3)

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Organic Syntheses, CV 3, 685

PALLADIUM CATALYSTS

$$Na_2PdCl_4 + CH_2O + NaOH \longrightarrow Pd + HCOONa$$

$$PdCl_2 + H_2 \longrightarrow \begin{array}{ll} Pd\text{-}BaSO_4 & (5\%\ Pd) \\ Pd\text{-}C & (5\%\ Pd) \\ Pd\text{-}C & (10\%\ Pd) \\ PdCl_2\text{-}C & (5\%\ Pd) \end{array}$$

Submitted by Ralph Mozingo
Checked by Homer Adkins and James E. Carnahan.

1. Procedure

(Note 1)

A. *Palladium on barium sulfate catalyst* (5% *Pd*). A solution (Note 2) of 8.2 g. of palladium chloride (0.046 mole) in 20 ml. (0.24 mole) of concentrated hydrochloric acid and 50 ml. of water is prepared. To a rapidly stirred, hot (80°) solution of 126.2 g. (0.4 mole) of reagent barium hydroxide octahydrate in 1.2 l. of distilled water contained in a 4-l. beaker (Note 3) and (Note 4) is added all at once 120 ml. (0.36 mole) of 6 *N* sulfuric acid. More 6 *N* sulfuric acid is added to make the suspension just acid to litmus (Note 5). To this hot barium sulfate suspension (Note 6) are added the palladium solution and 8 ml. (0.1 mole) of 37% formaldehyde solution. The suspension is then made slightly alkaline to litmus with 30% sodium hydroxide solution, constant stirring being maintained. The suspension is stirred 5 minutes longer, and then the catalyst is allowed to settle (Note 7). The clear supernatant liquid is decanted and replaced by water, and the catalyst is resuspended. The catalyst is washed by decantation eight to ten times. After the final decantation, the catalyst is collected on a 90-mm. medium-porosity sintered-glass funnel (Note 8). Most of the water is removed from the cake, but not enough to cause the cake to break or channel. The filter cake is washed with 250 ml. of water in five portions, the last being removed as completely as possible by filtration. The funnel and its contents are then placed in an oven at 80° until the catalyst is dry. The catalyst (93–98 g.) is powdered and stored in a tightly closed bottle (Note 9).

B. *Palladium on carbon catalyst* (5% *Pd*). A suspension of 93 g. of nitric acid-washed Darco G-60 (Note 10) in 1.2 l. of water contained in a 4-l. beaker (Note 3) and (Note 4) is heated to 80°. To this is added a solution of 8.2 g. (0.046 mole) of palladium chloride in 20 ml. (0.24 mole) of concentrated hydrochloric acid and 50 ml. of water (Note 2). Eight milliliters (0.1 mole) of 37% formaldehyde solution is added. The suspension is made slightly alkaline to litmus with 30% sodium hydroxide solution,

constant stirring being maintained. The suspension is stirred 5 minutes longer. The catalyst is collected on a filter and washed ten times with 250-ml. portions of water. After removal of as much water as possible by filtration, the filter cake is dried (Note 11), first in air at room temperature, and then over potassium hydroxide in a desiccator. The dry catalyst (93–98 g.) is stored in a tightly closed bottle.

C. *Palladium chloride on carbon* (5% *Pd*). A solution of 8.2 g. (0.046 mole) of palladium chloride in 20 ml. (0.24 mole) of concentrated hydrochloric acid and 50 ml. of water is prepared (Note 2). The solution is diluted with 140 ml. of water and poured over 92 g. of nitric acid-washed Darco G-60 (Note 10) in an 8-in. evaporating dish (Note 3). After the palladium chloride solution has been thoroughly mixed with the carbon, the whole mixture is dried, first on a steam bath and then in an oven at 100°, with occasional mixing until completely dry. The mass (98–100 g.) is powdered and stored in a closed bottle.

The required quantity of palladium chloride on carbon is transferred to a hydrogenation bottle and reduced with hydrogen in the solvent to be used for the hydrogenation (Note 12) and (Note 13). When no more hydrogen is absorbed by the catalyst, it is collected (Note 14) on a sintered-glass funnel and washed with more of the solvent to remove the hydrogen chloride, and then returned to the reduction bottle, the last being washed in with the solvent. The material to be hydrogenated is then added and the hydrogenation is completed in the usual way.

D. *Palladium on carbon catalyst* (10% *Pd*). A solution of 8.33 g. of palladium chloride in 5.5 ml. of concentrated hydrochloric acid and 40 ml. of water is prepared by heating the mixture on a steam bath (Note 2) and (Note 15). The resulting solution is poured into a solution of 135 g. of sodium acetate trihydrate in 500 ml. of water contained in a 1-l. reduction bottle (Note 16). Forty-five grams of Norit (Note 10) is added, and the mixture is hydrogenated until absorption ceases after 1–2 hours. The catalyst is collected on a Büchner funnel and washed with 2 l. of water in five portions. The filter cake, after removal of most of the water, is dried in air and then in a desiccator over calcium chloride (Note 11). The catalyst (48–50 g.) is stored, after being powdered, in a tightly closed bottle.

2. Notes

1. The four procedures given for the preparation of palladium catalysts differ in that in A the support is barium sulfate or barium carbonate whereas in the others the support is carbon. In procedures A and B, alkaline formaldehyde is the reducing agent; in C and D, hydrogen is used. The catalysts A, B, and D are prepared and stored until required with the palladium in the reduced form ready for use. In C,[1] the palladium salt is reduced to the metal as needed, so that there is no loss of activity during storage. Catalyst A is similar to that usually recommended for Rosenmund reductions; D is essentially that developed by Hartung[2] and extensively used by Cope[3] and others. Catalyst D carries twice as

much palladium per unit weight as the others.

Catalysts reduced with formaldehyde carry no adsorbed hydrogen and are less pyrophoric. Barium carbonate as a support may sometimes be advantageous in that the neutrality of the hydrogenation mixture may be maintained. Barium sulfate or barium carbonate may be a better support than carbon, which may, in some instances, so strongly adsorb the derived product that recovery is difficult or incomplete. Palladium may be more completely and easily recovered from a spent catalyst where carbon rather than barium sulfate is the support. In general, the submitter prefers a catalyst prepared according to procedure C.

2. Since palladium chloride dissolves rather slowly in aqueous acid, the mixture is heated on a steam bath for about 2 hours, or until solution is complete. If the dihydrate of palladium chloride is used the quantity should be increased to 9.9–10.0 g.

3. The entire preparation is carried out with all-glass or porcelain equipment in order to prevent contamination with iron or other metals.

4. The catalyst may be prepared in ten times the amount given here, with a 20-l. battery jar in place of the beaker.

5. The rapid addition of sulfuric acid is made to give finely divided barium sulfate.

6. An equal weight of precipitated barium carbonate (93 g.) may be substituted for the barium hydroxide and sulfuric acid to give a palladium on barium carbonate catalyst. The amount of hydrochloric acid should then be reduced to 8.2 ml.

7. After 5 minutes, the solution is colorless and free of palladium chloride.

8. A Büchner funnel may be used, but filtration through paper is very slow. The washing process may be carried out by centrifugation instead of filtration.

9. The palladium may be conveniently separated from the barium sulfate by solution in aqua regia. The used catalyst is collected from the reaction mixture on a sintered-glass funnel. The organic material is removed with suitable solvents, and the solvents are replaced by water. The palladium is dissolved in aqua regia and is washed out with dilute hydrochloric acid, the solutions being collected for recovery of the metal. For recovery of the palladium from carbon, the mass is ignited and the ash is extracted with aqua regia for several hours. The palladium solution is filtered, and any residue is reignited and then treated with alkaline formaldehyde solution to reduce any oxides of palladium which may have been formed, and which are only slowly soluble in aqua regia. The solids are collected on a filter, and the palladium is extracted with aqua regia.

10. Norit, Darco, or other carbons may be used. The carbon is heated on a steam bath with 10% nitric acid for 2–3 hours, washed free of acid with water, and dried at 100–110° before use.

11. The palladium on carbon catalysts should be dried at room temperature or the carbon may ignite. These catalysts are first dried in air and then over potassium hydroxide (or calcium chloride) in a desiccator.

12. The solvent is conveniently that in which the hydrogenation is to be done.

During the reduction of the palladium chloride, a neutral solvent is to be preferred; any acid or alkali needed for the hydrogenation is added after reduction of the catalyst.

13. The presence of hydrogen chloride during the hydrogenation of many organic compounds is desirable or without effect, so that the washing operations may be omitted in such cases. Thus, the palladium chloride on carbon may be used in the same manner as the prereduced catalysts, i.e., simply added before reduction to the solvent and the hydrogen acceptor.

14. The catalyst should be kept wet with the solvent during the washing process, as it is pyrophoric.

15. The resulting solution is approximately equivalent to 50 ml. of the commercial palladium chloride solution (p. 385) suggested by Hartung and Cope.[3]

16. The checkers reduced the palladium chloride, in three batches, in a 500-ml. bottle. The bottle was not shaken, but the contents were rapidly stirred under a pressure of 1.1 atmospheres of hydrogen. The reduction of each batch required about 5 hours.

3. Discussion

Palladium catalysts have been prepared by fusion of palladium chloride in sodium nitrate to give palladium oxide;[4,5] by reduction of palladium salts by alkaline formaldehyde[6,7,8] or sodium formate,[9] by hydrazine,[10] and by the reduction of palladium salts with hydrogen.[11] The metal has been prepared in the form of palladium black,[6,9] and in colloidal form in water containing a protective material,[10] as well as upon supports. The supports commonly used are asbestos[12] barium carbonate,[13] barium sulfate,[1,7,8,14] calcium carbonate,[15] carbon,[1,11,14,16] kieselguhr,[14,16] silica-gel,[17] and strontium carbonate.[18] The catalysts described here are prepared by modifications of the methods of Schmidt,[8] Rosenmund and Langer,[14] Mannich and Thiele,[11] and Hartung.[2,3]

Polyvinyl alcohol[19] and aluminum oxide[20] have been used as supports for palladium catalysts.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 385
- Org. Syn. Coll. Vol. 3, 626
- Org. Syn. Coll. Vol. 4, 408
- Org. Syn. Coll. Vol. 4, 536
- Org. Syn. Coll. Vol. 4, 887
- Org. Syn. Coll. Vol. 5, 989

References and Notes

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2. Hartung, *J. Am. Chem. Soc.*, **50**, 3373 (1928).
3. Alexander and Cope, *J. Am. Chem. Soc.*, **66**, 886 (1944).
4. Shriner and Adams, *J. Am. Chem. Soc.*, **46**, 1683 (1924).
5. *Org. Syntheses* Coll. Vol. **1**, 470 (1941).
6. Willstätter and Waldschmidt-Leitz, *Ber.*, **54**, 123 (1921).
7. Houben, *Die Methoden der organischen Chemie*, 3rd ed., Vol. II, p. 500, Verlag Georg Thieme, Leipzig, 1930.
8. Schmidt, *Ber.*, **52**, 409 (1919).
9. Zelinsky and Glinka, *Ber.*, **44**, 2309 (1911).
10. Paal and Amberger, *Ber.*, **37**, 124 (1904).
11. Mannich and Thiele, *Ber. deut. pharm. Ges.*, **26**, 36 (1916).
12. Zelinsky and Borisoff, *Ber.*, **57**, 150 (1924); Zelinsky and Turowa-Pollak, *Ber.*, **58**, 1295 (1925).
13. Harris, Stiller, and Folkers, *J. Am. Chem. Soc.*, **61**, 1242 (1939).
14. Rosenmund and Langer, *Ber.*, **56**, 2262 (1923).
15. Busch and Stöve, *Ber.*, **49**, 1063 (1916).
16. Sabalitschka and Moses, *Ber.*, **60**, 786 (1927).
17. Fester and Brude, *Ber.*, **56**, 2247 (1923).
18. Martin and Robinson, *J. Chem. Soc.*, **1943**, 491.
19. Kavanagh and Nord, *J. Am. Chem. Soc.*, **66**, 2126 (1944).
20. U. S. pat. 2,366,409 [*C. A.*, **39**, 2001 (1945)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

palladium black

dihydrate of palladium chloride

oxides of palladium

Polyvinyl alcohol

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrogen chloride, hydrochloric acid (7647-01-0)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

formaldehyde (630-08-0)

iron (7439-89-6)

nitric acid (7697-37-2)

calcium carbonate (471-34-1)

barium sulfate (7727-43-7)

carbon, Norit (7782-42-5)

potassium hydroxide (1310-58-3)

palladium (7440-05-3)

barium hydroxide (17194-00-2)

barium carbonate (513-77-9)

barium hydroxide octahydrate (12230-71-6)

hydrazine (302-01-2)

sodium formate

sodium nitrate

palladium oxide

palladium chloride

aluminum oxide (1344-28-1)

sodium acetate trihydrate (6131-90-4)

strontium carbonate (1633-05-2)

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Organic Syntheses, *CV 3*, *690*

PENTAACETYL *d*-GLUCONONITRILE

[Gluconpremonitrile, D-, pentaacetate]

Submitted by H. T. Clarke and S. M. Nagy.
Checked by W. E. Bachmann and Wayne Cole.

1. Procedure

To 350 ml. of anhydrous methanol contained in a 1-l. three-necked round-bottomed flask, to which is attached a reflux condenser protected by a drying tube, is added 20 g. (0.87 gram atom) of sodium (Note 1) in large pieces. The reaction is kept under control by cooling the flask in a pan of ice water. To the resulting solution of sodium methoxide is added a solution (Note 2) of 61 g. of hydroxylamine hydrochloride (0.88 mole) in 20 ml. of water; during the addition the mixture is swirled in order to avoid spattering. After 20 minutes the mixture is cooled to 0° and filtered with suction. The sodium chloride is washed with 350 ml. of anhydrous methanol. The combined filtrate and washings are warmed to 65° in a 3-l. round-bottomed flask, and a solution of 100 g. of finely powdered commercial crystalline glucose monohydrate (0.50 mole) in 200 ml. of warm 25% aqueous methanol is added, with stirring. The resulting solution is held at 65° for 2 hours and then concentrated under reduced pressure until no further distillate is obtained; the residue weighs 155–160 g. The resulting syrup (Note 3) is diluted with 300 ml. of methanol and again distilled, and this process is repeated once (Note 4).

A mixture of 100 g. of powdered, anhydrous sodium acetate and 677 ml. of 90% acetic anhydride (Note 5) is heated on a steam bath in a 3-l. round-bottomed flask under an efficient reflux condenser. Without interrupting the heating a solution of the syrupy glucose oxime in 50 ml. of glacial acetic acid and 100 ml. of cold acetic anhydride is added through a dropping funnel to the hot mixture (Note 6); this requires about 1 hour (Note 7). Heating is continued for another hour, and the bulk (380–420 ml.) of the acetic acid and any unchanged acetic anhydride is distilled under reduced pressure from a water bath. The residue is immediately stirred into 2 l. of cold water, stirred occasionally during the first 3 hours, and allowed to stand overnight.

After the mixture has been chilled to 0°, the brown, crystalline mass is filtered with suction and washed with 500 ml. of water. The solid is dissolved in 300 ml. of hot 95% ethanol, and the solution is heated with 10–15 g. of Norit for 5 minutes and filtered with suction. The filtrate is gradually cooled to 0°; the crystals are filtered with suction and washed with 20 ml. of cold ethanol. The weight of the first crop is 90–93 g. A second crop is obtained by concentrating the mother liquor under reduced pressure to 25 ml., boiling the solution with Norit, filtering, and chilling the filtrate to

0°. The total yield of colorless pentaacetyl *d*-gluconomitrile melting at 82.5–83.5° is 95–96 g. (50%).

2. Notes

1. In preparing free hydroxylamine, a little less than the theoretical amount of sodium is employed to avoid the presence of free alkali in the reaction mixture.
2. The hydroxylamine hydrochloride dissolves in the small amount of water when the mixture is warmed to about 125°.
3. The isolation of glucose oxime is unnecessary in this preparation.
4. The distillation with methanol serves to remove water almost completely.
5. If acetic anhydride of a higher concentration is available, correspondingly smaller quantities may be employed.
6. The viscous, syrupy glucose oxime dissolves with difficulty, and it may be necessary to warm the mixture slightly. If this is done, a pan of ice water should be at hand in order to cool the mixture should the temperature begin to rise rapidly.
7. In the process described in the literature, the oxime, sodium acetate, and acetic anhydride are allowed to react without dilution, a condition which frequently leads to an uncontrollably violent reaction.

3. Discussion

The above method for preparing glucose oxime is the modification of that of Jacobi[1] developed by Wohl,[2] who first converted the oxime into the pentaacetyl gluconomitrile by means of acetic anhydride. The latter reaction was later employed for the same purpose by Zemplén and Kiss.[3]

Pentaacetyl gluconomitrile has also been prepared by dehydration of pentaacetyl gluconamide with phosphorus oxychloride.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 101

References and Notes

1. Jacobi, *Ber.*, **24**, 696 (1891).
2. Wohl, *Ber.*, **26**, 730 (1893).
3. Zemplén and Kiss, *Ber.*, **60**, 165 (1927).
4. Ladenburg, Tischler, Wellman, and Babson, *J. Am. Chem. Soc.*, **66**, 1217 (1944).

Appendix

Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

acetic acid (64-19-7)

methanol (67-56-1)

acetic anhydride (108-24-7)

sodium acetate (127-09-3)

sodium chloride (7647-14-5)

sodium methoxide (124-41-4)

Norit (7782-42-5)

Phosphorus Oxychloride (21295-50-1)

sodium (13966-32-0)

Hydroxylamine hydrochloride (5470-11-1)

hydroxylamine (7803-49-8)

glucose monohydrate (14431-43-7)

pentaacetyl glucononitrile, PENTAACETYL d-GLUCONONITRILE

Glucononitrile, D-, pentaacetate (6272-51-1)

glucose oxime

pentaacetyl gluconamide

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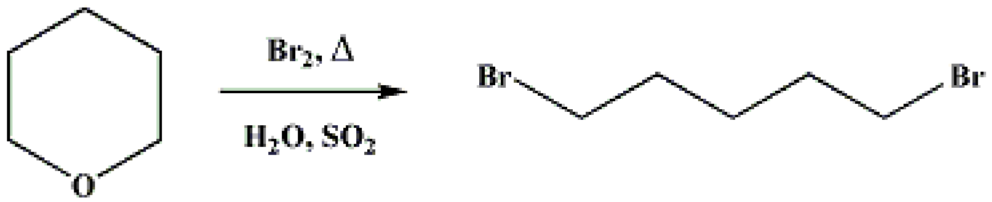
Organic Syntheses, CV 3, 692

PENTAMETHYLENE BROMIDE

[Pentane, 1,5-dibromo-]



Submitted by D. W. Andrus
Checked by Nathan L. Drake and Charles M. Eaker.

1. Procedure

A hydrobromic acid solution [*Org. Syntheses* Coll. Vol. **1**, 26 (1941)] is prepared in a 500-ml. round-bottomed flask by passing sulfur dioxide into a mixture of 120 g. (37.7 ml., 0.75 mole) of bromine, 50 ml. of water, and 150 g. of crushed ice. This is equivalent to a mixture of 253 g. (1.5 moles) of 48% hydrobromic acid and 74 g. of concentrated sulfuric acid. To the mixture 21.5 g. (0.25 mole) of tetrahydropyran (p. 794) is added, a reflux condenser is attached to the flask, and the light-brown homogeneous mixture is refluxed for 3 hours (Note 1).

The heavy lower layer is separated (Note 2), washed once with a saturated solution of sodium bicarbonate and once with water, and then dried over 4–5 g. of anhydrous calcium chloride. The crude product is decanted from the calcium chloride, and the drying agent is rinsed once or twice with a small quantity of ethyl bromide which is added to the main product. The mixture is distilled under reduced pressure, and the pentamethylene bromide, which weighs 46–47 g. (80–82%), is collected at 104–106°/19 mm.

2. Notes

1. The submitter refluxed the mixture for 10 hours, but the checkers obtained equally good yields in 3 hours.
2. The upper aqueous layer contains considerable unchanged hydrobromic acid. If this layer is distilled, about 150 g. (0.9 mole) of constant-boiling hydrobromic acid (b.p. 123–124°/748 mm.) may be recovered.

3. Discussion

The methods of preparing pentamethylene bromide are given in *Org. Syntheses* Coll. Vol. **1**, 428 (1941), where the preparation of the dihalide from benzoylpiperidine and phosphorus pentabromide is described in detail. The procedure given above is based

upon the work of Paul.[1]

References and Notes

1. Paul, *Bull. soc. chim. France*, (4) **53**, 1489 (1933).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

sodium bicarbonate (144-55-8)

HYDROBROMIC ACID (10035-10-6)

bromine (7726-95-6)

sulfur dioxide (7446-09-5)

Ethyl bromide (74-96-4)

Benzoylpiperidine (776-75-0)

pentamethylene bromide, Pentane, 1,5-dibromo- (111-24-0)

Tetrahydropyran (142-68-7)

phosphorus pentabromide (7789-69-7)

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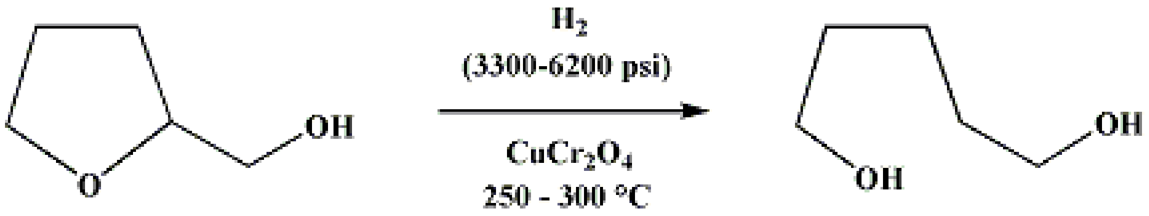
Organic Syntheses, CV 3, 693

1,5-PENTANEDIOL



Submitted by Daniel Kaufman and Wilkins Reeve.
Checked by Homer Adkins and Harry Billica.

1. Procedure

Five hundred and ten grams (5 moles) of pure tetrahydrofurfuryl alcohol (Note 1) and 50 g. of copper chromite (Note 2) are placed in a hydrogenation bomb having a void of 1.4 l. (Note 3). The bomb, in a suitable rocker assembly, is filled with hydrogen to a pressure of 3300 to 3500 lb. per sq. in. (Note 4). The bomb is rocked and heated. *The pressure must not at any time be allowed to go much above* 6000 *lb. per sq. in.* If the pressure rises higher than 6200 lb., the heating of the bomb should be stopped (Note 5). In a typical run, the pressure reaches a maximum of about 6100 lb. at 255° after 2 hours. The pressure then slowly falls to about 4400 lb. during another hour, as the temperature rises to a little over 300°. During the ensuing 6 hours, the pressure falls to about 3000 lb. while the temperature is held at 300–310°.

The bomb is allowed to cool to room temperature, where the pressure should be 1000–1100 lb. The contents of the bomb are poured into a beaker, and the bomb is rinsed twice with 100-ml. portions of acetone. The catalyst is removed by centrifuging, and the reaction mixture is distilled through a fractionating column (Note 6). A fraction boiling in the range 60–140°, containing α-methyltetrahydrofuran, water, and *n*-amyl alcohol, is distilled at atmospheric pressure (Note 7). Tetrahydrofurfuryl alcohol (80–110 g.) is recovered, boiling at 65–70°/10 mm.; the 1,5-pentanediol boiling at 118–120°/6 mm. is obtained in amounts varying from 200 g. to 244 g. The yield is 40–47% of the theoretical, without allowance being made for the recovered tetrahydrofurfuryl alcohol. The residue of products boiling above the glycol amounts to 25–35 g.

2. Notes

1. The tetrahydrofurfuryl alcohol available from the Quaker Oats Company, or the practical grade from the Eastman Kodak Company, has been used. If the material available does not hydrogenate satisfactorily, it may be purified by hydrogenation over Raney nickel at 150°/100–200 atm. pressure. A sample of good quality boils at 177–178°/740 mm. and does not become dark-colored when a few milliliters are shaken with 1 drop of concentrated sulfuric acid at room temperature.

2. The catalyst is prepared as described in Note 11 for the preparation of copper chromite.[1]

3. The hydrogenation bomb supplied under catalog No. 406–21, by the American Instrument Company, Silver Spring, Maryland, is satisfactory. The internal volume of the empty bomb should be at least 2.7 times that of the volume of tetrahydrofurfuryl alcohol added, as otherwise not enough hydrogen can be added for the completion of the reaction, without the use of excessively high pressures. The submitters maintained the pressure above 5500 lb. per sq. in. by intermittently adding hydrogen.

4. Temperatures higher than about 300° and pressures higher than 6000 lb. per sq. in. should not be used in the vessels and with the gauges ordinarily supplied for "high-pressure" hydrogenations. *Only clean equipment, in first-class condition, and under careful control, can be used safely and successfully in carrying out reactions under the conditions described*.

5. If hydrogenolysis does not occur, the pressure would be about 7000 lb. when a temperature of 300° is reached. If the pressure rises above 6200, starting with 3500 lb. at room temperature, it is evident that the quality of the catalyst or the alcohol is not satisfactory. Further attempts to prepare the glycol should be made with alcohol and catalyst of better quality, or starting with a pressure sufficiently low (3000 lb.) so that a safe operating pressure will not be exceeded.

6. A Vigreux-type column 60 cm. in length and 2 cm. in outside diameter was used for the fractionation. The submitters state that they have also used a column of similar dimensions, packed with glass helices, for a fractionation at atmospheric pressure. They recommended the Vigreux column under reduced pressure, as used by the checkers.

7. When acetone was not used for washing out the bomb, a fraction weighing 70–75 g. was obtained by the submitters. After drying over anhydrous potassium carbonate, they obtained, by fractional distillation, 3–6 g. of α-methyltetrahydrofuran, b.p. 80–81°, and 23–28 g. of *n*-amyl alcohol, b.p. 137–138°. The alcohol obtained was pure, and neither secondary amyl nor butyl alcohols could be detected.

3. Discussion

1,5-Pentanediol has been prepared by the reduction of methyl[2,3] or ethyl[4] glutarate, of 2,3-dihydropyran,[5] of δ-hydroxyvaleraldehyde,[6,7,8,9,10] and of furfural.[11] It has also been prepared from pentamethylene bromide by conversion to the diacetate and subsequent hydrolysis.[12] The procedure described is a modification of that of Connor and Adkins.[13]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 746

References and Notes

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2. Wojcik and Adkins, *J. Am. Chem. Soc.*, **55**, 4939 (1933).
3. Bennett and Reynolds, *J. Chem. Soc.*, **1935**, 138.
4. Adkins and Billica, *J. Am. Chem. Soc.*, **70**, 3121 (1948).
5. U. S. pat. 2,440,929 [*C. A.*, **42**, 5466 (1948)].
6. Paul, *Bull. soc. chim. France*, (5) **1**, 978 (1934).
7. Schniepp and Geller, *J. Am. Chem. Soc.*, **68**, 1646 (1946).
8. Woods and Saunders, *J. Am. Chem. Soc.*, **68**, 2111 (1946).
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10. U. S. pat. 2,497,812 [*C. A.*, **44**, 6428 (1950)].
11. Brit. pat. 627,293 [*C. A.*, **44**, 2564 (1950)].
12. Bennett and Heathcoat, *J. Chem. Soc.*, **1929**, 273.
13. Connor and Adkins, *J. Am. Chem. Soc.*, **54**, 4678 (1932).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

hydrogen (1333-74-0)

Raney nickel (7440-02-0)

acetone (67-64-1)

pentamethylene bromide (111-24-0)

Furfural (98-01-1)

1,5-Pentanediol (111-29-5)

tetrahydrofurfuryl alcohol (97-99-4)

n-amyl alcohol (71-41-0)

COPPER CHROMITE

δ-hydroxyvaleraldehyde (4221-03-8)

α-methyltetrahydrofuran (96-47-9)

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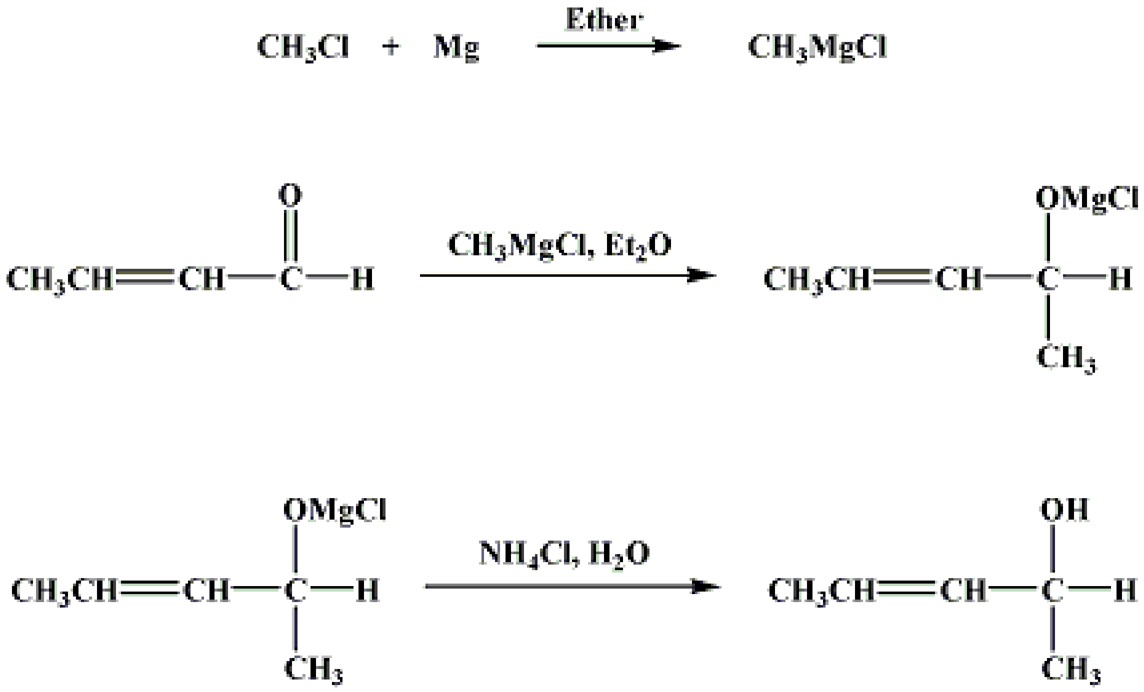
Organic Syntheses, CV 3, 696

3-PENTEN-2-OL



Submitted by E. R. Coburn
Checked by Homer Adkins, B. W. Winner, John Woods, R. F. McElwee, and Robert M. Ross.

1. Procedure

A 5-l. round-bottomed three-necked flask is equipped with a mechanical stirrer in a suitable seal (Note 1), a reflux condenser of the cold-finger type (Note 2) protected from moisture in the air by a drying tube, and a gas delivery tube extending nearly to the bottom of the flask. The flask is surrounded by an ice bath, and the cold finger is filled with solid carbon dioxide in acetone. Approximately 1.7 l. of dry ether and 61 g. (2.5 gram atoms) of magnesium are placed in the flask and cooled to about 0°. Methyl chloride (130 ml., 130 g., 2.6 moles) is condensed (Note 3) in a 250- to 300-ml. test tube held in a bath of solid carbon dioxide in acetone (Note 4). About 50 ml. of methyl chloride is allowed to distil from the test tube containing the methyl chloride through the gas delivery tube into the rapidly stirred mixture of ether and magnesium. The reaction mixture is then warmed until the reaction of methyl chloride and magnesium is under way. A crystal of iodine may be added if the reaction does not start readily. The methyl chloride is then allowed to distil into the reaction mixture during a period of about 3 hours. The reaction mixture and the tube containing the methyl chloride are cooled if the refluxing of the reaction mixture becomes so vigorous that the reflux condenser does not condense the methyl chloride. After all the methyl chloride has been added, the reaction mixture is warmed for 1 hour so that there is a gentle reflux.

At the end of this time, when almost all the magnesium has reacted, the Dry Ice cold

finger is replaced with a water condenser and the gas delivery tube with a dropping funnel. A solution of 142 g. (2.02 moles) of freshly distilled crotonaldehyde in 300 ml. of dry ether is added dropwise while the reaction mixture is stirred vigorously and cooled. The reaction mixture is allowed to stand at room temperature for 1 hour.

The Grignard addition compound is decomposed by adding 435 ml. of a saturated ammonium chloride solution (Note 5) dropwise, with vigorous stirring, to the thoroughly cooled reaction mixture. A dense white precipitate, too heavy to be stirred mechanically, forms and settles to the bottom of the flask. After the reaction mixture has been allowed to stand for 1 hour, the ether solution is poured off and the precipitate washed by decantation with two 300-ml. portions of ether.

The ether is removed by distillation, and the residual 3-penten-2-ol is distilled through a short column (Note 6) at atmospheric pressure. The yield of material boiling at 119–121° is 140–150 g. (81–86%). Pure 3-penten-2-ol boils at approximately 120°/740 mm.

2. Notes

1. A Hershberg type of stirrer is preferred. The submitter used a stirrer of tantalum with a mercury seal; the checkers used a Nichrome stirrer in a simple rubber seal.
2. The reflux condenser must be of very high capacity, as otherwise methyl chloride may be lost. The checkers used a cold-finger type of condenser in which the dimensions of the finger or container for the refrigerant were 30 cm. in length and 3 cm. in outside diameter. The glass jacket surrounding the finger was 4.5 cm. in outside diameter, but was drawn down to 1.3 cm. below the finger for convenience of insertion into one of the necks of the reaction flask.
3. Methyl chloride is led from a commercial cylinder to the bottom of the test tube used for measuring and storing the reagent. The tube is previously marked so that the desired volume (130 ml.) of methyl chloride may be readily measured.
4. The checkers also obtained equally good results with less effort by allowing a slow stream of dry methyl chloride to pass directly from the commercial cylinder into the reaction mixture until practically all the magnesium had reacted.
5. Hydrolysis of the Grignard complex with saturated ammonium chloride solution possesses the advantage that the resulting ethereal solution of the alcohol is neutral and sufficiently dry so that it need not be dried before distillation. The alcohol is dehydrated if it is distilled from a mixture containing even a trace of a mineral acid. Approximately 125 g. of ammonium chloride and 345 ml. of water are required for the saturated solution referred to above.
6. The submitter used a Hempel column. The checkers used a modified Widmer or Vigreux column, 1.3 cm. in diameter and 15 cm. in length.

3. Discussion

3-Penten-2-ol has been prepared by the addition of methylmagnesium iodide[1,2] or

bromide[3,4,5,6] to crotonaldehyde and by the partial dehydration of pentanediol,[7] and by the hydrolysis of 2-chloropentene-3.[8]

References and Notes

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7. Kyriakides, *J. Am. Chem. Soc.*, **36**, 996 (1914).
8. U. S. pat. 2,464,244 [*C. A.*, **43**, 4288 (1949)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ether (60-29-7)

ammonium chloride (12125-02-9)

magnesium (7439-95-4)

carbon dioxide (124-38-9)

methyl chloride (74-87-3)

iodine (7553-56-2)

acetone (67-64-1)

methylmagnesium iodide (917-64-6)

crotonaldehyde (123-73-9)

3-Penten-2-ol (1569-50-2)

pentanediol

2-chloropentene-3

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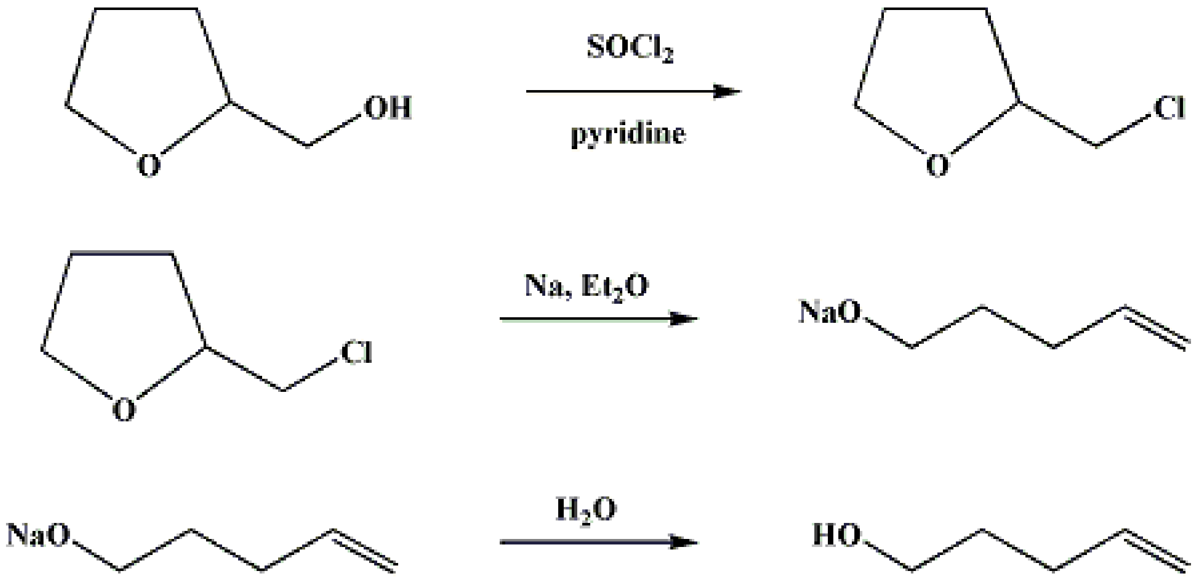
Organic Syntheses, CV 3, 698

4-PENTEN-1-OL



Submitted by L. A. Brooks and H. R. Snyder.
Checked by Nathan L. Drake and W. Mayo Smith.

1. Procedure

A. *Tetrahydrofurfuryl chloride.* In a 2-l. three-necked flask, fitted with a mechanical stirrer, a dropping funnel, and a thermometer, are placed 408 g. (4 moles) of freshly distilled tetrahydrofurfuryl alcohol (Note 1) and 348 g. (4.4 moles) of pyridine. To the rapidly stirred mixture, which is cooled in an ice bath, 500 g. (4.2 moles) of freshly distilled thionyl chloride (Note 1) is added from the dropping funnel at the rate of 3–5 drops per second. When one-third to one-half of the thionyl chloride has been added, a pasty crystalline mass begins to separate and the temperature begins to rise rapidly. The temperature should not be allowed to go above 60°. As more thionyl chloride is added the mass redissolves and a dark brown liquid forms. When the addition is complete, the bath is removed and the mixture is stirred for 3–4 hours. The liquid (or the slurry, if some crystallization has occurred) is poured into a beaker (Note 2) and extracted seven times with 500-ml. portions of ether (Note 3); the ether extracts are decanted and combined. The ether is removed by distillation, and the residue is washed three times with 100-ml. portions of water, dried over anhydrous magnesium sulfate, and distilled under reduced pressure. The yield of tetrahydrofurfuryl chloride boiling at 41–42° /11 mm. (47–48° /15 mm.) is 354–360 g. (73–75%).

B. *4-Penten-1-ol.* A 2-l. three-necked flask containing 112 g. (4.87 moles) of powdered sodium (Note 4) under 700 ml. of anhydrous ether is fitted with a mechanical stirrer, a separatory funnel, and a reflux condenser with a drying tube. A few milliliters (2–3) of a mixture of 300 g. (2.5 moles) of tetrahydrofurfuryl chloride and 300 ml. of anhydrous ether is added to the rapidly stirred suspension. A vigorous

reaction occurs, and the solution turns blue. The remainder of the solution of the chloride is then added dropwise over a period of 5 hours, during which time the flask is cooled in an ice bath (Note 5). When the addition is complete, stirring is continued for 2 hours. The suspension is decanted from any sodium that remains (Note 6) into a dry beaker and decomposed with sufficient ice water to give two liquid layers. The ether layer is separated and dried over magnesium sulfate. After the removal of the ether by distillation on a steam cone, the residue is distilled. The yield of 4-penten-1-ol boiling at 134–137° is 161–178 g. (76–83%).

2. Notes

1. Undistilled commercial thionyl chloride and Eastman practical tetrahydrofurfuryl alcohol may be used, but the yields are slightly lower (65–70%).
2. The checkers found it easier to separate the ethereal extract from the residue when the mixture was in a large separatory funnel.
3. The yield will be low if extraction is incomplete. It is advisable to stir with a heavy glass rod and break up any lumps that have formed.
4. The powdered sodium is prepared under hot xylene with the aid of a Hershberg stirrer; the xylene is decanted and replaced with ether.
5. The ice bath is not used until the reaction has definitely started.
6. Occasionally a little sodium is left on the bottom of the flask. This is destroyed with ethanol and the flask is washed with ice water.

3. Discussion

Tetrahydrofurfuryl chloride has been prepared from the alcohol and thionyl chloride[1] or phosphorus trichloride. 4-Penten-1-ol has been prepared from tetrahydrofurfuryl bromide or chloride and magnesium,[2,3] sodium,[4,5,6] sodium-potassium,[6] or lithium;[6] and by the reaction of allylmagnesium chloride with ethylene oxide, followed by hydrolysis.[7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 755
- Org. Syn. Coll. Vol. 6, 675

References and Notes

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2. Paul, *Bull. soc. chim. France*, (4) **53**, 424 (1933).
3. Robinson and Smith, *J. Chem. Soc.*, **1936**, 195.
4. Paul, *Bull. soc. chim. France*, (5) **2**, 745 (1935).
5. Gaubert, Linstead, and Rydon, *J. Chem. Soc.*, **1937**, 1971.

6. Paul and Normant, *Bull. soc. chim. France*, (5) **10**, 484 (1943).

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

tetrahydrofurfuryl bromide or chloride

ethanol (64-17-5)

ether (60-29-7)

thionyl chloride (7719-09-7)

magnesium (7439-95-4)

pyridine (110-86-1)

sodium (13966-32-0)

phosphorus trichloride (7719-12-2)

Ethylene oxide (75-21-8)

xylene (106-42-3)

tetrahydrofurfuryl alcohol (97-99-4)

lithium (7439-93-2)

magnesium sulfate (7487-88-9)

4-Penten-1-ol (821-09-0)

Tetrahydrofurfuryl chloride (3003-84-7)

sodium-potassium

Allylmagnesium chloride (2622-05-1)

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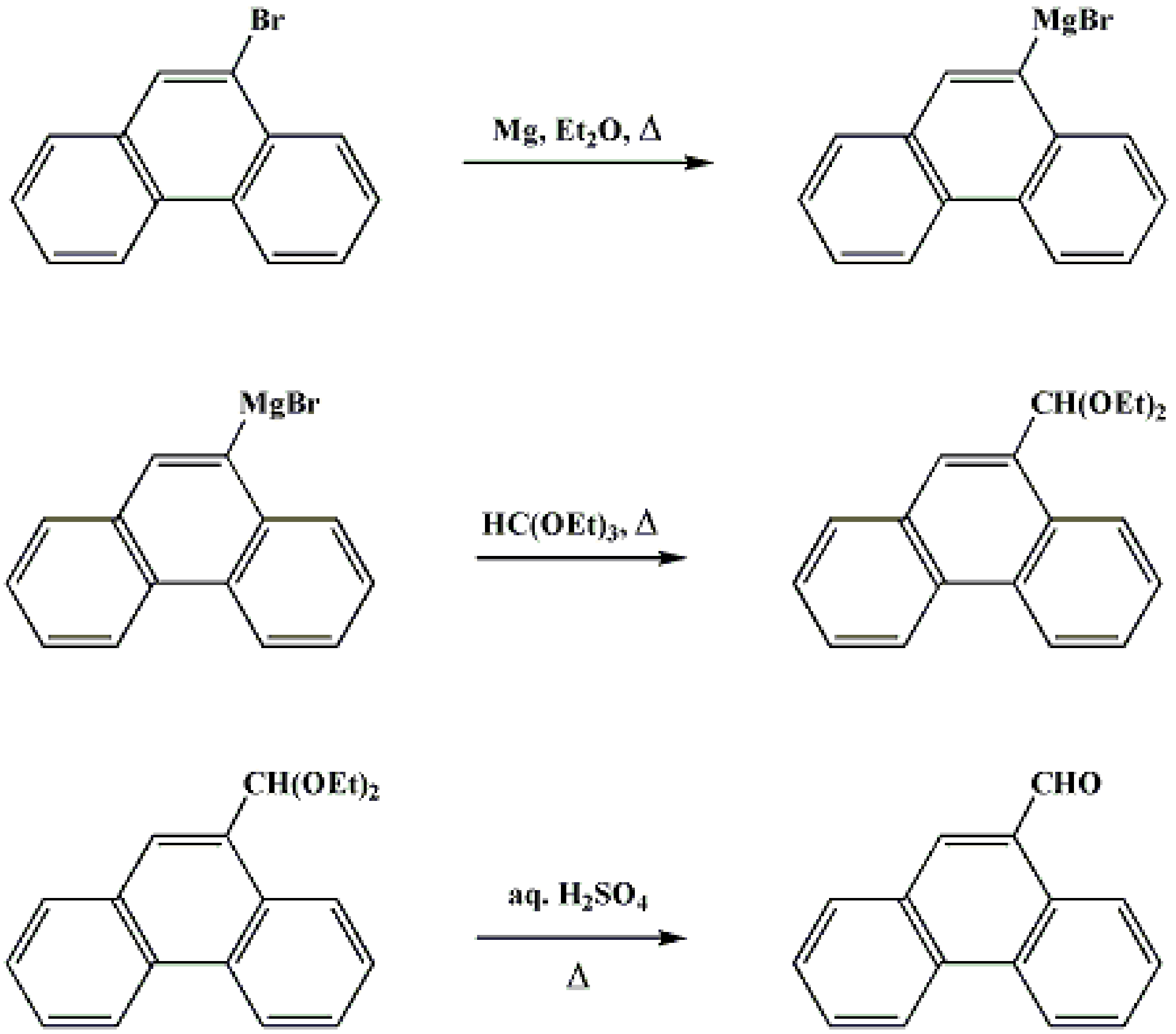
Organic Syntheses, CV 3, 701

PHENANTHRENE-9-ALDEHYDE

[9-Phenanthrenecarboxaldehyde]



Submitted by Clinton A. Dornfeld and George H. Coleman[1].
Checked by Robert E. Carnahan and Homer Adkins.

1. Procedure

A dry 5-l. three-necked flask is provided with a stirrer (Note 1), a nitrogen inlet tube, a 500-ml. Pyrex separatory funnel, and a large Allihn reflux condenser. To the upper end of the condenser are attached an outlet tube and a 1-l. separatory funnel. Both separatory funnels and the outlet tube are provided with calcium chloride drying tubes. To the flask is added 50.3 g. (2.07 gram atoms) of magnesium turnings (Note 2). Nitrogen gas, dried by bubbling through concentrated sulfuric acid, is passed in to displace the air in the flask. The nitrogen atmosphere is maintained until the hydrolysis of the Grignard addition product is completed. Five hundred and fourteen grams (2 moles) of crude 9-bromophenanthrene (p. 134) (Note 3) is melted and poured into the

Pyrex separatory funnel (Note 4). One liter of anhydrous ether (dried over sodium wire) is placed in the upper separatory funnel. About 200 ml. of the ether and 10 ml. of the melted bromophenanthrene are allowed to run into the reaction flask. The reaction of the bromophenanthrene with magnesium is initiated by the addition of a few crystals of iodine and 1 ml. of ethyl bromide; the reaction begins after the mixture is stirred for a few minutes without external heating. As the reaction proceeds, the ether and the bromo compound are added at rates sufficient to maintain gentle refluxing. The relative rates of addition should be such that the two separatory funnels will be emptied at about the same time. After the additions are complete, but while the reaction is still in progress, the Grignard reagent begins to precipitate on the sides of the flask. One liter of dry, thiophene-free benzene is added from the Pyrex separatory funnel at such a rate as to keep the Grignard reagent in solution. When refluxing due to the exothermic reaction stops, the mixture is heated at gentle reflux with stirring for 4 hours.

The mixture is allowed to cool until refluxing ceases, and 296.4 g. (2 moles) of ethyl orthoformate (Note 5) is added from the lower separatory funnel over a period of about 30 minutes. The mixture is then refluxed gently for 6 hours.

The reaction mixture is cooled with stirring in an ice bath, and 1 l. of cold 10% hydrochloric acid (Note 6) is added from the separatory funnel; the acid is added dropwise at first and more rapidly after the reaction subsides. The benzene-ether layer is separated from the aqueous layer and concentrated under reduced pressure in a 5-l. round-bottomed flask on a steam bath. One liter of 25% sulfuric acid is added to the residue, and the mixture. is refluxed gently for 12 hours.

The mixture is then cooled in an ice bath, the acid is decanted, and the residue is washed twice by decantation with water. The residue is dissolved in 1 l. of benzene in the same flask, and 1.5 l. of water and 1.2 kg. of sodium bisulfite are added. The flask is fitted with a stirrer, and the mixture is stirred vigorously overnight. The mixture is filtered through an 8-in. Büchner funnel, and the bisulfite addition product is washed on the funnel with 500 ml. of benzene.

The filter cake is broken up and returned to the same 5-l. flask. A saturated solution of sodium bicarbonate is added slowly (Note 7) with stirring until there is no further evidence of decomposition. The mixture is stirred for 2 hours longer. The solution is kept alkaline to litmus throughout by the addition of more sodium bicarbonate if necessary. The crude aldehyde is collected on an 8-in. Büchner funnel, washed with water, and allowed to dry as completely as possible. The product is dissolved in 1 l. of chloroform, the small aqueous layer is separated (Note 8), and the solution is dried with Drierite or another suitable drying agent.

A 250-ml. modified Claisen flask, equipped with a dropping funnel, a thermometer, a water-cooled condenser, and a receiver, is arranged for distillation. The chloroform solution is filtered into the dropping funnel, from which it is admitted to the flask slowly as the solvent is distilled (Note 9). When the solvent has been removed, the dropping funnel is replaced by a stopper and the condenser by a 250-ml. distilling

flask as a receiver. The residue is distilled at 160–170°/1 mm. The distillate weighs 206–216 g. (50–52%). This material is recrystallized once from glacial acetic acid (approximately 1 g. to 0.9 ml.) and then from ethanol (about 1 g. to 3 ml.) to give 166–174 g. (40–42% over-all yield) of phenanthrene-9-aldehyde melting at 100–101°.

2. Notes

1. A mercury seal may be used, but a glycerol-rubber tube seal is adequate.
2. The checkers operated on one-fifth the scale specified.
3. Crude bromophenanthrene prepared by the bromination of technical (90%) phenanthrene and purified by distillation only was used by the submitters in this preparation. The anthracene-9-aldehyde, which may be formed from the anthracene present as an impurity in "90% phenanthrene," does not form a sodium bisulfite addition product and so will not contaminate the phenanthrene-9-aldehyde. The checkers used 9-bromophenanthrene, m.p. 54–56° (p. 134), exclusively, but without any advantage in yield. The submitters report yields of 55–60% from pure 9-bromophenanthrene.
4. It is not feasible to add the 9-bromophenanthrene as an ether solution because of the limited solubility of the substance in this solvent. Since the melting point of the crude 9-bromophenanthrene is about 50° it is desirable to heat the melted material to 70° in order to prevent crystallization in the funnel. If the bromo compound begins to solidify in the funnel it may be melted again by careful heating with a microburner.
5. The ethyl orthoformate should be freshly distilled with rejection of the fraction boiling below 140°.
6. If this procedure is used for the preparation of the acetal instead of the aldehyde, it may be preferable to use ammonium chloride solution for hydrolysis instead of 10% hydrochloric acid.
7. The alkaline solution must be added carefully to avoid excessive foaming.
8. The water in the filter cake is removed with difficulty by drying in air or even in an oven under reduced pressure. If the water is not removed as indicated in the procedure, difficulty may be encountered in the early part of the distillation.
9. The distillation of the solvent may be carried out at reduced pressure if desired.

3. Discussion

Phenanthrene-9-aldehyde has been obtained by the Sonn and Müller synthesis from 9-phenanthroyl chloride,[2] by the Rosenmund reduction of 9-phenanthroyl chloride,[3] by the Gattermann hydrogen cyanide synthesis from phenanthrene,[4] and by the reaction of 9-phenanthrylmagnesium bromide with ethyl formate.[5] The procedure described above is an adaptation of the method of Miller and Bachman.[6] This Grignard method has also been used by others.[7]

References and Notes

1. Work done under contract with the Office of Scientific Research and Development.
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3. Mosettig and van de Kamp, *J. Am. Chem. Soc.*, **55**, 2996 (1933).
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6. Miller and Bachman, *J. Am. Chem. Soc.*, **57**, 768 (1935).
7. Hewett, *J. Chem. Soc.*, **1938**, 195; Weizmann, Bergmann, and Berlin, *J. Am. Chem. Soc.*, **60**, 1332 (1938).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

ether (60-29-7)

ammonium chloride (12125-02-9)

chloroform (67-66-3)

sodium bicarbonate (144-55-8)

magnesium, magnesium turnings (7439-95-4)

Ethyl bromide (74-96-4)

nitrogen (7727-37-9)

sodium bisulfite (7631-90-5)

iodine (7553-56-2)

sodium (13966-32-0)

anthracene (120-12-7)

Ethyl orthoformate

ethyl formate (109-94-4)

phenanthrene (85-01-8)

9-phenanthrylmagnesium bromide

anthracene-9-aldehyde (642-31-9)

9-Bromophenanthrene (573-17-1)

bromophenanthrene

Phenanthrene-9-aldehyde, 9-Phenanthrenecarboxaldehyde (4707-71-5)

9-phenanthroyl chloride

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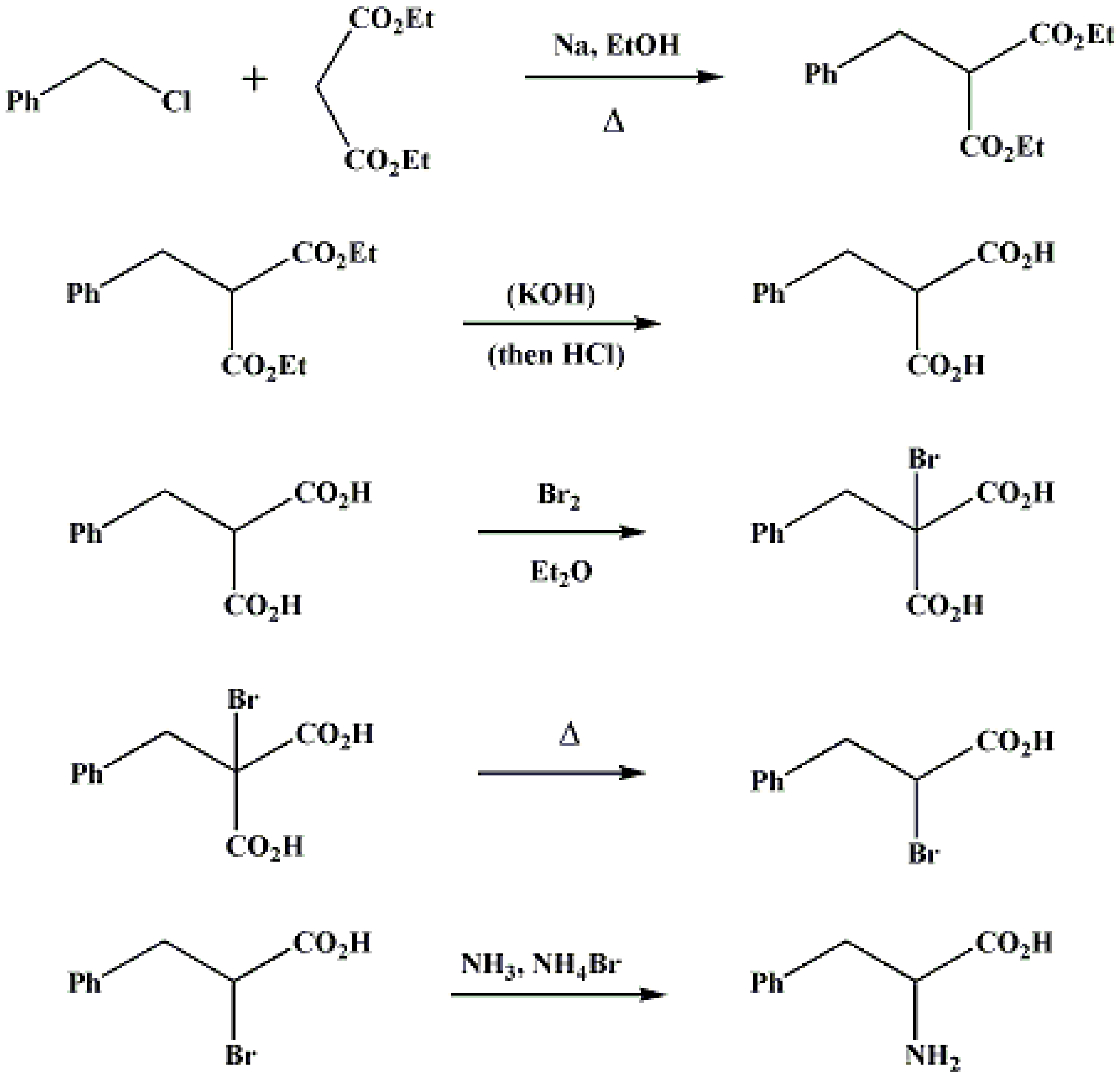
Organic Syntheses, CV 3, 705

dl-PHENYLALANINE

[Alanine, phenyl-]



Submitted by C. S. Marvel[1]
Checked by Lee Irvin Smith, R. T. Arnold, and K. L. Howard.

1. Procedure

A. *Diethyl benzylmalonate*. To 2.5 l. of absolute ethanol in a 5-l. three-necked flask set on a steam cone and equipped with a mercury-sealed stirrer, reflux condenser, and a 500-ml. dropping funnel is added 115 g. (5 gram atoms) of sodium cut in small slices. When all the sodium has reacted, a calcium chloride tube is placed on the condenser and 830 g. (5.18 moles) of diethyl malonate is added through the separatory funnel in a steady stream. This is followed by the dropwise addition of 632 g. (5 moles) of benzyl

chloride over a period of 2–3 hours. The mixture is refluxed, with stirring, until neutral to moist litmus paper (about 8–11 hours). The reflux condenser is then exchanged for a downward condenser, and the ethanol is distilled into another 5-l. three-necked flask equipped with a reflux condenser (Note 1). About 3 hours is required to remove the ethanol, and slightly more than 2 l. is recovered.

The residue is then treated with no more than 2 l. of water (Note 2) and shaken; if necessary, salt is added to make the ester layer separate sharply from the aqueous layer. The combined ester layers from two such runs are distilled from a 5-l. two-necked flask fitted with a well-wrapped 18-mm. Vigreux column. The fraction distilling at 145–155°/5 mm. is collected; it amounts to 1265–1420 g. (51–57%). The residue is chiefly diethyl dibenzylmalonate.

B. *α-Bromo-β-phenylpropionic acid*. Eight hundred and sixty grams of technical potassium hydroxide is dissolved in 850 ml. of water in a 12-l. round-bottomed flask equipped with a stirrer and set on a large steam cone. While the solution is still hot, 1 kg. (4 moles) of diethyl benzylmalonate is added from a dropping funnel over a period of 1 hour. The removal of alcohol vapors is facilitated by placing a tube connected to the water pump in the mouth of the flask. Heating and stirring are continued for 3 hours, and more water is added, if necessary, to keep the mass from solidifying. The flask is then cooled and the contents poured into a crock surrounded by an ice bath and equipped with a stirrer. Five hundred grams of ice is added to lower the temperature; when it reaches 20°, technical hydrochloric acid is added at such a rate that the temperature does not rise. The addition is slow at first, but more rapid when the excess alkali has been neutralized. The solid monopotassium salt that separates is returned to solution by adding the acid more rapidly and stirring by hand. When the reaction mixture is acid to Congo red paper, an excess of 150 ml. of acid is added and the contents of the crock are transferred to a 12-l. round-bottomed flask fitted with a stopper containing a large stopcock which barely pierces the stopper, and a glass tube which reaches to the bottom of the flask. In this way the flask may be used as a large separatory funnel if the stopper is wired in tightly.

The benzylmalonic acid is extracted with four 1-l. portions of ether; the ether extracts are combined in a 5-l. flask and allowed to stand over 150 g. of calcium chloride overnight. The ether layer is then decanted into a 5-l. flask equipped with an efficient reflux condenser, mercury-sealed stirrer, and dropping funnel. Two hundred and twenty-five milliliters of dry bromine is dropped in at such a rate that the ether refluxes (Note 3). The time required is about 4 hours. After the complete addition of bromine, 1 l. of water is added through the dropping funnel at such a rate that the ether merely refluxes (Note 4).

The ether layer of bromobenzylmalonic acid is separated by decantation and the ether removed by distillation. The residue is then decarboxylated by heating to a temperature of 130–135° in a 3-l. flask in an oil bath for 5 hours.

C. *dl-Phenylalanine.* The crude bromo acid is divided into four portions and each

portion is added to 2 l. of technical ammonium hydroxide (sp. gr. 0.90) in a 3-l. round-bottomed flask. The flask is well shaken, a rubber stopper is wired in, and the mixture is allowed to stand for a week. The contents of the four amination flasks (Note 5) are then combined in a 12-l. flask, 20 g. of Norit is added, and the flasks are heated on a steam cone overnight. The ammonia which is evolved is conducted into a gas-absorption trap or merely led into water by a tube from the flask. The solution is filtered while still hot; on cooling most of the phenylalanine precipitates. This is filtered, washed with 250 ml. of methanol, and the filtrate evaporated under the pressure of a water pump until more crystals form. The solution is then cooled and an additional crop of phenylalanine obtained, which is also washed with methanol. The yield of crude product is 500 g., but it is slightly wet; if it is dried overnight in an oven at about 80°, it will weigh 460 g. This need not be done, however, as the yield of pure product is the same whether or not the crude product is dried.

The phenylalanine is recrystallized as follows: the crude product is dissolved in 9 l. of water heated to 95° on a steam cone, treated with 15 g. of Norit, and filtered. Three liters of alcohol is added and the solution cooled in the ice chest overnight. The yield of pure product amounts to 367 g. An additional 45 g. may be obtained by evaporating the mother liquor under reduced pressure until crystals separate, adding an amount of alcohol equivalent to one-third the volume of the concentrated mother liquor, and cooling. Additional material may be obtained by continuing to work down all mother liquors. The yield, 412 g., is 62.4% based on the diethyl benzylmalonate. The white crystals decompose at 271–273° (uncor.) in a closed capillary (Note 6).

2. Notes

1. The sodium required for the next run can be added to the second flask as the alcohol distils into it.
2. Usually 1.5 l. of water suffices, and it is not necessary to add salt.
3. To start the bromination 10 ml. of bromine is added and the solution stirred until decolorized. After the reaction has been started in this manner, it runs very smoothly. When large amounts of the amino acid are to be prepared, it is more convenient to double the portion used in the bromination step.
4. Care must be taken not to add the water too fast, as the reaction mixture will foam out of the flask.
5. The aminations are usually colored, and frequently the flasks contain small deposits of oil on the bottom. This oil disappears in subsequent treatment.
6. The product thus obtained has the calculated amino nitrogen content.

3. Discussion

Methods of making *dl*-phenylalanine have been summarized [*Org. Syntheses* Coll. Vol. **2**, 489 (1943)]. The method described here is essentially the one originally described by Fischer.[2] For the preparation of large amounts of amino acids it is undoubtedly the cheapest and best procedure.

Additional preparative methods include the hydrolysis and decarboxylation of benzyl formamidomalonic ester,[3] benzylacetamidomalonic ester,[4] or benzylacetamidocyanoacetic ester.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 489

References and Notes

1. These directions are the result of the efforts of many men who have worked on the preparation of phenylalanine at the University of Illinois.
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3. Galat, *J. Am. Chem. Soc.*, **69**, 965 (1947).
4. Albertson and Archer, *J. Am. Chem. Soc.*, **67**, 308 (1945).
5. Albertson and Tullar, *J. Am. Chem. Soc.*, **67**, 502 (1945).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

benzyl formamidomalonic ester

benzylacetamidomalonic ester

benzylacetamidocyanoacetic ester

ethanol (64-17-5)

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

methanol (67-56-1)

ether (60-29-7)

bromine (7726-95-6)

nitrogen (7727-37-9)

Norit (7782-42-5)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

benzyl chloride (100-44-7)

ammonium hydroxide (1336-21-6)

diethyl malonate (105-53-3)

phenylalanine (63-91-2)

α-Bromo-β-phenylpropionic acid (42990-49-8)

Alanine, phenyl- (63-91-2)

diethyl dibenzylmalonate

Diethyl benzylmalonate (607-81-8)

benzylmalonic acid (616-75-1)

bromobenzylmalonic acid

DL-Phenylalanine (150-30-1)

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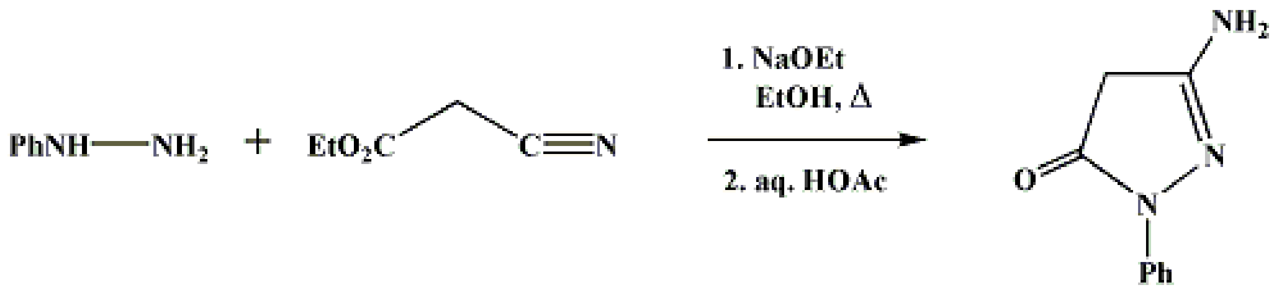
Organic Syntheses, *CV 3, 708*

1-PHENYL-3-AMINO-5-PYRAZOLONE

[5-Pyrazolone, 3-amino-1-phenyl-]



Submitted by H. D. Porter and A. Weissberger.
Checked by R. T. Arnold and K. Murai.

1. Procedure

Sodium ethoxide is prepared from 46 g. (2 gram atoms) (Note 1) of sodium and 800 ml. of absolute ethanol in a 2-l. three-necked flask equipped with stirrer and a reflux condenser. To the hot solution is added 113 g. (106 ml., 1 mole) of ethyl cyanoacetate followed by 108 g. (98 ml., 1 mole) of phenylhydrazine (Note 2), and the mixture is stirred and heated in an oil bath at 120° for 16 hours. Then most of the ethanol is removed under reduced pressure and the residue is dissolved in 1 l. of water; the mixture is warmed to about 50° and stirred to facilitate solution. After being cooled to room temperature, the solution is extracted with three 100-ml. portions of ether (Note 3). The aqueous phase is acidified by the addition of 100 ml. of glacial acetic acid, cooled in ice, and filtered. The crude product is washed on the filter with 100 ml. of 95% ethanol; it is then transferred to a flask and boiled with 500 ml. of the same solvent, and this mixture is cooled and filtered. The solid is washed with ethanol and dried. The tan crystalline 1-phenyl-3-amino-5-pyrazolone, melting with decomposition at 216–218°, weighs 76–82 g. (43–47%) (Note 4).

2. Notes

1. At least two equivalents of sodium ethoxide are necessary for the reaction, but larger amounts do not improve the yield. Sodium hydroxide in ethanol, or sodamide in benzene, cannot be substituted for the sodium ethoxide solution.
2. All the chemicals used were obtained from the Eastman Kodak Company.
3. Instead of the isolation of the product by concentration, solution in water, and extraction with ether, water may be added directly to the ethanolic solution and the resulting solution acidified. This procedure, however, often leads to a more highly colored product.
4. This material is sufficiently pure for most purposes. If desired, an almost white product may be obtained by two recrystallizations from dioxane (Norit). This treatment entails a 40% loss of the product and raises the melting point by only 2° (to 218–220°).

3. Discussion

The procedure is essentially that given by Conrad and Zart for the original preparation of the substance,[1] to which they assigned the incorrect structure of 1-phenyl-3-hydroxy-5-pyrazolone imide.[2] The compound may also be prepared in about the same yield by the reaction of phenylhydrazine with ethyl malonate monoimidoester.[3]

The procedure given has been applied with varying success to a number of aromatic and heterocyclic hydrazines.[4]

References and Notes

1. Conrad and Zart, *Ber.*, **39**, 2282 (1906).
2. Weissberger and Porter, *J. Am. Chem. Soc.*, **64**, 2133 (1942).
3. Weissberger, Porter, and Gregory, *J. Am. Chem. Soc.*, **66**, 1851 (1944).
4. Weissberger and Porter, *J. Am. Chem. Soc.*, **66**, 1849 (1944).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethyl malonate monoimidoester

ethanol (64-17-5)

acetic acid (64-19-7)

Benzene (71-43-2)

ether (60-29-7)

sodium hydroxide (1310-73-2)

Phenylhydrazine (100-63-0)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

Ethyl cyanoacetate (105-56-6)

dioxane (5703-46-8)

sodamide (7782-92-5)

1-Phenyl-3-amino-5-pyrazolone, 5-Pyrazolone, 3-amino-1-phenyl- (4149-06-8)

1-phenyl-3-hydroxy-5-pyrazolone imide

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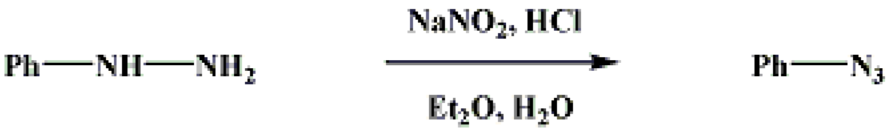
Organic Syntheses, CV 3, 710

PHENYL AZIDE

[Benzene, azido-]



Submitted by R. O. Lindsay and C. F. H. Allen.
Checked by R. L. Shriner and J. C. Lawler.

1. Procedure

In a 1-l. three-necked flask fitted with a stirrer, a thermometer, and a dropping funnel are placed 300 ml. of water and 55.5 ml. of concentrated hydrochloric acid. The flask is surrounded by an ice-salt bath, the stirrer is started, and 33.5 g. (0.31 mole) of phenylhydrazine (Note 1) is added dropwise (5–10 minutes is required). Phenylhydrazine hydrochloride separates as fine white plates. Stirring is continued, and, after the temperature has fallen to 0°, 100 ml. of ether is added, after which a previously prepared solution of 25 g. of technical sodium nitrite in 30 ml. of water is added from the dropping funnel at such a rate that the temperature *never* rises above 5°. This requires 25–30 minutes.

The reaction mixture is subjected to steam distillation until about 400 ml. of distillate is obtained. The ether layer is removed from the distillate, and the aqueous layer is extracted once with 25 ml. of ether. The combined ethereal solutions are dried over 10 g. of anhydrous calcium chloride. The dried solution is placed in a 200-ml. ordinary Claisen flask arranged for vacuum distillation. *The flask must be surrounded by a cylindrical wire screen, and a laminated glass screen must be interposed between the operator and the apparatus* (Note 2). The flask is immersed in a water bath at 25–30°, and the ether is removed under reduced pressure. Then the temperature of the water bath is raised to 60–65°, and the product is distilled under reduced pressure. Phenyl azide boils at 49–50° at 5 mm. (Note 3). A yield of 24–25 g. (65–68%) of the pungent, pale yellow, oily azide is obtained (Note 4).

2. Notes

1. The phenylhydrazine used was the best grade supplied by the Eastman Kodak Company. With technical material, or a preparation that was appreciably discolored, the yield was much less (45–50%), and a considerable amount of tar was formed.
2. Care must be exercised during the distillation. Phenyl azide explodes when heated at ordinary pressure, and occasionally at lower pressures. The water-bath temperature should never be permitted to rise above 80° at any time.

3. Phenyl azide boils at 66–68°/21 mm. with a bath temperature of 70–75°. It is advisable to use as low a bath temperature as possible and a pressure of 5 mm. or less. The checkers have used these directions repeatedly without any explosions.
4. The product should be stored in a brown glass bottle. It will keep for a month in a cool, dark place.

3. Discussion

Phenyl azide has been prepared by the action of nitrous acid upon phenylhydrazine hydrochloride;[1] of ammonia upon diazobenzene perbromide;[2] and by the reaction between a diazo salt and sodium azide,[3] hydroxylamine,[4] or *p*-toluenesulfonamide.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 74
- Org. Syn. Coll. Vol. 4, 380

References and Notes

1. Dimroth, *Ber.*, **35**, 1032 (1902).
2. Griess, *Ann.*, **137**, 68 (1866).
3. Nölting, *Ber.*, **26**, 86 (1893).
4. Fischer, *Ann.*, **190**, 96 (1877); Mai, *Ber.*, **25**, 372 (1892); **26**, 1271 (1893); Forster and Fierz, *J. Chem. Soc.*, **91**, 855, 1350 (1907).
5. Bretschneider and Rager, *Monatsh.*, **81**, 970 (1950).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

diazobenzene perbromide

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ether (60-29-7)

sodium nitrite (7632-00-0)

nitrous acid (7782-77-6)

Phenylhydrazine (100-63-0)

hydroxylamine (7803-49-8)

sodium azide (26628-22-8)

phenylhydrazine hydrochloride (59-88-1)

PHENYL AZIDE, Benzene, azido- (622-37-7)

p-toluenesulfonamide (70-55-3)

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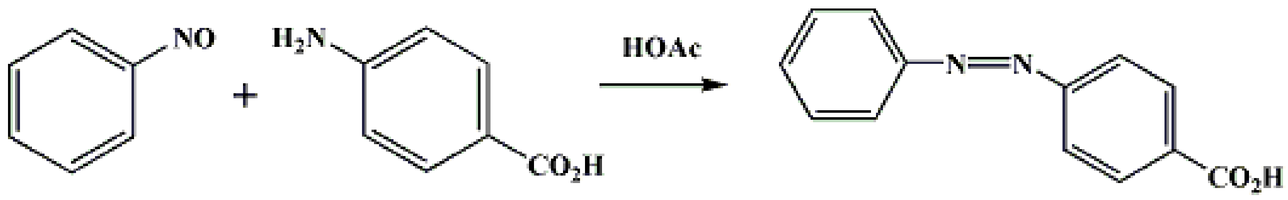
Organic Syntheses, CV 3, 711

p-PHENYLAZOBENZOIC ACID

[Benzoic acid, *p*-phenylazo-]



Submitted by Harry D. Anspon
Checked by W. E. Bachmann and N. C. Deno.

1. Procedure

Fifty-four grams (0.39 mole) of *p*-aminobenzoic acid is dissolved in 390 ml. of warm glacial acetic acid in a 1-l. Erlenmeyer flask. The solution is cooled to room temperature, 42 g. (0.39 mole) of nitrosobenzene (p. 668) is added, and the mixture is shaken until the nitrosobenzene dissolves. The flask is stoppered, and the solution is allowed to stand for 12 hours at room temperature. The product begins to crystallize after about 15 minutes.

The *p*-phenylazobenzoic acid is collected on a Büchner funnel (Note 1) and washed with acetic acid and with water. The yield of air-dried acid melting at 245–247° cor. is 62 g. (70%). By recrystallization from 95% ethanol (60 ml. per g.) the acid is obtained as orange-gold plates which melt at 248.5–249.5° cor.; the yield is 54 g. (61%).

2. Notes

1. The solution is not cooled below room temperature before filtering; cooling below 20° brings down impurities.

3. Discussion

The method employed here is essentially the one described by Angeli and Valori.[1]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 712

References and Notes

1. Angeli and Valori, *Atti accad. Lincei*, **22**, I, 132 (1913) [*C. A.*, **7**, 2223 (1913)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

acetic acid (64-19-7)

Nitrosobenzene (586-96-9)

p-aminobenzoic acid (150-13-0)

p-Phenylazobenzoic acid, Benzoic acid, p-phenylazo- (1562-93-2)

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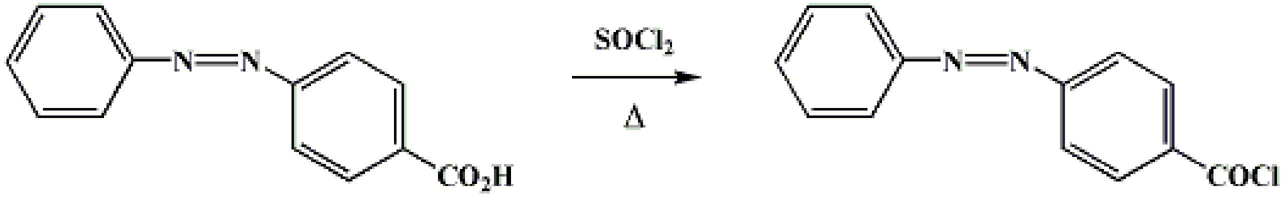
Organic Syntheses, CV 3, 712

p-PHENYLAZOBENZOYL CHLORIDE

[Benzoyl chloride, *p*-phenylazo-]



Submitted by George H. Coleman, Gust Nichols, Chester M. McCloskey, and Harry D. Anspon.
Checked by W. E. Bachmann and N. C. Deno.

1. Procedure

Fifty grams (0.22 mole) of recrystallized *p*-phenylazobenzoic acid (p. 711) (Note 1) and 50 g. (0.47 mole) of anhydrous sodium carbonate (Note 2) are placed in a 1-l. flask and thoroughly mixed by shaking. To this mixture is added 250 ml. (3.5 moles) of thionyl chloride (Note 3); a reflux condenser with a drying tube is fitted to the flask, and the mixture is refluxed for 1.5 hours (Note 4). A condenser is set for distillation, and as much as possible of the thionyl chloride is distilled on a steam bath (Note 5).

The acid chloride is dissolved by refluxing with 500 ml. of 90–100° ligroin, and the hot solution is decanted from the sodium carbonate onto a fluted filter. This process is repeated with three 150-ml. portions of ligroin. The combined filtrates are concentrated to 500 ml., filtered if necessary, and cooled to 0°. The acid chloride is collected on a Büchner funnel and pressed as dry as possible. It is washed twice with 30–60° petroleum ether and stored in a vacuum desiccator over phosphorus pentoxide and paraffin shavings (Note 6). The yield of orange-red crystals melting at 94.5–95.5° is 48 g. (89%).

2. Notes

1. The checkers found that 50 g. of unrecrystallized acid gave 45 g. of acid chloride melting at 92–94°. When this was recrystallized from 90–100° petroleum ether (10 ml. per g.), 41.5 g. of orange-red crystals melting at 94.5–95.5° was obtained. The over-all yield of pure acid chloride on the basis of unrecrystallized acid is the same. The use of unrecrystallized acid has an advantage in that the volume of solvent required for recrystallization of the acid chloride is much less than for the acid.
2. The use of sodium carbonate is unusual. It is claimed that the sodium carbonate prevents decomposition and tar formation during the reaction.
3. The checkers used Eastman Kodak Company's best grade of thionyl chloride.
4. Refluxing should be carried out under a hood or in an apparatus provided with a gas trap.
5. About 170 ml. of good thionyl chloride can be recovered.
6. The acid chloride holds the petroleum ether tenaciously. About a week is required for complete removal of the petroleum ether.

3. Discussion

p-Phenylazobenzoyl chloride (azoyl chloride) has been prepared by the action of thionyl chloride on the acid.[1,2] The method used is a modification of that of Ladenburg, Fernholz, and Wallis.[2]

References and Notes

1. Reich, *Biochem. J.*, **33**, 1001 (1939).
2. Ladenburg, Fernholz, and Wallis, *J. Org. Chem.*, **3**, 294 (1938).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ligroin

petroleum ether

azoyl chloride

thionyl chloride (7719-09-7)

sodium carbonate (497-19-8)

phosphorus pentoxide (1314-56-3)

p-Phenylazobenzoic acid (1562-93-2)

p-Phenylazobenzoyl chloride, Benzoyl chloride, p-phenylazo- (104-24-5)

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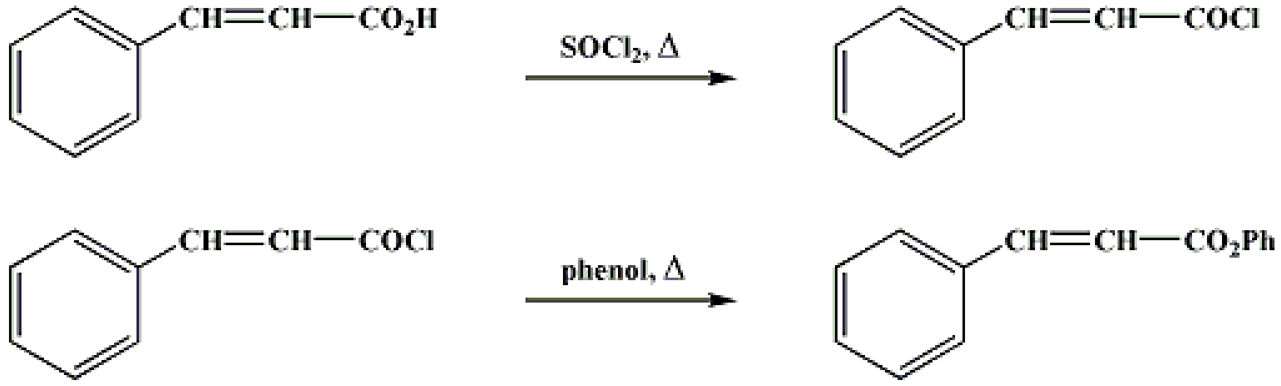
Organic Syntheses, CV 3, 714

PHENYL CINNAMATE

[Cinnamic acid, phenyl ester]



Submitted by Ennis B. Womack and J. McWhirter.
Checked by R. L. Shriner, N. S. Moon, and S. C. Kelton, Jr..

1. Procedure

A mixture of 148 g. (1 mole) of cinnamic acid and 119 g. (1 mole) of thionyl chloride (Note 1) is placed in a 500-ml. Claisen flask. The side arms are stoppered, and the flask is fitted with a reflux condenser. The apparatus is mounted at an angle so that the condensate will not run into the side arm. To the top of the condenser is attached an exit tube, for evolved hydrogen chloride and sulfur dioxide, leading to a gas-absorption trap. The mixture is heated on a steam bath, cautiously at first, until no further evolution of hydrogen chloride is noted (45–60 minutes), and then allowed to cool, and 94 g. (1 mole) of phenol (Note 2) is added. The mixture is again heated on the steam bath until the evolution of hydrogen chloride has ceased (about 1 hour). It is then placed on a sand bath and brought just to the reflux temperature in order to complete the reaction and remove the hydrogen chloride more completely (Note 3).

The reaction mixture is cooled and distilled under reduced pressure (Note 4). The fraction boiling at 190–210° at 15 mm. is collected. The distillate solidifies to a pale yellow solid melting at 64° to 69° and weighing 186–200 g. (83–89%). It is purified by grinding in a mortar to a powder and washing with 500 ml. of cold 2% sodium bicarbonate solution. The residue is recrystallized from 300 ml. of 95% ethanol. The recovery is 141–168 g. (63–75%) of pure white crystals melting at 75–76°.

2. Notes

1. The thionyl chloride should be redistilled before use. The material used in this preparation boiled at 75.0–75.5°.
2. The phenol used was Mallinckrodt's analytical reagent grade.
3. A sand-bath temperature of about 350° will effect refluxing. Prolonged heating on the sand bath causes considerable loss of product due to decomposition and polymerization and to the conversion of the acid to stilbene by the loss of carbon dioxide.
4. In carrying out the vacuum distillation, it is well not to include the manometer in the system until the unchanged phenol and most of the hydrogen chloride have been

removed. Bumping during the distillation may be minimized by holding the burner in the hand and directing the free flame at the surface of the boiling liquid. If the vapors are superheated too much, the boiling-point range may be 190–220° at 15 mm.

3. Discussion

Phenyl cinnamate and other phenolic esters have been prepared by heating the acid and phenol in the presence of phosphorus oxychloride,[1] and by heating the acid anhydride and phenol together in the presence of a dehydrating agent such as fused zinc chloride or anhydrous sodium acetate.[2] Phenyl cinnamate has also been prepared by the careful distillation of phenyl fumarate.[3]

References and Notes

1. Nencki, *Compt. rend.*, **108**, 254 (1889).
2. Franchimont, *Ber.*, **12**, 2059 (1879); Liebermann, *Ber.*, **21**, 1172 (1888).
3. Anschütz, *Ber.*, **18**, 1945 (1885).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

hydrogen chloride (7647-01-0)

sodium acetate (127-09-3)

thionyl chloride (7719-09-7)

sodium bicarbonate (144-55-8)

phenol (108-95-2)

sulfur dioxide (7446-09-5)

carbon dioxide (124-38-9)

Phosphorus Oxychloride (21295-50-1)

zinc chloride (7646-85-7)

cinnamic acid (621-82-9)

stilbene

Phenyl cinnamate, Cinnamic acid, phenyl ester (2757-04-2)

phenyl fumarate

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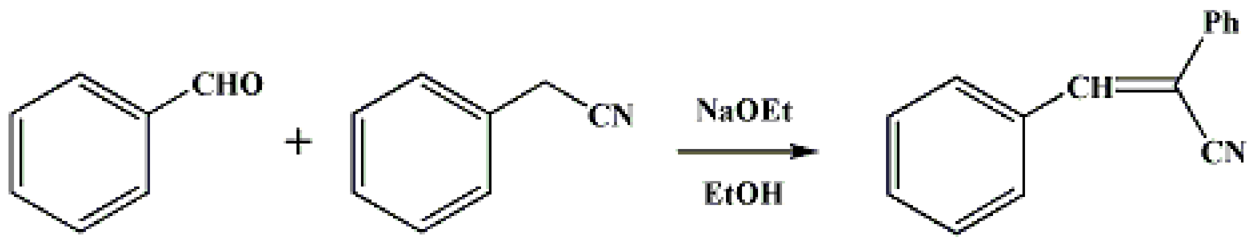
α-PHENYLCINNAMONITRILE

[Acrylonitrile, α-β-diphenyl-]



Submitted by Stanley Wawzonek and Edwin M. Smolin.
Checked by Cliff S. Hamilton and Karl W. R. Johnson.

1. Procedure

In a 2-l. beaker fitted with a strong, efficient, mechanical stirrer is placed a mixture of 106 g. (101 ml., 1 mole) of freshly distilled benzaldehyde and 117 g. (1 mole) of purified dry benzyl cyanide (Note 1), in 650 ml. of 95% ethanol (Note 2). To this mixture is added drop-wise, with stirring, a solution of 7 g. of sodium ethoxide in 50 ml. of absolute ethanol (Note 3). When 40–50 ml. has been added, the mixture becomes warm, turns cloudy, and solidifies. Mechanical stirring is continued as long as possible, and then the mixture is stirred by hand with a thick stirring rod in order to break up the lumps that form. The mixture is cooled in an ice bath (Note 4), and the product is separated by filtration. The filtrate is removed and may be saved (Note 5). The white mass is washed first with 200 ml. of distilled water, then with 50 ml. of 95% ethanol to remove unchanged reagents. The nitrile is dried at 25° and melts at 86–88°. The yield is 178–199 g. (87–97%) of product sufficiently pure for most purposes. Recrystallization from 700 ml. of 95% ethanol gives 170–187 g. (83–91%) of a pure, white product melting at 88° (Note 6).

2. Notes

1. The benzyl cyanide may be purified by a procedure described earlier.[1] If commercial benzyl cyanide is used, the yield is between 80% and 90% of a slightly yellow product. Two recrystallizations are necessary for purification.
2. Denatured alcohol (Formula 3A) containing 10% absolute methanol is a satisfactory solvent for recrystallization.
3. A 40% solution of sodium hydroxide may also be used as the condensing agent; 35–60 ml. is required. With this reagent, the product is less pure and needs an additional recrystallization. The yields range from 70% to 82%.
4. This preliminary cooling helps to prevent clogging of the 20-cm. Büchner funnel used during filtration.
5. An additional 10–21 g. of crude nitrile melting at 84–86° can be obtained by

evaporating the combined alcoholic filtrates to a volume of 300 ml. Two or three recrystallizations from 95% ethanol are necessary to raise the melting point to 88°.

6. Similar yields of substituted α-phenylcinnamonitriles can be obtained using *p*-methoxybenzyl cyanide and anisaldehyde, or benzyl cyanide and anisaldehyde.[2,3]

3. Discussion

α-Phenylcinnamonitrile can be prepared from benzaldehyde and benzyl cyanide with no solvent and with sodium ethoxide as a catalyst.[4] Sodium hydroxide[5] (40%) or piperidine[6] may also be used as catalysts. The nitrile has been made by the condensation of benzyl cyanide and excess benzyl chloride with strong sodium hydroxide at 170°[7,8] and by heating α,β-diphenylsuccinonitrile with alcohol at 180° in a sealed tube[9] or at 230–250° under 100–110 mm. pressure with palladium.[10]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 392

References and Notes

1. *Org. Syntheses* Coll. Vol. **1**, 108 (1941).
2. Wawzonek, *J. Am. Chem. Soc.*, **68**, 1157 (1946).
3. Niederl and Ziering, *J. Am. Chem. Soc.*, **64**, 885 (1942).
4. De Schuttenbach, *Ann. chim.*, (11) **6**, 90 (1936).
5. Walther, *J. prakt. Chem.*, (2) **53**, 454 (1896).
6. Knoevenagel, Ger. pat. 94,132 [*Chem. Zentr.*, **69**, 228 (1898)].
7. Neure, *Ann.*, **250**, 155 (1888).
8. Janssen, *Ann.*, **250**, 129 (1888).
9. Chalaney and Knoevenagel, *Ber.*, **25**, 297 (1892).
10. Knoevenagel and Bergdott, *Ber.*, **36**, 2861 (1903).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

methanol (67-56-1)

sodium hydroxide (1310-73-2)

benzaldehyde (100-52-7)

piperidine (110-89-4)

sodium ethoxide (141-52-6)

palladium (7440-05-3)

benzyl chloride (100-44-7)

Benzyl cyanide (140-29-4)

α-Phenylcinnamonitrile, Acrylonitrile, α-β-diphenyl- (2510-95-4)

α,β-diphenylsuccinonitrile (5424-86-2)

anisaldehyde (123-11-5)

p-methoxybenzyl cyanide (104-47-2)

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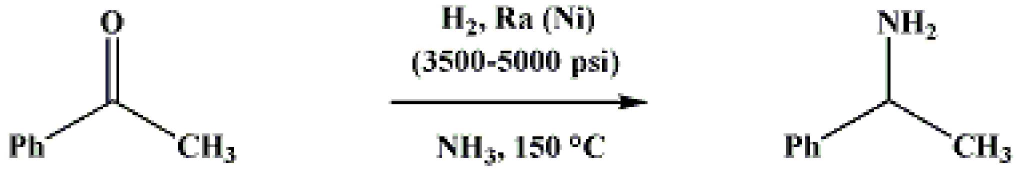
Organic Syntheses, CV 3, 717

α-PHENYLETHYLAMINE

[Benzylamine, α-methyl-]



Submitted by John C. Robinson, Jr. and H. R. Snyder.
Checked by Nathan L. Drake and Daniel Draper.

1. Procedure

In a 2-l. bomb are placed 720 g. (6 moles) of pure acetophenone and 1 tablespoon of Raney nickel catalyst (p. 181). After the cap and gauge block are securely fastened, 700 ml. (30 moles) of liquid ammonia is introduced (Note 1). The mixture is hydrogenated at 150° under 5000–3500 lb. (Note 2). The reaction is allowed to continue as long as hydrogen is absorbed, generally 4–6 hours. The bomb is cooled, the excess ammonia is allowed to escape, and the contents are filtered from the catalyst. The mixture is cooled in an ice bath, acidified to Congo red with concentrated hydrochloric acid (200–300 ml.), and steam-distilled for 10–12 hours to remove excess acetophenone (Note 3). The residue is then cooled and added slowly to 200 g. of solid sodium hydroxide in a flask surrounded by an ice bath. The amine is separated, and the aqueous layer is extracted with three 150-ml. portions of benzene. The extracts and amine are combined and dried over solid sodium hydroxide. After removal of the benzene, the residue is fractionated under diminished pressure. The yield of α-phenylethylamine (Note 4), b.p. 80–81°/18 mm., is 320–380 g. (Note 5) (44ndash;52%).

2. Notes

1. Liquid ammonia is introduced into the large bomb as follows: The cap and gauge block of the large bomb are tightened in place. The inner gas inlet tube is removed from the cap assembly of a smaller bomb (capacity about 250 ml.). This bomb is equipped with a test-tube-type liner which is kept chilled in a bath of Dry Ice while it is filled with liquid ammonia. This test tube is then placed in the small bomb, and the cap and gauge block are quickly (15–30 seconds) tightened. The bomb is then filled with hydrogen under high pressure and connected with the larger bomb by means of a short length of the conventional steel pressure tubing. The smaller bomb is inverted, and the valves are opened. This operation will introduce about 150 ml. of liquid ammonia at one time and may be repeated as often as necessary.

2. A booster pump is required, for it is quite important to keep the pressure above the minimum value of about 3500 lb. The temperature of the reduction is above the critical temperature of ammonia, and the pressure will not fall much below 3500 lb. At this point hydrogen must be pumped into the bomb until the pressure is about 5000 lb.; this process is repeated until the reaction is complete. If a safety disk is to be incorporated into the line, it *must not* be made of *copper*, as ammonia, even under 2–3 atm., rapidly attacks copper. A *special* disk of steel, nickel, or other suitable material is required.

3. It is necessary to heat the flask externally with a flame or the volume of the solution will greatly increase during the lengthy steam distillation.

4. According to the submitters, methyl amyl ketone (800 g.) and ammonia (600 ml.) have been converted to 2-aminoheptane, b.p. 139–141°, in exactly the same manner, in 50–55% yields. A slightly modified procedure was used in the preparation of *n*-heptylamine and furfurylamine. Heptaldehyde (320 g.) was dissolved in 500 ml. of methanol, and 150 ml. of liquid ammonia was added; the reduction was conducted as above. *n*-Heptylamine, b.p. 57–58°/23 mm., was obtained in yields of 53–63%. Freshly distilled furfural (290 g.) was dissolved in 500 ml. of methanol, 150 ml. of liquid ammonia was introduced, and the reduction carried out as usual. The product was removed, filtered, and fractionated directly. Furfurylamine, b.p. 144–146°, was obtained in 50% yield.

5. The yields are based upon the amount of acetophenone initially used and do not make allowances for the material recovered from the steam distillation. A small amount of di-(α-phenylethyl) amine, b.p. 61–62°/2 mm., may be recovered from the residues.

3. Discussion

α-Phenylethylamine has been prepared by reducing acetophenone with hydrogen at high pressures over nickel catalysts in the presence of ammonia;[1,2] with hydrogen at low pressures over a nickel catalyst in the presence of ammonia-saturated ethanol;[3] and with hydrogen at low pressures over a platinum catalyst in the presence of ammonia-saturated methanol containing ammonium chloride (69% yield).[4]

l-α-Phenylethylamine has been prepared through the oxime of *d*-α-phenylethyl methyl ketone by the Beckmann rearrangement;[5] from *d*-phenylmethylacethydroxamic acid by the Lossen rearrangement;[5] from *d*-hydratropic azide;[6,7] from *d*-hydratropic acid by the Schmidt reaction;[5] from *d*-hydratropamide by treatment with alkaline hypobromite;[8] and by the reduction of acetophenone oxime with lithium aluminum hydride.[9]

Other methods of preparing α-phenylethylamine are reviewed in *Org. Syntheses* Coll. Vol. 2, 503 (1943), where detailed directions are given for the preparation of this

amine from acetophenone and ammonium formate. The procedure given above was based upon that of Schwoegler and Adkins.[2]

Methods of preparing *d*- and *l*-α-phenylethylamine, based on the resolution of *dl*-α-phenylethylamine, are reviewed in *Org. Syntheses* Coll. Vol. 2, 506 (1943), where detailed directions are given for the resolution of this amine by *l*-malic and *d*-tartaric acids.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 50
- Org. Syn. Coll. Vol. 3, 229
- Org. Syn. Coll. Vol. 3, 720
- Org. Syn. Coll. Vol. 5, 909

References and Notes

1. Couturier, *Ann. chim.*, (11) **10**, 610 (1938).
2. Schwoegler and Adkins, *J. Am. Chem. Soc.*, **61**, 3499 (1939).
3. Mignonac, *Compt. rend.*, **172**, 223 (1921).
4. Alexander and Misegades, *J. Am. Chem. Soc.*, **70**, 1315 (1948).
5. Campbell and Kenyon, *J. Chem. Soc.*, **1946**, 25.
6. Bernstein and Whitmore, *J. Am. Chem. Soc.*, **61**, 1324 (1939).
7. Kenyon and Young, *J. Chem. Soc.*, **1941**, 263.
8. Arcus and Kenyon, *J. Chem. Soc.*, **1939**, 916.
9. Larsson, *Trans. Chalmers Univ. Technol., Gothenburg*, **94**, 15 (1950) [*C. A.*, **45**, 1494 (1951)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

D- and L-α-Phenylethylamine

oxime of d-α-phenylethyl methyl ketone

l-malic and d-tartaric acids

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

Benzene (71-43-2)

methanol (67-56-1)

ammonium chloride (12125-02-9)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

platinum (7440-06-4)

copper (7440-50-8)

nickel (7440-02-0)

Acetophenone (98-86-2)

hypobromite

Furfural (98-01-1)

Methyl amyl ketone (110-43-0)

α-Phenylethylamine, Benzylamine, α-methyl-, dl-α-phenylethylamine, l-α-Phenylethylamine (3886-69-9)

ammonium formate (540-69-2)

di-(α-phenylethyl) amine

acetophenone oxime

lithium aluminum hydride (16853-85-3)

2-aminoheptane (123-82-0)

furfurylamine (617-89-0)

d-hydratropic acid (492-37-5)

heptaldehyde (111-71-7)

n-heptylamine (111-68-2)

d-phenylmethylacethydroxamic acid

d-hydratropic azide

d-hydratropamide

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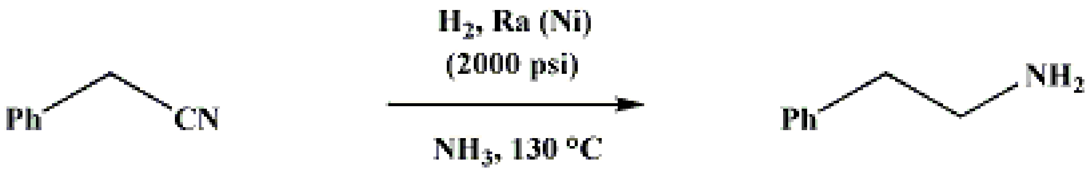
Organic Syntheses, *CV 3*, *720*

β-PHENYLETHYLAMINE

[Phenylethylamine]



Submitted by John C. Robinson, Jr. and H. R. Snyder.
Checked by Nathan L. Drake and Daniel Draper.

1. Procedure

In a 2-l. bomb are placed 1 kg. (8.55 moles) of pure (Note 1) benzyl cyanide and 1 tablespoon of Raney nickel catalyst (p. 181). After the cap is securely fastened down, 150 ml. of liquid ammonia is introduced (Note 2). Hydrogen is introduced until the pressure is about 2000 lb. The bomb is then heated to 120–130° and shaking is begun. The reduction is complete well within an hour (Note 1). The bomb is cooled and opened, and the contents are removed. The bomb is rinsed with a little ether, and the combined liquids are filtered from the catalyst. The ether is removed, and the residue is fractionated under reduced pressure. The yield is 860–890 g. (83–87%) of β-phenylethylamine, b.p. 90–93°/15 mm. (Note 3), (Note 4), (Note 5).

2. Notes

1. Benzyl cyanide, prepared according to *Org. Syntheses* Coll. Vol. 1, 107 (1941), should be distilled from Raney nickel. Minute traces of halide have a strong poisoning effect on the catalyst. If the reduction does not occur within an hour, the contents of the bomb should be removed and filtered. New catalyst is then added and the process is repeated.
2. The presence of ammonia in the reduction mixture reduces the amount of secondary amine formed. For directions for introducing the liquid ammonia, see Note 1 to the preparation of α-phenylethylamine (p. 718).
3. If several runs are made, a small amount of the secondary amine may be recovered from the combined residues. Di-(β-phenylethyl)-amine boils at 155–157°/4 mm.
4. Similarly *n*-amyl cyanide has been converted to *n*-hexylamine, b.p. 128–130°, in 67–70% yields.
5. It has been reported (R. N. Icke and C. E. Redemann, private communication) that β-phenylethylamine, as well as several substituted β-phenylethylamines, may be prepared in excellent yields by catalytic reduction of the corresponding cyanides in 10 *N* methanolic ammonia. An example of this procedure follows.

Commercial anhydrous methanol is saturated with ammonia gas at 0°; this solution is approximately 10 *N*. A solution of 58.5 g. (0.5 mole) of benzyl cyanide in 300 ml. of 10 *N* methanolic ammonia (the ratio of ammonia to benzyl cyanide should be at least 5:1 in order to minimize the formation of the secondary amine) is placed in a high-pressure hydrogenation bomb, 5–10 ml. of settled Raney nickel catalyst (p. 181) is added, the bomb is closed, and hydrogen is introduced until the pressure is 500–1000 lb. The bomb is shaken and heated to 100–125° until absorption of hydrogen ceases (about 2 hours). The bomb is cooled and opened, and the contents are removed. The bomb is rinsed with two or three 100-ml. portions of methanol, and the combined liquids are poured through a fluted filter to remove the catalyst. (*Caution! If the catalyst becomes dry, it is likely to ignite.*) The solvent and the ammonia are removed by distillation, and the residue is fractionated through a short column. The yield of β-phenylethylamine boiling at 92–93°/19 mm. (62–63°/4 mm.) is 51–54.5 g. (84–90%). The hydrochloride, after crystallization from dry ethanol, melts at 218–219°. This procedure has also been used for preparation of the following β-phenylethylamines from the cyanides; the yields of amines were uniformly high: 3,4-dimethoxyphenylethylamine, b.p. 119–119.5°/1 mm.; *o*-methylphenylethylamine, b.p. 67°/0.5 mm.; *m*-methylphenylethylamine, b.p. 68°/2 mm.; *p*-methylphenylethylamine, b.p. 71°/2 mm.; and 3,4-methylenedioxyphenylethylamine, b.p. 109°/2 mm.

3. Discussion

β-Phenylethylamine has been made by a number of reactions, many of which are unsuitable for preparative purposes. Only the most important methods, from a preparative point of view, are given here. The present method is adapted from that of Adkins,[1] which in turn was based upon those of Mignonac,[2] von Braun and coworkers,[3] and Mailhe.[4] Benzyl cyanide has been converted to the amine by catalytic reduction with palladium on charcoal,[5] with palladium on barium sulfate,[6] and with Adams' catalyst;[7] by chemical reduction with sodium and ethanol,[8] and with zinc dust and mineral acids.[9] Hydrocinnamic acid has been converted to the azide and thence by the Curtius rearrangement to β-phenylethylamine;[10] also the Hofmann degradation of hydrocinnamide has been used successfully.[11] β-Nitrostyrene,[12] phenylthioacetamide,[13] and the benzoyl derivative of mandelonitrile[14] all yield β-phenylethylamine upon reduction. The amine has also been prepared by cleavage of N-(β-phenylethyl) phthalimide[15] with hydrazine; by the Delépine synthesis from β-phenylethyl iodide and hexamethylenetetramine;[16] by the hydrolysis of the corresponding urethan and urea;[17] by reduction of phenylacetaldoxamine;[18] and by catalytic reduction of O-carbethoxymandelonitrile in the presence of acids.[19]

More recent methods for preparation of the amine include the lithium aluminum hydride reduction of β-nitrostyrene[20] and of phenylacetamide.[21]

The Raney nickel reduction of the nitrile in the presence of formamide is reported to give an 87% yield of the formylated primary amine.[22]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

benzoyl derivative of mandelonitrile

phenylacetaldoxamine

ethanol (64-17-5)

ammonia (7664-41-7)

methanol (67-56-1)

ether (60-29-7)

formamide (75-12-7)

hydrogen (1333-74-0)

nickel, Raney nickel (7440-02-0)

barium sulfate (7727-43-7)

zinc (7440-66-6)

sodium (13966-32-0)

palladium (7440-05-3)

Benzyl cyanide (140-29-4)

urea (57-13-6)

hydrazine (302-01-2)

Hydrocinnamic acid (501-52-0)

hexamethylenetetramine (100-97-0)

β-Nitrostyrene (102-96-5)

α-Phenylethylamine (3886-69-9)

Phenylethylamine, β-Phenylethylamine (64-04-0)

lithium aluminum hydride (16853-85-3)

n-amyl cyanide (628-73-9)

Di-(β-phenylethyl)-amine

3,4-dimethoxyphenylethylamine (120-20-7)

3,4-methylenedioxyphenylethylamine (1484-85-1)

hydrocinnamide (102-93-2)

phenylthioacetamide (645-54-5)

N-(β-phenylethyl) phthalimide

β-phenylethyl iodide (17376-04-4)

O-carbethoxymandelonitrile

Phenylacetamide (103-81-1)

n-hexylamine (111-26-2)

o-methylphenylethylamine

m-methylphenylethylamine

p-methylphenylethylamine (3261-62-9)

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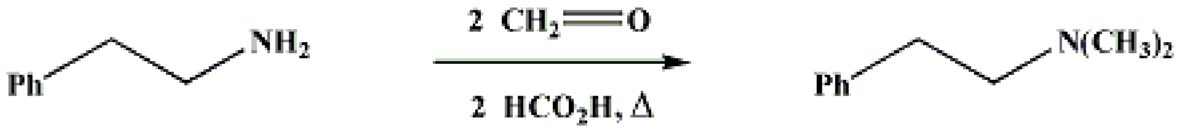
Organic Syntheses, CV 3, 723

β-PHENYLETHYLDIMETHYLAMINE

[Phenethylamine, N,N-dimethyl-]



Submitted by Roland N. Icke, Burnett B. Wisegarver, and Gordon A. Alles.
Checked by H. R. Snyder and James H. Saunders.

1. Procedure

To 51.2 g. (1 mole) of 90% formic acid in a 500-ml. round-bottomed flask (Note 1), cooled in running tap water, is added slowly 24.2 g. (0.2 mole) of β-phenylethylamine. To the resulting clear solution are added 45 ml. (0.6 mole) of formaldehyde solution (concentration, 37%) (Note 2) and a small boiling stone. The flask is connected to a reflux condenser and is placed in an oil bath which has been heated to 90–100°. A vigorous evolution of carbon dioxide begins after 2–3 minutes, at which time the flask is removed from the bath until the gas evolution notably subsides (15–20 minutes); then it is returned to the bath and heated at 95–100° for 8 hours.

After the solution has been cooled, 100 ml. of 4 *N* hydrochloric acid is added and the solution is evaporated to dryness under reduced pressure (water pump) from a water bath; the receiver is cooled in an ice bath. The pale yellow syrupy residue (or crystalline solid) is dissolved in 60–75 ml. of water, and the organic base is liberated by the addition of 50 ml. of 18 *N* sodium hydroxide solution. The upper (organic) phase is separated, and the lower (aqueous) phase is extracted with two 30-ml. portions of benzene. The combined organic base and benzene extracts are dried over 10 g. of anhydrous granular potassium carbonate (Note 3). After the benzene has been distilled slowly under slightly reduced pressure from a 125-ml. Claisen flask, the pressure is lowered further, and the product is distilled. The yield of colorless β-phenylethyldimethylamine boiling at 97–98°/22 mm. (Note 4) is 22–24.7 g. (74–83%) (Note 5).

2. Notes

1. A flask of this size is used because of the tendency of the solution to froth during the gas evolution. Frothing usually is not bad with this amine but is quite bothersome when the higher aliphatic amines (decylamine to octadecylamine) are methylated.
2. U.S.P. formaldehyde was used. The commercial aqueous-methanolic solution contains 37% formaldehyde by weight. It is sometimes called "40% formalin" because 100 ml. of the solution contains 40 g. of formaldehyde.

3. If complete separation of the benzene extracts from the aqueous solution is difficult, it is advantageous to dry the benzene solution roughly over 10 g. of the anhydrous potassium carbonate and to decant the resulting clear solution into another flask where it may be dried over 5 g. of fresh drying agent. The spent drying agent is rinsed with 15–20 ml. of benzene, and the rinsings are added to the main solution.

4. Another boiling point is 66–68°/6 mm. If the product is distilled through a short column (12–15 cm.) packed with glass helices, it boils constantly at 98°/22 mm. The recovery is somewhat lower when a column is used.

The product gives a negative carbylamine test and hence contains no significant amount of unchanged primary amine.

5. This methylation procedure is quite generally satisfactory for simple primary and secondary amines. For methylation of a secondary amine only half as much formaldehyde is required, although a larger amount does no harm. The submitters also have prepared, in uniformly good yields, benzyldodecylmethylamine (b.p. 180–182°/4 mm.) from benzyldodecylamine, and α-amylhexyldimethylamine (b.p. 115°/16 mm.) from α-amylhexylamine. It is reported[1] that the reaction can be successfully applied to the methylation of butylamine, benzylamine, tetramethylenediamine, piperidine, and α-phenyl-α-aminobutyric acid.

3. Discussion

The procedure given above is an adaptation of the methylation method first used by Sommelet and Ferrand[2] and developed more fully by Clarke, Gillespie, and Weisshaus.[1] β-Phenylethyldimethylamine has been prepared from β-phenylethylamine by alkylation with dimethyl sulfate;[3] by the reaction of β-phenylethylamine and of N-methyl-β-phenylethylamine with formaldehyde;[4] by catalytic reduction of phenylacetonitrile in the presence of dimethylamine;[5] by the reaction of dimethylamine with β-phenylethyl chloride[6,7,8] and with β-phenylethyl bromide;[8] and by the reaction of phenylacetaldehyde with dimethylamine.[9]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 315

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

sodium hydroxide (1310-73-2)

formaldehyde (630-08-0)

formic acid (64-18-6)

carbon dioxide (124-38-9)

dimethyl sulfate (77-78-1)

piperidine (110-89-4)

phenylacetonitrile (140-29-4)

β-phenylethyl chloride (622-24-2)

β-phenylethyl bromide (103-63-9)

benzylamine (100-46-9)

dimethylamine (124-40-3)

phenylacetaldehyde (122-78-1)

β-Phenylethylamine (64-04-0)

β-PHENYLETHYLDIMETHYLAMINE, Phenethylamine, N,N-dimethyl- (1126-71-2)

decylamine (2016-57-1)

octadecylamine (124-30-1)

benzyldodecylmethylamine

benzyldodecylamine

α-amylhexyldimethylamine

α-amylhexylamine (33788-00-0)

α-phenyl-α-aminobutyric acid (33875-38-6)

N-methyl-β-phenylethylamine (589-08-2)

Butylamine (109-73-9)

tetramethylenediamine (110-60-1)

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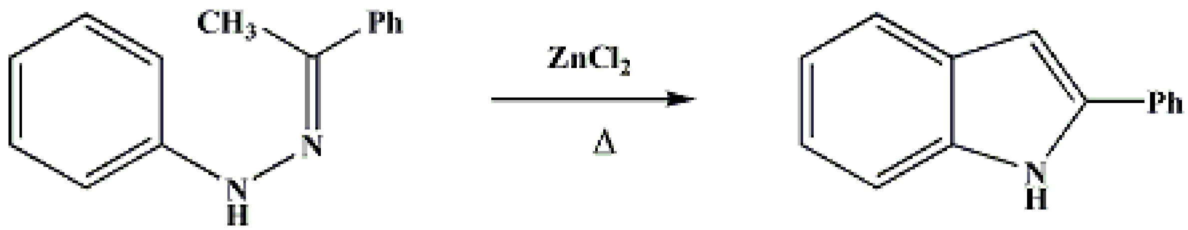
Organic Syntheses, CV 3, 725

2-PHENYLINDOLE

[Indole, 2-phenyl-]



Submitted by R. L. Shriner, W. C. Ashley, and E. Welch.
Checked by Homer Adkins, Alan K. Roebuck, and Harry Coonradt.

1. Procedure

In a tall 1-l. beaker is placed an intimate mixture of 53 g. (0.25 mole) of freshly prepared acetophenone phenylhydrazone (Note 1) and 250 g. of powdered anhydrous zinc chloride (Note 2). The beaker is immersed in an oil bath at 170°, and the mixture is stirred vigorously by hand. The mass becomes liquid after 3–4 minutes, and evolution of white fumes begins. The beaker is removed from the bath, and the mixture is stirred for 5 minutes. In order to prevent solidification to a hard mass, 200 g. of clean sand is thoroughly stirred into the reaction mixture. The zinc chloride is dissolved by digesting the mixture overnight on the steam cone with 800 ml. of water and 25 ml. of concentrated hydrochloric acid (sp. gr. about 1.2). The sand and crude 2-phenylindole are removed by filtration, and the solids are boiled with 600 ml. of 95% ethanol. The hot mixture is decolorized with Norit and filtered through a hot 10-cm. Büchner funnel, and the sand and Norit are washed with 75 ml. of hot ethanol. After the combined filtrates are cooled to room temperature, the 2-phenylindole is collected on a 10-cm. Büchner funnel and washed three times with small amounts (15–20 ml.) of cold ethanol. The first crop is quite pure; after drying in a vacuum desiccator over calcium chloride it weighs 30–33 g. and melts at 188–189° (cor.) (Note 3) and (Note 4).

A little Norit is added to the combined filtrate and washings, which are then concentrated to a volume of 200 ml. and filtered. The filtrate, on cooling, deposits a second crop of 5–6 g. (Note 5) of impure product, which melts at 186–188°. The total yield of 2-phenylindole is 35–39 g. (72–80%).

2. Notes

1. Acetophenone phenylhydrazone is prepared [1] by warming a mixture of 40 g. (0.33 mole) of acetophenone and 36 g. (0.33 mole) of phenylhydrazine on the steam cone for 1 hour. The hot mixture is dissolved in 80 ml. of 95% ethanol,

and crystallization is induced by agitation. The mixture is then cooled in an ice bath, and the product is removed and washed with 25 ml. of ethanol. There is obtained 54–57 g. of white product. A second crop of 4–10 g. is obtained by concentrating the combined filtrate and washings. The combined solids are dried under reduced pressure, over calcium chloride, for 30 minutes. The total yield of acetophenone phenylhydrazone, m.p. 105–106°, is 61–64 g. (87–91%).

2. It has been reported[2] that such a large amount of zinc chloride is not necessary, but the submitters found that equal parts of acetophenone phenylhydrazone and zinc chloride gave lower yields.

3. Using 3.2 times the quantities specified above, except that no sand was added in separating the product, the checkers have obtained yields of 75–80% of 2-phenylindole.

4. While drying, the surface of the product becomes very light green.

5. The filtrate still contains some 2-phenylindole, but great difficulty is encountered in trying to purify the crude material.

3. Discussion

2-Phenylindole has been prepared by heating benzoyl-*o*-toluidine in an atmosphere of hydrogen,[3] the reaction being improved by the use of sodium amyloxide as the condensing agent; by heating phenylacetaldehydephenylhydrazone with 5 parts of anhydrous zinc chloride;[4] by warming phenacyl bromide[5,6] or N-phenacylaniline with aniline,[7] aniline hydrochloride, or zinc chloride;[8] by elimination of water from *o*-aminodesoxybenzoin,[9] prepared in turn from *o*-nitrodesoxybenzoin; by dehydration of benzal-*o*-toluidine;[10] by the action of anhydrous zinc chloride[11] or boron trifluoride[12] upon the phenylhydrazone of acetophenone; by the action of potassium amide and potassium nitrate upon 2-phenyl-4-quinolinecarboxylic acid.[13] N^{15}-2-Phenylindole has been prepared from the α-N^{15}-phenylhydrazone of acetophenone.[14]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium amyloxide

o-aminodesoxybenzoin

o-nitrodesoxybenzoin

phenylhydrazone of acetophenone

N^{15}-2-Phenylindole

α-N^{15}-phenylhydrazone of acetophenone

ethanol (64-17-5)

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

aniline (62-53-3)

hydrogen (1333-74-0)

aniline hydrochloride (142-04-1)

Phenylhydrazine (100-63-0)

Acetophenone (98-86-2)

Norit (7782-42-5)

zinc chloride (7646-85-7)

potassium nitrate (7757-79-1)

boron trifluoride (7637-07-2)

Phenacyl bromide (70-11-1)

acetophenone phenylhydrazone

potassium amide

2-Phenylindole, Indole, 2-phenyl- (948-65-2)

phenylacetaldehydephenylhydrazone

N-phenacylaniline

2-phenyl-4-quinolinecarboxylic acid (132-60-5)

benzoyl-o-toluidine

benzal-o-toluidine

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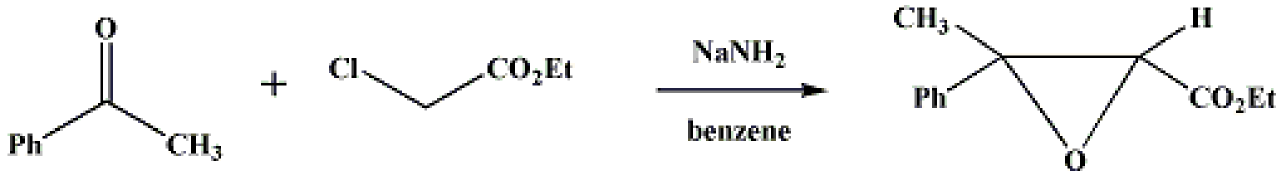
Organic Syntheses, CV 3, 727

PHENYLMETHYLGLYCIDIC ESTER

[Hydrocinnamic acid, α,β-epoxy-β-methyl-, ethyl ester]



Submitted by C. F. H. Allen and J. VanAllan.
Checked by Nathan L. Drake and Carl Blumenstein.

1. Procedure

To a mixture of 120 g. (118.5 ml., 1 mole) of acetophenone (Note 1), 123 g. (109 ml., 1 mole) of ethyl chloroacetate, and 200 ml. of dry benzene in a 1-l. three-necked round-bottomed flask, fitted with a stirrer and low-temperature thermometer, is added, over a period of 2 hours, 47.2 g. (1.2 moles) of finely pulverized sodium amide. The temperature is kept at 15–20° by external cooling (Note 2). After the addition has been completed, the mixture is stirred for 2 hours at room temperature, and the reddish mixture is poured upon 700 g. of cracked ice, with hand stirring. The organic layer is separated and the aqueous layer extracted once with 200 ml. of benzene. The combined benzene solutions are washed with three 300-ml. portions of water, the last one containing 10 ml. of acetic acid. The benzene solution is dried over 25 g. of anhydrous sodium sulfate, filtered, the drying agent rinsed with a little dry benzene, and, after removal of the solvent, the residue is fractionated under reduced pressure, using a modified Claisen flask. The fraction boiling at 107–113°/3 mm. is collected separately and used for the preparation of hydratropaldehyde (p. 733). Redistillation yields a product which boils at 111–114°/3 mm. (Note 3). The yield is 128–132 g. (62–64%) (Note 4).

2. Notes

1. The practical grades of ketone and ester were used.
2. The reaction is strongly exothermic, and much ammonia is evolved.
3. Other boiling points are 272–275°/760 mm. with decomposition; 153–159°/20 mm.; and 147–149°/12 mm.
4. There are several side reactions which reduce the yield. There are always unchanged ketone and ester in the low-boiling fraction, and also some chlorocinnamic ester.

3. Discussion

This is an example of a general reaction by which haloesters are condensed with ketones by means of sodium,[1] sodium ethoxide,[2,3] or sodium amide.[4,5,6]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 733

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Phenylmethylglycidic ester

acetic acid (64-19-7)

ammonia (7664-41-7)

Benzene (71-43-2)

sodium sulfate (7757-82-6)

Acetophenone (98-86-2)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

Ethyl chloroacetate (105-39-5)

sodium amide (7782-92-5)

hydratropaldehyde (93-53-8)

Hydrocinnamic acid, α,β-epoxy-β-methyl-, ethyl ester (77-83-8)

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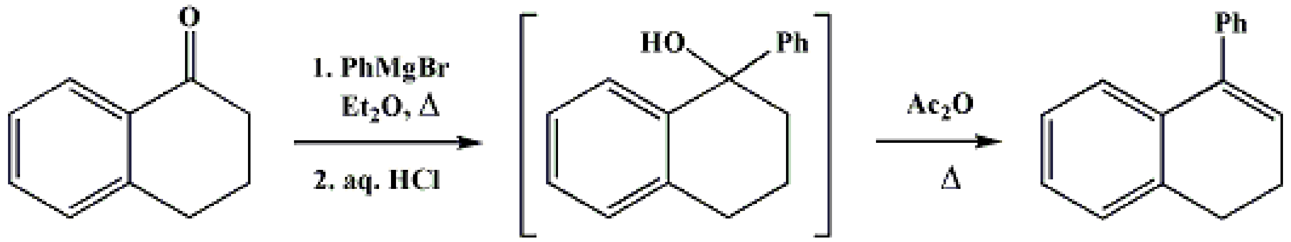
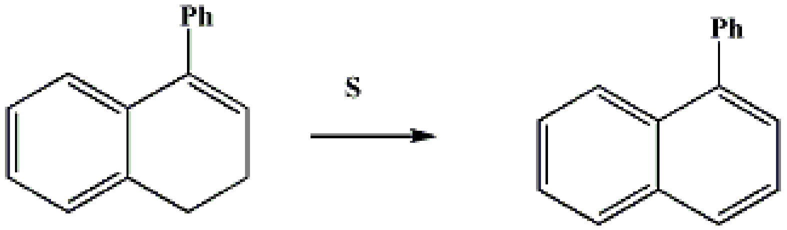
Organic Syntheses, CV 3, 729

1-PHENYLNAPHTHALENE

[Naphthalene, 1-phenyl-]





Submitted by Richard Weiss
Checked by C. F. H. Allen and F. P. Pingert.

1. Procedure

A. 1-*Phenyldialin.* A solution of phenylmagnesium bromide is prepared in the usual manner[1] from 11 g. (0.45 gram atom) of magnesium, 75 g. (0.48 mole) of bromobenzene, and 175 ml. of ether. As soon as the metal has reacted, a solution of 58.4 g. (0.4 mole) of α-tetralone in 60 ml. of ether is added from a dropping funnel as rapidly as possible so that vigorous refluxing is maintained; about 30 minutes is required. The reaction mixture is then heated under reflux for an additional 30 minutes and allowed to stand for 1 hour. The magnesium complex is decomposed by about 250 g. of ice and 40 ml. of concentrated hydrochloric acid. The ether layer is separated and distilled with steam to remove impurities (Note 1); about 6 hours is necessary, and approximately 4.5 l. of distillate is collected. The heavy residual oil is separated from the water, and 80 ml. of ether and 10 g. of calcium chloride are added. After 4–5 minutes, the calcium chloride is removed by filtration, and the ether is driven off by distillation on a steam bath. Twenty milliliters of acetic anhydride is then added, and the flask and contents are heated in a steam bath (Note 2) for 20–25 minutes. The mixture is finally distilled under reduced pressure through a 15-in. Widmer column (Note 3). The fraction which boils at 135–140°/2 mm. is collected; the yield is 35–40 g. (42–48%).

B. 1-*Phenylnaphthalene.* A mixture of 6 g. (0.18 mole) of powdered sulfur and 35 g. (0.17 mole) of 1-phenyldialin in a 200-ml. Claisen flask having a modified side arm is heated for 30 minutes in a metal bath the temperature of which is 250–270° (Note 4). At the end of this time the evolution of hydrogen sulfide will have ceased. The heavy oil (Note 5) is then distilled from the same flask; the yield is 32–33 g. (91–94%); the boiling range of the product is 134–135°/2 mm. or 189–190°/12 mm. (Note 6) and (Note 7)"/>.

2. Notes

1. Steam distillation removes unused bromobenzene, biphenyl, etc.
2. The reaction is best carried out in a 500-ml. Erlenmeyer flask or beaker which can be lowered into the steam pot and held by a cloth wrap.
3. If a fractionating column is not used, several distillations are necessary to secure a product with the boiling range given. When this distillation is done as described, subsequent operations are facilitated, and a column is not required for the final distillation of the hydrocarbon. Ebullition tubes are desirable in both distillations.
4. The temperature inside the flask should be 250°.
5. Significant amounts of hydrocarbon are lost with each change of flask. For this reason it is advisable to perform the dehydrogenation and distillation in the same flask.
6. Sometimes the hydrocarbon is blue, probably owing to traces of an azulene. The contaminant is easily removed by dissolving the hydrocarbon in an equal volume of hexane or petroleum ether and shaking this solution with an equal volume of 85% syrupy phosphoric acid until the color has been removed. The hydrocarbon is then obtained on evaporation of the solvent; it does not need redistillation.
7. The over-all yield is 40%, based on the α-tetralone.

3. Discussion

1-Phenylnaphthalene has been prepared by the reaction of α-halonaphthalenes with mercury diphenyl[2] or with benzene in the presence of aluminum chloride,[2] and by means of a Grignard synthesis, starting with either bromobenzene, or cyclohexyl chloride and α-tetralone[3,4] or with α-bromonaphthalene and cyclohexanone.[3,5,6,7] A 60% over-all yield has been reported for the Grignard preparation from cyclohexanone.[7] The formation of the hydrocarbon through the diazo reaction[8,9,10,11] appears to be less attractive than the method described. Dehydrogenation of the reduced naphthalene has been accomplished by the use of sulfur,[3] bromine,[5] platinum black, or selenium.[4]

References and Notes

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4. Cook and Lawrence, *J. Chem. Soc.*, **1936**,, 1432.
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8. Grieve and Hay, *J. Chem. Soc.*, **1938**, 108.
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

platinum black

mercury diphenyl

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether (60-29-7)

acetic anhydride (108-24-7)

magnesium (7439-95-4)

Cyclohexanone (108-94-1)

hydrogen sulfide (7783-06-4)

bromine (7726-95-6)

sulfur (7704-34-9)

aluminum chloride (3495-54-3)

phosphoric acid (7664-38-2)

bromobenzene (108-86-1)

Biphenyl (92-52-4)

α-Bromonaphthalene (90-11-9)

Naphthalene (91-20-3)

cyclohexyl chloride (542-18-7)

Phenylmagnesium bromide (100-58-3)

selenium

α-Tetralone (529-34-0)

hexane (110-54-3)

1-Phenylnaphthalene, Naphthalene, 1-phenyl- (605-02-7)

1-phenyldialin (643-79-8)

Azulene (275-51-4)

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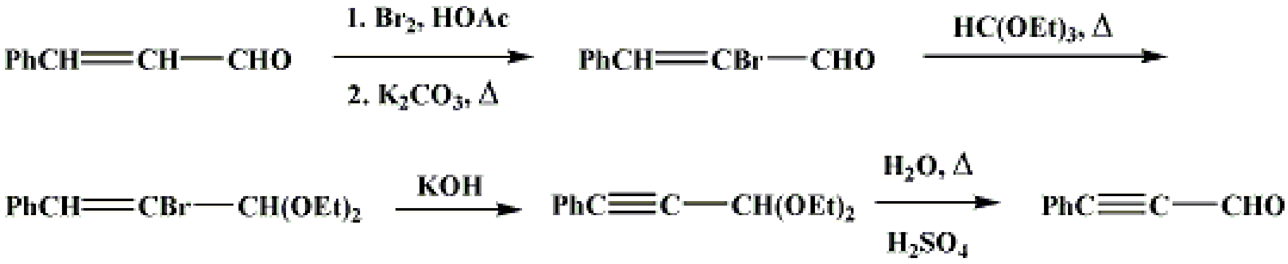
Organic Syntheses, *CV 3, 731*

PHENYLPROPARGYL ALDEHYDE

[Propiolaldehyde, phenyl-]



Submitted by C. F. H. Allen and C. O. Edens, Jr..
Checked by C. D. Heaton and C. R. Noller.

1. Procedure

A. *α-Bromocinnamic aldehyde*. A mixture of 44 g. (0.33 mole) of cinnamic aldehyde and 167 ml. of acetic acid in a 500-ml. three-necked round-bottomed flask, surrounded by a cold-water bath and fitted with a stirrer, reflux condenser, and dropping funnel, is stirred vigorously while 17.1 ml. (53.5 g., 0.33 mole) of bromine is added. This is followed by the addition of 23 g. (0.17 mole) of anhydrous potassium carbonate. When the evolution of gas has ceased, the mixture is refluxed for 30 minutes, then cooled and poured into 435 ml. of water in a 1-l. flask; a lower, reddish layer of crude α-bromoaldehyde separates. The flask is stoppered, cooled under running water, and shaken vigorously. The resulting granular solid is filtered with suction and dissolved without drying by warming with 220 ml. of 95% ethanol. After the addition of 50 ml. of water, the solution is warmed until it becomes clear and is then set aside to crystallize at room temperature and finally in a refrigerator. α-Bromocinnamic aldehyde separates as nearly colorless needles, which are filtered with suction, rinsed with 17 ml. of 80% ethanol, and air-dried. The yield of product melting at 72–73° is 52–60 g. (75–85%) (Note 1).

B. *α-Bromocinnamic aldehyde acetal*. In a 250-ml. flask are placed 45 g. (0.21 mole) of α-bromocinnamic aldehyde, 50 ml. (0.3 mole) of ethyl orthoformate, 40 ml. of absolute ethanol, and 0.5 g. of ammonium chloride. After the mixture has been refluxed for 30 minutes, it is transferred to a modified Claisen flask, and the low-boiling constituents are removed at atmospheric pressure and a bath temperature up to 150° (Note 2). The yield of acetal boiling at 146–149°/5 mm. and with n_D^{22} 1.5500 is 50–52 g. (82–86%).

C. *Phenylpropargyl aldehyde acetal*. A solution of 20.7 g. (0.25 mole) of potassium hydroxide in 200 ml. of absolute ethanol is added to 50 g. (0.18 mole) of α-bromocinnamic aldehyde acetal in a 500-ml. flask. The mixture is refluxed for 1.5 hours and poured into a 3-l. separatory funnel containing 1.5 l. of water. The oil that separates is extracted with three 170-ml. portions of chloroform, and the combined chloroform extracts are washed with three 75-ml. portions of water and then dried over 15 g. of anhydrous sodium sulfate. The chloroform is removed by distillation, and the residual oil is distilled from a modified Claisen flask. The yield of phenylpropargyl aldehyde acetal boiling at 153–156°/19 mm. is 28–31 g. (80–86%).

D. *Phenylpropargyl aldehyde*. Twenty-nine grams (0.14 mole) of the acetal is added to 140 ml. of water containing 10 ml. of concentrated sulfuric acid, and the mixture is heated on a steam bath with occasional shaking for 30 minutes. The aldehyde is then steam-distilled and extracted from the

distillate with two 250-ml. portions of ether. The ethereal solution is dried over 20 g. of anhydrous sodium sulfate, the solvent is removed, and the residue is distilled from a 100-ml. modified Claisen flask. The yield of phenylpropargyl aldehyde boiling at 114–117°/17 mm. and with n_D^{25} 1.6032 is 13–15 g. (70–81%).

2. Notes

1. The same percentage yield is obtained in runs three times as large.
2. Both the reaction and the distillation can be carried out in the same flask.

3. Discussion

The procedure given for the preparation of phenylpropargyl aldehyde is a modification of Claisen's directions[1] in part due to Kalff.[2] The monobromocinnamic aldehyde was described by Zincke.[3] Other methods of possible preparative value for the aldehyde are the interaction of sodium phenylacetylene,[4,5,6,7] or the Grignard reagent from phenylacetylene with ethyl orthoformate. Sodium[5] and lithium[8] phenylacetylene react with ethyl formate to yield the aldehyde.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 801

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ACETAL (105-57-7)

ethanol (64-17-5)

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

ether (60-29-7)

ammonium chloride (12125-02-9)

chloroform (67-66-3)

bromine (7726-95-6)

sodium sulfate (7757-82-6)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

Ethyl orthoformate

ethyl formate (109-94-4)

cinnamic aldehyde

Phenylacetylene (536-74-3)

lithium (7439-93-2)

PHENYLPROPARGYL ALDEHYDE, Propiolaldehyde, phenyl- (2579-22-8)

α-Bromocinnamic aldehyde, monobromocinnamic aldehyde (5443-49-2)

α-Bromocinnamic aldehyde acetal

phenylpropargyl aldehyde acetal

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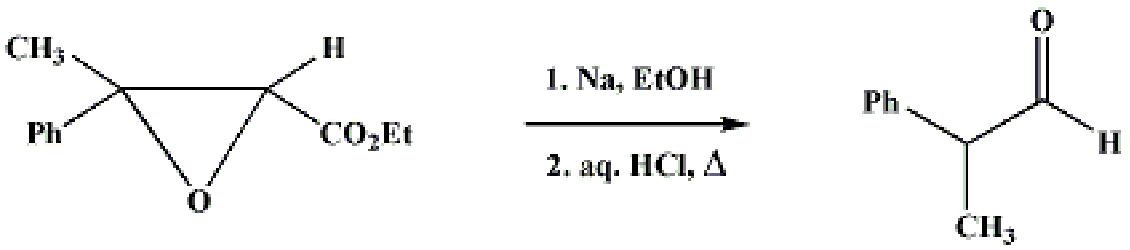
Organic Syntheses, CV 3, 733

α-PHENYLPROPIONALDEHYDE

[Hydratropaldehyde]



Submitted by C. F. H. Allen and J. Vanallan.
Checked by Nathan L. Drake and Carl Blumenstein.

1. Procedure

An ethanolic solution of sodium ethoxide is prepared in a 1-l. round-bottomed flask from 15.5 g. (0.67 gram atom) of sodium and 300 ml. of absolute ethanol (Note 1). One hundred thirty-three grams (0.64 mole) of phenylmethylglycidic ester (p. 727) is added to this solution slowly and with shaking. The flask is then cooled externally to 15°, and 15 ml. of water is slowly added; considerable heat is evolved, and the sodium salt soon begins to separate. After the mixture has stood overnight, the salt is filtered by suction and rinsed with one 50-ml. portion of ethanol and a similar amount of ether. The dried salt weighs 102–108 g. (80–85%) and melts at 255–256° with decomposition.

The salt is added to a dilute solution of hydrochloric acid prepared by mixing 300 ml. of water and 56 ml. of concentrated acid (sp. gr. 1.18); the acid should be contained in a 1-l. flask under a reflux condenser. The mixture is warmed gently, whereupon carbon dioxide is evolved and an oil separates. The flask is heated on a steam bath for 1.5 hours, and the oil is then extracted from the cooled mixture with 150 ml. of benzene. The extract is washed once with 200 ml. of water and distilled under reduced pressure, using an ordinary 500-ml. Claisen flask. The hydratropaldehyde distils at 90–93°/10 mm. or 73–76°/4 mm. (oil bath at 120–130°), leaving only a slight residue (3–5 g.). The yield is 56–60 g. (65–70%) (Note 2) and (Note 3).

2. Notes

1. The metal is placed in the flask, and the ethanol is added through the condenser as fast as refluxing will allow (p. 215, Note 1).
2. The generality of this reaction is limited only by the availability of the glycidic esters.
3. The 2,4-dinitrophenylhydrazone forms yellow prisms that melt at 135°.

3. Discussion

Hydratropaldehyde has been prepared by hydrolysis of phenylmethylglycidic ester,[1,2,3] by chromyl chloride oxidation of cumene,[4] by the elimination of halogen acid or water from halohydrins or glycols,[5,6,7] and by the distillation at ordinary pressure of methylphenylethylene oxide.[8,9]

Hydratropaldehyde has also been prepared by the catalytic addition of hydrogen and carbon monoxide to styrene.[10]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 727
- Org. Syn. Coll. Vol. 6, 1028

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Phenylmethylglycidic ester

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether (60-29-7)

hydrogen (1333-74-0)

carbon monoxide (630-08-0)

carbon dioxide (124-38-9)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

styrene (100-42-5)

cumene (98-82-8)

chromyl chloride

methylphenylethylene oxide (14212-54-5)

hydratropaldehyde, α-PHENYLPROPIONALDEHYDE (93-53-8)

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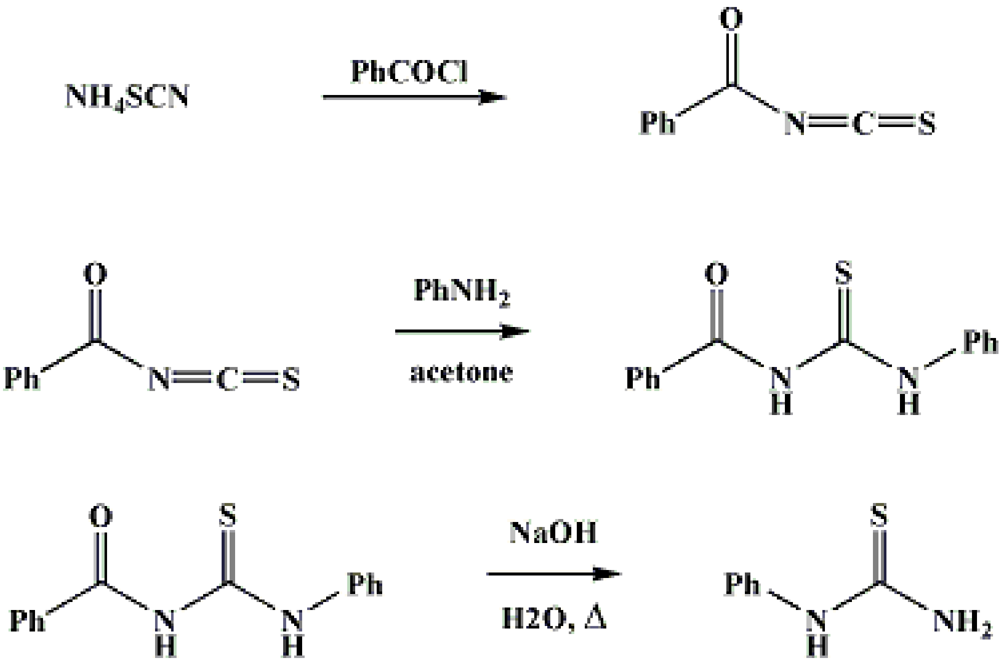
Organic Syntheses, CV 3, 735

α-PHENYLTHIOUREA

[Urea, 1-phenyl-2-thio-]



Submitted by Robert L. Frank and Paul V. Smith[1].
Checked by Richard T. Arnold and Sherman Sundet.

1. Procedure

In a 500-ml. three-necked flask fitted with a reflux condenser, a mechanical stirrer, and a 100-ml. dropping funnel are placed 17 g. (0.22 mole) of ammonium thiocyanate and 100 ml. of dry acetone (Note 1). Through the dropping funnel is added, with stirring, 28.2 g. (0.2 mole) of benzoyl chloride. After the addition is complete, the mixture is refluxed for 5 minutes. Then a solution of 18.6 g. (0.2 mole) of aniline in 50 ml. of dry acetone is added at such a rate that the solution refluxes gently. The mixture is poured carefully with stirring into 1.5 l. of water, and the resulting yellow precipitate (α-benzoyl-β-phenylthiourea) is separated by filtration. The crystals are heated for 5 minutes with a boiling solution of 30 g. of sodium hydroxide in 270 ml. of water. After the removal of a small amount of insoluble material by filtration, the solution is acidified with concentration hydrochloric acid and then made slightly basic with ammonium hydroxide. Upon standing, the solution deposits the crystalline product. The yield of oven-dried material (m.p. 151–153°) is 25.8 g. (85%). Recrystallization from ethanol yields 23.2 g. (76%) of white plates melting at 152.5–153°.

2. Notes

1. The acetone is dried for at least 48 hours over anhydrous calcium sulfate (Drierite) and distilled just before it is used.

3. Discussion

α-Phenylthiourea has been prepared by the action of ammonium thiocyanate,[2] thiocyanic acid,[3] thiuramdisulfide,[4] or silicon thiocyanate[5] on aniline; by the action of ammonium thiocyanate on aniline hydrochloride;[6] by the action of ammonia on phenyl isothiocyanate,[7] 1-phenyl-2-thiobiuret,[8] thiocarbanilide,[9] phenyldithiocarbamazide,[10] or phenyl isothiocyanate hexasulfide;[11] by the addition of hydrogen sulfide to monophenylcyanamide;[12] by the decomposition of salts of phenyldithiocarbamic acid in the presence of lead carbonate,[13] ammonium polysulfide,[14] or ammonium carbonate;[15] by the reaction of thiophosgene, aniline, and ammonia;[16] and by the action of hydrazine hydrate on phenyldithiobiuret.[17]

The preparation of α-phenylthiourea by the procedure described herein has not been reported, although Douglass and Dains[18] have applied the method to the preparation of various substituted phenyl derivatives.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 700

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

phenyl isothiocyanate hexasulfide

ammonium polysulfide

α-Phenylthiourea

α-benzoyl-β-phenylthiourea

salts of phenyldithiocarbamic acid

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ammonium carbonate

ammonia (7664-41-7)

ammonium thiocyanate (1762-95-4)

aniline (62-53-3)

sodium hydroxide (1310-73-2)

hydrogen sulfide (7783-06-4)

aniline hydrochloride (142-04-1)

calcium sulfate (7778-18-9)

acetone (67-64-1)

benzoyl chloride (98-88-4)

Thiophosgene (463-71-8)

ammonium hydroxide (1336-21-6)

hydrazine hydrate (7803-57-8)

PHENYL ISOTHIOCYANATE (103-72-0)

Urea, 1-phenyl-2-thio- (103-85-5)

thiocarbanilide (102-08-9)

thiocyanic acid (463-56-9)

thiuramdisulfide

silicon thiocyanate

1-Phenyl-2-thiobiuret (53555-72-9)

phenyldithiocarbamazide

monophenylcyanamide

phenyldithiobiuret

lead carbonate

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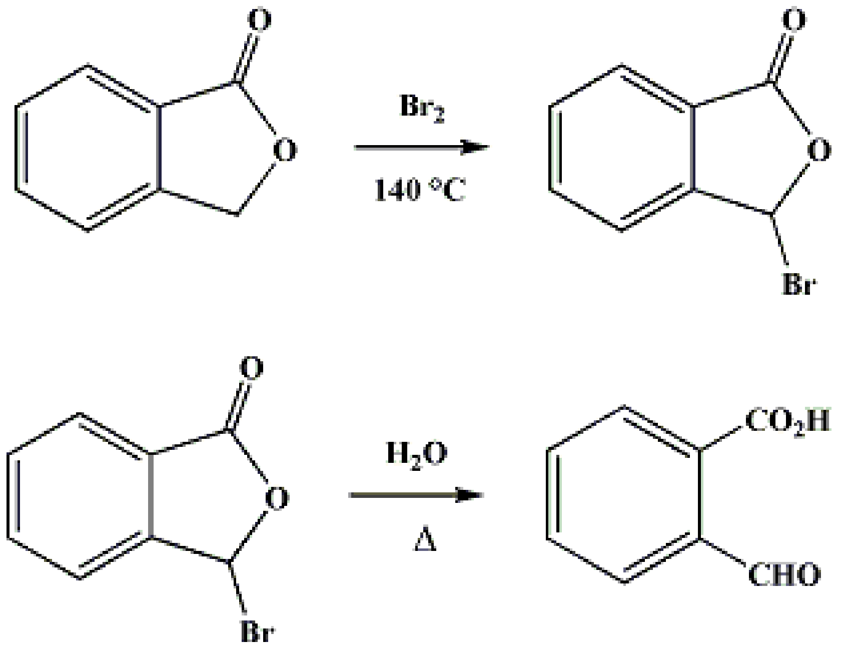
PHTHALALDEHYDIC ACID



Submitted by R. L. Shriner and F. J. Wolf.
Checked by Lee Irvin Smith, R. T. Arnold, and Walter Frajola.

1. Procedure

A. 2-*Bromophthalide.* The apparatus shown in .htmFig. 26 is used for the bromination. Flasks *A* and *B* are of 200-ml. capacity. Bromine is introduced by means of a current of carbon dioxide, which passes through mineral oil or sulfuric acid in the bubble counter, then through the bromine in flask *B*, and finally through the drying tower. The tower is conveniently made from a condenser jacket and is filled with anhydrous calcium chloride. Flask *A* is surrounded by an oil bath and is equipped with a thermometer, an outlet tube of wide bore connected to a gas-absorption trap, and a gas-inlet tube having an inside diameter of 2 mm. The inlet tube reaches to the bottom of the flask.

Fig. 26.

Fig. 26.

In the reaction flask *A* is placed 134 g. (1 mole) of phthalide (Note 1). In flask *B* is placed 160 g. (53.5 ml., 1 mole) of bromine. The oil bath is maintained at 140–155°, and the stream of carbon dioxide is started when the temperature of the phthalide has reached 140°. The temperature inside flask *A* is maintained at 135–150° (oil bath 140–155°) during the course of the reaction (Note 2). Carbon dioxide is introduced at such a rate that no bromine vapor is observed in the outlet tube (5–8 bubbles per second). The stream of carbon dioxide is continued for 30 minutes after all the bromine color

has disappeared from the train. The reaction is complete in 10–13 hours, depending upon the rate at which the bromine has been introduced into the reaction mixture.

While still warm, the reaction mixture is transferred to a 250-ml. modified Claisen flask fitted for distillation under reduced pressure. Any hydrogen bromide remaining in the reaction mixture is removed by heating at 120° under the vacuum of a water pump. The product is then distilled under reduced pressure. The fore-run of less than 15 g. is largely phthalide (Note 3). The 2-bromophthalide, which distils at 138–142°/4 mm. (128–132°/2 mm.), weighs 175–178 g. (82–83% based on the phthalide) (Note 4). It is water-clear and solidifies to a solid which melts at 69–73°.

The distilled product is pure enough for use in the subsequent hydrolysis, but it may be purified by recrystallization from 100 ml. of carbon tetrachloride. Upon cooling, 100 g. of pure 2-bromophthalide melting at 75° is obtained. An additional 30–40 g. of slightly yellow material is obtained by concentrating the mother liquor.

B. *Phthalaldehydic acid.* The entire distillate is placed in a 500-ml. flask and covered with 230 ml. of water. The flask is equipped with a mechanical stirrer and is heated on a steam cone. The hydrolysis is complete when the layer of 2-bromophthalide has disappeared (about 30 minutes). The reaction mixture is then placed in a refrigerator overnight, during which time the entire mass solidifies. The product is filtered, washed with two 50-ml. portions of ice water, and dried in the air. The yield of crude product melting at 60–65° (Note 5) is 140–160 g.

The crude product is recrystallized from 400 ml. of hot water and dried in the air. The recrystallized product is white, melts at 95–96°, and weighs 97–102 g. (78–83% based on the bromo compound or 65–68% based on the phthalide).

2. Notes

1. The phthalide used by the submitters and by the checkers was a commercial product, obtained from E. I. du Pont de Nemours and Company, Wilmington, Delaware. This product is no longer available. Phthalide may be prepared in 82.5% yield by hydrogenation of phthalic anhydride in benzene at 270° under 3000 lb. pressure in the presence of copper chromite[1] or, in yields of 61–71%, from phthalimide according to the procedure given in *Org. Syntheses* Coll. Vol. **2**, 526 (1943).
2. At a temperature below 135°, bromination does not take place readily. Above 155°, the reaction mixture becomes considerably darker, and the yield is lower.
3. A change in crystalline structure of the distillate is observed when all the phthalide has been removed.
4. The checkers consistently obtained yields of at least 87%, and in one run the yield of product melting at 78° was 95%.
5. In one run, the checkers obtained 180 g. of product which melted at 67°. This, after recrystallization, melted at 94.5–95° and weighed 121 g. This yield is 84.9% of the theoretical amount based on the bromo compound, or 80% based

on the phthalide. The crude product holds water tenaciously, but this is removed by allowing the product to stand in a vacuum desiccator over Drierite.

3. Discussion

To the methods listed in *Org. Syntheses* Coll. Vol. **2**, 523 (1943) may be added the hydrolysis of 2-chlorophthalide;[2] the action of carbon dioxide and sodium, under pressure, upon *o*-chlorobenzaldehyde;[3] and from the hydrolysis of methyl phthalaldehydate, obtained by the Rosenmund reduction of the acid chloride of methyl hydrogen phthalate.[4] The procedure described above is essentially that of Racine.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 145

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Drierite

acid chloride of methyl hydrogen phthalate

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

Benzene (71-43-2)

hydrogen bromide (10035-10-6)

bromine (7726-95-6)

carbon tetrachloride (56-23-5)

carbon dioxide (124-38-9)

phthalic anhydride (85-44-9)

sodium (13966-32-0)

Phthalimide (85-41-6)

COPPER CHROMITE

Phthalaldehydic acid (119-67-5)

2-chlorophthalide

Phthalide (87-41-2)

2-bromophthalide (6940-49-4)

methyl phthalaldehydate (4122-56-9)

o-chlorobenzaldehyde (89-98-5)

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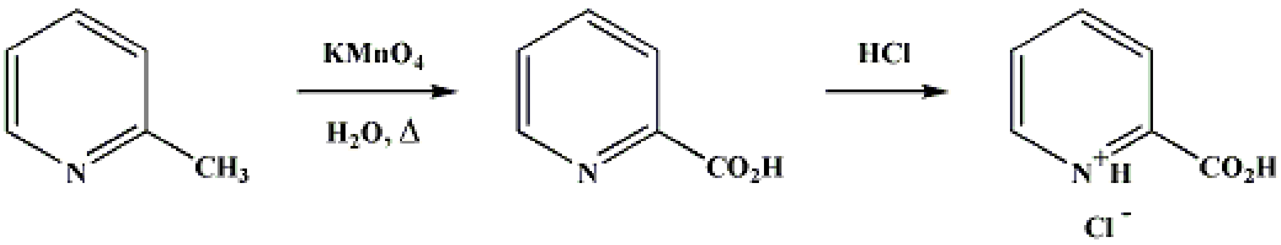
Organic Syntheses, CV 3, 740

PICOLINIC ACID HYDROCHLORIDE



Submitted by Alvin W. Singer and S. M. McElvain.
Checked by C. F. H. Allen and Alan Bell.

1. Procedure

In a 5-l. three-necked flask, fitted with a reflux condenser and stirrer, are placed 2500 ml. of water and 50 g. of α-picoline (0.54 mole) (Note 1). Ninety grams (0.57 mole) of potassium permanganate is added, and the solution is heated on a steam bath until the purple color has practically disappeared (about 1 hour). A second 90-g. portion of permanganate is then introduced, followed by 500 ml. of water, and the heating is continued until the purple color is destroyed (2–2.5 hours). The reaction mixture is allowed to cool slightly, and the precipitated oxides of manganese are filtered and washed well with 1 l. of hot water (Note 2). The filtrate is concentrated under reduced pressure to 150–200 ml., filtered, if necessary, and acidified to Congo red with concentrated hydrochloric acid (65–70 ml., sp. gr. 1.19). This acid solution is then evaporated to dryness under reduced pressure. The solid residue is refluxed for one hour with 250 ml. of 95% ethanol and filtered, and the extraction is repeated with 150 ml. of 95% ethanol. Dry hydrogen chloride is passed into the combined ethanolic filtrates until crystals begin to separate. The solution is then chilled to about 10° in a freezing mixture, the addition of hydrogen chloride being continued until the solution is saturated. The crystals of picolinic acid hydrochloride which separate are filtered and air-dried. The yield is 43–44 g. (50–51%), m.p. 228–230° (Note 3).

This hydrochloride may contain traces of potassium chloride, which can be removed by dissolving the hydrochloride in hot absolute ethanol (50 g. requires 1 l.) and filtering from insoluble material. An equal volume of dry ether is then added to the warm ethanolic solution, and, after cooling, the crystallized product is filtered. The recovery is 40–43 g., m.p. 210–212° (230°) (Note 3) and (Note 4).

2. Notes

1. The submitters used a picoline fraction, b.p. 128–132°, whereas the checkers used the practical product, Eastman Kodak Company, b.p. 128–134°. The same yield was obtained with a carefully fractionated picoline, boiling over the 1° range 128–129°.
2. The washed manganese dioxide does not contain an appreciable amount of acid.
3. When the melting point is determined in the ordinary manner, it is found to be 228–230° with decomposition. If, on approaching the melting point, the rate of heating is reduced to 1° in 5 minutes, the value 210–212° can be observed.
4. About 2 g. of potassium chloride is removed by this procedure. The unpurified material can be used for most purposes.

3. Discussion

Picolinic acid has been generally prepared by the permanganate oxidation of α-picoline and isolated through the copper salt.[1,2,3,4,5] In one instance,[6] it was isolated directly as in the present procedure. It has also been secured by the hydrolysis of ω-trichloropicoline,[7,8] and by the nitric acid oxidation of α-picoline.[9]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

oxides of manganese

ω-trichloropicoline

ethanol (64-17-5)

hydrogen chloride, hydrochloric acid (7647-01-0)

ether (60-29-7)

nitric acid (7697-37-2)

potassium permanganate (7722-64-7)

manganese dioxide (1313-13-9)

permanganate

potassium chloride (7447-40-7)

Picolinic acid hydrochloride (636-80-6)

picoline, α-picoline (109-06-8)

Picolinic acid (98-98-6)

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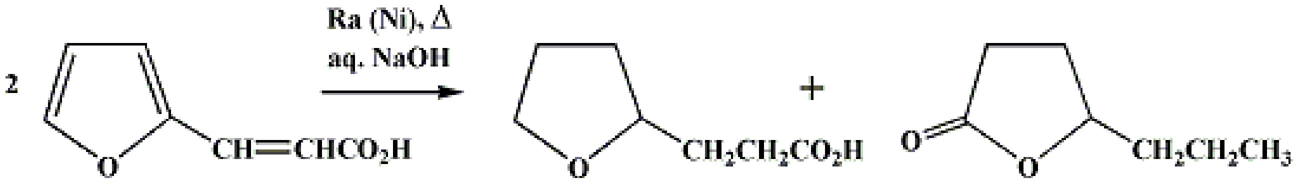
Organic Syntheses, CV 3, 742

γ-*n*-PROPYLBUTYROLACTONE AND β-(TETRAHYDROFURYL)PROPIONIC ACID

[Enanthic acid, γ-hydroxy-, lactone, and 2-furanpropionic acid, tetrahydro-]



Submitted by Erwin Schwenk, Domenick Papa, Hilda Hankin, and Helen Ginsberg.
Checked by Cliff S. Hamilton and Flaven E. Johnson.

1. Procedure

In a 2-l. beaker resting on a hot plate and equipped with a mechanical stirrer are placed 150 g. of sodium hydroxide (Note 1) dissolved in 800 ml. of water and 41.4 g. (0.3 mole) of furylacrylic acid (p. 425). The stirrer is started, and to the warm solution (Note 2) 100 g. of Raney nickel-aluminum alloy is added, in small portions, over a period of 4–4.5 hours (Note 3) and (Note 4). During the addition of the alloy, the temperature of the mixture is kept at 60–70° and then is raised to approximately 95° where it is held for an additional 2–3 hours, with stirring. From time to time sufficient water is added to the reaction mixture to maintain approximately the original volume. The hot solution is filtered by decantation, and the nickel residue (Note 5) is washed with two 50-ml. portions of hot 2% sodium hydroxide solution. The combined filtrates and washings are cooled and then immediately added slowly (Note 6), with good stirring, to 800 ml. of concentrated hydrochloric acid (Note 7). The solution at this point is strongly acid to Congo red paper (Note 8). The acidified solution is cooled and thoroughly extracted with three 200-ml. portions of ether (Note 9). The ether extracts are combined and washed once with 100 ml. of 10% sodium chloride solution, the ether is evaporated, and the residue is fractionally distilled in a modified Claisen flask. The yield of γ-*n*-propylbutyrolactone boiling at 84–85°/5 mm., n_D^{25} 1.4385, is 13.0–14.9 g. (33–37%), while the yield of β-(tetrahydrofuryl) propionic acid boiling at 123–124°/5 mm., n_D^{25} 1.4578, is 15.0–17.0 g. (34–39%) (Note 10), (Note 11).

2. Notes

1. Solid sodium hydroxide is used in order to take advantage of the heat of solution. If the mixture at this stage is allowed to cool, it will be necessary to heat the solution to 50–60° before the addition of the alloy is begun.
2. Some of the furylacrylic acid remains undissolved but goes into solution readily after the addition of the nickel-aluminum alloy is begun.
3. If any excessive frothing occurs during the addition of the alloy, a few drops of octyl alcohol can be added from time to time.
4. During the addition of the alloy, it is advantageous to stir the solution efficiently, the alloy being added in the vortex of the solution. If the addition of the alloy is made on the surface of the liquid, most of the hydrogen developed is lost without entering into the reaction.
5. The Raney nickel residue is quite active and will ignite if allowed to become dry. It may readily be disposed of by pouring into dilute mineral acid. This nickel residue is sufficiently active for various types of catalytic hydrogenations requiring the use of Raney nickel catalyst.

6. If the acidified mixture is allowed to become too hot, some of the material may be lost by steam distillation.
7. The alkaline solution is added to the hydrochloric acid in the manner described, since the reverse order of addition usually results in the precipitation of aluminum salts which dissolve only after considerable heating and stirring. The alkaline solution is added at such a rate that at no time is there any appreciable amount of solid present.
8. If insufficient hydrochloric acid is used at this stage, aluminum salts will precipitate and will make the ether extractions difficult because of the formation of emulsions.
9. The acidified solution has also been extracted with ether in a continuous liquid-liquid extractor, this extraction requiring approximately 20 hours. Only slightly higher yields of the two products are obtained by this modification.
10. According to the submitters an alternative procedure for the separation of γ-*n*-propylbutyrolactone and β-(tetrahydrofuryl) propionic acid is the following:
The ether extracts, after washing with salt solution, are extracted with one 100-ml. and two 50-ml. portions of 5% sodium carbonate solution. It is important that the ether solution be free of any mineral acid before the carbonate extractions are made. The residual ether solution, after being washed with 10% sodium chloride solution, is dried over sodium sulfate. The ether is removed by distillation, and the residue is distilled under reduced pressure. The yield of γ-*n*-propylbutyrolactone is 14.5 g. (36%), b.p. 78–80°/2 mm. The combined sodium carbonate extracts are acidified to Congo red paper with concentrated hydrochloric acid and then thoroughly extracted with one 100-ml. and two 50-ml. portions of ether. The combined ether extracts are washed with 10% sodium chloride solution and dried; and, after the ether is removed by distillation, the residue is distilled under reduced pressure. The yield of β-(tetrahydrofuryl)propionic acid is 15.9 g. (36%), b.p. 118–120°/2 mm.
11. The submitters have used this procedure for the reduction of β-(α-thenoyl) propionic acid[1] from which ω-hydroxycaprylic acid[2] has been obtained in a yield of 38%, melting at 54–55°, and δ-*n*-propylvalerolactone in a yield of 31%, boiling at 116–117°/10 mm.

3. Discussion

γ-*n*-Propylbutyrolactone has been obtained from γ-bromoenanthic acid on boiling with water,[3] from β, γ-hepteneoic acid and sulfuric acid,[4] and by distilling γ-propylparaconic acid.[5]

β-(Tetrahydrofuryl) propionic acid has been obtained from furylacrylic acid by catalytic reduction with platinum oxide,[6] with nickel on kieselguhr,[7] with platinum black,[8] or with Raney nickel.[9] It has also been obtained from β-furyl-β-propiolactone by reduction,[10] and from 2-tetrahydrofurylpropanol by oxidation.[11]

The reduction procedure described has been published.[12]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

platinum black

β-(α-thenoyl) propionic acid

β,γ-hepteneoic acid

γ-propylparaconic acid

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

platinum oxide

nickel (7440-02-0)

Furylacrylic acid (539-47-9)

octyl alcohol (111-87-5)

nickel-aluminum

γ-n-PROPYLBUTYROLACTONE, Enanthic acid, γ-hydroxy-, lactone (105-21-5)

β-(Tetrahydrofuryl)propionic acid, 2-furanpropionic acid, tetrahydro-, β-(tetrahydrofuryl) propionic acid (935-12-6)

ω-hydroxycaprylic acid (764-89-6)

γ-bromoenanthic acid

β-furyl-β-propiolactone

2-tetrahydrofurylpropanol

δ-n-propylvalerolactone (698-76-0)

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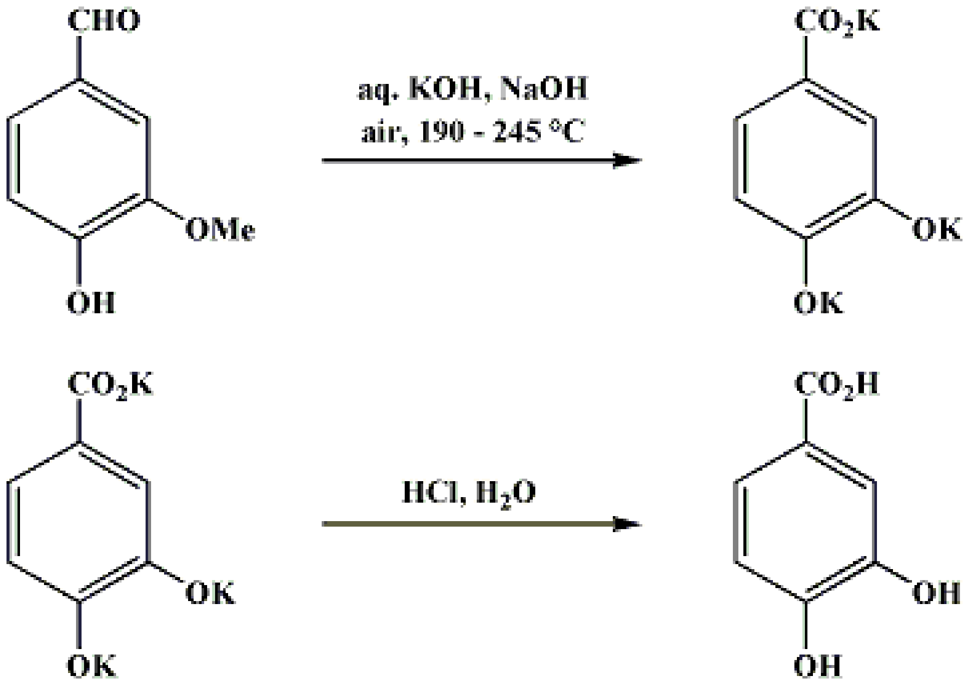
Organic Syntheses, CV 3, 745

PROTOCATECHUIC ACID

[Benzoic acid, 3,4-dihydroxy-]



Submitted by Irwin A. Pearl
Checked by C. F. H. Allen and Calvin Wolf.

1. Procedure

In a stainless-steel beaker of approximately 3-l. volume (180 mm. by 150 mm.) (Note 1), equipped with an efficient mechanical stainless-steel stirrer and heated by an electric hot plate, are placed 84 g. (2 moles) of 97% sodium hydroxide pellets, 332 g. (5 moles) of 85% potassium hydroxide pellets (Note 2), and 50 ml. of water. The mixture is stirred and heated. When the temperature of the fluid mixture reaches 160°, 152 g. (1 mole) of vanillin is added in portions over a period of 2.5–3 minutes at a rate sufficient to maintain the reaction (Note 3). The temperature at this point is 190–195°. Stirring is continued, and heat is applied until the temperature reaches 240–245° (Note 4). The temperature is maintained at 240–245° for 5 minutes. The hot plate is removed, and the mixture is allowed to cool with stirring. When the mixture has cooled to about 150–160°, 1 l. of water is added, and the mixture is stirred until all the fusion mixture is dissolved. The solution is transferred to a 4-l. beaker, another 500 ml. of water is added, and sulfur dioxide gas is introduced for 2 minutes (Note 5); the mixture is then completely acidified with 1.5 l. of 6 *N* hydrochloric acid. The acidified mixture is cooled in an ice bath (5°) for 2 hours, and the crystalline precipitate is filtered, washed on the filter with two 100-ml. portions of ice water, and air dried. The tan crystals of protocatechuic acid melting at 196–198° weigh 90–100 g. Extraction of the filtrate and washings with two 1-l. portions of ether yields an additional 45–55 g.

of protocatechuic acid melting at 190°. The total yield of crude protocatechuic acid amounts to 135–153 g. (89–99%) (Note 6).

2. Notes

1. In the checkers' opinion a 2-l. beaker is sufficiently large, and the contents are easier to stir. Iron or nickel pots have also been used.
2. The exact proportion of sodium hydroxide to potassium hydroxide is not too critical as long as the total amount of alkali is more than 7 moles. Mixtures containing from 10% to 60% sodium hydroxide become fluid between 120° and 130°. Increased percentages of sodium hydroxide in the mixture result in darker protocatechuic acid, but yields are not affected until 70% sodium hydroxide is reached.
3. This reaction is the oxidation of vanillin to vanillic acid with the liberation of hydrogen.
4. The demethylation of vanillic acid to protocatechuic acid takes place to a slight degree between 210° and 235° but goes to completion only at temperatures above 240–245°.
5. The sulfur dioxide treatment prevents the formation of a very dark-colored product when the reaction mixture is acidified with a strong acid.
6. The first crop of acid is light tan and is suitable for most purposes. It can be improved slightly by recrystallizing from hot water, with 3 ml. per g. and 1 g. of Norit for every 10 g. of acid; the recovery is 75%, the remainder being retained by the charcoal. This recrystallized acid is a cream color and melts at 199–200°. If the Norit is omitted, the recovery is 90%, m.p. 198–199°, and color unchanged.

The second crop is of decidedly inferior quality. It is easily purified as follows: Fifteen grams of crude product is dissolved in 100 ml. of 10% sodium hydroxide solution at room temperature, 2 g. of Norit is added, and the mixture is stirred for 10 minutes and filtered. Sulfur dioxide is then passed in for 2 minutes, after which 60 ml. of 6 *N* hydrochloric acid is added. After chilling and standing, 10 g. (67%) of purified protocatechuic acid, m.p. 196–198°, is recovered.

3. Discussion

The only practical method for the preparation of protocatechuic acid is by the alkaline fusion of vanillin.[1,2,3]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

sulfur dioxide (7446-09-5)

Norit (7782-42-5)

potassium hydroxide (1310-58-3)

vanillin (121-33-5)

protocatechuic acid, Benzoic acid, 3,4-dihydroxy- (99-50-3)

Vanillic acid (121-34-6)

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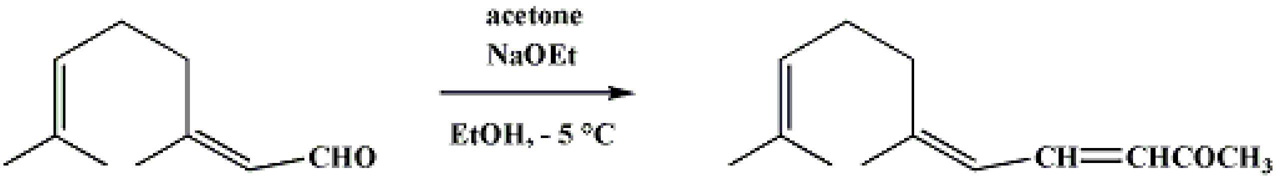
Organic Syntheses, *CV 3*, *747*

PSEUDOIONONE



Submitted by Alfred Russell and R. L. Kenyon.
Checked by Lee Irvin Smith, W. B. Renfrow, Jr., and Louis E. De Mytt.

1. Procedure

A. *Purification of citral*. In a 4-l. bottle are placed 1 l. of water, 1 kg. of crushed ice, 450 g. of anhydrous sodium sulfite (or an equivalent amount of hydrated sodium sulfite), 320 g. of sodium bicarbonate, and 270 g. (304 ml., 1.78 moles) of commercial citral (Note 1). A tightly fitting stopper is securely wired into place, and the bottle is shaken thoroughly for 5–6 hours. The solution, which contains very little unchanged citral, is extracted twice with 300-ml. portions of ether (Note 2).

A 5-l. round-bottomed flask is fitted with a 1-l. dropping funnel, the mouth of which is connected to a tube passing through the stopper of the flask, and the whole apparatus is rigidly attached to a shaker (Note 3). About one-half of the sulfite solution is placed in the flask and covered with 800 ml. of ether. In the dropping funnel is placed 800 ml. of 10% aqueous sodium hydroxide. Shaking is begun, and when the contents of the flask are thoroughly mixed, the sodium hydroxide solution is admitted in a thin continuous stream over a period of about 1 hour. After all the sodium hydroxide solution is added, shaking is continued for not longer than 5 minutes, and the mixture is then poured into a large separatory funnel. The aqueous layer is drawn off and the ether layer is set aside. The aqueous layer is returned to the separatory funnel, covered with 300 ml. of ether, and shaken with an additional 200 ml. of 10% aqueous sodium hydroxide. After separation, the aqueous layer is extracted once with 150 ml. of ether, and the combined ether extracts are then dried over anhydrous sodium sulfate.

The remaining half of the sulfite solution is subjected to the same treatment, and the total ether extract, after drying, is evaporated on a water bath. The residue is then distilled under reduced pressure, yielding 200–215 g. of almost colorless citral which boils at 84–85°/2 mm. (93–95°/5 mm.).

B. *Pseudoionone*. In a 2-l. round-bottomed flask, fitted with a mechanical stirrer, a dropping funnel, and a thermometer, are placed 203 g. (230 ml., 1.33 moles) of pure citral and 800 g. (110 ml., 13.8 moles) of acetone (C.P., dried over anhydrous potassium carbonate). The mixture is cooled to –5° (or below) in an ice-salt bath, vigorous stirring is begun, and there is added through the dropping funnel a cold solution of 9.2 g. (0.4 mole) of sodium in 200 ml. of absolute ethanol. The solution of sodium ethoxide is added at the maximum rate which will permit maintenance of the temperature at –5° or below (rapid dropping). After the addition is complete, stirring is continued for 3–4 minutes. A solution of 30 g. (0.2 mole) of tartaric acid in 200 ml. of water is added, and the mixture is *immediately* steam-distilled to remove the excess acetone. A white precipitate may form when the tartaric acid is added, but this disappears

during the steam distillation (Note 4). The mixture in the distilling flask is cooled in an ice bath, and the upper layer (about 380 ml.) is then removed and refluxed vigorously for 5–6 hours with three times its volume of 25% aqueous sodium bisulfite.

After cooling, the mixture is extracted twice with 200-ml. portions of ether to remove any material that has not reacted with the bisulfite. One-half of the aqueous solution is placed in the shaking extractor together with 650 ml. of ether. The calculated amount of 10% aqueous sodium hydroxide (1 mole of sodium hydroxide per mole of sodium bisulfite used) is now added as described for purification of the citral. Shaking is continued for 15 minutes after the addition of the alkali is complete (Note 5). The layers are separated (Note 6); the aqueous layer is returned to the separatory funnel and covered with 200 ml. of ether. After 100 ml. of 10% sodium hydroxide has been added, the mixture is vigorously shaken, and then the aqueous layer is removed and extracted with another 200-ml. portion of ether. The two ether extractions, one with addition of sodium hydroxide and one without, are repeated. The second half of the bisulfite solution is subjected to the same treatment as the first half, and all the ether extracts are combined (Note 7) and dried over anhydrous sodium sulfate. The ether is removed on the water bath, and the residual yellow-green oil is distilled under reduced pressure, yielding 120–130 g. (45–49% based upon 210 g. of pure citral) of pale yellow pseudoionone, boiling at 114–116°/2 mm. (124–126°/4 mm.).

2. Notes

1. Unless a pure pseudoionone free from isomers is wanted, it is not necessary to perform the elaborate purification of citral, or the elaborate purification of pseudoionone. The checkers, using commercial citral obtained from the Florasynth Laboratories, Inc., New York, found 90% of it to boil over a 3° range between 100° and 103°/7 mm. Using a solution of 203 g. of this distilled citral in 1 l. of commercial acetone, the checkers proceed as follows: The citral solution is cooled in an ice-salt bath to –10°, and one-fourth of the solution is forced, by dry compressed air, into a 500-ml. round-bottomed three-necked flask, fitted with a stirrer, dropping funnel, and an adjustable outlet tube long enough to reach to the bottom of the flask. The temperature is maintained at 0° to –5° while one-fourth of a solution of 9.2 g. of sodium in 200 ml. of absolute ethanol is added dropwise. After all the base is added, stirring is continued for 3 minutes, and then the reaction mixture is forced over into one-fourth of a solution of 33 g. of tartaric acid in 200 ml. of water. The elapsed time, from the addition of the first drop of base until the mixture is forced into the acid, is 14 minutes. The condensation is repeated three times more, and the combined acidified mixture is steam-distilled until 1 l. of distillate is obtained. It is important that the solution should remain slightly acid during steam distillation. The material remaining in the flask is cooled, the layers are separated, and the aqueous layer is extracted with ether. The combined organic layers are dried over sodium sulfate and then distilled. The yield of pseudoionone boiling at 123–124°/2.5 mm. is 177.8 g. (70% based upon the citral). By carrying out the condensation in small batches, the temperature is much more easily controlled and the yields are greatly improved. This pseudoionone, when catalytically reduced in a bomb, gave hexahydropseudoionol, boiling at 124–128°/10 mm., in a yield of more than 90%.
2. In handling these large quantities, much better results are obtained if extractions, etc., are carried out in portions.
3. A pressure outlet may be used, but the arrangement outlined here is quite sufficient. Citral and pseudoionone are both rapidly polymerized by contact with aqueous sodium

hydroxide. This apparatus continuously provides an intimate mixture of the sulfite solution with the ether. On decomposition, the free carbonyl compound is immediately extracted and prolonged contact with sodium hydroxide is thus avoided.

4. From the completion of addition of the sodium ethoxide solution to the steam distillation, fast work is advantageous, and all equipment should be in readiness before the addition is started. Allowing the solution to stand before addition of the tartaric acid may cause darkening and formation of gummy material. It is important that the solution should remain slightly acid during the steam distillation.

5. The pseudoionone bisulfite addition product, unlike that of citral, apparently decomposes rather slowly; if the separation is made too soon, some undecomposed bisulfite compound is left in solution. This is later decomposed and, in contact with the alkali, polymerizes to a dark red gum.

6. The checkers obtained three layers at this point—a lower aqueous layer, a dark red oily layer, and the upper ether layer. The ether layer was removed and the other two layers were returned for further treatment. The dark oily layer gradually disappeared during the subsequent extractions.

7. The checkers washed these ether extracts with a little water to ensure removal of any basic material.

3. Discussion

Pseudoinone has been prepared by the condensation of citral and acetone, using as condensing agent a saturated solution of barium hydroxide,[1] a solution of sodium ethoxide in ethanol,[2,3] or metallic sodium.[4] Impure products have been obtained from citral and acetone, using alcoholic sodium hydroxide as the condensing agent,[4] and by treatment of oil of lemon grass and acetone with bleaching powder, cobalt nitrate, and alcohol.[5,6,7]

Pseudoionone, together with methylpseudoionone, has been obtained by oxidation of geraniol by acetone or methyl ethyl ketone in the presence of an aluminum alcoholate.[8] It has also been prepared from linaloöl.[9]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Pseudoionone

pseudoionone bisulfite

methylpseudoionone

aluminum alcoholate

ethanol (64-17-5)

potassium carbonate (584-08-7)

ether (60-29-7)

sodium sulfite (7757-83-7)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

sodium bisulfite (7631-90-5)

acetone (67-64-1)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

tartaric acid (87-69-4)

barium hydroxide (17194-00-2)

methyl ethyl ketone (78-93-3)

citral (5392-40-5)

cobalt nitrate

geraniol (106-24-1)

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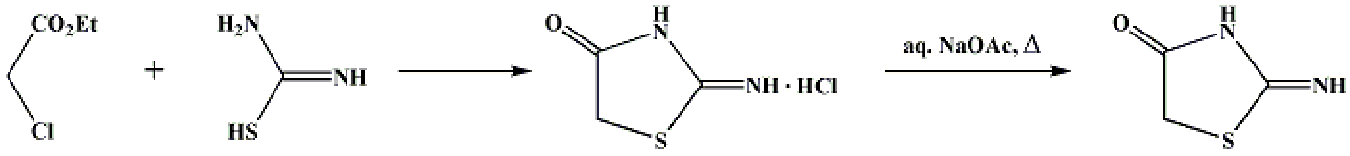
Organic Syntheses, CV 3, 751

PSEUDOTHIOHYDANTOIN

[4-Thiazolidone, 2-imino-]



Submitted by C. F. H. Allen and J. A. VanAllan.
Checked by H. R. Snyder and Frank X. Werber.

1. Procedure

In a 1-l. flask surmounted by a reflux condenser, 76 g. (1 mole) of thiourea, m.p. 174–176°, is dissolved in 500 ml. of 95% ethanol by refluxing for 10–15 minutes. Then 125 g. (108 ml., 1.02 moles) of ethyl chloroacetate is added slowly (15–20 minutes) through the condenser while gentle refluxing is continued. After the mixture has been refluxed for 3 hours longer, it is allowed to cool to room temperature and the solid is filtered by suction on a 14-cm. Büchner funnel. The filtrate is used to rinse any solid adhering to the walls of the reaction flask onto the filter. The crude product is pressed down firmly and washed with 50 ml. of ethanol (Note 1).

The crude hydrochloride is dissolved in 1.2 l. of hot, freshly boiled water (Note 2) in a 2-l. beaker, a boiling solution of 121 g. of sodium acetate trihydrate in 150 ml. of water is added, and the mixture is heated to boiling (Note 3). The resulting clear solution is stored in the ice chest overnight. The crystalline pseudothiohydantoin is filtered and dried to constant weight at 60°. The product weighs 92–95 g. (79–82%). A reproducible decomposition point of 255–258° can be determined with the aid of a melting-point bar (Note 4).

2. Notes

1. The yield of the crude hydrochloride, dried to constant weight, is about 126 g.; the decomposition range is 210–255°.
2. The water is boiled before use to expel dissolved oxygen, the presence of which in the solution may cause the final product to have a yellow color.
3. Prolonged boiling should be avoided, as hydrolysis of the imino group occurs very easily. When sodium carbonate is substituted for sodium acetate the yield drops 10%.
4. The decomposition point as measured in the ordinary manner varies with the temperature of the bath at the time of the introduction of the sample. When the melting-point bath is heated so that the temperature rises by 2° per minute, a sample introduced just as the temperature reaches 200° develops an observable brown color at 206° and then darkens so rapidly that no liquid phase can be identified; if, under the same conditions, the sample is introduced when the bath temperature is 238° the decomposition begins immediately but a liquid phase can be recognized when the bath temperature is in the range 241–243°.

3. Discussion

Pseudothiohydantoin has been obtained from thiourea and ethyl chloroacetate[1] and from thiourea and chloroacetic[2,3] or dichloroacetic acids.[4]

References and Notes

1. Klason, *Ber.*, **10**, 1352 (1877).
2. Andreasch, *Monatsh.*, **8**, 424 (1887).
3. Schmidt, *Arch. Pharm.*, **258**, 229 (1920).
4. Dixon, *J. Chem. Soc.*, **63**, 816 (1893).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Pseudothiohydantoin

chloroacetic

dichloroacetic acids

ethanol (64-17-5)

sodium acetate (127-09-3)

sodium carbonate (497-19-8)

oxygen (7782-44-7)

Ethyl chloroacetate (105-39-5)

thiourea (62-56-6)

sodium acetate trihydrate (6131-90-4)

4-Thiazolidone, 2-imino-

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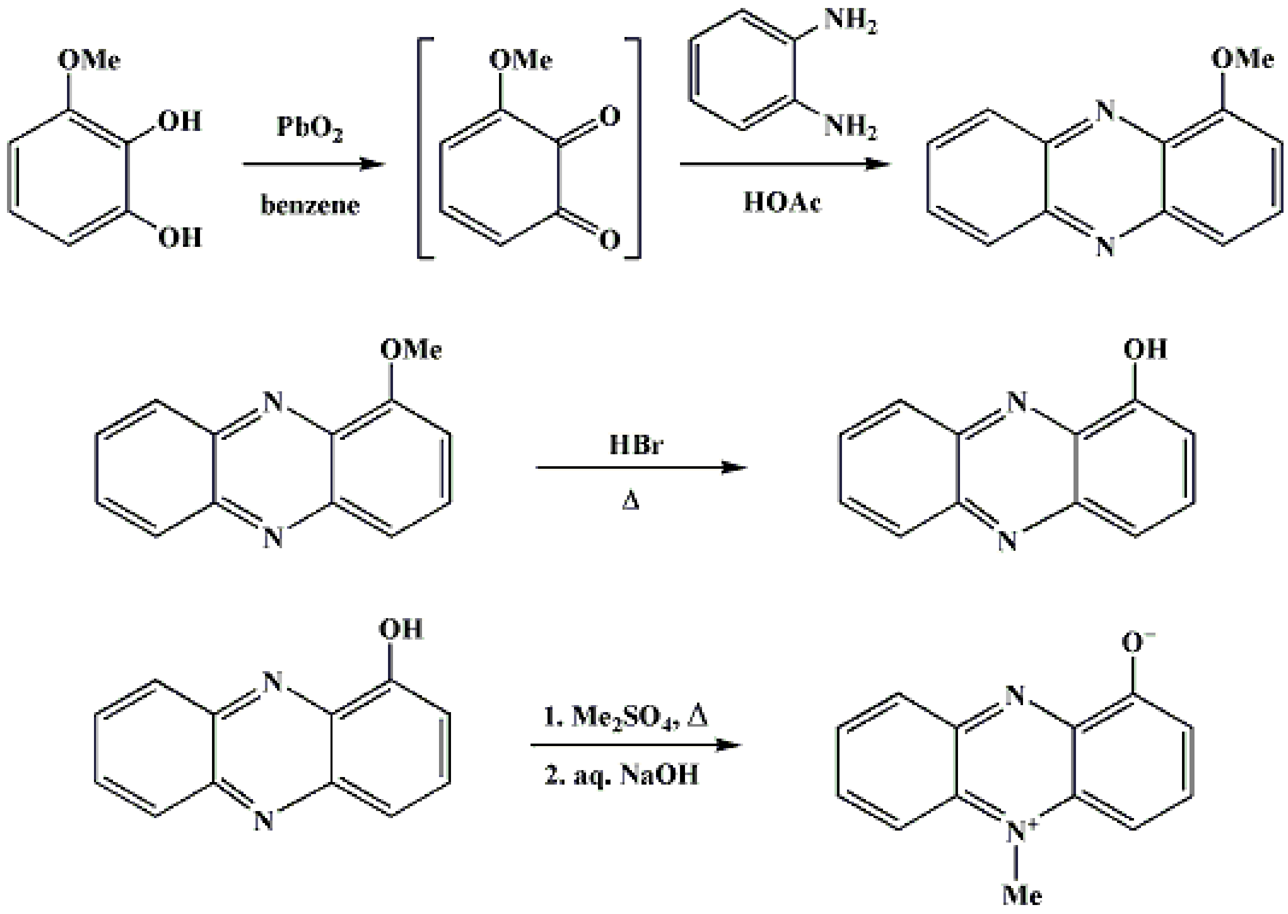
Organic Syntheses, CV 3, 753

PYOCYANINE



Submitted by Alexander R. Surrey
Checked by Lee Irvin Smith and Chien-Pen Lo.

1. Procedure

A. α-*Methoxyphenazine* (*condensation*). Two hundred grams (0.42 mole) of powdered lead dioxide (Note 1) is added to a solution of 10 g. (0.07 mole) of pyrogallol monomethyl ether (p. 759) in 3 l. of dry benzene in a 1-gal. narrow-necked acid bottle. The bottle and contents are placed in a shaking machine and shaken for 10–20 minutes (Note 2). The reddish brown solid is filtered through an 11-cm. Büchner funnel, and the filter cake is washed once with 400 ml. of benzene. To this filtrate there is added, immediately and with mechanical stirring, a solution of 6 g. (0.06 mole) of *o*-phenylenediamine (Note 3) in a mixture of 80 ml. of glacial acetic acid and 200 ml. of benzene. The solution, which becomes dark brown, is allowed to stand at room temperature for 1.5 hours; it is then divided into two portions and each portion is washed, in a 3-l. separatory funnel, three times with water, twice with 5% sodium hydroxide solution, and finally twice with water, 100-ml. portions being taken each time. Each of the benzene solutions is shaken with 50 g. of anhydrous sodium carbonate and 5 g. of Norit and filtered through an 11-cm. Büchner funnel. Each filtrate is stirred with 50–60 g. of activated alumina (Note 4) until a filtered sample shows a light-yellow color. The alumina is filtered on a folded filter and washed with benzene until the washings are almost colorless. The benzene is removed from the combined filtrates by distillation under reduced pressure on a water bath at 40–50°. The residual light-yellow solid (Note 5) is recrystallized by dissolving it in the least possible amount of hot pyridine, adding water to the point

of incipient precipitation, and cooling. The light-yellow crystals are filtered on a 7-cm. Büchner funnel, washed with water, and air-dried. The yield is about 5 g. (33%) of a product that melts at 167–169° (Note 6).

B. *α-Hydroxyphenazine* (*demethylation*). A solution of 4.2 g. (0.02 mole) of α-methoxyphenazine, from A above, in 125 ml. of 55% hydrobromic acid (Note 7) is placed in a 250-ml. round-bottomed flask fitted with a reflux condenser. The flask is immersed in an oil bath, and the solution is heated to 110–120° for 5 hours; the evolved gases are absorbed with water in a trap. The reaction mixture is cooled to room temperature, diluted with about 125 ml. of water, almost neutralized with sodium hydroxide (Note 8), and extracted six times with 30- to 40-ml. portions of ether. The combined ether extracts are extracted with 25-ml. portions of 10% sodium hydroxide solution (Note 9) until no more purple sodium salt is removed from the ether. The aqueous extracts are combined, made acid to litmus with dilute acetic acid, and re-extracted four times with 50-ml. portions of ether. The combined ether extracts are dried over anhydrous sodium sulfate, and the ether is removed by distillation on a steam bath. The residue is recrystallized as follows: It is dissolved in the least possible amount of hot ethanol, water is added to the point of incipient precipitation, then 0.5 g. of Norit is added, and the hot solution is filtered. The filtrate is cooled in ice water, and the orange solid is filtered on a 7-cm. Büchner funnel, washed with water, and dried in an oven at 100°. The yield is 2.7 g. (70%) of a product that melts at 153–155°.

C. *Pyocyanine* (*alkylation*). A solution of 2 g. (0.011 mole) of α-hydroxyphenazine in 13.4 g. (10 ml., 0.1 mole) of methyl sulfate (Note 10) is placed in a 250-ml. Erlenmeyer flask fitted with a calcium chloride drying tube and heated at 100° (oil bath) for 10 minutes. The solution is allowed to cool to room temperature, and about 75 ml. of dry ether is added. The dark brown solid is filtered on a 7-cm. Büchner funnel and washed with about 150 ml. of dry ether in several portions (Note 11).

The dry methosulfate, dissolved in about 30 ml. of water, is made alkaline with 2–3 ml. of 10% sodium hydroxide, and the solution is then extracted *exhaustively* with successive 15-ml. portions of chloroform until no more blue substance is removed from the aqueous solution (Note 12). The combined chloroform solutions are extracted three times with 20-ml. portions of 5% hydrochloric acid. The combined acid extracts are made alkaline to phenolphthalein with 10% sodium hydroxide and re-extracted *exhaustively* with 25-ml. portions of chloroform until no more blue substance is removed from the aqueous solution (Note 12). The combined chloroform solutions are dried over anhydrous sodium sulfate and decanted, and the chloroform is removed by distillation under reduced pressure. The blue crystalline residue is recrystallized by dissolving it in the least possible amount of water at 60° and then cooling the solution in an ice bath. The product is filtered on a 5-cm. Büchner funnel and dried in the dark in a vacuum desiccator over calcium chloride. The yield is 1.35 g. (58%) of dark blue needles that melt at 133° (Note 13).

2. Notes

1. Lead peroxide "analytical reagent" of low manganese content was used.
2. On a scale twelve times as large, a "Lightnin" stirrer was used for 20 minutes.
3. *o*-Phenylenediamine, m.p. 99–101°, from Eastman Kodak Company was used.
4. The amount of alumina needed depends upon the color of the benzene solution. Sufficient alumina (activated alumina, 80 mesh, from Aluminum Corporation of America) is taken so that the filtrate is only light yellow in color. On the larger scale only 100–200 g. of alumina was needed.
5. The residue, without recrystallization, is pure enough for the preparation of α-

hydroxyphenazine.
6. The submitter reports yields somewhat higher (33–40%) and states that, on a larger scale, the yields are slightly better than 40%.
7. The concentration of hydrobromic acid used ranged from 50% to 55%.
8. Concentrated sodium hydroxide solution (about 100 ml. of 35%) is used at the beginning of the neutralization, and dilute sodium hydroxide solution is added towards the end. The reaction mixture should be just faintly acid to litmus.
9. If any solid sodium salt separates during the extraction, it can be redissolved by adding water.
10. The methyl sulfate should be freshly distilled under reduced pressure.
11. The yield of methosulfate is practically quantitative.
12. The solution must be extracted *exhaustively*; the checkers found that thirty such extractions were required to remove all the product. A continuous extractor might be used at this point and certainly would be necessary for large-scale runs.
13. The same percentage yield was obtained with double the amounts specified above. The pyocyanine thus obtained can be stored in a vacuum desiccator in the dark for several weeks without appreciable decomposition. It slowly decomposes on longer standing to give the yellow α-hydroxyphenazine.

3. Discussion

This series of reactions is essentially the one described by Wrede and Strack.[1] Pyocyanine can also be prepared by the photochemical oxidation of phenazine methosulfate.[2]

A different synthesis of 1-hydroxyphenazine, starting with 2,6-dinitroaniline and *o*-iodonitrobenzene, has also been described.[3]

References and Notes

1. Wrede and Strack, *Ber.*, **62**, 2053, 2054 (1929); *Z. physiol. Chem.*, **74**, 181, 184, 185 (1929).
2. McIlwain, *J. Chem. Soc.*, **1937**, 1708.
3. Hegedüs, *Helv. Chim. Acta*, **33**, 766 (1950).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alumina

Pyocyanine

ethanol (64-17-5)

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

ether (60-29-7)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

HYDROBROMIC ACID (10035-10-6)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

Norit (7782-42-5)

pyridine (110-86-1)

methyl sulfate (75-93-4)

phenolphthalein (77-09-8)

manganese (7439-96-5)

α-Methoxyphenazine (2876-17-7)

pyrogallol monomethyl ether (934-00-9)

1-hydroxyphenazine, α-Hydroxyphenazine (528-71-2)

phenazine methosulfate

2,6-Dinitroaniline (606-22-4)

o-Phenylenediamine (95-54-5)

o-iodonitrobenzene (609-73-4)

Lead peroxide

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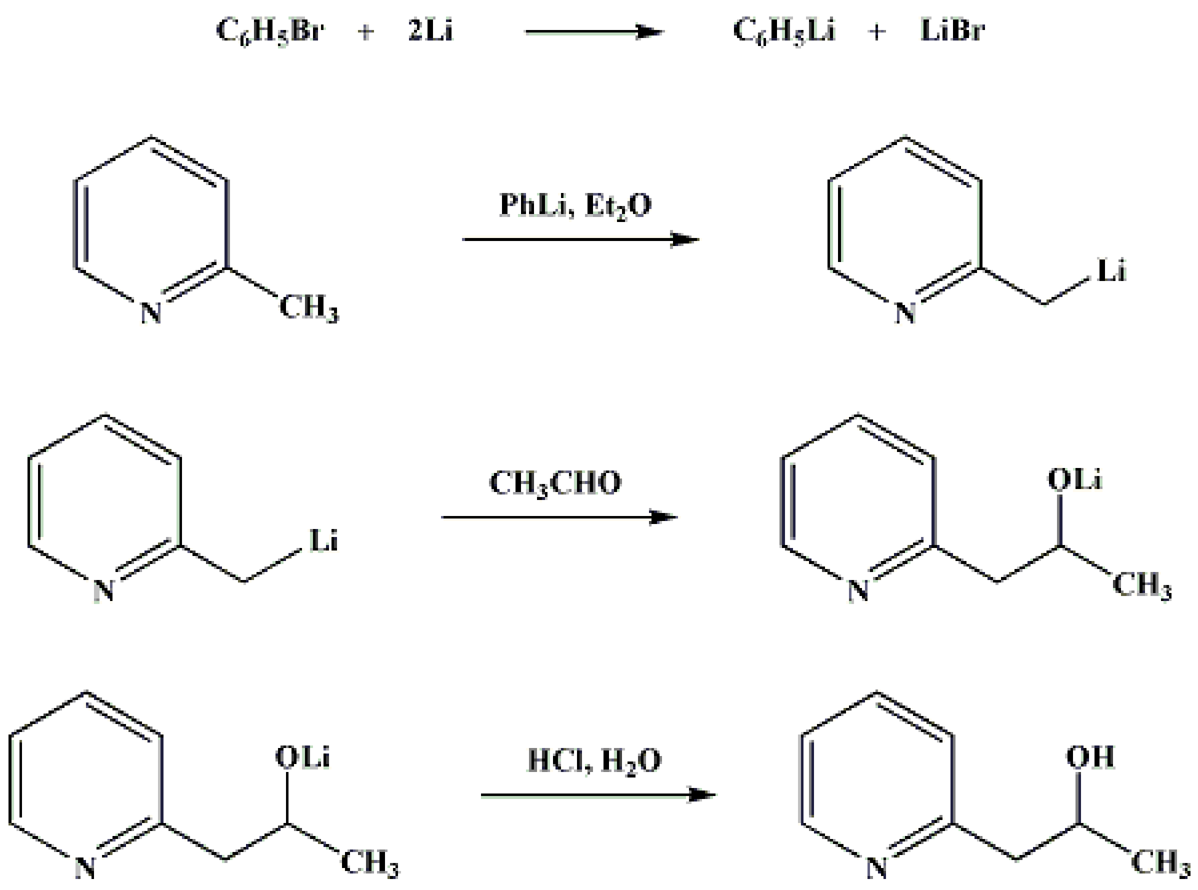
Organic Syntheses, CV 3, 757

1-(α-PYRIDYL)-2-PROPANOL

[2-(β-Hydroxypropyl)pyridine]



Submitted by L. A. Walter
Checked by C. F. H. Allen and James VanAllan.

1. Procedure

While a current of dry nitrogen is passed through the apparatus, 400 ml. of dry ether and 6.9 g. (1 gram atom) of lithium (in small pieces) (Note 1) are placed in a 1-l. three-necked flask fitted with a dropping funnel, mechanical stirrer, and reflux condenser protected from moisture. The stirrer is started, and 10–15 ml. of a solution of 79 g. (0.5 mole) of dry bromobenzene in 100 ml. of dry ether is added from the dropping funnel. The reaction usually starts immediately; if not, the flask may be warmed, and the remainder of the mixture is then added at such a rate that the ether refluxes gently. The mixture is stirred until the lithium disappears (Note 2).

Forty-six grams (0.5 mole) of α-picoline (Note 3) is then added, and the mixture is stirred at room temperature for 1 hour, during which time the dark red solution of picolyllithium is formed. The flask is then immersed in an ice-salt bath, and when the mixture is thoroughly chilled the nitrogen train is disconnected. Then 20 g. of dry

acetaldehyde in 50 ml. of dry ether (Note 4) is slowly dropped into the mixture over a period of 20 minutes. The red color entirely disappears. After 15 minutes, 100 ml. of water is slowly added and then 100 ml. of concentrated hydrochloric acid (sp. gr. 1.2). The aqueous layer is removed and poured, with stirring, into a warm solution of 300 g. of sodium carbonate decahydrate in 100 ml. of water (Note 5). The crude reaction product separates as an oil and is taken up in 300 ml. of chloroform. The precipitated lithium carbonate is filtered, transferred to a beaker, and stirred with four 200-ml. portions of chloroform. The chloroform extracts are decanted or filtered, and all the chloroform solutions are combined (Note 6). The chloroform is removed by distillation, and the residue is fractionated under reduced pressure through a good column. The 1-(α-pyridyl)-2-propanol boils sharply at 116–117°/17 mm. (124–125°/20 mm.). A small fore-run and a considerable amount of high-boiling residue are discarded. The yield is 30–34 g. (44–50% based on the α-picoline) (Note 7) and (Note 8). This product darkens on exposure to light, and it should be preserved in a brown glass bottle.

2. Notes

1. The most unsatisfactory operation of this preparation is cutting the lithium. It may be finely divided by rubbing the metal against a coarse wood rasp and allowing the filings to drop through a large paper funnel directly into the ether while a rapid stream of dry nitrogen is passed through the flask. This procedure is most convenient when a large piece of lithium is available and the amount of filings can be determined by the loss in weight. Larger pieces, cut with a knife [*Org. Syntheses* Coll. Vol. 2, 518 (1943)], can be used equally well (Note 2).

Bartlett, Swain, and Woodward[1] have published a convenient method for the preparation of lithium sand.

2. The time depends upon the size of the pieces; the solution may be stirred for 24 hours without affecting the yield.

3. The submitters used α-picoline, b.p. 128–130°, obtained from the Barrett Company. The checkers used practical α-picoline, b.p. 128–134°, freshly distilled under reduced pressure. Samples of picoline containing water should be carefully fractionated to remove the water as the α-picoline-water azeotrope, b. p. 93°.

4. Alternatively, the acetaldehyde may be distilled into the flask through the nitrogen inlet. During this operation, the outlet must be kept well above the surface, to prevent clogging. The introduction of aldehyde is stopped when the red color has disappeared.

5. A solution of 111 g. of anhydrous sodium carbonate in 150 ml. of water may be substituted.

6. If sodium hydroxide is used to liberate the amino alcohol from its salt, extraction with chloroform produces unworkable emulsions.

7. Equally good yields of 1-(α-pyridyl)-3-propanol, b.p. 116–118°/4 mm., may be obtained by using ethylene oxide in place of acetaldehyde.

8. The submitters obtained yields as high as 43 g. (60%).

3. Discussion

This procedure is based upon that of Ziegler.[2] 1-(α-Pyridyl)-2-propanol has also been prepared in poor yields (4–6 per cent) by heating α-picoline with aqueous acetaldehyde in sealed tubes.[3,4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 641

References and Notes

1. Bartlett, Swain, and Woodward, *J. Am. Chem. Soc.*, **63**, 3230 (1941).
2. Ziegler and Zeiser, *Ann.*, **485**, 174 (1931).
3. Ladenburg, *Ann.*, **301**, 140 (1898).
4. Meisenheimer and Mahler, *Ann.*, **462**, 308 (1928).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

acetaldehyde (75-07-0)

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium carbonate (497-19-8)

nitrogen (7727-37-9)

bromobenzene (108-86-1)

Ethylene oxide (75-21-8)

sodium carbonate decahydrate (6132-02-1)

lithium (7439-93-2)

picolyllithium

picoline, α-picoline (109-06-8)

1-(α-PYRIDYL)-2-PROPANOL, 2-(β-Hydroxypropyl)pyridine (5307-19-7)

lithium carbonate (554-13-2)

1-(α-pyridyl)-3-propanol (2859-68-9)

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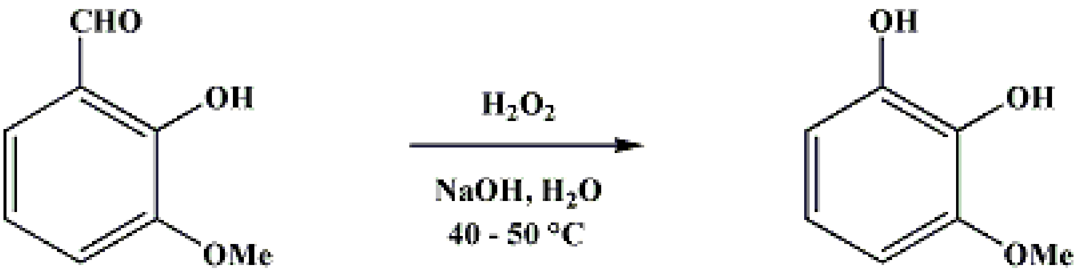
Organic Syntheses, *CV 3, 759*

PYROGALLOL 1-MONOMETHYL ETHER



Submitted by Alexander R. Surrey
Checked by Lee Irvin Smith and Chien-Pen Lo.

1. Procedure

The apparatus consists of a 1-l. three-necked flask fitted with a gas inlet tube extending about 3 cm. into the flask and connected to the flask through a bubbler, a thermometer extending to the bottom, a mechanical stirrer, and a reflux condenser connected at the upper end with an exit tube leading to the hood. The reaction is carried out in an atmosphere of illuminating gas (Note 1).

In the flask are placed 60.8 g. (0.4 mole) of 2-hydroxy-3-methoxybenzaldehyde (Note 2) and 200 ml. of 2 *N* sodium hydroxide (0.4 mole). The mixture is stirred until almost all the solid has dissolved. The stirrer is replaced by a dropping funnel which contains 284 ml. (0.5 mole) of 6% hydrogen peroxide (Note 3). With occasional shaking, the hydrogen peroxide is added in portions of 20–25 ml. About 1 hour is required for the addition; the temperature is kept between 40° and 50°. After the addition of the first portion of hydrogen peroxide, the temperature rises to about 45° and a dark solution results. The temperature is allowed to fall to 40° before the next portion of the peroxide is added.

After all the hydrogen peroxide is added, the reaction mixture is allowed to cool to room temperature and is then saturated with sodium chloride, after which it is extracted four times with 100-ml. portions of ether. The combined extracts are dried over sodium sulfate. The ether is removed by distillation on a steam bath, and the residue is then distilled under reduced pressure. Pyrogallol monomethyl ether is collected at 136–138°/22 mm. The yield is 38–44.5 g. (68–80%) of a colorless to light yellow oil which solidifies on standing (Note 4).

2. Notes

1. Nitrogen can be used in place of illuminating gas. The gas is introduced at the rate of about 3 bubbles per second.
2. Practical 2-hydroxy-3-methoxybenzaldehyde (Eastman Kodak Company) was used in this preparation. Care should be taken when working with this material

as its vapors are irritating and will cause sneezing.
3. The hydrogen peroxide solution was prepared by diluting 63 g. of a solution containing 27% hydrogen peroxide with water to 284 ml.

4. The procedure described is similar to that of Dakin[1] for the preparation of catechol.[2] The reaction has been carried out using four times the quantities specified here; the yield was 81% (C. F. H. Allen, private communication).

3. Discussion

Pyrogallol monomethyl ether has been prepared by the methylation of pyrogallol with dimethyl sulfate[3] or methyl iodide;[4] by the decarboxylation of 2,3-dihydroxy-4-methoxybenzoic acid;[5] and by the methylation of pyrogallol carbonate with diazomethane and subsequent hydrolysis.[6] The method described is taken from the improved procedure of Baker and Savage[7] for the preparation of pyrogallol monomethyl ether from *o*-vanillin by oxidation with hydrogen peroxide.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 753

References and Notes

1. Dakin, *Am. Chem. J.*, **42**, 477 (1909).
2. Dakin, *Org. Syntheses* Coll. Vol. **1**, 149 (1941).
3. Graebe and Hess, *Ann.*, **340**, 232 (1905).
4. Herzig and Pollak, *Monatsh.*, **25**, 811 (1904).
5. Herzig and Pollak, *Monatsh.*, **25**, 507 (1904).
6. Hillemann, *Ber.*, **71**, 41 (1938).
7. Baker and Savage, *J. Chem. Soc.*, **1938**, 1607.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

o-vanillin

ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

dimethyl sulfate (77-78-1)

Catechol (120-80-9)

hydrogen peroxide (7722-84-1)

Methyl iodide (74-88-4)

Diazomethane (334-88-3)

pyrogallol (87-66-1)

pyrogallol monomethyl ether, Pyrogallol 1-monomethyl ether (934-00-9)

2-hydroxy-3-methoxybenzaldehyde (148-53-8)

2,3-dihydroxy-4-methoxybenzoic acid (3934-81-4)

pyrogallol carbonate

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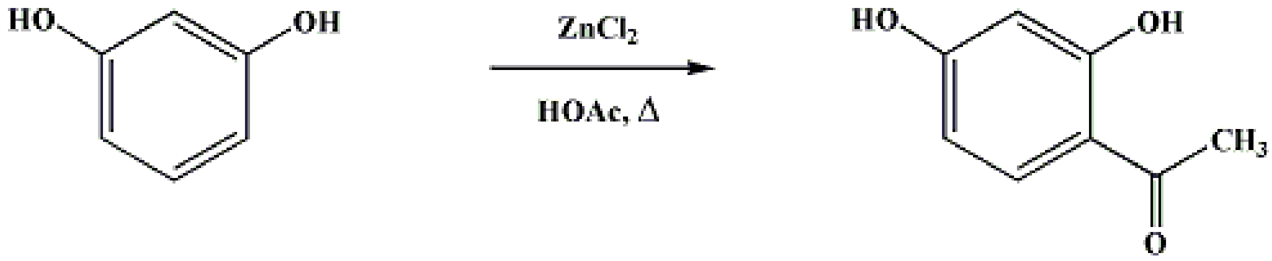
Organic Syntheses, CV 3, 761

RESACETOPHENONE

[Acetophenone, 2,4-dihydroxy-]



Submitted by S. R. Cooper
Checked by Nathan L. Drake, Harry D. Anspon, and Ralph Mozingo.

1. Procedure

One hundred and sixty-five grams (1.2 moles) of anhydrous zinc chloride (Note 1) is dissolved with the aid of heat in 165 g. (158 ml., 2.7 moles) of glacial acetic acid, which has been placed in a 1-l. beaker. To this hot mixture (about 140°), 110 g. (1 mole) of resorcinol is added with constant stirring. The solution is heated on a sand bath until it *just* begins to boil (about 152°). The flame is then removed and the reaction allowed to complete itself at a temperature not in excess of 159° (Note 2). After standing on the sand bath without further heating for 20 minutes, the solution is diluted with a mixture of 250 ml. of concentrated hydrochloric acid and 250 ml. of water. The dark red solution is placed in an ice bath and cooled at 5°. The resulting precipitate is collected on a filter and washed free from zinc salts with 1 l. of dilute (1:3) hydrochloric acid in 200-ml. portions. This orange-red product, after drying, weighs 104–110 g. and melts at 141–143°. It is distilled under reduced pressure (Note 3), and boils at 180–181° at 10 mm. (147–152° at 3–4 mm.). After most of the product has distilled, the temperature rises sharply, and the operation is discontinued when the temperature reaches 190°. The light-yellow distillate is removed from the receiver with hot ethanol and the ethanol is evaporated (Note 4). This product weighs 100–106 g. It is further purified as follows: the substance is dissolved in 1.8 l. of hot dilute (1:11) hydrochloric acid, filtered hot, and cooled to 5°. The crystals are removed by filtration, washed with two 200-ml. portions of ice water, and dried. The yield of tan-colored resacetophenone, melting at 142–144°, is 93–99 g. (61–65%).

2. Notes

1. Although finely ground zinc chloride dissolves more rapidly, lumps or sticks are satisfactory.
2. If the temperature rises much above the initial boiling point, the yield of red product increases at the expense of resacetophenone formation. The boiling point also may vary slightly.
3. Any convenient apparatus for distillation of a solid may be used.
4. It is convenient to remove most of the material by melting and pouring it out of the receiver. The remainder is removed with hot ethanol.

3. Discussion

Resacetophenone has been prepared by heating resorcinol with zinc chloride and acetic acid,[1,2] with zinc chloride and acetic anhydride,[2] with zinc chloride and acetyl chloride,[3] with boron trifluoride and acetic anhydride,[4] and with aluminum chloride and acetyl chloride.[5] It has been prepared by the action of zinc chloride on resorcinol diacetate,[2] by heating 4-methylumbelliferone with potassium hydroxide,[6] by heating resacetophenone carbonic acid,[7] and by the action of acetyl chloride on resorcinol.[8]

References and Notes

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6. Pechmann and Duisberg, *Ber.*, **16**, 2119 (1883).
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8. Cox, *Rec. trav. chim.*, **50**, 848 (1931).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Resacetophenone

Acetophenone, 2,4-dihydroxy-

resacetophenone carbonic acid

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

acetic anhydride (108-24-7)

acetyl chloride (75-36-5)

aluminum chloride (3495-54-3)

potassium hydroxide (1310-58-3)

zinc chloride (7646-85-7)

resorcinol (108-46-3)

boron trifluoride (7637-07-2)

4-methylumbelliferone (90-33-5)

resorcinol diacetate (108-58-7)

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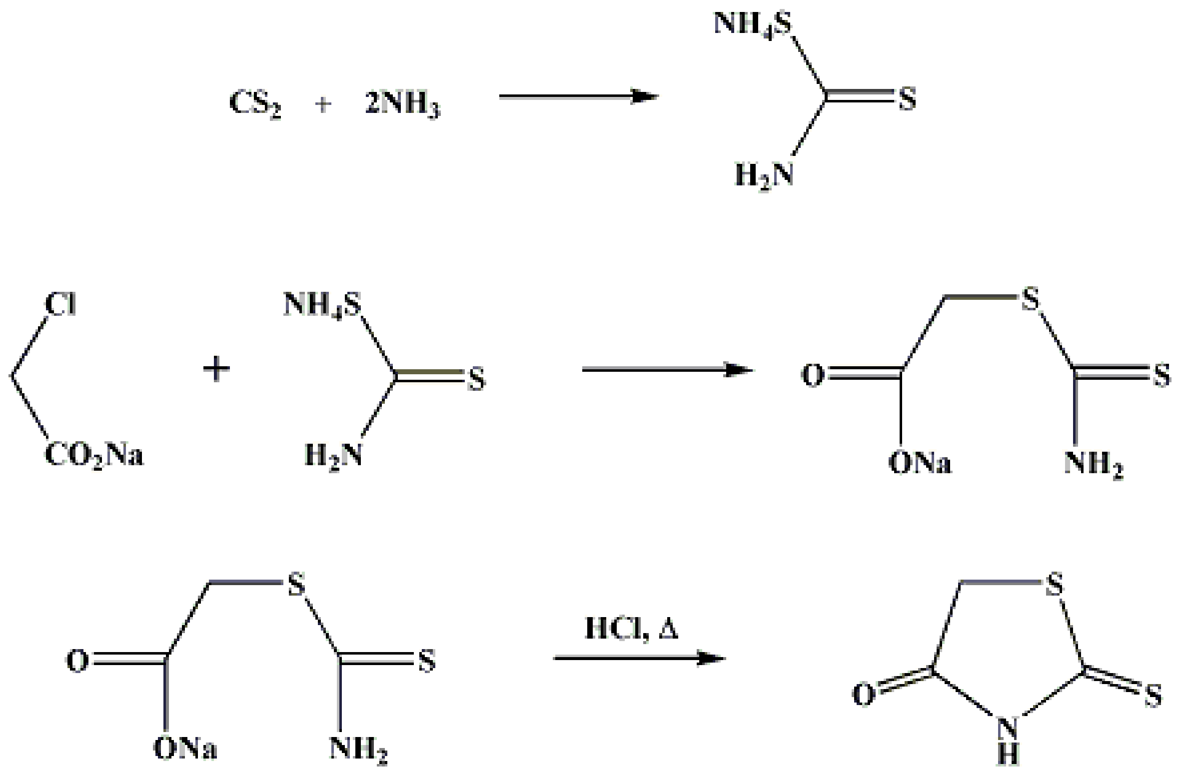
Organic Syntheses, CV 3, 763

RHODANINE



Submitted by C. Ernst Redemann, Roland N. Icke, and Gordon A. Alles.
Checked by H. R. Snyder and John H. Johnson.

1. Procedure

A. *Ammonium dithiocarbamate.* Gaseous ammonia is passed into 250 ml. of 95% ethanol (Note 1) contained in a 1-l. Erlenmeyer flask immersed in an ice bath until the gain in weight is 39 g. (2.3 moles). To this solution, still cooled by the ice bath, is added a well-cooled mixture of 76 g. (60 ml., 1 mole) of carbon disulfide and 200 ml. of ether. The flask is stoppered loosely (Note 2) and allowed to remain in the ice bath for 2–3 hours and then at room temperature overnight (Note 3). The mixture is again cooled in an ice bath or refrigerator, and the crystals are collected by filtration (*hood*), sucked dry, and washed on the filter with two 50-ml. portions of ether. Air is drawn through the crystals for 5 minutes (Note 4) to effect removal of most of the ether. The product is used promptly without further treatment; the weight of the lemon-yellow solid varies between 80 and 90 g., depending principally on the completeness of the removal of the solvent.

B. *Rhodanine*. Just before the filtration of the ammonium dithiocarbamate, a solution of sodium chloroacetate is prepared by dissolving 71 g. (0.75 mole) of chloroacetic acid in 150 ml. of water contained in a 1-l. wide-mouthed round-bottomed flask and neutralizing the acid with 40 g. (0.38 mole) of anhydrous sodium carbonate (or an equivalent amount of the hydrate) while stirring the solution mechanically. This

solution is cooled in an ice bath, and the ammonium dithiocarbamate from the preceding preparation is added during 5 minutes with continual stirring. As soon as the first portion of ammonium dithiocarbamate is added the solution becomes very dark in color. After all the dithiocarbamate has been added the ice bath is removed and stirring is discontinued. The solution is allowed to stand for 20–30 minutes longer, during which time the color changes to a clear yellow. In a 1-l. beaker 400 ml. of 6 *N* hydrochloric acid is heated to boiling, and the above solution (Note 5) is poured slowly with stirring into the hot acid. Heating is continued until the solution has attained a temperature of 90–95°, after which the solution is allowed to cool slowly to room temperature. The rhodanine separates as nearly colorless long blades which are collected by filtration, washed well with water, and dried. The product weighs 83–89 g. (83–89% based on the chloroacetic acid), and melts at 167–168°. Recrystallization from boiling glacial acetic acid (2 ml. per gram) raises the melting point to 168–168.5° (Note 6); the recovery, without reworking of the mother liquor, is 87%.

2. Notes

1. Absolute ethanol is satisfactory. Methanol may be used, but ammonium dithiocarbamate is much more soluble in methanol than in ethanol and the recovery will be lower.
2. The flask should be stoppered loosely to retard the escape of ammonia. It is not wise to stopper it tightly, as some gas is evolved and pressure may develop. Hydrogen sulfide is present in the gases evolved.
3. The success of the preparation depends upon securing ammonium dithiocarbamate of good quality. Although much solid sometimes separates within 1–2 hours, it contains a large amount of the very unstable ammonium trithiocarbamate.[1] After prolonged standing, the solid is nearly pure ammonium dithiocarbamate.
4. Ammonium dithiocarbamate is relatively unstable, and no attempt should be made to dry the compound thoroughly before use.
5. If this solution is not clear and free from solid impurities it should be filtered before addition to the acid.
6. The melting points observed with the aid of a hot-stage microscope are slightly higher—170–170.5° for the unrecrystallized material, and 170.5–171° for the purified product. Although rhodanine usually is described in the literature as melting with decomposition, the checkers observed no evidence of decomposition during melting under the microscope and found the melting point unchanged when molten samples in ordinary melting-point tubes were cooled and remelted.

3. Discussion

Rhodanine has been prepared by the reaction of chloroacetic acid with ammonium thiocyanate;[2] by the action of ethyl chloroacetate upon ammonium dithiocarbamate in

the presence of alcohol and hydrogen chloride;[3] by saturating a solution of thioglycolic acid and potassium thiocyanate in absolute ethanol with hydrogen chloride;[4] by ring closure of thiocarbamylthioglycolic acid in various ways.[5,6,7] The present method of preparation is adapted from that of Julian and Sturgis.[7]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

hydrogen chloride, hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ammonia (7664-41-7)

methanol (67-56-1)

ether (60-29-7)

ammonium thiocyanate (1762-95-4)

hydrogen sulfide (7783-06-4)

sodium carbonate (497-19-8)

chloroacetic acid (79-11-8)

sodium chloroacetate (3926-62-3)

carbon disulfide (75-15-0)

Ethyl chloroacetate (105-39-5)

potassium thiocyanate (333-20-0)

Rhodanine (141-84-4)

ammonium dithiocarbamate

ammonium trithiocarbamate

thioglycolic acid (68-11-1)

thiocarbamylthioglycolic acid

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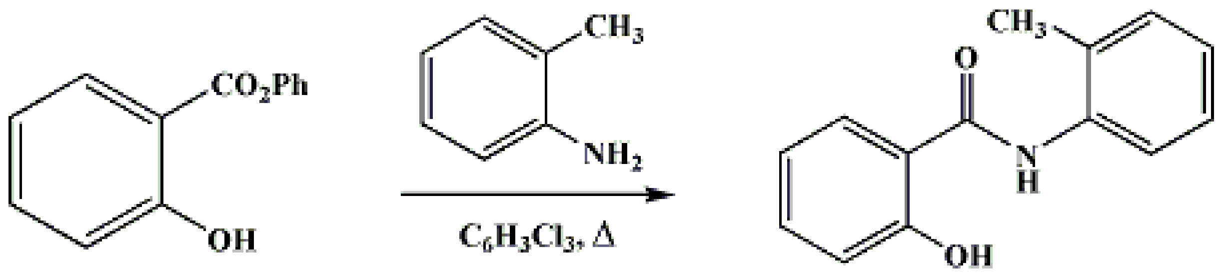
Organic Syntheses, CV 3, 765

SALICYL-*o*-TOLUIDE

[*o*-Salicylotoluide]



Submitted by C. F. H. Allen and J. VanAllan.
Checked by H. R. Snyder and R. L. Rowland.

1. Procedure

In a 250-ml. flask attached to a Vigreux column 30 cm. in over-all length (Note 1), a mixture of 42.8 g. (0.2 mole) of phenyl salicylate ("Salol," m.p. 42–43°), 26.7 g. (0.25 mole) of *o*-toluidine, and 60 g. of 1,2,4-trichlorobenzene (m.p. 15–16°), is heated at the boiling point, so that the phenol formed slowly distils. The temperature rises from 183° to 187° during the first hour, and 22–23 g. of distillate is collected. Heating is continued until the temperature rises to 202° and a total of 45–46 g. of distillate has been collected (Note 2). The flask is then removed, and to it are added 3 g. of Norit and 10 ml. of trichlorobenzene. The mixture is heated to boiling and filtered hot by suction. The filtrate is allowed to stand in the ice chest overnight. The crystalline amide is filtered by suction, slurried with 75 ml. of ligroin (b.p. 90–120°) at 35–40°, and filtered. After being dried to constant weight, the salicyl-*o*-toluide, m.p. 143–144°, amounts to 33–35 g. (73–77%) (Note 3), (Note 4) and (Note 5).

2. Notes

1. These are measurements of standard ground-glass equipment.
2. The checkers preferred α-methylnaphthalene (Eastman, practical) as the diluent. When it is used in the apparatus described the phenol does not distil, so that a reaction flask fitted with an air-cooled condenser is more convenient. The reactants in 60 g. of α-methylnaphthalene are heated in an oil bath at 230° for 1.5–2 hours. Three grams of Norit and 20 g. more of α-methylnaphthalene are then added, and the mixture is treated as described under Procedure. The yield and melting point of the product are identical with those described.
3. Since the pure material[1] melts at 144°, the product needs no further purification for ordinary purposes. It has a faint odor, which can be removed by recrystallization from aqueous ethanol (suitably by solution in 8–10 ml. of ethanol per gram of material and the addition of water just short of precipitation

from the hot solution). The loss in recrystallization is only about 5%; the melting point is unchanged.
4. By working up the filtrate, only about 2 g. of material of poor quality can be secured.
5. Other anilides can be prepared by this procedure.

Amine Used	*M.p of Anilide*	*Yield, %*
Aniline	131–132°	70
2,5-Dichloroaniline	228°	89
β-Naphthylamine	188°	84
2-Aminopyridine	206°	86
1-Aminoanthraquinone	278–284°	79

When the boiling point of the amine is widely different from that of phenol, a diluent is unnecessary though it facilitates purification. In the absence of a diluent, the hot melt is poured into ethanol and recrystallized, using a decolorizing carbon; there is considerable tendency towards crystallization during the filtration from the charcoal.
Salicylanilide (m.p. 131–132°) is obtained by heating the mixture without a diluent for 3 hours at 180–200° with a short air condenser, pouring the melt into 100 ml. of ethanol, and working up as above. The persistent pink color is not easily removed.

3. Discussion

Salicyl-*o*-toluide has been prepared only by the action of phosphorus oxychloride upon a mixture of salicylic acid and *o*-toluidine. The useful methods of preparation of salicylanilide are by the interaction of salicylic acid and aniline in the presence of phosphorus trichloride,[2,3,4] by heating phenyl salicylate and aniline,[5] and from *o*-hydroxybenzamide and bromobenzene in the presence of small amounts of sodium acetate and metallic copper.[6] A number of these and other anilides have been described.[7]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ligroin

ethanol (64-17-5)

sodium acetate (127-09-3)

aniline (62-53-3)

phenol (108-95-2)

salicylic acid

copper (7440-50-8)

decolorizing carbon, Norit (7782-42-5)

Phosphorus Oxychloride (21295-50-1)

bromobenzene (108-86-1)

phosphorus trichloride (7719-12-2)

2-aminopyridine (504-29-0)

phenyl salicylate (118-55-8)

1-aminoanthraquinone (82-45-1)

1,2,4-trichlorobenzene (120-82-1)

trichlorobenzene (87-61-6)

α-methylnaphthalene (90-12-0)

2,5-Dichloroaniline (95-82-9)

Salicylanilide (87-17-2)

β-naphthylamine (91-59-8)

o-toluidine (95-53-4)

Salicyl-o-toluide, o-Salicylotoluide (7133-56-4)

o-hydroxybenzamide (65-45-2)

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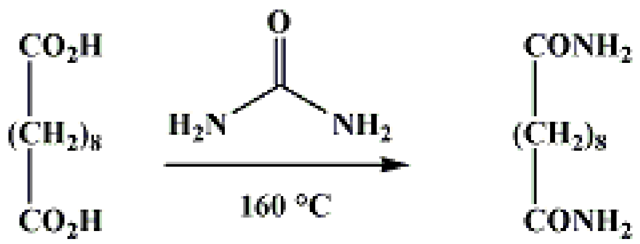
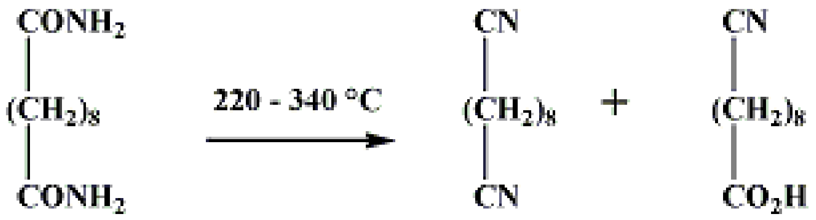
Organic Syntheses, CV 3, 768

SEBACONITRILE AND ω-CYANOPELARGONIC ACID

[Sebaconitrile and pelargonic acid, θ-cyano-]





Submitted by B. S. Biggs and W. S. Bishop.
Checked by C. F. H. Allen and J. VanAllan.

1. Procedure

A. *Sebaconitrile*. A 3-l. three-necked flask (Note 1), equipped with a mechanical stirrer (Note 2) and (Note 3) and a thermometer which dips into the liquid, is heated in an oil bath to 160°. In the flask are placed 505 g. (2.5 moles) of commercial sebacic acid (Note 4) and 180 g. (3 moles) of urea (Note 5), and the melt is heated with stirring for 4 hours at about 160° (Note 6). The oil bath is removed, the surplus oil is wiped off, the flask is insulated (Note 7), and the temperature is then raised, as rapidly as foaming permits, to 220° by means of a triple burner and wire gauze. It is important to continue the stirring for at least 5 minutes after 220° is attained; otherwise the mass will foam over during the subsequent distillation.

The stirrer is then replaced by a short still head connected to a long (90-cm.) air condenser and receiver (Note 8), and the product is distilled at atmospheric pressure as long as any distillate is obtained. The temperature of the vapor rises gradually to 340°. The distillate, which consists chiefly of water, dinitrile, acid nitrile, and sebacic acid, is poured into a large (2-l.) separatory funnel and, after the addition of 500 ml. of ether (Note 9), is extracted three times with 650-ml. portions of 5% ammonium carbonate (Note 10). The crude dinitrile which remains after the removal of the ether is distilled under reduced pressure; after a small fore-run (20–25 ml.) the main product is collected at 185–188°/12 mm. (Note 11). The yield of sebaconitrile is 190–200 g. (46–

49%) (Note 12).

B. *ω-Cyanopelargonic acid*. The combined ammoniacal extracts are heated nearly to boiling in a large enameled pot or 4-l. beaker and neutralized to phenolphthalein with concentrated hydrochloric acid (about 120 ml.) (Note 13). A hot solution of 400 g. of barium chloride is then added slowly with stirring, and the hot solution is filtered from the precipitated barium sebacate (Note 14) through a fluted filter paper or "Shark Skin" filter paper (Note 15) on a 20-cm. Büchner funnel. The barium salt of the cyano acid that separates on cooling is filtered on the same sized funnel and dissolved in 1 l. of hot water, and the solution is acidified to litmus with concentrated hydrochloric acid (about 30 ml.). The cyano acid separates as a clear oil. The filtrate from which the barium salt was filtered is acidified likewise to litmus with concentrated hydrochloric acid (about 50 ml.). The two oils are combined. The cyano acid is washed by decantation with three 200-ml. portions of hot water, separated completely from water, and dried in a vacuum desiccator over calcium chloride. The yield of ω-cyanopelargonic acid melting at 48–49° is 146–155 g. (32–34%) (Note 16).

2. Notes

1. Ground-glass equipment is preferable, since the final temperature is high enough to decompose rubber or cork stoppers.
2. The stirrer is a bent glass rod that will break up the foam produced.
3. Attention is called to the powerful but compact compressed-air stirrer, catalog No. 9224, of the A. H. Thomas Company. When a compressed-air line is available, such a stirrer is preferable to an electric motor.
4. Commercial grades of sebacic acid (m.p. 127–130°) and urea (m.p. 132–134°) were used; pure sebacic acid (m.p. 132–133°) gives only a slightly (13%) higher yield. Since the acid is light and bulky, it is convenient to melt it in an enameled pot (p. 614, Note 2) and pour the liquid into the preheated flask.
5. It is important to use the amount of urea which is specified. When 2 moles of urea per mole of sebacic acid was employed, the yield of sebaconitrile was only 27%.
6. At the end of this time the product consists almost entirely of sebacamide, which may be isolated if desired.
7. This insulation is easily accomplished by wrapping with asbestos rope, starting at the neck and winding as far down the bulge of the flask as possible. After the flask is clamped in place on the wire gauze, asbestos paper is bent around to enclose the bottom. Magnesia can also be used.
8. If the condenser is short, it is advisable to have a second receiver with a reflux condenser attached, because some dinitrile may be carried through by uncondensed steam. A water-cooled condenser should not be placed ahead of the first receiver, however, since the distillate contains some solid products (sebacic acid and products from urea).
9. Although not absolutely essential, the ether facilitates the operation. Benzene is not satisfactory.

10. Ammonium hydroxide (about 3%) is equally satisfactory. The aqueous extracts are saved.
11. Another boiling point is 201–203°/16 mm.
12. The submitters obtained 410–450 g. (50–55%) in runs twice this size.
13. The checkers used a *p*H meter and neutralized to *p*H 7.8.
14. This amounts to 43–45 g.
15. S & S "Shark Skin" filter paper has "high wet-strength" and a high resistance to acids and alkalies.
16. If the cyano acid obtained from the precipitated barium salt is worked up separately, it melts at 51–52°.

3. Discussion

Sebaconitrile has been obtained by heating sebacic acid in a stream of ammonia,[1] and from sebacamide by pyrolysis[2,3] or by dehydration with phosphorus pentachloride[4] or phosphorus oxychloride.[5] Sebacamide has been prepared from ethyl sebacate,[6,7] sebacoyl chloride,[7] or polysebacic anhydride[8] and ammonia; by heating sebacic acid with urea[2,3,9] or ammonium thiocyanate;[10] and by the electrolysis of adipic acid monoamide.[11]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

pelargonic acid, θ-cyano-

polysebacic anhydride

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

ammonium carbonate

ammonia (7664-41-7)

Benzene (71-43-2)

ether (60-29-7)

ammonium thiocyanate (1762-95-4)

phosphorus pentachloride (10026-13-8)

barium chloride (10361-37-2)

Phosphorus Oxychloride (21295-50-1)

urea (57-13-6)

ammonium hydroxide (1336-21-6)

phenolphthalein (77-09-8)

Ethyl sebacate (693-55-0)

sebacamide (1740-54-1)

sebacic acid (111-20-6)

Sebaconitrile (1871-96-1)

ω-CYANOPELARGONIC ACID (5810-19-5)

barium sebacate

adipic acid monoamide

sebacoyl chloride (111-19-3)

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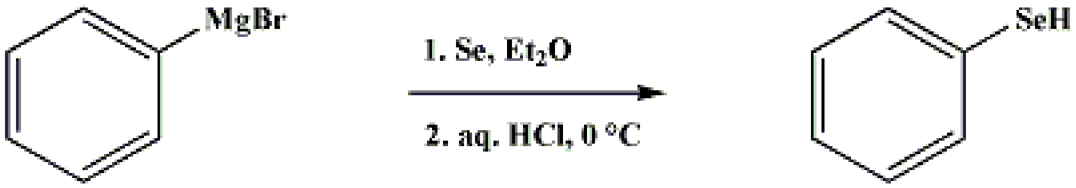
Organic Syntheses, CV 3, 771

SELENOPHENOL

[Benzeneselenol]



Submitted by Duncan G. Foster
Checked by C. F. H. Allen and H. W. J. Cressman.

1. Procedure

Most selenium compounds are toxic, and many have a vile odor. It is frequently advisable to work with them on alternate days. All manipulations should be done in a good hood. Rubber gloves should be worn, and it is well to keep the window of the hood down so that the glass is between the apparatus and the face of the operator.

Hydrogen selenide, a possible by-product, is very toxic, being comparable with hydrogen cyanide. Its accidental inhalation in small amounts may produce a sore throat.

A 500-ml. three-necked round-bottomed flask is fitted with an efficient reflux condenser, a glycerol-sealed mechanical stirrer, a dropping funnel, and a gas inlet tube extending nearly to the blades of the stirrer (Note 1). An absorption train,[1] with the addition in *J* of a safety tube which extends nearly to the bottom, is connected to the upper end of the reflux condenser (Note 2). A 2-cm. layer of water in *J* allows it to serve as a bubble counter; *K* is one-third filled with a 50% potassium hydroxide solution. The entire apparatus is set up in subdued light in a hood and swept with dry hydrogen (Note 3) and (Note 4). Phenylmagnesium bromide is prepared in the flask by the usual procedure[2] from 78.5 g. (0.5 mole) of bromobenzene, 12 g. (0.5 gram atom) of magnesium, and 500 ml. of dry ether. The dropping funnel is then replaced by an addition flask (p. 550) which contains 38 g. (0.48 gram atom) of dry powdered black selenium (Note 5). The solution is warmed sufficiently to bring about gentle refluxing, and the selenium is then added gradually over a period of 30 minutes at such a rate as to maintain gentle refluxing without heating. Stirring is continued for an additional 30 minutes (Note 6).

The contents of the flask are then poured upon 600 g. of cracked ice, and, with hand stirring, 75 ml. of hydrochloric acid (sp. gr. 1.18) is added. The cold mixture is now filtered through glass wool in an ordinary funnel into a 2-l. separatory funnel. The

aqueous layer is separated and extracted once with 250 ml. of ether (Note 7). The combined extract and main product are dried over 30 g. of calcium chloride, the ether is removed on a steam bath, and the residue is distilled using a 500-ml. modified Claisen flask. The selenophenol is collected at 57–59°/8 mm. or 84–86°/25 mm.; the yield is 43–54 g. (57–71%) (Note 6) and (Note 9) through (Note 14). The product should be sealed at once in a glass vial (Note 8).

2. Notes

1. Dry hydrogen or dry nitrogen may be used. The gas must be oxygen-free. Hydrogen tends to decrease the amount of oxidation to diselenide.

2. The submitter used a simpler train consisting of two small widemouthed bottles in series closed by stoppers bearing the necessary inlet and outlet tubes constructed of 10-mm. or larger glass tubing. In each flask was a shallow layer of 50% potassium hydroxide solution; the outlet tube of the first bottle extended nearly to the surface of the solution and dipped *below* the surface of the solution in the second bottle.

3. Most selenium compounds are affected by sunlight, and many by any bright light. It is often essential to use amber glassware or to wrap the flasks in light-proof paper.

4. Selenium compounds which contain an -SeH group are easily oxidizable in the air to diselenides. It is advantageous to replace the air by an inert gas, and to work as rapidly as possible.

5. The selenium is dried overnight in a vacuum desiccator over concentrated sulfuric acid.

6. The higher yields of selenophenol are favored by exclusion of air, rapid stirring, and not too rapid addition of selenium.

7. An alternative procedure is to extract the selenophenol by sodium hydroxide solution, and subsequently to acidify and extract the liberated substance. The yield of selenophenol is not improved by employing such a procedure, but it may be of value with some compounds.

8. The selenophenol is water-white but rapidly turns yellow in contact with the air.

9. The residue in the still (or alkali-insoluble material in the ether layer if Note 6 has been employed) contains diphenyl selenide (b.p. 167°/16 mm.) and diphenyl diselenide (m.p. 63°). It can be separated by a combination of distillation and crystallization from ethanol, but the amounts are small, and, unless the residues from several runs are combined, the procedure is not economical.

10. This is a general reaction. It can be used for preparing other selenophenols whenever the desired Grignard reagent can be obtained. The submitter has made the three selenocresols, *p*-bromophenylselenophenol, and *n*-butylselenol by this procedure. He has also obtained thiophenols by the substitution of sulfur for selenium.

11. The submitter has synthesized nine alkyl phenyl selenides in yields of 85–95% by treating ethanol solutions of the sodium salt (the selenophenol is

dissolved in the calculated amount of 50% aqueous sodium hydroxide diluted with ethanol) with the appropriate alkyl halide or sulfate.
12. Many selenophenols are more advantageously prepared by hydrolysis of the aryl selenocyanate.
13. It is well to have a hot sulfuric-nitric acid cleaning bath in the same hood, so that apparatus need not be handled in the open laboratory. The large separatory funnel is conveniently cleaned by pouring into it 50 ml. of concentrated nitric acid. After a few minutes, the acid reacts violently with selenides remaining on the sides. The oxides of nitrogen produced effectively clean the funnel, which can then be rinsed with water.
14. Water-soluble selenium compounds are poured down the sink in the hood and flushed with much water. Rubber stoppers and gloves can be freed from toxic compounds by soaking them for a few minutes in bromine or chlorine water and then in dilute sodium hydroxide solution.

3. Discussion

Selenophenol has been prepared from selenium tetrachloride and benzene in the presence of anhydrous aluminum chloride,[3] and by the procedure described,[4] which is a development of Taboury's.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 533

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

oxides of nitrogen

ethanol (64-17-5)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

magnesium (7439-95-4)

nitric acid (7697-37-2)

hydrogen cyanide (74-90-8)

bromine (7726-95-6)

nitrogen (7727-37-9)

sulfur (7704-34-9)

aluminum chloride (3495-54-3)

chlorine (7782-50-5)

potassium hydroxide (1310-58-3)

bromobenzene (108-86-1)

Phenylmagnesium bromide (100-58-3)

Diphenyl selenide (1132-39-4)

selenium

selenium tetrachloride (10026-03-6)

hydrogen selenide (7782-49-2)

Selenophenol

Benzeneselenol (645-96-5)

Diphenyl diselenide (1666-13-3)

p-bromophenylselenophenol

n-butylselenol

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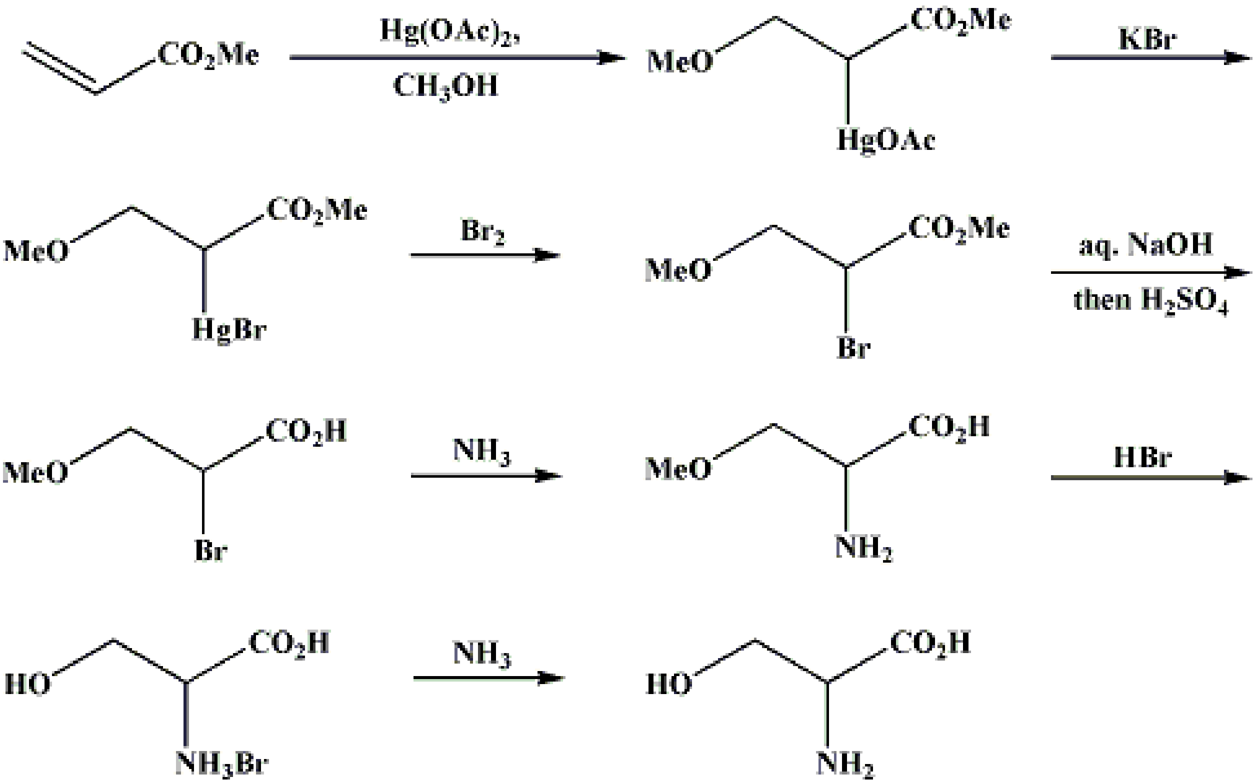
Organic Syntheses, CV 3, 774

dl-SERINE



Submitted by Herbert E. Carter and Harold D. West.
Checked by Nathan L. Drake and William A. Stanton.

1. Procedure

A. *Methyl α-bromo-β-methoxypropionate*. In a 5-l. flask is placed 450 g. of a 60% solution of methyl acrylate in methanol (Note 1) containing 3.1 moles of methyl acrylate (Note 2). To this solution are added 180 g. of methanol and 960 g. (3 moles) of mercuric acetate (Note 3). The mixture is allowed to stand at room temperature for 3 days with occasional shaking (Note 4). The flask is cooled in an ice bath, and a solution of 360 g. (3 moles) of potassium bromide in 1.2 l. of water is added with stirring during 15 minutes. The heavy oil that separates is extracted with 2.4 l. of chloroform (Note 5), and the aqueous layer is again extracted with 600 ml. of chloroform. The chloroform solutions are combined, washed three times with water, and carefully dried over anhydrous magnesium sulfate (Note 6).

The solution, filtered to remove the drying agent, is placed in a 4-l. beaker and warmed to 50°. The beaker is then exposed to direct sunlight (Note 7), and 450 g. (2.81 moles) of bromine is added with stirring (Note 8) as fast as it is used. The reaction starts slowly but accelerates rapidly, and considerable heat is evolved. The temperature of the solution should be kept below 55° (Note 9). The bromination usually requires 20–30 minutes. At the conclusion of the reaction, the flask is cooled for 15 minutes in an ice-salt bath, and the mercuric bromide is separated by filtration. The chloroform is removed by distillation

under reduced pressure through a 20-in. column, and the residue is fractionally distilled under reduced pressure from a modified Claisen flask. The yield is 480–510 g. (81–86% based on the mercuric acetate) of a product boiling at 70–80° at 6 mm. This material contains 5–10% of methyl α,β-dibromopropionate, which is not readily removed. Since the impurity causes no trouble in the synthesis of serine, the crude bromo ester is used in succeeding steps (Note 10).

B. *α-Bromo-β-methoxypropionic acid*. Eight hundred grams of the bromo ester and 1 l. of 0.5 *N* sodium hydroxide are placed in a 5 l. three-necked flask equipped with an efficient stirrer and a separatory funnel, and cooled with running tap water. The stirrer is started, and 800 ml. of 5 *N* sodium hydroxide is added during the course of 2 hours. After the addition is complete, the solution is stirred for 1 hour and then neutralized with an equivalent quantity of sulfuric acid (Note 11). The neutralized solution is extracted once with a 1-l. portion, and three times with 500-ml. portions, of ether. The ether extracts are combined, washed once with a cold saturated solution of sodium sulfate, and dried over anhydrous sodium sulfate; the ether is removed by distillation (Note 12). There remains 700–750 g. of crude bromo acid which is used without purification in the preparation of serine (Note 13).

C. *dl-Serine*. One-half (350–375 g.) of the crude bromomethoxypropionic acid prepared from the saponification of 800 g. of methyl α-bromo-β-methoxypropionate is heated with 3.5 l. of concentrated ammonium hydroxide in a glass-lined autoclave (Note 14) for 10–15 hours at 90–100°, and the solution from the bomb is concentrated to a thick syrup under reduced pressure (Note 15). Two liters of water is added, and the solution is concentrated to dryness. The cake is dissolved in 1.5 l. of 48% hydrobromic acid and refluxed for 2.5 hours. The resulting dark solution is concentrated to a volume of about 500 ml. and then cooled under the tap. The precipitated ammonium bromide is removed by filtration, and the filtrate is concentrated to a thick syrup (Note 16). One liter of water is added, and the solution is again concentrated to a thick syrup. The syrupy residue is dissolved in 375 ml. of warm water, and ammonium hydroxide is added carefully until a faint odor of ammonia persists after vigorous shaking. One and one-half liters of absolute ethanol is then added slowly (Note 17), and the mixture is allowed to stand overnight. The crude serine is filtered and the filtrate discarded. The precipitate is dissolved in 500 ml. of boiling water (Note 18), heated on the steam cone for 10 minutes with 10–15 g. of Darco (Note 19), and then filtered. Five hundred milliliters of absolute ethanol is added to the filtrate slowly with stirring. The mixture is cooled to 0° and is kept at this temperature for 1 hour with occasional stirring to ensure formation of a finely divided precipitate (Note 20). The serine is filtered, washed with ethanol and ether, and air-dried. The precipitates from several runs may be combined and recrystallized as above from 50% ethanol until a white product is obtained (one or two recrystallizations).

All the filtrates should be combined and evaporated to dryness under reduced pressure, and the residue should be recrystallized as above. The last concentrates (including filter paper and Darco washings), if quite dark, may be precipitated from 70% ethanol before recrystallizing. By this process a nearly quantitative recovery may be effected.

The over-all yield is 30 to 40% of the theoretical amount based on the mercuric acetate

(Note 21).

2. Notes

1. The solution of methyl acrylate in methanol was obtained from Rohm and Haas Company.
2. If the methyl acrylate solution has stood for some time, it is advisable to use a 10% excess, since the solution slowly deteriorates. A low yield of bromo ester is usually caused by insufficient methyl acrylate.
3. Six hundred and forty-eight grams (3 moles) of mercuric oxide and 345 ml. (360 g., 6 moles) of acetic acid may be used just as satisfactorily as mercuric acetate. The solution of these substances should be cooled in an ice bath and vigorously shaken for several minutes after the reagents have been mixed, since the reaction of mercuric oxide with acetic acid produces considerable heat.
4. At this time there is still a small amount of undissolved mercuric acetate (and mercuric oxide, if used). Longer standing does not improve the yield.
5. All solutions of the mercury compounds should be handled with care, as they are extremely vesicant to some individuals.
6. The brominations proceed more smoothly if the chloroform solution is washed free of methanol and dried.
7. The bromination may be carried out just as satisfactorily with the light from two No. 2 Photoflood lamps. These lamps should be mounted in suitable reflectors as near the surface of the solution as possible. The time required may be slightly longer.
8. An efficient mechanical stirrer is required. Near the end of the bromination the precipitate of mercuric bromide becomes quite heavy.
9. The temperature may be controlled by passing tap water through an 8-mm. glass cooling coil mounted in the beaker. The bromination proceeds rapidly at 45–55°, rather slowly at 35–40°, and practically ceases below 30°.
10. The crude ester may be used directly in the preparation of serine. However, greater ease of purification and slightly better yields make it advantageous to prepare the free acid. Pure methyl α-bromo-β-methoxypropionate is obtained by fractionally distilling the crude material under reduced pressure through a Widmer column. From 100 g. of crude material there is obtained 80–90 g. of pure ester, b.p. 73–75°/6 mm., n_D^{20} 1.4586.
11. It is advisable to keep the temperature below 30° during both the hydrolysis and neutralization.
12. The acid should not be heated for long periods. The last traces of ether should be removed under reduced pressure.
13. The crude bromo acid on standing 2–3 days may deposit an amorphous solid which is probably a polymerization product of α-bromoacrylic acid. If this is removed before the bromo acid is aminated, the subsequent purification of serine is much easier.
14. The checkers employed a simple autoclave, constructed as follows: A piece of 10-in. steam pipe 11 in. long and threaded at both ends was closed at one end by a standard pipe cap. A standard flange was screwed to the other end, and a blank companion flange seating on an "ammonia gasket" provided the closure for the top of the autoclave. A Pyrex battery jar 10 in. high and 8.5 in. in diameter fitted loosely

in the pipe and was protected from breakage due to contact with the sides and bottom of the pressure vessel by rings made of rubber tubing. The battery jar was covered with a loosely fitting germinating dish to prevent condensate from the top from dripping into the reaction mixture. After the bromo acid had been introduced into the battery jar, concentrated ammonia was poured into the annular space between the jar and the pipe to provide better heat transfer. The autoclave was heated in a wash tub containing water which was kept boiling by a steam coil.

15. All the concentrations under reduced pressure required in this preparation were carried out with the aid of an efficient water pump.
16. The distillate may be redistilled at atmospheric pressure to recover the hydrobromic acid.
17. Absolute ethanol (200 ml.) is added to the warm (60–70°) solution, and the sides of the flask are scratched to induce crystallization; the remainder of the ethanol is then added in large portions with stirring over a period of 1 hour.
18. Pure *dl*-serine is soluble in water to the extent of 50 g. per liter at 25°, 200 g. at 80°, and approximately 30 g. at 5–10°. The presence of impurities, however, will increase its solubility greatly.
19. Norit is not so satisfactory as Darco.
20. Slow precipitation tends to give large crystals with resulting inclusion of colored impurities.
21. The yield is directly dependent upon the quality of the methyl acrylate used.

3. Discussion

Serine has been prepared by the Strecker method from glycol aldehyde[1] and from ethoxyacetaldehyde[2,3,4] by the condensation of ethyl formate with ethyl hippurate followed by reduction and hydrolysis,[5,6] from the reaction product of chloromethyl ether with ethyl sodium phthalimidomalonate,[7] by amination of α-bromo-β-methoxypropionic acid with subsequent demethylation,[8] by hydrolysis of 5-(methoxymethyl) hydantoin,[9] by hydrolysis of ethyl α-acetamido-β-hydroxypropionate,[10] by hydrogenolysis of N-benzylserine,[11] and by reduction of the 2,4-dinitrophenylhydrazone of hydroxypyruvic acid.[12]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 813

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Darco

2,4-dinitrophenylhydrazone of hydroxypyruvic acid

ethanol (64-17-5)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

ammonia (7664-41-7)

methanol (67-56-1)

ether (60-29-7)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

ammonium bromide (12124-97-9)

HYDROBROMIC ACID (10035-10-6)

bromine (7726-95-6)

sodium sulfate (7757-82-6)

mercuric acetate (1600-27-7)

mercuric oxide (21908-53-2)

Norit (7782-42-5)

potassium bromide (7758-02-3)

ammonium hydroxide (1336-21-6)

ethyl formate (109-94-4)

chloromethyl ether (542-88-1)

methyl acrylate (96-33-3)

magnesium sulfate (7487-88-9)

Ethyl Sodium Phthalimidomalonate

mercuric bromide (7789-47-1)

methyl α,β-dibromopropionate (1729-67-5)

serine (56-45-1)

bromomethoxypropionic acid

Methyl α-bromo-β-methoxypropionate (27704-96-7)

α-bromoacrylic acid (10443-65-9)

glycol aldehyde (141-46-8)

ethoxyacetaldehyde

ethyl hippurate

α-Bromo-β-methoxypropionic acid (65090-78-0)

5-(methoxymethyl) hydantoin

ethyl α-acetamido-β-hydroxypropionate

N-benzylserine

DL-Serine (25821-52-7)

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Organic Syntheses, CV 3, 778

SODIUM AMIDE

$$2\ Na + 2\ NH_3 \xrightarrow{\Delta} 2\ NaNH_2 + H_2$$

Submitted by F. W. Bergstrom
Checked by C. F. H. Allen and C. V. Wilson.

1. Procedure

The apparatus is assembled as shown in .htmFig. 27. Ammonia gas from a commercial cylinder (Note 1) enters the system at *K*. *R* is a mercury trap which would serve as a safety valve if the system should become blocked by solidification of the amide owing to an accidental drop in temperature. *J* is a U-tube containing just enough mercury to seal the bend, and it serves to estimate the rate of ammonia flow. *I* is a Kjeldahl trap which prevents any mercury from being thrown into the fusion pot *A*, which (Note 2) is conveniently supported on a tripod set on bricks to raise it to a convenient height above the burner *M*. Through the cover of the fusion pot passes an outlet tube *B*, a thermometer well *T*, and the combined inlet tube *CDE*. The thermometer well is welded shut at the bottom and projects about 6 mm. below the wider inlet tube, to which it is welded at the top. A gland or packed joint *O*, through which the inlet passes, is packed with a few turns of asbestos cord, the upper hexagonal nut being turned down with a wrench so that ammonia will not escape past the packing and so that there will be sufficient resistance to hold *CDE* in any position to which it may be raised (Note 3). The rubber tubes *H, H'* should be of sufficient length (5–7 cm.) to be very flexible and facilitate manipulation of the hot cover. The outlet tube *B* is at least 10 mm. in diameter.

Fig. 27.

Fig. 27.

At the outset of the run the pot *A*, with the thermometer well in the position shown in the diagram, is heated to about 120° for 10 minutes in a slow stream of ammonia (Note 4). This serves to sweep the air and any traces of moisture from the system. The apparatus is then allowed to cool to 70–80°, the cover is removed, and a 250-ml. nickel crucible *F* is placed in the pot. The ammonia inlet *CDE* is raised to just above the top of the nickel crucible, in which is then placed approximately 175 g. (7.6 gram atoms) of clean sodium (Note 5). The pot is now heated with the full flame of the burner; the sodium melts in 5–10 minutes, whereupon the inlet tube *CDE* is pushed through the gland until it rests on the bottom of the crucible. When the temperature has reached 320°, the burner is turned down and adjusted to maintain the temperature at 350–360°. The ammonia flow is regulated so that the bubbles in *J* are just too rapid to count. After 3.5–4 hours (Note 6) and (Note 7), the temperature is lowered to about

320°, and the cover is lifted enough to see whether any unreacted metal remains; if none remains, the flame is removed and the crucible allowed to cool to 230–240°; at this temperature the burner is replaced and heating continued for 30 minutes to ensure removal of the bulk of the sodium hydride.

The burner is now extinguished, the ammonia shut off, and the pot cover removed by disconnecting at *H, H'*. The crucible is removed from the pot with tongs, and the molten amide is poured into a shallow iron tray, which has previously been heated to remove traces of moisture (Note 8). At this point it is essential to work rapidly to avoid solidification of the amide in the crucible (Note 9). As soon as the product has solidified sufficiently, the tray is transferred to a large desiccator to cool. When cold enough to handle, the tray is inverted on a clean heavy paper; the amide is removed by rapping the bottom of the pan and is at once transferred to convenient wide-mouthed bottles and covered with a petroleum fraction (Note 10) and (Note 11). The yields vary from 267 to 282 g. (90–95%) (Note 12), (Note 13), and (Note 14).

The sodium amide thus prepared is easily pulverized; it may be ground in a mortar under any hydrocarbon solvent. It is safer, though not necessary, where ether is to be used as a reaction medium, to grind the amide first under a hydrocarbon, the mixture being transferred to the reaction flask and then replaced by ether in the usual way (Note 15), (Note 16), and (Note 17).

2. Notes

1. Ordinary commercial cylinders of ammonia are used; it is unnecessary to dry the gas.
2. The fusion pot is obtainable on the market from the Denver Fire Clay Company (cast-iron crucible and cover, 0.25 gal., catalog No. 2136).
3. The gland *O* may be replaced by a sleeve or bushing and held in place by a set screw or by a clamp at any position desired.
4. Considerable time is saved by using a Meker or triple burner for raising the apparatus to reaction temperature, but an ordinary Tirrill burner is sufficient for the reaction.
5. The oxide coating or oil on commercial sodium should be removed before using. It is more convenient to use approximately 175 g. of sodium than to cut this exact amount.
6. The reaction time depends largely upon the rate at which the ammonia is admitted. If the current is too rapid there will be considerable splashing, and much of the molten amide will collect in the iron pot. Ordinarily the quantity of sodium specified will react completely in the time indicated. The total time for a run is slightly under 6 hours, of which not more than 2–2.5 hours of actual attention are required.
7. Any unreacted metal is easily visible as a globule, floating on the surface of the darker liquid. A flashlight aids in rapid inspection.
8. A pan 2 cm. high and 13 cm. in diameter is suitable for a run of this size. Any oxide coat should be removed by heating to redness, cooling, and polishing with emery paper; otherwise the product is deeply colored where it comes into

contact with the pan. The same pan may be used repeatedly without further treatment other than cleaning and drying.

9. Some of the product invariably splashes out of the crucible onto the walls of the pot. If the quantity should be large (too rapid current of ammonia) it can be poured out, but if small it is chipped out after cooling.

10. Commercial "heptane" from petroleum, b.p. 90–100°, is preferable, but other fractions may be used. A 750-ml. bottle will hold the product from one run.

11. Alternatively, the amide is allowed to cool completely in the nickel crucible in a slow current of ammonia and removed when cold. *CDE* is raised above the melt before cooling.

12. The chief variation in the yield is due to loss by splashing; it is difficult to remove the amide that has soldified on the walls of the iron pot. Some loss is accounted for by the sodium hydride carried away with the effluent gas.

13. Runs of other sizes may be made in the same apparatus. With half the quantity of sodium specified, temperature control demands much more attention. With larger quantities, the nickel crucible is dispensed with and the carefully cleaned pot is used. The checkers used 260–270 g. of sodium and averaged a yield of 94%; the reaction time was increased by only 30 minutes. By arranging two series of apparatus in parallel, but connected to the same cylinder of ammonia, one operator can prepare twice as much amide in almost the same time.

14. The product is nearly white if the iron vessels are carefully cleaned but may be considerably on the gray side.

15. *Caution*. Sodium amide is a very reactive substance; it combines with oxygen and reacts explosively with water. The submitters recommended keeping the amide in sealed glass containers in an atmosphere of ammonia. The checkers preferred the use of petroleum fractions for greater convenience in handling; they have kept specimens under this solvent for 3 years without appreciable loss in activity.

When exposed to the atmosphere, sodium amide rapidly takes up moisture and carbon dioxide. When exposed to only limited amounts, as in imperfectly sealed containers, products are formed which render the resulting mixture highly explosive.[1] The formation of oxidation products is accompanied by the development of a yellow or brownish color. If such a change is noticed, the substance should be destroyed at once. This is conveniently accomplished by covering with much benzene, toluene, or kerosene and slowly adding dilute ethanol with stirring.

16. After the preparation is completed, the cooled reactor should be dismantled and the parts immediately washed with ethanol, care being taken that all traces of sodium amide have been destroyed before water is brought into contact with any part of the equipment.

17. The submitters have prepared potassium amide in yields of 95% in the same manner, but maintaining the temperature at 350–360° for the entire run. The apparatus should be rinsed with an ethanolbenzene mixture.

3. Discussion

Sodium amide has been prepared by the action of gaseous[2] or liquid[3] ammonia on sodium, by the action of ammonia on alloys of sodium,[4] and by the electrolysis of a solution of sodium cyanide[5] in liquid ammonia with a sodium amalgam electrode. A summary of the chemistry of alkali amides is given by Bergstrom and Fernelius.[1]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 320

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanolbenzene

ethanol (64-17-5)

ammonia (7664-41-7)

Benzene (71-43-2)

ether (60-29-7)

sodium cyanide (143-33-9)

oxygen (7782-44-7)

mercury (7439-97-6)

carbon dioxide (124-38-9)

toluene (108-88-3)

sodium (13966-32-0)

sodium amide (7782-92-5)

heptane (142-82-5)

sodium hydride (7646-69-7)

potassium amide

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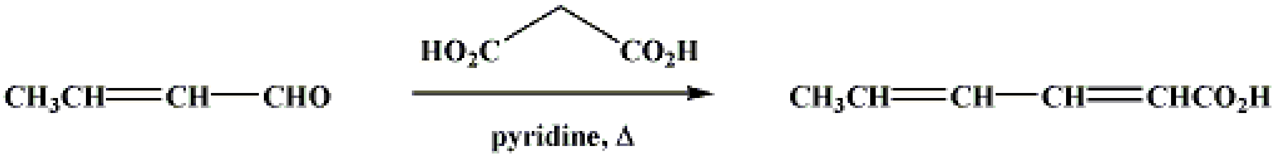
Organic Syntheses, CV 3, 783

SORBIC ACID



Submitted by C. F. H. Allen and J. VanAllan.
Checked by C. S. Hamilton and R. A. Alberty.

1. Procedure

A mixture of 80 g. (93.2 ml., 1.14 moles) of crotonaldehyde (b.p. 102–103°), 120 g. (1.15 moles) of malonic acid (m.p. 134–135°), and 120 g. (122 ml., 1.52 moles) of pyridine (b.p. 113–115°) is heated for 3 hours in a 1-l. flask on a steam bath under a reflux condenser. At the end of this period the evolution of carbon dioxide will have practically ceased. The flask and contents are then cooled in ice, and a solution of 42.5 ml. (0.76 mole) of concentrated sulfuric acid in 100 ml. of water is added with shaking. Most of the sorbic acid separates at once; the remainder is obtained by chilling the solution in an ice bath for 3 hours. The crude acid is filtered by suction and washed once with a small amount of ice water; it is recrystallized at once from 250 ml. of boiling water. The purified acid, which separates on standing overnight in the ice chest, is filtered; it melts at 134°. The yield is 36–41 g. (28–32%) (Note 1), (Note 2), and (Note 3).

2. Notes

1. The submitters have found that the percentage yield is the same when double the above quantities are used.
2. This is an example of a general reaction. If acetic acid is used as a solvent, the substituted malonic acids can be secured, whereas organic bases facilitate the loss of carbon dioxide. The product is generally a mixture from which but a single substance can be isolated.
3. The use of simple aldehydes gives better yields of unsaturated acids; this is especially noticeable when aromatic aldehydes are employed.[1] Mixtures of α,β- and β,γ-unsaturated acids have been reported when aliphatic aldehydes and certain basic catalysts are used.[2,3]

3. Discussion

Sorbic acid has been prepared from crotonaldehyde[4] or aldol[5] and malonic acid in pyridine solution; by hydrogen peroxide oxidation of the condensation product of crotonaldehyde and pyruvic acid;[6] and by the action of alkali on 3-hydroxy-4-hexenoic acid,[7,8] β,δ-disulfo-*n*-caproic acid,[9] parasorbic acid,[10,11] and 3,5-hexadienoic acid.[12]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

aldol

parasorbic acid

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

carbon dioxide (124-38-9)

pyridine (110-86-1)

hydrogen peroxide (7722-84-1)

Malonic acid (141-82-2)

Pyruvic acid (127-17-3)

crotonaldehyde (123-73-9)

Sorbic acid (110-44-1)

3-hydroxy-4-hexenoic acid

3,5-hexadienoic acid

β,δ-disulfo-n-caproic acid

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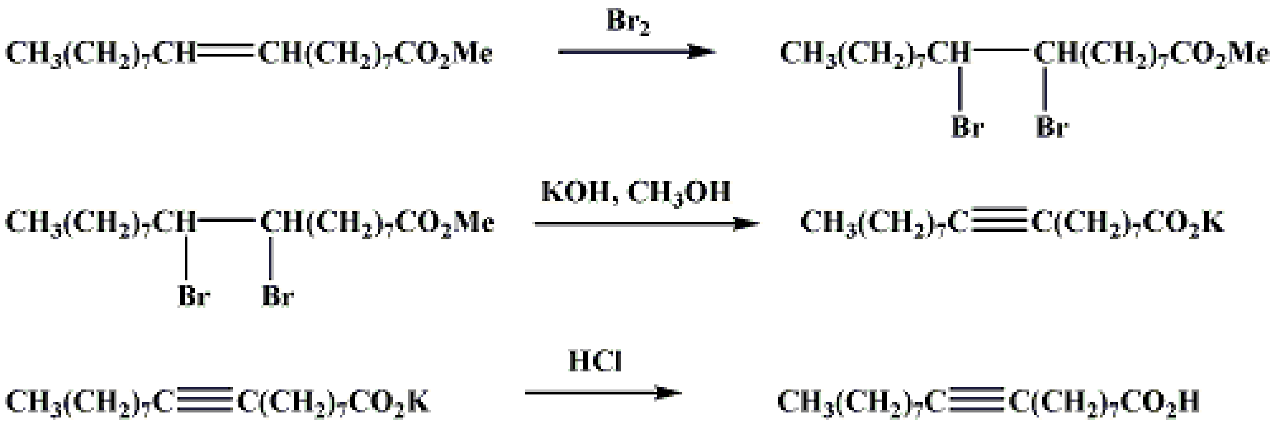
Organic Syntheses, CV 3, 785

STEAROLIC ACID



Submitted by Homer Adkins and R. E. Burks, Jr..
Checked by Arthur C. Cope and Harold R. Nace.

1. Procedure

Bromine is added dropwise with stirring to 35 g. (0.118 mole) of methyl oleate (Note 1) in a 500-ml. round-bottomed flask. The mixture is kept below 50° throughout the addition, which is continued until a slight excess of bromine is present; approximately the theoretical amount (18.9 g.) is decolorized. Methyl oleate (2–3 drops) is then added until the bromine color just disappears. *n*-Amyl alcohol (50 ml.) (Note 2) and potassium hydroxide pellets (40 g., 0.61 mole assuming 85% purity) are added to the flask, and the mixture is heated under reflux for 4 hours in an oil bath at 150°. Then approximately 50 ml. of the *n*-amyl alcohol is distilled at atmospheric pressure (Note 3). The residue on cooling solidifies into a tan-colored mass. Phenolphthalein is added as an indicator, the mixture is cooled in an ice bath, and concentrated hydrochloric acid is added in portions until the red color disappears but reappears on stirring of the viscous mass. This process is continued until the mixture remains colorless. Water (approximately 200 ml.) is added, and the mixture is allowed to come to room temperature. Concentrated hydrochloric acid is added until the mixture is acid to methyl orange. The mixture is again cooled in an ice bath; the oily layer solidifies into a wax, and the acidic water solution is decanted. The wax is dissolved in 100 ml. of 95% ethanol at room temperature, and water is added until the solution becomes turbid. The mixture is heated on a steam bath until a clear solution is formed, and then it is cooled in an ice bath and stirred while the product crystallizes. The semisolid mass is filtered, and the product is recrystallized three times from an ethanol-water mixture. After drying in a vacuum desiccator the yield is 11–14 g. (33–42%), m.p. 46–46.5°; neutral equivalent 279.7–281.4 (calcd. 280.4); hydrogen absorbed by catalytic reduction 94–100%.

2. Notes

1. The methyl oleate was prepared by esterification[1] of commercial U.S.P. grade oleic acid and fractionated through a Widmer column. The fractions used boiled at 140–144°/0.5 mm., 175–179°/2 mm., and had n_D^{25} 1.4500–1.4527 and an iodine number of

93–97 (calcd. 85.6) by iodine bromide titration.[2]

2. *n*-Amyl alcohol was selected as a solvent with a convenient boiling point for the dehydrohalogenation. Acetylenic triple bonds are attacked by water in the presence of strong alkali or strong acid.

3. Part of dehydrohalogenation occurs during the distillation of *n*-amyl alcohol at atmospheric pressure. If the solution was concentrated by distillation under reduced pressure, the product contained bromine and failed to crystallize.

3. Discussion

Stearolic acid has been prepared by the dehydrohalogenation of brominated olive or almond oil,[3] dibromostearic acid,[4] or dichlorostearic acid.[5] The procedure described is a modification of one used by Kino.[4].

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 851

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

hydrogen (1333-74-0)

bromine (7726-95-6)

potassium hydroxide pellets (1310-58-3)

iodine bromide (7789-33-5)

phenolphthalein (77-09-8)

n-amyl alcohol (71-41-0)

methyl oleate (112-62-9)

oleic acid (112-80-1)

Stearolic acid (506-24-1)

dibromostearic acid

dichlorostearic acid (56279-50-6)

methyl orange (547-58-0)

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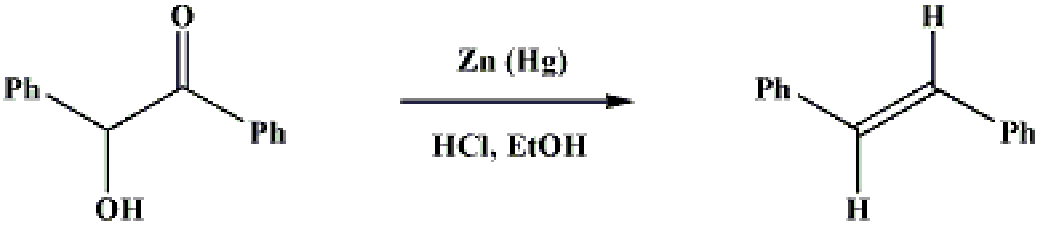
Organic Syntheses, CV 3, 786

trans-STILBENE



Submitted by R. L. Shriner and Alfred Berger.
Checked by W. E. Bachmann and Charles E. Maxwell.

1. Procedure

In a 4-l. beaker, equipped with a powerful mechanical stirrer which reaches nearly to the bottom, are placed 500 ml. of water and 50 g. of mercuric chloride. The stirrer is started, and 200 g. (3.06 gram atoms) of zinc dust (Note 1) is rapidly sifted into the suspension. Stirring is continued until the mercuric chloride dissolves (about 20–30 minutes). The zinc is then allowed to settle, the supernatant liquid is removed by decantation, and the amalgam is filtered and washed with 200 ml. of water. The zinc amalgam is returned to the beaker, which is now surrounded by an ice bath, and 500 ml. of 95% ethanol and 100 g. (0.48 mole) of benzoin are added. The stirrer is started, and 500 ml. of concentrated hydrochloric acid is added through a dropping funnel at such a rate that addition is complete in about 2 hours; throughout the reaction the temperature is maintained below 15°. Stirring is continued for about 2 hours more.

About 2 l. of cold water is added to the reaction mixture, and the insoluble material is collected on a Büchner funnel. The precipitate is transferred to a 2-l. beaker and extracted with two 600-ml. portions of hot ethanol. The combined extracts, on cooling, deposit long needles of stilbene which weigh 55–59 g. and melt at 116–121°. These are filtered with suction and are recrystallized from 600 ml. of 95% ethanol. The yield is 45–48 g. (53–57%) of colorless needless melting at 123–124°.

2. Notes

1. The zinc dust used was obtained from J. T. Baker and Company.

3. Discussion

The procedure described is essentially that of Ballard and Dehn.[1] Stilbene has also been prepared by reduction of desoxybenzoin,[2] benzaldehyde[3] and benzil;[2,4] by dehydrogenation of ethylbenzene,[5] toluene,[5,6,7] and bibenzyl;[6,8] by alkaline reduction of phenylnitromethane,[9] phenylnitroacetonitrile,[9] and desoxybenzoin;[10] by distillation

of benzyl sulfone,[11] benzyl sulfide,[11,12] calcium cinnamate,[13] cinnamic acid,[14] phenyl cinnamate,[15,16] and diphenyl fumarate,[11] by dehydrohalogenation of α,α'-dichlorobibenzyl[17] and benzyl chloride;[18] by dehalogenation of α,α,α',α'-tetrachlorobibenzyl[19] and benzal chloride;[20] by the coupling of cinnamic acid and phenyldiazonium chloride;[21] by dehydration of benzylphenylcarbinol,[17,22] benzyl ether,[23] and benzyl alcohol;[23,24] by treatment of benzaldehyde ethyl mercaptal with Raney nickel;[25] by pyrolysis of methyl benzyl dithiocarbonate;[26] and by catalytic desulfurization of trithiobenzaldehyde.[27] The diazonium coupling reaction[21] appears to have the widest applicability for the synthesis of substituted stilbenes.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 428

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Desoxybenzoin

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

phenyldiazonium chloride

benzaldehyde (100-52-7)

Raney nickel (7440-02-0)

Benzil (134-81-6)

Benzoin (119-53-9)

toluene (108-88-3)

zinc (7440-66-6)

benzyl chloride (100-44-7)

Benzyl alcohol (100-51-6)

benzyl ether (103-50-4)

mercuric chloride (7487-94-7)

ethylbenzene (100-41-4)

cinnamic acid (621-82-9)

benzal chloride (98-87-3)

Phenylnitromethane (622-42-4)

stilbene

α,α'-dichlorobibenzyl

Phenyl cinnamate (2757-04-2)

bibenzyl (103-29-7)

phenylnitroacetonitrile

benzyl sulfone (620-32-6)

calcium cinnamate

diphenyl fumarate

benzaldehyde ethyl mercaptal

methyl benzyl dithiocarbonate

trithiobenzaldehyde

Benzyl sulfide (538-74-9)

trans-Stilbene (103-30-0)

α,α,α',α'-tetrachlorobibenzyl

benzylphenylcarbinol (614-29-9)

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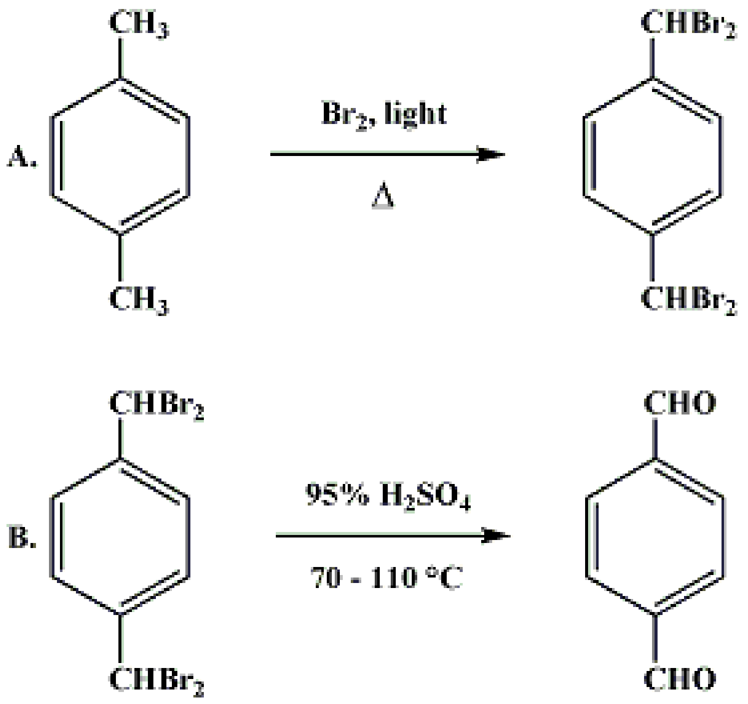
Organic Syntheses, CV 3, 788

TEREPHTHALALDEHYDE



Submitted by J. M. Snell and A. Weissberger.
Checked by R. L. Shriner and N. S. Moon.

1. Procedure

A. *α,α,α',α'-Tetrabromo-p-xylene*. A 1-l. three-necked flask is fitted with an oil-sealed mechanical stirrer, a 500-ml. dropping funnel, and a reflux condenser, the top of which is connected to a gas-absorption trap. A 300-watt tungsten lamp is clamped in such a position that its bulb is within 1 in. of the flask (Note 1). Into the flask is introduced 100 g. (0.94 mole) of dry *p*-xylene (m.p. 11–12°), and the flask is heated in an oil bath maintained between 140° and 160°. The stirrer is started, and, when the xylene starts boiling, 700 g. (224 ml., 4.38 moles) of dry bromine (Note 2) is gradually added through the dropping funnel at such a rate that there is never any large amount of unreacted bromine in the flask. Stirring and heating are continued throughout the reaction, which requires 6–10 hours. After all the bromine has reacted, the mixture is cooled and dissolved in 1 l. of warm chloroform. The chloroform solution is cooled in an ice bath and the product removed by filtration. It is light gray, melts at 165–169°, and weighs 250–258 g. After a second recrystallization from 1 l. of chloroform, 190–200 g. of light-gray crystals melting at 168–170° is obtained. An additional 15–20 g. may be obtained by concentrating the chloroform filtrate to 250 ml. and recrystallizing the precipitate from fresh chloroform. The total yield is 205–220 g. (51–55%).

B. *Terephthalaldehyde*. A 2-l. round-bottomed flask is fitted with a still head, capillary ebullition tube, and receiver in an assembly for a vacuum distillation. Into the flask are

introduced 84.3 g. (0.2 mole) of finely powdered tetrabromo-*p*-xylene and 200 ml. of concentrated sulfuric acid (95%). The reactants are thoroughly mixed by shaking. A vacuum is applied by means of a water pump, and a stream of air is allowed to pass through the capillary tube in order to facilitate the rapid removal of hydrogen bromide. The flask is heated in an oil bath to 70°, and, as the evolution of gas becomes less vigorous, the temperature of the bath is gradually raised to 110° (Note 3). The reaction is complete when a perfectly clear solution is obtained and no more gas is evolved (about 2.5 hours). The flask is then cooled and the contents are poured on 600 g. of crushed ice. The crystalline solid is collected on a filter, washed with a little water, and recrystallized from 600 ml. of 10% methanol with the aid of 1 g. of decolorizing carbon to remove the yellow color. The small amount of tetrabromoxylene which remains undissolved is separated with the carbon and washed on the filter with two 100-ml. portions of hot 10% methanol. The yield of pure product, m.p. 115–116°, is 21.7–22.5 g. (81–84%).

2. Notes

1. It is important to have light shining on the reaction mixture throughout the bromination. The bromination may also be accomplished by placing the flask in direct sunlight.
2. The bromine is dried by shaking it with two 200-ml. portions of concentrated sulfuric acid.
3. The mixture foams considerably and must be watched. The foaming can be controlled by raising the temperature slowly and regulating the vacuum. For this reason it is difficult to hydrolyze larger amounts of the tetrabromide.

3. Discussion

Terephthalaldehyde has been made by the action of lead nitrate on α,α'-dichloro-*p*-xylene[1] or α,α'-dibromo-*p*-xylene;[2] by the action of fuming nitric acid on dibromo-*p*-xylene;[3] by the hydrolysis of terephthaldehyde tetraacetate;[4] by the action of phosphorus pentachloride on *p*-xylyleneglycol monoethyl ether;[5] by the hydrolysis of α,α,α',α'-tetrachloro-*p*-xylene;[6] by the hydrolysis of α,α,α',α'-tetrabromo-*p*-xylene;[7] and by the Sommelet procedure.[8] The method described here is essentially the modification described by Weissberger and Bach.[9]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 578

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

methanol (67-56-1)

phosphorus pentachloride (10026-13-8)

chloroform (67-66-3)

nitric acid (7697-37-2)

hydrogen bromide (10035-10-6)

bromine (7726-95-6)

decolorizing carbon, carbon (7782-42-5)

lead nitrate (10099-74-8)

xylene, p-xylene (106-42-3)

Terephthalaldehyde (623-27-8)

α,α,α',α'-Tetrabromo-p-xylene, a,a,a',a'-Tetrabromo-p-xylene (1592-31-0)

terephthaldehyde tetraacetate

dibromo-p-xylene

p-xylyleneglycol monoethyl ether

α,α'-dichloro-p-xylene (623-25-6)

α,α'-dibromo-p-xylene

α,α,α',α'-tetrachloro-p-xylene

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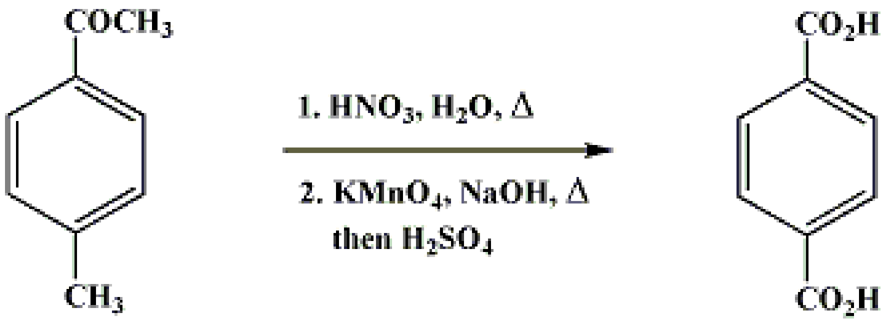
Organic Syntheses, *CV 3*, *791*

TEREPHTHALIC ACID



Submitted by C. F. Koelsch
Checked by C. F. H. Allen and J. VanAllan.

1. Procedure

One hundred grams (0.75 mole) of *p*-methylacetophenone[1] is added to a mixture of 250 ml. (4 moles) of concentrated nitric acid (sp. gr. 1.42) and 1 l. of water in a 3-l. flask, and the mixture is refluxed in a hood for 4 hours. After the mixture has been cooled, the sticky, yellow solid is collected on a 14-cm. Büchner funnel, pressed down well, and washed with 300 ml. of cold water.

The moist solid is mixed with 1 l. of water and 35 g. of sodium hydroxide in a 3-l. three-necked flask, fitted with a mechanical stirrer and a reflux condenser, and the stirred mixture is heated almost to its boiling point. Through the momentarily opened third neck of the flask is added, in portions of about 20 g., 300 g. (1.9 moles) of potassium permanganate, at such a rate that the boiling of the stirred mixture is maintained without external heating. After the addition has been completed, the mixture is refluxed for 2 hours; if any permanganate remains it is destroyed by the addition of 25 ml. of ethanol. The mixture is then filtered through a 14-cm. Büchner funnel, and the manganese dioxide is washed by removing it from the funnel, slurrying with 500 ml. of hot water (Note 1), and filtering.

The combined filtrates are heated nearly to boiling and acidified with a solution of 108 ml. of concentrated sulfuric acid (sp. gr. 1.84) in 400 ml. of water. After the mixture has been cooled to room temperature, the terephthalic acid is filtered and washed by stirring on the filter with three successive 100-ml. portions of cold water. The product is dried in an evaporating dish on a steam bath. The yield of terephthalic acid which sublimes at 300° or higher without melting is 105–109 g. (84–88%) (Note 2) and (Note 3).

2. Notes

1. This extraction yields 1–2 g. of the product.
2. The acid is analytically pure. There is no satisfactory solvent for the

recrystallization of large amounts of terephthalic acid. Small quantities may be recrystallized from acetic acid, but the purity of a properly precipitated and washed sample is not thereby improved.

3. The high yields of ethyl ester obtainable from the product attest its purity. A mixture of 50 g. of terephthalic acid, 500 ml. of absolute ethanol, and 25 ml. of sulfuric acid was boiled for 16 hours and then distilled to half its volume and poured into dilute aqueous sodium carbonate. There was obtained 56.7 g. of diethyl terephthalate (m.p. 42–44°), and from the wash water there was recovered 4.6 g. of terephthalic acid; these materials account for 93.3% of the original substance.

3. Discussion

Terephthalic acid has been obtained from a great many *p*-disubstituted derivatives of benzene or cyclohexane by oxidation with permanganate, chromic acid, or nitric acid. The following routes appear to have preparative value: from *p*-toluic acid,[2] *p*-methylacetophenone,[3] or dihydro-*p*-tolualdehyde[4] by oxidation with permanganate; from *p*-cymene by oxidation with sodium dichromate and sulfuric acid;[5] from *p*-dibromobenzene or from *p*-chloro- or *p*-bromobenzoic acid by heating at 250° with potassium and cuprous cyanides;[6] and from *p*-dibromobenzene[7] or *p*-iodobenzoic acid,[8] butyllithium, and carbon dioxide. It has been obtained also by the air oxidation of *p*-xylene in the presence of cobalt naphthenates.[9] Oxidations of *p*-toluic acid,[10] *p*-tolualdehyde,[11] and α-chloro-*p*-xylene[12] have been patented.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

p-chloro- or p-bromobenzoic acid

potassium and cuprous cyanides

ethanol (64-17-5)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

Benzene (71-43-2)

sodium hydroxide (1310-73-2)

nitric acid (7697-37-2)

potassium permanganate (7722-64-7)

sodium carbonate (497-19-8)

carbon dioxide (124-38-9)

cyclohexane (110-82-7)

chromic acid (7738-94-5)

sodium dichromate (7789-12-0)

manganese dioxide (1313-13-9)

p-xylene (106-42-3)

p-cymene (99-87-6)

butyllithium (109-72-8)

Terephthalic acid (100-21-0)

diethyl terephthalate (636-09-9)

p-Toluic acid (99-94-5)

p-dibromobenzene (106-37-6)

p-Methylacetophenone (122-00-9)

p-iodobenzoic acid (619-58-9)

p-Tolualdehyde (104-87-0)

dihydro-p-tolualdehyde

α-chloro-p-xylene (104-82-5)

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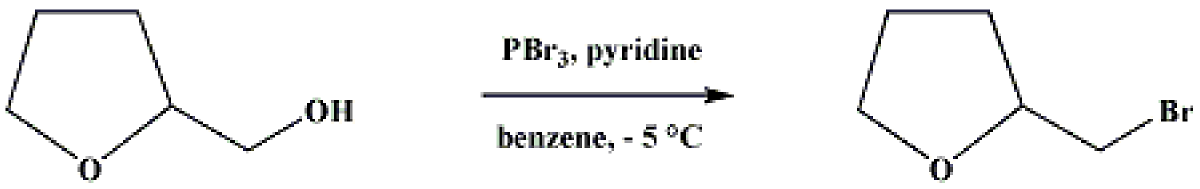
TETRAHYDROFURFURYL BROMIDE

[Furan, 2-(bromomethyl)tetrahydro-]



Submitted by L. H. Smith
Checked by John R. Johnson and R. L. Sawyer.

1. Procedure

In a 500-ml. three-necked flask, fitted with a mechanical stirrer, thermometer, separatory funnel, and calcium chloride tube, are placed 96 g. (56.5 ml., 0.36 mole) of redistilled phosphorus tribromide (b.p. 174–175°/740 mm.) and 50 ml. of dry benzene. From the separatory funnel, 15 g. of dry pyridine is added with stirring over a period of 15 minutes. The flask is then surrounded by an ice-salt mixture, and the contents are cooled to −5°. A mixture of 102 g. (1 mole) of redistilled tetrahydrofurfuryl alcohol (b. p. 79–80°/20 mm.) and 5 g. of dry pyridine (total pyridine, 20 g., 0.25 mole) is added slowly from the dropping funnel with stirring over a period of 4 hours. During this time the internal temperature is kept at −5° to −3°. Stirring is continued for 1 hour longer, and the cooling bath is then allowed to warm up to room temperature.

The mixture is allowed to stand for 24–48 hours (Note 1) and is then transferred to a 500-ml. Claisen flask. Two small portions of benzene are used for rinsing the flask. The benzene is distilled by reducing the pressure gradually to about 60 mm. and heating the flask gently in an oil bath (not above 90°). After the benzene has been removed, the pressure is reduced to 5–10 mm. and the bath is heated slowly to 150–155° until no more material distils (Note 2). The crude distillate (110–126 g.) is redistilled through an efficient column, and the purified tetrahydrofurfuryl bromide is collected at 69–70°/22 mm. (61–62°/13 mm., 49–50°/4 mm.) (Note 3). The yield is 90–102 g. (53–61%).

2. Notes

1. The yields were slightly higher when the mixture was allowed to stand for 48 hours.
2. Most of the material distils while the bath is at 100–120°. When the bath reaches 155–160° the mixture begins to decompose and white fumes are copiously evolved.
3. Unless a good fractionation is obtained, the material will contain some pyridine and will discolor in a few days. Carefully fractionated material will

remain colorless for 2 months or more. A considerable amount of dark, viscous residue remains in the distilling flask.

3. Discussion

Tetrahydrofurfuryl bromide has been obtained in low yields by the action of hydrobromic acid, or of phosphorus tribromide, on the corresponding alcohol.[1] The yield is improved markedly by use of phosphorus tribromide and pyridine.[2,3] The bromide has also been prepared by the action of potassium hydroxide on 4,5-dibromopentanol-1.[4]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Benzene (71-43-2)

HYDROBROMIC ACID (10035-10-6)

phosphorus tribromide (7789-60-8)

pyridine (110-86-1)

potassium hydroxide (1310-58-3)

tetrahydrofurfuryl alcohol (97-99-4)

Tetrahydrofurfuryl bromide, Furan, 2-(bromomethyl)tetrahydro- (1192-30-9)

4,5-dibromopentanol-1

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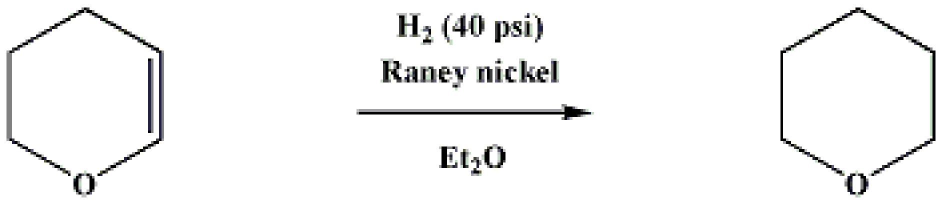
TETRAHYDROPYRAN

[Pyran, tetrahydro-]



Submitted by D. W. Andrus and John R. Johnson.
Checked by Nathan L. Drake and Charles M. Eaker.

1. Procedure

The hydrogenation is carried out in a low-pressure catalytic hydrogenation apparatus. Raney nickel catalyst (p. 181) is washed with ether three times on a Büchner funnel, then 8 g. of it is transferred under ether to the hydrogenation bottle. The bottle is fitted with a rubber stopper bearing a small dropping funnel and a glass tube that leads to one arm of a three-way stopcock. The other arms of the stopcock are connected respectively to a water pump and a source of inert gas (Note 1) in such a way that the ether can be pumped off and the bottle can then be filled with the inert gas. When this has been done, 50.5 g. (0.6 mole) of dihydropyran (p. 276) is introduced through the dropping funnel.

The bottle is connected to the hydrogenation apparatus and alternately evacuated and filled with hydrogen twice. Hydrogen is then admitted to the system until the pressure gauge reads 40 lb. The shaker is started, and the pressure drops to the theoretical value for absorption of 0.6 mole in 15–20 minutes; beyond this point shaking causes no further absorption of hydrogen (Note 2). The bottle is removed and the nickel catalyst is allowed to settle. The tetrahydropyran is decanted, but enough is left in the bottle to cover the catalyst (Note 3). The product boils at 85–86°, but it need not be distilled for many purposes. The yield is practically quantitative.

2. Notes

1. Purified nitrogen is a convenient inert gas, but natural gas containing no oxygen, or sulfur compounds, is equally suitable; the checkers used hydrogen.
2. As the catalyst becomes older, it loses its activity somewhat and a longer time is required for the pressure to drop to the theoretical value.
3. The same catalyst may be used many times. For the next run the dihydropyran is merely poured into the bottle containing the catalyst which is wet with the product of the previous run.

3. Discussion

Tetrahydropyran has been prepared by hydrogenation of dihydropyran using a platinum black catalyst;[1] by heating pentamethylene bromide with water;[2,3] or with water and zinc oxide in a sealed tube;[4] or by heating pentamethylene glycol with 3 volumes of 60% sulfuric acid in a pressure tube,[5] or dehydration of this glycol in the vapor phase over kaolin or aluminum oxide.[6]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 692

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

platinum black

kaolin

sulfuric acid (7664-93-9)

ether (60-29-7)

hydrogen (1333-74-0)

oxygen (7782-44-7)

nitrogen (7727-37-9)

sulfur (7704-34-9)

nickel, Raney nickel (7440-02-0)

pentamethylene bromide (111-24-0)

pentamethylene glycol (111-29-5)

Tetrahydropyran, Pyran, tetrahydro- (142-68-7)

zinc oxide

aluminum oxide (1344-28-1)

dihydropyran

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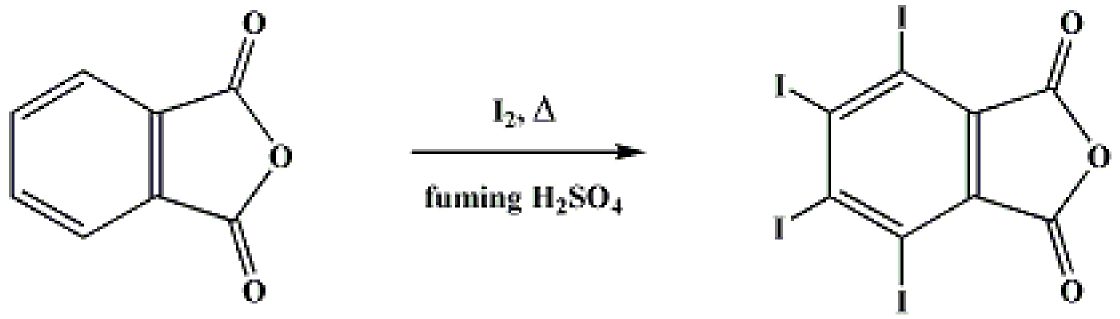
Organic Syntheses, CV 3, 796

TETRAIODOPHTHALIC ANHYDRIDE

[Phthalic anhydride, tetraiodo-]



Submitted by C. F. H. Allen, Homer W. J. Cressman, and H. B. Johnson.
Checked by H. R. Snyder and E. Van Heyningen.

1. Procedure

In a 3-l. three-necked flask with ground-glass joints are placed 148 g. (1.0 mole) of phthalic anhydride, 324 g. (60% of the total of 2.12 moles to be added) of iodine, and 600 ml. of 60% fuming sulfuric acid. The flask, fitted with an air condenser 90–100 cm. in length (Note 1), is arranged for heating by a water bath. A tube leads from the condenser to a gas trap.

The temperature of the water bath is raised cautiously to 45–50°, at which point the reaction begins (Note 2). Heating is continued until visible reaction has almost completely stopped. During this time (Note 3), the temperature has been raised gradually to 65°. The flask is then cooled by flooding the bath with ice water, and a second portion, 162 g. (30% of the total), of iodine is added. The flask is heated again at 65° until the reaction ceases. After cooling as before, the last portion, 54 g. (10% of the total), of iodine is added.

When reaction at 65° has ceased and the flask has been cooled, the condenser is removed, and the flask is arranged for heating on an oil bath in a well-ventilated area (Note 4). The temperature of the bath is raised to 175° and maintained at 170–180° until the evolution of sulfur trioxide and iodine fumes has slowed considerably (about 2 hours at 170°). The flask is allowed to cool to about 60° before the contents are poured into a beaker, which is allowed to stand overnight at room temperature.

The solid is filtered by suction on a glass filter cloth and is washed with two 100-ml. portions of concentrated sulfuric acid and then with three 200-ml. portions of water (Note 5). The light-yellow crystalline material is then transferred to a 3-l. beaker where it is stirred for 30 minutes with a solution of 20 g. of sodium bisulfite in 1.5 l. of water to remove the last traces of iodine. The heavy solid is allowed to settle to the bottom of the beaker, and the bisulfite solution is poured off. The crystals are washed

with three 1-l. portions of water, each portion being decanted as before (Note 6), and then are transferred to a funnel. The product is washed with an additional 1-l. portion of water and two 200-ml. portions of acetone and dried in an oven at 60°. The product amounts to 520–535 g. (80–82% based on the phthalic anhydride) (Note 7) and (Note 8) and melts at 327–328° (Note 9).

2. Notes

1. A water-cooled condenser maintained at 20–25° may be used.
2. Temporary cooling by cold water may be necessary to keep the reaction in check. It must be closely watched at this stage.
3. The lengths of the periods of heating are approximately 5, 3, and 1 hour, respectively. In a run of one-half the size described, the checkers found the periods required to be about 4, 1.5, and 1 hour, respectively.
4. This operation is carried on most conveniently out-of-doors. For the 0.5-mole run, the checkers fitted the flask to the gas trap with a U-tube of 2-cm. bore, having a ground-glass joint for the connection to the flask. The large-diameter tube permitted the operation to be carried out in a hood with no danger of clogging of the apparatus by sublimed iodine.
5. This method of working up the product is superior to the usual one of pouring on ice in that a purer material is obtained and a difficult recrystallization is thus avoided.
6. Some impurities tend to float and are removed with the wash water.
7. It was observed that sunlight or illumination by a Photoflood lamp tended to make the reaction more vigorous but did not produce any significant increase in yield.
8. Yields of the same order were obtained starting with 0.5, 1.0, and 10.0 moles of phthalic anhydride. In the runs with 10.0 moles of phthalic anhydride, a greater excess of iodine was found necessary; i.e., the weights of iodine added were 3240 g., 1620 g., 540 g., 500 g., 300 g. The lengths of the heating periods were approximately 72, 48, 24, 24, and 12 hours, respectively.
9. The melting point may vary from 325° to 332° but usually falls within a 2° range. No suitable solvent for recrystallization has been found. The recrystallized product always has a lower melting point than the original material.

3. Discussion

The method given is the only satisfactory one so far reported.[1,2,3,4,5]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

sulfur trioxide (7446-11-9)

sodium bisulfite (7631-90-5)

phthalic anhydride (85-44-9)

iodine (7553-56-2)

acetone (67-64-1)

Tetraiodophthalic anhydride, Phthalic anhydride, tetraiodo- (632-80-4)

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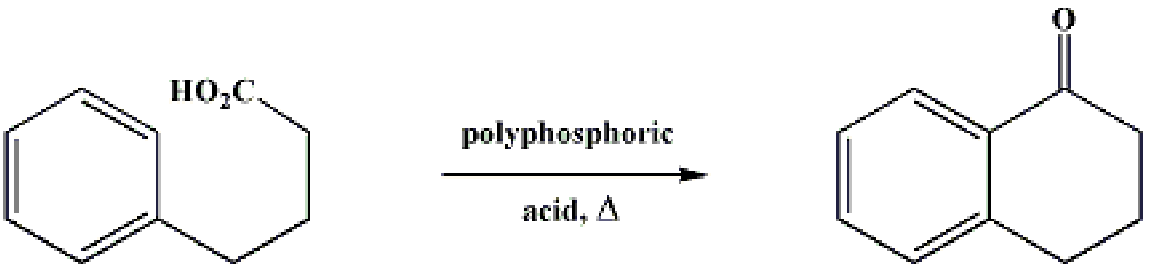
Organic Syntheses, CV 3, 798

α-TETRALONE

[1(2H)-Naphthalenone, 3,4-dihydro-]



Submitted by H. R. Snyder and Frank X. Werber.
Checked by E. C. Horning and G. N. Walker.

1. Procedure

In a 600-ml. beaker, 80 g. of polyphosphoric acid (Note 1) is warmed on a steam bath to 90°. There is then added in one lot, with manual stirring, 22.0 g. (0.134 mole) of molten γ-phenylbutyric acid (Note 2), previously warmed to 65–70°. The mixture is removed from the steam bath and is stirred steadily by hand for 3 minutes; during this time a temperature of 90° or slightly higher is maintained by the heat of the reaction. An additional 70 g. of polyphosphoric acid is then added, and the mixture is again warmed on a steam bath for 4 minutes while being stirred vigorously by hand. The resulting solution is allowed to cool to 60°, and is hydrolyzed by addition to 200 g. of ice and water.

When the hydrolysis is complete, as indicated by the disappearance of orange, viscous material and the appearance in its stead of yellow oil, the aqueous mixture is transferred to a 500-ml. separatory funnel and extracted with two portions of ether, 200 ml. and 100 ml., respectively. The extracts are combined and washed successively with 200 ml. of water, two 100-ml. portions of 5% sodium hydroxide solution (Note 3), 200 ml. of water, 100 ml. of 3% aqueous acetic acid, 100 ml. of 5% sodium bicarbonate solution, and 100 ml. of water. The ether solution is dried over anhydrous magnesium sulfate. The ether is removed either by evaporation on a steam bath or by distillation from a 50-ml. flask into which the solution is introduced continuously, as fast as the solvent is distilled, by means of a dropping funnel reaching below the side arm of the distilling head. The flask is fitted with a 6-in. Vigreux column, and the residual oil is distilled under reduced pressure. There is obtained 14.8–16.9 g. (75–86%) of colorless oil, b.p. 90–91°/0.5–0.7 mm. or 94–95°/2.1–2.3 mm. (Note 4).

2. Notes

1. Polyphosphoric acid obtained from the Victor Chemical Company, Chicago, was used.

2. γ-Phenylbutyric acid was obtained by catalytic reduction (palladium-charcoal) of β-benzoylpropionic acid and was purified by distillation; the yield of material, b.p. 133–135°/1.0–1.3 mm., was 96%.
3. The amount of unchanged γ-phenylbutyric acid obtained by acidification of the alkaline solution is negligible. When only 72 g. of polyphosphoric acid in one lot was employed in the reaction, there was recovered 1.5 g. of γ-phenylbutyric acid, and the yield of α-tetralone was 15.9 g. (81%).
4. The submitters have used polyphosphoric acid in the cyclization of hydrocinnamic acid, 2-bromo-5-methoxyhydrocinnamic acid, and *o*-benzoylbenzoic acid.

3. Discussion

Other methods of preparation have been reviewed in earlier volumes.[1,2] The method consisting of air oxidation of tetralin[2,3,4,5,6] has in some cases been aided by the use of copper oxide[4] or sulfate,[5] and has been said to yield a product which is contaminated with α-tetralol.[7] The ketone has also been prepared from γ-phenylbutyric acid by cyclization with phosphoric acid-phosphoric anhydride[8] and with hydrofluoric acid,[9] and from γ-phenylbutyryl chloride by the action of aluminum chloride.[10] The method described is essentially that of Synder and Werber.[11]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 569
- Org. Syn. Coll. Vol. 3, 223
- Org. Syn. Coll. Vol. 3, 312
- Org. Syn. Coll. Vol. 4, 898

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

polyphosphoric acid

acetic acid (64-19-7)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

hydrofluoric acid (7664-39-3)

aluminum chloride (3495-54-3)

copper oxide (1317-38-0)

Hydrocinnamic acid (501-52-0)

Tetralin (119-64-2)

magnesium sulfate (7487-88-9)

β-Benzoylpropionic acid (2051-95-8)

γ-Phenylbutyric acid (1821-12-1)

α-Tetralone, 1(2H)-Naphthalenone, 3,4-dihydro- (529-34-0)

γ-phenylbutyryl chloride

α-tetralol (529-33-9)

phosphoric acid-phosphoric anhydride (2466-09-3)

o-benzoylbenzoic acid (85-52-9)

2-bromo-5-methoxyhydrocinnamic acid

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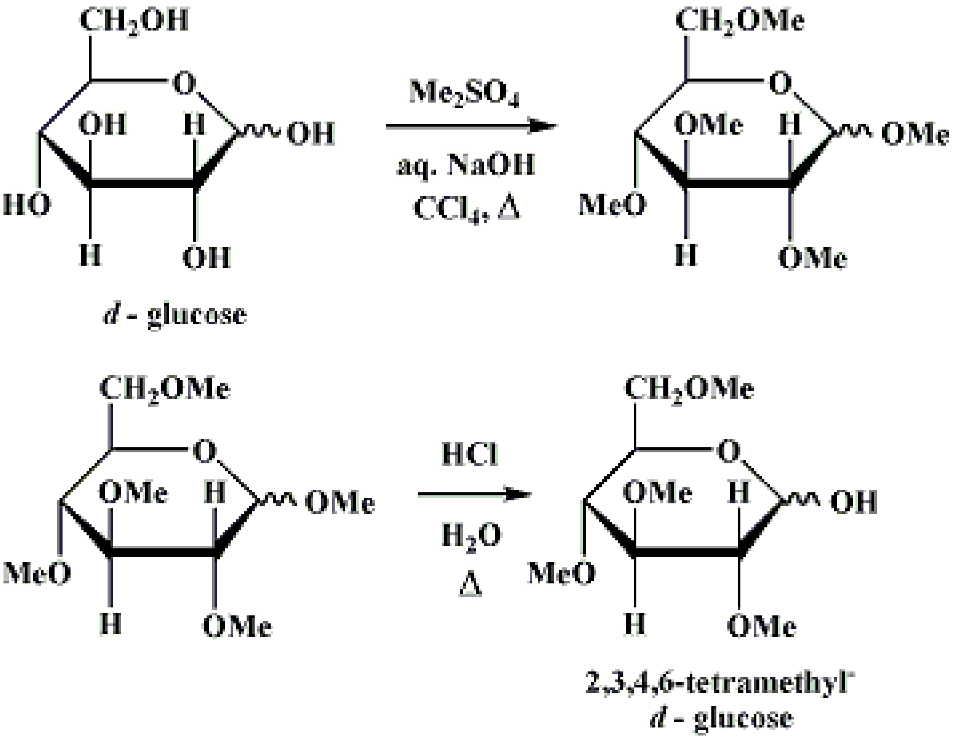
Organic Syntheses, CV 3, 800

2,3,4,6-TETRAMETHYL-*d*-GLUCOSE

[D-Glucose, 2,3,4,6-tetramethyl-]



Submitted by Edward S. West and Raymond F. Holden.
Checked by W. W. Hartman and A. J. Schwaderer.

1. Procedure

This preparation must be carried out in a hood having good ventilation. Methyl sulfate has a high vapor pressure in spite of its high boiling point and is very poisonous. Ammonia is a specific antidote and should be kept on hand to destroy any of the ester accidentally spilled. It is advisable to wash the hands in dilute ammonium hydroxide frequently.

In a 2-l. distilling flask immersed in a 4-l. water bath are placed 25 g. (0.14 mole) of anhydrous glucose (Note 1) and 15 ml. of water. The flask is fitted with a cork through which passes a strong mechanical stirrer (Note 2) and a dropping tube connected by rubber tubing and a screw clamp to a 500-ml. reservoir flask. The side tube of the flask is connected to a water condenser, fitted with a suction flask, from which fumes are led to a flue by a piece of tubing. The temperature of the water bath is raised to 55°, and the glucose is brought into solution with rapid stirring, which is maintained throughout the process. A mixture of 90 ml. (120 g., 9.5 moles) of methyl sulfate and 125 ml. of carbon tetrachloride is added from the reservoir as quickly as possible to the flask. The clamp is closed, and 400 ml. (580 g.) of 40% (by weight) sodium hydroxide is placed in the reservoir. The alkali is admitted to the flask at the rate of 1

drop in 2 seconds for 5 minutes, then 1 drop per second for 5 minutes, and then 3 drops per second until the distillation of carbon tetrachloride slackens or ceases. This is usually accomplished in 15–20 minutes and after the addition of 70–90 ml. of alkali. The heat of reaction generally maintains the proper temperature of 50–55° throughout this stage without the necessity of heating the water bath externally. The remainder of the alkali is added as quickly as possible, and the bath temperature raised to and maintained at 70–75°. Then 160 ml. (208 g., 1.65 moles) of methyl sulfate is placed in the reservoir immediately and added at the rate of 3–4 drops per second (slower if the mixture foams seriously).

After all the methyl sulfate has been added, the bath is boiled for 30 minutes with continued stirring. The contents of the flask are cooled, diluted with sufficient water to dissolve most of the separated sodium sulfate, and extracted four times with 150-ml. portions of chloroform; the chloroform and water layers are separated carefully. The combined chloroform extracts (Note 3) are placed in a 2- or 3-l. distilling flask (with condenser attached) with 400 ml. of 2 *N* hydrochloric acid, and the chloroform is removed by distillation. A rapid current of steam is then passed through the solution for 1 hour, care being taken to maintain the volume approximately constant by heating the flask. Five grams of Norite is added to the hot solution, which is then cooled and filtered. The filtrate is saturated with sodium sulfate and extracted four times with 150-ml. portions of chloroform. The combined chloroform extracts are dried with sodium sulfate, 1 g. of Norit is added, and the mixture is filtered. The chloroform is removed as completely as possible in a boiling water bath without vacuum and finally at the water pump. The heavy syrup is treated with 40–50 ml. of petroleum ether (30–60°) and shaken for a short time, whereupon it sets to a mass of crystals. After cooling in an ice bath for 30 minutes, the crystals are filtered, washed with a little cold petroleum ether, and dried over calcium chloride under reduced pressure. The yield is 15–18 g. (46–55%) (Note 3). The specific rotation, $[\alpha]_D^{26}$, in water was found to be about +79–79.5°, when $c = 4$; a drop of 15% ammonia was added to speed equilibration, and the readings were made 1 hour after the solution was prepared in a 2-dm. tube.

The slightly impure product is recrystallized from petroleum ether (b.p. 30–60°) containing 0.5% of anhydrous ether in a continuous extractor, using 100 ml. of solvent per 6–7 g. of compound. One crystallization is generally sufficient to give a pure product. The specific rotation of pure tetramethyl-*d*-glucose prepared by this method is approximately $[\alpha]_D^{20}$ +81.3° (Note 4).

2. Notes

1. α-Methylglucoside may be methylated in the same way as glucose, using four-fifths of the reagents and hydrolyzing the tetramethyl-α-methylglucoside (contained in the chloroform solution) for 3 hours instead of the 1 hour required for the mixture of α- and β-tetramethyl-methylglucosides obtained directly from glucose. Tetramethylglucose prepared in this way may show the correct rotation without recrystallization.

2. The stirrer consists of a 3/16-in. Monel rod formed into a 1-in. flattened loop at one end for stirring. The stirrer is passed through a closely fitting 3/8 by 5 in. brass bearing with a packing nut at the lower end, the top of the bearing being countersunk to facilitate oiling with heavy engine oil. This metal stirrer permits much more vigorous stirring (which is essential) than the ordinary glass apparatus.

3. The tetramethylmethylglucosides may be isolated from the chloroform solution by drying with sodium sulfate, distilling off the chloroform, and then vacuum-distilling the syrup. The distillation can be easily carried out in a distilling flask (100-ml.) filled with glass wool (which effectively prevents bumping) and having a low side arm. The glass wool materially lowers the distilling temperature. The mixture of α- and β-glucosides (approximately 85% β form) and the pure α form distil at about 88–90°/0.15 mm. under the above conditions, and they constitute the entire distillate after the solvent has been removed. The specific rotation, $[\alpha]_D$, lies between +9° and +12°, depending upon the proportion of isomers in the distillate; for the pure α form it is 151°/25°. The refractive index is 1.4445_D^{20} for the α,β mixture and 1.4460_D^{20} for the pure α isomer.

4. The correct value for any temperature between 5° and 37° may be calculated from the equation $[\alpha]_D^T = 85 - 0.1846t$. The melting point of the compound varies according to the proportion of α and β isomers present. After prolonged digestion with petroleum ether, the α isomer predominates and the melting point rises. A sample of the product recrystallized once melted at 90–93°, and after five recrystallizations it melted at 98°, without change in the optical rotation.

3. Discussion

Tetramethyl-*d*-glucose has been prepared by the action of methyl iodide and silver oxide on methylglucoside,[1] by the action of methyl sulfate and alkali on both methylglucoside and glucose,[2] and also by hydrolysis of various methylated polysaccharides, for example methyl decamethyl maltotrioside.[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 798

References and Notes

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Appendix

Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

α-Methylglucoside

tetramethyl-α-methylglucoside

methyl decamethyl maltotrioside

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ether (60-29-7)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

silver oxide (20667-12-3)

sodium sulfate (7757-82-6)

carbon tetrachloride (56-23-5)

Norite, Norit (7782-42-5)

ammonium hydroxide (1336-21-6)

Methyl iodide (74-88-4)

methyl sulfate (75-93-4)

glucose (492-62-6)

D-Glucose, 2,3,4,6-tetramethyl-, 2,3,4,6-Tetramethyl-D-glucose (7506-68-5)

Tetramethylglucose, tetramethyl-d-glucose

methylglucoside

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Organic Syntheses, CV 3, 803

TETRANITROMETHANE

[Methane, tetranitro-]

$$4\ (CH_3CO)_2O + 4\ HNO_3 \longrightarrow C(NO_2)_4 + 7\ CH_3CO_2H + CO_2$$

Submitted by Poe Liang
Checked by Nathan L. Drake and Ralph Mozingo.

1. Procedure

Caution! The product is toxic. The reaction should be carried out in a hood.

In a 250-ml. Erlenmeyer flask provided with a two-holed stopper which has a slit cut in one edge to serve as an air vent and which holds a thermometer, the bulb of which reaches almost to the bottom of the flask, is placed 31.5 g. (0.5 mole) of anhydrous nitric acid (Note 1). The flask is cooled below 10° in ice water, and 51 g. (0.5 mole) of acetic anhydride (Note 2) is slowly added from a buret through the second hole in the stopper in portions of about 0.5 ml. at a time. The temperature of the reaction mixture is never allowed to rise above 10° (Note 3). After about 5 ml. of the acetic anhydride has been added the reaction becomes less violent, and larger portions, increasing gradually from 1 to 5 ml., may be introduced at a time with constant shaking. After all the acetic anhydride has been added, the stopper and the thermometer are removed. The neck of the flask is wiped clean with a towel, and the flask is then covered with an inverted beaker and allowed to come up to room temperature in the original ice bath (Note 4).

The mixture is allowed to stand at room temperature for 7 days (Note 5), and the tetranitromethane is separated by pouring the mixture into 300 ml. of water in a 500-ml. round-bottomed flask and steam distilling (Note 6). The tetranitromethane passes over with the first 20 ml. of the distillate. The heavy product is separated from the upper layer of water, washed first with dilute alkali, finally with water, and dried over anhydrous sodium sulfate. The yield of tetranitromethane is 14–16 g. (57–65%). *The product should not be distilled, as it may decompose with explosive violence.* Tetranitromethane must be kept out of contact with aromatic compounds except in *very small* test portions, since violently explosive reactions can occur (Note 7).

2. Notes

1. The anhydrous nitric acid (sp. gr. > 1.53) is most easily obtained by slowly distilling ordinary fuming nitric acid from its own bulk of concentrated sulfuric acid. If ordinary concentrated nitric acid (sp. gr. 1.42) is used, it is advisable to distil twice from equal volumes of sulfuric acid. A technical grade of fuming nitric acid having a specific gravity of 1.60 was found to give satisfactory yields when used without further treatment; but an equivalent amount of a weaker

commercial acid, corresponding to 98% nitric acid by gravity, gave considerably lower yields. The use of more than the calculated amount of nitric acid decreases the yield of tetranitromethane.

2. According to the submitter, the purity of acetic anhydride is not so important as that of the nitric acid. Equivalent amounts of 99–100% and 94–95% acetic anhydride gave practically the same yield of tetranitromethane.

3. If the flask is not cooled, the reaction proceeds more and more vigorously as the temperature rises and may, if unchecked, become violent.

4. If the flask is removed from the ice bath after the addition of the anhydride, and allowed to stand at room temperature, the reaction may become violent with great loss of product.

5. The yield is only 35% after 2 days and no greater than 65% after 10–15 days. If it should be necessary to obtain the product in shorter time, the reaction mixture may be allowed to stand at room temperature for 48 hours and then slowly heated to 70° during an interval of 3 hours and maintained at 70° for 1 hour longer before pouring into water. The yield of a run carried out in this way was, according to the submitter, 40%.

6. It is most convenient to use a 50-ml. graduated separatory funnel as the receiver during the steam distillation, if it is desired to estimate roughly the yield of tetranitromethane, the density of which is 1.65 at 15°.

7. Tetranitromethane is a valuable reagent for detecting the presence of double bonds, especially those which do not give the ordinary reactions of such linkages.[1]

3. Discussion

The procedure described is essentially that of Chattaway.[2] Tetranitromethane has also been prepared by nitrating nitroform,[3] from acetic anhydride by the action of diacetylorthonitric acid,[4] from iodopicrin and silver nitrite,[5] from acetyl nitrate by heating with acetic anhydride or glacial acetic acid,[6] from nitrobenzene by distilling with a mixture of nitric acid and fuming sulfuric acid,[7] by adding acetic anhydride to nitrogen pentoxide or a mixture of nitrogen pentoxide and nitrogen peroxide,[8] by the action of acetic anhydride on highly concentrated nitric acid,[9] from toluene by nitration,[10] from acetylene by the action of nitric acid,[11] from nitrobenzene and a mixture of nitric and fuming nitric acids,[12] and from acetylene and ethylene by the action of nitric acid in the presence of a catalyst.[13]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

diacetylorthonitric acid

iodopicrin

sulfuric acid (7664-93-9)

acetylene (74-86-2)

acetic acid (64-19-7)

acetic anhydride (108-24-7)

nitric acid (7697-37-2)

sodium sulfate (7757-82-6)

toluene (108-88-3)

Nitrobenzene (98-95-3)

ethylene (9002-88-4)

silver nitrite (7783-99-5)

tetranitromethane, Methane, tetranitro- (509-14-8)

nitrogen peroxide

nitrogen pentoxide

nitroform

acetyl nitrate (591-09-3)

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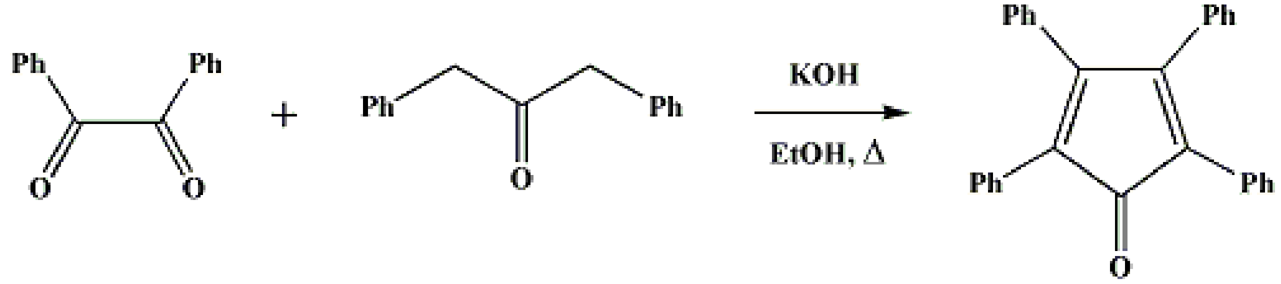
Organic Syntheses, CV 3, 806

TETRAPHENYLCYCLOPENTADIENONE

[Cyclopentadienone, tetraphenyl-]



Submitted by John R. Johnson and Oliver Grummitt.
Checked by Nathan L. Drake and Stuart Haywood.

1. Procedure

In a 500-ml. round-bottomed flask, 21 g. (0.1 mole) of benzil and 21 g. (0.1 mole) of dibenzyl ketone (Note 1) are dissolved in 150 ml. of hot ethanol. The flask is fitted with a reflux condenser, the temperature of the solution is raised nearly to the boiling point, and a solution of 3 g. of potassium hydroxide in 15 ml. of ethanol is added slowly in two portions through the condenser. When the frothing has subsided the mixture is refluxed for 15 minutes and then cooled to 0°. The dark crystalline product is filtered with suction and washed with three 10-ml. portions of 95% ethanol. The product melts at 218–220° and weighs 35–37 g. (91–96%) (Note 2).

2. Notes

1. The dibenzyl ketone should melt at 34–35°.
2. This product is sufficiently pure for most purposes. It may be crystallized from a mixture of ethanol and benzene, using 155–160 ml. solvent for 5 g. of tetraphenylcyclopentadienone; the melting point of the recrystallized material is 219–220°.

3. Discussion

Tetraphenylcyclopentadienone has been prepared by the action of phenylmagnesium bromide on benzaldiphenylmaleide,[1] and by reduction, dehydration, and oxidation of the methylenedesoxybenzoin obtained by condensing formaldehyde with desoxybenzoin.[2] The present procedure is essentially that of Dilthey.[3].

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 807
- Org. Syn. Coll. Vol. 5, 604

- Org. Syn. Coll. Vol. 5, 1037

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Desoxybenzoin

benzaldiphenylmaleide

methylenedesoxybenzoin

ethanol (64-17-5)

Benzene (71-43-2)

formaldehyde (630-08-0)

Benzil (134-81-6)

potassium hydroxide (1310-58-3)

Phenylmagnesium bromide (100-58-3)

dibenzyl ketone (102-04-5)

Tetraphenylcyclopentadienone, Cyclopentadienone, tetraphenyl- (479-33-4)

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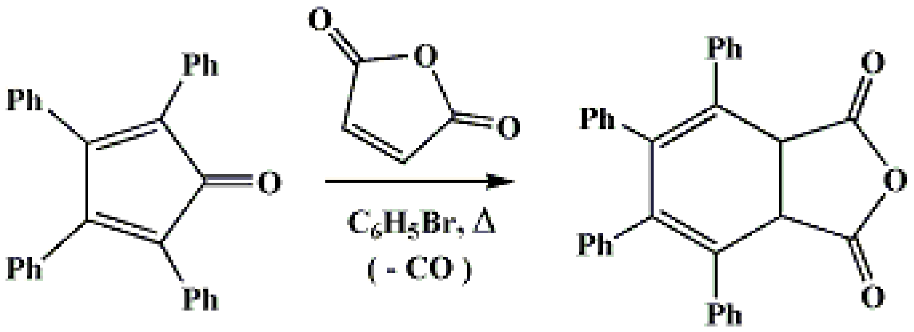
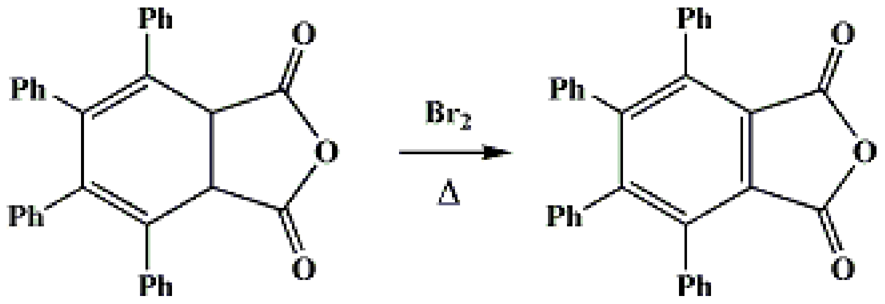
Organic Syntheses, CV 3, 807

TETRAPHENYLPHTHALIC ANHYDRIDE

[Phthalic anhydride, tetraphenyl-]





Submitted by Oliver Grummitt
Checked by Nathan L. Drake and Charles M. Eaker.

1. Procedure

An intimate mixture of 35 g. (0.094 mole) of tetraphenylcyclopentadienone (p. 806) and 9.3 g. (0.095 mole) of maleic anhydride is placed in a 200-ml. round-bottomed flask (Note 1), and to it is added 25 ml. of bromobenzene. After the mixture has been refluxed gently for 3.5 hours (Note 2), it is cooled (Note 3), a solution of 7 ml. of bromine in 10 ml. of bromobenzene is added through the condenser, and the flask is shaken until the reagents are thoroughly mixed. After the first exothermic reaction has subsided, the mixture is refluxed gently for 3 hours (Note 4). The flask is then immersed in a cooling bath and the temperature of the mixture is held at 0–10° for 2–3 hours. The mixture is filtered with suction, and the crystalline product is washed three times with 10-ml. portions of petroleum ether (b.p. 60–68°). After the product has been dried in the air, it weighs 37–38 g. (87–89%) and melts at 289–290°. It is light brown, but when pulverized it is almost colorless. The filtrate, when diluted with an equal volume of petroleum ether and cooled to 0–10°, yields an additional 2–3 g. of a less pure product which melts at 285–288°. The impure material may be purified by recrystallization from benzene, using 8–9 ml. of benzene per gram of solid (Note 5).

2. Notes

1. Ground-glass equipment is preferred; corks are attacked by the bromine used later.
2. The operation should be carried out in a hood because of the carbon monoxide evolved.
3. The tetraphenyldihydrophthalic anhydride may be isolated at this point in practically quantitative yields by cooling the mixture, filtering with suction, and washing the solid with three 10-ml. portions of petroleum ether (b.p. 60–68°). The yield is 41–42 g.; the product melts at 235–240°.
4. This operation should also be performed in a hood, or the top of the condenser should be connected to a suitable trap.
5. The crystallized product must be dried at 110° for 1–1.5 hours; otherwise benzene, possibly benzene of crystallization, will be retained by the solid indefinitely.

3. Discussion

Tetraphenylphthalic anhydride has been prepared by condensation of tetraphenylcyclopentadienone and maleic anhydride in nitrobenzene,[1] followed by dehydrogenation of the tetraphenyldihydrophthalic anhydride with sulfur.[2,3]

Tetraphenylphthalic anhydride has also been prepared by condensation of tetraphenylcyclopentadienone with chloromaleic anhydride;[4] and by oxidation of tetraphenylhydrindene with chromic acid[5] or oxidation of 7-carboxy-4,5,6,7-tetraphenyl-3*a*,4,7,7*a*-tetrahydroindene with potassium permanganate.[6]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

Benzene (71-43-2)

carbon monoxide (630-08-0)

potassium permanganate (7722-64-7)

bromine (7726-95-6)

sulfur (7704-34-9)

chromic acid (7738-94-5)

Nitrobenzene (98-95-3)

bromobenzene (108-86-1)

maleic anhydride (108-31-6)

Tetraphenylcyclopentadienone (479-33-4)

Tetraphenylphthalic anhydride, Phthalic anhydride, tetraphenyl- (4741-53-1)

tetraphenyldihydrophthalic anhydride

chloromaleic anhydride

tetraphenylhydrindene

7-carboxy-4,5,6,7-tetraphenyl-3a,4,7,7a-tetrahydroindene

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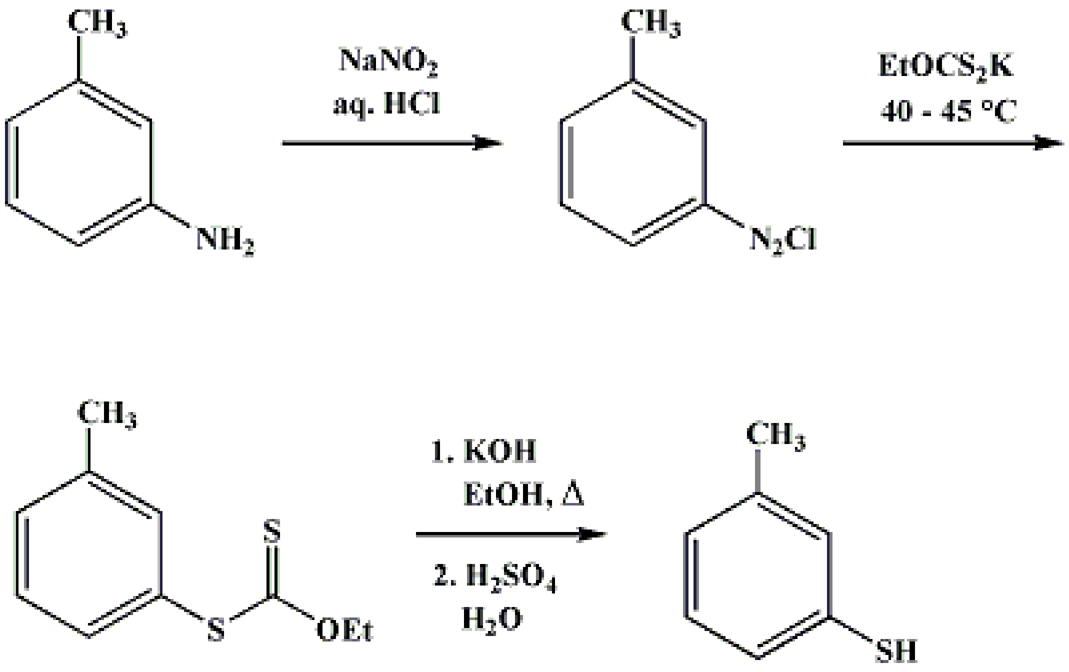
Organic Syntheses, *CV 3*, *809*

m-THIOCRESOL

[*m*-Toluenethiol; *m*-tolyl mercaptan]



Submitted by D. S. Tarbell and D. K. Fukushima.
Checked by C. F. H. Allen and John R. Byers, Jr..

1. Procedure

All the steps in this preparation, including sealing the product in bottles or ampoules, should be carried out under a good hood. Care should be exercised to avoid contact with m-thiocresol or its solutions since it is a skin irritant.

In a 1-l. flask, equipped with a mechanical stirrer and thermometer for reading low temperatures, and immersed in an ice bath, are placed 150 ml. of concentrated hydrochloric acid (sp. gr. 1.18) and 150 g. of crushed ice. The stirrer is started, and 80 g. (0.75 mole) of *m*-toluidine (b.p. 92–93°/15 mm.) is slowly added. The mixture is cooled to 0°, and a cold solution of 55 g. (0.8 mole) of sodium nitrite in 125 ml. of water is slowly added, the temperature being kept below 4°.

In a 2-l. flask equipped with a thermometer, dropping funnel, and stirrer is placed a solution of 140 g. of potassium ethyl xanthate (Note 1) in 180 ml. of water. This mixture is warmed to 40–45° and kept in that range during the slow addition of the cold diazonium solution (Note 2); about 2 hours is required (Note 3). After an additional 30 minutes at this temperature to ensure complete decomposition of the intermediate compound, the red, oily *m*-tolyl ethyl xanthate is separated and the aqueous layer is extracted twice, using 100-ml. portions of ether. The combined oil

and extracts are washed once with 100 ml. of 10% sodium hydroxide solution (Note 4) and then with several portions of water until the washings are neutral to litmus. The ether solution is dried over 25 g. of anhydrous calcium chloride, and the ether is removed by distillation. The crude residual *m*-tolyl ethyl xanthate is dissolved in 500 ml. of 95% ethanol, the solution brought to boiling, and the source of heat removed. To this hot solution is added slowly 175 g. of potassium hydroxide pellets so that the solution keeps boiling, and the mixture is refluxed until a sample is completely soluble in water (about 8 hours). Approximately 400 ml. of ethanol is then removed by distillation on a steam bath, and the residue is taken up in the minimum of water (about 500 ml.). The aqueous solution is extracted with three 100-ml. portions of ether, the extract being discarded. The aqueous solution is now made strongly acid to Congo red paper, using 6 *N* sulfuric acid (Note 5) (625–650 ml.). The acidified solution is placed in a 3-l. flask, 2 g. of zinc dust is added, and the *m*-thiocresol is distilled with steam. The lower layer of the *m*-thiocresol is separated; the aqueous layer is extracted with three 100-ml. portions of ether, the extracts being added to the oil. After drying with 50 g. of Drierite, the ether is removed by distillation, and the oily residue is distilled under reduced pressure. The yield of colorless *m*-thiocresol, b.p. 90–93°/25 mm., is 59–69 g. (63–75%) (Note 6) and (Note 7). It is best preserved in sealed glass bottles because of its disagreeable odor.

2. Notes

1. Eastman Kodak Company technical potassium ethyl xanthate was used.
2. The diazonium solution is left in the ice bath, and only 10- to 15-ml. portions are placed in the dropping funnel at one time.
3. Many diazonium solutions have been reported to react explosively with solutions of metallic polysulfides even at low temperatures.[1,2] A violent reaction with xanthates is mentioned only in one report.[3] Neither the authors nor the checkers observed any unusual reactivity during this preparation or with the procedure given for dithiosalicylic acid.[4] On a large scale (100 moles of *m*-toluidine) flashes of light have been occasionally observed (private communication, L. J. Roll).
4. This wash serves to remove any *m*-cresol present.
5. This acidification liberates carbon oxysulfide, which has a very disagreeable odor.
6. The refractive index is n_D^{25} 1.568–1.571.
7. Other boiling points are 195°/760 mm.; 120°/100 mm.; 107°/50 mm.

3. Discussion

The only practical laboratory procedure for preparing *m*-thiocresol is by the alkaline hydrolysis of *m*-tolyl ethyl xanthate, obtained from *m*-toluenediazonium chloride and potassium ethyl xanthate.[3,5] The procedure described is essentially that of Bourgeois.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 1050

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

carbon oxysulfide

Drierite

ethanol (64-17-5)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium nitrite (7632-00-0)

potassium hydroxide (1310-58-3)

zinc (7440-66-6)

potassium ethyl xanthate (140-89-6)

m-Thiocresol, m-Toluenethiol, m-tolyl mercaptan (108-40-7)

m-toluidine (108-44-1)

m-tolyl ethyl xanthate

m-cresol (108-39-4)

m-toluenediazonium chloride

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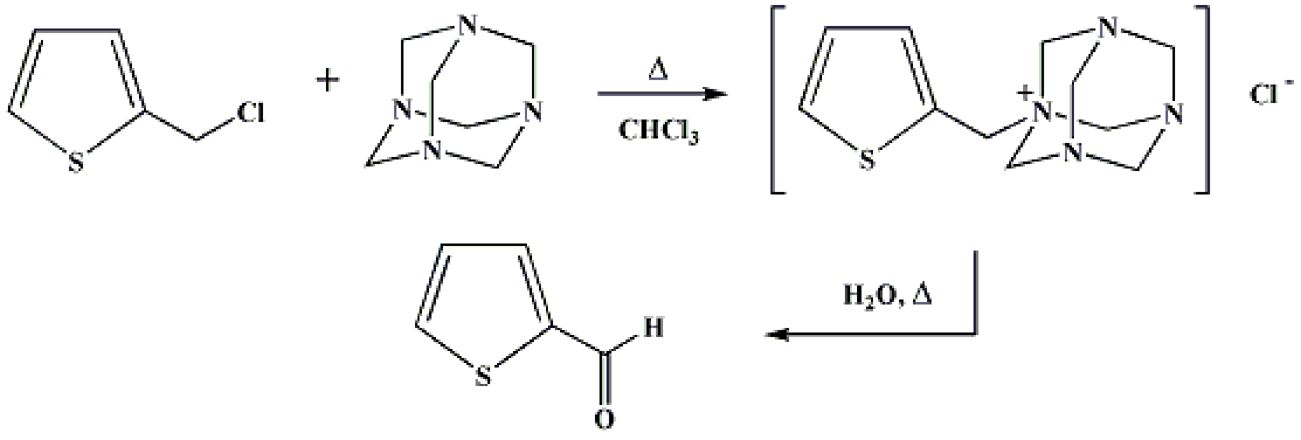
Organic Syntheses, CV 3, 811

2-THIOPHENEALDEHYDE



Submitted by Kenneth B. Wiberg
Checked by Cliff S. Hamilton and J. L. Pauley.

1. Procedure

A. *2-Thienylmethylhexamethylenetetrammonium chloride.* In a 1-l. round-bottomed flask are placed 67 g. (0.5 mole) of 2-chloromethylthiophene (p. 197), 400 ml. of chloroform, and 70 g. (0.5 mole) of hexamethylenetetramine. The flask is fitted with a reflux condenser, and the mixture is boiled gently for 30 minutes. The mixture is cooled, and filtered on a Büchner funnel. The precipitate is washed with 100 ml. of cold chloroform, drained thoroughly, and air-dried. The yield is 128–136 g. (94–99%) of a white powder.

B. *2-Thiophenealdehyde.* The hexamethylenetetrammonium salt is placed in a 2-l. round-bottomed flask containing 400 ml. of warm water. The flask is fitted for steam distillation, and steam is passed in until all the aldehyde has distilled (Note 1). The distillate is cooled, 10 ml. of 6 *N* acetic acid is added (Note 2), and the aldehyde is extracted with two 100-ml. portions of ether. The ether solution is dried over anhydrous calcium chloride, and the ether is evaporated on a steam bath until the volume of the solution has decreased to about 50 ml. The solution is placed in a 100-ml. Claisen flask, the ether is removed by distillation, and the aldehyde distilling at 89–91°/21 mm., n_D^{25} 1.5880, is collected. The yield is 27–30 g. (48–53%) of a colorless oily liquid which darkens slowly on standing (Note 3) and (Note 4).

2. Notes

1. About 1.5 l. of distillate is collected before all the thiophenealdehyde is distilled over.
2. The acetic acid is added to remove traces of amines that come over in the steam distillation. This method of purification must be used because of the high solubility of the bisulfite addition compound of the aldehyde.
3. If the aldehyde is to be stored for any period of time, the addition of a small amount of hydroquinone is advisable.
4. It has been reported (S. J. Angyal and D. F. Penman) that the procedure for 1-naphthaldehyde [*Org. Syntheses*, **30**, 67 (1950)] may also be followed with slight modification for the preparation of 2-thio-phenealdehyde. A mixture of 41.5 g. (0.31 mole) of 2-chloromethylthiophene, 88 g. (0.60 mole) of hexamethylenetetramine, 130 ml. of glacial acetic acid, and 130 ml. of water is swirled until, with considerable evolution of heat, the mixture has become homogeneous. The mixture is heated under reflux for 4 hours; at the end of this period, 125 ml. of concentrated

hydrochloric acid is added, and heating under reflux is continued for 5 minutes. After cooling, the mixture is extracted with three 100-ml. portions of ether. The combined ether extracts are dried (with anhydrous sodium or magnesium sulfate), and the ether is removed. The crude product is distilled through a short column under reduced pressure; after a fore-run of acetic acid the product is collected at 63–66°/6 mm. or 115–118°/65 mm. The yield is 25–26 g. (71–74%).

3. Discussion

2-Thiophenealdehyde has been prepared by the decarboxylation of 2-thienylglyoxalic acid,[1] by the action of 2-thienylmagnesium iodide on ethyl orthoformate followed by hydrolysis of the acetal,[2] in small yields by the Rosenmund reduction of 2-thiophenecarboxylic acid chloride,[3] in small yields by the action of hydrogen cyanide, hydrogen chloride, and aluminum chloride on thiophene, using benzene as a solvent,[4] by a series of reactions from 1-chloro-2,3-diketocyclopentane,[5] by the hydrolysis of 2-thenylmethylhexamethylenetetrammonium chloride in neutral solution,[6] by the action of N-methylformanilide on thiophene in the presence of phosphorus oxychloride,[7] by the acid hydrolysis of N-(2-thenyl)-2'-thenaldimine,[8] and by the oxidation of N,N-di-(2-thenyl)hydroxylamine with alkaline potassium permanganate.[9]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 915
- Org. Syn. Coll. Vol. 5, 121

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

2-thio-phenealdehyde

N-(2-thenyl)-2'-thenaldimine

ACETAL (105-57-7)

calcium chloride (10043-52-4)

hydrogen chloride, hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

ether (60-29-7)

chloroform (67-66-3)

hydroquinone (123-31-9)

potassium permanganate (7722-64-7)

hydrogen cyanide (74-90-8)

Phosphorus Oxychloride (21295-50-1)

aluminum chloride (3495-54-3)

sodium (13966-32-0)

Ethyl orthoformate

hexamethylenetetramine (100-97-0)

Thiophene (110-02-1)

magnesium sulfate (7487-88-9)

2-thienylmagnesium iodide

N-methylformanilide (93-61-8)

2-Chloromethylthiophene (765-50-4)

hexamethylenetetrammonium

2-Thiophenealdehyde, thiophenealdehyde (98-03-3)

2-thienylglyoxalic acid (4075-59-6)

2-thiophenecarboxylic acid chloride (5271-67-0)

1-chloro-2,3-diketocyclopentane

2-thenylmethylhexamethylenetetrammonium chloride

N,N-di-(2-thenyl)hydroxylamine

1-Naphthaldehyde (66-77-3)

2-Thienylmethylhexamethylenetetrammonium chloride

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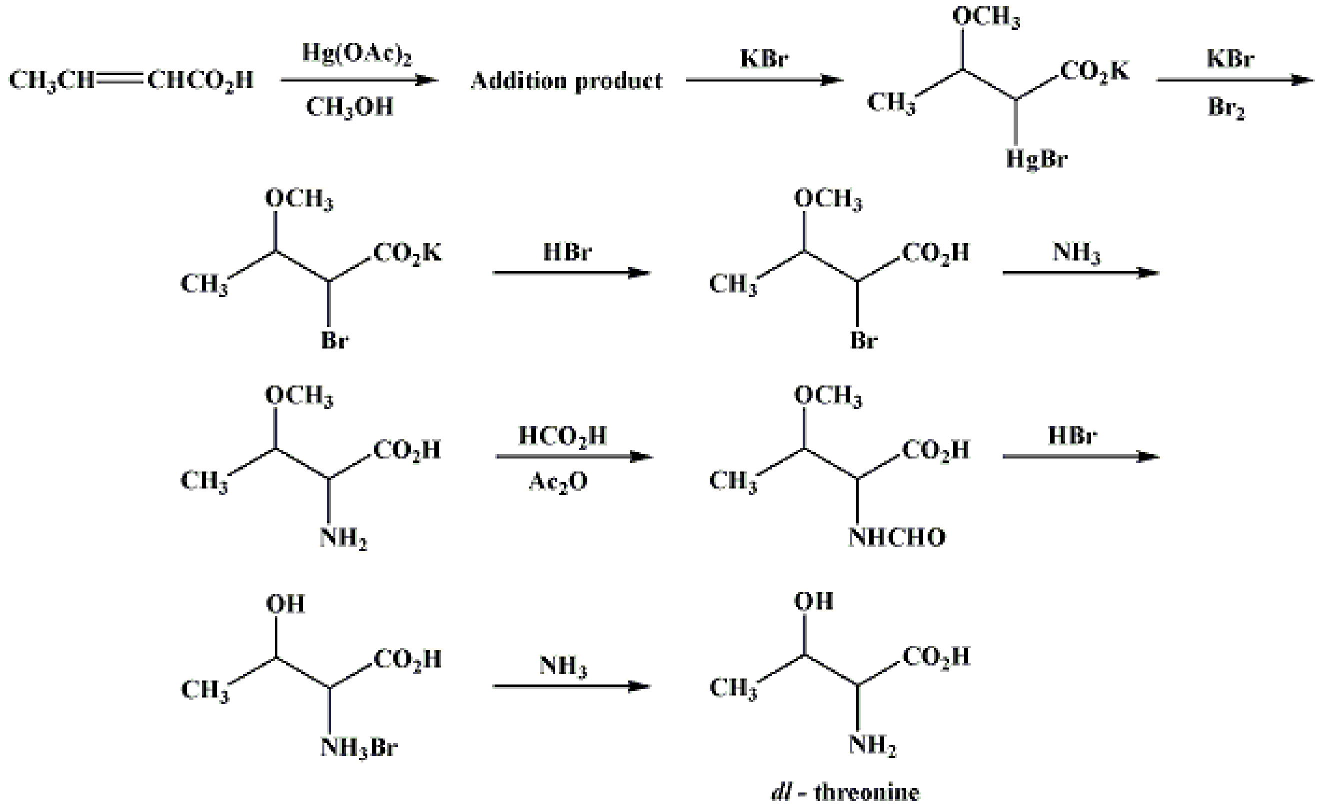
Organic Syntheses, CV 3, 813

dl-THREONINE



Submitted by Herbert E. Carter and Harold D. West.
Checked by Nathan L. Drake and William A. Stanton.

1. Procedure

A. *α-Bromo-β-methoxy-n-butyric acid.* In a 5-l. flask are placed 3 l. of methanol, 640 g. (2 moles) of mercuric acetate (Note 1), and 172 g. (2 moles) of crotonic acid (Note 2). The flask is warmed on a steam cone and shaken vigorously until the mercuric acetate dissolves (about 10 minutes). The solution is allowed to stand at room temperature for 48 hours (Note 3), then the precipitate is filtered, washed twice with 300-ml. portions of methanol, and air-dried. The yield is 625–650 g. (Note 4). This material is powdered and dissolved in a solution of 360 g. (3 moles) of potassium bromide in 2 l. of water, and the solution is placed in a 4-l. beaker, which is cooled in an ice bath and exposed to direct sunlight (Note 5). A solution of 320 g. (2 moles) of bromine and 360 g. (3 moles) of potassium bromide in 600 ml. of water is added with stirring during 20–40 minutes, a large excess of bromine being avoided. After 10–15 minutes' standing, any excess bromine is destroyed with sodium bisulfite. The bromo acids are isolated as follows: The solution is extracted once with 300 ml. of ether to remove a small amount of lachrymatory material and, after acidification with 400 ml. of 40% hydrobromic acid, is extracted again with six 800-ml. portions of ether. The ether extracts are combined, washed once with a small volume of cold water, and dried over anhydrous sodium sulfate. The ether is removed by distillation, leaving the crude bromo acid mixture.

The yield of crude bromo acids is 350–370 g. (88–93% based on the crotonic acid used in the first step). This material is used without purification in the preparation of aminomethoxybutyric acid.

The crude bromo acids may be freed from impurities by fractionation under reduced pressure. The fraction distilling below 125°/10 mm. (105°/3 mm.) is discarded; the remainder distils at 125–128°/10 mm. (105–107°/3 mm.) and consists of a mixture of stereoisomeric acids. The yield is 75–85% based on the crotonic acid used in the first step.

B. *dl-Threonine.* One hundred and seventy-five grams of crude bromomethoxybutyric acid is heated with 2 l. of concentrated ammonium hydroxide for 6 hours at 90–100° in a glass-lined autoclave (p. 777) (Note 6), The

solution is concentrated to a thick gum under reduced pressure (Note 7), water is added, and the solution is reconcentrated under reduced pressure. The residue is allowed to stand under acetone with frequent shaking (Note 8) until the material has crystallized completely (1–2 days). The acetone is decanted, and the residue dissolved in 1 l. of 85–90% formic acid (Note 9). The solution is warmed to 45°, and 350 g. (330 ml.) of acetic anhydride is added with stirring during 10 minutes. The heat of reaction causes the temperature of the solution to rise to 70–80°, and the temperature of the mixture is maintained within this range for about 15 minutes. The solution is next evaporated to dryness under reduced pressure. The residue is dissolved, while being warmed on the steam bath, in the minimum amount of water (Note 10), and the solution is cooled overnight in the icebox. The crystals are filtered and air-dried. This material is a mixture of formyl derivatives (Note 11). One recrystallization from 150 ml. of hot water yields about 25 g. of practically pure formyl-*dl*-O-methylthreonine melting at 174–176°. An additional 3–5 g. is obtained by working up the filtrates. The yield is 25% (Note 12).

Twenty-five grams (0.16 mole) of formyl-*dl*-O-methylthreonine is refluxed for 2 hours with 360 ml. of constant-boiling hydrobromic acid. The solution is concentrated under reduced pressure (Note 13). Sufficient water is added to dissolve all the residue, and the solution is reconcentrated under reduced pressure. The gummy residue is next dissolved in 450 ml. of absolute ethanol, and concentrated ammonium hydroxide is added until the odor of ammonia persists after vigorous shaking. The solution is cooled in the icebox overnight, and the crystals are filtered and dissolved in 3 volumes of hot water (about 5 ml. of water per gram of crude material). Seven volumes of absolute ethanol are added, and the solution is cooled to room temperature with scratching of the flask to induce crystallization. It is then cooled in an icebox overnight. The crystals are filtered and washed twice with 90-ml. portions of absolute ethanol and once with ether. The yield is 18–20 g. (85–90% based on the formyl-*dl*-O-methylthreonine) of pure *dl*-threonine, melting with decomposition at 234–235° (Note 14).

2. Notes

1. The mercuric acetate may be replaced by equivalent amounts of mercuric oxide and glacial acetic acid.
2. The crotonic acid was obtained from the Niacet Chemical Company and used without purification.
3. It is advisable to scratch the flask with a glass rod after 3–4 hours. This usually initiates precipitation of the addition product in a finely divided form. If this is not done, the addition product may crystallize slowly on the sides of the flask in a cake which is removed only with the greatest difficulty. It is also advantageous to stir the mixture mechanically for several hours after crystallization begins in order to prevent caking.
4. The exact yield cannot be calculated, since the structure of the addition product is unknown. The yield is almost quantitative, however, since only a small amount of mercury remains in the filtrate.
5. The bromination can be carried out equally successfully under the illumination of two No. 2 Photoflood lamps in suitable reflectors placed directly above the surface of the liquid. Under these conditions, however, the addition of the bromine requires 10–15 minutes longer.
6. According to the submitters the amination can be carried out in ordinary 500-ml. glass bottles if the temperature does not exceed 85°. The time of heating should then be extended to 8–10 hours.
7. All the concentrations under reduced pressure required in this preparation may be carried out at the pressure provided by an efficient water pump.
8. The material, if allowed to stand without shaking, solidifies to a hard cake. The shaking furthers extraction of certain gummy impurities which interfere with the separation to be carried out later.
9. If a mixture of *dl*-threonine and *dl*-allothreonine is desired instead of *dl*-threonine alone, the residue may be dissolved directly in 1.2 l. of 48% hydrobromic acid and refluxed for 2 hours. After removal of the hydrobromic acid under reduced pressure, the gummy residue is dissolved in warm water, and concentrated ammonium hydroxide is added slowly until a faint odor of ammonia persists after vigorous shaking. The solution is concentrated until crystals appear, and 3–4 volumes of ethanol is added. The acids are recrystallized by dissolving in the minimum amount of hot water (4–5 ml. per gram) and adding 4–5 volumes of ethanol. The solution is allowed to cool and permitted to stand overnight at room temperature.
10. If, after solution is complete on the steam bath, 10% more water is added, the quality of the product is better, but the yield is slightly less.
11. Formyl-*dl*-O-methylthreonine melts at 173–174°. Formyl-*dl*-O-methylallothreonine melts at 152–153°.
12. Crude *dl*-allothreonine may be obtained from the mother liquors by concentrating them to dryness, refluxing the residue with 10 volumes of 48% hydrobromic acid, and working up the solution as described for *dl*-threonine. The product contains a small amount of *dl*-threonine which can be largely removed by three or four recrystallizations from 50% ethanol. *dl*-Allothreonine of this purity melts at 242–243°.
13. Constant-boiling hydrobromic acid can be recovered by fractionating the distillate at atmospheric

pressure.
14. The melting points obtained by the checkers were consistently 3–4° above those given. The melting points of these compounds vary with the method of determination.

3. Discussion

α-Amino-β-hydroxybutyric acid has been prepared by a procedure similar to the one described, using ethyl crotonate as the starting material.[1] A mixture of the α-amino-β-hydroxy- and α-hydroxy-β-aminobutyric acids has been secured by treating crotonic acid with hypochlorous acid and heating the resulting product with dry ammonia under pressure.[2] A mixture containing threonine has been obtained by treatment of acetoacetic ester with sodium nitrite and acetic acid; the resultant ethyl oximinoacetoacetate was then converted by means of diethyl sulfate into ethyl O-ethyloximinoacetoacetate. This product was reduced by hydrogen and Raney nickel to an impure ethyl α-amino-β-hydroxybutyrate, which was then hydrolyzed to a mixture of *dl*-threonine and *dl*-allothreonine.[3] The method described has been published.[4]

Improvements in this method have been reported,[5] and an excellent synthesis from ethyl acetamidoacetoacetate has been described.[6]

Interconversion methods for obtaining *dl*-threonine from *dl*-allothreonine via the azlactone[7] or the oxazoline[6] have been reported.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

acetoacetic ester

α-amino-β-hydroxy- and α-hydroxy-β-aminobutyric acids

ethanol (64-17-5)

acetic acid (64-19-7)

ammonia (7664-41-7)

methanol (67-56-1)

ether (60-29-7)

acetic anhydride (108-24-7)

hydrogen (1333-74-0)

HYDROBROMIC ACID (10035-10-6)

bromine (7726-95-6)

sodium sulfate (7757-82-6)

formic acid (64-18-6)

sodium nitrite (7632-00-0)

sodium bisulfite (7631-90-5)

mercuric acetate (1600-27-7)

mercury (7439-97-6)

mercuric oxide (21908-53-2)

Raney nickel (7440-02-0)

acetone (67-64-1)

potassium bromide (7758-02-3)

hypochlorous acid (7790-92-3)

ammonium hydroxide (1336-21-6)

diethyl sulfate (64-67-5)

crotonic acid (3724-65-0)

ethyl crotonate (623-70-1)

aminomethoxybutyric acid

bromomethoxybutyric acid

α-Amino-β-hydroxybutyric acid

threonine, DL-Threonine (72-19-5)

ethyl oximinoacetoacetate

ethyl O-ethyloximinoacetoacetate

ethyl α-amino-β-hydroxybutyrate

ethyl acetamidoacetoacetate

oxazoline

formyl-dl-O-methylthreonine

dl-allothreonine (28954-12-3)

Formyl-dl-O-methylallothreonine

α-Bromo-β-methoxy-n-butyric acid (26839-91-8)

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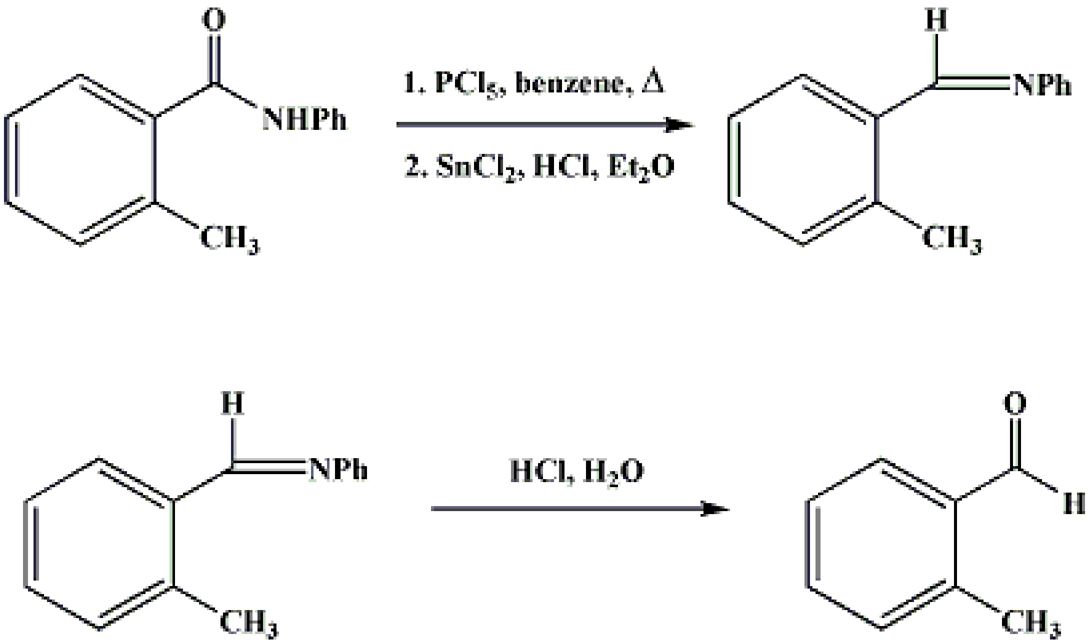
o-TOLUALDEHYDE



Submitted by Jonathan W. Williams, Charles H. Witten, and John A. Krynitsky.
Checked by W. E. Bachmann and N. C. Deno.

1. Procedure

Thirty grams (0.14 mole) of *o*-toluanilide (Note 1) and 20 ml. of dry benzene are placed in a 125-ml. Claisen flask which is fitted with a condenser for distillation under reduced pressure and set in a water bath. The bath is heated to 50°, and 30 g. (0.14 mole) of phosphorus pentachloride is added to the mixture over a period of 10 minutes. The bath is then heated to 75°, and this temperature is maintained for 15 minutes. The benzene and most of the phosphorus oxytrichloride are then removed by distillation at 20 mm. from a bath at 95°. The crude N-phenyl-*o*-toluimidyl chloride which remains as a viscous liquid is sufficiently pure for the next step.

A mixture of 50 g. (0.26 mole) of anhydrous stannous chloride (p. 627) and 225 ml. of dry ether is placed in a 1-l. three-necked round-bottomed flask fitted with a rubber-tube sealed stirrer, an inlet tube reaching nearly to the bottom of the flask, and a reflux condenser (Note 2) protected by a calcium chloride drying tube. The mixture is saturated with dry hydrogen chloride (Note 3) with continuous stirring. Within 3 hours all the stannous chloride dissolves, forming a clear viscous lower layer. The source of hydrogen chloride is then disconnected, and the freshly prepared imidyl chloride is transferred into the mixture with the aid of 25 ml. of dry ether (Note 4). Stirring is continued for 1 hour, and then the reactants are allowed to stand at room temperature for 12 hours.

Ice (about 100 g.) and then 100 ml. of cold water are added, the mixture is stirred for

10 minutes, and then the ether is removed by distillation (Note 5). To the residue in the flask is added sufficient water to make the total volume about 300 ml. Steam distillation is then carried out until the distillate comes over clear. This process requires about 1 hour. The aldehyde is extracted from the steam distillate with three equal portions of the ether recovered above, and the ether solution is dried for several hours over anhydrous sodium sulfate.

The ether is removed by dropping the solution slowly from a separatory funnel into a 50-ml. Claisen flask fitted with a condenser for downward distillation and heated on a steam bath (Note 6), and the residual aldehyde is distilled under reduced pressure. The yield of *o*-tolualdehyde boiling at 90–93°/19 mm. is 10.5–12 g. (62–70%).

2. Notes

1. The *o*-toluanilide was prepared by the reaction of *o*-tolylmagnesium bromide with phenyl isocyanate.[1] If the *o*-toluanilide has been recrystallized from petroleum ether, it may be necessary to melt the light fluffy crystals (to a more compact form) in order to get all the compound into the flask.
2. A reflux condenser is not necessary if the mixture is kept ice-cold during the addition of hydrogen chloride.
3. The checkers used hydrogen chloride from one of the cylinders of hydrogen chloride now available commercially.
4. At this point considerable evolution of heat occurs. A cold-water bath should be kept in readiness for application to the reaction flask.
5. The distillate, which may contain a small amount of *o*-tolualdehyde, is collected and used for the subsequent extraction.
6. In this step the recovered ether is collected in a dry atmosphere, and about 100 ml. of this ether is used in two portions to extract the sodium sulfate residue in order to transfer into the flask any small quantities of the aldehyde that may have been trapped by the drying agent.

3. Discussion

o-Tolualdehyde has been prepared by the oxidation of *o*-xylene,[2 3 4] by the oxidation of *o*-xylyl chloride,[5] by the oxidation of *o*-tolylcarbinol,[6] by the reaction of *o*-tolylmagnesium bromide with ethyl formate,[7] ethyl orthoformate,[8,9] ethoxymethyleneaniline,[9,10] N-methylformanilide,[8] or with carbon disulfide followed by treatment with semicarbazide,[9] and by the aluminum amalgam reduction of N,N'-diphenyl-N-carbethoxy-*o*-toluamidine.[11] The procedure described is based on the method of Sonn and Müller,[12] as studied for *o*-tolualdehyde by King, L'Ecuyer, and Openshaw.[13]

An excellent preparative method from α-bromo-*o*-xylene has been published.[14]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 932

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

phosphorus oxytrichloride

N-phenyl-o-toluimidyl chloride

imidyl chloride

hydrogen chloride (7647-01-0)

Benzene (71-43-2)

ether (60-29-7)

phosphorus pentachloride (10026-13-8)

sodium sulfate (7757-82-6)

stannous chloride

aluminum (7429-90-5)

carbon disulfide (75-15-0)

Ethyl orthoformate

ethyl formate (109-94-4)

semicarbazide (57-56-7)

phenyl isocyanate (103-71-9)

ethoxymethyleneaniline (6780-49-0)

N-methylformanilide (93-61-8)

o-Xylene (95-47-6)

o-Tolualdehyde (529-20-4)

o-toluanilide

o-tolylmagnesium bromide

o-xylyl chloride (608-23-1)

o-tolylcarbinol (89-95-2)

N,N'-diphenyl-N-carbethoxy-o-toluamidine

α-bromo-o-xylene (89-92-9)

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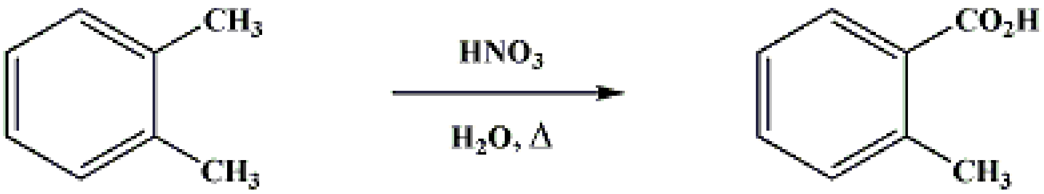
Organic Syntheses, CV 3, 820

o-TOLUIC ACID



Submitted by Harold E. Zaugg and Richard T. Rapala.
Checked by R. L. Shriner and Curtis M.Snow.

1. Procedure

In a 5-l. round-bottomed flask are placed 1.6 l. of water, 800 ml. of concentrated nitric acid (sp. gr. 1.42), and 400 ml. (364 g., 3 moles) of commercial 90% *o*-xylene (Note 1). A reflux condenser (40 cm. or longer) is fitted to the flask with a cork, and a gas-absorption trap is attached to the top of the condenser. The mixture is refluxed by heating in an oil bath kept between 145° and 155° for 55 hours (Note 2). At the end of this time the organic layer has settled to the bottom of the flask. The hot reaction mixture is poured with stirring into 1 kg. of ice in a 4-l. beaker. After cooling, the solid product is filtered, suspended in 2 l. of cold water, and filtered again. The wet product is dissolved by warming in 1 l. of 10% sodium hydroxide solution. After cooling, any unreacted xylene is separated by extraction with 250 ml. of ether. The aqueous layer is then heated on the steam bath with 5–10 g. of Norit and filtered hot with suction through a layer of Norit. The warm, clear red alkaline solution is added with vigorous mechanical stirring to 225 ml. of concentrated hydrochloric acid. The product is filtered from the warm solution, washed with cold water, and sucked as dry as possible on a Büchner funnel (Note 3).

The crude product is dissolved in 350 ml. of 95% ethanol and heated on the steam bath with 5 g. of Darco for 1 hour. The hot solution is filtered by gravity through a heated funnel. The filter paper is heated with an additional 70-ml. portion of 95% ethanol, and the mixture is filtered hot through a fresh paper, into the main solution. To the ethanolic solution, adjusted to a temperature of 55–60°, is added 480 ml. of warm (55–60°) water. After being cooled first to room temperature and then to ice-bath temperature, the crystallized product is filtered, washed with 250 ml. of cold 50% ethanol, and dried (Note 4). The yield of light-tan product melting at 99–101° amounts to 218–225 g. (53–55%) (Note 5) and (Note 6).

2. Notes

1. The *o*-xylene (90–92% purity) may be obtained from the Barrett Division of the Allied Chemical and Dye Corporation, 40 Rector Street, New York 6, New York.
2. It is not necessary that this heating be continuous. Longer times of refluxing

or mechanical stirring do not improve the yield.
3. The crude product after air drying for 24–30 hours weighs between 250 g. and 300 g. and melts at 94–98°.
4. If the humidity is low, the product may be air-dried; otherwise, it is best to dry in a vacuum desiccator overnight at room temperature. *o*-Toluic acid sublimes at higher temperatures.
5. The yield depends on the *o*-xylene content of the starting material. The yields stated are based on 90% *o*-xylene.
6. This product is pure enough for most purposes. Pure white needles of *o*-toluic acid may be obtained by recrystallization from water (2 l. of water for 20 g. of acid), Darco being used for decolorization. The recovery is about 85% of white needles melting at 101–103°.

3. Discussion

References to methods of preparation are given in earlier volumes.[1] *o*-Toluic acid has been prepared by the catalytic oxidation of *o*-xylene.[2]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium hydroxide (1310-73-2)

nitric acid (7697-37-2)

Norit (7782-42-5)

xylene (106-42-3)

o-Toluic acid (118-90-1)

o-Xylene (95-47-6)

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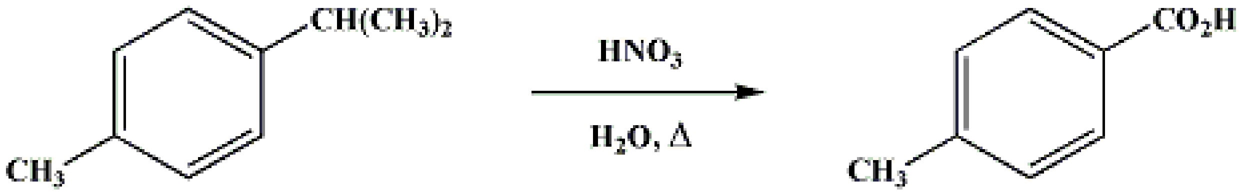
Organic Syntheses, *CV 3, 822*

p-TOLUIC ACID



Submitted by W. F. Tuley and C. S. Marvel.
Checked by H. T. Clarke and D. Blumenthal.

1. Procedure

In a 5-l. round-bottomed flask are mixed 2.7 l. of water and 750 ml. of concentrated nitric acid (sp. gr. 1.42). The flask is fitted with an efficient stirrer (Note 1) and a reflux condenser whose outlet is connected with a trap to remove oxides of nitrogen. One hundred and five grams (125 ml., 0.78 mole) of *p*-cymene (Note 2) is added, the stirrer is started, and the reaction mixture is boiled gently for 8 hours. It is then allowed to cool, and the solid which crystallizes is collected on a hardened filter paper in a Büchner funnel (Note 3). The crude product (Note 4) is washed with 200 ml. of water in small portions and then dissolved in 850 ml. of 1 *N* sodium hydroxide. The alkaline solution is placed in a 2-l. flask with 20 g. of zinc dust (Note 5) and distilled until the distillate runs clear (Note 6). The undissolved zinc is removed by filtration, and the yellowish filtrate is poured in a thin stream with vigorous stirring into 500 ml. of boiling 5 *N* hydrochloric acid. After cooling, the precipitated acid is filtered, washed with cold water until substantially free of chloride, and dried. About 80 g. of a light-brown powder is thus obtained.

The product is extracted for 6 hours with 300 ml. of toluene in the apparatus described in a previous volume[1] (Note 7). The toluene extract is chilled to 0°, and the light-brown crystals of *p*-toluic acid are filtered. This material weighs 56–58 g.; an additional 5 g. is obtained by concentrating the filtrate to 100 ml. The total yield of product melting at 174–177° is 60–63 g. (56–59%). The acid may be purified further with very little loss by dissolving it in 0.5 *N* sodium hydroxide, treating the solution with Norit, precipitating the acid by pouring the alkaline solution into excess hot hydrochloric acid, and recrystallizing the product from toluene (Note 8). The purified *p*-toluic acid melts at 176–177° and weighs about 55 g. (51%).

2. Notes

1. A stirrer of the tubular type, running in a bearing consisting of a glass tube which extends well below the surface of the liquid, is recommended.
2. The fraction of spruce turpentine which boils at 175–178° is satisfactory.
3. The filtrate contains too little dissolved product (about 4 g.) to repay

extraction. It can be employed for a subsequent run by adding sufficient concentrated nitric acid (about 300 ml.) to restore the specific gravity to its initial value, 1.115.

4. The crude product consists of *p*-toluic acid contaminated with small amounts of terephthalic acid, methyl *p*-tolyl ketone, and nitration products.

5. The zinc serves to reduce nitration products that are otherwise difficult to remove. The resulting amines remain in the filtrate after acidification.

6. About 300 ml. of distillate is collected, of which 5 ml. consists of methyl *p*-tolyl ketone.

7. About 4 g. of light-tan terephthalic acid remains on the filter paper.

8. The last traces of color are removed only with considerable difficulty by Norit. An alternative procedure consists in distilling the toluic acid under reduced pressure from a two-bulbed flask with a wide connecting tube and crystallizing the distillate from toluene.

3. Discussion

p-Toluic acid has been prepared by the oxidation of cymene,[2] *p*-xylene,[3,4] or dihydro-*p*-tolualdehyde;[5] by reaction of *p*-chlorotoluene and metallic sodium[6] or *p*-bromotoluene and butyllithium followed by carbonation;[7] by hydrolysis of *p*-tolunitrile;[8] by fusing *p*-tolyl phenyl ketone or di-*p*-tolyl ketone with potassium hydroxide;[9] and by reaction of oxalyl chloride with toluene in the presence of aluminum chloride.[10]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

sodium hydroxide (1310-73-2)

nitric acid (7697-37-2)

nitrogen (7727-37-9)

Norit (7782-42-5)

aluminum chloride (3495-54-3)

potassium hydroxide (1310-58-3)

toluene (108-88-3)

zinc (7440-66-6)

sodium (13966-32-0)

p-Chlorotoluene (106-43-4)

p-xylene (106-42-3)

p-Tolunitrile (104-85-8)

cymene, p-cymene (99-87-6)

butyllithium (109-72-8)

oxalyl chloride (79-37-8)

Terephthalic acid (100-21-0)

toluic acid, p-Toluic acid (99-94-5)

p-Bromotoluene (106-38-7)

methyl p-tolyl ketone (122-00-9)

dihydro-p-tolualdehyde

p-tolyl phenyl ketone (134-84-9)

di-p-tolyl ketone (611-97-2)

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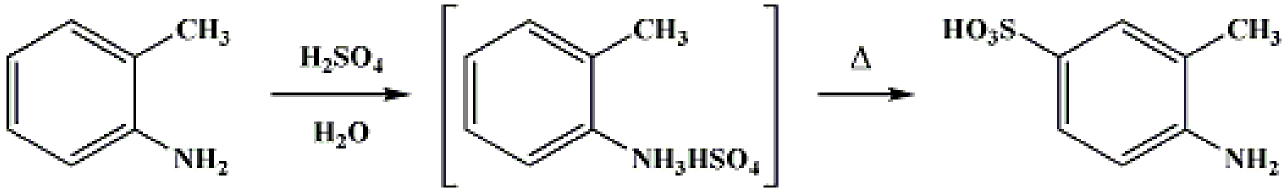
Organic Syntheses, CV 3, 824

o-TOLUIDINESULFONIC ACID

[*m*-Toluenesulfonic acid, 6-amino-]



Submitted by C. F. H. Allen and J. A. VanAllan.
Checked by R. L. Shriner and Charles R. Russell.

1. Procedure

In a 500-ml. three-necked round-bottomed flask, fitted with a stirrer, thermometer, and 250-ml. dropping funnel, are placed 19 ml. of water and 27.8 ml. (0.5 mole) of concentrated sulfuric acid (sp. gr. 1.84), and the whole is warmed to 70°. From the dropping funnel is added, dropwise, over a 30-minute period, 53.5 g. (0.5 mole) of *o*-toluidine (Note 1). The temperature is allowed to reach about 85° in order to prevent the separation of solid before all the amine has been added. When addition is complete, the temperature is raised to 100–105° for 5 minutes. The flask is then placed on a steam bath, the stirrer and dropping funnel are removed, and the flask is evacuated by means of a water pump to about 15 mm. (Note 2); after 21 hours all the water has been removed. The flask is then immersed in an oil bath, and the internal temperature is raised to 180° over a period of 2 hours and kept at 180–195° (bath temperature about 190–205°) for 7 hours while the same diminished pressure is maintained (Note 3). The crude product is dissolved in 1.3 l. of boiling water, and 99 g. of barium hydroxide octahydrate is added with stirring; the solution is now alkaline to litmus. After the addition of 3 g. of Norit, the solution is heated for 1.5 hours on a steam bath, and 17.5 ml. of concentrated sulfuric acid (sp. gr. 1.84) diluted with 20 ml. of water is added with good stirring. The solution is heated to 96° and filtered through a large, preheated Büchner funnel; the filter cake is rinsed with 100 ml. of boiling water (Note 4).

The filtrate is transferred to a 3-l. round-bottomed flask and concentrated under a pressure of about 50 mm. to a volume of 200 ml. (Note 5). After the mixture has been chilled overnight in a refrigerator, the crystalline acid (68–74 g.) is filtered by suction and dried (Note 6). An additional small amount (5–8 g.) can be obtained by evaporating the filtrate to dryness. This residue is allowed to remain in contact with 75 ml. of methanol for about an hour with occasional shaking. The solid is filtered, dried, and weighed. The total yield of *o*-toluidinesulfonic acid is 74–79 g. (79–83%) (Note 7) and (Note 8).

2. Notes

1. The amine used should boil over a range of not more than 2°.
2. If time is an important consideration, and a smaller yield (60%) is acceptable, the procedure may be modified: the acid sulfate is heated for 1 hour under reduced pressure; the temperature is then raised to 180° for 1 hour and finally to 180–190° for 3 hours. The solid residue is taken up in 1 l. of hot water and 55 ml. of 40% sodium hydroxide, a small amount of unchanged amine is distilled with steam, and the clear solution is treated with Norit and filtered as above. The acid is then precipitated by adding 65 ml. of concentrated

hydrochloric acid.

3. During this time the amine acid sulfate melts and loses water, and the product solidifies to a white crystalline mass.

4. Low yields may result from crystallization of some of the acid in the funnel at this point if the funnel is preheated insufficiently. Some acid may also be lost in the large bulk of inorganic solid. Filtration through the finely divided filter cake is often so slow that the under side and stem of the funnel collect large amounts of crystalline acid which is not rinsed out by the 100 ml. of boiling water. The use of a steam-heated Büchner funnel or prolonged preheating of an ordinary Büchner funnel does not seem to minimize this effect. It is advisable to remove the funnel after filtration is complete, and to take out the filter cake and rinse the funnel with two 100-ml. portions of boiling water. The combined washings are heated to boiling and filtered, and the filtrate is added to that obtained in the original filtration.

5. The flask should be equipped with a still head to prevent carry-over of the solution during distillation; a capillary jet is also an aid in this evaporation. Much of the acid separates during this concentration; the crystals are easily filterable.

6. The acid was spread out on a large filter paper and dried above a steam radiator for 48 hours. The literature reports the acid to be a monohydrate which loses its water of crystallization by drying at 120° for 3 hours. However, titration of the air-dried acid showed that it was not hydrated. A sample of the acid heated to 120° for 3 hours showed no change in neutral equivalent.

7. This aminosulfonic acid has no definite melting point. On a Maquenne block a decomposition range of 335–380° was observed.

8. The product secured by this procedure is free from sodium sulfate and isomeric sulfonic acids. Titrations of the first crop of crystals gave neutral equivalents ranging from 187.0 to 187.6; the calculated neutral equivalent is 187.2. The second crop is less pure since it had a neutral equivalent of about 177.

3. Discussion

o-Toluidinesulfonic acid has been obtained by a variety of reactions. Of these the ones of preparative value are the sulfonation of *o*-toluidine by fuming sulfuric acid;[1,2,3] the rearrangement of the amine sulfate or acid sulfate;[4,5] and the reduction of the corresponding nitrotoluenesulfonic acid.[6] The above procedure is based on the directions of Huber,[5] who has described the preparation of ten aminoarylsulfonic acids by this method.

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

methanol (67-56-1)

sodium hydroxide (1310-73-2)

sodium sulfate (7757-82-6)

Norit (7782-42-5)

barium hydroxide octahydrate (12230-71-6)

o-toluidine (95-53-4)

o-Toluidinesulfonic acid (98-33-9)

m-Toluenesulfonic acid, 6-amino- (88-44-8)

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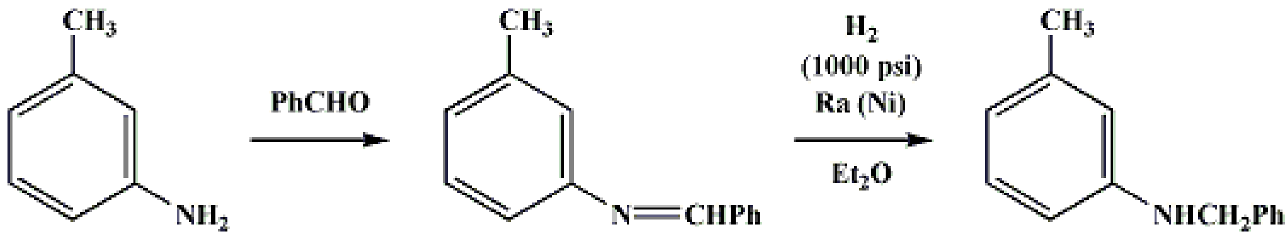
m-TOLYLBENZYLAMINE

[*m*-Toluidine, N-benzyl]



Submitted by C. F. H. Allen and James VanAllan.
Checked by Nathan L. Drake and Ralph Mozingo.

1. Procedure

One hundred and six grams (1 mole) of benzaldehyde (Note 1) and 107 g. (1 mole) of *m*-toluidine are mixed in a suitable flask; the temperature rises to about 60° (Note 2) and (Note 3). The mixture is cooled below 35° in cold water, 200 ml. of ether is added, and the solution is placed in the steel reaction vessel of a high-pressure hydrogenation apparatus. Eight to ten grams of Raney nickel catalyst (p. 181) is added, the bomb is closed, and hydrogen is admitted up to 1000 lb. pressure (Note 4). The bomb is shaken continuously at room temperature for 15 minutes (Note 5). The contents are removed, and the bomb is washed out with two 200-ml. portions of ether. After the catalyst has been separated by filtration (Note 6), the ether is removed by distillation and the product is distilled from a modified Claisen flask (Note 7). After a small fore-run the N-benzyl-*m*-toluidine boils at 153–157° /4 mm.; 315–317° /760 mm. The yield is 175–185 g. (89–94%) (Note 8) and (Note 9).

2. Notes

1. Technical grades of benzaldehyde (b.p. 57–59° /8 mm.) and *m*-toluidine (b.p. 76–77° /7 mm.) are satisfactory.
2. It is unnecessary to isolate the Schiff base.
3. The ether used as solvent may be replaced by an equal amount of 95% ethanol. If ethanol is used, cooling is unnecessary.
4. The initial pressure of hydrogen used is determined by the apparatus available. The drop in pressure depends upon the size of the bomb.
5. With a less active Raney nickel catalyst it may be necessary to carry out the reduction at a somewhat higher temperature. If necessary, the reaction mixture may be heated slowly to 60° and the reduction carried out at this temperature. The yield is then somewhat lower (82–84%).
6. The catalyst is filtered through paper on a Büchner funnel. Owing to its activity, suction should be discontinued as soon as all the liquid has passed through. If this precaution is not observed, a fire may result.
7. In some instances (*o*-tolylbenzylamine), a part of the product may crystallize and can be filtered.
8. The hydrochloride, m.p. 198–199°, may serve for characterization.
9. According to the submitters, other aromatic aldehydes and amines may be used in a similar manner with essentially the same yield of product. The exact procedure for isolation

of the amine will depend upon its physical properties. Benzaldehyde and *o*-toluidine yield *o*-tolylbenzylamine, m.p. 56–57° (hydrochloride, m.p. 165–166°), while *p*-tolylbenzylamine, obtained from *p*-toluidine, has a b.p. 162–163°/5 mm. (hydrochloride, m.p. 181–182°).

3. Discussion

N-Benzyl-*m*-toluidine has been prepared by the electrolytic reduction of benzal-*m*-toluidine,[1] and by hydrolysis of N-benzyl-N-formyl-*m*-toluidine, which was prepared in turn by the reaction of sodium N-formyl-*m*-toluidine with benzyl chloride.[2]

References and Notes

1. Law, *J. Chem. Soc.*, **1912**, 154.
2. Grunfeld, *Bull. soc. chim. France*, (5) **4**, 654 (1937).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium N-formyl-m-toluidine

ethanol (64-17-5)

ether (60-29-7)

hydrogen (1333-74-0)

benzaldehyde (100-52-7)

Raney nickel (7440-02-0)

benzyl chloride (100-44-7)

p-toluidine (106-49-0)

o-toluidine (95-53-4)

m-toluidine (108-44-1)

m-Tolylbenzylamine, N-benzyl-m-toluidine, m-Toluidine, N-benzyl (5405-17-4)

o-tolylbenzylamine (5405-13-0)

p-tolylbenzylamine

benzal-m-toluidine

N-benzyl-N-formyl-m-toluidine

N-benzyl-m-toluidine hydrochloride

o-tolylbenzylamine hydrochloride

p-tolylbenzylamine hydrochloride

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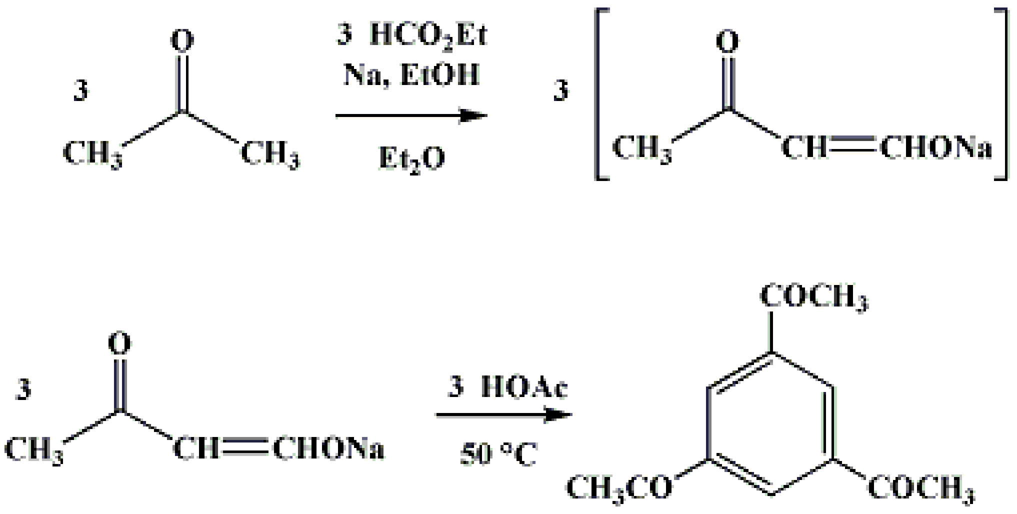
Organic Syntheses, CV 3, 829

1,3,5-TRIACETYLBENZENE

[Benzene, 1,3,5-triacetyl]



Submitted by Robert L. Frank and Robert H. Varland.
Checked by Arthur C. Cope and W. H. Jones.

1. Procedure

Sixty-nine grams (3.0 gram atoms) of freshly cut sodium is placed in a 1-l. round-bottomed flask with 400 ml. of dry xylene (Note 1) and heated until all the sodium is melted. The flask is closed with a rubber stopper and shaken vigorously to form finely powdered sodium (Note 2). When cool, the contents are transferred to a 5-l. three-necked round-bottomed flask, and the xylene is decanted. The powdered sodium is then washed with two 100-ml. portions of anhydrous ether by decantation, after which 1 l. of anhydrous ether is added. The flask is placed on a steam bath and fitted with a Hershberg stirrer, an upright condenser, and a 500-ml. dropping funnel. The condenser and funnel are protected from moisture by calcium chloride tubes. Through the dropping funnel is then added with stirring 138 g. (175 ml., 3.0 moles) of absolute ethanol at such a rate that gentle refluxing occurs. The mixture is refluxed and stirred for 6 hours after the addition is complete.

The reaction mixture is diluted with 1.5 l. of anhydrous ether, and a mixture of 174 g. (220 ml., 3.0 moles) of acetone (Note 3) and 222 g. (241 ml., 3.0 moles) of ethyl formate (Note 4) is placed in the dropping funnel and added to the flask over a period of 2 hours. Stirring is continued for 2 hours after the acetone and ethyl formate have been added (Note 5).

The reaction mixture is then rapidly extracted with five 1-l. portions of water (Note 6). Acetic acid is added to the water solution until it is acid to litmus. The acidified solution is warmed to 50° on a steam bath and maintained at approximately that

temperature for 2 hours. It is subsequently allowed to stand at room temperature for 48 hours, during which time the triacetylbenzene crystallizes.

The crude yellow crystalline solid (m.p. in the range 150–162°) is collected on a filter; the yield is 84–94 g. (41–46%). It is recrystallized by dissolving in hot ethanol (18 ml. of ethanol per gram), adding 2 g. of Norit, filtering through a steam-heated funnel (Note 7), and cooling the filtrate in an ice bath. The yield of shiny white crystals, m.p. 162–163°, is 62–79 g. (30–38%) (Note 8).

2. Notes

1. The first portion of this synthesis is very similar to the preparation of acetylacetone by the method of Adkins and Rainey (p. 17). The procedure and (Note 1),(Note 2),(Note 3),(Note 4),(Note 5),(Note 6) and (Note 8) for that synthesis may therefore be helpful in the present preparation.
2. A more finely powdered sodium can be obtained if paraffin oil ("Stanolind") is used in place of xylene (Gilbert Ashburn, private communication).
3. Acetone dried over calcium sulfate and distilled from phosphorus pentoxide is satisfactory.
4. The ethyl formate is dried over calcium sulfate and distilled.
5. If the solution becomes so thick as to make stirring difficult, it is advisable to add more anhydrous ether.
6. It is important that the extraction and acidification be carried out without delay. Oxidation of the intermediate product takes place readily on exposure to air and causes the solution to become dark in color.
7. If a steam-heated funnel is not used, a larger volume of ethanol should be employed to prevent crystallization during filtration.
8. The higher yield (38%) was obtained if the commercial absolute ethanol was dried by treatment with sodium and ethyl phthalate.[1]

3. Discussion

Triacetylbenzene has been prepared only by the condensation of acetone with ethyl formate followed by the trimerization of the intermediate acetylacetaldehyde.[2,3]

References and Notes

1. *Org. Syntheses* Coll. Vol. **2**, 155 (1943).
2. Claisen and Stylos, *Ber.*, **21**, 1145 (1888).
3. Kaushal, Sovani, and Deshapande, *J. Indian Chem. Soc.*, **19**, 107 (1942).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

acetic acid (64-19-7)

ether (60-29-7)

calcium sulfate (7778-18-9)

acetone (67-64-1)

Norit (7782-42-5)

sodium (13966-32-0)

xylene (106-42-3)

ethyl formate (109-94-4)

ethyl phthalate

Acetylacetone (123-54-6)

acetylacetaldehyde

1,3,5-Triacetylbenzene, Benzene, 1,3,5-triacetyl (779-90-8)

triacetylbenzene

phosphorus pentoxide (1314-56-3)

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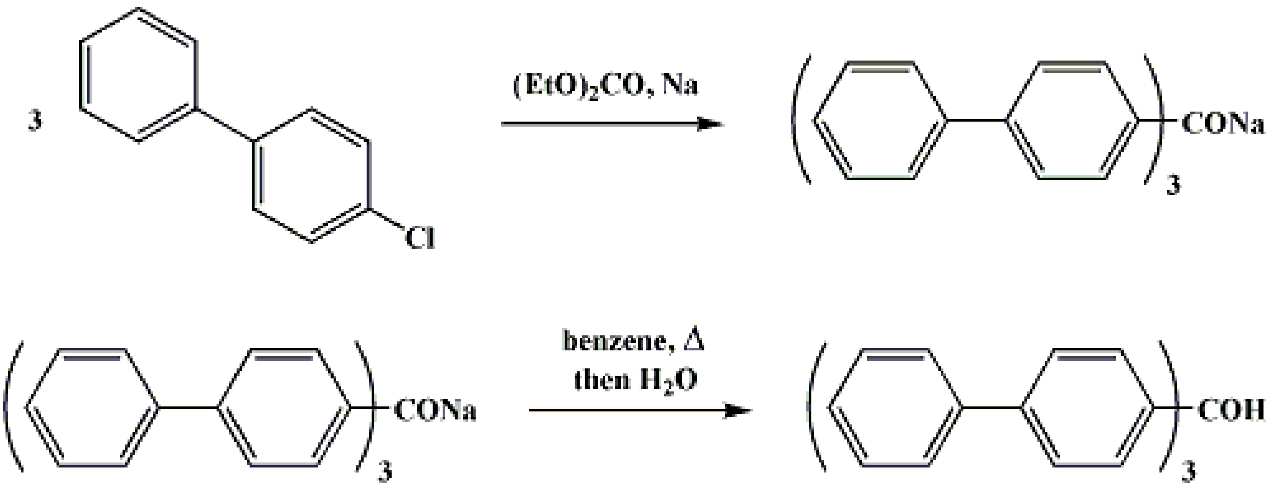
Organic Syntheses, CV 3, 831

TRIBIPHENYLCARBINOL

[Carbinol, tris-(4-phenylphenyl-)]



Submitted by A. A. Morton, J. R. Myles, and W. S. Emerson.
Checked by R. L. Shriner, Joseph Dec, and J. Harkema.

1. Procedure

In a 3-l. three-necked round-bottomed flask, equipped with a mercury-sealed stirrer and a 12-bulb reflux condenser, are placed 188.5 g. (1 mole) of *p*-chlorobiphenyl (Note 1), 47.2 g. (0.4 mole) of ethyl carbonate (Note 2), and 1.5 l. of anhydrous, thiophene-free benzene. The side tube is closed with a cork, stirring is begun, and the mixture is heated by means of a hot plate (Note 3). As soon as the mixture begins to boil, 2 g. of powdered sodium (Note 4) is added. The reaction starts in 1–2 minutes, as indicated by more vigorous refluxing and a change in color from yellow to brown (Note 5). Powdered sodium is then introduced in small portions, over a period of 1 hour, until an additional 28 g. has been added (total amount of sodium, 30 g.). The reaction mixture is refluxed and vigorously stirred (Note 6) for 2 hours. When the mixture has cooled somewhat, 75 to 100 ml. of absolute ethanol is added. After all the particles of sodium have reacted, 500 ml. of water is added, the condenser is arranged for downward distillation, and the benzene and unchanged *p*-chlorobiphenyl are removed by distillation from a steam bath (Note 7). The crude product remaining in the flask is separated by filtration, washed with 100–200 ml. of water, and pressed as dry as possible. The solid is dissolved in 600 ml. of xylene in a 1-l. distilling flask, and the solution is subjected to distillation until 25 to 50 ml. of distillate (xylene and water) has been collected. The solution is cooled somewhat, 1 to 2 g. Norit is added, and then the mixture is boiled for 5 minutes. The hot solution is filtered rapidly and the filtrate is cooled. The product is collected by filtration, washed with 25 to 50 ml. of cold xylene then with 200 ml. of petroleum ether, and dried. The tribiphenylcarbinol forms small white crystals which melt at 207–208°. The product weighs 57–65 g. (35–40%) (Note 8).

2. Notes

1. Technical *p*-chlorobiphenyl was purified by recrystallizing 300 g. of it from 750 ml. of petroleum ether. The recovery was 240–250 g.
2. Technical ethyl carbonate was washed successively with 10% aqueous sodium carbonate and saturated calcium chloride solution. It was then dried with magnesium sulfate and distilled. The fraction boiling at 124–125° was used.
3. A hot plate should be used to reduce the fire hazard. All flames in the vicinity should be extinguished.
4. The powdered sodium is prepared by melting 30 g. of the clean metal under 1 l. of dry xylene. The mixture is then stirred vigorously with a metal stirrer until the sodium is powdered.
5. If anhydrous reagents are used and the benzene solution is boiling, the reaction starts immediately. The reaction must start before more sodium is added.
6. The stirring must be sufficiently vigorous to prevent caking on the sides of the flask.
7. Unchanged *p*-chlorobiphenyl steam-distils along with the benzene. It is essential that it be removed, since a pure product is difficult to obtain by crystallization if unchanged chloro compound is present.
8. Better yields may be obtained in small-scale preparations if sodium chips are used. A solution of 19 g. of *p*-chlorobiphenyl, 5 g. of ethyl carbonate, and 50 ml. of anhydrous thiophene-free benzene is heated on a steam bath until refluxing begins. During 30 minutes 5 g. of sodium, cut into particles about 0.5 mm. square and 2 mm. thick, is dropped through the condenser. After the mixture has refluxed for 12 hours, it is decomposed and the product is isolated as described above, but with one-tenth the amounts of solvents. The yields range from 7 to 9 g. (47 to 55%), but the long period of refluxing required and the tedious cutting of the sodium chips make this method of value for small-scale preparations only. A large-scale run by this method gave only a 31% yield.

3. Discussion

Tribiphenylcarbinol has been prepared by the action of 4-xenylmagnesium iodide upon 4,4'-diphenylbenzophenone, or upon the methyl ester of *p*-phenylbenzoic acid;[1] and by the action of *p*-chlorobiphenyl upon ethyl carbonate in the presence of powdered sodium[2] or sodium wire.[3]

References and Notes

1. Schlenk, *Ann.*, **368**, 295 (1909).
2. Morton and Stevens, *J. Am. Chem. Soc.*, **53**, 4028 (1931); Morton and Emerson, *J. Am. Chem. Soc.*, **59**, 1947 (1937); Morton and Wood, private communication.
3. Bachmann and Wiselogle, *J. Org. Chem.*, **1**, 372 (1936).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

4-xenylmagnesium iodide

ethanol (64-17-5)

calcium chloride (10043-52-4)

Benzene (71-43-2)

sodium carbonate (497-19-8)

Norit (7782-42-5)

sodium, sodium wire (13966-32-0)

xylene (106-42-3)

magnesium sulfate (7487-88-9)

ethyl carbonate

TRIBIPHENYLCARBINOL

Carbinol, tris-(4-phenylphenyl-) (5341-14-0)

p-chlorobiphenyl (2051-62-9)

4,4'-diphenylbenzophenone

methyl ester of p-phenylbenzoic acid (720-75-2)

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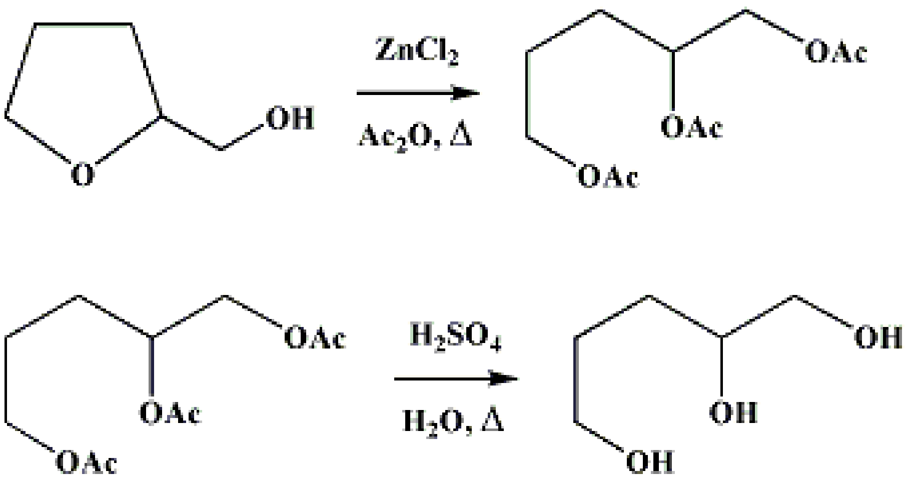
Organic Syntheses, CV 3, 833

1,2,5-TRIHYDROXYPENTANE

[1,2,5-Pentanetriol]



Submitted by Oliver Grummitt, James A. Stearns, and A. A. Arters.
Checked by Eugene Dineen, Christopher L. Wilson, and Charles C. Price.

1. Procedure

In a 5-l. three-necked flask fitted with a mercury-sealed mechanical stirrer, a 500-ml. dropping funnel, and an efficient reflux condenser are placed 2630 ml. (2856 g., 28 moles) of acetic anhydride and 57 g. of crushed anhydrous zinc chloride. This mixture is stirred and brought to gentle boiling. After 5–10 minutes at reflux, 680 ml. (714 g., 7 moles) of redistilled tetrahydrofurfuryl alcohol (Note 1) is added from the dropping funnel at such a rate that the mixture refluxes vigorously. This addition requires about 30 minutes. The mixture is then stirred and refluxed gently for 24 hours. After being cooled, about one-half of the liquid is decanted from the zinc chloride residue through a glass wool plug in a funnel into a 2-l. Claisen flask and then distilled under reduced pressure. The second portion is likewise distilled. The total weight of fore-run is 1740–1780 g. (Note 2). The 1,2,5-triacetoxypentane is collected at 155–165°/14 mm. The yield is 1500–1550 g. (87–90%).

Fifteen hundred grams (6.1 moles) of the ester and 1.2 l. of 1% sulfuric acid (6.9 ml. of concentrated acid in 1.2 l. of solution) are added to a 5-l. round-bottomed flask fitted with a reflux condenser. The mixture is heated strongly and agitated by tilting the ring stand back and forth until the two layers become homogeneous. This initial hydrolysis step requires 15–30 minutes. When homegenity is attained, the flask and condenser are set for steam distillation. The flask is heated by a Meker burner to maintain approximately constant volume, and the mixture is vigorously steam-distilled until 20 l. of distillate has been collected (Note 3). The residue is allowed to cool and then made basic to litmus paper by the addition of 10–20 g. of lime in small portions with vigorous agitation. The calcium sulfate is removed by suction filtration, the

filtrate tested again with litmus paper to make certain that it is basic (Note 4), and the filtrate distilled under reduced pressure. This is most conveniently done by placing about one-half of the solution in a 2-l. Claisen flask, heating the flask in an oil bath at 100–110°, and distilling the water under the pressure of the water pump. The remainder of the filtrate is added, the water is removed, and the distillation is continued with an oil or mercury-vapor pump. The yield of 1,2,5-trihydroxypentane collected at 167–170°/0.5–1.0 mm. is 460–520 g. (63–71%); n_D^{25} 1.4730 (Note 5).

2. Notes

1. Tetrahydrofurfuryl alcohol from the Quaker Oats Company was redistilled, and the portion boiling at 175–177° was used. If the 1001 industrial grade of alcohol is used without purification, the yield of triacetate is about 70% of the theoretical.
2. This consists mostly of acetic acid, acetic anhydride, and some tetrahydrofurfuryl acetate. By fractional distillation through a 15-in. glass-helix-packed column, in. in diameter, about 700 g. of acetic acid boiling at 117–125° and about 1075 g. of acetic anhydride boiling at 137–142° can be recovered.
3. With 10-mm. glass tubing for the steam inlet and outlet and an efficient condenser the maximum rate of steam distillation is 3 l. per hour. The 20 l. of distillate collected contains 95% of the calculated yield of acetic acid. The removal of the acetic acid is slow because the rate of hydrolysis in the final stages appears to be slow and the rate of acetic acid distillation is slow. The remainder of the acid is collected so slowly that it is not considered worth while to distil further, although the yield of product can be slightly increased.
4. If an acidic solution is distilled, the yield of product is decreased, probably because of dehydration and etherification reactions.
5. Analysis of this product for hydroxyl group content by the acetic anhydride-pyridine method gave 40.0%, compared to a calculated value of 42.5%, indicating a purity of 94%.

3. Discussion

1.2.5-Trihydroxypentane has been made by saponification of 1,2,5-triacetoxypentane with barium hydroxide[1,2] and by hydrolysis with 0.1 *N* hydrochloric acid.[3] The triacetoxypentane has been made by the action of potassium acetate and acetic anhydride on 4,5-dibromopentanol-1[1] or 1,2,5-tribromopentane[2,4] or 1-chloro-4,5-diacetoxypentane,[5] but it is most conveniently made by the reaction of acetic anhydride with tetrahydrofurfuryl alcohol.[3,4] The present method is a modification of that described by Wilson.[3]

References and Notes

1. Paul, *Compt. rend.*, **192**, 1574 (1931).
2. Paul, *Ann. chim.*, (10) **18**, 303 (1932).
3. Wilson, *J. Chem. Soc.*, **1945**, 48.
4. Paul, *Bull. soc. chim. France*, **53**, 417 (1933).
5. Paul, *Compt. rend.*, **211**, 645 (1940).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

acetic anhydride (108-24-7)

calcium sulfate (7778-18-9)

zinc chloride (7646-85-7)

barium hydroxide (17194-00-2)

tetrahydrofurfuryl alcohol (97-99-4)

potassium acetate (127-08-2)

4,5-dibromopentanol-1

1,2,5-Trihydroxypentane, 1,2,5-Pentanetriol, 1.2.5-Trihydroxypentane (14697-46-2)

1,2,5-Triacetoxypentane (5470-86-0)

tetrahydrofurfuryl acetate (637-64-9)

triacetoxypentane

1,2,5-tribromopentane

1-chloro-4,5-diacetoxypentane

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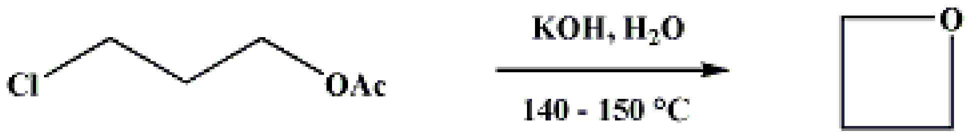
Organic Syntheses, CV 3, 835

TRIMETHYLENE OXIDE

[Oxetane]



Submitted by C. R. Noller
Checked by C. F. H. Allen and F. W. Spangler.

1. Procedure

A 3-l. Pyrex flask (Note 1) is fitted with an efficient mechanical stirrer, a dropping funnel, a thermometer, and an upright tube (Note 2) to act as an air condenser and to carry the trimethylene oxide vapors through a spiral condenser. In the flask are placed 1344 g. (24 moles) of potassium hydroxide and 120 ml. of water. The contents are heated to about 140° with stirring (Note 3). The upper part of the flask should be kept sufficiently hot so that the potassium hydroxide mush which is thrown up on the sides does not solidify. The spiral condenser is then packed with an ice-salt mixture, and 1092 g. (8 moles) of γ-chloropropyl acetate (p. 203) (Note 4) is slowly run into the flask by means of the dropping funnel so that the distillate comes over at the rate of about 1 drop a second. The time required for the addition is 1.5–3 hours. After all the ester has been added, the mixture is stirred, with continued heating at 140–150°, until the distillate amounts to 250–400 g., depending on how efficiently the air condenser has separated the trimethylene oxide from higher-boiling substances. About 100 g. of potassium hydroxide pellets is added to the crude distillate, which is then distilled through a 25-cm. fractionating column packed with -in. Berl Saddles. By careful distillation the trimethylene oxide can be obtained in a single fractionation, the portion boiling at 45–50° being collected. The higher-boiling residue still contains some trimethylene oxide, but consists mostly of water, allyl alcohol, and unchanged γ-chloropropyl acetate. The yield is 195–205 g. (42–44%). Redistillation over freshly fused potassium hydroxide gives a product boiling at 47–48°; n_D^{23} 1.3905.

2. Notes

1. A half-gallon jacketed iron autoclave may be employed.
2. A plain 90-cm. 10-mm. tube or a 30-cm. Vigreux column is equally satisfactory.
3. An electric heating mantle is advisable. The reaction is exothermic, and if it appears to become too vigorous the current is temporarily discontinued.
4. The submitter states that a yield of 20–25% may be obtained when trimethylene chlorohydrin is substituted for the acetate, with 2 moles of

potassium hydroxide and 10 ml. of water per mole of chlorohydrin.

3. Discussion

This procedure is an improvement upon that of Reboul,[1] and of Derick and Bissell.[2] Reboul, as also did Ipatow,[3] used trimethylene chlorohydrin, but the yield is higher from the acetate.

References and Notes

1. Reboul, *Ann. chim.*, (5) **14**, 495 (1878).
2. Derick and Bissell, *J. Am. Chem. Soc.*, **38**, 2478 (1916).
3. Ipatow, *J. Russ. Phys. Chem. Soc.*, **46**, 67 (1914) [*C. A.*, **8**, 1965 (1914); *Chem. Zentr.*, **85**, I, 2161 (1914)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Allyl alcohol (107-18-6)

potassium hydroxide, potassium hydroxide pellets (1310-58-3)

Trimethylene chlorohydrin (627-30-5)

Trimethylene oxide, Oxetane (503-30-0)

γ-Chloropropyl acetate (628-09-1)

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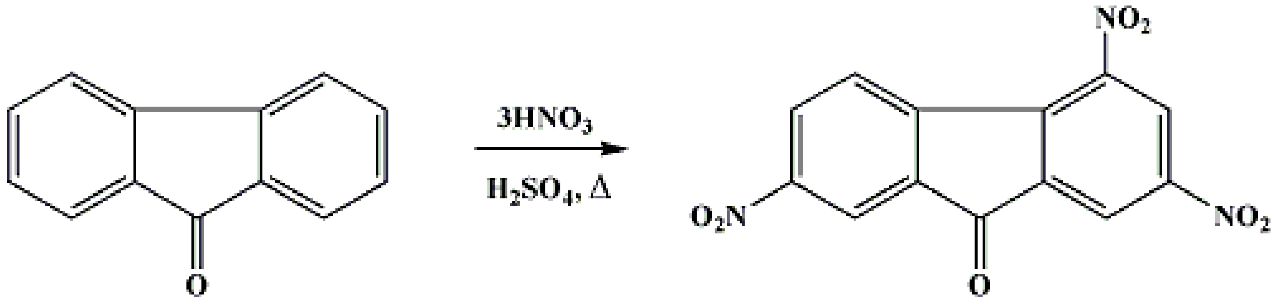
Organic Syntheses, CV 3, 837

2,4,7-TRINITROFLUORENONE

[9-Fluorenone, 2,4,7-trinitro-]



Submitted by E. O. Woolfolk and Milton Orchin.
Checked by Charles C. Price and Benjamin D. Halpern.

1. Procedure

In a well-ventilated hood, a 250-ml. dropping funnel, a thermometer, and a mechanical stirrer are connected by ground-glass joints to a 3-l. three-necked round-bottomed flask. Nine hundred milliliters of red fuming nitric acid (sp. gr. 1.59–1.60) is placed in the flask, and 675 ml. of concentrated sulfuric acid (sp. gr. 1.84) is added with stirring. The acid mixture is cooled to 20°, and the cooling bath is removed. A solution of 45 g. (0.25 mole) of fluorenone (Note 1). in 135 ml. of glacial acetic acid is added dropwise to the mixed acids over a period of about 40 minutes (Note 2). At the end of the addition, the temperature of the reaction mixture is about 45°. The stirrer, thermometer, and funnel are removed, the flask is attached to a reflux condenser with a ground-glass joint, and ground-glass stoppers are placed in the other two openings. The reaction mixture is refluxed for 1 hour and then poured (in the hood) slowly with shaking onto 7 kg. of cracked ice in a 12-l. flask. The product separates as a yellow solid and is filtered by suction and washed with 5 l. of water. The product and 2 l. of water are placed in a 5-l. round-bottomed flask, and steam is passed into the mixture for 1 hour to dissolve and remove acidic impurities (Note 3). The product is filtered by suction, washed with water until the washings are no longer acid to Congo red paper, and air-dried overnight. The material is further dried in a 1-l. round-bottomed flask connected to a water pump and heated in a water bath at 80–90° for several hours. The product is a yellow powder weighing 72–74 g. (91–94%) and melting at 166–171° (Note 4).

The crude product is dissolved in 350 ml. of boiling glacial acetic acid, and the hot solution is filtered by suction (Note 5). Any crystals that separate during the filtration are redissolved by heating the suction flask, and the solution is allowed to cool slowly. The small yellow needles that separate are filtered with suction and washed successively with small quantities of ethanol (30 ml.), water (50 ml.), and ethanol (30 ml.). The yield is 59–61 g. (75–78%) of 2,4,7-trinitrofluorenone, melting at 175.2–176.0°. Additional material can be recovered from the mother liquor by dilution with water, drying the precipitate so formed, and recrystallization from acetic acid. The second crop consists of about 5 g. of pure material, melting at 175.2–176.0°, which usually has a slightly darker color than the first crop.

2. Notes

1. Commercial fluorenone was recrystallized from benzene-ethanol to give material melting at 83–84°. Fluorenone can also be prepared conveniently from commercial fluorene according to the procedure of Huntress, Hershberg, and Cliff.[1] When the checkers nitrated unrecrystallized commercial fluorenone, m.p. 79–82°, the product obtained (yield 55.5 g.) was of a duller yellow color but melted at 175.5–176.5°.
2. Nitrogen oxides are evolved vigorously if the acetic acid solution of fluorenone is added to the acid mixture too rapidly.
3. If this treatment is omitted the recrystallized product has a brown color which is not removed by repeated recrystallizations.
4. The checkers observed melting points of 165–169° for the crude product.
5. Filter paper is not satisfactory for the filtration of hot acetic acid; a sintered-glass Büchner funnel is recommended.

3. Discussion

2,4,7-Trinitrofluorenone has been prepared by the nitration of fluorenone,[2,3] 2,7-dinitrofluorenone,[4] and 2,5-dinitrofluorenone.[4] The present method has been published[5] in connection with reports of the use of the reagent for the conversion of aromatic compounds to solid derivatives.

References and Notes

1. Huntress, Hershberg, and Cliff, *J. Am. Chem. Soc.*, **53**, 2720 (1931).
2. Schmidt and Bauer, *Ber.*, **38**, 3760 (1905). The material reported by these authors as 2,6,7-trinitrofluorenone was subsequently shown to be the 2,4,7-isomer (Bell, *J. Chem. Soc.*, **1928**, 1990).
3. Schmidt, Retzlaff, and Haid, *Ann.*, **390**, 231 (1912).
4. Ray and Francis, *J. Org. Chem.*, **8**, 58 (1943).
5. Orchin, Reggel, and Woolfolk, *J. Am. Chem. Soc.*, **69**, 1225 (1947); Orchin and Woolfolk, *J. Am. Chem. Soc.*, **68**, 1727 (1946).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

nitrogen oxides

ethanol (64-17-5)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

nitric acid (7697-37-2)

benzene-ethanol (60-12-8)

fluorene (86-73-7)

2,4,7-Trinitrofluorenone, 9-Fluorenone, 2,4,7-trinitro- (129-79-3)

fluorenone (486-25-9)

2,7-dinitrofluorenone (31551-45-8)

2,5-dinitrofluorenone

2,6,7-trinitrofluorenone

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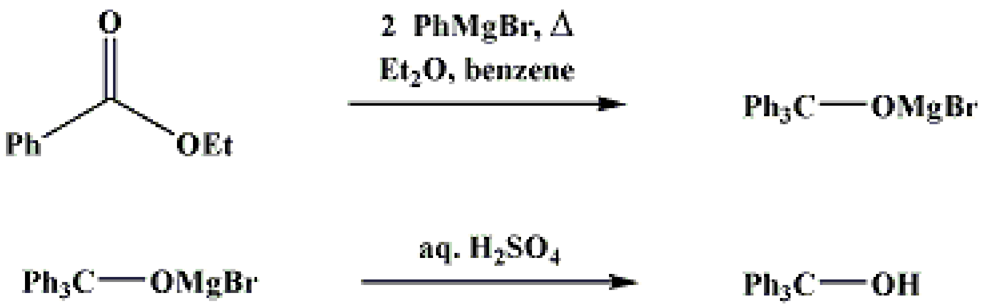
Organic Syntheses, CV 3, 839

TRIPHENYLCARBINOL

[Carbinol, triphenyl-]



Submitted by W. E. Bachmann and H. P. Hetzner.
Checked by R. L. Shriner and P. L. Southwick.

1. Procedure

In a 2-l. three-necked flask, fitted with a separatory funnel, a reflux condenser, and a mercury-sealed stirrer, 27 g. (1.1 gram atoms) of magnesium, 181 g. (122 ml., 1.15 moles) of bromobenzene, and a total of 450 ml. of anhydrous ether (Note 1) are converted into phenylmagnesium bromide by the procedure described in *Org. Syntheses* Coll. Vol. **1**, 226 (1941). Calcium chloride tubes are used to prevent the entrance of moisture through the condenser and the separatory funnel during the addition. In order to dissolve all the magnesium it may be necessary, in some instances, to continue stirring for longer than the prescribed 10 minutes after addition is complete.

To the Grignard solution, 75 g. (71.5 ml., 0.5 mole) of ethyl benzoate in 200 ml. of dry benzene (Note 2) is added at such a rate that the mixture refluxes gently. The flask is cooled in a pan of cold water during the addition, which requires about an hour. After the addition is complete, the mixture is refluxed for an hour on a steam bath. The reaction mixture is cooled in cooled an ice-salt bath and then poured slowly, with constant stirring, into a mixture of 1.5 kg. of cracked ice and 50 ml. of concentrated sulfuric acid. The mixture is stirred at intervals until all the solid that separates at the benzene-water interface has dissolved. If necessary, 50 g. of ammonium chloride is added to facilitate the decomposition of the magnesium salt, and additional benzene may be added if the amount present is insufficient to dissolve all the product. When the solids have disappeared, the benzene layer is separated and washed, successively, with 200 ml. of water, 200 ml. of a 5% solution of sodium bicarbonate, and finally with 200 ml. of water. The solvents are removed as completely as possible by distillation on a steam bath, and the remaining solution or solid mass is steam-distilled to remove biphenyl and unchanged bromobenzene. The product is filtered, washed with water, and dried. The crude triphenylcarbinol, which weighs 120–125 g., is recrystallized from carbon tetrachloride (4 ml. of solvent per gram of solid). The

weight of the first crop of colorless triphenylcarbinol is 110–115 g. (Note 3). A second crop may be obtained by heating the filtrate with a gram of Norit, then concentrating to about 125 ml. and cooling the solution. The total yield of triphenylcarbinol melting at 161–162° is 116–121 g. (89–93%) (Note 4).

2. Notes

1. Commercial anhydrous ether, before it is used, should be dried over slices of sodium, and the bromobenzene should be dried by distillation.
2. The benzene may be dried over anhydrous magnesium sulfate.
3. Triphenylcarbinol separates from carbon tetrachloride with solvent of crystallization. The solvent is readily lost on exposure of the crystals to air. The weight mentioned is that of the solvent-free product.
4. Practically the same yield of triphenylcarbinol was obtained from benzophenone and phenylmagnesium bromide; in this reaction only one-half as much Grignard reagent is required as that needed for the reaction with ethyl benzoate. To the cooled Grignard reagent prepared from 13.5 g. (0.55 gram atom) of magnesium, was added a solution of 91 g. (0.5 mole) of benzophenone in 200 ml. of dry benzene at such a rate that the mixture refluxes gently. After the mixture had been refluxed for 1 hour, the isolation of the triphenylcarbinol was carried out in the manner described above.

3. Discussion

Triphenylcarbinol has been obtained by the reaction between phenylmagnesium bromide and benzophenone,[1] methyl benzoate,[2] phosgene,[3] or ethyl or butyl pyrocarbonate;[4] by action of phenylsodium on benzophenone, benzoyl chloride, ethyl chlorocarbonate, or ethyl benzoate;[5] by hydrolysis of triphenylchloromethane;[6] and by oxidation of triphenylmethane.[7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 841

References and Notes

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6. Meissel, *Ber.*, **32**, 2422 (1899).
7. Law and Perkin, *J. Chem. Soc.*, **93**, 1637 (1908); Schwarz, *J. Am. Chem. Soc.*, **31**, 848 (1909).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethyl or butyl pyrocarbonate

sulfuric acid (7664-93-9)

Benzene (71-43-2)

ether (60-29-7)

ammonium chloride (12125-02-9)

sodium bicarbonate (144-55-8)

magnesium (7439-95-4)

carbon tetrachloride (56-23-5)

Norit (7782-42-5)

benzoyl chloride (98-88-4)

Benzophenone (119-61-9)

sodium (13966-32-0)

phosgene (75-44-5)

bromobenzene (108-86-1)

Biphenyl (92-52-4)

ethyl benzoate (93-89-0)

phenylsodium

Phenylmagnesium bromide (100-58-3)

methyl benzoate (93-58-3)

ethyl chlorocarbonate (541-41-3)

Triphenylmethane (519-73-3)

Triphenylchloromethane (76-83-5)

Triphenylcarbinol, Carbinol, triphenyl- (76-84-6)

magnesium sulfate (7487-88-9)

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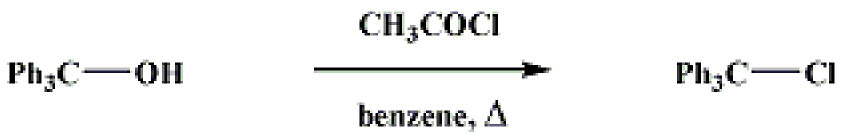
Organic Syntheses, CV 3, 841

TRIPHENYLCHLOROMETHANE

[Methane, chlorotriphenyl-]

[A. FROM TRIPHENYLCARBINOL AND ACETYL CHLORIDE]



Submitted by W. E. Bachmann
Checked by R. L. Shriner and Eldred Welch.

1. Procedure

A mixture of 250 g. of pure triphenylcarbinol (p. 839) and 80 ml. of dry benzene is placed in a 1-l. round-bottomed flask provided with a reflux condenser. The condenser is provided with a calcium chloride tube at the top (Note 1). The mixture is heated on a steam bath; when it is hot, 50 ml. of acetyl chloride (Note 2) is added through the top of the condenser. Heating is continued while the mixture is shaken vigorously. In about 5 minutes all the solid triphenylcarbinol disappears and a clear solution results. In the course of 10 minutes, an additional 100 ml. of acetyl chloride is added in 10-ml. portions. The solution is then refluxed for 30 minutes longer.

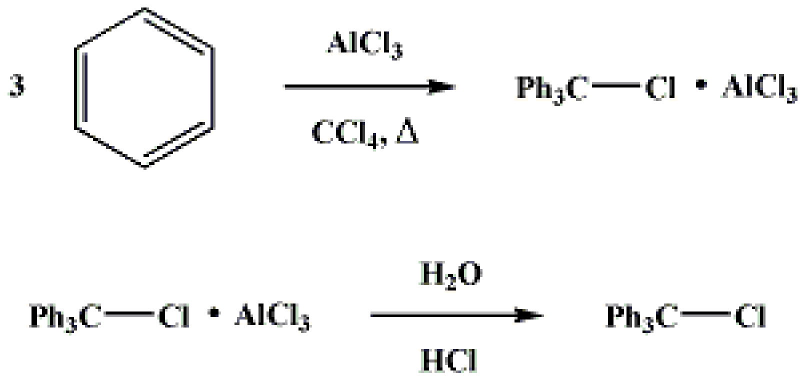
The solution is cooled by shaking the flask under running water, and during this operation 200 ml. of petroleum ether (Note 3) is added through the top of the condenser; the triphenylchloromethane separates in sugarlike crystals. The mixture is cooled in an ice bath for 1–2 hours, and the product is filtered and washed with 100–150 ml. of petroleum ether (Note 4). The colorless solid, after drying in a desiccator over soda-lime and paraffin (Note 5), weighs 212–224 g. (79–83%) and melts at 111–112° with slight previous softening. An additional 30–37 g. of colorless material may be obtained by concentrating the filtrate to a volume of about 75 ml. For this purpose, the petroleum ether and acetyl chloride are distilled at ordinary pressure, and the acetic acid under reduced pressure. The warm solution is treated with 2 g. of Norit, filtered, and again warmed with 2 g. of Norit. The mixture is filtered, 50 ml. of petroleum ether is added to the filtrate, and the solution is then cooled in an ice bath. The crystals of triphenylchloromethane are collected on a filter and washed with 70 ml. of cold petroleum ether. This second crop of material is pure white, like the first crop; the solid melts at 110.5–112° with previous softening (Note 6). The total yield is 249–254 g. (93–95%).

2. Notes

1. It is best to carry out the reaction under a hood.

2. The acetyl chloride should be of good quality. Good results were obtained with practical acetyl chloride which was distilled just before use.
3. Petroleum ether having a boiling point of 30–60° should be used because it is easily removed from the product.
4. The filtration should be rapid. Triphenylchloromethane is hydrolyzed by moisture in the air.
5. The final product is perfectly colorless and should have no sharp odor. This product is sufficiently pure for most purposes. It may be recrystallized by dissolving it in 100 ml. of hot benzene and cooling the solution after diluting it with 200 ml. of petroleum ether. If the product is kept in a bottle, the stopper should be coated with paraffin in order to keep out the moisture of the air.
6. Triphenylbromomethane may be made in a similar manner by substituting acetyl bromide for the acetyl chloride.

[B. FROM BENZENE AND CARBON TETRACHLORIDE, BY THE FRIEDEL-CRAFTS REACTION]



Submitted by C. R. Hauser and Boyd E. Hudson, Jr..
Checked by R. L. Shriner and Flavius W. Wyman.

1. Procedure

A mixture of 2 kg. (2.28 l., 25.6 moles) of dry thiophene-free benzene (Note 1) and 800 g. (470 ml., 5.2 moles) of dry sulfur-free carbon tetrachloride (Note 2) is placed in a 5-l. three-necked flask immersed in an ice bath and equipped with a mercury-sealed mechanical stirrer and a reflux condenser which is connected to a trap for the absorption of hydrogen chloride. The third neck of the flask is connected to a 1-l. Erlenmeyer flask by means of short pieces of large-bore (15-mm.) glass and rubber tubing (see Fig. 19, p. 550). In the Erlenmeyer flask is placed 600 g. (4.51 moles) of fresh resublimed aluminum chloride (Note 3). The Erlenmeyer flask is tilted and gently tapped, so that the aluminum chloride is added in small portions to the reaction mixture, and at such a rate that addition is completed in 1.5–2 hours. The reaction mixture is not allowed to reflux during the addition of the aluminum chloride. Fifteen minutes after all the aluminum chloride has been added, the ice bath is removed, and the reaction is allowed to proceed without further cooling. When no further heat is evolved, the mixture is refluxed until the evolution of hydrogen chloride subsides

(about 2 hours). The mixture is then allowed to cool to room temperature.

A 10-l. copper can (22.5 cm. in diameter and 30 cm. deep) (Note 4) is equipped with a powerful mechanical stirrer and a thermometer and is immersed to a depth of 20 cm. in an ice bath. A mixture of 1 l. of thiophene-free benzene and 2 l. of 6 *N* hydrochloric acid is placed in the copper vessel. The above reaction mixture is added to the vigorously stirred contents of the copper can at such a rate that the temperature does not rise above 25° (about 2 hours is required). When the addition is complete, the reaction flask is rinsed with a little ice water, and the rinsings are added to the hydrolysis mixture. Stirring is continued for 10 minutes longer. The benzene layer is decanted, and the aqueous layer is diluted with 1 l. of ice water. The aqueous layer is extracted with 500 ml. of benzene and is discarded. The combined benzene solutions are washed with 250 ml. of ice-cold hydrochloric acid and are dried for 2 hours in a stoppered flask over 250 g. of anhydrous calcium chloride.

The dried benzene solution is filtered through glass wool into a 5-l. flask fitted with a cork carrying a delivery tube and a thermometer which reaches within 5 cm. of the bottom of the flask. Several boiling chips are added, and the benzene is removed by distillation, slowly towards the last, until the temperature of the boiling residue reaches 120°. The residue is transferred to a 2-l. Erlenmeyer flask with the aid of 40–50 ml. of dry benzene and is cooled to about 40°. Twenty-five milliliters of acetyl chloride (Note 5) is added, and the mixture is heated nearly to the boiling point. The solution is vigorously shaken while it is cooled rapidly to room temperature; it is then chilled in ice water for 2 hours. The solid triphenylchloromethane is crushed thoroughly with a porcelain spatula and is filtered with suction. The filtrate is set aside, and the crystals are washed with three 300-ml. portions of ligroin (b.p. 70–90°) (Note 6). The solvent is removed from the product by allowing it to stand in a vacuum desiccator over mineral oil or paraffin shavings for 24 hours. The crystals are stirred occasionally, and the desiccator is evacuated to 5–10 mm. (Note 7). The light-greenish yellow crystals melt at 111–112° and weigh 870–940 g. (69–75% based on the aluminum chloride).

Second crops of crystals may be obtained by distilling, separately, the filtrate and washings until the temperature reaches 110° and 100°, respectively, and cooling the residues rapidly while they are shaken. The crystals are washed with minimum quantities of ligroin (b.p. 70–90°) and are dried as described for the first crop. The second crop from the filtrate weighs 70–80 g. and melts at 111–112° with sintering at 108°; that from the washings weighs 50–135 g. and melts at 110–111° with sintering at 107°. These second crops are darker in color than the first crop, and of the two second crops, that from the washings is the darker greenish yellow. The total yield of product varies from 1060 g. to 1085 g. (84–86% based on the aluminum chloride) (Note 8).

2. Notes

1. The presence of sulfur compounds, especially thiophene, in the reagents leads to low yields and a dark-colored product. A good grade of thiophene-free

benzene should be used. The benzene may be dried by distillation or by allowing it to stand over calcium chloride. The benzene which is recovered in this preparation may be used in future runs after it has been extracted with alkali, washed, and dried. Small amounts of carbon tetrachloride in the benzene do not interfere, since the quantities of benzene and carbon tetrachloride used are in excess of the relative quantity of the aluminum chloride.

2. A good grade of commercial carbon tetrachloride (b.p. 75–76°) may be used without a noticeable decrease in yield. However, if a colorless product is desired, sulfur-free C.P. carbon tetrachloride is recommended. The carbon tetrachloride may be dried in the same manner as the benzene.

3. The yield of triphenylchloromethane depends very much upon the quality of the aluminum chloride used. Fresh commercial resublimed aluminum chloride, in powder form, has been used in the preparation described.

4. The high thermal conductivity of copper makes possible rapid removal of heat during the hydrolysis; the presence of copper in the mixture does not appear to produce any undesirable effects. If a metal can is not available, a 3-gal. enameled bucket may be used.

5. A technical grade of acetyl chloride may be used, since the presence of small amounts of acetic acid does not interfere. The acetyl chloride serves to convert into triphenylchloromethane any triphenylcarbinol which may be present.

6. Technical ligroin (b.p. 90–120°) should be extracted several times with concentrated sulfuric acid, washed, and dried before use.

7. The vacuum desiccator shown in .htmFig. 28 has been in use in the research laboratories of the Eastman Kodak Company for some time, and has been found to be of great convenience when large amounts of materials must be handled. One of two similar round-bottomed flasks (*B*) is provided with a tube for connection to the vacuum pump. Although not necessary, a glass stopcock in this tube is a convenience, and it enables the flask to be used as a large separatory funnel. A glass sleeve *C*, which must not fit too loosely, serves as a guide for the union between the two flasks *A* and *B*. The sleeve carries a rubber gasket (*D*) which is most conveniently cut from an old inner tube. The gasket provides a tight seal for the vacuum, and the sleeve prevents the contact surfaces from slipping sidewise. *Without the guiding sleeve, the assembly is not safe*. Special guiding clamps may be used, but they offer no particular advantage. When in use, flask *A* contains the product and *B* contains the drying agent. *E* is a steam bath, and *F* is any convenient support. The apparatus, assembled from 5-l. stock flasks chosen at random, holds a vacuum of 2 mm. for 24 hours with the aid of a high-grade vacuum grease. This "dumb-bell desiccator" is particularly useful for synthetic work; frequently one operation may be eliminated, for flask *A* may be the vessel in which a reaction, or process of concentration, was performed and the product may be dried without transferring it, or flask *A* may be the vessel in which a subsequent reaction is to be carried out; while the product is drying, it may be stirred by rotating the assembly; and, within limits, the desiccator may be of any size desired. It is desirable to coat the flasks on the outside with a thin film of some soluble plastic, for the hazards are thereby greatly reduced; very little shattering occurred when evacuated flasks so coated

were experimentally "imploded." A comparative test, in which a highly hygroscopic syrup was used, indicated that, with this form of vacuum desiccator and with equal amounts of drying agent, operations may be performed about twice as rapidly as in the conventional model. When the flask *A* is warmed gently, the efficiency of the assembly is at least four times that of a conventional desiccator. (F. P. Pingert, private communication.)

Fig. 28.

Fig. 28.

8. The product may be stored satisfactorily in ordinary screw-top bottles, provided that they are well sealed with paraffin or some similar material. Triphenylchloromethane is slowly hydrolyzed to triphenylcarbinol by the moisture of the air. Partially hydrolyzed triphenylchloromethane may be purified by recrystallization from one-third its weight of benzene containing 5–25% of acetyl chloride. The product is washed with ligroin containing a little acetyl chloride.

3. Discussion

Triphenylchloromethane has been made by the action of phosphorus pentachloride,[1] hydrogen chloride,[2] or acetyl chloride[3] upon triphenylcarbinol. It has also been made by the reaction between carbon tetrachloride and benzene in the presence of aluminum chloride[4] or ferric chloride;[5] and by the action of phosphorus pentachloride,[6] or of sulfuryl chloride in the presence of peroxides,[7] upon triphenylmethane. Procedure A is based upon that of Gomberg and Davis;[3] procedure B is a modification of that originally reported by Gomberg[4] and later described by Gattermann and Wieland.[8]

References and Notes

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8. Gattermann and Wieland, *Laboratory Methods of Organic Chemistry*, p. 346, The Macmillan Company, New York, 1937.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ligroin

petroleum ether

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrogen chloride, hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

phosphorus pentachloride (10026-13-8)

acetyl chloride (75-36-5)

carbon tetrachloride (56-23-5)

copper (7440-50-8)

Norit (7782-42-5)

sulfuryl chloride (7791-25-5)

aluminum chloride (3495-54-3)

ferric chloride (7705-08-0)

Triphenylmethane (519-73-3)

Triphenylchloromethane, Methane, chlorotriphenyl- (76-83-5)

Triphenylcarbinol (76-84-6)

Thiophene (110-02-1)

acetyl bromide (506-96-7)

Triphenylbromomethane (596-43-0)

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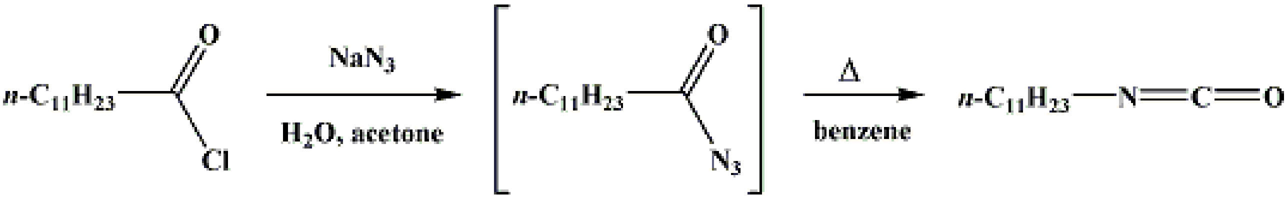
Organic Syntheses, *CV 3, 846*

UNDECYL ISOCYANATE



Submitted by C. F. H. Allen and Alan Bell.
Checked by Nathan L. Drake and John Sterling.

1. Procedure

In a 1-l. three-necked flask, equipped with a stirrer and a thermometer and immersed in an ice bath, is placed 46 g. (0.7 mole) of sodium azide (Note 1) in 150 ml. of water. A mixture of 109 g. (0.5 mole) of lauroyl chloride (b.p. 134–137°/11 mm.) and 150 ml. of acetone is then added from a separatory funnel to the well-stirred solution of the azide at such a rate that the temperature remains at 10–15°. After the mixture has been stirred at this temperature for an hour, the stirrer is stopped and, when the layers have separated, the lower water layer is removed carefully by suction through a glass capillary tube (Note 2). The upper layer is then added slowly to 500 ml. of benzene which has been warmed to 60° (Note 3). A rather rapid evolution of gas results, and the mixture is kept at 60–70° (Note 4) until no more nitrogen is evolved; the conversion of azide to isocyanate requires about an hour. The solution is filtered to remove any insoluble matter, and the benzene is removed by distillation from a modified Claisen flask. Distillation of the residue yields 80–85 g. of ester (81–86%) (Note 5) and (Note 6).

2. Notes

1. A practical grade of sodium azide such as that obtained from the Eastman Kodak Company is satisfactory.
2. It is important that the water be removed as completely as possible before the azide is added to the warm benzene. Failure to remove the water causes formation of the *sym*-disubstituted urea during decomposition of the azide. If the water is separated carefully, there will be no need to filter the benzene solution before the final distillation.
3. If the azide is added too rapidly, the solution may froth over; it is best to carry out this reaction in a 1-l. beaker.
4. The heat of reaction is usually sufficient to maintain the temperature at 60–70°.
5. On redistillation all the product boils at 103°/3 mm. A second distillation is unnecessary; the original ester is pure enough for all practical purposes.
6. This method is a general one for the preparation of isocyanates.[1]

3. Discussion

This procedure is one used by Schröter for preparing alkyl isocyanates.[1]

References and Notes

1. Schröter, *Ber.*, **42**, 3356 (1909).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sym-disubstituted urea

Benzene (71-43-2)

nitrogen (7727-37-9)

acetone (67-64-1)

sodium azide (26628-22-8)

UNDECYL ISOCYANATE (2411-58-7)

lauroyl chloride (112-16-3)

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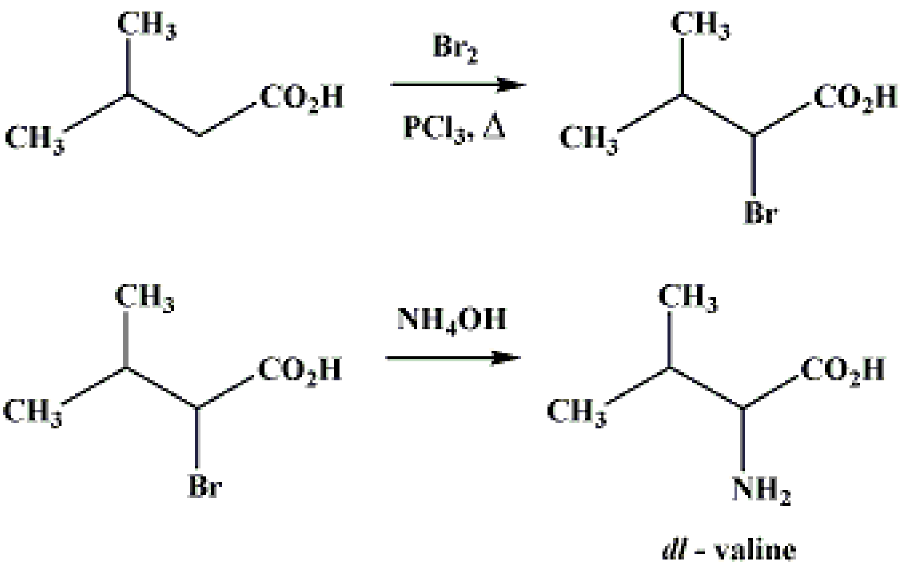
Organic Syntheses, CV 3, 848

dl-VALINE

[Isovaleric acid, α-amino]



Submitted by C. S. Marvel[1]
Checked by C. F. H. Allen and J. VanAllan.

1. Procedure

A. *α-Bromoisovaleric acid*. One kilogram of commercial isovaleric acid monohydrate is placed in a 3-l. round-bottomed flask together with 500 ml. of benzene. The water and benzene are distilled, using a short column, until the temperature of the vapor reaches 100°. The temperature rises rapidly when the benzene is removed. The residue is cooled, and 878 g. (934 ml., 8.6 moles) of it is placed in a 3-l. round-bottomed flask fitted with a long reflux condenser. The top of the condenser is connected by glass tubing to an empty 500-ml. Erlenmeyer flask which acts as a safety trap. A second outlet on the Erlenmeyer flask connects to a gas-absorption trap (Note 1). One and five-tenths kilograms (480 ml.) of dry bromine (Note 2) is added to the acid, and then 15 ml. of phosphorus trichloride is added through the top of the condenser.

The mixture is heated on an oil bath at 70–80° for 10–20 hours or until the condenser no longer shows the deep red color of bromine. Another 25-ml. portion of bromine is added and the flask heated as before. When the color has again disappeared, the temperature of the bath is slowly raised to 100–105° and maintained there for 1.5–2 hours.

The crude bromo acid is placed in a 2-l. modified Claisen flask and distilled under reduced pressure. The low-boiling fraction is mainly unbrominated acid (Note 3). The fraction boiling at 110–125°/15 mm. is collected. The yield is 1364–1380 g. (87.5–88.6%).

B. *dl-Valine.* To 2 l. of technical ammonium hydroxide (sp. gr. 0.90) in a 3-l. round-bottomed flask is added 330 g. (1.82 moles) of α-bromoisovaleric acid. A stopper is wired in and the flask allowed to stand at room temperature for a week. The contents from three such amination flasks are combined in a 12-l. flask, and the ammonia is removed by heating on the steam cone overnight. The solution is then concentrated to a thin paste (about 800 ml.) by means of a water pump (Note 4). The solid material is collected on a filter and, when dry, amounts to 470 g. This is recrystallized by dissolving in 2.4 l. of water heated to 95° on a steam cone, treating with 10 g. of Norit for 30 minutes, filtering hot, adding an equal volume of 95% ethanol, and cooling overnight in the icebox. The valine is collected on a filter and washed with 150 ml. of cold absolute ethanol. The yield is 200–235 g. A second crop is obtained by evaporating the filtrate from the recrystallization on the water pump until crystals form, adding an equal volume of 95% ethanol, and cooling as before. The amino acid obtained in this way amounts to 34 g.

The second filtrate from the recrystallization together with the filtrate from the original concentration is evaporated to dryness and extracted with 500 ml. of glacial acetic acid on a steam cone. The inorganic salts are filtered and the acetic acid is removed by distillation under reduced pressure. One liter of water is added, and it, too, is removed by distillation under reduced pressure. This operation is repeated. These three distillations require 1 day. The residue is dissolved in the minimum amount of hot water (about 300 ml.). The solution is then treated with Norit as before and filtered hot, and an equal volume of 95% ethanol is added. The yield on cooling overnight in the icebox is 34 g. An additional 8 g. can be obtained from the mother liquor by concentration and addition of ethanol as was done with the original mother liquor. The total yield of valine is 300–311 g. (47–48%), which decomposes at 280–282° in a sealed capillary (Note 5) and (Note 6).

2. Notes

1. The hydrogen bromide may be absorbed in water and constant-boiling hydrobromic acid formed (*Org. Syntheses* Coll. Vol. **1**, 26 (1941).
2. The bromine is dried by shaking with 1 l. of concentrated sulfuric acid.
3. The low-boiling fraction (56–80 g.) may be combined with the next portion of acid to be brominated, or several such fractions are collected and brominated together. In this latter case, only three-fifths as much bromine is used as in the original run.
4. This condition is attained when 1850–1950 ml. of distillate has been collected (5 hours).
5. The quantities stated for each fraction are approximate. If separations are incomplete, the melting point will be 275–280°.
6. Valine prepared in this manner has the calculated amino nitrogen content.

3. Discussion

Valine has been prepared by the action of ethanolic ammonia on α-chloroisovaleric acid;[2] by the action of aqueous ammonia on α-bromoisovaleric acid;[3] through the reaction of hexamethylenetetramine with α-bromoisovaleric acid in dioxane or dioxane-xylene (91% yield);[4] by the action of ammonia and ammonium carbonate,[5] or ammonium carbonate alone on α-bromoisovaleric acid;[6] by heating isopropylmalonazidic acid[7] or isopropylcyanoacetazide[8] in ethanol and subsequent hydrolysis; by the action of ammonia and hydrogen cyanide[9] or ammonium chloride and potassium cyanide[10] on isobutyraldehyde, followed by hydrolysis; by reaction of α-hydroxyisovaleronitrile with ammonia under pressure, followed by hydrolysis;[11] by reaction of isopropyl bromide with the sodium salt of acetamidomalonic ester or acetamidocyanoacetic ester,[12] and subsequent hydrolysis; by reduction of dimethylpyruvic acid phenylhydrazone;[13] by hydrolysis of α-carbomethoxy-α-phenylacetamidoisovaleronitrile;[14] and by the reaction of isobutyraldehyde with ammonium carbonate and sodium cyanide in aqueous methanol followed by hydrolysis.[15]

α-Bromoisovaleric acid has been prepared in several ways as described in an earlier volume.[16]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 93

References and Notes

1. These directions are the result of the efforts of a large number of men who have worked on the preparation of valine at the University of Illinois.
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

isopropylcyanoacetazide

sodium salt of acetamidomalonic ester or acetamidocyanoacetic ester

ethanol (64-17-5)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

ammonium carbonate

ammonia (7664-41-7)

Benzene (71-43-2)

methanol (67-56-1)

ammonium chloride (12125-02-9)

sodium cyanide (143-33-9)

hydrogen cyanide (74-90-8)

α-Bromoisovaleric acid (565-74-2)

HYDROBROMIC ACID, hydrogen bromide (10035-10-6)

bromine (7726-95-6)

Isopropyl bromide (75-26-3)

potassium cyanide (151-50-8)

Norit (7782-42-5)

phosphorus trichloride (7719-12-2)

ammonium hydroxide (1336-21-6)

xylene (106-42-3)

hexamethylenetetramine (100-97-0)

dioxane (5703-46-8)

isobutyraldehyde (78-84-2)

Isovaleric acid, α-amino, DL-Valine (516-06-3)

valine (72-18-4)

isovaleric acid monohydrate

α-chloroisovaleric acid

isopropylmalonazidic acid

α-hydroxyisovaleronitrile

dimethylpyruvic acid phenylhydrazone

α-carbomethoxy-α-phenylacetamidoisovaleronitrile

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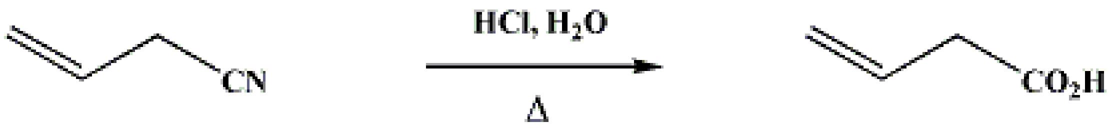
Organic Syntheses, CV 3, 851

VINYLACETIC ACID

[3-Butenoic acid]



Submitted by Edward Rietz
Checked by C. F. H. Allen and James VanAllan.

1. Procedure

In a 500-ml. flask attached to a reflux condenser is placed a mixture of 67 g. (80 ml., 1 mole) of allyl cyanide[1] (Note 1) and 100 ml. (1.2 moles) of concentrated hydrochloric acid (sp. gr. 1.19). The mixture is heated by a small flame and is shaken frequently. After 7–8 minutes, the reaction begins, a voluminous precipitate of ammonium chloride appears, the temperature rises rapidly, and the mixture refluxes. After 15 minutes the flame is removed, 100 ml. of water is added, and the upper layer of the acid is separated (Note 2). The aqueous layer is extracted with two 100-ml. portions of ether. The extracts and the acid are combined and distilled. Most of the ether is removed at atmospheric pressure (Note 3), (Note 4), and (Note 5), and the remainder is removed as the pressure is diminished. The acid is collected at 70–72°/9 mm. after a fore-run of approximately 40 g. The yield of crude acid is 50–53 g. (52–62%) (Note 5).

Although this product is pure enough for most purposes, it contains small amounts of by-products which cannot be removed by distillation. Further purification is accomplished by the following procedure: In a 250-ml. three-necked round-bottomed flask fitted with a stirrer, a small dropping funnel, and a thermometer for reading low temperatures, 24 g. of sodium hydroxide is dissolved in 80 ml. of water. While the temperature of *of the solution* is maintained at 8–15° by external cooling, 45 g. (40.5 ml.) of the impure vinylacetic acid is added; this operation requires 25 minutes. This solution is transferred to a 600-ml. conical separatory funnel and extracted with 50 ml. of chloroform (Note 6) and (Note 7). The alkaline solution is *immediately* transferred to a 1-l. beaker, and 300 ml. of dilute sulfuric acid (Note 8) and (Note 9) is added with stirring. This acid solution is *at once* extracted with three 100-ml. portions of chloroform (Note 7) and (Note 10). The solvent is then removed by distillation, first at atmospheric pressure and then at reduced pressure, from a 200-ml. modified Claisen flask. The residue is distilled under reduced pressure. Almost all the material boils at 69–70°/12 mm. (163°/760 mm.). The recovery is 30–33 g. (75–82%) (Note 11).

2. Notes

1. An improved procedure for preparation of allyl cyanide (3-butenenitrile) is as

follows: In a dry (washed with absolute ethanol and absolute ether) 500-ml. three-necked flask, equipped with a sealed mechanical stirrer and a 90-cm. bulb condenser set vertically and protected by a calcium chloride tube, are placed 85 g. of dry cuprous cyanide (commercial, or prepared as previously described;[1] dried for 72 hours in an oven at 110° just before use), 0.25 g. of potassium iodide, and 72.5 g. of allyl chloride (dried over calcium chloride and freshly distilled; b.p. 45–47°). The stirrer is started, and the mixture is heated on a water bath. After about 6 hours the reaction is substantially complete, as indicated by cessation of the refluxing; heating is continued for 1 hour beyond this point. With larger runs it may be necessary to moderate the reaction by removing the water bath when vigorous refluxing sets in. This usually occurs about 3–5 hours after heating is started. Runs of the size described do not require any special attention. The water bath is replaced by an oil bath, the condenser is set downward for distillation, and stirring is continued while the allyl cyanide is distilled into a 100-ml. distilling flask. Near the end of the distillation it may be necessary to discontinue stirring, and it is advisable to reduce the pressure somewhat to aid in the removal of the last portion of the product. The distillate is redistilled, and 50–53 g. (79–84%) of allyl cyanide boiling at 116–122° is collected. (Private communication from Curtis W. Smith and H. R. Snyder; checked by W. E. Bachmann and G. Dana Johnson.)

2. This amounts to 90–95 g. A separatory funnel of about 600-ml. capacity is the most convenient size.

3. The first ether extract contains 10 g. of nitrile; the second extract contains 4.5 g.

4. This procedure is shorter and less tedious than the more common method of drying and fractionating the ethereal solution.

5. A Dry Ice trap, inserted between the oil pump and the apparatus, condenses 5–10 g. of unchanged allyl cyanide. The yield of crude acid, after allowing for the recovered nitrile, is 62–72%.

6. This extraction removes about 1 g. of non-acidic impurity.

7. Ether can be substituted for chloroform without materially decreasing the yield.

8. This is prepared by diluting 16.5 ml. of concentrated sulfuric acid to 300 ml.

9. Contact with alkali results in the isomerization of vinylacetic acid to crotonic acid.

10. The first two extractions remove 27–28 g.; the last one, 3–4 g.

11. When cooled in a Dry Ice-acetone bath the acid should remain clear until it crystallizes at −36° to −35°. This indicates freedom from crotonic acid.[2]

3. Discussion

The only practical methods for the preparation of vinylacetic acid involve hydrolysis of allyl cyanide;[3,4] carbonation of allylmagnesium bromide[5,6] or an alkali salt of propylene.[7] The malonic acid synthesis is less satisfactory than the hydrolysis of allyl

cyanide.[4]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

allyl cyanide (3-butenenitrile)

ethanol (64-17-5)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ether (60-29-7)

ammonium chloride (12125-02-9)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

potassium iodide (7681-11-0)

Allyl cyanide (109-75-1)

Cuprous Cyanide (544-92-3)

allyl chloride (107-05-1)

Malonic acid (141-82-2)

crotonic acid (3724-65-0)

Vinylacetic acid, 3-Butenoic acid (625-38-7)

Allylmagnesium bromide (1730-25-2)

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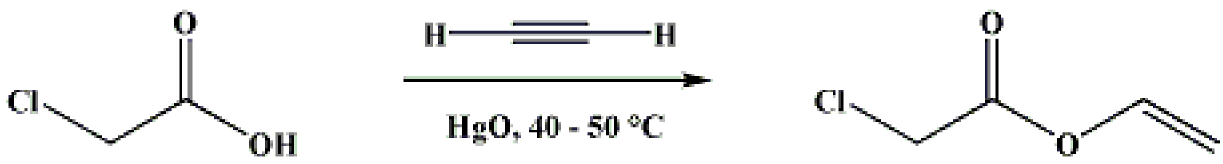
Organic Syntheses, CV 3, 853

VINYL CHLOROACETATE

[Acetic acid, chloro-, vinyl ester]



Submitted by Richard H. Wiley
Checked by Maynette Vernsten and Homer Adkins.

1. Procedure

Vinyl chloroacetate is lachrymatory.

A 1-l. three-necked flask is equipped with an efficient stirrer, a thermometer, a gas inlet tube 10 mm. in diameter, and a reflux condenser. The bulb of the thermometer and the lower end of the gas inlet tube are sufficiently close to the bottom of the flask to be covered by the reactants (Note 1). The upper end of the condenser is attached to a small gas-washing bottle containing enough water so that the rate of passage of the exit gases may be noted. The flask is charged with 200 g. (2.12 moles) of monochloroacetic acid, 0.2 g. of hydroquinone, and 20 g. of yellow mercuric oxide (Note 2). A slow stream of acetylene is passed through a spiral trap cooled in Dry Ice-acetone mixture, a mercury safety valve, an empty wash bottle, a sulfuric acid wash bottle, a soda-lime tower, and then into the reaction flask through the gas inlet tube. The stirrer is started, and the contents of the flask are heated gently with steam until the chloroacetic acid just melts (Note 3). The temperature of the reaction mixture is lowered to 40–50° after 30 minutes or as soon as the melting point of the mixture permits the lower temperature to be attained without solidification. An ice bath is used for cooling the mixture when necessary (Note 4). The stirrer is operated fast enough to throw the contents of the flask vigorously against the walls, in order to obtain the most rapid absorption. The absorption of acetylene, very rapid at first, becomes very slow after about 3 hours, and the introduction of the gas is discontinued (Note 5).

The contents of the flask are decanted and filtered or centrifuged to remove as much as possible of the finely divided mercury salt (Note 6). The filtrate is distilled from a Claisen flask, and 117–135 g. of material boiling at 45–55°/20 mm. is collected (Note 7). The distillate is fractionated, and 107–125 g. (42–49%) of vinyl chloroacetate, b.p. 37–38°/16 mm., n_D^{25} 1.4422, is collected (Note 8) and (Note 9).

2. Notes

1. The apparatus is similar to that previously shown[1] except that one of the inlet

tubes, T_1 or T_2, is replaced by a thermometer and the stirrer is equipped with a short sleeve which is connected to the shaft by a rubber tube moistened with glycerol.

2. Merck or Mallinckrodt Reagent grade or Baker C.P. monochloroacetic acid was used without further purification. Distillation of the acid did not improve the yield. Baker or Mallinckrodt yellow mercuric oxide, C.P., was used. The hydroquinone may be added at this point or before the distillation.

3. The submitter suggested that the mixture be heated to 50–55°. The melting point of the chloroacetic acid used by the checkers required that the temperature at the beginning of the reaction be somewhat above 60°. The chief difficulty in carrying out the reaction is due to solidification of chloroacetic acid in the inlet tube if the temperature of the reaction mixture is allowed to fall to the point where the mixture begins to crystallize. If the inlet tube becomes plugged, the pressure in the system will be relieved by the mercury safety valve. The safety valve may consist of a small bottle containing a layer of mercury and carrying a stopper fitted with two glass tubes; one of the tubes, extending just below the stopper, is connected to the acetylene line, and the other, which extends *just* beneath the surface of the mercury, is open to the air.

4. Higher temperatures are said to facilitate the formation of the ethylidene compound. Similar yields have been obtained, however, when the temperature was maintained at 50–55° during the entire reaction period.

5. Addition of more mercuric oxide at this time or after 1 hours' operation does not affect the rate of absorption or increase the yield. If less than 20 g. of mercuric oxide is used the yield is poorer; for example, an experiment with 10 g. of mercuric oxide resulted in a 37% yield of crude ester.

6. It is difficult to remove the finely divided mercury salt completely by decantation or filtration. All the suspended salt can be removed by centrifuging, but dissolved salt remains and separates from the solution on distillation. The suspended salt does not interfere if the product is distilled rapidly. Long-continued heating of the crude product, such as would be required in a careful fractionation, has resulted in a vigorous decomposition of the mixture.

7. Hydroquinone should be added to the crude ester immediately to stabilize it against polymerization. If it is to be kept for any length of time before refractionation it should be stored in a cold chest.

8. The submitter observed a somewhat higher boiling point (41–42°/15 mm.) and did not report the refractive index of the product. Both the submitter and checkers used a column 20 cm. in length, 12 mm. in diameter, packed with glass helices, and equipped with a partial take-off head. If the fractionation is carefully conducted, the product is sufficiently pure for most polymerization work. The compound should be stabilized with hydroquinone and stored in a cold chest if it is not to be used immediately.

9. According to the submitter the crude ester may also be purified as follows: The centrifuged reaction mixture is placed in a 1-l. separatory funnel with 500 ml. of ether and washed with 200-ml. portions of a 5% sodium carbonate solution until the unchanged acid is removed. Difficulty with emulsions is

sometimes encountered at this point. The ether layer is dried with anhydrous sodium sulfate, and the ether is evaporated on a water bath. The residue is fractionated as above.

3. Discussion

Vinyl chloroacetate has been prepared from acetylene and chloroacetic acid in the vapor phase at 250° with a zinc-cadmium catalyst,[2] and in the liquid phase with a mercury salt catalyst.[3] The procedure described is an adaptation of that employed by Klatte,[4] by Skirrow and Morrison,[5] and by others.[6]

References and Notes

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6. The preparation of vinyl esters has been reviewed by Ellis, *The Chemistry of Synthetic Resins*, Vol. II, p. 1017, Reinhold Publishing Corporation, New York, 1935.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

mercury salt

Dry Ice

acetylene (74-86-2)

ether (60-29-7)

glycerol (56-81-5)

hydroquinone (123-31-9)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

mercury (7439-97-6)

mercuric oxide (21908-53-2)

chloroacetic acid, monochloroacetic acid (79-11-8)

acetone (67-64-1)

zinc (7440-66-6)

cadmium (7440-43-9)

Vinyl chloroacetate, Acetic acid, chloro-, vinyl ester (2549-51-1)

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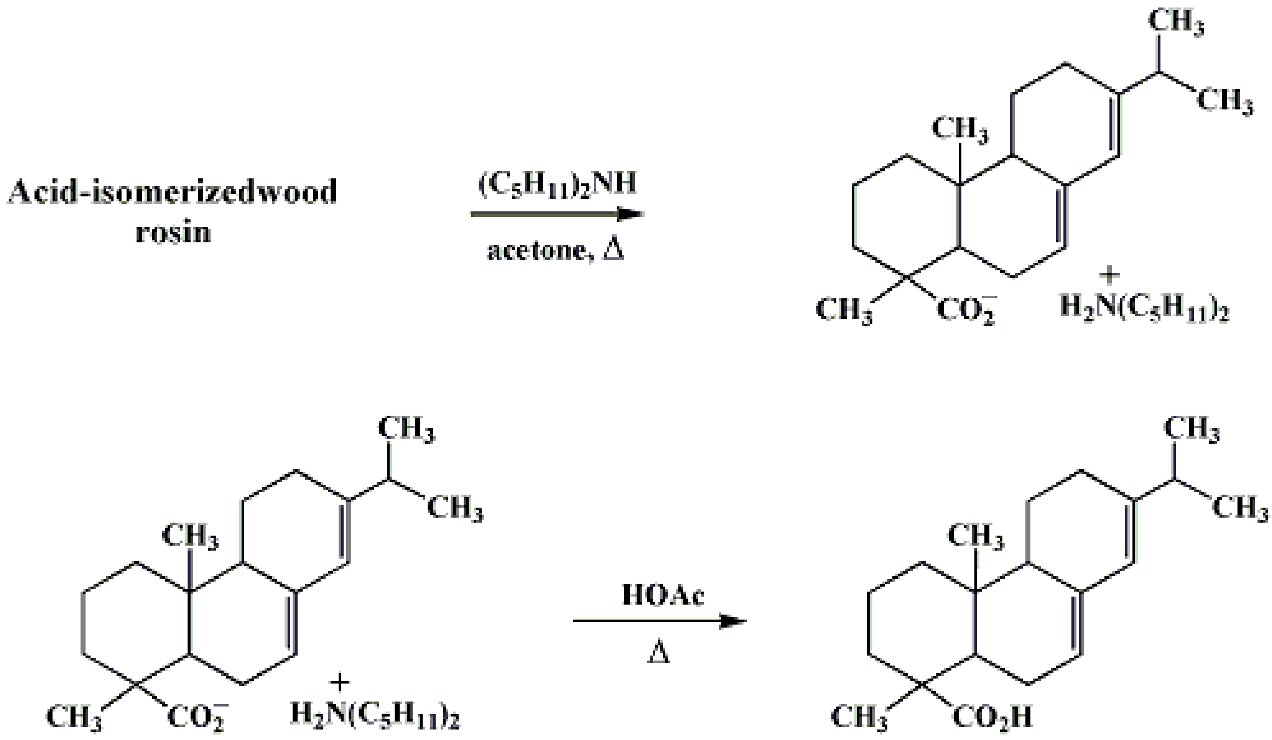
Organic Syntheses, CV 4, 1

ABIETIC ACID



Submitted by G. C. Harris and T. F. Sanderson[1].
Checked by R. T. Arnold and K. L. Lindsay.

1. Procedure

In a 2-l. round-bottomed flask fitted with a 35-cm. reflux condenser are placed 250 g. (0.74 mole) of N-grade wood rosin (Note 1), 740 ml. of 95% ethanol, and 42 ml. of hydrochloric acid (sp. gr. 1.19). A stream of carbon dioxide is passed over the surface of the solution by means of a glass tube which extends downward through the condenser during this reaction (Note 2). The mixture is boiled under reflux for 2 hours (Note 3). At the end of this time, the ethanol and acid are removed by steam distillation and the water is decanted. The residue is cooled to room temperature and dissolved in 1 l. of ether. The ether solution is extracted with water and dried over 200 g. of anhydrous sodium sulfate. The bulk of the ether is evaporated on the steam bath, and the last traces are removed by fusing the rosin over a free flame and under a vacuum furnished by a water aspirator. The molten rosin, blanketed continuously with carbon dioxide, is most conveniently handled by being poured into a paper boat; yield 245 g.; $[\alpha]_D^{24}$ −35° (Note 4).

The isomerized rosin, 245 g. (0.72 mole) (Note 1), is placed in a 1-l. Erlenmeyer flask and dissolved in 375 ml. of acetone by heating the mixture on a steam bath. To this solution, at incipient boiling, is added slowly and with vigorous agitation (Note 5) 127 g. (0.81 mole) of diamylamine[2] (Note 6). Upon cooling to room temperature, crystals appear in the form of rosettes. The mass is agitated, cooled well in an ice bath, and filtered by suction. The crystalline salt is washed on a Büchner funnel with 150 ml. of acetone and dried in a

vacuum oven at 50° for 1 hour. The optical rotation of this material is $[\alpha]_D^{24}$ −18° (Note 4). The solid is recrystallized four times from acetone. Each time a sufficient quantity (20 ml. per g.) of acetone is used to obtain complete solution, and the solvent is evaporated until incipient precipitation of the salt occurs. The yield of product is 118 g.; $[\alpha]_D^{24}$ −60° (Note 4). An additional 29 g. of product, having the same rotation, can be recovered from filtrates of the previous crystallizations.

The amine salt (147 g.) is placed in a 4-l. Erlenmeyer flask and dissolved in 1 l. of 95% ethanol by heating the mixture on a steam bath. To the solution, which has been cooled to room temperature (Note 7), is added 39 g. (35.8 ml.) of glacial acetic acid, and the solution is stirred. Water (900 ml.) is added cautiously at first and with vigorous agitation until crystals of abietic acid begin to appear; the remainder of the water is then added more rapidly. The abietic acid is collected on a Büchner funnel (Note 8) and washed with water until the acetic acid has been removed completely as indicated by tests with indicator paper. Recrystallization can be effected by dissolving the crude product in 700 ml. of 95% ethanol, adding 600 ml. of water as described above, and cooling the solution. The yield of abietic acid is 98 g. (40% based on the weight of isomerized rosin; $[\alpha]_D^{24}$ −106° (Note 4) and (Note 9). The ultraviolet absorption spectrum shows a maximum at 241 m•; α = 77.0 (Note 10).

2. Notes

1. The calculation of molar quantities is based on an acid number of 166 for N-grade wood rosin as obtained from Hercules Powder Company, Wilmington, Delaware. Acid number is the number of milligrams of potassium hydroxide required to neutralize 1 g. of sample.
2. Blanketing the rosin in solution or in the molten state with carbon dioxide serves to keep it out of contact with air to avoid oxidation.
3. The maximum negative optical rotation, $[\alpha]_D^{24}$ −35°, is obtained with a minimum reflux time of 2 hours.
4. Rotations are reported as those of 1% solutions in absolute ethanol.
5. The addition of the amine to the hot solution is necessary for the formation of the salt. However, it must be done slowly and with rapid stirring because of the resulting vigorous exothermic reaction.
6. Commercial diamylamine, a mixture of isomers, purchased from Sharples Chemicals Company, Philadelphia, Pennsylvania, was employed.
7. The acid is added to a cooled solution of the salt in ethanol to minimize the chance for isomerization of the liberated abietic acid.
8. An early filtration is desirable for the purpose of removing the abietic acid from the acidic solution where isomerization can take place. Washing with a large volume of water and recrystallizing assures the complete removal of acetic acid.
9. The pure acid is dried in a vacuum desiccator over sodium hydroxide or calcium sulfate and stored in an oxygen-free atmosphere. Undue exposure to higher temperatures will result in isomerization, and contact with oxygen will result in oxidation.
10. The absorption spectrum data were obtained from measurements made with a Beckman Ultraviolet Spectrophotometer. The formulas employed in making the

calculations use the term α, specific absorption coefficient. $\alpha = \log_{10} I_0/I/cl$ where I_0 = intensity of radiation transmitted by the solvent; I = intensity of radiation transmitted by the solution; c = concentration of solute in grams per liter; l = length in centimeters of solution through which the radiation passes.

3. Discussion

Abietic acid has usually been prepared[2] from rosin through the acid sodium salt ($3C_{20}H_{30}O_2 \cdot C_{19}H_{29}CO_2Na$) with the subsequent formation and recrystallization of the diamylamine salt. The acid is regenerated from the pure salt by decomposition of the latter with a weak acid such as acetic acid. In addition, it has been purified[3] through the potassium, piperidine, and brucine salts, as well as through abietic anhydride and trityl abietate. The acid is regenerated from the pure salts by decomposition of the latter with a weak acid such as acetic acid, and from the pure acid derivatives by treatment with potassium hydroxide.

Two improvements have been introduced in the first method[2] by the procedure described above: (1) the abietic content of the rosin is increased by isomerization, and (2) a much better recovery of acid is obtained by applying the amine salt technique directly to the isomerized rosin, thus eliminating the step involving the acid sodium salt.

References and Notes

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2. Palkin and Harris, *J. Am. Chem. Soc.*, **56**, 1935 (1934).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium sulfate (7757-82-6)

oxygen (7782-44-7)

carbon dioxide (124-38-9)

calcium sulfate (7778-18-9)

acetone (67-64-1)

potassium hydroxide (1310-58-3)

piperidine (110-89-4)

potassium (7440-09-7)

brucine

ABIETIC ACID (514-10-3)

diamylamine (2050-92-2)

abietic anhydride

trityl abietate

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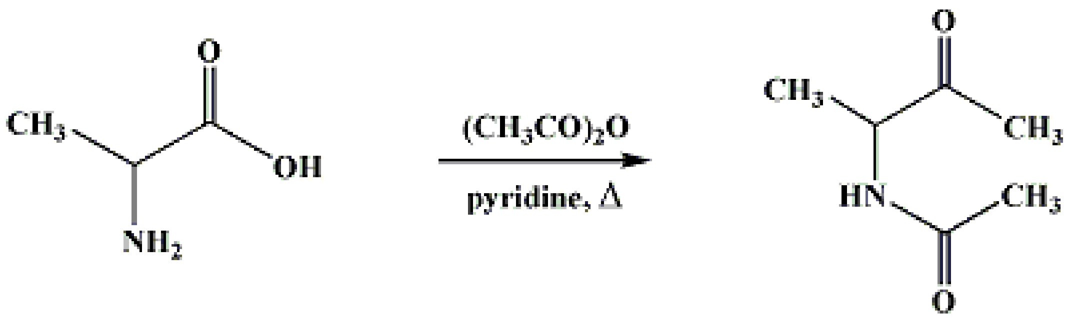
Organic Syntheses, CV 4, 5

3-ACETAMIDO-2-BUTANONE

[2-Butanone, 3-acetamido-]



Submitted by Richard H. Wiley and O. H. Borum[1].
Checked by R. S. Schreiber and B. D. Aspergren.

1. Procedure

A mixture of 156.6 g. (159 ml., 1.98 moles) of pyridine (Note 1), 239.9 g. (224 ml., 2.35 moles) of acetic anhydride (Note 2), and 35.1 g. (0.39 mole) of vacuum-dried alanine (Note 3) and (Note 4) is heated with stirring (Note 5) on the steam bath for 6 hours after solution is complete (Note 6). The excess pyridine and acetic anhydride, and the acetic acid, are removed at reduced pressure. The residue is distilled through a 15-cm. column, packed with glass helices, to give 41.5–47.5 g. of crude product, boiling at 110–125°/3 mm. Refractionation gives 41–45 g. (81–88%) of 3-acetamido-2-butanone; b.p. 102–106°/2 mm.; n_D^{25} 1.4558–1.4561 (Note 7).

2. Notes

1. A commercial C.P. grade can be used. The checkers used Merck A.R. grade.
2. A commercial grade, 95% minimum assay, can be used. The checkers used Merck A.R. grade.
3. Any good commercial grade material appears to be satisfactory.
4. Reducing the molar ratio of pyridine or anhydride to the amino acid reduces the yield.
5. Without stirring the yield is 46%.
6. With other amino acids, notably glycine and sarcosine, it is necessary to reflux the reactants 1–6 hours.
7. The checkers found it necessary to heat the column to obtain the maximum available product.

3. Discussion

This method, an adaptation of a previously described procedure,[2,3,4] has been used

with a variety of amino acids and anhydrides to give the following products: 1-phenyl-1-propionamido-2-butanone (75%);[5] acetamidoacetylacetone (60%);[5] N-methylacetamidoacetone;[6] 1-phenyl-2-acetamido-3-butanone (79%);[7] 1-phenyl-2-propionamido-3-pentanone (41%);[7] 1-phenyl-2-butyramido-3-hexanone (27%);[7] α-benzamidopropiophenone (42%);[7] α-benzamido-β-phenylpropiophenone (44%);[7] 1-phenyl-1-acetamidoacetone (72–90%);[8,9] 1-phenyl-1-benzamidoacetone (65%);[8] 1-phenyl-2-benzamido-3-butanone (78%);[8] 3-benzamido-2-butanone (65–88%);[8] and 3-acetamido-5-methyl-2-hexanone (73%).[10]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 27

References and Notes

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2. Dakin and West, *J. Biol. Chem.*, **78**, 91, 757 (1928).
3. Levene and Steiger, *J. Biol. Chem.*, **74**, 689 (1927); **79**, 95 (1928).
4. Wiley, *J. Org. Chem.*, **12**, 43 (1947).
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9. Rondestvedt, Manning, and Tabibian, *J. Am. Chem. Soc.*, **72**, 3183 (1950).
10. Borum, Ph.D. Thesis, University of North Carolina, 1949.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

acetic acid (64-19-7)

acetic anhydride (108-24-7)

alanine (56-41-7)

pyridine (110-86-1)

sarcosine (107-97-1)

Glycine (513-29-1)

3-Acetamido-2-butanone, 2-Butanone, 3-acetamido- (6628-81-5)

1-phenyl-1-propionamido-2-butanone

acetamidoacetylacetone

N-methylacetamidoacetone

1-phenyl-2-acetamido-3-butanone

1-phenyl-2-propionamido-3-pentanone

1-phenyl-2-butyramido-3-hexanone

α-benzamidopropiophenone

α-benzamido-β-phenylpropiophenone

1-phenyl-1-acetamidoacetone

1-phenyl-1-benzamidoacetone

1-phenyl-2-benzamido-3-butanone

3-benzamido-2-butanone

3-acetamido-5-methyl-2-hexanone

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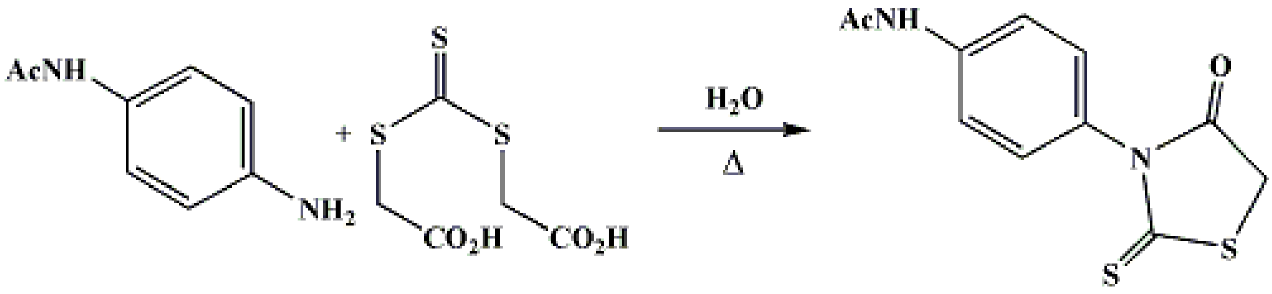
Organic Syntheses, CV 4, 6

N-(*p*-ACETYLAMINOPHENYL)RHODANINE

[Rhodanine, 3-(*p*-acetamidophenyl)-]



Submitted by R. E. Strube[1]
Checked by John D. Roberts and Stanley L. Manatt.

1. Procedure

In a 2-l. round-bottomed flask fitted with a mechanical stirrer and a reflux condenser are placed 30.0 g. (0.20 mole) of *p*-aminoacetanilide (Note 1) and 400 ml. of water. The mixture is heated on a steam bath with stirring, and to the clear solution is added at once a hot solution of 45.2 g. (0.20 mole) of trithiocarbodiglycolic acid (p. 967) in 500 ml. of water. Heating and stirring are continued for 5 hours (Note 2). The steam bath is then replaced by an ice bath, and the reaction mixture is cooled to 20–25°. The precipitate is removed by suction filtration. The solid is transferred to a 500-ml. Erlenmeyer flask containing 200 ml. of water. The mixture is heated on the steam bath to 70–75° while the lumps are crushed by a glass rod to obtain a homogeneous mixture. The mixture is filtered with suction while hot, and the flask is cleaned by rinsing it with small amounts of hot water. The solid on the filter is sucked as dry as possible and then transferred to a 2-l. round-bottomed flask fitted with a reflux condenser. Glacial acetic acid (1.5 l.) is added and the mixture is heated in an oil bath to vigorous reflux for 5 minutes (Note 3). A small amount of solid does not dissolve, and this is removed by filtration while hot (Note 4). The filtrate is stirred mechanically and cooled to 15–20° by an ice bath and kept at this temperature for 1 hour. The slightly yellow crystals are collected by suction filtration, washed successively with 25 ml. of glacial acetic acid, 100 ml. of ethanol, and 100 ml. of ether. The yield of air-dried material is 26–28 g. (49–53% yield). The compound decomposes on heating above 240° (Note 5).

2. Notes

1. *p*-Aminoacetanilide (white label) supplied by Eastman Kodak Company was used.
2. Within 10 minutes a precipitate is formed; the greater part of the reaction product is present after 2 hours' heating.
3. The purification should be carried out in a hood, since gas escapes during the heating and hot acetic acid is irritating to the eyes. The checkers used a 2-l. heating mantle instead of an oil bath.
4. The filtration of the hot acetic acid solution should be done with care. The flask was surrounded by a towel and rubber gloves were worn. The filtration can best be done in

two steps. Approximately half of the hot acetic acid solution is filtered through a large, fluted filter paper; the other half is heated again to reflux and then filtered through another fluted filter paper. Filtration through a steam-heated Büchner funnel may sometimes be troublesome, since the suction accelerates crystallization causing plugging of the funnel stem.

5. Analytical values: Calcd. for $C_{11}H_{10}N_2O_2S_2$: C, 49.62; H, 3.78; N, 10.52; S, 24.08. Found: C, 49.76; H, 3.76; N, 10.36; S, 24.07.

3. Discussion

This procedure is based on the method of Holmberg[2] for preparing N-substituted rhodanines. The synthesis of N-(*p*-acetylaminophenyl)rhodanine has not yet been reported in the literature.

References and Notes

1. The Upjohn Company, Kalamazoo, Michigan.
2. Holmberg, *J. prakt. Chem.*, **81**, 451 (1910).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

trithiocarbodiglycolic acid

ethanol (64-17-5)

acetic acid (64-19-7)

ether (60-29-7)

N-(p-ACETYLAMINOPHENYL)RHODANINE, Rhodanine, 3-(p-acetamidophenyl)- (53663-36-8)

p-aminoacetanilide (122-80-5)

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Organic Syntheses, CV 4, 8

9-ACETYLANTHRACENE

[Ketone, 9-anthryl methyl]

Submitted by Charles Merritt, Jr. and Charles E. Braun[1].
Checked by William S. Johnson and Ralph F. Hirschmann.

1. Procedure

Fifty grams (0.28 mole) of purified anthracene (Note 1) is suspended in 320 ml. of anhydrous benzene and 120 ml. (1.68 moles) of reagent grade acetyl chloride contained in a 1-l. three-necked flask. The flask is fitted with a thermometer which is immersed in the suspension, a calcium chloride drying tube, an efficient motor-driven sealed stirrer, and a rubber addition tube to which a 125-ml. Erlenmeyer flask containing 75 g. (0.56 mole) of anhydrous aluminum chloride is attached.[2]

The flask is surrounded by an ice-calcium chloride cooling mixture, and the aluminum chloride is added in small portions from the Erlenmeyer flask at such a rate that the temperature is maintained between –5° and 0°. After the addition is complete, the mixture is stirred for an additional 30 minutes, and the temperature is then allowed to rise slowly to 10°. The red complex which forms is collected with suction on a sintered-glass funnel and washed thoroughly with dry benzene (Note 2). The complex is added in small portions by means of a spatula with stirring to a 600-ml. beaker nearly filled with a mixture of ice and concentrated hydrochloric acid. The mixture is then allowed to come to room temperature, and the crude ketone is collected on a suction filter.

The product is digested under reflux for about 20 minutes with 100–150 ml. of boiling 95% ethanol. The suspension (Note 3) is cooled quickly almost to room temperature and filtered rapidly with suction to remove any anthracene. The 9-acetylanthracene, which separates in the filtrate, is redissolved by heating and allowed to crystallize by slowly cooling the solution (finally to 0–5° in an icebox) (Note 4). A second recrystallization from 95% ethanol yields 35–37 g. (57–60%) of light-tan granules of 9-acetylanthracene melting at 75–76° (Note 5).

2. Notes

1. The Eastman Kodak Company grade melting at 214–215° is satisfactory. Technical grade anthracene can be purified by codistillation with ethylene glycol. (See Fieser, *Experiments in Organic Chemistry*, 2nd ed., p. 345, footnote 13, D. C. Heath and Company, 1941.)
2. A regular Büchner funnel fitted with a mat of glass wool can be employed successfully. The filtration should be carried out as rapidly as possible, and the hydrolysis should be performed immediately thereafter if the humidity is high to minimize reaction on the funnel.
3. Most of the unreacted anthracene remains undissolved as a brown fluffy residue.
4. If the product has a tendency to separate as an oil, the addition of more solvent followed by heating to redissolve the material and subsequent cooling will usually yield a crystalline product.
5. Lüttringhaus and Kacer[3] reported the melting point as ca. 80°, but May and Mosettig[4] have found it to be 74–76°.

3. Discussion

The procedure described is essentially that of Lüttringhaus and Kacer[3] except for the method of isolation of the product, which is due to May.[5]

References and Notes

1. University of Vermont, Burlington, Vermont.
2. Fieser, *Experiments in Organic Chemistry*, 3rd ed., p. 265, Fig. 46.4, D. C. Heath and Company, 1955.
3. Lüttringhaus and Kacer, Ger. pat. 493,688 [*C. A.*, **24**, 2757 (1930)].
4. May and Mosettig, *J. Am. Chem. Soc.*, **70**, 686 (1948).
5. May, Private communication.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

acetyl chloride (75-36-5)

aluminum chloride (3495-54-3)

ethylene glycol (107-21-1)

anthracene (120-12-7)

9-Acetylanthracene, Ketone, 9-anthryl methyl (784-04-3)

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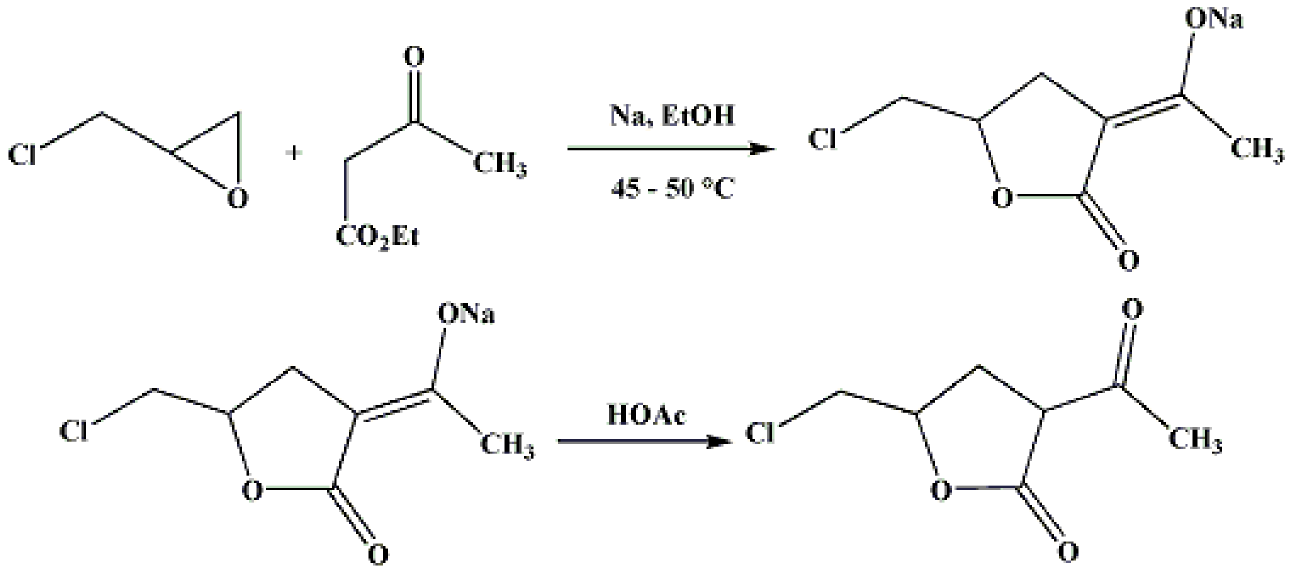
α-ACETYL-δ-CHLORO-γ-VALEROLACTONE

[Valeric acid, 2-acetyl-5-chloro-4-hydroxy-, γ-lactone]



Submitted by G. D. Zuidema, E. van Tamelen, and G. Van Zyl[1].
Checked by William S. Johnson and Herbert I. Hadler.

1. Procedure

A 1-l. three-necked round-bottomed flask is equipped with a sealed stirrer, a thermometer, a dropping funnel, and an efficient condenser, the upper end of which is protected with a calcium chloride drying tube. In this flask 23 g. (1 g. atom) of lustrous sodium (Note 1) is dissolved in 400 ml. of absolute ethanol (Note 2). The sodium is cut into about 25 pieces, and the entire amount is added at one time. It may be necessary to cool the flask in a cold-water bath if the reaction becomes violent. When all the sodium has dissolved, the solution is cooled to 50° and 130 g. (127 ml., 1 mole) of ethyl acetoacetate (Note 3) is added dropwise while the temperature is maintained between 45° and 50°. The resulting solution is cooled to about 35°, and 92.5 g. (78.4 ml., 1 mole) of epichlorohydrin (Note 4) is added dropwise with stirring over a period of 20 minutes. The temperature is then raised to 45° and is kept at 45–50° for 18 hours. The clear red-orange solution is cooled to 15°, and chilled glacial acetic acid (60–65 ml.) is added with stirring until the solution is just acid to litmus; a mush of sodium acetate crystals precipitates. The dropping funnel is replaced by a capillary tube, and the condenser is set for distillation. About three-fourths of the ethanol is removed under reduced pressure while air is bubbled into the mixture through the capillary tube (Note 5). Care is taken that the internal temperature does not exceed 100°.

The mushy residue is shaken with 250–300 ml. of water until the sodium acetate dissolves. The oily layer of lactone is separated, and the aqueous phase is extracted with two 100-ml. portions of ether. The combined oil and ether extracts are washed with 150 ml. of water and dried overnight over anhydrous sodium sulfate. The ether is removed under reduced pressure, and the product is distilled from a modified Claisen flask. The fraction boiling at 160–170°/11 mm. is collected; refractionation yields 107–114 g. (61–64%) of product boiling at 164–168°/11 mm. or 151–156°/8 mm.; n_D^{25} 1.4815–1.4830 (Note 6) and (Note 7).

2. Notes

1. The sodium must be present in an equivalent amount for best results. When 0.2 g. atom of sodium was used, the yield was only 10%.
2. It is necessary to maintain strictly anhydrous conditions in this reaction. The apparatus should be carefully predried and the absolute ethanol freshly prepared either by the diethyl phthalate method[2] or by the magnesium ethoxide method.[3]
3. Eastman Kodak Company white label quality ethyl acetoacetate (b.p. 78–79°/11 mm.) was used.
4. Epichlorohydrin may be prepared from glycerol-α,γ-dichlorohydrin.[4] It is also commercially available.
5. Unless this precaution is taken, there is considerable bumping due to the presence of the solid sodium acetate in the mixture.
6. The product may become slightly colored upon standing.
7. This reaction is typical of those between the following epoxides and ethyl acetoacetate:

Epoxide	Boiling Point of Product	% Yield of Product
Butadiene monoxide	148–151°/32 mm.	54
Propylene oxide	138–141°/26 mm.	49
Styrene oxide	164–167°/3 mm.	60
Ethyl glycidyl ether	160–163°/14–15 mm.	46
Phenyl glycidyl ether	195–197°/1 mm.	77

3. Discussion

α-Acetyl-δ-chloro-γ-valerolactone has been prepared only by the condensation of epichlorohydrin with ethyl acetoacetate. The preparation described is based on the method of Traube and Lehman.[5]

References and Notes

1. Hope College, Holland, Michigan.
2. Manske, *J. Am. Chem. Soc.*, **53**, 1106 (1931), footnote 9.
3. Lund and Bjerrum, *Ber.*, **64**, 210 (1931). Fieser, *Experiments in Organic Chemistry*, 3rd ed., p. 286, D. C. Heath and Company, Boston, Massachusetts, 1955.
4. *Org. Syntheses Coll. Vol.* **1**, 233 (1941).
5. Traube and Lehman, *Ber.*, **34**, 1980 (1901).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

glycerol-α,γ-dichlorohydrin

ethanol (64-17-5)

acetic acid (64-19-7)

ether (60-29-7)

sodium acetate (127-09-3)

Epichlorohydrin (106-89-8)

sodium sulfate (7757-82-6)

propylene oxide (75-56-9)

sodium (13966-32-0)

Ethyl acetoacetate (141-97-9)

Styrene oxide (96-09-3)

α-Acetyl-δ-chloro-γ-valerolactone, Valeric acid, 2-acetyl-5-chloro-4-hydroxy-, γ-lactone (3154-75-4)

Butadiene monoxide (930-22-3)

Ethyl glycidyl ether (4016-11-9)

Phenyl glycidyl ether (122-60-1)

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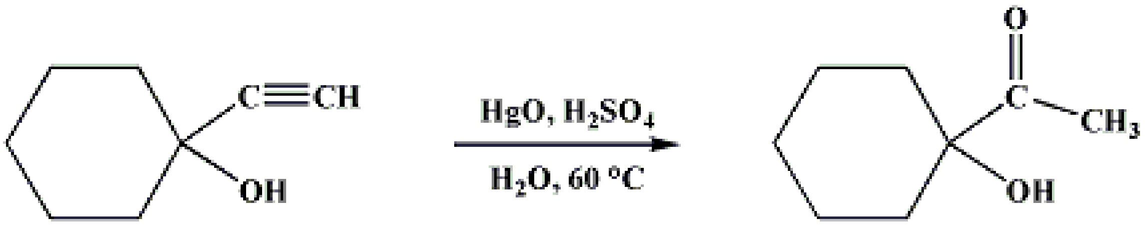
1-ACETYLCYCLOHEXANOL

[Ketone, 1-hydroxycyclohexyl methyl]



Submitted by Gardner W. Stacy and Richard A. Mikulec[1].
Checked by John C. Sheehan, George A. Mortimer, and Norman A. Nelson.

1. Procedure

In a 1-l. three-necked round-bottomed flask, equipped with a sealed stirrer, a reflux condenser, a thermometer, and a dropping funnel, is dissolved 5 g. of mercuric oxide (Note 1) in a solution of 8 ml. of concentrated sulfuric acid and 190 ml. of water. The solution is warmed to 60°, and 49.7 g. (0.40 mole) of 1-ethynylcyclohexanol (Note 2) is added dropwise over a period of 1.5 hours. After the addition has been completed, the reaction mixture is stirred at 60° for an additional 10 minutes and allowed to cool. The green organic layer which settles is taken up in 150 ml. of ether, and the aqueous layer is extracted with four 50-ml. portions of ether (Note 3). The combined ethereal extracts are washed with 100 ml. of saturated sodium chloride solution (Note 4) and dried over anhydrous sodium sulfate. The drying agent is removed, the ether is evaporated, and the residue is distilled under reduced pressure through a 15-cm. column packed with glass helices. The 1-acetylcyclohexanol is collected at 92–94°/15 mm. as a colorless liquid, n_D^{25} 1.4670, d_4^{25} 1.0248 (Note 5). The yield is 37–38 g. (65–67%).

2. Notes

1. Mallinckrodt mercuric oxide red (analytical reagent or N.F. 1x grade) was used.
2. 1-Ethynylcyclohexanol is available commercially. It may be prepared as reported by Saunders.[2]
3. To facilitate subsequent extractions, the solid material remaining after separation of as much of the aqueous phase as possible should be removed by gentle suction filtration and washed with 25 ml. of ether.
4. The sodium chloride solution removes the green color from the ether extract, leaving a yellow solution.
5. The checkers found b.p. 100°/21 mm., n_D^{25} 1.4662–1.4665, d_4^{25} 1.0235–

1.0238. Others have reported b.p. 92–94°/12 mm., d_0^{20} 1.0256;[3] b.p. 91°/11 mm., n_D^{11} 1.4726, d_4^{11} 1.1033;[4] b.p. 88.0–88.6°/12 mm., n_D^{28} 1.4712.[5] Establishing a criterion for the purity of the product is of particular importance because of the known tendency of ethynylcarbinols to undergo rearrangement.[5,6] The authors have reported that consecutive small fractions of the distillate possess a constant boiling point and refractive index. Furthermore, representative fractions, treated with periodic acid and subsequently with 2,4-dinitrophenylhydrazine, give cyclohexanone 2,4-dinitrophenylhydrazone in 83% over-all yield in a high state of purity.

3. Discussion

1-Acetylcyclohexanol has been prepared by the hydrolysis of 1-bromo-1-acetylcyclohexane[3] and of 1-acetoxy-1-acetylcyclohexane oxime,[7] by the hydration of 1-ethynylcyclohexanol,[4,5,8,9,10,11,12] by the treatment of 1-hydroxycyclohexanecarboxylic acid with methyllithium[13,14] and by the hydrolysis of 1-(isopropoxyethoxy)-1-(1-iminoethyl)cyclohexane.[15] and 1-(2-tetrahydropyranoxy)-1-(1-iminoethyl)cyclohexane.[16] The present procedure is based upon that of Stacy and Mikulec for the preparation of 1-acetylcyclopentanol.[6]

References and Notes

1. State College of Washington, Pullman, Washington.
2. *Org. Syntheses Coll. Vol.* **3**, 416 (1955).
3. Favorskii, *J. Russ. Phys. Chem. Soc.*, **44**, 1339 (1912) [*C. A.*, **7**, 984 (1913)].
4. Locquin and Wouseng, *Compt. rend.*, **176**, 516 (1923).
5. Newman, *J. Am. Chem. Soc.*, **75**, 4740 (1953).
6. Stacy and Mikulec, *J. Am. Chem. Soc.*, **76**, 524 (1954).
7. Wallach, *Ann.*, **389**, 191 (1912).
8. Bergmann, Brit. pat. 640,477 [*C. A.*, **45**, 1622 (1951)]; U. S. pat. 2,560,921 [*C. A.*, **46**, 3072 (1952)].
9. Stacy and Hainley, *J. Am. Chem. Soc.*, **73**, 5911 (1951).
10. Newman (to Ohio State University Research Foundation), U. S. pat. 2,853,520 [*C. A.*, **54**, 345 (1960)].
11. Papa, Ginsberg, and Villani, *J. Am. Chem. Soc.*, **76**, 4441 (1954).
12. Hennion and Watson, *J. Org. Chem.*, **23**, 656 (1958).
13. Billimoria and MacLagan, *Nature*, **167**, 81 (1951); *J. Chem. Soc.*, **1951**, 3067.
14. MacLagan and Billimoria, Brit. pat. 742,571 [*C. A.*, **50**, 16845 (1956)].
15. Tchoubar, *Compt. rend.*, **237**, 1006 (1953).
16. Elphimoff-Felkin, *Bull. soc. chim. France*, **1955**, 784.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

ether (60-29-7)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

mercuric oxide (21908-53-2)

2,4-Dinitrophenylhydrazine (119-26-6)

1-Ethynylcyclohexanol (78-27-3)

1-Acetylcyclohexanol, Ketone, 1-hydroxycyclohexyl methyl (1123-27-9)

periodic acid

cyclohexanone 2,4-dinitrophenylhydrazone (1589-62-4)

1-bromo-1-acetylcyclohexane

1-acetoxy-1-acetylcyclohexane oxime

1-hydroxycyclohexanecarboxylic acid

Methyllithium (917-54-4)

1-(isopropoxyethoxy)-1-(1-iminoethyl)cyclohexane

1-(2-tetrahydropyranoxy)-1-(1-iminoethyl)cyclohexane

1-acetylcyclopentanol

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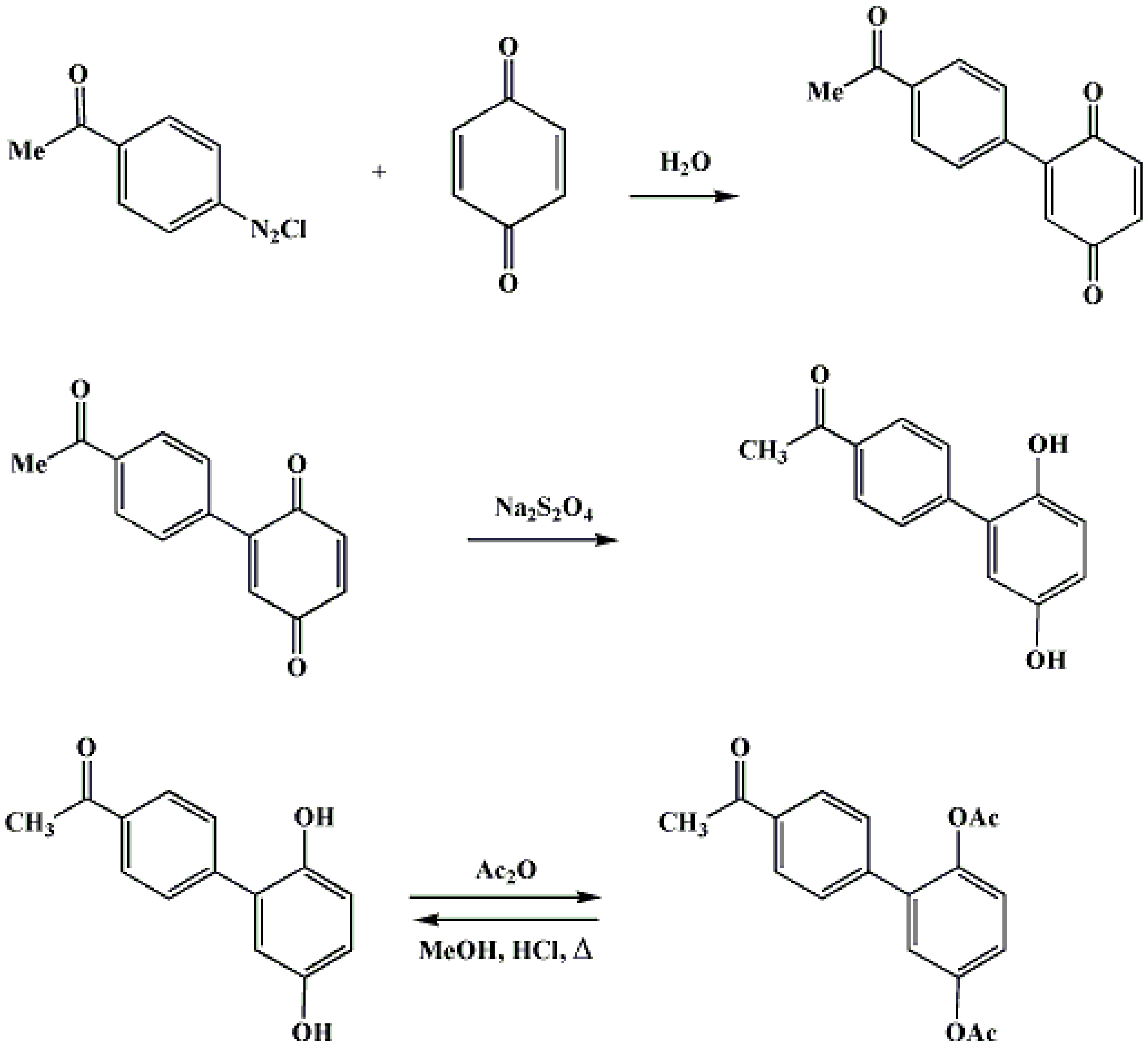
2-*p*-ACETYLPHENYLHYDROQUINONE

[Acetophenone, 4'-(2,5-dihydroxyphenyl)-]



Submitted by George A. Reynolds and J. A. VanAllan[1].
Checked by R. S. Schreiber and A. H. Nathan.

1. Procedure

In a 500-ml. beaker equipped with a mechanical stirrer are placed 27 g. (0.2 mole) of *p*-aminoacetophenone (Note 1), 100 g. of chopped ice, and 53 ml. of concentrated hydrochloric acid (sp. gr. 1.19). To the stirred mixture is added, over a period of 5 minutes, a solution of 13.8 g. (0.2 mole) of sodium nitrite dissolved in 75 ml. of water. The stirring is continued for 15 minutes, during which all the insoluble amine hydrochloride reacts to form the soluble diazonium compound (Note 2).

In a 4-l. beaker, equipped with a high-speed stirrer (Note 3), are placed 20 g. (0.185 mole) of

quinone (Note 4), 34 g. (0.4 mole) of sodium bicarbonate, 50 g. of chopped ice, and 500 ml. of water. About 10 ml. of the above diazonium salt solution is added (Note 5). After the frothing has subsided (Note 6), the diazonium salt solution is added in 10- to 20-ml. portions over a period of about an hour (Note 7). The temperature of the reaction mixture is kept below 15° during this period by the addition of ice. After the diazonium salt solution has been added, the mixture is allowed to warm to room temperature, and the stirring is continued for an additional hour. The precipitate of 2-*p*-acetylphenylquinone is collected on a Büchner funnel and washed thoroughly with approximately 1 l. of water. The yield of crude yellow-brown solid is 40–41 g. (96–98%). The melting point ranges from 125–135° to 134–136° (Note 8).

The crude quinone is dissolved in 250 ml. of chloroform (Note 9) and added to a solution of 40 g. of sodium hydrosulfite in 300 ml. of water. The mixture is shaken for 10 minutes, and the light-tan 2-*p*-acetylphenylhydroquinone which precipitates from solution is collected on a Büchner funnel and dried. The yield of crude hydroquinone is 32–37 g. (78–92%). The melting point ranges from 175–180° to 184–194° (Note 10).

A suspension of 35 g. (0.153 mole) of 2-*p*-acetylphenylhydroquinone in 77 ml. of acetic anhydride is treated with 0.5 ml. of concentrated sulfuric acid (sp. gr. 1.84). The hydroquinone goes into solution immediately with the evolution of much heat. The dark-colored solution is allowed to stand at room temperature overnight; then it is poured into 400 ml. of water. The acetylated material is collected by suction filtration and dried. The crude 2-*p*-acetylphenylhydroquinone diacetate is distilled at reduced pressure (b.p. 236–241°/1 mm. or 182–190°/0.1 mm.), and the hot distillate is poured into 20 ml. of *n*-butyl alcohol (Note 11). The product immediately separates as a colorless, crystalline mass, which is collected by suction filtration and dried. The yield is 32–35 g. (67–73%), m.p. 104–105°.

To a 300-ml. three-necked round-bottomed flask, equipped with a sealed stirrer, a condenser, and a gas inlet tube, is added a solution of 34 g. (0.11 mole) of 2-*p*-acetylphenylhydroquinone diacetate in 140 ml. of hot methanol. The solution is cooled to room temperature, causing some of the hydroquinone diacetate to crystallize. A slow stream of nitrogen is passed through the suspension, and 70 ml. of methanol containing 6.1 g. of anhydrous hydrogen chloride is added. The reaction mixture is stirred at room temperature for 2 hours under nitrogen, during which period the hydroquinone diacetate gradually dissolves. The pale yellow solution is poured onto 500 g. of chopped ice, and the colorless or faintly yellowish solid is collected by suction filtration and dried. The yield of *p*-acetylphenylhydroquinone melting at 193–194° is 24.8 g. (quantitative). The over-all yield of product based on quinone is 50–66%.

2. Notes

1. The purest grade of *p*-aminoacetophenone supplied by the Eastman Kodak Company was used without further purification.
2. This reaction has been successfully carried out on a 3-mole scale.
3. A "Lightnin" mixer (manufactured by the Mixing Equipment Company, Rochester, N. Y.) equipped with a propeller stirrer was used. If rapid stirring is not maintained, the reaction does not go to completion.
4. The checkers used a practical grade of quinone obtainable from the Eastman Kodak Company.
5. If nitrogen is not evolved immediately, the reaction may be initiated by the addition of a small amount of hydroquinone.

6. If the foaming becomes too violent, a few drops of octyl alcohol are added.
7. The checkers found it convenient to add the diazonium salt solution slowly from a dropping funnel. The time of addition was 25–45 minutes.
8. Recrystallization from butanol gives material melting at 139–140°. The pure substance is reported to melt at 152–153°.[2]
9. Ethanol can also be used as a solvent but has the disadvantage of more readily dissolving the hydroquinone, thus making it necessary to evaporate the solution nearly to dryness.
10. It is difficult to purify the crude hydroquinone by recrystallization; therefore the remainder of the procedure is recommended in order to obtain a highly purified product.
11. The checkers found it convenient to crystallize the viscous distillate from 125 ml. of methanol by chilling a hot solution in the refrigerator overnight. A small second crop amounting to about 2 g. may also be obtained by concentration of the mother liquors.

3. Discussion

This procedure is a modification of the method described for the preparation of 2-chlorophenylhydroquinone.[3] 2-*p*-Acetylphenylquinone has been prepared by carrying out the coupling in alcohol solution in the presence of sodium acetate instead of sodium bicarbonate.[2] Reduction by zinc, acetic acid, and a small amount of concentrated hydrochloric acid yielded 2-*p*-acetylphenylhydroquinone.[2]

References and Notes

1. Eastman Kodak Company, Rochester, New York.
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrogen chloride, hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

methanol (67-56-1)

acetic anhydride (108-24-7)

sodium acetate (127-09-3)

chloroform (67-66-3)

hydroquinone (123-31-9)

sodium bicarbonate (144-55-8)

nitrogen (7727-37-9)

sodium nitrite (7632-00-0)

sodium hydrosulfite (7775-14-6)

butanol, n-butyl alcohol (71-36-3)

zinc (7440-66-6)

Quinone (106-51-4)

octyl alcohol (111-87-5)

Hydroquinone diacetate (1205-91-0)

2-chlorophenylhydroquinone (117-71-5)

2-p-Acetylphenylhydroquinone, p-acetylphenylhydroquinone, Acetophenone, 4'-(2,5-dihydroxyphenyl)- (3948-13-8)

p-aminoacetophenone (99-92-3)

2-p-acetylphenylquinone

2-p-acetylphenylhydroquinone diacetate

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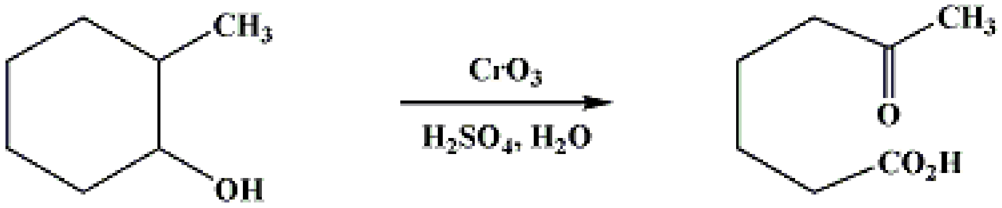
Organic Syntheses, CV 4, 19

δ-ACETYL-*n*-VALERIC ACID

[Heptanoic acid, 6-oxo-]



Submitted by J. R. Schaeffer and A. O. Snoddy[1].
Checked by Richard T. Arnold and H. W. Turner.

1. Procedure

A solution of 368 g. of 96% sulfuric acid in 664 ml. of water is cooled to room temperature and placed in a 3-l. three-necked flask provided with a mechanical stirrer, a thermometer, and a dropping funnel. To this acid solution is added 114 g. (1 mole) of 2-methylcyclohexanol (Note 1). A mixture of 220 g. (2.2 moles) of chromic oxide (Note 2) in 368 g. of 96% sulfuric acid and 664 ml. of water is added from the dropping funnel to the 2-methylcyclohexanol suspension at such a rate that the temperature of the mixture remains at 30 ± 2° (Note 3). Good agitation and an ice bath are necessary to control the temperature in this range. The mixture is stirred at 30 ± 2° for 1 hour and then at room temperature until all the chromic oxide is consumed (Note 4). The sulfuric acid solution is extracted with ether until the returns from the ether extractions fall to an insignificant amount. Approximately 10 extractions with 200-ml. portions of ether are required (Note 5). The ether extracts are combined, and the ether is removed by distillation on the steam bath. The resulting crude δ-acetyl-*n*-valeric acid is a yellow liquid with a sharp odor and amounts to about 130 g. The crude acid is purified by distillation through a 30-in. Vigreux column, using a variable take-off, a reflux ratio of 3:1, and a pressure of 1 mm. A fore-run of approximately 30 g. of material distilling up to 122°/1 mm. is obtained. The main fraction which distils at 122–123°/1 mm. is pure δ-acetyl-*n*-valeric acid and amounts to 66–79 g. (46–55%). The pure acid is a colorless crystalline hygroscopic solid which melts (sealed capillary) at 34–35° and is miscible with water in all proportions. The literature records the melting point of δ-acetyl-*n*-valeric acid as ranging from 31° to 42°.[2,3,4]

2. Notes

1. Eastman Kodak Company practical grade 2-methylcyclohexanol was used in this preparation.
2. Technical grade chromic oxide (99.5% CrO_3) in flake form was used.
3. An alcohol-Dry Ice bath is very convenient for this purpose; with this bath

only about 45 minutes is needed for the addition of the chromic oxide solution. A water-ice bath can be used, but a longer time will be required for the addition of the chromic oxide solution.

4. The chromic oxide content of the mixture at any time may be determined by titrating a test portion against standard ferrous ammonium sulfate solution. If the mixture is allowed to stand overnight at room temperature without stirring, it will be free from chromic oxide. A convenient procedure is to perform the oxidation in the afternoon and the extraction the next day.

5. A liquid-liquid continuous extractor is convenient for extracting the crude acid from the aqueous solution. With such apparatus, it is possible to extract all the crude δ-acetyl-*n*-valeric acid from the aqueous acid in 6–8 hours.

6. The fore-run and the still residue contain some δ-acetyl-*n*-valeric acid. These fractions may be combined and redistilled to yield an additional 5–10% of δ-acetyl-*n*-valeric acid, but the low cost of the starting materials and the ease of preparing the crude δ-acetyl-*n*-valeric acid scarcely justify the labor unless a considerable number of batches are being prepared.

3. Discussion

δ-Acetyl-*n*-valeric acid has been prepared by the oxidation of 1-methylcyclohexene with potassium permanganate;[5] by the oxidation of 2-methylcyclohexanone with chromic oxide and sulfuric acid,[6,7] with neutral potassium permanganate,[8] and by air in the presence of adipic acid and manganese nitrate;[9] by the reaction of methylzinc iodide on the ethyl ester of adipic acid chloride, followed by saponification of the ester so obtained;[10] by the saponification of the ethyl ester of diacetylvaleric acid;[2] by the hydrolysis of ethyl α-acetyl-δ-cyanovalerate with boiling 20% hydrochloric acid;[3] by the permanganate oxidation of 1-methyl-1,2-cyclopentanediol;[11] and by the alkaline cleavage of 2-acetylcyclopentanone.[12]

References and Notes

1. Procter and Gamble Company, Ivorydale, Ohio.
2. Perkin, *J. Chem. Soc.*, **57**, 229 (1890).
3. Derick and Hess, *J. Am. Chem. Soc.*, **40**, 551 (1918).
4. Blaise and Kohler, *Compt. rend.*, **148**, 490 (1909).
5. Wallach, *Ann.*, **329**, 371, 376 (1903).
6. Wallach, *Ann.*, **359**, 300 (1908).
7. Ruzicka, Seidel, Schinz, and Pfeiffer, *Helv. Chim. Acta*, **31**, 422 (1948).
8. Acheson, *J. Chem. Soc.*, **1956**, 4232.
9. Badische Anilin- und Soda-Fabrik, Ger. pat. 812,073 [*C. A.*, **47**, 2769 (1953)].
10. Blaise and Koehler, *Bull. soc. chim.*, [4] **7**, 222 (1910).
11. Adkins and Roebuck, *J. Am. Chem. Soc.*, **70**, 4041 (1948).
12. Hauser, Swamer, and Ringler, *J. Am. Chem. Soc.*, **70**, 4023 (1948).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethyl ester of adipic acid chloride

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ether (60-29-7)

Adipic acid (124-04-9)

potassium permanganate (7722-64-7)

ferrous ammonium sulfate (10045-89-3)

2-methylcyclohexanone (583-60-8)

Heptanoic acid, 6-oxo-, δ-ACETYL-n-VALERIC ACID (3128-07-2)

2-methylcyclohexanol (583-59-5)

chromic oxide (1308-38-9)

1-methylcyclohexene

manganese nitrate (10377-66-9)

methylzinc iodide

ethyl α-acetyl-δ-cyanovalerate

1-methyl-1,2-cyclopentanediol

2-acetylcyclopentanone (1670-46-8)

ethyl ester of diacetylvaleric acid

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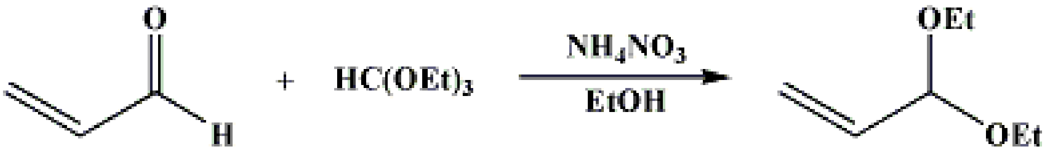
Organic Syntheses, CV 4, 21

ACROLEIN ACETAL

[Acrolein diethyl acetal]



Submitted by J. A. VanAllan[1]
Checked by T. L. Cairns and R. E. Benson.

1. Procedure

A warm solution of 3 g. of ammonium nitrate in 50 ml. of anhydrous ethanol is added to a mixture of 44 g. (52.4 ml., 0.79 mole) of acrolein and 144 g. (160 ml., 0.97 mole) of ethyl orthoformate, and the mixture is allowed to react at room temperature for 6–8 hours (Note 1). The light-red solution is filtered, 4 g. of sodium carbonate is added, and the reaction mixture is distilled from the sodium carbonate through a good column (Note 2). The fraction boiling at 120–125° is acrolein acetal and weighs 73–81 g. (72–80%); n_D^{25} 1.398–1.407 (Note 3).

2. Notes

1. Refluxing causes the formation of some resinous material. The solution remains warm for about 1.5 hours after mixing.

2. The column described by Pingert[2] is suggested.

3. This reaction appears to be of general application; crotonaldehyde diethyl acetal is formed in 68% yield; b.p. 145–147°; n_D^{25} 1.409. (In this preparation the amount of ethyl orthoformate used is reduced to exactly one equivalent since it distils at 142–143°. For this particular acetal, it is preferable to use ethyl orthosilicate according to Helferich.[3]) Tiglylaldehyde diethyl acetal is formed in 79% yield; b.p. 158–160°; n_D^{25} 1.419.

3. Discussion

These have been reviewed previously.[2,4] The procedure described above is an adaptation of a method reported in a German patent.[5] It has been claimed that the reaction of acrolein with ethanol in the presence of hydrochloric acid[2] produces a mixture of substances from which no acrolein acetal can be isolated.[6] More recently it has been reported[7] that acrolein acetal is formed in 62% yield from acrolein and

ethanol in the presence of *p*-toluenesulfonic acid.

References and Notes

1. Eastman Kodak Company, Rochester, New York.
2. *Org. Syntheses*, **25**, 1 (1945).
3. Helferich, Ger. pat. 404,256 (1924) [*Frdl.*, **14**, 228 (1921–1925)].
4. *Org. Syntheses Coll. Vol.* **2**, 17 (1943).
5. Schmidt, Ger. pat. 553,177 (1932) [*Frdl.*, **19**, 229 (1932)].
6. Hall and Stern, *Chem. & Ind. (London)*, **1950**, 775.
7. Weisblat, Magerlein, Myers, Hanze, Fairburn, and Rolfson, *J. Am. Chem. Soc.*, **75**, 5893 (1953).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

Acrolein (107-02-8)

sodium carbonate (497-19-8)

ammonium nitrate

Ethyl orthoformate

Acrolein acetal

Acrolein diethyl acetal (3054-95-3)

crotonaldehyde diethyl acetal

ethyl orthosilicate

Tiglylaldehyde diethyl acetal (51786-74-4)

p-toluenesulfonic acid (104-15-4)

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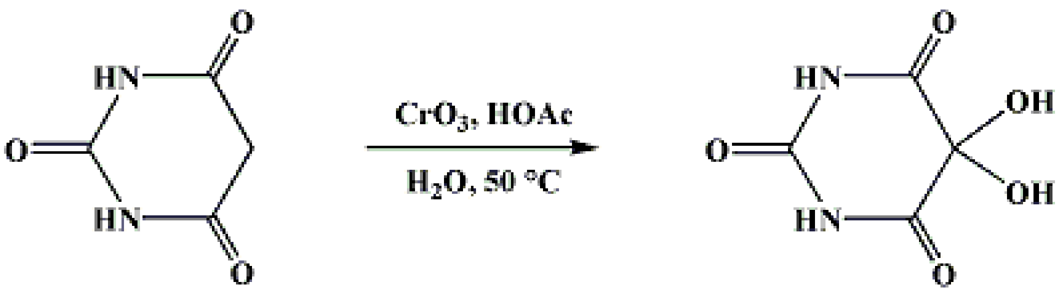
Organic Syntheses, CV 4, 23

ALLOXAN MONOHYDRATE

[Barbituric acid, 5,5-dihydroxy-]



Submitted by A. V. Holmgren and Wilhelm Wenner[1].
Checked by T. L. Cairns and R. W. Upson.

1. Procedure

In a 2-l. three-necked, round-bottomed flask with glass joints are placed 850 g. of commercial glacial acetic acid and 100 ml. of water. The flask is fitted with a stirrer. One of the side necks carries a reflux condenser and a thermometer reaching to the bottom of the flask; the other is provided with a stopper which can be replaced by a powder funnel. The flask is surrounded by a water bath. At room temperature 156 g. (1.53 moles) of 98–99% chromium trioxide (Note 1) is added, and the mixture is stirred for about 15 minutes to effect solution of the oxidizing agent.

One hundred and twenty-eight grams (1 mole) of barbituric acid is added in the course of about 25 minutes in portions approximating 15–20 g. The temperature of the mixture rises from about 25–30° at the beginning of the reaction to 50° and is held at that value until all the barbituric acid has been added (Note 2). During the addition, alloxan monohydrate begins to crystallize. The temperature of the solution is held at 50° for 25–30 minutes after completion of the addition of barbituric acid. Then the reaction slurry, which contains the major amount of alloxan monohydrate in crystalline form, is cooled to 5–10° and filtered through a 5-in. Büchner funnel fitted with a piece of filter cloth. The product is washed while still on the funnel with cold glacial acetic acid until the washings are practically colorless. In order to effect rapid drying, the acetic acid is finally washed out of the filter cake by means of 100–200 ml. of ether. The yellow alloxan monohydrate weighs 120–125 g. (75–78%) after drying; m.p. 254° (dec.). It is pure enough for most purposes (Note 3).

2. Notes

1. This amount was found to give best yields.
2. It is very important that the temperature does not rise above 50°. If the addition of barbituric acid is carried out too rapidly, the temperature rise cannot

be checked satisfactorily and the yield may drop considerably.
3. If entirely pure alloxan monohydrate is desired, this material is recrystallized according to the directions in an earlier volume of this series.[2]

3. Discussion

The methods for the preparation of alloxan have been reviewed earlier.[2] The present method is essentially that of Wenner.[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 25

References and Notes

1. Hoffmann-La Roche, Inc., Nutley, New Jersey.
2. *Org. Syntheses Coll. Vol.* **3**, 37, 39 (1955).
3. Wenner, U. S. pat. 2,445,898 [*C. A.*, **43**, 2227 (1949)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

acetic acid (64-19-7)

ether (60-29-7)

Barbituric acid (67-52-7)

chromium trioxide (1333-82-0)

Alloxan monohydrate (2244-11-3)

Alloxan (50-71-5)

Barbituric acid, 5,5-dihydroxy- (3237-50-1)

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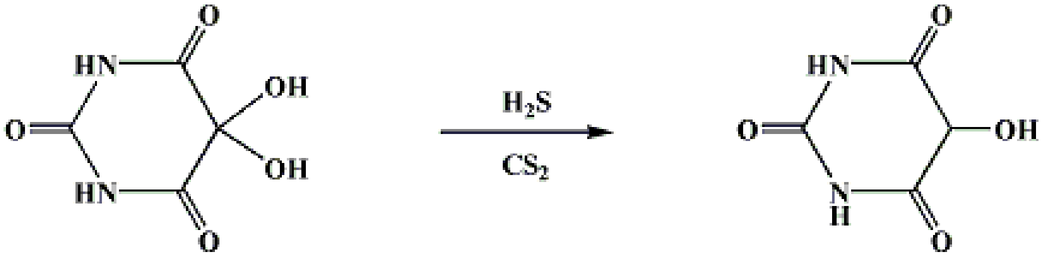
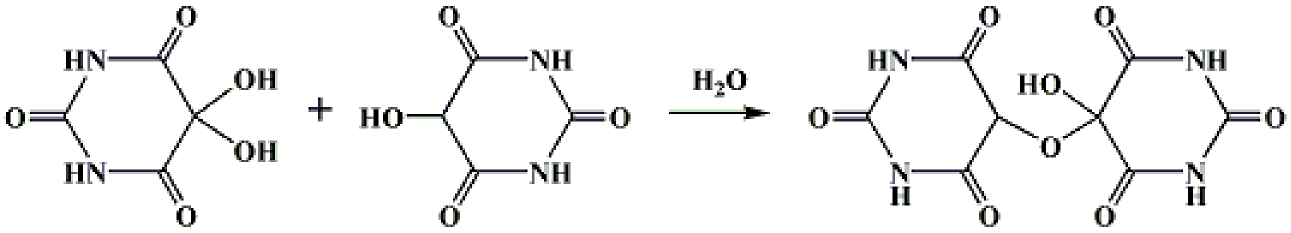
Organic Syntheses, *CV 4*, *25*

ALLOXANTIN DIHYDRATE



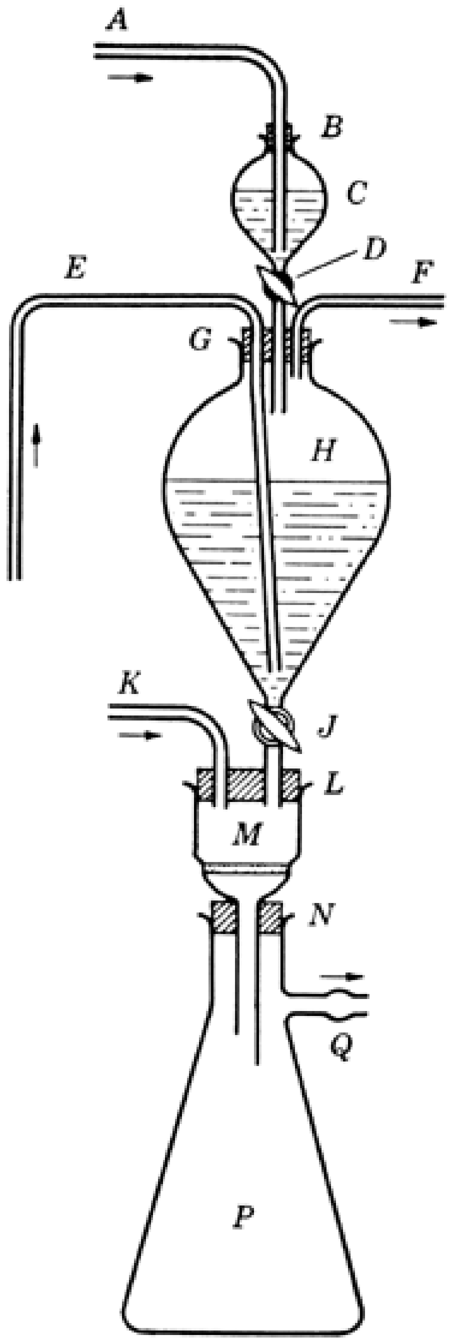


Submitted by R. Stuart Tipson[1]
Checked by T. L. Cairns and F. S. Fawcett.

1. Procedure

An apparatus is assembled in the hood, as shown in f.htmig. 1. In the 2-l. globe-shaped separatory funnel *H* (stopcock *J* closed) is placed 1.3 l. of deaerated water (Note 1). Three-holed rubber stopper *G* (bearing the stem of a 125-ml. separatory funnel *C* with stopcock *D* closed, a long inlet tube *E*, and a short outlet tube *F*) is inserted in the neck of *H*. In the neck of *C*, a rubber stopper *B*, provided with an inlet tube *A*, is inserted. *H* is flushed with nitrogen (Note 2) admitted at *E*. To the water is added 16.0 g. (0.1 mole) of alloxan monohydrate (Note 3), and the mixture is stirred by the flow of nitrogen through *E* until the alloxan monohydrate has dissolved. The nitrogen flow is discontinued, and hydrogen sulfide (Note 4) is passed in at *E* until the mixture is saturated with this gas and the aqueous solution is free from opalescence (about 2 hours). Carbon disulfide (100 ml.) is now added, and the mixture is agitated for 5 minutes by means of the hydrogen sulfide gas stream. The carbon disulfide layer is then cautiously withdrawn through *J* and discarded, and the aqueous solution is washed once more with 100 ml. of carbon disulfide which is separated and discarded. The hydrogen sulfide flow is discontinued, and nitrogen is passed in at *E* for about 2 hours or until the gas emerging at *F* gives no more than a faint test for hydrogen sulfide with lead acetate paper.

Fig. 1. Apparatus for preparation of alloxantin dihydrate.



Tubes *E* and *F* are now closed, stopper *B* is loosened, and *C* is flushed out with nitrogen admitted through tube *A*. Deaerated water (100 ml.) is placed in *C*, which is then flushed with nitrogen. To this water is added alloxan monohydrate (16.0 g.; 0.1 mole), and the mixture is stirred with *A*, while the nitrogen stream is continued, until the solid has dissolved. *B* is now pushed down to give a tight fit, a slight pressure of nitrogen is applied (at *A*), *F* and *D* are opened, and the solution is allowed to pass from *C* into *H*. To wash out traces of alloxan, a further 10 ml. of water is placed in *C* and run into *H*. *D* is closed, and nitrogen is passed in at *E* and out of *F* until the solutions are thoroughly mixed. *E* and *F* are now closed, and the mixture in *H* is allowed to stand until crystallization is complete (overnight). In the meantime, the stem of funnel *H* is inserted in one hole of the two-holed rubber stopper *L* (also bearing inlet tube *K*); *L* is inserted in the mouth of *M* (a 150-ml., Pyrex Büchner funnel with coarse, fritted-glass septum); and the stem of *M* is inserted in the rubber stopper *N* placed in the neck of a 2-liter Büchner flask *P* (side arm, *Q*). To flush out *M* and *P*, nitrogen is passed in at *K* and out of *Q*. *K* and *Q* are now closed, *F* is opened, and a slight pressure of nitrogen is applied at *F*. *Q* and *J* are opened, and, if necessary, slight suction is applied at *Q*. When all the suspension has passed out of *H*, the nitrogen stream is continued for a few minutes, to

remove as much as possible of the liquid clinging to the precipitate in *M*. Then *F*, *J*, and *Q* are closed. The Büchner funnel *M* and its contents are quickly removed, placed in a vacuum desiccator (preflushed with nitrogen), and dried to constant weight, at room temperature, over phosphorus pentoxide and soda-lime. The yield is 27–27.5 g. (84–85%) (Note 5), (Note 6), and (Note 7).

2. Notes

1. Deaerated water is prepared as follows. A boiling stone is added to distilled water which is then boiled under reflux for at least 5 minutes; it is cooled in ice to room temperature under an atmosphere of oxygen-free nitrogen.
2. For preparation of moist, oxygen-free nitrogen, the commercial gas is passed through (*a*) a 500-ml. Drechsel bottle containing a fresh solution of 25 g. of sodium hydroxide plus 5 g. of pyrogallol in 250 ml. of deaerated water, (*b*) a reversed, empty 500-ml. bottle, and (*c*) a 500-ml. bottle containing 250 ml. of deaerated water.
3. Alloxan monohydrate from Eastman Kodak Company is satisfactory. It is dried to constant weight over soda-lime and phosphorus pentoxide in the vacuum desiccator at room temperature. It should be colorless, and readily and completely soluble in 5 volumes of cold water. The sample employed assayed 99–100% alloxan monohydrate (p. 23) by Tipson and Cretcher's method.[2]
4. Commercial hydrogen sulfide is passed through a (reversed) empty 500-ml. Drechsel gas-washing bottle and then through 250 ml. of deaerated water in a similar bottle (not reversed).
5. The solubility of alloxantin dihydrate in water at room temperature is about 0.29 g. per 100 ml. of solution.[3] An additional 4 g. of product may be obtained by evaporation of the mother liquor to dryness at 25° under reduced pressure (nitrogen atmosphere).
6. The yield is slightly less if traces of crystals are left adhering to the inner walls of funnel *H*. The alloxantin obtained by dehydration of the product at 120–150° under reduced pressure for 2 hours melts with decomposition in 0.5 to 1 minute when placed in a block heated to 245°.[4]
7. The submitter reports that with minor modification the above hydrogen sulfide reduction procedure can be applied to the preparation of the *dialuric acid monohydrate* intermediate. The apparatus is assembled as in f.htmig. 1 with the exception that funnel *C* and its accessories are deleted. The above reduction procedure is followed initially, employing 500 ml. of deaerated water and 50 g. of alloxan monohydrate instead of the quantities shown above. After the saturation with hydrogen sulfide (determined by weighing) and the first agitation with carbon disulfide have been conducted as above, the funnel is assembled for filtration in an atmosphere of hydrogen sulfide (rather than nitrogen), and the suspension in *H* is filtered through *M* by manipulations analogous to those described. The colorless crystals of dialuric acid monohydrate are washed on the filter with an additional 100 ml. of carbon disulfide added portionwise via *H*, and, while wet with carbon disulfide and hydrogen sulfide, the crystals and funnel *M* are transferred to a shielded vacuum desiccator and dried over soda-lime and phosphorus pentoxide under high vacuum (Dry Ice-cooled trap). The yield is 44–44.5 g. (87–88%). Even at 300°, the compound exhibits no true melting or gas evolution. Heated at 2° per minute in an aluminum block (initial temperature, 150°) it appears unchanged at 200°, turns faintly pink at 203–206°, and gradually becomes reddish brown (229–232°) and then purplish black at about 270°.

3. Discussion

Methods of Preparation are reviewed in *Org. Syntheses Coll. Vol.* **3**, 42 (1955).

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 42

References and Notes

1. Mellon Institute of Industrial Research, Pittsburg, Pennsylvania.
2. Tipson and Cretcher, *Anal. Chem.*, **22**, 822 (1950).
3. Thunberg, *Skand. Arch. Physiol.*, **33**, 217 (1916) [*C. A.*, **11**, 456 (1917)]; Biilmann and Bentzon, *Ber.*, **51**, 522 (1918).
4. *Org. Syntheses Coll. Vol.* **3**, 42 (1955).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

soda-lime

sodium hydroxide (1310-73-2)

hydrogen sulfide (7783-06-4)

nitrogen (7727-37-9)

carbon disulfide (75-15-0)

pyrogallol (87-66-1)

alloxantin (76-24-4)

Alloxan monohydrate (2244-11-3)

Alloxan (50-71-5)

Alloxantin dihydrate (6011-27-4)

phosphorus pentoxide (1314-56-3)

dialuric acid monohydrate (444-15-5)

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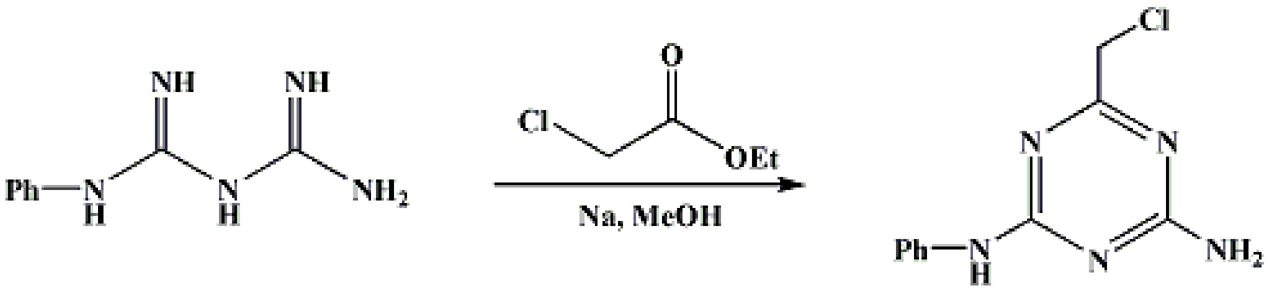
2-AMINO-4-ANILINO-6-(CHLOROMETHYL)-*s*-TRIAZINE

[*s*-Triazine, 2-amino-4-anilino-6-(chloromethyl)-]



Submitted by C. G. Overberger and Francis W. Michelotti[1].
Checked by B. C. McKusick and F. W. Stacey.

1. Procedure

Methanol (225 ml.) is placed in a 500-ml. two-necked flask equipped with a mechanical stirrer and a reflux condenser. Sodium (6.8 g., 0.30 g. atom) in small pieces is dropped down the condenser into the stirred methanol. The resultant solution is cooled to room temperature, and 64 g. (0.30 mole) of 1-phenylbiguanide hydrochloride (Note 1) is added. The mixture is stirred at room temperature for 20 minutes. The sodium chloride that precipitates is separated on a Büchner funnel and washed with 25 ml. of methanol.

The combined filtrates, which contain 1-phenylbiguanide as the free base, are placed in a 500-ml. three-necked flask equipped with a mechanical stirrer, a drying tube containing calcium chloride, and a dropping funnel, and 36.8 g. (0.30 mole) of ethyl chloroacetate (Note 2) is added at room temperature with stirring. The mixture is stirred at room temperature for 14 hours, during which time 2-amino-4-anilino-6-(chloromethyl)-*s*-triazine precipitates as a white solid. After being separated by filtration and air-dried, the triazine weighs 37–40 g. and melts at 138–140°. The methanol filtrate is added to 500 ml. of cold water. The mixture is cooled in an ice bath with stirring for 2 hours and filtered to remove an additional 10–12 g. of gray triazine, m.p. 140–142°. The total yield of crude product is 47–52 g.

The triazine is purified by recrystallizing it from 250 ml. of dioxane, using 2 g. of decolorizing carbon and filtering hot. The recrystallized triazine is dried for 5 hours at 60° (1–5 mm. pressure) in a vacuum oven (Note 3). It then weighs 31–33 g. (44–47%) (Note 4), m.p. 142–143° (Note 5).

2. Notes

1. 1-Phenylbiguanide hydrochloride can be obtained from American Cyanamid Company. If 1-phenylbiguanide itself is available, the triazine can be prepared in the

same way by dissolving 53 g. (0.30 mole) of 1-phenylbiguanide in 250 ml. of methanol, adding 36.8 g. of ethyl chloroacetate, and proceeding as before. The same yield is obtained whether one starts with the free base or its hydrochloride.

2. Ethyl chloroacetate from Fisher Scientific Company was used.

3. The checkers found that less rigorous drying failed to remove all the dioxane.

4. An additional 3–5 g. of the triazine, m.p. 141–143°, can be obtained by concentrating the dioxane filtrate to about 60 ml. and cooling the concentrate.

5. 2-Chloromethyl-4,6-diamino-*s*-triazine can be prepared in 82% yield by stirring a mixture of biguanide and ethyl chloroacetate in methanol in the same way.

3. Discussion

2-Amino-4-anilino-6-(chloromethyl)-*s*-triazine has been prepared from 1-phenylbiguanide and ethyl chloroacetate in the presence of methanol[2] or sodium methoxide at –40°.[3]

References and Notes

1. Polytechnic Institute of Brooklyn, Brooklyn, New York.
2. Schuller, U. S. pats. 2,822,364 and 2,848,452 [*C. A.*, **52**, 6807, 19169 (1958)].
3. Shapiro and Overberger, *J. Am. Chem. Soc.*, **76**, 97 (1954).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

methanol (67-56-1)

sodium chloride (7647-14-5)

sodium methoxide (124-41-4)

carbon (7782-42-5)

sodium (13966-32-0)

Ethyl chloroacetate (105-39-5)

dioxane (5703-46-8)

1-phenylbiguanide hydrochloride

1-phenylbiguanide (102-02-3)

triazine (289-96-3)

2-Amino-4-anilino-6-(chloromethyl)-s-triazine, s-Triazine, 2-amino-4-anilino-6-(chloromethyl)- (30355-60-3)

2-Chloromethyl-4,6-diamino-s-triazine

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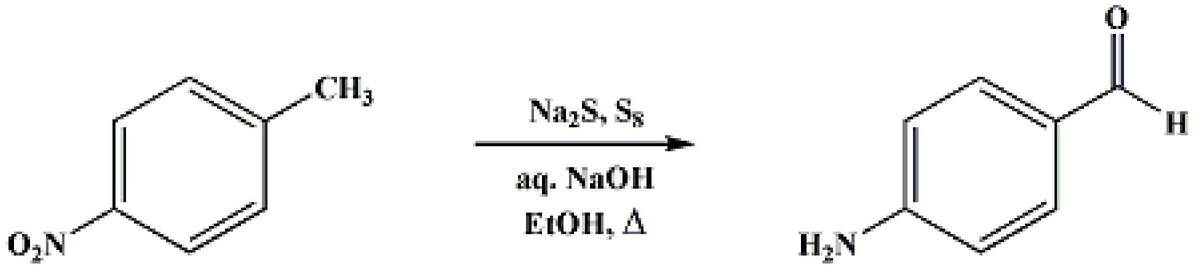
Organic Syntheses, *CV 4*, *31*

p-AMINOBENZALDEHYDE

[Benzaldehyde, *p*-amino-]



Submitted by E. Campaigne, W. M. Budde, and G. F. Schaefer[1].
Checked by Cliff S. Hamilton and R. C. Rupert.

1. Procedure

To 600 ml. of distilled water in a 1-l. beaker are added 30 g. (0.125 mole) of crystalline sodium sulfide nonahydrate (Note 1), 15 g. (0.47 g. atom) of flowers of sulfur, and 27 g. (0.67 mole) of sodium hydroxide pellets. The mixture is heated on a steam bath for 15–20 minutes with occasional stirring and then poured into a 2-l. round-bottomed flask containing a hot solution of 50 g. (0.36 mole) of *p*-nitrotoluene (Note 2) in 300 ml. of 95% ethanol. A reflux condenser is attached, and the mixture is heated under reflux for 3 hours. The resulting clear but deep red solution is rapidly steam-distilled until about 1.5–2 l. of condensate has been collected (Note 3). The distillate should be clear when the distillation is stopped. The residue in the 2-l. flask should have a volume of 500–600 ml.; if less, it should be diluted to this volume with boiling water. The solution is rapidly chilled in an ice bath with occasional vigorous shaking and stirring to induce crystallization. After 2 hours in the ice bath the golden yellow crystals of *p*-aminobenzaldehyde are collected on a Büchner funnel and washed with 500 ml. of ice water to remove sodium hydroxide (Note 4). The product is immediately placed in a vacuum desiccator over solid potassium hydroxide pellets for 24 hours. The yield of *p*-aminobenzaldehyde, m.p. 68–70°, amounts to 18–22 g. (40–50%). The product contains some impurities but is pure enough for most purposes (Note 5). It should be stored in a sealed bottle (Note 6).

2. Notes

1. Merck's reagent grade of sodium sulfide nonahydrate was used. Since sodium sulfide decomposes on contact with air, a freshly opened bottle should be employed. "Sodium Sulfhydrate" (Hooker Electrochemical Company hydrated sodium hydrosulfide) is also satisfactory; the amount should be based upon the formula $NaHS \cdot 2H_2O$, and an equivalent amount of sodium hydroxide in excess of the 27 g. is required.

2. The *p*-nitrotoluene used was Eastman Kodak Company practical grade.
3. The steam distillation should be carried out as rapidly as possible. The distillate contains ethanol, *p*-toluidine, and some unchanged *p*-nitrotoluene.

It has been reported[2] that a large amount of a dark oily tar may be present at this stage. Presumably it consists of Schiff's base polymers which have formed during the time necessary for reflux and steam distillation. The clear solution may be decanted from the oil, and the expected orange-yellow crystals of *p*-aminobenzaldehyde are obtained on cooling the solution.
The oily tar may be dissolved in boiling acetic anhydride, and upon dilution of the reaction mixture with water and partial concentration, crude *p*-acetamidobenzaldehyde separates. The latter may be purified by dissolving it in hot sodium bisulfite solution and fractionally precipitating the aldehyde by the addition of sodium hydroxide solution. From 12.3 g. of intractable tars there were obtained a first fraction which consisted of a dark sludge which was discarded, a second fraction which weighed 5.2 g., m.p. 150°, and a third which weighed 1.9 g., m.p. 147°. The melting point of *p*-acetamidobenzaldehyde is recorded[3] as 153°.
4. It is sometimes necessary to suspend the precipitate in about 200 ml. of ice water, stir it vigorously, and filter again to remove all traces of alkali.
5. The chief impurities are the polymeric condensation products of *p*-aminobenzaldehyde with itself. No satisfactory method for recrystallization has been found. If the melting point is high and a pure product is desired, it is best to extract with boiling water until the filtrate is clear, and extract the monomer from the water with ether. This procedure gives recoveries of 25–30%.
Readily purified aldehyde derivatives may be prepared in good yields from the crude polymer mixture. The oxime melts at 124°, the azine at 245°, and the phenylhydrazone at 175°.[4] If these derivatives are hydrolyzed, the same crude *p*-aminobenzaldehyde of broad melting range results.
6. Care must be taken to exclude all traces of acid fumes from *p*-aminobenzaldehyde, since they catalyze its self-condensation.

3. Discussion

p-Aminobenzaldehyde has been prepared by the action of sodium polysulfide upon *p*-nitrotoluene[5,6,7,8] on which the method described is based. It can be prepared also from *p*-nitrobenzyl alcohol and sodium sulfide,[6] by heating *p*-nitrobenzaldehyde with sodium bisulfite and decomposing the addition product with hydrochloric acid,[9] by the reduction of *p*-nitrobenzaldoxime with ammonium sulfide[3,10] and subsequent hydrolysis of the amino oxime, and by the decomposition of the benzenesulfonylhydrazide of *p*-aminobenzoic acid in the presence of powdered glass and sodium carbonate.[11]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 88

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium polysulfide

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ether (60-29-7)

acetic anhydride (108-24-7)

sodium hydroxide (1310-73-2)

sodium carbonate (497-19-8)

sulfur (7704-34-9)

sodium bisulfite (7631-90-5)

potassium hydroxide (1310-58-3)

sodium sulfide (1313-82-2)

ammonium sulfide

p-Nitrobenzaldehyde (555-16-8)

sodium hydrosulfide, Sodium Sulfhydrate

sodium sulfide nonahydrate (1313-84-4)

p-toluidine (106-49-0)

benzenesulfonyl-hydrazide (80-17-1)

p-Nitrobenzyl alcohol (619-73-8)

p-aminobenzoic acid (150-13-0)

p-nitrotoluene (99-99-0)

p-Aminobenzaldehyde, Benzaldehyde, p-amino- (17625-83-1)

p-nitrobenzaldoxime

p-acetamidobenzaldehyde (122-85-0)

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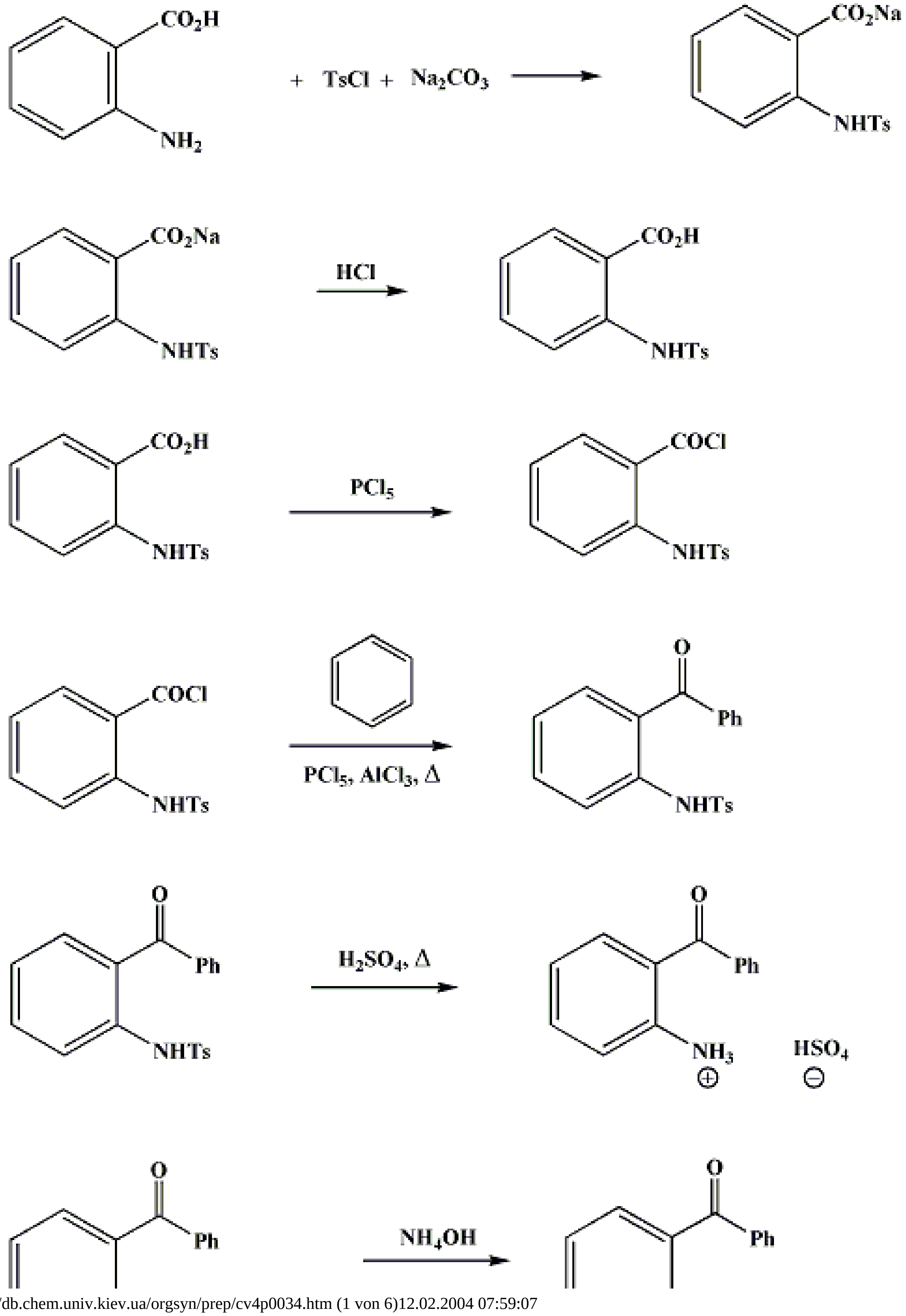
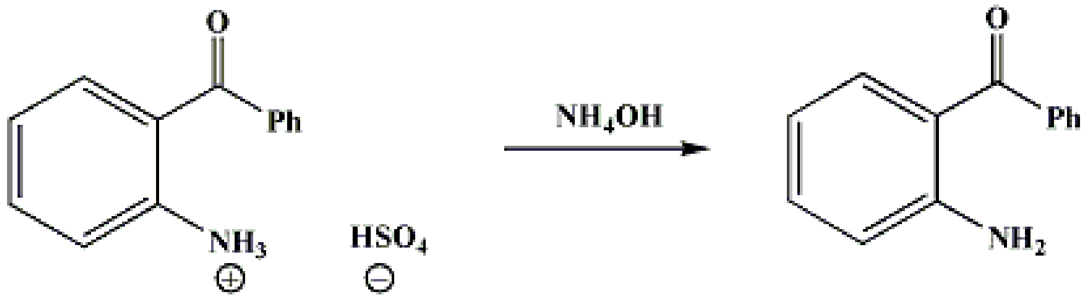
Organic Syntheses, CV 4, 34

2-AMINOBENZOPHENONE

[Benzophenone, 2-amino-]





Submitted by H. J. Scheifele, Jr. and D. F. DeTar[1].
Checked by R. T. Arnold and John D. Jones.

1. Procedure

A. *p-Toluenesulfonylanthranilic acid.* In a 5-l. three-necked flask equipped with a stirrer and a thermometer extending to the bottom of the flask are placed 1.5 l. of water and 260 g. (2.4 moles) of technical grade dry sodium carbonate (Note 1). While the mixture is warmed, 137 g. (1 mole) of anthranilic acid is added in three portions, and the temperature is raised to 70° to effect complete solution. The solution is allowed to cool to about 60°, and 230 g. (1.2 moles) of technical *p*-toluenesulfonyl chloride is added in 5 portions over a period of about 20 minutes (Note 2). When all the *p*-toluenesulfonyl chloride has been added, the reaction mixture is maintained at 60–70° for an additional 20 minutes. The temperature is raised to about 85°, 10 g. of Norit is added cautiously, and the solution is filtered by suction through a previously heated Büchner funnel.

In a 4-l. beaker equipped with a stirrer which can be operated above the liquid level to break the foam are placed 250 ml. of 12*N* hydrochloric acid and 250 ml. of water. The filtrate obtained above is cooled to about 50° and is added to the hydrochloric acid in small portions and at such a rate that the mixture does not foam over. If efficient stirring is used in the foam layer, this addition can be carried out in 5 minutes. The product is isolated by filtration through a Büchner funnel and is washed on the filter, first with a 250-ml. portion of dilute hydrochloric acid (prepared by diluting 50 ml. of 12*N* hydrochloric acid to about 250 ml.) to remove anthranilic acid, and then with 500 ml. of water. The product is sucked as dry as possible and is then spread in a thin layer and allowed to air dry for about 15 hours. When easily pulverizable, the material is transferred to an oven and dried for 3 hours at 100–120°.

There is obtained 257–265 g. (88–91%) of *p*-toluenesulfonylanthranilic acid as a pale lavender powder with a neutral equivalent of 294–300, which indicates a purity of 97–99% (Note 3). This product is suitable for conversion to 2-aminobenzophenone, but it may be recrystallized by dissolving in hot 95% ethanol (10 ml. per g.) and then adding water (4 ml. per g.). The recovery in the first crop is about 75% of material melting at 229–230° and having a neutral equivalent of 295.

B. *2-Aminobenzophenone*. In a dry 3-l. three-necked flask equipped with a stirrer, a reflux condenser connected to a hydrogen chloride trap, and a thermometer extending to the bottom of the flask are placed 146 g. (0.5 mole) of dry *p*-toluenesulfonylanthranilic acid, 1.5 l. of thiophene-free benzene, and 119 g. (0.57 mole) of phosphorus pentachloride. The mixture is stirred and heated at about 50° for 30 minutes. The murky solution (Note 4) is then cooled to 20–25°, and 290 g. (2.2 moles) of anhydrous

aluminum chloride is added in 4 portions. When addition is complete, the dark mixture is heated with stirring at about 80–90° for 4 hours. The mixture is cooled to room temperature and poured onto a mixture of 500 g. of ice and 40 ml. of 12*N* hydrochloric acid in a 5-l. round-bottomed flask. The benzene is best removed by vacuum distillation using a water aspirator (Note 5). The grainy, brown, crude product is separated by filtration on a Büchner funnel and washed thoroughly with dilute hydrochloric acid, with water, then with two 500-ml. portions of 5% sodium carbonate (to remove anthranilic acid and starting material), and finally with three 500-ml. portions of water (Note 6). The filter cake is sucked reasonably dry.

The crude, moist sulfonamide is dissolved in 1.6 l. of concentrated sulfuric acid by warming on the steam bath for 15 minutes. The sulfuric acid solution is divided into two equal parts, each of which is placed in a 4-l. beaker. The beakers are cooled in ice baths while 1.6 kg. of ice is added slowly and with stirring to the contents of each beaker. During the addition of the ice, phenyl *p*-tolyl sulfone separates. A total of 50 g. of Norit is added, and the solution is filtered (Note 7) and (Note 8).

The filtrates are best neutralized separately. Two 5-gal. crocks are half filled with crushed ice, and one-half of the total filtrate is poured into each. For neutralization, commercial 12*N* ammonium hydroxide is added slowly with stirring; a total of 4.8 l. is required. The solid is collected on a Büchner funnel, washed with water, and air-dried.

The product is obtained in the form of bright yellow crystals, m.p. 103–105°. The yield is 68–71 g. (69–72% based on *p*-toluenesulfonylanthranilic acid). This material is dissolved in 1 l. of hot 95% ethanol, treated with 15 g. of Norit, and filtered. The hot solution is diluted with 700 ml. of hot water and cooled. After a second recrystallization, the yield of hexagonal yellow plates is 47 g.; m.p. 105–106°. Another 6 g. of pure aminoketone can be recovered from the filtrate. The total yield of recrystallized 2-aminobenzophenone is 53 g. (54%) (Note 9).

2. Notes

1. If sodium hydroxide is used, the main product is the *p*-toluenesulfonic acid salt of anthranilic acid. This salt has properties quite similar to those of the desired *p*-toluenesulfonylanthranilic acid but is useless for the preparation of 2-aminobenzophenone.

2. It is advisable to have sodium hydroxide solution available in case carbon dioxide is evolved indicating that the amount of sodium carbonate used was insufficient.
There is a tendency for salts to precipitate from the mixture and for some foaming to occur if much less water is used.

3. The melting point of the *p*-toluenesulfonylanthranilic acid is not a good criterion of purity because the *p*-toluenesulfonic acid salt of anthranilic acid has about the same value. The neutral equivalents are widely different: 154 for the salt and 291 for *p*-toluenesulfonylanthranilic acid. The compound obtained in this preparation gives a negative test for anthranilic acid on diazotization and treatment with

alkaline β-naphthol solution. The probable impurity is the sodium salt of *p*-toluenesulfonylanthranilic acid.
4. When recrystallized *p*-toluenesulfonylanthranilic acid is used, the solution is clear at this point. The crude acid gives rise to a dark solution containing a small amount of suspended solid. The yield of 2-aminobenzophenone is the same in either case.
5. Steam distillation may also be used but should not be prolonged. If the contents of the flask are kept below 80°, the crude product is obtained as a fine powder. If the temperature becomes too high, the material melts and anthranilic acid is not easily removed from the solid mass obtained on cooling.
6. It is convenient to keep the wash solutions at 75–80°, but the temperature should not exceed 85° or part of the organic material will melt and clog the filter. It is advisable to transfer the solid to a 2-l. beaker to permit thorough washing. Most of the wash solution can be separated by decantation.
7. Phenyl *p*-tolyl sulfone may be isolated at this point by filtering the acid solution before using Norit. It can be purified by recrystallization from 95% ethanol; m.p. 125°.
8. The temperature of the solution should be 30–35°. If too cold some of the product will be retained on the filter, and if too hot the filter paper will be attacked by the acidic solution. 2-Aminobenzophenone is a weak base and separates as the free base from sulfuric acid solutions below about 4*N*.
9. 4'-Methyl-2-aminobenzophenone can be prepared similarly by substituting toluene for benzene. The yield of crude material, m.p. 85–88°, is 70%. On recrystallization from 95% ethanol, using 5 ml. per g., there is obtained, in two crops, a 70% recovery of 4'-methyl-2-aminobenzophenone, m.p. 92–93°. Because of the higher temperature required in the steam distillation (Note 5), the sulfonamide is obtained in a form difficult to purify. As a result the crude aminoketone usually contains 1–2 g. of aluminum oxide.

3. Discussion

The above procedure is essentially that of Ullmann and Bleier.[2] 2-Aminobenzophenone has also been prepared by reduction of 2-nitrobenzophenone,[3] by the Hofmann reaction of the amide of *o*-benzoylbenzoic acid with sodium hypobromite,[4] by the action of an excess of benzoyl chloride on aniline at 220°,[5] and by hydrolysis of the acetyl derivative which is obtained by the action of phenylmagnesium bromide on 2-methyl-3,1,4-benzoxaz-4-one (from anthranilic acid and acetic anhydride).[6] Various methods for the preparation of 2-aminobenzophenones have been summarized critically by Simpson, Atkinson, Schofield, and Stephenson.[7]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

p-toluenesulfonic acid salt of anthranilic acid

2-methyl-3,1,4-benzoxaz-4-one

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

acetic anhydride (108-24-7)

aniline (62-53-3)

sodium hydroxide (1310-73-2)

phosphorus pentachloride (10026-13-8)

sodium carbonate (497-19-8)

β-naphthol (135-19-3)

carbon dioxide (124-38-9)

Norit (7782-42-5)

benzoyl chloride (98-88-4)

aluminum chloride (3495-54-3)

toluene (108-88-3)

ammonium hydroxide (1336-21-6)

Anthranilic Acid (118-92-3)

Phenylmagnesium bromide (100-58-3)

sodium hypobromite

aluminum oxide (1344-28-1)

2-Aminobenzophenone, Benzophenone, 2-amino- (2835-77-0)

2-nitrobenzophenone (2243-79-0)

p-Toluenesulfonyl chloride (98-59-9)

o-benzoylbenzoic acid (85-52-9)

p-Toluenesulfonylanthranilic acid (6311-23-5)

phenyl p-tolyl sulfone (640-57-3)

sodium salt of p-toluenesulfonylanthranilic acid

4'-Methyl-2-aminobenzophenone

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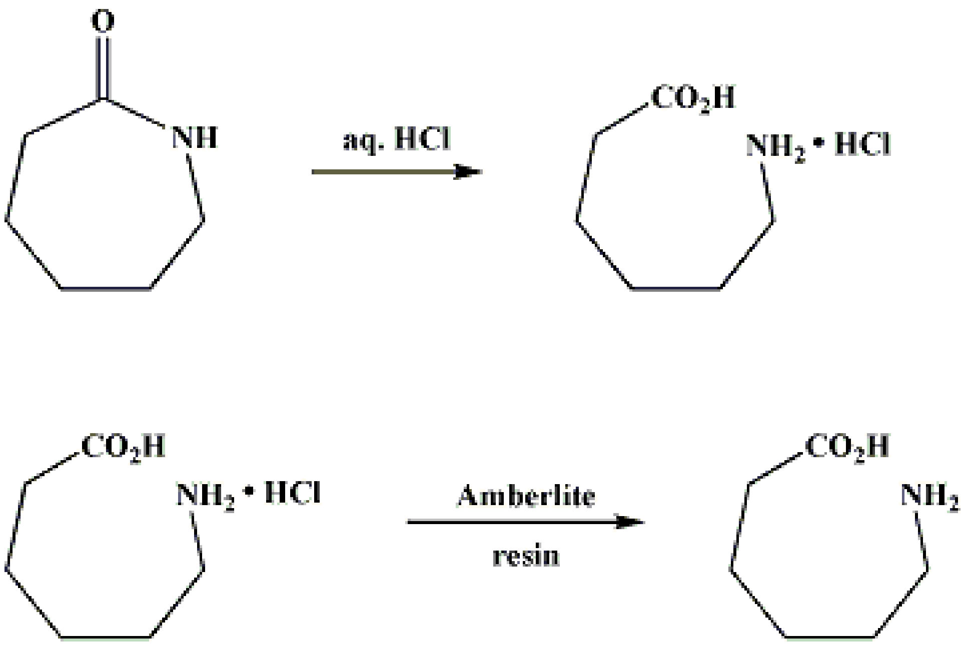
Organic Syntheses, *CV 4*, *39*

ε-AMINOCAPROIC ACID

[Hexanoic acid, 6-amino-]



Submitted by Cal Y. Meyers and Leonard E. Miller[1].
Checked by Richard T. Arnold and William R. Hasek.

1. Procedure

Into a 500-ml. round-bottomed flask containing 50 g. (0.44 mole) of 2-ketohexamethylenimine (ε-caprolactam) is poured a solution containing 45 ml. of concentrated hydrochloric acid (sp. gr. 1.19) dissolved in 150 ml. of water. The mixture is boiled for 1 hour, and the resulting yellow solution is decolorized with Norit and evaporated to dryness under reduced pressure on a steam bath (Note 1).

The resulting ε-aminocaproic acid hydrochloride is converted into the amino acid by means of a column containing Amberlite IR-4B resin (Note 2):

1. Construct the column as shown in f.htmig. 2.

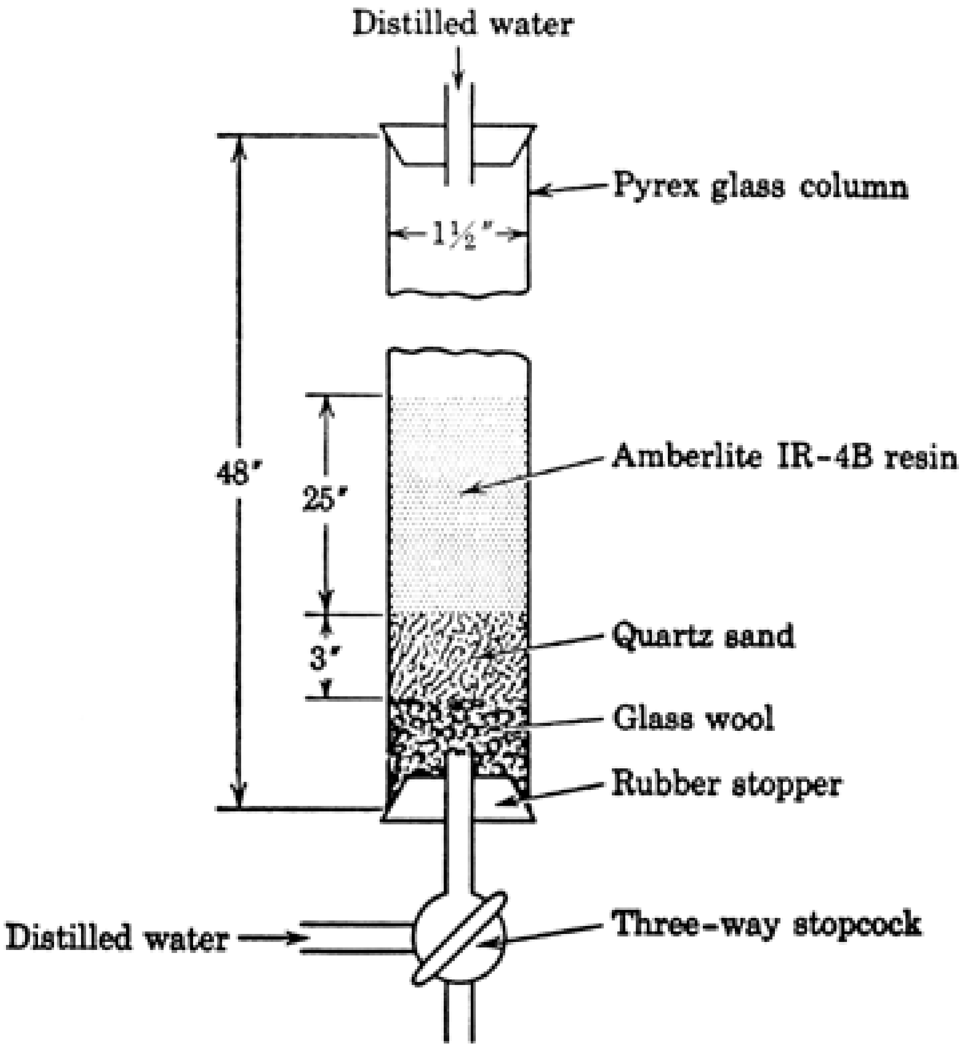
2. *Exhaustion.* Pass a 1% aqueous hydrochloric acid solution through the column (downflow) until the pH of the solution leaving the column decreases from 5.5–6.5 to about 2.

3. *Regeneration.* Now pass a 1% aqueous sodium hydroxide solution through the column (downflow) until the solution leaving the column is strongly alkaline.

4. *Classification.* Wash the resin (upflow) with 10 l. of distilled water.

5. Wash the resin with distilled water (downflow) (Note 3) until the salts are all washed out and the pH of the washings is 5.6–6.5. The column is now ready for use (Note 4).

Fig. 2.



The solid ε-aminocaproic acid hydrochloride is dissolved in 1 l. of distilled water. This solution is passed through the column (downflow) and followed by at least 2 l. of distilled water (Note 5).

The collected solution (pink) is concentrated by distillation, under reduced pressure, to a volume of about 100 ml. (Note 6), and the resulting orange-colored solution is decolorized with Norit. After the addition of 300 ml. of absolute ethanol and 500 ml. of ether, followed by vigorous shaking, a white solid forms within a few minutes. The ε-aminocaproic acid is collected on a Büchner funnel and dried in a vacuum desiccator until no more ether-alcohol odor is detected. A yield of 52 g. (90%) is obtained; m.p. 202–203°.

2. Notes

1. This hydrolysis is similar to that utilized previously.[2]
2. Obtained from the Resinous Products Division, Rohm and Haas Company, Philadelphia, Pennsylvania. The checkers found that this resin sometimes liberates carbon dioxide when treated with 1% hydrochloric acid. In such cases the total resin sample may be pretreated in a beaker with 1% hydrochloric acid until no more gas is evolved, and then a 30-in. (rather than 25-in.) column containing 1% hydrochloric acid is packed with resin. Further treatment of the resin is continued as described by the submitters.
3. Intermittent silver nitrate tests will indicate whether the solution is free of salts.
4. The liquid level of the column should always be above the resin when the column is not in use.
5. To assure the user that the resin is functioning, the eluant should be tested frequently for pH and the presence of salts. If the test for chloride ion becomes positive, or if the pH falls below 5.6, regeneration procedures are necessary; generally the column is good for two runs.
6. Excessive heating and excessive evaporation may result in peptide formation.

3. Discussion

ε-Aminocaproic acid has been prepared by the hydrolysis of ε-benzoylaminocapronitrile,[3] by the hydrolysis of diethyl ω-phthalimidobutylmalonate,[4] from cyclohexanone oxime by rearrangement and hydrolysis,[5] by hydrochloric acid hydrolysis of ε-caprolactam and removal of the acid by the use of litharge, silver oxide, etc.,[2] by alkaline hydrolysis of ε-caprolactam[6] or by hydrolysis of ε-caprolactam in the presence of a cation exchange resin,[7] by the reduction of δ-cyanovaleric acid[8] or the corresponding ethyl ester,[9] and by the hydrogenation of ε-oximinocaproic acid.[10]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alcohol, ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium hydroxide (1310-73-2)

silver oxide (20667-12-3)

silver nitrate (7761-88-8)

carbon dioxide (124-38-9)

Norit (7782-42-5)

ε-AMINOCAPROIC ACID, Hexanoic acid, 6-amino- (60-32-2)

2-Ketohexamethylenimine, ε-caprolactam (105-60-2)

ε-aminocaproic acid hydrochloride

ε-benzoylaminocapronitrile

Cyclohexanone oxime (100-64-1)

diethyl ω-phthalimidobutylmalonate

δ-cyanovaleric acid (5264-33-5)

ε-oximinocaproic acid

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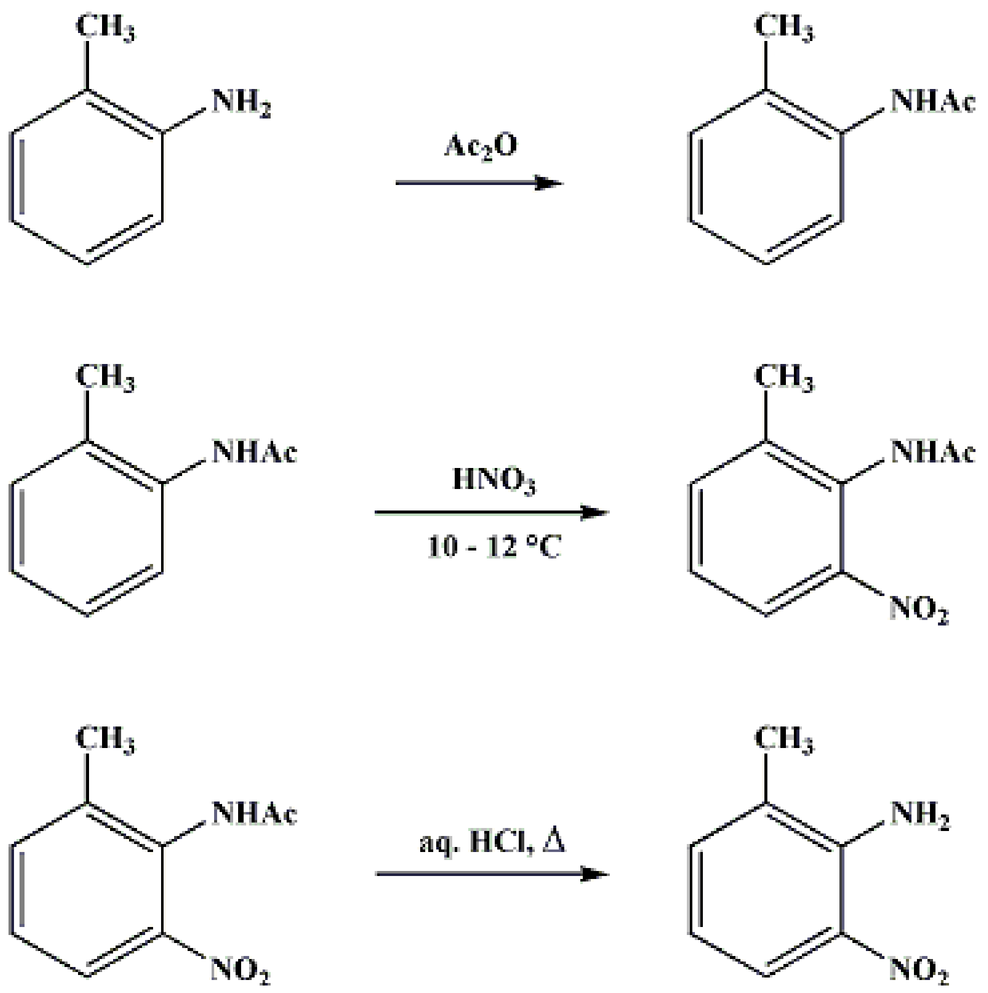
2-AMINO-3-NITROTOLUENE

[*o*-Toluidine, 6-nitro-]



Submitted by John C. Howard[1]
Checked by Charles C. Price and Joseph D. Berman.

1. Procedure

A 1-l. three-necked flask is fitted with a sealed Hershberg stirrer, a reflux condenser, and a dropping funnel. The flask is charged with 650 ml. of acetic anhydride, and 107 g. (107 ml., 1 mole) of *o*-toluidine (Note 1) is introduced from the dropping funnel. The mixture becomes very warm. After the amine has been completely added, the solution is cooled to 12–13° in an ice-salt bath (Note 2). During the cooling, the dropping funnel and condenser are replaced by another dropping funnel containing 126 ml. (2 moles) of 70% nitric acid and a thermometer which can be read to within 0.5° in the range from 10° to 20° (Note 3).

The nitric acid is added drop by drop to the cold slurry at a rate which maintains the temperature carefully within the limits of 10–12° (Note 4). If the temperature persists

in dropping, the addition is stopped after about 5 minutes. The ice bath is removed until the temperature rises 0.5°, the ice-salt bath is replaced, and addition is continued. As the reaction progresses, the acetotoluide which may have precipitated redissolves, and the solution becomes deeply colored. The addition is complete in 1–2 hours, and the nitro compounds may start to separate.

The solution is poured, with stirring, into 3 l. of ice water. The mixture of 4- and 6-nitroacetotoluides precipitates as a creamcolored solid which is collected on a large Büchner funnel. After thorough washing with four 500-ml. portions of ice water, the precipitate is partly dried by suction (Note 5). The moist product is then placed in a steam-distillation apparatus (Note 6), covered with 300 ml. of concentrated hydrochloric acid, and heated until the mixture boils. The acetotoluides are rapidly hydrolyzed, and the solution becomes dark red. Steam is then introduced, and the distillation is thus continued until 36 l. of distillate has been collected (Note 7) and (Note 8). The 2-amino-3-nitrotoluene, which separates as bright orange needles when the distillate is cooled, is collected on a large Büchner funnel. The dried product amounts to 75–84 g. (49–55%), m.p. 92–94°. The product may be further purified by a second steam distillation. Ten grams of the amine is distilled from 150 ml. of water, and 3 l. of distillate is collected, yielding 8.7 g. of 2-amino-3-nitrotoluene, m.p. 95–96° (cor.).

2. Notes

1. Commercially available *o*-toluidine, b.p. 75–77°/10 mm., is suitable. Redistillation of this material gave no significantly better results. The checkers obtained a 42% yield of 2-amino-3-nitrotoluene using practical grade *o*-toluidine directly, and a 57% yield after redistillation.
2. The flask should be immersed up to the neck in the slurry of ice and salt. During the cooling, the acetotoluide may suddenly precipitate, immobilizing the stirrer; a few turns manually break up the mass of crystals and allow the stirring to be continued.
3. A low-temperature thermometer with a range from –15° to +50° is suitable.
4. If the temperature is allowed to rise above 18°, violent if not explosive decomposition may ensue.
5. The precipitate can be air-dried to a constant weight of 150–160 g.
6. An efficient steam-distillation apparatus such as that described by Fieser[2] is recommended. A 12-l. round-bottomed flask cooled in a tub of ice serves as the receiver, which is equipped with an auxiliary vertical condenser attached to a gas absorption trap[3] to accommodate the hydrogen chloride which distils first.
7. The third 12-l. portion yields about 20 g. of 2-amino-3-nitrotoluene. The residue in the steam-distillation flask, about 20 g. of crude 2-amino-5-nitrotoluene, solidifies when cooled and may be separated by filtration. It can be recrystallized from 2 l. of hot water, yielding 14–15 g. of yellow plates, m.p. 130–131° (cor.).
8. Instead of separating the mixture of isomers by the slow steam distillation,

one may employ the procedure of Wepster and Verkade.[4] In the latter, the product from the nitration of *o*-methylacetanilide is treated with the Witt-Utermann solution,[5] which consists of a water-alcohol solution of potassium hydroxide. 2-Acetylamino-5-nitrotoluene is insoluble in this solution, while the 3-nitro isomer is soluble and may be recovered in high yield and a good state of purity by acidification of the red filtrate. Hydrolysis of the acetyl derivatives affords 2-amino-5-nitro-and 2-amino-3-nitrotoluene.

3. Discussion

2-Amino-3-nitrotoluene has been prepared by the nitration of oxalotoluide[6] and by the nitration of *o*-acetotoluide in acetic acid with fuming nitric acid,[7] with a mixture of nitric and sulfuric acid,[8] or with metal nitrates.[9]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 291
- Org. Syn. Coll. Vol. 9, 573

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

4- and 6-nitroacetotoluides

2-amino-5-nitro-and 2-amino-3-nitrotoluene

nitric and sulfuric acid

hydrogen chloride, hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

acetic anhydride (108-24-7)

nitric acid (7697-37-2)

potassium hydroxide (1310-58-3)

2-amino-5-nitrotoluene (99-52-5)

2-Amino-3-nitrotoluene, o-Toluidine, 6-nitro- (570-24-1)

acetotoluide (103-89-9)

water-alcohol

2-Acetylamino-5-nitrotoluene

o-toluidine (95-53-4)

o-methylacetanilide, o-acetotoluide (120-66-1)

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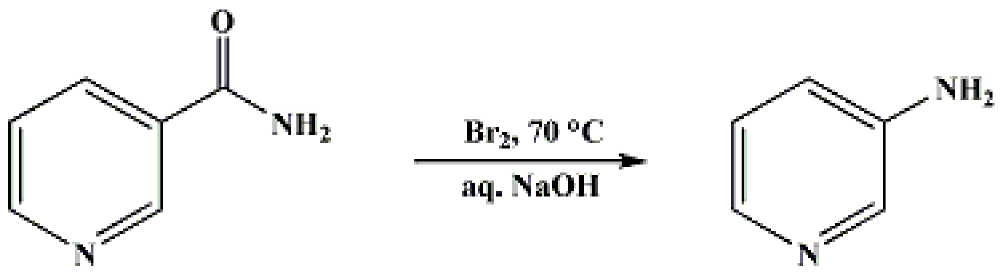
3-AMINOPYRIDINE

[Pyridine, 3-amino-]



Submitted by C. F. H. Allen and Calvin N. Wolf[1].
Checked by Cliff S. Hamilton and Marjorie Debrunner.

1. Procedure

In a 2-l. beaker equipped with a mechanical stirrer and immersed in an ice-salt bath is placed a solution of 75 g. (1.87 moles) of sodium hydroxide in 800 ml. of water. To the solution is added, with stirring, 95.8 g. (30.7 ml., 0.6 mole) of bromine. When the temperature of the solution reaches 0°, 60 g. (0.49 mole) of nicotinamide (Note 1) is added all at once with vigorous stirring. After being stirred for 15 minutes, the solution is clear. The ice-salt bath is replaced by a bath containing water at 75°, and the solution is stirred and heated at 70–75° for 45 minutes.

The solution is cooled to room temperature, saturated with sodium chloride (about 170 g. is required), and extracted with ether in a continuous extractor (Note 2). The extraction time is 15–20 hours. The ether extract is adjusted to a volume of 1 l., dried over 4–5 g. of sodium hydroxide pellets, and filtered, and the ether is removed by distillation from a steam bath. The residue crystallizes on cooling. The yield of dark red crystals melting at 61–63° is 39–41 g. (85–89%).

The crude product is dissolved in a mixture of 320 ml. of benzene and 80 ml. of ligroin (b.p. 60–90°) and heated on a steam bath with 5 g. of Norit and 2 g. of sodium hydrosulfite for 20 minutes. The hot solution is filtered by gravity, allowed to cool slowly to room temperature, and then chilled overnight in a refrigerator. The product is isolated by gravity filtration (Note 3), washed on the filter with 25 ml. of ligroin, and dried in a vacuum desiccator. The yield of white crystals melting at 63–64° amounts to 28–30 g. (61–65%). By concentrating the combined filtrate and washings to a volume of 150 ml., an additional 2–3g. of pale yellow crystals melting at 62–64° can be obtained. The total yield of 3-aminopyridine is 30–33 g. (65–71%).

2. Notes

1. The nicotinamide should be finely powdered to facilitate rapid solution.

2. The continuous extractor described by Pearl[2] was used. If the material is extracted in a separatory funnel, four 800-ml. portions and ten 500-ml. portions of ether are required to give the above yield.
3. Since 3-aminopyridine is somewhat hygroscopic, it tends to liquefy if collected on a suction filter.

3. Discussion

3-Aminopyridine has been prepared by heating nicotinamide in an alkaline potassium hypobromite solution at 70°;[3,4] by hydrolysis of β-pyridylurethane with oleum;[5] by heating 3-aminopyridine-2-carboxylic acid at 250°;[6] by reduction of 3-nitropyridine with zinc and hydrochloric acid;[7] by heating 3-bromopyridine with ammonia and copper sulfate in a sealed tube,[8,9] and by the hydrolysis of benzyl 3-pyridylcarbamate, prepared from nicotinic acid hydrazide through the corresponding azide.[10]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 27

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ligroin

β-pyridylurethane

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

Benzene (71-43-2)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

bromine (7726-95-6)

copper sulfate (7758-98-7)

sodium hydrosulfite (7775-14-6)

Norit (7782-42-5)

zinc (7440-66-6)

potassium hypobromite

3-Aminopyridine, Pyridine, 3-amino- (462-08-8)

nicotinamide (98-92-0)

3-aminopyridine-2-carboxylic acid

3-nitropyridine (2530-26-9)

3-bromopyridine (626-55-1)

benzyl 3-pyridylcarbamate

nicotinic acid hydrazide (553-53-7)

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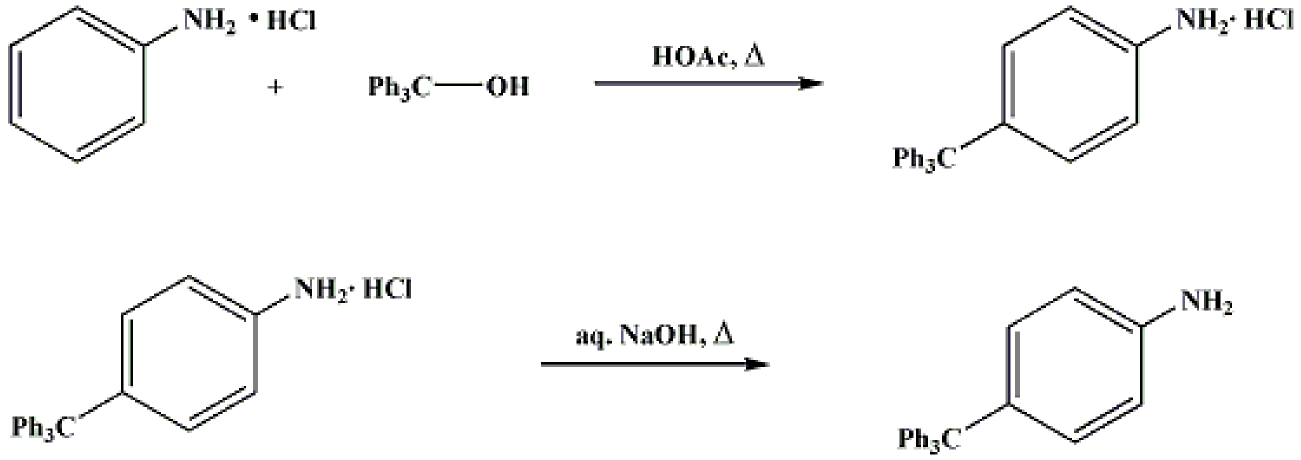
p-AMINOTETRAPHENYLMETHANE

[*p*-Toluidine, α,α,α-triphenyl-]



Submitted by Benjamin Witten and E. Emmet Reid[1].
Checked by Richard T. Arnold and Jerome J. Rosenbaum.

1. Procedure

Into a 1-l. round-bottomed flask equipped with a reflux condenser are introduced 100 g. (0.385 mole) of technical grade triphenylcarbinol (Note 1), 105 g. (0.81 mole) of dry aniline hydrochloride (Note 2), and 250 ml. of glacial acetic acid. The mixture is heated at the reflux temperature for 3 hours. During the period of reflux a clear brown homogeneous solution is formed. The solution while still hot is poured with stirring into a 4-l. beaker containing 2 l. of water. *p*-Aminotetraphenylmethane hydrochloride, which is not very soluble in water, separates as a light-brown solid. It is collected on a Büchner funnel and washed with 1 l. of water. The solid is then put back into the beaker, and a solution of 40 g. of sodium hydroxide in 2 l. of water is added. The mixture is heated to boiling for 1 hour to convert the hydrochloride to the free base (Note 3), which likewise is not very soluble in water. The mixture is allowed to cool to room temperature and is filtered with suction through a Büchner funnel. The solid material is washed with 500 ml. of water and is dried in an oven at 110–120°. The crude substance melts at 243–247°. It is purified by crystallization from 1.7 l. of toluene. The purified product (90–95 g., 70–74%) melts at 249–250° (Note 4).

2. Notes

1. Technical grade triphenylcarbinol is satisfactory, provided it is dry. The checkers obtained a final product having a higher melting point by starting with Eastman Kodak Company purest grade triphenylcarbinol.
2. The aniline hydrochloride must be dry if a good yield of product is to be obtained. Aniline hydrochloride can be prepared conveniently by mixing 75 g. of aniline and 80 ml. of concentrated hydrochloric acid in an evaporating dish and evaporating to dryness. The aniline hydrochloride should be dried in an oven at 110–120° before use. Aniline hydrochloride (Merck) which has been washed with ether and dried at 110–120° can be employed satisfactorily.
3. The mixture tends to bump during the period of heating. This bumping can be overcome by stirring the solution mechanically.

4. A product melting at 256–257° (uncor.)[2] was obtained by the checkers (Note 1).

3. Discussion

The procedure given is similar to one described by Ullmann and Münzhuber,[2] except that one-half as much aniline hydrochloride and two-thirds as much glacial acetic acid are used, and the time of reflux is reduced from 6 to 3 hours. *p*-Aminotetraphenylmethane can be prepared from triphenylchloromethane and aniline hydrochloride, following the same procedure outlined for triphenylcarbinol and aniline hydrochloride, except that a reaction time of 1 hour is sufficient. It has been prepared also from triphenylchloromethane and aniline.[3]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ether (60-29-7)

aniline (62-53-3)

sodium hydroxide (1310-73-2)

aniline hydrochloride (142-04-1)

toluene (108-88-3)

Triphenylchloromethane (76-83-5)

Triphenylcarbinol (76-84-6)

p-Aminotetraphenylmethane, p-Toluidine, α,α,α-triphenyl- (22948-06-7)

p-Aminotetraphenylmethane hydrochloride

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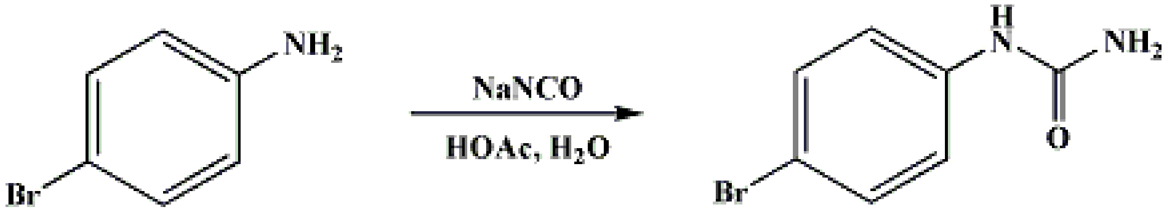
Organic Syntheses, CV 4, 49

ARYLUREAS
I. CYANATE METHOD
p-BROMOPHENYLUREA

[Urea, (*p*-bromophenyl)-]



Submitted by Frederick Kurzer[1]
Checked by Richard T. Arnold and Lester C. Krogh.

1. Procedure

In a 2-l. beaker, 86 g. (0.5 mole) of *p*-bromoaniline is dissolved in 240 ml. of glacial acetic acid and 480 ml. of water at 35°. This solution is treated with a solution of 65 g. (1 mole) of sodium cyanate (Note 1) in 450 ml. of water at 35° (Note 2). About 50 ml. of the sodium cyanate solution is added slowly with stirring until a white crystalline precipitate of the product appears. The rest is then added quickly with vigorous agitation (Note 3). The very rapid separation of the product is accompanied by a rise in the temperature to 50–55°. The thick, paste-like suspension is stirred for another 10 minutes, allowed to stand at room temperature for 2–3 hours, and diluted with 200 ml. of water. After cooling to 0°, the material is filtered with suction, washed with water, drained thoroughly, and dried. The yield of crude *p*-bromophenylurea, a white crystalline powder, is 95–100 g. (88–93%). The product is sufficiently pure for further synthetic work, but it can be recrystallized from aqueous ethanol (12 ml. of ethanol and 3 ml. of water per gram of crude material) to give a 65% recovery of lustrous white prisms of *p*-bromophenylurea, m.p. 225–227° (Note 4). This method is suitable for the preparation in excellent yields of a large number of arylureas (Note 5).

2. Notes

1. Comparable results are obtained with an equivalent quantity (81 g.) of potassium cyanate.
2. Instead of the solution, a well-stirred suspension of the cyanate in 150 ml. of water may be used with equal success.
3. Considerable frothing occurs with loss of some isocyanic acid (faint smell resembling that of sulfur dioxide). The foam collapses readily on stirring.
4. Melting points varying between 220° and 278° have been reported for *p*-

bromophenylurea (see Methods of Preparation). It has been shown[2] that the thermal conversion of arylureas to the corresponding diarylureas takes place extremely rapidly, even below the melting point. This is particularly true of arylureas containing certain substituents in the *para* position to the ureido grouping. Melting points of such compounds are therefore liable to be indefinite and correspond to mixtures of the *mono* and *sym* disubstituted urea, especially if the temperature is raised slowly.

Reproducible values for the melting points of such compounds, including *p*-bromophenylurea, have now been determined by the following simple procedure: After the approximate softening temperature or melting range of the urea derivative has been found, the bath temperature of the apparatus is raised a further 10–20° above that point and samples are inserted into the slowly cooling bath until a temperature is reached at which a specimen just fails to liquefy. Insertion of a further specimen at a temperature 1° higher causes instantaneous fusion and can be taken as the "melting point" of the urea derivative under examination. Under these conditions practically no conversion to a diarylurea occurs, and samples withdrawn immediately after fusion show nitrogen contents corresponding to the original arylurea. This method gives reproducible physical constants for urea derivatives whose properties preclude slow heating.

5. A list of substituted arylureas prepared by the method above is given in the accompanying table, which records slight variations in the quantities of starting materials employed and in the yields obtained.

The quantities of water recorded in column III are used for preparing the arylamine acetate solutions. The sodium cyanate is dissolved or suspended in the appropriate volume of water as detailed in the synthesis of *p*-bromophenylurea. The yields refer to the quantity of crude product. The substituted ureas thus obtained are usually sufficiently pure for further syntheses but can be recrystallized from ethanol.

SUBSTITUTED ARYLUREAS

I	II	III	IV	V	VI	VII
Arylurea	Arylamine, moles	Water, ml.	Acetic Acid, ml.,	Sodium Cyanate moles,	Initial Temperature, °C	Yield, %
p-Tolylurea	0.5	500	50	1.0	25	96
m-Tolylurea	0.5	400	75	1.0	30	86
o-Tolylurea	0.5	400	75	1.0	30	94
1-(4-Biphenylyl) urea	0.3	500	350	0.6	40	80
1-(2-Biphenylyl) urea	0.25	400	400	0.5	30	75

p-Methoxyphenylurea	0.3	150	30	0.6	40	94
p-Ethoxyphenylurea	0.5	500	75	1.0	25	95
m-Ethoxyphenylurea	0.3	500	120	0.6	20	54
o-Ethoxyphenylurea	0.5	500	170	1.0	20	88
m-Bromophenylurea	0.5	300	150	1.0	20	90
o-Bromophenylurea	0.5	100	250	1.0	25	92
o-Chlorophenylurea	0.5	100	200	1.0	25	92

3. Discussion

p-Bromophenylurea has been prepared by the bromination of phenylurea, using glacial acetic acid,[3,4] ethanol,[4] or chloroform[5] as solvents; by the action of potassium cyanate on *p*-bromoaniline hydrochloride;[4,6] and by the interaction of *p*-bromoaniline and ethyl allophanate.[7]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

acetic acid (64-19-7)

chloroform (67-66-3)

sulfur dioxide (7446-09-5)

nitrogen (7727-37-9)

Phenylurea (64-10-8)

potassium cyanate (590-28-3)

isocyanic acid (75-13-8)

sodium cyanate (917-61-3)

1-(4-Biphenylyl)urea

1-(2-Biphenylyl)urea

ethyl allophanate (626-36-8)

p-bromoaniline (106-40-1)

p-bromoaniline hydrochloride

p-Bromophenylurea, Urea, (p-bromophenyl)- (1967-25-5)

p-Tolylurea (622-51-5)

m-Tolylurea (63-99-0)

o-Tolylurea (614-77-7)

p-Methoxyphenylurea (1566-42-3)

p-Ethoxyphenylurea (150-69-6)

m-Ethoxyphenylurea (13142-86-4)

o-Ethoxyphenylurea

m-Bromophenylurea (2989-98-2)

o-Bromophenylurea (13114-90-4)

o-Chlorophenylurea (114-38-5)

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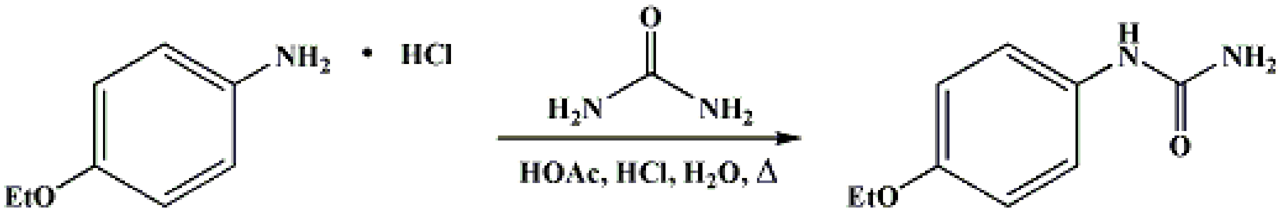
Organic Syntheses, CV 4, 52

ARYLUREAS
II. UREA METHOD
p-ETHOXYPHENYLUREA

[Dulcin]

[Urea, *p*-ethoxyphenyl-]



1. Procedure

A mixture of 870 g. (5 moles) of *p*-phenetidine hydrochloride and 1.2 kg. (20 moles) of urea is placed in a 12-l. round-bottomed flask (Note 1). To this mixture are added 2 l. of water, 40 ml. of concentrated hydrochloric acid, and 40 ml. of glacial acetic acid, and the well-shaken suspension is heated to boiling. The dark purple solution thus obtained is boiled vigorously for 45–90 minutes until the reaction is complete. The liquid remains clear during the first half of the heating period. Separation of the product begins during the last half and proceeds with increasing rapidity until the entire contents of the vessel suddenly set to a solid mass. The source of heat is immediately withdrawn at this point (Note 2).

After cooling to room temperature, the product is broken up with the addition of 1–1.5 l. of water, filtered with suction, washed with cold water, drained, and dried. The crude *p*-ethoxyphenylurea is obtained in a yield of 740–810 g. (82–90%) as a nearly white to pale yellow solid (Note 3). This material may be purified by recrystallization from boiling water (Note 4), when minute white plates, m.p. 173–174°, are obtained. The method is applicable to the preparation of other substituted arylureas (Note 5).

2. Notes

1. An enameled-steel vessel of approximately 2-gal. capacity is suitable for carrying out this reaction.
2. After removal of the heat source, a vigorous reaction may continue for a few minutes, and the reaction mixture tends to froth somewhat. It eventually sets to a sponge-like formation of a crystalline mass. In smaller-scale experiments the final stage of the reaction is more easily controlled. The checkers employed one-tenth the scale and conventional equipment.
3. The crude product contains varying small quantities of the symmetrical disubstituted compound, di-(*p*-ethoxyphenyl)urea [(p-$C_2H_5OC_6H_4NH)_2CO$]. This substance is removed in the crystallization from water (Note 4).
4. To 1 l. of boiling water, 35 g. of crude *p*-ethoxyphenylurea is added. The bulk of the urea dissolves readily, and the solution is decolorized by the addition of 3 g. of activated charcoal, boiled for 5 minutes, and quickly filtered with suction through a pre-heated

Büchner funnel. The colorless filtrate is slowly cooled to 0°, when lustrous minute plates of *p*-ethoxyphenylurea separate. An 80% recovery of material having m.p. 173–174° is obtained. Prolonged boiling of the solution should be avoided, since slow conversion to *sym*-di-(*p*-ethoxyphenyl) urea occurs under these conditions.

5. *p*-Anisidine hydrochloride (0.5 mole), When boiled with the proportionate quantities of urea and other reagents for 1 hour, gives 80–85% yields of *p*-methoxyphenylurea. Owing to the greater solubility of this product in water, less of the material separates during the heating period, but satisfactory crystallization occurs when the reaction liquid is slowly cooled to 0°. 1-Amino-2-naphthol hydrochloride gives 72–87% yields of 1-(2-hydroxy-1-naphthyl)urea.

3. Discussion

p-Ethoxyphenylurea has been prepared by the action of potassium cyanate on *p*-phenetidine hydrochloride[1] or *p*-phenetidine acetate,[2] and by the interaction of *p*-phenetidine with the following agents: phosgene in benzene or toluene and treatment of the product with ammonia;[3] urethan;[4] urea salts;[5] acetylurea;[6] and a mixture of urea and ammonium chloride.[7] It has been obtained from the reaction of phenetidine salts (usually the hydrochloride) with urea,[5,8] or with a mixture of sodium cyanide and sodium hypochlorite or peroxide.[9] *p*-Ethoxyphenylurea has also been prepared by heating *p*-ethoxyphenylurethan and ammonia to 100–180°;[4] by heating di-(*p*-ethoxyphenyl)urea with urea, ammonium carbamate, commercial ammonium carbonate,[10] or ethanol and ammonia;[11] by treating ammonium *p*-ethoxyphenyldithiocarbamate with lead carbonate in alcoholic solution;[12] by ethylating *p*-hydroxyphenylurea;[13] and by the action of ammonia on *p*-ethoxyphenyl isocyanate.[14]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Dulcin

sym-di-(p-ethoxyphenyl) urea

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ammonium carbonate

ammonia (7664-41-7)

Benzene (71-43-2)

ammonium chloride (12125-02-9)

sodium cyanide (143-33-9)

toluene (108-88-3)

phosgene (75-44-5)

urea (57-13-6)

ammonium carbamate (1111-78-0)

peroxide (7722-84-1)

sodium hypochlorite (7681-52-9)

potassium cyanate (590-28-3)

1-amino-2-naphthol hydrochloride (1198-27-2)

urethan (51-79-6)

1-(2-hydroxy-1-naphthyl)urea

acetylurea (591-07-1)

p-phenetidine (156-43-4)

p-phenetidine hydrochloride (637-56-9)

p-Methoxyphenylurea (1566-42-3)

p-Ethoxyphenylurea, Urea, p-ethoxyphenyl- (150-69-6)

di-(p-ethoxyphenyl)urea

p-Anisidine hydrochloride (20265-97-8)

p-phenetidine acetate

p-ethoxyphenylurethan

ammonium p-ethoxyphenyldithiocarbamate

p-hydroxyphenylurea

p-ethoxyphenyl isocyanate (32459-62-4)

lead carbonate

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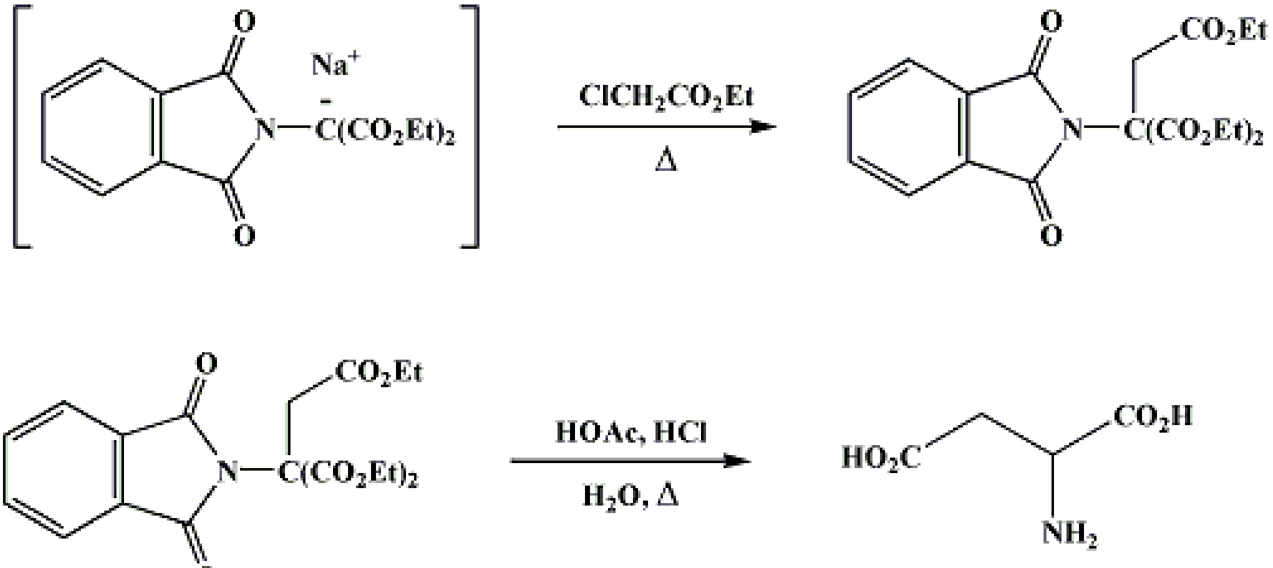
Organic Syntheses, *CV 4*, *55*

DL-ASPARTIC ACID



dl - aspartic acid

Submitted by M. S. Dunn and B. W. Smart[1].
Checked by H. T. Clarke and W. Pearlman.

1. Procedure

A. *Triethyl α-phthalimidoethane*-α,α,β-*tricarboxylate.* Three hundred and twenty-seven grams (1.0 mole) of diethyl sodium phthalimidomalonate[2] and 735 g. (6.0 moles) of ethyl chloroacetate (b.p. 144–145°) are placed in a 2-l. Claisen flask fitted with a reflux condenser and rubber stoppers. The mixture is heated under reflux in an oil bath at 150–160° for 2.25 hours. The excess ethyl chloroacetate is removed by distillation at 30 mm. until the heating bath temperature reaches 150° and no more distillate is obtained (Note 1). The brown residual mass is cooled and then extracted with 1250 ml. of ether. The oil dissolves, leaving a solid residue which is separated by filtration and washed with 750 ml. of ether. The combined ether extracts are distilled to remove ether, and the residual oil is heated on a steam bath under reduced pressure (35 mm.) to remove traces of ethyl chloroacetate. The yield of triethyl α-phthalimidoethane-α,α,β-tricarboxylate, dried at 45° for 48 hours, is 373–389 g. (95–99%) (Note 2).

B. DL-*Aspartic acid.* A mixture of 383 g. of the above crude product, 1 l. of concentrated hydrochloric acid, 1 l. of glacial acetic acid, and 1 l. of water is boiled under reflux in a 5-l. round-bottomed flask for 2–3 hours. The reflux condenser is then replaced by a fractionating column, and the mixture is slowly distilled until the temperature at the head of the column has risen to 108°. This requires about 13 hours. The distillate amounts to 1.5 l. (Note 3).

The residual mixture is allowed to cool, and the phthalic acid which crystallizes is removed by filtration and washed with 350 ml. of 1% hydrochloric acid (Note 4). The combined filtrate and washings are distilled nearly to dryness on a steam bath under reduced pressure; the bulk of the hydrochloric and acetic acids remaining is removed by slowly adding 300 ml.

of water through a dropping funnel while the distillation under reduced pressure is continued. The dark brown residue is warmed on a steam bath with 700 ml. of water, is allowed to cool, and is filtered to remove a small amount of black insoluble matter. The filtrate is decolorized with 2 g. of Norit, 200 ml. of hot water being used to wash the Norit. The volume of the combined filtrate and washings, amounting to about 1.2 l., is measured accurately, and a small portion is analyzed for chloride (Note 5). An amount of pyridine corresponding exactly to the chloride content is added, diluted with 500 ml. of 95% ethanol. The DL-aspartic acid, which crystallizes at once, is separated by filtration after the mixture has stood for 24 hours at room temperature and is washed with 50–100 ml. of cold water (Note 6).

The crude DL-aspartic acid, amounting to 58–60 g., is recrystallized from 600 ml. of hot water and yields 54 g. of pure DL-aspartic acid. The mother liquors on evaporation to about 90 ml. yield an additional 2–3 g. (Note 7). The total yield of pure colorless DL-aspartic acid is 56–57 g. (42–43%) (Note 8).

2. Notes

1. From 490 to 536 g. of ethyl chloroacetate (b.p. 144–145°) is recovered by the distillation.
2. Although this product cannot be purified by distillation, it contains almost the theoretical amount of nitrogen as shown by Kjeldahl analysis.
3. During the first few hours the distillate contains ethyl acetate; the distillate obtained during the first hour, amounting to 137 ml., distils below 99° and on saturation with sodium chloride yields 115 ml. of crude ethyl acetate.
4. The phthalic acid so obtained is brown and weighs 140–150 g.
5. The total amount of chloride found should be less than 1 mole.
6. The mother liquor contains too little DL-aspartic acid to justify its recovery. When the filtrate and washings are evaporated to a syrup and treated with 500 ml. of 95% ethanol, the pyridine hydrochloride dissolves completely, leaving 8–9 g. of crude glycine which yields little or no sparingly soluble DL-aspartic acid on treatment with a minimum quantity of cold water.
7. The final mother liquor from the recrystallization of DL-aspartic acid yields a small quantity (about 0.5 g.) of glycine.
8. The purity of the recrystallized DL-aspartic acid was established by nitrogen analysis by the Kjeldahl and Van Slyke methods. The decomposition point of this product is 325–348°.

3. Discussion

The above method for the preparation of DL-aspartic acid is a modification of one described by Dunn and Smart.[3] Other methods are: the decomposition of acid ammonium malate by heat;[4] the racemization of active aspartic acid[5] and active asparagine;[6] the reaction of maleic and fumaric acids with ammonia in a closed tube;[7] the reduction of oxalacetic ester oxime;[8] the reduction of silver fumarate by hydroxylamine hydrochloride;[9] the reduction of nitrosuccinic ester;[10] the catalytic reduction and amination of oxalacetic acid;[11] the hydrolysis of triethyl α-aminoethane-α,α,β-tricarboxylate;[12] the hydrolysis of β,β-

dicarbethoxy-β-acetylaminopropionic acid;[13] the hydrolysis of dimethyl (carbethoxy) formamidomalonate;[14] the oxidation of β-(2-furyl)-α-alanine by potassium permanganate;[15] and the hydrolysis of diethyl α-acetyl-α-aminosuccinate.[16]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

maleic and fumaric acids

nitrosuccinic ester

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ammonia (7664-41-7)

ethyl acetate (141-78-6)

ether (60-29-7)

potassium permanganate (7722-64-7)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

Norit (7782-42-5)

pyridine (110-86-1)

Ethyl chloroacetate (105-39-5)

Hydroxylamine hydrochloride (5470-11-1)

Glycine (513-29-1)

phthalic acid (88-99-3)

pyridine hydrochloride (628-13-7)

diethyl sodium phthalimidomalonate

asparagine (70-47-3)

DL-Aspartic acid (617-45-8)

aspartic acid (56-84-8)

silver fumarate

oxalacetic acid (328-42-7)

Triethyl α-phthalimidoethane-α,α,β-tricarboxylate (76758-31-1)

triethyl α-aminoethane-α,α,β-tricarboxylate

β,β-dicarbethoxy-β-acetylaminopropionic acid

dimethyl (carbethoxy)formamidomalonate

β-(2-furyl)-α-alanine

diethyl α-acetyl-α-aminosuccinate

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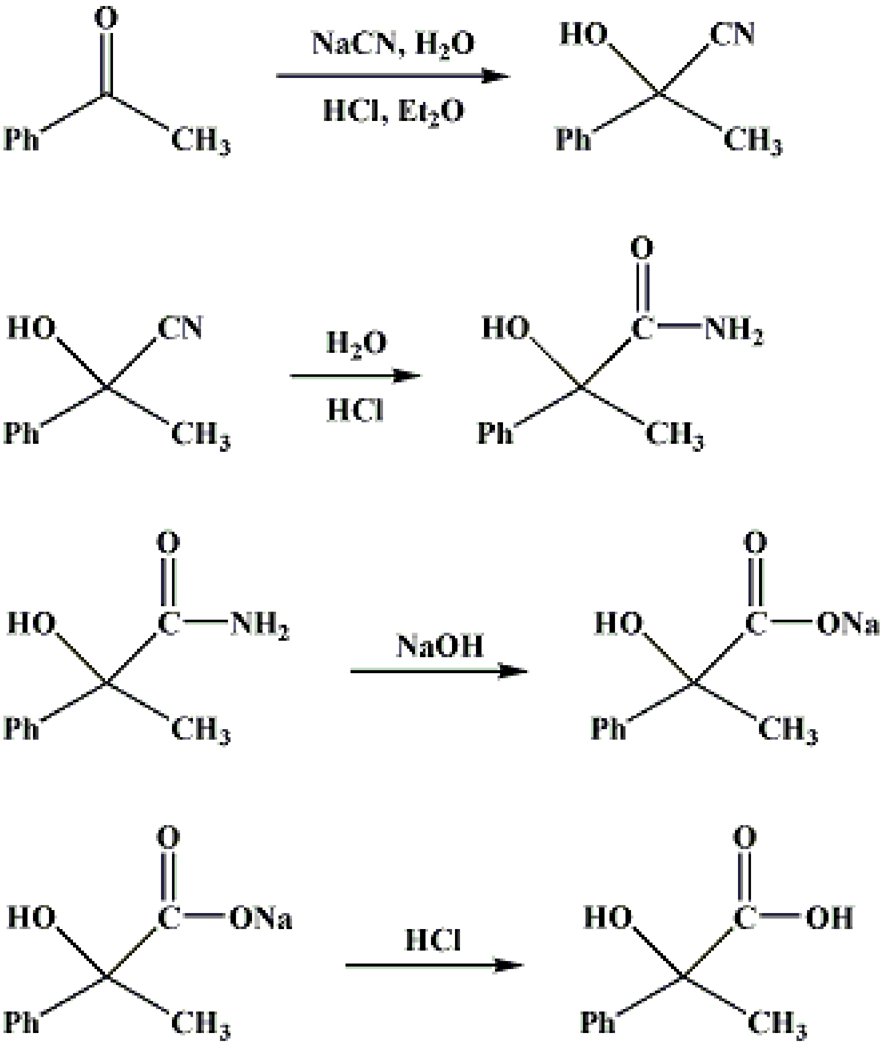
Organic Syntheses, CV 4, 58

ATROLACTIC ACID



Submitted by Ernest L. Eliel and Jeremiah P. Freeman[1].
Checked by Arthur C. Cope, William F. Gorham, and Roscoe A. Pike.

1. Procedure

Caution! This preparation must be conducted in a hood to avoid exposure to the poisonous hydrogen cyanide that is evolved.

In a 1-l. three-necked round-bottomed flask equipped with a Hershberg stirrer, a thermometer, and a 250-ml. dropping funnel are placed 80 g. (0.67 mole) of acetophenone, 60 ml. of ether, and 100 ml. of water. The apparatus is assembled in a well-ventilated hood, the flask is surrounded by an ice-salt bath, and 82 g. (1.67 moles) of granulated sodium cyanide is added all at once with vigorous stirring. When most of the sodium cyanide has dissolved and the temperature of the mixture has fallen to 5°, 140 ml. (1.7 moles) of concentrated hydrochloric acid is added from the dropping funnel at such a rate that the temperature remains between 5° and 10°. The

addition requires about 1.7 hours. After all the acid has been added, the cooling bath is removed and vigorous stirring is continued for 2 hours. The mixture is allowed to settle, and the liquid portion is decanted into a 1-l. separatory funnel. The water layer is returned to the reaction flask, and 100 ml. of water is added to dissolve the salts. The aqueous solution is extracted with four 50-ml. portions of ether, and the original ether layer and extracts are combined in a 500-ml. round-bottomed flask. The ether is distilled at 20–30 mm. pressure (water aspirator) (Note 1), and the residual oil is poured slowly with stirring into 160 ml. of concentrated hydrochloric acid in a 1-l. round-bottomed flask. The mixture then is saturated with hydrogen chloride gas in the hood (Note 2) and (Note 3) and allowed to stand overnight.

Part of the excess hydrogen chloride is removed by blowing (or drawing) air through the solution for 1 hour. The solution then is made alkaline by the slow addition of 50% aqueous sodium hydroxide. (Note 4) with mechanical stirring and cooling in an ice bath. Solid sodium hydroxide (24 g.) is added, and the mixture is steam-distilled until no more ammonia and acetophenone pass into the distillate (Note 5). About 3–4 l. of distillate is collected (Note 6).

Water is added to the residue if necessary to make the volume 700 ml., and the solution is treated with 2 g. of Norit and filtered with suction (Note 7). The filtrate is extracted with 100 ml. of ether (which is discarded), and acidified by the addition of 80 ml. of concentrated hydrochloric acid. After thorough chilling, preferably overnight in a refrigerator, the precipitated atrolactic acid is collected on a suction filter (Note 8) and air-dried at a temperature not exceeding 65°.

The crude product weighs somewhat more than 70 g. and contains water and sodium chloride. It is dissolved in 500 ml. of boiling benzene, the solution is filtered by gravity, and the solid in the flask and funnel is rinsed with 50 ml. of boiling benzene. The filtrate is concentrated by distillation until no more water collects in the distillate, and the residual solution (300–400 ml.) is cooled. The atrolactic acid which crystallizes is collected on a suction filter and washed with 25 ml. of cold benzene and 25 ml. of commercial pentane (b.p. 30–40°). After air-drying, the cream-colored product amounts to 42.9–43.5 g., m.p. 88–90° with shrinking at 82° (Note 9) and (Note 10). It is pure enough for most purposes but is intermediate in composition between the anhydrous acid and hemihydrate and contains about 3% sodium chloride. This product is dissolved in 200 ml. of boiling water and treated with 10 g. of Norit. The solution is filtered and cooled overnight at 0–5°. The pure, colorless crystals of atrolactic acid hemihydrate that separate are collected on a suction filter and air-dried. The yield is 33.5–34.7 g. (29–30%), m.p. 88–90° with softening beginning at 75°. The anhydrous acid can be obtained by drying the hemihydrate at 55°/1–2 mm.; m.p. 94.5–95°.

2. Notes

1. By maintaining ebullition with a capillary air inlet and cooling the receiver in

a bath containing Dry Ice and trichloroethylene, the distillation can be completed in 1 hour or less.
2. The solution becomes homogeneous when it is nearly saturated. An exothermic reaction begins within a few minutes, and some hydrogen chloride gas escapes.
3. The preparation should be carried to this point in 1 day; the time required is about 8 hours. All the operations must be conducted in a well-ventilated hood.
4. About 150 g. of the 50% sodium hydroxide solution is required.
5. The distillation flask should be heated so as to maintain a liquid volume of 600–700 ml.
6. Acetophenone (15–16.5 g., b.p. 92–94°/20 mm.) can be recovered by extracting the distillate with 100 ml. of pentane (b.p. 30–40°). The extract is dried over sodium sulfate, concentrated, and distilled.
7. Only a small amount of solid, in addition to the Norit, should be retained by the filter. If a copious precipitate of sodium atrolactate forms, it should be dissolved by the addition of more water.
8. Only small amounts of crude atrolactic acid are recovered by extracting the filtrate with ether.
9. If the yield is low, the mother liquors should be concentrated to a volume of 50 ml. A second crop of crystals can sometimes be obtained in that way.
10. The submitters have obtained the same yields in preparations on five times this scale.

3. Discussion

Atrolactic acid has been prepared by the oxidation of hydratropic acid with alkaline permanganate,[2] by hydrolysis of α-chloro- or α-bromohydratropic acid,[3,4] by sodium amalgam reduction of β,β-dibromoatrolactic acid,[5] from α-aminohydratropic acid and nitrous acid,[6,7] by permanganate oxidation of 2,5-dihydroxy-2,5-diphenyl-3-hexyne,[8] by reaction of ethyl phenylglyoxylate with methylmagnesium iodide followed by hydrolysis,[9] from pyruvic acid and phenylmagnesium bromide,[10] and from α,α-dibromopropiophenone and sodium hydroxide.[11] The last method could not be adapted to the preparation of the acid in large quantities by the submitters.

The synthesis of atrolactic acid through acetophenone cyanohydrin was first described by Spiegel[12] and has since been used by several other investigators.[6,13,14,15,16,17] The above preparation is adapted from the methods of McKenzie and Clough[15] and Freudenberg, Todd, and Seidler.[17]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

atrolactic acid hemihydrate

α-chloro- or α-bromohydratropic acid

hydrogen chloride, hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

Benzene (71-43-2)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium cyanide (143-33-9)

sodium chloride (7647-14-5)

hydrogen cyanide (74-90-8)

sodium sulfate (7757-82-6)

nitrous acid (7782-77-6)

Acetophenone (98-86-2)

Norit (7782-42-5)

sodium (13966-32-0)

Phenylmagnesium bromide (100-58-3)

methylmagnesium iodide (917-64-6)

ethyl phenylglyoxylate (1603-79-8)

Pentane (109-66-0)

Pyruvic acid (127-17-3)

acetophenone cyanohydrin

Atrolactic acid (515-30-0)

sodium atrolactate

hydratropic acid (492-37-5)

β,β-dibromoatrolactic acid

α-aminohydratropic acid (6945-32-0)

2,5-dihydroxy-2,5-diphenyl-3-hexyne

α,α-dibromopropiophenone

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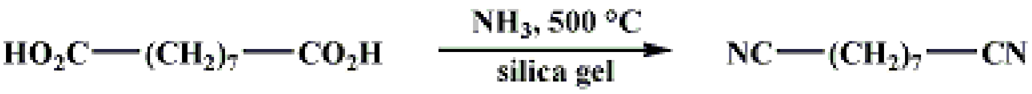
Organic Syntheses, CV 4, 62

AZELANITRILE



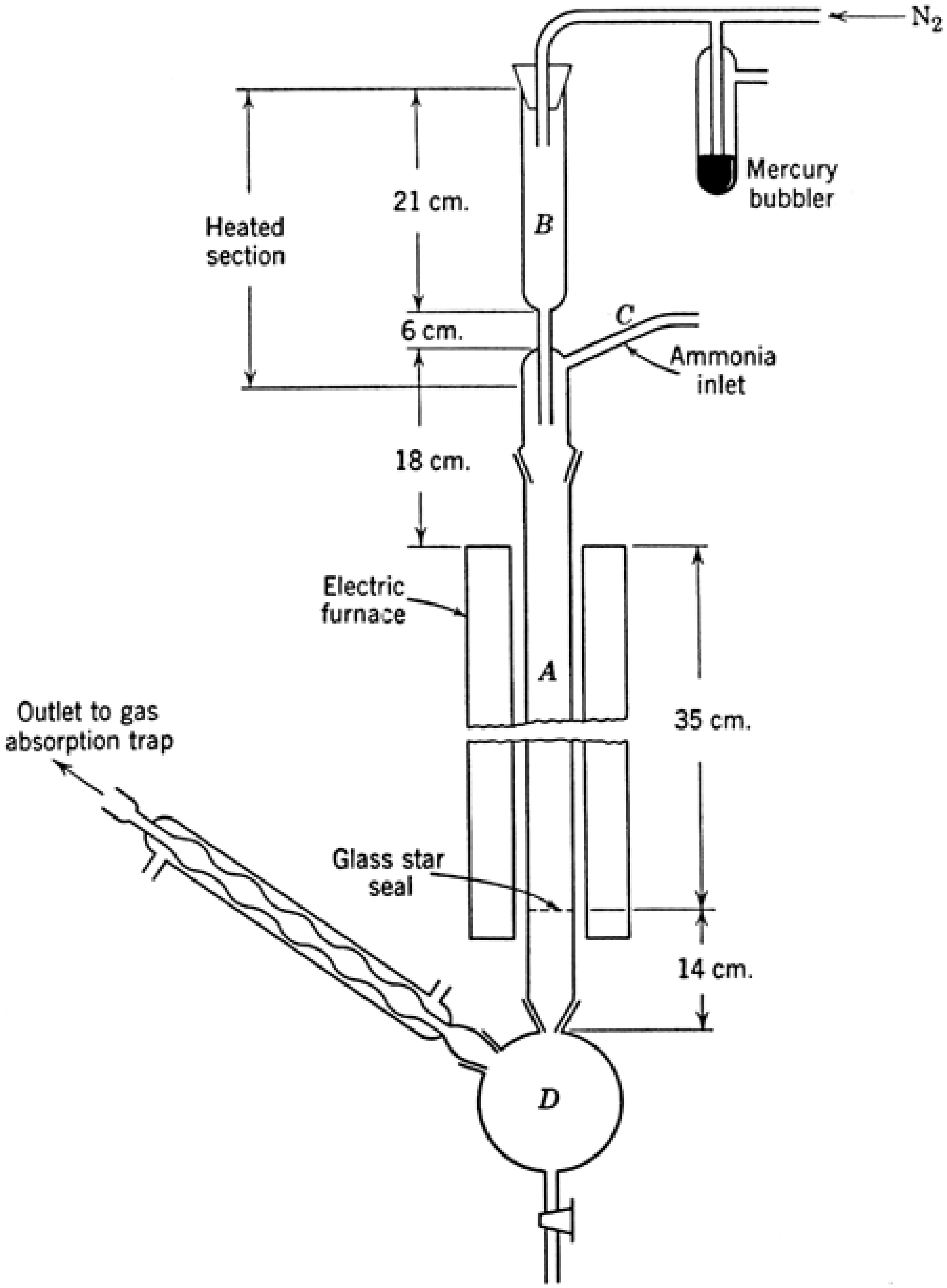
Submitted by Arthur C. Cope, Robert J. Cotter, and Leland L. Estes[1].
Checked by N. J. Leonard and R. W. Fulmer.

1. Procedure

Caution! This preparation should be conducted in a hood to avoid exposure to ammonia.

The reaction is carried out in the apparatus shown in f.htmig. 3. *A* is a Pyrex combustion tube, 54 cm. long and 3.5 cm. in diameter, having a glass star seal or indentations 14 cm. from the lower end to support the catalyst, and fitted with ground-glass joints. *B* is a Pyrex tube, 21 cm. long and 3.5 cm. in diameter, which has a 6-cm. length of 6-mm. capillary tubing attached at the lower end. The capillary tube is attached to a ground-glass joint and an inlet tube, *C*, is inserted above the end of the capillary tube. The top section of the apparatus (above the first ground-glass joint) is covered with asbestos and wound with 14 ft. of No. 22 Chromel A resistance wire. *D* is a 500-ml. round-bottomed two-necked flask with ground-glass joints and a 4-mm. stopcock sealed to the bottom. An efficient condenser is attached to the flask and connected to a gas absorption trap.[2] The hot junction of a pyrometer is placed in contact with the glass combustion tube *A* at its center, and the tube is wrapped with a thin layer of asbestos paper. An electric furnace with a 33-cm. heated section which is rated at 6.8 amp. (110 v.) is used to heat the combustion tube.

Fig. 3.



A piece of glass wool is placed on the star seal, and the combustion tube is filled with 74 g. (110 ml.) of 14- to 20-mesh silica gel (Note 1). The tube is heated to 500°, and nitrogen is passed through the column for 30 minutes to activate the catalyst. Anhydrous ammonia is then passed through the column at a rate of 3.9 moles per hour (Note 2). Molten azelaic acid, 100 g. (0.53 mole) (Note 3), is poured into the reservoir *B*, which is maintained at 108–112° by means of the electrically heated jacket, and

allowed to drop onto the hot silica gel over a 4-hour period (Note 4). After the azelaic acid has been added, ammonia is passed through the tube for an additional period of 30 minutes, with the temperature maintained at 500°, to complete the removal of product from the combustion tube.

Water (100 ml.) and ether (350 ml.) are added to the condensate in the receiver *D*, and the mixture is shaken. The aqueous layer is removed, and the ethereal solution is washed with 75 ml. of 6*N* sodium hydroxide solution. The ethereal solution is washed with water until the washings are neutral and is dried over anhydrous magnesium sulfate. The ether is removed under reduced pressure by warming with a water bath, and the residue is distilled through a Vigreux or packed column. The azelanitrile is collected at 120–121°/0.2 mm., 175–176°/6 mm., in a yield of 50–54 g. (63–68%), n_D^{25} 1.4443–1.4448 (Note 5) and (Note 6).

2. Notes

1. Refrigeration grade silica gel, 14- to 20-mesh, obtained from the Davison Chemical Corporation, Baltimore, Maryland, was used.
2. A manometer-type flow meter[3] was calibrated by passing ammonia through the meter into a standard solution of 4*N* hydrochloric acid containing a few drops of phenolphthalein solution. The time required for exact neutralization of a measured volume of acid was recorded, together with the pressure differential, in millimeters, between the manometer arms. The logarithm of the rate of flow in moles per hour plotted against the logarithm of the pressure, for various rates of flow, gave a straight-line plot which was used to determine flow rates for other pressure differentials.
3. Azelaic acid obtained from Emery Industries, Inc., Cincinnati, Ohio, was recrystallized from water to a melting point of 101–102°.
4. Comparable results have been obtained when the acid was added over a 2-hour period. It is desirable to maintain a nitrogen atmosphere over the acid at a pressure slightly above that of the ammonia flow to prevent reduction of the acid flow by salt formation in the capillary.
5. Cooling the receiver *D* may help prevent loss of product by mechanical carry-over in the gas flow.
6. This preparation illustrates a general method for producing nitriles from monocarboxylic[4] and dicarboxylic acids.[5]

3. Discussion

Azelanitrile has been prepared in 80% yield by treating 1,7-dibromoheptane with potassium cyanide;[6] by treating 1,7-diiodoheptane with potassium cyanide;[7] from azelaic acid through the intermediate acid chloride and diamide;[8] in 60–70% yield by the dehydration of the diamide of azelaic acid;[9] and by the action of sodium amide and acetonitrile on the 1,5-dihalopentanes.[10]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

diamide of azelaic acid

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ether (60-29-7)

acetonitrile (75-05-8)

sodium hydroxide (1310-73-2)

nitrogen (7727-37-9)

potassium cyanide (151-50-8)

phenolphthalein (77-09-8)

Azelaic acid (123-99-9)

magnesium sulfate (7487-88-9)

Azelanitrile (1675-69-0)

sodium amide (7782-92-5)

1,7-dibromoheptane (4549-31-9)

1,7-diiodoheptane (51526-03-5)

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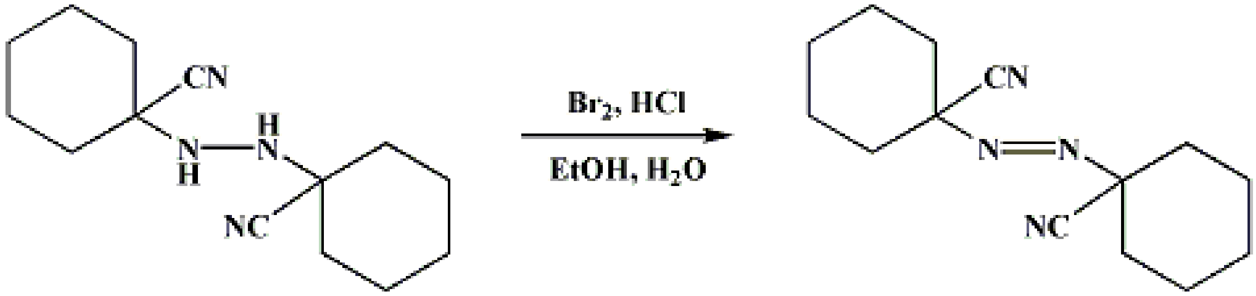
1,1'-AZO-*bis*-1-CYCLOHEXANENITRILE

[Cyclohexanecarbonitrile, 1,1'-azodi-]



Submitted by C. G. Overberger, Pao-tung Huang, and M. B. Berenbaum[1].
Checked by N. J. Leonard and E. H. Mottus.

1. Procedure

In a 600-ml. beaker equipped with a stirrer, thermometer, and dropping funnel are placed 24.6 g. (0.1 mole) of finely powdered 1,2-di-1-(1-cyano)cyclohexylhydrazine (p. **274**) and 130 ml. of 90% ethanol. To this mixture is added slowly, with cooling, 45 ml. of concentrated hydrochloric acid. The beaker is placed in an ice bath, and, after the suspension has been cooled to 10°, bromine is added at such a rate that the temperature does not rise above 15°. About 16–17 g. (about 0.1 mole) of bromine is required to reach the end point characterized by Permanent orange-yellow color. The reaction mixture is poured into 80 ml. of ice water. After 15 minutes the suspension is filtered with the aid of a Büchner funnel, washed with 250 ml. of water, and pressed dry. The solid is transferred to a 500-ml. Erlenmeyer flask, 120 ml. of boiling 95% ethanol is added, and the crude product is dissolved as rapidly as possible while being heated on a steam bath (Note 1). The solution is filtered through a fluted filter in a heated funnel, and the filtrate is placed in a refrigerator overnight. The solid is collected on a Büchner funnel and dried in a vacuum desiccator over calcium chloride. The yield of product is 20.5–22.0 g. (84–90%); m.p. 113.5–115.5° (Note 2) and (Note 3).

2. Notes

1. Prolonged heating of the solution will cause excessive decomposition of the azo compound.
2. This compound is stable indefinitely if stored at room temperature. Prolonged heating at temperatures of 80° or higher, however, will result in rapid decomposition involving possible hazards.[2]
3. 2,2'-Azo-*bis*-isobutyronitrile can be prepared in a similar manner. The product after recrystallization from 95% ethanol is obtained in a yield of 85–90%; m.p 102–103°. This compound must be regarded as an explosive.[2]

3. Discussion

1,1'-Azo-*bis*-1-cyclohexanenitrile has been prepared in a similar manner by Hartman.[3] The method has been substantiated by Overberger, O'Shaughnessy, and Shalit [4] and is a modification of that used originally by Thiele and Heuser[5] for the synthesis of 2,2'-azo-*bis*-isobutyronitrile.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 273
- Org. Syn. Coll. Vol. 4, 274

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

1,2-Di-1-(1-cyano)cyclohexylhydrazine

ethanol (64-17-5)

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

bromine (7726-95-6)

2,2'-Azo-bis-isobutyronitrile

1,1'-AZO-bis-1-CYCLOHEXANENITRILE, Cyclohexanecarbonitrile, 1,1'-azodi- (2094-98-6)

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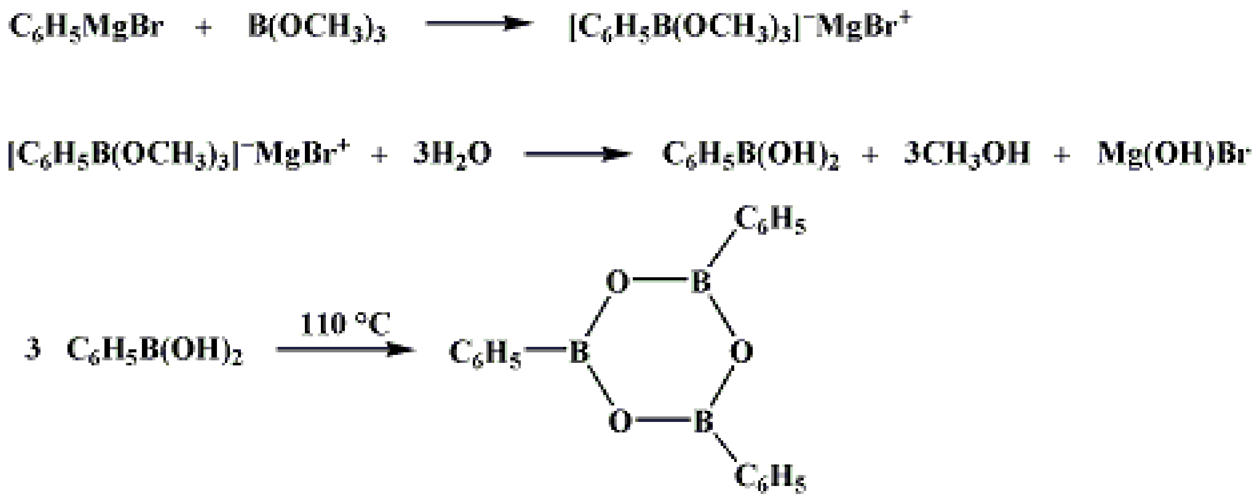
BENZENEBORONIC ANHYDRIDE

[Boroxin, triphenyl-]



Submitted by Robert M. Washburn, Ernest Levens, Charles F. Albright, and Franklin A. Billig[1].
Checked by B. C. McKusick and H. C. Miller.

1. Procedure

Caution! Benzeneboronic acid and its anhydride are toxic substances and may irritate mucous tissues such as those of the eyes. In case of contact, carefully wash exposed parts of the body with soap and water (Note 1).

The apparatus consists of a four-necked 5-l. round-bottomed Morton flask[2] fitted with a 500-ml. graduated dropping funnel with a pressure-equalizing side arm, a 1-l. graduated dropping funnel of the same type, a thermometer, an efficient mechanical stirrer (Note 2), and an inlet for dry nitrogen. The apparatus is thoroughly swept with dry nitrogen, and the reaction flask is charged with 1.5 l. of anhydrous ether, dry nitrogen (Note 3) being used for pressure transfer.

Three hundred thirty-six milliliters (312 g., 3 moles) of methyl borate is distilled directly into the 500-ml. dropping funnel shortly before starting the reaction (Note 4). One liter (544 g., 3 moles) of a 3*M* ethereal solution of phenylmagnesium bromide is pressure-transferred with dry nitrogen to the 1-l. dropping funnel (Note 5). During subsequent operations until the hydrolysis step, a positive pressure of 10–20 mm. of nitrogen is maintained in the closed system by means of a mercury bubbler to prevent access of atmospheric moisture. The ether is cooled to below −60° by a bath of Dry Ice and acetone and is kept below −60° all during the reaction (Note 6). The reactants are added to the well-stirred reaction mixture alternately in small portions, first 10 ml. of

methyl borate and then 30 ml. of phenylmagnesium bromide, the rate of addition being as rapid as is possible without the temperature of the mixture rising above –60° (Note 7). Stirring is continued for an additional 20 minutes below –60° after the addition of the reagents is completed.

The stirred mixture, maintained at or below 0°, is hydrolyzed by the addition of 200 ml. of distilled water during 5 minutes. It is then neutralized by addition of a solution of 84 ml. of concentrated sulfuric acid in 1.7 l. of distilled water during 15 minutes. The mixture is transferred to a 5-l. separatory funnel, the ether layer is separated, and the aqueous layer is extracted with three 250-ml. portions of ether.

The combined ether layer and extracts are transferred to a 5-l. round-bottomed flask equipped with a Hershberg stirrer,[3] a dropping funnel, a Claisen head with a water-cooled condenser, an electric heating mantle, and an ice-cooled receiver (Note 8). After approximately one-half of the ether has been removed by distillation from the stirred mixture, 1.5 l. of distilled water is added slowly while the distillation is continued until a head temperature of 100° is reached (Note 9).

While stirring is continued, the aqueous distilland is cooled in an ice bath (Note 10). The benzeneboronic acid, which separates as small white crystals, is collected on a Büchner funnel and washed with petroleum ether. The petroleum ether removes traces of dibenzeneborinic acid, which are seen in the hot mother liquor as globules of brown oil and which may color the product. The acid is dehydrated to benzeneboronic anhydride by heating it in an oven at 110° and atmospheric pressure for 6 hours (Note 11). Benzeneboronic anhydride is obtained as a colorless solid, weight 240–247 g. (77–79%) (Note 12), m.p. 214–216°.

2. Notes

1. A summary of the physiological activity of benzeneboronic acid may be found in reference [4].
2. The submitters found that for a preparation of this size a 1-inch Duplex Dispersator (Premier Mill Corp., Geneva, New York) operating at 7500 r.p.m. provided excellent agitation of the heterogeneous reaction mixture. For smaller preparations (1-l. flask) they found that a Stir-O-Vac (Labline, Inc., 217 N. Desplainer St., Chicago 6, Illinois) operating at 5000 r.p.m. was satisfactory. The type of agitation is very important for, whereas the submitters obtained yields of around 91%, the checkers obtained yields of only 77–80% with either a Morton stirrer[2] (excessive splashing deposited some of the reaction mixture on the warm upper walls of the flask) or a Polytron dispersion mill type of stirrer (there was too much hold-up in the stirrer housing).
3. Tank nitrogen was dried with phosphorus pentoxide.
4. Methyl borate (b.p. 68°) forms a 1:1 azeotrope (b.p. 54.6°) with methanol (b. p. 64°).[5] Since the presence of even a small amount of methanol reduces the

yield considerably more than would be expected from the stoichiometry, [46,7] methyl borate stocks should be freshly distilled through a good column to remove as fore-run any methyl borate-methanol azeotrope which may have been formed by hydrolysis during storage.

5. Mallinckrodt analytical reagent grade ether, dried over sodium, was used. The methyl borate was the commercial product of American Potash and Chemical Corporation containing 99% ester as received. The phenylmagnesium bromide was purchased as a 3.0*M* solution in ether from Arapahoe Special Products, Inc., Boulder, Colorado.

6. The yield of benzeneboronic anhydride is highly dependent upon the reaction temperature, as the following data of the submitters show. At a reaction temperature of 15° the yield was 49%; at 0°, 76%; –15°, 86%; –30°, 92%; –45°, 92%; –60°, 99%. The yields are based on the combined first and second crops of benzeneboronic acid.

7. At a given temperature, the maximum yield of benzeneboronic acid and the minimum amount of by-product dibenzeneborinic acid are obtained when neither reagent is present in excess. The addition of small increments of reactants is a convenient approximation imposed by the difficulty of adjusting stopcocks to small rates of flow. Alternatively, the Hershberg dropping funnel[8] or other metering device may be used to maintain the stoichiometry. Addition times, which depend upon the efficiency of stirring and heat transfer, vary from about 1 hour at –60° to 15 minutes at 0°.

8. Stirring is helpful during the ether distillation to prevent superheating.

9. Small amounts of benzene, phenol, and biphenyl, which may be formed in the reaction, are removed by the steam distillation. Enough water has been added to ensure solution of all of the product.

10. The product crystallizes at 43° with a temperature rise to 45°. The solubility of benzeneboronic acid in water (g./100 g. of water) is approximately 1.1 at 0° and 2.5 at 25°; the solubility-temperature relationship is linear to at least 45°.

11. If benzeneboronic acid rather than its anhydride is desired, it can be obtained by air-drying the moist acid in a slow stream of air nearly saturated with water. The yield of acid is 282–332 g. One can readily convert the anhydride to the acid by recrystallizing it from water. Benzeneboronic acid gradually dehydrates to the anhydride if left open to the atmosphere at room temperature and 30–40% relative humidity. The melting point observed is that of the anhydride because the acid dehydrates before it melts.

12. The submitters report a yield of 91% and state that an additional 27 g. (9%) of acid can be obtained from the aqueous mother liquor.

3. Discussion

The procedure described[4,6] is a modification of the method of Khotinsky and Melamed,[9] who first reported the preparation of boronic acids from Grignard reagents and borate esters. Benzeneboronic acid and the corresponding anhydride also have

been prepared by reaction of phenylmagnesium bromide with boron trifluoride;[10] by the reaction of phenyllithium with butyl borate;[11] by the reaction of diphenylmercury with boron trichloride;[12] by the reaction of benzene with boron trichloride in the presence of aluminum chloride;[13] and by the reaction of triphenylborane with boric oxide.[14]

The present procedure is also applicable to the synthesis of substituted benzeneboronic acids.[4] Benzeneboronic acid and its anhydride are of use as starting materials for the synthesis of phenylboron dichloride[15] and of various substituted boronic and borinic acids and esters.[7,16]

This preparation is referenced from:

- Org. Syn. 76, 86

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

boric oxide

sulfuric acid (7664-93-9)

Benzene (71-43-2)

methanol (67-56-1)

ether (60-29-7)

phenol (108-95-2)

nitrogen (7727-37-9)

aluminum chloride (3495-54-3)

sodium (13966-32-0)

Biphenyl (92-52-4)

Phenylmagnesium bromide (100-58-3)

Diphenylmercury (587-85-9)

Phenyllithium (591-51-5)

boron trifluoride (7637-07-2)

Benzeneboronic anhydride

Boroxin, triphenyl- (3262-89-3)

Benzeneboronic acid (98-80-6)

methyl borate

dibenzeneborinic acid

methyl borate-methanol

Butyl borate (688-74-4)

boron trichloride (10294-34-5)

triphenylborane (960-71-4)

phenylboron dichloride (873-51-8)

phosphorus pentoxide (1314-56-3)

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BENZHYDRYL β-CHLOROETHYL ETHER

[Ether, benzohydryl 2-chloroethyl]

Submitted by Shigehiko Sugasawa and Kunio Fujiwara[1].
Checked by N. J. Leonard, P. D. Thomas, and L. A. Miller.

1. Procedure

In a 500-ml. three-necked round-bottomed flask equipped with a sealed stirrer, a reflux condenser, and a dropping funnel are placed 36 g. (0.45 mole) of ethylene chlorohydrin (Note 1), 5 ml. of concentrated sulfuric acid, and 35 ml. of benzene. The mixture is warmed on a water bath, and to it is added, with efficient stirring, a solution of 55 g. (0.30 mole) of benzhydrol (Note 2) in 65 ml. of benzene (Note 3) during 30–50 minutes. The reaction mixture is heated at the reflux temperature for an additional 4 hours with stirring. To the cooled mixture is added about 35 ml. of benzene, and the combined benzene layer is washed with water and dried over calcium chloride. The drying agent is removed, the benzene is evaporated, and the residue is distilled under reduced pressure. The benzhydryl β-chloroethyl ether is collected at 144–148°/1.0 mm. (174–177°/4 mm.) as a colorless, viscous oil, n_D^{30} 1.5651, which should be removed from the receiver to a beaker or Erlenmeyer flask immediately after the distillation. The oil solidifies to a hard white mass, m.p. 27.4–27.8°, when kept in an ice chest (Note 4). The yield is 60.0–65.3 g. (81–88%).

2. Notes

1. Commercial ethylene chlorohydrin is dried over anhydrous sodium sulfate and distilled before use; b.p. 126–127°/743 mm. Excess is used to avoid the formation of dibenzhydryl ether as a by-product.
2. Eastman Kodak Company benzhydrol, m.p. 67–67.5°, can be used directly.
3. It is necessary to warm the mixture in order to complete the solution of benzhydrol in the benzene.
4. The checkers found this product to be analytically pure without recourse to further purification.

3. Discussion

This method is based on the process of the submitters.[2]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Ether, benzohydryl 2-chloroethyl

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

Benzene (71-43-2)

sodium sulfate (7757-82-6)

ethylene chlorohydrin (107-07-3)

Benzhydryl β-chloroethyl ether (32669-06-0)

benzhydrol (91-01-0)

dibenzhydryl ether (574-42-5)

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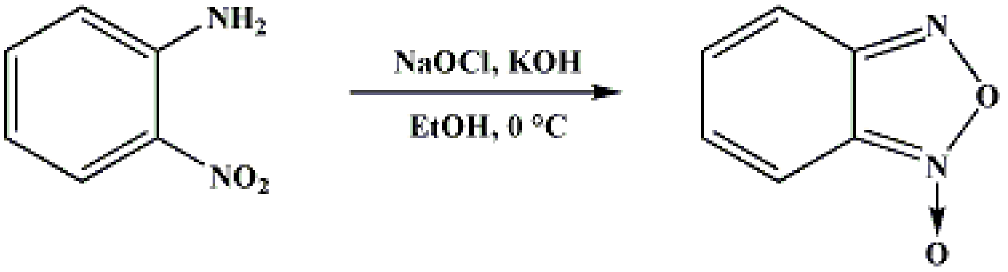
BENZOFURAZAN OXIDE

[Benzofurazan 1-oxide]

[I. HYPOCHLORITE OXIDATION OF *o*-NITROANILINE]



Submitted by F. B. Mallory[1]
Checked by T. L. Cairns and H. E. Simmons.

1. Procedure

A. *Sodium hypochlorite solution.* A solution of sodium hypochlorite[2] is prepared immediately before it is to be used. A mixture of 50 g. (1.25 moles) of sodium hydroxide and 200 ml. of water is swirled until the solid dissolves. The solution is cooled to 0°, and 100 g. of crushed ice is added. The flask is then placed in an ice bath, and chlorine gas from a tank is bubbled through the solution until 41 g. (0.58 mole) is absorbed. An excess of chlorine should be avoided. The solution of sodium hypochlorite is kept in the dark at 0° until needed.

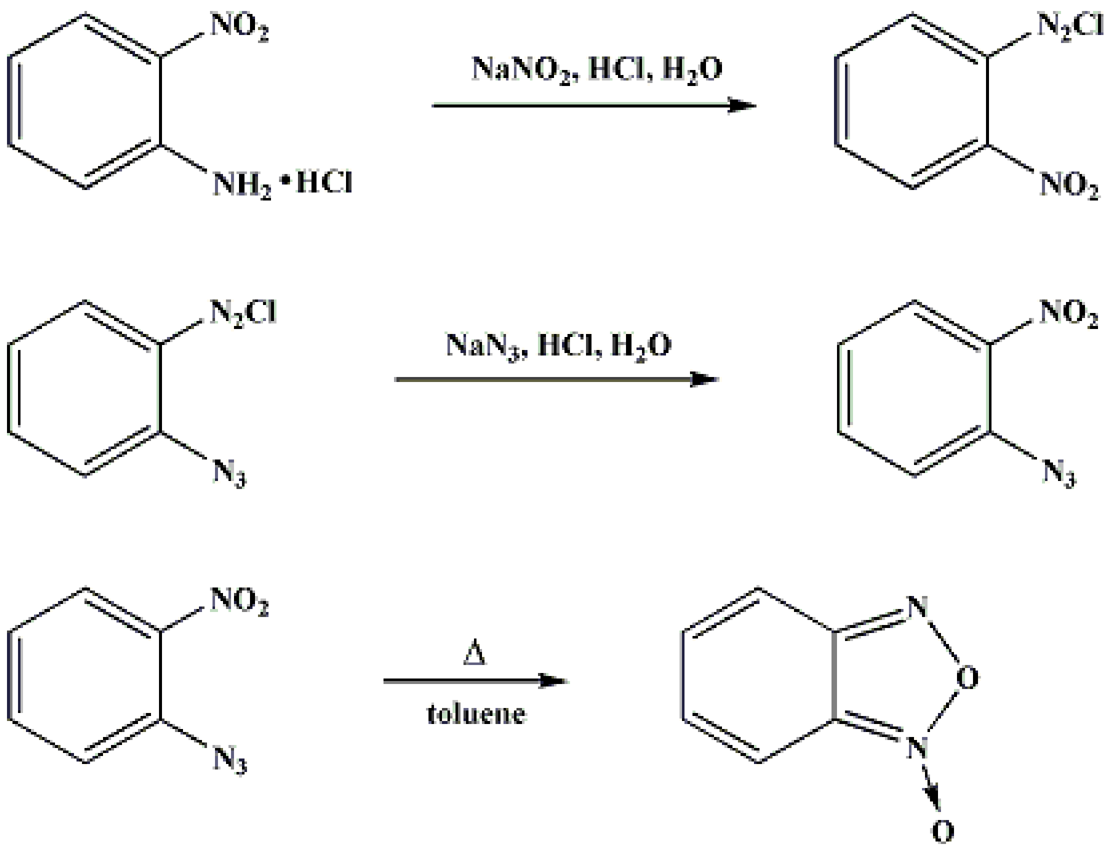
B. *Benzofurazan oxide.* A mixture of 21 g. (0.32 mole) of potassium hydroxide and 250 ml. of 95% ethanol in a 1-l. Erlenmeyer flask is heated on a steam bath until the solid dissolves (Note 1). *o*-Nitroaniline (40 g., 0.29 mole) (Note 2) is dissolved in the warm alkali solution. The resulting deep red solution is then cooled to 0°, and the sodium hypochlorite solution from part A is added slowly with good stirring over the course of 10 minutes (Note 3). The flocculent yellow precipitate is collected on a large Büchner funnel, washed with 200 ml. of water, and air-dried. The crude product weighs 36.0–36.5 g. and melts at 66–71° (Note 4). The product is purified by recrystallization from a solution made up from 45 ml. of 95% ethanol and 15 ml. of water. Material insoluble in the hot solvent is removed by filtration, and the hot filtrate is allowed to cool to room temperature. The yield of yellow benzofurazan oxide is 31.6–32.5 g. (80–82%), m.p. 72–73°.

2. Notes

1. A small residue of insoluble carbonate may be ignored.
2. Eastman Kodak white label grade material, melting at 71.5–73.5°, was used.

3. The temperature of the mixture should be kept close to 0° to avoid decomposition of the sodium hypochlorite and prevent formation of tarry materials that occurs at 10–12°. A Dry Ice-acetone bath was found convenient by the checkers.
4. There may be some material that does not melt under 100°, which is not present after recrystallization.

[II. DECOMPOSITION OF *o*-NITROPHENYLAZIDE]



Submitted by P. A. S. Smith and J. H. Boyer[3].
Checked by Arthur C. Cope, David J. Marshall, and Douglas S. Smith.

1. Procedure

A. *o-Nitrophenylazide.* A mixture of 28 g. (0.2 mole) of *o*-nitroaniline (Note 1), 80 ml. of water, and 45 ml. of concentrated hydrochloric acid is placed in a 500-ml. three-necked flask equipped with a stirrer, a thermometer, and a dropping funnel. The stirrer is started, and the flask is cooled in an ice-salt bath until the temperature of the mixture is 0–5°. After this temperature has been reached, the amine hydrochloride is diazotized by adding dropwise a solution of 14.5 g. of reagent grade sodium nitrite in 50 ml. of water. Stirring is then continued for 1 hour at 0–5°. The yellow-green solution is filtered from traces of insoluble impurities and poured into a 2-l. beaker surrounded by an ice bath. With stirring, a solution of 13 g. (0.2 mole) of sodium azide in 50 ml. of water is added (Note 2). Almost immediately the *o*-nitrophenylazide begins to precipitate as a light-cream to colorless solid, which is collected on a Büchner funnel

after the nitrogen evolution has ceased (15–20 minutes). The yield of *o*-nitrophenylazide, m.p. 52–55°, is 31–32 g. (94–97%). This crude product can be used for the preparation of benzofurazan oxide in Part B (Note 3).

The impure azide is dissolved in 110–120 ml. of 95% ethanol at 50–55° (Note 4), and 2 g. of activated carbon is added to aid in the removal of impurities. After being filtered through a steam-heated funnel, the warm solution is allowed to cool to room temperature, whereupon 14–15 g. of the product precipitates as light-yellow prisms, m.p. 53–55°. Concentration (Note 5) of the mother liquor to 30–40 ml. by evaporation at room temperature under an air stream causes the separation of an additional 7–8 g. of material, m.p. 52–54° (Note 6). The total yield of purified *o*-nitrophenylazide is 63–69%.

B. *Benzofurazan oxide.* A mixture of 16.4 g. (0.1 mole) of *o*-nitrophenylazide and 30 ml. of reagent grade toluene is placed in a 100-ml. round-bottomed flask equipped with a reflux condenser and is heated on a steam cone. Moderate nitrogen evolution commences immediately and continues for about 3 hours. When there are no more visible signs of gas evolution, the solution is cooled in an ice bath. After a few minutes, precipitation of light straw-colored clusters of prisms commences. About 6 g. of pure product, m.p. 70–72°, is obtained in this manner. Evaporation of the mother liquor yields another 4.5–5.5 g. of the oxide, slightly darker in color, m.p. 69–71°, which may be purified by recrystallization from 15 ml. of 70% ethanol to give material having a melting point of 70–71°. The total yield is 10.5–11.5 g. (77–85%).

2. Notes

1. If the *o*-nitroaniline is contaminated with *p*-nitroaniline, as it is likely to be, the yield and quality of the *o*-nitrophenylazide are lowered. The submitters obtained yields of 72–80% from *o*-nitroaniline melting at 70–71° obtained from the Eastman Kodak Company. The yields reported were obtained with *o*-nitroaniline melting at 72–73.5°.
2. A large container is necessary for this reaction because of excessive frothing which accompanies the nitrogen evolution. This step should be conducted in a hood to avoid possible exposure to hydrazoic acid.
3. A somewhat lower yield of benzofurazan oxide, m.p. 67–70°, is obtained if non-purified azide is used.
4. At this temperature there is no danger of decomposition. Loss of nitrogen commences at 80°.
5. Recrystallization of *o*-nitrophenylazide from a smaller volume of ethanol gives a considerably higher recovery, but it may be rather difficult to avoid separation of the product as an oil.
6. The submitters report that similar yields of phenylazide can be obtained from aniline in the same manner. Phenylazide must be distilled rather than recrystallized.[4]

3. Discussion

Benzofurazan oxide is prepared most conveniently by the hypochlorite oxidation of *o*-nitroaniline according to the method described, which is adapted from the procedure of Green and Rowe.[5]

Benzofurazan oxide also has been prepared by thermal decomposition of *o*-nitrophenylazide;[6,7] by oxidation of the dioxime of *o*-benzoquinone with dilute nitric acid or potassium ferricyanide in alkaline solution;[6] and by the oxidation of *o*-nitroaniline with phenyl iodosoacetate.[8]

The present synthesis of benzofurazan oxide from *o*-nitrophenylazide is a modification of the methods of Noelting and Kohn[7] and of Zincke and Schwarz.[6] The hypochlorite oxidation method has been used in the synthesis of various substituted benzofurazan oxides.[9]

o-Nitrophenylazide has been prepared by the action of sodium azide or hydrazine on *o*-nitrobenzenediazonium sulfate;[10] ammonia on *o*-nitrobenzenediazonium perbromide;[6,11] O-benzyl-hydroxylamine hydrochloride on *o*-nitrobenzenediazonium acetate;[12] sodium nitrite and hydrochloric acid on *o*-nitrophenylhydrazine;[6] and aqueous alkali on *o*-nitrobenzenediazo-4-semicar-bazinocamphor.[13]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrazoic acid

dioxime of o-benzoquinone

o-nitrobenzenediazonium perbromide

o-nitrobenzenediazo-4-semicar-bazinocamphor

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

sodium hydroxide (1310-73-2)

nitric acid (7697-37-2)

nitrogen (7727-37-9)

sodium nitrite (7632-00-0)

carbon (7782-42-5)

chlorine (7782-50-5)

potassium hydroxide (1310-58-3)

toluene (108-88-3)

sodium hypochlorite (7681-52-9)

hydrazine (302-01-2)

sodium azide (26628-22-8)

potassium ferricyanide (13746-66-2)

Benzofurazan oxide, Benzofurazan 1-oxide (480-96-6)

phenyl iodosoacetate

O-benzyl-hydroxylamine hydrochloride (2687-43-6)

o-NITROANILINE (88-74-4)

p-nitroaniline (100-01-6)

o-NITROPHENYLAZIDE (1516-58-1)

o-nitrobenzenediazonium sulfate

o-nitrobenzenediazonium acetate

o-nitrophenylhydrazine (3034-19-3)

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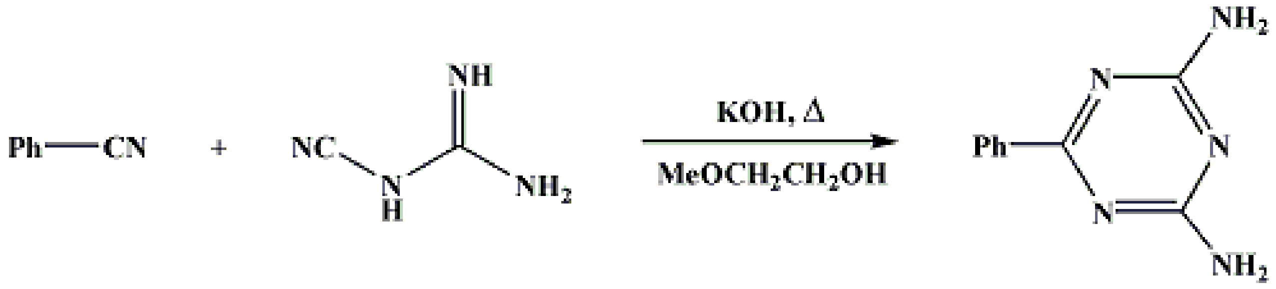
BENZOGUANAMINE

[*s*-Triazine, 2,4-diamino-6-phenyl-]



Submitted by J. K. Simons and M. R. Saxton[1].
Checked by T. L. Cairns and A. K. Schneider.

1. Procedure

Five grams of potassium hydroxide (85% KOH) is dissolved in 100 ml. of methyl Cellosolve (Note 1) in a 500-ml. flask (Note 2) fitted with a mechanical stirrer, reflux condenser, and a heating mantle. Dicyandiamide (50.4 g.; 0.6 mole) (Note 3) and benzonitrile (50 g.; 0.48 mole) are added, and the mixture is stirred and heated. A solution is formed, and, when the temperature reaches 90–110°, an exothermic reaction begins and the product separates as a finely divided white solid. The vigor of the reaction is kept under control by the refluxing of the solvent (Note 4).

When the exothermic reaction is ended, the slurry of product is stirred and refluxed for 5 hours to ensure complete reaction (Note 5). The mixture is then cooled and filtered. The product is washed by suspension in hot water (Note 6), filtered, and dried. The yield is 68–79 g. (75–87%). The product melts at 227–228° (Note 7).

2. Notes

1. The commercial solvent is used without purification. Other primary alcohols of similar or higher boiling point are suitable solvents.
2. The large flask is chosen to allow for better stirring and heat transfer.
3. The reaction may be carried out with exactly molar equivalents of reactants. Slightly better yields are obtained by using the 0.2 to 0.25 molar excess of dicyandiamide.
4. Boiling of the methyl Cellosolve dissipates the heat of reaction, which begins at about 90°. The submitters state that, in one preparation using 100 times the indicated quantities (21-l. flask), two condensers were used and intermittent cooling of the flask with a small stream of water kept the boiling from becoming too violent.
5. Yields reported were obtained after 5 hours under reflux. Preparation of other guanamines indicates an optimum yield after 2.5 hours under reflux.
6. Thorough washing with hot water serves to remove any dicyandiamide or melamine which may be present in the crude product. Benzoguanamine is slightly

soluble in hot water.

7. The Cellosolve filtrate may be evaporated to obtain further quantities of product, m. p. 227–228°, raising the total yield to 90–95%.

3. Discussion

Benzoguanamine has been prepared by the reaction of dicyandiamide with benzonitrile in a sealed tube at 220–230°,[2] with an excess of benzonitrile in the presence of piperidine and potassium carbonate,[3] with benzonitrile in a solvent in the presence of a basic catalyst,[4] with benzonitrile in liquid ammonia,[5] and with benzamidine hydrochloride at elevated temperatures.[6 7] It also has been prepared from the reaction of biguanide acetate with benzamidine hydrochloride,[8] or of biguanide sulfate with benzoyl chloride in an alkaline medium,[9] by the distillation of guanidine benzoate,[6] and from benzonitrile, urea, and ammonia.[10]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

dicyandiamide

potassium carbonate (584-08-7)

ammonia (7664-41-7)

Benzamidine hydrochloride (1670-14-0)

benzonitrile (100-47-0)

benzoyl chloride (98-88-4)

potassium hydroxide (1310-58-3)

piperidine (110-89-4)

cellosolve (107-21-1)

urea (57-13-6)

Benzoguanamine, s-Triazine, 2,4-diamino-6-phenyl- (91-76-9)

methyl Cellosolve (109-86-4)

melamine (108-78-1)

biguanide acetate

biguanide sulfate

guanidine benzoate

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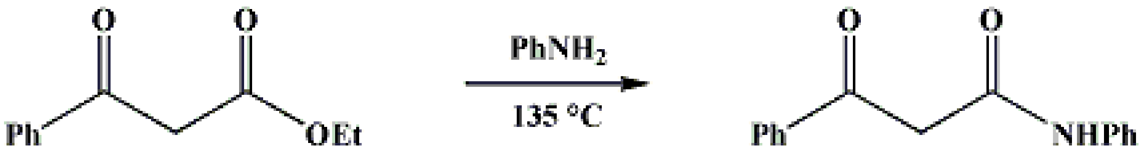
BENZOYLACETANILIDE

[Acetanilide, 2-benzoyl-]

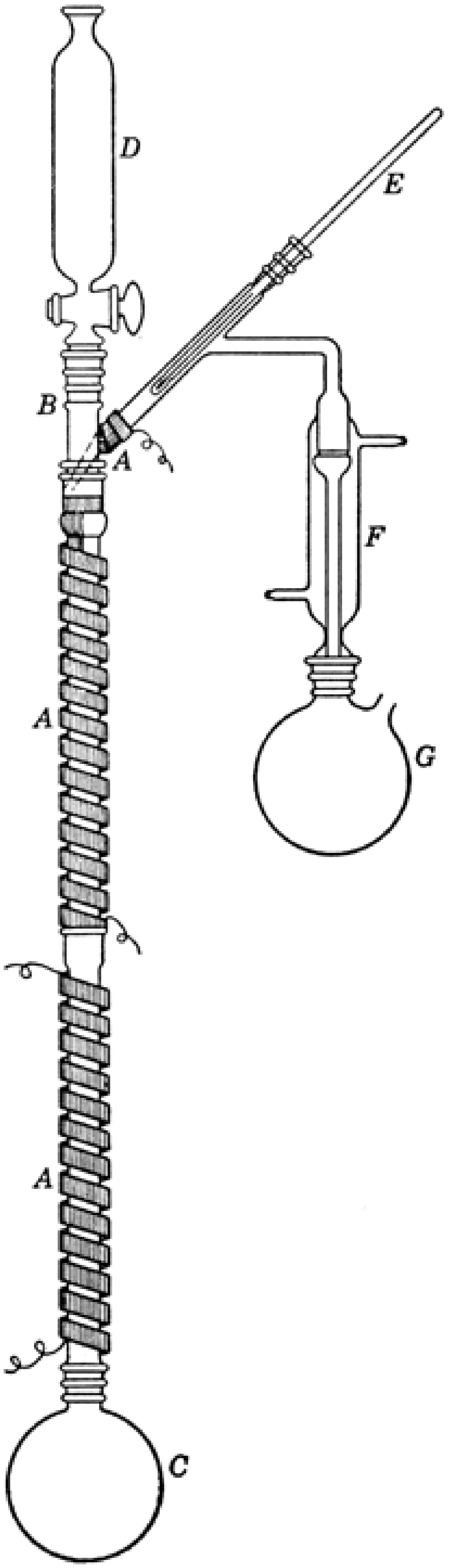


Submitted by C. F. H. Allen and W. J. Humphlett[1].
Checked by Max Tishler and R. Connell.

1. Procedure

A mixture of 105.7 g. (0.55 mole) of ethyl benzoylacetate and 46.6 g. (0.5 mole) of aniline (Note 1) is placed in the dropping funnel *D* (f.htmig.4) at the top of the continuous reactor (Note 2) and (Note 3) after the column has been heated to 135° (transformer set at 80 volts) (Note 4) and (Note 5). The reactants are then admitted to the column during about 15 minutes (this corresponds to a rate of amide formation of 396–400 g. per hour). Alcohol distils (Note 5) noticeably from the column during the addition and collects in flask *G*. At the completion of the reaction, 100 ml. of xylene is passed through the hot column to rinse out the residual amide (Note 6). An additional 200 ml. of xylene is added to the receiver *C*, and solution is effected by warming. After the solution has been cooled enough to induce crystallization, 100 ml. of petroleum ether (b.p. 35–60°) is added with manual stirring. The mixture is chilled to 15°, then the crystalline product is separated by suction filtration and washed 300–400 ml. of petroleum ether. The yield is 99–100 g. (83–84%), m.p. 106–106.5° (Note 7). The melting point of this product is not altered by recrystallization from benzene (Note 8),(Note 9),(Note 10).

Fig. 4.


D
E
B
A
F
A
G
A
C

2. Notes

1. Commercial grades of ethyl benzoylacetate and aniline were freshly redistilled before use.
2. The continuous reactor shown in f.htmig. 4 is of general utility for reactions that proceed at a rapid rate. Optimum conditions must be determined by experiment for each new product, but a high yield may often be secured. To determine a yield, it is necessary to run a given weight of the components through, rinse the column, and work up the combined products.
3. The reactor is built from stock pieces of glassware having 29/42 and 24/40 standard taper joints. It consists of a column 100 cm. long, of 2 cm. inside diameter, in two 50-cm. sections. The column is packed with 1/8-in. glass helices such as are used for packing distillation columns. The column is heated by two 275-watt flexible heating tapes *A*, 6 ft. long and in. wide, with lead wires connected to variable transformers, which are attached to a source of 110-volt power. The heating elements may be covered with asbestos tape if desired. At the bottom of the column is a 500-ml. flask *C* for receiving the product. At the top of the column is a 250-ml. addition funnel *D* (a cylindrical shape is convenient for calibration of volume or for winding with heating tape in instances where melting a solid or heating a solution is required). The addition funnel is connected to the column through a section *B* having a side arm provided with a thermometer *E* and a downward condenser *F* leading to a 500-ml. flask *G*, which has an outlet to the atmosphere for effluent gas.
4. It is always desirable to use a "wet" column; once a column has been used, this condition prevails. It is advantageous to admit a little xylene while regulating the heater, before addition of the reactants.
5. With two 275-watt heating tapes, the required temperature inside the column is secured at a voltage setting of about 80. If alcohol does not distil noticeably during the reaction, the internal temperature is not high enough and the transformer should be adjusted, or more time should be allowed for preheating the column.
6. Part of the product solidifies in the receiver.
7. This compares with 74–76% yield by the batch process.[2]
8. Recrystallization from benzene produces a whiter product in 92% recovery.
9. This procedure may be used to prepare other substituted anilides. If one of the components is a solid, it can be dissolved in an excess of the other. For instance, 46 g. of 2-amino-5-nitroanisole in 285 ml. of hot ethyl benzoylacetate is passed through in 30 minutes, with a transformer setting of 70 volts; then the column is rinsed with 50 ml. of the ester. The product crystallizes in the receiver and is separated by filtration; the filtrate is used to make up more of the reacting component mixture. The work-up yields 75–76 g. (89%) of amide with the correct melting point (178.5–180°) and color. When the same amide is made by a batch procedure, the yield is only 81% of a product melting at 130–150°. This illustrates the advantage of short time of exposure to heat in the continuous reactor.
10. This reactor has also been used with other types of reactions.

	Voltage	Time, hr.	Mole Ester	Yield, %
Ethyl benzalmalonate (batch)		18	0.63	90.8
(cont.)[3]	65	0.5	0.69	82
3-Carboxy-4-hydroxyquinoline[4]	90	0.66		35
4-Benzal-2-phenyl-5-oxazolone (batch)				64
(an azlactone) (cont.)[5]	60	0.25	>	73

3. Discussion

This preparation and oleoyl chloride (p.739) illustrate the use of the general form of a laboratory-sized continuous reactor.[6] This device has many advantages over the commonly used flasks (batch procedure). In particular, the short time of exposure to heat results in a better quality of product, as shown by less color, fewer side reactions, and better melting point, often unchanged by recrystallization. Furthermore, the unlimited capacity, very short reaction time, and use of concentrated solutions permit a larger output with no increase in size of apparatus and less delay required for removal of solvents.

The continuous reactor is most useful with reactions that take place at a relatively rapid rate. Its wide versatility enables it to be used in many types of reactions. Benzoylacetanilide was selected as an example because it has previously appeared in *Organic Syntheses.*[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 739

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

Benzene (71-43-2)

aniline (62-53-3)

xylene (106-42-3)

Ethyl benzalmalonate

Ethyl benzoylacetate (94-02-0)

Benzoylacetanilide, Acetanilide, 2-benzoyl- (85-99-4)

2-amino-5-nitroanisole (97-52-9)

3-Carboxy-4-hydroxyquinoline

4-Benzal-2-phenyl-5-oxazolone (842-74-0)

Oleoyl chloride (112-77-6)

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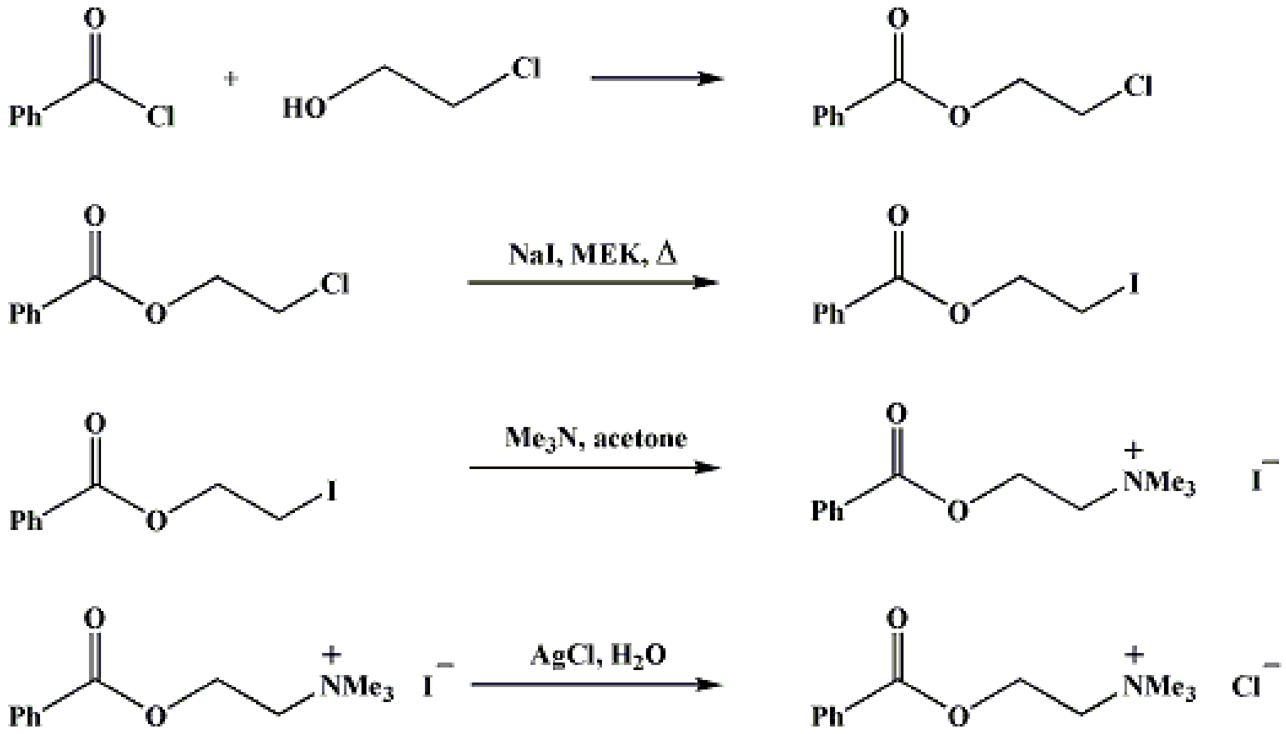
Organic Syntheses, CV 4, 84

BENZOYLCHOLINE IODIDE AND CHLORIDE

[Choline, chloride benzoate, and Choline, iodide benzoate]



Submitted by A. H. Ford-Moore[1]
Checked by R. L. Shriner and Calvin N. Wolf.

1. Procedure

A. *2-Chloroethyl benzoate.* In a 500-ml. round-bottomed flask attached to a 100-cm. air condenser by a ground-glass joint are placed 80.5g. (66ml., 1 mole) of redistilled ethylene chlorohydrin (b.p. 128–129°) and 140.5 g. (115.5 ml., 1 mole) of benzoyl chloride. The apparatus is set up in a good hood, and the mixture is warmed gently with a low flame until the reaction starts (Note 1). The source of heat is withdrawn until the reaction moderates and is then again applied for an additional 30 minutes, during which time the temperature rises to about 200–215°. The flask is fitted with a short column (about 20 cm.) and arranged for distillation. After volatile material has been removed by evacuation with a water pump at a bath temperature of 100–110° the residual liquid is fractionated under reduced pressure. The yield of 2-chloroethyl benzoate boiling at 101–104°/2 mm. is 165–168 g. (89–91%), n_D^{19} 1.5298.

B. *2-Iodoethyl benzoate.* A mixture of 170 g. of anhydrous sodium iodide and 1.2 l. of methyl ethyl ketone (Note 2) is heated on a steam bath for 1 hour with occasional shaking in a 3-l. round-bottomed flask fitted with a water-cooled reflux condenser. 2-Chloroethyl benzoate (162 g., 0.88 mole) is added to the mixture, and heating is maintained for an additional 22–24 hours with occasional shaking. The mixture is cooled to room temperature and filtered through a 15-cm. Büchner funnel with suction. The inorganic salts on the filter are washed with 200 ml. of methyl ethyl ketone, and the filtrate is concentrated by distillation of about 1 l. of the solvent. The residue is poured into 1 l. of water contained in a separatory funnel, which is shaken, and the lower layer is withdrawn. The latter is washed successively with 200 ml. of 10% sodium bisulfite

solution, 200 ml. of 5% sodium bicarbonate solution, and 100 ml. of water. It is dried with anhydrous magnesium sulfate (5–7 g.) and fractionated under reduced pressure. The yield of material boiling at 133–136°/2.5 mm., n_D^{15} 1.5820, is 190–196 g. (78–81%).

C. *Benzoylcholine iodide.* A solution of 194 g. (0.70 mole) of 2-iodoethyl benzoate in 200 ml. of dry acetone is treated with 270 ml. of a 19.5% solution of trimethylamine in acetone (Note 3) in a 1-l. Pyrex reagent bottle which is closed with a tightly fitting rubber stopper wired in place. The solution is allowed to stand at room temperature for 24 hours (Note 4), and at the end of this time the quaternary salt is separated by filtration with suction, washed with 200 ml. of dry acetone, and air-dried (Note 5). The weight of the quaternary iodide melting with decomposition at 247° is 200–210 g. (85–90%) (Note 6).

D. *Benzoylcholine chloride.* Silver chloride is prepared by dissolving 160 g. (0.94 mole) of silver nitrate in 500 ml. of boiling distilled water and adding 120 ml. of analytical reagent hydrochloric acid (sp. gr. 1.18) from a dropping funnel in a period of 15 minutes, with continuous stirring. The silver chloride is washed by decantation with three 300-ml. portions of boiling distilled water. The moist silver chloride is suspended in 750 ml. of water warmed to 50–60° in a 2-l. beaker, and 210 g. (0.63 mole) of benzoylcholine iodide is added in a period of 1 hour, with good mechanical stirring. After the addition is completed, stirring is continued for an additional 30 minutes without the application of heat. The mixture is cooled and filtered with suction. The silver salts on the filter are washed with 200 ml. of hot water (Note 7), and the combined filtrates are evaporated to dryness under reduced pressure (water pump). The residue is dried by twice distilling to dryness with 250 ml. of absolute ethanol and then once with 250 ml. of dry acetone, the last of the acetone being removed under reduced pressure. The product is recrystallized by dissolving it in 240 ml. of isopropyl alcohol (Note 8) and allowing the solution to cool in a refrigerator. It is filtered and dried, first at 100° and then in a vacuum desiccator over silica gel. The yield of pure product, m.p. 207° (dec.), is 125–132 g. (82–87%) (Note 9).

2. Notes

1. Usually the reaction starts at a temperature of 55° to 60° as evidenced by liberation of hydrogen chloride. If the reaction becomes too vigorous it may be moderated by applying a wet towel to the flask.
2. A purified grade of methyl ethyl ketone should be used. The technical material may be purified by allowing it to stand over solid anhydrous calcium chloride for 24 hours, decanting from the syrupy layer and solid through a filter, and then distilling; b.p. 79–80°.
3. The trimethylamine may be generated by the action of alkali on trimethylamine hydrochloride and dissolved in acetone.[2] The submitter prepared trimethylamine by the method of Sommelet and Ferrand[3] and obtained a 65% yield by the interaction of ammonia, formaldehyde, and formic acid. The checkers found that a commercial 25% solution of trimethylamine in methanol (210 ml.) gave the same yields as the acetone solution.
4. Increasing the reaction period to 48 hours gives an additional 5 to 7 g. of product.
5. If this preparation is carried out during periods of high humidity it is best to place the product in a vacuum desiccator, which is evacuated several times in order to remove the solvent. Anhydrous calcium chloride may be placed in the bottom of the desiccator.
6. This product is quite pure as shown by titration of iodide ion.
7. The silver residues are saved for the recovery of silver[4] and iodine.

8. The submitter states that the compound may be recrystallized by boiling with acetone under an upright condenser and adding ethanol cautiously down the condenser until the solid just dissolves. The substance is appreciably soluble in the cold solvent mixture. It is necessary to distil the mother liquor and recrystallize the residue from acetone-ethanol, for otherwise a considerable loss of product will occur. The checkers used isopropyl alcohol for crystallization.
9. Benzoylcholine chloride prepared by this method is pure as shown by titration of ionic chlorine. It is somewhat hygroscopic, though much less so than choline chloride. It is not appreciably hydrolyzed by boiling with water for 1 hour, although more prolonged heating leads to the formation of benzoic acid. Benzoylcholine chloride can be characterized as the picrate, m.p. 177°, formed by treating a strong aqueous solution with an appropriate amount of 0.5*N* calcium picrate and crystallizing the product from methyl ethyl ketone.

3. Discussion

2-Chloroethyl benzoate has been prepared from benzoyl chloride and ethylene chlorohydrin;[5,6,7] from benzoic acid, ethylene glycol, and hydrogen chloride[8] at 100°; from ethylene oxide and benzoyl chloride;[9] from benzoyl chloride and dioxane in the presence of titanium tetrachloride;[10] from benzoic acid, ethylene, and chlorine in the presence of various catalysts.[11] It has also been obtained by hydrolysis of 2-chloroethyl benzimidate;[12] by the action of bromomagnesium benzoate on 2-chloroethyl *p*-toluene-sulfonate;[13] and by the action of sodium benzoate on *bis*-(2-chloroethyl) sulfate.[14]

2-Iodoethyl benzoate has been obtained by the action of alcoholic sodium iodide on 2-chloroethyl benzoate.[5]

Benzoylcholine chloride has been prepared by heating choline chloride with benzoyl chloride[15] and by the action of trimethylamine on 2-chloroethyl benzoate.[16]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

BENZOYLCHOLINE IODIDE AND CHLORIDE

Choline, chloride benzoate

Choline, iodide benzoate

ethanol (64-17-5)

calcium chloride (10043-52-4)

hydrogen chloride, hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

methanol (67-56-1)

formaldehyde (630-08-0)

sodium bicarbonate (144-55-8)

silver chloride (7783-90-6)

silver nitrate (7761-88-8)

formic acid (64-18-6)

Benzoic acid (65-85-0)

sodium bisulfite (7631-90-5)

iodine (7553-56-2)

acetone (67-64-1)

benzoyl chloride (98-88-4)

chlorine (7782-50-5)

isopropyl alcohol (67-63-0)

sodium benzoate (532-32-1)

Ethylene oxide (75-21-8)

ethylene glycol (107-21-1)

ethylene (9002-88-4)

sodium iodide (7681-82-5)

ethylene chlorohydrin (107-07-3)

Trimethylamine (75-50-3)

Trimethylamine hydrochloride (593-81-7)

silver (7440-22-4)

magnesium sulfate (7487-88-9)

dioxane (5703-46-8)

methyl ethyl ketone (78-93-3)

acetone-ethanol (1071-73-4)

BENZOYLCHOLINE IODIDE (17518-43-3)

choline chloride (67-48-1)

2-Chloroethyl benzoate (939-55-9)

2-iodoethyl benzoate (39252-69-2)

Benzoylcholine chloride, D. Benzoylcholine chloride (2964-09-2)

calcium picrate

titanium tetrachloride (7550-45-0)

2-chloroethyl benzimidate

bromomagnesium benzoate

2-chloroethyl p-toluene-sulfonate (80-41-1)

bis-(2-chloroethyl) sulfate

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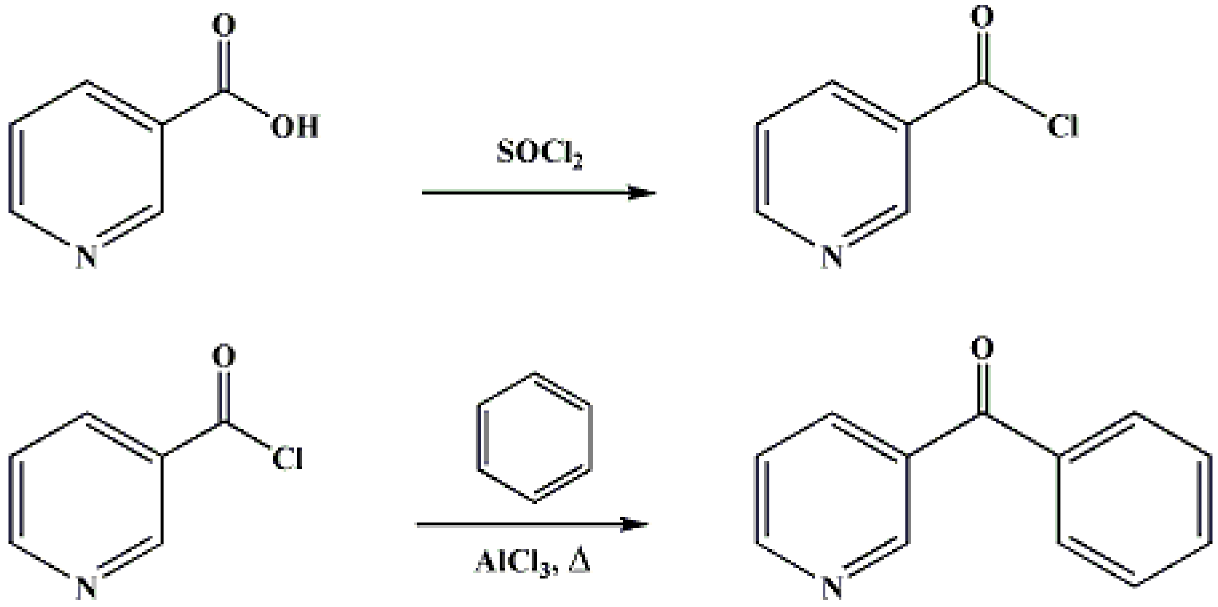
3-BENZOYLPYRIDINE

[Ketone, phenyl 3-pyridyl]



Submitted by Frank J. Villani and Mary S. King[1].
Checked by Max Tishler and Matthew A. Kozlowski.

1. Procedure

In a 2-l. three-necked flask, fitted with a sealed mechanical stirrer (Note 1), a reflux condenser protected with a calcium chloride tube, and a dropping funnel, is placed 123 g. (1 mole) of nicotinic acid (Note 2). The stirrer is started, and 500 ml. (818 g., 6.9 moles) of distilled thionyl chloride is added in a slow stream over a period of 15–20 minutes (Note 3). After the addition is complete, the mixture is heated on the steam bath with continuous stirring for 1 hour; then the reflux condenser is replaced by one set for downward distillation, and the excess thionyl chloride is removed by distillation at reduced pressure as heating on the steam bath is continued (Note 1) and (Note 3). After most of the thionyl chloride has been distilled, 200 ml. of anhydrous benzene is added, and the benzene is distilled at reduced pressure. An additional 500 ml. of anhydrous benzene is added; then the flask is fitted with a thermometer and a reflux condenser and is placed in an ice-salt bath. The stirrer is started, and 330 g. (2.5 moles) of anhydrous aluminum chloride is added in portions over a period of 1 hour as the internal temperature is held between 5° and 10°. The ice bath is removed, and the flask is permitted to warm to room temperature and is finally heated under reflux for 6 hours.

The dark red-brown reaction mixture is cautiously poured onto a mixture of 2 kg. of ice and 200 ml. of concentrated hydrochloric acid. The organic layer is separated and

discarded. The acid solution is extracted with three 500-ml. portions of ether (Note 4), which are discarded; then it is treated with 50% aqueous sodium hydroxide until the aluminum hydroxide which first forms redissolves (Note 5). After cooling, the organic material is extracted with five 300-ml. portions of chloroform. The combined chloroform extracts are washed with water, the solvent is removed by distillation on the steam bath, and the product is distilled. The yield of 3-benzoylpyridine (Note 6), b. p. 107–110°/0.3 mm. or 141–145°/4 mm., is 165–175 g. (90–96%), n_D^{26} 1.6088.

2. Notes

1. It is convenient to use a sealed stirrer, such as the Trubore stirrer, which may be left in the flask during the distillation of thionyl chloride and benzene at reduced pressure; however, the stirrer cannot be left running during this distillation, for it is stopped by the cake of acid chloride hydrochloride. The distillations are accomplished most conveniently if the dropping funnel is removed and replaced by a capillary and the stirrer is left in place but not running during the distillations.
2. Satisfactory results were obtained with nicotinic acid from either Eastman Organic Chemicals or Matheson, Coleman and Bell.
3. The submitters used thionyl chloride from Hooker Electrochemical Company. It was distilled and collected over a 1° range (78–79°). The first few drops of thionyl chloride are added cautiously as the initial reaction may be quite vigorous. Recovered thionyl chloride may be used for subsequent runs.
4. The ether extractions remove any diphenyl sulfoxide that is formed.
5. About 800–1000 ml. of 50% sodium hydroxide is required.
6. 4-Benzoylpyridine can be obtained by this procedure from isonicotinic acid in yields of 87–90%. This product is recrystallized from hexane, m.p. 72–73°.

3. Discussion

The described method of preparing 3-benzoylpyridine is a modification of that of Wolffenstein and Hartwich.[2] Other methods of preparing this compound are by the addition of phenylmagnesium bromide to 3-cyanopyridine,[3] the addition of 3-pyridyllithium to benzonitrile,[4] the chromic acid oxidation of phenyl-3-pyridylcarbinol,[5] and the decarboxylation of β-benzoylpicolinic acid obtained from quinolinic acid anhydride and benzene.[6]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether (60-29-7)

benzonitrile (100-47-0)

sodium hydroxide (1310-73-2)

thionyl chloride (7719-09-7)

chloroform (67-66-3)

aluminum chloride (3495-54-3)

chromic acid (7738-94-5)

Phenylmagnesium bromide (100-58-3)

Nicotinic acid (59-67-6)

aluminum hydroxide

hexane (110-54-3)

3-Benzoylpyridine, Ketone, phenyl 3-pyridyl (5424-19-1)

diphenyl sulfoxide (945-51-7)

4-Benzoylpyridine (14548-46-0)

3-cyanopyridine (100-54-9)

3-pyridyllithium

phenyl-3-pyridylcarbinol

β-benzoylpicolinic acid

quinolinic acid anhydride

isonicotinic acid (55-22-1)

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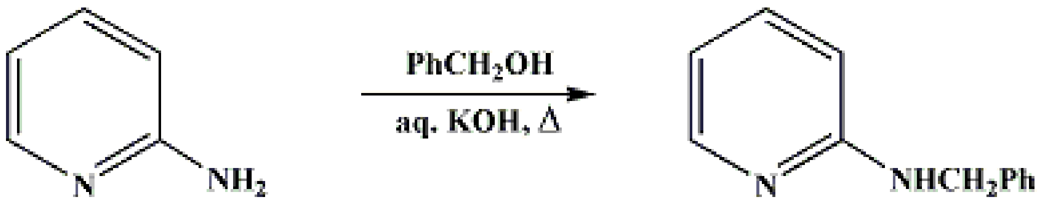
2-BENZYLAMINOPYRIDINE

[Pyridine, 2-benzylamino-]



Submitted by Yaïr Sprinzak[1]
Checked by Max Tishler and Matthew A. Kozlowski.

1. Procedure

A 500-ml. Claisen flask with a 35-mm. indented side arm (Note 1) is attached downward to a Liebig condenser for distillation. A thermometer, held by a cork stopper, is inserted through the neck of the flask and adjusted so that its bulb is close to the bottom. The flask is heated by means of an electric mantle or air bath. To the flask are charged 94 g. (1.0 mole) of 2-aminopyridine (Note 2), 150 g. (1.4 moles) of benzyl alcohol, and 9 g. of 85% potassium hydroxide. The mixture is heated to boiling and boiled vigorously enough to cause slow distillation of water accompanied by as little benzyl alcohol as possible (Note 3). The temperature of the boiling mixture rises gradually from 182° to 250° during a period of 30 minutes. The mixture is maintained at 250° for 3 minutes, then allowed to cool. The distillate amounts to 19–20 ml. of a water-rich layer and 2–4 ml. of a benzyl alcohol-rich layer.

The residual product is cooled to about 100° (Note 4) and poured into 250 ml. of water. The crystallized solid is crushed and collected on a 12-cm. Büchner funnel. Slight suction is applied at first, but, after most of the mother liquor has been removed, the crystals are pressed down with strong suction. The product is then washed thoroughly with water. After drying, the yield of colorless 2-benzylaminopyridine (Note 5) and (Note 6), m.p. 95–96°, amounts to 180–183 g. (98–99% of the theoretical amount). The product may be recrystallized from isopropyl alcohol with 90% recovery. For each gram of amine 3 ml. of solvent is employed. The melting point of recrystallized material is 96.0–96.7° (cor.), lit.[2] m.p. 97–98°.

2. Notes

1. A short Vigreux column or any other short column for distillation may be used.
2. 2-Aminopyridine was obtained from Matheson, Coleman and Bell, Inc., East Rutherford, New Jersey.
3. If the reaction mixture is heated too strongly or the vapors are inadequately

fractionated, correspondingly greater amounts of benzyl alcohol will distill, with concomitant loss of yield. The distillate should be clear, not milky.
4. If the product has partially solidified, it should be melted for easy handling.
5. By essentially the same procedure N,N'-dibenzyl-*p*-phenylenediamine has been obtained in 92% yield. The heating period requires 1 hour, and the final temperature is 260°.
6. N-Benzylaniline has been obtained in 90–94% yield by an appropriate modification[3] of this method.

3. Discussion

For 2-benzylaminopyridine the methods of preparation of significance are condensation of 2-pyridinesulfonic acid and benzylamine,[4] condensation of the alkali metal salts of 2-aminopyridine with benzyl chloride[5] or benzyl alcohol,[6] reductive alkylation of 2-aminopyridine in the presence of benzaldehyde and formic acid,[2] oxidation of N-benzyl-N-pyridylaminoacetonitrile or N-benzyl-N-pyridylaminoacetaldoxime,[7] and the method described here modified by use of an inert solvent.[8]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

formic acid (64-18-6)

benzaldehyde (100-52-7)

potassium hydroxide (1310-58-3)

isopropyl alcohol (67-63-0)

N-Benzylaniline (103-32-2)

benzyl chloride (100-44-7)

Benzyl alcohol (100-51-6)

2-aminopyridine (504-29-0)

benzylamine (100-46-9)

2-Benzylaminopyridine, Pyridine, 2-benzylamino- (6935-27-9)

2-pyridinesulfonic acid

N-benzyl-N-pyridylaminoacetonitrile

N-benzyl-N-pyridylaminoacetaldoxime

N,N'-dibenzyl-p-phenylenediamine

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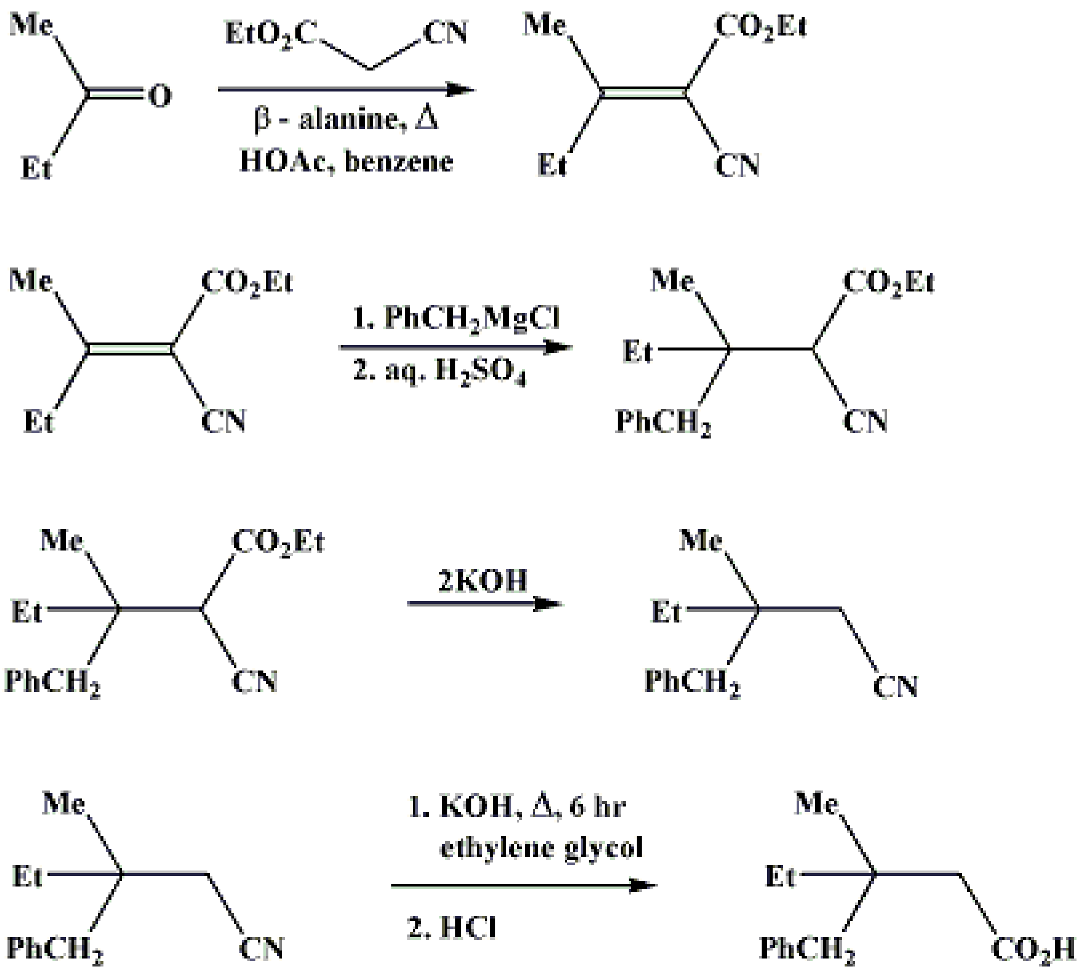
3-BENZYL-3-METHYLPENTANOIC ACID

[Valeric acid, 3-benzyl-3-methyl-]



Submitted by F. S. Prout, R. J. Hartman, E. P.-Y. Huang, C. J. Korpics, and G. R. Tichelaar[1].
Checked by James Cason, K. C. Dewhirst, E. J. Gauglitz, Jr., and William G. Dauben.

1. Procedure

A. *Ethyl sec-butylidenecyanoacetate.*. In a 1-l. round-bottomed flask fitted with a 24/40 joint are placed 0.45 g. of β-alanine, 113 g. (106 ml., 1.0 mole) of ethyl cyanoacetate (Note 1), 87 g. (108 ml., 1.2 moles) of butanone, 20 ml. of glacial acetic acid, and 100 ml. of benzene. A Barrett-type water separator (Note 2) and a condenser are attached to the flask, and the mixture is heated briskly under reflux until water ceases to be collected in the trap (7–12 hours).

The reaction mixture is decanted into a 500-ml. round-bottomed flask which is attached to a fractionating column (Note 3). The solvent is removed at atmospheric

pressure while the oil bath is heated finally at 160°. The residue is distilled at reduced pressure to furnish four fractions: (*a*) acetic acid and other materials boiling below 95°/16 mm.; (*b*) ethyl cyanoacetate, b.p. 95–110°/16 mm.; (*c*) intermediate, b.p. 110–124°/16 mm.; and (*d*) ethyl *sec*-butylidenecyanoacetate, b.p. 124–126°/16 mm., n_D^{25} 1.4640–1.4648. Fraction *d* amounts to 117–122 g., and refractionation of fraction *c* yields an additional 18–24 g.; total yield, 135–146 g. (81–87.5%) (Note 4).

B. *Ethyl 3-benzyl-2-cyano-3-methylpentanoate.* A 2-l. three-necked round-bottomed flask, fitted with a tantalum wire Hershberg stirrer, a condenser, and a separatory funnel, is arranged for use of a nitrogen atmosphere.[2] Magnesium (19.2 g., 0.79 g. atom) and 100 ml. of dry ether[3] are placed in the flask, and a solution of 100 g. (91 ml., 0.79 mole) of benzyl chloride in 500 ml. of dry ether is added in a period of 1.5–2.0 hours, with stirring, while the mixture boils spontaneously. The mixture is boiled for 15 minutes after completion of the addition, then a solution of 110 g. (0.66 mole) of ethyl *sec*-butylidenecyanoacetate in 130 ml. of benzene is added over a 30-minute period with spontaneous reflux. The reaction mixture is stirred and heated under reflux for an additional hour. A precipitate separates after about 30 minutes.

The reaction mixture is poured onto about 400 g. of cracked ice and is made acidic with 20% sulfuric acid. After two clear phases have formed the mixture is poured into a separatory funnel, and the lower layer is removed. This aqueous layer is extracted with two 100-ml. portions of benzene and discarded. The three organic extracts are washed separately and successively with 125 ml. of water and 125 ml. of saturated sodium chloride solution, then filtered successively through a layer of anhydrous sodium sulfate.

The combined extract (about 1 l.) is flash-distilled at atmospheric pressure from a 250-ml. Claisen flask. After the solvent and a small amount of fore-run (ca. 15 g., b.p. 45°/3 mm.) have been removed, the product is distilled to yield 157–162 g. (92–95%), b.p. 150–162°/3 mm. (bath temperature, 180–190°), n_D^{25} 1.5053–1.5063 (Note 5), (Note 6), and (Note 7).

C. *3-Benzyl-3-methylpentanenitrile.* Sixty-seven grams (1 mole) of potassium hydroxide (85%) is dissolved by heating in 360 ml. of ethylene glycol and is added to a 1-l. round-bottomed flask containing 155 g. (0.6 mole) of ethyl 3-benzyl-2-cyano-3-methylpentanoate (above). A condenser is attached with a rubber stopper, and the mixture is heated under gentle reflux for 3 hours (Note 8). The resulting two-phase mixture is cooled, diluted with 350 ml. of water, and extracted with three portions of ether (250 ml., 100 ml., 100 ml.). The three extracts are washed successively with 100 ml. of water and 100 ml. of saturated sodium chloride solution, then filtered through a layer of anhydrous sodium sulfate (Note 9). The combined extracts are flash-distilled at atmospheric pressure from a 250-ml. Claisen flask to remove the ether. The residue is distilled at reduced pressure to furnish 102–105 g. (91–93%) of nitrile, b.p. 150–160°/11 mm. (bath temperature, 190–200°), n_D^{25} 1.5111–1.5128 (Note 10) and (Note 11).

D. *3-Benzyl-3-methylpentanoic acid.* A solution of 112 g. (1.6 moles) of potassium hydroxide (85%) in 400 ml. of ethylene glycol is added to 93.6 g. (0.5 mole) of 3-benzyl-3-methylpentanenitrile in a 1-l. round-bottomed copper or stainless-steel flask. A condenser with a rubber stopper is attached, and the solution is heated under brisk reflux for 6 hours (Note 12). The reaction mixture is cooled, diluted with 400 ml. of water, and extracted with three portions of ether (250 ml., 100 ml., 100 ml.). The ether extracts are washed successively with two 75-ml. portions of water and then discarded (Note 13).

The combined aqueous phases are acidified to Congo red with 200 ml. of concentrated hydrochloric acid and extracted with three portions of benzene (200 ml., 75 ml., 75 ml.). The benzene extracts are washed successively with 100 ml. of water and 100 ml. of saturated sodium chloride solution, then filtered through anhydrous sodium sulfate. The combined extract is flash-distilled from a 250-ml. Claisen flask at atmospheric pressure (bath temperature, up to 160°). The residue is distilled at reduced pressure to give 94–96 g. (91–93%) of acid; b.p. 173–177°/7 mm. (bath temperature, 207–220°), n_D^{25} 1.5160–1.5163 (Note 14) and (Note 15).

2. Notes

1. Ethyl cyanoacetate was obtained from Kay-Fries Chemicals, 180 Madison Avenue, New York, New York.
2. The submitters used a Barrett Distilling Receiver, Corning No. 3622, Corning Glass Works, Corning, New York.
3. The submitters used a 60-cm. heated Vigreux column to effect this fractionation. The checkers used a similar column with partial take-off head.
4. Fractions *b*–*d* consist entirely of ethyl cyanoacetate and the product. Pure ethyl cyanoacetate and ethyl *sec*-butylidenecyanoacetate have n_D^{25} 1.4151 and 1.4650, respectively. The purity of fractions *b*–*d* can be estimated by their indexes of refraction, which are proportional to the weight per cent.
5. The pure product obtained by fractional distillation has n_D^{25} 1.5052. The product obtained by distillation from a Claisen flask is contaminated mainly with bibenzyl, b.p. 122–125°/3 mm., f.p. 44°. The purity of the product can be estimated by determination of the saponification equivalent in ethanol.
6. The use of dibenzylcadmium gave no improvement in yield.
7. Phenylmagnesium bromide gives a 79% yield of product, b.p. 178–180°/11 mm., n_D^{25} 1.5063; and *n*-propylmagnesium bromide gives 33–42% yields, b.p. 150–153°/22 mm., n_D^{25} 1.4429, of alkylation product when essentially the same procedure is used. The yield obtained with *n*-propylmagnesium bromide depends upon the efficiency of separation from the reduction product, ethyl *sec*-butylcyanoacetate, b.p. 126°/22 mm., n_D^{25} 1.4277.[4]
8. After 30 minutes of reflux the second phase begins to separate. The formation of this nitrile layer is probably complete after 2.5–3.0 hours. A small amount of solid, presumably ammonium carbonate, collects in the condenser during the

heating.

9. When the combined aqueous washes from three runs were acidified, extracted, and distilled, there was obtained 1.8 g. of 3-benzyl-3-methylpentanoic acid, n_D^{25} 1.5158.

10. This nitrile is contaminated with some lower-boiling bibenzyl and some higher-boiling amide. The pure nitrile, obtained by fractional distillation, has n_D^{25} 1.5110.

11. Hydrolyses of ethyl 2-cyano-3-methyl-3-phenylpentanoate and ethyl 2-cyano-3-ethyl-3-methylhexanoate (Note 7) by essentially this procedure gave 71% (b.p. 149–151°/16 mm., n_D^{25} 1.5149) and 68% (b.p. 103–104°/31 mm., n_D^{25} 1.4291) yields of nitriles, respectively. In the second case, about 12% additional yield of nitrile could be obtained from the acidic fraction, which contains some undecarboxylated product, 2-cyano-3-ethyl-3-methylhexanoic acid.

12. The two-phase solution becomes homogeneous after 1.5–2.0 hours of boiling. This alkaline solution is very corrosive, and a glass flask can be used only a few times in this reaction. A stainless-steel or copper flask is preferable.

13. If emulsions are encountered, the addition of a few milliliters of saturated aqueous sodium chloride clears them readily. The combined ether extracts contain 4–5 g. of solid, neutral material. This product is mainly bibenzyl, b.p. 138–143°/7 mm., f.p. 40°.

14. The best sample of this acid obtained by fractional distillation had n_D^{25} 1.5160; neut. equiv., 207.3 (calcd., 206.3).

15. Hydrolyses of 3-methyl-3-phenylpentanenitrile and 3-ethyl-3-methylhexanenitrile (Note 11) by the described procedure gave 88% and 95% yields of 3-methyl-3-phenylpentanoic acid (b.p. 190–194°/26 mm., n_D^{25} 1.5182) and 3-ethyl-3-methylhexanoic acid (b.p. 136–137°/15 mm., n_D^{25} 1.4377), respectively.

3. Discussion

Ethyl *sec*-butylidenecyanoacetate has been prepared by this condensation using various amino acids,[5] ammonium acetate,[6] sodium sulfate-piperidine,[7] and zinc chloride-aniline.[8]

The ethyl 3-benzyl-2-cyano-3-methylpentanoate, 3-benzyl-3-methylpentanenitrile, and 3-benzyl-3-methylpentanoic acid preparations follow the procedure given by Prout, Huang, Hartman, and Korpics.[9]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium sulfate-piperidine

zinc chloride-aniline

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ammonium carbonate

Benzene (71-43-2)

ether (60-29-7)

ammonium acetate (631-61-8)

magnesium (7439-95-4)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

potassium hydroxide (1310-58-3)

benzyl chloride (100-44-7)

ethylene glycol (107-21-1)

Ethyl cyanoacetate (105-56-6)

Phenylmagnesium bromide (100-58-3)

β-Alanine (107-95-9)

butanone (78-93-3)

bibenzyl (103-29-7)

3-Benzyl-3-methylpentanoic acid, Valeric acid, 3-benzyl-3-methyl- (53663-16-4)

Ethyl 3-benzyl-2-cyano-3-methylpentanoate (70289-04-2)

3-Benzyl-3-methylpentanenitrile

dibenzylcadmium

ethyl 2-cyano-3-methyl-3-phenylpentanoate

ethyl 2-cyano-3-ethyl-3-methylhexanoate (70289-02-0)

2-cyano-3-ethyl-3-methylhexanoic acid

3-methyl-3-phenylpentanenitrile (50843-73-7)

3-ethyl-3-methylhexanenitrile (138808-09-0)

3-methyl-3-phenylpentanoic acid

3-ethyl-3-methylhexanoic acid

ethyl 3-benzyl-2-cyano-3-methylpentanoate, 3-benzyl-3-methylpentanenitrile

n-propylmagnesium bromide

Ethyl sec-butylidenecyanoacetate (868-47-3)

ethyl sec-butylcyanoacetate

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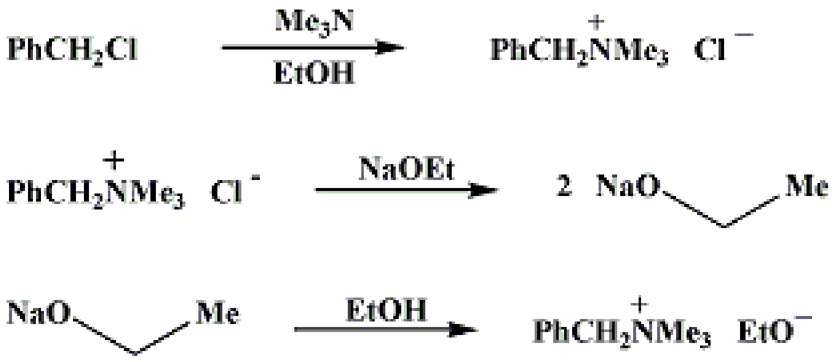
BENZYLTRIMETHYLAMMONIUM ETHOXIDE

[Ammonium, benzyltrimethyl-, ethoxide]



Submitted by W. J. Croxall, Marion F. Fegley, and H. J. Schneider[1].
Checked by John C. Sheehan and M. Gertrude Howell.

1. Procedure

A 3-l. three-necked flask (flask *A*) is fitted with a nitrogen inlet, a reflux condenser protected by a soda-lime tube, and a reflux condenser fitted with a dropping funnel protected by a soda-lime tube.

A second 3-l. three-necked flask (flask *B*) is fitted with a gas-tight modified Hershberg stirrer (Note 1), a gas inlet tube, and an appropriately designed gas outlet tube bearing a thermometer and connections leading to a soda-lime tube and an open-end mercury manometer. All rubber stoppers and connections are wired in place with 16-gauge copper wire.

Sodium (69 g., 3 g. atoms) is introduced into flask *A*, which had been flushed previously with nitrogen (Note 2). Ethanol (1.2 kg.) (Note 3) is added at such a rate that a continuous reflux is maintained. After the sodium is completely dissolved, the solution is allowed to cool to room temperature. During this period the benzyltrimethylammonium chloride is prepared.

A solution of 379.5 g. (3 moles) of benzyl chloride (Note 4) dissolved in 750 g. of anhydrous ethanol (Note 3) is placed in flask *B*. The system is flushed with trimethylamine previously dried by passage through a soda-lime tower. The gas outlet is closed and connected to the manometer. Over a period of 80 minutes, 195 g. (3.3 moles) of trimethylamine (Note 5) is introduced with stirring. The reaction is exothermic and must be cooled to keep the temperature below 50°. After the amine addition is complete, the solution is kept at 50° under an amine pressure of 5 cm. of mercury above atmospheric pressure for 1 hour. The mixture is then cooled to room temperature under an amine atmosphere.

The inlet tube of flask *B* is replaced by a rubber stopper bearing a short glass outlet tube and a glass inlet tube which is connected to an appropriately designed glass siphon outlet tube extending to the bottom of flask *A*. Gentle suction applied to the outlet tube of flask *B* draws the ethoxide solution slowly into flask *B*. The benzyltrimethylammonium chloride solution is stirred throughout the addition of the sodium ethoxide. After the transfer of the sodium ethoxide is completed, the finely divided precipitate of sodium chloride is allowed to settle overnight. When the sodium chloride has completely settled, the stopper bearing the inlet and outlet tubes is replaced by a stopper bearing a 15-in. length of 19-mm. glass tubing which is attached in turn by a gum rubber connection to a clean, dry, 1-gal. bottle fitted with an inlet tube and an outlet tube protected by soda-lime. The bottle is flushed with nitrogen before use. The 15-in. tube is adjusted so that the bottom is approximately in. above the level of the precipitated sodium chloride. With the open-end manometer sealed off by a screw clamp, nitrogen pressure is applied through the outlet tube of the flask until 1.7–1.9 kg. of supernatant liquor is forced from the flask into the bottle (Note 6). This solution contains 24–30% benzyltrimethylammonium ethoxide (2.1–2.7 moles), as determined by titration with 0.1*N* hydrochloric acid, using methyl red as indicator. This represents a yield of 70–90%. An additional 270–400 g. of solution is obtained by filtration of the residual mixture under nitrogen. To ensure rapid filtration, a filter aid, such as Filtercel (Note 7), must be employed. The filtrate contains 24–30% benzyltrimethylammonium ethoxide (0.3–0.7 mole). The total yield is 89–100%. The solutions are stored under nitrogen and refrigeration in bottles sealed with rubber stoppers which are wired in place (Note 8).

Three hundred and thirty-five grams of the 25% ethanolic solution of benzyltrimethylammonium ethoxide (0.43 mole) is placed under nitrogen in a 3-l. three-necked flask equipped with a gas inlet tube, a gas-tight modified Hershberg stirrer (Note 1), and a gas outlet tube fitted with a thermometer. All stoppers and rubber connections are wired in place with 16-gauge copper wire. There is obtained by evaporation at 40° (Note 9) under reduced pressure (Note 10) 97 g. (0.40 mole) of the ethoxide containing an equivalent of ethanol. The vacuum is broken with dry nitrogen.

2. Notes

1. The stirrer is of the type designed by Hershberg,[2] but it has a single paddle of 16-gauge Nichrome wire.
2. A bubble counter is employed for indicating nitrogen flow.
3. The water content of the ethanol, determined by Karl Fischer analysis, is 0.02–0.10%.
4. Benzyl chloride is redistilled before use. The fraction collected at 40–41° /6 mm. is used.
5. The flask is disconnected periodically from the gas train and stirring mechanism for weighing.
6. In small-scale preparations (approximately 0.5 mole) centrifugation of the total mixture is a convenient method for separation of the product from sodium

chloride.
7. Filtercel is supplied by Johns-Manville Corporation.
8. This method is more satisfactory than storage of the benzyltrimethylammonium ethoxide monoethanolate. The excess ethanol is removed as necessary.
9. The temperature is maintained by surrounding the flask with a warm water bath. Higher temperatures are not recommended because of the tendency of the quaternary ammonium ethoxide to decompose.
10. The bulk of the ethanol was removed by using a water pump (40–50 mm.) and collected in 1-l. and 200-ml. Dry Ice traps connected in series. The remaining ethanol was removed by using an oil pump protected with two 300-ml. Dry Ice traps.

3. Discussion

The procedure described is adapted from the preparation outlined by Meisenheimer.[3] The method has been applied by the authors to the preparation of benzyltrimethylammonium methoxide, dibenzyldimethylammonium methoxide, bisisopropylbenzyltrimethylammonium methoxide and benzyltriethylammonium ethoxide.

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Methyl Red

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

mercury (7439-97-6)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

benzyl chloride (100-44-7)

Trimethylamine (75-50-3)

Benzyltrimethylammonium ethoxide, Ammonium, benzyltrimethyl-, ethoxide (27292-06-4)

benzyltrimethylammonium chloride (56-93-9)

benzyltrimethylammonium ethoxide monoethanolate

ammonium ethoxide

benzyltriethylammonium ethoxide

benzyltrimethylammonium methoxide (122-08-7)

dibenzyldimethylammonium methoxide

bisisopropylbenzyltrimethylammonium methoxide

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BISCHLOROMETHYL ETHER

[Ether, bis(chloromethyl)-]

Submitted by Saul R. Buc[1]
Checked by Charles C. Price, Frederick V. Brutcher, and Jerome Cohen.

1. Procedure

Caution! It has been reported that exposure to bischloromethyl ether in low concentrations has caused severe irritation of the eyes and respiratory tract, and perhaps pulmonary edema.

Proper safeguards should be taken to prevent exposure to this material both during and after its preparation. It is recommended that all operations involving this compound be carried out in a good hood.

In a 1-l. three-necked flask immersed in an ice bath and provided with a stirrer, thermometer, and dropping funnel are placed 168 ml. (200 g.) of concentrated (37–38%) hydrochloric acid (2 moles) and 240 g. of paraformaldehyde (effectively 8 moles of formaldehyde). While the temperature is maintained below 10°, 452 ml. (6.9 moles) of chlorosulfonic acid is added dropwise at such a rate that gaseous hydrogen chloride is not lost from the mixture. This requires about 5.5 hours. The mixture is stirred for 4 hours in the melting ice bath and comes to room temperature. It may be allowed to stand overnight. The layers are separated, and the product (upper layer) is washed twice with ice water. Ice is added to the product, and 250 ml. of 40% sodium hydroxide is then added to the mixture slowly with vigorous agitation until the aqueous phase is strongly alkaline (Note 1). The product is separated and dried rapidly over potassium carbonate and then over potassium hydroxide, keeping the product cold during drying (Note 2). After separation of the drying agent by filtration, 350–370 g. (76–81%) of product sufficiently pure for many purposes is obtained. On distillation there is obtained 330–350 g. (72–76%) of bischloromethyl ether, boiling at 100–104°. Approximately 95% boils at 101–101.5°, n_D^{25} 1.4420 (Note 3).

2. Notes

1. Local overheating must be carefully avoided during the alkaline washing, since it may result in vigorous decomposition.
2. The washing and drying are carried out as rapidly as possible to avoid hydrolysis of the product.

3. The submitter reports that operation of this procedure on a scale of 72 moles of paraformaldehyde gave a crude yield of 3601 g. (87%) and a distilled yield of 3519 g. (85%).

3. Discussion

Bischloromethyl ether has been prepared by saturation of formalin with dry hydrogen chloride,[2,3,4] by the reaction of paraformaldehyde with phosphorus trichloride[5,6] or phosphorus oxychloride,[7,8] by solution of paraformaldehyde in concentrated sulfuric acid and treatment with ammonium chloride or dry hydrogen chloride,[9] and by suspension of paraformaldehyde in seventy[10] or eighty[11] percent sulfuric acid and treatment with chlorosulfonic acid. It is formed together with the asymmetrical isomer when methyl ether is chlorinated[12] and when paraformaldehyde is treated with chlorosulfonic acid.[13] It also is obtained when chloromethyl methyl ether is chlorinated by means of chlorine[14] or sulfuryl chloride.[15] The present method has been published.[16]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 218

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

hydrogen chloride, hydrochloric acid (7647-01-0)

ammonium chloride (12125-02-9)

sodium hydroxide (1310-73-2)

chlorosulfonic acid (7790-94-5)

formaldehyde, formalin (630-08-0)

methyl ether (115-10-6)

Phosphorus Oxychloride (21295-50-1)

sulfuryl chloride (7791-25-5)

chlorine (7782-50-5)

potassium hydroxide (1310-58-3)

phosphorus trichloride (7719-12-2)

Ether, bis(chloromethyl)- (542-88-1)

chloromethyl methyl ether (107-30-2)

Bischloromethyl ether

paraformaldehyde (30525-89-4)

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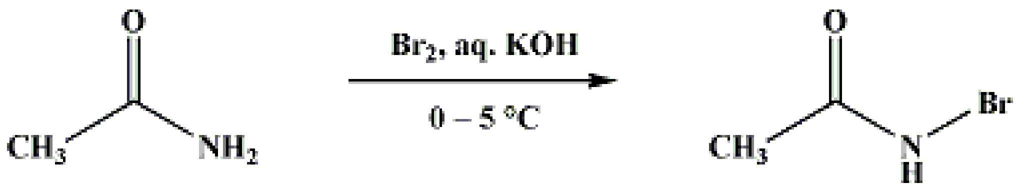
N-BROMOACETAMIDE

[Acetamide, N-bromo-]



Submitted by Eugene P. Oliveto and Corinne Gerold[1].
Checked by Richard T. Arnold and Carl G. Krespan.

1. Procedure

Twenty grams of acetamide (0.34 mole) is dissolved in 54 g. of bromine (0.34 mole) contained in a 500-ml. Erlenmeyer flask, and the solution is cooled to 0–5° in an ice bath. An ice-cold aqueous 50% potassium hydroxide solution is added in small portions with swirling and cooling until the color becomes a light yellow. Approximately 33–34 ml. of the caustic solution is required. The nearly solid reaction mixture is allowed to stand at 0–5° for 2–3 hours.

The mixture is treated with 40 g. of salt and 200 ml. of chloroform and warmed on the steam bath with vigorous swirling. After 2–3 minutes the clear red chloroform layer is decanted from the semisolid lower layer, and the extraction is repeated twice more with 200- and 100-ml. portions of chloroform respectively (Note 1). The combined extracts are dried over sodium sulfate, the solution is filtered by gravity through a fluted filter into a 2-l. Erlenmeyer flask, and 500 ml. of hexane is added with swirling. White needles of N-bromoacetamide begin to form at once (Note 2). After chilling for 1–2 hours, the crystals are collected with suction, washed with hexane, and air-dried. The yield is 19–24 g. (41–51%), m.p. 102–105° (Note 3), purity 98–100% (Note 4) and (Note 5).

2. Notes

1. Six additional extractions, using 50-ml. portions of chloroform, may produce an increase in yield of 4–5 g.
2. Occasionally it may be necessary to add seed crystals to promote crystallization.
3. Material melting as much as 10° lower is sometimes obtained. However, it still has a purity of better than 96% as determined by thiosulfate titration (Note 4). This may indicate the presence of small amounts of N,N-dibromoacetamide.
4. The purity is determined by titration with standard sodium thiosulfate solution. An accurately weighed sample of about 200 mg. is dissolved in water,

and a solution of approximately 1 g. of potassium iodide in 10 ml. of water is added. The solution is acidified with 10 ml. of 10% sulfuric acid and titrated with 0.1*N* thiosulfate to the starch end point.

$$\% \text{ N-bromoacetamide} = \frac{\text{ml. } S_2O_3^{-2} \times \text{normality} \times 69 \times 100}{\text{weight of sample (mg.)}}$$

5. The product is unstable and should be stored in a cool place protected from light.

3. Discussion

N-Bromoacetamide has been prepared from acetamide and bromine in the presence of potassium hydroxide,[2,3] zinc oxide,[4] or calcium carbonate.[4]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

Acetamide (60-35-5)

chloroform (67-66-3)

bromine (7726-95-6)

sodium sulfate (7757-82-6)

potassium iodide (7681-11-0)

sodium thiosulfate (7772-98-7)

calcium carbonate (471-34-1)

potassium hydroxide (1310-58-3)

zinc oxide

hexane (110-54-3)

N-Bromoacetamide, Acetamide, N-bromo- (79-15-2)

N,N-dibromoacetamide

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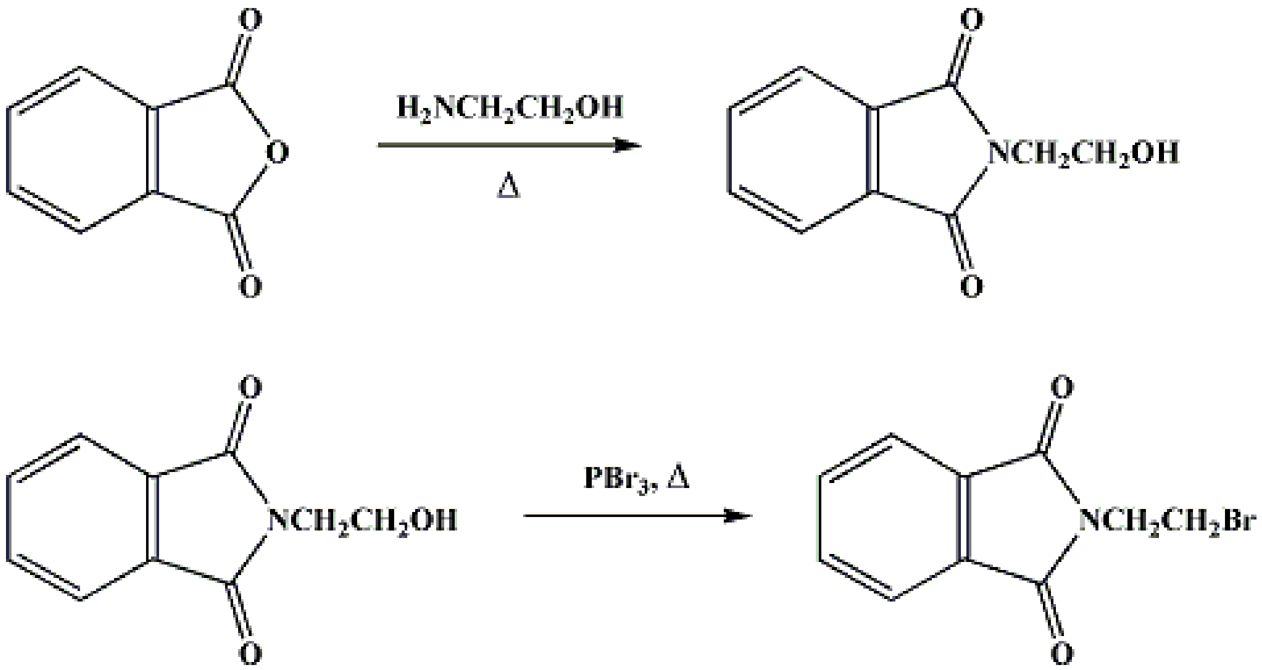
Organic Syntheses, CV 4, 106

β-BROMOETHYLPHTHALIMIDE

[Phthalimide, N-2-bromoethyl-]



Submitted by T. O. Soine and M. R. Buchdahl[1].
Checked by Cliff S. Hamilton and John D. Sculley.

1. Procedure

Caution! This preparation should be carried out in a hood.

In a 1-l. round-bottomed flask are placed 74 g. (0.5 mole) of phthalic anhydride and 30 ml. (0.5 mole) of freshly distilled monoethanolamine. The mixture is heated on a steam bath for 30 minutes; the initial reaction is vigorous (Note 1). The reaction mixture is cooled to room temperature, and a reflux condenser is attached to the flask. To the cooled reaction mixture is added slowly, with shaking, 32 ml. (91.3 g., 0.34 mole) of freshly distilled phosphorus tribromide. The reaction flask is then placed on a steam bath and heated under reflux with occasional shaking for 1.25 hours (Note 2). The hot liquid reaction mixture is poured with stirring onto 750 g. of crushed ice. When the ice has melted completely, the crude β-bromoethylphthalimide is collected on a Büchner funnel, washed with cold water, and allowed to dry for a few minutes. The crude product (Note 3) is dissolved in 1.2 l. of aqueous ethanol (50% by volume) with the aid of heat. If necessary a small amount of 95% ethanol is added to effect complete solution. The hot solution is filtered and cooled in a refrigerator. A white crystalline product weighing 94–99 g. is obtained. Concentration of the mother liquor to 400 ml. yields an additional 1–3 g. of product. The total yield of product is 95–102 g. (75–80%); m.p. 80–82°.

2. Notes

1. It is not necessary to isolate the intermediate β-hydroxyethylphthalimide before going on to the next step. However, recrystallization of the product from 250 ml. of boiling water yields an initial crop of white crystals; m.p. 128°. The mother liquors will deposit further material until a yield of 95% may be obtained.
2. The final reaction mixture should contain no undissolved material.
3. This product weighs approximately 110 g. when dry.

3. Discussion

β-Bromoethylphthalimide has been prepared by the method of Gabriel[2] as recorded by Salzberg and Supniewski.[3] Illg and Smolinski have carried out this reaction in a specially designed apparatus.[4] The procedure outlined above is a modification of the method given by Soine.[5]

References and Notes

1. University of Minnesota, Minneapolis, Minnesota.
2. Gabriel, *Ber.*, **20**, 2224 (1887); **21**, 566 (1888); **22**, 1137 (1889).
3. *Org. Syntheses Coll. Vol.* **1**, 119 (1941).
4. Illg and Smolinski, *Roczniki Chem.*, **23**, 426 (1949) [*C. A.*, **45**, 6173 (1951)].
5. Soine, *J. Am. Pharm. Assoc.*, **33**, 141 (1944).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

phosphorus tribromide (7789-60-8)

phthalic anhydride (85-44-9)

β-Bromoethylphthalimide

Phthalimide, N-2-bromoethyl- (574-98-1)

monoethanolamine (141-43-5)

β-hydroxyethylphthalimide

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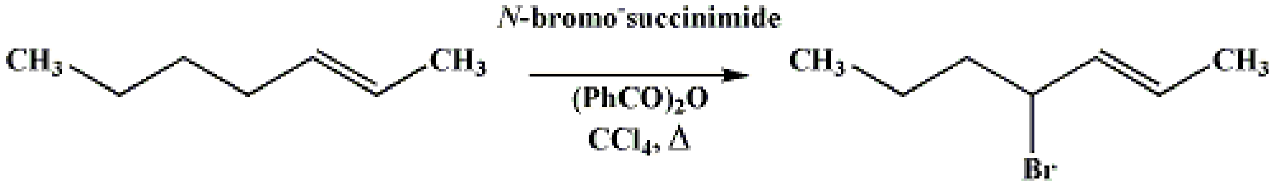
Organic Syntheses, *CV 4, 108*

4-BROMO-2-HEPTENE

[2-Heptene, 4-bromo-]



Submitted by F. L. Greenwood, M. D. Kellert, and J. Sedlak[1].
Checked by John D. Roberts and A. T. Bottini.

1. Procedure

In a 500-ml. round-bottomed flask fitted with a stirrer, nitrogen inlet tube, and reflux condenser are placed 40 g. (0.41 mole) of 2-heptene, 48.1 g. (0.27 mole) of N-bromosuccinimide, 0.2 g. of benzoyl peroxide, and 250 ml. of carbon tetrachloride (Note 1). The reaction mixture is stirred and heated under reflux in a nitrogen atmosphere for 2 hours (Note 2). The succinimide is removed by suction filtration, washed twice with 15-ml. portions of carbon tetrachloride and the carbon tetrachloride washings are combined with the filtrate (Note 3). The carbon tetrachloride solution is transferred to a 500-ml. Claisen flask modified so that the distilling arm carries a 25 × 300 mm. section packed with glass helices. The capillary is attached to a source of nitrogen and the carbon tetrachloride removed at 36–38°/190 mm. (Note 4).

The residue is transferred to a 125-ml. Claisen flask modified so that the distilling arm carries an 18 × 180 mm. section packed with glass helices. Nitrogen is led into the capillary, and, after a forerun of 1–3 g., there is collected 28–31 g. (58–64%) of 4-bromo-2-heptene, b. p. 70–71°/32 mm., n_D^{25} 1.4710–1.4715 (Note 5). A residue of 7–10 g. remains in the distilling flask (Note 6).

2. Notes

1. The 2-heptene was the pure grade material purchased from Phillips Petroleum Company, Bartlesville, Oklahoma. This olefin is comparable to material prepared by a Boord synthesis. The N-bromosuccinimide was obtained from Arapahoe Chemicals, Inc., Boulder, Colorado. The benzoyl peroxide was used as received from Distillation Products, Rochester, New York. The carbon tetrachloride was reagent grade, from J. T. Baker Chemical Company, Phillipsburg, New Jersey.
2. The reaction is not rapid, and benzoyl peroxide is necessary to effect reaction. Longer reflux times lead to darkening of the reaction mixture.
3. The succinimide recovered corresponded to 97–98% of the theoretical amount and analyzed for 0.4% active bromine.
4. Removal of the carbon tetrachloride at a lower pressure results in loss of product. Distillation at a pressure much above 200 mm. causes considerable darkening of the

liquid. Carbon tetrachloride removed at the higher pressure gives no precipitate with aqueous silver nitrate; this indicates the absence of product.

5. When first distilled, the product is nearly colorless. On standing under nitrogen in the refrigerator for several days, the material acquires a pale yellow color. Evidence for the identity of the product as 4-bromo-2-heptene is outlined in Reference [2].

6. This includes the liquid wetting the helices as well as the small amount of dark residue in the flask.

3. Discussion

Ziegler and coworkers[3] indicated that allylic methylene groups undergo bromine substitution more readily than allylic methyl groups. This has been shown[2] to be true, and the treatment of 2-heptene with N-bromosuccinimide gives rise to 4-bromo-2-heptene.

References and Notes

1. Tufts University, Medford, Massachusetts.
2. Greenwood and Kellert, *J. Am. Chem. Soc.*, **75**, 4842 (1953).
3. Ziegler et al., *Ann.*, **551**, 80 (1942).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silver nitrate (7761-88-8)

bromine (7726-95-6)

carbon tetrachloride (56-23-5)

nitrogen (7727-37-9)

benzoyl peroxide (94-36-0)

Succinimide (123-56-8)

N-bromosuccinimide (128-08-5)

4-Bromo-2-heptene, 2-Heptene, 4-bromo- (22118-57-6)

2-heptene

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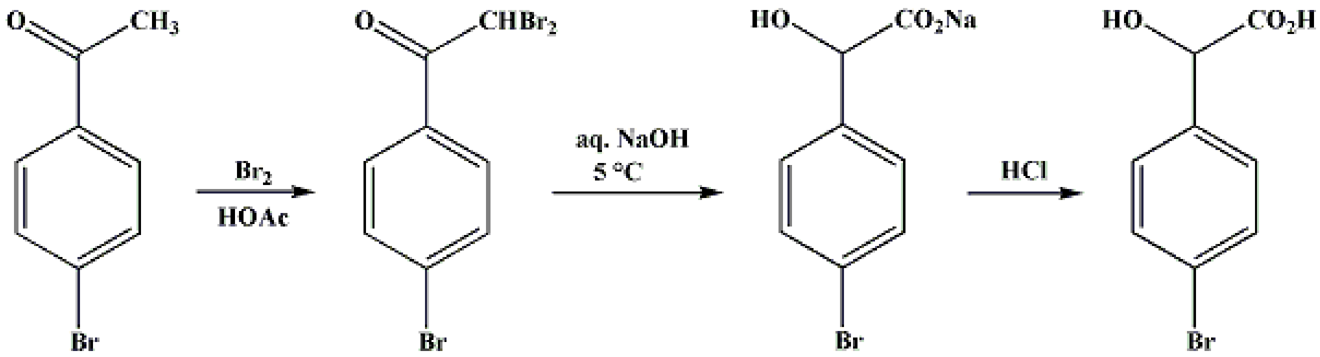
Organic Syntheses, CV 4, 110

p-BROMOMANDELIC ACID

[Mandelic acid, *p*-bromo]



Submitted by J. J. Klingenberg[1]
Checked by R. T. Arnold and C. D. Wright.

1. Procedure

A. *p,α,α-Tribromoacetophenone*. In a 1-l. three-necked flask (Note 1) equipped with an efficient mechanical stirrer, a dropping funnel, and a gas outlet leading to a hood or trap are placed 100 g. (0.5 mole) of *p*-bromoacetophenone (Note 2) and 300 ml. of glacial acetic acid. The resulting solution is stirred and cooled to 20°, and a solution of 26 ml. (0.5 mole) of bromine in 100 ml. of glacial acetic acid is added dropwise (Note 3). Crystals of the mono-α-brominated derivative separate during the addition, which requires about 30 minutes. When the addition is completed, a second solution of 26 ml. (0.5 mole) of bromine in 100 ml. of glacial acetic acid is added dropwise. Slight heating may be necessary to keep the reaction proceeding, as indicated by decolorization of the bromine, but the temperature should be kept as near 20° as possible. During the addition, which requires about 30 minutes, the solid dissolves and crystals of the di-α,α-brominated derivative appear toward the end of the addition. The flask is heated to dissolve the contents, which are transferred, preferably in a hood, to a 1-l. beaker and cooled rapidly by means of an ice-water bath (Note 4). The mixture is filtered with suction (Note 5), and the solid is washed with 50% ethanol until colorless. The air-dried product has a slight pink cast and melts at 89–91°. The yield is 130–135 g. (73–75%) (Note 6). A pure, white solid melting at 92–94° is obtained by recrystallization from ethanol, but the initial product is sufficiently pure for the next step.

B. *p-Bromomandelic acid*. In a Waring-type blender are placed 89 g. (0.25 mole) of *p*,α,α-tribromoacetophenone and 100–150 ml. of cold water. The mixture is stirred for 10–15 minutes, and the contents are transferred to a 1-l. wide-mouthed bottle. The mixing vessel is rinsed with 150–200 ml. of ice-cold water. The material from the rinse is combined with the mixture in the bottle, and sufficient crushed ice is added to bring the temperature below 10°. One hundred milliliters of a chilled aqueous solution containing 50 g. of sodium hydroxide is added slowly while the bottle is rotated (Note 7). The contents are stored for approximately 4–5 days in a refrigerator (5°) and are shaken occasionally. During this time most of the solid dissolves, but a slight amount remains as a yellow sludge and the liquid assumes a yellow to amber color. The mixture is filtered, and the insoluble material is discarded. An excess of concentrated hydrochloric acid is added to the filtrate. The entire resulting mixture containing a white solid is extracted with three 200-ml. portions of ether. The ether extracts are combined, dried over anhydrous sodium sulfate, and filtered into a 1-l. flask. The ether is carefully removed by distillation using a hot-water bath to give a yellow oil which solidifies when cooled. The product is recrystallized from 500 ml. of benzene. The crystals are collected by filtration and washed with benzene until the filtrate is colorless. The air-dried product (Note 8) weighs 40–48 g. (69–83% based on *p*,α,α-tribromoacetophenone), m.p. 117–119° (Note 9). A second recrystallization from 500 ml. of benzene is sometimes necessary.

2. Notes

1. The use of ground-glass equipment is desirable but not necessary.

2. The preparation of *p*-bromoacetophenone is described in *Organic Syntheses*.[2] The compound is also available from Eastman Kodak Company.
3. Sometimes the initation of the reaction is slow. The reaction may be started by heating the solution until the bromine is decolorized (approximately 45°), after which the reaction will proceed normally at 20°.
4. The checkers found that maximum yields of product were obtained when cooling was carried to the point where crystallization of the solvent commenced. The trace of crystalline solvent quickly melts during the filtering procedure.
5. These compounds are lachrymatory and should be kept away from the eyes.
6. An additional quantity of less pure material can be isolated from the glacial acetic acid mother liquid and alcohol filtrates by evaporation of the solvent. This, after recrystallization from ethanol, amounts to 15–30 g.
7. It is important that the reaction mixture be kept cold at this point. The amount of sludge and colored material increases as the temperature increases.
8. The last traces of benzene leave very slowly and if present lower the melting point. The product should be thoroughly dried in air or on a clay plate before the melting point is taken.
9. Under similar conditions, *p*-chloromandelic acid melting at 119–120° was obtained from *p*-chloroacetophenone in 54% yield and *p*-iodomandelic acid melting at 135–136° from *p*-iodoacetophenone in 21% yield.

3. Discussion

p-Bromomandelic acid has been prepared by the bromination of *p*-bromoacetophenone followed by alkaline hydrolysis;[3] by the alkaline hydrolysis of the product formed by the addition of chloral to *p*-bromophenylmagnesium bromide;[4] and by the condensation of bromobenzene and ethyl oxomalonate in the presence of stannic chloride followed by hydrolysis and decarboxylation.[5] *p*-Bromomandelic acid is a valuable reagent in the analyses of zirconium and hafnium.[6].

References and Notes

1. Xavier University, Cincinnati, Ohio.
2. *Org. Syntheses Coll. Vol.* **1**, 109 (1941).
3. Collect, *Bull. soc. chim. France*, [3] **21**, 67 (1899).
4. Hebert, *Bull. soc. chim. France*, [4] **27**, 45 (1920).
5. Riebsomer, Baldwin, Buchanan, and Burkett, *J. Am. Chem. Soc.*, **60**, 2974 (1938).
6. Hahn, *Anal. Chem.*, **23**, 1259 (1951); Klingenberg and Papucci, *Anal. Chem.*, **24**, 1861 (1952).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

ether (60-29-7)

sodium hydroxide (1310-73-2)

bromine (7726-95-6)

sodium sulfate (7757-82-6)

bromobenzene (108-86-1)

Ethyl oxomalonate

stannic chloride (7646-78-8)

chloral (75-87-6)

p,α,α-Tribromoacetophenone (13195-79-4)

zirconium

hafnium

p-iodoacetophenone (13329-40-3)

p-Bromoacetophenone (99-90-1)

p-Chloroacetophenone (99-91-2)

p-bromophenylmagnesium bromide

p-Bromomandelic acid, Mandelic acid, p-bromo (6940-50-7)

p-chloromandelic acid (492-86-4)

p-iodomandelic acid

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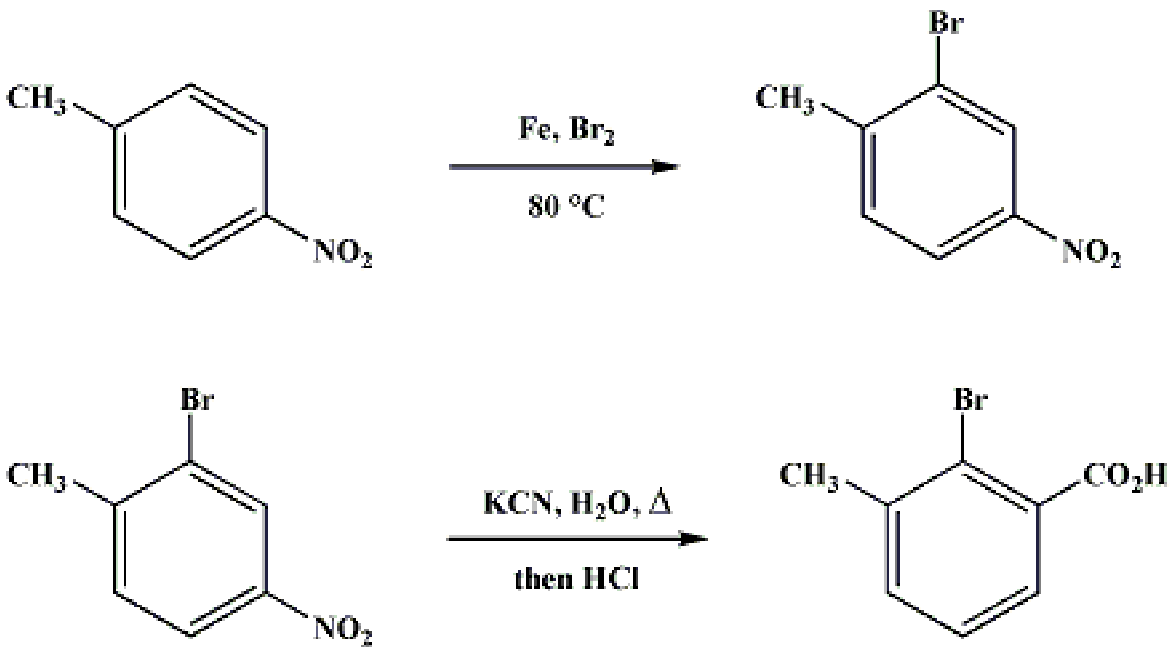
Organic Syntheses, *CV 4*, *114*

2-BROMO-3-METHYLBENZOIC ACID

[*m*-Toluic acid, 2-bromo-]



Submitted by J. F. Bunnett and M. M. Rauhut[1].
Checked by John D. Roberts and Marc S. Silver.

1. Procedure

A. *2-Bromo-4-nitrotoluene*. In a 200-ml. three-necked, round-bottomed flask provided with an efficient reflux condenser bearing a suitable trap for absorbing hydrogen bromide, a 100-ml. separatory funnel, and a ball-joint or mercury-sealed mechanical stirrer are placed 68.5 g. (0.5 mole) of *p*-nitrotoluene (Note 1) and 1.0 g. of iron powder. The mixture is heated to 75–80° by means of a water bath, vigorous stirring is begun, and 30.5 ml. (94.8 g., 0.59 mole) of bromine is added over the course of 30 minutes. After the addition of bromine is complete, the reaction mixture is maintained at 75–80° with continuation of stirring for an additional 1.5 hours.

The reaction mixture is poured with vigorous stirring into 750 ml. of ice-cold 10% sodium hydroxide solution, the solid is allowed to settle, and the supernatant liquid is decanted. To the residue is added 250 ml. of glacial acetic acid, and the mixture is heated until the solid is completely melted. The two liquid phases are thoroughly mixed by stirring, the mixture is cooled to 5° in an ice bath, and the supernatant liquid is decanted. The product is then heated with 500 ml. of 10% acetic acid until molten, stirred thoroughly, and cooled to room temperature. The aqueous liquor is decanted, and the cycle is repeated with 500 ml. of 1% sodium hydroxide solution (Note 2). The solid 2-bromo-4-nitrotoluene is collected on a Büchner funnel and thoroughly washed

with water. The moist product may be used directly in the next stage of the synthesis. It can be dried to yield 93–97 g. (86–90%) of light-brown material melting at 75–76°.

B. *2-Bromo-3-methylbenzoic acid*. *Caution! This procedure must be carried out in a hood with a good draft, because poisonous hydrogen cyanide is evolved.* In a 5-l. round-bottomed flask are placed 90 g. of potassium cyanide, 900 ml. of 2-ethoxyethanol (Note 3), 850 ml. of water, and the moist 2-bromo-4-nitrotoluene obtained above. A reflux condenser is attached, and the mixture is boiled for 16 hours (Note 4). To the hot, dark-red solution is then added 1.5 l. of water, and the mixture is acidified with concentrated hydrochloric acid. (*Caution! Hydrogen cyanide is evolved.*) The acidified mixture is boiled for 15 minutes to expel hydrogen cyanide and then allowed to cool to 35–40°. Five grams of diatomaceous earth is stirred in, and the mixture is filtered through a Büchner funnel precoated with a little diatomaceous earth. The solid is discarded, and the filtrate is extracted three times with 200-ml. portions of chloroform. The chloroform extracts are combined and extracted with three 100-ml. portions of 5% ammonium carbonate solution. The basic extracts are combined, acidified with concentrated hydrochloric acid, and cooled in an ice bath. The oil which first forms soon crystallizes.

The tarry solid is collected on a Büchner funnel, washed with 50 ml. of water, and dried. The dried solid is pulverized and boiled under reflux for 3 hours with 500 ml. of petroleum ether (b.p. 90–100°). The hot mixture is then filtered (fluted filter paper), and the solid is discarded. The filtrate is allowed to cool to room temperature, and the 2-bromo-3-methylbenzoic acid is collected by filtration. The white acid when dry weighs 7.5–8.5 g. (7–8%, based on the *p*-nitrotoluene) and melts at 134–136° (Note 5).

2. Notes

1. Eastman Kodak Company practical grade *p*-nitrotoluene was used.
2. The hot mixture of 2-bromo-4-nitrotoluene and 1% sodium hydroxide solution should be stirred vigorously during cooling in order to avoid obtaining the product as a solid cake. If stirring is omitted, subsequent treatment is less convenient.
3. Commercial Cellosolve was used.
4. An electric heating mantle is a convenient heat source.
5. The submitters report 11–14 g. (10–13%) of material having m.p. 132–135°, which yields, after crystallization from benzene, 9–13 g. product having m.p. 135–137°.

3. Discussion

Although 2-bromo-4-nitrotoluene has been obtained by several routes, it is most easily prepared by bromination of *p*-nitrotoluene.[2] The procedure given is adapted from that described by Cavill.[3] 2-Bromo-3-methylbenzoic acid has not been prepared by any other means; evidence for its structure is presented elsewhere.[4]

References and Notes

1. University of North Carolina, Chapel Hill, North Carolina.
2. Scheufelen, *Ann.*, **231**, 152 (1885); Lucas and Scudder, *J. Am. Chem. Soc.*, **50**, 244 (1928); Frejka and Vitha, *Publs. fac. sci. univ. Masaryk*, **20** (1925) [*Chem. Zentr.*, **96**, II, 1153 (1925)]; Higginbottom, Hill, and Short, *J. Chem. Soc.*, **1937**, 263; Truce and Amos, *J. Am. Chem. Soc.*, **73**, 3013 (1951).
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4. Bunnett and Rauhut, *J. Org. Chem.*, **21**, 934 (1956).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ammonium carbonate

Benzene (71-43-2)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

iron powder (7439-89-6)

hydrogen cyanide (74-90-8)

hydrogen bromide (10035-10-6)

bromine (7726-95-6)

potassium cyanide (151-50-8)

cellosolve (107-21-1)

2-ethoxyethanol (110-80-5)

2-Bromo-3-methylbenzoic acid, m-Toluic acid, 2-bromo- (53663-39-1)

2-Bromo-4-nitrotoluene (7745-93-9)

p-nitrotoluene (99-99-0)

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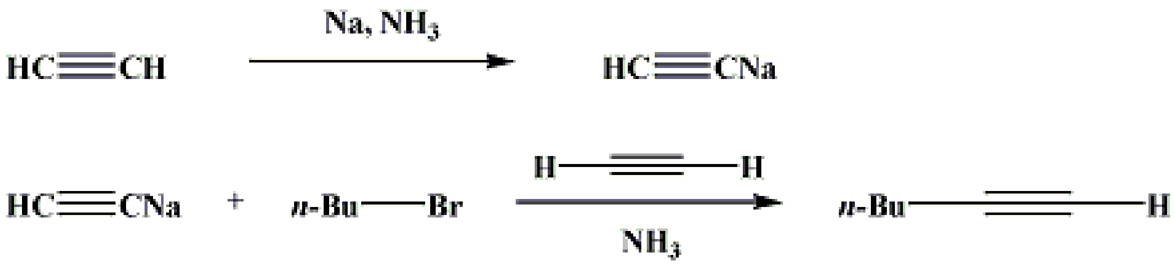
Organic Syntheses, *CV 4, 117*

n-BUTYLACETYLENE

[1-Hexyne]

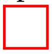
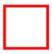


Submitted by Kenneth N. Campbell and Barbara K. Campbell[1].
Checked by R. S. Schreiber, M. F. Murray, and A. C. Ott.

1. Procedure

Caution! This preparation should be conducted in a hood to avoid exposure to ammonia.

A 5-l. three-necked flask is fitted with an efficient stirrer, mounted through a short glass bushing, and a long gas inlet tube which dips below the surface of the liquid ammonia. The third neck carries a device for holding sodium; this consists of a short piece of 10–12 mm. glass tubing, bent at a 45° angle, through which is passed a 12-in. piece of stout, flexible iron wire (picture wire is satisfactory). The lower end of the wire is attached to a stout iron fish-hook. (Sneck Hook No. 5/0 is satisfactory.)

The flask is charged with about 3 l. of liquid ammonia (Note 1), the stirrer is started, and a rapid stream of acetylene gas (about 5 bubbles per second) is passed in for about 5 minutes to saturate the ammonia. The acetylene from a tank is sufficiently purified by passage through a sulfuric acid wash bottle; a safety trap also should be inserted in the line. Sodium (92 g., 4 g. atoms) is cut in strips (about  by  by 3 in.) so that they can be inserted through the side neck of the flask. One of these pieces of sodium is attached to the fish-hook and is gradually lowered into the liquid ammonia while a rapid stream of acetylene is passed in. The sodium should be added at such a rate that the entire solution does not turn blue. If it does, the sodium should be raised above the level of the ammonia until the color is discharged (Note 2). The rest of the sodium is added in a similar manner; the addition requires about 45 minutes, depending on the rate of passage of the acetylene.

The acetylene is shut off, and the gas inlet tube and iron wire are removed, but not the bent glass tubing. A potassium hydroxide tower (Note 3) is attached to the end of this tubing, and a dropping funnel (Note 4) is mounted in the other neck of the flask. *n*-Butyl bromide (548 g., 428 ml., 4.0 moles) is added dropwise with stirring over a

period of 45–60 minutes (Note 5). The mixture is stirred for an additional 2 hours. Ammonium hydroxide (500 ml.) is then added dropwise, followed by about 1–1.5 l. of distilled water. When the frost on the outside of the flask is loose and can be pulled off easily, the contents of the flask are transferred to a large separatory funnel, and the lower aqueous layer is removed. The organic layer is washed with 100 ml. of distilled water, then with about 100 ml. of 6*N* hydrochloric acid (the aqueous layer should be tested to make sure that it remains acid; if not, another washing with acid should be carried out), and finally with about 100 ml. of 10% sodium carbonate solution. The material is dried over potassium carbonate, a small amount of solid sodium carbonate is added, and the liquid is fractionated through a helix-packed column of about 10–14 plates. The yield of pure *n*-butylacetylene is 230–252 g. (70–77%); b.p. 71–72°, n_D^{20} 1.3984–1.3990 (Note 6) and (Note 7).

2. Notes

1. More liquid ammonia should be added from time to time to maintain approximately the same level. Liquid ammonia can be handled in ordinary apparatus, and it is not necessary to use a Dewar flask or to cool the reaction flask in a Dry Ice bath, as a thick frost forms on the outside and partially insulates the contents. In making very volatile alkylacetylenes, such as ethylacetylene and propylacetylene, it is advisable to cool the apparatus in a Dry Ice bath, to minimize loss by entrainment, and to use a Dry Ice condenser. With the higher alkylacetylenes the use of a Dry Ice condenser, as recommended by Henne and Greenlee,[2] does not improve the yields enough to justify the extra trouble.
2. In order to see inside the flask a little alcohol may be poured over the outside.
3. This is not absolutely necessary except in damp weather, for the ammonia escaping through the outlet tube prevents the entrance of appreciable amounts of moisture.
4. A calibrated funnel is convenient, as the rate of addition may be judged better.
5. If the addition is carried out more slowly, the yield of product is lowered, unless a Dry Ice condenser is used.
6. The reaction may be carried out on a smaller scale without much loss in yield.
7. Other alkylacetylenes can be made in the same way from primary alkyl bromides. With *n*-propylacetylene the time of addition of *n*-propyl bromide should be about 45–60 minutes, and the yield is lower (40–50%), owing to losses by entrainment unless a Dry Ice condenser is used (b.p. 39–40°; n_D^{20} 1.3850). *n*-Amylacetylene (b.p. 98°; n_D^{20} 1.4088) and isoamylacetylene (b.p. 91–92°; n_D^{20} 1.4060) can be prepared in 70–80% yields by this method; the time of addition of the halide is 1.5–2.0 hours. *n*-Hexylacetylene (b.p. 76–77° /150 mm.; n_D^{20} 1.4157) can be obtained in 65% yields if a 1-mole excess of sodium acetylide is used. The halide is added during the course of 1 hour, and the mixture is stirred for an additional 3 hours before hydrolysis.
The method is not satisfactory for methyl- and ethylacetylenes or with secondary and tertiary alkyl halides or with primary alkyl halides above hexyl.

3. Discussion

n-Butylacetylene has been prepared from *n*-butyl bromide and sodium acetylide in liquid ammonia[2,3] or a mixture of tetrahydrofuran and dimethylformamide,[4] from *n*-butyl bromide and a slurry of calcium carbide and potassium hydroxide in dibutyl carbitol,[5] and from *n*-butyl bromide and ethynylmagnesium bromide at 80–90°.[6] It also has been obtained from the reaction of alcoholic potassium hydroxide on dibromohexanes,[7,8] and sodamide in xylene on 2-bromo-1-hexene.[9] *n*-Butylacetylene is formed, along with 2-ethoxy-1-hexene when 1-bromo-2-ethoxyhexane is caused to react with sodium in liquid ammonia.[10] It has been found[11] that a mixture of xylene and dimethylformamide is an excellent medium in which to carry out the alkylation of sodium acetylide with alkyl bromides.

The method described here is a modification of the one published by Vaughn, Vogt, Hennion, and Nieuwland.[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 532

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

calcium carbide

dibutyl carbitol

dibromohexanes

potassium carbonate (584-08-7)

acetylene (74-86-2)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

sodium carbonate (497-19-8)

n-butyl bromide (109-65-9)

n-PROPYL BROMIDE (106-94-5)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

ammonium hydroxide (1336-21-6)

xylene (106-42-3)

n-Amylacetylene (628-71-7)

sodamide (7782-92-5)

Tetrahydrofuran (109-99-9)

dimethylformamide (68-12-2)

sodium acetylide

1-Hexyne, n-BUTYLACETYLENE (693-02-7)

ethylacetylene (107-00-6)

propylacetylene, n-propylacetylene (627-19-0)

isoamylacetylene (2203-80-7)

ethynylmagnesium bromide

2-bromo-1-hexene

2-ethoxy-1-hexene

n-Hexylacetylene (629-05-0)

1-bromo-2-ethoxyhexane

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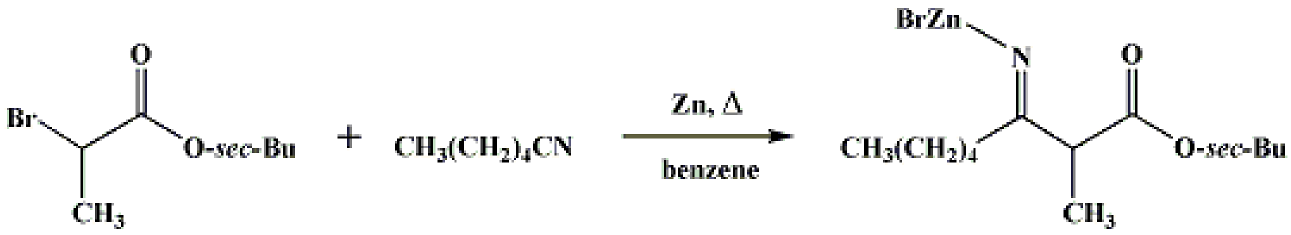
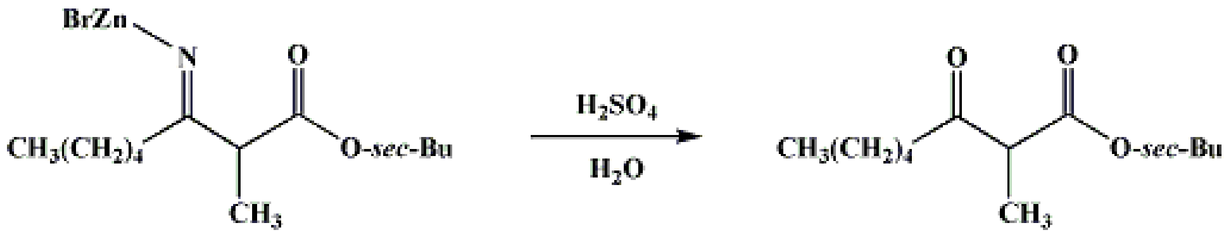
Organic Syntheses, *CV 4*, *120*

sec-BUTYL α-*n*-CAPROYLPROPIONATE

[Octanoic acid, 2-methyl-3-oxo-, *sec*-butyl ester]





Submitted by Kenneth L. Rinehart, Jr.[1]
Checked by John C. Sheehan and J. Iannicelli.

1. Procedure

A 2-l. three-necked round-bottomed flask is fitted with a condenser arranged for distillation, a 200-ml. dropping funnel, and a mercury-sealed mechanical stirrer. Connections are most conveniently made with ground-glass joints, and the flask is heated on a steam cone. Cupric bromide (0.4 g.), 39.2 g. (0.60 g. atom) of freshly sand-papered zinc foil cut into narrow strips, and 1.2 l. of benzene previously dried over sodium are added to the flask. To dry the apparatus and contents, 300 ml. of benzene is slowly distilled from the flask with stirring. Heating is interrupted, and the condenser is quickly arranged for reflux and fitted with a calcium chloride drying tube. To the flask are added rapidly with stirring 38.9 g. (0.40 mole) of *n*-capronitrile (Note 1) and 125.4 g. (0.60 mole) of *sec*-butyl α-bromopropionate (Note 2). Refluxing is resumed, and after a 3–5 minute induction period blackening of the zinc surface and clouding of the solution are noted as the first signs of reaction. Heating is maintained a total of 45 minutes, after which the solution is cooled for 15 minutes in an ice bath (Note 3).

To the cooled solution is added with vigorous stirring 400 ml. of ice-cold 12*N* sulfuric acid. The ice bath is removed, and stirring is continued at room temperature for a total of 2 hours (Note 4). The reaction mixture is poured into a 2-l. separatory funnel; after separation, the aqueous lower layer is drained into a 2-l. separatory funnel containing 800 ml. of water which has been used to wash the reaction flask. The aqueous layer is extracted twice with 200-ml. portions of benzene which have also been employed to rinse the reaction flask. The original organic layer and the combined benzene extracts are kept separate and are washed successively with 400-ml. portions of water, saturated sodium bicarbonate solution, and again with water. The two organic portions are combined and allowed to stand over anhydrous sodium sulfate until clear. The solvent is removed at atmospheric pressure by flash distillation through a fractionating column (Note 5). For this operation, a side-arm distilling flask equipped with a dropping funnel is heated by an oil bath whose temperature is maintained at 140–150°. After all the solvent has been added, the dropping funnel is replaced by a

capillary, and the last of the solvent is removed at reduced pressure furnished by a water pump. Finally, an oil pump is attached and the product is fractionated at about 5 mm. pressure (Note 6). After a small fore-run, *sec*-butyl α-*n*-caproylpropionate is obtained as a clear liquid; b.p. 112–114°/4.5 mm. (134–136°/12 mm.), n_D^{25} 1.4293 (Note 7) and (Note 8). The yield is 46.0–52.9 g. (50–58% based on *n*-capronitrile) (Note 9).

2. Notes

1. Commercial *n*-capronitrile (Eastman Kodak white label grade) is distilled through a fractionating column before use; b.p. 161–163°, n_D^{25} 1.4052.
2. α-Bromoesters are severe lachrymators, and it is necessary to conduct reactions involving them in a well-ventilated hood. *sec*-Butyl α-bromopropionate is prepared from commercially available ethyl α-bromopropionate (Sapon Laboratories, Inc., 543 Union Street, Brooklyn 15, New York) by transesterification with *sec*-butyl alcohol using sulfuric acid catalyst. The product boils at 97–98°/39 mm. and has n_D^{25} 1.4420. Darkening of the α-bromoester is prevented by storage over a few drops of mercury.
3. Unreacted zinc usually remains at this point, and the solution is yellow to brown. Most of the color is discharged on subsequent addition of the acid.
4. With 3-methylnonanoicnitrile it is necessary to continue the stirring in sulfuric acid for an additional period; a total of 19 hours is sufficient.
5. A 50 cm. by 8 mm. simple Podbielniak column[2] with partial-reflux head is adequate for this and subsequent distillations.
6. Fractionation at higher pressures and temperatures leads to some thermal decomposition of the product.
7. An analytical sample of a redistilled center cut had n_D^{25} 1.4302.
8. β-Ketoesters with alkyl substituents in the α-position give a blue-violet color with ferric chloride.[3] Copper chelates of the α-alkyl-β-ketoesters could not be isolated. The corresponding 5-pyrazolones, although often difficultly crystallizable, appear to be the most suitable derivatives. The 5-pyrazolone from *sec*-butyl α-*n*-caproylpropionate is prepared according to von Auwers and Dersch[4] and has a melting point of 80.4–82.9°.
9. This method is suitable for the preparation of mono- and di-α-substituted β-ketoesters. Bromoacetates fail in this reaction. Yields with ethyl α-bromopropionate are considerably lower (30–36% with capronitrile); however, ethyl esters are useful for higher-molecular-weight compounds whose *sec*-alkyl esters are cracked by distillation. With 3-pentyl α-bromopropionate, the yields are slightly higher (53–60% with capronitrile). Both aromatic and aliphatic nitriles are suitable; benzonitrile gives yields comparable to those obtained with capronitrile. Alkyl substitution in the α- and β-positions (cf. (Note 4)) of aliphatic nitriles lowers the yield to 29% and 38%, respectively; γ-substitution has no effect. Recently it has been shown that a significant improvement in the yields of ketoesters is obtained by the use of a mixture of benzene and ether as a solvent.[5]

3. Discussion

The procedure is essentially that of Horeau and Jacques[6] as modified by Cason, Rinehart, and Thornton.[7] The reaction described is that discovered by Blaise[8] and is more extensively discussed in the second-named paper. Ethyl α-*n*-caproylpropionate has been prepared by the alkylation of ethyl *n*-caproylacetate with methyl iodide in the presence of sodium ethoxide.[9] This method would not be expected to yield a pure product owing to contamination with starting ketoester and disubstituted

ketoester.

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

Benzene (71-43-2)

ether (60-29-7)

benzonitrile (100-47-0)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

mercury (7439-97-6)

zinc (7440-66-6)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

ferric chloride (7705-08-0)

Methyl iodide (74-88-4)

ethyl α-bromopropionate (535-11-5)

cupric bromide (7789-45-9)

capronitrile, n-capronitrile (628-73-9)

Octanoic acid, 2-methyl-3-oxo-, sec-butyl ester, sec-BUTYL α-n-CAPROYLPROPIONATE (53663-40-4)

3-methylnonanoicnitrile

5-pyrazolone

3-pentyl α-bromopropionate

sec-butyl alcohol (78-92-2)

sec-butyl α-bromopropionate (22710-17-4)

Ethyl α-n-caproylpropionate

ethyl n-caproylacetate

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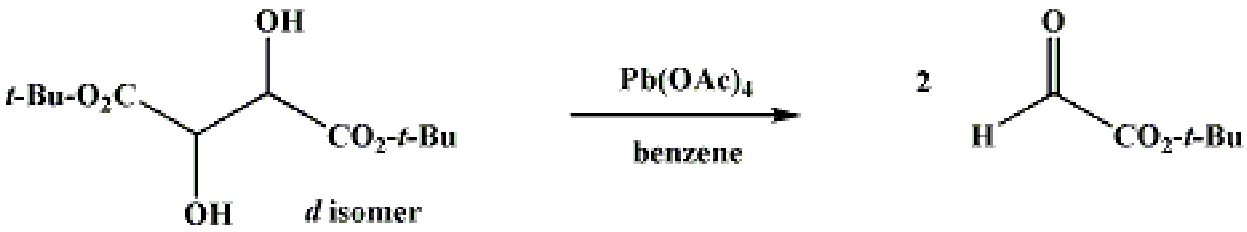
n-BUTYL GLYOXYLATE

[Glyoxylic acid, *n*-butyl ester]



Submitted by Frank J. Wolf and John Weijlard[1].
Checked by N. J. Leonard and L. A. Miller.

1. Procedure

In a 3-l. three-necked round-bottomed flask provided with a Hershberg stirrer and a thermometer are placed 1.25 l. of reagent-grade benzene and 325 g. (1.24 moles) of di-*n*-butyl *d*-tartrate (Note 1). The mixture is stirred rapidly, and 578 g. (1.30 moles) of lead tetraacetate (Note 2) is added over a period of about 25 minutes. The temperature is maintained below 30° by occasional cooling with cold water. After the addition is complete, the mixture is stirred for 1 hour, during which time the gummy salts become crystalline. The salts are removed by filtration with suction and washed with 500 ml. of benzene. The benzene and acetic acid are removed from the filtrate by distillation at 65°/50 mm. The residue is distilled at 20 mm. under nitrogen introduced through an ebullator, using a Vigreux column (2 by 30 cm.), and the fraction boiling between 65° and 79°/20 mm. (main portion at 68–74°) is collected as product. The crude *n*-butyl glyoxylate, which weighs 247–280 g. (77–87%), n_D^{20} 1.442–1.443, d_4^{25} 1.085, is satisfactory for most purposes (Note 3).

2. Notes

1. The di-*n*-butyl *d*-tartrate used was the purest grade from Eastman Kodak Company, m.p. 20–22°.
2. Lead tetraacetate was obtained from the G. Frederick Smith Chemical Company, Columbus, Ohio. It may also be prepared by the procedure described in *Inorganic Syntheses.*[2]
3. The product undergoes autoxidation and should be stored under nitrogen. Further purification may be effected by a second fractional distillation under nitrogen at reduced pressure. The product decomposes on boiling (159–161°) at atmospheric pressure.

3. Discussion

n-Butyl glyoxylate has not been described previously. *Anal.* Calcd. for $C_6H_{10}O_3$: C, 55.37; H, 7.75. Found: C, 54.95; H, 7.83. Ethyl glyoxylate has been prepared in good yield by oxidation of ethyl tartrate with red lead oxide[3] or sodium bismuthate.[4] These papers describe isolation of ethyl glyoxylate as carbonyl derivatives.

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

red lead oxide

acetic acid (64-19-7)

Benzene (71-43-2)

nitrogen (7727-37-9)

Ethyl glyoxylate (924-44-7)

ethyl tartrate

sodium bismuthate (12232-99-4)

n-BUTYL GLYOXYLATE, Glyoxylic acid, n-butyl ester (6295-06-3)

di-n-butyl d-tartrate

lead tetraacetate

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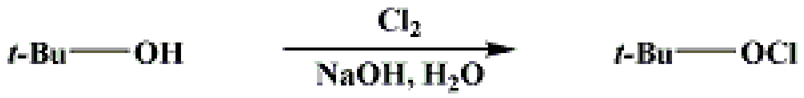
tert-BUTYL HYPOCHLORITE



Submitted by H. M. Teeter and E. W. Bell[1].
Checked by Charles C. Price and T. C. Schwann.

1. Procedure

Caution! This preparation should be carried out in a good hood. The product should be protected from strong light, over-heating, or exposure to rubber to avoid vigorous decomposition.

A solution of 80 g. (2 moles) (Note 1) of sodium hydroxide in about 500 ml. of water is prepared in a 2-l. three-necked round-bottomed flask equipped (Note 2) with a gas inlet tube reaching nearly to the bottom of the flask, a gas outlet tube, and a mechanical stirrer. The flask is placed in a water bath at 15–20° (Note 3), and, after the contents have cooled to this temperature, 74 g. (96 ml., 1 mole) of *tert*-butyl alcohol (Note 4) is added together with enough water (about 500 ml.) to form a homogeneous solution. With constant stirring, chlorine is passed into the mixture for 30 minutes at a rate of approximately 1 l. per minute (Note 5) and then for an additional 30 minutes at a rate of 0.5–0.6 l. per minute.

The upper oily layer is then separated with the aid of a separatory funnel (Note 6). It is washed with 50-ml. portions of 10% sodium carbonate solution until the washings are no longer acidic to Congo red. It is finally washed 4 times with an equal volume of water and dried over calcium chloride. The yield is 78–107 g. (72–99%) (Note 7); d_{20}^{20} 0.910; n_D^{20} 1.403. The product is best stored under an inert atmosphere (Note 8) in sealed bottles kept in the dark in a refrigerator (Note 9).

2. Notes

1. The submitters have successfully carried out this preparation in quantities up to 7 moles (519 g.) of *tert*-butyl alcohol using 2.25 hours for the addition of chlorine at each rate.
2. *tert*-Butyl hypochlorite reacts violently with rubber. The apparatus should therefore be assembled by means of ground-glass joints. Synthetic plastic tubing (Tygon) may be used instead of rubber tubing.
3. For 7-mole runs, a satisfactory bath consists of a 10-gal. earthenware jar fitted with a water inlet and an overflow device. The desired temperature is obtained by adjusting the rate of flow of tap water through the jar. The reaction can also be carried out successfully using an ice-water bath.

4. The *tert*-butyl alcohol was a commercial product obtained from the Shell Chemical Corporation, New York, New York.
5. Rates of flow are conveniently measured with the usual U-tube and capillary using one of the liquid Arochlors as the indicating fluid. The checkers did not use a flow meter but passed in chlorine rapidly at first and then slowly for 30 minutes after the initial rapid absorption.
6. In 7-mole runs carried out by the submitters, the bulk of the aqueous layer was removed conveniently by siphoning through the gas inlet tube.
7. This product, which is sufficiently pure for most purposes, contains about 2% free chlorine. It may be purified by distillation in an all-glass apparatus heated by a steam bath. The yield of pure product is 75–104 g. (69–96%); b.p. 77–78°/760 mm. Active chlorine assay indicates 97–98% purity for the crude product, 98–100% purity for the distilled material.
8. The inert atmosphere helps to minimize any tendency of vapors to ignite during sealing of the bottle. Filled bottles should be cooled in solid carbon dioxide before sealing.
9. When exposed to light, *tert*-butyl hypochlorite decomposes with formation of acetone and methyl chloride. When induced by radiation from an ultraviolet lamp, this decomposition proceeds rapidly enough to raise the temperature of the hypochlorite to the boiling point. The decomposition does not continue after irradiation is stopped. Customary room illumination does not induce the decomposition to a noticeable extent during ordinary handling of this material. However, a sealed glass bottle of hypochlorite should not be allowed to stand in light for a prolonged time as pressure sufficient to burst the bottle may be built up gradually.

3. Discussion

tert-Butyl hypochlorite has been prepared by the action of chlorine upon alkaline solutions of *tert*-butyl alcohol.[2,3,4,5] Solutions of *tert*-butyl hypochlorite have been prepared by shaking a solution of the alcohol in carbon tetrachloride,[6] fluorotrichloromethane (Freon 11), and other solvents[7] with aqueous hypochlorous acid. The procedure described is that of Teeter et al.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 184
- Org. Syn. Coll. Vol. 5, 208
- Org. Syn. Coll. Vol. 5, 909
- Org. Syn. Coll. Vol. 6, 936
- Org. Syn. Coll. Vol. 5, 183

References and Notes

1. Northern Regional Research Laboratory, U. S. Department of Agriculture, Peoria, Illinois.
2. Chattaway and Backeberg, *J. Chem. Soc.*, **1923**, 2999.
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

calcium chloride (10043-52-4)

sodium hydroxide (1310-73-2)

sodium carbonate (497-19-8)

carbon tetrachloride (56-23-5)

carbon dioxide (124-38-9)

methyl chloride (74-87-3)

acetone (67-64-1)

chlorine (7782-50-5)

hypochlorous acid (7790-92-3)

fluorotrichloromethane (75-69-4)

tert-butyl alcohol (75-65-0)

tert-Butyl hypochlorite (507-40-4)

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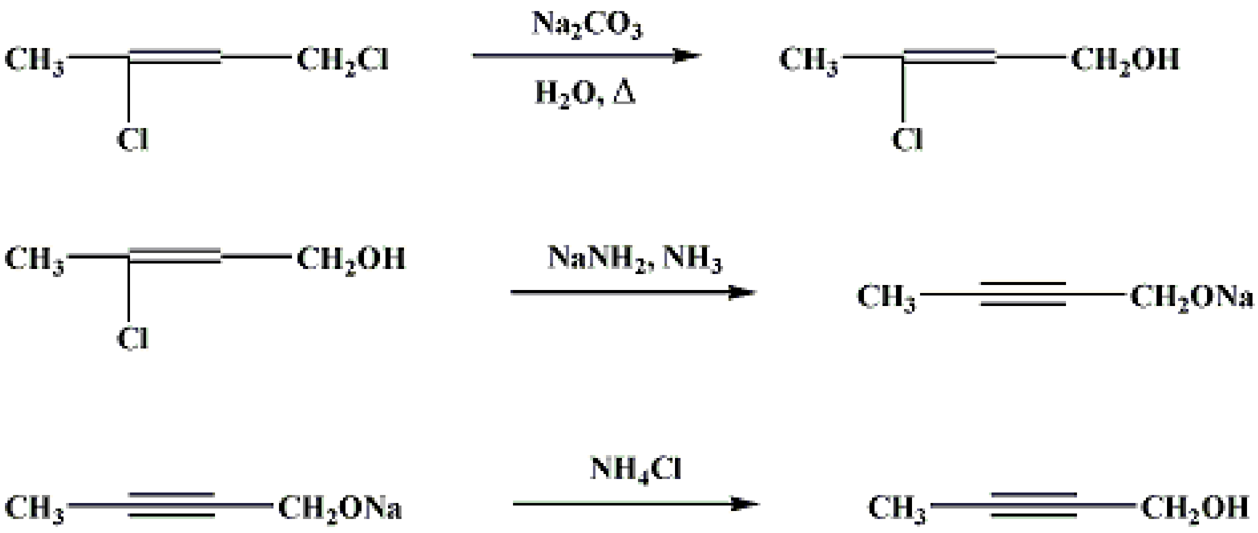
2-BUTYN-1-OL



Submitted by P. J. Ashworth, G. H. Mansfield, and M. C. Whiting[1].
Checked by John C. Sheehan, George Buchi, and Walfred S. Saari.

1. Procedure

Caution! The experimental procedure involving liquid ammonia should be conducted in a hood.

In a 3-l. three-necked round-bottomed flask fitted with a reflux condenser and a mercury-sealed stirrer, 250 g. (2 moles) of 1,3-dichloro-2-butene (Note 1) and 1.25 l. of 10% sodium carbonate are heated at reflux temperature for 3 hours. The 3-chloro-2-buten-1-ol is extracted with three 300-ml. portions of ether, which are then dried over anhydrous magnesium sulfate. The ether is removed by distillation through a 20-cm. Fenske column, and the residue is distilled from a 250-ml. Claisen flask, yielding 134 g. (63%) of 3-chloro-2-buten-1-ol, b.p. 58–60°/8 mm., n_D^{20} 1.4670.

A solution of sodium amide in liquid ammonia is prepared according to the procedure described on p. 763 using a 4-l. Dewar flask equipped with a plastic cover (Note 2) and a mechanical stirrer. Anhydrous liquid ammonia (3 l.) is introduced through a small hole in the plastic cover, and 1.5 g. of hydrated ferric nitrate is added followed by 65 g. (2.8 g. atoms) of clean, freshly cut sodium. The mixture is stirred until all the sodium is converted into sodium amide, after which 134 g. (1.26 moles) of 3-chloro-2-buten-1-ol is added over a period of 30 minutes. The mixture is stirred overnight, then 148 g. (2.8 moles) of solid ammonium chloride is added in portions at a rate that permits control of the exothermic reaction. The mixture is transferred to a metal bucket (5-l., preferably of stainless steel) and allowed to stand overnight in the hood while the ammonia evaporates. The residue is extracted thoroughly with five 250-ml. portions of ether, which is removed by distillation through a 20-cm. Fenske column. Distillation of the

residue yields 66–75 g. (75–85%) of 2-butyn-1-ol, b.p. 55°/8 mm., n_D^{20} 1.4550 (Note 3).

2. Notes

1. 1,3-Dichloro-2-butene was obtained from Eastman Kodak Company. Redistillation of the crude material did not appreciably alter the yield in the first stage of the reaction.
2. The checkers used an ordinary flask, well insulated, for this reaction.
3. Others have reported b.p. 91–93°/50 mm., n_D^{25} 1.4630;[2] b.p. 160.5°, n_D^{25} 1.4635;[3] b.p. 160–161°, n_D^{25} 1.4635, for 3-chloro-2-buten-1-ol, and b.p. 87–88° /100 mm., n_D^{25} 1.4520;[2] b.p. 140–141°, n_D^{25} 1.4517[4] for 2-butyn-1-ol.

3. Discussion

2-Butyn-1-ol has been prepared as above for the first stage[2,3,4] but using aqueous sodium hydroxide[2] and alcoholic potassium hydroxide[4] for the second stage. The reaction between propynylmagnesium bromide and formaldehyde also has been employed.[5,6,7]

References and Notes

1. Victoria University of Manchester, Manchester, England.
2. Hatch and Nesbitt, *J. Am. Chem. Soc.*, **72**, 729 (1950).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ammonia (7664-41-7)

ether (60-29-7)

ammonium chloride (12125-02-9)

sodium hydroxide (1310-73-2)

formaldehyde (630-08-0)

sodium carbonate (497-19-8)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

magnesium sulfate (7487-88-9)

sodium amide (7782-92-5)

ferric nitrate

2-Butyn-1-ol (764-01-2)

1,3-dichloro-2-butene

3-Chloro-2-buten-1-ol (40605-42-3)

propynylmagnesium bromide

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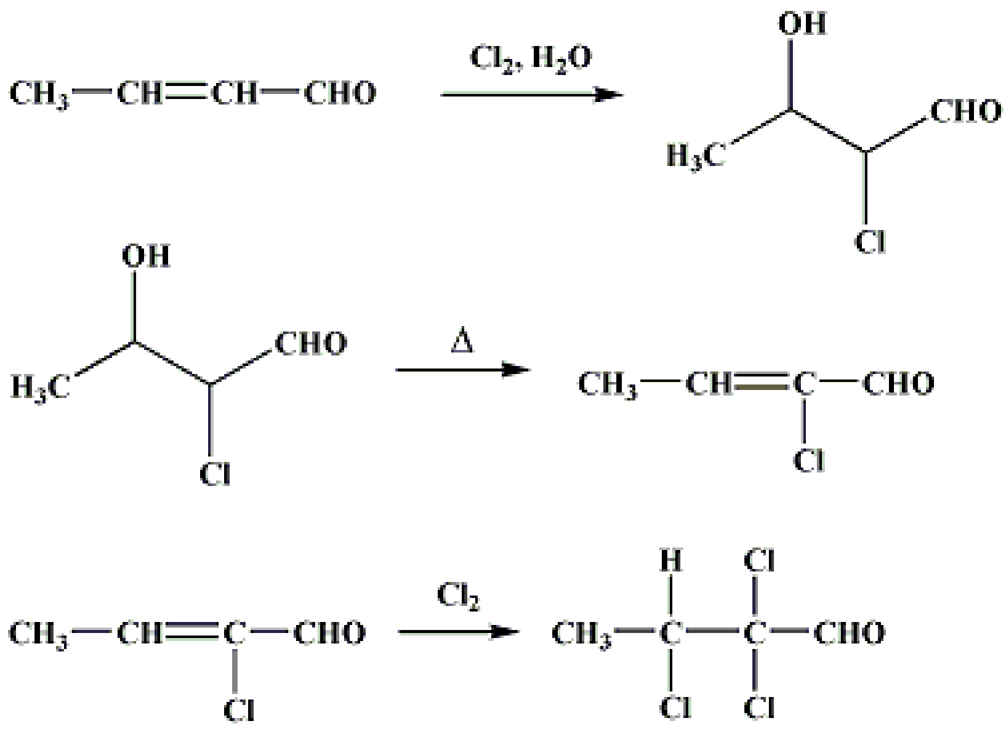
BUTYRCHLORAL

[Butyraldehyde, 2,2,3-trichloro-]



Submitted by Gus A. Ropp, W. E. Craig, and Vernon Raaen[1].
Checked by T. L. Cairns and H. N. Cripps.

1. Procedure

Crotnaldehyde (Note 1) (70 g., 1 mole) and 300 ml. of water are stirred with a glass-enclosed bar magnet while chlorine gas is passed in from a cylinder. The reaction vessel, equipped with a water-cooled reflux condenser, is cooled in an ice bath to maintain the temperature at about 10°, and the introduction of chlorine is continued for about 2 hours until the temperature does not rise rapidly when the bath is removed. At this point, the total weight increase is 70–80 g. and the upper oil layer has been converted entirely to a lower layer of viscous white oil. The reaction mixture is heated for 30 minutes at reflux temperature with slow stirring to dehydrate the chlorohydrin. The light-brown oil layer is extracted with chloroform, and the extract (Note 2) is washed twice with water and dried thoroughly over anhydrous magnesium sulfate in the refrigerator. The dry solution is filtered into a thoroughly dried flask (Note 3) equipped with a thermometer, a reflux condenser, and a bubbler tube for the introduction of dry chlorine. Over a period of 2.5 hours, chlorine, passed first through a drying tube filled with Drierite, is introduced. The temperature in the reaction mixture is kept at 0° to 10° by an ice bath, and chlorination is continued until the weight increase indicates that 1 mole of chlorine has been added. The reaction mixture is stirred for 1 hour longer in the ice bath. Then dry carbon dioxide (or nitrogen) is

bubbled through the solution at room temperature to remove excess chlorine. The reaction vessel is fitted to a dry 20-mm. by 12-in. Vigreux column wrapped with glass-wool insulation and equipped with a vacuum-jacketed, total take-off-type still head and a water-cooled condenser. The receiver is a dry tared flask with side arm leading to a manometer and, through a Drierite-filled U-tube, to a water pump. Dry carbon dioxide is passed through the still pot during the distillation. The chloroform is distilled (Note 4) at atmospheric pressure. The pressure is then decreased, and the pale yellow butyrchloral is distilled. The yield is 91–93 g. (52–53%); b.p. 57–60°/23 mm.; n_D^{25} = 1.4712–1.4740. The oil has a persistent and characteristic but not unpleasant odor (Note 5).

2. Notes

1. Best yields were obtained from Eastman's best grade crotonaldehyde which had been distilled immediately before use.
2. When this extract is dried and distilled, a high yield of α-chlorocrotonaldehyde, b.p. 147–148°, is obtained. This aldehyde is a powerful lachrymator.
3. Care is necessary to ensure absolute dryness of all glassware in which butyrchloral is contained since the aldehyde quickly forms a solid, insoluble hydrate.
4. If only a moderately pure sample of butyrchloral is needed as a reaction intermediate, the concentrate remaining after evaporation of the chloroform may be used.
5. For best yields, the entire series of reactions should be completed within 1 or 2 days. Distillation at higher pressures tends to cause some decomposition. Analysis of the product showed % Cl, 60.40, 60.64 (calculated % Cl, 60.63).

3. Discussion

Butyrchloral has been prepared by chlorination of acetaldehyde[2] and paraldehyde.[3] Butyrchloral hydrate has been prepared by treatment of α,β-dichlorobutyraldehyde with chlorine and water.[4] Butyrchloral has also been prepared[5] by treatment of crotonaldehyde with hydrogen chloride followed by chlorination. Brown and Plump have used a procedure similar to the one described here.[4]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Butyrchloral

Crotnaldehyde

Butyrchloral hydrate

acetaldehyde (75-07-0)

hydrogen chloride (7647-01-0)

chloroform (67-66-3)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

chlorine (7782-50-5)

magnesium sulfate (7487-88-9)

crotonaldehyde (123-73-9)

Butyraldehyde, 2,2,3-trichloro- (76-36-8)

α-chlorocrotonaldehyde (53175-28-3)

α,β-dichlorobutyraldehyde

paraldehyde (123-53-7)

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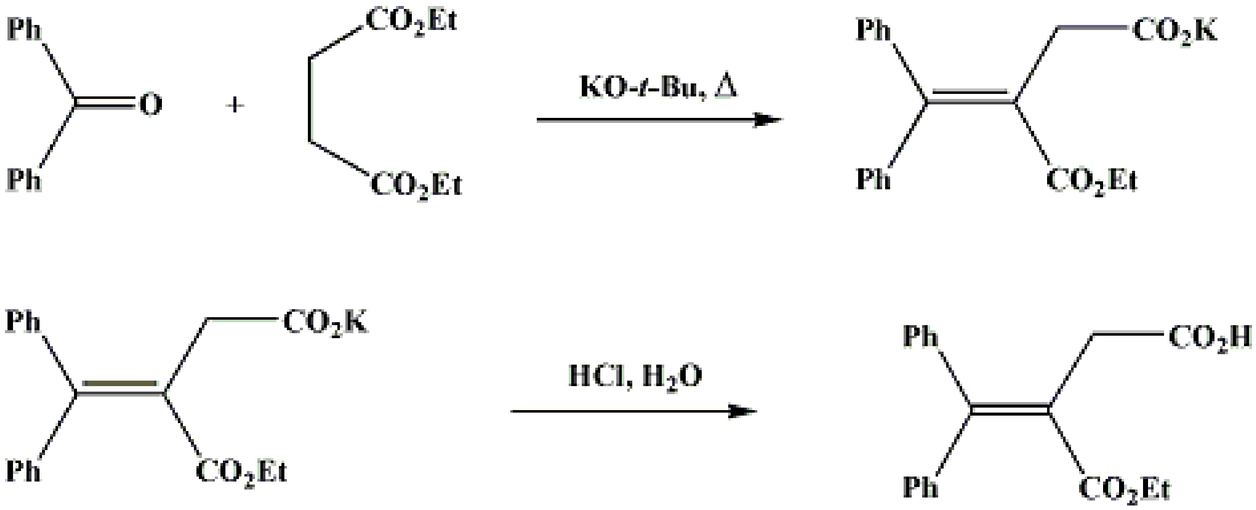
Organic Syntheses, CV 4, 132

β-CARBETHOXY-γ,γ-DIPHENYLVINYLACETIC ACID

[Succinic acid, α-benzhydrylidene-, α-ethyl ester]



Submitted by William S. Johnson and William P. Schneider[1].
Checked by Arthur C. Cope and Malcolm Chamberlain.

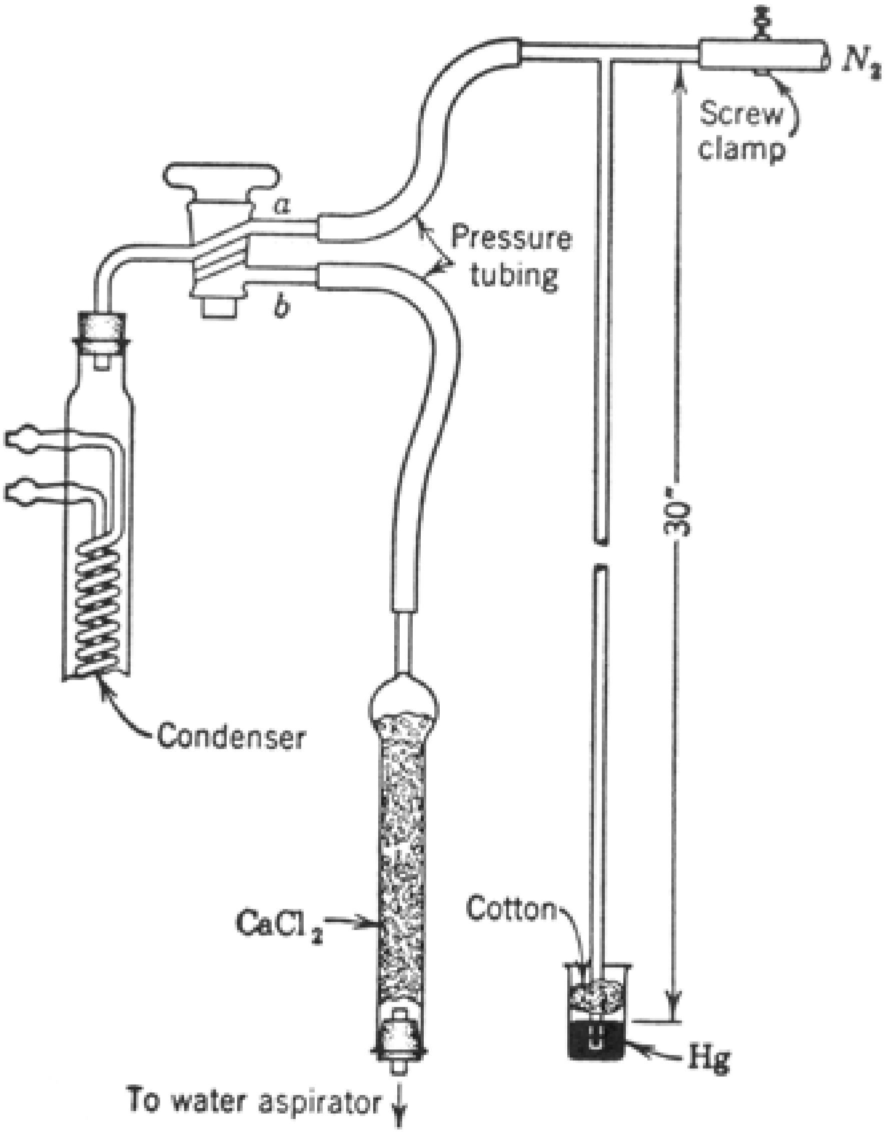
1. Procedure

Caution! See Note 3 concerning the safe handling of potassium.

The reaction is conducted in a 500-ml. round-bottomed flask attached (by a ground-glass joint) to a Pyrex reflux condenser, the top of which is connected to a three-way stopcock leading to (*a*) a source of nitrogen and a mercury trap and (*b*) a water aspirator (f.htmig. 5). The flask and condenser are dried by warming with a free flame while the system is under reduced pressure (stopcock turned to (*b*) to engage aspirator). Dry nitrogen (Note 1) is then admitted to the apparatus by turning the stopcock slowly to the position indicated in f.htmig. 5 while nitrogen is bubbling through the mercury trap. The cooled flask is quickly charged with 45 ml. of dry *tert*-butyl alcohol (Note 2) and 2.15 g. (0.055 g. atom) of potassium (Note 3) and is then reconnected to the apparatus. The flow of nitrogen is stopped, the screw clamp is closed, and the mixture is boiled under reflux until the potassium is dissolved (Note 4), hydrogen being liberated through the mercury trap. The solution is then cooled to room temperature while nitrogen is admitted to equalize the pressure. The flask is quickly disconnected just long enough for the addition of 9.11 g. (0.05 mole) of benzophenone (Note 5) and 13.05 g. (0.075 mole) of diethyl succinate (Note 5). The system is then evacuated (until the alcohol begins to boil) and filled with nitrogen. With the stopcock as shown in f.htmig. 5 and the screw clamp closed, the mixture is refluxed gently for 30 minutes (Note 6). It is then chilled, acidified with about 10 ml. of cold 1:1 hydrochloric acid, and distilled under reduced pressure (water aspirator) until most of the alcohol is

removed. Water is added to the residue, which is extracted thoroughly with ether, and the combined extracts are washed with successive portions of 1*N* ammonium hydroxide until a test portion gives no precipitate on acidification. The combined alkaline solutions are washed once with a fresh portion of ether and then added slowly with stirring to an excess of cold dilute hydrochloric acid. When the addition is complete the mixture should still be acidic to Congo red. The pale tan crystalline half-ester is separated on a suction funnel, washed well with water, and dried. The yield is 14.0–14.5 g. (92–94%), m.p. 120–124°. If a purer material is desired the product may be recrystallized by dissolving it in about 50 ml. of warm benzene, filtering, and adding an equal volume of petroleum ether (b.p. 40–60°). Upon cooling, 13.0–13.4 g. of almost colorless half-ester crystallizes, m.p. 123–124.5°.

Fig. 5. Apparatus for alternately evacuating and introducing nitrogen into the reaction vessel.



2. Notes

1. Ordinary tank nitrogen is dried satisfactorily by passage through a train

consisting of (*a*) a trap, (*b*) a wash bottle containing concentrated sulfuric acid, and (*c*) a drying tube containing fresh soda lime.

2. Commercial *tert*-butyl alcohol is dried by refluxing with sodium (about 3 g. per 100 ml.) until the metal is about two-thirds dissolved, and then distilling. It may be necessary to add fresh sodium in order to have free metal present throughout the distillation.

3. The following procedure is recommended for the safe handling of potassium. The metal may be cut conveniently under xylene (which has been dried over sodium wire) contained in a mortar. A beaker or crystallizing dish should *not* be used because it is too fragile. Each scrap obtained in cutting off the outer oxide-coated surface of the metal should be immediately transferred with tweezers to a second deep mortar containing dry xylene, where the accumulated residues are decomposed as described below as soon as the cutting operation is completed. In order to weigh the freshly cut metal it may be removed with tweezers, blotted rapidly with a piece of filter paper, and introduced into a tared beaker containing dry xylene. The weighed potassium is then introduced into the reaction mixture, the proper precautions, such as exclusion of air and moisture and rate of addition being taken, depending on the nature of the reaction involved. *Caution!* It is the small scraps of metal that adhere to the knife or float on top of the xylene that are most likely to start a fire.

Danger! Potassium residues have been known to explode even under a protective liquid. It is therefore important that all such residues be decomposed *immediately;* under no circumstances should they be stored. The mortar containing the scraps is moved to the rear of the hood and *tert*-butyl (not methyl or ethyl) alcohol is added in small portions from a medicine dropper or beaker at such a rate that the reaction does not become too vigorous. A square sheet of asbestos large enough to cover the mortar should be at hand. If the liquid should catch fire it may be extinguished easily by covering the mortar with the asbestos sheet. There should be no other inflammable material or flames in the hood during this treatment. Sufficient *tert*-butyl alcohol must be employed to ensure *complete* decomposition of all the potassium. Small specks of potassium usually remain in the first mortar used for the cutting operation; they should be decomposed in the hood by cautious addition of small amounts of *tert*-butyl alcohol as described above.

4. If the alcohol and apparatus have been properly dried, the dissolution of the potassium will be slow, requiring more than 4 hours of refluxing.

5. Eastman Kodak Company grade material is satisfactory if dried by redistillation.

6. The potassium salt of the half-ester may precipitate during the period of heating.

3. Discussion

β-Carbethoxy-γ,γ-diphenylvinylacetic acid has been prepared by the condensation of benzophenone with diethyl succinate in the presence of sodium ethoxide[2] or sodium

hydride.[3] The procedure described here is a modification involving the use of potassium *tert*-butoxide as the condensing agent.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 261
- Org. Syn. Coll. Vol. 4, 398
- Org. Syn. Coll. Vol. 4, 459
- Org. Syn. Coll. Vol. 5, 306
- Org. Syn. Coll. Vol. 5, 567
- Org. Syn. Coll. Vol. 5, 859
- Org. Syn. Coll. Vol. 5, 989
- Org. Syn. Coll. Vol. 5, 1060
- Org. Syn. Coll. Vol. 6, 51
- Org. Syn. Coll. Vol. 6, 436
- Org. Syn. Coll. Vol. 6, 507
- Org. Syn. Coll. Vol. 7, 149

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

tert-butyl (not methyl or ethyl) alcohol

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether (60-29-7)

hydrogen (1333-74-0)

nitrogen (7727-37-9)

Benzophenone (119-61-9)

sodium, sodium wire (13966-32-0)

sodium ethoxide (141-52-6)

ammonium hydroxide (1336-21-6)

potassium (7440-09-7)

xylene (106-42-3)

sodium hydride (7646-69-7)

Diethyl succinate (123-25-1)

β-CARBETHOXY-γ,γ-DIPHENYLVINYLACETIC ACID

Succinic acid, α-benzhydrylidene-, α-ethyl ester (5438-22-2)

tert-butyl alcohol (75-65-0)

potassium tert-butoxide (865-47-4)

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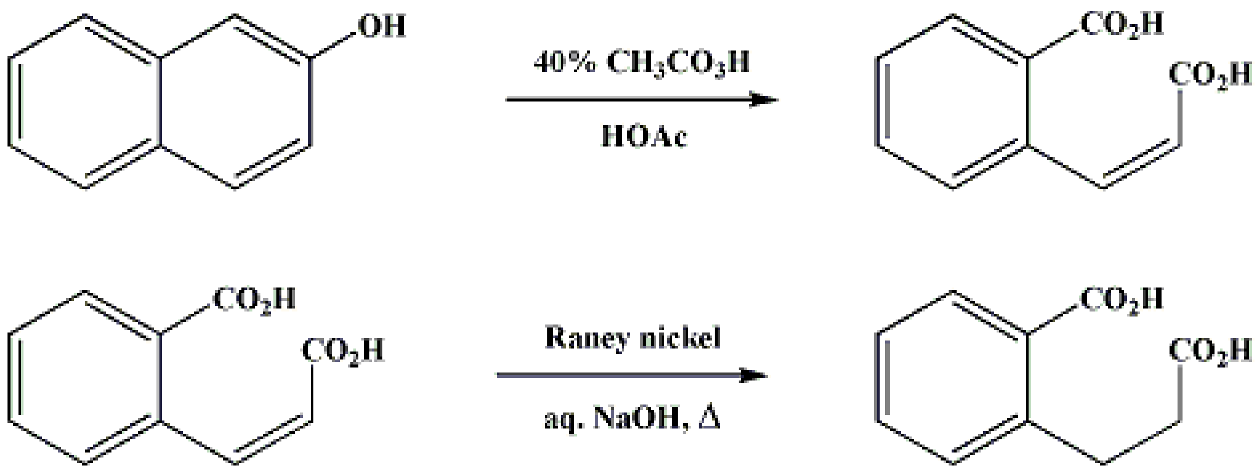
Organic Syntheses, CV 4, 136

β-(*o*-CARBOXYPHENYL)PROPIONIC ACID

[Hydrocinnamic acid, *o*-carboxy-]



Submitted by G. A. Page and D. S. Tarbell[1].
Checked by William S. Johnson, Shirley Rosenberg, and Robert D. Eberhardt.

1. Procedure

A. *o-Carboxycinnamic acid*. Eighty-eight grams (78 ml., 0.46 mole of peracid) of 40% peracetic acid (Note 1) is placed in a 250-ml. Erlenmeyer flask which is immersed in a water bath maintained at 25–30°. A 150-ml. dropping funnel is mounted so that the stem enters the flask to within about 4 cm. of the liquid surface. With mechanical stirring (Note 2), a cold solution of 20 g. (0.14 mole) of β-naphthol (Note 3) in 100 ml. of glacial acetic acid is added dropwise over a period of 4 hours to the peracid. With the appropriate rate of addition, the temperature of the reaction mixture slowly rises to 30–35° and should not exceed 40°. Solid material begins to separate from the orange solution when one-third or more of the naphthol solution is introduced. When the addition is complete, the mixture is stirred for 1 hour and the flask is allowed to stand in the water bath until the exothermic reaction ceases (usually 6–8 hours), then at room temperature for 4 days (Note 4). The solid material is collected by suction filtration and washed on the filter with sufficient (10–20 ml.) acetic acid to remove colored impurities. Drying in the air gives 19.6–20.1 g. of crude *o*-carboxycinnamic acid as a pale yellow crystalline solid (Note 4) and (Note 5).

The crude acid is purified by dissolving in 360–400 ml. of cold 5% sodium bicarbonate solution, filtering, and acidifying the filtrate with sufficient excess of mineral acid to turn Congo red paper blue. The product is separated by suction filtration, washed with water to remove mineral acid, and air-dried. Material thus obtained weighs 17.9–18.7 g. (67–70% yield). It melts generally (Note 6) between 202° and 205°, and is sufficiently pure (Note 7) for most practical purposes.

B. *β-(o-Carboxyphenyl)propionic acid*. In an open 1-l.wide-mouthed round-bottomed flask are placed 18 g. (0.094 mole) of *o*-carboxycinnamic acid and 550 ml. of 10% sodium hydroxide solution. The mixture is warmed to 90° (Note 8) on a steam bath and stirred mechanically. The steam bath is then removed while 54 g. (Note 9) of nickel-aluminum alloy (Raney catalyst) powder is added through the open neck of the flask in small portions (from the end of a spatula) at frequent intervals (Note 10). When addition of the alloy is complete (about 50 minutes), the mixture is stirred and maintained at 90–95° for 1 hour by warming on a steam bath. Distilled water is added as needed to maintain the total volume at approximately 550 ml. The hot mixture is filtered with suction, and the metallic residue is washed with 50 ml. of hot 10% sodium hydroxide solution and two 50-ml. portions of hot water in such a manner that the solid is always covered with liquid (Note 11). The cooled filtrate and washings are added dropwise with mechanical stirring to 300 ml. of concentrated hydrochloric acid (sp. gr. 1.19) in an open 2-l. beaker at such a rate that the temperature does not exceed 80–85° (Note 12). Separation of crystalline material begins almost immediately and is complete when the beaker contents have cooled to room temperature. The β-(*o*-carboxyphenyl)propionic acid is separated by suction filtration, washed with water, and air-dried (Note 13). The yield is 16.8–17.3 g. (92–95%), m.p. 165.5–167° (Note 14).

2. Notes

1. Commercial 40% (w/w) peracetic acid is available from the Becco Sales Corporation, Buffalo 7, New York. The use of a 3.3 molecular proportion of the peracid results in slightly higher and more consistent yields of product than when the theoretical 3.0 proportion is employed. The procedure gives the same yield (percentage) of product when using proportionately smaller quantities of reactants.
2. The operator should be protected by means of a safety shield. A glass (propeller-blade) stirrer passing through the open neck of the Erlenmeyer flask is convenient; rapid stirring is not essential.
3. β-Naphthol of C.P., U.S.P., or N.F. grade has been used with equal success.
4. After 15 hours' standing, 15.0–16.8 g. of crude *o*-carboxycinnamic acid may be recovered by filtration, washing, and drying.
5. The filtrate, either on concentration under reduced pressure or upon dilution with water, fails to yield more *o*-carboxycinnamic acid, but a crystalline by-product, presumably 4-(*o*-carboxyphenyl)-5,6-benzocoumarin,[2] may be encountered in small yield.
6. On melting, *o*-carboxycinnamic acid cyclizes to give the lactone of β-hydroxy-β-(*o*-carboxyphenyl)propionic acid (phthalideacetic acid), m.p. 153°. If the melting point is taken too slowly, or if the diacid is not washed completely free of mineral acid, it may therefore melt considerably below 200°. The reduction step (part *B*), however, proceeds normally with such material.
7. The acid may be recrystallized from aqueous ethanol to give small, white, felted prisms, m.p. 205°.

8. It is advisable to insert a thermometer only at intervals since the alkaline mixture attacks glassware to an appreciable extent on prolonged contact.
9. Using less than 50 g. of the alloy results in the same yield of final product, which, however, contains small amounts of unchanged *o*-carboxycinnamic acid. Equally good results are obtained when proportionately smaller quantities of reactants are used.
10. If excessive foaming is encountered it may be controlled as required by the addition of a few drops of octyl alcohol.
11. The metallic residue may ignite if allowed to dry on the filter. Disposal can be carried out by dissolving the residue in dilute nitric acid. *(Caution! Vigorous reaction.)*
12. With this order of addition, aluminum salts remain in solution, thus simplifying the procedure. External cooling may be applied in order to save time.
13. Extraction of the filtrate with ether gives an additional 0.4–0.5 g. of the crude acid after removal of solvent by distillation. It may be purified by conventional means to give an additional 0.25–0.35 g. of the pure product.
14. β-(*o*-Carboxyphenyl)propionic acid may be recrystallized from hot water (about 20 ml./g.), giving material m.p. 166.5–167.5°.

3. Discussion

o-Carboxycinnamic acid has been prepared by the hydrolysis of *o*-carboxycinnamonitrile,[3] by the opening of the lactone ring in phthalideacetic acid,[4,5] and by the dehydration of metallic salts of β-hydroxy-β-(*o*-carboxyphenyl)propionic acid.[4] It has also been obtained from β-naphthol by reaction with the following oxidizing agents: potassium permanganate in neutral or alkaline solutions;[6] 30% hydrogen peroxide in acetic acid;[7] and peracetic acid in acetic acid.[8] β-Naphthoquinone may be oxidized to give *o*-carboxycinnamic acid, with 30% hydrogen peroxide[9] or perbenzoic acid.[10] Naphthalene also yields this acid on oxidation with peracetic acid[11] The procedure described here is essentially that of Böeseken and Königsfeldt and of Greenspan.[8]

β(*o*-Carboxyphenyl)propionic acid has been prepared by the action of reagents (mostly potassium permanganate as an oxidant) upon di- and tetrahydronaphthalenes and their derivatives.[12] *o*-Carboxycinnamic acid has been reduced by means of sodium amalgam,[13] and cinnam-*o*-hydroxamic acid has been reduced catalytically,[14] to give the propionic acid. The dialdehyde of β-(*o*-carboxyphenyl)propionic acid has been oxidized to the diacid, using potassium permanganate in sodium carbonate solution.[15] The diacid has also been prepared by the action of heat upon *o*-carboxybenzylmalonic acid,[16] and from *o*-cyanohydrocinnamonitrile,[17] β-(*o*-cyanophenyl)propionic acid,[18] and ethyl *o*-cyanobenzylmalonate[19] by procedures involving hydrolysis. Hydrolytic cleavage of bis(1-keto-2-hydrindylidenemethyl)hydroxylamine and of 2-

cyanohydrindone-1[20] gives β-(*o*-carboxyphenyl)propionic acid. It has been obtained also by the nitric acid oxidation of α-tetralone.[21] The present procedure has been published[22] and is adapted from a general method for reducing cinnamic acids.[23]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 348

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Appendix

Compounds Referenced (Chemical Abstracts Registry Number)

peracid

nickel-aluminum alloy (Raney catalyst) powder

lactone of β-hydroxy-β-(o-carboxyphenyl)propionic acid (phthalideacetic acid)

dialdehyde of β-(o-carboxyphenyl)propionic acid

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

nitric acid (7697-37-2)

potassium permanganate (7722-64-7)

sodium carbonate (497-19-8)

naphthol (90-15-3)

β-naphthol (135-19-3)

sodium (13966-32-0)

Naphthalene (91-20-3)

hydrogen peroxide (7722-84-1)

octyl alcohol (111-87-5)

β-naphthoquinone (524-42-5)

α-Tetralone (529-34-0)

peracetic acid (79-21-0)

phthalideacetic acid (4743-58-2)

bis(1-keto-2-hydrindylidenemethyl)hydroxylamine

2-cyanohydrindone-1

Perbenzoic acid (93-59-4)

Hydrocinnamic acid, o-carboxy-, β-(o-Carboxyphenyl)propionic acid, β(o-Carboxyphenyl)propionic acid (776-79-4)

o-Carboxycinnamic acid (612-40-8)

4-(o-carboxyphenyl)-5,6-benzocoumarin

o-carboxycinnamonitrile

β-hydroxy-β-(o-carboxyphenyl)propionic acid

cinnam-o-hydroxamic acid

o-carboxybenzylmalonic acid

o-cyanohydrocinnamonitrile

β-(o-cyanophenyl)propionic acid

ethyl o-cyanobenzylmalonate

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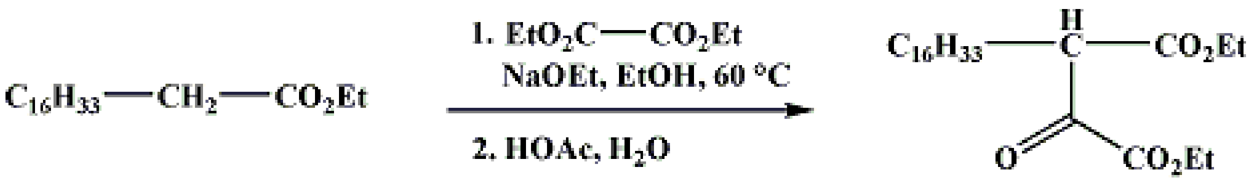
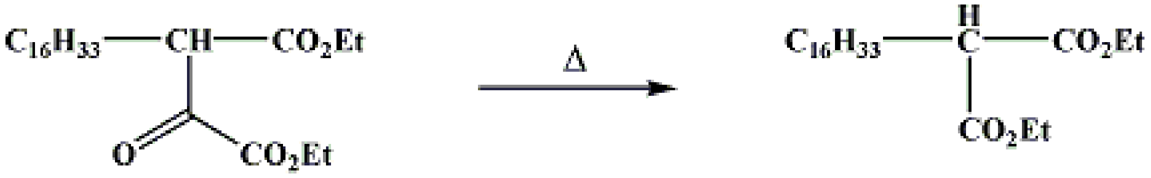
Organic Syntheses, CV 4, 141

CETYLMALONIC ESTER

[Malonic acid, cetyl-, diethyl ester]





Submitted by Don E. Floyd and Sidney E. Miller[1].
Checked by James Cason and George A. Gillies.

1. Procedure

A solution of sodium ethoxide in ethanol is prepared by adding 23 g. (1 g. atom) of freshly cut sodium metal, as -in. cubes, in portions of 3–4 g., to 300 ml. of absolute ethanol, contained in a 1-l. three-necked flask, fitted with a thermometer and an upright, water-cooled condenser, the open end of which is capped with a drying tube filled with a mixture of Drierite and coarse lime (Note 1). The sodium is added through the third neck of the flask, which is otherwise kept stoppered.

When all the sodium has dissolved, the condenser is removed and 584 g. (4 moles) of diethyl oxalate (Note 2) and 312 g. (1 mole) of ethyl stearate (Note 3) are quickly added. The condenser is replaced by a still head connected to a condenser and receiver arranged for distillation at reduced pressure. If a water aspirator is used, a drying tube filled with Drierite should be inserted in the line between the receiver and aspirator. The receiver is cooled in a bath of ice water. The reaction mixture is heated at 50°, and the pressure in the system is reduced to about 100 mm. The temperature is gradually raised to 60°, with the system at a pressure of 100 ± 10 mm., to remove the ethanol used as solvent and formed as by-product. This distillation requires 2–3 hours (Note 4).

The receiver is changed and the excess diethyl oxalate is distilled under reduced pressure in the range of 76–82°/15 mm. (Note 5). The residue in the reaction flask, a viscous, red-brown mass, consists of the sodio derivative of ethyl α-ethoxalylstearate (Note 6). To it is gradually added, without cooling, 66 g. (1.1 mole) of glacial acetic acid. As the mixture is stirred by hand, 1 l. of water is added. Finally, the mixture is stirred mechanically for a few minutes, then allowed to separate into layers. The

organic (upper) layer is taken up in 300 ml. of ether and washed well with sodium bicarbonate solution and with water; then the ether is removed by distillation from a steam bath.

The residual α-ethoxalyl ester is decarbonylated to cetylmalonic ester by heating at 160–170° under reduced pressure. A water aspirator is sufficient to facilitate removal of the carbon monoxide formed during the heating. The decarbonylation requires about 1–1.5 hours (Note 7). The cetylmalonic ester which remains as a dark liquid is fractionated under reduced pressure (Note 8).

A fore-run, consisting of ethyl stearate and an intermediate fraction, amounts to about 60 g., b.p. 185–204°/2 mm. (Note 8). The product is a colorless liquid amounting to 265–275 g. (68.5–71% yield), b.p. 204–208°/2 mm., n_D^{25} 1.4433 (Note 9) and (Note 10).

2. Notes

1. The evolved hydrogen should be led into a hood or out of a window to minimize the explosion hazard.
2. Diethyl oxalate can be dried satisfactorily by distilling a small portion from the bulk of the material. The water is removed with the distillate.
3. The ethyl stearate used by the checkers was prepared by esterifying commercial stearic acid (Armour Neo-Fat 1–65 or General Mills Aliphat 7) with 8 equivalents of absolute ethanol containing 10% by weight of concentrated sulfuric acid. The washed and dried product was distilled directly through a 60-cm. Vigreux column with a heated jacket and partial reflux head to give an 80% yield of material, b.p. 186.5–189°/3.5 mm., m.p. 32.2–34.2° (cor.). The purest grade of ethyl stearate as supplied by the Eastman Kodak Company is also satisfactory.
4. A column is not needed during distillation of the ethanol. When low-molecular-weight esters are substituted for ethyl stearate a suitable indented column should be used at this point to prevent loss of the ester. The reaction temperature should not be allowed to exceed 60°, because decomposition of the condensation product may result.
5. The contents of the flask should not be heated to a temperature higher than 90° during removal of the excess oxalate or some decomposition of the product may result. The recovered diethyl oxalate contains small amounts of ethanol and ethyl carbonate. It can readily be purified by fractional distillation; however, it is quite suitable for reuse in repeat preparations without purification.
6. This sodio derivative can be dissolved in a solvent such as toluene and employed as an intermediate for other reactions (alkylation, acylation, etc.).
7. The carbon monoxide evolved should be led into a hood to avoid the dangers of poisoning and explosion. No difficulties have been encountered at this stage, but precautions are advisable.
8. A 60-cm. column of the Vigreux type, with heated jacket and partial reflux

head, was found satisfactory by the checkers. Ethyl stearate may solidify in the condenser if a total reflux head is used. Refractionation of the fore-run gives an additional 30–40 g. (10–13%) of pure product. Material containing a few per cent of ethyl stearate can be obtained in 85–90% yield by simply distilling the total crude product from a Claisen flask.

9. Cetylmalonic acid, m.p. 115.5–120.5°, is obtained by saponification of the ester and one crystallization from acetone.

10. This general procedure is applicable to lower fatty acid esters.

3. Discussion

This method is based on the general procedure previously described by Floyd and Miller.[2] Cetylmalonic ester has also been prepared by condensation of ethyl stearate with ethyl carbonate[3] and by alkylation of sodiomalonic ester with cetyl iodide[4] or cetyl bromide.[5]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodiomalonic ester

Cetylmalonic ester

sodio derivative of ethyl α-ethoxalylstearate

ethanol (64-17-5)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

ether (60-29-7)

hydrogen (1333-74-0)

carbon monoxide (630-08-0)

sodium bicarbonate (144-55-8)

acetone (67-64-1)

toluene (108-88-3)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

ethyl carbonate

cetyl iodide (544-77-4)

stearic acid (57-11-4)

Malonic acid, cetyl-, diethyl ester (41433-81-2)

diethyl oxalate (95-92-1)

ethyl stearate (111-61-5)

Cetylmalonic acid (4371-64-6)

cetyl bromide (112-82-3)

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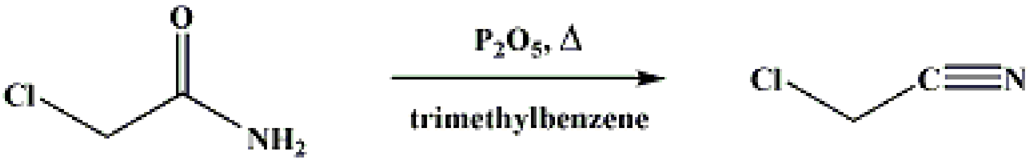
Organic Syntheses, CV 4, 144

CHLOROACETONITRILE

[Acetonitrile, chloro-]



Submitted by D. B. Reisner and E. C. Horning[1].
Checked by R. L. Shriner and Calvin N. Wolf.

1. Procedure

In a 3-l. round-bottomed three-necked flask fitted with an efficient mechanical stirrer, a reflux condenser, and a thermometer are placed 170 g. (1.2 moles) of phosphorus pentoxide, 187 g. (2 moles) of chloroacetamide[2] (Note 1), and 800 ml. of dry technical trimethylbenzene (Note 2). The mixture is refluxed gently with vigorous stirring for 1 hour. The reaction mixture is then allowed to cool to about 100° with continuous stirring, and the reflux condenser is replaced with a distilling adapter fitted with a thermometer and a water-cooled condenser.

The crude product and part of the solvent are distilled at atmospheric pressure (Note 3). The yield of crude product boiling at 124–128° is 121–131 g. (80–87%) (n_D^{25} 1.441–1.444). In order to obtain a pure product, the crude chloroacetonitrile is mixed with 10 g. of phosphorus pentoxide and redistilled through an efficient packed fractionating column (Note 4). The yield of pure chloroacetonitrile distilling at 123–124° is 93–106 g. (62–70%) (Note 5).

2. Notes

1. The practical grade of chloroacetamide obtainable from the Eastman Kodak Company can be used.
2. Technical trimethylbenzene with a boiling range of 166–174° is satisfactory.
3. About 200 ml. of solvent can be recovered. The remainder is left in the flask to facilitate removal of the residue.
4. A Fenske column packed with glass helices previously described in *Organic Syntheses*[3] is satisfactory. The product has n_D^{20} 1.426, d_4^{20} 1.1896, in good agreement with reported values.[4] When a Vigreux column was used the distillate had d_4^{20} 1.072 and n_D^{25} 1.430–1.436, indicating incomplete separation from the trimethylbenzenes (1,3,5-trimethylbenzene has d_4^{20} 0.86; n_D^{25} 1.494).
5. The product can also be distilled under reduced pressure; b.p. 60–61°/100 mm.; 30–32°/15 mm.

3. Discussion

Practical syntheses of chloroacetonitrile depend upon dehydration of chloroacetamide with phosphorus pentoxide. The present method uses a liquid reaction medium; in previous procedures the dry reagents were heated in the absence of solvent or liquid medium.[5,6]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

CHLOROACETAMIDE (79-07-2)

1,3,5-trimethylbenzene (108-67-8)

trimethylbenzene (526-73-8)

Chloroacetonitrile, Acetonitrile, chloro- (107-14-2)

phosphorus pentoxide (1314-56-3)

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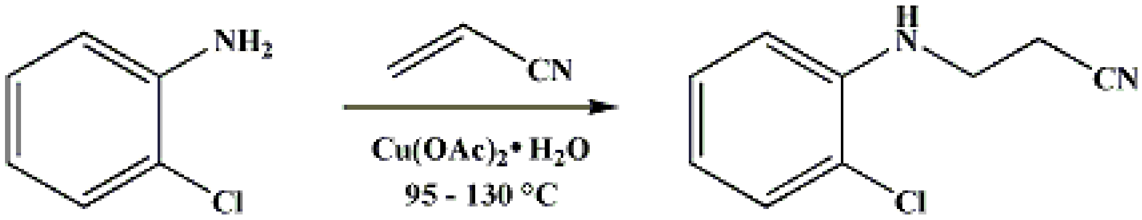
Organic Syntheses, CV 4, 146

3-(*o*-CHLOROANILINO)PROPIONITRILE

[Propionitrile, 3-*o*-chloroanilino-]



Submitted by S. A. Heininger[1]
Checked by John C. Sheehan and Alma M. Boston.

1. Procedure

A 500-ml. three-necked flask equipped with a stirrer, reflux condenser, and thermometer is charged with 255 g. (2.0 moles) of *o*-chloroaniline, 106 g. (2.0 moles) of acrylonitrile, and 10.2 g. (4.0% by weight of the amine) of cupric acetate monohydrate (Note 1). The mixture is then stirred and heated to reflux, beginning at about 95°. Refluxing is continued for 3 hours (Note 2), with the pot temperature rising to about 130° (Note 3).

The dark mixture is then transferred to a 500-ml. distilling flask fitted with a 15.2-cm. modified Vigreux column and the unchanged acrylonitrile (17–20 g.) collected at 100 mm. (water pump). The distillation is continued (vacuum pump) and the unchanged *o*-chloroaniline (110–120 g.), b.p. 57–60°/0.5 mm., is recovered. The 3-(*o*-chloroanilino) propionitrile (182–192 g.) is obtained as a colorless, somewhat viscous liquid, b.p. 139–141°/0.3 mm., n_D^{25} 1.5728–1.5735 (Note 4).

A pot residue of 30–35 g. remains (Note 5). The conversion of *o*-chloroaniline to 3-(*o*-chloroanilino) propionitrile is 50.5–53%, with a yield of 90–95% based on *o*-chloroaniline, and 53–65% based on acrylonitrile (Note 6).

2. Notes

1. The commercially available monohydrate form of cupric acetate was used. Anhydrous cupric acetate gives the same results. From 2% to 5% of catalyst by weight of the amine employed gives good yields of cyanoethylated products from a variety of anilines.
2. Slightly improved yields may be obtained by use of longer reaction times.
3. Maintaining the temperature at 100–110° for the same period of time gives equivalent results.
4. Physical constants for pure 3-(*o*-chloroanilino) propionitrile are: b.p. 139–

141°/0.3 mm., n_D^{25} 1.5734, d_{25}^{25} 1.2103.

5. The residue consists mainly of polyacrylonitrile and copper or copper salts. It is slowly soluble in acetone, more readily soluble in polyacrylonitrile solvents such as dimethylformamide or dimethyl sulfoxide, especially when warmed.

6. An attempt to prepare 3-(*o*-chloroanilino) propionitrile by the Cymerman-Craig procedure (*o*-chloroaniline hydrochloride, diethylamine, and acrylonitrile) (p. 205) gave no isolable product, with recovery of 75% of the *o*-chloroaniline as its acetyl derivative, m.p. 86–87°; reported m.p. 87–88°.[2] Thus representative *ortho*-substituted anilines can be cyanoethylated in much better yields by use of the cupric acetate catalyst than by the Cymerman-Craig route, which is known to be subject to steric interferences.[3] Comparative yields for cyanoethylation of *o*-toluidine substantiate this conclusion; cupric acetate gave 62%, whereas Cymerman-Craig reported 25%.[3] Bulky N-substituents appear to affect yields similarly: methyl-, ethyl-, *n*-propyl-, and isopropylanilines gave yields of 65%, 41%, 17.5%, and 0.5% by the exchange reaction,[3] whereas, with cupric acetate, *n*-butylaniline was cyanoethylated in 68% yield.

3. Discussion

Cupric acetate is an efficient catalyst for the cyanoethylation of all but nitro-substituted aromatic amines. It is particularly effective with anilines which give poor yields by known methods, i.e., those with substituents on the nitrogen atom or in the *ortho* position.[4]

Other known catalysts for cyanoethylation of aromatic amines include acetic acid,[5,6] acetic acid-cuprous chloride mixtures,[7,8] aniline salts,[9] and choline.[10] 3-Anilinopropionitriles may also be prepared by an exchange reaction between the aniline hydrochloride and diethylaminopropionitrile (p. 205).[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 205

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

acetic acid (64-19-7)

aniline hydrochloride (142-04-1)

copper (7440-50-8)

acetone (67-64-1)

cupric acetate (142-71-2)

diethylamine (109-89-7)

acrylonitrile (107-13-1)

dimethylformamide (68-12-2)

cupric acetate monohydrate (6046-93-1)

dimethyl sulfoxide (67-68-5)

acetic acid-cuprous chloride

choline (62-49-7)

diethylaminopropionitrile (5351-04-2)

o-toluidine (95-53-4)

o-chloroaniline (95-51-2)

3-(o-Chloroanilino)propionitrile, Propionitrile, 3-o-chloroanilino-, 3-(o-chloroanilino) propionitrile (94-89-3)

o-chloroaniline hydrochloride (137-04-2)

n-butylaniline (1126-78-9)

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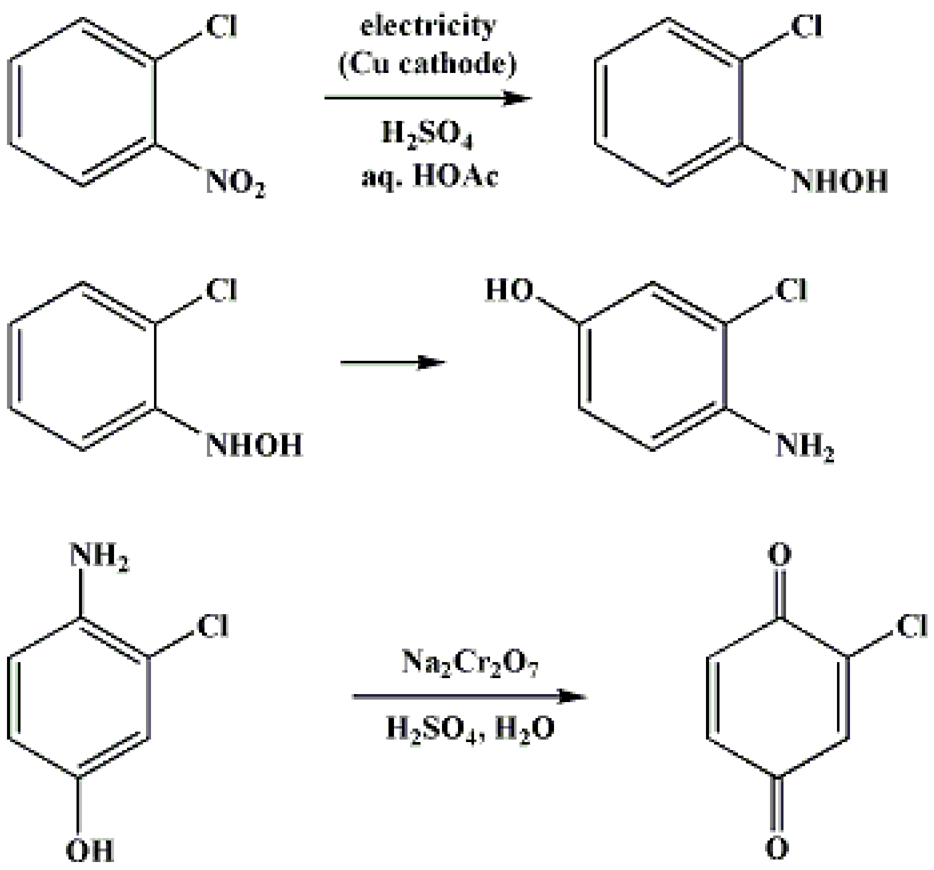
Organic Syntheses, CV 4, 148

CHLORO-*p*-BENZOQUINONE

[*p*-Benzoquinone, chloro-]



Submitted by R. E. Harman[1]
Checked by N. J. Leonard and R. W. Fulmer.

1. Procedure

A. *Apparatus*. The reduction is carried out in a 400-ml. beaker. The anode, a cylinder of sheet lead 3 in. in height and 2.25 in. in diameter, rests on the bottom of the beaker. Clamped inside the anode and extending almost to the bottom of the beaker is the catholyte chamber, a porous cup (Note 1) 5 in. deep and 1.75 in. in diameter. Clamped securely inside the cup and about 0.25 in. above its inside bottom surface is the cathode, a cylinder of 25-gauge sheet copper 6 in. long and 1.25 in. in diameter. It is provided with a row of seven vertical slots 0.25 in. wide and 1.25 in. long, evenly spaced around its circumference; the lower ends of the slots are about 2.5 in. from the bottom of the cathode (Note 2). Both electrodes are provided with binding posts for connection to the circuit. A stirrer is constructed with two double propeller blades attached to the shaft, one about 1.5 in. above the other, at a pitch that will direct the flow of liquid downward. The mechanically driven stirrer is set to run deep inside the cathode (Note 3).

The current may be drawn from a commercially available battery charger (Note 4) or from a storage battery, each capable of operating at about 6 volts. Experiment has shown that the considerable ripple in the output of the charger has no adverse effect on the reduction. A transformer in the input to the charger, or a variable resistance in the battery circuit, and a 0–3 ampere range d.c. ammeter complete the apparatus.

B. *Reduction of o-chloronitrobenzene*. The stirrer is set in position carefully inside the cathode, which is clamped in place at the top. The porous cup, previously impregnated with the electrolyte, is charged with 11.5 g. (0.073 mole) of *o*-chloronitrobenzene (Note 5) and about 80 ml. of a mixture of acetic acid (70 ml.), concentrated sulfuric acid (22 ml.), and water (8 ml.) (Note 6). The cup is then clamped securely in position, and the beaker containing the anode is supported just clear of the bottom of the porous cup and filled with the same solution of aqueous sulfuric and acetic acids to the same level as the liquid inside the cup. The stirrer is started, the current turned on, and the system observed for a few minutes until the current has become stable. It is then adjusted at some convenient value no greater than 2 amperes.

The temperature will rise slowly and should be maintained at 30–45° throughout the reduction, with cooling as necessary. The system requires no attention while in operation except for occasional inspection and possibly the addition of a few milliliters of 90% acetic acid to maintain the surface of the catholyte at the desired level (Note 7).

C. *Oxidation of 4-amino-3-chlorophenol*. When the reduction is complete (Note 8), the system is disassembled, the catholyte poured into a flask, and the apparatus rinsed with hot water into the same flask. The combined catholyte and washings are extracted with ether in a continuous-type liquid-liquid extractor to remove the acetic acid almost completely (Note 9). The residual aqueous acid solution of the aminophenol (Note 10) is made up to 4*N* in sulfuric acid by adding 20 ml. of concentrated sulfuric acid and diluting with water to 400 ml.

At room temperature there is added in one portion a solution of 11 g. (0.037 mole, 50% excess over the theoretical amount) of sodium dichromate dihydrate in 20 ml. of water. A rise in temperature of some 6–7° will be observed; it is desirable to moderate the temperature by external cooling if it should rise above 35°.

After the mixture has been allowed to stand at room temperature for at least an hour (Note 11), a few grams of clean sand is added and the dark red mixture is filtered with suction. The filtrate is extracted with ether (100 ml., then 4–5 portions of about 30 ml. each), and each extract is used in turn to extract the filter cake.

The ether extracts are combined; the ether is removed by distillation (Note 12), and the dark red tarry residue subjected to steam distillation. Some 40–50 ml. of distillate is collected after solid quinone no longer appears in the condenser (total volume about 150 ml.).

There is obtained by filtration 5.0–5.5 g. (48–53%) of yellow chloro-*p*-quinone of m.p. 53–55°; ether extraction of the filtrate yields a further 1.0 g., which brings the total

yield to 58–63% (Note 12) and (Note 13). Crystallization from a small volume of aqueous ethanol (85–90%) raises the melting point to 55–56°.

2. Notes

1. A Norton dense grade Alundum extraction thimble has been found suitable. Deposition of silicic acid in the interstices of the cup to decrease transfer of material is desirable. This is accomplished by soaking the cup for an hour in 20% water glass, draining off the excess, and then keeping the cup totally immersed for 3 hours in 20% aqueous sulfuric acid.[2] Finally, the cup is stored completely immersed in the electrolyte.

2. This cathode design, with the stirring described, is regarded as preferable to the combination used by Lukens[3] and much simpler in construction. It provides better dispersion of the organic material, a feature which is particularly necessary if these reductions are carried out in aqueous solution (Note 6).

3. Very rapid and efficient stirring is required to strip the intermediate *o*-chlorophenylhydroxylamine from the cathode so that the acid-catalyzed rearrangement to 4-amino-3-chlorophenol may occur rather than reduction of the substituted hydroxylamine to *o*-chloroaniline.

4. A Battery Booster, type 6-AC-4, manufactured by **P. R.** Mallory and Company, Inc., Indianapolis, Indiana, gave good service.

5. Material equivalent to Eastman Kodak Company white label grade was used. It has been found that the same results are obtained using *m*-chloronitrobenzene. Likewise, either *o*- or *m*-nitrotoluene may be used in the preparation of toluquinone (Note 13).

6. The submitter states that lower yields of quinones (50–65%) are obtained by using as the electrolyte 75% by weight aqueous sulfuric acid. The catholyte at the end of the reduction is diluted to about 500 ml. (4*N* in sulfuric acid) and oxidized directly. The low solubility of the nitro compounds in the aqueous acid makes exceedingly efficient stirring a necessity, and the cell must be maintained at 50–60° during the reduction to keep the nitro compound molten and so promote the formation of a fine emulsion. Solid aminophenol sulfate sometimes crystallizes near the end of the reduction, and evolution of hydrogen near the end of the run may force the pasty material out the top of the porous cup. In general, these difficulties are more troublesome than the continuous extraction necessitated by the use of acetic acid in the catholyte.

7. In operation, a flood of electrolyte should be observable pouring over the lower ends of the slots in the cathode.

8. Complete reduction of the nitro compound is assured by the use of about 1.2 equivalents of current (9.4 ampere-hours), but a larger excess of current is no disadvantage.

9. It has been found satisfactory to continue the extraction for 30 minutes after the volume of the aqueous phase no longer decreases visibly. Saturated aqueous sodium bicarbonate washes may be used to effect removal of the acetic acid from ether solutions of alkyl quinones. The cascade distribution apparatus

devised by Kies and Davis[4] is useful for this purpose. As halogenated quinones have been found to be unstable to bicarbonate, the acetic acid must be removed before oxidation of the corresponding aminophenols.

10. It has been found that the sulfates of the aminophenols may be obtained in yields about the same as those recorded for the quinones by concentrating the aqueous catholytes under reduced pressure after removal of the acetic acid.

11. It is recommended that the oxidation mixture be stored in a refrigerator if more than 6–8 hours must elapse before the work-up is completed.

12. Prolonged heating after removal of the ether may lead to sublimation of the product, with resulting lower yield.

13. Essentially the same procedure, with alteration only in the temperature during the oxidation, is stated by the submitter to be satisfactory for the preparation of several other *p*-benzoquinones. For *p*-benzoquinone itself and for toluquinone (both in 80% yield) the oxidation is best carried out at 5–10°; for 3-chlorotoluquinone (70% yield), at 15–20°; for 2,5-dichloroquinone (50% yield), at 55–60°. In the last case, some of the weakly basic aminophenol is ether extracted along with the acetic acid; it may be recovered by distilling most of the ether and acetic acid under reduced pressure, extracting the dark residue with two 25-ml. portions of 1*N* sodium hydroxide, and making the alkaline extract neutral or slightly acid with sulfuric acid. Normal oxidation is carried out after combining this suspension of aminophenol with the original aqueous solution. The low vapor pressure of 2,5-dichloroquinone precludes the use of steam distillation; however, the quinone precipitates directly from the oxidation mixture as a tan solid and may be purified readily by sublimation, followed by crystallization from ethanol. An excellent sublimation apparatus that will easily handle 10-g. quantities of this quinone has been described.[5]
This method has given only 25% yield of methoxyquinone which is highly sensitive to acid and requires a special isolation procedure.[6]

3. Discussion

The present method is the result of a study by Cason, Harman, Goodwin, and Allen.[6,7] The sequence of electrolytic reduction followed by oxidation has been used for the preparation of 5-bromotoluquinone,[8] 5-chlorotoluquinone,[9] and 3-chlorotoluquinone.[10] The preparation of an intermediate *p*-aminophenol from the corresponding aromatic nitro compound by electrolytic reduction is a useful general method.[11,12,13,14,15,16,17,18] Chloro-*p*-quinone has been prepared by acid dichromate oxidation of chlorohydroquinone[19,20,21,22] or 2-chloro-4-aminophenol.[23,24] It has been shown that pure chloro-*p*-quinone is obtained only with some difficulty when chlorohydroquinone is used.[7] Potassium bromate also has been used to oxidize chlorohydroquinine to chloro-*p*-quinone.[25]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

o- or m-nitrotoluene

ethanol (64-17-5)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

potassium bromate (7758-01-2)

m-Chloronitrobenzene (121-73-3)

o-chloronitrobenzene (88-73-3)

p-benzoquinone (106-51-4)

sodium dichromate dihydrate (10588-01-9)

4-amino-3-chlorophenol

silicic acid (7699-41-4)

toluquinone

aminophenol sulfate

3-chlorotoluquinone

2,5-dichloroquinone

methoxyquinone

5-bromotoluquinone

5-chlorotoluquinone

chlorohydroquinone (615-67-8)

2-chloro-4-aminophenol (3964-52-1)

chlorohydroquinine

p-aminophenol (123-30-8)

o-chloroaniline (95-51-2)

Chloro-p-benzoquinone, p-Benzoquinone, chloro- (695-99-8)

o-chlorophenylhydroxylamine

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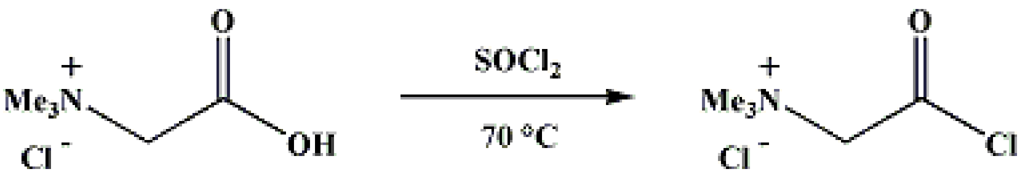
Organic Syntheses, CV 4, 154

N-CHLOROBETAINYL CHLORIDE

[Ammonium chloride, [(chloroformyl)methyl]trimethyl-]



Submitted by B. Vassel and W. G. Skelly[1].
Checked by John C. Sheehan and J. Iannicelli.

1. Procedure

Caution! This preparation should be conducted in a good hood.

A 1-l. round-bottomed flask is equipped with an internal thermometer, a sealed stirrer, and a reflux condenser, the upper end of which is protected with a calcium chloride drying tube. In this flask are placed 307 g. (2 moles) of dry, pulverized betaine hydrochloride (Note 1) and 285 g. (174 ml., 2.4 moles) of thionyl chloride. The mixture is stirred and heated slowly. When the internal temperature reaches 68° copious evolution of sulfur dioxide and hydrogen chloride occurs, and the mass becomes pasty. The temperature is maintained with stirring at 68–70° for 1.5 hours (Note 2).

Warm (80°) dry toluene (150 ml.) is added to the melt, and stirring is continued for 5 minutes. The entire mass is quickly poured into a dry beaker (Note 3) and slowly stirred, manually, until the entire mass has crystallized (Note 4). The cool toluene is decanted rapidly, and 150 ml. of warm toluene is added. The mixture is heated sufficiently to melt the crystals (about 68°), then allowed to cool again with stirring. The toluene is decanted once more, and 150 ml. of hot (60°) dry benzene is added. The mass is melted once more and cooled with stirring. The crystalline mass, with the benzene layer still covering it, is transferred rapidly to a Büchner funnel sufficiently large to hold all the contents of the beaker. The funnel is immediately covered with a rubber diaphragm, and suction is applied (Note 5). The crystals are quickly covered with 150 ml. of dry methylene chloride, dried with suction, and quickly transferred into a glass vacuum oven at 50° (Note 6). The yield of N-chlorobetainyl chloride is 337–344 g. (98–100%) of 98–100% purity if moisture was rigorously excluded (Note 7).

2. Notes

1. The betaine hydrochloride was obtained from International Minerals and

Chemical Corporation. It was pulverized, dried at 105° for 3 hours, ground again, and dried once more at 105° for 3 hours.

2. The mixture should be fluid after about the first 20 minutes of heating. If at this stage the betaine hydrochloride has not completely lost its granular appearance it is probable that it had not been adequately dried or that the reaction temperature had been below 68°. If it is considered that the betaine hydrochloride had not been dry enough the reaction may be completed by adding an additional 41 g. (25 ml., 0.34 mole) of thionyl chloride and continuing the stirring and heating for 1.25 hours.

3. Success in the isolation of the pure acid chloride depends upon the rigorous exclusion of moisture. The acid chloride hydrolyzes to the hydrochloride with great rapidity when exposed to even traces of moist air. During the stirring of the warm melt, care must be exercised that a layer of toluene covers the melt at all times.

4. If the melt is permitted to crystallize without stirring, a hard glasslike layer forms which cannot be broken up without exposure to air.

5. The rubber diaphragm is sold by Fisher Scientific Company as dental dam. It is held in place by two strong rubber bands. The suction flask is protected from moisture by attachment of a calcium chloride drying tube to the vacuum line if a water aspirator is used.

6. The dried acid chloride is conveniently stored in about 25 bottles with tightly fitting plastic screw caps which are kept in a desiccator over phosphorus pentoxide. In this manner the acid chloride is exposed to a minimum of atmospheric moisture when reactions are run which require only part of the preparation.

7. The same yield and purity were obtained when 1229 g. (8 moles) of betaine hydrochloride was used. In this case the volumes of toluene, benzene, and methylene chloride do not have to be increased proportionally if narrow, tall beakers are used. About 300 ml. of each is sufficient.

3. Discussion

N-Chlorobetainyl chloride has been prepared by treating betaine hydrochloride with either thionyl chloride,[2] phosphorus pentachloride in acetyl chloride,[3,4] or phosphorus pentachloride in phosphorus oxychloride.[5] None of the patents mentions the instability of the acid chloride towards moisture or describes a method for the isolation of the pure product.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

N-Chlorobetainyl chloride

hydrogen chloride (7647-01-0)

Benzene (71-43-2)

phosphorus pentachloride (10026-13-8)

acetyl chloride (75-36-5)

thionyl chloride (7719-09-7)

sulfur dioxide (7446-09-5)

Phosphorus Oxychloride (21295-50-1)

toluene (108-88-3)

methylene chloride (75-09-2)

Ammonium chloride, [(chloroformyl)methyl]trimethyl- (53684-57-4)

betaine hydrochloride

phosphorus pentoxide (1314-56-3)

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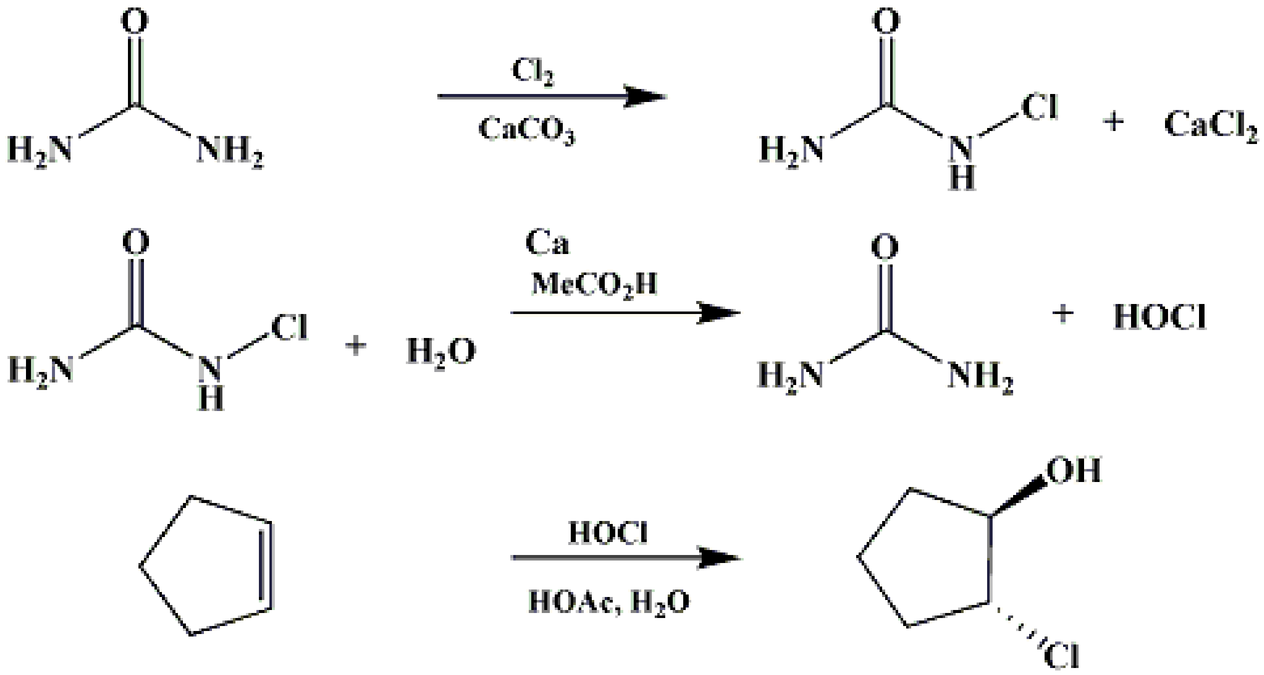
trans-2-CHLOROCYCLOPENTANOL

[Cyclopentanol, 2-chloro-, trans-]



Submitted by Hugh B. Donahoe and Calvin A. Vanderwerf[1].
Checked by Arthur C. Cope and Elbert C. Herrick.

1. Procedure

A mixture of 150 g. (2.5 moles) of urea, 125 g. (1.25 moles) of reprecipitated calcium carbonate, and 150 ml. of water in a 2-l. three-necked flask is tared and cooled in an ice-salt bath. The flask is equipped with a thermometer which extends into the reaction mixture, a gas inlet tube, an outlet tube leading to a gas-absorption trap,[2] and a slip- or mercury-sealed mechanical stirrer which will disperse chlorine gas below the surface of the liquid (Note 1).

A rapid stream of chlorine gas is bubbled into the mixture at 0–15° with vigorous stirring until an increase in weight of about 95 g. has occurred (30–40 minutes) (Note 2). A 250-ml. portion of water at room temperature is added to the suspension, which is then filtered by suction through rather porous filter paper on a 16-cm. Büchner funnel. The filtrate is removed and cooled in an ice bath, and the filter cake is washed on the funnel with a 250-ml. portion of water at room temperature. The filtrate is poured back in the funnel and sucked through the filter cake repeatedly until no more solid appears to dissolve, and then is combined with the original filtrate (Note 3).

The cold filtrates (solutions of monochlorourea) are transferred to a 3-l. two-necked flask immersed in an ice-salt bath. The flask is equipped with a slip- or mercury-sealed mechanical stirrer and an efficient reflux condenser. To the flask are added 500 g. of ice,

100 ml. of glacial acetic acid, and 136 g. (2.0 moles) of cyclopentene (or 1.43 times the weight increase in grams during introduction of the chlorine) (Note 4). Mechanical stirring is begun and is continued while the flask is kept packed in ice until the cyclopentene (the top layer) disappears and a heavy oil settles to the bottom (Note 5).

The solution is saturated with sodium chloride and distilled with steam until all the 2-chlorocyclopentanol is collected, which requires distillation of a volume of about 2 l. The distillate is saturated with sodium chloride, the oily layer separated, and the aqueous layer extracted four times with 300-ml. portions of ether. The ether extracts are added to the oil, and the solution is washed with a saturated sodium chloride solution and dried over anhydrous sodium sulfate. The ether is removed by distillation, and the product is distilled under reduced pressure through a total condensation, variable take-off, 15 by 1.5 cm. column packed with glass helices. A trap cooled with Dry Ice is placed in the vacuum line between the column and the pump. Low-boiling fractions, b.p. 43–81°/15 mm., amount to 19–40 g. (Note 6). The *trans*-2-chlorocyclopentanol is collected at 81–82°/15 mm. in a yield of 126–135 g. (52–56%); n_D^{25} 1.4770 (Note 7).

2. Notes

1. Rapid absorption of chlorine depends on efficient stirring and dispersal of the gas through the liquid phase. A stirrer which disperses the gas through the solution by vigorous agitation may be used (p.891) or the gas may be introduced through the stirrer.[3]
2. The actual weight of chlorine absorbed is equal to the sum of the weight increase noted plus the weight of carbon dioxide formed minus the relatively small weight of carbon dioxide that remains dissolved in the reaction mixture.
3. The combined filtrates may be titrated with 1*N* sodium thiosulfate solution to determine the yield of monochlorourea.[4] This preparation of monochlorourea is a modification of procedures previously described.[4,5]
4. Best yields result when an excess of cyclopentene is used, as specified. The weight increase should be roughly 95 g., and the amount of cyclopentene should be varied proportionately by using 1.43 times the weight increase in grams.
5. The stirring time is about 12–15 hours. It is advantageous to allow the ice to melt and the reaction mixture to come to room temperature during the last 2–3 hours.
6. The fractions boiling at 43–48°/15 mm. and 48–81°/15 mm. contain a mixture of 1,2-dichlorocyclopentane and *cis*- and *trans*-2-chlorocyclopentanol.[6,7]
7. The yield is based on the weight of cyclopentene, although this reagent is used in slight excess.

3. Discussion

2-Chlorocyclopentanol has been prepared by the reaction of dry hydrogen chloride[8] or thionyl chloride[9] with 1,2-cyclopentanediol, and by the addition of hypochlorous acid to

cyclopentene.[6,7,8,10]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrogen chloride (7647-01-0)

acetic acid (64-19-7)

ether (60-29-7)

thionyl chloride (7719-09-7)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

sodium thiosulfate (7772-98-7)

carbon dioxide (124-38-9)

calcium carbonate (471-34-1)

chlorine (7782-50-5)

urea (57-13-6)

hypochlorous acid (7790-92-3)

Cyclopentene (142-29-0)

monochlorourea

Cyclopentanol, 2-chloro-, trans-, trans-2-Chlorocyclopentanol (20377-80-4)

2-chlorocyclopentanol, cis- and trans-2-chlorocyclopentanol

1,2-dichlorocyclopentane (31025-65-7)

1,2-cyclopentanediol

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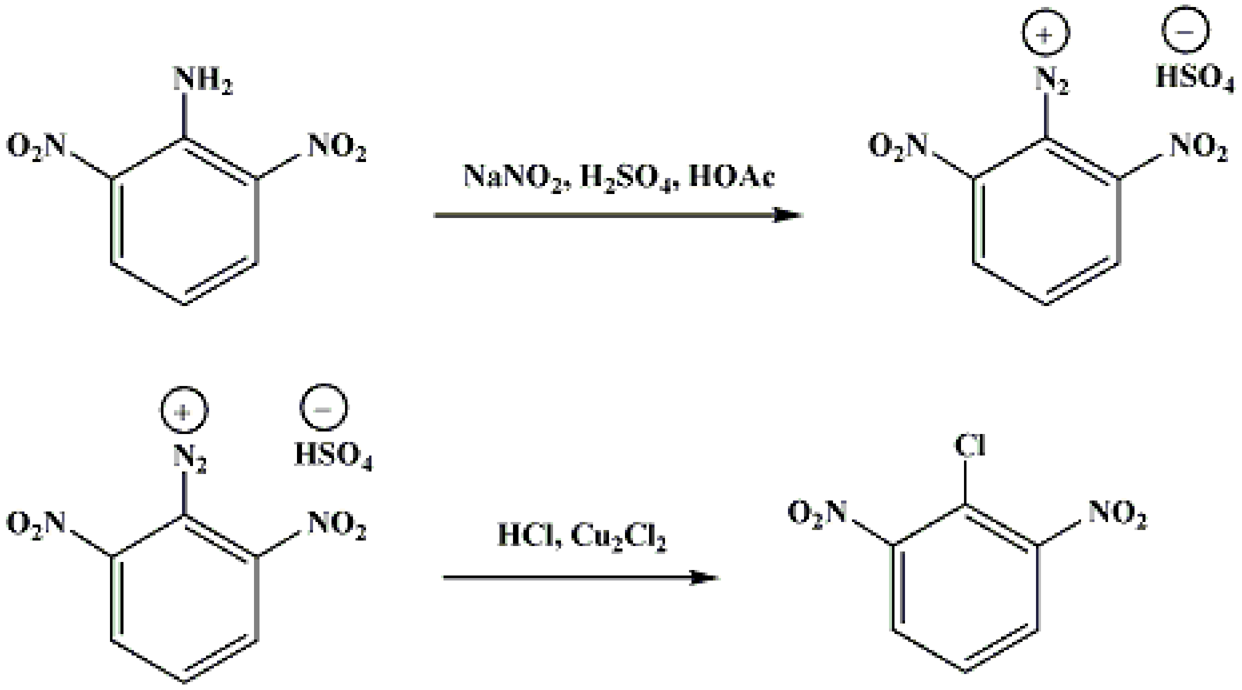
1-CHLORO-2,6-DINITROBENZENE

[Benzene, 2-chloro-1,3-dinitro-]



Submitted by F. D. Gunstone and S. Horwood Tucker[1].
Checked by Arthur C. Cope, David J. Marshall, and Ronald M. Pike.

1. Procedure

Concentrated sulfuric acid (160 ml.) is placed in a 1-l. three-necked flask fitted with a glass stirrer and a thermometer, and 15.2 g. (0.22 mole) of solid sodium nitrite is added over a period of 10–15 minutes with stirring. After the addition is completed, the temperature is raised to 70° and the mixture is stirred until all the sodium nitrite dissolves. The solution is cooled to 25–30° with an ice bath, and a solution of 36.6 g. (0.2 mole) of 2,6-di-nitroaniline (p.364) in 400 ml. of hot glacial acetic acid is added slowly, with stirring, at such a rate that the temperature remains below 40° (Note 1). After the addition is completed, the solution is stirred at 40° for 0.5 hour. A solution of 44 g. (0.44 mole) of cuprous chloride in 400 ml. of concentrated hydrochloric acid is prepared in a 2-l. beaker and cooled in an ice bath, and the solution of the diazonium salt is added in portions over a period of about 5 minutes, with manual stirring, at a rate which keeps the effervescence from becoming too vigorous. The mixture becomes hot during the addition, and it is stirred intermittently while being cooled in an ice bath until the effervescence slackens. It is then heated on a steam bath with occasional stirring until the temperature reaches 80°. After about 20 minutes at that temperature the effervescence ceases, and then an equal volume of water is added and the mixture is cooled in an ice bath. After several hours the yellow, crystalline 1-chloro-2,6-dinitrobenzene is collected on a suction filter, washed with water, and dried (Note 2).

The product, which is sufficiently pure for most purposes without recrystallization, is obtained in a yield of 28.7–30 g. (71–74%); m.p. 86–88°. The product can be recrystallized from 90% (by volume) acetic acid (2 ml. per g.) or by dissolving it in hot benzene (1.5 ml. per g.) and adding petroleum ether (3 ml. per g.); m.p. 86–87°.

2. Notes

1. The temperature of diazotization is critical. Lower yields are obtained if the temperature rises above 40°.
2. 1-Chloro-2,6-dinitrobenzene is a skin irritant, and contact with it should be avoided.

3. Discussion

1-Chloro-2,6-dinitrobenzene has been prepard from 2,6-dinitroaniline by the Sandmeyer reaction,[2,3,4] from 2,6-dinitrophenol and phosphorus oxychloride in the presence of N,N-diethylaniline,[5] and from the mixture of isomers (in which 1-chloro-2,4-dinitrobenzene is present in largest amount) obtained by nitrating *o*-nitrochlorobenzene.[3,6] The mixture of 2,4- and 2,6-dinitro-chlorobenzene has been separated by the use of solution of sodium hydroxide in ethanol and water.[7]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

2,4- and 2,6-dinitro-chlorobenzene

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

sodium hydroxide (1310-73-2)

sodium nitrite (7632-00-0)

Phosphorus Oxychloride (21295-50-1)

cuprous chloride (7758-89-6)

o-nitrochlorobenzene (88-73-3)

1-chloro-2,4-dinitrobenzene (97-00-7)

N,N-diethylaniline (91-66-7)

1-Chloro-2,6-dinitrobenzene, Benzene, 2-chloro-1,3-dinitro- (606-21-3)

2,6-Dinitroaniline, 2,6-di-nitroaniline (606-22-4)

2,6-dinitrophenol (573-56-8)

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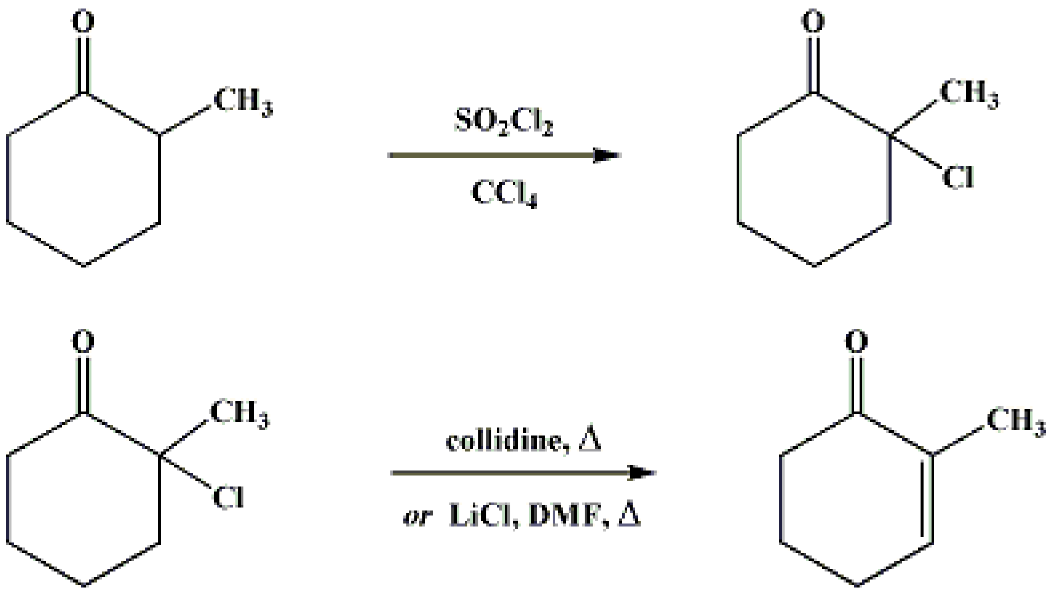
2-CHLORO-2-METHYLCYCLOHEXANONE and 2-METHYL-2-CYCLOHEXENONE

[(Cyclohexanone, 2-chloro-2-methyl-) and (2-Cyclohexen-1-one, 2-methyl-)]



Submitted by E. W. Warnhoff, D. G. Martin, and William S. Johnson[1].
Checked by M. S. Newman, G. R. Kahle, and D. E. Reid.

1. Procedure

A. *2-Chloro-2-methylcylohexanone.* A 3-l. three-necked flask, fitted with a sealed mechanical stirrer with glass blade, a dropping funnel, and an outlet tube connected to a gas-absorption trap,[2] is charged with a solution of 224 g. (2.0 moles) of 2-methylcyclohexanone (Note 1) in 1 l. of dry carbon tetrachloride. A solution of 179 ml. (297 g., 2.2 moles) of sulfuryl chloride (Note 2) in 300 ml. of dry carbon tetrachloride is added from the dropping funnel over a 1-hour period with stirring. The slightly exothermic reaction is moderated by cooling the flask with a bath of water at room temperature. After the addition is complete, stirring is continued for 2 hours. The yellow solution is then washed successively with three 300-ml. portions of water, two 200-ml. portions of saturated sodium bicarbonate solution, and one 200-ml. portion of saturated salt solution, and finally dried over anhydrous magnesium sulfate.

The solvent is removed by distillation through a 15-cm. Vigreux column, first at atmospheric pressure and finally at reduced pressure (water aspirator). The residue is satisfactory for the preparation of 2-methyl-2-cyclohexenone described below (part B). Distillation through the column gives, after a small fore-run, 243–248 g. (83–85%) of colorless 2-chloro-2-methylcyclohexanone, b.p. 94–96°/27mm., n_D^{25} 1.4672, d_4^{25}

1.088 (Note 3).

B. *2-Methyl-2-cyclohexenone. (a) Collidine method.* The crude (undistilled) 2-chloro-2-methylcyclohexanone prepared as described above (part A) is transferred to a 1-l. three-necked flask fitted with a stout sealed Hershberg wire stirrer and two efficient reflux condensers, one attached to each side neck; and 290 ml. (266 g., 2.2 moles) of 2,4,6-collidine (Note 2) is added rapidly through one of the condensers with stirring. The flask is heated to 145–150° (bath temperature) with an oil bath until there ensues a sudden exothermic reaction which results in vigorous boiling of residual carbon tetrachloride. The reaction is essentially complete within 1 minute, and the mixture becomes very viscous with suspended collidine hydrochloride. The heating is discontinued, and, as the reaction mixture cools and becomes viscous enough to impede stirring, a total of 500 ml. of benzene is added cautiously (with vigorous boiling) through a condenser in order to maintain fluidity. The collidine hydrochloride is collected by suction filtration on a 10-cm. sintered glass suction filter, then transferred to a beaker, triturated with 300 ml. of benzene, and refiltered. After repetition of this treatment, the weight of residual salt is about 303 g. (96%).

The combined dark-brown filtrates are washed (Note 4) with two 300-ml. portions of 10% hydrochloric acid saturated with sodium chloride, with one 300-ml. portion of saturated sodium bicarbonate solution, and with one 300-ml. portion of saturated salt solution, and finally dried over anhydrous magnesium sulfate. The benzene is removed by distillation through a 15-cm. Vigreux column, and then all material boiling at 70–97°/56 mm. is collected (Note 5). Fractionation of this material through a 20-cm. heated column packed with steel saddles gives, after a fore-run of benzene, 100–109 g. (45–49% yield from 2-methylcyclohexanone) of colorless 2-methyl-2-cyclohexenone, b.p. 98–101°/77 mm., n_D^{25} 1.4830–1.4835, d_4^{25} 0.972, λ_{max}^{alc} 234 m• (ε 9660) (Note 6).

(b) *Lithium chloride method.* A 1-l. three-necked flask, fitted with a sealed Hershberg wire stirrer, a thermometer, and a tube leading to a source of nitrogen, is charged with 26 g. of lithium chloride, 250 ml. of dimethylformamide (Note 7) and crude 2-chloro-2-methylcyclohexanone prepared as described above (part A, half-scale) from 112 g. of 2-methylcyclohexanone. The stirrer is started, the air swept out with nitrogen, and the flask immersed in an oil bath maintained at 100°. The temperature of the reaction mixture rises to 100° in about 10 minutes, then to 112° and back to 105° in another 25 minutes. At the end of this time the mixture is cooled, 1-l. each of ether and of 2.5% sulfuric acid is added, and the mixture is stirred for about 4 hours to hydrolyze the dimethylformamide. The aqueous layer is separated, saturated with sodium chloride, and extracted with four 150-ml. portions of ether. These extracts are combined with the original ether layer, washed with saturated sodium chloride solution and saturated sodium bicarbonate solution, and finally dried over anhydrous sodium sulfate. The ether is removed by distillation through a 15-cm. Vigreux column, and then a fraction boiling at 79–107°/28 mm. is collected. Redistillation through a 20-cm. heated column packed with steel saddles gives 47–50 g. (43–45% yield from 2-methylcyclohexanone)

of colorless 2-methyl-2-cyclohexenone, b.p. 83–85.5°/35 mm., n_D^{25} 1.4833–1.4840, λ_{max}^{alc} 234 m• (ε 9680) (Note 6).

2. Notes

1. 2-Methylcyclohexanone is available commercially. In the present work it was prepared as follows. A 3-l. three-necked flask, fitted with a Hershberg wire stirrer, dropping funnel, and a thermometer, is charged with a solution of 228 g. (2.0 moles) of 2-methylcyclohexanol (Eastman Kodak Company practical grade) in 1 l. of benzene. A solution of 238 g. of sodium dichromate dihydrate in 1 l. of water containing 324 ml. of concentrated sulfuric acid and 100 ml. of acetic acid is added from the funnel over a period of 2.5 hours with stirring. The temperture of the reaction mixture is maintained (ice bath) at 10° or slightly below during the addition and also during a 3-hour stirring period after the addition. The aqueous layer is separated, diluted with 250 ml. of water, and extracted with two 300-ml. portions of benzene. These extracts are combined with the original benzene layer, and the whole is washed in sequence with 500 ml. of water, 400 ml. of saturated sodium bicarbonate solution, and 400 ml. of saturated salt solution. After the solution has been dried over anhydrous magnesium sulfate, the benzene is removed by distillation through a 20-cm. Vigreux column. Distillation of the residue through a 20-cm. column packed with steel saddles gives 193–200 g. (85–88% yield) of 2-methylcyclohexanone, b.p. 162.5–163.5°/742 mm., n_D^{25} 1.4459.

2. Eastman Kodak Company practical grade.

3. The homogeneity of this product has been demonstrated.[3] It is stable for long periods if stored in a brown bottle over a little magnesium oxide.

4. Excessive washing with aqueous solution is avoided as the product has appreciable solubility in water.

5. The dark oily distillation residue (about 72 g.) distils at 140–200° /1 mm. and consists mainly of the dimer of 2-methylenecyclohexanone which can be isolated in 23% yield.[3]

6. On standing, the ketone gradually turns yellow, and the refractive index increases. Redistillation of such material gives pure ketone.

7. Supplied by Matheson, Coleman and Bell.

3. Discussion

The only published method for producing pure 2-chloro-2-methylcyclohexanone is by the action of sulfuryl chloride on 2-methylcyclohexanone.[3] Direct chlorination gives mixtures of the 2- and 6-chloro compounds.[3]

2-Methyl-2-cyclohexenone has been prepared by the action of nitrosyl chloride on 1-methylcyclohexene, followed by dehydrohalogenation with sodium methoxide[4] or sodium acetate,[5] and hydrolysis of the resulting oxime; in an impure condition by

several methods;[6,7 8,9,10,11,12,13] by dehydration of the ketol produced by the reaction of methylmagnesium iodide with 1,2-cyclohexanedione;[8,14] by reduction of the enol methyl ether produced by the reaction of diazomethane with 1,2-cyclohexanedione;[15] by bromination of 2-methylcyclohexanone with N-bromosuccinimide, followed by dehydrobromination with pyridine or with 2,4-dinitrophenylhydrazine;[16] by treatment of 5-heptenoic acid chloride with stannic chloride;[17] and by the present method.[3] The use of lithium chloride in dimethylformamide for the dehydrohalogenation is an adaptation of the method of Holysz.[18]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 666
- Org. Syn. Coll. Vol. 7, 249

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

ether (60-29-7)

sodium acetate (127-09-3)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

carbon tetrachloride (56-23-5)

nitrogen (7727-37-9)

sodium methoxide (124-41-4)

sulfuryl chloride (7791-25-5)

pyridine (110-86-1)

methylmagnesium iodide (917-64-6)

nitrosyl chloride (2696-92-6)

stannic chloride (7646-78-8)

magnesium sulfate (7487-88-9)

Diazomethane (334-88-3)

2,4-Dinitrophenylhydrazine (119-26-6)

magnesium oxide

sodium dichromate dihydrate (10588-01-9)

dimethylformamide (68-12-2)

N-bromosuccinimide (128-08-5)

2,4,6-collidine (108-75-8)

2-methylcyclohexanone (583-60-8)

2-methylcyclohexanol (583-59-5)

1-methylcyclohexene

2-Methyl-2-cyclohexenone, 2-Cyclohexen-1-one, 2-methyl- (1121-18-2)

2-Chloro-2-methylcyclohexanone, Cyclohexanone, 2-chloro-2-methyl- (10409-46-8)

collidine hydrochloride

Lithium chloride (7447-41-8)

2-methylenecyclohexanone

1,2-Cyclohexanedione (765-87-7)

5-heptenoic acid chloride

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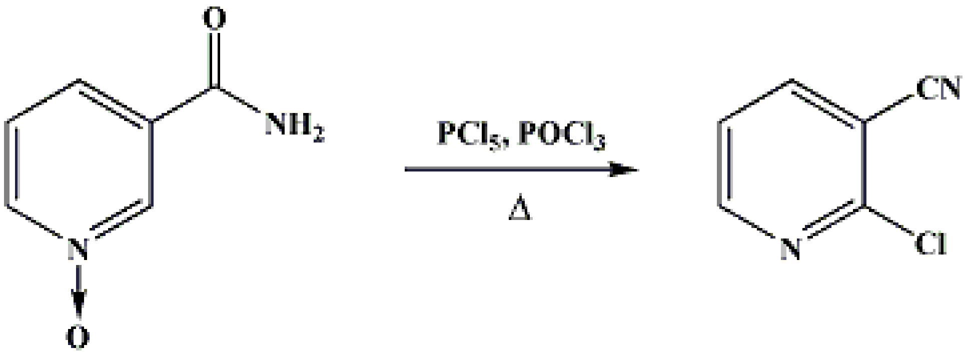
2-CHLORONICOTINONITRILE

[Nicotinonitrile, 2-chloro-]



Submitted by E. C. Taylor, Jr.[1] and Aldo J. Crovetti[2].
Checked by Charles C. Price and Walter A. Schroeder.

1. Procedure

This preparation should be conducted in a good hood.

In a 1-l. round-bottomed flask are placed 85.0 g. (0.62 mole) of nicotinamide-1-oxide (p. 704) and 180.0 g. (0.86 mole) of phosphorus pentachloride (Note 1), and the solids are thoroughly mixed. Two hundred and forty-three milliliters of phosphorus oxychloride is added slowly with shaking. A spiral condenser provided with a drying tube is attached to the flask which is then placed in an oil bath preheated to 60–70°. The temperature is slowly (20–25 minutes) raised to 100°, during which time the reaction mixture is occasionally shaken. In the range 100–105° the evolution of hydrogen chloride gas increases, and a spontaneous, vigorous refluxing of the phosphorus oxychloride begins. The reaction flask is removed from the oil bath, and the rate of refluxing is controlled by the application of an ice-water bath (Note 2). After the vigorous reaction has subsided (about 5 minutes) the oil bath is replaced, and heating under reflux is continued at 115–120° for 1.5 hours.

After the reaction mixture has been cooled, the excess phosphorus oxychloride is distilled under reduced pressure (80–100 mm.) (0.5–1.0 hour). Near the end of the distillation the product begins to sublime into the still head. The residual dark-brown oil is poured with stirring into an 800-ml. beaker containing 280–300 g. of crushed ice (Note 3) and (Note 4). The volume of the ice-water mixture is brought to 600 ml. and allowed to stand at 5° overnight. The crude light-brown product is filtered by suction and washed with water.

The solid is suspended in 300 ml. of 5% sodium hydroxide at 15° (Note 5). The mixture is stirred for 30 minutes, and the solid is filtered by suction and washed with water until the filtrates are no longer alkaline. The procedure is repeated, but stirring is

continued for 0.75–1.0 hour. After the solid has been filtered by suction, washed, and pressed as dry as possible, it is dried under reduced pressure over phosphorus pentoxide for 12–16 hours.

The solid is transferred to a Soxhlet thimble (45 × 125 cm.) containing a 5-cm. layer of anhydrous sodium carbonate on the bottom (Note 6), and the solid is extracted for 2 to 3 hours with anhydrous ether (700–800 ml.). The total volume of ether is brought to 800–900 ml. The ethereal solution is treated with charcoal and boiled for 10–15 minutes under reflux; then the solution is filtered by suction (Note 7). After evaporation of solvent, 30–33 g. (35–39%) of white 2-chloronicotinonitrile is obtained, m.p. 105–106° (Note 8).

2. Notes

1. *To avoid exposure to irritating fumes, the phosphorus pentachloride and oxychloride are handled in the hood. The heating under reflux is also carried out in the hood.*
2. The reaction becomes very exothermic and if uncontrolled there is serious flooding of the condenser. The reaction mixture also becomes dark red to black when the reaction temperature is not controlled.
3. It is difficult to transfer all the oil before solidification starts in the flask. The residual solid is removed by melting on the steam bath and pouring on ice. By repeating this procedure several times, almost all the product can be removed from the flask. Any remaining solid is removed by adding cold water to the flask, breaking the solid with a spatula, and swirling the mixture out of the flask.
4. It is important to stir as rapidly as possible to break the product into small pieces. The beaker should be secured by a large clamp. If the stirring is too slow or the oil is poured too fast, large clumps result which do not solidify completely.
5. Most of the acidic impurities are removed in this step.
6. The sodium carbonate retains any residual moisture and acidic impurities. After the extraction, a brown, gummy, hygroscopic mass remains in the thimble.
7. The checkers found a sintered-glass filter funnel suitable.
8. This product may be recrystallized from ligroin-acetone with 80–85% recovery. Analysis of the product after such recrystallization gave the following analytical results: Calcd. for $C_6H_3ClN_2$: C, 51.98; H, 2.16; Cl, 25.63; N, 20.21. Found: C, 52.41; H, 2.39; Cl, 25.43; N, 19.60.

3. Discussion

The preparation described here is a modification of that reported by Taylor and Crovetti.[3] 2-Chloronicotinonitrile has also been prepared by the dehydration of 2-chloronicotinamide[4] and by the Sandmeyer reaction on 3-amino-2-chloropyridine.[5]

References and Notes

1. Princeton University, Princeton, New Jersey.

2. University of Illinois, Urbana, Illinois.
3. Taylor and Crovetti, *J. Org. Chem.*, **19**, 1633 (1954).
4. Späth and Koller, *Ber.*, **56**, 880 (1923).
5. von Schickh, Binz, and Schulz, *Ber.*, **69**, 2593 (1936).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

phosphorus pentachloride and oxychloride

hydrogen chloride (7647-01-0)

ether (60-29-7)

sodium hydroxide (1310-73-2)

phosphorus pentachloride (10026-13-8)

sodium carbonate (497-19-8)

Phosphorus Oxychloride (21295-50-1)

2-Chloronicotinonitrile, Nicotinonitrile, 2-chloro- (6602-54-6)

nicotinamide-1-oxide (1986-81-8)

2-chloronicotinamide (10366-35-5)

3-amino-2-chloropyridine (6298-19-7)

phosphorus pentoxide (1314-56-3)

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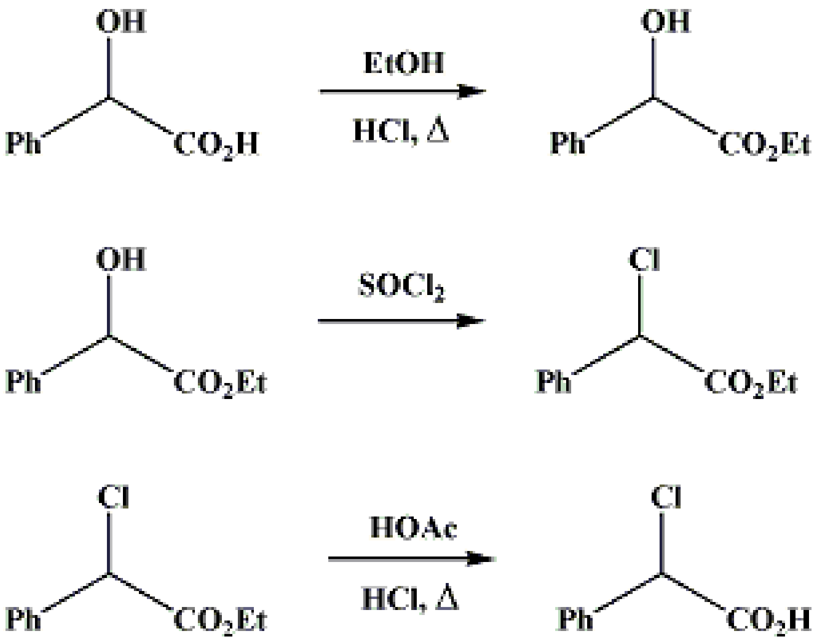
α-CHLOROPHENYLACETIC ACID

[Acetic acid, chlorophenyl-]



Submitted by Ernest L. Eliel, Milton T. Fisk, and Thomas Prosser[1].
Checked by James Cason, Lois J. durham, and Gerhard J. Fonken.

1. Procedure

A. *Ethyl mandelate*. To 152 g. (1.0 mole) of mandelic acid and 200 ml. of absolute ethanol in a 1-l. round-bottomed flask equipped with a reflux condenser, there is added 100 ml. of absolute ethanol containing about 10 g. of anhydrous hydrogen chloride (Note 1). The solution is heated under reflux on a steam bath for 5 hours, then poured into 1 l. of ice water in a 3-l. beaker (Note 2). A saturated aqueous solution of sodium bicarbonate is added until the mixture is faintly alkaline (Note 3). It is then extracted with two 300-ml. portions of ether in a 2-l. separatory funnel. The ether extracts are washed with a 200-ml. portion of water and dried over 50 g. of anhydrous sodium sulfate. The dried ether solution is concentrated by distillation from a 250-ml. Claisen flask, and the residue is distilled at reduced pressure. There is obtained 147–154 g. (82–86%) of ethyl mandelate, b.p. 144–145°/16 mm. The ester may crystallize upon standing for a prolonged period. It melts at 30.5–31.5°.

B. *Ethyl α-chlorophenylacetate*. Ethyl mandelate (135 g., 0.75 mole) is dissolved in 98 g. (59 ml., 0.82 mole) of thionyl chloride (Note 4) contained in a 500-ml. round-bottomed flask equipped with a reflux condenser capped with a drying tube. The apparatus is allowed to stand in a hood overnight (about 16 hours), at the end of which time the solution is heated under reflux for 30 minutes on a steam bath. The solution is

then poured into 750 ml. of ice water contained in a 2-l. separatory funnel (Note 5), and the mixture is extracted with two 300-ml. portions of ether. The combined ether extracts are washed with two 250-ml. portions of saturated aqueous sodium bicarbonate solution and one 250-ml. portion of water. The washed extracts are dried over 45 g. of anhydrous sodium sulfate and concentrated by distillation. The residue is distilled from a 250-ml. Claisen flask at reduced pressure. The yield of ethyl α-chlorophenylacetate is 121–127 g. (81–85%), b.p. 134–136°/15 mm., n_D^{20} 1.5149.

C. *α-Chlorophenylacetic acid*. A solution of 119 g. (0.6 mole) of ethyl α-chlorophenylacetate in 238 ml. of glacial acetic acid and 119 ml. of concentrated hydrochloric acid, contained in a 1-l. round-bottomed flask, is heated under reflux in a hood for 1.5 hours (Note 6). At the end of the heating period the solution is concentrated by heating in an oil bath at 100° at reduced pressure (15–20 mm.) until no further material is distilled (Note 7). The residue is allowed to cool to room temperature and poured slowly, with stirring, into 1-l. of ice-cold saturated sodium bicarbonate solution contained in a 2-l. beaker. Solid sodium bicarbonate is added in small portions until the solution becomes neutral to universal indicator paper (Note 8). The solution is then extracted with two 200-ml. portions of ether in a 2-l. separatory funnel (Note 9), (Note 10). The aqueous phase is placed in a 3-l. beaker and acidified cautiously with ice-cold 12*N* sulfuric acid until the mixture is acid to Congo red paper (Note 11). The oily suspension is extracted with two 200-ml. portions of ether in a 2-l. separatory funnel. The ether extracts are washed with two 100-ml. portions of water and dried over 45 g. of anhydrous sodium sulfate. The dried ether extract is transferred to a 1-l. Erlenmeyer flask and concentrated on a steam bath until ether is no longer distilled. To the residue there is added 500 ml. of warm (50–60°) concentrated hydrochloric acid (in a hood), and the suspension is allowed to cool with occasional swirling (Note 12). Crystallization is completed by chilling in ice, and the product is collected on a sintered-glass funnel. After the product has been dried as much as possible on the funnel it is dried to constant weight in a vacuum desiccator over solid potassium hydroxide. The yield of dry acid is 82–84 g. (80–82%), m.p. 77.5–79.5°. It is satisfactory for most purposes. If very pure material is desired the acid may be recrystallized from three volumes of hexane to give material, m.p. 78.5–79.5°, in 90–95% recovery.

2. Notes

1. The hydrogen chloride may be generated by the method described in *Organic Syntheses*, Coll. Vol. **1**, 293 (1941). It should be dried by passage through concentrated sulfuric acid. The hydrogen chloride may be taken directly from a cylinder, if one is available.
2. The flask should be rinsed with a small portion of water.
3. The amount of bicarbonate solution varies, depending on the weight of hydrogen chloride used. There is usually required 250–350 ml.
4. The submitters used Matheson thionyl chloride without further purification.

5. The flask should be rinsed with a small portion of ether.
6. The solution becomes homogeneous after a few minutes of heating.
7. The checkers found that about 250–270 ml. of distillate is obtained under these conditions.
8. About 90–130 g. of sodium bicarbonate is usually required.
9. When the combined ether layers are dried over sodium sulfate and concentrated, and the residue is distilled at reduced pressure, about 11 g. (10%) of unchanged ethyl α-chlorophenylacetate, b.p. 134–137°/15 mm., is recovered.
10. The solution should be kept ice-cold during the extraction, which must be carried out rapidly lest hydrolysis of the chlorophenylacetic acid to mandelic acid take place.
11. About 70 ml. of acid is required. A 25-ml. excess of 12*N* sulfuric acid is recommended in order to ensure the acidity of the mixture.
12. The objective of the hydrochloric acid treatment is to remove small amounts of mandelic acid from the product. If seed crystals are available, the slurry should be seeded as it is cooled.

3. Discussion

α-Chlorophenylacetic acid has been prepared from mandelonitrile and hydrochloric acid in a sealed tube,[2,3] from mandelic acid and hydrochloric acid in a sealed tube,[4] from α-nitrostyrene and hydrochloric acid in a sealed tube,[5] from phenylglycine, hydrochloric acid, and sodium nitrite,[6] from mandelic acid and phosphorus pentachloride (to give the acid chloride which is then hydrolyzed),[7] and, in poor yield, from mandelic acid and thionyl chloride.[8] In the method described, ethyl mandelate is prepared according to Fischer and Speier.[9] The conversion to the chloroester and the acid hydrolysis step are modifications of a preparation described by McKenzie and Barrow.[8]

References and Notes

1. University of Notre Dame, Notre Dame, Indiana.
2. Spiegel, *Ber.*, **14**, 239 (1881).
3. Meyer, *Ann.*, **220**, 41 (1883).
4. Radziszewski, *Ber.*, **2**, 208 (1869).
5. Priebs, *Ann.*, **225**, 336 (1884).
6. Jochem, *Z. physiol. Chem.*, **31**, 123 (1900).
7. Bischoff and Walden, *Ann.*, **279**, 122 (1894).
8. McKenzie and Barrow, *J. Chem. Soc.*, **99**, 1916 (1911).
9. Fischer and Speier, *Ber.*, **28**, 3252 (1895).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrogen chloride, hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ether (60-29-7)

phosphorus pentachloride (10026-13-8)

Mandelic acid (90-64-2)

thionyl chloride (7719-09-7)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

sodium nitrite (7632-00-0)

potassium hydroxide (1310-58-3)

mandelonitrile (532-28-5)

hexane (110-54-3)

Ethyl mandelate (4358-88-7)

α-Chlorophenylacetic acid, Acetic acid, chlorophenyl-, chlorophenylacetic acid (4755-72-0)

Ethyl α-chlorophenylacetate (4773-33-5)

α-nitrostyrene

phenylglycine (103-01-5)

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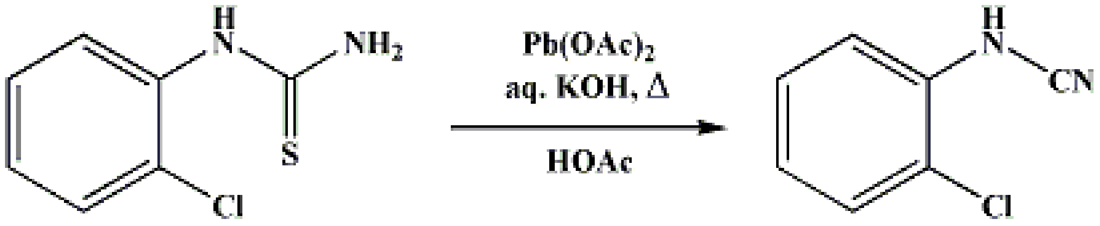
o-CHLOROPHENYLCYANAMIDE

[Carbanilonitrile, *o*-chloro-]



Submitted by Frederick Kurzer[1]
Checked by Cliff S. Hamilton and David B. Capps.

1. Procedure

To a suspension of 37.4 g. (0.2 mole) of *o*-chlorophenylthiourea (p. 180) in 300 ml. of water at 100°, contained in a 3-l. beaker, is added a boiling solution of 132 g. (2 moles) of 85% potassium hydroxide in 300 ml. of water. The resulting solution is immediately treated with a hot saturated solution of 83.5 g. (0.22 mole) of lead acetate trihydrate, added as rapidly as possible and with good stirring (Note 1). The reaction mixture, from which large quantities of lead sulfide separate instantly, is boiled for 6 minutes and cooled to 0°, and the lead sulfide is filtered with suction by means of a large Büchner funnel (Note 2). The colorless filtrate is acidified at 0–5° (Note 3) by the slow addition with stirring of 120–140 ml. of glacial acetic acid. The white crystalline precipitate of nearly pure *o*-chlorophenylcyanamide which separates is collected by filtration on a suction filter and is washed with six 150-ml. portions of ice water. The crystalline mass of white plates is filtered, drained, and dried (Note 4). The yield of product, melting at 100–104°, is 26–28 g. (85–92%).

Recrystallization from benzene-light petroleum ether (8 ml. and 4 ml. respectively per gram of the dried precipitated material) gives lustrous needles of *o*-chlorophenylcyanamide, m.p. 105–106° (60–70% recovery) (Note 5). The above method is generally applicable and affords an excellent route to arylcyanamides (Note 6).

2. Notes

1. The exothermic reaction may cause the contents of the beaker to froth vigorously if the lead acetate solution is added too quickly. The reaction is readily controlled by adding the liquid in a rapid, thin stream with good stirring.
2. The use of a hardened filter paper or two thicknesses of ordinary filter paper is recommended. The black filter cake of lead sulfide may be extracted once again with 100 ml. of boiling 4% potassium hydroxide solution, and the extracts

combined with the main filtrate.
3. The temperature of the solution is kept below 5° by the addition of suitable quantities of clean ice.
4. The product is sufficiently pure for use in further syntheses.
5. In benzene solution or in the solid state, *o*-chlorophenylcyanamide does not polymerize on storage for several months at 20–30°.
6. The desulfurization of arylthioureas can be used generally for preparing arylcyanamides in excellent yields. The submitter reports that α-naphthylcyanamide, melting at 124–128°, can be prepared in yields of 77–90% by this method.

3. Discussion

o-Chlorophenylcyanamide has been prepared by the action of lead acetate on *o*-chlorophenylthiourea.[2] The method is based on the analogous preparation of phenylcyanamide.[3]

References and Notes

1. University of London, London, England.
2. Kurzer, *J. Chem. Soc.*, **1949**, 3033.
3. Rathke, *Ber.*, **12**, 772 (1879); Krall et al., *J. Indian Chem. Soc.*, **19**, 343 (1942); **23**, 373 (1946).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

α-naphthylcyanamide

acetic acid (64-19-7)

Benzene (71-43-2)

lead sulfide

potassium hydroxide (1310-58-3)

lead acetate

phenylcyanamide

o-Chlorophenylthiourea (5344-82-1)

o-Chlorophenylcyanamide, Carbanilonitrile, o-chloro- (45765-25-1)

lead acetate trihydrate

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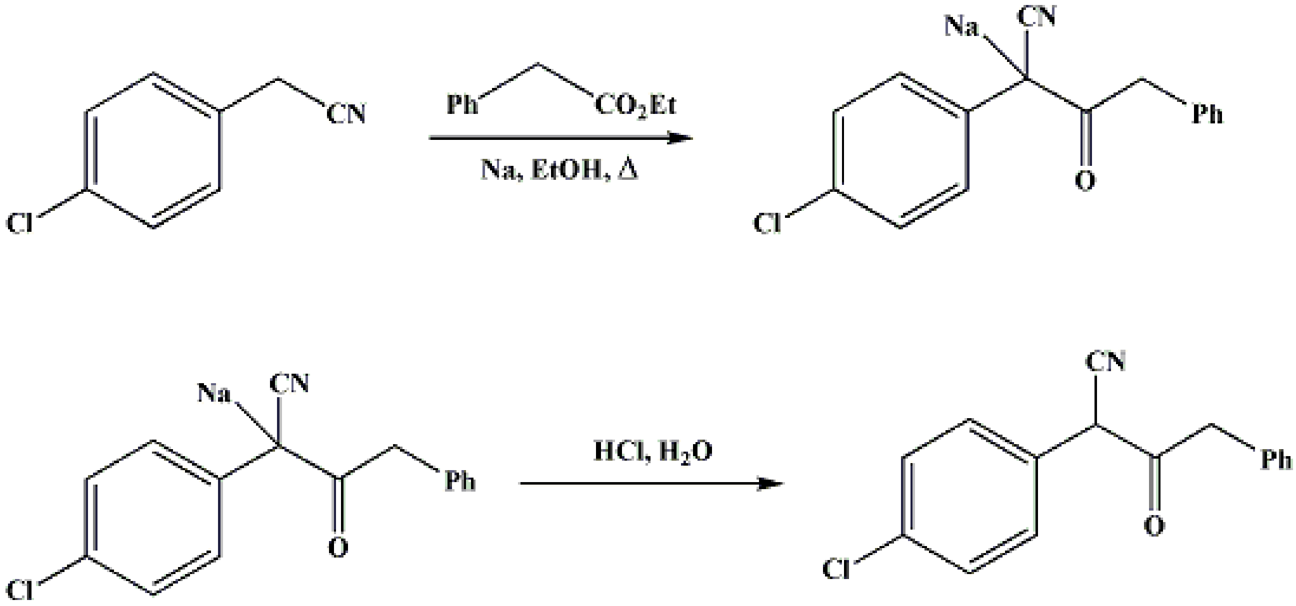
α-(4-CHLOROPHENYL)-γ-PHENYLACETOACETONITRILE

[Acetoacetonitrile, 2-(*p*-chlorophenyl)-4-phenyl-]



Submitted by Stephen B. Coan and Ernest I. Becker[1].
Checked by Charles C. Price and G. Venkat Rao.

1. Procedure

A solution of 11.5 g. (0.5 g. atom) of sodium is prepared in 150 ml. of absolute ethanol (Note 1) in a 500-ml. three-necked flask equipped with a stirrer, a condenser, and a dropping funnel. While this solution is refluxing with stirring, a mixture of 37.8 g. (0.25 mole) of 4-chlorophenylacetonitrile and 50.8 g. (0.31 mole) of ethyl phenylacetate is added through the dropping funnel over a period of 1 hour. The solution is refluxed for 3 hours, cooled, and poured into 600 ml. of cold water. The aqueous alkaline mixture is extracted three times with 200-ml. portions of ether and the ether extracts discarded. The aqueous solution is acidified with cold 10% hydrochloric acid and extracted three times with 200-ml. portions of ether. The ether solution is then extracted once with 100 ml. of water, twice with 100 ml. each of 10% sodium bicarbonate solution, and once with 100 ml. of water, the aqueous extracts being discarded in turn. The organic phase is dried with anhydrous sodium sulfate, filtered through a fluted filter, and the ether removed by distillation. The yield of α-(4-chlorophenyl)-γ-phenylacetoacetonitrile is 58–62 g. (86–92%), m.p. 128.5–130.0°. For many purposes, this crude product may be used without further purification. If a purer product is desired, however, it may be recrystallized from methanol or aqueous methanol (Note 2) to yield 50–55 g. (74–82%), m.p. 131.0–131.2° (Note 3).

2. Notes

1. Comparable results were obtained when fresh commercial grade (2-B) anhydrous ethanol was used.
2. For recrystallization, a solution of the nitrile in 3–4 ml. of hot methanol per gram was treated with Darco G-60 and filtered on a fluted paper. Distilled water was added to the hot solution until incipient crystallization was observed. In general the final solvent was approximately 90%

methanol.
3. The above method has been used in the preparation of other ring-substituted diphenylacetoacetonitriles. The method is equally successful when applied to the condensation of phenylacetonitrile with the ethyl ester of a 4-substituted phenylacetic acid. The table summarizes the results reported by the submitters.

DIPHENYLACETOACETONITRILES

Acetoacetonitrile	Yield, %	M.P.
From Phenylacetonitrile and an Ethyl 4-Substituted Phenylacetate		
α-Phenyl-γ-phenyl-	82	79.4–80.0°
α-Phenyl-γ-(4-methylphenyl)-	84	88.0–89.0°
α-Phenyl-γ-(4-methoxyphenyl)-	81	69.5–70.4°
α-Phenyl-γ-(4-bromophenyl)-	80	94.0–95.0°
α-Phenyl-γ-(4-methylthiophenyl)-	85	85.0–85.2°
From 4-Substituted Phenylacetonitrile and Ethyl Phenylacetate		
α-(4-Fluorophenyl)-γ-phenyl-	75	111.8–112.0°

3. Discussion

The above procedure is a modification of that described by Walther and Hirschberg.[2] α,γ-Diphenylacetoacetonitrile has been prepared by the condensation of phenylacetonitrile with ethyl phenylacetate in the presence of sodium ethoxide without solvent.[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 176

References and Notes

1. Polytechnic Institute of Brooklyn, Brooklyn 2, New York.
2. Walther and Hirschberg, *J. prakt. Chem.*, [2] **67**, 377 (1903).
3. Walther and Schickler, *J. prakt. Chem.*, [2] **55**, 305 (1897).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

a-Phenyl-?-phenyl-Acetoacetonitrile

a-Phenyl-?-(4-methylphenyl)-Acetoacetonitrile

a-Phenyl-?-(4-methoxyphenyl)-Acetoacetonitrile

a-Phenyl-?-(4-bromophenyl)-Acetoacetonitrile

a-Phenyl-?-(4-methylthiophenyl)-Acetoacetonitrile

a-(4-Fluorophenyl)-?-phenyl-Acetoacetonitrile

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

methanol (67-56-1)

ether (60-29-7)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

phenylacetonitrile (140-29-4)

Ethyl phenylacetate (101-97-3)

α-(4-CHLOROPHENYL)-γ-PHENYLACETOACETONITRILE, Acetoacetonitrile, 2-(p-chlorophenyl)-4-phenyl- (35741-47-0)

4-chlorophenylacetonitrile (140-53-4)

Acetoacetonitrile

α,γ-Diphenylacetoacetonitrile

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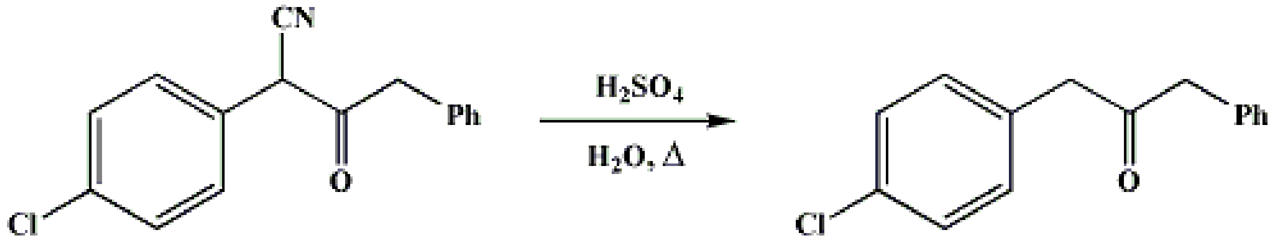
1-(*p*-CHLOROPHENYL)-3-PHENYL-2-PROPANONE

[2-Propanone, 1-(*p*-chlorophenyl)-3-phenyl-]



Submitted by Stephen B. Coan and Ernest I. Becker[1].
Checked by Charles C. Price and G. Venkat Rao.

1. Procedure

In a 250-ml. three-necked flask equipped with a stirrer and a condenser are placed 75 ml. of 60% sulfuric acid and 25 g. (0.093 mole) of α-(4-chlorophenyl)-γ-phenylacetoacetonitrile (p. 174). While being stirred, the mixture is heated at reflux until the evolution of carbon dioxide ceases (Note 1) and (Note 2). The mixture is cooled, poured into 200 ml. of ice water, and extracted three times with 150-ml. portions of ether. The ether solution is washed once with 50 ml. of water, twice with 100-ml. portions of 10% sodium hydroxide solution, and then with 50 ml. of water. After drying over sodium sulfate and filtering, the ether is distilled on a steam bath, affording 15–17 g. (66–75%) of 1-(*p*-chlorophenyl)-3-phenyl-2-propanone, m.p. 34.5–35.5°. Recrystallization from 160 ml. of petroleum ether (b. p. 40–60°) gives 12–13 g. (53–57%) of product, m.p. 35.9–36.5° (Note 3).

2. Notes

1. The hydrolysis and decarboxylation of the nitrile require from 18 to 24 hours.
2. The evolution of carbon dioxide is conveniently observed by passing the effluent gases through a saturated solution of barium hydroxide.
3. The submitters report that a similar procedure has been used in the preparation of other monosubstituted dibenzyl ketones from α-phenyl-γ-(4-substituted phenyl) acetoacetonitriles.

Product	Yield, %	M.P.
1,3-Diphenyl-2-propanone	65–71	34.2–34.5°
1-(*p*-Tolyl)-3-phenyl-2-propanone	66	30.8–31.2°
1-(*p*-Bromophenyl)-3-phenyl-2-propanone	50	53.8–54.2°
1-(*p*-Fluorophenyl)-3-phenyl-2-propanone	50	36.0–36.5°
1-(*p*-Methylthiophenyl)-3-phenyl-2-propanone	40	43.9–44.2°

1-(*p*-Methoxyphenyl)-3-phenyl-2-propanone[a]	19	46.6–47.4°

a It is necessary to employ 5 ml. of glacial acetic acid and 5 ml. of 20% aqueous hydrochloric acid, instead of the sulfuric acid, per gram of ketonitrile as reaction solvent in order to obtain the desired product.

3. Discussion

This method of preparation of 1-(*p*-chlorophenyl)-3-phenyl-2-propanone has been reported by Coan and Becker.[2] The method utilized is a modification of that described for the formation of 1,3-diphenyl-2-propanone from α,γ-diphenylacetoacetonitrile.[3,4]

References and Notes

1. Polytechnic Institute of Brooklyn, Brooklyn 2, New York.
2. Coan and Becker, *J. Am. Chem. Soc.*, **76**, 501 (1954).
3. Meyer, *J. prakt. Chem.*, [2] **52**, 81 (1895).
4. Walther and Schickler, *J. prakt. Chem.*, [2] **55**, 305 (1897).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

α-phenyl-γ-(4-substituted phenyl)acetoacetonitriles

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium sulfate (7757-82-6)

carbon dioxide (124-38-9)

barium hydroxide (17194-00-2)

1,3-Diphenyl-2-propanone (102-04-5)

α-(4-CHLOROPHENYL)-γ-PHENYLACETOACETONITRILE (35741-47-0)

α,γ-Diphenylacetoacetonitrile

1-(p-CHLOROPHENYL)-3-PHENYL-2-PROPANONE, 2-Propanone, 1-(p-chlorophenyl)-3-phenyl- (35730-03-1)

1-(p-Tolyl)-3-phenyl-2-propanone

1-(p-Bromophenyl)-3-phenyl-2-propanone

1-(p-Fluorophenyl)-3-phenyl-2-propanone

1-(p-Methylthiophenyl)-3-phenyl-2-propanone

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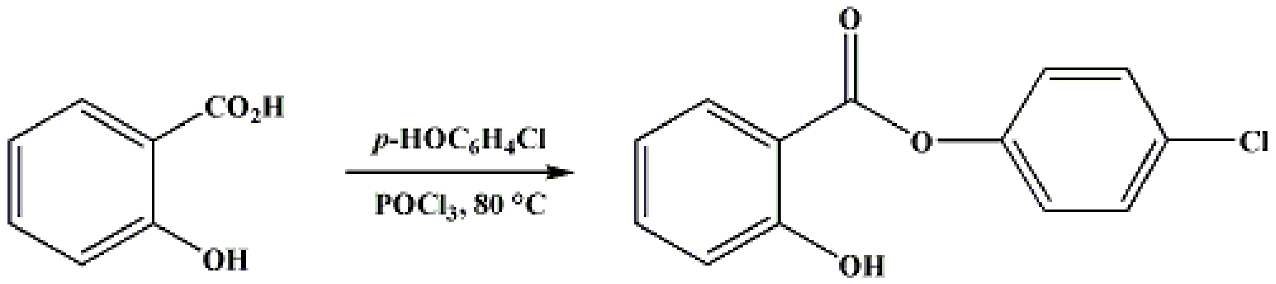
p-CHLOROPHENYL SALICYLATE

[Salicylic acid, *p*-chlorophenyl ester]



Submitted by Norman G. Gaylord and P. M. Kamath[1].
Checked by R. T. Arnold and J. John Brezinski.

1. Procedure

To a mixture of 138.1 g. (1 mole) of salicyclic acid and 128.6 g. (1 mole) of *p*-chlorophenol in a 2-l. round-bottomed flask fitted with a thermometer reaching to the bottom of the flask and a reflux condenser with a drying tube (Note 1) is added 58.3 g. (0.38 mole) of phosphorus oxychloride. The mixture is heated with occasional swirling, and the temperature is maintained at 75–80°. At the end of 4 hours the reactants have been reduced to a molten mass, and this is poured slowly, with vigorous stirring, into a solution of 120 g. of sodium carbonate in 800 ml. of water. The precipitated ester is collected on a filter and washed with four 200-ml. portions of water. The yield of crude, air-dried, *p*-chlorophenyl salicylate is 174–189 g. (70–76%); m.p. 65–66°. Recrystallization from absolute ethanol yields 136–154 g. (55–62%) of pure product; m.p. 69.5–70.5°. A second crop may be obtained by concentration of the filtrate from the first crop or by the addition of water (Note 2).

2. Notes

1. It is advisable to attach the drying tube to a water trap[2] in order to prevent the escape of hydrogen chloride into the atmosphere.
2. The above method has been used in the preparation of other substituted phenyl salicylates to give the following yields of recrystallized products with the indicated melting points.

	Yield, (%)	M.P.
o-Chlorophenyl ester	67	52.0–52.4°
p-Nitrophenyl ester	53	151.5–151.9°
p-*tert*-Butylphenyl ester	42	63.0–63.4°
p-Phenylphenyl ester	66	109.2–109.6°
o-Phenylphenyl ester	70	89.2–89.5°

These esters, with the exception of the *p*-nitrophenyl derivative, can be recrystallized

from absolute ethanol. The nitro compound is recrystallized from dioxane.

3. Discussion

Substituted phenyl salicylates can be prepared by heating salicylic acid and the appropriate phenol in the presence of phosphorus oxychloride,[3,4,5] phosphorus trichloride,[4,5] phosphorus pentachloride,[4,6] phosgene,[4] or thionyl chloride,[4] or by heating the phenol and salol.[7]

References and Notes

1. Polytechnic Institute of Brooklyn, Brooklyn, New York.
2. *Org. Syntheses Coll. Vol.* **1**, 97 (1941).
3. Seifert, *J. prakt. Chem.*, [2] **31**, 472 (1885); Nencki and Heyden, Ger. pats. 38,973 [*Ber.*, **20R**, 351 (1887)] and 43,713 [*Ber.*, **21R**, 554 (1888)]; Walther and Zipper, *J. prakt. Chem.*, [2] **91**, 399 (1915); Krauz and Remenec, *Collection Czechoslov. Chem. Communs.*, **1**, 610 (1929) [*C. A.*, **24**, 1365 (1930)]; Kolloff and Page, *J. Am. Chem. Soc.*, **60**, 948 (1938).
4. Nencki and Heyden, Ger. pat. 70,519 [*Ber.*, **26R**, 967 (1893)].
5. Harris and Christiansen, *J. Am. Pharm. Assoc.*, **24**, 553 (1935); U. S. pat. 2,141,172 [*C. A.*, **33**, 2655 (1939)].
6. Tozer and Smiles, *J. Chem. Soc.*, **1938**, 1897.
7. Cohn, *J. prakt. Chem.*, [2] **61**, 550 (1900).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

salicyclic acid

salol

ethanol (64-17-5)

hydrogen chloride (7647-01-0)

phosphorus pentachloride (10026-13-8)

thionyl chloride (7719-09-7)

sodium carbonate (497-19-8)

salicylic acid

Phosphorus Oxychloride (21295-50-1)

phosgene (75-44-5)

phosphorus trichloride (7719-12-2)

dioxane (5703-46-8)

p-chlorophenol (106-48-9)

p-Chlorophenyl salicylate, Salicylic acid, p-chlorophenyl ester (2944-58-3)

o--Chlorophenyl salicylate

p-Nitrophenyl salicylate

p-tert-Butylphenyl salicylate

p-Phenylphenyl salicylate

o-Phenylphenyl salicylate

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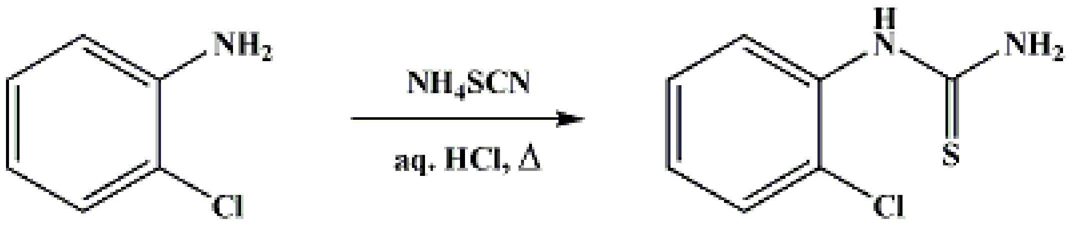
o-CHLOROPHENYLTHIOUREA

[Urea, 1-(*o*-chlorophenyl)-2-thio-]



Submitted by Frederick Kurzer[1]
Checked by Cliff S. Hamilton and David B. Capps.

1. Procedure

To a suspension of 38.3 g. (31.5 ml., 0.30 mole) of *o*-chloroaniline in 300 ml. of warm water is added, with stirring, 27.5 ml. (0.33 mole) of concentrated hydrochloric acid (12*N*). The resulting solution is placed in a 500-ml. porcelain evaporating dish, 25 g. (0.33 mole) of ammonium thiocyanate is added (Note 1), and the mixture is heated on the steam bath for 1 hour (Note 2). The liquid, from which a mass of large needles of *o*-chloroaniline thiocyanate separates, is allowed to cool, set aside at room temperature for 1 hour (Note 3), and then evaporated slowly to dryness over a period of 2–3 hours. The crystalline residue is crushed finely, 300 ml. of water is added, and again the mixture is evaporated slowly. The dry grayish white residual powder is heated finally on the steam bath for 4–5 hours.

The resulting mixture of crude *o*-chlorophenylthiourea and ammonium chloride (58–62 g.) is powdered finely and suspended in 300 ml. of water. The mixture is warmed slowly to 70° with mechanical stirring, then allowed to cool to 35°, and the solid is filtered with suction. The yield of crude *o*-chlorophenylthiourea, melting at 140–144°, is 30–35 g. (54–63%).

The crude material is dissolved in 60 ml. of absolute ethanol, the solution boiled with decolorizing carbon for a few minutes, and the clear, nearly colorless filtrate (Note 4) diluted with 100 ml. of hot benzene and 20 ml. of light petroleum ether (b.p. 60–80°). The white crystalline mass of *o*-chlorophenylthiourea, which separates gradually on cooling and standing, is separated by filtration under reduced pressure, washed with light petroleum ether, and dried, m.p. 144–146°. The yield of purified material is 20–24 g. (36–43%). Evaporation of the mother liquors and crystallization of the residue from a proportionally smaller volume of solvents yields a second crop (6–8 g.) (Note 5).

2. Notes

1. A good commercial grade of *o*-chloroaniline and pure ammonium thiocyanate are satisfactory for this preparation.
2. Comparable results are obtained when three times the quantities specified are used.
3. Uninterrupted evaporation of the initial reaction mixture sometimes tends to give a partly oily product from which only smaller yields can be obtained.
4. The filtration is best effected by the use of reduced pressure employing a preheated Büchner funnel and filter flask.
5. According to the submitter the method is generally applicable to the synthesis of aromatic thioureas. For example, phenylthiourea may be prepared in yields of 37–42%.

3. Discussion

o-Chlorophenylthiourea has been prepared from *o*-chlorophenylisothiocyanate and ammonia,[2] by the interaction of *o*-chloroaniline hydrochloride[3] or sulfate[4] with sodium thiocyanate in chlorobenzene, or with ammonium thiocyanate in aqueous solution.[4,5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 172

References and Notes

1. University of London, London, England.
2. Dyson and George, *J. Chem. Soc.*, **125**, 1705 (1924).
3. Dalgliesh and Mann, *J. Chem. Soc.*, **1945**, 900.
4. Elderfield and Short, *J. Org. Chem.*, **18**, 1092 (1953).
5. Kurzer, *J. Chem. Soc.*, **1949**, 3033.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

Benzene (71-43-2)

ammonium chloride (12125-02-9)

ammonium thiocyanate (1762-95-4)

carbon (7782-42-5)

chlorobenzene (108-90-7)

phenylthiourea (103-85-5)

sodium thiocyanate (540-72-7)

o-Chlorophenylthiourea, Urea, 1-(o-chlorophenyl)-2-thio- (5344-82-1)

o-chloroaniline (95-51-2)

o-chloroaniline hydrochloride (137-04-2)

o-chloroaniline thiocyanate

o-chlorophenylisothiocyanate (2740-81-0)

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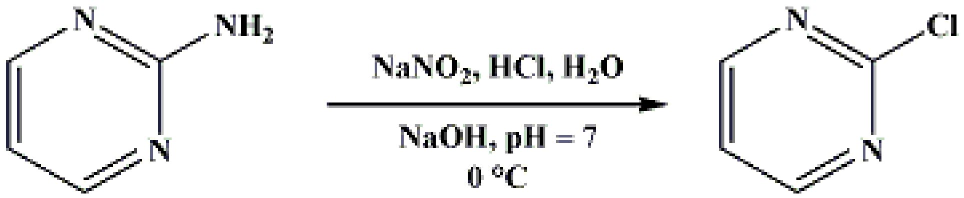
Organic Syntheses, CV 4, 182

2-CHLOROPYRIMIDINE

[Pyrimidine, 2-chloro-]



Submitted by Irving C. Kogon, Ronald Minin, and C. G. Overberger[1].
Checked by Charles C. Price and T. L. V. Ulbricht.

1. Procedure

Caution! This procedure should be carried out in a good hood.

In a 3-l. three-necked round-bottomed flask fitted with a stirrer and a low-temperature thermometer is placed 500 ml. of concentrated hydrochloric acid (6.0 moles), and the solution is cooled to 0°. To the cooled solution, 142 g. (1.5 moles) of 2-aminopyrimidine (Note 1) is added portionwise with stirring until a homogeneous solution is obtained. The solution is cooled to –15° (Note 2), and a 500-ml. dropping funnel is fitted to the flask. A cold solution of 207 g. (3.0 moles) of sodium nitrite in 375 ml. of water is then added dropwise with stirring over a period of 55 minutes, the reaction temperature being maintained at –15° to –10° (Note 3). The solution is stirred an additional hour, and the temperature is allowed to rise to –5°. The mixture is then carefully neutralized to about pH 7 with a 30% solution of sodium hydroxide (about 3.0 moles), care being taken not to allow the temperature to rise above 0° (Note 4). The solid which forms, consisting of 2-chloropyrimidine and sodium chloride, is collected by filtration and washed thoroughly with ether to dissolve all the 2-chloropyrimidine. The cold solution is extracted with four 75-ml. portions of ether (Note 5). The combined extracts are dried over anhydrous sodium sulfate, the solvent is removed, and the residue is recrystallized from isopentane to give white crystals of 2-chloropyrimidine. The yield is 44–46 g. (26–27%), m.p. 64.5–65.5°.

2. Notes

1. Purchased from the Matheson, Coleman and Bell Company, Norwood, Ohio.
2. Cooling below –15° causes the mixture to solidify.
3. Care should be exercised since at this point nitrogen oxides are being evolved. Addition should be started cautiously, as there tends to be a rapid initial rise in temperature.
4. Yields are appreciably reduced if the temperature is allowed to rise above 0°.

5. Filtration and extraction should be performed immediately or extensive decomposition occurs.

3. Discussion

2-Chloropyrimidine has been prepared by Howard[2] and by Sperber, Papa, Schwenk, Sherlock, and Fricano[3] by a similar procedure. The compound also has been obtained from 2-hydroxypyrimidine hydrochloride by treatment with a mixture of phosphorus pentachloride and phosphorus oxychloride[4] or by treatment with phosphorus oxychloride alone.[5] The present procedure has been published.[6]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 336

References and Notes

1. Polytechnic Institute of Brooklyn, Brooklyn 2, New York.
2. Howard, U. S. pat. 2,477,409 [*C. A.*, **43**, 8105 (1949)].
3. Sperber, Papa, Schwenk, Sherlock, and Fricano, *J. Am. Chem. Soc.*, **73**, 5752 (1951).
4. Matsukawa and Ohta, *J. Pharm. Soc. Japan*, **69**, 491 (1949) [*C. A.*, **44**, 3456 (1950)].
5. Copenhaver and Kleinschmidt, Brit. pat. 663,302 [*C. A.*, **46**, 10212 (1952)].
6. Overberger and Kogon, *J. Am. Chem. Soc.*, **76**, 1065 (1954).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

nitrogen oxides

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium hydroxide (1310-73-2)

phosphorus pentachloride (10026-13-8)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

sodium nitrite (7632-00-0)

Phosphorus Oxychloride (21295-50-1)

isopentane (78-78-4)

2-Chloropyrimidine, Pyrimidine, 2-chloro- (1722-12-9)

2-aminopyrimidine (109-12-6)

2-hydroxypyrimidine hydrochloride (38353-09-2)

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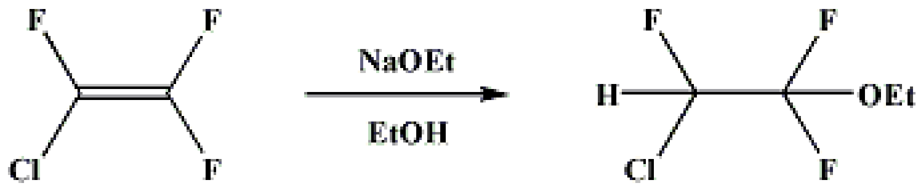
2-CHLORO-1,1,2-TRIFLUOROETHYL ETHYL ETHER

[Ether, 2-chloro-1,1,2-trifluoroethyl ethyl]



Submitted by Bruce Englund[1]
Checked by R. S. Schreiber and Burris D. Tiffany.

1. Procedure

The apparatus used is shown in f.htmig. 6 (Note 1). A solution of sodium ethoxide prepared by dissolving 2.5 g. (0.11 g. atom) of clean sodium in 230 g. (292 ml., 5 moles) of absolute ethanol under anhydrous conditions is added to the reaction tube *C*. Tube *C* thus charged is weighed and placed in position with the gas inlet tube, fitted with fritted-glass dispersion cylinder *D*, extending nearly to the bottom. Several inches of ethanol is placed in tube *G*, which serves as a flow indicator. The traps *A* and *F* are provided to protect against suck-back if the gas flow is interrupted. The seal at *B* is a sleeve of rubber tubing. Any efficient reflux condenser *E* is satisfactory.

Fig. 6.

Fig. 6.

Chlorotrifluoroethylene (Note 2) is introduced at such a rate, controlled by the needle valve, that it is essentially all absorbed in the reaction tube *C*, as indicated by the escape of little or no gas through tube *G*. At this rate, 233 g. (2 moles) (Note 3) is absorbed in 2–2.5 hours, during which the temperature rises to the point of reflux (Note 4).

When the required amount of chlorotrifluoroethylene has been absorbed, the reaction mixture is poured into 500 ml. of water. The product separates as a light-yellow oil, which is separated, washed with 250 ml. of water, and dried over 20 g. of anhydrous calcium chloride. From 233 g. of chlorotrifluoroethylene (2 moles), the yield of crude product is 300–315 g. (92–97%). This material is suitable for use in preparation of ethyl chlorofluoroacetate (p. 423). It may be fractionated through an efficent column to give 285–300 g. (88–92%) of pure chlorotrifluoroethyl ethyl ether, b.p. 87–88°, n_D^{25} 1.3427.

2. Notes

1. The reaction tube *C* may be of any convenient size. The tube used by the submitter was 300 by 55 mm., fitted with a 55/35 standard taper ground-glass joint. The checkers used a 500-ml. calibrated dropping funnel which was convenient for following the increase in volume during the absorption of the chlorotrifluoroethylene. For safety, a heavy grease such as Cello-Grease was used in the stopcock.
2. The chlorotrifluoroethylene used was inhibited polymerization grade, supplied by the Kinetic Chemicals Division, Organic Chemicals Department, E. I. du Pont de Nemours and Company, Wilmington, Delaware.
3. The amount of chlorotrifluoroethylene absorbed is determined by weighing the reaction tube *C* and contents. A convenient alterntive is to note the increase in volume of the reaction mixture, which in this case amounts to 165 ml.
4. The rate of absorption is slow at first but increases as the temperature rises.

3. Discussion

2-Chloro-1,1,2-trifluoroethyl ethyl ether has been prepared by the base-catalyzed addition of ethanol to 1-chloro-1,2,2-trifluoroethylene.[2,3,4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 423

References and Notes

1. Chemical Department, Experimental Station, E. I. du Pont de Nemours and Company, Wilmington, Delaware.
2. Hanford and Rigby, U. S. pat. 2,409,274 [*C. A.*, **41**, 982 (1947)].
3. Park, Vail, Lea, and Lacher, *J. Am. Chem. Soc.*, **70**, 1550 (1948).
4. Barr, Rapp, Pruett, Bahner, Gibson, and Lafferty, *J. Am. Chem. Soc.*, **72**, 4480 (1950).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

calcium chloride (10043-52-4)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

chlorotrifluoroethyl ethyl ether, 2-Chloro-1,1,2-trifluoroethyl ethyl ether, Ether, 2-chloro-1,1,2-trifluoroethyl ethyl (310-71-4)

Chlorotrifluoroethylene, 1-chloro-1,2,2-trifluoroethylene (79-38-9)

ethyl chlorofluoroacetate (401-56-9)

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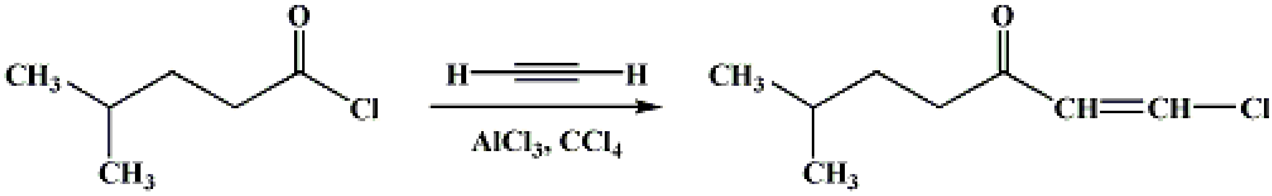
β-CHLOROVINYL ISOAMYL KETONE

[1-Hepten-3-one, 1-chloro-6-methyl-]



Submitted by Charles C. Price and Joseph A. Pappalardo[1].
Checked by R. S. Schreiber, Wm. Bradley Reid, Jr., and R. W. Jackson.

1. Procedure

Caution! This preparation should be carried out in a good hood.

A 1-l. three-necked flask fitted with a mercury-sealed stirrer, a gas inlet tube, and a gas outlet tube protected by a calcium chloride drying tower (Note 1) is surrounded by an ice-water bath. The system is flushed slowly with acetylene for 3 minutes (Note 2). Carbon tetrachloride (260 g.) (Note 3) is poured into the flask, and acetylene is bubbled through at a saturation rate for 3 minutes. Aluminum chloride (98 g., 0.74 mole) (Note 4) is added, and acetylene is bubbled continuously through the mixture with stirring for 5 minutes.

The gas inlet tube is replaced by a dropping funnel protected by a calcium chloride drying tube. Isocaproyl chloride (84.7 g., 0.63 mole) (Note 5) is added to the reaction mixture with stirring over a period of 20 minutes. The dropping funnel is replaced by the gas inlet tube (inlet tube wiped with a dry towel), and, with stirring, acetylene is bubbled just below the surface of the mixture at a rate noticeably above the saturation rate. After 15 minutes to 1 hour the rate of absorption of acetylene suddenly becomes very rapid, and the acetylene is passed through as rapidly as it is absorbed (Note 6). The introduction of acetylene is continued for 30 minutes after the rapid absorption (which lasts 1–2 hours) has subsided.

The reaction mixture is poured with stirring onto a mixture of 700 g. of crushed ice and 300 ml. of a saturated solution of sodium chloride. The organic layer is separated, and the aqueous layer is extracted with three 100-ml. portions of ether. To the combined organic layers is added 2 g. of hydroquinone, and the mixture is dried over calcium chloride (Note 7).

The liquid is decanted from the solid, and the solid is washed with 50 ml. of carbon tetrachloride. The carbon tetrachloride layers are combined and 2 g. of hydroquinone is added. The solution is then distilled from a Claisen flask at such a pressure as to maintain a distillation temperature of about 30°. When most of the solvent has been removed it is discarded, and the residue is distilled as rapidly as possible until the temperature reaches about 90° at 5 mm. Redistillation from a Claisen flask with a short Vigreux side arm gives a colorless liquid; yield 55–65 g. (54–64%) (Note 8); b.p. 96–98°/20 mm.; n_D^{25} 1.4619 (Note 9).

2. Notes

1. A rubber tube with an eye-dropper is attached to the tower. The tip of the eye-dropper is immersed in mineral oil to indicate the absorption of acetylene.

2. The reaction is carried out in a well-ventilated hood to remove excess acetylene. All subsequent operations are also carried out in the hood because the product of the reaction has an objectionable odor. The acetylene used is passed through a train consisting of an empty 300-ml. bottle, a 300-ml. bottle containing 150 ml. of concentrated sulfuric acid (through which acetylene passes by means of a gas dispersion tube), a pressure-release valve, and another empty 300-ml. bottle.

3. Carbon tetrachloride (C.P. grade) decanted from calcium chloride was used.

4. Baker and Adamson Company powdered aluminum chloride was used.

5. Eastman Kodak Company white label grade isocaproyl chloride was redistilled, and the middle 80% portion was used.

6. To keep the temperature in the immediate vicinity of the flask from rising, the ice bath should be stirred occasionally.

7. The combined organic layers should be allowed to stand in a separatory funnel about 30 minutes before drying because some additional water separates on standing.

8. The checkers consistently obtained yields of 75–76%.

9. This preparation works equally well for the isobutyl and isohexyl homologs. For β-chlorovinyl methyl ketone, which is both a lachrymator and a vesicant, the initial rapid rate of absorption of acetylene begins only after 3–9 hours.

3. Discussion

Carpmael,[2] Yakubovich and Merkulova,[3] and Price and Pappalardo[4] have used this general reaction to make β-chlorovinyl ketones from a variety of acid chlorides, employing various solvents and acidic catalysts. Bayer and Nelles[5] made β-chlorovinyl ketones by the reaction of an acid chloride and vinyl chloride.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 558

References and Notes

1. University of Notre Dame, Notre Dame, Indiana.
2. Carpmael, Brit. pat. 461,080 [*C. A.*, **31**, 4676 (1937)].
3. Yakubovich and Merkulova, *J. Gen. Chem. U.S.S.R.*, **16**, 55 (1946) [*C. A.*, **41**, 91 (1947)].
4. Price and Pappalardo, *J. Am. Chem. Soc.*, **72**, 2613 (1950).
5. Bayer and Nelles, U. S. pat. 2,137,664 [*C. A.*, **33**, 1758 (1939)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

calcium chloride (10043-52-4)

acetylene (74-86-2)

ether (60-29-7)

hydroquinone (123-31-9)

sodium chloride (7647-14-5)

carbon tetrachloride (56-23-5)

aluminum chloride (3495-54-3)

β-Chlorovinyl isoamyl ketone, 1-Hepten-3-one, 1-chloro-6-methyl- (18378-90-0)

Isocaproyl chloride (38136-29-7)

β-chlorovinyl methyl ketone

vinyl chloride (9002-86-2)

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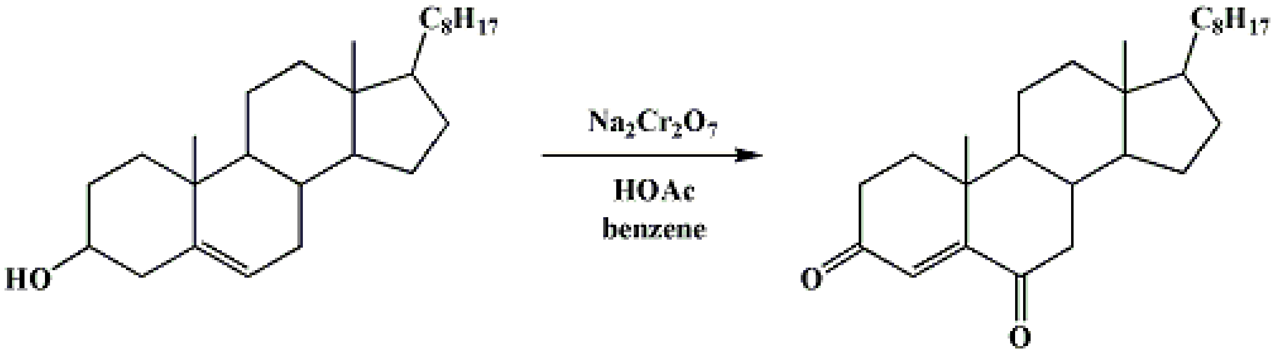
Δ4-CHOLESTEN-3,6-DIONE

[Cholest-4-ene-3,6-dione]



Submitted by Louis F. Fieser[1]
Checked by William S. Johnson and David G. Martin.

1. Procedure

A 500-ml. Erlenmeyer flask containing 64 g. (10 oxygen equivalents) of sodium dichromate dihydrate and 225 ml. of acetic acid is heated and swirled until all the solid has dissolved, and then is cooled in an ice bath to bring the temperature of the solution to 15°. In a 1-l. Erlenmeyer flask 25 g. (0.065 mole) of commercial cholesterol is dissolved in 225 ml. of benzene by brief warming, and the solution is cooled to 20°; 225 ml. of acetic acid is added, the solution is cooled to 15°, and the dichromate solution (at 15°) is poured in, whereupon a thick orange paste of cholesteryl chromate, $(C_{27}H_{45}O)_2CrO_2$, separates. The flask is immersed in an ice-water bath that is allowed to stand in a refrigerator for 40–48 hours. No stirring or other attention is required in this period; the temperature soon drops to 0° (Note 1), and the chromate dissolves in a few hours.

The resulting brown solution is poured into a separatory funnel and shaken with 225 ml. of 30–60° petroleum ether. After brief standing, the mixture when viewed against a strong light can be seen to have separated into a reddish upper hydrocarbon layer and a smaller, very dark lower layer containing chromium compounds and acetic acid. The lower layer is drawn off and discarded. Then 50 ml. of water is added to the hydrocarbon layer, and the mixture is shaken and allowed to settle. Another lighter-colored, lower layer is drawn off and discarded, and the process is repeated with 50 ml. more water. The hydrocarbon layer, now light in color, is then shaken with 110 ml. of Claisen's alkali (Note 2); this first portion neutralizes the residual acetic acid and acidic oxidation products and extracts some of the enedione as the yellow enolate. The funnel is allowed to stand, with occasional twirling, until the lower layer has settled to a clear yellow solution; the upper hydrocarbon layer acquires a dirty red-brown color. The extract is drawn off into a wide-mouthed 2-l. separatory funnel charged with 200 ml. of water, 600 g. of ice, 200 ml. of 36% hydrochloric acid, and 300 ml. of ether (Note 3). The hydrocarbon layer is extracted in the same way with five more 100-ml. portions of Claisen's alkali and then discarded (Note 4).

After the last alkaline extract has been run into the receiving funnel, this is shaken and the

aqueous layer is drawn off and discarded. The light-yellow ethereal layer is run into a smaller funnel and shaken with 100 ml. of 5% sodium carbonate solution and 30 ml. of saturated sodium chloride solution (Note 5). This extraction is repeated a second time (Note 6). The carbonate extract is either discarded or worked up for recovery of acidic oxidation products (Note 7). The ethereal solution is finally shaken with 100 ml. of saturated sodium chloride solution, filtered into a round-bottomed flask (Note 8) by gravity through a paper containing 25 g. of anhydrous magnesium sulfate, and evaporated to dryness. The residue is initially an oil, but when the last traces of solvent are removed by evacuating the flask (Note 8), reheating, and re-evacuating, it is obtained as a yellow solid (about 13 g.). This is taken up in 125 ml. of boiling methanol, and crystallization is allowed to proceed, first at room temperature and then at 0°. Δ^4-Cholesten-3,6-dione separates in glistening, thin, yellow plates, m.p. 124–125°; yield in the first crop, 9.0–9.3 g. Concentration of the filtrate affords a second crop of 0.7–1.2 g., melting in the range 118–121.5°; total yield, 10.0–10.2 g. (39–40%).

2. Notes

1. The temperature of the oxidation is highly critical. When the mixture, initially at 15°, is allowed to stand in a refrigerator at an air temperature of 4–8°, the temperature of the reaction mixture during the first 7 hours is in the range 18–5° (exothermic); yields of enedione after varying reaction periods are as follows: 7 hours, 27%; 15–22 hours, 32.5% (less-pure product). At 25° the enedione is oxidized completely to acids in about 18 hours.
2. Sufficient Claisen's alkali for one run is made by dissolving 175 g. of potassium hydroxide pellets in 125 ml. of distilled water, cooling to room temperature, adding 500 ml. of methanol, and again cooling; this gives 655–665 ml. of solution.
3. Δ^4-Cholesten-3,6-dione is sensitive to air oxidation under certain conditions, particularly in alkaline solution. If the protective procedure specified is not followed the reaction product may be deep red and tarry.
4. The residual solution contains a little cholesterol, 0.2–0.3 g. of Δ^4-cholesten-3,6-dione, and small amounts of products derived from the oxidation of cholestanol and other companions.
5. Sodium chloride speeds up the separation of layers.
6. The sodium carbonate extract contains only a few milligrams of the enedione.
7. The oxidation procedure described affords a mixture of acids from which no component is easily isolable. When the oxidation is allowed to proceed in the temperature range 18-5° for 15–22 hours, as described in (Note 1), isolation of the Diels acid (3,4-seco-Δ^5-cholesten-3,4-dioic acid) is easily accomplished as follows. The carbonate extract is acidified and shaken with ether, and the clear aqueous layer is discarded. The ethereal solution, which may contain some suspended Diels acid, is not dried but is run into a flask and diluted with an equal volume of acetone. The mixture is evaporated to a volume of 15–20 ml. and cooled, and the Diels acid is collected as a white powder, m.p. 280–285°; yield 0.5 g.
8. A round-bottomed flask is recommended in order to withstand the evacuation process.

3. Discussion

Mauthner and Suida[2] isolated, as one of three neutral products resulting from the oxidation of cholesterol with aqueous chromic acid in acetic acid solution, the substance later identified as Δ^4-cholesten-3,6-dione. The present procedure is based upon results of a reinvestigation of the oxidation by a low-temperature, non-aqueous procedure.[3]

References and Notes

1. Harvard University, Cambridge 38, Massachusetts.
2. Mauthner and Suida, *Monatsh.*, **17**, 579 (1896); Windaus, *Ber.*, **39**, 2249 (1906); Ross, *J. Chem. Soc.*, **1946**, 737.
3. Fieser, *J. Am. Chem. Soc.*, **75**, 4386 (1953).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

Δ^4-Cholesten-3,6-dione

3,4-seco-Δ^5-cholesten-3,4-dioic acid

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

methanol (67-56-1)

ether (60-29-7)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

oxygen (7782-44-7)

acetone (67-64-1)

potassium hydroxide (1310-58-3)

chromic acid (7738-94-5)

magnesium sulfate (7487-88-9)

cholestanol (80-97-7)

Cholesterol (57-88-5)

sodium dichromate dihydrate (10588-01-9)

cholesten-3,6-dione

Cholest-4-ene-3,6-dione (984-84-9)

cholesteryl chromate

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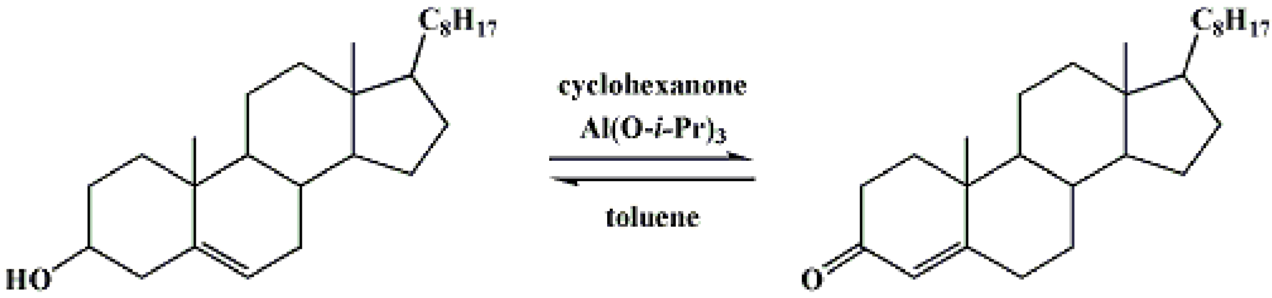
Δ4-CHOLESTEN-3-ONE

[Cholest-4-en-3-one]



Submitted by Jerome F. Eastham and Roy Teranishi[1].
Checked by James Cason, James Jiu, and Elmer J. Reist.

1. Procedure

To a 5-l. three-necked flask, equipped with a sealed mechanical stirrer, a dropping funnel, and a take-off reflux condenser, are added 2 l. of sulfur-free toluene and two boiling chips. The openings of the dropping funnel and the condenser are protected by drying tubes containing Drierite. A portion (200 ml.) of the toluene is distilled from the flask (take-off cock open) in order to dry the system by azeotropic distillation; then 100 g. (0.26 mole) of cholesterol and 500 ml. of cyclohexanone (Note 1) are added to the flask. After an additional 50 ml. of toluene has been distilled, a solution of 28 g. (0.14 mole) of aluminum isopropoxide (Note 2) in 400 ml. of dry toluene (Note 3) is added dropwise over a period of approximately 30 minutes. During this time toluene is distilled at a rate slightly greater than the rate of addition of catalyst solution, so that when the addition is complete about 600 ml. of toluene has distilled. An additional 300 ml. of toluene is distilled, and the murky orange-colored reaction mixture is then allowed to cool to room temperature.

Four hundred milliliters of a saturated aqueous solution of potassium-sodium tartrate (Note 4) is added to the mixture, and the organic layer becomes clear and orange. The stirrer assembly is removed, and the mixture is steam-distilled until about 6 l. of distillate has been collected. The residual mixture is cooled and extracted successively with one 300-ml. portion and two 100-ml. portions of chloroform. The combined extracts are washed with two 100-ml. portions of water and dried over anhydrous magnesium sulfate. The chloroform is removed by distillation on the steam bath at reduced pressure (water aspirator). The residual viscous amber oil (Note 5) is dissolved by heating in 150 ml. of methanol. When the solution has cooled to about 40°, seeds of cholestenone are added, and the flask is wrapped with a small towel to ensure slow cooling (Note 6). After the bulk of the material has crystallized, which requires several hours, the mixture is stored at 0° overnight (Note 7). The product is collected by suction filtration, washed with 40–50 ml. of methanol previously cooled in an ice-salt bath, then dried at reduced pressure, first at room temperature and finally at 60°. The yield of light-cream-colored Δ^4-cholesten-3-one is 81–93 g. (81–93%), m.p. 76–79°. Recrystallization from methanol gives material melting at 79.5–80.5° in 90% recovery (Note 8).

2. Notes

1. Commercial cholesterol, m.p. 146–149°, is satisfactory if dried at reduced pressure at 100° for 48 hours. The cyclohexanone is simply distilled before use, b.p. 153–155°.
2. Directions for the preparation of aluminum isopropoxide are given by Young, Hartung, and Crossley.[2] This compound is also commercially available. Turbidity of the catalyst solution is to be expected and is not detrimental.
3. Toluene is dried satisfactorily by distilling about 20% of it and using the residue, which is cooled with protection from moisture.
4. Either Rochelle or Seignette salt is satisfactory. The tartrate ion serves to keep the aluminum ion in solution.
5. Prolonged heating is not necessary, since the chloroform remaining with the residual oil does not hamper the crystallization.
6. Seed crystals may be obtained by transferring a few drops of the solution to a small test tube, then cooling and scratching.

Ordinarily the cholestenone will separate as an oil from a solution saturated much above 50°. In this event, rather than working with larger volumes of methanol, small portions of chloroform may be added to the solution to lower the saturation temperature to a point at which seed crystals do not turn to oil. The best yield of good crystalline product is realized by inducing crystallization at the highest possible temperature in order to obtain a large initial crop of crystals. A second crop is difficult if not impossible to obtain by direct crystallization.

The towel should be placed around the flask only after crystallization, rather than oil formation, is assured. The towel is carefully removed occasionally during the first hour to ascertain whether oil is forming on top of the crystals. If so, the solution is warmed slightly in order to redissolve the oil but not the crystals. The product is quite impure if it first separates as an oil which later crystallizes.

7. If initial crystallization is not induced at 40° or above, a further period of cooling in an ice-salt bath is necessary to obtain the best yield.
8. In order to avoid large volumes, it is recommended that 700 ml. of methanol be employed to recrystallize 90 g. of cholestenone and that either chloroform or acetone be used to increase the solubility of the cholestenone to the required amount.

3. Discussion

The methods of preparation of Δ^4-cholesten-3-one have been summarized in an earlier volume.[3] In addition, it has been obtained by the deacetylation of 3-acetoxy-3,5-cholestadiene.[4] The present modification is less laborious than the earlier[3] method.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 195
- Org. Syn. Coll. Vol. 6, 293
- Org. Syn. Coll. Vol. 6, 762

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Δ^4-Cholesten-3-one

methanol (67-56-1)

chloroform (67-66-3)

Cyclohexanone (108-94-1)

acetone (67-64-1)

toluene (108-88-3)

aluminum isopropoxide

magnesium sulfate (7487-88-9)

Cholesterol (57-88-5)

Cholestenone

Cholest-4-en-3-one (601-57-0)

potassium-sodium tartrate

3-acetoxy-3,5-cholestadiene

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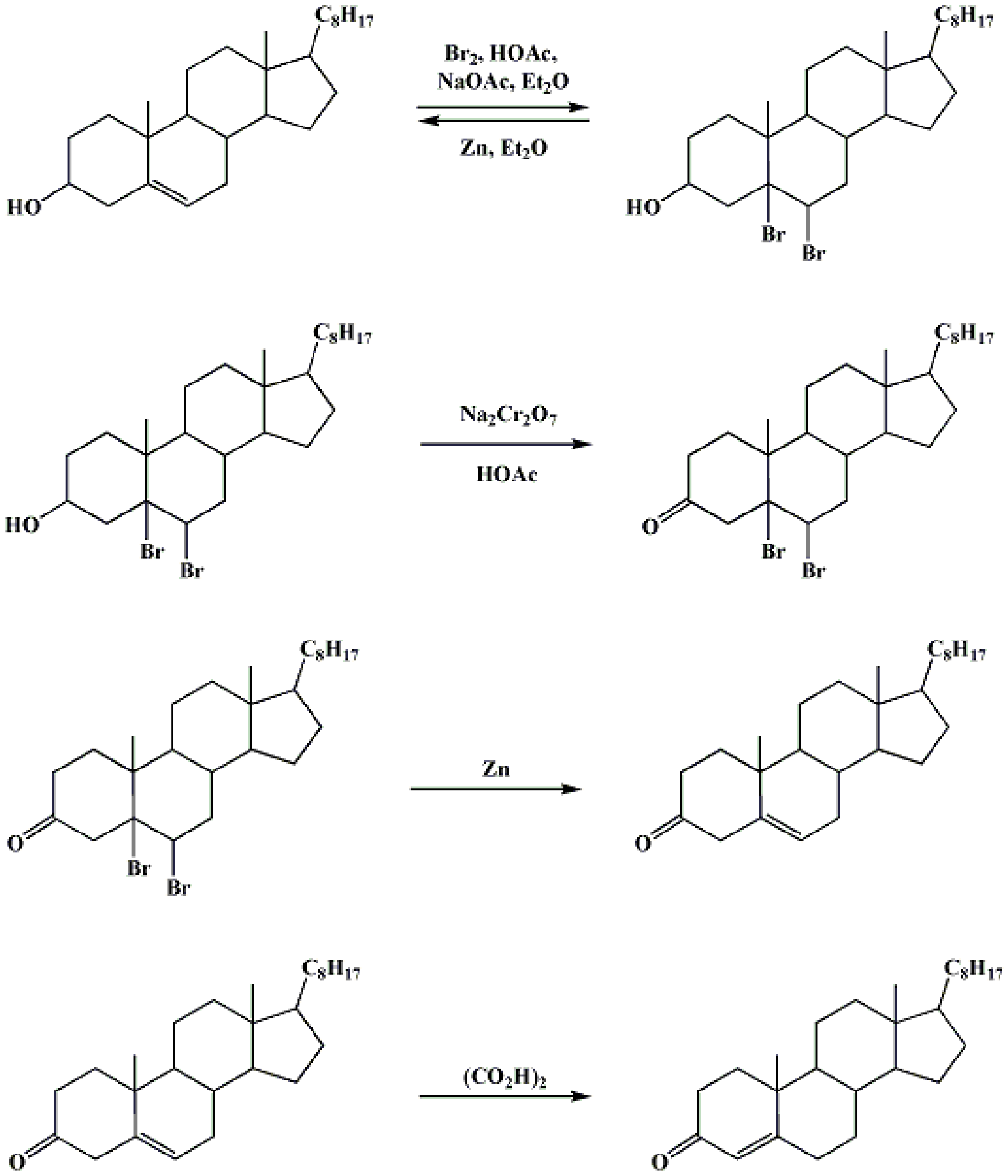
Organic Syntheses, CV 4, 195

CHOLESTEROL, Δ5-CHOLESTEN-3-ONE, AND Δ4-CHOLESTEN-3-ONE

[Cholesterol, Cholest-5-en-3-one, and Cholest-4-en-3-one]



Submitted by Louis F. Fieser[1]
Checked by William S. Johnson and David G. Martin.

1. Procedure

A. *Cholesterol dibromide*. In a 4-l. beaker 150 g. (0.39 mole) of commercial cholesterol (Note 1) is dissolved in 1 l. of absolute ether by warming on the steam bath and stirring with a stout glass rod; the solution is then cooled to 25°. A second solution is prepared by adding 5 g. of powdered anhydrous sodium acetate (0.06 mole) (Note 2) to 600 ml. of acetic acid, stirring the mixture and breaking up the lumps with a flat stirring rod; 68 g. (0.4 mole) of bromine is then added and the solution is poured with stirring into the cholesterol solution. The solution turns yellow and promptly sets to a stiff paste of dibromide. The mixture is cooled in an ice bath to 20°, and then the product is collected on a 16-cm. Büchner funnel (Note 3). The cake is pressed down and washed with acetic acid until the filtrate is completely colorless; 500 ml. is usually sufficient. A second crop of satisfactory dibromide is obtained by adding 800 ml. of water to the combined filtrate and washings, collecting the precipitate, and washing it with acetic acid until colorless. Dibromide moist with acetic acid is satisfactory for most transformations; dry dibromide, even when highly purified by repeated crystallization, begins to decompose (darkens) within a few weeks. When material prepared as described is dried to constant weight at room temperature, it is obtained as the 1:1 dibromide/acetic acid complex. Yields obtained in the first and second crops, respectively, are: 171–186 g. and 13–25 g., total yield 197–199 g. (84–85%) (Note 1).

B. *Cholesterol from the dibromide.* The acetic acid-moist filter cake of dibromide from 150 g. of cholesterol is transferred (Note 3) to a 3-l. round-bottomed flask and covered with 1.2 l. of U.S.P. ether, and the suspension is stirred mechanically above a bucket of ice and water that can be raised as required (Note 4), (Note 5). Forty grams (0.61 g. atom) of fresh zinc dust is added in the course of 5 minutes. The first 5- to 10-g. portion is added without cooling; when the reaction has started, as evidenced by solution of part of the dibromide and by ebullition, the cooling bath is raised during the remainder of the addition. At the end, the ice bath is lowered, and the mixture, which soon sets to a paste of white solid (Note 6), is stirred for 15 minutes longer. Then 50 ml. of water is added to dissolve the white solid, and the ethereal solution is decanted into a separatory funnel and washed with 400 ml. of water containing 25 ml. of 36% hydrochloric acid. After three more washings with 400-ml. portions of water, the solution is shaken thoroughly with 300 ml. of water and 150 ml. of 25% sodium hydroxide solution, and the ethereal solution is tested with moist blue litmus paper to make sure that all the acetic acid is removed (Note 7). The solution is then dried over magnesium sulfate and evaporated to a volume of 600 ml., methanol (600 ml.) is added, and the solution is evaporated to the point where crystallization just begins (about 1 l.). After standing at room temperature and then at 0–4°, the main crop of cholesterol is collected and dried at room temperature; yield 108–110 g., m.p. 149.5–150° (Note 8). A second crop of 8.4–10.4 g., m.p. 148–149°, is obtained after evaporation of the mother liquor to a volume of 250 ml. (Note 9); total yield 117–120 g. (78–80% from commercial cholesterol) (Note 10).

C. *5α,6β-Dibromocholestan-3-one*. The moist dibromide from 150 g. of cholesterol (part A) is suspended in 2 l. of acetic acid in a 5-l. round-bottomed flask equipped with a stirrer and mounted over a bucket of ice and water that later can be raised to immerse the flask (Note 5). The suspension is stirred at room temperature (25–30°), and a solution, preheated to 90°, of 80 g. (2 oxygen equivalents) of sodium dichromate dihydrate in 2 l. of acetic acid is poured in through a funnel (Note 3). The mixture reaches a temperature of 55–58° during the oxidation, and all the solid dissolves in 3–5 minutes. After another 2 minutes the ice bucket is raised until the flask is immersed; stirring is then stopped, and the mixture is allowed to stand in the ice bath without disturbance for 10 minutes to allow the dibromoketone to separate in easily filterable crystals. With stirring resumed, the temperature is brought to 25° and then, after addition of 400 ml. of water, to 15°. The product is collected on a 21-cm. Büchner funnel, and the filter cake is drained until the flow of filtrate amounts to no more than 25 drops per minute. The suction is released, the walls of

the funnel are washed down with methanol, and 200 ml. of methanol is added. After a few minutes' standing, suction is applied and the crystals are drained thoroughly of solvent before they are washed in the same way with 200 ml. of fresh methanol. The last drops of filtrate should be completely colorless. Dried to constant weight at room temperature in a dark cupboard, the dibromoketone consists of shiny white crystals, m.p. 73–75° (dec.), $[\alpha]_D^{25}$ –47° chloroform (*c* = 2.11) (Note 11); yield about 171 g. (96% in the oxidation or 81% from cholesterol).

D. Δ^5-*Cholesten-3-one*. (Note 12) The moist 5α,6β-dibromocholestan-3-one from 150 g. of cholesterol is transferred to a 3-l. round-bottomed flask and covered with 2 l. of U.S.P. ether and 25 ml. of acetic acid. The suspension is stirred mechanically, and ice bath is raised into position (Note 5), and the temperature is brought to 15°. The ice bath is then lowered, and 5 g. of fresh zinc dust is added. As soon as the exothermic reaction of debromination sets in, the temperature is controlled to 15–20° by cooling during the addition (in about 5 minutes) of 35 g. more zinc dust. The ice bath is then lowered, and the ethereal solution containing suspended zinc dust is stirred for 10 minutes longer. With continued stirring, 40 ml. of pyridine is added; this precipitates a white zinc salt (Note 13). The mixture is filtered through a Büchner funnel, and the filter cake is washed well with ether. The colorless filtrate is washed with three 600-ml. portions of water and then shaken thoroughly with 600 ml. of 5% aqueous sodium bicarbonate solution until free from acetic acid as indicated by testing the ethereal solution with moist blue litmus paper. The solution is dried over magnesium sulfate and evaporated to a volume of about 1 l.; 500 ml. of methanol is added, and the evaporation is continued until the volume is approximately 1.2 l. Crystallization is allowed to proceed at room temperature, then at 0–4°, and the large colorless prisms are collected by suction filtration; yield in the first crop 87–94 g., melting point in the range 124–129° (camphorlike odor), $[\alpha]_D^{25}$ –2.5° chloroform (*c* = 2.03), no selective absorption at 242 m•. Concentration of the mother liquor gives a second crop of 12–19 g. melting in the range 117–125° and suitable for conversion to Δ^4-cholesten-3-one; total yield 106–108 g. (71–72% from cholesterol).

E. Δ^4-*Cholesten-3-one*. A mixture of 100 g. of Δ^5-cholesten-3-one (0.26 mole), 10 g. (0.11 mole) of anhydrous oxalic acid (Note 14), and 800 ml. of 95% ethanol is heated on the steam bath until all the solid is dissolved (15 minutes) and for 10 minutes longer, and then is allowed to stand at room temperature. If crystallization has not started after a period of several hours, the solution is seeded or scratched. After crystallization has proceeded at room temperature and then at 0–4°, the large, colorless, prismatic needles that separate are collected by suction filtration; yield in the first crop 88–92 g., m.p. 81–82°, $[\alpha]_D^{25}$ 92° chloroform (*c* = 2.01); $\lambda_{max.}^{ethanol}$ 242 m• (ε = 17,000). A second crop (5.0–7.5 g., melting in the range 78–82°) is obtained after concentration of the mother liquor to a volume of about 100 ml., and a third crop (3–4 g., low melting) by dilution with water. Recrystallization of these crops from 95% ethanol gives a total of 6.8–8.1 g. of satisfactory material, m.p. 81–82°; total yield 96–98 g. (68–69% over-all yield from cholesterol).

2. Notes

1. Cholesterol of high quality and of recent production was employed. Cholesterol undergoes slow autoxidation in the solid state, and samples that have been in storage for a few years give lower yields of dibromide. The checkers used U.S.P. material, m.p. 149–150°, as supplied by Wilson Company, Chicago, Illinois.
2. The yield of dibromide dropped from 84% to 73% when no buffering sodium acetate was used. No improvement resulted from doubling the quantity of sodium acetate specified. Buffered bromination in a stirred suspension of acetic acid (no ether) at 20° raised the yield to 89%, but this material on debromination afforded sterol of low melting point (145–147°) containing halogen (Beilstein test).

3. The operation should be done in a hood, and the hands should be protected with Neoprene gloves.
4. If dry dibromide is used, 25 ml. of acetic acid is added to the suspension.
5. The ice bucket is conveniently mounted on an automobile jack.
6. The solid appears to be a complex of cholesterol and a zinc salt.
7. If the acetic acid is not removed some cholesteryl acetate may be formed during the evaporation.
8. The melting-point determination should be done in an evacuated capillary tube. In an open tube autoxidation occurs readily enough to lower the melting point when the bath is heated very slowly.
9. The residual mother liquor contains about 4 g. of material containing bromine not removed by repetition of the treatment with zinc dust.
10. Purification of cholesterol through the dibromide completely eliminates cholestanol, 7-dehydrocholesterol, and lathosterol (Δ^7-cholestenol). The first crop of material from methanol-ether is also free from cerebrosterol (24-hydroxycholesterol) and 25-hydroxycholesterol, a product of autoxidation present in cholesterol that has been stored in the crystalline state for a few years with access to air. When material of highest purity is desired, only first-crop dibromide should be employed, since debromination of second-crop material gives sterol melting at 146–147° and giving a positive Beilstein test.
11. Dibromocholestanone sometimes begins to decompose (turns purplish) after standing in the dark for a few hours; it rapidly darkens when dried at 70° or when exposed to bright sunlight. Hence it is advisable to use the material moist with methanol directly after preparation.
12. For success in the preparation of this labile non-conjugated ketone in high yield and purity, the intermediates, cholesterol dibromide and dibromocholestanone, should be processed further in the solvent-moist state as soon as prepared. The three reactions can be completed easily in one day.
13. If the bulk of the ionic zinc is not precipitated at this point it will cause troublesome emulsions when the solution is washed with water.
14. When isomerization of 100-g. batches of non-conjugated ketone was effected in ethanol under catalysis by either hydrochloric acid or sodium hydroxide (followed by neutralization of the yellow enolate solution with acetic acid), a permanent yellow coloration developed, the first-crop material was yellowish and melted at 78–80°, and the second-crop material was very impure.

3. Discussion

Cholesterol dibromide has been prepared by unbuffered[2] and buffered[3] bromination of cholesterol and oxidized to 5α,6β-dibromocholestan-3-one with acid permanganate,[2] chromic acid,[4,5,6] and sodium dichromate.[3] Regeneration of sterols, or more usually of sterol acetates, from their dibromides has been accomplished by use of zinc dust in boiling acetic acid,[2] sodium iodide,[7] ferrous chloride,[8] and chromous chloride,[9] and by the method[3] here described. Δ^5-Cholesten-3-one has been prepared by debromination of dibromocholestanone with zinc dust in boiling ethanol or methanol[5] and by zinc dust in ether containing a little acetic acid.[3]

The Oppenauer oxidation of cholesterol to Δ^4-cholesten-3-one of m.p. 77–79° in 70–93% yield has been reported in these volumes (p. 192).[10] Isomerization of Δ^5-cholesten-3-one by a mineral acid or a base has been conducted satisfactorily only on a micro scale;[5] the method of isomerization

with oxalic acid has been reported.[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 293

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Δ^4-Cholesten-3-one

Δ^5-Cholesten-3-one

7-dehydrocholesterol

lathosterol

Δ^7-cholestenol

cerebrosterol

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

methanol (67-56-1)

ether (60-29-7)

sodium acetate (127-09-3)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium bicarbonate (144-55-8)

bromine (7726-95-6)

oxygen (7782-44-7)

Oxalic acid (144-62-7)

pyridine (110-86-1)

zinc (7440-66-6)

chromic acid (7738-94-5)

sodium dichromate (7789-12-0)

sodium iodide (7681-82-5)

magnesium sulfate (7487-88-9)

cholestanol (80-97-7)

Cholesterol (57-88-5)

Cholesteryl acetate (604-35-3)

sodium dichromate dihydrate (10588-01-9)

Cholesterol dibromide (1857-80-3)

Cholest-4-en-3-one (601-57-0)

Cholest-5-en-3-one (601-54-7)

5α,6β-dibromocholestan-3-one (2515-09-5)

24-hydroxycholesterol

25-hydroxycholesterol

Dibromocholestanone

ferrous chloride (7758-94-3)

chromous chloride (10049-05-5)

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Organic Syntheses, CV 4, 201

COUMALIC ACID

Submitted by Richard H. Wiley and Newton R. Smith[1,2].
Checked by C. F. H. Allen and George A. Reynolds.

1. Procedure

In a 2-l. round-bottomed flask are placed 200 g. (1.49 moles) of powdered malic acid (Note 1) and 170 ml. of concentrated sulfuric acid. To this suspension are added three 50-ml. portions of 20–30% fuming sulfuric acid at 45-minute intervals. After the evolution of gas has slackened, the solution is heated on a water bath for 2 hours with occasional shaking. The reaction mixture is then cooled and poured slowly onto 800 g. of crushed ice with stirring. After standing 24 hours, the acid is filtered on a Büchner funnel, washed with three 50-ml. portions of ice-cold water, and dried on a water bath. The yield of crude acid, melting at 195–200°, is 75–80 g. (Note 2) and (Note 3).

One-half of the crude product is dissolved in five times its weight of hot methanol, and the solution is boiled with 3 g. of Norit or decolorizing carbon. The solution is filtered while hot and cooled in an ice bath. The precipitate is collected on a filter and washed with 25 ml. of cold methanol. The mother liquors are used to recrystallize the remaining crude material. The yield of bright yellow coumalic acid, melting at 206–209°, is 68–73 g. (65–70%) (Note 4).

2. Notes

1. A technical free-flowing powder, melting at 126–128°, was used.
2. This washing is essential to remove the mineral acid and to avoid partial esterification that otherwise takes place during the methanol recrystallization step.
3. The submitters state that an additional 10–12 g. of crude acid can be obtained from the filtrate by extraction with ether in a continuous extractor.
4. Depending on the color of the crude acid, several additional recrystallizations may be required to obtain a colorless product.

3. Discussion

This procedure is essentially that of von Pechmann.[3] Esters of coumalic acid may be obtained by heating the sulfuric acid solution with the appropriate alcohol.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 532
- Org. Syn. Coll. Vol. 5, 982

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2. The submitters wish to thank the Research Corporation for a grant under which this work was done.
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

methanol (67-56-1)

ether (60-29-7)

carbon, Norit (7782-42-5)

malic acid (617-48-1)

Coumalic acid (500-05-0)

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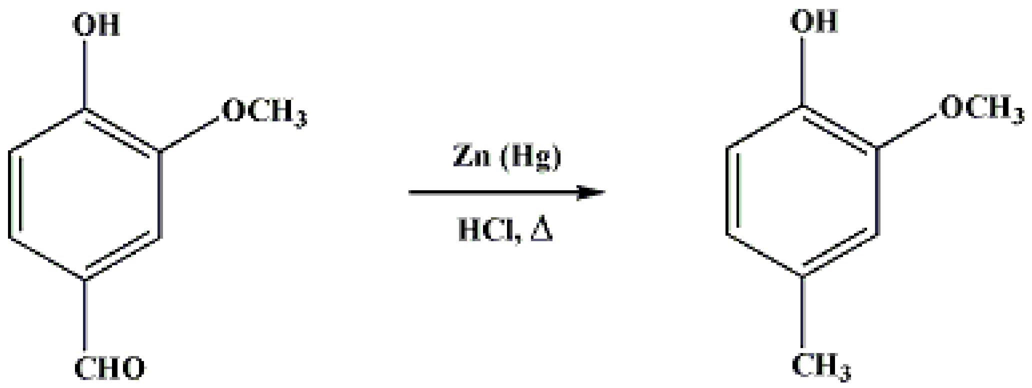
Organic Syntheses, CV 4, 203

CREOSOL



Submitted by R. Schwarz and H. Hering[1].
Checked by R. L. Shriner and C. L. Furrow, Jr..

1. Procedure

In a 5-l. three-necked flask fitted with a stopper, a reflux condenser, and a 250-ml. dropping funnel are placed 1.5 kg. (22.9 g. atoms) of amalgamated zinc (Note 1) and 800 ml. of concentrated hydrochloric acid. The flask is heated to cause gentle refluxing to occur. A solution of 152 g. (1.0 mole) of vanillin in 450 ml. of 95% ethanol and 1.5 l. of concentrated hydrochloric acid (Note 2) is added dropwise through the dropping funnel over an 8-hour period (Note 3). After the addition of the vanillin is complete the mixture is refluxed for 30 minutes more. The liquid, consisting of two layers, is decanted from the zinc (Note 4) into a 4-l. separatory funnel. The aqueous layer is removed and washed three times with 200-ml. portions of benzene, and the benzene extracts are combined with the crude creosol separated initially. The residual amalgamated zinc is washed twice with 100-ml. portions of benzene, and this benzene solution is added to the combined extracts. The extracts are washed twice with 200-ml. portions of 5% sodium bicarbonate solution, and the resultant precipitate of metallic salts is removed by filtration. The solution is washed once with 200 ml. of water.

The benzene is removed under reduced pressure by distillation on a steam bath. The residue is distilled under reduced pressure, the fraction boiling at 78–79°/4 mm., at 104–105°/15 mm., or at 219–222.5°/760 mm. being collected. A yield of 83–92.5 g. (60–67%) of colorless or pale yellow creosol is obtained, d_4^{25} , 1.092; n_D^{20} 1.5354 (Note 5) and (Note 6).

2. Notes

1. The amalgamated zinc may be prepared by adding 1500 g. of clean granulated zinc to 600 ml. of 5% mercuric chloride solution. After standing for 2 hours

with occasional shaking, the liquid is decanted and the zinc is used immediately. Alternatively,[2] 1500 g. of granulated zinc is added to a solution of 62.5 g. of mercuric chloride and 62.5 ml. of concentrated hydrochloric acid in 1875 ml. of water. The mixture is shaken for about 5 minutes, the liquid decanted, and the zinc used immediately.

2. The vanillin is first dissolved in ethanol by warming gently, and then 1.5 l. of concentrated hydrochloric acid (*d* = 1.19) is added. A clear yellow solution is obtained, which soon becomes blue-green.

3. It is advisable to avoid overheating the upper parts of the flask to prevent some brown-red tarry masses from forming.

4. The recovered zinc (900–950 g.) can be used for further preparations by adding more zinc and renewing amalgamation.

5. The submitters report yields up to 103 g. (75%), but this yield could not be consistently obtained by the checkers.

6. The reduction of vanillin by the Clemmensen method using toluene as an auxiliary solvent has been reported.[3] By following these directions, a yield of 49% of creosol was obtained with large amounts of tar.

3. Discussion

creosol (also called 2-methoxy-*p*-cresol, 4-methylguaiacol, and 3-methoxy-4-hydroxytoluene) has been obtained by the fractionation of beach creosote tar,[4] by the reduction of vanillin by electrolytic methods,[5,6] by hydrogen and palladium on charcoal or barium sulfate,[7,8] with hydrazine,[9] and by amalgamated zinc and hydrochloric acid.[3,10,11] It has also been prepared by methylation of 4-methylcatechol with methyl iodide[12,13] or with methyl sulfate[14] and is reported to be formed by the distillation of the calcium salt of 3-methoxy-4-hydroxyphenylacetic acid.[15]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

hydrogen (1333-74-0)

sodium bicarbonate (144-55-8)

barium sulfate (7727-43-7)

toluene (108-88-3)

zinc (7440-66-6)

palladium (7440-05-3)

mercuric chloride (7487-94-7)

Methyl iodide (74-88-4)

methyl sulfate (75-93-4)

hydrazine (302-01-2)

vanillin (121-33-5)

3-methoxy-4-hydroxytoluene (93-51-6)

4-methylcatechol (452-86-8)

2-methoxy-p-cresol, 4-methylguaiacol

Creosol (93-51-6)

calcium salt of 3-methoxy-4-hydroxyphenylacetic acid

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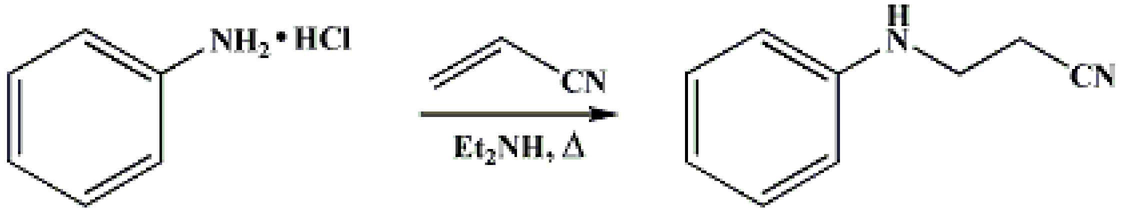
Organic Syntheses, CV 4, 205

N-2-CYANOETHYLANILINE

[Propionitrile, 3-anilino-]



Submitted by J. Cymerman-Craig and M. Moyle[1].
Checked by William S. Johnson and Duff S. Allen, Jr..

1. Procedure

A mixture of 12.95 g. (0.10 mole) of aniline hydrochloride (Note 1), 6.6 g. (0.12 mole) of acrylonitrile, and 9.1 g. (0.12 mole) of diethylamine (Note 2) is placed in a 100-ml. round-bottomed flask fitted with an efficient reflux condenser and heated for 2.5 hours in a bath maintained at 180°.

The melt is cooled to 0°, 50 ml. of 10% aqueous sodium hydroxide solution is added, and the mixture is extracted with four 50-ml. portions of chloroform. The combined chloroform extracts are washed with two 25-ml. portions of water, and these in turn are extracted with 10 ml. of chloroform. The organic layers are combined and dried partially over anhydrous sodium sulfate. The solvent is removed by distillation on the steam bath, and the residue is distilled at reduced pressure from a 50-ml. distilling flask. After a fore-run of about 4 g. (Note 3), b.p. 60–70°/1.5 mm. (bath temperature taken up to 125°), the cyanoethylaniline is collected at 115–120°/0.01 mm. The product solidifies in the form of colorless plates, m.p. 48–51° (Note 4). The yield is 10.5–11.4 g. (72–78%) (Note 5).

2. Notes

1. An equimolar quantity of aniline benzenesulfonate may be used in place of the hydrochloride.
2. No reaction occurs if the diethylamine is omitted.
3. In a typical run this fraction weighed 4.4 g. and contained 1.6 g. of aniline (estimated as acetanilide) and 2.8 g. of 3-diethylaminopropionitrile.
4. Reported properties are b.p. 178–186°/16 mm. and m.p. 51.5°.[2]
5. The submitters have found that other arylamines may be employed in a similar manner in place of aniline. Thus N-2-cyanoethyl-*p*-anisidine was obtained in 76% yield as plates, m.p. 62–64°, b.p. 130–140°/0.01 mm.; N-2-cyanoethyl-*m*-chloroaniline, in 42% yield as needles, m.p. 44–46°, b.p. 125–

130°/0.01 mm.; N,N'-bis-2-cyanoethyl-*o*-phenylenediamine, in 70% yield as needles, m.p. 116–118°, b.p. 190–200°/0.01 mm.; and N,N'-bis-2-cyanoethyl-*p*-phenylenediamine in 22% yield as plates, m.p. 138–139°.

3. Discussion

N-2-Cyanoethylaniline has been prepared (accompanied by much of the N,N'-bis-2-cyanoethyl compound) by heating aniline, acrylonitrile, and acetic acid in an autoclave,[2,3] or at refluxing temperature for 10 hours in the presence of various inorganic catalysts.[4] The substance also has been obtained, free of the N,N'-bis-2-cyanoethyl compound from aniline salts and β-diethylaminopropionitrile.[5,6,7] A number of other cyanoethylated compounds have been heated with aniline and water to form N-2-cyanoethylaniline,[8] and a study has been made of the conditions for the addition of aromatic amines to acrylonitrile.[9]

Heininger[10] has shown that cupric acetate is a superior catalyst for the cyanoethylation of aniline; N-2-cyanoethylaniline has been obtained in 73% yield by this method. The use of cupric acetate as a catalyst in cyanoethylation is demonstrated in the procedure for the preparation of 3-(*o*-chloroanilino) propionitrile (p. 146).

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 146

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

acetic acid (64-19-7)

aniline (62-53-3)

Acetanilide (103-84-4)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium sulfate (7757-82-6)

aniline hydrochloride (142-04-1)

cupric acetate (142-71-2)

diethylamine (109-89-7)

acrylonitrile (107-13-1)

3-diethylaminopropionitrile, β-diethylaminopropionitrile (5351-04-2)

N-2-Cyanoethylaniline, Propionitrile, 3-anilino-, cyanoethylaniline (1075-76-9)

aniline benzenesulfonate

3-(o-chloroanilino) propionitrile (94-89-3)

N-2-cyanoethyl-p-anisidine

N-2-cyanoethyl-m-chloroaniline

N,N'-bis-2-cyanoethyl-o-phenylenediamine

N,N'-bis-2-cyanoethyl-p-phenylenediamine

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CYANOGEN IODIDE

[Iodine cyanide]

$$NaCN + I_2 \xrightarrow[Et_2O]{H_2O} ICN + NaI$$

Submitted by B. Bak and A. Hillebert[1].
Checked by R. T. Arnold and H. E. Fritz.

1. Procedure

Caution! Cyanogen iodide is relatively volatile and highly toxic. Therefore, these operations should be conducted in a good hood.

A three-necked 500-ml. flask is surrounded by an ice-water bath and provided with a stirrer and thermometer. Twenty-seven grams (0.55 mole) of sodium cyanide is dissolved in 100 ml. of water, added to the reaction flask, and cooled to 0°. To this, in 3- to 4-g. portions, is added with good stirring a total of 127 g. (0.50 mole) of iodine over a period of 30–40 minutes. A given portion of iodine is not added until the preceding one has reacted almost completely. Ten minutes after the addition of iodine is completed, 120 ml. of peroxide-free ether is added and the mixture is stirred for a few minutes until the precipitated cyanogen iodide has dissolved in the ethereal layer. The entire contents are then transferred to a previously cooled separatory funnel, and the aqueous layer is separated. This aqueous solution is again extracted successively with 100-ml. and 80-ml. portions of cold, peroxide-free ether. The combined ethereal extracts are poured into a 500-ml. round-bottomed flask, and the ether is evaporated under reduced pressure at room temperature. To the slightly brown crude product, which weighs about 90 g., is added 120 ml. of water. A slightly diminished pressure (atm.) is maintained while the contents in the closed flask are heated at 50° for 15 minutes with occasional vigorous shaking (Note 1). The mixture is then cooled to 0°, and the crystalline cyanogen iodide is separated from the light yellow mother liquor by suction on a sintered-glass funnel or filter plate (Note 2). The crude product is washed with six 25-ml. portions of ice water, removed from the sintered-glass funnel, and air-dried (in a good hood) for 1 hour at room temperature. Colorless cyanogen iodide weighing about 59 g. (77%) is obtained; m.p. 141–144° (Note 3).

Cyanogen iodide of highest purity may be produced in the following way. The above crude product is dissolved in 150 ml. of boiling chloroform, and the solution is filtered through a plug of glass-wool on a hot-water funnel into a 250-ml. Erlenmeyer flask. This solution, after being cooled at room temperature for 15 minutes, is placed in an ice-salt bath and cooled to –10° (Note 4). By means of suction filtration, the

crystalline product is collected on a sintered-glass funnel, washed with three 15-ml. portions of cold chloroform (0°), and freed from the last traces of solvent by being placed on a watch glass and exposed to the atmosphere (in a good hood) at room temperature for 1 hour. Practically colorless needle-shaped crystals weighing 45 g. (59%) are obtained; m.p. 146–147° (Note 3) and (Note 5).

Removal of 100 ml. of chloroform from the above filtrate by means of evaporation under reduced pressure at room temperature and subsequent cooling permits isolation of an additional 2 g. of cyanogen iodide; m.p. 146–147°. The total yield thus becomes 47 g. (62% based on iodine).

2. Notes

1. In this way sodium iodide, soluble in the solution of cyanogen iodide in ether [complex formation of $NaI_2(CN)$], is removed. This complex is avoided in the procedure by Ketelaar and Kruyer[2] in which chlorine is used. The method adopted here is faster and simpler and gives almost the same yield of purified cyanogen iodide.
2. Contact with filter paper must be avoided.
3. Determinations of the melting point of cyanogen iodide must be made using a sealed capillary which is kept totally immersed in the heating bath.
4. When the chloroform solution is cooled, a small aqueous layer is observed which finally separates as ice. The ice is filtered with cyanogen iodide but melts on the filter plate and is removed with the chloroform used as washing liquid.
5. Owing to the volatility of cyanogen iodide, the yield is slightly dependent on the speed of operation. By the above method sublimation as a means of purification is avoided. If, however, sublimation is desirable, it can be accomplished with appreciable speed only under reduced pressure and at temperatures at which cyanogen iodide is slowly decomposed into iodine and cyanogen. The vacuum must be constantly renewed during the operation.

3. Discussion

Cyanogen iodide has been prepared from mercuric cyanide and iodine,[3] potassium cyanide and iodine,[4] and sodium cyanide and iodine.[5]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ether (60-29-7)

chloroform (67-66-3)

sodium cyanide (143-33-9)

cyanogen

potassium cyanide (151-50-8)

iodine (7553-56-2)

chlorine (7782-50-5)

sodium iodide (7681-82-5)

mercuric cyanide (592-04-1)

Cyanogen iodide, Iodine cyanide (506-78-5)

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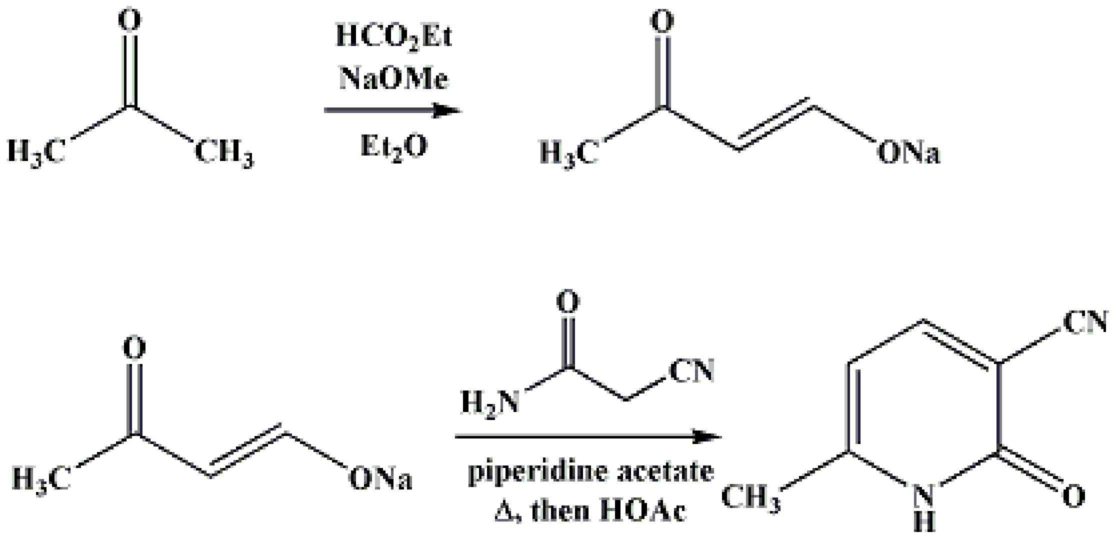
3-CYANO-6-METHYL-2(1)-PYRIDONE

[Nicotinonitrile, 1,2-dihydro-6-methyl-2-oxo-]



Submitted by Raymond P. Mariella[1]
Checked by Arthur C. Cope, James E. Krueger, and David J. Marshall.

1. Procedure

In a 2-l. three-necked flask fitted with a Hershberg stirrer sealed by a lubricated rubber sleeve, a dropping funnel, and a reflux condenser attached to a calcium chloride drying tube are placed 46.5 g. (0.86 mole) of sodium methoxide (Note 1) and 1 l. of ether (dried over sodium wire). The flask is cooled in an ice bath, and a mixture of 46.4 g. (0.8 mole) of acetone (Note 2) and 59.2 g. (0.8 mole) of ethyl formate (Note 3) is added through the dropping funnel at a rate of about 2 drops per second, with stirring, during a period of about 1 hour. Stirring is continued 15 minutes longer with the ice bath in place and then 1 hour after it is removed. The reflux condenser is replaced by a condenser set for distillation, and the ether is distilled by heating the mixture in a water bath at a temperature which is not allowed to rise above 70°. Stirring is continued as long as possible during the distillation. The last of the ether is removed by distillation under reduced pressure with the aid of a water aspirator (Note 4).

To the solid residue of sodium formylacetone remaining in the flask are added a solution of 67 g. (0.8 mole) of cyanoacetamide (Note 5) in 400 ml. of water and piperidine acetate (prepared by adding piperidine to 8 ml. of glacial acetic acid in 20 ml. of water until the solution is just basic to litmus). The flask is equipped with a reflux condenser, and the mixture is heated under reflux for 2 hours. At the end of this time 200 ml. of water is added, and the solution is acidified (to litmus) with acetic acid, causing separation of the product as a voluminous yellow precipitate. The mixture is cooled in an ice bath for 2 hours, and the product is collected on a suction

filter, washed on the filter with three 100-ml. portions of ice water, and dried (Note 6). The yield of 3-cyano-6-methyl-2(1)-pyridone is 59–67 g. (55–62%); m.p. 292–294° (dec., cor.) (Note 7), (Note 8), and (Note 9).

2. Notes

1. Commercial sodium methoxide obtained from the Mathieson Alkali Works was used. If the commercial product is not available, sodium methoxide can be prepared by dissolving clean sodium in dry methanol and removing the excess methanol by distillation and finally by heating the residue to 200° under good vacuum furnished by an oil pump (protected by Dry Ice traps).[2]
2. Reagent grade acetone is dried over potassium carbonate and distilled.
3. Commercial ethyl formate was purified by the procedure described earlier.[3]
4. If not all the ether is removed, it will be impossible to obtain the reflux temperature needed for the subsequent condensation, in which case the remainder of the ether must be removed by a preliminary distillation after adding the aqueous solution of cyanoacetamide and piperidine acetate.
5. Either Eastman Kodak Company white label grade cyanoacetamide or a product prepared according to the procedure described previously[4] can be used.
6. The product retains water tenaciously and is best dried in a vacuum oven at 70–100° at a pressure of 30 mm. or lower.
7. Melting points determined in the ordinary way are unsatisfactory because gradual decomposition occurs over a broad temperature range. Reproducible melting points were obtained by placing the sample in a melting-point tube and displacing the air in the tube with nitrogen introduced through a fine capillary (prepared by drawing out a piece of glass tubing, which then was attached to a nitrogen cylinder through a T-tube dipping into 1–2 cm. of mercury). The nitrogen-filled melting-point tube was sealed quickly, and the melting point was determined by placing the tube in a bath 10° below the melting point and raising the temperature 2° per minute.
8. Analysis of the crude product is approximately 0.9% low in carbon. Analytically pure 3-cyano-6-methyl-2(1)-pyridone, m.p. 296.5–298.5° (dec., cor., under nitrogen), can be obtained by one recrystallization from 50% (by volume) ethanol, using 66 ml. per g. of product and treating the hot solution with Darco. Recovery of the product is 60%, and concentration of the mother liquor yields impure material.
9. A similar procedure can be used for preparing other 2(1)-pyridones. For example, 3-cyano-6-isobutyl-2(1)-pyridone can be obtained from the sodium salt of formylmethyl isobutyl ketone, and 3-cyano-5,6-dimethyl-2(1)-pyridone can be prepared from the sodium salt of α-formylethyl methyl ketone.[5]

3. Discussion

The procedure used for preparing the sodium salt of formylacetone is a modification of

a previously described procedure.[2] 3-cyano-6-methyl-2(1)-pyridone has been prepared by the condensation of β-ethoxycrotonaldehyde diethyl acetal[6] or acetoacetaldehyde bismethylacetal[7] with cyanoacetamide, and by the condensation of the sodium salt of formylacetone with cyanoacetamide.[8]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

3-Cyano-6-methyl-2(1)-pyridone

sodium formylacetone

3-cyano-6-isobutyl-2(1)-pyridone

sodium salt of formylmethyl isobutyl ketone

3-cyano-5,6-dimethyl-2(1)-pyridone

sodium salt of α-formylethyl methyl ketone

sodium salt of formylacetone

ethanol (64-17-5)

potassium carbonate (584-08-7)

acetic acid (64-19-7)

methanol (67-56-1)

ether (60-29-7)

nitrogen (7727-37-9)

mercury (7439-97-6)

acetone (67-64-1)

sodium methoxide (124-41-4)

carbon (7782-42-5)

sodium (13966-32-0)

piperidine (110-89-4)

CYANOACETAMIDE (107-91-5)

ethyl formate (109-94-4)

Nicotinonitrile, 1,2-dihydro-6-methyl-2-oxo- (4241-27-4)

piperidine acetate

β-ethoxycrotonaldehyde diethyl acetal

acetoacetaldehyde bismethylacetal

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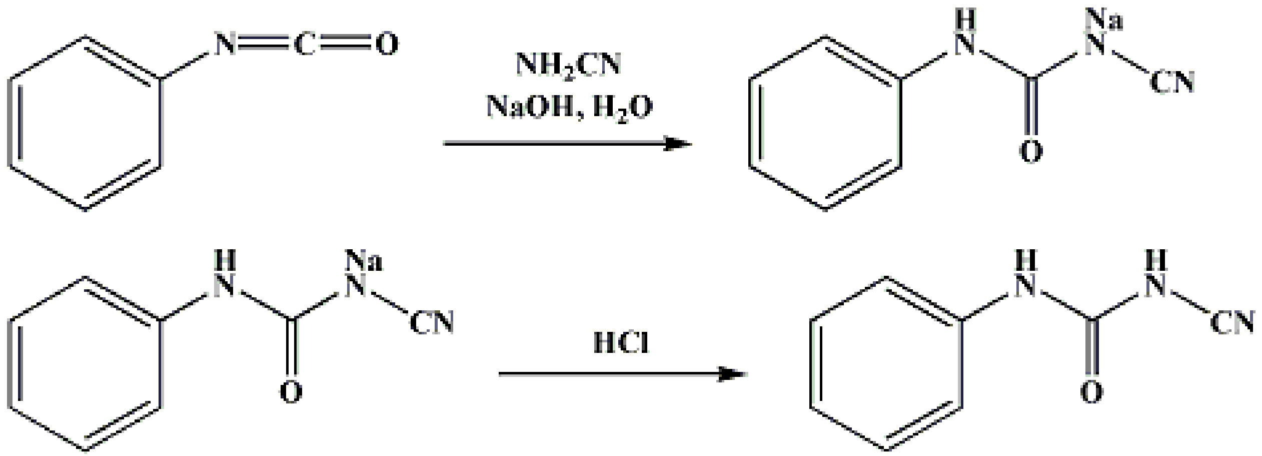
1-CYANO-3-PHENYLUREA

[Urea, 1-cyano-3-phenyl-]



Submitted by Frederick Kurzer and J. Roy Powell[1].
Checked by John C. Sheehan and Ernest R. Gilmont.

1. Procedure

To a solution of 16.8 g. (0.40 mole) of cyanamide in 50 ml. of water (Note 1) contained in a 400-ml. flask or beaker is added 50 ml. of aqueous 3*N* sodium hydroxide (0.15 mole). To the resulting solution, cooled to 15–18°, is added, in 2-ml. portions with shaking over a 15–18 minute period, 23.8 g. (22.0 ml., 0.2 mole) of phenyl isocyanate. The isocyanate dissolves rapidly, while the temperature rises slightly. The mixture is maintained at 20–25° by occasional external cooling in ice water. When half the phenyl isocyanate has been introduced, a second portion of 50 ml. (0.15 mole) of 3*N* sodium hydroxide is added to keep the reaction mixture strongly alkaline throughout the experiment. When addition is complete (Note 2), the slightly turbid liquid is diluted with 40 ml. of water and is filtered immediately under reduced pressure (Note 3) to remove undissolved impurities and traces of separated diphenylurea (Note 4). The cyanourea is precipitated from the clear colorless filtrate by the slow addition of concentrated hydrochloric acid with stirring until a permanent turbidity just appears (Note 3). Cracked ice (30–40 g.) is added to lower the temperature to 18–20°. Precipitation is then completed in this temperature range by the alternate addition of concentrated hydrochloric acid (total volume required, approximately 30 ml.) and cracked ice until the suspension is acid to Congo red. The crude cyanourea forms a microcrystalline, white precipitate, which, after storage at 0° for 3 hours, is collected by filtration under reduced pressure (Note 5) and is washed with two portions of cold water (20–25 ml.) (Note 6). The crude product is drained thoroughly, air-dried at room temperature, and finally dried to constant weight in a desiccator over phosphorus pentoxide. The yield of crude 1-cyano-3-phenylurea (Note 7), m.p. 122–126° with

decomposition (Note 8), varies between 29 and 30.5 g. (90–95%). The dried material is purified as follows. A solution of the crude product in 100 ml. of boiling acetone is diluted slowly with gentle swirling with 30–40 ml. of petroleum ether (boiling range 40–60°). As crystallization proceeds, an additional 20–30 ml. of petroleum ether is added carefully at such a rate that the supernatant liquid does not become turbid. After 15 minutes at room temperature, the mixture is set aside at 0°. The product is collected by filtration under reduced pressure and washed successively with 50 ml. of an acetone-petroleum ether mixture (1:3) and 50 ml. of petroleum ether. 1-Cyano-3-phenylurea thus obtained forms colorless lustrous needles, m.p. 127–128° with decomposition (Note 8), yield 20–21.5 g. (62–67%). Slow dilution of the filtrates with petroleum ether to a total volume of 350–400 ml. and storage at 0° affords a second crop, m.p. 123–126° (dec.), of satisfactory purity; yield 4–5 g. (12–16%). The synthesis is generally applicable to the preparation of 1-cyano-3-arylureas (Note 9).

2. Notes

1. The checkers used 16.8 g. of Eastman Kodak Company cyanamide (P1995) without further purification. A convenient method of preparing cyanamide from commercial calcium cyanamide has been described (p.645). According to the submitters, an aqueous solution of crude cyanamide is satisfactory in the present synthesis and is obtained by adapting this published procedure (p.645) as follows. The residual crude cyanamide remaining after evaporation of the ethereal extracts (which need not be dried previously) is dissolved readily in the appropriate volume of cold water. A small quantity of water-insoluble oily or semisolid by-products is removed by shaking the solution with carbon and filtering the liquid through a small ordinary filter, followed by rinsing with a few milliliters of water. The clear filtrate is suitable for the subsequent operation.
In order to allow for small losses in the filtration and for the presence of impurities (such as solvent and oily by-products) an excess of approximately 10–15% by weight of crude cyanamide is allowed.
2. The reaction is completed when the liquid no longer has the odor of phenyl isocyanate; shaking is continued until this stage is reached.
3. The reaction mixture is not cooled during the addition of the last two or three portions of phenyl isocyanate, so that the final temperature is near 25°; this procedure prevents separation of the sodium salt of cyanophenylurea, which crystallizes readily at low temperatures. For the same reason, the filtered solution of the salt is not precooled, but rather is cooled during the precipitation of the free cyanourea.
4. The residue on the filter is rinsed with 5–10 ml. of water, in order to redissolve any small quantities of the sodium salt of cyanophenylurea that may have been collected.
5. The aqueous filtrate does not deposit any further material on storage at 0° and is discarded.
6. For the purpose of washing, the filter cake on the funnel is covered with ice water. After being allowed to remain in contact for a few seconds, the liquid is quickly drained under reduced pressure. The second portion of washing water should no longer be acid to Congo red.

7. According to the submitters the crude material may turn very pale pink on drying, but the product is again colorless after recrystallization. The checkers found that the crude product could be dried to less than 0.2% moisture by drawing air through the filter cake for 3 hours.
8. The decomposition temperature is somewhat influenced by the rate of heating. The material does not form a clear melt during the decomposition.
9. According to the submitters 1-cyano-3-α-naphthylurea[2] is obtained similarly from α-naphthyl isocyanate in 85–90% yields. Crystallization from acetone-petroleum ether (12 and 6 ml., respectively, per gram of crude product; recovery approximately 60% per crystallization) yields lustrous prisms, m.p. 148–149° with decomposition.

3. Discussion

1-Cyano-3-phenylurea, first obtained by the alkaline hydrolysis of 5-anilino-3-*p*-toluyl-1,2,4-oxadiazole,[3] has been prepared by the condensation of phenyl isocyanate and the sodium salt of cyanamide.[4] However, in these publications an incorrect structural assignment for the product was made. 1-Cyano-3-phenylurea is obtained also, together with other products, by warming gently 1-cyano-3-phenylthiourea with caustic soda in the presence of ethylene chlorohydrin,[5] or by gradually adding caustic potash to a boiling solution of 1-phenyldithiobiuret and ethylene chlorohydrin in ethanol.[5]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

caustic soda

petroleum ether

calcium cyanamide

sodium salt of cyanophenylurea

caustic potash

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

sodium hydroxide (1310-73-2)

acetone (67-64-1)

carbon (7782-42-5)

ethylene chlorohydrin (107-07-3)

diphenylurea (603-54-3)

phenyl isocyanate (103-71-9)

cyanamide (420-04-2)

1-phenyldithiobiuret

1-Cyano-3-phenylurea, Urea, 1-cyano-3-phenyl- (41834-91-7)

1-cyano-3-α-naphthylurea

α-naphthyl isocyanate (86-84-0)

1-cyano-3-phenylthiourea

phosphorus pentoxide (1314-56-3)

5-anilino-3-p-toluyl-1,2,4-oxadiazole

sodium salt of cyanamide

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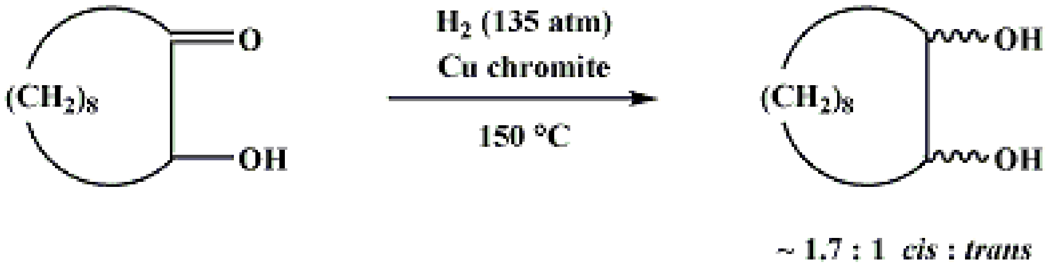
1,2-CYCLODECANEDIOL



Submitted by A. T. Blomquist and Albert Goldstein[1].
Checked by N. J. Leonard and F. H. Owens.

1. Procedure

A mixture of 140 g. (0.82 mole) of sebacoin (p. 840) (Note 1), 50 g. of copper chromite catalyst[2] (Note 2), and 230 ml. of 95% ethanol is placed in an 800-ml. high-pressure hydrogenation bomb (Note 3). Hydrogen is admitted to the bomb at 135 atm., and the bomb is heated to 150°. When this temperature is reached, the shaker is started. The temperature is stabilized at 150° after its initial rapid fluctuation, and the hydrogenation is allowed to proceed until the mixture ceases to absorb hydrogen (2–4 hours). The heating and shaking are discontinued, and the bomb is allowed to cool to room temperature. The excess hydrogen is vented, and the bomb is dismantled.

The *cis*-1,2-cyclodecanediol will have crystallized out of solution, while the *trans*-diol remains in the ethanol. The entire mixture is washed out of the bomb with 95% ethanol (about 1 l.). The *cis*-glycol is redissolved by heating the ethanolic mixture at reflux temperature. Filter aid ("Celite") is added to the mixture, and the hot mixture is filtered through a bed of filter aid on a Büchner funnel to remove the catalyst. The ethanol is removed from the filtrate by distillation on a steam bath under water-pump pressure. The residue is dissolved in a minimum of hot 1:1 benzene-ethanol solution (about 250 ml.), and the *cis*-diol crystallizes upon cooling to room temperature. The crystals are collected by filtration, and the mother liquor is concentrated to dryness on a steam bath under water-pump pressure. The residue is again dissolved in a minimum of hot 1:1 benzene-ethanol (about 100 ml.), and additional *cis*-diol crystallizes upon cooling in a refrigerator. The process is repeated using 50 ml. of 1:1 benzene-ethanol solvent. The total yield of *cis*-1,2-cyclodecanediol is 68–73 g. (48–52%), m.p. 137–138°.

The *trans*-diol remains in the mother liquor and may be recovered by complete evaporation of the solvent followed by recrystallization of the residue from pentane. The yield of *trans*-1,2-cyclodecanediol is 38–45 g. (27–32%), m.p. 53–54°.

2. Notes

1. A sebacoin-sebacil mixture may be used.
2. A commercial catalyst was employed by the submitters: Harshaw Chemical Company, CU-0202P; 556–002.
3. A suitable apparatus is the "Aminco" high-pressure hydrogenation apparatus, manufactured by the American Instrument Company, Silver Spring, Maryland.

3. Discussion

1,2-Cyclodecanediol has been prepared by the hydrogenation of sebacoin in the presence of Raney nickel[3] or platinum,[4] by the reduction of sebacoin with aluminum isopropoxide[4] or lithium aluminum hydride,[4] and by the oxidation of cyclodecene with osmium tetroxide and pyridine.[3]

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3. Prelog, Schenker, and Günthard, *Helv. Chim. Acta*, **35**, 1598 (1952); Prelog, Urech, Bothner-By, and Würsch, *Helv. Chim. Acta*, **38**, 1095 (1955).
4. Blomquist, Burge, and Sucsy, *J. Am. Chem. Soc.*, **74**, 3636 (1952).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Sebacoin

ethanol (64-17-5)

hydrogen (1333-74-0)

platinum (7440-06-4)

nickel (7440-02-0)

pyridine (110-86-1)

aluminum isopropoxide

Pentane (109-66-0)

benzene-ethanol (60-12-8)

COPPER CHROMITE

lithium aluminum hydride (16853-85-3)

osmium tetroxide (20816-12-0)

1,2-Cyclodecanediol (21014-77-7)

cyclodecene

cis-1,2-cyclodecanediol

trans-1,2-cyclodecanediol

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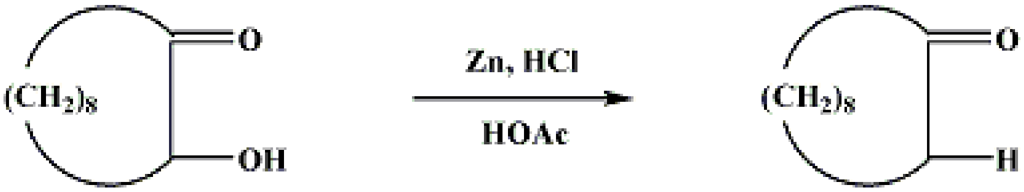
Organic Syntheses, CV 4, 218

CYCLODECANONE



Submitted by Arthur C. Cope, John W. Barthel, and Ronald Dean Smith[1].
Checked by N. J. Leonard and J. C. Little.

1. Procedure

A 1-l. round-bottomed three-necked flask is fitted with a sealed stirrer (Note 1), a dropping funnel, and a reflux condenser, through which a thermometer extends nearly to the bottom of the flask. In the flask are thoroughly mixed 40.5 g. (0.62 g. atom) of zinc dust (Note 2) and 100 ml. of glacial acetic acid, and to this mixture is added 42.5 g. (0.25 mole) of sebacoin (p.840) (Note 3). The mixture is stirred rapidly, and 90 ml. of concentrated C.P. hydrochloric acid is added dropwise during a period of 5 to 10 minutes, or as fast as control of foaming and temperature permits. The temperature must be kept between 75 and 80° (Note 4), and cooling by a water bath may be necessary during the addition of the hydrochloric acid. Stirring is continued for 1.5 hours at 75–80°. Thirty minutes after the initial addition of hydrochloric acid, and again 30 minutes later, 90-ml. portions of concentrated hydrochloric acid are added to the mixture while the temperature is maintained at 75–80°. After the reaction is complete, the remaining zinc is separated from the cooled mixture by decantation (Note 5). The liquid phase is diluted with 700 ml. of saturated aqueous sodium chloride solution and extracted with four 250-ml. portions of ether, each of which is first used to wash the residual zinc (Note 6). The ether extracts are combined and washed with 250 ml. of saturated sodium chloride solution, three 250-ml. portions of 10% sodium carbonate solution (foaming!), and finally 250 ml. of saturated sodium chloride solution. The ethereal solution is dried over anhydrous magnesium sulfate (about 25 g. is needed). After the drying agent has been removed by filtration and the solvent by distillation, the residue is distilled at reduced pressure through an efficient column (Note 7). After a small fore-run consisting mostly of cyclodecane, cyclodecanone is collected at 99–101°/8 mm. The yield is 29–30 g. (75–78%), n_D^{25} 1.4808–1.4810 (Note 8).

2. Notes

1. A metal stirrer must not be used. A simple glass stirrer with a ball-joint seal is satisfactory.

2. Mallinckrodt technical grade may be used.[2] If Mallinckrodt analytical reagent

zinc dust is used, the reaction temperature must be maintained at 50–55° instead of 75–80°.
3. Pure sebacoin gives a colorless product. A sebacoin-sebacil mixture must first be purified by recrystallization from pentane as described (p.841). The sebacil apparently is not reduced completely according to the accompanying directions and thus may contaminate the product (Note 7).
4. The reaction temperature is important. At temperatures below 75° some sebacoin remains unreduced, while at temperatures above 80° considerable cyclodecane is formed. The submitters report that the reaction run at the reflux temperature gives cyclodecanone in 27% yield and cyclodecane in 32% yield.
5. The product should be isolated and distilled as quickly as possible inasmuch as the unreacted sebacoin is readily oxidized to sebacil, which cannot be separated from the cyclodecanone by simple distillation.
6. The residual zinc may be pyrophoric.
7. For efficient separation of cyclodecanone from cyclodecane, a 60-cm. column of the simple Podbielniak type[3] may be used. Removal of sebacil cannot be accomplished readily by fractional distillation, since cyclodecanone and sebacil have virtually identical boiling points.
8. Cyclodecanone regenerated from its semicarbazone, m.p. 203.5–205.5°, has n_D^{25} 1.4806.

3. Discussion

The procedure described is a modification of the directions of Prelog, Frenkiel, Kobelt, and Barman.[4] Cyclodecanone has been prepared by the dehydration of sebacoin followed by catalytic hydrogenation,[5] by the pyrolysis of the thorium or yttrium salt of nonane-1,9-dicarboxylic acid,[6] and by the ring enlargement of cyclononanone,[7] as well as by the reduction of sebacoin.[8]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 277

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Sebacoin

sebacoin-sebacil

thorium or yttrium salt of nonane-1,9-dicarboxylic acid

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ether (60-29-7)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

zinc (7440-66-6)

Pentane (109-66-0)

magnesium sulfate (7487-88-9)

Cyclodecanone (1502-06-3)

cyclodecane (293-96-9)

cyclononanone (3350-30-9)

Sebacil (96-01-5)

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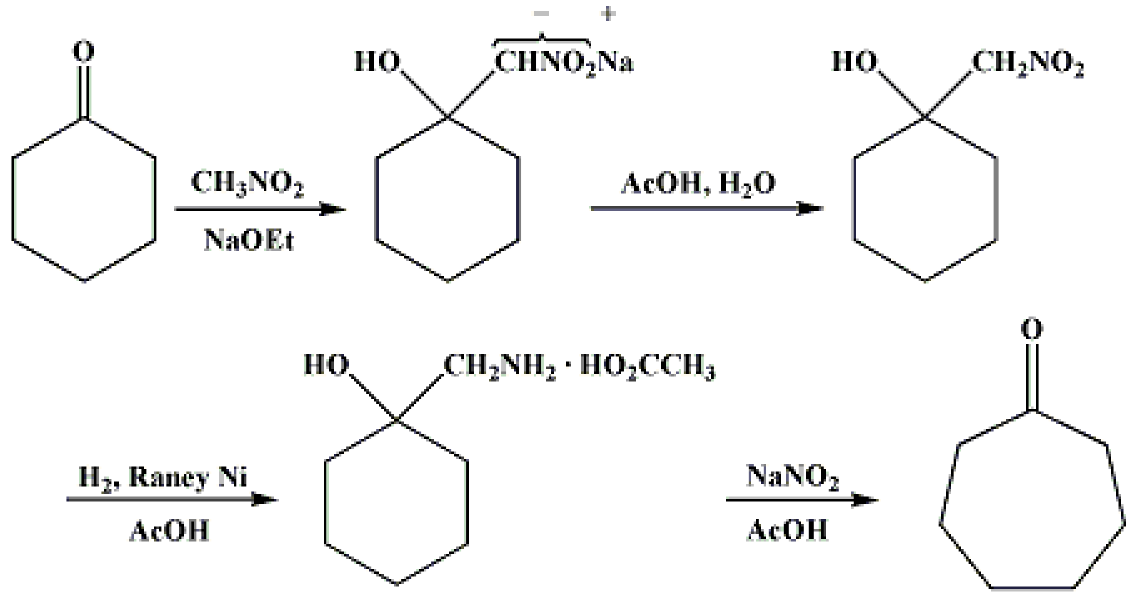
Organic Syntheses, CV 4, 221

CYCLOHEPTANONE

[I. NITROUS ACID METHOD]



Submitted by Hyp J. Dauben, Jr., Howard J. Ringold, Robert H. Wade, David L. Pearson, and Arthur G. Anderson, Jr.[1].
Checked by Arthur C. Cope, Warren N. Baxter, and Robert J. Cotter.

1. Procedure

Caution! The sodium salt of 1-(nitromethyl)cyclohexanol may be an explosive (Note 1).

A solution of sodium ethoxide is prepared by adding 57.5 g. (2.5 g. atoms) of clean sodium to 1.2 l. of absolute ethanol (Note 2) in a 3-l. three-necked flask equipped with an Allihn reflux condenser fitted with a drying tube, a large sturdy sealed Hershberg stirrer, and a dropping funnel. After the sodium has dissolved, the solution is cooled to 40° and the condenser is replaced by a thermometer extending into the liquid. A mixture of 245.5 g. (258.5 ml., 2.5 moles) of redistilled cyclohexanone and 198 g. (175 ml., 3.25 moles) of redistilled nitromethane (Note 3) is added dropwise with vigorous stirring over the course of about 3 hours at a rate that maintains an internal temperature of 45 ± 3° (Note 4). After addition is complete, the white, pasty mass is stirred for an additional 3 hours without cooling or heating and then is allowed to stand overnight. The resulting suspension is cooled with an ice bath, and the white sodium salt of 1-(nitromethyl)cyclohexanol is collected on a 25-cm. Büchner funnel and dried by suction for about 1 hour (Note 1). The sodium salt cake is broken up and transferred to a 4-l. beaker equipped with a Hershberg stirrer and immersed in an ice bath. A cold solution of 184 g. (175 ml., 3 moles) of glacial acetic acid in 1250 ml. of water is added in a single portion, and the mixture is stirred for 10–30 minutes to complete dissolution. The oily layer of 1-(nitromethyl)cyclohexanol is separated, and the aqueous layer is extracted with three 100-ml. portions of ether. The ether extracts and the 1-(nitromethyl)cyclohexanol are combined, dried briefly over magnesium sulfate, and concentrated by distillation from a steam

bath with a water aspirator at 20–35 mm. to remove ether and excess nitromethane. The crude, undistilled 1-(nitromethyl)cyclohexanol (Note 5) is dissolved in 450 ml. of glacial acetic acid in a 2-l. externally cooled stainless-steel hydrogenation bottle (Note 6). Three heaping teaspoonfuls of W-4 Raney nickel catalyst[2] are added, and the mixture is shaken with hydrogen at 40–45 p.s.i., with cooling to maintain the temperature below 35°, until about 90% of the theoretical amount (7.5 moles) is taken up and absorption ceases (Note 7). The catalyst is separated by filtration with suction through Filter-Cel, and the filtrate (sometimes green or tan) containing the 1-(aminomethyl)cyclohexanol is used directly in the next step (Note 8).

The filtrate is transferred to a 5-l. round-bottomed flask, immersed in an ice-salt mixture and equipped with a Hershberg stirrer, a thermometer, and a dropping funnel. The solution is diluted with 2.3 l. of ice water; then an ice-cold solution of 290 g. (4.2 moles) of sodium nitrite in 750 ml. of water is added dropwise during a period of about 1 hour with stirring and cooling (ice-salt bath) to maintain the temperature at –5°. The mixture is stirred for an additional period of 1 hour and then allowed to come to room temperature overnight as the ice in the cooling bath melts. The acetic acid in the reaction mixture is neutralized by the addition of small portions of solid sodium bicarbonate, and the neutral (to litmus paper) solution is then steam-distilled until about 2 l. of distillate is collected. The oily cycloheptanone layer is separated, the aqueous layer is extracted with three 100-ml. portions of ether, and the combined organic layers are dried briefly over magnesium sulfate. Most of the ether is removed by distillation through a 17 by 2.5 cm. glass helix-packed column at atmospheric pressure (Note 9). The residue is then distilled through the same column, and the fraction boiling at 80–85°/30 mm. is collected. The yield of cycloheptanone is 112–118 g. (40–42%), n_D^{25} 1.4600 (Note 10) and (Note 11).

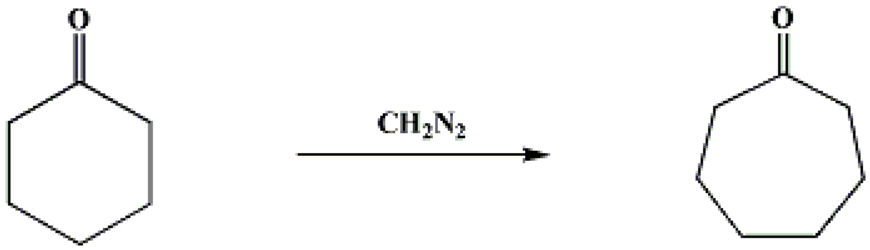
2. Notes

1. It has been reported[3] that when the crude product from the condensation of 2 moles of nitromethane (as the sodium salt in absolute ethanol) with 1 mole of 1,1,3,3-tetramethylcyclobutane-2,4-dione (dimethylketene dimer) was filtered, and the filter cake was dried on a porous clay plate, a violent explosion occurred upon addition of the dried powder to crushed ice.
This experience suggests that it may be inadvisable to dry completely the sodium salt of 1-(nitromethyl)cyclohexanol, and that the material should be handled with considerable caution. Also, in other procedures where salts of nitro compounds are involved, and the extent of the reaction and the nature of the products are not known with certainty, the salts probably should not be filtered, but should be neutralized in the reaction mixtures and the free nitro alcohols separated by suitable means.
2. Commercial absolute ethanol is used without additional drying. The submitters state that the use of absolute ethanol may be avoided by employment of the alternative condensation procedure of Wood and Cadorin[4] using 5 mole per cent of sodium hydroxide in aqueous methanol at 15–20° for 6 hours, but the yield of 1-(nitromethyl)cyclohexanol is appreciably lower (51%).
3. Cyclohexanone is dried over magnesium sulfate or calcium sulfate (Drierite) for 1 day and distilled; the fraction boiling at 152.5–154° (uncor.) is used. Nitromethane is dried in the same manner and distilled; small quantities of acidic impurities are removed in the fore-run, and the fraction boiling at 101.5–102.5° (uncor.) is used. Drying is frequently

unnecessary when good grades of cyclohexanone and nitromethane are used.
4. Efficient stirring of the pasty reaction mixture is necessary to obtain maximum yield.
5. Removal of residual amounts of acetic acid in the crude product is unnecessary; their presence is actually preferable to the presence of traces of bases, such as any sodium bicarbonate remaining from neutralization, which reverse the condensation on attempted distillation of 1-(nitromethyl)cyclohexanol.[4] The submitters state that, in preparations conducted on twice the scale specified, fractional distillation of the residue yielded 620–670 g. (78–84%) of 1-(nitromethyl)cyclohexanol, b.p. 129–132°/19 mm., n_D^{25} 1.4835.
6. A Pyrex bottle can be used; it must be enclosed to prevent possible injury by fragments of glass in case of explosion.
7. Catalytic hydrogenation of 1-(nitromethyl)cyclohexanol in acetic acid solvent is a markedly exothermic reaction, and, unless the temperature is moderated to about 35°, low yields of 1-(aminomethyl)cyclohexanol result owing to hydrogenolysis and deactivation of the catalyst. Cooling can be accomplished by running cold water through a copper coil surrounding the hydrogenation bottle or by periodically adding ice to the container in which the bottle is placed. Considerable cooling is necessary during initial stages of the hydrogenation, but cooling below 25° greatly retards the reduction. Absorption of hydrogen is usually complete in 15–18 hours under these conditions, but longer times may be required, depending on the temperature and pressure and on the amount and activity of the catalyst.
8. 1-(Aminomethyl)cyclohexanol can be isolated as its acetic acid salt by the addition of 2 volumes of ether to the acetic acid solution or to the residue after removal of the acetic acid under reduced pressure, followed by trituration and refrigeration overnight. After filtration of the first crop of crystals, m.p. 118–121°, a second crop of the salt, m.p. 113–116°, is obtained on removal of the dissolved nickel from an aqueous solution of the concentrated filtrate by saturation with hydrogen sulfide, concentration, and treatment with ether. Total yields of the air-dried crude acetic acid salt of 1-(aminomethyl) cyclohexanol obtained from 100–350 g. lots of 1-(nitromethyl)cyclohexanol in this manner ranged from 69% to 94%.
9. Distillation of the product from a modified Claisen flask and collection of the fraction boiling at 67–77°/20 mm. (largely 69–72°) gave 140–149 g. of impure cycloheptanone, n_D^{25} 1.4570–1.4590, containing about equal amounts (10–15 g.) of lower-boiling and higher-boiling (mainly 1-(nitromethyl)cyclohexanol) contaminants, which were separated by distillation through the glass helix-packed column.
10. The submitters state that the yields of cycloheptanone obtained from 60- to 700-g. quantities of the crude acetic acid salt of 1-(aminomethyl)cyclohexanol (isolated by the procedure of ((Note 8)) were 57–65%.
11. Small quantities of cycloheptanone are prepared more conveniently by the diazomethane method[5] or by dry distillation of suberic acid salts[6,7,8] or suberic acid admixed with iron filings and barium hydroxide.[9]

[II. DIAZOMETHANE METHOD]

$$p\text{-}CH_3C_6H_4SO_2N(NO)CH_3 + C_2H_5OH \xrightarrow{\text{aq. KOH}} p\text{-}CH_3C_6H_4SO_2OC_2H_5 + CH_2N_2$$



Submitted by Th. J. de Boer and H. J. Backer[10].
Checked by James Cason, John B. Rogan, and Wm. G. Dauben.

1. Procedure

Caution! Diazomethane is very toxic; therefore the operations must be carried out in a well-ventilated hood. (See p. 250.)

In a 500-ml. round-bottomed flask, provided with a mechanical stirrer (Note 1), a thermometer, and a dropping funnel, are placed 49 g. (0.5 mole) of cyclohexanone (Note 2), 125 g. (0.58 mole) of *p*-tolylsulfonylmethylnitrosamide (p. 943), 150 ml. of 95% ethanol, and 10 ml. of water (Note 3). The nitroso compound is largely undissolved. The stirrer is adjusted so that only the upper portion of solution is stirred and the precipitate moves slightly. The thermometer bulb is placed in the liquid.

The reaction mixture is cooled to about 0° with an ice-salt bath; then with gentle stirring a solution of 15 g. of potassium hydroxide in 50 ml. of 50% aqueous ethanol is added dropwise very slowly from the dropping funnel. After the addition of 0.5–1 ml. of the alkaline solution a brisk evolution of nitrogen commences and the temperature rises. The rate of addition is adjusted so that the temperature is maintained at 10–20° (Note 4). The addition of the alkali requires about 2 hours, during which the nitroso compound gradually disappears. The orange-yellow solution is stirred for an additional 30 minutes, then 2*N* hydrochloric acid (about 50 ml.) is added until the solution is acidic to litmus paper.

A solution of 100 g. of sodium bisulfite (Note 5) in 200 ml. of water is added as stirring is continued. After a few minutes a thick precipitate separates. The mixture is stirred or preferably shaken mechanically at room temperature with exclusion of air for 10 hours. The bisulfite addition product is separated by suction filtration, washed with ether until colorless, and decomposed in a flask with a lukewarm solution of 125 g. of sodium carbonate in 150 ml. of water. The ketone layer is separated, the aqueous layer is extracted with four 25-ml. portions of ether, and the combined organic layers are dried over anhydrous sodium sulfate. Most of the ether is removed by distillation at atmospheric pressure, and the residual oil is distilled at reduced pressure (Note 6).

After a few drops of fore-run, practically all the liquid distils at 64–65°/12 mm. The yield of cycloheptanone is 18.5–20.2 g. (33–36%) (Note 6).

2. Notes

1. If it is desired to determine the amount of nitrogen evolved, then it is necessary to use a sealed stirrer and a discharge tube for the nitrogen; however, observing the amount of nitrogen evolved affords no particular advantage. The temperature exerts sufficient control on the reaction rate, and dissolution of the nitroso compound indicates the progress of the reaction.
2. Cyclohexanone was distilled before use, b.p. 154–155°.
3. The water keeps in solution the potassium *p*-toluenesulfonate, which is formed by partial saponification of the ester.
4. In some experiments, the temperature was allowed to rise temporarily to 35° without mishap, but the lower temperature is preferred for reasons of safety.
5. Cycloöctanone, which is a by-product, is removed at this stage since it does not form an adduct with bisulfite.
6. The checkers found it desirable to distil the product through a fractionating column in order to effectively remove the small fore-run and a smaller after-run. The pattern obtained in a 50-cm. column of the simple Podbielniak type follows: fraction 1, 1.13 g., b.p. up to 63°/12 mm., n_D^{25} 1.4549; fraction 2, 19.44 g., b.p. 63–64°/12 mm., n_D^{25} 1.4592; fraction 3, 0.55 g., b.p. > 64°/12 mm., n_D^{25} 1.4604. A center cut of fraction 2 had n_D^{25} 1.4590.

3. Discussion

Cycloheptanone has been prepared by variations of two general routes, ring closure and ring enlargement. Ring-closure methods that have been employed are: (*a*) dry distillation of calcium[6] (35–50% yield), thorium[7] (45% yield), cerium[7] (45% yield), and zinc or magnesium[8] (55–60% yield) salts of suberic acid; (*b*) pyrolysis of a mixture of suberic acid, iron filings, and barium hydroxide[9] (40% yield) or pyrolysis of suberic acid in the presence of catalytic amounts of thorium oxide;[11] (*c*) Dieckmann condensation of diethyl suberate with sodium ethoxide in ether[12] or potassium *tert*-butoxide in xylene under high dilution conditions;[13] (*d*) Thorpe-Ziegler condensation of suberonitrile using preferably sodium methylanilide in ether by a high-dilution technique followed by hydrolysis and decarboxylation (80–85% yield);[14] and (*e*) dehydrohalogenation of suberyl chloride using triethylamine by a high-dilution technique (33% yield).[15] Ring-enlargement methods that have been used are: (*a*) diazomethane on cyclohexanone (33–36% yield)[5] and (*b*) catalytic reduction of cyclohexanone cyanohydrin[16] or electrolytic reduction of 1-(nitromethyl)cyclohexanol[17] and treatment of the resulting 1-(aminomethyl)cyclohexanol with nitrous acid, and hydrogenation of tetrahydrobenzonitrile (from acrylonitrile and butadiene) to cyclohexylmethylamine which then is caused to react with nitrous acid.[18]

Procedure I represents an improved modification of the procedure of Dauben, Ringold, Wade, and Anderson,[19] and Procedure II is a modification of earlier diazomethane methods and employs the relatively stable *p*-tolylsulfonylmethylnitrosamide (p. 943).

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Drierite

acetic acid salt of 1-(aminomethyl)cyclohexanol

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

methanol (67-56-1)

ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

magnesium (7439-95-4)

iron (7439-89-6)

Cyclohexanone (108-94-1)

hydrogen sulfide (7783-06-4)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

sodium nitrite (7632-00-0)

nitrous acid (7782-77-6)

sodium bisulfite (7631-90-5)

thorium oxide

calcium sulfate (7778-18-9)

nickel (7440-02-0)

potassium hydroxide (1310-58-3)

zinc (7440-66-6)

calcium (7440-70-2)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

barium hydroxide (17194-00-2)

xylene (106-42-3)

Nitromethane (75-52-5)

magnesium sulfate (7487-88-9)

butadiene (106-99-0)

Diazomethane (334-88-3)

Cerium (7440-45-1)

acrylonitrile (107-13-1)

thorium (7440-29-1)

Cycloheptanone (502-42-1)

1-(Nitromethyl)cyclohexanol (3164-73-6)

1-(aminomethyl)cyclohexanol (4000-72-0)

1,1,3,3-tetramethylcyclobutane-2,4-dione (933-52-8)

suberic acid (505-48-6)

diethyl suberate (2050-23-9)

suberonitrile (629-40-3)

sodium methylanilide

suberyl chloride (10027-07-3)

triethylamine (121-44-8)

cyclohexanone cyanohydrin (931-97-5)

tetrahydrobenzonitrile

cyclohexylmethylamine (3218-02-8)

Cyclooctanone (502-49-8)

potassium tert-butoxide (865-47-4)

potassium p-toluenesulfonate

p-Tolylsulfonylmethylnitrosamide

sodium salt of 1-(nitromethyl)cyclohexanol

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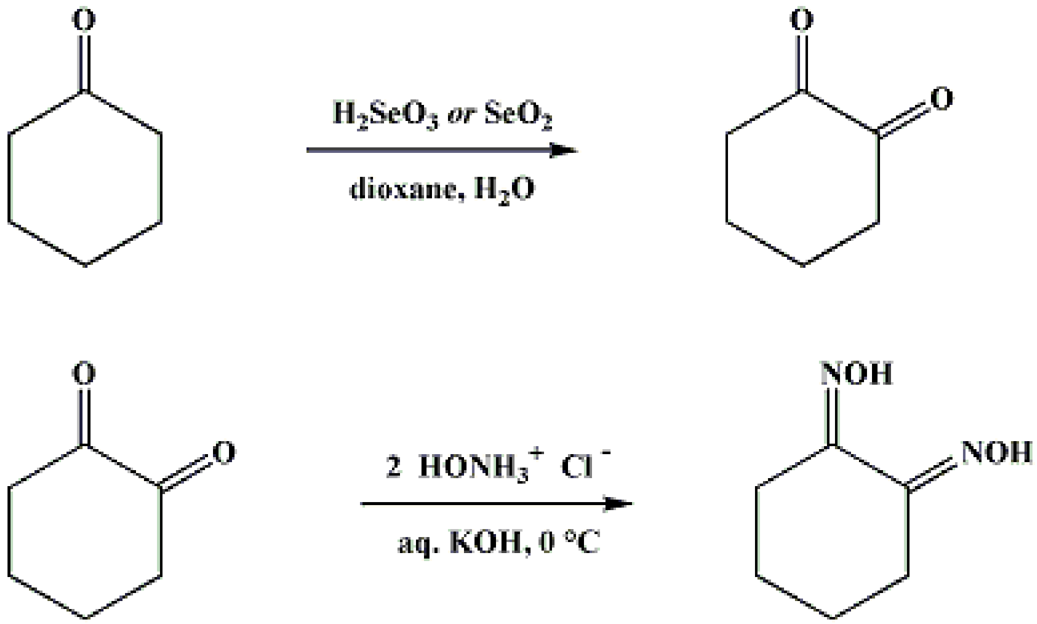
1,2-CYCLOHEXANEDIONE DIOXIME



Submitted by Clifford C. Hach, Charles V. Banks, and Harvey Diehl[1].
Checked by R. T. Arnold and Philip N. Gordon.

1. Procedure

A. 1,2-*Cyclohexanedione*. A 3-l. round-bottomed flask, fitted with stirrer and dropping funnel, is placed in a water bath containing a copper coil through which cooling water may be circulated. In the 3-l. flask is placed 1708 g. (17.4 moles, 1.8 l.) of cyclohexanone (Note 1). Tap water is circulated through the cooling coil (Note 2), and a solution containing 387 g. (3 moles) of selenious acid (H_2SeO_3) (Note 3), 500 ml. of dioxane, and 100 ml. of water is added dropwise and with stirring to the cyclohexanone over a period of 3 hours. The reaction mixture immediately turns yellow, and red amorphous selenium gradually appears. Stirring is continued for 5 additional hours at water-bath temperatures and then for 6 more hours at room temperature. Removal of the bulky, amorphous selenium is accomplished with the aid of a 6-in. Büchner funnel. The selenium is returned to the reaction flask and extracted with 300 ml. of boiling 95% ethanol for 1 hour (Note 4). The solution, obtained by decantation from the compact gray selenium, is combined with the above filtrate in a 4-l. distilling flask. Distillation under reduced pressure gives two fractions. The lower-boiling fraction (25–60°/16 mm.) consists mainly of ethanol, water, dioxane, and cyclohexanone; the higher-boiling one (60–90°/16 mm.) contains cyclohexanone and 1,2-cyclohexanedione with traces of water and dioxane. The yield of crude product is approximately 322 g.

The higher-boiling fraction is redistilled (Note 5), and again two fractions, boiling at 25–75°/16 mm. and 75–79°/16 mm., are collected. The latter fraction is essentially

pure 1,2-cyclohexanedione and crystallizes at 34° to ice-like crystals which become light yellow-green when exposed to the air; yield 202.5 g. (60% based on selenous acid). A considerable amount of light-brown, clear, resinous residue remains in the distilling flask.

B. *1,2-Cyclohexanedione dioxime*. In a 1-l. Erlenmeyer flask is placed 200 ml. of water and 100 g. of cracked ice. To this ice-water mixture is added 86.9 g. (1.25 moles) of hydroxylammonium chloride. An ice-cold basic solution is prepared by dissolving 82.4 g. (1.25 moles) of 85% potassium hydroxide in 50 ml. of water and then adding 150 g. of cracked ice. The ice-cold potassium hydroxide solution is added to the hydroxylammonium chloride solution, and the mixture is thoroughly shaken. To the mixture is added about 0.5 g. of nioxime (1,2-cyclohexanedione dioxime) with stirring (Note 6). The solution turns red owing to the reaction of the nioxime with quantities of iron and other impurities in the reagents. Four grams of Norit is added; the mixture is thoroughly shaken and then filtered with the aid of a 5-in. Büchner funnel. After this operation the filtrate should be water white.

The cold solution is transferred to a 1-l. Erlenmeyer flask and is placed in an ice bath. To the stirred solution is added slowly 56 g. (0.5 mole) of melted 1,2-cyclohexanedione. Precipitation of the 1,2-cyclohexanedione dioxime should take place almost immediately. If not, the solution may be seeded to initiate rapid precipitation. The mixture is stirred for 30 minutes after the addition of the 1,2-cyclohexanedione, and the precipitate is then collected on a 5-in. Büchner funnel. The precipitate is thoroughly washed with water to remove inorganic salts. The 1,2-cyclohexanedione dioxime is partially dried by suction and finally dried in a vacuum desiccator to give snow-white crystals; yield 52.5 g. (74%); m.p. 185–188° (darkening at 170°) (Note 7). The crude 1,2-cyclohexanedione dioxime is recrystallized from 550 ml. of water using 2.5 g. of iron-free Norit; yield 39.3 g. (55%); m.p. 186–188°.

2. Notes

1. The cyclohexanone need not be freshly distilled. Commercial cyclohexanone, obtained from the Barrett Division, Allied Chemical & Dye Corporation, New York, New York, gave practically the same yield as carefully fractionated cyclohexanone.
2. If too much selenous acid is added at once, or the cooling discontinued, the solution will heat up and the reaction will become extremely vigorous with subsequent decrease in yield.
3. Selenous acid or selenium dioxide can apparently be used interchangeably.
4. The selenium filtered from the reaction mixture is refluxed with 3 l. of 95% ethanol for 1 hour; this converts the red amorphous form to the gray hexagonal form and frees it of organic matter. This metallic selenium is removed by filtration, washed with water, and converted to the dioxide by the method of Baker and Maxson.[2]
5. A distilling head such as J-1104 obtained from Scientific Glass Apparatus

Company, Bloomfield, New Jersey, was used.
6. This treatment must obviously be omitted on the first preparation; the product will be light pink rather than snow white, as obtained when the reagents are purified in this manner.
7. This material is 96.5% pure as determined by precipitation of the nickel compound and is satisfactory as an analytical reagent.

3. Discussion

1,2-Cyclohexanedione has been prepared by brominating cyclohexanone and treating the resulting 2,6-dibromocyclohexanone with aqueous potassium hydroxide to obtain the dihydroxy compound which loses water to yield the dione;[3] by heating divinyl glycol with copper;[4] and by oxidizing cyclohexanone with selenium dioxide in an ethanolic solution.[5,6]

1,2-Cyclohexanedione dioxime has been prepared by oximating 1,2-cyclohexanedione with hydroxylammonium chloride in aqueous potassium hydroxide solution;[3,6] by oximating 2-isonitrosocyclohexanone with hydroxylammonium chloride;[7,8] by oximating sodium 2-isonitrosocyclohexanone with hydroxylammonium chloride in methanolic solution;[6] and by the reaction of hydroxylamine with 2-chloro-[9] or 2-bromocyclohexanone,[10] and with perhydro-4a,9a-epoxydibenzo-*p*-dioxin-5a,10a-diol.[11]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

iron (7439-89-6)

Cyclohexanone (108-94-1)

copper (7440-50-8)

nickel (7440-02-0)

Norit (7782-42-5)

selenium dioxide (7446-08-4)

potassium hydroxide (1310-58-3)

hydroxylamine (7803-49-8)

dioxane (5703-46-8)

selenium

selenious acid, selenous acid (7783-00-8)

1,2-Cyclohexanedione (765-87-7)

1,2-Cyclohexanedione dioxime, nioxime (492-99-9)

hydroxylammonium chloride

2,6-dibromocyclohexanone

divinyl glycol (764-78-3)

2-isonitrosocyclohexanone

sodium 2-isonitrosocyclohexanone

2-bromocyclohexanone

perhydro-4a,9a-epoxydibenzo-p-dioxin-5a,10a-diol

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Organic Syntheses, CV 4, 232

CYCLOHEXENE SULFIDE

[7-Thiabicyclo[4.1.0]heptane]

Submitted by Eugene E. van Tamelen[1]
Checked by Charles C. Price and Paul F. Kirk.

1. Procedure

Ninety-eight grams (1 mole) of cyclohexene oxide (Note 1) is divided into two approximately equal portions; one portion is added to a solution of 121 g. (1.25 moles) of potassium thiocyanate in 100 ml. of water and 75 ml. of 95% ethanol. After standing for 3–4 hours (Note 2) the clear solution is transferred to a 1-l. flask equipped with a mechanical stirrer. The second portion of oxide is added, and the resulting solution is stirred vigorously for 36 hours at room temperature. The supernatant layer and the aqueous phase are then decanted from the precipitated potassium cyanate into a 1-l. separatory funnel. The potassium cyanate is rinsed with 50 ml. of ether, which is subsequently added to the separatory funnel and used to extract the cyclohexene sulfide. The ether extract is washed twice with 50-ml. portions of saturated sodium chloride solution and then dried over anhydrous sodium sulfate. The excess ether is removed on the steam bath, and the residual liquid is distilled under reduced pressure through an 18-in. Vigreux column while the distillate is being cooled in ice. The main fraction boils at 71.5–73.5°/21 mm. (69–71°/19 mm.) (Note 3); n_D^{25} 1.5306–1.5311. A fore-run, boiling up to 71.5°/21 mm., yields more of the product on redistillation. The total yield of cyclohexene sulfide is 81.5–83.5 g. (71–73%).

2. Notes

1. The cyclohexene oxide (b.p. 129–134°) was prepared from 2-chlorocyclohexanol.[2]
2. During this time a temperature rise of about 5° occurs.
3. Cyclohexene sulfide can be stored at about 5° in a closed container for at least a month without apparent decomposition.

3. Discussion

Cyclohexene sulfide has been prepared by the action of thiourea, potassium

thiocyanate, or ammonium thiocyanate on cyclohexene oxide,[3] by the hydrolysis of S-(*trans*-2-hydroxycyclohexyl)thiuronium sulfate in sodium carbonate solution,[4] and by the alkaline hydrolysis of 2-mercaptocyclohexyl acetate or 2-acetylmercaptocyclohexyl acetate.[5].

The method described above is a modification of that of Snyder, Stewart, and Ziegler.[6]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

ether (60-29-7)

ammonium thiocyanate (1762-95-4)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

2-Chlorocyclohexanol (1561-86-0)

Cyclohexene oxide (286-20-4)

potassium thiocyanate (333-20-0)

potassium cyanate (590-28-3)

thiourea (62-56-6)

Cyclohexene sulfide, 7-Thiabicyclo[4.1.0]heptane (286-28-2)

2-mercaptocyclohexyl acetate

2-acetylmercaptocyclohexyl acetate

S-(trans-2-hydroxycyclohexyl)thiuronium sulfate

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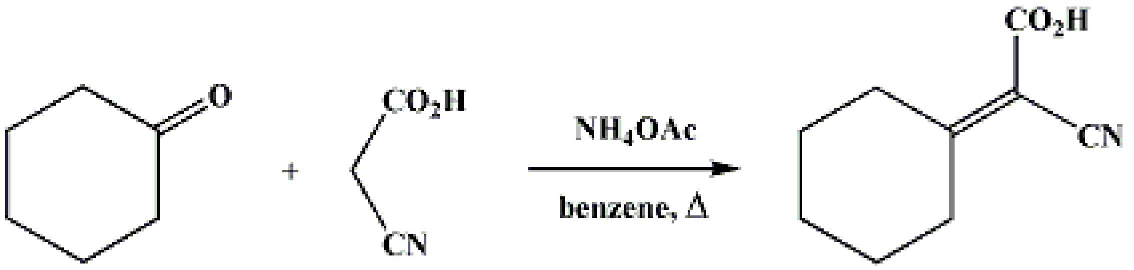
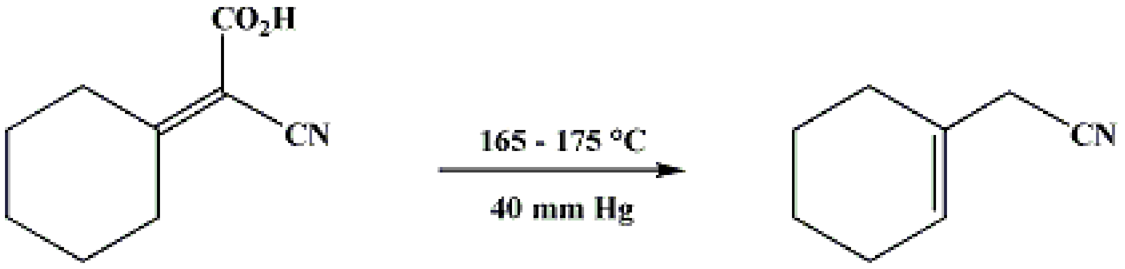
Organic Syntheses, CV 4, 234

CYCLOHEXYLIDENECYANOACETIC ACID AND 1-CYCLOHEXENYLACETONITRILE

[$\Delta^{1,\alpha}$-Cyclohexaneacetic acid, α-cyano-, and 1-Cyclohexene-1-acetonitrile]





Submitted by Arthur C. Cope, Alfred A. D'Addieco, Donald Edward Whyte, and Samuel A. Glickman[1].
Checked by T. L. Cairns and R. E. Heckert.

1. Procedure

In a 500-ml. round-bottomed flask equipped with a side arm through which a capillary tube is inserted (Note 1) are placed 108 g. (1.1 moles) of cyclohexanone (Note 2), 85 g. (1.0 mole) of cyanoacetic acid (Note 3), 3.0 g. (0.04 mole) of ammonium acetate (Note 4), and 75 ml. of benzene. The flask is attached to a modified Dean and Stark constant water separator,[2,3] which in turn is attached to an efficient reflux condenser. The mixture is heated in an oil bath at 160–165° so that a vigorous reflux is maintained, and the water that collects in the separator is removed at intervals. The theoretical amount of water (18 ml.) is collected in the course of 2 hours, and the mixture is heated under reflux for an additional 1 hour. At this point, Part A is followed for the isolation of cyclohexylidenecyanoacetic acid, or Part B for the preparation of 1-cyclohexenylacetonitrile.

A. *Cyclohexylidenecyanoacetic acid*. The benzene solution is diluted with an additional 100 ml. of hot benzene and transferred to a 1-l. separatory funnel. The solution is allowed to cool until it is slightly above room temperature, and then 200 ml.

of ether is added, small portions being used to rinse the reaction flask. After the solution has cooled to room temperature, it is washed with two 50-ml. portions of cold water (Note 5). The emulsion which normally forms at this point is broken by slow filtration through a Büchner funnel. The ether is removed, and the benzene solution is concentrated to approximately 300 ml. by distillation under reduced pressure. The solution is allowed to cool slowly to room temperature and then is cooled to about 10° in a refrigerator (Note 6). Cyclohexylidenecyanoacetic acid crystallizes as colorless prisms (Note 7). It is collected on a Büchner funnel, washed with two 100-ml. portions of cold benzene (10°), and dried in a vacuum desiccator to constant weight (88–92 g.). The filtrate and washings are concentrated by distillation under reduced pressure to about 150 ml. and cooled as in the first crystallization. The second crop of crystals is separated by filtration, washed with two 50-ml. portions of cold benzene (10°), and dried in a vacuum desiccator to constant weight (21–25 g.). Further concentration of the mother liquor and washings to a volume of about 75 ml. followed by cooling, filtering, washing with two 10-ml. portions of cold benzene, and drying yields an additional 2–5 g. The total yield of cyclohexylidenecyanoacetic acid, m.p. 110–110.5°, is 108–126 g. (65–76%).

B. *1-Cyclohexenylacetonitrile*. The benzene solution is allowed to cool to about 50°, and the flask is attached to a Vigreux column. The benzene is removed under reduced pressure, whereupon the residual cyclohexylidenecyanoacetic acid solidifies. The flask is then heated slowly in an oil bath to 165–175° while the system is evacuated with a water pump to a pressure of 35–45 mm. (not lower). The acid melts, decarboxylation occurs very rapidly, and the crude 1-cyclohexenylacetonitrile distils at 100–120°/35–45 mm.

The crude product is diluted with 50 ml. of ether, washed with 10 ml. of 5% sodium carbonate solution then with 10 ml. of water, and dried over anhydrous sodium sulfate. The ether is removed by distillation, and the residue is distilled under reduced pressure. 1-Cyclohexenylacetonitrile is collected as a colorless liquid, b.p. 74–75°/4 mm. (110–112°/25 mm.), n_D^{25} 1.4769, in a yield of 92–110 g. (76–91%).

2. Notes

1. The capillary aids ebullition in the distillation under reduced pressure in Part B and may be omitted if cyclohexylidenecyanoacetic acid is to be prepared according to Part A.
2. Commercial cyclohexanone obtained from the Barrett Division of the Allied Chemical and Dye Corporation was used.
3. Good quality commercial cyanoacetic acid was used. It may be purchased from the Benzol Products Company, Newark, New Jersey.
4. The amount of ammonium acetate specified permits completion of the condensation in a relatively short reaction period.
5. The product is washed with water to remove small amounts of ammonium acetate and acetamide which are formed from the ammonium acetate during the

condensation.
6. If the rate of cooling is too fast at this point, very small crystals difficult to wash are formed. The rate and time of cooling also control the proportions of product found in the three fractions.
7. The solvated crystals effloresce upon drying, leaving a white solid which is easily powdered.

3. Discussion

Cyclohexylidenecyanoacetic acid has been prepared by the condensation of cyclohexanone and cyanoacetic acid in the presence of piperidine[4,5] or basic ion-exchange resins,[6], and by the hydrolysis of ethyl cyclohexylidenecyanoacetate.[4]

1-Cyclohexenylacetonitrile has been prepared by the decarboxylation of cyclohexylidenecyanoacetic acid;[4,5] by the dehydration of 1-cyclohexenylacetamide;[5] by the condensation of cyclohexanone and cyanoacetic acid in the presence of piperidine;[7] by the condensation of cyclohexanone and ethyl cyanoacetate in the presence of sodium ethoxide;[4,8] and by the condensation of cyclohexanone and cyanoacetic acid in the presence of ammonium acetate followed by decarboxylation.[9] Ammonium acetate also has been used as a catalyst for the condensation of ketones with ethyl cyanoacetate.[3,10]

In a number of instances the decarboxylation of α,β-unsaturated (conjugated) cyanoacetic acids has been found to yield β,γ-unsaturated (unconjugated) nitriles.[5,11]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 108

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

$\Delta^{1,\alpha}$-Cyclohexaneacetic acid, α-cyano-

Acetamide (60-35-5)

Benzene (71-43-2)

ether (60-29-7)

ammonium acetate (631-61-8)

Cyclohexanone (108-94-1)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

piperidine (110-89-4)

sodium ethoxide (141-52-6)

Ethyl cyanoacetate (105-56-6)

cyanoacetic acid (372-09-8)

Cyclohexylidenecyanoacetic acid (37107-50-9)

1-Cyclohexenylacetonitrile, 1-Cyclohexene-1-acetonitrile (6975-71-9)

ethyl cyclohexylidenecyanoacetate

1-cyclohexenylacetamide

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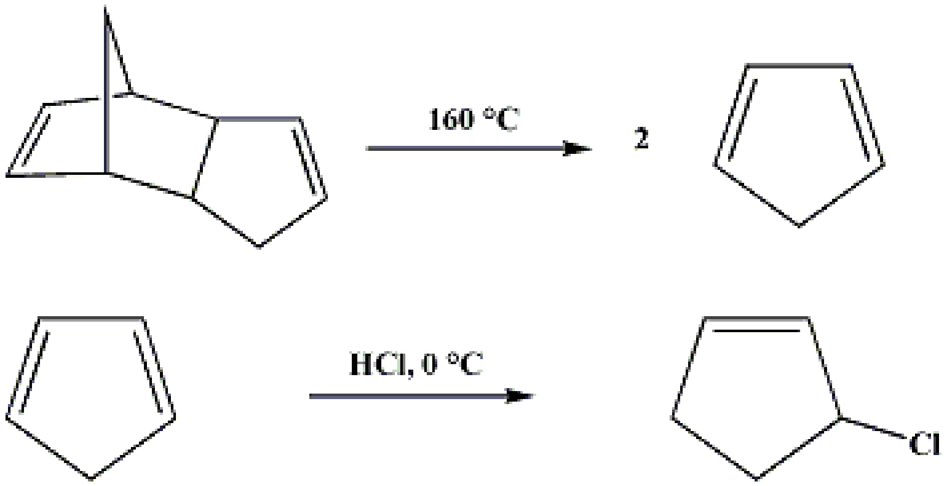
Organic Syntheses, CV 4, 238

CYCLOPENTADIENE AND 3-CHLOROCYCLOPENTENE

[Cyclopentene, 3-chloro-]



Submitted by Robert Bruce Moffett[1]
Checked by R. T. Arnold and George P. Scott.

1. Procedure

A. *Cyclopentadiene*. Two hundred milliliters (195 g.) of technical dicyclopentadiene (Note 1) is placed in a 500-ml. two-necked round-bottomed flask equipped with thermometer and an upright Friedrichs-type condenser (through which water at 50° (Note 2) is circulated). The ground-glass (Note 3) outlet of the Friedrichs condenser is connected to the side arm of a simple distilling head fitted with a thermometer and attached to an efficient water-cooled condenser held in a vertical position. At the lower end of this condenser is a receiver which consists of a carefully weighed 500-ml. two-necked round-bottomed flask immersed in a Dry Ice bath (Note 4) and protected from the air by a calcium chloride drying tube.

The flask containing dicyclopentadiene is now heated by means of an electric heating mantle or oil bath to approximately 160°, or until cyclopentadiene distils smoothly at 38–46° and a little dicyclopentadiene refluxes from the cold-finger (Friedrichs) condenser. After two-thirds of the dicyclopentadiene has been pyrolyzed (during the course of 4–5 hours), the residue in the flask may tend to become viscous and a higher temperature for the pyrolysis will be required in order to obtain rapid distillation of cyclopentadiene. In such an event it is desirable to discard the residue while it is still hot and mobile.

Cyclopentadiene dimerizes rapidly at room temperature and should be used immediately (Note 5) or stored at Dry Ice temperatures. As obtained above, the

product has a refractive index of about 1.433 at 25° and is quite satisfactory as a starting material for the following preparation (Note 6). The yield, which is determined by weighing the receiving flask plus product, depends upon the quality of dicyclopentadiene employed (Note 7).

B. *3-Chlorocyclopentene*. The flask containing cyclopentadiene is weighed and the quantity of cyclopentadiene determined (Note 8). A thermometer and gas inlet tube are passed through a two-holed rubber stopper which is fitted to the center neck of the flask; the side neck is fitted with a calcium chloride drying tube. While the flask containing cyclopentadiene is being cooled in a Dry Ice bath (Note 9), dry hydrogen chloride (Note 10) is passed in rapidly. During this operation the temperature of the reaction mixture must be kept below 0° and the flask swirled to ensure good mixing. From time to time the flask is detached, wiped dry, and weighed quickly in order to determine the amount of hydrogen chloride that has been added. An excess is to be avoided, and it is advisable to stop the addition about 10% short of the theoretical quantity.

For many purposes, this crude 3-chlorocyclopentene, either as such or in solution (Note 5), may be used without purification (Note 11) and (Note 12). If a purer product is desired, however, it may be distilled according to the following procedure.

The flask containing the crude product is equipped with a capillary tube and distilling head and surrounded by a water bath, which may be heated by a hot plate or steam cone. A water-cooled condenser connects the distilling head with the center neck of a two-necked receiver which is surrounded by a Dry Ice bath. The outer neck of the receiver is fitted with a Dry Ice condenser arranged in such a way that vapors which first escape the receiver are condensed and returned to it. This apparatus is connected through a second Dry Ice trap and soda-lime tower (Note 13) to a vacuum pump. A fore-run is removed at a bath temperature of 20° and a pressure of about 15 mm. The receiver is changed, and the product is distilled at 18–25°/5 mm. The temperature of the water bath should not exceed 30°. 3-Chlorocyclopentene is obtained as a colorless liquid in a yield of 70–90% based on cyclopentadiene; n_D^{26} 1.4708.

2. Notes

1. Coarse iron filings or turnings may be added to speed up the rate of depolymerization,[2] but they are of questionable value.
2. Water at 50° may be obtained by carefully mixing streams of hot and cold water taps. A more elegant method is to circulate water from a thermostatically controlled constant-temperature bath.
It has been suggested[3] that a modification of the equipment described for the preparation of dehydroacetic acid,[4] but without the fractionating column, is very convenient for the depolymerization of dicyclopentadiene. The partial condenser is filled with methylene chloride or other liquid with a boiling point in this range, and attached directly to the flask which contains the dicyclopentadiene.

This arrangement eliminates the inconvenience of maintaining a supply of water at 50°.
3. It is desirable to use ground-glass jointed equipment throughout.
4. An ice-salt bath may be used but is not so effective. A very convenient fluid for use in Dry Ice baths is ethylene glycol monomethyl ether (methyl Cellosolve, Carbide and Carbon Chemicals Corporation, New York, New York).
5. If the cyclopentadiene is to be used in solution, it is convenient to collect it directly in a flask containing a weighed amount of the desired solvent (e.g., toluene or ether).
6. Further purification, if desired, may be accomplished by distillation at about 20 mm. while collecting the product in a Dry Ice cooled receiver.
7. The checkers used Eastman Kodak Company blue lable grade dicyclopentadiene and obtained yields approximating 87%.
8. This reaction should be carried out with undiluted cyclopentadiene if reasonably pure distilled 3-chlorocyclopentene is to be isolated. However, if a distilled product is not required, a solution of cyclopentadiene (Note 5) may be used. 3-Chlorocyclopentene is somewhat more stable in solution.
9. If Dry Ice is not available, an ice-salt bath may be used but then the hydrogen chloride must be added at a much slower rate.
10. Hydrogen chloride gas from a cylinder is most convenient; however, it may be generated if desired.[2]
11. If the temperature has been kept sufficiently low and an excess of hydrogen chloride avoided, the product will be a clear (or only slightly turbid) colorless, mobile liquid. If an excess of hydrogen chloride seems to be present, or if the product is dark, distillation is advisable.
12. 3 Chlorocyclopentene is unstable at room temperature and soon polymerizes to a black tar which is very difficult to remove from the apparatus. It should be used at once or stored at temperatures well below 0°. All apparatus must be cleaned as soon as possible after completion of the experiment. Ground-glass joints, if not separated soon after the reaction is completed, may become cemented together.
13. In spite of the Dry Ice cooled trap and soda-lime tower, some low-boiling material (as evidenced by the odor) often reaches the pump. It is therefore recommended that an old pump be used and the oil changed immediately after the experiment.

3. Discussion

The only practical laboratory preparation of cyclopentadiene is by the depolymerization of dicyclopentadiene.[5,6,7,8] 3-Chlorocyclopentene has been prepared by the addition of hydrogen chloride to cyclopentadiene.[9,10,11,12,13]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 738
- Org. Syn. Coll. Vol. 5, 60
- Org. Syn. Coll. Vol. 5, 96
- Org. Syn. Coll. Vol. 7, 339
- Org. Syn. Coll. Vol. 8, 31
- Org. Syn. Coll. Vol. 8, 298
- Org. Syn. Coll. Vol. 9, 67

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrogen chloride (7647-01-0)

ether (60-29-7)

iron (7439-89-6)

toluene (108-88-3)

methylene chloride (75-09-2)

Dehydroacetic acid (520-45-6)

methyl Cellosolve, ethylene glycol monomethyl ether (109-86-4)

CYCLOPENTADIENE (542-92-7)

3-Chlorocyclopentene, Cyclopentene, 3-chloro-, 3 Chlorocyclopentene (96-40-2)

dicyclopentadiene

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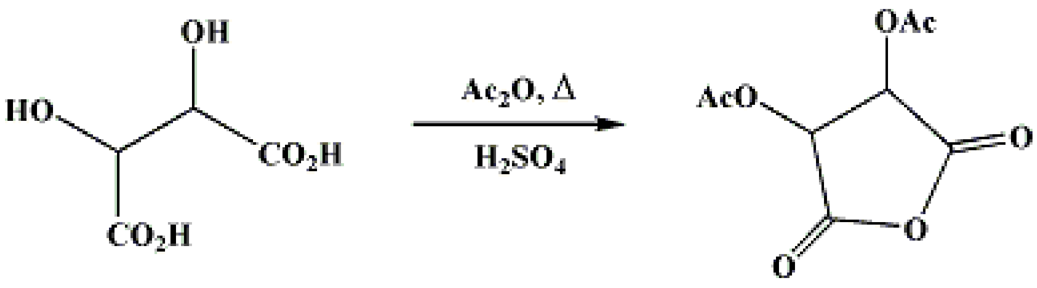
DIACETYL-*d*-TARTARIC ANHYDRIDE

[Tartaric anhydride, diacetate of *d*-]



l - isomer

Submitted by R. L. Shriner and C. L. Furrow, Jr.[1].
Checked by N. J. Leonard and R. R. Sauers.

1. Procedure

In a 500-ml. three-necked round-bottomed flask fitted with a liquid-sealed stirrer and two reflux condensers (Note 1) is placed 40 g. (0.27 mole) of anhydrous, powdered *d*-tartaric acid (Note 2). A solution of 1.2 ml. of concentrated sulfuric acid in 136 g. (126 ml., 1.33 moles) of acetic anhydride is added, and the stirrer is started. The mixture warms up, and the tartaric acid goes into solution. The solution is heated gently (Note 1) under reflux with stirring for 10 minutes. The solution is poured into a beaker and cooled for 1 hour in an ice bath. The crude crystalline product is collected on a 15-cm. Büchner funnel (Note 3), washed twice with 20-ml. portions of dry benzene, stirred mechanically with 175 ml. of cold absolute ether, filtered, and placed in a vacuum desiccator over phosphorus pentoxide and paraffin shavings for 24 hours. The yield of diacetyl-*d*-tartaric anhydride is 41–44.5 g. (71–77%), m.p. 133–134° (Note 4), $[\alpha]_D^{20}$ 97.2° in dry chloroform (*c* = 0.47).

2. Notes

1. The reaction may be quite vigorous at its start, and the use of a large flask with two condensers is advised.
2. The anhydrous *d*-tartaric acid was obtained from Matheson, Coleman and Bell, East Rutherford, New Jersey.
3. Additional but lower-grade product may be acquired by pouring the mother liquor into petroleum ether and filtering the mixture. The recovered product is washed twice with absolute ether, filtered, and dried. About 7 g. of product, m.p. 129–131°, is thus obtained.
4. The product is not stable and should be prepared only as needed. It may be kept in a vacuum desiccator over phosphorus pentoxide and paraffin, but the melting point drops about 1 degree during the first 4 days and then remains

constant at approximately 132–134°. If placed in an ordinary stoppered bottle, the product becomes gummy and the melting point falls to about 100° within 3 days. Attempts to recrystallize the anhydride invariably led to decomposition and lowered melting point.

3. Discussion

The acetylation of *d*-tartaric acid with acetic anhydride has been effected by means of sulfuric acid,[2,3] hydrogen chloride,[4] or 85% phosphoric acid.[5]

References and Notes

1. State University of Iowa, Iowa City, Iowa.
2. Chattaway and Parkes, *J. Chem. Soc.*, **123**, 663 (1923).
3. Roberts, *J. Chem. Soc.*, **1952**, 3315.
4. Lucas and Baumgarten, *J. Am. Chem. Soc.*, **63**, 1653 (1941).
5. Fuchs (to Emulsol Corp.), Brit. pat. 674,710 [*C. A.*, **47**, 4904 (1953)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

Tartaric anhydride, diacetate of d-

sulfuric acid (7664-93-9)

hydrogen chloride (7647-01-0)

Benzene (71-43-2)

ether (60-29-7)

acetic anhydride (108-24-7)

chloroform (67-66-3)

phosphoric acid (7664-38-2)

tartaric acid (87-69-4)

phosphorus pentoxide (1314-56-3)

D-tartaric acid (147-71-7)

Diacetyl-D-tartaric anhydride

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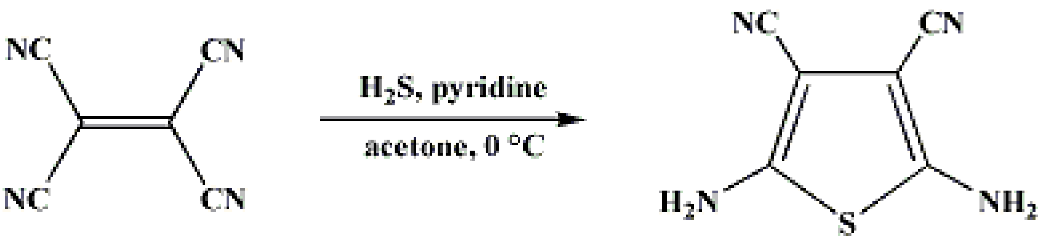
2,5-DIAMINO-3,4-DICYANOTHIOPHENE

[3,4-Thiophenedicarbonitrile, 2,5-diamino-]



Submitted by W. J. Middleton[1]
Checked by James Cason and Ralph J. Fessenden.

1. Procedure

Since carbon disulfide is highly flammable and hydrogen sulfide highly toxic, this reaction should be carried out in a hood, with due precaution against fire. It is also recommended that tetracyanoethylene not be allowed to come into contact with the skin.

A 1-l. three-necked flask is fitted with a sealed mechanical stirrer, a condenser protected by a drying tube, a thermometer, and an inlet tube extending to the bottom of the flask. A solution of 25.6 g. (0.2 mole) of recrystallized tetracyanoethylene (p. 877) in 300 ml. of acetone is placed in the flask, and 300 ml. of carbon disulfide is added. The flask and its contents are cooled to 0° by means of a salt-ice bath. With good stirring, hydrogen sulfide is passed into the reaction mixture at a moderate rate while the temperature is maintained at 0–5°. The solution becomes milky after a few minutes owing to the formation of colloidal sulfur. The hydrogen sulfide addition is continued for about 30 minutes, or until the solution is thoroughly saturated.

The hydrogen sulfide addition is temporarily suspended, and 100 ml. of pyridine is added rapidly in one portion through the condenser as the solution is stirred vigorously (Note 1). The solution becomes clear, and then 2,5-diamino-3,4-dicyanothiophene begins to precipitate immediately. The hydrogen sulfide addition is resumed and is continued for about 30 minutes while the temperature of the reaction mixture is maintained at 0–5°. Finally, the reaction mixture is stirred for an additional 30 minutes at 0–5°, then the yellow precipitate of the thiophene is collected on a Büchner funnel, thoroughly washed with about 500 ml. of acetone, and dried in the air or in a vacuum desiccator. The yield of crude product of yellow or buff color amounts to 30–31 g. (92–95%).

This material is sufficiently pure for most purposes. If a purer product is desired, the crude material is dissolved in 300 ml. of dimethylformamide, 10 g. of activated

alumina (48–100 mesh) is added, and the mixture is filtered. The filtrate is heated to 80–90° on a steam bath, then 1 l. of boiling water is added immediately (Note 2). The resultant mixture is cooled in an ice bath, and the light buff crystals of 2,5-diamino-3,4-dicyanothiophene that separate are collected on a Büchner funnel and thoroughly washed with 500 ml. of acetone; weight 26–28 g. (79–85%). The product has no definite melting point but sublimes with some decomposition when heated above 250°.

2. Notes

1. Unless the pyridine is added quite rapidly, some of the product will begin to precipitate before all of the sulfur has dissolved, and the final product will be contaminated with sulfur.
2. This operation should be carried out as rapidly as possible, since prolonged heating in dimethylformamide results in loss of product.

3. Discussion

2,5-Diamino-3,4-dicyanothiophene has been prepared only by the action of hydrogen sulfide or sodium sulfide on tetracyanoethylene or tetracyanoethane.[2] Unlike most aminothiophenes, 2,5-diamino-3,4-dicyanothiophene is very stable and can be stored indefinitely. Its amino groups show the normal reactivity of aromatic amines. For example, they readily condense with aromatic aldehydes to form highly colored bis-anils.[2] Hot 10% sodium hydroxide rearranges 2,5-diamino-3,4-dicyanothiophene to 2-amino-3,4-dicyano-5-mercaptopyrrole.[2]

References and Notes

1. Contribution No. 483 from Central Research Department, Experimental Station, E. I. du Pont de Nemours & Co., Wilmington, Delaware.
2. Middleton, Englehardt, and Fisher, *J. Am. Chem. Soc.*, **80**, 2822 (1958).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alumina

sodium hydroxide (1310-73-2)

hydrogen sulfide (7783-06-4)

sulfur (7704-34-9)

acetone (67-64-1)

pyridine (110-86-1)

carbon disulfide (75-15-0)

sodium sulfide (1313-82-2)

dimethylformamide (68-12-2)

2,5-Diamino-3,4-dicyanothiophene, 3,4-Thiophenedicarbonitrile, 2,5-diamino- (17989-89-8)

Tetracyanoethylene (670-54-2)

tetracyanoethane

2-amino-3,4-dicyano-5-mercaptopyrrole

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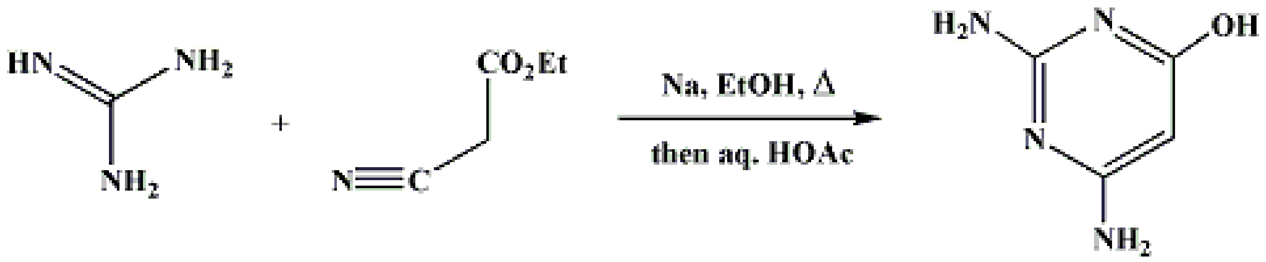
2,4-DIAMINO-6-HYDROXYPYRIMIDINE

[4-Pyrimidinol, 2,6-diamino-]



Submitted by J. A. VanAllan[1]
Checked by Cliff S. Hamilton and John D. Sculley.

1. Procedure

A solution of sodium ethoxide is prepared from 23 g. (1 g. atom) of sodium and 250 ml. of anhydrous ethanol in a 1-l. round-bottomed flask fitted with a reflux condenser carrying a calcium chloride drying tube. After the sodium has dissolved, the solution is cooled and 113 g. (1 mole) of ethyl cyanoacetate is added (Note 1). This mixture is allowed to stand while a second solution of sodium ethoxide of the same volume and concentration is prepared. To this solution is added 97 g. (1.02 moles) of guanidine hydrochloride. The sodium chloride is separated by filtration, and the clear filtrate containing guanidine is added to the solution of ethyl sodiocyanoacetate. This mixture is heated for 2 hours under reflux and is then evaporated to dryness at atmospheric pressure. The solid product is dissolved in 325 ml. of boiling water and acidified with 67 ml. of glacial acetic acid. Upon cooling of the solution, 101–103 g. (80–82%) of yellow needles separates; m.p. 260–270° (dec.) (Note 2).

2. Notes

1. Eastman Kodak Company white label grade of ethyl cyanoacetate was used by the checkers.
2. Analyses carried out by the checkers showed that the product is quite pure.

3. Discussion

This procedure is a modification of the method of Traube,[2] which has been studied by Berezovskii and Strel'chunas.[3] The reaction has been carried out in the presence of alkali or alkali earth hydroxides.[4]

References and Notes

1. Eastman Kodak Company, Rochester, New York.
2. Traube, *Ber.*, **33**, 1371 (1900); Ger. pat. 135,371 [*Frdl.*, **6**, 1192 (1900–1902)].
3. Berezovskii and Strel'chunas, *Trudy Vsesoyuz. Nauch. Issledovatel. Vitamin Inst.*, **5**, 28 (1954) [*C. A.*, **51**, 7379 (1957)].
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

acetic acid (64-19-7)

sodium chloride (7647-14-5)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

Ethyl cyanoacetate (105-56-6)

guanidine (113-00-8)

2,4-Diamino-6-hydroxypyrimidine, 4-Pyrimidinol, 2,6-diamino- (56-06-4)

guanidine hydrochloride (50-01-1)

ethyl sodiocyanoacetate

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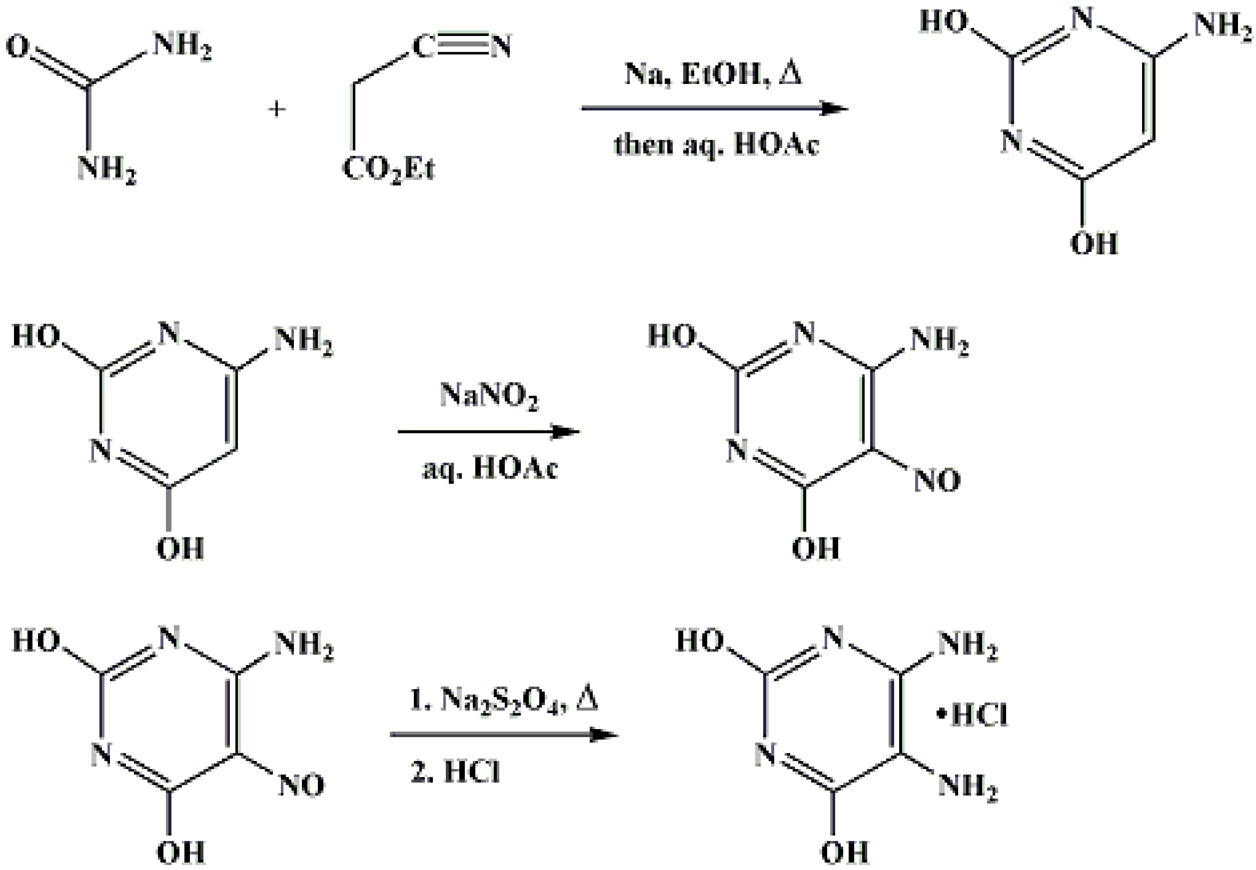
DIAMINOURACIL HYDROCHLORIDE

[Uracil, 5,6-diamino-, hydrochloride]



Submitted by Wm. R. Sherman and E. C. Taylor, Jr.[1].
Checked by T. L. Cairns and D. S. Acker.

1. Procedure

In a 3-l., three-necked flask (Note 1) equipped with a reflux condenser and an efficient stirrer is placed 1 l. of absolute (99.8%) ethanol. To this is added 39.4 g. (1.72 g. atom) of sodium, and, after solution is complete (Note 2), 91.5 ml. (97.2 g., 0.86 mole) of ethyl cyanoacetate (Note 3) and 51.5 g. (0.86 mole) of urea are added. The mixture is heated under reflux on a steam bath with vigorous stirring for 4 hours. After about 2 hours, the reaction mixture becomes practically solid, and the stirrer may have to be stopped. At the end of the reaction time, 1 l. of hot (80°) water is added to the reaction mixture, and stirring is resumed. After complete solution has taken place, the stirred mixture is heated at 80° for 15 minutes and is then neutralized to litmus with glacial acetic acid (Note 4). Additional glacial acetic acid (75 ml.) is added, followed by cautious addition of a solution of 64.8 g. (0.94 mole) of sodium nitrite dissolved in 70 ml. of water. The rose-red nitroso compound separates almost immediately as an expanded precipitate which almost stops the stirrer. After a few minutes the nitroso

compound is removed by filtration and washed twice with a small amount of ice water. The moist material is transferred back to the 3-l. flask, and 430 ml. of warm water (50°) is added.

This procedure should be conducted in a good hood. The slurry is stirred while being heated on a steam bath, and solid sodium hydrosulfite is added until the red color of the nitroso compound is completely bleached (Note 5). Then an additional 30 g. of sodium hydrosulfite is added; the light tan suspension is stirred with heating for 15 minutes more and is allowed to cool. The dense diaminouracil bisulfite is filtered from the cooled solution, washed well with water, and partially dried.

The crude product is readily purified by conversion to its hydrochloride salt. The bisulfite salt is transferred to a wide-mouthed 1-l. flask, and concentrated hydrochloric acid is added until the consistency of the resulting mixture is such as to permit mechanical stirring (100 to 200 ml. of acid). The slurry is heated on a steam bath with stirring for 1 hour (*Hood!*). The tan diaminouracil hydrochloride is filtered on a sintered glass funnel, washed well with acetone, and vacuum-dried over phosphorus pentoxide. The yield of diaminouracil hydrochloride is 104–124 g. (68–81%) (Note 6) and (Note 7).

2. Notes

1. Since the reaction mixture becomes almost solid after nitrosation, one of the necks of the flask should be of large diameter to facilitate removal of the product.
2. The usual precautions must be observed with respect to the hydrogen evolved. The reflux condenser is capped with a drying tube after hydrogen evolution ceases. The sodium ethoxide must be used immediately after its preparation, for it discolors rapidly and in this state leads to an impure product.
3. Eastman Kodak white label grade, Dow Chemical, and Kay-Fries ethyl cyanoacetate were all used with equal success.
4. Caution must be exercised in the addition of the glacial acetic acid in order to avoid frothing of the hot solution. The frothing becomes most vigorous as the 6-aminouracil begins to precipitate from the solution. The heating and subsequent neutralization assure cyclization of the initially formed cyanoacetylurea to 6-aminouracil. The nitrosation is carried out on the two-phase (solid-liquid) system.
5. The amount of sodium hydrosulfite used depends on its age and quality. The submitters never had to use more than 250 g. per run.
6. The preparation may be interrupted after the nitroso compound has been separated or after the crude bisulfite salt has been isolated. This preparation has been satisfactorily carried out on a scale seven times that given.
7. If placed in a preheated melting-point block, the product melts with decomposition in the range 300–305°. Diaminouracil hydrochloride in 0.1*N* hydrochloric acid has a well-defined absorption peak at 260 m•, log ε = 4.24.

Satisfactory analyses for nitrogen and chlorine are difficult to obtain with this type of compound although good results are obtained for carbon and hydrogen.

3. Discussion

The procedure for the formation of diaminouracil bisulfite is slightly modified from that of Cain, Mallette, and Taylor,[2] which in turn is derived from preparations of Bogert and Davidson,[3] and Traube.[4] The sulfate salt may be formed in lower yield than the hydrochloride described here by dissolving the bisulfite salt in aqueous base and precipitating with sulfuric acid.[3,4] The hydrochloride is appreciably soluble in water, while the sulfate salt is only slightly soluble.

Other methods of reducing the nitroso compound include the use of ammonium sulfide[4] and hydrogenation utilizing Adams catalyst.[5]

Bredereck, Hennig, and Pfleiderer[6] describe a method for the formation of diaminouracil from uric acid which involves acetylation and subsequent hydrolysis of the acetyl derivative. This preparation was attempted on a large scale by the submitters without success (even when the acetylation step was carried out twice on the same material).

References and Notes

1. University of Illinois, Urbana, Illinois.
2. Cain, Mallette, and Taylor, *J. Am. Chem. Soc.*, **68**, 1996 (1946).
3. Bogert and Davidson, *J. Am. Chem. Soc.*, **55**, 1668 (1933).
4. Traube, *Ber.*, **33**, 1371 (1900).
5. E. C. Taylor, Jr., unpublished results.
6. Bredereck, Hennig, and Pfleiderer, *Ber.*, **86**, 321 (1953).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

hydrogen (1333-74-0)

nitrogen (7727-37-9)

sodium nitrite (7632-00-0)

sodium hydrosulfite (7775-14-6)

acetone (67-64-1)

carbon (7782-42-5)

chlorine (7782-50-5)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

urea (57-13-6)

Ethyl cyanoacetate (105-56-6)

ammonium sulfide

uric acid

Diaminouracil hydrochloride (53608-89-2)

Uracil, 5,6-diamino-, hydrochloride

diaminouracil bisulfite

6-aminouracil

cyanoacetylurea (1448-98-2)

diaminouracil

phosphorus pentoxide (1314-56-3)

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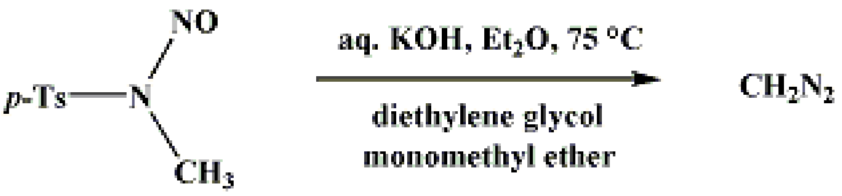
Organic Syntheses, CV 4, 250

DIAZOMETHANE

[Methane, diazo-]



Submitted by Th. J. de Boer and H. J. Backer[1].
Checked by James Cason, Max J. Kalm, and R. F. Porter.

1. Procedure

Caution! Diazomethane is toxic and prone to cause development of specific sensitivity; in addition, it is potentially explosive. Hence one should wear heavy gloves and goggles while performing this experiment and should work behind a safety screen or a hood door with safety glass. Also, it is recommended that ground joints and sharp surfaces be avoided. Thus all glass tubes should be carefully fire-polished, connections should be made with rubber stoppers, and separatory funnels should be avoided, as should etched or scratched flasks. Furthermore, at least one explosion of diazomethane has been observed at the moment crystals (sharp edges!) suddenly separated from a supersaturated solution. Stirring by means of a Teflon-coated magnetic stirrer is greatly to be preferred to swirling the reaction mixture by hand, for there has been at least one case of a chemist whose hand was injured by an explosion during the preparation of diazomethane in a hand-swirled reaction vessel.

It is imperative that diazomethane solutions not be exposed to direct sunlight or placed near a strong artificial light, because light is thought to have been responsible for some of the explosions that have been encountered with diazomethane. Particular caution should be exercised when an organic solvent boiling higher than ether is used. Because such a solvent has a lower vapor pressure than ether, the concentration of diazomethane in the vapor above the reaction mixture is greater and an explosion is more apt to occur.

Most diazomethane explosions take place during its distillation. Hence diazomethane should not be distilled unless the need justifies it. An ether solution of diazomethane satisfactory for many uses can be prepared as described by Arndt,[2] where nitrosomethylurea is added to a mixture of ether and 50% aqueous potassium hydroxide and the ether solution of diazomethane is subsequently decanted from the aqueous layer and dried over potassium hydroxide pellets (not sharp-edged sticks!).

When distilled diazomethane is required, the present procedure is particularly good because at no time is much diazomethane present in the distilling flask.

The hazards associated with diazomethane have been discussed by Gutsche,[3] and LeWinn[4] has reported on a fatal case of diazomethane poisoning.

A 125-ml. distilling flask is fitted with a condenser set for distillation and with a long-stem dropping funnel. The condenser is connected by means of an adapter to a 250-ml. Erlenmeyer flask. Through a second hole in the stopper of the Erlenmeyer flask is placed an outlet tube bent so as to pass into and nearly to the bottom of a second Erlenmeyer flask which is not stoppered. Both receivers are cooled in an ice-salt mixture; in the first is placed 10 ml. of ether (Note 1), and in the second 35 ml. of ether. The inlet tube passes below the surface of the ether in the second flask.

In the distilling flask are placed a solution of 6 g. of potassium hydroxide dissolved in 10 ml. of water, 35 ml. of Carbitol (Note 2), 10 ml. of ether (Note 1), and the "Teflon"-coated bar of a magnetic stirrer (Note 3). The dropping funnel is attached and adjusted so that the stem is just above the surface of the solution in the distilling flask. There is placed in the dropping funnel a solution of 21.5 g. (0.1 mole) of *p*-tolylsulfonylmethylnitrosamide (p.943) in 125 ml. of ether (Note 4). The distilling flask is heated in a water bath (Note 3) at 70–75°, the stirrer is started, and the nitrosamide solution is added at a regular rate during 15–20 minutes. As soon as all the nitrosamide solution has been added, additional ether (Note 1) is placed in the dropping funnel and added at the previous rate until the distillate is colorless. Usually 50–100 ml. additional of ether is required. The distillate contains 2.7–2.9 g. (64–69%) of diazomethane, as determined by titration[2] (Note 5) and (Note 6).

2. Notes

1. If an alcohol-free solution of diazomethane is required, absolute ether should be used throughout this preparation.
2. The Carbitol (monoethyl ether of diethylene glycol) was the Carbide and Carbon Chemicals Company product, which was distilled before use, b.p. 192–196°. It is a suitable solvent to render the reactants mutually soluble. Aqueous alkali with an ether solution of the nitrosamide does not yield diazomethane.
3. The same results may be obtained by an occasional careful agitation of the flask by hand; however, an explosion during this agitation by hand would be unfortunate. If the flask is placed in contact with the bottom of a beaker containing the heated water, and the magnetic stirring unit is placed in contact with the beaker, the bar may be spun satisfactorily. The checkers used the magnetic stirring apparatus, no. 9235-R, supplied by the A. H. Thomas Company, Philadelphia, Pa., and heated the water bath with the thermostated electric immersion heater, "Chill Chaser," model S-1005, supplied by the Still-Man Company, New York 56, N. Y. Satisfactory results should also be obtained

by use of a combined heater and magnetic stirrer, such as no. 25210T supplied by the Will Corporation, New York 12, N. Y.
4. Nitrosamide prepared as described (p. 943), not recrystallized, is suitable for the present preparation. The solubility of the nitrosamide in ether drops sharply with temperature; below 20°, more than the specified amount of ether may be required, especially if recrystallized nitrosamide is used.
5. If an entirely dry solution of diazomethane is required, round pellets of potassium hydroxide should be used.[2]
6. The submitters reported that, in cases where the presence of alcohol in diazomethane solutions is not objectionable, they utilized ethanol as the solvent for the reaction mixture in which the diazomethane was prepared. They believe that ethanol has an advantage over Carbitol in that mixing of the reactants is achieved readily during the distillation, since the mixture is not viscous (see *Caution*).
They used the same apparatus as described in the present procedure with the following exceptions: (1) the reaction flask was of 200-ml. capacity, (2) the first receiver was an empty 500-ml. Erlenmeyer flask, and the second flask of 100-ml. capacity contained 40 ml. of ether, and (3) a magnetic stirrer was not employed. In the reaction flask was placed a solution of 10 g. of potassium hydroxide in 15 ml. of water and 50 ml. of 95% ethanol. The water bath was heated to 60–65° and a solution of 43 g. (0.2 mole) of *p*-tolylsulfonylmethylnitrosamide (p.943) in 200 ml. of ether was added from the dropping funnel in 45 minutes. After all had been added, ether (about 30 ml.) was introduced through the dropping funnel until the condensing ether became colorless. The combined solutions in the receivers contained 5.9–6.1 g. (70–73%) of diazomethane.

3. Discussion

The more important methods of preparation of diazomethane include those from nitrosomethylurea,[2] nitrosomethylurethan,[5] N-nitroso-β-methylaminoisobutyl methyl ketone,[6] and 1-methyl-1-nitroso-3-nitroguanidine.[7,8] It also has been prepared from N-nitrosoacetamide,[9] from N,N'-dimethyl-N,N'-dinitrosoöxamide and methylamine[10] or other alkaline reagents,[11] from nitrosyl chloride and methylamine,[12] from the reaction of bis-(N-methyl-N-nitroso) terephthalamide with alkali,[13] and by treatment of the sodium salt of formaldehyde oxime with chloramine.[14]

The advantage of the present method[15] resides in the stability of the starting material and the manipulative advantage resulting from its solubility in organic solvents.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 78

- Org. Syn. Coll. Vol. 4, 221
- Org. Syn. Coll. Vol. 4, 943
- Org. Syn. Coll. Vol. 5, 231
- Org. Syn. Coll. Vol. 5, 351
- Org. Syn. Coll. Vol. 5, 877
- Org. Syn. Coll. Vol. 5, 1099
- Org. Syn. Coll. Vol. 6, 386
- Org. Syn. Coll. Vol. 6, 432
- Org. Syn. Coll. Vol. 6, 576
- Org. Syn. Coll. Vol. 6, 613
- Org. Syn. Coll. Vol. 8, 196

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4. LeWinn, *Am. J. Med. Sci.*, **218**, 556 (1949).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Carbitol

ethanol (64-17-5)

ether (60-29-7)

potassium hydroxide, potassium hydroxide pellets (1310-58-3)

methylamine (74-89-5)

nitrosyl chloride (2696-92-6)

Diazomethane, Methane, diazo- (334-88-3)

Nitrosomethylurea

nitrosomethylurethan

chloramine (10599-90-3)

N-Nitroso-β-methylaminoisobutyl methyl ketone (16339-21-2)

1-methyl-1-nitroso-3-nitroguanidine (674-81-7)

N-nitrosoacetamide

bis-(N-methyl-N-nitroso) terephthalamide

monoethyl ether of diethylene glycol (111-90-0)

p-Tolylsulfonylmethylnitrosamide

sodium salt of formaldehyde oxime

N,N'-dimethyl-N,N'-dinitrosooxamide

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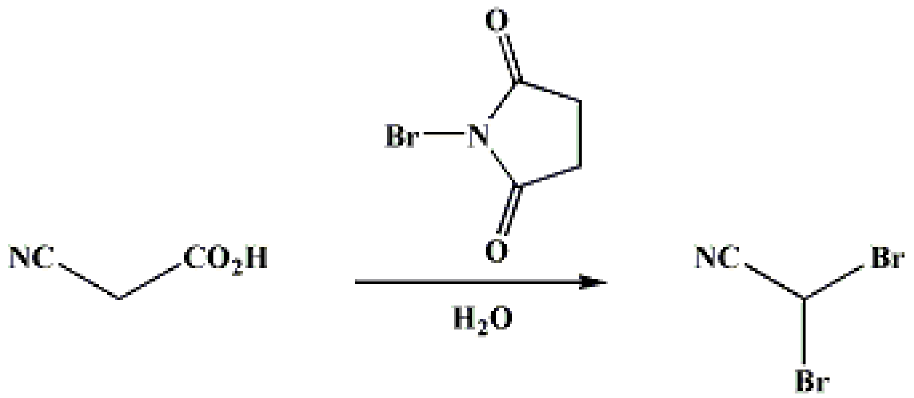
DIBROMOACETONITRILE

[Acetonitrile, dibromo-]



Submitted by James W. Wilt and James L. Diebold[1].
Checked by B. C. Mckusick and H. E. Knipmeyer.

1. Procedure

A solution of 63.8 g. (0.75 mole) of cyanoacetic acid (Note 1) in 750 ml. of cold water is placed in a 2-l. beaker. N-Bromosuccinimide (267 g., 1.5 moles) (Note 2) is added in portions with good mechanical stirring over a period of about 6 minutes (Note 3). The slightly exothermic reaction which attends the separation of the dibromoacetonitrile as a heavy oil is completed in about 20 minutes, after which time the beaker is placed in an ice bath and allowed to cool for 2 hours (Note 4).

The precipitated succinimide is collected on a large Büchner funnel atop a 2-l. filter flask and is washed with six 50-ml. portions of methylene chloride. The lower organic layer in the filtrate is separated from the aqueous phase, which is extracted with two 25-ml. portions of methylene chloride. The organic layer and the extracts are combined, washed vigorously with 50 ml. of a 5% sodium hydroxide solution (Note 5) and three 80-ml. portions of water, and dried over 10 g. of anhydrous sodium sulfate for several hours in a flask wrapped with aluminum foil (Note 6).

The colorless dried oil is distilled through a 45-cm. Widmer column (Note 7). Most of the methylene chloride is removed by heating the contents of the distillation pot to 75° at atmospheric pressure. The pressure is then lowered to about 20 mm., and 112–129 g. (75–87%) of dibromoacetonitrile is collected as a colorless oil, b.p. 70–72°/20 mm., n_D^{25} 1.540–1.542, d_4^{20} 2.369 (Note 8) and (Note 9).

2. Notes

1. Commercial cyanoacetic acid (Eastman Kodak Company), m.p. 67–71.5°,

about 98% pure, was found satisfactory for this preparation.
2. N-Bromosuccinimide obtained from Matheson, Coleman and Bell, Inc., as well as from Arapahoe Chemicals, Inc., was used as received. The N-chlorosuccinimide (Note 9) was commercial material from Arapahoe Chemicals, Inc.
3. The N-bromosuccinimide should be added as rapidly as possible consistent with the foaming produced by evolution of carbon dioxide.
4. About one-third of the succinimide (50–53 g.) precipitates from the solution during the cooling period, thus rendering the subsequent purification of the nitrile easier. Sometimes the solution must be seeded to start the precipitation. The checkers found it necessary to store the mixture in a refrigerator over-night in order to obtain 50–53 g. of succinimide.
5. The basic aqueous phase becomes pink through action of the base on dibromoacetonitrile.
6. Pure dibromoacetonitrile is fairly stable to air and light, but traces of basic impurities cause it to become discolored (Note 5). Protective shielding retards this coloration.
7. Unless an efficient column is used, some nitrile distils over with the methylene chloride. The checkers used a 120-cm. spinning-band column.
8. The product shows good shelf stability, but, as a precautionary measure, it is best stored under nitrogen in a sealed brown vessel. Dichloroacetonitrile (Note 9) is less sensitive and may be stored in an ordinary glass-stoppered brown bottle.
9. In exactly the same fashion, from 63.8 g. (0.75 mole) of cyanoacetic acid and 200.3 g. (1.5 moles) of N-chlorosuccinimide there may be obtained 45–54 g. (55–65%) of colorless dichloroacetonitrile, b.p. 110–112°/760 mm., n_D^{25} 1.439, d_4^{20} 1.369. Since this reaction is slightly slower, 30 minutes should be allowed for the reaction before chilling.

3. Discussion

Dibromoacetonitrile has been prepared by the dehydration of dibromoacetamide with phosphorous pentoxide[2,3] and by the present method.[4] An early report that dibromoacetonitrile can be obtained from cyanoacetic acid by treatment with bromine,[5] a method similar to that described here, was later shown to be wrong.[2] Dibromoacetonitrile has been prepared also by the bromination of ethyl cyanoacetate in the presence of magnesium oxide.[6]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

phosphorous pentoxide

sodium hydroxide (1310-73-2)

bromine (7726-95-6)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

Ethyl cyanoacetate (105-56-6)

cyanoacetic acid (372-09-8)

methylene chloride (75-09-2)

Succinimide (123-56-8)

magnesium oxide

N-bromosuccinimide (128-08-5)

dichloroacetonitrile (3018-12-0)

Dibromoacetonitrile, Acetonitrile, dibromo- (3252-43-5)

N-chlorosuccinimide (128-09-6)

dibromoacetamide

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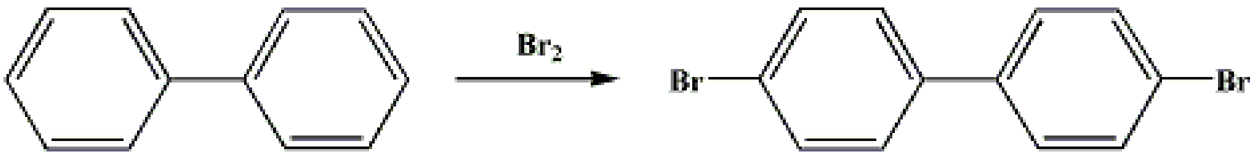
4,4'-DIBROMOBIPHENYL

[Biphenyl, 4,4'-dibromo-]



Submitted by Robert E. Buckles and Norris G. Wheeler[1].
Checked by R. S. Schreiber, Wm. Bradley Reid, Jr., and Robert W. Jackson.

1. Procedure

In a 15-cm. evaporating dish is placed 15.4 g. (0.10 mole) of finely powdered biphenyl (Note 1). The dish is set on a porcelain rack in a 30-cm. desiccator with a 10-cm. evaporating dish under the rack containing 39 g. (12 ml., 0.24 mole) of bromine. The desiccator is closed, but a very small opening is provided for the escape of hydrogen bromide (Note 2). The biphenyl is left in contact with the bromine vapor for 8 hours (or overnight). The orange solid is then removed from the desiccator and allowed to stand in the air under a hood for at least 4 hours (Note 3). At this point, the product weighs about 30 g. and has a melting point in the neighborhood of 152°. The crude 4,4'-dibromobiphenyl is dissolved in 75 ml. of benzene, filtered, and cooled to 15°. The resulting crystals are filtered, giving a yield of 23.4–24.0 g. (75–77%) of 4,4'-dibromobiphenyl, m.p. 162–163° (Note 4).

2. Notes

1. The checkers used Eastman Kodak Company white label grade of biphenyl.
2. If a vacuum desiccator is used, the stopcock can be opened slightly to allow for the escape of hydrogen bromide.
3. The standing period allows hydrogen bromide and bromine to escape from the crystals.
4. 4,4'-Dibromobibenzyl can be prepared in the same manner. Eighteen grams (0.10 mole) of finely divided bibenzyl is left in contact with the vapor from 39 g. (12 ml., 0.24 mole) of bromine for 24 hours. The desiccator is put under an opaque cover to keep out light, which causes the formation of α,α'-dibromobibenzyl. The somewhat sticky reaction product is allowed to stand overnight. The crude product is dissolved in 300 ml. of isopropyl alcohol, filtered, and cooled. A yield of 15.0–17.0 g. (44–50%) of 4,4'-dibromobibenzyl, m.p. 113–114°, is obtained.

3. Discussion

This method is a modification of that of Buckles, Hausman, and Wheeler.[2] 4,4'-Dibromobiphenyl has also been prepared by the bromination of biphenyl in water,[3] carbon disulfide,[4] and glacial acetic acid;[5] by the bromination of a mixture of biphenylsulfonic acids in dilute sulfuric acid;[6] by the action of sodium carbonate[7] or ethanol[8] on the perbromide obtained from the reaction of diazotized benzidine with bromine water; and by passing *p*-dibromobenzene vapor through a red-hot tube.[9]

4,4'-Dibromobibenzyl has been prepared by the bromination of bibenzyl in water;[10] by the reaction of *p*-bromobenzyl bromide with zinc dust in water;[11] and by the reaction of bromobenzene with ethylene oxide in the presence of anhydrous aluminum chloride.[12]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

bromine water

ethanol (64-17-5)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

Benzene (71-43-2)

hydrogen bromide (10035-10-6)

sodium carbonate (497-19-8)

bromine (7726-95-6)

aluminum chloride (3495-54-3)

zinc (7440-66-6)

isopropyl alcohol (67-63-0)

bromobenzene (108-86-1)

carbon disulfide (75-15-0)

Biphenyl (92-52-4)

Ethylene oxide (75-21-8)

benzidine (92-87-5)

α,α'-dibromobibenzyl (5789-30-0)

bibenzyl (103-29-7)

p-dibromobenzene (106-37-6)

4,4'-DIBROMOBIPHENYL, Biphenyl, 4,4'-dibromo- (92-86-4)

p-bromobenzyl bromide (589-15-1)

4,4'-Dibromobibenzyl (19829-56-2)

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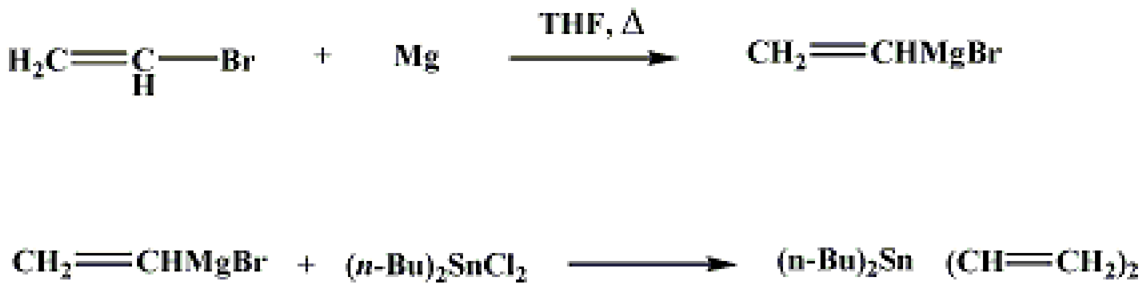
DI-*n*-BUTYLDIVINYLTIN

[Tin, dibutyldivinyl-]



Submitted by Dietmar Seyferth[1]
Checked by Melvin S. Newman and S. Ramachandran.

1. Procedure

In a 2-l. three-necked flask, equipped with a Dry Ice-acetone reflux condenser, a mechanical stirrer, and a 250-ml. dropping funnel, is placed 29.2 g. (1.2 g. atoms) of magnesium turnings. Enough tetrahydrofuran (THF) (Note 1) to cover the magnesium is added, stirring is begun, and about 5 ml. of vinyl bromide (Note 2) is added. After the reaction has started (Note 3), an additional 350 ml. of the THF is added. The rest of the vinyl bromide (140 g., 1.3 moles, total), dissolved in 120 ml. of THF, is added at such a rate that a moderate reflux is maintained. After the addition has been completed, the solution is refluxed for 30 minutes (Note 4). The Grignard solution is then cooled to room temperature, and the Dry Ice-acetone condenser is replaced with a water condenser which is fitted with a Drierite-filled drying tube. A solution of 135 g. (0.44 mole) of di-*n*-butyltin dichloride (Note 5) in 250 ml. of THF (Note 6) is then added, with stirring, at such a rate that a moderate reflux is maintained. After the addition has been completed, the reaction mixture is refluxed for 20 hours. The mixture is cooled to room temperature and is hydrolyzed by the slow addition of 150 ml. of a saturated ammonium chloride solution (Note 7). The organic layer is then decanted and the residual salts are washed thoroughly with 3 portions of ether, the washings being added to the organic layer. The ether and the THF are stripped off at atmospheric pressure; a Claisen distillation head is used. The residue is distilled at reduced pressure using a vacuum-jacketed Vigreux column equipped with a total-reflux partial take-off head to give 95–116 g. (74–91%) of di-*n*-butyldivinyltin, b.p. 60° /0.4 mm., n_D^{25} 1.4797 (Note 8) and (Note 9).

2. Notes

1. Tetrahydrofuran, obtained from the Electrochemicals Department of E. I. du Pont de Nemours & Co., was distilled from lithium aluminum hydride prior to use. It is not advisable to leave THF purified in this manner standing around for

longer periods, since, in the absence of the inhibitor present in the commercial material, peroxides form fairly rapidly. (See also p. 793, Note 2).

2. Vinyl bromide, obtained from the Matheson Company, was redistilled prior to use. The distillate was collected in a receiver cooled with a Dry Ice-acetone mixture and protected from day-light.

3. In most cases the formation of the Grignard reagent began in the absence of any initiator. In cases where the reaction did not begin within a few minutes, 0.5 ml. of methyl iodide served to initiate attack on the magnesium.

4. In small-scale preparations of vinylmagnesium bromide it is advisable to carry out the reaction in an atmosphere of dry nitrogen in order to prevent hydrolysis and oxidation of the Grignard reagent. In larger-scale preparations such as the one described here, where a considerable excess of Grignard reagent is used, such precautions are not necessary.

5. Di-*n*-butyltin dichloride is a commercial product of Metal and Thermit Corporation, Rahway, New Jersey.

6. The checkers found that 250 ml. of dry ether was equally effective.

7. Enough saturated ammonium chloride solution is added to cause coagulation of the inorganic salts to a particle size of about 2–5 mm. in diameter; the volume of solution required varies but averages about 100–120 ml. per mole of Grignard reagent. If the hydrolysis is stopped at this point, a clear, essentially dry organic layer results, and in most instances no further drying is required before distillation.

8. This general procedure has been used to prepare[2,3] a large number of vinyltin compounds, including:

$CH_2{=}CHSnR_3$ (R = CH_3, C_2H_5, *n*-C_3H_7, *n*-C_4H_9, C_6H_5)

$(CH_2{=}CH)_2SnR_2$ (R = CH_3, *n*-C_4H_9, $(CH_3)_3SiCH_2$, C_6H_5)

$(CH_2{=}CH)_3SnR$ (R = *n*-CH_4H_9, CH_6H_5)

$(CH_2{=}CH)_4Sn$

9. Grignard reagents other than vinylmagnesium bromide may be used in this general procedure. The initial use of a Dry Ice-acetone condenser, is then not required. Use of the THF solvent provides a distinct advantage over the method recently described in detail (p. 881), in which ether is used as a solvent, since fewer steps are required.

3. Discussion

The above procedure is essentially that described previously by the author.[2] Di-*n*-butylvinyltin has been prepared by the reaction between vinylmagnesium chloride with either di-*n*-butyltin dichloride or di-*n*-butyltin oxide.[4] The preparation of vinylmagnesium bromide was first described by Normant.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 83

- Org. Syn. Coll. Vol. 6, 488

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ether (60-29-7)

ammonium chloride (12125-02-9)

magnesium, magnesium turnings (7439-95-4)

nitrogen (7727-37-9)

Methyl iodide (74-88-4)

Tetrahydrofuran, THF (109-99-9)

lithium aluminum hydride (16853-85-3)

Tin, dibutyldivinyl-, DI-n-BUTYLDIVINYLTIN (7330-43-0)

vinyl bromide (593-60-2)

vinylmagnesium bromide (1826-67-1)

vinylmagnesium chloride (3536-96-7)

di-n-butyltin oxide (818-08-6)

di-n-butyltin dichloride (683-18-1)

Di-n-butylvinyltin

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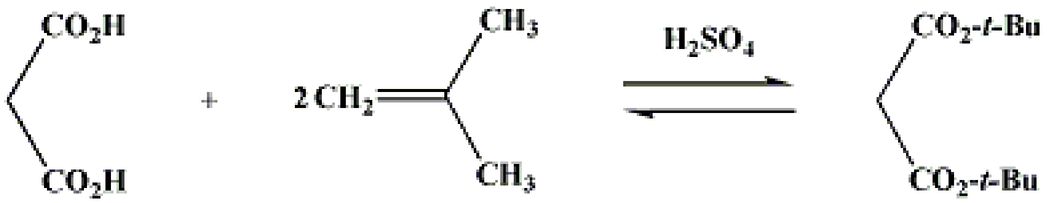
DI-*tert*-BUTYL MALONATE

[Malonic acid, di-*t*-butyl ester]

[I. ISOBUTYLENE METHOD]



Submitted by Allen L. McCloskey, Gunther S. Fonken, Rudolph W. Kluiber, and William S. Johnson[1].
Checked by James Cason, Gerhard J. Fonken, and William G. Dauben.

1. Procedure

A 500-ml. Pyrex heavy-walled narrow-mouthed pressure bottle is charged with 100 ml. of ether (Note 1), 5 ml. of concentrated sulfuric acid, 50.0 g. (0.48 mole) of malonic acid, and approximately 120 ml. (about 1.5 moles) of isobutylene (Note 2), which is liquefied by passage into a large test tube immersed in a Dry Ice-acetone bath. The bottle is closed with a rubber stopper which is clamped or wired securely in place (Note 3) and is shaken mechanically at room temperature until the suspended malonic acid dissolves (Note 4). The bottle is chilled in an ice-salt bath and opened; then the contents are poured into a separatory funnel containing 250 ml. of water, 70 g. of sodium hydroxide, and 250 g. of ice. The mixture is shaken (carefully at first), the layers are separated, and the aqueous portion is extracted with two 75-ml. portions of ether. The organic layers are combined, dried over anhydrous potassium carbonate, and filtered into a dropping funnel attached to the neck of a 125-ml. modified Claisen flask (Note 5). The flask is immersed in an oil bath at about 100°, and the excess isobutylene and ether are removed by flash distillation effected by allowing the solution to run in slowly from the dropping funnel. The dropping funnel is then removed, and the residue is distilled at reduced pressure. The fraction boiling at 112–115°/31 mm. is collected. The yield of colorless di-*tert*-butyl malonate is 60.0–62.0 g. (58–60%), n_D^{25} 1.4158–1.4161, freezing point –5.9 to –6.1° (Note 6) and (Note 7).

2. Notes

1. Increase in the concentrations of reactants and product by elimination of the solvent shifts the equilibrium to the right and thus increases the yield of ester. In several runs by the checkers in which the described procedure was followed except that ether was omitted, isobutylene was increased to 240 ml. (3 moles), and shaking was continued for 12–15 hours to effect solution, yields of 88–91%

were obtained. When ether was used as solvent, the larger amount of isobutylene raised the yield to only 73%. The submitters, however, have found that in the procedure without solvent the yield is more variable (in the range 69–92%), complete solution of the acid sometimes fails to occur, and in runs requiring long shaking for complete solution there is formed a lower-boiling substance the separation of which requires fractional distillation. Without solvent, there is usually an exothermic reaction as the mixture warms up. In the size run described this is no disadvantage, but in larger runs the heat evolved might be sufficient to cause the reaction to get out of control.

2. Technical grade isobutylene supplied by the Matheson Company was used.

3. The pressure during reaction on this scale does not exceed 40 p.s.i.

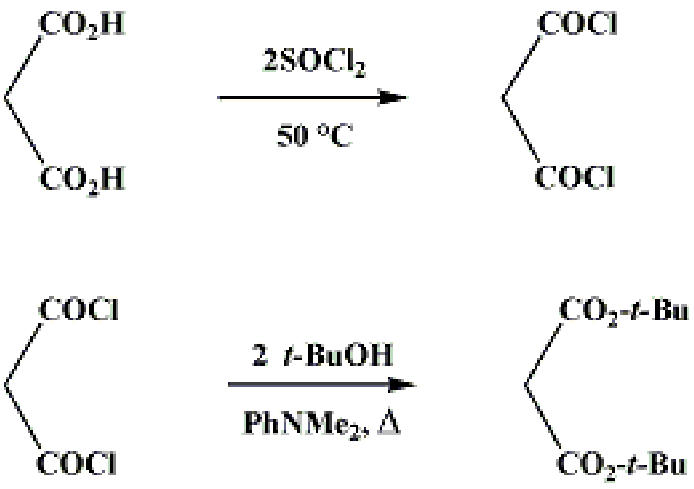
4. Solution is usually complete within 6 hours, but sometimes as long as 12 hours may be required.

5. The flask should be carefully washed with alkali before rinsing and drying, to ensure the removal of traces of acid which will catalyze the decomposition of the ester on warming to give isobutylene, carbon dioxide, and acetic acid. Once this decomposition begins, as evidenced by severe foaming, it is auto-catalyzed (by the acetic acid formed) and cannot be prevented from continuing at an accelerated rate except by rewashing the product and apparatus with alkali. The addition of some solid potassium carbonate or magnesium oxide before distillation has been used with some *tert*-butyl esters to aid in inhibiting incipient decomposition. This treatment, however, does not appear to be necessary in the present preparation.

6. This preparation has been carried out by H. C. Dehm on a larger scale. From 150 g. of malonic acid, 200 ml. of ether, 10 ml. of concentrated sulfuric acid, and 375 ml. of isobutylene, there was obtained after shaking for 22 hours in a 1-l. bottle 201.3 g. (64% yield) of ester, $n_D^{24.2}$ 1.4161.

7. Other esters that have been prepared by this general procedure are: *tert*-butyl acetate, 50% yield, b.p. 94–97°/738 mm., n_D^{25} 1.3820; *tert*-butyl chloroacetate, 63% yield, b.p. 56–57°/16–17 mm., n_D^{25} 1.4204–1.4210 (carried out by R. C. Hunt); *tert*-butyl bromoacetate, 65% yield, b.p. 74–76°/25 mm., n_D^{25} 1.4162; *tert*-butyl α-chloropropionate, yield 63%, b.p. 52–53°/12 mm., n_D^{25} 1.4163 (carried out by J. S. Belew); *tert*-butyl *o*-benzoylbenzoate, 70% yield, m.p. 65–69°; di-*tert*-butyl succinate (dioxane was used instead of ether as solvent), 52% yield, b.p. 105–107°/7 mm., m.p. 31.5–35°; di-*tert*-butyl glutarate, 60% yield, b. p. 113–119°/9 mm., n_D^{25} 1.4215; di-*tert*-butyl β,β-dimethylglutarate, 67% yield, b.p. 72–75°/1 mm., n_D^{25} 1.4246.

[II. ACID CHLORIDE METHOD]



Submitted by Chittaranjan Raha[2]
Checked by William S. Johnson and Rudolph W. Kluiber.

1. Procedure

A. *Malonyl dichloride*. In a 250-ml. Erlenmeyer flask (Note 1) fitted by a ground-glass joint to a reflux condenser capped with a calcium chloride drying tube are placed 52 g. (0.5 mole) of finely powered, dry malonic acid (Note 2) and 120 ml. (about 1.65 mole) of thionyl chloride (Note 3). The flask is warmed for 3 days in a heating bath kept at 45–50° (Note 4). During this period the mixture, which is agitated occasionally by gentle swirling, gradually darkens to a deep brownish red or sometimes a blue color. Finally the mixture is heated at 60° for 5–6 hours. After cooling, it is transferred to a 125-ml. modified Claisen flask and distilled at reduced pressure (water aspirator). A calcium chloride guard tube is inserted between the vacuum line and the apparatus, and the flask is heated with a bath rather than a free flame. After a small fore-run of thionyl chloride, the malonyl chloride distils at 58–60°/28 mm. The pale yellow product amounts to 50.5–60 g. (72–85% yield), n_D^{29} 1.4572.

B. *Di-tert-butyl malonate*. A 1-l. three-necked flask is fitted with a thermometer, a mercury- or rubber sleeve-sealed mechanical stirrer, a reflux condenser protected by a calcium chloride guard tube, and a dropping funnel (either pressure-equalized or protected by a calcium chloride guard tube). A mixture of 100 ml. (about 1 mole) of *tert*-butyl alcohol, dried by distillation from sodium (p. 134, Note 2), and 80 ml. (0.63 mole) of dry dimethylaniline (Note 5) is placed in the flask, the stirrer is started, and a solution of 28.0 g. (0.2 mole) of malonyl dichloride in about 60 ml. of dry, alcohol-free chloroform (Note 6) is added slowly from the dropping funnel while the reaction flask is cooled in an ice bath. The reaction is strongly exothermic, and the rate of dropping is regulated so that the temperature of the mixture does not exceed 30°. After the addition is complete (about 30 minutes) the light-greenish mixture is heated under reflux for 4 hours. The mixture is then cooled, 150 ml. of ice-cold 6*N* sulfuric acid is added with stirring, and the product is extracted with three 250-ml. portions of ether (Note 7). The combined ether extracts are washed once with 6*N* sulfuric acid, twice with water, twice with 10% potassium carbonate, and once with saturated sodium

chloride, and are finally dried over anhydrous sodium sulfate to which a small amount of potassium carbonate is added. The ether is removed by distillation at reduced pressure (water aspirator), and the residue (to which a pinch of magnesium oxide is added) is distilled at reduced pressure from a modified Claisen flask (Note 8). The yield of colorless di-*tert*-butyl malonate, distilling at 65–67°/1 mm., 110–111°/22 mm., is 35.8–36.2 g. (83–84%), n_D^{25} 1.4159, m.p. about −6°.

2. Notes

1. Better results are obtained by using a flat-bottomed flask, which permits the insoluble malonic acid to be distributed over a greater surface.
2. The reaction mixture is heterogeneous at first, and if the acid is not finely powdered, some of it remains unreacted. Attempts to carry out the reaction on a larger scale resulted in some charring and lower yields.
3. Eastman Kodak Company white label quality thionyl chloride is satisfactory.
4. The temperature range is critical, and yields are lower if it is not controlled carefully. The use of pyridine as a catalyst is not recommended as it produces charring even after relatively short reaction periods.
5. J. T. Baker dimethylaniline (purified grade) is satisfactory without distillation.
6. The chloroform was dried over and distilled from anhydrous calcium chloride just before use.
7. The dimethylaniline may be recovered from the aqueous layer where it is dissolved as the salt.
8. Di-*tert*-butyl malonate, like most *tert*-butyl esters, decomposes readily on heating in the presence of traces of acids. It is therefore desirable to give all glassware to be used for distillation of the material an alkali rinse before use. The addition of a small amount of magnesium oxide also helps to inhibit the decomposition during distillation.[3] When decomposition starts, foaming is generally observed. In this event the addition of glass wool to the distillation flask helps to keep the product from foaming over.

3. Discussion

Procedure I is a modification[3] of the method of Altschul[4] for preparing *tert*-butyl esters. Di-*tert*-butyl malonate also has been prepared by the reaction of malonyl dichloride and *tert*-butyl alcohol in the presence of a base,[5,6], and by the reaction of carbon suboxide with *tert*-butyl alcohol.[7] Procedure II is based on the former[5] method and developed from studies initiated by P. C. Mukharji of the University College of Science and Technology, Calcutta.

Malonyl dichloride has been prepared from malonic acid and thionyl chloride,[5,8,9,10,11,12] and from carbon suboxide and anhydrous hydrogen chloride.[13] The present procedure is adapted from that of Staudinger and Bereza[10] and of Backer and Homan.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 417
- Org. Syn. Coll. Vol. 6, 414
- Org. Syn. Coll. Vol. 7, 142

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

carbon suboxide

calcium chloride (10043-52-4)

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

hydrogen chloride (7647-01-0)

acetic acid (64-19-7)

ether (60-29-7)

sodium hydroxide (1310-73-2)

thionyl chloride (7719-09-7)

chloroform (67-66-3)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

carbon dioxide (124-38-9)

pyridine (110-86-1)

sodium (13966-32-0)

dimethylaniline (121-69-7)

Malonic acid (141-82-2)

dioxane (5703-46-8)

magnesium oxide

isobutylene (9003-27-4)

Malonyl dichloride (1663-67-8)

tert-butyl alcohol (75-65-0)

tert-Butyl acetate (540-88-5)

tert-Butyl chloroacetate (107-59-5)

Di-tert-butyl malonate, Malonic acid, di-t-butyl ester (541-16-2)

tert-butyl bromoacetate (5292-43-3)

tert-butyl α-chloropropionate (40058-88-6)

tert-butyl o-benzoylbenzoate

di-tert-butyl succinate (926-26-1)

di-tert-butyl glutarate (43052-39-7)

di-tert-butyl β,β-dimethylglutarate

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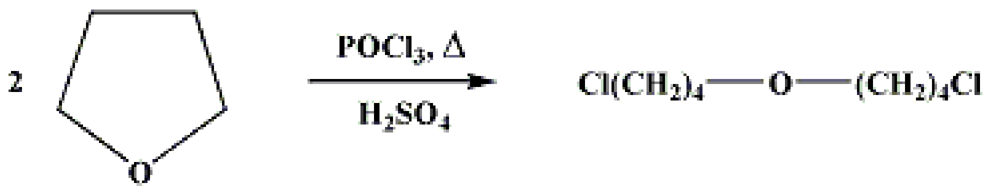
4,4'-DICHLORODIBUTYL ETHER

[Ether, *bis*(4-chlorobutyl)]



Submitted by Kliem Alexander and H. V. Towles[1].
Checked by Arthur C. Cope, Malcolm Chamberlain, and Mark R. Kinter.

1. Procedure

Caution! This preparation should be conducted in a good hood because some hydrogen chloride is evolved.

In a 2-l. three-necked flask fitted with a mercury-sealed stirrer (Note 1), a reflux condenser connected to a calcium chloride tube, and a thermometer is placed 360 g. (406 ml., 5 moles) of dry tetrahydrofuran (Note 2). The flask is surrounded by an ice bath, stirring is started, and 256 g. (153 ml., 1.67 moles) of phosphorus oxychloride is added rapidly. The mixture is cooled to 10–15°, and 50 ml. of concentrated sulfuric acid (sp. gr. 1.84) is added during the course of 3–10 minutes at a rate that does not cause the temperature to rise above 40°. The ice bath is then removed and the mixture is heated cautiously over a low luminous flame until an exothermic reaction becomes evident at about 88–90° (Note 3). By moderate cooling or warming as may be required the temperature is maintained at 90–100° until the exothermic reaction ceases, as indicated by the increased rate of heating required to maintain the reaction temperature, and thereafter for an additional 10 minutes (Note 4). Six hundred milliliters of water is added, the mixture is heated under reflux for 30 minutes and then distilled through a downward condenser until the vapor temperature reaches 99–100° (Note 5).

The dark reaction mixture is cooled to room temperature, transferred to a separatory funnel, and extracted with 225 ml. of ether. The ether extract is washed with four 100-ml. portions of water and dried over anhydrous sodium sulfate or magnesium sulfate. The mixture is filtered, the ether is removed by distillation, and the residual liquid is fractionated under reduced pressure from a modified Claisen flask. The yield of colorless 4,4'-dichlorodibutyl ether, b.p. 84–86°/0.5 mm. (116–118°/10 mm.), n_D^{25} 1.4562, d_4^{25} 1.0690, is 257–268 g. (52–54% based on tetrahydrofuran) (Note 6).

2. Notes

1. Efficient stirring is necessary to permit good control of the reaction temperature.
2. The same yield of 4,4'-dichlorodibutyl ether was obtained from redistilled tetrahydrofuran dried over sodium or a good-quality commercial grade obtained from the Electrochemicals Department of the E. I. du Pont de Nemours and Company and dried over Drierite.
3. About 30 minutes is required for the temperature to reach 88–90°. The temperature rises rapidly to 76°, at which point refluxing of tetrahydrofuran accompanied by evolution of some hydrogen chloride occurs. Thereafter refluxing gradually diminishes and the temperature increases approximately as follows: 0 minutes, 76°; 5 minutes, 77°; 10 minutes, 78°; 15 minutes, 80°; 20 minutes, 85°; 25 minutes, 94°; 27 minutes, 100°.
4. The temperature is easily kept within the range 90–100° by occasional cooling with an ice-water bath. Above 100° the reaction tends to become violent, resulting in excessive evolution of hydrogen chloride and a lower yield of the product. The exothermic phase of the reaction is usually complete in 15–20 minutes.
5. Refluxing with water serves to decompose phosphorus-containing complexes and facilitates isolation of the product. The aqueous distillate contains small amounts of 1,4-dichlorobutane and unchanged tetrahydrofuran.
6. The product as obtained with these physical constants is analytically pure.

3. Discussion

The procedure described is based on one reported by Alexander and Schniepp.[2] 4,4'-Dichlorodibutyl ether also has been prepared by the action of thionyl chloride on tetrahydrofuran[3] or 1,4-butanediol,[4] and by heating 4-chlorobutanol and hydrogen chloride under pressure.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 529

References and Notes

1. Northern Regional Research Laboratory, U. S. Department of Agriculture, Peoria, Illinois.
2. Alexander and Schniepp, *J. Am. Chem. Soc.*, **70**, 1839 (1948).
3. Krzikalla and Maier, PB 631, Office of Technical Services, U. S. Department of Commerce; Lutkova, Kutsenko, and Itkina, *Zhur. Obshchei Khim.*, **25**, 2102 (1955) [*C. A.*, **50**, 8584 (1956)].
4. Haga et al. (to Mitsubishi Chemical Industries Co.), Jap. pats. 1268, 1271 (1953) [*C. A.*, **48**, 2086 (1954)]; Jap. pat. 5124 (1952) [*C. A.*, **48**, 8812 (1954)].
5. Trieschmann, U. S. pat. 2,245,509 [*C. A.*, **35**, 5914 (1941)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Drierite

sulfuric acid (7664-93-9)

hydrogen chloride (7647-01-0)

ether (60-29-7)

thionyl chloride (7719-09-7)

sodium sulfate (7757-82-6)

Phosphorus Oxychloride (21295-50-1)

sodium (13966-32-0)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

1,4-butanediol

4-chlorobutanol (928-51-8)

1,4-dichlorobutane (110-56-5)

Ether, bis(4-chlorobutyl), 4,4'-DICHLORODIBUTYL ETHER (6334-96-9)

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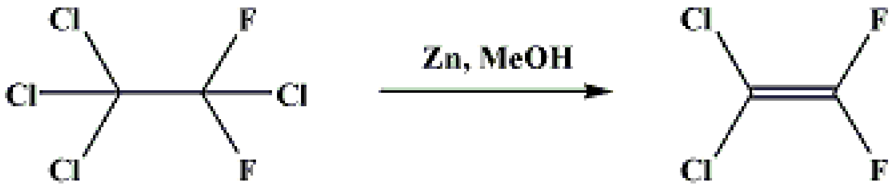
1,1-DICHLORO-2,2-DIFLUOROETHYLENE

[Ethylene, 1,1-dichloro-2,2-difluoro-]



Submitted by J. C. Sauer[1]
Checked by Charles C. Price and Maseh Osgan.

1. Procedure

In a 500-ml. three-necked round-bottomed flask equipped with a 100-ml. separatory funnel, a thermometer, and a short fractionating column (Note 1) leading through a condenser to a 100-ml. tared receiver are charged 150 ml. of methanol, 42.2 g. (0.65 g. atom) of powdered zinc, and 0.2 g. of zinc chloride. Acetone cooled in a Dry Ice-acetone bath is circulated through the condenser, and the distillation receiver is immersed in ice water (Note 2). The mixture in the flask is heated to 60–63°, and a 10–15-ml. portion of a solution consisting of 122.4 g. (0.6 mole) of 1,1,1,2-tetrachloro-2,2-difluoroethane (Note 3) in 50 ml. of methanol is added dropwise over a period of a few minutes. The reaction generally becomes moderately vigorous at this point, and refluxing of 1,1-dichloro-2,2-difluoroethylene part-way up the column is observed. The heating bath is removed at this time. Addition of the ethane derivative is continued at such a rate that the temperature of the refluxing liquid at the head of the column is maintained at 18–22°. The flask may require occasional shaking to prevent the zinc dust from agglomerating. The take-off rate of the ethylene derivative is adjusted to about one-half the rate of input of the ethane derivative. During this addition, the temperature in the distillation flask drops to 45–50°. The addition of the ethane derivative requires 45 minutes to 1 hour. The heating bath is replaced, and another hour is required to complete the dehalogenation and to distil the last of the product. The temperature in the distillation flask during this period gradually rises to 69–70°. There is collected in the receiver 71–76 g. (89–95% yield) (Note 4) of 1,1-dichloro-2,2-difluoroethylene, distilling at 18–21° (Note 5), n_D^{0} , 1.3730–1.3746.

2. Notes

1. A 16-in. column packed with platinum gauze and fitted with a variable take-off was used by the submitter. The checkers used a 20 × -in jacketed column packed with 1/16-in. glass helices.
2. The checkers used a Dry Ice-acetone-cooled cold-finger condenser fitted with a partial take-off adapter.

3. Tetrachlorodifluoroethane (CCl_3-$CClF_2$) is sold under the trade name "Genetron-131" by the General Chemical Division, Allied Chemical and Dye Corporation, 40 Rector Street, New York 6, N. Y. The sample, as received, melted at 38–40°. According to infrared data, the compound was 95–99% pure. Distillation through a high-precision, spinning band column showed about 10% distilling at 86–90° (mostly 90°), another 10% at 90–90.5°, and the remainder at 91°. All fractions were essentially the same by infrared analysis. The first fraction melted at about 35°, and the main fraction melted at 40.5°.[2]
4. This product contains 1–1.7% methanol and a trace of the starting material.
5. This figure is slightly above the true boiling point of 1,1-dichloro-2,2-difluoroethylene. Upon redistillation in a low-temperature still fitted with a thermocouple, about 95% of this material distilled at 17°,[3] n_D^3 1.3710.

3. Discussion

1,1-Dichloro-2,2-difluoroethylene has been prepared by the zinc dehalogenation method in ethanol.[2,3] This compound also has been prepared by dehydrochlorination of 1,2,2-trichloro-1,1-difluoroethane by sodium hydroxide,[4] by a solution of potassium hydroxide in aqueous methanol,[5] by passing it over active carbon containing barium chloride or strontium chloride,[6] or by thermal cleavage at 590°.[7] In addition, it has been obtained by the thermal cleavage of 1,1,2,2-tetrachloro-3,3,4,4-tetrafluorocyclobutane at 650° over aluminum fluoride.[8]

References and Notes

1. Contribution No. 285 from the Chemical Department, Experimental Station, E. I. du Pont de Nemours and Company, Wilmington, Delaware.
2. Locke, Brode, and Henne, *J. Am. Chem. Soc.*, **56**, 1726 (1934).
3. Henne and Wiest, *J. Am. Chem. Soc.*, **62**, 2051 (1940).
4. Frederick (to B. F. Goodrich Co.), U. S. pat. 2,709,181 [*C. A.*., **50**, 5017 (1956)].
5. McBee, Hill, and Bachman, *Ind. Eng. Chem.*, **41**, 70 (1949).
6. Alexander Wacker Gesellschaft für electrochemische Industrie G.m.b.H., Brit. pat. 723,715 [*C. A.*, **50**, 5720 (1956)].
7. Padbury and Tarrant (to American Cyanamid Company), U. S. pat. 2,566,807 [*C. A.*, **46**, 2561 (1952)].
8. Miller and Calfee (to Allied Chemical and Dye Corp.), U. S. pat. 2,674,631 [*C. A.* **49**, 4007 (1955)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

methanol (67-56-1)

sodium hydroxide (1310-73-2)

barium chloride (10361-37-2)

acetone (67-64-1)

carbon (7782-42-5)

potassium hydroxide (1310-58-3)

zinc (7440-66-6)

zinc chloride (7646-85-7)

1,1-Dichloro-2,2-difluoroethylene, Ethylene, 1,1-dichloro-2,2-difluoro- (79-35-6)

1,1,1,2-tetrachloro-2,2-difluoroethane, Tetrachlorodifluoroethane (76-11-9)

1,2,2-trichloro-1,1-difluoroethane (354-21-2)

strontium chloride (10476-85-4)

1,1,2,2-tetrachloro-3,3,4,4-tetrafluorocyclobutane (336-50-5)

aluminum fluoride

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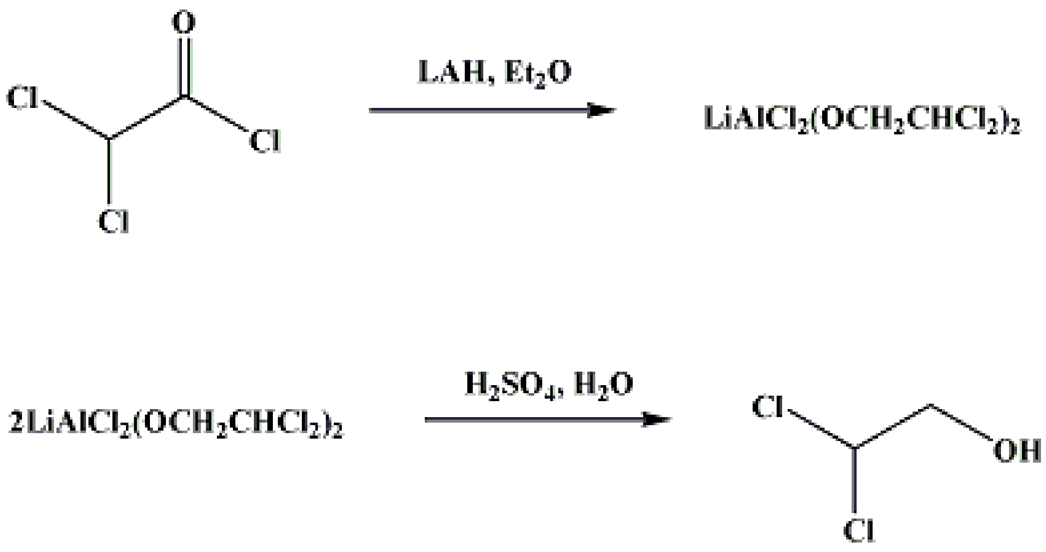
2,2-DICHLOROETHANOL

[Ethanol, 2,2-dichloro-]



Submitted by C. E. Sroog and H. M. Woodburn[1].
Checked by R. S. Schreiber and C. J. Lintner, Jr..

1. Procedure

Caution! This procedure should be carried out in a good hood, and a spark-proof motor should be used.

A 1-l. three-necked flask having ground-glass joints is fitted with an efficient reflux condenser, a dropping funnel, and a mercury-sealed stirrer, and all exits are protected by drying tubes (Note 1). In the flask are placed 300 ml. of rigorously dried ether (Note 2) and 13.6 g. (0.36 mole) of pulverized lithium aluminum hydride (Note 3). After the mixture has been stirred for 15 minutes, a milky suspension is produced. A solution of 88.6 g. (0.60 mole) of dichloroacetyl chloride in 75 ml. of dry ether is added from the dropping funnel (Note 4) at a rate such as to produce gentle reflux. The process is completed in about 2.5 hours (Note 5).

Agitation is continued for 30 minutes after all the chloride has been introduced, and the excess hydride is then destroyed by the careful, dropwise addition of water to the stirred and cooled reaction mixture. The hydrolysis is accompanied by the formation of a white curdy mass of aluminum hydroxide, and the mixture has a semisolid consistency when the hydride has been completely decomposed (Note 6). With constant stirring, 500 ml. of 10% sulfuric acid is then added slowly to the mass. Stirring is continued for 30 minutes, and the solution becomes clear during this period.

The ether layer is separated, and the solvent is removed by distillation under

atmospheric pressure, and the dark-colored residue is fractionated under reduced pressure through a 25-cm. column packed with glass helices. The fraction boiling at 37–38.5°/6 mm. is collected; it weighs 44–45 g. (64–65%); n_D^{25} 1.4626; d_4^{25} 1.404 (Note 7).

2. Notes

1. To prevent partial hydrolysis of the lithium aluminum hydride, the checkers found it desirable to dry the glassware by flaming while dry nitrogen was being swept through the apparatus.
2. Anhydrous ether is recommended since a solvent containing moisture will react to coat the hydride with oxides which will retard its rate of solution. The checkers used ether dried over sodium wire.
3. The hydride can be pulverized rapidly and safely by breaking the large pieces with a spatula, followed by careful crushing with a mortar and pestle.
4. The acid chloride was obtained from the Eastman Kodak Company and was used without prior treatment. The submitters report[2] that dichloroacetyl acid or ethyl dichloroacetate may be substituted for dichloroacetyl chloride but that the reaction appears to be smoother with the acid chloride.
5. The acid chloride should be added slowly since the reaction appears to have a short induction period and it is undesirable to accumulate a large quantity of unreacted material.
6. The decomposition of the hydride is accompanied by the vigorous evolution of hydrogen. Cessation of hydrogen formation is evidence that the hydride is completely decomposed.
7. The following constants have been reported in the literature for 2,2-dichloroethanol: d_4^{15} 1.415;[2] d_4^{19} 1.416; $n_D^{17.3}$ 1.4752.[3]

3. Discussion

2,2-Dichloroethanol has been prepared by the reaction of dichloroacetaldehyde with zinc dialkyls[4] and aluminum alkoxides.[3]

References and Notes

1. University of Buffalo, Buffalo, New York.
2. Sroog, Chih, Short, and Woodburn, *J. Am. Chem. Soc.*, **71**, 1710 (1949).
3. Boeseken, Tellegen, and Plusje, *Rec. trav. chim.*, **57**, 73 (1938).
4. de Lacre, *Compt. rend.*, **104**, 1184 (1887).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

dichloroacetyl acid

sulfuric acid (7664-93-9)

ether (60-29-7)

hydrogen (1333-74-0)

nitrogen (7727-37-9)

sodium wire (13966-32-0)

aluminum hydroxide

dichloroacetyl chloride (79-36-7)

lithium aluminum hydride (16853-85-3)

ethyl dichloroacetate (535-15-9)

2,2-Dichloroethanol, Ethanol, 2,2-dichloro- (598-38-9)

dichloroacetaldehyde (16086-14-9)

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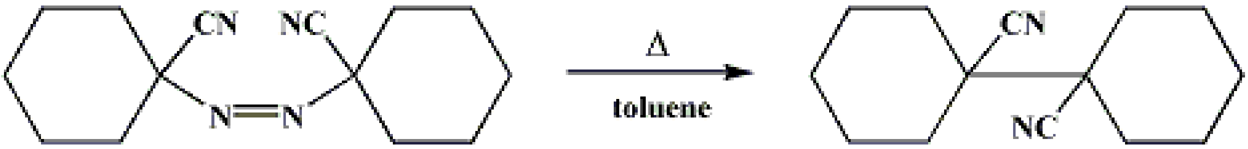
1,1'-DICYANO-1,1'-BICYCLOHEXYL

[[Bicyclohexyl]-1,1'-dicarbonitrile]



Submitted by C. G. Overberger and M. B. Berenbaum[1].
Checked by N. J. Leonard and E. H. Mottus.

1. Procedure

In a 200-ml. flask equipped with a reflux condenser are placed 20 g. (0.082 mole) of 1,1'-azo-*bis*-1-cyclohexanenitrile (p. 66) and 50 ml. of toluene. The solution is heated under gentle reflux for 8 hours, and the reaction mixture is placed in a refrigerator overnight. The product is collected on a Büchner funnel and air-dried; yield 11.5–12.2 g. (65–69%); m.p. 224.5–225.5° (Note 1).

2. Notes

1. Tetramethylsuccinonitrile can be prepared from 2,2'-azo-*bis*-isobutyronitrile in a similar manner.[2] In this case petroleum ether (b.p. 60–70°) is added to the reaction mixture before cooling it overnight. The yield is 75–81% of the theoretical amount; m.p. 168–170°. Sublimation at 20–50 mm. raises the melting point to 170.5–171.5° with very little loss of material.

3. Discussion

1,1'-Dicyano-1,1'-bicyclohexyl has been prepared previously by Hartman[3] in a similar manner. The procedure has been substantiated by Overberger, O'Shaughnessy, and Shalit.[4]

References and Notes

1. Polytechnic Institute of Brooklyn, Brooklyn, New York.
2. Thiele and Heuser, *Ann.*, **290**, 1 (1896).
3. Hartman, *Rec. trav. chim.*, **46**, 150 (1927).
4. Overberger, O'Shaughnessy, and Shalit, *J. Am. Chem. Soc.*, **71**, 2661 (1949).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

toluene (108-88-3)

Tetramethylsuccinonitrile (3333-52-6)

2,2'-Azo-bis-isobutyronitrile

1,1'-AZO-bis-1-CYCLOHEXANENITRILE (2094-98-6)

1,1'-DICYANO-1,1'-BICYCLOHEXYL, [Bicyclohexyl]-1,1'-dicarbonitrile (18341-40-7)

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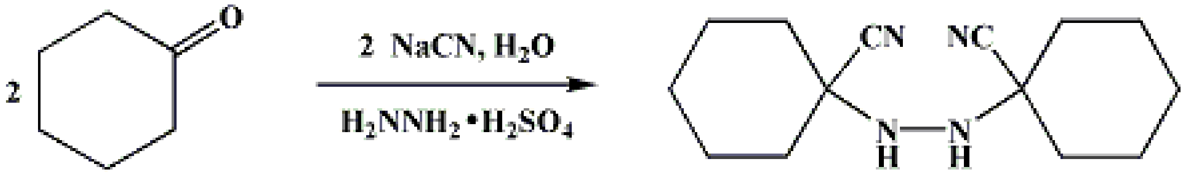
1,2-DI-1-(1-CYANO)CYCLOHEXYLHYDRAZINE

[Cyclohexanecarbonitrile, 1,1'-hydrazodi-]



Submitted by C. G. Overberger, Pao-tung Huang, and M. B. Berenbaum[1].
Checked by N. J. Leonard and E. H. Mottus.

1. Procedure

Caution! These operations should be conducted in an efficient hood.

In a 600-ml. screw-capped bottle are placed 15.4 g. (0.32 mole) of sodium cyanide, 20.5 g. (0.16 mole) of hydrazine sulfate (Note 1), and 400 ml. of ice water. The bottle is capped to prevent loss of hydrogen cyanide (Note 2) and held in an ice bath for 15 minutes. To the cooled mixture is added 29.4 g. (0.3 mole) of cyclohexanone. The bottle is recapped and cooled for an additional 15 minutes. The bottle is then shaken intermittently over a period of 6 hours and allowed to stand an additional 14 hours. The bottle is cooled again before opening. The suspension is filtered by means of suction, and the cake is washed thoroughly with 250 ml. of ice water. After the crude product has been pressed dry on the filter (Note 3), it is transferred to a 500-ml. Erlenmeyer flask and 150 ml. of boiling 95% ethanol is added. The suspension is brought into solution as rapidly as possible by warming on a hot plate (Note 4) and is filtered quickly through a prewarmed 7.5-cm. Büchner funnel. An additional 10 ml. of hot 95% ethanol is used to dissolve any organic residue on the filter, and the combined filtrates are warmed to redissolve any precipitate. The solution is allowed to stand undisturbed for 6 hours in an icebox. The product is collected on a Büchner funnel, washed with 15 ml. of cold 95% ethanol, and then dried over solid calcium chloride in a vacuum desiccator. The yield of product is 24.5–26 g. (66–70%); m.p. 147–149° (Note 5).

2. Notes

1. Technical hydrazine sulfate of known purity is suitable.
2. Both hydrazine and hydrogen cyanide are toxic, and appropriate precautions should be taken.
3. The checkers have used the dry, crude product directly in the conversion to 1,1'-azo-*bis*-1-cyclohexanenitrile (see p. 66) with an over-all yield of 72% based upon cyclohexanone.

4. Excessive or prolonged heating will result in a decreased yield owing to decomposition of the product.
5. 1,2-Di-2-(2-cyano)propylhydrazine (2,2'-hydrazo-*bis*-isobutyronitrile) may be prepared in a similar manner from acetone. The crude product (m.p. 89–91°; yield 88–93%) can be oxidized directly to 2,2'-azo-*bis*-isobutyronitrile. The dried impure material can be recrystallized from ether; m.p. 91.5–92.5°; (72–77%).

3. Discussion

1,2-Di-1-(1-cyano)cyclohexylhydrazine has been prepared by a procedure similar to that used by Hartman.[2] The procedure has been substantiated by Overberger, O'Shaughnessy, and Shalit.[3]

References and Notes

1. Polytechnic Institute of Brooklyn, Brooklyn, New York.
2. Hartman, *Rec. trav. chim.*, **46**, 150 (1927).
3. Overberger, O'Shaughnessy, and Shalit, *J. Am. Chem. Soc.*, **71**, 2661 (1949).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

1,2-Di-1-(1-cyano)cyclohexylhydrazine

1,2-Di-2-(2-cyano)propylhydrazine (2,2'-hydrazo-bis-isobutyronitrile)

ethanol (64-17-5)

calcium chloride (10043-52-4)

ether (60-29-7)

Cyclohexanone (108-94-1)

sodium cyanide (143-33-9)

hydrogen cyanide (74-90-8)

acetone (67-64-1)

Hydrazine sulfate (10034-93-2)

hydrazine (302-01-2)

2,2'-Azo-bis-isobutyronitrile

1,1'-AZO-bis-1-CYCLOHEXANENITRILE (2094-98-6)

Cyclohexanecarbonitrile, 1,1'-hydrazodi- (17643-01-5)

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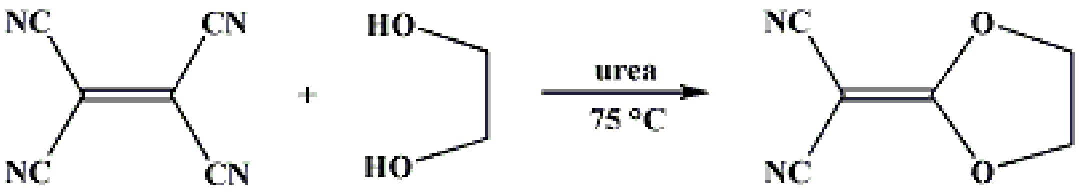
DICYANOKETENE ETHYLENE ACETAL

[1,3-Dioxolane-$\Delta^{2,\alpha}$-malononitrile]



Submitted by C. L. Dickinson and L. R. Melby[1].
Checked by James Cason, Edwin R. Harris, and William T. Miller.

1. Procedure

Caution! This preparation must be carried out in a good hood because hydrogen cyanide is evolved. It is inadvisable to allow contact of tetracyanoethylene with the skin.

Urea (4.0 g., 0.067 mole) is dissolved in 50 ml. of distilled ethylene glycol (Note 1) contained in a 125-ml. Erlenmeyer flask. Finely divided recrystallized tetracyanoethylene (p. 877) (25.6 g., 0.20 mole) is added, and the flask is heated on a steam bath at 70–75° with frequent stirring by hand with a thermometer until solution is complete (about 15 minutes). The resultant brownish yellow solution is then cooled in ice water, and the precipitated dicyanoketene ethylene acetal is collected on a Büchner funnel. The acetal is first washed with two 25-ml. portions of cold ethylene glycol and then washed thoroughly with cold water to remove the ethylene glycol. The dicyanoketene ethylene acetal, which may be dried in air or in a vacuum desiccator, is obtained in the form of large slightly pink needles, m.p. 115–116.5° (Note 2); yield 21–23 g. (77–85%).

2. Notes

1. Moisture in the ethylene glycol leads to lowered yields. Satisfactory results are obtained with glycol collected at 199.5–201° from a simple distillation.
2. The color may be removed by recrystallization from ethanol after treatment with decolorizing carbon; however, the melting point is not improved and occasionally is found to be lowered.

3. Discussion

The synthesis of dicyanoketene ethylene acetal described here is a slight modification of one published recently.[2] The procedure has been applied successfully to the

synthesis of dicyanoketene dimethyl acetal and dicyanoketene diethyl acetal.[2]

Dicyanoketene ethylene acetal reacts with tertiary amines to give quaternary ammonium inner salts.[2] Similarly, it reacts with sulfides to give sulfonium inner salts.[2] These products are generally solids that can be used to characterize tertiary amines and sulfides. Dicyanoketene acetals can be converted to pyrimidines, pyrazoles, or isoxazoles in one step.[3]

References and Notes

1. Contribution No. 481 from Central Research Department, Experimental Station, E. I. du Pont de Nemours & Co., Wilmington, Delaware.
2. Middleton and Engelhardt, *J. Am. Chem. Soc.*, **80**, 2788 (1958).
3. Middleton and Engelhardt, *J. Am. Chem. Soc.*, **80**, 2829 (1958).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

1,3-Dioxolane-$\Delta^{2,\alpha}$-malononitrile

ethanol (64-17-5)

hydrogen cyanide (74-90-8)

decolorizing carbon (7782-42-5)

ethylene glycol (107-21-1)

urea (57-13-6)

Tetracyanoethylene (670-54-2)

Dicyanoketene ethylene acetal (5694-65-5)

dicyanoketene dimethyl acetal

dicyanoketene diethyl acetal

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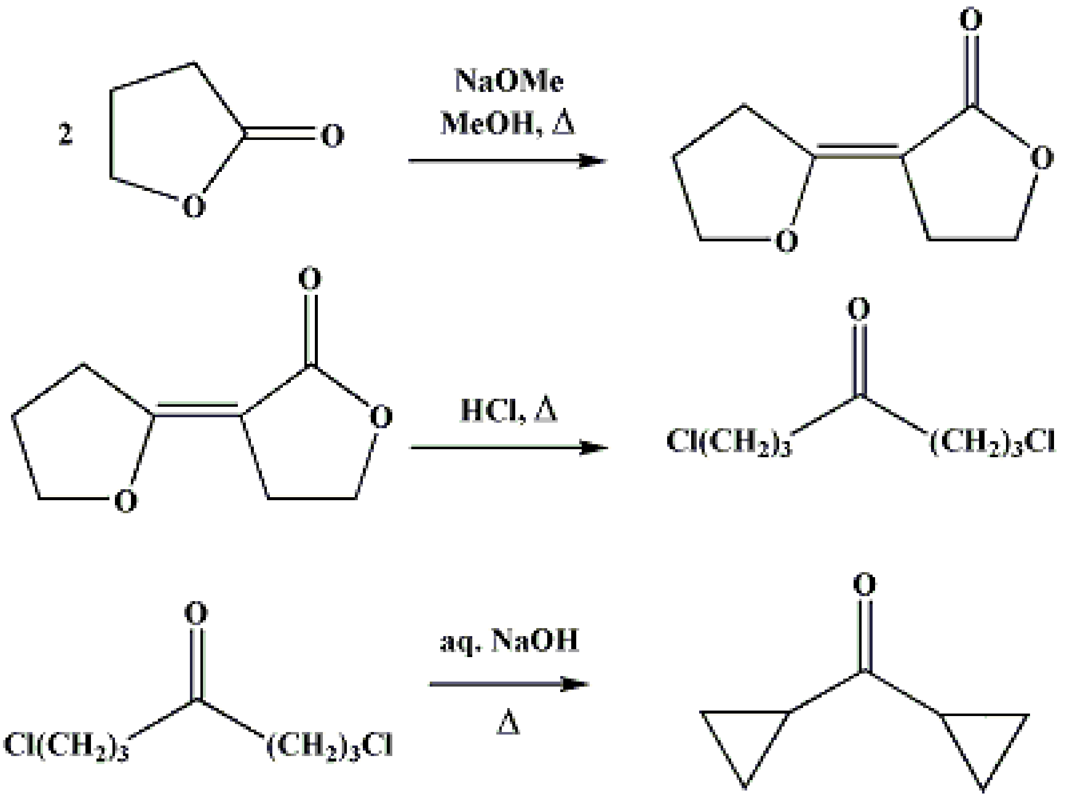
Organic Syntheses, CV 4, 278

DICYCLOPROPYL KETONE

[Ketone, dicyclopropyl]



Submitted by Omer E. Curtis, Jr., Joseph M. Sandri, Richard E. Crocker, and Harold Hart[1].
Checked by V. Boekelheide, R. Taber, and D. S. Tarbell.

1. Procedure

A solution of sodium methoxide is prepared from 50 g. (2.17 g. atoms) of freshly cut sodium and 600 ml. of absolute methanol (Note 1) in a 3-l. three-necked flask placed on a steam bath and equipped with a sealed stirrer (Note 2), dropping funnel, and a condenser set downward for distillation (Note 3). To the stirred solution is added in one portion 344 g. (4.0 moles) of γ-butyrolactone (Note 4), and the flask is heated until methanol distils at a rapid rate. After 475 ml. of methanol is collected, a filter flask or other suitable device equipped with a side arm is connected to the condenser. This receiver is surrounded by an ice bath, and reduced pressure from an aspirator is applied cautiously (frothing) with continuous stirring. An additional 50–70 ml. of methanol is collected in this way. The residue presumably is dibutyrolactone (Note 5).

The condenser is set for reflux, and the steam bath is replaced with a more potent source of heat (electric heating mantle, oil bath, or direct flame). Concentrated hydrochloric acid is added with stirring, cautiously at first because a considerable

amount of carbon dioxide is evolved. A total of 800 ml. of acid is added in about 10 minutes (Note 6). The mixture is heated under reflux with stirring for 20 minutes, then cooled in an ice bath (Note 7). A solution of 480 g. of sodium hydroxide in 600 ml. of water is added to the stirred mixture as rapidly as possible, without allowing the temperature to go above 50° (Note 8). The mixture is then heated under reflux for an additional 30 minutes.

The condenser is arranged for downward distillation, and a total of 650 ml. of ketone-water mixture is collected as distillate. Sufficient potassium carbonate is added to saturate the aqueous layer, and about 130 ml. of ketone is separated. The aqueous layer is extracted with three 100-ml. portions of ether, and the combined ether and ketone layers are dried over 25 g. of anhydrous magnesium sulfate. The product remaining after removal of the ether is distilled through an efficient column. The yield of dicyclopropyl ketone boiling at 72–74°/33 mm., n_D^{25} 1.4654, is 114–121 g. (52–55%) (Note 9).

2. Notes

1. Commercial sodium methoxide (117 g.) in 520 ml. of methanol may be used instead of metallic sodium.
2. The stirrer should be sturdy and capable of giving vigorous agitation.
3. It is desirable to have the condenser arranged for reflux during preparation of the methanolic sodium methoxide, if it is made from sodium metal.
4. Commercial lactone (available from General Aniline and Film Corporation, 435 Hudson Street, New York 14, New York) should be redistilled, b.p. 88–90°/12 mm., before use.
5. Dibutyrolactone can be isolated as a crystalline solid, m.p. 86–87°, from this residue.[2] The preparation can be interrupted at this point without jeopardizing the yield.
6. The color of the mixture changes from yellow through dark orange to dark reddish brown.
7. At this point, the following procedure may be used to prepare 1,7-dichloro-4-heptanone. To the cooled, stirred solution is added 200 ml. of ether, which brings the dense dichloroketone to the upper layer. The latter is separated, and the acid layer is extracted with two 100-ml. portions of ether. The combined ether layers are dried over 25 g. of anhydrous calcium chloride. After removal of the solvent, the residue is distilled through an efficient column. The yield of 1,7-dichloro-4-heptanone, b.p. 106–110°/4 mm., n_D^{25} 1.4713, is 263–278 g. (72–76%). The material takes on a purple cast rapidly and should be stored in a refrigerator.
8. Considerable salt separates at this point but does not interfere with the subsequent steps.
9. According to the submitters, a similar procedure can be applied to substituted lactones; di-(2-methylcyclopropyl) ketone, b.p. 65–67°/7 mm., n_D^{25} 1.4600, has been made from γ-valerolactone in 50% yield.

3. Discussion

This procedure is a modification of one recently described in the literature.[3] The first step is based on early work of Fittig[4] and Volhard[5] as modified by Spencer and Wright.[2] The third step, ring closure of a γ-haloketone,[5] is well known (p.597). Dicyclopropyl ketone was reported to form in small amounts from the decarboxylation of cyclopropanecarboxylic acid over thoria,[6] but there is some doubt[3] about the product.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

thoria

dibutyrolactone

calcium chloride (10043-52-4)

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

methanol (67-56-1)

ether (60-29-7)

sodium hydroxide (1310-73-2)

carbon dioxide (124-38-9)

sodium methoxide (124-41-4)

sodium (13966-32-0)

magnesium sulfate (7487-88-9)

Cyclopropanecarboxylic acid (1759-53-1)

Dicyclopropyl ketone, Ketone, dicyclopropyl (1121-37-5)

γ-butyrolactone (96-48-0)

1,7-Dichloro-4-heptanone (40624-07-5)

di-(2-methylcyclopropyl) ketone

γ-valerolactone (108-29-2)

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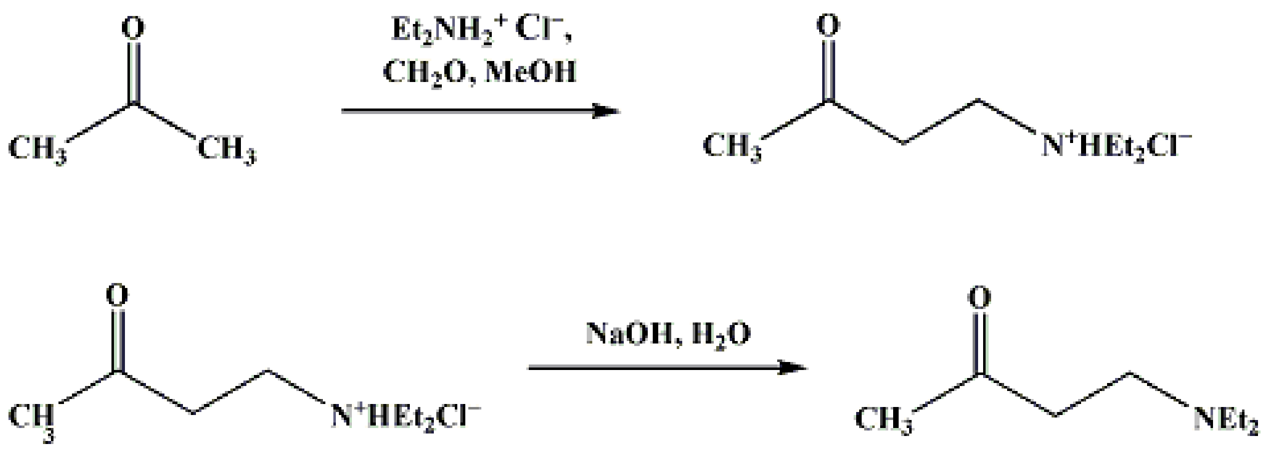
1-DIETHYLAMINO-3-BUTANONE

[2-Butanone, 4-diethylamino-]



Submitted by Alfred L. Wilds, Robert M. Nowak, and Kirtland E. McCaleb[1].
Checked by William S. Johnson and Duane Zinkel.

1. Procedure

In a 3-l. round-bottomed flask equipped with a reflux condenser (Note 1) are placed 176 g. (1.60 moles) of diethylamine hydrochloride (Note 2), 68 g. (2.26 moles) of paraformaldehyde, 600 ml. (8.2 moles) of acetone, 80 ml. of methanol, and 0.2 ml. of concentrated hydrochloric acid. The mixture is heated for 12 hours at a moderate to vigorous rate of reflux (Note 3). The light-yellow solution, in which a small amount of gelatinous solid remains, is cooled, and a cold solution of 65 g. of sodium hydroxide in 300 ml. of water is added. The mixture is extracted with three 200-ml. portions of ether, the combined extracts are washed with two 150-ml. portions of saturated sodium chloride solution, and the washes are re-extracted with two 150-ml. portions of ether.

The combined ether solutions are dried overnight with about 80 g. of anhydrous sodium sulfate, filtered, and then distilled under reduced pressure (5 to 12 mm.) (Note 4) through a 20-cm. asbestos-wrapped Vigreux distilling column, with an efficient water-cooled condenser (Note 5). After the solvent and a small fore-run have been distilled, 150–171 g. (66–75%) of 1-diethylamino-3-butanone is collected as a light-yellow to nearly colorless liquid, b.p. 63–67°/7mm. (75–77°/15mm.), n_D^{25} 1.4300–1.4310. The product may contain a small amount of 1,1-bis(diethylaminomethyl)acetone (the bis-Mannich base), which can interfere with some uses of this product. Refractionation gives relatively pure material, 142–161 g. (62–70%), b.p. 72–75°/10mm., n_D^{25} 1.4301–1.4307, d_4^{25} 0.8626, M_D (found) 43.2–43.3, M_D (calcd.) 43.1 (Note 6).

2. Notes

1. Ground-glass joints are desirable.
2. A good grade of commercial diethylamine hydrochloride (Eastman Kodak white label grade or Matheson, Coleman and Bell) is satisfactory without purification.
3. At first some bumping may occur if the heating is too vigorous; mechanical stirring may reduce this, but does not improve the yield. The submitters found an electrically heated oil bath or a steam bath to be satisfactory, but *not a heating mantle.*
4. If the temperature of distillation is too high, or if a heating mantle is used, decomposition to methyl vinyl ketone may occur. The submitters used an electrically heated oil bath and prefer pressures below 12 mm. to minimize decomposition. A more elaborate fractionating column necessitating a higher bath temperature or prolonged heating is also undesirable. If the material stands more than one or two days before distillation it may decompose.
5. Unless the condenser is efficient, some product will be lost; a Dry Ice-cooled trap located between the receiver and the pump is recommended.
6. This product gave satisfactory analytical values: Calcd. for $C_8H_{17}NO$: C, 67.1; H, 12.0. Found: C, 67.2; H, 11.9. The neutral equivalent of various samples, titrated potentiometrically with standard hydrochloric acid solutions, ranged between 144 and 145 (calcd. 143.2).

3. Discussion

1-Diethylamino-3-butanone has been prepared by the Mannich reaction,[2,3,4,5,6,7] and by the condensation of methyl vinyl ketone with diethylamine hydrochloride in the presence of acetic anhydride.[8] The present procedure is a modification of that described by Wilds and Shunk.[5]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

methanol (67-56-1)

ether (60-29-7)

acetic anhydride (108-24-7)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

acetone (67-64-1)

diethylamine hydrochloride (660-68-4)

methyl vinyl ketone (78-94-4)

1-Diethylamino-3-butanone, 2-Butanone, 4-diethylamino- (3299-38-5)

1,1-bis(diethylaminomethyl)acetone

paraformaldehyde (30525-89-4)

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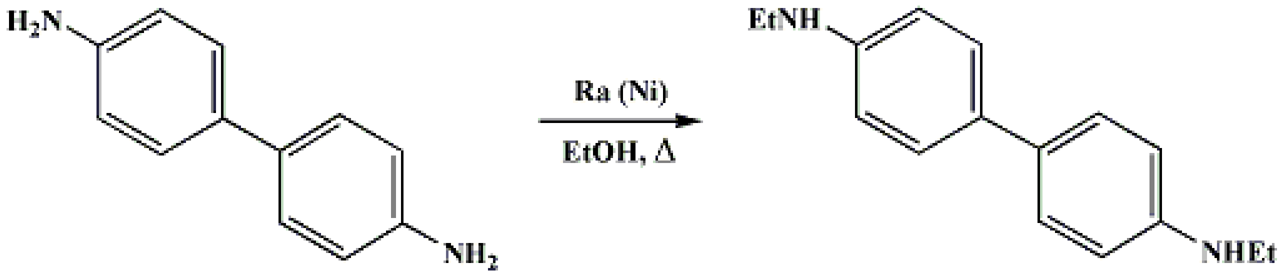
N,N'-DIETHYLBENZIDINE

[Benzidine, N,N'-diethyl-]



Submitted by Rip G. Rice and Earl J. Kohn[1].
Checked by Max Tishler, W. H. Jones, and W. F. Benning.

1. Procedure

In a 5-l. three-necked flask, fitted with an efficient stirrer (Note 1), a stopper, and a reflux condenser, are placed, in order, 184.2 g. (1 mole) of benzidine (Note 2), 500 ml. of commercial absolute ethanol, about 125 g. of Raney nickel,[2] and 500 ml. of ethanol. The mixture is heated under reflux with stirring for a total of 15 hours (Note 3). The volume is brought to 3 l. with 95% ethanol, and about 150 g. of filter aid ("Super-Cel") is added with stirring. The mixture is heated to boiling, filtered rapidly through a -in. layer of filter aid on a Büchner funnel into a 4-l. filter flask (Note 4) and (Note 5), and the nickel is washed well with hot 95% ethanol (Note 6). The filtrate is concentrated to a volume of 1.5 l., cooled slowly to room temperature, then chilled in a refrigerator and filtered. The yield is 185–202 g. (77–84%) of light gray or purplish gray flakes, m.p. 105–115°.

The crude product is dissolved in 1.5 l. of hot 95% ethanol, the solution is treated with 5 g. of activated carbon, and the mixture is filtered rapidly with suction. The filtrate is made up to 1.5 l. with 95% ethanol and heated to dissolve the solid. The solution is allowed to cool slowly to room temperature, then chilled in a refrigerator and filtered. The yield is 143–161 g. (60–67%) of colorless flakes melting at 115–116° (Note 7).

2. Notes

1. Efficient stirring is necessary to keep the nickel uniformly distributed throughout the reaction mixture; otherwise, the yield is decreased considerably.
2. The submitters used benzidine obtained by neutralization of an aqueous solution of C. P. benzidine dihydrochloride (Matheson, Coleman and Bell) with 20% sodium hydroxide solution, followed by crystallization from 60–70% ethanol. The benzidine prepared in this manner was in the form of light tan flakes. Freshly prepared benzidine should be used for the best results.
3. The refluxing time does not have to be continuous. The submitters heated the reaction mixture for 7 hours, allowed the mixture to stand overnight, and continued the refluxing the next day.
4. This operation should be carried out in a well-ventilated hood.

5. To prevent clogging of the Büchner funnel during filtration it is necessary to preheat the funnel and keep it hot during filtration.
6. The nickel is pyrophoric and must be kept moist to prevent spontaneous ignition.

7. The method has been applied successfully by the submitters[3] to the preparation of N, N'-dibutylbenzidine (61% crude yield), N-ethyl-, N-propyl-, N-butyl-, N-amyl-, and N-benzylani- lines (80–84% yields), N-hexylaniline (72%), and N-isobutyl- and N-isoamylanilines (41, 49%). N-Propylbutylamine was obtained from propyl alcohol and butylamine in 57% yield. The submitters state that no alkylation of benzidine took place with methyl alcohol or of aniline with methyl, isopropyl, or *sec*-butyl alcohol. The method has been applied to the synthesis of other N-alkyl and N-cycloalkyl aromatic amines.[4,5]

3. Discussion

N,N'-Diethylbenzidine has been prepared by heating ethyl iodide, benzidine, and ethanol in a pressure tube at water-bath temperature,[6,7] and by the reaction of diethylzinc on benzene-diazonium chloride.[7] The method described here is a modification of that of Shah, Tilak, and Venkataraman.[8]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

methyl, isopropyl, or sec-butyl alcohol

ethanol (64-17-5)

methyl alcohol (67-56-1)

aniline (62-53-3)

sodium hydroxide (1310-73-2)

benzene-diazonium chloride

nickel, Raney nickel (7440-02-0)

carbon (7782-42-5)

propyl alcohol (71-23-8)

diethylzinc (557-20-0)

benzidine (92-87-5)

Ethyl iodide (75-03-6)

benzidine dihydrochloride

N-hexylaniline (4746-32-1)

N-Propylbutylamine (20193-21-9)

Butylamine (109-73-9)

N,N'-DIETHYLBENZIDINE, Benzidine, N,N'-diethyl- (6290-86-4)

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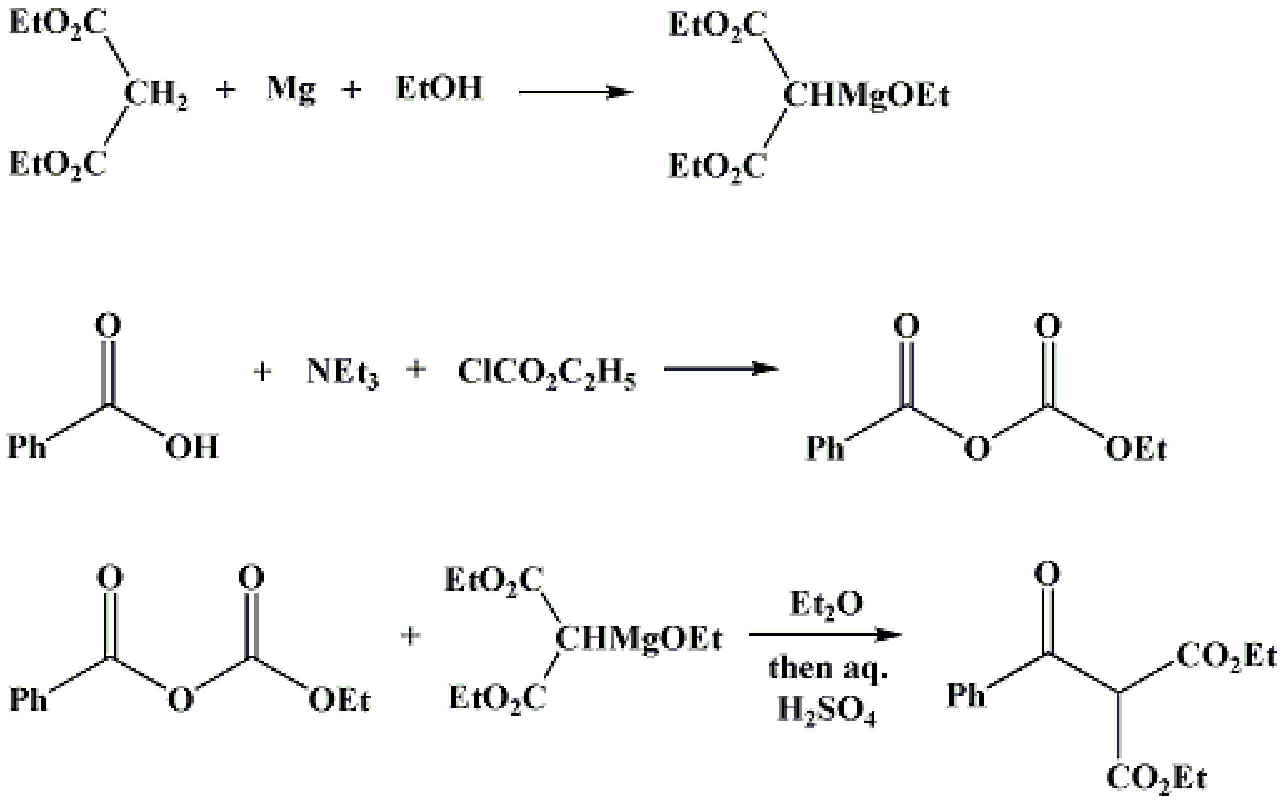
Organic Syntheses, CV 4, 285

DIETHYL BENZOYLMALONATE

[Malonic acid, benzoyl-, diethyl ester]



Submitted by John A. Price and D. S. Tarbell[1].
Checked by T. L. Cairns and C. L. Dickinson.

1. Procedure

A. *Ethoxymagnesiummalonic ester (Note 1)*. In a 250-ml. three-necked flask equipped with a dropping funnel and an efficient reflux condenser fitted with a calcium chloride drying tube are placed 5.0 g. (0.2 g. atom) of magnesium turnings (Grignard), 5 ml. of absolute alcohol (Note 2), 0.2 ml. of carbon tetrachloride, and 6 ml. of a mixture of 32.0 g. (30.2 ml., 0.2 mole) of diethyl malonate (Note 3) and 16 ml. of absolute alcohol. The reaction will proceed in a few minutes and may require occasional cooling before the addition of the remainder of the diethyl malonate solution. The addition should be controlled so that the reaction goes at a fairly vigorous rate. When the reaction mixture has cooled to room temperature, 60 ml. of ether dried over sodium wire is cautiously (Note 4) added. When the reaction again appears to subside, gentle heating by means of a steam bath is begun and continued until nearly all the magnesium has disappeared (Note 5). The alcohol and ether are removed by distillation, first at atmospheric pressure and then at reduced pressure secured with a water pump. To the partially crystalline product is added 60 ml. of dry benzene, and the solvent is again removed by distillation at atmospheric and then reduced pressure (Note 6). The residue is dissolved in 60 ml. of dry ether to await the completion of the mixed carbonic-carboxylic anhydride preparation.

B. *Mixed benzoic-carbonic anhydride (Note 7)*. In a 500-ml. three-necked flask, equipped with a low-temperature thermometer, an efficient sealed stirrer, and an adaptive joint carrying a drying tube and a dropping funnel, is placed a solution of 24.4 g. (0.2 mole) of benzoic acid (Note 8) and 20.2 g. (0.2 mole) of triethylamine (Note 9) in 200 ml. of dry toluene. The solution is cooled below 0° by means of an ice-salt mixture, and 21.7 g. (0.2 mole) of ethyl chlorocarbonate (Note 10) is added at such a rate that the temperature does not rise above 0° (approximate time for addition is 25–30 minutes). Triethylamine hydrochloride precipitates both during the addition and while the mixture is stirred for 15–25 minutes thereafter.

C. *Diethyl benzoylmalonate*. The dropping funnel used for the chlorocarbonate addition is replaced by another into which the ethereal solution of the ethoxymagnesium compound has been transferred. Approximately 30 ml. of dry ether is used to rinse the flask, and this is also added to the dropping funnel. The ether solution is added to the mixed anhydride with stirring, as the temperature is held at –5° to 0°. After the mixture has been allowed to stand overnight and to come to room temperature during this time, it is treated cautiously with 400 ml. of 5% sulfuric acid; then the aqueous solution is separated and extracted once with ether. The two organic layers are combined, washed once with dilute sulfuric acid and then with a concentrated sodium bicarbonate solution until no further benzoic acid is obtained from acidification of the bicarbonate extracts (Note 11). The organic layer is washed with water and dried over anhydrous sodium sulfate. After removal of the sodium sulfate by filtration, the solvent is removed at water-pump pressure from a water bath held at about 50°. The resulting product is purified by distillation through a 30-cm. Vigreux column, and the fraction boiling at 144–149°/0.8 mm. is collected (Note 12). The yield is 35.8–39.4 g. (68–75%), n_D^{25} 1.5063–1.5066.

2. Notes

1. The described procedure is essentially the same as that reported by Lund and Voigt.[2] A similar preparation has been described by Reynolds and Hauser (p. 708).
2. A commercial grade is satisfactory for this preparation.
3. Commercial malonic ester was redistilled at reduced pressure to give material with n_D^{20} 1.4047.
4. The ether dissolves the crystalline cake which has formed on cooling. This releases unreacted material and vigorous reaction again sets in.
5. From 6 to 8 hours is required for this operation.
6. The benzene removes any residual alcohol which may interfere with the subsequent acylation.[3]
7. The mixed carbonic anhydride procedure[4,5,6] has been useful in the preparation of amide linkages and thiol esters. Mixed carbonic anhydrides have successfully acylated, under very mild conditions, the carbanions derived from diethyl ethylmalonate and diethylcadmium.[7] The latter gives as a product the corresponding ketone. Mixed anhydrides derived from acetic and acetylsalicylic acids give results similar to those described here.[7]
8. A good reagent grade of benzoic acid is satisfactory.
9. Redistillation of a commercial grade gave material boiling at 87.0–87.2°.
10. Redistillation of a commercial grade gave material boiling at 90.8–92.0°.
11. If the benzoic acid is not all removed at this stage, it is troublesome during the final

distillation.
12. The fore-run, if giving a positive test with ferric chloride reagent, may be redistilled to give increased yields.

3. Discussion

Diethyl benzoylmalonate has been prepared by treatment of the copper derivative of ethyl benzoylacetate with ethyl chlorocarbonate.[8] It has also been obtained by the action of benzoyl chloride on the magnesium derivative of diethyl malonate,[9] and on a mixture of malonic ester and sodium methoxide[10,11] or sodium.[12,13] This compound has been found to be obtainable in higher yield by the reaction of benzoyl chloride and the ethoxymagnesium derivative.[14] The present method has been described in a previous communication and is of interest as an illustration of the use of mixed carbonic anhydrides as acylating agents.[7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 247

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Ethoxymagnesiummalonic ester

benzoic-carbonic anhydride

copper derivative of ethyl benzoylacetate

magnesium derivative of diethyl malonate

alcohol (64-17-5)

sulfuric acid (7664-93-9)

Benzene (71-43-2)

ether (60-29-7)

sodium bicarbonate (144-55-8)

magnesium, magnesium turnings (7439-95-4)

sodium sulfate (7757-82-6)

carbon tetrachloride (56-23-5)

Benzoic acid (65-85-0)

sodium methoxide (124-41-4)

benzoyl chloride (98-88-4)

toluene (108-88-3)

sodium, sodium wire (13966-32-0)

ferric chloride (7705-08-0)

diethyl malonate (105-53-3)

ethyl chlorocarbonate (541-41-3)

triethylamine (121-44-8)

Diethyl benzoylmalonate, Malonic acid, benzoyl-, diethyl ester (1087-97-4)

Triethylamine hydrochloride (554-68-7)

diethyl ethylmalonate (133-13-1)

diethylcadmium

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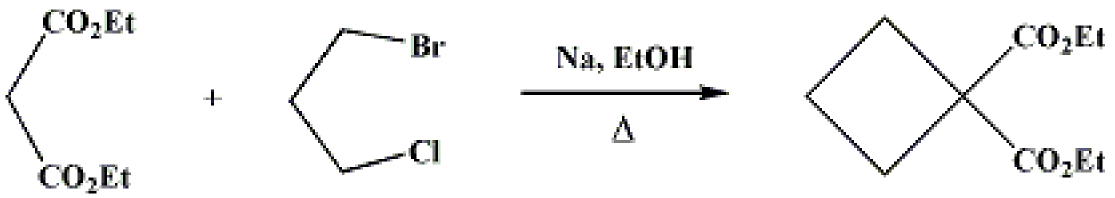
Organic Syntheses, CV 4, 288

DIETHYL 1,1-CYCLOBUTANEDICARBOXYLATE

[1,1-Cyclobutanedicarboxylic acid, diethyl ester]



Submitted by Raymond P. Mariella and Richard Raube[1].
Checked by William S. Johnson, William DeAcetis, and Herbert Title.

1. Procedure

A solution of sodium ethoxide is prepared by adding 138 g. (6.0 g. atoms) of fresh-cut sodium in small pieces to 2.5 l. of absolute ethanol in a 5-l. round-bottomed flask fitted with an efficient reflux condenser capped with a calcium chloride drying tube (Note 1). In a three-necked 5-l. round-bottomed flask, equipped with a reflux condenser capped with a calcium chloride tube, a rubber-sealed mechanical stirrer, and an inlet tube for addition of the sodium ethoxide solution, are mixed 480 g. (3.0 moles) of diethyl malonate (Note 2) and 472 g. (3.0 moles) of trimethylene chlorobromide (Note 3). The mixture is heated to 80° and vigorously stirred while the sodium ethoxide solution is slowly forced into the flask by means of dry air pressure. The rate of addition is regulated so that the reaction mixture refluxes smoothly. After the addition is complete (this requires about 1.5 hours), the mixture is refluxed, with continued stirring (Note 4), for an additional 45 minutes. Upon completion of the reflux period, the alcohol is removed by distillation (Note 4), 90–95% of the alcohol being recovered. The reaction mixture is cooled, and 900 ml. of cold water is added. After the sodium halides are completely dissolved, the organic layer is separated and the aqueous layer is extracted with three 500-ml. portions of ether. The organic layer and the ether extracts are combined, shaken with 50 ml. of saturated salt solution, and dried over 100 g. of anhydrous sodium sulfate. The solution is filtered, the ether is removed by distillation on a steam bath, and the residue, which weighs 600–625 g., is distilled through a short Vigreux column. The yield of product boiling at 91–96°/4 mm. is 320–330 g. (53–55%) (Note 5).

2. Notes

1. It is important to maintain strictly anhydrous conditions throughout this reaction. The equipment should be carefully predried and the absolute ethanol freshly prepared (preferably by the magnesium ethoxide method[2]) and distilled directly into the reaction flask. If the volume of ethanol is less than 2.5 l. the

sodium ethoxide may not remain in solution. It is convenient to employ a three-necked flask carrying two condensers for this operation and to add the sodium through the third neck, which is otherwise kept stoppered.
2. Material boiling at 95.2–95.8°/14 mm., n_D^{25} 1.4120, was used.
3. Trimethylene chlorobromide can be obtained commercially. Material boiling at 141–142°/755 mm., n_D^{25} 1.4843, was used.
4. The stirring must be continued during this operation; otherwise the mixture will bump badly.
5. This material, n_D^{25} 1.433–1.434, d_{20}^{25} 1.042–1.044, is of fair purity and can be hydrolyzed and decarboxylated[3,4] to give cyclobutanecarboxylic acid in more than 80% yield. In order to obtain a highly pure product it may be necessary to fractionally distil the material. For example, on slow redistillation of a product prepared as described above through a 3-ft. Vigreux column at a high reflux ratio, the checkers obtained 8.5% of forerun n_D^{25} 1.4287–1.4328, 43% of diethyl 1,1-cyclobutanedicarboxylate, n_D^{25} 1.4332–1.4335, and 2.5% of higher-boiling material n_D^{25} 1.4362–1.4427. The pure product is reported to boil at 104.6°/12 mm., 85.2°/3.5 mm. or 60.0°/0.5 mm., n_D^{25} 1.4336, d_{20}^{25} 1.0470.[5]

3. Discussion

Diethyl 1,1-cyclobutanedicarboxylate has been prepared by the alkylation of diethyl sodiomalonate with trimethylene dibromide,[3,4,6,7] trimethylene diiodide,[7] or trimethylene chlorobromide.[8,9] It is claimed that the yield of product from the latter reaction may be increased by the use of a mixture of benzene and ethanol as a solvent.[10] Diethyl 1,1-cyclobutanedicarboxylate also may be obtained by the peroxide-catalyzed addition of hydrogen bromide to diethyl allylmalonate followed by intramolecular alkylation.[11] The procedure described here is that of Mariella and Raube.[8]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 271

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

Benzene (71-43-2)

ether (60-29-7)

hydrogen bromide (10035-10-6)

trimethylene dibromide (109-64-8)

sodium sulfate (7757-82-6)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

Trimethylene chlorobromide (109-70-6)

diethyl malonate (105-53-3)

Cyclobutanecarboxylic acid (3721-95-7)

Diethyl 1,1-cyclobutanedicarboxylate, 1,1-Cyclobutanedicarboxylic acid, diethyl ester (3779-29-1)

diethyl sodiomalonate

trimethylene diiodide (627-31-6)

diethyl allylmalonate (2049-80-1)

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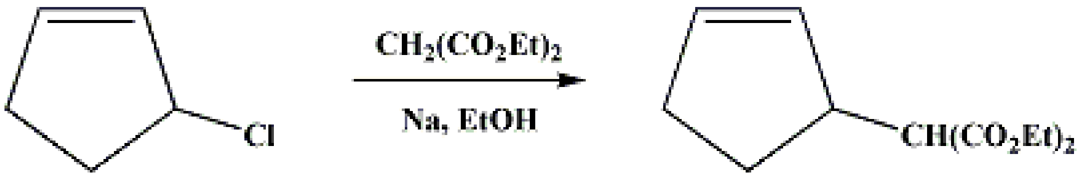
Organic Syntheses, *CV 4*, *291*

DIETHYL Δ²-CYCLOPENTENYLMALONATE

[2-Cyclopentene-1-malonic acid, diethyl ester]



Submitted by Robert Bruce Moffett[1]
Checked by R. T. Arnold and George P. Scott.

1. Procedure

Nine hundred and twenty-five milliliters of absolute ethanol (Note 1) is placed in a 2-l. three-necked round-bottomed flask, fitted with a mercury or glycerin-sealed stirrer (Note 2), dropping funnel, and reflux condenser. To this is added 46 g. (2 g. atoms)[2] of freshly cut sodium, a few pieces at a time and at such a rate that the reaction proceeds rapidly but the solvent does not reflux too vigorously. When most of the sodium has dissolved, a calcium chloride drying tube is fitted to the top of the condenser and 320 g. (2 moles) of redistilled diethyl malonate is added from the dropping funnel. Then 205 g. (2 moles) of 3-chlorocyclopentene (p. 42) (Note 3) is added at such a rate that a gentle reflux is maintained. Toward the end of the addition, it is desirable to test the reaction mixture with pH test paper, and the addition should be stopped if the solution becomes acidic.

When the addition is complete, the condenser is set downward for distillation, the stirring is continued, and most of the ethanol is removed by distillation on a steam bath (Note 4). After cooling, the reaction mixture is diluted with sufficient water to dissolve the salt, and the layers are separated. The aqueous layer is extracted with 50 ml. of ether. The ethereal solution is added to the ester, and the resulting solution is washed with saturated salt solution and dried over anhydrous magnesium sulfate. The ethereal solution is transferred to a Claisen flask, the solvent is evaporated, and the product is distilled under reduced pressure. The fraction boiling at about 85–140°/12 mm. is collected and redistilled through an efficient fractionating column (Note 5). The product distils at 130°/12 mm. (Note 6). The yield is about 276.5 g. (61%); n_{D}^{20} 1.4536.

2. Notes

1. The preparation of absolute ethanol has been described earlier.[3]

2. The glycerin-sealed stirrer has been described earlier.[2]

3. It is not necessary to use redistilled 3-chlorocyclopentene; however, if large

amounts of impurities are present, difficulty may be encountered in obtaining a pure product.
4. If a glycerin-sealed stirrer is used, the rate of solvent evaporation may be accelerated by means of gentle water-pump suction.
5. Careful fractionation is necessary in order to secure a pure product. The submitter used a 12-in. column packed with 1/8-in. glass helices. The fore-run should be redistilled to separate any ester it may contain.
6. Other boiling points are 140°/18 mm.; 97°/1 mm.

3. Discussion

Diethyl Δ^2-cyclopentenylmalonate has been prepared by the alkylation of malonic ester with 3-chlorocyclopentene.[4,5,6,7,8]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Diethyl Δ^2-cyclopentenylmalonate

ethanol (64-17-5)

ether (60-29-7)

sodium (13966-32-0)

diethyl malonate (105-53-3)

magnesium sulfate (7487-88-9)

3-Chlorocyclopentene (96-40-2)

2-Cyclopentene-1-malonic acid, diethyl ester (53608-93-8)

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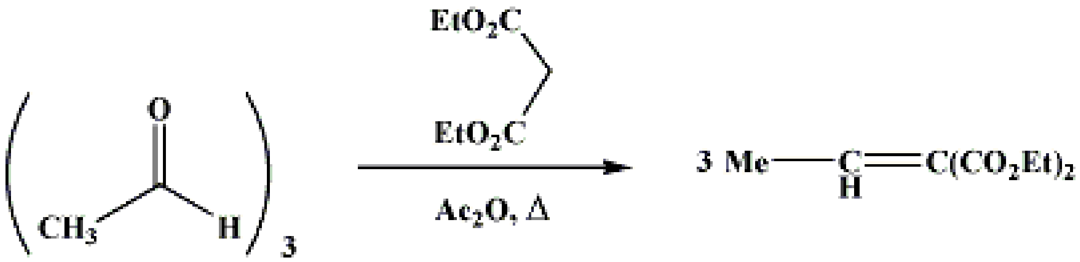
Organic Syntheses, CV 4, 293

DIETHYL ETHYLIDENEMALONATE

[Malonic acid, ethylidene-, diethyl ester]



Submitted by William S. Fones[1]
Checked by Arthur C. Cope, Harris E. Petree, and E. R. Trumbull.

1. Procedure

In a 1-l. three-necked flask, equipped with a thermometer and a reflux condenser, are placed 60 g. of paraldehyde (0.45 mole, equivalent to 1.35 moles of acetaldehyde) and 100 ml. (1.06 moles) of acetic anhydride. Ice water is circulated through the condenser, and the reaction mixture is protected from atmospheric moisture by a drying tube containing Drierite. The temperature of the mixture is raised slowly by heating with an electric mantle to 125°, at which point gentle refluxing begins. Then 100 g. (0.62 mole) of diethyl malonate is added in 15-ml. portions at a rate of 1 portion every 30 minutes. During the addition of diethyl malonate, the temperature gradually drops to about 100°, and the mixture is heated so as to maintain a reflux rate of 30–60 drops per minute. After the addition is complete, the reaction mixture is heated under reflux for 4 hours at the specified rate.

The reflux condenser is replaced by a Claisen distillation head, and the reaction mixture is distilled until the temperature of the vapor reaches 140°. The residue is transferred to a smaller flask and fractionated through a 30-cm. column packed with glass helices. A low-boiling fraction containing ethylidene diacetate and diethyl malonate is collected first, followed by 79–89.5 g. (68–77%) of diethyl ethylidenemalonate; b.p. 102–106°/10 mm.; n_D^{25} 1.4394 (Note 1) and (Note 2).

2. Notes

1. The submitter obtained a yield of 70% when three times the above quantities were used, in which case the diethyl malonate was added at a rate of 90 ml. per hour.

2. Horton[2] has reported that a higher yield of diethyl ethylidenemalonate has been obtained by the following procedure. A mixture of 50 g. of redistilled malonic ester, 50 g. of acetic anhydride and 28.5 g. of acetaldehyde, enclosed in a hydrogenation bomb, was mixed and heated at 100° for 24 hours without

shaking. The bomb contents were transferred with the aid of benzene, and three pooled runs were distilled through a 15-in. Vigreux column at 18–20 mm. A fore-run of diethyl malonate was removed, and then 149.8 g. (86.2%) of diethyl ethylidenemalonate was collected at 106–109°/13 mm. The product was stored at 5°.

3. Discussion

Diethyl ethylidenemalonate has been prepared by heating acetaldehyde, diethyl malonate, and acetic anhydride;[3,4] by heating the same reagents plus zinc chloride;[5] by treating acetaldehyde and diethyl malonate with sodium ethoxide or piperidine;[6] and by heating diethyl malonate, ethylidene bromide, and ethanolic sodium ethoxide.[7]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

acetaldehyde (75-07-0)

Benzene (71-43-2)

acetic anhydride (108-24-7)

piperidine (110-89-4)

sodium ethoxide (141-52-6)

zinc chloride (7646-85-7)

diethyl malonate (105-53-3)

Diethyl ethylidenemalonate, Malonic acid, ethylidene-, diethyl ester (1462-12-0)

ethylidene diacetate (542-10-9)

ethylidene bromide (557-91-5)

paraldehyde (123-53-7)

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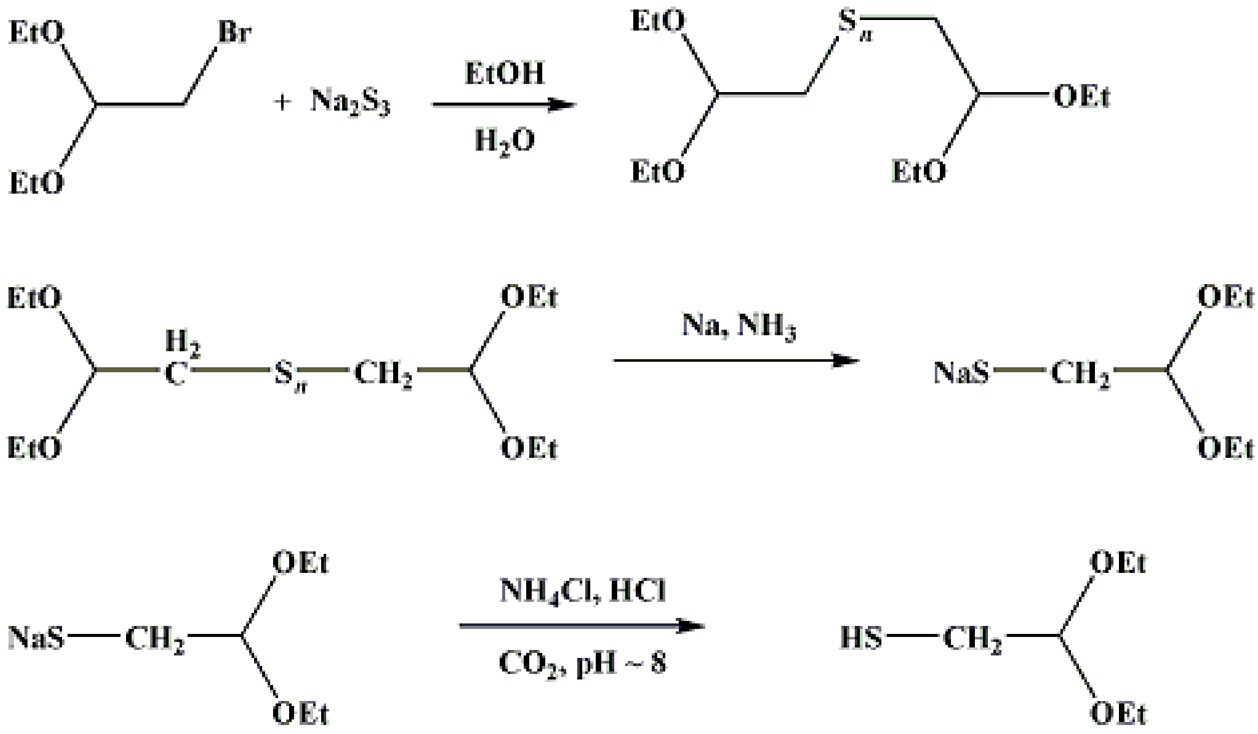
Organic Syntheses, CV 4, 295

DIETHYL MERCAPTOACETAL

[Acetaldehyde, mercapto-, diethyl acetal]



Submitted by William E. Parham and Hans Wynberg[1].
Checked by Max Tishler and George Purdue.

1. Procedure

A. *1,1,1',1'-Tetraethoxyethyl polysulfide* (Note 1). In a 5-l. round-bottomed flask, equipped with a stirrer, a reflux condenser, and an addition funnel, 540 g. (2.25 moles) of sodium sulfide enneahydrate (Note 2) is dissolved in 2.7 l. of boiling 95% ethanol. Sulfur (144 g., 4.5 g. atoms) is added, and the solution is heated under reflux until it has assumed a deep-red color (10 minutes). The source of heat is removed, and 588 g. (3 moles) of diethyl bromoacetal (Note 3) is added over a period of about 30 minutes at such a rate that the solution boils gently. The mixture is heated under reflux for an additional 4 hours. During the last hour of heating, ethanol is allowed to distil from the reaction flask, and after the first 700 ml. of distillate is collected sodium bicarbonate (135 g.) (Note 4) is added to the reaction mixture. A total of 2.0–2.5 l. of ethanol is collected. Water (1.5 l.) is added, and the upper layer is separated. The aqueous layer is extracted with two 250-ml. portions of ether, and the combined organic layers are washed successively with two 100-ml. portions of 10% sodium hydroxide solution, three 100-ml. portions of water, and two 250-ml. portions of saturated sodium chloride solution, and are dried over potassium carbonate. The ether is removed by distillation, and the residue is brought to constant weight by heating for about 1 hour on the steam

bath at 10–15 mm. pressure. The orange liquid obtained in this way (Note 5) weighs 450–500 g. and has n_D^{25} 1.515–1.517.

B. *Diethyl mercaptoacetal*. A 12-l. three-necked flask, equipped with an efficient Hershberg stirrer, a Dry Ice condenser, and a stopper, is placed in an enameled container (Note 6). The flask is charged with 500 g. (1.38 moles, calculated as tetrasulfide) of 1,1,1',1'-tetraethoxyethyl polysulfide and 500 ml. of anhydrous ether. The condenser is filled with acetone and Dry Ice, and the contents of the flask are cooled by means of acetone and Dry Ice kept at −35° to −45°. Liquid ammonia (Note 7) is introduced into the stirred solution until 4.5–5.0 l. has been added (Note 8). The solution is stirred for several minutes to ensure homogeneity, and 200 g. (8.7 g. atoms) of sodium is added in 2- to 5-g. lumps to the mixture over a period of 30–45 minutes. The last 2–10 g. of sodium causes the solution to turn deep blue. The mixture is stirred for 30 additional minutes, and ammonium chloride (about 200 g.) is cautiously added with stirring until the blue color is discharged. The cooling bath is removed and replaced by a bath of hot water into which steam may be introduced. The mixture is stirred while the ammonia is removed by distillation or evaporation (the distillation should be continued until the residue can no longer be stirred or is difficult to stir). The soft, semisolid mass containing small amounts of ammonia is cooled in ice, and 1 l. of ice-cold water is added with stirring. When most of the solid has dissolved, ice-cold hydrochloric acid is added cautiously, with frequent checks of the pH, until a pH of 8.0–8.5 is reached. The pH is then adjusted to 7.8–8.0 (preferably by a pH meter) by passing carbon dioxide into the cold solution (Note 9). The oil is separated from the aqueous layer, which is extracted with two 300-ml. portions of ether. The combined organic layers are washed successively with 100 ml. of water and two 100-ml. portions of saturated sodium chloride, and are dried over magnesium sulfate. The ether is removed by distillation, and the residue is distilled from a 500-ml. flask using a small Vigreux column or a Claisen head. The product (Note 10) weighs 320–372 g. (77–90% yield, based on polysulfide; 71–83% yield, based on bromoacetal), boils at 62–64°/12 mm., and has n_D^{25} 1.4391–1.4400. The residue, 23–27 g., n_D^{25} 1.4702–1.4730, consists mainly of 1,1,1',1'-tetraethoxyethyl sulfide.

2. Notes

1. These directions have been used equally successfully with twice, one-third, and one-fifth the amounts specified. The reaction of chloro- or bromoacetal with sodium disulfide results in the formation of a considerable quantity of the corresponding monosulfide which is not subsequently reduced to mercaptan. Polysulfides are, however, easily reduced to mercaptans. 1,1,1',1'-Tetramethoxyethyl polysulfide has been prepared from commercially available dimethyl chloroacetal in a similar fashion. A 10-hour heating period and the addition of 5 g. of potassium iodide per 100 g. of acetal are recommended in the latter preparation.
2. The sodium sulfide ($Na_2S \cdot 9H_2O$) should be crystalline and finely divided.
3. The procedure used for the preparation of diethyl bromoacetal (b.p. 78–

79°/24 mm., n_D^{20} 1.4418) is that of Bedoukian.[2]
4. Di- and polysulfides are cleaved by strong alkali. The bicarbonate is added as a buffer.
5. Analysis of this material showed it to have the average composition calculated for a tetrasulfide; the yield of product, calculated as tetrasulfide, is 83–92%.
6. In order to use as little coolant as possible the flask should fit the container snugly.
7. All normal precautions should be observed during the handling of these large quantities of ammonia and sodium. A well-ventilated hood, a gas mask, and a bucket of sand were available to the submitters. The only hazard in this reaction may arise if too much ammonia escapes and the sodium does not react properly as a consequence. The addition of 0.5–1.0 l. of ammonia to the reaction mixture after the sodium has been added is a useful precaution.
8. The submitters measured the liquid ammonia in a 1-l. graduated cylinder.
9. Complete neutralization of the salt of mercaptoacetal with mineral acid may result in hydrolysis of the acetal.
10. Mercaptoacetal is sensitive to acid and oxygen. The product should be stored in a dry, alkali-washed bottle under nitrogen in a refrigerator.

3. Discussion

Diethyl mercaptoacetal has been prepared by treating diethyl bromoacetal with potassium hydrosulfide;[3] by the reduction of 1,1,1',1'-tetraethoxyethyl disulfide[3] with lithium aluminum hydride; by reduction of 1,1-diethoxyethyl benzyl sulfide,[3,4] 1,1,1',1'-tetraethoxyethyl disulfide,[3] and 1,1,1',1'-tetraethoxyethyl polysulfide[3] with sodium and liquid ammonia. The method described is adapted from the last-named preparation. Dimethyl mercaptoacetal has been prepared by the same methods.[3]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

1,1,1',1'-Tetraethoxyethyl polysulfide

sodium sulfide enneahydrate

diethyl bromoacetal

1,1,1',1'-Tetramethoxyethyl polysulfide

dimethyl chloroacetal

ethanol (64-17-5)

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ether (60-29-7)

ammonium chloride (12125-02-9)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

oxygen (7782-44-7)

potassium iodide (7681-11-0)

nitrogen (7727-37-9)

sulfur (7704-34-9)

carbon dioxide (124-38-9)

acetone (67-64-1)

sodium (13966-32-0)

sodium sulfide (1313-82-2)

sodium disulfide

potassium hydrosulfide (1310-61-8)

magnesium sulfate (7487-88-9)

lithium aluminum hydride (16853-85-3)

Diethyl mercaptoacetal (53608-94-9)

Acetaldehyde, mercapto-, diethyl acetal

1,1,1',1'-tetraethoxyethyl sulfide

1,1,1',1'-tetraethoxyethyl disulfide

1,1-diethoxyethyl benzyl sulfide

Dimethyl mercaptoacetal

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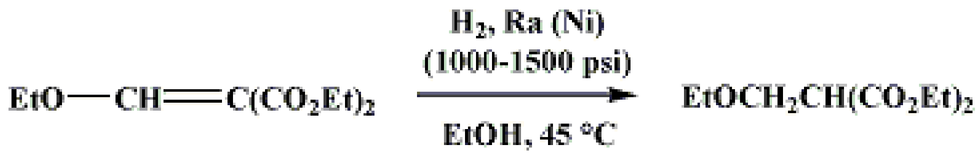
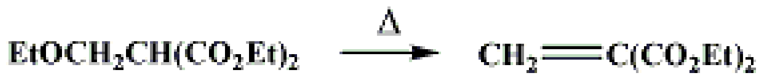
DIETHYL METHYLENEMALONATE

[Malonic acid, methylene-, diethyl ester]





Submitted by Wayne Feely and V. Boekelheide[1].
Checked by Max Tishler, Barbara P. Birt, and Arthur A. Patchett.

1. Procedure

A solution of 108 g. (0.5 mole) of diethyl ethoxymethylenemalonate (Note 1) in 100 ml. of commercial absolute alcohol is placed in an apparatus for high-pressure hydrogenation together with 10 g. of Raney nickel catalyst (Note 2). The pressure in the bomb is raised to 1000–1500 lb. with hydrogen, and the temperature is adjusted to 45° (Note 3). The bomb is shaken, and the reaction is allowed to proceed for 12–20 hours, during which time 0.5 mole of hydrogen is absorbed.

The apparatus is allowed to cool to room temperature, the pressure is released, and the catalyst is removed by filtration. Concentration of the filtrate under reduced pressure at room temperature yields a colorless oil (Note 4).

The residual oil is transferred to a distillation flask (Note 5), and the flask is carefully warmed with a small flame (Note 6). After a fore-run of ethanol is collected, the variable transformer controlling the heating tape is set at a voltage to give an internal temperature in the distilling head of 80–100° before distillation. The flask is then heated to effect slow distillation at atmospheric pressure. About 10–13 g. of fore-run is collected before the temperature of the distillate vapor reaches 200°. The main fraction (68–71 g., 79–82%) is collected between 200° and 216° as a colorless oil. For most purposes, the fore-run is sufficiently pure that it can be combined with the main fraction to give an over-all yield of 78–81 g. (91–94%) (Note 7). Diethyl methylenemalonate polymerizes on standing to a white solid, from which the monomer can be recovered by slow distillation. The diethyl methylenemalonate should be distilled just prior to use (Note 8).

2. Notes

1. Diethyl ethoxymethylenemalonate can be prepared by the method of Parham and Reed.[2] The submitters used diethyl ethoxymethylenemalonate obtained commercially from Kay-Fries Chemicals Inc., 180 Madison Avenue, New York 16, New York.

2. Raney nickel catalyst can be prepared by the method of Mozingo.[3] The submitters used Raney nickel catalyst obtained commercially from the Gilman Paint and Varnish Company, Chattanooga, Tennessee.

3. At higher temperatures (about 70°) the diethyl ethoxymethylmalonate formed tends to eliminate ethanol, forming diethyl methylenemalonate which is hydrogenated to diethyl methylmalonate.

4. This oil, n_D^{20} 1.4254, is presumably diethyl ethoxymethylmalonate, as evidenced by its infrared and ultraviolet absorption spectra. It is relatively stable and can be stored at room temperature without change. If the concentration of the filtrate under vacuum is carried out by heating on a steam bath instead of by keeping it at room temperature, the diethyl ethoxymethylmalonate undergoes elimination of ethanol to some extent, giving diethyl methylenemalonate directly. The yield of diethyl methylenemalonate obtained eventually is not altered by this procedure.

5. The distillation apparatus is shown in f.htmig. 7. The upper part of the flask and the short column are wrapped in electrical heater tape, which is operated during distillation of the product.

Fig. 7.

Fig. 7.

6. The elimination of ethanol is slightly exothermic. It is advisable to heat the flask cautiously with a small flame until the reaction starts and then to remove the flame until the reaction subsides.

7. The fore-run has a refractive index (usually about n_D^{22} 1.4154) lower than that of the main fraction (about n_D^{22} 1.4250). The combined fractions show refractive indices in the range n_D^{22} 1.4210–1.4259.

8. When the solid polymer from the above preparation was slowly distilled to recover diethyl methylenemalonate, there was obtained 57 g. of colorless oil, b. p. 210–216° /730 mm., n_D^{20} 1.4220.

3. Discussion

Diethyl methylenemalonate was prepared first by Perkin[4] from formaldehyde and malonic ester, and more recently a study has been made of the effect of various catalysts on this system.[5] An alternative procedure involving the reaction of methylene chloride or iodide with sodiomalonic ester has been developed by Tanatar.[6] Diethyl methylenemalonate also is formed when hexaethyl pentane-1,1,3,3,5,5-hexacarboxylate is treated with methylene iodide and sodium ethoxide,[7] or when

methyl chloromethyl ether is caused to react with sodiomalonic ester.[8] Diethyl methylenemalonate has been obtained from paraformaldehyde[9] and vapor and liquid reactions of formaldehyde with diethyl malonate in the presence of various catalysts.[10]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

methylene chloride or iodide

ethanol (64-17-5)

hydrogen (1333-74-0)

formaldehyde (630-08-0)

Raney nickel (7440-02-0)

sodium ethoxide (141-52-6)

diethyl malonate (105-53-3)

Methylene iodide (75-11-6)

methyl chloromethyl ether (107-30-2)

diethyl methylmalonate (609-08-5)

diethyl ethoxymethylenemalonate (87-13-8)

Diethyl methylenemalonate, Malonic acid, methylene-, diethyl ester (3377-20-6)

diethyl ethoxymethylmalonate

hexaethyl pentane-1,1,3,3,5,5-hexacarboxylate

paraformaldehyde (30525-89-4)

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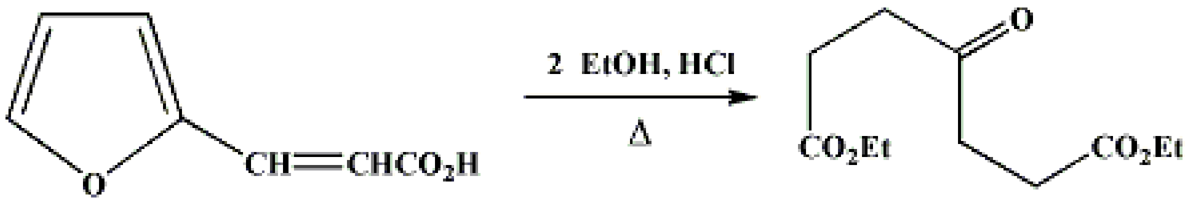
Organic Syntheses, CV 4, 302

DIETHYL γ-OXOPIMELATE

[Heptanedioic acid, 4-oxo-, diethyl ester]



Submitted by W. S. Emerson and R. I. Longley, Jr.[1].
Checked by William S. Johnson and I. A. David.

1. Procedure

A 3-l. three-necked flask equipped with a stirrer, reflux condenser, and gas inlet tube is charged with 476 g. (3.45 moles) of furylacrylic acid[2] and 1580 g. (about 33 moles) of 95% ethanol (Note 1). The mixture is heated to boiling, and anhydrous hydrogen chloride is introduced at such a rate that the mixture becomes saturated after 90 minutes. The gas inlet tube is replaced by a stopper, and a 2-ft. Vigreux column is substituted for the reflux condenser. About 250 ml. of solvent is removed by distillation at atmospheric pressure; then another 300 ml. is removed while the pressure is slowly reduced (water aspirator). The residue is cooled and stirred with a solution of about 260 g. of sodium carbonate in water (Note 2). The mixture is extracted with two 250-ml. portions of benzene, and the combined extracts are washed with 100 ml. of water (Note 3). Distillation of the organic portion through a 2-ft. Vigreux column yields, after a small fore-run, 579–657 g. (73–83%) of diethyl γ-oxopimelate, b.p. 116–121° /0.3 mm., n_D^{25} 1.4395–1.4400.

2. Notes

1. If absolute ethanol is used the yield is much lower.
2. A slight excess of sodium carbonate is used. The amount required depends on the amount of hydrogen chloride remaining after the distillation.
3. Sodium chloride may be added if the layers do not separate.

3. Discussion

Diethyl γ-oxopimelate has been prepared by saturating an ethanol solution of furylacrylic acid[3,4,5,6,7] or γ-oxopimelic acid dilactone with hydrogen chloride[5] or sulfuric acid.[8] It was found as a by-product in the esterification of furylacrylic acid with ethanol in the presence of *p*-toluenesulfonic acid.[9] A mechanism has been

proposed for the formation of esters of γ-oxopimelic acid from furylacrylic acid.[10] The present procedure is a modification of the original Marckwald process.[3,4]

References and Notes

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8. Reppe et al., *Ann.*, **596**, 80 (1955).
9. Murahashi, *Bull. Inst. Phys. Chem. Research (Tokyo)*, **22**, 476 (1943) [*C. A.*, **42**, 1205 (1948)].
10. Gavat and Glineschi, *Rev. chim. (Bucharest)*, **7**, 575 (1956) [*C. A.*, **52**, 1991 (1958)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

γ-oxopimelic acid dilactone

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrogen chloride (7647-01-0)

Benzene (71-43-2)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

Furylacrylic acid (539-47-9)

DIETHYL γ-OXOPIMELATE, Heptanedioic acid, 4-oxo-, diethyl ester (6317-49-3)

γ-oxopimelic acid (502-50-1)

p-toluenesulfonic acid (104-15-4)

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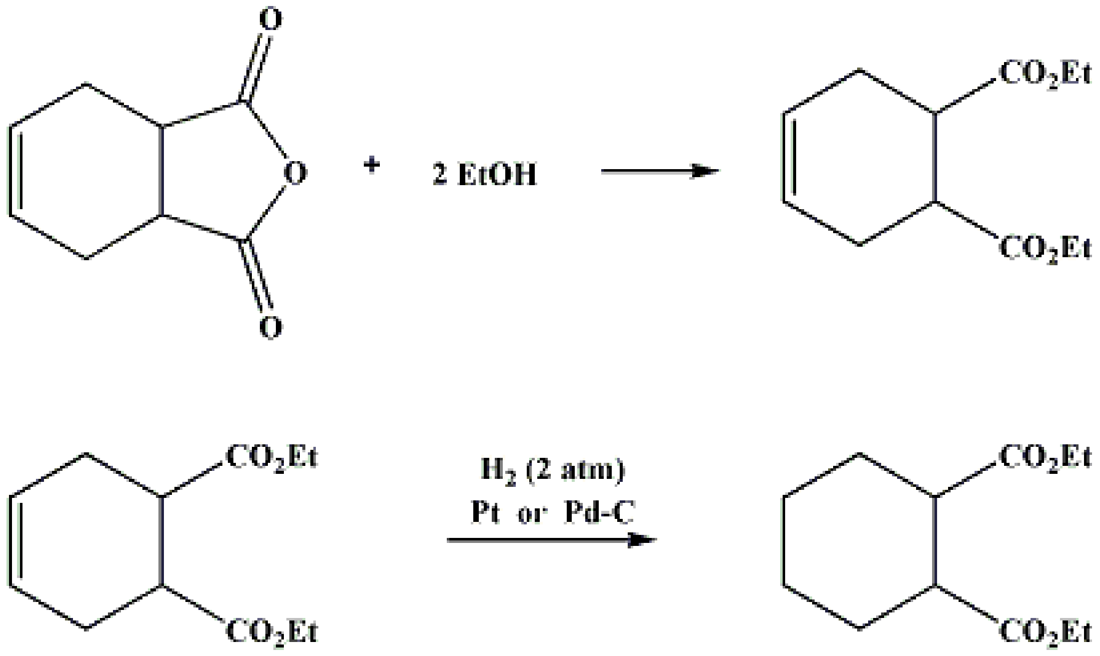
Organic Syntheses, CV 4, 304

DIETHYL *cis*-Δ4-TETRAHYDROPHTHALATE AND DIETHYL *cis*-HEXAHYDROPHTHALATE

[4-Cyclohexene-1,2-dicarboxylic acid, diethyl ester, *cis*-, and 1,2-Cyclohexanedicarboxylic acid, diethyl ester, *cis*-]



Submitted by Arthur C. Cope and Elbert C. Herrick[1].
Checked by Charles C. Price and George A. Cypher.

1. Procedure

A. *Diethyl cis-Δ^4-tetrahydrophthalate.* In a 2-l. round-bottomed flask are placed 228 g. (1.5 moles) of *cis*-Δ^4-tetrahydrophthalic anhydride (p. 890), 525 ml. (9 moles) of commercial absolute ethanol, and 2.5 g. of *p*-toluenesulfonic acid monohydrate. The flask is connected to a reflux condenser and heated in an oil bath maintained at 95–105° for 12–16 hours.

At this time 270 ml. of toluene is added to the mixture and the condenser is changed for distillation. An azeotropic mixture of ethanol, toluene, and water is distilled at 75–78° with the bath at 105–110°. When the temperature begins to drop (Note 1), 525 ml. of commercial absolute ethanol is added and the mixture is again heated under reflux for 12–16 hours (Note 2). Again 270 ml. of toluene is added, and the azeotropic mixture is distilled until the vapor temperature falls to 68°. After the residue is cooled, the system is evacuated to 25–35 mm. and the remaining ethanol and toluene are distilled.

The residual liquid is diluted with 200 ml. of ether. The ether solution is washed twice

with 100-ml. portions of 3% sodium carbonate solution (Note 3). The combined carbonate solutions are extracted three times with 100-ml. portions of ether, and the ether solutions are combined and washed with 100 ml. of distilled water. The ether solution is dried over magnesium sulfate, filtered, and concentrated, and the residue is distilled under reduced pressure. The yield of product boiling at 129–131°/5 mm., n_D^{25} 1.4605–1.4610, is 280–292 g. (83–86%) (Note 4).

B. *Diethyl cis-hexahydrophthalate.* The reaction is carried out in a low-pressure catalytic hydrogenation apparatus.[2] In a 500-ml. Pyrex centrifuge bottle are placed 0.5 g. of Adams platinum oxide catalyst (Note 5) and 20 ml. of commercial absolute ethanol (Note 6). The bottle is connected to a calibrated low-pressure hydrogen tank and alternately evacuated and filled with hydrogen twice. Hydrogen is then admitted to the system until the pressure is 1–2 atmospheres (15–30 lb.), and the bottle is shaken for 20–30 minutes to reduce the platinum oxide. The shaker is stopped, the bottle is evacuated, and air is admitted. Two hundred and twenty-six grams (1 mole) of diethyl *cis*-Δ^4-tetrahydrophthalate is placed in the bottle. The container in which the ester was weighed is rinsed with 10 ml. of absolute ethanol, which is added to the ester. The bottle is alternately evacuated and filled with hydrogen twice. Hydrogen is admitted to the system until the pressure is 25–30 lb. (approximately 2 atmospheres), and the bottle is shaken until the pressure drop indicates that the theoretical amount (1 mole) of hydrogen has been taken up and the absorption ceases (3–5 hours). The bottle is evacuated and then air is admitted. The catalyst is removed by filtration through a small Hirsch funnel. The bottle is washed with 15 ml. of alcohol, which is poured through the funnel. Most of the solvent is distilled at 25–35 mm. Distillation of the residue under reduced pressure yields 215–219 g. (94–96%) of diethyl *cis*-hexahydrophthalate, b.p. 130–132°/ 9 mm., n_D^{25} 1.4508–1.4510 (Note 7).

2. Notes

1. A period of 5–8 hours is required for this distillation and for the similar subsequent distillation.
2. If the second period of reflux and azeotropic distillation is omitted the yield is decreased to 66%.
3. The product should be washed with sodium carbonate solution until the aqueous solution remains basic.
4. Dimethyl *cis*-Δ^4-tetrahydrophthalate can be prepared by a similar procedure. *cis*-Δ^4-Tetrahydrophthalic anhydride (228 g., 1.5 moles) is heated under reflux with 364 ml. (9 moles) of commercial anhydrous methanol and 2.5 g. of *p*-toluenesulfonic acid monohydrate for 12–16 hours. At this time 270 ml. of toluene is added and the mixture is distilled. When the distillation temperature drops from 68–70° to 45°, after about 4–6 hours, 364 ml. of absolute methanol is added and the mixture again is heated under reflux for 12–16 hours. An additional 270 ml. of toluene is added, and distillation is continued for 4–6 hours. The residual liquid is purified by a procedure similar to the one described for the ethyl ester. The yield of dimethyl *cis*-Δ^4-tetrahydrophthalate, boiling at

120–122°/5 mm., n_D^{25} 1.4700, is 239 g. (80%).

5. The platinum oxide catalyst was obtained from Baker and Company, Newark, New Jersey. Platinum oxide may also be obtained from the American Platinum Works, Newark, New Jersey.

6. The reduction also may be carried out using 1 g. of palladium on carbon,[3] in which case no solvent is required and prereduction of the catalyst is unnecessary.

7. Dimethyl *cis*-hexahydrophthalate also may be prepared by a similar reduction of dimethyl *cis*-Δ^4-tetrahydrophthalate. With 0.5 g. of prereduced Adams platinum oxide catalyst, 198 g. (1 mole) of dimethyl *cis*-Δ^4-tetrahydrophthalate was reduced to give 196 g. (98%) of dimethyl *cis*-hexahydrophthalate, b.p. 110–112°/5 mm., n_D^{25} 1.4570.

3. Discussion

Diethyl *cis*-hexahydrophthalate has been prepared from *cis*-hexahydrophthalic acid, absolute ethanol, and sulfuric acid,[4,5] and from *cis*-hexahydrophthalic anhydride, absolute ethanol, and sulfuric acid.[6] Diethyl *cis*-Δ^4-tetrahydrophthalate has been prepared from *cis*-Δ^4-tetrahydrophthalic acid or its anhydride, ethanol, and sulfuric acid.[7] Dimethyl *cis*-Δ^4-tetrahydrophthalate and dimethyl *cis*-hexahydrophthalate have been synthesized by the procedures of this preparation.[8]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 890
- Org. Syn. Coll. Vol. 6, 454

References and Notes

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2. Suitable apparatus is described in *Org. Syntheses Coll. Vol.* **1**, 61 (1941).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Diethyl cis-Δ^4-tetrahydrophthalate

cis-Δ^4-Tetrahydrophthalic anhydride

Dimethyl cis-Δ^4-tetrahydrophthalate

cis-Δ^4-tetrahydrophthalic acid or its anhydride

ethanol (64-17-5)

sulfuric acid (7664-93-9)

methanol (67-56-1)

ether (60-29-7)

hydrogen (1333-74-0)

sodium carbonate (497-19-8)

platinum oxide

carbon (7782-42-5)

toluene (108-88-3)

palladium (7440-05-3)

magnesium sulfate (7487-88-9)

p-toluenesulfonic acid monohydrate (6192-52-5)

Diethyl cis-hexahydrophthalate, 1,2-Cyclohexanedicarboxylic acid, diethyl ester, cis- (10138-59-7)

4-Cyclohexene-1,2-dicarboxylic acid, diethyl ester, cis- (4841-85-4)

Dimethyl cis-hexahydrophthalate (1687-29-2)

cis-hexahydrophthalic acid (610-09-3)

cis-hexahydrophthalic anhydride

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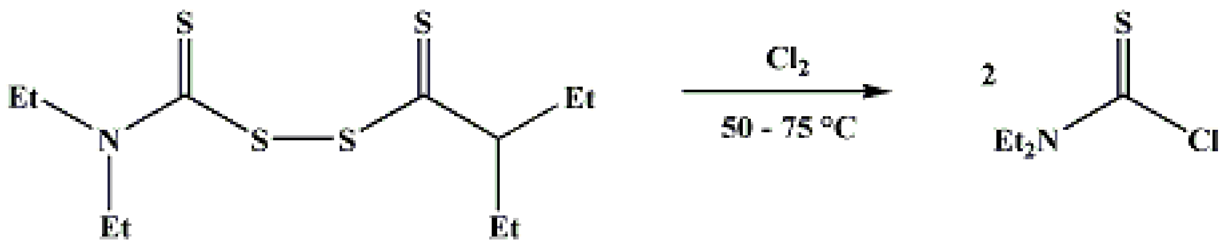
DIETHYLTHIOCARBAMYL CHLORIDE

[Carbamoyl chloride, diethylthio-]



Submitted by R. H. Goshorn, W. W. Levis, Jr., E. Jaul, and E. J. Ritter[1].
Checked by T. L. Cairns and H. E. Cupery.

1. Procedure

A 200-ml. three-necked flask, equipped with a mechanical stirrer arranged to permit escape of gas, a thermometer, and a gas-inlet tube 10 mm. in diameter (Note 1), is placed in a vessel to which cooling water may be added. The entire apparatus is placed in a well-ventilated hood (Note 2). The flask is charged with 74 g. (0.25 mole) of dry (Note 3), molten (70°) tetraethylthiuram disulfide (Note 4). The molten mass is stirred vigorously, and chlorine is passed through a safety trap and is introduced below the surface of the liquid through the inlet tube. The reaction is exothermic, and the temperature is held at 70–75° by adjusting the rate of chlorine addition and by surrounding the reaction flask with cold water. After approximately 6 g. of chlorine has been absorbed, the temperature is lowered to 50–55° and held in this range for the remainder of the chlorination (Note 5). When about 90% of the theoretical amount of chlorine has been added, sulfur begins to precipitate and the reaction mass changes from a clear yellow-to-red solution to a cloudy yellow mixture. The reaction is considered complete when 18 g. (0.25 mole) of chlorine has been absorbed (measured by gain in weight of the reaction mixture). The time required for the chlorination is about 40 minutes.

The crude reaction product at 50° consists of a reddish yellow upper layer of diethylthiocarbamyl chloride saturated with sulfur (Note 6) and a viscous lower layer of amorphous sulfur saturated with diethylthiocarbamyl chloride. The mechanical stirrer is replaced by a 6-in. glass-helix-packed column arranged for distillation. A magnetic stirrer is used throughout the distillation. The diethylthiocarbamyl chloride is distilled under reduced pressure, b.p. 80–85°/1 mm. (Note 7) and (Note 8), m.p. 48–51°. The yield is 71–72 g. (94–95%) (Note 9) and (Note 10).

2. Notes

1. A tube of smaller diameter may be used, but a tube 10 mm. in diameter is

recommended to minimize plugging.

2. The hood serves to carry away unabsorbed chlorine and diethylthiocarbamyl chloride vapors. The fumes are irritating to the eyes, nose, and throat and may have other injurious physiological effects.

3. The quality of the product depends to a large extent upon the purity of the tetraethylthiuram disulfide used. Since the yield is decreased in proportion to the quantity of water present, reagents used should be dry. Dry Sharples Tetraethylthiuram Disulfide No. 163 was found to be satisfactory without further purification.

4. An alternative method is to add chlorine to a solution or suspension of tetraethylthiuram disulfide in an inert liquid medium such as carbon tetrachloride. If the quantity and nature of the solvent are such as to dissolve the diethylthiocarbamyl chloride, most of the liberated sulfur can be separated mechanically and the chloride isolated by distillation after evaporation of the solvent.

5. As the chlorination progresses, the melting point of the reaction mass becomes lower so that after about one-third of the theoretical quantity of chlorine has been added the temperature may be dropped to 50°, which is approximately the melting point of the final product. The low temperature is desirable because there is less danger of overheating at the point of entry of the chlorine.

6. If the crude product is held at 50–55° for 6–8 hours, approximately 70% of the theoretical amount of free sulfur precipitates and may be separated by decantation and filtration. The remaining 30% of the theoretical quantity of sulfur remains in solution in the diethylthiocarbamyl chloride.

7. Good fractionation is not necessary, and a better product can usually be obtained by a rapid distillation than by a slow distillation at a high reflux ratio. A column with a 6- or 8-in. packed section gives a sufficiently pure product for most purposes.

The distillation may be carried out at higher pressures with only slightly more decomposition. At a pressure of 13–14 mm. diethylthiocarbamyl chloride distils at 117–120°. If the pot temperature is above 140° decomposition becomes appreciable, and at 160–190° a vigorous decomposition occurs, especially when a relatively large amount of sulfur is present.

8. The crude diethylthiocarbamyl chloride need not be distilled if sulfur does not interfere in the reaction for which the chloride is to be used and if sulfur can be readily separated from the product. At approximately 105° all the sulfur liberated by the chlorination of tetraethylthiuram disulfide will dissolve in the diethylthiocarbamyl chloride, forming a homogeneous product which may be used on the basis of 100% conversion of the disulfide to the chloride.

9. The submitters used a scale 10 times larger than that given here and obtained yields of 89–94%.

10. The submitters have prepared the following thiocarbamyl chlorides by the chlorination of the corresponding disulfides: dimethylthiocarbamyl chloride, b. p. 90–95° /0.5 mm., m.p. 42.5–43.5°, carbon tetrachloride reaction medium;

diisopropylthiocarbamyl chloride, m.p. 69–71°, benzene reaction medium;
diisobutylthiocarbamyl chloride, m.p. 46–48°, no solvent.

3. Discussion

Billeter prepared diethylthiocarbamyl chloride[2] and other carbamyl chlorides[3,4] by the reaction of the appropriate amine hydrochloride with thiophosgene. Free amines also have been used in this reaction.[5] Diethylthiocarbamyl chloride has been obtained from the reaction of trichloromethanesulfenyl chloride with sodium diethyl dithiocarbamate.[6] The present procedure represents an adaptation of the Ritter process.[7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 824

References and Notes

1. Pennsylvania Salt Manufacturing Company, Wyndmoor, Pennsylvania.
2. Billeter, *Ber.*, **26**, 1681 (1893).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Benzene (71-43-2)

carbon tetrachloride (56-23-5)

sulfur (7704-34-9)

chlorine (7782-50-5)

Thiophosgene (463-71-8)

Diethylthiocarbamyl chloride, Carbamoyl chloride, diethylthio- (88-11-9)

tetraethylthiuram disulfide (97-77-8)

dimethylthiocarbamyl chloride (16420-13-6)

diisopropylthiocarbamyl chloride

diisobutylthiocarbamyl chloride

trichloromethanesulfenyl chloride (594-42-3)

sodium diethyl dithiocarbamate (20624-25-3)

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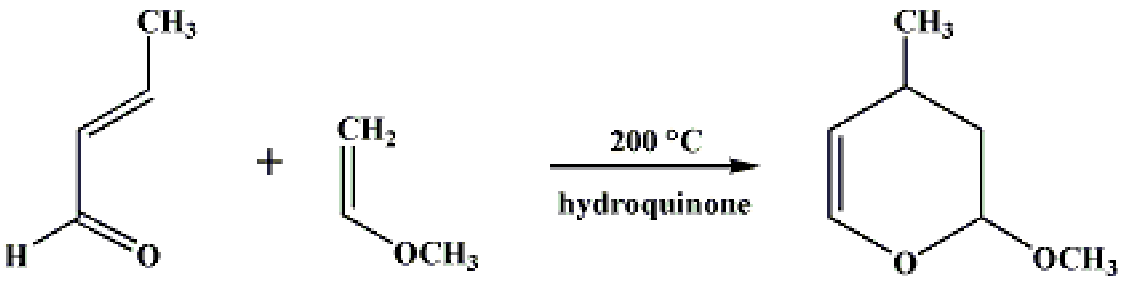
3,4-DIHYDRO-2-METHOXY-4-METHYL-2H-PYRAN

[2H-Pyran, 3,4-dihydro-2-methoxy-4-methyl-]



Submitted by Raymond I. Longley, Jr., William S. Emerson, and Albert J. Blardinelli[1].
Checked by T. L. Cairns and T. E. Young.

1. Procedure

In a high-pressure autoclave, arranged for agitation by shaking or rocking, are placed 286 g. (336 ml., 4.08 moles) of crotonaldehyde, 294 g. (5.06 moles) of methyl vinyl ether, and 1.1 g. of hydroquinone (Note 1) and (Note 2). The autoclave is heated to 200° (Note 3) and held there for 12 hours. The autoclave is cooled and vented, and the black product is distilled through a 1 by 60 cm. helix-packed column. The yield of 3,4-dihydro-2-methoxy-4-methyl-2H-pyran is 270–297 g. (52–57%), b.p. 42–50° /19 mm., n_D^{25} 1.4349–1.4374 (Note 4), (Note 5), and (Note 6).

2. Notes

1. The purer grade of crotonaldehyde supplied by the Eastman Kodak Company was used. Methyl vinyl ether was obtained from the Matheson Chemical Company.
2. The submitters condensed the methyl vinyl ether in the aldehyde cooled to 0° and then charged this mixture to a precooled autoclave. The checkers cooled the autoclave containing the crotonaldehyde to −70°, evacuated, and condensed the required amount of methyl vinyl ether directly into the autoclave.
3. The autoclave should be capable of withstanding a pressure of 3000 p.s.i. This provides a margin of safety, since at 220° the pressure is about 2600 p.s.i.
4. Pure 3,4-dihydro-2-methoxy-4-methyl-2H-pyran boils at 135–138° /760 mm. and at 79–80° /100 mm. and has n_D^{25} 1.4370.
5. The submitters used approximately three times the quantities reported here and obtained yields of 82–83%.
6. Under comparable conditions the submitters found that the corresponding dihydropyran derivatives were similarly obtained by the condensation of acrolein with methyl vinyl ether in 80–81% yield, with ethyl vinyl ether (77–

85% yield), with *n*-butyl vinyl ether (82% yield), with ethyl isopropenyl ether (50% yield), and with *n*-butyl cyclohexenyl ether (40% yield). Other α,β-unsaturated carbonyl compounds that have thus been condensed with ethyl vinyl ether are crotonaldehyde (87% yield), methacrolein (40% yield), α-ethyl-β-*n*-propylacrolein (54% yield), cinnamaldehyde (60% yield), β-furylacrolein (85% yield), methyl vinyl ketone (50% yield), benzalacetone (75% yield), and benzalacetophenone (74% yield).

3. Discussion

3,4-Dihydro-2-methoxy-4-methyl-2H-pyran has been prepared only by the addition of methyl vinyl ether to crotonaldehyde.[2,3,4,5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 660
- Org. Syn. Coll. Vol. 4, 816

References and Notes

1. Monsanto Chemical Company, Dayton 7 Ohio.
2. Longley and Emerson, *J. Am. Chem. Soc.*, **72**, 3079 (1950).
3. Smith, Norton, and Ballard, *J. Am. Chem. Soc.*, **73**, 5267 (1951).
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5. N. V. de Bataafsche Petroleum Maatschappij, Brit. pat. 653,764 [*C. A.*, **47**, 5452 (1953)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Acrolein (107-02-8)

hydroquinone (123-31-9)

Benzalacetophenone (94-41-7)

Benzalacetone (122-57-6)

cinnamaldehyde

crotonaldehyde (123-73-9)

methyl vinyl ketone (78-94-4)

3,4-Dihydro-2-methoxy-4-methyl-2H-pyran, 2H-Pyran, 3,4-dihydro-2-methoxy-4-methyl- (53608-95-0)

methyl vinyl ether (9003-09-2)

ethyl vinyl ether (109-92-2)

ethyl isopropenyl ether (926-66-9)

methacrolein (78-85-3)

β-furylacrolein (623-30-3)

n-butyl vinyl ether (111-34-2)

n-butyl cyclohexenyl ether

α-ethyl-β-n-propylacrolein

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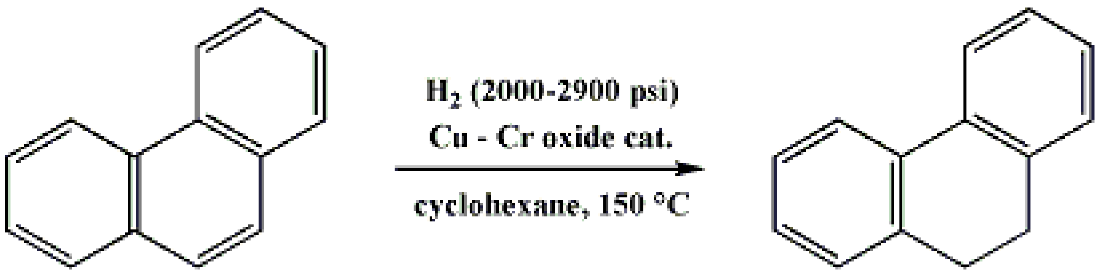
9,10-DIHYDROPHENANTHRENE

[Phenanthrene, 9,10-dihydro-]



Submitted by Donald D. Phillips[1]
Checked by William S. Johnson and David C. Remy.

1. Procedure

A. *Purification of phenanthrene.* 1. By azeotropic distillation.[2] A mixture of 300 g. of commercial phenanthrene (Note 1), 90 g. of maleic anhydride, and 600 ml. of xylene, contained in a 2-l. round-bottomed flask, is heated under reflux for 20 hours (Note 2). The initially yellow solution rapidly turns to a dark brown on heating. This solution is cooled to room temperature and filtered by suction to remove any insoluble adduct. The filtrate is then extracted with two 100-ml. portions of dilute sodium hydroxide, and the basic extracts are discarded. The organic phase is next washed with water and saturated sodium chloride solution, and finally is filtered through a layer of anhydrous magnesium sulfate. The excess xylene is removed by distillation, first at atmospheric pressure; then the final portions are removed at reduced pressure. The residue, while still hot, is poured into a large mortar and, after solidification, is powdered to a convenient size. The yield of crude phenanthrene is 230–240 g.

A solution of 52 g. of the crude phenanthrene in 400 ml. of diethylene glycol (Note 3) is azeotropically distilled through a small column (Note 4). A fore-run of approximately 50 g. is collected at 155–165°/100 mm., followed by the main fraction of 390–400 g., b.p. 140–141°/21 mm. (Note 5). The fore-run contains considerable fluorene and should be discarded. The main fraction is added to five times its volume of water, and the precipitated hydrocarbon is collected by suction filtration and washed well with water to remove the last traces of diethylene glycol. The colorless product (41–43 g.) is heated under reflux for 3 hours with about 450 ml. of 95% ethanol containing approximately 9 g. of Raney nickel catalyst. The hot solution is filtered with slight suction through a sintered-glass funnel. On being concentrated to about 250 ml. and cooled, the filtrate deposits 33–35 g. (63–67%) of colorless phenanthrene, m. p. 97.5–98°.

2. By sodium treatment.[3] Commercial phenanthrene (Note 1) is treated with maleic

anhydride as described above (part 1), and 170 g. of the residue is added to a 1-l. three-necked flask equipped with a Hershberg mercury-sealed Nichrome stirrer,[4] an air condenser, and a thermometer. Ten grams of sodium is added, and the mixture is vigorously stirred at 190–200° for 6 hours. The dark residue is cooled to about 80°, and 300 ml. of benzene is added. The mixture is brought to reflux with stirring and, while still hot, is *cautiously* filtered through a coarse sintered-glass funnel with *gentle* suction (Note 6). The benzene is removed by distillation at atmospheric pressure, and the residual phenanthrene is distilled through a small column (Note 4) adapted to the distillation of solids to give 125–130 g. (74–76%) of colorless phenanthrene, b.p. 183–183.5°/15 mm. This product is heated under reflux for 3 hours with about 1.2 l. of 95% ethanol containing approximately 9 g. of Raney nickel catalyst, and the hot solution is filtered as described under paragraph 1. The filtrate on cooling deposits 115–120 g. (68–71%) of colorless phenanthrene, m.p. 97–98°.

B. *Catalytic reduction.* A hydrogenation bomb of approximately 300 ml. total capacity is charged with 29.5 g. (0.17 mole) of purified phenanthrene (Note 7); then 70 ml. of cyclohexane (Note 8) and 1.5 g. of copper chromium oxide catalyst (Note 9) are added. The bomb is filled with hydrogen to an initial pressure of 2000 p.s.i. at 20° and heated with shaking to 150° (maximum pressure about 2900 p.s.i.). The hydrogenation proceeds rapidly under these conditions, and about 85% of the theoretical uptake is complete within 1.75–2 hours. The reaction is interrupted at this point (Note 10), and the catalyst is removed by centrifugation or filtration. The cyclohexane is evaporated, and the residue is distilled through a small column (Note 4). After a small fore-run (0.2–0.3 g.) distilling below 182°, there is collected 21–23 g.(70–77% yield) of 9,10-dihydrophenanthrene, b.p. 183–184°/25 mm., n_D^{25} 1.6401–1.6416. The residue consists of 4.5–5.0 g. (15–17%) of phenanthrene, m.p. 96.5–98°, which may be recycled.

2. Notes

1. Technical grade phenanthrene (80–90%) is satisfactory for this preparation.
2. An electric heating mantle is convenient for this operation.
3. Technical diethylene glycol may be used with satisfactory results.
4. The submitter used a 65-cm. Podbielniak type column equipped with partial reflux head.[5] For distillation of the sodium-treated phenanthrene the checkers employed a 6-in. Vigreux column. For the fractionation of the dihydrophenanthrene, the checkers employed a 15-cm. spinning-band column obtainable from Nester and Faust, Exton, Pennsylvania.
5. At these concentrations, the azeotrope is solid and adequate heating of the condenser and receivers must be provided by an infrared lamp or similar device. The use of twice this amount of diethylene glycol is reported[2] to give a liquid azeotrope but requires the distillation of proportionately larger amounts, for the azeotrope has nearly the same boiling point as diethylene glycol.
6. The finely divided sodium presents a serious fire hazard, and as much of it as

possible should be retained in the flask. This may be accomplished by careful decantation. The material that is collected on the funnel should always be covered with a layer of solvent and should not be allowed to become dry. The residues may be safely destroyed by placing the funnel and flask in a large pail and adding about 1 l. of isopropyl alcohol. This operation is best conducted out-of-doors.

7. Phenanthrene purified by the sodium treatment was found superior to that from the azeotropic distillation, but both products gave satisfactory results. A good grade of commercially available phenanthrene ("white label" grade supplied by the Eastman Kodak Company), although recrystallized and treated with Raney nickel, resisted hydrogenation under the described conditions.

8. Cyclohexane as supplied by Matheson Company was used without further purification. The use of ethanol as solvent[6] gave inconsistent results, and the yield of 9,10-dihydrophenanthrene never exceeded 50%. Erratic results were also obtained when the solvent was omitted.

9. Copper-chromium oxide (HJS2) was prepared as reported by Adkins and coworkers.[7]

10. If the hydrogenation is allowed to proceed to completion, the product is contaminated with considerable polyhydrogenated material, as indicated by its low refractive index. The optimum time for obtaining about 85% hydrogenation may vary with the purity of the phenanthrene and activity of the catalyst. The purest 9,10-dihydrophenanthrene is obtained when the lower limits of hydrogen uptake are realized, although the yield is correspondingly lower.

3. Discussion

9,10-Dihydrophenanthrene has been prepared from 2,2'-bis(bromomethyl)biphenyl and sodium;[8] from the reduction of 2,2'-diiodobibenzyl in the presence of 1% palladium on barium carbonate catalyst;[9] by the hydrogenation of phenanthrene in the presence of nickel[8] or copper-chromium oxide catalyst;[3,6,10] by the coupling of 2,2'-bis(bromomethyl)biphenyl with lithium phenyl;[11] and by the thermal decomposition of 1,1-(*o*,*o*'-biphenylenebismethylene)-2-*p*-toluenesulfonylhydrazine.[12]

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1. Cornell University, Ithaca, New York.
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium-treated phenanthrene

lithium phenyl

1,1-(o,o'-biphenylenebismethylene)-2-p-toluenesulfonylhydrazine

ethanol (64-17-5)

Benzene (71-43-2)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

cyclohexane (110-82-7)

nickel, Raney nickel (7440-02-0)

sodium (13966-32-0)

isopropyl alcohol (67-63-0)

palladium (7440-05-3)

barium carbonate (513-77-9)

xylene (106-42-3)

magnesium sulfate (7487-88-9)

Copper-Chromium Oxide

fluorene (86-73-7)

phenanthrene (85-01-8)

maleic anhydride (108-31-6)

diethylene glycol (111-46-6)

9,10-Dihydrophenanthrene, Phenanthrene, 9,10-dihydro- (776-35-2)

copper chromium oxide

dihydrophenanthrene

2,2'-bis(bromomethyl)biphenyl

2,2'-diiodobibenzyl

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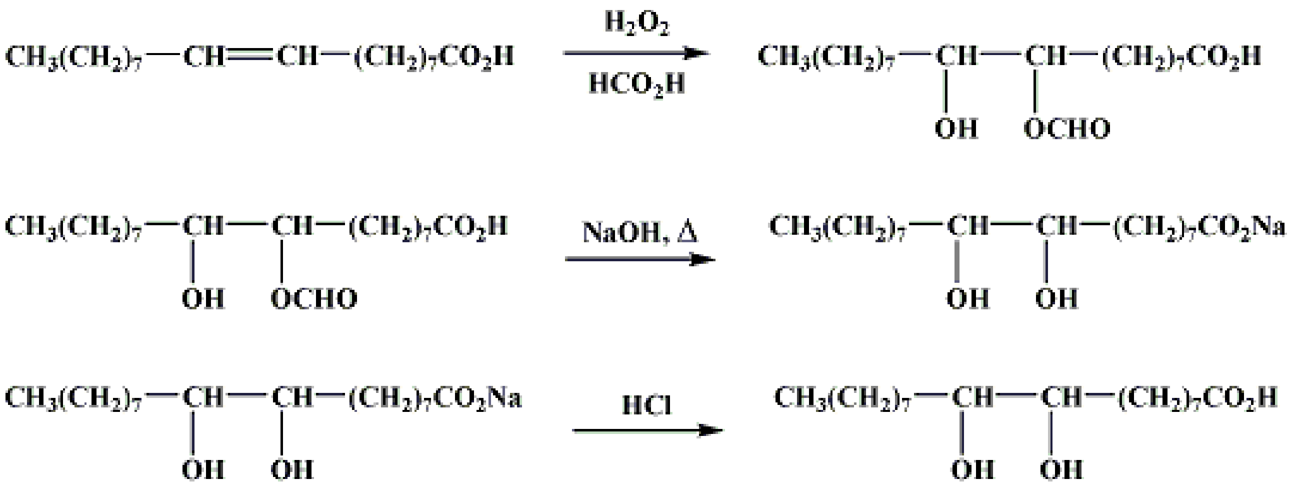
Organic Syntheses, *CV 4, 317*

9,10-DIHYDROXYSTEARIC ACID

[low-melting isomer]

[Octadecanoic acid, 9,10-dihydroxy-]



Submitted by Daniel Swern, John T. Scanlan, and Geraldine B. Dickel[1].
Checked by John D. Roberts and Edgar F. Kiefer.

1. Procedure

To a well-stirred mixture of 141 g. (0.5 mole) of oleic acid (Note 1) and 425 ml. of formic acid (Note 2) in a 1-l. three-necked flask at 25° is added the appropriate amount (Note 3) of 30% (100 volume) hydrogen peroxide (approximately 60 g.) over a 15-minute period (Note 4). The reaction becomes mildly exothermic after a lag of about 5–10 minutes, and homogeneous after about 20–30 minutes. The temperature is maintained at 40° with a cold water bath at the beginning, and with a warm water bath or heating mantle toward the end, of the reaction. After about 3 hours or after analysis has indicated that the peroxide has been consumed (Note 5), the formic acid is removed by distillation under reduced pressure (b.p. 50°/125 mm.) in a stream of gas (carbon dioxide or nitrogen) to prevent bumping (Note 6). The residue in the flask, which consists of hydroxyformoxystearic acids, is heated for 1 hour at 100° with an excess of 3*N* aqueous sodium hydroxide, and the hot, amber-colored soap solution is cautiously poured into an excess of 3*N* hydrochloric acid with stirring. The oil which separates is allowed to solidify, and the aqueous layer is discarded. The tan-colored solid is remelted on the steam bath by addition of hot water and stirred well to remove residual salts and water-soluble acids (Note 7). When the oil has solidified, the aqueous layer is discarded, and the solid is broken into small pieces and dissolved in 400 ml. of 95% ethanol by heating on the steam bath. After crystallization at 0° for several hours, the product is collected on a filter and dried under vacuum. The yield of crude 9,10-dihydroxystearic acid is 75–80 g., m.p. 85–90°. After a second recrystallization from 250 ml. of 95% ethanol, the product weighs about 60–65 g. and melts at about 90–92°. A third recrystallization may be necessary to produce a pure product melting at 94–95°. The over-all yield is 55–60 g. (50–55%, based on the available oleic acid) (Note 8).

2. Notes

1. The checkers used commercial U.S.P. oleic acid, which has an iodine number of about 60–70 and contains 65–75% oleic acid. The submitters report that, if highly purified oleic acid is used, the yield of fairly pure 9,10-dihydroxystearic acid is almost quantitative, but the purification procedure for oleic acid [*Biochem. Preparations*, **2**, 100 (1952)] is more lengthy and inconvenient than the purification of the hydroxylation product. The over-all yield is approximately the same in either case.
2. The formic acid employed is the 98–100% grade. The submitters report that the 90% grade of acid is satisfactory, but the reaction mixture remains heterogeneous throughout. They also state that, instead of formic acid, an equal volume of glacial acetic acid containing 2.5% by weight of concentrated sulfuric acid may be employed. With acetic acid-sulfuric acid, a 6-hour reaction time is required. However, the yield of 9,10-dihydroxystearic acid is slightly lower than the yield obtained when formic acid is employed and the iodine number of the crude reaction product is about 6–9.
3. If commercial oleic acid is used, the iodine number should be determined beforehand and the quantity of hydrogen peroxide adjusted accordingly. The hydrogen peroxide should be assayed immediately before use; "100 volume peroxide" usually contains about 30% hydrogen peroxide by weight. This determination is conveniently carried out by weighing 0.2–0.3 g. of the hydrogen peroxide solution into an Erlenmeyer flask with a ground-glass stopper and adding 20 ml. of a glacial acetic acid-chloroform solution (3:2 by volume). Two milliliters of saturated aqueous potassium iodide solution is added, and the mixture is allowed to stand for 5 minutes. Distilled water (75 ml.) is added and the liberated iodine titrated with 0.1*N* sodium thiosulfate solution to a starch end point. This procedure is also satisfactory for determining the peroxide content of the oxidation mixture, except that 1–2 g. samples are taken [cf. Wheeler, *Oil & Soap*, **9**, 89 (1932)].
4. The submitters state that in one-tenth scale preparations the hydrogen peroxide solution can be added in 1 portion. In larger runs the addition may require 30 minutes to 1 hour.
5. The reaction time ranges from 1.5 to about 4 hours. Progress of the reaction should be followed by determining the peroxide content of the oxidation mixture at half-hour intervals after all the hydrogen peroxide has been added. Approximately all the peroxide should be consumed before distillation is attempted.
6. Instead of removing the formic acid by distillation, the reaction mixture may be poured into a large quantity of water and the oily layer dissolved in ether. The ether solution is washed free of formic acid and then subjected to distillation to remove the ether; hydroxyformoxystearic acids are left as a residue. The submitters found that, in larger-scale operations (five or more times the size of the run described), no ether was required and the oily layer was washed with water until free of formic acid. When acetic acid containing sulfuric acid was employed as the solvent, the reaction mixture was poured into hot water, and the oil which formed was separated mechanically or by extraction with ether.
7. The pH of the wash water should be below 6 in order to be certain that all soap in the product has been converted to free acid. If the pH is above 6, a small quantity of 3*N* hydrochloric acid should be added and the stirring continued for several minutes.
8. The submitters report that the high-melting isomer of 9,10-dihydroxystearic acid can be prepared from elaidic acid [*Biochem. Preparations*, **3**, 118 (1953)] by essentially the procedure described for oleic acid. With elaidic acid, instead of removing the formic acid by distillation, the reaction mixture may be poured into hot water and the oil which forms separated mechanically. The product is not readily soluble in ether. When acetic acid containing sulfuric acid is employed as the solvent, the reaction mixture is poured into *hot* water with thorough mixing, allowed to cool to room temperature, and filtered. The subsequent procedure (saponification and acidification) is the same as that described for the hydroxylation of oleic acid except that the crude dihydroxystearic acid, obtained after

acidification of the soap, cannot be melted with hot water during the washing but is merely stirred well at 95–100° on the steam bath with a large quantity of hot water (Note 7). About 5 ml. of ethanol per gram of solute should be used in the recrystallization. The pure product melts at 130–131°. The yield depends on the purity of the starting material; if highly purified elaidic acid is used, the yield is about 80% after one recrystallization.

3. Discussion

The procedures described have been published.[2] Other procedures, which are not so satisfactory as the ones described, have also been published.[3,4]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

acetic acid-chloroform

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ether (60-29-7)

sodium hydroxide (1310-73-2)

formic acid (64-18-6)

potassium iodide (7681-11-0)

sodium thiosulfate (7772-98-7)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

iodine (7553-56-2)

hydrogen peroxide (7722-84-1)

oleic acid (112-80-1)

dihydroxystearic acid

9,10-Dihydroxystearic acid, Octadecanoic acid, 9,10-dihydroxy- (120-87-6)

acetic acid-sulfuric acid

elaidic acid (112-79-8)

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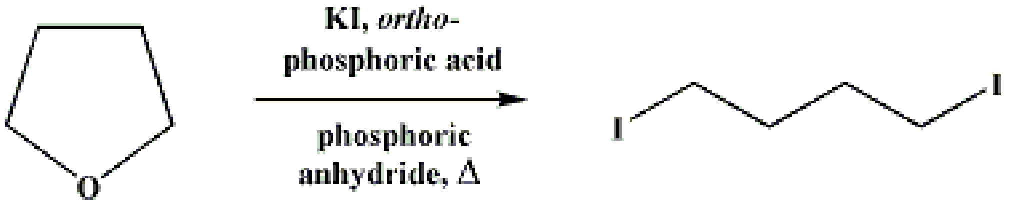
Organic Syntheses, CV 4, 321

1,4-DIIODOBUTANE

[Butane, 1,4-diiodo-]



Submitted by Herman Stone and Harold Shechter[1].
Checked by Cliff S. Hamilton and R. C. Rupert.

1. Procedure

Tetrahydrofuran (36 g., 0.5 mole) (Note 1) is added to a mixture of potassium iodide (332 g., 2 moles), 85% orthophosphoric acid (231 g., 135 ml., 2 moles), and phosphoric anhydride (65 g.) (Note 2), (Note 3), and (Note 4) in a 1-l. three-necked flask equipped with a sealed mechanical stirrer, a reflux condenser, and a thermometer. The mixture is stirred and heated at its reflux temperature for 3 hours, during which time a dense oil separates from the acid layer. The stirred mixture is cooled to room temperature, and 150 ml. of water and 250 ml. of ether are added (Note 5). The ether layer is separated, decolorized with dilute aqueous sodium thiosulfate solution, washed with cold saturated sodium chloride solution, and dried over anhydrous sodium sulfate. The ether is removed by distillation on a steam bath, and the residue is distilled under reduced pressure from a modified Claisen flask. The portion boiling at 108–110°/10 mm. is collected. The yield of colorless 1,4-diiodobutane (n_D^{20} 1.615; d_4^{20} 2.300) (Note 6) is 143–149 g. (92–96%).

2. Notes

1. Tetrahydrofuran was obtained by the submitters from E. I. du Pont de Nemours and Company.
2. The specified mixture of commercial 85% orthophosphoric acid and phosphoric anhydride corresponds to a 95% orthophosphoric acid solution. The phosphoric anhydride is placed in the dry flask, and the 85% orthophosphoric acid is added with stirring. After the mixture has cooled to room temperature, solid potassium iodide is added. The solution should be cooled, before addition of the potassium iodide, to prevent evolution of hydrogen iodide and formation of iodine. After the tetrahydrofuran is added, the mixture can be heated as desired since the hydrogen iodide reacts as rapidly as it is formed.
3. Orthophosphoric acid of 95% concentration is most efficient for effecting cleavage of tetrahydrofuran. Commercial orthophosphoric acid (85%) may be

used; however, the yield drops to 82% and approximately 10% of the tetrahydrofuran is recovered. Anhydrous orthophosphoric acid and tetraphosphoric acid cannot be employed conveniently because of the limited solubility of hydrogen iodide in these reagents.

4. This procedure has been used successfully to convert simple aliphatic ethers into their corresponding iodides. Yields of iodides obtained in the reaction of di-*n*-butyl ether and diisopropyl ether with potassium iodide and 95% orthophosphoric acid were 81 and 90% respectively. Small quantities of the corresponding alcohols were also isolated as products from these reactions.

5. Usually one extraction with ether is sufficient to decolorize the acid layer; if this fails, an additional extraction with 100 ml. of ether is recommended.

6. The checkers obtained values of: n_D^{25} 1.619; d_4^{26} 2.349. The product darkens slowly on standing.

3. Discussion

1,4-Diiodobutane has been prepared in 51% yield by the reaction of phosphorus, iodine, and tetrahydrofuran.[2] It has also been prepared by the reaction of hydriodic acid with phenoxybutyl iodide[3,4] and with the diisoamyl ether of 1,4-butanediol.[5] Sulfuric acid has been used in place of phosphoric acid in the reaction described in the present procedure.[6]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 368

References and Notes

1. Ohio State University, Columbus, Ohio.
2. Heisig, *J. Am. Chem. Soc.*, **61**, 525 (1939).
3. von Braun and Beschke, *Ber.*, **39**, 4357 (1906).
4. Marvel and Tannenbaum, *J. Am. Chem. Soc.*, **44**, 2650 (1922).
5. Hamonet, *Compt. rend.*, **132**, 345 (1901).
6. Bräuniger and Mengering, *Pharmazie*, **14**, 191 (1959) [*C. A.*, **54**, 548 (1960)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

ether (60-29-7)

sodium chloride (7647-14-5)

PHOSPHORUS (7723-14-0)

sodium sulfate (7757-82-6)

potassium iodide (7681-11-0)

sodium thiosulfate (7772-98-7)

iodine (7553-56-2)

orthophosphoric acid (7664-38-2)

hydriodic acid, hydrogen iodide (10034-85-2)

di-n-butyl ether (142-96-1)

Tetrahydrofuran (109-99-9)

diisopropyl ether (108-20-3)

phosphoric anhydride (2466-09-3)

1,4-Diiodobutane, Butane, 1,4-diiodo- (628-21-7)

tetraphosphoric acid

phenoxybutyl iodide

diisoamyl ether of 1,4-butanediol

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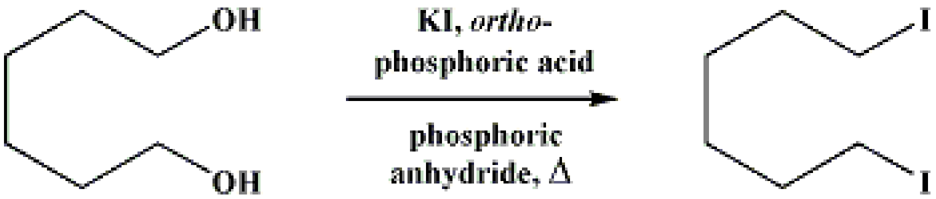
1,6-DIIODOHEXANE

[Hexane, 1,6-diiodo-]



Submitted by Herman Stone and Harold Shechter[1].
Checked by T. L. Cairns, B. C. McKusick, and G. V. Mock.

1. Procedure

In a 1-l. three-necked flask, equipped with a short reflux condenser, a sealed mechanical Hershberg stirrer, and a thermometer, is placed 65 g. (0.46 mole) of phosphoric anhydride, and 231 g. of 85% orthophosphoric acid (135 ml., 2 moles) is added (Note 1). After the stirred mixture has cooled to room temperature, 332 g. (2 moles) of potassium iodide and 59 g. (0.5 mole) of recrystallized 1,6-hexanediol (Note 2), (Note 3), and (Note 4) are added. The mixture is stirred and heated at 100–120° for 3–5 hours, during which time the homogeneous solution separates into two phases, and finally a dense oil settles through the acid layer. The stirred mixture is cooled to room temperature, and 150 ml. of water and 250 ml. of ether are added (Note 5). The ether layer is separated, decolorized by shaking with 50 ml. of 10% sodium thiosulfate solution, washed with 200 ml. of cold saturated sodium chloride solution, and dried with 50 g. of anhydrous sodium sulfate. The ether is removed by distillation on a steam bath, and the product is distilled from a modified Claisen flask under reduced pressure. The fraction boiling at 123–128°/4 mm. is collected. The yield of 1,6-diiodohexane is 140–144 g. (83–85%), n_{D}^{15} 1.585, m.p. 10° (Note 6) and (Note 7).

2. Notes

1. The specified mixture of commercial 85% orthophosphoric acid and phosphoric anhydride corresponds to 95% orthophosphoric acid. Ninety-five per cent orthophosphoric acid is recommended for this reaction. If 85% orthophosphoric acid is used, the reaction proceeds more slowly and the yield is reduced.

2. 1,6-Hexanediol,[2] m.p. 40–41°, was prepared by catalytic reduction of diethyl adipate with hydrogen over copper chromite catalyst. It can also be purchased from Columbia Organic Chemicals Company, Inc.

3. The solution must be cool before the potassium iodide is added to avoid the evolution of hydrogen iodide and formation of iodine. After the 1,6-hexanediol

has been added, the mixture can be heated as desired since the hydrogen iodide reacts as rapidly as it is formed.
4. This procedure has been used successfully for conversion of various aliphatic and alicyclic alcohols to the corresponding iodides. Yields of iodides from 1-propanol, 2-methyl-1-propanol, 2-methyl-2-propanol, and cyclohexanol were 95, 88, 90, and 79.5%, respectively.
5. Usually one extraction of the reaction product with ether is sufficient to remove the color from the acid layer.
6. Slightly yellow 1,6-diiodohexane crystallizes as white needles when cooled in an ice-water mixture. The addition of a few drops of mercury to the yellow product produces a nearly colorless liquid.
7. The submitters reported yields of 93–95% and a melting point of 8.5–9.0°.

3. Discussion

1,6-Diiodohexane has been prepared in 73% yield by the reaction of 1,6-hexanediol, red phosphorus, and iodine.[3] It has also been prepared by reactions of hydrogen iodide and 1,6-diphenoxyhexane[4] and 1,6-diethoxyhexane,[5] respectively. Physical constants have been reported by Dionneau.[6] The method described here has been published.[7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 368

References and Notes

1. Ohio State University, Columbus, Ohio.
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3. Müller and Rölz, *Ber.*, **61**, 571 (1928).
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5. Farmer, Laroia, Switz, and Thorpe, *J. Chem. Soc.*, **1927**, 2951.
6. Dionneau, *Ann. chim.*, [9] **3**, 257 (1915).
7. Stone and Shechter, *J. Org. Chem.*, **15**, 491 (1950).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

red phosphorus

ether (60-29-7)

hydrogen (1333-74-0)

Cyclohexanol (108-93-0)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

potassium iodide (7681-11-0)

sodium thiosulfate (7772-98-7)

mercury (7439-97-6)

iodine (7553-56-2)

orthophosphoric acid (7664-38-2)

1-propanol (71-23-8)

hydrogen iodide (10034-85-2)

2-methyl-1-propanol (78-83-1)

COPPER CHROMITE

1,6-Hexanediol (629-11-8)

diethyl adipate (141-28-6)

1,6-Diiodohexane, Hexane, 1,6-diiodo- (629-09-4)

phosphoric anhydride (2466-09-3)

2-methyl-2-propanol (75-65-0)

1,6-diphenoxyhexane (10125-18-5)

1,6-diethoxyhexane

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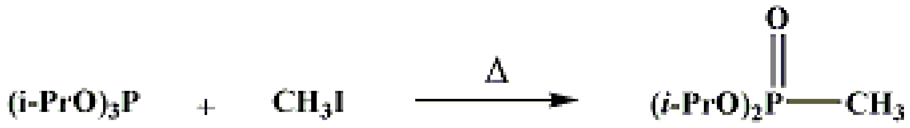
Organic Syntheses, CV 4, 325

DIISOPROPYL METHYLPHOSPHONATE

[Phosphonic acid, methyl-, diisopropyl ester]



Submitted by A. H. Ford-Moore and B. J. Perry[1].
Checked by William S. Johnson and James Ackerman.

1. Procedure

A 2-l. round-bottomed flask containing 284 g. (113 ml., 2 moles) of methyl iodide[2] is fitted with an efficient water-cooled condenser and a dropping funnel which is charged with 416 g. (453 ml., 2 moles) of triisopropyl phosphite (Note 1). A few pieces of porous plate are added to the methyl iodide, and about 50 ml. of the phosphite is introduced. The mixture is heated over a gauze with a free flame until an exothermic reaction begins. The flame is then withdrawn and the remainder of the phosphite is added at such a rate that the mixture keeps boiling briskly. Towards the end of the addition it may be necessary to reapply heat. After the addition is complete, the mixture is boiled under reflux for 1 hour. The condenser is replaced by a 50–75 cm. Vigreux column attached to a condenser set for distillation, and the bulk of the isopropyl iodide is distilled at 85–95° (atmospheric pressure). The residue is transferred to a pear-shaped flask for distillation through a 75-cm. Vigreux column under reduced pressure. The remainder of the isopropyl iodide is distilled at water-pump pressure, a Dry Ice trap being interposed between the receiver and the pump in order to effect complete condensation. A total of 310 g. (91%) of isopropyl iodide is thus recovered. The residue is then fractionated at vacuum-pump pressure. Except for a small fore-run and residue, the product distils almost entirely at 51°/1.0 mm. (46°/0.8 mm.). The yield of colorless product is 308–325 g. (85–90%); n_D^{20} 1.4101, n_D^{25} 1.4081; d_4^{24} 0.985, d_4^{10} 0.997 (Note 2).

2. Notes

1. The triisopropyl phosphite is prepared according to the procedure for triethyl phosphite (p. 955) and should be free from any diisopropyl hydrogen phosphite. The latter substance does not enter into the reaction but is difficult to remove from the final product. The starting material was supplied to the submitters by Messrs. Albright, Wilson and Company, Oldbury, Birmingham, England.
2. Diisopropyl ethylphosphonate can be obtained by a similar procedure, using the appropriate amount of ethyl iodide in place of methyl iodide. Ethyl iodide is less reactive, and it is necessary to apply heat during the addition of the phosphite and to allow the mixture to reflux for 7 hours after the addition. On a

2*M* scale the yield is 354 g. (91%), b.p. 61°/0.7 mm., n_D^{25} 1.4108, d_4^{25} 0.968. The recovery of isopropyl iodide is 317 g. (93%).

Diethyl ethylphosphonate may be obtained by refluxing 332 g. (348 ml., 2 moles) of triethyl phosphite and 250 g. (1.6 moles) of ethyl iodide, for 3 hours. After distillation of 231 g. (92%) of ethyl iodide, the residue is fractionated under reduced pressure, giving 329 g. (98.5%) of product, b.p. 56°/1 mm. (58.5°/1.8 mm.); n_D^{25} 1.4141, n_D^{20} 1.4161; d_4^{25} 1.022.

Diethyl methylphosphonate may be prepared similarly by refluxing one molar equivalent of triethyl phosphite with one mole of methyl iodide, but it is very difficult to separate the product from the small amount of diethyl ethylphosphonate that is formed simultaneously by the interaction of the phosphite with the ethyl iodide liberated in the reaction. The pure substance boils at 51°/1 mm., n_D^{25} 1.4117, d_4^{25} 1.050.

3. Discussion

Diisopropyl methylphosphonate has been prepared from diisopropylethyl phosphite and methyl iodide,[3] and by treating sodium diisopropylphosphonate with methyl chloride.[4] The method described here for the preparation of diisopropyl methylphosphonate is a modification of the Arbusov rearrangement.[5]

References and Notes

1. Chemical Defence Experimental Station, Porton, Nr. Salisbury, Wilts, England.
2. *Org. Syntheses Coll. Vol.* **2**, 404 (1943).
3. Landauer and Rydon, *J. Chem. Soc.*, **1953**, 2224.
4. Smith, U. S. pats. 2,853,507 [*C. A.*, **53**, 7989 (1959)], 2,880,224 [*C. A.*, **53**, 15978 (1959)].
5. Arbusov, *Chem. Zentr.*, [II] **77**, 1640 (1906); Ford-Moore and Williams, *J. Chem. Soc.*, **1947**, 1465.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

methyl chloride (74-87-3)

Methyl iodide (74-88-4)

Ethyl iodide (75-03-6)

isopropyl iodide (75-30-9)

Diisopropyl methylphosphonate, Phosphonic acid, methyl-, diisopropyl ester (1445-75-6)

triisopropyl phosphite (116-17-6)

phosphite

Triethyl phosphite (122-52-1)

diisopropyl hydrogen phosphite

Diisopropyl ethylphosphonate (1067-69-2)

Diethyl ethylphosphonate (78-38-6)

Diethyl methylphosphonate (683-08-9)

diisopropylethyl phosphite

sodium diisopropylphosphonate

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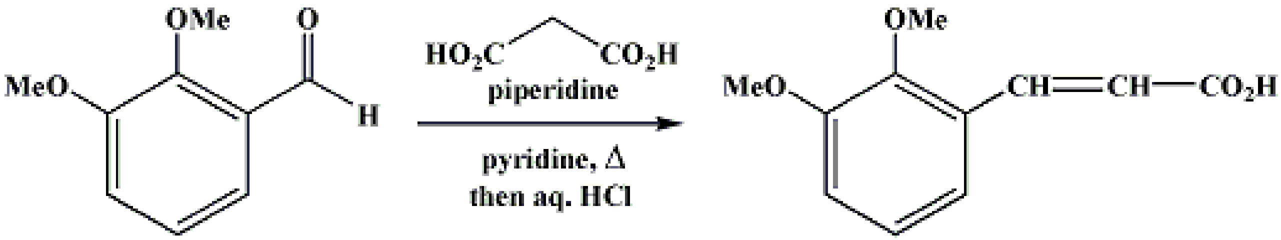
Organic Syntheses, CV 4, 327

2,3-DIMETHOXYCINNAMIC ACID

[Cinnamic acid, 2,3-dimethoxy-]



Submitted by J. Koo, M. S. Fish, G. N. Walker, and J. Blake[1].
Checked by T. L. Cairns and A. E. Barkdoll.

1. Procedure

In a 3-l. round-bottomed flask (Note 1), fitted with a reflux condenser and a thermometer, are placed 208 g. (2 moles) of malonic acid (Note 2) 166 g. (1 mole) of 2,3-dimethoxybenzaldehyde (Note 3), and 400 ml. of pyridine. The malonic acid is dissolved by shaking and warming on a steam bath (Note 4). Piperidine (15 ml.) is then added, the reflux condenser and thermometer are fitted into place (Note 5), and the mixture is heated to 80°. About 30 minutes should be allowed for this rise in temperature. An internal temperature of 80–85° is maintained for 1 hour, and the material is finally heated under reflux (109–115°) for an additional 3 hours (Note 6).

After being cooled the reaction mixture is poured into a large beaker containing 4 l. of cold water. The mixture is acidified by slowly adding with stirring 500 ml. of concentrated hydrochloric acid; it should be strongly acidic at this point. The light-brown crystals are separated by suction filtration and washed 4 times with 150-ml. portions of cold water. The crude acid is dissolved in a solution of 80 g. of sodium hydroxide in 3 l. of water. The resulting is filtered, diluted with an additional 1.2 l. of water, and acidified by adding with stirring 600 ml. of 1:1 hydrochloric acid. The mixture is filtered, and the crystalline material is washed with three 150-ml. portions of cold water. The product is dried at 60–70° (Note 7). The yield is 180–205 g. (87–98%), m.p. 174–178° (Note 8). Further purification is usually not necessary, but it may be accomplished by recrystallization from methyl ethyl ketone, using 12 ml. of solvent per gram of acid. The hot solution is filtered rapidly through a steam-heated Büchner funnel and chilled for several hours. A recovery of 70% of product, m.p. 179–180°, may be obtained.

2. Notes

1. A large flask is preferred to ensure against possible loss by foaming.
2. An excess of malonic acid is necessary for high yields. An equimolecular amount of malonic acid results in yields as low as 50%.
3. A practical grade of 2,3-dimethoxybenzaldehyde gives satisfactory results. It is convenient to weigh and transfer this material as a liquid.
4. If the malonic acid is not in solution before addition of the piperidine, the reaction cannot be controlled properly. It is advisable to heat the mixture to 50° to effect solution.
5. The thermometer may be suspended in the mixture through the condenser by means of a long wire.

6. Evolution of carbon dioxide begins at about 55–60°. The prescribed temperatures are necessary to prevent undue foaming.
7. The product should be dried to constant weight in an oven. Drying for several days is usually required.
8. This method is a general one. It can be used with a variety of substituted aromatic aldehydes.

3. Discussion

2,3-Dimethoxycinnamic acid has been prepared by heating 2,3-dimethoxybenzaldehyde with acetic anhydride and sodium acetate at 200°[2] and by the condensation of 2,3-dimethoxybenzaldehyde and ethyl acetate with sodium, followed by hydrolysis.[3] The present preparation represents an adaption of the Doebner reaction.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 731

References and Notes

1. University of Pennsylvania, Philadelphia, Pennsylvania.
2. von Krannichfeldt, *Ber.*, **46**, 4021 (1913).
3. Perkin and Robinson, *J. Chem. Soc.*, **105**, 2387 (1914).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

acetic anhydride (108-24-7)

sodium acetate (127-09-3)

sodium hydroxide (1310-73-2)

carbon dioxide (124-38-9)

pyridine (110-86-1)

sodium (13966-32-0)

piperidine (110-89-4)

Malonic acid (141-82-2)

methyl ethyl ketone (78-93-3)

2,3-Dimethoxycinnamic acid, Cinnamic acid, 2,3-dimethoxy- (7461-60-1)

2,3-dimethoxybenzaldehyde (86-51-1)

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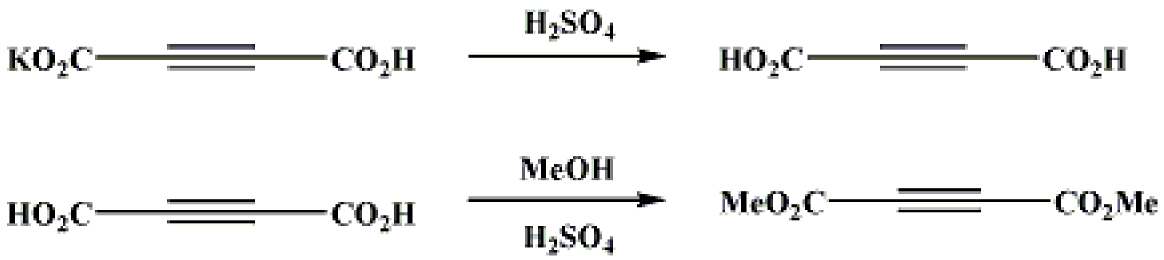
Organic Syntheses, CV 4, 329

DIMETHYL ACETYLENEDICARBOXYLATE

[Acetylenedicarboxylic acid, dimethyl ester]



Submitted by E. H. Huntress, T. E. Lesslie, and J. Bornstein[1].
Checked by T. L. Cairns and M. J. Hogsed.

1. Procedure

To 400 g. (510 ml., 12.5 moles) of methanol (commercial grade) in a 2-l. round-bottomed flask is added in small portions with cooling 200 g. (111 ml., 2.04 moles) of concentrated sulfuric acid. To this cooled solution is added 100 g. (0.66 mole) of the potassium acid salt of acetylenedicarboxylic acid (Note 1). The flask is fitted with a stopper holding a calcium chloride drying tube and allowed to stand with occasional swirling for 4 days at room temperature.

The liquid in the flask is then decanted from the inorganic salt, which is washed with 500 ml. of cold water. The solutions are combined and extracted with five 500-ml. portions of ether. The ether extracts are combined and washed successively with 200 ml. of cold water, 150 ml. of saturated sodium bicarbonate solution (Note 2), and 200 ml. of cold water and then dried over anhydrous calcium chloride. After removal of the ether by distillation from a steam bath, the ester is distilled under reduced pressure from a modified Claisen flask. The yield of ester boiling at 95–98°/19 mm. is 67–82 g. (72–88%) (Note 3) and (Note 4); n_D^{25} 1.4444–1.4452.

2. Notes

1. The potassium acid salt of acetylenedicarboxylic acid is commercially obtainable from the National Aniline Division, Allied Chemical and Dye Corporation, New York, New York. Directions for the preparation of the free acid are given in earlier volumes.[2,3]
2. If the ether extract is not washed with sodium bicarbonate solution, considerable loss occurs during the distillation of the ester because of decomposition in the flask.
3. Dimethyl acetylenedicarboxylate is a powerful lachrymator and vesicant; it should be handled with extreme care. Even traces of ester on the skin should be washed off at once with 95% ethanol followed by washing with soap and water.

4. The same general method has been used by the submitters to prepare diethyl acetylenedicarboxylate. In this case absolute ethanol was used, and the ether extract was dried over anhydrous magnesium sulfate. The yield of diethyl ester from 100 g. of the acid potassium salt of acetylenedicarboxylic acid was 57–59 g. (51–53%); b.p. 96–98°/8 mm.; n_D^{25} 1.4397.

3. Discussion

Dimethyl acetylenedicarboxylate has been prepared by refluxing the acid potassium salt of acetylenedicarboxylic acid with methanol and sulfuric acid.[4,5] The method described here is a substantial improvement over the method of Moureu and Bongrand,[6] who prepared it from acetylenedicarboxylic acid, absolute methanol, and sulfuric acid.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 444
- Org. Syn. Coll. Vol. 5, 985
- Org. Syn. Coll. Vol. 6, 196
- Org. Syn. Coll. Vol. 8, 298

References and Notes

1. Massachusetts Institute of Technology, Cambridge, Massachusetts.
2. *Org. Syntheses Coll. Vol.* **2**, 10 (1943).
3. *Org. Syntheses*, **18**, 3 (1938).
4. Baudrowski, *Ber.*, **15**, 2694 (1882).
5. Curtius and Heynemann, *J. prakt. Chem.*, [2] **91**, 66 (1915).
6. Moureu and Bongrand, *Ann. chim.*, [9] **14**, 11 (1920).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

potassium acid salt of acetylenedicarboxylic acid

acid potassium salt of acetylenedicarboxylic acid

ethanol (64-17-5)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

methanol (67-56-1)

ether (60-29-7)

sodium bicarbonate (144-55-8)

Acetylenedicarboxylic acid (142-45-0)

magnesium sulfate (7487-88-9)

Dimethyl acetylenedicarboxylate, Acetylenedicarboxylic acid, dimethyl ester (762-42-5)

diethyl acetylenedicarboxylate (762-21-0)

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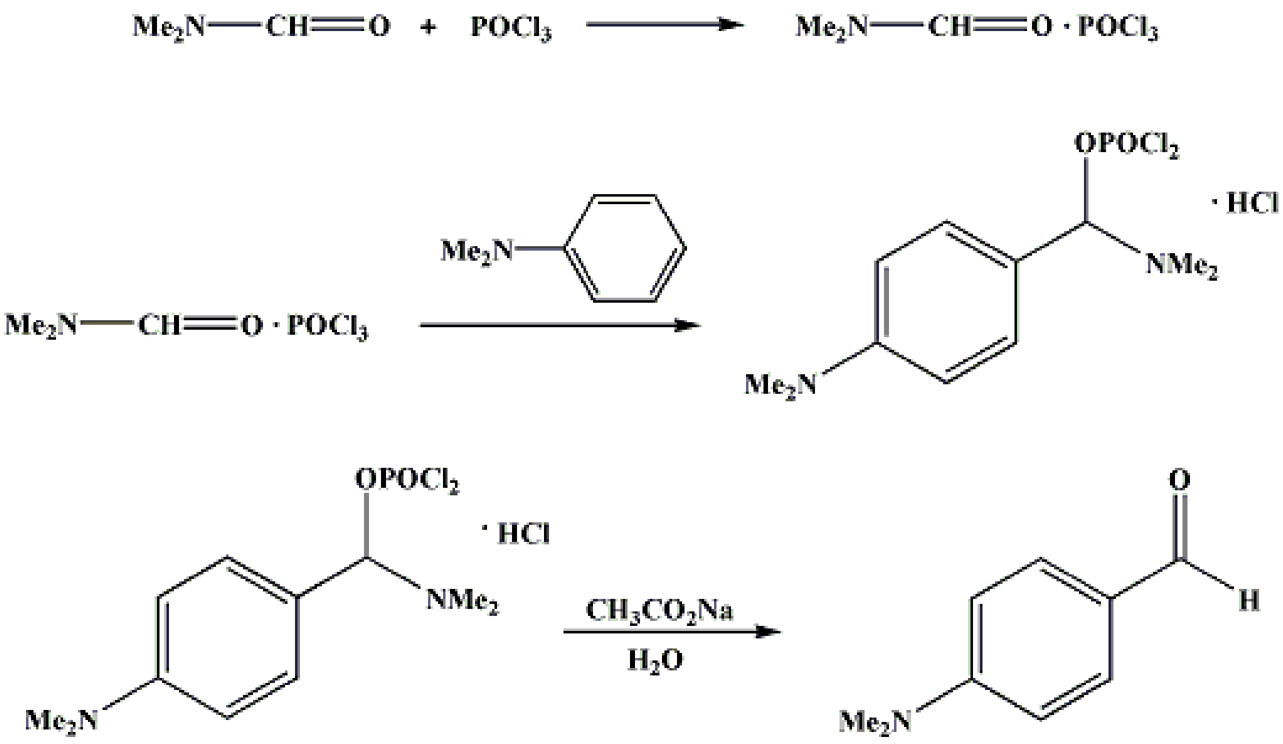
Organic Syntheses, CV 4, 331

p-DIMETHYLAMINOBENZALDEHYDE

[Benzaldehyde, *p*-dimethylamino-]



Submitted by E. Campaigne and W. L. Archer[1].
Checked by N. J. Leonard and R. W. Fulmer.

1. Procedure

In a 2-l. three-necked round-bottomed flask, equipped with a sealed stirrer, dropping funnel, and a reflux condenser topped by a calcium chloride tube, is placed 440 g. (6 moles) of dimethylformamide (Note 1). While the flask is carefully cooled in an ice bath, 253 g. (1.65 moles) of phosphorus oxychloride is added dropwise with stirring. An exothermic reaction occurs with the formation of the phosphorus oxychloride-dimethylformamide complex. When all the phosphorus oxychloride has been added, and the heat of the reaction has subsided, 200 g. (1.65 moles) of dimethylaniline (Note 2) is added dropwise with stirring. When the addition of the dimethylaniline is complete, a yellow-green precipitate begins to form. The reaction mixture is heated on a steam bath, and stirring is continued for 2 hours. The yellow-green precipitate redissolves when heating is begun. The mixture is then cooled and poured over 1.5 kg. of crushed ice in a 5-l. beaker. Any precipitate that remains in the flask may be washed into the ice mixture with cold water. The solution is neutralized to pH 6–8 (Universal Test Paper) by the dropwise addition of approximately 1.5 l. of saturated aqueous sodium acetate with vigorous stirring (Note 3). *p*-Dimethylaminobenzaldehyde begins to precipitate soon after the addition of the sodium acetate is begun. The neutral mixture (total volume about 4.5 l.) is stored in the refrigerator overnight (Note 4). The greenish-tinted crystalline precipitate is filtered by suction, with the aid of a rubber dam, and washed several times with water on the filter. The green color is readily removed during the washing. The very light-yellow to nearly colorless product, after air-drying, weighs 198–208 g. (80–84%) and melts at 73–74°. It is essentially pure and useful

for most purposes as obtained (Note 5).

2. Notes

1. The dimethylformamide is available as technical grade DMF from the Grasselli Chemicals Department of E. I. du Pont de Nemours and Company. Dimethylformamide can be prepared by the method of Mitchell and Reid[2] from dimethylamine and formic acid.
2. Dimethylaniline free from monomethylaniline (Eastman Kodak Company) is used.
3. It is possible to neutralize the acid solution partially with sodium hydroxide before the sodium acetate is added, but it is more difficult to avoid localized heating by this method. It is important to keep the reaction mixture below 20° during the neutralization, by the addition of ice if necessary, since any excessive increase in temperature of the aqueous solution leads to the formation of greenish blue dyestuffs, which are very difficult to remove from the product.
4. The mixture may turn orange-colored when allowed to stand overnight.
5. If a purer product is desired, the aldehyde may be purified by the method described by Adams and Coleman.[3]

3. Discussion

p-Dimethylaminobenzaldehyde has been prepared from dimethylaniline, formaldehyde, and *p*-nitrosodimethylaniline in 56–59% yield,[3] by the formylation of dimethylaniline with N-methylformanilide in approximately 50% yield,[4] by the formylation of dimethylaniline with dimethylformamide,[5] and by the condensation of methyl formate with *p*-dimethylaminophenylmagnesium chloride in tetrahydrofuran.[6]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 539
- Org. Syn. Coll. Vol. 4, 831

References and Notes

1. Indiana University, Bloomington, Indiana.
2. Mitchell and Reid, *J. Am. Chem. Soc.*, **53**, 1879 (1931).
3. *Org. Syntheses Coll. Vol.* **1**, 214 (1941).
4. Vilsmeier and Haack, *Ber.*, **60**, 119 (1927).
5. Brit. pat. 607,920 [*C. A.*, **43**, 2232 (1949)].
6. Ramsden (to Metal & Thermit Corp.), Brit. pat. 806,710 [*C. A.*, **54**, 2264 (1960)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

phosphorus oxychloride-dimethylformamide complex

sodium acetate (127-09-3)

sodium hydroxide (1310-73-2)

formaldehyde (630-08-0)

formic acid (64-18-6)

Phosphorus Oxychloride (21295-50-1)

dimethylaniline (121-69-7)

methyl formate (107-31-3)

dimethylamine (124-40-3)

monomethylaniline (100-61-8)

Tetrahydrofuran (109-99-9)

N-methylformanilide (93-61-8)

dimethylformamide (68-12-2)

p-Dimethylaminobenzaldehyde, Benzaldehyde, p-dimethylamino- (100-10-7)

p-nitrosodimethylaniline (138-89-6)

p-dimethylaminophenylmagnesium chloride

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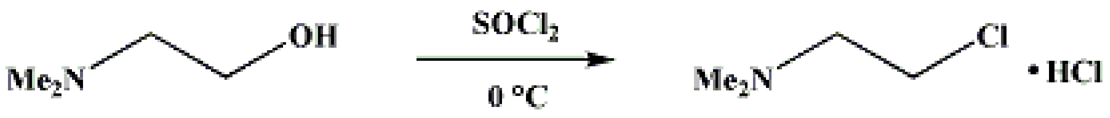
Organic Syntheses, CV 4, 333

β-DIMETHYLAMINOETHYL CHLORIDE HYDROCHLORIDE

[Ethylamine, 2-chloro-N,N-dimethyl-, hydrochloride]



Submitted by Luther A. R. Hall, Verlin C. Stephens, and J. H. Burckhalter[1].
Checked by Richard T. Arnold and William Lee.

1. Procedure

Caution! This preparation should be conducted in a good hood.

In a dry 1-l. flask fitted with a sealed mechanical stirrer, an efficient reflux condenser, and a 500-ml. dropping funnel is placed 290 g. (2.44 moles) of thionyl chloride (Note 1). The reaction flask must be cooled in an ice bath throughout the entire period of operation, as the reaction is very exothermic. β-Dimethylaminoethanol (210 g., 2.35 moles) (Note 2) is added dropwise through the funnel to the cooled thionyl chloride (Note 3) over a period of an hour, during which time there is a copious evolution of sulfur dioxide (Note 4). After all the β-dimethylaminoethanol has been added, the ice bath is removed and the reaction mixture is stirred for another hour (Note 5). The temperature of the mixture is 35–50°. At this point the reaction mixture consists of a brown semisolid slush of the desired product together with a slight excess of thionyl chloride.

The entire contents of the reaction flask are transferred to a 2-l. beaker (or wide-mouthed Erlenmeyer flask) containing approximately 1 l. of absolute ethanol (Note 6). The resulting brown solution is heated to boiling on a hot plate, during which time there is a copious evolution of gases (Note 6). The solution is filtered hot, leaving a small amount of insoluble material. Upon cooling of the filtrate in a salt-ice bath, the desired product is obtained as beautiful white crystals which are collected on a Büchner funnel and dried in a vacuum desiccator over phosphorus pentoxide (Note 7). The yield of pure product melting at 201.5–203° is 227–272 g. (67–80%).

Upon evaporation of the last filtrate to one-third of its volume and cooling in a salt-ice bath, an additional 33–69 g. (10–20%) of good-quality product is obtained. The total yield is 296–305 g. (87–90%).

2. Notes

1. Eastman Kodak Company practical grade thionyl chloride is satisfactory.
2. A good commercial grade (Eastman Kodak Company or Union Carbide and Carbon Corporation) of β-dimethylaminoethanol is satisfactory.
3. Continued and efficient cooling of the reaction vessel is needed to prevent too vigorous an evolution of sulfur dioxide and a subsequent loss of thionyl chloride through trapping of this reagent by effluent gases. Cooling also prevents too high a reaction temperature. The reaction proceeds more smoothly if the temperature is kept below 50°.
4. Care should be taken that the dropping funnel inlet does not become clogged with solid product. If the tip of the dropping funnel is in such a position that the drops of β-dimethylaminoethanol fall directly into the thionyl chloride and do not drain down the walls of the flask, mechanical difficulties are reduced markedly. The reaction must be carried out in an efficient hood or with a suitable trap in order to remove the noxious sulfur dioxide formed.
5. The reaction mixture may be stirred for a longer time and allowed to stand overnight without affecting the yield.
6. The ethanol not only converts the excess thionyl chloride to gaseous by-products (sulfur dioxide, hydrogen chloride, and ethyl chloride) but also serves as the recrystallizing solvent for the desired product. The checkers found that about 80% of this thick product can be poured directly into 800 ml. of ethanol. Two hundred milliliters of warm ethanol should be used to decompose the product remaining in the reaction flask. This is combined with the main portion.
7. The product is somewhat hygroscopic, especially in humid weather. It should be dried in a vacuum desiccator to prevent the formation of hydrated forms.

3. Discussion

β-Dialkylaminoethyl bromide hydrobromides have been known for many years. However, the standard method of preparation requires large volumes of hydrobromic acid.[2] The less expensive analogous chlorides are preferred since their preparation is simpler and their reactivity is sufficient for the synthesis of well-known drugs.[3] Ordinarily β-dialkylaminoalkyl chloride hydrochlorides are prepared in good yield by treatment of β-dialkylaminoalkanols with an excess of thionyl chloride in chloroform or benzene.[4] An article on the German commercial preparation of Atabrine refers to the action of thionyl chloride on β-diethylaminoethanol hydrochloride without solvent.[5] The present method has been published.[6]

References and Notes

1. University of Kansas, Lawrence, Kansas.
2. *Org. Syntheses Coll. Vol.* **2**, 92 (1943).
3. Huttrer et al., *J. Am. Chem. Soc.*, **68**, 1999 (1946).
4. Burger, *J. Am. Pharm. Assoc., Sci. Ed.*, **36**, 372 (1947); Tchoubar and Letellier-Dupré, *Bull. soc. chim. France*, **1947**, 792; Elderfield et al., *J. Am. Chem. Soc.*, **68**, 1579

(1946); Marechal and Bagot, *Ann. pharm. franç.*, **4**, 172 (1946); Giral and Cascajares, *Ciencia (Mex.)*, **5**, 105 (1944) [*C. A.*, **41**, 4892 (1947)]; Ward, U. S. pat. 2,072,348 [*C. A.*, **31**, 2614 (1937)]; Mannich and Baumgarten, *Ber.*, **70**, 210 (1937); Brit. pat. 456,338 [*C. A.*, **31**, 2230 (1937)]; French pat. 802,416 [*C. A.*, **31**, 1824 (1937)]; Slotta and Behnisch, *Ber.*, **68**, 754 (1935); Gough and King, *J. Chem. Soc.*, **1928**, 2436; Meister, Lucius, and Brüning, Brit. pat. 167,781 [*Brit. Abstracts*, **122**, 529 (1922)].

5. Greene, *Am. J. Pharm.*, **120**, 39 (1948).
6. Burckhalter, Stephens, and Hall, *J. Am. Pharm. Assoc.*, **39**, 271 (1950).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

hydrogen chloride (7647-01-0)

Benzene (71-43-2)

thionyl chloride (7719-09-7)

chloroform (67-66-3)

HYDROBROMIC ACID (10035-10-6)

sulfur dioxide (7446-09-5)

ethyl chloride (75-00-3)

β-Dimethylaminoethyl chloride hydrochloride, Ethylamine, 2-chloro-N,N-dimethyl-, hydrochloride (4584-46-7)

β-dimethylaminoethanol (108-01-0)

β-diethylaminoethanol hydrochloride (4620-71-7)

phosphorus pentoxide (1314-56-3)

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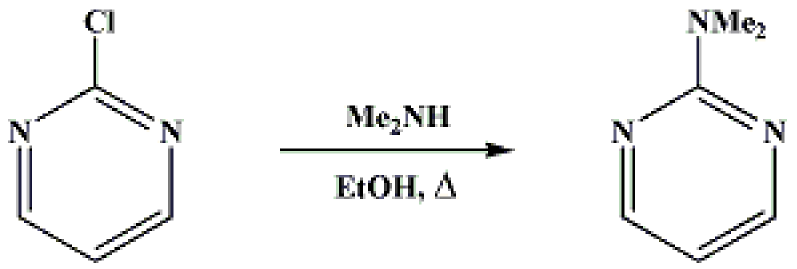
Organic Syntheses, CV 4, 336

2-(DIMETHYLAMINO)PYRIMIDINE

[Pyrimidine,2-dimethylamino-]



Submitted by C. G. Overberger, Irving C. Kogon, and Ronald Minin[1].
Checked by Charles C. Price and T. L. V. Ulbricht.

1. Procedure

In a 250-ml. three-necked flask equipped with a reflux condenser and a gas-inlet tube are placed 45.6 g. (0.4 mole) of 2-chloropyrimidine (p. 182) and 150 ml. of absolute ethanol. The mixture is refluxed for 6 hours while anhydrous dimethylamine is bubbled into the solution (Note 1). The solution is cooled, and 100 ml. of ethanol is removed by distillation using a water aspirator. The residue is chilled in an ice bath for 1 hour, and 75 ml. of ether is added to cause precipitation of dimethylamine hydrochloride. After the removal of dimethylamine hydrochloride and solvent, the residue is distilled at reduced pressure from a Claisen flask (Note 2). The fraction boiling at 85–86°/28 mm. is collected; yield 40–42.5 g. (81–86%), n_D^{25} 1.5420 (Note 3).

2. Notes

1. Anhydrous dimethylamine may be conveniently prepared by allowing 25% aqueous dimethylamine to drop onto solid potassium hydroxide, the gas evolved being dried by passage over solid potassium hydroxide.
2. The compound is hygroscopic, and care should be taken to prevent exposure to air.
3. N-Methylaminopyrimidine is similarly prepared; b.p. 96–98°/28 mm., m.p. 57.5–58.5° (65% yield).

3. Discussion

Similar procedures for this preparation have been reported by Brown and Short[2] and by Copenhaver and Kleinschmidt.[3]

References and Notes

1. Polytechnic Institute of Brooklyn, Brooklyn 2, New York.
2. Brown and Short, *J. Chem. Soc.*, **1953**, 331.
3. Copenhaver and Kleinschmidt, Brit. pat. 663,303 [*C. A.*, **46**, 10212 (1952)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

ether (60-29-7)

potassium hydroxide (1310-58-3)

dimethylamine hydrochloride (506-59-2)

dimethylamine (124-40-3)

2-Chloropyrimidine (1722-12-9)

2-(Dimethylamino)pyrimidine, Pyrimidine,2-dimethylamino- (5621-02-3)

N-Methylaminopyrimidine

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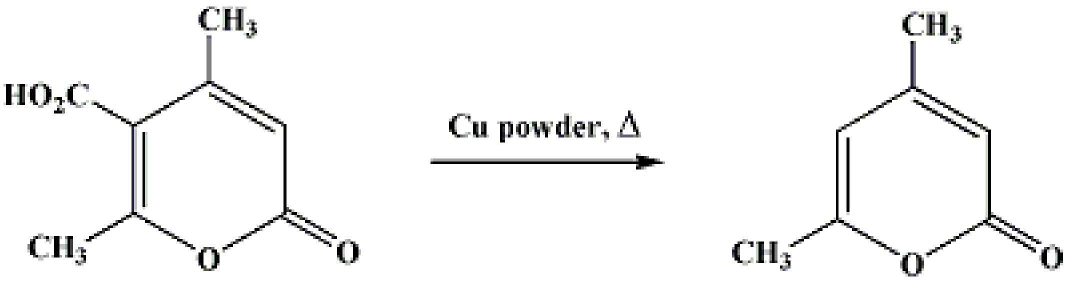
Organic Syntheses, CV 4, 337

4,6-DIMETHYLCOUMALIN

[Sorbic acid, 5-hydroxy-3-methyl, δ-lactone]



Submitted by Newton R. Smith and Richard H. Wiley[1,2].
Checked by R. S. Schreiber and H. H. Fall.

1. Procedure

In a 125-ml. Claisen flask, equipped with a capillary for vacuum distillation and a thermometer, are placed 50 g. (0.3 mole) of isodehydroacetic acid (p. 549) and 2 g. of copper powder (Note 1). A 125-ml. simple distilling flask, cooled by a water jet, is used as a vacuum receiver and is attached to a water aspirator. The Claisen flask is heated at atmospheric pressure in an oil bath at 230–235° for 45 minutes or until the decarboxylation has ceased. The pressure on the system is then slowly reduced, and the dimethylcoumalin is distilled directly from the reaction flask (Note 2). The crude dimethylcoumalin (34–35 g., 92–95%) is redistilled from a Claisen flask. The yield of 4,6-dimethylcoumalin is 30–32 g. (81–87%); b.p. 140–142°/35 mm. (Note 3); m.p. 50–51°.

2. Notes

1. Copper chromite catalyst may be substituted.
2. The submitters recommend 3 hours for decarboxylation. At 45-minute intervals the pressure on the system is reduced and the dimethylcoumalin distilled directly from the reaction flask. After the distillation slackens, the pressure is returned to atmospheric and the decarboxylation is continued. However, the checkers found that the decarboxylation is virtually completed during the first 45-minute period.
3. The checkers observed a boiling point of 134–136°/35 mm. for 4,6-dimethylcoumalin. The melting point, however, was identical with that reported by the submitters.

3. Discussion

4,6-Dimethylcoumalin has been prepared by the decarboxylation of isodehydroacetic

acid in sulfuric acid or by heating,[3] and by the distillation of 4-methyl-2-pyrone-6-acetic acid.[4]

References and Notes

1. University of Louisville, Louisville, Kentucky.
2. The submitters wish to thank the Research Corporation for a grant under which this work was done.
3. Hantzsch, *Ann.*, **222**, 17 (1883).
4. Rice and Vogel, *Chem. & Ind. (London)*, **1959**, 992.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

4,6-Dimethylcoumalin

Isodehydroacetic acid

sulfuric acid (7664-93-9)

copper powder (7440-50-8)

COPPER CHROMITE

Sorbic acid, 5-hydroxy-3-methyl, δ-lactone (675-09-2)

dimethylcoumalin

4-methyl-2-pyrone-6-acetic acid

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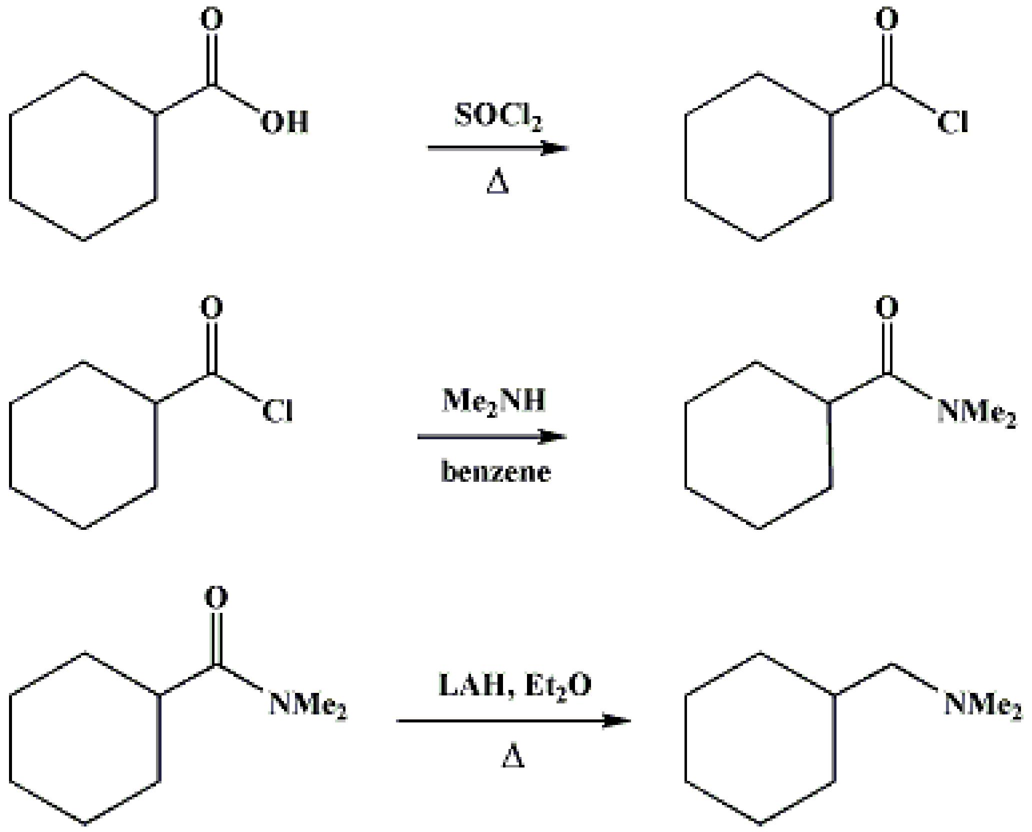
Organic Syntheses, CV 4, 339

N,N-DIMETHYLCYCLOHEXYLMETHYLAMINE

[Cyclohexanemethylamine, N,N-dimethyl-]



Submitted by Arthur C. Cope and Engelbert Ciganek[1].
Checked by William E. Parham and Robert Koncos.

1. Procedure

A. *N,N-Dimethylcyclohexanecarboxamide.* In a 1-l. three-necked flask equipped with a reflux condenser and a dropping funnel, both carrying drying tubes, is placed 128 g. (1.0 mole) of cyclohexanecarboxylic acid (Note 1). Thionyl chloride (179 g., 1.5 moles) (Note 1) is added during 5 minutes to the acid, with stirring by a magnetic stirrer. The flask is placed in an oil bath and heated at a bath temperature of 150° for 1 hour. The reflux condenser is then replaced by a distillation head (Note 2), 200 ml. of anhydrous benzene is added, and the mixture is distilled until the temperature of the vapors reaches 95°. The mixture is cooled, another 200 ml. of anhydrous benzene is added, and the distillation is continued until the temperature of the vapors again reaches 95°. The cooled residual acid chloride is transferred with a little benzene to a dropping funnel which is attached to a 2-l. three-necked flask. The flask is fitted with an efficient mechanical stirrer and a drying tube and is immersed in an ice bath. A solution of 135 g. (3.0 moles) of anhydrous dimethylamine (Note 1) in 150 ml. of anhydrous benzene is introduced into the flask. The acid chloride is added very slowly

from the dropping funnel to the vigorously stirred solution, the addition taking about 2 hours. The mixture is then stirred at room temperature overnight. Two hundred milliliters of water is added, the layers are separated, and the aqueous phase is extracted with two 100-ml. portions of ether. The extracts are combined with the benzene layer, washed with saturated sodium chloride solution, and dried over 100 g. of anhydrous magnesium sulfate. Most of the solvent is removed by distillation through a 20-cm. Vigreux column at atmospheric pressure, and the residual liquid is distilled through the column under reduced pressure. The fraction boiling at 85–86°/1.5 mm. is collected (Note 3). The yield of N,N-dimethylcyclohexanecarboxamide is 133–138 g. (86–89%), n_D^{25} 1.4800–1.4807.

B. *N,N-Dimethylcyclohexylmethylamine*. In a 3-l. three-necked flask equipped with a reflux condenser and a dropping funnel, both protected by drying tubes, is placed a suspension of 32 g. (0.85 mole) of lithium aluminum hydride (Note 4) in 400 ml. of anhydrous ether (Note 5). The mixture is stirred with a magnetic stirrer using a 40-mm. Teflon-covered stirring bar. A solution of 133 g. (0.86 mole) of N,N-dimethylcyclohexanecarboxamide in 300 ml. of anhydrous ether (Note 5) is added at such a rate as to maintain gentle reflux. The addition requires about 1 hour. The flask is then placed in an electric heating mantle, and the mixture is stirred and heated under reflux for 15 hours. The heating mantle is replaced by an ice bath, and the flask is fitted with an efficient mechanical, sealed stirrer. Water (70 ml.) is added slowly with vigorous stirring. Stirring is continued for 30 minutes after the addition of water is complete. A cold solution of 200 g. of sodium hydroxide in 500 ml. of water is added at once, and the flask is fitted for steam distillation. The mixture is steam-distilled until the distillate is neutral; about 1.5 l. is collected. The distillate is acidified by careful addition, with water cooling, of 95 ml. of concentrated hydrochloric acid. The two layers are separated and the ether layer washed with 50 ml. of 10% hydrochloric acid. The combined acidic solutions are concentrated until no more distillate comes over at steam bath temperature and 20 mm. pressure. The residue is dissolved in 200 ml. of water, the solution cooled, and 110 g. of sodium hydroxide pellets is added slowly, with stirring and external cooling with ice. The two layers are separated, and the aqueous phase is extracted with three 100-ml. portions of ether (Note 6). The combined amine layer and ether extracts are dried over 40 g. of potassium hydroxide pellets for 3 hours. The drying agent is separated by decantation, and the solvent is removed by distillation through a 20-cm. Vigreux column. The residue, on distillation under reduced pressure, yields 106–107 g. (88%) of N,N-dimethylcyclohexylmethylamine, b.p. 76°/29 mm., n_D^{25} 1.4462–1.4463.

2. Notes

1. The material as supplied by the Eastman Kodak Company (white label grade) may be used without further purification.
2. No fractionating column was used.
3. In some runs, small amounts of sulfur-containing compounds distilled together with the amide. These impurities did not affect the yield and purity of the N,N-dimethylcyclohexylmethylamine obtained in the subsequent reduction

with lithium aluminum hydride.
4. Lithium aluminum hydride as supplied by Metal Hydrides Inc., Beverly, Massachusetts, may be used without prior pulverization.
5. Mallinckrodt absolute ethyl ether (reagent grade) may be used without further drying.
6. The checkers added enough water to dissolve most of the solid before the second and third ether extractions.

3. Discussion

N,N-Dimethylcyclohexylmethylamine has been prepared by reduction of N,N-dimethylcyclohexanecarboxamide with lithium aluminum hydride;[2,3] by the action of dimethylformamide on cyclohexanecarboxaldehyde;[4] by methylation of cyclohexylmethylamine[3,5] and of N-methylcyclohexylmethylamine by the Clarke-Eschweiler method (treatment with formaldehyde and formic acid) and by the action of dimethylamine on cyclohexylmethyl bromide.[6]

N,N-Dimethylcyclohexanecarboxamide has been prepared by the action of dimethylamine on cyclohexanecarbonyl chloride.[2,3,7]

The experimental procedure described is a modification of the method reported by Mousseron, Jacquier, Mousseron-Canet, and Zagdoun[2] and by Baumgarten, Bower, and Okamoto.[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 492
- Org. Syn. Coll. Vol. 9, 559

References and Notes

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Appendix

Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether, ethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

formaldehyde (630-08-0)

thionyl chloride (7719-09-7)

sodium chloride (7647-14-5)

formic acid (64-18-6)

potassium hydroxide (1310-58-3)

Cyclohexanecarboxylic acid (98-89-5)

magnesium sulfate (7487-88-9)

dimethylamine (124-40-3)

lithium aluminum hydride (16853-85-3)

dimethylformamide (68-12-2)

cyclohexylmethylamine (3218-02-8)

N,N-Dimethylcyclohexylmethylamine, Cyclohexanemethylamine, N,N-dimethyl- (16607-80-0)

N,N-Dimethylcyclohexanecarboxamide (17566-51-7)

Cyclohexanecarboxaldehyde (2043-61-0)

N-methylcyclohexylmethylamine

cyclohexylmethyl bromide (2550-36-9)

cyclohexanecarbonyl chloride (2719-27-9)

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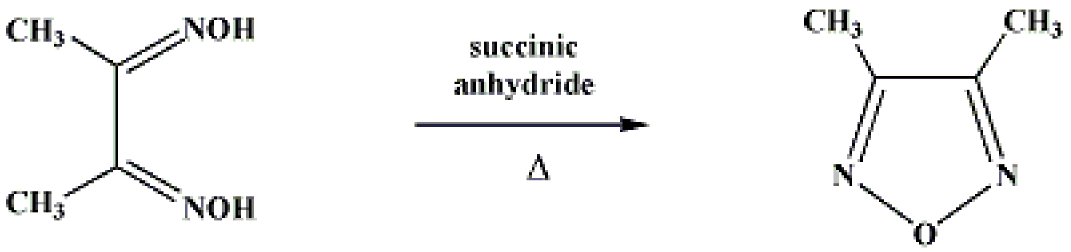
Organic Syntheses, CV 4, 342

DIMETHYLFURAZAN

[Furazan, 3,4-dimethyl-]



Submitted by Lyell C. Behr and John T. Brent[1].
Checked by T. L. Cairns and J. E. Carnahan.

1. Procedure

One hundred grams (1 mole) of succinic anhydride and 116 g. (1 mole) of dimethylglyoxime (Note 1), both finely ground, are intimately mixed and introduced into a 1-l. three-necked flask which is equipped with a sealed mechanical stirrer, a thermometer reaching nearly to the bottom of the flask, and an outlet tube connected to a water-cooled condenser arranged for distillation. The mixture is heated slowly with an electric mantle or oil bath, and stirring is commenced as soon as practicable (Note 2). The mixture liquefies at about 100°, and a rapid reaction begins at 150–170° accompanied by a sudden rise in temperature. This initial rapid reaction can be controlled readily by removing the heater when the temperature reaches 170° and applying a cooling bath until the inside temperature is 150° (Note 3). Heat is then applied again, and distillation of the product begins at a flask temperature of 160° and continues until the temperature reaches 200°. The stirrer is stopped, the receiver is changed, and, after the flask and contents have cooled to about 120°, 50 ml. of water is added. The thermometer is replaced by an inlet tube, and steam is passed in until no more insoluble material passes over. Usually collection of about 200–300 ml. of distillate is sufficient. The distillate is extracted with two 100-ml. portions of ether, and the extracts are combined with the dimethylfurazan obtained by direct distillation (Note 4). The ether solution is dried for a short time over anhydrous magnesium sulfate. The drying agent is removed by filtration, and the ether is evaporated on a steam bath. The residue is distilled at atmospheric pressure through a short column, and after a fore-run, consisting chiefly of biacetyl, the dimethylfurazan distils at 154–159° as a colorless liquid, n_D^{25} 1.4234–1.4243, m.p. –7.2 to –6.6°. The yield is 59–63 g. (60–64%).

2. Notes

1. A good grade of both reagents should be used. The better-quality products supplied by the Eastman Kodak Company are satisfactory.

2. The mixture may be difficult to stir mechanically below its melting point unless a powerful motor is used.
3. The temperature usually climbs to about 190° during this interval, and some dimethylfurazan distils rapidly.
4. The product obtained by direct distillation contains some water, but the dimethylfurazan can be readily separated.

3. Discussion

Dimethylfurazan has been obtained from dimethylglyoxime by heating with water, aqueous ammonia, or aqueous sodium hydroxide.[2,3] The usual acid dehydrating agents fail.

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ammonia (7664-41-7)

ether (60-29-7)

sodium hydroxide (1310-73-2)

magnesium sulfate (7487-88-9)

Succinic anhydride (108-30-5)

DIMETHYLGLYOXIME (95-45-4)

biacetyl (431-03-8)

Dimethylfurazan, Furazan, 3,4-dimethyl- (4975-21-7)

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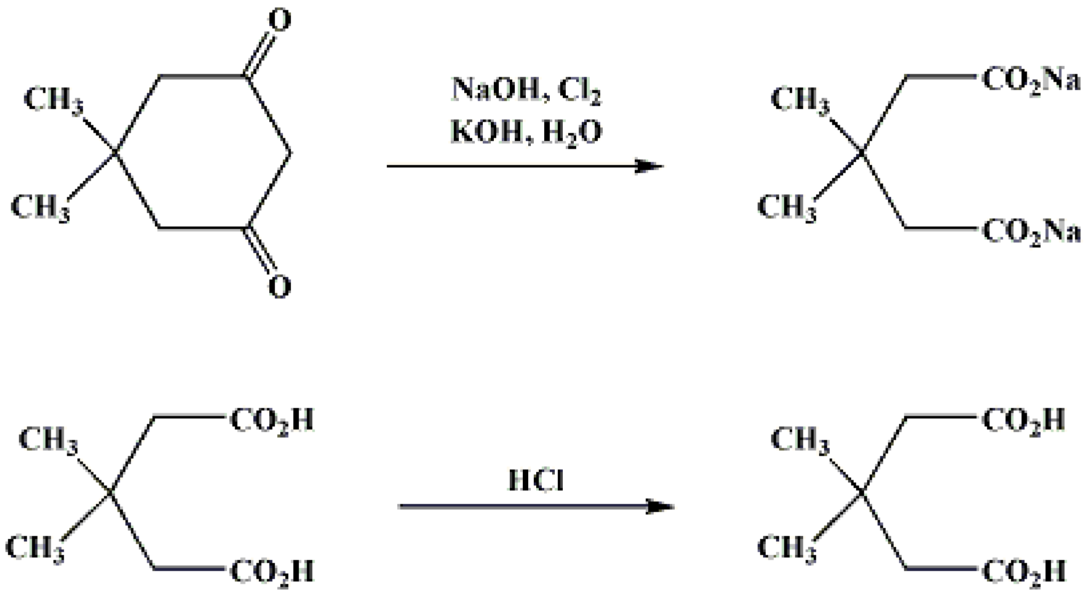
Organic Syntheses, CV 4, 345

β,β-DIMETHYLGLUTARIC ACID

[Glutaric acid, 3,3-dimethyl-]



Submitted by Walter T. Smith and Gerald L. McLeod[1].
Checked by William S. Johnson and Donald D. Cameron.

1. Procedure

A solution of 218 g. (5.45 moles) of sodium hydroxide in 300 ml. of water in a 3-l. three-necked flask is cooled to room temperature. To this solution 1250 g. of ice is added, and a stream of chlorine is passed in rapidly through a delivery tube having a small opening and extending almost to the bottom of the liquid. The passage of the chlorine is continued until 161 g. (2.27 moles) has been absorbed. The flask is then fitted with a mechanical stirrer, a thermometer, and a 500-ml. separatory funnel.

Seventy grams (0.5 mole) of methone[2] is dissolved in a solution of 65 g. (1.16 moles) of potassium hydroxide in 525 ml. of water. The solution is cooled to room temperature, poured into the separatory funnel, and run slowly with stirring into the sodium hypochlorite solution. The temperature rises gradually to 35–40° during the addition. After the addition has been completed, the solution is stirred for 6–8 hours until the temperature drops to room temperature.

Without interrupting the stirring, 50 g. of sodium sulfite is added to decompose the excess sodium hypochlorite, and the solution is acidified to Congo red by adding concentrated hydrochloric acid slowly with stirring to avoid foaming. The acid solution is then concentrated by distillation until salts just begin to precipitate (Note 1).

The mixture is then cooled to room temperature, 300 ml. of ether and enough water are

added to dissolve all of the precipitate, and the whole is transferred to a 3-l. separatory funnel. The layers are separated, and the aqueous portion is extracted with three 200-ml. portions of ether. The ether extracts are combined and dried for several hours over 15–20 g. of anhydrous magnesium sulfate. The ether is then removed by distillation. This may be conveniently carried out by fitting a 250-ml. Claisen flask with a separatory funnel in order to add the solution as the ether distils. When only 150–200 ml. of solution remains in the flask, the distillation is stopped and the residue is poured into a small beaker. The remaining ether is removed by heating on a steam bath, and the residue solidifies on cooling. The colorless, crystalline β,β-dimethylglutaric acid is dried in air. The yield is 73–77 g. (91–96%), m.p. 97–99°. Crystallization from 100–125 ml. of benzene gives 65–73 g. (81–91%) of acid, m.p. 100–102° (Note 2).

2. Notes

1. The chloroform formed in the reaction comes over during the early stages of this distillation. The precipitation of salts usually begins after the solution has been concentrated to about one-half the original volume.

2. The melting points given in the literature are 101°,[3] 101–102°,[4] 103–104°,[5] and 98–100°.[6]

3. Discussion

β,β-Dimethylglutaric acid has been prepared by heating dimethylpropanetricarboxylic acid above its melting point;[3] by hydrolysis of the condensation product of ethyl cyanoacetate and ethyl β,β-dimethylacrylate;[7] by the action of sulfuric acid on diethyl β,β-dimethyl-α,α'-dicyanoglutarate;[8] by hydrolysis of the nitrile obtained by the action of calcium cyanide on β,β-dimethylbutyrolactone;[4] by the action of sulfuric acid on β,β-dimethyl-α,α'-dicyanoglutarimide;[9] and by the action of sodium hypobromite on methone.[5] The present procedure is essentially that of Walker and Wood.[6]

References and Notes

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2. *Org. Syntheses Coll. Vol.* **2**, 200 (1943).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

diethyl β,β-dimethyl-α,α'-dicyanoglutarate

β,β-dimethyl-α,α'-dicyanoglutarimide

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether (60-29-7)

sodium sulfite (7757-83-7)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

chlorine (7782-50-5)

potassium hydroxide (1310-58-3)

Ethyl cyanoacetate (105-56-6)

calcium cyanide (592-01-8)

sodium hypochlorite (7681-52-9)

sodium hypobromite

magnesium sulfate (7487-88-9)

methone (126-81-8)

β,β-Dimethylglutaric acid, Glutaric acid, 3,3-dimethyl- (4839-46-7)

dimethylpropanetricarboxylic acid

ethyl β,β-dimethylacrylate (638-10-8)

β,β-dimethylbutyrolactone

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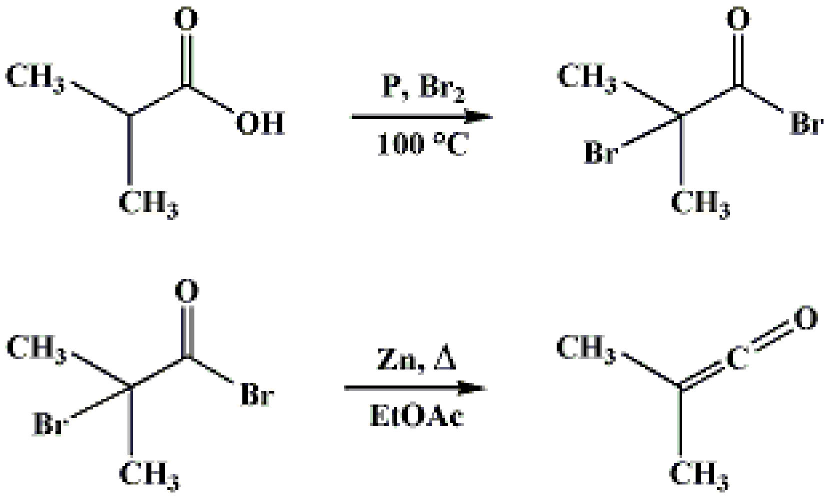
Organic Syntheses, *CV 4, 348*

DIMETHYLKETENE

[Ketene, dimethyl-]



Submitted by C. W. Smith and D. G. Norton[1].
Checked by T. L. Cairns and J. C. Sauer.

1. Procedure

A. *α-Bromoisobutyryl bromide.* To a mixture of 250 g. (2.85 moles) of isobutyric acid and 35 g. (0.28 mole) of red phosphorus in a 1-l. three-necked flask, fitted by ground-glass joints to a dropping funnel, mechanical stirrer, and reflux condenser, is added, dropwise with stirring, 880 g. (5.5 moles) of bromine. After the addition is complete, the solution is warmed to 100° over a period of 6 hours. The unreacted bromine and hydrogen bromide are removed under reduced pressure (30 mm.). The α-bromoisobutyryl bromide is decanted from the phosphorous acid and fractionated through a short helices-packed column. After a considerable fore-cut, the main fraction, 493–540 g. (75–83%), is collected at 91–98° (100 mm.).

B. *Dimethylketene* (Note 1). The apparatus for this preparation consists of a 500-ml. flask equipped with an inlet tube for nitrogen and a dropping funnel and fitted to a 6-in. modified Claisen still head leading to a tared spiral inlet trap having stop-cocks on the inlet and exit sides and cooled in Dry Ice-acetone (Note 2). This trap is connected to a vacuum line, and the reaction is carried out at 300 mm. pressure. After 40 g. (0.61 g. atom) of zinc turnings and 300 ml. of ethyl acetate have been placed in the flask and the system has been flushed with nitrogen (free of oxygen and moisture) and heated to incipient boiling, 111 g. (0.48 mole) of α-bromoisobutyryl bromide is added dropwise at such a rate that the ethyl acetate boils gently. A slow stream of nitrogen is continued throughout the reaction. Dimethylketene distils along with ethyl acetate and is obtained in 46–54% yield as a 9–10% solution in ethyl acetate (15–18 g. of dimethylketene in 190–200 ml. of ethyl acetate) (Note 3).

2. Notes

1. This ketene reacts rapidly with oxygen to form an explosive peroxide. Drops of solution allowed to evaporate in air may detonate. Washing with water is an efficient means of decontamination.
2. If simple traps are used, it is necessary to use two in series to condense all the dimethylketene and ethyl acetate.
3. The concentration of dimethylketene is determined by titration of an aliquot at ice temperatures with 0.1*N* sodium hydroxide using phenolphthalein indicator. Under these conditions, blank determinations indicate that ethyl acetate is not hydrolyzed.
The identity of the dimethylketene may be determined (and an approximate check made on the concentration) by adding 35 g. of dimethylketene solution to 15 g. of aniline in 75 ml. of ether. After 2–3 minutes, the ether solution is washed with dilute hydrochloric acid, dilute potassium carbonate, then water, and the ether is evaporated. Isobutyroanilide, m.p. 102–103° (103–104° after one recrystallization, no melting-point depression in mixture with an authentic sample), is obtained in about 90% yield based on the concentration of dimethylketene indicated by titration.

3. Discussion

The preparation of ketenes has been discussed by Hanford and Sauer in *Organic Reactions*.[2] Dimethylketene has been prepared by the treatment of α-bromoisobutyryl bromide with zinc,[3] and by the pyrolysis of isobutyrylphthalimide,[4] dimethylmalonic anhydride,[5] or α-carbomethoxy-α, β-dimethyl-β-butyrolactone.[6] Dimethylketene dimer has been prepared by heating isobutyryl chloride with a tertiary amine. Pyrolysis of the dimer yields dimethylketene.[7]

α-Bromoisobutyryl bromide has been prepared in a two-step process involving the bromination of isobutyric acid to α-bromoisobutyric acid followed by treatment with phosphorus tribromide.[8] A one-step process utilizing the Hell-Volhard-Zelinsky reaction[9] is more satisfactory.

References and Notes

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3. Staudinger and Klever, *Ber.*, **39**, 968 (1906).
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6. Ott, *Ann.*, **401**, 159 (1913).

7. See reference 2, p. 136.
8. Taufen and Murray, *J. Am. Chem. Soc.*, **67**, 754 (1945).
9. Volhard, *Ann.*, **242**, 161 (1887).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

red phosphorus

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

ether (60-29-7)

aniline (62-53-3)

sodium hydroxide (1310-73-2)

hydrogen bromide (10035-10-6)

bromine (7726-95-6)

oxygen (7782-44-7)

phosphorus tribromide (7789-60-8)

nitrogen (7727-37-9)

zinc, zinc turnings (7440-66-6)

phenolphthalein (77-09-8)

isobutyryl chloride (79-30-1)

phosphorous acid (13598-36-2)

isobutyric acid (79-31-2)

Dimethylketene, Ketene, dimethyl- (598-26-5)

α-bromoisobutyryl bromide (20769-85-1)

Isobutyroanilide (4406-41-1)

isobutyrylphthalimide

dimethylmalonic anhydride

α-carbomethoxy-α, β-dimethyl-β-butyrolactone

α-bromoisobutyric acid (2052-01-9)

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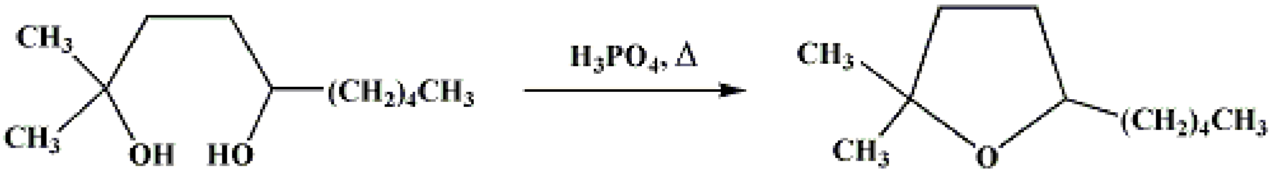
5,5-DIMETHYL-2-*n*-PENTYLTETRAHYDROFURAN

[Furan, tetrahydro-2,2-dimethyl-5-pentyl-]



Submitted by J. Colonge and R. Marey[1].
Checked by V. Boekelheide and H. Kaempfen.

1. Procedure

In a 100-ml., three-necked, round-bottomed flask, fitted with a sealed mechanical stirrer, a reflux condenser, and a thermometer reaching to the bottom of the flask, are placed 37.6 g. (0.2 mole) of 2-methyl-2,5-decanediol (p.601) and 17 g. of 85% phosphoric acid. The limpid liquid obtained is heated and maintained at 125° for 40 minutes. Then the acidic lower layer is discarded, and the organic layer is washed with three or four 50-ml. portions of lukewarm distilled water.

Distillation of the resulting crude oil using a simple fractionating column gives 32–33 g. (94–97%) of pure 5,5-dimethyl-2-*n*-pentyltetrahydrofuran as a colorless liquid boiling at 31–33°/1.5 mm.; n_D^{25} 1.4257 (Note 1).

2. Notes

1. The submitters have also prepared 5,5-dimethyl-2-heptyltetrahydrofuran, n_D^{25} 1.4360, by a similar dehydration of 2-methyl-2,5-undecanediol obtained from the reaction of methylmagnesium bromide and γ-undecanoic acid lactone.

3. Discussion

There is no report on the preparation of 5,5-dimethyl-2-*n*-pentyltetrahydrofuran.

References and Notes

1. École de Chimie Industrielle de Lyon and Établissement Descollonges Frères (Lyon).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

phosphoric acid (7664-38-2)

methylmagnesium bromide (75-16-1)

Furan, tetrahydro-2,2-dimethyl-5-pentyl-, 5,5-DIMETHYL-2-n-PENTYLTETRAHYDROFURAN (53684-53-0)

2-Methyl-2,5-decanediol (53731-34-3)

5,5-dimethyl-2-heptyltetrahydrofuran

2-methyl-2,5-undecanediol

γ-undecanoic acid lactone (104-67-6)

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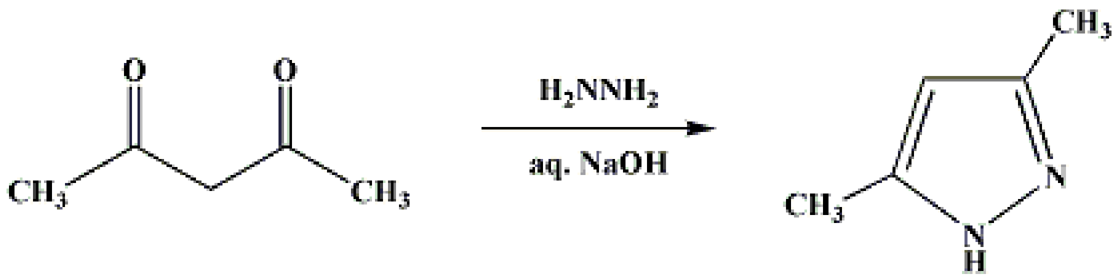
Organic Syntheses, CV 4, 351

3,5-DIMETHYLPYRAZOLE

[Pyrazole, 3,5-dimethyl-]



Submitted by Richard H. Wiley and Peter E. Hexner[1].
Checked by William S. Johnson and Robert J. Highet.

1. Procedure

Sixty-five grams (0.50 mole) of hydrazine sulfate (Note 1) is dissolved in 400 ml. of 10% sodium hydroxide in a 1-l. round-bottomed flask, fitted with a separatory funnel, a thermometer, and a stirrer. The flask is immersed in an ice bath and cooled. When the temperature of the mixture reaches 15° (Note 2), 50 g. (0.50 mole) of acetylacetone (Note 3) is added dropwise with stirring while the temperature is maintained at about 15°. The addition requires about 30 minutes to complete, and the mixture is stirred for 1 hour at 15° (Note 4). The contents of the flask are diluted with 200 ml. of water to dissolve precipitated inorganic salts, transferred to a 1-l. separatory funnel, and shaken with 125 ml. of ether. The layers are separated, and the aqueous layer is extracted with four 40-ml. portions of ether. The ether extracts are combined, washed once with saturated sodium chloride solution, and dried over anhydrous potassium carbonate. The ether is removed by distillation, and the slightly yellow residue of crystalline 3,5-dimethylpyrazole obtained by drying at reduced pressure (approximately 20 mm.) weighs 37–39 g. (77–81%), m.p. 107–108°. This product, which is of good quality, can be recrystallized from about 250 ml. of 90–100° petroleum ether without significant change in appearance or melting point. The yield after drying in a vacuum desiccator containing paraffin chips is 35–37 g. (73–77%) (Note 5).

2. Notes

1. Hydrazine sulfate supplied by the Eastman Kodak Company is satisfactory, or it may be prepared by a previously described procedure.[2]
2. A precipitate of sodium sulfate may form at this point.
3. Union Carbide and Carbon Corporation technical 2,4-pentanedione was used without purification.
4. The 3,5-dimethylpyrazole precipitates during this period.

5. Recrystallization from methanol or ethanol gives practically colorless material of the same melting point, but it is more difficult to obtain good recovery owing to the high solubility of the pyrazole in these solvents.

3. Discussion

3,5-Dimethylpyrazole has been prepared from acetylacetone and hydrazine hydrate in ethanol[3] or hydrazine sulfate in aqueous alkali.[4,5,6] The latter method is preferred, because the reaction with hydrazine hydrate is sometimes violent.[3,4] 3,5-Dimethylpyrazole also has been prepared by hydrolysis and decarboxylation of the 1-carbamido- or 1-carboxamidine derivatives, obtained by reaction of semicarbazide[7] or aminoguanidine[8] with acetylacetone, and from 1,2-pentadien-4-one and hydrazine hydrate.[9]

References and Notes

1. University of Louisville, Louisville, Kentucky.
2. *Org. Syntheses Coll. Vol.* **1**, 309 (1941).
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7. Posner, *Ber.*, **34**, 3980 (1901).
8. Thiele and Dralle, *Ann.*, **302**, 294 (1898).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

ethanol (64-17-5)

potassium carbonate (584-08-7)

methanol (67-56-1)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

hydrazine hydrate (7803-57-8)

Hydrazine sulfate (10034-93-2)

semicarbazide (57-56-7)

Acetylacetone, 2,4-pentanedione (123-54-6)

aminoguanidine

3,5-Dimethylpyrazole, Pyrazole, 3,5-dimethyl- (67-51-6)

pyrazole (288-13-1)

1,2-pentadien-4-one (2200-53-5)

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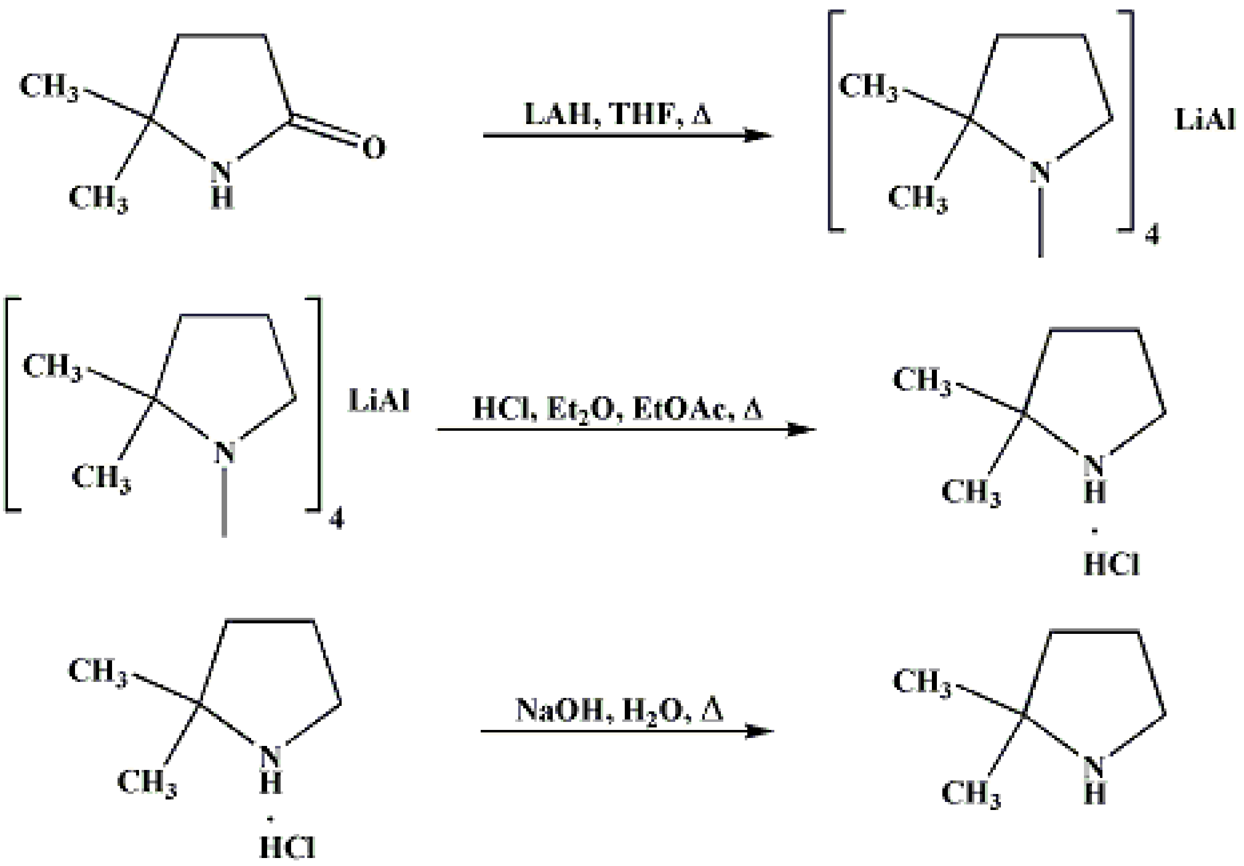
2,2-DIMETHYLPYRROLIDINE

[Pyrrolidine, 2,2-dimethyl-]



Submitted by Robert Bruce Moffett[1]
Checked by N. J. Leonard and J. W. Curry.

1. Procedure

A 3-l. three-necked round-bottomed flask is placed on a steam bath and fitted with a mercury-sealed Hershberg stirrer, a dropping funnel, and an efficient reflux condenser topped with a tube containing soda lime and calcium chloride. In this flask are placed 38 g. (1 mole) of pulverized lithium aluminum hydride (Note 1) and 400 ml. of dry tetrahydrofuran (Note 2). The mixture is heated under reflux with stirring for 15 minutes or until most of the lithium aluminum hydride has dissolved. A solution of 90.5 g. (0.8 mole) of 5,5-dimethyl-2-pyrrolidone (p.357) in 200 ml. of dry tetrahydrofuran (Note 2) is added slowly at such a rate that the solvent refluxes gently without external heating. When the addition is complete and the initial reaction subsides, the mixture is stirred and heated at gentle reflux for 8 hours.

The condenser is then set for downward distillation, and, while the mixture is stirred, about 450 ml. of solvent is distilled (Note 3) and (Note 4). The condenser is reset in

the reflux position, and 300 ml. of ether (commercial anhydrous) is added slowly from the dropping funnel with vigorous stirring. This is followed by 50 ml. of ethyl acetate added very slowly with vigorous stirring and finally by 500 ml. of 6*N* hydrochloric acid added in the same manner.

The condenser is again set downward, and the dropping funnel is replaced by a tube reaching nearly to the bottom of the flask. Steam is passed in, and the distillation is continued for several minutes after the boiling point reaches 100° (Note 5). The distillate is discarded. The mixture in the flask is cooled, and to it is added carefully 350 ml. of 12*N* sodium hydroxide with stirring (Note 6). The alkaline mixture is then steam-distilled until the distillate is no longer basic (Note 7).

The 2,2-dimethylpyrrolidine may be recovered from the aqueous distillate in two ways: (*a*) the distillate can be extracted continuously with ether;[2] or (*b*) the distillate can be acidified with hydrochloric acid and concentrated to dryness under reduced pressure to give crude 2,2-dimethylpyrrolidine hydrochloride. The base is then liberated by adding an excess of saturated aqueous sodium hydroxide solution. The oily layer is separated. The aqueous layer and salt are extracted several times with ether, which is combined with the amine. In either case the ether solution is dried thoroughly over anhydrous potassium carbonate (Note 8).

The drying agent is removed by filtration, and the ether is stripped through a short helices-packed column. The residue is fractionally distilled at 103–105°/745 mm.;n_D^{20} 1.4330;n_D^{25} 1.4304; d_4^{25} 0.8211. The yield is 53–62 g. (67–79%).

2. Notes

1. The hydride can be pulverized rapidly and safely by breaking the large pieces with a spatula, followed by careful crushing with a mortar and pestle. Caution must be observed because the solid may inflame on prolonged grinding or abrasion. The hydride dust is caustic and irritating.
2. Tetrahydrofuran from E.I. du Pont de Nemours and Company can be dried conveniently by adding to it lithium aluminum hydride in small portions until no further reaction (evolution of hydrogen) ensues. After the mixture has been stirred for a few minutes, most of the tetrahydrofuran is distilled from it with stirring (to prevent bumping) (Note 3), and collected in a receiver protected from moisture by a calcium chloride tube.
3. Care must be taken in distilling solutions of lithium aluminum hydride. Explosions have been reported[3] toward the end of distillations of such solutions, especially if they contained carbon dioxide. It is therefore recommended that these distillations be carried out behind a shield and that not more than *three-fourths* of the solvent be removed.
4. If this tetrahydrofuran is collected in a receiver protected from moisture it may be used in subsequent runs.

5. This steam distillation removes ether, tetrahydrofuran, and other volatile neutral products. If too much water accumulates in the flask, it may be heated in an electric heating mantle after most of the ether has been removed.
6. At this point the mixture should be a very strongly basic, mobile, milky slurry.
7. From time to time an aliquot of the distillate being collected can be titrated with standard acid to determine whether significant amounts of amine are distilling.
8. Sufficient drying agent should be used so that no aqueous liquid phase appears.

3. Discussion

2,2-Dimethylpyrrolidine has been prepared by the hydrogenation of 5-amino-2,2-dimethylpyrroline-N-oxide or 5-imino-2,2-dimethylpyrrolidine in the presence of Raney nickel[4] or by reduction with sodium and alcohol.[4] The present procedure has been published.[5]

References and Notes

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4. Buckley and Elliott, *J. Chem. Soc.*, **1947**, 1508.
5. Moffett and White, *J. Org. Chem.*, **17**, 407 (1952).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

soda lime

amine

calcium chloride (10043-52-4)

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

carbon dioxide (124-38-9)

Raney nickel (7440-02-0)

sodium (13966-32-0)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

hydride

2,2-Dimethylpyrrolidine, Pyrrolidine, 2,2-dimethyl- (35018-15-6)

5,5-Dimethyl-2-pyrrolidone (5165-28-6)

2,2-dimethylpyrrolidine hydrochloride

5-amino-2,2-dimethylpyrroline-N-oxide

5-imino-2,2-dimethylpyrrolidine

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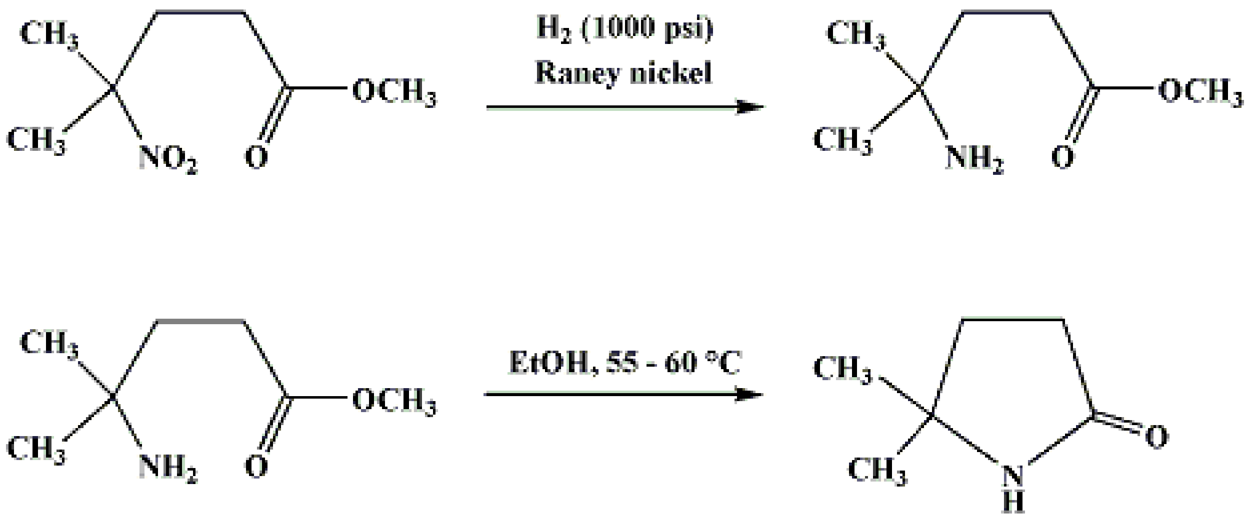
5,5-DIMETHYL-2-PYRROLIDONE

[2-Pyrrolidinone, 5,5-dimethyl-]



Submitted by R. B. Moffett[1]
Checked by N. J. Leonard, W. E. Smith, and B. L. Ryder.

1. Procedure

To a solution of 148 g. (0.845 mole) of methyl γ-methyl-γ-nitrovalerate (p.652) in 500 ml. of commercial absolute ethanol (total volume about 632 ml.) in a 2.5-l. rocking high-pressure bomb is added 12.5–25.0 g. (Note 1) of W-5[2] Raney nickel catalyst (Note 2), previously rinsed with absolute ethanol. The bomb head and fittings are placed in position, including a thermocouple attached to a semi-automatic heating control (Micromax). Hydrogen is introduced into the bomb until the pressure reaches 1000 1b. per sq. in. (Note 3).

The bomb is rocked and the temperature of the solution is raised carefully to 55° during the course of 0.5–1.0 hour (Note 4). The hydrogen uptake begins at 40–51°, and during the reaction period the temperature is held at 55–60°. The rate of pressure drop is 50–100 lb. per sq. in. each 15 minutes. The rocking of the bomb is continued, and the temperature is maintained at 60° until the pressure reading is constant for 1 hour, in order to ensure completion of the reaction.

After the bomb has been cooled the contents are removed and allowed to stand until the catalyst has settled (Note 5). The mixture is filtered, and the filtrate is transferred to a Claisen flask placed in an oil bath. The solvent is removed by distillation at atmospheric pressure, and the oil-bath temperature is raised to 200°. After temporary cooling, the residue in the flask is distilled under reduced pressure. The 5,5-dimethyl-2-pyrrolidone boils at 126.5–128.5°/12 mm. and solidifies in the receiver. The yield is 84–92 g. (88–96%); m.p. 42–43° (Note 6).

2. Notes

1. It is unnecessary and may in fact be dangerous to use a larger amount of catalyst.
2. The checkers have found that commercial grade Raney nickel (Gilman Paint and Varnish Company) is a satisfactory substitute for W-5 catalyst. The yields obtained with the two catalysts are identical, but the hydrogenation requires 2–3 hours with commercial catalyst compared with 1–1.5 hours for W-5 catalyst.
3. The theoretically required drop in hydrogen pressure for a free space of 1868 ml. and equivalent to 2.535 moles of hydrogen is 507 lb. per sq. in. The theoretical pressure drop will vary with the free space when bombs of different capacity are used. The observed pressure drop usually exceeds the theoretical by about 10%.
4. Since batches of Raney nickel may vary in activity, caution must be exercised during the heating period. The temperature should not exceed 60° at any time.
5. Filtration through Hiflo Super-Cel (Johns-Manville Company) speeds the operation but lowers the final yield.
6. The product can be recrystallized from petroleum ether (b.p. 30–38°).

3. Discussion

5,5-Dimethyl-2-pyrrolidone has been prepared by the hydrolysis of 5-imino-2,2-dimethylpyrrolidine in the presence of Raney nickel[3] or by the hydrogenation of 5-amino-2,2-dimethylpyrroline-N-oxide in the presence of Raney nickel.[3] The preparation by this method has been published.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 354

References and Notes

1. The Upjohn Company, Kalamazoo, Michigan.
2. Adkins and Billica, *J. Am. Chem. Soc.*, **70**, 695 (1948).
3. Buckley and Elliott, *J. Chem. Soc.*, **1947**, 1508.
4. Moffett and White, *J. Org. Chem.*, **17**, 407 (1952).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

ethanol (64-17-5)

hydrogen (1333-74-0)

Raney nickel (7440-02-0)

5,5-Dimethyl-2-pyrrolidone, 2-Pyrrolidinone, 5,5-dimethyl- (5165-28-6)

5-amino-2,2-dimethylpyrroline-N-oxide

5-imino-2,2-dimethylpyrrolidine

Methyl γ-methyl-γ-nitrovalerate (16507-02-1)

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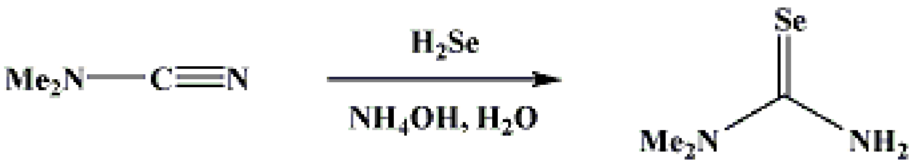
N,N-DIMETHYLSELENOUREA

[Urea, 1,1-dimethyl-2-seleno-]



Submitted by Frank Bennett and Ralph Zingaro[1].
Checked by C. F. H. Allen and K. C. Kennard.

1. Procedure

Caution! Hydrogen selenide is very toxic. This preparation should be carried out in a well-ventilated hood. The operator should wear rubber gloves. The apparatus should be screened from bright light.

A mixture of 37 g. (0.5 mole) of dimethylcyanamide (Note 1), 75 ml. of concentrated ammonium hydroxide, and 25 ml. of water is placed in a 250-ml. round-bottomed three-necked flask fitted with a stirrer, thermometer, and glass delivery tube (Note 2). The solution is stirred slowly, while hydrogen selenide (Note 3) is slowly bubbled in, maintaining the temperature at 20–30° by occasional external cooling. At the end of the reaction (4–5 hours) when there is no more gas evolution from the generator (4–5 hours), the flask and contents are cooled to 5–10° and stirred vigorously for one-half hour. The solid is then collected on a 9-cm. Büchner funnel and washed with 250 ml. of ice-cold 95% ethanol. The crude, gray product weighs 65–73 g. (81–91%).

For purification, it is dissolved in 9–9.5 l. of boiling benzene (Note 4). The solution is filtered rapidly, using a 32-cm. folded filter in an 8-in. short-stem glass funnel. The recovery is 59–70 g. The fine, white crystals, which melt at 169–170° (Note 5), are stored in a brown glass bottle under nitrogen (Note 6), (Note 7), (Note 8).

2. Notes

1. The practical grade, b.p. 162–164°, obtained from the Eastman Kodak Company, was used.
2. A tube 8 mm. in diameter is used. A sintered-glass gas addition tube is quickly clogged by selenium.
3. Hydrogen selenide is generated from iron or aluminum selenide and a mineral acid. In a 2-l. three-necked, flask, fitted with sealed stirrer, reflux condenser, and dropping funnel are placed 135 g. (1 mole) of powdered iron selenide (Note 9) and 350 ml. of water. The generator is heated on a steam cone, while 350 ml. of concentrated hydrochloric acid is admitted slowly with stirring, so that the

hydrogen selenide is evolved at a steady rate. (The generation of gas is regulated both by the rate of heating and the rate of addition of acid, so that the gas is absorbed almost entirely; it is led from the top of the condenser to the delivery tube.) The amount of selenide used is sufficient. The residual liquid in the generator is left open to the air overnight in a hood. Then sufficient 50% sodium hydroxide solution is added to make it basic, and the whole is flushed down the sink, using a large amount of water.

4. Recrystallization from benzene affords a product that has superior storage qualities. A liter dissolves 5–6 g. at the boiling point.

5. The melting point is unchanged by further recrystallization.

6. The product turns pink, and eventually gray, if exposed to air for an extended period. It should be stored under nitrogen.[2]

7. The submitters indicate that N,N-diethylselenourea may be prepared similarly, using diethylcyanamide. In this case, a solution of 50 ml. each of concentrated aqueous ammonium hydroxide and ethanol is used as a solvent. The reaction is carried out at 60°, the solvent being replenished as needed by a solution containing 80 ml. of ethanol and 20 ml. of concentrated ammonium hydroxide. The yield of crude material is 65–80%. Recrystallization from benzene gives a white product, m.p. 117–118°.

8. The procedure gives a commensurate yield when carried out on twice the scale.

9. Iron selenide can be obtained from the Canadian Copper Refiners Ltd., Montreal, Quebec.

3. Discussion

The procedure used is that of Zingaro, Bennett, and Hammar.[2]

References and Notes

1. Camera Works Division, Eastman Kodak Company, Rochester 17, New York.
2. Zingaro, Bennett, and Hammar, *J. Org. Chem.*, **18**, 292 (1953).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

sodium hydroxide (1310-73-2)

iron (7439-89-6)

nitrogen (7727-37-9)

ammonium hydroxide (1336-21-6)

selenium

hydrogen selenide (7782-49-2)

N,N-Dimethylselenourea, Urea, 1,1-dimethyl-2-seleno- (5117-16-8)

dimethylcyanamide (1467-79-4)

aluminum selenide (1302-82-5)

iron selenide

N,N-diethylselenourea (15909-81-6)

diethylcyanamide (617-83-4)

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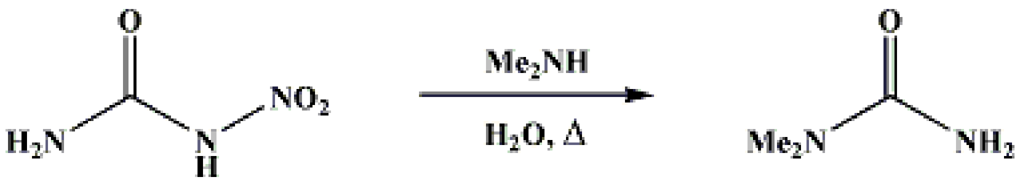
asym-DIMETHYLUREA

[Urea, 1,1-dimethyl-]



Submitted by Frederick Kurzer[1]
Checked by William S. Johnson and William T. Tsatsos.

1. Procedure

In a 1.5-l. beaker (Note 1), 191 ml. (180 g.) of aqueous 25% dimethylamine solution (1.0 mole) is diluted with 64 ml. of water and treated with 116 g. (1.1 moles) of nitrourea.[2] The temperature of the resulting brownish liquid rises spontaneously to 35–42°. The solution is warmed to 56–60°, and a reaction sets in vigorously with evolution of nitrous oxide. External cooling with water is applied when required; the reaction temperature is maintained below 70° during the first 5–7 minutes and below 85° during the second period of 5–7 minutes. After a total of 10–15 minutes, the effervescence slackens and the reaction mixture is kept at 90–100° until the evolution of gas has completely ceased. This usually requires an additional 15–20 minutes.

The resulting liquid is heated with about 1 g. of activated carbon and is filtered with suction while hot; the clear, faintly colored filtrate is transferred to an evaporating dish and heated on a steam bath to remove most of the water. The residual, somewhat viscous, liquid (about 120 ml.) is then transferred to a beaker; the evaporating dish is rinsed with 10 ml. of water, and this solution is added to the contents of the beaker. To this is added 95% ethanol (50 ml.), and the mixture is warmed to effect solution. On cooling, large crystals separate which, at 0°, almost fill the bulk of the solution. The crystalline mass is broken up with a glass rod, collected on a suction filter, and washed quickly, while on the filter, with two successive portions of ice water (Note 2), drained, and air-dried (Note 3). The yield of large, colorless prismatic crystals of *asym*-dimethylurea is 35–40 g. (40–45%); m.p. 182–184° (Note 4).

The combined filtrates, on further evaporation and dilution with 95% ethanol as above, yield an additional 15–20 g. of material of approximately the same quality, bringing the total yield up to 57–68%. In a series of preparations, yields can be further increased a few per cent by carrying over mother liquors to subsequent batches.

2. Notes

1. The reaction mixture froths considerably in the initial stages, and the use of a

sufficiently large reaction vessel is important.
2. Since *asym*-dimethylurea is appreciably soluble in water, enough ice water is added to just cover the crystals on the filter, and suction is applied immediately.
3. A slight odor of dimethylamine, which persists, disappears when the product is dried at 80° for 1–2 hours.
4. The use of nitrourea is generally applicable to the preparation of urea derivatives and usually affords the required carbamide in excellent yield.[3,4]

3. Discussion

asym-Dimethylurea has been prepared by the interaction of dimethylamine sulfate and potassium cyanate[5] or dimethylamine and nitrourea.[3] It is also obtained by the hydrolysis of dimethylcyanamide in acid[6] and alkaline[7] media. Other reactions yielding the product include the action of dimethylamine on methyl γ-methylallophanate[8] or diethoxymethyleneimine,[9] and the hydrolysis of 1,1,2-trimethylisourea[10] or methyl dimethylthiocarbamate.[11]

References and Notes

1. School of Medicine, University of London, London, England.
2. *Org. Syntheses Coll. Vol.* **1**, 417 (1941).
3. Davis and Blanchard, *J. Am. Chem. Soc.*, **51**, 1798 (1929).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

asym-DIMETHYLUREA

ethanol (64-17-5)

carbon (7782-42-5)

urea, carbamide (57-13-6)

Nitrourea (556-89-8)

potassium cyanate (590-28-3)

dimethylamine (124-40-3)

dimethylcyanamide (1467-79-4)

Urea, 1,1-dimethyl- (598-94-7)

nitrous oxide (10024-97-2)

dimethylamine sulfate

methyl γ-methylallophanate

diethoxymethyleneimine

1,1,2-trimethylisourea

methyl dimethylthiocarbamate (16703-45-0)

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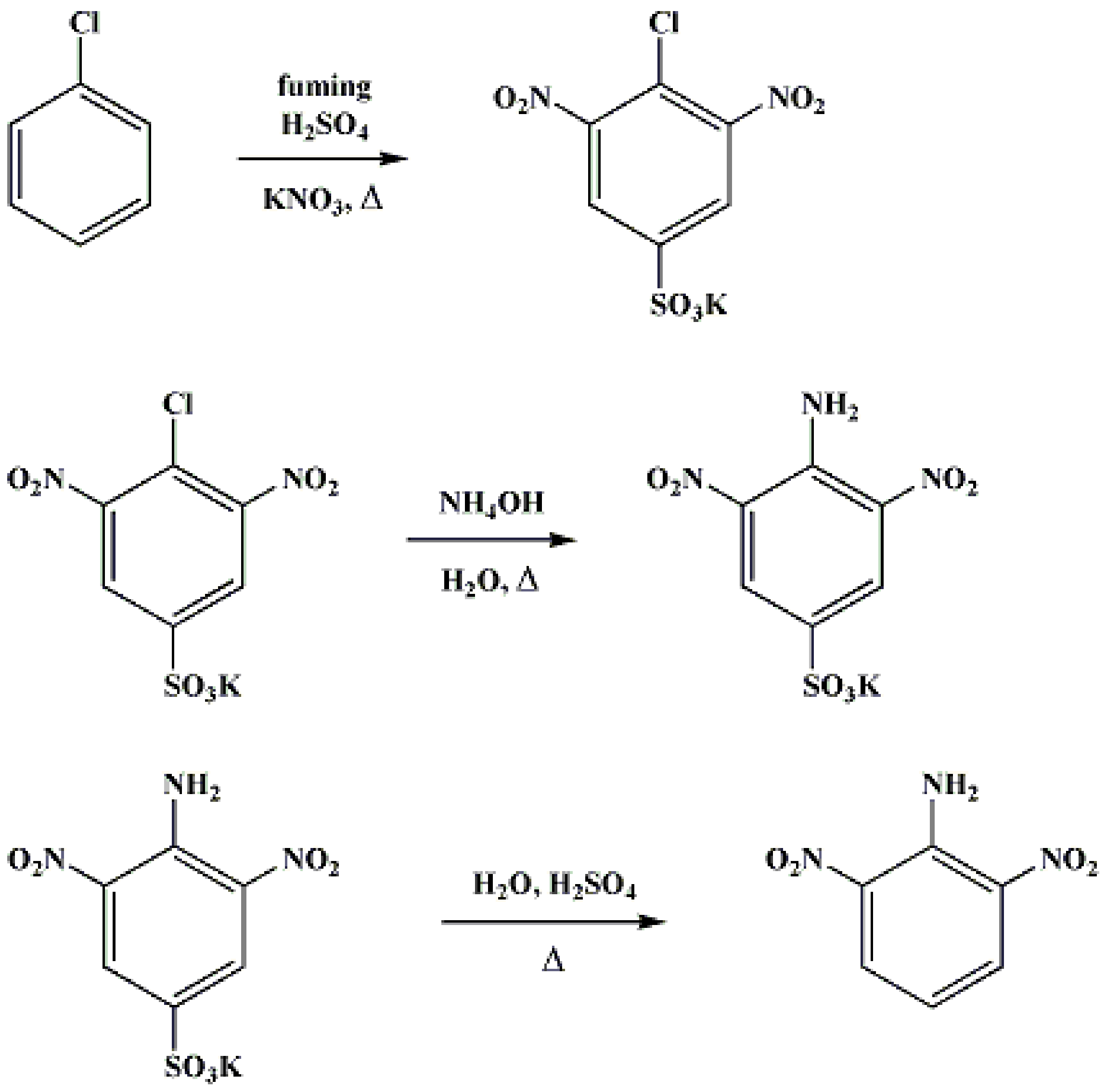
2,6-DINITROANILINE

[Aniline, 2,6-dinitro-]



Submitted by Harry P. Schultz[1]
Checked by Arthur C. Cope and Douglas S. Smith.

1. Procedure

In a 1-l. round-bottomed flask fitted with a mechanical stirrer are placed 50 ml. (55.4 g., 0.49 mole) of chlorobenzene (Note 1), 300 ml. of concentrated sulfuric acid (sp. gr. 1.84), and 50 ml. (92 g.) of fuming sulfuric acid (containing approximately 25% free sulfur trioxide). The mixture is stirred and heated on a steam bath for 2 hours and then cooled to room temperature. The stirrer is removed from the reaction flask and replaced with a thermometer. To the clear solution is added 170 g. (1.68 moles) of potassium nitrate in 4 portions. The temperature of the mixture during this time is held

at 40–60° by cooling the flask and its contents in ice water. After the mixture has been swirled briefly in the reaction flask to dissolve most of the potassium nitrate, it is heated to 110–115° (Note 2) and held at that temperature for 20 hours. The hot contents of the flask are poured onto 2 kg. of cracked ice. After the ice has melted, the yellow precipitate is filtered with suction and pressed as dry as possible.

Without further drying, the potassium 4-chloro-3,5-dinitrobenzenesulfonate is recrystallized from 600 ml. of boiling water (Note 3). Insoluble material is removed by decantation and filtration of the hot solution. The solution is cooled to 5–10° for 12 hours, and the crystalline potassium salt is collected on a suction filter, pressed as dry as possible, and placed at once in a solution of 400 ml. of concentrated ammonium hydroxide (sp. gr. 0.90) in 400 ml. of water. The solution is boiled for 1 hour under a reflux condenser which has been connected to a gas absorption trap,[2] and then is cooled at 5–10° for 12 hours. The orange, crystalline potassium 4-amino-3,5-dinitrobenzenesulfonate is filtered with suction and pressed as dry as possible on a 10-cm. Büchner funnel.

The damp salt is placed in a solution of 200 ml. of concentrated sulfuric acid (sp. gr. 1.84) and 200 ml. of water in a 1-l. round-bottomed flask, and the mixture is boiled vigorously under reflux for 6 hours (Note 4). The hot acid solution is poured onto 1 kg. of cracked ice, filtered on a 7.5-cm. Büchner funnel, slurried twice with 100-ml. portions of water, and pressed as dry as possible on the funnel. The damp, impure 2,6-dinitroaniline is dissolved in 500 ml. of hot 95% ethanol, and the solution is boiled under reflux for 10 minutes with 3 g. of Norit and 3 g. of filter aid. The hot ethanol solution is filtered through a heated funnel (Note 5) and cooled slowly to room temperature. Light-orange needles of 2,6-dinitroaniline separate and are collected on a suction filter and air-dried. The yield is 27.4–32.3 g. (30–36%) (Note 6), m.p. 139–140°.

2. Notes

1. The best grade of Eastman Kodak Company chlorobenzene was used.
2. Since the reaction is moderately exothermic during the first 4 hours, the temperature of the reaction mixture must be controlled carefully. A gas trap[2] may be used to absorb the small amount of nitrogen dioxide evolved, or the reaction may be carried out in a hood. Excessive fuming is avoided if the temperature is kept in the range 110–115°.
3. If the potassium 4-chloro-3,5-dinitrobenzenesulfonate is not recrystallized before ammonolysis very impure 2,6-dinitroaniline is obtained.
4. The condenser should be cleared occasionally with a small glass rod to remove the 2,6-dinitroaniline that may collect there.
5. The funnel must be heated to avoid crystallization during filtration.
6. The solubility of pure 2,6-dinitroaniline in 95% ethanol at room temperature is about 0.4 g. per 100 ml.

3. Discussion

2,6-Dinitroaniline has been prepared by the ammonolysis of 2,6-dinitroanisole,[3] 2,6-dinitroiodobenzene,[4] 2,6-dinitrophenyl 4-nitrobenzyl ether,[5] and 2,6-dinitrochlorobenzene;[6] by the rearrangement of *o*-nitrophenylnitramine;[7] and by the desulfonation of potassium 4-amino-3,5-dinitrobenzenesulfonate.[8,9,10] The method described above is based on the procedures of Ullmann[8] and Welsh.[9]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 160

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

sulfuric acid (7664-93-9)

sulfur trioxide (7446-11-9)

Norit (7782-42-5)

chlorobenzene (108-90-7)

nitrogen dioxide (10102-44-0)

ammonium hydroxide (1336-21-6)

potassium (7440-09-7)

potassium nitrate (7757-79-1)

2,6-dinitrochlorobenzene (606-21-3)

2,6-Dinitroaniline, Aniline, 2,6-dinitro- (606-22-4)

potassium 4-chloro-3,5-dinitrobenzenesulfonate

potassium 4-amino-3,5-dinitrobenzenesulfonate

2,6-dinitroanisole

2,6-dinitroiodobenzene

2,6-dinitrophenyl 4-nitrobenzyl ether

o-nitrophenylnitramine

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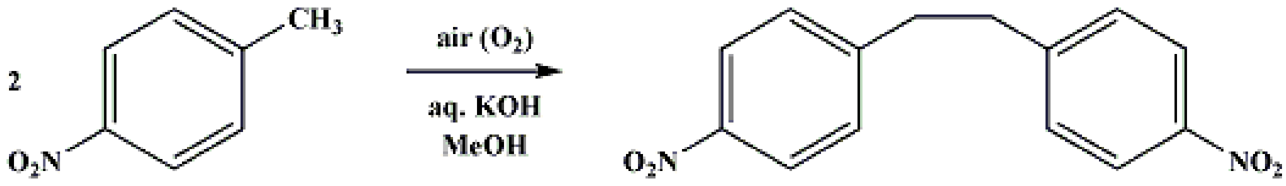
p,p'-DINITROBIBENZYL

[Bibenzyl, 4,4'-dinitro-]



Submitted by Herbert O. House[1]
Checked by John C. Sheehan and J. Iannicelli.

1. Procedure

In a 3-l. three-necked flask equipped with a mechanical stirrer and an inlet tube extending to the bottom of the flask is placed 2 l. of 30% methanolic potassium hydroxide (Note 1). The flask is immersed in an ice bath, and, when the solution has cooled to 10°, 100 g. (0.73 mole) of *p*-nitrotoluene (Note 2) is added to the flask. Vigorous stirring is begun, and a rapid stream of air from a compressed-air source is passed through the inlet tube. After 3 hours the ice bath is removed and the passage of air through the mixture is continued with uninterrupted, vigorous stirring for an additional 5 hours. The reaction mixture is immediately filtered with suction (Note 3), and the solid, while still on the filter, is washed with 2 l. of boiling water followed by 300 ml. of 95% ethanol at room temperature. The product is allowed to dry thoroughly in air and then is dissolved in a minimum quantity of boiling benzene (Note 4). The hot solution is filtered to remove a small amount of insoluble red-orange material and is allowed to cool. The *p,p*'-dinitrobibenzyl crystallizes as orange needles, m.p. 178–180°. The yield is 73–75 g. (74–76%). A second recrystallization from benzene gives yellow needles, m.p. 179–180°.

2. Notes

1. Thirty per cent methanolic potassium hydroxide may be prepared by dissolving 680 g. of C.P. (minimum 85%) potassium hydroxide pellets in 2 l. of methanol.
2. A good grade of *p*-nitrotoluene, m.p. 51–52°, such as supplied by the Eastman Kodak Company, was used.
3. A double layer of ordinary filter paper is satisfactory for this filtration.
4. Two to three liters of benzene is required. The checkers found the use of a heated funnel to be advantageous.

3. Discussion

p,p'-Dinitrobibenzyl has been prepared by the nitration of bibenzyl;[2] by the action of alkaline zinc chloride on *p*-nitrobenzyl chloride;[3] by the action of alkali on *p*-nitrotoluene;[4] by the oxidation of α,α-bis(*p*-nitrobenzyl) hydrazine with mercuric oxide;[5] and by the present method.[6] The course of the oxygen absorption in the latter reaction has been followed kinetically.[7]

References and Notes

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7. Tsuruta, Nagatomi, and Furukawa, *Bull. Inst. Chem. Research*, *Kyoto Univ.*, **30**, 46 (1952) [*C. A.*, **48**, 11369 (1954)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

methanolic potassium hydroxide

α,α-bis(p-nitrobenzyl) hydrazine

ethanol (64-17-5)

Benzene (71-43-2)

methanol (67-56-1)

oxygen (7782-44-7)

mercuric oxide (21908-53-2)

potassium hydroxide (1310-58-3)

zinc chloride (7646-85-7)

bibenzyl (103-29-7)

p-nitrotoluene (99-99-0)

p-nitrobenzyl chloride (100-14-1)

p,p'-DINITROBIBENZYL, Bibenzyl, 4,4'-dinitro- (736-30-1)

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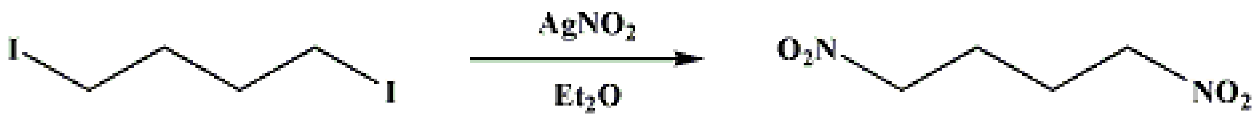
Organic Syntheses, CV 4, 368

1,4-DINITROBUTANE

[Butane, 1,4-dinitro-]



Submitted by Henry Feuer and Gerd Leston[1].
Checked by John C. Sheehan and J. Iannicelli.

1. Procedure

The reaction is carried out in 1-l. three-necked round-bottomed flask fitted with a ball-sealed mechanical stirrer, a reflux condenser, and a dropping funnel. The openings of the condenser and dropping funnel are protected from moisture by drying tubes. In the flask, which is protected from light (Note 1), are placed 170 g. (1.1 moles) of silver nitrite and 300 ml. of absolute ether. The silver nitrite is suspended by vigorous stirring, and the mixture is cooled to 0° by an ice bath. Then 155 g. (0.5 mole) of 1,4-diiodobutane (p.321) is added dropwise over a period of 3 hours. The temperature is maintained at 0° for an additional 2 hours, and then the reaction mixture is allowed to come slowly to room temperature (25°) by permitting the ice in the cooling bath to melt (Note 2). Twenty-four hours after the addition of the diiodobutane has been completed, the solution is tested for unreacted iodide (Note 3). If the test is negative, the mixture is filtered and the silver iodide washed with a total of 200 ml. of benzene (Note 4). The ethereal solution and the benzene washings are combined, and the solvents are distilled on a steam bath, the pressure being reduced (water aspirator) toward the end of the distillation.

In a 500-ml. three-necked flask equipped with a mechanical stirrer, a dropping funnel, and a thermometer is placed 200 ml. of concentrated sulfuric acid. The flask is immersed in an ice-salt bath, and the acid is cooled to 0–5°. The crude dinitrobutane is added dropwise with vigorous stirring at such a rate that the temperature does not exceed 8°. Stirring is continued for an additional 10 minutes after completion of the addition. The solution is poured cautiously onto 1 kg. of crushed ice with manual stirring. The ice is allowed to melt, and the product is separated by suction filtration, washed with water, and air-dried. Recrystallization from methanol at –70°, using a Dry Ice-methylene chloride cooling bath, yields 30–34 g. (41–46%) of 1,4-dinitrobutane, m.p. 33–34° (Note 5), (Note 6), (Note 7), and (Note 8).

2. Notes

1. All light should be excluded. It is most convenient to run the reaction in a dark room.

2. The cooling bath should not be removed, or the temperature of the mixture will rise above room temperature.
3. The Beilstein test is carried out in the following manner: A copper wire is cleaned in the flame of Bunsen burner and allowed to cool. The stirring is stopped, and the wire is inserted carefully into the clear ether solution so as not to touch the silver iodide at the opening and at the bottom of the flask. The wire is withdrawn and held in the reducing part of the flame. A green color constitutes a positive test, and stirring is resumed until the test is negative.
4. An alternative method of purification is to wash the silver iodide with 250 ml. of methanol instead of benzene. The ether is evaporated, and the residue is combined with the methanol solution. The product is crystallized at −70°. Recrystallization of this crude product from methanol at −70° gives the same yields as the other method of purification.
5. The methanol solution may be treated with charcoal if a colorless product is not obtained.
6. Starting with 169 g. of 1,6-diiodohexane (p.323), 1,6-dinitrohexane may similarly be obtained in 46–48% yield, m.p. 36.5–37.5°. The alternative procedure of isolation described in Note 4 may also be used.
7. 1,3-Dinitropropane may be prepared in a similar manner starting with 148 g. of 1,3-diiodopropane (supplied by the Eastman Kodak Company and by the Eastern Chemical Corporation). However, the dinitro compound is a liquid and has to be purified in the following manner: The crude 1,3-dinitropropane is extracted from the aqueous acid layer with four 150-ml. portions of benzene. The benzene is removed by distillation at atmospheric pressure, and the residue is distilled from a 50-ml. Claisen flask, b.p. 108–110°/1 mm., n_D^{20} 1.465. The yield is 24–25 g. (36–37%). It is colorless during the distillation but rapidly turns yellow on storage. If the aqueous layer is extracted continuously with benzene or ether for 24 hours an additional 3 g. of product may be obtained.
8. 1,5-Dinitropentane may be prepared in a similar manner starting with 162 g. of 1,5-diiodopentane prepared from tetrahydropyran according to the directions for 1,4-diiodobutane (p.321). The dinitro compound is a liquid and is obtained by extracting the aqueous acid layer with three 125-ml. portions of benzene. The benzene is removed by distillation at atmospheric pressure, and the residue is distilled from a 50-ml. Claisen flask. The fraction, b.p. 134°/1.2 mm., amounts to 36.6 g. (45% yield), n_D^{20} 1.461. The distillate is colorless but rapidly turns yellow.

3. Discussion

1,3-Dinitropropane,[2,3] 1,4-dinitrobutane,[4,5] 1,5-dinitropentane,[4,5] and 1,6-dinitrohexane[5] have been prepared by the method described here, which is that of Victor Meyer. 1,4-Dinitrobutane also has been obtained by the hydrolysis of dipotassium α,α'-dinitroadiponitrile.[6]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

dipotassium α,α'-dinitroadiponitrile

sulfuric acid (7664-93-9)

Benzene (71-43-2)

methanol (67-56-1)

ether (60-29-7)

charcoal (7782-42-5)

Tetrahydropyran (142-68-7)

silver nitrite (7783-99-5)

1,6-Diiodohexane (629-09-4)

1,3-diiodopropane (627-31-6)

1,4-Diiodobutane (628-21-7)

1,4-Dinitrobutane, Butane, 1,4-dinitro- (4286-49-1)

diiodobutane

silver iodide (7783-96-2)

dinitrobutane

1,6-dinitrohexane

1,3-Dinitropropane (6125-21-9)

1,5-Dinitropentane (6848-84-6)

1,5-diiodopentane (628-77-3)

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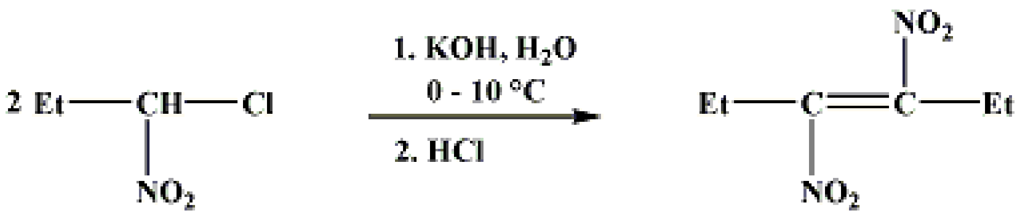
Organic Syntheses, CV 4, 372

3,4-DINITRO-3-HEXENE

[3-Hexene, 3,4-dinitro-]



Submitted by D. E. Bisgrove, J. F. Brown, Jr., and L. B. Clapp[1].
Checked by John C. Sheehan, Richard L. Wasson, and Herbert O. House.

1. Procedure

This procedure involves the possibility of an explosion and therefore must be conducted with caution.

In a 1-l. three-necked flask equipped with a mechanical stirrer, a thermometer, and a dropping funnel, and cooled externally with an ice-salt bath, is placed a solution of 118 g. (1.8 moles) of U.S.P. 85% potassium hydroxide (Note 1) in 300 ml. of water. The temperature of the solution is maintained between 0° and 10° (with the addition of ice to the flask if necessary) while 247 g. (205 ml., 2.0 moles) of 1-chloro-1-nitropropane (Note 2) is added from a dropping funnel over a 20-minute period. The cooling bath is removed, and concentrated hydrochloric acid is added dropwise (Note 1) until the momentary green coloration produced by the addition of each drop of acid spreads rapidly throughout the solution (near a pH of 9). The temperature of the solution rises to about 70° with the separation of a deep-green oily layer. Stirring is continued until the reaction mixture reaches room temperature (about 3 hours).

After the green oil has been separated, it is washed with 75 ml. of a warm *(Caution! (Note 3))* 20% solution of potassium hydroxide in water to remove, as its potassium salt, the 1,1-dinitropropane formed as a by-product. The remaining 100–110 g. of oil is diluted with 90 ml. of 95% ethanol, and the green solution is cooled in an ice-salt bath to –5° to –10°. The crystalline product is collected on a cold (Note 4) 5.5-cm. Büchner funnel and washed with two 5-ml. portions of ice-cold alcohol. The yield is 50 g. of impure crystals.

Distillation of the alcoholic filtrate *(Caution! (Note 5))* under reduced pressure and in an atmosphere of nitrogen permits the isolation of an additional 8–10 g. of 3,4-dinitro-3-hexene. The blue oil boiling below 75°/20 mm. is discarded. To the undistilled residue is added 25 ml. of 95% ethanol, the resulting solution is cooled in an ice-salt bath, and the crystals are collected on a cold Büchner funnel and washed with 5 ml. of ice-cold alcohol. The combined crops of crystals are recrystallized from 80 ml. of 95%

ethanol. The pure 3,4-dinitro-3-hexene separates as light-yellow needles, m.p. 31–32°, weight 50–55 g. (29–32%) (Note 6).

2. Notes

1. Although slightly less than an equivalent amount of potassium hydroxide is used, the last of the 1-chloro-1-nitropropane dissolves slowly, and the pH drops sufficiently to allow rapid reaction only after a variable (usually about 3 hours) period of standing. The reaction may also be started by heating one spot on the container with a jet of steam, but it is more convenient and reliable to initiate reaction by cautious addition of acid in the manner described.
2. The 1-chloro-1-nitropropane used was the commercial grade obtained from Commercial Solvents Corporation. The yield was unchanged when a distilled sample, b.p. 143°, was used.
3. *The temperature of the potassium hydroxide solution should not be above 35° when used.* The submitters report the isolation of 15–20 g. (9–12%) of potassium 1-nitropropylnitronate from the cooled extract. The checkers, having been advised that *this product is a hazardous explosive*, discarded the warm alkaline extract. If 1,1-dinitropropane is not desired (its preparation has been described[2]), it is recommended that it be extracted as its more soluble sodium salt by washing the green oil with sodium hydroxide solution rather than potassium hydroxide solution.
4. It is necessary to keep the Büchner funnel cold since the crystals melt near room temperature. An external cooling jacket for the funnel can be fabricated from a metal can by cutting a hole in the bottom of the can of such size that it fits high enough on a rubber stopper to allow a tight fit between the rubber stopper and the suction flask. The cooling jacket is filled with crushed Dry Ice. The checkers employed a 60-mm. sintered glass funnel surrounded by a 400-ml. beaker, in the bottom of which was a hole large enough to accommodate a No.3 rubber stopper surrounding the stem of the funnel.
5. *Distillation behind safety glass in a nitrogen atmosphere appears advisable in view of the nature of polynitro compounds* although the submitters have not had an explosion in the preparation of 3,4-dinitro-3-hexene.
6. 2,3-Dinitro-2-butene may be prepared from 1-chloro-1-nitroethane by the same procedure, in 30% yield. The compound melts at 28–28.5° and has a boiling point of 135°/11 mm. Commercially available 1-chloro-1-nitroethane contains about 10% 1,1-dichloro-1-nitroethane and 2-chloro-2-nitropropane which cannot be separated by distillation, but these impurities do not interfere with the preparation. *Distillation of 2,3-dinitro-2-butene behind safety glass in a nitrogen atmosphere is advisable.* The submitters, in preparing this compound, have had one explosion over a period of ten years.

3. Discussion

The action of a sodium bicarbonate solution or a 10% sodium hydroxide solution on 1-

chloro-1-nitropropane will produce 3,4-dinitro-3-hexene. The procedure described here is a modification of that described by Nygaard and Noland.[3]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

potassium 1-nitropropylnitronate

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

nitrogen (7727-37-9)

potassium hydroxide (1310-58-3)

3,4-Dinitro-3-hexene, 3-Hexene, 3,4-dinitro- (53684-54-1)

1-chloro-1-nitropropane (600-25-9)

1,1-dinitropropane (601-76-3)

2,3-Dinitro-2-butene (24335-44-2)

1-chloro-1-nitroethane (598-92-5)

2-chloro-2-nitropropane (594-71-8)

1,1-dichloro-1-nitroethane (594-72-9)

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Organic Syntheses, CV 4, 375

DIPHENYLACETALDEHYDE

[Acetaldehyde, diphenyl-]

Submitted by Donald J. Reif and Herbert O. House[1].
Checked by M. S. Newman and W. H. Powell.

1. Procedure

In a 1-l. separatory funnel is placed a solution of 39.2 g. (0.2 mole) of *trans*-stilbene oxide (Note 1) in 450 ml. of reagent benzene. To the solution is added 13.2 ml. (0.1 mole) of boron trifluoride etherate (Note 2). The solution is swirled, allowed to stand for 1 minute (Note 3), and then washed with two 300-ml. portions of water. The organic layer is separated, and the benzene is removed by distillation (Note 4). The residual crude aldehyde is purified by distillation under reduced pressure. The product, collected at 115–117°/0.6 mm., amounts to 29–32 g. (74–82%), n_D^{25} 1.5875–1.5877 (Note 5).

2. Notes

1. The *trans*-stilbene oxide (p.860) should be free of *trans*-stilbene, since the stilbene, if present, is not altered by the reaction conditions and will contaminate the final product.
2. A practical grade of boron trifluoride etherate, purchased from Eastman Kodak Company, was redistilled before use. The pure etherate boils at 126°.
3. Longer reaction times result in a marked decrease in the yield of diphenylacetaldehyde.
4. The submitters found that distillation of the benzene solution is necessary to obtain an anhydrous product. If the benzene solution is dried over magnesium sulfate and the benzene removed under reduced pressure, the diphenylacetaldehyde is contaminated with water.
5. The product obtained by this procedure, when treated with 2,4-dinitrophenylhydrazine,[2] produced the 2,4-dinitrophenylhydrazone of diphenylacetaldehyde, m.p. 146.8–147.8°, in 94% yield.

3. Discussion

Diphenylacetaldehyde has been prepared by the isomerization of 1,2-dihydroxy-1,2-diphenylethane either thermally[3] or in the presence of sulfuric acid,[4,5,6] oxalic acid,[7] or acetic anhydride.[8] The aldehyde has also been produced by the reaction of 2,2-dipheny1-2-hydroxyethyl ether with sulfuric acid[6,7] or oxalic acid;[7,9] by the reaction of hydrochloric acid with 2-amino-1,1-diphenylethanol;[10] by the reaction of hydrobromic[11] or hydrochloric[12] acid with 2-diethylamino-1,1-diphenylethanol; by the hydrolysis of β,β-diphenylvinyl ethyl ether;[13] by the thermal rearrangement of deoxybenzion;[14] by the hydrolysis and decarboxylation of the glycidic ester obtained from ethyl chloroacetate and benzophenone;[15] by passing a mixture of diphenylacetic and formic acid over thorium oxide on pumice at 450°;[16] and by the hydrolysis of diphenylacetaldehyde enol methyl ether (obtained from benzophenone and methoxymethylenetriphenylphosphorane).[17]

Diphenylactaldehyde also has been prepared by the isomerization of *trans*-stilbene oxide in the presence of sodium bisulfite[18] or lithium diethylamide,[19] or by the isomerization of either *cis*- or *trans*-stilbene oxide in the presence of boron trifluride etherate.[2] The procedure chosen illustrates the ready isomerization of substituted ethylene oxides to carbonyl compounds. The procedure is applicable to substituted epoxides in which one of the carbon atoms of the oxirane ring is bonded either to two other carbon atoms or to an aromatic nucleus or a carbon-carbon double bond.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 1028

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

2,4-dinitrophenylhydrazone

2,2-dipheny1-2-hydroxyethyl ether

deoxybenzion

diphenylacetic and formic acid

pumice

diphenylacetaldehyde enol methyl ether

Diphenylactaldehyde

cis- or trans-stilbene oxide

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

acetic anhydride (108-24-7)

Oxalic acid (144-62-7)

sodium bisulfite (7631-90-5)

thorium oxide

carbon (7782-42-5)

Benzophenone (119-61-9)

oxirane (75-21-8)

ethylene (9002-88-4)

Ethyl chloroacetate (105-39-5)

magnesium sulfate (7487-88-9)

2,4-Dinitrophenylhydrazine (119-26-6)

stilbene

Diphenylacetaldehyde, Acetaldehyde, diphenyl- (947-91-1)

boron trifluoride etherate, boron trifluride etherate (109-63-7)

1,2-dihydroxy-1,2-diphenylethane

2-amino-1,1-diphenylethanol

2-diethylamino-1,1-diphenylethanol

β,β-diphenylvinyl ethyl ether

methoxymethylenetriphenylphosphorane

lithium diethylamide

carbon-carbon

trans-Stilbene oxide (1439-07-2)

trans-Stilbene (103-30-0)

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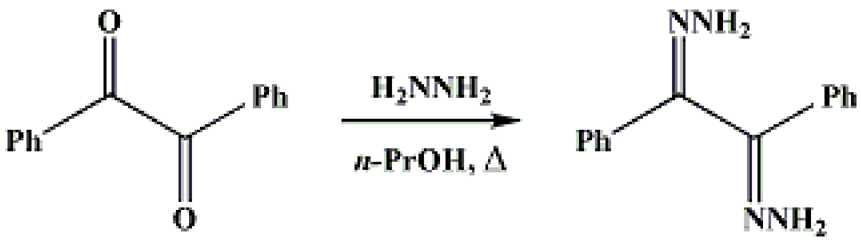
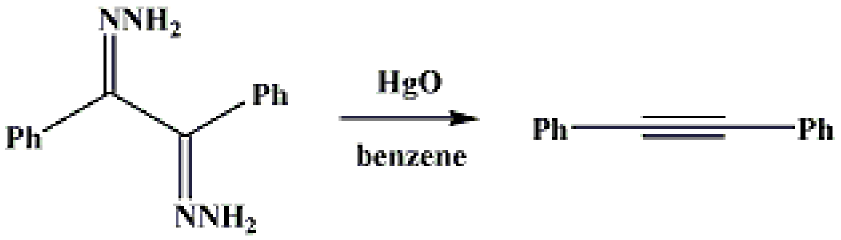
Organic Syntheses, CV 4, 377

DIPHENYLACETYLENE

[Acetylene, diphenyl-]





Submitted by Arthur C. Cope, Douglas S. Smith, and Robert J. Cotter[1].
Checked by Charles C. Price and Thomas F. McKeon, Jr..

1. Procedure

A solution of 105.1 g. (0.5 mole) of benzil (Note 1) in 325 ml. of *n*-propyl alcohol is prepared in a 1-l. round-bottomed flask which is fitted with an efficient reflux condenser. To this solution 76 g. (1.30 moles) of 85% hydrazine hydrate (Note 2) is added, and the mixture (Note 2) is heated under reflux for 60 hours. The solution is cooled with an ice bath, and the benzil dihydrazone is separated by suction filtration. The crystals are washed with 200 ml. of cold, absolute ethanol and dried (Note 3) on the suction filter for 1 hour. The yield of benzil dihydrazone is 99–106 g. (83–89%), m. p. 150–151.5°.

The benzil dihydrazone is added to 480 ml. of reagent grade benzene in a 1-l. three-necked flask fitted with a reflux condenser and a sealed stirrer. A small amount of yellow mercuric oxide (2–4 g.) is added to the mixture with stirring to keep the benzil dihydrazone suspended, and the mixture is warmed slightly on a steam bath. Nitrogen is evolved, and the mixture turns gray. Additional yellow mercuric oxide is then introduced in small portions so as to keep the reaction mixture gently refluxing until a total of 240 g. (1.11 moles) has been added. The mixture is stirred for 1 hour and allowed to stand overnight. It is then filtered, and the residue (mercury and mercuric oxide) is washed with 100 ml. of benzene, which is combined with the original red benzene is filtrate. After drying over anhydrous sodium sulfate, the benzene is removed by distillation under reduced pressure by heating with a water bath. The

residue is distilled from a flask connected to a short distillation head at 95–105°/0.2–0.3 mm. and yields 60–65 g. (67–73% from benzil) of diphenylacetylene, m.p. 59–60°. The product can be recrystallized from 100 ml. of 95% ethanol, m.p. 60–61° (Note 4).

2. Notes

1. Eastman Kodak Company white label grade benzil or material prepared by the procedure described in *Organic Syntheses*[2] is satisfactory.
2. Hydrazine hydrate (85%) as supplied by the Edwal Laboratories was used. On addition of this reagent to the benzil solution, the monohydrazone of benzil precipitates, but it redissolves readily on heating.
3. Benzil dihydrazone should not be dried in a vacuum desiccator, for it sublimes easily.
4. Diphenylacetylene prepared by this method has the advantage of being uncontaminated with stilbene, with which it forms a solid solution not readily separable.[3] Di-*p*-tolylacetylene[4] and α-naphthylphenlacetylene[5] have been prepared by the same method in high yields.

3. Discussion

In addition to the methods mentioned in a previous preparation,[6] diphenylacetylene has been prepared by the action of potassium hydroxide on 5,5-diphenyl-3-nitroso-2-oxazolidone (100%),[7] on *meso*-stilbene dibromide in triethylene glycol,[8] and on stilbene tetrabromide in butyl alcohol;[9] by the condensation of bromobenzene with sodium phenylacetylide in liquid ammonia,[10] by the oxidation of benzil dihydrazone with silver trifluorocetate in triethylamine,[11] and by the pyrolysis of α-benzoylbenzylidenetriphenylphosphorane.[12] The present procedure is a modification of that of Schlenk and Bergmann.[13]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 531

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

monohydrazone of benzil

α-naphthylphenlacetylene

ethanol (64-17-5)

ammonia (7664-41-7)

Benzene (71-43-2)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

mercury (7439-97-6)

mercuric oxide (21908-53-2)

butyl alcohol (71-36-3)

Benzil (134-81-6)

potassium hydroxide (1310-58-3)

bromobenzene (108-86-1)

n-propyl alcohol (71-23-8)

hydrazine hydrate (7803-57-8)

sodium phenylacetylide

stilbene

Diphenylacetylene, Acetylene, diphenyl- (501-65-5)

triethylamine (121-44-8)

Benzil dihydrazone (4702-78-7)

5,5-diphenyl-3-nitroso-2-oxazolidone

triethylene glycol (112-27-6)

stilbene tetrabromide

silver trifluorocetate

α-benzoylbenzylidenetriphenylphosphorane

Di-p-tolylacetylene

meso-stilbene dibromide

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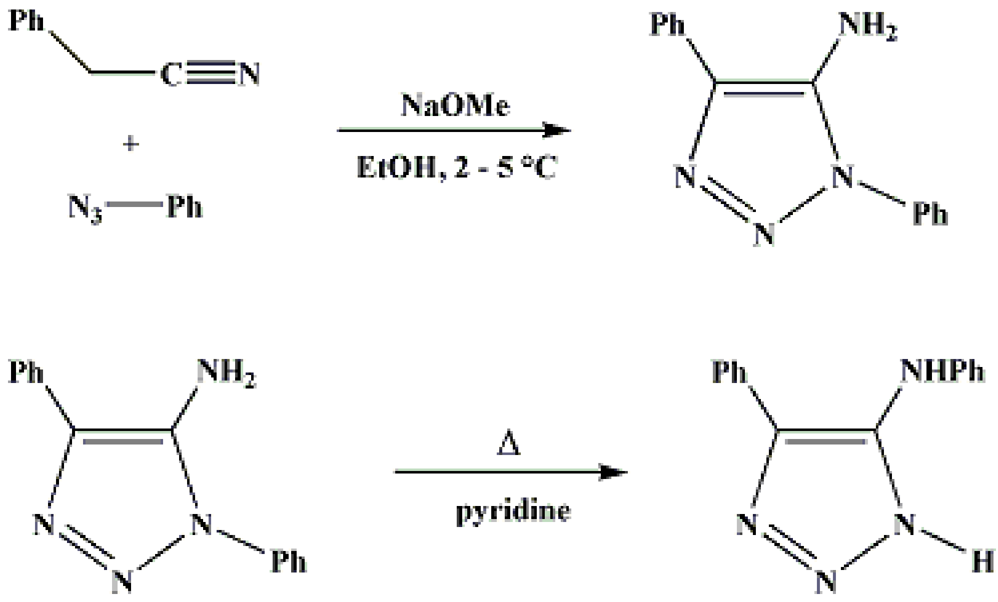
Organic Syntheses, *CV 4*, 380

1,4-DIPHENYL-5-AMINO-1,2,3-TRIAZOLE AND 4-PHENYL-5-ANILINO-1,2,3-TRIAZOLE

[1H-1,2,3-Triazole, 5-amino-1,4-diphenyl-]

[1H-1,2,3-Triazole, 4-phenyl-5-(phenylamino)-]



Submitted by Eugene Lieber, Tai Siang Chao, and C. N. Ramachandra Rao[1].
Checked by T. L. Cairns and E. L. Martin.

1. Procedure

A. *1,4-Diphenyl-5-amino-1,2,3-triazole.* A 500-ml. three-necked flask is equipped with a sealed stirrer, a thermometer well, and a dropping funnel which is protected by a drying tube and has a pressure-equalizing side arm. A mixture of 35.7 g. (0.3 mole) of phenyl azide (Note 1) and 38.6 g. (0.33 mole) of phenylacetonitrile (Note 2) is placed in the flask. The flask is immersed in an ice-water mixture contained in a 1-gal. Thermos flask. After the reaction mixture has cooled to about 2°, a solution of 24.3 g. (0.45 mole) of sodium methoxide (Note 3) in 150 ml. of absolute ethanol is added dropwise during the course of 2 hours. The reaction mixture is then stirred at 2–5° in the ice-water bath for a period of 48 hours (Note 4). After the cooling bath has been removed and the flask allowed to warm spontaneously to room temperature, the mixture is filtered by suction on a sintered glass funnel, and the collected product is washed with three 50-ml. portions of absolute ethanol. The dried product weighs 62–65 g. (88–92%) and consists of white, fine platelike crystals, m.p. 169–171°. Recrystallization from benzene does not alter the melting point (Note 5).

B. *4-Phenyl-5-anilino-1,2,3-triazole.* Six grams (0.025 mole) of 1,4-diphenyl-5-amino-

1,2,3-triazole is dissolved in 20 g. of dry pyridine (distilled from solid sodium hydroxide) and heated under reflux for 24 hours (Note 6). The reaction mixture (Note 7) is poured into 1 l. of ice water. The product separates as a slightly yellowish milky oil which is converted to white needle-like crystals by stirring the mixture and scratching the beaker with a glass rod. The product is collected by suction filtration, washed with water, suction-dried, and recrystallized from aqueous ethanol (Note 8). The yield is 5.5–5.6 g. (92–93%) of fine white needle-like crystals, m.p. 167–169° (Note 9), soluble in hot water and ether, but difficultly soluble in benzene.

2. Notes

1. Prepared by the method of Lindsay and Allen, *Org. Syntheses*, Coll. Vol. **3**, 710 (1955). The phenyl azide used had b.p. 41–43°/5 mm., $n_D^{25.5}$ 1.5567. The boiling point deviates slightly from that given by Lindsay and Allen, namely 49–50°/5 mm.; however, it agrees fairly well with the other value given by these authors, namely 66–68°/21 mm., and with the values of Darapsky,[2] and the vapor pressure determinations by Carothers,[3] as shown by a plot of log p vs. $1/T$.
2. The Eastman product was used without purification.
3. Anhydrous sodium methoxide from Matheson Chemical Corporation was used.
4. The yield and purity of the product, i.e., with respect to decreased content of acidic isomer (4-phenyl-5-anilino-1,2,3-triazole), depends upon maintaining a low temperature throughout the entire reaction.
5. The product is essentially pure. 1,4-Disubstituted-5-amino-1,2,3-triazoles are readily isomerized;[4] accordingly, care must be exercised in the recrystallization of such products from solvents. It has been found by experiment that the best practice, in order to avoid isomerization, is to heat the benzene to boiling before addition of the product for recrystallization. Repeated tests have shown that a single careless recrystallization of the product from benzene can increase the content of acidic isomer by as much as 4%. Polar solvents must be avoided. The purity of the product can be determined[5] by titration in glacial acetic acid, using perchloric acid (in glacial acetic acid) as titrant and methyl violet (0.2 g. of methyl violet in 100 ml. of chlorobenzene) as visual indicator (the first appearance of blue color is taken as the end point).
6. This is more than enough time to allow for the complete irreversible isomerization. The extent of isomerization is checked by removing a small quantity of the reaction mixture, isolating the product by dilution with water, and testing its solubility in dilute potassium hydroxide solution. It should be completely soluble.
7. If any solid material is present, it should be removed by filtration.
8. The acidic isomer can be recrystallized from ethanol without the formation of any of the basic isomer. The checkers used for each gram of product 5 ml. of ethanol and 2.5 ml. of water. After solution of the product, treatment with Darco and filtration, 2.5 ml. of water was added to the hot solution.

9. The purity of the acidic isomer is best determined[5] by titration against sodium methoxide in dimethylformamide, using potentiometric indicator. This test showed the present product to be free of basic isomer.

3. Discussion

The present method is a modification of that first reported by Dimroth.[6] The method of irreversible isomerization in boiling pyridine was first reported by Dimroth[7] for the conversion of 1-phenyl-5-amino-1,2,3-triazole to 5-anilino-1,2,3-triazole.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

methyl violet

ethanol (64-17-5)

acetic acid (64-19-7)

Benzene (71-43-2)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium methoxide (124-41-4)

chlorobenzene (108-90-7)

pyridine (110-86-1)

potassium hydroxide (1310-58-3)

phenylacetonitrile (140-29-4)

dimethylformamide (68-12-2)

PHENYL AZIDE (622-37-7)

1,4-Diphenyl-5-amino-1,2,3-triazole, 1H-1,2,3-Triazole, 5-amino-1,4-diphenyl-

(29704-63-0)

1H-1,2,3-Triazole, 4-phenyl-5-(phenylamino)-, 4-Phenyl-5-anilino-1,2,3-triazole (53684-55-2)

perchloric acid (7601-90-3)

1-phenyl-5-amino-1,2,3-triazole

5-anilino-1,2,3-triazole

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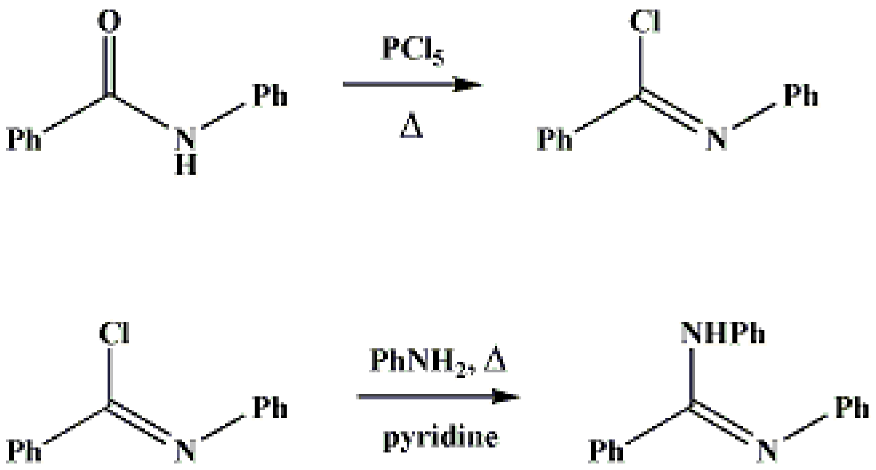
N,N'-DIPHENYLBENZAMIDINE

[Benzamidine, N,N'-diphenyl-]



Submitted by Arthur C. Hontz and E. C. Wagner[1].
Checked by R. S. Schreiber and Wm. Bradley Reid, Jr..

1. Procedure

In a 1-l. three-necked round-bottomed flask (Note 1) are placed 90.0 g. (0.456 mole) of benzanilide[2] (Note 2) previously dried in an oven at 120° (Note 3) and 95 g. (0.456 mole) (Note 4) of phosphorus pentachloride. The solids are mixed by shaking, and lumps are reduced by manipulation with a rod. A short reflux condenser and a small dropping funnel are attached.

The mixture is heated in an electric mantle or oil bath at 110° for 30 minutes and heated under reflux at 160° for 90 minutes or until active evolution of hydrogen chloride ceases (Note 5). To the mixture are added slowly through a dropping funnel first 36.4 g. (0.46 mole) of pyridine (Note 6) previously dried over pellet-form potassium hydroxide, and then 42.4 g. (0.456 mole) of freshly distilled aniline. The contents of the flask are mixed by swirling. The mixture is heated at 160° for about 20 minutes or until the red color is discharged, at which point the flask is removed from the source of heat. The mixture is cooled to about 90°, and 250 ml. of water is added slowly through the dropping funnel with agitation to ensure separation of the solid product in granular form. After the mixture has cooled to room temperature, the solid is collected on a Büchner funnel and air-dried.

The crude diphenylbenzamidine hydrochloride is transferred to a 1-l. beaker and treated with 500 ml. of 28% ammonia water (hood). The mixture is stirred mechanically and warmed very gently for an hour. The diphenylbenzamidine is collected on a Büchner funnel and air-dried. The melting point of the product at this stage is 130–136°.

To purify the product it is recrystallized from 80% ethanol (Note 7), using 8–10 ml. per gram of diphenylbenzamidine. The small insoluble residue of unconverted hydrochloride which may remain (Note 8) is removed by filtering the hot solution. The solution is chilled in an ice-salt bath, and the crystalline product is collected on a Büchner funnel, pressed dry, and finally dried in the air or in an oven at 100°. The yield is 91–100 g. (73–80%) (Note 9) of product having a melting point of 142–144° (Note 10) and (Note 11). Recrystallization of 100 g. of this material from 800 ml. of 80% ethanol gives 87 g. (87% recovery) of pure N,N'-diphenylbenzamidine, m.p. 144–145°.

2. Notes

1. An all-glass apparatus is desirable as cork connections are attacked during formation of the imido chloride. The checkers used mechanical stirring.
2. The benzanilide should be of good quality, or tarry material will form and interfere with purification of the product. Benzanilide is readily made by the Schotten-Baumann procedure from aniline, 10% aqueous sodium hydroxide, and benzoyl chloride in the proportions 6:30:5, and after crystallization from 95% ethanol is sufficiently pure.
3. The use of benzanilide dried by fusion[3] did not improve the yield.
4. The use of one-fourth an equivalent of phosphorus pentachloride, in an attempt to utilize fully the dehydroxylating capacity of both phosphorus pentachloride and the derived phosphorus oxychloride, led to a low yield of diphenylbenzamidine (50%) and to formation of tarry material that interfered with purification. By use of phosphorus oxychloride[4] instead of the pentachloride, a temperature of 170° was required to keep the mixture liquid, tarry material was considerable, and the operation was generally unsatisfactory.
5. Isolation of the imido chloride by distillation under reduced pressure offers no advantage.
6. Pyridine serves to make all the aniline available. It does not prevent combination of hydrogen chloride with the N,N'-diphenylbenzamidine even when two equivalents of pyridine are used. In the presence of pyridine the reaction mixture is a suspension and is easily handled. In the absence of pyridine it solidifies to a cake, which must be pulverized to permit liberation of the amidine from the hydrochloride.
7. A series of tests showed ethanol of 78–82% by weight (sp. gr. 0.8344–0.8442 at 25.5°; 84–87% by volume) to be the best solvent. To dissolve 1.0 g. of N,N'-diphenylbenzamidine at the boiling point required 15.5 ml. of 94% (by weight) ethanol, 7.24 ml. of 80% ethanol, and 11 ml. of 71% ethanol, and the recoveries on chilling were respectively 45%, 73%, and 45%; ten intermediate concentrations of ethanol gave results consistent with these. The solubility of N,N'-diphenylbenzamidine in methanol is greater than in ethanol, but recovery is relatively low.
8. The undissolved residue is unchanged hydrochloride and is usually small. If

considerable it may be re-treated with ammonia and the free base recovered.
9. By chilling to 20° the yield is about 68% of pure material that melts at 144–145°. A second crop of less pure material can be obtained from the mother liquor by concentrating and chilling. By chilling in a Dry Ice-ethanol bath the yield is about 80% but the product is less pure. Admixed tarry material may be removed in large part by extraction with cold ether, in which the tar dissolves readily.
10. The checkers used a Fisher-Johns block.
11. This method is capable of extension to the preparation of other N,N'-disubstituted amidines.[5] In some preparations it may be advantageous to remove phosphorus oxychloride by distillation under reduced pressure before addition of the amine. The method is not wholly satisfactory for preparation of N,N'-diarylformamidines, which are better made by the orthoformic ester method[6] During preparation of diphenylacetamidine considerable gluey material formed by decomposition of the intermediate N-phenylacetimidochloride[7] is an impediment to the isolation of the product.[8] This amidine is better prepared by the method of Sen and Ray.[9]

3. Discussion

N,N'-Diphenylbenzamidine and closely related amidines have been made by several procedures which involve interaction of amines with N-substituted imido chlorides either preformed[10] or formed *in situ* from an acylamine by action of phosphorus trichloride,[11] phosphorus oxychloride,[4] or phosphorus pentachloride.[5] Diphenylbenzamidine is formed from aniline and benzanilidochloroiodide,[12] from aniline and phenyl benzimido ether,[13] and from aniline hydrochloride and N-phenylbenzamidine.[14] It is obtained also from carbanilide and benzoyl chloride,[15] from carbodiphenylimide and phenylmagnesium bromide,[16] from aniline hydrochloride and benzonitrile at 220–240°,[17] and from benzanilide and phenyl isocyanate.[18] Amidines, including diphenylbenzamidine, are obtainable from nitriles by heating with ammonium or amine salts of sulfonic acids,[19] by heating benzotrichloride with amines,[20] and from Schiff bases by action of *tert*-amyl hypochlorite.[21] Good yields are claimed for a patented process using an acylamine, benzenesulfonyl chloride, and amine in the presence of pyridine.[22] The method described is based on the procedures of Wallach[3] and Hill and Cox.[5]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ammonia water

N-phenylacetimidochloride

phenyl benzimido ether

carbodiphenylimide

ethanol (64-17-5)

hydrogen chloride (7647-01-0)

ammonia (7664-41-7)

methanol (67-56-1)

ether (60-29-7)

aniline (62-53-3)

benzonitrile (100-47-0)

sodium hydroxide (1310-73-2)

phosphorus pentachloride (10026-13-8)

aniline hydrochloride (142-04-1)

Benzanilide (93-98-1)

benzoyl chloride (98-88-4)

Benzenesulfonyl chloride (98-09-9)

Phosphorus Oxychloride (21295-50-1)

pyridine (110-86-1)

potassium hydroxide (1310-58-3)

benzotrichloride (98-07-7)

phosphorus trichloride (7719-12-2)

Phenylmagnesium bromide (100-58-3)

Carbanilide (102-07-8)

phenyl isocyanate (103-71-9)

diphenylacetamidine

diphenylbenzamidine hydrochloride

diphenylbenzamidine, N,N'-Diphenylbenzamidine, Benzamidine, N,N'-diphenyl- (2556-46-9)

benzanilidochloroiodide

N-Phenylbenzamidine (1527-91-9)

tert-amyl hypochlorite

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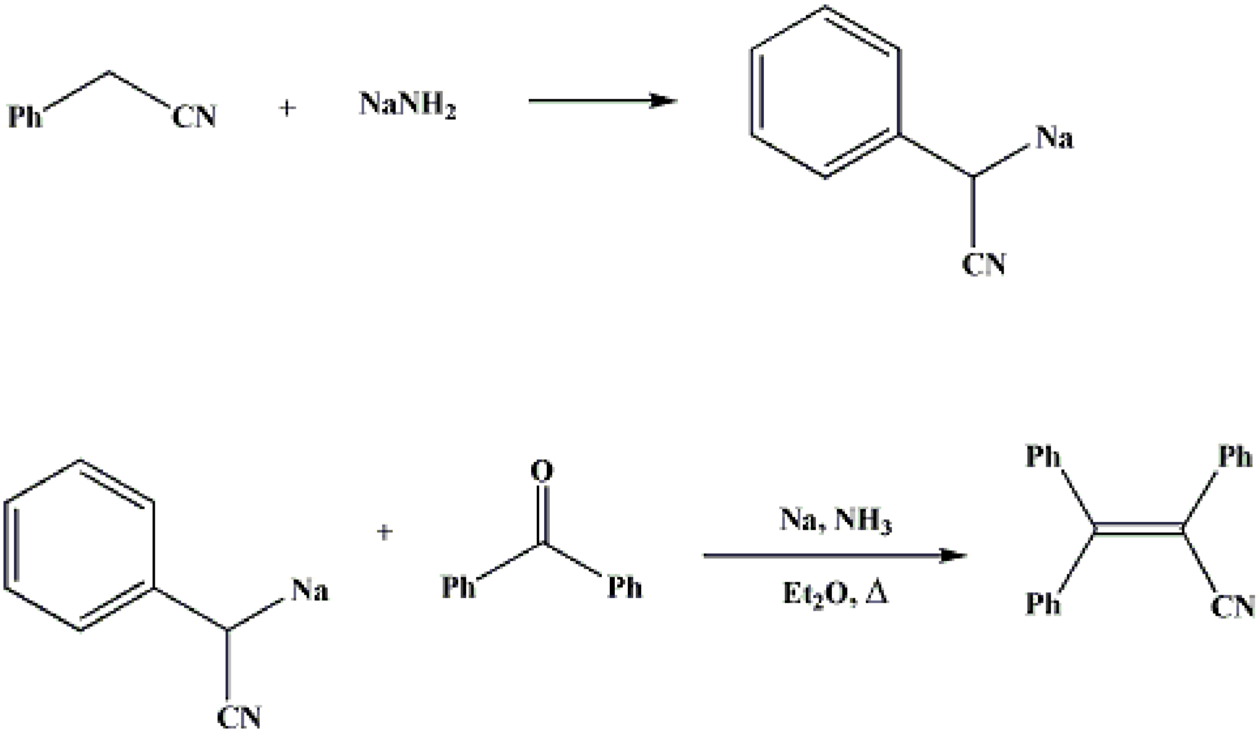
α,β-DIPHENYLCINNAMONITRILE

[Acrylonitrile, 2,3,3-triphenyl-]



Submitted by Stanley Wawzonek and Edwin M. Smolin[1].
Checked by Arthur C. Cope and Malcolm Chamberlain.

1. Procedure

Caution! This preparation should be conducted in a hood to avoid exposure to ammonia.

A solution of sodium amide in liquid ammonia is prepared according to a procedure previously described (Note 1) in a 2-l. three-necked round-bottomed flask fitted with a reflux condenser attached to a soda-lime tower which is connected to a gas absorption trap,[2] a mercury-sealed mechanical stirrer, and an inlet tube. Anhydrous liquid ammonia (350 ml.) is introduced through the inlet tube, and about 0.3 g. of hydrated ferric nitrate and 13.7 g. (0.59 g. atom) of freshly cut sodium are added (Note 1) and (Note 2).

After the conversion of sodium to sodium amide is complete, the inlet tube is replaced with a 500-ml. dropping funnel and the flask is cooled in a bath of Dry Ice and trichloroethylene. Benzyl cyanide (69 g., 0.59 mole) (Note 3) is added dropwise with stirring during about 20 minutes. The cooling bath is removed, and the solution is stirred for an additional period of 20 minutes, after which 700 ml. of dry ether is added slowly through the dropping funnel. The solution is allowed to stand or is warmed gently with a

water bath until it comes to room temperature. The rate of addition of ether and subsequent warming are controlled so that the ammonia which is vaporized passes through the gas absorption trap rather than escaping in part through the mercury seal of the stirrer. When most of the ammonia has been removed, an additional 300-ml. portion of dry ether is added (Note 4). The flask is then heated on a hot water bath. By turning off the cooling water of the reflux condenser for a short time, a small amount of ether is allowed to distil out of the reaction mixture in order to remove as much of the ammonia as possible (Note 5). The condenser water is then turned on again, and dry nitrogen lines under a positive pressure of 2–3 cm. of mercury (maintained by a T-tube dipping into mercury) are attached to the top of the dropping funnel and the reflux condenser. A solution of 200 g. (1.1 moles) of benzophenone (Note 6) and (Note 7) in 300 ml. of dry ether (Note 8) is added through the dropping funnel during a period of 15 minutes, and the mixture is heated under reflux with stirring for 24 hours. At the end of this period the solution contains a reddish brown precipitate. The mixture is allowed to cool, and 250 ml. of water is added slowly through the dropping funnel. The aqueous and ether layers are separated in a 2-l. separatory funnel, and the water layer is filtered directly through a 15-cm. Büchner funnel. The aqueous filtrate is discarded. The ether layer also is run into the funnel, and the filtrate is concentrated to a volume of about 80 ml. The solid that separates is added to the solid previously collected on the filter. The crude reddish brown product is recrystallized from 600 ml. of glacial acetic acid. α,β-Diphenylcinnamonitrile separates as white crystals which are collected on a suction filter, washed with 100 ml. of water, and dried at 110° for 24 hours. The yield of a pure product melting at 166–167° is 83–110 g. (50–66%).

2. Notes

1. The procedures for preparing sodium amide and the sodium derivative of benzyl cyanide are described in *Organic Syntheses.*[3] Another procedure for preparing sodium amide (p.763) is convenient and should be equally satisfactory.
2. If vaporization of ammonia reduces the liquid volume to less than 250 ml. before the conversion of sodium to sodium amide is complete, more ammonia should be added through the inlet tube.
3. The benzyl cyanide used should be washed with warm 50% sulfuric acid to remove benzyl isocyanide[4] and redistilled.
4. Some of the ether is lost through the reflux condenser during vaporization of the ammonia.
5. Traces of ammonia remain in the reaction mixture after this procedure.
6. A smaller excess of benzophenone results in a lowered yield.
7. The benzophenone should be dried by redistillation or storage over phosphorus pentoxide in a vacuum desiccator.
8. The mixture of benzophenone and ether should be warmed gently until the solid dissolves.

3. Discussion

α,β-Diphenylcinnamonitrile has been prepared by the condensation of benzophenone with the sodium[5] or lithium[6] derivative of benzyl cyanide, or from benzophenone, benzyl cyanide, and sodium ethoxide.[7] It has been obtained also by heating benzyl cyanide with benzophenone dichloride at 200°.[8]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium derivative of benzyl cyanide

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

ammonia (7664-41-7)

ether (60-29-7)

nitrogen (7727-37-9)

mercury (7439-97-6)

Benzophenone (119-61-9)

sodium (13966-32-0)

benzophenone dichloride

sodium ethoxide (141-52-6)

Benzyl cyanide (140-29-4)

Benzyl isocyanide (10340-91-7)

sodium amide (7782-92-5)

ferric nitrate

Acrylonitrile, 2,3,3-triphenyl-, α,β-Diphenylcinnamonitrile (6304-33-2)

phosphorus pentoxide (1314-56-3)

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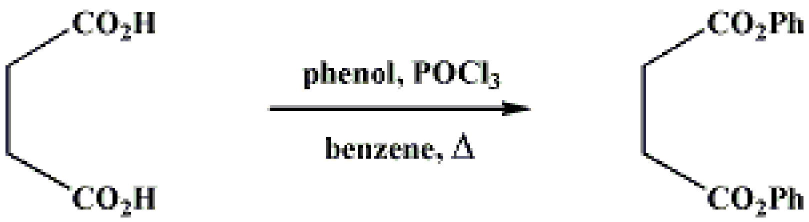
Organic Syntheses, CV 4, 390

DIPHENYL SUCCINATE

[Succinic acid, diphenyl ester]



Submitted by Guido H. Daub and William S. Johnson[1].
Checked by James Cason, Robert A. Wessman, and William G. Dauben.

1. Procedure

A mixture of 118 g. (1 mole) of succinic acid, 188 g. (2 moles) of phenol, and 138 g. (83 ml., 0.9 mole) of phosphorus oxychloride (Note 1) is placed in a 2-l. round-bottomed flask fitted with an efficient reflux condenser capped with a calcium chloride tube (Note 2) and (Note 3). The mixture is heated on a steam bath in a hood (Note 3) for 1.25 hours, 500 ml. of benzene is added, and the refluxing is continued for an additional hour. The hot benzene solution is decanted from the red syrupy residue of phosphoric acid and filtered by gravity into a 1-l. Erlenmeyer flask. The syrupy residue is extracted with two 100-ml. portions of hot benzene, which are also filtered into the Erlenmeyer flask. The combined benzene solutions are concentrated to a volume of about 600 ml. (Note 4), and the pale yellow solution is allowed to cool, whereupon the diphenyl succinate separates as colorless crystals. It is filtered with suction on a Büchner funnel, washed with three 50-ml. portions of ether, and dried on a porous plate at 40°. The yield of diphenyl succinate, m.p. 120–121°, is 167–181 g. (62–67%) (Note 5).

2. Notes

1. The use of a larger proportion of phosphorus oxychloride failed to improve the yield and in general gave an inferior product.
2. Ground-glass joints are preferred; however, burnt-cork stoppers may be used.
3. Provision should be made to dispose of the hydrogen chloride which is evolved during the reaction.
4. If the mother liquor is concentrated further before removal of phenol and phosphorus oxychloride a dark, impure product is obtained.
5. If desired, a second crop may be obtained by the following procedure: The mother liquor is extracted in a 1-l. separatory funnel with eight 50-ml. portions of 5% potassium hydroxide solution. Each extract is extracted in turn with a 50-ml. portion of benzene. The two benzene solutions are washed in turn with a 50-

ml. portion of water and two 50-ml. portions of saturated sodium chloride solution. All the benzene solutions are combined, dried over anhydrous sodium sulfate, filtered, and concentrated to a volume of 150 ml. Cooling yields a second crop of diphenyl succinate, which is collected, washed, and dried as described for the first crop. The yield is 13–27 g. (5–10%), m.p. 118–120°.

3. Discussion

The above procedure is a modification of that described by Rasinski.[2] Diphenyl succinate has also been prepared by the reaction of phenol and succinic acid in the presence of phosphorus pentoxide in toluene[3] and by the treatment of phenol with succinyl chloride.[4]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrogen chloride (7647-01-0)

Benzene (71-43-2)

ether (60-29-7)

phenol (108-95-2)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

Succinic acid (110-15-6)

Phosphorus Oxychloride (21295-50-1)

potassium hydroxide (1310-58-3)

toluene (108-88-3)

phosphoric acid (7664-38-2)

succinyl chloride (543-20-4)

Diphenyl succinate, Succinic acid, diphenyl ester (621-14-7)

phosphorus pentoxide (1314-56-3)

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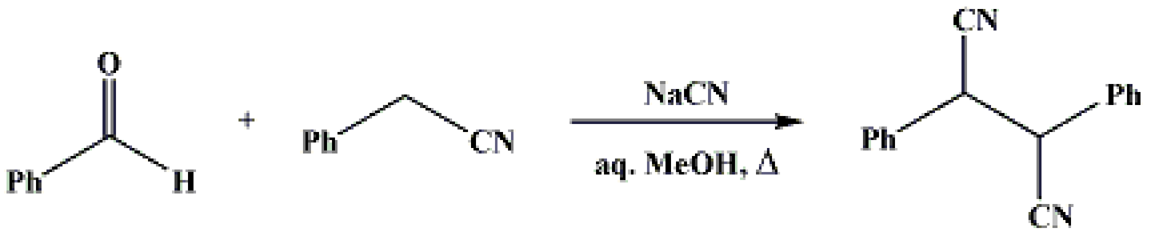
2,3-DIPHENYLSUCCINONITRILE

[Succinonitrile, 2,3-diphenyl-]

[I. METHOD A]



Submitted by R. B. Davis and J. A. Ward, Jr.[1].
Checked by B. C. McKusick and R. L. Morgan.

1. Procedure

Caution! These operations should be conducted in a good hood.

A 1-l. three-necked flask is fitted with a stirrer, a condenser, a dropping funnel, and a heating mantle. Sixty-one grams (1.25 moles) of sodium cyanide and 100 ml. of distilled water are added, and the mixture is warmed with stirring for about 15 minutes while the sodium cyanide dissolves. Then 400 ml. of methanol (Note 1) is introduced, and the mixture is rapidly heated to gentle reflux. Fifty grams (0.42 mole) of benzyl cyanide is added all at once, followed by dropwise addition of a solution of 53 g. (0.50 mole) of benzaldehyde and 30 g. (0.26 mole) of benzyl cyanide (Note 2). The addition requires about 40 minutes, during which time the reaction mixture turns from yellow to green and crystalline 2,3-diphenylsuccinonitrile begins to separate (Note 3). The reaction mixture is stirred at gentle reflux for 30 minutes after the addition is complete. The reaction mixture, now blue in color, becomes brown as it is cooled to room temperature.

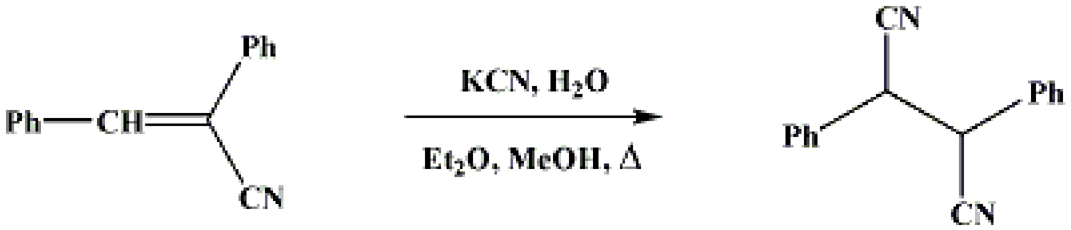
The nitrile is separated from the cooled reaction mixture by suction filtration, washed successively with 150-ml. portions of 75% aqueous methanol, water, 75% aqueous methanol, and ether, and dried in air overnight. It is obtained as a colorless solid that weighs 84–89 g. (72–77%) and melts over a range of 1–2° between 202° and 206° (Note 4). It is the *meso*-isomer of 2,3-diphenylsuccinonitrile mixed with a small amount of the *dl*-isomer. Recrystallization from glacial acetic acid (about 27 ml. per g.), followed by washing with 150-ml. portions of water, 75% aqueous methanol, and ether, yields 79–84 g. (68–72%) of the pure *meso*-isomer, m.p. 238–239° (Note 5).

2. Notes

1. Reagent grade methanol, very low in acetone content, is used; that available

from Rascher and Betzold or Baker is satisfactory.
2. The benzyl cyanide, chlorine-free benzaldehyde, and reagent grade granular sodium cyanide obtainable from Matheson, Coleman and Bell, are satisfactory.
3. Initial precipitation, occurring during the course of the addition, is exothermic. Hence gentle reflux is advised, and the operator should be prepared to remove the heating mantle for a few minutes should the refluxing become vigorous. Early seeding, if seed is available, is helpful in this regard.
4. Prepared mixtures of the isomeric nitriles have been reported to melt over a range of 1–2° between 206° and 221°.[2]
5. The checkers used a calibrated thermometer and observed a melting point of 229–230° for an analytically pure sample which was heated in an open capillary in an oil bath.

[II. METHOD B]



Submitted by J. A. McRae and R. A. B. Bannard[3].
Checked by R. T. Arnold and Stuart W. Fenton.

1. Procedure

Caution! This preparation should be conducted in a good hood.

Two hundred and five grams (1 mole) of α-phenylcinnamonitrile,[4] 2250 ml. of methanol, and 750 ml. of ether are placed in a 5-l. round-bottomed flask fitted with a two-necked adapter supporting a 1-l. separatory funnel and reflux condenser. The α-phenylcinnamonitrile is dissolved by gentle heating, and the solution is heated under reflux. A solution of 274 g. (4 moles) of 95% potassium cyanide in 600 ml. of water (which has been preheated to 45°) is added rapidly from the separatory funnel (Note 1). A small amount of potassium cyanide precipitates. The solution is heated under reflux for 1 hour, after which a solution of 154 g. (2 moles) of ammonium acetate in 250 ml. of water is added rapidly from the separatory funnel (Note 2). Heating is discontinued, and the mixture is allowed to stand for 24 hours. The slightly orange-yellow crystalline product is collected on a Büchner funnel and washed, first with two 300-ml. portions of water at 60° to remove inorganic salts, then with 800 ml. of 70% methanol for removal of water and some unreacted α-phenylcinnamonitrile, and finally with two 300-ml. portions of ether for further drying. The colorless needles thus obtained consist of a mixture of the stereoisomeric α,α'-diphenylsuccinonitriles and, after drying at room temperature for 6 hours, weigh 213–218 g. (92–94%). This mixture of stereoisomers melts over a 1–2° range in the region of 202–206° (Note 3).

The mixed dinitrile can be recrystallized from glacial acetic acid (using 27 ml. per g.) to give pure *meso*-α,α'-diphenylsuccinonitrile. Residual acetic acid is removed readily by washing the crystalline product with small portions of water, aqueous methanol (70%), and ether; yield 95–98% (based on mixed dinitrile); m.p. 240–241.5° (cor.).

2. Notes

1. Care must be exercised to avoid superheating of the solution before addition of the cyanide; otherwise ether and α-phenylcinnamonitrile will be lost through the condenser. Superheating can be avoided by adding a boiling chip periodically as the solution approaches its boiling point. No difficulty with superheating occurs after the cyanide has been added.
2. Addition of the ammonium acetate solution may be omitted; the yield is then 203–208 g. (87.5–89.6%).
3. The mixture of dinitriles has been reported to melt over a 1–2° range in the region of 206–221°.[2] Analysis of a sample of the mixture of dinitriles produced by the present method showed that no impurities are present.

3. Discussion

A mixture of the stereoisomeric 2,3-diphenylsuccinonitriles has been obtained by the interaction of benzyl cyanide, benzal chloride, and potassium cyanide in aqueous ethanolic solutions;[2] by warming α-phenylcinnamonitrile with excess potassium cyanide in aqueous ethanolic solution with,[5] or without,[6,7] subsequent addition of dilute acetic acid; by heating under reflux an aqueous ethanolic solution of α-phenylcinnamonitrile and excess potassium cyanide with subsequent addition of saturated ammonium or magnesium chloride solution;[8] by the action of sunlight on a mixture of benzyl cyanide and benzophenone;[9] and by treatment of benzyl cyanide with sodium methylate and ethereal iodine solution.[10]

In addition, 2,3-diphenylsuccinonitriles have been prepared by treating α-bromo- or α-chlorobenzyl cyanide with sodium iodide in acetone solution,[11] and by the condensation of benzyl cyanide, benzaldehyde, and sodium cyanide.[12] The mixture of stereoisomeric 2,3-diphenylsuccinonitriles has been separated into the *meso* compound and the racemic form.[13]

Method I is more practical than Method II, which had been developed earlier, since it affords 2,3-diphenylsuccinonitrile in a single procedure and in good yields from readily available materials.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

meso-α,α'-diphenylsuccinonitrile

ammonium or magnesium chloride

α-bromo- or α-chlorobenzyl cyanide

acetic acid (64-19-7)

methanol (67-56-1)

ether (60-29-7)

ammonium acetate (631-61-8)

sodium cyanide (143-33-9)

potassium cyanide (151-50-8)

benzaldehyde (100-52-7)

iodine (7553-56-2)

acetone (67-64-1)

sodium methylate (124-41-4)

Benzophenone (119-61-9)

Benzyl cyanide (140-29-4)

sodium iodide (7681-82-5)

benzal chloride (98-87-3)

α-Phenylcinnamonitrile (2510-95-4)

2,3-Diphenylsuccinonitrile, Succinonitrile, 2,3-diphenyl- (5424-86-2)

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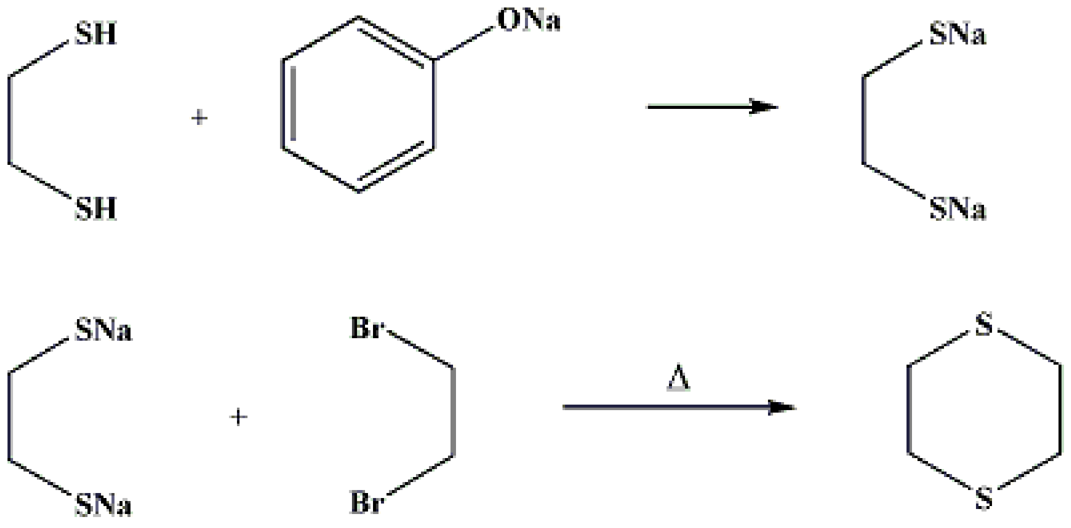
Organic Syntheses, CV 4, 396

p-DITHIANE



Submitted by Richard G. Gillis and A. B. Lacey[1].
Checked by B. C. McKusick and R. J. Harder.

1. Procedure

In a 3-l. round-bottomed flask fitted with a mechanical stirrer and a reflux condenser is placed 2.0 l. of anhydrous ethanol. To this is added 11.5 g. (0.5 g. atom) of sodium cut into small pieces. When the sodium is completely dissolved, 23.6 g. (21.0 ml., 0.25 mole) of 1,2-ethanedithiol (p. 401) is added, followed by 47.0 g. (21.7 ml., 0.25 mole) of ethylene dibromide. The mixture is stirred and heated under reflux for 4 hours, cooled, and filtered to remove some sodium bromide mixed with polyethylene sulfide. The solid is washed with 100 ml. of ethanol, and the combined filtrates are distilled with stirring. When bumping becomes troublesome, as it generally does when 1.3–1.5 l. of distillate has been collected, the hot reaction mixture is filtered to remove sodium bromide, and the sodium bromide is washed with 100 ml. of hot ethanol.

The combined filtrates are returned to the reaction vessel, and distillation with stirring is continued until virtually all the ethanol has been removed. The distillation is stopped when crystals of *p*-dithiane appear in the condenser or when dilution of the distillate with water causes a milky appearance or the formation of a small quantity of crystals. One liter of water is added to the residue, and the stirred mixture is distilled, using the apparatus of f.htmig. 8 (Note 1), until no more *p*-dithiane solidifies in the condenser.

Fig. 8. Apparatus for steam distillation of a solid.

Fig. 8. Apparatus for steam distillation of a solid.

The dithiane is filtered and dried over phosphorus pentoxide or sodium hydroxide in a desiccator at atmospheric pressure. It melts at 112–113° and weighs 16.5–18.1 g. (55–60%).

2. Notes

1. The apparatus illustrated is convenient for the steam distillation of compounds which solidify in the condenser. By having the water condenser vertical, it can easily be cleared with a glass rod. No solidification occurs in the side arm, which behaves as a short air condenser. The adapter shown need not be specially constructed but may be assembled from commercially available components; the dimensions and joint sizes are not critical.

3. Discussion

The procedure described is essentially that of Victor Meyer.[2] *p*-Dithiane has also been obtained from the pyrolysis of the polymer formed by the reaction of ethylene dibromide and potassium sulfide, either alone[3,4,5] or in phenol,[6] and by the treatment of 2-mercaptoethanol with a cation exchange resin.[7]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

polyethylene sulfide

ethanol (64-17-5)

sodium hydroxide (1310-73-2)

phenol (108-95-2)

sodium bromide (7647-15-6)

sodium (13966-32-0)

ethylene dibromide (106-93-4)

potassium sulfide (1312-73-8)

2-mercaptoethanol (60-24-2)

1,2-ethanedithiol (540-63-6)

dithiane (505-20-4)

phosphorus pentoxide (1314-56-3)

p-Dithiane (505-29-3)

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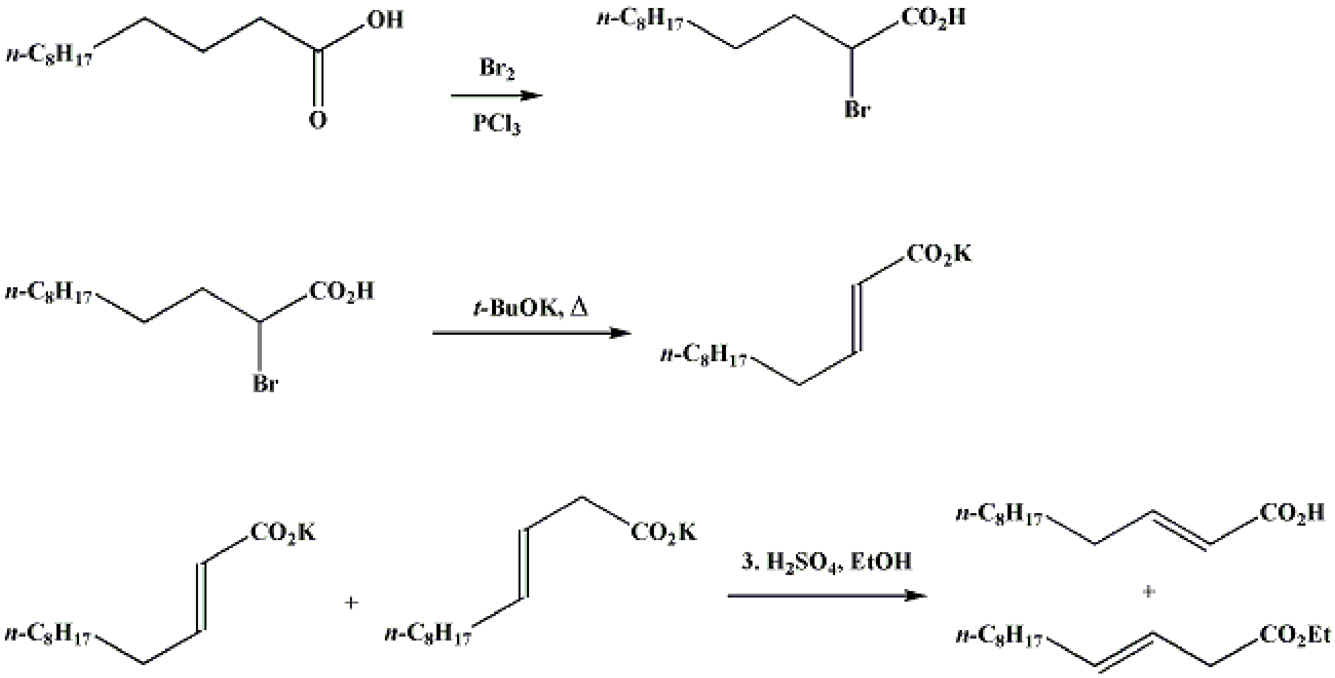
Organic Syntheses, CV 4, 398

trans-2-DODECENOIC ACID



Submitted by C. Freeman Allen and Max J. Kalm[1].
Checked by William S. Johnson and Alan D. Lourie.

1. Procedure

Caution! The bromination step should be carried out in a hood, and appropriate precautions should be employed in handling potassium (Note 1).

A dry 125-ml. three-necked flask fitted (glass joints) with a sealed mechanical stirrer, an addition funnel, and a reflux condenser capped with a calcium chloride drying tube, is charged with 30.0 g. (0.15 mole) of dodecanoic acid (Note 2) and 0.6 ml. (0.007 mole) of phosphorus trichloride. The mixture is heated at 90–95° (bath temperature), and 8.5 ml. (0.165 mole) of dry bromine (Note 3) is added in one portion with stirring. After stirring for 3 hours at 90–95°, an additional 7.7 ml. (0.15 mole) of dry bromine is added, and the heating and stirring are continued for an additional 7 hours. The dark reaction mixture is then cooled, dissolved in about 100 ml. of carbon tetrachloride, and shaken vigorously with two 100-ml. portions of water. The organic solution is filtered through anhydrous sodium sulfate, and the solvent and excess bromine are removed by distillation at steam-bath temperature and reduced pressure (water aspirator). The residue of bromo acid, which is pale orange in color, is slowly and cautiously added at room temperature to a solution of potassium *tert*-butoxide which has been prepared from 14.7 g. (0.375 g. atom) of potassium (Note 1) and 350 ml. of dry *tert*-butyl alcohol (Note 1), and is contained in a 1-l. flask fitted with a reflux condenser that is protected from moisture with a calcium chloride tube. The resultant thick suspension is heated at gentle reflux for 3–4 hours on a steam bath, then cooled, diluted with about 1 l. of water, and acidified to Congo red with 5*N* sulfuric acid. The mixture, containing the precipitated liquid dodecenoic acids, is extracted with two 100-ml. portions of hexane (or a comparable petroleum ether fraction), and the combined hexane solutions are washed with water and dried by filtration through anhydrous sodium sulfate. The hexane is removed by flash distillation, and the residual acid is fractionally distilled through a 2-ft. Podbielniak-type column (Note 4) and (Note 5). After a small fore-run, the main fraction of dodecenoic acids is collected over a 3° range at about 166–169°/3 mm. The yield is 14–15 g. (47–50%), n_D^{25} ca. 1.4610 (Note 6).

The distilled mixture of dodecenoic acids is dissolved in 150 ml. of commercial absolute ethanol containing 1.3 ml. of concentrated sulfuric acid and allowed to stand in a stoppered flask for 2 hours at 20°. The solution is diluted with 600 ml. of water and extracted with two 150-ml. portions of 60–68° petroleum ether. The extracts are washed with water and percolated through a Kies extraction apparatus (Note 7) consisting of three stages containing, respectively, 9.9 g. of 85% potassium hydroxide (0.15 mole) in 250 ml. of 20% ethanol, 2.5 g. of 85% potassium hydroxide (0.038 mole) in 125 ml. of 20% ethanol, and 125 ml. of water. An additional 250 ml. of petroleum ether is then passed through the extraction apparatus. The three aqueous layers are combined, acidified to Congo red with 5*N* sulfuric acid, and extracted with

petroleum ether. The combined organic layers are washed with water and dried over anhydrous sodium sulfate. The solvent is removed by flash distillation and the residue distilled in a modified Claisen flask. The yield of colorless 2-dodecenoic acid, b.p. 155–158°/3 mm., 127–130°/0.15 mm., is 8–10 g. (27–34%), n_D^{25} 1.4629, λ_{max} 210 m• (ε 13,650) in hexane, m.p. 13–18°.

2. Notes

1. The precautions for handling potassium and the procedure for preparing anhydrous potassium *tert*-butoxide have already been described (p.134).
2. The submitters employed a sample of dodecanoic acid, m.p. 42.5–43°, obtained by fractional distillation of commercial material. The checkers used Eastman Kodak Company yellow label grade dodecanoic acid, m.p. 44.5–45°. If a product free of homologous material is desired, purified dodecanoic acid should be used as starting material.
3. The bromine was dried with phosphorus pentoxide and filtered into the addition funnel through a plug of glass wool.
4. A simplified Podbielniak column[2] was employed. Other columns of comparable efficiency should be suitable.
5. This distillation is of importance; if omitted, the final 2-dodecenoic acid is difficult to purify.
6. The mixture of dodecenoic acids exhibited λ_{max} at 210 m• (ε 11,980) in hexane. From the extinction coefficient (13,650) for the pure 2-isomer and that (about 1000) for the 3-isomer, it is calculated that this mixture contains about 13% of the latter. A small amount of dodecanoic acid also appears to be present.
7. The Kies extraction apparatus[3] is useful in minimizing emulsion formation. The checkers performed the countercurrent extractions successfully in separatory funnels. The solutions must be mixed by mild rocking of the funnels; otherwise serious emulsions will be produced.

3. Discussion

Higher-molecular-weight normal 2-alkenoic acids have been prepared in poor yields by the Doebner condensation of aldehydes with malonic acid,[4,5,6] and by the Reformatsky reaction of aldehydes with ethyl bromoacetate followed by dehydration.[7] The α-iodo acid, prepared from the bromo acid, has been dehydrohalogenated with potassium hydroxide in ethanol,[8] but large quantities of the α-hydroxy acid are formed as a by-product which is difficult to separate in some instances. It has been reported that 2-dodecenoic acid is formed by the treatment of 3-tridecen-2-one with sodium hypobromite.[9] The present procedure is an adaptation of a published procedure.[4]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

ethanol (64-17-5)

sulfuric acid (7664-93-9)

bromine (7726-95-6)

sodium sulfate (7757-82-6)

carbon tetrachloride (56-23-5)

potassium hydroxide (1310-58-3)

phosphorus trichloride (7719-12-2)

potassium (7440-09-7)

Malonic acid (141-82-2)

sodium hypobromite

dodecanoic acid (143-07-7)

Ethyl bromoacetate (105-36-2)

hexane (110-54-3)

tert-butyl alcohol (75-65-0)

2-dodecenoic acid

3-tridecen-2-one

phosphorus pentoxide (1314-56-3)

potassium tert-butoxide (865-47-4)

trans-2-Dodecenoic acid (4412-16-2)

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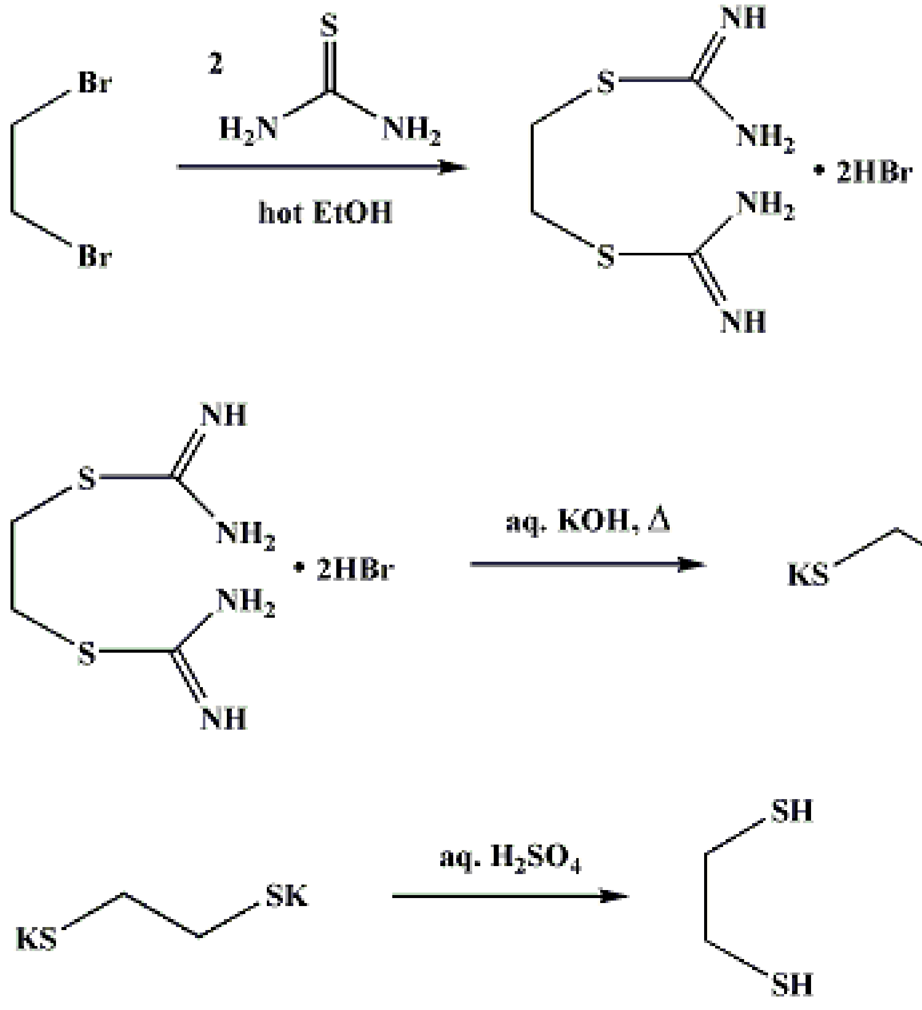
Organic Syntheses, CV 4, 401

ETHANEDITHIOL

[1,2-Ethanedithiol]



Submitted by A. John Speziale[1]
Checked by R. S. Schreiber and R. W. Kratz.

1. Procedure

Caution! This preparation requires the use of a good hood.

In a 5-l. round-bottomed flask fitted with an efficient reflux condenser are placed 2750 ml. of 95% ethanol and 609 g. (8.0 moles) of thiourea. The mixture is brought to the reflux temperature on a steam bath, and the refluxing solution is almost clear. The steam is turned off, and 751.5 g. (4.0 moles) of ethylene dibromide is added in one portion. Within 5 minutes a vigorous reaction (Note 1) ensues and ethylene diisothiuronium bromide separates from solution. The exothermic reaction is allowed to continue to completion without further application of heat. The isothiuronium salt is collected by filtration and dried. The salt melts with decomposition at 225–227° (Note 2) and weighs 1104 g. (81%).

Concentration of the filtrate to a volume of about 250 ml. and recrystallization from 95% ethanol of the crude isothiuronium salt which separates gives an additional 130 g. of material. The total yield of the salt is 1234 g. (90%).

A mixture of 255 g. (0.75 mole) of ethylene diisothiuronium bromide and 640 g. (9.7 moles) of 85% potassium hydroxide in 1360 ml. of water is placed in a 5-l. round-bottomed three-necked flask and boiled under reflux for 5 hours. Ammonia is evolved during the reflux period. The flask is then equipped with a separatory funnel, a gas-inlet tube, and a condenser set for steam distillation (Note 3). Nitrogen is admitted through the inlet tube, and a cooled solution of 415 ml. of sulfuric acid in 760 ml. of water is added dropwise (Note 4). The addition is continued until the reaction mixture becomes acid to Congo red paper, and then a 20% excess of acid is added. Approximately 725–850 ml. of the acid solution is required. The heat of neutralization is sufficient to distil part of the dithiol. At the end of the addition of the acid, the passage of nitrogen is discontinued and steam is admitted through the inlet tube. The steam distillation is continued until about 3 l. of distillate is collected. The oil is separated from the water in the distillate, which is then extracted with two 500-ml. portions of ether. The ether solution and the oil are dried separately over calcium chloride. After evaporation of the solvent, the residue is added to the oil and the crude product is fractionated through a 10-in. Vigreux column under reduced pressure in an atmosphere of nitrogen. The ethanedithiol boils at 63°/46 mm. (Note 5) and weighs 39–44 g. (55–62%); n_D^{20} 1.5589.

2. Notes

1. The reaction may be so vigorous that external cooling is required. A cloth wet with ice water and applied to the flask is sufficient to control the reaction.
2. The melting point seems to depend upon the rate of heating. Use of a Fisher-Johns melting-point apparatus gives a value of 240–242°.
3. At this point the reaction *must* be carried out in a good hood. The vapors of ethanedithiol may cause severe headache and nausea.
4. The alkaline solution should be at room temperature before the acidification is begun.
5. In one run the checkers observed a boiling point of 69°/46 mm.

3. Discussion

Ethanedithiol has been prepared from ethylene dichloride[2] or ethylene dibromide[3] and alcoholic potassium hydrosulfide; from ethylene dibromide and alcoholic sodium hydrosulfide;[4] from ethylene dichloride[5] or ethylene dibromide[6] and alcoholic sodium hydrosulfide under pressure; from ethylene dibromide and thiourea;[7] and by the catalytic hydrogenation with cobalt trisulfide[8] or nickel-on-kieselguhr[9] of the mixture resulting from the reaction of ethylene and sulfur. The present method is a

modification of one described by Mathias.[7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 396

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethylene diisothiuronium bromide

ethanol (64-17-5)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

ammonia (7664-41-7)

ether (60-29-7)

ethylene dichloride (107-06-2)

nitrogen (7727-37-9)

sulfur (7704-34-9)

potassium hydroxide (1310-58-3)

ethylene (9002-88-4)

ethylene dibromide (106-93-4)

potassium hydrosulfide (1310-61-8)

thiourea (62-56-6)

sodium hydrosulfide

1,2-ethanedithiol (540-63-6)

Ethanedithiol

cobalt trisulfide

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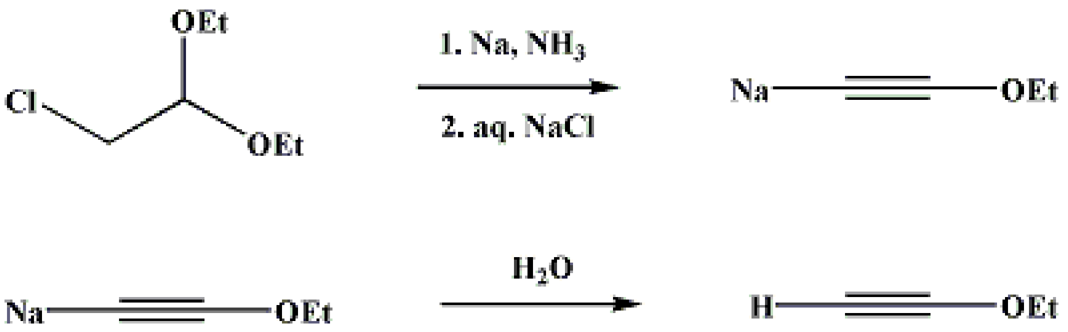
Organic Syntheses, CV 4, 404

ETHOXYACETYLENE

[Ether, ethyl ethynyl]



Submitted by E. R. H. Jones, Geoffrey Eglinton, M. C. Whiting, and B. L. Shaw[1].
Checked by Arthur C. Cope and Ronald M. Pike.

1. Procedure

Caution! This preparation should be conducted in a hood to avoid exposure to ammonia, and thorough shielding of the apparatus is recommended.

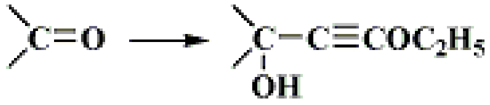
A solution of sodium amide in liquid ammonia is prepared according to a procedure previously described (Note 1) in a 1-l. three-necked flask (Note 2) equipped with a cold-finger condenser (cooled with Dry Ice) attached through a soda-lime tower to a gas absorption trap[2] and an inlet tube. Anhydrous liquid ammonia (500 ml.) is introduced from a commercial cylinder through the inlet tube, and 0.5 g. of hydrated ferric nitrate is added, followed by 38 g. (1.65 g. atoms) of clean, freshly cut sodium (Note 3). The inlet tube is replaced with a 100-ml. dropping funnel, and the mixture is agitated manually (Note 2) until all the sodium is converted into sodium amide, after which 76.5 g. (0.50 mole) of diethylchloroacetal (Note 4) is added over a period of 15–20 minutes. The mixture is swirled for an additional period of 15 minutes, after which the ammonia is evaporated in a stream of pure nitrogen. The flask is cooled to −70° in a Dry Ice-trichloroethylene bath (Note 5), and 325 ml. of a saturated solution of sodium chloride which has been cooled to −20° is added all at once and as rapidly as possible with vigorous agitation (Note 6). The flask is then fitted with a still head connected to a trap cooled to −70° with Dry Ice, and the contents of the flask are slowly heated to 100° on a steam bath (Note 7). The condensate is allowed to warm to 0°, after which the trap is again cooled to −70° and the mixture is neutralized by the dropwise addition of a saturated aqueous solution of sodium dihydrogen phosphate. The aqueous layer is frozen by cooling with Dry Ice, and the supernatant liquid is decanted and dried over about 4 g. of anhydrous calcium chloride. The drying agent is removed by filtration, and the filtrate is distilled (Note 8) through a column containing

a 20-cm. section packed with glass helices at partial reflux, yielding 20–21.2 g. (57–60%) of ethoxyacetylene, b.p. 49–51°/749 mm., n_D^{25} 1.3790 (Note 9), (Note 10), (Note 11), and (Note 12).

2. Notes

1. One of the procedures for converting sodium to sodium amide described in *Organic Syntheses* is used (p. 763).[3]
2. The flask is clamped to the free end of a long (30-in.) Duraluminium rod which is fixed at the other (top) end to a rigid frame. The rod is clamped in a vertical position, and by moving the free end the contents of the flask can be swirled very conveniently.
The submitters used a 1-l. round-bottomed flask mounted in the same way, without provision for cooling or a condenser cooled with Dry Ice, and were successful in preparing sodium amide and adding diethylchloroacetal before excessive loss of liquid ammonia occurred. Conversion of sodium to sodium amide sometimes requires a considerable period of time, in which case use of the apparatus specified avoids difficulty and the necessity of adding more liquid ammonia.
3. More liquid ammonia should be added through the inlet tube if vaporization reduces the liquid volume to less than 300 ml.
4. Diethylchloroacetal (chloroacetaldehyde diethylacetal) supplied by Eastman Kodak Company is satisfactory.
5. *Important! This sodium derivative is extremely pyrophoric, and at this point and during the addition of the saturated sodium chloride solution it is essential that the contents of the flask be kept out of contact with air.* When the flask is immersed in the Dry Ice bath the nitrogen stream is increased to counteract the diminution in pressure due to rapid cooling.
6. The checkers found that a dropping funnel equipped with a pressure-equalizing tube provided the most satisfactory mode of addition.
7. It is advisable to allow the mixture to warm to room temperature gradually before applying heat.
8. The distillation should be conducted in a hood since the product has lachrymatory properties.
9. Others have reported b.p. 28°/300 mm., n_D^{20} 1.3812,[4] and b.p. 48–50°/760 mm.[5]
10. The submitters have used a similar procedure for the preparation of methoxyacetylene, b.p. 22.5–23.5°, n_D^{16} 1.3693, from commercial dimethylchloroacetal in 60% yield. *Caution! Minor explosions have been reported to occur during the addition of saturated sodium chloride solution to the sodium derivative of methoxyacetylene. They may have resulted from ignition of the methoxyacetylene by particles of sodium which adhered to the walls of the flask. It is recommended that all apparatus be shielded during the preparation of methoxyacetylene.*
11. Ethoxyacetylene has proved to be a useful reagent for the conversion of

ketones to acetylenic carbinols:



which can be converted to α,β-unsaturated aldehydes, esters, and acids:[6]

It has been used in the synthesis of vitamin A aldehyde[7] and in the preparation of an intermediate in one of the total syntheses of cortisone.[8]

12. It has been reported[9] that the following modified procedure eliminates the dangers associated with the preparation of ethoxyacetylene.

The initial operations were the same as described above except that 46 g. (2 g. atoms) of sodium was employed (per 76.5 g. of chloroacetal), and the reaction mixture was stirred mechanically for 2 hours after the addition of the diethylchloroacetal. The dropping funnel and stirrer were removed and the flask was closed with a stopper provided with a wide plastic tube that came within 1 mm. of the bottom. The other end was placed near the bottom of an open 2-l. flask which contained 1 kg. of finely crushed ice.

When the stopper was fitted, the contents of the reaction flask were transferred to the ice by the ammonia pressure. The walls of the flask were rinsed with a little liquid ammonia and the washings also were forced onto the ice. The cold hydrolysis mixture was shaken repeatedly with 50-ml. portions of high-boiling petroleum (b.p. > 160°). The combined extracts were washed with ice water and dried over anhydrous sodium sulfate. Distillation afforded 21–23 g. (60–66%) of material which boiled at 49–55°/760 mm., n_D^{20} 1.3820.

3. Discussion

Ethoxyacetylene has been prepared from β-bromovinyl ethyl ether[4] or β-chlorovinyl ethyl ether[10] and potassium hydroxide; from α,β-dibromoethyl ethyl ether and potassium hydroxide;[5] and from diethyl chloroacetal, diethyl bromoacetal, α,β-dichloroethyl ethyl ether, or α,β-dibromoethyl ethyl ether and sodium amide.[11]

References and Notes

1. University of Manchester, Manchester, England.
2. *Org. Syntheses Coll. Vol.* **2**, 4 (1943).
3. *Org. Syntheses Coll. Vol.* **3**, 219 (1955).
4. Jacobs, Cramer, and Hanson, *J. Am. Chem. Soc.*, **64**, 223 (1942).
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6. Heilbron, Jones, Julia, and Weedon, *J. Chem. Soc.*, **1949**, 1823.
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8. Sarett, Arth, Lukes, Beyler, Poos, Johns, and Constantin, *J. Am. Chem. Soc.*, **74**, 4974 (1952).
9. Arens and Brandsma, Private communication.
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11. Eglinton, Jones, Shaw, and Whiting, *J. Chem. Soc.*, **1954**, 1860.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

diethyl bromoacetal

diethylchloroacetal

dimethylchloroacetal

sodium derivative of methoxyacetylene

petroleum

diethyl chloroacetal

calcium chloride (10043-52-4)

ammonia (7664-41-7)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

sodium amide (7782-92-5)

ferric nitrate

α,β-Dibromoethyl ethyl ether (2983-26-8)

Ethoxyacetylene, Ether, ethyl ethynyl (927-80-0)

sodium dihydrogen phosphate (7558-80-7)

chloroacetaldehyde diethylacetal (621-62-5)

methoxyacetylene (6443-91-0)

cortisone

β-bromovinyl ethyl ether

β-chlorovinyl ethyl ether

α,β-dichloroethyl ethyl ether (623-46-1)

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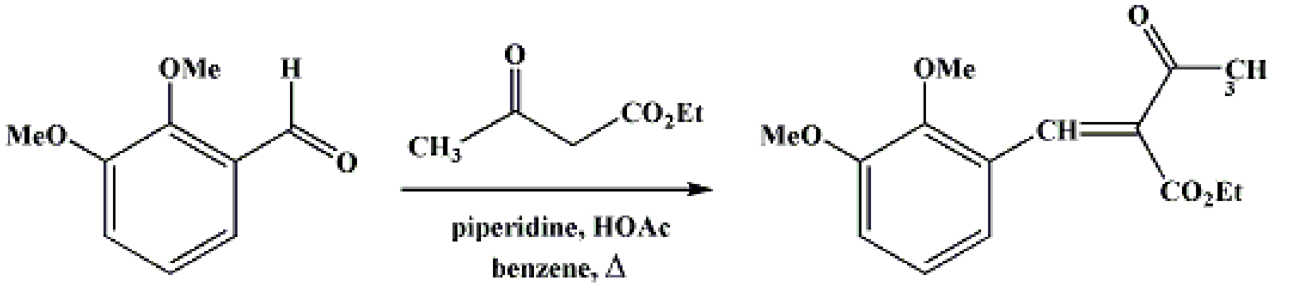
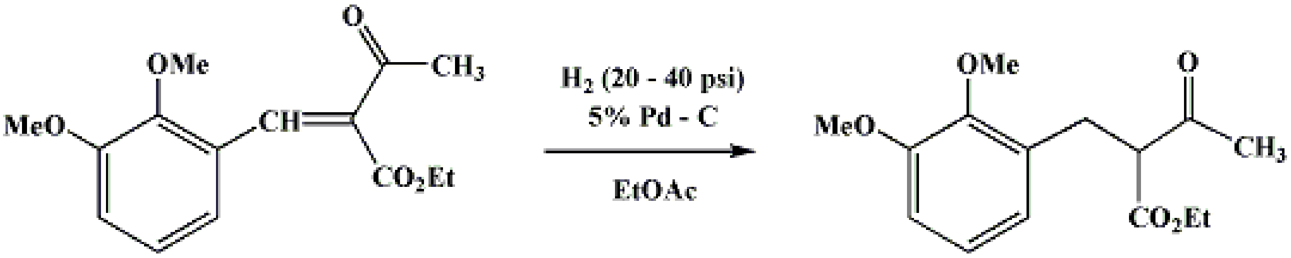
ETHYL α-ACETYL-β-(2,3-DIMETHOXYPHENYL)-PROPIONATE

[Hydrocinnamic acid, α-acetyl-2,3-dimethoxy-, ethyl ester]





Submitted by E. C. Horning, J. Koo, M. S. Fish, and G. N. Walker[1].
Checked by T. L. Cairns and Charles W. Todd.

1. Procedure

A. *Ethyl α-acetyl-β-(2,3-dimethoxyphenyl)acrylate.* In a 1-l. round-bottomed flask fitted with a water-benzene separator[2] and a reflux condenser are placed 183 g. (1.1 moles) of 2,3-dimethoxybenzaldehyde (Note 1) and 130 g. (1.0 mole) of ethyl acetoacetate. The water-benzene separator is filled with benzene, an additional 70 ml. of benzene is added to the mixture, and the 2,3-dimethoxybenzaldehyde is brought into solution by warming. Piperidine (4 ml.) and glacial acetic acid (12 ml.) are added, and the mixture is heated under reflux for 2–3 hours (Note 2). The mixture is cooled, poured into a separatory funnel with 800 ml. of ether, and washed successively with 200-ml. portions of 5% hydrochloric acid, 5% sodium bicarbonate solution, and 5% acetic acid, and twice with water. The extract is dried over anhydrous magnesium sulfate (about 250 g.). After filtration, the ether and benzene are distilled under atmospheric pressure, and the residue is distilled under reduced pressure. The yield of viscous, yellow oil collected at 186–190°/2 mm. (Note 3) is 180–199 g. (64–72%), n_D^{25} 1.5507–1.5508.

B. *Ethyl α-acetyl-β-(2,3-dimethoxyphenyl)propionate.* The product obtained in Part A is divided into two approximately equal portions, and to each are added 125 ml. of ethyl acetate and 5 g. of 5% palladium-on-carbon catalyst (Note 4). Each solution is shaken with hydrogen at pressures between 20 and 40 lb. in a low-pressure apparatus. About 45 minutes is usually needed for complete reduction. The two solutions are then combined, and the catalyst is removed by filtration and washed with 20 ml. of ethyl acetate. The ethyl acetate is distilled at atmospheric pressure, and distillation of the residue under reduced pressure yields 158–176 g. (56–63% over-all) of a colorless

product collected at 175–177°/3 mm., n_D^{25} 1.5042–1.5044 (Note 3) and (Note 5).

2. Notes

1. A practical grade of 2,3-dimethoxybenzaldehyde, although discolored, is satisfactory. It is best handled and weighed as a liquid. This is done by warming the container on a steam bath for several minutes.
2. The time of reflux is determined by the rate at which water separates from the reaction mixture. In general, the theoretical amount of water (18 ml.) is collected in the water separator after about 1 hour, but additional refluxing usually results in the separation of another 4–5 ml. Anhydrous materials are not necessary for the reaction.
3. Using a 6-in. Vigreux column with a wide side arm, the checkers observed a boiling point of 166–168°/3 mm. for ethyl α-acetyl-β-(2,3-dimethoxyphenyl)propionate and 176–179°/2 mm. for the acrylate.
4. These quantities are convenient for hydrogenation in a Parr low-pressure apparatus; if a larger apparatus is available, it is unnecessary to divide the material. The palladium-on-carbon catalyst is prepared by Hartung's method,[3] using sufficient Norit to give a 5% catalyst. A few chips of Dry Ice should be placed in the bottle before the catalyst is added to provide an inert atmosphere. The checkers used a catalyst obtained from Baker and Company, Inc., 113 Astor Street, Newark, New Jersey.
5. The same procedure may be used with other aromatic aldehydes. The acrylate ester prepared from veratraldehyde is a crystalline compound melting at 82.5–84.5°. It may be purified by distillation under reduced pressure, b.p. 190–196°/0.8 mm. The yield is 53–63%. The hydrogenated product is obtained as a colorless oil, b.p. 180–183°/1.0 mm., in 38–44% over-all yield.

3. Discussion

Substituted α-benzylacetoacetic esters have usually been prepared by the general method of Leuchs,[4] in which ethyl acetoacetate is alkylated in ethanol solution with benzyl chloride and sodium ethoxide. The present method is based upon Cope's[5] procedure for the condensation of carbonyl compounds with ethyl acetoacetate, followed by catalytic reduction of the condensation product.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 550

References and Notes

1. University of Pennsylvania, Philadelphia, Pennsylvania.
2. *Org. Syntheses Coll. Vol.* **3**, 382 (1955).
3. *Org. Syntheses Coll. Vol.* **3**, 685 (1955), Method D.
4. Leuchs, *Ber.*, **44**, 1510 (1911).
5. Cope and Hofmann, *J. Am. Chem. Soc.*, **63**, 3456 (1941).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

palladium-on-carbon

α-benzylacetoacetic esters

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

ethyl acetate (141-78-6)

ether (60-29-7)

hydrogen (1333-74-0)

sodium bicarbonate (144-55-8)

Norit (7782-42-5)

piperidine (110-89-4)

sodium ethoxide (141-52-6)

benzyl chloride (100-44-7)

Ethyl acetoacetate (141-97-9)

magnesium sulfate (7487-88-9)

Veratraldehyde (120-14-9)

acrylate

2,3-dimethoxybenzaldehyde (86-51-1)

ETHYL α-ACETYL-β-(2,3-DIMETHOXYPHENYL)-PROPIONATE, Hydrocinnamic acid, α-acetyl-2,3-dimethoxy-, ethyl ester, Ethyl α-acetyl-β-(2,3-dimethoxyphenyl)propionate (53608-80-3)

Ethyl α-acetyl-β-(2,3-dimethoxyphenyl)acrylate (19411-81-5)

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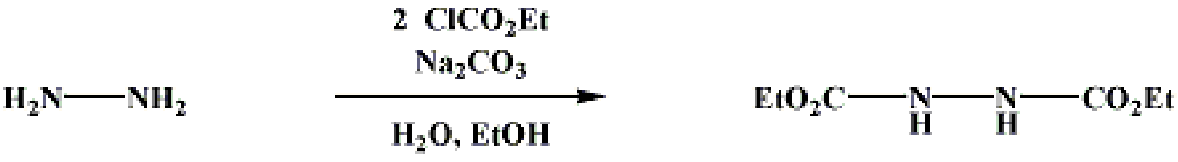
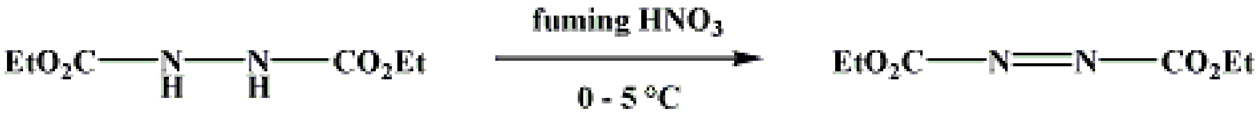
Organic Syntheses, *CV 4*, *411*

ETHYL AZODICARBOXYLATE

[Formic acid, azodi-, diethyl ester]





Submitted by J. C. Kauer[1]
Checked by William G. Dauben and Robert L. Cargill.

1. Procedure

A. *Ethyl hydrazodicarboxylate.* In a 3-l., three-necked flask equipped with a mechanical stirrer, two 500-ml. dropping funnels, and a thermometer (Note 1), is placed a solution of 75 g. (1.5 moles) of 100% hydrazine hydrate (or 88.5 g. of 85% hydrazine hydrate) in 750 ml. of 95% ethanol. The reaction flask is cooled in an ice bath. When the solution temperature drops to 10°, 326 g. (3 moles) of ethyl chloroformate is added dropwise with stirring at a rate sufficient to maintain the temperature between 15° and 20°. After exactly one-half of the ethyl chloroformate has been introduced, a solution of 159 g. (1.5 moles) of sodium carbonate in 750 ml. of water is added dropwise simultaneously with the remaining ethyl chloroformate. The addition of these two reactants is regulated so that the temperature does not rise above 20°. The addition of the chloroformate should be completed slightly in advance of the sodium carbonate, thus maintaining an excess of the chloroformate in the solution at all times. During the course of the addition of the reagents, a precipitate is formed.

After addition of the reactants is complete, the walls of the flask are washed down with 200 ml. of cold water, and the reaction mixture is allowed to stir for 30 minutes. The precipitate is then collected on a Büchner funnel, washed well with a total of 1 l. of cold water, and dried in a vacuum oven at 80°. There is obtained 215–225 g. (81–85%) of ethyl hydrazodicarboxylate which melts at 131–133°. It is sufficiently pure for the preparation of ethyl azodicarboxylate (Note 2) and (Note 3).

B. *Ethyl azodicarboxylate. Caution! Both ethyl and methyl azodicarboxylate are sensitive to heat. Thus, in a sealed capillary they explode violently when heated by a flame. Overheating is to be avoided, and distillations should be from a bath, not an*

electrically heated mantle. Distillations should be well shielded. Since copious fumes of nitrogen oxides are evolved during the oxidation by nitric acid, this operation and the subsequent work-up should be carried out in an efficient hood.

A mixture of 200 g. of ethyl hydrazodicarboxylate in 125 ml. of 70% nitric acid is placed in a 1-l., three-necked flask equipped with a mechanical stirrer, gas-outlet tube, and thermometer. The flask is cooled in an ice bath, and, when the temperature of the solution reaches 5°, 220 ml. of ice-cold yellow fuming nitric acid (90–95% HNO_3, d_{15} = 1.49–1.50) is added. The reaction mixture is maintained at 0–5° for 2 hours with stirring and is then carefully poured on a stirred mixture of 500 g. of ice, 500 ml. of ice water, and 100 ml. of methylene chloride in a 2-l. beaker placed in a metal pan (Note 4). After the ice melts, the solution is transferred carefully to a 2-l. separatory funnel. The organic (lower) layer is removed, and the acid layer is extracted (Note 5) with three 100-ml. portions of methylene chloride. The combined organic layers are washed twice with 100-ml. portions of ice water and are then stirred mechanically for 10 minutes with 500 ml. of ice-cold 10% potassium bicarbonate solution. The layers are separated in a separatory funnel, and the organic layer is finally washed with 100 ml. of ice water and dried quickly with a small portion of anhydrous magnesium sulfate that is removed by filtration. The solution is dried overnight with a fresh portion of anhydrous magnesium sulfate. *Caution! The following distillations should be well shielded.* The methylene chloride is removed on a steam bath under reduced pressure, and the residue is rapidly distilled without fractionation under vacuum (1–5 mm.) from a flask immersed in an oil bath whose temperature is raised gradually from 75° to 130°. The crude distillate is then fractionally distilled under vacuum through a short column packed with glass helices, using an oil bath to heat the distillation flask. After a short fore-run, the main fraction is collected at 93–95°/5 mm. There is obtained 138–158 g. (70–80%) of ethyl azodicarboxylate which freezes at 6° (Note 6), (Note 7), and (Note 8).

2. Notes

1. The thermometer and one of the funnels are fitted to a two-necked adapter so that, when the thermometer bulb is immersed in the solution, the range between 10° and 20° is easily visible.
2. Ethyl hydrazodicarboxylate may be purified by crystallization from dilute ethanol; m.p. 134–135°.
3. Methyl hydrazodicarboxylate, which is much more soluble in water than the ethyl ester, may be prepared by the following modification of the above procedure.
A solution of 100 g. (2 moles) of hydrazine hydrate in 500 ml. of 95% alcohol is treated as described above with a total of 378 g. (4 moles) of methyl chloroformate while maintaining the temperature below 20°. During the addition of the last half of the chloroformate, a warm (30–35°) solution of 212 g. (2 moles) of sodium carbonate in 800 ml. of water is added. The resulting slurry is stirred for 30 minutes, and the precipitate is filtered on a Büchner funnel, washed with 100 ml. of ice water, and air-dried. The filtrate is concentrated at reduced

pressure (12–25 mm.) on a water bath to 700 ml. and is cooled in ice. The precipitate is filtered, washed with 100 ml. of ice water, and air-dried. The combined crops of crude methyl hydrazodicarboxylate are dried at 60° in a vacuum oven and are then stirred successively with two 800-ml. portions of warm acetone to separate inorganic impurities. The acetone solution is filtered, and evaporated at reduced pressure to yield 260 g. (88%) of methyl hydrazodicarboxylate (m.p. 127–131°) of sufficient purity for preparation of methyl azodicarboxylate.

A purer product (m.p. 131–132°) may be obtained by warming the acetone solution to 50° and adding to it 1.8 l. of hexane or heptane also warmed to 50°. The solution is seeded and allowed to cool slowly.

4. As a safety precaution, in case the beaker should break, it is placed in a metal pan.

5. The separatory funnel should be carefully vented at frequent intervals since large quantities of nitrogen oxides are liberated.

6. The submitter found that methyl azodicarboxylate can be prepared by a modification of this procedure. It is somewhat more water-soluble and much more susceptible to hydrolysis than the ethyl ester.

A mixture of 200 g. (1.35 moles) of methyl hydrazodicarboxylate, 400 ml. of chloroform (washed with water and dried over calcium chloride), and 250 ml. of concentrated nitric acid is cooled to 5°, and 350 ml. of ice-cold yellow fuming (90–95%) nitric acid is added. The solution is stirred for 2 hours at 0–5° and is poured onto 1 kg. of crushed ice. After most of the ice has melted, the organic layer is separated (Note 5) and is washed quickly with two 500-ml. portions of ice water containing some ice. It is then stirred for 2 minutes with a mixture of 300 ml. of ice-cold 10% potassium bicarbonate solution and 200 g. of crushed ice. The organic layer is separated, washed quickly with ice water, and dried and distilled as described for the ethyl ester. There is obtained 148 g. (75%) of methyl azodicarboxylate which boils at 90–91°/15 mm. and freezes at 10° (Note 7).

7. The submitter has found that methyl azodicarboxylate is often more reactive than the ethyl ester. Moreover, adducts prepared from the methyl ester are generally higher melting and lower boiling than those from the ethyl ester, and thus more easily purified.

8. A frequent annoying by-product of the reactions of azodicarboxylic esters is the corresponding hydrazodicarboxylate. In the case of the methyl ester this impurity is easily removed because of its moderate solubility in water and low solubility in such solvents as carbon tetrachloride.

3. Discussion

Ethyl hydrazodicarboxylate has been prepared by the reaction of ethyl chloroformate with hydrazine hydrate[2] or hydrazine sulfate in the presence of alkali.[3]

Ethyl azodicarboxylate has been prepared by oxidation of ethyl hydrazodicarboxylate

with hypochlorous acid,[4] concentrated nitric acid,[3] and a mixture of concentrated and fuming nitric acid.[5,6]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 544

References and Notes

1. Contribution No. 633, from the Central Research Department, Experimental Station, E. I. du Pont de Nemours and Co., Wilmington, Delaware.
2. Curtius and Heidenreich, *J. prakt. Chem.*, **52**, 476 (1895); Vogelesang, *Rec. trav. chim.*, **65**, 789 (1946).
3. Ingold and Weaver, *J. Chem. Soc.*, **127**, 381 (1925).
4. Rabjohn, *Org. Syntheses Coll. Vol.* **3**, 375 (1955).
5. Curtius and Heidenreich, *Ber.*, **27**, 774 (1894).
6. Diels and Fritzsche, *Ber.*, **44**, 3018 (1911).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

nitrogen oxides

ethyl and methyl azodicarboxylate

ethanol (64-17-5)

calcium chloride (10043-52-4)

chloroform (67-66-3)

nitric acid (7697-37-2)

sodium carbonate (497-19-8)

carbon tetrachloride (56-23-5)

acetone (67-64-1)

hypochlorous acid (7790-92-3)

hydrazine hydrate (7803-57-8)

Hydrazine sulfate (10034-93-2)

methylene chloride (75-09-2)

ethyl chloroformate (541-41-3)

magnesium sulfate (7487-88-9)

chloroformate

heptane (142-82-5)

methyl chloroformate (79-22-1)

Ethyl azodicarboxylate

Formic acid, azodi-, diethyl ester (1972-28-7)

Ethyl hydrazodicarboxylate

hexane (110-54-3)

methyl azodicarboxylate

potassium bicarbonate (298-14-6)

Methyl hydrazodicarboxylate

hydrazodicarboxylate

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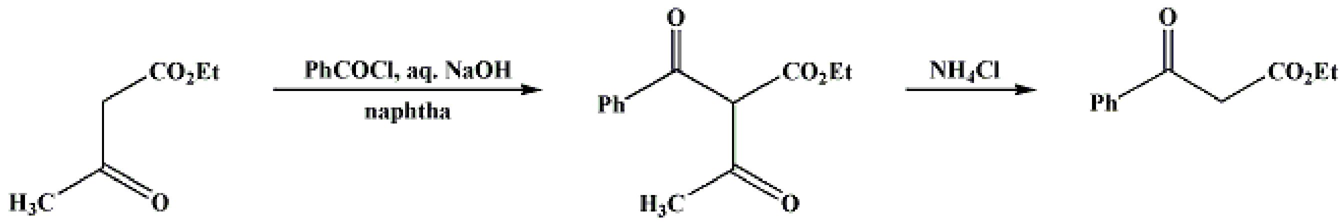
Organic Syntheses, CV 4, 415

ETHYL BENZOYLACETATE

[Acetic acid, benzoyl-, ethyl ester]



Submitted by J. M. Straley and A. C. Adams[1].
Checked by Max Tishler and M. A. Kozlowski.

1. Procedure

In an open 3-l. three-necked flask, equipped with an efficient mechanical stirrer (Note 1) and two dropping funnels, are placed 500 ml. of water, 250 ml. of technical naphtha boiling at 95–110°, and 195 g. (1.5 moles) of freshly distilled ethyl acetoacetate. The mixture is cooled to 5° with a water-ice bath, and 65 ml. of 33% sodium hydroxide solution (33 g. sodium hydroxide in 100 g. solution) is added. As the temperature is maintained below 10° (Note 2) and the pH near 11 (Note 3), the mixture is stirred vigorously (Note 1), and there are added simultaneously from the two dropping funnels 230 g. (1.62 moles) of benzoyl chloride and 270 ml. of 33% sodium hydroxide solution. This addition should be made during about 2 hours. After addition is complete, the cooling bath is removed, and the mixture is allowed to come to room temperature. In order to ensure complete reaction, the mixture is finally brought to 35° during about 1 hour. The stirrer is then stopped, and the aqueous layer is separated and placed in a 2-l. Erlenmeyer flask (Note 4).

To the mixture is added 80 g. of technical ammonium chloride; then it is stirred slowly overnight. The specific gravity is brought to 1.13 by the addition of about 90 g. of sodium chloride, after which the mixture is transferred to a separatory funnel. About 10 ml. of benzene is used to rinse the flask and is added to the separatory funnel. The aqueous layer is withdrawn (Note 5), and the oil is washed three times with 100-ml. portions of cold water.

An additional 40 ml. of benzene is added (to accomplish drying on distillation), and the product is distilled under reduced pressure, using a short still head with no fractionating column (Note 6). The yield of ethyl benzoylacetate, b.p. 145–150°/12 mm., is 197–203 g. (68–71%) (Note 4).

2. Notes

1. Good stirring is essential. Slow stirring results in low yields.
2. Temperatures above 10° did not result in consistently good yields.
3. Lower pH did not give good yields. The pH was checked by means of filter paper, which had been dipped in an alcoholic solution of alizarin and then dried.
4. The naphtha layer may be used without further treatment for the next run. Yields of 76% have been obtained on such a second run without making allowance for recovered ethyl acetoacetate. Distillation of the naphtha layer together with the fore-run from the final distillation of ethyl benzoylacetate yields 11–14 g. of recovered ethyl acetoacetate and about 235 ml. of naphtha.
5. As high as 62 g. of benzoic acid has been recovered by acidification of the aqueous layer.
6. The chief impurity in the crude ester is a high-boiling material of unknown composition.

3. Discussion

The methods of preparation have been listed in two earlier volumes.[2,3] The present method, which is an adaptation of a process found in German documents,[4] is a shorter, more simple procedure which does not require use of dry solvent or metallic sodium.

References and Notes

1. Research Laboratories, Tennessee Eastman Company, Kingsport, Tennessee.
2. *Org. Syntheses Coll. Vol.* **2**, 266 (1943).

3. *Org. Syntheses Coll. Vol.* **3**, 381 (1955).
4. B.I.O.S., *Final Rept.* **1149**, 115.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

naphtha

Benzene (71-43-2)

ammonium chloride (12125-02-9)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

Benzoic acid (65-85-0)

benzoyl chloride (98-88-4)

sodium (13966-32-0)

Ethyl acetoacetate (141-97-9)

Ethyl benzoylacetate, Acetic acid, benzoyl-, ethyl ester (94-02-0)

alizarin (72-48-0)

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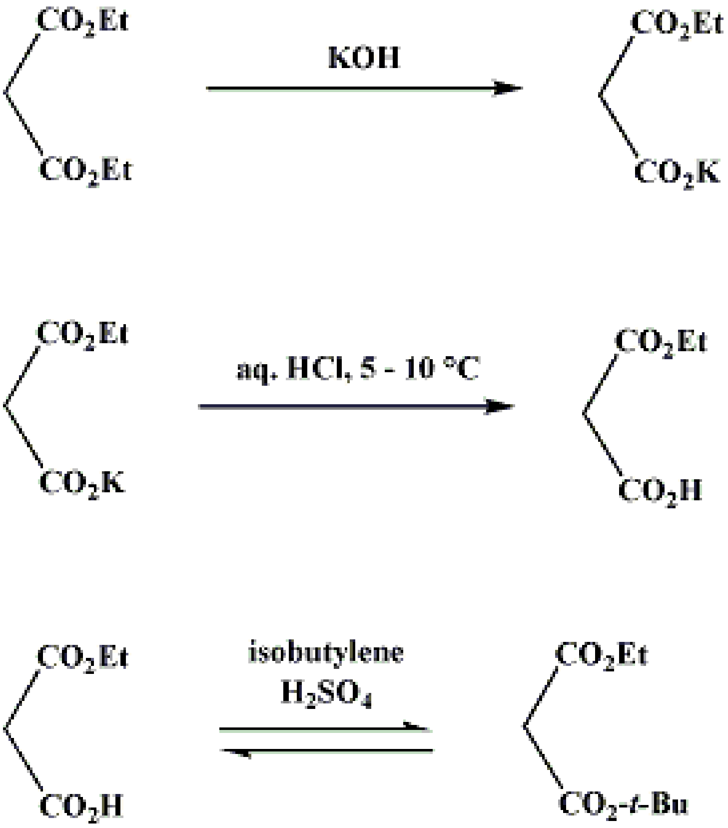
Organic Syntheses, CV 4, 417

ETHYL *tert*-BUTYL MALONATE

[Malonic acid, *tert*-butyl ethyl ester]



Submitted by R. E. Strube[1]
Checked by William S. Johnson and Duff S. Allen, Jr..

1. Procedure

A 2-l. three-necked flask, equipped with a sealed stirrer, a dropping funnel and a reflux condenser provided with a calcium chloride drying tube, is charged with 100 g. (0.625 mole) of diethyl malonate (Note 1) and 400 ml. of commercial absolute ethanol. Stirring is started, and a solution of 35 g. of potassium hydroxide pellets (Note 2) in 400 ml. of commercial absolute ethanol is added at room temperature during a period of 1 hour. A white crystalline precipitate forms during the addition, and, after all the hydroxide has been added, stirring is continued for an additional 2 hours. After the mixture has stood overnight, it is heated to boiling on the steam bath and filtered while hot with suction (Note 3). Precipitation of the potassium ethyl malonate is completed by cooling the filtrate in an ice bath. The salt is collected by suction filtration, washed with a small amount of ether, and dried under reduced pressure at room temperature. An additional amount of the potassium salt is obtained by concentrating the mother liquors on the steam bath to about 100–125 ml. The total yield is 80–87 g. (75–82%).

A 250-ml. three-necked flask provided with a stirrer, a dropping funnel, and a

thermometer is charged with 80 g. (0.470 mole) of potassium ethyl malonate and 50 ml. of water. The mixture is cooled to 5° with an ice bath, and 40 ml. of concentrated hydrochloric acid is added over a 30-minute period while the temperature is maintained below 10°. The mixture is filtered with suction, and the precipitate of potassium chloride washed with 75 ml. of ether. The aqueous layer of the filtrate is separated and washed with three 50-ml. portions of ether. The combined ether solutions are dried over anhydrous magnesium sulfate; then most of the solvent is removed by distillation at atmospheric pressure, and the remainder under reduced pressure. Finally, the liquid residue of monoethyl malonate is dried at 50°/1 mm. for 1 hour. The yield is 58–62 g. (93–100%).

A 500-ml. Pyrex heavy-walled, narrow-mouthed pressure bottle is charged with 100 ml. of ether and 3.5 ml. of concentrated sulfuric acid. The solution is cooled with an ice bath to 5°, and 56 g. (0.42 mole) of monoethyl malonate and approximately 60 ml. (about 0.75 mole) of isobutylene (Note 4) are added. The bottle is immediately closed with a rubber stopper, which is clamped or wired in place, and is shaken mechanically at room temperature overnight (Note 5). The bottle is chilled in an ice-salt bath and then opened. The reaction mixture is poured into a 1-l. Erlenmeyer flask containing a cooled solution of 50 g. of sodium hydroxide in 200 ml. of water and 200 g. of ice. The mixture is swirled a few times and then transferred to a separatory funnel (Note 6). The layers are separated, and the aqueous portion is extracted with two 75-ml. portions of ether. The organic layers are combined and dried over anhydrous magnesium sulfate. The solution is concentrated in a 125-ml. round-bottomed flask (Note 7) and distilled at reduced pressure through a 10-cm. Vigreux column. The fraction distilling at 98–100°/22 mm. or 107–109°/24 mm. is collected. The yield is 42–47 g. (53–58%), n_D^{25} 1.4128, n_D^{23} 1.4142.

2. Notes

1. Diethyl malonate as supplied by the Eastman Kodak Company (white label grade) or by Abbott Laboratories may be used without further purification.
2. Potassium hydroxide (85% minimum assay) obtained from the Mallinckrodt Chemical Works is satisfactory.
3. A steam-heated Büchner or a warmed sintered glass funnel is recommended.
4. Technical grade isobutylene supplied by Matheson Company was used. The isobutylene gas is liquefied by passage into a large test tube immersed in a Dry Ice-acetone bath.
5. For convenience, the reaction was carried out overnight. The reaction time may probably be shortened (compare the preparation of di-*tert*-butyl malonate, p. 261).
6. The mixture may be filtered, if necessary, to remove ice.
7. Since traces of acid will decompose the ester during the distillation, it is essential to wash the distillation apparatus carefully with a sodium hydroxide solution before rinsing and drying. The addition of some potassium carbonate or magnesium oxide before distillation is recommended (see Note 5 on p. 262).

3. Discussion

Ethyl *tert*-butyl malonate has been prepared by adding *tert*-butyl acetate and ethyl carbonate to sodium triphenylmethyl,[2] and from ethyl malonyl chloride and *tert*-butyl alcohol.[3] The present procedure is an adaptation of that for the preparation of di-*tert*-butyl malonate (p. 261).

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 213

References and Notes

1. The Upjohn Company, Kalamazoo, Michigan.
2. Hauser, Abramovitch, and Adams, *J. Am. Chem. Soc.*, **64**, 2714 (1942).
3. Breslow, Baumgarten, and Hauser, *J. Am. Chem. Soc.*, **66**, 1287 (1944).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium triphenylmethyl

ethanol (64-17-5)

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium hydroxide (1310-73-2)

potassium hydroxide (1310-58-3)

diethyl malonate (105-53-3)

monoethyl malonate (1071-46-1)

potassium chloride (7447-40-7)

magnesium sulfate (7487-88-9)

ethyl carbonate

magnesium oxide

isobutylene (9003-27-4)

tert-butyl alcohol (75-65-0)

potassium ethyl malonate (6148-64-7)

ethyl malonyl chloride

tert-Butyl acetate (540-88-5)

Di-tert-butyl malonate (541-16-2)

Ethyl tert-butyl malonate, Malonic acid, tert-butyl ethyl ester (32864-38-3)

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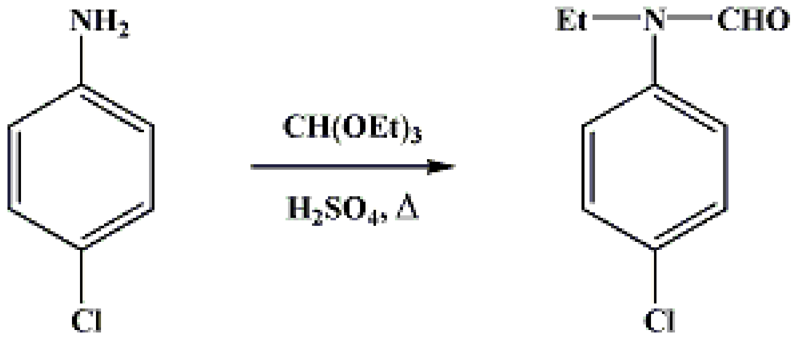
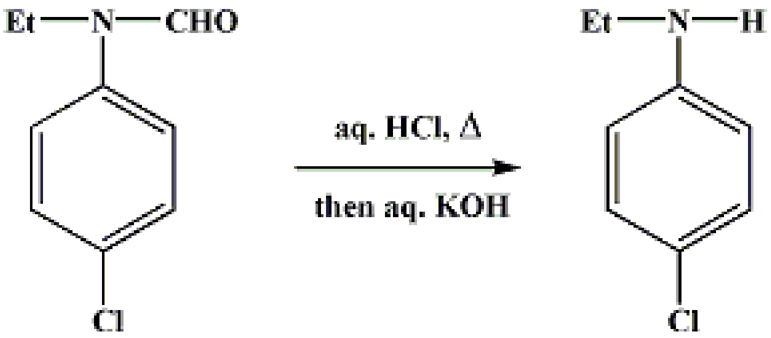
Organic Syntheses, CV 4, 420

N-ETHYL-*p*-CHLOROANILINE

[Aniline, *p*-chloro-N-ethyl-]





Submitted by Royston M. Roberts and Paul J. Vogt[1].
Checked by James Cason and Milton Finger.

1. Procedure

A. *N-Ethyl-p-chloroformanilide.* In a 300-ml. round-bottomed flask, equipped with a side tubulature just large enough to accommodate a thermometer, are placed 63.8 g. (0.50 mole) of *p*-chloroaniline and 111 g. (0.75 mole) of triethyl orthoformate (Note 1), and then 2.0 g. (0.02 mole) of concentrated sulfuric acid is added with mixing. The flask is attached to a 30-cm. column 2 cm. in diameter packed with glass helices (Note 2), which is surmounted by a distillation head equipped with a thermometer and condenser. A thermometer is connected through a slip joint made from a short section of rubber tubing to the side tubulature so that its bulb is in the reaction mixture; then the flask is heated in an oil bath. When the temperature of the oil bath reaches 115–120°, the reaction mixture begins to boil, and ethanol soon begins to distil at a vapor temperature of 78–80° at the top of the column. During the course of about 1 hour the bath temperature is raised to about 175°. This promotes a steady distillation of ethanol at a rate which begins to decrease after 30 minutes. The amount of ethanol that distils (70–75 ml.) is always in excess of the stoichiometric amount. Finally, the reaction mixture is kept in the oil bath at 175–180° for 30 minutes (Note 3); an additional small

amount of volatile material distils during this time.

After the reaction mixture has cooled somewhat the flask is disconnected from the column, a Claisen head is attached, and the product is distilled at reduced pressure (Note 4). After a fore-run of about 20 g. (not readily condensed below 40 mm. pressure), the faintly yellow product is collected at 124–126°/3 mm., weight 73–79 g. (80–86%), n_D^{25} 1.5525–1.5540 (Note 4).

B. *N-Ethyl-p-chloroaniline.* In a 500-ml. round-bottomed flask are placed 70 g. (0.38 mole) of N-ethyl-*p*-chloroformanilide and 170 ml. of 10% hydrochloric acid. The mixture is heated under reflux for 1 hour, cooled, then neutralized, and finally made basic with 15% potassium hydroxide solution. The lower layer of N-ethyl-*p*-chloroaniline is separated, and the aqueous layer is saturated with potassium carbonate and extracted with two 200-ml. portions of ether. The ether extracts are combined with the bulk of the product, washed with two 100-ml. portions of water, and then dried over calcium chloride. After the ether has been removed by distillation, the residue is distilled at reduced pressure from a 125-ml. Claisen flask. N-Ethyl-*p*-chloroaniline is collected at 108–110°/5 mm. or 149–150°/40 mm., n_D^{25} 1.5650–1.5661, weight 52–55 g. (87–92%) (Note 5).

2. Notes

1. The checkers used, without purification, white label grades of *p*-chloroaniline and triethyl orthoformate from Eastman Organic Chemicals; the submitters used triethyl orthoformate from Kay-Fries Chemicals Inc., New York.
2. It is most convenient to make connections with standard taper joints. The checkers used with equal satisfaction a 50-cm. column randomly packed with short sections of glass tubing.
3. The submitters report that during this heating period the temperature of the reaction mixture may rise as high as 185–190° on account of an exothermic reaction; however, the checkers did not observe this temperature rise of the reaction mixture. The submitters also report that in some of the preparations mentioned in Note 5 the reaction is more exothermic and the temperature may rise as high as 244°, but this does not cause difficulty.
4. The submitters distilled the product through the 30-cm. packed column which was wrapped with a heating tape for this purpose. If this is done, there are collected about 20 g. of recovered triethyl orthoformate at 65–67°/40 mm. and about 2 g. of ethyl N-*p*-chlorophenylformimidate at 82–83°/40 mm., followed by the product, which has n_D^{25} 1.5559. The checkers obtained the same results when this distillation was carried out through a fractionating column; however, the yield and properties of N-ethyl-*p*-chloroaniline obtained from this material were the same as those of amine obtained from material distilled through a Claisen head.
5. This method is suitable for the mono-N-alkylation of other primary aromatic amines. Trimethyl and triethyl orthoformate are commercially available, and other alkyl orthoformates can be obtained readily from them by

transesterification.[2] The following have been prepared in a similar manner by the submitters.[3]

Product	Yield,%	B.P., °C./mm.	n_D (*t*, °C)
N-Methylaniline	44	104–105/40	1.5701 (22)
N-Ethylaniline	66	92–93/16	—
N-Isoamylaniline	58	149–151/40	1.5212 (25)
N-Methyl-*m*-toluidine	67	120–121/40	1.5557 (25)
N-Ethyl-*m*-toluidine	69	125–127/40	1.5451 (23)
N-Methyl-*p*-chloroaniline	77	141–142/40	1.5799 (25)

3. Discussion

N-Ethyl-*p*-chloroaniline has been prepared by alkylation of *p*-chloroaniline with ethyl bromide[4,5] and by reduction of aceto-*p*-chloroanilide with lithium aluminum hydride.[6] The present procedure, which is based on the results of an investigation by Roberts and Vogt,[3] is a convenient general method for preparation of pure N-alkyl aromatic amines.

References and Notes

1. University of Texas, Austin, Texas.
2. Alexander and Busch, *J. Am. Chem. Soc.*, **74**, 554 (1952); Roberts, Higgins, and Noyes, *J. Am. Chem. Soc.*, **77**, 3801 (1955).
3. Roberts and Vogt, *J. Am. Chem. Soc.*, **78**, 4778 (1956).
4. Hofmann, *Ann.*, **74**, 143 (1850).
5. Crowther, Mann, and Purdie, *J. Chem. Soc.*, **1943**, 58.
6. Bory and Mentzer, *Bull. soc. chim. France*, **1953**, 814.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

amine

Trimethyl and triethyl orthoformate

aceto-p-chloroanilide

ethanol (64-17-5)

calcium chloride (10043-52-4)

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ether (60-29-7)

Ethyl bromide (74-96-4)

potassium hydroxide (1310-58-3)

triethyl orthoformate (122-51-0)

N-Methylaniline (100-61-8)

lithium aluminum hydride (16853-85-3)

N-Ethylaniline (103-69-5)

N-Isoamylaniline

p-chloroaniline (106-47-8)

N-Ethyl-m-toluidine (102-27-2)

N-Ethyl-p-chloroaniline, Aniline, p-chloro-N-ethyl- (13519-75-0)

N-Ethyl-p-chloroformanilide (26772-93-0)

ethyl N-p-chlorophenylformimidate

N-Methyl-m-toluidine (696-44-6)

N-Methyl-p-chloroaniline (932-96-7)

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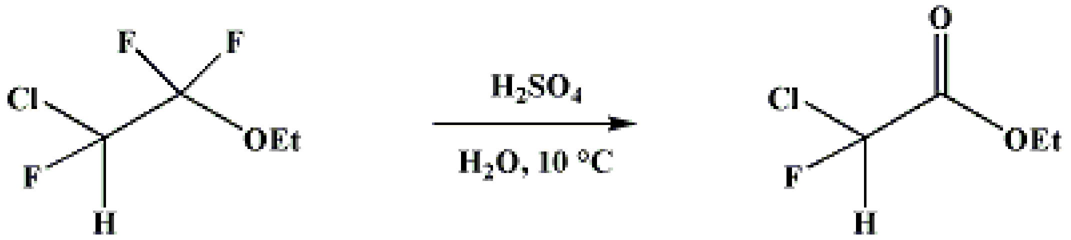
Organic Syntheses, *CV 4, 423*

ETHYL CHLOROFLUOROACETATE

[Acetic acid, chlorofluoro-, ethyl ester]



Submitted by Bruce Englund[1]
Checked by R. S. Schreiber and Burris D. Tiffany.

1. Procedure

Hydrogen fluoride vapors are highly corrosive and poisonous. An efficient hood should be used, and rubber gloves should be worn when dismantling the equipment.

A 2-l. three-necked round-bottomed flask is fitted with a mechanical stirrer and a 500-ml. dropping funnel (Note 1). The third neck is fitted with a thermometer and a length of rubber tubing to lead evolved hydrogen fluoride to the rear of the hood away from the operator. The flask is charged with 340 g. (2.09 moles) of crude 2-chloro-1,1,2-trifluoroethyl ethyl ether (p. 184) and cooled in an ice bath until the temperature of the halo ether is below 5°. From the dropping funnel, 228 ml. of 96% sulfuric acid (420 g., 4.1 moles) is added at such a rate that the temperature can be maintained at 5–15°. The addition requires 30–45 minutes, during which evolution of hydrogen fluoride begins. The reaction mixture is stirred at 10° for 2 hours, then carefully poured onto a mixture of 1 kg. of crushed ice and 500 ml. of water. The product, a nearly white oil, settles out as the lower layer. It is separated, washed until free of acid with three 25-ml. portions of saturated sodium bicarbonate solution (Note 2), then with four 25-ml. portions of water, and dried over 10 g. of Drierite. The weight of crude dried ester is 200–210 g. (68–71%). Fractional distillation gives 190–200 g. (65–68% yield) of pure ethyl chlorofluoroacetate, b.p. 129–130°, n_D^{25} 1.3925 (Note 3).

2. Notes

1. The hydrogen fluoride evolved etches the glass reaction vessel, but the same equipment may be used for 4–6 runs.
2. If the crude product is not washed free of acid considerable decomposition occurs during distillation with consequent reduction in yield.
3. The checkers found it necessary to use a moderately efficient (2 by 12 cm. helix-packed) column to effect satisfactory fractionation.

3. Discussion

Ethyl chlorofluoroacetate has been prepared by the action of sulfuric acid[2] or silica[3] on 2-chloro-1,1,2-trifluoroethyl ethyl ether, and by the reaction of sulfuryl chloride with ethyl fluoroacetate in the presence of benzoyl peroxide.[4] The procedure given is essentially that of Young and Tarrant.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 184

References and Notes

1. Chemical Department, Experimental Station, E. I. du Pont de Nemours and Company, Wilmington, Delaware.
2. Young and Tarrant, *J. Am. Chem. Soc.*, **71**, 2432 (1949).
3. Hanford and Rigby, U. S. pat. 2,409,274 [*C. A.*, **41**, 982 (1947)].
4. Bergmann, Moses, Neeman, Cohen, Kaluszyner, and Reuter, *J. Am. Chem. Soc.*, **79**, 4174 (1957).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica

Drierite

sulfuric acid (7664-93-9)

sodium bicarbonate (144-55-8)

hydrogen fluoride (7664-39-3)

sulfuryl chloride (7791-25-5)

benzoyl peroxide (94-36-0)

2-Chloro-1,1,2-trifluoroethyl ethyl ether (310-71-4)

ethyl chlorofluoroacetate, Acetic acid, chlorofluoro-, ethyl ester (401-56-9)

ethyl fluoroacetate (459-72-3)

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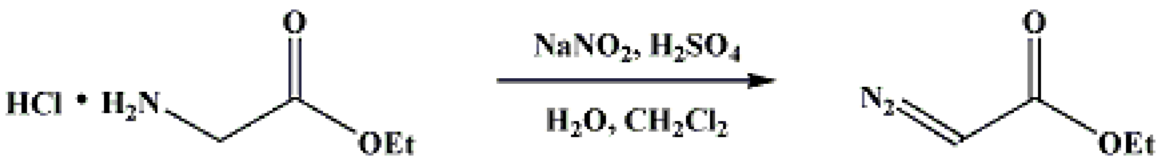
Organic Syntheses, CV 4, 424

ETHYL DIAZOACETATE

[Acetic acid, diazo-, ethyl ester]



Submitted by N. E. Searle[1]
Checked by Melvin S. Newman, G. F. Ottmann, and C. F. Grundmann.

1. Procedure

Diazoacetic esters are potentially explosive and therefore must be handled with caution. They are also toxic and prone to cause development of specific sensitivity. A well-ventilated hood should be used for the entire procedure.

A solution of 140 g. (1 mole) of ethyl glycinate hydrochloride[2] in 250 ml. of water is mixed with 600 ml. of methylene chloride in a 2-l. four-necked round-bottomed flask fitted with a stirrer, dropping funnel, thermometer, and nitrogen inlet tube, and cooled to −5° (Note 1). The flask is flushed with nitrogen and an ice-cold solution of 83 g. (1.2 moles) of sodium nitrite in 250 ml. of water is added with stirring. The temperature is lowered to −9° (Note 1), and 95 g. of 5% (by weight) sulfuric acid is added from the dropping funnel during a period of about 3 minutes (Note 2). The temperature may rise to a maximum of +1° with the cooling bath at −23° (Note 3). The reaction terminates within 10 minutes, when heat is no longer evolved.

The reaction mixture is transferred to an ice-cold 2-l. separatory funnel, and the yellow-green methylene chloride layer is run into 1 l. of cold 5% sodium bicarbonate solution. The aqueous layer is extracted once with 75 ml. of methylene chloride. The methylene chloride and sodium bicarbonate solutions are returned to the separatory funnel and shaken until no trace of acid remains, as shown by indicator paper (Note 4). The golden yellow organic layer is separated, transferred to a dry separatory funnel, and shaken for 5 minutes with 15 g. of granular anhydrous sodium sulfate. The dried ethyl diazoacetate solution is filtered through a cotton plug inserted in the separatory funnel stem, and the bulk of the solvent is distilled through an efficient column at a pressure of about 350 mm. (Note 5). The last traces of solvent are removed at a pressure of 20 mm. and a maximum pot temperature of 35° (Note 6). The yield is 90–100 g. (79–88%) of yellow oil, n_D^{25} 1.462. This product is pure enough for most synthetic work (Note 7) and (Note 8).

2. Notes

1. Lower temperatures may induce the solid methylene chloride dihydrate to separate and interfere with stirring. An acetone bath into which lumps of Dry Ice are introduced as required affords easily controlled cooling.
2. The stated amount of acid has been found sufficient to provide the strongly acidic medium which the reaction requires.
3. Higher reaction temperatures may result in reduced yields.
4. Traces of acid must be eliminated before the diazoacetate solution is concentrated.
5. Efficient solvent separation is indicated by absence of yellow color in the distillate. An 18-in. column packed with Berl saddles is satisfactory.
6. Higher temperatures should be avoided because of the explosive character of ethyl diazoacetate. The product should be placed in dark brown bottles and kept in a cool place. It should be used as soon as possible.
7. Distillation through a 7-in. column packed with glass helices gives a 65% over-all yield, b.p. 29–31°/5 mm. *Anal.* Calcd. for $C_4H_6N_2O_2$: N, 24.55. Found: N, 24.76. Heart-cut material has a refractive index of n_D^{25} 1.4616.[3] Principal loss is due to elimination of nitrogen with formation of high-boiling esters. Both the crude and the distilled products appear to function equally well as synthetic intermediates. *Distillation, even under reduced pressure, is dangerous, for the substance is explosive.*
8. The procedure has proved satisfactory for the preparation of the methyl, butyl, *n*-hexyl, 2-ethylhexyl, and decyl esters of diazoacetic acid.[4] *The methyl ester should be handled with particular caution since heat causes it to detonate with extreme violence.*

3. Discussion

Ethyl diazoacetate has been prepared from sodium nitrite and ethyl glycinate hydrochloride in the presence of diethyl ether.[5] The present procedure utilizes the unique ability of methylene chloride solvent to protect the diazoacetic ester from decomposition by aqueous mineral acid.[4] Hammond claims that the use of halogenated hydrocarbons, such as carbon tetrachloride, leads to a 95% yield of ethyl diazoacetate.[6]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 258
- Org. Syn. Coll. Vol. 6, 913
- Org. Syn. Coll. Vol. 7, 438

References and Notes

1. Contribution No. 360 from the Chemical Department, Experimental Station, E. I. du Pont de Nemours and Company, Wilmington, Delaware.

2. *Org. Syntheses Coll. Vol.* **2**, 310 (1943).
3. Data obtained by V. A. Engelhardt and H. E. Cupery.[1]
4. Searle (to E. I. du Pont de Nemours and Company), U. S. pat. 2,490,714 [*C. A.*, **44**, 3519 (1950)].
5. *Org. Syntheses Coll. Vol.* **3**, 392 (1955).
6. Hammond (to National Distillers Products Corp.), U. S. pats. 2,691,649 and 2,691,650 [*C. A.*, **49**, 11690 (1955)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

methyl, butyl, n-hexyl, 2-ethylhexyl, and decyl esters

sulfuric acid (7664-93-9)

diethyl ether (60-29-7)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

carbon tetrachloride (56-23-5)

nitrogen (7727-37-9)

sodium nitrite (7632-00-0)

methylene chloride (75-09-2)

ethyl diazoacetate, Acetic acid, diazo-, ethyl ester (623-73-4)

ethyl glycinate hydrochloride (623-33-6)

methylene chloride dihydrate

diazoacetate, diazoacetic acid

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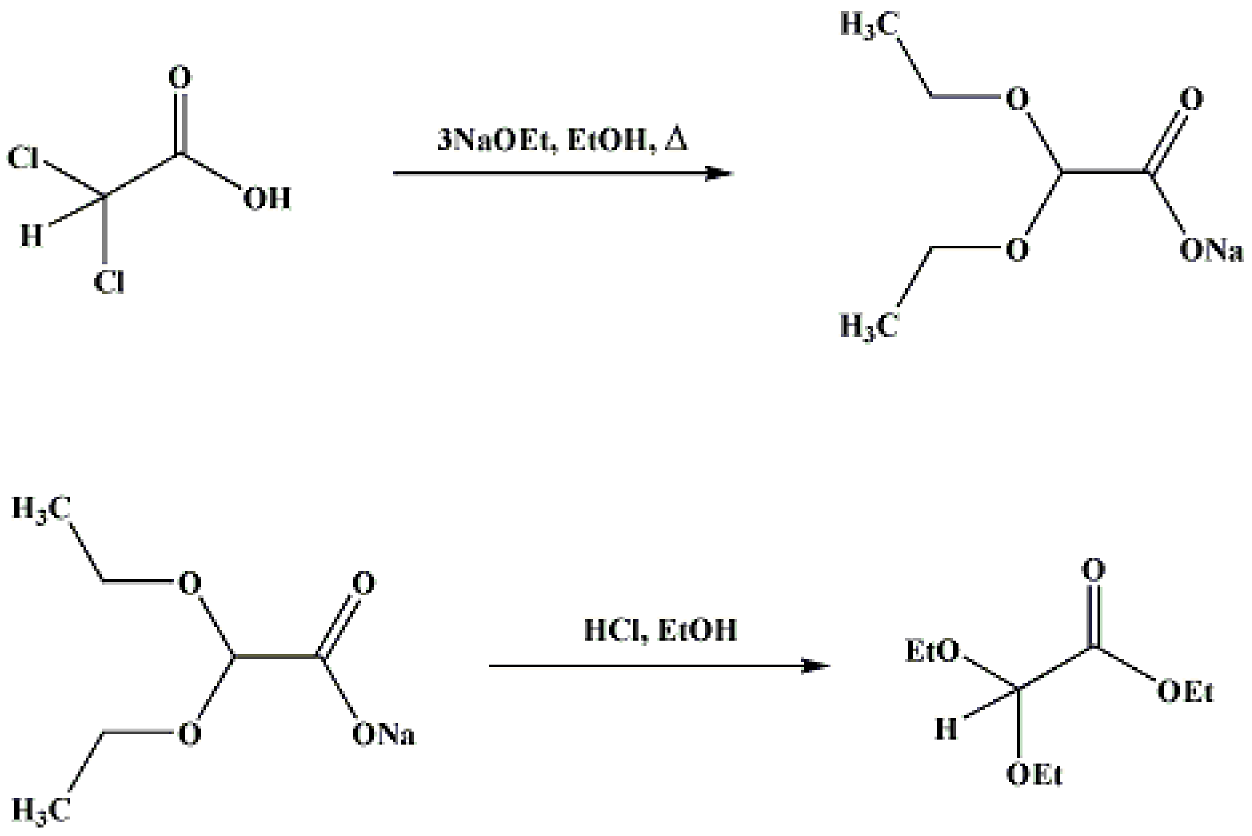
Organic Syntheses, CV 4, 427

ETHYL DIETHOXYACETATE

[Glyoxylic acid, ethyl ester, diethyl acetal]



Submitted by Robert Bruce Moffett[1]
Checked by Charles C. Price and Charles E. Scott.

1. Procedure

A 2-l. three-necked flask (Note 1), fitted with a sealed stirrer (Note 2) and an efficient reflux condenser (protected by a calcium chloride tube), is surrounded by a water bath. Sodium ethoxide is prepared in this flask by adding 31 g. (1.35 g. atoms) of sodium in portions to 450 ml. of absolute ethanol (Note 3). When practically all the sodium has dissolved, 50 g. (0.39 mole) of dichloroacetic acid is added with stirring at such a rate that the solvent refluxes smoothly. About 20 minutes is required. Sodium chloride soon begins to separate, and the solution becomes a yellow-orange color. After the initial reaction subsides, the mixture is heated under reflux with stirring for 3.5 hours.

The water is removed from the water bath and replaced by an ice-salt mixture. A thermometer is placed in the flask with the bulb below the surface of the liquid, and the mixture is cooled below 0°. Then a solution of about 27 g. (0.75 mole) of hydrogen chloride in 200 ml. of absolute ethanol (Note 4) is slowly added (Note 5) during about 40 minutes with stirring and cooling at such a rate that the temperature does not rise above 10°. The mixture is allowed to come to room temperature, and the stirring is

continued for 3 hours. It is then allowed to stand overnight. The reaction mixture is again cooled to 0°, and the excess acid is neutralized to approximately pH 7 by slowly adding sodium ethoxide solution (Note 6). The mixture is tested from time to time during the addition of the alkali by placing a drop on moistened pH test paper. About 75 ml. of sodium ethoxide solution is required. The mixture is then filtered through a large Büchner funnel (Note 7), and the precipitate is extracted thoroughly with ether which is added to the alcoholic filtrate. The solid is discarded.

Most of the solvent is removed by distillation through a Vigreux column under reduced pressure (about 40 mm.) and a pot temperature less than 40°. The product is then transferred to a smaller flask (Note 8). The remainder of the solvent is removed through the Vigreux column at a pressure of about 15 mm. and a boiling point up to about 40°. A Dry Ice-cooled receiver (Note 9) is then attached, and the pressure is lowered by means of a high-vacuum pump. The crude product is distilled until no more material comes over while the flask is heated on a steam bath. This crude product, b.p. 87–88°/17 mm., 69–70°/10 mm., n_D^{25} 1.4073–1.4076, may be redistilled, a pinch of calcium carbonate being added, through an efficient column (Note 10) at a pressure of about 12 mm. The fore-run (boiling point up to about 60°/12 mm.) is discarded. The fraction, b.p. 60–81°/12 mm., is saved for redistillation with a subsequent run. The main fraction is obtained at a boiling range of 81–83°/12 mm. The yield of ethyl diethoxyacetate is 31–34 g. (45–50%) of colorless liquid, n_D^{25} 1.4075.

2. Notes

1. The submitter reports equally satisfactory results when the reaction is carried out in a 12-l. flask on ten times the scale described here.
2. A Hershberg stirrer is excellent for the purpose and may be connected by a mercury seal or a rubber seal[2] lubricated with glycerol (p. 546).
3. The absolute ethanol is dried with sodium and diethyl phthalate.[3]
4. The alcoholic hydrogen chloride can be prepared by passing hydrogen chloride from a cylinder (use safety trap) into 200 ml. of absolute ethanol cooled by an ice bath. From time to time a sample may be withdrawn and titrated with standard alkali to determine the concentration. The exact amount is not critical, but a considerable excess of hydrogen chloride must be used. If several runs are to be made it is convenient to prepare a large quantity of alcoholic hydrogen chloride at one time.
5. Precautions should be taken to prevent absorption of atmospheric moisture by the hydrogen chloride solution. The dropping funnel should be closed or protected by a calcium chloride tube.
6. Enough sodium ethoxide solution for four runs can be made in a 500-ml. flask by adding 18.4 g. of sodium portionwise to 300 ml. of absolute ethanol.
7. If difficulty in the filtration is encountered a filter aid may be used.
8. At this point it is convenient to combine several runs for distillation.
9. The Dry Ice-cooled receiver is conveniently constructed from a two-necked

round-bottomed flask immersed up to the necks in a Dry Ice-ethanol mixture.
10. The submitter used a column packed with 12 in. of 1/8-in. glass helices and fitted with a variable reflux head. The checkers used a 12-in. Vigreux column.

3. Discussion

Ethyl diethoxyacetate has been prepared from dichloroacetic acid by the action of sodium ethoxide followed by esterification of the intermediate diethoxyacetic acid. This esterification has been carried out with ethyl iodide on the sodium salt or on the silver salt.[4,5,6] It has been more conveniently done with ethanol and acid.[7,8,9] Poorer yields are reported when the dichloroacetic acid is first esterified and then treated with sodium ethoxide.[10] Ethyl diethoxyacetate also has been prepared by the reaction of ethanol with the hemiacetal of ethyl glyoxylate in the presence of hydrogen chloride,[11] and by the treatment of 1,2-diethoxy-1,1,2-trichloroethane or 1,2-diethoxy-1-chloroethane with ethanol in the presence of pyridine.[12]

References and Notes

1. The Upjohn Company, Kalamazoo, Michigan.
2. *Org. Syntheses Coll. Vol.* **3**, 368 (1955).
3. *Org. Syntheses Coll. Vol.* **2**, 155 (1943).
4. Schreiber, *Z. Chem.*, **1870**, 167; *Jahresber. Fortschr. Chem.*, **1870**, 642.
5. Johnson and Cretcher, Jr., *J. Biol. Chem.*, **26**, 106 (1916).
6. Rugeley and Johnson, *J. Am. Chem. Soc.*, **47**, 2997 (1925).
7. Wohl and Lange, *Ber.*, **41**, 3612 (1908).
8. Blaise and Picard, *Bull. soc. chim.*, [4] **11**, 539 (1912).
9. Johnson and Cretcher, Jr., *J. Am. Chem. Soc.*, **37**, 2147 (1915).
10. Cope, *J. Am. Chem. Soc.*, **58**, 570 (1936).
11. Korte, Paulus, and Störiko, *Ann.*, **619**, 63 (1958).
12. Baganz, Domaschke, and Krüger, *Chem. Ber.*, **92**, 3167 (1959).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Glyoxylic acid, ethyl ester, diethyl acetal

hemiacetal of ethyl glyoxylate

ethanol (64-17-5)

hydrogen chloride (7647-01-0)

ether (60-29-7)

glycerol (56-81-5)

sodium chloride (7647-14-5)

calcium carbonate (471-34-1)

pyridine (110-86-1)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

dichloroacetic acid (79-43-6)

Ethyl iodide (75-03-6)

diethyl phthalate (84-66-2)

Ethyl diethoxyacetate (6065-82-3)

diethoxyacetic acid

1,2-diethoxy-1,1,2-trichloroethane

1,2-diethoxy-1-chloroethane

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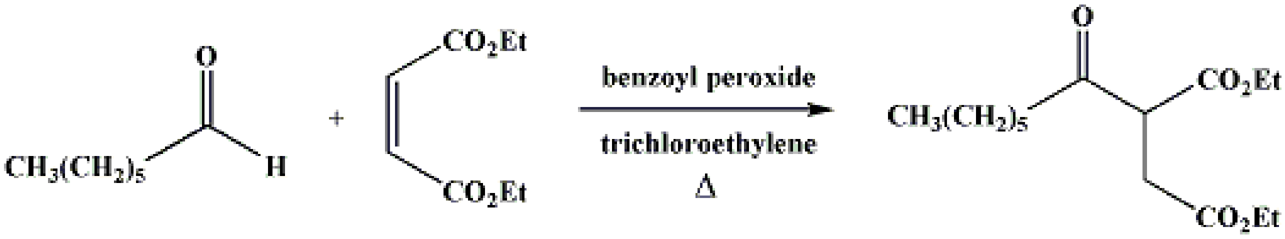
Organic Syntheses, CV 4, 430

ETHYL ENANTHYLSUCCINATE

[Succinic acid, heptanoyl-, diethyl ester]



Submitted by Tracy M. Patrick, Jr. and Floyd B. Erickson[1].
Checked by T. L. Cairns and R. D. Cramer.

1. Procedure

A mixture of 228 g. (2.0 moles) of enanthaldehyde (Note 1) and 172 g. (1.0 mole) of ethyl maleate (Note 2) is placed in a jacketed flask (f.htmig. 9) (Note 3) with condensers attached to the flask and the jacket openings. The jacket is charged with trichloroethylene (Note 4), which is heated to reflux, and, when the reaction mixture reaches 84–85°, 0.5 g. of benzoyl peroxide is added to the mixture through the condenser. After 3–8 hours an additional 0.5-g. portion of benzoyl peroxide is added, and heating is continued for a total of 18–24 hours (Note 5).

Fig. 9.

Fig. 9.

The reaction mixture is distilled through a short (8- to 12-in.) Vigreux column to give 108–111 g. of recovered enanthaldehyde, b.p. 64–65°/38 mm.; 6–16 g. of an intermediate fraction, b.p. 82–128°/1 mm.; and 202–216 g. (71–76% yield) of ethyl enanthylsuccinate, b.p. 119–122°/0.7 mm., n_D^{25} 1.4392–1.4398 (Note 6), (Note 7), and (Note 8).

2. Notes

1. Good-quality enanthaldehyde such as the white label grade supplied by Eastman Kodak Company was distilled before use. It is best stored in a brown bottle under nitrogen for protection against oxidation.
2. Ethyl maleate from Commercial Solvents Corporation, Terre Haute, Indiana, was distilled before use. Ethyl fumarate can be used also, but the yield of product is lower since a much greater proportion of high-boiling compounds is obtained. Al-dehydes do not undergo free-radical addition to maleic anhydride under these conditions.
3. Although this piece of apparatus is not essential, it provides a convenient means of controlling the temperature for a mildly exothermic reaction which must be carried out overnight without close supervision. The submitters carried out one experiment in an ordinary apparatus heated by a mantle. The poorer temperature control (70–91°) resulted in a yield of only 44%.
4. Any other stable liquid having a boiling point in the neighborhood of 80–90° could be substituted for trichloroethylene.

5. The reaction time is not critical. For the sake of convenience the reaction can be started early in the day, the second portion of peroxide added before leaving in the evening, and heating discontinued upon arrival the following morning.
6. The submitters collected material boiling in the range 128–150°/1 mm. and found this product to be satisfactory for the preparation of γ-oxocapric acid (Note 7).
7. The submitters state that ethyl enanthylsuccinate can be hydrolyzed and decarboxylated to γ-oxocapric acid. The reaction is carried out by heating 57 g. of the keto ester with a solution of 140 ml. of concentrated sulfuric acid in 250 ml. of water. The mixture is stirred while the ethanol is removed gradually by distillation over a period of 3 hours. The acid is taken up in benzene, extracted from the benzene with aqueous alkali, and liberated from the alkaline solution by acidification with concentrated hydrochloric acid. After recrystallization from 50% ethanol about 29 g. (78% yield) of γ-oxocapric acid is obtained as colorless crystals, m.p. 69–70°.
The submitters also state that γ-caprilactone can be prepared by hydrogenation of 50 g. of γ-oxocapric acid in 150 ml. of ethanol over 5 g. of Raney nickel at 135° and 1000 p.s.i. Filtration and distillation gives about 38 g. (83% yield) of γ-caprilactone, b.p. 109–110°/2.5 mm., n_D^{25} 1.4470.
8. A number of other acylsuccinic esters can be prepared in a similar fashion from the appropriate saturated aliphatic aldehydes and maleic esters.[2,3] The procedure is equally adaptable to the preparation of α-acyltricarballylic esters from aldehydes and aconitates[2]. Good temperature control (80–90°) is most important for success in these reactions.

3. Discussion

Ethyl enanthylsuccinate has been prepared by the free-radical addition of enanthaldehyde to ethyl maleate.[2]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

γ-caprilactone

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

nitrogen (7727-37-9)

Raney nickel (7440-02-0)

ethyl fumarate (2459-05-4)

benzoyl peroxide (94-36-0)

maleic anhydride (108-31-6)

trichloroethylene (79-01-6)

Ethyl enanthylsuccinate

Succinic acid, heptanoyl-, diethyl ester (41117-78-6)

enanthaldehyde (111-71-7)

ethyl maleate (3990-03-2)

γ-oxocapric acid

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Organic Syntheses, CV 4, 433

ETHYLENIMINE

Submitted by C. F. H. Allen, F. W. Spangler, and E. R. Webster[1].
Checked by R. S. Schreiber, A. C. Ott, and M. F. Murray.

1. Procedure

Caution! This preparation should be carried out in a good hood, and it is advisable to use rubber gloves.

In a 5-l. flask surmounted by a water-cooled still head connected to a 30-in. spiral condenser set for downward distillation and connected to a well-cooled receiver (Note 1), 564 g. (4 moles) of β-aminoethylsulfuric acid (Note 2) is mixed with 1760 g. (1230 ml.) of 40% sodium hydroxide solution (704 g. of sodium hydroxide in 1056 ml. of water). The mixture is heated with a free flame until it just begins to boil. At this point external heating is discontinued (Note 3). The reaction that begins at the boiling point keeps the mixture boiling for several minutes. When this initial reaction has subsided, heating is resumed and about 500 ml. of distillate is collected as quickly as possible in the well-cooled receiver. To the chilled distillate 450–500 g. of potassium hydroxide pellets is added gradually, whereupon the imine separates as an upper layer. The organic layers from four such 4-mole runs are combined and left overnight in a refrigerator over about 400 g. of potassium hydroxide pellets. The aqueous layers are combined and distilled through a wrapped 10-in. Vigreux column attached to a 30-in. spiral condenser. The distillate boiling at 50–100° is chilled thoroughly, and 200–250 g. of potassium hydroxide pellets is added gradually. The upper layer of crude ethylenimine is separated and combined with the larger portion of base (Note 4) and (Note 5).

If an aqueous layer appears during drying of the combined organic layers, the upper layer (about 575–600 g.) is again separated, 200 g. of potassium hydroxide pellets is added, and the whole is distilled through the same apparatus as that used for distilling the aqueous portion. If no layer appears, the base is decanted from the hydroxide and distilled from a fresh 200-g. portion of potassium hydroxide. The fraction boiling at 50–100° (about 350 g.) is collected and dried over 100 g. of potassium hydroxide pellets.

The crude ethylenimine is separated and dried over fresh 100-g. portions of potassium hydroxide until an aqueous layer no longer appears (Note 6). It is then decanted from the drying agent and redistilled from 100 g. of potassium hydroxide.

The yield of ethylenimine (b.p. 56–58°) is 235–250 g. (34–37%). A stick of sodium hydroxide is added to act as a preservative, and the material is best stored in sealed bottles in a refrigerator (Note 7), (Note 8), and (Note 9).

2. Notes

1. Cooling the receiver in a freezing mixture will cut the loss of the distillate to a minimum.
2. β-Aminoethylsulfuric acid of excellent quality is available from the B. F. Goodrich Company.
3. It is well to have an ice bath available to control the exothermic reaction, which may become quite violent.
4. The use of an efficient distilling column is recommended because the crude base contains higher-boiling by-products. One of these is the dimer, N-β-aminoethylethylenimine; b.p. 126–127.5°.
5. It has been suggested that the portion of ethylenimine, boiling at 50–100°, might be collected directly on distillation without separating the organic layer from the aqueous potassium hydroxide layer. This is not advisable, because heating ethylenimine in the presence of a base appears to increase polymerization. The quantity of the organic base contained in the concentrated aqueous solution of potassium hydroxide is sufficient, however, to warrant this distillation of the aqueous layer.
6. If the original separation is done carefully and if sufficient potassium hydroxide is used, an aqueous layer will separate during the first drying only. Should this not be the case, it may be worth while to combine all aqueous portions obtained and redistil them to obtain any material boiling at 50–100°.
7. Yields of 26.5% and 32% of ethylenimine have been reported.[2,3]
8. Ethylenimine is strongly caustic and burns the skin. Inhalation of the vapor causes acute inflammation of the eyes, nose, and throat, with symptoms resembling those of bronchitis. After two or three days, the irritation subsides and the tissues return to normal, without suffering any apparent permanent injury. Continued exposure to the vapor may cause an individual to acquire an extreme sensitivity to it. Ethylenimine is also very inflammable and polymerizes with explosive violence under certain conditions.[4,5]
9. Redistillation over fresh potassium hydroxide of the residue from this final distillation gives an additional 10–15 g. of ethylenimine, boiling at 56–58°. This redistillation is advisable when the residues from three to four 16-mole batches are combined.

3. Discussion

Ethylenimine has been prepared from β-bromoethylamine hydrobromide by reaction with silver oxide,[6] potassium hydroxide,[7] or sodium methoxide;[8] from β-chloroethylamine hydrochloride by reaction with sodium methoxide[8] or sodium

hydroxide;[9] from β-aminoethylsulfuric acid by reaction with sodium hydroxide;[2,3,4,10,11] and by heating oxazolidone, or substances yielding it, to 100–300°.[12]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium hydroxide (1310-73-2)

silver oxide (20667-12-3)

sodium methoxide (124-41-4)

potassium hydroxide (1310-58-3)

β-Bromoethylamine hydrobromide (2576-47-8)

Ethylenimine (9002-98-6)

β-aminoethylsulfuric acid (926-39-6)

N-β-aminoethylethylenimine

β-chloroethylamine hydrochloride (870-24-6)

oxazolidone (497-25-6)

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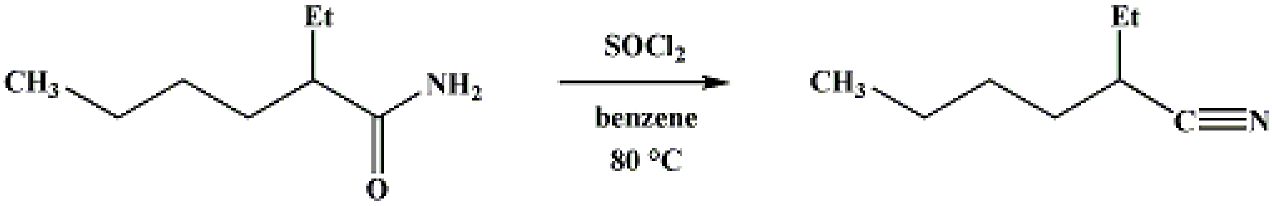
Organic Syntheses, CV 4, 436

2-ETHYLHEXANONITRILE

[Hexanenitrile, 2-ethyl-]



Submitted by John A. Krynitsky and Homer W. Carhart[1].
Checked by H. R. Snyder and Richard S. Colgrove.

1. Procedure

In a 1-l. round-bottomed flask, bearing an efficient reflux condenser (Note 1), are placed 286 g. (2 moles) of 2-ethylhexanamide (Note 2), 300 ml. of dry benzene (Note 3), and 357 g. (218 ml., 3 moles) of thionyl chloride (Note 4). The flask is placed in a water bath, which is heated quickly to 75–80° and maintained at that temperature for 4.5 hours (Note 5). The reaction mixture is transferred to a 1.5-l. beaker and cooled in an ice bath. A mixture of 100 g. of crushed ice and 100 ml. of water is added to decompose the excess thionyl chloride. Cold 50% potassium hydroxide solution is added in small portions, with stirring, until the mixture is alkaline to litmus (Note 6). The mixture is transferred to a separatory funnel, and the layers are separated. The aqueous portion is extracted with 100 ml. of benzene. The benzene solutions are combined and washed once with 150 ml. of 1% sodium carbonate solution and twice with 150-ml. portions of water (Note 7). The mixture is distilled from a modified Claisen flask, the bulk of the solvent being removed at atmospheric pressure. The yield of nitrile is 215–236 g. (86–94%); b.p. 118–120°/100 mm. (Note 8), (Note 9), and (Note 10).

2. Notes

1. Unless the temperature of the water supplied to the condenser is below 20°, a larger amount of thionyl chloride may be required. The condenser should be attached to a gas trap.
2. The 2-ethylhexanamide was prepared in 86–88% yield from technical 2-ethylhexanoic acid (Carbide and Carbon Chemicals Corporation) by a method similar to that described previously,[2] except that the crude amide was filtered directly from the reaction mixture, washed well with water, and dried. The resulting product, which melted at 99–101°, was used without further purification. If the pure amide is desired, this product may be recrystallized (with 83–90% recovery) from 50% ethanol. For 100 g. of amide, 2 l. of 50% ethanol is used, and the hot solution is decolorized with charcoal. The product thus obtained is in the form of white needles which melt at 102–103°.
3. Benzene dried over sodium was used.
4. The submitters used Eastman Kodak Company white label grade thionyl chloride. The checkers purified commercial thionyl chloride (Hooker Electrochemical Company,

refined grade) by the method of Cottle.[3]
5. It is advisable to carry out the reaction in a hood, as hydrogen chloride and sulfur dioxide are evolved. The evolution of gases stops just before the end of the specified heating period.
6. Approximately 150–200 ml. of the potassium hydroxide solution is required.
7. Drying of the solution is unnecessary, since the water present is removed in the next step by azeotropic distillation with benzene.
8. The checkers collected the product at 70.5–72°/10 mm.; n_D^{25} 1.4145.
9. Benzonitrile also can be prepared by this method in comparable yields, but a longer reaction time (7 hours) is required. The method was found to be unsatisfactory for the preparation of the nitriles of azelaic and phthalic acids from the corresponding diamides.
10. The submitters prepared palmitonitrile in more than 90% yield by heating the amide with a benzene solution of thionyl chloride for 6 hours followed directly by distillation. The nitrile so obtained was contaminated with a product having a strong sulfurous odor which could be removed by washing with aqueous mercuric acetate. By the described procedure, palmitonitrile free from objectionable odor was prepared in 80% yield. Troublesome emulsions were formed during the neutralization and washing steps; the addition of a small amount of ethanol aided in breaking the emulsions.

3. Discussion

Racemic 2-ethylhexanonitrile has been obtained only by the action of phosphorus pentachloride on 2-ethylhexanaldoxime;[4] the levorotatory form has been prepared from the active amide by the method described.[5] Other amides have been converted to nitriles by dehydration with thionyl chloride.[5,6]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Racemic 2-ethylhexanonitrile

ethanol (64-17-5)

hydrogen chloride (7647-01-0)

Benzene (71-43-2)

benzonitrile (100-47-0)

phosphorus pentachloride (10026-13-8)

thionyl chloride (7719-09-7)

sodium carbonate (497-19-8)

sulfur dioxide (7446-09-5)

mercuric acetate (1600-27-7)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

2-ETHYLHEXANONITRILE, Hexanenitrile, 2-ethyl- (4528-39-6)

2-ethylhexanamide (4164-92-5)

2-ethylhexanoic acid (149-57-5)

palmitonitrile (629-79-8)

2-ethylhexanaldoxime

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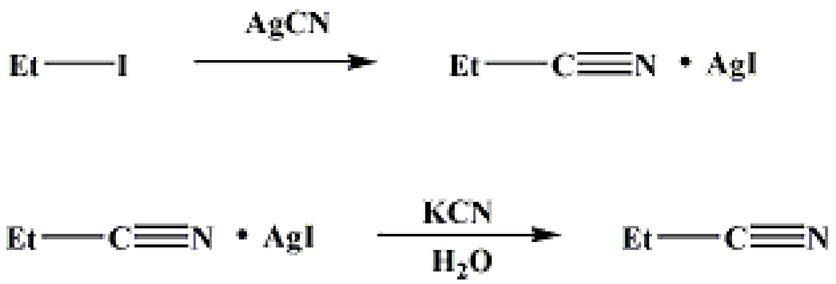
Organic Syntheses, CV 4, 438

ETHYL ISOCYANIDE



Submitted by H. L. Jackson and B. C. McKusick[1].
Checked by N. J. Leonard and L. E. Coleman, Jr..

1. Procedure

Caution! This preparation should be carried out in a well-ventilated hood because ethyl isocyanide has a vile odor. Since ethyl isocyanide has been known to explode,[2] all operations in which it is heated, including its distillation, should be carried out behind a shield of safety glass.

Silver cyanide (454 g., 3.40 moles) is added with stirring to 530 g. (3.40 moles) of ethyl iodide in a 3-l. three-necked round-bottomed flask, equipped with a reflux condenser and a sealed Hershberg stirrer. The third neck of the flask is closed with a stopper. The lower third of the flask is immersed in a steam bath, and the mixture is stirred vigorously until it turns to a viscous, homogeneous, brown liquid (1.7–2.3 hours). Stirring is interrupted, the steam bath is removed, and the stirrer is raised to a position just above the liquid (Note 1). Water (300 ml.) is added through the condenser to avoid loss of product during the addition. Potassium cyanide (610 g., 9.37 moles) and 260 ml. of water are then added through the third neck of the flask, and the mixture is stirred for about 10 minutes, during which the heavy brown liquid below the aqueous solution disappears and a brown layer of ethyl isocyanide appears above the aqueous solution. Stirring is discontinued, the reflux condenser is replaced by one arranged for distillation, and a thermometer extending into the aqueous layer is placed in the third neck. A receiver immersed in an ice bath is attached to the condenser, and the reaction mixture is heated by means of an electric heating mantle, causing a mixture of oil and water to distil. When the distillate contains almost no oil (Note 2), the distillation is discontinued (Note 3). The receiver contains about 200 ml. of crude ethyl isocyanide and 50 ml. of water. Sodium chloride (7 g.) is dissolved in the aqueous layer, and the ice-cold mixture is poured into a separatory funnel. The aqueous layer is separated and discarded. The ethyl isocyanide is washed with two 50-ml. portions of ice-cold saturated aqueous sodium chloride solution and is dried overnight with 10 g. of anhydrous magnesium sulfate. The decanted material is distilled through a 5- to 10-plate column (Note 4), giving 88–102 g. (47–55% yield) of

ethyl isocyanide, b.p. 77–79°/760 mm., n_D^{20} 1.3632. The fore-run, b.p. 63–77°/760 mm., amounts to 15–46 g. and contains 10–15% of ethyl iodide and possibly a few drops of water. Additional pure ethyl isocyanide can be obtained by drying and redistilling this fore-run.

2. Notes

1. Sometimes the liquid crystallizes to a dense solid which immobilizes the stirrer if it has not been raised. The crystallization has no effect on subsequent steps except to necessitate a longer period of stirring after the potassium cyanide is added.
2. The temperature of the residual mixture is 115–120° at this point.
3. The aqueous cyanide solution, which is very toxic, can be disposed of by flushing it down the drain with a large volume of water.
4. The submitters used an 18-in. spinning-band column (inside diameter 10 mm.). The checkers employed a 12-in. helix-packed column.

3. Discussion

Ethyl isocyanide has been obtained by treating ethylamine and chloroform with potassium hydroxide,[3] by pyrolyzing the complex between ethyl isothiocyanate and triethylphosphine,[4] by heating cyanocobaltic (III) acid with ethanol,[5] by passing ethylene and hydrogen cyanide through an electric discharge,[6] or by heating ethyl iodide with silver cyanide[7,8,9] or other metal cyanides.[8,10] The present procedure differs from earlier ones using silver cyanide mainly in that a stirrer is employed. By this modification more than half of the silver cyanide can be converted to ethyl isocyanide, contrary to the belief of the earlier workers, who thought that this was precluded by formation of a complex, $C_2H_5NC{\cdot}AgCN$.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 772
- Org. Syn. Coll. Vol. 7, 27

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

cyanocobaltic (III) acid

ethanol (64-17-5)

chloroform (67-66-3)

sodium chloride (7647-14-5)

hydrogen cyanide (74-90-8)

potassium cyanide (151-50-8)

potassium hydroxide (1310-58-3)

ethylene (9002-88-4)

magnesium sulfate (7487-88-9)

Ethyl iodide (75-03-6)

ethyl isothiocyanate (542-85-8)

silver cyanide (506-64-9)

Ethyl isocyanide (624-79-3)

ethylamine (75-04-7)

triethylphosphine (554-70-1)

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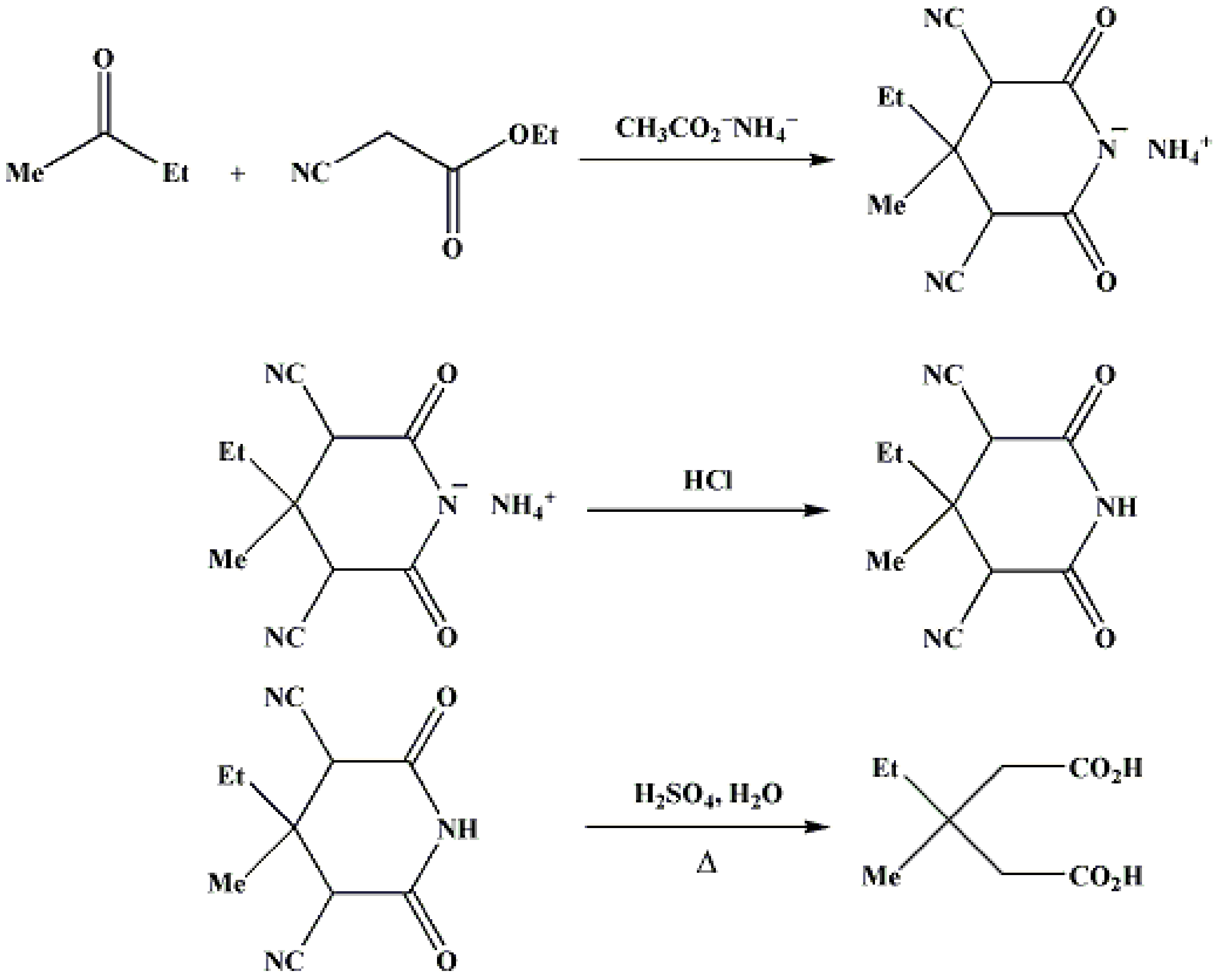
Organic Syntheses, CV 4, 441

β-ETHYL-β-METHYLGLUTARIC ACID

[Glutaric acid, 3-ethyl-3-methyl-]



Submitted by H. H. Farmer and Norman Rabjohn[1].
Checked by Melvin S. Newman and Robert Harper.

1. Procedure

A. *α,α'-Dicyano-β-ethyl-β-methylglutarimide*. In a 2-l. round-bottomed flask are placed 452 g. (4.0 moles) of ethyl cyanoacetate, 144 g. (2.0 moles) of methyl ethyl ketone, 2 g. of ammonium acetate, and 800 ml. of 95% ethanol which contains 80 g. (4.7 moles) of anhydrous ammonia (Note 1) and (Note 2). The flask is stoppered and placed in a refrigerator.

After about 12 hours, the ammonium salt of the imide which has precipitated is removed by filtration (Note 3), washed on a Büchner funnel with about 200 ml. of ether and air-dried. It is dissolved in the minimum amount (about 800 ml.) of boiling water, and the solution is made acid to Congo red paper with concentrated hydrochloric acid. The free imide precipitates immediately and forms a white slurry which is cooled in an ice bath. The imide is collected on a Büchner funnel and dried at 100° in an oven, or in a vacuum desiccator. The yield is 266–287 g. (65–70%), m.p. 187–191° (Note 4).

B. *β-Ethyl-β-methylglutaric acid.* A mixture of 280 g. (1.36 moles) of α,α'-dicyano-β-ethyl-β-methylglutarimide (Note 5) and 1.35 l. of 65% (by weight) sulfuric acid is heated under reflux in a 5-l. round-bottomed flask for 8–10 hours (Note 6). The mixture is allowed to cool, and the precipitate is removed by filtration on a sintered glass (or other suitable type) filter. The crude β-ethyl-β-methylglutaric acid is recrystallized from water (Note 7). The yield of product is 174–191 g. (73–80%), m.p. 78–80°.

2. Notes

1. The ethyl cyanoacetate and methyl ethyl ketone were Eastman Kodak Company white label grade chemicals and were used without further purification. Commercial absolute ethanol was found to give a slightly better yield of the ammonium salt of the imide.
2. It is convenient to pass gaseous ammonia into the ethanol. It is advisable to carry out the preparation and manipulation of the ammonia solution in a hood.
3. The mother liquor is returned to the refrigerator and a second and a third crop of crystals may be collected after 24 and 48 hours. The first crop of crystals usually comprises 95% of the total yield.
4. In taking the melting point of this compound there was still some solid remaining at 200°. The crude imide is satisfactory for conversion to β-ethyl-β-methylglutaric acid and need not be dried before hydrolysis.
5. Although the ammonium salt of the imide may be hydrolyzed to the acid, the free imide appears to give better results.
6. The large flask is used because considerable foaming occurs during the first 2–3 hours of reaction.
7. A ratio of 3 ml. of water to 1 g. of acid gives satisfactory results. The use of activated carbon during the recrystallization is recommended.

3. Discussion

α,α'-Dicyano-β-ethyl-β-methylglutarimide apparently has been prepared only from the condensation of methyl ethyl ketone, ethyl cyanoacetate, and ammonia.[2,3,4,5,6]

β-Ethyl-β-methylglutaric acid has been prepared by the acid hydrolysis of α,α'-dicyano-β-ethyl-β-methylglutarimide,[2,3,4,5,6] 3-cyano-4-ethyl-6-imino-2-keto-4-methylpiperidine-5-carboxamide or the diimide of β-ethyl-β-methylpropane-α,α,α',α'-tetracarboxylic acid;[7] by the oxidation of β-ethyl-β-methyl-δ-valerolactone with chromic acid;[8] and by the reaction of sodium hypobromite on 1,4-dimethyl-1-ethyl-3,5-cyclohexanedione.[9]

The present procedure is essentially that of Guareschi[2] as detailed by Vogel.[4]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

diimide of β-ethyl-β-methylpropane-α,α,α',α'-tetracarboxylic acid

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ether (60-29-7)

ammonium acetate (631-61-8)

carbon (7782-42-5)

chromic acid (7738-94-5)

Ethyl cyanoacetate (105-56-6)

sodium hypobromite

methyl ethyl ketone (78-93-3)

β-Ethyl-β-methylglutaric acid, Glutaric acid, 3-ethyl-3-methyl- (5345-01-7)

3-cyano-4-ethyl-6-imino-2-keto-4-methylpiperidine-5-carboxamide

β-ethyl-β-methyl-δ-valerolactone

1,4-dimethyl-1-ethyl-3,5-cyclohexanedione

α,α'-Dicyano-β-ethyl-β-methylglutarimide

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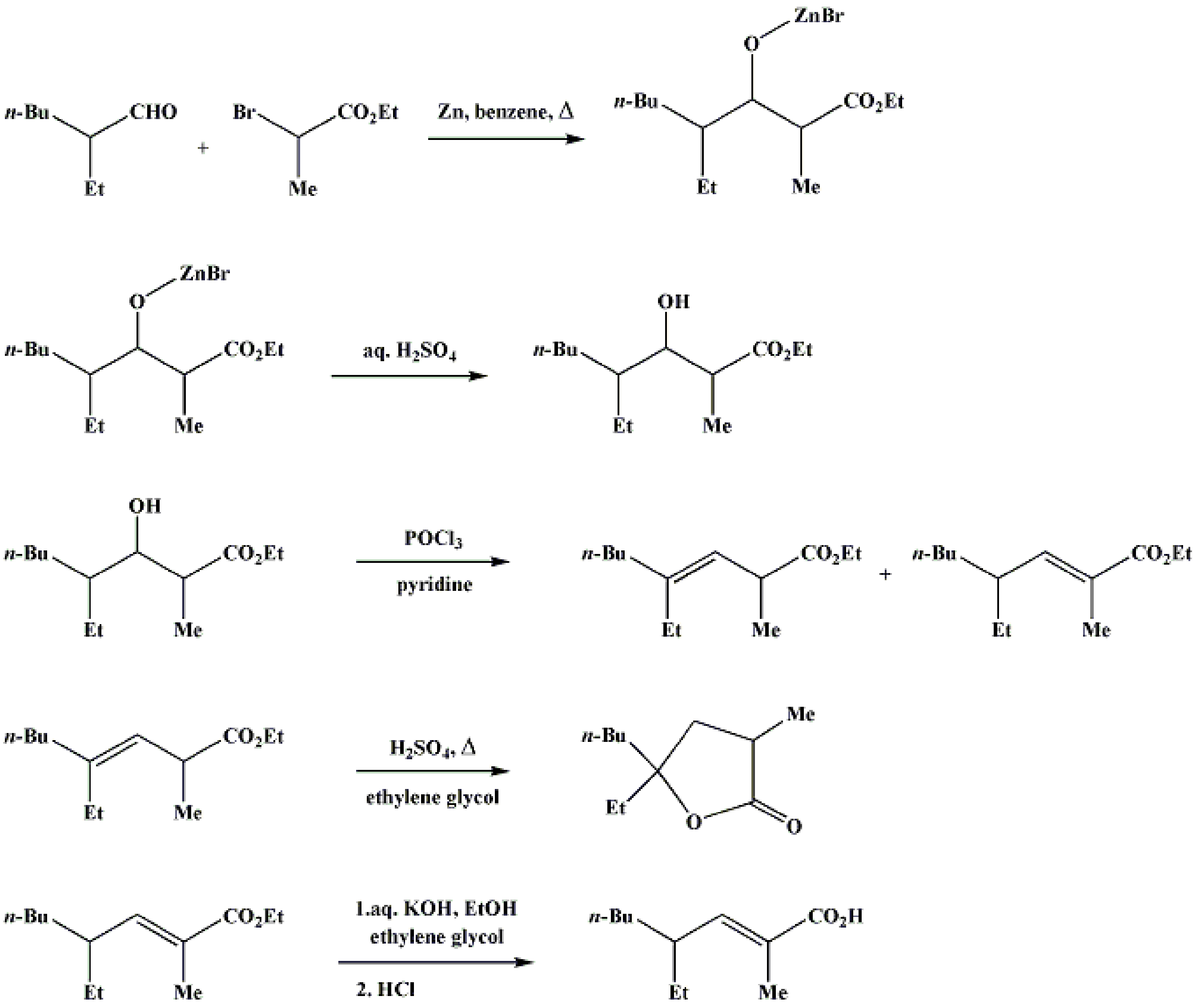
4-ETHYL-2-METHYL-2-OCTENOIC ACID

[2-Octenoic acid, 4-ethyl-2-methyl-]



Submitted by Kenneth L. Rinehart, Jr. and Edward G. Perkins[1].
Checked by Melvin S. Newman and Joseph H. Manhart.

1. Procedure

A 3-l. three-necked flask is equipped with a mercury-sealed mechanical stirrer prepared from tantalum wire, a condenser arranged for distillation, and a 500-ml. pressure-equalizing dropping funnel. The flask is heated on a steam cone, and a slow stream of nitrogen is introduced from a cylinder through a line connected to the top of the dropping funnel. To the flask are added 98.1 g. (1.50 g. atoms) (Note 1) of freshly sandpapered zinc foil which has been cut into narrow strips and rolled loosely, and 750 ml. of thiophene-free benzene previously dried over sodium. To dry the apparatus and contents, 175–200 ml. of benzene is slowly distilled with stirring. Heating is interrupted, and the condenser is quickly arranged for reflux. A U-tube just closed with mercury is attached to the top of the condenser, and nitrogen flow is adjusted so that it bubbles slowly through the mercury. The benzene is heated once again to reflux, and a solution of 64.1 g. (0.50 mole) of 2-ethylhexanal (Note 2) and 271.5 g. (1.50 moles) of ethyl α-bromopropionate *(Caution! (Note 3))* in 500 ml. of dried benzene is placed in the dropping funnel. The first 50 ml. of the solution is added to the flask at once. Usually reaction begins immediately, as evidenced by darkening of the zinc surface and clouding of the solution, but in some cases as much as 15 minutes elapses before the start of reaction. When the reaction has started, the remainder of the aldehyde-bromo ester solution is added during 1 hour, with stirring, as the solution is maintained under reflux. After addition is complete the mixture is heated for an additional 2 hours under reflux, and then cooled to room temperature.

The nitrogen line is removed, and to the solution is added 750 ml. of 12*N* sulfuric acid; the resulting mixture is stirred

vigorously for 1 hour, and then decanted into a 3-l. separatory funnel. After the two phases have separated, the lower aqueous layer is drawn off into a 3-l. separatory funnel containing 1 l. of water which has been used to wash the reaction flask, and the diluted mixture is extracted twice with 350-ml. portions of benzene which have also been employed to rinse the reaction flask. The original organic layer and the combined benzene extracts are kept separate and are washed successively with 500-ml. portions of water, saturated sodium bicarbonate solution, and again with water. The two organic portions are now combined, allowed to stand over anhydrous sodium sulfate until clear, then transferred to a 2-l. distilling flask, from which solvent is distilled at atmospheric pressure, last traces under aspirator pressure. The residue remaining in the flask weighs 150–165 g. (Note 4) and is dehydrated without further purification.

To the residue which contains the crude hydroxy ester there is added 710 g. of pyridine (commercial reagent, C.P. grade), and the mixture is cooled to about 5° in an ice bath. To the cooled solution is added slowly with vigorous swirling 155 g. of phosphorus oxychloride (commercial reagent, C.P.); white crystals form almost immediately. The mixture is allowed to stand 8 hours at room temperature and is finally heated for 1.5 hours on the steam bath (Note 5). It is then cooled to room temperature and decanted into a 5-l. separatory funnel containing 1.25 kg. of cracked ice. Crystals that remain in the flask are decomposed with an additional 125 g. of ice. The flask is rinsed with 1.5 l. of water, and then with 400 ml. of hexane. These washes are added to the material in the separatory funnel. After the two layers have been shaken together thoroughly and then separated, the aqueous phase is extracted with two additional 400-ml. portions of fresh hexane. The three hexane extracts are not combined, but are washed in turn with two 500-ml. portions of 2*N* hydrochloric acid to remove pyridine. Excess hydrochloric acid is removed by washing with three 200-ml. portions of water to pH 4. The clear amber-colored solution is dried over anhydrous sodium sulfate, and solvent is removed by distillation as before. The residue, which weighs 120–135 g. and consists mainly of ethyl 4-ethyl-2-methyl-2-(and-3-)octenoates, is not distilled but is heated with sulfuric acid to convert the Δ^3-isomer to γ-lactone (Note 6), (Note 7), and (Note 8).

To the residue is added 600 ml. of ethylene glycol, followed by 40 ml. of concentrated sulfuric acid. The resulting mixture is heated under vigorous reflux for 20 hours, and then cooled and transferred to a 2-l. stainless-steel or copper flask. To this material is added a solution prepared from 325 g. of potassium hydroxide, 300 ml. of water, and 300 ml. of 95% ethanol. The resultant solution is heated under reflux for 1 hour, and then cooled and transferred to a 5-l. separatory funnel, where it is diluted with 3 l. of water and acidified with 600 ml. of concentrated hydrochloric acid. The organic liquid which separates is diluted with 300 ml. of hexane and separated from the aqueous layer, which is extracted three additional times with 300-ml. portions of hexane. The hexane extracts are washed to pH 4 with three 300-ml. portions of water, and then combined and dried over anhydrous sodium sulfate. For removal of solvent by flash distillation, a 150-ml. round-bottomed flask, equipped with a ground joint attached to a distillation head and side tubulature attached to a dropping funnel, is heated by an oil bath whose temperature is maintained at 130–140°. After all the solution has been added at about the rate of distillation, the dropping funnel is replaced by a capillary, and the last of the solvent is removed at reduced pressure furnished by a water pump. The flask is finally attached to an efficient fractionating column (Note 9), and the residue of mixed α,β-unsaturated acid and γ-lactone is distilled carefully at reduced pressure. After 1–5 g. of fore-run, there are obtained 25–28.5 g. (27–31%) of 4-ethyl-4-hydroxy-2-methyloctanoic acid, γ-lactone, b.p. 118–121°/5.0 mm., n_D^{25} 1.4469–1.4473 (Note 10), 2–3 g. of intermediate, and 27.5–32 g. (30–35%) of 4-ethyl-2-methyl-2-octenoic acid, b.p. 140–143°/5.0 mm., n_D^{25} 1.4613–1.4625 (Note 11).

2. Notes

1. The yield in this reaction is improved by an excess of zinc and bromo ester relative to aldehyde. The present ratio of zinc:bromo ester:aldehyde (3:3:1) gives 87% of intermediate β-hydroxy ester; when the ratio is reduced to 2:3:1, the yield is lowered to about 68%.
2. Commercially available 2-ethylhexanal (Eastman practical grade) is purified by fractional distillation; b.p. 163–163.2°/atm., n_D^{25} 1.4133. Other aldehydes are conveniently prepared by the Rosenmund reduction.[2] If the aldehyde is relatively unstable toward autoxidation,[3] a catalytic amount (0.5–1.0 g.) of hydroquinone is added with the aldehyde-bromo ester solution.
3. Ethyl α-bromopropionate is available commercially (Sapon Laboratories, n_D^{25} 1.4452) and is employed without purification. *Bromo esters are severe lachrymators, and operations that involve transferring these compounds from one vessel to another should be conducted in a well-ventilated hood.*
4. If ethyl 4-ethyl-2-methyl-3-hydroxyoctanoate is isolated by distillation of this residue, the yield is about 100 g. (87%), b.p. 122–124°/4.9 mm., n_D^{25} 1.4415.
5. During heating, the mixture becomes dark brown; however, most of the color is removed by subsequent washing with hydrochloric acid. If terminal heating is omitted, the yield in the dehydration step is reduced by approximately 15%.
6. If no separation of isomers is required, as when the mixture is to be hydrogenated, the mixed esters may be obtained by distillation; yield 75–90 g. (71–85%, based on starting aldehyde). It is extremely difficult to separate the Δ^2- from the Δ^3-ester by fractional distillation, as the two boil only 7° apart; however, by careful fractionation and refractionation through an 0.8 × 125-cm. simple Podbielniak column with partial-reflux head,[4] it is possible to obtain[3] pure ethyl 4-ethyl-2-methyl-2-octenoate, b.p. 102–103°/4.8 mm., n_D^{25} 1.4478, and a nearly pure sample of ethyl 4-ethyl-2-methyl-3-octenoate, b.p. 94–95°/4.8 mm., n_D^{25} 1.4393.

7. When α,γ-dialkyl-β,γ-unsaturated esters and acids are heated with acid, they are slowly converted to γ-lactones. The corresponding α,β-unsaturated isomers are recovered unchanged.[3] Treating a mixture of the two isomeric esters or acids with sulfuric acid in refluxing glycol thus destroys the unconjugated isomer, while leaving the conjugated compound intact. Whereas the isomeric esters and acids have very similar boiling points (Note 6), the γ-lactone boils 20–25° lower than the Δ^2-acid and thus may be separated easily from the acid by fractional distillation. The acid may also be extracted from the lactone with sodium carbonate, or its barium salt may be precipitated by methanolic barium hydroxide. Lactonization as a means of obtaining Δ^2-acid free from Δ^3-isomer is useful for unsaturated acids or esters having an α-alkyl substituent. Conjugated acids or esters without an α-alkyl substituent undergo acid-catalyzed isomerization to the Δ^3-isomer and subsequent lactonization with loss in yield of the Δ^2-compound.[5] In the latter case, use may be made of the differential rate either of bromine addition[6] or of esterification[3] for the conjugated and unconjugated compounds as a means of obtaining pure conjugated acid.

8. In the present case, the proportion of Δ^2-isomer in the original dehydration mixture may be estimated to be 42% of the total unsaturated esters, while an equilibrium mixture contains about 67% of the conjugated compound.[3] Thus the amount of conjugated isomer in the mixture may be considerably increased by base-catalyzed isomerization of the unsaturated esters. For other unsaturated esters, both the composition of the dehydration mixture[3,7] and the equilibrium ratio of the two isomers[3,8] vary, depending on the position and nature of alkyl substituents on the chain, and equilibration is not always desirable. For suitable compounds the following procedure is advantageous; scrupulous protection against moisture is essential.

A 2-l. round-bottomed flask is fitted with a coil condenser (cooling water *inside* the coil) having a large free space in the center and is protected from atmospheric moisture by a calcium chloride tube. The apparatus is dried thoroughly with a Bunsen burner, and 1.5 l. of commercial ethylene glycol is introduced into the flask, together with 50 ml. of diethyl phthalate. The glycol is heated (with salt bath or electric mantle) to a temperature slightly under reflux, the calcium chloride tube is removed, and 50 g. of sodium is added cautiously, in suitable pieces, through the condenser. It is necessary to wait after the addition of each piece, for sodium melts at these temperatures and dissolves in glycol exothermically with vigorous evolution of hydrogen. After all the sodium has been added, the solution is heated for 1 hour under reflux. The condenser is arranged for distillation into a graduated thoroughly dried pressure-equalizing dropping funnel, and, as before, the system is protected by a calcium chloride tube. Heating is resumed, and the first 300 ml. of distilled glycol, which contains any remaining water, is discarded. The separatory funnel is replaced by a 1-l. stainless-steel flask with standard taper joint, which has been thoroughly dried with a burner. In this flask is collected the next 750 ml. of distilled glycol. The condenser and a calcium chloride tube are transferred to the steel flask, the contents are heated to a temperature slightly under boiling, and 57.5 g. of sodium is added in large pieces as before. The residue of unsaturated esters is introduced from a large pipet, a boiling chip is added, and the mixture is heated for 20 hours under reflux. It is then cooled to room temperature and decanted cautiously into a 2-l. round-bottomed flask containing a mixture of 210 ml. of glycol and 70 ml. of concentrated sulfuric acid. To the flask is added an additional 70 ml. of concentrated sulfuric acid, and after the mixture has been heated under reflux for 12 hours it is worked up as described in the final paragraph of the main procedure. Upon fractional distillation of the products, there are obtained 17.5–23.9 g. (19–26%) of 4-ethyl-4-hydroxy-2-methyloctanoic acid, γ-lactone, and 34.1–39.6 g. (38–43%) of 4-ethyl-2-methyl-2-octenoic acid. In this instance, therefore, the yield of Δ^2-acid is increased approximately one-third by isomerizing the dehydration products before converting the Δ^3-acid to lactone.

9. An 0.8 × 125-cm. simple Podbielniak column[4] with partial reflux head is a suitable type.

10. An analytical sample of 4-ethyl-4-hydroxy-2-methyloctanoic acid, γ-lactone, has b.p. 115–117°/4.3 mm., n_D^{25} 1.4462.

11. An analytical sample of 4-ethyl-2-methyl-2-octenoic acid has b.p. 141–142°/4.6 mm., n_D^{25} 1.4628.

3. Discussion

The procedure employed has been previously described by Cason and Rinehart[3] and is a modification of the standard Reformatsky procedure.[9,10] The Reformatsky reaction, which has been reviewed elsewhere,[9] has been widely employed with ketones, somewhat less frequently with aldehydes, and very seldom with α-alkyl aliphatic aldehydes.

4-Ethyl-2-methyl-2-octenoic acid has been prepared only by this method. An alternative synthesis of α-alkyl-α,β-unsaturated acids proceeds via α-bromination of the saturated acid, followed by dehydrohalogenation with quinoline at elevated temperatures.[11] The present method is especially well adapted to preparation of α,γ-dialkyl-α,β-unsaturated acids.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

glycol

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

hydrogen (1333-74-0)

hydroquinone (123-31-9)

sodium bicarbonate (144-55-8)

sodium carbonate (497-19-8)

bromine (7726-95-6)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

mercury (7439-97-6)

Phosphorus Oxychloride (21295-50-1)

pyridine (110-86-1)

potassium hydroxide (1310-58-3)

zinc, zinc foil (7440-66-6)

sodium (13966-32-0)

ethylene glycol (107-21-1)

barium hydroxide (17194-00-2)

Quinoline (91-22-5)

ethyl α-bromopropionate (535-11-5)

hexane (110-54-3)

diethyl phthalate (84-66-2)

4-ETHYL-2-METHYL-2-OCTENOIC ACID, 2-Octenoic acid, 4-ethyl-2-methyl- (6975-97-9)

2-ethylhexanal (123-05-7)

4-ethyl-4-hydroxy-2-methyloctanoic acid, γ-lactone

Ethyl 4-ethyl-2-methyl-3-hydroxyoctanoate

ethyl 4-ethyl-2-methyl-2-octenoate

ethyl 4-ethyl-2-methyl-3-octenoate

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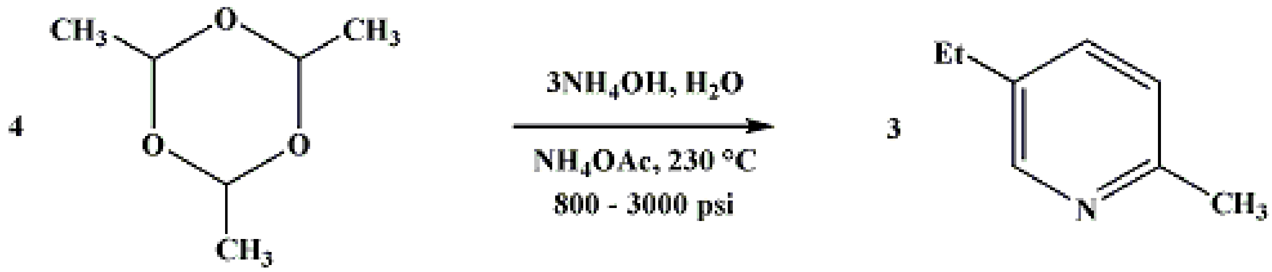
5-ETHYL-2-METHYLPYRIDINE

[2-Picoline, 5-ethyl-]



Submitted by Robert L. Frank, Frederick J. Pilgrim, and Edward F. Riener[1,2].
Checked by R. S. Schreiber and T. L. Alderson.

1. Procedure

Two hundred and sixty-seven grams (296 ml., 4.38 moles) of 28% aqueous ammonium hydroxide, 207.5 g. (209 ml., 1.57 moles) of paraldehyde, and 5.0 g. (0.065 mole) of ammonium acetate are heated to 230° with continuous agitation in a 2-l. steel reaction vessel (Note 1), and the temperature is maintained at 230° for 1 hour (Note 2). The autoclave is then allowed to cool, and the two layers of the reaction mixture are separated (Note 3). To the non-aqueous layer is added 60 ml. of chloroform, causing separation of water which is combined with the aqueous layer. The aqueous layer is extracted with three 50-ml. portions of chloroform, and the extracts are combined with the main portion of the chloroform solution. After removal of the chloroform by distillation at atmospheric pressure, fractional distillation under reduced pressure through a 30-cm. Fenske-type column[3] gives a fore-run of water, paraldehyde, and α-picoline, b.p. 40–60°/17 mm., followed by 72–76 g. (50–53%) of 5-ethyl-2-methylpyridine, b.p. 65–66°/17 mm.; n_D^{20} 1.4971 (Note 4).

2. Notes

1. A steel reaction vessel of the type used for high-pressure catalytic hydrogenations is satisfactory. The pressure of the reaction mixture ranges from 800 to 3000 lb. A larger volume of reactants should not be used in a 2-l. reaction vessel.
2. The reaction is exothermic and in some reaction vessels may cause the temperature to rise above 230° for a short period. This has no apparent effect on the yield of product. The temperature measured is that of a thermocouple inserted in a well in the cover of the autoclave and corresponds to about 250° if the thermocouple is in the wall of the autoclave.
3. The mixture contains a small amount of solid material, apparently due to slight corrosion of the steel reaction vessel. If the solid causes the formation of an emulsion, it can be removed by filtration.
4. The yield may be increased to 60–70% by use of an 8:1 molar ratio of ammonium hydroxide to paraldehyde, but this is generally inconvenient because of the greatly

increased volume of the reaction mixture.

3. Discussion

5-Ethyl-2-methylpyridine (also known as "aldehyde-collidine") has been prepared by heating aldehyde-ammonia;[4] aldehyde-ammonia and acetaldehyde[5,6,7] or paraldehyde;[7,8,9] aldol-ammonia and ammonia;[10] paraldehyde and ammonia;[11,12,13] acetamide,[14] or acetamide and phosphorus pentoxide[15] ethylene glycol and ammonium chloride;[16] ethylidene chloride[17,18] or bromide[19] and amonia; ethylidene chloride and acetamide, ethylamine, or *n*-amylamine;[16] crotonic acid and a calcium chloride-ammonia complex;[20] and by passage of acetylene[21] or acetaldehyde[22] and ammonia over alumina and other catalysts.

A study has been made of catalysts for the present reaction,[23] and a mechanism for the synthesis of pyridine and its derivatives by the Beyer-Chichibabin method has been published.[24]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alumina

aldehyde-ammonia

aldol-ammonia

amonia

calcium chloride-ammonia complex

acetaldehyde (75-07-0)

acetylene (74-86-2)

Acetamide (60-35-5)

ammonia (7664-41-7)

ammonium acetate (631-61-8)

ammonium chloride (12125-02-9)

chloroform (67-66-3)

pyridine (110-86-1)

ethylene glycol (107-21-1)

ammonium hydroxide (1336-21-6)

crotonic acid (3724-65-0)

α-picoline (109-06-8)

ethylamine (75-04-7)

5-Ethyl-2-methylpyridine, 2-Picoline, 5-ethyl- (104-90-5)

ethylidene chloride (75-34-3)

phosphorus pentoxide (1314-56-3)

n-amylamine (110-58-7)

paraldehyde (123-53-7)

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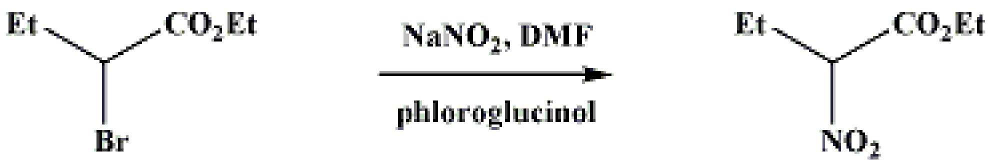
ETHYL α-NITROBUTYRATE

[Butyric acid, 2-nitro-, ethyl ester]



Submitted by Nathan Kornblum and Robert K. Blackwood[1].
Checked by James Cason, Joanne Facaros, and William G. Dauben.

1. Procedure

Ethyl α-bromobutyrate (58.5 g., 0.30 mole) (Note 1) is poured into a stirred mixture of 600 ml. of N,N-dimethylformamide (DMF) (Note 1), 36 g. of sodium nitrite (0.52 mole) (Note 1), and 40 g. of anhydrous phloroglucinol (0.32 mole) (Note 2) contained in a 1-l. three-necked flask equipped with a sealed stirrer. The flask is closed, except for a tube containing calcium chloride, and immersed in a water bath maintained at room temperature (Note 3). Stirring is continued for 2.5 hours (Note 4); then the reaction mixture is poured into 1.2 l. of ice water layered over with 300 ml. of ether (Note 5). After separation of the upper layer, the aqueous phase is extracted with four 100-ml. portions of ether. The combined extracts are washed with four 100-ml. portions of water and then dried over anhydrous magnesium sulfate. The magnesium sulfate is removed by suction filtration and washed with four 25-ml. portions of ether which are combined with the filtered extract.

The ether is distilled through a small column (Note 6), under reduced pressure, from a 1-l. flask which is heated by a bath whose temperature is gradually raised to about 60°. The residual yellow liquid is transferred, with the aid of a little anhydrous ether, to a 100-ml. flask, and the remaining solvent is distilled through the column under reduced pressure. Rectification of the residue yields 2–3 g. of fore-run boiling in the range 33–71°/1 mm. which is followed by 33–36 g. (68–75%) of colorless ethyl α-nitrobutyrate, b.p. 71°/1 mm., n_D^{20} 1.4233 (Note 7), (Note 8), and (Note 9).

2. Notes

1. The ethyl α-bromobutyrate employed was redistilled Eastman Kodak white label grade material, b.p. 64°/15 mm., n_D 1.4479. Technical DMF (du Pont) was used, and the sodium nitrite was an analytical grade.
Subsequent to the checking of this preparation, the submitters reported that DMSO (dimethyl sulfoxide) may be a somewhat better solvent for this preparation than is DMF. Since sodium nitrite is more soluble in DMSO, only

250 ml. of this solvent is required for the preparation. The more concentrated solution permits a reduction in reaction time to about 1.5 hours.

2. Ringwood Chemical Corporation technical grade phloroglucinol dihydrate was rendered anhydrous by heating for 3 hours at 110°. By reacting rapidly with any ethyl α-nitritobutyrate formed, it prevents nitrosation of the α-nitro ester. In the absence of phloroglucinol all the ethyl α-nitrobutyrate is destroyed.[2,3]

3. The reaction mixture becomes homogeneous and turns deep redbrown shortly after the addition of the α-bromo ester. The deep color is, presumably, due to nitrosated phloroglucinol; however, this in no way interferes with subsequent isolation of product.

4. Two hours allows more than sufficient time for complete reaction. Since the yield is not critically dependent on this factor, no attempt was made to establish the minimum reaction time. Even after a 17-hour reaction time there is no decrease in yield.

5. Approximately 200 ml. of this ether is required to saturate the aqueous DMF layer.

6. A 60 × 1 cm. externally heated column, packed with 1/8-in. glass helices and equipped with a total reflux variable take-off head, was used by the submitters.

7. Toward the end of the rectification the jacket of the column is heated to 90–95° in order to obtain the last few grams of product.

8. The ethyl α-nitrobutyrate dissolves rapidly in 10% aqueous sodium hydroxide and dissolves completely in saturated aqueous sodium carbonate on shaking for 2–3 minutes.

9. This procedure has been applied successfully to the synthesis of other α-nitro esters from α-bromo esters,[3] as listed below; ethyl bromoacetate is exceptional in that it fails to give ethyl nitroacetate.

SYNTHESIS OF α-NITRO ESTERS FROM α-BROMO ESTERS

α-Nitro Ester	Reaction Time, hr.	Yield, %
Ethyl α-nitropropionate	2	62
Ethyl α-nitrocaproate	5	74
Ethyl α-nitroisobutyrate[a]	44	78
Ethyl α-nitroisovalerate	150	67
Ethyl α-phenyl-α-nitroacetate	2.5	70

[a] No phloroglucinol employed.

3. Discussion

Ethyl α-nitrobutyrate may be prepared in 75% yield by the reaction of silver nitrite with ethyl α-iodobutyrate,[4] in 82% yield by the reaction of sodium nitrite with ethyl α-

bromobutyrate in dimethyl sulfoxide,[5] and in 51% and 46% yields from the appropriately substituted malonic or acetoacetic ester by nitration with acetone cyanohydrin nitrate, followed by cleavage of the nitrated esters by means of sodium hydride.[6] It also has been prepared in 18% yield by direct nitration and subsequent decarboxylation of diethyl ethylmalonate.[7] The present method offers the advantage of using sodium nitrite.

References and Notes

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6. Emmons and Freeman, *J. Am. Chem. Soc.*, **77**, 4391 (1955).
7. Kornblum and Eicher, *J. Am. Chem. Soc.*, **78**, 1494 (1956); Ulpiani, *Atti. reale accad. Lincei*, [5] **13**, II, 346 (1904).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethyl α-nitritobutyrate

ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium carbonate (497-19-8)

sodium nitrite (7632-00-0)

Phloroglucinol (108-73-6)

phloroglucinol dihydrate (6099-90-7)

magnesium sulfate (7487-88-9)

silver nitrite (7783-99-5)

Ethyl bromoacetate (105-36-2)

N,N-dimethylformamide, DMF (68-12-2)

sodium hydride (7646-69-7)

dimethyl sulfoxide, DMSO (67-68-5)

diethyl ethylmalonate (133-13-1)

Ethyl α-nitrobutyrate, Butyric acid, 2-nitro-, ethyl ester (2531-81-9)

Ethyl α-bromobutyrate (533-68-6)

ethyl nitroacetate (626-35-7)

Ethyl α-nitropropionate (2531-80-8)

Ethyl α-nitrocaproate

Ethyl α-nitroisovalerate

Ethyl α-phenyl-α-nitroacetate

ethyl α-iodobutyrate

Acetone cyanohydrin nitrate (40561-27-1)

Ethyl α-nitroisobutyrate

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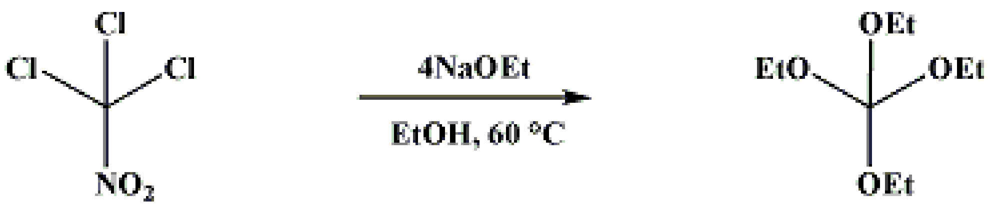
Organic Syntheses, CV 4, 457

ETHYL ORTHOCARBONATE

[Orthocarbonic acid, tetraethyl ester]



Submitted by John D. Roberts and Robert E. McMahon[1].
Checked by William S. Johnson and William E. Loeb.

1. Procedure

This preparation should be conducted in a hood to avoid exposure to chloropicrin.

A solution of sodium ethoxide is prepared under nitrogen from 70 g. (3.04 g. atoms) of sodium and 2 l. of absolute ethanol (Note 1) in a 3-l. three-necked flask which is equipped with mechanical stirrer, efficient reflux condenser, dropping funnel, and a thermometer which dips below the level of the liquid in the flask. Chloropicrin (100 g., 0.61 mole) (Note 2) is placed in the dropping funnel, and the stirred solution is heated to 58–60° with a water bath. The chloropicrin is added at a rate of 30–35 drops per minute until the reaction becomes self-sustaining (about 20 minutes), at which point the water bath is removed and the balance of the chloropicrin is added at a rate sufficient to maintain the temperature at 58–60° (Note 3). When the addition, which requires nearly 2 hours, is complete, the stirrer is stopped and the mixture is allowed to stand overnight.

The flask is connected to a 2 by 50 cm. Vigreux column equipped with a total-reflux partial take-off head, and all but about 400 ml. of the ethanol is removed at 200 mm. pressure with a reflux ratio greater than 5:1 (Note 4).

The residue is cooled, diluted with 1.2 l. of water, and transferred to a 2-l. separatory funnel. The organic layer is separated, washed with 200 ml. of saturated salt solution, and dried over anhydrous magnesium sulfate. The aqueous layer is extracted with a total of 800 ml. of ether used in several small portions. The ethereal extracts are combined, washed first with 500 ml. of water then with 500 ml. of saturated salt solution, and finally dried over anhydrous magnesium sulfate. The ether is removed through a 1.8 by 25 cm. glass-helix-packed fractionating column with a total-reflux partial take-off head. The residue is combined with the balance of the crude product and distilled through the fractionating column at atmospheric pressure. The yield of ethyl orthocarbonate is 54–57.5. g. (46–49%); b.p. 158–161°; n_D^{25} 1.3905–1.3908.

2. Notes

1. The absolute ethanol was a good commercial grade and contained less than 0.1% of water according to the paraffin-oil test.[2]
2. Chloropicrin is a skin irritant and a lachrymator. No difficulty was experienced when the preliminary steps were carried out in a good hood.
3. Care should be taken to regulate the temperature and rate of addition of chloropicrin as specified in order to avoid accumulation of unreacted chloropicrin in the reaction mixture during the induction period; otherwise the reaction, which is strongly exothermic, may get out of control.
4. A water bath should be used as a heat source to avoid over-heating, which leads to lowered yields. This distillation should be carried out carefully to prevent loss of product by co-distillation with the ethanol.

3. Discussion

The above procedure is essentially that of Tieckelmann and Post.[3] Ethyl orthocarbonate has been prepared by the reaction of chloropicrin and sodium ethoxide by Bassett[4] and Röse.[5] Thiocarbonyl perchloride has been reported[3,6] to react with sodium ethoxide to give good yields of ethyl orthocarbonate.

References and Notes

1. Massachusetts Institute of Technology, Cambridge, Massachusetts.
2. Robertson, *Laboratory Practice of Organic Chemistry*, p. 177, The Macmillan Company, New York, 1943.
3. Tieckelmann and Post, *J. Org. Chem.*, **13**, 265 (1948).
4. Bassett, *Ann.*, **132**, 54 (1864).
5. Röse, *Ann.*, **205**, 249 (1880).
6. Connolly and Dyson, *J. Chem. Soc.*, **1937**, 827.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

chloropicrin

Thiocarbonyl Perchloride

ethanol (64-17-5)

ether (60-29-7)

nitrogen (7727-37-9)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

magnesium sulfate (7487-88-9)

Ethyl orthocarbonate

Orthocarbonic acid, tetraethyl ester (78-09-1)

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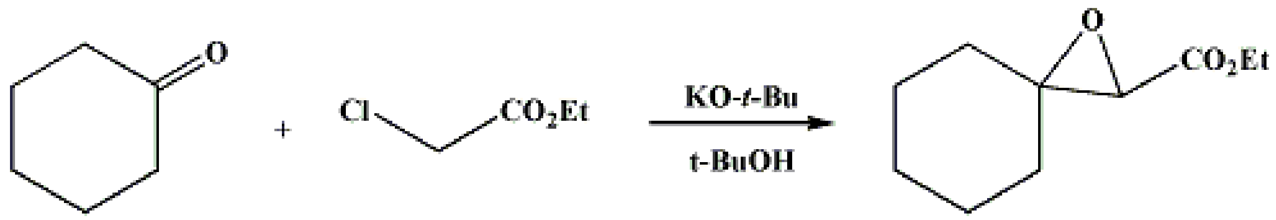
Organic Syntheses, *CV 4, 459*

ETHYL β,β-PENTAMETHYLENEGLYCIDATE

[1-Oxaspiro[2.5]octane-2-carboxylic acid, ethyl ester]



Submitted by Richard H. Hunt, Leland J. Chinn, and William S. Johnson[1].
Checked by N. J. Leonard and F. P. Hauck, Jr..

1. Procedure

The reaction is conducted in a 500-ml. round-bottomed three-necked flask to which are attached (ground-glass joints) a rubber slip-sleeve-sealed wire stirrer, a thermometer, and a pressure-equalized dropping funnel. The top of the dropping funnel is connected to a system for exhausting and filling with nitrogen (p. 133). The apparatus is flame-dried at reduced pressure, and the flask is charged with 14.50 g. (0.148 mole) of freshly distilled cyclohexanone and 18.15 g. (0.148 mole) of freshly distilled ethyl chloroacetate. A solution of 6.0 g. (0.153 g. atom) of potassium in 125 ml. of dry *tert*-butyl alcohol (Note 1) and (Note 2) is introduced into the dropping funnel, and the system is exhausted and filled with nitrogen. The flask is cooled with an ice bath, stirring is commenced, and the solution of potassium *tert*-butoxide is added from the dropping funnel over a period of about 1.5 hours, the temperature of the reaction mixture being maintained at 10–15°. After the addition is complete, the mixture is stirred for an additional 1–1.5 hours at about 10°. Most of the *tert*-butyl alcohol is removed by distillation from the reaction flask at reduced pressure (water aspirator) and a bath temperature of 100°. The oily residue is taken up in ether. The ether solution is washed with water, then with saturated aqueous sodium chloride solution, and is finally dried over anhydrous sodium sulfate. The residue obtained on evaporation of the ether is distilled through a 6-in. Vigreux column to give 22.5–26.0 g. (83–95% yield) of colorless glycidic ester, b.p. 134–137°/21 mm., 147–152°/30 mm., n_D^{25} 1.4568–1.4577 (Note 3).

2. Notes

1. The preparation of potassium *tert*-butoxide is carried out according to a procedure already described (p.132). Particular attention should be paid to the precautions in handling potassium.
2. The *tert*-butyl alcohol may be dried over sodium (p.134). Scrupulously dry *tert*-butyl alcohol may be prepared by distilling alcohol thus treated from calcium hydride (about 1 g./4 l.), obtainable from Metal Hydrides, Inc.
3. This material is of satisfactory quality, as shown by its conversion to solid

derivatives in good yield.[2]

3. Discussion

Ethyl β,β-pentamethyleneglycidate has been prepared in 65% yield by the condensation of cyclohexanone with ethyl chloroacetate in the presence of sodium ethoxide,[3,4] and in 50% yield in the presence of sodium in xylene.[4,5] The present procedure employs potassium *tert*-butoxide as the condensing agent.[2]

References and Notes

1. University of Wisconsin, Madison, Wisconsin.
2. Johnson, Belew, Chinn, and Hunt, *J. Am. Chem. Soc.*, **75**, 4995 (1953).
3. Darzens and Lefebure, *Compt. rend.*, **142**, 714 (1906); Rodinov and Kiseleva, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk*, **1952**, 278 [*C. A.*, **47**, 3300 (1953)]; *Akad. Nauk S.S.S.R., Inst. Org. Khim., Sintezy Org. Soedinenii, Sbornik*, **2**, 57 (1952) [*C. A.*, **48**, 570 (1954)].
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5. Lunt and Sondheimer, *J. Chem. Soc.*, **1950**, 2957; Martynov, *Zhur. Obshchei Khim.*, **23**, 2006 (1953) [*C. A.*, **49**, 3124 (1955)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ether (60-29-7)

Cyclohexanone (108-94-1)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

Ethyl chloroacetate (105-39-5)

potassium (7440-09-7)

xylene (106-42-3)

tert-butyl alcohol (75-65-0)

Ethyl β,β-pentamethyleneglycidate, 1-Oxaspiro[2.5]octane-2-carboxylic acid, ethyl ester (6975-17-3)

calcium hydride (7789-78-8)

potassium tert-butoxide (865-47-4)

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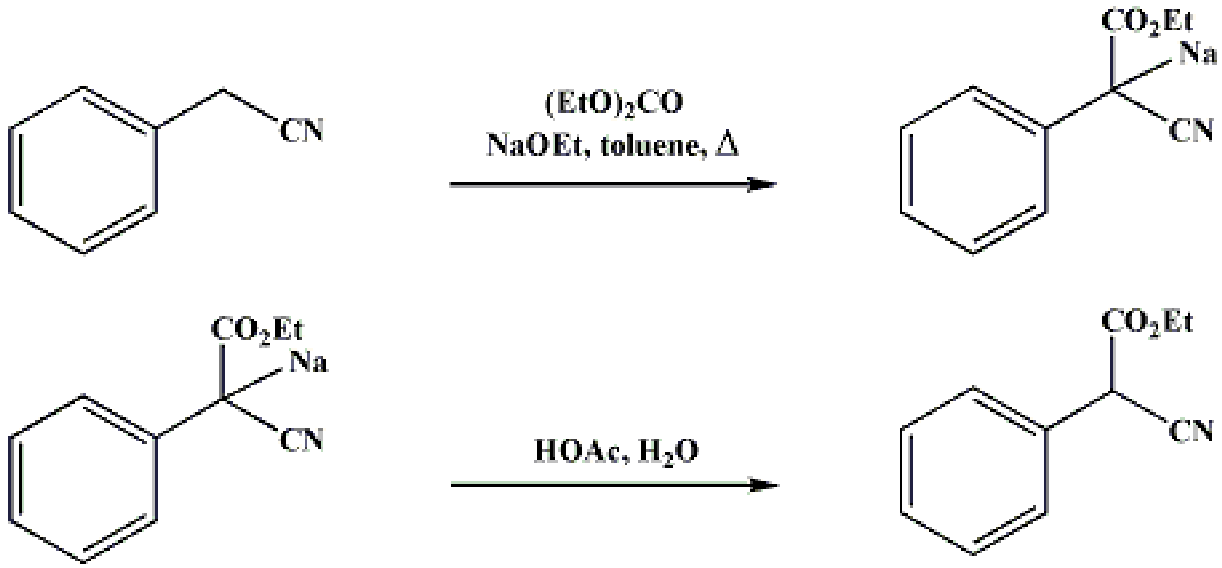
ETHYL PHENYLCYANOACETATE

[Acetic acid, cyanophenyl-, ethyl ester]



Submitted by E. C. Horning and A. F. Finelli[1].
Checked by William S. Johnson and H. Wynberg.

1. Procedure

Sodium ethoxide is prepared from 12.0 g. (0.52 g. atom) of sodium and 300 ml. of anhydrous ethanol in a 1-l. three-necked round-bottomed flask fitted with a reflux condenser carrying a calcium chloride tube. After the sodium has dissolved completely, the condenser is arranged for distillation under reduced pressure and the excess ethanol is removed by heating the flask on a steam bath while the system is maintained at the pressure obtained with an ordinary aspirator (Note 1).

As rapidly as possible, after removal of the ethanol, the flask is fitted with a rubber-sealed stirrer, a dropping funnel, a distilling head containing a thermometer, and a condenser arranged for distillation into a flask protected by a calcium chloride tube. There are then added 300 ml. (292 g., 2.5 moles) of dry diethyl carbonate, 80 ml. of dry toluene, and 58.5 g. (0.50 mole) of phenylacetonitrile (Note 2). The flask is heated, with good stirring, and the cake of sodium ethoxide soon dissolves. When distillation has started, dry toluene is added dropwise at about the same rate that the distillate is collected. Approximately 200–250 ml. of toluene should be added in a period of 2 hours (Note 3) while stirring and distillation are continued.

The mixture is cooled and transferred to a 1-l. beaker. After addition of 300 ml. of cold water, the aqueous phase is acidified with 35–40 ml. of acetic acid. The layers are separated and the water solution is extracted with three 75-ml. portions of ether. The

organic solutions are combined, washed with 100 ml. of water, and dried over anhydrous magnesium sulfate. The low-boiling solvents are removed by distillation at atmospheric pressure, and the residue is distilled under reduced pressure through a short (15-cm.) Vigreux column. After a 1–5 g. forerun, the product is collected at 125–135°/3–5 mm. (Note 4). The yield is 66–74 g. (70–78%).

2. Notes

1. The success of this procedure is dependent upon the quality of the sodium ethoxide. The ethanol should be dried before use,[2] and the sodium ethoxide should not be heated to a temperature higher than 90–100°. The dry material can be transferred, but in this case it is advisable to prepare it in the flask in which it is to be used.
2. Commercial phenylacetonitrile should be distilled before use. The diethyl carbonate and toluene are dried by distillation.
3. Any ethanol remaining in the sodium ethoxide, together with the ethanol produced during the reaction, is removed during this period. The progress of the carbethoxylation reaction can be followed by temperature readings. During the first half of the heating period distillation usually occurs at a vapor temperature of 80–85°, but as the reaction nears completion and the ethanol is removed, the temperature rises to 110–115°. Near the end of the period, the sodium salt of ethyl phenylcyanoacetate appears as a precipitate.
4. Other observed boiling points are 129–131°/3 mm., 145–150°/7–8 mm. The product is a colorless liquid, n_D^{25} 1.5012-1.5019.

3. Discussion

This procedure is a modification of the method of Wallingford, Jones, and Homeyer.[3] The carbethoxylation of phenylacetonitrile is the only method of preparative value for this compound.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 776

References and Notes

1. University of Pennsylvania, Philadelphia, Pennsylvania.
2. *Org. Syn. Coll. Vol.* **2**, 155 (1943).
3. Wallingford, Jones, and Homeyer, *J. Am. Chem. Soc.*, **64**, 576 (1942); Testa, Fontanella, Christiani, and Fava, *Ann.*, **614**, 158 (1958).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium salt of ethyl phenylcyanoacetate

ethanol (64-17-5)

acetic acid (64-19-7)

ether (60-29-7)

toluene (108-88-3)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

phenylacetonitrile (140-29-4)

magnesium sulfate (7487-88-9)

diethyl carbonate (105-58-8)

Ethyl phenylcyanoacetate, Acetic acid, cyanophenyl-, ethyl ester (4553-07-5)

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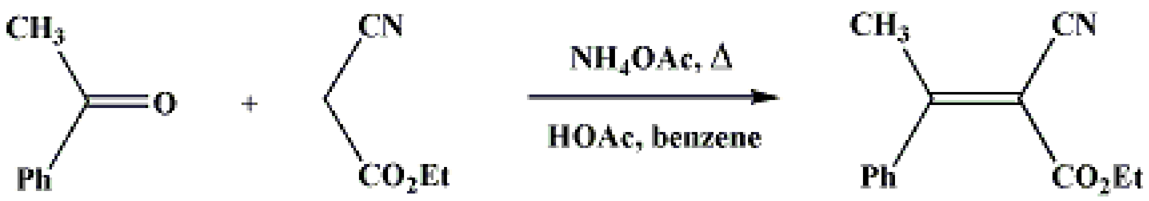
Organic Syntheses, CV 4, 463

ETHYL (1-PHENYLETHYLIDENE)CYANOACETATE

[Cinnamic acid, α-cyano-β-methyl-, ethyl ester]



Submitted by S. M. McElvain and David H. Clemens[1].
Checked by W. E. Parham, Perry W. Kirklin, Jr., and Wayland E. Noland.

1. Procedure

In a 1-l. three-necked round-bottomed flask fitted with a Hershberg stirrer and a constant water separator (Note 1) surmounted by a reflux condenser are placed 120 g. (1 mole) of acetophenone, 113 g. (1 mole) of ethyl cyanoacetate (Note 2), 15.4 g. (0.2 mole) of ammonium acetate, 48.0 g. (0.8 mole) of glacial acetic acid, and 200 ml. of benzene. The reaction mixture is stirred and heated under reflux for 9 hours during which time 28–33 ml. of lower layer is collected in the water separator (Note 3). To the cooled reaction mixture is added 100 ml. of benzene, and the whole is extracted with three 100-ml. portions of water. The combined aqueous layers are extracted with 30 ml. of benzene, which is then added to the organic layer from the previous extraction. Anhydrous magnesium sulfate (15 g.) is added, and, after swirling occasionally for 10 minutes, the mixture is filtered by suction and the magnesium sulfate washed with two 25-ml. portions of benzene. The benzene is removed by distillation at reduced pressure and the residual oil distilled rapidly through a 15-cm. column. The yield of ester is 113–125 g. (52–58%), b.p. 135–160° (0.35 mm.) (Note 4).

2. Notes

1. A typical water separator has been described by Cope et al.[2]
2. Eastman Kodak white label grade acetophenone and ethyl cyanoacetate are used without further purification. The checkers used Matheson, Coleman, and Bell acetophenone and ethyl cyanoacetate without further purification.
3. The checkers used ammonium acetate which was slightly moist; consequently 33.5–34.5 ml. of lower layer was collected.
4. The checkers report the refractive index of the product to be $n_D^{25.1}$ 1.5468–1.5469.

3. Discussion

The above procedure is essentially that described by Cope et al.[2] Ethyl (1-phenylethylidene)cyanoacetate has been prepared also by condensing acetophenone with ethyl cyanoacetate in the presence of zinc chloride and aniline,[3] and other catalysts.[4] Additional aralkylidenecyano esters have been prepared by the present procedure.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 662

References and Notes

1. University of Wisconsin, Madison, Wisconsin.
2. Cope, Hofmann, Wyckoff, and Hardenbergh, *J. Am. Chem. Soc.*, **63**, 3452 (1941).
3. Scheiber and Meisel, *Ber.*, **48**, 238 (1915).
4. Cragoe, Robb, and Sprague, *J. Org. Chem.*, **15**, 381 (1950).
5. McElvain and Clemens, *J. Am. Chem. Soc.*, **80**, 3915 (1958).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

acetic acid (64-19-7)

Benzene (71-43-2)

ammonium acetate (631-61-8)

aniline (62-53-3)

Acetophenone (98-86-2)

zinc chloride (7646-85-7)

Ethyl cyanoacetate (105-56-6)

magnesium sulfate (7487-88-9)

ETHYL (1-PHENYLETHYLIDENE)CYANOACETATE, Cinnamic acid, α-cyano-β-methyl-, ethyl ester

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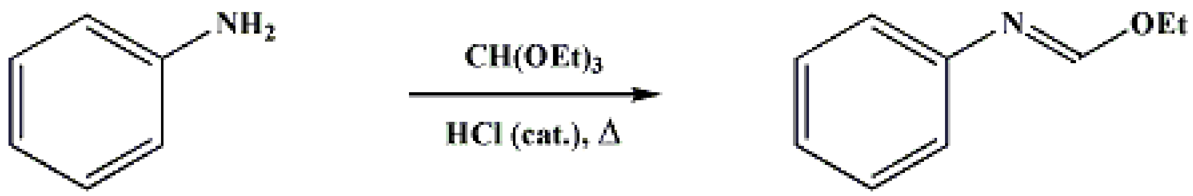
ETHYL N-PHENYLFORMIMIDATE

[Formimidic acid, N-phenyl-, ethyl ester]



Submitted by Royston M. Roberts and Paul J. Vogt[1].
Checked by T. L. Cairns and J. J. Drysdale.

1. Procedure

A 500-ml. flask is equipped with a capillary through a side opening, and 94 g. (1.01 moles) of aniline and 1 ml. of concentrated hydrochloric acid are added. A 12-in. glass-helix-packed column is attached (Note 1), and the water introduced with the acid is removed by boiling; about 1 ml. of aniline is collected after the water has distilled. The flask and its contents are then cooled to room temperature, and 222 g. (1.50 moles) of ethyl orthoformate is added. The column is reattached, and ethanol (Note 2) is distilled as it is produced; the theoretical amount (92 g., 116 ml.) is obtained in about 2.25 hours.

The reaction mixture is allowed to cool slightly, and the pressure is lowered to 40 mm. (Note 3). The excess ethyl orthoformate is distilled at 65°/40 mm. After a small intermediate fraction of about 4 g., b.p. 65–117°/40mm., the product distils at 117–118°/40mm. (b.p. 87–88°/10mm.; n_D^{25} 1.5248); the yield is 118–127 g. (78–84%). The residue amounts to about 14 g. and is mainly N,N'-diphenylformamidine (Note 4).

2. Notes

1. A Vigreux column may also be used since it is not difficult to separate the ethanol from ethyl orthoformate, the next most volatile component present. A total reflux, partial take-off head was used. Heat was supplied by an electric mantle; the column was heated with a glass-covered heating tape during the distillation of excess ethyl orthoformate and product.
2. A small amount (5–10 ml.) of lower-boiling material usually comes over before the ethanol; this is probably ethyl formate, produced by hydrolysis of the ethyl orthoformate.
3. A pressure regulator may conveniently be used in conjunction with a water aspirator.
4. If several runs are to be made, the residue may be saved and used as starting material, since the reaction proceeds via the initial formation of N,N'-

diphenylformamidine and its subsequent reaction with ethyl orthoformate.[2,3].

3. Discussion

Ethyl N-phenylformimidate has been prepared from silver formanilide and ethyl iodide,[4] and from aniline and ethyl orthoformate.[3] This method incorporates the discovery[2] of the necessity of acid catalysis for satisfactory yields by the latter process.

References and Notes

1. University of Texas, Austin, Texas.
2. Roberts, *J. Am. Chem. Soc.*, **71**, 3848 (1949).
3. Claisen, *Ann.*, **287**, 363 (1895); Roberts and Vogt, *J. Am. Chem. Soc.*, **78**, 4778 (1956).
4. Comstock and Clapp, *Am. Chem. J.*, **13**, 527 (1891).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

aniline (62-53-3)

Ethyl orthoformate

ethyl formate (109-94-4)

N,N'-diphenylformamidine

Ethyl iodide (75-03-6)

Ethyl N-phenylformimidate, Formimidic acid, N-phenyl-, ethyl ester (6780-49-0)

silver formanilide

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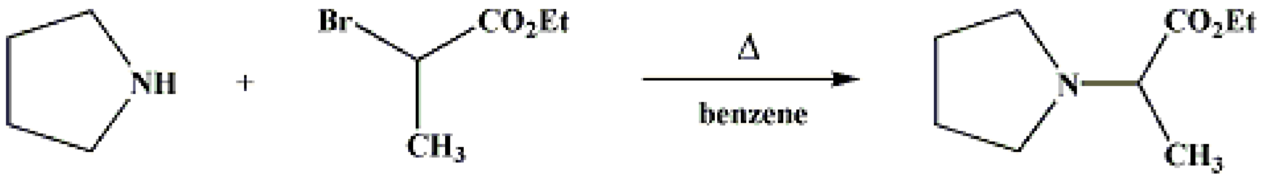
Organic Syntheses, CV 4, 466

ETHYL α-(1-PYRROLIDYL)PROPIONATE

[1-Pyrrolidineacetic acid, α-methyl-, ethyl ester]



Submitted by Robert Bruce Moffett[1]
Checked by N. J. Leonard and S. Gelfand.

1. Procedure

A 1-l. three-necked round-bottomed flask is placed on a steam bath and fitted with a stirrer, reflux condenser, and dropping funnel. A solution of 181 g. (1 mole) of ethyl α-bromopropionate in 200 ml. of benzene is placed in the flask (Note 1), and 148 g. (2.1 moles) of pyrrolidine (Note 2) is added slowly with stirring at such a rate that the solvent refluxes gently. When the addition is complete (about 1 hour is required), the mixture is heated under reflux for 1 hour. After being cooled, the mixture is poured into about 500 ml. of ice water and acidified with dilute hydrochloric acid. The aqueous layer is separated, washed once with ether, and made strongly basic with cold 40% sodium hydroxide solution. The basic ester is extracted with four 200-ml. portions of ether. The ether extracts are combined, washed with 100 ml. of water, and dried over anhydrous potassium carbonate. The drying agent is removed by filtration and the ether by distillation. The residue is distilled under reduced pressure through a short fractionating column; b.p. 84°/12 mm. (95–96°/19 mm., 99.5–100.5°/23 mm., 104–105°/30 mm.); n_D^{20} 1.4478, n_D^{25} 1.4450; d_4^{25} 0.9724. The yield is 137–156 g. (80–91%).

2. Notes

1. The yield of product is lowered appreciably if the solution is preheated before addition of the pyrrolidine.
2. Pyrrolidine is obtainable from E. I. du Pont de Nemours and Company, Electrochemicals Division, Niagara Falls, New York.

3. Discussion

Ethyl α-(1-pyrrolidyl)propionate has been prepared by the reaction of pyrrolidine with ethyl α-bromopropionate.[2]

References and Notes

1. The Upjohn Company, Kalamazoo, Michigan.
2. Moffett, *J. Org. Chem.*, **14**, 862 (1949).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether (60-29-7)

sodium hydroxide (1310-73-2)

ethyl α-bromopropionate (535-11-5)

pyrrolidine (123-75-1)

Ethyl α-(1-pyrrolidyl)propionate, 1-Pyrrolidineacetic acid, α-methyl-, ethyl ester (26846-86-6)

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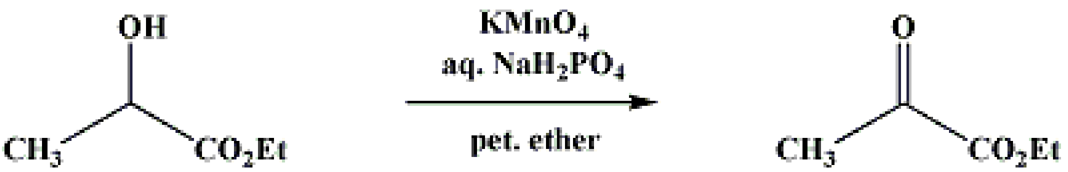
Organic Syntheses, CV 4, 467

ETHYL PYRUVATE

[Pyruvic acid, ethyl ester]



Submitted by J. W. Cornforth[1]
Checked by Charles C. Price, Kenneth N. Campbell, and John Warnke.

1. Procedure

In a 1-l. round-bottomed flask fitted with a thermometer and a mechanical stirrer are placed 130 ml. of saturated aqueous magnesium sulfate solution, 500 ml. of light petroleum ether (Note 1), 50 g. (0.42 mole) of ethyl lactate (Note 2), and 20 g. (0.13 mole) of sodium dihydrogen phosphate dihydrate. The stirrer is started (Note 3), the temperature is brought to 15° by means of an ice-water bath, and 55 g. (0.35 mole) of powdered potassium permanganate is added during 25–30 minutes. Stirring is continued until the oxidation is complete (Note 4), the temperature being kept near 15° throughout the process. The petroleum ether solution is decanted and the sludge stirred with three 50-ml. portions of light petroleum ether. The combined petroleum ether extracts are evaporated on a steam bath under a short fractionating column (Note 5). The residual oil is shaken thoroughly with two 10-ml. portions of a saturated aqueous calcium chloride solution (Note 6) and then distilled under reduced pressure. Almost the whole product boils at 56–57°/20 mm. The yield is 25–27 g. (51–54%) of nearly pure ethyl pyruvate, n_D^{20} 1.4053. This product compares favorably with material prepared by esterification of pyruvic acid (Note 7). Further purification may be effected through the sodium bisulfite compound (Note 8).

2. Notes

1. Petroleum ether, b.p. 40–60°, was washed with concentrated sulfuric acid before use. The checkers used the hexane fraction of petroleum.
2. The ethyl lactate should be of good quality, as its impurities tend to appear in the final product. The submitter used a good commercial grade supplied by British Industrial Solvents, Ltd. Its specification included an ester content of not less than 99% (calculated as ethyl lactate).
The commercial 99% ethyl lactate available to the checkers did not give satisfactory results. It was purified by distillation through a fractionating column 8 by in., packed with glass beads. The portion having the following properties was used: b.p. 154–155°, n_D^{20} 1.4125, d_4^{20} 1.0302.

3. The thick lower layer is stirred continuously and not too fast. Vigorous agitation of the upper layer is not advisable. A short Hershberg wire stirrer was used.
4. The oxidation requires about 2.5 hours. Unreduced permanganate is easily detected by spotting on filter paper. If a cake of manganese dioxide is formed beyond the compass of the stirrer, it should be pushed down. It is rarely necessary to do this more than once.
5. The distillate of petroleum ether, which contains ethanol and some ethyl pyruvate, can be recovered for another run by shaking with a little concentrated sulfuric acid.
6. This treatment removes unoxidized ethyl lactate. Each shaking should be continued for 5 minutes. It is convenient to separate the layers by centrifuging. Droplets of calcium chloride solution should not be present in the oil when it is to be distilled, or some polymerization will occur.
7. No satisfactory criterion of purity for ethyl pyruvate is available in the literature. The submitter used a method of assay which was devised[2] for the estimation of aldehydes. One hundred and sixteen milligrams of the ester is weighed in a 100-ml. conical flask, dissolved in 5 ml. of water, and treated with 0.3 ml. of saturated sodium bisulfite solution. After 1–2 minutes, a little starch solution is added, the mixture is chilled, and 0.1*N* iodine solution is run in as rapidly as possible until the blue color is stable for a few seconds (about 12 ml. is required). Six milliliters of saturated sodium bicarbonate solution is added, and titration with iodine solution is carried out in the ordinary way. The end point is stable for 1 minute or more. The theoretical volume of 0.1*N* iodine required for pure ethyl pyruvate in the second stage is 20 ml. Thus if *n* ml. is required the estimated purity is 5*n*%. The results are perfectly consistent but may be slightly lower than the true values owing to dissociation of the bisulfite complex. The results from four different samples are as tabulated.

Method of Preparation	Estimated Ethyl Pyruvate Content, %
(1) Oxidation of ethyl lactate	95
(2) Esterification of once-distilled pyruvic acid	93–94
(3) Sample (2) twice redistilled; fraction b.p. 147–148° taken	96
(4) Sample (1) purified through bisulfite complex (Note 8)	98.5

8. The bisulfite compound is best made in small batches. The ester (2.2 ml.) in a large test tube is underlaid with 3.6 ml. of saturated sodium bisulfite solution. The tube is chilled in a freezing mixture, and the layers are shaken together. Crystallization occurs rapidly, especially if seed crystals are present. After 3 minutes, 10 ml. of ethanol is added and the crystalline product is washed on a

filter with ethanol and ether. The yield is 3.0 g. Sixteen grams of the bisulfite complex is mixed with 32 ml. of saturated magnesium sulfate solution, and 5 ml. of 40% formaldehyde is added. After shaking, the oil is separated and the aqueous layer extracted with a little ether, which is added to the oil. After drying with magnesium sulfate the product is distilled at low pressure and affords 5.5 g. of ethyl pyruvate, b.p. 56°/20 mm. On redistillation, the purified ester boils at 147.5°/ 750 mm., n_D^{20} 1.4052, f.p. around –50°.

3. Discussion

Ethyl pyruvate can be prepared by esterification of pyruvic acid[3,4] or by catalytic oxidation of ethyl lactate with air or oxygen.[5,6] A process has been patented for the oxidation of ethyl lactate by acidified permanganate in dilute aqueous solution.[7] Ethyl pyruvate also has been obtained by the treatment of pyruvaldehyde diethyl acetal with N-bromosuccinimide,[8] by the reaction of pyruvyl chloride with ketene,[9] and by the reaction of pyruvic acid with diethyl pyrocarbonate.[10] Of minor interest are the preparations by pyrolysis of ethyl α-triphenylmethoxypropionate[11] and by the action of diethylamine on ethyl *meso*-α,α'-dibromoadipate.[12]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 610

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

bisulfite complex

ethyl meso-α,α'-dibromoadipate

ethanol (64-17-5)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

ether (60-29-7)

formaldehyde (630-08-0)

sodium bicarbonate (144-55-8)

potassium permanganate (7722-64-7)

oxygen (7782-44-7)

sodium bisulfite (7631-90-5)

iodine (7553-56-2)

manganese dioxide (1313-13-9)

diethylamine (109-89-7)

Ketene (463-51-4)

Pyruvic acid (127-17-3)

ethyl lactate (687-47-8)

pyruvyl chloride (78-95-5)

magnesium sulfate (7487-88-9)

N-bromosuccinimide (128-08-5)

hexane (110-54-3)

Ethyl pyruvate, Pyruvic acid, ethyl ester (617-35-6)

sodium dihydrogen phosphate dihydrate (13472-35-0)

pyruvaldehyde diethyl acetal

diethyl pyrocarbonate (1609-47-8)

ethyl α-triphenylmethoxypropionate

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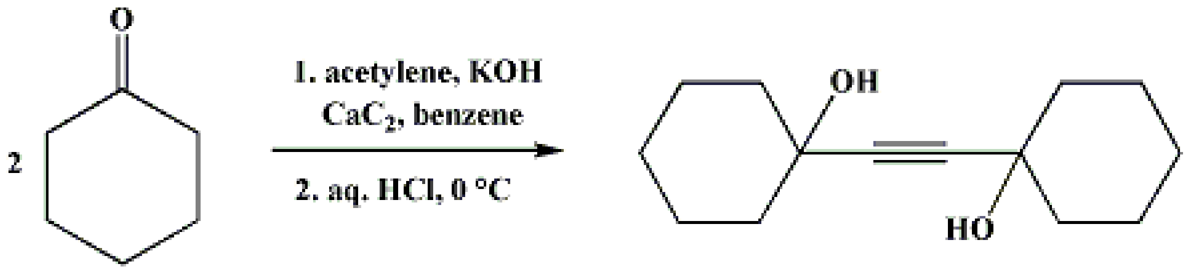
Organic Syntheses, CV 4, 471

1,1'-ETHYNYLENE-*bis*-CYCLOHEXANOL

[Cyclohexanol, 1,1'-ethynylenedi-]



Submitted by G. Forrest Woods and Louis H. Schwartzman[1].
Checked by Richard T. Arnold and Stuart W. Fenton.

1. Procedure

In a 2-l. three-necked flask (Note 1), fitted with a dropping funnel, condenser (equipped with a Drierite tube), and efficient stirrer driven by a powerful motor, is placed a mixture of 600 ml. of benzene, 56 g. (0.85 mole) of 85% potassium hydroxide (Note 2), and 76.4 g. of powdered calcium carbide (Note 3). While this mixture is being stirred vigorously, 85 g. (0.87 mole) of cyclohexanone is added over a period of 0.5–1 hour. The mixture is dark gray and will become warm, but no external cooling is necessary. Stirring is continued, and within 24 hours the contents congeal (Note 4). This semisolid is allowed to stand for an additional 4 days (Note 5).

The flask is immersed in an ice bath, and a solution containing 200 ml. of concentrated hydrochloric acid and 200 ml. of water is added cautiously (Note 6) over a period of 4–6 hours. The dark solid is separated by filtration with the aid of a large Büchner funnel. This impure product is air-dried and digested with 900 ml. of boiling carbon tetrachloride, and the insoluble portion is collected on a Büchner funnel and subsequently extracted with 100 ml. of hot acetone and again filtered. When the filtrates are kept overnight in a refrigerator, 47.3–50.3 g. (49–52%) of a colorless crystalline product separates; m.p. 106.5–109°. Partial evaporation of the combined filtrates, followed by effective cooling, gives an additional 7.8–12.9 g. (8–13%) of 1,1'-ethynylene-*bis*-cyclohexanol; m.p. 100–109° (Note 7).

2. Notes

1. The submitters employed a 12-l. resin flask equipped with Lightning Stirrer whose shaft and blades were of stainless steel when using 10 times the quantity of starting materials reported here.
Any evolution of acetylene is best accommodated by a rubber tube which leads outside or to a good hood.

2. Either pellets or flakes of potassium hydroxide are powdered in a ball mill.
3. Technical calcium carbide of approximately 100 mesh was obtained from the Union Carbide and Carbon Corporation, New York, New York. The amount of calcium carbide used is in excess and based on an activity of 75%.
4. Stirring is continued until the mass has set solidly; it is desirable for a channel to exist around the stirrer shaft to facilitate the subsequent decomposition.
5. Decreased yields result from shorter periods of standing.
6. It is advisable to bore several holes into the solid mass by means of a stirring rod in order to permit better contact with the acid. Initial addition of the acid should be slow, and a total of 4–6 hours should be allowed for this operation, since considerable heat and acetylene are evolved.
7. The product can be recrystallized from carbon tetrachloride or acetone, or sublimed at reduced pressure, to yield a product melting at 109–111°.

3. Discussion

This method is based on the procedure of Kazarin.[2] The same substance has been prepared by the reaction of the dimagnesium halide[3] or dilithium derivative[4] of acetylene with cyclohexanone, and also by the reaction of cyclohexanone with acetylene in the presence of potassium *tert*-butoxide followed by the preparation of the Grignard reagent of this compound and reaction again with cyclohexanone.[5]

It has been claimed that the yield of the present reaction is improved when it is carried out in the presence of an acetal or ethylene glycol dialkyl ether.[6] Petrov et al.[7] have reported that they obtained almost a 100% yield of the glycol when cyclohexanone was treated with acetylene and double the amount of potassium hydroxide.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

calcium carbide

acetylene (74-86-2)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

Cyclohexanone (108-94-1)

carbon tetrachloride (56-23-5)

acetone (67-64-1)

potassium hydroxide (1310-58-3)

potassium tert-butoxide (865-47-4)

1,1'-ETHYNYLENE-bis-CYCLOHEXANOL, Cyclohexanol, 1,1'-ethynylenedi- (78-54-6)

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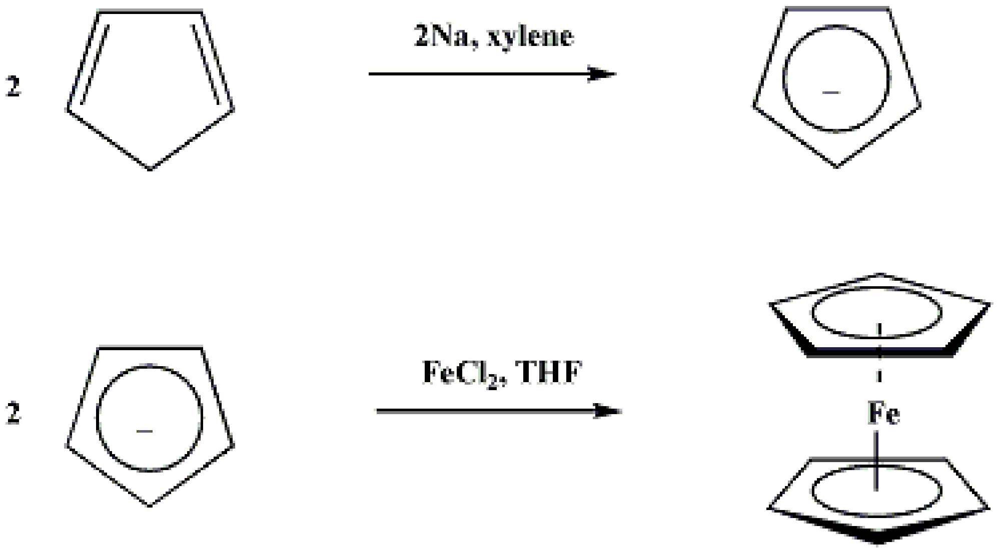
Organic Syntheses, CV 4, 473

FERROCENE

[Iron, dicyclopentadienyl-]

[I. METALLIC SODIUM METHOD]

$$2/3\ FeCl_3 + 1/3\ Fe \longrightarrow FeCl_2$$



Submitted by G. Wilkinson[1]
Checked by N. J. Leonard, Kenneth L. Rinehart, Jr., Donald J. Casey, and Sung Moon.

1. Procedure

In a 250-ml. three-necked flask, fitted with a mechanical stirrer, a reflux condenser, and an inlet for admission of nitrogen, is placed 100 ml. of tetrahydrofuran (Note 1). With stirring, 27.1 g. (0.166 mole) of anhydrous ferric chloride is added in portions, followed by 4.7 g. (0.084 g. atom) of iron powder (Note 2). The mixture is heated with stirring under nitrogen at the reflux temperature for 4.5 hours, giving a gray powder with a brown supernatant liquid.

During this time, a second system is assembled, consisting of a 500-ml. three-necked flask fitted with a mechanical stirrer, a reflux condenser topped with a calcium chloride-filled drying tube attached to a xylene-filled bubbler, and a pressure-equalizing dropping funnel through which a slow stream of nitrogen is passed into the flask. In the flask are placed 200 ml. of sodium-dried xylene and 11.5 g. (0.5 g. atom) of sodium. The mixture is heated to boiling, and the sodium is finely dispersed by rapid stirring (Note 3). Stirring is continued while the mixture is allowed to cool in a

nitrogen atmosphere. The cooled mixture is allowed to settle, and the bulk of the xylene is siphoned. Tetrahydrofuran (200 ml.) (Note 1) is added through the separatory funnel, and to the stirred mixture, cooled in ice, is added 42 ml. (0.5 mole) of cyclopentadiene (Note 4) in portions during 1 hour (Note 5). Stirring is continued for 2–3 hours in the cold, after which only a small amount of sodium remains unreacted.

The cooled contents of the 250-ml. flask containing ferrous chloride (Note 6) are added to the cold sodium cyclopentadienide solution while passing a stream of nitrogen through both flasks. The combined mixture is stirred for 1.25 hours at a temperature just below reflux. Solvent is removed by distillation, and the ferrocene is extracted from the residue with several portions of refluxing petroleum ether (b.p. 40–60°). The product is obtained by evaporation of the petroleum ether solution. Ferrocene may be purified by recrystallization from pentane or cyclohexane (hexane, benzene, and methanol have also been used) or by sublimation. The yield is 31–34 g. (67–73%) (Note 7), m.p. 173–174°.

2. Notes

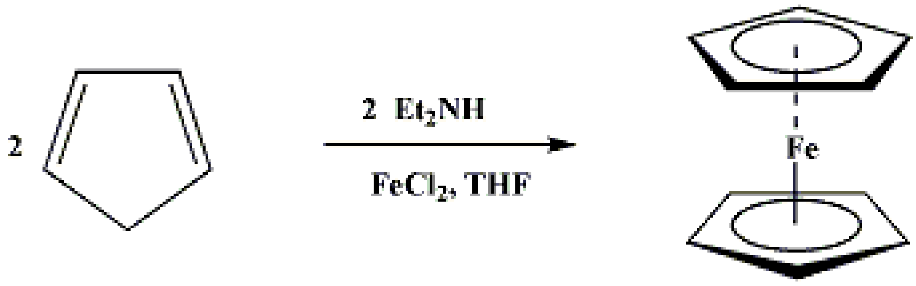
1. Tetrahydrofuran may be purified by refluxing over solid potassium hydroxide, followed by distillation from lithium aluminum hydride. Tetrahydrofuran may be replaced by ethylene glycol dimethyl ether (dimethoxyethane). The submitter has indicated that either solvent may be freed conveniently from water, alcohols, and moderate amounts of peroxides by passing the commercial solvent through a column (2 in. diameter × 2–3 ft. length) of Linde Air Products "Molecular Sieves" (type 13X 1/16-in. pellets), at a rate of approximately 100 ml. per minute.
2. The quality of the iron used in preparing the ferrous chloride has a marked effect on the yield of ferrocene. The checkers employed Rascher and Betzold (730 N. Franklin, Chicago, Ill.) 300-mesh iron powder, reduced by hydrogen. When 40-mesh iron filings were used, the yield of ferrocene was much lower (ca. 33%).
3. The checkers employed a "Mixmaster"-type motor and a Hershberg stirrer made from tantalum wire.
4. Cyclopentadiene, b.p. 40°, is obtained by heating commercial 85% dicyclopentadiene (e.g., from Matheson, Coleman and Bell Company, Norwood, Ohio) under a short column (in. diameter × 8–12 in. length) filled with glass helices. The distilled cyclopentadiene is collected in a receiver which is maintained at Dry Ice temperature until the cyclopentadiene is used. Methylcyclopentadiene and other substituted cyclopentadienes such as indene may also be employed for the synthesis of the correspondingly substituted ferrocenes. In these cases, the reaction of the hydrocarbon with sodium is much slower than with cyclopentadiene, and refluxing for several hours is required to complete the reaction.
5. Under the best conditions, sodium cyclopentadienide gives pale yellow or

orange solutions. Traces of air lead to red or purple solutions, as does insufficiently purified solvent, without, however, lowering the reaction yield appreciably. If 1,2-dimethoxyethane is used, in which sodium cyclopentadienide is less soluble than in tetrahydrofuran, white crystals may be obtained at this point.

6. Ferrous chloride may be substituted by ferric chloride directly, with a corresponding reduction in yield, since the sodium cyclopentadienide solution will reduce ferric chloride.

7. The submitter reported yields up to 90% by this method.

[II. DIETHYLAMINE METHOD]



Submitted by G. Wilkinson[1]
Checked by N. J. Leonard, Kenneth L. Rinehart, Jr., and Peter Woo.

1. Procedure

The conditions given in the preceding preparation are used for obtaining a suspension of 0.25 mole of ferrous chloride in 100 ml. of tetrahydrofuran (Note 1), contained in a 250-ml. flask. The tetrahydrofuran is then removed under reduced pressure until the residue is almost dry. The flask is cooled in an ice bath, and to the residue is added a mixture of 42 ml. (0.5 mole) of cyclopentadiene and approximately 100 ml. (about 1 mole) of diethylamine. The mixture is stirred vigorously at room temperature for 6–8 hours or, conveniently, overnight. The excess amine is removed under reduced pressure, and the residue is extracted repeatedly with refluxing petroleum ether. The extract is filtered hot, and the solvent is evaporated to leave ferrocene. The product is purified by recrystallization from pentane or cyclohexane or by sublimation. The yield is 34–39 g. (73–84%), m.p. 173–174°.

2. Notes

1. All precautions with regard to the purification of tetrahydrofuran, the quality of the iron powder, the rapid stirring, the maintenance of a nitrogen atmosphere, and the handling of cyclopentadiene, described in the preceding preparation, are followed.

3. Discussion

The methods of preparation of ferrocene have been reviewed by Pauson[2] and by Fischer.[3] Ferrocene has been made by the reaction of ferric chloride with cyclopentadienylmagnesium bromide,[4] by the direct thermal reaction of cyclopentadiene with iron metal,[5] by the direct interaction of cyclopentadiene with iron carbonyl,[6] by the reaction of ferrous oxide and cyclopentadiene in the presence of chromic oxide,[7] by the reaction of ferrous chloride with sodium cyclopentadienide in liquid ammonia,[8] and from cyclopentadiene and ferrous acetylacetone-dipyridine complex.[9] Method I is based on that developed by Wilkinson and his co-workers for ferrocene and many analogous compounds.[10]

Although not so generally applicable for the preparation of dicyclopentadienyl metal compounds as the sodium cyclopentadienide procedure, Method II represents the simplest preparation of ferrocene. The amine procedure also may be employed for dicyclopentadienylnickel (about 80% yield), using nickel bromide obtained by the action of bromine on nickel metal powder and 1,2-dimethoxyethane as the solvent. The method of preparation given here is a modified version[10d] of that originally described,[11] and it has been studied by others.[12,13]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 60
- Org. Syn. Coll. Vol. 5, 434
- Org. Syn. Coll. Vol. 5, 1001
- Org. Syn. Coll. Vol. 6, 145
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

Ferrocene

sodium-dried xylene

ferrous acetylacetone-dipyridine complex

ammonia (7664-41-7)

Benzene (71-43-2)

methanol (67-56-1)

hydrogen (1333-74-0)

iron, iron filings, iron powder (7439-89-6)

bromine (7726-95-6)

nitrogen (7727-37-9)

cyclohexane (110-82-7)

nickel metal powder (7440-02-0)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

ferric chloride (7705-08-0)

xylene (106-42-3)

diethylamine (109-89-7)

Pentane (109-66-0)

tantalum wire (7440-25-7)

indene (95-13-6)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

hexane (110-54-3)

chromic oxide (1308-38-9)

ferrous chloride (7758-94-3)

CYCLOPENTADIENE (542-92-7)

dicyclopentadiene

Iron, dicyclopentadienyl-

sodium cyclopentadienide (4984-82-1)

ethylene glycol dimethyl ether, 1,2-dimethoxyethane (110-71-4)

dimethoxyethane (534-15-6)

Methylcyclopentadiene

cyclopentadienylmagnesium bromide

iron carbonyl

ferrous oxide

dicyclopentadienylnickel

nickel bromide

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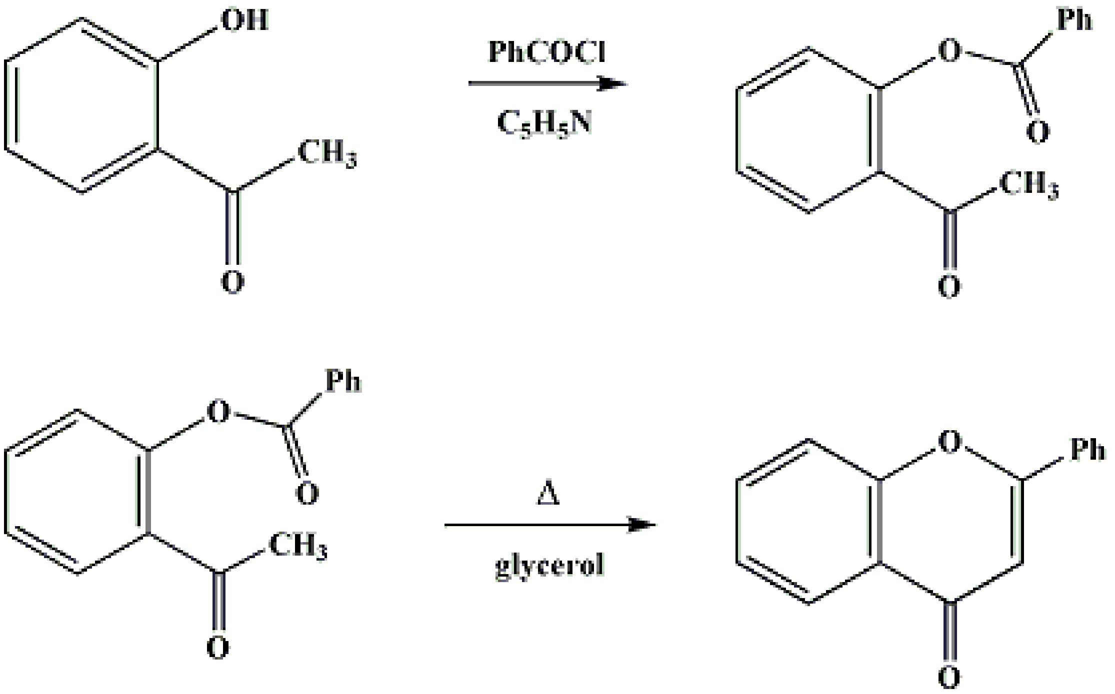
Organic Syntheses, CV 4, 478

FLAVONE

[Method 1]



Submitted by T. S. Wheeler[1]
Checked by R. L. Shriner and Donald A. Scott.

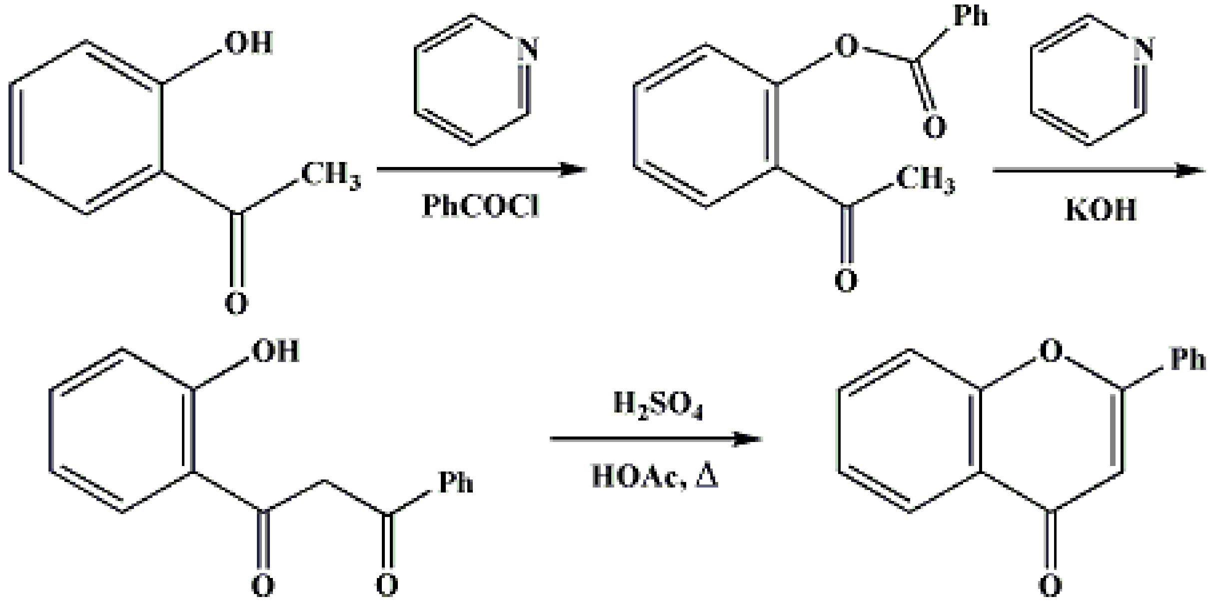
1. Procedure

A. *o-Benzoyloxyacetophenone.* In a 100-ml. conical flask fitted with a calcium chloride drying tube are placed 13.6 g. (12 ml., 0.1 mole) of *o*-hydroxyacetophenone,[2] 21.1 g. (17.4 ml., 0.15 mole) of benzoyl chloride, and 20 ml. of pyridine (Note 1). The temperature of the reaction mixture rises spontaneously, and when no further heat is evolved (about 15 minutes) the mixture is poured with good stirring into 600 ml. of 3% hydrochloric acid containing 200 g. of crushed ice. The product is collected on a Büchner funnel and washed with 20 ml. of methanol, then with 20 ml. of water. The product is sucked as dry as possible and air-dried at room temperature. The yield of dry crude product melting at 81–87° is 22–23 g. It is recrystallized from 25 ml. of methanol, and the *o*-benzoyloxyacetophenone is obtained as white crystals; yield 19–20 g. (79–83%); m.p. 87–88°.

B. *Flavone.* In a 500-ml. round-bottomed three-necked flask, equipped with a mercury-sealed mechanical stirrer, a thermometer, and an air condenser closed with a calcium chloride drying tube in the second neck, are placed 20 g. (0.083 mole) of *o*-benxoyloxyacetophenone and 200 ml. of freshly distilled anhydrous glycerol (Note 2). A stream of nitrogen, dried by passage through a wash bottle containing sulfuric acid,

is introduced through the third neck. The mixture is heated and maintained at 260° for two hours while being stirred continuously. The contents are cooled below 100° and then poured into 2 l. of water which is rendered slightly alkaline with aqueous sodium hydroxide. The mixture is stirred for 15 minutes, cooled, and kept at 0° (in a refrigerator) for 48 hours. The tan-colored crystals of flavone are collected on a filter and dried at 50°. The yield of crude product amounts to about 10 g.; m.p. 90–93°. The crude material is dissolved in 400 ml. of hot ligroin (b.p. 60–70°). Repeated partial evaporation of the solvent in stages, each followed by cooling, gives successive crops of flavone as white needles. The yield of pure flavone amounts to 8–9 g. (43–48%); m. p. 96–97°.

[Method 2]



1. Procedure

A. *o-Benzoyloxyacetophenone.* This is prepared as in Method 1.

B. *o-Hydroxydibenzoylmethane.* A solution of 20 g. (0.083 mole) of *o*-benzoyloxyacetophenone in 75 ml. of pyridine (Note 1) is prepared in a 300-ml. beaker and warmed to 50°. To the solution is added 7 g. of hot pulverized 85% potassium hydroxide (Note 3), and the mixture is mechanically stirred for 15 minutes, during which time a copious precipitate of the yellow potassium salt of *o*-hydroxydibenzoylmethane forms (Note 4). The mixture is cooled to room temperature and acidified with 100 ml. of 10% acetic acid. The diketone separates as a light-yellow precipitate which is collected on a filter and sucked dry (Note 5). The yield of crude *o*-hydroxydibenzoylmethane is 16–17 g. (80–85%); m.p. 117–120°.

C. *Flavone.* To a solution of 16.6 g. (0.069 mole) of the crude diketone in 90 ml. of glacial acetic acid, contained in a 250-ml. conical flask, is added, with shaking, 3.5 ml. of concentrated sulfuric acid. The mixture is heated under a reflux condenser on a

steam bath for 1 hour with occasional shaking and is then poured onto 500 g. of crushed ice with vigorous stirring. After the ice has melted, the crude flavone is collected on a filter, washed with water (about 1 l.) until free from acid, and finally dried at 50°. The yield of product is 14.5–15 g. (94–97%); m.p. 95–97°. The over-all yield of flavone based on *o*-hydroxyacetophenone is 59–68%. The product may be recrystallized from ligroin as in Method 1.

2. Notes

1. Commercial pyridine is dried over solid sodium hydroxide and distilled through a fractionating column.
2. Glycerol is twice distilled under reduced pressure and used immediately in the reaction.
3. The potassium hydroxide is pulverized rapidly in a mortar previously heated at 100°.
4. The mixture usually becomes so thick and pasty that hand stirring is necessary.
5. *o*-Hydroxydibenzoylmethane can be crystallized from 95% ethanol and forms crystals melting at 120°, which give a strong enol reaction with ferric chloride. Crystallization is not necessary here.

3. Discussion

o-Benzoyloxyacetophenone has been prepared by the action of benzoyl chloride on a pyridine solution of *o*-hydroxyacetophenone.[3] The rearrangement of *o*-benzoyloxyacetophenone to *o*-hydroxydibenzoylmethane by alkali has been described.[4,5] The latter diketone has been made by the base-catalyzed condensation of ethyl benzoate with *o*-hydroxyacetophenone.[6] The cyclization of *o*-hydroxydibenzoylmethane described in Method 2 is based on the work of Doyle, Gogan, Gowan, Keane, and Wheeler.[5] Cyclization has also been effected by use of glacial acetic acid containing hydrogen chloride or sodium acetate.[4]

Other methods of preparing flavone include: the action of ethanolic alkali on 2'-acetoxy-α,β-dibromochalcone;[7] Claisen condensation of ethyl *o*-ethoxybenzoate and acetophenone, and cyclization of the resulting 1,3-diketone with hydriodic acid;[8] and treatment of 3-bromoflavanone with potassium hydroxide in ethanol.[9] Flavone has also been prepared from ethyl phenylpropiolate by condensation with sodium phenoxide and subsequent cyclization with phosphorus pentachloride in benzene;[10] by fusing *o*-hydroxyacetophenone with benzoic anhydride and sodium benzoate;[11] by the dehydrogenation of 2'-hydroxychalcone with selenium dioxide;[12] by the action of alkali on flavylium chloride;[13] by the acid hydrolysis of 3-benzoyl-4-

hydroxycoumarin;[14] by the condensation of benzamide with 2-hydroxyacetophenone;[15] and by heating β-morpholino-2-chlorochalcone which cyclizes to 4-morpholinoflavylium chloride, and which in turn may be hydrolyzed to flavone.[16]

Method 1 is a new procedure for the direct production of flavone from *o*-benzoyloxyacetophenone and has been successfully applied to the synthesis of other flavones. Method 2, which involves the Baker-Venkataraman transformation, is recommended because of its high over-all yield and the reproducibility of the results. Mozingo and Adkins' method[6] is satisfactory, but the yield of *o*-hydroxydibenzoylmethane is variable.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ligroin

o-benxoyloxyacetophenone

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrogen chloride, hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

methanol (67-56-1)

sodium acetate (127-09-3)

sodium hydroxide (1310-73-2)

phosphorus pentachloride (10026-13-8)

glycerol (56-81-5)

nitrogen (7727-37-9)

Acetophenone (98-86-2)

benzoyl chloride (98-88-4)

Benzoic anhydride (93-97-0)

benzamide (55-21-0)

pyridine (110-86-1)

selenium dioxide (7446-08-4)

potassium hydroxide (1310-58-3)

sodium benzoate (532-32-1)

hydriodic acid (10034-85-2)

ferric chloride (7705-08-0)

ethyl benzoate (93-89-0)

sodium phenoxide

ethyl phenylpropiolate (2216-94-6)

2-hydroxyacetophenone (582-24-1)

Flavone (525-82-6)

3-bromoflavanone

flavylium chloride

3-benzoyl-4-hydroxycoumarin

β-morpholino-2-chlorochalcone

4-morpholinoflavylium chloride

o-Hydroxyacetophenone (118-93-4)

o-Benzoyloxyacetophenone (4010-33-7)

o-Hydroxydibenzoylmethane (1469-94-9)

ethyl o-ethoxybenzoate

potassium salt of o-hydroxydibenzoylmethane

2'-acetoxy-α,β-dibromochalcone

2'-hydroxychalcone

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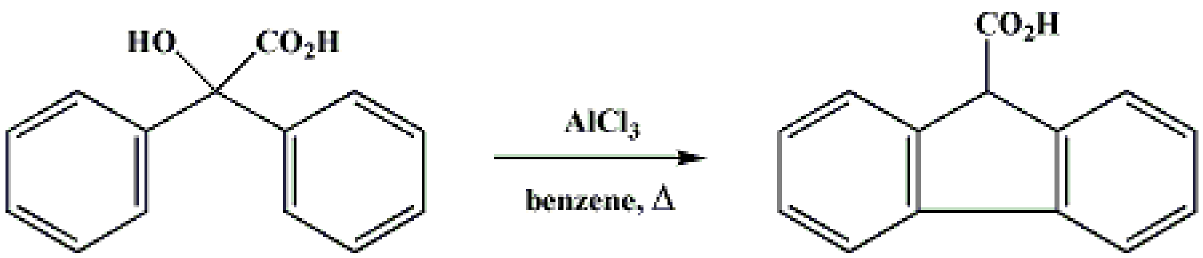
9-FLUORENECARBOXYLIC ACID

[Fluorene-9-carboxylic acid]



Submitted by Henry J. Richter[1]
Checked by Richard T. Arnold, B. C. W. Hummel, and W. J. Wolf.

1. Procedure

Caution! Because of the evolution of considerable amounts of hydrogen chloride, this preparation must be conducted in a good hood or the apparatus must be attached to a gas trap.

A mixture of 45.6 g. (0.2 mole) of benzilic acid (Note 1) in 700 ml. of anhydrous thiophene-free benzene, contained in a 2-l. three-necked flask fitted with a reflux condenser (attached to a calcium chloride drying tube) and a motor-driven sealed stirrer, is cooled in an ice bath until a crystalline mass results. To the stirred mixture is added, in one portion, 80 g. (0.6 mole) of anhydrous aluminum chloride. The stirred mixture is heated until refluxing begins and is maintained at this temperature for 3 hours. During this period much hydrogen chloride is evolved, and the initially yellow solution soon becomes deep red. The solution is cooled and decomposed by the cautious addition of small pieces of ice, and then 400 ml. of water is added cautiously, followed by 200 ml. of concentrated hydrochloric acid. The benzene is removed by steam distillation, and the product is separated by filtration from the hot mixture. The lumps of product are crushed and extracted with 400 ml. of boiling 10% sodium carbonate solution. The mixture is filtered, and the extraction is repeated on the undissolved residue with an additional 200 ml. of hot 10% sodium carbonate solution. The basic filtrates are combined, 3–4 g. of Norit is added, and the mixture is heated to boiling. The Norit is separated by filtration, and the cooled solution is strongly acidified with cold concentrated hydrochloric acid (Note 2). The solid is collected on a Büchner funnel, washed with two 100-ml. portions of water, and dried (Note 3). The 9-fluorenecarboxylic acid so obtained weighs 39–41 g. (93–97%) and melts at 215–222°.

This product can be further purified by stirring it for several minutes with 200 ml. of benzene at 45°. The insoluble portion is collected on a Büchner funnel and washed first with 40 ml. of cold benzene and then with 40 ml. of petroleum ether (b.p. 28–

38°). There is thus obtained 30–34 g. (71–81%) of almost colorless 9-fluorenecarboxylic acid melting at 219–222° with some previous sintering (Note 4).

2. Notes

1. The Distillation Products Industries grade melting at 150–151° is satisfactory.
2. Good results are usually obtained if the temperature during neutralization is not allowed to exceed 15°.
3. If the occluded hydrochloric acid and aluminum salts are effectively removed during the washing operation, this product can be dried in a steam oven without discoloration.
4. The melting points reported for this compound range from 210° to 230° [2,3,4,5,6] and appear to be a function of the rate of heating. The product obtained above, showing a neutralization equivalent of 215–218 (calculated 210), has proved very satisfactory. The acid may be further purified by crystallization from 50% ethanol using 5–6 ml./g. There is then obtained 60–70% of acid melting at 221–223° with some previous sintering. All melting points are uncorrected.

3. Discussion

The procedure described is essentially that of Arnold, Parham, and Dobson[2] based on the reaction reported by Vorlander and Pritzsche.[3] This acid has also been prepared from ethyl trichloroacetate in benzene with aluminum chloride,[4] from fluorene by metalation with *n*-butyllithium,[5,6] sodium triphenylmethyl,[7] lithium triphenylgermanium,[8] lithium in tetrahydrofuran,[9] phenyllithium,[6] *o*-tolyllithium,[6] mesityllithium,[6] potassium hydroxide,[10] or ethylsodium-diethylzinc complex followed by carbonation,[11] from diphenyleneketene and water,[12] and from 9-fluorenylmagnesium bromide and carbon dioxide.[13]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

sodium triphenylmethyl

lithium triphenylgermanium

ethylsodium-diethylzinc complex

ethanol (64-17-5)

hydrogen chloride, hydrochloric acid (7647-01-0)

Benzene (71-43-2)

sodium carbonate (497-19-8)

aluminum (7429-90-5)

carbon dioxide (124-38-9)

Norit (7782-42-5)

aluminum chloride (3495-54-3)

Benzilic acid (76-93-7)

potassium hydroxide (1310-58-3)

Phenyllithium (591-51-5)

lithium (7439-93-2)

fluorene (86-73-7)

n-butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

9-FLUORENECARBOXYLIC ACID, Fluorene-9-carboxylic acid (1989-33-9)

ethyl trichloroacetate (515-84-4)

diphenyleneketene

9-fluorenylmagnesium bromide

mesityllithium

o-Tolyllithium

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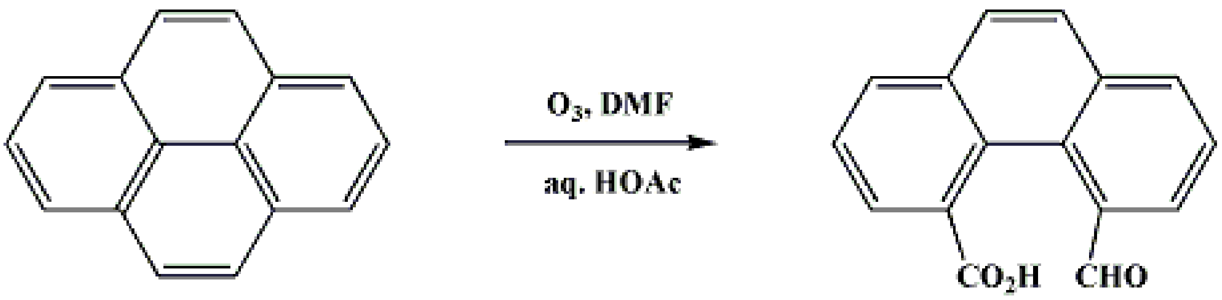
5-FORMYL-4-PHENANTHROIC ACID

[4-Phenanthrenecarboxylic acid, 5-formyl-]



Submitted by R. E. Dessy and M. S. Newman[1].
Checked by J. D. Roberts and D. I. Schuster.

1. Procedure

A solution of 25 g. (0.125 mole) of pyrene (Note 1) in 100 ml. of dimethylformamide (Note 2) and (Note 3) is treated with a 50% excess of ozone (Note 4). The solution of the ozonide is added at a moderate rate, with stirring, to 500 ml. of 1% aqueous acetic acid. The suspension is allowed to stand overnight (Note 5), and the resulting solid is collected by filtration and washed with water.

The moist solid is suspended in 200 ml. of 10% aqueous potassium hydroxide solution, and the suspension is boiled for 5 minutes. The hot solution is filtered, and the remaining solid is again extracted, using 100 ml. of potassium hydroxide solution.

To the dark-brown combined filtrates is added 100 ml. of potassium hypochlorite solution (Note 6), and the resulting solution is permitted to stand overnight. The mixture is then heated on a steam bath for 4 hours. The resulting orange solution is filtered while hot, and 100 ml. of 35% sodium hydroxide solution is added. The solution is cooled to 5°, the resulting solid is collected by filtration and washed with a small amount of saturated sodium chloride solution.

The moist sodium salt is digested with 50 ml. of cold 6*N* hydrochloric acid, and after several hours the mixture is filtered and the resulting solid acid dried.

The crude acid is dissolved in 100 ml. of boiling dimethylformamide, and 100 ml. of hot glacial acetic acid is added. Water is added to the hot solution until it becomes cloudy, and then just enough dimethylformamide is added to render the solution clear again. It is cooled to 5°, and the resulting acid collected by filtration and washed with glacial acetic acid. Upon drying, 10–11.5 g. (32–38%) of 5-formyl-4-phenanthroic acid (Note 7), melting at 272–276° (Note 8), is obtained.

2. Notes

1. Technical pyrene, Reilly Tar and Chemical Corp., was employed. Purification did not improve the over-all yield, and purer pyrene is not sufficiently soluble in dimethylformamide.
2. Freshly distilled dimethylformamide should be employed. The yields with the technical grade solvent were very erratic.
3. Complete solution is attained by heating the mixture for 5 minutes on a steam bath.
4. An ozonizer similar to that described by Henne and Perilstein[2] was employed. At an oxygen flow rate of 30 l./hr. it produced about 30 millimoles of O_3 per hour (3% conversion). Under these conditions the ozonization of 25 g. of pyrene requires about 6 hours.
5. Filtration of the hydrolyzate immediately after decomposition is difficult because of the fine nature of the solid. Upon standing, coagulation takes place to yield a granular brown solid.
6. The potassium hypochlorite solution was prepared[3] from the calcium hypochlorite sold by Mathieson Chemical Corporation under the trade name HTH. If the HTH reagent used is not fresh, it is found that subsequent heating of the filtrate with the potassium hypochlorite solution does not result in an orange solution. The solution remains dark brown, and the product is distinctly brown. The yield is not affected.
7. Unpublished experiments indicate that 5-formyl-4-phenanthroic acid exists mainly in the cyclic hydroxylactone form.
8. The checkers found that the melting point depends on the rate of heating. A reproducible melting point was obtained if the sample was placed in the bath at 270° and the temperature raised at the rate of two degrees per minute.

3. Discussion

The only reported method of preparation of 5-formyl-4-phenanthroic acid is by the reaction described here.[4]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

oxygen (7782-44-7)

potassium hydroxide (1310-58-3)

potassium hypochlorite

ozone (10028-15-6)

calcium hypochlorite (7778-54-3)

pyrene (129-00-0)

dimethylformamide (68-12-2)

5-Formyl-4-phenanthroic acid, 4-Phenanthrenecarboxylic acid, 5-formyl- (5684-15-1)

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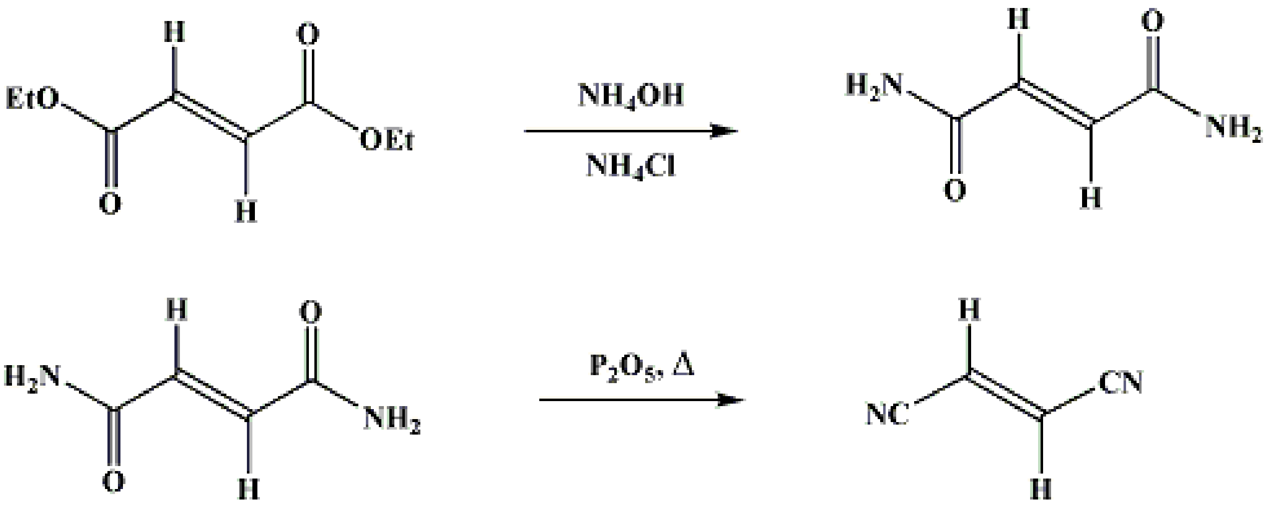
FUMARONITRILE



Submitted by David T. Mowry and John Mann Butler[1].
Checked by Charles C. Price and Richard D. Gilbert.

1. Procedure

Caution! Fumaronitrile is both a vesicant and a lachrymator.

A. *Fumaramide.* A mixture of 516 g. (3.0 moles) of diethyl fumarate (Note 1) and (Note 2), 600 ml. of concentrated ammonium hydroxide (28%, sp. gr. 0.90, 9.0 moles), and 60 g. of ammonium chloride is placed in a 2-l. flask equipped with a stirrer and a thermometer. The reaction mixture is stirred at 25–30° with slight cooling for 7 hours (Note 3). The thick slurry of fumaramide is then filtered with suction, reslurried with 1 l. of water, filtered, and washed with about 50 ml. of ethanol. The white crystalline product is then dried in air or in an oven below 75° (Note 4). The yield is 270–300 g. (80–88%).

B. *Fumaronitrile.* The dry, finely powdered amide (Note 5) (228 g., 2.0 moles) and 613 g. (4.3 moles) of phosphorus pentoxide are placed in a 3-l. flask and thoroughly mixed by shaking. The flask is connected to a 1-l. suction flask receiver by means of a short 17-mm. i.d. 60° elbow extending about 15 cm. into the receiver. The receiver is cooled by immersion in an ice bath or by cold running water. The system is evacuated to 15–30 mm. by means of a water aspirator. The flask is then heated with one or two burners, using large soft flames. Heating should be started at the side and moved toward the bottom as the reaction progresses (Note 6). The reaction mass froths and blackens, and the product distils and sublimes into the receiver. The elbow leading to the receiver must be heated occasionally to melt condensed fumaronitrile. Heating is continued until no more fumaronitrile distils from the reaction flask (1.5 to 2 hours) (Note 7). The product, usually white and sufficiently pure (m.p. 93–95°) for most purposes, is obtained in a yield of 125–132 g. (80–85%). The product is recrystallized conveniently (in a fume hood) by dissolving it in 150 ml. of hot benzene and decanting or filtering the solution into 500 ml.

of hexane or petroleum ether (Note 8) and (Note 9). The yield of long, glistening prisms, m.p. 96°, amounts to 117–125 g. (75–80%).

2. Notes

1. Diethyl fumarate liquid and vapors often cause reddening and itching of the skin, which usually disappear after a few hours.
2. Dimethyl fumarate gives equally good results but is less convenient to handle because it is a solid.
3. Additional ammonium hydroxide may be added if the slurry becomes too thick.
4. Temperatures higher than 75° often cause yellowing of the amide and excessive foaming during the dehydration with phosphorus pentoxide.
5. The amide is considered sufficiently dry if no heat is evolved when a sample is shaken vigorously in a test tube with phosphorus pentoxide powder.
6. On somewhat smaller runs it may be more convenient to effect heating by the use of a wax or Wood's metal bath or an electric mantle. A bath or mantle temperature of 200° is sufficient for optimum yield. The reaction may froth vigorously if heated too rapidly or if the fumaramide is impure.
7. The cooled reaction flasks are easily cleaned by first soaking overnight in water and then rinsing with dilute sodium hydroxide solution.
8. *Caution!* This should be done in a hood. Fumaronitrile vapors and dust are irritating to the mucous membranes and are both vesicatory and lachrymatory. In the event of skin contact, the area should be washed promptly and thoroughly with soap and water to avoid irritation and blistering.
9. The principal impurities are a benzene-insoluble brown tar and hexane-soluble ethyl β-cyanoacrylate.

3. Discussion

The preparation described is based on the method of deWolf and van de Straete.[2] Fumaronitrile also has been prepared by the reaction of diiodoethylene with cuprous cyanide[3] and by hydrolyzing the product from the reaction of hydrogen cyanide with chloroacrylonitrile.[4] Pace claims that the yield of nitrile is improved when fumaramide is heated with phosphorus pentoxide in the presence of metal powders such as magnesium, cadmium, zinc, iron, and aluminum.[5]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

ethanol (64-17-5)

Benzene (71-43-2)

ammonium chloride (12125-02-9)

sodium hydroxide (1310-73-2)

magnesium (7439-95-4)

iron (7439-89-6)

hydrogen cyanide (74-90-8)

Cuprous Cyanide (544-92-3)

aluminum (7429-90-5)

zinc (7440-66-6)

ammonium hydroxide (1336-21-6)

diethyl fumarate (623-91-6)

cadmium (7440-43-9)

hexane (110-54-3)

Fumaronitrile (764-42-1)

Fumaramide (627-64-5)

Dimethyl fumarate (624-49-7)

ethyl β-cyanoacrylate

diiodoethylene

chloroacrylonitrile

phosphorus pentoxide (1314-56-3)

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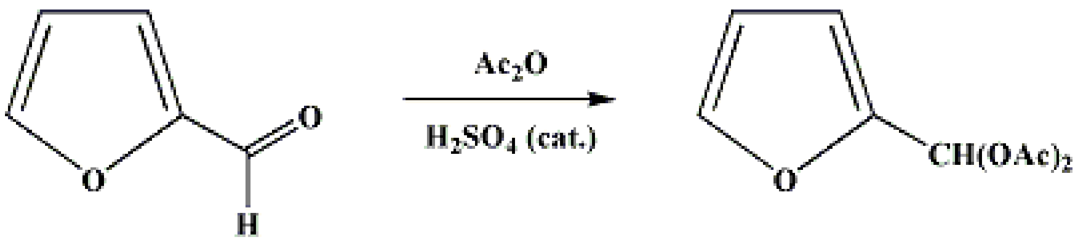
FURFURAL DIACETATE

[2-Furanmethanediol, diacetate]



Submitted by R. T. Bertz[1]
Checked by James Cason, William G. Dauben, W. B. Fearing, and B. P. Summerer.

1. Procedure

In a 300-ml. Claisen flask, whose side neck is elongated by a 10-cm. indented section, 102 g. (1 mole) of acetic anhydride and 0.1 ml. (Note 1) of concentrated sulfuric acid are mixed by hand swirling. The mixture is cooled to 10° by swirling in an ice bath, then there is added, during about 10 minutes, 96 g. (1 mole) of recently distilled furfural (Note 2). The temperature is maintained at 10–20°. After addition is complete and the contents of the flask have been well mixed by swirling, the cooling bath is removed and the reaction allowed to warm up spontaneously. A maximum temperature of about 35° is usually reached in about 5 minutes. After the temperature has dropped to that of the room (20–30 minutes), 0.4 g. (Note 1) of anhydrous sodium acetate is added, the flask is fitted for distillation at reduced pressure, and the mixture is distilled from an oil bath. A fore-run, weighing 50–70 g. and consisting principally of a mixture of acetic anhydride, furfural, and furfural diacetate (Note 3), is collected at 50–140°/20 mm. (Note 4). The product, collected at 140–142°/20 mm., weighs 129–139 g. (65–70%) and melts at 52–53° (Note 4) and (Note 5).

2. Notes

1. In order to freeze the equilibrium during distillation, it is imperative that the sulfuric acid catalyst be previously neutralized by sodium acetate; hence it is important that the small quantities of sulfuric acid and sodium acetate be measured carefully.
2. The furfural used by the checkers was collected at 158–163°. In several runs made with technical grade furfural, which had been stored several years and was black and opaque, a satisfactory product was obtained but yields were 45–53%.
3. This fore-run turns black on standing, but if stored no more than a few days it may be assumed to be an equimolar mixture of furfural and acetic anhydride and may be used as starting material for subsequent runs. If no additional runs are to

be made, the yield may be increased by 5–10% by redistilling the fore-run.
4. If collection of the product is started too soon it rapidly darkens and becomes partly liquid on standing. It is advisable to begin collecting the product only after a small sample of distillate, collected separately, sets to a crystalline mass on cooling. Products collected in this manner darkened slightly but remained solid after storage for 2 months. Original distillation of the reaction mixture through a 50-cm. column appeared not to improve the stability to storage, but a sample redistilled in a Claisen flask remained nearly white after storage for 6 months. All stored samples have a strong odor of acetic acid.
5. The submitter has carried out the preparation similarly on a 10-mole scale.

3. Discussion

Furfural diacetate has been prepared from furfural and acetic anhydride in the presence of various catalysts, including cation-exchange resins.[2,3,4,5] It has been claimed that the furfural diacetate preparation of Knoevenagel is improved by the addition of water to the reaction product, followed by ether extraction.[6] The present method is adapted to recovery and reuse of unreacted starting materials.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

acetic anhydride (108-24-7)

sodium acetate (127-09-3)

Furfural (98-01-1)

Furfural diacetate

2-Furanmethanediol, diacetate (613-75-2)

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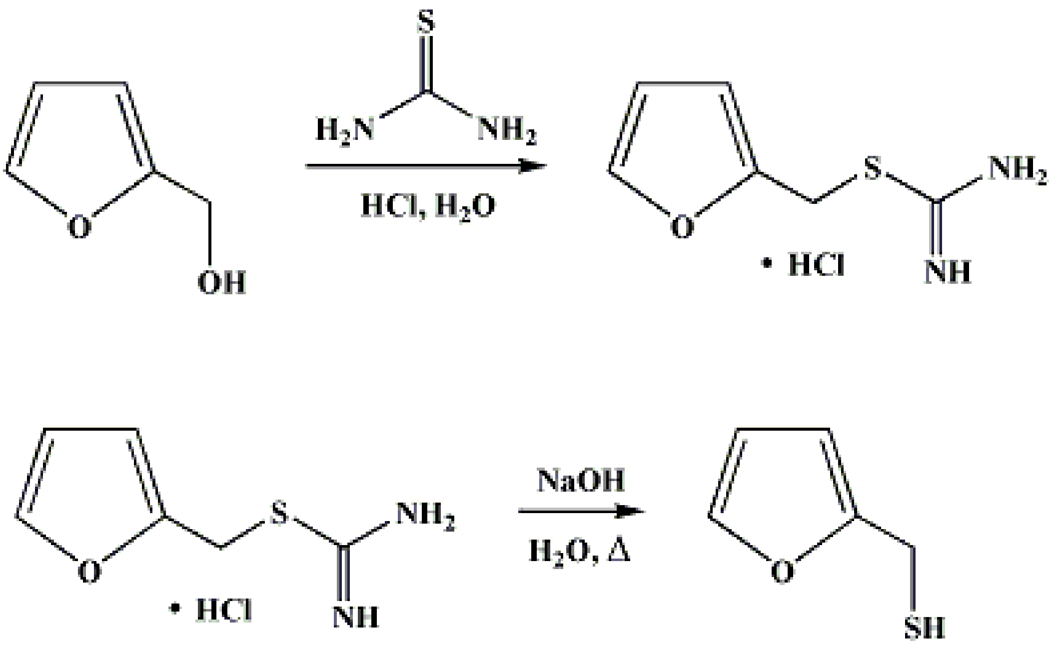
2-FURFURYL MERCAPTAN

[2-Furanmethanethiol]



Submitted by Helmer Kofod[1]
Checked by Richard T. Arnold and Erich Marcus.

1. Procedure

The following operations should be carried out in an effective hood (Note 1).

In a 3-l. round-bottomed flask are placed 380 g. (5 moles) of thiourea (Note 2), 500 ml. of water, and 400 ml. of concentrated hydrochloric acid (12.5*N*) (Note 3). The solid is dissolved by gentle heating, and the solution is cooled to 30°. Furfuryl alcohol (490 g., 434 ml., 5 moles) (Note 4) is added to the reaction mixture. The reaction, which usually commences spontaneously within a few minutes (Note 5), is strongly exothermic and should be controlled by suitable cooling with tap water so as to hold the temperature near 60° (Note 6). When the reaction subsides, cooling is discontinued and the clear, dark green solution is allowed to stand at room temperature for 12 hours.

A solution of 225 g. of sodium hydroxide (Note 3) in 250 ml. of water is poured into the reaction mixture. A heavy brown oil separates, consisting of S-2-furfurylisothiourea, which has already partially decomposed to 2-furfuryl mercaptan. The flask is quickly fitted with a steam-inlet tube and condenser. Steam distillation is continued as long as the distillate contains oily drops. The mercaptan is separated from the aqueous phase by means of a separatory funnel (Note 7) and (Note [*****note*****]). The product is dried with calcium chloride; yield 313–340 g. (55–

60%). The 2-furfuryl mercaptan so obtained is of a high degree of purity (Note 9) but can be distilled without decomposition in a nitrogen atmosphere; b.p. 160°/759 mm., 84°/65 mm., n_D^{20} 1.533.

2. Notes

1. The odor of the mercaptan is extremely disagreeable, and the substance in high concentration causes headache. An effective hood is absolutely essential.
2. The checkers employed practical grade thiourea obtained from Matheson, Coleman and Bell, East Rutherford, New Jersey.
3. It is desirable to determine the exact concentration of the hydrochloric acid and the composition of the sodium hydroxide by titration.
4. The checkers employed practical grade furfuryl alcohol obtained from the Eastman Kodak Company.
5. If the reaction does not start, the flask is heated gently until a spontaneous temperature rise sets in.
6. Temperatures above 60° and particularly supplementary refluxing are to be avoided since under these conditions the sensitive furan ring is attacked.
7. The mercaptan is almost insoluble in water, and the aqueous phase contains too little product to justify extraction.
8. It is convenient to use a 2-l. separatory funnel as a receiver during the steam distillation.
9. The checkers found the undistilled product to be essentially pure; n_D^{25} 1.5285. The distilled material was obtained with only mechanical losses; b.p. 84°/65 mm., n_D^{25} 1.5280.

3. Discussion

Furfuryl mercaptan cannot be prepared according to the classical method using furfuryl chloride and potassium sulfide.[2] It has been prepared by reduction of 2-furfuryl disulfide, obtained from furfural and ammonium hydrosulfide.[3] The mercaptan has also been obtained in 33% yield[2] by the reaction of furfuryl chloride with thiourea and subsequent decomposition of the intermediate S-2-furfurylisothiourea according to the general method described in *Organic Syntheses.*[4] In the present method, which has been published previously, the use of the very unstable and difficulty available furfuryl halides is avoided.[5]

The formation of mercaptans directly from alcohols may be applied to the preparation of a large number of mercaptans, but usually much longer reaction periods or higher temperatures and higher concentrations of hydrogen halides are required.[6] Under such conditions the furan ring is destroyed.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

S-2-furfurylisothiourea

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

sodium hydroxide (1310-73-2)

nitrogen (7727-37-9)

potassium sulfide (1312-73-8)

Furan (110-00-9)

Furfural (98-01-1)

Furfuryl alcohol (98-00-0)

thiourea (62-56-6)

2-Furfuryl mercaptan

2-Furanmethanethiol, Furfuryl mercaptan (98-02-2)

furfuryl chloride

2-furfuryl disulfide

ammonium hydrosulfide (12135-76-1)

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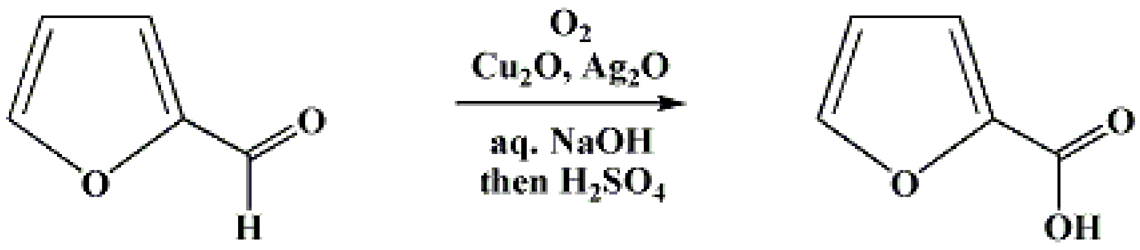
2-FUROIC ACID



Submitted by R. J. Harrisson and M. Moyle[1].
Checked by James Cason and W. N. Baxter.

1. Procedure

A 1-l. flask (Note 1) is fitted with a condenser, an efficient stirrer, two dropping funnels, a thermometer extending well into the flask, and a delivery tube which extends far enough to be below the surface of the stirred liquid.

To the flask is added 250 ml. of a 2.5% solution of sodium hydroxide and a cuprous oxide-silver oxide catalyst (Note 2). In the two dropping funnels are placed, respectively, 96 g. (1.0 mole) of furfural (Note 3) and a solution of 40 g. (1.0 mole) of sodium hydroxide in 100 ml. of water. The contents of the flask are heated to about 55°, vigorous stirring is started, and a rapid stream of oxygen is bubbled through as the contents of the two funnels are added simultaneously (Note 4) to the reaction mixture at such a rate (20–25 min.) as to maintain the temperature at 50–55° (Note 5) without external heating. After the additions have been completed, vigorous stirring and passage of oxygen are continued until the temperature drops below 40° (15–30 min., depending on the rate of oxygen flow).

The catalyst is separated by filtration, and the aqueous solution is extracted with three 30-ml. portions of ether (Note 6), acidified with 30% sulfuric acid, boiled for 45 min. (Note 7) with 6–7 g. of carbon, then filtered hot. The filtrate is cooled to 0° and allowed to stand at this temperature for 1 hour or longer. The 2-furoic acid, which separates as pale pink needles, m.p. 130–132°, is collected by suction filtration and washed with small portions of ice water (Note 8). The yield is 96–101 g. (86–90%).

2. Notes

1. Since oxygen is passed through the solution at 55°, it is best to operate under a reflux condenser. Ground joint fittings are not essential but convenient. The checkers used a 4-necked flask with ground joints; the thermometer was hung through the condenser, and one neck was arranged for attachment of the gas delivery tube and one of the separatory funnels.
2. The catalyst used is commercial cuprous oxide (9.6 g., 10% of the weight of

the furfural) and commercial silver nitrate (0.5 g., 0.5% of the weight of the furfural) in 15 ml. of water. The cuprous oxide is suspended in the rapidly stirred 2.5% sodium hydroxide solution, and the solution of silver nitrate is added to give a dark brown suspension of cuprous oxide and silver oxide which is used directly. So long as oxygen is being passed through the reaction mixture, the life of the catalyst appears to be unlimited.

3. A sample of commercial furfural is purified by simple distillation or steam distillation immediately before use. The submitters have carried out this reaction on an 8-mole scale following the same procedure except that a total reaction time of about 4 hours was required.

4. The simultaneous addition of furfural and sodium hydroxide maintains the concentration of sodium hydroxide at about 2.5%, at which concentration only a small percentage of furfuryl alcohol is formed in the accompanying Cannizzaro reaction.

5. Below 50°, the reaction is too slow; above 55°, the reaction becomes violent and cooling becomes necessary. Frothing may be checked by addition of small amounts of benzene.

6. Ether extraction at this stage removes furfuryl alcohol (about 12 g.). If this is not removed, the reaction mixture becomes resinous on acidification and heating.

7. During the period of boiling in acid solution a small amount of polymeric material forms, and this is separated when the charcoal is removed by filtration.

8. The solubility of 2-furoic acid in water is 2.8 g. per 100 ml. at 0°; however, its solubility in the salt solution resulting from the reaction is quite low. Usually it is not possible to obtain further material from the filtrate by salting out with sodium chloride; however, in case a lowered yield is obtained in the first crop it may be profitable to investigate the possibility of obtaining additional material from the filtrate.

3. Discussion

2-Furoic acid has been made by oxidation of lactose followed by pyrolysis, by the oxidation of 2-acetylfuran, 2-methylfuran, or furfuryl alcohol using potassium ferricyanide in alkaline medium, and by other methods already listed.[2] In addition, furfural has been oxidized to furoic acid by air in the presence of sodium hydroxide and silver nitrate,[3] by hydrogen peroxide in the presence of pyridine or picoline,[4] by sodium or potassium hypochlorite,[5] by means of sodium hydroxide in methanol or sodium hydroxide in methanol followed by hydrogen peroxide,[6] and by sodium hydroxide in the presence of a copper oxide-silver oxide-carbon catalyst.[7]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

Benzene (71-43-2)

methanol (67-56-1)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

silver oxide (20667-12-3)

silver nitrate (7761-88-8)

oxygen (7782-44-7)

carbon (7782-42-5)

pyridine (110-86-1)

cuprous oxide

hydrogen peroxide (7722-84-1)

2-Furoic acid, furoic acid (88-14-2)

copper oxide (1317-38-0)

Furfural (98-01-1)

Furfuryl alcohol (98-00-0)

sodium hypochlorite (7681-52-9)

potassium hypochlorite

potassium ferricyanide (13746-66-2)

picoline (109-06-8)

lactose

2-acetylfuran (1192-62-7)

2-methylfuran (534-22-5)

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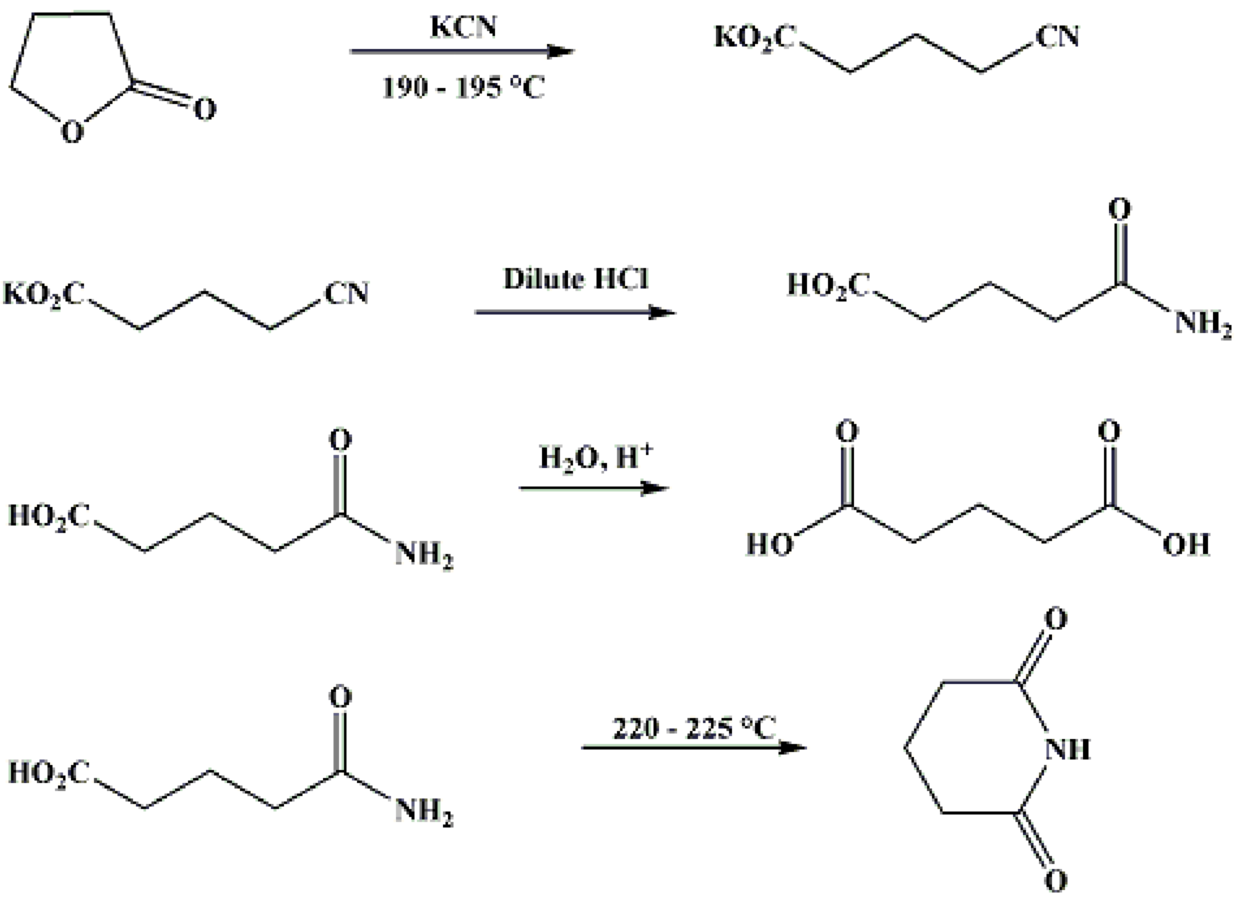
Organic Syntheses, CV 4, 496

GLUTARIC ACID AND GLUTARIMIDE

[1. FROM γ-BUTYROLACTONE]



Submitted by G. Paris, L. Berlinguet, and R. Gaudry[1].
Checked by James Cason and Edwin R. Harris.

1. Procedure

This preparation should be carried out in a good hood since poisonous hydrogen cyanide may be evolved.

In a 500-ml. three-necked flask fitted with a sealed mechanical stirrer and a reflux condenser are placed 86 g. (1 mole) of γ-butyrolactone (Note 1) and 72 g. (1.1 moles) of potassium cyanide (Note 2). As the contents of the flask are stirred, the mixture is heated in an oil bath for 2 hours at a temperature of 190–195° (Note 3). There is an initial vigorous reaction which soon subsides. After the completion of the heating period the mixture is cooled to about 100°, and the potassium salt of the cyano acid is dissolved in about 200 ml. of hot water. The warm solution is cautiously acidified to Congo red by the addition of about 90 ml. of concentrated hydrochloric acid. The resultant solution, which contains glutaric acid monoamide and potassium chloride, is used to prepare glutaric acid or glutarimide.

A. *Glutaric acid*. To the solution of monoamide is added 200 ml. of concentrated hydrochloric acid, and the mixture is heated under reflux in the hood for 1 hour. The reaction mixture is evaporated to dryness under reduced pressure, and the residue is dried by brief heating on a steam bath at reduced pressure. The residual crystalline solid is broken up, ground in a mortar, and extracted with four 200-ml. portions of boiling chloroform. The combined hot extracts are filtered by gravity through a fluted paper on a heated funnel and then concentrated to about 400 ml. After the solution has been cooled in water to effect crystallization, the glutaric acid is collected by suction filtration, washed with cold chloroform, and dried. The yield of slightly discolored glutaric acid, suitable for many purposes, is 105–110 g. (79.5–83.5%), m.p. 95–97°.

If a pure grade of glutaric acid is desired, it is decolorized by boiling for about 1 hour with 10 g. of charcoal in water solution. The charcoal is removed by filtration (Note 4), the water is evaporated under reduced pressure, and the dry residue is recrystallized from chloroform. The yield of white glutaric acid, m.p. 98–99°, is 94–99 g. (71–75%).

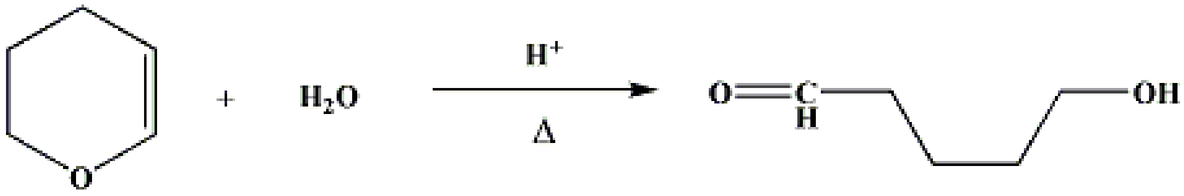
B. *Glutarimide*. The solution containing the monoamide is extracted with six 50-ml. portions of ether. The ether solution is dried over anhydrous sodium sulfate (or by filtering by gravity through a layer of the drying agent), and then the ether is evaporated by heating on a steam bath; the last portion is removed at reduced pressure. The oily residue of glutaric acid monoamide is placed in a 300-ml. round-bottomed flask which is fitted with a bent tube attached to a short condenser, and the flask is immersed in a bath (Note 5) held at 220–225°. Heating is continued until water no longer distils (3–4 hours). The cooled glutarimide is dissolved in about 200 ml. of water, and the solution is boiled for about 30 minutes with about 2 g. of charcoal. The charcoal is removed by filtration, water is removed by distillation at reduced pressure, and the dry residue is crystallized from about 125 ml. of 95% ethanol, with final cooling in an ice bath. The yield of glittering white crystals of glutarimide, m.p. 152–154°, is 65.5–73.5 g. (58–65%) (Note 6).

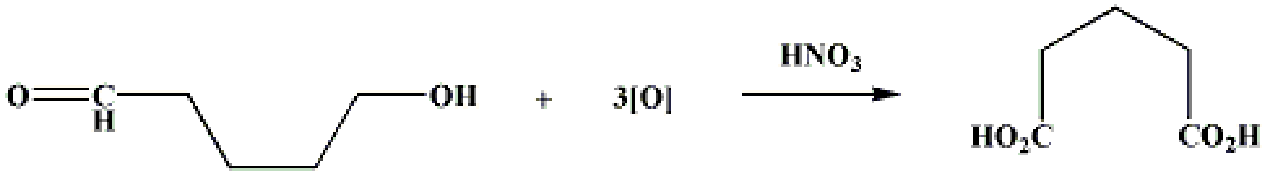
2. Notes

1. Butyrolactone from Eastern Chemical Corporation, 34 Spring Street, Newark 2, New Jersey, was used without purification.
2. Satisfactory results were obtained with potassium cyanide, 96–98% purity, from General Chemical Company or with material indicated as of 95% minimum purity, from Merck & Co., Inc. If potassium cyanide pellets are employed, they should be pulverized before use.
3. Since the reaction mixture is acidified after the heating period, it is most convenient to carry out the reaction in a forced-draft hood in order to provide protection against hydrogen cyanide. If higher temperatures than those specified are used, the reaction may get out of control during the initial vigorous reaction.
4. If filtration by gravity through a fluted paper fails to remove the last traces of charcoal, the filtrate should be refiltered by suction through a thin mat of filter aid such as Supercel.
5. The submitters used an oil bath. The checkers used a salt bath consisting of an

equimolar mixture of potassium nitrate and sodium nitrite (Heat Transfer Salt). A salt bath should be handled only with proper precautions, which include wearing goggles and gloves and supporting the bath on a stand bolted to the bench.
6. This material is suitable for preparation of N-bromoglutarimide, as follows. In a 1-l. beaker, provided with a mechanical stirrer, 65 g. of potassium hydroxide is dissolved in 200 ml. of water. The vigorously stirred solution is cooled to about –5°, and as the temperature is maintained below 0° there is added gradually 113 g. (1 mole) of glutarimide and cracked ice. To this mixture is added in one portion 160 g. (1 mole) of bromine; then stirring is continued for 1 minute. The mixture is filtered by suction, and the precipitate is dissolved in hot water. On cooling, there crystallizes about 94 g. (49%) of N-bromoglutarimide which melts at about 165°. This product is usually suitable for use as a brominating agent. Pure N-bromoglutarimide, m.p. 180–185°, is obtained only after several recrystallizations from water.

[II. FROM DIHYDROPYRAN]





Submitted by J. English, Jr. and J. E. Dayan[2].
Checked by Arthur C. Cope and Mark R. Kniter.

1. Procedure

In a 1-l. round-bottomed flask equipped with a reflux condenser are placed 400 ml. of 0.2*N* nitric acid (5 ml. of concentrated nitric acid, sp. gr. 1.42, and 395 ml. of water) and 168.3 g. (2 moles) of dihydropyran (Note 1). The mixture is heated on a steam bath or a boiling water bath; the yellowish upper layer dissolves suddenly after 25 to 45 minutes of heating. The flask is swirled to aid the dissolution at this time, and the period of heating is extended for an additional 5 to 10 minutes.

While the hydrolysis of the dihydropyran is taking place, 800 g. (575 ml., 9.25 moles) of concentrated nitric acid (sp. gr. 1.42) is placed in a 2-l. three-necked flask and cooled in an ice-salt bath in a well-ventilated hood. The flask should be equipped with an efficient stirrer, separatory funnel, reflux condenser, and a thermometer. When the temperature of the solution reaches 0°, 5.75 g. of sodium nitrite is added and stirring is continued until most of it has dissolved; the solution becomes yellow.

The solution obtained by the hydrolysis of dihydropyran is placed in the separatory funnel, and about 10 ml. is added to the nitric acid solution at a temperature below 0°. After the evolution of brown nitrogen dioxide fumes begins (in about 10 minutes), the addition is continued at a rate that allows the temperature to be held below 10° (Note 2). The addition requires about 3 hours (Note 3) and (Note 4). When the addition is completed, the blue-green solution is stirred for an additional 1.5 hours as brown fumes continue to be evolved. The cooling bath then is removed and stirring is continued as the temperature is allowed to rise slowly to 25–30° (Note 5). As the reaction nears completion, the color changes from blue-green to green to light yellow. Appearance of the light yellow color indicates the end of the reaction and normally requires 2 to 3 hours after the addition is completed. The volume of the solution then is reduced either by evaporation on a steam bath or by distillation under reduced pressure.

In the latter method, after removal of all the water, an additional 100 ml. of water is added and the distillation is repeated to remove the remaining nitric acid. The solid residue remaining from either method of removing water from the reaction mixture is recrystallized from a mixture of 100 ml. of ether and 1 l. of benzene. Insoluble sodium nitrate and succinic acid are removed by filtration of the hot solution. Upon cooling, 185–198 g. (70–75%) of glutaric acid is obtained in the first crop, m.p. 89.5–91.5° (Note 6). On concentrating the benzene solution to 200 ml. and cooling, an additional 18–23 g. of crude glutaric acid can be obtained (Note 7).

2. Notes

1. Dihydropyran is available from the Electrochemicals Department, E. I. du Pont de Nemours and Company, or can be prepared by the dehydration of tetrahydrofurfuryl alcohol.[3]
2. More efficient cooling may shorten the time required for the addition.
3. As the hydrolyzed dihydropyran solution cools, it may become cloudy and δ-hydroxyvaleraldehyde may separate as a red liquid. The separation can be avoided by continuing to heat most of the solution while a small part is left in the separatory funnel, but it is not essential, for the yield is not affected by the separation of phases at this point. Oxidation of the pure aldehyde in a similar manner is stated to give a 90% yield of glutaric acid.[4]
4. The separatory funnel is removed after the addition is completed to facilitate the removal of nitrogen oxides.
5. Care should be taken that the temperature does not rise above room temperature; if this occurs much succinic acid is produced. If the temperature rises too high the cooling bath should be replaced again until the temperature does not exceed 25–30° on its removal.
6. The glutaric acid obtained has a neutralization equivalent of 66.3 (theory 66.1) and is suitable for most synthetic work.
7. This material melts at 80–82° and can be purified by recrystallization. In a series of preparations it is advantageous to save these residues and combine them for recrystallization.

3. Discussion

Methods of preparation of glutaric acid are given in an earlier procedure.[5] In addition to these, glutaric acid has been obtained by the oxidation of glutaraldehyde in the presence of catalysts,[6] by the ozonization of cyclopentene followed by permanganate cleavage of the ozonide,[7] by the nitric acid oxidation of 2-cyanocy-clopentanone,[8] by the oxidation of pentamethylene glycol with nitrogen tetroxide,[9] and by the condensation of acrylonitrile with ethyl malonate, followed by acid hydrolysis of the mono- and di-adduct.[10]

Glutarimide has been prepared from glutaric acid and sulfamide[11] or formamide,[12] by distillation of ammonium glutarate,[13] by hydrolysis of pentanedinitrile with acetic acid,[14] and by oxidation of piperidine with hydrogen peroxide.[15]

Method I, based on a published procedure,[16] offers a more convenient synthesis of glutaric acid and its imide and may be readily adapted to a large scale.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 824

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

nitrogen oxides

2-cyanocy-clopentanone

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

ether (60-29-7)

formamide (75-12-7)

chloroform (67-66-3)

nitric acid (7697-37-2)

hydrogen cyanide (74-90-8)

bromine (7726-95-6)

sodium sulfate (7757-82-6)

potassium cyanide, potassium cyanide pellets (151-50-8)

sodium nitrite (7632-00-0)

Succinic acid (110-15-6)

potassium hydroxide (1310-58-3)

piperidine (110-89-4)

hydrogen peroxide (7722-84-1)

nitrogen dioxide (10102-44-0)

pentanedinitrile (544-13-8)

ethyl malonate (1071-46-1)

nitrogen tetroxide

Glutaric acid (110-94-1)

pentamethylene glycol (111-29-5)

tetrahydrofurfuryl alcohol (97-99-4)

sodium nitrate

potassium chloride (7447-40-7)

Cyclopentene (142-29-0)

acrylonitrile (107-13-1)

dihydropyran

δ-hydroxyvaleraldehyde (4221-03-8)

γ-butyrolactone, Butyrolactone (96-48-0)

Glutarimide (1121-89-7)

glutaric acid monoamide

N-bromoglutarimide (3699-18-1)

glutaraldehyde (111-30-8)

sulfamide (7803-58-9)

ammonium glutarate

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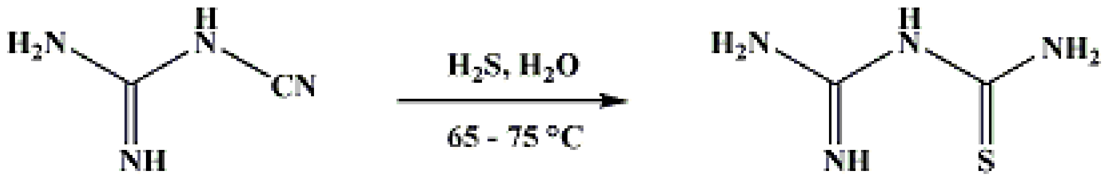
Organic Syntheses, CV 4, 502

GUANYLTHIOUREA

[Urea, 1-amidino-2-thio-]



Submitted by Frederick Kurzer[1]
Checked by John C. Sheehan, George Buchi, and David Knutson.

1. Procedure

A 500-ml. three-necked round-bottomed flask, supported in a water bath equipped with a thermostat, is fitted with a vertical air-condenser and, on the side necks, with a thermometer and a gas delivery tube, both of which nearly reach the bottom of the vessel. The flask contains a solution of 42 g. (0.5 mole) of N-cyanoguanidine (dicyandiamide) (Note 1) in 200 ml. of water (Note 2). This is kept at 75° during 12 hours, and at 65–70° during an additional 25–30 hours (Note 3) while a fairly slow stream (Note 4) of hydrogen sulfide is passed through (Note 5). The resulting deep yellow liquid is allowed to cool to 45° while passage of hydrogen sulfide is continued; it is made strongly alkaline with 15 ml. of 40% aqueous sodium hydroxide and is freed from suspended impurities (consisting usually of finely divided black particles) by rapid filtration under reduced pressure (Note 6). The clear, yellow filtrate is allowed to cool slowly to room temperature, when lustrous prismatic leaflets separate gradually. Crystallization is completed by storing the flask and contents at 0° for 24 hours. The crystalline mass is broken up with a spatula, collected by filtration, and washed with three 20-ml. portions of ice water, the second and third portions of washing liquid being collected separately and discarded (Note 7). The yield of crude guanylthiourea, forming large, nearly colorless prisms, m.p. 160–164° (dec., with previous sintering at 154–158° or somewhat lower) (Note 8), varies between 29.5 and 32.5 g. (50–55%).

The material is purified as follows: The large crystals are powdered (Note 9) and boiled with successive portions of methanol until solution is complete, the saturated extracts being decanted and collected; approximately 8–9 ml. of methanol per gram of crude solid is required. The combined hot solution is filtered, if necessary, with suction, is allowed to cool slowly to room temperature, and is then stored at 0° overnight. Almost pure guanylthiourea, forming colorless prisms, m.p. 170–172° (dec., with previous sintering in the range 166–170°), is collected by filtration and washed with a little methanol. The recovery, per crystallization, varies from 65% to 70%. Most of the material contained in the mother liquors may be obtained by evaporation to small volume (Note 10) and forms one or two crops of satisfactory quality (melting point ranging between 166° and 170°).

2. Notes

1. A good reagent grade of N-cyanoguanidine is satisfactory in this synthesis.
2. The smallest possible volume of water is employed to ensure direct crystallization of the product when the solution is finally allowed to cool. Smaller volumes than the stated amount of water, however, tend to block the delivery tube with separated crystalline material, particularly in the beginning stages of the reaction, when much of the less-soluble reactant is still present.
3. The total time of heating may be made up of several shorter periods. On being cooled overnight the reaction mixture deposits a thick crust of crystalline solid on the walls of the flask. After 8 hours, large, spikelike prisms of unchanged N-cyanoguanidine predominate, but later the separated mass consists of massive rhombic prisms of guanylthiourea, with small needles of 2,4-dithiobiuret filling the spaces between the prisms. Solution is once again rapidly effected when the temperature is raised to 70°, with passage of hydrogen sulfide.
4. A rate of 3–4 bubbles of hydrogen sulfide per second is satisfactory. Toward the end of the time of reaction, a slower stream suffices.
5. Since hydrogen sulfide is only slowly absorbed, most of the gas escapes through the air condenser. The reaction must therefore be performed in an efficient hood.
6. A preheated Büchner flask and filter of 5- to 7-cm. diameter carrying a double layer of filter paper are employed.
7. 2,4-Dithiobiuret may be isolated from the alkaline filtrate as follows: The stirred alkaline filtrate is acidified to Congo red with 25–30 ml. of concentrated hydrochloric acid. A pale yellow powdery solid is rapidly precipitated, with evolution of hydrogen sulfide; after storage at 0°, the solid (dry weight 7.5–9.0 g.) is collected by filtration, washed three times with 30-ml. portions of ice water, and pressed semidry. This material is added to boiling water (100 ml.) and stirred at 95–100° for 2 minutes, and the undissolved yellow powdery impurities (1.0–1.5 g., consisting largely of sulfur) are quickly removed by filtration with suction through a preheated funnel. The clear, pale yellow filtrate is rapidly filled with crystals, which are collected after storage at 0° for 12 hours. The yield of crude 2,4-dithiobiuret, forming small yellow needles, m.p. 178–180° (dec., previously sintering at 172–175°) is 5.5–7.0 g. (8–10%) (Note 11). Two crystallizations from boiling water (12 ml. per gram, recovery per crystallization: 80–90%) (Note 12), one with addition of carbon, affords nearly white lustrous needles of 2,4-dithiobiuret, m.p. 180–182° (dec., previously sintering slightly at 178–180°) (Note 13).
8. Colorless guanylthiourea melts to a pale yellow liquid, which resolidifies to a yellow crystalline mass on cooling; partial rearrangement to guanidine thiocyanate occurs during the fusion.
9. When ground in a mortar, the crude guanylthiourea evolves small quantities of occluded hydrogen sulfide.
10. The methanolic filtrates are rapidly distilled to approximately half volume at

low temperature in a good vacuum. The solution is likely to froth considerably, and the use of a relatively large distilling flask is recommended. Small quantities of solid separating on the walls of the flask are redissolved by heating the residual liquid once again on a steam bath.

11. The yield of dithiobiuret increases on lengthening the time of reaction. After 100 hours' passage of hydrogen sulfide the yields of guanylthiourea and dithiobiuret were 25–35% and 15–18%, respectively.

12. Crystallization is carried out by adding the solid to the appropriate volume of boiling water, stirring at 95–100° for about 1 minute, and removing small quantities of suspended yellow impurities by filtration under reduced pressure using carefully preheated apparatus. When cooled slowly, the clear filtrate deposits the product in the form of large, lustrous needles.

13. On analysis, this material gives carbon, hydrogen, nitrogen, and sulfur percentages in excellent agreement with the calculated values. Two additional crystallizations from ethanol-water (10 ml. each, per gram) raise the melting point to 183–185° (dec.). These decomposition temperatures are somewhat influenced by the rate of heating; the quoted values are observed when the specimen is inserted at 160° and the bath temperature is raised at the approximate rate of 8° per minute.

3. Discussion

Guanylthiourea has been prepared by the prolonged interaction of saturated aqueous hydrogen sulfide with N-cyanoguanidine[2,3] or an amidinourea salt[4] at 60–80°. It is formed in small quantities when thiourea is heated with thiophosgene or phosphorus pentachloride at 100–110°.[5] Guanylthiourea also results from the acid hydrolysis of 4,6-diamino-2-thio-1,3,5-thiadiazine.[6,7] In all these syntheses the product is collected as a sparingly soluble salt, the base being subsequently isolated by comparatively laborious methods, e.g. from the oxalate[2] or the phosphate.[7] The present procedure,[8] based on Bamberger's method,[2] allows the direct isolation of the base. Small quantities of 2,4-dithiobiuret, which are also formed in this reaction as a by-product, are readily separated.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

N-cyanoguanidine (dicyandiamide)

amidinourea salt

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

methanol (67-56-1)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

phosphorus pentachloride (10026-13-8)

hydrogen sulfide (7783-06-4)

nitrogen (7727-37-9)

sulfur (7704-34-9)

carbon (7782-42-5)

Thiophosgene (463-71-8)

guanidine thiocyanate

thiourea (62-56-6)

Guanylthiourea, Urea, 1-amidino-2-thio- (2114-02-5)

N-cyanoguanidine (461-58-5)

2,4-dithiobiuret, dithiobiuret (541-53-7)

4,6-diamino-2-thio-1,3,5-thiadiazine

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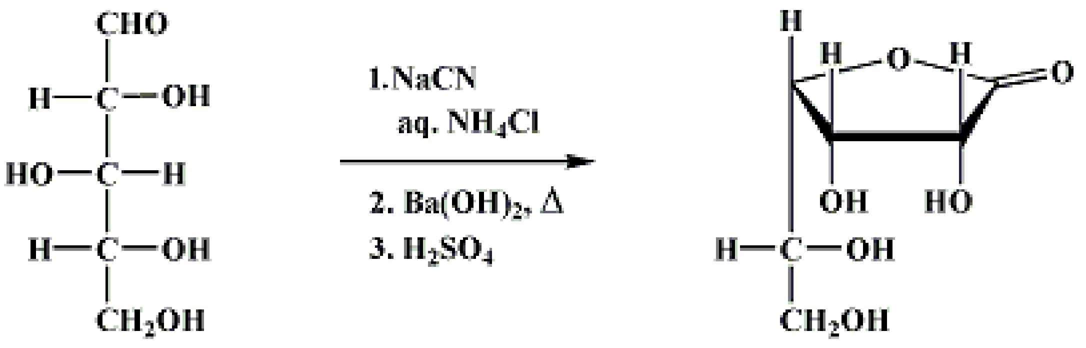
Organic Syntheses, CV 4, 506

D-GULONIC-γ-LACTONE

[D-Gulonic acid, γ-lactone]



d - gulonic acid　　　　*d* - gulonic acid, γ - lactone

Submitted by J. V. Karabinos[1]
Checked by R. T. Arnold, Fred Smith, and Bertha Lewis.

1. Procedure

In a 500-ml. glass-stoppered Erlenmeyer flask, 30 g. (0.2 mole) of D-xylose and 10.7 g. (0.2 mole) of ammonium chloride are dissolved in 100 ml. of distilled water. Cracked ice (100 g.) is added to this mixture, followed by 10 g. (0.2 mole) of sodium cyanide, and the solution is maintained at 0–5° for 48 hours. Powdered barium hydroxide octahydrate (63 g., 0.2 mole) is added along with 100 ml. of water to the cyanohydrin mixture (Note 1), which is heated on a steam bath for 2 hours with occasional stirring. The basic barium gulonate (Note 2), which is allowed to separate overnight at 5°, is collected by filtration and washed with cold water (0°) until the washings are chloride-free. Excessive washing of the barium salt is to be avoided because of its solubility. The barium salt is suspended in 200 ml. of water, and the barium ion is precipitated quantitatively by sulfate ion (Note 3). After removal of the barium sulfate by suction filtration, the filtrate and washings are concentrated to a colorless syrup on a steam bath in a stream of dry air (Note 4). The resultant syrup is dissolved in 50 ml. of hot ethylene glycol monomethyl ether (methyl Cellosolve), sufficient ethyl acetate is added to incipient turbidity, and the solution is seeded with D-gulonic-γ-lactone (Note 5). The lactone, which is allowed to crystallize overnight, is collected by suction filtration, washed with ethanol and dried in a vacuum over at 60°. The D-gulonic-γ-lactone (Note 6) has a melting point of 181–183° which is unchanged by recrystallization from aqueous ethanol. The yield is 10.7–11.6 g. (30–33%) (Note 7).

2. Notes

1. The barium hydroxide serves to hydrolyze any unchanged nitriles as well as to precipitate the aldonic acid.
2. The barium gulonate is undoubtedly contaminated with some epimeric idonate. The lactone of the latter substance is removed by recrystallization of the gulonic lactone from methyl Cellosolve.
3. It is convenient to titrate the suspended barium salt with 18*N* sulfuric acid (approx. 12–14 ml.) to a pH of 1.5 using a pH meter. After removal of the barium sulfate the slight excess of sulfate ion may be precipitated using barium chloride solution. The end point is taken when several drops of filtrate show no turbidity either upon addition of sulfuric acid or barium chloride solution.
4. Concentration in this manner allows sufficient time for the gulonic acid to be converted to the lactone in the presence of a trace of hydrochloric acid. The checkers observed also that an easily crystallized lactone was always obtained if concentration under reduced pressure was employed.
5. Crystallization is speeded considerably by seeding.
6. A small amount of less pure lactone may be obtained by evaporation of the mother liquor to a syrup and repetition of the methyl Cellosolve-ethyl acetate crystallization.
7. The submitter has reported yields up to 39% using the above procedure.

3. Discussion

The present method is adapted from that of Fischer[2] employing recently developed modifications of the cyanohydrin synthesis.[3,4]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

ammonium chloride (12125-02-9)

sodium cyanide (143-33-9)

barium chloride (10361-37-2)

barium sulfate (7727-43-7)

barium hydroxide (17194-00-2)

barium hydroxide octahydrate (12230-71-6)

methyl Cellosolve, ethylene glycol monomethyl ether (109-86-4)

D-Gulonic-γ-lactone, d-Gulonic acid, γ-lactone (6322-07-2)

d-xylose

barium gulonate

gulonic lactone

gulonic acid

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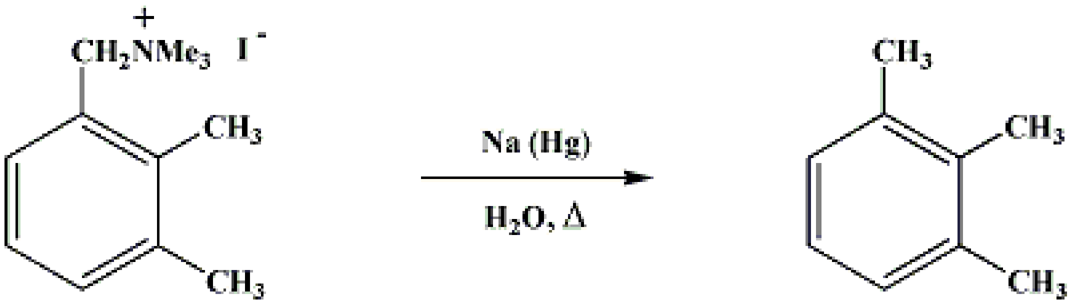
Organic Syntheses, CV 4, 508

HEMIMELLITENE

[Benzene, 1,2,3-trimethyl-]



Submitted by W. R. Brasen and C. R. Hauser[1].
Checked by William S. Johnson, Donald W. Stoutamire, and A. L. Wilds.

1. Procedure

A 3-l. round-bottomed three-necked flask, fitted with a reflux condenser and a sealed stirrer, is charged with 2 l. of hot water and 100 g. (0.33 mole) of 2,3-dimethylbenzyltrimethylammonium iodide (Note 1). The stirred suspension is heated on the steam bath, and 2760 g. of 5% sodium amalgam (Note 2) is added in 200- to 250-g. portions over a period of 45 minutes. Stirring and heating are continued for 24 hours; then the mixture is steamdistilled until no more oily material comes over. The distillate (1–1.5 l.) is extracted with three 50-ml. portions of ether. The combined extracts are washed with 50 ml. of 10% hydrochloric acid and 50 ml. of saturated sodium chloride solution, and dried over anhydrous calcium chloride. After removal of the ether by distillation, the residue is distilled from a Claisen flask, giving 33.5–35.5 g. (85–90% yield) of colorless hydrocarbon, b.p. 171–174°. On redistillation 85–90% of the material distils at 173–174°, n_D^{25} 1.5116–1.5120.

2. Notes

1. The methiodide is prepared from 2,3-dimethylbenzyldimethylamine according to the procedure for producing the lower homolog (p. 587, Notes 5 and 8).
2. The sodium amalgam is prepared in a 1-l. filter flask fitted with a two-hole rubber stopper carrying a dropping funnel and an outlet tube. The flask is charged with 138 g. (6 g. atoms) of sodium and 300 ml. of mineral oil. With a stream of nitrogen passing through the side arm of the flask, the flask is heated on a hot plate covered with an asbestos pad until the sodium melts, and then 2622 g. of mercury is added rapidly from the dropping funnel over a 1–2 minute period with swirling. The whole operation is carried out in a large pan to catch material in case of breakage. A vigorous exothermic reaction occurs, and the

hands must be adequately protected with several layers of cloth or heavy gloves as the temperature approaches 400°. If the addition is rapid enough, the amalgam will be a liquid; otherwise the material will be partially solid and must be heated vigorously to produce a homogeneous melt. The mineral oil is decanted from the molten amalgam, which is poured into a shallow metal pan while still warm and is cut or broken (with a hammer) into small pieces as it solidifies. It is finally washed with petroleum ether and stored in a tightly stoppered bottle or under petroleum ether.

3. Discussion

Hemimellitine has been prepared by the action of sodium on 2,3-dimethyliodobenzene and methyl iodide,[2] by the reduction of the chloromethylation product of *o*-xylene,[3] by the catalytic hydrogenolysis of 2,3-dimethylbenzyl alcohol,[4] and by treatment of 1,5,5,6-tetramethyl-1,3-cyclohexadiene with a catalyst prepared from sodium and *o*-chlorotoluene.[5] The present procedure is based on the method of Kantor and Hauser.[6]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

mercury (7439-97-6)

sodium (13966-32-0)

o-Chlorotoluene (95-49-8)

Methyl iodide (74-88-4)

Hemimellitene, Benzene, 1,2,3-trimethyl-, Hemimellitine (526-73-8)

2,3-dimethylbenzyltrimethylammonium iodide

2,3-dimethylbenzyldimethylamine (15848-75-6)

2,3-dimethyliodobenzene (31599-60-7)

2,3-dimethylbenzyl alcohol (13651-14-4)

1,5,5,6-tetramethyl-1,3-cyclohexadiene

o-Xylene (95-47-6)

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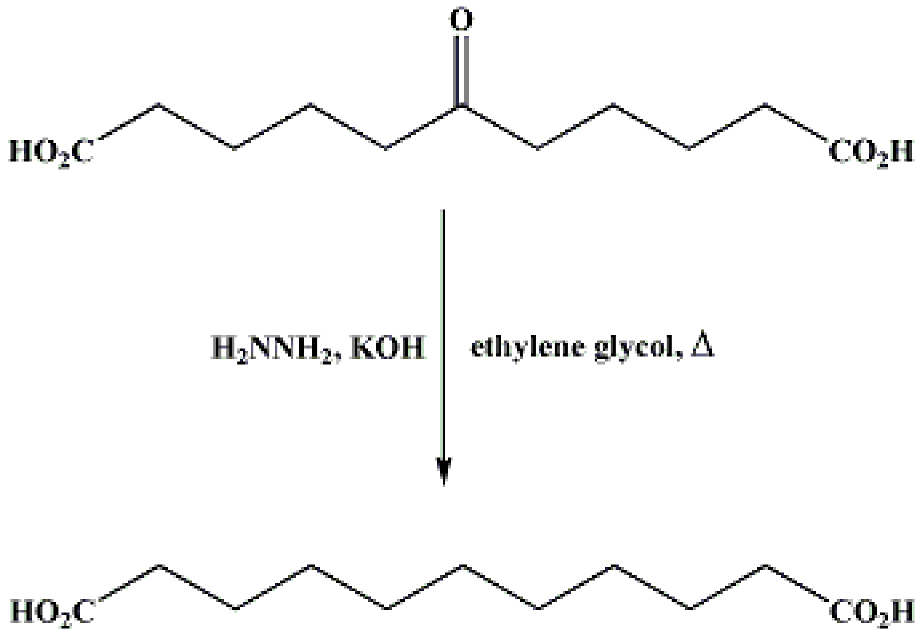
Organic Syntheses, CV 4, 510

HENDECANEDIOIC ACID

[Undecanedioic acid]



Submitted by Lois J. Durham, Donald J. McLeod, and James Cason[1].
Checked by N. J. Leonard, D. H. Dybvig, and K. L. Rinehart, Jr..

1. Procedure

A 500-ml. round-bottomed flask is attached by a well-lubricated ground-glass joint to a reflux condenser with a side take-off having a stopcock which may be opened to permit distillation. In the flask are placed 170 ml. of commercial diethylene glycol and 30 g. (0.46 mole) of potassium hydroxide (U.S.P., or reagent grade, 85%). This mixture is heated carefully *(Caution! (Note 1))* until the potassium hydroxide begins to melt and go into solution; then the heat is removed intermittently until the exothermic dissolution is completed. After the solution has been cooled to 80–100°, the condenser is removed and there are added to the flask 35 g. (0.152 mole) of 6-ketohendecanedioic acid (p. 555) and 22 ml. (22.4 g., 0.38 mole) of commercial 85% hydrazine hydrate. The condenser is immediately replaced, and the mixture is warmed cautiously until any exothermic reaction is complete and then heated under reflux for 1 hour.

A thermometer is suspended through the condenser by copper wire so that the bulb is in the heated liquid, the stopcock of the take-off attachment is opened, and the mixture is distilled sufficiently slowly so that the froth does not rise out of the flask. When the liquid temperature has reached 205–210° (after about 30 ml. of distillate has been collected), the stopcock in the takeoff is closed, the thermometer is removed, and the mixture is heated under reflux for 3 hours. If the temperature is checked during this heating period, it is usually found to be in the range 190–200°.

At the end of the heating period the reaction mixture is cooled to about 100–110° (at lower temperatures a gelatinous precipitate separates) and is then poured into 150 ml. of water contained in a 1-l. Erlenmeyer flask. An additional 100 ml. of water is used to rinse the reaction flask. The diluted mixture is acidified to Congo red by slow addition of 6*N* hydrochloric acid as the mixture is stirred vigorously to ensure conversion of any precipitated potassium salt to the free acid. The mixture is then cooled by tap water for at least 30 minutes (Note 2). The white precipitate is collected by suction filtration, transferred to a beaker, and is heated with about 250 ml. of water until the solid has melted (Note 3). As the mixture is cooled, it is stirred vigorously by hand until the oil has resolidified. After the mixture has been cooled again, the precipitated acid is collected by suction filtration, washed with water, and dried (Note 4). The yield of hendecanedioic acid, m.p. 110.5–112° (Note 5), is 28.5–30.6 g. (87–93%).

2. Notes

1. When the temperature becomes high enough for the potassium hydroxide to melt under the diethylene glycol, solution occurs rapidly with evolution of heat sufficient to drive material out of the top of the condenser if the source of external heat is not removed immediately. For this reason it is wise not to add the compound being reduced until after solution has been accomplished; moreover, in the case of keto acids there is some evidence that yields are lowered somewhat if the acid is added before solution of the potassium hydroxide. Since diethylene glycol does not present a serious fire hazard, this initial heating is probably best done with a small flame which may be easily removed quickly. Subsequent heating with an electric mantle is recommended.
2. Somewhat higher yields appear to be obtained when the mixture is allowed to stand overnight.
3. Remelting the solid acid over water removes occluded impurities, including salt and diethylene glycol. Moreover, acid which has crystallized in lumps is dried faster than the initial fine precipitate.
4. The submitters suggest recrystallization from benzene as a means of purification.
5. The acid is probably polymorphic,[2] since the melting point varies somewhat with the rate of heating and a solidified melt remelts more sharply than do the original crystals.

3. Discussion

Hendecanedioic acid has been prepared by hydrolysis of the corresponding dinitrile, obtained from 1,9-dibromononane or 1,9-diiodononane;[3,4,5] by oxidation of 11-hydroxyhendecanoic acid;[6,7] by the Arndt-Eistert synthesis from 9-carbethoxynonanoyl[8] and nonanedioyl chloride;[9] by the Willgerodt reaction on undecylenic acid;[10] and by treatment of (5,5'-dicarboxy-2,2'-dithienyl)-methane with

Raney nickel catalyst and alkali.[11] The present method, previously described briefly,[12,13] appears to represent the most convenient preparation of dibasic acids having an odd number of carbon atoms greater than ten. It has been applied to several other dibasic acids.[14]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

(5,5'-dicarboxy-2,2'-dithienyl)-methane

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

Raney nickel (7440-02-0)

potassium hydroxide (1310-58-3)

hydrazine hydrate (7803-57-8)

1,9-dibromononane (4549-33-1)

diethylene glycol (111-46-6)

9-carbethoxynonanoyl chloride

Hendecanedioic acid, Undecanedioic acid (1852-04-6)

6-Ketohendecanedioic acid (3242-53-3)

1,9-diiodononane (24613-65-8)

11-hydroxyhendecanoic acid (3669-80-5)

nonanedioyl chloride (123-98-8)

undecylenic acid (112-38-9)

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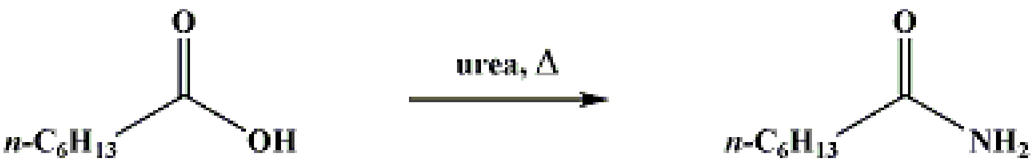
Organic Syntheses, *CV 4*, *513*

n-HEPTAMIDE

[Heptanamide]



Submitted by J. L. Guthrie and Norman Rabjohn[1].
Checked by William S. Johnson and Duane Zinkel.

1. Procedure

In a 1-l. round-bottomed flask, fitted with a thermometer extending nearly to the bottom, are placed 60 g. (1 mole) of urea and 69 g. (0.5 mole) of 95% *n*-heptanoic acid (Note 1). A condenser (Note 2) is attached to the flask, and the mixture is heated by means of an electric mantle. When the temperature reaches 140°, the urea is in solution, and a rather vigorous evolution of gas occurs which continues for several minutes. The temperature is maintained at 170–180° for 4 hours (Note 3), and then the mixture is allowed to cool.

As soon as the temperature drops to 110–120°, 400 ml. of 5% sodium carbonate solution is added carefully through the condenser, and the mixture is shaken vigorously (Note 4). The mixture is cooled in an ice bath, and the product is collected on a Büchner funnel. The solid, when dry, is slightly colored, and weighs 57–64 g., m. p. 85–91°.

The crude material is boiled for a few minutes with 200 ml. of 95% ethanol and a small amount of decolorizing carbon (Note 5). The mixture is filtered by gravity, and 800 ml. of water is added to the filtrate. The resulting slurry is cooled in an ice-salt bath and the solid is collected by filtration on a Büchner funnel. The product, which is almost colorless is air-dried. It weighs 44–48 g. (68–74%) and melts at 91–94° (Note 6). Evaporation of the filtrate under reduced pressure and reprecipitation of the residue from 20 ml. of 95% ethanol and 80 ml. of water affords an additional 3–4 g. (5–6%) of material which melts at 90–93°.

2. Notes

1. Eastman Kodak Company, yellow label brand (95%), *n*-heptanoic acid was used.
2. A condenser should be chosen which has an inside diameter of at least 1.5 cm.; otherwise frequent loosening of the sublimate is required to prevent clogging. A 3-ft., air-cooled tube with an internal diameter of about 2.5 cm. serves as a satisfactory condenser.

3. Temperatures below 170° lead to slightly lower yields, and temperatures above 180° cause excessive sublimation of urea. Although the reaction is nearly complete after 2 hours, the yield appears to be improved by additional heating.
4. Failure to make the mixture basic leads to the formation of a greasy, colored product.
5. A small amount of solid does not dissolve in the alcohol.
6. Recrystallization from dilute ethanol affords colorless material, m.p. 94–95°.

3. Discussion

Heptamide has been prepared by heating heptanoic acid with ammonia in a sealed tube[2] at 230°, by treating heptanoic anhydride with ammonia,[3] by passing ammonia through heptanoic acid[4] at 125–190°, by the rearrangement of heptaldehyde oxime in the presence of Raney nickel in a quartz tube at 150° for 5 minutes,[5] by the Willgerodt reaction with 2-, 3-, or 4-heptanone or heptanal,[6,7] and by the action of ammonia on heptanoyl chloride.[8]

The procedure described is based on the method of E. Cherbuliez and F. Landolt,[9] by which formic and acetic acids were converted into the corresponding amides.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Heptamide

heptaldehyde oxime

2-, 3-, or 4-heptanone

ethanol (64-17-5)

ammonia (7664-41-7)

sodium carbonate (497-19-8)

Raney nickel (7440-02-0)

decolorizing carbon (7782-42-5)

urea (57-13-6)

Heptanoic acid, n-HEPTANOIC ACID (111-14-8)

Heptanal (111-71-7)

heptanoic anhydride (626-27-7)

heptanoyl chloride (2528-61-2)

Heptanamide (628-62-6)

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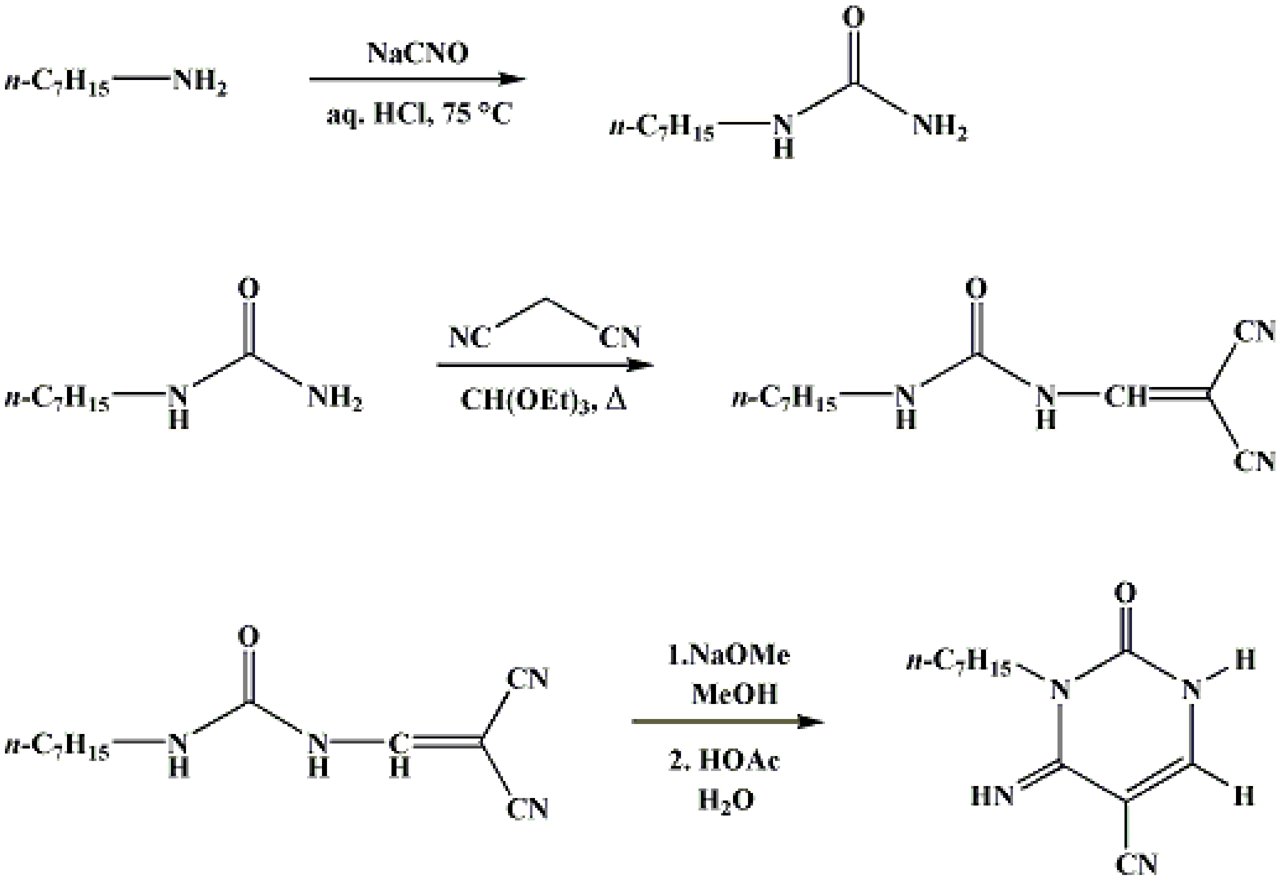
Organic Syntheses, CV 4, 515

3-*n*-HEPTYL-5-CYANOCYTOSINE

[2(1H)-Pyrimidinone, 5-cyano-3-heptyl-4(3)-imino-]



Submitted by Barbara B. Kehm and Calvert W. Whitehead[1].
Checked by M. S. Newman and K. G. Ihrman.

1. Procedure

A. *N-n-Heptylurea.* To a mixture of 24.1 g. (0.21 mole) of *n*-heptylamine (Note 1), 35 g. of cracked ice, and 150 ml. of ice-cold water is added 38 ml. of 5*N* hydrochloric acid (Note 2) with stirring. The mixture is heated on the steam bath at 70–80°, and 14.3 g. (0.22 mole) of sodium cyanate is added portion-wise. After 2–4 hours of continued heating, two layers separate. The product crystallizes on standing overnight at room temperature. It is collected on a Büchner funnel, washed with 100 ml. of cold water, and drained as dry as practical by suction. This solid is dissolved in 125 ml. of boiling ethyl acetate, and the resulting solution is cooled to room temperature. The white crystalline N-*n*-heptylurea is filtered and dried on a porcelain plate at room temperature. A yield of 28.5–29.5 g. (86–88%) of product melting at 110–111° is obtained (Note 3).

B. *3-n-Heptylureidomethylenemalononitrile.* In a 250-ml. round-bottomed flask fitted with a heating mantle and a reflux condenser are placed 28.5 g. (0.18 mole) of N-*n*-heptylurea, 11.9 g. (0.18 mole) of malononitrile (Note 4), and 26.7 g. (0.18 mole) of triethyl orthoformate (Note 4). The mixture is heated under reflux for 2 hours and then cooled in ice. The solid product is

collected by suction filtration on a Büchner funnel. The filtrate is concentrated on the steam bath to incipient crystallization, cooled, and filtered. The two lots of tan solid, 41–42 g., thus obtained are dissolved in 75 ml. of 75% ethyl alcohol in a 250-ml. beaker, 2 g. of decolorizing carbon is added, and the mixture is boiled for 2–3 minutes with constant stirring (necessary to avoid vigorous bumping). The hot solution is filtered by gravity into a 250-ml. Erlenmeyer flask through fluted filter paper. The flask is stoppered and cooled in the refrigerator for 4 hours. The solid product is collected by suction filtration on a Büchner funnel and washed four times with 10-ml. portions of distilled water. The white crystalline 3-*n*-heptylureidomethylenemalononitrile is dried at 50° in a vacuum oven. It melts at 130–132° and amounts to 33.8–34.8 g. (80–83%) (Note 5).

C. *3-n-Heptyl-5-cyanocytosine.* In a 250-ml. Erlenmeyer flask are placed 33.8 g. (0.145 mole) of 3-*n*-heptylureidomethylenemalononitrile and 70 ml. of methanol; then 8.5 g. (0.16 mole) of sodium methoxide (Note 6) is added carefully in small portions (Note 7). The resulting solution is allowed to stand at room temperature for 3 days in the stoppered flask. The contents of the flask are dissolved in 300 ml. of cold water in an 800-ml. beaker, and the solution is stirred as 11 ml. of glacial acetic acid is added. The precipitated solid is collected by suction filtration on a Büchner funnel and washed with three 40-ml. portions of distilled water. The undried product is dissolved in 600 ml. of hot ethyl alcohol; then the solution is filtered into a 1-l. flask by gravity through a fluted filter paper, concentrated on the steam bath to 200 ml., and cooled in the refrigerator for 4 hours. The 3-*n*-heptyl-5-cyanocytosine crystallizes in white needles, melts at 192–197° (Note 8), and amounts to 29.7–31.1 g. (88–92%) (Note 9).

Recrystallization of 20 g. of this product from 230 ml. of hot ethyl alcohol affords 17.8 g. of fine colorless needles, m.p. 199.5–202.5°.

2. Notes

1. *n*-Heptylamine is available from Sapon Laboratories, P. O. Box 599, Lynbrook, New York, and from Distillation Products Industries, Rochester 3, New York.
2. If excess acid is present, considerable foaming may occur on addition of sodium cyanate.
3. The melting point for N-*n*-heptylurea given in the literature[2] is 110–111°.
4. Commercially available reagents were employed.
5. The melting point for *n*-heptylureidomethylenemalononitrile is reported[3] to be 130–132°. An additional 1–1.5 g. may be obtained by evaporating the filtrate to a volume of 100 ml.
6. Sodium methoxide is available from Mathieson Chemical Corporation, Niagara Falls, New York. Alternatively, a solution prepared by dissolving 3.6 g. of sodium in 70 ml. of methanol may be used.
7. Upon addition of sodium methoxide to the methanol solution considerable heat is evolved.
8. The melting point of 3-*n*-heptyl-5-cyanocytosine is given in the literature[4] as 200°.
9. The submitters obtained comparable yields in all steps using 144.2 g. (1.25 moles) of heptylamine and correspondingly larger amounts of all reagents.

3. Discussion

N-*n*-Heptylurea has been prepared by the action of nitrourea on *n*-heptylamine.[5]

3-*n*-Heptyl-5-cyanocytosine has been prepared by a variation of this procedure by Whitehead.[4]

The procedure described here has given equally good yields of other 3-alkyl-5-cyanocytosines and 3-cycloalkyl-5-cyanocytosines; however, it does not yield 3-aryl-5-cyanocytosines from arylureas.

References and Notes

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3. Whitehead, *J. Am. Chem. Soc.*, **75**, 674 (1953).
4. Whitehead and Traverso, *J. Am. Chem. Soc.*, **77**, 5871 (1955).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethyl alcohol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ethyl acetate (141-78-6)

methanol (67-56-1)

sodium methoxide (124-41-4)

decolorizing carbon (7782-42-5)

sodium (13966-32-0)

triethyl orthoformate (122-51-0)

Nitrourea (556-89-8)

Malononitrile (109-77-3)

sodium cyanate (917-61-3)

2(1H)-Pyrimidinone, 5-cyano-3-heptyl-4(3)-imino-

heptylamine, n-heptylamine (111-68-2)

3-n-HEPTYL-5-CYANOCYTOSINE (53608-90-5)

N-n-heptylurea (42955-46-4)

3-n-heptylureidomethylenemalononitrile

n-heptylureidomethylenemalononitrile

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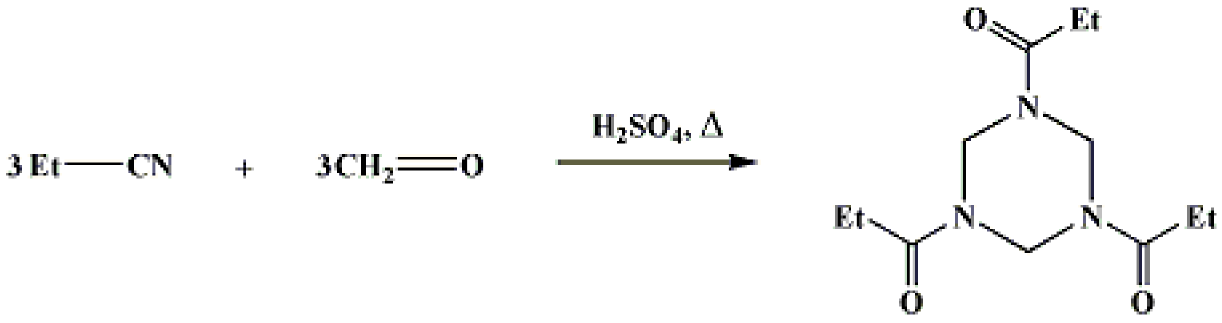
Organic Syntheses, CV 4, 518

HEXAHYDRO-1,3,5-TRIPROPIONYL-*s*-TRIAZINE

[*s*-Triazine, hexahydro-1,3,5-tripropionyl]



Submitted by W. O. Teeters and M. A. Gradsten[1].
Checked by Arthur C. Cope and Mark R. Kinter.

1. Procedure

In a 3-l. three-necked flask equipped with a mechanical stirrer, a dropping funnel, a reflux condenser, and a thermometer are placed 110 g. (138 ml., 2 moles) of propionitrile (Note 1) and 8 g. (4.35 ml.) of concentrated sulfuric acid (sp. gr. 1.84). To the stirred mixture, which is heated to 90°, is added gradually a solution of 60 g. of trioxane (equivalent to 2 moles of formaldehyde) in 110 g. (138 ml., 2 moles) of propionitrile. During the addition the temperature of the reaction mixture is kept between 95° and 105° (Note 2). When the addition is complete (30 to 60 minutes) (Note 3) the reaction mixture is heated under reflux for an additional 3 hours, the internal temperature being kept at approximately 105°. The mixture is then allowed to cool to room temperature; during the cooling period the product crystallizes. The light-brown crystals are collected by filtration with suction on a Büchner funnel (Note 4). The solid (160 to 170 g.) is washed three times with 100-ml. portions of ether and air-dried. The crude yellow product (130 to 135 g., melting point between 164° and 170°) is recrystallized from 160 ml. of 90% ethanol. The product is collected on a Büchner funnel, washed on the funnel with 100 ml. of ether, and air-dried. In this way 105 to 115 g. (62 to 68%) of white crystals of hexahydro-1,3,5-tripropionyl-*s*-triazine melting at 170–172° is obtained (Note 5). Recrystallization from 95% ethanol (2.4 ml. per g.) results in 91% recovery of an analytically pure product, m.p. 173.2–174.1° (cor.).

2. Notes

1. A practical grade of propionitrile obtained from the Eastman Kodak Company was used.
2. During the addition external heating may be discontinued and the internal temperature regulated by the rate of addition.
3. The reaction mixture turns from light yellow to a reddish brown color during

the addition.
4. An appreciable amount of propionitrile (100 to 110 g.) can be recovered from the filtrate. If subsequent batches of hexahydro-1,3,5-tripropionyl-*s*-triazine are being prepared the filtrate can be added to the next charge without isolating the propionitrile. To counteract the accumulation of impurities, activated carbon may be used in the recrystallization of the reaction product.
5. Another 35 to 50 g. of a less pure product (m.p. 160–165°) may be isolated by concentrating the mother liquor.

3. Discussion

A hexahydro-1,3,5-triacyl-*s*-triazine was first prepared by Duden and Scharff[2] from ammonium chloride, formalin, and benzoyl chloride or from hexamethylenetetramine and benzoyl chloride. Procedures similar to the one described[3,4] also have been used for the preparation of hexahydro-1,3,5-triacetyl-, tri(β-chloropropionyl)-, triacrylyl-, trimethacrylyl-, and tribenzoyl-*s*-triazine. Several of these compounds also have been prepared by Wegler and Ballauf[5] from the corresponding nitriles and paraformaldehyde in the presence of acetic anhydride and sulfuric acid.

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hexahydro-1,3,5-triacyl-s-triazine

hexahydro-1,3,5-triacetyl-, tri(β-chloropropionyl)-, triacrylyl-, trimethacrylyl-, and tribenzoyl-s-triazine

ethanol (64-17-5)

sulfuric acid (7664-93-9)

ether (60-29-7)

acetic anhydride (108-24-7)

ammonium chloride (12125-02-9)

formaldehyde, formalin (630-08-0)

carbon (7782-42-5)

benzoyl chloride (98-88-4)

hexamethylenetetramine (100-97-0)

propionitrile (107-12-0)

trioxane

Hexahydro-1,3,5-tripropionyl-s-triazine, s-Triazine, hexahydro-1,3,5-tripropionyl (30805-19-7)

paraformaldehyde (30525-89-4)

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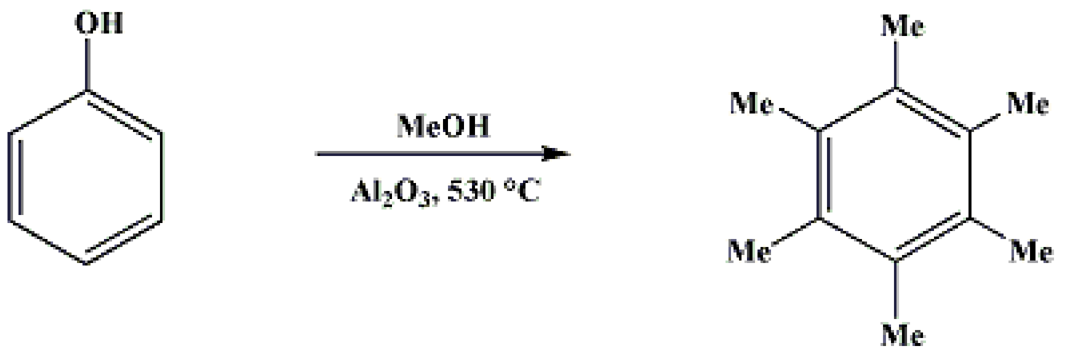
Organic Syntheses, CV 4, 520

HEXAMETHYLBENZENE

[Benzene, hexamethyl-]



Submitted by N. M. Cullinane, S. J. Chard, and C. W. C. Dawkins[1].
Checked by T. L. Cairns and D. C. England.

1. Procedure

A solution of 100 g. (1.06 moles) of phenol in 1 l. of methanol is allowed to drop at a rate of 110 ml. per hour (Note 1) over an activated alumina catalyst (Note 2) heated to 530° (Note 3). The exit from the hot tube is attached to a receiver arranged to lead by-product gases to an efficient hood (Note 4). After addition of the methanol solution is finished, the pale yellow product is transferred to a Büchner funnel and washed with methanol. The yield of crude product melting at 135–145° is 112–115 g. (65–67%). Recrystallization from ethanol (50 g. in 650 ml.) gives 85% recovery or from benzene (50 g. in 130 ml.) gives 60% recovery of colorless hexamethylbenzene, m.p. 165–166°.

2. Notes

1. The submitters used a rate of 250 ml. per hour with a 2-in.-diameter tube, 16 in. long, packed with 300 g. of alumina, and a temperature in the catalyst bed about 370–380°. The checkers used 34 g. of alumina packed in a 7/8-in.-diameter tube 13 in. long.
2. The submitters used 4- to 8-mesh alumina from Peter Spence and Sons, Widnes, Lancashire, England. The checkers used 8- to 14-mesh Alorco H-41 obtained from the Aluminum Company of America, 1200 Alcoa Building, Pittsburgh 19, Pennsylvania.
3. Automatically controlling the outside of the catalyst tube to 370–400° gives a hot spot in the catalyst bed of 530° at the rate specified in equipment used by the checkers.
4. Gases formed in the reaction included carbon monoxide, methane, and hydrogen. The exact equation for the reaction is not known.

3. Discussion

Hexamethylbenzene has been prepared by passing the mixed vapors of acetone and methanol over alumina at 400°.[2] Briner, Plüss, and Paillard[3] have obtained it by passing different phenols mixed with methanol in an atmosphere of dry carbon dioxide over alumina at 410–440°. Hexamethylbenzene also has been prepared by the trimerization of dimethylacetylene in the presence of triethylchromium,[4] or a mixture of triisobutylaluminum and titanium tetrachloride.[5] The present method is based upon that of Cullinane and Chard.[6]

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5. Franzus, Canterino, and Wickliffe, *J. Am. Chem. Soc.*, **81**, 1514 (1959).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alumina

phenols

activated alumina

ethanol (64-17-5)

Benzene (71-43-2)

methanol (67-56-1)

hydrogen (1333-74-0)

carbon monoxide (630-08-0)

phenol (108-95-2)

carbon dioxide (124-38-9)

acetone (67-64-1)

methane (7782-42-5)

Hexamethylbenzene, Benzene, hexamethyl- (87-85-4)

titanium tetrachloride (7550-45-0)

dimethylacetylene (503-17-3)

triethylchromium

triisobutylaluminum (100-99-2)

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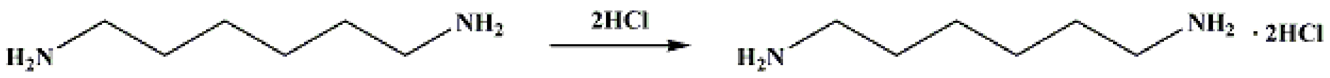
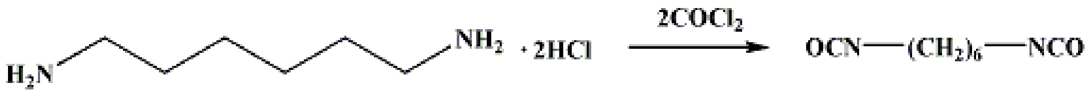
Organic Syntheses, CV 4, 521

HEXAMETHYLENE DIISOCYANATE

[Isocyanic acid, hexamethylene ester]





Submitted by Mark W. Farlow[1]
Checked by R. L. Shriner and Robert C. Johnson.

1. Procedure

Caution! Hexamethylenediamine, hexamethylene diisocyanate, and phosgene are highly toxic. Exposure to vapors or solutions containing these materials should be avoided. All operations should be conducted in a hood.

A. *Hexamethylenediammonium chloride*. To a solution of 116 g. (1.0 mole) of hexamethylenediamine (Note 1) in 145 ml. of methanol in a 1-l. beaker is added slowly from a dropping funnel 175 ml. of concentrated hydrochloric acid (sp. gr. 1.19). The mixture is well stirred during the addition and cooled externally to keep the contents below 30°. The hexamethylenediammonium chloride is then precipitated by adding the solution slowly with stirring to approximately 2 l. of acetone. The precipitate is collected on a Büchner funnel, washed with 100 ml. of cold acetone, and dried in a vacuum oven at 75° for 12–18 hours (Note 2). The yield of dry product amounts to 170–187 g. (90–99%), m.p. 243–246° (Note 3).

B. *Hexamethylene diisocyanate*. A suspension of 94.5 g. (0.50 mole) of finely powdered hexamethylenediammonium chloride in 500 ml. of anhydrous redistilled amylbenzene (or tetralin) (Note 4) is prepared in a 1-l. three-necked flask fitted with an efficient mechanical stirrer (Note 5), a water-cooled reflux condenser, a thermometer, and a phosgene inlet tube (Note 6) extending well below the surface of the suspension. Stirring is started, the mixture is heated to 180–185° (Note 7), and gaseous chlorine-free phosgene (Note 8) is delivered to the mixture at a rate of about 33 g. (0.33 mole) per hour. Hydrogen chloride and excess phosgene escape through the condenser. The temperature is carefully maintained between 180° and 185°; after 8–15 hours (Note 9) solution of the hexamethylenediammonium chloride is essentially complete and hydrogen chloride is no longer evolved (Note 10). The reaction mixture is then filtered through a suction filter, and the filtrate is distilled at reduced pressure through a fractionating column, giving amylbenzene, b.p. 65–75° /10 mm. (Note 11), and 70–80 g. (84–95%) of hexamethylene diisocyanate boiling at 120–125° /10 mm. (92–96° /1 mm., 108–111° /5 mm.); n_D^{20} 1.4585; d_4^{20} 1.0528 (Note 12).

2. Notes

1. Hexamethylenediamine may be obtained from the Polychemicals Department, E. I. du Pont de Nemours and Company, Inc., Wilmington, Delaware. Usually the commercial product is a 70% aqueous solution from which the water may be distilled at atmospheric pressure. The residue is suitable for preparing the dihydrochloride.
2. Thorough drying of the hydrochloride is essential to the success of the next step. Overnight drying in a vacuum oven at 70–100° is effective. The dry salt is not appreciably hygroscopic, but it should be preserved in a well-stoppered bottle until used.
3. This salt shows a marked tendency to sublime at and above 200°.
4. It is preferable to add the hexamethylenediaommnium chloride in three portions. This modification facilitates stirring and prevents clumping of the solid.[2]
Commercial amylbenzene is dried by distillation, and the fraction boiling at 184–194° is collected. This solvent has been withdrawn from the market (1950) and hence tetralin may be substituted. Commercial tetralin

is washed with ferrous sulfate solution and distilled; the fraction boiling at 202–206° is used. *o*-Dichlorobenzene also has been recommended as a solvent.[3] When the latter was employed,[2] it was found advisable to use recovered material, since it contained some component that acted as a solvent for the hydrochloride. The phosgene was absorbed more rapidly, and the reaction was completed in only 9 hours.

5. Efficient agitation of the gas-liquid-solid reaction mixture is conducive to a high rate of reaction. The use of a reaction flask modified with creases[4] has given good results.

6. The end of the inlet tube should have a very coarse fritted glass disk in order to promote rapid reaction. A tube with a bulb in which many fine holes have been blown may also be used, but the reaction time is longer. If the inlet tube becomes clogged, it may be cleaned quickly by removing it from the reaction flask and dipping in warm cresol, which dissolves any polyhexamethylene urea that may form. The tube is then rinsed with amylbenzene or tetralin and replaced in the reaction flask.

7. The temperature of the reaction mixture should be maintained between 180° and 185° in order to obtain as rapid a reaction as possible. Higher temperatures lead to the formation of polyhexamethylene urea. A run carried out at the boiling point of tetralin (206°) gave an 84% yield of polymer.

8. Phosgene is available from the Niagara Chlorine Products Co., Inc., Lockport, New York, or the Matheson Co., Inc., Rutherford, New Jersey. When phosgene containing small amounts of chlorine is used, the reaction appears to proceed normally but the product and recovered solvent are contaminated with chlorine-containing impurities. Chlorine in phosgene can be detected by bubbling a stream of the gas rapidly through clean mercury. Chlorine reacts with and discolors the mercury, whereas pure phosgene leaves the mercury unchanged. If chlorine is present, it may be removed by bubbling the phosgene through two wash bottles containing cottonseed oil.

9. The time required for complete reaction is dependent on the reaction temperature, on the design of the phosgene inlet tube, on the efficiency of agitation, and on the rate of phosgene addition. It is important that the reaction be continued until practically all the hexamethylenediammonium chloride has disappeared. If unreacted amine salt is present, it has a tendency to sublime with the diisocyanate during distillation.

10. When moist air is blown through a glass tube held at the end of the condenser, across the current of phosgene containing hydrogen chloride, the fogging typical of hydrogen chloride gas in a moist atmosphere is produced. Pure phosgene gives no visible effect under similar conditions.

11. The recovered solvent is suitable for succeeding preparations. If tetralin is used as the reaction medium, it is recovered as the low-boiling fraction, b.p. 60–70°/8 mm.

12. If the product contains chlorine as indicated by the alcoholic silver nitrate test, it may be purified by adding a small amount of anhydrous calcium oxide (0.5 g. per 50 g. of product) and redistilling under reduced pressure.

3. Discussion

Hexamethylene diisocyanate has been prepared by the action of phosgene on hexamethylenediammonium chloride[5] or on hexamethylenediammonium carbonate.[6] Metal chlorides such as those of cobalt, iron, mercury, or zinc have been stated to promote the reaction.[3] It has been claimed[7] that the vapor-phase reaction of an hexamethylenediamine-toluene solution with phosgene at 280–300° affords an 80% yield of the diisocyanate.

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hexamethylenediaommnium chloride

polyhexamethylene urea

hexamethylenediamine-toluene

hydrogen chloride, hydrochloric acid (7647-01-0)

methanol (67-56-1)

iron (7439-89-6)

silver nitrate (7761-88-8)

ferrous sulfate (13463-43-9)

mercury (7439-97-6)

acetone (67-64-1)

chlorine (7782-50-5)

zinc (7440-66-6)

phosgene (75-44-5)

cresol (95-48-7)

calcium oxide

Tetralin (119-64-2)

Amylbenzene (538-68-1)

cobalt (7440-48-4)

Hexamethylene diisocyanate, Isocyanic acid, hexamethylene ester (822-06-0)

hexamethylenediamine (124-09-4)

hexamethylenediammonium chloride

hexamethylenediammonium carbonate

o-dichlorobenzene (95-50-1)

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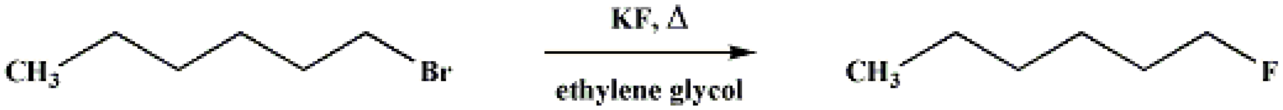
Organic Syntheses, CV 4, 525

n-HEXYL FLUORIDE

[Hexane, 1-fluoro-]



Submitted by Arthur I. Vogel, James Leicester, and William A. T. Macey[1].
Checked by T. L. Cairns and C. W. Tullock.

1. Procedure

The 1-fluoroalkanes are the most toxic of the fluoro compounds. This fact, together with their relatively high volatility, emphasizes the need for care in handling these materials. This preparation should be carried out in a good hood and the operator should wear rubber gloves (Note 1).

In a thoroughly dry 500-ml. three-necked round-bottomed flask, equipped with a mercury-sealed stirrer, a 100-ml. dropping funnel and a short fractionating column (Note 2), is placed a mixture of 116 g. (2.0 moles) of anhydrous finely powdered potassium fluoride (Note 3) and 200 g. of dry ethylene glycol (Note 4). The fractionating column carries a thermometer and is connected to a downward double-surface condenser with a filter flask as receiver. The round flask is heated at a bath temperature of 160–170°, and 165 g. (1.0 mole) of *n*-hexyl bromide, b.p. 154–156° (Note 5), is added dropwise during 5 hours; liquid passes over intermittently at 60–90° (temperature at the top of the fractionating column). The bath temperature is allowed to fall to 110–120°, and a slow stream of air is drawn through the apparatus by attaching the side arm of the filter flask to a water pump and replacing the dropping funnel by a narrow-bore tube dipping just below the surface of the liquid; stirring is maintained during this operation. It is advisable to interpose a U-tube cooled in ice between the water pump and the receiver in order to recover any uncondensed liquid. The combined distillates are then distilled at atmospheric pressure through an efficient fractionating column; after a small fore-run (up to 10 g.) of 1-hexene, the crude *n*-hexyl fluoride is collected at 89–92° (46–48 g.). The crude product is purified by cooling in ice and adding 1-ml. portions of a solution containing 9.0 g. of bromine and 6.0 g. of potassium bromide in 50 ml. of water until the organic layer acquires an orange color; after each addition the mixture is shaken vigorously for a minute or so. The volume of bromine-potassium bromide solution required is usually less than 5 ml. The aqueous layer is separated, the organic layer is washed with saturated aqueous potassium bromide solution until color-less and finally with water. The liquid is dried with anhydrous magnesium sulfate and distilled through an efficient fractionating column; the *n*-hexyl flouride is collected at 91–92°. This procedure yields 42–47 g. (40–45% over-all yield based on the bromide employed) of a water-white product, n_D^{20} 1.375, n_D^{25} 1.372–1.373, d_4^{20} 0.8011. It has been kept for 1 year without change of physical properties and therefore appears to be stable (Note 6).

2. Notes

1. Data giving lethal doses of the 1-fluoroalkanes in mice may be found in Pattison's

Toxic Aliphatic Fluorine Compounds, Elsevier Publishing Company, 1959, and in Pattison, *J. Am. Chem. Soc.*, **79**, 2311 (1957). It has been estimated that 0.1–0.2 g. of *n*-hexyl fluoride would be a fatal dose for a human being.[2]

2. Any fractionating column of moderate efficiency is satisfactory. The submitters employed a 20-cm. Dufton column containing a spiral 10 cm. in length, 2 cm. in diameter, with 8 turns of the helix. A 20–25 cm. Vigreux column may also be used.

3. Pure laboratory grade anhydrous potassium fluoride is finely ground and kept for 48 hours in an oven at 180–210°; it is stored in a desiccator. Before use, the powdered salt is dried for 3 hours at 180° and ground again in a warm (50°) glass mortar.

4. Laboratory grade ethylene glycol is redistilled under diminished pressure, and the fraction boiling at 85–90°/7 mm. is used as the solvent for the potassium fluoride.

5. The *n*-hexyl bromide may be prepared from redistilled *n*-hexyl alcohol by the red phosphorus-bromine procedure or may be purchased from Eastman Kodak Company.

6. The procedure described has been employed by the submitters for the preparation of the alkyl fluorides listed below. Due regard must be paid to the boiling point of the alkyl bromide; as a general rule the bath temperature is maintained at about the boiling point of the alkyl bromide, with a minimum value (for *n*-amyl fluoride) of about 140–150°. For bromides of higher boiling point, the bath temperature is held at about 190°. In all cases, after the alkyl bromide has been added, the bath is allowed to cool 10–20° below the original reaction temperature, and a slow stream of air is drawn through the apparatus; the alkyl fluoride and ethylene glycol which pass over are collected, and the latter is removed by washing with water.

Alkyl fluoride	B.P.	d_4^{20}	n_D^{20}	n_D^{25}	Yield,%
n-Amyl	63.5–65°	0.7917	1.3597	1.3562	27
n-Heptyl	119–121°	0.8060	1.3861	1.3833	35
n-Octyl	144–146°	0.8137	1.3955	1.3927	34
n-Nonyl	166–169°	0.8159	1.4033	1.4002	46
n-Decyl	186–188°	0.8197	1.4095	1.4068	37
n-Undecyl	70–71.5°/3 mm.	0.8239	1.4151	1.4122	45
n-Dodecyl	93–95°/3 mm.	0.8257	1.4192	1.4162	34
n-Tetradecyl	119–121°/3 mm., m.p. 8°	0.8277	1.4266	1.4236	43
n-Hexadecyl	150–152°/2 mm., m.p. 19°	0.8313	1.4322	1.4295	27

3. Discussion

Alkyl fluorides have been prepared by reaction between elementary fluorine and the paraffins,[3] by the addition of hydrogen fluoride to olefins,[4] by the reaction of alkyl halides with mercurous fluoride,[5] with mercuric fluoride,[6] with silver fluoride,[7] or with potassium fluoride under pressure,[8] and by the reaction of potassium fluoride with *n*-hexyl methanesulfonate[9] or *n*-hexyl *p*-toluenesulfonate.[10] The procedure used is based on that of Hoffmann[11] involving interaction at atmospheric pressure of anhydrous potassium fluoride with an alkyl halide in the presence of ethylene glycol as a solvent for the inorganic halide; a small amount of olefin accompanies the alkyl fluoride produced and is readily removed by treatment with bromine-potassium bromide solution.

The reaction of *n*-hexyl bromide with potassium fluoride in several glycols has been studied,[12] and the methods for the preparation of alkyl monofluorides have been reviewed.[13]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

red phosphorus

bromide (24959-67-9)

bromine (7726-95-6)

hydrogen fluoride (7664-39-3)

ethylene glycol (107-21-1)

potassium bromide (7758-02-3)

n-HEXYL ALCOHOL (111-27-3)

magnesium sulfate (7487-88-9)

potassium fluoride (7789-23-3)

1-hexene (592-41-6)

Hexane, 1-fluoro-, n-HEXYL FLUORIDE, n-hexyl flouride (373-14-8)

bromine-potassium bromide

Fluorine (7782-41-4)

mercurous fluoride (13967-25-4)

mercuric fluoride (7783-39-3)

silver fluoride (7775-41-9)

n-Nonyl fluoride (463-18-3)

n-hexyl bromide (111-25-1)

n-amyl fluoride (592-50-7)

n-hexyl methanesulfonate

n-hexyl p-toluenesulfonate (3839-35-8)

n-Heptyl fluoride

n-Octyl fluoride

n-Decyl fluoride

n-Undecyl fluoride

n-Dodecyl fluoride

n-Tetradecyl fluoride

n-Hexadecyl fluoride

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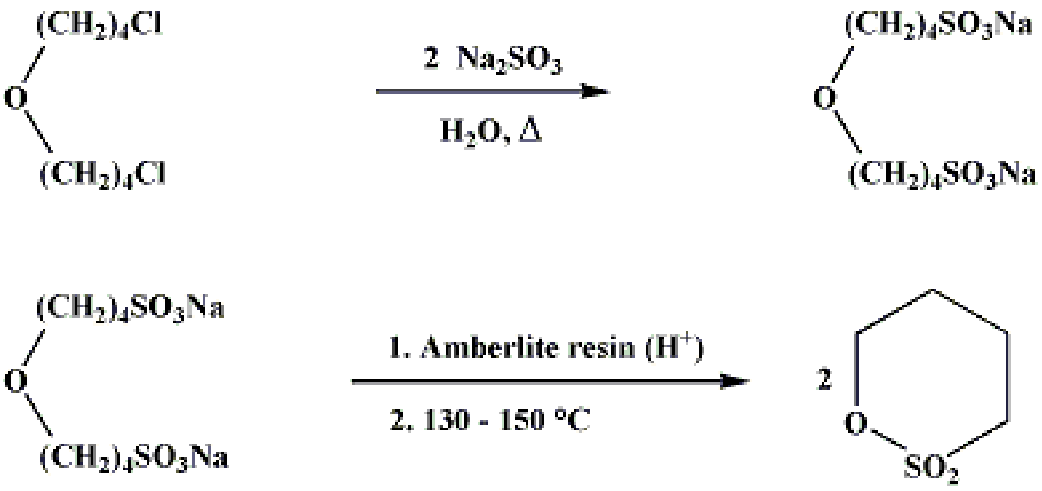
Organic Syntheses, *CV 4*, 529

4-HYDROXY-1-BUTANESULFONIC ACID SULTONE

[1-Butanesulfonic acid, 4-hydroxy-, δ-sultone]



Submitted by A. O. Snoddy[1]
Checked by T. L. Cairns and W. R. Brasen.

1. Procedure

A mixture of 132.5 g. (1.05 moles) of sodium sulfite, 99.5 g. (0.5 mole) of bis-4-chlorobutyl ether (Note 1), and 450 ml. of water is placed in a creased 1-l. three-necked flask fitted with an efficient sealed stirrer and a reflux condenser. The third neck of the flask is closed with a stopper, and the mixture is heated and stirred vigorously under reflux until the ether has dissolved (Note 2). At the end of this time, heating is discontinued, and 60 ml. of concentrated C.P. hydrochloric acid is cautiously added to the solution. The mixture is then boiled with stirring until sulfur dioxide is no longer evolved. Solid barium chloride dihydrate (or a 10% aqueous solution of this salt) is added to the hot solution (Note 3) until all sulfate has been precipitated; then the barium sulfate is removed by suction filtration through a layer of filter aid.

The filtered solution is diluted to 21. with water and passed through a column of ion-exchange resin (Note 4) and (Note 5). A test portion of the effluent should yield no ash on evaporation and ignition of the residue. The column is washed with water until the effluent is no longer acid to litmus, and the washings are added to the original eluent. The total eluent is evaporated (Note 6) at reduced pressure (water aspirator) until the volume is about 250 ml.; then it is transferred to a 500-ml. pot which is equipped for vacuum distillation and attached to a short Vigreux column. After most of the remaining water and hydrochloric acid have been removed at the pressure obtainable with an aspirator, an oil pump is attached (Note 7), and the heating bath is cautiously raised to a temperature in the range 130–150°. The distillate is allowed to stand in a

separatory funnel until the layers have separated (several hours may be required), then the crude sultone is withdrawn and distilled (Note 8) at reduced pressure. The yield of sultone, b.p. 134–136°/4 mm., is 99–109 g. (72–80%), n_D^{25} 1.4619–1.4625, d^{25} 1.3347, m.p. 12.5–14.5°.

2. Notes

1. Material supplied by Matheson, Coleman and Bell was used without purification.
2. This reaction may be carried out under pressure in a rocking autoclave at 180° in about 8 hours. When it is carried out under reflux with vigorous stirring in a creased flask it is complete in about 20 hours, whereas 50–60 hours is required if an ordinary flask is used.
3. Any sulfate ions resulting from oxidation of sulfite should be removed; otherwise they will be converted to sulfuric acid in the subsequent procedure and destroy sultone. Ordinarily, 12–13 g. of barium chloride dihydrate is required. The end point of the addition is conveniently determined with tetrahydroquinone indicator used in spot tests on filter paper [cf. *Ind. Eng. Chem., Anal. Ed.*, **9**, 331 (1937)].
4. Rohm & Haas Amberlite IR-120, which has been developed with 3*N* hydrochloric acid and then washed free from chlorides with water, is used in the form of a column 6 cm. in diameter and 55 cm. in length. Such a column contains approximately 1.1 kg. of resin (50% moisture) and is equivalent to about 2.2 moles of hydrogen chloride.
5. The checkers found that the procedure of Helberger and Lantermann,[2] which avoids the use of an ion-exchange resin, is also satisfactory in case it is regarded as inconvenient to set up the resin column. According to this procedure, after completion of the reaction with sodium sulfite, anhydrous hydrogen chloride is passed into the hot solution to liberate sulfur dioxide. After removal of sulfate as in the described procedure, the undiluted aqueous solution is saturated with hydrogen chloride gas at a temperature below 25°. The precipitated sodium chloride is removed by suction filtration, the filter cake is washed with two 50-ml. portions of 12*N* hydrochloric acid, and then the combined filtrate and washings are worked up as described for the cluent from the resin column.
6. The checkers found that satisfactory results may also be obtained if the water is evaporated by heating the solution on a steam bath as air is aspirated through it.
7. At the bath temperature specified, and low pressure, dehydration and distillation occur; if a pressure of about 4 mm. is maintained, the vapor temperature is in the range 132–138°. The temperature of the bath should be raised slowly and with caution, or else the contents of the pot may froth through the column into the distillate. The receiver should be cooled in a Dry Ice-acetone bath to prevent vapors from reaching the oil pump.
8. Water is nearly insoluble in the sultone. The small amount of water and a very volatile impurity which are present in the crude sultone distil rapidly before the sultone is collected. An efficient cold trap should be used to protect the pump

from the volatile materials.

3. Discussion

4-Hydroxy-1-butanesulfonic acid sultone has been made through the chlorosulfonation of 1-chlorobutane,[3] from 4-chlorobutyl acetate[2,4] which is prepared through the reaction of tetrahydrofuran and acetyl chloride,[2] from 4-chlorobutanol,[4] and from bis-4-chlorobutyl ether.[2] 4-Hydroxy-1-butanesulfonic acid sultone also has been obtained by treating sodium 4-hydroxybutane-1-sulfonate with cation-exchange resins,[5] by heating methoxybutanesulfonic acid under reduced pressure at 150–180°,[6] by concentrating an alcohol solution of 4-hydroxy-butanesulfonic acid under reduced pressure,[7] and by heating 4-chloro-butanesulfonic acid with copper oxide and steam.[8]

Both 4-chlorobutanol and bis-4-chlorobutyl ether can be prepared from tetrahydrofuran (p. 266). The procedure described is based on the method of Helberger and Lantermann.[2]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

1-Butanesulfonic acid, 4-hydroxy-, δ-sultone

tetrahydroquinone

sulfuric acid (7664-93-9)

hydrogen chloride, hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium sulfite (7757-83-7)

acetyl chloride (75-36-5)

sodium chloride (7647-14-5)

sulfur dioxide (7446-09-5)

barium sulfate (7727-43-7)

1-chlorobutane (109-69-3)

copper oxide (1317-38-0)

barium chloride dihydrate (10326-27-9)

Tetrahydrofuran (109-99-9)

4-chlorobutanol (928-51-8)

4-Hydroxy-1-butanesulfonic acid sultone (1633-83-6)

4-hydroxy-butanesulfonic acid

bis-4-chlorobutyl ether (6334-96-9)

4-chlorobutyl acetate (6962-92-1)

sodium 4-hydroxybutane-1-sulfonate

methoxybutanesulfonic acid

4-chloro-butanesulfonic acid

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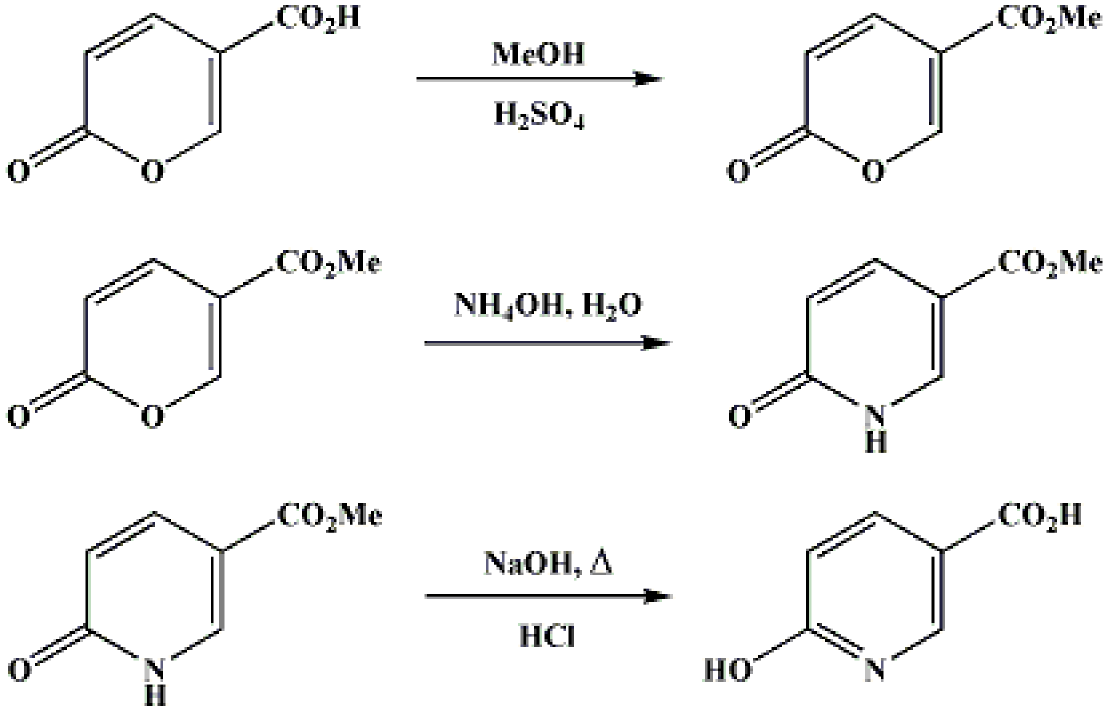
Organic Syntheses, CV 4, 532

6-HYDROXYNICOTINIC ACID

[Nicotinic acid, 6-hydroxy-]



Submitted by J. H. Boyer and W. Schoen[1].
Checked by T. L. Cairns and W. J. Linn.

1. Procedure

A. *Methyl coumalate.* In a 500-ml. round-bottomed flask provided with a thermometer is placed 139 ml. of concentrated sulfuric acid. To the acid is added, with swirling, 50 g. (0.36 mole) of pulverized coumalic acid (p. 201) in small portions. The reaction is slightly exothermic, and the mixture is maintained between 20° and 30° by occasional immersion of the flask into an ice bath. Methanol (70 ml.) is then added in small portions with frequent swirling, and the temperature is held between 25° and 35°. The mixture is heated on a steam bath for 1 hour, cooled to about 40°, and poured slowly with stirring into 800 ml. of water in a 2-l. beaker while the temperature is maintained below 40° by an ice bath (Note 1). Anhydrous sodium carbonate is added in small portions with stirring until the mixture is slightly alkaline (Note 2). The precipitated ester is freed of inorganic salts by slurrying four times with 100-ml. portions of cold water, filtered, and air-dried overnight. The yield of methyl coumalate, m.p. 68–70°, is 17.5–24.5 g. (32–45%). This crude product is used for the preparation of 6-hydroxynicotinic acid.

B. *6-Hydroxynicotinic acid.* In a 500-ml. beaker provided with a thermometer, magnetic stirring, and external cooling is placed 117 ml. of 14% ammonium

hydroxide. With stirring, 45 g. (0.29 mole) of methyl coumalate is added over a period of 10 minutes, during which time the solution is kept below 20°. Stirring is continued for an additional 45 minutes at about 20° (Note 3).

A solution of 600 ml. of approximately 17% aqueous sodium hydroxide is placed in a 2-l. beaker and heated almost to the boiling point. At the end of the 45-minute period, the ammoniacal solution is added to the hot sodium hydroxide solution, and the mixture is heated rapidly to the boiling point. After it has boiled vigorously for 5 minutes, the stirred solution is cooled in an ice bath to room temperature. With the temperature held below 30°, concentrated hydrochloric acid is added with stirring until the solution is strongly acid (Note 4). The heavy, yellow, microcrystalline solid which separates after stirring and cooling for about an hour is collected on a Büchner funnel, washed twice with water, and dried at 80°. The yield of bright yellow 6-hydroxynicotinic acid, m.p. 299–300° (dec., uncor.), is 29–37 g. (72–91%) (Note 5).

2. Notes

1. A turbid, brown solution containing a small amount of fine precipitate is obtained.
2. A small amount of curdy, brown precipitate is obtained at first. About 220 g. of anhydrous sodium carbonate is required.
3. Most of the ester dissolves; a turbid, red solution is formed.
4. About 250 ml. of acid is required.
5. The product is sufficiently pure for further synthetic work; a purer product may be obtained by recrystallization from 50% aqueous acetic acid.

3. Discussion

The procedure for preparing methyl coumalate is based on a method described by von Pechmann.[2] Methyl coumalate has also been prepared by direct esterification of the reaction mixture from malic acid and fuming sulfuric acid[3] and from coumalyl chloride and methanol.[4]

The procedure for preparing 6-hydroxynicotinic acid is also based on a method described by von Pechmann.[5] 6-Hydroxynicotinic acid has also been prepared by decarboxylation of 6-hydroxy-2,3-pyridinedicarboxylic acid;[6,7] by heating 6-hydrazinonicotinic acid or its hydrazide with hydrochloric acid;[8] by the action of carbon dioxide on the sodium salt of α-pyridone at 180–200° and 20 atm.;[9] by heating the nitrile of 6-chloronicotinic acid with alcoholic sodium hydroxide or hydrochloric acid;[10] from 6-aminonicotinic acid;[11,12] by the prolonged action of concentrated ammonium hydroxide on methyl coumalate;[3] and by carbonating 2-hydroxypyridine in the presence of potassium carbonate.[13]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

methanol (67-56-1)

sodium hydroxide (1310-73-2)

sodium carbonate (497-19-8)

carbon dioxide (124-38-9)

ammonium hydroxide (1336-21-6)

malic acid (617-48-1)

Coumalic acid (500-05-0)

6-Hydroxynicotinic acid, Nicotinic acid, 6-hydroxy- (5006-66-6)

Methyl coumalate (6018-41-3)

coumalyl chloride

6-hydrazinonicotinic acid

6-chloronicotinic acid (5326-23-8)

6-aminonicotinic acid (3167-49-5)

2-hydroxypyridine (142-08-5)

6-hydroxy-2,3-pyridinedicarboxylic acid

sodium salt of α-pyridone

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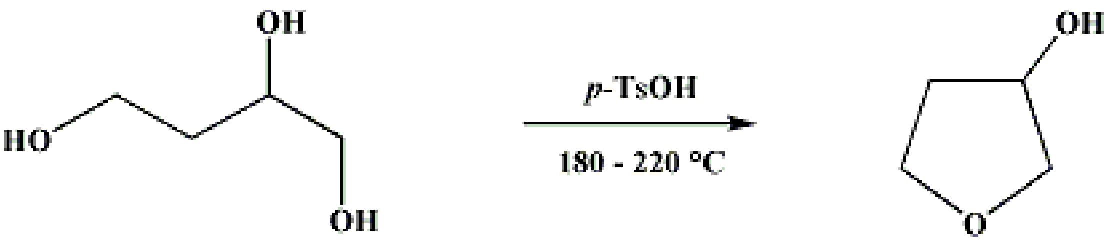
Organic Syntheses, CV 4, 534

3-HYDROXYTETRAHYDROFURAN

[Furan, 3-hydroxy-1,2,3,4-tetrahydro-]



Submitted by Hans Wynberg and A. Bantjes[1].
Checked by John C. Sheehan and Gregory L. Boshart.

1. Procedure

A 500-ml. flask is charged with 318 g. (3 moles) of 1,2,4-trihydroxybutane (Note 1) and 3 g. of *p*-toluenesulfonic acid monohydrate. A few Carborundum boiling chips are added, the flask is equipped with a 30.5-cm. Vigreux column, condenser, and receiver arranged for vacuum distillation, and the contents are heated, with swirling, to dissolve the acid (Note 2). The flask is then heated in a bath held at 180–220° so that 300–306 g. of distillate, b.p. 85–87°/22 mm., is collected over a period of 2–2.5 hours (Note 3). The colorless liquid obtained is refractionated, the same apparatus being used, and two fractions are collected: the first, 50–60 g., b.p. 42–44°/24 mm., n_D^{25} 1.3343, is mainly water. After a negligible intermediate fraction, 215–231 g. (81–88%) of pure 3-hydroxytetrahydrofuran, b.p. 93–95°/26 mm., n_D^{25} 1.4497, d_4^{20} = 1.095, is collected (Note 4).

2. Notes

1. Supplied by the General Aniline and Film Corporation.
2. Considerable darkening occurs even when the acid is well dispersed. The yield appears not to be affected.
3. Other temperatures are: b.p. 75–77°/16 mm.; 90–92°/28 mm. This first distillate contains 14% (±3%) of water as determined by interpolation of the refractive indices.
4. Calcd. M_D = 21.64. Found: 21.72. As obtained by this single fractionation the submitters found the alcohol to be analytically pure: Calcd. for $C_4H_8O_2$: C, 54.53; H, 9.14. Found: C, 54.74; H, 9.32. Others have reported: b.p. 50°/1 mm., n_D^{18} 1.4486, d_4^{20} = 1.090,[2] and b.p. 81°/13 mm., $d>^{18}$ = 1.07, n_D^{18} 1.4478.[3]

3. Discussion

3-Hydroxytetrahydrofuran has been obtained during the preparation of 1,2,4-

trihydroxybutane,[3] by hydrolysis of 4-chloromethyl-1,3-dioxane[2] and by acid catalyzed dehydration of 1,2,4-trihydroxybutane.[4] The present procedure is similar to that described by Reppe.[4]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Carborundum

3-Hydroxytetrahydrofuran, Furan, 3-hydroxy-1,2,3,4-tetrahydro- (453-20-3)

1,2,4-trihydroxybutane (42890-76-6)

4-chloromethyl-1,3-dioxane

p-toluenesulfonic acid monohydrate (6192-52-5)

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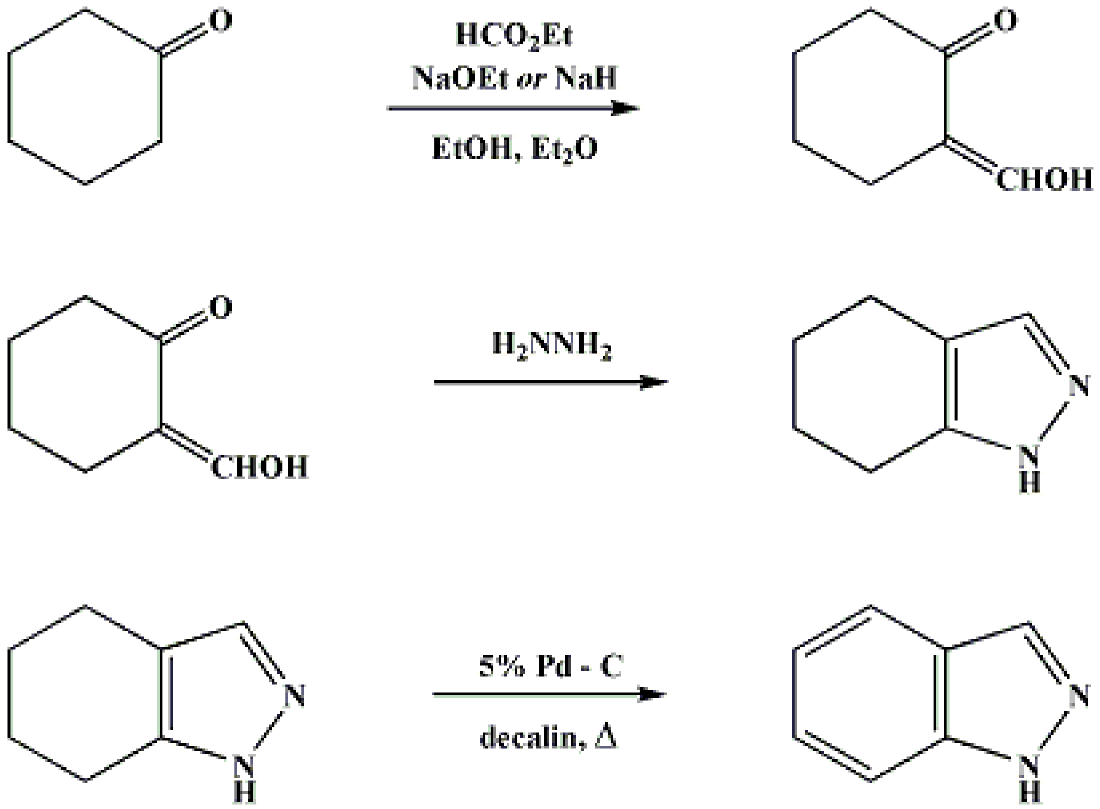
Organic Syntheses, CV 4, 536

INDAZOLE

[1H-Indazole]



Submitted by C. Ainsworth[1]
Checked by Max Tishler, George Gal, and G. A. Stein.

1. Procedure

A. *2-Hydroxymethylenecyclohexanone*, *Method 1.* A mixture of 23 g. (1 g. atom) of sodium metal cut in approximately 1-cm. cubes, 2 l. of dry ether, 98 g. (103 ml., 1 mole) of redistilled cyclohexanone, and 110 g. (120 ml., 1.5 moles) of ethyl formate is placed in a 5-l. three-necked flask equipped with a stirrer, stopper, and vent tube. The reaction is initiated by the addition of 5 ml. of ethyl alcohol to the stirred mixture, which is then placed in a cold water bath. Stirring is continued for 6 hours. After standing overnight, 25 ml. of ethyl alcohol is added, and the mixture is stirred for an additional hour. After the addition of 200 ml. of water, the mixture is shaken in a 3-l. separatory funnel. The ether layer is washed with 50 ml. of water, and the combined aqueous extracts are washed with 100 ml. of ether. The aqueous layer is acidified with 165 ml. of 6*N* hydrochloric acid, and the mixture is extracted twice with 300 ml. of ether. The ether solution is washed with 25 ml. of saturated sodium chloride solution and then is dried by the addition of approximately 30 g. of anhydrous magnesium sulfate powder. The drying agent is removed by suction filtration, and the ether is

evaporated on the steam bath. The residue is distilled under reduced pressure using a 6-inch Vigreux column. After a small fore-run there is obtained 88–94 g. (70–74%) of 2-hydroxymethylenecyclohexanone, b.p. 70–72°/5 mm., n_D^{25} 1.5110 (Note 1).

2-Hydroxymethylenecyclohexanone, *Method 2.* A mixture of 50 g. (1 mole) of 48% sodium hydride dispersed in mineral oil (Note 2), 2 l. of dry ether, and 5 ml. of ethyl alcohol is placed in a 5-l. three-necked flask equipped with a stirrer, dropping funnel, and vent tube. The reaction vessel is cooled by means of a cold water bath, and a solution of 98 g. (103 ml., 1 mole) of redistilled cyclohexanone and 110 g. (120 ml., 1.5 moles) of ethyl formate is added dropwise during 1 hour. Stirring is continued for 6 hours (Note 3), and the solution is allowed to stand overnight. After the addition of 20 ml. of ethyl alcohol, the mixture is stirred for 1 hour. Water (200 ml.) is added to the flask with stirring, the mixture is shaken in a 3-l. separatory funnel and the organic layer separated. The product is isolated according to the procedure described in Method 1. The yield of 2-hydroxymethylenecyclohexanone is the same by both methods.

B. *4,5,6,7-Tetrahydroindazole.* A solution of 63 g. (0.5 mole) of 2-hydroxymethylenecyclohexanone and 500 ml. of methyl alcohol contained in a 2-l. beaker is treated with 25 ml. (0.5 mole) of hydrazine hydrate in small portions (Note 4). After standing for 30 minutes the mixture is concentrated by warming under reduced pressure on the steam bath. To aid in removing the water, 100 ml. of ethyl alcohol is added, and again the mixture is concentrated by heating under reduced pressure. The residue is dissolved in about 100 ml. of hot petroleum ether (Note 5), and after cooling in an ice bath for 1 hour the solid that separates is collected by suction filtration and washed with a small amount of cold petroleum ether. The crude 4,5,6,7-tetrahydroindazole, m.p. 79–80°, weighs 58–60 g. (95–98%) and is sufficiently pure to be used in the next step (Note 6) and (Note 7).

C. *Indazole.* A mixture of 50 g. (0.41 mole) of 4,5,6,7-tetrahydroindazole, 35 g. of 5% palladium on carbon (Note 8) and 1 l. of dry decalin is placed in a 3-l. round-bottomed flask and heated under reflux for 24 hours. The hot mixture is filtered by suction, using a previously heated Büchner funnel, and the filtrate is allowed to cool. After standing overnight, the indazole that separates is collected by suction filtration, washed with 100 ml. of petroleum ether, and air-dried. The solid is dissolved in 750 ml. of hot benzene, and about 4 g. of decolorizing carbon is added. The mixture is filtered through a fluted filter paper and then is refiltered, using the same filter paper. Two liters of warm petroleum ether is added, and the solution is cooled in an ice bath for 2 hours. The indazole (m.p. 146–147°) is collected by suction filtration and after air drying weighs 24–25 g. (50–52%).

2. Notes

1. 2-Hydroxymethylenecyclohexanone begins to polymerize after standing at room temperature for several days.

2. Available from Metal Hydrides Inc., Beverly, Massachusetts.
3. After an hour or so, the ether comes to a boil, and the reaction mixture is cooled in a cold water bath.
4. The reaction is exothermic but is contained in the beaker.
5. The petroleum ether fraction used was Skellysolve B (boiling range 60–70°).
6. 4,5,6,7-Tetrahydroindazole can be distilled, b.p. 135–140°/5 mm. It is recrystallized from petroleum ether and melts at 84°.
7. The petroleum ether purification step may be eliminated with equally satisfactory results. After dehydration with ethyl alcohol, the residue is dried under reduced pressure to constant weight and used directly for the next step.
8. The palladium catalyst is prepared according to *Organic Syntheses Coll. Vol.* **3**, 686 (1955). It can be reused for the dehydrogenation of 4,5,6,7-tetrahydroindazole to indazole. The yield is somewhat better with used catalyst than with fresh catalyst.

3. Discussion

2-Hydroxymethylenecyclohexanone has been prepared by the reaction of cyclohexanone and alkyl formates.[2,3,4]

4,5,6,7-Tetrahydroindazole has been prepared by the hydrolysis of 1-carbamyl-4,5,6,7-tetrahydroindazole.[2,3] It was first prepared in the Lilly Research Laboratories by Dr. N. Easton by the reaction of 2-hydroxymethylenecyclohexanone and hydrazine hydrate.

Indazole has been prepared according to the method reported in *Organic Syntheses*.[5] Recently, indazole has been prepared by the hydrolysis or reduction of 3-cyanoindazole,[6] by heating 1-*o*-tolyl-3,3-dimethyltriazine,[7] by the coupling of N-nitroso-*o*-benzo-(or aceto-)toluidide,[8,9,10] and by the decomposition of *cis*-2-stilbenediazonium fluoroborate.[11] The present method employs milder reaction conditions.[12]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 650
- Org. Syn. Coll. Vol. 6, 389
- Org. Syn. Coll. Vol. 6, 590
- Org. Syn. Coll. Vol. 9, 180

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

N-nitroso-o-benzo-(or aceto-)toluidide

ethyl alcohol (64-17-5)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

methyl alcohol (67-56-1)

ether (60-29-7)

Cyclohexanone (108-94-1)

sodium chloride (7647-14-5)

decolorizing carbon (7782-42-5)

sodium (13966-32-0)

palladium, palladium on carbon (7440-05-3)

hydrazine hydrate (7803-57-8)

ethyl formate (109-94-4)

magnesium sulfate (7487-88-9)

sodium hydride (7646-69-7)

Indazole, 1H-Indazole (271-44-3)

2-Hydroxymethylenecyclohexanone (823-45-0)

4,5,6,7-Tetrahydroindazole (2305-79-5)

decalin (91-17-8)

1-carbamyl-4,5,6,7-tetrahydroindazole

3-cyanoindazole

1-o-tolyl-3,3-dimethyltriazine

cis-2-stilbenediazonium fluoroborate

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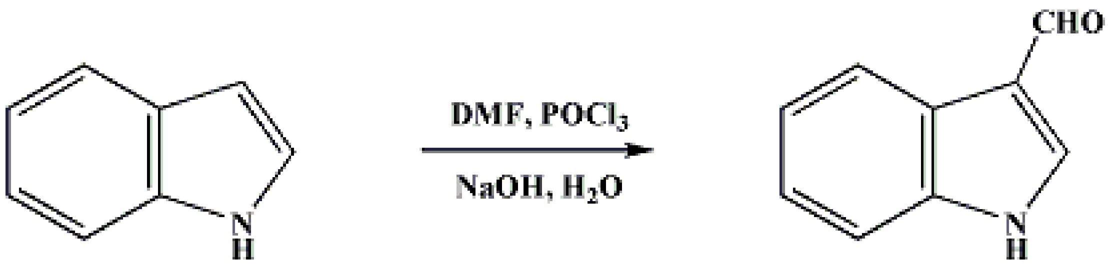
Organic Syntheses, CV 4, 539

INDOLE-3-ALDEHYDE

[Indole-3-carboxaldehyde]



Submitted by Philip N. James and H. R. Snyder[1].
Checked by Virgil Boekelheide and Richard N. Knowles.

1. Procedure

In a 1-l. round-bottomed, three-necked flask fitted with an efficient mechanical stirrer, a drying tube containing Drierite, and a 125-ml. dropping funnel is placed 288 ml. (274 g., 3.74 moles) of freshly distilled dimethylformamide (Note 1). The flask and its contents are cooled in an ice-salt bath for about 0.5 hour, and 86 ml. (144 g., 0.94 mole) of freshly distilled phosphorus oxychloride (Note 2) is subsequently added with stirring to the dimethylformamide over a period of 0.5 hour. The pinkish color of the formylation complex may be observed during this step. The 125-ml. dropping funnel is replaced with a 200-ml. dropping funnel, and a solution of 100 g. (0.85 mole) of indole (Note 3) in 100 ml. (95 g., 1.3 moles) of dimethylformamide is added to the yellow solution over a period of 1 hour during which time the temperature should not rise above 10°. Once the solution is well mixed, the dropping funnel is replaced with a thermometer, and the temperature of the viscous solution is brought to 35°. The syrup is stirred efficiently at this temperature for 1 hour, or for 15 minutes longer than is necessary for the clear yellow solution to become an opaque, canary-yellow paste (Note 4). At the end of the reaction period, 300 g. of crushed ice is added to the paste (Note 5) with careful stirring, producing a clear, cherry-red aqueous solution.

This solution is transferred with 100 ml. of water to a 3-l. three-necked flask containing 200 g. of crushed ice and fitted with an efficient mechanical stirrer and a separatory funnel containing a solution of 375 g. (9.4 moles) of sodium hydroxide in 1 l. of water. The aqueous base is added dropwise with stirring until about one-third of it has been added (Note 6). The remaining two-thirds is added rapidly with efficient stirring (Note 7), and the resulting suspension is heated rapidly to the boiling point and allowed to cool to room temperature, after which it is placed in a refrigerator overnight. The precipitate is collected on a filter and resuspended in 1 l. of water. Most of the inorganic material dissolves, and the product is then collected on a filter, washed with three 300-ml. portions of water and air-dried, yielding about 120 g. (97%) of indole-3-aldehyde, m.p. 196–197°. The indole-3-aldehyde resulting from this

procedure is sufficiently pure for most purposes, but it may be recrystallized from ethanol if desired (Note 8).

2. Notes

1. Freshly distilled Merck reagent grade or du Pont technical grade, dimethylformamide, b.p. 151–153°, was used.
2. Mallinckrodt analytical reagent grade phosphorus oxychloride was freshly distilled, b.p. 106–108°.
3. Dow Chemical Company indole was employed. It was recrystallized once (150 g. per 1.8 l.) from 60–90° petroleum ether, m.p. 52–53°.
4. The precipitation described here did not occur in all runs, but no appreciable effect on the yield or purity of the final product was noticed if the stirring and heating of the greenish yellow solution were continued for at least one hour.
5. Reaction between the non-aqueous paste and water (or ice) is exothermic, so it is sometimes helpful to cool the paste in an ice bath before adding the ice. In any case, no trouble should be encountered provided the 300 g. of ice is added at once.
6. The point at which rapid addition should begin is easily recognized by the disappearance of the red color of the solution and the appearance of a greenish blue or greenish yellow color.
7. Near the end of the addition, the entire contents of the flask may set up solid, stopping the stirrer. The use of a powerful stirrer at this point is desirable, for by the addition of about 100 ml. of water with rapid stirring, the cake is returned to the condition of a thick slurry. During the heating period which follows, the setting-up may again occur, but rapid and efficient stirring is usually sufficient to break up the cake. By the time the temperature has reached the boiling point, a clear yellow-orange solution should be obtained.
There is considerable evolution of dimethylamine during the heating period, especially near the boiling point.
8. About 8.5 ml. of 95% ethanol is required per gram of aldehyde. The recovery of aldehyde in this recrystallization is seldom better than 85%, and the melting point is raised only 1–2°. Concentration of mother liquors to about 15% of their original volume yields another 12–13% of aldehyde which is nearly as pure as the first crop.

3. Discussion

Indole-3-aldehyde may be prepared by direct formylation of indole with dimethylformamide[2,3] or N-methylformanilide[4] using phosphorus oxychloride as a catalyst, by the Reimer-Tiemann reaction,[5,6] by a modified Gattermann reaction on 2-carbethoxyindole,[6] by formylation of the potassium salt of indole with carbon monoxide under vigorous conditions of heat and pressure,[3] by the Grignard reaction,[7] by hydrolysis and decarboxylation of the anil of 3-indolylglyoxylic acid,[8] by a modified Sommelet reaction on gramine[9] and on indole itself,[10] and by oxidation and

hydrolysis of N-skatyl-N-phenylhydroxylamine.[11] The method described above is essentially that of Smith.[2] It is far superior to other methods reported for the preparation of indole-3-aldehyde because it is extremely simple and convenient, the yield of aldehyde is nearly quantitative, and the product is obtained in a state of high purity. Two other examples of the use of the dimethylformamide procedure are described in *Organic Syntheses* (pp. 331, 831).

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 656

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

anil of 3-indolylglyoxylic acid

N-skatyl-N-phenylhydroxylamine

ethanol (64-17-5)

sodium hydroxide (1310-73-2)

carbon monoxide (630-08-0)

Phosphorus Oxychloride (21295-50-1)

dimethylamine (124-40-3)

N-methylformanilide (93-61-8)

dimethylformamide (68-12-2)

Indole (120-72-9)

Indole-3-aldehyde, Indole-3-carboxaldehyde (487-89-8)

2-carbethoxyindole (3770-50-1)

gramine (87-52-5)

potassium salt of indole

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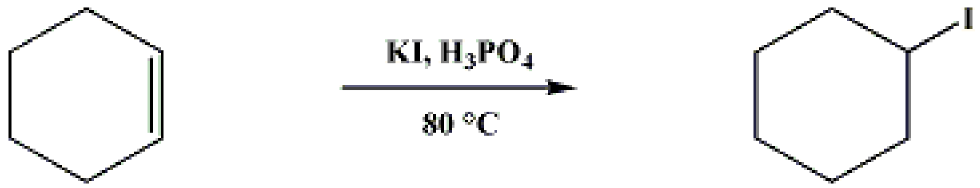
Organic Syntheses, CV 4, 543

IODOCYCLOHEXANE

[Cyclohexane, iodo-]



Submitted by Herman Stone and Harold Shechter[1].
Checked by T. L. Cairns and V. A. Engelhardt.

1. Procedure

Forty-one grams (0.5 mole) of cyclohexene (Note 1) is added to a mixture of 250 g. (1.5 moles) of potassium iodide in 221 g. (2.14 moles) of 95% orthophosphoric acid (Note 2), (Note 3), and (Note 4) contained in a 1-l. three-necked flask equipped with a reflux condenser, a sealed mechanical stirrer, and a thermometer. The mixture is stirred and heated at 80° for 3 hours, after which it is allowed to cool and treated with 150 ml. of water and 250 ml. of ether with continued stirring (Note 5) and (Note 6). The ether extract is separated, decolorized with 50 ml. of 10% aqueous sodium thiosulfate solution, washed with 50 ml. of saturated sodium chloride solution, and dried with anhydrous sodium sulfate (50 g.). The ether is evaporated on a steam bath, and the product is distilled from a modified Claisen flask under reduced pressure. The portion boiling at 48–49.5°/4 mm. is collected. The yield of iodocyclohexane is 93–95 g. (88–90%), n_D^{20} 1.551, d_4^{20} 1.625.

2. Notes

1. Cyclohexene was obtained from Eastman Kodak Company.
2. The 95% orthophosphoric acid is prepared by adding 174 g. (102 ml., 1.5 moles) of 85% phosphoric acid with stirring to 47 g. of phosphoric anhydride. The solution should be cooled to room temperature before the addition of potassium iodide; otherwise evolution of hydrogen iodide and formation of iodine will take place. After the cyclohexene has been added, the mixture can be heated as desired, since the hydrogen iodide reacts as rapidly as it is generated.
3. Although 95% orthophosphoric acid is recommended for this method, commercial phosphoric acid (85%) may be used, but the reaction proceeds more slowly and the yield is lower.
4. This procedure has been used for the conversion of other olefins to iodides in excellent yield. Yields of 2-iodohexane and 2,3-dimethyl-2-iodobutane from 1-hexene and 2,3-dimethyl-2-butene were 94.5 and 91.4%, respectively.

5. Excess potassium iodide can be recovered by filtering the acid layer, after adding sufficient water to dissolve precipitated inorganic phosphates.
6. If the acid layer has an iodine color, another extraction with 100 ml. of ether is recommended.

3. Discussion

Iodocyclohexane has been prepared by the action of phosphorus and iodine on cyclohexanol,[2] and from hydrogen iodide and cyclohexanol,[3] chlorocyclohexane,[4] or cyclohexyl ether.[5] It has also been prepared by reaction of potassium iodide and chlorocyclohexane,[6] by the reaction of iodine with cyclohexyldiphenyl phosphite,[7] and by the condensation of triphenyl phosphite, methyl iodide, and cyclohexanol.[8]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ether (60-29-7)

Cyclohexanol (108-93-0)

Cyclohexene (110-83-8)

sodium chloride (7647-14-5)

PHOSPHORUS (7723-14-0)

sodium sulfate (7757-82-6)

potassium iodide (7681-11-0)

sodium thiosulfate (7772-98-7)

iodine (7553-56-2)

phosphoric acid, orthophosphoric acid (7664-38-2)

hydrogen iodide (10034-85-2)

chlorocyclohexane (542-18-7)

Methyl iodide (74-88-4)

2,3-dimethyl-2-butene (563-79-1)

phosphoric anhydride (2466-09-3)

1-hexene (592-41-6)

Iodocyclohexane, Cyclohexane, iodo- (626-62-0)

2-iodohexane

2,3-dimethyl-2-iodobutane

cyclohexyl ether

cyclohexyldiphenyl phosphite

triphenyl phosphite (101-02-0)

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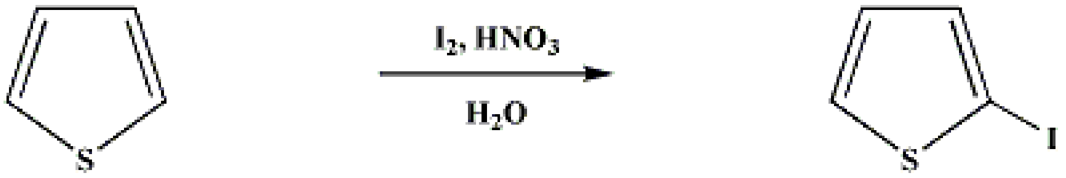
Organic Syntheses, CV 4, 545

2-IODOTHIOPHENE

[Thiophene, 2-iodo-]



Submitted by Henry Y. Lew and C. R. Noller[1].
Checked by Cliff S. Hamilton and Frank A. Bower.

1. Procedure

In a 200-ml. three-necked flask fitted with a mechanical stirrer (Note 1), a reflux condenser, and a separatory funnel, and set up in a hood, are placed 38 g. (0.15 mole) of iodine and 42 g. (39 ml., 0.50 mole) of thiophene (Note 2). A solution of 28 ml. (0.44 mole) of nitric acid (sp. gr. 1.42) diluted with an equal volume of water is placed in the separatory funnel, from which approximately one-fourth of the nitric acid is added slowly and with vigorous stirring. Slight heating may be necessary to start the reaction, but once initiated it proceeds vigorously with the evolution of brown oxides of nitrogen. Cooling with an ice bath may be necessary to control the reaction. After the evolution of gases has subsided, the remaining nitric acid is added dropwise, and the reaction proceeds smoothly at room temperature with continual evolution of oxides of nitrogen. After all the nitric acid has been added, the solution is heated under reflux on a water bath for 30 minutes.

The reaction mixture is allowed to stand, and the red organic layer is separated, mixed with 40 ml. of 10% sodium hydroxide solution, and steam-distilled (Note 3). The yellow oil is separated, dried over anhydrous calcium chloride, and distilled at reduced pressure from a modified Claisen flask. The yield is 43–45 g. (68–72%); b.p. 89–93°/36 mm.; n_D^{25} 1.6465.

2. Notes

1. The seal for the mechanical stirrer used (.htmFig. 10) is made from two one-hole rubber stoppers and a piece of glass tubing with glycerin as a seal and lubricant. According to the submitters, it is better than a mercury seal, not only for reactions where halogens, halogen acids, or compounds that react with mercury are present, but also for practically any other reaction since the handling of mercury always requires a considerable amount of care.
The glass tubing *D*, about 10 cm. in length, is just large enough in diameter to permit the stirrer *E* to rotate freely. The smaller of the two one-hole rubber

stoppers, *A*, is bored to a depth of about 7 mm. with a cork-borer whose diameter is approximately 3 mm. larger than that of tubing *D*, and then this section is cut out with a pair of scissors. Rubber stopper *B* is 10–15 mm. larger in diameter than *A*. When assembled, tubing *D* fits tightly in rubber stopper *B*, and protrudes out at the top about 4 mm., and rubber stopper *A* fits tightly about stirrer *E* and rests on top of rubber stopper *B*. Glycerol is used as a seal and as a lubricant between the contact surfaces of rubber stoppers *A* and *B*, and the portion of tubing *D* protruding out of rubber stopper *B* acts as a wall in preventing glycerol from flowing down inside the tubing. When the stirrer motor is on, rubber stopper *A* rotates with stirrer *E*. Rubber stopper *C* fits tightly over tubing *D* and in the mouth of the reaction flask.

Fig. 10. Seal for a mechanical stirrer made from rubber stoppers and glass tubing using glycerol as a seal and lubricant.

Fig. 10. Seal for a mechanical stirrer made from rubber stoppers and glass tubing using glycerol as a seal and lubricant.

2. When the preparation is carried out in larger quantities, evolution of heat accompanies the mixing of iodine and thiophene, and unless the mixture is stirred well, it will solidify into a hard mass. By keeping the quantities reasonably small, this tendency to solidify is reduced to a minimum.

3. Toward the end of the distillation a small amount (0.5–2.0 g.) of 2-iodo-5-nitrothiophene is collected in the condenser and the receiver. The amount formed increases with increase in the temperature of the reaction mixture.

3. Discussion

2-Iodothiophene has been prepared by the action of iodine and mercuric oxide on thiophene.[2] The present method has been published.[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 427
- Org. Syn. Coll. Vol. 4, 667

References and Notes

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2. Meyer and Kreis, *Ber.*, **17**, 1558 (1884); Thyssen, *J. prakt. Chem.*, [2] **65**, 5 (1902); *Org. Syntheses Coll. Vol.* **2**, 357 (1943).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

calcium chloride (10043-52-4)

sodium hydroxide (1310-73-2)

glycerol, glycerin (56-81-5)

nitric acid (7697-37-2)

nitrogen (7727-37-9)

mercury (7439-97-6)

mercuric oxide (21908-53-2)

iodine (7553-56-2)

Thiophene (110-02-1)

2-IODOTHIOPHENE, Thiophene, 2-iodo- (3437-95-4)

2-iodo-5-nitrothiophene

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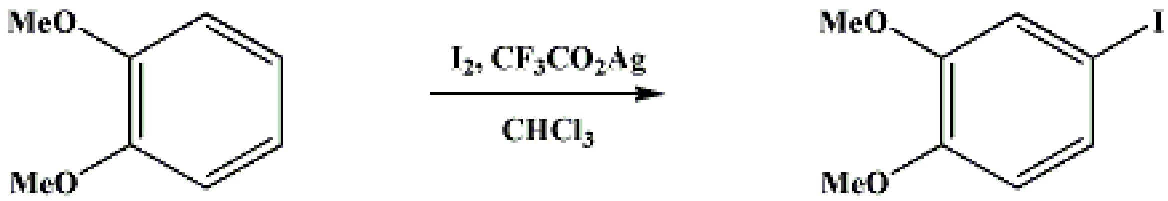
Organic Syntheses, CV 4, 547

4-IODOVERATROLE

[Veratrole, 4-iodo-]



Submitted by Donald E. Janssen and C. V. Wilson[1].
Checked by Max Tishler and George Purdue.

1. Procedure

A. *Silver trifluoroacetate.* To a suspension of 187 g. (0.81 mole) of silver oxide (Note 1) in 200 ml. of water is added 177 g. (1.55 moles) of trifluoroacetic acid (Note 2). The resulting solution is filtered, and the filtrate is evaporated to dryness under reduced pressure. The dry silver trifluoroacetate thus obtained is purified by placing it in a Soxhlet thimble and extracting with ether, or by dissolving the salt in 1.2 l. of ether, filtering through a thin layer of activated carbon, and evaporating the filtered ether solution to dryness. The yield of colorless crystalline salt obtained after removal of the ether is 300 g. (88%).

B. *4-Iodoveratrole.* In a 3-l. three-necked round-bottomed flask, fitted with a sealed stirrer, a dropping funnel, and a reflux condenser protected with a drying tube, is placed 110 g. (0.5 mole) of dry silver trifluoroacetate (Note 3). The flask is flamed to remove all moisture, and 69 g. (0.5 mole) of dry veratrole is added (Note 2). To the stirred suspension a solution of 127 g. (0.5 mole) of iodine in 1.6 l. of chloroform is added through the dropping funnel over a period of 2 hours. After stirring an additional hour, the mixture is filtered and the precipitated silver iodide is washed with 100 ml. of chloroform. The solvent is removed from the filtrate and washings under vacuum, and the residue is distilled through an 8-in. Vigreux column. The fraction boiling at 152–155°/15 mm. weighs 112–120 g. and constitutes a yield of 85–91% (Note 4) and (Note 5).

2. Notes

1. The silver oxide was prepared by adding, with manual stirring, 66 g. of 98% sodium hydroxide (1.62 moles) in 2 l. of water to a solution of 274 g. (1.62 moles) of silver nitrate in 500 ml. of water. The precipitate was collected by filtration and washed with water until free from alkali. The wet cake can be dried or preferably used moist for reaction with trifluoroacetic acid.
2. The trifluoroacetic acid and veratrole used were Eastman Kodak Company

white label grade.
3. Commercially available silver acetate may be used in place of the silver trifluoroacetate, but the yield is somewhat lower (75–80%).
4. The product, n_D^{25} 1.612, solidifies on chilling. Recrystallization from ethanol gives solid of melting point 34–35°.
5. Iodination in the presence of mercuric oxide[2,3,4,5,6] gives yields of about 40–55%, and even after careful distillation the product is contaminated with mercury salts.

3. Discussion

4-Iodoveratrole has been prepared by iodination of veratrole in the presence of mercuric oxide[2,3,4,5,6] and by methylation of 4-iodoguaiacol with methyl iodide in alcoholic sodium ethoxide solution.[7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 71
- Org. Syn. Coll. Vol. 8, 586

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

ether (60-29-7)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

silver oxide (20667-12-3)

silver nitrate (7761-88-8)

mercuric oxide (21908-53-2)

iodine (7553-56-2)

activated carbon (7782-42-5)

sodium ethoxide (141-52-6)

Methyl iodide (74-88-4)

silver acetate (563-63-3)

veratrole (91-16-7)

silver iodide (7783-96-2)

4-IODOVERATROLE, Veratrole, 4-iodo- (5460-32-2)

trifluoroacetic acid (76-05-1)

silver trifluoroacetate (2966-50-9)

4-iodoguaiacol

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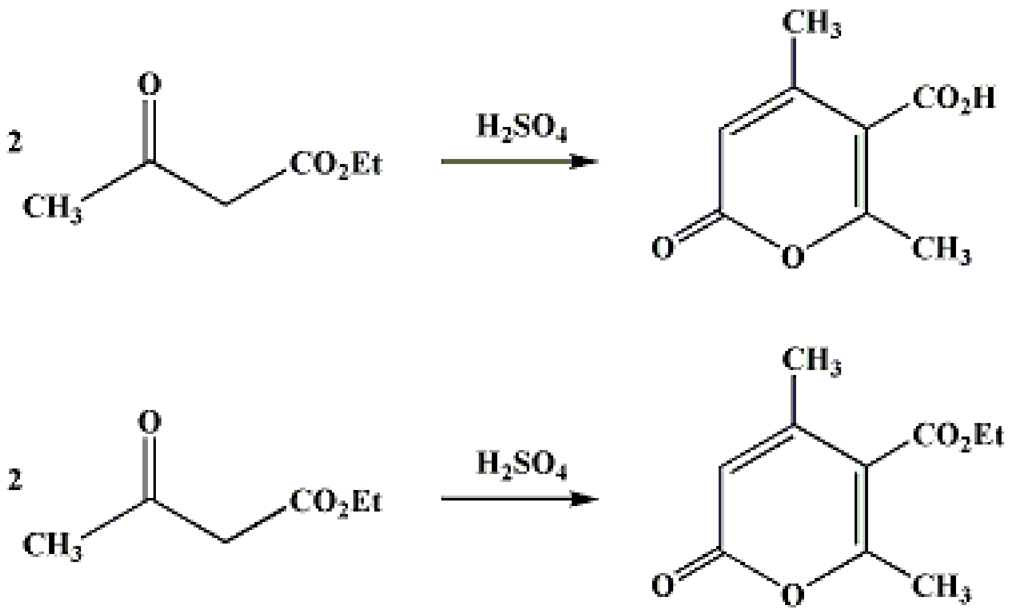
Organic Syntheses, CV 4, 549

ISODEHYDROACETIC ACID AND ETHYL ISODEHYDROACETATE

[Coumalic acid, 4,6-dimethyl-, and coumalic acid, 4,6-dimethyl-, ethyl ester]



Submitted by Newton R. Smith and Richard H. Wiley[1,2].
Checked by R. S. Schreiber and H. H. Fall.

1. Procedure

In a 2-l. three-necked flask fitted with a thermometer, a stirrer, and a dropping funnel is placed 900 ml. of concentrated sulfuric acid. To the acid, cooled in an ice bath, is added, with stirring, 635 ml. (650 g., 5 moles) of ethyl acetoacetate (Note 2) at such a rate that the temperature remains between 10° and 15°. When all the ester has been added, the flask is stoppered with a calcium chloride drying tube and allowed to stand at room temperature. After 5–6 days (Note 3) the reaction mixture is poured onto 2 kg. of crushed ice while being stirred vigorously with a wooden paddle. The solid is collected on a large Büchner funnel, washed with two 200-ml. portions of cold water, and sucked as dry as possible.

The filtrate, *ca.* 4 l. in volume, is extracted with three 1.5-l. portions of ether (Note 4), and the sulfuric acid mother liquors are discarded. The ether extracts are combined and used to dissolve the solid mixture of acid and ester. If necessary, more ether can be added to assist in dissolving the solid. The ether solution is washed with 50 ml. of cold water and extracted with approximately ten 100-ml. portions of saturated sodium carbonate solution until all the isodehydroacetic acid has been removed (Note 5). The combined sodium carbonate extracts are acidified with an excess of concentrated

hydrochloric acid, and the finely divided acid which precipitates is redissolved by heating to the boiling point. The hot solution is filtered with the aid of suction and is cooled in an ice bath; the solid is collected on a filter. The crude isodehydroacetic acid is dissolved in 400 ml. of hot water, and this solution is treated with decolorizing carbon, filtered, and cooled slowly to effect crystallization. The yield of isodehydroacetic acid is 91–115 g. (22–27%); m.p. 154–155°.

The ether extract, which contains ethyl isodehydroacetate, is dried for 24 hours over anhydrous sodium sulfate, and the ether is then removed by heating on a water bath. The residue is distilled from a 250-ml. Claisen flask, under reduced pressure, to give 130–175 g. (27–36%) of ethyl isodehydroacetate; b.p. 185–192°/35 mm.; m.p. 18–20° (Note 6) and (Note 7).

2. Notes

1. Two equations are written since isodehydroacetic acid is not esterified rapidly and its ester is not hydrolyzed rapidly under the conditions used here.
2. The checkers used Eastman Kodak Company white label grade ethyl acetoacetate as received.
3. If the reaction mixture is allowed to stand only 24 hours, the yields drop about 10% for both the acid and its ester.
4. Occasionally a large amount of carbon dioxide is present in the solution, and caution should be exercised in the extraction with ether.
5. The checkers found it convenient to test the pH of the extract with Hydrion papers. When the pH of the extract became the same as that of the saturated sodium carbonate solution, the color of the extract changed from green to orange. Thereafter, extraction was continued until neutralization of small aliquots with concentrated hydrochloric acid produced no solid.
6. The fore-run of 30–40 g. consists mostly of a mixture of 4,6-dimethyl-1,2-pyrone and ethyl isodehydroacetate.
7. The ester may be hydrolyzed to the acid by heating on a steam bath with 5 times its weight of concentrated sulfuric acid for 5–8 hours. The yield of acid is 40–50% with about 30% of the original ester recovered.

3. Discussion

Isodehydroacetic acid has been prepared by the action of sulfuric acid on acetoacetic ester.[3,4,5] The ethyl ester has been prepared by the action of dry hydrogen chloride on acetoacetic ester[6,7] and by the sodium-catalyzed condensation of ethyl β-chloroisocrotonate with ethyl acetoacetate.[3] The methyl ester of isodehydroacetic acid has been prepared by the thermal rearrangement of pyrazolines.[8]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 337

References and Notes

1. University of Louisville, Louisville, Kentucky.
2. The submitters wish to thank the Research Corporation for a grant under which this work was done.
3. Anshutz, Bendix, and Kerp, *Ann.*, **259**, 148 (1890).
4. Hantzsch, *Ann.*, **222**, 1 (1884).
5. Wiley and Smith, *J. Am. Chem. Soc.*, **73**, 3531 (1951).
6. Duisberg, *Ber.*, **15**, 1387 (1882).
7. Goss, Ingold, and Thorpe, *J. Chem. Soc.*, **123**, 348 (1923).
8. Büchner and Schröder. *Ber.*, **35**. 782 (1902).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

acetoacetic ester

Isodehydroacetic acid

Ethyl isodehydroacetate

Coumalic acid, 4,6-dimethyl-

coumalic acid, 4,6-dimethyl-, ethyl ester

4,6-dimethyl-1,2-pyrone

methyl ester of isodehydroacetic acid

sulfuric acid (7664-93-9)

hydrogen chloride, hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

carbon dioxide (124-38-9)

decolorizing carbon (7782-42-5)

Ethyl acetoacetate (141-97-9)

ethyl β-chloroisocrotonate

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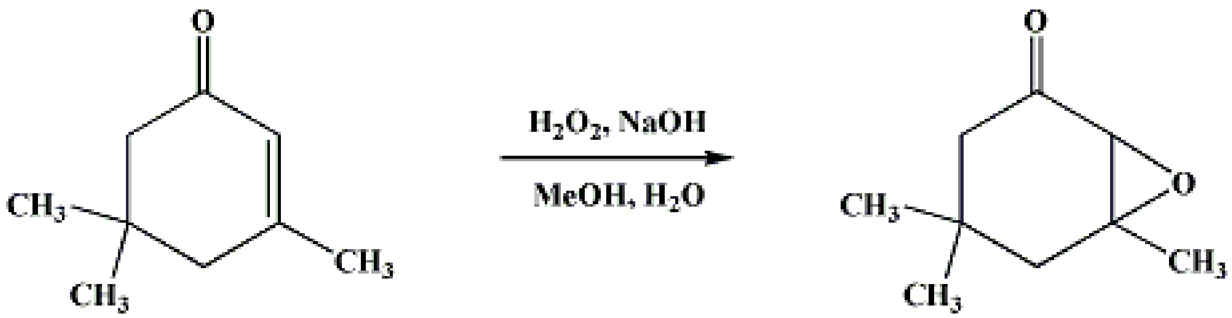
Organic Syntheses, CV 4, 552

ISOPHORONE OXIDE

[Cyclohexanone, 2,3-epoxy-3,5,5-trimethyl-]



Submitted by Richard L. Wasson and Herbert O. House[1].
Checked by James Cason and Ralph J. Fessenden.

1. Procedure

In a 1-l. three-necked flask, equipped with a dropping funnel, a mechanical stirrer, and a thermometer, is placed a solution of 55.2 g. (0.4 mole) of isophorone (Note 1) and 115 ml. (1.2 moles) of 30% aqueous hydrogen peroxide (*Caution! avoid contact with skin*) in 400 ml. of methanol. After the contents of the flask have been cooled to 15° by means of an ice bath, 33 ml. (0.2 mole) of 6*N* aqueous sodium hydroxide is added, dropwise and with stirring, over a period of 1 hour. During the addition the temperature of the reaction mixture is maintained at 15–20° with a bath of cold water (Note 2). After the addition is complete, the resulting mixture is stirred for 3 hours as the temperature of the reaction mixture is maintained at 20–25° (Note 3) and (Note 4). The reaction mixture is then poured into 500 ml. of water, and the resulting mixture is extracted with two 400-ml. portions of ether. The combined extracts are washed with water and dried over anhydrous magnesium sulfate. After the bulk of the ether has been removed by distillation (or flash distillation) through a 30-cm. Vigreux column (Note 5) at atmospheric pressure, the residual liquid is distilled through the Vigreux column under reduced pressure. The yield of isophorone oxide (Note 4) is 43–44.5 g. (70–72%), b.p. 70–73°/5 mm., n_D^{25} 1.4500–1.4510.

2. Notes

1. A technical grade of isophorone, b.p. 80–84°/9 mm., n_D^{25} 1.4755, purchased from Eastman Kodak Company, was employed for this preparation.
2. If the temperature of the reaction mixture is less than 15°, the reaction does not begin. When the resulting mixture is subsequently warmed to room temperature the exothermic reaction which results is difficult to control (Note 3).
3. If the temperature of the reaction mixture is allowed to rise above 30°, the yield of isophorone oxide is diminished.

4. If desired, the course of the reaction may be followed by means of the optical density of the reaction mixture at 235 m•. The ultraviolet spectrum of isophorone has a maximum at 235 m• (ε 13,300); the ultraviolet spectrum of isophorone oxide has a maximum at 292 m• (ε 43). A total reaction time of 4 hours under the conditions specified was found to be ample for the complete conversion of isophorone to its oxide. If the conversion is not complete, the product cannot be separated from the unchanged isophorone without recourse to precise fractional distillation. The absence of isophorone from the final product may be verified by examination of the spectrum at 235 m•.

5. When the checkers distilled the product through a simple type of Podbielniak column of 65-cm. length, with heated jacket and partial reflux head, the boiling range was 1°, 74–75°/6 mm., but the yields and index of refraction were the same as those reported by the submitters.

3. Discussion

Isophorone oxide has been prepared by the epoxidation of isophorone with alkaline hydrogen peroxide.[2,3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 957
- Org. Syn. Coll. Vol. 6, 679

References and Notes

1. Massachusetts Institute of Technology, Cambridge 39, Massachusetts.
2. Treibs, *Ber.*, **66**, 1483 (1933).
3. House and Wasson, *J. Am. Chem. Soc.*, **79**, 1488 (1957).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

methanol (67-56-1)

ether (60-29-7)

sodium hydroxide (1310-73-2)

hydrogen peroxide (7722-84-1)

magnesium sulfate (7487-88-9)

Isophorone oxide, Cyclohexanone, 2,3-epoxy-3,5,5-trimethyl- (10276-21-8)

isophorone

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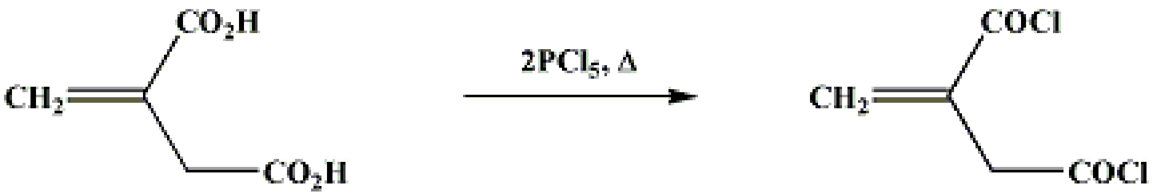
Organic Syntheses, CV 4, 554

ITACONYL CHLORIDE



Submitted by Henry Feuer and Stanley M. Pier[1].
Checked by William S. Johnson and Ernest F. Silversmith.

1. Procedure

In a 500-ml. round-bottomed flask fitted with a reflux condenser and a drying tube leading to a gas-absorption trap[2] are placed 234 g. (1.1 mole) of phosphorus pentachloride (Note 1) and 65 g. (0.5 mole) of itaconic acid (Note 2). The reagents are mixed by shaking the flask; after a few minutes a vigorous reaction commences, resulting in partial liquefaction of the mixture and copious evolution of hydrogen chloride. When the initial reaction subsides, the mixture is gently heated to cause reflux of phosphorus oxychloride until all the solid dissolves; then heating is continued for an additional 15 minutes (Note 3). The reflux condenser is replaced by a 12-in. Vigreux column, and the phosphorus oxychloride is removed by distillation at reduced pressure provided by a water aspirator (Note 4), the major portion coming over at about 45°/85 mm. When all the phosphorus oxychloride has been removed, the pressure is reduced (vacuum pump) and the material boiling at 70–75°/2 mm. is collected. Liquid boiling in this range weighs 50–55 g., representing a yield of 60–66%. This material, n_D^{20} 1.4915, n_D^{25} 1.4900, is pure enough for most purposes, but it may be further refined by distillation through a packed column, yielding 47–53 g. of a water-white liquid, n_D^{20} 1.4919, boiling at 71–72°/2 mm.

2. Notes

1. The slight molar excess of phosphorus pentachloride has been found to increase the yield of product. It is best to use apparatus with ground-glass joints.
2. Chas. Pfizer and Company technical grade itaconic acid was employed without purification.[3]
3. Heating for a longer period results in a rather sudden change in color from pale yellow to deep orange or red, and a decrease in yield.
4. Considerable dissolved hydrogen chloride is liberated at this point and passes into the water aspirator. A mechanical vacuum pump should not be used at this stage because it would be damaged by corrosion.

3. Discussion

Itaconyl chloride has been prepared previously only by the reaction of itaconic anhydride with phosphorus pentachloride.[4]

References and Notes

1. Purdue University, Lafayette, Indiana.
2. *Org. Syntheses Coll. Vol.* **2**, 4 (1943).
3. *Org. Syntheses* Coll. Vol. **2**, 369 (1943).
4. Petri, *Ber.*, **14**, 1635 (1881).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrogen chloride (7647-01-0)

phosphorus pentachloride (10026-13-8)

Phosphorus Oxychloride (21295-50-1)

Itaconic anhydride (2170-03-8)

Itaconic acid (97-65-4)

Itaconyl chloride (1931-60-8)

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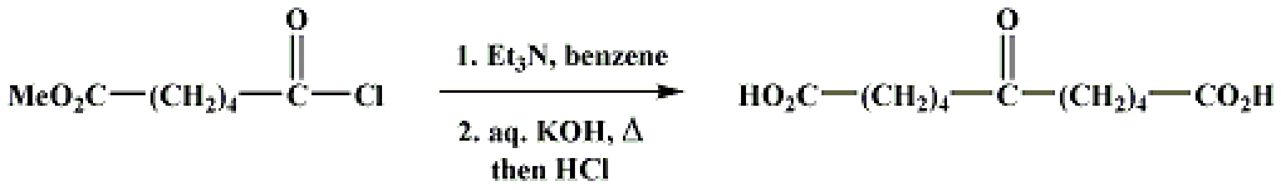
Organic Syntheses, CV 4, 555

6-KETOHENDECANEDIOIC ACID

[Undecanedioic acid, 6-oxo-]



Submitted by Lois J. Durham, Donald J. McLeod, and James Cason[1].
Checked by N. J. Leonard, D. H. Dybvig, and K. L. Rinehart, Jr..

1. Procedure

In a 1-l. three-necked flask fitted with a sealed mechanical stirrer, a 125-ml. dropping funnel, a thermometer, and a drying tube filled with calcium chloride, are placed 500 ml. of dry benzene (Note 1) and 89.3 g. (0.5 mole) of δ-carbomethoxyvaleryl chloride (Note 2). The thermometer is adjusted to extend into the stirred liquid but not into the path of the stirrer. The mixture is cooled, with stirring, to 3–5° in an ice bath, then 50.6 g. (0.5 mole) of triethylamine (Note 3) is added as rapidly as is consistent with keeping the temperature of the reaction mixture below 25° (3–5 minutes). When the mildly exothermic reaction has subsided, the ice bath is removed and a warm water bath is used to raise the temperature of the reaction mixture to 33–35° during 10–15 minutes. A heavy white precipitate of triethylamine hydrochloride separates. After the reaction mixture has been warmed to about 35°, the water bath is removed and stirring is continued without heating for 30 minutes.

The reaction mixture is filtered (Note 4) with suction, and the amine salt is washed with about 200 ml. of benzene. The filtrate and washings are combined and transferred to a 1-l. round-bottomed flask, benzene is removed at reduced pressure, and to the residue is added 500 ml. of 2*N* aqueous potassium hydroxide. This mixture is heated under reflux for 4 hours, by which time the solution should become completely homogeneous. The cooled solution is extracted with three 100-ml. portions of ether, then acidified to Congo red with concentrated hydrochloric acid (approximately 95 ml.). After the solution has been cooled in ice for at least 1 hour, the precipitated white solid is collected by suction filtration, washed with water, and recrystallized from a minimal amount of hot water (105–125 ml. required at about 90°). The yield of colorless 6-ketohendecanedioic acid, m.p. 108–109° (Note 5) is 35–37 g. (60–64%).

2. Notes

1. A quantity of thiophene-free benzene is conveniently dried by distilling about one-fourth of it, then cooling the residue with protection from moisture by use of a calcium chloride tube.
2. This ester acid chloride is prepared by allowing 100 g. (0.63 mole) of redistilled commercial methyl hydrogen adipate (b.p. 155–156°/7 mm., 172–173°/13 mm.) to stand overnight at room temperature with 150 g. (1.25 moles) of thionyl chloride. A Claisen head is attached, and the thionyl chloride is removed at aspirator pressure on a

steam bath. A pump is attached, and the ester acid chloride is distilled; the yield is at least 94 g. (84%), b.p. 114–115°/1 mm.

3. Triethylamine purified by drying over sodium hydroxide pellets and distilling from α-naphthyl isocyanate was found to give no better results than amine which had been distilled through a half-meter Vigreux column and collected over the range 89.5–90°.

4. Frequently the flocculent precipitate of triethylamine hydrochloride is filtered with some difficulty; accordingly, a sufficiently large Büchner funnel should be used for the filtration.

5. Titration of this acid gives an equivalent weight in the range 115–116 (theory, 115). The highest melting point recorded for this acid is 111°.[2]

3. Discussion

6-Ketohendecanedioic acid has been prepared by the reactions described,[3,4] by the dialkylation of diethyl acetonedicarboxylate with ethyl γ-iodobutyrate in the presence of sodium ethoxide followed by hydrolysis and decarboxylation,[2,5] and by the permanganate oxidation of 6-(1'-cyclohexenyl)-1-hexene,[6] by the reaction of 1-morpholinocyclohexene with glutaryl chloride in the presence of triethylamine,[7] and by hydrolysis of the reaction product obtained by treating bromomagnesium cyclopentanone-2-carboxylate with adipyl chloride.[8] The present method is a simplification of the procedure originally described by Sauer.[3] This method is practical for the preparation of symmetrical keto dibasic acids and esters.[9]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 510

References and Notes

1. University of California, Berkeley, California.
2. English, *J. Am. Chem. Soc.*, **63**, 941 (1941).
3. Sauer, *J. Am. Chem. Soc.*, **69**, 2444 (1947).
4. Cason, Taylor, and Williams, *J. Org. Chem.*, **16**, 1187 (1951).
5. Leonard and Goode, *J. Am. Chem. Soc.*, **72**, 5404 (1950).
6. Kreuchunas, *J. Am. Chem. Soc.*, **75**, 4278 (1953).
7. Hünig and Lücke, *Chem. Ber.*, **92**, 652 (1959).
8. Plesek, *Chem. listy*, **49**, 1840 (1955) [*C. A.*, **50**, 9294 (1956)].
9. Blomquist, Johnson, Diuguid, Shillington, and Spencer, *J. Am. Chem. Soc.*, **74**, 4203 (1952).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether (60-29-7)

sodium hydroxide (1310-73-2)

thionyl chloride (7719-09-7)

potassium hydroxide (1310-58-3)

sodium ethoxide (141-52-6)

adipyl chloride (111-50-2)

methyl hydrogen adipate (627-91-8)

α-naphthyl isocyanate (86-84-0)

triethylamine (121-44-8)

Triethylamine hydrochloride (554-68-7)

6-Ketohendecanedioic acid, Undecanedioic acid, 6-oxo- (3242-53-3)

δ-carbomethoxyvaleryl chloride (35444-44-1)

diethyl acetonedicarboxylate (570-08-1)

ethyl γ-iodobutyrate (7425-53-8)

1-morpholinocyclohexene (670-80-4)

glutaryl chloride (2873-74-7)

bromomagnesium cyclopentanone-2-carboxylate

6-(1'-cyclohexenyl)-1-hexene

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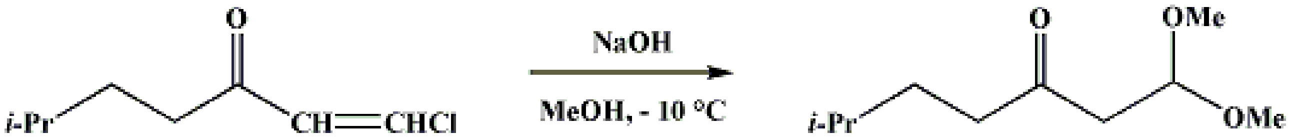
Organic Syntheses, CV 4, 558

β-KETOISOÖCTALDEHYDE DIMETHYL ACETAL

[Heptanal, 6-methyl-3-oxo-, 1-dimethyl acetal]



Submitted by Charles C. Price and Joseph A. Pappalardo[1].
Checked by R. S. Schreiber, Wm. Bradley Reid, Jr., and R. W. Jackson.

1. Procedure

A dry 1-l. three-necked flask fitted with a mercury-sealed stirrer, a calcium chloride drying tube, and a 500-ml. dropping funnel, protected by a calcium chloride drying tube, is surrounded by an ice-salt mixture at –11°. Anhydrous methanol (130 ml.) (Note 1) and (Note 2) and 161 g. (1 mole) of β-chlorovinyl isoamyl ketone (p. 186) are poured into the flask (Note 3). A solution of 43 g. (1.04 moles) of sodium hydroxide (97%) and 350 ml. of absolute methanol (Note 4) is added dropwise with stirring over a period of 2 hours, during which time the bath temperature is kept between –11° and –8°.

The reaction mixture is poured, with stirring, into 1 kg. of a saturated sodium chloride solution (Note 5). The mixture is extracted with four 100-ml. portions of low-boiling petroleum ether. The extracts are combined and dried over anhydrous potassium carbonate. The liquid is decanted, the potassium carbonate is washed with 25 ml. of low-boiling petroleum ether, and the solution is added to the main fraction. A pinch of anhydrous potassium carbonate is added to the petroleum ether solution, and the solution is then distilled from a Claisen flask to give a colorless liquid; yield 151–169 g. (80–90%); b.p. 122–125°/25 mm.; n_D^{25} 1.4260; d_4^{25} 0.932 (Note 6).

2. Notes

1. Absolute methanol (C.P. grade) was used.
2. The checkers ran this preparation at one-third the scale described here and obtained equivalent results.
3. When this procedure is used to make the dimethyl acetal of β-ketobutyraldehyde, the methanol and β-chlorovinyl methyl ketone must be mixed quickly and cooled well. If these two liquids are placed in the same flask without immediate cooling and mixing, the ketone may decompose rapidly with the evolution of heat and large amounts of hydrogen chloride.
4. It takes about 1 hour of shaking to dissolve the sodium hydroxide pellets.
5. If this reaction is used to prepare the water-soluble dimethyl acetal of β-ketobutyraldehyde, the product of the reaction is not poured into the saturated sodium chloride solution. Instead, the methanol solution is filtered from the sodium chloride and distilled.
6. The product darkens a little on standing but undergoes no change in refractive index.

3. Discussion

The preparation described[2] has been used by Nelles[3] to make a variety of β-ketoacetals.

References and Notes

1. University of Notre Dame, Notre Dame, Indiana.
2. Price and Pappalardo, *J. Am. Chem. Soc.*, **72**, 2613 (1950).
3. Nelles, U. S. pat. 2,091,373 [*C. A.*, **31**, 7444 (1937)]; Brit. pat. 466,890 [*C. A.*, **31**, 7886 (1937)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

dimethyl acetal

potassium carbonate (584-08-7)

hydrogen chloride (7647-01-0)

methanol (67-56-1)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

β-ketobutyraldehyde

β-Chlorovinyl isoamyl ketone (18378-90-0)

β-chlorovinyl methyl ketone

Heptanal, 6-methyl-3-oxo-, 1-dimethyl acetal

β-Ketoisooctaldehyde dimethyl acetal (53684-58-5)

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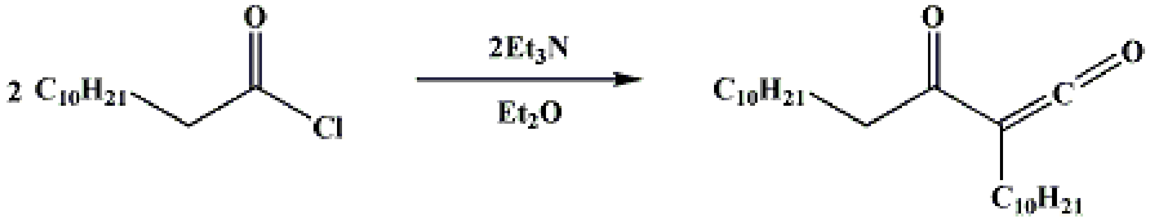
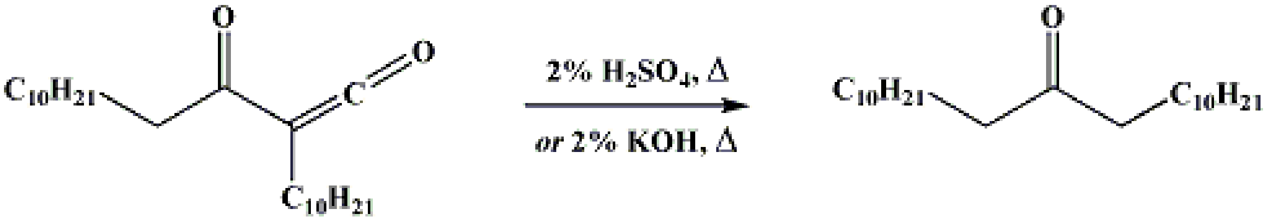
Organic Syntheses, CV 4, 560

LAURONE

[12-Tricosanone]





Submitted by J. C. Sauer[1]
Checked by William S. Johnson and H. C. Dehm.

1. Procedure

Into a 3-l. three-necked round-bottomed flask fitted with a mechanical stirrer, dropping funnel, and reflux condenser provided with a calcium chloride drying tube is placed 1260 ml. (approximately 900 g.) of anhydrous ether. Stirring is commenced, and 153.0 g. (0.7 mole) of lauroyl chloride (Note 1) is added rapidly through one of the flask openings. The solution is cooled in ice water, and 70.7 g. (0.7 mole) of triethylamine (Note 2) is added over a period of 10 minutes through the dropping funnel in a fine stream. Stirring is discontinued after 1 hour, and the mixture is allowed to come to room temperature. After 12 to 24 hours, the mixture of decylketene dimer (Note 3) and triethylamine hydrochloride is extracted once with 125 ml. of an aqueous 2% sulfuric acid solution to remove the amine salt.

Procedure A. The wet ether layer is transferred to a 3-l. distillation flask and distilled to remove most of the solvent. The warm oily residue is transferred to a 1-l. beaker and mixed with 500 ml. of 2% potassium hydroxide solution. The mixture is heated on a steam bath for 1 hour with occasional stirring and is then chilled in ice water. The waxy cake which settles out on top of the aqueous suspension is skimmed from the surface and dissolved in a mixture of 400 ml. each of acetone and methanol. The hot solution is filtered through a steam-jacketed funnel and cooled in ice water, and the precipitate is collected on a Büchner funnel with suction. The product is washed on the funnel with cold methanol; after air drying overnight it amounts to 55–65 g. (46–55%), m.p. 62–64°.

Procedure B. The following alternative isolation procedure yields a somewhat purer product. The wet ether layer which has been washed with dilute sulfuric acid to remove

amine salt is transferred to a 3-l. distillation flask, 150 ml. of 2% sulfuric acid is added, and the mixture is distilled until nearly all the ether is removed. The hot, oily layer is separated in a separatory funnel and distilled (Note 4). The yield of the fraction distilling at 215–230°/3 mm. is 64–75 g. (54–63%). After recrystallization from 750 ml. of acetone, the laurone weighs 55–65 g. (46–55%), m.p. 68–69° (Note 5).

2. Notes

1. A commercial lauric acid, such as that available from Armour and Company, was converted into the acid chloride by reaction with thionyl chloride. The checkers employed 1 kg. of thionyl chloride for 1201 g. of acid. The product was distilled through a 12-in. Vigreux column, giving 1145 g. (87%) of colorless acid chloride, f. p. −15° to −18°.
2. Triethylamine was purified by the following procedure: fractional distillation, addition of about 2% phenyl isocyanate to the distillate, and redistillation.
3. If desired, decylketene dimer can be isolated at this point by filtering the reaction mixture and concentrating the filtrate. The mixture should be handled at all times under anhydrous conditions. The filtration should be carried out by the inverted filtration method.[2] Difficulties are usually encountered in the filtration step since the amine salt frequently separates as a gel. Seeding the ether solution of lauroyl chloride with triethylamine hydrochloride usually aids in preventing this gel formation. It is necessary to rinse the amine salt several times with ether to extract the dimer, which is usually contaminated with traces of triethylamine hydrochloride.
4. The electrically heated fractionating column used by the submitter for distilling laurone is pictured in part in .htmFig.11. This still, with a column length of 8 in., was designed by Dr. H. J. Sampson of the Rayon Department of E. I. du Pont de Nemours and Company, Inc., Waynesboro, Virginia.

Fig. 11.

Fig. 11.

5. Other acid chlorides of the type RCH_2COCl can be similarly dehydrochlorinated. For example, caproyl chloride (1.2 moles) was converted to di-*n*-amyl ketone, b.p. 98–102°/15 mm., in 60–71.5% yield. In this case, it was found preferable to remove the amine salt from the reaction mixture by washing with 2% sulfuric acid. The butylketene dimer was then extracted from the reaction mixture by washing with 5% sodium hydroxide solution; the alkaline solution was acidified with sulfuric acid and steam-distilled. The oily layer in the distillate was separated and fractionated.

3. Discussion

Laurone has been prepared by hydrating and decarboxylating decylketene dimer.[3] It has also been prepared by distilling calcium laurate;[4] by heating lauric acid with phosphorus pentoxide;[5] by heating barium laurate under reduced pressure;[6] by the ester condensation of ethyl laurate with sodium ethoxide[7] or of methyl laurate with sodium hydride[8] or

diisopropylamino-magnesium bromide[9] followed by ketonic hydrolysis; by catalytic ketonization of lauric acid over a chromate catalyst;[10] or by passing lauric acid over thorium dioxide at 400°.[11]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 514

References and Notes

1. E. I. du Pont de Nemours and Company, Wilmington, Delaware.
2. *Org. Syntheses Coll. Vol.* **2**, 610 (1943).
3. Sauer, *J. Am. Chem. Soc.*, **69**, 2444 (1947); Piekarski, *J. recherches centre natl. recherche sci., Labs. Bellevue* (*Paris*), No. **40**, 197 (1958) [*C. A.*, **52**, 19922 (1958)].
4. Overbeck, *Ann.*, **84**, 289 (1852).
5. Kipping, *J. Chem. Soc.*, **57**, 980 (1890).
6. Krafft, *Ber.*, **15**, 1711 (1882).
7. Strating, Backer, Lolkema, and Benninga, *Rec. trav. chim.*, **55**, 903 (1936).
8. Hansley, U. S. pat. 2,108,156 [*C. A.*, **33**, 6342 (1939)].
9. Frostick and Hauser, *J. Am. Chem. Soc.*, **71**, 1350 (1949).
10. Wortz, U. S. pat. 2,108,156 [*C. A.*, **32**, 2542 (1938)].
11. Pickard and Kenyon, *J. Chem. Soc.*, **99**, 57 (1911).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

methanol (67-56-1)

ether (60-29-7)

sodium hydroxide (1310-73-2)

thionyl chloride (7719-09-7)

thorium dioxide

acetone (67-64-1)

potassium hydroxide (1310-58-3)

sodium ethoxide (141-52-6)

phenyl isocyanate (103-71-9)

ethyl laurate (106-33-2)

lauric acid (143-07-7)

sodium hydride (7646-69-7)

lauroyl chloride (112-16-3)

chromate

triethylamine (121-44-8)

Triethylamine hydrochloride (554-68-7)

Laurone, 12-Tricosanone (540-09-0)

decylketene

caproyl chloride (142-61-0)

butylketene

calcium laurate (4696-56-4)

barium laurate (4696-57-5)

methyl laurate (111-82-0)

diisopropylamino-magnesium bromide

phosphorus pentoxide (1314-56-3)

di-n-amyl ketone (927-49-1)

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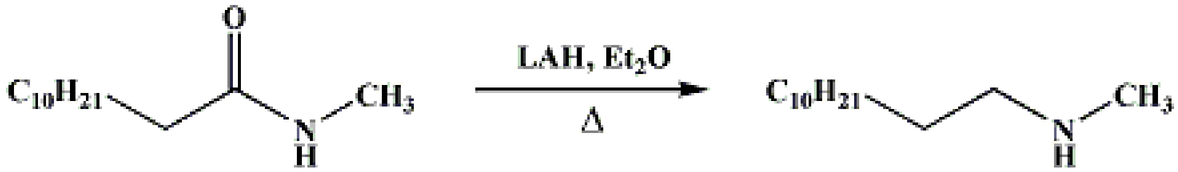
Organic Syntheses, CV 4, 564

LAURYLMETHYLAMINE

[Dodecylamine, N-methyl-]



Submitted by C. V. Wilson and J. F. Stenberg[1].
Checked by N. J. Leonard and C. W. Schimelpfenig.

1. Procedure

In a 5-l. three-necked flask, fitted with a ball-joint sealed stirrer and a Soxhlet extractor (70 mm. internal diameter × 300 mm. length of body) carrying a large-capacity condenser, are placed 1.8 l. of dry ether (Note 1) and 38 g. (1 mole) of finely divided lithium aluminum hydride (Note 2). In the Soxhlet cup is placed 160 g. (0.75 mole) (Note 3) of N-methyllauramide (m.p. 67–69°) (Note 4). The mixture is heated under gentle reflux with efficient stirring over a 5-hour period and then stirred overnight at room temperature (Note 5); the N-methyllauramide is extracted from the cup during the first 3 hours.

The excess lithium aluminum hydride and the metallic complexes are decomposed by the careful addition of 82 ml. of distilled water, from a dropping funnel, to the well-stirred mixture. The reaction mixture is stirred for an additional 30 minutes, filtered with suction, and the solid is washed with several 100-ml. portions of ether. After the ether is removed from the filtrates, the residual oil is distilled under reduced pressure. The yield of laurylmethylamine, a colorless liquid boiling at 110–115°/1.2–1.5 mm., is 121–142 g. (81–95%) (Note 6).

2. Notes

1. It is preferable to use ether subjected to final drying by distillation from lithium aluminum hydride.
2. The yield depends upon the use of high-quality, fresh lithium aluminum hydride.
3. If a Soxhlet extractor having a smaller capacity is employed, the cup will have to be recharged during the course of the reaction.
4. N-Methyllauramide, N-methylmyristamide, and N-methylpelargonamide can be prepared in 95–98% yield by adaptation of the method used by Roe, Scanlan, and Swern[2] for the preparation of amides of oleic and 9,10-dihydroxystearic acids.

5. Stirring overnight is a matter of convenience. In the preparation of methylnonylamine, refluxing for an hour after the addition of the amide was found by the submitters to be sufficient.
6. Methylnonylamine and methylmyristylamine were prepared by the submitters in 89–92% yield using the same procedure; with methylmyristylamine a longer reflux period was required, owing to the lower solubility of the amide.

3. Discussion

Laurylmethylamine has been prepared by the reaction of lauryl alcohol with methylamine under pressure in the presence of catalysts at high temperature,[3] by heating lauryl chloride with methylamine in alcoholic or aqueous medium under pressure,[4,5,6] by the reaction of lauryl halides with aqueous methylamine,[7] by the hydrolysis of *o*-carboxy-N-methyl-N-laurylbenzenesulfonamide,[8] and by the pyrolysis of β-cyanoethyllaurylmethylamine.[9] Cetylmethylamine has been prepared by the catalytic debenzylation of benzylcetylmethylamine.[10]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ether (60-29-7)

Lauryl alcohol (112-53-8)

methylamine (74-89-5)

lithium aluminum hydride (16853-85-3)

Laurylmethylamine, Dodecylamine, N-methyl- (7311-30-0)

N-methyllauramide (27563-67-3)

N-methylpelargonamide

methylnonylamine (39093-27-1)

methylmyristylamine

lauryl chloride (112-52-7)

β-cyanoethyllaurylmethylamine

Cetylmethylamine

benzylcetylmethylamine

o-carboxy-N-methyl-N-laurylbenzenesulfonamide

N-methylmyristamide (7438-09-7)

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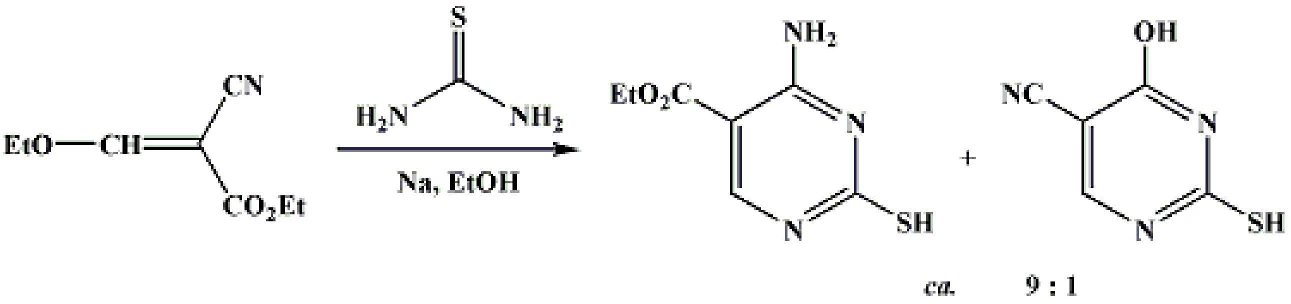
2-MERCAPTO-4-AMINO-5-CARBETHOXYPYRIMIDINE AND 2-MERCAPTO-4-HYDROXY-5-CYANOPYRIMIDINE

[5-Pyrimidinecarboxylic acid, 4-amino-2-mercapto-, ethyl ester]

[5-Pyrimidinecarbonitrile, 4-hydroxy-2-mercapto-]



Submitted by T. L. V. Ulbricht, Takuo Okuda, and Charles C. Price[1].
Checked by B. C. McKusick and Stephen Proskow.

1. Procedure

A. *2-Mercapto-4-amino-5-carbethoxypyrimidine.* A 5-l. three-necked, round-bottomed flask mounted in a heating mantle is fitted with a 250-ml. dropping funnel, an efficient, sealed, mechanical stirrer, and a reflux condenser connected to a calcium chloride drying tube. Absolute ethanol (625 ml.) is placed in the flask, the stirrer is started, and 23 g. (1 g. atom) of freshly cut sodium is added in portions. After the sodium has dissolved, 76.1 g. (1 mole) of thiourea is added to the warm, stirred solution in one portion. When the bulk of the thiourea has dissolved, 169 g. (1 mole) of liquefied ethyl ethoxymethylenecyanoacetate is added from the dropping funnel to the stirred mixture over a period of 2 hours (Note 1). This rate of addition keeps the reaction mixture warm. The solution is then stirred and gently refluxed for 6 hours. The sodium salt of the carbethoxypyrimidine may precipitate during the course of the reaction.

The reaction mixture is cooled to 50–60°, and 1.75 l. of water is added, followed by 65 ml. of acetic acid to make the mixture distinctly acidic. The resulting suspension is stirred and boiled for 5 minutes in order to effect complete decomposition of the sodium salt.

The mixture is cooled to 25°, and the crystalline 2-mercapto-4-amino-5-carbethoxypyrimidine is collected on a 10-cm. Büchner funnel and washed successively with five 50-ml. portions of water, 50 ml. of acetone, and 50 ml. of ether (Note 2). The carbethoxypyrimidine weighs 152–159 g. (76–80%) and melts with decomposition at 259–260° (Note 3) after being dried for 5 hours at 110° and atmospheric pressure. It is in the form of a cream-colored powder that is sufficiently pure for synthetic purposes. Pure carbethoxypyrimidine can be obtained by recrystallizing the crude product once from 50% acetic acid, using 170 ml. per gram of pyrimidine.

B. *2-Mercapto-4-hydroxy-5-cyanopyrimidine.* The aqueous filtrate from which the crude 2-mercapto-4-amino-5-carbethoxypyrimidine separated is cooled overnight at 0°, and the cyanopyrimidine that precipitates is collected on a suction filter. The crude product is recrystallized from about 200 ml. of 10% acetic acid with 1 g. of decolorizing charcoal added. Two additional recrystallizations done similarly give the pure cyanopyrimidine as faintly yellow crystals, m.p. 265–272° (dec.) (Note 3).

The yield is 10–18 g. (7–12%).

2. Notes

1. Ethyl ethoxymethylenecyanoacetate can be prepared in the laboratory from ethyl cyanoacetate and ethyl orthoformate according to the directions of de Bellemont.[2] The submitters and checkers used a commercial product, m.p. 45–50°, obtained from Kay-Fries, Inc., New York. The liquefied product is weighed and poured into the dropping funnel. An infrared heating lamp is used to keep it liquid during the addition.
2. For complete removal of a yellow impurity, the product should be stirred well with each portion of water before filtration. If the solid is not washed with organic solvents, drying of the caked product will be slow.
3. The decomposition point is greatly dependent on the rate of heating. The checkers found that the carbethoxypyrimidine heated on a Fisher-Johns melting-point block at a rate of 4° per minute decomposed at 280–285°. Under the same conditions, the cyanopyrimidine decomposed at 285–289°. Both products started to darken around 260°. In the infrared, the carbethoxypyrimidine has a strong band at 5.88 • and no absorption in the 4.4 • range, whereas the cyanopyrimidine has a strong band at 4.48 • and no absorption at 5.88 •.

3. Discussion

The described procedure is based on the methods of Johnson and Ambler[3] and Anderson et al.,[4] as modified by Ulbricht and Price.[5] This procedure is illustrative of a general method of preparing pyrimidines, wherein one condenses thiourea, guanidine, or an amidine with alkoxymethylenemalonic esters, alkoxymethylenecyanoacetic esters, or alkoxymethylenemalononitrile. Kenner and Todd recently reviewed the synthesis of pyrimidines.[6]

2-Mercapto-4-amino-5-carbethoxypyrimidine has been converted to 2-methylmercapto-4-amino-5-hydroxymethylpyrimidine,[5] an antimetabolite possessing antitumor activity,[7] by methylation of the mercapto group followed by reduction of the ester group to a hydroxymethyl group with lithium aluminum hydride.[5]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium salt of the carbethoxypyrimidine

decolorizing charcoal

amidine

ethanol (64-17-5)

acetic acid (64-19-7)

ether (60-29-7)

acetone (67-64-1)

sodium (13966-32-0)

Ethyl cyanoacetate (105-56-6)

Ethyl orthoformate

thiourea (62-56-6)

pyrimidine (289-95-2)

guanidine (113-00-8)

lithium aluminum hydride (16853-85-3)

2-Mercapto-4-amino-5-carbethoxypyrimidine, 5-Pyrimidinecarboxylic acid, 4-amino-2-mercapto-, ethyl ester (774-07-2)

2-Mercapto-4-hydroxy-5-cyanopyrimidine, 5-Pyrimidinecarbonitrile, 4-hydroxy-2-mercapto- (23945-49-5)

ethyl ethoxymethylenecyanoacetate

carbethoxypyrimidine (42839-08-7)

cyanopyrimidine (14080-23-0)

2-methylmercapto-4-amino-5-hydroxymethylpyrimidine

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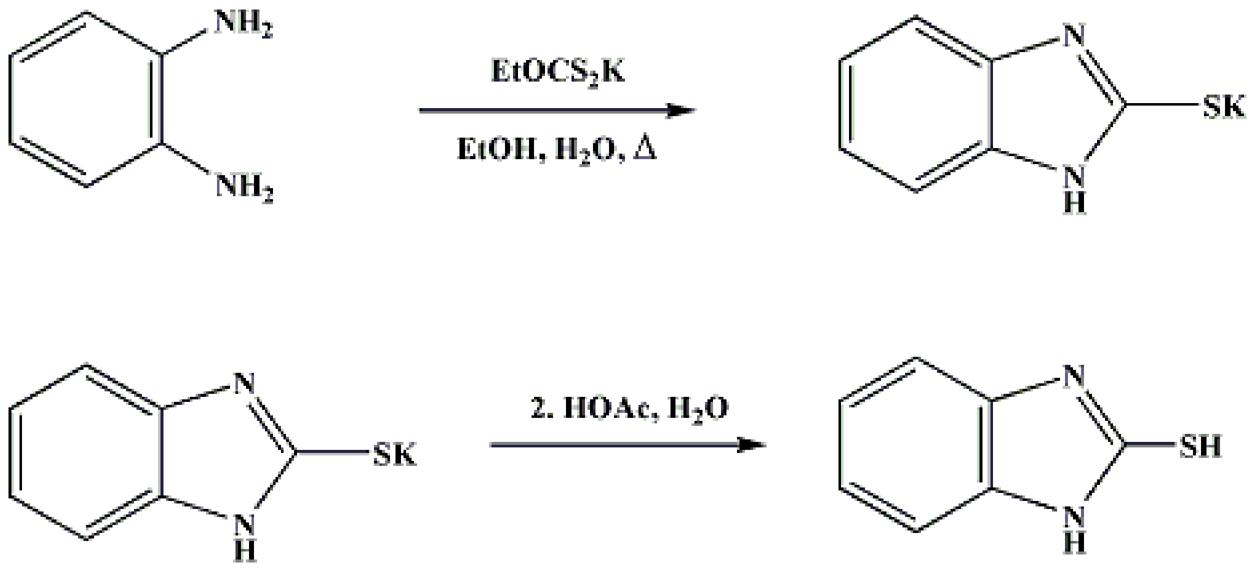
2-MERCAPTOBENZIMIDAZOLE

[2-Benzimidazolethiol]



Submitted by J. A. VanAllan and B. D. Deacon[1].
Checked by Cliff S. Hamilton and Yao-Hua Wu.

1. Procedure

A mixture of 32.4 g. (0.3 mole) of *o*-phenylenediamine,[2] 52.8 g. (0.33 mole) of potassium ethyl xanthate (Note 1), 300 ml. of 95% ethanol, and 45 ml. of water in a 1-l. flask is heated under reflux for 3 hours. Norit (12 g.) is then added cautiously, and after the mixture has been heated at the reflux temperature for 10 minutes the Norit is removed by filtration. The filtrate is heated to 60–70°, 300 ml. of warm tap water (60–70°) is added, and then 25 ml. of acetic acid in 50 ml. of water is added with good stirring. The product separates as glistening white crystals, and the mixture is placed in a refrigerator for 3 hours to complete the crystallization. The product is collected on a Büchner funnel and dried overnight at 40°. The yield is 37.8–39 g. (84–86.5%) of 2-mercaptobenzimidazole melting at 303–304° (cor.) (Note 2) and (Note 3).

2. Notes

1. The potassium ethyl xanthate may be replaced by 19 g. of potassium hydroxide and 26 g. (21 ml., 0.34 mole) of carbon disulfide. The yield and quality of the product are the same.
2. The quality of the product is excellent. Recrystallization may be effected from 95% ethanol as a solvent. Recovery is about 90%; there is no change in the melting point.
3. 2-Mercaptobenzoxazole, m.p. 193–195°, can be prepared in 80% yield by a

similar procedure, using *o*-aminophenol in place of *o*-phenylenediamine.

3. Discussion

2-Mercaptobenzimidazole has also been prepared from *o*-phenylenediamine by heating the thiocyanate to 120–130°;[3] by heating with aqueous potassium thiocyanate (in which case 2-aminophenylthiourea is a by-product);[4] by the action of thiophosgene in chloroform;[5] by heating with carbon disulfide in alcohol[6] or in water;[7] and by heating the hydrochloride with thiourea to 170–180°.[8]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

acetic acid (64-19-7)

chloroform (67-66-3)

o-aminophenol (95-55-6)

Norit (7782-42-5)

potassium hydroxide (1310-58-3)

carbon disulfide (75-15-0)

Thiophosgene (463-71-8)

potassium thiocyanate (333-20-0)

thiocyanate

potassium ethyl xanthate (140-89-6)

thiourea (62-56-6)

o-Phenylenediamine (95-54-5)

2-Mercaptobenzimidazole, 2-Benzimidazolethiol (583-39-1)

2-Mercaptobenzoxazole (2382-96-9)

2-aminophenylthiourea (3394-09-0)

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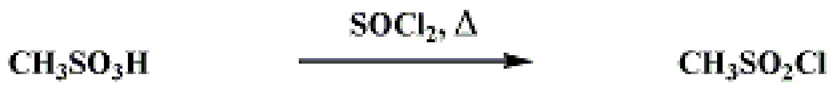
Organic Syntheses, CV 4, 571

METHANESULFONYL CHLORIDE



Submitted by Peter J. Hearst and C. R. Noller[1].
Checked by R. S. Schreiber, B. D. Aspergren, and R. V. Heinzelmann.

1. Procedure

In a 1-l. three-necked flask fitted with a mechanical stirrer, a reflux condenser, a thermometer, and a separatory funnel (Note 1), and set up in a hood, is placed 152 g. (105 ml., 1.5 moles) of methanesulfonic acid (Note 2). The acid is heated to 95° on a steam bath, and 238 g. (146 ml., 2.0 moles) of thionyl chloride (Note 3) is added over a period of 4 hours. The temperature is kept at 95° throughout the addition and for 3.5 hours after it is completed.

The product is transferred to a modified Claisen flask (Note 4) and distilled under reduced pressure, heat being supplied by an oil bath (Note 5). Most of the thionyl chloride distils at room temperature. The yield of almost colorless product distilling at 64–66°/20 mm. (Note 6) is 122–143 g. (71–83%); n_D^{23} 1.451.

2. Notes

1. The checkers recommend the use of silicone grease on all glass joints.
2. The methanesulfonic acid is a commercial product supplied by the Standard Oil Company of Indiana and reported to be 95% pure and to contain 2% water.
3. Eastman Kodak Company thionyl chloride (b.p. 75–76°) was used without further purification.
4. The checkers used a Claisen head with an attached 10-cm. Vigreux column.
5. A free flame should be avoided, because local superheating causes charring and decomposition. The fumes from the decomposition cause the product (which normally is colorless) to darken. The bath temperature should not exceed 115° at the end of the distillation.
6. The checkers observed a boiling point of 61–62°/18 mm.

3. Discussion

Methanesulfonyl chloride has been prepared by the chlorination of methyl thiocyanate,[2] S-methylthiourethan,[3] sodium methylthiosulfate,[4] S-methylisothiuronium sulfate[5] or S-methylisothiuronium *p*-toluenesulfonate,[6] and dimethyl disulfide in the presence of water;[7] from sodium methanesulfonate by the action of phosphorus pentachloride,[8,9] phosphorus oxychloride,[9] or benzotrichloride;[10]

from methanesulfonic acid by the action of phosphorus pentachloride[11] or thionyl chloride;[12] or by the reaction of methylmagnesium iodide with sulfuryl chloride.[13]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

S-methylisothiuronium sulfate

S-methylisothiuronium p-toluenesulfonate

phosphorus pentachloride (10026-13-8)

thionyl chloride (7719-09-7)

Phosphorus Oxychloride (21295-50-1)

sulfuryl chloride (7791-25-5)

benzotrichloride (98-07-7)

methylmagnesium iodide (917-64-6)

methyl thiocyanate (556-64-9)

Methanesulfonyl chloride (124-63-0)

methanesulfonic acid (75-75-2)

S-methylthiourethan

sodium methylthiosulfate

dimethyl disulfide (624-92-0)

sodium methanesulfonate (2386-57-4)

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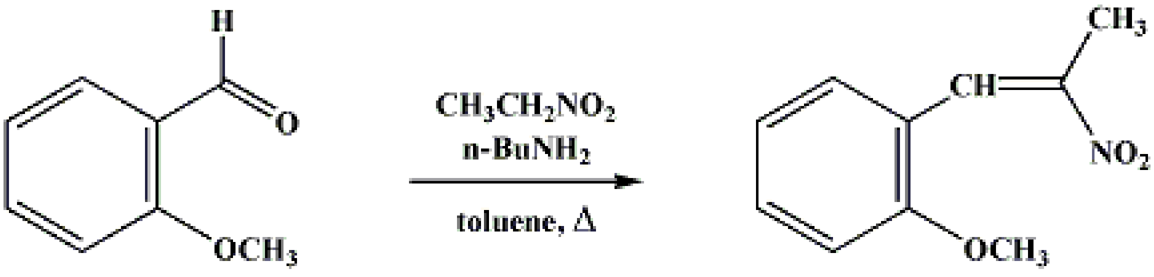
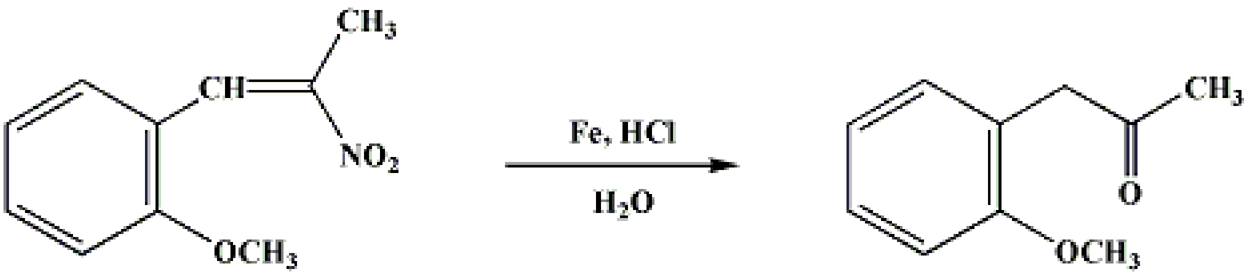
Organic Syntheses, CV 4, 573

o-METHOXYPHENYLACETONE

[2-Propanone, 1-(*o*-methoxyphenyl)-]





Submitted by R. V. Heinzelman[1]
Checked by M. Tishler and H. L. Slates.

1. Procedure

A. *1-(o-Methoxyphenyl)-2-nitro-1-propene*. A 1-l. round-bottomed flask is fitted with an electric heating mantle, a modified Dean and Stark water separator (Note 1), and a reflux condenser. To the flask are added in this order 200 ml. of reagent-grade toluene, 136 g. (1.0 mole) of *o*-methoxybenzaldehyde (Note 2), 90 g. (1.1 moles) of commercial nitroethane (Note 3), and 20 ml. of *n*-butylamine (Note 4). The solution is heated to produce a rapid reflux until the separation of water ceases (Note 5). The toluene solution is used directly in the next step (Note 6).

B. *o-Methoxyphenylacetone.* A 3-l. three-necked round-bottomed flask is equipped with an electric heating mantle, two reflux condensers, a dropping funnel, and a high-speed whip stirrer (Note 7). The toluene solution from Part A is placed in the flask, and 500 ml. of water, 200 g. of powdered iron (Note 8), and 4 g. of ferric chloride are added. With vigorous agitation the suspension is heated to about 75°, and 360 ml. of concentrated hydrochloric acid is added over a 2-hour period (Note 9); heating and stirring are continued for an additional 30 minutes.

The suspension is transferred to a 5-l. three-necked round-bottomed flask and subjected to steam distillation until 7–10 l. are collected (Note 10). The toluene layer

is removed, and the aqueous layer is extracted with 1 l. of fresh toluene. The combined toluene layers are agitated for 30 minutes with a solution of 26 g. of sodium bisulfite in 500 ml. of water (Note 11). The toluene layer is washed with water, and the solvent is removed at water-pump pressure on the steam bath. The resulting orange liquid weighs 107–120 g.. (65–73%); n_D^{20} 1.5250–1.5270, and is sufficiently pure for most uses. It is purified by distillation through a 12-in. Vigreux column, and the fraction boiling at 128–130°/14 mm. is collected. The yield is 102–117 g. (63–71%, based on the methoxybenzaldehyde used), n_D^{20} 1.5250–1.5260 (Note 12), (Note 13).

2. Notes

1. The model manufactured by the Corning Glass Works, Corning, New York, and listed as No. 3622 was used. See also *Org. Syntheses Coll. Vol.* **3**, 382 (1955).
2. *o*-Methoxybenzaldehyde is available from Eastman Kodak Company, Rochester, New York, and from the Matheson Company, East Rutherford, New Jersey. It may also be prepared according to Baeyer and Villiger.[2]
3. The nitroethane was obtained from Commercial Solvents Corporation, Terre Haute, Indiana, as a 90% pure product. The amount used is a 10% excess based on its nitroethane content. The chief contaminant is 2-nitropropane, which does not interfere in the reaction.
4. It is desirable to swirl the flask after each addition to prevent the formation of layers.
5. Half of the water is collected in about an hour, and the theoretical amount (18 ml.) in about 5 hours. Water removal usually ceases at about 105% of theory. Insufficient reflux rate causes incomplete water removal or an unduly prolonged reaction time.
6. The pure nitroölefin can be obtained by removing the toluene on the steam bath at water-pump pressure and recrystallizing the resulting oil from ethanol or petroleum ether. With petroleum ether, particularly, the volume should be great enough that the product remains in solution until the solution temperature is sufficiently low to prevent oiling out. Addition of seed crystals will encourage crystallization. Alternatively, the yellow oil may be distilled at reduced pressure. The nitroölefin boils at 135–138°/1 mm. and crystallizes in the receiver when seeded. The yield is 150–175 g. (80–90%). The yellow crystals melt at 51–52° when pure. Although no difficulty has been experienced with this compound, the usual safety precautions should be observed when distilling an unsaturated nitro compound. The material is somewhat lachrymatory and irritates the skin.
7. Rapid agitation is necessary to keep the iron in suspension and to mix the two liquid layers.
8. A 40-mesh grade was used, but material up to 100 mesh has been used successfully. However, with the finer material the reaction is somewhat more vigorous.
9. The reaction mixture should reflux vigorously. When the addition time is increased to 6 hours, the yield is not appreciably changed. The iron-acid ratio appears to be important; however, doubling the amounts of both ingredients

produces no change in yield.
10. The 5-l. flask is either heated with an electric mantle or placed on a steam bath to prevent condensation of steam and increase in volume of the suspension. The steam distillation must be continued beyond the point at which the distillate becomes clear.
11. The bisulfite treatment removes any aldehydic material present at this point. Since this ketone is quite inert to sodium bisulfite, the yield is not lowered by this procedure.
12. The pure ketone has n_D^{20} 1.5240 and a boiling point of 128–130° /14 mm., 150° /30 mm. Insufficient removal of *o*-methoxybenzaldehyde will cause the refractive index to be high to the extent of about 0.0003 for each per cent present. The use of distilled nitroölefin eliminates the aldehyde, but this advantage is offset by the distillation hazard and slightly lower over-all yields.
13. This procedure is quite general for other aromatic aldehydes. An excess of bisulfite must be avoided in the washing step, since many phenyl-substituted acetones react appreciably with it.

3. Discussion

The present procedure is that described by the submitter.[3] It is an improved modification of that described by Hoover and Hass[4] for the corresponding *para* isomer. *o*-Methoxyphenylacetone also has been prepared from the glycidic ester,[5] by the hydrogenation of *o*-methoxybenzalacetone,[6] by treating *o*-methoxyphenylacetyl chloride with methylzinc iodide,[7] by the hydrolysis of *o*-methoxy-α-acetylbenzyl cyanide,[8] by the oxidation of 1-(*o*-methoxyphenyl) propene with lead oxide in acetic acid,[9] and by the condensation of *o*-methoxybenzoyl chloride with diethyl ethoxymagnesiummalonate, followed by hydrolysis of the substituted malonic ester.[10] The methods of synthesis of *o*-methoxyphenylacetone have been studied.[11]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

iron (7439-89-6)

lead oxide

sodium bisulfite (7631-90-5)

toluene (108-88-3)

ferric chloride (7705-08-0)

methylzinc iodide

n-butylamine (109-73-9)

nitroethane (79-24-3)

methoxybenzaldehyde, o-methoxybenzaldehyde (135-02-4)

2-nitropropane (79-46-9)

diethyl ethoxymagnesiummalonate

o-Methoxyphenylacetone, 2-Propanone, 1-(o-methoxyphenyl)- (5211-62-1)

o-methoxybenzalacetone

o-methoxyphenylacetyl chloride

o-methoxy-α-acetylbenzyl cyanide

1-(o-methoxyphenyl) propene

o-methoxybenzoyl chloride (21615-34-9)

1-(o-Methoxyphenyl)-2-nitro-1-propene (6306-34-9)

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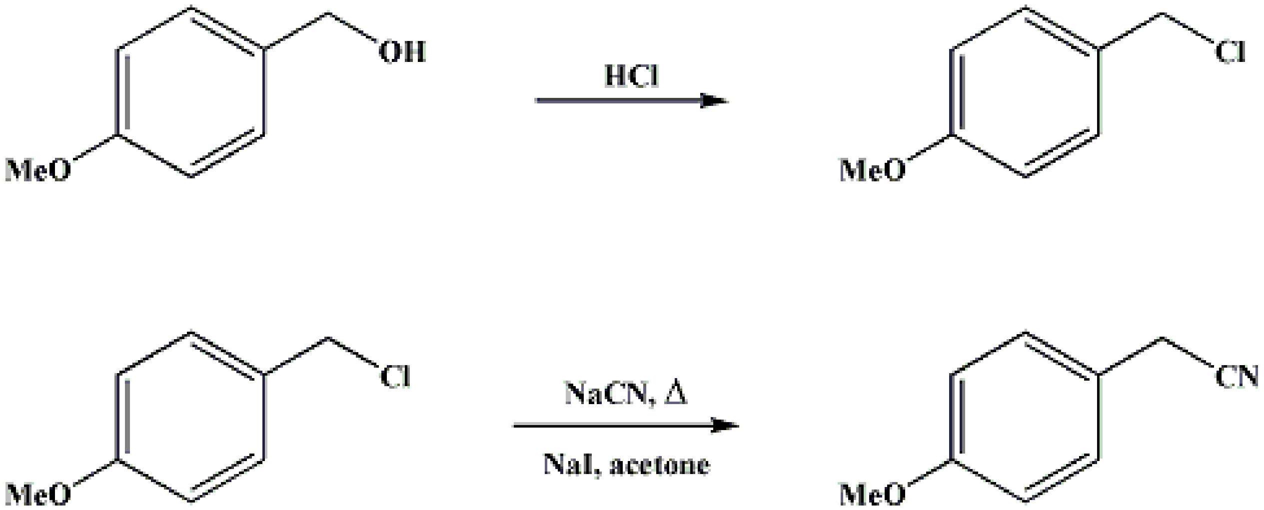
Organic Syntheses, CV 4, 576

p-METHOXYPHENYLACETONITRILE

[Acetonitrile, *p*-methoxyphenyl-]



Submitted by Kurt Rorig, J. Derland Johnston, Robert W. Hamilton, and Thomas J. Telinski[1].
Checked by William S. Johnson, Stanley Seltzer, and Peter Yates.

1. Procedure

In a 1-l. flask fitted with a paddle-blade stirrer are placed 138 g. (1 mole) of anisyl alcohol (Note 1) and 248 ml. of concentrated hydrochloric acid. After stirring vigorously for 15 minutes the contents of the flask are transferred to a separatory funnel. The lower layer (anisyl chloride) is separated, dried over 20 g. of granular calcium chloride for about 30 minutes, and filtered to remove the drying agent.

In a 2-l. three-necked round-bottomed flask, fitted with an efficient sealed stirrer and a reflux condenser capped by a drying tube, are placed the dried anisyl chloride (Note 2) and (Note 3), 73.6 g. (1.5 moles) of finely powdered sodium cyanide, 10 g. of sodium iodide, and 500 ml. of dry acetone (Note 4). The heterogeneous reaction mixture is heated under reflux with vigorous stirring for 16–20 hours, then cooled and filtered with suction. The solid on the filter is washed with 200 ml. of acetone and discarded (Note 5). The combined filtrates are distilled to remove the acetone. The residual oil is taken up in 300 ml. of benzene and washed with three 100-ml. portions of hot water. The benzene solution is dried over anhydrous sodium sulfate for about 15 minutes, and the solvent is removed by distillation at the reduced pressure of the water aspirator (Note 6). The residual *p*-methoxyphenylacetonitrile is purified by distillation under reduced pressure through an 8-in. Vigreux column; b.p. 94–97°/0.3 mm.; n_D^{25} 1.5285–1.5291. The yield is 109–119 g., or 74–81% based on anisyl alcohol (Note 7) and (Note 8).

2. Notes

1. Givaudan-Delawanna (330 W. 42nd Street, New York 18, N. Y.) "Anisic Alcohol" of 97% minimum purity was used.
2. The crude anisyl chloride is unstable. It should be used the same day it is made.
3. This step should be performed in a well-ventilated hood.
4. The acetone is dried over about one-quarter its volume of granular calcium chloride for one day. The dried acetone is then filtered and distilled.
5. This residue should be discarded with due regard for the unused sodium cyanide it contains.
6. The undistilled *p*-methoxyphenylacetonitrile weighs 125–139 g. (85–95%) and has a refractive index close to that of the distilled product. It can be used for many purposes, such as condensation with aromatic aldehydes to yield α-*p*-methoxyphenylcinnamonitriles, without further purification.
7. The submitters have carried out this preparation on five times the scale described here with comparable yields.
8. This method is particularly applicable to the more reactive benzyl halides which are easily hydrolyzed in the aqueous media usually employed for the metathetical reaction with alkali cyanides. For example, anisyl chloride treated with sodium cyanide in aqueous dioxane gives, as a by-product, 5–10% of anisyl alcohol as determined by infrared analysis. The use of anhydrous acetone not only prevents hydrolysis to the alcohol but also decreases the formation of isonitriles. This method was also applied successfully by the submitters to the preparation of *p*-chlorophenylacetonitrile in 74% yield.

3. Discussion

This method is an adaptation of that of Dengel.[2] *p*-Methoxyphenylacetonitrile can also be prepared by the metathetical reaction of anisyl chloride with alkali cyanides in a variety of aqueous solvent mixtures;[3,4,5,6,7,8,9,10,11] by the nitration of phenylacetonitrile, followed by reduction, diazotization, hydrolysis, and methylation;[12,13] by the reduction of α-benzoxy-*p*-methoxyphenylacetonitrile (prepared from anisaldehyde, sodium cyanide, and benzoyl chloride);[14] by the reaction of acetic anhydride with the oxime of *p*-methoxyphenylpyruvic acid;[15] and through the condensation of *p*-methoxybenzaldehyde with rhodanine.[16]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

oxime of p-methoxyphenylpyruvic acid

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

acetic anhydride (108-24-7)

sodium cyanide (143-33-9)

sodium sulfate (7757-82-6)

acetone (67-64-1)

benzoyl chloride (98-88-4)

phenylacetonitrile (140-29-4)

Anisic Alcohol (90-05-1)

sodium iodide (7681-82-5)

dioxane (5703-46-8)

Rhodanine (141-84-4)

p-chlorophenylacetonitrile (140-53-4)

anisyl alcohol (150-76-5)

anisyl chloride (623-12-1)

anisaldehyde, p-methoxybenzaldehyde (123-11-5)

p-Methoxyphenylacetonitrile, Acetonitrile, p-methoxyphenyl- (104-47-2)

α-benzoxy-p-methoxyphenylacetonitrile

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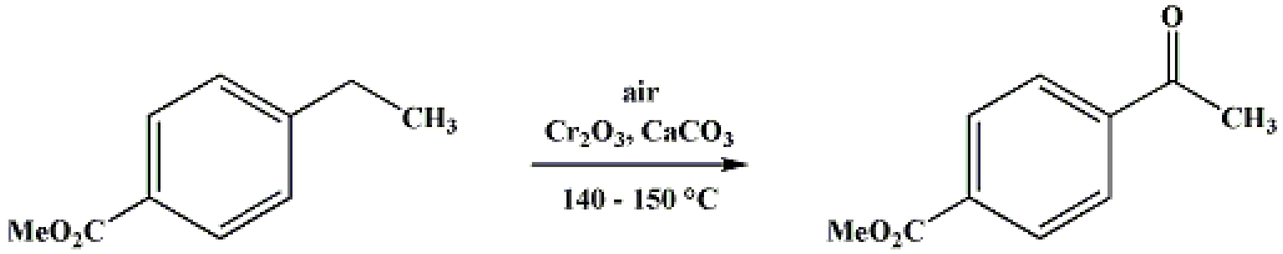
Organic Syntheses, CV 4, 579

METHYL *p*-ACETYLBENZOATE

[Benzoic acid, *p*-acetyl-, methyl ester]



Submitted by William S. Emerson and George F. Deebel[1].
Checked by Arthur C. Cope and Warren N. Baxter.

1. Procedure

A 200-ml. three-necked flask is equipped with a thermometer, a mechanical stirrer, a gas inlet tube extending as far into the flask as the stirrer permits, and a trap (designed to return the heavier layer of the condensate) (Note 1) which is attached to a bulb and a coil-type reflux condenser connected in series. Methyl *p*-ethylbenzoate (98 g., 0.6 mole) (Note 2) and a mixture of 1 g. of chromium oxide and 4 g. of calcium carbonate, prepared by grinding the solids together in a mortar, are added. An air line with a bleed control valve (Note 3) is connected from the top of the condenser to a water aspirator. The flask is heated with a hemispherical electric mantle (Note 4).

The mixture is stirred vigorously at a temperature of 140–150°, and air is drawn through it (Note 5). for 24 hours while the water formed is collected in the trap (Note 6). At the end of this period, the mixture is cooled, diluted with 100 ml. of benzene (Note 7), and filtered with suction to remove the catalyst (Note 8). The catalyst is washed with 10 ml. of benzene on the funnel, and the washings are combined with the filtrate. The benzene is distilled from the clear, yellow solution (conveniently at a pressure of 100 mm. or lower to avoid superheating and partial decomposition of the product) through a fractionating column (Note 9). After removal of the benzene, the pressure is reduced and the residue is fractionally distilled. There is obtained 29–32 g. of unreacted methyl *p*-ethylbenzoate (b.p. 118–121°/16 mm.), and 43–45 g. (40–42% conversion and 60% yield) of methyl *p*-acetylbenzoate; b.p. 149–150°/7 mm. (Note 10) and (Note 11). The high-boiling residue weighs 13–18 g. The crude methyl *p*-acetylbenzoate can be purified by crystallization from the minimum amount of 1:1 benzene-commercial hexane required for solution with a recovery of 82–85%, collected in two crops; m. p. 92–95°.

2. Notes

1. A Dean and Stark trap[2] modified to provide for continuous return of the heavier organic layer is most convenient. Such a trap can be constructed like a small Wehrli extractor.[3]
2. Methyl *p*-ethylbenzoate was prepared from ethylbenzene (1 kg.), which was converted

to *p*-ethylacetophenone by adding aluminum chloride (792 g.), followed by acetyl chloride (462 g.), which was added with stirring at 0–5° over a period of 3 hours. The mixture was stirred for 1 hour longer, allowed to stand overnight, and washed with iced dilute hydrochloric acid. The ethylbenzene was removed by distillation, and the crude product was oxidized to *p*-ethylbenzoic acid with alkaline hypochlorite.[4] Recrystallization of the crude acid from 95% ethanol yielded 350 g. (41%) of the pure acid; m.p. 110–112°. Esterification with methanol in the presence of hydrogen chloride[4] yielded methyl *p*-ethylbenzoate (77–79%).

3. A T-tube in the connection between the top of the condenser and the water aspirator is attached to a Bunsen burner. The needle valve of the burner serves as a bleed control valve, regulating the amount of air drawn through the reaction mixture.

4. An oil bath can be used.

5. The air stream should be introduced as rapidly as possible, preferably at a rate which will just permit return of the liquid from the coil condenser. It is equally satisfactory to force air through the mixture from a cylinder or compressed-air line if the air is clean and free from oil. Use of a rapid stream of air and vigorous stirring prevents the catalyst from settling.

6. Removal of the water should be as complete as possible, in order to prevent coagulation of the catalyst, which retards the oxidation.

7. The benzene serves to keep the methyl *p*-acetylbenzoate in solution. If crystallization occurs, the mixture should be warmed to dissolve the ester before filtration.

8. The catalyst should be removed completely, because distillation of the product in the presence of small amounts of the catalyst results in some decomposition with a corresponding lowering of the yield. Use of a filter aid such as Super-Cel aids in separating the catalyst.

9. The submitters used a 120-cm. Vigreux column in distilling the benzene and a 60-cm. Vigreux column in fractionating the product. The checkers used a Widmer column with a 17-cm. spiral for the entire distillation.

10. Cooling water should not be circulated through the condenser during distillation of the product, because the methyl *p*-acetylbenzoate tends to crystallize in the condenser.

11. The submitters have obtained similar yields (40–54% conversion and 60–66% yield) in oxidations on 10 times this scale.

3. Discussion

Methyl *p*-acetylbenzoate has been prepared by the esterification of *p*-acetylbenzoic acid with methanol in the presence of hydrogen chloride,[5] by the hydrogenation of methyl *p*-trichloroacetylbenzoate in the presence of a palladium on calcium carbonate catalyst,[6] and by the air oxidation of methyl *p*-ethylbenzoate.[4]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

benzene-commercial hexane

ethanol (64-17-5)

hydrogen chloride, hydrochloric acid (7647-01-0)

Benzene (71-43-2)

methanol (67-56-1)

acetyl chloride (75-36-5)

calcium carbonate (471-34-1)

aluminum chloride (3495-54-3)

palladium (7440-05-3)

ethylbenzene (100-41-4)

chromium oxide (1308-38-9)

Methyl p-acetylbenzoate, Benzoic acid, p-acetyl-, methyl ester (3609-53-8)

Methyl p-ethylbenzoate (7364-20-7)

p-ethylacetophenone (937-30-4)

p-ethylbenzoic acid (619-64-7)

p-acetylbenzoic acid (586-89-0)

methyl p-trichloroacetylbenzoate

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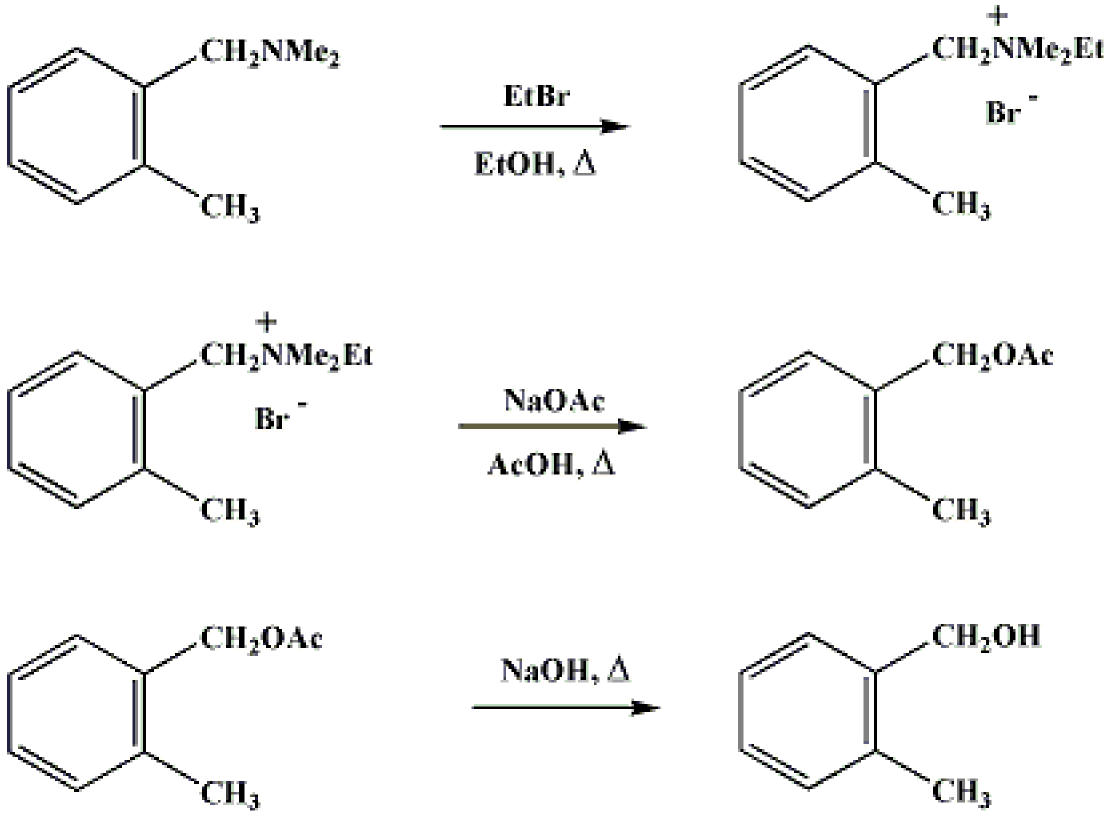
Organic Syntheses, *CV 4*, *582*

o-METHYLBENZYL ALCOHOL

[Benzyl alcohol, *o*-methyl-]



Submitted by W. R. Brasen and C. R. Hauser[1].
Checked by William S. Johnson, Donald W. Stoutamire, and A. L. Wilds.

1. Procedure

A. *o-Methylbenzyl acetate*. A solution of 29.8 g. (0.20 mole) of 2-methylbenzyldimethylamine (p.585) and 32.7 g. (0.30 mole) of ethyl bromide in 40 ml. of absolute ethanol is placed in a 500-ml. round-bottomed flask fitted with a reflux condenser capped with a calcium chloride drying tube. The solution is heated under reflux on the steam bath for 1 hour; then an additional 10.8 g. (0.10 mole) of ethyl bromide is added and the heating continued for an additional 3 hours. The solvent and residual ethyl bromide are removed to reduced pressure (water aspirator) while the flask is heated in a water bath kept at about 60° (Note 1). The oily residue is treated with about 300 ml. of absolute ether, and on scratching crystallization is induced. The product is collected on a Büchner funnel, washed with two 50-ml. portions of anhydrous ether, and dried in a vacuum desiccator. The yield of colorless 2-methylbenzylethyldimethylammonium bromide is 47.5–49.0 g. (92–95%) (Note 2). It is hygroscopic and should therefore not be exposed to moist air.

In a 500-ml. round-bottomed flask, fitted with a reflux condenser capped with a calcium chloride drying tube, are placed 38.7 g. (0.15 mole) of the quaternary ammonium bromide (Note 3) described above, 24.6 g. (0.3 mole) of fused sodium acetate, and 100 ml. of glacial acetic acid. The mixture is boiled under reflux for 24 hours (Note 4) and then allowed to cool. It is transferred to a large beaker (Note 5), 250 ml. of water is added, and the acid is partially neutralized by the addition of 84 g. of solid sodium bicarbonate. The mixture is extracted with three 75-ml. portions of ether, and the combined ether solutions are washed with two or more 50-ml. portions of saturated sodium bicarbonate solution until all the acetic acid has been removed. The ether layer is then washed with 50 ml. of saturated sodium chloride solution and dried over anhydrous sodium sulfate. The ether is removed by distillation, and the residue is distilled under reduced pressure. The yield of colorless liquid acetate, b.p. 119–121°/15 mm. or 129–131°/31 mm., is 21.6–22.4 g. (88–91%), n_D^{25} 1.5041–1.5045 (Note 6).

B. *o-Methylbenzyl alcohol*. A solution of 5 g. (0.12 mole) of sodium hydroxide in 50 ml. of water is added to a solution of 16.4 g. (0.1 mole) of 2-methylbenzyl acetate (prepared as described above, part A) in 50 ml. of methanol contained in a 250-ml. round-bottomed flask fitted with a reflux condenser. The mixture is boiled under reflux for 2 hours, cooled, diluted with 50 ml. of water, and extracted with three 75-ml. portions of ether. The combined ether solutions are washed with 50 ml. of water and 50 ml. of saturated sodium chloride solution and dried over anhydrous sodium sulfate. The solvent is removed by distillation, finally at reduced pressure to remove the last traces of methyl alcohol, and the residue is dissolved in 50 ml. of boiling 30–60° petroleum ether. The colorless crystals obtained on cooling, finally in the ice bath, are collected by suction filtration, washed with a few milliliters of cold petroleum ether, and air-dried. Concentration of the mother liquors to 6–7 ml. and cooling gives an additional crop. The total yield of product melting between 33–34° and 35–36° is 11.6–11.8 g. (95–97%) (Note 7).

2. Notes

1. A capillary ebullition tube is used to prevent bumping.
2. 2,3-Dimethylbenzylethyldimethylammonium bromide can be prepared similarly in comparable yield. The salts are suitable for use in the displacement reaction without purification.
3. The ethobromides are preferable to methiodides in this reaction, because the former salts are more soluble in glacial acetic acid and do not liberate halogen as do the iodides.
4. The sodium acetate dissolves as the mixture reaches reflux temperature, but a small amount of solid (perhaps sodium bromide) remains undissolved throughout the heating.
5. Considerable foaming may occur during the neutralization, and material may be lost if the process is carried out in a small narrow-mouthed vessel.
6. The submitters have used the same procedure for the preparation of 2,3-

dimethylbenzyl acetate from the corresponding quaternary salt (Note 2). The yield of material b.p. 127–129°/9 mm. was 94%.
7. Hydrolysis of 2,3-dimethylbenzyl acetate (Note 6) by this procedure gave 2,3-dimethylbenzyl alcohol, m.p. 65–66°, in 96% yield.

3. Discussion

The vicinal methylbenzyl alcohols have been prepared in general by the abnormal reaction of the appropriately substituted Grignard reagent with formaldehyde.[2] The present method is preferred over the former because it yields purer products than the Grignard approach.

o-Methylbenzyl alcohol also has been prepared by the lithium aluminum hydride reduction of *o*-toluic acid[3] or ethyl *o*-toluate,[4] and by the hydrolysis of *o*-xylyl bromide.[4]

References and Notes

1. Duke University, Durham, North Carolina. Work supported by the Office of Ordnance Research.
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

ethanol (64-17-5)

acetic acid (64-19-7)

methyl alcohol, methanol (67-56-1)

ether (60-29-7)

sodium acetate (127-09-3)

sodium hydroxide (1310-73-2)

formaldehyde (630-08-0)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

ammonium bromide (12124-97-9)

sodium bromide (7647-15-6)

Ethyl bromide (74-96-4)

sodium sulfate (7757-82-6)

lithium aluminum hydride (16853-85-3)

2,3-dimethylbenzyl alcohol (13651-14-4)

2-Methylbenzyldimethylamine (4525-48-8)

2-methylbenzylethyldimethylammonium bromide

2-methylbenzyl acetate, o-Methylbenzyl acetate (17373-93-2)

2,3-Dimethylbenzylethyldimethylammonium bromide

2,3-dimethylbenzyl acetate

o-Toluic acid (118-90-1)

o-Methylbenzyl alcohol, Benzyl alcohol, o-methyl- (89-95-2)

ethyl o-toluate (87-24-1)

o-xylyl bromide (576-23-8)

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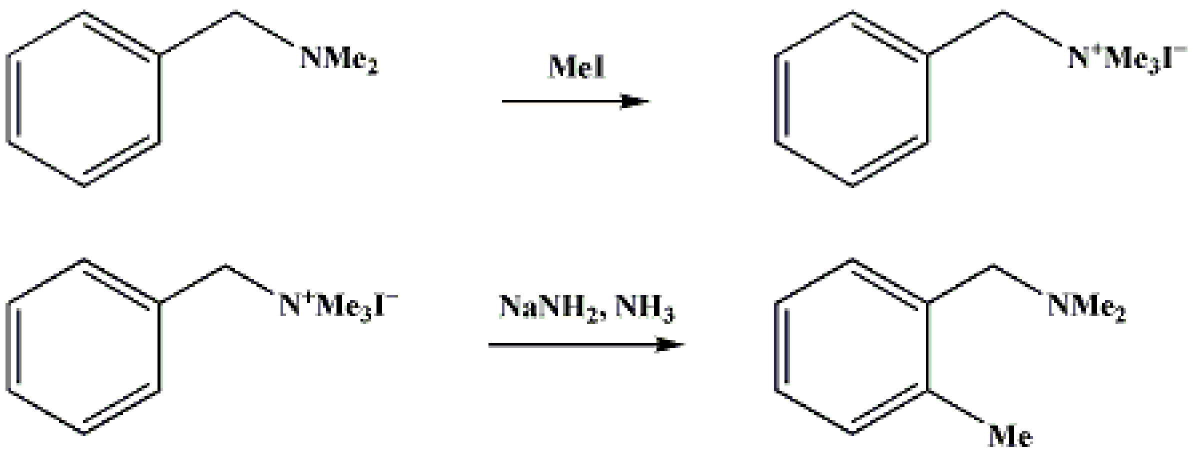
Organic Syntheses, CV 4, 585

2-METHYLBENZYLDIMETHYLAMINE

[Benzylamine, N,N,*o*-trimethyl-]



Submitted by W. R. Brasen and C. R. Hauser[1].
Checked by William S. Johnson, Mary E. Mills, and A. L. Wilds.

1. Procedure

A. *Benzyltrimethylammonium iodide.* A solution of 135 g. (1 mole) of N,N-dimethylbenzylamine (Note 1) in 200 ml. of commercial absolute ethanol (Note 2) is placed in a three-necked flask fitted with a 125-ml. dropping funnel, a reflux condenser, and a rubber slip-sleeve-sealed stirrer. The openings of the dropping funnel and condenser are protected from atmospheric moisture with drying tubes. While the solution is stirred rapidly, 190 g. (1.34 moles) of methyl iodide contained in the dropping funnel is added slowly at first, then at such a rate as to cause gentle refluxing of the solution. After the addition is complete (30 minutes), the solution is boiled under reflux on the steam bath for 30 minutes more and transferred to a 2-l. Erlenmeyer flask with the aid of an additional 25-ml. of absolute ethanol for rinsing. On cooling to room temperature a large portion of the methiodide crystallizes, and the remaining material is then precipitated by the addition of 1 l. of anhydrous ether with stirring (Note 3). The product is separated by suction filtration, washed with two 100-ml. portions of anhydrous ether (Note 4), and dried in air at room temperature. The yield of benzyltrimethylammonium iodide, m.p. 178–179° (dec.), is 260–274 g. (94–99%), and is pure enough for most purposes (Note 5).

B. *2-Methylbenzyldimethylamine*. *(Caution! This preparation should be conducted in a good hood to avoid exposure to ammonia).* To 800 ml. of liquid ammonia contained in a 2-l. three-necked flask fitted with a rubber slip-sleeve-sealed wire stirrer and an air-cooled reflux condenser, sodium is added in small pieces until the blue color persists (Note 6). At this point 0.5 g. of granulated ferric nitrate is added, and then 27.8 g. (1.2 g. atoms) of sodium (cut into approximately 0.5-g. pieces), is introduced at such a rate

that stirring is not hindered. After all the sodium has been added (about 15 minutes), the mixture is stirred until the blue color disappears and the grayish-black suspension of sodium amide remains (15–20 minutes). Stirring is discontinued, and the mixture is swirled to wash down the mirror of sodium which forms on the upper walls of the flask (Note 7).

A 500-ml. Erlenmeyer flask is charged with 277 g. (1 mole) of benzyltrimethylammonium iodide (prepared as described in Part A) and is connected with a short section of large-diameter rubber tubing to the third neck of the flask containing the sodium amide. Stirring is started, and the salt is shaken in at a steady rate and as rapidly as possible without serious loss of material through the condenser. This operation requires about 10–15 minutes (Note 8). The greenish-violet color, which is first produced by addition of the salt, persists for about 15 minutes after all the material has been added. During this and the subsequent reaction period, more ammonia is added as necessary to maintain the original volume. The mixture is stirred for an additional 2 hours, and then 27 g. (0.5 mole) of ammonium chloride is added cautiously to destroy excess sodium amide.

The flask is fitted with a dropping funnel, and enough (about 100 ml.) water is added, dropwise at first, to bring all the solid material into solution. The mixture is stirred until it reaches room temperature, 70 ml. of ether is added, and the organic layer is separated. The water layer is extracted with two 70-ml. portions of ether, and the combined ether solutions are washed with two 50-ml. portions of saturated salt solution and dried over anhydrous potassium carbonate. After filtration and removal of the ether by distillation, the amine is distilled through a 10-cm. Vigreux column. The fraction, b.p. 72–73°/9 mm.., 97–99°/13 mm., or 197–198°/atm., amounts to 134–141.5 g. (90–95% yield), n_D^{20} 1.5050–1.5060 (Note 8). On redistillation all but about 5% of the material is recovered, b.p. 78–79°/12 mm., n_D^{20} 1.5049–1.5052.

2. Notes

1. N,N-Dimethylbenzylamine supplied by the Rohm and Haas Company was used without purification.
2. Methanol may be substituted in the preparation of this as well as other quaternary salts, which, however, are generally more soluble in this medium and therefore require a larger volume of ether for complete precipitation.
3. This isolation procedure produces a granular product which is more desirable for use in the rearrangement reaction than the fluffy material obtained on rapid cooling.
4. The ether should be free of peroxides; otherwise iodine will be liberated from the salt and will color the product.
5. This procedure is suitable for the preparation of the following quaternary salts with changes only in the proportion of ethanol employed: 2-methylbenzyltrimethylammonium iodide, using 350 ml. of ethanol per mole of amine (yield 98–99%), and 2,3-dimethylbenzyltrimethylammonium iodide,

using 500 ml. of ethanol per mole of amine (yield 98–99%).
6. Only about 0.05 g. of sodium is required unless the ammonia is quite wet.
7. The complete removal of sodium is indicated by the lack of formation of blue coloration when the solution is swirled over the upper walls of the flask.
8. Essentially the same procedure may be used for the preparation of 2,3-dimethylbenzyldimethylamine from 2-methylbenzyltrimethylammonium iodide except that the time of addition of the latter to the sodium amide is increased to 75 minutes. The checkers found it necessary also to use a larger volume of ammonia. Thus, on a 0.3-mole scale, 1 l. of ammonia was employed, and a total of 600 ml. more ammonia was added during the reaction to maintain the volume at 800–1000 ml.
Owing to the formation of neutral side products, the reaction mixture is extracted with excess 4*N* hydrochloric acid, and the mixture of amines is liberated from the acid solution by neutralization with sodium hydroxide. The amine fraction is taken up in ether and dried over anhydrous sodium sulfate or solid sodium hydroxide. After removal of the ether, the 2,3-dimethylbenzyldimethylamine distils at 101–102°/15 mm., 107–109°/19 mm., n_D^{23} 1.5100–1.5102. The yield is 60–70%.

3. Discussion

This procedure is based on the method of Kantor and Hauser.[2] 2-Methylbenzyldimethylamine has also been prepared from *o*-xylyl bromide and hexamethylenetetramine.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 508
- Org. Syn. Coll. Vol. 4, 582

References and Notes

1. Duke University, Durham, North Carolina. Work supported by the Office of Ordnance Research.
2. Kantor and Hauser, *J. Am. Chem. Soc.*, **73**, 4122 (1951).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

methanol (67-56-1)

ether (60-29-7)

ammonium chloride (12125-02-9)

sodium hydroxide (1310-73-2)

sodium sulfate (7757-82-6)

iodine (7553-56-2)

sodium (13966-32-0)

Methyl iodide (74-88-4)

hexamethylenetetramine (100-97-0)

sodium amide (7782-92-5)

ferric nitrate

2,3-dimethylbenzyltrimethylammonium iodide

2,3-dimethylbenzyldimethylamine (15848-75-6)

2-Methylbenzyldimethylamine, Benzylamine, N,N,o-trimethyl- (4525-48-8)

N,N-dimethylbenzylamine (103-83-3)

benzyltrimethylammonium iodide

2-methylbenzyltrimethylammonium iodide

o-xylyl bromide (576-23-8)

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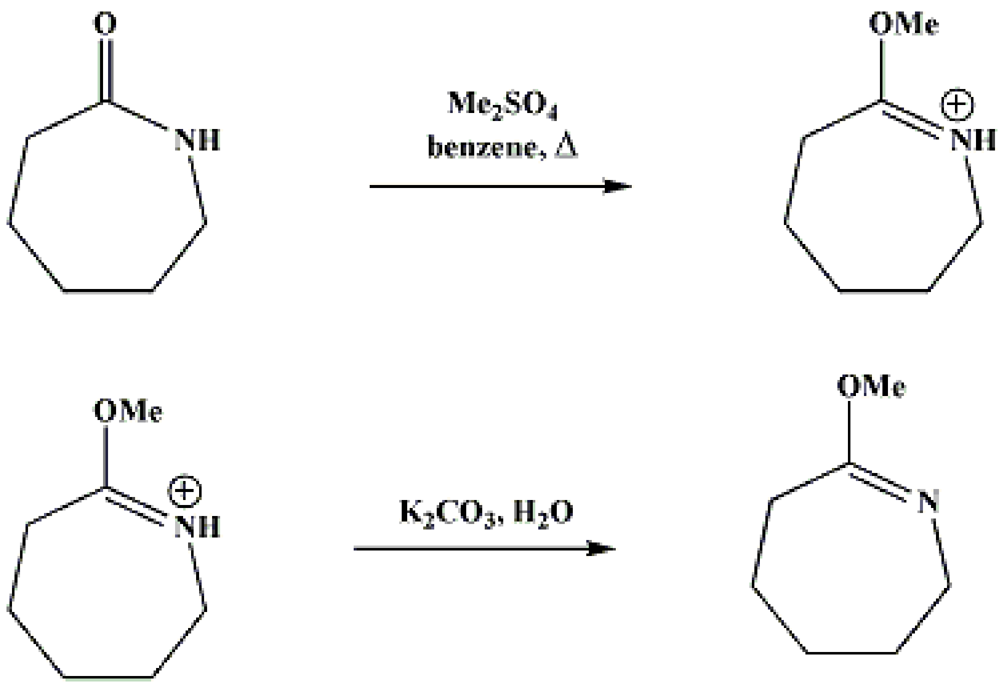
Organic Syntheses, CV 4, 588

O-METHYLCAPROLACTIM

[2H-Azepine, 7-methoxy-3,4,5,6-tetrahydro-]



Submitted by Richard E. Benson and Theodore L. Cairns[1].
Checked by Charles C. Price, Kenneth N. Campbell, and Richard Mcbride.

1. Procedure

In a 5-l. three-necked flask equipped with a reflux condenser, a sealed mechanical stirrer, and a 1-l. dropping funnel are placed 678 g. (6.0 moles) of ε-caprolactam[2] and 2 l. of benzene (Note 1). The mixture is heated on a steam bath to reflux temperature, during which time all the solid dissolves. At this point 569 ml. (757 g., 6.0 moles) of dimethyl sulfate (Note 1) is added with stirring in a thin stream through the dropping funnel. The rate is about 4 ml. per minute, and the addition requires 2.5 hours. The stirring and heating are continued for an additional 2 hours, during which time two separate phases appear in the reaction mixture. The stirring is then discontinued and the mixture is heated under reflux for an additional 14 hours.

The mixture is cooled to room temperature, and 600 ml. of 50% potassium carbonate is added slowly through the dropping funnel with stirring (Note 2) to the reaction mixture over a period of 30 minutes. After the vigorous evolution of carbon dioxide has subsided, the mixture is stirred (Note 2) slowly for 30 minutes. The potassium methyl sulfate (Note 3) present is removed by filtration, the solid filter cake is washed with two 100-ml. portions of ether,and the washings are combined with the original filtrate. The filtrate is transferred to a 4-l. separatory funnel, the aqueous layer

withdrawn, and the organic layer transferred to a 3-l. round-bottomed flask. The ether and benzene are removed by distillation at slightly reduced pressure (200–600 mm.) and the product distilled through an 8-in. Vigreux column. After a fore-run of benzene and O-methylcaprolactim, the fraction boiling at 65–67°/24 mm., n_D^{25} 1.4610, d_4^{25} 0.9598, is collected. The yield is 450–473 g. (59–62%). An additional quantity of the imino ether can be recovered from the fore-run by distillation through an efficient column, making the total yield 463–517 g. (61–68%) (Note 4).

2. Notes

1. Commercial grade reagents were used throughout. The ε-caprolactam was obtained from the Explosives Department, E. I. du Pont de Nemours and Company, Inc., Wilmington, Delaware.
2. Vigorous stirring at this point should be avoided or otherwise an emulsion will be formed that is difficult to break.
3. The solid that separated was not identified, but it was presumed to be potassium methyl sulfate.
4. The corresponding O-ethyl derivative (b.p. 81–82°/26 mm.) can be prepared in 52% yield by a similar procedure.

3. Discussion

O-Methylcaprolactim has been prepared by the reaction of cyclohexanone oxime, *p*-toluenesulfonyl chloride, and methanol;[3] and by the procedure[4] described above, which is a modification of the method given in the patent literature.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 263

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

potassium carbonate (584-08-7)

Benzene (71-43-2)

methanol (67-56-1)

ether (60-29-7)

carbon dioxide (124-38-9)

dimethyl sulfate (77-78-1)

ε-caprolactam (105-60-2)

Cyclohexanone oxime (100-64-1)

O-Methylcaprolactim, 2H-Azepine, 7-methoxy-3,4,5,6-tetrahydro- (2525-16-8)

potassium methyl sulfate (562-54-9)

p-Toluenesulfonyl chloride (98-59-9)

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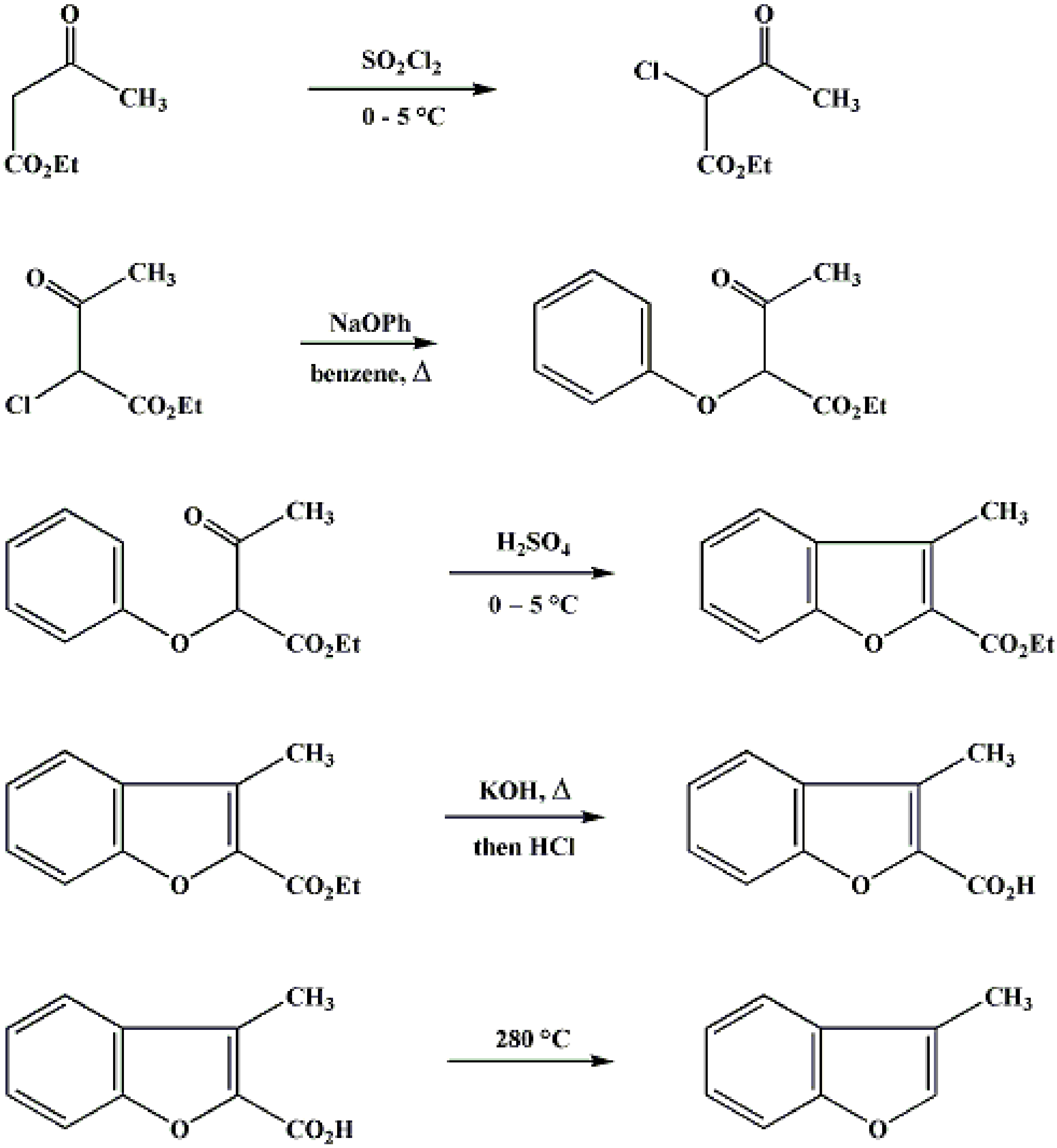
Organic Syntheses, CV 4, 590

3-METHYLCOUMARONE

[Benzofuran, 3-methyl-]



Submitted by Werner R. Boehme[1]
Checked by James Cason and Kenneth L. Rinehart.

1. Procedure

A. *Ethyl 3-methylcoumarilate*. Dry sodium phenolate (116 g., 1 mole) (Note 1) and 1 l. of dry thiophene-free benzene (Note 2) are placed in a 2-l. three-necked flask fitted with

mechanical stirrer, dropping funnel, and reflux condenser with drying tube. The suspension is heated to the boiling point on the steam bath, heating is moderated, and 165 g. (1 mole) of ethyl α-chloroacetoacetate (Note 3) is added with stirring through the dropping funnel at such a rate as to maintain gentle refluxing (Note 4). Refluxing and stirring are continued on the steam bath for 4 hours after the addition of the chloroester has been completed. The light brown suspension is cooled to room temperature, extracted with two 500-ml. portions of water, and dried superficially by filtration through a layer of anhydrous magnesium sulfate. The solvent is removed by distillation on the steam bath under water-aspirator vacuum. The brown oil remaining consists of crude ethyl α-phenoxyacetoacetate and weighs 188–200 g. (85–90%).

Concentrated sulfuric acid (195 ml.) is placed in a 2-l. three-necked flask immersed in an ice-salt bath and fitted with a dropping funnel, a thermometer, and a mechanical stirrer. Ethyl α-phenoxyacetoacetate (195 g.) is added with stirring through the dropping funnel while the temperature within the flask is maintained below 5°. About 1 hour is required for the addition. The mixture, which solidifies soon after all the ester has been added, is allowed to stand in the ice bath for 1 hour longer. Ice (500 g.) and water (500 ml.) are added with stirring and external cooling. The mixture is then extracted with two 250-ml. portions of benzene. The combined extracts are washed with 100 ml. of water, then with 100 ml. of saturated aqueous sodium bi-carbonate solution, and finally are dried superficially by filtration through a layer of anhydrous magnesium sulfate. The solvent is distilled from the dried extracts, and the residue is fractionated under reduced pressure from a 250-ml. Claisen flask fitted with a short air condenser. The pale-yellow oil boils at 162–167°/16 mm. and solidifies on cooling. The product is triturated with a little petroleum ether (b.p. 35–60°) and dried at room temperature. The almost colorless rhombic plates, melting at 49–51°, weigh 60–75 g. (34–42%).

B. *3-Methylcoumarilic acid.* Ethyl 3-methylcoumarilate (70 g.) and 500 ml. of 10% aqueous potassium hydroxide solution are refluxed for 1 hour. The clear yellowish solution is acidified while hot (Note 5) with a slight excess of concentrated hydrochloric acid to precipitate the 3-methylcoumarilic acid. The suspension is cooled to room temperature, and the colorless solid is filtered with suction. The filter cake is resuspended in 500 ml. of cold water, stirred vigorously for several minutes, and filtered again with suction. The colorless powder, after being dried in a desiccator under reduced pressure, weighs 54–57 g. (90–95%) and melts at 192–193°.

C. *3-Methylcoumarone*. Dry 3-methylcoumarilic acid (50 g.) is distilled from a 250-ml. Claisen flask fitted with a long air condenser and immersed in a Wood's metal bath heated slowly to 280°. Carbon dioxide is evolved, and a cloudy liquid distils at 190–220°. The crude product is purified by redistillation through a Vigreux column (Note 6). The clear colorless distillate, weighing 31.5–33 g. (84–88%), boils at 195–197°, n_D^{25} 1.5520.

2. Notes

1. Sodium phenolate may be prepared *in situ* by evaporating molar equivalents of phenol and sodium hydroxide solution in the reaction flask on the steam bath under reduced pressure and drying the residue by heating the flask for several hours longer

on the steam bath under reduced pressure. The solid cake of dry sodium phenolate breaks up in the succeeding step of the synthesis.
2. Benzene is conveniently dried by slowly distilling about 20% of it and cooling the residue with protection from atmospheric moisture by use of a calcium chloride tube.
3. Ethyl α-chloroacetoacetate is prepared by the general method of Allihn.[2] *Caution! Since the substance is a severe lachrymator and gases evolved during the preparation are difficult to absorb, the entire preparation should be carried out in a hood.* In a 1-l. three-necked flask fitted with dropping funnel, a thermometer, and a mechanical stirrer, and connected to a gas-absorption trap,[3] is placed 260 g. (2 moles) of technical grade ethyl acetoacetate. Sulfuryl chloride (270 g., 2 moles) is added slowly with stirring and external cooling, the temperature being maintained between 0° and 5°. About 3 hours is required for the addition. The solution is allowed to stand overnight at room temperature, and hydrogen chloride and sulfur dioxide are removed at 40–50° under water-aspirator vacuum. The residual dark-amber liquid is distilled through a short Vigreux column at reduced pressure. After a small fore-run, the ethyl α-chloroacetoacetate distils at 85–89°/17 mm. The yield of colorless liquid is 308–321 g. (93–97%). The checkers, using a 12-cm. unheated Vigreux column, obtained this yield only after redistilling the combined fore-run and after-run. Ethyl α-chloroacetoacetate is currently available from Distillation Products Industries, Rochester, New York.
4. The time of addition is 20–30 minutes. Some external heating is usually necessary to maintain reflux during the addition.
5. If the solution is allowed to cool much below 70° the potassium salt of 3-methylcoumarilic acid crystallizes in the form of colorless needles.
6. The checkers used an 18-in. Podbielniak column with simple wire spiral, heated jacket, and partial-reflux head.

3. Discussion

3-Methylcoumarone has been prepared by the cyclization of ethyl α-phenoxyacetoacetate followed by hydrolysis and de-carboxylation of the resulting ethyl 3-methylcoumarilate,[4] by debromination and rearrangement of 3,4-dibromo-4-methyl-coumarin to 3-methylcoumarilic acid followed by decarboxylation,[4,5] by cyclization of phenoxyacetone with concentrated sulfuric acid,[6] and by treatment of 3-coumaranone with methyl-magnesium iodide followed by dehydration of the resulting carbinol.[7]

The procedure described is a modification of the method of Hantzsch.[4]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

hydrogen chloride, hydrochloric acid (7647-01-0)

Benzene (71-43-2)

sodium hydroxide (1310-73-2)

phenol (108-95-2)

sulfur dioxide (7446-09-5)

carbon dioxide (124-38-9)

sulfuryl chloride (7791-25-5)

potassium hydroxide (1310-58-3)

methyl-magnesium iodide (917-64-6)

Ethyl acetoacetate (141-97-9)

sodium phenolate

magnesium sulfate (7487-88-9)

3-Methylcoumarone, Benzofuran, 3-methyl- (21535-97-7)

ethyl α-chloroacetoacetate (609-15-4)

ethyl α-phenoxyacetoacetate

sodium bi-carbonate

3,4-dibromo-4-methyl-coumarin

phenoxyacetone (621-87-4)

3-coumaranone (7169-34-8)

Ethyl 3-methylcoumarilate (22367-82-4)

3-Methylcoumarilic acid (24673-56-1)

potassium salt of 3-methylcoumarilic acid

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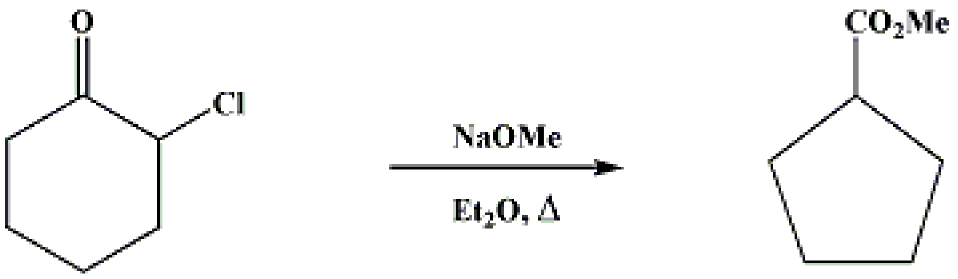
Organic Syntheses, CV 4, 594

METHYL CYCLOPENTANECARBOXYLATE

[Cyclopentanecarboxylic acid, methyl ester]



Submitted by D. W. Goheen and W. R. Vaughan[1].
Checked by N. J. Leonard, M. J. Konz, W. H. Pittman, and K. L. Rinehart, Jr..

1. Procedure

A dry 1-l. three-necked, round-bottomed flask is equipped with an efficient stirrer (Note 1), a spiral reflux condenser, and a dropping funnel, and all openings are protected by calcium chloride drying tubes. A suspension of 58 g. (1.07 moles) of sodium methoxide (Note 2) and (Note 3) in 330 ml. of anhydrous ether (Note 4) is added, and stirring is begun. To the stirred suspension is added dropwise a solution of 133 g. (1 mole) of 2-chlorocyclohexanone[2] (Note 5) and (Note 6) diluted with 30 ml. of dry ether. The exothermic reaction is regulated by the rate of addition of the chloroketone; about 40 minutes is required for the addition. After the addition of the chloroketone is complete, the mixture is stirred and heated under reflux for 2 hours (Note 7) and is then cooled. Water is added until the salts are dissolved (Note 8). The ether layer is separated, and the aqueous layer is saturated with sodium chloride. After extraction of the aqueous layer two 50-ml. portions of ether, the ethereal solutions are combined and washed successively with 100-ml. portions of 5% hydrochloric acid, 5% aqueous sodium bicarbonate solution, and saturated sodium chloride solution. The ether solution is dried over magnesium sulfate, and the magnesium sulfate is removed by filtration and washed with ether. Removal of the ether by distillation at atmospheric pressure leaves the crude ester, which is distilled, with fractionation (Note 9), at 70–73°/48 mm., n_D^{25} 1.4341. The yield of methyl cyclopentanecarboxylate is 72–78 g. (56–61%) (Note 10).

2. Notes

1. A mercury seal and a Hershberg stirrer made from tantalum wire are suitable.
2. Commercial (Matheson Co., Inc.) sodium methoxide is most convenient. The reaction can be run using sodium methoxide prepared from sodium and methanol, but this procedure is more tedious since it requires the removal of a

considerable amount of methanol.
3. A slight excess of sodium methoxide should always be used. When an equivalent amount is employed, slightly lower yields are obtained.
4. Commercial anhydrous analytical reagent ether, from sealed cans, was employed by the checkers without further drying.
5. The 2-chlorocyclohexanone[2] employed by the checkers had b.p. 98–99°/14.5 mm., n_D^{25} 1.4826. Purity is critical in determining the yield of methyl cyclopentanecarboxylate.
6. Chlorocyclohexanone is added to the sodium methoxide, since the reverse mode of addition results in lower yields through increased formation of high-boiling condensation products.
7. The submitters report that equivalent yields are obtained when the mixture is allowed to stand overnight after the addition of the chloroketone is complete.
8. The checkers found that approximately 175 ml. of water is required.
9. The checkers employed a Podbielniak column, 0.8 × 125 cm., with tantalum wire spiral and partial reflux head.[3]
10. The residue of higher-boiling material arises from the condensation of both the starting material and the product under the influence of sodium methoxide.

3. Discussion

Methyl cyclopentanecarboxylate has been prepared by the Favorskii rearrangement of 2-chlorocyclohexanone with sodium methoxide.[4] Other alkyl esters of cyclopentanecarboxylic acid have been prepared by employing the corresponding alkoxides with 2-chlorocyclohexanone.[4,5,6] The Favorskii reaction has been reviewed elsewhere.[7]

The methyl ester has also been obtained by esterification of cyclopentanecarboxylic acid.[8] The acid in turn, has been prepared by the Favorskii rearrangement,[6,7,9,10,11] by the reaction of cyclopentyl Grignard reagent with carbon dioxide,[12] by the carbonylation of cyclopentyl alcohol with nickel carbonyl[13] or with formic acid in the presence of sulfuric acid,[14] by the hydrogenation of cyclopentene-1-carboxylic acid prepared from ethyl cyclopentanone-2-carboxylate[15] or from cyclopentanone cyanohydrin,[16] and from cyclopentene and carbon monoxide in the presence of sulfuric acid.[17]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

methanol (67-56-1)

ether (60-29-7)

carbon monoxide (630-08-0)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

formic acid (64-18-6)

carbon dioxide (124-38-9)

sodium methoxide (124-41-4)

sodium (13966-32-0)

magnesium sulfate (7487-88-9)

ethyl cyclopentanone-2-carboxylate (611-10-9)

cyclopentyl alcohol (96-41-3)

Cyclopentene (142-29-0)

nickel carbonyl

2-Chlorocyclohexanone, chlorocyclohexanone (822-87-7)

Methyl cyclopentanecarboxylate, Cyclopentanecarboxylic acid, methyl ester (4630-80-2)

cyclopentanecarboxylic acid (3400-45-1)

cyclopentene-1-carboxylic acid

cyclopentanone cyanohydrin

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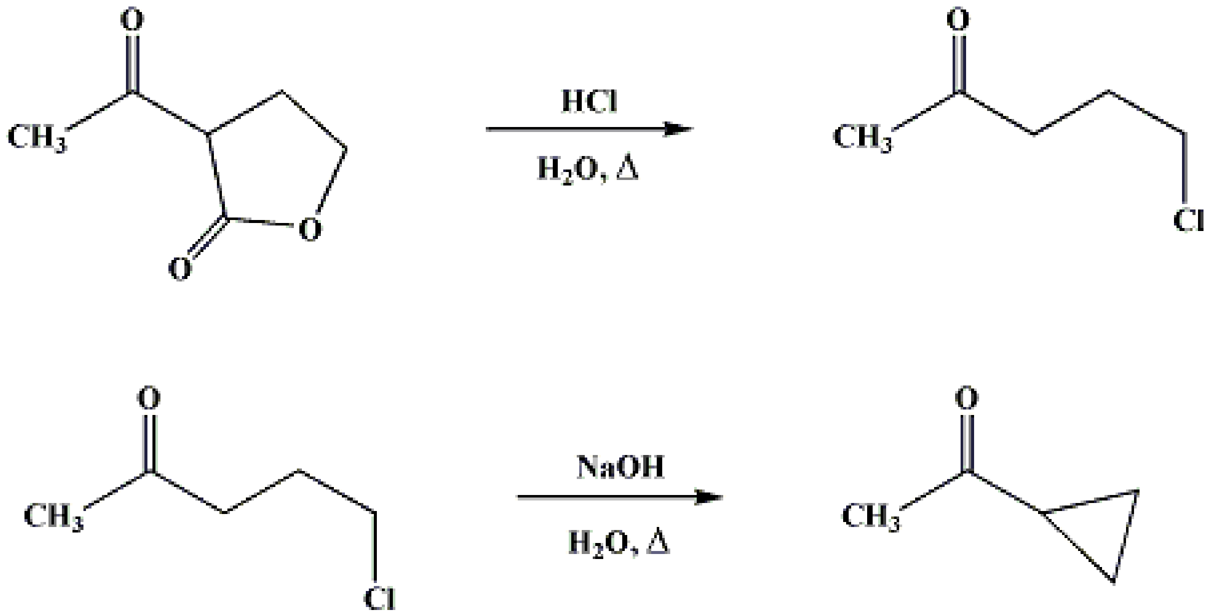
Organic Syntheses, CV 4, 597

METHYL CYCLOPROPYL KETONE

[Ketone, cyclopropyl methyl]



Submitted by George W. Cannon, Ray C. Ellis, and Joseph R. Leal[1].
Checked by R. S. Schreiber, Wm. Bradley Reid, Jr., and R. D. Birkenmeyer.

1. Procedure

A. *5-Chloro-2-pentanone.* A mixture of 450 ml. of concentrated hydrochloric acid, 525 ml. of water, and 384. g. (3 moles) of α-acetyl-γ-butyrolactone (Note 1) and a boiling chip are placed in a 2-l. distilling flask fitted with a 90-cm. bulb-type condenser and a receiver immersed in an ice water bath (Note 2). Carbon dioxide is evolved immediately. Heating of the reaction mixture is begun at once, and the temperature is raised at such a rate that the reaction mixture does not foam into the condenser. In about 10 minutes the color changes from yellow to orange to black, the effervescence begins to subside, and distillation commences. The distillation is continued as rapidly as possible (Note 3). After 900 ml. of distillate has been collected, 450 ml. of water is added to the distilling flask and another 300 ml. of distillate is collected.

The yellow organic layer in the distillate is separated (Note 4), and the aqueous layer is extracted with three 150-ml. portions of ether. The ether extracts are combined with the organic layer and dried for 1 hour over 25 g. of calcium chloride. A saturated calcium chloride layer forms in the bottom. The ether solution is decanted and dried with an additional 25 g. of calcium chloride. The ether is removed by distillation through a 30-cm. column packed with glass helices and fitted with a total condensation, variable take-off head. The residual crude 5-chloro-2-pentanone weighs

287–325 g. (79–90%) (Note 5). When 290 g. of this material is fractionated through a wrapped 12-in. Vigreux column, the major portion boils at 70–72°/20 mm., n_D^{25} 1.4371, and weighs 258–264 g. (89–91%).

B. *Methyl cyclopropyl ketone*. A 2-l. three-necked flask is fitted with a sweep-type stirrer made from -in. iron rod (Note 6), a reflux condenser, and a 500-ml. dropping funnel. In the flask is placed a solution of 180 g. (4.5 moles) of sodium hydroxide pellets in 180 ml. of water. To this solution is added over a period of 15–20 minutes 361.5 g. (342 ml., approximately 3 moles) of the crude 5-chloro-2-pentanone (Note 7). If the reaction mixture does not begin to boil during the addition, boiling is initiated by slight heating of the flask and is continued for 1 hour. Three hundred and seventy milliliters of water is then added slowly to the reaction mixture over a 20-minute period, and the mixture is heated under reflux for an additional hour.

The condenser is arranged for distillation, and a water-ketone mixture is distilled until all the organic layer is removed from the reaction mixture. The aqueous layer of the distillate is saturated with potassium carbonate, and the upper layer of methyl cyclopropyl ketone is separated. The aqueous layer is extraced with two 150-ml. portions of ether. The ether extracts and the ketone layer are combined and dried over 25 g. of calcium chloride for 1 hour. The ether solution is decanted and dried with an additional 25 g. of calcium chloride. The dried ether solution is fractionated through the 30-cm. column described in Part A (Note 8). The yield of methyl cyclopropyl ketone, b.p. 110–112°, n_D^{25} 1.4226, is 193–210 g. (77–83%).

2. Notes

1. Available from U. S. Industrial Chemicals, Inc. Its preparation has been described by several workers.[2,3,4]
2. Efficient condensation is important; otherwise some of the product is swept out by the carbon dioxide, and the yield of the chloride is decreased.
3. Any delay in distilling the chloride results in a decrease in yield. If the reaction mixture is allowed to stand overnight before removal of the chloride, the yield is less than 50%.
4. The chloride is usually the bottom layer. However, occasionally some of it also will be found on top. If so, the addition of 50–100 ml. of ether will cause all the chloride to be in the upper layer and will facilitate separation.
5. Corresponding runs beginning with 128 g. (1 mole) of α-acetyl-γ-butyrolactone gave 107–112 g. (89–93%) of crude 5-chloro-2-pentanone. The checkers consistently obtained yields of 79–81% using U. S. Industrial Chemicals, Inc., lactone.
6. A Hershberg stirrer constructed with a -in. iron or stainless-steel shaft is also satisfactory. Glass stirrers are not recommended because they may break.
7. The use of distilled chloride does not result in better over-all yields.
8. A fractionating column is necessary for the separation of the ether-ketone solution. With an ordinary distilling flask, a ketone-ether mixture, b.p. 41°, is

obtained with a resultant decrease in the yield of pure ketone. A well-insulated or preferably heated column is necessary for good fractionation.

3. Discussion

Methyl cyclopropyl ketone has been prepared from ethyl acetoacetate and ethylene bromide,[5] and by the action of methylmagnesium bromide on cyclopropyl cyanide.[6,7] The procedure described for its preparation from 5-chloro-2-pentanone is similar to that of Zelinsky and Dengin[8] and has been employed by Smith and Rogier.[9] Methyl cyclopropyl ketone also has been obtained by heating trimethyl-γ-acetopropylammonium bromide[10] or 5-bromo-2-pentanone with potassium hydroxide.[11]

5-Chloro-2-pentanone has been prepared by a number of methods,[12] including treatment of acetopropyl alcohol with gaseous hydrogen chloride.[13] The procedure given is essentially that of Boon[14] and of Forman.[15] A similar procedure has been used for the preparation of the corresponding bromo-and iodoketones.[14]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 278

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

calcium chloride (10043-52-4)

potassium carbonate (584-08-7)

hydrogen chloride, hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium hydroxide (1310-73-2)

carbon dioxide (124-38-9)

potassium hydroxide (1310-58-3)

ethylene bromide (106-93-4)

Ethyl acetoacetate (141-97-9)

α-acetyl-γ-butyrolactone (517-23-7)

methylmagnesium bromide (75-16-1)

Cyclopropyl cyanide (5500-21-0)

Methyl cyclopropyl ketone, Ketone, cyclopropyl methyl (765-43-5)

acetopropyl alcohol (1071-73-4)

5-Chloro-2-pentanone (5891-21-4)

trimethyl-γ-acetopropylammonium bromide

5-bromo-2-pentanone

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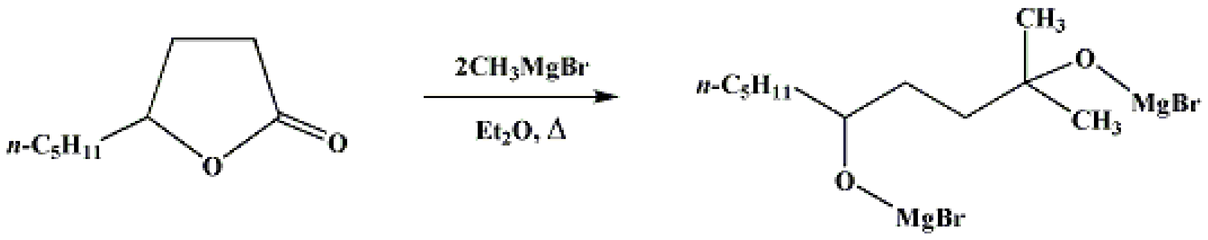
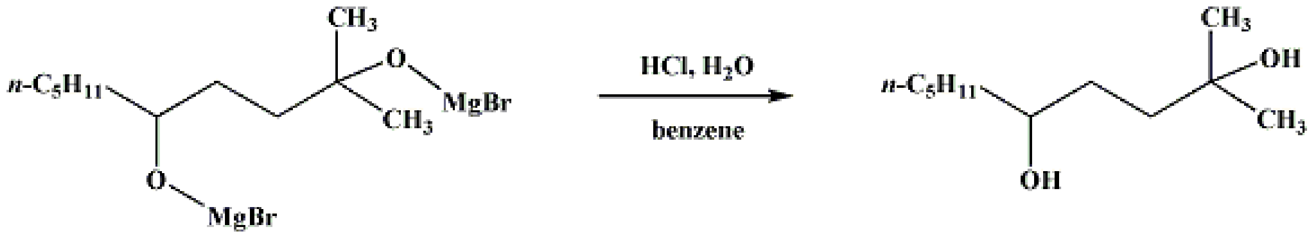
Organic Syntheses, CV 4, 601

2-METHYL-2,5-DECANEDIOL

[2,5-Decanediol, 2-methyl-]





Submitted by J. Colonge and R. Marey[1].
Checked by V. Boekelheide and H. Kaempfen.

1. Procedure

A 2-l. flask containing 1.0 l. of anhydrous ether (Note 1) is fitted with a stopper bearing an inlet tube dipping below the surface of the ether and an outlet tube protected by a calcium chloride drying tube. After the ether has been cooled thoroughly in an ice-salt bath, the flask is placed on a balance and cold methyl bromide (Note 2) is introduced through the inlet tube until the gain in weight is 200 g. (2.1 moles).

In a 3-l. three-necked flask, equipped with a sealed mechanical stirrer, reflux condenser, and a pressure-equalizing separatory funnel (Note 3), are placed 48 g. (2 g. atoms) of magnesium turnings, 500 ml. of anhydrous ether, and a small crystal of iodine. The cold methyl bromide solution is transferred to the separatory funnel and slowly added, with stirring. The reaction starts spontaneously, and the remainder of the methyl bromide is added at a rate such that the solution boils gently under reflux. Generally, the addition is complete at the end of 1–2 hours and all the magnesium should be dissolved. After the stirred solution of methylmagnesium bromide is well cooled by using an ice bath, a solution of 78.0 g. (0.5 mole) of γ-nonanoic lactone (Note 4) in 100 ml. of dry ether is added slowly over a period of 30 minutes. When the addition is complete, the mixture is placed on a steam bath and boiled under reflux for 2 hours. Then the condenser is arranged for downward distillation (Note 5), and the ether is removed.

To the thick, syrupy residue is added 200 ml. of benzene, and, after the solution is cooled in an ice bath and the condenser is set for reflux, 350 ml. of water is slowly added through the separatory funnel, with stirring. This is followed by the cautious addition of 325 ml. of a 20% solution of hydrochloric acid, and stirring is continued untill all the precipitate dissolves. The organic layer is then separated, and the aqueous layer and flask are washed with 50 ml. benzene. The combined benzene extracts are washed successively with water, a 5% solution of sodium carbonate, and again with water. Concentration of the benzene solution gives 88.5 g. of an oily residue. Careful fractional distillation (Note 6) of this residue gives, after a fore-run, 53.0 g. (57%) of the pure 2-methyl-2,5-decanediol boiling at 65–69°/2 mm., n_D^{25} 1.4420.

2. Notes

1. Commercial anhydrous ether should be dried over sodium or sodium hydride before use.
2. Commercial methyl bromide (Eastman Kodak Company, Rochester, New York) was used without purification.
3. The separatory funnel is fitted to an adapter tube extending to the bottom of the flask so that the methyl bromide solution is introduced below the surface of the mixture. A drying tube is placed in the condenser outlet.
4. Commercial γ-nonanoic lactone (Aldrich Chemical Co., Milwaukee, Wisconsin) was purified by distillation prior to use. The refractive index of the pure lactone is n_D^{25} 1.4449.
5. As the removal of ether proceeds, the viscous solution becomes difficult to stir and stirring may be stopped without harm.
6. The checkers found that an ordinary Vigreux column wasineffective in separating lower-boiling impurities. An efficient fractionating column 1m. in length and of 5 mm. I.D. gave excellent results. The infrared spectrum of the product gave no evidence of impurities.

3. Discussion

The preparation of 2-methyl-2,5-decanediol has not been described elsewhere in the literature.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 350

References and Notes

1. École de Chimie Industrielle de Lyon and Établissement Descollonges Frères (Lyon).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether (60-29-7)

magnesium, magnesium turnings (7439-95-4)

sodium carbonate (497-19-8)

iodine (7553-56-2)

sodium (13966-32-0)

methyl bromide (74-83-9)

methylmagnesium bromide (75-16-1)

sodium hydride (7646-69-7)

2-Methyl-2,5-decanediol, 2,5-Decanediol, 2-methyl- (53731-34-3)

γ-nonanoic lactone (104-61-0)

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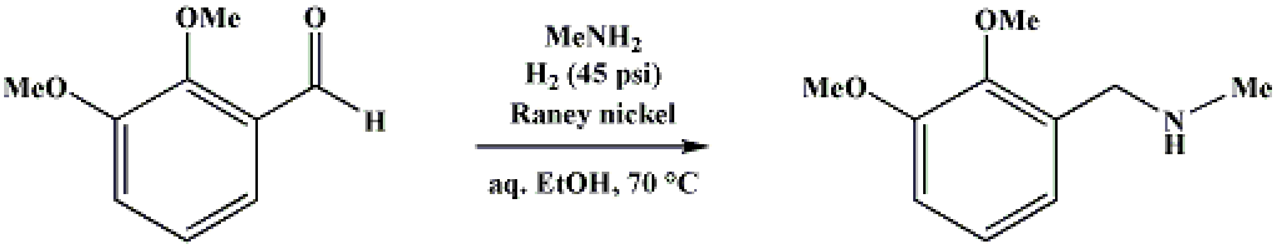
Organic Syntheses, CV 4, 603

N-METHYL-2,3-DIMETHOXYBENZYLAMINE

[Benzylamine, 2,3-dimethoxy-N-methyl-]



Submitted by Don M. Balcom and C. R. Noller[1].
Checked by Homer Adkins and Walter W. Gilbert.

1. Procedure

To a solution of 41.6 g. (0.25 mole) of purified 2,3-dimethoxybenzaldehyde (Note 1) in 150 ml. of 95% ethanol is added 23.4 g. (0.75 mole) of methylamine in 50 to 75 ml. of water (Note 2). The mixture is heated to boiling and placed in a 500-ml. heavywalled bottle (Note 3), and 6 g. of Raney nickel catalyst is added (Note 4). The bottle is connected to a low-pressure hydrogenation apparatus,[2] the system is flushed with hydrogen, and the mixture is shaken with hydrogen at an initial pressure of 45 lb. until 0.25 mole of hydrogen is absorbed and the absorption ceases (Note 5).

After the completion of the reduction the catalyst is removed by filtration and the alcohol is evaporated on the steam bath. To the resulting syrupy solution is added about 85 ml. of 3*N* hydrochloric acid (sufficient to make the solution acid to Congo red paper). The solution is extracted with three 50-ml. portions of ether. The aqueous layer is made alkaline with 50 ml. of 6*N* sodium hydroxide, and the amine layer is separated. The aqueous layer is extracted with three 50-ml. portions of ether, and the extracts are combined with the amine layer. The ether solution is dried overnight with solid potassium hydroxide and is filtered to remove suspended matter; the flask is rinsed with 25 ml. of ether. The ether is removed on a steam bath, and the amine is distilled under reduced pressure from a modified Claisen flask having a 15-cm. indented column. The N-methyl-2,3-dimethoxybenzylamine distils at 120–124°/8 mm. and is obtained in a yield of 39–42 g. (86–93%) (Note 6) and (Note 7).

2. Notes

1. The 2,3-dimethoxybenzaldehyde employed was a darkcolored product supplied by the Monsanto Chemical Company or Eastman Kodak Company. It was purified by distilling at reduced pressure and crystallizing from methanol, after which it was colorless and melted at 52–54°.
2. The submitters used 72 g. of a 33% water solution of methylamine; the checkers used 100 g. of a 23% solution.
3. The submitters used a pint hydrogenation bottle wound with 30 ft. of No. 24 Nichrome wire insulated with asbestos paper. Before the reaction the current was

adjusted by means of a variable transformer so that the solution was maintained at approximately 70° during the reaction. The checkers used a 500-ml. centrifuge bottle without provision for heating.

4. The submitters used Raney nickel catalyst prepared as described by Mozingo.[3] The checkers used W-6 Raney nickel catalyst.[4]

5. The time required depends upon the activity of the catalyst and the temperature of reaction. The submitters reported that 90–95% of the calculated amount of hydrogen was taken up in 90 minutes at 70° whereas 20 hours was required at room temperature. The checkers found the reaction to be complete after 36 to 41 minutes, the temperature dropping during the period from 70° to 30° since no provision was made for heating. When the whole hydrogenation was carried out at room temperature the period of reaction was 90 minutes with the W-6 Raney nickel catalyst.

6. The submitters state that with a 1:1 mole ratio of aldehyde to amine the yield dropped to 75%, presumably because more of the aldehyde was reduced.

7. The submitters report that similar yields of methylarylamines were obtained from benzaldehyde, anisaldehyde, veratraldehyde, and piperonal.

3. Discussion

N-Methyl-2,3-dimethoxybenzylamine has been prepared by the reaction of 2,3-dimethoxybenzyl chloride with methylamine[5] and by the catalytic reduction of a mixture of 2,3-dimethoxybenzaldehyde and methylamine using Adams' platinum catalyst.[6]

References and Notes

1. Stanford University, Stanford, California.
2. *Org. Syntheses Coll. Vol.* **1**, 61 (1941).
3. *Org. Syntheses Coll. Vol.* **3**, 181 (1955).
4. Adkins and Billica, *J. Am. Chem. Soc.*, **70**, 695 (1948); *Org. Syntheses Coll. Vol.* **3**, 176 (1955).
5. Douetteau, *Bull. soc. chim. France*, [4] **11**, 655 (1912); Ishii and Mariani, *Anales asoc. quím. argentina*, **33**, 167 (1945) [*C. A.*, **41**, 2399 (1947)].
6. Sapp, Dissertation, Stanford University, 1940.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

W-6 Raney nickel

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

methanol (67-56-1)

ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

platinum (7440-06-4)

benzaldehyde (100-52-7)

Raney nickel (7440-02-0)

potassium hydroxide (1310-58-3)

methylamine (74-89-5)

Veratraldehyde (120-14-9)

piperonal (120-57-0)

2,3-dimethoxybenzaldehyde (86-51-1)

N-Methyl-2,3-dimethoxybenzylamine, Benzylamine, 2,3-dimethoxy-N-methyl- (53663-28-8)

2,3-dimethoxybenzyl chloride

anisaldehyde (123-11-5)

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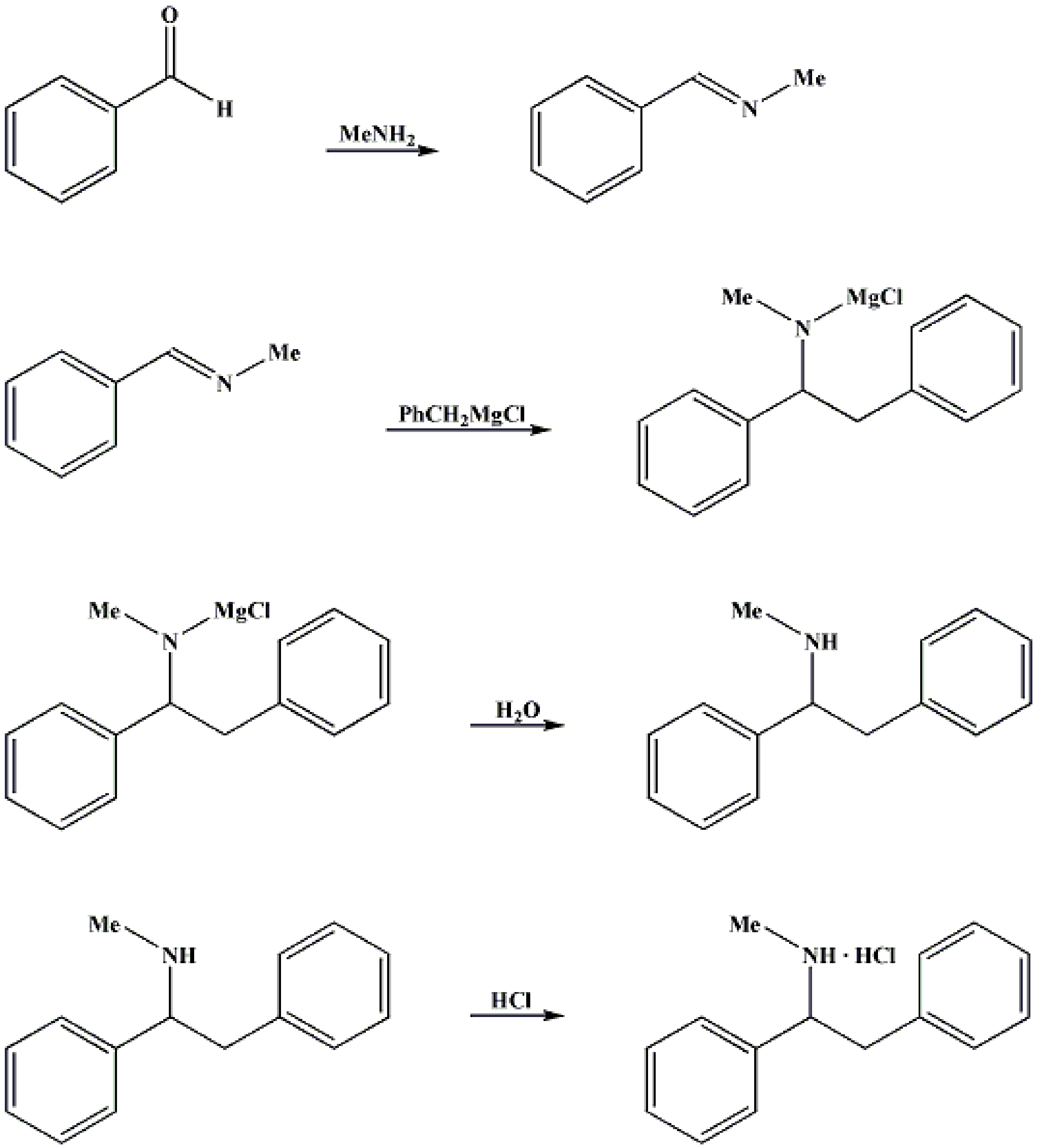
Organic Syntheses, CV 4, 605

N-METHYL-1,2-DIPHENYLETHYLAMINE AND HYDROCHLORIDE

[Ethylamine, 1,2-diphenyl-N-methyl-]



Submitted by Robert Bruce Moffett[1]
Checked by N. J. Leonard and L. A. Miller.

1. Procedure

A. *N-Benzylidenemethylamine*. A solution of 31.9 g. (0.3 mole) of benzaldehyde in 80 ml. of

benzene contained in a 300-ml. round-bottomed flask is cooled to approximately 10°. To this is added a solution of 14 g. (0.45 mole) of anhydrous methylamine in 50 ml. of benzene (Note 1). On standing, the solution becomes warm and turns milky. After 1 hour the flask is connected to a DeanStark water separator[2] which is attached to a reflux condenser, and the solvent is caused to reflux until no more water separates (Note 2). The water separator is then replaced by an 8-in. Vigreux column (Note 3), and the solution is distilled under reduced pressure. After removal of the solvent, the product distils at 92–93°/34 mm. The yield is 31–34 g. (87–95%) of colorless liquid, n_D^{25} 1.5497, n_D^{20} 1.5528.

B. *N-Methyl-1,2-diphenylethylamine*. Benzylmagnesium chloride is prepared in a 1-l. three-necked flask as described previously,[3] using 19.5 g. (0.8 g. atom) of magnesium, 92 ml. (102 g., 0.8 mole) of benzyl chloride, and 300 ml. of anhydrous ether. From the dropping funnel a solution of 24.0 g. (0.2 mole) of N-benzylidenemethylamine in 50 ml. of anhydrous ether or benzene (Note 3) is added slowly to the Grignard reagent with stirring. After being stirred at reflux temperature for 2 hours, the mixture is cooled and poured slowly into a mixture of ice and 200 ml. of concentrated hydrochloric acid. The layers are separated, the ether layer is extracted with 100 ml. of water, and the ether solution is discarded. The aqueous layer and water extract are combined, washed with 100 ml. of ether, and made strongly basic with about 600 ml. of 20% aqueous sodium hydroxide solution. The aqueous suspension of magnesium hydroxide is extracted with 800 ml. of ether in a continuous extractor for 48 hours. The ether extract is washed with about 150 ml. of water and dried over anhydrous potassium carbonate. The solution is filtered from the drying agent, the solvent is removed by distillation on a steam bath, and the residue is distilled from a Claisen flask under reduced pressure. The product distils at 83–90°/0.04 mm., 90–93°/0.2 mm., 94–97°/0.3 mm. The yield is 38.4–40.5 g. (91–96%) of colorless liquid, n_D^{25} 1.5640,n_D^{20} 1.5667.

C. *N-Methyl-1,2-diphenylethylamine hydrochloride*. Hydrogen chloride gas (Note 4) is passed into a stirred solution of 30 g. (0.14 mole) of N-methyl-1,2-diphenylethylamine in 500 ml. of anhydrous ether until saturated or until a drop of the ether on moistened pH test paper indicates that it is strongly acid. The hydrochloride separates as a colorless crystalline precipitate. It is collected on a suction filter, washed with ether, and dried. The yield is 34.2–35.1 g. (97–100%), and the product is practically pure, m.p. 184–186°. If desired it can be recrystallized by dissolution in a little methanol followed by addition of absolute ether.

2. Notes

1. Methylamine is most conveniently obtained commercially in cylinders. However, it can be generated by adding 50% aqueous sodium hydroxide solution dropwise to a flask containing the hydrochloride, and allowing the amine to distil. It can also be generated by allowing an aqueous solution of methylamine to drop into a flask containing solid sodium or potassium hydroxide. The methylamine is distilled directly below the surface of a weighed quantity of benzene kept just above its freezing point. The resulting solution is reweighed to determine the concentration, or an aliquot can be titrated with standard acid.
2. The collection of the theoretical amount of water (about 5.4 ml.) requires approximately 3 hours.
3. For the preparation of N-methyl-1,2-diphenylethylamine it is not absolutely necessary to distil the N-benzylidenemethylamine. The dried benzene solution can be used directly.
4. Hydrogen chloride gas is most conveniently obtained in a cylinder which should be connected to the outlet tube through a safety trap. It can be generated if desired.[4]

3. Discussion

The only practical method for preparing N-benzylidenemethylamine is by the reaction of benzaldehyde with methylamine.[5,6,7]

N-Methyl-1,2-diphenylethylamine has been prepared in 8% yield by the Leuckart reaction from deoxybenzoin and methylammonium formate[8] and by the present method.[9]

References and Notes

1. The Upjohn Company, Kalamazoo, Michigan.
2. *Org. Syntheses Coll. Vol.* **3**, 382 (1955).
3. *Org. Syntheses Coll. Vol.* **1**, 471 (1941).
4. *Org. Syntheses Coll. Vol.* **1**, 293, 534 (1941).
5. Zaunschirm, *Ann.*, **245**, 279 (1888).
6. Kindler, *Ann.*, **431**, 187 (1923).
7. Campbell, Helbing, Florkowski, and Campbell, *J. Am. Chem. Soc.*, **70**, 3868 (1948).
8. Goodson, Wiegand, and Splitter, *J. Am. Chem. Soc.*, **68**, 2174 (1946).
9. Moffett and Hoehn, *J. Am. Chem. Soc.*, **69**, 1792 (1947).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

N-METHYL-1,2-DIPHENYLETHYLAMINE AND HYDROCHLORIDE

potassium carbonate (584-08-7)

hydrogen chloride, hydrochloric acid (7647-01-0)

Benzene (71-43-2)

methanol (67-56-1)

ether (60-29-7)

sodium hydroxide (1310-73-2)

magnesium (7439-95-4)

benzaldehyde (100-52-7)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

benzyl chloride (100-44-7)

benzylmagnesium chloride (6921-34-2)

magnesium hydroxide

methylamine (74-89-5)

N-Methyl-1,2-diphenylethylamine, Ethylamine, 1,2-diphenyl-N-methyl- (53663-25-5)

N-benzylidenemethylamine (622-29-7)

N-Methyl-1,2-diphenylethylamine hydrochloride (7400-77-3)

deoxybenzoin (451-40-1)

methylammonium formate

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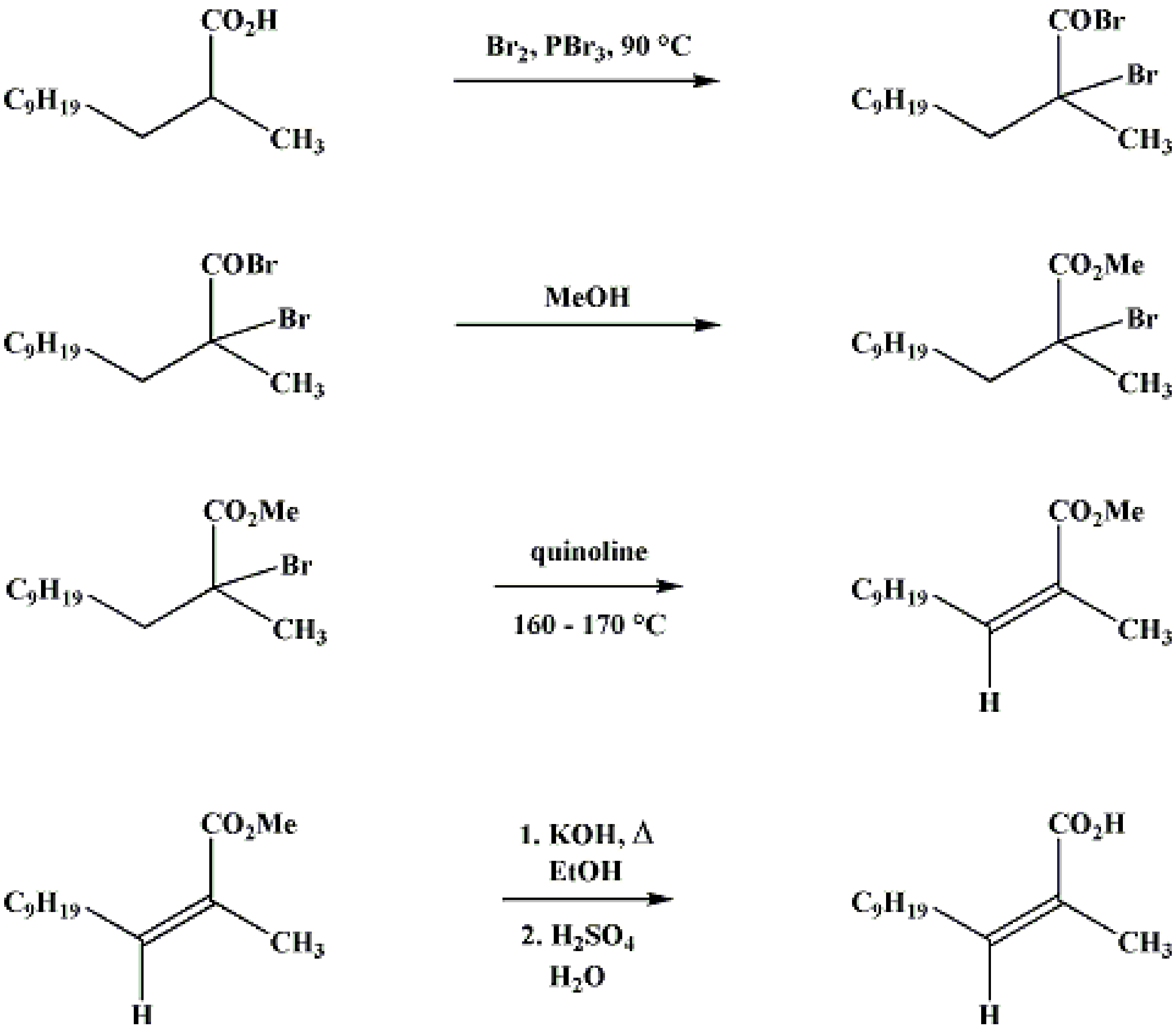
Organic Syntheses, CV 4, 608

trans-2-METHYL-2-DODECENOIC ACID

[trans-2-Dodecenoic acid, 2-methyl-]



Submitted by C. Freeman Allen and Max J. Kalm[1].
Checked by William S. Johnson and H. W. Whitlock, Jr..

1. Procedure

Caution! The bromination and dehydrobromination steps should be carried out in a hood.

Thirty grams (0.14 mole) of 2-methyldodecanoic acid is brominated exactly as described in the preparation of 2-methylenedodecanoic acid (p.616). The crude product, after the 18-hour heating period, is allowed to cool; then 56 ml. (1.4 moles) of commercial absolute methanol is added at such a rate that the exothermic reaction is kept under control (Note 1). The resultant pale-orange two-phase mixture is heated under reflux

with stirring for 15 minutes, cooled, and diluted with 150 ml. of water containing about 2 g. of sodium sulfite. The bromo ester is extracted with two portions (75 ml. and 25 ml.) of petroleum ether (Note 2). The extracts are combined, washed with water, and dried over anhydrous sodium sulfate. The solvent is removed by flash distillation of the filtered solution from a 250-ml. flask heated on a steam bath, and the last traces of solvent are eliminated by reducing the pressure with a water aspirator. The crude bromo ester remaining amounts to 41.5–42.5 g. and is thermally unstable to distillation at reduced pressure.

The crude bromo ester is mixed with 82.5 ml. (0.70 mole) of pure quinoline(Note 3) in a 250-ml. round-bottomed flask equipped with an air condenser, and the mixture is heated for 3 hours with an oil bath maintained at 160–170°. The black mixture is cooled, treated with 150 ml. of 20% hydrochloric acid, then shaken thoroughly with 200 ml. of petroleum ether (Note 2) until most of the tarry material has dissolved(Note 4). The aqueous phase is separated and washed with an additional 200 ml. of petroleum ether, and the combined organic extracts are washed with 10% hydrochloric acid and then with water. This washing cycle is repeated until the washes are colorless (two acid washes usually suffice); finally, the petroleum ether solution is washed once more with water. The organic layer is dried over anhydrous sodium sulfate, the solvent is flash-distilled as described above, and the residual liquid ester is distilled through a 61-cm. Podbielniak-type column(Note 5). The colorless unsaturated ester (Note 6) distils at 153–154°/14.5 mm. after a small fore-run. The yield is 22–27 g. (70–85.5% based on 2-methyldodecanoic acid), n_D^{25} 1.4520–31, λ_{max} 214 m•, ε 12,300, in hexane (Note 7), λ_{max} 217 m•, ε 12,800, in 95% ethanol.

The ester is hydrolyzed by heating under reflux for 1.5 hours with 50 ml. of 95% ethanol and 4.4 g. of 85% potassium hydroxide (0.066 mole) for each 10 g. (0.044 mole) of ester. Two-thirds of the ethanol is removed by distillation; then the residue is diluted with five volumes of water and acidified to Congo red with 5*N* sulfuric acid. The organic acid is extracted with two 150-ml. portions of petroleum ether (Note 2), washed with water, and dried over anhydrous sodium sulfate. The petroleum ether is removed from the extracts by flash distillation as described above, and the residual acid is distilled at reduced pressure through a 61-cm. Podbielniak-type column (Note 5). The 2-methyl-2-dodecenoic acid, distilling at 166–168°/3 mm., is obtained in 68–83% over-all yield (20–24.5 g. from 22–27 g. of ester) (Note 8) and (Note 9), m.p. 28.5–32° to 29.5–32.4°, λ_{max} 218 m•, ε 12,900, in hexane (Note 7), λ_{max} 216–217 m•, ε 12,800, in 95% ethanol.

2. Notes

1. About 20 minutes is required. It may be desirable to cool the flask during the addition.
2. Commercial hexane, b.p. 65–68°, from petroleum fractionation is satisfactory.
3. Eastman Kodak Company white label grade *synthetic* quinoline was used. The use of coal tar quinoline introduces nonextractable aromatic impurities which contaminate the product.
4. The tarry material apparently consists of quinoline salts and some insoluble

polymers.

5. A simplified Podbielniak column was employed.[2] Other columns of comparable efficiency should be suitable.

6. This methyl *trans*-2-methyl-2-dodecenoate is contaminated with 10–15% of methyl 2-methylenedodecanoate. Little, if any, *cis* isomer, which boils at the same temperature as the methylene isomer, is present. The methylene ester, which boils less than 10° below the desired isomer, can be separated by careful fractionation through an efficient column such as the 1.5-m. simple Podbielniak-type column.[2] The esters are more easily fractionated than are the higher-boiling acids.

A significant fraction of the α,β-unsaturated ester is transformed into an unidentified material of similar molecular weight when stored for several weeks in contact with air. The contaminant cannot be separated by ordinary distillation. The acid is much more stable to storage.

7. Optically pure hexane is preferred to ethanol as a solvent for absorption measurements below about 220 m•. Commercial hexane from petroleum fractionation can usually be rendered optically pure by stirring overnight twice with 15% fuming sulfuric acid (1 lb. of the acid to about 3 l. of hexane), followed by a wash with 5% aqueous sodium hydroxide and distillation from sodium hydroxide pellets.

8. The carbon-carbon double bond is not isomerized to a detectable extent during saponification of the ester or distillation of the acid; thus the 2-methyl-2-dodecenoic acid will have the same isomeric composition as the sample of ester from which it was obtained, and it consists entirely of α,β-unsaturated isomers.

9. *trans*-2-Methyl-2-dodecenoic acid, freed from isomeric impurities by fractionation through a 1.5-m. Podbielniak-type column, distilled at 146–147°/1.4 mm., λ_{max} 217 m•, ε 14,500, in hexane. Since several consecutive fractions showed these properties, they are believed to represent the properties of the pure isomer. The quantity of such material recovered is entirely dependent on the efficiency of the column and the distillation procedure. Pure samples of solid acids may be readily secured by crystallization. Those prepared[3] by this procedure include: 2-methyl-2-eicosenoic acid, m.p. 66.3–67.6°, λ_{max} 217 m•, ε 13,490, in 54% yield; 2-methyl-2-hexacosenoic acid, m.p. 85.4–86.2°, λ_{max} 217 m•, ε 14,000, in 20% yield; 2,4-dimethyl-2-pentacosenoic acid, m.p. 69.5–70.3°, λ_{max} 218 m•, ε 14,550, in 19% yield. The lowered yields arise from difficulties in purification of the higher molecular weight isomers.

3. Discussion

2-Methyl-2-dodecenoic acid has been prepared by bromination of methyl 2-methyldodecanoate with N-bromosuccinimide, followed by dehydrobromination with quinoline and saponification of the ester.[4] The present procedure is an adaptation of the method of Cason, Allinger, and Williams.[4]

References and Notes

1. University of California, Berkeley, California.
2. Cason and Rapoport, *Laboratory Text in Organic Chemistry*, 2nd ed., p. 293, Prentice-Hall, Inc., Englewood Cliffs, New Jersey, 1962.
3. Cason and Kalm, *J. Org. Chem.*, **19**, 1836 (1954).
4. Cason, Allinger, and Williams, *J. Org. Chem.*, **18**, 842 (1953).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

methanol (67-56-1)

sodium sulfite (7757-83-7)

sodium hydroxide (1310-73-2)

sodium sulfate (7757-82-6)

potassium hydroxide (1310-58-3)

Quinoline (91-22-5)

N-bromosuccinimide (128-08-5)

hexane (110-54-3)

trans-2-Dodecenoic acid, 2-methyl-, trans-2-Methyl-2-dodecenoic acid (53663-29-9)

2-methyldodecanoic acid (2874-74-0)

2-Methylenedodecanoic acid (52756-21-5)

2-methyl-2-dodecenoic acid

methyl 2-methylenedodecanoate

2-methyl-2-eicosenoic acid

2-methyl-2-hexacosenoic acid

2,4-dimethyl-2-pentacosenoic acid

methyl 2-methyldodecanoate

methyl trans-2-methyl-2-dodecenoate

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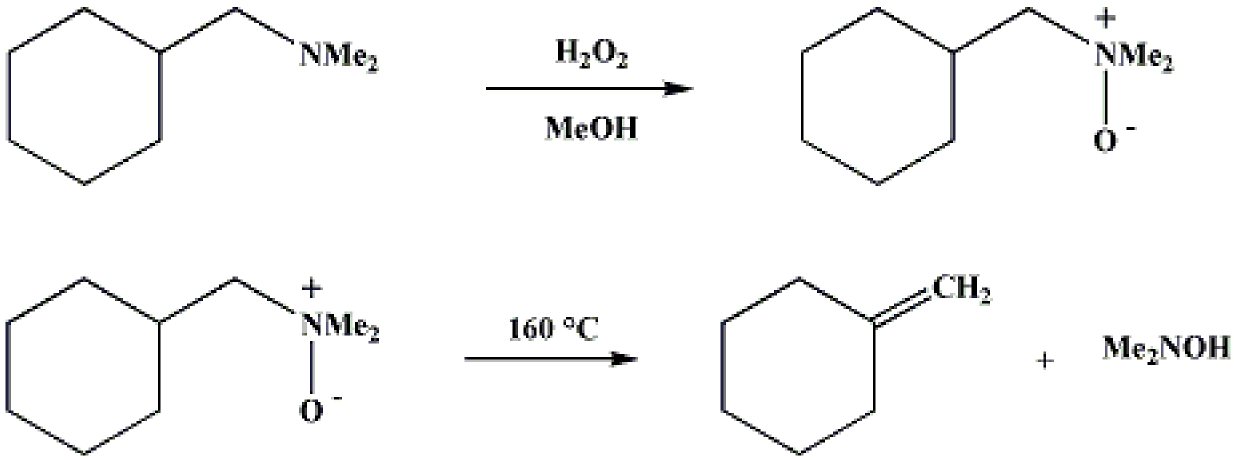
Organic Syntheses, *CV 4*, *612*

METHYLENECYCLOHEXANE AND N,N-DIMETHYLHYDROXYLAMINE HYDROCHLORIDE

[Cyclohexane, methylene-]

[Hydroxylamine, N,N-dimethyl-, hydrochloride]



Submitted by Arthur C. Cope and Engelbert Ciganek[1].
Checked by William E. Parham and Robert Koncos.

1. Procedure

In a carefully cleaned 500-ml. Erlenmeyer flask, covered with a watch glass, are placed 49.4 g. (0.35 mole) of N,N-dimethylcyclohexylmethylamine (Note 1), 39.5 g. (0.35 mole) of 30% hydrogen peroxide, and 45 ml. of methanol. The homogeneous solution is allowed to stand at room temperature for 36 hours. After 2 and 5 hours hydrogen peroxide (39.5-g. portions each time) is added (Note 2), (Note 3). The excess hydrogen peroxide is destroyed by stirring the mixture with a small amount of platinum black (Note 4) until the evolution of oxygen ceases. The solution is filtered into a 500-ml. round-bottomed flask and concentrated at a bath temperature of 50–60° (Note 5), a water aspirator being used initially and an oil pump finally, until the amine oxide hydrate solidifies. A Teflon-covered stirring bar is introduced into the flask, which is then connected by a 20-cm. column to a trap (reversed to avoid plugging) cooled in Dry Ice-acetone. The flask is heated in an oil bath to 90–100°, and the apparatus is evacuated to a pressure of ca. 10 mm. with stirring of the liquefied amine oxide hydrate. When the content of the flask resolidifies, the temperature of the oil bath is raised to 160°. The amine oxide decomposes completely within about 2 hours at this temperature. Water (100 ml.) is added to the contents of the trap. The olefin layer is removed with a pipette and washed with two 5-ml. portions of water, two 5-ml. portions of ice-cold 10% hydrochloric acid (Note 6), (Note 7), and one 5-ml. portion of 5% sodium bicarbonate solution. The olefin is cooled in a Dry Ice-acetone

bath and filtered through glass wool (Note 8). Distillation over a small piece of sodium through a semimicro column[2] yields 26.6–29.6 g. (79–88%) of methylenecyclohexane, b.p. 100–102° (Note 9), n_D^{25} 1.4474 (Note 10).

The aqueous layer is combined with the two neutral aqueous extracts and acidified by addition of 45 ml. of concentrated hydrochloric acid. The solution is concentrated under reduced pressure at 60–70° until no more distillate comes over. The residue, which solidifies on cooling, is dried in a vacuum desiccator over potassium hydroxide pellets to yield 30.7–32.7 g. (90–96%) of crude N,N-dimethylhydroxylamine hydrochloride, m.p. 103–106° (sealed tube). Crystallization from 40 ml. of isopropyl alcohol gives 26.6–30.7 g. (78–90%) of the pure hydrochloride, m.p. 106–108° (sealed tube).

2. Notes

1. The preparation of N,N-dimethylcyclohexylmethylamine is described on p.339<.htm/A>.
2. Many amines are oxidized much more rapidly than the one used in this preparation, and it is often necessary to cool such reaction mixtures in order to avoid decomposition of the amine oxide or a vigorous exothermic reaction.
3. The completion of the oxidation should be tested by adding 1 drop of an alcoholic phenolphthalein solution and 3 drops of water to 1 drop of the oxidation mixture on a porcelain spot plate. Amine oxides give no color with phenolphthalein.
4. Prepared by the procedure of Feulgen, *Ber.*, **54**, 360 (1921), and added as an aqueous suspension.
5. Some amine oxides decompose at slightly elevated temperatures. In these cases, removal of the solvents should be carried out at room temperature. It is convenient to use a rotary evaporator for removal of the solvents.
6. Methylenecyclohexane does not rearrange to 1-methylcyclohexene under these conditions. In preparations of those olefins which are more sensitive to acid, washing with acid should be omitted.
7. By making the acid extracts strongly alkaline, extracting the basic material with ether, and distilling the ether extracts, 1.0–2.5 g. (2–5%) of N,N-dimethylcyclohexylmethylamine containing a small amount of a higher-boiling basic compound of unknown structure may be recovered.
8. The material obtained in this manner is of high purity before distillation; it has the same refractive index as the distilled methylenecyclohexane, and no impurities could be detected by gas chromatographic analysis on two different columns.
9. Most of the material boils at 101–102°; the small fore-run has the same refractive index as the main fraction.
10. 1-Methylcyclohexene is completely absent, as shown by gas chromatography on a column packed with 30% by weight of a 52% solution of silver nitrate in tetraethylene glycol (Dow Chemical Company) on 48–100 mesh "firebrick" at 60°. It is estimated that the presence of less than 0.01% of this

isomer could have been detected.

3. Discussion

The present preparation of methylenecyclohexane is an example of an amine oxide pyrolysis. This route from amines to olefins in many cases yields pure olefins where the alternative method, the Hofmann exhaustive methylation reaction, is accompanied by some rearrangement to more stable isomeric olefins.

Methylenecyclohexane has been prepared by treatment of cyclohexylmethyl iodide with alcoholic potassium hydroxide solution,[3] by thermal decarboxylation of cyclohexylideneacetic acid and of cyclohexane-1-acetic acid,[4,5,6] and of cyclohexane-1,1-diacetic acid;[7] by pyrolysis of the xanthate,[8] the acetate,[9,10,11,12,13] and the stearate[14] of cyclohexanemethanol; by the action of triphenylphosphine-methylene on cyclohexanone;[15] by the pyrolysis of N,N-dimethylcyclohexylmethylamine methohydroxide[16,17] and of N,N-dimethylcyclohexylmethylamine N-oxide;[16,17] and by treatment of benzylhexahydrobenzyldimethylammonium bromide with sodium amide in liquid ammonia.[18]

N,N-Dimethylhydroxylamine has been prepared by the action of methylmagnesium iodide on ethyl nitrate.[19]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

platinum black

N,N-dimethylcyclohexylmethylamine methohydroxide

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

methanol (67-56-1)

ether (60-29-7)

sodium bicarbonate (144-55-8)

Cyclohexanone (108-94-1)

silver nitrate (7761-88-8)

oxygen (7782-44-7)

potassium hydroxide, potassium hydroxide pellets (1310-58-3)

sodium (13966-32-0)

isopropyl alcohol (67-63-0)

hydrogen peroxide (7722-84-1)

cyclohexanemethanol (100-49-2)

methylmagnesium iodide (917-64-6)

phenolphthalein (77-09-8)

sodium amide (7782-92-5)

ethyl nitrate (625-58-1)

1-methylcyclohexene

N,N-Dimethylcyclohexylmethylamine (16607-80-0)

Methylenecyclohexane, Cyclohexane, methylene- (1192-37-6)

N,N-DIMETHYLHYDROXYLAMINE HYDROCHLORIDE, Hydroxylamine, N,N-dimethyl-, hydrochloride (16645-06-0)

tetraethylene glycol (112-60-7)

cyclohexylmethyl iodide

cyclohexylideneacetic acid

cyclohexane-1-acetic acid (5292-21-7)

cyclohexane-1,1-diacetic acid (4355-11-7)

triphenylphosphine-methylene

N,N-dimethylcyclohexylmethylamine N-oxide

benzylhexahydrobenzyldimethylammonium bromide

N,N-Dimethylhydroxylamine (5725-96-2)

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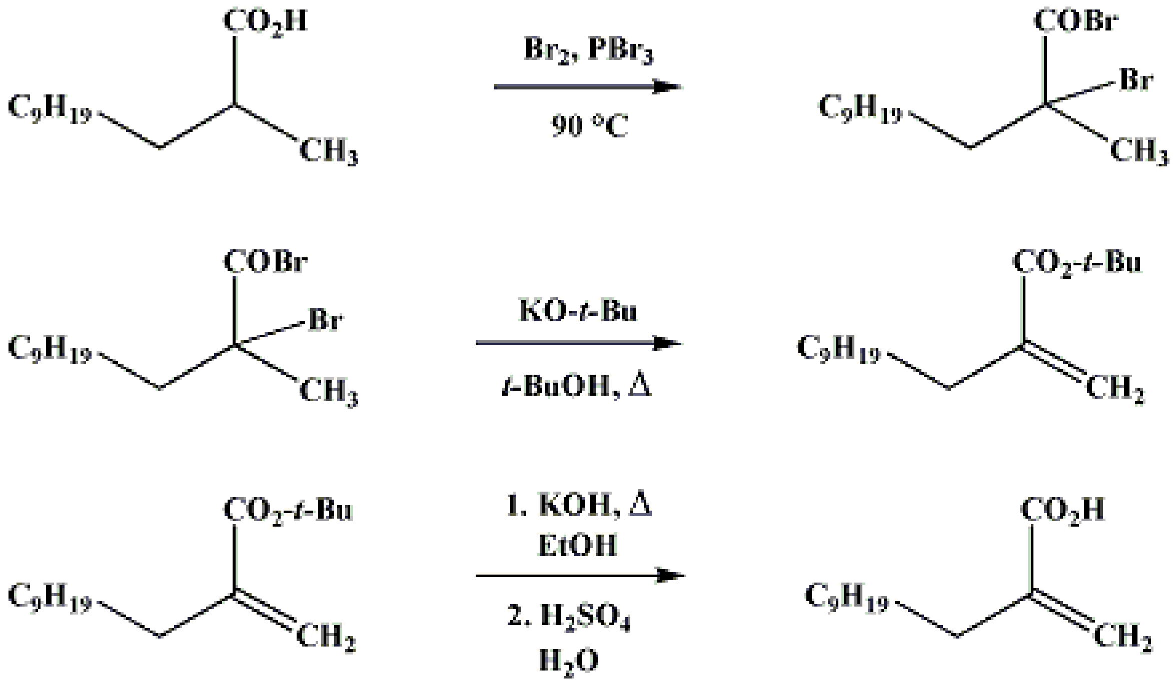
Organic Syntheses, CV 4, 616

2-METHYLENEDODECANOIC ACID

[Dodecanoic acid, 2-methylene-]



Submitted by C. Freeman Allen and Max J. Kalm[1].
Checked by William S. Johnson and Kenneth L. Williamson.

1. Procedure

Caution! The bromination step should be carried out in a hood, and appropriate precautions should be employed in handling potassium (Note 1).

A 250-ml. three-necked flask fitted (glass joints) with a sealed mechanical glass stirrer, an addition funnel, and a reflux condenser capped with a calcium chloride drying tube is charged with 30.0 g. (0.140 mole) of 2-methyldodecanoic acid (Note 2) and 13.7 ml. (0.144 mole) of phosphorus tribromide (Note 3). Stirring is commenced, and 14.6 ml. (0.284 mole) of dry bromine (Note 4) is introduced slowly from the addition funnel until the reaction mixture retains a deep bromine coloration. The addition requires about 10 minutes to this stage (Note 5). The remainder of the bromine is then added all at once, and the flask heated in a bath maintained at 85–90° (Note 6) for 1.5 hours. An additional 3.6 ml. (0.07 mole) of bromine is then added and the heating at 85–90° continued for 18 hours. The mixture is cooled to room temperature and poured into a 1-l. separatory funnel containing about 150 ml. of water and 200 g. of cracked ice. The transfer is completed with the addition of 150 ml. of benzene, and the separatory funnel is shaken vigorously for about 10 minutes, during which time most of the ice melts and the originally denser organic phase becomes the

upper phase. The aqueous layer is separated and washed with 100 ml. of benzene, while the organic layer is vigorously shaken with another 200-ml. portion of ice water. This ice-water wash is also shaken with the 100-ml. portion of benzene and is then discarded. The combined benzene extracts are filtered through anhydrous sodium sulfate to remove suspended water; then the benzene and residual bromine are removed under reduced pressure (water aspirator) at a bath temperature of 70° or below (Note 7). The crude bromoacyl bromide is added slowly, at room temperature, to a solution of 13.7 g. (0.35 g. atom) of potassium metal (Note 1) in 300 ml. of dry *tert*-butyl alcohol (Note 1) contained in a well-dried 1-l. flask fitted with a reflux condenser that is protected from moisture with a calcium chloride drying tube. The resultant suspension is heated at reflux for 1 hour, cooled, and diluted with three volumes of water. The mixture, containing insoluble *tert*-butyl 2-methylenedodecanoate, is extracted with two 100-ml. portions of low-boiling petroleum ether (Note 8) and (Note 9). The combined petroleum ether extracts are washed with water and filtered through anhydrous sodium carbonate into a distilling flask from which the solvent is flash-distilled. The residual *tert*-butyl 2-methylenedodecanoate is then distilled through a 61-cm. Podbielniak-type column (Note 10) at 129–130°/3.0 mm.; the yield is 18.5–21 g. of semipurified ester, n_D^{25} 1.4405–1.4413 (Note 11) and (Note 12).

The *tert*-butyl 2-methylenedodecanoate is hydrolyzed by heating under reflux with ethanolic potassium hydroxide for 6 hours; 40 ml. of 95% ethanol and 3.7 g. (0.056 mole) of 85% potassium hydroxide are used for each 10 g. (0.037 mole) of the ester. The hydrolysis mixture is cooled, diluted with three volumes of water, and extracted with two 100-ml. portions of petroleum ether which are discarded. The aqueous phase is acidified to Congo red with 5*N* sulfuric acid, and the 2-methylenedodecanoic acid is extracted with two 150-ml. portions of low-boiling petroleum ether (Note 8). These extracts are combined, washed with three 100-ml. portions of water to ensure complete removal of *tert*-butyl alcohol, and dried by filtration through anhydrous sodium sulfate. The solvent is removed by flash distillation, and the acid is subjected to rapid distillation from a Claisen flask (Note 13). 2-Methylenedodecanoic acid containing less than 5% of 2-methyl-2-dodecenoic acid is collected at 149–151°/1.7 mm., m.p. about 32°, λ_{max} 209 m•, ε 7800, in hexane (Note 14). The yield is 10.5–12 g. (35–40% from 2-methyldodecanoic acid), not including the acid obtained on acidification of the dehydrohalogenation mixture (Note 9).

2. Notes

1. The precautions for handling potassium and the procedure for preparing anhydrous potassium *tert*-butoxide have already been described (p.132.htm).
2. 2-Methyldodecanoic acid was prepared as follows according to the method of Cason, Allinger, and Williams.[2] A three-necked flask fitted with a sealed mechanical stirrer, dropping funnel, and efficient reflux condenser is charged with 1.4 l. of absolute ethanol; then, while stirring, 48.3 g. (2.1 g. atoms) of

sodium is added gradually in small pieces. The dropping funnel is charged with 383 g. (2.2 moles) of diethyl methylmalonate (Matheson, Coleman and Bell) which is added to the sodium ethoxide solution over a period of about 20 minutes; then the mixture is boiled under reflux for 5 minutes. The dropping funnel is charged with 442 g. (2.0 moles) of *n*-decyl bromide (Eastman Kodak Company, white label brand) which is added to the mixture as rapidly as is allowed by the exothermic reaction. After the addition is complete (about 20 minutes), the mixture is boiled under reflux for 2 hours, then neutralized with a few drops of glacial acetic acid. About two-thirds of the alcohol is removed by distillation, and 2 l. of water is added to the residue. The organic phase is separated, and the aqueous phase extracted with three 250-ml. portions of benzene. The organic phase and extracts are combined, washed with water, and dried over anhydrous sodium sulfate. The residue obtained upon evaporation of the solvent is treated with a solution of 447.5 g. of 85% potassium hydroxide pellets in 3.5 l. of 95% ethanol and the mixture heated at reflux, with stirring, for 4 hours. About two-thirds of the solvent is removed by distillation, 3 l. of water is added, followed by sufficient (about 2 l.) 6*N* sulfuric acid (cooling is necessary) to bring the pH of the solution to 1–2. The organic phase is separated, and the aqueous phase (containing some precipitated sulfates) is extracted with two portions of ether. The organic phase and extracts are combined, washed with water, then with saturated sodium chloride solution, and finally dried over anhydrous sodium sulfate. The residue obtained upon evaporation of the ether is heated at 180–190°, at which temperature decarboxylation occurs smoothly over a 20-minute period. The material is then distilled from a modified Claisen flask. The yield of product, b.p. 159–161°/4.4 mm., is 262–318 g. (61–74%), n_D^{25} 1.4404–1.4408.

3. Phosphorus tribromide (Eastman Kodak Company, white label brand) was freshly distilled before use. The full molar equivalent accelerates the desired α-bromination.

4. Bromine is conveniently dried over phosphorus pentoxide, then filtered into the addition funnel through a plug of glass wool.

5. The first mole equivalent of bromine reacts with the phosphorus tribromide to form the solid pentabromide which, in turn, is rapidly consumed in the formation of the acyl bromide.

6. The temperature is critical. At lower temperatures the reaction is very slow, and at higher temperatures partial dehydrobromination and subsequent allylic bromination result in contamination of the product with dienoic acid, as evidenced by the characteristic intense absorption at 275 m• in hexane.

7. Higher temperatures at this point tend to promote dehydrobromination under the acidic conditions with the formation of 2-methyl-2-dodecenoic acid.

8. Commercial hexane from petroleum fraction (b.p. 65–68°) is satisfactory.

9. Acidification of the alkaline aqueous layer to Congo red with 5*N* sulfuric acid liberates 2–4 g. of crude 2-methylenedodecanoic acid which can be isolated by extraction with petroleum ether as described below. Distillation of such material gave a product which did not crystallize readily.

10. A simplified Podbielniak column[3] was employed. Other columns of comparable efficiency should be suitable.
11. If the distillation is carried out in a Claisen flask, the final product is impure, apparently contaminated with about 10% of 2-methyl-2-dodecenoic acid.
12. Pure *tert*-butyl 2-methylenedodecanoate may be isolated by refractionation of this product through an efficient column. The yield in such an experiment was 15–17 g. of material with n_D^{25} 1.4400.
13. Fractionation through a column results in some isomerization.
14. 2-Methylenedodecanoic acid, free from any isomeric impurities, can be obtained by recrystallization from acetone. The pure acid is recovered in over 70% yield, m.p. 33.3–34.2°, λ_{max} 210 m•, ε 7500, in hexane. It is very difficult to obtain pure methylene acid from Claisen-distilled *tert*-butyl ester (cf. (Note 11)).

3. Discussion

This preparation is based on the method of Cason, Allinger, and Williams.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 608

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

ethanol (64-17-5)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

Benzene (71-43-2)

ether (60-29-7)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

bromine (7726-95-6)

sodium sulfate (7757-82-6)

phosphorus tribromide (7789-60-8)

acetone (67-64-1)

potassium hydroxide, potassium hydroxide pellets (1310-58-3)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

potassium (7440-09-7)

diethyl methylmalonate (609-08-5)

hexane (110-54-3)

tert-butyl alcohol (75-65-0)

2-methyldodecanoic acid (2874-74-0)

2-Methylenedodecanoic acid, Dodecanoic acid, 2-methylene- (52756-21-5)

2-methyl-2-dodecenoic acid

n-decyl bromide (112-29-8)

phosphorus pentoxide (1314-56-3)

potassium tert-butoxide (865-47-4)

tert-butyl 2-methylenedodecanoate

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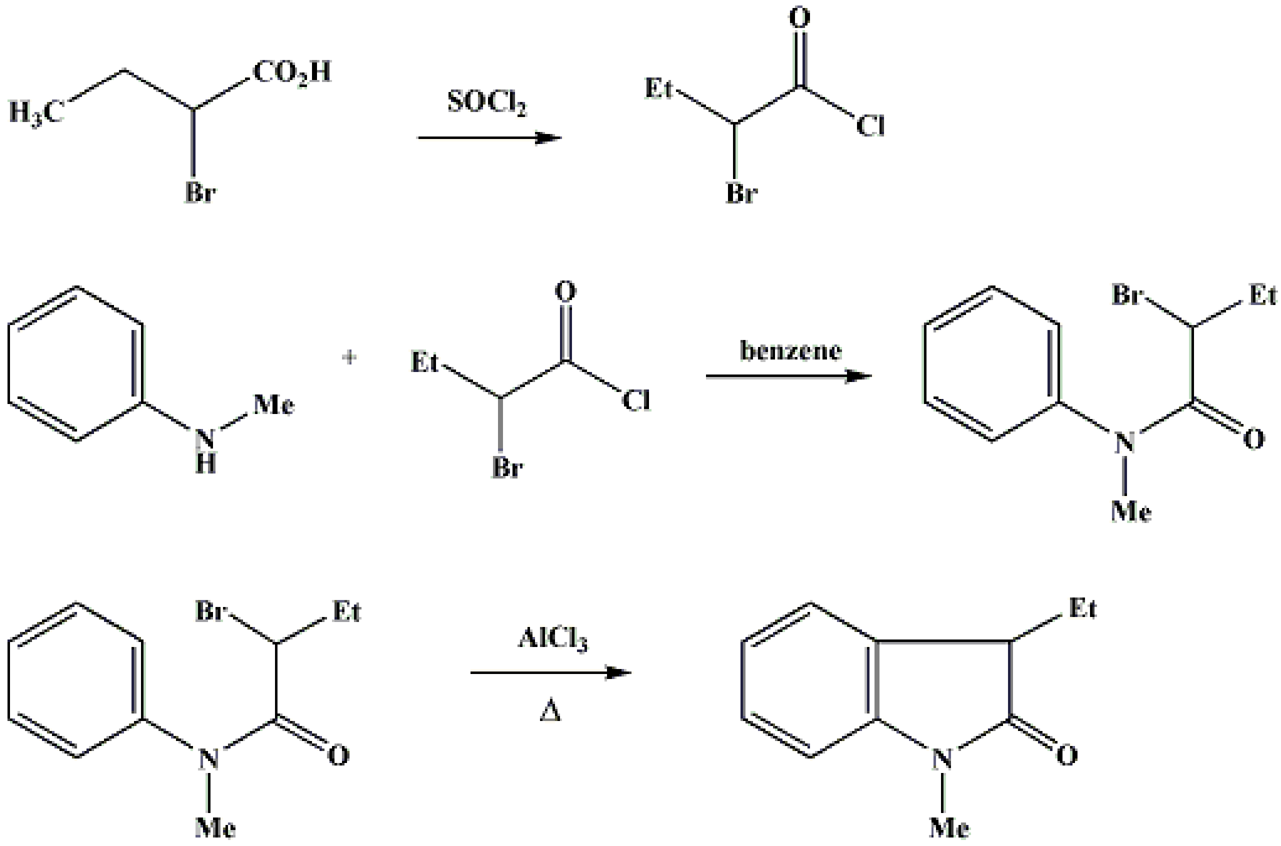
Organic Syntheses, CV 4, 620

1-METHYL-3-ETHYLOXINDOLE

[Oxindole, 3-ethyl-1-methyl]



Submitted by M. W. Rutenberg and E. C. Horning[1].
Checked by William S. Johnson and C. A. Erickson.

1. Procedure

In a 500-ml. round-bottomed flask fitted with a calcium chloride drying tube are placed 226 g. (1.35 moles) of α-bromo-*n*-butyric acid (Note 1) and 284 g. (175 ml., 2.39 moles) of thionyl chloride (Note 2). A small piece of porous plate is added, and the reaction mixture is allowed to stand at room temperature for 48 hours (Note 3). The excess thionyl chloride is removed by distillation, and the acid chloride is collected at 147–153° (Note 4). The yield of colorless product is 168–197 g. (67–78%).

In a 1-l. three-necked flask fitted with a Hershberg wire stirrer, a reflux condenser equipped with a calcium chloride drying tube, and a dropping funnel, are placed 237 g. (2.21 moles) of methylaniline (Note 5) and 300 ml. of dry benzene (Note 6). Stirring is started, and the reaction mixture is cooled in an ice-water bath during the dropwise addition of 197 g. (1.06 moles) of α-bromo-*n*-butyryl chloride diluted with approximately 40 ml. of dry benzene. The addition requires approximately 1 hour, and the reaction mixture becomes thick owing to the separation of methylaniline hydrochloride. The mixture is stirred for an additional 30 minutes and is then set aside protected by a calcium chloride tube for approximately 12 hours. The colorless methylaniline hydrochloride is removed by filtration with suction and washed with two 25-ml.

portions of benzene. The combined filtrate and washings are washed with three 100-ml. portions of 5% hydrochloric acid to remove excess methylaniline, and then with two 100-ml. portions of water (Note 7). The benzene layer is dried over anhydrous magnesium sulfate. The drying agent is removed by filtration and the solvent is removed by distillation (the last traces of solvent are removed with an aspirator) to give N-methyl-α-bromo-*n*-butyranilide (Note 8).

The crude N-methyl-α-bromo-*n*-butyranilide is placed in a 500 ml. three-necked round-bottomed flask equipped with a Hershberg wire stirrer and a reflux condenser fitted with a calcium chloride drying tube. To the stirred liquid, cooled in an ice-water bath, is added 281 g. (2.1 moles) of aluminum chloride (reagent grade, powdered) in portions over a period of about 30 minutes (Note 9). A thermometer is then introduced, and the cooling bath is replaced by a source of heat (Note 10). The reaction commences at about 80° with the evolution of hydrogen bromide (Note 11) and becomes very vigorous at 95–105°. At this point, no external heat need be applied, because the heat of reaction carries the temperature to 110–115°. When the reaction slows down, the temperature is raised to 160–170°, and the dark mixture is then allowed to cool to about 80–90°. The reaction mixture is poured *cautiously* into a 3-l. beaker about one-fourth full of cracked ice. Additional ice is added as required. The last traces of product are removed from the flask with the aid of hydrochloric acid and ice. Concentrated hydrochloric acid (75 ml.) is added to aid the decomposition of the aluminum chloride complex. The brown oil is separated after adding 75 ml. of ether, and the aqueous layer is extracted with two 100-ml. portions of ether. The combined organic layers are washed with two 75-ml. portions of 5% hydrochloric acid, two 100-ml, portions of water, two 75-ml. portions of saturated sodium bicarbonate solution, and two 100-ml. portions of water. After drying over anhydrous magnesium sulfate the ether is distilled, and the residue is distilled under reduced pressure. The main fraction is collected at 103–107°/0.5 mm. The yield is 126–131 g. (68–71% based on the acid chloride) of pale yellow 1-methyl-3-ethloxindole, n_D^{25} 1.5569–1.5580.

2. Notes

1. The α-bromo-*n*-butyric acid obtained from the Eastman Kodak Company, which had a boiling range of 2°, proved to be satisfactory.
2. Commercial thionyl chloride was distilled before use.
3. The reaction mixture is allowed to stand under an efficient hood during this period. A yield of 166 g. of product may be obtained by refluxing the mixture for 2.5 hours in a 1-l. flask equipped with condenser and drying tube.
4. The submitters used apparatus fitted with ground-glass joints for this and subsequent operations.
5. Redistilled N-methylaniline was used, b.p. 195–196°.
6. The benzene was dried by distillation.
7. Sodium chloride was added to the hydrochloric acid solution and to the wash water to reduce emulsion formation.
8. The crude N-methyl-α-bromo-*n*-butyranilide may be used directly for the ring closure or, if desired, may be purified by distillation (b.p. 117–118°/0.4 mm., 125–127°/0.8 mm., 175–184°/24 mm.).
9. The aluminum chloride is introduced into the reaction mixture without exposure to the atmosphere.[2] The mixture becomes quite viscous, and a powerful stirrer is needed.
10. An electric heating jacket was found to be most satisfactory.
11. The reaction should be carried out under an efficient hood with provision for the absorption of evolved hydrogen bromide.

3. Discussion

This method is a general one for the preparation of oxindoles and 1-methyoxindoles, and is based on the procedure of Stollé[3] as developed by Julian and Pikl.[4]

1-Methyl-3-ethyloxindole has been prepared previously by methylation of 3-ethyloxindole with methyl iodide.[5] It has also been made from 1-methyloxindole by acylation with ethyl acetate in the presence of sodium ethoxide, followed by hydrogenation over a palladium catalyst.[6]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

1-methyl-3-ethloxindole

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ethyl acetate (141-78-6)

ether (60-29-7)

thionyl chloride (7719-09-7)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

hydrogen bromide (10035-10-6)

aluminum chloride (3495-54-3)

sodium ethoxide (141-52-6)

palladium (7440-05-3)

Methyl iodide (74-88-4)

magnesium sulfate (7487-88-9)

methylaniline, N-Methylaniline (100-61-8)

1-Methyl-3-ethyloxindole, Oxindole, 3-ethyl-1-methyl (2525-35-1)

methylaniline hydrochloride (2739-12-0)

3-ethyloxindole

1-methyloxindole (61-70-1)

α-bromo-n-butyric acid (80-58-0)

α-bromo-n-butyryl chloride (22118-12-3)

N-methyl-α-bromo-n-butyranilide

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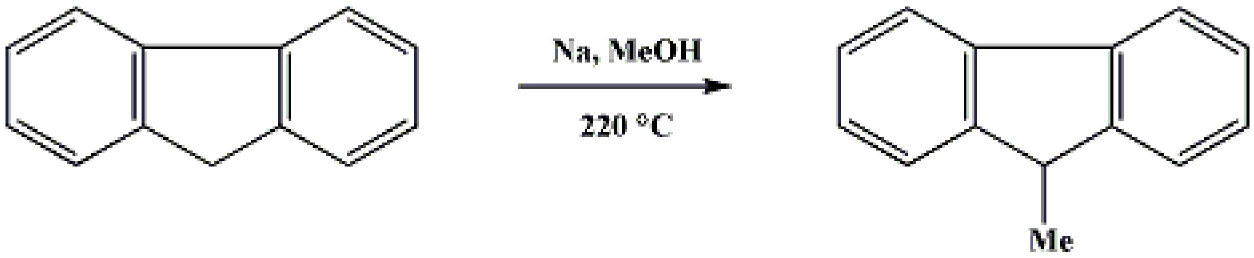
Organic Syntheses, CV 4, 623

9-METHYLFLUORENE

[Fluorene, 9-methyl-]



Submitted by Kurt L. Schoen and E. I. Becker[1].
Checked by William S. Johnson and V. B. Haarstad.

1. Procedure

An 850-ml. steel bomb is charged with a solution of 23 g. (1.0 g. atom) of sodium in 450 ml. of absolute methanol and 113 g. (0.68 mole) of fluorene (Note 1). The vessel is then closed, heated to 220° (Note 2), and rocked for 16 hours (Note 3). The reaction vessel is allowed to cool, and the contents are transferred to a 2-l. beaker with the aid of small volumes of benzene and then water to complete the transfer. The reaction mixture is diluted with an equal volume of water, neutralized with concentrated hydrochloric acid, and extracted with three 150-ml. portions of benzene. The combined benzene extracts are washed with three 200-ml. portions of water, and the solvent is removed by distillation at atmospheric pressure. The residue is recrystallized from methanol (1 l. per 100 g. of solute) to give 96–106 g. (78–86% yield) (Note 4) of colorless 9-methylfluorene, m.p. 44–45° (Note 5).

2. Notes

1. A commercial grade of fluorene was purified by crystallization from methanol until the m.p. was 113–114°.
2. In the checkers' experience the temperature must not be below 220° or a diminution in yield will result.
3. Without rocking, the crude product is colored and the yield is slightly lower.
4. This is a total yield of material obtained in 2–3 crops. In a typical run the first crop amounted to 90 g., m.p. 44–45°, and the second, obtained on concentrating and cooling the mother liquor, amounted to 16 g., m.p. 44–45°.
The crude product may alternatively be purified by rapid distillation at reduced pressure to give 114–116 g., b.p. 95–100°/1 mm. Redistillation affords 102–105 g. (83–86% yield), b.p. 96–98°/0.6 mm., of colorless 9-methylfluorene which solidifies.
5. The submitters state that the procedure is general and has been carried out with normal alcohols from C_1 to C_7. In an analogous procedure 10 g. of fluorene

was treated with 40 ml. of alcohol and 2.3 g. of sodium (in a Carius tube) to give 52–84% of redistilled 9-alkylfluorene. 9-*n*-Octadecylfluorene was prepared from 13.3 g. of fluorene, 16.2 g. of *n*-octadecyl alcohol, and 2 g. of sodium. In this case the reaction was carried out in a flask (equipped with a condenser) that was heated in an oil bath for 16 hours at 210°. The solid product was purified by crystallization.

Product	B.P./1 mm.	n_D^{25}	d_4^{25}	Yield, %
9-Ethylfluorene	123–124°	1.6180	1.0508	84
9-*n*-Propylfluorene	126–128°	1.6050	1.0326	72
9-*n*-Butylfluorene	140°	1.5956	1.0197	78
9-*n*-Pentylfluorene	144–146°	1.5929	1.0153	66
9-*n*-Hexylfluorene	156–158°	1.5757	0.9900	68
9-*n*-Heptylfluorene	163–165°	1.5717	0.9827	58
9-*n*-Octadecylfluorene	65–66.4°(m.p.)	—	—	92

3. Discussion

Generally, fluorene has been alkylated in the 9-position by reaction of 9-acyl- or ester-substituted fluorenes with sodium alkoxide and an alkyl halide followed by removal of the activating group, by treating a 9-fluorenyl organometallic compound with an alkyl halide, by reduction of a 9-fluorenylidene derivative, by hydrogenolysis of a 9-alkyl-9-hydroxyfluorene, by hydrogenolysis of a 9-halogen-9-alkylfluorene, and by cyclization of a diphenylalkylcarbinol with phosphorus pentoxide.[2] The present procedure is based on the method of Shoen and Becker.[3]

9-Methylfluorene has been prepared by cleavage of ethyl 9-methyl-9-fluorenylglyoxylate,[4] by the decarboxylation of 9-methylfluorene-9-carboxylic acid,[4] by the decarboxylation of 9-fluorenylacetic acid,[5] by the cleavage of 9-methyl-9-acetylfluorene with alcoholic potassium hydroxide or soda-lime,[6] by the reduction of 9-methyl-9-fluorenol with hydriodic acid in acetic acid,[7] by the reaction of 9-fluorenyllithium[8] or -sodium[9] with methyl iodide or methyl sulfate,[9] by the cyclization of diphenylmethylcarbinol over platinum-on-carbon at 300°,[10] by the reaction of ethyl 9-methoxymethyl-9-fluorenylcarboxylate,[11] by the diazotization and heating of 2-ethyl-2-aminobiphenyl,[12] by the dehydration and then reduction of 9-methyl-9-fluorenol,[13] by the thermal decomposition of tetramethylammonium 9-fluorenide,[14] and by recovery from coal tar.[15]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

methanol (67-56-1)

platinum (7440-06-4)

carbon (7782-42-5)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

hydriodic acid (10034-85-2)

Methyl iodide (74-88-4)

methyl sulfate (75-93-4)

fluorene (86-73-7)

9-Methylfluorene, Fluorene, 9-methyl- (2523-37-7)

9-Ethylfluorene (2294-82-8)

ethyl 9-methyl-9-fluorenylglyoxylate

9-methylfluorene-9-carboxylic acid

9-fluorenylacetic acid (6284-80-6)

9-methyl-9-acetylfluorene

9-methyl-9-fluorenol

9-fluorenyllithium

diphenylmethylcarbinol (1883-32-5)

ethyl 9-methoxymethyl-9-fluorenylcarboxylate

2-ethyl-2-aminobiphenyl

tetramethylammonium 9-fluorenide

phosphorus pentoxide (1314-56-3)

9-n-Octadecylfluorene

n-octadecyl alcohol (112-92-5)

9-n-Propylfluorene

9-n-Butylfluorene

9-n-Pentylfluorene

9-n-Hexylfluorene

9-n-Heptylfluorene

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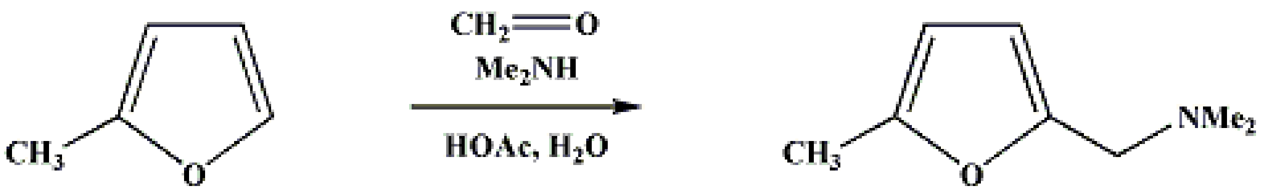
Organic Syntheses, CV 4, 626

5-METHYLFURFURYLDIMETHYLAMINE

[Furfurylamine, N,N,5-trimethyl-]



Submitted by Ernest L. Eliel and Milton T. Fisk[1].
Checked by James Cason, Mary S. Nakata, and William G. Dauben.

1. Procedure

To 200 ml. of glacial acetic acid in a 1-l. round-bottomed flask is added slowly, with cooling in an ice bath, 151 ml. (54 g. of dimethylamine, 1.2 moles) of 40% aqueous dimethylamine solution, followed by 90 ml. (36 g. of formaldehyde, 1.2 mole) of 37% aqueous formaldehyde (formalin) solution. The flask is removed from the ice bath and equipped with a reflux condenser, through which 82 g. (90 ml., 1 mole) of 2-methylfuran (Note 1) is added all at once. Upon gentle swirling of the flask, an exothermic reaction may set in spontaneously; if it does not, the flask is heated on a steam bath until reaction commences. In any event, the spontaneous reaction is allowed to proceed without further external heating. When it ceases, the reaction mixture is heated on a steam bath for another 20 minutes, cooled, and without delay poured into a cold solution of 250 g. of sodium hydroxide (Note 2) in 800 ml. of water.

The reaction mixture is steam-distilled until the distillate is only faintly alkaline (Note 3). To the distillate is added sodium hydroxide (Note 2) to the extent of 10 g. for each 100 ml. of distillate. The strongly alkaline solution is cooled and extracted with two 300-ml. portions of ether. The combined ether layers are dried over 25 g. of solid potassium hydroxide (Note 4), decanted, and concentrated. The residue is distilled under reduced pressure; the yield of 5-methylfurfuryldimethylamine boiling at 62–63°/13 mm. is 96–106 g. (69–76%), n_D^{25} 1.4616–1.4620.

2. Notes

1. The submitters used du Pont 2-methylfuran. Since the stabilizer contained in this material inhibits the reaction, it should be removed before use. The liquid is stored over solid potassium hydroxide (10 g. for each 100 ml. of 2-methylfuran) for 24 hours, decanted, and stored over the same amount of fresh potassium hydroxide at least overnight. A more rapid but less convenient method of removing the stabilizer is to extract the liquid with 10% aqueous potassium hydroxide until the extracts are only faintly colored.

2. The submitters used commercial sodium hydroxide flakes.
3. The steam distillate amounts to 2–3 l.
4. If a large aqueous phase appears, the amine should be decanted and dried further over a fresh portion of potassium hydroxide pellets.

3. Discussion

The first preparation of 5-methylfurfurylamines by the Mannich reaction was by Holdren and Hixon.[2] The present modification has been published[3] without the stem-distillation step, which facilitates separation of the product.

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

acetic acid (64-19-7)

ether (60-29-7)

sodium hydroxide (1310-73-2)

formaldehyde, formalin (630-08-0)

potassium hydroxide, potassium hydroxide pellets (1310-58-3)

dimethylamine (124-40-3)

2-methylfuran (534-22-5)

5-Methylfurfuryldimethylamine, Furfurylamine, N,N,5-trimethyl- (14496-35-6)

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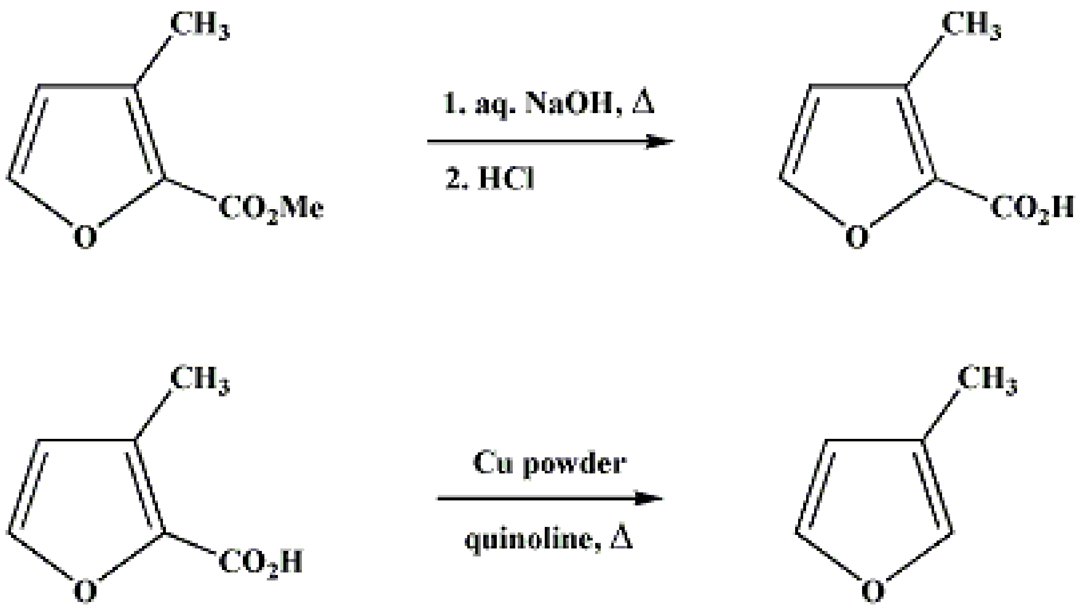
Organic Syntheses, CV 4, 628

3-METHYL-2-FUROIC ACID AND 3-METHYLFURAN

[2-Furoic acid, 3-methyl-]

[Furan, 3-methyl-]



Submitted by D. M. Burness[1]
Checked by James Cason and Robert B. Hutchison.

1. Procedure

A. *3-Methyl-2-furoic acid*. A mixture of 35 g. (0.25 mole) of methyl 3-methyl-2-furoate (p.649.htm) and 80 ml. of aqueous 20% sodium hydroxide is heated under reflux for 2 hours. The solution is cooled, acidified with about 50 ml. of concentrated hydrochloric acid (sp. gr. 1.18), stirred vigorously for a few minutes to ensure freeing of the acid from its salt, then cooled to room temperature before the product is collected by suction filtration. The product is washed with about 25 ml. of water used in two portions, drained well on the funnel, then dried. The yield of essentially pure 3-methyl-2-furoic acid is 28.5–29.5 g. (90–93%), m.p. 134–135° (Note 1).

B. *3-Methylfuran*. A mixture of 25 g. of 3-methyl-2-furoic acid, 50 g. of quinoline (Note 2), and 4.5 g. of copper powder is placed in a 125-ml. round-bottomed flask attached by a ground joint to a 30-cm. simple Vigreux column which delivers to a water-cooled condenser. The condenser is connected to a small distilling flask which serves as receiver, with the tip of the condenser extending to the edge of the bulb of the flask. The receiver is cooled in an ice-salt bath (Note 3). The round-bottomed flask is heated by means of an electric mantle or liquid bath.

When the quinoline is heated to boiling by raising the bath temperature to about 250°,

carbon dioxide is evolved at a moderate rate; the reaction is usually completed in 2–3 hours. Near the end of the reaction, heat is increased to about 265°, and the last distillate is collected until the temperature at the top of the column begins to rise rapidly above 65°. The contents of the receiver are decanted from any ice present and dried over about 1.5 g. of anhydrous magnesium sulfate, followed by Drierite, in a tightly closed flask. Redistillation yields 13.5–14.5 g. (83–89%) of colorless 3-methylfuran, b.p. 65.5–66°, n_D^{25} 1.4295–1.4315 (Note 4) and (Note 5).

2. Notes

1. In a run thirty times the size described, the submitter obtained a yield of 85%.
2. The quinoline should be dried by distillation from anhydrous barium oxide.
3. For larger runs, the side arm of the distilling flask should be attached to a cold trap immersed in an ice-salt bath, for about 10% of the product is likely to pass through the first receiver.
4. The product turns yellow on standing, even overnight. It can be stabilized with 0.1% hydroquinone or similar material.[2]
5. The submitter obtained similar results in runs about twenty times the size described. Over-all yields for the four steps starting with 4,4-dimethoxy-2-butanone (p.649.htm) were consistently in the range 50–55%.

3. Discussion

3-Methyl-2-furoic acid has been prepared by the oxidation of 3-methyl-2-furaldehyde[3] and by the degradation of 3-methyl-2-isovalerylfuran (Elsholtzia ketone).[4] 3-Methylfuran has been prepared by the present method[5] and more recently by a three-step method starting with methallyl chloride and ethyl orthoformate.[6] Circuitous routes from citric acid[7] and malic acid[8] have also been used.

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Drierite

hydrochloric acid (7647-01-0)

sodium hydroxide (1310-73-2)

citric acid (77-92-9)

hydroquinone (123-31-9)

barium oxide

carbon dioxide (124-38-9)

copper powder (7440-50-8)

Ethyl orthoformate

Quinoline (91-22-5)

magnesium sulfate (7487-88-9)

malic acid (617-48-1)

3-Methyl-2-furoic acid, 2-Furoic acid, 3-methyl- (4412-96-8)

3-Methylfuran, Furan, 3-methyl- (930-27-8)

Methyl 3-methyl-2-furoate (6141-57-7)

4,4-dimethoxy-2-butanone (5436-21-5)

3-methyl-2-furaldehyde

3-methyl-2-isovalerylfuran

methallyl chloride (563-47-3)

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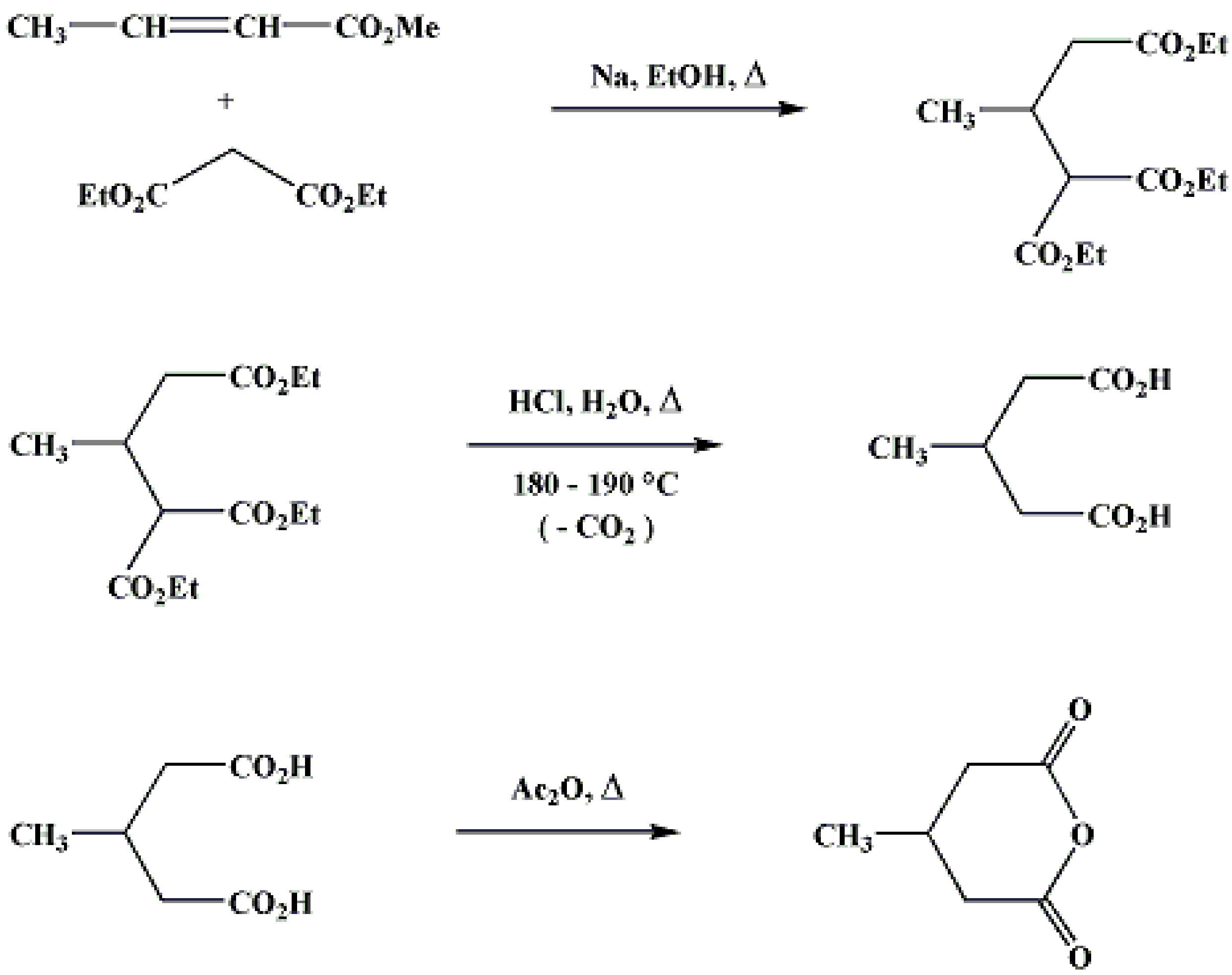
Organic Syntheses, CV 4, 630

β-METHYLGLUTARIC ANHYDRIDE

[Glutaric anhydride, 3-methyl-]



Submitted by James Cason[1]
Checked by B. C. McKusick, R. D. Smith, and W. R. Hatchard.

1. Procedure

A. *Triethyl 2-methyl-1,1,3-propanetricarboxylate* (not isolated). A 1-l. three-necked flask is fitted with a mechanical stirrer, a reflux condenser protected by a calcium chloride tube, and a 250-ml. dropping funnel. All parts of the apparatus should be scrupulously dry. Three hundred milliliters of anhydrous ethanol (Note 1) is placed in the flask, and 14.1 g. (0.61 g. atom) of clean sodium, cut in pieces as large as will easily pass through a neck of the flask, is added rapidly. The neck of the flask is immediately closed, and the mixture is stirred until all the sodium has dissolved; the cooling bath is removed, and heat is applied if the reaction becomes sluggish at the end.

After all the sodium has dissolved, a mixture of 115 g. (0.72 mole) of diethyl malonate

(Note 2) and 60 g. (0.60 mole) of methyl crotonate (Note 2) is added from the separatory funnel. This addition is made as rapidly as is consistent with keeping the exothermic reaction under control. After the exothermic reaction has subsided, the mixture is heated for 1 hour under reflux with stirring. An oil bath is recommended for heating. At the end of the heating period the condenser is changed to a position for distilling, and the temperature of the oil bath is raised sufficiently to distil alcohol fairly rapidly from the stirred mixture. Distillation is continued until most of the alcohol has been distilled. There is left a residue of the sodio derivative of triethyl 2-methyl-1,1,3-propanetricarboxylate (Note 3). If water is added to obtain the free ester, considerable heat is generated and cooling must be adequate to prevent partial hydrolysis of the ester by the alkali liberated. For present purposes there is no advantage in attempting isolation of the ester, and the residue is processed as described below.

B. *β-Methylglutaric anhydride*. The residue described above is cooled in an ice bath during the successive addition of 200 ml. of water and 450 ml. of concentrated hydrochloric acid. The resultant mixture is heated under reflux, with stirring, for 8 hours (Note 4). The condenser is again set for distillation, the bath temperature is raised, and, with continued stirring, water and alcohol are distilled. The bath is finally heated to 180–190° until gas evolution ceases (usually about 1 hour).

The stirrer is removed, 125 ml. of technical acetic anhydride is added to the residue, and, after thorough mixing, the mixture is heated on a steam bath for 1 hour. The condenser protected by a calcium chloride tube is left attached, and the other necks of the flask are closed. At the end of the heating period salt is removed from the cooled reaction mixture by filtering it with suction, using a filter aid mat, into a 250-ml. Claisen flask. The reaction vessel and filter are washed with a few milliliters of acetic acid.

The combined filtrate and washings are distilled at reduced pressure, using a water pump, until all acetic acid and acetic anhydride have been removed. An oil pump is then connected, and the distillation is continued. β-Methylglutaric anhydride is collected at 118–122°/3.5 mm. The yield of semisolid anhydride (Note 5) is 46–58 g. (60–76%) (Note 6).

2. Notes

1. Commercial absolute ethanol from a freshly opened bottle is often satisfactory; otherwise it can be dried by treatment with sodium,[2] sodium ethoxide and diethyl phthalate,[3] magnesium methoxide,[4] or aluminum *tert*-butoxide.[5]

2. Because commercial diethyl malonate is likely to contain small amounts of water and acid, it should be distilled from a Claisen flask at reduced pressure before use. The material used should be collected over a two- or three-degree range. The boiling point of malonic ester is 98°/20 mm.

Commercial methyl crotonate is rather impure and should be distilled at atmospheric pressure through a simple Vigreux or packed column which is 40–60 cm. in length. The fraction used should be collected over a two-degree range, and 70–85% of material boiling in such a range may usually be obtained from the commercial product. The boiling point is 117–118°.
3. Because of transesterification, the ester is principally the triethyl ester.
4. Sometimes the mixture becomes homogeneous after 3–5 hours, and heating can be stopped. At other times oily material remains even after 8 hours, but nothing is gained by further heating.
5. Pure β-methylglutaric anhydride melts at 46°.[6] The β-methylglutaric anhydride obtained in this preparation varies in its appearance at 25° from an almost completely crystalline mass to a mixture of about one-third solid and two-thirds liquid. However, the submitter has found that product of either appearance can be converted to methyl hydrogen β-methylglutarate in 80–85% yield. Further purification is troublesome, and the product of the present procedure is pure enough for most purposes.
6. The submitter has obtained yields of 85–90%.

3. Discussion

β-Methylglutaric anhydride is obtained from the acid, which has been prepared by condensation of acetaldehyde with cyanoacetamide[7,8] or by the oxidation of 3-methyl-1,3-cyclohexanedione with periodic acid.[9] The present method, which is a simplification of that published by Ställberg-Stenhagen,[10] gives a higher yield and is much better adapted to the preparation of large quantities.

References and Notes

1. University of California, Berkeley, California.
2. *Org. Syntheses Coll. Vol.* **1**, 259 (1941).
3. *Org. Syntheses Coll. Vol.* **2**, 155 (1943).
4. *Org. Syntheses Coll. Vol.* **1**, 249 (1941).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

3-methyl-1,3-cyclohexanedione

sodio derivative of triethyl 2-methyl-1,1,3-propanetricarboxylate

ethanol (64-17-5)

acetaldehyde (75-07-0)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

acetic anhydride (108-24-7)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

CYANOACETAMIDE (107-91-5)

diethyl malonate (105-53-3)

magnesium methoxide

diethyl phthalate (84-66-2)

periodic acid

β-Methylglutaric anhydride, Glutaric anhydride, 3-methyl- (4166-53-4)

methyl crotonate (623-43-8)

Triethyl 2-methyl-1,1,3-propanetricarboxylate

methyl hydrogen β-methylglutarate

ALUMINUM tert-BUTOXIDE

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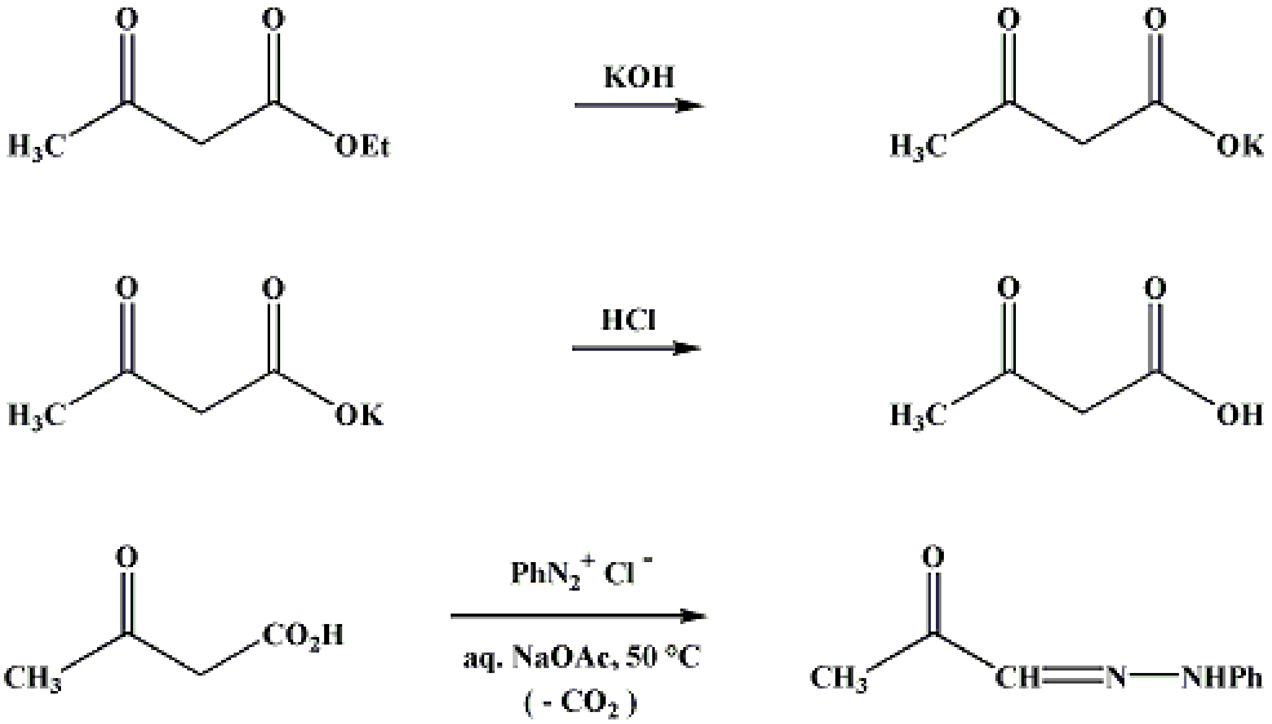
Organic Syntheses, CV 4, 633

METHYLGLYOXAL-ω-PHENYLHYDRAZONE

[Pyruvaldehyde, 1-phenylhydrazone]



Submitted by George A. Reynolds and J. A. VanAllan[1].
Checked by T. L. Cairns and C. T. Handy.

1. Procedure

In a 4-l. beaker equipped with a mechanical stirrer is placed a solution of 35 g. (0.53 mole) of 85% potassium hydroxide in 1120 ml. of water. To the solution is added, with stirring, 65 g. (64 ml., 0.5 mole) of ethyl acetoacetate (Note 1). The mixture is allowed to stand at room temperature for 24 hours.

Forty-seven grams (48 ml., 0.5 mole) of aniline is dissolved in 200 ml. of aqueous hydrochloric acid (prepared from equal volumes of concentrated acid and water) in a 2-l. beaker. The beaker is equipped with a mechanical stirrer and immersed in an ice-salt bath. After the solution has cooled to ±5°, 36 g. (0.52 mole) of sodium nitrite dissolved in 1 l. of water is added slowly, with stirring, from a separatory funnel. The tip of the stem of the separatory funnel should dip well below the surface of the liquid. The rate of addition is adjusted to maintain the temperature below 10°. A drop of the reaction mixture is tested from time to time with starch-iodide paper (Note 2). The sodium nitrite solution is added until nitrous acid persists in the solution during a 5-minute interval.

The solution of potassium acetoacetate is cooled to 0°, and 45 ml. of concentrated hydrochloric acid in 150 ml. of ice water is added slowly with stirring (Note 3). The diazonium salt solution is then added over a period of 20 minutes, and the mixture is made

basic by the addition of 82 g. of sodium acetate dissolved in 300 ml. of water (Note 4). The temperature of the reaction mixture is raised slowly to 50° and maintained at this value for 2 hours; the solid that separates is collected on a filter and dried. The yield of crude product is 72–77 g. (89–95%). Purification can be effected by recrystallization from 200 ml. of toluene. The purified product weights 59–66 g. (73–82%) (Note 5) and (Note 6); m.p. 148–150°.

2. Notes

1. Commercial ethyl acetoacetate was used.
2. The test is made by diluting the test drop on a watch glass with about 1 ml. of water and then placing a drop of this solution on the starch-iodide paper.
3. The solution is neutralized slowly in order to keep it cold so that the acetoacetic acid will not be decomposed.
4. The reaction proceeds much more rapidly in basic solution.
5. An additional 4–6 g. of product separates slowly from the filtrate.
6. This general procedure is effective for the preparation of many types of phenylhydrazones. For example, a substituted diazo compound can be employed.[2] Alkylated acetoacetic esters[3] and ethyl benzoylacetate[4] may be used. For the higher homologs, the α-formyl derivatives of ketones may be used in place of ethyl acetoacetate.[5,6] Ethyl pyridylacetates may also be substituted for ethyl acetoacetate.[7] The products in these cases are the phenylhydrazones of 2-acylpyridines.

3. Discussion

The procedure described is essentially that of Japp and Klingemann.[3] Methylglyoxal-ω-phenylhydrazone may also be prepared by heating phenylazoacetoacetic acid at 170–180°[8,9] or by warming ethyl phenylazoacetoacetate with a solution of sodium hydroxide in dilute ethanol.[8,9]

References and Notes

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9. Japp and Klingemann, *Ann.*, **247**, 198 (1888).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

METHYLGLYOXAL-ω-PHENYLHYDRAZONE

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

sodium acetate (127-09-3)

aniline (62-53-3)

sodium hydroxide (1310-73-2)

sodium nitrite (7632-00-0)

nitrous acid (7782-77-6)

potassium hydroxide (1310-58-3)

toluene (108-88-3)

Ethyl acetoacetate (141-97-9)

Ethyl benzoylacetate (94-02-0)

Pyruvaldehyde, 1-phenylhydrazone (5391-74-2)

potassium acetoacetate

acetoacetic acid (541-50-4)

phenylazoacetoacetic acid

ethyl phenylazoacetoacetate

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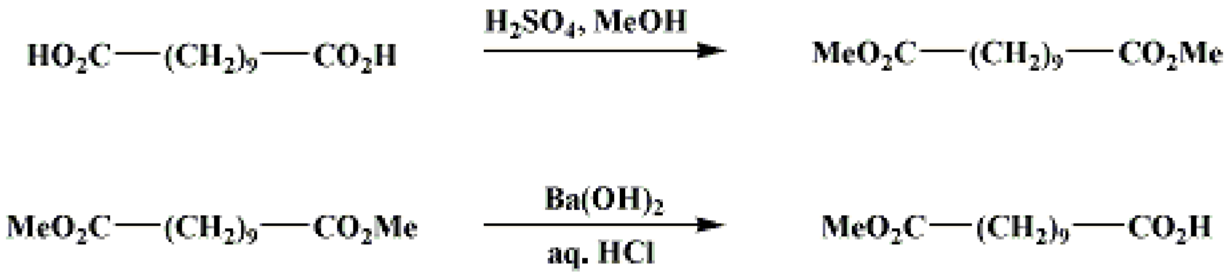
Organic Syntheses, CV 4, 635

METHYL HYDROGEN HENDECANEDIOATE

[Undecanedioic acid, methyl ester]



Submitted by Lois J. Durham, Donald J. McLeod, and James Cason[1].
Checked by N. J. Leonard, D. H. Dybvig, and K. L. Rinehart, Jr..

1. Procedure

Dimethyl hendecanedioate is prepared by heating 23 g. (0.106 mole) of hendecanedioic acid (p.510.htm) under reflux for 2 hours with a solution of 8 ml. of concentrated sulfuric acid in 80 ml. of methanol. After the reaction mixture has been diluted with 3 volumes of water, it is extracted with two 75-ml. portions of benzene. The benzene extracts are washed successively with 250-ml. portions of water, 5% aqueous sodium carbonate solution, and water. After the benzene has been removed under reduced pressure, the residue (Note 1) is transferred to a 250-ml. Erlenmeyer flask containing 127 ml. of a 0.915*N* solution of barium hydroxide (0.058 mole) in commercial anhydrous methanol (Note 2). The flask is immediately closed with a soda-lime tube and swirled to mix the solution. The barium salt of the half ester begins to precipitate after about 2 minutes.

After the flask has been allowed to stand at room temperature (20–25°) for at least 17 hours (Note 3), the barium salt is collected by suction filtration and washed with about 20 ml. of methanol (Note 4). The moist barium salt is shaken for a few minutes in a separatory funnel with a mixture of 100 ml. of 4*N* hydrochloric acid and 100 ml. of ether. The aqueous layer, together with any precipitated barium chloride, is removed and extracted again with 100 ml. of ether. The two ether extracts are combined and washed with three 100-ml. portions of water, the solvent is removed, and the residue (Note 5) is distilled through a half-meter column (Note 6). There is essentially no fore-run (see (Note 4)). The pure half ester is collected at 165–168°/2 mm., weight 14.6–15.7 g. (60–64%), m.p. 44–46° (Note 7).

2. Notes

1. The submitters state that the residue may be distilled to give dimethyl hendecanedioate in 98% yield (25.5 g.).

2. An approximately 1.0*N* solution of *anhydrous* barium hydroxide in methanol is prepared, and the exact normality is determined by titration, The checkers employed 143 ml. of an 0.814*N* solution of barium hydroxide in anhydrous methanol. This procedure is not suitable for making ethyl esters on account of the low solubility of barium hydroxide in ethanol.

3. Periodic titration of aliquots of the reaction mixture has shown that after 16 hours about 95% of the original barium hydroxide has reacted.

4. If an insufficient amount of methanol is employed to wash the precipitate, a considerable quantity of recovered diester, b.p. ca. 145°/2 mm., is obtained as a fore-run in the fractional distillation of the product. The diester may be recovered by dilution of the filtrate with water and extraction.

5. The crude product obtained directly from the barium salt is 90–95% half ester, and the remainder is diacid. This material may be used directly in reactions where small amounts of diacid are not objectionable; however, distillation is necessary in order to obtain a pure sample of half ester. This distillation is simplified because there is no lower-boiling diester and only a small amount of higher-boiling diacid.

6. The submitters used a simple type of Podbielniak column.[2] The checkers used a 122-cm. column of similar design.

7. Titration of this half ester gives an equivalent weight, within experimental error, of the calculated value of 230.3. The yield in this preparation may be regarded as close to theoretical on the basis of recovery and re-use of diacid and diester.

3. Discussion

Methyl hydrogen hendecanedioate has been reported as a by-product in the ozonolysis of methyl 11-dodecenoate,[3] but the only preparative procedure reported is that presently described.[4] Half esters have usually been prepared by partial esterification[5] and direct fractional distillation of the three products of the reaction; however, some modification[6] of this procedure is required for the higher-boiling half esters. The present method[4,7] is considerably less laborious than the partial esterification procedure and is a particular advantage for higher-boiling esters where a prolonged fractional distillation at high temperatures permits disproportionation of the half ester. This method is not satisfactory for lower-molecular-weight half esters, for their salts are too soluble in methanol. Sebacic acid gives satisfactory results by this method; azelaic acid, poor results; and lower-molecular-weight dibasic acids fail to give significant amounts of half ester.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 463

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

methanol (67-56-1)

ether (60-29-7)

sodium carbonate (497-19-8)

barium chloride (10361-37-2)

barium hydroxide (17194-00-2)

Azelaic acid (123-99-9)

sebacic acid (111-20-6)

Hendecanedioic acid (1852-04-6)

Methyl hydrogen hendecanedioate, Undecanedioic acid, methyl ester (3927-60-4)

Dimethyl hendecanedioate (4567-98-0)

methyl 11-dodecenoate

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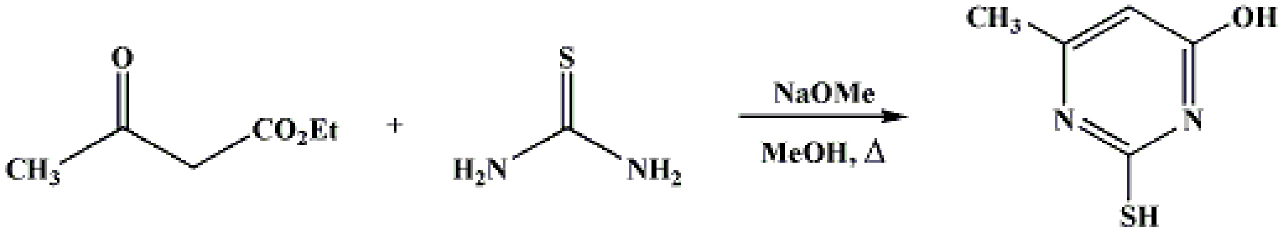
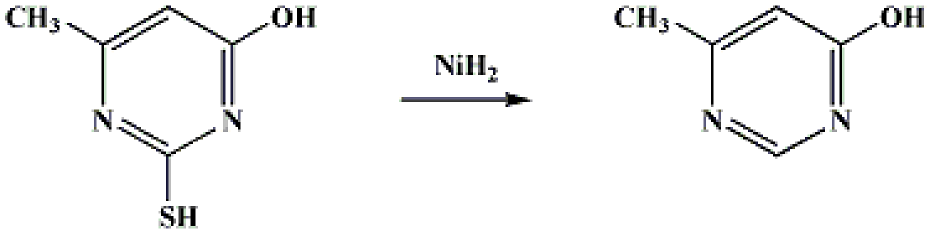
Organic Syntheses, CV 4, 638

4-METHYL-6-HYDROXYPYRIMIDINE

[4-Pyrimidinol, 6-methyl-]





Submitted by H. M. Foster and H. R. Snyder[1].
Checked by R. T. Arnold and P. E. Throckmorton.

1. Procedure

A. *2-Thio-6-methyluracil*. In a 2-l. flask are placed 76 g. (1 mole) of thiourea, 130 g. (1 mole) of commercial ethyl acetoacetate, 120 g. of commercial sodium methoxide, and 900 ml. of methanol. The reaction mixture is heated gently on the steam bath and is permitted to evaporate to dryness in a hood over a period of about 8 hours. The residue is dissolved in 1 l. of hot water; the solution is treated with a few grams of activated carbon and is filtered. The hot filtrate is carefully treated (Note 1) with 120 ml. of glacial acetic acid. The thiouracil precipitates rapidly and is collected on a 4-in. Büchner funnel. The still wet solid filter cake is suspended in a boiling solution of 1 l. of water and 20 ml. of glacial acetic acid. The slurry is stirred and mixed thoroughly to break up lumps and is then refrigerated.

The product is collected on a 4-in. Büchner funnel and is washed with about 200 ml. of cold water in four portions. The solid is permitted to drain (with suction) for several hours and is then transferred to an oven at 70° for more complete drying. The yield of oven-dried 2-thio-6-methyluracil is 98–119 g. (69–84%). This material is sufficiently pure for the desulfurization reaction (Note 2).

B. *4-Methyl-6-hydroxypyrimidine*. To a hot solution of 10 g. (0.07 mole) of 2-thio-6-methyluracil in 200 ml. of distilled water and 20 ml. of concentrated aqueous ammonia in a 500-ml. round-bottomed flask is added 45 g. (wet paste) of Raney nickel catalyst (Note 3). About 30 ml. of distilled water is used to wash all the nickel catalyst into the reaction flask. The mixture is heated under reflux in a hood for about 1.5 hours. The catalyst is permitted to settle, and the clear solution is decanted and filtered by gravity. The catalyst is washed with two 75-ml. portions of hot water and is discarded (Note 4). The combined filtrate and washings (Note 5)

are evaporated to dryness on a steam bath. The residue is placed in an oven at 70° to complete the drying process (Note 6). The yield of crude pyrimidine, m.p. 136–142°, is 7.0–7.2 g. (90–93%).

The crude product is best purified by sublimation under reduced pressure (100–110°/1 mm.) (recovery 90–95%). Purification can also be effected by recrystallization from acetone (recovery 80–90%), ethyl acetate (recovery 70–80%), or ethanol (recovery 60–70%). The purified 4-methyl-6-hydroxypyrimidine melts at 148–149°.

2. Notes

1. The hot solution tends to foam and froth badly when the acetic acid is added, and if care is not taken mechanical loss of product may result.
2. 2-Thio-6-methyluracil does not possess a clearly defined melting point but shows marked decomposition above 280°.[2]
3. The activity of the Raney nickel catalyst greatly affects the yield of the desulfurized pyrimidine. A catalyst described by Brown[3] gave very satisfactory results. A Raney nickel C described by Hurd and Rudner[4] is perhaps a more reactive catalyst; however, the yield of desulfurized pyrimidine was not sufficiently better to warrant its use.
4. Care must be taken not to allow the nickel to dry too completely lest it ignite.
5. The filtrate and washings should be clear and colorless. If the solution is blue or green (indicative of the presence of dissolved nickel) the solution should be treated with hydrogen sulfide, or better with dimethylglyoxime and ammonia, to precipitate the nickel.
6. The 4-methyl-6-hydroxypyrimidine is surprisingly volatile, and loss of product may occur if the material is heated on the steam bath for an appreciable period of time.

3. Discussion

4-Methyl-6-hydroxypyrimidine can be prepared by heating 2,6-dichloro-4-methylpyrimidine with red phosphorus and hydriodic acid[5] and by treating 2-thio-6-methyluracil with hydrogen peroxide.[6] The present synthesis is modeled after the work of Brown,[3] who has described the desulfurization of several thiopyrimidines.

The procedure for the synthesis of 2-thio-6-methyluracil is a modification of the method described by Wheeler and Merriam[7] for the preparation of 2-methylthio-6-methyluracil.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

red phosphorus

2-Thio-6-methyluracil

ethanol (64-17-5)

acetic acid (64-19-7)

ammonia (7664-41-7)

ethyl acetate (141-78-6)

methanol (67-56-1)

hydrogen sulfide (7783-06-4)

nickel, Raney nickel (7440-02-0)

acetone (67-64-1)

sodium methoxide (124-41-4)

carbon (7782-42-5)

hydrogen peroxide (7722-84-1)

hydriodic acid (10034-85-2)

Ethyl acetoacetate (141-97-9)

thiourea (62-56-6)

DIMETHYLGLYOXIME (95-45-4)

4-Methyl-6-hydroxypyrimidine, 4-Pyrimidinol, 6-methyl- (3524-87-6)

2,6-dichloro-4-methylpyrimidine (5424-21-5)

2-methylthio-6-methyluracil

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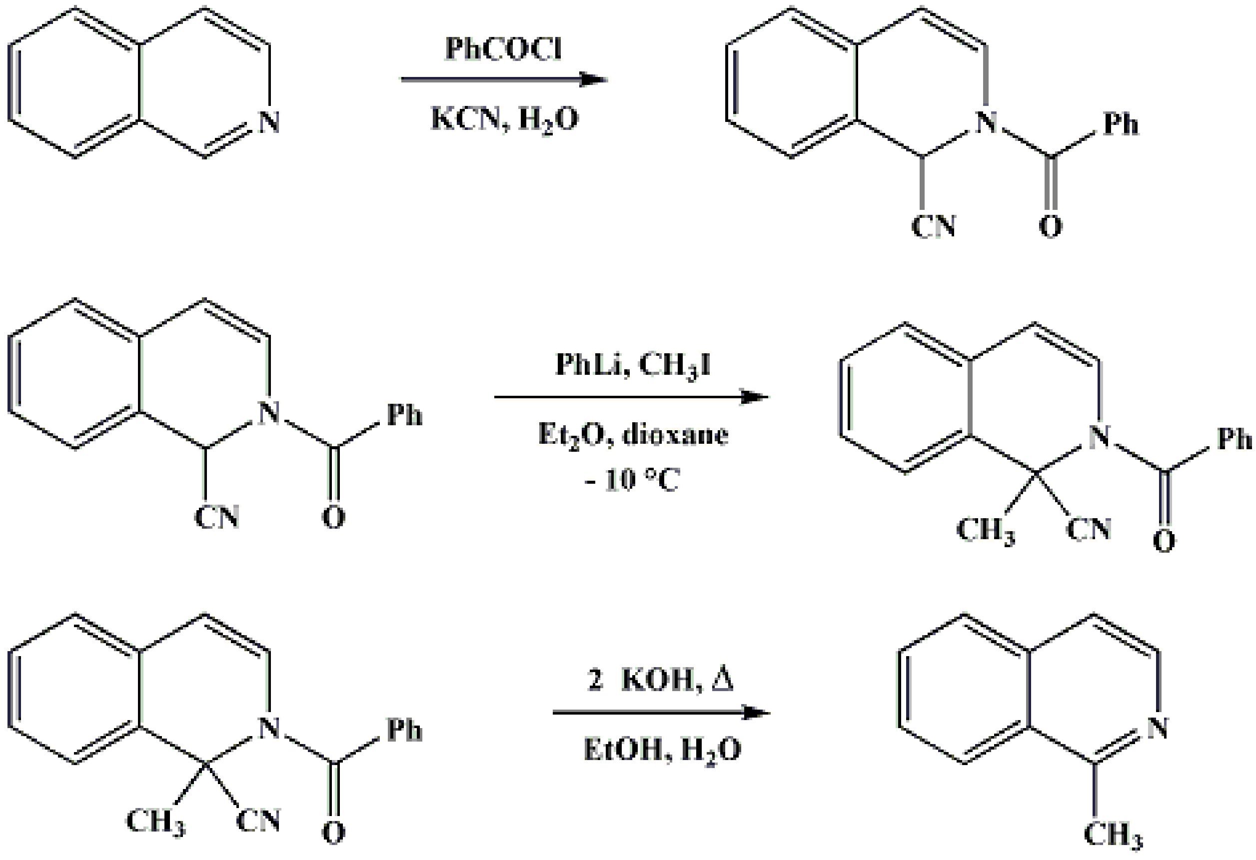
Organic Syntheses, CV 4, 641

1-METHYLISOQUINOLINE

[Isoquinoline, 1-methyl-]



Submitted by J. Weinstock and V. Boekelheide[1].
Checked by N. J. Leonard, Terry W. Milligan, and William R. Sherman.

1. Procedure

Caution! All the operations should be carried out in a well-ventilated hood because of the toxic nature of hydrogen cyanide and the cyanide solutions.

A. *1-Cyano-2-benzoyl-1,2-dihydroisoquinoline*[2] (*Reissert's compound*[3]) *(Note 1)*. In a 5-l. three-necked flask equipped with a Hershberg stirrer, a dropping funnel, and a condenser is placed a solution of 391 g. (6.0 moles) of potassium cyanide in 2.5 l. of water and 258 g. (2.0 moles) of isoquinoline (freshly distilled from zinc dust). The mixture is maintained below 25° by immersion in an ice bath (Note 2). The stirrer is started, and, when the isoquinoline has formed an emulsion with the aqueous solution, 562 g. (4.0 moles) of benzoyl chloride is added over 3 hours. The stirring is continued another hour or until the Reissert's compound has separated as small, hard, tan spheres. The reaction mixture is cooled further in the ice bath, and the product is collected on a large Büchner funnel. It is washed on the funnel with successive portions of 400 ml. of

water, 400 ml. of 3*N* hydrochloric acid, and 500 ml. of water. The product is then recrystallized from 2–3 l. of commercial absolute ethanol using 2.5 g. of activated carbon to effect partial decolorization of the solution. The hot filtration to remove the carbon is done by means of a heated Büchner funnel. The filtrate is cooled in an ice bath and filtered when cold. Long standing in the presence of the supernatant liquid causes the adsorption of dark material by the product. The cream-colored crystals which separate are collected on a Büchner funnel. washed with 100 ml. of cold 95% ethanol, and dried in air overnight. The yield of dry 1-cyano-2-benzoyl-1,2-dihydroisoquinoline, m.p. 125–127°, sufficiently pure for use in the next step, is 303–400 g. (58–77%).

B. *2-Benzoyl-1-cyano-1-methyl-1,2-dihydroisoquinoline*. A 3-l. round-bottomed flask, a 500-ml. dropping funnel, a condenser, and a stirrer are dried in an oven and then arranged so that a nitrogen atmosphere can be maintained in the flask with the use of a mercury bubbler. The apparatus is flushed with dry nitrogen for 1 hour, and 83.5 g. (0.32 mole) of 1-cyano-2-benzoyl-1,2-dihydroisoquinoline, 350 ml. of dry dioxane (Note 3), and 100 ml. of anhydrous ether are added. The stirrer is started, and, when the solid is dissolved completely, the flask is immersed in an ice-salt bath at −10°. Then 450 ml. of a 0.78*N* ether solution of phenyllithium (0.35 mole) (Note 4) is added dropwise, with stirring, during 30 minutes. The reaction mixture turns a deep red, and as the addition is continued a red solid separates. Ten minutes after the addition is complete 56.2 g. (0.40 mole) of methyl iodide is added, and the reaction mixture is stirred in the cold for 2 hours, then overnight at room temperature. The reaction mixture is transferred to a separatory funnel and washed with three 50-ml. portions of water. The organic solution is filtered, and the solvent is removed under reduced pressure. If the residue does not crystallize immediately upon evaporation of the solvent, crystallization may be induced by scratching the sides of the flask and cooling. The crystals are transferred to a Büchner funnel, washed on the funnel with 50 ml. of cold 95% ethanol, and dried. The yield of dry 2-benzoyl-1-cyano-1-methyl-1,2-dihydroisoquinoline in the form of cream-colored crystals, m.p. 120–122°, is 62–63 g. (71–72%) (Note 5).

C. *1-Methylisoquinoline*. In a 500-ml. round-bottomed flask equipped with a reflux condenser are placed 62.2 g. (0.227 mole) of 2-benzoyl-1-cyano-1-methyl-1,2-dihydroisoquinoline, 50 ml. of 95% ethanol, and a solution of 37.6 g. (0.57 mole) of 85% potassium hydroxide in 100 ml. of water. The mixture is heated under reflux for 1.5 hours, during which time the solid dissolves and the solution becomes homogeneous. After the solution has cooled, it is extracted with four 75-ml. portions of ether. The combined ethereal extracts are washed with two 25-ml. portions of water and dried with anhydrous magnesium sulfate. After removal of the drying agent by filtration and of the solvent by concentration under vacuum, the residue is distilled under reduced pressure to give 24–26 g. (74–80%) of colorless 1-methylisoquinoline, b.p.81°/1 mm.; n_D^{25} 1.6102, n_D^{20} 1.6119 (Note 6).

2. Notes

1. This is essentially the procedure of Padbury and Lindwall.[2]
2. If the mixture is not kept cold during the addition of the benzoyl chloride, the product is likely to be highly colored.
3. The dioxane is dried as described by Fieser.[4] It is kept in a glass-stoppered bottle sealed with wax. The ether is commercial anhydrous ether dried over sodium wire.
4. A convenient preparation of phenyllithium is described by Wittig.[5] The ethereal solution may be titrated by adding an aliquot to water and titrating to the methyl orange end point with standardized hydrochloric acid.
5. Another 10 g. (11%) of impure 2-benzoyl-1-cyano-1-methyl-1,2-dihydroisoquinoline may be obtained by adding water to the cold mother liquor until it becomes turbid. The mixture is heated until the turbidity disappears, and the resulting solution is cooled slowly, then refrigerated. The additional product obtained by this method is contaminated with Reissert's compound and should not be used in the next step if pure 1-methylisoquinoline is desired.
6. This method may be used to prepare other 1-substituted isoquinolines. The submitters have prepared 1-benzylisoquinoline and 1-butylisoquinoline by this method.[6]

3. Discussion

1-Methylisoquinoline has been prepared by the catalytic dehydrogenation of 1-methyl-3,4-dihydroisoquinoline prepared by the Bischler-Napieralski reaction, which involves treating β-phenylethylacetamide with a strong dehydrating reagent at elevated temperatures.[7,8,9,10,11,12] 1-Methyl-3,4-dihydroisoquinoline has been prepared from β-phenylethylacetamide by using polyphosphoric acid, and the same reagent produced some 1-methylisoquinoline from N-acetyl-*dl*-phenylalanine.[13] 1-Methylisoquinoline has also been prepared from β-phenyl-β-hydroxyethylacetamide by using phosphorus pentoxide,[14] and by cyclization of the Schiff base obtained from acetophenone and aminoacetal[15] or from α-phenylethylamine and glyoxalsemiacetal.[16]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 115

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

polyphosphoric acid

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ether (60-29-7)

hydrogen cyanide (74-90-8)

nitrogen (7727-37-9)

potassium cyanide (151-50-8)

Acetophenone (98-86-2)

carbon (7782-42-5)

benzoyl chloride (98-88-4)

potassium hydroxide (1310-58-3)

zinc (7440-66-6)

sodium wire (13966-32-0)

Methyl iodide (74-88-4)

Phenyllithium (591-51-5)

magnesium sulfate (7487-88-9)

dioxane (5703-46-8)

α-Phenylethylamine (3886-69-9)

1-Methylisoquinoline, Isoquinoline, 1-methyl- (1721-93-3)

isoquinoline (119-65-3)

1-Cyano-2-benzoyl-1,2-dihydroisoquinoline (844-25-7)

2-Benzoyl-1-cyano-1-methyl-1,2-dihydroisoquinoline

1-Benzylisoquinoline (6907-59-1)

1-butylisoquinoline

1-methyl-3,4-dihydroisoquinoline

β-phenylethylacetamide (877-95-2)

β-phenyl-β-hydroxyethylacetamide

glyoxalsemiacetal

phosphorus pentoxide (1314-56-3)

methyl orange (547-58-0)

N-acetyl-dl-phenylalanine

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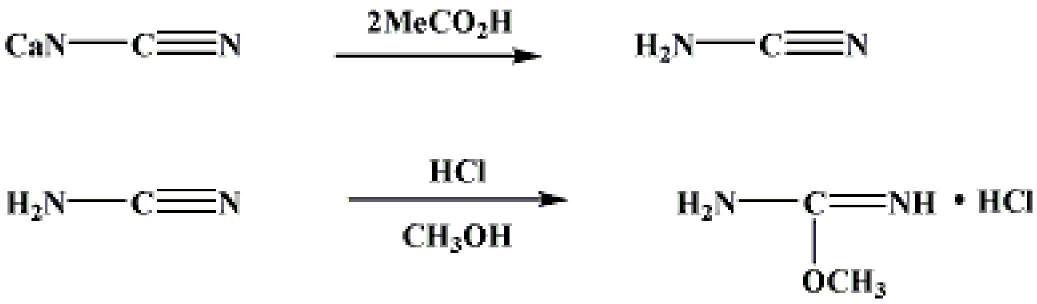
Organic Syntheses, CV 4, 645

METHYLISOUREA HYDROCHLORIDE

[Pseudourea, 2-methyl-, hydrochloride]



Submitted by Frederick Kurzer and Alexander Lawson[1].
Checked by William S. Johnson and William T. Tsatsos.

1. Procedure

A. *Cyanamide*. In a large mortar are placed 57 g. (54 ml., 0.75 mole) (Note 1) of glacial acetic acid and 135 ml. of water (Note 2). To this solution, 40 g. (0.5 mole) of calcium cyanamide (Note 3) is added slowly (Note 4) with good stirring and grinding. As the introduction of the calcium cyanamide proceeds, small quantities of acetylene are evolved, while the initially thin cream gradually turns into a thick, dark-gray to black paste. The mixture must remain acidic to litmus throughout the addition. After being dried at 40–50° for 12–18 hours in a vacuum oven, at a pressure of 30 mm. or less, the material is obtained as a pale-gray, dry powder. This is extracted exhaustively in a Soxhlet apparatus, for 2- to 3-hour periods, with two successive 400-ml. portions of ether (Note 5) containing a few drops of dilute acetic acid. The ethereal extracts (Note 6) are each dried over 30-g. portions of anhydrous sodium sulfate and combined, and the solvent is removed under reduced pressure (Note 7). The colorless, viscous, oily residue of cyanamide is suitable for use in the next stage. The yield of cyanamide is 10.5–15.8 g. (50–75% calculated on the basis of the formula CaNCN) (Note 8) and (Note 9).

B. *Methylisourea hydrochloride*. The crude cyanamide obtained as described above (Part A) is taken up in 100 ml. of anhydrous methanol, and the clear solution is decanted from a trace of insoluble oily material if necessary. Anhydrous hydrogen chloride is passed into the clear colorless liquid until an increase in weight amounting to 1 g. of hydrogen chloride per gram of crude cyanamide (1.15 moles) is attained. During the addition of the hydrogen chloride, the cyanamide solution is maintained at room temperature by external ice-cooling. The resulting clear liquid is set aside for 3–4 days, and the methanol is removed by distillation under reduced pressure. The residual colorless crystalline solid is dried in a vacuum desiccator containing potassium hydroxide and phosphorus pentoxide; it consists of methylisourea

hydrochloride. The yield is 1.8–2.1 g. per gram of cyanamide (69–80%) (Note 10).

The material may be crystallized from boiling methanol (1 ml. per gram of crude material) and forms lustrous, colorless, thick, prismatic needles, which melt with decomposition (Note 11) and (Note 12). They are separated by suction filtration at 0° (Note 13) and quickly rinsed with a very little ice-cold methanol. The product is hygroscopic and is quickly pressed between filter paper, then dried in a vacuum desiccator over phosphorus pentoxide. The filtrates yield a further crop on partial evaporation under reduced pressure, the total recovery of recrystallized material being 85–90% (Note 14).

2. Notes

1. The exact amount of acetic acid required by a particular sample of calcium cyanamide is first determined volumetrically as follows: A weighed sample of calcium cyanamide (approximately 1 g.) is suspended in about 50 ml. of distilled water and titrated with standard hydrochloric acid (preferably of approximately normal strength), using phenolphthalein as indicator. Acid is added until the pink color of the indicator does not reappear within 2–3 minutes. From the results of the titration the amount of acetic acid required is calculated by proportion, a 10% excess being allowed to ensure that the reaction mixture remains acid throughout the experiment.
2. In order to facilitate drying at a later stage, as little water is used as will produce a paste that can still be effectively mixed.
3. Commercial calcium cyanamide (nitrolime), containing carbon and small quantities of calcium carbide, is suitable for this preparation.
4. The addition of the calcium cyanamide to the acid should be slow enough to ensure thorough mixing and to prevent the reaction mixture from becoming hot.
5. The checkers found it desirable to saturate the ether (by shaking) with water before extraction. The Soxhlet extraction should not be prolonged for more than 3–4 hours. If a longer extraction period is employed, a fresh portion of ether should be used so that the extracted material will not be subjected to heat for too long a period.
6. Cyanamide may be kept unchanged at 0° in ethereal solution in the presence of traces of acetic acid. The ethereal extracts from several runs of calcium cyanamide may therefore be combined and worked up collectively.
7. Distillation is best carried out from a previously weighed small flask, and the weighed residue of cyanamide is immediately dissolved in methanol for the next stage.
8. The yields of cyanamide from commercial calcium cyanamide vary from sample to sample but do not fluctuate greatly for one particular specimen. The present procedure was found to be satisfactory for preparing 15- to 30-g. batches of cyanamide.
9. If desired, the cyanamide may be crystallized from a mixture of ether and benzene; however, the crystallization is difficult because of the tendency of the material to oil.

10. This material is satisfactory for most synthetic purposes without further purification.
11. Methylisourea hydrochloride decomposes on heating with evolution of methyl chloride. The decomposition temperature depends on the rate of heating, but reproducible values are obtainable if the rate of heating is controlled. Samples of pure (98–99%) (Note 12) methylisourea hydrochloride, introduced into the melting-point tube without undue previous exposure to atmospheric moisture, placed in the melting-point bath at 60°, and heated at the rate of 12° per minute, sinter at 118–119° and decompose at 122–124° (the mass moving rapidly up in the melting-point tube).
12. The purity of the crystallized product, determined volumetrically by Volhard's method, exceeds 98%. In this procedure, 10 ml. of a 1% solution of methylisourea hydrochloride is acidified with a few drops of nitric acid and treated with 20 ml. of 0.1*N* silver nitrate. After removel of the silver chloride by filtration, the excess of the silver nitrate is estimated with 0.1*N* thiocyanate solution, using ferric alum as indicator. Alternatively, 10-ml. portions of 0.1*N* silver nitrate, acidified with nitric acid, may be titrated directly with the 1% methylisourea hydrochloride solution in the presence of tartrazine.
Owing to the presence of small quantities of free hydrochloric acid in the crude product, the above procedures are applicable to recrystallized specimens only.
13. It has been suggested[2] that it is best to cool the solution to −10°, cool the wash solvent to −15° in ice-salt, and to put some of the cold solvent through the funnel before filtration (the addition of a few chips of Dry Ice to this solvent on the funnel is helpful).
14. Methylisourea hydrochloride should be kept in a desiccator, even for brief storage, and especially for extended periods of time.

3. Discussion

Methylisourea hydrochloride has been prepared by the action of hydrogen chloride on a suspension of silver cyanamide[3] or a solution of cyanamide[4,5] in methanol,[4] and by the action of dimethyl sulfate on urea.[6] The free base is obtained by treating the salt with powdered potassium hydroxide in a water-ether mixture[4] or with sodium methoxide in methanol.[7]

An alternative laboratory preparation of cyanamide and a selection of references to the literature have appeared in *Inorganic Syntheses*.[8] The present method is that of Werner.[9]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 213
- Org. Syn. Coll. Vol. 5, 966

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

calcium cyanamide

calcium carbide

silver cyanamide

acetylene (74-86-2)

hydrogen chloride, hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

methanol (67-56-1)

ether (60-29-7)

nitric acid (7697-37-2)

silver chloride (7783-90-6)

silver nitrate (7761-88-8)

sodium sulfate (7757-82-6)

dimethyl sulfate (77-78-1)

methyl chloride (74-87-3)

sodium methoxide (124-41-4)

carbon (7782-42-5)

potassium hydroxide (1310-58-3)

urea (57-13-6)

phenolphthalein (77-09-8)

cyanamide (420-04-2)

Methylisourea hydrochloride

Pseudourea, 2-methyl-, hydrochloride (5329-33-9)

tartrazine

phosphorus pentoxide (1314-56-3)

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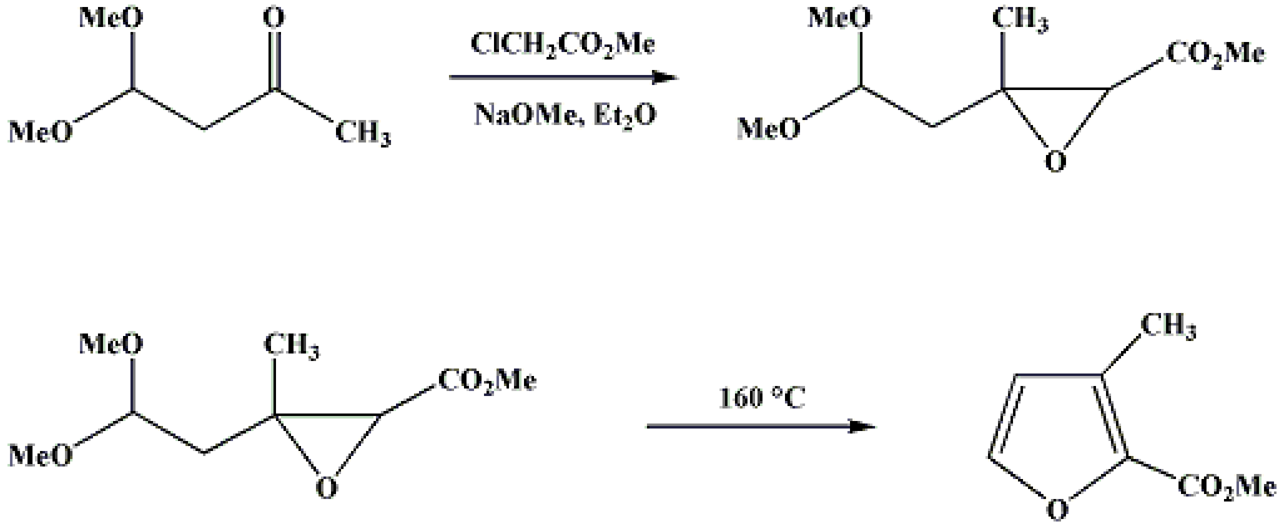
Organic Syntheses, CV 4, 649

METHYL 3-METHYL-2-FUROATE

[2-Furoic acid, 3-methyl-, methyl ester]



Submitted by D. M. Burness[1]
Checked by James Cason and Robert B. Hutchison.

1. Procedure

A. *Methyl 5,5-dimethoxy-3-methyl-2,3-epoxypentanoate.* A 2-l. three-necked flask is equipped with a sealed centrifugal stirrer (Note 1), a thermometer inserted through an adapter with a side arm connected to a source of dry nitrogen, and a 250-ml. Erlenmeyer addition flask.[2] The apparatus is dried with a free flame in a slow stream of nitrogen; from this point the reaction is conducted in an atmosphere of nitrogen (Note 2).

A mixture of 132 g. (1.0 mole) of 4,4-dimethoxy-2-butanone (Note 3), 174 g. (1.6 moles) of methyl chloroacetate (Note 3), and 800 ml. of dry ether is placed in the reaction flask, then 86 g. (1.6 moles) of sodium methoxide (Note 4) is placed in the addition flask. The solution is cooled in an ice-salt bath to −10°, then the sodium methoxide is added gradually at a rate such that a temperature below −5° can be maintained (about 2 hours). The mixture is stirred for an additional 2 hours (Note 5) and then allowed to come to room temperature overnight. It is cooled again to 0° and made slightly acidic by the addition of a solution of 10 ml. of glacial acetic acid in 150 ml. of water. The ether is decanted, and the residual slurry is extracted with three 100-ml. portions of ether. The combined ether solutions are washed in a separatory funnel with 50 ml. of saturated sodium chloride solution to which is added 1-g. portions of sodium bicarbonate until the washings are no longer acidic. After each bicarbonate addition, the mixture is shaken for at least 1 minute before a test for acidity is made. Finally, the ether phase is washed with saturated sodium chloride solution, then dried over 20–25 g. of anhydrous magnesium sulfate. Distillation of the solvent leaves a nearly quantitative yield of crude glycidic ester (Note 6).

B. *Methyl 3-methyl-2-furoate.* The crude glycidic ester prepared as described above is placed

in a 300-ml. flask which is attached to a 12-cm. column filled with 3/16-inch glass helices (or a 50-cm. simple Vigreux column) and heated in a liquid bath. When the pot temperature reaches about 160°, or before, methanol begins to distil. Heating is continued until the distillation of methanol essentially ceases and about the theoretical amount (64 g.) has been collected. After the heating bath has been allowed to cool, the product is distilled at reduced pressure; b.p. 72–78°/8 mm., yield 91–98 g. (65–70%) (Note 7). The ester solidifies in the receiver as an essentially pure compound, m.p. 34.5–36.5° (Note 8).

2. Notes

1. A stirring assembly which makes use of a lubricated ball-joint seal[3] is convenient. The checkers used a Hershberg stirrer rather than a centrifugal stirrer.
2. Maintenance of a low positive pressure of nitrogen on the system is accomplished by insertion of a T-tube in the nitrogen line for attachment of a U-tube whose bend is just closed with mineral oil.
3. The 4,4-dimethoxy-2-butanone[4] may be obtained from Aldrich Chemical Co., Milwaukee, Wisconsin, under the name of 3-ketobutyraldehyde dimethyl acetal. This and the methyl chloroacetate are preferably dried over Drierite and distilled before use. The pure acetal has b.p. 55–56°/8 mm., n_D^{25} 1.4119. The presence of 4-methoxy-3-buten-2-one, which raises the index of refraction, can be tolerated as an impurity, for it leads to the same reaction product.[5] Commercial methyl chloroacetate usually contains considerable low-boiling material which is best separated by distillation through a 50-cm. simple Vigreux column. The chloroacetate is collected at 131–132°.
4. The submitter reports that the commercial 95% "Sodium Methylate" from Mathieson Chemical Corp. is satisfactory, provided that either fresh material or material which has been opened previously only under dry nitrogen is used. The checkers experienced such erratic results with commercial sodium methoxide (even previously unopened bottles) that freshly prepared material was used. For this purpose, 37 g. of clean sodium, cut in 1- to 3-g. pieces, was added portionwise to 800 ml. of stirred anhydrous methanol contained in a 2-l. three-necked flask equipped with a condenser. After the sodium had dissolved, the methanol was removed by distillation at reduced pressure, and the residual white sodium methoxide was dried by heating at 150° under aspirator vacuum.
5. The stream of nitrogen may be discontinued at this point if the outlet tube from the flask is closed with a Drierite tube.
6. The submitter reports that the residual glycidic ester was distilled through a 15-cm. Vigreux column to yield 185–195 g. of crude product, b.p. 113–122°/8 mm. Redistillation through a 25-cm. column packed with 3/16-inch glass helices was reported to give 157–164 g. (77–80%) of product; b.p. 93°/0.7 mm. to 89°/1 mm.; n_D^{25} 1.4405–1.4419. The drop in boiling point was attributed to decomposition during distillation to yield methanol and methyl 3-methyl-2-furoate. The checkers found that in most runs the product obtained from the first distillation consisted largely of the furoate. The submitter has prepared methyl 5,5-dimethoxy-3-phenyl-2,3-epoxypentanoate by essentially the same procedure as here described.
7. In a run 15 times this size, a 71% yield was obtained by the submitter.
8. Recrystallization from ethanol raises the melting point to 36.5–37°.

3. Discussion

Methyl 5,5-dimethoxy-3-methyl-2,3-epoxypentanoate has been prepared only by the procedure described or in like manner from 4-methoxy-3-buten-2-one.[5]

Methyl 3-methyl-2-furoate has been prepared previously, presumably from the acid.[6]

References and Notes

1. Eastman Kodak Co., Rochester, New York.
2. *Org. Syntheses Coll. Vol.* **3**, 550 (1955).
3. *Organic Chemical Bulletin*, **24**, No. 3, Eastman Kodak Co., Rochester, New York, 1952.
4. Burness, U. S. pat. 2,760,985 [*C. A.*, **51**, 2854 (1957)].
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Drierite

ethanol (64-17-5)

acetic acid (64-19-7)

methanol (67-56-1)

ether (60-29-7)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

chloroacetate (79-11-8)

sodium methoxide, sodium methylate (124-41-4)

sodium (13966-32-0)

methyl chloroacetate (96-34-4)

magnesium sulfate (7487-88-9)

bicarbonate (71-52-3)

Methyl 3-methyl-2-furoate, 2-Furoic acid, 3-methyl-, methyl ester (6141-57-7)

4,4-dimethoxy-2-butanone, 3-ketobutyraldehyde dimethyl acetal (5436-21-5)

4-methoxy-3-buten-2-one

furoate

methyl 5,5-dimethoxy-3-phenyl-2,3-epoxypentanoate

Methyl 5,5-dimethoxy-3-methyl-2,3-epoxypentanoate

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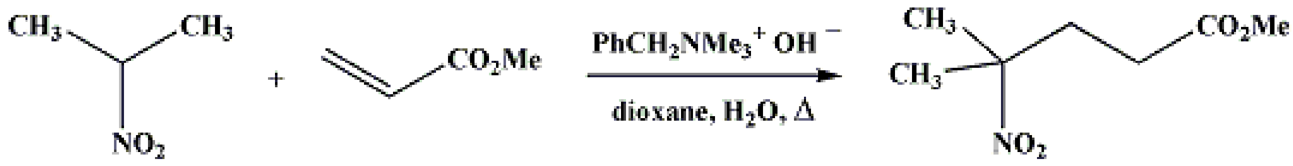
Organic Syntheses, CV 4, 652

METHYL γ-METHYL-γ-NITROVALERATE

[Valeric acid, 4-methyl-, 4-nitro-, methyl ester]



Submitted by R. B. Moffett[1]
Checked by N. J. Leonard and B. L. Ryder.

1. Procedure

A 500-ml. three-necked flask is fitted with a stirrer, a dropping funnel, and a thermometer placed so that the bulb is near the bottom of the flask. In the flask are placed 89 g. (1 mole) of 2-nitropropane (Note 1), 50 ml. of dioxane, and 10 ml. of a 40% aqueous solution of benzyltrimethylammonium hydroxide (Triton B) (Note 2), and the contents of the flask are warmed to 70°. Eighty-six grams (1 mole) of redistilled methyl acrylate (Note 3) is added, with stirring, during 15 minutes. The temperature rises to about 100° during the addition and then drops to about 85°. The mixture is stirred and heated on a steam bath for 4 hours. After cooling, the contents of the flask are acidified with dilute hydrochloric acid and extracted with ether. The ether layer is washed twice with water, then with approximately 50 ml. of 0.1% sodium bicarbonate solution, and finally again with water. After the ethereal solution has been dried over anhydrous sodium sulfate, the drying agent is separated, the solvent is removed by distillation, and the product is distilled through a short fractionating column. A nearly colorless oil is obtained in a yield of 140–151 g. (80–86%); b.p. 79°/1 mm.; n_D^{20} 1.4408.

2. Notes

1. 2-Nitropropane from Commercial Solvents Corporation, Terre Haute, Indiana, was redistilled before use.
2. Available from Commercial Solvents Corporation or Rohm and Haas Company, Philadelphia, Pennsylvania.
3. Although the submitter knows of no case of an explosion with this type of nitro compound, it is recommended that adequate safety shields be employed during both the reaction and the distillation.

3. Discussion

Methyl γ-methyl-γ-nitrovalerate has been prepared by the Michael-type condensation of 2-nitropropane with methyl acrylate in the presence of a quaternary ammonium hydroxide[2] or triethylamine.[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 357
- Org. Syn. Coll. Vol. 5, 445

References and Notes

1. The Upjohn Company, Kalamazoo, Michigan.
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3. Kloetzel, *J. Am. Chem. Soc.*, **70**, 3571 (1948).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

benzyltrimethylammonium hydroxide (Triton B)

quaternary ammonium hydroxide

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

methyl acrylate (96-33-3)

dioxane (5703-46-8)

triethylamine (121-44-8)

Methyl γ-methyl-γ-nitrovalerate, Valeric acid, 4-methyl-, 4-nitro-, methyl ester (16507-02-1)

2-nitropropane (79-46-9)

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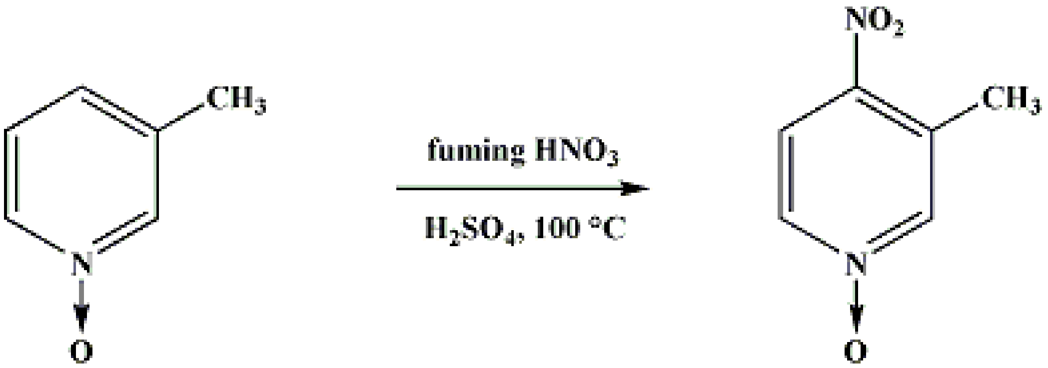
Organic Syntheses, *CV 4*, *654*

3-METHYL-4-NITROPYRIDINE-1-OXIDE

[3-Picoline, 4-nitro-, 1-oxide]



Submitted by E. C. Taylor, Jr.[1] and Aldo J. Crovetti[2].
Checked by Max Tishler and Henry B. Lange.

1. Procedure

One hundred and eighty grams (1.65 moles) of liquefied 3-methylpyridine-1-oxide (Note 1) is added to 630 ml. of cold (0–5°) sulfuric acid (sp. gr. 1.84) contained in a 3-l. round-bottomed flask immersed in an ice-salt bath. The resulting mixture is cooled to about 10°, and 495 ml. of fuming yellow nitric acid (sp. gr. 1.50) is added in 50-ml. portions with shaking. An efficient spiral condenser (52 × 4 cm.) is attached to the flask, and the latter is placed in an oil bath. The temperature is slowly raised to 95–100° during 25–30 minutes, at which time gas evolution begins. After about 5 minutes the rate of gas evolution increases, and the oil bath is removed. A spontaneous and vigorous reaction commences which must be controlled by the application of an ice-water bath (Note 2). After the vigorous reaction has subsided to a moderate rate (about 5 minutes) the ice-water bath is removed, and the reaction is allowed to proceed for an additional 5–10 minutes. The oil bath is then replaced, and heating is continued at 100–105° for 2 hours.

The reaction mixture is cooled to 10° and poured onto 2 kg. of crushed ice carbonate in a 4-l. beaker. Addition of 1.36 kg. of sodium carbonate monohydrate (*Hood!*) (Note 3) in small portions with stirring causes the separation of the yellow crystalline product along with sodium sulfate. The mixture is then allowed to stand for 3 hours to expel nitrogen oxides. The yellow solid is collected by suction filtration, thoroughly washed with water, and rendered as dry as possible on the filter. The filtrates (about 4 l.) are transferred to a separatory funnel.

The collected solid is extracted twice with 400–500 ml. portions of boiling chloroform, the combined extracts are used to extract the aqueous filtrates contained in the separatory funnel, and the extraction is repeated with several fresh 500-ml. portions of chloroform. The combined chloroform extracts are then given preliminary

drying over anhydrous sodium sulfate and evaporated to dryness by distillation under reduced pressure. The residue is transferred to a 2-l. Erlenmeyer flask and dissolved in 1.5 l. of boiling acetone. The acetone solution is concentrated on a steam bath to 800–900 ml. (crystallization begins when the volume is about 1 l.) and then cooled at 5° for 6–8 hours. The product is filtered by suction, the filtrates are removed and saved, and the collected solid is washed with ether and dried. The yield is 162–173 g. (64–68%), m.p. 137–138°. The acetone filtrates mentioned above are boiled down to 150 ml. and chilled in an ice bath, and the crude product so obtained (m.p. 131–135°) is recrystallized from acetone to give an additional 13.5–16.5 g., m.p. 136–138°. The total yield is 178–187 g. (70–73%).

2. Notes

1. Freshly distilled 3-methylpyridine-1-oxide (b.p. 101–103°/0.7–0.8 mm.) will remain in a supercooled liquid state for several hours before solidifying. The highly hygroscopic solid may be melted on a steam bath in a tightly closed, previously weighed flask, and the melt poured slowly into the sulfuric acid. A large amount of heat is liberated in the mixing.
3-Methylpyridine-1-oxide (3-picoline-1-oxide) may be prepared by a method similar to that employed for pyridine-1-oxide (p.828.htm). To a mixture of 600–610 ml. of glacial acetic acid and 200 g. (2.15 moles) of freshly distilled 3-methylpyridine (b.p. 141–143°) contained in a 2-l round-bottomed flask is added, with shaking, 318 ml. (2.76 moles) of cold (5°) 30% hydrogen peroxide. The mixture is heated in an oil bath for 24 hours, with the internal temperature adjusted to 70 ± 5° The excess acetic acid and water are removed under reduced pressure (30 mm.), and, after 500 ml. of distillate has been collected, the residue is diluted with 200 ml. of water and concentrated again, with the collection of 200 ml. of distillate. The residual mixture is cooled to 0–5° in an ice-salt bath, and 500 ml. of cold (0–5°) 40% acqueous sodium hydroxide solution is added slowly with shaking. The strongly alkaline solution is extracted with 2 l. of chloroform, and the extracts are given preliminary drying over anhydrous sodium carbonate. The extracts are filtered and concentrated by distillation under reduced pressure. The product is distilled under vacuum, b.p. 84–85°/0.3 mm., and the yield of 3-methylpyridine-1-oxide is 175–180 g. (73–77%).
2. Vigorous refluxing with evolution of nitrogen oxides occurs. Serious flooding of the condenser may result if no cooling is applied.
3. During the addition of sodium carbonate, large volumes of nitrogen oxides are evolved. In experiments where smaller quantities of sodium carbonate were used, lower yields (ca. 62%) were obtained.

3. Discussion

3-Methylpyridine-1-oxide has been prepared by the oxidation of 3-methylpyridine with hydrogen peroxide in glacial acetic acid,[3,4] with 40% peracetic acid and sodium acetate,[5] and with perbenzoic acid in benzene.[6]

3-Methyl-4-nitropyridine-1-oxide has been prepared by the nitration of 3-methylpyridine-1-oxide hydrochloride with a mixture of concentrated sulfuric acid and potassium nitrate,[5] and by the nitration of 3-Methylpyridine-1-oxide with a mixture of concentrated sulfuric acid and fuming nitric acid.[7] The preparation of this compound has been mentioned briefly by Talikowa.[8]

References and Notes

1. Princeton University, Princeton, New Jersey.
2. University of illinois, Urbana, Illinois.
3. Ochiai, Ikehara, Kato, and Ikekawa, *J. Pharm. Soc. Japan*, **71**, 1385 (1951) [*C. A.*, **46**, 7101 (1952)].
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6. Matsumura, *J. Chem. Soc. Japan*, **74**, 446 (1953) [*C. A.*, **48**, 6442 (1954)].
7. Itai and Ogura, *J. Pharm. Soc. Japan*, **75**, 292 (1955) [*C. A.*, **50**, 1808 (1956)].
8. Talikowa, *Wiadomosci Chem.*, **7**, 169 (1953) [*C. A.*, **48**, 1337 (1954)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

Benzene (71-43-2)

ether (60-29-7)

sodium acetate (127-09-3)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

nitric acid (7697-37-2)

sodium carbonate (497-19-8)

carbonate (3812-32-6)

sodium sulfate (7757-82-6)

acetone (67-64-1)

hydrogen peroxide (7722-84-1)

potassium nitrate (7757-79-1)

peracetic acid (79-21-0)

3-METHYL-4-NITROPYRIDINE-1-OXIDE, 3-Picoline, 4-nitro-, 1-oxide (1074-98-2)

3-methylpyridine-1-oxide, 3-picoline-1-oxide (1003-73-2)

pyridine-1-oxide (694-59-7)

3-methylpyridine (108-99-6)

3-methylpyridine-1-oxide hydrochloride

sodium carbonate monohydrate (5968-11-6)

Perbenzoic acid (93-59-4)

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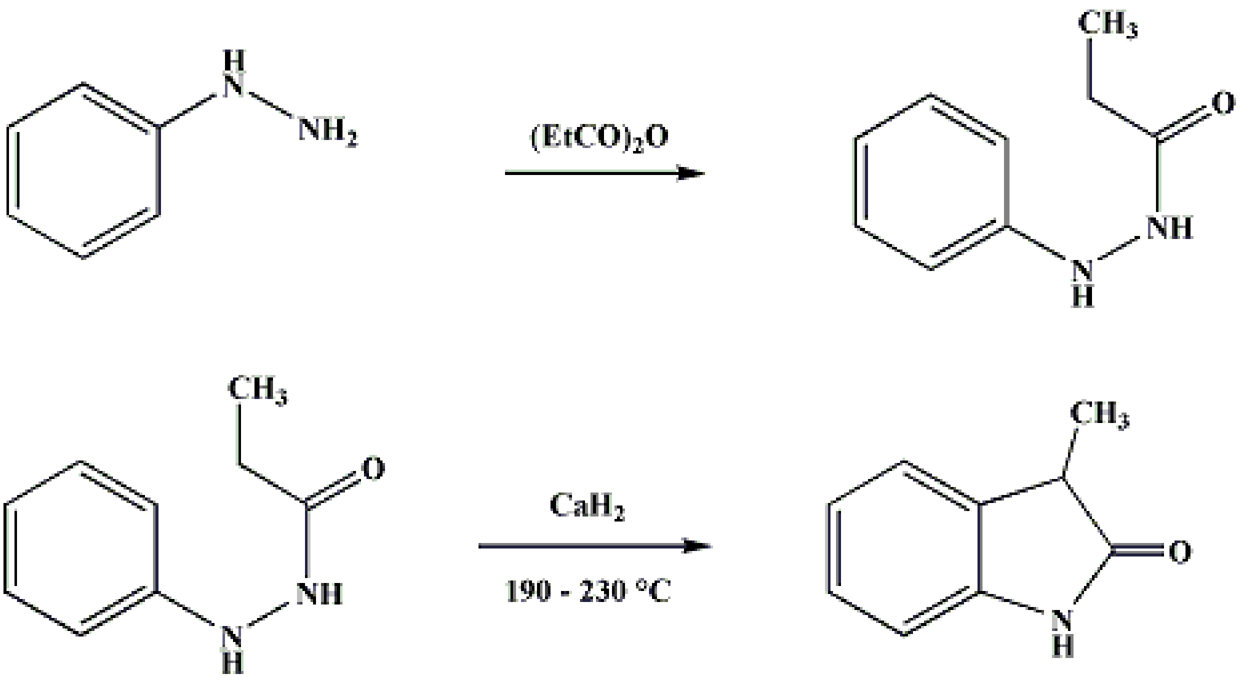
Organic Syntheses, CV 4, 657

3-METHYLOXINDOLE

[Oxindole, 3-methyl-]



Submitted by Abraham S. Endler and Ernest I. Becker[1].
Checked by James Cason and Warren N. Baxter.

1. Procedure

A. β-*Propionylphenylhydrazine*. To 130 g. (1.0 mole) of propionic anhydride(Note 1), contained in a 500-ml. wide-mouthed Erlenmeyer flask which is cooled in an ice bath, there is added slowly with swirling 108 g. (1.0 mole) of phenylhydrazine(Note 1) at such a rate that the maximum temperature does not exceed 60°. After addition is complete, the flask is corked (not so tightly as to give a vacuum which may collapse the flask) and allowed to stand 72 hours at room temperature. At the end of this period, the resultant solid cake is broken up and slurried with 100 ml. of toluene. The suspension is cooled to 5° in an ice bath; then the product is collected by suction filtration and washed with 200 ml. of a mixture of equal parts of cyclohexane and toluene, precooled to 5°. The yield of vacuum-dried, almost white crystals, m.p. 158–159°, is 140–145 g. (85–88%).

B. *3-Methyloxindole.* A mixture of 33 g. (0.20 mole)(Note 2) of β-propionylphenylhydrazine and 14 g. (0.33 mole) of freshly ground commercial calcium hydride (Note 3) is placed in a 500-ml. round-bottomed flask, which is equipped with a 15-cm. air condenser of 2.5 cm. in diameter. The flask is immersed to two-thirds its depth in an oil bath, in a forced-draft hood, and the bath is heated, cautiously as 190° is approached. In the range 190–215°, a very vigorous exothermic

reaction sets in (sometimes after a brief delay), and considerable gas and vapor is expelled through the air condenser. The vigorous reaction abates in 5 minutes or less, and the oil bath is raised to about 230°. After heating at this temperature has been continued for 30 minutes, the flask is removed from the bath and cooled to room temperature.

A mixture of 50 ml. of methanol and 20 ml. of water is cautiously added to the cooled reaction mixture, and this is followed by slow addition of concentrated hydrochloric acid (Note 4) until the pH is brought to 1–2 (Hydrion test paper). When effervescence has stopped, 50 ml. of water is added, and the contents of the flask are boiled gently for 1 hour. Additional concentrated hydrochloric acid is added as needed to maintain the specified pH (Note 5). At this point, all solid material should have been decomposed. The mixture is transferred to a 600-ml. beaker, using 10 ml. of methanol to wash out the flask, sufficient sodium hydroxide is added (Note 6) to bring the pH to about 3 (Hydrion test paper or more accurately with methyl orange indicator), and water is added to bring the volume to about 300 ml. The mixture is stirred in an ice bath until the oily layer solidifies, and the crude crystalline material is collected by suction filtration at about 15° and washed with 100 ml. of water. After vacuum drying at 70°, the yield of crude product is 16–19 g., but this material should be purified before further use.

The crude product is distilled in a short-path distillation apparatus composed of a 125-ml. Claisen flask connected by a ground-glass joint to a receiver which is a 300-ml. round-bottomed flask with side tubulature for evacuation. A 50-g. portion(Note 7) of crude 3-methyloxindole is placed in the distillation flask, which is completely immersed in an oil bath. The product is collected at approximately 132° /1.5 mm. The solid distillate is dissolved in 75 ml. of hot methanol, then 25 ml. of hot water is added. After crystallization has been continued for 24 hours at about 20°, there is obtained 35–37 g. (41–44% from β-propionylphenylhydrazine) of light-yellow crystals, m.p. 122.5–123.5° (softening at 121.5°) (Note 8). Five grams of less pure material is recoverable from the mother liquor and may be distilled with a succeeding batch.

2. Notes

1. Phenylhydrazine and propionic anhydride from Fisher Scientific Company were used without purification by the submitters. The checkers distilled the propionic anhydride before use, since old samples contained considerable propionic acid.
2. The ring closure is so highly exothermic that runs no larger than that described as recommended. Several lots may be combined for distillation, as suggested in the description.
3. The checkers used 40-mesh calcium hydride, from Metal Hydrides, Inc. The submitters report that there may also be used freshly ignited lime (22 g., 0.39 mole), but with a reduction of 10–20% in the yield.
4. The amount of concentrated hydrochloric acid is usually 40 ml. or more,

depending on the quality of the calcium hydride.

5. This procedure is for the purpose of hydrolyzing unchanged starting material.

6. The final pH is brought to about 3 in order to minimize the solubility of 3-methyloxindole in strong acid without precipitating the phenylhydrazine which is present at this point.

7. The checkers obtained the same yields when the product of a single ring closure was distilled and crystallized.

8. After two crystallizations from butanol and two from toluene, the product may be obtained in about 25% recovery as white crystals of m.p. 123.8–124.6°.

3. Discussion

3-Methyloxindole has been prepared by the reduction of α-(2-nitrophenyl)propionic acid,[2] by heating β-propionylhydrazine with lime[3] or with sodium alkoxides,[4] by the reduction of the benzoyl derivative of oxindole-3-aldehyde[5] or 3-(methylaminometehylene)-oxindole,[6] and by the oxidation of skatole with potassium persulfate.[7]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

β-Propionylphenylhydrazine

β-propionylhydrazine

3-(methylaminometehylene)-oxindole

hydrochloric acid (7647-01-0)

methanol (67-56-1)

sodium hydroxide (1310-73-2)

propionic acid (79-09-4)

Phenylhydrazine (100-63-0)

cyclohexane (110-82-7)

butanol (71-36-3)

toluene (108-88-3)

potassium persulfate (7727-21-1)

propionic anhydride (123-62-6)

calcium hydride (7789-78-8)

3-Methyloxindole, Oxindole, 3-methyl- (1504-06-9)

oxindole-3-aldehyde

skatole (83-34-1)

methyl orange (547-58-0)

α-(2-nitrophenyl)propionic acid

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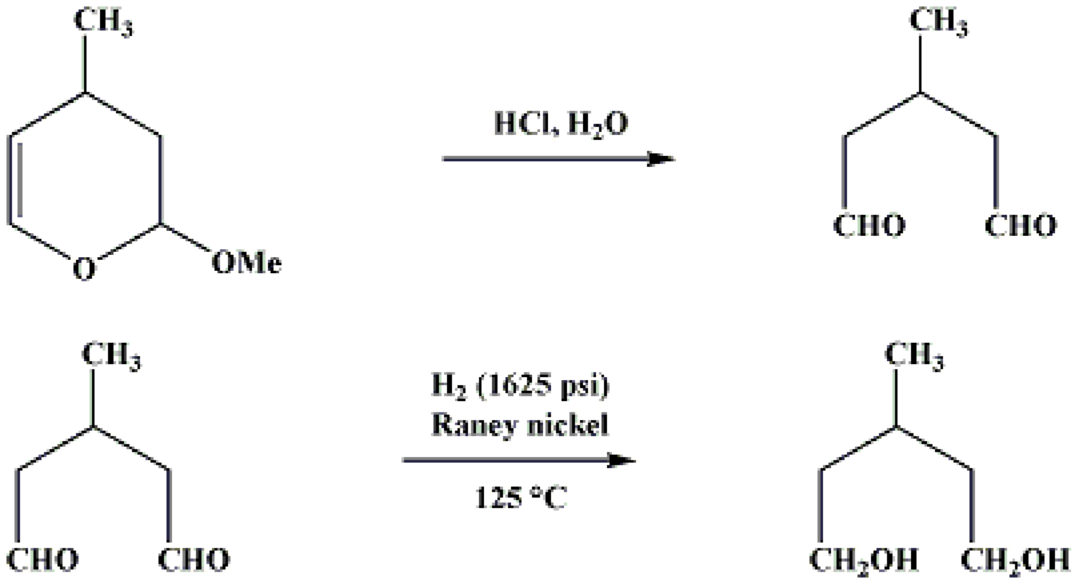
Organic Syntheses, CV 4, 660

3-METHYL-1,5-PENTANEDIOL

[1,5-Pentanediol, 3-methyl-]



Submitted by Raymond I. Longley, Jr. and William S. Emerson[1].
Checked by T. L. Cairns and John F. Harris, Jr..

1. Procedure

In a 2-l. three-necked flask equipped with a stirrer and thermometer are placed 336 g. (2.62 moles) of 3,4-dihydro-2-methoxy-4-methyl-2H-pyran (p. 311), 630 ml. of water, and 24 ml. of concentrated hydrochloric acid (sp. gr. 1.19). The mixture is stirred for 2 hours, during which the temperature may reach 50° but should not be permitted to rise higher. Solid sodium bicarbonate is then added until the solution is neutral to pH indicator paper (Note 1). The entire reaction mixture weighing about 1 kg. together with 39 g. of Raney nickel[2] is introduced into a 3-l. stainless-steel rocking hydrogenation autoclave. A hydrogen pressure of at least 1625 p.s.i. (Note 2) is applied, and the autoclave is heated to 125° and held there with shaking for 4 hours. The mixture is allowed to cool overnight, and the catalyst is separated either by suction filtration through Filter-Cel or by centrifugation. The solution is distilled through a 12-in. Vigreux column. After the methanol and water are separated, the 3-methyl-1,5-pentanediol distils at 139–146°/17 mm., 149–150°/25 mm. The yield is 251–256 g. (81–83%), n_D^{25} 1.4512–1.4521.

2. Notes

1. The submitters report that β-methylglutaraldehyde may be isolated at this point from an analogous hydrolysis. The hydrolysis is carried out with 196 g. of 3,4-dihydro-2-methoxy-4-methyl-2H-pyran in 650 ml. of water and 15 ml. of

concentrated hydrochloric acid for 3 hours. After neutralization with sodium bicarbonate, the solution is saturated with sodium chloride and extracted continuously with ether for 20 hours. The ether is removed by distillation, and the product is dried thoroughly by azeotropic distillation using a benzene-hexane mixture. Distillation affords β-methylglutaraldehyde, b.p. 85–86°/15 mm., n_D^{25} 1.4307–1.4351. Yields up to 90% have been secured. The aldehyde polymerizes on standing but is stable as a 50% solution in water or ether. The monomer may be recovered by careful destructive distillation of the polymer.

2. The initial hydrogen pressure should be high enough that it does not fall below 1000 p.s.i. during the shaking period.

3. Discussion

3-Methyl-1,5-pentanediol has been prepared by the hydrogenation of ethyl β-methylglutarate;[3] by the hydrogenation of ethyl β-methyl-α,γ-dicarbethoxyglutarate;[4] by the hydrogenation of β-methylglutaraldehyde;[5] and by heating 3,4-dihydro-2-methoxy- 4-methyl-2H-pyran with water, hydrogen, and copper-chromium oxide, nickel on kieselguhr,[5] or Raney nickel catalyst.[6]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 677

References and Notes

1. Central Research Department, Monsanto Chemical Company, Dayton 7, Ohio.
2. *Org. Syntheses Coll. Vol.* **3**, 181 (1955).
3. Paden and Adkins, *J. Am. Chem. Soc.*, **58**, 2487 (1936).
4. Wojcik and Adkins, *J. Am. Chem. Soc.*, **55**, 4939 (1933).
5. Longley, Emerson, and Shafer, *J. Am. Chem. Soc.*, **74**, 2012 (1952); Ashley, Collins, Davis, and Sirett, *J. Chem. Soc.*, **1958**, 3298.
6. Smith, U. S. pat. 2,546,019 [*C. A.*, **45**, 7589 (1951)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

3,4-dihydro-2-methoxy- 4-methyl-2H-pyran

hydrochloric acid (7647-01-0)

methanol (67-56-1)

ether (60-29-7)

hydrogen (1333-74-0)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

nickel, Raney nickel (7440-02-0)

Copper-Chromium Oxide

benzene-hexane (1077-16-3)

3,4-Dihydro-2-methoxy-4-methyl-2H-pyran (53608-95-0)

3-Methyl-1,5-pentanediol, 1,5-Pentanediol, 3-methyl- (4457-71-0)

β-Methylglutaraldehyde (6280-15-5)

ethyl β-methylglutarate

ethyl β-methyl-α,γ-dicarbethoxyglutarate

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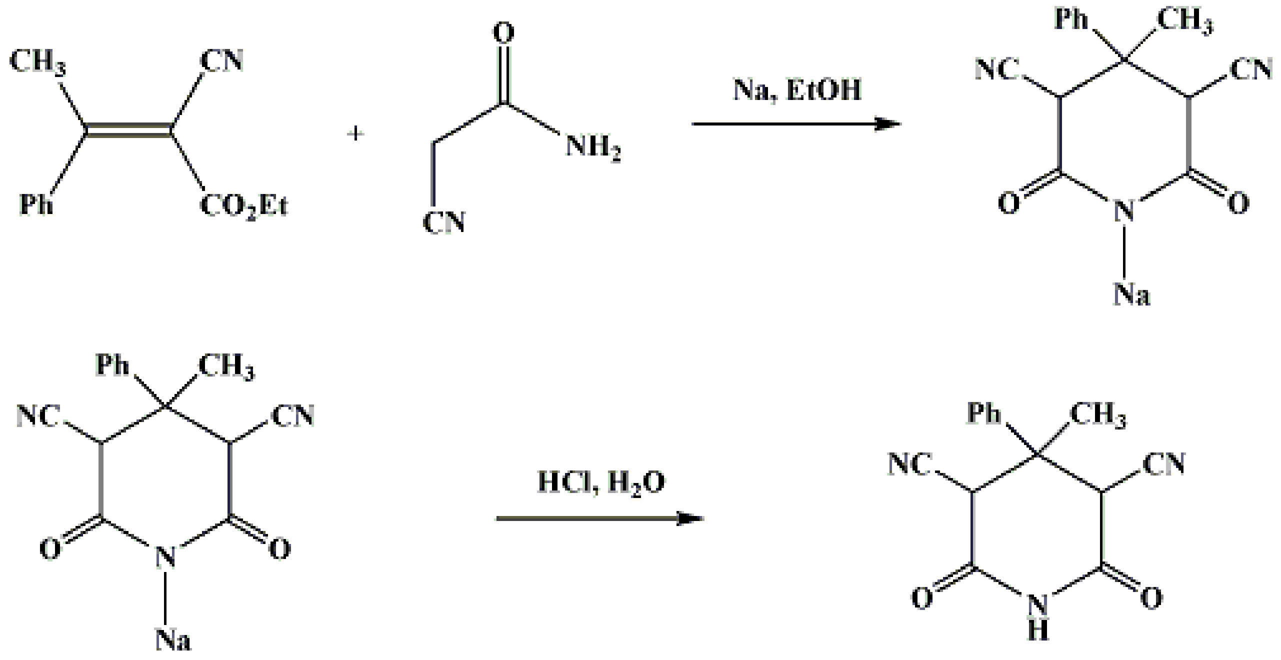
Organic Syntheses, CV 4, 662

β-METHYL-β-PHENYL-α,α'-DICYANOGLUTARIMIDE

[Glutarimide, 2,4-dicyano-3-methyl-3-phenyl-]



Submitted by S. M. McElvain and David H. Clemens[1].
Checked by W. E. Parham, Perry W. Kirklin, Jr., and Wayland E. Noland.

1. Procedure

In a 2-l. Erlenmeyer flask fitted with a reflux condenser and arranged for magnetic stirring are placed 400 ml. of absolute ethanol (Note 1) and 11.5 g. (0.5 g. atom) of sodium added in small portions. After the sodium has reacted (Note 2), the clear solution is cooled to room temperature, and 42.0 g. (0.5 mole) of finely powdered cyanoacetamide (Note 3) is added with stirring over a period of 1 minute. Immediately thereafter 107.6 g. (0.5 mole) of ethyl (1-phenylethylidene)cyanoacetate (p. 463) is added. After about 20 minutes, the mixture becomes homogeneous and is allowed to stand at room temperature for 2 hours. Water (650 ml.) is added, followed by 100 ml. of concentrated hydrochloric acid in 1 portion. The resulting suspension is stirred thoroughly with a glass rod and placed in a refrigerator overnight. The product is then filtered by suction. The filter cake is sucked as dry as possible using a rubber dam, stirred to a paste with a mixture of 150 ml. of water and 50 ml. of 95% ethanol, and sucked dry. This process is repeated using 200 ml. of water, and the product is dried to constant weight in an oven at 45°. The yield is 114–116 g. (90–92%) of the dicyanoglutarimide, m.p. 274–278° (dec.) (Note 4).

2. Notes

1. Commercially available absolute ethanol is used without further drying.
2. The checkers report that the sodium ethoxide solution should be used promptly in order to avoid the formation of colored impurities.

3. Eastman Kodak white label grade is used after grinding in a mortar.
4. Recrystallization from absolute ethanol gives glistening plates melting at 286–287° (dec.).

3. Discussion

β-Methyl-β-phenyl-α,α'-dicyanoglutarimide has been prepared in low yield by the Guareschi condensation of acetophenone, ethyl cyanoacetate, and ammonia.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 664

References and Notes

1. University of Wisconsin, Madison, Wisconsin.
2. Phalnikar and Nargund, *J. Univ. Bombay*, **6**, Pt. II, 102 (1937) [*C. A.*, **32**, 3763 (1938)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

β-METHYL-β-PHENYL-α,α'-DICYANOGLUTARIMIDE

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

Acetophenone (98-86-2)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

CYANOACETAMIDE (107-91-5)

Ethyl cyanoacetate (105-56-6)

ETHYL (1-PHENYLETHYLIDENE)CYANOACETATE

Glutarimide, 2,4-dicyano-3-methyl-3-phenyl- (6936-95-4)

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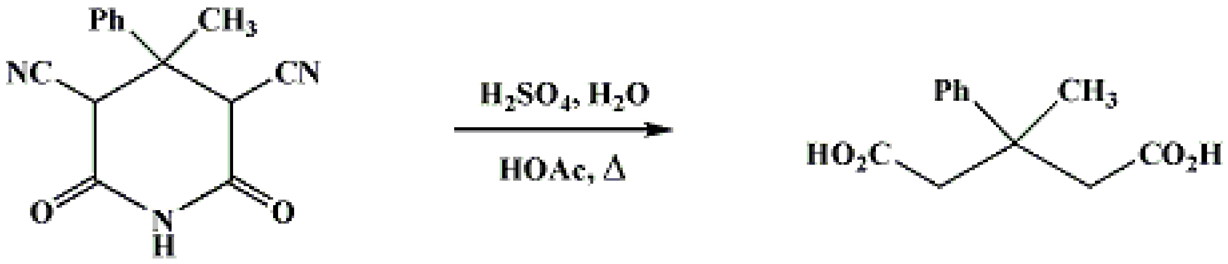
Organic Syntheses, *CV 4, 664*

β-METHYL-β-PHENYLGLUTARIC ACID

[Glutaric acid, 3-methyl-3-phenyl-]



Submitted by S. M. McElvain and David H. Clemens[1].
Checked by W. E. Parham, Perry W. Kirklin, Jr., and Wayland E. Noland.

1. Procedure

In a 3-l. round-bottomed flask fitted with a small glass paddle stirrer and a reflux condenser are placed 101 g. (0.4 mole) of β-methyl-β-phenyl-α,α'-dicyanoglutarimide (p. 662), and a mixture of 500 ml. of water, 500 g. of concentrated sulfuric acid, and 400 ml. of glacial acetic acid. Without starting the stirrer (Note 1), the mixture is heated under reflux for 2 hours. Then the stirrer is cautiously started, and reflux is continued for a total of 80 hours. The reaction mixture is transferred to a 6-l. Erlenmeyer flask, 3 l. of water is added and the mixture cooled in a refrigerator overnight. The precipitated acid is filtered by suction (Note 2), washed with 100 ml. of water, and air-dried to constant weight. The crude, dry product is swirled for 5 minutes with 200 ml. of benzene, filtered by suction, washed with two 100-ml. portions of benzene, and again air-dried. The yield of acid, m.p. 136–140°, is 64.5–68 g. (72.5–76.5%) (Note 3) and (Note 4).

2. Notes

1. Use of the stirrer during the first 2 hours of the hydrolysis results in excessive foaming.
2. In some runs a small amount of dark tar adhered to the side of the flask. This material was not isolated in the filtration.
3. The product is pure enough for most purposes, but it may be further purified by recrystallization from water (100 ml. for 20 g. of acid) to give material melting at 140–142° in 95% yield.
4. If the alkyl group of a β-alkyl-β-phenyl-α,α'-dicyanoglutarimide is larger than the methyl group, the hydrolysis to the corresponding glutaric acid should be modified as described by McElvain and Clemens, *J. Am. Chem. Soc.*, **80**, 3915 (1958).

3. Discussion

β-Methyl-β-phenylglutaric acid has been prepared by the hydrolysis of β-methyl-β-phenyl-α,α'-dicyanoglutarimide with sulfuric acid, and also by acid hydrolysis of the condensation product of 1,1-dichloroethylbenzene and ethyl sodiomalonate.[2]

References and Notes

1. University of Wisconsin, Madison, Wisconsin.
2. Phalnikar and Nargund, *J. Univ. Bombay*, **6**, Pt. II, 102 (1937) [*C. A.*, **32**, 3763 (1938).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

β-METHYL-β-PHENYL-α,α'-DICYANOGLUTARIMIDE

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

Benzene (71-43-2)

β-Methyl-β-phenylglutaric acid, Glutaric acid, 3-methyl-3-phenyl- (4160-92-3)

1,1-dichloroethylbenzene

ethyl sodiomalonate

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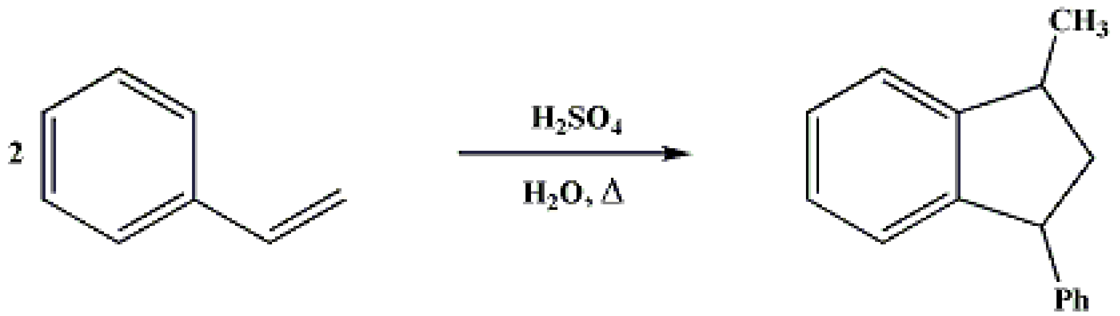
Organic Syntheses, CV 4, 665

1-METHYL-3-PHENYLINDANE

[Indan, 1-methyl-3-phenyl-]



Submitted by Milton J. Rosen[1]
Checked by R. T. Arnold and William K. Witsiepe.

1. Procedure

In a 500-ml. three-necked round-bottomed flask fitted with a mechanical stirrer and a reflux condenser are placed 50 g. (0.48 mole) of styrene (Note 1) and a previously cooled solution of 100 ml. of concentrated sulfuric acid in 150 ml. of water. The mixture is stirred vigorously (Note 2) and heated under reflux in an oil bath for approximately 4 hours.

Without interrupting stirring or heating, 50 ml. of concentrated sulfuric acid is added slowly through the condenser, and the mixture is stirred and heated for an additional 12 hours (Note 3).

The reaction mixture is cooled, cautiously poured into 250 ml. of cold water with stirring, and allowed to separate into layers. The upper hydrocarbon layer is removed, and the lower layer is extracted with three 50-ml. portions of ether. The combined ether extracts and hydrocarbon layer are washed successively with about 30 ml. each of a saturated solution of sodium bicarbonate, water, and a saturated solution of calcium chloride, and then dried over anhydrous calcium chloride. The ether is removed by distillation, and the product is distilled under reduced pressure. The yield of 1-methyl-3-phenylindane, b.p. 168–169°/16 mm. (Note 4), n_D^{20} 1.5811 ± 0.0005, is 38.5–40.5 g. (77–81%) (Note 5).

2. Notes

1. Commercial styrene, distilled from a water bath at about 80–100 mm. pressure just before use, is employed.
2. It is essential to use an efficient stirring device, capable of forming a dispersion of the styrene in the acid layer.

3. The sulfuric acid is added in two portions in order to minimize higher-polymer formation.[2]
4. The product also distils at 150–151°/6.5 mm.
5. The submitter states that α-methylstyrene can be converted to 1,1,3-trimethyl-3-phenylindane, b.p. 154–155°/8 mm.., m.p. 50.4–52.1°, by the same general procedure. The yield is 86–89% of the theoretical amount. The 1,1,3-trimethyl-3-phenylindane may be purified further by one recrystallization from three times its weight of 80% isopropyl alcohol. The yield of purified product, m.p. 51.8–52.3°, is 80–83% (based on the original weight of monomer used).

3. Discussion

1-Methyl-3-phenylindane has been prepared by the treatment of dimeric styrene[3] with aqueous sulfuric acid, and by the hydrogenation of 1-methyl-3-phenyl-Δ^2-indene.[4]

References and Notes

1. Brooklyn College, Brooklyn, New York.
2. Rosen, *J. Org. Chem.*, **18**, 1701 (1953).
3. Spoerri and Rosen, *J. Am. Chem. Soc.*, **72**, 4918 (1950).
4. Müller and Körmendy, *J. Org. Chem.*, **18**, 1237 (1953).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

1-methyl-3-phenyl-Δ^2-indene

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

ether (60-29-7)

sodium bicarbonate (144-55-8)

isopropyl alcohol (67-63-0)

styrene (100-42-5)

1-Methyl-3-phenylindane, Indan, 1-methyl-3-phenyl- (6416-39-3)

α-methylstyrene (98-83-9)

1,1,3-trimethyl-3-phenylindane

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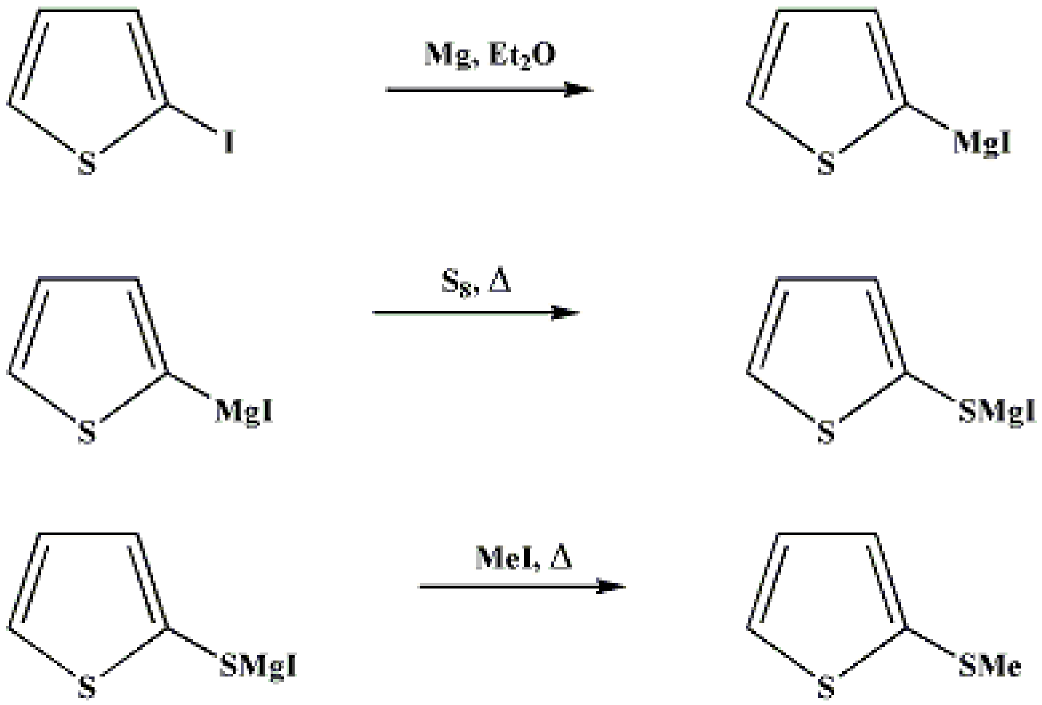
Organic Syntheses, CV 4, 667

METHYL 2-THIENYL SULFIDE

[Thiophene, 2-(methylthio)-]



Submitted by J. Cymerman-Craig and J. W. Loder[1].
Checked by Charles C. Price and E. A. Dudley.

1. Procedure

In a 1-l. three-necked flask fitted with a liquid-sealed mechanical stirrer, a reflux condenser, and a dropping funnel are placed 8 g. (0.33 g. atom) of magnesium turnings and 600 ml. of absolute ether. There is placed in the dropping funnel 70 g. (0.33 mole) of 2-iodothiophene (p.545), the stirrer is started, and about 10 ml. of the iodothiophene is added. The reaction generally begins within a few minutes (Note 1), and the iodothiophene is then added dropwise at such a rate that moderate refluxing occurs. When the addition is complete, the mixture is refluxed gently until only a small residue of unreacted magnesium remains. The solution is then cooled in an ice bath, the dropping funnel is removed, and 10.7 g. (0.33 g. atom) of finely powdered sulfur (Note 2) is added (Note 3), the funnel is replaced, and the mixture is refluxed (Note 4) for 45 minutes. The solution is again cooled in an ice bath, and 22.6 ml. (0.36 mole) of methyl iodide is added dropwise from the funnel, and the stirring is then discontinued (Note 5). The reaction mixture is refluxed 10 hours. It is then cooled, and an aqueous solution of ammonium chloride is run in with vigorous stirring (Note 6). The liquid is transferred to a separatory funnel, the lower aqueous layer is run off, and the ethereal solution is washed three times with a 2% solution of potassium hydroxide, then with water, and finally is dried over anhydrous sodium sulfate. The ether is removed by

distillation at ordinary pressure, and the residual dark liquid is distilled under reduced pressure. The yield of colorless methyl 2-thienyl sulfide is 23–26 g. (53–60%), b.p. 82–86°/22 mm., n_D^{25} 1.5978 (Note 7) and (Note 8).

2. Notes

1. If the reaction does not start, it may be assisted by the addition of a small amount of methylmagnesium iodide in ethereal solution.
2. The sulfur was distilled and then ground in a mortar before use.
3. The mechanical stirring is continued. The sulfur dissolves during the refluxing period to give a clear yellow solution. A sludge which adheres to the bottom of the flask may form, but the yield is unaltered.
4. On reheating, a vigorous reaction with the sulfur occurs. A means of cooling the reaction flask should be at hand to ensure control of the reaction.
5. The solution may be left overnight at this stage, sealed under nitrogen.
6. The decomposition of the unreacted Grignard reagent is best carried out in a hood to remove the strong odor of thiols.
7. Considerable decomposition occurs if distillation is attempted at atmospheric pressure. The product is sometimes pale yellow, and darkens slightly on standing.
8. A dark oil remains which decomposes at this pressure when strongly heated.

3. Discussion

Methyl 2-thienyl sulfide has been prepared by the action of phosphorus trisulfide on dimethyl succinate[2] and by the action of methyl iodide on the sodium salt of 2-thiophenethiol,[3] both of which methods are of little preparative value. The procedure described above is that of Cymerman-Craig and Loder.[4] 2-Bromothiophene has been used in the latter method in place of the iodine derivative.[5]

References and Notes

1. University of Sydney, Sydney, Australia.
2. Steinkopf and Leonhardt, *Ann.*, **495**, 166 (1932).
3. Meyer and Neure, *Ber.*, **20**, 1756 (1887).
4. Cymerman-Craig and Loder, *J. Chem. Soc.*, **1954**, 237.
5. Gol'dfarb, Kalik, and Kirmalova, *Zhur. Obshchei Khim.*, **29**, 2034 (1959) [*C. A.*, **54**, 8775 (1960)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

phosphorus trisulfide

ether (60-29-7)

ammonium chloride (12125-02-9)

magnesium, magnesium turnings (7439-95-4)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

sulfur (7704-34-9)

iodine (7553-56-2)

potassium hydroxide (1310-58-3)

Methyl iodide (74-88-4)

methylmagnesium iodide (917-64-6)

2-IODOTHIOPHENE, iodothiophene (3437-95-4)

Methyl 2-thienyl sulfide, Thiophene, 2-(methylthio)- (5780-36-9)

dimethyl succinate (106-65-0)

2-Bromothiophene (1003-09-4)

sodium salt of 2-thiophenethiol

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Organic Syntheses, CV 4, 669

METHYL β-THIODIPROPIONATE

[Propionic acid, 3,3'-thiodi-, dimethyl ester]

Submitted by Edward A. Fehnel and Marvin Carmack[1].
Checked by Arthur C. Cope and James J. Ryan.

1. Procedure

Caution! This preparation should be conducted in a hood to avoid exposure to poisonous hydrogen sulfide.

A mixture of 150 g. (1.74 moles) of methyl acrylate (Note 1), 100 g. (0.73 mole) of sodium acetate trihydrate, and 800 ml. of 95% ethanol (Note 2) is placed in a 2-l. two-necked flask fitted with an efficient reflux condenser and a sintered-glass bubbler tube which reaches almost to the bottom of the flask. The mixture is heated on the steam bath until all the solid is dissolved and the solution is refluxing gently. A steady stream of hydrogen sulfide gas (Note 3) is introduced into the boiling solution through the bubbler tube while heating is continued for a period of 25 hours. The gas flow is then stopped, the condenser is changed for distillation, and the solvent, along with some unreacted methyl acrylate, is distilled from the mixture on the steam bath. About 200 ml. of ether and 400 ml. of water are added to the residue in the flask, and after thorough agitation the layers are separated. The aqueous layer is washed with four 50-ml. portions of ether, and the washings are added to the original ether layer. The combined ether extracts are dried over anhydrous sodium sulfate, the ether is removed by distillation on the steam bath, and the residue is distilled under reduced pressure. Methyl β-thiodipropionate is obtained as a colorless oil, b.p. 162–164°/18 mm., 138–139°/6mm.; n_D^{25} 1.4713. The yield is 128–145 g. (71–81%).

2. Notes

1. A good grade of commercial methyl acrylate containing hydroquinone is entirely satisfactory. Material of doubtful quality may be redistilled (into a receiver containing hydroquinone), b.p. 78–81°.
2. Either methanol or 95% ethanol may be used as the solvent. No ester interchange was observed to occur under the conditions employed.
3. Commercial tank hydrogen sulfide was used. The flow was regulated by passing the gas through a gas-washing bottle containing a little water. A rate of about 3–5 bubbles per second was maintained during the reaction.

3. Discussion

β-Thiodipropionic acid esters have been prepared by the addition of hydrogen sulfide to the

corresponding acrylic esters in the presence of basic catalysts with [2] or without [3] solvents. The ethyl ester has also been prepared by the treatment of ethyl β-chloropropionate with sodium sulfide.[4]

References and Notes

1. University of Pennsylvania, Philadelphia, Pennsylvania.
2. I. G. Farbenind. A.-G., Fr. pat. 797,606 [*Chem. Zentr.*, **107, II**, 1062 (1936)] [*C. A.*, **30**, 8244 (1936)]; Ger. pat. 669,961 [*C. A.*, **33**, 5415 (1939)].
3. Gershbein and Hurd, *J. Am. Chem. Soc.*, **69**, 241 (1947).
4. Arndt and Bekir, *Ber.*, **63**, 2393 (1930).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Methyl β-thiodipropionate

ethanol (64-17-5)

methanol (67-56-1)

ether (60-29-7)

hydroquinone (123-31-9)

hydrogen sulfide (7783-06-4)

sodium sulfate (7757-82-6)

sodium sulfide (1313-82-2)

methyl acrylate (96-33-3)

sodium acetate trihydrate (6131-90-4)

ethyl β-chloropropionate (623-71-2)

Propionic acid, 3,3'-thiodi-, dimethyl ester (4131-74-2)

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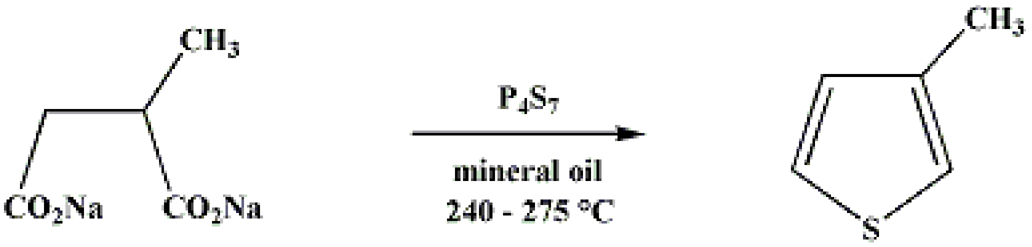
Organic Syntheses, CV 4, 671

3-METHYLTHIOPHENE

[Thiophene, 3-methyl-]



Submitted by R. F. Feldkamp and B. F. Tullar[1].
Checked by Cliff S. Hamilton, Y. H. Wu, and William J. Raich.

1. Procedure

Caution! This preparation should be conducted in a well-ventilated hood to avoid exposure to hydrogen sulfide.

A 1-l. three-necked round-bottomed flask is fitted with a ground-glass-sealed stirrer, an immersed thermometer, a gas inlet tube, an addition funnel (Note 1), and a distilling head, wrapped with asbestos cloth, connected to a condenser arranged for distillation. The flask is charged with 150 ml. of mineral oil (Note 2), and the system is thoroughly swept out with a slow stream of carbon dioxide admitted through the gas inlet tube while the flask is heated with an electric heating mantle. When the temperature of the oil reaches 240–250°, a slurry of 90 g. (0.51 mole) of powdered anhydrous disodium methylsuccinate (Note 3) and 100 g. (0.287 mole) of phosphorus heptasulfide (Note 4) in 250 ml. of mineral oil is placed in the addition funnel. With efficient stirring and a slow continuous stream of carbon dioxide passing through the system, the slurry is added to the hot mineral oil at such a rate as to effect fairly rapid distillation of 3-methylthiophene accompanied by considerable gas evolution (mostly hydrogen sulfide). During the addition, which requires about 1 hour, the temperature is maintained at 240–250° (Note 5). The temperature is then raised to 275° and stirring continued in the inert atmosphere for an additional hour or until distillation ceases. The total distillate, amounting to 33–38 ml., is washed with two 50-ml. portions of 5% sodium hydroxide solution and finally with 50 ml. of water (Note 6). The crude 3-methylthiophene is then distilled (Note 7). A small fore-run is discarded, and the fraction boiling between 112° and 115° is collected. The yield is 26–30 g. (52–60%), n_D^{25} 1.5170 ± 0.0005 (Note 8), (Note 9), and (Note 10).

2. Notes

1. A gravity funnel fitted with a glass rod of suitable diameter is satisfactory for

regulating the addition of the slurry.

2. Dowtherm A may also be used as a solvent for this reaction. However, because the boiling point (about 265°) is close to the reaction temperature, considerable quantities of Dowtherm distil along with the 3-methylthiophene. The total distillate amounts to 60–75 ml., which after washing and fractionally distilling gives the same yield as with mineral oil. Dowtherm gives a more fluid slurry and final residue and can be easily recovered by distillation at reduced pressure.

3. Disodium methylsuccinate was made by hydrogenating a concentrated solution of itaconic acid supplied by Chas. Pfizer and Company in aqueous sodium hydroxide (pH 8.7) over Raney nickel catalyst at 50 p.s.i. and 80–100°. After the catalyst was removed by filtration, the product was isolated by evaporation of the water and the residue was dried in a vacuum oven at 70–80°.

4. Phosphorous heptasulfide was obtained from the Oldbury Electrochemical Company. It has been shown[2] that the 'phosphorus trisulfide' used by earlier workers for such fusions was actually somewhat impure phosphorus heptasulfide.

5. The rate of addition of the slurry and the reaction temperature should be carefully controlled. About two-thirds of the crude 3-methylthiophene distillate is collected during the addition of the slurry. Further heating at 260–275° gives the remainder of the material.

6. An emulsion may be obtained on further washing with water. A small amount of sodium chloride (2–3 g.) dissolved in the wash water assists in breaking such emulsions.

7. Rather violent foaming may occur during this distillation but is easily controlled in a 250-ml. flask. The distilling head and flask may be wrapped in asbestos cloth in order to increase the speed of distillation.

8. When fresh mineral oil was used (first run), a yield of 52–54% was obtained. However, when the recovered mineral oil (Note 9) was used, the yield increased to 60%.

9. The reaction residue is allowed to cool to room temperature and is filtered by suction. The dark mineral oil filtrate may be reused in the process. The malodorous filter cake is not pyrophoric and is almost completely soluble in water or dilute alkali with liberation of hydrogen sulfide.

10. The submitters obtained comparable yields on twice the scale described. They also applied the same procedure to disodium succinate to give a 25% yield of thiophene comparable to the yield obtained by dry fusion.[3]

3. Discussion

3-Methylthiophene has been prepared by the dry fusion of a salt of methylsuccinic acid and phosphorus 'trisulfide.'[4] This reaction was later investigated quite completely in respect to ratio of reactants, rate of heating, carbon dioxide atmosphere, and dilution of reactants with sand.[5] An excellent technical method for preparing methylthiophenes has been described which involves a vapor-phase reaction of preheated sulfur with

pentanes.[6] 3-Methylthiophene has also been prepared by adding 50% crude isoprene (amylenes) to molten sulfur at 350°,[7] and by passing a mixture of 2-methyl-2-butene and sulfur dioxide over a chromium oxide-aluminum oxide catalyst at 450°.[8]

References and Notes

1. Sterling-Winthrop Research Institute, Rensselaer, New York.
2. Pernert and Brown, *Chem. Eng. News*, **27**, 2143 (1949).
3. *Org. Syntheses Coll. Vol.* **2**, 578 (1943).
4. Volhard and Erdmann, *Ber.*, **18**, 454 (1885).
5. Linstead, Noble, and Wright, *J. Chem. Soc.*, **1937**, 915.
6. Rasmussen and Hansford, U. S. pat. 2,450,686 [*C. A.*, **43**, 1067 (1949)].
7. Shepard, Henne, and Midgley, Jr., *J. Am. Chem. Soc.*, **56**, 1355 (1934).
8. Yur'ev and Khmel'nitskii, *Doklady Akad. Nauk S.S.S.R.*, **92**, 101 (1953) [*C. A.*, **48**, 10725 (1954)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

phosphorus trisulfide

phosphorus heptasulfide

Phosphorous heptasulfide

phosphorus 'trisulfide.'

chromium oxide-aluminum oxide

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

hydrogen sulfide (7783-06-4)

sulfur dioxide (7446-09-5)

sulfur (7704-34-9)

carbon dioxide (124-38-9)

nickel (7440-02-0)

Thiophene (110-02-1)

Itaconic acid (97-65-4)

2-methyl-2-butene (513-35-9)

disodium succinate (150-90-3)

ISOPRENE (78-79-5)

Methylsuccinic acid (498-21-5)

3-Methylthiophene, Thiophene, 3-methyl- (616-44-4)

disodium methylsuccinate

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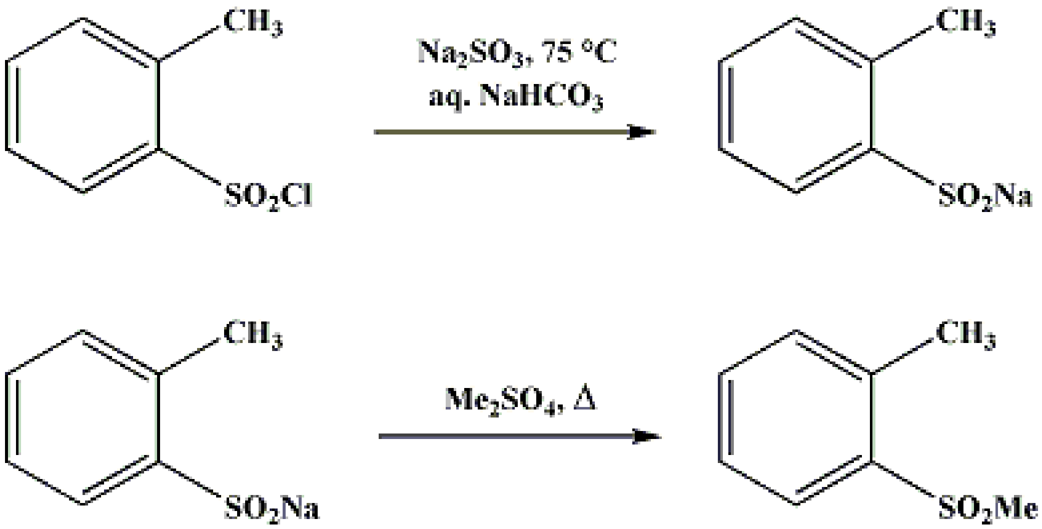
Organic Syntheses, CV 4, 674

METHYL *p*-TOLYL SULFONE

[Sulfone, methyl *p*-tolyl]



Submitted by L. Field and R. D. Clark[1].
Checked by John C. Sheehan and M. Gertrude Howell.

1. Procedure

In a 4-l. beaker (Note 1) provided with a mechanical stirrer and thermometer are placed 600 g. (4.76 moles) of anhydrous sodium sulfite, 420 g. (5.0 moles) of sodium bicarbonate, and 2.4 l. of water. The mixture is heated on a hot plate at 70–80° and is maintained at this temperature by switching the hot plate off occasionally, while 484 g. (2.54 moles) of *p*-toluenesulfonyl chloride (Note 2) is added in portions of 5–10 g., with stirring, during 3 hours. When addition is complete, the mixture is heated and stirred at 70–80° for 1 hour (Note 3). The mixture is then removed from the hot plate and allowed to stand for 4 to (preferably) 10 hours.

The solid sodium *p*-toluenesulfinate which separates is collected by filtration and mixed with 400 g. (4.76 moles) of sodium bicarbonate and 490 g. (370 ml., 3.88 moles) of dimethyl sulfate (Note 4) in a 3-l. three-necked round-bottomed flask equipped with a mechanical stirrer, a reflux condenser, and a 1-l. separatory funnel containing 925 ml. of water. Water (75–100 ml.) is added from the separatory funnel to make the mixture fluid enough for stirring. The remainder of the water is then added dropwise, with stirring, during 3 hours. The mixture is then heated under reflux for 20 hours.

After the mixture is cooled to 75°, 200 ml. of benzene is added (Note 5). The mixture is stirred briefly, and the liquid is decanted from the solid into a 5-l. separatory funnel. The aqueous layer is separated and extracted again with 200 ml. of benzene. The aqueous layer is then returned to the separatory funnel, and the solid in the reaction

flask is washed in with it by means of 2 l. of water. The mixture is shaken with 200-ml. portions of benzene until all solid has dissolved (usually three portions of benzene suffice). All the benzene extracts are combined and dried with 20 g. of anhydrous calcium chloride. The drying agent is removed by filtration and washed with two 20-ml. portions of benzene. Benzene is removed from the filtrate by distillation under reduced pressure (Note 6), and the solid which separates is dried further at about 10 mm. and room temperature to constant weight. The yield (Note 2) of methyl *p*-tolyl sulfone is 298–317 g. (69–73%), m.p. 83–87.5°. Further purification is generally unnecessary, but, if desired, the product may be recrystallized from carbon tetrachloride or ethanol-water (1:1). The submitters state that the method may be extended to the preparation of methyl phenyl sulfone and, presumably, of methyl aryl sulfones generally (Note 7).

2. Notes

1. A porcelainized metal bucket is a convenient alternative.
2. The submitters used Eastman Kodak Company practical grade; although the solid is somewhat oily, the m.p. is 66–68°. The checkers used *p*-toluenesulfonyl chloride purchased from Matheson, Coleman and Bell and obtained a yield of 78–82%.
3. The volume at the end of the heating period should not exceed 2.4 l. If, after 1 hour of heating, the volume exceeds 2.4 l., the mixture is heated longer.
4. Eastman Kodak Company practical grade was used, b.p. 69–70°/10 mm. Dimethyl sulfate is toxic and must be handled with caution. This part of the preparation should be run in a hood with provision for containing the contents should breakage occur. It is unlikely that any dimethyl sulfate survives the 20-hour reflux period however, and the submitters reported that no difficulty whatever was encountered in handling the mixture after this point without special precautions; nevertheless, they recommend that the possible presence of dimethyl sulfate be borne in mind. Ammonia is a specific antidote for dimethyl sulfate and should be at hand to destroy any accidentally spilled. A solution of a detergent in dilute ammonia water may be used to clean glassware used in transfers. The hazards associated with dimethyl sulfate are described by Sax.[2]
5. Extraction with benzene improves the yield somewhat but offers the more important advantage of permitting effective drying of the sulfone when it is to be used in metalation reactions. If this advantage is not sought, the reaction mixture simply can be allowed to cool to room temperature and to stand until crystallization is complete (2–3 hours). The solid is then collected by filtration and washed with water (about six 200-ml. portions) until the washings give no precipitate with barium chloride solution. The yield is 272 g. (63%); it can be increased by 12.6 g. (66%) by extraction of the mother liquor and wash water. The sulfone thus obtained contains only 0.25% of benzene-insoluble material and has m.p. 86.5–87.5°.
6. If the benzene is removed at a temperature not exceeding 50°, the sulfone is obtained as well-formed crystals.

7. According to the submitters, methyl phenyl sulfone[3] is obtained similarly from benzenesulfonyl chloride in 66–69% yields, m.p. 86–88°.

3. Discussion

Methyl *p*-tolyl sulfone has been prepared by oxidation of methyl *p*-tolyl sulfide with hydrogen peroxide[4,5] or ruthenium tetroxide,[6] by alkylation of sodium *p*-toluenesulfinate with methyl iodide[7,8] or with methyl potassium sulfate,[9] by decarboxylation of *p*-tolylsulfonylacetic acid,[7] by thermal decomposition of tetramethylammonium *p*-toluenesulfinate,[10] by reaction of *cis*-bis-(*p*-tolylsulfonyl) ethene with sodium hydroxide (low yield),[11] by the reaction of methanesulfonyl chloride with toluene in the presence of aluminum chloride (mixture of isomers),[12] by reaction of alkali with 3-*p*-tolylsulfonyl-7-hydroxynaphtho-α-pyrone,[13] by heating allyl *p*-tolyl sulfone with sodium hydroxide;[14] and by the decomposition of sodium *p*-toluenesulfonyl-acetate.[15]

The method described here is that of Field and Clark.[3] It involves preparation of sodium *p*-toluenesulfinate by the procedure of Oxley et al.[8] and alkylation by modification of a method used by Baldwin and Robinson[16] for the preparation of methyl phenyl sulfone.

References and Notes

1. Vanderbilt University, Nashville, Tennessee.
2. Sax, *Handbook of Dangerous Materials*, p. 147, Reinhold Publishing Corporation, New York, 1951.
3. Field and Clark, *J. Org. Chem.*, **22**, 1129 (1957).
4. Zincke and Frohneberg, *Ber.*, **43**, 837 (1910).
5. Gilman and Beaber, *J. Am. Chem. Soc.*, **47**, 1449 (1925).
6. Djerassi and Engle, *J. Am. Chem. Soc.*, **75**, 3838 (1953).
7. Otto, *Ber.*, **18**, 154 (1885).
8. Oxley, Partridge, Robson, and Short, *J. Chem. Soc.*, **1946**, 763.
9. Otto, *Ann.*, **284**, 300 (1895).
10. Meyer, *Chem. Zentr.*, **80**, 1800 (1909).
11. Truce and McManimie, *J. Am. Chem. Soc.*, **76**, 5745 (1954).
12. Truce and Vriesen, *J. Am. Chem. Soc.*, **75**, 5032 (1953).
13. Tröger and Dunkel, *J. prakt. Chem.*, **104**, 311 (1922).
14. Backer, Strating, and Drenth, *Rec. trav. chim.*, **70**, 365 (1951).
15. O'Connor and Verhoek, *J. Am. Chem. Soc.*, **80**, 288 (1958).
16. Baldwin and Robinson, *J. Chem. Soc.*, **1932**, 1445.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

3-p-tolylsulfonyl-7-hydroxynaphtho-α-pyrone

calcium chloride (10043-52-4)

ammonia (7664-41-7)

Benzene (71-43-2)

sodium sulfite (7757-83-7)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

carbon tetrachloride (56-23-5)

dimethyl sulfate (77-78-1)

barium chloride (10361-37-2)

Benzenesulfonyl chloride (98-09-9)

aluminum chloride (3495-54-3)

toluene (108-88-3)

hydrogen peroxide (7722-84-1)

Methyl iodide (74-88-4)

Methanesulfonyl chloride (124-63-0)

methyl potassium sulfate (562-54-9)

methyl phenyl sulfone (3112-85-4)

ruthenium tetroxide (20427-56-9)

p-Toluenesulfonyl chloride (98-59-9)

Sodium p-toluenesulfinate

Methyl p-tolyl sulfone, Sulfone, methyl p-tolyl (3185-99-7)

methyl p-tolyl sulfide (623-13-2)

p-tolylsulfonylacetic acid (3937-96-0)

tetramethylammonium p-toluenesulfinate

cis-bis-(p-tolylsulfonyl)ethene

allyl p-tolyl sulfone (3112-87-6)

sodium p-toluenesulfonyl-acetate

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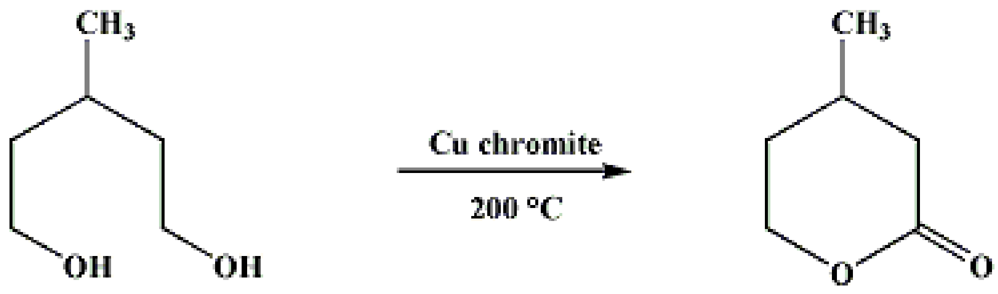
β-METHYL-δ-VALEROLACTONE

[Valeric acid, 5-hydroxy-3-methyl-, δ-lactone]



Submitted by Raymond I. Longley, Jr. and William S. Emerson[1].
Checked by T. L. Cairns and W. W. Gilbert.

1. Procedure

A 1-l. three-necked flask fitted with an efficient stirrer, a thermometer, and a reflux condenser attached to a device for measuring gas evolution (Note 1) is charged with 197 g. (1.67 moles) of 3-methyl-1,5-pentanediol (p. 660) and 10 g. of copper chromite (Note 2). The mixture is heated rapidly to 200° (Note 3) with good stirring and is held at 195–205° for 1.5–3.0 hours, during which time 3.1 cu. ft. of hydrogen is evolved (Note 4). The product is distilled directly from the flask with stirring through a 2 by 120 cm. Vigreux column (Note 5). The yield of β-methyl-δ-valerolactone is 172–180 g. (90–95%), b.p. 110–111°/15 mm., n_D^{25} 1.4495.

2. Notes

1. A standard wet test meter may be used.
2. Copper chromite is prepared according to *Organic Syntheses*[2] and washed with sodium bicarbonate solution. The glycol is slurried with sodium bicarbonate and filtered before use.
3. At this point gas evolution becomes so rapid that the temperature tends to drop slightly.
4. If gas evolution subsides more catalyst may be added.
5. The column is substituted for the reflux condenser in the same set-up. Stirring during distillation prevents serious bumping.

3. Discussion

β-Methyl-δ-valerolactone has been prepared by heating 3-methyl-1,5-pentanediol with copper chromite in the liquid phase,[3] by passing the vapors of 3-methyl-1,5-pentanediol over copper on pumice,[3] by heating 2-methoxy-4-methyl-3,4-dihydro-2H-

pyran with water and copper chromite,[3] by treating 3-methylglutaraldehyde with aqueous alkali,[3] and by reducing β-methylglutaric anhydride with sodium and ethanol.[4] The present method was first developed by Kyrides and Zienty.[5]

References and Notes

1. Monsanto Chemical Company, Dayton 7, Ohio.
2. *Org. Syntheses Coll. Vol.* **2**, 142 (1943).
3. Longley, Emerson, and Shafer, *J. Am. Chem. Soc.*, **74**, 2012 (1952); Emerson, Longley, and Shafer (to Monsanto Chemical Co.), U. S. pat. 2,680,118 [*C. A.*, **49**, 6315 (1955)].
4. Sircar, *J. Chem. Soc.*, **1928**, 898.
5. Kyrides and Zienty, *J. Am. Chem. Soc.*, **68**, 1385 (1946).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

hydrogen (1333-74-0)

sodium bicarbonate (144-55-8)

copper (7440-50-8)

sodium (13966-32-0)

COPPER CHROMITE

2-methoxy-4-methyl-3,4-dihydro-2H-pyran (53608-95-0)

β-Methylglutaric anhydride (4166-53-4)

3-Methyl-1,5-pentanediol (4457-71-0)

3-methylglutaraldehyde (6280-15-5)

β-Methyl-δ-valerolactone, Valeric acid, 5-hydroxy-3-methyl-, δ-lactone (1121-84-2)

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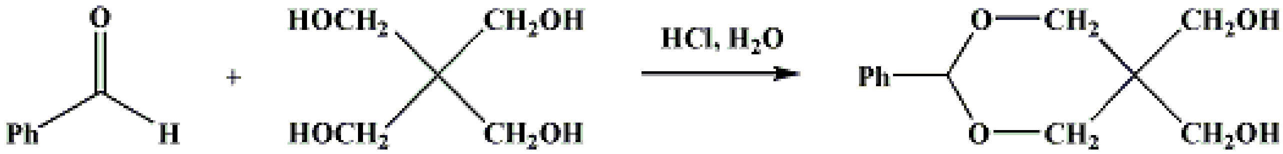
MONOBENZALPENTAERYTHRITOL

[*m*-Dioxane-5,5-dimethanol, 2-phenyl-]



Submitted by C. H. Issidorides and R. Gulen[1].
Checked by M. S. Newman and Arlen B. Mekler.

1. Procedure

In an open 3-l. three-necked flask are placed 180 g. (1.32 moles) of pentaerythritol (Note 1) and 1.3 l. of water. The flask is fitted with an efficient mechanical stirrer and a graduated dropping funnel containing 147 g. (1.38 moles) of benzaldehyde (Note 2). The mixture in the flask is heated until all the solid dissolves and is then allowed to cool undisturbed (Note 3).

When the solution has cooled to room temperature, stirring is started and 6.6 ml. of concentrated hydrochloric acid is added through the open neck of the flask, followed by 30 ml. of benzaldehyde from the dropping funnel. When the precipitate of monobenzalpentaerythritol starts forming, dropwise addition of benzaldehyde is begun (Note 4). After the addition of benzaldehyde is completed, the mixture is stirred for an additional 3 hours (Note 5). The precipitate is collected (Note 6) on a Büchner funnel and washed with ice-cold water which has been made slightly alkaline by addition of sodium carbonate. The solid is transferred to a 3-l. round-bottomed flask, 1 l. of water (slightly alkaline with sodium carbonate) is added, and the mixture is heated to 100° (Note 7). After about 10 minutes at this temperature the hot mixture is filtered quickly through a fluted filter paper (Note 8). The solid remaining on the filter paper is washed with 50 ml. of hot water (made slightly alkaline with sodium carbonate) (Note 9). The combined aqueous filtrates are cooled in an ice bath for several hours, and the crystals are collected on a Büchner funnel and dried. The dry product is heated under reflux for 15 minutes in an Erlenmeyer flask with 200 ml. of toluene, and the hot mixture is allowed to cool to room temperature, with continuous agitation (stirring rod) to prevent formation of hard lumps. Finally, the mixture is cooled in an ice bath for 5 hours, and the solid product is collected on a Büchner funnel and dried (Note 10). The yield of monobenzalpentaerythritol melting at 134–135° is 215–227 g. (73–77%).

2. Notes

1. Eastman Kodak Company white label grade pentaerythritol was used. The checkers used a commercial sample obtained from the Heyden Chemical Corporation.
2. The third neck may be left open and used later for addition of hydrochloric acid and for introduction of the thermometer.
3. The temperature of the solution should not be allowed to go below 25°; otherwise pentaerythritol will precipitate.
4. The addition should take about 2.5 hours. The temperature of the mixture should be kept at 25–29°.

5. If stirring is continued for a substantially longer period, the yield of monobenzalpentaerythritol is somewhat decreased.
6. The product should be collected immediately, as losses result if there is delay at this point.
7. The mixture should be stirred continuously during the heating. The use of a mechanical stirrer is recommended.
8. Use of a steam-heated funnel is recommended.
9. The solid remaining finally on the filter paper may be recrystallized from 1-butanol to give 1–2 g. of dibenzalpentaerythritol melting at 159–160°.
10. The product and the toluene in the Erlenmeyer flask form a solid mass which is difficult to remove. The operation is made easier by adding 70 ml. of ice-cold toluene to the flask and stirring, before transferring the product to the Büchner funnel. One or two additional 20-ml. portions of cold toluene may be used to remove the product completely.

3. Discussion

The procedure described is based on the method of E. Bograchov.[2]

References and Notes

1. American University of Beirut, Beirut, Lebanon.
2. E. Bograchov, *J. Am. Chem. Soc.*, **72**, 2268 (1950).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

sodium carbonate (497-19-8)

benzaldehyde (100-52-7)

1-butanol (71-36-3)

toluene (108-88-3)

Pentaerythritol (115-77-5)

Monobenzalpentaerythritol

dibenzalpentaerythritol

m-Dioxane-5,5-dimethanol, 2-phenyl- (2425-41-4)

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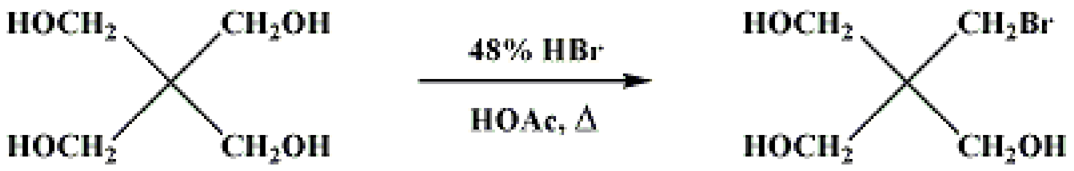
MONOBROMOPENTAERYTHRITOL

[1,3-Propanediol, 2-(bromomethyl)-2-(hydroxymethyl)-]



Submitted by S. Wawzonek, A. Matar, and C. H. Issidorides[1].
Checked by Charles C. Price and G. Venkat Rao.

1. Procedure

In a 3-l. two-necked flask (Note 1) fitted with a dropping funnel and a reflux condenser are placed 200 g. (1.47 moles) of pentaerythritol, 1.5 l. of glacial acetic acid, and 17 ml. of 48% hydrobromic acid (Note 2). After a reflux period of 1.5 hours, 170 ml. of 48% hydrobromic acid is added and the solution is heated under reflux for an additional 3 hours. At the end of this time 96 ml. of 48% hydrobromic acid is added and the heating under reflux is continued for 3 hours. The solution is distilled under reduced pressure to remove as much of the acetic acid and the water as possible, first on a steam bath and finally for 15 minutes in an oil bath at 140–150°, as the pressure is reduced to 10 mm. The viscous residue is transferred to a 2-l. flask and treated with 750 ml. of 98% ethanol and 50 ml. of 48% hydrobromic acid. The flask is provided with an efficient fractionating column (Note 3), and the solution is fractionated slowly until about 500 ml. of distillate is collected. Then a second 750-ml. portion of ethanol is added, and the fractionation is continued slowly until 750 ml. more distillate is collected (Note 4). Finally, the flask is fitted with a Claisen head and a condenser set for downward distillation, and the remaining alcohol is removed as completely as possible under reduced pressure.

Benzene (500 ml.) is added to the residue and distilled at atmospheric pressure. The last traces of benzene are removed by heating for 15 minutes in an oil bath at 150°, as the pressure is reduced to 8 mm. The same procedure is repeated, using a second 500-ml. portion of benzene (Note 5). The viscous residue is then heated under reflux for several hours with 500 ml. of dry ether, with frequent shaking, until it becomes white and granular (Note 6). After cooling thoroughly, the ether is decanted, and the solid is washed twice with two 200-ml. portions of dry ether. The solid is powdered thoroughly and dried in a vacuum desiccator. The dry solid is then extracted exhaustively in a Soxhlet extractor with 600 ml. of dry ether (Note 7). The ether extract is cooled overnight in an ice bath, and the precipitated monobromopentaerythritol is collected by filtration and washed with two 200-ml. portions of cold, dry ether. The yield of crude product melting at 72–73° is 145–160 g.

(49–54% of the theoretical). One recrystallization from a mixture of 3 parts of chloroform and 2 parts of ethyl acetate by volume raises the melting point to 75–76°, recovery 75–85%.

2. Notes

1. For best results the flask should have standard-taper, ground-glass fittings.
2. Eastman Kodak Company white label grade pentaerythritol and 48% hydrobromic acid were used.
3. A 40-cm. column packed with glass beads is satisfactory.
4. The fractionation should be carried out slowly to ensure complete alcoholysis of the bromoacetate. The boiling point during the collection of the first 500 ml. of distillate remains constant at around 72°, corresponding to the ethanol-ethyl acetate azeotrope.
5. The purpose of this operation is to remove completely the water present in the product. Toluene may be substituted for benzene.
6. If the product has a tendency to form a hard mass, it is advisable to break up the solid with a stirring rod.
7. The extraction is very slow and requires several hours for completion, depending upon the rate of refluxing of the ether. Usually crystals of the monobromopentaerythritol begin to deposit on the walls of the extraction flask after the first hour. At the end of the extraction 30–35 g. of unchanged pentaerythritol remains in the extraction thimble. Dibromopentaerythritol, formed as a side product, is present in the ether washings.

3. Discussion

Monobromopentaerythritol has been prepared by the action of 66% hydrobromic acid on pentaerythritol in glacial acetic acid[2] and by the action of 66% hydrobromic acid on pentaerythritol[3] at 120°. The procedure described is a modification of the method of Beyaert and Hansens.[3]

References and Notes

1. State University of Iowa, Iowa City, Iowa.
2. Beyaert and Hansens, *Natuurw. Tijdschr. (Ghent)*, **22**, 249 (1940) [*C. A.*, **37**, 5373 (1943)].
3. Barbiere and Matti, *Bull. soc. chim. France* [5]**5**, 1565 (1938).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

acetic acid (64-19-7)

Benzene (71-43-2)

ethyl acetate (141-78-6)

ether (60-29-7)

chloroform (67-66-3)

HYDROBROMIC ACID (10035-10-6)

toluene (108-88-3)

Pentaerythritol (115-77-5)

Monobromopentaerythritol

1,3-Propanediol, 2-(bromomethyl)-2-(hydroxymethyl)- (19184-65-7)

Dibromopentaerythritol

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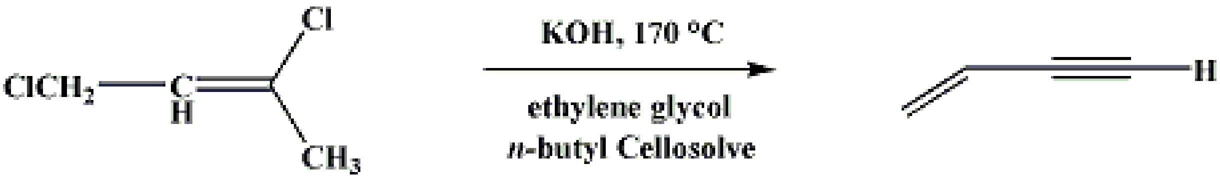
MONOVINYLACETYLENE

[1-Buten-3-yne]



Submitted by G. F. Hennion, Charles C. Price, and Thomas F. McKeon, Jr.[1].
Checked by Max Tishler and John E. Allegretti.

1. Procedure

A 2-l. three-necked flask, heated by a Carbowax bath, is equipped with a motor-driven Trubore stirrer, Teflon paddle, Trubore bearing (Note 1), a Friedrichs condenser, and a 250-ml. dropping funnel. The dropping funnel is connected to the flask by a 24/40 ground-glass joint with a side arm made of 7-mm. tubing. The side arm is connected through a calcium chloride drying tower and a bubbler to a nitrogen tank.

The top of the condenser is connected to a horizontal tube (ca. 2 × 25 cm.) partially filled with granular anhydrous calcium chloride. The horizontal tube is then connected to a 100-ml. graduated cylinder immersed in an acetone-Dry Ice mixture for collection of the product. The cylinder is also equipped with an escape tube protected by a calcium chloride drying tube.

Four hundred grams of powdered technical potassium hydroxide flakes (Note 2) is placed in the flask, and 500 ml. of ethylene glycol is added. This mixture is stirred vigorously while adding 100 ml. of *n*-butyl Cellosolve (Note 3). The system is swept with a rapid stream of nitrogen for 15–20 minutes while the temperature of the oil bath is raised to 165–170°. The flow of nitrogen is then reduced to a rate just sufficient to maintain an atmosphere of nitrogen in the system.

One hundred and twenty-five grams of 1,3-dichloro-2-butene (1.0 mole) (Note 4) is added at a rate of about 3 drops per second. Addition should be complete in 0.75–1 hour (Note 5). During the addition the temperature of the oil bath is maintained at 165–170° (Note 6), and the reaction mixture is stirred vigorously. Heating is continued for 1 hour after the addition of dichlorobutene is complete.

The yield of crude product obtained is 31.2 g. (39 ml., 60%) (Note 7) and (Note 8). The crude product may be purified by distillation through a low-temperature column (Note 9) to yield 22.4–24.8 g. (28–31 ml., 43–48%) of monovinylacetylene, b.p. 0–6° (Note 10) The storage of monovinylacetylene in the presence of oxygen has been reported to lead to explosive compounds. It is therefore suggested that the product be

stored under an inert atmosphere.

2. Notes

1. An oil-sealed stirrer was found unsuitable because the pressure drop through the system was greater than the pressure drop across the oil-sealed stirrer. The Trubore stirrer and bearing were purchased from Ace Glass Inc., Vineland, New Jersey.
2. The potassium hydroxide was weighed as flakes, then ground rapidly with a mortar and pestle to roughly the consistency of granulated sugar, and added as soon as possible to the reaction flask to minimize moisture uptake. The flakes may be used directly without grinding, the only difference being that the mixture of potassium hydroxide, glycol, and Cellosolve should be heated for a slightly longer time before any dichlorobutene is added in order to allow as complete a dispersion as possible.
3. The butyl Cellosolve is added to control the foaming during the reaction.
4. The dichlorobutene used was Eastman Kodak Company technical grade. Distillation before use was not observed to increase the yields.
5. The rate of addition is very important. If the time of addition of 1 mole of dichlorobutene goes much beyond 1 hour, the yield will decrease noticeably.
6. This is apparently an optimum temperature. Lower temperatures lead to lower yields, while higher temperatures do not change the yield appreciably.
7. The calculations of yields are based on $d^{-80} = 0.8$ extrapolated from data at higher temperature.[2]
8. The preparation also has been run on a 2-mole scale, using double the quantities specified in a 3-l. flask. The yields obtained were comparable to those obtained on the 1-mole scale.
9. The low-temperature column shown in .htmFig. 12 was 75 cm. long, made of 7-mm. glass tubing. The entire column was surrounded by an evacuated, silvered jacket. The column, for the lower 60 cm., was a tightly coiled spiral (3.8 cm. diameter). The remaining length was straight and was surrounded by a coolant cup in which liquid of any temperature could be placed to control the refluxing temperature. For the purpose, a calcium chloride-water-Dry Ice mixture was used to keep the temperature of the cup at approximately –5 to 0°. The vapor from the column was condensed and collected in a graduated cylinder immersed in an acetone-Dry Ice bath (Note 10). The major features of infrared spectra of the vapor from redistilled product are summarized in Table I (Note 11).
10. Warming the still pot with 60° water was necessary to distil all the volatile gases toward the end of the distillation.
11. The spectrum of the fractionated monovinylacetylene was comparable, in band peaks and intensities, with previously reported spectra. A previously reported band at 5.8 •, however, was not found in any of the samples, suggesting that an impurity was present in the sample previously reported.

Fig. 12. Low-temperature distillation column.

Fig. 12. Low-temperature distillation column.

TABLE I THE MAJOR BANDS FOR THE INFRARED SPECTRUM OF MONOVINYLACETYLENE GAS

(350 mm. pressure, 5-cm. cell)

Wavelength, •	Absorption, %	Wavelength, •	Absorption, %
3.02	93	6.20	87
3.22	62	7.0–7.15	33
3.30	67	7.9–8.1	98
4.73	9	9.17	49
5.13	19	9.37	18
5.41	59	10.2–11.2	99
5.46	52	13.67	27
5.80	—		

3. Discussion

Monovinylacetylene has been prepared by the decomposition of a diquaternary ammonium base,[3] by the dimerization of acetylene,[4] by the dehydrohalogenation of dihalobutenes in liquid ammonia,[5] and by heating dimethylvinylethynylcarbinol with potassium hydroxide.[6] The procedure described has been published.[7]

References and Notes

1. University of Notre Dame, Notre Dame, Indiana.
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

calcium chloride (10043-52-4)

acetylene (74-86-2)

ammonia (7664-41-7)

oxygen (7782-44-7)

nitrogen (7727-37-9)

potassium hydroxide (1310-58-3)

ethylene glycol, cellosolve (107-21-1)

Monovinylacetylene, 1-Buten-3-yne (689-97-4)

1,3-dichloro-2-butene

dichlorobutene

butyl Cellosolve, n-butyl Cellosolve (111-76-2)

dimethylvinylethynylcarbinol (690-94-8)

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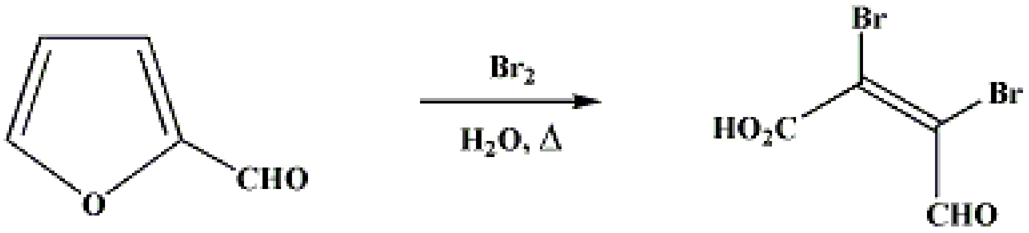
Organic Syntheses, CV 4, 688

MUCOBROMIC ACID

[Acrylic acid, 2,3-dibromo-3-formyl-]



Submitted by G. A. Taylor[1]
Checked by B. C. McKusick, E. L. Martin, and W. R. Brasen.

1. Procedure

A mixture of 50 g. (45 ml., 0.52 mole) of freshly distilled furfural and 500 ml. of water is stirred vigorously in a 2-l. three-necked round-bottomed flask equipped with a dropping funnel and a thermometer that dips into the liquid. The flask is immersed in an ice bath, and 450 g. (144 ml., 2.81 moles) of bromine is added, while the temperature of the reaction mixture is kept below 5° (Note 1). After the addition is complete, the thermometer is replaced by a reflux condenser, and the mixture is stirred and boiled for 30 minutes. The reflux condenser is replaced by a still head and condenser, and excess bromine is removed by distilling the liquid until the distillate is almost colorless (Note 2).

The reaction mixture is evaporated to dryness under reduced pressure at a water pump on a steam bath, using a trap cooled in ice and salt to condense the hydrobromic acid (Note 3). The solid residue is cooled in an ice bath and triturated with 30–50 ml. of ice water. A few grams of sodium bisulfite, dissolved in water, is added to discharge a slight yellow discoloration. The cold mixture is filtered with suction to separate crude mucobromic acid, which is washed with two small portions of ice water. The crude mucobromic acid weighs 125–132 g. (93–99%). It is dissolved in about 110 ml. of boiling water, 2–5 g. of decolorizing carbon is added, the hot mixture is stirred for 10 minutes and filtered, and the filtrate is cooled to 0–5°. Colorless crystals of mucobromic acid separate from the filtrate; weight 100–112 g. (75–83%); m.p. 124–125°.

2. Notes

1. If the temperature is allowed to rise much above 10°, the yield is considerably reduced. Without cooling, the mixture becomes quite hot, the yield is decreased by half, and tarry material is formed.
2. Mucobromic acid can be obtained in about 63% yield (85 g.) by adding 5 g.

of decolorizing carbon at this point, stirring the mixture at the boil for 10 minutes, filtering it hot, and cooling the filtrate to 0°. The crude mucobromic acid that crystallizes, weight about 105 g., is recrystallized from 120 ml. of water.
3. It is important to get rid of all the hydrobromic acid, for its presence increases the amount of mucobromic acid lost in the trituration step.

3. Discussion

This preparation is adapted from that described by Simonis.[2] It closely follows the practical details given in *Organic Syntheses*[3] for the preparation of mucobromic acid from the relatively expensive furoic acid.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 844

References and Notes

1. Department of Biochemistry and Dyson Perrins Laboratory, Oxford University, Oxford, England.
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

HYDROBROMIC ACID (10035-10-6)

bromine (7726-95-6)

sodium bisulfite (7631-90-5)

carbon (7782-42-5)

furoic acid (88-14-2)

Furfural (98-01-1)

Mucobromic acid, Acrylic acid, 2,3-dibromo-3-formyl- (488-11-9)

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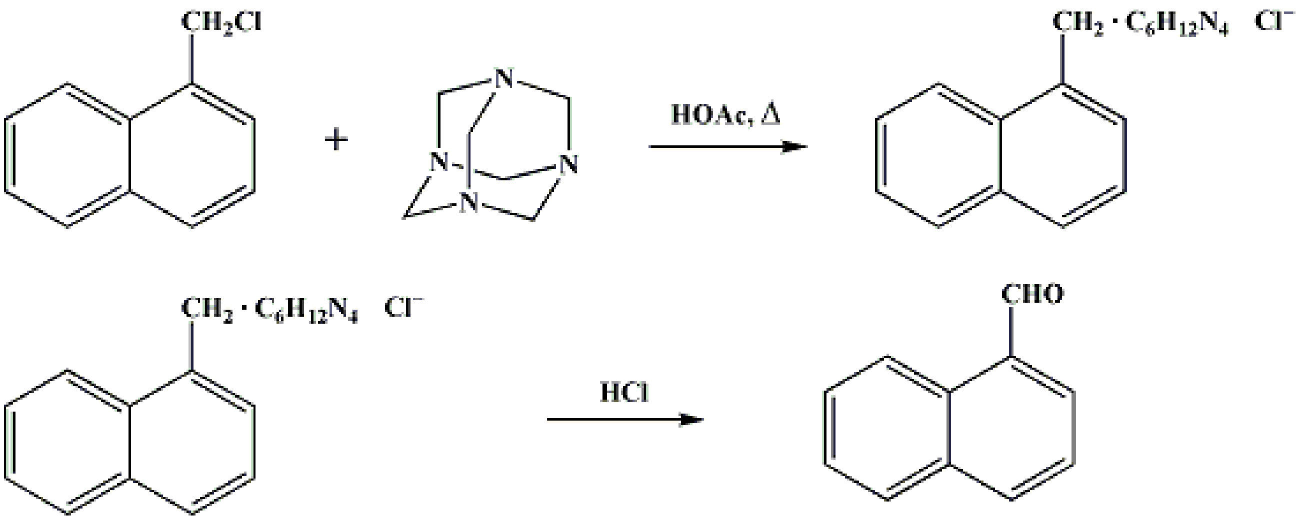
Organic Syntheses, CV 4, 690

1-NAPHTHALDEHYDE



Submitted by S. J. Angyal, J. R. Tetaz, and J. G. Wilson[1].
Checked by R. S. Schreiber and Paul E. Marlatt.

1. Procedure

Precautions should be taken to avoid contact with 1-chloromethylnaphthalene, which is a lachrymator and a vesicant, and with the aldehyde, which seems to possess the same properties to a lesser degree.

In a 1-l. flask fitted with a reflux condenser are placed 106 g. (0.6 mole) of 1-chloromethylnaphthalene[2] (Note 1), 168 g. (1.2 moles) of hexamethylenetetramine, 250 ml. of glacial acetic acid, and 250 ml. of water. This mixture is heated under reflux for 2 hours. In about 15 minutes the solution becomes homogeneous, and then an oil starts to separate. After the reflux period, 200 ml. of concentrated hydrochloric acid is added and refluxing is continued for an additional 15 minutes (Note 2). After cooling, the mixture is extracted with 300 ml. of ether; the ether layer is washed three times with 100-ml. portions of water, then with 100 ml. of 10% sodium carbonate solution (Note 3), and again with 100 ml. of water. The ether extract is dried with about 15 g. of anhydrous sodium sulfate and filtered, and the ether is removed by distillation. The residual liquid is distilled under reduced pressure, the distillate being collected at 105–107°/0.2 mm. or 160–162°/18 mm. (Note 4). The yield of colorless 1-naphthaldehyde freezing between 0.0° and 2.5° (Note 5) is 70–77 g. (75–82%).

2. Notes

1. The chloromethylnaphthalene used melted at 24–26°. Material with a lower melting point can be used, but the yield is correspondingly smaller; e.g., a sample having a melting point of 15–18° gave a 73% yield of slightly impure 1-naphthaldehyde.
The checkers found that crude chloromethylnaphthalene obtained from the preparation in *Organic Syntheses*[2] could be used with good results. Naphthalene, paraformaldehyde, hydrochloric acid, and phosphoric acid are heated under reflux according to the procedure described. After the crude product is washed with water, 10% potassium carbonate, and water, it is dissolved directly in 500 ml. of glacial acetic acid, diluted with 500 ml. of water, and treated with hexamethylenetetramine by the procedure described above. The over-all yield of almost colorless 1-naphthaldehyde is 162 g., b.p. 162–164°/18 mm.; n_D^{25} 1.6503 (52% yield based on naphthalene).

In this variation of the preparation, it is best to use a wide-bore tube as a condenser to remove the unreacted naphthalene. After the naphthalene has been distilled, the wide-bore tube is replaced with an ordinary condenser and the naphthaldehyde is distilled in the usual manner.
2. The various amines and aldehydes present combine to form Schiff's bases. If these are not hydrolyzed by a strong acid, they will contaminate the final product.
3. Care should be exercised when washing the solution with sodium carbonate because some carbon dioxide is evolved.
4. The brown distillation residue contains some methylene-α-naphthylmethylamine.
5. The melting point of 1-naphthaldehyde given by Stephen[3] (33–34°) is apparently incorrect. A sample that was purified through the bisulfite addition compound and redistilled had a freezing point of 2.5°.
In no instance could the checkers obtain a completely colorless product even though it was redistilled several times with ordinary laboratory distilling apparatus.

3. Discussion

1-Naphthaldehyde has been prepared from calcium α-naphthoate by distillation with calcium formate;[4] from α-naphthyl-carbinol by oxidation with chromic acid,[5,6] N-bromosuccinimide,[7] or N-chlorosuccinimide;[8] from α-naphthylglyoxylic acid by heating with aniline and hydrolyzing the anil;[9] and from α-naphthylmagnesium bromide and ethoxymethyleneaniline [10,11] or ethyl orthoformate.[12,13] This Grignard reagent also has been converted to the dithioacid with carbon disulfide and the acid taken to 1-naphthaldehyde (through the semicarbazone).[14]

1-Naphthaldehyde has been made from α-naphthonitrile by reduction with stannous chloride,[3,15,16] sodium triethoxyaluminohydride, [17] lithium triethoxyaluminohydride, [18] or diisobutylaluminum hydride; [19] from naphthalene by the action of aluminum chloride, hydrogen cyanide, and hydrochloric acid,[20] by treatment with dichloromethyl methyl ether in the presence of stannic chloride, [21] and by the reaction with carbon monoxide in the presence of boron trifluoride and hydrogen fluoride; [22] from α-naphthoyl chloride by reduction with lithium tri-*tert*-butoxyaluminohydride; [23] from α-naphthoic acid N,N-dimethylamide by reduction with lithium diethoxyaluminohydride; [24] from the 1,3-diphenyltetrahydroimidazole derivative of 1-naphthaldehyde by hydrolysis;[25] from the reaction of α-naphthylmethylpyridinium bromide with *p*-nitrosodimethylaniline and hydrolysis of the resulting nitrone; [26] by the decomposition of 1-(benzenesulfonhydrazidocarbonyl) naphthalene with sodium carbonate; [27] and by the oxidation of α-methylnaphthalene with selenium dioxide. [28]

1-Naphthaldehyde has been obtained by means of the Sommelet reaction [29] from α-chloro- or α-bromomethylnaphthalene and hexamethylenetetramine in aqueous alcohol [30,31,32,33,34] or glacial acetic acid. [35,36,37] This method has been improved in the present procedure by the use of 50% acetic acid as a solvent.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 811
- Org. Syn. Coll. Vol. 5, 121

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

1,3-diphenyltetrahydroimidazole derivative of 1-naphthaldehyde

1-(benzenesulfonhydrazidocarbonyl) naphthalene

α-chloro- or α-bromomethylnaphthalene

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ether (60-29-7)

aniline (62-53-3)

carbon monoxide (630-08-0)

hydrogen cyanide (74-90-8)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

stannous chloride

carbon dioxide (124-38-9)

hydrogen fluoride (7664-39-3)

aluminum chloride (3495-54-3)

selenium dioxide (7446-08-4)

phosphoric acid (7664-38-2)

chromic acid (7738-94-5)

carbon disulfide (75-15-0)

Naphthalene (91-20-3)

Ethyl orthoformate

hexamethylenetetramine (100-97-0)

stannic chloride (7646-78-8)

α-naphthylmagnesium bromide

α-naphthoyl chloride (879-18-5)

boron trifluoride (7637-07-2)

calcium formate (544-17-2)

α-Naphthonitrile (86-53-3)

ethoxymethyleneaniline (6780-49-0)

N-bromosuccinimide (128-08-5)

1-Chloromethylnaphthalene, chloromethylnaphthalene (86-52-2)

α-methylnaphthalene (90-12-0)

N-chlorosuccinimide (128-09-6)

1-Naphthaldehyde, naphthaldehyde (66-77-3)

methylene-α-naphthylmethylamine

calcium α-naphthoate

α-naphthyl-carbinol (4780-79-4)

α-naphthylglyoxylic acid

sodium triethoxyaluminohydride

lithium triethoxyaluminohydride

diisobutylaluminum hydride (1191-15-7)

Dichloromethyl methyl ether (4885-02-3)

α-naphthoic acid N,N-dimethylamide

lithium diethoxyaluminohydride

α-naphthylmethylpyridinium bromide

p-nitrosodimethylaniline (138-89-6)

lithium tri-tert-butoxyaluminohydride

paraformaldehyde (30525-89-4)

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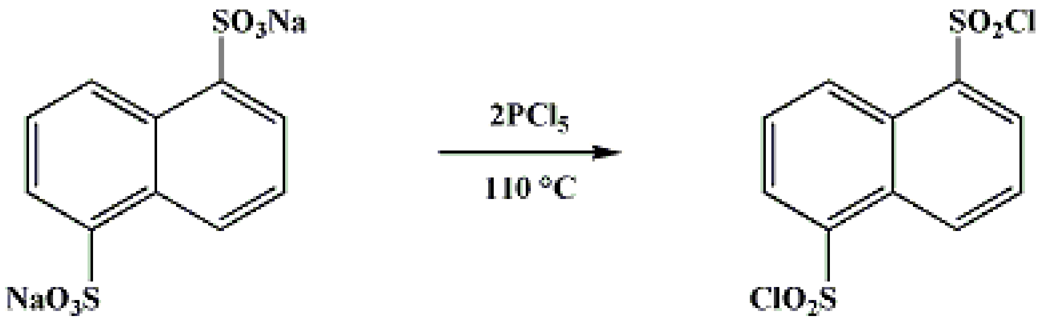
Organic Syntheses, *CV 4*, *693*

NAPHTHALENE-1,5-DISULFONYL CHLORIDE

[1,5-Naphthalenedisulfonyl chloride]



Submitted by P. D. Caesar[1]
Checked by R. T. Arnold and George P. Scott.

1. Procedure

In a 1-l. round-bottomed flask is placed a mixture of 204.3 g. (1 mole) of finely divided phosphorus pentachloride and 132.8 g. (0.4 mole) of the disodium salt of naphthalene-1,5-disulfonic acid which has been dried previously at 140° for 48 hours (Note 1). The flask is provided with an air condenser which is fitted at the top with a calcium chloride drying tube. It is then placed in an oil bath which is heated to 110°, and the mixture is maintained at that temperature for 1 hour. The condenser is removed for brief intervals now and then during the heating period, and the reactants are stirred by means of a glass rod. At the end of the heating period, the product is a thick paste.

The flask and contents are placed on a steam cone and heated for 2 hours under vacuum (furnished by a water aspirator) (Note 2) in order to remove the phosphorus oxychloride formed in this process as well as most of the unreacted phosphorus pentachloride. The dry cake is pulverized in a mortar and transferred to a 4-l. beaker. To this is added 750 ml. of distilled water and 2 l. of chloroform. The mixture is placed on a steam bath, heated to boiling, and stirred vigorously until nearly all the solid dissolves. By means of a separatory funnel the layers are separated while still hot. The chloroform solution is again heated to boiling and filtered through a large fluted filter into an Erlenmeyer flask.

After sufficient chloroform has been evaporated to give a solution volume approximating 250 ml., the solution is cooled in an ice bath and the crystalline product collected on a filter. By further concentration of the mother liquor, an additional quantity of naphthalene-1,5-disulfonyl chloride is obtained. A total yield of 85–115 g. (65–88%) of recrystallized material results; m.p. 181–183°.

2. Notes

1. The powdered solids should be thoroughly mixed before heating. This may be done by inserting a rubber stopper into the neck of the reaction flask and shaking vigorously for about 2 minutes. However, an appreciable pressure develops in the flask and care must be taken in removing the stopper.
2. The reaction flask should be connected to the receiver by a tube of large bore and equipped, preferably, with ground-glass fittings. Two traps between the receiver and the aspirator are desirable to assure no contact between the phosphorus chlorides and water.

3. Discussion

Naphthalene-1,5-disulfonyl chloride has been prepared by the reaction of naphthalene with chlorosulfonic acid; [2,3,4,5,6,7] however, the yields are generally poor and the conditions difficult to reproduce. It also has been obtained by treating disodium 1,5-naphthalene-disulfonate with chlorosulfonic acid.[8] The present method has been published.[9]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 695

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

chlorosulfonic acid (7790-94-5)

phosphorus pentachloride (10026-13-8)

chloroform (67-66-3)

Phosphorus Oxychloride (21295-50-1)

Naphthalene (91-20-3)

Naphthalene-1,5-disulfonyl chloride, 1,5-Naphthalenedisulfonyl chloride (1928-01-4)

disodium 1,5-naphthalene-disulfonate, disodium salt of naphthalene-1,5-disulfonic acid

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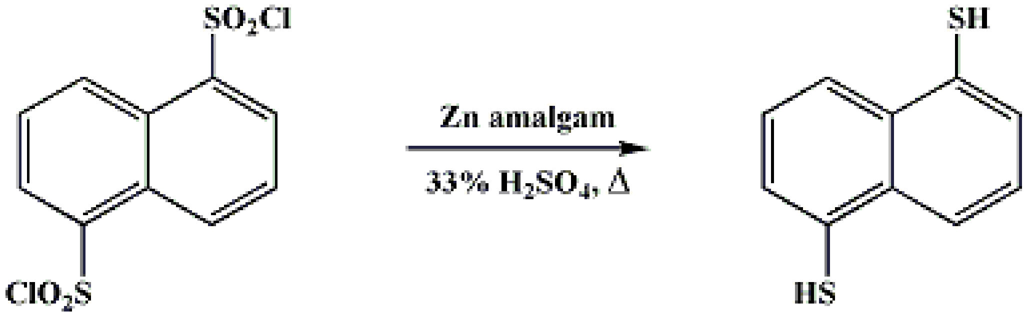
Organic Syntheses, CV 4, 695

1,5-NAPHTHALENEDITHIOL



Submitted by P. D. Caesar[1]
Checked by Richard T. Arnold, W. E. Parham, and R. M. Scribner.

1. Procedure

A 2-l. round-bottomed flask having standard-taper, ground-glass fittings is equipped with a bulb condenser (Note 1) and an efficient Hershberg stirrer. To this are added with stirring 600 g. (2.0 moles) of 33% sulfuric acid, 20 g. (0.06 mole) of finely divided 1,5-naphthalenedisulfonyl chloride (p. 693), and 100 g. (1.5 g. atoms) of zinc dust amalgam (Note 2) at room temperature (Note 3). The zinc dust amalgam is added directly after the disulfonyl chloride in the course of 2–5 minutes. The mixture is heated to reflux, held there for about 6 hours, and allowed to cool overnight without agitation (Note 4).

The product is filtered, and the precipitate is extracted with a total of 1 l. of warm ether (Note 5). The combined ether extracts are evaporated to a volume of 50 ml., cooled, and filtered. The filtrate is further evaporated to a volume of about 10 ml., cooled, and again filtered. The precipitates melt at 119–121° and total 7.1–9.1 g. This represents a yield of 60–77%.

The 1,5-naphthalenedithiol can be further purified to a melting point of 120–121° by sublimation under high vacuum in a molecular still, followed by reprecipitation of the water-soluble disodium salt of the sublimate from excess hydrochloric acid. The pure compound obtained from 9.1 g. of product weighs 8.6 g. (73%).

2. Notes

1. The product collects in the condenser, and it may be necessary to clear the condenser with a glass rod.
2. A good grade of zinc and mercury(II) chloride should be used. The zinc dust amalgam is prepared by dissolving 20 g. of mercury(II) chloride in a solution of 10 ml. of concentrated hydrochloric acid in 300 ml. of distilled water, and adding quickly, with stirring, 100 g. of zinc dust (Schaar chemicals, 95% purity). After 10–15 minutes of stirring and crushing lumps, the mixture is

filtered through a Büchner funnel, and the zinc dust amalgam is carefully washed with a total of 500 ml. of distilled water containing a trace of hydrochloric acid. The water is then removed by ethanol, the ethanol by ether, and most of the ether by air. It is advisable to remove the zinc dust amalgam from the Büchner funnel and add it to the reduction mixture before all the ether is removed to assure minimum contact with the air.

An occasional batch of zinc dust failed to effect the desired reduction, possibly because of excessive oxide deposition on the surface of the zinc. It is suggested, therefore, that the surface of the zinc dust be cleaned with dilute hydrochloric acid just before amalgamation.

3. This technique eliminates the long induction period at 0° and the violent foaming described in the preparation of thiophenol.[2] However, in a larger-scale operation it would be advisable to check the rate of addition of the zinc dust somewhat, lest an exception arise.

4. The overnight period was a matter of convenience and is not considered to be vital to the completeness of the reaction.

5. When unamalgamated zinc dust is used, a considerable proportion of yellow insoluble product is often noted at this point. Since the disulfide has been isolated as an intermediate in a similar reduction of *m*-chlorosulfonylbenzoic acid,[3] it is probable that this material is a mixture of disulfides of varying molecular weight.

3. Discussion

This method has been applied successfully to the preparation of phenoxybenzene-4,4'-dithiol (84% of the theoretical amount), diphenylmethane-4,4'-dithiol, and *m*-sulfhydrylbenzoic acid[3] (80%). It did not prove satisfactory for the preparation of higher-melting thiols of lower solubility, such as 2,7-naphthalenedithiol, 2,6-naphthalenedithiol, and 4,4'-biphenyldithiol. These were better prepared by the use of tin(II) chloride 2-hydrate in glacial acetic acid saturated with hydrogen chloride.[4]

1,5-Naphthalenedithiol can be prepared by adding 1,5-naphthalenedisulfonyl chloride to an ethanol solution of tin(II) chloride 2-hydrate saturated with hydrogen chloride.[5] An 80% yield of the crude dithiol melting at 103° was previously reported using zinc dust and sulfuric acid.[6]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

phenoxybenzene-4,4'-dithiol

diphenylmethane-4,4'-dithiol

m-sulfhydrylbenzoic acid

tin(II) chloride 2-hydrate

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrogen chloride, hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ether (60-29-7)

zinc (7440-66-6)

mercury(II) chloride (7487-94-7)

Thiophenol (108-98-5)

1,5-Naphthalenedisulfonyl chloride (1928-01-4)

1,5-Naphthalenedithiol (5325-88-2)

2,7-naphthalenedithiol

2,6-naphthalenedithiol

m-chlorosulfonylbenzoic acid (4025-64-3)

4,4'-biphenyldithiol

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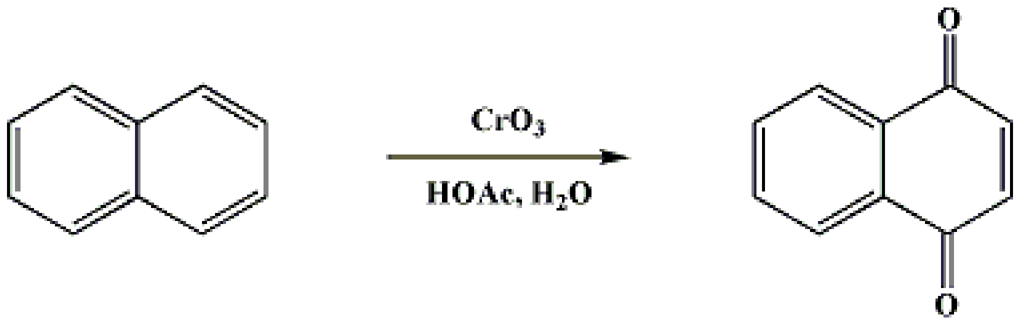
Organic Syntheses, CV 4, 698

1,4-NAPHTHOQUINONE



Submitted by E. A. Braude and J. S. Fawcett[1].
Checked by Charles C. Price, R. S. Schreiber, R. D. Birkenmeyer, Paul F. Kirk, and William Bradley Reid, Jr..

1. Procedure

In a 2-l. three-necked flask, fitted with a mechanical stirrer, a 1-l. dropping funnel, and a thermometer, is placed a solution of 120 g. (1.2 moles) of pure chromium trioxide (Note 1) in 150 ml. of 80% aqueous acetic acid. The flask is surrounded by a freezing mixture of ice and salt, and, when the temperature of the contents of the flask has fallen to 0°, a solution of 64 g. (0.5 mole) of naphthalene in 600 ml. of glacial acetic acid is gradually added, with constant stirring, over a period of 2–3 hours. The internal temperature is maintained at about 10–15°. Stirring is continued overnight, during which time the reaction mixture and cooling bath gradually attain room temperature (Note 2). The dark green solution is then set aside for 3 days and occasionally stirred.

The crude naphthoquinone is precipitated by pouring the reaction mixture into 6 l. of water. The yellow precipitate is filtered, washed with 200 ml. of water, and dried in a desiccator. The product can be crystallized from 500 ml. of petroleum ether (b.p. 80–100°) (Note 3) and separates in the form of long yellow needles, m.p. 124–125°. The yield is 14–17 g. (18–22%) (Note 4).

2. Notes

1. An equivalent quantity of technical grade chromium trioxide, ground to a fine powder, may be employed.
2. It is necessary to continue vigorous stirring at this stage in order to prevent local overheating and to keep the mixture from setting to a solid mass.
3. Crystallization from petroleum ether (b.p. 80–100°) is far more convenient than steam distillation as a method of purification, and a product of high purity is obtained after a single crystallization. The checkers used Skellysolve C (b.p. 88–115°) with consistent results. Crystallization from ether has also been employed.[2]

4. The yield is substantially unchanged on increasing the proportion of chromium trioxide used in the oxidation. The submitters report consistent yields of 25–28 g. (32–35%).

3. Discussion

The present method of preparation is adapted from Miller.[3] Although the yield is relatively low, the method is less costly and time-consuming than those starting from α-naphthol[2] or 1,4-benzoquinone.[4] Other methods that have been employed include the oxidation of naphthalene with hydrogen peroxide,[5] the oxidation of 1,4-naphthalenediamine[6] and naphthylaminesulfonic acid[7] and the oxidation of 4-amino-1-naphthol prepared by electrolytic reduction of 1-nitronaphthalene.[8]

References and Notes

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2. Conant and Fieser, *J. Am. Chem. Soc.*, **46**, 1862 (1924); Fieser and Fieser, *J. Am. Chem. Soc.*, **57**, 491 (1935); *Org. Syntheses Coll. Vol.* **1**, 383 (1946).
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7. Monnet, Reverdin, and Nolting, *Ber.*, **12**, 2306 (1879).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

Skellysolve C

acetic acid (64-19-7)

ether (60-29-7)

α-naphthol (90-15-3)

Naphthalene (91-20-3)

hydrogen peroxide (7722-84-1)

1,4-benzoquinone (106-51-4)

1,4-Naphthoquinone, naphthoquinone (130-15-4)

1,4-naphthalenediamine (2243-61-0)

1-nitronaphthalene (86-57-7)

chromium trioxide (1333-82-0)

naphthylaminesulfonic acid

4-amino-1-naphthol

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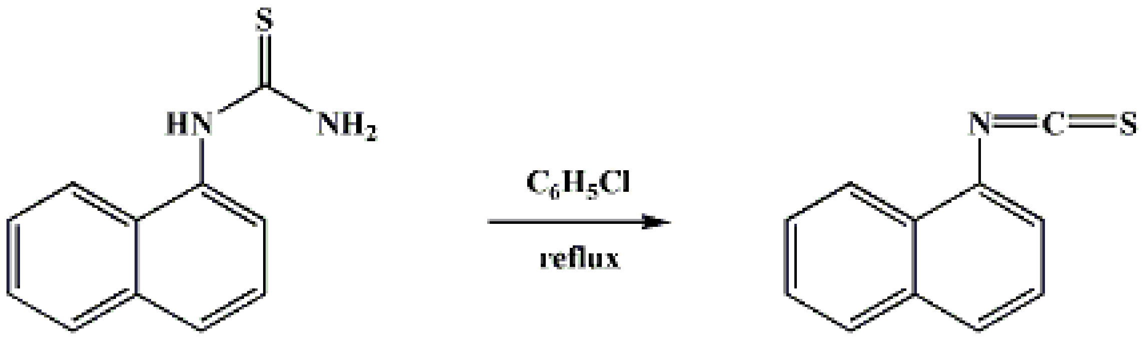
Organic Syntheses, CV 4, 700

α-NAPHTHYL ISOTHIOCYANATE

[Isothiocyanic acid, 1-naphthyl ester]



Submitted by J. Cymerman-Craig, M. Moyle, and R. A. White[1].
Checked by N. J. Leonard and F. H. Owens.

1. Procedure

In a 500-ml. round-bottomed flask fitted with a reflux condenser are placed 16.2 g. (0.08 mole) of dry α-naphthylthiourea (Note 1) and 180 ml. of redistilled chlorobenzene. The flask is heated at the reflux temperature by means of an electric heating mantle. Evolution of ammonia begins almost at once, and all of the solid dissolves after 30–45 minutes. The solution is maintained at reflux for 8 hours (Note 2) and then is evaporated on a steam bath at water-pump pressure to remove all of the chlorobenzene. The residue crystallizes on cooling and is extracted with four 30-ml. portions of boiling hexane (Note 3). Removal of solvent from the combined hexane extracts affords pale yellow crystals of α-naphthyl isothiocyanate, m.p. 58–59°. The yield is 12.7–13.0 g. (86–88%). Recrystallization from hexane (9 ml. of hexane for 1 g. of solute) gives colorless needles, melting point unchanged (Note 4).

2. Notes

1. α-Naphthylthiourea may be prepared by the method of Frank and Smith, *Org. Syntheses Coll. Vol.* **3**, 735 (1955), or by the method of de Clermont, *Ber.*, **9**, 446 (1876), and Bertram, *Ber.*, **25**, 48 (1892).
2. The checkers found that a 24-hour heating period increased the yield of α-naphthyl isothiocyanate to 95%.
3. A fifth extraction yields no further product. The residue insoluble in hexane was found by the submitters to consist of 1.3–1.9 g. of a mixture of equal parts of di-α-naphthylthiourea and α-naphthylthiourea, m.p. 178–181°.
4. The method is generally applicable to the preparation of aryl isothiocyanates. Using this procedure, the submitters have prepared the following isothiocyanates, with the yields and times of refluxing indicated: phenyl, 44%, 8

hours; *o*-chlorophenyl, 46, 8; *p*-bromophenyl, 73, 8; *p*-biphenylyl, 49, 6; β-naphthyl, 70, 10; 9-phenanthryl, 70, 10; 1-pyrenyl, 72, 10.

3. Discussion

Aryl isothiocyanates can be prepared by the action of thiophosgene on the arylamine[2] (this reaction fails with naphthyl compounds),[3] by fission of a *sym*-diarylthiourea with acidic reagents[4] (this reaction involves the loss of half the amine used), and by the decomposition of an ammonium aryldithiocarbamate[5] (low yields are reported for naphthyl and other compounds).[5,6] The procedure described here is that of Baxter, Cymerman-Craig, Moyle, and White.[7]

References and Notes

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2. *Org. Syntheses Coll. Vol.* **1**, 165 (1941).
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4. Werner, *J. Chem. Soc.*, **59**, 396 (1891).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

α-naphthylthiourea

ammonia (7664-41-7)

chlorobenzene (108-90-7)

Thiophosgene (463-71-8)

PHENYL ISOTHIOCYANATE (103-72-0)

hexane (110-54-3)

α-Naphthyl isothiocyanate, Isothiocyanic acid, 1-naphthyl ester (551-06-4)

di-α-naphthylthiourea

p-bromophenyl isothiocyanate (1985-12-2)

o-chlorophenyl isothiocyanate (2740-81-0)

p-biphenylyl isothiocyanate

2-naphthyl isothiocyanate

9-phenanthryl isothiocyanate

1-pyrenyl isothiocyanate

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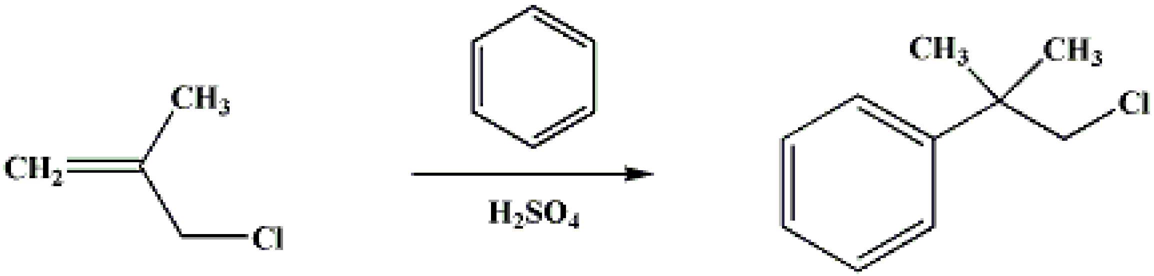
Organic Syntheses, CV 4, 702

NEOPHYL CHLORIDE

[Benzene, (2-chloro-1,1-dimethylethyl)-]



Submitted by W. T. Smith, Jr. and J. T. Sellas[1].
Checked by N. J. Leonard and R. O. Kerr.

1. Procedure

In a 2-l. three-necked flask equipped with a mechanical stirrer, thermometer, and dropping funnel are placed 500 g. (570 ml., 6.4 moles) of benzene (Note 1) and 34.6 g. (18.8 ml.) of concentrated sulfuric acid (sp. gr. 1.84). The resultant mixture is brought to 20°. To this is added dropwise 201 g. (219 ml., 2.22 moles) of methallyl chloride (Note 2) over a period of 12 hours, during which time vigorous stirring is maintained and the temperature is kept at 20° with the aid of a water bath. The mixture, which becomes an amber color, is stirred for an additional 12 hours.

The reaction mixture is then transferred to a 1-l. separatory funnel, and the sulfuric acid layer is removed. The remaining benzene solution is then washed with four 200-ml. portions of distilled water (Note 3). In this step the amber color disappears and the liquid becomes colorless. The benzene solution is dried with anhydrous sodium sulfate and transferred to a 1-l. distilling flask. The benzene is removed by distillation under a pressure of about 45 mm. The liquid residue is poured into a 500-ml. flask and distilled through a 40-cm. Vigreux column under reduced pressure. The yield of neophyl chloride boiling at 97–98° /10 mm. is 262–275 g. (70–73%) (Note 4) and (Note 5); n_D^{20} 1.5250.

2. Notes

1. The benzene is purified by washing with three 80-ml. portions of concentrated sulfuric acid and then drying with anhydrous sodium sulfate. It is used directly after removal of the sodium sulfate by filtration.
2. The methallyl chloride used was a redistilled commercial sample and had the following properties: b.p. 71–72° /760 mm., n_D^{20} 1.4274, d_4^{20} 0.918.
3. To ensure good results it is necessary to remove all of the sulfuric acid by washing the mixture thoroughly with water. The final washing should be neutral

to litmus.

4. If the residue in the distilling flask is dissolved in ether, treated with activated carbon, and evaporated to dryness, the solid so obtained can be recrystallized from about 25 ml. of 95% ethanol to give 10 g. (2.7%) of *p*-di(chloro-*tert*-butyl)benzene; m.p. 54.5–55.0°.

5. In a run in which the temperature was kept at 10–15° during the addition of methallyl chloride, the methallyl chloride was added over a period of 1 hour. Stirring was continued for 1 hour, and the reaction mixture was worked up as described above to give a 53% yield.

3. Discussion

(Chloro-*tert*-butyl)benzene has been prepared by the direct chlorination of *tert*-butylbenzene in the presence of strong light;[2] by chlorination of *tert*-butylbenzene with sulfuryl chloride in the presence of benzoyl peroxide;[3] by the action of thionyl chloride on the corresponding alcohol;[4] and by the hydrogen fluoride-catalyzed alkylation of benzene with methallyl chloride.[5] The sulfuric acid-catalyzed alkylation described here is based on the procedure of Whitmore, Weisgerber, and Shabica.[6] A variation using a shorter reaction time has also been described.[7]

References and Notes

1. State University of Iowa, Iowa City, Iowa.
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

sulfuric acid (7664-93-9)

Benzene (71-43-2)

ether (60-29-7)

thionyl chloride (7719-09-7)

sodium sulfate (7757-82-6)

carbon (7782-42-5)

sulfuryl chloride (7791-25-5)

benzoyl peroxide (94-36-0)

methallyl chloride (563-47-3)

Neophyl chloride, Benzene, (2-chloro-1,1-dimethylethyl)-, (Chloro-tert-butyl)benzene (515-40-2)

tert-butylbenzene (98-06-6)

p-di(chloro-tert-butyl)benzene

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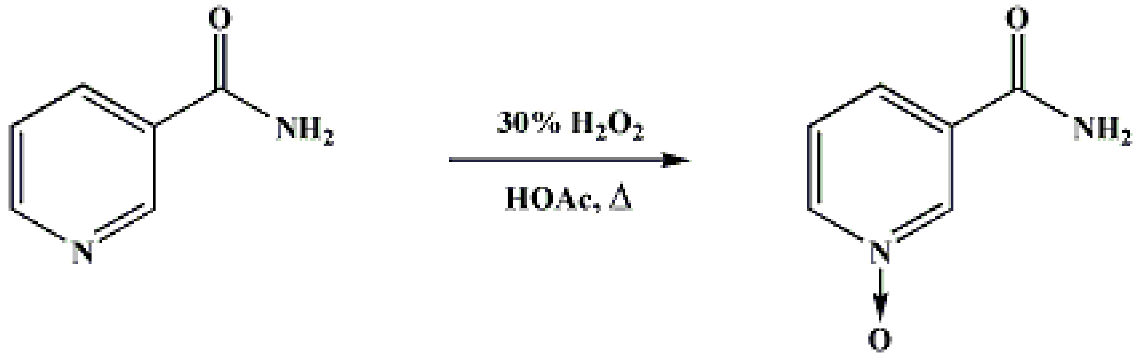
Organic Syntheses, CV 4, 704

NICOTINAMIDE-1-OXIDE



Submitted by E. C. Taylor, Jr.[1] and Aldo J. Crovetti[2].
Checked by Charles C. Price and Walter A. Schroeder.

1. Procedure

In a 2-l. round-bottomed flask with ground-glass joint (Note 1) are placed 100 g. (0.82 mole) of powdered nicotinamide (Note 2) and 1 l. of C.P. glacial acetic acid, and the mixture is warmed with occasional shaking on a steam bath until a clear solution is obtained. To this mixture is added 160 ml. (1.39 moles) of cold 30% hydrogen peroxide. An air condenser is attached to the reaction flask, and the mixture is heated on a steam bath for 3.5 hours.

The reaction mixture is then distilled under reduced pressure (80–100 mm.) (Note 3). After 600–700 ml. has distilled, the mixture is diluted with 150–200 ml. of distilled water and the distillation is continued. The product separates near the end of the distillation, causing somewhat vigorous bumping for a short period. When the bumping has almost ceased, the pressure is reduced to 20 mm. and the distillation continued almost to dryness (Note 4).

The major portion of wet solid is removed from the flask and transferred to a 1-l. Erlenmeyer flask. The remaining solid is washed out with a little distilled water, and the washings are transferred to the flask. The solid is dissolved in the smallest amount of boiling water required, the flask removed from the heat source, and 50 ml. of ethyl alcohol added (Note 5). The flask is allowed to cool slowly, and, after the major portion of the product has separated, the flask is cooled to 5° overnight. The solid is removed by filtration and washed with cold alcohol, then acetone, and finally ether. The white, crystalline, air-dried product weighs 82–93 g. (73–82%), m.p. 291–293° dec. (rapid heating); the compound starts to turn brown at about 280–285° (Note 6).

2. Notes

1. Since hydrogen peroxide attacks rubber stoppers, glass-jointed equipment is recommended.

2. U.S.P. Niacinamide (Mallinckrodt) was used.
3. For the distillation, the still head consisted of a Claisen-type adapter with a parallel side arm (24/40 standard taper joints), 21 cm. high and 10.5 cm. wide. An ordinary straight still head is attached to the parallel side arm. This large still head prevents any bumping solid from entering the condenser.
4. Distilling to complete dryness exposes the solid to prolonged heating and causes oxidation of the product, which is obtained colored and in lower yield.
5. The alcohol serves to retain the brown color upon recrystallization and to decompose any excess hydrogen peroxide.
6. Because of the questionable value of the melting point as a criterion of purity, the checkers analyzed two samples of the product: Calcd. for $C_6H_6N_2O$: C, 52.17; H, 4.34. Found (Sample 1): C, 52.34; H, 4.44. Found (Sample 2): C, 52.61, 52.63; H, 4.46, 4.53.

3. Discussion

The procedure given is essentially that described by Taylor and Crovetti.[3] Nicotinamide-1-oxide (m.p. 275–276° dec.) has also been prepared by the alkaline hydrolysis of nicotinonitrile-1-oxide[4] and by the action of ammonium hydroxide on methyl nicotinate-1-oxide.[5] The melting point of the product prepared by the latter synthesis is reported to be 282–284° dec.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 166

References and Notes

1. Princeton University, Princeton, New Jersey.
2. University of Illinois, Urbana, Illinois.
3. Taylor and Crovetti, *J. Org. Chem.*, **19**, 1633 (1954).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Niacinamide

ethyl alcohol (64-17-5)

acetic acid (64-19-7)

ether (60-29-7)

acetone (67-64-1)

hydrogen peroxide (7722-84-1)

ammonium hydroxide (1336-21-6)

nicotinamide (98-92-0)

nicotinamide-1-oxide (1986-81-8)

nicotinonitrile-1-oxide (14906-64-0)

methyl nicotinate-1-oxide

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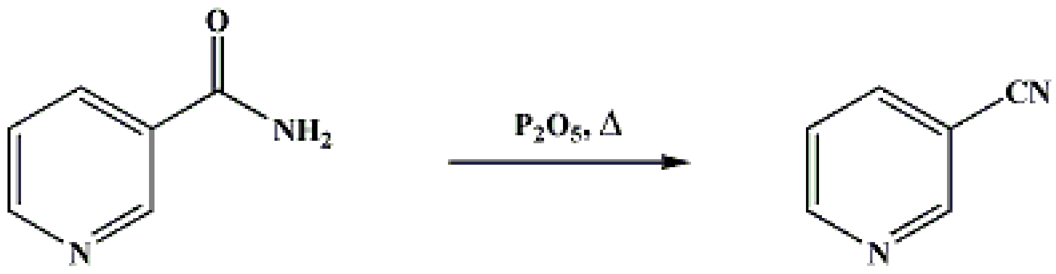
NICOTINONITRILE



Submitted by Peyton C. Teague and William A. Short[1].
Checked by Arthur C. Cope, John C. Sheehan, and Louis A. Cohen.

1. Procedure

In a dry 1-l. round-bottomed flask are placed 100 g. (0.82 mole) of powered nicotinamide and 100 g. (0.70 mole) of phosphorus pentoxide. The flask is stoppered and shaken to mix the two powders. It is then connected by means of a 10-mm. i.d. tube to an 80-cm. air condenser arranged for distillation. A 125-ml. Claisen flask immersed in an ice-salt bath is used as the receiver (Note 1). The pressure is reduced to 15–20 mm., and the mixture is heated with a large free flame of a high-temperature burner (such as a Fisher or Meker type). The flame is moved about freely to melt the material as rapidly as possible, and then the mixture is heated vigorously until nothing more comes over or until foam reaches the top of the flask (15–20 minutes). The apparatus is allowed to cool (Note 2), and the product is rinsed out of the tube and condenser with ether (Note 3). The ether solution is added to the distillate, the ether is distilled on a steam bath, and the product is distilled at atmospheric pressure using an air condenser. The yield of nicotinonitrile, boiling at 205–208° and melting at 50–51°, is 71–72 g. (83–84%).

2. Notes

1. To prevent possible clogging of the condenser by the solid nicotinonitrile, the end of the condenser should not be constricted and should not extend far into the receiver.
2. The residue left in the flask may be removed by carefully adding water, allowing the mixture to stand overnight, and then washing repeatedly with water.
3. A small amount of material insoluble in ether but soluble in water remains in the condenser. The nicotinonitrile can be washed from the condenser more easily with acetone. If acetone is used, it should be removed by distillation under reduced pressure before the product is distilled.

3. Discussion

The method described is essentially that of La Forge.[2] Nicotinonitrile has also been prepared from nicotinic acid by heating with ammonium acetate and acetic acid,[3] from 3-pyridinesulfonic acid by fusion of the sodium salt with sodium cyanide,[4] from 3-bromopyridine and cuprous cyanide,[5] from nicotinamide and benzenesulfonyl or *p*-toluenesulfonyl chloride in pyridine,[6] from nicotinic acid and ammonia in the presence of a dehydrating catalyst,[7] from β-picoline and ammonia,[8] and from heating a mixture of nicotinic acid and lead thiocyanate.[9]

References and Notes

1. University of South Carolina, Columbia, South Carolina.
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3. Adkins, Wolff, Pavlic, and Hutchinson, *J. Am. Chem. Soc.*, **66**, 1293 (1944).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

benzenesulfonyl or p-toluenesulfonyl chloride

acetic acid (64-19-7)

ammonia (7664-41-7)

ether (60-29-7)

ammonium acetate (631-61-8)

sodium cyanide (143-33-9)

Cuprous Cyanide (544-92-3)

acetone (67-64-1)

pyridine (110-86-1)

Nicotinic acid (59-67-6)

nicotinamide (98-92-0)

3-bromopyridine (626-55-1)

Nicotinonitrile (100-54-9)

β-picoline (108-99-6)

3-pyridinesulfonic acid (636-73-7)

phosphorus pentoxide (1314-56-3)

lead thiocyanate

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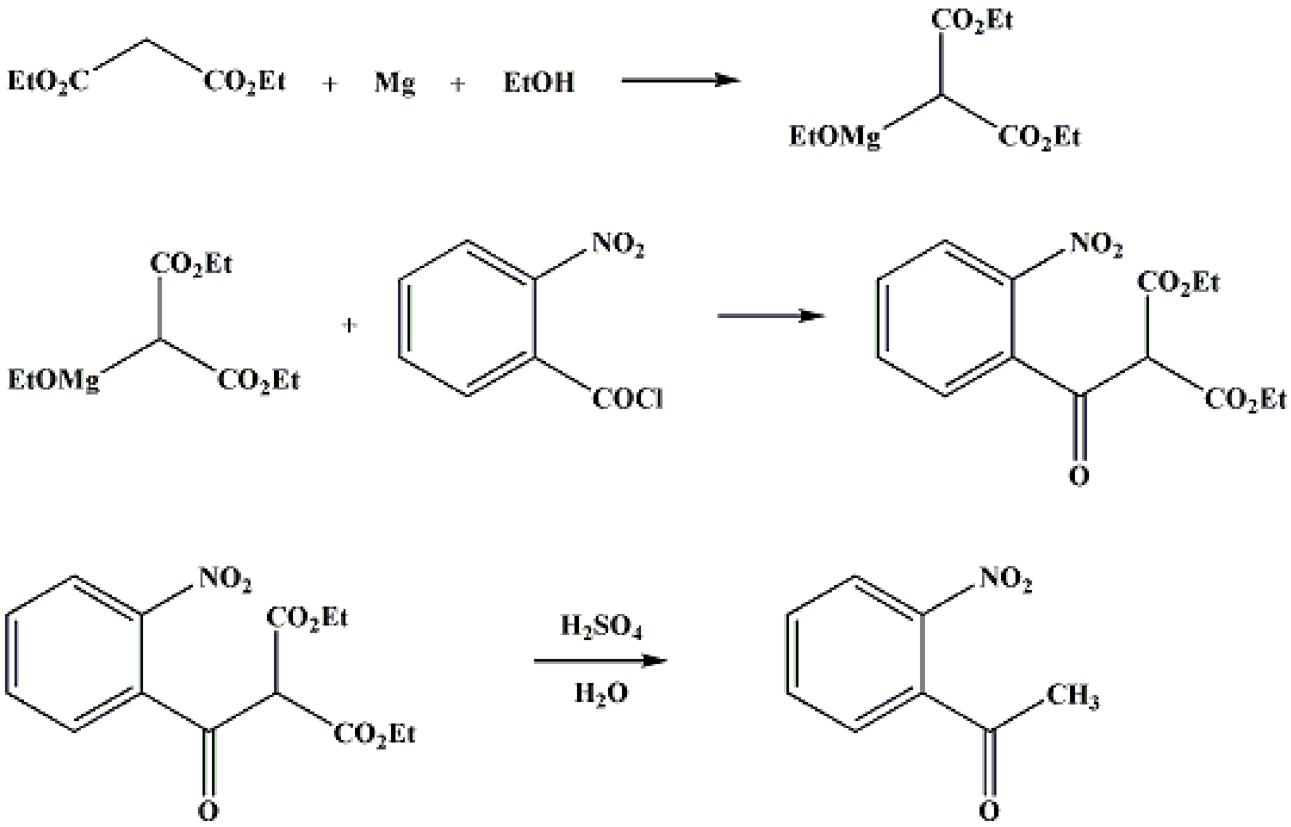
Organic Syntheses, CV 4, 708

o-NITROACETOPHENONE

[Acetophenone, 2'-nitro-]



Submitted by George A. Reynolds and Charles R. Hauser[1].
Checked by Cliff S. Hamilton and Yao-Hua Wu.

1. Procedure

In a 500-ml. three-necked round-bottomed flask equipped with a mercury-sealed stirrer, a dropping funnel, and a reflux condenser (protected by a drying tube) is placed 5.4 g. (0.22 g. atom) of magnesium turnings. Five milliliters (0.085 mole) of absolute ethanol and 0.5 ml. of carbon tetrachloride are added. If the reaction does not start immediately, the flask is heated for a short time on a steam bath. After the reaction has proceeded for several minutes, 150 ml. of absolute ether is added cautiously with stirring. A solution of 35.2 g. (0.22 mole) of diethyl malonate (Note 1), 20 ml. (0.34 mole) of absolute ethanol, and 25 ml. of absolute ether is added with stirring at such a rate that rapid boiling is maintained; heat is supplied when necessary. The mixture is heated under reflux on a steam bath for 3 hours, at which time most of the magnesium has dissolved. To the gray solution is added 37 g. (0.2 mole) of *o*-nitrobenzoyl chloride (Note 2), dissolved in 50 ml. of ether, in a period of 15 minutes. Heating under reflux on the steam bath is continued throughout the addition of the *o*-nitrobenzoyl chloride and until the green solution becomes too viscous to stir. The reaction mixture is cooled and shaken with dilute sulfuric acid (25 g. of concentrated sulfuric acid in 200 ml. of water) until all the solid has dissolved (Note 3).

The ether phase is separated and the aqueous layer extracted with 75 ml. of ether. The ether extracts are combined and washed with water, and the solvent is removed by distillation.

To the crude diethyl *o*-nitrobenzoylmalonate is added a solution of 60 ml. of glacial acetic acid, 7.6 ml. of concentrated sulfuric acid, and 40 ml. of water, and the mixture is heated under reflux for 4 hours (Note 4) or until no more carbon dioxide is evolved. The reaction mixture is chilled in an ice bath, made alkaline with 20% sodium hydroxide solution, and extracted with several portions of ether. The combined ethereal extracts are washed with water and dried with anhydrous sodium sulfate followed by Drierite, and the solvent is removed by distillation. On fractional distillation of the residue, 27.0–27.4 g. (82–83%) of light-yellow *o*-nitroacetophenone boiling at 158–159° /16 mm. is obtained (n_D^{25} 1.548, n_D^{20} 1.551, d_4^{25} 1.236) (Note 5).

2. Notes

1. The checkers found that the yield of final product was cut in half unless the commercial grade of diethyl malonate was purified by distillation.
2. The *o*-nitrobenzoyl chloride can be prepared from the commercially available acid and thionyl chloride. It has been reported[2] that, when a particularly pure sample of *o*-nitrobenzoyl chloride was used, no difficulty was encountered in stirring the reaction mixture, and that the precipitate formed in a granular state. As a consequence, the subsequent decomposition with sulfuric acid was simple and rapid. The final product boiled at 107° /0.5 mm., and melted at 26.8°; the supercooled liquid had n_D^{25} 1.5499.
3. The solution of the magnesium complex, which is difficult to decompose, is facilitated by mechanical shaking of the mixture for 30 minutes.
4. The decarboxylation is almost complete within 2 to 3 hours.
5. *p*-Nitroacetophenone may be prepared in 73% yield by a similar procedure. Various other methyl ketones have been prepared by this procedure.[3] It has been reported[2] that *o*-chloroacetophenone was obtained in 82% yield by this method; the product possessed the following physical properties; b.p. 70° /1.5 mm., n_D^{25} 1.5404; it did not solidify at –50°.

3. Discussion

This procedure is an adaptation of one described by Walker and Hauser.[3] Schofield and Swain[4] state that, in their opinion, for both convenience and economy, this method[3] is the best yet described for the preparation of *o*-nitroacetophenone.

o-Nitroacetophenone has also been prepared by the treatment of ethyl *o*-nitrobenzoylacetoacetate with sulfuric acid in ethanol,[5] by the direct nitration of acetophenone,[6,7] by the reaction of *o*-nitrobenzaldehyde with diazomethane,[8] by the oxidation of *o*-nitroethylbenzene with potassium permanganate,[9] by the hydrolysis of *o*-nitroacetophenone oxime (obtained by the nitrosation of *o*-nitroethylbenzene with amyl nitrate),[10] and by the oxidation of *o*-nitrophenylmethylcarbinol with chromic acid.[10]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 285
- Org. Syn. Coll. Vol. 8, 247

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1. Duke University, Durham, North Carolina.
2. Ford-Moore, Private communication.
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Drierite

ethanol (64-17-5)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

ether (60-29-7)

sodium hydroxide (1310-73-2)

thionyl chloride (7719-09-7)

magnesium, magnesium turnings (7439-95-4)

potassium permanganate (7722-64-7)

sodium sulfate (7757-82-6)

carbon tetrachloride (56-23-5)

carbon dioxide (124-38-9)

Acetophenone (98-86-2)

chromic acid (7738-94-5)

diethyl malonate (105-53-3)

o-Nitrobenzaldehyde (552-89-6)

Diazomethane (334-88-3)

amyl nitrate (1002-16-0)

o-Nitroacetophenone, Acetophenone, 2'-nitro- (577-59-3)

o-nitrobenzoyl chloride (610-14-0)

diethyl o-nitrobenzoylmalonate

p-Nitroacetophenone (100-19-6)

o-chloroacetophenone (2142-68-9)

ethyl o-nitrobenzoylacetoacetate

o-nitroethylbenzene (6125-24-2)

o-nitroacetophenone oxime

o-nitrophenylmethylcarbinol (15121-84-3)

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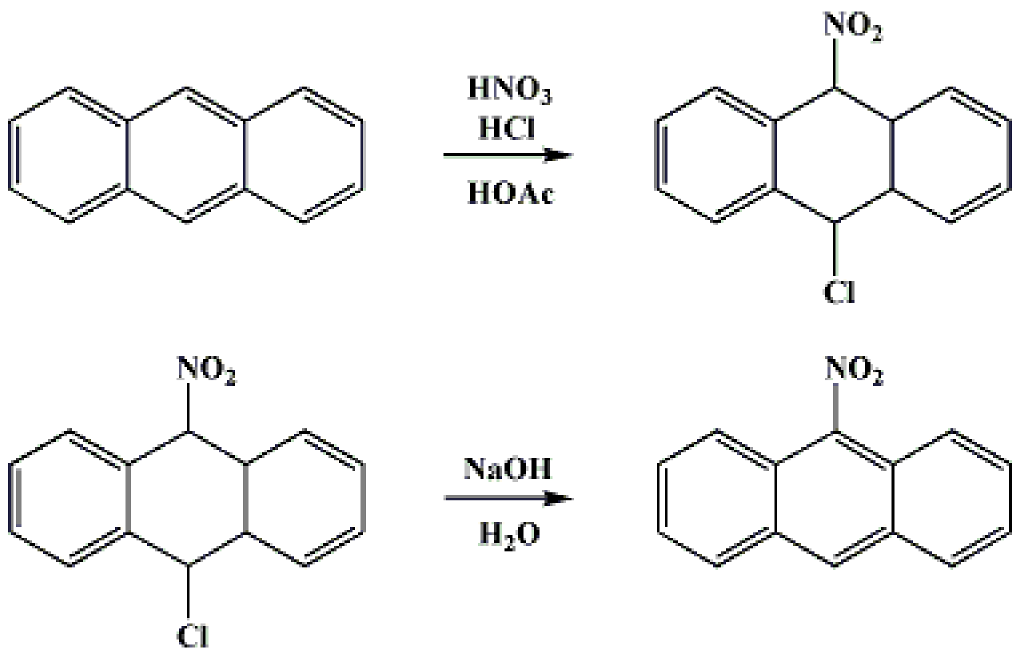
Organic Syntheses, CV 4, 711

9-NITROANTHRACENE

[Anthracene, 9-nitro-]



Submitted by Charles E. Braun, Clinton D. Cook, Charles Merritt, Jr., and Joseph E. Rousseau[1].
Checked by William S. Johnson, George N. Sausen, and Paul R. Shafer.

1. Procedure

Twenty grams (0.112 mole) of finely powdered anthracene (Note 1) is suspended in 80 ml. of glacial acetic acid (Note 2) in a 500-ml. three-necked round-bottomed flask fitted with a 150-ml. dropping funnel, a thermometer, and an efficient motor-driven stirrer. The flask is immersed in a water bath at 20–25°, and 8 ml. (0.126 mole) of concentrated nitric acid (70% by weight, sp. gr. 1.42), essentially free of oxides of nitrogen, is added slowly from the dropping funnel with vigorous stirring. The rate of addition is controlled so that the reaction temperature does not exceed 30°. About 15–20 minutes is required for this step.

After all the nitric acid has been added, the mixture is stirred until a clear solution is obtained (about 30 minutes), and stirring is then continued for an additional 30 minutes. The solution is filtered to remove any anthracene, and a mixture of 50 ml. (0.60 mole) of concentrated hydrochloric acid (37% by weight, sp. gr. 1.19) and 50 ml. of glacial acetic acid is added slowly to the filtrate with vigorous stirring. The pale-yellow precipitate of 9-nitro-10-chloro-9,10-dihydroanthracene which forms is separated by suction filtration on a sintered-glass funnel and is washed with two 25-ml. portions of glacial acetic acid and then with water until the washings are neutral. The product is removed from the funnel and triturated thoroughly with 60 ml. of warm

(60–70°) 10% sodium hydroxide solution (Note 3). The crude orange nitroanthracene is separated from the warm slurry by suction filtration and is treated with four 40-ml. portions of 10% sodium hydroxide solution (Note 3). The product is finally washed thoroughly with warm water until the washings are neutral to litmus. This treatment requires about 1.5–2 l. of water. The crude 9-nitroanthracene is air-dried and recrystallized from glacial acetic acid (Note 2) and (Note 4). The yield of bright orange-yellow needles is 15–17 g. (60–68%), m.p. 145–146°.

2. Notes

1. Anthracene of good quality is required. The Eastman Kodak Company product, m.p. 215–217°, is satisfactory, or practical grade anthracene may be purified by codistillation with ethylene glycol.[2]

2. The checkers employed E. I. du Pont de Nemours and Company, Inc., C.P. acetic acid, which was further purified by distillation from potassium permanganate.

3. The checkers found it desirable to carry out the trituration by grinding the mixture in a mortar, because the nitrochloride has a tendency to form small, hard granules which otherwise may not come in contact with the alkali. The later treatments with alkali may be carried out satisfactorily in a beaker, or directly on the funnel, if thorough mixing is obtained. It is desirable to remove as much of the mother liquor as possible by suction from each of the alkali treatments.

4. For recrystallization, 10 ml. of glacial acetic acid is used for each gram of dried product. It is important that the dissolution be carried out rapidly; otherwise some decomposition may occur, producing anthraquinone as a contaminant. A satisfactory technique is to add the crude, dried, and crushed product rapidly in small portions to the total amount of boiling acetic acid. The solution should then be filtered through a steam-heated funnel.

3. Discussion

The procedure described is a modification of that of Dimroth.[3] 9-Nitroanthracene has also been prepared by nitration of anthracene with copper nitrate in glacial acetic acid and with diacetylorthonitric acid.[4] Other methods include direct nitration in acetic acid solution with nitric acid and acetic anhydride,[5] or by nitryl fluoride.[6]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

oxides of nitrogen

diacetylorthonitric acid

nitryl fluoride

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

acetic anhydride (108-24-7)

sodium hydroxide (1310-73-2)

nitric acid (7697-37-2)

potassium permanganate (7722-64-7)

Anthraquinone (84-65-1)

ethylene glycol (107-21-1)

anthracene (120-12-7)

copper nitrate (3251-23-8)

9-Nitroanthracene, Anthracene, 9-nitro- (602-60-8)

9-nitro-10-chloro-9,10-dihydroanthracene

nitroanthracene

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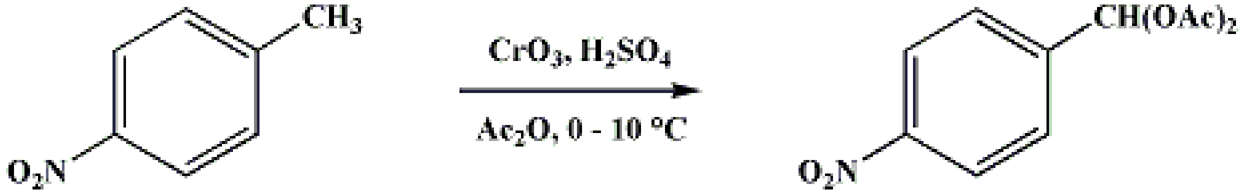
Organic Syntheses, CV 4, 713

o- AND *p*-NITROBENZALDIACETATE

[Toluene-α,α-diol, *o*-nitro-, diacetate]

[Toluene-α,α-diol, *p*-nitro-, diacetate]



Submitted by Tamio Nishimura[1]
Checked by T. L. Cairns and R. E. Foster.

1. Procedure

A. *p-Nitrobenzaldiacetate*. In a 2-l., three-necked flask provided with a mechanical stirrer, dropping funnel, and thermometer, surrounded by an ice-salt bath, are placed 400 ml. of acetic anhydride (Note 1) and 50 g. (0.36 mole) of *p*-nitrotoluene (Note 2). To this solution is added slowly, with stirring, 80 ml. of concentrated sulfuric acid. When the mixture has cooled to 0°, a solution of 100 g. (1.0 mole) of chromium trioxide (Note 3) in 450 ml. of acetic anhydride is added slowly, with stirring, at such a rate that the temperature does not exceed 10° (Note 4), and stirring is continued for 2 hours at 5–10° in an ice-water bath after the addition is complete. The contents of the flask are poured into two 3-l. beakers one-third filled with chipped ice, and water is added until the total volume is 5–6 l. The solid is separated by suction filtration and washed with water until the washings are colorless. The product is suspended in 300 ml. of 2% aqueous sodium carbonate solution and stirred. After thorough mixing, the solid is collected on a filter (Note 5), washed with water and finally with 20 ml. of ethanol. The product, after drying in a vacuum desiccator, weighs 60–61 g. (65–66% of the theoretical amount), m.p. 121–124° (Note 6).

B. *o-Nitrobenzaldiacetate*. *o*-Nitrotoluene (the fraction boiling at 217–219° of commercial product) is treated in a manner exactly similar to that for *p*-isomer, except that the reaction mixture is stirred mechanically for 3 hours at 5–10° after the addition of chromium trioxide is complete. Washing of the crude product with ethanol is omitted; instead, the crude product is heated under reflux with petroleum ether for 30 minutes. The product melts at 82–84° with preliminary softening. The yield is 33.6–34.5 g. (36–37%).

2. Notes

1. The industrial grade of acetic anhydride was used without further purification.

2. Commercial *p*-nitrotoluene (m.p. 53–54°) was used.
3. The chromium trioxide was of 97% purity. Cooling is necessary on dissolving chromium trioxide in acetic anhydride. *Caution! Addition of acetic anhydride to solid chromium trioxide has resulted in explosive decompositions. The trioxide should be added in small portions to the cooled anhydride.*
4. With a good ice-salt bath, the time required for the addition is 1.5–2.0 hours.
5. By acidification of the sodium carbonate washings, 2–4 g. of *p*-nitrobenzoic acid, m.p. 235–237°, is obtained.
6. A similar procedure may be used for the preparation of *p*-cyanobenzaldiacetate from *p*-tolunitrile. Information submitted by Rorig and Nicholson, of G. D. Searle and Company, indicates that the critical step in this preparation is to maintain the reaction temperature below 10° throughout the process. Exposure of *p*-cyanobenzaldiacetate to excess chromic, acetic, and sulfuric acids causes a reduction in yield. During the oxidation care should be taken to prevent chromium trioxide from adhering to the walls of the flask above the reaction mixture and then dropping in large amounts into the solution.

3. Discussion

These have been reviewed in an earlier volume.[2] *p*-Nitrobenzaldehyde has also been prepared in 32% yield by heating *p*-nitrobenzyl chloride with potassium *tert*-butylperoxide.[3] The preparation of *o*-nitrobenzaldiacetate has been described in an earlier volume.[4]

o- and *p*-Nitrobenzaldiacetate also have been obtained from the corresponding aldehydes by reaction with acetic anhydride in the presence of phosphoric acid.[5]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

o- and p-Nitrobenzaldiacetate

potassium tert-butylperoxide

ethanol (64-17-5)

sulfuric acid (7664-93-9)

acetic anhydride (108-24-7)

sodium carbonate (497-19-8)

phosphoric acid (7664-38-2)

o-nitrotoluene (88-72-2)

p-Tolunitrile (104-85-8)

chromium trioxide (1333-82-0)

p-Nitrobenzaldiacetate, Toluene-α,α-diol, p-nitro-, diacetate (2929-91-1)

p-Nitrobenzaldehyde (555-16-8)

o-Nitrobenzaldiacetate, Toluene-α,α-diol, o-nitro-, diacetate (6345-63-7)

p-NITROBENZOIC ACID (62-23-7)

p-nitrotoluene (99-99-0)

p-nitrobenzyl chloride (100-14-1)

p-cyanobenzaldiacetate

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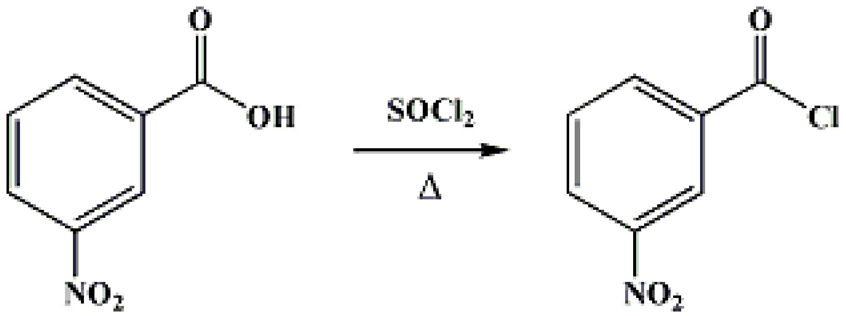
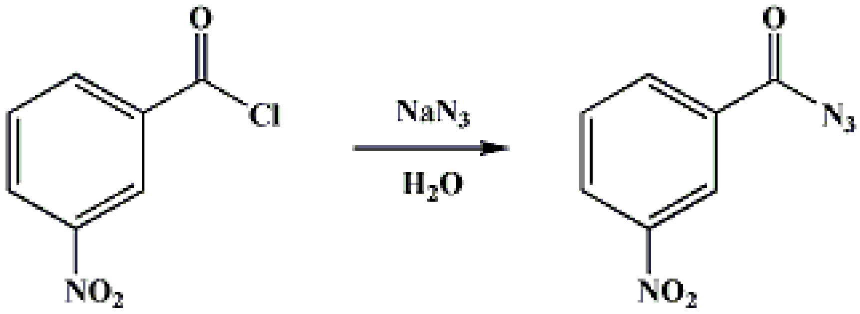
m-NITROBENZAZIDE

[Benzoyl azide, *m*-nitro-]





Submitted by Jon Munch-Petersen[1]
Checked by William S. Johnson and W. David Wood.

1. Procedure

A. *m-Nitrobenzoyl chloride.* In a 1-l. round-bottomed flask are placed 200 g. (1.2 moles) of crude *m*-nitrobenzoic acid[2] and 500 g. (300 ml., 4.2 moles) of thionyl choride (Note 1). The flask is fitted (ground-glass joint) with a reflux condenser carrying a calcium chloride drying tube leading to a gas-absorption trap[3] and is heated on a steam bath for 3 hours. The condenser is then set for downward distillation, and as much of the excess thionyl chloride as possible is distilled at the temperature of the steam bath. The residue is transferred to a 250-ml. Claisen flask and distilled at reduced pressure (water pump), b.p. 153–154° /12 mm. (Note 2). The yield is 200–217 g. (90–98%), m.p. 33°.

B. *m-Nitrobenzazide.* In a 2-l. round-bottomed flask fitted with an efficient mechanical stirrer is placed a solution of 78 g. (1.2 moles) of commercial sodium azide in 500 ml. of water (Note 3). The flask is surrounded by a water bath kept at 20–25°. The stirrer is started, and over a period of about 1 hour a solution of 185.5 g. (1 mole) of *m*-nitrobenzoyl chloride in 300 ml. of acetone (previously dried over anhydrous potassium carbonate) is added from a dropping funnel. *m*-Nitrobenzazide separates at

once as a white precipitate. Stirring is continued for 30 minutes after the addition is complete; then 500 ml. of water is added and the reaction mixture stirred for an additional 30 minutes. The azide is separated on a suction filter, washed with water, and dried in the air. The yield of crude product, m.p. 68°, is 189 g. (98%) (Note 4). It may be recrystallized from a mixture of equal parts of benzene and ligroin (b.p. 100–140°), when the temperature is kept below 50° (Note 5). The product thus obtained consists of almost colorless crystals, m.p. 68–69° (Note 6), the recovery being 80–90% (Note 7).

2. Notes

1. Eastman Kodak Company white label grade thionyl chloride is satisfactory.
2. Since the product crystallizes readily, water cooling should be applied only at the receiver, not at the side arm.
3. The reaction should preferably be carried out in a hood, as hydrazoic acid may be liberated in small amounts. This compound, which is volatile, is highly toxic, and its inhalation may cause temporary headache and giddiness.
4. This product is sufficiently pure for general reagent use. *m*-Nitrobenzazide is recommended[4,5,6,7] as a reagent for the characterization and estimation of aliphatic and aromatic hydroxyl compounds. It reacts to form nicely crystalline *m*-nitrophenylcarbamic esters,[5,6,8] in which the nitro group may be titrated with titanous chloride. With amines it forms substituted *m*-nitrophenylureas.[9,10]
5. At higher temperatures a Curtius rearrangement into the isocyanate may occur, nitrogen being liberated. An alternative procedure for recrystallization (preferred by the checkers) consists in dissolving the crude product in a small amount of benzene (if the solution is discolored it may be treated with decolorizing carbon) and adding an equal volume of ligroin. On seeding, the product crystallizes.
6. The melted compound decomposes with liberation of nitrogen.
7. Using the same procedure, *p*-nitrobenzazide, m.p. 71–72° (Note 6), may be prepared. The yield of crude product is 90%, and of recrystallized product 70%.

3. Discussion

m-Nitrobenzazide has been prepared by the action of nitrous acid on *m*-nitrobenzhydrazide, which is obtained by treating methyl *m*-nitrobenzoate with hydrazine hydrate.[5,7] The procedure described here is mentioned by Naegeli and Tyabji[11] and is similar to that given for benzazide.[12]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ligroin

thionyl choride

potassium carbonate (584-08-7)

Benzene (71-43-2)

thionyl chloride (7719-09-7)

nitrogen (7727-37-9)

nitrous acid (7782-77-6)

acetone (67-64-1)

decolorizing carbon (7782-42-5)

hydrazine hydrate (7803-57-8)

sodium azide (26628-22-8)

m-Nitrobenzoic acid (121-92-6)

titanous chloride

Methyl m-nitrobenzoate (618-95-1)

m-Nitrobenzazide

Benzoyl azide, m-nitro- (3532-31-8)

m-nitrobenzoyl chloride (121-90-4)

p-nitrobenzazide

m-nitrobenzhydrazide (618-94-0)

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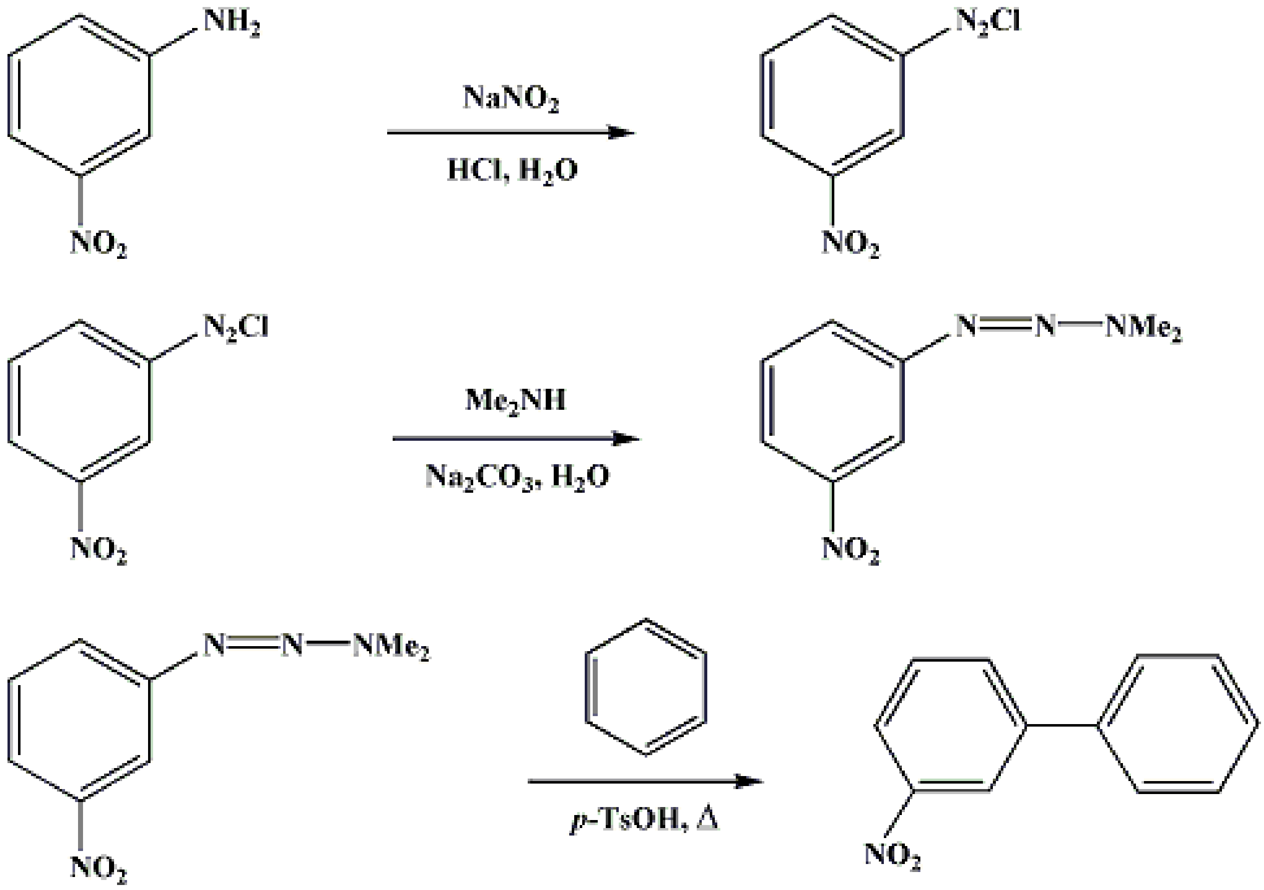
m-NITROBIPHENYL

[Biphenyl, 3-nitro-]



Submitted by C. E. Kaslow and R. M. Summers[1].
Checked by James Cason and B. H. Walker.

1. Procedure

A. *1-(m-Nitrophenyl)-3,3-dimethyltriazene*. To a 3-l. three-necked flask containing 276 g. (2 moles) of technical grade *m*-nitroaniline (Note 1) are added 250 ml. of concentrated hydrochloric acid and 500 ml. of hot water. The contents of the flask are heated to about 85° to dissolve the *m*-nitroaniline; then 550 ml. of concentrated hydrochloric acid is added, and the solution is cooled rapidly. A stirrer, a thermometer, and a long-stemmed dropping funnel are attached to the flask, and its contents are then cooled to –3 to –5° by means of a salt-ice bath. A solution of 144 g. (2.09 moles) of sodium nitrite in 350 ml. of water is added dropwise under the surface of the acid solution while it is being stirred. The rate of addition is regulated (Note 2) so that the temperature does not rise above 0°. The stirring is continued for 15–20 minutes after the sodium nitrite solution has been added; then a solution of 8–10 g. of urea in 25 ml. of water is added during about 15 minutes (foaming), and the stirring is discontinued. The diazonium salt solution must be kept cold while the next step is proceeding.

Two and one-half liters of water in a 3-gal. crock is stirred vigorously with a mechanical stirrer, and 870 g. (7 moles) of pulverized sodium carbonate monohydrate (Note 3) is added portionwise (Note 4). Crushed ice is added to the sodium carbonate suspension until the temperature is lowered to 10°; then 423 g. (2.35 moles) of 25% dimethylamine solution (Note 5) is added. The ice-cold *m*-nitrobenzenediazonium chloride solution is added over a period of 25–35 minutes under the surface of the vigorously stirred dimethylamine solution by means of a dropping funnel (Note 6) while the temperature is maintained at about 10° by the addition of ice. The solution is stirred for 15–20 minutes after the addition is complete. The crude yellow triazene is removed by filtration on a large Büchner funnel. The cake is washed twice by removal and thorough mixing with 2–2.5 l. of water. After the second washing the cake is pressed as dry as possible, then removed and dissolved in 1.8–2.0 l. of boiling 95% ethanol contained in a 4-l. flask under a reflux condenser. The triazene is allowed to crystallize as the ethanol is cooled in water, then removed by filtration, and washed with two 200-ml. portions of 95% ethanol. After drying in air at room temperature, the yield of 1-(*m*-nitrophenyl)-3,3-dimethyltriazene is 348–365 g. (89–94%), m.p. 100.8–101.5°.

B. *m-Nitrobiphenyl*. To a 5-l. three-necked flask equipped with a sealed mechanical stirrer, a dropping funnel, and a reflux condenser are added 116.4 g. (0.6 mole) of 1-(*m*-nitrophenyl)-3,3-dimethyltriazene and 2.5 l. of benzene. The benzene solution is heated to maintain refluxing and stirred vigorously while a solution of 148 g. (0.8 mole) of 94% toluenesulfonic acid (Note 7) in 750 ml. of benzene is added dropwise (Note 8) over a period of 4–4.5 hours. The refluxing is continued for 1–1.5 hours (Note 9) after the toluenesulfonic acid has been added. The solution is allowed to cool somewhat, 800 ml. of water is added cautiously with stirring through the separatory funnel, and then the water layer is removed. The benzene layer is extracted twice with 500-ml. portions of water, then three times with 500-ml. portions of 5% sodium hydroxide solution, and finally with a 500-ml. portion of water. The benzene solution is shaken with 30–40 g. of anhydrous calcium chloride to remove most of the water. The benzene is removed by distillation by dripping it into a 500-ml. Claisen flask which is heated sufficiently to maintain a rapid rate of distillation. After most of the benzene is removed, the residue is transferred to a 125-ml. Claisen flask. The low-boiling material is removed at a pressure of 20–30 mm. up to a bath temperature of 135–140°. The residue is then distilled at 0.1 mm. pressure. After a fore-run of nitrobenzene (2–5 ml.), the *m*-nitrobiphenyl is distilled (Note 10) at 115–118° at 0.1 mm. while the bath temperature is maintained at 155–160°. The yield of the crude yellow oil is 50–60 g. (42–50%) (Note 11). For purification, the substance is dissolved in 50 ml. of hot methanol. Upon cooling, two layers separate. Crystallization is induced by scratching the inner surface with a glass rod. When the crystalline mass is cold, the yellow solid is removed by filtration and washed with two 30-ml. portions of cold methanol. After drying in air, the yield of *m*-nitrobiphenyl is 40–50 g. (34–42%), m.p. 58.5–59.5°.

2. Notes

1. E. I. du Pont de Nemours and Company technical product, m.p. 111–112°, was used.

2. The time required for the addition varies from 1.5 to 2 hours.
3. There must be an excess of sodium carbonate to prevent the troublesome frothing caused by the liberation of carbon dioxide near the end of the coupling reaction.
4. The addition must be regulated so as to prevent the formation of large chunks of sodium carbonate decahydrate.
5. Obtained from Eastman Organic Chemicals Department, Distillation Products Industries, Rochester, New York.
6. Small portions are added to the separatory funnel while the main portion is kept in the ice bath.
7. Monsanto Chemical Company anhydrous toluenesulfonic acid, which is about 80% of the *para* isomer, was used.
8. Some toluenesulfonic acid hydrate which does not dissolve in benzene must be pushed through the stem of the funnel by means of a wire or a thin glass rod.
9. The evolution of nitrogen gas may be followed by attaching a bubble counter containing kerosene to the top of the reflux condenser. Generally, the evolution of nitrogen is complete within an hour.
10. The *m*-nitrobiphenyl has a tendency to crystallize in the side arm of the Claisen flask. Arrangements must be made to keep the side arm sufficiently warm to prevent crystallization.
11. After the oil has congealed to a solid, the substance melts at 53–57°.

3. Discussion

The procedure described for the preparation of 1-(*m*-nitrophenyl)-3,3-dimethyltriazene is the method of Elks and Hey,[2] and the preparation of *m*-nitrobiphenyl is also a modification of their procedure. The other principal methods for the preparation of *m*-nitrobiphenyl are the decomposition of N-nitroso-*m*-nitroacetanilide in benzene[3] and the decomposition of alkaline *m*-nitrobenzenediazohydroxide in benzene.[4] Other methods that have been reported include the decomposition of potassium *m*-nitrobenzenediazotate in benzene with acetyl chloride,[5] the decomposition of *m*-nitrobenzoyl peroxide in boiling benzene,[6] the decomposition of benzenediazonium borofluoride in nitrobenzene[7] at 70°, and the reduction of 4-(3'-nitrophenyl)-benzenediazonium acid sulfate in boiling ethanol.[8]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

potassium m-nitrobenzenediazotate

4-(3'-nitrophenyl)-benzenediazonium acid sulfate

ethanol (64-17-5)

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

methanol (67-56-1)

sodium hydroxide (1310-73-2)

acetyl chloride (75-36-5)

sodium carbonate (497-19-8)

nitrogen (7727-37-9)

sodium nitrite (7632-00-0)

carbon dioxide (124-38-9)

Nitrobenzene (98-95-3)

urea (57-13-6)

nitroaniline

sodium carbonate decahydrate (6132-02-1)

dimethylamine (124-40-3)

benzenediazonium borofluoride

toluenesulfonic acid (88-20-0)

Biphenyl, 3-nitro-, m-Nitrobiphenyl (2113-58-8)

sodium carbonate monohydrate (5968-11-6)

toluenesulfonic acid hydrate

m-nitroaniline (99-09-2)

m-nitrobenzoyl peroxide

m-nitrobenzenediazonium chloride

1-(m-Nitrophenyl)-3,3-dimethyltriazene (20241-06-9)

N-nitroso-m-nitroacetanilide

m-nitrobenzenediazohydroxide

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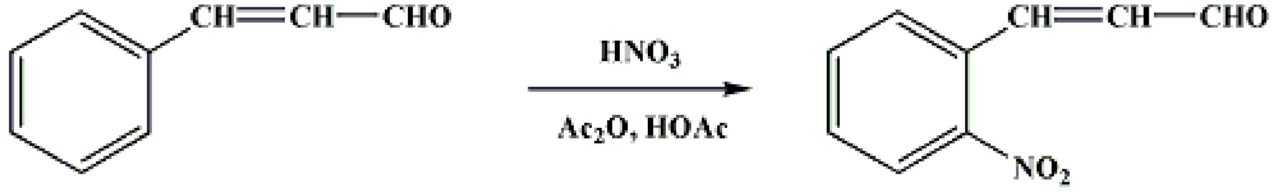
Organic Syntheses, *CV 4*, *722*

o-NITROCINNAMALDEHYDE

[Cinnamaldehyde, *o*-nitro-]



Submitted by Robert E. Buckles and M. Peter Bellis[1].
Checked by Richard T. Arnold and James D. Groves.

1. Procedure

A 1-l. three-necked round-bottomed flask, fitted with a dropping funnel and a mechanical stirrer, is cooled in an ice-salt mixture. To the flask are added 55.5 g. (50 ml., 0.42 mole) of freshly distilled cinnamaldehyde (Note 1) and 225 ml. of acetic anhydride. When the temperature of the solution has reached 0–5° a solution of 18 ml. of concentrated nitric acid (sp. gr. 1.42) in 50 ml. of glacial acetic acid is added slowly through the dropping funnel while the mixture is stirred. The time of addition is 3–4 hours, during which the temperature is kept below 5°. After the addition is complete, the mixture is allowed to warm slowly to room temperature. The reaction flask is then dismantled and stoppered, and the reaction mixture is allowed to stand 2 days.

At the end of this time, hydrochloric acid (20%) is added cautiously to the cooled solution until a precipitate begins to appear (Note 2). The addition of acid is then stopped, and the solution is allowed to cool in an ice bath or refrigerator until precipitation of the solid is completed. The light-yellow needles are collected on a Büchner funnel and dried in air. About 24 g. of *o*-nitrocinnamaldehyde, m.p. 125–127°, is obtained (Note 3). Additional product can be isolated by cautiously adding water to the mother liquor until precipitation is observed and then cooling the resultant mixture for several hours in an ice bath. Recrystallization from 95% ethanol gives 5–10 g. of *o*-nitrocinnamaldehyde, m.p. 126–127°. The total yield is 27–34 g. (36–46%).

2. Notes

1. As with other aromatic aldehydes, cinnamaldehyde is readily oxidized by air to its corresponding carboxylic acid. The latter must be separated just before the use of the aldehyde.
2. A good deal of heat is evolved when the hydrochloric acid is added to the reaction mixture, owing to the hydrolysis of acetic anhydride. The reaction mixture will become excessively hot unless it is cooled in an ice bath.
3. The product obtained is pure enough for most purposes. Recrystallization from 95% ethanol yields a nearly white product, m.p. 126–127.5°.

3. Discussion

o-Nitrocinnamaldehyde has been prepared by the condensation of *o*-nitrobenzaldehyde with acetaldehyde.[2,3] The direct nitration of cinnamaldehyde with potassium nitrate in sulfuric acid yields *o*-nitrocinnamaldehyde along with *p*-nitrocinnamaldehyde.[3] *o*-Nitrocinnamaldehyde has been obtained in 85% yield by the nitration of cinnamaldehyde diacetate.[4] The nitration of cinnamaldehyde in acetic anhydride yields *o*-nitrocinnamaldehyde as the only product,[5] and the procedure is the basis for the method given above.

References and Notes

1. State University of Iowa, Iowa City, Iowa.
2. Baeyer and Drewsen, *Ber.*, **16**, 2205 (1883).
3. Diehl and Ein horn, *Ber.*, **18**, 2335 (1885).
4. Davey and Gwilt, *J. Chem. Soc.*, **1955**, 1384.
5. Mills and Evans, *J. Chem. Soc.*, **117**, 1035 (1920).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

acetaldehyde (75-07-0)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

acetic anhydride (108-24-7)

nitric acid (7697-37-2)

cinnamaldehyde

potassium nitrate (7757-79-1)

o-Nitrobenzaldehyde (552-89-6)

cinnamaldehyde diacetate

o-Nitrocinnamaldehyde, Cinnamaldehyde, o-nitro- (1466-88-2)

p-nitrocinnamaldehyde

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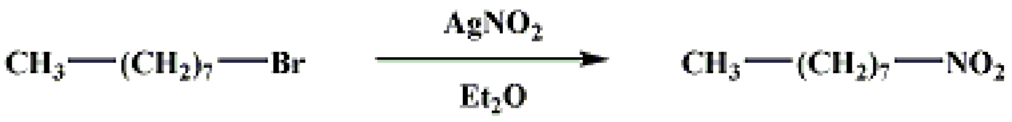
Organic Syntheses, CV 4, 724

1-NITROÖCTANE

[Octane, 1-nitro-]



Submitted by N. Kornblum and H. E. Ungnade[1].
Checked by John C. Sheehan and M. Gertrude Howell.

1. Procedure

1-Bromoöctane (96.5 g., 0.5 mole) (Note 1) is added dropwise during 2 hours to a stirred suspension of silver nitrite (116 g., 0.75 mole) (Note 2) in 150 ml. of dry ether (Mallinckrodt anhydrous), contained in a 500-ml. three-necked round-bottomed flask equipped with dropping funnel, reflux condenser, and a sealed Hershberg-type stirrer (Trubore) and immersed in a 1-gal. Dewar flask filled with ice and water (Note 3). The mixture is stirred for 24 hours in an ice bath. The bath is removed, and stirring is continued at room temperature (26–28°) until the supernatant liquor gives a negative test for halides (approximately 40 hours, (Note 4) and (Note 5).

The silver salts are removed by filtration, slurried with two 100-ml. portions of dry ether, and the ether washings are added to the ethereal solution of reaction products (Note 6). The combined ethereal solutions are distilled at atmospheric pressure through a 2 × 45 cm. column packed with 4-mm. Pyrex helices (Note 7). The residue remaining after removal of the ether is fractionated under reduced pressure. The yellow liquid distilling at 37°/3 mm. has n_D^{20} 1.4127–1.4129 and weighs 11.3 g. (14%); this is 1-octyl nitrite. It is followed by an interfraction of b.p. 38–70°/3 mm., n_D^{20} 1.4133–1.4320, yield 6.83 g., which contains some nitrite, some 1-octanol, and a little 1-nitroöctane. Finally, pure, colorless 1-nitroöctane distils at 66°/2 mm., n_D^{20} 1.4321–1.4323, yield 59.6–63.6 g. (75–80%) (Note 8) and (Note 9).

2. Notes

1. 1-Bromoöctane b.p. 50–51°/0.8 mm., n_D^{20} 1.4526, was employed.
2. Silver nitrite can be prepared as follows: silver nitrate (169.9 g., 1 mole) dissolved in 500 ml. of distilled water is added in small portions, with vigorous shaking, to a solution of 76 g. (1.1 mole) of sodium nitrite, dissolved in 250 ml. of distilled water contained in a 1-l. Erlenmeyer flask. (These operations are best carried out under a yellow safelight or, in any case, with minimum exposure to light.) Then the mixture is allowed to stand in the dark for 1 hour. The yellow precipitate is collected by filtration with suction, suspended in 250 ml. of distilled water, and again filtered. The washing is repeated twice, and the

product is collected by filtration and dried to constant weight in a vacuum desiccator over potassium hydroxide pellets; yield 134 g. (87%). The silver nitrite drying process can be facilitated by washing the material with methanol.

3. It is preferable to carry out the entire reaction in a dark room equipped with a yellow safelight. The reaction mixture should be protected from moisture by means of drying tubes.

4. The stirrer is stopped, and the precipitate is allowed to settle. Unchanged alkyl halide is detected in the supernatant liquor by the Beilstein test (copper wire spiral) or by adding a few drops of the ethereal solution to alcoholic silver nitrate.

5. According to the submitters, with primary straight-chain bromides the time needed to reach a negative test for halide is 24 hours at 0° followed by 48 ± 12 hours at room temperature. When primary straight-chain iodides are employed, the reaction time is shorter: 24 hours at ice temperature followed by 36 ± 12 hours at room temperature.

6. It is more difficult to remove an alcohol from the corresponding nitroalkane than it is to separate the nitrite ester and the nitroalkane. Minimal exposure to a moist atmosphere is, therefore, desirable since anhydrous ether is hygroscopic and nitrite esters hydrolyze readily, especially if a little acid is present.

7. A column of high efficiency is undesirable because of the thermal instability of the nitrite, and a column of lesser efficiency cannot accomplish a complete separation of the products. The column used by the submitters was equipped with a total condensate, partial take-off head with small holdup.

8. 1-Nitroöctane is completely soluble in aqueous alkali. It is converted to a crystalline colorless sodium salt on shaking with 20% aqueous sodium hydroxide, and this salt dissolves completely on adding enough water to make the solution 10% aqueous base. That the nitro compound is free from nitrate is shown by the absence of the infrared absorption bands at 6.15, 7.85 and 11.6 • characteristic of nitrate esters.

9. A recent study[2] has shown that this is a general reaction for primary straight-chain bromides and iodides; in contrast, primary chlorides fail to react. Primary bromides and iodides having branched chains also give excellent yields of nitro compounds, especially if the branching is not on the carbon *alpha* to the one holding the halogen (Table I).

TABLE I YIELDS OF NITRO COMPOUNDS

Halide	RNO_2, %	Halide	RNO_2, %
n-Butyl Br	73	*n*-Octyl I	83
n-Butyl I	74	Isoamyl Br	72
n-Hexyl Br	76	Isoamyl I	78
n-Hexyl I	78	Isobutyl Br	18
n-Heptyl Br	79	Isobutyl I	59
n-Heptyl I	82	Neopentyl I	0
n-Octyl Br	80		

The reaction of silver nitrite with secondary halides gives yields of nitroparaffins in the vicinity of 15%, while with tertiary halides the yields are even lower (0–5%). There is no question that the reaction of silver nitrite with alkyl halides is useful only for the synthesis of primary nitroparaffins.

3. Discussion

The present procedure is based on a published paper.[2] 1-Nitroöctane has been prepared from 1-iodoöctane and silver nitrite,[3] from octane by boiling with nitric acid,[4,5] from 1-nitrooctylene by catalytic hydrogenation,[6] from *n*-octaldehyde oxime and peroxytrifluoroacetic acid in acetonitrile,[7] and from 1-bromoöctane and sodium nitrite in dimethyl sulfoxide or dimethylformamide.[8] 1-Nitroöctane also has been obtained from *n*-octyl *p*-toluenesulfonate and sodium nitrite in 17% yield.[9]

References and Notes

1. Purdue University, Lafayette, Indiana.
2. Kornblum, Taub, and Ungnade, *J. Am. Chem. Soc.*, **76**, 3209 (1954).
3. Eichler, *Ber.*, **12**, 1883 (1879).
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5. Urbanski and Slon, *Roczniki Chem.*, **17**, 161 (1937) [*C. A.*, **31**, 6190 (1937)].
6. de Mauny, *Bull. soc. chim. France*, **7**, 133 (1940) [*C. A.*, **34**, 5413 (1940)].
7. Emmons and Pagano, *J. Am. Chem. Soc.*, **77**, 4557 (1955).
8. Kornblum and Powers, *J. Org. Chem.*, **22**, 455 (1957).
9. Drahowzal and Klamann, *Monatsh.*, **82**, 975 (1951).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

n-Butyl Br

n-Octyl I

n-Butyl I

Isoamyl Br

n-Hexyl Br

Isoamyl I

n-Hexyl I

Isobutyl Br

n-Heptyl Br

Isobutyl I

n-Heptyl I

Neopentyl I

n-Octyl Br

n-octaldehyde oxime

methanol (67-56-1)

ether (60-29-7)

acetonitrile (75-05-8)

sodium hydroxide (1310-73-2)

nitric acid (7697-37-2)

silver nitrate (7761-88-8)

1-Bromooctane (111-83-1)

sodium nitrite (7632-00-0)

nitrite (14797-65-0)

potassium hydroxide pellets (1310-58-3)

nitro (10102-44-0)

silver nitrite (7783-99-5)

1-Octanol (111-87-5)

1-iodooctane (629-27-6)

dimethylformamide (68-12-2)

octane (111-65-9)

dimethyl sulfoxide (67-68-5)

Octane, 1-nitro-, 1-Nitrooctane (629-37-8)

1-octyl nitrite

1-nitrooctylene

peroxytrifluoroacetic acid

n-octyl p-toluenesulfonate (3386-35-4)

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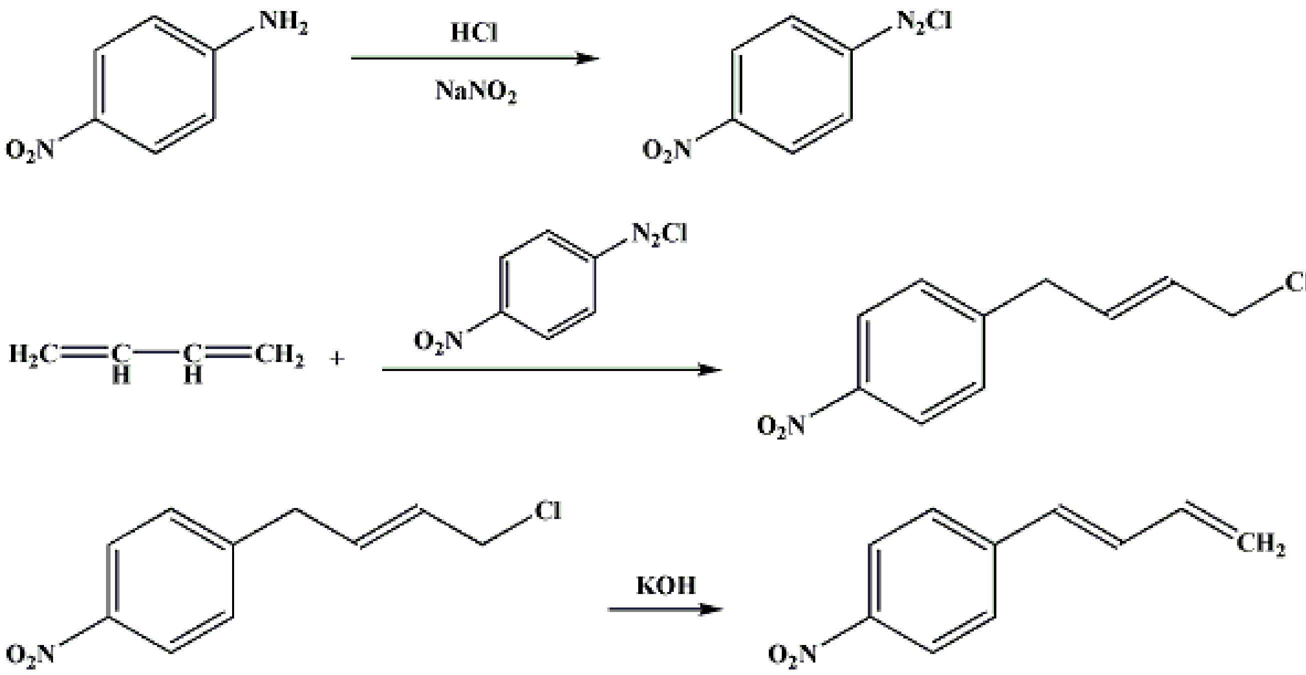
Organic Syntheses, CV 4, 727

1-(*p*-NITROPHENYL)-1,3-BUTADIENE

[1,3-Butadiene, 1-(*p*-nitrophenyl)-]



Submitted by Gus A. Ropp and Eugene C. Coyner[1].
Checked by Arthur C. Cope and David J. Marshall.

1. Procedure

A. *1-(p-Nitrophenyl)-4-chloro-2-butene*. *p*-Nitroaniline hydrochloride is prepared by heating 138 g. (1.0 mole) of *p*-nitroaniline (Note 1) with 240 ml. of concentrated hydrochloric acid and 100 ml. of water on a steam bath for 15 minutes with occasional stirring. The mixture is cooled in an ice-salt bath and stirred rapidly in order to precipitate the hydrochloride as fine crystals. Cracked ice (100 g.) is added, and a solution of 70 g. of sodium nitrite is added dropwise with rapid mechanical stirring during a 1-hour period while the temperature of the reaction mixture is held between −4° and +4.5° by cooling with the ice-salt bath. The mixture is stirred for an additional period of 20 minutes and then is filtered through a chilled funnel into an ice-cooled filter flask. The filtrate is kept below 4° (Note 2) and is added through a dropping funnel during 90 minutes to a cold, vigorously stirred mixture composed of 1 l. of acetone, a solution of 80 g. of sodium acetate trihydrate in 100 ml. of water, a solution of 30 g. of cupric chloride in 50 ml. of water, and 130 ml. of liquid butadiene (Note 3). The reaction mixture is kept at −3° to +2° by means of an ice-salt bath while the diazonium salt solution is added. After the addition is completed the cooling bath is removed and the mixture is stirred for 16 hours. One liter of ether is added, and after several minutes' stirring the ethereal layer is separated, washed with four 1-l. portions of water, and dried over 20 g. of anhydrous magnesium sulfate. The solvent is removed by distillation at 15 mm. by heating on a steam bath, leaving a dark brown oily residue (187–199 g.) of crude 1-(*p*-nitrophenyl)-4-chloro-2-butene (Note 4).

B. *1-(p-Nitrophenyl)-1,3-butadiene*. The crude 1-(*p*-nitrophenyl)-4-chloro-2-butene obtained in Part A is dissolved in a mixture of 500 ml. of ligroin, b.p. 90–100°, and 500 ml. of benzene; 5 g. of decolorizing carbon is added, and the mixture is heated under reflux for 2 hours. After filtration to separate the decolorizing carbon the solvents are removed by distillation from a steam bath under reduced pressure, and the residual clear oil is dissolved in 400 ml. of methanol. A solution of 112 g. of potassium hydroxide in 600 ml. of methanol is added from a dropping funnel during 30 minutes while the mixture is stirred mechanically and kept at 15–30° by cooling with a bath of cold water. After being stirred for an additional period of 5 minutes the mixture, which contains some precipitated product, is poured into 1.2 l. of cold water. The crude product is collected on a filter,

washed well with cold water, and air-dried. It is dissolved in 700 ml. of hot ligroin, b.p. 90–100°, and the solution is treated with 5 g. of decolorizing carbon, and filtered. On cooling, 1-(*p*-nitrophenyl)-1,3-butadiene separates as a yellow crystalline solid which is collected on a filter and dried in a desiccator. The yield of pure product, m.p. 77–79° (Note 5), is 100–108 g. (57–62% based on *p*-nitroaniline).

2. Notes

1. Either a pure grade of *p*-nitroaniline obtained from the Eastman Kodak Company or a technical grade purified by one recrystallization from ethanol was used, m.p. 147.5–148°.
2. The filtrate is kept in an ice-salt bath and transferred to the dropping funnel in small amounts in order to keep the temperature below 4°.
3. Butadiene from a commercial cylinder is passed through an 8-mm. glass tube leading to the bottom of a graduated cylinder cooled with Dry Ice and acetone, where it condenses and is measured as a liquid.
4. The submitters report that small samples of the crude product can be distilled in order to obtain pure 1-(*p*-nitrophenyl)-4-chloro-2-butene, b.p. 160–165°/1 mm.
5. Two recrystallizations from ligroin raise the melting point of the 1-(*p*-nitrophenyl)-1,3-butadiene to a constant value of 78.6–79.4°. The product can be kept for several weeks in a dark bottle at room temperature without evidence of decomposition.

3. Discussion

1-(*p*-Nitrophenyl)-1,3-butadiene has been prepared only by the method described,[2] which is an example of the Meerwein reaction (addition of diazonium salts to a carbon-carbon double bond with the elimination of nitrogen).[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 21

References and Notes

1. University of Tennessee, Knoxville, Tennessee.
2. Coyner and Ropp, *J. Am. Chem. Soc.*, **70**, 2283 (1948); Dombrovskii, *Doklady Akad. Nauk S.S.S.R.*, **111**, 827 (1956) [*C. A.*, **51**, 9507 (1957)].
3. Müller, *Angew. Chem.*, **61**, 179 (1949).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ligroin

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

methanol (67-56-1)

ether (60-29-7)

nitrogen (7727-37-9)

sodium nitrite (7632-00-0)

acetone (67-64-1)

decolorizing carbon (7782-42-5)

potassium hydroxide (1310-58-3)

cupric chloride (7758-89-6)

magnesium sulfate (7487-88-9)

butadiene (106-99-0)

sodium acetate trihydrate (6131-90-4)

1-(p-Nitrophenyl)-1,3-butadiene, 1,3-Butadiene, 1-(p-nitrophenyl)- (20264-89-5)

p-nitroaniline (100-01-6)

p-nitroaniline hydrochloride (15873-51-5)

1-(p-Nitrophenyl)-4-chloro-2-butene (98011-65-5)

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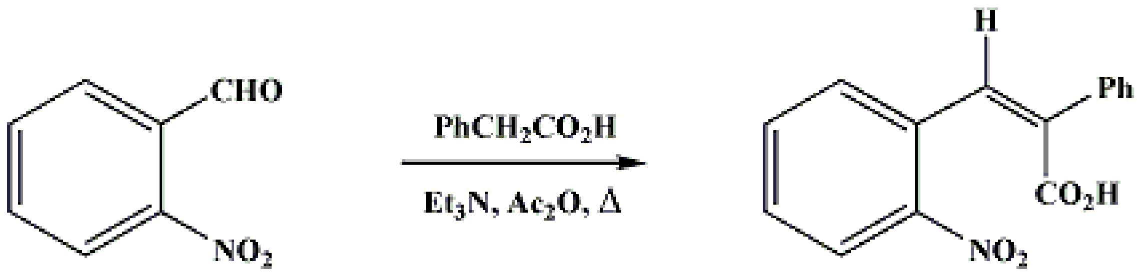
Organic Syntheses, *CV 4*, 730

trans-*o*-NITRO-α-PHENYLCINNAMIC ACID

[Acrylic acid, *trans*-3-(*o*-nitrophenyl)-2-phenyl-]



Submitted by DeLos F. DeTar[1]
Checked by Charles C. Price and J. D. Berman.

1. Procedure

A mixture of 30.2 g. (0.20 mole) of *o*-nitrobenzaldehyde,[2] 40 g. (0.29 mole) of phenylacetic acid, 100 ml. (1.08 moles) of acetic anhydride, and 20 g. (0.20 mole) of triethylamine is refluxed for 15 minutes in a 500-ml. flask. The solution is cooled to 90°, and 100 ml. of cold water is added over a 5-minute period at a rate that maintains the temperature above 90° (Note 1). The solution is filtered at 95–100° and cooled to 20°. *trans*-*o*-Nitro-α-phenylcinnamic acid precipitates in the form of light-orange crystals. It is separated by filtration and washed with 60 ml. of 50% acetic acid and with water. The dried acid weighs 39–42 g. (72–78%) and melts at 195–198°, which corresponds to a purity of about 98% (Note 2). After recrystallization from 500 ml. of toluene, it is in the form of yellow prisms weighing 38–39 g. (71–72%) and melting at 197.8–198.3°.

2. Notes

1. If the temperature gets too high, more cold water may be added. If the water is added too rapidly at first, the temperature drops below 90° and the rate of hydrolysis becomes very slow. Heating such an incompletely hydrolyzed mixture above 90° may cause it to boil violently.
2. Approximate melting points of mixtures of the *trans*- and *cis*-*o*-nitro-α-phenylcinnamic acids are as follows:

Per Cent *cis*	Sinter Point	M.P.
33		134–185°
23	130°	136–187°
13	131°	165–192°
8	135°	184–196°

3.5	140°	192–198°
1.5	170°	195–198°
—	196°	197.8–198.3°

3. Discussion

trans-o-Nitro-α-phenylcinnamic acid has been prepared by the condensation of *o*-nitrobenzaldehyde with sodium phenylacetate in the presence of acetic anhydride with[3] or without[4] fused zinc chloride as a catalyst. It has also been prepared by the condensation of *o*-nitrobenzaldehyde with phenylacetic acid in the presence of acetic anhydride and triethylamine.[5]

References and Notes

1. University of South Carolina, Columbia, South Carolina.
2. *Org. Syntheses Coll. Vol.* **3**, 641 (1955).
3. Pschorr, *Ber.*, **29**, 496 (1896).
4. Oglialoro and Rosini, *Gazz. chim. ital.*, **20**, 396 (1890).
5. Bakunin and Peccerillo, *Gazz. chim. ital.*, **65**, 1145 (1935).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

acetic acid (64-19-7)

acetic anhydride (108-24-7)

toluene (108-88-3)

Phenylacetic acid (103-82-2)

zinc chloride (7646-85-7)

o-Nitrobenzaldehyde (552-89-6)

sodium phenylacetate (114-70-5)

triethylamine (121-44-8)

trans-o-Nitro-α-phenylcinnamic acid, Acrylic acid, trans-3-(o-nitrophenyl)-2-phenyl- (19319-35-8)

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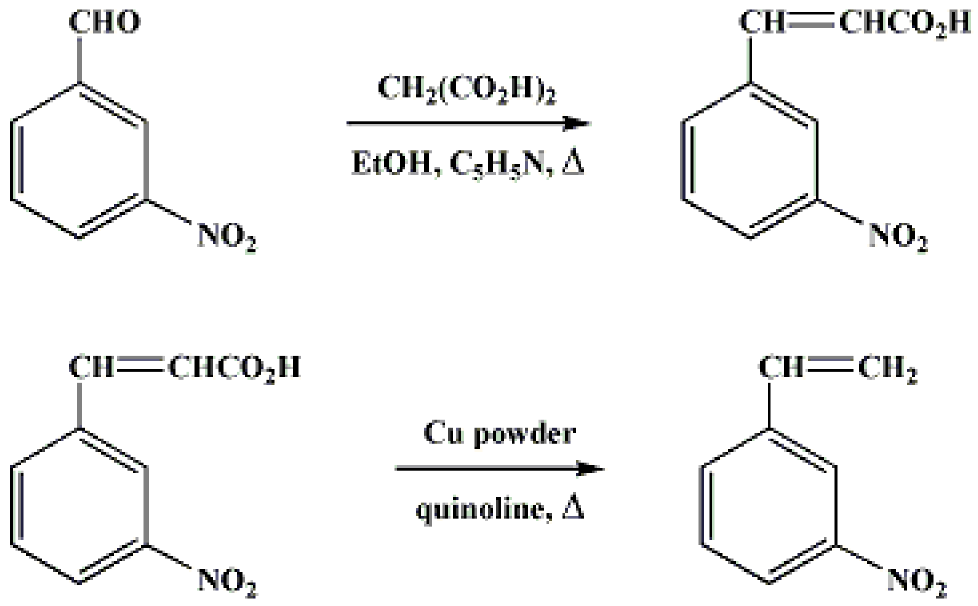
Organic Syntheses, CV 4, 731

m-NITROSTYRENE

[Styrene, *m*-nitro-]



Submitted by Richard H. Wiley and Newton R. Smith[1].
Checked by Richard T. Arnold, William E. Parham, and Darwin D. Davis.

1. Procedure

A. *m-Nitrocinnamic acid*. In a 1-l. round-bottomed flask fitted with a reflux condenser are placed 151 g. (1 mole) of *m*-nitrobenzaldehyde (Note 1), 115 g. (1.1 moles) of malonic acid, 250 ml. of 95% ethanol, and 25 ml. of pyridine. The mixture is heated on a steam bath under gentle reflux for 6–8 hours and cooled. The large masses of crystals are broken up with a spatula, and the reaction mixture is cooled in an ice bath. The solid is collected on a Büchner funnel, and the residue is washed with 100 ml. of cold ethanol and then with two 100-ml. portions of ether. The crude *m*-nitrocinnamic acid is suspended in 300 ml. of ethanol and digested on a steam plate for 2–3 hours. The mixture is cooled and filtered, and the solid is air-dried. The product, 144–155 g. (75–80%), is a light-yellow solid and melts at 200–201° (Note 2).

B. *m-Nitrostyrene*. In a 250-ml. two-necked flask equipped with a 250° thermometer and an air condenser are placed 30 g. (0.155 mole) of *m*-nitrocinnamic acid, 2 g. of copper powder, and 60 ml. of dry quinoline (Note 3). The flask is heated with a Bunsen burner to 185–195°, during which time a steady stream of carbon dioxide is evolved. After 2–3 hours (Note 4), the reaction mixture is cooled and poured into a mixture of 75 ml. of concentrated hydrochloric acid and 175 g. of ice. The *m*-nitrostyrene is isolated by steam distillation, approximately 1 l. of distillate being collected. The aqueous distillate is extracted with three 50-ml. portions of chloroform,

which are combined and dried over anhydrous sodium sulfate. A 50-ml. Claisen flask, equipped with a dropping funnel, is heated on a steam bath, and the filtered chloroform extract is added dropwise. Heating is continued until all the solvent has been removed. The residue is then distilled at 3–5 mm. pressure. Following a small fore-run of less than 1 g. (Note 5), the *m*-nitrostyrene distils as a yellow liquid. The yield is 13–14 g. (56–60%), b.p. 90–96°/3.5 mm., n_D^{20} 1.5836, n_D^{27} 1.5800–1.5802 (Note 6) and (Note 7).

2. Notes

1. The checkers used technical *m*-nitrobenzaldehyde melting at 53–56°.
2. This procedure has been used by the submitters and others to prepare the following cinnamic acids from substituted benzaldehydes: *o*-nitrocinnamic acid (70%),[2] *p*-nitrocinnamic acid (77%),[2] *m*-cyanocinnamic acid (71%),[3] *o*-chlorocinnamic acid (82%),[4] *m*-chlorocinnamic acid (53%),[4] *p*-chlorocinnamic acid (73%),[4] 2,4-dichlorocinnamic acid (70%),[4] 3,4-dichlorocinnamic acid (81%),[4] *m*-bromocinnamic acid (31%),[4] *p*-methoxycinnamic acid (60%),[4] and 3,4-dimethoxycinnamic acid (77%).[4]
The method constitutes a simple preparation of ethanol-insoluble cinnamic acids, of a high degree of purity when compared with the Perkin reaction[5] or the usual procedure for the Doebner reaction (p. 327), which uses a large excess of pyridine. A useful modification of this reaction is to warm the reactants on a steam plate in the absence of alcohol.[6,7]
3. Quinoline that has been purified by steam distillation of an acid solution should be used. Crude quinoline sometimes contains non-basic, high-boiling impurities such as nitrobenzene, which make the purification of *m*-nitrostyrene more difficult.
4. The checkers obtained a lower yield (9–11 g.) when a 2-hour heating period was used. The reaction must be carried out at 195° until the evolution of carbon dioxide has practically ceased (usually 2.75 hours). The checkers used Mallinckrodt copper powder.
5. The checkers obtained essentially no fore-run and only trace amounts of solid residue. The refractive index of the first 200 mg. was n_D^{27} 1.5800; of the center fractions, n_D^{27} 1.5802; and of the last 700 mg., n_D^{27} 1.5800.
6. This procedure has been used in the preparation of other nitrostyrenes in the following yields: *o*-nitrostyrene (40%),[2] *p*-nitrostyrene (41%),[2] and 3-nitro-4-hydroxystyrene (60%).[2] A better procedure for more volatile styrenes involves simultaneous decarboxylation and codistillation with quinoline from the reaction flask. This method has been used to prepare the following styrenes: *o*-chlorostyrene (50%),[4] *m*-chlorostyrene (65%),[4] *p*-chlorostyrene (51%),[4] *m*-bromostyrene (47%),[4] *o*-methoxystyrene (40%),[4] *p*-methoxystyrene (76%),[4] *m*-

cyanostyrene (51%),[3] and *p*-formylstyrene (52%).[8]

7. Larger runs usually give smaller percentage yields.

3. Discussion

m-Nitrocinnamic acid has been prepared from *m*-nitrobenzaldehyde with sodium acetate and acetic anhydride,[5] and by the condensation of *m*-nitrobenzaldehyde with malonic acid in the presence of bases.[7,9]

m-Nitrostyrene has been prepared by boiling the sodium salt of β-bromo-β-(*m*-nitrophenyl) propionic acid;[10] by the dehydration of *m*-nitrophenylmethylcarbinol with phosphorus pentoxide,[11] potassium bisulfate,[12] or phosphoric acid[13]; by the decarboxylation of *m*-nitrocinnamic acid;[14] and by the condensation of *m*-nitrobenzaldehyde with acetic anhydride over bentonite at high temperatures.[15]

References and Notes

1. University of Louisville, Louisville, Kentucky.
2. Wiley and Smith, *J. Am. Chem. Soc.*, **72**, 5198 (1950).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

bentonite

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ether (60-29-7)

acetic anhydride (108-24-7)

sodium acetate (127-09-3)

chloroform (67-66-3)

sodium sulfate (7757-82-6)

carbon dioxide (124-38-9)

potassium bisulfate (7646-93-7)

copper powder (7440-50-8)

pyridine (110-86-1)

phosphoric acid (7664-38-2)

Nitrobenzene (98-95-3)

Quinoline (91-22-5)

Malonic acid (141-82-2)

2,4-dichlorocinnamic acid

3,4-dichlorocinnamic acid

3,4-dimethoxycinnamic acid

3-nitro-4-hydroxystyrene

phosphorus pentoxide (1314-56-3)

m-Nitrobenzaldehyde (99-61-6)

m-Nitrocinnamic acid (555-68-0)

p-nitrocinnamic acid (619-89-6)

m-Chlorostyrene (2039-85-2)

o-Chlorostyrene (2039-87-4)

p-Chlorostyrene (1073-67-2)

m-Bromostyrene (2039-86-3)

o-nitrocinnamic acid

m-Nitrostyrene, Styrene, m-nitro- (586-39-0)

m-cyanocinnamic acid

o-chlorocinnamic acid (3752-25-8)

m-chlorocinnamic acid (1866-38-2)

p-chlorocinnamic acid (1615-02-7)

m-bromocinnamic acid (32862-97-8)

p-methoxycinnamic acid

o-nitrostyrene

p-nitrostyrene (100-13-0)

o-methoxystyrene (612-15-7)

p-methoxystyrene (637-69-4)

m-cyanostyrene

p-formylstyrene (1791-26-0)

m-nitrophenylmethylcarbinol (52022-77-2)

sodium salt of β-bromo-β-(m-nitrophenyl) propionic acid

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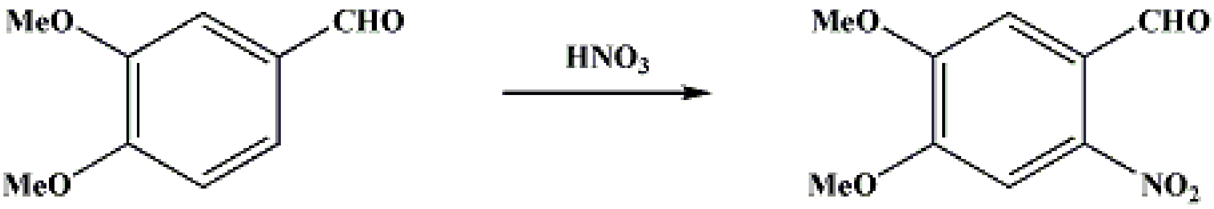
Organic Syntheses, CV 4, 735

6-NITROVERATRALDEHYDE

[Veratraldehyde, 6-nitro-]



Submitted by Charles A. Fetscher[1]
Checked by Richard T. Arnold, W. E. Parham, and Donald A. Leister.

1. Procedure

The product of this reaction is quite sensitive to light, and the entire procedure should be carried out in semidarkness (Note 1).

A wide-mouth 1-l. Erlenmeyer flask is supported inside a water bath of at least 2-l. capacity so that the bottom of the flask is not in contact with the bottom of the bath. The bath is filled with water at about 15° to cover at least half the height of the flask. The flask is fitted with a moderate-speed stainless-steel propeller-type stirrer, and 350 ml. of nitric acid (sp. gr. 1.4) at 20° is poured into it. Veratraldehyde,[2] 70 g. (0.42 mole) (Note 2), is crushed at least as fine as rice grains and is slowly added in small portions to the acid. The rate of addition should be such that it requires about 1 hour to add all the aldehyde. It is helpful, although not usually necessary, to add two or three ice cubes to the bath at the start of the nitration. The internal temperature is checked from time to time and should be held between 18° and 22°. The mixture is stirred for 10 minutes after the addition of the last of the aldehyde.

The mixture is then poured into 4 l. of vigorously agitated cold water (Note 3) in a suitable opaque container. From this point onward the protection of the product from light is extremely important. The stirring is continued for a few minutes; then the batch is filtered through a 24-cm. Büchner funnel. The container and funnel are kept covered with an opaque sheet of some kind except while the transfer is being made. The cake is sucked down well and then returned to the crock and reslurried a few minutes with 2 l. of cold water. It is then refiltered, pressed out well with a spatula, and drained as well as possible.

The filter cake at this point is 60% to 80% water, and the material is sensitive to heat and to light. The drying, therefore, is difficult and slow, and the exact procedure will depend upon the equipment available. One satisfactory method is to set the Büchner funnel containing the wet material in a large forced-draft oven for 8 hours at 50°. The material, still very wet, is then easily spread on a tray and is placed in a dark but ventilated storeroom, where it is allowed to air-dry for 48 hours or until the weight of

the product is less than about 90 g. The product now contains from 10% to 20% of water and is best recrystallized without more thorough drying.

The material is dissolved in 2 l. of boiling 95% ethanol. It is not necessary to filter this solution for the first crystallization. Upon standing overnight, the solution is solid with precipitate. This structure is easily broken up and is filtered on a large Büchner funnel. The mother liquor is concentrated to about 700 ml. and allowed to cool. The second crop of solid is added to the first and dried in a vacuum oven at 50° overnight. The dry material weighs 65–70 g., corresponding to a yield of 73–79%, and melts at 129–131°. It is sufficiently pure for most purposes. One additional crystallization from 1 l. of 95% ethanol gives 55–60 g. of pure material, melting at 132–133°.

2. Notes

1. A sample of 6-nitroveratraldehyde of original melting point 133°, after 9 hours' exposure to the diffused light of the laboratory, showed a melting point of 88–95°. A small quantity of 6-nitrosoveratric acid, m.p. 185–190°, was isolated from the altered material.
2. The veratraldehyde should have a minimum melting point of 43°. Since there is no difficulty in controlling this reaction, larger batches would undoubtedly be as efficient. The phenomenal bulk of the product and the necessity of minimizing exposure to light make it impractical to handle appreciably more at one time. Smaller batches are perfectly feasible, although it is suggested that for very small amounts of aldehyde somewhat more than the proportional quantity of nitric acid be used. It has been found satisfactory to use 100 ml. of acid with 15 g. of aldehyde.
3. If less water is used, the material is more difficult to break up and wash adequately, and the crude material is more heat-sensitive. Very vigorous agitation is desirable during this precipitation.

3. Discussion

6-Nitroveratraldehyde has always been prepared by direct nitration of the aldehyde. This preparation is a modification of that given by Salway.[3]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

nitric acid (7697-37-2)

Veratraldehyde (120-14-9)

6-Nitroveratraldehyde, Veratraldehyde, 6-nitro- (20357-25-9)

6-nitrosoveratric acid

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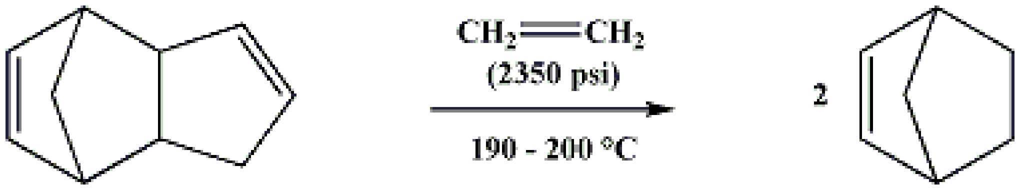
Organic Syntheses, CV 4, 738

NORBORNYLENE

[2-Norbornene]



Submitted by J. Meinwald and N. J. Hudak[1].
Checked by J. D. Roberts, C. M. Sharts, and W. G. Woods.

1. Procedure

A 1-l. steel bomb is charged with 200 g. (1.5 moles) of dicyclopentadiene (Note 1). The bomb is flushed with ethylene (Note 2) and then filled while shaking to an initial pressure of 800–900 p.s.i. at 25°. Shaking is continued as the bomb is slowly heated (Note 3) to 190–200° and maintained at this temperature for 7 hours (Note 4). At the end of this period, the reaction vessel is cooled and vented, and the crude product is transferred to a simple distillation apparatus (Note 5). A fraction boiling between 93° and 100° is collected, yield 162–202 g. (57–71%, based on dicyclopentadiene) (Note 6). The norbornylene may be redistilled with negligible losses to give a final product, b.p. 94–97°/740 mm., m.p. 44–44.5° (sealed capillary).

2. Notes

1. The dicyclopentadiene used by the submitters was supplied by the Enjay Company. No preliminary purification is required. Technical (85%) dicyclopentadiene has been found by the checkers to give 54–56% yields of norbornylene without preliminary purification.
2. C.P. grade ethylene was obtained from the Matheson Company.
3. To avoid complications due to the exothermic nature of this reaction,[2] a rate of heating of about 50° per hour was adopted (cf. (Note 6)).
4. Near 180°, the maximum pressure (about 2350 p.s.i.) is developed.
5. In spite of the low melting point of norbornylene, the product has a remarkable tendency to crystallize. Care should therefore be taken to prevent premature solidification of the distillate. A short-path, air-cooled assembly using rather wide-diameter tubing is convenient for this purpose.
6. The submitters report the same yields using a 3-l. bomb and 3.68 moles of dicyclopentadiene. Larger-scale preparations may necessitate special control procedures.

3. Discussion

The procedure described above is essentially that of Thomas.[2] Norbornylene has also been prepared by the addition of ethylene to monomeric cyclopentadiene[3] (p. 238), by dehydration of β-norborneol with phosphorus pentoxide,[4] and by dehydrohalogenation of norbornyl chloride or bromide using quinoline.[4,5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 852
- Org. Syn. Coll. Vol. 6, 142

References and Notes

1. Cornell University, Ithaca, New York.
2. Thomas, *Ind. Eng. Chem.*, **36**, 310 (1944); Thomas and Universal Oil Products, U. S. pat. 2,340,908 [*C. A.*, **38**, 4273 (1944)].
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

β-norborneol

norbornyl chloride or bromide

ethylene (9002-88-4)

Quinoline (91-22-5)

CYCLOPENTADIENE (542-92-7)

dicyclopentadiene

Norbornylene (498-66-8)

2-Norbornene

phosphorus pentoxide (1314-56-3)

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Organic Syntheses, CV 4, 739

OLEOYL CHLORIDE

Submitted by C. F. H. Allen, J. R. Byers, Jr., and W. J. Humphlett[1].
Checked by Max Tishler and R. Connell.

1. Procedure

Seventy grams (0.25 mole) of oleic acid (Note 1) is placed in the dropping funnel *H* of the tangential apparatus (.htmFig. 13; (Note 2)). The thionyl chloride distillation is started and regulated (Note 2); the upper part of the column should be filled with the vapor, and reflux should be constant and steady. The acid is dropped in at the top of the column over a period of 35 minutes (120 g. per hour). The product that collects in the receiver *I* contains about 25–27% of thionyl chloride (Note 2) if the heated lower leg *K* is employed. The product in receiver *I* is heated on a steam bath under reduced pressure until the more volatile components are completely removed. The residue of crude acid chloride weighs 72–74 g. (97–99% yield). The infrared spectrum of this product shows no trace of a carboxyl band (Note 1), (Note 3), and (Note 4).

Fig. 13.

Fig. 13.

The crude acid chloride will serve for most purposes. It can be distilled at very low pressures (b.p. 99–109°/25 •) to yield a water-white product; n_D^{25} 1.4580–1.4613 (Note 5). Small amounts of oleoyl chloride may be distilled at higher pressures; b.p. 180–185°/1–2 mm. The infrared absorption curve of the oleic acid obtainable by hydrolysis is the same as that of the oleic acid used; thus no isomerization during the reaction is indicated.

2. Notes

1. The oleic acid used by the submitters had a freezing point of –2° to +13° and a boiling point of 182–187°/1–2 mm. It was a 90% middle cut from Emerson 233 as obtained from Emery Industries, Inc., Cincinnati, Ohio. The checkers found that the amount of color in the product was a function of the purity of the oleic acid. The product from distilled Emerson 233 was dark red-brown, whereas that from a purified grade of oleic acid was pale yellow.

2. The tangential apparatus[2] is built from stock pieces of glassware having 24/40 standard taper glass joints, and it is clamped to two ring stands. The reactor

consists of a column 50 cm. long and 2 cm. inside diameter, packed with 1/8-in. glass helices of the type used for packing distillation columns, and wrapped with a 275-watt flexible heating tape *A*, 6 ft. long and in. wide, with lead wires connected to a variable transformer such as the Powerstat or Variac, which is attached to a source of 110-volt power. Near the bottom of the column is a heated side arm connection *B* to a three-necked flask reservoir *C*. The use of the leg *K*, wrapped with a heating tape, removes much of the excess of thionyl chloride and is particularly advantageous with acid chlorides (such as oleoyl chloride) that are sensitive to heat. The crude effluent from the reactor ordinarily contains 40–50% of thionyl chloride, which is reduced one-half or more by this leg. It is not essential for use with chlorides insensitive to heat. Vapor supplied by boiling the liquid in the reservoir is forced to circulate via *B* through the column by sufficient heat input to the column and the lower leg *K*; the excess escapes at the top through the side arm *D* which is connected to a Friedrichs condenser *E*. The bottom of the condenser is connected to a Y-shaped section with an outlet *F* for effluent gas and a return *G* which extends below the surface of the liquid in the reservoir. At the top of the column is a 250-ml. dropping funnel *H* for admitting reactants to the column. Since oleic acid is a liquid at room temperature, heating of this funnel is not required in the present preparation. At the bottom of the column is a 500-ml. flask *I* for receiving the product.

3. Other acid chlorides can be prepared similarly. (*a*) Palmitoyl chloride: Palmitic acid is a solid at room temperatures (m.p. 61–62°) and is not sufficiently soluble in palmitoyl chloride or thionyl chloride, and so these cannot be used as solvents. It is admitted to the reactor in the melted condition by warming the acid in the dropping funnel *H*. The quality of the chloride naturally depends on the homogeneity of the starting acid; palmitic acid usually contains a little stearic acid, which does not affect the melting point. Palmitoyl chloride, n_D^{25} 1.4489, can be obtained as a water-white product by distillation at very low pressures (b.p. 110°/15–24 •), or with negligible decomposition at boiling points as high as 165°.

(*b*) Ricinoleoyl chloride: b.p. 205–210°/8 mm., 125–130°/25 •; n_D^{25} 1.4759; this substance decomposes significantly at the higher distillation temperature.

(*c*) 2,4-Di-*tert*-amylphenoxyacetyl chloride: In this instance, the corresponding solid acid (20 g.) is dissolved in the acid chloride (80 g.) as a solvent and admitted at the rate of 70 g. of acid per hour. The crude acid chloride, after removal of the excess thionyl chloride, contains about 1% of unchanged acid (infrared determination). The yield of distilled acid chloride, b.p. 143–146°/2 mm., n_D^{25} 1.5062, is 85%.

4. The described procedure is not suitable for all acids. For instance, the acid chloride must not have a boiling point so near that of thionyl chloride that they are inseparable by distillation. Certain high-molecular-weight acids give dehydration products, presumably diketenes: e.g., behenic and dihydroxystearic acids.

5. The refractive index will vary with the purity of the oleic acid. Oleic acid

purified by low-temperature crystallization and by conversion to the oleic acid-urea complex (95.3% oleic, 0.7% linoleic) yielded a product with n_D^{25} 1.4613.

3. Discussion

This modification of the continuous reactor (cf. benzoylacetanilide, p. 80) with countercurrent distillation is preferred for reactions in which a large amount of solvent or excess of one reactant is essential, but increase of total volume is undesirable. It is especially useful if the substances involved are heat-sensitive; with this apparatus the reactants are heated for only a few minutes at most. It is particularly applicable to the preparation of acid chlorides from carboxylic acids and thionyl chloride (cf. (Note 3) and (Note 4)). An indefinite amount of product can be prepared by replenishing the reactants as they are consumed.

Oleoyl chloride has been prepared by treatment of oleic acid with thionyl chloride,[3] phosphorus trichloride or pentachloride, and oxalyl chloride.[4] The highest yield (86%) reported was secured by use of oxalyl chloride in carbon tetrachloride, but the more economical phosphorus trichloride gave a yield of 60%. The standard procedures for obtaining aliphatic acid chlorides have been described many times without inclusion of details other than physical properties. Only references to the procedures useful in the laboratory are given.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 80

References and Notes

1. Eastman Kodak Company, Rochester, New York.
2. Allen, Byers, Humphlett, and Reynolds, *J. Chem. Educ.*, **32**, 394 (1955).
3. Verkade, *Rec. trav. chim.*, **62**, 393 (1943); Fierz-David and Kuster, *Helv. Chim. Acta*, **22**, 82 (1939).
4. Bauer, *Oil & Soap*, **23**, 1 (1946).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

oleic acid-urea complex

phosphorus trichloride or pentachloride

thionyl chloride (7719-09-7)

carbon tetrachloride (56-23-5)

phosphorus trichloride (7719-12-2)

oleic acid (112-80-1)

palmitic acid (57-10-3)

stearic acid (57-11-4)

oxalyl chloride (79-37-8)

Benzoylacetanilide (85-99-4)

Oleoyl chloride (112-77-6)

Palmitoyl chloride (112-67-4)

Ricinoleoyl chloride

2,4-Di-tert-amylphenoxyacetyl chloride (88-34-6)

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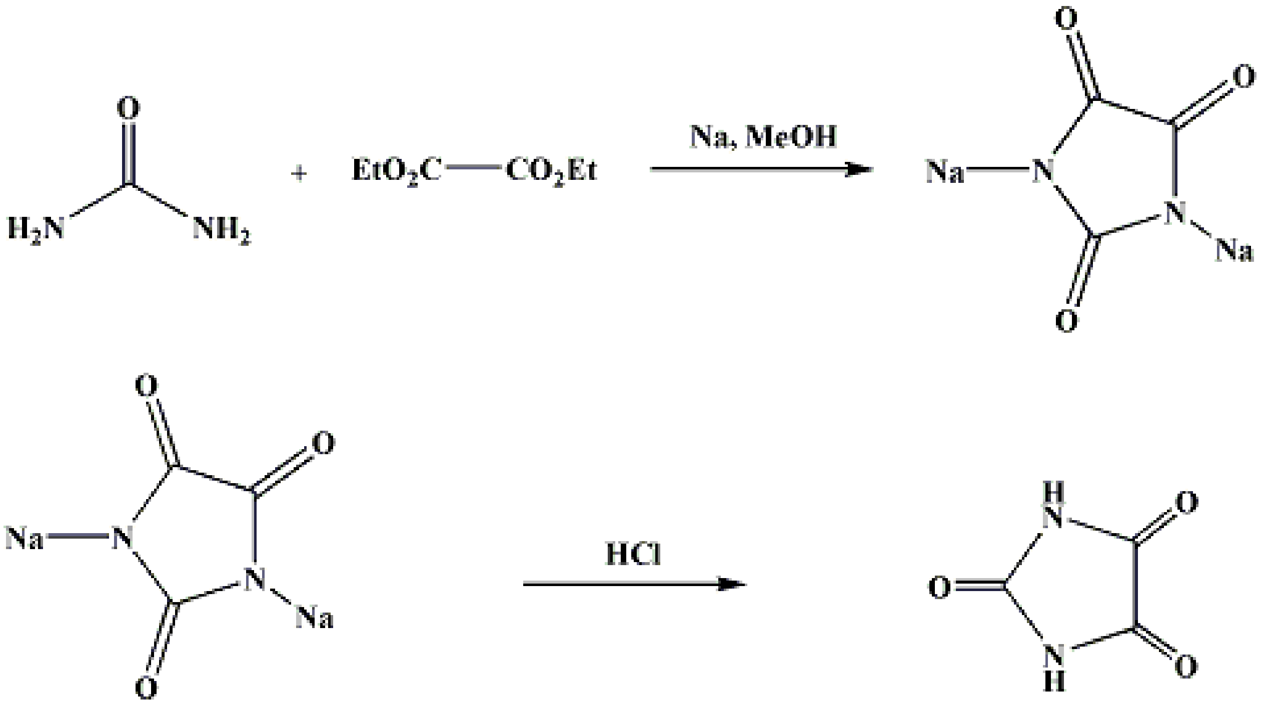
Organic Syntheses, CV 4, 744

PARABANIC ACID



Submitted by Joseph I. Murray[1]
Checked by M. S. Newman and Tadamichi Fukunaga.

1. Procedure

Eight hundred fifty milliliters of absolute methanol (magnesium-dried) is distilled directly, through a condenser, into a 1-l. three-necked reaction flask equipped with a sealed mechanical stirrer and an efficient reflux condenser protected by a drying tube. After about 300 ml. of methanol has been distilled, the drying tube is removed from the reflux condenser, and small pieces of clean sodium are added to the stirred methanol at such a rate that the alcohol vapors do not escape from the condenser (Note 1). When a total of 23 g. (1 g. atom) of sodium has been added, the drying tube is replaced, the distillation of methanol is completed (Note 1), and the system is brought to a temperature of 20–25° (other temperatures are less favorable). The inlet condenser is removed, 30 g. (0.5 mole) of dry finely ground urea (Note 2) is quickly added to the reaction mixture, and the opening is then closed by attaching a dropping funnel. When the urea has dissolved completely, the addition of 70 g. (0.48 mole) of diethyl oxalate (Note 2) is begun (Note 3). A white precipitate forms immediately. Stirring is continued for 1 hour after the addition of the ester has been completed (Note 4). One hundred milliliters of concentrated hydrochloric acid is added dropwise to the mixture at a rate that causes little increase in the solution temperature, stirring is continued for a few minutes, and the mixture is filtered. The residue is washed twice with a small quantity of methanol, and the filtrate and washings are transferred to a 2-l. two-necked flask equipped with a sealed stirrer and a vacuum take-off. The alcohol is removed under the

reduced pressure of a good water aspirator (Note 5). The practically dry solid residue is washed from the evaporator with water which is used as the recrystallization solvent (Note 6). When the bulk of the solid has dissolved, the solution is cooled slightly below the boiling point, 2 g. of activated carbon is added, and the solution is filtered through a hot Büchner funnel by use of moderate suction. The solution yields a white, crystalline precipitate of parabanic acid upon standing in a refrigerator overnight. The yield of purified, dried product melting at 241–243° with decomposition is 39–41.5 g. (71.5–76%).

2. Notes

1. The checkers used Mallinckrodt analytical reagent methanol without drying and distilling. The sodium was added to 300 ml. of the methanol, and the remainder of the methanol was added dropwise. The results obtained in this way were the same as those described by the submitter.
The hydrogen released during the formation of the sodium methoxide prevents moisture from entering the system. More rapid addition of the sodium and reduced loss of methanol vapor are realized if the reaction flask is surrounded by an ice bath during the addition of the metal. Calcium chloride should not be used in the drying tube because of possible clogging. Drierite ($CaSO_4$) is preferable.
2. The checkers used reagent grade urea (Baker) and diethyl oxalate (Matheson, Coleman and Bell), without purification.
3. Ester addition must be quite slow (2 drops per second or less) to prevent emulsion formation and extremely low yields.
4. At the end of 1 hour, the precipitated salt should be in a fine crystalline form which settles readily when the stirring is momentarily stopped. A viscous, creamy suspension which is poorly mixed by the stirring usually gives poor yields. Factors contributing to this condition have been found to be: insufficient amount of solvent initially, too rapid addition of ester, and improper temperature control.
5. Considerable frothing may be encountered during the first stages of the evaporation, particularly when a steam bath is used to hasten removal of the solvent. Rapid stirring helps to cut down frothing and lessens bumping.
6. The solid may go into solution rather slowly even in boiling water.

3. Discussion

Parabanic acid can be prepared by the condensation of urea with diethyl oxalate in an ethanolic solution of sodium ethoxide,[2] by reaction of urea with an ethereal solution of oxalyl chloride,[3] by oxidizing uric acid with an acid solution of perhydrol,[4] or by the action of hot, concentrated nitric acid on uric acid.[5] The present method gives better yields than the previously reported methods and is better adapted to larger-scale preparations.

References and Notes

1. University of Buffalo, Buffalo, New York.
2. Michael, *J. prakt. Chem.*, [2]**35**, 457 (1886).
3. Biltz and Topp, *Ber.*, **46**, 1387 (1913).
4. Biltz and Schiemann, *Ber.*, **59**, 721 (1926).
5. Behrend and Asche, *Ann.*, **416**, 226 (1918).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Perhydrol

Drierite ($CaSO_4$)

ethanolic solution of sodium ethoxide

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

methanol (67-56-1)

hydrogen (1333-74-0)

nitric acid (7697-37-2)

sodium methoxide (124-41-4)

carbon (7782-42-5)

sodium (13966-32-0)

urea (57-13-6)

uric acid

oxalyl chloride (79-37-8)

diethyl oxalate (95-92-1)

Parabanic acid (120-89-8)

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Organic Syntheses, CV 4, 746

1,4-PENTADIENE

[I. METHOD A]

Submitted by R. E. Benson and B. C. McKusick[1].
Checked by N. J. Leonard and A. G. Cook.

1. Procedure

The apparatus (f.htmig. 14) is similar to that described on p. 795 and in a previous volume.[2] It consists of a Pyrex glass reaction tube, 90 cm. long by 45 mm. in outside diameter, mounted vertically in an electric furnace about 50 cm. long. Attached to the top of the tube are a graduated dropping funnel (Note 1), an inlet tube for nitrogen, and a thermocouple well extending to the bottom of the heated section and holding a movable thermocouple. The entire heated section, which begins 10 cm. from the top of the tube, is packed with Pyrex glass rings 10 mm. in outside diameter by about 10 mm. in length held in place by a plug of glass wool supported by indentations in the tube. The lower end of the tube is attached to a 1-l. round-bottomed flask immersed in an ice bath and having a side arm from which vapors pass successively through a trap immersed in an ice bath and a trap immersed in a bath of Dry Ice and acetone. Each trap is capable of holding about 200 ml. of liquid. The temperature of the hottest part of the tube, which is located near the middle of the heated section, is raised to 575° ± 10° while nitrogen (Note 2) is passed successively through a flowmeter and the tube at a rate of 4–6 1./hr. Under these conditions (Note 3), 658 g. (645 ml., 3.5 moles) of 1,5-pentanediol diacetate (Note 4) is added to the tube over a period of 3.5 hours. The contents of the three receivers are combined and distilled at atmospheric pressure through a 15-cm. indented Claisen-type still head; the condenser is cooled with ice water, and the receiver is immersed in an ice bath. The fraction boiling at 25–55°, wt. 170–190 g., is redistilled through a 60-cm. column packed with glass helices or a column of similar efficiency to give 150–170 g. (63–71%) of 1,4-pentadiene, b.p. 26–27.5° /760 mm., n_D^{25} 1.3861–1.3871 (Note 5).

Fig. 14.

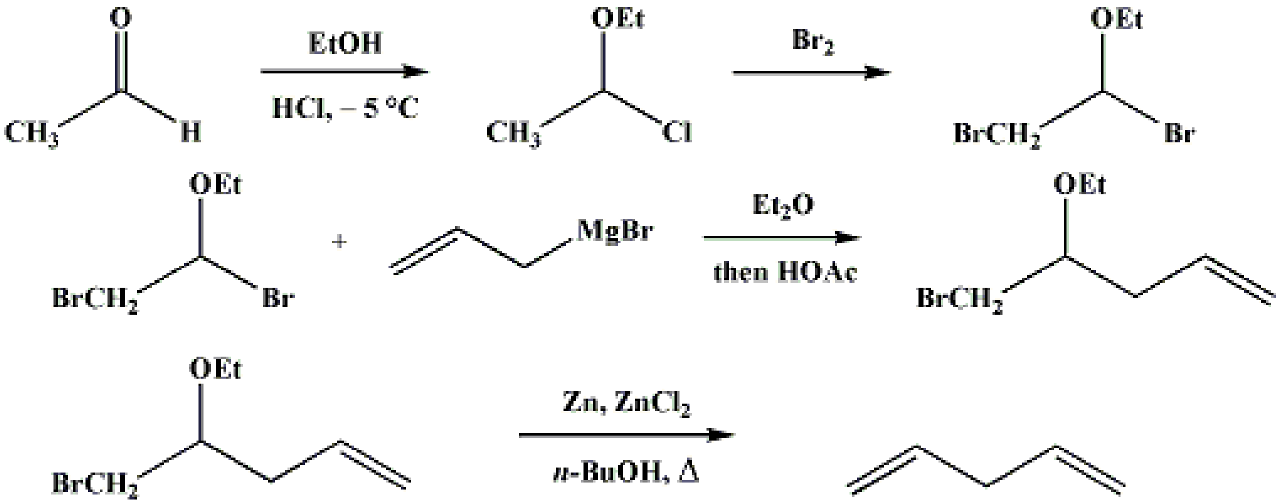
Fig. 14.

2. Notes

1. A Hershberg dropping funnel[3] modified by addition of a pressure-equalizing arm (. htmFig. 14) makes it easy to add the diacetate at a constant rate.
2. A dry, oxygen-free grade of commercial nitrogen is used. Nitrogen can be omitted without diminishing the yield by more than a few per cent.
3. As the addition of the diacetate begins, the temperature of the hottest part of the tube (the location of which generally shifts lower at this time) decreases, necessitating an increase in current in the electric furnace.
4. 1,5-Pentanediol diacetate,[4,5] b.p. 85–90° /0.9 mm., n_D^{25} 1.4253, is obtained in 92–94%

yield by adding a 10% excess of acetic anhydride to 1,5-pentanediol[6] at 120–140°, heating the mixture under reflux for 2 hours, and distilling it at reduced pressure. The practical grade of 1,5-pentanediol sold by Eastman Kodak Company may be used.
5. The residue from the first distillation is a mixture of acetic acid, 4-penten-1-ol acetate, and 1,5-pentanediol diacetate. Another 15–35 g. (6–15%) of 1,4-pentadiene can be obtained by passing the residue through the pyrolysis tube under the conditions described above.

[II. METHOD B]



Submitted by Oliver Grummitt, E. P. Budewitz, and C. C. Chudd[7].
Checked by William S. Johnson, E. Saito, and Donald J. Reif.

1. Procedure

A. *α-Chloroethyl ethyl ether*. A mixture of 200 g. (201 ml.) of redistilled paraldehyde, b.p. 121–122.5° (equivalent to 4.54 moles of acetaldehyde), and 200 g. (254 ml., 4.34 moles) of absolute ethanol is placed in a 1-l. three-necked flask fitted with a mechanical stirrer and a gas inlet tube reaching to the bottom of the flask. The mixture is cooled to –5° in a mixture of Dry Ice and acetone, and dry hydrogen chloride (Note 1) is passed into the stirred reaction mixture maintained at about –5° until 200 g. (5.48 moles) has been absorbed. During this operation, which requires about 2 hours, the reaction mixture separates into two layers. The upper layer of crude α-chloroethyl ethyl ether is removed, and the dissolved hydrogen chloride is swept out by bubbling dry nitrogen gas through the mixture. The product is dried overnight with 25–50 g. of anhydrous calcium sulfate (Note 2). The yield of crude α-chloroethyl ethyl ether (Note 3) is 411–432 g. (87–92% based on ethanol). The product is not distilled, since it decomposes readily.

B. *α,β-Dibromoethyl ethyl ether*. Four hundred and twenty-five grams (3.92 moles) of the crude α-chloroethyl ethyl ether (part A) is placed in a dry 1-l. three-necked flask, fitted with a dropping funnel, mechanical stirrer, and an outlet tube leading to a gas absorption trap[8] to dispose of the hydrogen chloride evolved. The flask is cooled in an ice bath, and 625 g. (200 ml., 3.92 moles) of bromine is added in small portions from the dropping funnel with stirring. The reaction mixture is allowed to become almost colorless after each addition. When all of the bromine has been added (5–6 hours), a slow current of dry nitrogen is bubbled through the reaction mixture to sweep out the hydrogen chloride (Note 4). The product is dried overnight

with 25–50 g. of anhydrous calcium sulfate and then distilled at reduced pressure (Note 5). The yield of colorless α,β-dibromoethyl ethyl ether is 599–663 g. (66–73% based on the α-chloroethyl ethyl ether), b.p. 70–75° /27 mm., n_D^{20} 1.5097–1.5102.

C. *Allylmagnesium bromide* (Note 6). In a dry 5-l. three-necked flask, equipped with a sealed stirrer, a reflux condenser and drying tube, a pressure-equalized dropping funnel, and a nitrogen inlet tube, are placed 195 g. (8.0 g. atoms) of dry magnesium turnings and 2.4 l. of anhydrous ether. The flask is cooled in an ice bath, a small crystal of iodine is added, and a solution of 400 g. (287 ml., 3.31 moles) of allyl bromide (redistilled, b.p. 69–71°) in an equal volume of anhydrous ether is added dropwise over a period of 17 hours. During the reaction a slow stream of dry, oxygen-free nitrogen is passed through the flask. After the addition is complete, the reaction mixture is stirred for 30 minutes. The Grignard reagent is decanted into a dry, graduated storage bottle; the residue in the flask is washed with 150–200 ml. of dry ether; and the wash liquid is added to the storage bottle. Samples of the clear supernatant solution are analyzed by acidimetric titration.[9] The yield of allylmagnesium bromide is 2.62–2.95 moles (79–89%).

D. *α-Allyl-β-bromoethyl ethyl ether*. The same apparatus is used as in the preparation of allylmagnesium bromide. The flask is charged with an amount of the Grignard solution (part C) equivalent to 2.78 moles of allylmagnesium bromide (or chloride) and cooled in an ice bath. A solution of 580 g. (2.5 moles) of α,β-dibromoethyl ethyl ether (part B) in an equal volume of anhydrous ether is added slowly with stirring over a period of 3–4 hours. The mixture is allowed to stand overnight and is then hydrolyzed with 75 ml. of 20% acetic acid followed by 500 ml. of water. The ether layer is separated, washed with four 100-ml. portions of 10% aqueous sodium bicarbonate solution followed by four 100-ml. portions of saturated aqueous sodium chloride solution, dried over 100 g. of anhydrous calcium sulfate, and distilled under reduced pressure. The yield of colorless α-allyl-β-bromoethyl ethyl ether is 370–396 g. (77–82% based on the α,β-dibromoethyl ethyl ether), b.p. 72–75° /21 mm., n_D^{20} 1.4600–1.4606.

E. *1,4-Pentadiene*. A 2-l. three-necked flask is equipped with a sealed stirrer and a 28-cm. reflux condenser, at the top of which is a 2.5 × 35 cm. Vigreux fractionating column attached to an efficient condenser arranged for distillation. Water at 35–40° is pumped through the reflux condenser, ice water is pumped through the downward condenser, and the receiver is ice-cooled and attached to a trap cooled by Dry Ice. The flask is charged with 380 g. (1.97 moles) of α-allyl-β-bromoethyl ethyl ether (part D) in 550 ml. of *n*-butyl alcohol; then 550 g. (8.4 g. atoms) of zinc dust and 2 g. of anhydrous zinc chloride are added. The mixture is stirred vigorously and heated gradually to the point where the pentadiene distils at a rate of about one drop every 2 seconds. The reflux condenser and column return most of the butyl alcohol to the flask. The reaction takes 5–6 hours for completion. The distillate is washed with five 100-ml. portions of ice water to remove most of the butyl alcohol and is then dried overnight with 15 g. of calcium chloride. The crude dry product is distilled through a 2.5 × 35 cm. Vigreux column to give 97–102 g. (72–76%) of colorless 1,4-pentadiene, b.p. 26–27° /740 mm., n_D^{20} 1.3887–1.3890.

2. Notes

1. Commercial hydrogen chloride from a cylinder is dried by passage through a train consisting of a wash bottle of concentrated sulfuric acid, a 25-cm. calcium chloride tube, and finally an empty safety trap.
2. This ether is a lachrymator, hydrolyzes rapidly in the presence of moisture, and

resinifies readily at temperatures above 0°. It is advisable to store it in a Dry Ice chest during drying and until the next step is to be run. Hydrolysis at low temperatures appears to be negligible.

3. Analysis of the crude material for chlorine gave 31.74% (calcd. 32.69%).

4. It is necessary to remove the hydrogen chloride because it promotes decomposition of the dibromoether.

5. Distillation is required to remove aldehyde, alcohol, and water which would react with the Grignard reagent in the next step. α,β-Dibromoethyl ethyl ether is also a lachrymator.

6. Either allylmagnesium bromide or allylmagnesium chloride may be used. The former is more conveniently prepared in higher yield and in a more concentrated solution, but allyl chloride is considerably less expensive than allyl bromide. The submitters state that the chloride is prepared just as the bromide with the following exceptions: the temperature is maintained between −10 and −15° with a Dry Ice-acetone cooling bath; 76.5 g. (82 ml., 1 mole) of allyl chloride (b.p. 45–47°) dissolved in an equal volume of dry ether is used (the amounts of all other reagents are unaltered); the addition is carried out over a 12-hour period, then the cooling bath is removed, and the mixture (containing considerable solid) is stirred until it reaches room temperature, during which time most of the solid material dissolves. The yield of allylmagnesium chloride as determined by acidimetric titration[9] is 0.67–0.69 mole (67–69%).

3. Discussion

1,4-Pentadiene has been prepared by the interaction of allyl bromide and vinyl bromide in the presence of magnesium;[10] by the pyrolysis of 1,5-pentanediol diacetate[4,5] or 4-penten-1-ol acetate;[5,11] by the reaction of α-allyl-β-bromoethyl ethyl ether with zinc;[12,13] by the thermal decomposition of dimethyl(4-pentenyl)amine oxide;[14] and by the reaction of vinylmagnesium bromide with allyl bromide.[15]

Method I is based on the work of Schniepp and Geller[4] and of Paul and Tchelitcheff,[5] while Method II is essentially that of Shoemaker and Boord[12] with some modifications.[13]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 235
- Org. Syn. Coll. Vol. 5, 679
- Org. Syn. Coll. Vol. 5, 949
- Org. Syn. Coll. Vol. 6, 606
- Org. Syn. Coll. Vol. 9, 28

References and Notes

1. Chemical Department, Experimental Station, E. I. du Pont de Nemours and Company, Wilmington, Delaware.
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3. *Org. Syntheses Coll. Vol.* **2**, 129 (1943).
4. Schniepp and Geller, *J. Am. Chem. Soc.*, **67**, 54 (1945).
5. Paul and Tchelitcheff, *Bull. soc. chim. France*, [5] **15**, 108 (1948).

6. *Org. Syntheses Coll. Vol.* **3**, 693 (1955).
7. Western Reserve University, Cleveland, Ohio.
8. *Org. Syntheses Coll. Vol.* **2**, 4 (1943).
9. Gilman, Zoellner, and Dickey, *J. Am. Chem. Soc.*, **51**, 1577 (1929).
10. Kogerman, *J. Am. Chem. Soc.*, **52**, 5060 (1930).
11. Paul and Normant, *Bull. soc. chim. France*, [5] **11**, 367 (1944).
12. Shoemaker and Boord, *J. Am. Chem. Soc.*, **53**, 1505 (1931).
13. Kistiakowsky, Ruhoff, Smith, and Vaughan, *J. Am. Chem. Soc.*, **58**, 146 (1936); Elsner and Wallsgrove, *J. Inst. Petrol.*, **35**, 259 (1949).
14. Cope and Bumgardner, *J. Am. Chem. Soc.*, **79**, 960 (1957).
15. Normant, *Compt. rend.*, **239**, 1811 (1954).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

allylmagnesium bromide (or chloride)

ethanol (64-17-5)

calcium chloride (10043-52-4)

acetaldehyde (75-07-0)

hydrogen chloride (7647-01-0)

acetic acid (64-19-7)

ether (60-29-7)

acetic anhydride (108-24-7)

sodium bicarbonate (144-55-8)

magnesium, magnesium turnings (7439-95-4)

sodium chloride (7647-14-5)

bromine (7726-95-6)

Allyl bromide (106-95-6)

nitrogen (7727-37-9)

allyl chloride (107-05-1)

calcium sulfate (7778-18-9)

butyl alcohol, n-butyl alcohol (71-36-3)

iodine (7553-56-2)

chlorine (7782-50-5)

zinc (7440-66-6)

zinc chloride (7646-85-7)

1,5-Pentanediol (111-29-5)

α,β-Dibromoethyl ethyl ether (2983-26-8)

pentadiene (504-60-9)

Allylmagnesium chloride (2622-05-1)

Allylmagnesium bromide (1730-25-2)

vinyl bromide (593-60-2)

vinylmagnesium bromide (1826-67-1)

1,4-Pentadiene (591-93-5)

1,5-pentanediol diacetate (6963-44-6)

α-chloroethyl ethyl ether (51202-81-4)

α-Allyl-β-bromoethyl ethyl ether (22089-55-0)

4-penten-1-ol acetate (1576-85-8)

dimethyl(4-pentenyl)amine oxide

paraldehyde (123-53-7)

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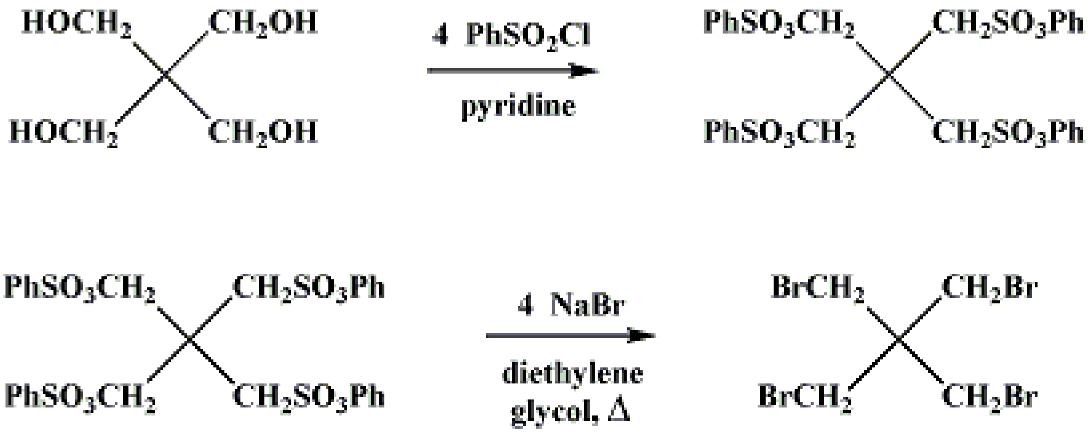
Organic Syntheses, CV 4, 753

PENTAERYTHRITYL TETRABROMIDE

[Propane, 1,3-dibromo-2,2-bis(bromomethyl)-]



Submitted by Hershel L. Herzog[1]
Checked by T. L. Cairns and D. W. Woodward.

1. Procedure

In a 5-l. three-necked round-bottomed flask equipped with a powerful mechanical stirrer (Note 1), a thermometer, and a 1-l. dropping funnel are placed 130 g. (0.96 mole) of technical grade pentaerythritol (Note 2) and 650 ml. of pyridine. The stirrer is started, and to the resulting suspension is added dropwise 750 g. (4.24 moles) of benzenesulfonyl chloride (Note 3) at such a rate that the temperature of the reaction does not rise above 30–35°. The addition requires about 2 hours. The resulting slurry is stirred at 40° for 1 hour after the addition is complete. The slurry is then added slowly (Note 4) to a vigorously stirred solution of 800 ml. of concentrated hydrochloric acid in 1 l. of water and 2 l. of methanol contained in a 9 by 15 in. battery jar. The resulting suspension of granular white pentaerythrityl benzenesulfonate is cooled by addition of 500 g. of ice, filtered with suction, and washed with 5 l. of water and then with 1 l. of cold methanol in two portions.

The crude, slightly wet pentaerythrityl benzenesulfonate is added to 1 l. of diethylene glycol (Note 5) in a 4-l. Erlenmeyer flask equipped with a Hershberg stirrer. Then 600 g. (5.8 moles) of sodium bromide is added, and the mixture is heated in an oil bath at 140–150° with slow stirring (60–120 r.p.m.) overnight. The resulting orange mixture is allowed to cool to about 90°, 2 l. of ice water is added rapidly with stirring, and finally the mixture is cooled to 10° by direct addition of ice. The precipitate is filtered with suction, washed with 2 l. of water, and pressed dry. The yield is 315–323 g. of a crude tan crystalline solid, m.p. 147–149°. The solid is dissolved in 2 l. of boiling acetone and filtered by gravity on a steam-heated funnel. On cooling, the solution deposits colorless glistening plates, which are filtered with suction and washed with 100 ml. of cold 95% ethanol, yielding 150–160 g. of pentaerythrityl tetrabromide, m.p. 159–160°

(Note 6). By repeated concentration and cooling of the mother liquor, an additional 90–100 g. of pentaerythrityl tetrabromide, m.p. 156.5–158° (Note 6), is obtained. The combined yield is 228–260 g. (68–78%) (Note 7).

2. Notes

1. A powerful stirrer is necessary to mix the reactants, particularly in the later stages of the reaction when the mixture is quite viscous. The submitter and checkers used a "Lightnin" stirrer.
2. Heyden Chemical Corporation technical grade pentaerythritol (Pentek) was found to be satisfactory. It contains about 90% pentaerythritol, the remainder being principally dipentaerythritol.
3. Eastman Kodak Company practical grade benzenesulfonyl chloride was used.
4. Crystallization is extremely slow at first and becomes satisfactory only when the mixture is well seeded. It is well to remove a small portion first and work it up in the hydrochloric acid solution with a spatula to induce crystallization. The mixture should be added slowly at first but more rapidly toward the end.
5. Eastman Kodak Company practical grade diethylene glycol was used.
6. The checkers observed melting points about 2° lower.
7. The yield is based on the assumption that 90% of the starting material is pentaerythritol.

3. Discussion

The procedure given was developed by Buchman, Herzog, and Fujimoto.[2] Pentaerythrityl bromide has also been prepared from phosphorus tribromide and pentaerythritol,[3] and by the action of hydrobromic acid on pentaerythrityl tetraacetate in acetic acid.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 153

References and Notes

1. California Institute of Technology, Pasadena, California.
2. Buchman, Herzog, and Fujimoto, unpublished results.
3. *Org. Syntheses Coll. Vol.* **2**, 476 (1943).
4. Perkin and Simonsen, *J. Chem. Soc.*, **87**, 860 (1905).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

dipentaerythritol

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

methanol (67-56-1)

HYDROBROMIC ACID (10035-10-6)

sodium bromide (7647-15-6)

phosphorus tribromide (7789-60-8)

acetone (67-64-1)

Benzenesulfonyl chloride (98-09-9)

pyridine (110-86-1)

Pentaerythritol (115-77-5)

Pentaerythrityl bromide, Pentaerythrityl tetrabromide, Propane, 1,3-dibromo-2,2-bis (bromomethyl)- (3229-00-3)

pentaerythrityl tetraacetate (597-71-7)

diethylene glycol (111-46-6)

pentaerythrityl benzenesulfonate

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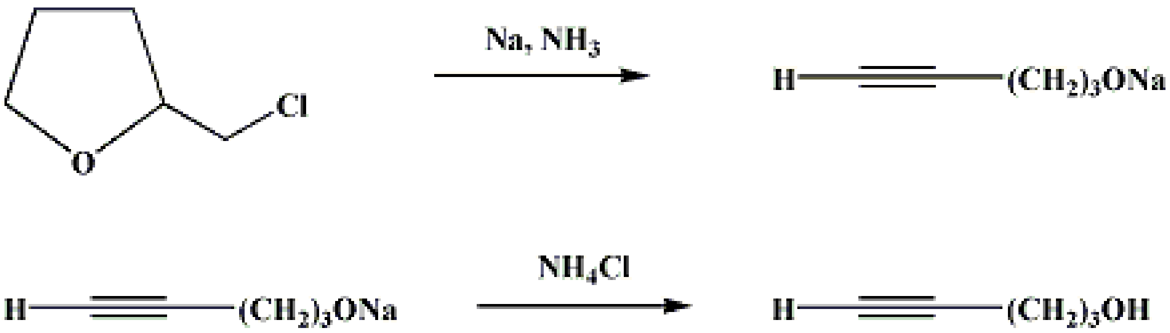
Organic Syntheses, CV 4, 755

4-PENTYN-1-OL



Submitted by E. R. H. Jones, Geoffrey Eglinton, and M. C. Whiting[1].
Checked by Arthur C. Cope and Ronald M. Pike.

1. Procedure

Caution! This preparation should be conducted in a hood to avoid exposure to ammonia.

A solution of sodium amide in liquid ammonia is prepared according to a procedure previously described (Note 1) in a 3-l. three-necked round-bottomed flask equipped with a cold-finger condenser (cooled with Dry Ice) attached through a soda-lime tower to a gas-absorption trap,[2] a mercury-sealed stirrer, and an inlet tube. Anhydrous liquid ammonia (1 l.) is introduced from a commercial cylinder through the inlet tube, and 1 g. of hydrated ferric nitrate is added, followed by 80.5 g. (3.5 g. atoms) of clean, freshly cut sodium (Note 1) and (Note 2). The inlet tube is replaced with a 250-ml. dropping funnel, and the mixture is stirred until all the sodium is converted into sodium amide, after which 120.5 g. (1 mole) of tetrahydrofurfuryl chloride[3] (Note 3) is added over a period of 25 to 30 minutes. The mixture is stirred for an additional period of 1 hour, after which 177 g. (3.3 moles) of solid ammonium chloride is added in portions at a rate that permits control of the exothermic reaction. The flask is allowed to stand overnight in the hood while the ammonia evaporates. The residue is extracted thoroughly with ten 250-ml. portions of ether, which are decanted through a Büchner funnel (Note 4). The ether is distilled, and the residue is fractionated at a reflux ratio of about 5 to 1, through a column containing a 20-cm. section packed with glass helices yielding 63–71 g. (75–85%) of 4-pentyn-1-ol, b.p. 70–71° /29 mm., n_D^{25} 1.4443 (Note 5).

2. Notes

1. Procedures for converting sodium to sodium amide are given on p. 763 and in a previous volume.[4]

2. More liquid ammonia should be added through the inlet tube if vaporization reduces the liquid volume to less than 750 ml.
3. Freshly distilled tetrahydrofurfuryl alcohol should be used in the preparation of tetrahydrofurfuryl chloride according to the procedure of *Organic Syntheses*.[3]
4. Ether extraction of the solid must be thorough or the yield will be reduced. A large Soxhlet extractor may be used if desired.
5. Others have reported b.p. 154–155°, n_D^{19} 1.4432;[5] b.p. 154–155°, $n_D^{22.5}$ 1.4450.[6] A sample purified through the silver derivative had b.p. 77° /37 mm., n_D^{15} 1.4464. The α-naphthylurethan of 4-pentyn-1-ol crystallized as needles from 60–80° petroleum ether; m.p. 79–80°.

3. Discussion

4-Pentyn-1-ol has been prepared from 4-penten-1-ol[3] by bromination followed by dehydrobromination with alkali;[6] by the reaction of 3-bromodihydropyran or 3,4-dihydro-2H-pyran with *n*-butylsodium, *n*-butyllithium, or *n*-butylpotassium;[5,7] by the reaction of dihydropyran or 2-methylenetetrahydrofuran with *n*-amylsodium or *n*-butyllithium;[7] by the reduction of ethyl 4-pentynoate with lithium aluminum hydride;[8] and by the method used in this preparation.[9]

References and Notes

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3. *Org. Syntheses Coll. Vol.* **3**, 698 (1955).
4. *Org. Syntheses Coll. Vol.* **3**, 219 (1955).
5. Paul and Tchelitcheff, *Compt. rend.*, **230**, 1473 (1950); Paul, *Angew. Chem.*, **63**, 304 (1951); Paul, *Bull. soc. chim. France*, **18**, 109 (1951).
6. Lespieau, *Compt. rend.*, **194**, 287 (1932).
7. Paul and Tchelitcheff, *Bull. soc. chim. France*, **19**, 808 (1952).
8. Colonge and Gelin, *Bull. soc. chim. France*, **1954**, 799.
9. Eglinton, Jones, and Whiting, *J. Chem. Soc.*, **1952**, 2873.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

α-naphthylurethan of 4-pentyn-1-ol

ammonia (7664-41-7)

ether (60-29-7)

ammonium chloride (12125-02-9)

sodium (13966-32-0)

tetrahydrofurfuryl alcohol (97-99-4)

sodium amide (7782-92-5)

n-butyllithium (109-72-8)

ferric nitrate

lithium aluminum hydride (16853-85-3)

dihydropyran

2-methylenetetrahydrofuran

n-amylsodium

4-Penten-1-ol (821-09-0)

Tetrahydrofurfuryl chloride (3003-84-7)

4-Pentyn-1-ol (5390-04-5)

3-bromodihydropyran

3,4-dihydro-2H-pyran (110-87-2)

ethyl 4-pentynoate (63093-41-4)

n-butylsodium

n-butylpotassium

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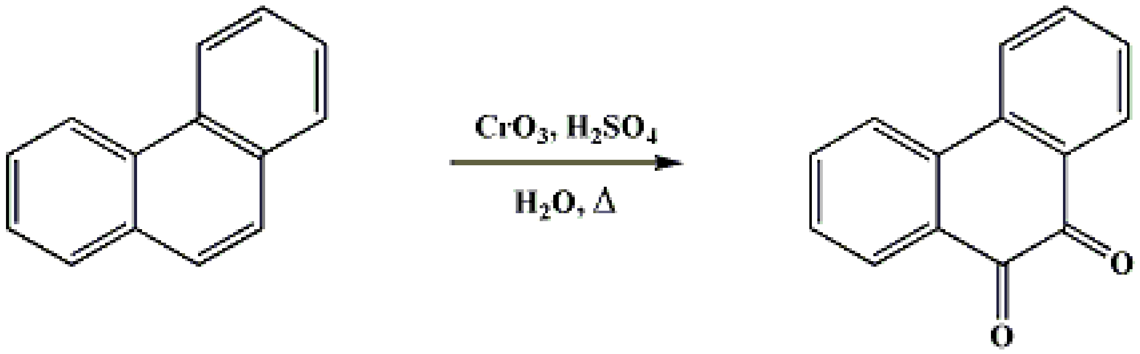
Organic Syntheses, CV 4, 757

PHENANTHRENEQUINONE



Submitted by Ray Wendland and John LaLonde[1].
Checked by William S. Johnson and Sol Shulman.

1. Procedure

In a 3-l. three-necked flask equipped with a reflux condenser, a sealed mechanical stirrer, and a 1-l. dropping funnel, are placed 100 g. (0.56 mole) of phenanthrene (Note 1), 210 g. (2.1 moles) of chromic acid (Note 2), and 1 l. of water. The stirrer is started, and 450 ml. of concentrated sulfuric acid is added from the dropping funnel into the suspension at such a rate that gentle boiling is induced (Note 3). After addition of the sulfuric acid is complete, a mixture of 210 g. (2.1 moles) of chromic acid and 500 ml. of water is added carefully to the reaction mixture from the dropping funnel (Note 4). The resulting mixture is boiled under reflux for 20 minutes.

After being cooled to room temperature the reaction mixture is poured into an equal volume of water and chilled to 10° in an ice bath. The crude precipitate is separated by suction filtration and thoroughly washed with cold water until the washings no longer show any chrome green color. The precipitate is triturated with three 300-ml. portions of boiling water and filtered to remove the diphenic acid formed in the reaction. The precipitate is then triturated with several (4–6) 300-ml. portions of hot 40% sodium bisulfite solution and again filtered (Note 5). The insoluble material is a mixture of anthraquinone and some resinous products derived from anthracene and other contaminants present in the starting material (Note 6). The sodium bisulfite filtrates are combined and cooled to 5° in an ice bath. The precipitate which separates is collected by suction filtration; then it is transferred to a 1-l. beaker and finely dispersed in 300 ml. of water. To this suspension is added, with good stirring, 500 ml. of a saturated solution of sodium carbonate. The deep orange phenanthrenequinone which is liberated is separated by suction filtration (Note 7), washed well with cold water, and dried on a porcelain plate. The yield of product, melting at 205–208° cor., is 52–56 g. (44–48%). Further purification may be accomplished by crystallization from 95% ethanol (100 ml./ g.). The recovery of first-crop material is over 80%, m.p. 208.5–210° cor.

2. Notes

1. Reilly Tar and Chemical Company practical grade phenanthrene is crystallized from boiling toluene using Norit. One crystallization is sufficient to produce material melting at about 99.5°. The checkers employed Eastman Kodak Company technical grade (90%) phenanthrene.
2. Technical grade chromic acid (99.5% CrO_3) in flake form was used.
3. It is safe to add 100 ml. of acid all at once to start the oxidation, but as soon as the temperature rises to 70–75° the remainder must be added slowly in order to avoid violent boiling.
4. One-half (250 ml.) of the mixture is added carefully (the reaction may become vigorous at this stage), and 20–25 minutes is allowed for the oxidation to proceed spontaneously. The remaining mixture is then added slowly.
5. A heated Büchner funnel is preferably used to prevent clogging by crystallization.
6. The anthraquinone may be purified by extracting the insoluble material with a 150-ml. solution of potassium hydroxide and sodium hydrosulfite (approximately 10% by weight of each). The resulting red solution is quickly filtered by suction, and hydrogen peroxide is added to the filtrate until a yellow precipitate appears. Dilute hydrochloric acid is added until the mixture is acidic to litmus, and the precipitate is collected by suction filtration, washed well with water, and air-dried. Five to seven grams of anthraquinone, m.p. 280–283°, may thus be obtained.
7. The filtrate should be treated with more sodium carbonate to test for completeness of precipitation.

3. Discussion

Phenanthrenequinone has been prepared by treatment of phenanthrene with chromic acid in acetic acid;[2] potassium dichromate in sulfuric acid;[3,4,5] hydrogen peroxide in acetic acid;[6,7] selenium dioxide above 250°;[8] iodic acid in acetic acid,[9] and chromyl chloride.[10] It also can be prepared from benzil with aluminum chloride at 120°[11] and from biphenyl-2,2'-dialdehyde with potassium cyanide.[12]

References and Notes

1. North Dakota State University, Fargo, North Dakota.
2. Graebe, *Ann.*, **167**, 131 (1873); Kato, Maezawa, and Hashimoto, *Yûki Gôsei Kagaku Kyokaishi*, **15**, 402 (1957) [*C. A.*, **51**, 16392 (1957)].
3. Anschütz and Schultz, *Ann.*, **196**, 32 (1879).
4. Oyster and Adkins, *J. Am. Chem. Soc.*, **43**, 208 (1921).
5. Underwood and Kochmann, *J. Am. Chem. Soc.*, **46**, 2069 (1924).
6. Henderson and Boyd, *J. Chem. Soc.*, **1910**, 1659.
7. Charrier and Moggi, *Gazz. chim. ital.*, **57**, 736 (1927).
8. Postowsky and Lugowkin, *Ber.*, **68**, 852 (1935).

9. Fuson and Tomboulian, *J. Am. Chem. Soc.*, **79**, 956 (1957).
10. Wheeler, *Can. J. Research*, **36**, 949 (1958).
11. Scholl and Schwarzer, *Ber.*, **55**, 324 (1922).
12. Mayer, *Ber.*, **45**, 1105 (1912).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Diphenic acid

biphenyl-2,2'-dialdehyde

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

sodium carbonate (497-19-8)

potassium cyanide (151-50-8)

sodium hydrosulfite (7775-14-6)

sodium bisulfite (7631-90-5)

Anthraquinone (84-65-1)

Norit (7782-42-5)

aluminum chloride (3495-54-3)

Benzil (134-81-6)

selenium dioxide (7446-08-4)

potassium hydroxide (1310-58-3)

toluene (108-88-3)

chromic acid (7738-94-5)

hydrogen peroxide (7722-84-1)

anthracene (120-12-7)

phenanthrenequinone (84-11-7)

iodic acid (7782-68-5)

potassium dichromate (7778-50-9)

chromyl chloride

phenanthrene (85-01-8)

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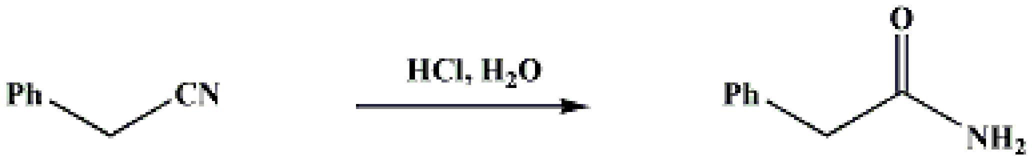
Organic Syntheses, CV 4, 760

PHENYLACETAMIDE

[Acetamide, 2-phenyl-]



Submitted by Wilhelm Wenner[1]
Checked by William S. Johnson and Robert E. Ireland.

1. Procedure

In a 3-l. three-necked round-bottomed flask equipped with glass joints are placed 200 g. (1.71 moles) of benzyl cyanide (Note 1) and 800 ml. of 35% hydrochloric acid (Note 2). The flask is fitted with a reflux condenser, a thermometer, and an efficient mechanical stirrer (Note 3). At a bath temperature of about 40° (Note 4) the mixture is stirred vigorously. Within a period of 20–40 minutes the benzyl cyanide goes into solution (Note 3). During this time, the temperature of the reaction mixture rises about 10° above that of the bath. The homogeneous solution is kept in the bath with, or without, stirring for an additional 20–30 minutes (Note 5). The warm water in the bath is replaced by tap water at about 15–20°, and the thermometer is replaced by a dropping funnel from which 800 ml. of cold distilled water is added with stirring (Note 6). After the addition of about 100–150 ml., crystals begin to separate. When the total amount of water has been added, the mixture is cooled externally with ice water for about 30 minutes (Note 7). The cooled mixture is filtered by suction. Crude phenylacetamide remains on the filter and is washed with two 100-ml. portions of water. The crystals are then dried at 50–80°. The yield of crude phenylacetamide is 190–200 g. (82–86%). It is sufficiently pure for most purposes although it contains traces of phenylacetic acid. If pure phenylacetamide is desired, the crude, wet solid is stirred for about 30 minutes with 500 ml. of a 10% solution of sodium carbonate, collected on a suction funnel, washed with two 100-ml. portions of cold water, and dried. The yield of this product is 180–190 g. (78–82%); m.p. 154–155° (Note 8) and (Note 9).

2. Notes

1. The quality of the benzyl cyanide markedly affects the yields. Material prepared according to directions given previously[2] is satisfactory. Several commercially available grades were also found to be usable without distillation.
2. The hydrochloric acid must be of at least 30% strength.
3. Efficient stirring is of prime importance for satisfactory reaction, because

intimate mixing of the heterogeneous mixture is necessary. The rate of dissolution of the nitrile depends on the efficiency of the stirring.

4. The reaction proceeds slowly at lower temperatures. Temperatures above 50° are not recommended because of the high volatility of hydrochloric acid.

5. This additional warming ensures complete reaction of some dissolved benzyl cyanide. The phenylacetamide is not readily hydrolyzed under these conditions.

6. The rate of addition is not critical.

7. If phenylacetic acid is desired, the suspension of phenylacetamide is refluxed with stirring and the phenylacetamide redissolves. After about 30 minutes, the mixture becomes turbid and the product begins to separate as an oil. After 6 hours the mixture is cooled, first with tap water and then by an ice-water bath. When the temperature has dropped to about 40–50°, the phenylacetic acid crystallizes. After cooling at 0° for about 4 hours (the acid is rather soluble in warm water), the mixture is filtered by suction. The crude, colorless phenylacetic acid is washed with two 100-ml. portions of cold water and dried in a desiccator. The yield of crude acid is 180–195 g. (77.5–84%). It melts at 66–70° and is sufficiently pure for most purposes. The mother liquor on extraction with two 150-ml. portions of benzene and evaporation yields an additional 3–5 g. of acid. To prepare the pure acid, vacuum distillation (as described by Adams and Thal[3]) is simpler and gives higher yields than recrystallization from ligroin.

8. Further purification is effected by recrystallization from 95% ethanol or benzene, yielding the pure compound of m.p. 156°.

9. The following arylacetamides have been prepared from the corresponding nitriles by the same method in the indicated yields:[4] *p*-methylphenylacetamide (70%), *p*-isopropylphenylacetamide (90%), 1-naphthylacetamide (54%), 5,6,7,8-tetrahydro-2-naphthylacetamide (90%), *p*-methoxyphenylacetamide (76%), 3,4-dimethoxyphenylacetamide (82%), and 2,3-dimethoxyphenylacetamide (91%). Only in the cases of the alkoxy-substituted nitriles are the resulting amides soluble in the reaction mixture; the other nitriles do not dissolve completely at any time during the reaction.

3. Discussion

Phenylacetamide has been obtained by a wide variety of reactions: from benzyl cyanide with water at 250–260°;[5] from benzyl cyanide with water and cadmium oxide at 240°;[6] from benzyl cyanide with sulfuric acid;[7,8] by saturation of an acetone solution of benzyl cyanide with potassium hydrosulfide;[9] from benzyl cyanide with sodium peroxide;[10] by electrolytic reduction of benzyl cyanide in sodium hydroxide;[11] from ethyl phenylacetate with alcoholic[12] or aqueous[13] ammonia; from phenylacetic acid with ammonium acetate[14] or urea;[15] from diazoacetophenone with ammoniacal silver solution;[16] from phenylacetic acid imino ether hydrochloride and water;[17] from acetophenone with ammonium polysulfide;[18] from benzoic acid;[19] by heating the

ammonium salt of phenylacetic acid;[20] and by heating cinnamic acid with a mixture of sulfur and ammonium hydroxide.[21]

The literature on the preparation of phenylacetic acid is reviewed in an earlier volume of this series.[3]

The present method is that of Wenner[22] and is applicable to other arylacetonitriles.[4]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ligroin

ammonium polysulfide

ammoniacal silver

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

Benzene (71-43-2)

ammonium acetate (631-61-8)

sodium hydroxide (1310-73-2)

sodium carbonate (497-19-8)

Benzoic acid (65-85-0)

sulfur (7704-34-9)

acetone solution of benzyl cyanide (67-64-1)

Acetophenone (98-86-2)

Benzyl cyanide (140-29-4)

Phenylacetic acid (103-82-2)

urea (57-13-6)

sodium peroxide

ammonium hydroxide (1336-21-6)

potassium hydrosulfide (1310-61-8)

cinnamic acid (621-82-9)

Ethyl phenylacetate (101-97-3)

cadmium oxide

Phenylacetamide, Acetamide, 2-phenyl- (103-81-1)

1-naphthylacetamide (86-86-2)

5,6,7,8-tetrahydro-2-naphthylacetamide

3,4-dimethoxyphenylacetamide

2,3-dimethoxyphenylacetamide

Diazoacetophenone (3282-32-4)

phenylacetic acid imino ether hydrochloride

p-methylphenylacetamide

p-isopropylphenylacetamide

p-methoxyphenylacetamide (6343-93-7)

ammonium salt of phenylacetic acid

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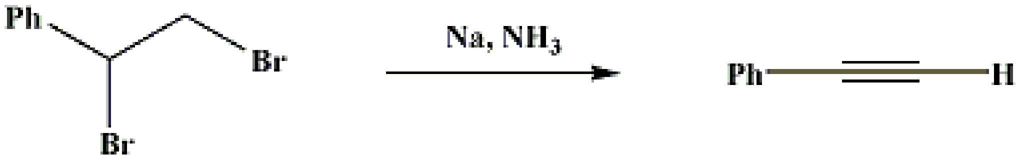
Organic Syntheses, CV 4, 763

PHENYLACETYLENE

[Benzene, ethynyl-]



Submitted by Kenneth N. Campbell and Barbara K. Campbell[1].
Checked by R. S. Schreiber and H. E. Cupery.

1. Procedure

Avoid contact with styrene dibromide, which is a skin irritant. This preparation should be conducted in a hood to avoid exposure to ammonia.

A 5-l. three-necked flask is equipped with a high-speed, motor-driven stirrer passing through a bushing in the center neck (Note 1). The side necks are equipped with rubber stoppers each carrying a short length of 8-mm. glass tubing, bent at right angles. A 10–12 in. length of stout, flexible iron wire is passed through one of these pieces of tubing. Two liters of liquid ammonia (Note 2) and 2 g. of ferric nitrate hydrate are placed in the flask. One hundred grams of sodium (4.35 g. atoms) is cut into rectangular pieces about 3 by by in. in size. One of the pieces of sodium is hooked onto the lower end of the iron wire and lowered into the liquid ammonia. Stirring is not necessary during this part of the reaction, but it is advisable. When the lump of sodium has reacted, the solution turns from blue to gray, and the remaining pieces of sodium are added in the same manner. The addition requires about 45 minutes (Note 3).

The stopper carrying the iron wire is removed, 2 g. of anil is added, and then 528 g. (2 moles) of finely powdered, dry styrene dibromide is added gradually with vigorous stirring. The addition requires about 1 hour (Note 4). Stirring is continued for 2 hours (Note 5) after the addition has been completed, after which 600 ml. of concentrated ammonium hydroxide is added, followed by 1 l. of distilled water, and the mixture is allowed to stand until the frost on the outside of the flask is entirely melted.

The aqueous solution is then steam-distilled from the same flask (Note 6) until no more oil passes over. This usually requires about 6 hours, and 1.5–2 l. of distillate is collected. The phenylacetylene in the distillate is separated and washed several times with distilled water to remove ammonia (Note 7). The washed material is dried over anhydrous magnesium sulfate and distilled through an efficient column (Note 8) under reduced pressure. Almost the entire product distils at 73–74°/80 mm. The yield is 93–

106 g. (45–52%); n_D^{20} 1.5465–1.5484.

2. Notes

1. A suitable stirrer has been described earlier.[2]
2. Additional liquid ammonia should be added from time to time. Liquid ammonia can be handled satisfactorily in fairly large amounts in an open flask, as the frost that quickly forms on the outside of the flask slows down evaporation.
3. This is an excellent method for making sodium amide for many purposes. If the sodium amide is to be used in another solvent, the solvent should be added to the liquid ammonia after the sodium amide is prepared; the ammonia is allowed to evaporate, and the last traces of ammonia are expelled by heating the flask on a steam bath.
4. The styrene dibromide must not be added too rapidly, or the heat of reaction may cause rapid boiling of the ammonia and possible loss of part of the mixture.
5. In one run an increase of this stirring period to 2.8 hours resulted in an 11% increase in yield.
6. Because the large amount of ammonia that comes over may entrain considerable phenylacetylene, a very efficient cooling system[3] is essential.
7. If acid is used to remove the ammonia, the product is likely to be dark colored.
8. The checkers used an 18-in. column packed with Berl saddles.

3. Discussion

Phenylacetylene has been prepared by treatment of β-bromostyrene with potassium hydroxide[4] and with sodium amide in liquid ammonia;[5] from styrene dibromide by treatment with sodium amide in liquid ammonia[6] or potassium hydroxide in methanol;[7] and by the reduction of phenylchloroacetylene.[8]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 128
- Org. Syn. Coll. Vol. 4, 387
- Org. Syn. Coll. Vol. 4, 404
- Org. Syn. Coll. Vol. 4, 755
- Org. Syn. Coll. Vol. 4, 801

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ammonia (7664-41-7)

methanol (67-56-1)

iron wire (7439-89-6)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

ammonium hydroxide (1336-21-6)

Phenylacetylene, Benzene, ethynyl- (536-74-3)

β-bromostyrene (103-64-0)

styrene dibromide (93-52-7)

magnesium sulfate (7487-88-9)

sodium amide (7782-92-5)

ferric nitrate hydrate

phenylchloroacetylene (1483-82-5)

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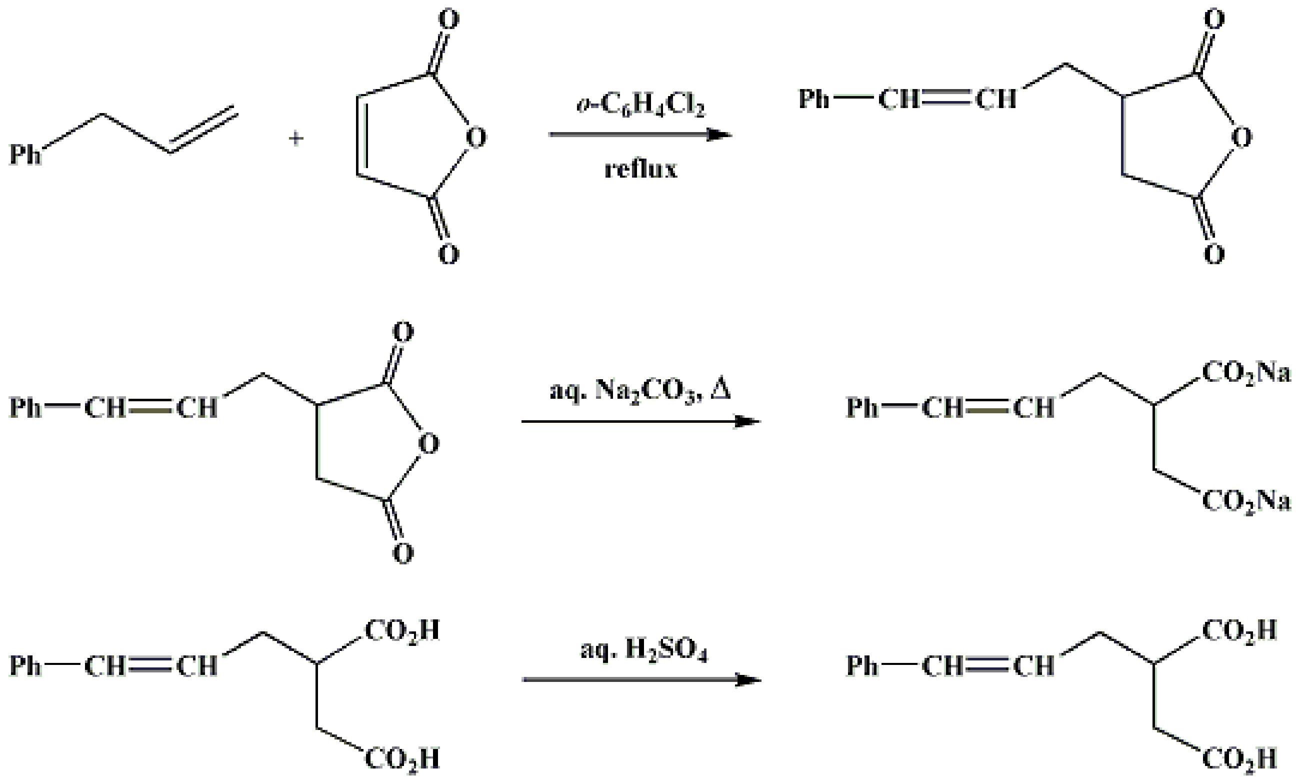
Organic Syntheses, *CV 4, 766*

γ-PHENYLALLYLSUCCINIC ACID

[Succinic acid, cinnamyl-]



Submitted by Christian S. Rondestvedt, Jr.[1]
Checked by Charles C. Price and Wm. J. Belanger.

1. Procedure

A mixture of 35.4 g. (0.3 mole) of allylbenzene, 29.4 g. (0.3 mole) of maleic anhydride, and 50 ml. of *o*-dichlorobenzene (Note 1) in a 200-ml. round-bottomed flask is heated under reflux for 22 hours under an air condenser. While the orange mixture cools to 50°, the flask is equipped for vacuum distillation. At a bath temperature below 130°, the solvent and unreacted starting materials are removed by vacuum distillation with a water pump. The boiling range is 66–72°/23 mm. The viscous residue is poured while hot into a 125-ml. sausage flask (Note 2), and the transfer is completed with small amounts of acetone. After removal of the acetone by vacuum distillation with a water pump, the product is distilled, b.p. 199–206°/2 mm. (bath temperature 220–270°), to give 27–35 g. (42–54%) of a pale yellow liquid which solidifies readily (Note 3).

The product is melted in the receiver and poured into 100 ml. of benzene. An additional 25 ml. of hot benzene is used to rinse the receiver. The benzene solution is brought to boiling, filtered, and diluted with approximately 100 ml. of petroleum ether (60–75°) until faintly turbid. It is reheated to boiling, allowed to cool, and finally refrigerated for 4 hours. The white crystals are collected on a Büchner funnel, washed with two 25-ml. portions of cold 1:1 benzene-petroleum ether, pressed dry, and airdried. The yield of anhydride melting at 103–105° is 24–31 g. (37–48%) (Note 4).

The anhydride is readily hydrolyzed by boiling a mixture of 21.6 g. (0.1 mole) of anhydride, 22.0 g. (0.207 mole) of anhydrous sodium carbonate, and 250 ml. of water for 2 hours on a hot plate. The

pale yellow solution is cooled and extracted with 100 ml. of isopropyl ether (Note 5). The ether extract is washed with 50 ml. of water, and the combined water layers are acidified to Congo red by the slow addition of 10% sulfuric acid. The acid separates as an oil which quickly solidifies on cooling and stirring. It is collected on a Büchner funnel, washed with cold water, pressed dry on the funnel, and finally air-dried. The yield is 22 g. (94% based on the anhydride), m.p. 140–143°. The acid is conveniently recrystallized from acetonitrile (Note 6), using 5 ml. per gram of crude acid. The recovery of pure acid having a melting point of 142–143° is 85% (Note 7).

2. Notes

1. Allylbenzene can be prepared from phenylmagnesium bromide and allyl bromide.[2] The maleic anhydride used was Eastman Kodak Company white label grade. Slightly higher yields are obtained if it is freshly distilled at 25 mm. Commercial *o*-dichlorobenzene should be distilled before use.
2. A suitable flask is prepared from a 525-ml. distilling flask by replacing the narrow side arm with a 150-mm. length of 10-mm. tubing. The side arm of a second flask is cut off to 25 mm., and the two flasks are connected by inserting the 10-mm. side arm into the bulb of the second flask.
A few boiling stones or sticks are added to the first flask containing the material to be distilled, a rubber stopper bearing a thermometer is inserted, and vacuum is applied to the shortened side arm of the receiver.
3. A Wood's metal bath is convenient as a high-temperature heat source.
4. Once-crystallized anhydride is sufficiently pure for conversion to the acid. A second recrystallization gives pure material, m.p. 106.0–106.5°.
5. Ethyl ether may be used. The aqueous layers must then be heated to boiling and cooled before acidification; otherwise the acid is slow to crystallize.
6. Acetonitrile is most convenient, but ethanol, aqueous acetic acid, or aqueous dioxane may be used.
7. The acid is partially dehydrated near its melting point. The reported melting point was observed by immersing the capillary at 140° and heating at 2° per minute.

3. Discussion

γ-Phenylallylsuccinic anhydride and the derived acid have been prepared by heating maleic anhydride with excess allylbenzene in an autoclave at 170–175° for 24 hours.[3] The above procedure is more convenient since an autoclave is unnecessary.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

benzene-petroleum ether

ethanol (64-17-5)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

Benzene (71-43-2)

ether, ethyl ether (60-29-7)

acetonitrile (75-05-8)

sodium carbonate (497-19-8)

Allyl bromide (106-95-6)

acetone (67-64-1)

Phenylmagnesium bromide (100-58-3)

dioxane (5703-46-8)

isopropyl ether (108-20-3)

maleic anhydride (108-31-6)

γ-Phenylallylsuccinic acid, Succinic acid, cinnamyl- (5671-91-0)

allylbenzene (300-57-2)

γ-Phenylallylsuccinic anhydride (7508-06-7)

o-dichlorobenzene (95-50-1)

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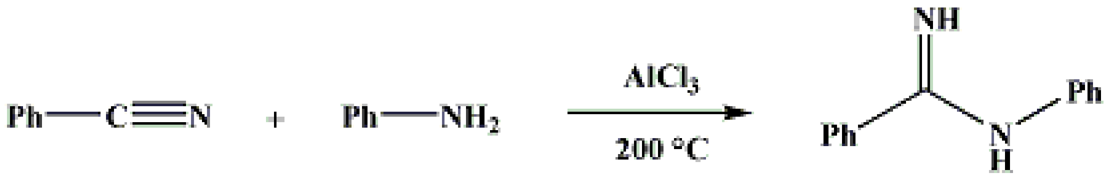
Organic Syntheses, CV 4, 769

N-PHENYLBENZAMIDINE

[Benzamidine, N-phenyl-]



Submitted by F. C. Cooper and M. W. Partridge[1].
Checked by T. L. Cairns, R. E. Benson, and V. J. Webers.

1. Procedure

Sixty-two grams (61 ml., 0.67 mole) of aniline (Note 1) is mixed with 68.5 g. (0.66 mole) of benzonitrile in a 250-ml., wide-mouthed flask, and, during about 20 minutes, 89 g. (0.67 mole, calculated as $AlCl_3$) of a freshly opened sample of powdered, anhydrous aluminum chloride is added in portions with thorough stirring (Note 2). The mixture is then heated at 200° for 30 minutes (Note 3), and, while still molten, is poured slowly into a thoroughly stirred mixture of 20 ml. of concentrated hydrochloric acid and 1.6 l. of water. After the addition of 20 g. of activated carbon, the suspension is stirred while being externally cooled in running water and is then filtered through a kieselguhr filter (Note 4). The filtrate is poured in a steady stream into a stirred solution of 220 g. of sodium hydroxide in 1.2 l. of water. The flocculent precipitate is collected on alkali-resistant paper in a 12-cm. Büchner funnel with the aid of suction, washed with water (Note 5), broken up thoroughly, and air-dried at room temperature to constant weight. The yield of white product, m.p. 111–115°, is 90–96 g. (69–74%). This material is sufficiently pure for most purposes. Recrystallization from benzene (60 ml. per 10 g. of amidine) yields 56–74 g. of white powder; concentration of the mother liquors raises the total yield of N-phenylbenzamidine to 69–86 g. (53–66%), melting at 114–115.5°.

2. Notes

1. It is preferable to use aniline freshly redistilled from a small quantity of zinc dust.
2. The reaction is strongly exothermic. Although loss of reagents by volatilization is small, it is advisable to close the flask with a loose plug of cotton wool.
3. Below about 180° the mixture is too stiff to be stirred, but at 200° it is a mobile liquid.
4. A suitable filter is prepared by distributing a slurry of 10–15 g. of "Super-Cel" in water on a filter paper in a 12-cm. Büchner funnel and washing with water with the aid of suction until a clear filtrate is obtained.

5. Washing is best effected by vigorously stirring the cake with water until it is completely dispersed, collecting again, and draining well; three such washings are usually sufficient.

3. Discussion

This method is based on the procedure of Oxley, Partridge, and Short.[2] N-Phenylbenzamidine has also been prepared by heating aniline hydrochloride with benzonitrile or thiobenzamide[3] or by heating aniline benzenesulfonate with benzonitrile;[4] by the action of sodium or sodamide on a mixture of aniline and benzonitrile;[5] by treating phenylcyanamide with phenylmagnesium bromide;[6] by the interaction of aniline and benziminoethyl ether hydrochloride;[7] by the reaction between N-phenylbenzimidyl chloride and ammonia;[8] by the action of sodamide on benzylidene aniline;[7,9] by hydrogenating benzanilide oxime;[10] by treating benzophenone oxime benzenesulfonate with ammonia;[11] and by the reaction of 2-nitrobutyl benzimidate hydrochloride with aniline.[12]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

N-phenylbenzimidyl chloride

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

Benzene (71-43-2)

aniline (62-53-3)

benzonitrile (100-47-0)

sodium hydroxide (1310-73-2)

aniline hydrochloride (142-04-1)

benzylidene aniline (538-51-2)

carbon (7782-42-5)

aluminum chloride (3495-54-3)

zinc (7440-66-6)

sodium (13966-32-0)

Phenylmagnesium bromide (100-58-3)

sodamide (7782-92-5)

thiobenzamide (2227-79-4)

phenylcyanamide

aniline benzenesulfonate

N-Phenylbenzamidine, Benzamidine, N-phenyl- (1527-91-9)

benziminoethyl ether hydrochloride

benzanilide oxime

benzophenone oxime benzenesulfonate

2-nitrobutyl benzimidate hydrochloride

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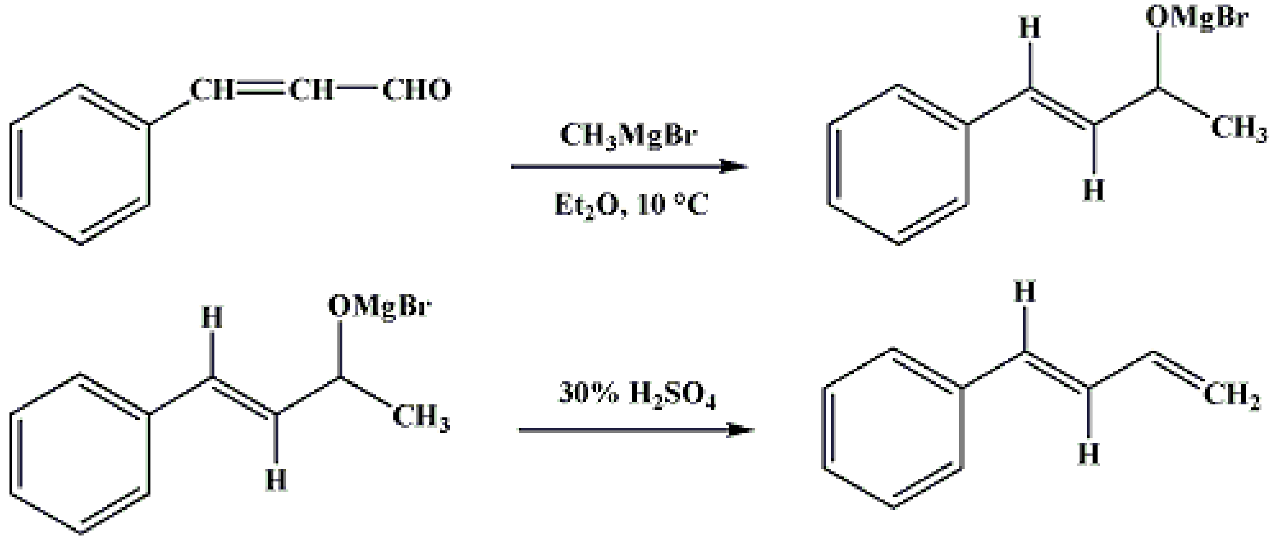
Organic Syntheses, CV 4, 771

trans-1-PHENYL-1,3-BUTADIENE

[1,3-Butadiene, 1-phenyl-, *trans*-]



Submitted by Oliver Grummitt and Ernest I. Becker[1].
Checked by Charles C. Price and T. L. Patton.

1. Procedure

In a 1-l. three-necked flask equipped with a mercury-sealed stirrer, a reflux condenser protected with a calcium chloride drying tube, a separatory funnel, a nitrogen inlet tube, and a thermometer is placed 0.515 mole of methylmagnesium bromide in 250–350 ml. of ether (a 1.5–2.0*N* solution). The mixture is cooled to a temperature below 10° by means of an ice-water bath, the stirrer is started, and a solution of 66.1 g. (0.50 mole) of cinnamaldehyde (Note 1) in 60 ml. of absolute ether is added, the rate of addition being controlled so that the temperature is kept below 10°. Throughout the addition, which takes about 1 hour, a slow stream of dry nitrogen is passed through the flask (Note 2).

The flask is detached from the condenser and stirrer, and its contents are transferred to a 500-ml. separatory funnel. The apparatus is then reassembled, without the nitrogen inlet tube or the drying tube, and 175 ml. of 30% sulfuric acid (by weight) is placed in the flask. Without cooling, but with efficient stirring with a Hershberg Nichrome wire stirrer at 1500–1700 r.p.m. (Note 3),[2] the ethereal solution of the cinnamaldehyde-methylmagnesium bromide adduct is added rapidly to the acid. The time for this addition (5–7 minutes) is limited by the efficiency of the condenser. Heat then is applied to maintain gentle reflux until the *total* time elapsed from the initiation of hydrolysis is 20 minutes. The contents of the flask are *immediately* transferred to a 1-l. separatory funnel, the lower aqueous layer is discarded, and the ether layer is washed successively with 50 ml. of water, a mixture of 50 ml. of 5% aqueous sodium hydroxide and 50 ml. of saturated ammonium chloride solution, and 50 ml. of water. Before each of the washings the air in the separatory funnel is displaced with nitrogen. When the second wash solution is added, 0.3 g. of phenyl-β-

naphthylamine is dissolved in the ether layer. The washed solution is dried with 20 g. of anhydrous sodium sulfate for 30 minutes and then with 15 g. of anhydrous potassium carbonate for 12 hours.

The ethereal solution is filtered and concentrated by distillation from a steam bath to a residual volume of 80–100 ml. Some water separates at this time, and the mixture is cooled and then dried with about 15 g. of anhydrous potassium carbonate. The concentrated solution is filtered into a 125-ml. modified Claisen flask[3] and distilled under reduced pressure in a nitrogen atmosphere into a receiver containing 0.3 g. of phenyl-β-naphthylamine. In this manner 52–54 g. (80–83%) of crude *trans*-1-phenyl-1,3-butadiene is obtained, b.p. 81–85°/10–11 mm.; n_D^{25} 1.606–1.608, which may contain some methylstyrylcarbinol and water. This material is dried with 5 g. of anhydrous potassium carbonate, filtered, and distilled as before. The yield of *trans*-1-phenyl-1,3-butadiene is 47–49 g. (72–75%), b.p. 78–81°/8 mm.; n_D^{25} 1.607–1.608. This product is satisfactory for most purposes (Note 4) and (Note 5).

2. Notes

1. Cinnamaldehyde obtained from the Eastman Kodak Company was purified by washing a solution in an equal volume of ether with aqueous sodium carbonate and then with water, dried, and distilled under nitrogen; b.p. 101–102°/2–3 mm.; n_D^{20} 1.6195.
2. The procedure may be altered at this point so that *trans*-methylstyrylcarbinol is obtained. It is necessary, however, to observe the precaution that all apparatus coming in contact with the *trans*-methylstyrylcarbinol be free from traces of acid. The solution is stirred for 30 minutes after the addition is complete. Then 125 ml. of a saturated solution of ammonium chloride (about 28%), which has been neutralized to litmus with concentrated ammonium hydroxide, is added dropwise, the temperature being held at 5–10°. This addition takes from 1 to 1.5 hours. After decanting the ether layer, breaking up the precipitate and extracting it with two 60-ml. portions of absolute ether, and adding the extracts to the main solution, the solution is distilled from a steam bath until the residual volume is about 100 ml. The solution is transferred to a Claisen flask, and the residual ether is removed by evacuation with a water pump. After the discard of a small fore-run, the product is collected at 93–94°/1.5 mm.; yield, 65–67 g. (88–90%).
Upon cooling at 0–10° the *trans*-methylstyrylcarbinol forms a mass of white crystals melting at 30–34°. These may be purified by crystallization from petroleum ether (b. p. 30–35°) -methylene chloride (6:1). For each 30 g. of the carbinol, 350 ml. of the solvent mixture is used. The solution is cooled to −75° to −80° in Dry Ice and kept at that temperature for about 3 hours. The solution is filtered quickly by suction through a chilled funnel, washed with the cold solvent mixture, and dried in a vacuum desiccator. The yield of pure *trans*-methylstyrylcarbinol is 28.5 g., m.p. 33.5–34.5°; n_D^{35} 1.5598; d_4^{35} 0.9995.
3. The stirring must be vigorous in order to mix the ether and aqueous layers. This is absolutely essential for the production of reasonable yields. Slower stirring necessitates a longer time for the hydrolysis with consequent longer contact time between the 1-phenyl-1,3-butadiene and the sulfuric acid, which results in extensive

polymerization of the product and corresponding decrease in yield.
4. Pure *trans*-1-phenyl-1,3-butadiene was obtained by distillation of the twice-distilled product under nitrogen through a 12-plate column of the total reflux-variable takeoff type[2] after adding 0.5% of phenyl-β-naphthylamine. The packed section of the column was an 18-in. section of Pyrex tubing (10 mm. o.d.) filled with 4-mm. single-turn glass helices. Insulation was provided by means of a vacuum jacket, and heat losses were compensated by resistance wire wound on the jacket.
About 50% of the sample taken was collected, b.p. 86°/11 mm.; n_D^{25} 1.6086–1.6090; d_4^{25} 0.9235–0.9239.
5. Present evidence indicates that 1-phenyl-1,3-butadiene[4] prepared by this method is the *trans* isomer.[5]

3. Discussion

1-Phenyl-1,3-butadiene has been prepared by the decarboxylation of allocinnamylideneacetic acid[6] and of cinnamylidenemalonic acid;[7] the dehydration of methylstyrylcarbinol from the Grignard addition of methylmagnesium halide to cinnamaldehyde;[8] the rearrangement and dehydration of the alcohol intermediate formed by the Grignard addition of phenylmagnesium bromide to crotonaldehyde;[9] the formation of methylstyrylcarbinol, its conversion to methylstyrylcarbinyl chloride, and dehydrohalogenation;[10] a modified Wurtz reaction in which benzyl chloride is coupled with allyl chloride by means of sodium in liquid ammonia;[11] the condensation of styrene and acetaldehyde and dehydration of the intermediate in the presence of sulfuric acid in acetic acid;[12] and by the dehydrochlorination of 4-chloro-1-phenyl-2-butene (prepared by the condensation of butadiene with benzenediazonium chloride).[13] Reference [12] describes the preparation of 1-phenyl-1,3-butadiene by pyrolysis of 1-phenyl-1,3-butyleneglycol diacetate and 2,6-dimethyl-4-phenyl-1,3-dioxane. The present method is a modification of the procedure of von der Heide.[8]

trans-Methylstyrylcarbinol has been prepared by several methods: the hydrolysis of the addition product formed from methylmagnesium halide and cinnamaldehyde in a variety of ways;[10,14] hydrolysis of the addition compound formed from styrylmagnesium bromide and acetaldehyde;[4] hydrolysis and hydrogenation of the product formed in the Grignard reaction of phenylethynylmagnesium bromide and acetaldehyde;[15] the addition of hypobromous acid to 1-phenyl-1,3-butadiene followed by reduction with sodium amalgam in acetic acid;[16] the allylic rearrangement of 1-phenyl-1-acetoxy-3-butene to 1-phenyl-3-acetoxy-1-butene followed by saponification;[17] and the reduction of benzalacetone by means of aluminum isopropoxide.[18] The method employed here is essentially that of Kenyon, Partridge, and Phillips.[14]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

phenyl-β-naphthylamine

cinnamaldehyde-methylmagnesium bromide

allocinnamylideneacetic acid

acetaldehyde (75-07-0)

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

ammonia (7664-41-7)

ether (60-29-7)

ammonium chloride (12125-02-9)

sodium hydroxide (1310-73-2)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

allyl chloride (107-05-1)

benzenediazonium chloride

Benzalacetone (122-57-6)

sodium (13966-32-0)

aluminum isopropoxide

benzyl chloride (100-44-7)

hypobromous acid (13517-11-8)

ammonium hydroxide (1336-21-6)

cinnamaldehyde

methylene chloride (75-09-2)

styrene (100-42-5)

butadiene (106-99-0)

styrylmagnesium bromide

methylmagnesium bromide (75-16-1)

crotonaldehyde (123-73-9)

methylstyrylcarbinol

1-phenyl-1,3-butadiene (31915-94-3)

cinnamylidenemalonic acid (4472-92-8)

methylstyrylcarbinyl chloride

4-chloro-1-phenyl-2-butene

1-phenyl-1,3-butyleneglycol diacetate

2,6-dimethyl-4-phenyl-1,3-dioxane

phenylethynylmagnesium bromide

1-phenyl-1-acetoxy-3-butene

1-phenyl-3-acetoxy-1-butene

trans-1-Phenyl-1,3-butadiene, 1,3-Butadiene, 1-phenyl-, trans- (16939-57-4)

trans-Methylstyrylcarbinol (17488-65-2)

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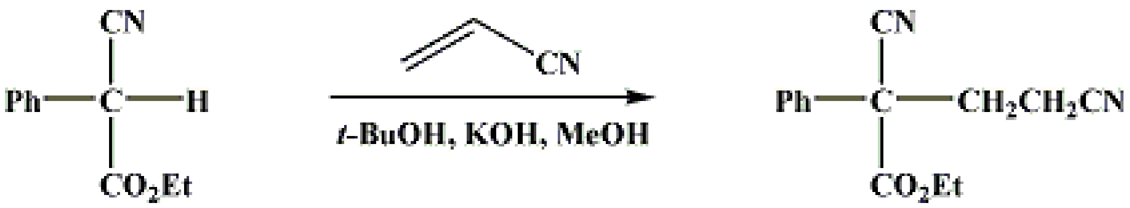
Organic Syntheses, *CV 4*, 776

α-PHENYL-α-CARBETHOXYGLUTARONITRILE

[Butyric acid, 2,4-dicyano-2-phenyl-, ethyl ester]



Submitted by E. C. Horning and A. F. Finelli[1].
Checked by William S. Johnson and H. Wynberg.

1. Procedure

In a 500-ml. three-necked flask equipped with a stirrer, a dropping funnel, and a thermometer is placed a solution of 57.0 g. (0.30 mole) of ethyl phenylcyanoacetate (p. 461) in 80 ml. of *tert*-butyl alcohol. The solution is heated to 40°, and with stirring the dropwise addition of a solution of 33.0 g. (0.62 mole) of acrylonitrile (Note 1) in 30 ml. of *tert*-butyl alcohol is started. After the addition of about 10–15 drops, 1.0 ml. of a 30% solution of potassium hydroxide in methanol is added, and the temperature is maintained at 40–45° by occasional external cooling while the remaining solution is added slowly. When about one-half of the acrylonitrile has been added, an additional 1.0 ml. of the potassium hydroxide solution is added to ensure the presence of a basic catalyst throughout the reaction. When the addition is completed (after about 30 minutes) and the temperature is no longer maintained above 40° by the exothermic reaction (another 30 minutes), the mixture is heated with a hot-water bath to keep the temperature at 40–45° for 1 hour.

The solution is diluted with 250 ml. of water and acidified with 30–40 ml. of 10% hydrochloric acid. The product is separated after the addition of 100 ml. of ether, and the aqueous solution is extracted with two 50-ml. portions of ether. The combined extracts are washed with 50 ml. of water and dried over anhydrous magnesium sulfate. The ether is distilled at atmospheric pressure, and the residue is distilled under reduced pressure through a short (15-cm.) Vigreux column. After a fore-run of a few grams, the product is collected at 157–167° /0.5–1 mm. (Note 2). The yield is 50–61 g. (69–83%).

2. Notes

1. The acrylonitrile should be distilled before use. Acrylonitrile vapors are toxic, and the distillation as well as the subsequent reaction should be carried out in a hood.
2. Other observed boiling points are 165–167° /1 mm., 195–200° /6 mm. The

product is a colorless, viscous oil, n_D^{25} 1.5100–1.5103.

3. Discussion

α-Phenyl-α-carbethoxyglutaronitrile has been prepared by the reaction of ethyl α-cyanophenylacetate with β-chloropropionitrile in the presence of sodium amide.[2] The present procedure has been published,[3] and it follows the general method described by Bruson[4] for the cyanoethylation of arylacetonitriles.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 790

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

methanol (67-56-1)

ether (60-29-7)

potassium hydroxide (1310-58-3)

magnesium sulfate (7487-88-9)

sodium amide (7782-92-5)

acrylonitrile (107-13-1)

β-chloropropionitrile (542-76-7)

tert-butyl alcohol (75-65-0)

Ethyl phenylcyanoacetate, ethyl α-cyanophenylacetate (4553-07-5)

α-Phenyl-α-carbethoxyglutaronitrile, Butyric acid, 2,4-dicyano-2-phenyl-, ethyl ester (53555-70-7)

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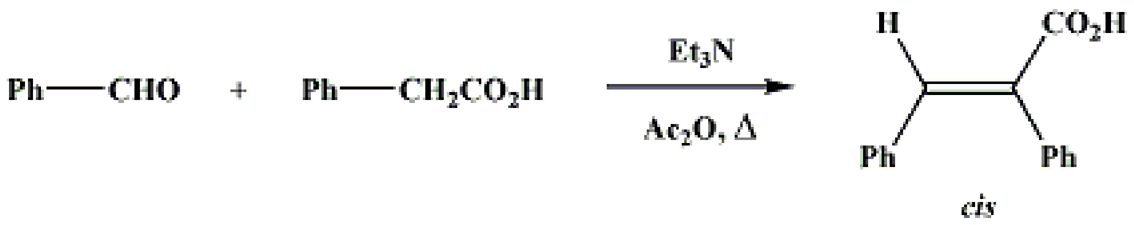
Organic Syntheses, CV 4, 777

α-PHENYLCINNAMIC ACID

[Acrylic acid, 2,3-diphenyl-]



Submitted by Robert E. Buckles and Keith Bremer[1].
Checked by T. L. Cairns and J. C. Lorenz.

1. Procedure

In a 500-ml. round-bottomed flask are placed 40.5 ml. (42.4 g., 0.40 mole) of freshly purified benzaldehyde (Note 1), 54.6 g. (0.40 mole) of phenylacetic acid,[2] 40 ml. of anhydrous triethylamine (Note 2), and 80 ml. of acetic anhydride (Note 3). The mixture is boiled gently under reflux for 5 hours. After the heating period is over, the 500-ml. flask containing the reaction mixture is incorporated into a steam-distillation apparatus (Note 4). The reaction mixture is distilled with steam until the distillate coming over is no longer cloudy, and then about 50 ml. more of the distillate is collected. The distillate can be discarded. The aqueous residue is cooled, and the solution is then separated from the solid by decantation. The solid is dissolved in 500 ml. of hot 95% ethanol, and 500 ml. of water, including the solution originally decanted from the crude solid, is added to the hot solution. The mixture is heated to boiling, and 2 g. of decolorizing carbon is added. The hot solution is filtered, and the filtrate is immediately acidified to Congo red with 6*N* hydrochloric acid. The solution is cooled, and the resulting crystals are removed from the mixture by filtration. The yield of crude α-phenylcinnamic acid (m.p. around 161–165°) is 60–67 g. The product is purified by crystallization from aqueous ethanol (Note 5). The over-all yield of purified product, m.p. 172–173°, is 48–53 g. (54–59%). The product is the isomer with the two phenyl groups *cis* to each other since decarboxylation yields *cis*-stilbene[3] (see p. 857).

2. Notes

1. Benzaldehyde, suitable for this synthesis, is purified in the following way. A 60-g. (58-ml.) sample is washed with two 20-ml. portions of 10% sodium carbonate and then with water. It is then dried over 5–10 g. of anhydrous magnesium sulfate. A few small crystals of hydroquinone or catechol are added with the drying agent. The dry benzaldehyde is decanted through a cotton plug

into a Claisen flask; it is distilled under reduced pressure, preferably below 30 mm.

2. Sharples anhydrous grade triethylamine was used without further purification.

3. The acetic anhydride is carefully fractionated; the 137–139° fraction is collected.

4. A simple steam-distillation apparatus such as that given by Fieser[4] is entirely satisfactory. It is usually necessary to heat the distillation flask with a steam bath or a small flame in order to minimize the accumulation of excess water in the flask.

5. The submitters used 5 ml. of 95% ethanol and 5 ml. of water per gram of crude product for recrystallization. The checkers found use of 3:2 ethanol:water by volume more convenient.

3. Discussion

α-Phenylcinnamic acid has been prepared by the distillation of benzylmandelic acid,[5] by the condensation of phenylacetyl chloride[6] or phenylacetic acid[7] with benzaldehyde in the presence of triethylamine; by the reaction of sodium or potassium phenylacetate with benzaldehyde in acetic anhydride;[8,9,10,11] and by the treatment of ethyl α-bromo-α,β-diphenylpropionate with potassium hydroxide.[12] The most convenient synthesis appears to be that described above.[13,14,15]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 857

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium or potassium phenylacetate

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

acetic anhydride (108-24-7)

hydroquinone (123-31-9)

sodium carbonate (497-19-8)

benzaldehyde (100-52-7)

decolorizing carbon (7782-42-5)

potassium hydroxide (1310-58-3)

Phenylacetic acid (103-82-2)

Catechol (120-80-9)

magnesium sulfate (7487-88-9)

phenylacetyl chloride (103-80-0)

triethylamine (121-44-8)

α-Phenylcinnamic acid, Acrylic acid, 2,3-diphenyl- (3368-16-9)

benzylmandelic acid

ethyl α-bromo-α,β-diphenylpropionate

cis-Stilbene (645-49-8)

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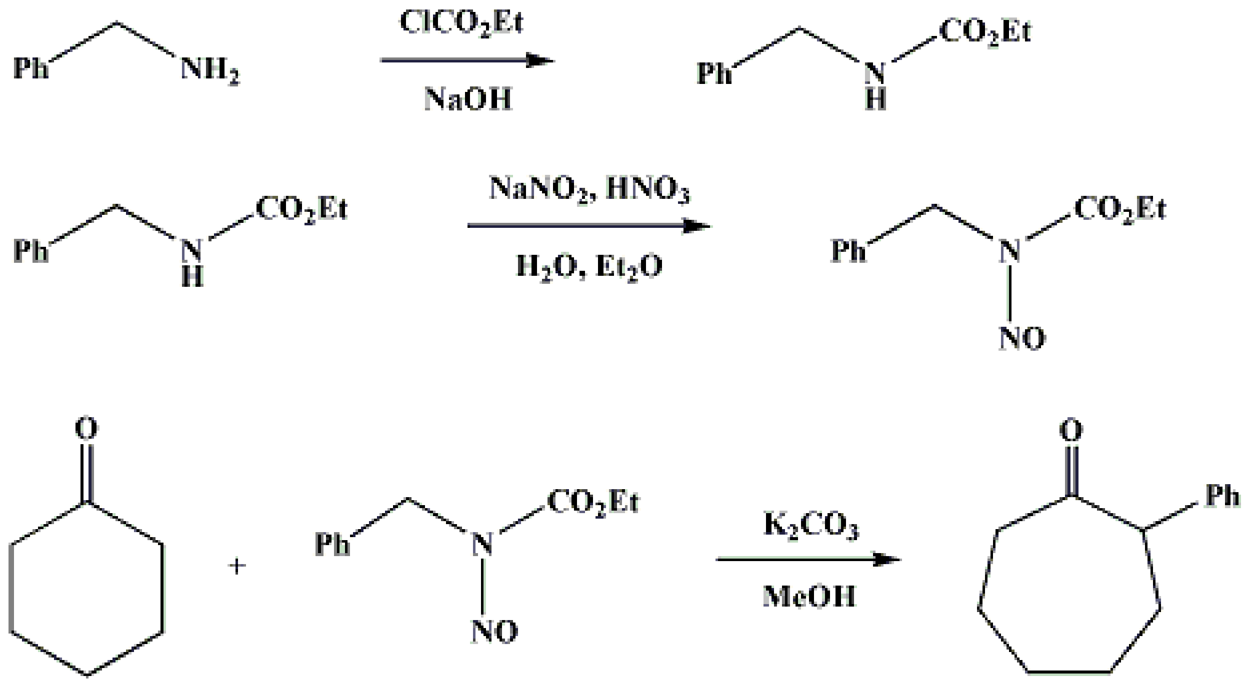
Organic Syntheses, CV 4, 780

2-PHENYLCYCLOHEPTANONE

[Cycloheptanone, 2-phenyl-]



Submitted by C. David Gutsche and Herbert E. Johnson[1].
Checked by N. J. Leonard and F. P. Hauck, Jr..

1. Procedure

A. *Ethyl N-benzylcarbamate.* A 12-l. three-necked flask fitted with a sturdy Hershberg-type stirrer and two 1-l. addition funnels is immersed in an ice bath and charged with 1 kg. (9.33 moles) of benzylamine, 500 ml. of ice water, and 1.5 kg. of chopped ice. To the stirred mixture 525 g. (4.83 moles) of ethyl chlorocarbonate is added dropwise while the temperature is maintained at 10–15° (1.0–1.5 hours) (Note 1). An additional 500 ml. of water and 1 kg. of chopped ice are then added to the flask, and a second 525-g. portion (4.83 moles) of ethyl chlorocarbonate is introduced. Simultaneously with this, an ice-cold solution of 400 g. (10 moles) of sodium hydroxide in 1.3 l. of water is added dropwise at such a rate that equal fractions of the ethyl chlorocarbonate and sodium hydroxide solutions are introduced over equal periods of time, the temperature being maintained throughout at 10–15° (2.5–3.0 hours). The reaction mixture is stirred for an additional 30 minutes and is then filtered through a Büchner funnel. The solid product is washed with copious amounts of cold water and is air-dried to yield 1.6 kg. (96%) of glistening white crystals, m.p. 45–47°.

B. *Ethyl N-nitroso-N-benzylcarbamate* (Note 2). In a 12-l. three-necked flask fitted with a thermometer, a 2-l. addition funnel (Note 3), and a gas outlet tube are placed a

solution of 360 g. (2.0 moles) of ethyl N-benzylcarbamate in 2 l. of ether and a solution of 1.2 kg. (17.4 moles) of sodium nitrite in 2 l. of water. A stirrer is not used. The reaction mixture is cooled by means of a water bath to 20° and treated with a solution of 1 l. each of concentrated nitric acid and water, contained in the addition funnel. Enough of this solution is added to impart a permanent green color to the aqueous layer, and the remainder is then added over a period of 5 hours at such a rate as to keep the aqueous phase green (Note 4) and the temperature at 25–30°. The reaction mixture is allowed to stand an additional 30 minutes, and the layers are separated. The ether layer is washed with 200-ml. portions of 10% potassium carbonate solution (Note 5) until the evolution of gas ceases and is then dried over anhydrous potassium carbonate. The ether is removed under vacuum on a water bath kept below 50° (Note 6), a residue of 400–415 g. (95–99%) of a bright orange oil (Note 7) being left.

C. *2-Phenylcycloheptanone.* In a 2-l. three-necked flask fitted with a 500-ml. addition funnel, a sealed Hershberg stirrer, and a reflux condenser (Note 8) are placed 392 g. (4.0 moles) of freshly distilled cyclohexanone, 30 g. of finely powdered potassium carbonate, and 400 ml. of absolute methanol. To the stirred mixture is added 415 g. (2.0 moles) of ethyl N-nitroso-N-benzylcarbamate over a period of 1.5 hours during which time the reaction temperature is maintained at 25° by means of an ice-water bath. The dark red reaction mixture is then allowed to stand at room temperature until the evolution of nitrogen has ceased (24–28 hours) (Note 9). The solid material is removed by filtration, the lower-boiling materials are removed by evaporation under reduced pressure on the steam bath (Note 10), and the residue is distilled through an efficient column. A fore-run consisting of 30–60 g. of material is discarded or refractionated (Note 10), and the fraction with b.p. 94–96°/0.4 mm. (124–126°/2 mm., 136–138°/4 mm.) is collected. It amounts to 155–177 g. (41–47%) of 2-phenylcycloheptanone, n_D^{20} 1.5395–1.5398, which is pure enough for most purposes, but which may be purified further by recrystallization from petroleum ether (b.p. 30–60°) and obtained as colorless, very long needles; m.p. 21–23° (Note 11).

2. Notes

1. During this time ethyl N-benzylcarbamate begins to separate from solution as a white solid.
2. Although the benzyl nitroso compound appears to be a much less active vesicant than the methyl nitroso compound, it is, nevertheless, a wise precaution to wear heavy rubber gloves during the isolation of this product.
3. The stem of the addition funnel should reach to the bottom of the flask.
4. The color may appear yellow green, emerald green, or blue-green, depending upon the size of the run, the amount of nitric acid that has been added, and the room lighting.
5. Seven to nine portions of carbonate solution are sufficient if each portion is shaken very thoroughly with the ether solution. Caution should be observed because of pressure build-up in the separatory funnel!

6. Ethyl N-nitroso-N-benzylcarbamate is heat sensitive and, if the temperature is too high, *may detonate violently*. The submitters state that attempts to distil the nitroso compound under high vacuum have resulted in explosions.
7. The submitters state that the nitroso compound is stable at low temperature and can be stored in a refrigerator for several months or longer with no signs of deterioration.
8. The reflux condenser is an optional but convenient appendage for the third neck of the flask. To follow the evolution of nitrogen during the reaction, the exit from the condenser can be led either to a eudiometer tube (theoretical nitrogen evolution about 50 l. for the experiment described) or to a bubbler.
9. It is necessary to allow the reaction mixture to stand for a rather prolonged period, since about 40% of the nitrogen is evolved during this time.
10. The lower-boiling material includes methyl benzyl ether, which may be isolated, by careful fractionation through an efficient column, in about 25% yield, b.p. 74–77°/30 mm.
11. In a similar fashion the following 2-arylcycloheptanones have been prepared by the submitters:

	Yield, %	Melting Point, or Refractive Index at 25°
2-(*o*-Methylphenyl)cycloheptanone	29	1.5348
2-(*p*-Methylphenyl)cycloheptanone	26	57–58°
2-(*o*-Methoxyphenyl) cycloheptanone	7	1.5407
2-(*m*-Methoxyphenyl) cycloheptanone	42	1.5418
2-(*p*-Methoxyphenyl) cycloheptanone	20	58–59°

3. Discussion

Ethyl N-benzylcarbamate and its nitroso compound have been prepared by methods similar to those described for ethyl N-methylcarbamate and its nitroso compound.[2,3] 2-Phenylcycloheptanone has been prepared by the reaction of ethyl N-nitroso-N-benzylcarbamate[4] with cyclohexanone,[5] by the reaction of phenyldiazomethane with cyclohexanone,[6] by the reaction of ethyl N-nitroso-N-methylcarbamate with 2-phenylcyclohexanone,[5] and by the rearrangement of 1-phenyl-2-cyclohexylethylene oxide.[7]

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6. Burger, Walter, Bennet, and Turnbull, *Science*, **112**, 306 (1950); Gutsche and Jason, *J. Am. Chem. Soc.*, **78**, 1184 (1956).
7. Tiffeneau, Weill, Gutmann, and Tchoubar, *Compt. rend.*, **201**, 277 (1935).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

potassium carbonate (584-08-7)

methanol (67-56-1)

ether (60-29-7)

sodium hydroxide (1310-73-2)

nitric acid (7697-37-2)

Cyclohexanone (108-94-1)

nitrogen (7727-37-9)

sodium nitrite (7632-00-0)

ethyl chlorocarbonate (541-41-3)

benzylamine (100-46-9)

Ethyl N-methylcarbamate (105-40-8)

ethyl N-nitroso-N-methylcarbamate (615-53-2)

2-Phenylcycloheptanone, Cycloheptanone, 2-phenyl- (14996-78-2)

Ethyl N-benzylcarbamate (2621-78-5)

Ethyl N-nitroso-N-benzylcarbamate (6558-76-5)

methyl benzyl ether (538-86-3)

phenyldiazomethane (766-91-6)

2-phenylcyclohexanone (1444-65-1)

1-phenyl-2-cyclohexylethylene oxide

2-(o-Methylphenyl)cycloheptanone

2-(p-Methylphenyl)cycloheptanone

2-(o-Methoxyphenyl)cycloheptanone

2-(m-Methoxyphenyl)cycloheptanone

2-(p-Methoxyphenyl)cycloheptanone

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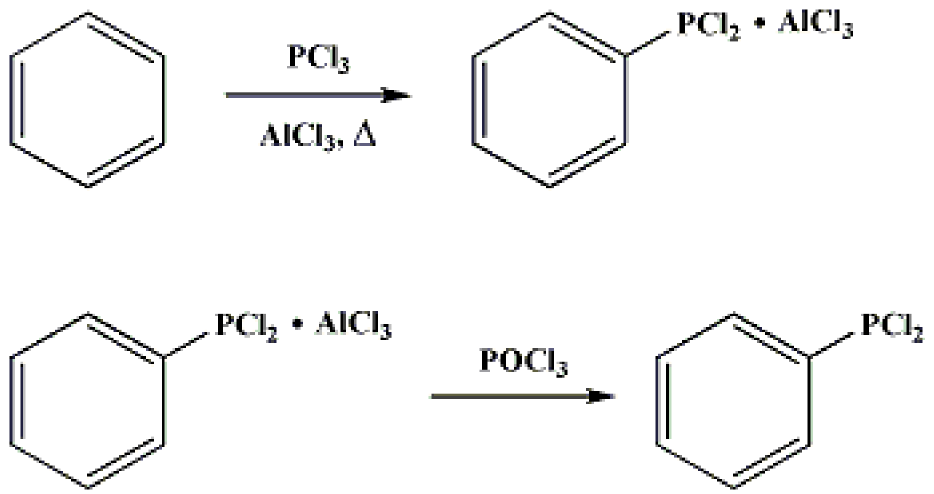
Organic Syntheses, CV 4, 784

PHENYLDICHLOROPHOSPHINE

[Phosphonous dichloride, phenyl-]



Submitted by B. Buchner and L. B. Lockhart, Jr.[1].
Checked by Cliff S. Hamilton and P. J. Vanderhorst.

1. Procedure

In an all-glass apparatus consisting of a 1-l. three-necked flask equipped with a long-stem thermometer, a rubber-sealed mechanical stirrer, and a suitable condenser (Note 1) are placed 165 g. (1.2 moles) of phosphorus trichloride, 23.4 g. (0.3 mole) of benzene, and 53 g. (0.4 mole) of anhydrous aluminum chloride. The mixture is stirred continuously and heated (Note 2). As the temperature increases, the mixture becomes a homogeneous yellow solution and begins to reflux. After 2 hours, the reaction mixture is heated under reflux as vigorously as possible (Note 3). At the end of the third hour, the evolution of hydrogen chloride has almost ceased. The heat source is removed, and, while the mixture is still hot, 62 g. (0.4 mole) of phosphorus oxychloride is added gradually (Note 4) from a dropping funnel (Note 5). The granular precipitate of aluminum chloride-phosphorus oxychloride complex settles rapidly. After the apparatus is disassembled, 6–8 petroleum ether extractions of 100 ml. each are performed to remove phenyldichlorophosphine and the unreacted starting materials from the reaction flask. The residue is transferred to a Büchner funnel and washed with several small portions of petroleum ether, and the combined extracts and washings are concentrated under reduced pressure. Crude phenyldichlorophosphine is removed by distilling to dryness under reduced pressure and is purified by fractionating through a satisfactory column (Note 6). The product distils at 68–70°/1 mm. (90–92°/10 mm.), n_D^{25} 1.5962 (Note 7), and weighs 38.5–42 g. (72–78%).

2. Notes

1. The submitters and checkers used a Friedrichs condenser. The condenser outlet was connected to a gas absorption trap filled with sodium hydroxide solution to neutralize escaping acid vapors. A tube filled with Drierite was inserted between the condenser and trap to absorb moisture which might diffuse from the trap.
2. Slow heating is desirable to prevent too rapid evolution of hydrogen chloride.
3. Cold water, approximately 0°, is circulated by means of a water pump in order to increase the efficiency of the condenser.
4. The reaction between phosphorus oxychloride and aluminum chloride is exothermic.
5. The thermometer is replaced by a dropping funnel.
6. The submitters and checkers employed a 20-cm. column packed with glass helices.
7. The checkers obtained an average value of n_D^{24} 1.5919.

3. Discussion

Phenyldichlorophosphine has been prepared by the vaporphase reaction of benzene and phosphorus trichloride over pumice in a hot tube[2] and by the action of diphenylmercury[3] or phenylzinc bromide[4] on phosphorus trichloride. The method described here is a Michaelis' modification of a Friedel-Crafts reaction.[5] It has been claimed[6] that pyridine is advantageous for the removal of aluminum chloride from the reaction mixture.

References and Notes

1. Naval Research Laboratory, Washington, D. C.
2. Michaelis, *Ber.*, **6**, 601 (1873).
3. Michaelis, *Ann.*, **181**, 288 (1876).
4. Weil, Prijs, and Erlenmeyer, *Helv. Chim. Acta*, **35**, 1412 (1952).
5. Michaelis, *Ber.*, **12**, 1009 (1879); Buchner and Lockhart, *J. Am. Chem. Soc.*, **73**, 755 (1951).
6. Gefter, *Zhur. Obshchei Khim.*, **28**, 1338 (1958) [*C. A.*, **52**, 19999 (1958)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

Drierite

aluminum chloride-phosphorus oxychloride complex

hydrogen chloride (7647-01-0)

Benzene (71-43-2)

sodium hydroxide (1310-73-2)

Phosphorus Oxychloride (21295-50-1)

aluminum chloride (3495-54-3)

pyridine (110-86-1)

phosphorus trichloride (7719-12-2)

Diphenylmercury (587-85-9)

Phenyldichlorophosphine, Phosphonous dichloride, phenyl- (644-97-3)

phenylzinc bromide

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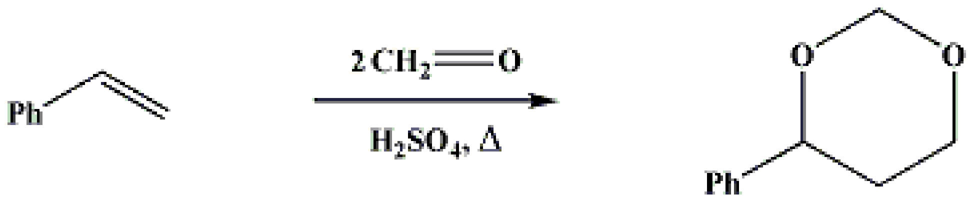
Organic Syntheses, CV 4, 786

4-PHENYL-*m*-DIOXANE

[*m*-Dioxane, 4-phenyl-]



Submitted by R. L. Shriner and Philip R. Ruby[1].
Checked by Richard T. Arnold, W. E. Parham, and John E. Franz.

1. Procedure

In a 2-l. round-bottomed flask, fitted with a reflux condenser and mechanical stirrer, are placed 675 g. (8.3 moles) of 37% formalin, 48 g. of sulfuric acid (sp. gr. 1.84), and 312 g. (3 moles) of styrene. The resulting mixture is gently refluxed and stirred for 7 hours. The mixture is cooled, and 500 ml. of benzene is stirred in. The layers are separated, and the aqueous layer is extracted with 500 ml. of benzene. The benzene solutions are combined and washed with two 750-ml. portions of water. The benzene is removed by distillation, and the residual liquid is fractionated under reduced pressure. At 2 mm. pressure a forerun is collected separately, up to a temperature of 96° (Note 1); then the main fraction is collected at 96–103°/2 mm. The yield of 4-phenyl-*m*-dioxane amounts to 353–436 g. (72–88%): n_D^{20} 1.5300–1.5311: d_4^{20} 1.092–1.093 (Note 2).

2. Notes

1. The amount of fore-run and the yield depend on the efficiency of the fractionation. With a 7-cm. distilling head, a fore-run of 75 g. boiling at 84–96°/2 mm. was collected, whereas with a heated Vigreux column (2 cm. by 35 cm.) the fore-run amounted to only 11 g. and the higher yields were obtained. The fore-run may be refractionated to obtain additional product. The checkers used a 2 cm. by 20 cm. column packed with stainless-steel helices, and collected their product (72–75% yield) over a 1° boiling range (94–95°/2 mm., n_D^{20} 1.5300).

2. This modification of the Prins[2] reaction has been applied to other olefins.[3] The aryl olefins give the best yields; see the tabulation.

Aryl Olefin	Yield of Substituted *m*-Dioxane, %

α-Methylstyrene	58
Propenylbenzene	66
Anethole	89
Isosafrole	84
1-(3',4'-Dimethoxyphenyl)-1-propene	68
1-(*p*-Cumyl)-1-propene	96

3. Discussion

4-Phenyl-*m*-dioxane was obtained by Prins[2] by the reaction between styrene and formaldehyde in the presence of sulfuric acid. The correct structure was pointed out by Fourneau, Benoit, and Firmenich.[4] The above procedure is essentially that given by Shortridge[5] and by Beets[3] and mentioned in a patent.[6] Methylphenylcarbinol has been substituted for styrene.[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 798

References and Notes

1. State University of Iowa, Iowa City, Iowa.
2. Prins, *Chem. Weekblad*, **14**, 932 (1917); **16**, 1072, 1510 (1919); *Proc. Acad. Sci. Amsterdam*, **22**, 51 (1919).
3. Beets, *Rec. trav. chim.*, **70**, 20 (1951); Beets and Van Essen, *Rec. trav. chim.*, **70**, 25 (1951); Drukker and Beets, *Rec. trav. chim.*, **70**, 29 (1951).
4. Fourneau, Benoit, and Firmenich, *Bull. soc. chim. France*, **47**, 858 (1930).
5. Shortridge, *J. Am. Chem. Soc.*, **70**, 873 (1948).
6. Engel, U. S. pat. 2,417,548 [*C. A.*, **41**, 3493 (1947)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

1-(p-Cumyl)-1-propene

sulfuric acid (7664-93-9)

Benzene (71-43-2)

formaldehyde, formalin (630-08-0)

styrene (100-42-5)

methylphenylcarbinol (98-85-1)

propenylbenzene

isosafrole (120-58-1)

α-methylstyrene (98-83-9)

Anethole (104-46-1)

m-Dioxane (505-22-6)

4-Phenyl-m-dioxane, m-Dioxane, 4-phenyl- (3141-24-0)

1-(3',4'-Dimethoxyphenyl)-1-propene

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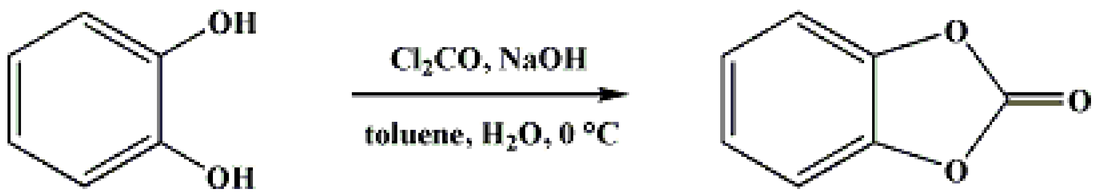
Organic Syntheses, CV 4, 788

o-PHENYLENE CARBONATE

[Carbonic acid, *o*-phenylene ester]



Submitted by R. S. Hanslick, W. F. Bruce, and A. Mascitti[1].
Checked by Arthur C. Cope, Harris E. Petree, and Elmer R. Trumbull.

1. Procedure

Caution! This preparation should be conducted in a hood to avoid exposure to toxic phosgene.

In a 5-l. three-necked flask, filled with nitrogen, 110 g. (1.0 mole) of recrystallized catechol (Note 1) is dissolved in 250 ml. of deaerated water (Note 2) containing 88 g. (2.2 moles) of sodium hydroxide. The flask is fitted with a gas inlet tube, a thermometer dipping into the liquid, and an efficient glass mechanical stirrer with a gas-tight rubber slip seal and is immersed in an ice-salt bath. A positive nitrogen pressure of about 1 cm. is maintained by attaching the inlet tube to a source of nitrogen through a line containing a T-tube dipping into mercury. A solution of 200–225 g. (2.0–2.3 moles) of commercial phosgene in 750 ml. of toluene is prepared at 0° by bubbling the gas into toluene in a tared flask (Note 3), and the solution is added to the flask in portions of about 50 ml. with good mechanical stirring over a period of 60 to 75 minutes. During the addition the temperature is maintained at 0–5° by periodic addition to the mixture of clean cracked ice, free from dirt and iron rust. After addition of the toluene solution of phosgene is completed, the mixture is stirred at 0–5° for 1 hour and then allowed to come to room temperature. The mixture is filtered with suction, and the solid is pressed on the funnel to remove as much water as possible. The aqueous portion of the filtrate is separated, and the solid on the funnel is added to the toluene in the filtrate and dissolved by warming. The warm toluene solution is filtered and distilled under reduced pressure (water aspirator) until the product begins to crystallize. The residue is warmed to redissolve the solid, and then chilled. The *o*-phenylene carbonate is collected on a suction filter and dried in a vacuum desiccator; the yield is 98–110 g., m.p. 119–120°.

Concentration of the filtrate yields a second crop of impure product, which is recrystallized from toluene and then melts at 119–120°. The combined yield of pure white *o*-phenylene carbonate from the first and second crops is 107–116 g. (79–85%).

2. Notes

1. Catechol obtained from the Koppers Company, Pittsburgh, Pennsylvania, was recrystallized from toluene.
2. Water that was deaerated by boiling was used, and an atmosphere of nitrogen essentially free from oxygen (such as the Seaford grade of the Air Reduction Company) was maintained, in order to prevent discoloration of the alkaline solution of catechol due to oxidation.
3. Phosgene from a commercial cylinder was used (Matheson Company or Ohio Chemical Company). For the preparation of a solution of phosgene in toluene see *Organic Syntheses.*[2]

3. Discussion

o-Phenylene carbonate has been prepared by the distillation of *o*-hydroxyphenyl ethyl carbonate[3] and by the reaction of catechol with phosgene.[3,4]

References and Notes

1. Research Laboratory, Wyeth Institute, Philadelphia, Pennsylvania.
2. *Org. Syntheses Coll. Vol.* **3**, 167 (1955).
3. Einhorn and Lindenberg, *Ann.*, **300**, 141 (1898).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

iron rust

sodium hydroxide (1310-73-2)

oxygen (7782-44-7)

nitrogen (7727-37-9)

mercury (7439-97-6)

toluene (108-88-3)

phosgene (75-44-5)

Catechol (120-80-9)

o-Phenylene carbonate, Carbonic acid, o-phenylene ester (2171-74-6)

o-hydroxyphenyl ethyl carbonate

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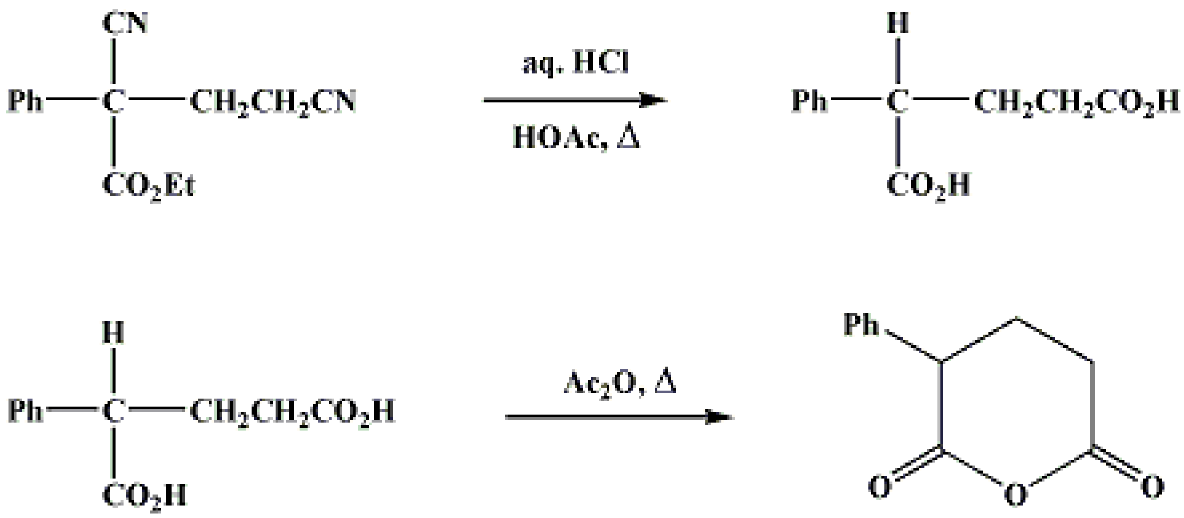
Organic Syntheses, CV 4, 790

α-PHENYLGLUTARIC ANHYDRIDE

[Glutaric anhydride, 2-phenyl-]



Submitted by E. C. Horning and A. F. Finelli[1].
Checked by William S. Johnson and H. Wynberg.

1. Procedure

In a 500-ml. flask equipped with a reflux condenser are placed 48.4 g. (0.20 mole) of α-phenyl-α-carbethoxyglutaronitrile (p. 776), 225 ml. of hydrochloric acid (sp. gr. 1.19), and 50 ml. of acetic acid. The mixture is heated under reflux for 10 hours. The solution is cooled, transferred to a 1-l. separatory funnel, and diluted with 300 ml. of water. The α-phenylglutaric acid is extracted with five 100-ml. portions of ether-ethyl acetate (1:1) (Note 1). The extracts are combined, washed once with saturated sodium chloride solution, and dried over anhydrous magnesium sulfate. The solvents are removed as completely as possible by distillation from a steam bath, and the residue is transferred to a 200-ml. flask. Acetic anhydride (50 ml.) is added, and the solution is heated under gentle reflux for 1 hour. The excess acetic anhydride is removed by distillation at atmospheric pressure, and the residue is distilled under reduced pressure through a short (15-cm.) Vigreux column with an air-cooled side arm. The product is collected at 178–188°/0.5–1 mm. (Note 2). The yield is 31.1–32.7 g. (82–86%); m.p. 90–94°.

This material may be recrystallized by dissolving the product in hot ethyl acetate (2 ml. per g. of the anhydride) and adding an equal volume of hexane or 60–68° petroleum ether slowly to the hot solution. The solution is allowed to cool, and when crystallization occurs (usually at 40–50°) an additional volume (2 ml. per g. of the anhydride) of hexane is added. The mixture is cooled, and the crystalline product is removed by filtration and washed with cold hexane (5 ml. per g. of the anhydride).

The recovery of colorless material, m.p. 95–96°, is 90–92%.

2. Notes

1. The extraction may be facilitated by saturation of the aqueous layer with sodium chloride.
2. It is necessary to flame the column and side arm. The product obtained in this way is a light-yellow or cream-colored solid which need not be recrystallized unless a colorless sample is desired. If the final distillation is carried out too slowly or at pressures above 2 mm. considerable decomposition may occur, reducing the yield of the product.

3. Discussion

α-Phenylglutaric acid has been prepared by the hydrolysis and decarboxylation of diethyl α-phenyl-α-carbethoxyglutarate (prepared by the alkylation of diethyl phenylmalonate with ethyl β-iodopropionate) with hydrochloric acid.[2] The anhydride may be obtained from the acid by direct distillation under reduced pressure, although the use of acetic anhydride results in a purer product.

References and Notes

1. University of Pennsylvania, Philadelphia, Pennsylvania.
2. Fichter and Merckens, *Ber.*, **34**, 4175 (1901).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ethyl acetate (141-78-6)

ether (60-29-7)

acetic anhydride (108-24-7)

sodium chloride (7647-14-5)

magnesium sulfate (7487-88-9)

diethyl phenylmalonate (83-13-6)

hexane (110-54-3)

α-Phenyl-α-carbethoxyglutaronitrile (53555-70-7)

α-Phenylglutaric anhydride, Glutaric anhydride, 2-phenyl- (2959-96-8)

α-phenylglutaric acid

diethyl α-phenyl-α-carbethoxyglutarate

ethyl β-iodopropionate (6414-69-3)

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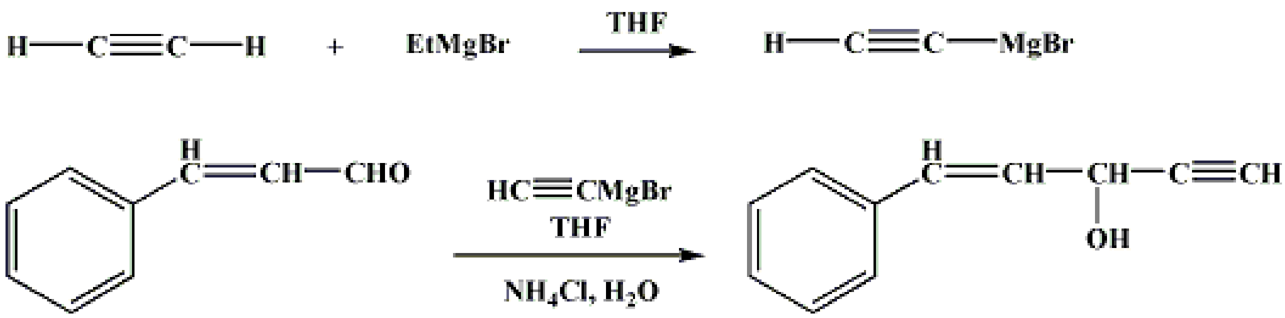
Organic Syntheses, *CV 4*, *792*

1-PHENYL-1-PENTEN-4-YN-3-OL

[1-Penten-4-yn-3-ol, 1-phenyl-]



Submitted by Lars Skattebøl, E. R. H. Jones, and Mark C. Whiting[1].
Checked by Melvin S. Newman and Raymond E. Dessy.

1. Procedure

A. *Ethynylmagnesium bromide.* A 500-ml. three-necked flask, equipped with a sealed mechanical stirrer, a reflux condenser, and a pressure-equalized dropping funnel, is arranged for carrying out a reaction in an atmosphere of nitrogen by fitting into the top of the condenser a T-tube attached to a low-pressure supply of nitrogen and to a mercury bubbler. For later use there is also prepared a dry 1-l. three-necked flask equipped with a sealed mechanical stirrer, a gas inlet tube which will dip below the surface of 200 ml. of liquid in the flask, a 500-ml. dropping funnel, and a gas outlet protected by a calcium chloride drying tube.

The 500-ml. flask is dried by warming with a soft flame as a slow stream of nitrogen is passed through the system. A solution of ethylmagnesium bromide is prepared in this flask from 12 g. (0.5 g. atom) of magnesium turnings, 60 g. (0.55 mole) of ethyl bromide (dried over calcium chloride), and 300 ml. of tetrahydrofuran (Note 1) and (Note 2).

After the preparation of ethylmagnesium bromide is completed, the separatory funnel is replaced by a bent tube which reaches the bottom of the flask and is bent at the outer end for downward delivery (Note 3). The warm (40–50°) solution is forced under nitrogen pressure (by carefully pinching off the tube to the mercury bubbler) into the 500-ml. separatory funnel which has been prepared for attachment to the 1-l. flask. After all the solution has passed into the separatory funnel, nitrogen flow is allowed to continue briefly in order to displace the air above the solution, then the funnel is stoppered loosely and attached to the 1-l. flask. Two hundred milliliters of purified tetrahydrofuran is now placed in the flask, acetylene (Note 4) is introduced through the gas-inlet tube at the rate of 15–20 l. per hour, and the stirrer is started. After 5 minutes, about 5 ml. of the solution of ethylmagnesium bromide is added in 1 portion. Almost at once, there appears a froth of ethane which is easily distinguishable from the larger bubbles of acetylene. When the frothing subsides, portionwise addition of the ethylmagnesium bromide solution is continued until the total solution has been added. This requires about 3 hours, and the temperature of the reaction rises 5–10° above room temperature. The solution of ethynylmagnesium bromide is homogeneous at 30° (Note 5).

B. *1-Phenyl-1-penten-4-yn-3-ol.* The stirred solution of ethynylmagnesium bromide is cooled in ice water as there is added dropwise during about 45 minutes a solution of 47.5 g. (0.36 mole) of

freshly distilled cinnamaldehyde (Note 6) in 50 ml. of purified tetrahydrofuran. After addition is complete, stirring is continued overnight as the solution is allowed to warm to room temperature. The brown homogeneous reaction mixture is added carefully to 1.5 l. of cooled saturated ammonium chloride solution, then the aqueous phase is extracted with three 250-ml. portions of ether. The ether extracts are combined with the tetrahydrofuran solution and dried over anhydrous magnesium sulfate. After evaporation of the solvent, the product is distilled (Note 7) at a pressure of about 0.1 mm., with the heating bath at about 90°. The distillate, which solidifies on cooling, is crystallized from petroleum ether (b.p. 40–60°) to yield 33–39 g. (58–69%) of the unsaturated alcohol of m.p. 67–68° (Note 8).

2. Notes

1. If less solvent is used, the ethylmagnesium bromide may crystallize on cooling.
2. If ether is substituted for tetrahydrofuran in this preparation, the acetylenic glycol is the sole product. The submitters purified the tetrahydrofuran by shaking with potassium hydroxide pellets, heating under reflux with sodium metal, and finally distilling. They report that heating under reflux with sodium diphenylketyl gives a better sample of tetrahydrofuran, but that this does not improve the yield.
The checkers purified the solvent by shaking with potassium hydroxide, distilling from lithium aluminum hydride, then storing over sodium wire.
3. It is advisable to prepare the delivery tube prior to its need.
4. The submitters purified the acetylene by passing it through a trap cooled to −80°, then through concentrated sulfuric acid, and finally through soda-lime. The checkers purified the acetylene by passing it first through a tower of 10-mesh alumina, then through concentrated sulfuric acid.
5. No outside cooling is employed during the preparation of ethynylmagnesium bromide. If this solution of ethynylmagnesium bromide is cooled to 0°, a crystalline complex separates. If part of the solvent is evaporated, even at 40° under reduced pressure, there occurs disproportionation to acetylene and the bisbromomagnesium derivative.
6. Methyl ethyl ketone, crotonaldehyde, and acrolein react similarly with ethynylmagnesium bromide. The respective yields of acetylenic alcohols are 69%, 84%, and 40%.
7. The submitters used a still of the evaporative type, such as a Hickman still. The checkers used a similar still modified to include a magnetic stirring bar. This modification greatly decreases the time required for removal of the last traces of solvent, minimizes the danger of bumping just before evaporative distillation occurs, and increases the rate of distillation of the product.
8. The checkers report yields as high as 84% and believe that the use of magnetic stirring in the Hickman still is responsible for the higher yield.

3. Discussion

The preparation of ethynylmagnesium bromide in ether has been described;[2,3] however, the subsequent history of the compound has been controversial. The submitters have been unable to prepare ethynylcarbinols by the earlier procedures.

1-Phenyl-1-penten-4-yn-3-ol has been prepared in liquid ammonia from cinnamaldehyde and sodium acetylide in 2% yield,[4] and from the sodium bisulfite compound of cinnamaldehyde and sodium acetylide in 13.5% yield.[5] The present procedure has been published.[6]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 258
- Org. Syn. Coll. Vol. 8, 606
- Org. Syn. Coll. Vol. 5, 976

References and Notes

1. The Dyson Perrins Laboratory, Oxford, England.
2. Salkind and Rosenfeld, *Ber.*, **57**, 1690 (1924).
3. Grignard, Lapayre, and Tcheou, *Compt. rend.*, **187**, 517 (1928).
4. Jones and McCombie, *J. Chem. Soc.*, **1942**, 733.
5. Cymerman and Wilks, *J. Chem. Soc.*, **1950**, 1208.
6. Jones, Skattebøl, and Whiting, *J. Chem. Soc.*, **1956**, 4765.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

soda-lime

sodium diphenylketyl

sodium bisulfite compound of cinnamaldehyde

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

acetylene (74-86-2)

ammonia (7664-41-7)

ether (60-29-7)

ammonium chloride (12125-02-9)

Acrolein (107-02-8)

magnesium turnings (7439-95-4)

Ethyl bromide (74-96-4)

nitrogen (7727-37-9)

potassium hydroxide (1310-58-3)

sodium, sodium wire (13966-32-0)

cinnamaldehyde

ethylmagnesium bromide (925-90-6)

magnesium sulfate (7487-88-9)

ethane (74-84-0)

methyl ethyl ketone (78-93-3)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

sodium acetylide

crotonaldehyde (123-73-9)

ethynylmagnesium bromide

1-Phenyl-1-penten-4-yn-3-ol, 1-Penten-4-yn-3-ol, 1-phenyl- (14604-31-0)

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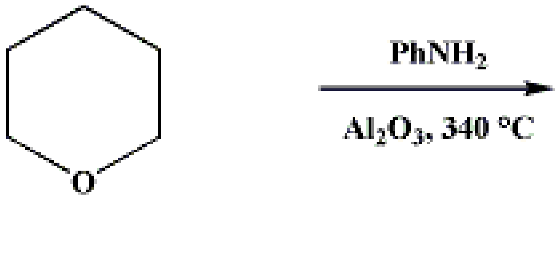
Organic Syntheses, CV 4, 795

1-PHENYLPIPERIDINE

[Piperidine, 1-phenyl]



Submitted by A. N. Bourns, H. W. Embleton, and Mary K. Hansuld[1].
Checked by R. T. Arnold, William E. Parham, and Carl Serres.

1. Procedure

The apparatus (.htmFig. 15) consists of a reaction tube, 100 cm. long and 3 cm. in diameter, provided with an inlet tube to which a graduated dropping funnel is connected. The lower end of the reaction tube is fitted with a Friedrichs condenser and receiver. A thermocouple well, concentric with the reaction tube, is passed through the upper end by means of a standard ground-glass joint. The tube is packed with 200 ml. of 4- to 8-mesh alumina (Note 1) held in place by a plug of glass wool supported by indentations in the tube, followed by 100 ml. of marble chips which serve as a vaporizer and preheater for the reactants. The reaction tube is supported in an electrically heated furnace (Note 2) extending from the inlet tube to the joint connecting the condenser.

Fig. 15.

Fig. 15.

The reaction tube is heated to 330–340° (Note 3) and is swept out with a stream of nitrogen gas. A solution of 258 g. (3 mole) of tetrahydropyran (Note 4) and 559 g. (6 mole) of aniline is then placed in the graduated funnel and introduced into the reaction tube at a rate of 90–100 ml. per hour. The product, which is collected in a 1-l. flask containing 10 g. of sodium chloride, consists of a light-yellow oil and a lower aqueous layer. After the addition of the reactants is complete, a slow stream of nitrogen is passed through the reaction tube for 20–30 minutes to remove any product adsorbed on the catalyst. The lower aqueous layer is separated and discarded, and the upper organic layer is dried over sodium hydroxide pellets. The product is fractionated under reduced pressure using a Whitmore-Lux column[2] (Note 5) only to remove the small amount of unchanged tetrahydropyran and excess aniline. The column is permitted to drain, and the residue is distilled from an ordinary Claisen flask under reduced

pressure. 1-Phenylpiperidine is obtained as a colorless or very light-yellow liquid, b.p. 123–126°/12.5 mm., 133–136°/21 mm., n_D^{25} 1.5603. The yield is 403–435 g. (83–90% based on tetrahydropyran) (Note 6).

2. Notes

1. The catalyst employed was Alcoa Activated Alumina (Grade F-1, 4- to 8-mesh) from the Aluminum Company of America. A fresh catalyst is brought to a condition of maximum activity by passing a slow stream of air through the catalyst bed for 94 hours at 390–405°. Without this pretreatment, yields are 5–10% lower than those reported here. The catalyst is reactivated after each run by passing air through it for 39 hours at 390–405°.

2. The furnace may be of the construction described in a previous volume.[3] It is desirable, although not essential, to provide separately controlled heating elements for each of the two packed zones of the reaction tube.

3. The temperature of the furnace is measured by a thermocouple which can be moved to various positions in the thermocouple well. The catalyst temperature should be maintained at 325–345°, although it may be as low as 320° at the ends of the catalyst zone, depending unon the construction of the furnace.

4. Eastman Kodak Company practical grade tetrahydropyran may be used without purification.

5. A column of equivalent efficiency may be employed.

6. 1-*m*-Tolylpiperidine (b.p. 141–143°/16 mm., n_D^{25} 1.5535) and 1-*p*-tolylpiperidine (b.p. 140–143°/15 mm., n_D^{25} 1.5509) may be prepared in 85–90% yield by a similar procedure. 1-*o*-Tolylpiperidine (b.p. 123–125°/15 mm., n_D^{25} 1.5391) is obtained in 60% yield under similar reaction conditions, but it is necessary to fractionate the product in order to obtain pure material.

3. Discussion

1-Phenylpiperidine has been prepared by warming aniline with 1,5-dibromopentane;[4,5] heating 5-anilino-1-bromopentane;[6] the dehydration of 5-anilino-1-pentanol over alumina;[7] the electrolytic reduction of N-phenylglutarimide;[8] the catalytic hydrogenation of 1-phenyl-3-hydroxypyridinium chloride;[9] the action of bromobenzene on piperidine in the presence of lithium[10] or sodium amide;[11] the reaction of fluorobenzene, 1-methylpiperidine, and phenyllithium;[12] the action of diphenylsulfone on piperidine in the presence of sodamide;[13] the diazotization and deamination of 1-(2-aminophenyl)piperidine[14] and of 1-(4-aminophenyl)piperidine;[15] the reduction of N-phenylglutarimide with lithium aluminum hydride;[16] the reaction of pentamethylene glycol dibenzenesulfonate with aniline;[17] the action of lithium piperidide on chlorobenzene;[18] and the present method.[19]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 746

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alumina

lithium piperidide

aniline (62-53-3)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

chlorobenzene (108-90-7)

diphenylsulfone (127-63-9)

piperidine (110-89-4)

1,5-dibromopentane (111-24-0)

bromobenzene (108-86-1)

Tetrahydropyran (142-68-7)

Phenyllithium (591-51-5)

Fluorobenzene (462-06-6)

sodamide (7782-92-5)

lithium aluminum hydride (16853-85-3)

1-Phenylpiperidine, Piperidine, 1-phenyl (4096-20-2)

5-anilino-1-bromopentane

5-anilino-1-pentanol

N-phenylglutarimide

1-phenyl-3-hydroxypyridinium chloride

1-methylpiperidine (626-67-5)

1-(2-aminophenyl)piperidine (39643-31-7)

1-(4-aminophenyl)piperidine (2359-60-6)

pentamethylene glycol dibenzenesulfonate

1-m-Tolylpiperidine

1-p-tolylpiperidine

1-o-Tolylpiperidine (7250-70-6)

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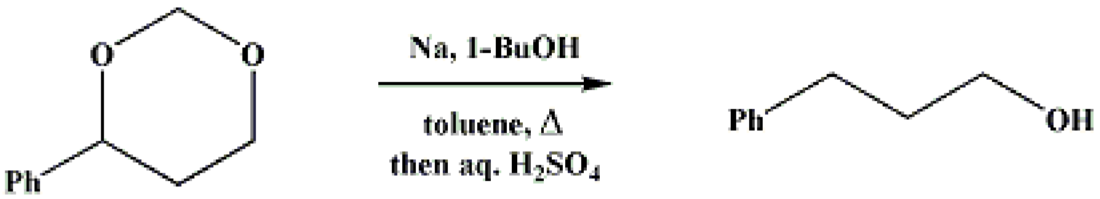
Organic Syntheses, *CV 4*, *798*

3-PHENYL-1-PROPANOL

[1-Propanol, 3-phenyl-]



Submitted by R. L. Shriner and Philip R. Ruby[1].
Checked by Richard T. Arnold, W. E. Parham, and Hans Wynberg.

1. Procedure

In a 5-l. round-bottomed flask, equipped with two reflux condensers and a mechanical stirrer (Note 1), are placed 800 g. (925 ml.) of dry toluene and 168 g. (7.3 g. atoms) of sodium. The toluene is heated to boiling, the sodium is melted, and the stirrer is started. The source of external heat is removed, and a solution of 328 g. (2 moles) of 4-phenyl-*m*-dioxane (p. 786) in 311 g. (4.2 moles) of 1-butanol (Note 2) is added through the top of one of the condensers. The vapors should reflux about halfway up the condensers; about 30 to 60 minutes is used for the addition (Note 3). The mixture is cooled to room temperature, and a solution of 100 ml. of concentrated sulfuric acid in 800 ml. of water is added slowly with stirring. After the water layer is separated and discarded, 500 ml. of water is again added to the organic layer. Dilute sulfuric acid (5%) is added with shaking until the water layer is neutral to litmus paper. After the water layer is separated and discarded, the toluene and 1-butanol are removed from the organic layer by distillation. The remaining liquid is fractionated under reduced pressure (Note 4) to give 224–227 g. (82.2–83.4%) of 3-phenyl-1-propanol, b.p. 95–97°/0.4 mm. or 113–115°/3 mm., n_D^{20} 1.5268–1.5269, d_4^{20} 1.004–1.008.

2. Notes

1. The condenser should have a large bore to prevent flooding. A wide-sweep stirrer such as a Hershberg stirrer should be used, and the stirring motor must be capable of operating under heavy loads. The checkers suggest that the minimum size for the stirrer be 8-mm. glass rod.
2. The butanol should be freshly dried and distilled.
3. The addition must be as rapid as possible. An additional 100 to 400 ml. of toluene may have to be added to facilitate stirring.
4. A heated 35-cm. Vigreux column is recommended, but a Claisen flask can be used if care is taken. If a Claisen flask is used, the distillation must not be carried out too rapidly, particularly near the end, at which point some of the residue tends to codistil.

3. Discussion

Ethyl cinnamate has been reduced to 3-phenyl-1-propanol with sodium and ethanol,[2,3,4,5] hydrogen and copper chromite,[6] and sodium and ammonia.[7] The alcohol has also been prepared by reduction of the glyceride of cinnamic acid with sodium and amyl alcohol;[8] by reduction of cinnamic acid with lithium aluminum hydride;[9] by reduction of cinnamoyl chloride with sodium borohydride;[10] and by reduction of ethyl dihydrocinnamate with sodium and ethanol.[2,11] Cinnamaldehyde has been reduced to 3-phenyl-1-propanol with hydrogen and palladium.[12,13] platinum,[14,15,16] or nickel,[17,18,19,20] nickel in alkaline solution (no hydrogen),[21] lithium aluminum hydride,[22] electrolysis at a mercury[23] or lead[24] electrode, and with an unmentioned catalyst.[25] Reduction of cinnamyl alcohol to 3-phenyl-1-propanol has been effected by use of sodium and ethanol,[26] sodium amalgam and water,[27,28] hydrogen and nickel[29] or palladium,[30] sodium and ammonia,[31] and lithium aluminum hydride.[32] Other syntheses have been brought about by reduction of ethyl α,β-epoxy-β-phenyldihydrocinnamate with sodium and amyl alcohol;[33] by reduction of ethyl benzoylacetate with hydrogen and copper chromite;[34] by reduction of acetonephenyllactic acid with hydrogen and copper chromite;[35] by reaction of ethyl alcohol with sodium benzylate;[36] by reaction of benzylmagnesium chloride with a mixture of ethylene chlorohydrin and ethylmagnesium chloride;[37] by reaction of trimethylene oxide with phenylmagnesium bromide;[38] by condensation of benzylmagnesium chloride with ethylene oxide;[39] and by hydrogenolysis of 1-phenyl-1,3-propanediol over nickel-on-kieselguhr.[40]

The reduction of 4-phenyl-*m*-dioxane to give 3-phenyl-1-propanol, as described here, is based on the procedure of Beets,[41] who used sodium and diisobutylcarbinol. Other substituted *m*-dioxanes may also be converted to substituted 3-aryl-1-propanols by the same procedure.[42] 3-Phenyl-1-propanol also has been obtained in 85% yield by the reduction of 4-phenyl-*m*-dioxane over copper chromite catalyst.[43]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

glyceride of cinnamic acid

ethyl dihydrocinnamate

ethyl α,β-epoxy-β-phenyldihydrocinnamate

acetonephenyllactic acid

ethyl alcohol, ethanol (64-17-5)

sulfuric acid (7664-93-9)

ammonia (7664-41-7)

hydrogen (1333-74-0)

lead (7439-92-1)

mercury (7439-97-6)

platinum (7440-06-4)

butanol, 1-butanol (71-36-3)

nickel (7440-02-0)

toluene (108-88-3)

sodium (13966-32-0)

palladium (7440-05-3)

Ethylene oxide (75-21-8)

benzylmagnesium chloride (6921-34-2)

Phenylmagnesium bromide (100-58-3)

Ethyl cinnamate (103-36-6)

cinnamic acid (621-82-9)

ethylene chlorohydrin (107-07-3)

cinnamaldehyde

Trimethylene oxide (503-30-0)

amyl alcohol (71-41-0)

COPPER CHROMITE

Ethyl benzoylacetate (94-02-0)

cinnamyl alcohol (104-54-1)

lithium aluminum hydride (16853-85-3)

cinnamoyl chloride

3-Phenyl-1-propanol, 1-Propanol, 3-phenyl- (122-97-4)

sodium borohydride (16940-66-2)

sodium benzylate

ethylmagnesium chloride (2386-64-3)

1-phenyl-1,3-propanediol

diisobutylcarbinol (108-82-7)

4-Phenyl-m-dioxane (3141-24-0)

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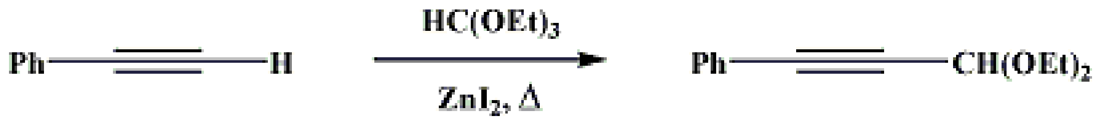
Organic Syntheses, CV 4, 801

PHENYLPROPARGYLALDEHYDE DIETHYL ACETAL

[Propiolaldehyde, phenyl-, diethyl acetal]



Submitted by B. W. Howk and J. C. Sauer[1].
Checked by N. J. Leonard and S. W. Blum.

1. Procedure

Into a 300-ml. three-necked flask equipped with a nitrogen inlet, a thermometer, and a short fractionating column (Note 1) are charged 74.1 g. (0.50 mole) of triethyl orthoformate, 51.0 g. (0.50 mole) of phenylacetylene (Note 2), and 3.0 g. of zinc iodide (Note 3). Ethanol is slowly distilled from the reaction mixture, which must be heated to about 135° before refluxing in the still-head begins. A total of 29–35 ml. of distillate, b p. 65–88° (mostly 78°), is collected over a period of about 1 hour as the temperature of the reaction mixture gradually rises to 200° to 210° (Note 4). The reaction mixture is cooled to room temperature and filtered with suction. The flask and the small amount of precipitate on the filter paper are washed with 5 ml. of ether. The filtrate and ether washings are combined and distilled. After a small fore-run, phenylpropargylaldehyde diethyl acetal is collected at 99–100°/2 mm. The yield is 73–80 g. (72–78%), n_D^{25} 1.5153–1.5158. The synthesis is applicable to the preparation of other propargyl aldehyde acetals (Note 5).

2. Notes

1. The checkers found a 12-inch Vigreux column satisfactory.
2. The checkers purchased phenylacetylene (p. 763) from Gesellschaft für Teerverwertung mbH., Duisburg-Meiderich, Germany.
3. The submitters report that zinc nitrate appears to be equivalent to zinc iodide as a catalyst and that zinc chloride (commercial anhydrous grade) is satisfactory but requires 2–3 hours of heating and gives 64–70% yield.
4. Yields are lower under forcing conditions of prolonged heating.
5. The method has been applied by the submitters[2] to the preparation of cyclohexylmethylpropiolaldehyde diethyl acetal (54% yield) from cyclohexylmethylacetylene and triethyl orthoformate; of phenylethynyl *n*-butyl dimethyl ketal (40% yield) from phenylacetylene and trimethyl *n*-orthovalerate; and of phenylethynyl methyl diethyl ketal (34% yield) from phenylacetylene and triethyl orthoacetate. *n*-Butylpropiolaldehyde diethyl acetal was isolated in

32% yield by heating an equimolar mixture of 1-hexyne and triethyl orthoformate containing catalytic amounts of a zinc chloride-zinc iodide catalyst under autogenous pressure at 190° for 3 hours.

3. Discussion

The described method of preparing phenylpropargylaldehyde diethyl acetal is that of Howk and Sauer.[2] The method for synthesizing phenylpropargylaldehyde diethyl acetal previously published in *Organic Syntheses*[3] involves three steps beginning with cinnamaldehyde; over-all yields are 49–62%. Other methods of preparative value are the interaction of the Grignard reagent of phenylacetylene with triethyl orthoformate, or the sodium derivative of phenylacetylene with either triethyl orthoformate or ethyl formate. These reactions are discussed critically by Raphael.[4] Phenylpropargylaldehyde diethyl acetal has also been made by the action of the phenyl Grignard reagent with the diethyl acetal of chloropropiolaldehyde.[5]

The acetylenic acetals are easily hydrolyzed to the corresponding aldehydes in high yields in the presence of dilute acids.[3,4] Acetylenic acetals have also been of value in the synthesis of α,β-unsaturated ethylenic acetals or aldehydes by partial catalytic hydrogenation of the triple bond.[4]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

phenylethynyl n-butyl dimethyl ketal

phenylethynyl methyl diethyl ketal

zinc chloride-zinc iodide

sodium derivative of phenylacetylene

diethyl acetal of chloropropiolaldehyde

ethanol (64-17-5)

ether (60-29-7)

zinc chloride (7646-85-7)

cyclohexylmethylacetylene (17715-00-3)

triethyl orthoformate (122-51-0)

ethyl formate (109-94-4)

cinnamaldehyde

Phenylacetylene (536-74-3)

1-Hexyne (693-02-7)

Phenylpropargylaldehyde diethyl acetal (6142-95-6)

Propiolaldehyde, phenyl-, diethyl acetal

zinc iodide

zinc nitrate (13778-30-8)

cyclohexylmethylpropiolaldehyde diethyl acetal

triethyl orthoacetate (78-39-7)

trimethyl n-orthovalerate (13820-09-2)

n-Butylpropiolaldehyde diethyl acetal (18232-30-9)

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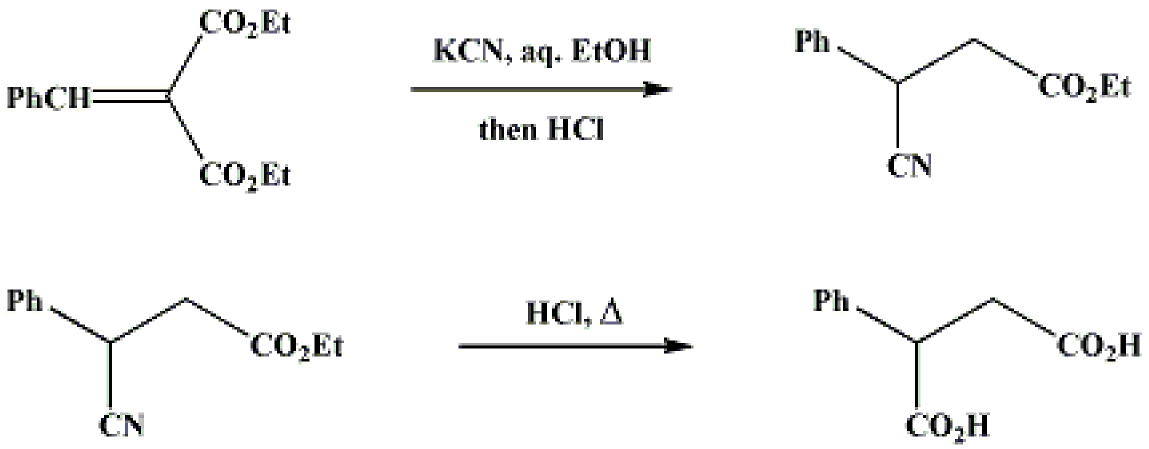
Organic Syntheses, CV 4, 804

PHENYLSUCCINIC ACID

[Succinic acid, phenyl-]



Submitted by C. F. H. Allen and H. B. Johnson[1].
Checked by H. R. Snyder, D. J. Mann, and Leonard E. Miller.

1. Procedure

Caution! This preparation should be conducted in a well-ventilated hood to avoid exposure to hydrogen cyanide.

A. *Ethyl β-phenyl-β-cyanopropionate.* In a 5-l. round-bottomed three-necked flask suspended in an oil bath and fitted with a mechanical stirrer, a reflux condenser, and a 250-ml. dropping funnel is placed a solution of 200 g. (0.81 mole) of diethyl benzalmalonate[2] in 2 l. of absolute ethanol. The stirrer is started, and a solution of 56 g. (0.86 mole) of potassium cyanide in 100 ml. of water is added rapidly from the separatory funnel; a small amount of the potassium cyanide precipitates. The temperature of the oil bath is raised to 70° and maintained at 65–75° for 18 hours.

The mixture is cooled to 15°, and the precipitated potassium bicarbonate is collected on a Büchner funnel. The solid (weight 70–72 g.) is washed on the funnel with 100 ml. of 95% ethanol. The combined filtrate and wash liquor is transferred to a 5-l. round-bottomed flask and made slightly acid *(Caution! (Note 1))* with dilute hydrochloric acid (about 15–20 ml. of the 10% acid is required). The solution is then concentrated under reduced pressure to a semi-solid residue (Note 1). The cooled residue is shaken with a mixture of 300 ml. of water and 500 ml. of ether. The material dissolves completely; the water layer is separated and washed with 200 ml. of ether. The ether solutions are combined, dried over 20 g. of calcium chloride, filtered into a 2-l. round-bottomed flask equipped with a glass joint, and concentrated by distillation (heating on a steam bath). The crude ethyl β-phenyl-β-cyanopropionate remains as a clear red oil

weighing 130–140 g. It is sufficiently pure for use in the next step (Note 2).

B. *Phenylsuccinic acid.* To the crude ester obtained above is added 500 ml. of concentrated hydrochloric acid (sp. gr. 1.19). The flask is fitted to a condenser (Note 3), and the mixture is heated under reflux for 18 hours (Note 4). At the end of this time only a small amount of red oil remains (Note 5). The mixture is cooled, and the nearly solid cake which forms is broken up and collected on a glass filter cloth (Note 5). The crude tan-colored phenylsuccinic acid is washed with 300 ml. of cold water and dried at 60°. It then weighs 105–110 g. (67–70%) and melts at 163–164° (Note 6) and (Note 7).

2. Notes

1. Since hydrogen cyanide may be liberated during the acidification and the subsequent concentration, both operations should be carried out in a well-ventilated hood.
2. The pure ester can be obtained by distillation under reduced pressure (b.p. 161–164°/8 mm.).
3. Glass-jointed equipment is required in this step. The flask with a glass joint was used in the preceding operation only to avoid the necessity of transferring the product after the evaporation.
4. Hydrogen chloride is evolved during the first part of the refluxing; it may be disposed of by absorption in water in a gas trap.[3]
5. The red, oily impurity usually distributes itself as a film on the surface of the liquid and as a lump at the bottom of the flask. It solidifies on cooling and is most conveniently removed as a solid; the thin crust on the surface is lifted with a spatula, and the lump at the bottom of the flask is left undisturbed when the product is collected on the filter.
6. The pure acid can be obtained by recrystallization from water. For each 10 g. of acid about 300 ml. of water and 0.5 g. of Norit are required. The recovery is 85–90% of pure white acid melting at 165.5–166°.
7. The checkers found the product at this stage to be of sufficient purity for conversion to phenylsuccinic anhydride.

3. Discussion

Preparative methods for phenylsuccinic acid have been listed in an earlier volume.[4] More recent procedures have been based on the hydrolysis of ethyl α-phenyl-β-cyanopropionate,[5] tetraethyl 1-phenyl-1,1,2,2-ethanetetracarboxylate,[6] diethyl (α-phenyl-β-nitroethyl) malonate,[7] and ethyl[8] or methyl 2,3-dicyano-3-phenylpropionate.[9]

The procedure given above is more economical of time and materials than that previously published.[4] Applications of the present method, due originally to Bredt and Kallen,[10] have been published.[11,12]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

calcium chloride (10043-52-4)

hydrogen chloride, hydrochloric acid (7647-01-0)

ether (60-29-7)

hydrogen cyanide (74-90-8)

potassium cyanide (151-50-8)

Norit (7782-42-5)

Phenylsuccinic acid, Succinic acid, phenyl- (635-51-8)

diethyl benzalmalonate (5292-53-5)

potassium bicarbonate (298-14-6)

Ethyl β-phenyl-β-cyanopropionate (14025-83-3)

phenylsuccinic anhydride (1131-15-3)

ethyl α-phenyl-β-cyanopropionate

tetraethyl 1-phenyl-1,1,2,2-ethanetetracarboxylate

diethyl (α-phenyl-β-nitroethyl) malonate

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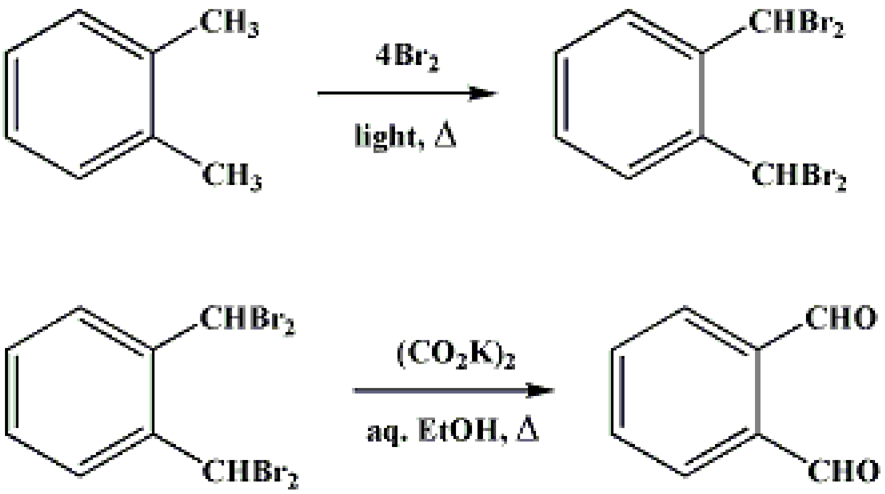
Organic Syntheses, CV 4, 807

o-PHTHALALDEHYDE

[Phthalaldehyde]



Submitted by J. C. Bill and D. S. Tarbell[1].
Checked by Arthur C. Cope and Harris E. Petree.

1. Procedure

This preparation should be conducted in a hood, and rubber gloves should be worn, to avoid exposure to bromine as well as the by-product o-xylylene dibromide which is a lachrymator and skin irritant.

A. α,α,α',α'-*Tetrabromo-o-xylene*. In a 2-l. three-necked flask equipped with an oil-lubricated Trubore stirrer, a dropping funnel, a thermometer extending nearly to the bottom of the flask, and a reflux condenser (Note 1) attached to a gas absorption trap[2] is placed 117 g. (1.1 moles) of dry *o*-xylene (Note 2). An ultraviolet lamp such as a General Electric R.S. Reflector Type 275-watt sun lamp is placed about 1 cm. from the flask so as to admit the maximum amount of light. The stirrer is started, and the *o*-xylene is heated to 120° with an electric heating mantle. A total of 700 g. (4.4 moles) of bromine (N.F. grade) is added in portions from the dropping funnel to the reaction flask at such a rate that the bromine color is removed as fast as it is added. After approximately one-half of the bromine has been added, the temperature is slowly increased to 175° for the remainder of the addition; the mixture becomes very dark toward the end of the reaction. The bromine can be added rapidly at first, but toward the end it must not be added at a rate exceeding 4–5 drops per minute in order to avoid loss of a visible amount of bromine with the evolved hydrogen bromide. After all the bromine has been added (10–14 hours), the mixture is illuminated and stirred at 170° for 1 hour. After removal of the stirrer, etc., the mixture is cooled and allowed to stand overnight to crystallize in the reaction flask exposed to the air.

The dark, solid tetrabromide is dissolved in 2 l. of hot chloroform (Note 3) and treated with 100 g. of 325-mesh Norit. The mixture is filtered with slight suction, the Norit is washed with hot chloroform, and the Norit treatment is repeated. The tancolored filtrate from the second Norit treatment is concentrated to 250–300 ml. by distillation under reduced pressure and chilled to 0°. The solid product is collected on a cold Büchner funnel and washed with a small amount of cold chloroform. The filtrate is concentrated further and cooled to obtain a second crop of crystals, which is purified by recrystallization from chloroform. The yield of the tetrabromide obtained from the first crop (white) and second crop after recrystallization (light tan) is 344–370 g. (74–80%), m.p. 115–116°.

B. *o-Phthalaldehyde.* The α,α,α',α'-tetrabromo-*o*-xylene (344–370 g.) obtained as described above, part A, is placed in a 5-l. round-bottomed flask with 4 l. of 50% (by volume) ethanol and 275 g. of potassium oxalate. The mixture is heated under reflux for 50 hours (a clear yellow solution is formed after 25–30 hours). About 1750 ml. of the ethanol is then removed by distillation (which is stopped before the product begins to steam-distil), and 700 g. of disodium monohydrogen phosphate dodecahydrate ($Na_2HPO_4 \cdot 12H_2O$) is added to the aqueous residue. The mixture is steam-distilled rapidly (Note 4), using an efficient condenser, until 10–12 l. of distillate is collected and the distillate no longer gives a black color test for *o*-phthalaldehyde[3] when a portion is treated with concentrated ammonium hydroxide followed by glacial acetic acid. The distillate is then saturated with sodium sulfate at room temperature and divided into portions of approximately 4 l.; each portion is extracted first with 200 ml. and then with six 100-ml. portions of ethyl acetate. The combined ethyl acetate extracts are dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue is crystallized from 90–100° ligroin, and a second crop is obtained by concentration of the mother liquor. The total yield of *o*-phthalaldehyde, m.p. 55.5–56°, is 87–94 g. (74–80% based on the tetrabromide, or 59–64% based on *o*-xylene).

2. Notes

1. Best results are obtained if an all-glass apparatus with ground-glass connections is used, as noted by Wawzonek and Karll.[4]
2. Pure commercial *o*-xylene (99% or higher purity) is dried by distillation until the distillate shows no further turbidity, and the residue is used.
3. The chloroform is allowed to stand over anhydrous calcium chloride overnight to remove water and ethanol.
4. The submitters state that the steam distillation is much more efficient if superheated (175–180°) steam is used, in which case special care must be taken to condense all the distillate.

3. Discussion

o-Phthalaldehyde has been made by the action of potassium hydroxide on *o*-(dichloromethyl)benzaldehyde,[5] by the hydrolysis of α,α,α',α'-tetrachloro-*o*-xylene,[6] by the hydrolysis of the α,α,α',α'-tetraacetate of *o*-phthalaldehyde,[3] by the oxidation of α,α'-dihydroxy-*o*-xylene with selenium dioxide[7] or N-chlorosuccinimide,[8] and by the reduction of phthalic acid N-methylanilide with diisobutylaluminum hydride.[9] The present method is essentially that of Thiele and Günther.[10,11] Hydrolysis of the tetrabromide may also be carried out by treatment with fuming sulfuric acid followed by water.[12] For small-scale preparations of *o*-phthalaldehyde the reduction of N,N,N',N'-tetramethylphthalamide with lithium aluminum hydride is the method of preference.[13]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ligroin

o-phthalaldehyde

α,α,α',α'-tetraacetate of o-phthalaldehyde

ethanol (64-17-5)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

ethyl acetate (141-78-6)

chloroform (67-66-3)

hydrogen bromide (10035-10-6)

bromine (7726-95-6)

sodium sulfate (7757-82-6)

Norit (7782-42-5)

selenium dioxide (7446-08-4)

potassium hydroxide (1310-58-3)

ammonium hydroxide (1336-21-6)

lithium aluminum hydride (16853-85-3)

PHTHALALDEHYDE (643-79-8)

N-chlorosuccinimide (128-09-6)

diisobutylaluminum hydride (1191-15-7)

o-Xylylene dibromide (91-13-4)

Tetrabromo-o-xylene

potassium oxalate

disodium monohydrogen phosphate dodecahydrate (10039-32-4)

phthalic acid N-methylanilide

α,α'-dihydroxy-o-xylene (612-14-6)

o-Xylene (95-47-6)

o-(dichloromethyl)benzaldehyde

α,α,α',α'-tetrabromo-o-xylene (13209-15-9)

α,α,α',α'-tetrachloro-o-xylene

N,N,N',N'-tetramethylphthalamide

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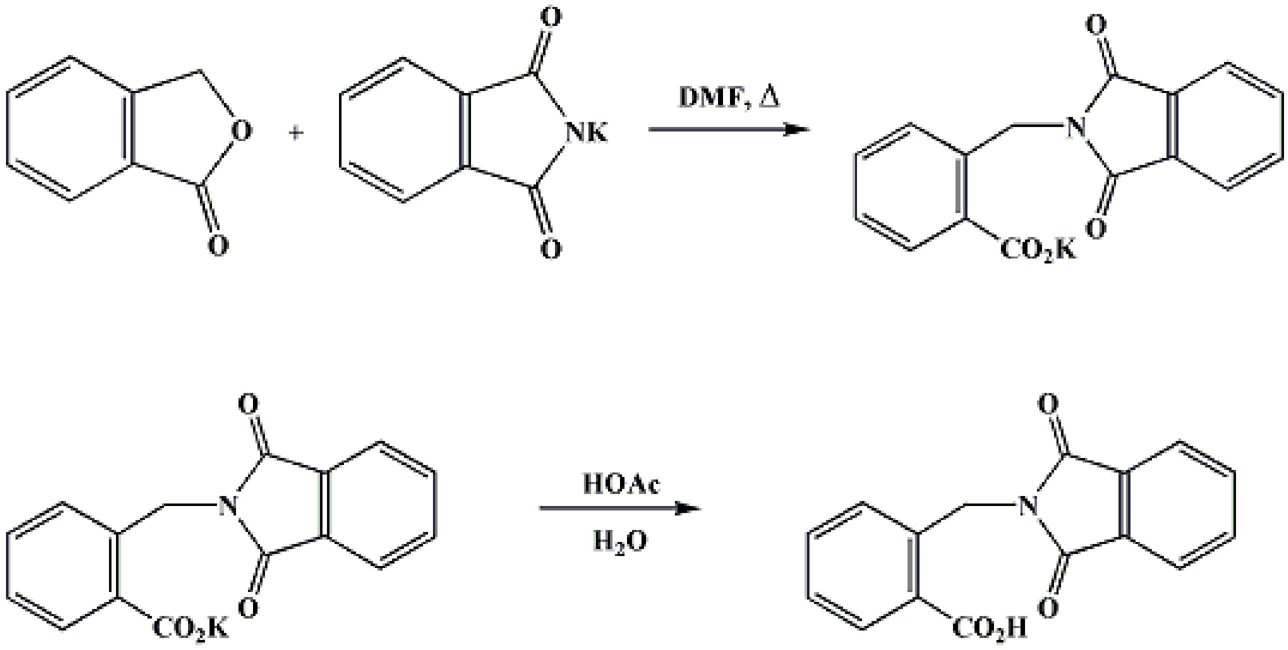
Organic Syntheses, *CV 4, 810*

α-PHTHALIMIDO-*o*-TOLUIC ACID

[*o*-Toluic acid, α-phthalimido-]



Submitted by J. Bornstein, P. E. Drummond, and S. F. Bedell[1].
Checked by John C. Sheehan and Y. L. Yeh.

1. Procedure

A 2-l. three-necked round-bottomed flask, fitted with a sealed stirrer and a reflux condenser carrying a drying tube, is charged with 100 g. (0.75 mole) of phthalide (Note 1), 150 g. (0.81 mole) of potassium phthalimide (Note 2), and 500 ml. of dimethylformamide (Note 3). The stirred suspension is heated under reflux by means of an electric mantle for 5 hours; the deep blue solution is then cooled to room temperature (Note 4). A solution of 300 ml. of glacial acetic acid in 500 ml. of water is added in one portion to the stirred reaction mixture, and the resulting yellow suspension, which becomes slightly warm, is stirred for an additional 30 minutes.

The precipitate is separated by suction filtration, pressed on the funnel, and washed successively with three 100-ml. portions of water and two 100-ml. portions of 95% ethanol. The product is transferred to a 1-l. Erlenmeyer flask, boiled for 10 minutes with 400 ml. of 60% ethanol with occasional stirring, filtered hot, washed twice with 50-ml. portions of 95% ethanol, and then dried in an oven at 90–100° for 6–12 hours. The crude α-phthalimido-*o*-toluic acid, which weights 140–155 g., is divided into two equal portions, and each portion is dissolved in boiling propionic acid (Note 5). Each solution is treated with 1 tablespoon of Norit and filtered through an electrically heated gravity funnel. The filtrates are allowed to cool slowly to room temperature and are then refrigerated overnight. The crystals from the two portions are collected by suction filtration in one funnel and washed on the funnel with 400 ml. of 95% ethanol. The product is dried over potassium hydroxide in a vacuum desiccator. The yield of nearly white crystals of α-phthalimido-*o*-toluic acid is 126–141 g. (60–67% based on phthalide), m.p. 265.0–266.5°.

2. Notes

1. The phthalide was prepared according to *Organic Syntheses*[2] and was also purchased from Aldrich Chemical Company. The commercial product (200 g.) was recrystallized in 50-g. portions from 1.5 l. of water, the mother liquor from the first crop being employed for recrystallization of the subsequent portions. Each portion was treated with 2 tablespoons of Norit, filtered hot, allowed to cool to room temperature with occasional stirring, and then cooled to 5° before collecting the crystals which were washed on the funnel with small quantities of cold water. Final drying was effected in a vacuum desiccator containing phosphorus pentoxide.

2. Eastman Kodak Company potassium phthalimide (200 g.) was digested with 450 ml. of boiling acetone for 15 minutes, filtered hot, washed on the funnel with 100 ml. of acetone, and dried at 100° for 6 hours.

3. The dimethylformamide was obtained from Eastman Kodak Company and was used without further purification.

4. The reaction mixture is most conveniently cooled by allowing it to stand at room temperature overnight. Occasionally the potassium salt of α-phthalimido-*o*-toluic acid precipitates at this point, but this does not interfere with the subsequent operations.

5. Approximately 1.33 l. of propionic acid is required for 78 g. of the crude α-phthalimido-*o*-toluic acid. Glacial acetic acid may be used as the solvent, but considerably larger volumes are required than when propionic acid is employed. This step should be carried out in a hood, since hot propionic acid vapors are very irritating.

3. Discussion

The present procedure is that described by the submitters.[3] α-Phthalimido-*o*-toluic acid has also been prepared by the acidolysis of the corresponding ethyl ester, obtained from the reaction of ethyl α-bromo-*o*-toluate with potassium phthalimide.[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 951

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

acetic acid (64-19-7)

propionic acid (79-09-4)

acetone (67-64-1)

Norit (7782-42-5)

potassium hydroxide (1310-58-3)

Potassium Phthalimide (1074-82-4)

Phthalide (87-41-2)

dimethylformamide (68-12-2)

phosphorus pentoxide (1314-56-3)

α-Phthalimido-o-toluic acid, o-Toluic acid, α-phthalimido- (53663-18-6)

ethyl α-bromo-o-toluate

potassium salt of α-phthalimido-o-toluic acid

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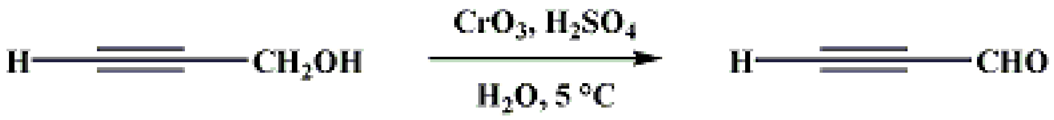
Organic Syntheses, CV 4, 813

PROPIOLALDEHYDE



Submitted by J. C. Sauer[1]
Checked by John C. Sheehan and E. R. Gilmont.

1. Procedure

Caution! Propiolaldehyde is a lachrymator.

A 3-l. three-necked round-bottomed flask is fitted with a thermometer, a graduated dropping funnel (Note 1), a stirrer (Note 2), a fine capillary tube for introducing nitrogen near the bottom of the flask, and an exit tube attached through a manometer to three traps set in series. In the flask are placed 360 ml. of 33% (by volume) propargyl alcohol [112.1 g. (120 ml., 2.0 moles)] (Note 3) and a cooled solution of 135 ml. of sulfuric acid and 200 ml. of water. The flask is cooled in an ice-salt mixture. While the contents of the flask are cooling, the first trap is cooled to about −15° with acetone and Dry Ice. The last two traps in the series are cooled to −78° with acetone and Dry Ice (Note 4). The pressure in the system is reduced to 40–60 mm., nitrogen is introduced through the capillary, and the mixture is stirred vigorously. A solution of 210 g. of commercial chromium trioxide (2.1 moles) in 400 ml. of water and 135 ml. of sulfuric acid is added dropwise in the course of about 3 hours while maintaining a reaction temperature of 2–10°. After the addition of the chromium trioxide, the ice bath is removed, and the flask is permitted to warm to room temperature while the pressure is gradually lowered to 14–20 mm. to remove the last of the aldehyde. The condensates of the three traps are combined (Note 5) and dried over anhydrous magnesium sulfate. The propiolaldehyde is distilled through a 16-in. column packed with platinum gauze. The fraction distilling at 54–57° weighs 38–44 g. (35–41%), n_D^{25} 1.4050 (Note 6) and (Note 7).

2. Notes

1. The end of the dropping funnel extends about 2 in. into the flask from the opening and is drawn into a capillary. This is done to ensure the introduction of the chromic acid solution in the form of small droplets.

2. A "Trubore" stirring system with a 29/26 joint was used for stirring under vacuum.

3. Propargyl alcohol is available from the General Aniline and Film Corporation, Easton, Pennsylvania.

4. If the cooling bath for the first trap is lowered much below −15°, plugging of

the trap is likely to occur. These traps are connected so that the vapor enters the larger, annular space, impinging on the cold wall before entering (and possibly plugging) the smaller inner tube.

5. The material in the first trap contains a considerable amount of water. In order to facilitate separation, the checkers saturated this mixture with sodium chloride. The upper layer, consisting of nearly pure propiolaldehyde, was combined with the contents of the second and third traps and dried over 5 g. of anhydrous magnesium sulfate. Distillation through a 12-in. vacuum-jacketed Vigreux column gave directly propiolaldehyde comparable in yield and quality with the final product described by the submitter in (Note 6).

6. Considerable water is carried into the traps, and the distillate contains 3–10% water. The last of the water can be removed by drying the distillate a second time over magnesium sulfate and redistilling. In this way there is obtained 30–37 g. (28–34%) of propiolaldehyde distilling at 55–56°, n_D^{25} 1.4032–1.4034.

7. The material should be stored in glass-stoppered bottles, since contaminants from rubber stoppers may be sufficient to catalyze decomposition. A sample of propiolaldehyde underwent no noticeable change after four months' storage in a Dry Ice chest. However, this aldehyde undergoes extremely vigorous polymerization or decomposition in the presence of alkalies. For example, propiolaldehyde undergoes a change with almost explosive force in the presence of pyridine. Accordingly, *exceptional care should be used in the handling of propiolaldehyde.*

3. Discussion

The procedure described is that of Wille, Saffer, and Weisskopf.[2] Propiolaldehyde also has been prepared by the oxidation of propargyl alcohol using ammonium dichromate,[3] potassium dichromate,[4] or manganese dioxide in sulfuric acid.[5] In addition, it has been obtained by the electrolytic oxidation of propargyl alcohol[6] and by warming the dimethyl or diethyl acetal of propiolaldehyde with dilute sulfuric acid.[7]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

dimethyl or diethyl acetal of propiolaldehyde

sulfuric acid (7664-93-9)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

acetone (67-64-1)

pyridine (110-86-1)

chromic acid (7738-94-5)

manganese dioxide (1313-13-9)

potassium dichromate (7778-50-9)

magnesium sulfate (7487-88-9)

chromium trioxide (1333-82-0)

ammonium dichromate

Propiolaldehyde (624-67-9)

propargyl alcohol (107-19-7)

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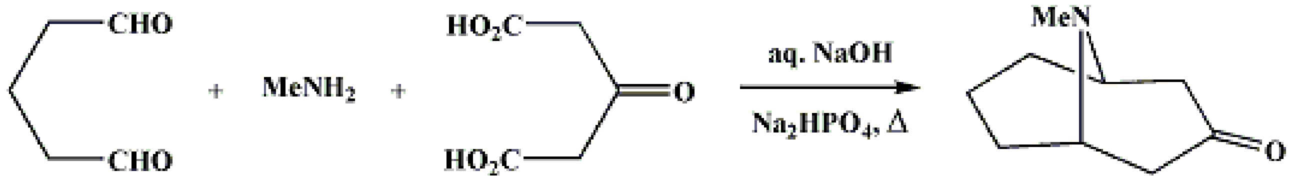
Organic Syntheses, CV 4, 816

PSEUDOPELLETIERINE



Submitted by Arthur C. Cope, Hugh L. Dryden, Jr., and Charles F. Howell[1].
Checked by N. J. Leonard, D. F. Morrow, and W. D. Smart.

1. Procedure

In a 3-l. round-bottomed flask equipped with a mechanical stirrer and flushed with a slow stream of nitrogen are placed 22 ml. (0.26 mole) of concentrated hydrochloric acid (sp. gr. 1.18), 165 ml. of "deoxygenated" water (Note 1), and 64 g. (0.5 mole) of 2-ethoxy-3,4-dihydro-2H-pyran (b.p. 62–65°/50 mm., n_D^{25} 1.4378) (Note 2). The mixture is stirred vigorously for 20 minutes and then allowed to stand for 1 hour.

To the resulting colorless solution of glutaraldehyde are added, in order, 350 ml. of water, 50 g. (0.74 mole) of commercial methylamine hydrochloride dissolved in 500 ml. of water, 83 g. (0.57 mole) of acetonedicarboxylic acid (Note 3) dissolved in 830 ml. of water, and a solution of 88 g. (0.25 mole) of disodium hydrogen phosphate dodecahydrate and 7.3 g. (0.18 mole) of sodium hydroxide dissolved in 200 ml. of water by heating. Carbon dioxide is evolved, and the pH of the solution, initially 2.5, increases to 4.5 after the mixture has been stirred under nitrogen for 24 hours. Concentrated hydrochloric acid (33 ml.) is added, and the solution is heated on the steam bath for 1 hour to complete the decarboxylation (Note 4). After the solution has been cooled to room temperature, 75 g. of sodium hydroxide in 100 ml. of water is added (Note 5), and the basic mixture is extracted with eight 250-ml. portions of methylene chloride (Note 6). The combined methylene chloride extracts are dried over sodium sulfate, concentrated to about 500 ml. (Note 7), and filtered through a layer of 400 g. of alumina (Note 8) packed in a 50-mm. column. The column is eluted with methylene chloride until about 1.5 l. of eluate has been collected. The eluate is concentrated under reduced pressure to yield crystalline but yellow pseudopelletierine. The solid is sublimed at 40° and 0.3 mm. to yield 47–55.5 g. (61–73%) of crude, nearly colorless pseudopelletierine (Note 9). The product is dissolved in 100 ml. of boiling pentane, 3 ml. of water is added, and the mixture is boiled until the aqueous layer disappears. After thorough chilling in a refrigerator, the crystals which separate are collected on a filter and washed well with ice-cold pentane. Evaporation of the combined filtrate and washings to 20 ml., followed by filtration and washing, yields a second crop of almost equally pure material. The combined pseudopelletierine hemihydrate weighs 47–55 g. and melts at 47–48.5°. Sublimation of the hemihydrate as described above removes the water of hydration and yields 44–52 g. (58–68%) of pure, colorless pseudopelletierine, m.p. 63–64° (sealed tube). Anhydrous material which has been prepared in this manner does not decompose on storage

under dry conditions.

2. Notes

1. "Deoxygenated" water is prepared by passing a stream of nitrogen through ordinary distilled water and is used throughout the preparation until the condensation has been completed. The use of ordinary distilled water may lower the yield by no more than a few per cent.
2. This compound is prepared by the addition of ethyl vinyl ether to acrolein, under conditions similar to those described for a similar addition of methyl vinyl ether to crotonaldehyde (p. 311); see Longley and Emerson, *J. Am. Chem. Soc.*, **72**, 3079 (1950). Glutaraldehyde is available currently as a 30% aqueous solution from Carbide and Carbon Chemicals Company, 30 East 42nd Street, New York.
3. The preparation of acetonedicarboxylic acid is described in *Org. Syntheses Coll. Vol.* **1**, 10 (1941). The acid may also be obtained from Chas. Pfizer & Company, 630 Flushing Avenue, Brooklyn 6, New York.
4. Omission of the decarboxylation step decreases the yield of crude material to 57%. The temperature should reach about 80°.
5. The pH rises to about 12. A lower pH allows extraction of more of the dark-brown resin. The extraction must be performed promptly since the product can undergo self-condensation at this pH.
6. The employment of ether instead of methylene chloride requires the use of a continuous extractor for 2 days.
7. The checkers found that the purification of the pseudopelletierine could be simplified, at least in those preparations in which commercial acetonedicarboxylic acid was used. Thus, the crude product obtained by evaporation to dryness of the methylene chloride extracts can be sublimed directly. Two sublimations give pseudopelletierine of m.p. 62–64°, in 58–62% yield, comparable to the product obtained after the more extended purification procedure described in the text.
8. Chromatographic alumina (400 g.) is treated with 500 ml. of ethyl acetate at room temperature. After 48 hours, the alumina is collected on a filter and washed first with 1 l. of distilled water and then with 1 l. of methanol. After drying in air, the alumina is activated by heating at 120° for 3 hours at 50–100 mm.
9. Resublimation directly may serve for the final purification (Note 7). Distillation is inconvenient because of the tendency of pseudopelletierine to crystallize in the condenser. The distilled product darkens rather rapidly even in the cold and melts at 47–53°. The once sublimed product also darkens slowly even when kept under dry nitrogen in a refrigerator. If anhydrous pseudopelletierine is exposed to moist air, the hemihydrate is formed, m.p. about 48°.

3. Discussion

Pseudopelletierine has been obtained from the bark of the pomegranate tree (*Punica granatum* L.).[2,3,4,5] The synthesis of the alkaloid from glutaraldehyde, methylamine, and calcium acetonedicarboxylate was first achieved by Menzies and Robinson.[6] The synthetic method subsequently was improved by Schöpf and Lehmann,[7] and others.[8,9] The condensation of a dialdehyde with an amine and acetonedicarboxylic acid to form a heterobicyclic compound (an alkaloid or alkaloid analog, usually employing mild or so-called "physiological" conditions) is sometimes referred to as a Robinson-Schöpf synthesis.

The experimental procedure described is essentially one reported by Ziegler and Wilms[8] as

subsequently modified,[9] except that the glutaraldehyde is prepared from 2-ethoxy-3,4-dihydro-2H-pyran instead of cyclopentene ozonide[8] or pyridine via dihydropyridine and glutaraldehyde dioxime.[9] Essentially these procedures have been reported briefly by other investigators.[10] Pseudopelletierine also has been prepared by the Dieckmann condensation of 1-methyl-2,6-piperidinediacetic acid diethyl ester with sodium.[11]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Pseudopelletierine

pseudopelletierine hemihydrate

cyclopentene ozonide

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether (60-29-7)

sodium hydroxide (1310-73-2)

Acetonedicarboxylic acid

Acrolein (107-02-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

pyridine (110-86-1)

sodium (13966-32-0)

Pentane (109-66-0)

Methylamine hydrochloride (593-51-1)

methylamine (74-89-5)

methylene chloride (75-09-2)

crotonaldehyde (123-73-9)

methyl vinyl ether (9003-09-2)

ethyl vinyl ether (109-92-2)

glutaraldehyde (111-30-8)

disodium hydrogen phosphate dodecahydrate (10039-32-4)

2-ethoxy-3,4-dihydro-2H-pyran

calcium acetonedicarboxylate

dihydropyridine

glutaraldehyde dioxime

1-methyl-2,6-piperidinediacetic acid diethyl ester

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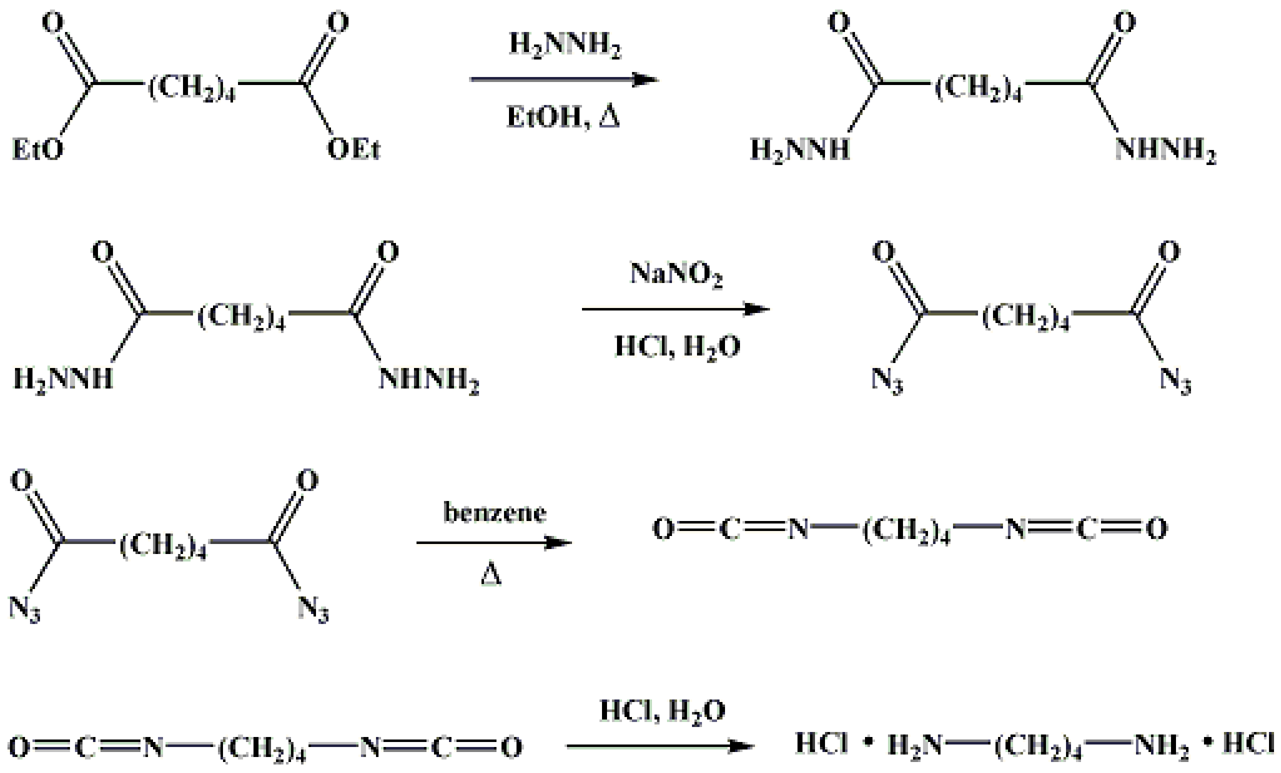
Organic Syntheses, CV 4, 819

PUTRESCINE DIHYDROCHLORIDE

[1,4-Butanediamine dihydrochloride]



Submitted by Peter A. S. Smith[1]
Checked by James Cason and Wm. DeAcetis.

1. Procedure

A. *Adipyl hydrazide.* A solution of 120 ml. of 85% aqueous hydrazine hydrate (105 g., 2.0 moles) (Note 1) and 25 ml. of absolute ethanol is brought to a gentle boil in a 500-ml. three-necked flask provided by means of ground glass joints with a ball joint-sealed mechanical stirrer (Note 2), a reflux condenser, and a dropping funnel. One hundred and one grams (0.5 mole) of diethyl adipate[2] is added dropwise to the boiling stirred solution at such a rate that a separate liquid phase does not accumulate in the reaction mixture (Note 3). This operation requires 1–2 hours, at the end of which time the contents of the flask will have largely crystallized. The boiling is continued for 5 minutes after the completion of the addition, and the contents of the flask are then cooled to room temperature with running water. The crystals are washed onto a Büchner funnel with the aid of about 100 ml. of absolute ethanol used in several portions. The precipitate is dried by suction, and the product is washed once with 25 ml. of ether. After drying in air (or at 100°) the adipyl hydrazide weighs 77–80 g. (88–92%) and is of good quality, with a melting point about 170° (Note 4). Concentration of the filtrate to a volume of about 25 ml. in an air stream on a steam bath yields an additional 2.5 g. of nearly pure material; total yield 91–95%.

B. *Putrescine dihydrochloride.* A 2-l. wide-mouthed Erlenmeyer flask containing 200 ml. of concentrated hydrochloric acid and 400 g. of cracked ice is clamped in an ice-salt bath and

provided with an efficient stirrer (inefficient stirring may lower the yield). The stirring is started, and 80 g. (0.46 mole) of adipyl hydrazide is added all at once, followed by 500 ml. of ether (Note 5). While the temperature is maintained below 10° (Note 6), a solution of 80 g. (1.15 moles) of sodium nitrite in 150 ml. of water is added over about 30 minutes through a dropping funnel whose stem reaches below the bottom of the ether layer, but not into the path of the stirrer. *The operations in the next paragraph should be conducted without delay after the completion of the addition of the nitrite.*

The cold reaction mixture, which may be freed from suspended solid by rapid filtration through a cotton plug, is transferred to a 2-l. or 3-l. separatory funnel, and the aqueous layer is drawn off into the original reaction flask. The ether layer is poured into a 2-l. Erlenmeyer flask containing about 50 g. of anhydrous calcium chloride, and this flask is placed in the ice bath in which the diazotization was run. The cold aqueous layer is then extracted with two 100-ml. portions of chilled ether, which are combined with the first ether extract. After 5 minutes with occasional swirling, the ether solution of adipyl azide (Note 7) is sufficiently dry, and it is poured into a 2-l. round-bottomed flask containing 350–400 ml. of benzene (Note 8). The calcium chloride is rinsed with a 50-ml. portion of ether, which is added to the same flask.

The ether is distilled gently from a steam bath, preferably through a short fractionating column; nitrogen will be evolved at the same time. When the volume of the contents of the flask has reached about 400 ml., the flask is heated strongly on the steam bath for about 15 minutes to complete the decomposition of the azide (Note 9). The flask is removed from the steam bath, and 200 ml. of concentrated hydrochloric acid is added cautiously to the hot solution (Note 10). The flask is allowed to stand with occasional swirling until the carbon dioxide evolution has ceased (about 15 minutes). The mixture is heated strongly on a steam bath for about 15 minutes more, and the solvents are then distilled from a steam bath under aspirator vacuum (Note 11). When the contents of the flask have become a crystalline paste, the vacuum is temporarily disconnected, and the inner walls of the flask are washed down with about 50 ml. of ethanol. The vacuum is renewed cautiously, and the mixture is distilled to dryness (Note 12).

The residue of crystalline putrescine dihydrochloride is rinsed onto a Büchner funnel with the aid of 100–200 ml. of absolute ethanol used in several portions. The last portions of ethanol are used as wash liquid for the crystals. The crystals are finally pressed dry and washed with 25 ml. of ether. The air-dried product weighs 53–55 g. (72–74%) and melts above 275°. Analysis for chlorine indicates that the salt is anhydrous. Concentration of the filtrate to a volume of about 25 ml. yields an additional 1–2 g.; total yield 73–77%. The entire synthesis may be completed in one day.

2. Notes

1. Eastman Kodak Company practical grade was used.
2. Mechanical stirring is not strictly necessary; however, severe bumping is sometimes encountered if it is not used. Hydrazine attacks both cork and rubber. If a dropping funnel with ground glass joint is not available, an ordinary dropping funnel may be placed at the top of the reflux condenser.
3. If unreacted ester is allowed to accumulate, some secondary hydrazide may be formed, with consequent loss of yield in the next step.

4. The melting point of adipyl hydrazide reported in the literature[3] is 171°; however, values as high as 179° have been observed. The checkers observed values of 174–177° and 179–181° for products of two runs, when the crystals were placed on a hot stage after the temperature had reached 160°.
5. Ethanol-free ether should be used. Dropwise addition of 50 ml. of concentrated sulfuric acid to 1 l. of ether, and distillation of the ether from a steam bath gives a satisfactory solvent.
6. To maintain this temperature at the rate of addition of the nitrite indicated will probably require the occasional addition of cracked ice to the reaction mixture. Only occasional checking of the temperature is necessary. If the temperature is kept below 0°, slightly better yields are obtained. The addition of Dry Ice directly to the ether layer accomplishes this easily. Temperatures above 10° cause a loss in yield, but apparently create no hazard.
7. Ethereal solutions of adipyl azide are quite safe, but the free azide is somewhat explosive and should not be isolated. If storage of an intermediate is desired, the azide should be converted to the urethane by the procedure given below. The urethane is quite stable to storage; also, the procedure *via* the urethane gives improved yields in some amine syntheses.
The dried ethereal solution of adipyl azide is added to a 2-l. flask containing 400 ml. of absolute ethanol, and the ether and some of the ethanol are distilled on a steam bath through a short fractionating column. When the volume has reached about 200 ml., the solution may be poured into a 500-ml. Erlenmeyer flask, and the remainder of the solvents removed on a steam bath by means of an air stream. The residual, waxy, crystalline cake of N,N'-dicarbethoxyputrescine weighs 84–91 g. (79–85%) and melts at 76–81°. It may be kept indefinitely.
If the urethane is to be hydrolyzed immediately, there is no need to isolate it. Instead, after distillation of most of the ether and alcohol from the flask in which the urethane is formed, 700 ml. of concentrated hydrochloric acid is added, and the mixture is heated under reflux for 4 hours. The solution is then distilled from a steam bath under aspirator vacuum (Note 11), and the putrescine dihydrochloride is isolated as described above. The total yield is 55–57 g. (74–77%).
The isolated urethane may be hydrolyzed by this procedure at any time. For the hydrolysis step, the yield is 89–91%.
8. Commercial benzene may be used.
9. The rearrangement of the azide is complete when nitrogen evolution ceases. This is usually concluded in the time indicated, but occasionally takes longer.
10. Carbon dioxide is evolved copiously at this point and may cause the solution to foam over if the acid is not added cautiously.
11. Alternatively, the solution may be poured into a 1-l. flask for this operation.
12. Solid putrescine dihydrochloride should not be heated unduly long at 100°, as it may turn pink.

3. Discussion

Putrescine dihydrochloride has been prepared by the Hofmann degradation of adipamide;[3,4,5] by the Curtius degradation of adipyl hydrazide through the urethane;[6] by the Curtius degradation of adipyl azide obtained from adipyl chloride and sodium azide;[7] by the Schmidt degradation of adipic acid with hydrogen azide;[8] by the reduction of succinonitrile,[9]

succinaldoxime,[10,11] or γ-phthalimidobutyronitrile[12,13] with sodium; from N-benzoyl-γ-iodobutylamine;[14] and by the hydrolysis of 1,4-di-(N-phthalimido)butane.[15]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether (60-29-7)

Adipic acid (124-04-9)

nitrogen (7727-37-9)

sodium nitrite (7632-00-0)

carbon dioxide (124-38-9)

chlorine (7782-50-5)

sodium (13966-32-0)

hydrazine hydrate (7803-57-8)

hydrazine (302-01-2)

sodium azide (26628-22-8)

γ-phthalimidobutyronitrile

adipyl chloride (111-50-2)

diethyl adipate (141-28-6)

Putrescine dihydrochloride, 1,4-Butanediamine dihydrochloride (333-93-7)

adipyl hydrazide (1071-93-8)

adipyl azide

adipamide (628-94-4)

hydrogen azide

succinonitrile (110-61-2)

succinaldoxime

N-benzoyl-γ-iodobutylamine

1,4-di-(N-phthalimido)butane

N,N'-dicarbethoxyputrescine

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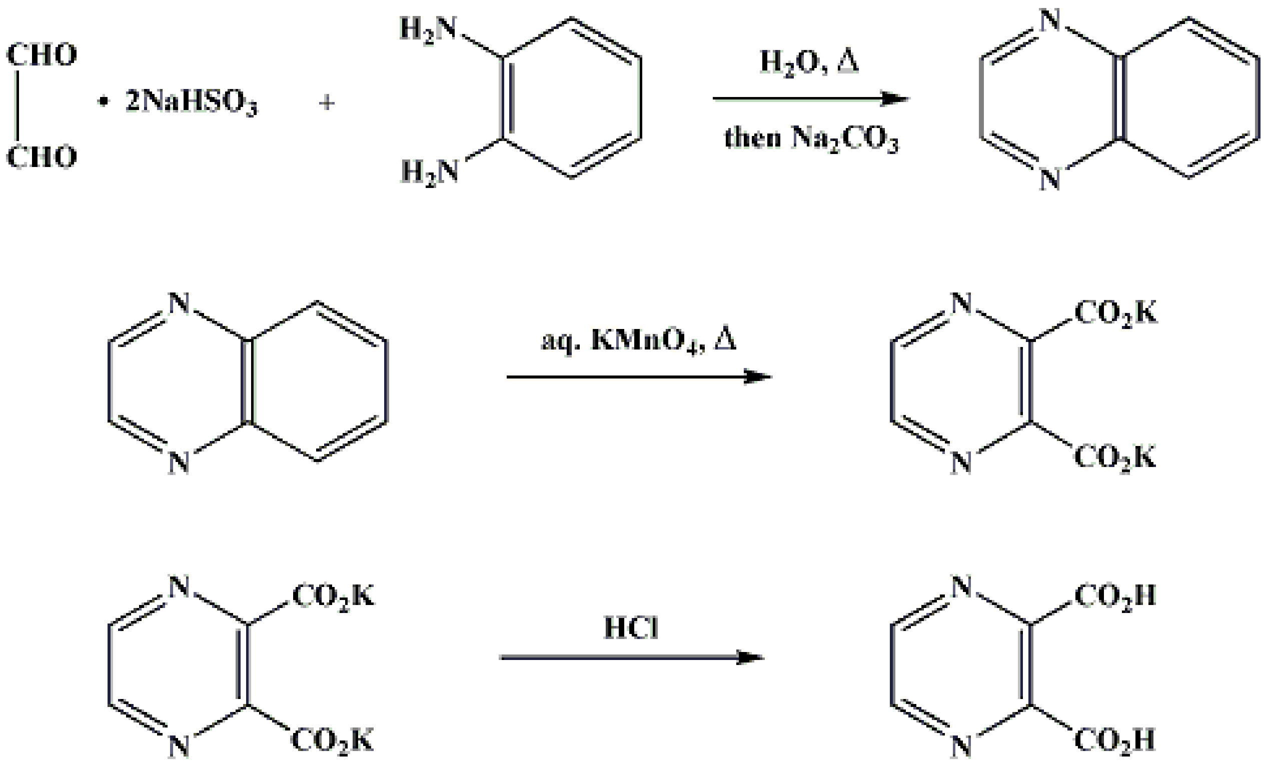
Organic Syntheses, CV 4, 824

2,3-PYRAZINEDICARBOXYLIC ACID



Submitted by Reuben G. Jones and Keith C. McLaughlin[1].
Checked by H. R. Snyder and R. E. Heckert.

1. Procedure

A. *Quinoxaline.* One hundred thirty-five grams (1.25 moles) of *o*-phenylenediamine[2] is dissolved in 2 l. of water, and the solution is heated to 70°. With stirring, a solution of 344 g. (1.29 moles) of glyoxal-sodium bisulfite[3] (Note 1) in 1.5 l. of hot water (about 80°) is added to the *o*-phenylenediamine solution. The mixture is allowed to stand for 15 minutes and then is cooled to about room temperature and 500 g. of sodium carbonate monohydrate (Note 2) is added. The quinoxaline separates as an oil or as a crystalline solid if the mixture is sufficiently cool. The mixture is extracted with three 300-ml. portions of ether. The combined extracts are dried over anhydrous magnesium sulfate or sodium sulfate, filtered, and concentrated on the steam bath. The residual liquid, consisting of almost pure quinoxaline, is distilled under reduced pressure, and the fraction boiling at 108–112°/12 mm. (m.p. 29–30°) is collected. It weighs 138–147 g. (85–90%) (Note 3).

B. *2,3-Pyrazinedicarboxylic acid.* A 12-l. three-necked flask is provided with an efficient mechanical stirrer, a reflux condenser, and a 1-l. dropping funnel. In the flask are placed 4 l. of hot (about 90°) water and 145 g. (1.12 moles) of quinoxaline. With rapid stirring a saturated aqueous solution of 1050 g. (6.6 moles) of potassium permanganate (Note 4) is added through the dropping funnel in a thin stream. The rate of addition of the

permanganate solution is adjusted so that the reaction mixture boils gently. The addition requires about 1.5 hours.

The reaction mixture is cooled somewhat (Note 5) and filtered through a large Büchner funnel. The manganese dioxide cake is removed from the funnel and stirred to a smooth paste with 1 l. of fresh water. The slurry is filtered, and the washing is repeated. The total filtrate, about 10 l., is evaporated under reduced pressure on the steam bath to a volume of approximately 3 l. (Note 6). The solution is swirled or stirred gently while 550 ml. (6.6 moles) of 36% hydrochloric acid is cautiously added (Note 7). Evaporation under reduced pressure is then continued until a moist cake of solid potassium chloride and 2,3-pyrazinedicarboxylic acid remains in the flask (Note 8).

The moist cake is scraped from the flask and allowed to dry in a 16-in. porcelain evaporating dish until the odor of hydrochloric acid is faint (about 24 hours, but this time can be reduced to about 8 hours if a gentle stream of air is directed onto the solid). The solid material is returned to the dried flask and mixed thoroughly with about 200 ml. of water. Two liters of acetone is added, and the mixture is boiled under reflux for 15 minutes, then cooled to room temperature and filtered through a 6-in. Büchner funnel. The solid on the filter is returned to the flask, treated with 100 ml. of water, and extracted with 1 l. of boiling acetone as before (Note 9). The acetone filtrates are combined and distilled from a steam bath, finally under diminished pressure.

The solid in the flask is dissolved by refluxing with 2.5 l. of acetone. The mixture is cooled slightly, treated with 10 g. of decolorizing carbon, refluxed for an additional 5-minute period, and filtered hot. Evaporation of the pale yellow acetone filtrate leaves the acid as a light-tan crystalline solid. If the product still possesses an odor of hydrochloric acid it is dried in a vacuum desiccator over sodium hydroxide pellets for a few hours. Finally the product is dried in an oven at 100° for several hours (Note 10) and (Note 11). The yield of material melting at 165–167° (dec.) is 140–145 g. (75–77%) (Note 12).

If a purer product is desired the material may be recrystallized (with about 17% loss) from 150 ml. of water; the hot solution is decolorized with carbon. The melting point after drying at 110° for several hours is then 183–185° (dec.) (Note 11) and (Note 13).

2. Notes

1. In the absence of sodium bisulfite, aqueous glyoxal solutions react with *o*-phenylenediamine to give only about 30% yields of quinoxaline together with large quantities of resinous by-products. Therefore, if an aqueous glyoxal solution is to be used in this preparation it should be mixed with a water solution of two molar equivalents of sodium bisulfite before it is added to the *o*-phenylenediamine solution.
2. Potassium carbonate or sodium hydroxide may also be used.
3. 2-Methylquinoxaline may be prepared in 88–92% yields from *o*-phenylenediamine and pyruvic aldehyde-sodium bisulfite by this same procedure.
4. The volume of this solution can be held to the minimum, about 3–5 l., by dissolving the permanganate in hot water (90–100°).

5. The only reason for cooling is to make the flask easier to handle during the filtration.
6. A 5-l. round-bottomed flask fitted with a separatory funnel for continuous addition of the solution during the concentration is convenient.
7. There is a vigorous evolution of carbon dioxide, and unless the acid is added slowly the contents of the flask may foam over.
8. Excess hydrochloric acid is present, and the 2,3-pyrazinedicarboxylic acid tends to darken and decompose if it is heated too strongly or for too long a time.
9. The ease with which the dicarboxylic acid is removed from the potassium chloride depends upon the amount of water present. The potassium chloride should be set aside for an additional extraction if the yield of the crude product is low.
10. Drying at 100° converts any of the hydrated 2,3-pyrazinedicarboxylic acids to the anhydrous form.
11. The product darkens somewhat on heating.
12. 2-Methyl-5,6-pyrazinedicarboxylic acid may be prepared in 70–75% yields from 2-methylquinoxaline by this same procedure. The crude acid (m.p. 155–160°, dec) is somewhat unstable at elevated temperatures. It should not be heated above 100° for long periods of time. In order to obtain pure 2-methyl-5,6-pyrazinedicarboxylic acid (m.p. 175°, dec.) the crude product is best recrystallized from acetone.
13. The melting point is dependent on the rate of heating and the temperature of the bath at the time the sample is inserted. The figure given was obtained by insertion of the sample tube into a bath at 160°.

3. Discussion

Quinoxaline has been prepared by the reaction of glyoxal with *o*-phenylenediamine,[4] and 2-methylquinoxaline by the reaction of pyruvic aldehyde[5] or isonitrosoacetone[6] with *o*-phenylenediamine. 2,3-Pyrazinedicarboxylic acid has been prepared by the permanganate[7] or electrolytic[8] oxidation of quinoxaline. 2-Methyl-5,6-pyrazinecarboxylic acid has been obtained from 2-methylquinoxaline in the same way.[6,9] Also, the monopotassium salt of pyrazine-2,3-dicarboxylic acid has been prepared by the oxidation of quinoxaline with potassium permanganate.[10]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

2-Methyl-5,6-pyrazinecarboxylic acid

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

ether (60-29-7)

glyoxal (107-22-2)

sodium hydroxide (1310-73-2)

potassium permanganate (7722-64-7)

sodium sulfate (7757-82-6)

sodium bisulfite (7631-90-5)

carbon dioxide (124-38-9)

acetone (67-64-1)

decolorizing carbon, carbon (7782-42-5)

manganese dioxide (1313-13-9)

potassium chloride (7447-40-7)

magnesium sulfate (7487-88-9)

o-Phenylenediamine (95-54-5)

sodium carbonate monohydrate (5968-11-6)

2,3-Pyrazinedicarboxylic acid (89-01-0)

glyoxal-sodium bisulfite

Quinoxaline (91-19-0)

2-Methylquinoxaline (7251-61-8)

pyruvic aldehyde-sodium bisulfite

2-Methyl-5,6-pyrazinedicarboxylic acid

pyruvic aldehyde (78-98-8)

isonitrosoacetone

monopotassium salt of pyrazine-2,3-dicarboxylic acid

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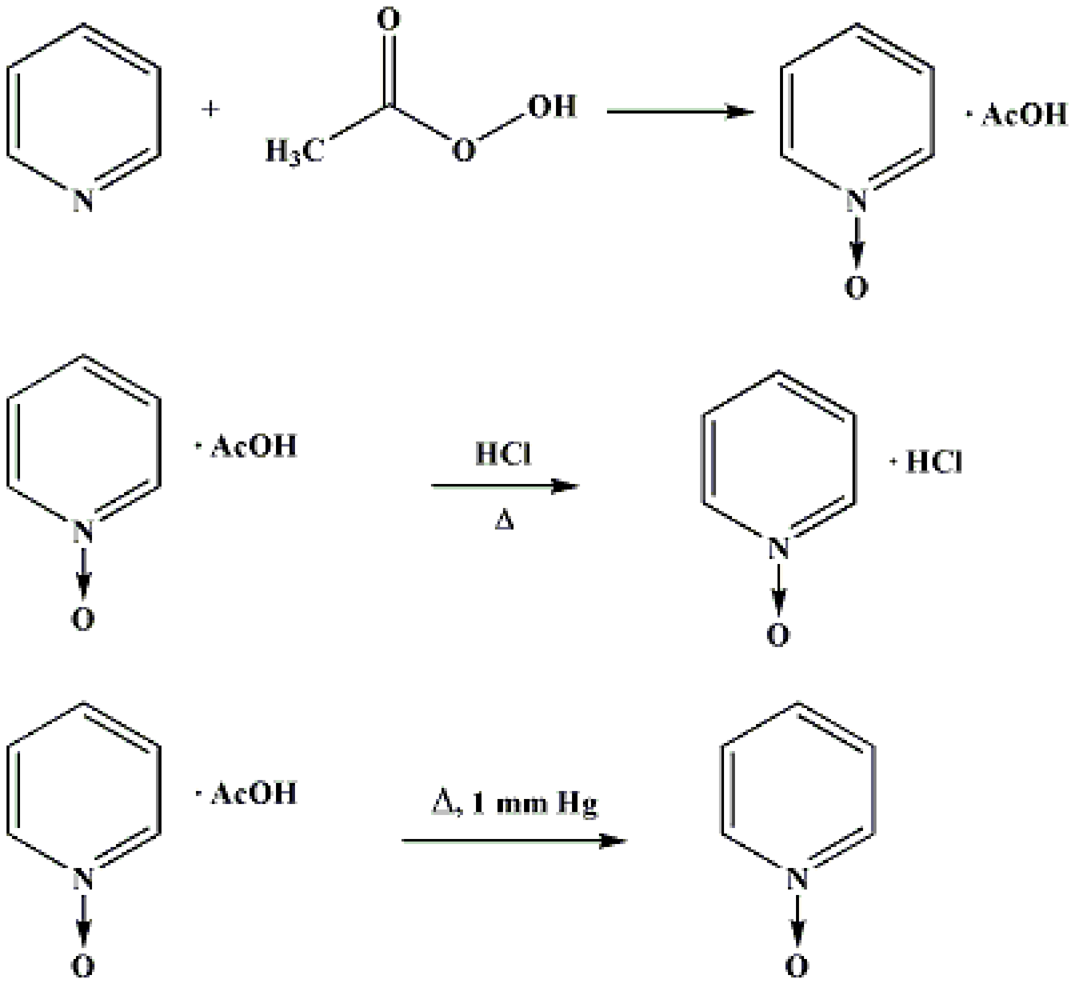
Organic Syntheses, CV 4, 828

PYRIDINE-N-OXIDE

[Pyridine-1-oxide]



Submitted by Harry S. Mosher, Leslie Turner, and Allan Carlsmith[1].
Checked by N. J. Leonard and E. D. Sutoris.

1. Procedure

In a 1-l. three-necked flask equipped with a stirrer (Note 1), a thermometer, and a dropping funnel is placed 110 g. (1.39 moles) of pyridine. The pyridine is stirred, and 250 ml. (285 g., 1.50 moles) of 40% peracetic acid (Note 2) is added at such a rate that the temperature reaches 85° and is maintained there. After the addition, which requires 50–60 minutes, the mixture is stirred until the temperature drops to 40°.

A. *Pyridine-N-oxide hydrochloride.* The acetate is converted to the hydrochloride by bubbling a slight excess over the theoretical amount (51 g.) of gaseous hydrogen chloride into the reaction mixture by way of a 7-mm. gas inlet tube which replaces the dropping funnel in the reaction flask. The acetic acid and excess peracetic acid are removed by warming on the steam bath under vacuum (Note 3). The residual pyridine-

N-oxide hydrochloride is purified by heating under reflux for 30 minutes with 300 ml. of isopropyl alcohol, cooling to room temperature, and filtering. The colorless crystals are washed with 50 ml. of isopropyl alcohol followed by 50 ml. of ether. The yield is 139–152 g. (76–83%) (Note 4), m.p. 179.5–181°.

B. *Pyridine-N-oxide.* The acetic acid solution is evaporated on the steam bath under the pressure of a water aspirator, and the residue (180–190 g.) is distilled at a pressure of 1 mm. or less in an apparatus suitable for collecting a solid distillate (Note 5). The vacuum pump must be protected with a Dry Ice trap capable of holding about 60 ml. of acetic acid, which distils as the pyridine-N-oxide acetate dissociates at low pressure. Heat is provided by an oil bath, the temperature of which is not allowed to rise above 130° (Note 6). The product is collected at 100–105°/1mm. (95–98°/0.5 mm.). The yield is 103–110 g. (78–83%) of colorless solid, m.p. 65–66° (sealed capillary). The base is deliquescent and must be stoppered immediately.

2. Notes

1. A convenient seal for stirring under vacuum (see (Note 3)) is made by running an 8-mm. glass rod, with propeller or paddle stirrer at the end, through the outside member of an 18/9 spherical joint which is inserted into a suitable rubber stopper. The inner member of the 18/9 spherical joint is then slipped over the stirrer and held in place with a piece of rubber tubing. This rotating seal may then be lubricated with a drop of oil. Alternatively, one may use a Trubore stirring system.
2. Becco peracetic acid (40%) was used. The composition and properties of this commercial preparation are described fully in *Bulletin* 4 of the Buffalo Electro-Chemical Company, Buffalo, New York. The manufacturer's recommendations for storing and handling should be followed. Experiments using proportionate amounts of 10% or 20% peracetic acid in acetic acid were equally successful. The strength of the peracetic acid, as well as the progress of the reaction, can be determined iodimetrically.[2]
3. The vacuum evaporation proceeds much more smoothly and rapidly if the mixture is stirred mechanically during the process.
4. The submitters report that the same procedure is successful with four times the amounts given here. With the increased amounts, a water bath is used for cooling during the initial addition, which then requires about 45 minutes.
5. *Caution! Before distillation, absence of peroxide should be established by test with potassium iodide.*
The apparatus for distillation of solids in vacuum described in *Organic Syntheses*[3] is satisfactory, as is a combination of standard taper flasks, short column, and adaptors.
6. It is imperative that the pressure be maintained at 1 mm. or lower. Decomposition is usually extensive at higher pressures; however, the removal of the acetic acid may be initiated at 5–10 mm. pressure. The oil-bath temperature must not exceed 130° if decomposition is to be avoided. A fore-run of 15–20 g., b.p. 90–98°/0.5 mm., can be saved and redistilled in combination with similar

cuts from successive runs. About 9–10 g. (7%) of additional crystalline pyridine-N-oxide is obtained per run in this manner.

3. Discussion

Pyridine-N-oxide has been prepared by oxidation of pyridine with perbenzoic acid,[4] with monoperphthalic acid,[5] with peracetic acid (hydrogen peroxide and acetic acid),[6,7] and with hydrogen peroxide and other carboxylic acids.[7].

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Monoperphthalic acid

hydrogen chloride (7647-01-0)

acetic acid (64-19-7)

ether (60-29-7)

potassium iodide (7681-11-0)

pyridine (110-86-1)

isopropyl alcohol (67-63-0)

hydrogen peroxide (7722-84-1)

peracetic acid (79-21-0)

pyridine-1-oxide, PYRIDINE-N-OXIDE (694-59-7)

pyridine-N-oxide hydrochloride

pyridine-N-oxide acetate

Perbenzoic acid (93-59-4)

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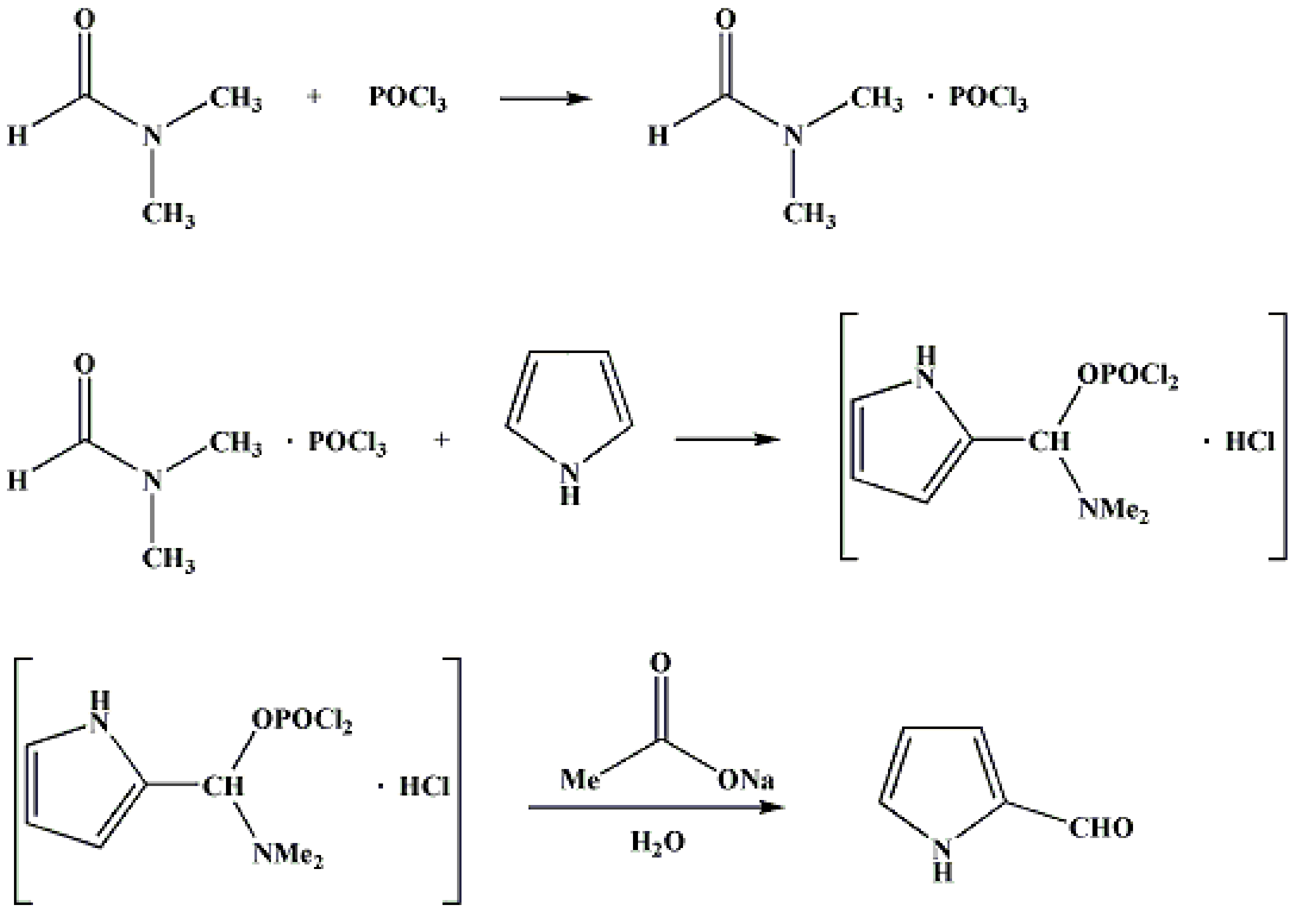
Organic Syntheses, CV 4, 831

2-PYRROLEALDEHYDE

[Pyrrole-2-carboxaldehyde]



Submitted by Robert M. Silverstein, Edward E. Ryskiewicz, and Constance Willard[1].
Checked by Max Tishler and George Purdue.

1. Procedure

In a 3-l. three-necked round-bottomed flask, fitted with a sealed stirrer, a dropping funnel, and a reflux condenser, is placed 80 g. (1.1 moles) of dimethylformamide (Note 1). The flask is immersed in an ice bath, and the internal temperature is maintained at 10–20°, while 169 g. (1.1 moles) of phosphorus oxychloride is added through the dropping funnel over a period of 15 minutes. An exothermic reaction occurs with the formation of the phosphorus oxychloride-dimethylformamide complex. The ice bath is removed, and the mixture is stirred for 15 minutes (Note 2).

The ice bath is replaced, and 250 ml. of ethylene dichloride is added to the mixture. When the internal temperature has been lowered to 5°, a solution of 67 g. (1.0 mole) of freshly distilled pyrrole in 250 ml. of ethylene dichloride is added through a clean dropping funnel to the stirred, cooled mixture over a period of 1 hour. After the addition is complete, the ice bath is replaced with a heating mantle, and the mixture is stirred at the reflux temperature for 15 minutes, during which time there is copious evolution of hydrogen chloride.

The mixture is then cooled to 25–30°, and to it is added through the dropping funnel a solution of 750 g. (5.5 moles) of sodium acetate trihydrate (Note 3) in about 1 l. of water, cautiously at first, then

as rapidly as possible. The reaction mixture is again refluxed for 15 minutes, vigorous stirring being maintained all the while (Note 4).

The cooled mixture is transferred to a 3-l. separatory funnel, and the ethylene dichloride layer is removed. The aqueous phase is extracted three times with a total of about 500 ml. of ether. The ether and ethylene chloride solutions are combined and washed with three 100-ml. portions of saturated aqueous sodium carbonate solution, which is added cautiously at first to avoid too rapid evolution of carbon dioxide. The non-aqueous solution is then dried over anhydrous sodium carbonate, the solvents are distilled, and the remaining liquid is transferred to a Claisen flask and distilled from an oil bath under reduced pressure (Note 5). The aldehyde boils at 78° at 2 mm.; there is very little fore-run and very little residue. The yield of crude 2-pyrrolealdehyde is 85–90 g. (89–95%), as an almost water-white liquid which soon crystallizes. A sample dried on a clay plate melts at 35–40°. The crude product is purified by dissolving in boiling petroleum ether (b.p. 40–60°), in the ratio of 1 g. of crude 2-pyrrolealdehyde to 25 ml. of solvent, and cooling the solution slowly to room temperature, followed by refrigeration for a few hours. The pure aldehyde is obtained from the crude in approximately 85% recovery. The over-all yield from pyrrole is 78–79% of pure 2-pyrrolealdehyde, m.p. 44–45°.

2. Notes

1. The dimethylformamide is available as technical grade DMF from the Grasselli Chemicals Department of E. I. duPont de Nemours and Company, Wilmington, Delaware.
2. If the ice bath is not removed, the mixture may solidify and must be dissolved by adding solvent and heating slightly. Mixing of the reactants at ice-bath temperature prevents discoloration. Practical grades of materials were used.
3. The use of sufficient sodium acetate is essential. If the acidic reaction products are not neutralized, the yield drops to as low as 15–20% of badly discolored product which cannot be readily purified.
4. Efficient stirring must be maintained to keep the two phases in close contact. Hydrolysis is not complete if the mixture is not heated.
5. The use of a wide-bore condenser and a simple receiver, without a stopcock, is preferable. Usually the product does not solidify at once, but occasionally it crystallizes during distillation. The use of a fraction cutter is not necessary or advisable.

3. Discussion

2-Pyrrolealdehyde has been prepared from pyrrole, chloroform, and potassium hydroxide;[2] from pyrrolemagnesium iodide and ethyl, propyl, or isoamyl formate;[3] from 2-furaldehyde dimethyl acetal and ammonium acetate;[4] and, by the method here described, from pyrrole, phosphorus oxychloride, and dimethylformamide.[5] Smith[5] has suggested a possible intermediate in this process. The method has also been applied to substituted pyrroles[6] and is similar to that described on p. 331 for the preparation of *p*-dimethylaminobenzaldehyde from dimethylaniline.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 539

References and Notes

1. Stanford Research Institute, Stanford, California.

2. Bamberger and Djierdjian, *Ber.*, **33**, 536 (1900); Fischer, Beller, and Stern, *Ber.*, **61B**, 1074 (1928).
3. Tschelinzeff and Terentjeff, *Ber.*, **47**, 2653 (1914); Putochin, *Zhur. Russ. Fiz. Khim. Obshchestva*, **59**, 809 (1927); Putochin, *Ber.*, **59B**, 1993 (1926).
4. Elming and Clauson-Kaas, *Acta Chem. Scand.*, **6**, 867 (1952).
5. Silverstein, Ryskiewicz, and Chaikin, *J. Am. Chem. Soc.*, **76**, 4485 (1954); Smith, *J. Chem. Soc.*, **1954**, 3842.
6. Ryskiewicz and Silverstein, *J. Am. Chem. Soc.*, **76**, 5802 (1954); Chu and Chu, *J. Org. Chem.*, **19**, 266 (1954); Silverstein, Ryskiewicz, Willard, and Koehler, *J. Org. Chem.*, **20**, 668 (1955).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

phosphorus oxychloride-dimethylformamide complex

ethyl, propyl, or isoamyl formate

hydrogen chloride (7647-01-0)

ether (60-29-7)

ammonium acetate (631-61-8)

sodium acetate (127-09-3)

chloroform (67-66-3)

sodium carbonate (497-19-8)

ethylene chloride, ethylene dichloride (107-06-2)

carbon dioxide (124-38-9)

Phosphorus Oxychloride (21295-50-1)

potassium hydroxide (1310-58-3)

dimethylaniline (121-69-7)

Pyrrole (109-97-7)

dimethylformamide (68-12-2)

sodium acetate trihydrate (6131-90-4)

2-Pyrrolealdehyde, Pyrrole-2-carboxaldehyde (1003-29-8)

pyrrolemagnesium iodide

2-furaldehyde dimethyl acetal

p-Dimethylaminobenzaldehyde (100-10-7)

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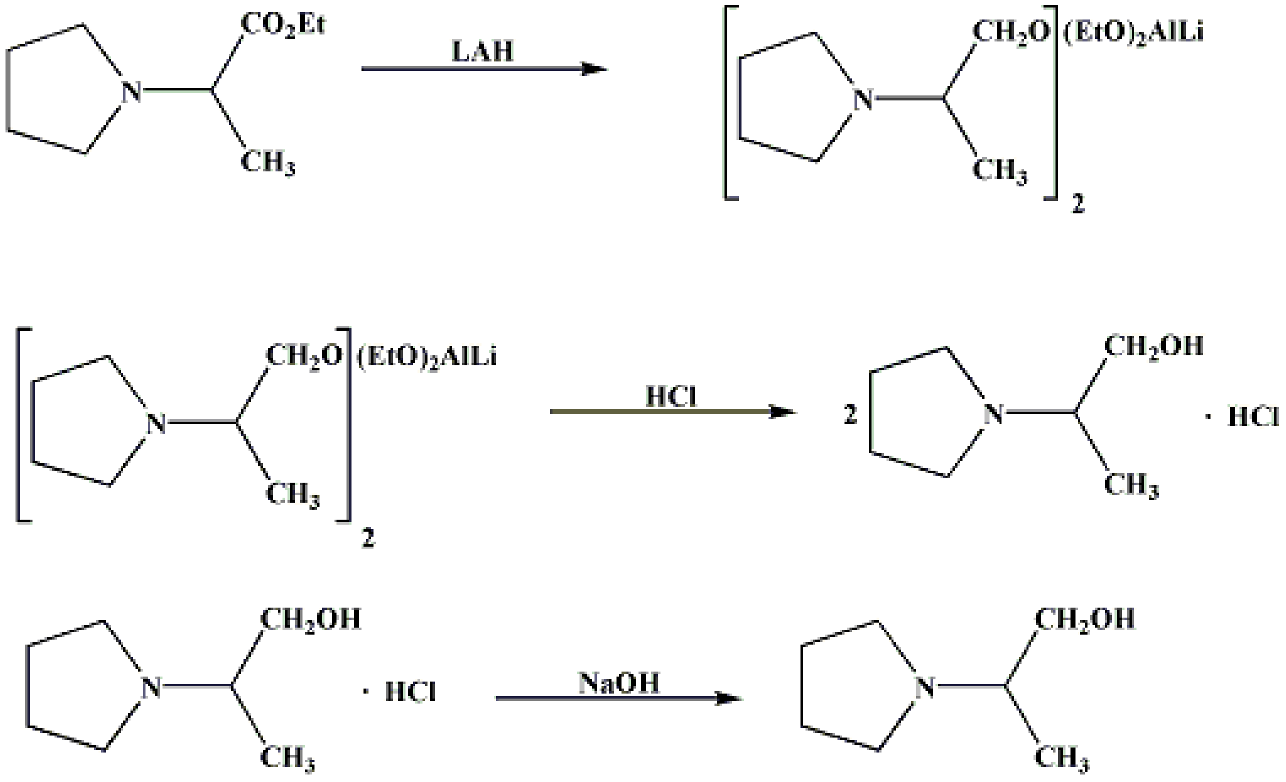
Organic Syntheses, CV 4, 834

2-(1-PYRROLIDYL)PROPANOL

[1-Pyrrolidineëthanol, β-methyl-]



Submitted by Robert Bruce Moffett[1]
Checked by N. J. Leonard and S. Gelfand.

1. Procedure

A 2-l. three-necked round-bottomed flask in an electric heating mantle is fitted with a mercury-sealed Hershberg stirrer, a dropping funnel, and an efficient reflux condenser topped with a tube containing soda lime and calcium chloride. In this flask are placed 21.3 g. (0.56 mole) of pulverized lithium aluminum hydride (Note 1) and 300 ml. of dry ether. The mixture is heated under reflux until most of the hydride has dissolved. A solution of 157.3 g. (0.92 mole) of ethyl α-(1-pyrrolidyl)propionate (p.466) in 200 ml. of dry ether is then added slowly with vigorous stirring at such a rate that the solvent refluxes gently. When the addition is complete and the initial reaction subsides, the mixture is stirred at the reflux temperature an additional 30 minutes. The excess lithium aluminum hydride is decomposed by adding 50 ml. of ethyl acetate slowly with stirring. This is followed by 600 ml. of 6*N* hydrochloric acid, added slowly with vigorous stirring.

The mixture is transferred to a separatory funnel. The water layer is separated, washed once with ether, and made strongly alkaline by the addition of 1 l. of 6*N* sodium hydroxide (Note 2). The mixture is returned to the original 2-l. three-necked flask. An attachment for continuous ether extraction is placed in one of the side necks,[2] and 6-in. extension columns are placed in the other two necks. The stirrer is fitted through the center column and neck. Ether is added through the column attached to the side neck until the proper ether level is attained. A stopper is then placed

on this column. The stirrer is run at such a rate that gentle swirling is accomplished without hindering the separation of the ether layer, and the continuous extraction with ether is continued until test with pH paper indicates that the ether coming over contains no more basic material. The ether solution of the product is thoroughly dried over anhydrous potassium carbonate (Note 3). The drying agent is removed by filtration, and the solvent by distillation at atmospheric pressure and finally at water-pump pressure. The residue is distilled at reduced pressure through a short fractionating column; b.p. 95–96°/20 mm. (109–110°/40 mm., 80°/11 mm.); n_D^{20} 1.4780; n_D^{25} 1.4758; d_4^{25} 0.9733. The yield is 95–106 g. (80–90%).

2. Notes

1. The hydride can be pulverized rapidly and safely by breaking the large pieces with a spatula, followed by careful crushing with a mortar and pestle. Caution must be observed because the solid may inflame on prolonged grinding or abrasion. The hydride dust is caustic and irritating.
2. At this point the mixture should be a mobile milky slurry. The submitter suggests that, if the mixture is too thick to extract, more water or base may be added.
3. Sufficient drying agent should be used so that no aqueous liquid phase appears.

3. Discussion

2-(1-Pyrrolidyl)propanol has been prepared by the lithium aluminum hydride reduction of ethyl α-(1-pyrrolidyl)propionate.[3]

References and Notes

1. The Upjohn Company, Kalamazoo, Michigan.
2. *Org. Syntheses Coll. Vol.* **1**, 277 (1941).
3. Moffett, *J. Org. Chem.*, **14**, 862 (1949).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

ether (60-29-7)

sodium hydroxide (1310-73-2)

lithium aluminum hydride (16853-85-3)

Ethyl α-(1-pyrrolidyl)propionate (26846-86-6)

2-(1-Pyrrolidyl)propanol, 1-Pyrrolidineethanol, β-methyl- (53663-19-7)

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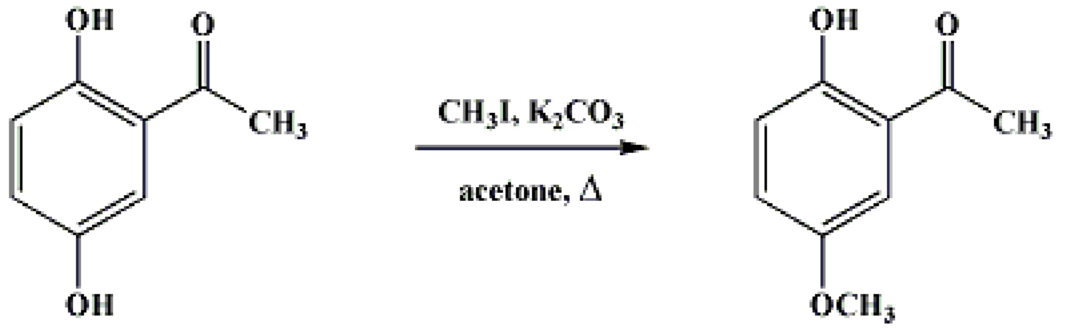
Organic Syntheses, CV 4, 836

QUINACETOPHENONE MONOMETHYL ETHER

[Acetophenone, 2'-hydroxy-5'-methoxy-]



Submitted by G. N. Vyas and N. M. Shah[1].
Checked by William S. Johnson and R. T. Keller.

1. Procedure

In a 1-l. round-bottomed flask fitted with a reflux condenser and a calcium chloride guard tube are placed 30.0 g. (0.197 mole) of quinacetophenone[2] (Note 1) and 300 ml. of acetone (Note 2). The mixture is warmed on a steam bath to dissolve the quinacetophenone. The resulting greenish solution is cooled to room temperature under tap water, and 28 g. (0.20 mole) of anhydrous potassium carbonate is added followed by 42 g. (0.295 mole) of methyl iodide. The mixture is allowed to reflux on a water bath at 60–70° for about 6 hours (Note 3).

As much of the acetone as possible is removed by distillation on the water bath (Note 4), and the residual dark-colored liquid is cooled and acidified with 2*N* sulfuric acid with cooling under the water tap. The resulting mixture is steam-distilled until no oily drops are seen collecting in the condenser. The distillate, which amounts to about 2.5 l., is allowed to stand overnight at room temperature, and the greenish crystals are separated by suction filtration, washed twice with cold water, and air-dried. The yield of quinacetophenone monomethyl ether, m.p. 48–50°, is 18–21 g. (55–64%) (Note 5).

The brown solution remaining in the distilling flask is filtered while hot; on being cooled it gives 6–7 g. of brownish needles of crude quinacetophenone.

2. Notes

1. The quinacetophenone[2] is dried in an oven at 100–110° for 2–3 hours.
2. The acetone is dried over anhydrous potassium carbonate and distilled.
3. The temperature of the water bath should not exceed 70°; otherwise serious bumping may occur.
4. The recovered acetone may be reused for another methylation.

5. The submitters state that the *dimethyl* ether of quinacetophenone is conveniently prepared by the following procedure: In a 1-l. round-bottomed flask fitted with a reflux condenser 60 g. (0.39 mole) of quinacetophenone[2] is dissolved in 300 ml. of ethanol by heating. The source of heat is then removed, and to the hot solution are alternately added in five installments with shaking a solution of sodium hydroxide (40 g. in 100 ml. of water) and dimethyl sulfate (120 g.). The heat evolved during the reaction makes the solution boil. After the addition is complete (about 20 minutes), the reaction mixture is made alkaline by the further addition of 10 g. of sodium hydroxide in 20 ml. of water and is allowed to reflux on the water bath for 3 hours. The dark mixture is distilled to remove most of the ethanol, and the residual liquid in the flask is steam-distilled. The distillate, which amounts to about 2.5 l., is cooled in an ice bath and saturated with sodium chloride, whereupon a thick oil settles to the bottom. Most of the aqueous layer is decanted, and the remaining oil is extracted with ether and dried over calcium chloride. The ether is removed by distillation, and the residue is fractionated at reduced pressure to give 50–52 g. (71–74% yield) of material boiling at 152–156°/15 mm., m.p. 20–22°.

3. Discussion

Quinacetophenone monomethyl ether has been prepared by the methylation of quinacetophenone with dimethyl sulfate and alkali,[3] by the partial demethylation of quinacetophenone dimethyl ether;[4] and by the acetylation of hydroquinone dimethyl ether with acetyl chloride in the presence of aluminum chloride.[5] It also has been obtained as a by-product in the preparation of quinacetophenone dimethyl ether.[6]

References and Notes

1. M. R. Science Institute, Gujarat College, Ahmedabad, India.
2. *Org. Syntheses Coll. Vol.* **3**, 280 (1955).
3. Kostanecki and Lampe, *Ber.*, **37**, 774 (1904).
4. Baker, Brown, and Scott, *J. Chem. Soc.*, **1939**, 1926.
5. Oliverio and Lugli, *Gazz. chim. ital.*, **78**, 16 (1948); Wiley, *J. Am. Chem. Soc.*, **73**, 4205 (1951).
6. Kauffmann and Beisswenger, *Ber.*, **38**, 792 (1905).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Quinacetophenone monomethyl ether

quinacetophenone

dimethyl ether of quinacetophenone

quinacetophenone dimethyl ether

ethanol (64-17-5)

calcium chloride (10043-52-4)

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

ether (60-29-7)

sodium hydroxide (1310-73-2)

acetyl chloride (75-36-5)

sodium chloride (7647-14-5)

dimethyl sulfate (77-78-1)

acetone (67-64-1)

aluminum chloride (3495-54-3)

Methyl iodide (74-88-4)

hydroquinone dimethyl ether (150-78-7)

Acetophenone, 2'-hydroxy-5'-methoxy- (705-15-7)

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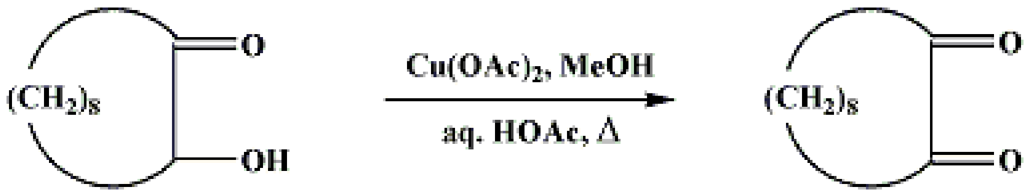
Organic Syntheses, CV 4, 838

SEBACIL

[1,2-Cyclodecanedione]



Submitted by A. T. Blomquist and Albert Goldstein[1].
Checked by N. J. Leonard and J. C. Little.

1. Procedure

Fifty-one grams (0.30 mole) of sebacoin (Note 1), 25 ml. of methanol, 120 g. of cupric acetate monohydrate (0.60 mole), and 300 ml. of 50% aqueous acetic acid are mixed in a 1-l. flask equipped with an efficient mechanical stirrer and a reflux condenser. The mixture is heated over a free flame until refluxing occurs. The color of the mixture changes from blue to red at approximately 75°. Refluxing is continued for 1 minute. The mixture is then allowed to cool, with stirring, to about 40° (Note 2). The mixture is filtered through filter aid ("Celite") on a sintered glass funnel to remove cuprous oxide, and the filtrate is transferred to a 2-l. separatory funnel (Note 3). Saturated aqueous sodium chloride solution. (310 ml.) is added to the filtrate, which is then extracted with three 150-ml. portions of ether. The combined ether extracts are washed with three 250-ml. portions of saturated salt solution, four 250-ml. portions of 5% sodium bicarbonate solution (foaming!), and once again with 250 ml. of saturated salt solution. The ether solution is then dried over 20 g. of anhydrous sodium or magnesium sulfate. The ether is removed by distillation at atmospheric pressure, and the residue is transferred to a 100-ml. flask and distilled under vacuum. The yield of sebacil is 44.4–45.1 g. (88–89%), b.p. 104–106°/10 mm. (Note 4).

2. Notes

1. The sebacoin-sebacil mixture obtained from the sebacoin preparation (p. 840) was used.
2. The sebacil may tend to crystallize during filtration if the reaction mixture is too cool.
3. The "Celite"-cuprous oxide mixture is extracted with three 50-ml. portions of ether, and the combined extracts are used as the first ether portion for the extraction of the sebacil-containing aqueous solution.
4. 1,2-Cyclononanedione has been prepared from 2-hydroxycyclononanone in 67–72% yield by this procedure.[2]

3. Discussion

1,2-Cyclodecanedione has also been prepared by oxidation of sebacoin with chromium trioxide in acetic acid.[3,4] Cupric acetate in acetic acid has been used for oxidation of an α-hydroxyketone by Ruggli and Zeller.[5]

References and Notes

1. Cornell University, Ithaca, New York.
2. Blomquist, Liu, and Bohrer, *J. Am. Chem. Soc.*, **74**, 3643 (1952).
3. Blomquist, Burge, and Sucsy, *J. Am. Chem. Soc.*, **74**, 3636 (1952).
4. Prelog, Schenker, and Günthard, *Helv. Chim. Acta*, **35**, 1610 (1952).
5. Ruggli and Zeller, *Helv. Chim. Acta*, **28**, 741 (1945).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium or magnesium sulfate

Sebacoin

sebacoin-sebacil

Celite

acetic acid (64-19-7)

methanol (67-56-1)

ether (60-29-7)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

cuprous oxide

cupric acetate (142-71-2)

chromium trioxide (1333-82-0)

cupric acetate monohydrate (6046-93-1)

1,2-Cyclodecanedione, Sebacil (96-01-5)

1,2-Cyclononanedione

2-hydroxycyclononanone

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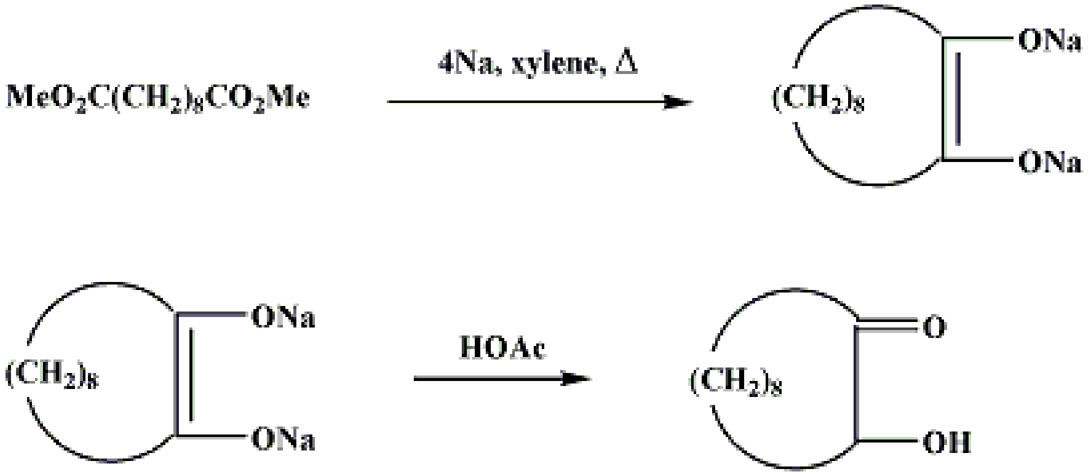
Organic Syntheses, CV 4, 840

SEBACOIN

[Cyclodecanone, 2-hydroxy-]



Submitted by Norman L. Allinger[1]
Checked by N. J. Leonard, J. C. Little, and F. H. Owens.

1. Procedure

The apparatus[2] consists of a 3-l. three-necked round-bottomed creased flask, with standard ball joints and an indented cone-shaped bottom (Note 1), which is heated by means of an electric mantle and is equipped with a high-speed stirrer of stainless steel driven by a 10,000 r.p.m. motor (Note 2). One side neck is fitted with a bulb-type air-cooled condenser (Note 3), on top of which fits a 1-l. pressure-equalizing Hershberg dropping funnel (Note 4). The top of the dropping funnel is connected in turn to a U-tube containing a 1-cm. head of mercury. The entire apparatus is securely fastened to a sturdy support.

In the flask is placed 900 ml. of xylene (Note 5), and a slow stream of purified nitrogen (Note 6) is passed through the system from which the dropping funnel has been temporarily removed. The stirrer is run at slow speed, and the solvent is brought to a gentle reflux. The air stream cooling the condenser is shut off, the mercury valve is disconnected from the condenser, and a few milliliters of solvent is allowed to distil out the top of the condenser (Note 7). The dropping funnel (Note 8), containing a solution of 115 g. (0.50 mole) of dimethyl sebacate (Note 9) and 500 ml. of xylene (Note 5) is then inserted between the top of the condenser and the mercury valve. The air to the condenser is then turned on, and the electric mantle is turned off. The solvent is allowed to cool below its boiling point, and the stirrer is gradually brought to a stop. Throughout these operations the nitrogen flow is adjusted to keep air out of the system. Through a side neck is then added 50.6 g. (2.20 g. atoms) of crust-free sodium metal cut into lumps of convenient size. The side neck is closed, and the stirrer and the

heater are turned on. The sodium is dispersed by stirring at about 6000–8000 r.p.m. for 10 minutes, and, with continued heating and stirring at a rate somewhat slower (to give suitable mixing), the dropwise addition of the ester solution is begun at such a rate as to be complete in about 24 hours (Note 10) and (Note 11).

Heating and stirring are continued for 1 hour after the addition is completed. The stirrer is then slowed, heating is stopped, the heater is removed, and the reaction flask is allowed to cool for about 15 minutes (Note 12). The reaction flask is then cooled in a water bath, and is finally thoroughly cooled in an ice bath. A solution of 140 ml. of glacial acetic acid in an equal volume of xylene is then added dropwise during about 30 minutes with continued cooling and stirring (Note 13). After addition of 450 ml. of water, stirring is stopped, the nitrogen is turned off, and the flask is disconnected from the apparatus. The two-phase mixture is filtered through a large Büchner funnel with suction to remove a small amount of gum, and the filtrate is then poured into a 3-l. separatory funnel. The aqueous phase is drawn off, extracted with 100 ml. of xylene, and is discarded. The xylene phases are washed in series with 100 ml. of water, and are combined and dried with 10 g. of anhydrous magnesium sulfate. The solution is filtered into a 3-l. round-bottomed flask, and the bulk of the xylene is distilled with the aid of an aspirator (Note 14) and (Note 15). The residue is transferred to a smaller flask and is distilled through a 2-ft. Vigreux column, the fraction boiling at 134–138°/14 mm. or 124–128°/9 mm. being collected as a yellowish liquid weighing 57–63 g. (67–74%). This material solidifies on standing and is sufficiently pure for most purposes (Note 16) and (Note 18). For further purification it may be crystallized from 150 ml. of pentane by cooling to −10° in an ice-salt bath for several hours. The mixture is filtered, and the crystals are washed with 50 ml. of pentane which has been cooled to –80°. The pure product thus obtained is a white granular crystalline solid, m. p. 38–39°, weighing 53–56 g. (63–66%) (Note 17) and (Note 18).

2. Notes

1. A flask having this shape gives the most efficient mixing.[2]
2. A one-fourth-horsepower motor is adequate. A suitable motor is manufactured by Bodine Electric Company, Chicago, Illinois.
3. The use of a water-cooled glass condenser is not recommended since it might accidentally be broken and thereby cause water to flow into the flask. A metal water-cooled condenser has also been used and is satisfactory.
4. Adapted from that described in *Org. Syntheses*, Coll. Vol. **2**, 129 (1943).
5. The xylene used was purified by heating under reflux with sodium overnight and then distilling, b.p. 137–142°.
6. Linde high-purity dry nitrogen was used without further treatment.
7. The fumes may be taken off by attaching an aspirator. This procedure assures removal of all moisture from the system.
8. The funnel is dried before use with a flame and is then closed with a drying tube and allowed to cool.
9. The ester used was Eastman Kodak Company technical grade shaken with

sodium carbonate, dried and distilled. The ester boils at 158–160°/11 mm.
10. The reaction time can be lengthened considerably without effect. If, however, the time is shortened appreciably, the yield may be markedly lowered.
11. Initially the reaction may take on various colors, red, purple, etc., but after a short time a dull gray-brown color appears, which is gradually replaced by a yellow-brown or olive-drab color.
12. It is important that the reaction mixture be kept out of contact with the air until it has been acidified.
13. When sufficient acetic acid has been added, the dark color of the reaction mixture is replaced by a white color, and the mixture is often quite thick. More acetic acid is not harmful.
14. Nitrogen is led through the capillary during the distillations.
15. The xylene thus recovered is purified (Note 5) and is used in the next preparation.
16. This material slowly decomposes upon standing. It may be stored for at least several months with only slight decomposition if it is kept under nitrogen in the dark and at 0°. The compound appears to be stable when pure.
17. Homologs having a ring containing 10 to 18 carbons have been prepared in an analogous manner in yields from 46 to 85%.[3]
18. This preparation has also been carried out on a 1.0 mole scale by the checkers, using a 5-l. creased flask. Comparable yields are obtainable.

3. Discussion

Sebacoin has been prepared by the cyclization of methyl or ethyl sebacate with sodium metal.[3,4,5,6,7,8]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 216
- Org. Syn. Coll. Vol. 4, 218
- Org. Syn. Coll. Vol. 4, 838
- Org. Syn. Coll. Vol. 5, 277

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1. University of California, Los Angeles, California.
2. Morton and Redman, *Ind. Eng. Chem.*, **40**, 1190 (1948).
3. Stoll and Rouvé, *Helv. Chim. Acta*, **30**, 1822 (1947).
4. Prelog, Frenkiel, Kobelt, and Barman, *Helv. Chim. Acta*, **30**, 1741 (1947).
5. Stoll and Hulstkamp, *Helv. Chim. Acta*, **30**, 1815 (1947).
6. Hansley (to E. I. du Pont de Nemours and Company), U. S. pat. 2,228,268 [*C. A.*, **35**, 2534 (1941)].
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8. Prelog, Schenker, and Günthard, *Helv. Chim. Acta*, **35**, 1598 (1952).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Sebacoin

methyl or ethyl sebacate

acetic acid (64-19-7)

sodium carbonate (497-19-8)

nitrogen (7727-37-9)

sodium (13966-32-0)

xylene (106-42-3)

Pentane (109-66-0)

magnesium sulfate (7487-88-9)

Cyclodecanone, 2-hydroxy- (96-00-4)

dimethyl sebacate (106-79-6)

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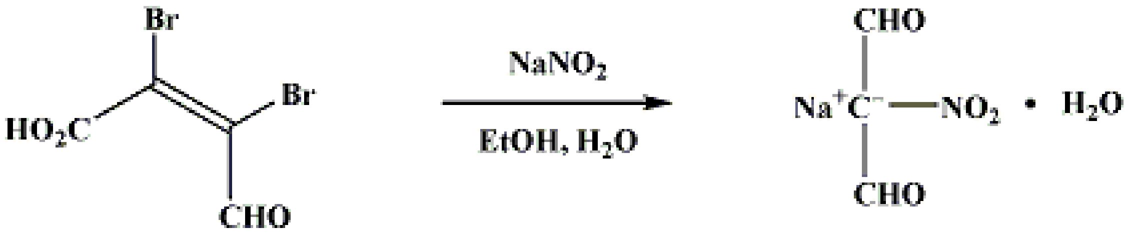
Organic Syntheses, CV 4, 844

SODIUM NITROMALONALDEHYDE MONOHYDRATE

[Malonaldehyde, nitro-, sodium derivative]



Submitted by Paul E. Fanta[1]
Checked by Cliff S. Hamilton and Philip J. Vanderhorst.

1. Procedure

Caution! The sodium salt of nitromalonaldehyde is impact-sensitive and thermally unstable and should be handled as a potentially explosive material.

In a 2-l. three-necked round-bottomed flask, equipped with a thermometer, a dropping funnel, a mechanical stirrer and a gas vent (Note 1), are placed 258 g. (3.74 moles) of sodium nitrite and 250 ml. of water. The contents of the flask are heated and stirred to dissolve the solid. A solution of 258 g. (1 mole) of mucobromic acid (p. 688) in 250 ml. of warm 95% ethanol is placed in the dropping funnel and added dropwise with constant stirring over a period of 70–80 minutes. A mildly exothermic reaction occurs; the solution in the flask becomes deep red, and gas is evolved. During the addition, the temperature is kept at 54 ± 1° by intermittent application of an ice bath to the flask (Note 2). The mixture is stirred for an additional 10 minutes at 54 ± 1°. While being stirred continuously, it is then cooled to 0–5° by application of an ice bath. The fine, yellow precipitate is collected on a previously chilled Büchner funnel.

The slightly moist cake of crude product is transferred to a 1-l. flask and heated to boiling with a mixture of 400 ml. of 95% ethanol and 100 ml. of water. The hot solution is filtered to remove a fine yellow solid, and the clear red filtrate is cooled to 0–5°. The recrystallized product is collected on a Büchner funnel and dried in air at room temperature. The yield is 57–65 g. (36–41%) of pink or tan needles of sodium nitromalonaldehyde monohydrate (Note 3).

2. Notes

1. The gases evolved are slightly irritating; they should be vented to a trap,[2] or the apparatus should be set up in a hood.
2. The yield is not increased and a darker, less pure product is obtained if the

reaction is run at a higher temperature or for a longer time.
3. The checkers found the product to be quite pure. An almost quantitative yield of 2-amino-5-nitropyrimidine was obtained by reaction of the product with guanidine.

3. Discussion

The procedure above is a modification of the method of Hill and Torrey,[3] which was also studied by Johnson[4] and others.[5,6]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 1004

References and Notes

1. Illinois Institute of Technology, Chicago, Illinois.
2. *Org. Syntheses Coll. Vol.* **2**, 4 (1943).
3. Hill and Torrey, *Am. Chem. J.*, **22**, 89 (1899).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

SODIUM NITROMALONALDEHYDE MONOHYDRATE

Malonaldehyde, nitro-, sodium derivative

sodium salt of nitromalonaldehyde

ethanol (64-17-5)

sodium nitrite (7632-00-0)

guanidine (113-00-8)

Mucobromic acid (488-11-9)

2-amino-5-nitropyrimidine (3073-77-6)

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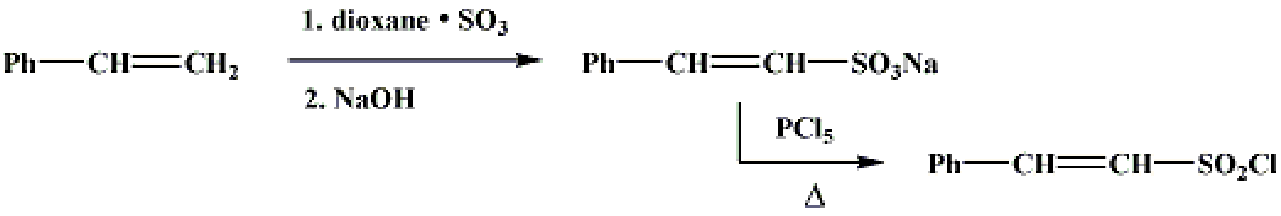
Organic Syntheses, CV 4, 846

SODIUM β-STYRENESULFONATE AND β-STYRENESULFONYL CHLORIDE

[Ethenesulfonic acid, 2-phenyl-, sodium salt]

[Ethenesulfonyl chloride, 2-phenyl-]



Submitted by Christian S. Rondestvedt, Jr. and F. G. Bordwell[1].
Checked by T. L. Cairns and H. E. Winberg.

1. Procedure

A. *Sodium β-styrenesulfonate*. In a 3-l. three-necked flask, equipped with a drying tube, a sealed stirrer, and a ground-glass stopper, is placed 800 ml. of ethylene chloride (Note 1). The flask with fittings is weighed and then connected through the third neck to a sulfur trioxide distillation apparatus (Note 2). Sulfur trioxide is distilled into the flask until about 300 g. has been collected. During the distillation the flask is cooled with a large pan of cold water (Note 3). The distillation is stopped, the condenser is disconnected and replaced by the glass stopper, and the flask is again weighed.

The stopper is replaced by a thermometer, and the other side neck is equipped with a two-way adapter to hold a dropping funnel and a drying tube. The sulfur trioxide solution is cooled below –5deg; with an ice-salt bath, then an amount of dioxane (Note 4) equivalent to the sulfur trioxide is added slowly with vigorous stirring at such a rate that the temperature does not exceed 5° (Note 5).

One molar equivalent of styrene (Note 6) dissolved in 2 volumes of ethylene chloride is added with stirring to the suspension of dioxane sulfotrioxide. The temperature is maintained below 10° during the hour required for addition, during which the suspension of colorless solid changes to a milky tan solution. The cooling bath is removed, and stirring is continued for an additional hour. After standing overnight, the nearly clear yellow solution is heated under reflux for 2 hours on the steam bath. The solution, now dark brown, is allowed to cool, is poured into 3 l. of ice water, and is stirred or shaken to ensure transfer of the sulfonic acid to the water (Note 7). The emulsion is neutralized with sodium hydroxide solution (Note 8), the layers are separated, and the aqueous phase is extracted with two 500-ml. portions of isopropyl ether (Note 9).

Several crops of crystals are now taken by evaporating the aqueous solution to the saturation point on a hot plate with stirring, then cooling. Each crop is dried for 2 hours at 100° and analyzed for unsaturation by the bromate-bromide titration method (Note 10). The first two crops usually total about 380 g. (based on 300 g. of sulfur trioxide), 49% yield, and are about 95% pure by titration. They may be further purified by one recrystallization from water, with about 80%

recovery of 99 + % pure salt.

The third crop generally weighs about 100 g. and is about 80% pure; the fourth crop weighs about 75 g., and is about 60% pure (Note 11). For purification, the third crop is recrystallized from the mother liquor resulting from the recrystallization of the combined first and second crops; the fourth crop is recrystallized from the third-crop mother liquor. An additional recrystallization from water is usually required to obtain material of 95 + % purity.

The total weight of 95 + % pure sodium β-styrenesulfonate from 300 g. of sulfur trioxide is 450–500 g. (58–65% yield) (Note 12) and (Note 13).

B. *β-Styrenesulfonyl chloride*. One hundred grams of dry sodium β-styrenesulfonate (Note 14) is placed in a 500-ml. round-bottomed flask and thoroughly mixed with 120 g. of powdered phosphorus pentachloride with vigorous shaking. The flask is attached to a reflux condenser capped with a drying tube and heated on the steam bath until the reaction mixture liquefies, then for an additional 4 hours. The phosphorus oxychloride is removed by distillation at reduced pressure (water aspirator) on the steam bath. The semisolid residue is extracted three times by boiling for 15 minutes with 100-ml. portions of chloroform. The residue in the flask is dissolved in 200 ml. of ice water and extracted with 100 ml. of chloroform. The combined chloroform solutions are washed with 200 ml. of water, two 100-ml. portions of 5% sodium bicarbonate, and finally with 100 ml. of water. After drying for 2 hours over calcium chloride, the solution is treated with 3 g. of Norit, filtered, and concentrated to 150 ml., and 200 ml. of 60–68° petroleum ether is added. On cooling, 81–86 g. (83–88% yield) of β-styrenesulfonyl chloride separates as colorless needles, m.p. 88–90°. Recrystallization raises the melting point to 89–90° (Note 15), (Note 16), and (Note 17).

2. Notes

1. A good grade of ethylene chloride is dried by slowly distilling a portion and rejecting the wet fore-run. Technical grade material should be carefully fractionated before use; the fraction boiling at 82.6–82.8° gives excellent results.
2. The apparatus for distillation of sulfur trioxide is constructed from a 500-ml. round-bottomed flask, connected by a ground joint to a 6-in. section of 20-mm. glass tubing. A safety tube (8-mm. tubing) reaching to the bottom of the flask is attached at the top by means of a ground joint; it is convenient to bend the top of the tube so that any acid drip can be caught in a beaker. A side arm, sealed in near the top of the wide tube, leads through a ground joint to an air condenser consisting of a 30-in. length of 12-mm. tubing, which terminates in a ground joint (with a drip tip) to fit the reaction flask. It is imperative that the apparatus be all glass, since sulfur trioxide rapidly attacks rubber or cork connections.
Sulfur trioxide is distilled by heating 60% fuming sulfuric acid contained in the flask. Spent acid may be fortified with "Sulfan B," stabilized liquid sulfur trioxide obtainable from the General Chemical Company, 40 Rector St., New York. Undiluted Sulfan B solidifies in the flask after a few heatings, and subsequent reheating may be dangerous.
3. Only slight cooling is needed at this stage. Stirring may be intermittent, if more convenient. If the sulfur trioxide solidifies above the level of the ethylene chloride from excessive cooling, it may easily be melted by warming the flask with a soft flame.
4. Dioxane is purified by refluxing for 12 hours with an excess of sodium, then distilling. The fraction boiling at 99.6–99.8° is collected and stored over calcium chloride or, preferably, calcium hydride.

5. If the temperature is allowed to rise much above 5°, charring results and the product is discolored. A Dry Ice bath may be used to advantage. The reagent thus prepared should be used within a few hours, since dioxane is slowly attacked by sulfur trioxide.

6. Stabilized styrene of monomeric quality is used directly. The small amount of stabilizer does not interfere with the reaction.

7. In small runs, ether may be used to break the emulsion, thus permitting the separation of the layers before neutralization. In large runs, excessively large amounts of ether are required and it is preferable to neutralize first.

8. Methyl red serves as a convenient indicator. Slightly more than 1 mole of sodium hydroxide is required per mole of sulfur trioxide. Other metal salts can be prepared, using a suitable hydroxide or carbonate for the neutralization.

9. Ethyl ether may be substituted, but its greater water solubility is a disadvantage. Evaporation of the combined organic layers at reduced pressure below 40° leaves a residue of about 5% (based on sulfur trioxide) of 2,4-diphenylbutane-1,4-sultone, which may be purified (60% recovery) by recrystallization from acetone-water; m.p. 147–149°. The yield of sultone may be increased to about 25% of pure material by using 3 moles of styrene per mole of sulfur trioxide.

10. A sample (approximately 0.2 g.) is weighed accurately and dissolved in 25 ml. of water; then 25 ml. of 0.1*N* hydrochloric acid and 0.2 g. of potassium bromide are added. The solution is titrated with 0.07*M* potassium bromate until a permanent yellow color is produced. Potassium iodide (0.1 g.) is added, and the solution is backtitrated to a starch end point with 0.1*N* sodium thiosulfate. The blue color returns in about a minute since the high acidity promotes air oxidation of excess iodide. The accuracy is only slightly less if the appearance of a faint yellow bromine color is taken as the end point. One mole of potassium bromate is equivalent to 3 of sodium β-styrenesulfonate.

11. Further crops may be taken, but the recovery of pure material from them is not worth the time required. They consist mainly of sodium 2-phenyl-2-hydroxyethane-1-sulfonate along with some sodium sulfate.

12. The procedure may be modified to prepare sodium 2-phenyl-2-hydroxyethane-1-sulfonate. The temperature during the addition of styrene is maintained below 0°. After 30 minutes of additional stirring at 0°, the mixture is hydrolyzed in ice water without heating. The crops of salts are analyzed, and those that are low in unsaturation are recrystallized from 70% aqueous ethanol. The more unsaturated crops are recrystallized from the mother liquors. The yield is 45–50% of material with less than 5% unsaturation.

13. Since the sodium sulfonates have no definite melting points, they may be converted to crystalline benzylthiuronium, *p*-chlorobenzylthiuronium, aniline, or *p*-toluidine salts for characterization.[2]

14. The salt is dried at 100° for 4 hours, then powdered.

15. An additional 6–7 g. of product, m.p. 88–89°, may be obtained by evaporation of the mother liquors and distillation of the residue as rapidly as possible at 2 mm. (bath temperature 120–140°). The total yield is thus 88–92%; in smaller runs, yields up to 96% are frequently obtained. Large batches cannot be distilled satisfactorily.

16. Carbon tetrachloride may also be used as a recrystallization solvent. The product should be stored in a tightly closed brown bottle to retard its slow decomposition.

17. The checkers used one-third quantities throughout both parts of this preparation with comparable results.

3. Discussion

Salts of β-styrenesulfonic acid have been prepared by the sulfonation of styrene with dioxane sulfotrioxide,[2] by heating styrene with ammonium sulfamate,[3] by the reaction of styrene with sodium bisulfite in the presence of oxygen,[4] and by the sulfonation of styrene with pyridine sulfotrioxide.[5]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

Methyl Red

benzylthiuronium, p-chlorobenzylthiuronium, aniline, or p-toluidine salts

ethanol (64-17-5)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ether, ethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

phosphorus pentachloride (10026-13-8)

sulfur trioxide (7446-11-9)

chloroform (67-66-3)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

oxygen (7782-44-7)

carbon tetrachloride (56-23-5)

potassium iodide (7681-11-0)

sodium thiosulfate (7772-98-7)

ethylene chloride (107-06-2)

sodium bisulfite (7631-90-5)

Norit (7782-42-5)

Phosphorus Oxychloride (21295-50-1)

potassium bromate (7758-01-2)

sodium (13966-32-0)

potassium bromide (7758-02-3)

styrene (100-42-5)

dioxane (5703-46-8)

isopropyl ether (108-20-3)

calcium hydride (7789-78-8)

β-Styrenesulfonyl chloride, Ethenesulfonyl chloride, 2-phenyl- (4091-26-3)

Ethenesulfonic acid, 2-phenyl-, sodium salt, Sodium β-styrenesulfonate (2039-44-3)

dioxane sulfotrioxide

2,4-diphenylbutane-1,4-sultone

sodium 2-phenyl-2-hydroxyethane-1-sulfonate

ammonium sulfamate (7773-06-0)

pyridine sulfotrioxide

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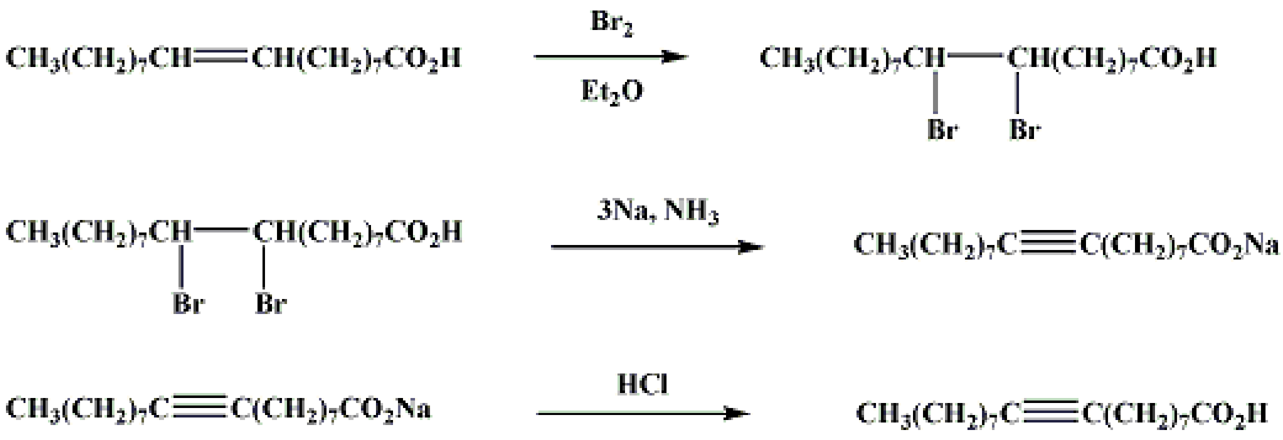
Organic Syntheses, CV 4, 851

STEAROLIC ACID



Submitted by N. A. Khan, F. E. Deatherage, and J. B. Brown[1].
Checked by Max Tishler, W. J. Paleveda, and E. F. Schoenewaldt.

1. Procedure

Bromine is added dropwise with stirring to a solution of 100 g. (0.35 mole) of oleic acid of at least 95% purity (Note 1) in 400 ml. of dry ether maintained at 0–5°, until the color of bromine persists. About 53 g. (0.33 mole) of bromine is needed; the excess is removed by addition of a few drops of oleic acid.

The sodamide required for dehydrobromination is prepared[2] in a 5-l. three-necked flask fitted with a sealed Hershberg stirrer, a gas inlet tube, and a large cold-finger condenser charged with Dry Ice-acetone. The condenser outlet is connected to a safety trap followed by a bubbler tube containing concentrated aqueous ammonia. Liquid ammonia (1.9 l., (Note 2)) is introduced into the flask through the inlet tube (*Hood!*); then 1.6 g. of anhydrous ferric chloride (c.p., black) is added in one portion with vigorous stirring. After 5–10 minutes, 3 g. of sodium is dropped into the brown solution to convert the iron salt into the catalytic form. After the evolution of hydrogen has ceased, the remainder of the sodium (total 43 g., 1.87 g. atoms) is added in small pieces with continued stirring. Gray, grainy crystals of sodamide settle out as the reaction proceeds.

The ethereal solution of dibromostearic acid, prepared as described above, is introduced slowly from a dropping funnel into the reaction flask. After the reaction has been allowed to proceed for 6 hours with continuous stirring, 60 g. of solid ammonium chloride (1.12 moles) is added in portions to destroy excess sodamide. The ammonia is allowed to evaporate until there remains a dry-appearing solid, and then 1 l. of water is added. The mixture is warmed to 60–70° under nitrogen (Note 3) and acidified by the addition of an excess (50 ml.) of concentrated aqueous hydrochloric acid. The aqueous layer is removed by siphoning, and the organic layer is washed with four 500-ml. portions of hot (60°) water. The aqueous layer is separated each time by siphoning. After the fourth washing, the oily product is solidified by cooling the flask in an ice bath, and the residual water is drained off. The crude product is dried on the steam bath under vacuum (Note 4).

The crude acid is dissolved in 500 ml. of petroleum ether at room temperature. The small

amount of amorphous solid which may separate is removed by filtration through Supercel, and the filtrate is concentrated under reduced pressure to 300 ml. Chilling to 0–5° yields a first crop of tan crystals which is collected by suction filtration and washed with the minimum amount of ice-cold petroleum ether. Concentration of the mother liquors to 150 ml. and chilling yields a second crop of brownish crystals. The combined crops are dissolved in 300 ml. of petroleum ether, and the light-red solution is chilled to 0–5°. The almost white to light-tan crystals are collected, washed with a small amount of cold petroleum ether, and dried in a vacuum desiccator. There is obtained 51.5–61.5 g. (52–62%) of stearolic acid, m.p. 46–46.5° (Note 5).

2. Notes

1. Oleic acid of acceptable purity may be prepared from olive oil fatty acids by the method of Brown and Shinowara,[3] Wheeler and Riemenschneider,[4] Brown and Foreman,[5] or Khan, Deatherage, and Brown.[6] It may also be purchased from the Hormel Institute, Austin, Minnesota.

2. Experience has shown that about 5 g. atoms of sodium should be used for each mole of oleic acid used as starting material. For each gram atom of sodium, 0.8–1.0 g. of ferric chloride, 1 l. of liquid ammonia, and 0.5–0.7 mole of ammonium chloride are necessary. The sodamide reaction proceeds best in comparatively dilute liquid ammonia solution.

3. The liquid stearolic acid is highly susceptible to autoxidation in the presence of air,[7] and this portion of the work-up should be conducted in a nitrogen atmosphere.

4. Alternatively, the product obtained after acidification may be taken up in ether, and the ether extract washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness under reduced pressure. This procedure is reported by the submitters to be more convenient for preparations on a smaller scale, and to give a slightly improved yield.

5. This stearolic acid has been thoroughly characterized[6] by the freezing-point curve, ultraviolet and infrared spectra, ozonization, and hydrogenation. It has been shown to be free both of positional isomers and of olefinic acids such as oleic and elaidic acids. Its properties include: m.p. 46–46.5°, iodine number (Wijs titration, 30 minutes) 89.5, $n^{54.5}_{D}$ 1.4510, $n^{61.5}_{D}$ 1.4484, neutral equivalent 279.2–279.6 (theory 280.4), hydrogen uptake 95–100% of theory for a triple bond. The last trace of color is difficult to remove by recrystallization from petroleum ether. It can be removed, however, by crystallization from a 20–30% solution in acetone at –5° to –8°, or from an 8–10% solution at –20°, or by distillation (b.p. 189–190° /2mm.).

3. Discussion

Nearly all methods for preparation of stearolic acid involve dehydrohalogenation of a 9,10-dihalostearic acid, or its esters, with alcoholic potassium hydroxide; the most recent method is that of Adkins and Burks.[8] These methods employ drastic conditions, which result in poorer yields than those obtainable on dehydrohalogenation with sodamide.[6] Methyl 9,10-dibromostearate, on dehydrobromination with sodamide, yields stearolamide[6] (m.p. 82–83°) which may be hydrolyzed to stearolic acid. For preparative purposes, however, this method offers no special advantage over that described here.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

9,10-dihalostearic acid

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ether (60-29-7)

ammonium chloride (12125-02-9)

hydrogen (1333-74-0)

bromine (7726-95-6)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

acetone (67-64-1)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

ferric chloride (7705-08-0)

oleic acid (112-80-1)

sodamide (7782-92-5)

Stearolic acid (506-24-1)

dibromostearic acid

Methyl 9,10-dibromostearate (25456-04-6)

stearolamide

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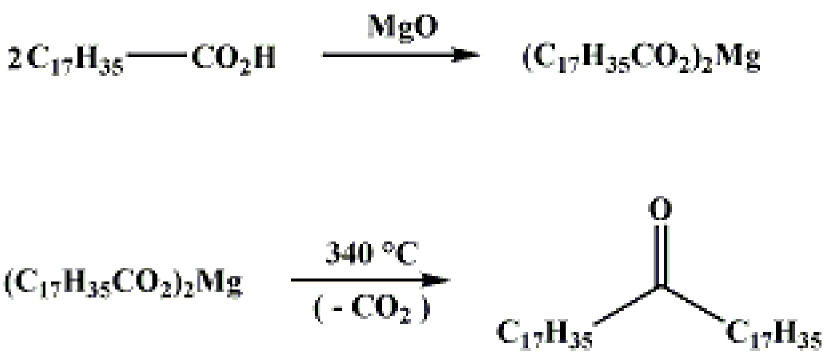
Organic Syntheses, CV 4, 854

STEARONE

[18-Pentatriacontanone]



Submitted by A. G. Dobson and H. H. Hatt[1].
Checked by R. L. Shriner and Philip R. Ruby.

1. Procedure

In a 1-l. round-bottomed flask, fitted with a heated reflux condenser maintained at 100–110° (Note 1), are placed 44 g. of stearic acid (Note 2) and 20 g. (0.5 mole) of magnesium oxide (Note 3). The flask is immersed in a Wood's metal bath heated at 335–340° (Note 4). After the reaction has proceeded for 1 hour, 10-g. portions of melted stearic are added down the condenser at 15-minute intervals until an additional 240 g. (284 g., 1 mole total) has been added (Note 5). The heating is continued until the total reaction time is 10 hours.

The reaction flask is removed from the metal bath and allowed to cool to about 100°, and the liquid contents are poured with stirring into 1 l. of 4*N* sulfuric acid in a 3-l. beaker. This mixture is boiled with vigorous mechanical stirring until the frothing ceases (Note 6) and the upper layer is clear (about 2 hours). The lower aqueous layer is then siphoned off, and the upper layer is boiled for 1 hour with 1 l. of water. The water layer is separated, and the upper layer is boiled with 1 l. of a 5% sodium hydroxide solution for 1 hour with vigorous stirring. The ketone layer is then separated and boiled for 1 hour each with three successive 1 l. portions of hot water (Note 7) with good stirring.

The crude stearone is allowed to solidify and is then broken up and dried by pressing between filter paper. The crude yield is 230–240 g. (91–95%). The product melts at 84–86° and has an acid value of zero. It is purified by dissolving in 1.2 l. of a 2:1 mixture of benzene and absolute ethanol, filtering hot, and allowing to crystallize (Note 8). After a second crystallization from the same mixed solvents, the stearone is obtained as glistening white flakes, melting clear at 89–89.5° (shrinks at 87–88°). The yield is 204–220 g. (81–87%) (Note 9).

2. Notes

1. The condenser, attached to the flask by a ground-glass joint, is a Pyrex tube 50 cm. long and 20 mm. in internal diameter, wound with No. 26 Nichrome wire covered with asbestos paper. It is connected to a variable transformer and adjusted so as to maintain a temperature of 100–110°. A copper Liebig condenser heated by steam is also suitable provided that the inner tube has a diameter of about 20 mm.

2. The purity and melting point of the final product are dependent on the purity of the stearic acid. If Armour's Neo-Fat 1-65, m.p. 64–67° (90–95% stearic acid) is recrystallized first from 95% ethanol and then from acetone, a stearic acid melting from 67° to 68° results which yields a stearone with a melting point of 88–89° (shrinks at 86–88°).

In order to obtain stearone with the highest melting point, the checkers found it necessary to purify the above recrystallized stearic acid by converting it to the methyl ester and fractionating this ester under reduced pressure, using a 30-in. electrically heated packed fractionating column. The fraction boiling at 180–182°/4 mm., n_D^{40} 1.4364, is collected. The methyl stearate solidifies on cooling and melts at 38–39°. Saponification and acidification yielded white crystals of stearic acid melting clear at 69–69.3° (cor.).

Commercial "stearone" (Armour) is made from Neo-Fat 1-60 (which is approximately 75% stearic and 25% palmitic acid) and melts at 80–84°.

3. Merck's reagent-grade magnesium oxide is suitable. The submitters recommend 10 g. of catalyst, but this amount gave a stearone with m.p. 87–88°. The larger amount, 20 g., gave a product melting clear at 89–89.5°.

4. The temperature of the bath should not be allowed to rise above 345°. Decomposition products are formed which lower the melting point of the final product.

5. With the rate of addition of stearic acid given, the decomposition of magnesium stearate maintains an excess of magnesium oxide in the reaction mixture. Each addition of stearic acid should take 1 to 2 minutes. Thus frothing of the reaction mixture is held under control; a brisk evolution of steam with a little entrained stearic acid follows each addition but quickly subsides and is followed by a steady effervescence due to the liberation of carbon dioxide.

6. A little unchanged magnesium stearate may cause frothing at this stage, which may be controlled by the addition of a few drops of 2-octanol and by vigorous stirring, which hastens decomposition of the soap.

7. The removal of fatty acids from neutral higher aliphatic compounds requires vigorous stirring of the hot aqueous and organic phases.

8. The solubility of stearone falls rapidly with temperature; a hot jacketed funnel is used with gentle suction.

9. This is a general method for the preparation of higher aliphatic ketones. It has been found suitable for the preparation of ketones from fatty acids containing 12 to 20 carbon atoms.

3. Discussion

Stearone has been prepared by heating the alkaline earth salts of stearic acid,[2] by reaction of liquid stearic acid with iron,[3,4,5] with alumina,[6] with manganous oxide and carbonate,[7] or with magnesium.[8] It has been prepared by passing stearic acid vapor over various catalysts: manganous oxide,[9] thoria aerogel,[10] or manganous oxide with chromium sesquioxide.[9] The literature contains numerous preparations from stearic acid using almost any metal or alkaline-earth oxides. It also has been obtained by the saponification of ethyl α-stearoylstearate with potassium hydroxide.[11]

Kino[12] studied the reaction of stearic acid with magnesium oxide, with alloys of magnesium, and many other metals, at high temperatures, and obtained stearone. The present method was developed from a reëxamination of this reaction.[13]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alumina

manganous oxide and carbonate

thoria aerogel

chromium sesquioxide

ethanol (64-17-5)

sulfuric acid (7664-93-9)

Benzene (71-43-2)

sodium hydroxide (1310-73-2)

magnesium (7439-95-4)

iron (7439-89-6)

carbon dioxide (124-38-9)

acetone (67-64-1)

potassium hydroxide (1310-58-3)

2-Octanol (123-96-6)

magnesium oxide

palmitic acid (57-10-3)

manganous oxide

stearic acid (57-11-4)

Stearone, 18-Pentatriacontanone (504-53-0)

methyl stearate (112-61-8)

magnesium stearate (557-04-0)

ethyl α-stearoylstearate

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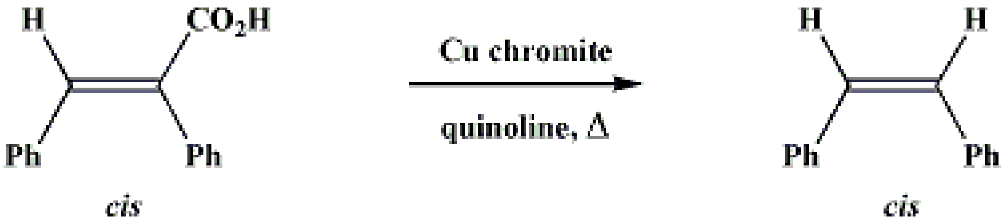
Organic Syntheses, *CV 4*, *857*

cis-STILBENE



Submitted by Robert E. Buckles and Norris G. Wheeler[1].
Checked by T. L. Cairns and J. C. Lorenz.

1. Procedure

A 500-ml. three-necked flask is fitted with a reflux condenser and a thermometer, the bulb of which reaches far enough into the flask to be covered by the liquid. A solution of 46.0 g. (0.205 mole) of α-phenylcinnamic acid (p. 777) (Note 1) in 280 ml. (307 g., 2.38 moles) of quinoline (Note 2) is added to the flask along with 4.0 g. of copper chromite.[2] The reaction flask is heated by means of a mantle or an oil bath until the temperature of the reaction mixture reaches 210–220°. The mixture is kept within this temperature range for 1.25 hours. The solution is then cooled immediately and added to 960 ml. of 10% hydrochloric acid in order to dissolve the quinoline (Note 3). The product is extracted from this mixture with two 200-ml. portions of ether followed by a 100-ml. portion. The combined ether extracts are filtered to remove particles of catalyst, washed with 200 ml. of 10% sodium carbonate, and dried over anhydrous sodium sulfate. The dry solution is removed from the drying agent by filtration and heated on a steam bath to distil the ether. The residue is dissolved in a hexane fraction, b.p. 60–72° (Skellysolve B); the solution is cooled to 0° and filtered to remove *trans*-stilbene, if any. The hydrocarbon solvent is removed by distillation, and the *cis*-stilbene is distilled. The yield is 23–24 g. (62–65%), b.p. 133–136° /10 mm., 95–97° /1 mm.; n_D^{25} 1.6183–1.6193, n_D^{20} 1.6212–1.6218 (Note 4).

2. Notes

1. The isomer of α-phenylcinnamic acid of m.p. 172–173° is used (p. 777). The isomer of m.p. 137–139° yields *trans*-stilbene on decarboxylation.[3]
2. Practical grade quinoline containing about 10% of isoquinoline and quinaldine can be used. If the quinoline contains water, the desired temperature can be reached by distillation of a small amount of quinoline directly from the reaction mixture.
3. The quinoline can be recovered by neutralization of the aqueous solution, extraction of the quinoline into ether, and distillation of the dried (over barium oxide) ether extract.

4. The product obtained from this type of decarboxylation is reported to contain only about 5% of *trans*-stilbene.[4] A sample made according to the above directions can be treated with bromine in carbon tetrachloride at room temperature in the dark to give an 80–85% yield of the *dl*-dibromide which arises from *trans* addition to *cis*-stilbene. The *meso*-dibromide, which is very insoluble and easily separated, is obtained only to the extent of 10% or less. Part of the latter product may arise from the action of bromine atoms on *cis*-stilbene rather than from *trans* addition to *trans*-stilbene. The *cis*-stilbene prepared by this method is readily and completely soluble in cold absolute ethanol. It freezes solid at about −5°. Its ultraviolet absorption coefficient (ε) is 1.10×10^4 at 274 m• and 8.7×10^3 at 294 m•, quite different from *trans*-stilbene.

3. Discussion

cis-Stilbene has been prepared by the partial hydrogenation of tolan;[5,6] by the electrolytic reduction of tolan;[7] by the reduction of tolan with a copper-zinc couple;[8] by the reduction of the low-melting isomer of α-bromostilbene with zinc dust in 90% alcohol;[9] by the illumination of *trans*-stilbene with ultraviolet light;[10] by the decarboxylation of the high-melting isomer of α-phenylcinnamic acid in the presence of barium hydroxide;[3] by heating tolan with diisobutylaluminum hydride[11] or zinc and acetic acid;[12] and by the reaction of *cis*-bromostilbene with butyllithium followed by treatment with methanol.[13] The present method is based on that of Taylor and Crawford.[14]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 777

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

copper-zinc couple

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

methanol (67-56-1)

ether (60-29-7)

sodium carbonate (497-19-8)

bromine (7726-95-6)

sodium sulfate (7757-82-6)

barium oxide

carbon tetrachloride (56-23-5)

Tolan (108-88-3)

zinc (7440-66-6)

barium hydroxide (17194-00-2)

Quinoline (91-22-5)

COPPER CHROMITE

α-bromostilbene

quinaldine (91-63-4)

butyllithium (109-72-8)

hexane (110-54-3)

isoquinoline (119-65-3)

diisobutylaluminum hydride (1191-15-7)

α-Phenylcinnamic acid (3368-16-9)

trans-Stilbene (103-30-0)

cis-Stilbene (645-49-8)

cis-bromostilbene

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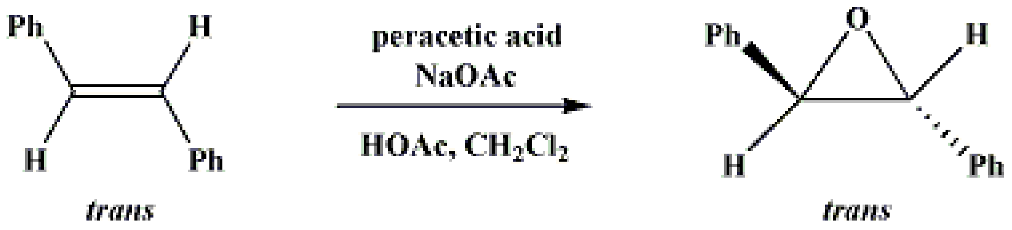
Organic Syntheses, CV 4, 860

trans-STILBENE OXIDE

[Bibenzyl, α,α'-epoxy-]



Submitted by Donald J. Reif and Herbert O. House[1].
Checked by Melvin S. Newman and Donald K. Phillips.

1. Procedure

In a 1-l. three-necked flask equipped with stirrer, dropping funnel, and thermometer is placed a solution of 54 g. (0.3 mole) of *trans*-stilbene (Note 1) in 450 ml. of methylene chloride. The methylene chloride solution is cooled to 20° with an ice bath, and then the cooling bath is removed. A solution of peracetic acid (0.425 mole) in acetic acid (Note 2) containing 5 g. of sodium acetate trihydrate is added dropwise and with stirring to the reaction mixture during 15 minutes. The resulting mixture is stirred for 15 hours, during which time the temperature of the reaction mixture is not allowed to rise above 35° (Note 3) and (Note 4). The contents of the flask are poured into 500 ml. of water, and the organic layer is separated. The aqueous phase is extracted with two 150-ml. portions of methylene chloride, and the combined methylene chloride solutions are washed with two 100-ml. portions of 10% aqueous sodium carbonate and then with two 100-ml. portions of water. The organic layer is dried over magnesium sulfate, and the methylene chloride is distilled, the last traces being removed under reduced pressure. The residual solid is recrystallized from methanol (3 ml./g. of product) to yield 46–49 g. (78–83%) of crude *trans*-stilbene oxide, m.p. 66–69° (Note 5). An additional recrystallization from hexane (3 ml./g. of product) sharpens the melting point of the product to 68–69°. The yield is 41–44 g. (70–75%).

2. Notes

1. *trans*-Stilbene (Eastman Kodak Company) may be used directly. A slightly higher yield is obtained if the stilbene is crystallized once from alcohol.
2. Approximately 40% peracetic acid in acetic acid is available (Becco Chemical Division, Food Machinery and Chemical Corporation, Buffalo 7, New York). Sodium acetate is added to neutralize a small amount of sulfuric acid which is present in the commercial product. The peracetic acid concentration should be determined by titration.[2] The peracetic acid solution used by the

submitters contained 0.497 g. (0.00655 mole) of peracid per milliliter. Consequently 65 ml. (0.425 mole) of this solution was used in the reaction.
3. Without further cooling, the temperature of the reaction mixture usually rises to 32–35° after 1–2 hours and then gradually falls.
4. The progress of the epoxidation can be followed by measuring periodically the optical density of the reaction mixture at 295 m•. The reaction time and temperature specified in the procedure were found to reduce the optical density of the reaction mixture at 295 m• (and, accordingly, the *trans*-stilbene concentration) to less than 3% of its initial value. If more than this amount of unchanged *trans*-stilbene remains in the crude product, it cannot be removed by recrystallization from either methanol or hexane. Even after repeated crystallization the melting point of the product does not rise above 66–67°. Pure *trans*-stilbene oxide can be isolated from such a mixture if the mixture is treated with additional peracetic acid to convert the remaining *trans*-stilbene to *trans*-stilbene oxide.
5. This melting point and yield are obtained after the crystalline product which separates from methanol has been dried under reduced pressure for 12 hours. This drying process is unnecessary if the product is subsequently to be recrystallized from hexane.

3. Discussion

trans-Stilbene oxide has been prepared by the reaction of silver oxide with the methiodide of 1,2-diphenyl-2-dimethylaminoethanol,[3,4] by the reaction of hydrazine with hydrobenzoin,[5] and by the reaction of peracetic acid[6,7] or perbenzoic acid[8] with *trans*-stilbene. The procedure described illustrates the use of a commercially available peracetic acid solution for the epoxidation of carbon double bonds. Since the reaction of *trans*-stilbene and other olefins conjugated with aromatic nuclei with peracids is slow, the procedure for the epoxidation of unconjugated olefins should be modified by the use of a lower reaction temperature, a shorter reaction time, and a longer period of time for the addition of the peracid.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 375
- Org. Syn. Coll. Vol. 6, 312

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

peracid

methiodide of 1,2-diphenyl-2-dimethylaminoethanol

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

methanol (67-56-1)

sodium acetate (127-09-3)

silver oxide (20667-12-3)

sodium carbonate (497-19-8)

hydrazine (302-01-2)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

stilbene

peracetic acid (79-21-0)

sodium acetate trihydrate (6131-90-4)

hexane (110-54-3)

hydrobenzoin

Perbenzoic acid (93-59-4)

trans-Stilbene oxide (1439-07-2)

trans-Stilbene (103-30-0)

Bibenzyl, α,α'-epoxy-

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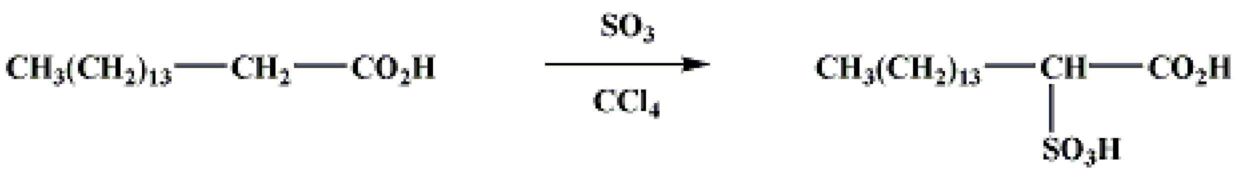
Organic Syntheses, CV 4, 862

α-SULFOPALMITIC ACID

[Hexadecanoic acid, 2-sulfo-]



Submitted by J. K. Weil, R. G. Bistline, Jr., and A. J. Stirton[1].
Checked by James Cason and Gerhard J. Fonken.

1. Procedure

Caution! Rubber gloves and a protective face shield should be worn while handling liquid sulfur trioxide, and the reaction should be carried out in a hood.

A 2-l. three-necked round-bottomed flask, with standard-taper ground-glass joints, is equipped for heating with an electric mantle or an oil bath, and fitted with a ball joint-sealed mechanical stirrer, a thermometer well, a graduated, pressure-equalizing dropping funnel, and a small vent. The dropping funnel, which should have a close-fitting stopcock well lubricated with heavy silicone grease, is placed so as to discharge sulfur trioxide well above the surface of the reaction mixture. Palmitic acid (200 g., 0.78 mole) (Note 1) and 600 ml. of carbon tetrachloride (Note 2) are added to the flask. Solution of the palmitic acid is endothermic and causes the temperature of the mixture to fall 5 to 10° below room temperature (Note 3). Stabilized liquid sulfur trioxide, 53 ml. (100 g., 1.25 moles) (Note 4), is added dropwise from the dropping funnel to the stirred mixture. Solution of palmitic acid becomes complete, the solution darkens, and the temperature rises to 45° as the sulfur trioxide is added over a 30-minute period. The reaction mixture is finally heated for 1 hour at 50–65° with continued stirring and is then chilled in an ice bath before the accessories are removed from the flask. The necks are closed with glass stoppers, and the reaction mixture is refrigerated at about −15° overnight (Note 5).

Crystallized solids are filtered by suction (Note 6), washed with cold carbon tetrachloride, and dried at room temperature in a vacuum desiccator to constant weight (1 to 2 days). The crude dark product weighs 197–223 g. (75–85%), and is usually satisfactory for the preparation of derivatives such as salts (Note 7) and esters.[2] One crystallization from acetone (7 ml./g.) at −20° yields a light gray solid, with neutralization equivalent within 1–2% of the theoretical value of 168, in a yield of 178–197 g. (68–75%). Two or three additional crystallizations (leaving a yield of only 25–30%) are required to give an almost colorless crystalline solid, m.p. 90–91° (Note 8). Once crystallized material is moderately stable to storage in a container protected

from moisture, but slow darkening occurs, especially in presence of sunlight.

2. Notes

1. A purified fatty acid is recommended for the preparation of a pure α-sulfo acid. Purified palmitic acid (m.p. 60.8–61.4°, neutralization equivalent 256.2) is prepared by twice recrystallizing a good commercial grade of palmitic acid from acetone at 0°, using a solvent ratio of 10 ml. to 1 g. However, the reaction may be applied to commercial saturated higher fatty acids, if the iodine number is sufficiently low. The checkers obtained similar results with recrystallized Neo-Fat 1-56 (Armour and Company, Chicago, Ill.) or Eastman white label grade palmitic acid.

2. Other chlorinated solvents such as tetrachloroethylene or chloroform may be used in place of carbon tetrachloride. *Caution! The reaction of sulfur trioxide with chlorinated solvents has been reported*[3] *to give phosgene and other toxic products. Adequate venting of all by-product gases is essential.*

3. The mixture which is a slurry at 15° may be used or it may be warmed to about 30° to give a clear solution. If the slurry is warmed before sulfur trioxide addition, it is usually not necessary to heat after all of the sulfur trioxide has been added.

4. Liquid sulfur trioxide may be purchased in stabilized form as Sulfan B,[4] m.p. 17°, b.p. about 45°. Caution must be exercised in handling sulfur trioxide. The liquid is highly corrosive to the skin and the vapor may cause injury if inhaled. The powerful oxidizing and dehydrating effects of sulfur trioxide should not be underestimated. The liquid may be stored in a glass-stoppered bottle if the stopper is lubricated with a heavy silicone grease. Because the liquid reacts violently with water the bottle lip should be wiped free of any moisture to avoid spattering when the liquid is poured. If solidification of sulfur trioxide should occur as the result of hydration, the vented (*Hood!*) solid may be liquefied by gentle application of heat from an infrared lamp.

5. Shorter refrigerating periods at temperatures up to +5° give slightly lower yields.

6. Since the mixture filters rather slowly, even after storage overnight, a Büchner funnel of at least 20 cm. diameter should be used, and a hard grade of filter paper (such as Whatman No. 50) is recommended. Use of a rubber dam helps to express solvent and exclude moisture from the hygroscopic product.

7. The monosodium salt $CH_3(CH_2)_{13}CH(SO_3Na)CO_2H$ may be prepared by neutralizing only the sulfonic acid group or by adding aqueous sodium sulfate to a hot aqueous solution of the crude α-sulfo acid and cooling to room temperature. The monosodium salt crystallizes in white plates, leaving most of the color in the filtrate. The disodium salt is formed by further neutralization with sodium hydroxide.

8. α-Sulfolauric, α-sulfomyristic, α-sulfostearic, and α-sulfobehenic acids have been prepared by this procedure. The table shows the melting point and neutralization equivalent after at least four recrystallizations and a 12-hour

drying period at 76° under 1 mm. pressure. There is some uncertainty in the melting points because of the hygroscopic character of the α-sulfo acids.

	Neutralization Equivalent		
	Found	Theoretical	M.P.
α-Sulfolauric acid	142	140.4	86.5–88°
α-Sulfomyristic acid	154	154.2	85–86.5°
α-Sulfopalmitic acid	171	168.2	90–91°
α-Sulfostearic acid	182	182.2	96–97°
α-Sulfobehenic acid	212	210.3	95–97°

3. Discussion

Other direct methods for the sulfonation of the higher fatty acids are by the use of sulfur trioxide vapor[5] or by the use of chlorosulfonic acid.[6] Indirect methods are also available for the preparation of α-sulfo fatty acids and their salts from an α-bromo fatty acid made by the Hell-Volhard-Zelinsky reaction. The bromo compound may be converted directly to the sodium salt of a sulfonic acid through the Strecker reaction[7] or may be converted to the mercaptan and oxidized to the sulfonate.[8] Sulfonation of the lower fatty acids has been studied by Backer and co-workers.[9]

α-Sulfonation with sulfur trioxide appears to be generally applicable to carboxylic acids having an α-methylene group.

References and Notes

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9. For example, de Boer, *Rec. trav. chim.*, **71** 814 (1952).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

monosodium salt $CH_3(CH_2)_{13}CH(SO_3Na)CO_2H$

sodium hydroxide (1310-73-2)

chlorosulfonic acid (7790-94-5)

sulfur trioxide (7446-11-9)

chloroform (67-66-3)

sodium sulfate (7757-82-6)

carbon tetrachloride (56-23-5)

acetone (67-64-1)

phosgene (75-44-5)

tetrachloroethylene (127-18-4)

palmitic acid (57-10-3)

α-Sulfopalmitic acid, Hexadecanoic acid, 2-sulfo- (1782-10-1)

α-Sulfolauric acid

α-Sulfomyristic acid

α-Sulfostearic acid

α-Sulfobehenic acid

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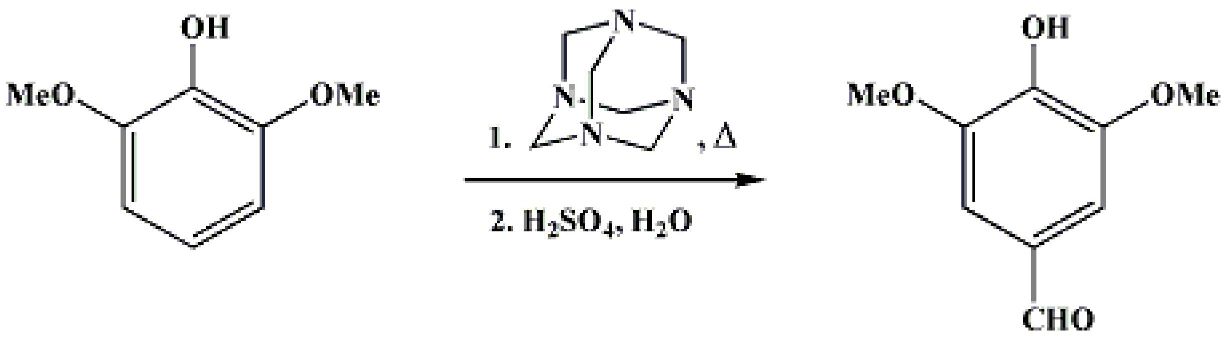
Organic Syntheses, CV 4, 866

SYRINGIC ALDEHYDE

[Syringaldehyde]



Submitted by C. F. H. Allen and Gerhard W. Leubner[1].
Checked by R. S. Schreiber, Wm. Bradley Reid, Jr., and R. W. Jackson.

1. Procedure

A well-stirred (Note 1) and (Note 2) mixture of 740 ml. of glycerol and 216 g. of boric acid, in a 2-l. three-necked round-bottomed flask fitted with a thermometer and a condenser for downward distillation, is dehydrated by heating in an oil bath to *exactly* 170°. This temperature is maintained for 30 minutes and then allowed to drop. When the temperature has fallen to 150°, a mixture of 154 g. (1 mole) of pyrogallol-1,3-dimethyl ether and 154 g. (1.1 moles) of hexamethylenetetramine (Note 3) is added as rapidly as possible through the neck holding the thermometer. The temperature drops to approximately 125°. Rapid heating is immediately started but is slowed down when the temperature begins to reach 145° and stopped at 148°. The reaction must be watched and controlled *very carefully* when this temperature is reached, since the reaction becomes exothermic at this point (Note 4), (Note 5), and (Note 6). The temperature is maintained at 150–160° for approximately 6 minutes (Note 7). At the end of this reaction time the mixture is cooled to 110° as rapidly as possible (Note 6) and (Note 8), and a previously prepared solution of 184 ml. of concentrated sulfuric acid in 620 ml. of water is added to the reaction mixture. After being stirred for 1 hour, the mixture is cooled to 25° in an ice bath. The boric acid, which separates from the solution, is removed by filtration (Note 9) and washed free of mother liquor with 400 ml. of water. The filtrate and washings are combined and extracted with three 500-ml. portions of chloroform (Note 10), (Note 11), and (Note 12).

The chloroform solution is then extracted with a filtered solution of 180 g. of sodium bisulfite in 720 ml. of water (Note 13) by stirring rapidly with a Hershberg stirrer for 1 hour. The separated bisulfite solution is washed twice with chloroform, filtered, and acidified in a hood with a solution of 55 ml. of concentrated sulfuric acid in 55 ml. of water. After careful heating on a steam bath for a short time, air is bubbled through the

hot solution until all the sulfur dioxide has been expelled. The product, which separates as a mixture of crystals and oil, readily solidifies upon cooling (Note 14). The syringic aldehyde is collected by filtration, washed with cold water, and dried in an oven at 40° to give 62.5–66 g. of light-tan material, melting at 110.5–111°, which still contains a small amount of foreign material that does not melt at 300°. Recrystallization of the crude product from aqueous methanol using 30 ml. of water and 3 ml. of methanol for each 10 g. of aldehyde gives 56–59 g. (31–32%) of product melting clear at 111–112° (uncor.). A second extraction of the chloroform solution with a filtered solution of 60 g. of sodium bisulfite in 240 ml. of water gives an additional 3–4 g. of product.

2. Notes

1. The use of a Hershberg[2] stirrer is recommended.
2. It is desirable to conduct this preparation in a hood because of the large volume of ammonia liberated in the second step.
3. Eastman Kodak Company white label grade pyrogallol-1,3-dimethyl ether was used. A larger excess of hexamethylenetetramine in a small trial run did not improve the yield.
4. The reaction mixture darkens rapidly, and there is a vigorous evolution of ammonia.
5. The temperature usually rises to 160° within 5 minutes, and cooling is necessary.
6. Cooling is accomplished by playing a stream of cold water over the outside of the flask.
7. There is undoubtedly some leeway in these conditions. The same yields were obtained when the temperature was maintained at 150–160° for periods of 5 to 9 minutes. Longer reaction times, without rapid cooling after the heating period, lowered the yield. Reaction times of 15 minutes, 30 minutes, and 1 hour gave yields of 20.8%, 10.0%, and 6.5%, respectively. Liggett and Diehl,[3] after having run a large number of other Duff reactions, have come to the conclusion that the temperature may vary between 145° and 175° without detriment to the yield.
8. About 3 to 5 minutes is required for cooling.
9. If not removed, the boric acid makes extraction of the product impossible or very difficult. Since the boric acid is finely divided, filtration is extremely slow unless large Büchner funnels, preferably with large holes, are employed. The checkers avoided the difficulty by using a filter cloth at this point.
10. The product cannot be isolated by steam distillation of the reaction mixture.
11. Syringic aldehyde is much more soluble in chloroform than in ether. Extraction is essentially complete since a fourth extraction gave only a 0.3–0.7% increase in yield.
12. If the aldehyde is isolated directly by concentration of the chloroform solution, the color is darker, and the melting point and yield are lower.
13. This represents a large excess of sodium bisulfite, but smaller amounts remove a smaller percentage of the syringic aldehyde from the chloroform

solution. When larger amounts of bisulfite are employed, extraction of the product is still incomplete.
14. The product should be cooled to just 15° and filtered immediately. Longer and further cooling causes sodium sulfate to crystallize from the mixture. Very little product remains in the filtrate.

3. Discussion

This procedure is a modification of the method described by Manske and co-workers.[4] Syringic aldehyde has also been obtained by numerous other procedures from pyrogallol-1,3-dimethyl ether[5,6,7,8] from gallic acid,[9,10,11] and from vanillin.[12]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

ammonia (7664-41-7)

methanol (67-56-1)

ether (60-29-7)

chloroform (67-66-3)

glycerol (56-81-5)

sulfur dioxide (7446-09-5)

sodium sulfate (7757-82-6)

sodium bisulfite (7631-90-5)

hexamethylenetetramine (100-97-0)

boric acid (10043-35-3)

vanillin (121-33-5)

Syringic aldehyde, Syringaldehyde (134-96-3)

pyrogallol-1,3-dimethyl ether

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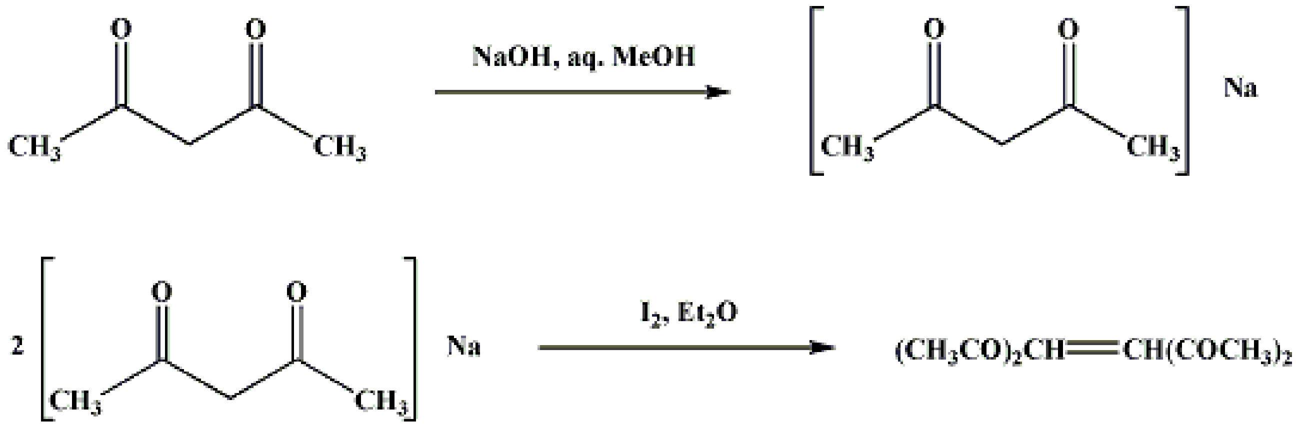
Organic Syntheses, CV 4, 869

TETRAACETYLETHANE

[2,5-Hexanedione, 3,4-diacetyl-]



Submitted by Robert G. Charles[1]
Checked by Virgil Boekelheide and Henry Fleischer.

1. Procedure

A. *Sodium acetylacetonate*. A solution is prepared by dissolving 40 g. (1 mole) of sodium hydroxide in 50 ml. of water and adding to this 200 ml. of methanol. This solution is added, slowly with hand stirring, to 100 g. (1 mole) of acetylacetone (2,4-pentanedione) contained in a 500-ml. Erlenmeyer flask (Note 1). The creamy-white crystalline salt separates from solution immediately. The flask is stoppered and cooled in ice (or in a refrigerator) for 2 hours or overnight. The sodium salt is collected on a Büchner funnel and washed with two small portions of cold methanol (Note 2). After the salt is air-dried, it is dried further either by allowing it to stand in a vacuum desiccator at room temperature or by heating it in a vacuum oven at 100° for 3 hours (Note 3). The anhydrous product, which is stable and can be stored indefinitely in a stoppered jar, weighs 70–80 g. (57–66%).

B. *Tetraacetylethane*. Sodium acetylacetonate is ground to a fine powder in a mortar, and 24.4 g. (0.2 mole) of the anhydrous material or 28.9 g. of the hydrate (Note 3) is weighed into a 1-l. Erlenmeyer flask. After 300 ml. of ether has been added, the suspension is stirred vigorously at room temperature with a magnetic stirrer. To the stirred mixture is added, dropwise from a separatory funnel, a solution of 25.4 g. (0.1 mole) of iodine dissolved in 300 ml. of ether. The rate of addition is maintained roughly constant by occasional adjustments of the stopcock, and the total addition is completed in about 2.5 hours. The reaction mixture is then poured into a large Erlenmeyer flask, and the ether is allowed to evaporate overnight at room temperature in a hood (Note 4). To the contents of the flask there is then added 500 ml. of water, and the mixture is allowed to stand for 2 hours. The remaining solid is collected on a Büchner funnel, washed several times with water, and finally dried in a vacuum desiccator. The yield (Note 5) of white solid, m.p. 185–188°, is 11–13 g. For purification, the product is taken up in 500–700 ml. of boiling methanol and the hot solution is filtered through a semi-fluted filter paper in a heated funnel. The filtrate is allowed to stand in the refrigerator for several hours. There is collected from the filtrate 8.0–11.7 g. (41–59%) of white crystals, m.p. 192–193° (cor.).

2. Notes

1. Eastman practical grade acetylacetone was found to be sufficiently pure for the preparation.
2. Washing with methanol decreases the yield somewhat but improves the purity of the product visibly. Additional, but less pure, sodium salt can be obtained if desired by combining the filtrate and washings, and evaporating.
3. The sodium salt dried in a vacuum oven is anhydrous, while that dried in a vacuum desiccator was found to contain 15.6% water.
4. Some hazard is always involved in the evaporation of ether to dryness. To minimize the hazard, peroxide-free ether should be used and the evaporation conducted behind a shield. No difficulties have been encountered in the submitter's laboratory with a number of these preparations using previously unopened cans of anhydrous ether. If desired, the ether could be recovered by distillation. The explosive hazard is probably increased, however, by such a procedure.
5. The yield is essentially the same whether anhydrous or hydrated sodium acetylacetonate is used.

3. Discussion

Tetraacetylethane has been prepared previously both by the use of sodium metal[2] and of sodium hydride[3] with acetylacetone followed by addition of iodine. Also, the compound has been prepared in low yield by the reaction of diacetyl peroxide with acetylacetone[4] and by the electrolysis of acetylacetone in an alcohol-water solution.[2] The present method, although similar to those first mentioned, is somewhat more convenient and does not require anhydrous conditions.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Sodium acetylacetonate

methanol (67-56-1)

ether (60-29-7)

sodium hydroxide (1310-73-2)

iodine (7553-56-2)

sodium (13966-32-0)

Acetylacetone, 2,4-pentanedione (123-54-6)

sodium hydride (7646-69-7)

Tetraacetylethane

2,5-Hexanedione, 3,4-diacetyl- (5027-32-7)

diacetyl peroxide (110-22-5)

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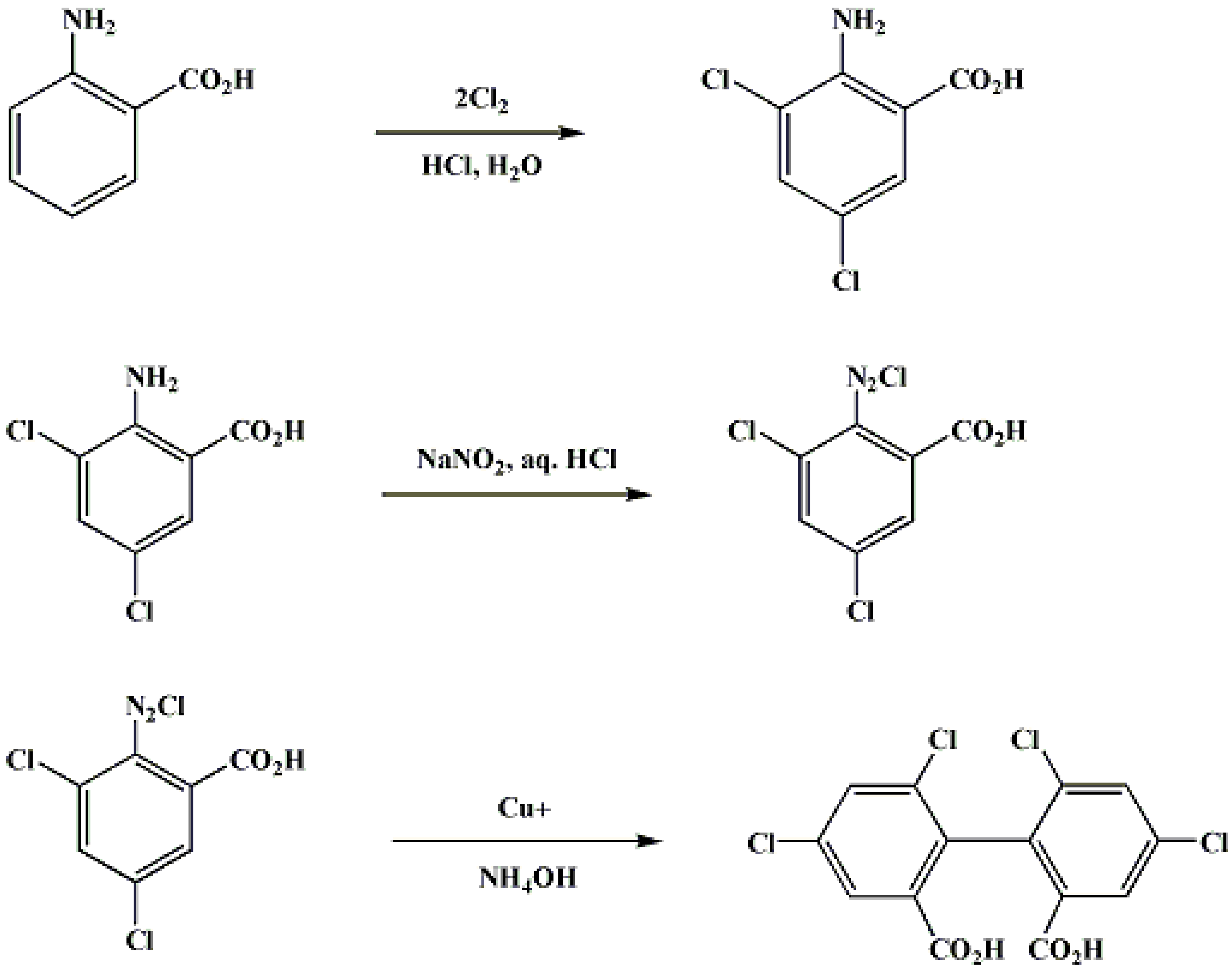
Organic Syntheses, CV 4, 872

dl-4,4',6,6'-TETRACHLORODIPHENIC ACID

[*dl*-Diphenic acid, 4,4',6,6'-tetrachloro-]



Submitted by Edward R. Atkinson, Donald M. Murphy, and James E. Lufkin[1].
Checked by R. S. Schreiber, Wm. Bradley Reid, Jr., and R. D. Birkenmeyer.

1. Procedure

A. *3,5-Dichloro-2-aminobenzoic acid*. A solution of 45 g. (0.33 mole) of anthranilic acid, 150 ml. of concentrated hydrochloric acid, and 850 ml. of water is placed in a 2-l. three-necked flask in a hood and weighed. While the solution is stirred rapidly, chlorine is introduced until the reaction mixture gains 45 g. (0.63 mole) in weight (Note 1). The flask is surrounded by a water bath to maintain the temperature of the reaction mixture below 30° during the chlorination procedure. The reaction mixture is filtered by suction, using a large (10–12 in.) Büchner funnel; the crude product is washed with water and then dried at room temperature (Note 2). There is obtained 55–65 g. of crude product melting at about 205°. The crude product is leached with 4 ml. of boiling benzene per gram, filtered by suction, and washed on the filter with 1 ml. of cold benzene per gram. After drying at room temperature, there is obtained 46.5–53 g. (69–78%) of crude 3,5-dichloro-2-aminobenzoic acid. The melting point of this material should not be lower than 211° (Note 3) and (Note 4).

B. *Diazotization of 3,5-dichloro-2-aminobenzoic acid*. Fifty grams (0.24 mole) of 3,5-dichloro-2-aminobenzoic acid is dissolved in a solution of 12 g. (0.3 mole) of sodium hydroxide in 700 ml. of water. To this solution is added 20 g. (0.29 mole) of sodium nitrite, and the solution is cooled to 10° (Note 5). One hundred milliliters of concentrated hydrochloric acid (sp. gr. 1.191) and 200 ml. of water are placed in a 2-l three-necked flask and cooled to 10°. The cold solution of sodium 3,5-dichloro-2-aminobenzoate and sodium nitrite is then added to the hydrochloric acid solution with cooling (10°) and efficient stirring at such a rate that no appreciable accumulation of undiazotized amine results (Note 6). At the conclusion of the diazotization, the resulting solution is stirred a few minutes with 2 g. of diatomaceous earth and filtered by suction (Note 7).

C. *Preparation of the reducing agent.* One hundred and twenty-five grams (0.5 mole) of cupric sulfate pentahydrate is dissolved in 500 ml. of water contained in a 3-l. three-necked flask equipped with a mechanical stirrer, and then 210 ml. of concentrated ammonium hydroxide (sp. gr. 0.90) is added with stirring. The solution is cooled to 10°. A solution of 40 g. (0.57 mole) of hydroxylamine hydrochloride in 140 ml. of water is prepared and also cooled to 10°. To the hydroxylamine hydrochloride solution there is added 95 ml. of 6*N* sodium hydroxide solution, and if not entirely clear, it is filtered by suction. This hydroxylamine solution is immediately added to the ammoniacal cupric sulfate solution with stirring. Reduction occurs at once with the evolution of nitrogen, and the solution becomes pale blue. If this solution is not used at once, it should be protected from the air.

D. *dl-4,4',6,6'-Tetrachlorodiphenic acid.* The reducing solution prepared above is cooled to 10° and maintained at 10–15° during the addition of the diazo solution from Part B, which is added from dropping funnel. A feed tube having a 2-mm. opening and dipping well below the surface of the reducing solution should be attached to the stem of the dropping funnel. The feed tube should be bent upward at the end and so placed that mixing of the reducing solution occurs rapidly (Note 8). The diazo solution is added at approximately 25 ml. per minute, and excessive foaming is suppressed by the addition of small amounts of ether (Note 9). At the conclusion of the reaction (Note 10), the ammoniacal solution is transferred to two 4-l. beakers, heated to 80–90°, and rapidly acidified to litmus with concentrated hydrochloric acid with vigorous stirring (Note 11). At this point acidification is continued more carefully until the solution is acid to Congo red (Note 12). A total excess of 100 ml. of acid is then added, and the solution is allowed to stand overnight. The product is filtered by suction and washed on the filter with four 250-ml. portions of water. After drying, the yield of crude product, melting at 180–215°, is 29–38.5 g. (63–84%).

The crude product is dissolved in 3.5 ml. of concentrated sulfuric acid per gram, heated with stirring to 150° for 5 minutes, and allowed to cool overnight. The resulting product is filtered by suction through a sintered-glass funnel and washed on the filter with three 15-ml. portions of concentrated sulfuric acid at room temperature. The filter cake is removed from the funnel and boiled with 50 ml. of water to remove adherent sulfuric acid. The product is then filtered and dried. The above procedure yields 19–22 g. (41–48%) of almost colorless *dl*-4,4'6,6'-tetrachlorodiphenic acid melting at 243–250° (uncor.) (Note 13). Pure acid may be obtained by a second recrystallization from concentrated sulfuric acid. Twenty grams of crude *dl*-4,4',6,6'-tetrachlorodiphenic acid, m.p. 243°, recrystallized from 70 ml. of concentrated sulfuric acid yields 6.54 g. (33% recovery) of colorless product melting at 258–259°.

2. Notes

1. The rate of flow of chlorine is adjusted so that the reaction mixture is saturated with gas and some gas escapes from the surface of the solution. An indication of proper duration of chlorination is the development of a distinct brown color in the suspension. Further chlorination leads to a decrease in yield with the formation of polychloro products.[2] The time required for chlorination is about 1 hour.
2. Drying at elevated temperatures gives an inferior product because of the formation of polychloro by-products at this stage.
3. Pure 3,5-dichloro-2-aminobenzoic acid[3] has a melting point of 231°. The product described here is adequate for the subsequent step.
4. This procedure can be performed using 10 times the quantities specified. The chlorination is carried out in a jar having a capacity of 12–14 l. Chlorine is introduced by means of a copper tube coiled at the bottom of the jar and perforated in several places. The time of chlorination is 2 hours. The percentage yield is the same as that for the scale described above.
5. This solution is almost saturated with the sodium salt of 3,5-dichloro-2-aminobenzoic acid. If crystallization occurs, additional water may be added. Obviously, temperatures below 10° should be avoided.
6. As the salt solution enters the acid solution, there is a momentary precipitation of the amino acid, which dissolves rapidly as it is diazotized. The checkers found that this addition took about 2 hours.
7. The diazo solution may be stored as long as 1 day at 10–15°. The insoluble gelatinous material that forms during storage should be removed by filtration just before use. The filter flask used at this point should be cooled in an ice bath to prevent further decomposition of diazo solution.
8. This trap arrangement prevents premature reaction of the entering diazo solution with ammonia, which otherwise would be carried up the feed tube by ascending bubbles of nitrogen.
9. The rate of addition is not a critical factor. More rapid addition requires more vigorous stirring and may lead to troublesome foaming.
10. The solution may stand for a week before being used.
11. The checkers recommend the use of a Hershberg stirrer.
12. Basic copper salts which precipitate during the acidification redissolve before the Congo red end point is reached if the later stages of acidification are performed carefully with adequate stirring.
13. This procedure is adaptable to 10 times the quantities specified here. Diazotization is carried out in a 12-l. jar. The diazo solution is allowed to stand overnight to facilitate the separation, by decantation or siphoning, of the non-diazotizable impurities whose large-scale filtration is tedious. The main synthesis is performed in a carboy having a capacity of not less than 30 l. The metal stirrer is protected by a coat of paraffin wax. Several addition tubes are used for the diazo solution. By adding appropriate quantities of ice, the necessity of external cooling for these large vessels is avoided. The yield is 39–42% of material melting at 244–250°.

3. Discussion

3,5-Dichloro-2-aminobenzoic acid can be prepared by the chlorination of anthranilic acid in glacial acetic acid solution[3] and by the action of sulfuryl chloride on anthranilic acid.[4,5] The

procedure above is derived from a detailed study of the chlorination reaction.[2]

The method described for the preparation of *dl*-4,4',6,6'-tetrachlorodiphenic acid is based on the work of Atkinson and Lawler[6] but employs a more suitable reducing agent than that[7] previously used to convert diazotized anthranilic acid to diphenic acid. The product can be resolved into its optically active forms,[6] which are stable to racemization.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

dl-4,4',6,6'-TETRACHLORODIPHENIC ACID

dl-Diphenic acid, 4,4',6,6'-tetrachloro-

dl-4,4'6,6'-tetrachlorodiphenic acid

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ammonia (7664-41-7)

Benzene (71-43-2)

ether (60-29-7)

sodium hydroxide (1310-73-2)

nitrogen (7727-37-9)

cupric sulfate (7758-98-7)

sodium nitrite (7632-00-0)

copper (7440-50-8)

sulfuryl chloride (7791-25-5)

chlorine (7782-50-5)

ammonium hydroxide (1336-21-6)

Anthranilic Acid (118-92-3)

Hydroxylamine hydrochloride (5470-11-1)

cupric sulfate pentahydrate (7758-99-8)

3,5-Dichloro-2-aminobenzoic acid (2789-92-6)

sodium 3,5-dichloro-2-aminobenzoate, sodium salt of 3,5-dichloro-2-aminobenzoic acid

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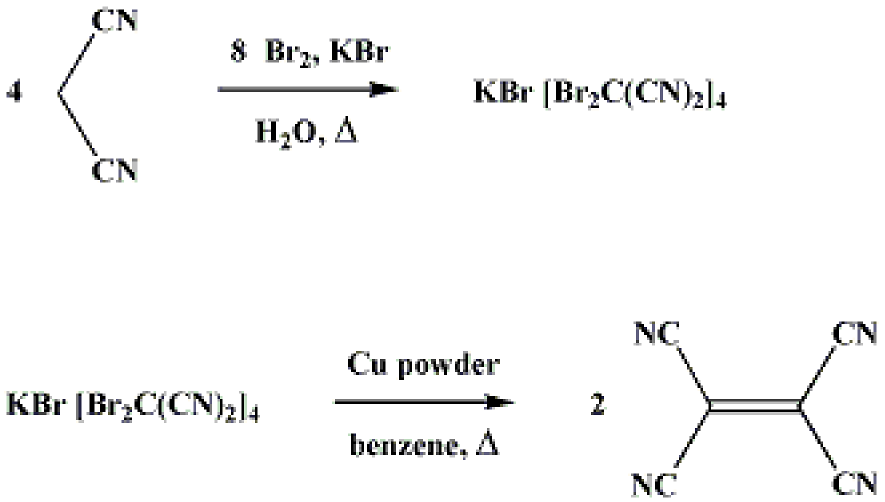
Organic Syntheses, CV 4, 877

TETRACYANOETHYLENE

[Ethenetetracarbonitrile]



Submitted by R. A. Carboni[1]
Checked by James Cason and Edwin R. Harris.

1. Procedure

Caution! Tetracyanoethylene slowly evolves hydrogen cyanide when exposed to moist air at room temperature. This material should be handled under a hood, and contact with the skin should be avoided. The first step in the preparation should also be carried out under a hood, since bromine is used.

A. *Dibromomalononitrile-potassium bromide complex.* In a 2-l. three-necked flask equipped with an efficient stirrer, a dropping funnel, and a thermometer are placed 900 ml. of cold water, 99 g. (1.5 moles) of malononitrile (Note 1), and 75 g. (0.63 mole) of potassium bromide. The flask is then placed in an ice-water bath, the stirrer is started, and the thermometer is adjusted to extend into the liquid but not into the path of the stirrer. When the temperature of the mixture has dropped to 5–10° (much solid crystallizes), 488 g. (158 ml. at 25°, 3.05 moles) of bromine is added over a period of 2.5 hours. The stirring is continued for an additional 2 hours, while the temperature is held at 5–10°. The precipitated solid complex is collected on a Büchner funnel, washed with 150 ml. of ice-cold water and sucked as dry as possible for about 1 hour (Note 2) and (Note 3). The grainy product is then dried to constant weight in a vacuum desiccator over phosphorus pentoxide, at the pressure obtained with an aspirator (Note 4) and (Note 5). The yield of light-yellow product is 324–340 g. (85–89%) (Note 3).

B. *Tetracyanoethylene*. A mixture of 254 g. (0.25 mole) of the dibromomalononitrile-potassium bromide salt and 1 l. of dry benzene is placed in a 2-l. three-necked flask fitted with a sealed mechanical stirrer and a reflux condenser. The stirrer is started

(Note 6), and 100 g. (1.57 g. atoms) of precipitated copper powder (Note 7) is added. The mixture is heated at reflux with constant stirring for 10–16 hours. The benzene layer becomes progressively deeper yellow as the reaction proceeds. At the end of the reaction period, the hot mixture is filtered by gravity, using a fluted paper. Most of the heavy solid is easily retained in the flask and is heated under reflux with 300 ml. of dry benzene, with stirring, for 30 minutes. Filtration of the hot mixture is carried out as before. Two 25-ml. portions of hot benzene are used to wash the precipitate and are decanted through the filter.

The combined filtrates are concentrated to approximately 350 ml. and cooled overnight at about 5°. The crystals are filtered by suction, washed with two 25-ml. portions of cold benzene, and dried in a vacuum desiccator (Note 8). The product weighs 35–40 g. (55–62%) and melts at 197–199° in a sealed capillary tube (Note 9) and (Note 10). This material is suitable for subsequent reactions if it is used within a day or two, although it gives somewhat lower yields than obtained with recrystallized material. This product may be purified, to yield material stable to storage, by recrystallization from nine times its weight of dry chlorobenzene (Note 11). There is recovered 85–90% of light beige crystals (Note 12) and (Note 13) melting at 199–200° (sealed capillary tube.).

2. Notes

1. The malononitrile was obtained from the Winthrop-Stearns Corp., New York, N. Y., and melted at 30–31°.
2. The vapors of dibromomalononitrile-potassium bromide complex are irritating to the eyes and nose. The solid causes discoloration of the skin on contact. Manipulations should be carried out with gloves in a hood.
3. An additional few grams of product separates from the filtrate during this period, and a little more separates during 1–2 days' standing. This material amounts to 10–20 g. (2.5–5%) additional yield satisfactory for the next step.
4. The product may also be dried in a vacuum oven at 50°; however, the deposition of some free dibromomalononitrile on the walls of the oven renders this method of drying less advantageous. If an oil pump is used to evacuate the desiccator, it should be protected by an adequate trap containing solid sodium hydroxide.
5. It is essential that the complex be thoroughly dried; otherwise the yield of tetracyanoethylene in the subsequent step is materially decreased.
6. Dryness of the complex may be assured, and checked, by attaching a distillation head to the third neck of the flask and distilling benzene until the distillate has run clear for a few milliliters. If the apparatus and reagents were properly dried, only 10–20 ml. of slightly cloudy distillate should be observed.
7. The precipitated copper powder, Grade MD 98, was obtained from Metals Disintegrating Co., Elizabeth, New Jersey.
8. The crude product retains the odor characteristic of dibromomalononitrile and will stain the skin. Pure tetracyanoethylene is practically odorless.
9. The capillary is sealed in order to prevent sublimation; it should not be

evacuated unless totally immersed in the heating bath, otherwise sublimation into the cooler part of the sealed capillary will occur.

10. A small additional quantity of less pure product may be obtained by heating the mother liquor with 20 g. of fresh copper powder for 1 hour with stirring, then filtering and concentrating the filtrate to about 100 ml. An equal volume of cyclohexane is added to the hot concentrate, and the mixture is cooled at about 5° for about 30 minutes. Following this procedure in one run, the checkers obtained a yield of 2.9 g. which was recrystallized from 26 g. of chlorobenzene to give 2.1 g. of unattractive material with a poor melting point.

11. The solubility of tetracyanoethylene in chlorobenzene apparently increases sharply as the boiling point of the solvent is approached. Thus the crystals should be extracted in boiling chlorobenzene. Chlorobenzene may be conveniently dried by distilling until the distillate no longer runs cloudy (azeotrope, b.p. 90°, 28.4% water).

12. The crystals, which are yellow when wet with chlorobenzene, become light-colored as the solvent is removed during drying.

13. If an especially good product is desired, the recrystallized material is sublimed at 130–140° /1 mm. A still better product with no trace of color may be obtained by subliming the recrystallized tetracyanoethylene through activated carbon. For example, 35 g. of tetracyanoethylene is placed in a glass thimble and covered with 20–25 g. of activated wood charcoal chips (4–8 mesh). The mouth of the thimble is covered with a coarse grade of filter paper which is held in place by wiring. The thimble is placed in a sublimer, and the sublimation is carried out at 1–2 mm. (bath temperature 175–190°). The tetracyanoethylene is recovered in 80–90% yield as a colorless, hard crystalline mass that melts at 201–202° (sealed tube).

3. Discussion

The procedure given above for the dibromomalononitrile-potassium bromide complex is essentially that of Ramberg and Wideqvist.[2] Tetracyanoethylene has also been prepared by passing malononitrile and chlorine through a hot tube at 400°.[3] The present procedure, based on that described by Cairns et al.,[3] appears to be the best preparative method. Metals, other than copper, have been used to effect the reaction.[4] Tetracyanoethylene, the first example of a percyanoölefin, has shown exceptional reactivity in a number of addition reactions. For example, it is a very active dienophile, reacting rapidly at room temperature with many 1,3-dienes to give the corresponding Diels-Alder products.[5] With aromatic hydrocarbons, it forms π-complexes of characteristic colors ranging from yellow to green,[6] and it has been used as a color-forming reagent in paper chromatography of aromatic compounds.[7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 243

- Org. Syn. Coll. Vol. 4, 276
- Org. Syn. Coll. Vol. 4, 953
- Org. Syn. Coll. Vol. 5, 1007
- Org. Syn. Coll. Vol. 5, 1013

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Benzene (71-43-2)

sodium hydroxide (1310-73-2)

hydrogen cyanide (74-90-8)

bromine (7726-95-6)

copper (7440-50-8)

cyclohexane (110-82-7)

carbon (7782-42-5)

chlorobenzene (108-90-7)

chlorine (7782-50-5)

potassium bromide (7758-02-3)

Malononitrile (109-77-3)

Tetracyanoethylene, Ethenetetracarbonitrile (670-54-2)

Dibromomalononitrile-potassium bromide

dibromomalononitrile

phosphorus pentoxide (1314-56-3)

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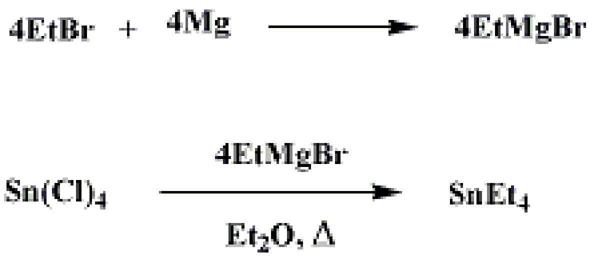
Organic Syntheses, CV 4, 881

TETRAETHYLTIN

[Tin, tetraethyl-]



Submitted by G. J. M. Van Der Kerk and J. G. A. Luijten[1].
Checked by M. S. Newman and L. L. Wood.

1. Procedure

A 2-l. three-necked flask is fitted with a reflux condenser (Note 1), a stirrer (Note 2), and a dropping funnel. The flask is suspended in a steam cone, which can also be used as a cooling bath. In the flask is placed 50 g. (2.05 g. atoms) of fine magnesium turnings (Note 3). In the dropping funnel is first introduced 5 ml. of a solution of 250 g. (175 ml., 2.3 moles) of ethyl bromide in 500 ml. of absolute ether. Three drops of bromine is mixed with the 5 ml., and the mixture is added to the magnesium. The Grignard reaction which starts at once (Note 4) is maintained by gradually adding the remainder of the ethyl bromide-ether solution. When the spontaneous reaction subsides, the mixture is heated gently under reflux with stirring for 30 minutes.

The flask is then cooled in ice, and in the course of about 20 minutes 83 g. of tin tetrachloride (37 ml., 0.32 mole) is added with vigorous stirring (Note 5). The mixture is heated at the reflux temperature for 1 hour, after which the condenser is set for distillation. During 1.5 hours the ether is removed by distillation while the flask is heated by an ample supply of steam (Note 6) and (Note 7).

The flask is again cooled in ice, the collected ether is returned to the reaction mixture, and the latter is decomposed by slowly adding first 85 ml. of ice water, then 400 ml. of ice-cold 10% hydrochloric acid. After stirring for some minutes, the contents of the flask are transferred to a separatory funnel. The layers are separated, and the ether layer is filtered through a folded filter and dried with calcium chloride (Note 8).

The ether is removed by distillation, and the crude tetraethyltin is distilled under water-pump vacuum, using a water bath for heating. The yield of tetraethyltin boiling at 63–65° /12 mm. is 67–72 g. (89–96%), n_D^{25} 1.4693–1.4699, d_4^{25} 1.1916 (Note 9).

2. Notes

1. A wide condenser must be employed to permit an ample reflux of ether.
2. A seal is recommended as described in *Org. Syntheses Coll. Vol.* **3**, 368 (1955), Note 1.
3. The submitters have carried out this preparation on a three-fold scale with comparable yields.
4. In general bromine starts Grignard reactions more quickly than the usually employed iodine.
5. For adding the tin tetrachloride it is advisable to use a dropping funnel which contains no ether vapor, since the latter gives troublesome formation of solid etherate.
6. The stirrer must be stopped at the beginning of the distillation or it will break, for the contents of the flask turn into a solid mass.
7. Removal of the ether is necessary to permit raising the reaction temperature. The temperature at the center of the mass reaches 60–65°. During the 1.5 hours of distillation, about 200 ml. of ether is collected, the remainder being firmly bound as etherates.
8. To obtain a product free from traces of triethyltin halide the dried ethereal solution is treated with dry ammonia, and the precipitate formed is removed by filtration.
9. The submitters report that the same yields in terms of percentages are obtained if the procedure is applied to the preparation of tetra-*n*-propyltin and tetra-*n*-butyltin.

3. Discussion

Tetraethyltin has been prepared from tin-sodium alloy and ethyl iodide;[2] from tin-sodium-zinc alloy and ethyl bromide;[3,4] from tin tetrachloride and ethylmagnesium bromide;[5,6,7,8] or triethylaluminum;[9] from tin-magnesium alloy and ethyl bromide or chloride;[10,11,12] and from stannous chloride and ethyllithium.[13] The method described is essentially that of Pfeiffer and Schnurmann.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 258

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethyl bromide or chloride

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ether (60-29-7)

magnesium, magnesium turnings (7439-95-4)

bromine (7726-95-6)

Ethyl bromide (74-96-4)

stannous chloride

iodine (7553-56-2)

ethylmagnesium bromide (925-90-6)

tin tetrachloride (7646-78-8)

Ethyl iodide (75-03-6)

Tetraethyltin, Tin, tetraethyl- (597-64-8)

tin-sodium

tin-sodium-zinc

triethylaluminum (97-93-8)

tin-magnesium

ethyllithium

tetra-n-propyltin (2176-98-9)

tetra-n-butyltin (1461-25-2)

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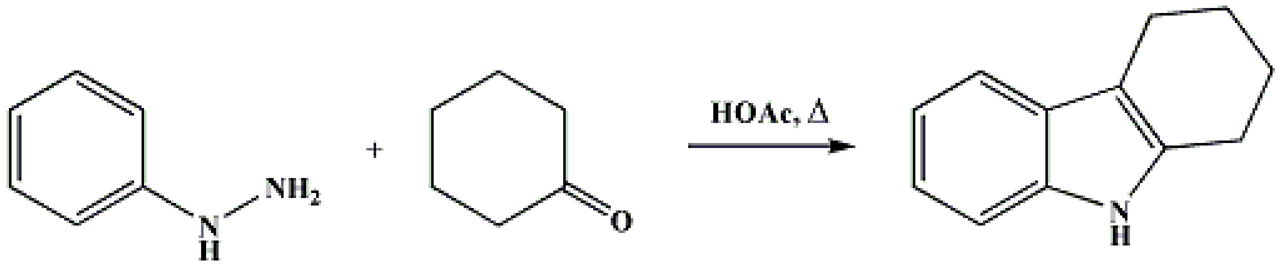
Organic Syntheses, CV 4, 884

1,2,3,4-TETRAHYDROCARBAZOLE

[Carbazole, 1,2,3,4-tetrahydro-]



Submitted by Crosby U. Rogers and B. B. Corson[1].
Checked by Charles C. Price, Kenneth N. Campbell, and Robert P. Kane.

1. Procedure

A mixture of 98 g. (1 mole) (Note 1) of cyclohexanone and 360 g. (6 moles) of acetic acid contained in a 1-l. three-necked round-bottomed flask equipped with a reflux condenser, a slip-sealed stirrer, and a dropping funnel is heated under reflux and stirred while 108 g. (1 mole) of phenylhydrazine is added during 1 hour. The mixture is heated under reflux for an additional hour and poured into a 1.5-l. beaker and stirred by hand (Note 2) while it solidifies. It is then cooled to about 5° and filtered with suction, the filtrate being cooled in ice and refiltered through the filter cake. The final filtrate is discarded. The filter cake is washed with 100 ml. of water and finally with 100 ml. of 75% ethanol. Each wash is allowed to soak into the filter cake before it is sucked dry. The crude solid is air-dried overnight (Note 3) and crystallized (Note 4) from 700 ml. of methanol after treatment with decolorizing carbon (Note 5); yield 120–135 g. of 1,2,3,4-tetrahydrocarbazole, m.p. 115–116° (Note 6). The mother liquor is concentrated to one-fourth of its original volume and yields an additional 10 g. of product (total yield 76–85%) (Note 7).

2. Notes

1. Equivalent amounts of cyclohexanone (after suitable compensation for purity) and phenylhydrazine are used. The cyclohexanone was about 90% pure (analyzed by the procedure of Bryant and Smith[2]). Instead of analyzing the ketone, it is safe to assume 90% purity.
2. The stirring should be sufficiently vigorous to prevent the formation of lumps.
3. The crude product requires 50–70 hours of air-drying to attain constant weight (145–155 g., 85–91%). It is preferable to crystallize the partially dried product.
4. The approximate solubility of 1,2,3,4-tetrahydrocarbazole in 100 ml. of methanol at 10°, 35°, and 55° is 5, 12, and 18 g. respectively.
5. A heated funnel is desirable for filtration of the hot solution, for the product separates on slight cooling.
6. The capillary melting point of tetrahydrocarbazole ranges from 113° to 114° with slow heating and from 116° to 118° with fast heating.
7. 1,2-Benzo-3,4-dihydrocarbazole may be prepared by the same general procedure. A

solution of 172 ml. (2 moles) of concentrated hydrochloric acid (sp. gr. 1.18) in 500 ml. of water is heated at the reflux temperature and stirred in a 2-l. three-necked round-bottomed flask equipped with a reflux condenser, a slip-sealed stirrer, and a dropping funnel while 108 g. (1 mole) of phenylhydrazine is added during 5 minutes. α-Tetralone (p. 898) (146 g., 1 mole or a correspondingly larger amount of material of 90% purity; see (Note 1)) is added in a period of 1 hour, and the mixture is stirred and heated under reflux for an additional hour. The product is cooled to room temperature with stirring, and the beadlike product is filtered, washed as above, and crystallized from 2.3 l. of methanol after treatment with decolorizing carbon. The first crop amounts to 105–110 g. and the second crop to 75–80 g., making the total yield 82–87%; m.p. 163–164°.

3. Discussion

1,2,3,4-Tetrahydrocarbazole has been prepared from cyclohexanone phenylhydrazone,[3,4,5,6,7,8,9] by the direct reaction of cyclohexanone with phenylhydrazine,[10] by the reaction of 2-chlorocyclohexanone with aniline,[11] by heating 2-phenylcyclohexanone oxime,[12] by the reaction of 2-hydroxycyclohexanone with aniline,[13] by treatment of cyclohexanone phenylhydrazone with a cation-exchange resin,[14] and by the hydrogenation of carbazole.[15] 1,2-Benzo-3,4-dihydrocarbazole has been prepared from the phenylhydrazone of α-tetralone[16] and by the direct reaction of α-tetralone with phenylhydrazine.[10]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

1,2-Benzo-3,4-dihydrocarbazole

phenylhydrazone of α-tetralone

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

methanol (67-56-1)

aniline (62-53-3)

Cyclohexanone (108-94-1)

Phenylhydrazine (100-63-0)

decolorizing carbon (7782-42-5)

carbazole (86-74-8)

α-Tetralone (529-34-0)

2-Chlorocyclohexanone (822-87-7)

1,2,3,4-Tetrahydrocarbazole, Carbazole, 1,2,3,4-tetrahydro- (942-01-8)

tetrahydrocarbazole

2-phenylcyclohexanone oxime

2-hydroxycyclohexanone

cyclohexanone phenylhydrazone

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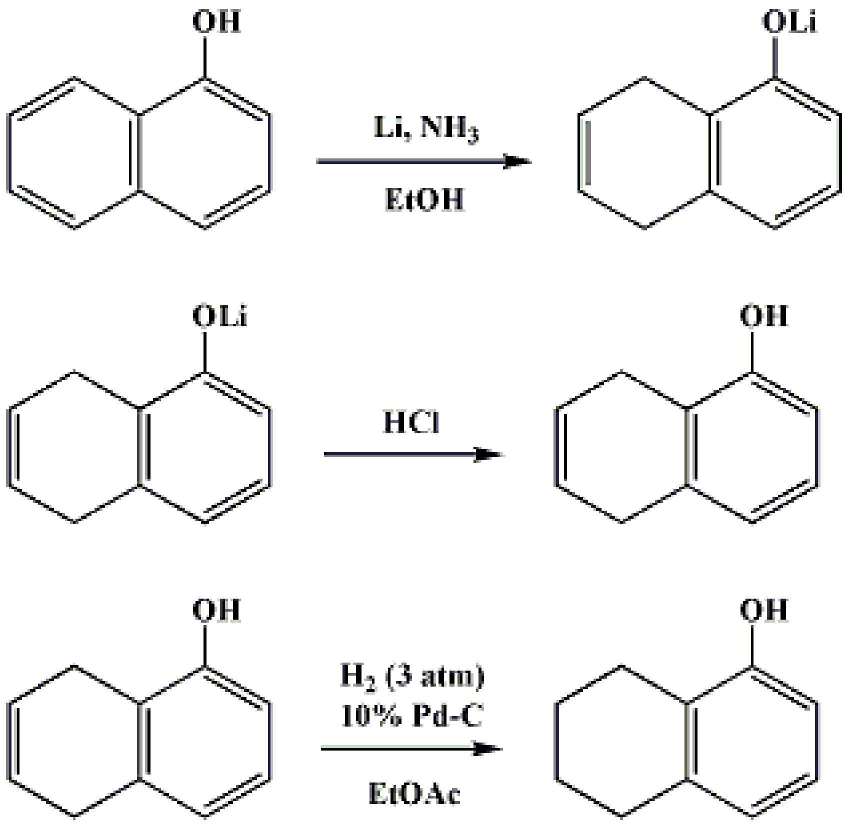
Organic Syntheses, CV 4, 887

ar-TETRAHYDRO-α-NAPHTHOL

[1-Naphthol, 5,6,7,8-tetrahydro-]



Submitted by C. David Gutsche and Hugo H. Peter[1].
Checked by John C. Sheehan, George H. Buchi, and Dwain M. White.

1. Procedure

A 3-l. three-necked flask, equipped with a Dry Ice condenser (Note 1), a sealed Hershberg-type stirrer, and an inlet tube, is set up in a hood and charged with 108 g. (0.75 mole) of α-naphthol (Note 2). The stirrer is started, and to the rapidly stirred flask contents (Note 3) is added 1 l. of liquid ammonia as rapidly as possible (about 5 minutes). When the naphthol has gone into solution (about 10 minutes), 20.8 g. (3.0 g. atoms) of lithium metal (Note 4) is added in small pieces and at such a rate as to prevent the ammonia from refluxing too violently (Note 5). After the addition of the lithium has been completed (about 45 minutes), the solution is stirred for an additional 20 minutes and is then treated with 170 ml. (3.0 moles) of absolute ethanol which is added dropwise over a period of 30–45 minutes (Note 6). The condenser is removed, stirring is continued, and the ammonia is evaporated in a stream of air introduced through the inlet tube. The residue is dissolved in 1 l. of water, and, after the solution has been extracted with two 100-ml. portions of ether, it is carefully acidified with concentrated hydrochloric acid. The product formed is taken into ether with three 250-

ml. extractions, and then the ether extract is washed with water and dried over anhydrous sodium sulfate. The ether is removed by evaporation to yield 106–108 g. (97–99%) of crude 5,8-dihydro-1-naphthol, m.p. 69–72°. This material is dissolved in 250 ml. of ethyl acetate and hydrogenated with 3.0 g. of 10% palladium on charcoal catalyst (Note 7) at 2–3. atm. pressure in a Parr apparatus until the theoretical amount of hydrogen has been absorbed (about 45 minutes). The catalyst is removed by filtration, and the solvent is removed by distillation to leave 105–107 g. of an oil which quickly solidifies, m.p. 67–69.5°. Recrystallization from 250 ml. of petroleum ether (b.p. 88–98°) gives 93–97 g. (84–88%) of almost colorless crystals, m.p. 68–68.5°.

2. Notes

1. A cold-finger type of condenser approximately 10 × 40 cm. is satisfactory.
2. Eastman's white label grade α-naphthol or equivalent is the most satisfactory starting material. Technical grade α-naphthol may be used, but it gives an inferior product that is difficult to purify.
3. Rapid stirring during the addition of the ammonia is necessary to prevent the formation of a hard cake and resultant interference with the stirrer.
4. Lithium metal strip (Metalloy Corporation, Rand Tower, Minneapolis, Minnesota) is wiped to remove the protective grease and then placed in petroleum ether (b.p. 32–37°). Pieces are cut with scissors, air-dried to remove solvent, and added to the reaction mixture.
5. During the addition of the lithium the solution turns deep blue. After this has occurred (after about one-third of the lithium has been added), the rate of addition can be increased considerably.
6. Toward the end of the addition of the alcohol, foaming may occur but may be subdued by reducing the rate of stirring.
7. See Mozingo [*Org. Syntheses Coll. Vol.* **3**, 686 (1955)] for the preparation of this catalyst.

3. Discussion

ar-Tetrahydro-α-naphthol has been prepared by sodium and reduction of α-naphthylamine followed by diazotization and hydrolysis;[2,3] by sodium and amyl alcohol [4,5,6] or lithium and ethylamine[7] reduction of α-naphthol; by sulfonation of tetralin followed by sodium hydroxide fusion;[8] and by catalytic reduction of α-naphthol.[9] *ar*-Dihydro-α-naphthol has been prepared by reduction of α-naphthol with sodium and alcohols[10] and with sodium and ammonia.[11] The use of lithium in related systems has been investigated and provides the basis for the preparation described.[12]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 400

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

α-naphthylamine

ar-Tetrahydro-α-naphthol

ar-Dihydro-α-naphthol

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ethyl acetate (141-78-6)

ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

sodium sulfate (7757-82-6)

α-naphthol, naphthol (90-15-3)

sodium (13966-32-0)

palladium (7440-05-3)

amyl alcohol (71-41-0)

lithium (7439-93-2)

Tetralin (119-64-2)

ethylamine (75-04-7)

1-Naphthol, 5,6,7,8-tetrahydro- (529-35-1)

5,8-dihydro-1-naphthol

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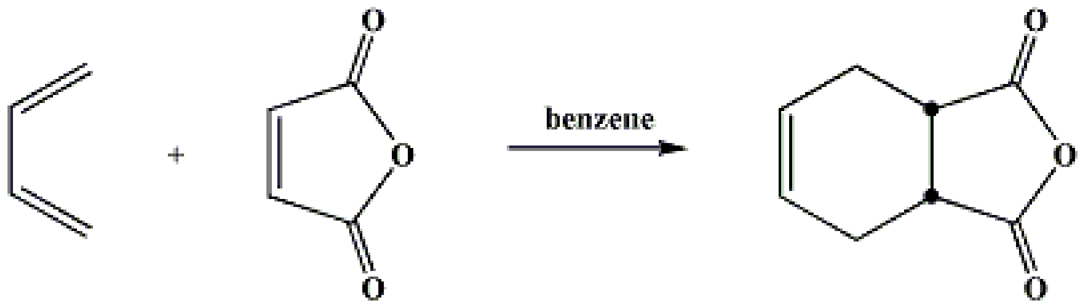
Organic Syntheses, CV 4, 890

cis-Δ4-TETRAHYDROPHTHALIC ANHYDRIDE

[4-Cyclohexene-1,2-dicarboxylic anhydride, *cis*-]



Submitted by Arthur C. Cope and Elbert C. Herrick[1].
Checked by Charles C. Price, Kenneth N. Campbell, and Robert P. Kane.

1. Procedure

The apparatus shown in .htmFig. 16, consisting of a 2-l. three-necked round-bottomed flask fitted with an efficient stirrer (Note 1), a gas-inlet tube, a thermometer, and a reflux condenser, is assembled in a ventilated hood. Bubbler tubes containing benzene are attached to the gas inlet tube and the top of the reflux condenser, and 500 ml. of dry benzene and 196 g. (2 moles) of maleic anhydride (Note 2) are placed in the flask. Stirring is begun, the flask is heated with a pan of hot water, and butadiene is introduced (from a commercial cylinder controlled by a needle valve) at a rapid rate (0.6–0.8 l. per minute). When the temperature of the solution has reached 50° (within 3–5 minutes) the pan of water is removed. The exothermic reaction causes the temperature to reach 70–75° in 15–25 minutes. The rapid stream of butadiene is nearly completely absorbed for 30–40 minutes, after which the rate is decreased until the reaction is completed (equal rates of bubbling in the two bubbler tubes) after 2–2.5 hours. The solution is poured into a 1-l. beaker at once to avoid crystallization of the product in the reaction flask. The beaker is covered and the mixture is kept at 0–5° overnight.

The product is collected on a large Büchner funnel and washed with 250 ml. of 35–60° petroleum ether. A second crop (5–15 g.) obtained by diluting the filtrate with an additional 250 ml. of petroleum ether is separated by filtration, combined with the first crop in a large crystallizing dish, and dried to constant weight (1–2 hours) in an oven at 70–80°. The yield of *cis*-Δ^4-tetrahydrophthalic anhydride is 281.5–294.5 g. (93–97%), m.p. 99–102° (Note 3).

Fig. 16. Assembly of apparatus for addition of butadiene to maleic anhydride.

Fig. 16. Assembly of apparatus for addition of butadiene to maleic anhydride.

2. Notes

1. Any stirrer that produces sufficiently vigorous agitation to disperse the gas through the liquid is satisfactory. It was found to be unnecessary to introduce the gas below the surface of the liquid.
2. A good grade of commercial maleic anhydride was used, m.p. 52–54°.
3. The product is analytically pure and suitable for use in preparing diethyl *cis*-Δ^4-tetrahydrophthalate (p. 304). Recrystallization from ligroin[2] or ether[3] raises the m.p. to 103–104°.

3. Discussion

cis-Δ^4-Tetrahydrophthalic anhydride has been prepared by the reaction of maleic anhydride and butadiene.[2,3,4,5,6] The procedure described is adapted from the one used by Kohler and Jansen.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 157
- Org. Syn. Coll. Vol. 4, 304

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ligroin

petroleum ether

Diethyl cis-Δ^4-tetrahydrophthalate

cis-Δ^4-Tetrahydrophthalic anhydride

Benzene (71-43-2)

butadiene (106-99-0)

maleic anhydride (108-31-6)

4-Cyclohexene-1,2-dicarboxylic anhydride, cis- (935-79-5)

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Organic Syntheses, CV 4, 892

TETRAHYDROTHIOPHENE

[Thiophene, tetrahydro-]

Submitted by J. Keith Lawson, William K. Easley, and William S. Wagner[1].
Checked by William S. Johnson and W. David Wood.

1. Procedure

A 5-l. round-bottomed three-necked flask equipped with a mechanical stirrer, a reflux condenser (Note 1), and two 250-ml. dropping funnels (mounted with the aid of a Y-tube) is charged with 1.7 l. of dimethylformamide (Note 2). The flask is heated until the dimethylformamide is almost refluxing. Then, with stirring, 280 ml. (318 g., 2.5 moles) of 1,4-dichlorobutane and a solution of 359 g. (2.75 moles) of 60% sodium sulfide (Note 2) in 1 l. of hot water are added simultaneously from the dropping funnels at such a rate that the mixture refluxes without application of heat (Note 3). After the addition is complete (about 1.5 hours), the mixture is heated at reflux with stirring for an additional 2 hours. The condenser is arranged for distillation, and 600 ml. of distillate is collected (Note 4). The distillate is made alkaline by adding 20 g. of sodium hydroxide, and sodium chloride is added to the saturation point. The aqueous layer is separated and discarded, and the crude tetrahydrothiophene layer is dried over solid potassium hydroxide. Distillation through a 30-cm. Vigreux column gives, after a small fore-run (Note 5), 160–172 g. (73–78%) of colorless tetrahydrothiophene, b.p. 119–121°, n_D^{25} 1.5000–1.5014 (Note 6) and (Note 7).

2. Notes

1. The reaction should be carried out in a hood, or the outlet of the condenser should be connected to a fume trap.
2. Technical grade DMF is available from the Grasselli Chemicals Department of E.I. duPont de Nemours and Company. The 1,4-dichlorobutane was obtained from the Electrochemicals Department, E. I. duPont de Nemours and Company. Technical Baker and Adamson fused chip sodium sulfide assaying 60% sodium sulfide was used. The checkers obtained somewhat lower yields when the appropriate amount of reagent grade $Na_2S\cdot 9H_2O$ was employed instead of the technical material.
3. The addition of the reactants takes approximately 1.3 hours and should be carried out so that the addition of both reactants is completed at approximately

the same time.
4. The dimethylformamide solution may be used repeatedly if each time the volume is reduced by the distillation of the remaining water. After two runs the accumulated sodium chloride should be removed by filtration.
5. A small amount of dimethylamine is always present in the crude product. This is removed before collection of the product by operating the column under total reflux for 1–2 hours. The vent of the still head should be connected to a hood during this operation. If foaming does not subside after this treatment the use of a 1-l. still pot is indicated.
6. When several runs are made, an additional amount of the product can be obtained by redrying and redistilling the foreruns. The submitters have obtained yields as high as 90% on a larger-scale operation.
7. The reaction may also be carried out in aqueous medium with an increase in the time of reaction to 4 hours. By this method the submitters obtained a 78% yield on a large-scale run. When only a single run is to be made, this procedure may be preferred as a matter of economy.

3. Discussion

Tetrahydrothiophene has been prepared by the reaction of 1,4-diiodobutane and potassium sulfide;[2] by the reaction of 1,4-dibromobutane[3,4] or 1,4-dichlorobutane[5,6,7] and sodium sulfide; by the reaction of tetramethylene glycol and hydrogen sulfide in the presence of alumina at high temperature;[8] by the reaction of tetrahydrofuran and hydrogen sulfide in the presence of alumina at high temperature;[9,10,11,12] by the hydrogenation of thiophene with molybdenum disulfide[13] or palladium on charcoal[14] as catalyst; and by treatment of S-(4-hydroxybutyl)isothiourea chloride hydrochloride with base.[15]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alumina

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

hydrogen sulfide (7783-06-4)

potassium hydroxide (1310-58-3)

palladium (7440-05-3)

sodium sulfide (1313-82-2)

potassium sulfide (1312-73-8)

Thiophene (110-02-1)

dimethylamine (124-40-3)

Tetrahydrofuran (109-99-9)

tetramethylene glycol

1,4-dichlorobutane (110-56-5)

dimethylformamide, DMF (68-12-2)

1,4-Diiodobutane (628-21-7)

Tetrahydrothiophene, Thiophene, tetrahydro- (110-01-0)

1,4-dibromobutane (110-52-1)

molybdenum disulfide

S-(4-hydroxybutyl)isothiourea chloride hydrochloride

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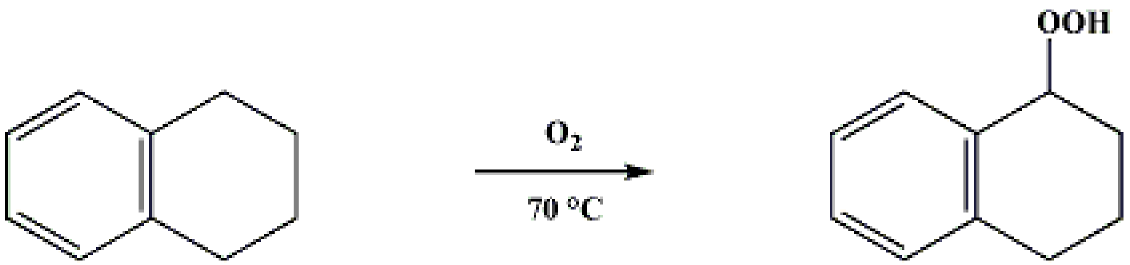
Organic Syntheses, CV 4, 895

TETRALIN HYDROPEROXIDE

[Hydroperoxide, (1,2,3,4-tetrahydro-1-naphthyl)-]



Submitted by H. B. Knight and Daniel Swern[1].
Checked by John C. Sheehan and Curt W. Beck.

1. Procedure

In a 1-l. round-bottomed three-necked flask, equipped with a thermometer, a reflux condenser, and two fritted-glass gas dispersion tubes (Note 1), is placed 600 g. (4.54 moles) of pure tetralin (Note 2). The flask is placed in a constant-temperature bath at 70°, and a finely dispersed stream of oxygen is passed through the tetralin until the peroxide content of the reaction mixture is 25–30% as shown by an active oxygen content of 2.4–2.9% (Note 3). This oxidation requires 24–48 hours. The reaction mixture is then distilled (Note 4) in an all-glass apparatus at 0.2–0.4 mm. through a 60 by 2.5 cm. Vigreux column, until a pot temperature of 70° is reached. About 370–380 g. of unoxidized tetralin, boiling at 32–45°/0.2–0.4 mm., is recovered. The pot residue is a slightly viscous amber-colored oil which weighs 225–235 g. and consists of about 80% tetralin hydroperoxide (Note 5). To obtain the pure hydroperoxide the residue is dissolved in 450 ml. of toluene and the solution is cooled to −50° with stirring (Note 6). After standing at −50° for 1 hour, the slurry is separated by suction filtration (Note 7) and the precipitate is dried at room temperature at 1–2 mm. There is thus obtained 120–125 g. of moderately pure tetralin hydroperoxide, m.p. 50.2–52.0°, active oxygen content 9.20% (Note 8). Recrystallization from 480 ml. of toluene at −30° yields 80–85 g. (44–57% yield based on the peroxide content of the oxidized tetralin) of pure tetralin hydroperoxide as a colorless solid, m.p. 54.0–54.5°, active oxygen content, 9.70% (Note 9).

2. Notes

1. Rubber connections must be avoided because rubber is rapidly attacked by tetralin. Convenient gas dispersion tubes are Pyrex No. 39533.
2. Pure tetralin was prepared from the practical grade supplied by the Eastman Kodak Company by the procedure of George and Robertson:[2] Three kilograms

was fractionally distilled through a packed column, the fraction boiling at 204–207° being retained (2.7 kg.). This was gently shaken with 1 lb. of mercury, and the upper layer was carefully decanted through fluted filter paper. The crude tetralin was next shaken with saturated aqueous mercuric acetate solution, and the aqueous layer and a small amount of orange precipitate were discarded. The hydrocarbon was then shaken with 5 successive 300-ml. portions of concentrated sulfuric acid, once with 10% sodium hydroxide, and finally with water until the washings were neutral. The tetralin was dried over anhydrous calcium chloride and distilled through a packed column in a nitrogen atmosphere. In this way, 2 kg. of pure tetralin was obtained, b.p. 206–207°, n_D^{20} 1.5428.

3. Active oxygen content is determined iodometrically:[3] In an iodine flask, an accurately weighed sample (0.1–0.3 g.) is dissolved in 20 ml. of an acetic acid-chloroform solution (3:2 by volume), and 2 ml. of saturated aqueous potassium iodide solution is added. The flask is immediately flushed with nitrogen, stoppered, and allowed to stand at room temperature for 15 minutes. Fifty milliliters of water is then added with good mixing, and the liberated iodine is titrated with 0.1*N* sodium thiosulfate, employing starch as indicator. A blank titration, which usually does not exceed 0.2 ml., is also run. One milliliter of 0.1*N* sodium thiosulfate is equivalent to 0.00821 g. of tetralin hydroperoxide.

4. The distillation should be conducted behind a safety shield.

5. Peroxide loss up to this point is negligible provided an all-glass apparatus has been used throughout and the distillation temperature has not exceeded 70°.

6. A Dry Ice-ethanol bath is convenient for cooling the solution.

7. Filtration may be carried out in a suction funnel surrounded by a Dry Ice-ethanol cooling bath, or using a cold box maintained at −50°.

8. Pure tetralin hydroperoxide has an active oxygen content of 9.74%.

9. Tetralin hydroperoxide is a convenient model compound for many studies in peroxide chemistry. It remains colorless and does not decrease in peroxide content for months if stored in the dark at or below 0°. Storage under warm summer conditions for several months results in decomposition to a dark, viscous liquid.

3. Discussion

Tetralin hydroperoxide has been prepared by the oxidation of tetralin in the presence of cobalt naphthenate,[4] manganese stearate,[5] and ceric stearate or naphthenate.[6] Tetralin hydroperoxide, produced by the oxidation of tetralin, may be separated from reaction products by formation of its sodium salt.[7] The kinetics of the liquid-phase oxidation of tetralin have been studied.[8] The present procedure is adapted from that reported by Hartmann and Seiberth[9] and Hock and Susemihl.[10]

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9. Hartmann and Seiberth, *Helv. Chim. Acta*, **15**, 1390 (1932).
10. Hock and Susemihl, *Ber.*, **66**, 61 (1933).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

acetic acid-chloroform

cobalt naphthenate

naphthenate

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

sodium hydroxide (1310-73-2)

oxygen (7782-44-7)

potassium iodide (7681-11-0)

sodium thiosulfate (7772-98-7)

nitrogen (7727-37-9)

mercuric acetate (1600-27-7)

mercury (7439-97-6)

iodine (7553-56-2)

toluene (108-88-3)

peroxide (7722-84-1)

Tetralin (119-64-2)

Tetralin hydroperoxide, Hydroperoxide, (1,2,3,4-tetrahydro-1-naphthyl)- (26447-24-5)

hydroperoxide

manganese stearate (3353-05-7)

ceric stearate

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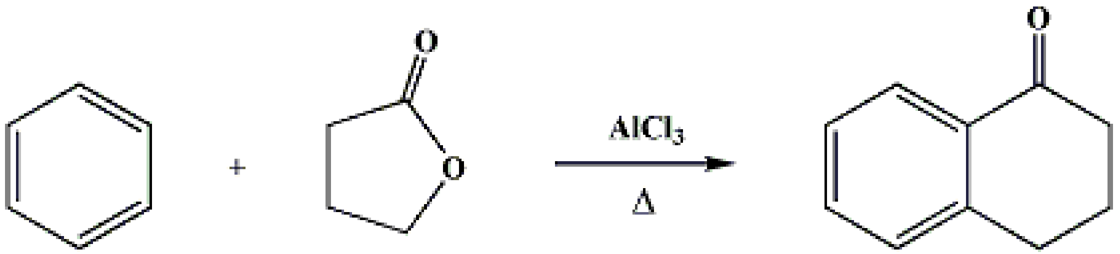
Organic Syntheses, CV 4, 898

α-TETRALONE

[1(2H)-Naphthalenone, 3,4-dihydro-]

[I. METHOD A]



Submitted by Cecil E. Olson and Alfred R. Bader[1].
Checked by James Cason, Gerhard J. Fonken, and William G. Dauben.

1. Procedure

A 3-l. three-necked flask is fitted with a mercury-sealed stirrer, an efficient condenser capped by a drying tube filled with calcium chloride, and a wide-bore rubber tube leading to a 1-l. Erlenmeyer flask. One liter of dry, thiophene-free benzene and 104 g. (1.21 moles) of γ-butyrolactone (Note 1) are placed in the 3-l. flask. Six hundred grams (4.5 moles) of reagent grade anhydrous aluminum chloride (Note 2) is placed in the Erlenmeyer flask and is added to the stirred reaction mixture during a period of 2 hours. The mixture becomes dark brown, refluxes gently, and evolves hydrogen chloride. After addition of all the catalyst, the mixture is heated on a steam bath with continued stirring for 16 hours. It is then cooled to room temperature and poured onto 3 kg. of crushed ice drenched with 500 ml. of concentrated hydrochloric acid. The lower aqueous layer is separated and extracted with about 500 ml. of toluene. The brown, organic, upper layer and the toluene extract are combined, washed successively with water, 20% potassium hydroxide solution, and water, and distilled under reduced pressure to remove benzene, toluene, and traces of water. Distillation of the residue in a Claisen flask (Note 3) yields 160–170 g. (91–96%) of α-tetralone, b.p. 75–85°/0.3 mm., n_D^{25} 1.565–1.568 (Note 4) and (Note 5). There is a residue consisting of 130–150 g. of red-purple viscous oil.

2. Notes

1. A commercial grade of butyrolactone supplied by the General Aniline and Film Corporation, 230 Park Avenue, New York 17, New York, was used by the submitters. The checkers used material from Eastern Chemical Corporation, 34 Spring Street, Newark 2, New Jersey, which was distilled before use, b.p. 208–210°.

2. The checkers found technical grade aluminum chloride, containing a little ferric chloride, equally satisfactory. After 150–200 g. of aluminum chloride is added there is usually a rather sudden and vigorous evolution of hydrogen chloride accompanied by refluxing. It is advisable to interrupt addition of aluminum chloride at this point until the mixture is refluxing smoothly.

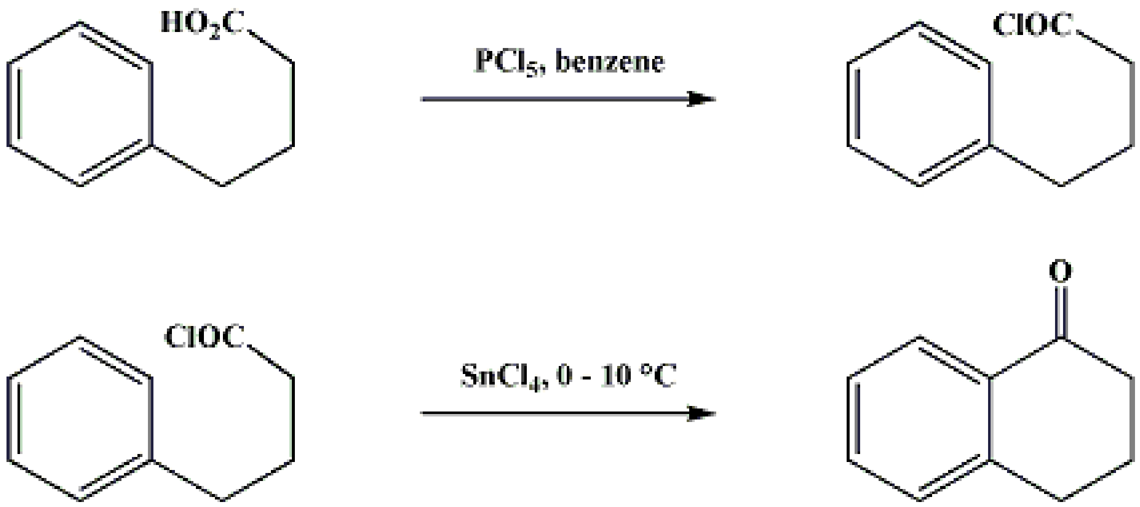
3. The checkers distilled the product through a 0.5-meter packed column with heated jacket and partial reflux head. The yield was 148–155 g. (85–88%), b.p. 143–145°/20 mm., n_D^{25} 1.5669–1.5671. There was a fore-run of 10–15 g. and an after-run of about 8 g., b.p. 145–180°/20 mm.

4. The submitters state that varying the amounts of aluminum chloride varied the yields as shown in the table.

$AlCl_3$, g.	α-Tetralone, g.	Yield, %
400	119	68
500	151	86
600	165	94
700	166	95

5. Replacing the butyrolactone with 120 g. (1.20 moles) of γ-valerolactone in an otherwise identical procedure yields 150–160 g. (79–84%) of 4-methyl-1-tetralone, b.p. 108–110°/1 mm.

[II. METHOD B]



Submitted by G. Dana Johnson[2]
Checked by James Cason, William G. Dauben, Bradford H. Walker, and Charles E. Stehr.

1. Procedure

In a dry 2-l. three-necked round-bottomed flask, fitted with a gas-tight stirrer and a reflux condenser carrying at the top a calcium chloride drying tube connected to a gas-

absorption trap (a good hood is preferable), are placed 98.5 g. (0.6 mole) of γ-phenylbutyric acid[3] and 200 ml. of dry thiophene-free benzene (Note 1). After the solution has been cooled, with stirring, for a few minutes in an ice bath, 125 g. (0.6 mole) of phosphorus pentachloride is added during 5 minutes (Note 2). After the ice bath is removed the contents of the flask are heated during 20 minutes (vigorous evolution of hydrogen chloride) to the boiling point by means of a water bath, and refluxing is continued for about 5 minutes. As stirring is continued the flask is cooled in an ice-salt bath until the internal temperature (Note 3) reaches about −10°. With continued efficient cooling, there is added during 30–40 minutes a solution of 150 ml. (1.28 moles) of anhydrous stannic chloride in 150 ml. of dry thiophene-free benzene (Note 1), as the temperature is maintained below 15°. The reaction is highly exothermic, and hydrogen chloride is rapidly evolved. Stirring is continued for 1 hour at 0–10°, at the end of which time the thermometer is replaced by the condenser and the complex is decomposed by careful addition of 300 g. of ice followed by 250 ml. of concentrated hydrochloric acid. This two-phase mixture is heated to reflux, with vigorous stirring, on a water bath for about 25 minutes or until hydrogen chloride is no longer evolved (Note 4).

The cooled reaction mixture is separated in a separatory funnel, and the aqueous phase is extracted with three 50-ml. portions of benzene. These extracts are combined with each other but kept separate from the original organic phase; each wash solution is used first with the original organic phase, then the extracts. The washes are 150 ml. of water (Note 4), 100 ml. of 10% sodium carbonate solution, 100 ml. of water, and finally 50 ml. of saturated sodium chloride solution (Note 5). Solvent is distilled from the combined extracts, and the residue is distilled at reduced pressure in a Claisen flask. The yield of α-tetralone, b.p. 135–137°/ 15 mm., n_D^{25} 1.5671–1.5672, is 75–80 g. (85–91%).

2. Notes

1. A total of 350 ml. of dry benzene is required. It may be dried by allowing it to stand for a few days with about 1 g. of sodium wire, or by slowly distilling about 20% of a lot of benzene and cooling the residue with protection from atmospheric moisture by use of a calcium chloride tube.
2. It is convenient to weigh the phosphorus pentachloride in an Erlenmeyer flask which is then attached to a side neck of the three-necked flask by a 6-in. length of wide-bore thin-walled rubber tubing.
3. The condenser is replaced by a thermometer extending into the stirred liquid. The thermometer is inserted through a wide-bore T-tube whose side outlet is protected by a calcium chloride tube.
4. The stannic chloride complex is decomposed relatively slowly. Addition of 5–10 ml. of ether facilitates the decomposition. If the decomposition is not completed during the heating period, the wash with water gives a troublesome precipitation of stannic hydroxide. If this occurs the organic phase should either be heated for 30 minutes with, or allowed to stand overnight with, 100 ml. of 6*N*

hydrochloric acid.

5. The wash with saturated salt solution usually gives a clean separation and removes most of the water from the organic phase. No additional drying is necessary since the remaining water is removed by azeotropic distillation with benzene.

3. Discussion

Other methods of preparation of α-tetralone have been reviewed in earlier volumes.[4,5] Further references to the preparation of α-tetralone by the oxidation of tetralin include the use of oxygen in the presence of cobaltous chloride and acetic acid[6] and chromic anhydride.[7,8] Beyerman[9] and Eastham[10] state that the α-tetralone obtained by the air oxidation of tetralin contains α-tetralol, which cannot be separated readily by fractional distillation. The former recommends removing the α-tetralol by treatment with chromic acid in acetic acid below 15°, while the latter investigator suggests that the reaction product be dissolved in an equal volume of 75% sulfuric acid, and the mixture extracted with hexane. The hexane extract is discarded, the acid layer is then diluted with 2 volumes of water and again extracted with hexane. The α-tetralone recovered from this hexane extract by washing, concentrating, and distilling melts at 6–7°. Eastham[10] believes that the melting point rather than the refractive index should be used as a test of purity of α-tetralone. α-Tetralone also has been obtained from tetrahydronaphthalene peroxide and sodium hydroxide or cupric chloride.[11]

4-Methyl-1-tetralone has been prepared from γ-phenylvaleric acid and sulfuric acid[12] and from γ-phenylvaleryl chloride and aluminum chloride.[13,14]

Method I is based on the procedure of Truce and Olson.[15]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 884
- Org. Syn. Coll. Vol. 7, 319

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

hydrogen chloride, hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

ether (60-29-7)

sodium hydroxide (1310-73-2)

phosphorus pentachloride (10026-13-8)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

oxygen (7782-44-7)

aluminum chloride (3495-54-3)

potassium hydroxide (1310-58-3)

toluene (108-88-3)

sodium (13966-32-0)

chromic acid (7738-94-5)

cupric chloride (7758-89-6)

ferric chloride (7705-08-0)

chromic anhydride

stannic chloride (7646-78-8)

Tetralin (119-64-2)

γ-Phenylbutyric acid (1821-12-1)

α-Tetralone, 1(2H)-Naphthalenone, 3,4-dihydro- (529-34-0)

hexane (110-54-3)

α-tetralol (529-33-9)

γ-butyrolactone, Butyrolactone (96-48-0)

γ-valerolactone (108-29-2)

4-methyl-1-tetralone (19832-98-5)

stannic hydroxide

cobaltous chloride

tetrahydronaphthalene peroxide

γ-phenylvaleric acid

γ-phenylvaleryl chloride

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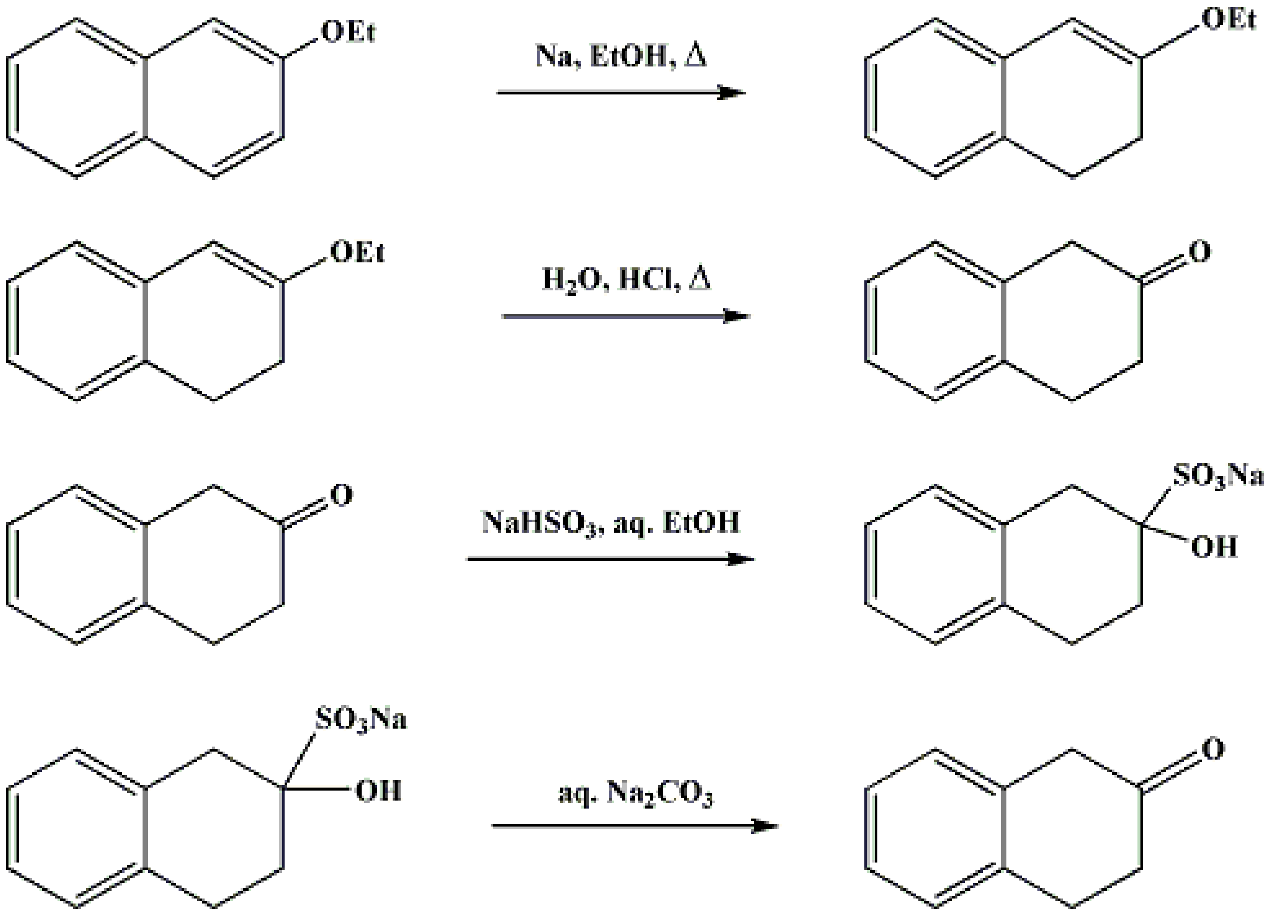
Organic Syntheses, CV 4, 903

β-TETRALONE

[2(1H)-Naphthalenone, 3,4-dihydro-]



Submitted by M. D. Soffer, M. P. Bellis, Hilda E. Gellerson, and Roberta A. Stewart[1].
Checked by N. J. Leonard and R. C. Fox.

1. Procedure

A. *Reduction and hydrolysis.* A solution of 129 g. (0.75 mole) of β-naphthyl ethyl ether in 1.5 l. of 95% ethanol is prepared in a 5-l. three-necked flask fitted with a mechanical stirrer, a bulb condenser topped by a Friedrichs condenser, and a Y-tube to allow for the introduction of nitrogen and sodium. The apparatus is flushed thoroughly with nitrogen, the nitrogen flow is reduced, and 225 g. (9.8 g. atoms) of sodium is added in small portions (Note 1), with efficient stirring, at a rate sufficient to maintain vigorous boiling. The hydrogen liberated passes through the condensers and a delivery tube into a hood or directly out a window. When approximately two-thirds of the sodium has been introduced, an additional 375 ml. of 95% ethanol is added to reduce the viscosity of the reaction mixture. Approximately 1.5 hours is required for the addition of the sodium. Near the end of this period, the rate of the reaction decreases and heat is supplied by means of an electric heating mantle to maintain the reflux temperature (Note 2).

After all the sodium has dissolved, the hydrogen is thoroughly swept from the system with nitrogen and the heating is discontinued. The Y-tube is replaced by a separatory funnel, and 750 ml. of water is added cautiously (Note 3), with stirring, followed by 1.5 l. of concentrated hydrochloric acid (Note 3). The acidic mixture containing precipitated sodium chloride is heated, with stirring, at the reflux temperature for 30 minutes, and then allowed to cool.

The mixture is extracted with ten 175-ml. portions of benzene or 1:1 benzene-ether mixture (Note 4). The combined extract is washed with 75-ml. portions of water until the washings are neutral to litmus. The organic solvent is removed by distillation on a steam bath. The crude oily residue is converted directly (Note 5) to the β-tetralone bisulfite addition product.

B. *Bisulfite addition product of β-tetralone.* To a solution of 325 g. (3.12 moles) of sodium bisulfite (commercial purified grade) in 565 ml. of water is added 175 ml. of 95% ethanol. The mixture is allowed to stand overnight, and the precipitated sodium bisulfite is removed by filtration. The filtrate is added to the crude β-tetralone, and the mixture is shaken vigorously. Within a few minutes the addition product separates as a voluminous precipitate. The mixture is kept cold for several hours, shaken periodically, and then filtered with the aid of suction. The precipitate is washed well, first with 125 ml. of 95% ethanol, then four times with 125-ml. portions of ether (Note 6). The colorless addition product is air-dried (Note 5) and is stored in air-tight containers. The yield is 113–131 g. (60–70% based on β-naphthyl ethyl ether) (Note 7).

C. *Regeneration of β-tetralone.* Fifty grams (0.20 mole) of β-tetralone bisulfite addition product is suspended in 250 ml. of water, and 75 g. (0.6 mole) of sodium carbonate monohydrate is added. At this point the pH of the solution is approximately 10. The mixture is extracted with five 100-ml. portions of ether (Note 8). The combined extract is washed with 100 ml. of 10% hydrochloric acid, then with 100-ml. portions of water until the washings are neutral to litmus, and is dried over anhydrous magnesium sulfate. The ether is removed by distillation, and the residue is distilled from a Claisen flask under reduced pressure, preferably in a nitrogen atmosphere. The pure β-tetralone is obtained as a colorless distillate; b.p. 70–71°/0.25 mm. (92–94°/1.8 mm., 114–116°/4.5 mm.); n_D^{20} 1.5594. The yield is 17–21 g. (40–50% based on β-naphthyl ethyl ether).

2. Notes

1. The sodium is cut into pieces about 2 in. by 0.5 in. by 0.5 in. and is kept under benzene until used.
2. The concentrated sodium ethoxide solution must be kept hot throughout the process; otherwise a voluminous precipitate separates and the mixture congeals.
3. Both the hydrolysis of the sodium ethoxide and the subsequent neutralization are very exothermic. The water and the acid may be added fast enough to maintain vigorous refluxing, but care must be exercised to keep the reaction under control. When the neutralization is complete, the refluxing subsides, and at this point the

excess hydrochloric acid may be added rapidly.

4. Ether is somewhat miscible with the reaction mixture, but the benzene-ether mixture, or benzene alone, is satisfactory.

5. In this step the β-tetralone is separated from starting material and other neutral substances in the reaction mixture. β-Tetralone is sensitive to air oxidation; therefore it should not be stored in the free state. The bisulfite addition product is stable, and the dry material can be stored indefinitely without deterioration.

6. In order to obtain a product of high quality, the washing must be thorough. This is accomplished best by suspending the precipitate in the wash solvent and mixing well before filtering.

7. The yield of the bisulfite addition product is subject to variation owing to coprecipitation of sodium bisulfite.

8. The ether extract and the water layer may be tested for the presence of β-tetralone or the bisulfite addition product by the tetralone blue test.

Tetralone blue test. A few drops of the organic solvent layer or the aqueous phase is shaken in a test tube with 2 ml. of 95% ethanol, and 10 drops of 25% sodium hydroxide solution is poured down the side of the tube. In the presence of air a deep blue color appears at the interface within 1 minute.

3. Discussion

β-Tetralone has been prepared by a variety of methods, but the only practical procedures are ones involving reduction of β-naphthyl methyl ether with sodium and alcohol[2] or with sodium and liquid ammonia,[3] high-pressure catalytic hydrogenation of β-naphthol,[4] catalytic oxidation of 2-tetralol by hydrogen transfer with ethylene,[5] or the condensation of ethylene with phenylacetyl chloride in the presence of aluminum chloride.[6]

The procedure described here is an adaptation[7] of the method of Cornforth, Cornforth, and Robinson.[2]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

Benzene (71-43-2)

ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

β-naphthol (135-19-3)

sodium bisulfite (7631-90-5)

β-naphthyl methyl ether (93-04-9)

aluminum chloride (3495-54-3)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

ethylene (9002-88-4)

magnesium sulfate (7487-88-9)

phenylacetyl chloride (103-80-0)

β-naphthyl ethyl ether (93-18-5)

tetralone (529-34-0)

sodium carbonate monohydrate (5968-11-6)

β-Tetralone, 2(1H)-Naphthalenone, 3,4-dihydro- (530-93-8)

β-tetralone bisulfite

2-tetralol (530-91-6)

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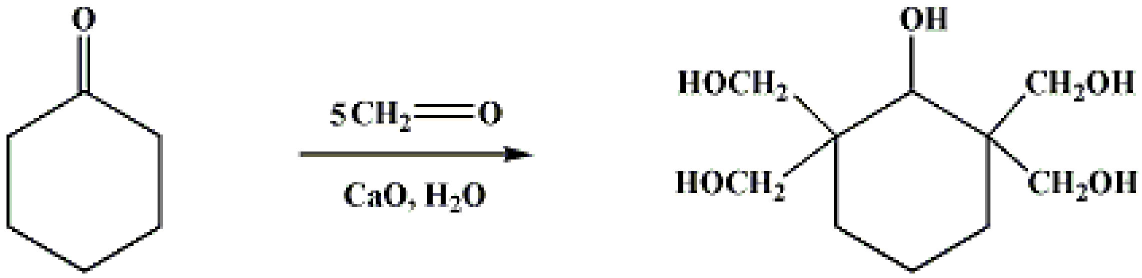
Organic Syntheses, *CV 4*, *907*

2,2,6,6-TETRAMETHYLOLCYCLOHEXANOL

[1,1,3,3-Cyclohexanetetramethanol, 2-hydroxy-]



Submitted by Harold Wittcoff[1]
Checked by R. S. Schreiber, Wm. Bradley Reid, Jr., and John L. White.

1. Procedure

2

A mixture of 196 g. (206 ml., 2 moles) of freshly distilled cyclohexanone, 332 g. (11 moles) of 99.5% paraformaldehyde (Note 1), and 1.8 l. of water is placed in a 5-l. flask equipped with a thermometer and an efficient stirrer. The mixture is cooled to 10–15° by an ice-water bath, and 70 g. (1.25 moles) of calcium oxide is added through a powder funnel over a period of 10–15 minutes. The temperature is allowed to rise slowly to 40° and is kept there by means of the cooling bath until the addition is complete. Stirring is maintained throughout. The reaction mixture is stirred for an additional 30 minutes. During this time the temperature usually falls to approximately 35°, and at this point the cooling bath is removed. The reaction mixture is then made slightly acid (pH 6–6.5) by the addition of 11–13 ml. of aqueous 87% formic acid. It is best to stir the reaction mixture for 30 minutes after neutralization in order to make sure that any suspended particles of lime are neutralized. If at the end of this time the solution is not acid, more formic acid should be added. The reaction mixture is then evaporated under reduced pressure to dryness (Note 2). The residue, which consists of a mixture of product and calcium formate, is mixed with 1 l. of absolute methanol. On warming, the organic material dissolves and the calcium formate settles to the bottom of the flask. A practically colorless solution of the product is obtained by filtration with suction (Note 3) through a heated funnel. The insoluble calcium formate is washed with about 50 ml. of methanol. Approximately one-half of the methanol is removed under reduced pressure, and the residual syrupy solution (Note 4) is allowed to crystallize in an ice chest for 24 hours. Thereafter the product is filtered and washed with 50 ml. of methanol. The mother liquor and washings are combined and set aside. With a mortar and pestle, the crystals are triturated successively with three 200–300-ml. portions of acetone, filtered, and air-dried. By continued evaporation of the mother liquor and washings, at least two successive crops of product are obtained, and these

are processed as described above (Note 5). The total yield of product melting at 128–129° is 320–374 g. (73–85%). Recrystallization of 100 g. of material, m.p. 128–129°, from 175 ml. of absolute methanol yields 84 g. of pure product melting at 129–130°.

2. Notes

1. An equivalent quantity of aqueous formaldehyde free from methanol may be used.
2. The evaporation may be carried out in an ordinary distillation apparatus, but it is essential to stir the mixture to prevent bumping. It is advantageous from the point of view of speed and convenience to employ the method described below. A 3-l. three-necked flask is fitted with an efficient rubber-sealed stirrer, an upright steam-heated condenser, the upper end of which is joined to a separatory funnel, and an outlet tube connected to a long water-cooled condenser placed for downward distillation. The end of this condenser is fitted to a 2-l. two-necked flask which is connected to a good water pump and immersed in an ice bath. The apparatus, with the exception of the separatory funnel, is placed under vacuum. The aqueous solution contained in a separatory funnel is slowly passed through the upright condenser into the three-necked flask heated on a steam bath. The syrupy residue collects in the flask, and the water vapor is removed through the condenser fitted for downward distillation. The residue is heated until no more water is removed. The total time required to strip off the water is 30 to 60 minutes.
3. The checkers found that suction filtration was very slow, owing to the very finely divided material that collected on the funnel. This was corrected by adding a filtering aid (Celite) to the crude mixture and filtering by suction, using an ordinary Büchner funnel (6-in. size). After removal of the solid by suction filtration, the methanol volume was reduced as indicated.
4. The submitter reported that it was preferable to carry out the crystallizations in metal beakers since the crystals were very hard to remove without breakage, but the checkers experienced no such difficulty.
5. Runs employing six times the quantities specified here have been carried out in 22-l. flasks with similar results.

3. Discussion

2,2,6,6-Tetramethylolcyclohexanol has been prepared by Mannich and Brose[3] by condensing cyclohexanone with formaldehyde in the presence of calcium oxide and precipitating the catalyst as calcium sulfate.

References and Notes

1. General Mills, Inc., Minneapolis, Minnesota.
2. This procedure forms a portion of the subject matter of U. S. pat. 2,462,031 [*C. A.*, **44**, 656 (1950)]; U. S. pat. 2,493,733 [*C. A.*, **44**, 3017 (1950)]; U. S. pat. 2,527,853 [*C. A.*, **45**, 2262 (1951)].
3. Mannich and Brose, *Ber.*, **56**, 833 (1923).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

methanol (67-56-1)

formaldehyde (630-08-0)

Cyclohexanone (108-94-1)

formic acid (64-18-6)

calcium sulfate (7778-18-9)

acetone (67-64-1)

calcium oxide

calcium formate (544-17-2)

2,2,6,6-Tetramethylolcyclohexanol, 1,1,3,3-Cyclohexanetetramethanol, 2-hydroxy- (5416-55-7)

paraformaldehyde (30525-89-4)

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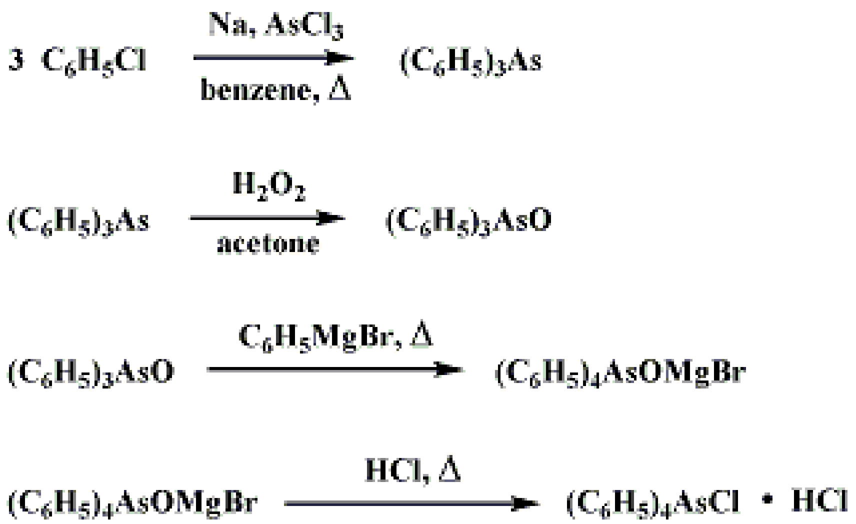
Organic Syntheses, CV 4, 910

TETRAPHENYLARSONIUM CHLORIDE HYDROCHLORIDE

[Arsonium chloride, tetraphenyl-, hydrochloride]



Submitted by R. L. Shriner and Calvin N. Wolf[1].
Checked by Cliff S. Hamilton and Yao-Hua Wu.

1. Procedure

Caution! All steps in the following preparations should be performed under a hood, since volatile arsenic compounds may be liberated.

A. *Triphenylarsine.* In a 2-l. round-bottomed three-necked flask is placed 130 g. (5.65 g. atoms) of powdered sodium[2] covered with 900 ml. of benzene. The flask is fitted with an Allihn condenser, a mercury-sealed mechanical Hershberg stirrer, and a 500-ml. dropping funnel in which is placed a mixture of 170 g. (0.94 mole) of arsenic trichloride and 272 g. (2.42 moles) of chlorobenzene. About 10 ml. of the arsenic trichloride-chlorobenzene mixture is dropped into the flask, and the reaction mixture is stirred and heated on a steam bath until it darkens and boils spontaneously. The steam bath is removed, and the remainder of the arsenic trichloride-chlorobenzene mixture is added dropwise, with stirring, over a period of 1–1.5 hours at such a rate that gentle boiling is maintained (Note 1). When the addition is complete, the mixture is stirred and heated under reflux on a steam bath for 12 hours.

The reaction mixture is filtered while hot through a large Büchner funnel, and the filtrate is collected in a 3-l. filter flask. The residue (Note 2) is washed on the funnel with two 200-ml. portions of hot benzene, pressed as dry as possible, and then transferred to a 1-l. beaker, boiled with 300 ml. of benzene, and filtered, the same funnel and flask being used. This extraction process is repeated twice.

The combined benzene filtrates are subjected to distillation from a steam bath to remove the benzene. The flask containing the residual red oil is connected to a water pump and heated under reduced pressure in an oil bath at 110–120° for 2 hours to remove unreacted starting materials. When cooled, the crude triphenylarsine solidifies to a light brown solid which melts at 57–59°. The yield is 230–240 g. (93–97%). The crude product is dissolved in 650–700 ml. of hot 95% ethanol and placed in a refrigerator overnight. The crystals are collected on a Büchner funnel and washed with 50 ml. of cold 95% ethanol. The yield is 218–225 g. (88–91%) of white crystals which melt at 61°.

B. *Triphenylarsine oxide.* In a 500-ml. round-bottomed flask equipped with a mechanical stirrer, a thermometer, and a 100-ml. dropping funnel is placed 100 g. (0.33 mole) of the recrystallized triphenylarsine (Note 3) dissolved in 200 ml. of acetone. To the solution 46 g. (0.41 mole) of 30% hydrogen peroxide is added dropwise, with stirring, over a period of 20–30 minutes. A water-ice bath is used to maintain the temperature at 25–30°. When the addition is complete, stirring is continued for 30 minutes, and the acetone is then removed by distillation.

The flask containing the residual yellow oil is fitted with a water trap and condenser, and 120 ml. of benzene is added. The water is then removed by azeotropic distillation (Note 4). When the removal of water is complete, the triphenylarsine oxide is crystallized by cooling the flask in an ice bath for 1.5–2 hours. The light-brown crystals are collected on a Büchner funnel and washed on the funnel with 25 ml. of cold benzene. The crude product weighs 97–98.5 g. (91–93%) and melts at 186–188°. The crude product is transferred to a porcelain dish and triturated with 50 ml. of benzene, collected on a Büchner funnel, pressed as dry as possible, and washed with 25 ml. of cold benzene. After drying in the air, the triphenylarsine oxide amounts to 89–92 g. (84–87%) of white crystals, melting at 189°.

C. *Tetraphenylarsonium chloride hydrochloride.* In a 2-l. round-bottomed three-necked flask fitted with a condenser, a mercury-sealed mechanical Hershberg stirrer, and a dropping funnel is placed 40 g. (0.124 mole) of triphenylarsine oxide dissolved in 1 l. of hot benzene. To this solution there is added with vigorous stirring a solution of phenylmagnesium bromide which is prepared from 34.6 g. (0.22 mole) of bromobenzene, 6.0 g. (0.25 g. atom) of magnesium, and 200 ml. of dry ether. A brown viscous solid separates. The mixture is stirred for 15 minutes and then stirred and heated under reflux on a steam bath for 30 minutes. The solvent is removed by decantation, and the viscous solid is washed with 500 ml. of benzene. The addition product is then hydrolyzed with 100 ml. of water containing 5 ml. of concentrated hydrochloric acid.

The hydrolysis mixture is transferred to a 1-l. round-bottomed flask fitted with a reflux condenser, and 500 ml. of concentrated hydrochloric acid is added (Note 5). The mixture is heated on a steam bath for 1.5–2 hours. The flask is cooled in an ice bath; the crystals are collected on a sintered-glass funnel and washed with 200 ml. of ice-

cold concentrated hydrochloric acid and then with 200 ml. of ice-cold dry ether. The crude product weighs 50–56 g. The product is dissolved in a mixture of 50 ml. of water and 150 ml. of concentrated hydrochloric acid by boiling under reflux. The tetraphenylarsonium chloride hydrochloride separates when the solution is cooled in an ice bath. The white needles are collected on a sintered-glass funnel and washed with 50 ml. of ice-cold concentrated hydrochloric acid and then with 200 ml. of ice-cold dry ether. The yield of tetraphenylarsonium chloride hydrochloride melting at 204–208° with decomposition is 42–45 g. (74–80%).

2. Notes

1. If the addition of the arsenic trichloride-chlorobenzene mixture is too rapid, the reaction becomes vigorous and must be moderated with a cooling bath.
2. Before being discarded, the residue should be treated with ethanol to destroy unreacted sodium.
3. If crude triphenylarsine is used, the final product is difficult to purify
4. Triphenylarsine oxide is partly converted to the dihydroxide when heated with water. However, it is not hygroscopic under ordinary conditions.[3]
5. The hydrolysis product consists mainly of tetraphenylarsonium bromide, which is converted to tetraphenylarsonium chloride hydrochloride by crystallization from concentrated hydrochloric acid.

3. Discussion

Triphenylarsine has been prepared by the action of arsenic triiodide[4] or arsenic trichloride[5] on phenylmagnesium bromide and by the action of sodium and arsenic trichloride on chlorobenzene[6] or bromobenzene.[7] The method described here is essentially that of Pope and Turner.[6]

Triphenylarsine oxide has been prepared by the action of sodium hydroxide on triphenylarsine dibromide,[8] by the action of potassium permanganate on triphenylarsine,[9] and by the action of hydrogen peroxide on triphenylarsine.[10] The method described here is essentially that of Vaughan and Tarbell.[10]

Tetraphenylarsonium chloride hydrochloride has been prepared by the action of phenylmagnesium bromide on triphenylarsine oxide.[11] The method described here is essentially that of Blicke and Monroe.[11]

References and Notes

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3. Blicke and Cataline, *J. Am. Chem. Soc.*, **60**, 419 (1938).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

arsenic trichloride-chlorobenzene

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether (60-29-7)

sodium hydroxide (1310-73-2)

magnesium (7439-95-4)

potassium permanganate (7722-64-7)

acetone (67-64-1)

chlorobenzene (108-90-7)

sodium (13966-32-0)

bromobenzene (108-86-1)

hydrogen peroxide (7722-84-1)

Phenylmagnesium bromide (100-58-3)

Tetraphenylarsonium chloride hydrochloride, Arsonium chloride, tetraphenyl-, hydrochloride (123334-18-9)

arsenic trichloride (7784-34-1)

Triphenylarsine (603-32-7)

Triphenylarsine oxide (1153-05-5)

tetraphenylarsonium bromide

arsenic triiodide (7784-45-4)

triphenylarsine dibromide

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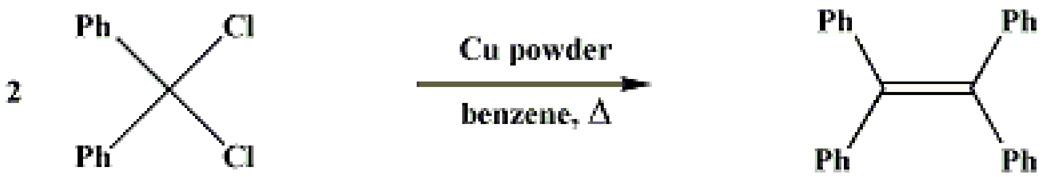
Organic Syntheses, CV 4, 914

TETRAPHENYLETHYLENE

[Ethylene, tetraphenyl-]



Submitted by Robert E. Buckles and George M. Matlack[1].
Checked by T. L. Cairns and C. J. Albisetti.

1. Procedure

A solution of 75 g. (0.32 mole) of diphenyldichloromethane (Note 1) in 250 ml. of anhydrous benzene is placed in a 500-ml. round-bottomed flask fitted with a reflux condenser. To the solution is added 50 g. (0.78 g. atom) of powdered copper (Note 2). The mixture is boiled gently for 3 hours. The hot solution is filtered, and 250 ml. of absolute ethanol is added to the filtrate. On cooling 25–31 g. (47–60%) of light yellow crystals, m.p. 222–224°, are obtained. The mother liquor is concentrated to about 200 ml. by distillation from a 1-l. Claisen flask. Cooling the residue yields 6–12 g. of yellow product. Crystallization of this crude material from a 1:1 by volume mixture (12 ml. for each gram) of absolute ethanol and benzene gives an additional 2.5–10 g. of tetraphenylethylene, m.p. 223–224°. The total yield is 29–37 g. (55–70%).

2. Notes

1. Diphenyldichloromethane is conveniently prepared from benzophenone and phosphorus pentachloride.[2] A product of b.p. 180–181°/17 mm. is obtained in about 90% yield.
2. The checkers used bronze powder obtained from George Benda, Inc., Boonton, New Jersey. Some varieties of copper powder tended to form a dense paste which did not disperse readily and resulted in lower yields.

3. Discussion

This procedure is adapted from the method of Schlenk and Bergmann.[3] Tetraphenylethylene has been prepared by the reaction of diphenylmethane with diphenyldichloromethane;[4] by the reaction of diphenyldichloromethane with silver or zinc;[4] by the reaction of thiobenzophenone with copper;[5] by the reaction of diphenylmethane with sulfur;[6] by the reduction of benzophenone with amalgamated zinc in the presence of hydrochloric acid;[7] by the rearrangement of 1,2,2,2-

tetraphenylethanol with acetyl chloride;[8] by the reaction of diphenylmethane with bromine, followed by treatment of the product with sodium iodide in acetone;[9] by the reaction of 1,2-difluoro-1,2-diphenylethylene with phenyllithium;[10] by the reaction of diphenylchloromethane with sodium or potassium amide in liquid ammonia;[11] and by treatment of 2,2,3,3-tetraphenylpropionitrile with potassium amide in liquid ammonia.[12]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

amalgamated zinc

sodium or potassium amide

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

Benzene (71-43-2)

phosphorus pentachloride (10026-13-8)

acetyl chloride (75-36-5)

bromine (7726-95-6)

sulfur (7704-34-9)

copper, copper powder (7440-50-8)

acetone (67-64-1)

Benzophenone (119-61-9)

zinc (7440-66-6)

diphenyldichloromethane (2051-90-3)

Diphenylmethane (101-81-5)

sodium iodide (7681-82-5)

Phenyllithium (591-51-5)

silver (7440-22-4)

Thiobenzophenone (1450-31-3)

potassium amide

Tetraphenylethylene, Ethylene, tetraphenyl- (632-51-9)

1,2,2,2-tetraphenylethanol

1,2-difluoro-1,2-diphenylethylene

diphenylchloromethane (90-99-3)

2,2,3,3-tetraphenylpropionitrile

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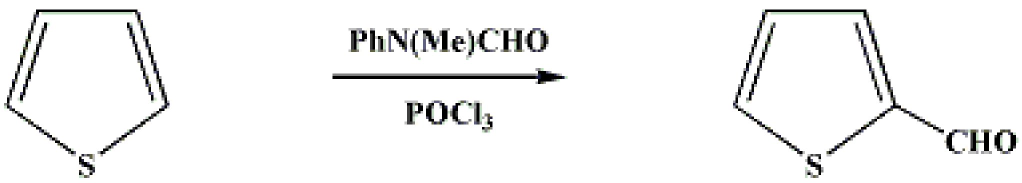
Organic Syntheses, CV 4, 915

2-THENALDEHYDE

[2-Thiophenecarboxaldehyde]



Submitted by Arthur W. Weston and R. J. Michaels, Jr.[1].
Checked by Cliff S. Hamilton and Joe R. Willard.

1. Procedure

The reaction is carried out in a 500-ml. three-necked round-bottomed flask fitted with ground-glass joints and equipped with a thermometer, a mechanical stirrer, a dropping funnel, and a calcium chloride tube. In the flask are placed 135 g. (1.0 mole) of N-methylformanilide (Note 1) and 153 g. (91 ml., 1.0 mole) of phosphorus oxychloride, and the mixture is allowed to stand for 30 minutes (Note 2). Mechanical stirring is then begun, and the flask is immersed in a cold-water bath while 92.4 g. (1.1 moles) of thiophene is added at such a rate that the temperature is maintained at 25–35° (Note 3). After the addition is complete, the reaction mixture is stirred 2 hours longer at the same temperature and is then allowed to stand at room temperature for 15 hours. The dark, viscous solution is poured into a vigorously stirred mixture of 400 g. of cracked ice and 250 ml. of water. The aqueous layer is separated and extracted with three 300-ml. portions of ether. The ether extracts are combined with the organic layer and washed twice with 200-ml. portions of dilute hydrochloric acid (Note 4) to remove all traces of N-methylaniline (Note 5). These aqueous washings are in turn extracted with 200 ml. of ether, and the ether extract is added to the ether solution of the product. The combined ether extracts are washed twice with 200-ml. portions of saturated sodium bicarbonate solution (Note 6), then with 100 ml. of water, and finally are dried over anhydrous sodium sulfate. The yellow oil obtained by concentrating the ether solution is distilled from a 100-ml. flask fitted with a satisfactory column (Note 7). The yield of 2-thiophenecarboxaldehyde boiling at 97–100°/27 mm., n_D^{23} 1.5893, is 80–83 g. (71–74%). The product darkens on standing.

2. Notes

1. Directions for preparing this intermediate have been published.[2]
2. The temperature of the mixture rises slowly to 40–45°, and a color change from yellow to red also occurs.
3. If the temperature is allowed to exceed 35°, a lower yield of aldehyde results.
4. This solution is prepared by mixing 50 g. of concentrated hydrochloric acid

and 400 ml. of water. The aldehyde has appreciable solubility in strongly acidic solutions.

5. The original aqueous layer and the acidic extracts are combined, cooled, and made strongly alkaline with 450 ml. of 40% sodium hydroxide solution. The liberated N-methylaniline is extracted with three 200-ml. portions of ether. The ether extracts are combined, washed with 100 ml. of water, dried over anhydrous sodium sulfate, and concentrated. Distillation of the residue from a 200-ml. flask equipped with an 11-cm. Vigreux column gives 95.6 g. (89%) of N-methylaniline boiling at 96–100°/27 mm.; n_D^{23} 1.5717.

6. Care must be taken in adding the bicarbonate solution, as vigorous foaming occurs until neutralization is complete.

7. The submitters used an 11-cm. Vigreux column; the checkers employed a 10-in. column of the same type.

3. Discussion

In addition to the methods given earlier,[3] 2-thenaldehyde has been prepared by the decarboxylation of 2-thienylglyoxylic acid;[4] by the hydrolysis of the acetal obtained by the action of 2-thienylmagnesium iodide on ethyl orthoformate;[4] by the oxidation of 2-thenyl alcohol;[5] by treatment of N-2-thenylformaldimine with ammonium chloride and formaldehyde;[6] by the action of 2-thienylmagnesium bromide on ethyl formate;[7] by the reaction of thiophene with dimethylformamide in the presence of phosphorus oxychloride;[8] by the condensation of thiophene with 1,4-diformylpiperazine in the presence of phosphorus oxychloride;[9] and by the reaction of thiophene with dichloromethyl methyl ether in the presence of stannic chloride.[10]

The present procedure is a modification of a previously described method.[11] [12]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 811

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

ether (60-29-7)

ammonium chloride (12125-02-9)

sodium hydroxide (1310-73-2)

formaldehyde (630-08-0)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

Phosphorus Oxychloride (21295-50-1)

Ethyl orthoformate

ethyl formate (109-94-4)

Thiophene (110-02-1)

stannic chloride (7646-78-8)

N-Methylaniline (100-61-8)

2-thienylmagnesium iodide

N-methylformanilide (93-61-8)

dimethylformamide (68-12-2)

2-thenyl alcohol (636-72-6)

2-Thenaldehyde, 2-Thiophenecarboxaldehyde (98-03-3)

2-thienylglyoxylic acid (4075-59-6)

Dichloromethyl methyl ether (4885-02-3)

N-2-thenylformaldimine

2-thienylmagnesium bromide

1,4-diformylpiperazine (4164-39-0)

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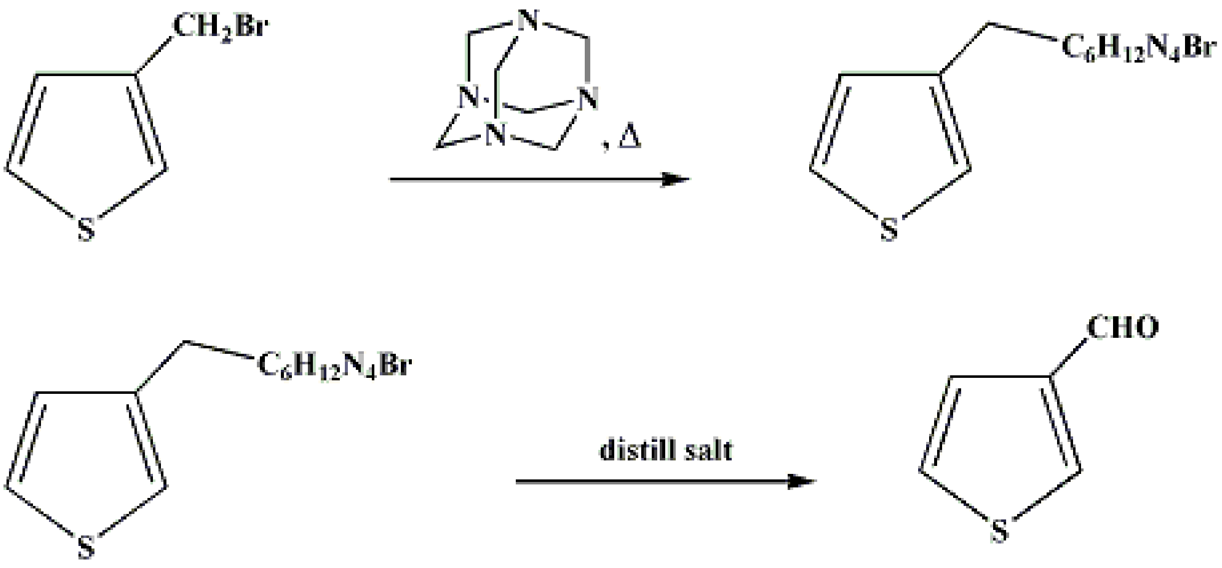
Organic Syntheses, CV 4, 918

3-THENALDEHYDE

[3-Thiophenecarboxaldehyde]



Submitted by E. Campaigne, R. C. Bourgeois, and W. C. McCarthy[1].
Checked by Charles C. Price and E. A. Dudley.

1. Procedure

Hexamethylenetetramine (77 g., 0.55 mole) is dissolved in 200 ml. of chloroform, and 88 g. (0.5 mole) of 3-thenyl bromide (p.921) is added as rapidly as possible with shaking (Note 1). A reflux condenser is attached, and the mixture is refluxed over a steam bath for 30 minutes. After being cooled, the mixture of chloroform and crystalline product (Note 2) is poured into 250 ml. of water and stirred until all the salt dissolves. The chloroform layer is separated and washed twice with 125-ml. portions of water, and the combined water extracts are steam-distilled. When the distillate comes over clear (about 1 l. of distillate is usually collected), it is acidified with a little hydrochloric acid (Note 3) and extracted with three 100-ml. portions of ether. After drying over Drierite, the ether is evaporated, and the residue is distilled. 3-Thenaldehyde is collected at 72–78°/12 mm. or 195–199°/744 mm., n_D^{20} = 1.5860 (Note 4). The yield is 30–40 g. (54–72%).

2. Notes

1. The reaction mixture refluxes spontaneously, and it is necessary to be cautious in adding the reagents to prevent the chloroform from boiling over.
2. The crystalline hexamine salt may be isolated and recrystallized at this step. It softens at 120° and melts with decomposition at 150°.
3. The Sommelet procedure[2] yields a mixture of aldehyde and amines.

Acidification removes the amines from the ether extract.
4. The checkers obtained the product, b.p. 80–81°/14 mm.

3. Discussion

3-Thenaldehyde has previously been prepared by Steinkopf and Schmitt[3] from 3-thienylmagnesium iodide and ethyl orthoformate in low yield. The first application of the method described here was reported by Campaigne and LeSuer.[4] 3-Thenaldehyde also has been obtained from 3-thenoic acid by the Sonn-Müller procedure[5] and from 3-bromothiophene by treatment with butyllithium and dimethylformamide.[6]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 919
- Org. Syn. Coll. Vol. 5, 121

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2. Sommelet, *Compt. rend.*, **157**, 852 (1913).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Drierite

hydrochloric acid (7647-01-0)

ether (60-29-7)

chloroform (67-66-3)

Ethyl orthoformate

hexamethylenetetramine (100-97-0)

butyllithium (109-72-8)

dimethylformamide (68-12-2)

3-Thenaldehyde

3-Thiophenecarboxaldehyde (498-62-4)

3-Thenyl bromide

3-thienylmagnesium iodide

3-Thenoic acid

3-Bromothiophene (872-31-1)

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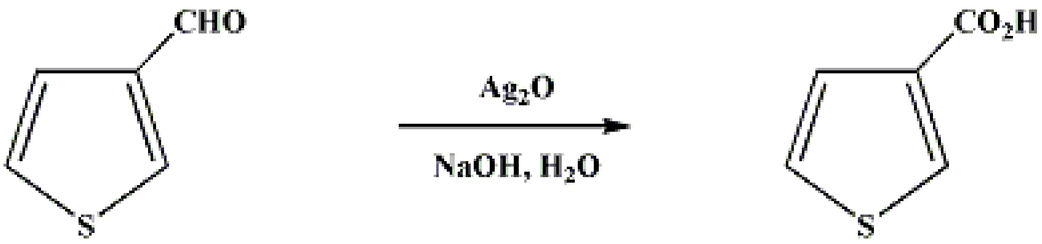
Organic Syntheses, CV 4, 919

3-THENOIC ACID

[3-Thiophenecarboxylic acid]



Submitted by E. Campaigne and William M. LeSuer[1].
Checked by Charles C. Price and E. A. Dudley.

1. Procedure

Silver oxide is prepared by adding a solution of 150 g. (0.88 mole) of silver nitrate in 300 ml. of water to a solution of 70 g. (1.75 moles) of sodium hydroxide in 300 ml. of water. Continuous shaking during the addition ensures complete reaction and results in a brown semisolid mixture. To this mixture, contained in a 1-l. flask which is cooled in an ice bath, is added 47.5 g. (0.425 mole) of 3-thenaldehyde (p. 918) in small portions with stirring. The oxidation is complete in about 5 minutes after the last of the aldehyde has been added. The black silver suspension is removed by suction filtration (Note 1) and is washed with several portions of hot water. The cold combined filtrate and washings are acidified with concentrated hydrochloric acid, precipitating 49 g. of 3-thenoic acid, which melts at 136–137°. Concentration of the mother liquors gives another 3–4 g. of acid, making a total of 52–53 g. (95–97%). Recrystallization of this acid from water raises the melting point to 137–138°.

2. Notes

1. This silver dissolves readily in concentrated nitric acid and may be used over and over in oxidations.

3. Discussion

3-Thenoic acid has been prepared in low yield by oxidation of 3-methylthiophene with potassium permanganate,[2,3,4] dilute nitric acid, chromic acid, and hydrogen peroxide,[4] and by reductive dechlorination of chloro-3-thenoic acid.[4] Starting with 3-iodothiophene, which is difficult to obtain, good yields are obtained by the Grignard procedure[5] or with cuprous cyanide and potassium cyanide in a sealed tube.[6] 3-Thenoic acid has been made also from 3-bromothiophene by reaction with cuprous

cyanide in quinoline, followed by hydrolysis,[7] and by carbonation of the Grignard reagent from 3-bromothiophene which is prepared by entrainment with ethyl bromide.[8]

Oxidation of the aldehyde was not used earlier because of the difficulty of obtaining the aldehyde, which is now readily available by the Sommelet synthesis from 3-thenyl bromide. Campaigne and LeSuer[9] also used alkaline permanganate as the oxidizing agent, but the yields decreased to 40–60%. The present procedure gives an over-all yield from 3-methylthiophene of about 45%.

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9. Campaigne and LeSuer, *J. Am. Chem. Soc.*, **70**, 1555 (1948).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

sodium hydroxide (1310-73-2)

nitric acid (7697-37-2)

potassium permanganate (7722-64-7)

silver oxide (20667-12-3)

silver nitrate (7761-88-8)

Ethyl bromide (74-96-4)

Cuprous Cyanide (544-92-3)

potassium cyanide (151-50-8)

chromic acid (7738-94-5)

hydrogen peroxide (7722-84-1)

Quinoline (91-22-5)

silver (7440-22-4)

3-Methylthiophene (616-44-4)

3-Thenaldehyde

3-Thenyl bromide

3-Thenoic acid

3-Bromothiophene (872-31-1)

3-Thiophenecarboxylic acid (88-13-1)

chloro-3-thenoic acid

3-iodothiophene (10486-61-0)

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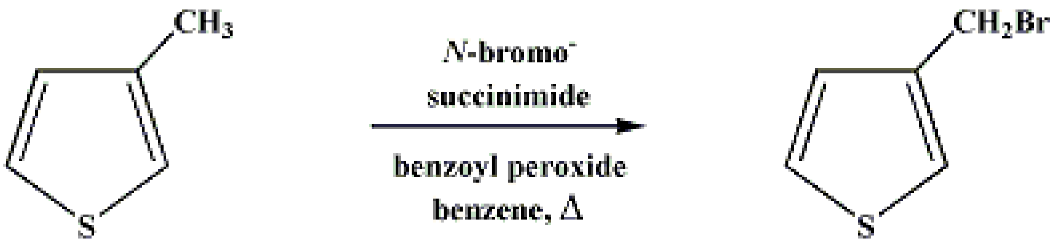
Organic Syntheses, CV 4, 921

3-THENYL BROMIDE

[Thiophene, 3-bromomethyl-]



Submitted by E. Campaigne and B. F. Tullar[1].
Checked by Charles C. Price and E. A. Dudley.

1. Procedure

Caution! This preparation should be run in a well-ventilated hood.

A 5-l. three-necked flask (Note 1) is fitted with a stirrer, an efficient reflux condenser, and a wide-mouthed funnel with a 15-cm. water-cooled stem (Note 2). A solution of 220 g. (2.24 moles) of 3-methylthiophene (Note 3) and 4 g. of benzoyl peroxide in 700 ml. of dry benzene is brought to vigorous reflux in this flask, and a mixture of 356 g. (2 moles) of N-bromosuccinimide (Note 4) and 4 g. of benzoyl peroxide is added portionwise through the wide-mouthed funnel. The dry powder is added as rapidly as the violent foaming will permit (Note 5) and is worked down through the stem of the funnel with a stirring rod. Refluxing benzene washes the lower part of the funnel continuously. The total addition requires about 20 minutes. As soon as the foaming from the last addition of N-bromosuccinimide has subsided, the flask is cooled, first with a water bath and then an ice bath. The succinimide is filtered off and washed once with dry benzene.

The filtrate is immediately transferred to a distilling flask, and the benzene is removed at reduced pressure (Note 6). The residue is distilled at 1 mm., and the fraction boiling between 75° and 78° is collected (Note 7). The major portion boils at 76° and has n_D^{25} 1.6030. This procedure yields 250–280 g. (71–79%) of a water-white product, which remains colorless for several days when stored over calcium carbonate in a refrigerator (Note 8).

2. Notes

1. The large volume of the flask is desirable to control foaming.
2. The checkers used a short, large-bore condenser.
3. Commercial 3-methylthiophene, formerly available from Socony-Vacuum Oil

Company, was used. 3-Methylthiophene is now available from Winthrop-Stearns, Inc., Special Chemicals Division, New York 18, N. Y.
4. N-Bromosuccinimide can be prepared in an active state by two slight modifications of the Ziegler procedure.[2] A slight molar excess of sodium hydroxide is used, and the reaction mixture is stirred vigorously while the bromine, dissolved in an equal volume of carbon tetrachloride, is added rapidly. This produces a finely crystalline white product which is ready for use as soon as it is filtered from the water and carbon tetrachloride and thoroughly dried. The yields are generally improved by this procedure, and the N-bromosuccinimide is ready to use sooner than the product described by Ziegler et al.[2] Acetic acid is an excellent solvent for crystallization of crude *N*-bromosuccinimide.
5. Unless the reaction mixture is maintained at strong reflux during this addition, considerable nuclear bromination occurs with a corresponding decrease in 3-thenyl bromide yield.
6. If necessary to interrupt the procedure, the benzene solution of 3-thenyl bromide may be stored over calcium carbonate and distilled directly from the carbonate later. The addition of a little calcium carbonate before distillation avoids the formation of a difficultly removable tarry residue.
7. *Caution! This distillation should be carried out behind a safety shield.* Thenyl bromide is a powerful lachrymator, and some individuals may develop extensive irritation of the skin upon exposure to its vapors. The checkers observed boiling points of 78–82°/2 mm. and 80–85°/3 mm.
8. The product contains a trace of 2-bromo-3-methylthiophene, but no 2-bromo-3-thenyl bromide, and is sufficiently pure for most purposes. Samples of 3-thenyl bromide have sometimes exploded without warning, leaving deposits of black resinous material. However, storage over calcium carbonate slows this acid-catalyzed reaction. The addition of a small amount of a tertiary amine likewise increases the stability.

3. Discussion

The only method of preparative interest is that described by Campaigne and LeSuer,[3] upon which the present method is based. This method has been applied by Dittmer and others.[4]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

acetic acid (64-19-7)

Benzene (71-43-2)

sodium hydroxide (1310-73-2)

bromine (7726-95-6)

carbon tetrachloride (56-23-5)

calcium carbonate (471-34-1)

benzoyl peroxide (94-36-0)

N-bromosuccinimide (128-08-5)

3-Methylthiophene (616-44-4)

3-Thenyl bromide

Thiophene, 3-bromomethyl- (34846-44-1)

Thenyl bromide

2-bromo-3-methylthiophene (14282-76-9)

2-bromo-3-thenyl bromide

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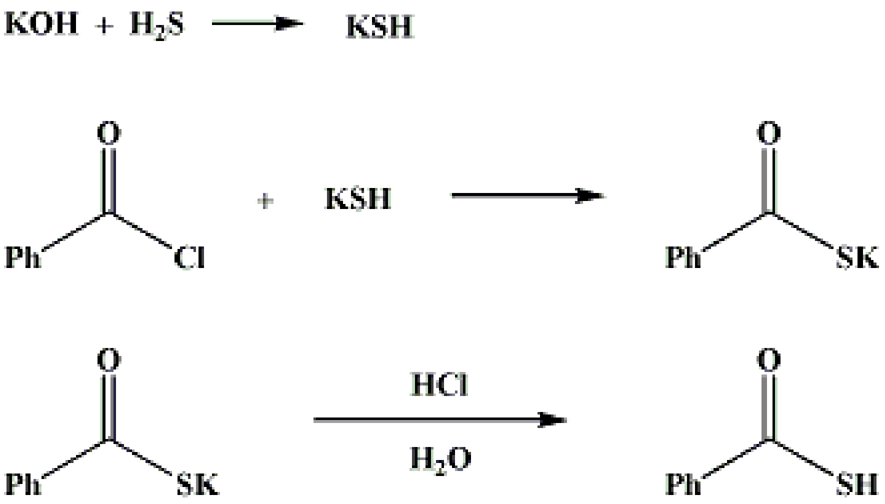
Organic Syntheses, CV 4, 924

THIOBENZOIC ACID

[Benzoic acid, thio]



Submitted by Paul Noble, Jr. and D. S. Tarbell[1].
Checked by William S. Johnson and Robert A. Kloss.

1. Procedure

A solution of 200 g. (3 moles) of potassium hydroxide (85%) pellets in 800 ml. of 90% ethanol (Note 1) is prepared with mechanical stirring in a 2-l. three-necked round-bottomed flask. The flask is fitted with a 500-ml. dropping funnel and a gas inlet tube extending to the bottom of the flask, and hydrogen sulfide is passed in through the inlet tube with stirring and cooling until the solution is saturated and does not give an alkaline reaction with phenolphthalein (Note 2) and (Note 3). The mixture is further cooled to 10–15° by means of an ice bath, and 200 g. (1.41 moles) of freshly distilled benzoyl chloride (Note 4) is introduced drop-wise over a period of about 1.5 hours with stirring while the temperature is kept below 15°. After the addition of the benzoyl chloride has been completed, the reaction mixture is stirred for an additional hour. The potassium chloride which precipitates during the addition is separated quickly by filtration through a Büchner funnel and is washed with about 200 ml. of 95% ethanol. The filtrate is placed in a 2-l. round-bottomed flask fitted with a condenser arranged for distillation and evaporated to dryness under reduced pressure on a steam bath (Note 5). The solid residue, consisting mainly of potassium thiobenzoate, is dissolved in about 700 ml. of cold water (Note 6), and the solution is filtered if considerable insoluble material is present (Note 4). The alkaline solution is extracted with 500 ml. of benzene in order to remove any neutral material. The aqueous layer is then acidified with cold 6*N* hydrochloric acid (Note 6) and extracted with two 500-ml. portions of peroxide-free ether (Note 7). The ether layer is washed with several portions of cold water and dried over anhydrous sodium sulfate. The ether is evaporated under reduced

pressure on a steam bath (Note 5), and the residue is fractionated immediately through a short (15–20 cm.) Vigreux column at reduced pressure, dry nitrogen being admitted through the capillary (Note 8). After a very small fore-run, the yellow-orange thiobenzoic acid distils at 85–87°/10 mm. (95–97°/15 mm.); yield 120–150 g. (61–76%); n_D^{20} 1.6027. Upon refractionation, the light-yellow thiobenzoic acid, as determined by titration with standard base or alcoholic iodine, is about 99.5% pure; n_D^{20} 1.6030.

2. Notes

1. No improvement in yield was observed by substitution of absolute ethanol. The 90% is preferable to 95% ethanol, because a much smaller volume is required to dissolve the potassium hydroxide.
2. The preparation should be conducted in a well-ventilated hood or provision should be made for an exhaust tube and attachment to a gas-absorption trap.
3. The gas inlet tube should be of moderately large diameter to prevent becoming plugged with crystals during the saturation with hydrogen sulfide.
4. The use of benzoyl chloride which has not been redistilled lowers the yield by 20–30%. The use of a molar equivalent of benzoyl chloride leads to the formation of considerable benzal *bis*-thiobenzoate, $C_6H_5CH(SCOC_6H_5)_2$, which has been isolated previously as a product from the action of benzoyl chloride on potassium sulfide in ethanol.[2]
5. In order to prevent oxidation, it is inadvisable to allow the solution to stand for any appreciable time up to this point. The evaporation should be carried out without the use of a capillary. The checkers found it convenient to employ mechanical stirring (rubber-sealed stirrer) during the reduced-pressure distillation in order to prevent bumping.
6. If the temperature is allowed to rise, considerable oxidation may occur.
7. Suitable peroxide-free ether is prepared by washing ether with an equal volume of a dilute, weakly acidic solution of ferrous sulfate.
8. It is necessary to fractionate as rapidly as possible in order to prevent oxidation to the disulfide, which occurs almost completely even in the presence of nitrogen if the column is too long or if the distillation is carried out too slowly. Oil-pumped nitrogen is dried through an absorption tower containing soda lime and calcium chloride before passing to the distillation apparatus. The column should be vacuum jacketed or provided with a heated jacket.

3. Discussion

The method described is adapted from the procedures of Kym[3] and Engelhardt, Latschinoff, and Malyscheff.[4] Thiobenzoic acid has been prepared by the reaction of benzoyl chloride with potassium sulfide,[4] hydrogen sulfide in pyridine,[5,6] and magnesium bromide hydrosulfide.[7] It is formed from dibenzoyl disulfide with

potassium hydrosulfide,[4] potassium hydroxide,[4,8] and ammonia.[9] It is also formed from dibenzoyl sulfide, from phenyl benzoate, and from benzoic anhydride with alcoholic potassium hydrosulfide.[4] It has been obtained from dibenzoyl sulfide and hydrogen sulfide,[10] carbon oxysulfide and phenylmagnesium bromide,[11,12] dibenzyl disulfide and sodium ethoxide,[13] benzyl chloride and sulfur in the presence of potassium hydroxide,[14] and benzylthiosulfuric acid and alkali.[15,16]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

carbon oxysulfide

peroxide-free ether

dibenzoyl sulfide

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

Benzene (71-43-2)

ether (60-29-7)

hydrogen sulfide (7783-06-4)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

sulfur (7704-34-9)

ferrous sulfate (13463-43-9)

iodine (7553-56-2)

benzoyl chloride (98-88-4)

Benzoic anhydride (93-97-0)

pyridine (110-86-1)

potassium hydroxide (1310-58-3)

sodium ethoxide (141-52-6)

benzyl chloride (100-44-7)

potassium hydrosulfide (1310-61-8)

Phenylmagnesium bromide (100-58-3)

potassium sulfide (1312-73-8)

phenolphthalein (77-09-8)

potassium chloride (7447-40-7)

phenyl benzoate (93-99-2)

dibenzoyl disulfide (644-32-6)

Thiobenzoic acid, Benzoic acid, thio (98-91-9)

potassium thiobenzoate

magnesium bromide hydrosulfide

dibenzyl disulfide (150-60-7)

benzylthiosulfuric acid

benzal bis-thiobenzoate

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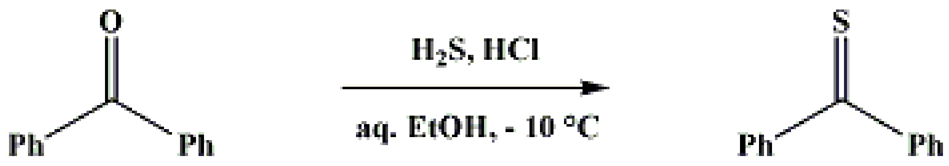
Organic Syntheses, CV 4, 927

THIOBENZOPHENONE

[Benzophenone, thio-]



Submitted by B. F. Gofton and E. A. Braude[1].
Checked by Charles C. Price and J. Frank Gillespie.

1. Procedure

Caution! This preparation should be conducted in a good hood.

A 250-ml. three-necked flask is equipped with a rubber-sealed mechanical stirrer, two gas-inlet tubes, and a mercury-sealed escape valve consisting of an outlet tube dipping into a test tube of mercury. A solution of 25 g. (0.14 mole) of benzophenone in 125 ml. of 95% ethanol is placed in the flask, which is cooled in an ice-salt freezing mixture. Hydrogen sulfide and hydrogen chloride are passed simultaneously into the stirred solution for 3 hours (Note 1). Within 1 hour the solution becomes blue. After 3 hours, the flow of hydrogen chloride is stopped and hydrogen sulfide alone is passed for a further 20 hours, with continued ice cooling. Toward the end of the reaction, the contents of the flask assume an intense violet color. The solid thiobenzophenone (23–25 g.) is filtered from the ice-cold solution in an atmosphere of carbon dioxide (Note 2), immediately dried under high vacuum (Note 3), and recrystallized twice from about 20 ml. of petroleum ether (b.p. 60–80°), giving long needles, m.p. 53–54°. The yield of purified product, is 18–21 g. (66–77%).

2. Notes

1. Hydrogen chloride was generated by dropping concentrated sulfuric acid on ammonium chloride. Hydrogen sulfide was generated in a Kipp's apparatus from iron sulfide and hydrochloric acid. (The checkers used tank hydrogen sulfide.)
2. A convenient filtration apparatus for this purpose may be constructed by cutting the bottom off a bottle and then inserting a Büchner funnel through a stopper in the mouth of the bottle. The space between the bottle and the funnel is then packed with Dry Ice.
3. It has been found essential to dry the crude material immediately after filtration; otherwise it changes into a blue oil after standing for a few hours.

3. Discussion

The method described here is adapted from the procedure of Staudinger and Freudenberger.[2] It has been found to be more convenient and to give more reproducible results than the two-stage procedure given in *Organic Syntheses*,[3] where references to other methods of preparation are also cited. Thiobenzophenone has been prepared also from benzophenone anil and thiolacetic acid.[4]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

benzophenone anil

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrogen chloride, hydrochloric acid (7647-01-0)

ammonium chloride (12125-02-9)

hydrogen sulfide (7783-06-4)

mercury (7439-97-6)

carbon dioxide (124-38-9)

Benzophenone (119-61-9)

Thiobenzophenone, Benzophenone, thio- (1450-31-3)

iron sulfide

Thiolacetic acid

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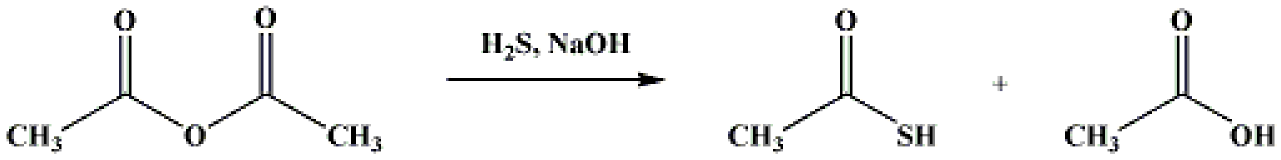
Organic Syntheses, CV 4, 928

THIOLACETIC ACID

[Acetic acid, thiol-]



Submitted by E. K. Ellingboe[1]
Checked by Arthur C. Cope and Malcolm Chamberlain.

1. Procedure

Caution! All the steps of this procedure should be carried out under a hood because of the highly toxic nature of hydrogen sulfide and the probable toxicity and persistent unpleasant odor of thiolacetic acid.

A 200-ml. three-necked flask is fitted with a mercury-sealed glass stirrer, a reflux condenser, and a gas inlet tube and thermometer, both of which extend into the lower half of the flask. The top of the condenser is connected to a mercury bubbler tube, and the gas inlet tube is attached to the inlet tube of a gas-washing bottle which serves as a safety trap to prevent liquid from being drawn into the hydrogen sulfide source. The gas-washing bottle is connected through a drying tube containing anhydrous calcium sulfate (Drierite) to a T-tube. The vertical arm of the T-tube dips into mercury and forms a safety valve; the other arm is connected to a commercial cylinder (Note 1) or other source of hydrogen sulfide. To the flask are added 107 g. (100 ml., 1 mole) of 95% acetic anhydride and 1 g. (0.025 mole) of powdered sodium hydroxide. The assembly of the flask, condenser, inlet tube, and thermometer is weighed and arranged so that the amount of hydrogen sulfide introduced can be determined by subsequent weighing. The stirrer is started, and hydrogen sulfide is passed into the mixture as rapidly as possible without much loss of the gas through the bubbler connected to the top of the condenser. The temperature of the mixture rises to 55° within 30 minutes and is kept at 50–55° by intermittent cooling. The temperature begins to drop after 14–17 g. of hydrogen sulfide has been absorbed and is maintained at 50–55° by external heating. After a total reaction period of 6 hours, hydrogen sulfide ceases to be absorbed and the gain in weight amounts to about 31 g.

The reaction mixture is transferred to a 250-ml. Claisen flask (Note 2) and distilled rapidly at 200 mm. in order to separate the sodium salts (Note 3). The distillate of thiolacetic acid and acetic acid, b.p. 35–82°/200 mm., amounts to 120–124 g. It is fractionally distilled at atmospheric pressure through an efficient, variable take-off type column[2] with a 30- to 40-cm. section packed with glass helices. The fraction boiling at 86–88°, n_D^{25} 1.4612, is nearly pure thiolacetic acid and amounts to 55–57.5 g. (72–76%) based on the acetic anhydride (Note 4) and (Note 5). The residual liquid is mainly acetic acid. If distillation is continued after separation of the thiolacetic acid, the vapor temperature rises rapidly to the boiling point of acetic acid.

2. Notes

1. Cylinders of hydrogen sulfide are available from the Matheson Company, Inc., East Rutherford, New Jersey.
2. An all-glass distillation assembly equipped with ground joints is advisable because the hot vapor of thiolacetic acid rapidly softens rubber stoppers.
3. The product decomposes excessively if fractionation is attempted in the presence of the sodium salts. In larger-scale preparations the initial distillation should be conducted in small batches or, preferably, in a continuous stripping still.
4. Refractionation yields pure thiolacetic acid (with about 10% loss) with the following physical constants: b.p. 87°/760 mm., 50°/200 mm., 34°/100 mm.; n_D^{25} 1.4630; d_4^{25} 1.0634. Higher boiling points at atmospheric pressure have been reported: 88–91°,[3] 89°,[4] and 93°.[5]
5. The submitter has prepared thiolacetic acid in yields of 65–70 g. (85–92%) by a similar procedure in which the reaction mixture is placed in the glass bottle (provided with a heating jacket and thermometer or thermocouple) of a low-pressure hydrogenation apparatus.[6] The mixture is shaken and hydrogen sulfide is introduced at 25–35 p.s.i., with repressuring to 35–40 p.s.i. whenever the pressure drops to 10 p.s.i. The heat of reaction raises the temperature to 60–65° in 12–15 minutes, after which the internal temperature is maintained at 60° by heating. Hydrogen sulfide absorption becomes negligible after 4 hours, and the mixture is allowed to cool while under pressure, vented, and the product is isolated in the manner described. The reaction also was conducted in a steel autoclave or hydrogenation bomb at the full pressure of hydrogen sulfide in a commercial cylinder (about 300 p.s.i. at room temperature). Hydrogen sulfide poisons the ordinary hydrogenation catalysts, and low-pressure cylinders or hydrogenation bombs exposed to hydrogen sulfide may not be suitable for subsequent use in catalytic hydrogenations.

3. Discussion

Thiolacetic acid has been prepared from acetic acid and phosphorus pentasulfide;[5] from acetyl chloride and potassium hydrosulfide;[7] by the hydrolysis of diacetyl sulfide;[8] from acetic anhydride and hydrogen sulfide;[3,4,9,10] and from acetyl chloride and hydrogen sulfide in the presence of aluminum chloride.[11] The procedure described[9] differs from other procedures employing acetic anhydride and hydrogen sulfide[3,4] most importantly in the use of alkaline rather than acidic catalysts, which the submitter found to cause slower absorption of hydrogen sulfide under pressure and to yield considerable diacetyl sulfide in addition to thiolacetic acid. Other alkaline catalysts which have been used to effect the reaction between acetic anhydride and hydrogen sulfide are triethylamine[12] and pyridine.[13]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

calcium sulfate (Drierite)

acetic acid (64-19-7)

acetic anhydride (108-24-7)

sodium hydroxide (1310-73-2)

acetyl chloride (75-36-5)

hydrogen sulfide (7783-06-4)

mercury (7439-97-6)

aluminum chloride (3495-54-3)

pyridine (110-86-1)

potassium hydrosulfide (1310-61-8)

phosphorus pentasulfide

triethylamine (121-44-8)

Thiolacetic acid

Acetic acid, thiol- (1918-77-0)

diacetyl sulfide (3232-39-1)

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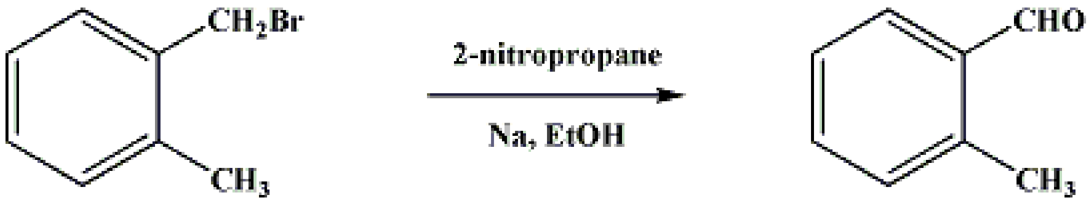
Organic Syntheses, CV 4, 932

o-TOLUALDEHYDE



Submitted by H. B. Hass and Myron L. Bender[1].
Checked by Arthur C. Cope and Malcolm Chamberlain.

1. Procedure

Eleven and one-half grams (0.5 g. atom) of sodium is dissolved in 500 ml. of absolute ethanol in a 1-l. round-bottomed flask. Forty-six grams (0.52 mole) of 2-nitropropane is added, then 92.5 g. (0.50 mole) of *o*-xylyl bromide (Note 1). The flask is attached to a reflux condenser connected to a drying tube and shaken at intervals for 4 hours. The reaction mixture, originally at room temperature, becomes warm spontaneously, and a white precipitate of sodium bromide forms (Note 2).

After a reaction period of 4 hours the sodium bromide is separated by filtration and the ethanol is removed by distillation on a steam bath. The residue of product and sodium bromide is dissolved in 100 ml. of ether and 150 ml. of water. The ether layer is washed with two 50-ml. portions of 10% sodium hydroxide solution to remove any acetoxime and excess 2-nitropropane and is then washed with 50 ml. of water. The ether layer is separated and is dried with 15 g. of anhydrous sodium sulfate, and the ether is removed by distillation on a steam bath.

The crude product is distilled from a Claisen flask under reduced pressure. The yield of *o*-tolualdehyde boiling at 68–72°/6 mm., n_D^{25} 1.5430, is 41–44 g. (68–73%) (Note 3).

2. Notes

1. *o*-Xylyl bromide may be obtained from the Eastman Kodak Company or may be prepared by the light-catalyzed bromination of *o*-xylene.[2]
2. The solution is originally supersaturated with the sodium salt of 2-nitropropane, and a precipitate of this salt may be mistaken for sodium bromide.
3. This is a general method for the preparation of substituted benzaldehydes. The following aldehydes have been prepared by the same general procedure.[3]

Aldehyde	Yield, %

p-Bromobenzaldehyde	75
Benzaldehyde	73
p-Carbomethoxybenzaldehyde	72
p-Cyanobenzaldehyde	70
p-Trifluoromethylbenzaldehyde	77

3. Discussion

A procedure for the preparation of *o*-tolualdehyde from *o*-toluanilide by the Sonn-Müller method has been published in *Organic Syntheses*.[4] In addition to the alternative methods of preparation listed there, *o*-tolualdehyde has been prepared from *o*-xylyl bromide[5] or chloride[6] and hexamethylenetetramine; by the Stephen reduction of *o*-tolunitrile;[7] by the reduction of the latter with lithium triethoxyaluminohydride[8] or sodium triethoxyaluminohydride;[9] by the condensation of crotonaldehyde with barium or calcium oxide at 300°;[10] by the oxidation of *o*-methylbenzyl alcohol with N-chlorosuccinimide;[11] by the reaction of ethyl orthoformate with *o*-tolylmagnesium bromide;[12] by the reaction of the *o*-tolylmagnesium chloride-tetrahydrofuran complex with methyl formate;[13] and by the procedure of the present preparation.[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 818

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

barium or calcium oxide

o-tolylmagnesium chloride-tetrahydrofuran complex

ethanol (64-17-5)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium bromide (7647-15-6)

sodium sulfate (7757-82-6)

benzaldehyde (100-52-7)

sodium (13966-32-0)

Ethyl orthoformate

ACETOXIME

methyl formate (107-31-3)

hexamethylenetetramine (100-97-0)

o-Tolunitrile (529-19-1)

chloride

crotonaldehyde (123-73-9)

N-chlorosuccinimide (128-09-6)

2-nitropropane (79-46-9)

sodium triethoxyaluminohydride

lithium triethoxyaluminohydride

o-Xylene (95-47-6)

p-Bromobenzaldehyde (1122-91-4)

p-cyanobenzaldehyde (105-07-7)

o-Tolualdehyde (529-20-4)

o-toluanilide

o-tolylmagnesium bromide

o-Methylbenzyl alcohol (89-95-2)

o-xylyl bromide (576-23-8)

p-Carbomethoxybenzaldehyde (1571-08-0)

p-Trifluoromethylbenzaldehyde (455-19-6)

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Organic Syntheses, CV 4, 934

p-TOLUENESULFENYL CHLORIDE

Submitted by Frederick Kurzer and J. Roy Powell[1].
Checked by Richard S. Schreiber and Fred Kagan.

1. Procedure

Caution! This preparation should be conducted in a good hood.

Chlorine (Note 1) is passed into 300 ml. of anhydrous carbon tetrachloride (Note 2) contained in a 500-ml. three-necked round-bottomed flask equipped with a mechanical stirrer, a dropping funnel protected from atmospheric moisture by a calcium chloride tube, and a gas-inlet tube equipped with a sintered-glass tip (Note 3). The amount of chlorine contained in the resulting yellow-green liquid, estimated volumetrically (Note 4), varies between 25 and 32 g. The gas-inlet tube is replaced by a calcium chloride tube, and the reaction vessel is cooled externally with ice water and protected from light by being covered with a towel.

One or two crystals of iodine are added to the chlorine solution, and a solution of *p*-toluenethiol (7.3 g. per 10 g. of dissolved chlorine, i.e., halogen in 140% excess) (Note 5) in 50 ml. of anhydrous carbon tetrachloride (Note 2) is added dropwise over a period of approximately 1 hour. The initial slight turbidity disappears gradually, a bright orange solution being formed (Note 6). After an additional 30 minutes' stirring, the solvent and excess chlorine are rapidly removed under reduced pressure at the lowest possible temperature (Note 7), the crude sulfenyl chloride being left as an orange-red mobile liquid (Note 8). For batches starting with 24.8 g. (0.2 mole) of *p*-toluenethiol, the yield varies between 27 and 30.5 g. (85–96%).

Rapid distillation under reduced pressure affords *p*-toluenesulfenyl chloride as a red mobile liquid boiling at 66–68°/0.8 mm. (74–76°/1.5 mm.; 82–84°/3.5 mm.) (Note 9). The yield of redistilled material varies between 24.5 and 28 g. (77–88%).

2. Notes

1. The checkers used tank chlorine obtained from the Ohio Chemical and Surgical Equipment Company, Detroit, Michigan. The gas was dried with concentrated sulfuric acid and used with no further purification. The rate of chlorine addition was regulated so that no chlorine escaped from the carbon

tetrachloride solution. After 1.5–2.0 hours, 27–33 g. of chlorine was absorbed. The submitters generated chlorine by the action of concentrated hydrochloric acid on potassium permanganate.

2. The carbon tetrachloride is treated with a small quantity of phosphorus pentoxide, and the suspension is set aside for 1–2 hours. The clear supernatant liquid is first decanted into a dry flask and gently shaken. Any droplets of phosphoric acid are retained on the walls of this vessel; the anhydrous solvent is then easily decanted.

3. During the slow absorption of chlorine, the solution is satisfactorily protected from atmospheric moisture by means of a plug of cotton wool through which the gas-inlet tube passes. The temperature of the solution does not rise, and external cooling is not required.

4. A 2-ml. aliquot of the solution, withdrawn by means of a safety pipet, is added to 20 ml. of water containing 2 g. of potassium iodide, and the liberated iodine is titrated with good shaking with standard sodium thiosulfate solution.

5. When a smaller excess of chlorine is used poorer yields of sulfenyl chloride are obtained, a larger proportion of *p*-tolyldisulfide being formed.

6. The checkers found that the turbidity persisted throughout the addition of the *p*-toluenethiol and that a small amount of an orange-yellow solid was present at the end of the addition. This material dissolved during the concentration under reduced pressure.

7. Since traces of sulfenyl chloride are carried over with the carbon tetrachloride, the distillate varies from light to deep yellow during the concentration. Recovery of this material by repeated distillation is not economical.

8. This material is suitable for use in further synthesis without purification by distillation, particularly if the presence of a few per cent of *p*-tolyl disulfide is of no consequence.

9. The checkers found that 76% of the product boiled at 64–66°/1.1 mm. and 24% boiled at 66–74°/1.1 mm.; however, the index of refraction of the two fractions was constant (n_D^{20} 1.6018–1.6019). As the first few drops of distillate were green, they were discarded.

3. Discussion

p-Toluenesulfenyl chloride has been prepared by the action of chlorine on a solution of *p*-toluenethiol or *p*-tolyl disulfide in anhydrous carbon tetrachloride.[2,3,4] Benzenesulfenyl chloride has also been obtained by the interaction of hydrogen chloride and N,N-diethylbenzenesulfenamide[5] and by reaction of benzenethiol with N-chlorosuccinimide.[6] A comprehensive review dealing with sulfenyl halides and related compounds is available.[7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 981

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfenyl chloride

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrogen chloride, hydrochloric acid (7647-01-0)

potassium permanganate (7722-64-7)

carbon tetrachloride (56-23-5)

potassium iodide (7681-11-0)

sodium thiosulfate (7772-98-7)

iodine (7553-56-2)

chlorine (7782-50-5)

phosphoric acid (7664-38-2)

Benzenethiol (108-98-5)

N-chlorosuccinimide (128-09-6)

Benzenesulfenyl chloride (931-59-9)

N,N-diethylbenzenesulfenamide

phosphorus pentoxide (1314-56-3)

p-Toluenesulfenyl chloride (933-00-6)

p-toluenethiol (106-45-6)

p-tolyl disulfide, p-tolyldisulfide (103-19-5)

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Organic Syntheses, CV 4, 937

p-TOLUENESULFINYL CHLORIDE

Submitted by Frederick Kurzer[1]
Checked by Richard S. Schreiber and Fred Kagan.

1. Procedure

Caution! This reaction should be conducted in a hood to avoid exposure to sulfur dioxide and hydrogen chloride.

To 179 g. (109 ml., 1.5 moles) of thionyl chloride (Note 1) contained in a 250-ml. round-bottomed flask, 42.8 g. (0.2 mole) of powdered sodium *p*-toluenesulfinate dihydrate[2] (Note 1) is added in portions at room temperature over a 10- to 15-minute period. A vigorous reaction occurs with the evolution of hydrogen chloride and sulfur dioxide. As the first portions of the sulfinate are added, the temperature of the reaction mixture rises, but it soon drops to approximately 0° as the addition proceeds (Note 2). The resulting reaction mixture, a clear yellow liquid containing a white opaque solid, is protected from atmospheric moisture by means of a calcium chloride drying tube and is set aside at room temperature for 1.5–2 hours. During this time slight effervescence continues (Note 3) and the white opaque suspended material gradually disintegrates to a finely divided translucent deposit.

The excess thionyl chloride is removed by distillation under reduced pressure (15–20 mm.) with the bath temperature below 50°, and the last traces are eliminated by one or two evaporations under reduced pressure after the addition of 50-ml. portions of anhydrous ether (Note 4). The residue consists of a viscous yellow oil containing a suspension of white granular inorganic solid. The crude sulfinyl chloride is readily dissolved by three successive treatments with portions of anhydrous ether (50, 30, and 30 ml., respectively) which are decanted without difficulty from most of the inorganic residue (Note 5). Removal of the solvent by distillation at reduced pressure leaves the sulfinyl chloride as a clear, pale, straw-yellow oil. The yield is 30–32 g. (86–92%) (Note 6). Distillation at reduced pressure (Note 5) yields *p*-toluenesulfinyl chloride as a deep yellow mobile oil, b.p. 113–115°/3.5 mm. or 99–102°/0.5 mm. (Note 7). The yield of redistilled material is 23–26 g. (66–74%). A small quantity (2–3 g.) of a dark tarry residue remains in the distilling flask.

2. Notes

1. Redistilled thionyl chloride is recommended. No difficulties were encountered

when the color of the reagent was deep yellow. The sodium *p*-toluenesulfinate dihydrate should be thoroughly air-dried to remove mechanically bound water.

2. When smaller quantities are used the thionyl chloride may be added to the sulfinate in one portion. After an initial rise, the temperature drops to about 0°. With larger quantities this procedure is not practicable.

3. If the sodium *p*-toluenesulfinate is not finely powdered, reaction occurs more slowly with emission of slight crackling sounds.

4. The ether was dried over calcium chloride and finally over phosphorus pentoxide. The checkers found that after the ether evaporations the odor of thionyl chloride was still present. The last traces of thionyl chloride were best removed at a pressure of 1–2 mm. When free of thionyl chloride the residue no longer has the pungent odor of either hydrogen chloride or sulfur dioxide but has a faint odor typical of sulfonyl chlorides.

5. If it is desired to distil the sulfinyl chloride subsequently, any traces of suspended material must be removed by filtration of the ethereal solution through a small filter, preferably into the distilling flask. It is advantageous to concentrate the ethereal solution to a small volume before filtering since more concentrated solutions of sulfinyl chloride in ether have less tendency to take up moisture from the atmosphere. The filter is rinsed with a little anhydrous ether.

The checkers used an inverted funnel connected to a source of dry nitrogen to provide an inert atmosphere for the filtration. The filtration was carried out as completely as possible directly beneath the inverted funnel through which a rapid stream of nitrogen flowed.

6. The sulfinyl chloride thus obtained is satisfactory for further preparative work. The checkers found that the average yield of crude material after removal of inorganic salts by filtration was about 81%.

7. On being heated, the sulfinyl chloride undergoes transient color changes (green), and the redistilled material may be darker in color than the pale yellow residue obtained after the removal of the ether.

For distillation the checkers employed a Claisen head with a fraction cutter. Approximately 90% of the product distilled at 93–96°/1.1 mm., $n_D^{23.5}$ 1.6004, and 10% distilled at 98–100°/1.3–1.6 mm., $n_D^{23.5}$ 1.5998. The total yield of distilled material in two runs averaged 74%.

3. Discussion

Arylsulfinyl chlorides have been prepared by treating the corresponding arylsulfinic acids with an excess of thionyl chloride in the absence of solvents, either with gentle heating[3,4,5,6,7,8] or at room temperature.[9] The use of nearly equimolecular proportions of the reactants, and of ether as diluent in this reaction, has been claimed[10,11] to yield a cleaner product. *p*-Toluenesulfinyl chloride may be obtained directly from the hydrated sodium salt of *p*-toluenesulfinic acid by the action of a large excess of thionyl chloride, and the present procedure is based on this variation.[12]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfonyl chlorides

sulfinyl chloride

calcium chloride (10043-52-4)

hydrogen chloride (7647-01-0)

ether (60-29-7)

thionyl chloride (7719-09-7)

sulfur dioxide (7446-09-5)

nitrogen (7727-37-9)

phosphorus pentoxide (1314-56-3)

Sodium p-toluenesulfinate, sodium salt of p-toluenesulfinic acid

p-Toluenesulfinyl chloride (10439-23-3)

sodium p-toluenesulfinate dihydrate (7257-26-3)

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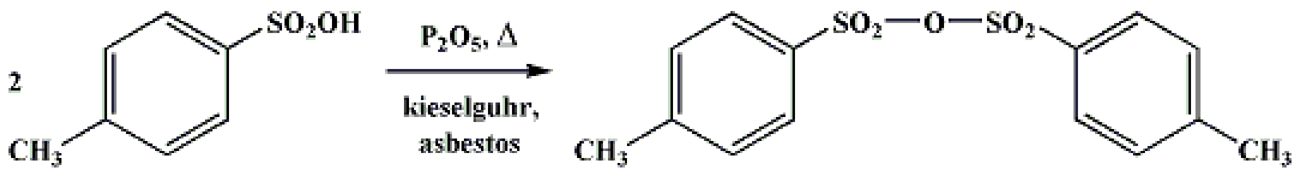
Organic Syntheses, *CV 4, 940*

p-TOLUENESULFONIC ANHYDRIDE



Submitted by L. Field and J. W. McFarland[1].
Checked by William S. Johnson, Raymond R. Hindersinn, and A. G. Fisher.

1. Procedure

A mixture of 213 g. (1.5 moles) of phosphorus pentoxide and 14 g. of kieselguhr (Note 1) is prepared by shaking in a dry, stoppered 1-l. Erlenmeyer flask. About one-half of the mixture is then added to a mixture of 7 g. of asbestos (Note 1) and 190 g. (1.0 mole) of *p*-toluenesulfonic acid monohydrate (Note 2) in a 1-l. round-bottomed flask with one standard-taper neck protected from atmospheric moisture with a drying tube containing calcium chloride. The mixture, which soon becomes quite hot, is allowed to stand for 1 hour with occasional swirling. It is then heated in an oil bath held at about 125° for 9 hours, the remainder of the phosphorus pentoxide mixture being added in four portions during the first 3 hours. During this total 9-hour period the mass is mixed as well as possible with a metal spatula from time to time.

The drying tube is replaced by a condenser, and 400 ml. of ethylene chloride (Note 3) is added. The mixture is heated under reflux for several minutes. The flask is closed with a glass stopper and shaken well (Note 4). A thin pad of glass wool is then inserted into the lower part of the flask neck, and the extract is decanted. This extraction and decantation process is repeated with three 100-ml. portions of ethylene chloride. The extracts are combined in a 1-l. round-bottomed flask, the solvent is removed by distillation under reduced pressure, and the molten solid is swirled briefly at 3 mm. pressure until cessation of bubbling indicates complete removal of solvent. The dark oily solid, which is formed on cooling, amounts to 138–143 g. and melts in the range 80–124° (sealed tube) (Note 5). This material is purified by dissolving it in the minimum amount (about 200 ml.) of boiling anhydrous benzene (Note 6) and (Note 7) and, after cooling to about 50°, adding 300 ml. of anhydrous ether (Note 7). After crystallization is well advanced, the mixture is stored at −5° overnight. The solvent is removed by forcing it under nitrogen pressure either through a 6-mm. glass tube packed with glass wool up to a constriction about 1 in. from the bottom or through a sintered-glass filter stick. Residual solvent is removed at 3-mm. pressure through a stopcock which is then closed to permit storage of the anhydride at low pressure (Note 8). The yield is 77–114 g. (47–70%) of light brown or gray prisms. The product, which softens at about 90° and melts at 110–127° (sealed tube) (Note 5), is sufficiently pure for most purposes (Note 9).

2. Notes

1. It is satisfactory to use the Super-Cel brand of kieselguhr supplied by Johns-Manville Company and asbestos of the type used in Gooch crucibles. Inclusion of these inert materials facilitates mixing and extraction of the product.
2. A good commercial grade of *p*-toluenesulfonic acid monohydrate, m.p. 104–106°, was used.
3. A good commercial grade of ethylene chloride, b.p. 83–84°, was used. It is dried by distilling a portion.

4. If shaking is too violent, the gummy residue that clings to the flask may be dislodged, and the flask may break. After extraction is complete, the phosphorus pentoxide residue can be removed from the flask by adding water and replacing this by fresh water as the mixture becomes hot.
5. Even brief exposure to moist air causes a lowering of the melting point. The melting-point tube is therefore best filled by inserting it into material ground against the flask bottom or by using a dry box; the tube is then quickly sealed. The melting point of pure *p*-toluenesulfonic anhydride is 129.5–131.5°, with softening about 120° (sealed tube).[2]
6. Commercial grades of anhydrous ether and benzene which have been allowed to stand over sodium are satisfactory. Dry glassware should be used for transferring the solvents.
7. Usually a small amount of material remains undissolved. This material does not affect the melting point significantly but can be removed if desired by forcing the solution, kept hot by an electric heating mantle, through the filter arrangement described above into a dry flask protected from moisture by a calcium chloride tube.
8. In order to open the flask, air is admitted slowly through a calcium chloride tube. The melting point of the anhydride drops somewhat during prolonged storage with occasional opening, but the purity does not seem to be affected appreciably.[2]
9. The broad melting range apparently results from an unusual sensitivity of this property to small amounts of impurities.[2] The melting point can be raised by further recrystallizations.

3. Discussion

p-Toluenesulfonic anhydride has been prepared from the acid salt by the use of thionyl chloride[3] and phosphorus pentoxide,[2] and from the acid or sodium salt by treatment with a mixture of phosphorus pentachloride and phosphorus oxychloride.[4] It also has been obtained by heating oxime *p*-toluenesulfonates,[5] by reaction of *p*-toluenesulfonic acid with di-*p*-tolylcarbodiimide,[6] and by the interaction of methoxyacetylene and *p*-toluenesulfonic acid.[7]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

oxime p-toluenesulfonates

calcium chloride (10043-52-4)

Benzene (71-43-2)

ether (60-29-7)

phosphorus pentachloride (10026-13-8)

thionyl chloride (7719-09-7)

ethylene chloride (107-06-2)

nitrogen (7727-37-9)

Phosphorus Oxychloride (21295-50-1)

sodium (13966-32-0)

methoxyacetylene (6443-91-0)

p-toluenesulfonic acid (104-15-4)

phosphorus pentoxide (1314-56-3)

p-toluenesulfonic acid monohydrate (6192-52-5)

p-Toluenesulfonic anhydride (4124-41-8)

di-p-tolylcarbodiimide

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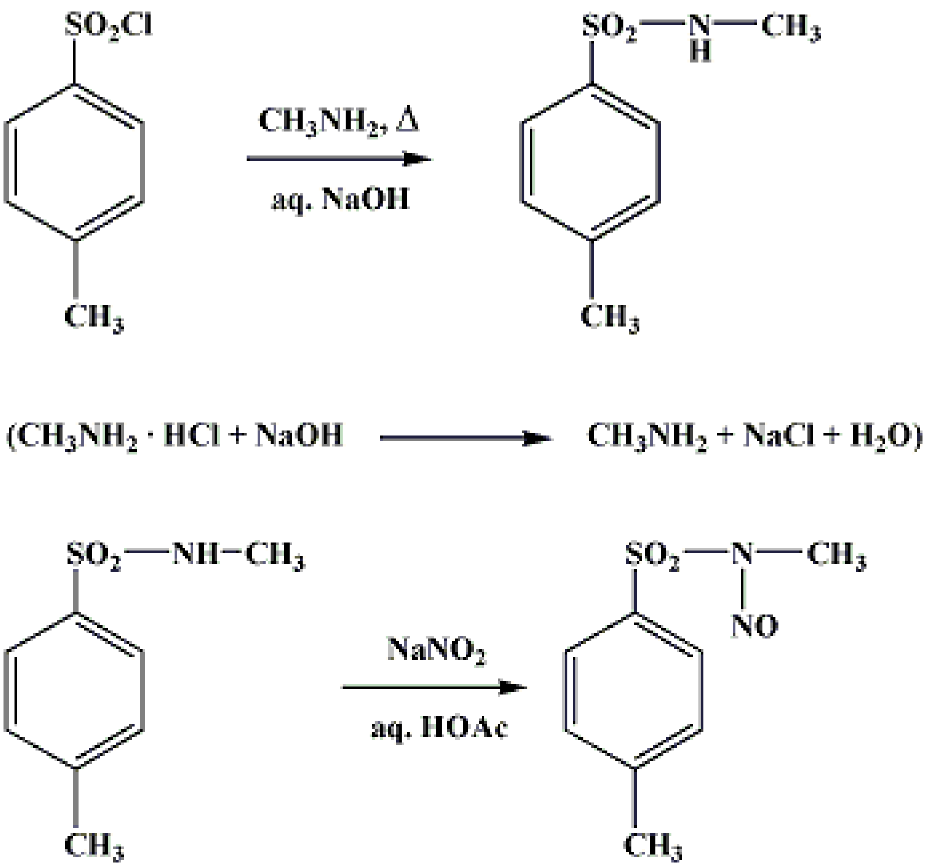
Organic Syntheses, CV 4, 943

p-TOLYLSULFONYLMETHYLNITROSAMIDE

[*p*-Toluenesulfonamide, N-methyl-N-nitroso-]



Submitted by Th. J. de Boer and H. J. Backer[1].
Checked by James Cason, John B. Rogan, and Wm. G. Dauben.

1. Procedure

A total of 320 g. (1.68 moles) of *p*-toluenesulfonyl chloride (Note 1) is divided into three portions of 190, 90, and 40 g.; and a solution of alkali is prepared by dissolving 70 g. of sodium hydroxide in 70 ml. of water with cooling. The 190-g. portion of the sulfonyl chloride is added with swirling during about 5 minutes to 210 ml. (2.1 moles) of 33% aqueous methylamine (or 174 ml. of the 40% solution) contained in a 1-l. round-bottomed flask. The mixture is allowed to heat up to 80–90° in order to maintain the sulfonylmethylamide (m.p. 78°) in a molten condition (Note 2). After all this portion of the sulfonyl chloride has been added, the mixture is shaken vigorously. Boiling is prevented by mild cooling with water in order to avoid an excessive loss of methylamine.

As soon as the mixture has become acidic (Note 3), as indicated by testing a drop on litmus paper, 50 ml. of the 50% sodium hydroxide solution is added carefully with swirling. This is followed immediately by gradual addition of the 90-g. portion of the

sulfonyl chloride as before. When the mixture has again become acidic (Note 3), 25 ml. of the sodium hydroxide solution is added, followed by the final 40 g. of the sulfonyl chloride. After the mixture has again become acidic, the remainder of the sodium hydroxide solution is added. The liquid phase of the final mixture should be alkaline (Note 4).

After the walls of the flask have been rinsed with a little water, the reaction is completed by heating the mixture, consisting of two layers and a precipitate of sodium chloride, on a steam bath for 15 minutes with vigorous mechanical stirring. The hot reaction mixture (Note 2) and (Note 5) is then poured into 1.5 l. of glacial acetic acid contained in a 5-l. round-bottomed flask, and the smaller flask is rinsed clean with 250 ml. of acetic acid (Note 6). The solution is cooled in an ice bath to about 5° (Note 7) and stirred mechanically as a solution of 124 g. (1.8 moles) of sodium nitrite in 250 ml. of water is added from a dropping funnel during about 45 minutes. The temperature of the mixture is kept below 10°, and stirring is continued for 15 minutes after addition is complete. During the reaction, the nitroso compound separates as a yellow crystalline product.

One liter of water is added to the mixture; then the precipitate is separated by suction filtration, pressed on the funnel, and washed with about 500 ml. of water. The product is transferred to a beaker, stirred well with about 500 ml. of cold water, then filtered and washed again on the funnel. This process is again repeated if necessary to remove the odor of acetic acid. After drying to constant weight in a vacuum desiccator over sulfuric acid, the product melts in the range between 55° and 60° (Note 8). The yield is 306–324 g. (85–90%) (Note 9) and (Note 10).

2. Notes

1. The *p*-toluenesulfonyl chloride used by the submitters was a product recrystallized from a 1:20 mixture of benzene: 60–80° petroleum ether, and it melted at 67.5–69°. The checkers employed material obtained from Distillation Products Industries. Sulfonic acid may be removed from old samples of the sulfonyl chloride by thorough washing with cold water followed by immediate drying in a vacuum desiccator over sulfuric acid.
2. At lower temperatures, the sulfonylmethylamide is likely to form a hard cake. In smaller runs, e.g. 0.2 mole, the mixture heats up considerably less; therefore, the reaction mixture should be warmed on a steam bath after the first addition of sulfonyl chloride and thereafter as necessary.
3. The reaction mixture may not become acidic after a given addition of sulfonyl chloride, especially the first one. If such is the case, no more than 5 minutes need be allowed between successive sulfonyl chloride and alkali additions. The whole procedure requires about 30 minutes.
4. If the final mixture is acidic, indicating excessive loss of methylamine, sufficient methylamine should be added to render the mixture basic. This situation is more likely to occur in smaller runs (0.1–0.2 mole).
5. The precipitate of sodium chloride need not be removed before nitrosation; it

dissolves when the final product is washed with water.

6. The total amount of 1750 ml. of acetic acid is necessary to dissolve the amide completely at lower temperatures. With less acetic acid, it is difficult to secure complete nitrosation, even with very efficient stirring of the suspension.

In one experiment with 750 ml. of acetic acid, the resulting impure product was washed first with water to remove acetic acid and then with 1*N* sodium hydroxide to remove *p*-tolylsulfonylmethylamide (the nitroso compound is not attacked by cold aqueous sodium hydroxide). The yield of *p*-tolylsulfonylmethylnitrosamide was 76%, m.p. 58–60°. Acidification of the alkaline wash yielded (9% recovery) the *p*-tolysulfonylmethylamide, m.p. 77.5–78.5°.

7. An ice-salt mixture may be used for more efficient cooling, but reaction temperatures below 0° should be avoided because the total amount of acetic acid is just sufficient to keep the sulfonylmethylamide in solution above 0°.

8. A melting point in the lower part of this range generally indicates contamination with *p*-tolylsulfonylmethylamide, which may be removed as described in (Note 6); however, this purification is not necessary since the presence of this amide does not interfere in the preparation of diazomethane.

9. *Caution!* Although this material has been kept at room temperature for years without significant change, there has been reported one instance in which a sample stored for several months detonated spontaneously. For long periods of storage, it is recommended that the material be recrystallized and placed in a dark bottle. Recrystallization is best accomplished by dissolution in boiling ether (1 ml. per g.), addition of an equal volume of low-boiling petroleum ether (technical pentane), and cooling over night in a refrigerator. Other solvents (benzene, carbon tetrachloride, chloroform) may be used for recrystallization, but the maximum temperature should not exceed 45°.

10. *p*-Tolylsulfonylmethylnitrosamide is a useful substance for the preparation of diazomethane (p. 250). It is apparently of low toxicity. Its properties afford advantages over other nitroso compounds which have been used for preparation of diazomethane.

3. Discussion

p-Tolylsulfonylmethylnitrosamide has been prepared previously by adding sodium nitrite to an acid aqueous suspension of *p*-tolylsulfonylmethylamide.[2,3,4] The present method is more rapid and gives higher yields.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 221
- Org. Syn. Coll. Vol. 4, 250
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfonyl chloride

petroleum ether

sulfonic acid

p-tolysulfonylmethylamide

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

Benzene (71-43-2)

ether (60-29-7)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium chloride (7647-14-5)

carbon tetrachloride (56-23-5)

sodium nitrite (7632-00-0)

Pentane (109-66-0)

methylamine (74-89-5)

Diazomethane (334-88-3)

sulfonylmethylamide

p-Toluenesulfonyl chloride (98-59-9)

p-Tolylsulfonylmethylnitrosamide

p-Toluenesulfonamide, N-methyl-N-nitroso- (80-11-5)

p-tolylsulfonylmethylamide

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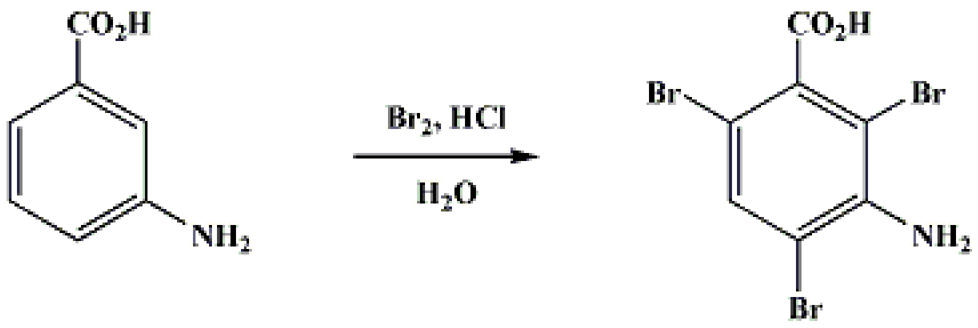
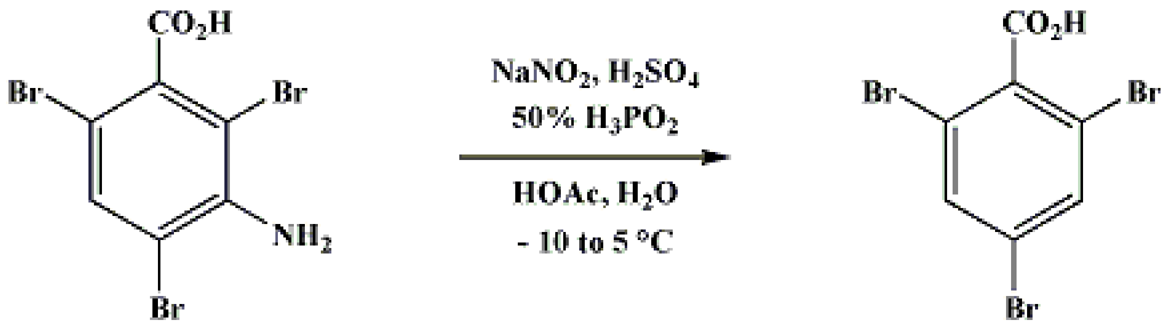
Organic Syntheses, *CV 4, 947*

2,4,6-TRIBROMOBENZOIC ACID

[Benzoic acid, 2,4,6-tribromo-]





Submitted by Michael M. Robison and Bonnie L. Robison[1].
Checked by N. J. Leonard and Kenneth Conrow.

1. Procedure

A. *3-Amino-2,4,6-tribromobenzoic acid.* The bromination apparatus consists of a 2-l. three-necked standard-taper flask *A*, equipped with a "Trubore" stirrer and attached by rubber stoppers and glass tubing to two filter flasks, *B* and *C*, as shown in .htmFig. 17. The 250-ml. flask *C*, which serves as a bubbler and trap, is half-filled with water, and its side arm is connected to a water pump. The reaction flask *A* is charged with 27.4 g. (0.2 mole) of *m*-aminobenzoic acid (Note 1), 165 ml. of concentrated hydrochloric acid, and 780 ml. of water, after which it is surrounded by an ice bath, and the stirrer is started. One hundred and forty grams (45 ml., 0.88 mole) of bromine is placed in the vaporization flask *B*, which is then surrounded by a water bath heated to 40–50°. Bromine vapor is drawn through the reaction mixture at a moderate rate by applying suction at the water pump. Stirring and cooling of the mixture are continued throughout the reaction period, during which time the product precipitates (Note 2). The bromination requires about 3 hours and is complete when the slurry assumes a distinct yellow color.[2]

Fig. 17.

Fig. 17.

The cream-colored solid is separated at once by filtration and washed thoroughly with water to remove excess bromine water and acids. It is used in the next step without drying. The melting range of the crude product is usually 170–172°.

B. *2,4,6-Tribromobenzoic acid.* A 5-l. three-necked flask, equipped with a mechanical stirrer and thermometer and surrounded by an ice-salt bath, is charged with a precooled mixture of 1.02 l. of concentrated sulfuric acid and 500 ml. of water. Cooling during the reaction period is assisted by the ice-salt bath, but is effected chiefly by periodic additions of large amounts of crushed Dry Ice directly to the reaction mixture. The temperature of the stirred mixture is lowered to –5° to –10° and 37 g. (0.54 mole) of sodium nitrite is added in small portions over a period of about 15 minutes. Cold 50% hypophosphorous acid (193 ml., 1.86 moles) (Note 3) is then added over a period of 10–15 minutes, the temperature still being maintained below –5°. A solution of the bromination product in 1.85 l. of glacial acetic acid is then added to the stirred diazotizing solution from a dropping funnel. During the 1–1.25 hours required to complete this addition the temperature is held between –10° and –15° (Note 4). Stirring of the slurry is continued for approximately 2 hours longer, and during this period the temperature is allowed to rise gradually to +5°. The loosely stoppered flask is kept in a refrigerator for 36 hours (Note 5), during which time nitrogen and some oxides of nitrogen are evolved *(Caution!)*. Most of the acetic acid is then removed by volatilization in a current of steam, 3 l. of distillate being collected. During the steam distillation the product starts to precipitate from the clear solution, and nitrogen dioxide and some hydrogen sulfide are given off. The residual liquid is cooled, and the product is collected on a sintered-glass funnel and washed with water. It is next suspended in 800 ml. of water, and approximately 9 g. of anhydrous sodium carbonate is added with shaking to bring it into solution. The yellow liquid is filtered to remove small quantities of insoluble impurities, and the acid is reprecipitated by acidification to pH 1–2 with 5% hydrochloric acid, while swirling vigorously. The cream-colored precipitate is separated by filtration, washed with water, and dried. The yield of 2,4,6-tribromobenzoic acid, sufficiently pure for preparative purposes, is 50–57.5 g. (70–80%), m.p. 192.5–194.5° (Note 6).

2. Notes

1. Matheson Company *m*-aminobenzoic acid was used without further purification.
2. Efficient stirring and cooling are necessary at this stage to obtain a final product that is not colored.
3. Baker "purified" hypophosphorous acid was used.
4. Near the end of the addition of the acetic acid solution it is usually desirable to raise the stirrer temporarily to break up the lumps which form at the surface of the solution.

5. The temperature of the refrigerator was approximately 6°.
6. The product may be recrystallized from 1:2 acetic acid-water (about 8 ml./g.), but this process effects little improvement in melting point or color, even when activated carbon is used.

3. Discussion

2,4,6-Tribromobenzoic acid has been prepared by the deamination of 2,4,6-tribromo-3-aminobenzoic acid (reagents not specified),[3] by hydrolysis of 2,4,6-tribromobenzonitrile,[4,5,6,7] and by oxidation of the tribromotoluene,[8,9] the benzyl chloride,[10] the aldehyde,[11] and the glyoxylic acid.[12] The present method is a modification of that of Bunnett, Robison, and Pennington.[13]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

oxides of nitrogen

hypophosphorous acid

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

hydrogen sulfide (7783-06-4)

sodium carbonate (497-19-8)

bromine (7726-95-6)

nitrogen (7727-37-9)

sodium nitrite (7632-00-0)

carbon (7782-42-5)

benzyl chloride (100-44-7)

nitrogen dioxide (10102-44-0)

glyoxylic acid (298-12-4)

2,4,6-tribromobenzonitrile

2,4,6-Tribromobenzoic acid, Benzoic acid, 2,4,6-tribromo- (633-12-5)

2,4,6-tribromo-3-aminobenzoic acid, 3-Amino-2,4,6-tribromobenzoic acid (6628-84-8)

tribromotoluene (6320-40-7)

m-aminobenzoic acid (99-05-8)

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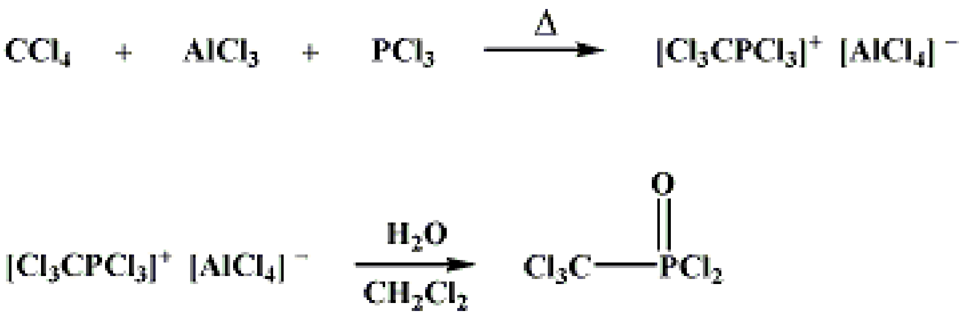
Organic Syntheses, CV 4, 950

TRICHLOROMETHYLPHOSPHONYL DICHLORIDE

[Phosphonic dichloride, (trichloromethyl)-]



Submitted by Kenneth C. Kennard and Cliff S. Hamilton[1].
Checked by John C. Sheehan and J. L. Yeh.

1. Procedure

Caution! This preparation should be conducted in a hood.

In a 2-l. round-bottomed three-necked flask, fitted with an efficient reflux condenser, mechanical stirrer, and dropping funnel (Note 1), are placed 133.3 g. (1 mole) of anhydrous powdered aluminum chloride, 137.4 g. (1 mole) of phosphorus trichloride, and 184.6 g. (1.2 moles) of carbon tetrachloride (Note 2). The reactants are stirred slowly until they are thoroughly mixed, and then heat is applied carefully until the reaction begins. At this point the liquid boils vigorously, and the reaction mixture becomes thicker so that faster stirring is necessary. Finally, the stirrer is stopped when the mixture becomes solid. After the reaction has cooled for 30 minutes, 1 l. of methylene chloride is run into the flask (Note 3), and the solvent is stirred vigorously until the solid is finely suspended (Note 4). The reflux condenser is replaced by a low-temperature thermometer which dips into the reaction mixture, the suspension is cooled in a Dry Ice-acetone bath, and the temperature is kept at –10° to –20° as distilled water (180 g., 10 moles) is added dropwise with vigorous stirring over a period of about 25 minutes (Note 5). After the water addition is complete, stirring is continued for 15 minutes without the cold bath.

The apparatus is dismantled, and the reaction mixture is filtered quickly by suction through a 1.5-cm. layer of filter aid on an 11-cm. Büchner funnel placed on a 2-l. filter flask. The filter cake is pressed down well and washed with three 50-ml. portions of methylene chloride. The filtrate is immediately protected from moisture by calcium chloride tubes, and the solvent is removed by distillation from a 2-l. flask. After the solution has been concentrated to about 225 ml., the hot liquid is poured into a suitable container (Note 6), and the remaining solvent is removed under reduced pressure (Note 7). The yield is 192–199 g. (81–84%) of a white, crystalline solid which melts at

155–156°.

2. Notes

1. The equipment is dried and protected from atmospheric moisture by calcium chloride tubes.
2. It is important that the reactants are pure; otherwise the complex is colored. If the containers are freshly opened, C.P. reagents are satisfactory.
3. The methylene chloride must be redistilled from aluminum chloride to prevent coloration of the product.
4. If the solid adheres to the flask, the flask is heated lightly with a free flame to loosen it.
5. Vigorous stirring is necessary to prevent caking of the aluminum chloride hydrate and to prevent localized hydrolysis. The checkers found that exactly 7 moles of water gave a somewhat improved yield, but handling was more difficult.
6. The submitters used a 500-ml. round-bottomed wide-mouthed flask.
7. The product may be warmed to aid solvent removal, but it is decomposed by prolonged heating above 60°.

3. Discussion

The aluminum chloride process[2,3] is a general method for the preparation of alkylphosphonyl dichlorides. Trichloromethylphosphonyl dichloride has been made also by the chlorination of chloromethyldichlorophosphonic dichloride in the presence of light or other catalysts[4] and by the reaction of tetrachloro(trichloromethyl) phosphorane with sulfur dioxide.[5] The procedure described here is essentially that of Kennard and Hamilton[6] and is based on the procedure of Kinnear and Perren.[2]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Trichloromethylphosphonyl dichloride

chloromethyldichlorophosphonic dichloride

calcium chloride (10043-52-4)

sulfur dioxide (7446-09-5)

carbon tetrachloride (56-23-5)

aluminum chloride (3495-54-3)

phosphorus trichloride (7719-12-2)

methylene chloride (75-09-2)

Phosphonic dichloride, (trichloromethyl)- (21510-59-8)

aluminum chloride hydrate

tetrachloro(trichloromethyl)phosphorane

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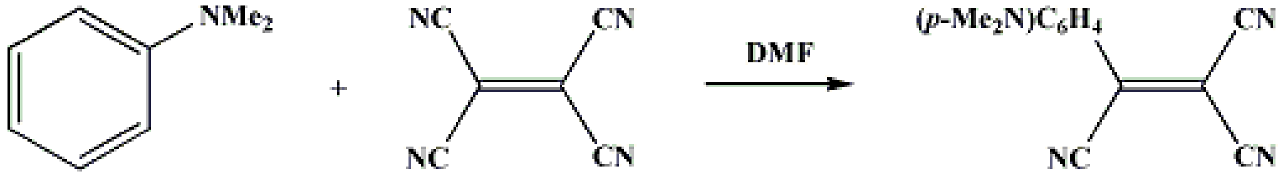
Organic Syntheses, CV 4, 953

p-TRICYANOVINYL-N,N-DIMETHYLANILINE

[Ethenetricarbonitrile, *p*-dimethylaminophenyl-]



Submitted by B. C. McKusick and L. R. Melby[1].
Checked by James Cason and Ralph J. Fessenden.

1. Procedure

Caution! Because hydrogen cyanide is formed in this reaction, all operations up to the recrystallization of the product should be carried out in a good hood. Contact of tetracyanoethylene with the skin should be avoided.

A solution of 26.6 g. (28 ml., 0.22 mole) of N,N-dimethylaniline in 65 ml. of dimethylformamide is placed in a 250-ml. beaker clamped about 30 cm. above the base of a ring stand. The beaker is provided with a mechanical stirrer and thermometer. An iron ring is attached to the ring stand below the beaker so that the temperature of the reaction mixture can be controlled by raising or lowering an ice bath or hot water bath. Recrystallized tetracyanoethylene (p. 877) (25.6 g., 0.20 mole) is added in small portions over a period of about 5 minutes with good stirring. The rate of addition is such as to maintain the temperature at 45–50°, and occasional cooling with an ice bath may be necessary to keep the temperature within this range.

When all the tetracyanoethylene has been added, the reaction mixture is stirred at 45–50° for 10 minutes, and heat is supplied as needed by a water bath. *p*-Tricyanovinyl-N,N-dimethylaniline generally crystallizes out as a dark-blue solid during this period. At the end of the heating period, the mixture is chilled in an ice bath for 30 minutes. The tricyanovinyl compound is collected on a Büchner funnel, pressed dry with the help of a filter dam, and washed successively with 20 ml. of methanol and 40 ml. of ether. It weighs 25–30 g. after being dried in air.

The crude product is purified by recrystallization from 160–180 ml. of acetic acid. The solution (Note 1) is allowed to cool slowly to room temperature, and *p*-tricyanovinyl-N,N-dimethylaniline is collected on a Büchner funnel and washed successively with 20 ml. of methanol and 40 ml. of ether. The product, 23–26 g. (52–58%), is obtained as dark-blue needles, m.p. 173–175° (Note 2).

2. Notes

1. The acetic acid solution is so deep a red color that it is necessary to hold the flask over a bright light in order to determine when all the solid has dissolved. The solution will dye the skin with a fast red color.

2. Although the crystals have a very dark blue appearance, the solutions are deep red; in acetone, λ_{max} 517 m• (ε 41,500).

3. Discussion

p-Tricyanovinyl-N,N-dimethylaniline has been prepared by adding hydrogen cyanide to *p*-dimethylaminobenzalmalononitrile and oxidizing the adduct.[2] The present procedure, an adaptation of one that has been published,[2] is the more convenient preparative method. It can be applied to a wide variety of secondary and tertiary aromatic amines to give *p*-tricyanovinylarylamines that, like the present one, are dyes.[2] Other types of aromatic compounds also condense with tetracyanoethylene in this manner. Thus one can obtain 4-tricyanovinyl-2,6-dimethylphenol from 2,6-dimethylphenol, 2-tricyanovinylpyrrole from pyrrole, and 9-tricyanovinylphenanthrene from phenanthrene.[3]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

acetic acid (64-19-7)

methanol (67-56-1)

ether (60-29-7)

hydrogen cyanide (74-90-8)

acetone (67-64-1)

N,N-dimethylaniline (121-69-7)

Pyrrole (109-97-7)

phenanthrene (85-01-8)

dimethylformamide (68-12-2)

Tetracyanoethylene (670-54-2)

4-tricyanovinyl-2,6-dimethylphenol

2,6-dimethylphenol (576-26-1)

2-tricyanovinylpyrrole

9-tricyanovinylphenanthrene

p-Tricyanovinyl-N,N-dimethylaniline, Ethenetricarbonitrile, p-dimethylaminophenyl- (6673-

15-0)

p-dimethylaminobenzalmalononitrile (2826-28-0)

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Organic Syntheses, CV 4, 955

TRIETHYL PHOSPHITE

[Ethyl phosphite]

Submitted by A. H. Ford-Moore and B. J. Perry[1].
Checked by William S. Johnson and James Ackerman.

1. Procedure

A solution of 138 g. (175 ml., 3 moles) of absolute ethanol (Note 1) and 447 g. (477 ml., 3 moles) of freshly distilled diethylaniline in 1 l. of dry petroleum ether (b.p. 40–60°) is placed in a 3-l. three-necked flask fitted with a sealed stirrer, an efficient reflux condenser, and a 500-ml. dropping funnel (Note 2) which is charged with a solution of 137.5 g. (87.5 ml., 1 mole) of freshly distilled phosphorus trichloride in 400 ml. of dry petroleum ether (b.p. 40–60°). The flask is cooled in a cold-water bath. With vigorous stirring (Note 3), the phosphorus trichloride solution is introduced at such a rate that the mixture boils gently towards the end of the addition. After the addition, which requires about 30 minutes, the mixture is heated under gentle reflux for about 1 hour with stirring. The suspension, containing a copious precipitate of diethylaniline hydrochloride, is then cooled and filtered with suction through a sintered-glass funnel. The cake of the amine salt is well compressed and washed with five 100-ml. portions of dry petroleum ether (b.p. 40–60°). The filtrate and washings are combined and concentrated by distillation at water-bath temperature through a 75-cm. Vigreux column. The residue is transferred to a pear-shaped flask and distilled under water-pump vacuum through a 75-cm. Vigreux column. After a small fore-run, the product is collected at 57–58°/16 mm. (51–52°/13 mm., 43–44°/10 mm.). The yield of colorless product is 138 g. (83%), n_D^{25} 1.4104–1.4106, d_4^{20} 0.963 (Note 4) and (Note 5).

2. Notes

1. It is important that the ethanol be thoroughly anhydrous. The checkers employed ethanol dried over magnesium ethoxide.[2]
2. It is convenient to connect the dropping funnel to the flask by a piece of 20-mm. glass tubing about 10 cm. long which is sleeved into the neck of the flask by a section of rubber tubing. By this means, the rate of introduction of the phosphorus trichloride solution may be readily observed and clogging by the copious precipitate of diethylaniline hydrochloride is obviated.
3. If efficient mixing is not obtained, hydrogen chloride may be liberated locally and one of the ethyl groups eliminated as ethyl chloride with the resulting

appearance of diethyl hydrogen phosphite in the final distillate.

4. The recovered petroleum ether and fore-run contain some of the product. By using the recovered petroleum ether in subsequent runs and adding the fore-run before the final distillation, the yield is increased to 86–90%.

5. Triisopropyl phosphite is prepared similarly, using anhydrous isopropyl alcohol in place of ethanol. It has the following properties: b.p. 43.5°/1.0 mm; n_D^{25} 1.4080; d_4^{17} 0.917.

3. Discussion

The method described here is essentially that of McCombie, Saunders, and Stacey[3] except that diethylaniline is employed in place of dimethylaniline or pyridine. Diethylaniline has the advantage that the hydrochloride formed in the reaction is very easily filtered and is non-hygroscopic. Triethyl phosphite has been prepared also from phosphorus trichloride and ethanol in the presence of other tertiary amines, such as tributylamine and triamylamine;[4] in the presence of ammonia,[5] aniline,[6] and ammonium carbamate.[7] It also has been obtained from the reaction of magnesium ethoxide with phosphorus trichloride.[8]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 325
- Org. Syn. Coll. Vol. 6, 448

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

ethanol (64-17-5)

hydrogen chloride (7647-01-0)

ammonia (7664-41-7)

aniline (62-53-3)

pyridine (110-86-1)

isopropyl alcohol (67-63-0)

phosphorus trichloride (7719-12-2)

ammonium carbamate (1111-78-0)

dimethylaniline (121-69-7)

diethylaniline (91-66-7)

magnesium ethoxide (2414-98-4)

ethyl chloride (75-00-3)

triisopropyl phosphite (116-17-6)

Triethyl phosphite (122-52-1)

Ethyl phosphite

diethylaniline hydrochloride

diethyl hydrogen phosphite (762-04-9)

triamylamine (621-77-2)

tributylamine (102-82-9)

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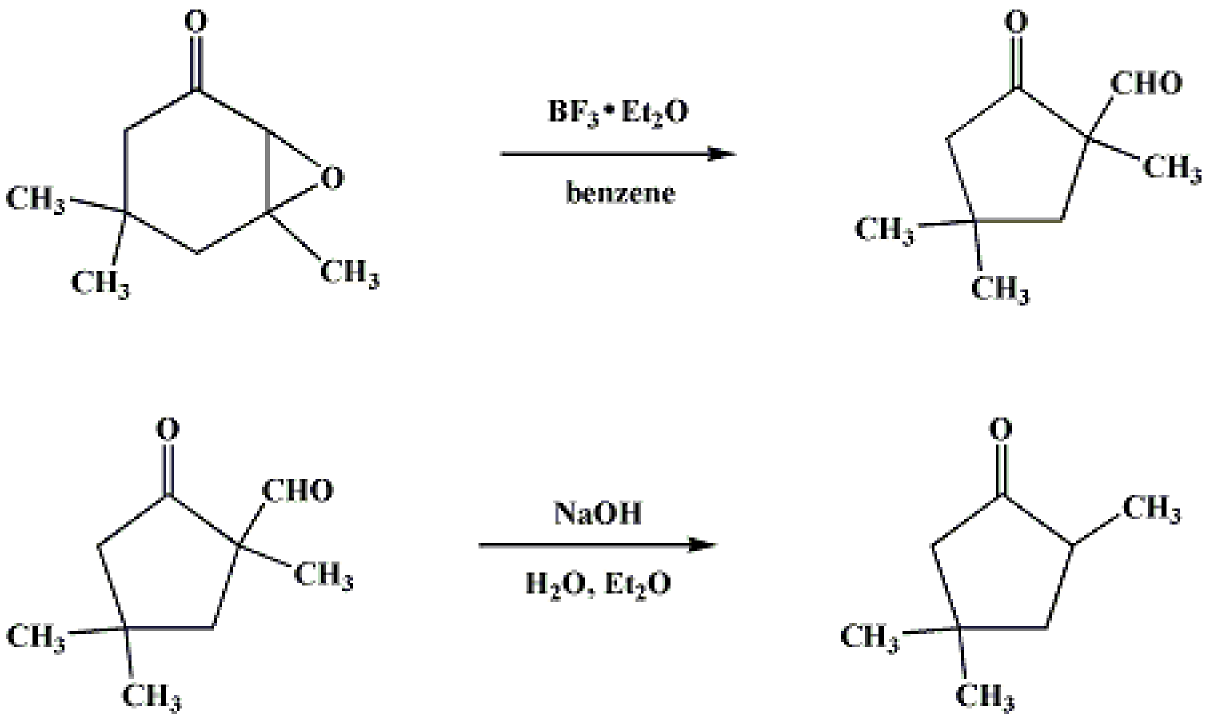
Organic Syntheses, CV 4, 957

2,4,4-TRIMETHYLCYCLOPENTANONE

[Cyclopentanone, 2,4,4-trimethyl-]



Submitted by George D. Ryerson, Richard L. Wasson, and Herbert O. House[1].
Checked by James Cason and Ralph J. Fessenden.

1. Procedure

In a 1-l. separatory funnel is placed a solution of 38.6 g. (0.25 mole) of isophorone oxide (Note 1) in 400 ml. of reagent grade benzene. To the solution is added 20 ml. (0.16 mole) of boron trifluoride etherate (Note 2). The resulting solution is mixed by swirling, allowed to stand for 30 minutes, then diluted with 100 ml. of ether and washed with 100 ml. of water (Note 3). The organic layer is shaken for 1–2 minutes with a solution of 40 g. (1.0 mole) of sodium hydroxide in 200 ml. of water (Note 4) and then washed with a second 100–ml. portion of water. The combined aqueous solutions are cooled briefly in running water and then extracted with two 50-ml. portions of ether. The ethereal extracts are added to the benzene-ether solution (Note 5), and the combined solution, after drying over anhydrous magnesium sulfate, is concentrated by distillation through a Claisen head. When the temperature of the distillate reaches about 80° (Note 6), the residual liquid is fractionally distilled (Note 7) under reduced pressure. The yield of 2,4,4-trimethylcyclopentanone, b.p. 61–62°/21 mm., n_D^{28} 1.4278–1.4288, is 17.7–19.8 g. (56–63%) (Note 8).

2. Notes

1. The preparation of isophorone oxide is described on p. 552
2. A practical grade of boron trifluoride etherate, purchased from Eastman Kodak Company, was redistilled before use. The pure etherate boils at 126°.
3. If the organic layer is dried over magnesium sulfate and fractionally distilled at this point, both 2,4,4-trimethylcyclopentanone and 2-formyl-2,4,4-trimethylcyclopentanone, b.p. 49–50° (2 mm.), n_D^{25} 1.4495, may be isolated. The pot residue from this distillation contains a small amount of the enol form of 3,5,5-trimethyl-1,2-cyclohexanedione which crystallizes from petroleum ether as white needles, m.p. 92–93°.
4. The specified period of shaking is sufficient to ensure complete deformylation of the intermediate β-ketoaldehyde. Ordinarily, no difficulty is experienced with emulsification provided that the recommended quantity (or more) of ether is added to the reaction mixture.
5. Acidification of the residual aqueous solution followed by extraction with ether permits the isolation of about 1 g. of the enol form of 3,5,5-trimethyl-1,2-cyclohexanedione (Note 3).
6. At this point about 150–200 ml. of liquid remains in the still pot. If the distillation is continued, the peppermint-like odor of the product, 2,4,4-trimethylcyclopentanone, can be detected in the distillate.
7. The submitters used a 24-cm. jacketed Vigreux column for this distillation. The checkers used a simple type of Podbielniak column, 50 cm. in length, with heated jacket and partial reflux head; after the last of the benzene had been distilled through the column, the following fractions were received:

Wt., g.	B.P./15 mm.	n_D^{28}
0.7	35–54°	1.4288
0.7	54–55°	1.4278
7.5	55°	1.4278
9.5	55°	1.4278
4.9	Residue, m.p. 80–90°	

Thus a rather good sample of product may be obtained without use of fractionating equipment.
8. If an appreciable quantity of higher-boiling material (consisting of 2-formyl-2,4,4-trimethylcyclopentanone; (Note 4)) remains after the product has been collected, the residue should be dissolved in ether and shaken with aqueous sodium hydroxide as described in the procedure. After the ethereal extract has been dried over magnesium sulfate, distillation will permit the isolation of an additional quantity of 2,4,4-trimethylcyclopentanone.

3. Discussion

2,4,4-Trimethylcyclopentanone has been prepared by the oxidation of 1-hydroxy-2,4,4-trimethylcyclopentanecarboxylic acid with lead dioxide in sulfuric acid,[2] by the

hydrogenation of 2,4,4-trimethyl-2-cyclopentenone,[3,4] by the Clemmensen reduction of dimethyldihydroresorcinol,[5,6] by the distillation of powdered 2,4,4-trimethyladipic acid with sodium hydroxide,[7] and by the saponification and decarboxylation of ethyl 2-keto-1,4,4-trimethylcyclopentanecarboxylate.[8,9] The rearrangement of isophorone oxide[10] appears to represent the optimum combination of favorable yield and convenient procedure.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

β-ketoaldehyde

sulfuric acid (7664-93-9)

Benzene (71-43-2)

ether (60-29-7)

sodium hydroxide (1310-73-2)

magnesium sulfate (7487-88-9)

dimethyldihydroresorcinol

boron trifluoride etherate (109-63-7)

Isophorone oxide (10276-21-8)

2,4,4-Trimethylcyclopentanone, Cyclopentanone, 2,4,4-trimethyl- (4694-12-6)

2-formyl-2,4,4-trimethylcyclopentanone

3,5,5-trimethyl-1,2-cyclohexanedione

1-hydroxy-2,4,4-trimethylcyclopentanecarboxylic acid

2,4,4-trimethyl-2-cyclopentenone

2,4,4-trimethyladipic acid

ethyl 2-keto-1,4,4-trimethylcyclopentanecarboxylate

lead dioxide

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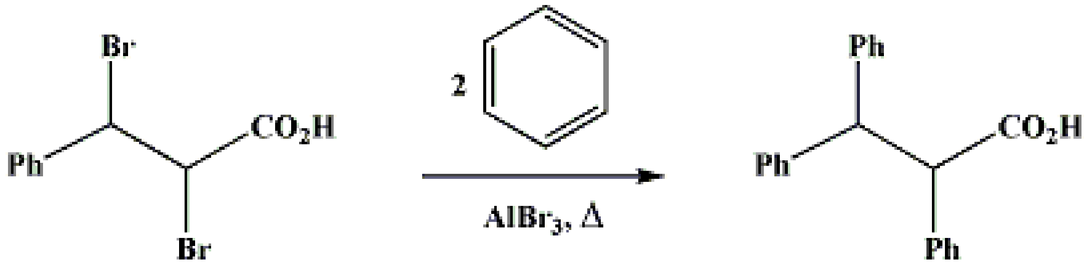
Organic Syntheses, CV 4, 960

α,β,β-TRIPHENYLPROPIONIC ACID

[Propionic acid, 2,3,3-triphenyl-]



Submitted by C. P. Krimmel, L. E. Thielen, E. A. Brown, and W. J. Heidtke[1].
Checked by William S. Johnson, A. L. Wilds, and J. S. Jellinek.

1. Procedure

A 5-l. three-necked flask is fitted with a mechanical rubber-sleeved stirrer, a dropping funnel, and a reflux condenser capped with a calcium chloride tube leading to a gas-absorption trap.[2] The system is flame-dried, and the flask is charged with 308 g. (1 mole) of α,β-dibromohydrocinnamic acid (Note 1) and 800 ml. of dried (by distillation) thiophene-free benzene. While the α,β-dibromohydrocinnamic acid is maintained in suspension by stirring (Note 2), a freshly prepared solution of 294 g. (1.1 moles) of anhydrous aluminum bromide (Note 3) in 400 ml. of anhydrous thiophene-free benzene is added from the dropping funnel over a period of 30 minutes. The clear orange-to-red solution is then heated under reflux with stirring for 4 hours.

The mixture is cooled to room temperature and maintained there with the aid of a cooling bath while 500 ml. of concentrated hydrochloric acid is added slowly from the dropping funnel. The mixture should be stirred vigorously during this addition, which requires about 30 minutes and is accompanied by copious evolution of hydrogen bromide (Note 4) and separation of the α,β,β-triphenylpropionic acid as a thick white slurry. Stirring is continued for an additional 30 minutes, 2 l. of water is added, and the product is separated by suction filtration. The waxy filter cake is washed with two 250-ml. portions of water, then dried overnight at room temperature and finally at 75° (Note 5). The crude, almost colorless α,β,β-triphenylpropionic acid amounts to 287–302 g. (95–100% yield), m.p. 215–218°. Recrystallization by dissolution in 3 l. of isopropyl alcohol (Note 6), followed by concentration of the filtered solution to 1.5 l. before cooling, yields 200–236 g. (66–78%) of colorless needles, m.p. 220–221°.

2. Notes

1. α,β-Dibromohydrocinnamic acid is conveniently prepared by the method of Reimer.[3] The checkers employed the following procedure. To a gently boiling

solution of 296 g. (2 moles) of cinnamic acid in 2 l. of C.P. carbon tetrachloride contained in a 5-l. three-necked flask fitted with a reflux condenser, a dropping funnel, and a mechanical stirrer is added slowly (1.5 hours) with stirring 320 g. (2 moles) of bromine dissolved in 200 ml. of carbon tetrachloride. After 25–50% of the bromine is added, the α,β-dibromohydrocinnamic acid begins to precipitate with evolution of heat. Stirring and heating are continued for an additional 30 minutes after all the bromine is added. The mixture is cooled to room temperature; the product is separated by suction filtration and is washed with a small amount of cold carbon tetrachloride. The air-dried product amounts to 558–580 g. (91–94% yield) of colorless crystals, m.p. 197–198° to 202–204°.

2. If a solution instead of suspension is used, troublesome gel formation may occur during the aluminum bromide addition.

3. Colorless, crystalline, anhydrous aluminum bromide supplied by the Westvaco Chemical Division, Food Machinery and Chemical Corporation, New York, New York, was used. When dissolved in dry benzene at room temperature with mechanical stirring, a perfectly clear yellow solution results, if the reagents are of high purity.

4. If stirring is not sufficiently vigorous of if the temperature is too low, the evolution of hydrogen bromide may be delayed and then may begin abruptly and be difficult to control.

5. If the wet product is introduced directly into the drying oven it may darken slightly.

6. If the solution is appreciably colored it may be treated with decolorizing carbon at this point. Toluene or dilute ethanol may also be used for the recrystallization, but these solvents are less satisfactory.

3. Discussion

α,β,β-Triphenylpropionic acid has been prepared by the alkaline hydrolysis of the addition product of phenylmagnesium bromide and methyl α-phenylcinnamate;[4] by the reaction of α-phenylcinnamic acid with benzene in the presence of aluminum chloride;[5] by the reaction of α,β-dibromohydrocinnamic acid with benzene in the presence of aluminum bromide or ferric chloride;[6] by the reaction of phenylacetic acid with benzhydryl chloride in the presence of sodamide;[7] and by the reduction of 2,3,3-triphenylacrylonitrile with benzyl alcohol and alkali, followed by hydrolysis of the crude product.[8] The procedure described here is a modification of the method of Earl and Wilson.[6]

References and Notes

1. G. D. Searle and Company, Chicago, Illinois.
2. *Org. Syntheses Coll. Vol.* **2**, 4 (1943).
3. Reimer, *J. Am. Chem. Soc.*, **64**, 2510 (1942).

4. Kohler and Heritage, *Am. Chem. J.*, **33**, 156 (1905).
5. Eijkman, *Chem. Weekblad*, **5**, 655 (1908) (*Chem. Zentr.*, **1908 II**, 1100).
6. Earl and Wilson, *J. Proc. Roy. Soc. N. S. Wales*, **65**, 178 (1932) [*C. A.*, **26**, 2976 (1932)].
7. Hauser and Chambers, *J. Am. Chem. Soc.*, **78**, 4996 (1957).
8. Avramoff and Sprinzak, *J. Am. Chem. Soc.*, **80**, 493 (1958).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

hydrogen bromide (10035-10-6)

bromine (7726-95-6)

carbon tetrachloride (56-23-5)

decolorizing carbon (7782-42-5)

aluminum chloride (3495-54-3)

toluene (108-88-3)

isopropyl alcohol (67-63-0)

Benzyl alcohol (100-51-6)

Phenylacetic acid (103-82-2)

ferric chloride (7705-08-0)

Phenylmagnesium bromide (100-58-3)

cinnamic acid (621-82-9)

aluminum bromide

sodamide (7782-92-5)

2,3,3-triphenylacrylonitrile (6304-33-2)

α-Phenylcinnamic acid (3368-16-9)

benzhydryl chloride (90-99-3)

α,β,β-Triphenylpropionic acid, Propionic acid, 2,3,3-triphenyl- (53663-24-4)

methyl α-phenylcinnamate

α,β-dibromohydrocinnamic acid (6286-30-2)

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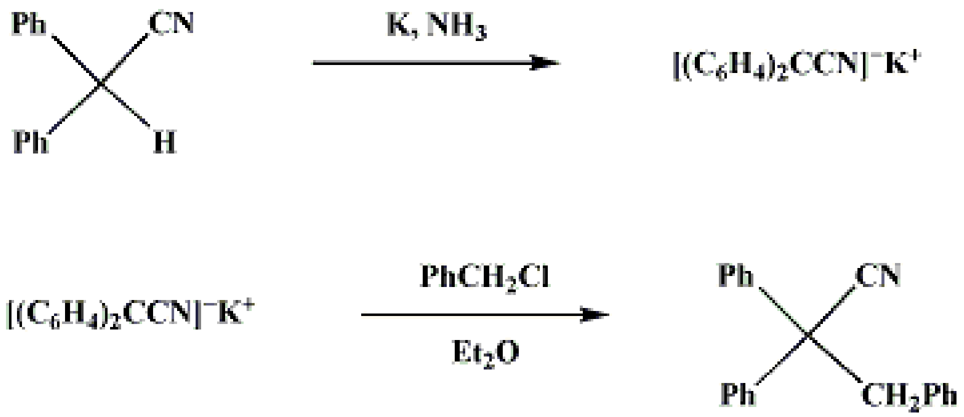
Organic Syntheses, CV 4, 962

α,α,β-TRIPHENYLPROPIONITRILE

[Propionitrile, 2,2,3-triphenyl-]



Submitted by C. R. Hauser and W. R. Dunnavant[1].
Checked by Virgil Boekelheide and Donald R. Arnold.

1. Procedure

Caution! This preparation should be conducted in a hood to avoid exposure to ammonia.

A suspension of potassium amide (0.23 mole) in liquid ammonia is prepared in a 1-l. three-necked flask equipped with an air condenser (without drying tube), a ball-sealed mechanical stirrer, and a dropping funnel. Commercial anhydrous liquid ammonia (500 ml.) is introduced into the flask from a cylinder through an inlet tube. To the stirred ammonia is added a small piece of potassium metal. After the appearance of a blue color, a few crystals (about 0.25 g.) of ferric nitrate hydrate are added, followed by small pieces of potassium (Note 1) until 9.0 g. (0.23 g. atom) has been added. After all the potassium has been converted to the amide (Note 2), 44.6 g. (0.23 mole) of diphenylacetonitrile (Note 3) is added and the resulting greenish-brown solution is stirred for 5 minutes. To this is added, over 10 minutes, 30.5 g. (0.24 mole) of benzyl chloride (Note 4) in 100 ml. of anhydrous ether. The orange solution is stirred for 1 hour, and the ammonia is then evaporated on a steam bath as 300 ml. of anhydrous ether is being added. To the ether solution is added 300 ml. of water, whereupon the crude nitrile precipitates. The ether is then removed by distillation and the crude nitrile is collected on a Büchner funnel. The yield of crude, light-tan α,α,β-triphenylpropionitrile is 64 g. (98–99%). The nitrile is dissolved in 1.3 l. of hot ethanol, treated with Norit, and filtered. The filtrate is held at room temperature overnight, and the product collected by filtration. A second crop is obtained by concentration of the mother liquor. The total yield of α,α,β-triphenylpropionitrile, m.

p. 126.5–127.5°, is 62.2–65.5 g. (95–99% yield) (Note 5).

2. Notes

1. The potassium is cut in about 0.5-g. pieces, stored under kerosene, and blotted with filter paper before addition.
2. Conversion is indicated by the discharge of the deep-blue color. This generally requires about 20 minutes.
3. Diphenylacetonitrile supplied by the Eastman Kodak Company was used without purification.
4. Eastman Kodak Company practical grade benzyl chloride was vacuum-distilled; the fraction, b.p. 63°/12 mm., was used.
5. Under comparable conditions the corresponding alkylations of diphenylacetonitrile with α-phenethyl chloride and benzhydryl chloride have been effected to form 2,3,3-triphenylbutyronitrile and 2,2,3,3-tetraphenylpropionitrile in yields of 88 and 96% respectively.[2]

3. Discussion

The method used is that of Hauser and Brasen.[2]

The benzylation of diphenylacetonitrile with benzyl chloride to form α,α,β-triphenylpropionitrile has been previously effected in 83% yield by sodium ethoxide in ethanol,[3] in 67% yield by methylmagnesium iodide in ether,[4] and in unreported yield by sodium amide in ether.[5]

References and Notes

1. Duke University, Durham, North Carolina. Work supported by the Office of Ordnance Research.
2. Hauser and Brasen, *J. Am. Chem. Soc.*, **78**, 82 (1956).
3. Neure, *Ann.*, **250**, 140 (1889).
4. Sisido, Nozaki, and Kurihara, *J. Am. Chem. Soc.*, **72**, 2270 (1950).
5. Ramart, *Bull. soc. chim. France*, [4] **35**, 196 (1924).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

ammonia (7664-41-7)

ether (60-29-7)

Norit (7782-42-5)

sodium ethoxide (141-52-6)

benzyl chloride (100-44-7)

potassium (7440-09-7)

methylmagnesium iodide (917-64-6)

α-phenethyl chloride (622-24-2)

sodium amide (7782-92-5)

Diphenylacetonitrile (86-29-3)

potassium amide

ferric nitrate hydrate

benzhydryl chloride (90-99-3)

α,α,β-TRIPHENYLPROPIONITRILE, Propionitrile, 2,2,3-triphenyl- (5350-82-3)

2,3,3-triphenylbutyronitrile

2,2,3,3-tetraphenylpropionitrile

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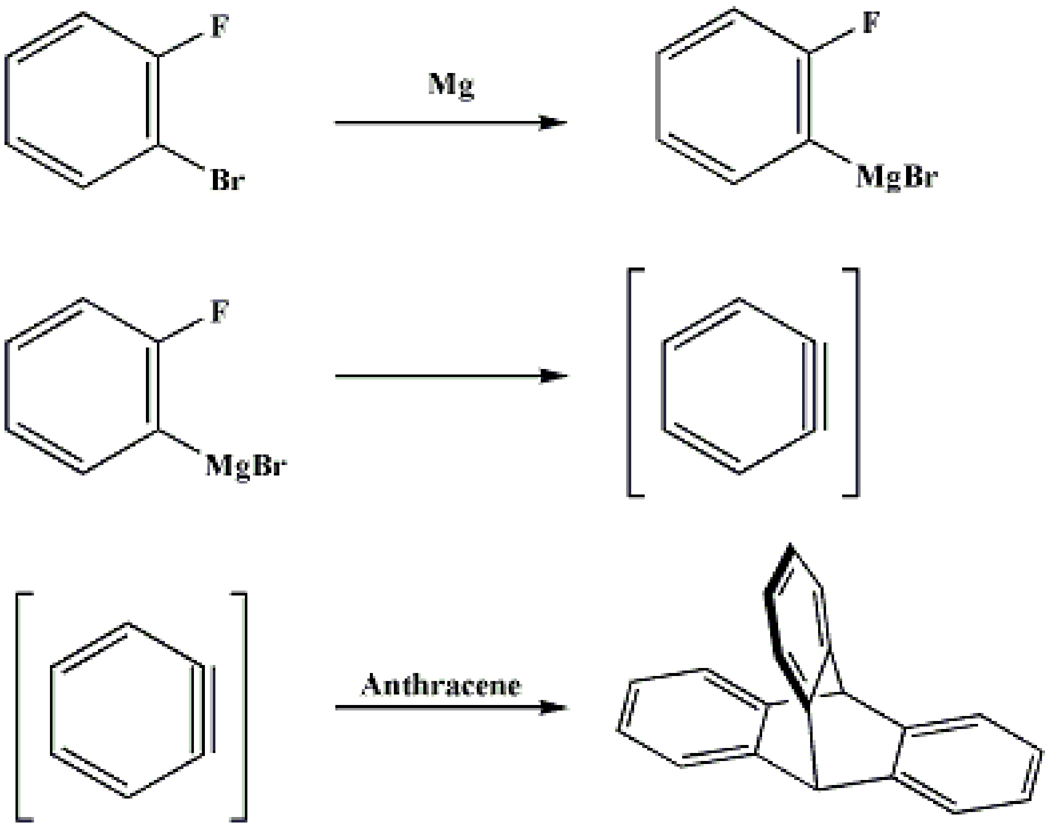
Organic Syntheses, CV 4, 964

TRIPTYCENE

[9,10-*o*-Benzenoanthracene, 9,10-dihydro-]



Submitted by George Wittig[1]
Checked by John D. Roberts, M. C. Caserio, E. S. Johnson, and L. Skattebøl.

1. Procedure

A 200-ml. three-necked flask, equipped with a ball-and-socket sealed mechanical stirrer, a pressure-compensated dropping funnel, and a reflux condenser connected to a mercury bubbler (Note 1), is charged with 0.8 g. (0.033 g. atom) of magnesium turnings, 7.5 g. (0.042 mole) of anthracene, and 35 ml. of anhydrous tetrahydrofuran (Note 2). In the dropping funnel there is placed a solution of 5.26 g. (0.03 mole) of *o*-fluorobromobenzene (Note 3) in 15 ml. of tetrahydrofuran. The system is flushed with dry nitrogen for 30 minutes to remove air. The gas flow is then stopped in order to prevent extensive loss of tetrahydrofuran. The mixture is heated to and maintained at 60° (bath temperature), and one-quarter of the *o*-fluorobromobenzene solution is added with stirring. The appearance of a yellow color which evidences the start of reaction may not be observed immediately, and another quarter of the solution is then added dropwise over a period of about 45 minutes. When the reaction commences, the remaining solution is added dropwise over a period of 1 hour, after which the mixture is refluxed gently for 90 minutes. The almost homogeneous dark-brown mixture is

poured into 100 ml. of methanol, which precipitates much of the unreacted anthracene. Without filtering, the solvents are removed under reduced pressure and the yellow residue is treated with two 50-ml. portions of 5% hydrochloric acid, filtered, and vacuum-dried. The dry, yellow residue (10 g.) is dissolved in 45 ml. of hot xylene, then 5.0 g. (0.051 mole) of maleic anhydride is added. The mixture is refluxed for 20 minutes and set aside at room temperature for 2 hours. The maleic anhydride-anthracene adduct (about 9 g.) is removed by filtration, and the brown filtrate is refluxed for 2 hours with 80 ml. of 2*N* sodium hydroxide solution. When cool, the organic layer is separated, washed three times with 50-ml. portions of water (Note 4), and dried over calcium chloride. The solvent is removed at reduced pressure. The brown residue is dissolved in 70 ml. of carbon tetrachloride and chromatographed on 280 g. of acid-washed alumina, using 1 l. of the same solvent to elute. After evaporation of the solvent, there remains 2.4–2.9 g. of a yellow residue which is digested with two 10-ml. portions of pentane (Note 5). The residual crude triptycene is an almost white crystalline solid of melting point 240–248°. The yield is 2.14 g. (28%) (Note 6). Recrystallization of this material from cyclohexane gives pure white crystals of melting point 255–256°.

2. Notes

1. The mercury bubbler seals the system from the air. It is connected to the top of the reflux condenser by means of 8-mm. glass tubing more than 76 cm. high. The pressure in the system may be varied by adjusting the depth of the lower end of the tube. A constant stream of dry nitrogen may be substituted for the mercury bubbler, but this inevitably results in some loss of tetrahydrofuran.
2. Tetrahydrofuran may be purified by distillation from lithium aluminum hydride.
3. *o*-Fluorobromobenzene as supplied by the Aldrich Chemical Company, Milwaukee, Wisconsin, may be used without further purification.
4. Small amounts of sodium chloride may be added to facilitate separation of the phases.
5. The main impurity is a yellow oil which is readily soluble in pentane.
6. The checkers report a yield of 1.35–1.68 g. (18–22%) of triptycene of melting point 245–255°.

3. Discussion

Triptycene has been prepared by Bartlett and co-workers[2] in a seven-step synthesis. It also has been obtained by the reaction of fluorobenzene with anthracene in the presence of butyllithium[3] and by the reduction of the anthracene-benzoquinone adduct with lithium aluminum hydride or sodium borohydride.[4] The present method has been published.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 60

References and Notes

1. University of Tübingen, Tübingen, Germany.
2. Bartlett, Ryan, and Cohen, *J. Am. Chem. Soc.*, **64**, 2649 (1942).
3. Wittig and Benz, *Angew. Chem.*, **70**, 166 (1958).
4. Craig and Wilcox, *J. Org. Chem.*, **24**, 1619 (1959).
5. Wittig and Benz, *Chem. Ber.*, **91**, 873 (1958).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Triptycene

maleic anhydride-anthracene adduct

anthracene-benzoquinone

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

methanol (67-56-1)

sodium hydroxide (1310-73-2)

magnesium turnings (7439-95-4)

sodium chloride (7647-14-5)

carbon tetrachloride (56-23-5)

nitrogen (7727-37-9)

mercury (7439-97-6)

cyclohexane (110-82-7)

anthracene (120-12-7)

xylene (106-42-3)

Pentane (109-66-0)

Fluorobenzene (462-06-6)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

maleic anhydride (108-31-6)

lithium aluminum hydride (16853-85-3)

sodium borohydride (16940-66-2)

o-fluorobromobenzene (1072-85-1)

9,10-o-Benzenoanthracene, 9,10-dihydro- (477-75-8)

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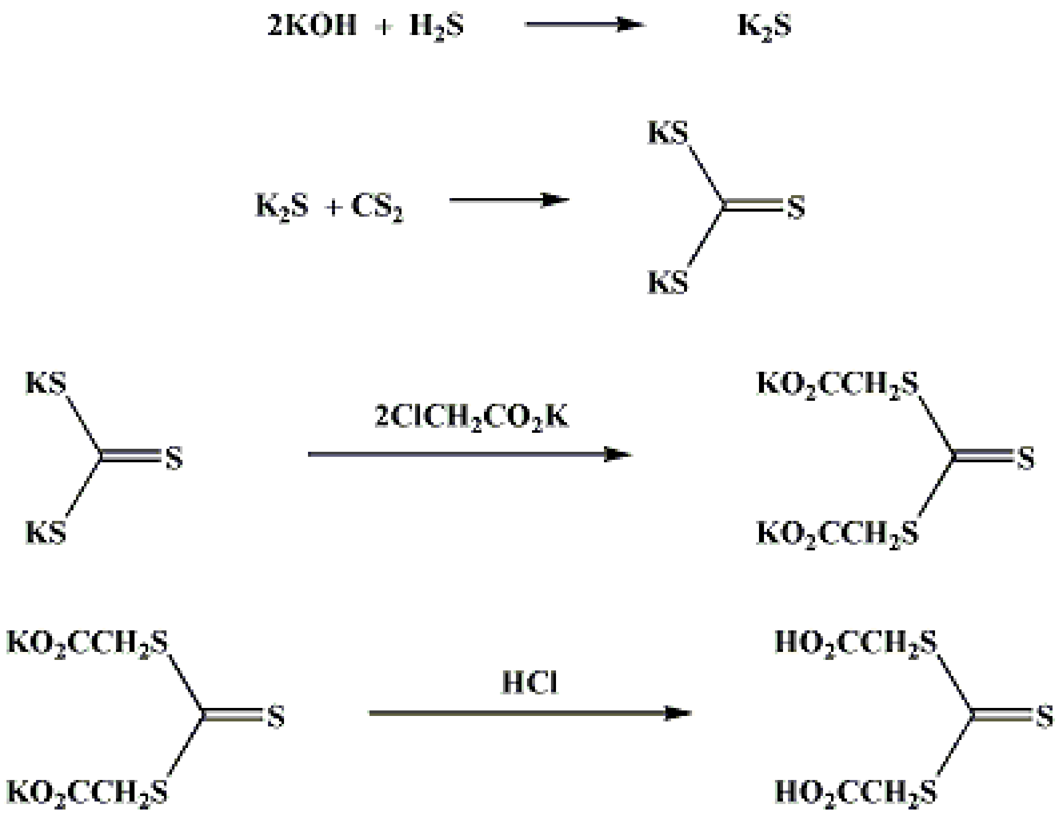
Organic Syntheses, CV 4, 967

TRITHIOCARBODIGLYCOLIC ACID

[Carbonic acid, trithio-, bis[carboxymethyl] ester]



Submitted by R. E. Strube[1]
Checked by John D. Roberts and Stanley L. Manatt.

1. Procedure

In a 300-ml. three-necked, round-bottomed flask equipped with a magnetic stirrer and a gas-inlet tube reaching below the surface of the liquid is placed a solution of 63 g. (0.96 mole) of potassium hydroxide (Note 1) in 100 ml. of water. The solution is cooled in ice, and hydrogen sulfide is bubbled through (Note 2) with stirring until the gain of weight is 33–34 g. (Note 3). The solution is then poured into a 3-l. three-necked, round-bottomed flask provided with a stirrer, a gas-inlet tube, a reflux condenser, and a thermometer reaching into the liquid. The small flask is rinsed with 25 ml. of ice water and the rinsings added to the rest of the solution. Then 63 g. (0.96 mole) of potassium hydroxide is added and allowed to dissolve. The 3-l. flask is then well flushed with nitrogen and, at a temperature of about 30°, 76.0 g. (1.0 mole) of carbon disulfide (Note 4) is added at once. The mixture is stirred vigorously for 2 hours (Note 5) while nitrogen is passed through at a rate of about one bubble per second (Note 6) and the temperature is kept at 35–38° (Note 7). Then the gas supply is disconnected and the dark-red solution is cooled in an ice bath.

A solution of 189 g. (2.0 moles) of chloroacetic acid (Note 8) in 300 ml. of water is neutralized to litmus with a solution containing approximately 135 g. (2.1 moles) of potassium hydroxide in 300 ml. of water. The resulting potassium chloroacetate solution is placed in a dropping funnel and added to the stirred potassium thiocarbonate solution obtained above at such a rate that the temperature does not go above 40°. After the addition is complete, the stirring is continued for 1 hour at room temperature. Then 200 ml. of concentrated hydrochloric acid is added while the temperature is kept below 20° by cooling in an ice bath. Finally, the reaction mixture is stirred for 30 minutes at room temperature. The yellow precipitate is filtered and washed twice with 150-ml. portions of ice water. The crude material is dried under reduced pressure in a vacuum desiccator over calcium chloride to constant weight (about 2 days). The drying is expedited if the lumps are occasionally broken up. The yield of yellow product having m.p. 169–174° (uncor.) (Note 9) is 152–160 g. (67–71%).

2. Notes

1. Potassium hydroxide pellets, Mallinckrodt, 85% minimum KOH assay, were used.
2. A bubbler filled with mercury was placed between the gas cylinder and the gas-inlet tube. A good hood should be used throughout the procedure because hydrogen sulfide is toxic in minute concentrations.
3. Two to three hours is required to saturate the solution. The submitter used the same 3-l. flask to prepare the potassium sulfide and to carry out the subsequent reaction. The checkers found the smaller flask more convenient for following the hydrogen sulfide uptake.
4. Carbon disulfide, Mallinckrodt, analytical grade reagent, was used.
5. The carbon disulfide layer usually disappears in about 45 minutes, but longer times may be required if the stirring is not effective.
6. Contact of the reaction mixture with atmospheric oxygen is to be avoided, but the gas flow should be kept slow enough to minimize loss of carbon disulfide. A bubbler filled with water was placed between the gas cylinder and the gas-inlet tube.
7. A water bath kept at 40–43°, or an electrically heated mantle may be used.
8. Chloroacetic acid, m.p. 62–64°, Eastman Kodak, was used.
9. The submitter reports yields of 160–175 g. (71–77%) of product melting at 166–172°. Recrystallization from water gives 150–165 g. (66–73%) of material melting at 174–176° (cor.).

3. Discussion

Trithiocarbodiglycolic acid can be prepared by heating an aqueous solution of the alkali salts of thiocarbonylethoxythioglycolic acid,[2,3] by heating an aqueous solution of potassium methylxanthate and sodium monochloroacetate,[3] and by heating an

aqueous solution of potassium thiocarbonate and sodium monochloroacetate.[3] The compound is also formed by heating an aqueous solution of potassium ethyltrithiocarbonate and sodium monochloroacetate,[4] and by heating an aqueous solution of thiocarbonylglycolic acid-thioglycolic acid with ammonia[5] or aniline.[6] The procedure described is adapted from that of Holmberg.[7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 6

References and Notes

1. Research Division, The Upjohn Company, Kalamazoo, Michigan.
2. Holmberg, *J. prakt. Chem.*, **71**, 271 (1905).
3. Biilmann, *Ann.*, **348**, 134 (1906).
4. Holmberg, *J. prakt. Chem.*, **75**, 182 (1907).
5. Ahlqvist, *J. prakt. Chem.*, **99**, 55 (1919).
6. Holmberg, *J. prakt. Chem.*, **84**, 645 (1911).
7. Holmberg, *J. prakt. Chem.*, **71**, 279 (1905).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

trithiocarbodiglycolic acid

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

aniline (62-53-3)

hydrogen sulfide (7783-06-4)

oxygen (7782-44-7)

nitrogen (7727-37-9)

mercury (7439-97-6)

chloroacetic acid (79-11-8)

sodium monochloroacetate (3926-62-3)

potassium hydroxide (1310-58-3)

carbon disulfide (75-15-0)

potassium sulfide (1312-73-8)

potassium chloroacetate

Carbonic acid, trithio-, bis[carboxymethyl] ester (6326-83-6)

potassium thiocarbonate

thiocarbonylethoxythioglycolic acid

potassium methylxanthate

potassium ethyltrithiocarbonate

thiocarbonylglycolic acid-thioglycolic acid

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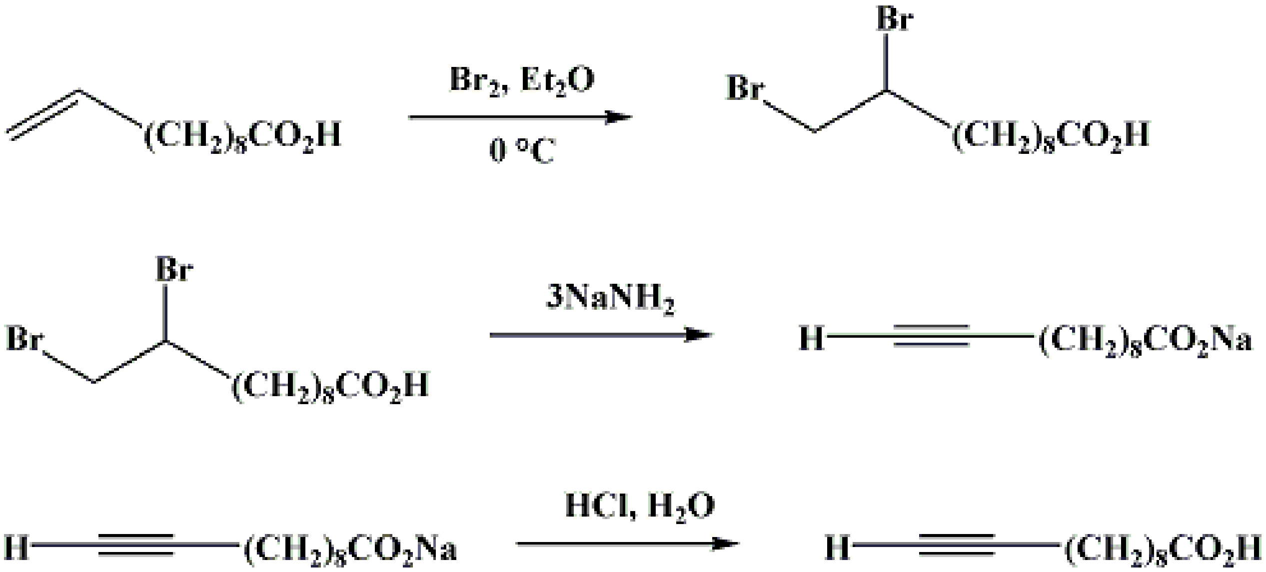
Organic Syntheses, *CV 4*, *969*

10-UNDECYNOIC ACID



Submitted by N. A. Khan[1]
Checked by T. L. Cairns and D. H. Smith.

1. Procedure

Caution! All reactions involving liquid ammonia must be carried out in an effective hood.

Bromine (approximately 15 ml.) is added dropwise to 50 g. (0.271 mole) of 10-undecenoic acid (Note 1) dissolved in 210 ml. of dry ether with constant stirring while the temperature is maintained below 0° until the color of bromine persists. The excess bromine is then removed by the addition of a few drops of 10-undecenoic acid.

The sodamide for dehydrobromination of dibromohendecanoic acid is prepared according to the method of Khan et al.,[2] with some modifications (Note 2). A 3-l. three-necked flask is equipped with a stirrer and a Dry Ice-acetone cold finger reflux condenser attached through a drying tube to a trap and a bubbler filled with a saturated ammonia solution. After the condenser has been cooled with a mixture of Dry Ice and acetone, 1.5 l. of liquid ammonia is introduced into the flask through an inlet tube. Stirring is started, and 1.2–1.5 g. of ferric chloride (C.P., anhydrous, black) is added to the liquid ammonia in one portion as quickly as possible. Within 20 seconds after this addition, 6 g. of metallic sodium is dropped into the brown solution in two portions in order to convert the iron salt into catalytic iron. When the evolution of hydrogen gas ceases, the remainder of the sodium (total amount, 27.7 g., 1.2 g. atoms) is added in pieces and the solution is stirred for an additional 30 minutes (Note 3).

Finally, the solution of 10,11-dibromohendecanoic acid in absolute ether is added slowly from a separatory funnel to the reaction flask. The reaction mixture is then stirred for 6 hours. After an additional hour (Note 4) of stirring, during which time the cold-finger condenser is removed from the system, an excess of solid ammonium chloride (40 g., 0.74

mole) is introduced slowly into the reaction mixture to destroy excess sodamide. The ammonia is allowed to evaporate, 400–500 ml. of water is added, and the mixture is stirred until all the solid is broken up and dissolved (Note 5).

The water solution containing the sodium salt of the product is acidified with 6*N* hydrochloric acid and then extracted with three 200-ml. portions of ether. The ethereal extracts are combined, washed with water (until the aqueous phase shows a pH in the range 5–6), and then dried over anhydrous sodium sulfate. After removal of the solvent, the red-colored residual oil is fractionally distilled through a packed column (Note 6). The middle portion (26–28 g.) distilling at 124–130°/3 mm. is crystallized twice from petroleum ether (b.p. 30–60°) to obtain white crystals of 10-undecynoic acid. The end fractions also yield some white product after 4–5 crystallizations. A total yield of 19–24 g. (38–49%) is obtained; m.p. 42.5–43°.

2. Notes

1. 10-Undecenoic acid (undecylenic acid, commercial grade) may be obtained from the Eastman Kodak Company. The pure grade acid is also used with good results. However, for general purposes, no difficulty is encountered in preparing 10-undecynoic acid from the commercial grade acid if the final fractionation by vacuum distillation is carried out carefully.
2. The experiences with this particular preparation have led to some changes in the procedure of preparing sodamide. However, for large-scale preparation (larger than that reported here), Khan et al.[2] and Greenlee and Henne[3] have given very specific details of the methods that are to be followed. It is to be noted that the use of a Hershberg stirrer (with a rubber stopper and a powerful high-speed motor) is advantageous.
3. The complete transformation of metallic sodium into sodamide may be checked by the method of Greenlee and Henne.[3] When the evolution of hydrogen gas ceases (bubbler), it may be assumed that the above transformation is complete.
4. The checkers observed the yield to be increased somewhat by the less convenient procedure of allowing the ammonia to evaporate slowly for 12–15 hours.
5. More water may be added if needed.
6. The fractionation has also been carried out with better results through a Todd Scientific versatile column.

3. Discussion

Experiments in the submitter's laboratory have shown that the yield obtained on dehydrobromination of dibromohendecanoic acid with ethanolic potassium hydroxide[4,5,6,7] is very poor, usually lower than 30% On the other hand, the dehydrobromination with sodamide in liquid ammonia is smooth and very satisfactory.[8] The directions employed here represent a modification of those of Lauer and Gensler.[9]

References and Notes

1. Ohio State University, Columbus, Ohio.
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

Dry Ice

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ether (60-29-7)

ammonium chloride (12125-02-9)

hydrogen (1333-74-0)

iron (7439-89-6)

bromine (7726-95-6)

sodium sulfate (7757-82-6)

acetone (67-64-1)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

ferric chloride (7705-08-0)

sodamide (7782-92-5)

undecylenic acid (112-38-9)

10-Undecynoic acid (2777-65-3)

10-undecenoic acid (112-38-9)

dibromohendecanoic acid

10,11-dibromohendecanoic acid

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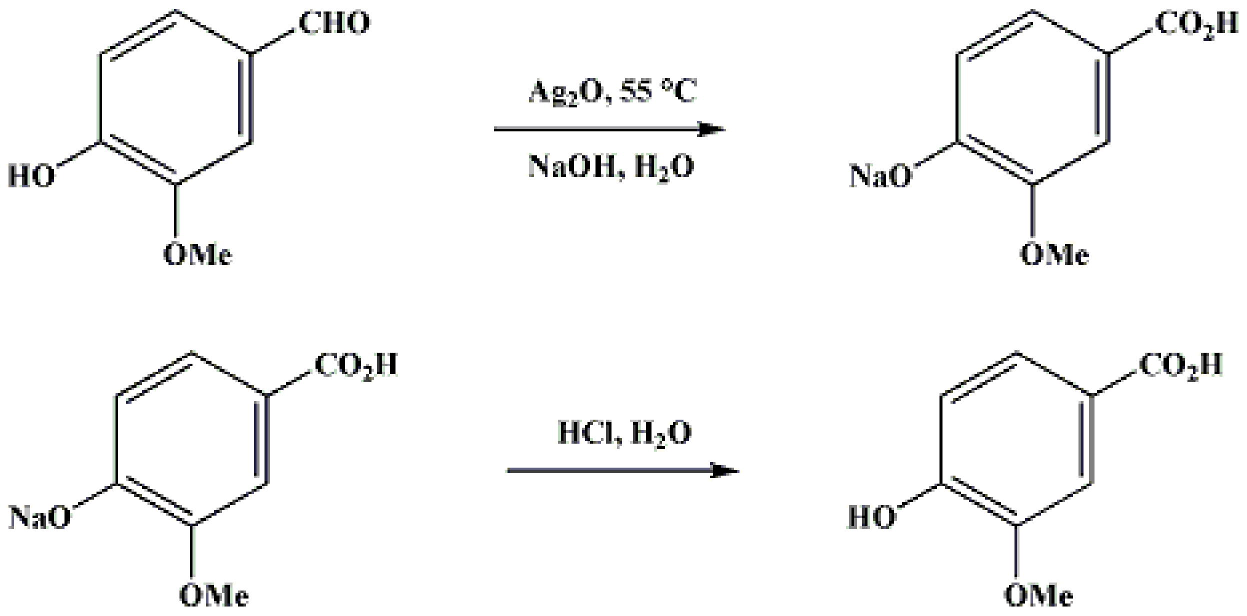
Organic Syntheses, CV 4, 972

VANILLIC ACID

[I. SILVER OXIDE METHOD]



Submitted by Irwin A. Pearl[1]
Checked by R. L. Shriner and Calvin N. Wolf.

1. Procedure

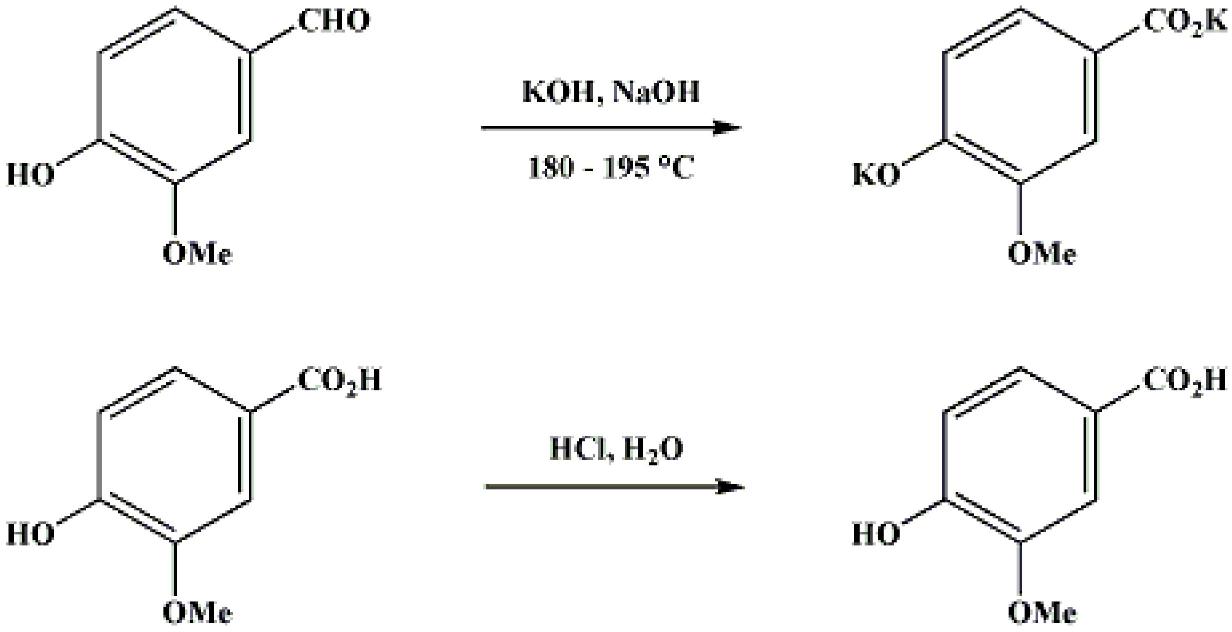
A solution of 170 g. (1.0 mole) of silver nitrate in 1 l. of water in a 2-l. beaker is treated, with stirring, with a solution of 44 g. (1.07 moles) of 97% sodium hydroxide in 400 ml. of water (Note 1). The mixture is stirred for 5 minutes, and the silver oxide is collected on an 11-cm. Büchner funnel with suction and washed free of nitrates with water (Note 2). The wet, freshly precipitated silver oxide is transferred to a 4-l. beaker (Note 1), covered with 2 l. of water, and treated with 200 g. (4.85 moles) of 97% sodium hydroxide pellets with vigorous stirring. If the temperature of the mixture at this point is below 55°, the mixture is warmed to 55–60°. With continued stirring at 55–60° (Note 3), 152 g. (1.0 mole) of vanillin (Note 4) is added; the reaction begins after a few minutes. The silver oxide is transformed to fluffy metallic silver, and considerable heat is evolved. Stirring is continued for 10 minutes, the mixture is filtered, and the precipitated silver is washed with 100 ml. of hot water. A rapid stream of sulfur dioxide gas (Note 5) is passed into the combined filtrate and washings for 2 minutes, and the resulting solution is poured into 1.1 l. of 1:1 hydrochloric acid with vigorous stirring. The resulting mixture, which should be acid to Congo red, is cooled to 15–20°. The vanillic acid is collected on a Büchner funnel, pressed to remove the mother liquor, washed with 150 ml. of ice water (Note 6), sucked as dry as possible, and air-dried. The yield is 140–160 g. (83–95%) of white needles melting at 209–210°. This product is pure enough for most purposes, but it may be purified by

recrystallization from water containing a little sulfur dioxide, 1.2 l. of water being used per 100 g. of product. Pure white needles melting at 210–211° are obtained with a recovery of 90–97%.

2. Notes

1. This reaction should be performed in glass apparatus with a glass stirrer. If stainless steel is employed, the resulting vanillic acid may be dark in color.
2. The presence of nitrates in the solution will cause the formation of nitro acids when the final acidification takes place.
3. Fifty to fifty-five degrees was found to be the critical temperature for this reaction. If the reactants are mixed cold, heat must be applied to raise the temperature above 50°, at which point the reaction begins. Mixing of the reactants at temperatures much higher than 60° results in a violent reaction.
4. Commercial U.S.P. vanillin is satisfactory.
5. The treatment with sulfur dioxide prevents the product from becoming tan in color.
6. Extraction of the combined filtrate and washings with three 200-ml. portions of ether, followed by removal of the ether by distillation, yields an additional 4–20 g. of product melting at 206–208°. It may be purified by recrystallization from water containing a little sulfur dioxide to give white needles melting at 209–210°.

[II. CAUSTIC FUSION METHOD]



Submitted by Irwin A. Pearl[1]
Checked by R. L. Shriner and Robert C. Johnson.

1. Procedure

In a stainless-steel beaker of approximately 2-l. capacity (120 mm. by 165 mm.)

equipped with an efficient mechanical Nichrome or Monel stirrer (Note 1) and heated by an electric hot plate are placed 178 g. (4.3 moles) of 97% sodium hydroxide pellets, 178 g. (2.7 moles) of 85% potassium hydroxide pellets (Note 2), and 50 ml. of water. The mixture is stirred and heated to 160°, at which temperature the hot plate is turned off. Twenty-five grams of vanillin is added. The temperature drops somewhat, and after a very short time a vigorous reaction begins which raises the temperature to 180–195°. An additional 127 g. (total of 1.0 mole) of vanillin is gradually added to the reaction mixture during a period of 10–12 minutes at a rate sufficient to maintain the reaction temperature (Note 3). After all the vanillin has been added, stirring is continued for 5 minutes. The hot plate is removed, and the mixture is allowed to cool with stirring. When the mixture cools to about 150–160°, 1 l. of water is added and the mixture is stirred until all the fusion mixture is dissolved. The solution is transferred to a 4-l. beaker, 500 ml. of water being used to rinse the stirrer and metal beaker. Sulfur dioxide gas is introduced for 1 minute (Note 4), and the reaction mixture is cooled to room temperature. The mixture is acidified with about 1.2 l. of 6*N* hydrochloric acid using Congo red as the indicator and keeping the mixture cool during addition of the acid by stirring and cooling in an ice bath. The mixture is cooled, and the light-tan precipitate is filtered, washed with 150 ml. of ice water, and dried. The yield of vanillic acid melting at 206–208° is 150–160 g. (89–95%) (Note 5). The product can be recrystallized from water, using 1.2 l. per 100 g. of vanillic acid. A 90–97% recovery of nearly white vanillic acid melting at 209–210° is obtained.

2. Notes

1. An efficient stirrer can be made from No. 8 Nichrome or Monel metal wire in a rectangular shape of dimensions such that it is about two-thirds the height of the beaker and has a clearance of 1–2 mm. with the sides of the beaker (.htmFig. 18). A rigid form is maintained by spot-welding the crossed wires. The metal beaker must be firmly clamped. It is important that there be effective stirring throughout all the reaction mixture in order to prevent caking, excessive local temperature rises, and foaming.

Fig. 18. Apparatus for caustic fusion of vanillin.

Fig. 18. Apparatus for caustic fusion of vanillin.

2. The exact proportion of sodium hydroxide to potassium hydroxide is not critical as long as the total amount of alkali is more than 7 moles. Alkali mixtures containing more than 70% sodium hydroxide are not desirable because they are not as fluid as other mixtures.
3. The temperature of the mixture should not be allowed to rise much above 200° for any length of time because traces of protocatechuic acid will be formed and contaminate the vanillic acid.
4. The sulfur dioxide treatment prevents the product from becoming tan in color.
5. An additional few per cent may be obtained by ether extraction of the filtrate.

3. Discussion

Vanillic acid has been prepared from vanillin in small amounts by action of moist air,[2] exposure to sunlight and nitrobenzene,[3] reaction with soil bacteria,[4] ozone,[5] and by caustic fusion.[6,7] High yields of vanillic acid have been obtained from vanillin by controlled caustic fusion,[8] oxidation with silver oxide,[9,10] mercuric oxide,[11] and gold oxide,[11] and by the Cannizzaro reaction of vanillin in the presence of a silver catalyst.[12] Vanillic acid has been prepared indirectly from vanillin by the hydrolysis of acetyl-vanillic acid prepared by oxidation with peracetic acid of acetyl-vanillin,[13] by the hydrolysis of acetovanillonitrile prepared by the reaction of vanillin oxime with acetic anhydride,[14] and by the action of hydrazoic acid on vanillin, followed by hydrolysis of the intermediate 4-hydroxy-3-methoxybenzonitrile.[15] The procedures described are essentially those reported by Pearl.[8,9,16]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrazoic acid

hydrochloric acid (7647-01-0)

ether (60-29-7)

acetic anhydride (108-24-7)

sodium hydroxide (1310-73-2)

silver oxide (20667-12-3)

silver nitrate (7761-88-8)

sulfur dioxide (7446-09-5)

mercuric oxide (21908-53-2)

potassium hydroxide (1310-58-3)

Nitrobenzene (98-95-3)

silver (7440-22-4)

ozone (10028-15-6)

vanillin (121-33-5)

protocatechuic acid (99-50-3)

peracetic acid (79-21-0)

Vanillic acid (121-34-6)

gold oxide

acetyl-vanillic acid

acetyl-vanillin (881-68-5)

acetovanillonitrile

vanillin oxime

4-hydroxy-3-methoxybenzonitrile (4421-08-3)

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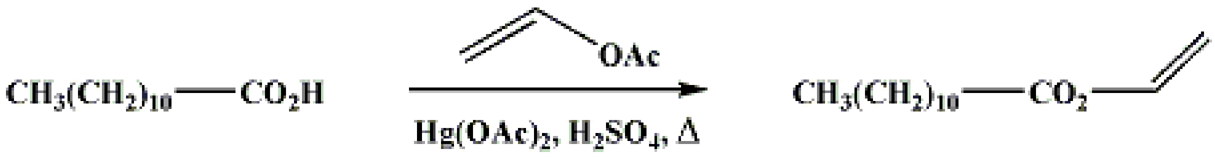
Organic Syntheses, CV 4, 977

VINYL LAURATE AND OTHER VINYL ESTERS

[Lauric acid, vinyl ester]



Submitted by Daniel Swern and E. F. Jordan, Jr.[1].
Checked by William S. Johnson and Leland J. Chinn.

1. Procedure

In a 500-ml. round-bottomed three-necked flask provided with a thermometer, a reflux condenser, and a gas inlet tube through which a stream of nitrogen is passed (Note 1) are placed 206 g. (2.4 moles) of freshly distilled vinyl acetate (Note 2) and 80 g. (0.4 mole) of lauric acid (Note 3). The lauric acid is dissolved by warming, and 1.6 g. of mercuric acetate is added. The mixture is shaken by hand for about 30 minutes, and 0.15 ml. of 100% sulfuric acid is added dropwise (Note 4). The solution is heated under reflux for 3 hours, then 0.83 g. of sodium acetate trihydrate is added to neutralize the sulfuric acid. The excess vinyl acetate is recovered by distillation at atmospheric pressure (vapor temperature about 70–80°) until the pot temperature reaches 125° (Note 5). The distillation is completed at 10 mm. or lower (Note 5), and, after the collection of a small quantity of low-boiling material, fairly pure vinyl laurate (Note 6) is obtained as a colorless liquid, b.p. 142–143°/10 mm. (138–139°/8 mm.; 124–126°/3 mm.). The yield is 50–57 g. (55–63%). Redistillation (Note 7) yields 48–53 g. (53–59%) of pure vinyl laurate, b.p. 142–142.5°/10 mm. (120–120.5°/2 mm.); n_D^{25} 1.4387 (Note 8) and (Note 9).

2. Notes

1. All operations should be conducted in a nitrogen atmosphere to minimize the formation of polymer.
2. An Eastman Kodak Company practical grade of vinyl acetate is satisfactory. It was distilled immediately before use through a 48 by in. column packed with 3/32-in. single-turn Pyrex glass helices. The checkers employed material obtained from the Niacet Chemicals Division, Niagara Falls, New York, distilled once through a 12-in. Vigreux column, b.p. 73°/746 mm.
3. Lauric acid, m.p. 44°, was prepared from the commercial acid obtained from Armour and Company, Chicago, Illinois. The acid was recrystallized twice from acetone at −40° (10 ml. of acetone per gram of acid) and distilled under reduced pressure through a well-insulated, electrically heated 30 by 1 in. column packed

with ☐-in. Berl saddles. Pure lauric acid has a boiling point of 167–168°/8 mm. and n_D^{45} 1.4316. The Eastman Kodak Company grade of lauric acid melting at 43–44° is satisfactory.

4. The 100% sulfuric acid is prepared by cautiously adding 7.3 g. of fuming sulfuric acid containing 30% sulfur trioxide to 10 g. of 95% sulfuric acid.

5. An electrically heated 18 by ☐ in. Vigreux column was employed.

6. The vinyl laurate, which has an acid number of about 2, usually contains a small quantity of mercury at this stage, from which it can be separated by decantation.

7. Sufficient sodium bicarbonate is added to the pot charge to neutralize the free acid present (Note 6).

8. Additional properties of vinyl laurate are n_D^{35} 1.4345 and d_4^{30} 0.8639. If the iodine number is determined by the Wijs method, a 200% excess of iodine chloride solution and a 1-hour reaction period should be employed in order to obtain values which are 97–99% of the theoretical value.

9. Vinyl caproate, caprylate, pelargonate, caprate, myristate, palmitate, stearate, 10-hendecenoate (undecylenate) and oleate can be prepared in a similar manner, except that in the preparation of the palmitate and stearate the fatty acids are added to a solution of mercuric acetate and sulfuric acid in vinyl acetate. Vinyl stearate is not redistilled, but the once-distilled product is recrystallized from acetone at 0° (3 ml. of acetone per gram of vinyl stearate). The amount of mercuric acetate employed was 2%, and the amount of 100% sulfuric acid was 0.3–0.4%, of the weight of the stearic acid. Average yields and properties of these vinyl esters are given in the table.

Vinyl Ester	Yield, %	Boiling Point °C.	Boiling Point mm.	n_D^{30}	d_4^{30}
Caproate	40	98–99	100	1.4159	0.8837
Caprylate	55	134–135	100	1.4256	0.8719
Pelargonate	55	133–133.5	50	1.4291	0.8689
Caprate	45	148	50	1.4320	0.8670
Myristate	60	147–148	4.8	1.4407	0.8617
Palmitate (m.p. 26.7–27.1°)	35	168–169	4.5	1.4438	0.8602
Stearate (m.p. 35–36°)	30	187–188	4.3	1.4423 (at 40°)	0.8517 (at 40°)
10-Hendecenoate	70	124–124.5	10	1.4442	0.8799
Oleate	60	178	2.8	1.4533	0.8691

The acids used for preparing the vinyl esters tabulated were Eastman Kodak

Company pure grade except for the following, which were obtained from the companies indicated and purified by fractionation through an efficient fractionating column: caproic acid, b.p. 96°/8 mm., Carbide and Carbon Chemicals Corporation, New York; caprylic acid, b.p. 124–125°/8 mm., capric acid, b.p. 145–146°/8 mm., Armour and Company, Chicago, Illinois; pelargonic acid, b.p. 176°/64 mm., Emery Industries, Cincinnati, Ohio; 10-hendecenoic (undecylenic) acid, b.p. 177–180°/25 mm., Baker Castor Oil Company, New York. Oleic acid was prepared from olive-oil fatty acids by low-temperature crystallization and distillation.[2]

3. Discussion

The procedure described is substantially that of Toussaint and MacDowell,[3] with minor modifications.[4] Vinyl esters of long-chain aliphatic acids have also been prepared by the reaction of acetylene with the appropriate acids,[5,6,7,8] but this reaction is not so convenient for small-scale laboratory preparations.

The interchange reaction of vinyl acetate with lauric acid in the presence of mercuric sulfate has been studied,[9] and vinyl laurate has been obtained also from lauryl chloride and acetaldehyde in the presence of pyridine.[10]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Vinyl caproate, caprylate, pelargonate, caprate, myristate, palmitate, stearate, 10-hendecenoate (undecylenate) and oleate

acetaldehyde (75-07-0)

sulfuric acid (7664-93-9)

acetylene (74-86-2)

sulfur trioxide (7446-11-9)

sodium bicarbonate (144-55-8)

nitrogen (7727-37-9)

mercuric acetate (1600-27-7)

mercury (7439-97-6)

iodine (7553-56-2)

acetone (67-64-1)

pyridine (110-86-1)

Caproic acid (142-62-1)

mercuric sulfate (7783-35-9)

oleic acid (112-80-1)

iodine chloride (7790-99-0)

caprylic acid (124-07-2)

stearic acid (57-11-4)

lauric acid (143-07-7)

Pelargonic acid (112-05-0)

vinyl acetate (108-05-4)

sodium acetate trihydrate (6131-90-4)

stearate

lauryl chloride (112-52-7)

10-hendecenoic acid (112-38-9)

Vinyl laurate, Lauric acid, vinyl ester (2146-71-6)

palmitate

Vinyl stearate (111-63-7)

capric acid (334-48-5)

Vinyl Caproate

vinyl caprylate

vinyl pelargonate

vinyl caprate

vinyl myristate

vinyl palmitate

vinyl 10-hendecenoate

vinyl oleate

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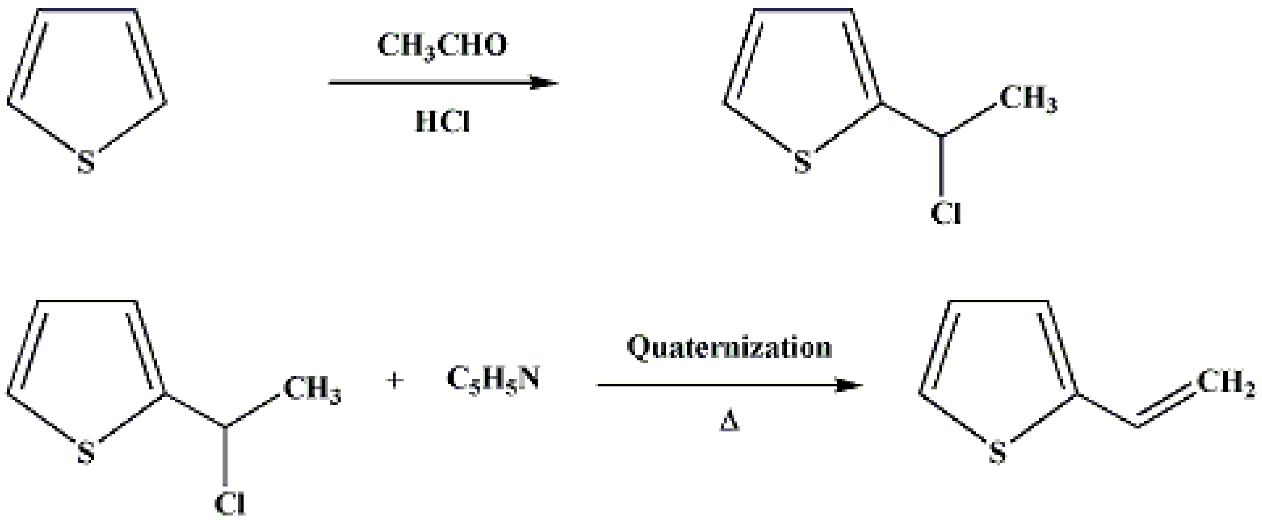
Organic Syntheses, CV 4, 980

2-VINYLTHIOPHENE

[Thiophene, 2-vinyl-]



Submitted by W. S. Emerson and T. M. Patrick, Jr.[1].
Checked by Max Tishler, P. Tishler, and F. W. Bollinger.

1. Procedure

A 2-l. three-necked flask is fitted with a thermometer, a stirrer, a gas inlet tube which will reach beneath the surface of the liquid, and a vent. The flask is placed in a bath of acetone to which Dry Ice can be added. To the flask are charged 336 g. (318 ml., 4.0 moles) of thiophene (Note 1), 176 g. (177 ml., 1.33 moles) of paraldehyde, and 300 ml. of concentrated hydrochloric acid. While this mixture is stirred and maintained at 10–13° (Note 2) by means of Dry Ice, gaseous hydrogen chloride is bubbled in. At the end of 25 minutes the solution is saturated (Note 3).

The contents of the flask are poured onto 300 g. of ice, the layers are separated, and the organic portion is washed three times with 200-ml. portions of ice water (Note 4). The organic layer is added, with some cooling (Note 5), to 316 g. (322 ml., 4.0 moles) of pyridine and 2.0 g. of α-nitroso-β-naphthol in a 1-l. distilling flask. The aqueous layer is extracted with two 100-ml. portions of ether, and the combined ethereal extract is used to wash each aqueous wash in turn (Note 6). The ethereal layer is concentrated on the steam bath under a stream of nitrogen and combined with the organic mixture in the distilling flask. The mixture is allowed to stand for 1.5 hours before distillation. The distillation is performed under reduced nitrogen pressure. The distillate is collected over 1.0 g. of α-nitroso-β-naphthol in an ice-cooled receiver at successively lower pressures ending at 125°/50 mm. (Note 7). The distillate is poured onto a mixture of 400 g. of ice and 400 ml. of concentrated hydrochloric acid. The layers are separated, and the organic portion is washed successively with 100-ml. portions of 1% hydrochloric acid, water,

and 2% ammonia.

The organic layer is filtered through 1 cm. of anhydrous magnesium sulfate on a sintered-glass funnel into a 500-ml. distilling flask. The aqueous layer is extracted with two 100-ml. portions of ether which are combined and used to extract the aqueous washes. The ethereal layer is washed with 50 ml. of saturated salt solution and filtered through the same funnel into a fresh suction flask. The funnel is finally washed with two 50-ml. portions of ether. The ethereal washes are concentrated on a steam bath under nitrogen (Note 8) and combined with the filtrate in the distilling flask. The filtrate is fractionally distilled under nitrogen through a 2-cm. column, 35 cm. high, packed with 6-mm. glass helices (Note 9). The column is jacketed and provided with a heater inside the jacket to minimize heat losses during distillation. The receiver is cooled in an ice bath, and the distillate is collected in three fractions, thiophene 45.6–27.9 g., b.p. 36°/150 mm.–35°/100 mm. (Note 10), intermediate 11.8–4.8 g., b.p. 35°/100 mm.–80°/98 mm., and 2-vinylthiophene (Note 11) and (Note 12) 191.3–224.0 g., b.p. 65–67°/50 mm., n_D^{25} 1.5701, lit.[2] b.p. 65.5–66.5°/48 mm., lit.[3] n_D^{25} 1.4698. The yield is 50–55% of the theoretical amount based on the thiophene consumed. The undistilled residue amounts to about 27 g. and the distillate in the Dry Ice-acetone trap to about 4 g.

2. Notes

1. Specific gravities at 25° were used to determine the volumes of reagents. Eastman Kodak Company thiophene, b.p. 83–85°, n_D^{25} 1.5252, and U.S.P. paraldehyde were used.
2. The submitters used an ice-salt bath, but the checkers found a Dry Ice-acetone bath more convenient and almost indispensable. Temperature control is important. Small deviations from the prescribed range result in a lower yield.
3. When the solution is saturated, copious fumes of hydrogen chloride are evolved from the vent. The reaction should not be continued beyond this point. With an ice-salt bath the time required for addition of hydrogen chloride was 35 minutes.
4. The yield will be much lower if the washing process is not carried out quickly.
5. If the mixture is too cold, the quaternization reaction will be delayed. On the other hand, if no cooling is provided, the reaction mixture may boil over spontaneously because of the exothermic nature of the reaction. Heat cracks the quaternary compound to 2-vinylthiophene which, if not removed by distillation, may undergo thermal polymerization.
6. Omission of this ethereal extraction will reduce the quoted yield by about 2 per cent.
7. At this temperature and pressure volatilization of pyridine hydrochloride occurs. Passage of vapors during the distillation through a Dry Ice-acetone trap yields 8.8 g. of thiophene contaminated with its original odoriferous impurities and 2.2 g. of an aqueous layer, both of which were discarded.
8. Omission of this ethereal extraction will reduce the quoted yield by about 6 per cent.
9. A packed column is essential to achieve the degree of fractionation required.
10. The distillation is conducted so as to keep the pot temperature below 90° until

about 90% of the product has been distilled. This is done to minimize thermal polymerization of the product.

11. If the intermediate and product fractions are not to be used immediately, α-nitroso-β-naphthol is added as a stabilizer.

12. 5-Chloro-2-vinylthiophene and 5-bromo-2-vinylthiophene have been prepared in 47% and 35% yields, respectively, by essentially the same procedure.

3. Discussion

2-Vinylthiophene has been prepared by the dehydration of α-(2-thienyl)ethanol[3,4,5,6,7] or β-(2-thienyl)ethanol;[8] by the condensation of vinyl chloride with 2-thienylmagnesium bromide in the presence of cobaltous chloride;[9] by the dehydrochlorination of α-(2-thienyl)ethyl chloride;[10] and by the dehydrogenation of 2-ethylthiophene.[11]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrogen chloride, hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ether (60-29-7)

nitrogen (7727-37-9)

acetone (67-64-1)

pyridine (110-86-1)

α-nitroso-β-naphthol (131-91-9)

Thiophene (110-02-1)

magnesium sulfate (7487-88-9)

pyridine hydrochloride (628-13-7)

vinyl chloride (9002-86-2)

cobaltous chloride

2-thienylmagnesium bromide

2-Vinylthiophene, Thiophene, 2-vinyl- (1918-82-7)

5-Chloro-2-vinylthiophene

5-bromo-2-vinylthiophene

α-(2-thienyl)ethanol

β-(2-thienyl)ethanol (5402-55-1)

α-(2-thienyl)ethyl chloride

2-ethylthiophene (872-55-9)

paraldehyde (123-53-7)

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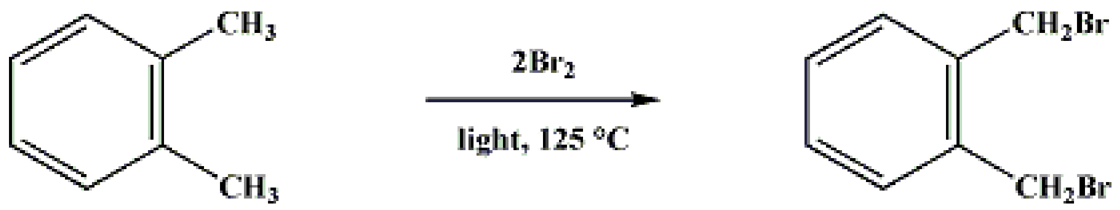
Organic Syntheses, CV 4, 984

o-XYLYLENE DIBROMIDE

[*o*-Xylene, α,α'-dibromo-]



Submitted by Emily F. M. Stephenson[1]
Checked by William S. Johnson, C. W. Taylor, and William DeAcetis.

1. Procedure

Caution! o-Xylylene dibromide is a powerful and persistent lachrymator. The preparation and all subsequent handling of this substance should, therefore, be carried out in an efficient hood with adequate protection by rubber gloves. A gas mask should be at hand for emergency. All apparatus coming in contact with the dibromide should be immersed in alcoholic alkali contained in a large crock with a lid. A period of 24 hours is sufficient for decontamination. Waste substances such as filter paper and corks usually require several days of such soaking before they can be safely discarded.

A 1-l. three-necked round-bottomed flask is fitted with a rubber slip-sleeve-sealed stirrer, a dropping funnel with the tip extended to reach almost to the bottom of the flask (Note 1), and an efficient condenser leading to a gas absorption trap.[2] *o*-Xylene (106 g., 1 mole) (Note 2) is placed in the flask, which is heated with an oil bath and illuminated with a sun lamp (Note 3) placed 1–5 cm. from the upper portion of the flask. When the temperature of the *o*-xylene reaches 125°, the dropwise addition of 352 g. (2.2 moles) of bromine is commenced with stirring. The rate of addition is regulated so that all the bromine is introduced in 1.5 hours. The mixture is stirred at 125° under illumination for an additional 30 minutes. It is then allowed to cool to 60° and poured into 100 ml. of boiling 60–68° petroleum ether contained in a beaker, the transfer being assisted with small amounts of warm solvent. As the homogeneous solution cools slowly to room temperature it is stirred frequently to prevent caking of the brown crystalline product that separates. After the mixture is cool and the bulk of the dibromide has crystallized, the beaker is placed in a refrigerator for 12 hours (Note 4). The product is then separated by suction filtration, washed twice with 25-ml. portions of cold petroleum ether, and then pressed on the filter until nearly dry. Final drying is effected in a vacuum desiccator containing solid potassium hydroxide. The brown crystalline product amounts to 123–140 g. (48–53% yield), the melting point ranging between 89° and 94° (Note 5).

2. Notes

1. It is convenient to seal a short inner tube inside the stem of the dropping funnel so that the rate of addition can be observed readily. The introduction of the bromine below the surface of the *o*-xylene through an extended stem, about 4-mm. inside diameter, results in better mixing of reactants and less loss of bromine vapors.

2. The submitter used *o*-xylene obtained from Light and Company, Wraysbury, Middlesex, England. It was refluxed with sodium, then distilled from sodium, b. p. 144–144.5°, and stored over sodium.

The checkers employed the white label grade of *o*-xylene supplied by Eastman Kodak Company without further purification.

3. The submitter employed a 600-watt lamp, and the checkers used a 275-watt General Electric sun lamp.

4. Occasional stirring during the first 3–4 hours of this chilling period helps to prevent caking of the product on the side of the beaker.

5. This product is satisfactory for most preparative work. Further purification may be effected by recrystallization from 95% ethanol (3 ml./g.), to give material melting at 93–94° in 80–85% recovery. Other solvents that have been used for recrystallization are petroleum ether (British Drug House, "Analar," b. p. 60–80°) (19 ml./g.), and chloroform (1 ml./g.).

3. Discussion

o-Xylylene dibromide has been prepared from *o*-xylene by direct bromination[3] or by treatment with N-bromosuccinimide;[4] by the direct bromination of *o*-xylyl bromide;[5] and by the action of concentrated hydrobromic acid on the monophenyl ether of α,α'-dihydroxy-*o*-xylene.[6] The present procedure is essentially that of Perkin[3] as modified by Cope and Fenton.[7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 1064

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

ethanol (64-17-5)

chloroform (67-66-3)

HYDROBROMIC ACID (10035-10-6)

bromine (7726-95-6)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

monophenyl ether (101-84-8)

N-bromosuccinimide (128-08-5)

o-Xylylene dibromide, o-Xylene, α,α'-dibromo- (91-13-4)

α,α'-dihydroxy-o-xylene (612-14-6)

o-Xylene (95-47-6)

o-xylyl bromide (576-23-8)

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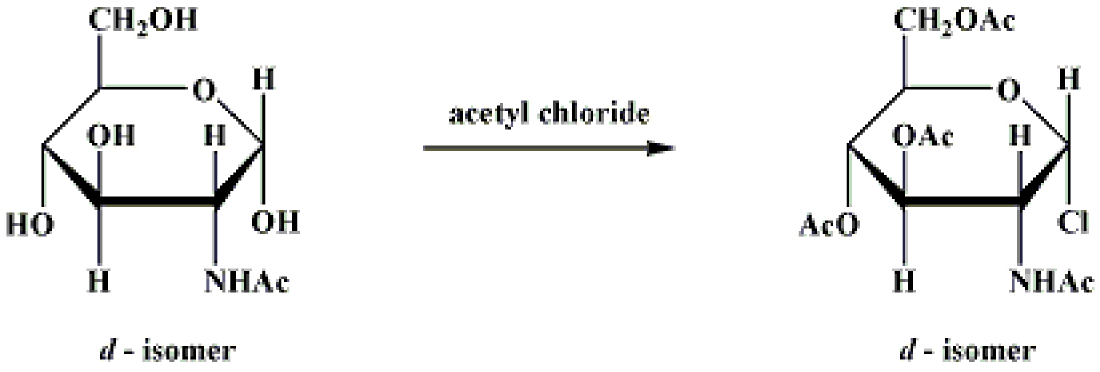
Organic Syntheses, CV 5, 1

2-ACETAMIDO-3,4,6-TRI-*O*-ACETYL-2-DEOXY-α-D-GLUCOPYRANOSYL CHLORIDE

[Glucopyranosyl chloride, 2-acetamido-2-deoxy-,triacetate, α-D-]



Submitted by Derek Horton[1]
Checked by A. L. Johnson and B. C. McKusick.

1. Procedure

In a 500-ml. round-bottomed flask equipped with a magnetic stirrer bar and a reflux condenser protected by a tube of calcium chloride is placed 100 ml. of acetyl chloride; this operation and the subsequent reaction are conducted in a hood. The condenser is temporarily removed, and 50 g. (0.226 mole) of dried 2-acetamido-2-deoxy-D-glucose (*N*-acetylglucosamine) (Note 1) is added in the course of 2 or 3 minutes with good stirring. The mixture is stirred for 16 hours without external heating at a room temperature of approximately 25°. The mixture boils spontaneously during the first hour of reaction. It is a clear, viscous, amber liquid at the end of the reaction (Note 2).

Through the condenser there is added 400 ml. of chloroform (U. S. P. grade), and the solution is poured with vigorous stirring onto 400 g. of ice and 100 ml. of water in a 3-l. beaker. The mixture is transferred to a 1-l. separatory funnel and shaken. The organic solution is drawn off without delay into a 3-l. beaker containing ice and 400 ml. of saturated sodium bicarbonate solution. The mixture in the beaker is stirred, and the neutralization is completed by shaking the mixture in the separatory funnel. The organic layer is run directly into a flask containing about 25 g. of anhydrous magnesium sulfate. The entire washing procedure should be completed within 15 minutes (Note 3). The solution is shaken or stirred with the drying agent for 10 minutes (Note 4). The drying agent is separated on a 7.5-cm. Büchner funnel and is well washed with *dry, alcohol-free* chloroform or methylene chloride (Note 5). The filtrate passes through an adaptor directly into a 1-l. round-bottomed flask. The filtrate is concentrated to 75 ml. on a rotary evaporator at 50°, and dry ether (500 ml.) is rapidly added with swirling to the warm solution (Note 6). Crystallization usually begins after about 30 seconds. The flask is stoppered and set aside for 12 hours at

room temperature.

The product is scraped from the walls of the flask and broken up by means of a curved spatula. The solid is collected on a 12.5-cm. Büchner funnel, washed with two 150-ml. portions of dry ether, dried by suction on the filter for 5 minutes, and stored in a desiccator over sodium hydroxide and phosphorus pentoxide. Analytically pure 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride is obtained; weight 55–65 g. (67–79%); m.p. 127–128° (Fisher-Johns apparatus) (Note 7); typical -$NHCOCH_3$ absorptions at 6.09 • and 6.49 • in the infrared; nmr ($CDCl_3$) δ 6.25 and $J_{1,2}$ 3.5 Hz for the H-1 doublet. Evaporation of the mother liquors and addition of ether to the concentrated solution gives an additional 4–6 g. (5–7%) of crystalline product, m.p. 125–127°, that is sufficiently pure for most purposes. The pure product may be stored in an open dish in a desiccator at room temperature for at least 3 years without decomposition (Note 8).

2. Notes

1. Suitable material is available from Pfanstiehl Laboratories, Waukegan, Illinois. It may also be prepared from the hydrochloride of 2-amino-2-deoxy-D-glucose (D-glucosamine) in 95% yield by a facile procedure.[2] The 2-acetamido-2-deoxy-D-glucose should be dried at 25° (1 mm.) for at least 12 hours before use. If this material is in the form of a powder rather than compact crystals, more acetyl chloride may have to be added in order to get a stirrable mixture; the checkers found that an extra 50 ml. of acetyl chloride did not lower the yield.
2. The reaction mixture may be left for longer periods, as over a weekend, without adverse effect. If the ambient temperature is too low, undissolved material may be present after 16 hours, in which case a longer period of stirring is indicated, or the reaction mixture may be gently heated (not above 30°).
3. It is essential that isolation of the product be conducted rapidly and at 0° throughout, especially while the solution is acidic. All apparatus and solutions should be at hand before the reaction mixture is poured on ice. The product reacts fairly rapidly with water in the presence of an acid catalyst, undergoing acetyl migration to give the water-soluble 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-α-D-glucopyranose hydrochloride.
4. An extended period of drying is unnecessary and should be avoided.
5. Commercial methylene chloride is usually sufficiently dry to use without pretreatment is place of dry, alcohol-free chloroform. The checkers used a pressure funnel under dry nitrogen for the filtration; filtration was rapid and exposure to atmospheric moisture was slight.
6. The solution must not be evaporated to a volume that permits crystallization to begin before the ether is added. The addition of ether should be sufficiently rapid that the heavy syrup is diluted to a clear, homogeneous solution before crystallization begins.
7. The checkers observed m.p. 118–119° when an open capillary tube containing a sample of analytical purity was placed in a stirred oil bath at 100° with the

temperature rising several degrees a minute. The melting point of benzoic acid, determined simultaneously, was 122–123°. The checkers found $[\alpha]^{24}D$ | + 110° (*c.* 1, $CHCl_3$); literature values range from +109.7° to 118°.

8. Material of lesser purity may decompose within a much shorter time. If the product is exposed to moist air, it is converted into 1,3,4,6-tetra-*O*-acetyl-2-amino-deoxy-α-D-glucopyranose hydrochloride, which is insoluble in chloroform.

3. Discussion

The direct one-step preparation of 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride was reported by Micheel and co-workers,[3] and the described procedure is essentially the method of Horton and Wolfrom.[4] The product was first prepared through a two-step route from 2-amino-2-deoxy-D-glucose hydrochloride by Baker and co-workers,[5] and a number of adaptations of this method have been described.[6,7,8]

4. Merits of Preparation

The procedure permits acetylation of the sugar and replacement of the 1-acetoxy group by chlorine in one operation in only 2–3 hours of working time, gives good yields of pure product, and does not require gaseous hydrogen chloride. The two-step procedure from 2-amino-2-deoxy-D-glucose hydrochloride[5,6,7] is time-consuming, and yields are very low if the acetylated intermediate is isolated.[8] The yield is better when the second stage is performed without isolation, of the intermediate,[9] but gaseous hydrogen chloride is required, and the preparation takes considerably more working time than the method described.

The product is used in the preparation of glycoside, thioglycoside, oligosaccharide, and glycosylamine derivatives of 2-acetamido-2-deoxy-D-glucose.[10] A number of these compounds are current interest; several seem to be involved in viral penetration of cells, and others are of interest in the synthesis of model substrates for enzymes. The product has the α-D configuration, and normally reacts to give glycosides with the β-D configuration, presumably through participation of the acetamido group in a bicyclic, closed-ion intermediate. Under controlled conditions it reacts with water to give 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-α-D-glucopyranose hydrochloride.[11]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Glucopyranosyl chloride, 2-acetamido-2-deoxy-,triacetate, α-D-

hydrochloride of 2-amino-2-deoxy-D-glucose

glycoside

thioglycoside

oligosaccharide

glycosylamine

hydrogen chloride (7647-01-0)

ether (60-29-7)

sodium hydroxide (1310-73-2)

acetyl chloride (75-36-5)

chloroform (67-66-3)

sodium bicarbonate (144-55-8)

nitrogen (7727-37-9)

Benzoic acid (65-85-0)

sugar

chlorine (7782-50-5)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

2-amino-2-deoxy-D-glucose hydrochloride (66-84-2)

D-glucosamine

phosphorus pentoxide (1314-56-3)

N-acetylglucosamine, 2-acetamido-2-deoxy-D-glucose

2-ACETAMIDO-3,4,6-TRI-O-ACETYL-2-DEOXY-α-D-GLUCOPYRANOSYL CHLORIDE (3068-34-6)

1,3,4,6-tetra-O-acetyl-2-amino-2-deoxy-α-D-glucopyranose hydrochloride

1,3,4,6-tetra-O-acetyl-2-amino-deoxy-α-D-glucopyranose hydrochloride

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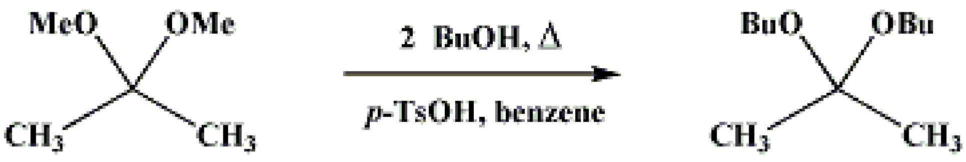
Organic Syntheses, CV 5, 5

ACETONE DIBUTYL ACETAL

[Propane, 2,2-dibutoxy-]



Submitted by N. B. Lorette and W. L. Howard[1].
Checked by Max Tishler and Stanley Nusim..

1. Procedure

A mixture of 312 g. (3 moles) of acetone dimethyl acetal (Note 1), 489 g. (6.6 moles) of butanol, 1.0 l. of benzene, and 0.2 g. of *p*-toluenesulfonic acid is placed in a 3-l. flask. The flask is connected to a packed fractionating column and the solution distilled until the azeotrope of benzene and methanol, boiling at 58°, is completely removed (Note 2). The contents of the boiler are then cooled below the boiling point and a solution of 0.5 g. of sodium methoxide in 20 ml. of methanol (Note 3) is added all at once with stirring. The flask is replaced for further distillation, and most of the remaining benzene is distilled at atmospheric pressure. The pressure is then reduced, and the remaining benzene and unreacted butanol are removed (Note 4). Finally, the pressure is reduced to 20 mm., the last traces of low-boiling materials are taken to the cold trap, and the product is distilled. After a small fore-run, acetone dibutyl acetal is collected at 88–90°/20 mm. The yield is 421–453 g. (74.6–80.3%), n_D^{25} 1.4105, d_4^{25} 0.8315.

2. Notes

1. Commercial acetone dimethyl acetal (2,2-dimethoxypropane) from the Dow Chemical Company was used without further treatment.
2. About 570 ml. of this azeotrope is obtained. The methanol produced may be estimated by washing an aliquot with about two volumes of water in a graduated cylinder. The methanol content is approximately the difference between the initial volume and that of the residual benzene phase, and about 230 ml. is obtained, depending on the efficiency of fractionation. Other hydrocarbons, e.g., hexane or cyclohexane, can be used for the removal of methanol.
The submitters' distillation was carried out in a 19 × 1200-mm. vacuum-jacketed silvered column fitted with a magnetically operated vapor-takeoff head controlled by a timed relay. The checkers found that a 19 × 340-mm. vacuum-jacketed column fitted with a magnetically operated liquid takeoff and packed with -in. glass Raschig rings was sufficient for carrying out the distillation. The checkers, using a reflux ratio of 2.7 to 1 throughout the distillation, found

the total time required to be 19 hours.
Since the required separations are not difficult, any reasonably efficient fractionating column may be used.
3. Other soluble non-volatile bases may be used.
4. It is best to keep the temperature of the distilland below 125–150°, because pyrolysis of the product becomes progressively more serious at higher temperatures. The pressure is reduced to a convenient value when the distilland temperature reaches 125°. For example, a pressure of 200 mm. will allow the condensation of the benzene without resort to special cooling.

3. Discussion

Acetone dibutyl acetal has been prepared from isopropenyl acetate and butanol,[2] from butanol and isopropenyl butyl ether obtained from the reaction of butanol with propyne,[3] and by orthoformic ester synthesis.[4,5]

4. Merits of Preparation

The preparation described here is a modification of previously used alkoxyl interchange reactions, but it is more convenient because the use of the azeotrope-forming solvent permits the virtually complete removal of the by-product alcohol under mild conditions. The method is general for most primary and secondary alcohols, including those with functional groups which are stable under the mild conditions used.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Benzene (71-43-2)

methanol (67-56-1)

cyclohexane (110-82-7)

butanol (71-36-3)

sodium methoxide (124-41-4)

isopropenyl acetate (108-22-5)

hexane (110-54-3)

Acetone dibutyl acetal, Propane, 2,2-dibutoxy- (141-72-0)

acetone dimethyl acetal, 2,2-dimethoxypropane (77-76-9)

isopropenyl butyl ether

propyne (74-99-7)

p-toluenesulfonic acid (104-15-4)

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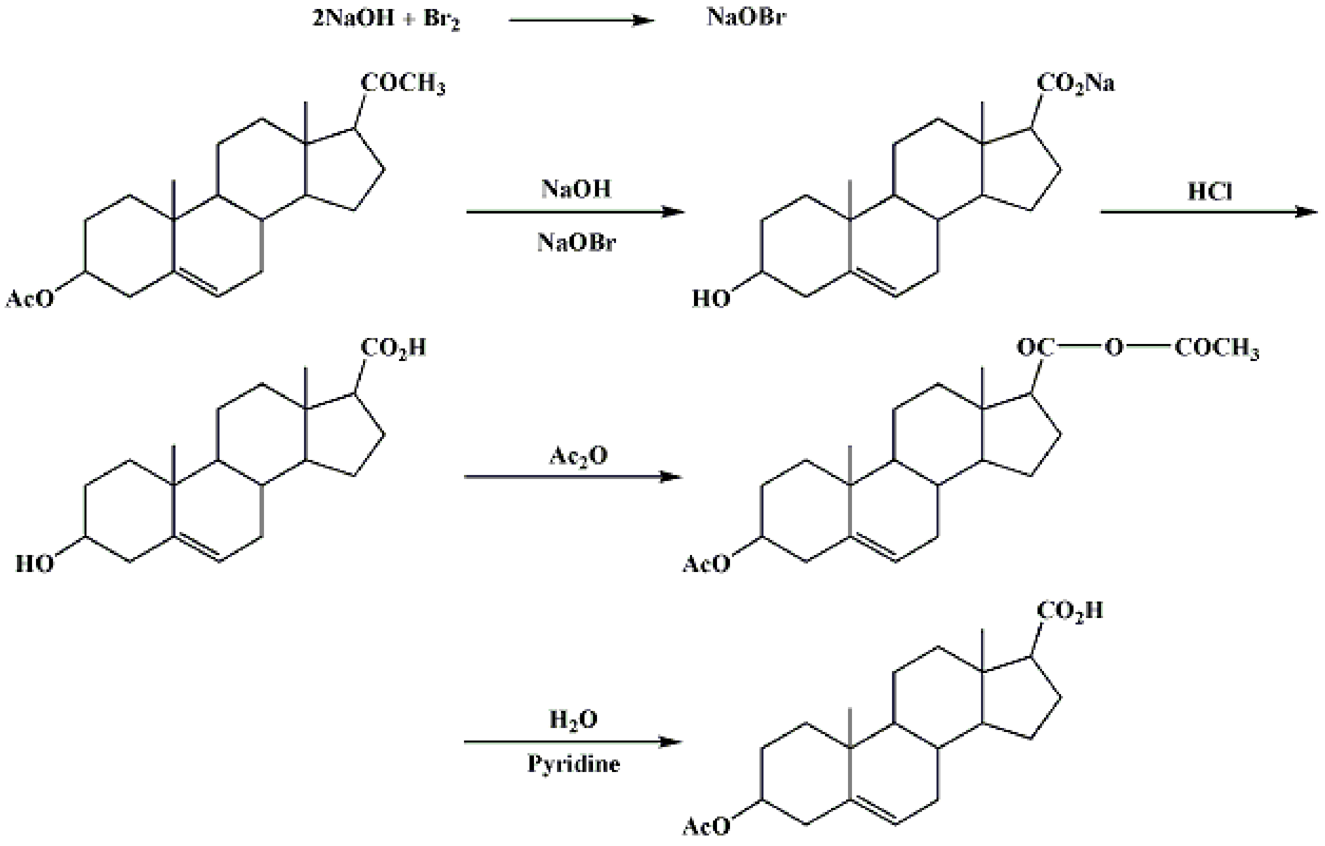
Organic Syntheses, CV 5, 8

3β-ACETOXYETIENIC ACID

[3β-Acetoxy-5-androstene-17β-carboxylic acid]



Submitted by J. Staunton and E. J. Eisenbraun[1].
Checked by W. G. Dauben and J. H. E. Fenyes..

1. Procedure

A solution of 42 g. (1.05 moles) of sodium hydroxide in 360 ml. of water is placed in a 1-l. three-necked, round-bottomed flask fitted with a mechanical stirrer and a thermometer and is cooled to −5° in an ice-salt bath. The stirrer is started, and 43 g. (0.263 mole) of bromine is added from a separatory funnel at such a rate that the temperature remains below 0° (addition time about 5 minutes). The ice-cold solution is diluted with 240 ml. of dioxane (Note 1) that has previously been cooled to 13–14° (Note 2). This solution is kept at 0° until required.

A solution of 28.8 g. (0.08 mole) of 3β-acetoxy-5-pregnen-20-one (pregnenolone acetate) (Note 3) in 1.1 l. of dioxane (Note 1) is diluted with 320 ml. of water and placed in a 5-l. three-necked, round-bottomed flask fitted with a mechanical stirrer and a thermometer (Note 4). The stirrer is started and the mixture is cooled in ice. When the internal temperature has fallen to 8°, the cold hypobromite solution is added in a steady stream. The temperature of the reaction mixture is maintained below 10° throughout the reaction. A white precipitate begins to form after 10 minutes, and the solution becomes colorless during 1 hour. The mixture is stirred for an additional 2 hours, and then the excess sodium hypobromite is destroyed by the addition of a solution of 10 g. of anhydrous sodium sulfite in 100 l. of water (Note 5).

The stirrer and thermometer are removed and the flask is fitted with a condenser for reflux. The mixture is heated under reflux for 15 minutes, and the solution, while still hot (90°), is acidified by the cautious addition of 50 ml. of concentrated hydrochloric acid (Note 6). The clear yellow solution is kept at 5° for 24 hours. The crystalline precipitate is collected by suction filtration, washed with water, and dried at 100° at atmospheric pressure. The yield of 3β-hydroxyetienic acid, m.p. 274–276°, is 18–20 g. An additional 3–5 g. of product can be obtained by subjecting the filtrate to steam distillation until a white precipitate is formed. The etienic acid collected from the cooled solution melts at 268–272°. The total yield is 23–24 g. (91–95%).

The 3β-hydroxyetienic acid is placed in a 500-ml. round-bottomed flask fitted with a condenser protected with a drying tube and is dissolved with warming in 150 ml. of dry pyridine. After the solution has cooled to room temperature, 20 ml. of acetic anhydride is added; a white crystalline precipitate starts to form immediately. After the mixture has stood for 18–24 hours, it is treated with 20 ml. of water and boiled until the precipitate has dissolved (Note 7). The clear solution is diluted with 70 ml. of water and allowed to cool. The crystalline product is collected by suction filtration, washed with water, and dried in a vacuum oven at 105°/20 mm. The yield of 3β-acetoxyetienic acid, m.p. 235–238°, is 23–24 g. Recrystallization from glacial acetic acid gives a purer product, m.p. 238–240°. The yield is 16–18 g. (55–63% based on the amount of pregnenolone acetate used).

2. Notes

1. Dioxane as supplied by Matheson-Coleman Bell Co. was used without purification.
2. The temperature of the hypobromite solution is kept below 10° to avoid the formation of sodium bromate.
3. Pregnenolone acetate (3β-acetoxy-5-pregnen-20-one) supplied by Syntex S. A., Apartado Postal 2679, Mexico, D. F., was used.
4. It is advisable to carry out any operation involving dioxane in a fume hood.
5. Although this amount of sodium sulfite is sufficient to destroy the excess sodium hypobromite, the solution may still give a positive test with starch-iodide paper because of the presence of peroxides in the dioxane used. It is not necessary to destroy these peroxides before proceeding.
6. The solution should be swirled gently during the addition of the hydrochloric acid. Since this operation causes the dioxane to boil, it must be carried out in a fume hood.
7. The anhydride of etienic acid is hydrolyzed in this process to give the soluble acid. Prolonged boiling should be avoided to prevent extensive attack on the less readily hydrolyzed acetate group.

3. Discussion

3β-Hydroxy-Δ^5-etiocholenic acid has been prepared from pregnenolone acetate by the action of sodium hypoiodite;[2] by oxidation of the furfurylidene derivative;[3] and by oxidation of the benzylidene derivative of the 5,6-dibromide followed by debromination.[4] The side chain of 3β-hydroxy-Δ^5-bisnorcholenic acid has been systematically degraded to give the etienic acid.[5] Two syntheteic approaches have involved, respectively, the replacement of the halogen in 17-chloro-3-acetoxy-Δ^5-androstene by an alkali metal followed by treatment with carbon dioxide[6] and the conversion of dehydroandrosterone acetate to its cyanohydrin, which then was successively dehydrated, hydrolyzed, and selectively hydrogenated to furnish 3β-hydroxyetienic acid.[7,8].

4. Merits of Preparation

3β-Acetoxyetienic acid has been found to be particularly suitable for the resolution of alcohols. Thus it was employed by Woodward and Katz for the resolution of 1α-hydroxydicyclopentadiene;[9] by Djerassi, Warawa, Wolff, and Eisenbraun for the resolution of *trans*-3-*tert*-butylcyclohexanol;[10] and by Djerassi and Staunton for the resolution of *cis*,*cis*-1-decalol.[11]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

3β-Hydroxy-Δ^5-etiocholenic acid

benzylidene derivative of the 5,6-dibromide

3β-hydroxy-Δ^5-bisnorcholenic acid

17-chloro-3-acetoxy-Δ^5-androstene

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

acetic anhydride (108-24-7)

sodium sulfite (7757-83-7)

sodium hydroxide (1310-73-2)

bromine (7726-95-6)

carbon dioxide (124-38-9)

acetate

pyridine (110-86-1)

sodium bromate (7789-38-0)

hypobromite

sodium hypobromite

dioxane (5703-46-8)

3β-Acetoxyetienic acid, 3β-Acetoxy-5-androstene-17β-carboxylic acid (7150-18-7)

3β-acetoxy-5-pregnen-20-one

pregnenolone acetate

3β-hydroxyetienic acid

etienic acid

sodium hypoiodite

furfurylidene

1α-hydroxydicyclopentadiene

trans-3-tert-butylcyclohexanol

cis,cis-1-decalol

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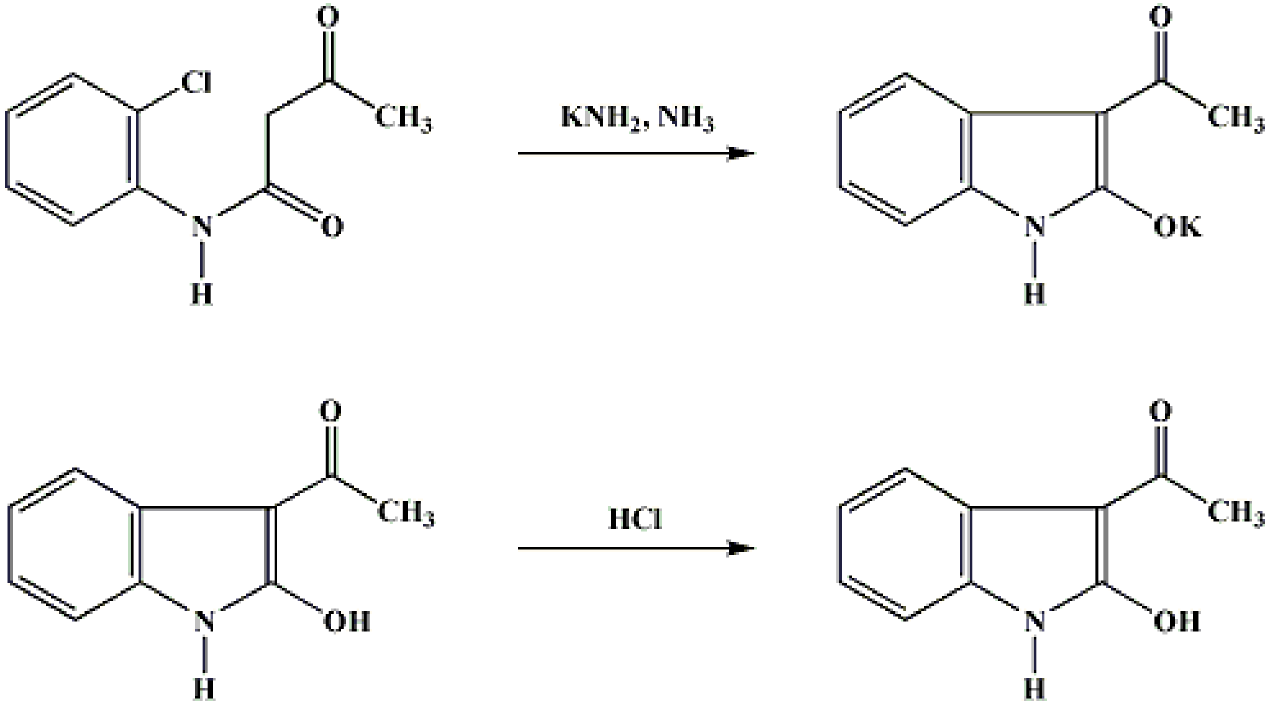
Organic Syntheses, CV 5, 12

3-ACETYLOXINDOLE

[Oxindole, 3-acetyl-]

$$2K + 2NH_3 \longrightarrow 2KNH_2 + H_2$$



Submitted by J. F. Bunnett, B. F. Hrutfiord, and S. M. Williamson[1].
Checked by B. C. McKusick and D. C. Blomstrom..

1. Procedure

An apparatus resembling that pictured by Schlatter[2] is assembled in a good hood. Two 5-l. three-necked flasks are mounted side by side about 10 cm. apart and about 10 cm. above the bench top or stand base. These are referred to as the "left" and "right" flasks. Each flask is provided with a dry ice condenser in the outermost neck, and each condenser is protected from the air by a soda-lime drying tube. Each flask is provided through the center neck with a motor-driven stirrer. The left stirrer should have a large sweep blade, and the right stirrer should have a small propeller-type blade. The bearing on each stirrer should be capable of holding a small positive pressure (the submitters used ball-joint bearings). The innermost neck of each flask is fitted with a two-holed rubber stopper. One hole in each stopper is for nitrogen supply; a short piece of glass tubing is inserted through each stopper, and these pieces of glass tubing are connected by rubber tubes to a glass "Y" tube which in turn is connected by rubber tubing to a tank of dry nitrogen. The rubber tubes between the "Y" tube and the flasks are provided with pinch clamps so that the flow of nitrogen can be directed into either flask or into both at once. The other hole in each stopper is for transfer of liquid ammonia from the right flask to the left. A glass tube reaching to the very bottom of the right flask is inserted through the right stopper. A glass tube is inserted through the

left stopper so that it projects only a few centimeters into the left flask. These glass tubes are bent so that they point toward each other, and they are connected by a piece of rubber tubing provided with a pinch clamp.

With nitrogen flowing and all pinch clamps open, the apparatus is flamed to drive away traces of moisture. The condensers are then provided with dry ice covered by isopropyl alcohol, and the lower part of the right flask is embedded in crushed dry ice. Liquid ammonia (4 l.) is introduced into the right flask through the nitrogen inlet from which the rubber tubing is temporarily disconnected, and 105.8 g. (0.5 mole) of *o*-acetoacetochloroanilide (Note 1) is placed in the left flask. In order to destroy any water in the ammonia, the right stirrer is started and small pieces of potassium metal are dropped into the ammonia, by briefly lifting the right two-holed stopper, until the blue color persists for 3 minutes. The nitrogen connection to the left flask is clamped shut and, by partially blocking the escape of nitrogen from the right drying tube, about 1 l. of ammonia is forced into the left flask. The connection between the two flasks is now clamped shut. Brief operation of the left stirrer facilitates solution of the *o*-acetoacetochloroanilide in the ammonia.

Potassium metal (78 g.; 2 moles) is cut into chunks just small enough to pass through the neck of the right flask; these are stored in a beaker under xylene until needed. About 5 g. of potassium is introduced into the right flask by briefly lifting the two-holed stopper. The right stirrer is started and the potassium is allowed to dissolve. To the resulting deep blue solution is added 0.1 g. of finely crushed ferric nitrate hydrate, a catalyst for the reaction of potassium with ammonia. The solution should begin to boil with evolution of hydrogen. (*Caution: No flames or sparks should be nearby.*) The rest of the potassium is added at such a rate as to maintain active gas evolution (Note 2). Stirring is continued in the right flask until all the potassium is consumed, i.e., until the blue color disappears. The right flask now contains a solution of potassium amide in liquid ammonia; 30–60 minutes is required for its preparation.

The tube between the two flasks is opened by releasing the pinch clamp, and the left stirrer is started. With nitrogen flow to the left flask still blocked, the potassium amide solution is caused to flow into the left flask by partially blocking the right nitrogen exit. The solution in the left flask slowly assumes a chartreuse color. As soon as the right flask is as nearly empty as the apparatus will permit, nitrogen flow is opened to the left flask and closed to the right flask and the connection between the two flasks is clamped shut. The right flask is then disconnected and immediately cleaned by rinsing it carefully with ethyl or isopropyl alcohol to destroy potassium amide and then washing it with water. (*Caution: Potassium amide is inflammable and will ignite on contact with moisture.*)

The solution in the left flask is stirred for 30 minutes after all the potassium amide has been added. The nitrogen inlet is briefly removed and 120 g. (1.5 moles) of ammonium nitrate is added; this discharges the chartreuse color. (*Caution: Vigorous foaming occurs.*) Ethyl ether (500 ml.) is added and the dry ice condenser is replaced by a standard water-cooled condenser. The ammonia is evaporated by allowing the stirred reaction mixture to warm to room temperature; this takes several hours and it is convenient to have it occur overnight.

Water (1.5 l.) is added and the mixture is transferred to a separatory funnel. The lower aqueous layer, which contains the potassium salt of 3-acetyloxindole, is separated and is then extracted with ethyl ether three times to remove a purple impurity. The aqueous layer is then made acidic to litmus by addition of hydrochloric acid; this causes precipitation of crude, tan-colored 3-acetyloxindole. The mixture is chilled, and the product is collected by suction filtration and washed well on the filter with water. The yield of crude 3-acetyloxindole, m.p. 204–206°, is 65–68 g. (74–78%). It may be purified by recrystallizing it from 1.7 l. of chloroform in the presence of 2 g. of decolorizing carbon. A heated filter funnel must be used in separating the carbon because the product starts to crystallize only slightly below the boiling point of chloroform. The recrystallized 3-acetyloxindole weighs 53–59 g. (61–67%) and is in the form of white needles, m.p. 204–205.5°.

2. Notes

1. The *o*-acetoacetochloroanilide used was the technical product of Union Carbide Chemicals Co.; m.p. 107–109°.
2. If the reaction of potassium with liquid ammonia slows down before all the potassium is consumed, an additional pinch of ferric nitrate hydrate is added.

3. Discussion

3-Acetyloxindole has been made by condensing ethyl acetate with oxindole in the presence of sodium ethoxide[3] and by heating N-acetyloxindole with sodium amide in xylene.[4] The present method was developed by Hrutfiord and Bunnett.[5] It illustrates a general principle for the synthesis of heterocyclic and homocyclic compounds. This principle involves the creation of an intermediate species that is of the benzyne type and has a nucleophilic center located so that it can add, intramolecularly, to the "triple bond" of the benzyne structure. Other applications of the principle using essentially the present procedure are the conversion of thiobenz-*o*-bromoanilide or thiobenz-*m*-bromoanilide to 2-phenylbenzothiazole (90% and 68% respectively), of benz-*o*-chloroanilide to 2-phenylbenzoxazole (69%),[5] of *o*-chlorohydrocinnamonitrile to 1-cyanobenzocyclobutene (61%),[6] and of methanesulfone(N-methyl-*o*-chloro)anilide to 1-methyl-2,1-benzisothiazoline 2,2-dioxide (66%).[7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 60

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

o-acetoacetochloroanilide

ethyl or isopropyl alcohol

thiobenz-o-bromoanilide

thiobenz-m-bromoanilide

benz-o-chloroanilide

methanesulfone(N-methyl-o-chloro)anilide

1-methyl-2,1-benzisothiazoline 2,2-dioxide

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

benzyne (71-43-2)

ethyl acetate (141-78-6)

ethyl ether (60-29-7)

hydrogen (1333-74-0)

chloroform (67-66-3)

nitrogen (7727-37-9)

decolorizing carbon, carbon (7782-42-5)

isopropyl alcohol (67-63-0)

sodium ethoxide (141-52-6)

potassium (7440-09-7)

ammonium nitrate

xylene (106-42-3)

sodium amide (7782-92-5)

potassium amide

ferric nitrate hydrate

3-Acetyloxindole, Oxindole, 3-acetyl- (17266-70-5)

oxindole (59-48-3)

2-phenylbenzothiazole (883-93-2)

2-phenylbenzoxazole (833-50-1)

1-Cyanobenzocyclobutene

N-acetyloxindole

o-chlorohydrocinnamonitrile (7315-17-5)

potassium salt of 3-acetyloxindole

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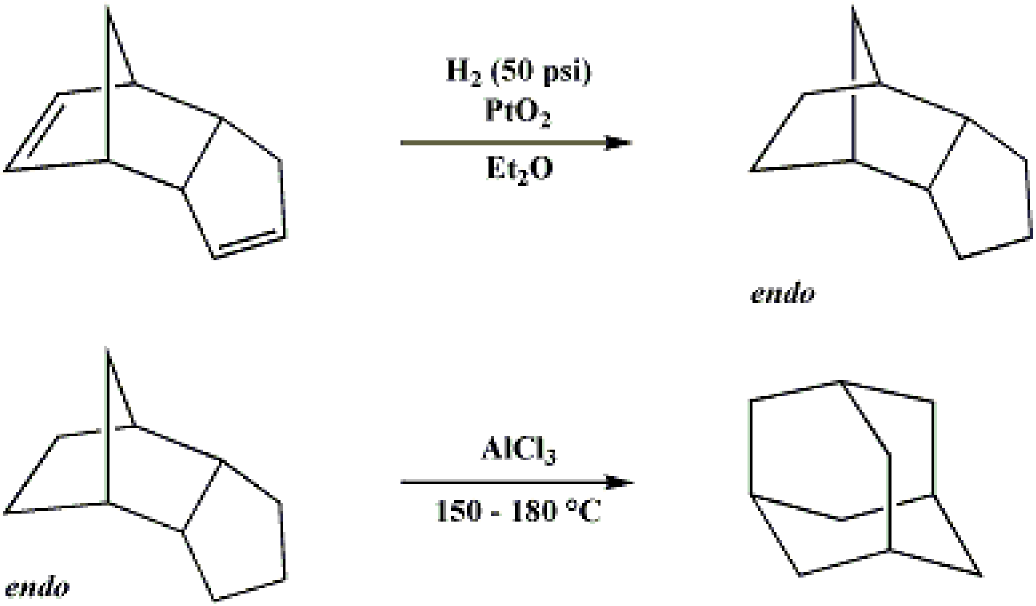
Organic Syntheses, CV 5, 16

ADAMANTANE

[Tricyclo[3.3.1.1[3,7]] decane]



Submitted by Paul von R. Schleyer, M. M. Donaldson, R. D. Nicholas, and C. Cupas[1].
Checked by William G. Dauben and Fred G. Willey.

1. Procedure

A. *endo-Tetrahydrodicyclopentadiene*. A solution of 200 g. (1.51 moles) of purified dicyclopentadiene (Note 1) in 100 ml. of dry ether containing 1.0 g. of platinum oxide is hydrogenated at 50 p.s.i. hydrogen pressure using a Parr apparatus. The reaction mixture becomes quite warm during the initial stage of the hydrogenation,[2] and the uptake of 2 mole equivalents of hydrogen requires 4–6 hours. The catalyst is removed by suction filtration, and the filtrate is distilled at atmospheric pressure through a 30-cm. Vigreux column.

When the removal of the ether is complete, the condenser at the top of the column is replaced by a wide-diameter adapter the bottom of which is placed in a receiver flask immersed in an ice bath. The adapter is heated (Note 2) to prevent premature solidification of the distillate. The distillation is continued and the *endo*-tetrahydrodicyclopentadiene, b.p. 191–193°, is collected. The yield is 196–200 g. (96.5–98.4%). The melting point depends on the purity of the starting material but generally is above 65°.

B. *Adamantane*. In a 500-ml. Erlenmeyer flask having a 24/40 standard taper joint are placed 200 g. (1.47 moles) of molten *endo*-tetrahydrodicyclopentadiene and a

magnetic stirring bar. A well-greased inner joint (2.2 × 15 cm., 24/40) is fitted into the top of the flask to serve as an air condenser, and 40 g. of anhydrous aluminum chloride is added through the opening (Note 3). The reaction mixture is simultaneously stirred and heated at 150–180° (Note 4), (Note 5) by means of a combination magnetic stirrer-hot plate. Aluminum chloride sublimes to the top of the flask, especially at the beginning of the reaction, and the accumulated sublimate is, from time to time, pushed down into the reaction liquid. After the mixture has been heated for 8–12 hours, the flask is removed from the hot plate-stirrer and the black contents upon cooling separate into two layers. The upper layer, a brown mush of adamantane and other products, is decanted carefully from the lower black tarry layer into a 600-ml. beaker. The Erlenmeyer flask is rinsed five times with a total of 250 ml. of petroleum ether (b. p. 30–60°) with decantation into the same beaker (Note 6), (Note 7). The petroleum ether suspension is warmed until all the adamantane is in solution; there should be an appreciable excess of solvent. The solution is decolorized by careful addition of 10 g. of chromatography-grade alumina, the hot solution filtered, and the alumina and the beaker washed thoroughly with solvent. The nearly colorless filtrate (Note 8) is concentrated to a volume of about 200 ml. by distillation and then cooled in a Dry Ice-acetone bath. The solid adamantane is removed by suction filtration and there results 27–30 g. (13.5–15.0%) of crystals, melting point about 255–260° (Note 9), (Note 10). One recrystallization from petroleum ether raises the melting point to 268–270° (Note 11), (Note 12).

2. Notes

1. Technical grade dicyclopentadiene is purified by distillation at water pump pressure through a 30-cm. Vigreux column, and the fraction boiling at 64–65°/14 mm. (72–73°/22 mm.) is used in the reaction. The best material is solid or semisolid at room temperature.
2. The adapter can readily be heated by placing an infrared lamp above it.
3. The evolution of heat initially observed is due to the exothermic rearrangement of *endo*-tetrahydrodicyclopentadiene to its *exo*-isomer.[3]
4. The temperature of the reaction is followed by inserting a thermometer into the reaction flask through the joint.
5. Other methods of heating and stirring may be used but are more troublesome because of the tendency of aluminum chloride to sublime and clog top-mounted stirrers.
6. If appreciable amounts of tar have been transferred to the beaker, repeat the decantation and washing process into a clean beaker.
7. The tarry flasks and beakers can be cleaned easily with acetone. *Do not use water* until all the tar has been removed.
8. If necessary, the filtrate should be warmed to dissolve all the adamantane.
9. The melting point must be taken in a sealed capillary, and the sealed portion must be completely immersed in the liquid of the melting-point bath.
10. Additional adamantane, 2–6 g., can be obtained by distilling the mother liquors through a 10-cm. Vigreux column and chilling the fraction boiling between 180° and 200°. The filtrate from the collection of the second portion of

adamantane consists mostly of *exo*-tetrahydrodicyclopentadiene.[3] The amount of this fraction, 30–100 g., depends on the severity of the rearrangement conditions. Much non-distillable residue is obtained. Conversion of the 180–200° fractions to adamantane is brought about by treating them with aluminum chloride as before, and the yields are comparable.

11. The recrystallization is not necessary unless material of the highest purity is desired.

12. 1-Methyladamantane and 1,3-dimethyladamantane can be prepared by analogous isomerizations.[4]

3. Discussion

Adamantane can be isolated from petroleum, where it is found in minute yield.[5] Two multistep syntheses starting with tetraethylbicyclo[3.3.1]nonane-2,6-dione-1,3,5,7-tetracarboxylate have been reported.[6] Also, starting with *endo*-tetrahydrodicyclopentadiene, it has been found that a catalyst composed of aluminum chloride and hydrogen chloride will bring about the rearrangement to adamantane in 30–40% yield, but the reaction must be performed in a hydrogen atmosphere at high pressure.[7] A recent patent describes the conversion in up to 30% yield using a boron trifluoride-hydrogen fluoride catalyst under pressure.[8] The present method is based on the published procedure of the submitters and is the preferred method by virtue of the greater convenience.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 20
- Org. Syn. Coll. Vol. 6, 48
- Org. Syn. Coll. Vol. 6, 378

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alumina

petroleum ether

hydrogen chloride (7647-01-0)

ether (60-29-7)

hydrogen (1333-74-0)

platinum oxide

hydrogen fluoride (7664-39-3)

acetone (67-64-1)

aluminum chloride (3495-54-3)

boron trifluoride (7637-07-2)

dicyclopentadiene

Adamantane, Tricyclo[3.3.1.1^{3,7}] decane (281-23-2)

1-Methyladamantane (768-91-2)

1,3-dimethyladamantane (702-79-4)

tetraethylbicyclo[3.3.1]nonane-2,6-dione-1,3,5,7-tetracarboxylate

endo-Tetrahydrodicyclopentadiene, exo-tetrahydrodicyclopentadiene (6004-38-2)

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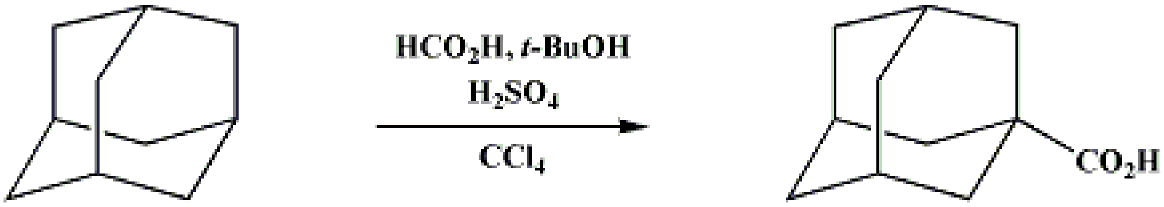
Organic Syntheses, CV 5, 20

1-ADAMANTANECARBOXYLIC ACID



Submitted by H. Koch and W. Haaf[1].
Checked by W. W. Prichard and B. C. McKusick.

1. Procedure

Caution! Because carbon monoxide is evolved, the reaction should be carried out in a good hood.

A 1-l. three-necked flask equipped with stirrer, thermometer, dropping funnel, and gas-outlet tube is charged with 470 g. (255 ml., 4.8 moles) of 96% sulfuric acid (Note 1), 100 ml. of carbon tetrachloride (Note 2), and 13.6 g. (0.100 mole) of adamantane.[2] The well-stirred mixture is cooled to 17–19° in an ice bath, and 1 ml. of 98% formic acid is added. Then a solution of 29.6 g. (38 ml., 0.40 mole) of *t*-butyl alcohol in 55 g. (1.2 moles) of 98–100% formic acid is added dropwise; the rate of addition and the cooling are regulated so that the addition requires 1–2 hours, and the temperature of the reaction mixture is kept at 17–25°. The reaction mixture is stirred for an additional 30 minutes and poured onto 700 g. of crushed ice. The layers are separated, and the upper, acid layer is extracted with three 100-ml. portions of carbon tetrachloride.

The combined carbon tetrachloride layers are shaken with 110 ml. of 15*N* ammonium hydroxide (Note 3), and the crystalline ammonium 1-adamantanecarboxlate that separates is collected on a Büchner funnel having a coarse fritted disk. The salt is washed with 20 ml. of cold acetone and suspended in 250 ml. of water. The suspension is made strongly acidic with 25 ml. of 12*N* hydrochloric acid and extracted with 100 ml. of chloroform. The chloroform layer is dried over anhydrous sodium sulfate and evaporated to dryness on a steam bath (Note 4). The residue is crude 1-adamantanecarboxylic acid; weight 12–13 g. (67–72%) (Note 5); m.p. 173–174°. Recrystallization of this product from a mixture of 30 ml. of methanol and about 10 ml. of water gives 10–11 g. (56–61%) of pure acid, m.p. 175–176.5° (Note 6).

2. Notes

1. Acid concentrations of 95–98% are satisfactory. The yield falls with concentrations lower than 95%.
2. Cyclohexane or *n*-hexane can be used in place of carbon tetrachloride.

Technical "normal hexane" may contain substantial amounts of methylcyclopentane and isohexane that lower the yield through formation of C_7-acids that are hard to remove.
3. A large amount of trimethylacetic acid and a small amount of at least one C_9-acid and one C_{13}-acid are formed from the *t*-butyl alcohol. The treatment with ammonia separates 1-adamantanecarboxylic acid from these acids, the ammonium salts of which remain in solution.
4. Acid that is satisfactory for most purposes may be obtained by interrupting the evaporation of the chloroform solution when crystals start to appear, cooling the concentrated chloroform solution to 0–5°, and collecting the acid on a Büchner funnel. The acid melts at 173–174°.
5. The checkers obtained similar yields when the quantity of reactants was increased fivefold.
6. As an alternative purification procedure, the checkers have esterified the crude acid by refluxing it for 2 hours with three times its weight of methanol and 2 ml. of 98% sulfuric acid. The solution is poured into 10 volumes of water and extracted with the minimum amount of chloroform required to give a clean separation of layers. The chloroform solution is washed with water, dried over calcium chloride, and distilled from a Claisen flask with an indented neck. Methyl 1-adamantanecarboxylate is collected at 77–79° (1 mm.); m.p. 38–39°. Hydrolysis of the ester with the calculated amount of 1*N* potassium hydroxide followed by acidification yields 1-adamantanecarboxylic acid; m.p. 175–176.5°; 90% overall recovery.

3. Discussion

1-Adamantanecarboxylic acid can be prepared by carboxylation of 1-adamantanol[3] or 1-bromoadamantane[3,4] by formic acid and 96% sulfuric acid; by carboxylation of adamantane by formic acid, *t*-butyl alcohol, and 96% sulfuric acid;[5] and by carboxylation of adamantane by formic acid and 130% sulfuric acid.[6]

4. Merits of the Preparation

This procedure illustrates a general method of carboxylating saturated hydrocarbons that have a tertiary hydrogen.[7] It has been used to convert isopentane to 2,2-dimethylbutanoic acid, 2,3-dimethylbutane to 2,2,3-trimethylbutanoic acid, and methylcyclohexane to 1-methylcyclohexanecarboxylic acid. The preparation of 1-methylcyclohexanecarboxylic acid by a variation of this procedure is described on p. 739 of this volume.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 739

8

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ammonium 1-adamantanecarboxlate

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

methanol (67-56-1)

hydrogen (1333-74-0)

carbon monoxide (630-08-0)

chloroform (67-66-3)

sodium sulfate (7757-82-6)

formic acid (64-18-6)

carbon tetrachloride (56-23-5)

cyclohexane (110-82-7)

acetone (67-64-1)

potassium hydroxide (1310-58-3)

ammonium hydroxide (1336-21-6)

methylcyclohexane (108-87-2)

Trimethylacetic acid (75-98-9)

isopentane (78-78-4)

n-hexane (110-54-3)

t-butyl alcohol (75-65-0)

Adamantane (281-23-2)

1-Adamantanecarboxylic acid (828-51-3)

methylcyclopentane (96-37-7)

isohexane (107-83-5)

Methyl 1-adamantanecarboxylate (711-01-3)

1-Adamantanol (768-95-6)

1-bromoadamantane (768-90-1)

2,2-dimethylbutanoic acid (595-37-9)

2,3-dimethylbutane (79-29-8)

2,2,3-trimethylbutanoic acid

1-Methylcyclohexanecarboxylic acid (1123-25-7)

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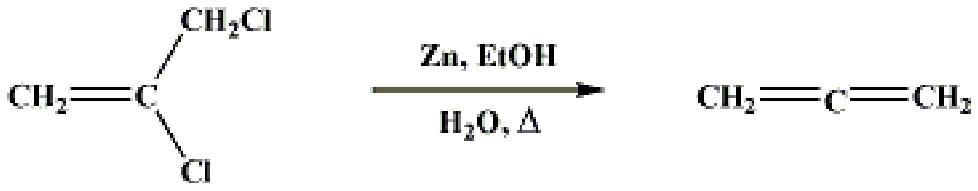
Organic Syntheses, CV 5, 22

ALLENE



Submitted by H. N. Cripps[1] and E. F. Kiefer[2].

Checked by W. E. Russey, R. D. Birkenmeyer, and F. Kagan[3].

1. Procedure

A 1-l. three-necked flask is equipped with a Hershberg stirrer operating in a ground-glass bearing (Note 1), a 250-ml. pressure-equalizing dropping funnel, and a coil condenser. The exit from the condenser is connected to a train consisting of a trap (of at least 50-ml. capacity below the bottom of the inlet tube) cooled in ice, a drying tube (about 6 in. long by 1 in. I.D.) filled with indicating Drierite and calcium chloride, an efficient trap of at least 150-ml. capacity cooled in Dry Ice-acetone to –70° or below, and a drying tube containing Drierite. A mixture of 95% ethanol (400 ml.), water (80 ml.), and 300 g. (4.6 g. atoms) of zinc dust is placed in the reaction flask. The addition funnel is charged with 260 g. (2.34 moles) of 2,3-dichloropropene (Note 2), the reaction mixture is stirred and heated to reflux, and the 2,3-dichloropropene is added dropwise at such a rate that reflux is maintained without external heating (2–3 hours). After the addition is complete, heating is resumed for 1 hour. The ice-cooled trap is warmed to about 25°, and the residual allene is purged from the reaction flask with a very slow stream of nitrogen.

The trap cooled in Dry Ice-acetone contains about 105 g. of crude product which, when distilled through a column packed with glass helices (Note 3), yields about 75 g. (80%) of allene (Note 4). No external heat is needed during the distillation. The distillation flask is allowed to warm to room temperature, the distillation beginning at a liquid temperature of –34° and virtually stopping at about 10°. The distilled product contains no detectable ethanol, water, 2,3-dichloropropene, or methylacetylene as determined by gas-liquid chromatography (Note 5).

2. Notes

1. The stirrer should be smooth running and gas-tight. The stirring motor (air-driven) should have a high torque because the reaction mixture tends to agglomerate as the reaction proceeds.
2. 2,3-Dichloropropene from Distillation Products or Columbia Chemicals was employed.
3. A vacuum-jacketed column 1 ft. long by 1 in. I.D. packed with glass helices

(4 mm. O.D.) is satisfactory for this distillation. It is fitted with a cold finger in the top of the column cooled by means of acetone that has been cooled in a Dry Ice bath. The fraction cutter is jacketed and similarly cooled. A small circulating pump is used to circulate acetone successively through copper coils in a Dry Ice bath, the fraction cutter, and the cold finger. When the fraction cutter is full, the bottom may be attached to a cooled, evacuated gas cylinder and the allene sucked into the cylinder.

4. The allene contains up to 3% of 2-chloropropene, determined by its vapor-phase infrared spectrum and by vapor-phase chromatography (Note 5).

5. The checkers used an F and M Model 500 gas chromatographic apparatus (F and M Scientific Corporation, P. O. Box 245, Avondale, Penn.) equipped with a polyester column (pentaerythritol adipate, 20% W/W on Chromasorb P, LAC-2-R446) 1 ft. by in. O.D., helium flow 45 cc. per minute, column temperature 50°, block temperature 215°, injector temperature 225°. This system was able to separate allene from methylacetylene and 2-chloropropene.

3. Discussion

Although many routes to allene are described in the literature, most preparations give a mixture of allene and methylacetylene. The virtue of the present preparation, which is essentially that described by Gustavson and Demjanoff,[4] is that it gives allene in a reproducible manner with 2-chloropropene as its only impurity.

Allene is an extremely useful reagent for cycloaddition reactions giving cyclobutane derivatives.[5] Allene dimer is also a useful and versatile starting material.[6]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 459

References and Notes

1. Contribution No. 566 from the Central Research Department, Experimental Station, E. I. du Pont de Nemours and Co., Wilmington, Delaware.
2. Gates and Crellin Laboratories of Chemistry, California Institute of Technology, Pasadena, California. Present Address: Department of Chemistry, University of Hawaii, Honolulu, Hawaii.
3. The Upjohn Company, Kalamazoo, Michigan.
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Appendix

Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

nitrogen (7727-37-9)

copper (7440-50-8)

acetone (67-64-1)

zinc (7440-66-6)

2,3-dichloropropene (78-88-6)

Allene (463-49-0)

methylacetylene (74-99-7)

2-chloropropene (557-98-2)

pentaerythritol adipate

helium (7440-59-7)

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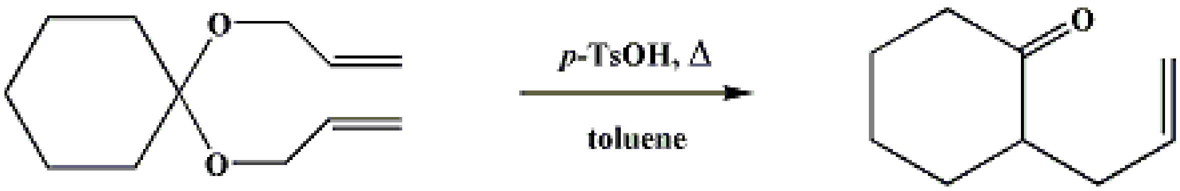
Organic Syntheses, CV 5, 25

2-ALLYLCYCLOHEXANONE

[Cyclohexanone, 2-allyl-]



Submitted by W. L. Howard and N. B. Lorette[1].
Checked by Melvin S. Newman and W. S. Gaugh.

1. Procedure

A solution of 196 g. (1 mole) of cyclohexanone diallyl acetal (Note 1), 150 g. of toluene, and 0.10 g. of *p*-toluenesulfonic acid is distilled through a good fractionating column (Note 2). In about 3 hours, 110 g. of distillate boiling at 91–92° (Note 3) is obtained and the temperature in the head then rises abruptly. The residue in the distilling flask is cooled and washed with 5 ml. of aqueous potassium carbonate to remove the acid. The remaining solution is passed through a filter containing anhydrous powdered magnesium sulfate and returned to the still. Most of the remaining toluene is removed by distillation at 100 mm. pressure (b.p. 52°). The receiver is changed, the pressure is reduced to 15 mm., and the last of the toluene is collected in a cold trap. The residual oil is rapidly vacuum-distilled to separate the product from a higher-boiling residue. Redistillation yields 117–126 g. (85–91%) of 2-allylcyclohexanone, b.p. 86–88°/15 mm., n_D^{25} 1.4670.

2. Notes

1. The preparation of cyclohexanone diallyl acetal is described on p. 292.
2. A 14-in. helices-packed column is sufficient.
3. This distillate is the azeotrope of toluene and allyl alcohol whose composition is about 50% allyl alcohol by weight.[2]

3. Discussion

2-Allylcyclohexanone has been prepared from the sodium derivative of cyclohexanone by alkylation with allyl bromide[3] or with allyl iodide,[4] and by ketonic hydrolysis of ethyl 1-allyl-2-ketocyclohexanecarboxylate.[5,6]

4. Merits of Preparation

This procedure, when combined with the preparation of allyl ketals (p. 292), provides a general method for obtaining allyl substitution alpha to a carbonyl group. A discussion of some of these applications, as well as the vinyl allyl ether rearrangement which is involved, has been given by Hurd and Pollack.[7] Also, the procedure can be repeated to allow the introduction of more than one allyl group.

References and Notes

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2. L. H. Horsley and co-workers, *Advances in Chem. Ser.*, No. 6, Azeotropic Data, American Chemical Society, Washington, 1955, p. 83.
3. C. A. VanderWerf and L. V. Lemmerman, *Org. Syntheses* Coll. Vol. 3, 44 (1955).
4. R. Cornubert, *Ann. Chim.*, [9] **16, 145** (1921).
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6. R. Grëwe, *Ber.*, **76**, 1075 (1943).
7. C. D. Hurd and M. A. Pollack, *J. Am. Chem. Soc.*, **60**, 1905 (1938).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium derivative of cyclohexanone

potassium carbonate (584-08-7)

Allyl bromide (106-95-6)

Allyl alcohol (107-18-6)

allyl iodide (556-56-9)

toluene (108-88-3)

magnesium sulfate (7487-88-9)

2-Allylcyclohexanone, Cyclohexanone, 2-allyl- (94-66-6)

ethyl 1-allyl-2-ketocyclohexanecarboxylate

Cyclohexanone diallyl acetal (53608-84-7)

p-toluenesulfonic acid (104-15-4)

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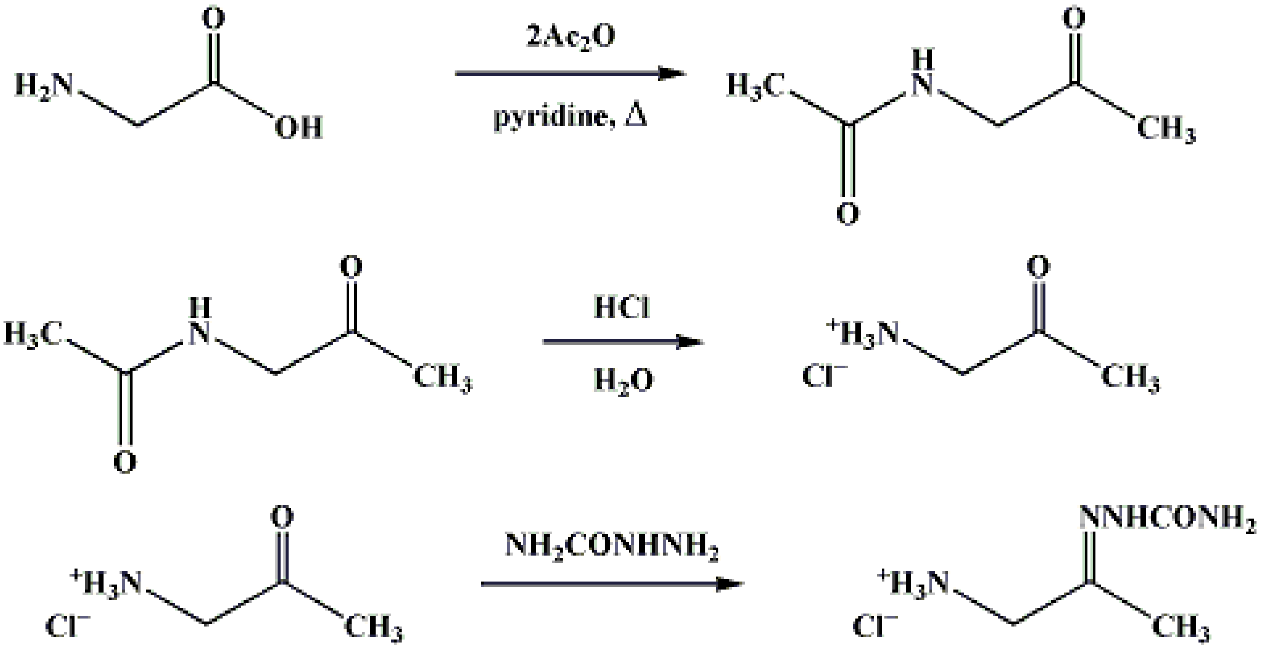
Organic Syntheses, CV 5, 27

AMINOACETONE SEMICARBAZONE HYDROCHLORIDE

[Amino-2-propanone, semicarbazone hydrochloride]



Submitted by John D. Hepworth[1]
Checked by W. T. Nolan and V. Boekelheide.

1. Procedure

A. *Acetamidoacetone*. A mixture of 75.0 g. (1.0 mole) of glycine (Note 1), 475 g. (485 ml., 6 moles) of pyridine (Note 1), and 1190 g. (1.1 l., 11.67 moles) of acetic anhydride (Note 1) and (Note 2) is heated under reflux with stirring for 6 hours (Note 3) in a 3-l., three-necked, round-bottomed flask. The reflux condenser is replaced by one set for downward distillation, and the excess pyridine, acetic anhydride, and acetic acid are removed by distillation under reduced pressure. The residue is transferred to a simple distillataion apparatus such as a Claisen flask and is distilled to give 80–90 g. (70–78%) of a pale yellow oil, b.p. 120–125° (1 mm.). This product is of satisfactory purity for use in step B.

B. *Aminoacetone hydrochloride*. A mixture of 175 ml. of concentrated hydrochloric acid and 175 ml. of water is added to 52 g. (0.45 mole) of the acetamidoacetone from step A contained in a 1-l. round-bottomed flask. The mixture is boiled under reflux under a nitrogen atmosphere (Note 4) for 6 hours. The resulting solution is concentrated using a flash evaporator held below 60° and with the condensation trap for solvent being cooled by a dry ice-acetone bath. The dark red oily residue (40–45 g.) is satisfactory for use in step C (Note 5).

C. *Aminoacetone semicarbazone hydrochloride*. The product from step B is dissolved in 250 ml. of absolute alcohol in a 1-l. Erlenmeyer flask, and to this solution is added a solution of 48 g. of semicarbazide hydrochloride (Note 1) in 100 ml. of water. The mixture is allowed to stand at room temperature for 2 hours, the crystalline precipitate is collected by suction filtration, and the off-white product is washed on the filter with absolute alcohol. The crystals, after air-drying, amount to 54–58 g. (72–78%) and melt at 208–210°. The product is essentially pure and can be used for most purposes without further purification (Note 6).

2. Notes

1. The glycine, pyridine, acetic anhydride, and semicarbazide hydrochloride employed were of reagent grade and were used directly as supplied.
2. This ratio of pyridine to acetic anhydride has been found to be the most satisfactory.
3. It is necessary that the mixture actually boil under reflux or the yield may drop to 25–30%.
4. The checkers used high-purity nitrogen. If ordinary commercial nitrogen is employed, the oxygen should be removed by passing the gas through Fieser's solution.
5. Aminoacetone hydrochloride is very hygroscopic and is best stored as the semicarbazone. If the compound itself is desired, however, the dark red oil is dried under reduced pressure over phosphorus pentoxide. The resulting crystalline aminoacetone hydrochloride can be purified by dissolving it in absolute ethanol and precipitating it by the addition of dry ether.
6. For further purification, the semicarbazone hydrochloride may be recrystallized from aqueous ethanol to give colorless crystals, m.p. 212°.

3. Discussion

This preparation is based on the procedure used to synthesize 3-acetamido-2-butanone.[2] Aminoacetone hydrochloride has been prepared from isopropylamine via the N,N-dichloroisopropylamine,[3] from hexamethylenetetramine and chloroacetone,[4] by reduction of nitroacetone[5] or isontirosoacetone,[6] and from phthalimidoacetone by acid hydrolysis,[6] cited as the most convenient method of preparation.[7] The semicarbazone has been prepared previously in the same manner.[8].

4. Merits of the Preparation

Aminoacetone is a versatile starting material for many syntheses, particularly for the preparation of heterocycles. The present procedure describes a convenient method for its preparation in a form suitable for storage. The aminoacetone can be generated from aminoacetone semicarbazone hydrochloride *in situ* as needed.

References and Notes

1. Department of Chemistry, College of Technology, Huddersfield, England; present address, North Lindsey Technical College, Scunthorpe, England.
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

semicarbazone

semicarbazone hydrochloride

isontirosoacetone

alcohol, ethanol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ether (60-29-7)

acetic anhydride (108-24-7)

oxygen (7782-44-7)

nitrogen (7727-37-9)

pyridine (110-86-1)

Glycine (513-29-1)

hexamethylenetetramine (100-97-0)

chloroacetone (78-95-5)

aminoacetone (298-08-8)

isopropylamine (75-31-0)

3-Acetamido-2-butanone (6628-81-5)

Aminoacetone semicarbazone hydrochloride, Amino-2-propanone, semicarbazone hydrochloride (10469-70-2)

Acetamidoacetone (7737-16-8)

semicarbazide hydrochloride (563-41-7)

Aminoacetone hydrochloride

N,N-dichloroisopropylamine

nitroacetone (10230-68-9)

phthalimidoacetone (3416-57-7)

phosphorus pentoxide (1314-56-3)

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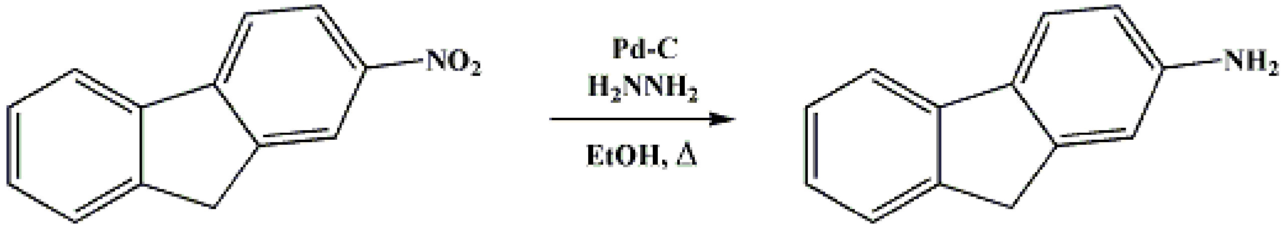
Organic Syntheses, CV 5, 30

2-AMINOFLUORENE

[2-Flurenylamine]



Submitted by P. M. G. Bavin[1]
Checked by John C. Sheehan and Roger E. Chandler..

1. Procedure

In a 2-l. three-necked round-bottomed flask, equipped with a mechanical stirrer (Note 1), reflux condenser, and dropping funnel, are placed 30 g. of pure 2-nitrofluorene, m.p. 157° [*Org. Syntheses*, Coll. Vol. **2**, 447 (1943)], and 250 ml. of 95% ethanol. After warming to 50° on a steam bath, 0.1 g. of palladized charcoal catalyst (previously moistened with alcohol) is added (Note 2) and the stirrer is started. About 15 ml. of hydrazine hydrate is added from the dropping funnel during 30 minutes (Note 3). At this point an additional 0.1 g. of catalyst (previously moistened with alcohol) is added and the mixture is heated until the alcohol refluxes gently. After 1 hour the nitrofluorene has dissolved completely and the supernatant liquor is almost colorless.

The catalyst is removed by filtration with gentle suction through a thin layer of Celite (Note 4). The flask is rinsed with 30 ml. of hot alcohol which is then used to wash the catalyst and Celite. The combined filtrates are concentrated under reduced pressure to about 50 ml. (Note 5) and then heated to boiling at atmospheric pressure. When 250 ml. of hot water is added slowly, 2-aminofluorene is precipitated as a colorless, crystalline powder. After cooling in an ice bath, the 2-aminofluorene is collected, washed with water, and dried in the dark in a vacuum desiccator. The product melts at 127.8–128.8° (Note 6) and amounts to 24–25 g. (93–96%).

2. Notes

1. If the stirring is omitted, the nitrofluorene takes longer to dissolve.
2. A suitable catalyst is 10% palladium-on-charcoal, such as is supplied by Baker and Company, Inc., 113 Astor Street, Newark 5, New Jersey.
3. The reaction is exothermic, and too rapid addition of the hydrazine may cause the mixture to foam out of the condenser.
4. *Caution! The catalyst is often pyrophoric and should be kept moistened with alcohol.* Celite is a diatomaceous earth filter aid.
5. A rotary evaporator is very convenient for the concentration since some of the amine invariably crystallizes toward the end.
6. The melting point is that reported in *Organic Syntheses*, Coll. Vol. **2**, 448 (1943), for a recrystallized sample.

3. Discussion

The preparation of 2-aminofluorene reported previously in *Organic Syntheses* [Coll. Vol. **2**, 448 (1943)] we based on the method of Diels.[2]

The present procedure illustrates a general method for the reduction of aromatic nitro compounds to aromatic amines using hydrazine and a hydrogenation catalyst such as palladium, platinum, nickel, iron, or rethenium. The literature on this procedure up to 1963 has been reviewed.[3] In many instances the catalytic hydrazine reductions give yields of amine equal to or better than those obtained by direct catalytic hydrogenation or other reduction methods. Both the apparatus and the procedure are simple. Under appropriate conditions the method may be used for the dehalogenation of aliphatic and aromatic halides,[3] a reaction for which palladium appears to be a specific catalyst. The method has also been used for the reduction of azobenzene and azoxybenzene to hydrazobenzene (80–90%),[4] as well as for the synthesis of steroid aziridines by reduction of mesylate esters by vicinal azido alcohols (using Raney nickel).[5]

References and Notes

1. National Research Council of Canada Post-doctorate Fellow, 1954-56, at the University of Ottawa, Ottawa, Ontario.
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3. A. Furst, R. C. Berlo, and S. Hooton, *Chem. Rev.*, **65**, 51 (1965).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

2-Flurenylamine

palladized charcoal catalyst

palladium-on-charcoal

ethanol (64-17-5)

iron (7439-89-6)

platinum (7440-06-4)

nickel, Raney nickel (7440-02-0)

palladium (7440-05-3)

hydrazine hydrate (7803-57-8)

hydrazine (302-01-2)

Azoxybenzene (495-48-7)

Azobenzene (103-33-3)

2-Nitrofluorene (607-57-8)

2-Aminofluorene (153-78-6)

Nitrofluorene

rethenium

hydrazobenzene (122-66-7)

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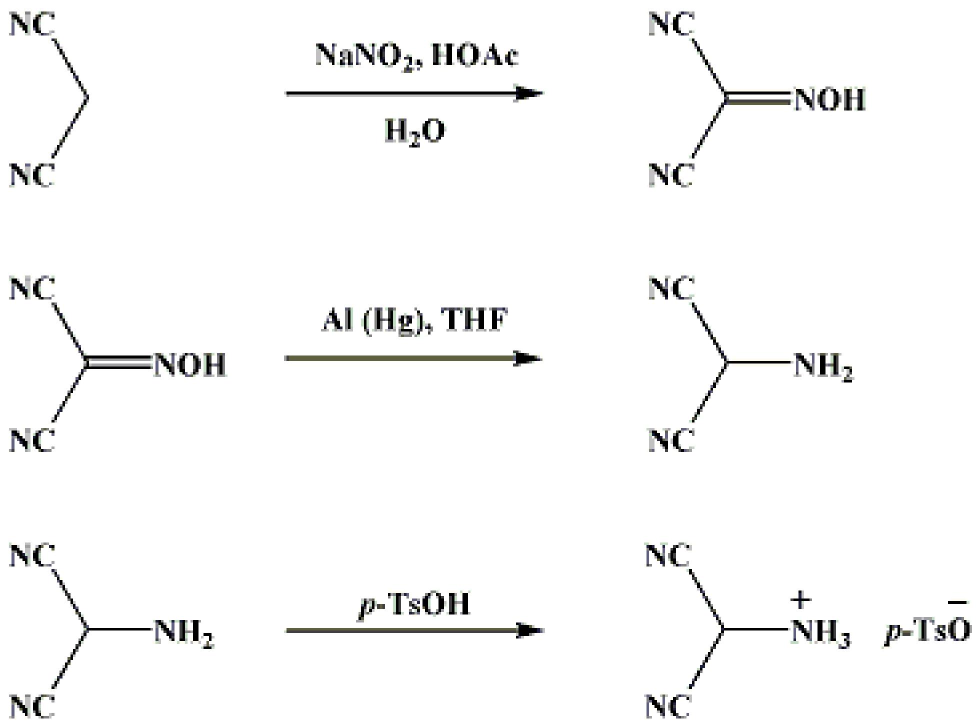
Organic Syntheses, CV 5, 32

AMINOMALONONITRILE *p*-TOLUENESULFONATE

[Malononitrile, amino-, *p*-toluenesulfonate]



Submitted by J. P. Ferris, R. A. Sanchez, and R. W. Mancuso[1].
Checked by O. W. Webster and R. E. Benson.

1. Procedure

A. *Oximinomalononitrile*. Malononitrile (Note 1) (25 g., 0.38 mole) is dissolved in a mixture of 20 ml. of water and 100 ml. of acetic acid in a 1-l. round-bottomed flask equipped with a stirrer, a thermometer, and a powder funnel. The solution is cooled to –10° with a dry ice-acetone bath, and 50 g. (0.72 mole) of granulated sodium nitrite is added in approximately 2-g. portions over a 30-minute period while the temperature is maintained at 0° to –10°. After the addition is complete a wet ice bath is used to maintain the temperature below 5° while the mixture is stirred for 4 hours. Four hundred milliliters of tetrahydrofuran (Note 2) and 400 ml. of ether are added in separate portions, and the mixture is stored at –40° overnight. The mixture is filtered rapidly, and the solid is washed with a mixture of 200 ml. of tetrahydrofuran (Note 2) and 200 ml. of ether. The filtrate and washings are combined and concentrated by distillation to a volume of 250 ml. by the use of a water aspirator and a bath at 40° (Note 3). This solution of oximinomalononitrile is used directly in the next step.

B. *Aminomalononitrile p-toluenesulfonate*. Aluminum foil (13.7 g., 0.51 g. atom) is cut into half-inch squares and is covered with a 5% aqueous solution of mercuric chloride until a mercury coating is visible on the aluminum (*ca.* 30 seconds). The

mercuric chloride solution is decanted, and the amalgamated aluminum is washed twice with water, once with ethanol, and twice with tetrahydrofuran (Note 2). The amalgamated aluminum is transferred to a 2-l. round-bottomed flask fitted with a condenser, a stirrer, and a 250-ml. addition funnel and is covered immediately with 300 ml. of tetrahydrofuran (Note 2). The mixture is cooled in a dry ice-acetone bath, and the solution of oximinomalononitrile from procedure A is added with stirring over a 15-minute period while the temperature is maintained at −15° to −30°. Stirring is continued for an additional 5 minutes. The dry-ice acetone bath is then removed, and the mixture is allowed to warm to room temperature. (*Caution! Cooling with a dry ice-acetone bath is usually needed to control the reaction.*) After the spontaneous reaction subsides, the mixture is warmed to reflux until most of the aluminum is consumed (45 minutes). The reaction mixture is cooled to room temperature, 200 ml. of ether is added with stirring, and the aluminum salts are removed by vacuum filtration through Celite filter aid. The solid is washed with 250 ml. of tetrahydrofuran (Note 2) followed by 500 ml. of ether (Note 3) and (Note 4). The original filtrate and washings are combined and concentrated to about 250 ml. by the use of a water aspirator and a bath at 40°. To the resulting brown solution is slowly added with stirring a mixture of 60 g. (0.32 mole) of *p*-toluenesulfonic acid monohydrate as a slurry in 250 ml. of ether (Note 5). The total volume is brought to 1 l. with ether, the mixture is cooled to 0°, and the crystalline solid is collected by vacuum filtration. The product is washed successively with 200 ml. of ether, 200 ml. of cold (0°) acetonitrile, and 200 ml. of ether and dried at 25° (1 mm.) to give light tan crystals, m.p. 169–171° (dec.); yield, 75–79 g. (78–82%).

This product is suitable for most synthetic purposes. An almost colorless product may be obtained by recrystallization from boiling acetonitrile (100 ml. dissolves 1.8 g. of product) with treatment with activated carbon. The recovery of aminomalononitrile *p*-toluenesulfonate, m.p. 172° (dec.), is *ca.* 80%.

2. Notes

1. Commercial malononitrile is purified by dissolving 260 g. in 1 l. of ether, refluxing the solution with 5 g. of activated carbon for 10 minutes, and filtering through Celite under vacuum. The malononitrile crystallizes from the filtrate as a result of the cooling and concentration during the filtration. It is collected by filtration and washed with 350 ml. of cold (–20°) ether to give 214 g. of white crystals.
2. Tetrahydrofuran from Fisher Scientific Co. was used by the checkers. *[Caution! See page 976 for a warning regarding the purification of tetrahydrofuran.]*
3. Occasionally a precipitate may form in the filtrate. It is removed by filtration before proceeding to the next step.
4. Additional washing is necessary if the washings are not colorless at this point.
5. One can check for complete precipitation of the aminomalononitrile by adding *p*-toluenesulfonic acid to the clear supernatant liquid.

3. Discussion

The present procedure is a modification of the original synthesis.[2] Previous reports of the synthesis of aminomalononitrile are in error.[2] Oximinomalononitrile was prepared by a modification of the procedure of Ponzio.[3]

4. Merits of the Preparation

This procedure provides a convenient synthesis of aminomalononitrile, which has been demonstrated to be a useful intermediate for the preparation of substituted imidazoles, thiazoles, oxazoles, purines, and purine-related heterocycles.[2] It is also a convenient starting material for the preparation of diaminomaleonitrile.[2,4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 344

References and Notes

1. The Salk Institute for Biological Studies, San Diego, California [Present address (J.P. F.): Department of Chemistry, Rensselaer Polytechnic Institute, Troy, New York 12181].
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3. G. Ponzio, *Gazz. Chim. Ital.*, **61**, 561 (1931).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Amalgamated aluminum

ethanol (64-17-5)

acetic acid (64-19-7)

ether (60-29-7)

acetonitrile (75-05-8)

sodium nitrite (7632-00-0)

aluminum, Aluminum foil (7429-90-5)

mercury (7439-97-6)

carbon (7782-42-5)

mercuric chloride (7487-94-7)

Malononitrile (109-77-3)

Tetrahydrofuran (109-99-9)

Oximinomalononitrile (36568-05-5)

aminomalononitrile

Diaminomaleonitrile (1187-42-4)

p-toluenesulfonic acid (104-15-4)

p-toluenesulfonic acid monohydrate (6192-52-5)

Aminomalononitrile p-toluenesulfonate, Malononitrile, amino-, p-toluenesulfonate (5098-14-6)

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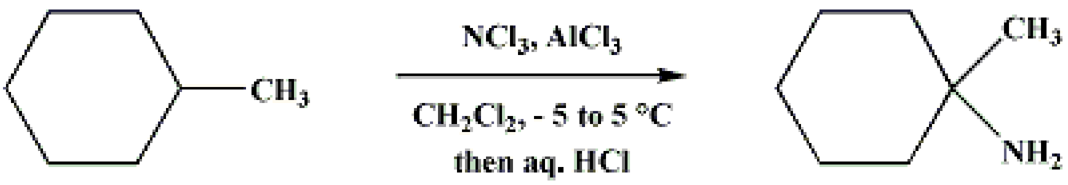
Organic Syntheses, CV 5, 35

1-AMINO-1-METHYLCYCLOHEXANE

[Cyclohexylamine, 1-methyl-]



Submitted by Peter Kovacic and Sohan S. Chaudhary[1].
Checked by R. A. Haggard and William D. Emmons.

1. Procedure

Caution! The reactions should be carried out in a hood behind a protective screen since trichloramine is noxious and potentially explosive; however, no difficulties from decomposition have been encountered under the conditions described.

A. *Trichloramine*. A mixture of 600 ml. of water (Note 2), 900 ml. of methylene chloride (Note 3), and 270 g. (1.32 moles) of calcium hypochlorite (Note 4) is cooled to 0–10° in a 3-l., three-necked, vented flask equipped with a stirrer, a thermometer, and a dropping funnel. A solution of 66.0 g. (1.23 moles) of ammonium chloride in 150 ml. of concentrated hydrochloric acid and 450 ml. of water is added dropwise with stirring over a 1-hour period at 0–10°. After an additional 20 minutes of stirring, the organic layer is separated, washed with three 200-ml. portions of cold water, and dried over anhydrous sodium sulfate. The yellow solution is filtered, and the trichloramine concentration is determined by iodometric titration (Note 5).

B. *1-Amino-1-methylcyclohexane*. A 3-l. three-necked flask is fitted with a paddle stirrer, a condenser, a thermometer, and a dropping funnel with an extension for below-surface addition. Provision is made for introduction of nitrogen by use of a side-arm adapter. The vessel is charged with 196 g. (2.0 moles) of methylcyclohexane (Note 6) and 106 g. (0.80 mole) of anhydrous aluminum chloride. A solution (*ca.* 600 ml.) of trichloramine (0.40 mole) in methylene chloride is added with efficient stirring over a period of 2 hours at −5° to 5° (Note 7). Throughout the reaction a stream of nitrogen is passed through the flask (Note 8). The brown mixture is stirred for an additional 20–30 minutes at the same temperature.

The reaction mixture is then added with good stirring to a slurry of 800–900 g. of ice and 50 ml. of concentrated hydrochloric acid (Note 9). The layers are separated, and the dark organic layer is washed with three 100-ml. portions of 5% hydrochloric acid and discarded. Traces of non-basic organic material are removed from the combined aqueous layer and washings by extraction with pure ether (Note 10) until the extract is

colorless. The aqueous solution is treated with 600 ml. of 50% aqueous sodium hydroxide (Note 11) with cooling, and the basic organic product is extracted with three 125-ml. portions of pure ether (Note 10). The ethereal solution is dried over sodium sulfate, and the solvent is distilled on the steam bath to give 42–46 g. of a clear, amber product (Note 12). To this crude product is added 10 g. of triethylenetetramine (Note 13). Distillation through a small Vigreux column yields 21.5–30 g. (48–67%, based on trichloramine) of 1-amino-1-methylcyclohexane, b.p. 44–49° (20–25 mm.), n^{22}D 1.4516 (Note 14).

2. Notes

1. The stoichiometry of the reaction is not known.
2. Deionized water is used throughout.
3. Commercial methylene chloride was distilled before use by the submitters. The checkers used reagent grade methylene chloride without distillation.
4. Calcium hypochlorite is obtained as "HTH" (Olin Mathieson Chemical Co., 70% purity).
5. Iodometric determination of positive chlorine is carried out as follows: 2.0 g. of potassium iodide or sodium iodide is dissolved in 10 ml. of water, and 40 ml. of glacial acetic acid is added. Into this solution is pipetted 1.0 ml. of the methylene chloride solution of trichloramine. The liberated iodine is titrated with 0.100*N* sodium thiosulfate. The solution is found to be 0.6–0.7*M* in trichloramine. Storage for several days at 0–5° results in negligible decomposition, although it is not recommended unless adequate safety precautions are observed. Excess methylene chloride-trichloramine solution can be conveniently disposed of by its slow addition to a cold, stirred, dilute aqueous solution of sodium metabisulfite.
6. A pure grade of methylcyclohexane (Eastman Organic Chemicals) is used. Subsequent to the checking of this preparation, the submitters reported 69–72% yields with 78.4 g. (0.80 mole) of methylcyclohexane.[2] In this case a 1-l. three-necked flask is employed for the reaction; the remainder of the procedure is unchanged.
7. Cooling is accomplished with either an ice-salt bath or preferably a dry ice-acetone bath. The time of addition can be reduced to 1 hour by use of the latter. However, if the temperature is much below that designated, unchanged trichloramine accumulates, resulting eventually in an uncontrollable reaction.
8. Purging with nitrogen results in some increase in yield. If the flow is too vigorous, trichloramine is lost by volatilization.
9. The mixture can be stored overnight at this stage.
10. High-purity ether (*e.g.*, Baker Analyzed Reagent) is used since a grade of lower quality gives a product that is more difficult to purify because of contamination with alcohol.
11. Excess sodium hydroxide is needed to dissolve the aluminum-containing precipitate.
12. The last portion of solvent is carefully removed at the water aspirator.

13. Triethylenetetramine (redistilled, Eastman Organic Chemicals) prevents bumping and foaming and acts as a chaser for the distillation.
14. The product contains less than 10% of lower-boiling impurities determined (by the checkers) by vapor-phase chromatography with a column packed with 15% XF-1150 on Chromosorb W. Further purification can be effected readily with good recovery by drying over sodium hydroxide pellets and fractionating at atmospheric pressure through an efficient spinning band column, with collection of the fraction, b.p. 142–146°, n^{22}_{D} 1.4522.

3. Discussion

In addition to the present method,[2] 1-amino-1-methylcyclohexane has been synthesized by the following procedures: Ritter reaction, *e.g.*, with 1-methylcyclohexanol (76%, 67%)[3,4] or 1-methylcyclohexene (35%);[4] Hofmann reaction with 1-methylcyclohexanecarboxamide (80% as hydrochloride);[5] reduction of 1-methyl-1-nitrocyclohexane (63%);[5] Schmidt reaction with 1-methylcyclohexanecarboxylic acid (42%).[6]

4. Merits of the Preparation

This procedure constitutes the first example of one-step conversion of a *t*-alkane to the corresponding *t*-alkylamine. Other hydrocarbons in this class, such as isobutane, have also been aminated with good results.[7] Only a very limited number of convenient routes, *e.g.*, the Ritter reaction, are available for the preparation of *t*-carbinamines. The present preparation illustrates a simple method that utilizes a novel substrate.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium metabisulfite

methylene chloride-trichloramine

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ether (60-29-7)

ammonium chloride (12125-02-9)

sodium hydroxide (1310-73-2)

sodium sulfate (7757-82-6)

potassium iodide (7681-11-0)

sodium thiosulfate (7772-98-7)

nitrogen (7727-37-9)

iodine (7553-56-2)

aluminum chloride (3495-54-3)

chlorine (7782-50-5)

sodium iodide (7681-82-5)

methylcyclohexane (108-87-2)

methylene chloride (75-09-2)

calcium hypochlorite (7778-54-3)

1-methylcyclohexene

1-Methylcyclohexanecarboxylic acid (1123-25-7)

1-Amino-1-methylcyclohexane, Cyclohexylamine, 1-methyl- (6526-78-9)

trichloramine (10025-85-1)

triethylenetetramine (112-24-3)

1-Methylcyclohexanol (590-67-0)

1-methylcyclohexanecarboxamide

1-methyl-1-nitrocyclohexane

isobutane (75-28-5)

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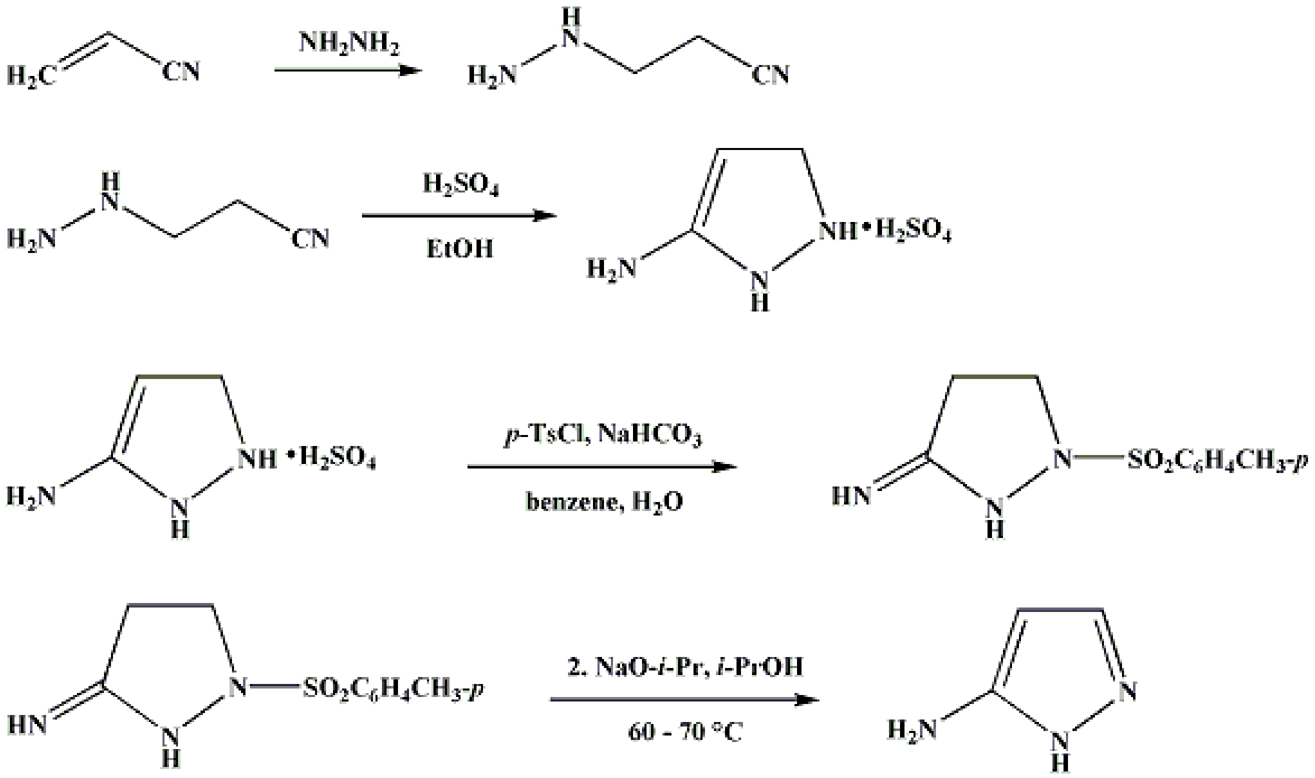
3(5)-AMINOPYRAZOLE

[Pyrazole, 3(or 5)-amino-]



Submitted by H. Dorn and A. Zubek[1].
Checked by L. G. Vaughan and R. E. Benson.

1. Procedure

A. *β-Cyanoethylhydrazine*. To a 2-l. two-necked flask fitted with a thermometer and a pressure-equalizing funnel are added a large magnetic stirring bar and 417 g. (6.00 moles of $N_2H_4 \cdot H_2O$) of 72% aqueous hydrazine hydrate. Acrylonitrile (318 g., 6.00 moles) is gradually added with stirring during 2 hours. The internal temperature is kept at 30–35° by occasional cooling of the flask. The funnel is replaced by a distillation condenser. Removal of water by distillation at 40 mm. at a bath temperature of 45–50° gives 490–511 g. (96–100%) of β-cyanoethylhydrazine as a yellow oil that is suitable for use in the next step. This product can be purified by distillation; b.p. 76–79° (0.5 mm.).

B. *3-Amino-3-pyrazoline sulfate*. In a 2-l. four-necked flask equipped with a reflux condenser, a dropping funnel, a thermometer, and a mechanical stirrer with four blades (Note 1) is placed 308 g. (169 ml., 3.0 moles) of 95% sulfuric acid (sp. gr. 1.834). Absolute ethanol (450 ml.) is added dropwise over 20–30 minutes. The internal temperature is maintained at 35° by cooling. A solution of 85.1 g. (1.00 mole) of β-cyanoethylhydrazine in 50 ml. of absolute ethanol is added with vigorous stirring over 1–2 minutes without further cooling (Note 1). The mixture warms spontaneously to 88–90° and is kept at this temperature for 3 minutes until the product begins to crystallize. The temperature of the stirred mixture is gradually lowered during the next hour to 25° by cooling with water, and the mixture is then allowed to stand at room temperature for 15–20 hours. The crystals are collected by filtration and washed three times with 80 ml. of absolute ethanol and finally with 80 ml. of ether. After being dried at 80° the product weighs 177–183 g. (97–100%), m.p. 143–144° (Note 2). The product is sufficiently pure for use in the following step; it may be recrystallized from methanol to give white needles, m.p. 144–145° (Note 2).

C. *3-Imino-1-(p-tolylsulfonyl)Pyrazolidine*. To a 3-l. four-necked flask fitted with a condenser, a

thermometer, a wide-mouthed funnel, and a high-speed mechanical stirrer having five pairs of blades are added 183 g. (1.00 mole) of 3-amino-3-pyrazoline sulfate and 1 l. of water. Sodium bicarbonate (210 g., 2.5 moles) is gradually added during 10 minutes with stirring. The rate of stirring is increased to 5000–6000 r.p.m., and a solution of 229 g. (1.20 moles) of *p*-toluenesulfonyl chloride in 400 ml. of benzene containing 0.5 g. of sodium dodecylbenzenesulfonate (Note 3) is added at one time. Three further portions of sodium bicarbonate are added sequentially: 25.2 g. (0.30 mole) after 15 minutes; 16.8 g. (0.20 mole) after 30 minutes; 16.8 g. (0.20 mole) after 55 minutes. The mixture is stirred for 5 hours at 18–25°, occasional cooling being required. Sodium bicarbonate (8.4 g., 0.10 mole) is added, then 200 ml. of ether, and stirring is continued for another hour. The colorless product is collected by filtration on a sintered-glass funnel, washed with three 50-ml. portions of ether followed by 50 ml. of water and dried at 90°. The yield is 139–180 g. (58–75%); m.p. 183–185° (Note 4). The product is used directly in the next step.

D. *3(5)-Aminopyrazole* (Note 5). *(Caution! Because hydrogen gas is evolved, this reaction should be conducted in an efficient hood in the absence of an ignition source.)* A solution of sodium isopropoxide is prepared from 18.4 g. (0.80 g. atom) of sodium and 500 ml. of isopropyl alcohol in a 2-l. four-necked flask fitted with a mechanical stirrer, a thermometer, a reflux condenser, and a stopper. The reflux condenser is fitted with a nitrogen-inlet line attached to a bubbler device to maintain an anhydrous atmosphere. After all the sodium has dissolved, the temperature is adjusted to 60–70°, the stopper is replaced by a wide-mouthed funnel, and 191 g. (0.80 mole) of 3-imino-1-(*p*-tolylsulfonyl)-pyrazolidine is added gradually over 10 minutes to the hot solution under a blanket of nitrogen. The funnel is replaced by the stopper, and the mixture is stirred vigorously and then refluxed briefly. Stirring is continued, and the mixture is allowed to cool to room temperature during 2 hours. The precipitated sodium *p*-toluenesulfinate (140–142 g.) is removed by filtration and washed with a total of 100 ml. of isopropyl alcohol in several portions. The filtrate is treated twice with 4-g. portions of Norit activated carbon. The solvent is removed by distillation, the final trace being removed at a bath temperature of 50° (20 mm.) to give 62–66 g. (93–99%) of 3(5)-aminopyrazole as a light yellow oil. This is purified by distillation to give the product as a yellow oil, b.p. 100–102° (0.01 mm.), in 74–84% recovery (Note 6). The product crystallizes on cooling; m.p. 37–39° (Note 7). Its n.m.r. spectrum (60 MHz, dimethyl sulfoxide-d_6) shows two one-proton doublets at δ 7.33 and 5.52 p.p.m. (J = 2 Hz) and a broad three-proton singlet at δ 7.05 p.p.m. that is absent after addition of D_2O.

2. Notes

1. A stirrer with large blades operating at high speed is essential. Inadequate stirring results in solidification of the reaction mixture and makes proper washing of the product very difficult.
2. The checkers found melting points of 138–141° and 140–142°. After three recrystallizations from methanol the product has a melting point of 139.7–140°. The product appeared to be unstable to prolonged heating in methanol.
3. This salt serves as an emulsifying agent.
4. A sample, m.p. 184–185°, prepared by recrystallization of the product from nitromethane, gives satisfactory elemental analytical data. Its n.m.r. spectrum (60 MHz, dimethyl sulfoxide-d_6) reveals that the compound exists in the iminopyrazolidine form under these conditions; signals at δ 7.72 p.p.m. (doublet, J = 8.4 Hz), 7.40 p.p.m. (doublet, J = 8.4 Hz), 6.1 p.p.m. (broad singlet; absent after addition of D_2O), 3.4 p.p.m. (triplet, J = 9.0 Hz), and 2.4 p.p.m. (sharp singlet superimposed on triplet) with relative intensities of 2:2:2:2:5. The signals at 7.72 and 7.40 p.p.m. are assigned to the four aromatic protons, that at 6.1 p.p.m. to the two N-H protons, that at 3.4 p.p.m. to one pair of methylene protons, and that at 2.4 p.p.m. to the second pair of methylene protons plus the protons of the methyl group.
5. 3(5)-Aminopyrazole may also be obtained by hydrolysis of 3-imino-1-(*p*-tolylsulfonyl)pyrazolidine with aqueous alkali. In this case the pyrazolidine (239 g., 1.00 mole) is added to a solution of 40 g. (1.0 mole) of sodium hydroxide in 250 ml. of water at 75°, the resulting solution is stirred briefly, and the water is removed at reduced pressure. 3(5)-Aminopyrazole is separated from the sodium *p*-toluenesulfinate by several extractions with isopropyl alcohol.
6. In order to obtain maximum recovery the submitters conducted the distillation of 120 g. of crude product for 7–10 hours.
7. The checkers observed b.p. 119–121° (1.0 mm.) and m.p. 34–37°.

3. Discussion

3(5)-Aminopyrazole has been prepared by a Curtius degradation of pyrazole-3(5)-carboxylic acid hydrazide,[2,3] by saponification and decarboxylation of ethyl 3-aminopyrazole-4-carboxylate[4] obtained from ethyl ethoxymethylenecyanoacetate and hydrazine, and by the present procedure.[5,6]

4. Merits of the Preparation

This procedure represents the most convenient synthesis of 3(5)-aminopyrazole. It employs readily available starting materials and gives excellent yields in all steps.[5,6] *p*-Toluenesulfonyl chloride can be replaced by other arenesulfonyl chlorides. 3-Imino-1-arylsulfonylpyrazolidines can be alkylated with dimethyl sulfate or with alkyl *p*-toluenesulfonates in dimethylformamide to give salts of 1-alkyl-2-arylsulfonyl-5-amino-4-pyrazolines from which arenesulfinate can be eliminated as described in procedure D. In this fashion 1-alkyl-5-aminopyrazoles can be easily prepared.[6]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

D_2O

3(5)-Aminopyrazole

Pyrazole, 3(or 5)-amino-

ethanol (64-17-5)

sulfuric acid (7664-93-9)

Benzene (71-43-2)

methanol (67-56-1)

ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

nitrogen (7727-37-9)

dimethyl sulfate (77-78-1)

Norit activated carbon (7782-42-5)

sodium (13966-32-0)

isopropyl alcohol (67-63-0)

sodium isopropoxide (683-60-3)

hydrazine hydrate (7803-57-8)

hydrazine (302-01-2)

Nitromethane (75-52-5)

methylene (2465-56-7)

acrylonitrile (107-13-1)

dimethylformamide (68-12-2)

ethyl ethoxymethylenecyanoacetate

β-Cyanoethylhydrazine (353-07-1)

3-Amino-3-pyrazoline sulfate (29574-26-3)

sodium dodecylbenzenesulfonate (2211-98-5)

pyrazolidine (504-70-1)

ethyl 3-aminopyrazole-4-carboxylate (6994-25-8)

p-Toluenesulfonyl chloride (98-59-9)

Sodium p-toluenesulfinate

3-imino-1-(p-tolylsulfonyl)pyrazolidine, 3-imino-1-(p-tolylsulfonyl)-pyrazolidine (1018-36-6)

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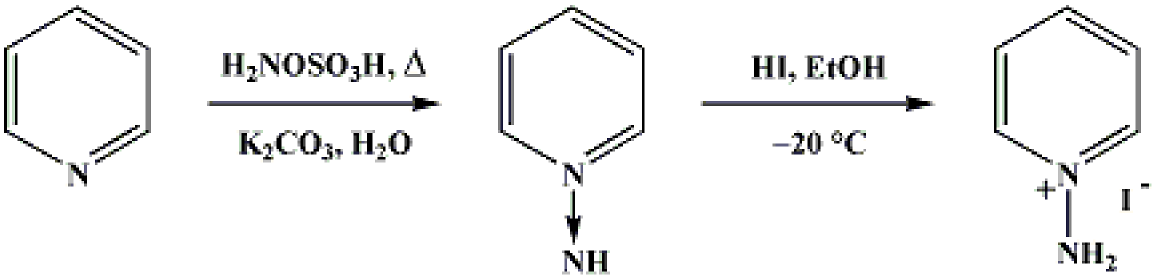
1-AMINOPYRIDINIUM IODIDE

[Pyridinium, 1-amino-, iodide]



Submitted by R. Gösl and A. Meuwsen[1].
Checked by N. A. Fedoruk and V. Boekelheide.

1. Procedure

To a freshly prepared solution of 11.3 g. (0.10 mole) of hydroxylamine-O-sulfonic acid (Note 1) in 64 ml. of cold water there is added 24 ml. (24 g., 0.30 mole) of pyridine (Note 2). The mixture is heated at about 90° on a steam bath for 20 minutes. It is then cooled to room temperature with stirring, and 13.8 g. (0.10 mole) of potassium carbonate is added. The water and excess pyridine are removed from the mixture by heating it at 30–40° in a rotatory evaporator in conjunction with a water aspirator. The residue is treated with 120 ml. of ethanol, and the insoluble precipitate of potassium sulfate is removed by filtration.

Fourteen milliliters (22 g., 0.10 mole) of 57% hydriodic acid is added to the filtrate, and the resulting solution is stored at –20° for 1 hour (Note 3). The solid that separates is collected; weight 15.5–17.5 g. Recrystallization of this solid from about 100 ml. of absolute ethanol gives 14–16 g. (63–72%) of 1-aminopyridinium iodide as almost-white crystals, m.p. 160–162° (Note 4).

2. Notes

1. Hydroxylamine-O-sulfonic acid may be purchased from Ventron Corporation or prepared according to the directions in *Inorganic Syntheses.*[2]
Because aqueous solutions of hydroxylamine-O-sulfonic acid are not very stable, it is very important to use freshly prepared solutions. The purity of hydroxylamine-O-sulfonic acid should be checked by iodometric titration. If it is less than 85–90% pure, the yield of 1-aminopyridinium iodide will suffer. The acid can be purified by dissolving it in an equal weight of water and then precipitating it by stirring 7 volumes of acetic acid into the solution.
2. The pyridine was distilled before use. When the conversion is carried out in

the presence of potassium carbonate using an equimolar amount of pyridine instead of an excess, the yields obtained are 20–30% lower.[3]

3. The temperature is kept at −20° or lower by a bath of dry ice and methanol. If the temperature rises above −20°, an appreciable quantity of 1-aminopyridinium iodide may redissolve and be lost.

4. The melting point recorded for 1-aminopyridinium iodide is 161–162°.[3]

3. Discussion

The formation of 1-aminopyridinium chloride has been accomplished by the acid hydrolysis of N-(*p*-acetaminobenzenesulfonimido) pyridine.[4] Also, the rearrangement of a substituted diazepine has been observed to give a 1-aminopyridine derivative.[5] The present procedure is an adaptation of that described by Gösl and Meuwsen.[3]

4. Merits of the Preparation

This procedure is a convenient and general method for preparing asymmetrically substituted hydrazines.[3] This is illustrated by the following examples reported by the submitters[3] (% yields in parentheses): methylamine to methylhydrazinium hydrogen sulfate (49–53%); ethylamine to ethylhydrazinium hydrogen oxalate (51%); butylamine to butylhydrazinium hydrogen sulfate (49–56%); piperidine to 1-aminopiperidinium hydrogen oxalate (32%); dibutylamine to 1,1-dibutylhydrazinium hydrogen oxalate (34%); trimethylamine to 1,1,1-trimethylhydrazinium hydrogen oxalate (79–85%); 2-picoline to 1-amino-2-methylpyridinium iodide (57%); 2,4-lutidine to 1-amino-2,4-dimethylpyridinium iodide (40%); 2,6-lutidine to 1-amino-2,6-dimethylpyridinium iodide (34%); 2,4,6-collidine to 1-amino-2,4,6-trimethylpyridinium iodide (30%); and quinoline to 1-aminoquinolinium iodide (32%).

Primary, secondary, and tertiary amines can be aminated by chloramine also, but pyridine nitrogens have been aminated only by hydroxylamine-O-sulfonic acid.

It has been shown that, on treatment with base, 1-aminopyridinium iodide undergoes 1,3-dipolar addition with ethyl propiolate or dimethyl acetylenedicarboxylate; thus the N-aminoheterocycles may serve as convenient starting materials for the synthesis of a variety of unusual fused heterocycles.[6]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

N-(p-acetaminobenzenesulfonimido) pyridine

ethanol (64-17-5)

potassium carbonate (584-08-7)

acetic acid (64-19-7)

potassium sulfate (37222-66-5)

pyridine (110-86-1)

piperidine (110-89-4)

hydriodic acid (10034-85-2)

Quinoline (91-22-5)

methylamine (74-89-5)

Trimethylamine (75-50-3)

2,6-Lutidine (108-48-5)

chloramine (10599-90-3)

2,4,6-collidine (108-75-8)

2-picoline (109-06-8)

Butylamine (109-73-9)

Dimethyl acetylenedicarboxylate (762-42-5)

ethylamine (75-04-7)

1-Aminopyridinium iodide, Pyridinium, 1-amino-, iodide (6295-87-0)

Hydroxylamine-O-sulfonic acid (2950-43-8)

1-aminopyridinium chloride

ethylhydrazinium hydrogen oxalate

butylhydrazinium hydrogen sulfate

1-aminopiperidinium hydrogen oxalate

Dibutylamine (111-92-2)

1,1-dibutylhydrazinium hydrogen oxalate

1,1,1-trimethylhydrazinium hydrogen oxalate

1-amino-2-methylpyridinium iodide

2,4-lutidine (108-47-4)

1-amino-2,4-dimethylpyridinium iodide

1-amino-2,6-dimethylpyridinium iodide

1-amino-2,4,6-trimethylpyridinium iodide

1-aminoquinolinium iodide

ethyl propiolate (623-47-2)

methylhydrazinium hydrogen sulfate

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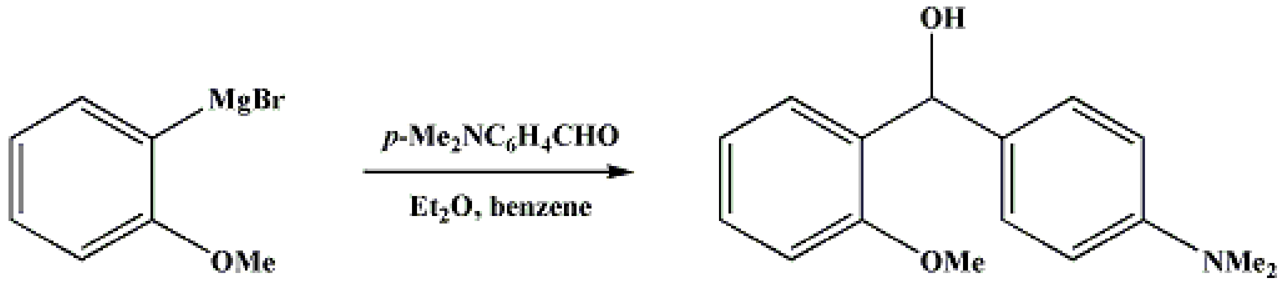
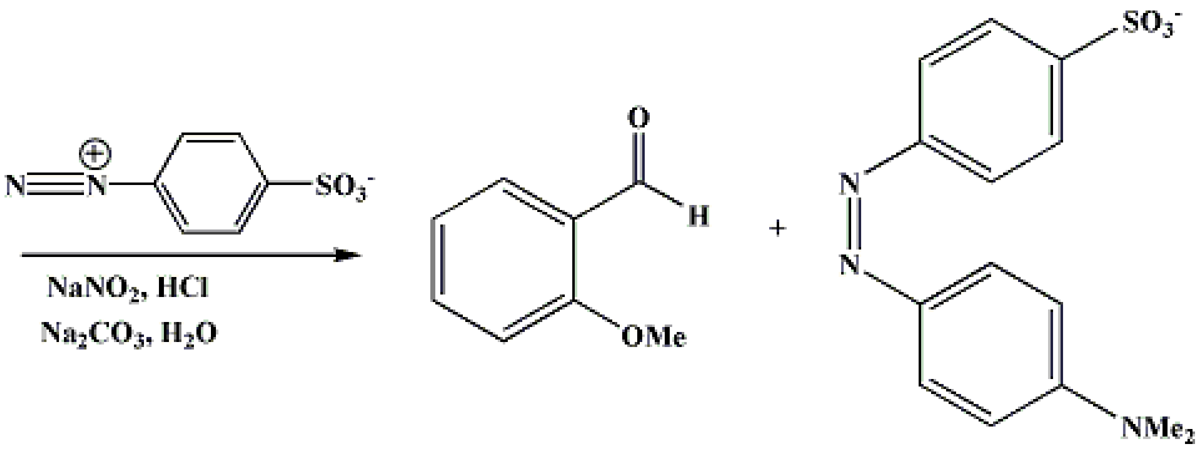
o-ANISALDEHYDE





Submitted by A. J. Sisti[1]
Checked by G. L. Walford and Peter Yates.

1. Procedure

A. *4-Dimethylamino-2'-methoxybenzhydrol*. An ethereal solution of *o*-methoxyphenylmagnesium bromide is prepared in the usual manner[2] with 250 ml. of anhydrous ether, 14.5 g. (0.60 g. atom) of magnesium, and 100 g. (0.53 mole) of *o*-bromoanisole (Note 1). A solution of 60 g. (0.40 mole) of *p*-dimethylaminobenzaldehyde (Note 2) in 200 ml. of anhydrous benzene is added dropwise to the Grignard reagent (Note 3). After the addition is completed, the reaction mixture is stirred for 10 hours at room temperature. The magnesium complex, which forms a very thick suspension, is decomposed with a solution of 75 g. of ammonium chloride in 450 ml. of water. The ether-benzene layer is separated, washed with 100 ml. of water, and dried over calcium sulfate (Note 4). The solvent is removed under reduced pressure, and the residue is induced to crystallize by trituration with a little petroleum ether (30–60°). Recrystallization of the solid from benzene-petroleum ether (30–60°) gives 4-dimethylamino-2'-methoxybenzhydrol (59–60 g., 57–58%), m.p. 75–80°.

B. *o-Anisaldehyde*. In a 3-l. three-necked flask fitted with a mechanical stirrer and a nitrogen inlet tube are placed 60 g. (0.35 mole) of sulfanilic acid (Note 5), 18 g. (0.17 mole) of anhydrous sodium carbonate, and 400 ml. of water. Stirring is started, and the resulting solution is cooled to 0–5° in an ice bath. Nitrogen is passed into the reaction flask, and a nitrogen atmosphere is maintained throughout the reaction. To the cooled solution is added three-quarters of a solution of 24.2 g. (0.35 mole) of sodium nitrite in 75 ml. of water, followed

by 32 ml. of concentrated hydrochloric acid. During the diazotization the temperature of the solution is maintained below 5° by the addition of ice in small pieces. After a few minutes another 32 ml. of acid is added. Further additions of the sodium nitrite solution are made slowly until a positive test for excess nitrous acid is observed (Note 6). The diazonium solution is buffered to pH 6 by the addition of a cooled solution of 50 g. of sodium acetate in 125 ml. of water. A solution of 52 g. (0.20 mole) of 4-dimethylamino-2'-methoxybenzhydrol in 500 ml. of acetone is added rapidly, followed by an additional 500 ml. of acetone. The reaction mixture becomes red almost immediately, and stirring is continued for 30 minutes. at 0–5°. The cooling bath is replaced by a warm water bath (50–60°), and stirring is continued for an additional 30 minutes. The reaction mixture is diluted with an equal volume of water and extracted with three 750-ml. portions of ether. The combined ethereal extracts are washed with water until all the dissolved methyl orange is removed, then dried over calcium sulfate. The ether is removed under reduced pressure, and the residue is distilled to yield 19–20.5 g. (69–75%) of colorless liquid, b.p. 79–80° (1.5 mm.), n^{25}_D 1.5586 (Note 7).

2. Notes

1. *o*-Bromoanisole obtained from Eastman Kodak Company was used without further purification.
2. A good commercial grade (Matheson, Coleman and Bell) of *p*-dimethylaminobenzaldehyde was used without further purification.
3. In one run the checkers cooled the reaction mixture in an ice bath throughout the addition. In another run only initial cooling was used. There was no difference in yield.
4. The checkers found that separation of the aqueous and organic phases is very difficult if the mixture is shaken. In one run shaking and washing were omitted without affecting the yield or purity of the product.
5. Eastman white label sulfanilic acid was used without purification.
6. Excess nitrous acid causes an *immediate* blue color at the point of contact with starch-iodide test paper. At all times there must be an excess of mineral acid (Congo red test paper).
7. The submitters found for the 2,4-dinitrophenylhydrazone m.p. 252–254° (lit.[2] m.p. 249–250°). The checkers found m.p. 34–36° for *o*-anisaldehyde (lit.[3] m.p. 37°) and m.p. 249–251° for the 2,4-dinitrophenylhydrazone.

3. Discussion

o-Anisaldehyde is commercially available. However, this procedure illustrates a method of general applicability[4,5,6] for the preparation of aromatic, aliphatic, and unsaturated aldehydes and ketones.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

2,4-dinitrophenylhydrazone

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether (60-29-7)

ammonium chloride (12125-02-9)

sodium acetate (127-09-3)

magnesium (7439-95-4)

sodium carbonate (497-19-8)

nitrogen (7727-37-9)

sodium nitrite (7632-00-0)

nitrous acid (7782-77-6)

calcium sulfate (7778-18-9)

acetone (67-64-1)

sulfanilic acid (121-57-3)

o-Anisaldehyde (135-02-4)

p-Dimethylaminobenzaldehyde (100-10-7)

o-methoxyphenylmagnesium bromide

o-bromoanisole (578-57-4)

methyl orange (547-58-0)

4-Dimethylamino-2'-methoxybenzhydrol

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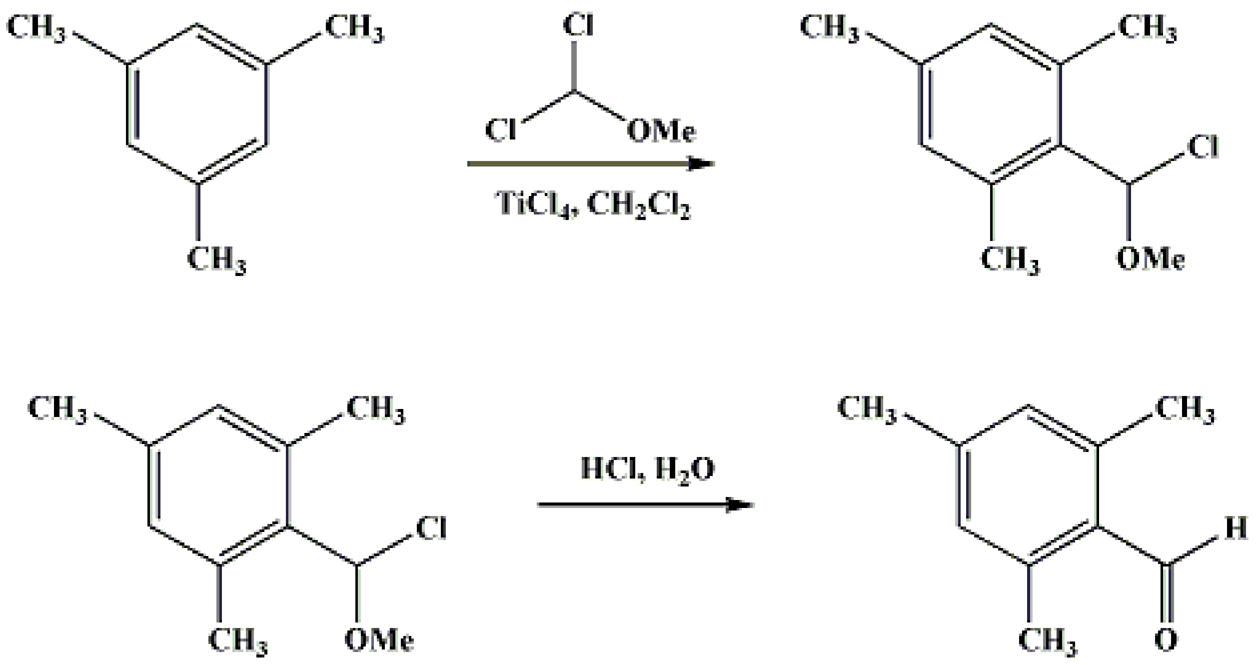
Organic Syntheses, *CV 5*, *49*

AROMATIC ALDEHYDES. MESITALDEHYDE

[Benzaldehyde, 2,4,6-trimethyl-]



Submitted by A. Rieche, H. Gross, and E. Höft[1].
Checked by G. N. Taylor and K. B. Wiberg.

1. Procedure

A solution of 72 g. (0.60 mole) of mesitylene in 375 ml. of dry methylene chloride is placed in a 1-l. three-necked flask equipped with a reflux condenser, a stirrer, and a dropping funnel. The solution is cooled in an ice bath, and 190 g. (110 ml., 1.0 mole) of titanium tetrachloride is added over a period of 3 minutes. While the solution is stirred and cooled, 57.5 g. (0.5 mole) of dichloromethyl methyl ether[2] is added dropwise over a 25-minute period. The reaction begins (as indicated by evolution of hydrogen chloride) when the first drop of chloro ether is added. After the addition is complete, the mixture is stirred for 5 minutes in the ice bath, for 30 minutes without cooling, and for 15 minutes at 35°.

The reaction mixture is poured into a separatory funnel containing about 0.5 kg. of crushed ice and is shaken thoroughly. The organic layer is separated, and the aqueous solution is extracted with two 50-ml. portions of methylene chloride. The combined organic solution is washed three times with 75-ml. portions of water. A crystal of hydroquinone is added to the methylene chloride solution (Note 1) which is then dried over anhydrous sodium sulfate. After evaporation of the solvent, the residue is distilled to give the crude product, b.p. 68–74° (0.9 mm.). After redistillation there is obtained 60–66 g. (81–89%) of mesitaldehyde; b.p. 113–115° (11 mm.), n^{20}D 1.5538.

2. Notes

1. Hydroquinone retards the autoxidation of the aldehyde.

3. Discussion

Mesitaldehyde may be prepared from mesitylmagnesium bromide by the reaction with orthoformate esters[3] or ethoxymethyleneaniline;[3] from acetylmesitylene by oxidation with potassium permanganate;[4] from mesitoyl chloride by reduction;[5] from mesityllithum by the reaction with iron pentacarbonyl;[6] and from mesitylene by treatment with formyl fluoride and boron trifluoride,[7] by treatment with carbon monoxide, hydrogen chloride, and aluminum chloride,[8] or by various applications of the Gatterman synthesis.[9,10,11]

4. Merits of the Preparation

The preparation of mesitaldehyde is an example of a generally applicable method for the preparation of aromatic aldehydes by treatment of aromatic compounds with dichloromethyl methyl ether.[12] Aldehydes derived from polynuclear aromatic compounds,[12,13] phenols,[14] phenol ethers,[12] and hetero-aromatic compounds[12] are also obtained using this procedure. In addition, colchicine derivatives have been formylated[15] by means of dichloromethyl methyl ether.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 365

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrogen chloride (7647-01-0)

carbon monoxide (630-08-0)

hydroquinone (123-31-9)

potassium permanganate (7722-64-7)

sodium sulfate (7757-82-6)

aluminum chloride (3495-54-3)

Mesitylene (108-67-8)

methylene chloride (75-09-2)

boron trifluoride (7637-07-2)

ethoxymethyleneaniline (6780-49-0)

Mesitaldehyde, Benzaldehyde, 2,4,6-trimethyl- (487-68-3)

Mesitoyl chloride (938-18-1)

mesitylmagnesium bromide

titanium tetrachloride (7550-45-0)

Dichloromethyl methyl ether (4885-02-3)

acetylmesitylene

iron pentacarbonyl

formyl fluoride (1493-02-3)

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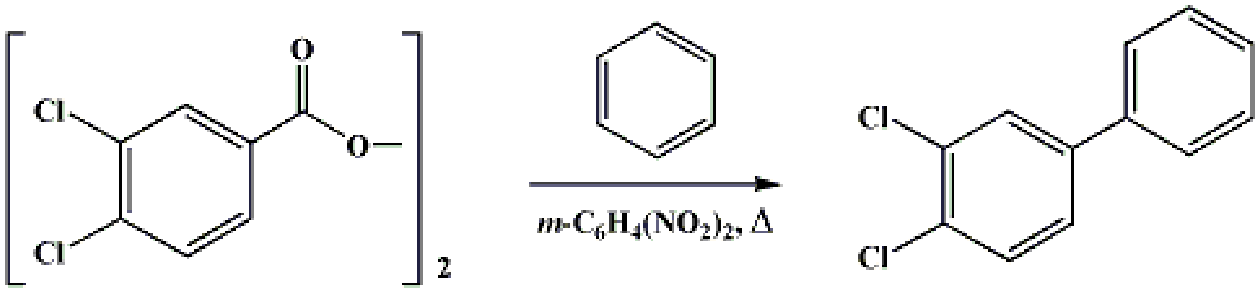
ARYLBENZENES: 3,4-DICHLOROBIPHENYL

[Biphenyl, 3,4-dichloro-]



Submitted by D. H. Hey and M. J. Perkins[1].
Checked by K. K.-W. Shen and K. B. Wiberg.

1. Procedure

Thirty-eight grams (0.1 mole) of bis-3,4-dichlorobenzoyl peroxide (Note 1) is added to a boiling solution of 3 g. of *m*-dinitro-benzene in 800 ml. of dry reagent grade benzene contained in a 1-l. round-bottomed flask, and the resulting solution is boiled under reflux for 40 hours. The solvent is then distilled from the red solution until the residual volume is about 200 ml. (Note 2), and the mixture is allowed to cool. The 3,4-dichlorobenzoic acid which separates is removed by suction filtration, washed with a little cold benzene, and then with 100 ml. of petroleum ether (b.p. 80–100°). The combined filtrate and washings are further concentrated by distillation (Note 2) to about 60 ml., cooled, and a small second crop of 3,4-dichlorobenzoic acid is removed and washed with a little benzene followed by a little petroleum ether. The total yield of acid, m.p. 208–210° (Lit.[2] m.p. 208–209°), is 18.2 g. (95%) (Note 3). The filtrate and washings are combined (Note 4) and chromatographed on a column of basic alumina (30 cm. x 3.5 cm.) which is eluted with petroleum ether (b.p. 40–60°). Solvent is distilled from the eluate (Note 5), and the residual crude 3,4-dichlorobiphenyl is distilled under reduced pressure using a short air condenser and a receiver chilled in ice. There is obtained 17.3–18.0 g. (78–81%) of almost pure 3,4-dichlorobiphenyl (b.p. 146–150° at 2 mm.) which sets to a colorless solid, m.p. 44–47° (Note 6).

2. Notes

1. The bis-3,4-dichlorobenzoyl peroxide may be prepared as follows.[3,4] To a 2-l. beaker containing 400 ml. of water which is cooled to 0–5° in an ice bath is added slowly 40 g. (0.51 mole) of sodium peroxide. A dropping funnel containing 167.6 g. (0.8 mole) of 3,4-dichlorobenzoyl chloride in 400 ml. of dry toluene is supported over the beaker. The peroxide solution is cooled and stirred vigorously while the toluene solution is added drop-wise over a 1-hour period. The solution is stirred for an additional 2 hours. The precipitate is filtered using a suction funnel, washed with

600 ml. of cold water, and dried in air overnight. There is obtained 114 g. (75%) of bis-3,4-dichlorobenzoyl peroxide, m.p. 135° dec. The crude product is purified by dissolving it in chloroform and precipitating by the addition of methanol, m.p. 139° dec.

2. Solvent removal may conveniently be carried out with a rotary evaporator to obviate bumping caused by separation of the dichlorobenzoic acid from the boiling solution.

3. In syntheses of other arylbenzenes, in which the acid by-product is more soluble, it may be extracted from the reaction mixture with aqueous sodium bicarbonate or removed in the subsequent chromatography.

4. At this point the solvent is largely petroleum ether. Appreciable quantities of benzene in the mixture to be chromatographed tend to carry some of the dinitrobenzene through the alumina.

5. After removal of the solvent from the eluate, almost pure white 3,4-dichlorobiphenyl crystallizes, m.p. 44–48°. It may be purified by recrystallization from methanol as an alternative to vacuum distillation.

6. The product may be freed from a trace (1%) of biphenyl present as an impurity by recrystallization from methanol which raises the melting point to 47–48°. The literature values range from 46°[5] to 49–50°.[6]

3. Discussion

3,4-Dichlorobiphenyl has been prepared by the arylation of benzene using the Gomberg procedure starting with 3,4-dichloroaniline,[5] and using the acid-catalyzed decomposition of 1-(3,4-dichlorophenyl)-3,3-dimethyltriazene in benzene.[6] The arylation procedure given above, which utilizes a diaroyl peroxide as the aryl radical source, provides a route arylbenzenes which involves simple operations and gives a good yield of pure product. In the absence of the nitro compound, the mode of action of which has been discussed in terms of two somewhat different mechanisms,[7,8] the yields of aroic acids and arylbenzenes are commonly below 50%,[9] and the arylbenzene may be contaminated with aryldihydrobenzenes.[10] The present procedure has been used to prepare a variety of simple arylbenzenes in isolated yields ranging from 70 to 90%. If a nitro substituent is present in the peroxide, high yields are obtained without the addition of further nitro compound.[9]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

Benzene (71-43-2)

methanol (67-56-1)

chloroform (67-66-3)

sodium bicarbonate (144-55-8)

toluene (108-88-3)

Biphenyl (92-52-4)

sodium peroxide

3,4-Dichlorobiphenyl, Biphenyl, 3,4-dichloro- (2974-92-7)

bis-3,4-dichlorobenzoyl peroxide

3,4-dichlorobenzoic acid (51-44-5)

3,4-dichlorobenzoyl chloride (3024-72-4)

dichlorobenzoic acid (50-45-3)

dinitrobenzene (528-29-0)

3,4-dichloroaniline (95-76-1)

1-(3,4-dichlorophenyl)-3,3-dimethyltriazene

m-dinitro-benzene (99-65-0)

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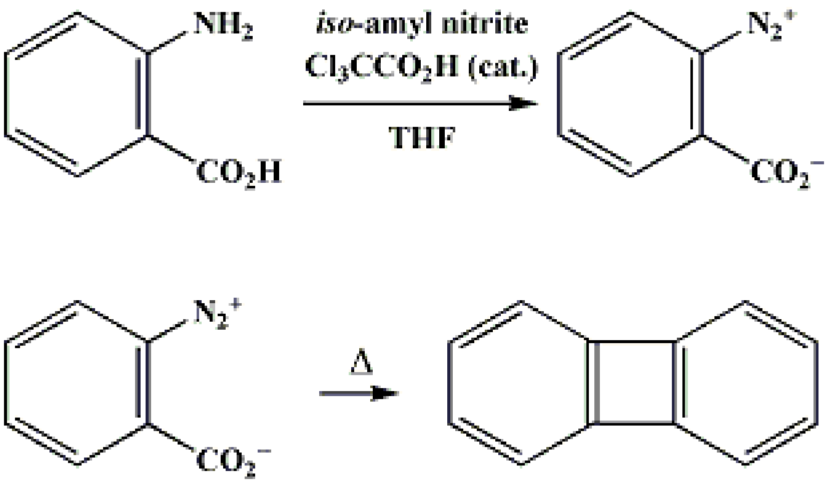
Organic Syntheses, CV 5, 54

BENZENEDIAZONIUM-2-CARBOXYLATE AND BIPHENYLENE

[Benzenediazonium, *o*-carboxy-, hydroxide, inner salt]



Submitted by Francis M. Logullo, Arnold H. Seitz, and Lester Friedman[1].
Checked by G. D. Abrams, Hermann Ertl, and Peter Yates.

1. Procedure

Caution! Benzenediazonium-2-carboxylate when dry detonates violently on being scraped or heated, and it is strongly recommended that it be kept wet with solvent at all times. It should be prepared and used in a hood behind a safety screen. A wet towel or sponge should be kept within easy reach with which to deactivate any spilled material, which should then be disposed of by flooding with water.

A. *Benzenediazonium-2-carboxylate*. A solution of 34.2 g. (0.25 mole) of anthranilic acid (Note 1) and 0.3 g. of trichloroacetic acid (Note 2) in 250 ml. of tetrahydrofuran (Note 3) is prepared in a 600-ml. beaker equipped with a thermometer and cooled in an ice-water bath. The solution is stirred magnetically, and 55 ml. (48 g., 0.41 mole) of isoamyl nitrite (Note 4) is added over a period of 1–2 minutes. A mildly exothermic reaction occurs, and the reaction mixture is maintained at 18–25° and stirred for a further 1–1.5 hours. A transient orange to brick-red precipitate may appear (Note 5) which is slowly converted to the tan product. When the reaction is completed, the mixture is cooled to 10°, and the product is collected by suction filtration on a plastic Buchner funnel and washed on the funnel with cold tetrahydrofuran until the washings are colorless. *(Caution! The filter cake should not be allowed to become dry.)* The benzene-diazonium-2-carboxylate is then washed with two 50-ml. portions of 1,2-dichloroethane to displace the tetrahydrofuran, and the solvent-wet material is used in the next step (Note 6), (Note 7), and (Note 8).

B. *Biphenylene*. The solvent-wet benzenediazonium-2-carboxylate is washed from the funnel into a 400-ml. beaker with *ca*. 150 ml. of 1,2-dichloroethane, dispensed from a plastic wash bottle, with the aid of a plastic spatula (Note 9). The resultant slurry is added during 3–5 minutes to 1250 ml. of gently boiling, stirred 1,2-dichloroethane in a 2-l. beaker on a magnetic stirrer-hot plate in the hood (Note 10). Frothing ceases a few minutes after completion of the addition, and the mixture assumes a clear red-brown color, signaling the end of the reaction.

A 1-l., two-necked, round-bottomed flask is equipped with a 1-l. addition funnel and a Claisen distillation head and water-cooled condenser. The cooled reaction mixture is transferred to the funnel, and enough of it is admitted to the flask to half-fill the latter. The 1,2-dichloroethane, b.p. 83–84°, is distilled with the use of magnetic stirring to maintain even ebullition; the remainder of the reaction mixture is added from the funnel at a rate such that the flask remains about half-full. When *ca*. 75 ml. of dark residue remains in the flask, 300 ml. of ethylene glycol is added. An air condenser is substituted for the water-cooled condenser, and distillation is recommenced. A forerun, b.p. <150°, is discarded, and the fraction, b.p. 150–197°, is collected (Note 11). The distillate is cooled to 10°, and the product is collected by suction filtration, washed with 10–15 ml. of cold ethylene glycol and several times with water, and dried at atmospheric, pressure over phosphorus pentoxide. The yield of biphenylene, m.p. 109–112°, is 4.0–5.6 g. (21–30%, based on anthranilic acid). Additional biphenylene (0.2–0.5 g.) can be obtained from the mother liquor and ethylene glycol washings by redistillation or dilution with water (Note 12).

2. Notes

1. The submitters used practical grade anthranilic acid from Mallinckrodt Chemical Works.
2. Perfluorobutyric or trifluoroacetic acid may be used in place of trichloroacetic acid. Strong mineral acids and acetic acid are wholly unsatisfactory. If a catalyst is not used, the product is of poor quality and the yield only 30%. Trichloroacetic acid is conveniently added as a solution in tetrahydrofuran (0.01 g./ml.).
3. The submitters used commercial tetrahydrofuran. The checkers found that the product yield was the same when either practical grade or Fisher Certified reagent grade tetrahydrofuran was used.
4. The submitters used "amyl nitrite" U.S.P. from Mallinckrodt Chemical Works; isoamyl nitrite supplied by Matheson, Coleman and Bell is apparently the same material. They found that other alkyl nitrites (ethyl, *n*-butyl, *t*-butyl, *n*-amyl) may be used with equal success. Subsequent to the checking of this procedure, they reported that the amount of nitrite can be reduced to a 20% molar excess.
5. This precipitate is apparently 2,2'-dicarboxydiazoaminobenzene.
6. The product should be used immediately because it deteriorates slowly at room temperature. It is freed of tetrahydrofuran by washing with the solvent to

be used in subsequent reactions and transferred as a slurry in that solvent (cf. p. htmrocedure B). Traces of water, if present, do not appear to interfere with subsequent reactions of diazonium carboxylates, as observed in the submitters' laboratory.

7. The submitters have found that this procedure works equally well with many substituted anthranilic acids; however, it does not work with 3-chloro-, 5-cholro, 4-nitro-, 5-nitro-, and 4,5-benzoanthranilic acids.

8. Although it strongly recommended that the product not be dried, particularly when prepared on the scale described here, the following slightly modified procedure can be used for the preparation of solvent-free benzenediazonium-2-carboxylate. A solution of 2.74 g. (0.020 mole) of anthranilic acid and 0.030 g. of trichloroacetic acid in 30 ml. of tetrahydrofuran is prepared in a 100-ml. beaker equipped with a thermometer and cooled in a bath of *ca.* 25 g. of crushed ice. The solution is stirred magnetically, and 5 ml. (4.4 g., 0.038 mole) of isoamyl nitrite (Note 4) is added during *ca.* 0.5 minute. The mixture is stirred and allowed to warm to room temperature over a period of 1 hour. It is cooled to 10°, and the product is collected by suction filtration with the use of a plastic Buchner funnel and plastic spatula and washed with ice-cold tetrahydrofuran until the washings are colorless. The yield of air-dried (30 minutes) benzenediazonium-2-carboxylate is 2.55–2.88 g. (86–97%). *(Caution! Danger of detonation! See above.)* (Note 13).

9. The checkers transferred the benzenediazonium-2-carboxylate to the beaker with the aid of gentle air pressure (Note 13) and then slurried it with *ca.* 150 ml. of 1,2-dichloroethane.

10. The checkers added the slurry via a large, medium-bore, glass funnel with fire-polished edges. In one of three runs a small, sharp report was heard, apparently from a source above the liquid in the beaker; the yield of biphenylene in this run did not differ significantly from that obtained in the other runs.

11. The checkers found it necessary to heat the condenser with a microburner from time to time to prevent clogging with biphenylene. The submitters have reported that this can be avoided by connecting the Claisen head via an adapter to a two-necked receiving flask fitted with an upright water-cooled condenser and cooled by immersion in ice-water.

12. For convenient preparation and workup of larger amounts of biphenylene, several runs can be combined after the decomposition of the benzenediazonium-2-carboxylate. Thus the submitters obtained 19.1 g. (25%) of air-dried biphenylene by combining four batches. They found that the use of larger amounts of 1,2-dichloroethane resulted in a moderate increase in yield; by combining four batches, each prepared in 2. 75 l. of 1,2-dichloroethane in a 4-l. beaker, they obtained 22.8 g. (30%) of product.

13. The checkers transferred the solvent-moist product to a tared Petri dish by means of gentle puff of compressed air through the stem of the funnel; solid adhering to the filter paper and funnel was transferred to the dish with the aid of a soft rubber policeman, which was also used to spread the product over the surface of the dish. The product was then air-dried for 30 minutes in the hood.

3. Discussion

Benzenediazonium-2-carboxylate[2] and its substituted derivatives[3] have been prepared by diazotization of anthranilic acids in the presence of hydrochloric acid followed by dehydrochlorination of the resultant diazonium carboxylate hydrochlorides with silver oxide.

Biphenylene has been prepared in low yield by the reaction of 2,2'-dibromobiphenyl or 2,2'-biphenyliodonium iodide with cuprous oxide,[4] by the action of cupric chloride on 2,2'-biphenyl-dimagnesium dibromide,[5] from 2,2'-diiodobiphenyl via dibenzomercurole (*o*,*o*'-biphenylenemercury) (49%),[6] by pyrolysis or photolysis of phthaloyl peroxide (27%),[7] by reaction of *o*-fluoro-bromobenzene with lithium amalgam (24%),[8] by reaction of *o*-bromoiodobenzene with magnesium (12%),[9] and by the decomposition of diphenyliodonium-2-carboxylate,[10] 1,2,3-benzothia-diazole-1,1-dioxide,[11] benzenediazonium-2-carboxylate,[12,13] and by the oxidation of 1-aminobenzotriazole with lead tetraacetate (83%).[14]

4. Merits of the Preparation

These procedures illustrate facile methods for the preparation of benzenediazonium-2-carboxylate and its derivatives[15] and of biphenylene and certain biphenylene derivatives.[13] The latter preparation is far more convenient and proceeds in much better yield than do previous, syntheses, which involve more steps, less accessible intermediates, and more complicated techniques.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 196

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Perfluorobutyric or trifluoroacetic acid

2,2'-biphenyliodonium iodide

o,o'-biphenylenemercury

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

magnesium (7439-95-4)

silver oxide (20667-12-3)

1,2-dichloroethane (107-06-2)

cuprous oxide

ethylene glycol (107-21-1)

cupric chloride (7758-89-6)

amyl nitrite (463-04-7)

Anthranilic Acid (118-92-3)

lithium (7439-93-2)

Isoamyl nitrite (110-46-3)

trichloroacetic acid (76-03-9)

Tetrahydrofuran (109-99-9)

phthaloyl peroxide

Benzenediazonium-2-carboxylate, benzene-diazonium-2-carboxylate (1608-42-0)

Biphenylene (259-79-0)

dibenzomercurole

diphenyliodonium-2-carboxylate (1488-42-2)

1,2,3-benzothia-diazole-1,1-dioxide (37150-27-9)

1-aminobenzotriazole (1614-12-6)

o-fluoro-bromobenzene (1072-85-1)

phosphorus pentoxide (1314-56-3)

Benzenediazonium, o-carboxy-, hydroxide

o-bromoiodobenzene (583-55-1)

lead tetraacetate

2,2'-dicarboxydiazoaminobenzene

2,2'-dibromobiphenyl

2,2'-biphenyl-dimagnesium dibromide

2,2'-diiodobiphenyl

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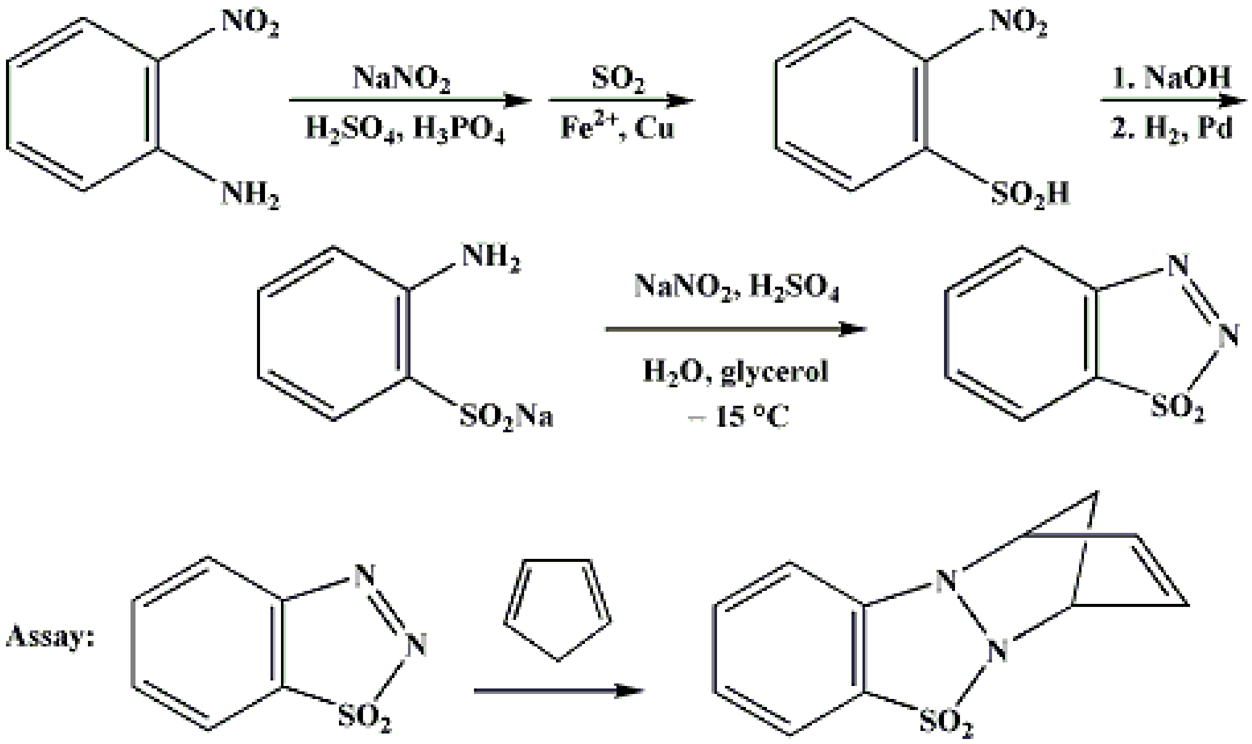
Organic Syntheses, *CV 5, 60*

1,2,3-BENZOTHIADIAZOLE 1,1-DIOXIDE



Submitted by G. Wittig and R. W. Hoffmann[1].
Checked by C. D. Smith, R. A. Clement, and B. C. McKusick.

1. Procedure

A. *2-Nitrobenzenesulfinic acid* (*Note 1*). *Caution! This reaction should be done in a good hood because noxious fumes are released.*

2-Nitroaniline (13.8 g., 0.10 mole) (Note 2) is dissolved in a hot solution of 75 ml. of 96% sulfuric acid, 100 ml. of phosphoric acid (density 1.7), and 50 ml. of water in a 1-l. beaker. A stirrer and a thermometer are introduced into the mixture, and the beaker is immersed in an ice bath. A solution of 8.3 g. (0.12 mole) of sodium nitrite in 25 ml. of water is added dropwise to the well-stirred solution at such a rate that the temperature is maintained at 10–15°. Excess nitrite is destroyed by adding sulfamic acid in small portions (Note 3). The mixture is cooled to −10° in an ice-salt bath, and about 50 ml. of liquid sulfur dioxide (Note 4) is poured into the well-stirred reaction. The product is immediately poured onto a mixture of 55.6 g. (0.20 mole) of $FeSO_4 \cdot 7\ H_2O$ and 1 g. of defatted copper powder in a wide 2-l. beaker. Nitrogen and excess sulfur dioxide bubble off with much foaming.

After 30 minutes the solid sulfinic acid is separated on a fritted-glass filter. The sulfinic acid is dissolved from the filter by a mixture of 750 ml. of ether and 750 ml. of methylene chloride. The solution is dried over calcium chloride and evaporated to dryness under reduced pressure (bath temperature 25°) (Note 5). The residue is

suspended in 50 ml. of water, and small portions of dilute ammonia are added to the well-stirred suspension until it has a pH of 9 (Note 6). Insoluble impurities are separated by filtration, and 2-nitrobenzenesulfinic acid is precipitated from the filtrate by adding 5-ml. portions of 6*N* hydrochloric acid with cooling; the sulfinic acid precipitated by each portion of acid is separately collected on a Buchner funnel (Note 7). The acid, a pale yellow solid, is dried on a clay plate in a vacuum desiccator over potassium hydroxide pellets, m.p. 120–125° (dec.), weight 9.4–14.9 g. (50–80%). If the 2-nitrobenzenesulfinic acid is to be used for the hydrogenation of the next step high purity is required, and it is generally advisable to reprecipitate the acid once more in the same way (Note 8).

B. *Sodium 2-aminobenzenesulfinate*. 2-Nitrobenzenesulfinic acid (3.74 g., 0.020 mole) is suspended in 10 ml. of water, and sufficient 1*N* NaOH (about 20 ml.) is added to the well-stirred mixture to dissolve the acid and bring the pH to 9. Palladium oxide (0.2–1.0 g., (Note 9)) is suspended in 20 ml. of water in a 200-ml. glass hydrogenation bottle. The bottle is attached to a hydrogenation apparatus such as that of Adams and Voorhees,[2] and the suspension is shaken with hydrogen under a pressure of 1–3 atm. until the palladium oxide is reduced. The solution of 2-nitrobenzenesulfinic acid is added, and the mixture is shaken under a hydrogen pressure of 1–3 atm. The solution becomes completely decolorized in 2–6 hours, during which time about 95% of the calculated amount of hydrogen is absorbed. The catalyst is separated by filtration and washed with two 20-ml. portions of water, which are added to the filtrate. The filtrate, which may have a yellowish color, is evaporated to dryness under reduced pressure (bath temperature 45°). The residue, a white or light yellow solid, is sodium 2-aminobenzenesulfinate. After being dried in a desiccator over calcium chloride, it weighs 3.05–3.20 g. (85–89%).

C. *1,2,3-Benzothiadiazole 1,1-dioxide*. *Caution! 1,2,3-Benzothiadiazole 1,1-dioxide in the solid state can explode spontaneously, particularly on being warmed, jolted, or scratched. For most purposes it need not be isolated, but can be used in solutions, which are relatively safe. Any operations involving the solid material should be done very carefully, using good shielding.*

A solution of 1.43 g. (0.0080 mole) of sodium 2-aminobenzenesulfinate in the least possible amount of water is combined with a solution of 0.55 g. (0.0080 mole) of sodium nitrite in the least amount of water. A mixture of 16 ml. of 2*N* sulfuric acid and 22 ml. of glycerol is placed in a 250-ml. three-necked flask equipped with a dropping funnel, a low-temperature thermometer, and a stirrer, and the flask is immersed in a bath of acetone and dry ice. The stirred mixture is cooled to –15°, and the solution of sodium 2-aminobenzenesulfinate and sodium nitrite is added dropwise over a period of about 5 minutes; the cooling and rate of addition are such as to maintain the temperature at –15° ± 3°. The mixture is stirred for an additional 2 hours at this temperature, and 30 ml. of ether is added. The product is stirred vigorously for a few minutes and then allowed to warm to –6° with gentle stirring. The ether layer is decanted or transferred by means of a chilled pipet into a vessel cooled in a dry ice bath,

and the reaction mixture is again cooled to –15°. In this way the reaction mixture is extracted with five 20-ml. portions of ether. After the last extraction the aqueous layer is frozen solid and the ether layer is poured off. The combined extracts are dried at –20°, first over calcium chloride and then over phosphorus pentoxide; a cold room at –20° is particularly convenient for this operation. The solution is transferred to a tared distillation flask immersed in an ice bath (Note 10), and the ether is removed by evaporation under reduced pressure. The flask is weighed rapidly and dried in a desiccator over phosphorus pentoxide at –20° (*Caution!* (Note 11)(Note 12)). The residue is 1,2,3-benzothiadiazole 1,1-dioxide in the form of yellow-brown needles; weight 0.77–1.04 g. (57–77%). It explodes between 45° and 60° (Note 13).

2. Notes

1. This is essentially the method of J. Lange.[3]
2. Technical material of Badische Anilin & Soda-Fabrik is satisfactory.
3. To detect nitrous acid, a drop of the mixture is diluted with water and tested with starch iodide paper.
4. It is convenient to condense sulfur dioxide from a cylinder in a calibrated trap cooled in a dry ice bath.
5. After the procedure had been checked, the submitters recommended the following time-saving modification. The methylene chloride-ether solution of the sulfinic acid is extracted with one 80-ml. portion and two 35-ml. portions of 2*N* sodium hydroxide solution. The extracts are combined and the sulfinic acid is precipitated with 5-ml. portions of 6*N* hydrochloric acid as described in the text.
6. An excess of ammonia leads to products that are contaminated with ammonium chloride.
7. In this way one avoids an excess of hydrochloric acid which, if it adheres to the product, causes its gradual decomposition.
8. The checkers dissolved the crude acid in the minimum amount of 2*N* sodium hydroxide (about 3 ml./g.) and reprecipitated it in 5 portions with 2*N* hydrochloric acid; recovery 75–85%. Alternatively, they added the acid to boiling ethyl acetate (9 ml./g.), added decolorizing carbon to the solution, boiled the mixture for 5 minutes, separated the carbon by filtration, and cooled the hot filtrate; recovery 45–55%. The checkers found no difference in the infrared spectra of material purified in the two ways, but recrystallized material was reduced more quickly by hydrogen.
9. The submitters used 0.2 g. of palladium oxide prepared by the method of Shriner and Adams[4] and required 2 hours for complete hydrogenation under a hydrogen pressure of 1 atm. The checkers used 1.0 g. of palladium oxide (75.7%) from Engelhard Industries, 113 Astor Street, Newark, New Jersey, and required 4 hours for complete hydrogenation under a hydrogen pressure of 2–3 atm. Conditions should be chosen to give complete hydrogenation within 6 hours or colored by-products may be formed.
10. Not quite half of the flask should dip into the ice water or the layer of ice forming on the flask may be hard to remove.

11. 1,2,3-Benzothiadiazole 1,1-dioxide slowly decomposes even at 0°; hence it should always be used on the day on which it is made. For most purposes it is not necessary to isolate the dioxide; the ether solution can be used, or solutions in other solvents can be prepared by adding the other solvent and distilling off the ether under reduced pressure (bath temperature 0°). In this way larger amounts of the dioxide than are described in this procedure can be handled without danger.
12. 1,2,3-Benzothiadiazole 1,1-dioxide can be conveniently assayed and characterized without isolation by forming its adduct with cyclopentadiene.[5] The following procedure illustrates characterization; for assay the same procedure can be applied to an aliquot, with all amounts scaled down in proportion. The dried ether extract of 1,2,3-benzothiadiazole 1,1-dioxide prepared from 1.43 g. (0.0080 mole) of sodium 2-aminobenzenesulfinate is concentrated to about 20 ml. at 0°, and 20 ml. of acetonitrile at –20° is added. Twenty milliliters of cold, freshly prepared cyclopentadiene[6] is added. The mixture is kept overnight at –10° to 0°. Solvent and excess cyclopentadiene are removed by evaporation at 0° under reduced pressure to leave 1.20–1.28 g. (64–68% based on sodium 2-aminobenzenesulfinate) of crude 1:1 adduct, m.p. 87° (dec.). For purification it is dissolved in 20 ml. of methylene chloride, 70 ml. of ether is added, and the solution is kept at –70°. Adduct decomposing at 90° crystallizes; recovery is about 75%. From pure, crystalline 1,2,3-benzothiadiazole 1,1-dioxide the yield of adduct is 92–98%.
13. Purer product can be obtained by reducing 1,2,3-benzothiadiazole 1,1-dioxide with zinc and acetic acid to 1,2,3-benzothiadiazoline 1,1-dioxide, which is oxidized back with lead tetraacetate.[5]

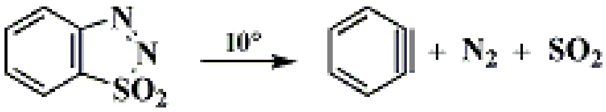
3. Discussion

1,2,3-Benzothiadiazole 1,1-dioxide has been prepared only by the present method.[5]

4. Merits of the Preparation

1,2,3-Benzothiadiazole 1,1-dioxide decomposes smoothly in solution at 10° to give dehydrobenzene ("benzyne"), nitrogen, and sulfur dioxide.[5,7] In this way, as well as by the thermal decomposition of benzenediazonium-2-carboxylate,[8,9] it is possible to obtain dehydrobenzene in the absence of organometallic or strongly alkaline reagents; for this reason the choice of the reaction partner for dehydrobenzene is hardly limited at all. Compared to dry benzenediazonium-2-carboxylate, 1,2,3-benzothiadiazole 1,1-dioxide possesses the following advantages as a source of dehydrobenzene: the explosive compound does not need to be isolated and the decomposition temperature is lower. Solvent-wet benzenediazonium-2-carboxylate, being insoluble in most organic media, is less generally useful than 1,2,3-benzothiadiazole 1,1-dioxide but is more convenient to prepare.[9] Because of their special reaction conditions, other methods of obtaining dehydrobenzene without using an organometallic compound[10] are not so

generally applicable. Earlier volumes of *Organic Syntheses* illustrate the preparation of dehydrobenzene by the action of magnesium on *o*-fluorobromobenzene[11] and a type of ring closure in which a dehydrobenzene is an intermediate.[12] Methods of generating dehydrobenzenes and the reactions of these reactive substances were recently reviewed.[13]



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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

H_2O

dehydrobenzene

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ammonia (7664-41-7)

ethyl acetate (141-78-6)

ether (60-29-7)

ammonium chloride (12125-02-9)

hydrogen (1333-74-0)

acetonitrile (75-05-8)

sodium hydroxide (1310-73-2)

glycerol (56-81-5)

magnesium (7439-95-4)

sulfur dioxide (7446-09-5)

nitrogen (7727-37-9)

sodium nitrite (7632-00-0)

nitrous acid (7782-77-6)

copper powder (7440-50-8)

potassium hydroxide (1310-58-3)

zinc (7440-66-6)

phosphoric acid (7664-38-2)

methylene chloride (75-09-2)

palladium oxide

sulfamic acid (5329-14-6)

CYCLOPENTADIENE (542-92-7)

Benzenediazonium-2-carboxylate (1608-42-0)

1,2,3-Benzothiadiazole 1,1-dioxide (37150-27-9)

2-Nitrobenzenesulfinic acid (13165-79-2)

2-Nitroaniline (88-74-4)

Sodium 2-aminobenzenesulfinate (50827-53-7)

1,2,3-benzothiadiazoline 1,1-dioxide

o-fluorobromobenzene (1072-85-1)

phosphorus pentoxide (1314-56-3)

lead tetraacetate

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Organic Syntheses, CV 5, 66

BENZOYL FLUORIDE

Submitted by George A. Olah and Stephen J. Kuhn[1].
Checked by John A. Dupont and William D. Emmons.

1. Procedure

Caution! Anhydrous hydrogen fluoride is toxic and in contact with skin can cause serious burns. This preparation should be carried out in a well-ventilated hood. Rubber gloves and safety goggles should be worn by the operator. In case of contact with hydrogen fluoride wash the affected skin area immediately with copious amounts of water, and apply a calcium gluconate paste (Note 1).

Hydrogen fluoride (50 g., 2.5 moles) is distilled from the cylinder through a polyethylene tube into a 250-ml. polyethylene transfer bottle which has been previously weighed and calibrated. A vent is provided during this process by inserting a large-gauge hypodermic needle through the bottle cap. No provision against atmospheric moisture is necessary. The bottle is cooled in a dry ice-acetone bath, and 45–50 ml. of liquid hydrogen fluoride is collected. The amount of liquid obtained can be determined by weight difference; however, since an excess of hydrogen fluoride is employed, the exact weight need not be determined. The time required for collection of the hydrogen fluoride can be appreciably shortened by placing the cylinder in a pan of warm water.

The reaction itself is carried out in a 1-l. polyolefin bottle (Note 2) or fused silica flask (Note 3) fitted with an inlet tube (Note 4) leading to the bottom of the reaction vessel and a reflux condenser which is connected to a hydrogen chloride absorber or which leads directly to the hood. A condenser suitable for work with anhydrous hydrogen fluoride can easily be prepared from a glass-jacketed polyolefin, Teflon®, silica, or copper tube (Note 5).

Benzoyl chloride (281 g., 2.0 moles) is placed in the reaction vessel, and the hydrogen fluoride gas is then introduced by its distillation from the transfer bottle through the inlet tube. Prior to this distillation the hypodermic needle is closed off by a metal cap. The hydrogen fluoride is added over a period of approximately 1 hour. Generally, external cooling is not needed, as the evaporating hydrogen chloride cools the reaction mixture. When the addition is completed, the reaction mixture is warmed to 30–40° and kept at this temperature for 1 hour. The mixture is then washed in an ordinary

glass separatory funnel (Note 6) with 500 ml. of ice water in which 12.5 g. (0.2 mole) of boric acid is dissolved (Note 7). The organic layer is quickly separated, and to it are added 10 g. of anhydrous sodium fluoride and 10 g. of anhydrous sodium sulfate (Note 7). The mixture is allowed to stand for 30 minutes and is then filtered and distilled through a short Vigreux column. The yield of benzoyl fluoride b.p. 159–161°, $n^{15}\text{D}$ 1.4988 (Note 8), is 187–200 g. (75–80%).

2. Notes

1. An alternative treatment which has been used with good results at Rohm and Haas Company is, after throughly washing the exposed area with tap water, to soak the burned area in an ice-cold 0.2% solution of Hyamine 1622 (a product of Rohm and Haas Company) in 70% aqueous ethanol for 1 hour. It has also been stated that soaking the affected area with ice and water for 1 hour is almost as effective.[2]
2. Polyolefin bottles of suitable size are commercially available. One inconvenience occasionally observed with bottles which have not previously been in contact with hydrogen fluoride is the formation of a slight pink color in the reaction mixture, possibly due to the plasticizers. This coloration does not affect either the yields or the purity of the product, however, because the color is generally eliminated after the product is washed and treated with sodium fluoride.
3. No color problem exists when fused silica equipment, preferably with normal joints lubricated with a fluorinated grease, is used.
4. The inlet tube can be either polyolefin, Teflon®, fused silica, or copper.
5. Silica or copper gives much better heat transfer than do plastic tubes. The checkers found, however, that the use of a condenser was superfluous and that substitution of a simple polyethylene tube long enough to vent the off-gas away from the operator and apparatus was quite satisfactory.
6. Although some slight etching can take place, at this stage glass equipment is entirely safe, and no contamination of the product occurs.
7. The crude product contains hydrogen fluoride which is removed by the addition of boric acid to the wash water (H_3BO_3 + 4HF HBF_4 + $3H_2O$). The sodium fluoride disposes of any hydrogen fluoride remaining in the benzoyl fluoride (NaF + HF $NaHF_2$).
8. Benzoyl fluoride is a potent lachrymator and is undoubtedly toxic. It is advisable to rinse all glassware with acetone followed by 10% aqueous ammonia before removing the glassware from the hood.

3. Discussion

Benzoyl fluoride can also be prepared by the reaction of anhydrous hydrogen fluoride[3,4,5] or potassium fluoride[6] with benzoic anhydride and by the halogen

exchange of benzoyl chloride with alkali fluorides, such as NaF,[7] KF,[6] KHF_2,[8] Na_2SiF_6,[9] or various other metal fluorides.[10]

4. Merits of the Preparation

The described procedure, first applied by Colson and Fredenhagen,[3,4] is useful for the preparation of a wide variety of acyl fluorides.[5] The yields are normally 80–90%. Some examples of acyl fluorides prepared are listed in Table I. Benzoyl fluoride can also be employed as a convenient source of acyl fluoride by reaction with acetic acid.[11]

TABLE I

Product	B.P., °C.
Propionyl fluoride	43
n-Butyryl fluoride	69
Isobutyryl fluoride	61
Valeryl fluoride	90
Isovaleryl fluoride	81
Caproyl fluoride	122
Heptanoyl fluoride	40 (15 mm.)
Octanoyl fluoride	62 (15 mm.)
Pelargonyl fluoride	81 (15 mm.)
Decanoyl fluoride	92 (15 mm.)
Fluoroacetyl fluoride	54
Chloroacetyl fluoride	77
Dichloroacetyl fluoride	85
Trichloroacetyl fluoride	67
Bromoacetyl fluoride	104
Phthaloyl fluoride	84 (15 mm.)
Phenylacetyl fluoride	85 (15 mm.)

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 332
- Org. Syn. Coll. Vol. 6, 628

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

KF

KHF_2

Na_2SiF_6

ethanol (64-17-5)

hydrogen chloride (7647-01-0)

acetic acid (64-19-7)

ammonia (7664-41-7)

sodium sulfate (7757-82-6)

hydrogen fluoride (7664-39-3)

copper (7440-50-8)

acetone (67-64-1)

benzoyl chloride (98-88-4)

Benzoic anhydride (93-97-0)

boric acid (10043-35-3)

sodium fluoride, NaF (7681-49-4)

potassium fluoride (7789-23-3)

Benzoyl fluoride (455-32-3)

calcium gluconate

Propionyl fluoride

Isobutyryl fluoride

Valeryl fluoride

Isovaleryl fluoride

Caproyl fluoride

Heptanoyl fluoride

Octanoyl fluoride

Pelargonyl fluoride (463-18-3)

Decanoyl fluoride

Fluoroacetyl fluoride

Chloroacetyl fluoride

Dichloroacetyl fluoride

Trichloroacetyl fluoride

Bromoacetyl fluoride

Phthaloyl fluoride

Phenylacetyl fluoride

n-Butyryl fluoride

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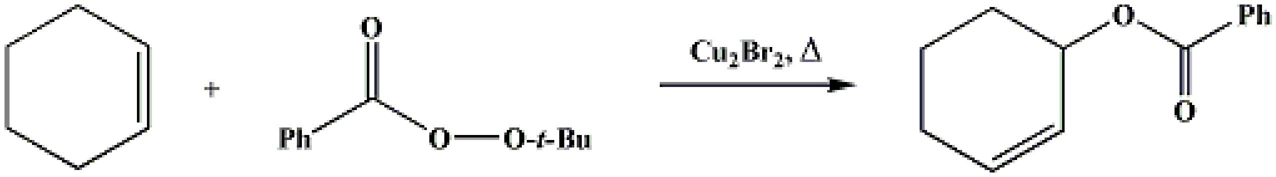
Organic Syntheses, *CV 5*, *70*

3-BENZOYLOXYCYCLOHEXENE

[2-Cyclohexen-1-ol, benzoate]



Submitted by Knud Pedersen, Preben Jakobsen, and Sven-Olov Lawesson[1].
Checked by R. Schöllhorn and R. Breslow.

1. Procedure

Caution! This reaction should be carried out behind a safety screen. The solvent removal and product distillation steps should also be carried out behind a screen to minimize danger due to contamination of the product with undetected peroxides.

A 250-ml., three-necked, round-bottomed flask equipped with a sealed mechanical stirrer, a reflux condenser, and a pressure-equalizing dropping funnel is set up for conducting a reaction in an atmosphere of nitrogen by fitting into the top of the condenser a T-tube attached to a low-pressure supply of nitrogen and to a mercury bubbler. In the flask are placed 41 g. (0.50 mole) of cyclohexene and 0.05 g. (0.00035 mole) of cuprous bromide, and the mixture is heated in an oil bath at 80–82°. When the temperature of the mixture reaches that of the oil bath, 40 g. (0.21 mole) of *t*-butyl perbenzoate (Note 1) is added dropwise with stirring over a 1-hour period, during which the color of the now homogeneous solution becomes blue. Stirring and heating are continued for an additional 3.5 hours (Note 2). The cooled reaction mixture is washed with two 50-ml. portions of dilute aqueous sodium carbonate to remove benzoic acid (Note 3). The remaining organic phase is washed with water until neutral and dried over anhydrous sodium sulfate. The excess of cyclohexene is removed by distillation under reduced pressure, and the residue (Note 4) is distilled through a short Vigreux column to give 29–33 g. (71–80%) of 3-benzoyloxycyclohexene, b.p. 97–99° (0.15 mm.), n^{20}_D 1.5376–1.5387 (Note 5).

2. Notes

1. *t*-Butyl perbenzoate is supplied by Lucidol Division, Wallace and Tiernan, Inc., Buffalo 5, New York, or L. Light and Co., Ltd., Colorbrook, Bucks, England. The Lucidol product contains 98% *t*-butyl perbenzoate.
2. The progress of the reaction can most conveniently be followed by periodic examination of the infrared spectrum of the mixture ($\nu_{C=O}$ for peroxybenzoate: 1775 cm.$^{-1}$). After all of the perester has been added, *ca.* 3 hours is required for its consumption.
3. After acidification of the aqueous phase 1.5–2 g. of benzoic acid can be isolated.
4. It is recommended that an infrared spectrum be run on the residue before the distillation to check for the absence of perester (Note 2).
5. The same yield is obtained when the scale is increased threefold.

3. Discussion

The procedure is that of Kharasch, Sosnovsky, and Yang.[2]

4. Merits of the Preparation

The reaction described is of considerable general utility for the preparation of benzoyloxy derivatives of unsaturated hydrocarbons.[2,3,4,5,6,7,8] Reactions of *t*-butyl perbenzoate with various other classes of compounds in the presence of catalytic amounts of copper ions produce benzoyloxy derivatives. Thus this reaction can also be used to effect one-step oxidation of saturated hydrocarbons,[9,10] esters,[5,11] dialkyl and aryl alkyl ethers,[12,13,14] benzylic ethers,[11,15] cyclic ethers,[13,16] straight-chain and benzylic sulfides,[12,17,18,19] cyclic sulfides,[11,19] amides,[11] and certain organosilicon compounds.[20] Reviews[20,21] of these reactions are available.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

t-butyl perbenzoate

Cyclohexene (110-83-8)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

Benzoic acid (65-85-0)

cuprous bromide (7787-70-4)

3-Benzoyloxycyclohexene, 2-Cyclohexen-1-ol, benzoate (3352-93-0)

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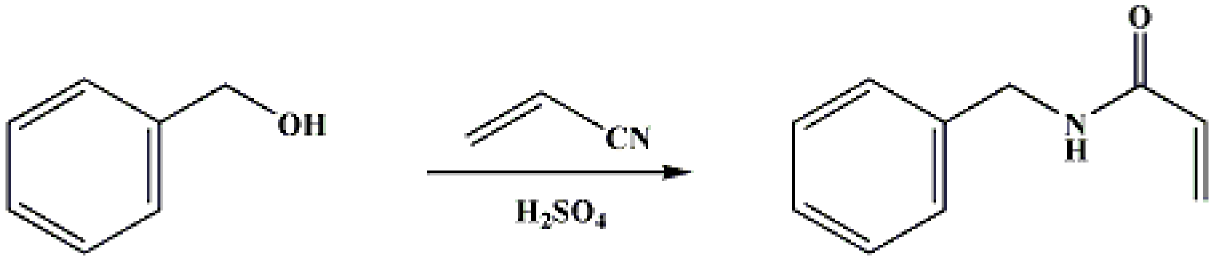
N-BENZYLACRYLAMIDE

[Acrylamide, N-benzyl-]



Submitted by Chester L. Parris[1]
Checked by William E. Parham, Wayland E. Noland, and Joan M. Weinmann.

1. Procedure

In a 1-l., three-necked, round-bottomed flask equipped with a sealed Hershberg stirrer,[2] a 125-ml. dropping funnel, and a thermometer is placed 200 g. (250 ml., 3.78 moles) of acrylonitrile (Note 1). The flask is immersed in an ice-water bath, and then 75 ml. of concentrated sulfuric acid is added dropwise over a period of about 1 hour while the temperature is maintained at 0–5°. From a clean dropping funnel (Note 2), 108.1 g. (105 ml., 1.0 mole) of benzyl alcohol (Note 3) is added dropwise over about 1 hour at the same temperature. The clear, yellow mixture is held below 5° for about 3 hours longer and is then allowed to warm slowly to room temperature. After 2 days of stirring at room temperature the mixture is poured into a 2-l. separatory funnel containing about 1 l. of water and chopped ice. The mixture is shaken thoroughly and the resulting oil is taken up with 200 ml. of ethyl acetate. The aqueous phase is separated and extracted twice more with 200-ml. portions of solvent. The organic extracts are combined and washed successively with four 250-ml. portions of saturated sodium chloride solution, four 250-ml. portions of saturated sodium bicarbonate solution, and again with four portions of the salt solution. The neutral ethyl acetate extract is dried over 20 g. of anhydrous magnesium sulfate and filtered. The filtrate is concentrated and the residue is distilled under reduced pressure. A fore-run of 1–3 g. of semisolid is obtained up to 120°/0.02 mm. The product is then collected as a light-yellow oil, b.p. 120–130°/0.01–0.02 mm., which solidifies in the chilled receiver. The distillate (97–101 g.) is melted on a steam bath and dissolved in a mixture of 50 ml. of benzene and 50 ml. of hexane. The solution is transferred quantitatively to a 500-ml. Erlenmeyer flask and the solvent evaporated on a steam bath. The oily residue is placed in a refrigerator for at least 1 day to ensure complete crystallization. The white solid is transferred to a Büchner funnel with the aid of a little ice-cold hexane. After drying in air, the yield is 95–100 g. (59–62%) of N-benzylacrylamide, m.p. 65–68° (Note 4).

2. Notes

1. Commercial acrylonitrile from American Cyanamid Company was redistilled, b.p. 77–78°.
2. The dropping funnel which has been wetted with sulfuric acid should be washed and thoroughly dried, or a fresh funnel employed.
3. Benzyl alcohol from Fisher Scientific Company was used without further purification.
4. The product is of suitable purity for further reactions. It may be obtained analytically pure, m.p. 70–72°, by recrystallization from benzene. The reported melting point is 69°.[3]

3. Discussion

N-Benzylacrylamide has been prepared by dehydrohalogenation of N-benzyl-β-chloropropionamide with aqueous potassium hydroxide,[3] and by the reaction of acetylene with carbon monoxide and benzylamine.[4] The procedure described is the method of Parris and Christenson.[5]

4. Merits of Preparation

The alternative methods of preparation of N-benzylacrylamide are reported in patents, and no yields are given. One of them requires two steps and costlier intermediates; the other appears to be more suitable for plant than for laboratory preparation. The procedure presented involves a simple, one-step reaction taking place under mild conditions, employing inexpensive reactants and affording satisfactory yields.

The N-alkylation of nitriles with aralkyl alcohols, a special case of the Ritter reaction,[6] is a novel general reaction. The following compounds were prepared by this procedure in the corresponding yields: N-benzylacetamide (48%), N-(2,4-dimethylbenzyl)-acetamide (40%), N-(4-methoxybenzyl)-acetamide (60%), N,N'-diacrylyl-*p*-xylene-α-α'-diamine (64%), N,N'-diacetyl-4,6-dimethyl-*m*-xylene-α,α'-diamine (62%). Another example of the Ritter reaction is given elsewhere in this volume.[7]

The title compound is of special interest and utility as a polymerizable monomer.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 471

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

acetylene (74-86-2)

Benzene (71-43-2)

ethyl acetate (141-78-6)

carbon monoxide (630-08-0)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

potassium hydroxide (1310-58-3)

Benzyl alcohol (100-51-6)

magnesium sulfate (7487-88-9)

benzylamine (100-46-9)

acrylonitrile (107-13-1)

hexane (110-54-3)

N-BENZYLACRYLAMIDE, Acrylamide, N-benzyl- (13304-62-6)

N-benzyl-β-chloropropionamide (501-68-8)

N-benzylacetamide (588-46-5)

N-(2,4-dimethylbenzyl)-acetamide

N-(4-methoxybenzyl)-acetamide

N,N'-diacrylyl-p-xylene-α-α'-diamine

N,N'-diacetyl-4,6-dimethyl-m-xylene-α,α'-diamine

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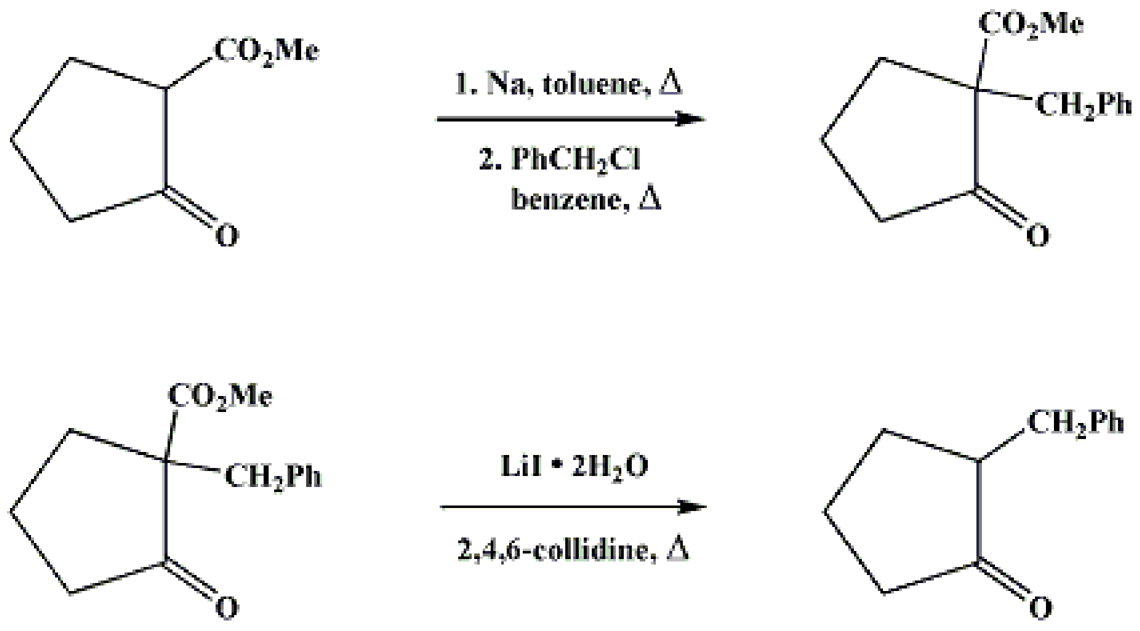
2-BENZYLCYCLOPENTANONE



Submitted by Fritz Elsinger[1]
Checked by William G. Dauben and W. Todd Wipke.

1. Procedure

A. *2-Benzyl-2-carbomethoxycyclopentanone*. A dry 2-l. three-necked flask is fitted with a Vibromischer stirrer (Note 1), a reflux condenser, and a 250-ml. dropping funnel with a pressure-equalizing side tube.[2] A nitrogen-inlet tube is connected to the top of the dropping funnel, and an outlet tube is placed on the top of the condenser and connected to a mercury valve. The latter consists of a U-tube the bend of which is just filled with mercury.

To the flask are added 13.4 g. (0.58 mole) of clean sodium and 200 ml. of absolute toluene. The Vibromischer stirrer is activated, the toluene heated to reflux, and the agitation continued at this temperature until all the sodium is pulverized into a very fine sand. The agitation is ceased, and the solution is allowed to cool to room temperature. The nitrogen flow rate is increased, the Vibromischer stirrer is replaced with a conventional sealed mechanical stirrer with a Teflon® blade, and a solution of 85 g. (0.6 mole) of 2-carbomethoxycyclopentanone (Note 2) in 450 ml. of absolute benzene is placed in the addition funnel.

The stirrer is started, and the solution in the addition funnel is added over a 2-hour period without external heating (Note 3). After the addition is complete, the mixture is heated under reflux for 2.5 hours, at the end of which time the mixture has a pasty consistency. A solution of 106 g. (0.84 mole) of benzyl chloride in 100 ml. of dry benzene is added in one portion, the mixture heated under reflux for 14 hours, and the

solution (Note 4) poured into 600 ml. of water. The benzene layer is separated, the aqueous layer extracted twice with ether, and the combined benzene-ether extract washed with 100 ml. of water and dried over anhydrous sodium sulfate. The solvent is removed under reduced pressure using a rotary evaporator, and the residual liquid distilled to yield 108–116 g. (81–86%) of colorless 2-benzyl-2-carbomethoxycyclopentanone, b.p. 126–128° (0.5 mm.) (Note 5).

B. *2-Benzylcyclopentanone*. A mixture of 30 g. (0.177 mole) of lithium iodide dihydrate (Note 6) and (Note 7) and 140 ml. of dry 2,4,6-collidine (Note 8) in a 300-ml. three-necked flask fitted with a dropping funnel, a reflux condenser, and a nitrogen-inlet system (as in step A) is heated to reflux. As soon as all the lithium iodide has dissolved (Note 9), 30 g. (0.129 mole) of 2-benzyl-2-carbomethoxycyclopentanone dissolved in 30 ml. of 2,4,6-collidine (Note 10) is added to the boiling, faintly yellow solution; and during this process the solution turns darker in color and a precipitate forms (Note 11). Evolution of carbon dioxide begins immediately, and its formation can be followed by passing the nitrogen flush through a saturated barium hydroxide solution. The mixture is heated under reflux and a nitrogen atmosphere for 19 hours, at the end of which time the evolution of carbon dioxide is very slow (Note 12).

The mixture is cooled and poured onto a mixture of 200 ml. of 6*N* hydrochloric acid, 200 ml. of ether, and 100 g. of ice. The residue in the flask is dissolved in a mixture of 6*N* hydrochloric acid and methylene chloride, and this mixture is added to the main reaction. The aqueous layer is separated and extracted with two 100-ml. portions of ether. The combined ethereal solution is washed once with 70 ml. of 6*N* hydrochloric acid, once with 2*N* sodium carbonate solution, twice with saturated sodium chloride solution, and dried over anhydrous sodium sulfate. The solvent is removed under reduced pressure, and the residue is distilled to yield 16–17 g. (72–76%) of colorless 2-benzylcyclopentanone, b.p. 83–85° (0.3 mm.), 108–110° (0.75 mm.) (Note 13).

2. Notes

1. This stirring apparatus is available from Ag. für Chemie Apparatebau, Mannedorf, Zurich, Switzerland.
2. The submitter prepared the material from dimethyl adipate following the procedure published by Pickney[3] for the diethyl ester. The checkers obtained their material by fractional distillation of mixed carbomethoxy- and carbethoxycyclopentanone available from Arapahoe Chemical Co., Boulder, Colorado.
3. If the 2-carbomethoxycyclopentanone is added in one portion, the yield of the product drops to 67%.
4. At the end of the reflux period, the reaction mixture is a nonviscous solution containing a white precipitate.
5. The semicarbazone melts at 168–170°.
6. Lithium iodide dihydrate is available from Fluka A. G., Buchs, S. G., Switzerland. The checkers used the trihydrate and, by means of a Dean Stark

trap[4] attached between the flask and the condenser, 1 mole of water was removed via azeotropic distillation with collidine.

7. In cases where a carbomethoxy group is desired to be selectively cleaved in the presence of a readily hydrolyzed ester group, such as an acetate of a secondary alcohol, anhydrous lithium iodide must be employed.[5] In order to avoid partial decomposition of the salt to iodine, it is best dried by slowly heating it to 150° in a high vacuum. The solubility of anhydrous lithium iodide in boiling collidine or lutidine is slightly less than that of the dihydrate, but it still is adequate for the reaction. In the present case, the use of the anhydrous salt lowers the yield of the 2-benzylcyclopentanone to 67%, and a large amount of a product, believed to be a dimer, boiling around 200° (0.5 mm.) is obtained.

8. For the cleavage of less hindered esters, the lower-boiling 2,6-lutidine (b.p. 143°) can be used as the solvent.

9. The development of a small amount of iodine is difficult to avoid. The nitrogen atmosphere is essential to keep this salt decomposition to a minimum.

10. Methyl esters react more rapidly with lithium iodide than do ethyl esters, which in turn react more rapidly than esters of secondary alcohols. On the other hand, *t*-butyl esters are cleaved very readily with a catalytic amount of lithium iodide.

11. A precipitate remains throughout the reaction.

12. By using three mole equivalents of lithium iodide dihydrate, at the end of 6.5 hours of reflux a 77% yield of 2-benzyl-cyclopentanone is obtained.

13. The semicarbazone melts at 204–205°.

3. Discussion

This preparation of 2-benzyl-2-carbomethoxycyclopentanone is based on a procedure described by Baker and Leeds[6] for the ethyl ester, and the methyl ester has not been previously prepared. The ethyl ester, also, has been prepared by the alkylation of 2-carbethoxycyclopentanone with benzyl chloride in the presence of potassium hydroxide in acetaldehyde dipropylacetal.[7] The preparation and isolation of the potassium salt of 2-carbethoxycyclopentanone can be readily achieved in a very simple way using aqueous alcoholic potassium hydroxide; by reaction of this salt with a variety of different halides in anhydrous media many 2-alkyl-2-carbethoxycyclopentanones have been prepared.[8,9]

The preparation of 2-benzylcyclopentanone from 2-benzyl-2-carbomethoxycyclopentanone has not been previously reported. Starting with the ethyl ester, however, the compound has been prepared by heating the ester for many hours with concentrated hydrochloric acid.[6,10] The direct alkylation of cyclopentanone with benzyl chloride in the presence of sodium amide in liquid ammonia goes only in a poor yield.[11]

4. Merits of the Preparation

This procedure illustrates a general method for the selective splitting of a carbomethoxy group in the presence of easily hydrolyzed esters of other alcohols, such as the easily hydrolyzed equatorial acetoxy group. The specificity of the reaction is not affected by steric hindrance, and a highly hindered methyl ester can be split in the presence of other less hindered esters of secondary alcohols. Normal alkaline saponification goes in exactly the opposite way.

The present case simply illustrates another utility of the ester cleavage reaction, *i.e.*, the cleavage of a β-keto ester with concomitant decarboxylation under only slightly basic conditions. The method should be particularly applicable to systems which are prone to undergo reverse Claisen reactions.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

diethyl ester

carbomethoxy- and carbethoxycyclopentanone

potassium salt of 2-carbethoxycyclopentanone

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

Benzene (71-43-2)

ether (60-29-7)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

mercury (7439-97-6)

carbon dioxide (124-38-9)

acetate

iodine (7553-56-2)

potassium hydroxide (1310-58-3)

toluene (108-88-3)

sodium (13966-32-0)

benzyl chloride (100-44-7)

Cyclopentanone (120-92-3)

barium hydroxide (17194-00-2)

methylene chloride (75-09-2)

2-Carbethoxycyclopentanone (611-10-9)

2,6-Lutidine (108-48-5)

lutidine (583-61-9)

sodium amide (7782-92-5)

2,4,6-collidine (108-75-8)

collidine

2-Benzylcyclopentanone, 2-benzyl-cyclopentanone (2867-63-2)

2-carbomethoxycyclopentanone (10472-24-9)

2-benzyl-2-carbomethoxycyclopentanone (10386-81-9)

lithium iodide dihydrate

lithium iodide (10377-51-2)

dimethyl adipate (627-93-0)

acetaldehyde dipropylacetal (105-82-8)

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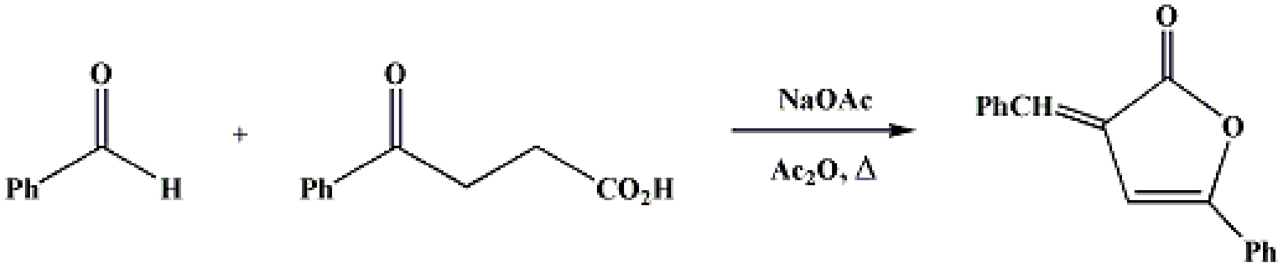
α-BENZYLIDENE-γ-PHENYL-Δ^{β,γ}-BUTENOLIDE

[Cinnamic acid, α-(β-hydroxystyryl)-, γ-lactone]



Submitted by Robert Filler, Edmund J. Piasek, and Hans A. Leipold[1].
Checked by S. Trofimenko and B. C. McKusick.

1. Procedure

The apparatus consists of a 200-ml., three-necked, round-bottomed flask fitted with thermometer, reflux condenser, and gas-inlet tube. The flask is charged with 17.8 g. (0.10 mole) of 3-benzoylpropionic acid (Note 1), 10.6 g. (10.6 ml., 0.10 mole) of benzaldehyde, 61.3 g. (57 ml., 0.60 mole) of acetic anhydride, and 8.2 g. (0.10 mole) of powdered anhydrous sodium acetate (freshly fused). The flask is placed in an oil bath maintained at a temperature of 95–100° and is kept there for 2 hours while dry oxygen-free nitrogen is passed through the reaction mixture (Note 2). At the end of this time the flask is removed from the oil bath, and the hot solution is decanted from the sodium acetate into a 250-ml. Erlenmeyer flask. The solution is kept at 0–5° in a refrigerator for 1 hour, during which time α-benzylidene-γ-phenyl-Δ^{β,γ}-butenolide separates as an orange solid.

About 40 ml. of 95% ethanol is added to the contents of the flask, and the butenolide is brought into suspension by thoroughly breaking up all lumps with a spatula. The suspension is filtered with suction, and the filter cake is washed with 30 ml. of cold 95% ethanol and then with 100 ml. of boiling water to remove any sodium acetate present. The butenolide is obtained as a yellow solid, m.p. 149–154°, weight 11.1–12.4 g. (45–50%), after being dried overnight in a vacuum desiccator. This product, which is pure enough for most purposes, may be further purified by crystallization from 95% ethanol (Note 3).

2. Notes

1. 3-Benzoylpropionic acid[2] is available from Aldrich Chemical Co., Milwaukee, Wisconsin.
2. Oxygen is removed from the nitrogen gas by passing the latter through Brady solution, which consists of zinc amalgam, sodium hydroxide, and sodium anthraquinone-β-sulfonate.[3] It has been shown that oxidizing agents induce formation of a Pechmann dye, a deep red substance which is difficult to remove from the butenolide.[4]
3. About 75 ml. of ethanol is used for every gram of butenolide to be dissolved. Clarification of the solution with charcoal should be avoided because the butenolide tends to separate from solution during filtration and clogs the steam-jacketed funnel. The

crystallized butenolide melts at 150–152°.

3. Discussion

α-Benzylidene-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide has been prepared by the condensation of benzaldehyde with 3-benzoylpropionic acid in the presence of acetic anhydride and sodium acetate[5,6] or in the presence of a mixture of dimethylformamide and sulfur trioxide.[7] The butenolide has also been obtained by reaction of α-chloromethylene-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide with benzene in the presence of anhydrous aluminum chloride.[8]

The method described above may be used for the preparation of a wide variety of butenolides substituted in the arylidene ring with either electron-withdrawing or electron-releasing substituents. γ-Lactones such as α-benzylidene-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide are isoelectronic with azlactones, but have received much less attention. Like the azlactone ring, the butenolide ring may be opened readily by water, alcohols, or amines to form keto acids, keto esters, or keto amides.[9] α-Benzylidene-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide is smoothly isomerized by aluminum chloride to 4-phenyl-2-naphthoic acid[10] in 70% yield via intramolecular alkylation. Grignard reagents add 1,4 to the α,β-unsaturated carbonyl system, with the lactone ring remaining intact,[11] while phenyllithium leads to ring opening and the formation of 1,1-diphenyl-2-phenacylcinnamyl alcohol.[11] The butenolide gives reduced dilactones, on treatment with lithium aluminum hydride.[12]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

α-Benzylidene-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide

α-chloromethylene-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide

benzylidene-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide

1,4 to the α,β-unsaturated carbonyl

ethanol (64-17-5)

Benzene (71-43-2)

acetic anhydride (108-24-7)

sodium acetate (127-09-3)

sodium hydroxide (1310-73-2)

sulfur trioxide (7446-11-9)

oxygen (7782-44-7)

nitrogen (7727-37-9)

benzaldehyde (100-52-7)

aluminum chloride (3495-54-3)

zinc (7440-66-6)

Phenyllithium (591-51-5)

3-benzoylpropionic acid (2051-95-8)

lithium aluminum hydride (16853-85-3)

dimethylformamide (68-12-2)

sodium anthraquinone-β-sulfonate (131-08-8)

4-phenyl-2-naphthoic acid

1,1-diphenyl-2-phenacylcinnamyl alcohol

Cinnamic acid, α-(β-hydroxystyryl)-, γ-lactone (4361-96-0)

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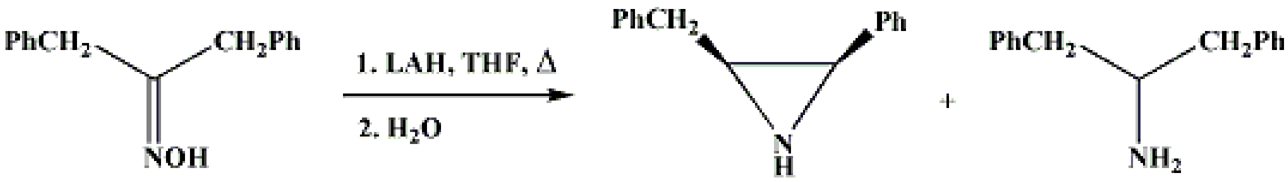
cis-2-BENZYL-3-PHENYLAZIRIDINE

[Aziridine, 2-benzyl-3-phenyl-, *cis*-]



Submitted by Katsumi Kotera and Keizo Kitahonoki[1].
Checked by Donald R. Strobach and R. E. Benson.

1. Procedure

In a 1-l., four-necked, round-bottomed flask fitted with a sealed mechanical stirrer, a thermometer, a dropping funnel, and a reflux condenser protected from atmospheric moisture with a drying tube containing calcium chloride are placed 350 ml. of dry tetrahydrofuran (Note 1) and 3.80 g. (0.100 mole) of powdered lithium aluminum hydride (Note 2). The slurry is stirred while a solution of 11.27 g. (0.0500 mole) of dibenzyl ketoxime (Note 3) in 80 ml. of dry tetrahydrofuran is added dropwise with cooling at 20° over a 10-minute period. The contents of the flask are gradually heated to reflux (Note 4) with stirring in an oil bath at 90° (external temperature) for 3 hours (Note 5); at *ca.* 62° the color of the mixture turns from the initial pale green to a permanent, light chocolate color (reaction may be exothermic at this point). The mixture is cooled with ice water and decomposed by gradual addition of 12 ml. of water at a temperature below 20°. The precipitate is collected by filtration, washed with 100 ml. of ether, and added to 200 ml. of ether. This mixture is stirred for *ca.* 10 minutes and filtered, and the residue is washed with 100 ml. of ether. The ethereal extracts and washings are combined with the original filtrate, dried over anhydrous sodium sulfate over-night, and concentrated with a rotary evaporator at 30° (20 mm.) to give 10.60–11.0 g. of a pale yellow oil (Note 6).

The product is dissolved in 100 ml. of petroleum ether, b.p. 30–40°, with warming, and the solution is transferred to a chromatographic column consisting of 75 g. of silica gel (Note 7). The product is eluted sequentially with (A) 300 ml. of petroleum ether, (B) 300 ml. of 3:1 (v/v) petroleum ether: benzene, (C) 300 ml. of 1:1 (v/v) petroleum ether:benzene, (D) 600 ml. of 1:3 (v/v) petroleum ether: benzene, and (E) 600 ml. of benzene. Fractions A and B are discarded (Note 8). The oil (8.50–9.15 g.) obtained by distillation of the solvent from the combined fractions C, D, and E is dissolved in 65 ml. of petroleum ether. Cooling gives 5.00–6.61 g. of colorless needles, m.p. 44–45° (Note 9). Concentration of the filtrate and cooling yield successive crops of product, m.p. 41–45°. The total yield is 7.45–8.15 g. (71–78%) (Note 9).

2. Notes

1. Tetrahydrofuran of laboratory chemical grade supplied by Fisher Scientific Co. was used without further purification by the checkers. The submitters used tetrahydrofuran purified by the method of *Org. Syntheses*, Coll. Vol. **4**, 259 (1963). *[Caution! See this volume, page 976, for a warning regarding purification of tetrahydrofuran.]*
2. Obtained from Metal Hydrides, Inc.
3. The submitters used oxime prepared from Tokyo Kasei G. R. grade dibenzyl ketone in the

usual manner and recrystallized from ether-petroleum ether; m.p. 123–124° (yield 93%).[2] The checkers prepared the oxime in the following manner. A mixture of 50 g. (0.24 mole) of 1,3-diphenyl-2-propanone (Eastman Organic Chemicals, practical grade), 50 g. (0.72 mole) of hydroxylamine hydrochloride, 250 ml. of reagent grade pyridine, and 250 ml. of ethanol was heated under reflux for 2 hours. The solvent was removed by distillation at reduced pressure, and the residue was triturated with 250 ml. of cold water. The solid was collected by filtration and washed with a small volume of cold water. Crystallization of the moist product from ethanol gave 50.5 g. (94%) of dibenzyl ketoxime, m.p. 122–124°.

4. The internal temperature is 66°. At lower temperatures the reaction takes longer, and the yield of the aziridine is lower. The submitters found that the yield is 66% after 6 hours at a reaction temperature of 50° and 55% after 30 hours at a temperature of 20° and 44 hours at –20°.

5. The consumption of the oxime can be checked by thin-layer chromatography on silica gel G with the solvent system chloroform/methanol (95/5 v/v) and a spray reagent consisting of 5% potassium dichromate in 40% sulfuric acid. The oxime appears as an immediate dark spot and the aziridine as a yellow spot. The checkers observed identical mobilities (R_f 0.8) for both compounds.

6. The submitters found that purification of the oil by direct crystallization gives only a small amount of the pure product. Attempted purification by distillation did not give satisfactory results.

7. Silica gel, particle size 0.2–0.5 mm. (Catalog No. 7733), of E. Merck A. G. (Darmstadt) was used.

8. The fractions are tested by thin-layer chromatography on silica gel G with the solvent system and spray reagent described in (Note 5).

9. The product is sufficiently pure for most purposes. The pure sample after additional recrystallizations melts at 44.7–45.1°.

3. Discussion

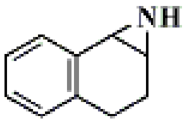
In addition to the present method,[3,4,5] 2-benzyl-3-phenylaziridine has been obtained from O-substituted dibenzyl ketoximes,[3,5] chalcone oxime[4] and 3,5-diphenyl-2-isoxazoline[6] by a reduction similar to that described here.

4. Merits of the Preparation

The present preparation illustrates the general method for the synthesis of aziridines by reduction of ketoximes[3,4,5] and their O-acyl and -alkyl derivatives[3,5,6] having an aromatic ring attached to carbon α or β to the oximino function and of aldoximes[4] having the aromatic ring attached to the carbon atom β to the oximono group. It has also been applied to oximes of cyclic[3,4,7] and bridged[3,8,9,10] ring ketones, such as α- and β-tetralone, 1,2,3,4-dibenzo-1,3-cycloheptadien-6-one, and bicyclo [2.2.2] octanone and its benzo analogs. Examples of aziridines prepared by this method are given in Table I; derivatives of the products are listed in Table II. Because of the accessibility of oximes the present method provides a more convenient synthesis of several types of aziridines than do other methods.[11] Furthermore, the reaction proceeds stereoselectively to give the *cis*-substituted aziridine.[3] A review[10] of the present synthetic method including mechanistic aspects[3,5,6] is available. The effect of oxime configuration (*syn* or *anti*) has been investigated.[4,9,12] The addition of N-methyl-*n*-butylamine (*in situ*) has been found to increase the reaction rate and yield of aziridine.[10]

TABLE I AZIRIDINES PREPARED BY REDUCTION OF OXIMES

WITH LITHIUM ALUMINUM HYDRIDE

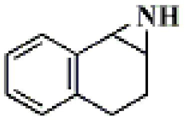
Parent Ketone or Aldehyde	Aziridine	M.P., °C	Yield, %
Acetophenone	2-Phenylaziridine	(Oil)[a]	17
Phenylacetaldehyde	2-Phenylaziridine	(Oil)[a]	34
1-Acetonaphthone	2-(α-Naphthyl)-aziridine	66–67	64
3-Phenyl-2-butanone	2-(α-Methylbenzyl)-aziridine	(Oil)[b]	38
1-Tetralone		52–53.5[c]	11

[a]Cf. F. Wolfheim, *Ber.*, **47**, 1440 (1914); S. Gabriel and J. Colman, *Ber.*, **47**, 1866 (1914); S. J. Brois, *J. Org. Chem.*, **27**, 3532 (1962); A: Hassner and C. C. Heathcock, *Tetrahedron Letters*, 1125 (1964).

[b]Along with this formation of 2,3-dimethyl-2-phenylaziridine (oil, 10%) has been reported [G. Alvernhe and A. Raurent, *Bull. Soc. Chim. France*, 3003 (1970)].

[c]Cf. G. Drefahl and K. Ponsold, *Ber.*, **93**, 519 (1960); A. Hassner and C. Heathcock, *Tetrahedron*, **20**, 1037 (1964).

TABLE II DERIVATIVES OF AZIRIDINES PREPARED BY REDUCTION OF OXIMES WITH LITHIUM ALUMINUM HYDRIDE

Aziridine	1-(Phenyl-carbamoyl) Derivative, M.P., °C	1-(*p*-Nitrobenzoyl) Derivative, M.P., °C	Derived Thiazolidine-2-thione, M.P., °C
2-Phenyl-aziridine		120–122.5	170–171[a,b] 168–169[b,c]
2-(α-Naphthyl)-aziridine	133.5–135		235–237 (dec.)
2-(α-Methylbenzyl)-aziridine		65–66 and 178–179[d]	96.5–97.5 and 165.5–166[d]
	157–158		188.5–190.5

[a]Aziridine prepared from acetophenone.

[b]Cf. C. S. Dewey and R. A. Bafford, *J. Org. Chem.*, **30**, 491 (1965).

[c]Aziridine prepared from phenylacetaldehyde.

[d]Presumably *erythro* and *threo* isomers.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

α- and β-tetralone

1,2,3,4-dibenzo-1,3-cycloheptadien-6-one

ethanol (64-17-5)

sulfuric acid (7664-93-9)

Benzene (71-43-2)

methanol (67-56-1)

ether (60-29-7)

chloroform (67-66-3)

sodium sulfate (7757-82-6)

Acetophenone (98-86-2)

carbon (7782-42-5)

pyridine (110-86-1)

Hydroxylamine hydrochloride (5470-11-1)

potassium dichromate (7778-50-9)

aziridine (9002-98-6)

dibenzyl ketone, 1,3-Diphenyl-2-propanone (102-04-5)

phenylacetaldehyde (122-78-1)

Tetrahydrofuran (109-99-9)

1-Tetralone (529-34-0)

oximino

lithium aluminum hydride (16853-85-3)

dibenzyl ketoxime (1788-31-4)

2-benzyl-3-phenylaziridine

chalcone oxime

3,5-diphenyl-2-isoxazoline

bicyclo [2.2.2] octanone (2716-23-6)

2-Phenylaziridine, 2-Phenyl-aziridine

2-(α-Naphthyl)-aziridine

3-Phenyl-2-butanone

2-(α-Methylbenzyl)-aziridine

2,3-dimethyl-2-phenylaziridine

N-methyl-n-butylamine (110-68-9)

cis-2-Benzyl-3-phenylaziridine, Aziridine, 2-benzyl-3-phenyl-, cis- (1605-08-9)

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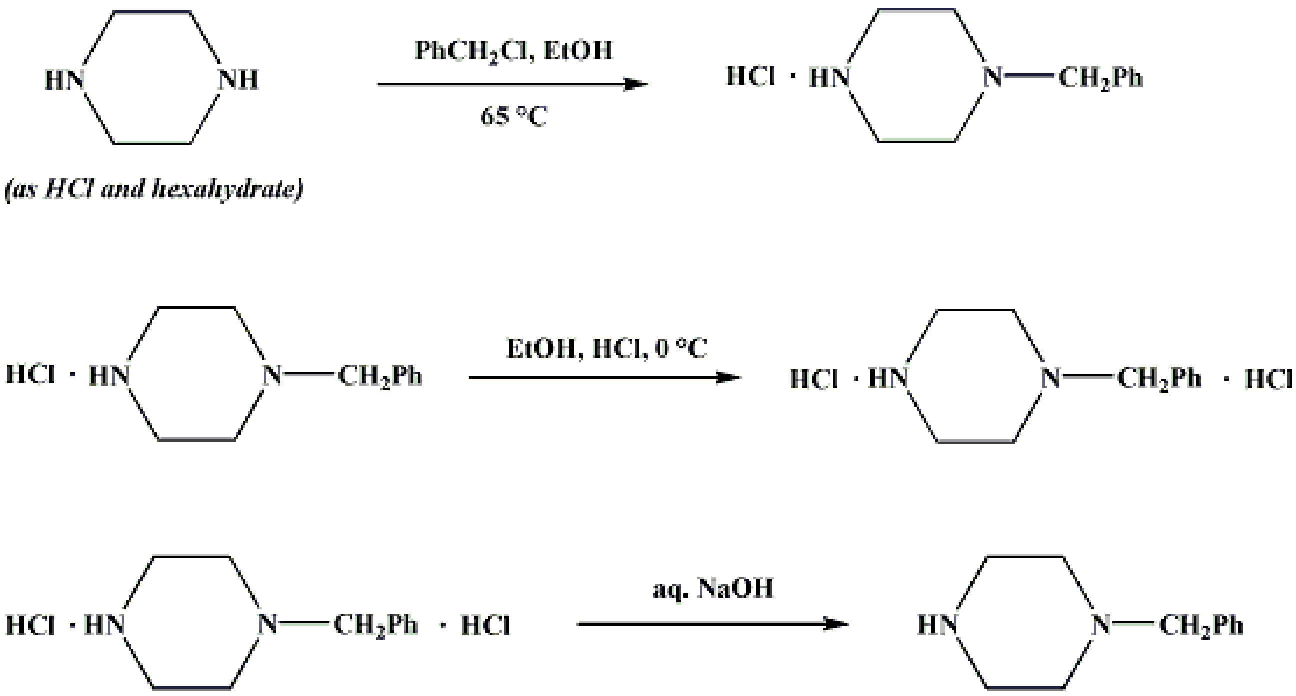
1-BENZYLPIPERAZINE

[Piperazine, 1-benzyl-]



Submitted by J. Cymerman Craig and R. J. Young[1].
Checked by James Cason and Taysir Jaouni.

1. Procedure

A solution of 24.3 g. (0.125 mole) of piperazine hexahydrate in 50 ml. of absolute ethanol, contained in a 250-ml. Erlenmeyer flask, is warmed in a bath at 65° as there is dissolved in the solution, by swirling, 22.1 g. (0.125 mole) of piperazine dihydrochloride monohydrate (Note 1). As warming in the bath at 65° is continued, there is added during 5 minutes, with vigorous swirling or stirring, 15.8 g. (14.3 ml., 0.125 mole) of recently distilled benzyl chloride. The separation of white needles commences almost immediately. After the solution has been stirred for an additional 25 minutes at 65°, it is cooled, and the unstirred solution is kept in an ice bath for about 30 minutes. The crystals of piperazine dihydrochloride monohydrate are collected by suction filtration, washed with three 10-ml. portions of ice-cold absolute ethanol, and then dried. Recovery of the dihydrochloride is 21.5–22.0 g. (97–99%) (Note 2).

The combined filtrate and washings from the piperazine dihydrochloride are cooled in an ice bath and treated with 25 ml. of absolute ethanol saturated at 0° with dry hydrogen chloride (Note 3). After the solution has been well mixed, it is cooled for 10–15 minutes in an ice bath. The precipitated white plates of 1-benzylpiperazine dihydrochloride are collected by suction filtration, washed with dry benzene, and dried. The product, which melts at about 280° with decomposition, after sintering at about 254° (Note 4), amounts to 29.0–29.5 g. (93–95%). A solution of this salt in 50 ml. of water is made alkaline (pH > 12) with about 60 ml. of 5*N* sodium hydroxide, then extracted twelve times with 20-ml. portions (Note 5) of chloroform. The combined extracts are dried over anhydrous sodium sulfate, and the pale-brown oil (Note 6) remaining after removal of solvent is distilled at reduced pressure in a Claisen flask. The yield of pure 1-benzylpiperazine, b.p. 122–124°/2.5 mm., n_D^{25} 1.5440–1.5450, is 14.3–16.5 g. (65–75%).

2. Notes

1. Piperazine dihydrochloride monohydrate, which is recovered almost quantitatively in this procedure, may be purchased from K and K Laboratories, Jamaica 33, New York, or from L. Light and Co., Ltd., Poyle, Colnbrook, Bucks, England. It may be readily prepared in essentially quantitative yield from the free base by the following procedure.
A brisk stream of hydrogen chloride gas is passed for 5–8 minutes into a solution of 24.3 g. (0.125 mole) of piperazine hexahydrate in 50 ml. of absolute ethanol contained in a 250-ml. Erlenmeyer flask. A wide gas-inlet tube (about 10 mm.) is used to avoid clogging, and the flask is cooled in an ice bath to keep the temperature at about 25°. After the gas stream has been discontinued, the contents of the flask are cooled to about 0°, and the crystalline product is collected by suction filtration and washed with two 25-ml. portions of ice-cold absolute ethanol. The yield is about 22 g. (0.125 mole).
2. If the filtrate from this isolation is evaporated to dryness at reduced pressure, crude 1-benzyl-4-piperazinium chloride is left as a residue. For removal of any piperazine dihydrochloride, the chloride may be crystallized after rapidly filtering a hot solution in about 50 ml. of absolute ethanol. Concentration of the filtrate, followed by cooling, gives 12.4 g. (84%) of 1-benzyl-4-piperazinium chloride as prismatic plates, m.p. 167–168°. This salt may be converted to the dihydrochloride by treatment with ethanolic hydrogen chloride.
3. When absolute ethanol is saturated with hydrogen chloride at 0°, the resultant solution is about 10.5*N* in hydrogen chloride.
4. The melting point has been reported as 253° by Baltzly and co-workers.[2]
5. The checkers found continuous extraction with chloroform to be convenient.
6. The free base rapidly absorbs carbon dioxide on exposure to air and should therefore be protected during both manipulation and storage. The undistilled oil may be converted in good yield to 1-benzoyl-4-benzylpiperazine hydrochloride, m.p. 245–245.5°, by treatment with benzoyl chloride in benzene solution.

3. Discussion

1-Benzylpiperazine has been prepared[2,3] by the reaction of piperazine and benzyl chloride, followed by fractionation of piperazine, and the mono- and dibenzyl derivatives. It has also been obtained[4] by alkaline hydrolysis of 1-benzyl-4-carbethoxypiperazine. The present method, which is a modification of that first reported by Cymerman Craig, Rogers, and Tate,[5] is simple and yields an easily purified product.

4. Merits of Preparation

The benzyl group, easily removed by hydrogenolysis, is an ideal blocking group for the preparation of 1-monosubstituted, and of 1,4-unsymmetrically disubstituted, piperazines.

Published methods for preparation of 1-benzylpiperazine involve either fractionation of mixtures of piperazine and its 1-benzyl- and 1,4-dibenzyl derivatives or the use of 1-carbethoxypiperazine as an intermediate. The procedure here described is simple; it yields, in 30 minutes, pure 1-benzylpiperazine dihydrochloride, stable to storage, from readily available starting materials, and free of any disubstituted compound.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 904

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

hydrogen chloride (7647-01-0)

Benzene (71-43-2)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium sulfate (7757-82-6)

carbon dioxide (124-38-9)

benzoyl chloride (98-88-4)

benzyl chloride (100-44-7)

1-Benzylpiperazine, Piperazine, 1-benzyl- (2759-28-6)

piperazine hexahydrate (142-63-2)

piperazine dihydrochloride monohydrate

piperazine dihydrochloride (142-64-3)

1-benzylpiperazine dihydrochloride

1-benzyl-4-piperazinium chloride

1-benzoyl-4-benzylpiperazine hydrochloride

piperazine (110-85-0)

1-benzyl-4-carbethoxypiperazine

1-carbethoxypiperazine (120-43-4)

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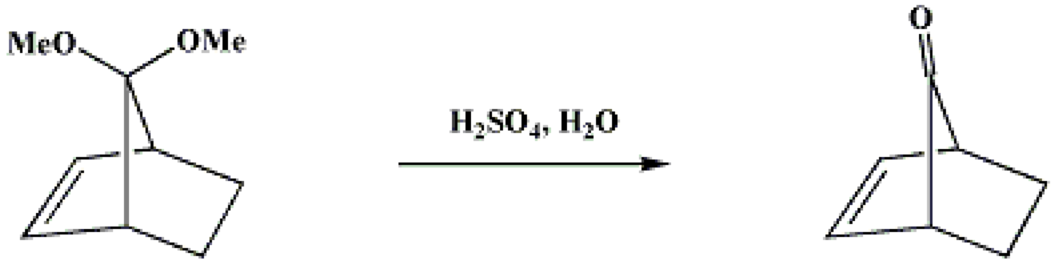
BICYCLO[2.2.1]HEPTEN-7-ONE

[2-Norbornen-7-one]



Submitted by P. G. Gassman and J. L. Marshall[1].
Checked by William G. Dauben and James L. Chitwood.

1. Procedure

Into a 250-ml. Erlenmeyer flask are placed 45.9 g. (0.298 mole) of 7,7-dimethoxybicyclo[2.2.1]heptene (Note 1), 75 ml. of 5% aqueous sulfuric acid, and a Teflon-coated magnetic stirring bar. The flask is stoppered, and the mixture is stirred vigorously with a magnetic stirrer for 20 hours. The mixture is extracted with three 40-ml. portions of pentane, and the combined extracts are dried over anhydrous magnesium sulfate. The drying agent is removed by filtration, and the solvent is distilled through a 12-in. Vigreux column. Fractional distillation of the residual oil yields 28.9 g. (90%) of colorless bicyclo[2.2.1]hepten-7-one, b.p. 96–100° (115 mm.), n^{25}D 1.4786 (Note 2) and (Note 3).

2. Notes

1. The preparation of 7,7-dimethoxybicyclo[2.2.1]heptene is described on p. 424.
2. The checkers, working at half-scale, obtained an 85% yield of product, b.p. 93–97° (118 mm.).
3. This material is extremely volatile and should be handled with care.

3. Discussion

Bicyclo[2.2.1]hepten-7-one has been prepared by the oxidation of *anti*-7-hydroxybicyclo[2.2.1]heptene with chromic acid in acetone[2] and with aluminum *t*-butoxide in benzene with benzoquinone as the hydrogen acceptor.[3] The procedure described here is essentially that of Gassman and Pape.[4]

4. Merits of the Preparation

Bicyclo[2.2.1]hepten-7-one is a useful intermediate in the synthesis of a variety of norbornane derivatives. The present procedure involves a four-step synthesis from hexachlorocyclopentadiene with a 39% overall yield. The next best method[3] involves a four-step synthesis from norbornadiene with a 15% overall yield.

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

Benzene (71-43-2)

hydrogen (1333-74-0)

acetone (67-64-1)

chromic acid (7738-94-5)

Pentane (109-66-0)

benzoquinone (106-51-4)

magnesium sulfate (7487-88-9)

Bicyclo[2.2.1]hepten-7-one, 2-Norbornen-7-one (694-71-3)

7,7-Dimethoxybicyclo[2.2.1]heptene (875-04-7)

hexachlorocyclopentadiene

norbornadiene

aluminum t-butoxide

anti-7-hydroxybicyclo[2.2.1]heptene

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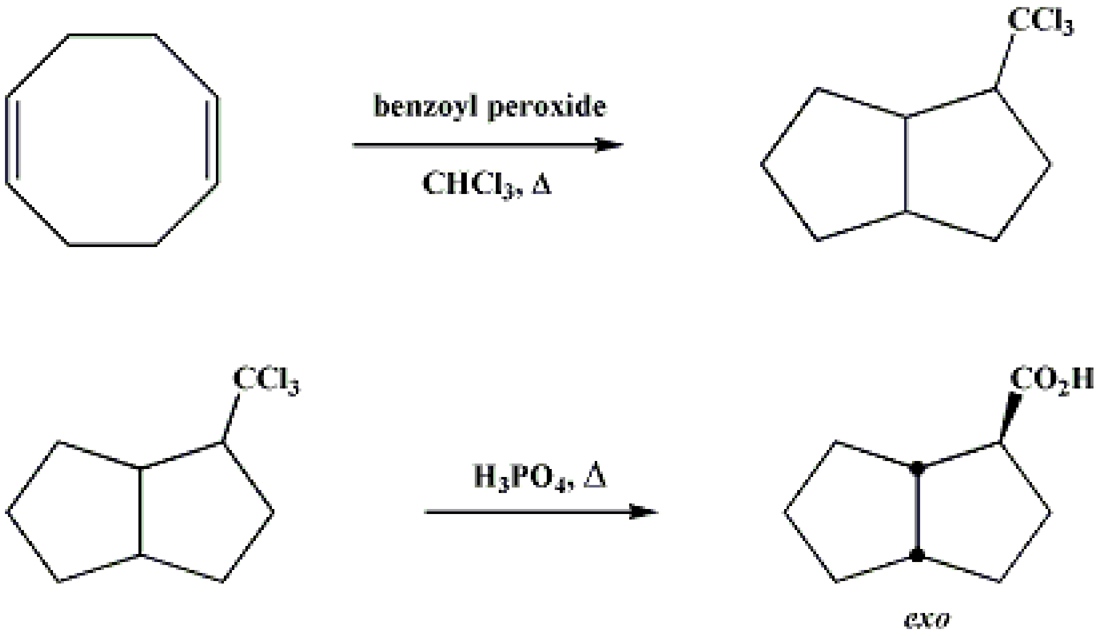
exo-cis-BICYCLO[3.3.0]OCTANE-2-CARBOXYLIC ACID

[1-Pentalenecarboxylic acid, octahydro-]



Submitted by R. Dowbenko[1]
Checked by E. J. Corey and B. W. Erickson.

1. Procedure

A. *2-(Trichloromethyl)bicyclo[3.3.0]octane*. To a 5-l. three-necked flask equipped with a mechanical stirrer, a reflux condenser, and a thermometer are added 325 g. (3.0 moles) of *cis,cis*-1,5-cyclooctadiene (Note 1), 3 l. of chloroform (Note 2), and 14.6 g. (0.06 mole) of benzoyl peroxide. The resulting solution is stirred and refluxed (63–65°) on the steam bath (Note 3) for a total of 5 days. Four 7.3 g.-(0.03 mole-)portions of benzoyl peroxide are added, one on each consecutive day of reaction (Note 4). After a total of 5 days at reflux, the reaction mixture is cooled and washed with three 250-ml. portions of aqueous sodium bicarbonate (Note 5) and with 250 ml. of water, all the washes being discarded. The chloroform solution is dried with 30 g. of magnesium sulfate and filtered. The filtrate is distilled at atmospheric pressure using a short (8-in.) Vigreux column to collect 2760–2790 ml. of chloroform, b.p. 55–64°, which is discarded. The pressure is reduced and distillation continued to obtain two fractions: (1) b.p. 31° (47 mm.) to 65° (0.2 mm.), 300 g.; (2) b.p. 65–153° (0.2 mm.), 169 g. (Note 6). Fraction 2 is refractionated with the same Vigreux column to obtain 106–117 g. (approximately 35% based on unrecovered *cis,cis*-1,5-cyclooctadiene) of 2-(trichloromethyl)bicyclo[3.3.0]octane, b.p. 116–125° (5 mm.), n^{25}D 1.5110–1.5115 (Note 7). The product is pure (by gas chromatography) (Note 8) and may be used in

the next step.

B. *exo-cis-Bicyclo[3.3.0]octane-2-carboxylic acid*. A mixture of 100 g. (0.440 mole) of 2-(trichloromethyl)bicyclo[3.3.0]octane and 500 ml. of 85% phosphoric acid is put into a 1-l. three-necked flask equipped with a mechanical stirrer, a reflux condenser, and a thermometer. The mixture is stirred and heated at 150° for 16 hours, during which time it evolves hydrogen chloride and darkens. The product is then allowed to cool and is poured into a separatory funnel. One liter of water is added and the resulting mixture is extracted with four 250-ml. portions of ether. The combined ether extract is then extracted with four 250-ml. portions of 2% aqueous sodium hydroxide (Note 9), and the resulting alkaline extract is washed with 100 ml. of ether to remove any neutral material (Note 10). The alkaline extract is acidified (to pH 2–3) with concentrated hydrochloric acid, and the oil which precipitates is extracted with three 250-ml. portions of ether. The resulting ether extract is dried with 15 g. of magnesium sulfate, filtered, and evaporated at 50° (30 mm.). The residue is then distilled at reduced pressure to obtain 29–32 g. (43–47%) of *exo*-*cis*-bicyclo[3.3.0]octane-2-carboxylic acid, b.p. 91–96° (0.15 mm.), n^{25}D 1.4839–1.4847 (Note 11).

2. Notes

1. The compound was obtained from Cities Service Research and Development Co., Petrochemical Development Department, Sixty Wall Tower, New York 5, New York. Analysis by gas chromatography showed it to be pure, and it was used without further purification.
2. Either technical or pure grade chloroform may be used.
3. It may also be refluxed with boiling chips without stirring. A heating mantle may be used in place of a steam bath.
4. The portions of peroxide may be added as such or, more conveniently and safely, as solutions in 25 ml. of chloroform over a period of 10–15 minutes.
5. It is important that all benzoic acid be removed by washing at this point because otherwise it will codistil with the product and will be difficult to separate by distillation.
6. Fraction 1 is discarded. If desired, it may be redistilled at atmospheric pressure to obtain, in addition to chloroform, 182 g. (1.68 moles) of *cis,cis*-1,5-cyclooctadiene, b.p. 145–157°.
7. The higher-boiling fraction, b.p. 129° (5 mm.) to 138° (0.2 mm.), amounts to 35–50 g. and contains at least four compounds.
8. A 2-ft. column of 20% UCON Polar 50 HB 5100 on Chromosorb W, 130°, retention time 5 minutes.
9. Because of the high acidity of the ether extract it is more convenient to use sodium hydroxide than sodium bicarbonate.
10. This ether wash may be combined with the main neutral fraction and distilled to obtain 29–30 g. (33–34%) of 2-(dichloromethylene)bicyclo[3.3.0]octane, b.p. 53–56° (0.1 mm.), n^{25}D 1.5179–1.5182 (pure by gas

chromatography) (column as in (Note 8), 125°, retention time 4 minutes).

11. Analysis by gas chromatography shows the acid to be pure (column as in (Note 8)), retention time 4 minutes at 175°.

3. Discussion

exo-*cis*-Bicyclo[3.3.0]octane-2-carboxylic acid has been prepared from *cis*-bicyclo[3.3.0]-2-octanone cyanohydrin,[2] by Beckmann rearrangement of tetrahydro-*exo*-dicyclopentadiene-9-one oxime,[3] and by the present method.[4]

4. Merits of the Preparation

This two-step procedure appears to be by far the most convenient one for preparing *exo*-*cis*-bicyclo[3.3.0]octane-2-carboxylic acid from the readily available starting materials. The first step of the procedure is also illustrative of the method of obtaining 2-substituted bicyclo[3.3.0]octanes[4,5] from *cis,cis*-1,5-cyclooctadiene.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

tetrahydro-exo-dicyclopentadiene-9-one oxime

hydrogen chloride, hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium bicarbonate (144-55-8)

Benzoic acid (65-85-0)

phosphoric acid (7664-38-2)

peroxide (7722-84-1)

benzoyl peroxide (94-36-0)

magnesium sulfate (7487-88-9)

1-Pentalenecarboxylic acid, octahydro-

2-(Trichloromethyl)bicyclo[3.3.0]octane (18127-07-6)

2-(dichloromethylene)bicyclo[3.3.0]octane

exo-cis-Bicyclo[3.3.0]octane-2-carboxylic acid (18209-43-3)

cis,cis-1,5-cyclooctadiene

cis-bicyclo[3.3.0]-2-octanone cyanohydrin

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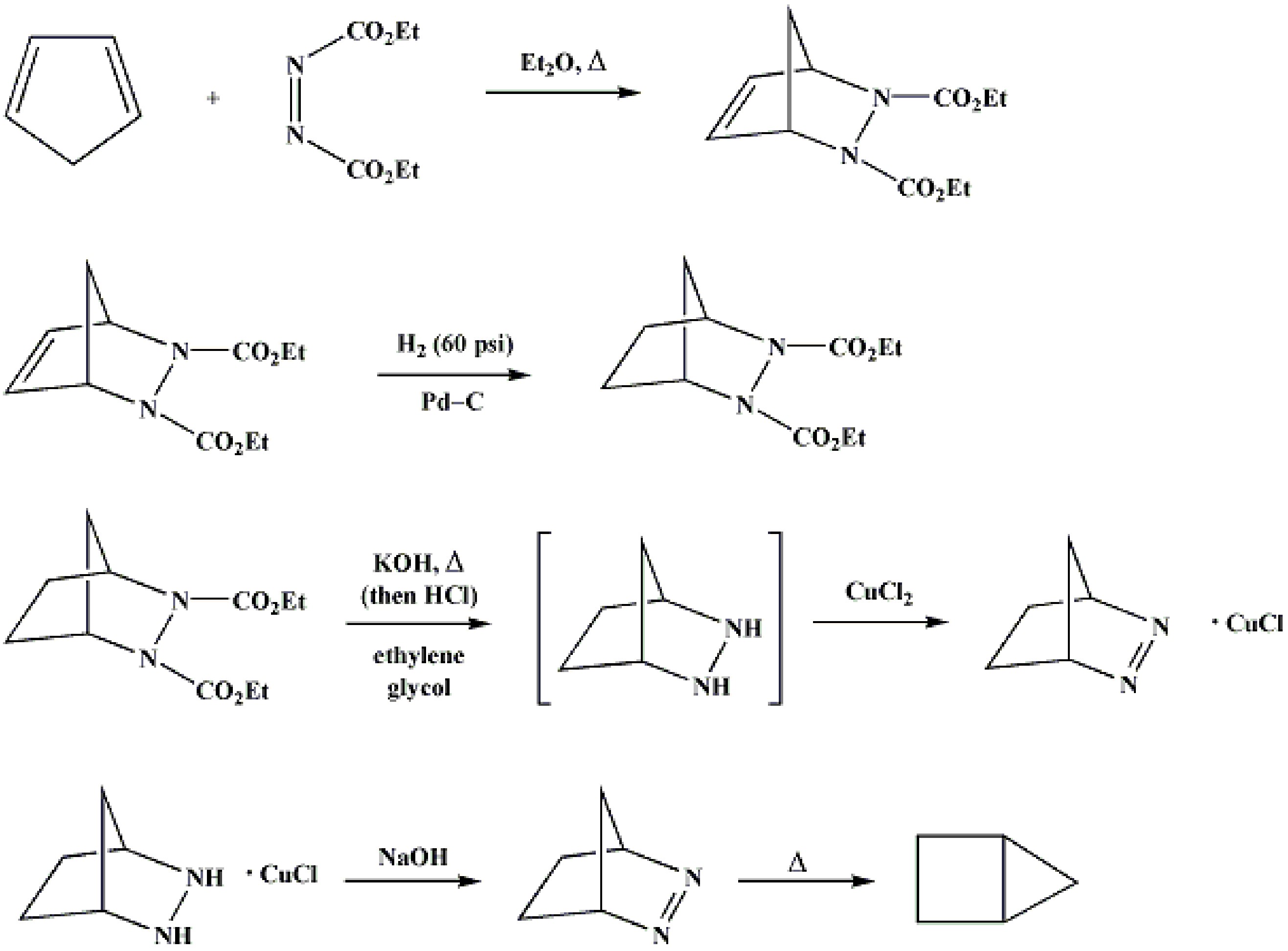
BICYCLO[2.1.0]PENTANE



Submitted by P. G. Gassman and K. T. Mansfield[1].
Checked by G. N. Taylor and K. B. Wiberg.

1. Procedure

A. *Diethyl 2,3-diazabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate*. In a 1-l., three-necked, round-bottomed flask equipped with a constant-pressure dropping funnel, a mechanical stirrer, and a reflux condenser is placed 174 g. (1.0 mole) of ethyl azodicarboxylate[2] in 150 ml. of ether. Freshly prepared cyclopentadiene[3] (70 g., 1.06 moles) is added dropwise over a 1-hour period to the stirred ethereal solution of diethyl azodicarboxylate. During the addition a gentle reflux is maintained by external cooling with an ice-water bath as needed. When the addition is complete, the reaction mixture is allowed to stand for 4 hours, or less if the yellow color of the azodicarboxylic acid ester disappears. The dropping funnel and condenser are replaced by a glass stopper and a short distillation head, respectively. The ether and unreacted diene are distilled off on a steam bath and the residue is transferred to a 500-ml. round-bottomed boiling flask equipped with a 30-cm. Vigreux column. After a small forerun the diethyl 2,3-diazabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate distills to give 218–228 g. (91–95%) of a colorless or very pale yellow, viscous liquid, b.p. 119–120° (0.4 mm.).

B. *Diethyl 2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylate*. A mixture of 112 g. (0.47 mole) of diethyl 2,3-diazabicyclo[2.2.1] hept-5-ene-2,3-dicarboxylate and 125 ml. of absolute ethanol is placed in a standard Paar bottle along with 0.2 g. of 5% palladium on carbon catalyst (Note 1). The bottle is attached to the Paar hydrogenation apparatus, and shaking is begun using an initial pressure of 60 p.s.i. After 2 hours, hydrogen uptake ceases. The mixture is gravity-filtered twice and the ethanol is removed using a rotary evaporator. The entire procedure is repeated on a second batch and the crude product from the combined runs is placed in a 500-ml. round-bottomed boiling flask fitted with a 15-cm. Vigreux column. Fractional distillation gives 218–223 g.

(95–97%) of diethyl 2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylate, b.p. 107–108° (0.05 mm.), n^{22}D = 1.4730.

C. *2,3-Diazabicyclo[2.2.1]hept-2-ene*. A slow stream of nitrogen is bubbled through 1.2 l. of ethylene glycol (Note 2) for 20 minutes in a mechanically stirred 2-l. three-necked flask with mild heating (Note 3). The gas inlet tube is replaced with a condenser and a thermometer which reaches below the level of the ethylene glycol, and 275 g. (4.2 moles) of reagent grade potassium hydroxide pellets (85% pure) is added in four portions. A constant-pressure dropping funnel containing 223 g. (0.92 moles) of diethyl 2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylate is connected and the reaction vessel is flushed with nitrogen. The ethylene glycol solution is heated to 125° and the diethyl 2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylate is added as rapidly as is permitted by its viscous nature. The heating source is removed whenever the reaction temperature approaches 130°. After the addition is complete, the reaction mixture is stirred at 125° for 1 hour. The reaction mixture is allowed to cool and then poured *slowly* into a 4-l. beaker which contains 1 kg. each of ice and water and 450 ml. of concentrated hydrochloric acid *(Caution. Vigorous foaming occurs)* (Note 4). When the acidification is complete, the reaction mixture is warmed to about 40° and neutralized with 5*N* ammonium hydroxide. Half of this neutral solution is transferred to a second 4-l. beaker and subsequent operations are carried out on both batches.

The solution is stirred slowly and *ca.* 25 ml. of 2*N* cupric chloride solution is added slowly. The blue-green color of the cupric chloride is rapidly discharged and a brick red coloration occurs, followed by the precipitation of voluminous bright red crystals of the cuprous chelate of 2,3-diazabicyclo[2.2.1]hept-2-ene. The *p*H is adjusted to 5–6 by the addition of 5*N* ammonium hydroxide. Addition of 25 ml. of the cupric chloride solution followed by neutralization of the generated hydrochloric acid with 5*N* ammonium hydroxide is repeated five times. The precipitate is collected by filtration and the filtrate is again treated with 25-ml. portions of cupric chloride solution and 5*N* ammonium hydroxide. The procedure is repeated until the filtrate is clear red at *p*H 3–4 and returns to a cloudy green at *p*H 6 with no further formation of precipitate (Note 5).

The combined precipitate from the two batches is carefully washed with 500 ml. of 20% ammonium chloride solution, two 400-ml. portions of 95% ethanol, and two 300-ml. portions of cold water. The product is sucked as dry as possible in the suction funnel.

The damp product is broken up and transferred to a 1-l. flask containing a magnetic stirring bar and 400 ml. of water. A cold solution of 60 g. of sodium hydroxide in 100 ml. of water is added slowly with magnetic stirring. The stirred yellow-orange suspension is then continuously extracted with 700 ml. of pentane for 48 hours.

The pentane extract is dried over 10 g. of anhydrous potassium carbonate. After removal of the drying agent by filtration, the pentane is slowly removed from the product by distillation through a 20-cm. Hempel column packed with glass helices (Note 6). When the pentane is removed, a white crystalline residue remains which weighs 78–83 g. (88–94% yield based on the hydrogenated Diels-Alder adduct). This 2,3-diazabicyclo [2.2.1] hept-2-ene melts at 98.0–99.5° (Note 7).

D. *Bicyclo[2.1.0]pentane*. Finely powdered 2,3-diazabicyclo[2.2.1]hept-2-ene (83 g., crude product from above) is placed in a 500-ml., one-necked, round-bottomed flask. The flask is heated at 130–140° in an oil bath to completely remove any traces of pentane. A 25-cm. unpacked Hempel column is installed and connected directly to a 100-ml. receiver flask having a side arm to which is attached a drying tube packed with silica gel. The receiver is cooled in a dry ice-acetone bath. The azobicyclic is pyrolyzed by heating the oil bath to 180–195°. At the preferred rate of pyrolysis, the starting material condenses about one fourth of the way up the column. Occasional flaming of the column may be necessary to prevent plugging of the column by the solidifying starting material. At the end of the pyrolysis (8 hours) only a small, black, nonvolatile residue remains: The condensed bicyclo[2.1.0]pentane is allowed to warm to room temperature, dried over anhydrous magnesium sulfate, and the drying agent removed by filtration through glass wool into a 100-ml. distillation flask. *(Caution! Bicyclo[2.1.0]pentane is a very volatile hydrocarbon and requires appropriate handling for high yields.)* Distillation leaves a residue of about 1 g. of the starting azobicyclic and affords 53.5–55.5 g. (90.0–93.5%) of bicyclo[2.1.0]pentane, b. p. 45.5°, n^{20}D 1.4220 (Note 8).

2. Notes

1. The submitters effected the hydrogenation using a medium-capacity, rocker-type, high-pressure hydrogenator with an initial hydrogen pressure of 700 p.s.i. By employing these conditions, the reaction

time is reduced to 20–30 minutes. The yield is unchanged.
2. Technical grade ethylene glycol such as that sold by Union Carbide Corp. is suitable for this purpose.
3. A large oil bath supported by a laboratory jack is used for this and subsequent operations when rapid removal of the heat source might be necessary.
4. Foaming may easily be controlled even with rapid addition of the basic solution by vigorous stirring employing the mechanical stirrer used during the reaction.
5. The precipitation of copper oxides in slightly alkaline solution should not be confused with the formation of the bright red crystals of the organocuprous complex.
Recrystallization of the crude copper complex from boiling 20% ammonium chloride (*p*H 4) affords lustrous brick red needles. Analytically pure material is obtained on a second recrystallization from 0.001*N* hydrochloric acid followed by drying over phosphorus pentoxide.
6. If the supersaturated pentane solution tends to foam toward the end of the distillation, the pot should be allowed to cool. This causes the product to crystallize. Once the crystals start to form, foaming is no longer a problem.
7. This material may be further purified (m.p. 99.5–100.0°) by recrystallization from pentane or methanol, or by sublimation at 85° (60 mm.). Owing to the unusually high vapor pressure of this product, large losses may be encountered on recrystallization or sublimation unless due care is exercised.
8. If all the pentane is removed before pyrolysis, the bicyclo [2.1.0]pentane shows no impurities on vapor phase chromatography with a 20% Dow 710 on 50/60 U Anaprep column. Analysis by n.m.r. also revealed the absence of any traces of cyclopentene in the spectrum consisting of three complex multiplets at 0.3–0.8, 1.1–1.7, and 1.9–2.4 p.p.m. (downfield from internal tetramethylsilane reference).

3. Discussion

The procedure described is a modification of that developed by Diels[4] and Criegee.[5] Bicyclo[2.1.0]pentane has been prepared by the pyrolysis of 2,3-diazabicyclo[2.2.1]hept-2-ene,[5,6] the photolysis of 2,3-diazabicyclo[2.2.1]hept-2-ene,[7] the pyrolysis of N-phenyl-2-oxo-3-azabicyclo[2.2.1]heptane,[8] and the addition of methylene to cyclobutene.[9]

The procedure described is suitable for the preparation of bicyclo [2.1.0]pentane on a large scale. The product is obtained free of impurities and the general method is relatively safe. The starting materials are readily available. The hydrolysis of the diester is very reproducible, a feature that was not true of the literature procedure.[4] The pyrolysis step is much simpler and cleaner than the published description.[5] In addition, the procedure described gives a general method of hydrazo oxidation and for the pyrolysis of azo compounds. Oxidations of the type described in this procedure have been used to prepare a wide variety of cyclic azo compounds. Highly unstable azo compounds have been isolated as the stable crystalline cupric chloride complexes.[10,11,12] The thermolysis (and/or photolysis) of appropriately substituted cyclic azo compounds has become a highly useful method for the preparation of strained ring systems.[13,14,15,16,17,18]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

cuprous chelate of 2,3-diazabicyclo[2.2.1]hept-2-ene

ethanol (64-17-5)

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

methanol (67-56-1)

ether (60-29-7)

ammonium chloride (12125-02-9)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

nitrogen (7727-37-9)

carbon (7782-42-5)

potassium hydroxide (1310-58-3)

palladium (7440-05-3)

ethylene glycol (107-21-1)

cupric chloride (7758-89-6)

ammonium hydroxide (1336-21-6)

Pentane (109-66-0)

magnesium sulfate (7487-88-9)

Cyclopentene (142-29-0)

methylene (2465-56-7)

Ethyl azodicarboxylate

diethyl azodicarboxylate (1972-28-7)

CYCLOPENTADIENE (542-92-7)

Bicyclo[2.1.0]pentane, bicyclo [2.1.0]pentane (185-94-4)

Diethyl 2,3-diazabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate, diethyl 2,3-diazabicyclo[2.2.1] hept-5-ene-2,3-dicarboxylate (14011-60-0)

Diethyl 2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylate (18860-71-4)

2,3-Diazabicyclo[2.2.1]hept-2-ene, 2,3-diazabicyclo [2.2.1]hept-2-ene

tetramethylsilane (75-76-3)

N-phenyl-2-oxo-3-azabicyclo[2.2.1]heptane

cyclobutene (822-35-5)

phosphorus pentoxide (1314-56-3)

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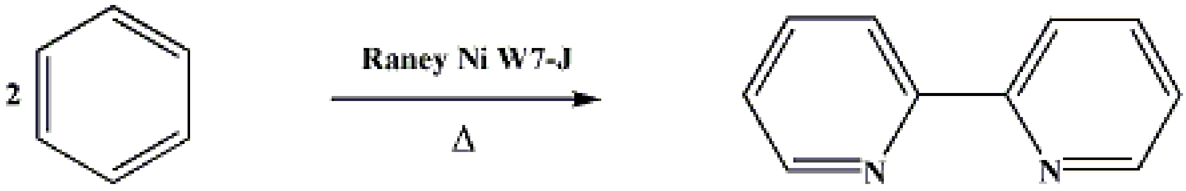
2,2'-BIPYRIDINE



Submitted by W. H. F. Sasse[1]
Checked by Victor A. Snieckus and V. Boekelheide.

1. Procedure

A. *Degassed Raney nickel catalyst (W7-J). Caution! Raney nickel catalysts which have been prepared by the usual methods should not be heated in vacuum, as large quantities of heat and hydrogen may be given off suddenly, and dangerous explosions may result.*[2,3]

In a hood a 2-l., wide-mouthed Erlenmeyer flask containing 600 ml. of distilled water is placed in an empty water bath and fitted with an efficient stainless steel stirrer, so that its blades are half immersed. The stirrer is started, and 160 g. of sodium hydroxide is dissolved in the water. Then 125 g. of 1:1 aluminum-nickel alloy (Note 1) is added in portions as rapidly as possible, but at such a rate that no material is lost by frothing with the stirrer running at full speed (Note 2). When all the alloy has been added the stirrer is slowed down, and the catalyst is washed down from the sides of the flask with distilled water. As soon as the reaction has subsided the water bath is filled with boiling water, and the catalyst is slowly stirred while the volume is kept up by the occasional addition of distilled water so that the catalyst is well covered at all times. After 6 hours, stirring and heating are discontinued, and the catalyst is allowed to stand at room temperature for 12–15 hours. It is then washed by decantation with ten 250-ml. portions of distilled water and transferred to a 1-l., round-bottomed, three-necked flask by means of distilled water. The total volume of catalyst and water is adjusted to 300 ml., and the flask placed in a cold water bath which is equipped with a thermometer. One side arm is fitted with a 100-ml. dropping funnel, and the other two necks are each connected to a 3-l. Büchner flask by short lengths of thick-walled, wide-bore rubber tubing (Note 3), (Note 4). One of the Büchner flasks is connected to a vacuum gauge and then to an efficient water pump. The other Büchner flask is connected directly to a second, equally efficient water pump. To control the pressure inside the apparatus, a screw clamp is placed between each Büchner flask and each pump (Note 5). With these clamps completely closed both pumps are turned on fully. The pressure inside the apparatus is now gradually reduced by opening the clamps at such a rate that no excessive frothing occurs. When both clamps are fully open, the water bath is heated slowly until the water in the reaction flask begins to boil. The bath is kept at this temperature until there is no more water left in the flask (Note 6). Then, with both clamps fully opened, the temperature of the water bath is raised to 100°

during 15–20 minutes and kept at this temperature for 2 hours. After this time the catalyst is allowed to cool to 50–60°; it is now ready for use.

B. *2,2'-Bipyridine*. With the apparatus set as described above, 100 ml. of pure pyridine (Note 7) is poured into the dropping funnel, and the screw clamps are completely closed. Immediately afterward about 80 ml. of the pyridine is run slowly onto the catalyst from the dropping funnel. Under no circumstances is any air allowed to enter the flask. The flask is then shaken carefully in order to wet the catalyst as much as possible with pyridine. Another 80 ml. of pyridine is added in the same way, and the flask is shaken again. Finally 40 ml. of pyridine is added, and air is allowed to enter the flask. The connections to the Büchner flask are removed, and a reflux condenser is fitted. The reaction mixture is then boiled gently under reflux (Note 8). After about 48 hours the flask is allowed to cool to about 60°, and most of the liquid is decanted (*Hood!*) and filtered through a sintered-glass funnel (Note 9) into a 500-ml. round-bottomed flask. Then 50 ml. of fresh pyridine is added to the catalyst in the reaction flask, and the mixture is heated to reflux for 10 minutes. The flask contents are allowed to cool to about 60° and the pyridine is decanted and filtered as before. This extraction is repeated two more times. The flask containing the filtrates is then equipped for vacuum distillation (Note 10), and most of the pyridine is removed on a water bath under reduced pressure (20–30 mm.) at a bath temperature not exceeding 40°. Toward the end of the distillation the bath temperature is raised to about 75° for 10 minutes (Note 11). The residue from this distillation is extracted with 100 ml. of boiling petroleum ether (Note 12), and the insoluble cream-colored material is collected by filtration and washed with three 25-ml. portions of the boiling petroleum ether (Note 13). The filtrate is chromatographed over alumina (Note 14) using petroleum ether (60–90°) for elution. The first 2 l. of eluate is collected, concentrated to 100 ml., and allowed to stand overnight in a refrigerator. The crude solid (23–24 g.) is collected and recrystallized from about 80 ml. of petroleum ether (60–90°) to give 21.0 g. of 2,2'-bipyridine as white crystals, m.p. 70–71° (Note 15), (Note 16).

2. Notes

1. The nickel-aluminum alloy used was supplied by British Drug Houses (through the Ealing Corporation in the U.S.A.). Average particle size was about 4 • as measured by a Fisher Sub-sieve Sizer. Alloys of a finer particle size (about 2.85 •) gave rise to considerable loss of catalyst during the washing and lost hydrogen during the degassing procedure in a much more vigorous fashion.
2. With a motor running at approximately 3500–4500 r.p.m. the addition of the alloy is completed in less than 10 minutes. Alcohol should not be added to the catalyst to control the frothing.
3. The Büchner flasks are included in the apparatus to accommodate relatively large quantities of hydrogen which are sometimes given off suddenly by the catalyst during the later stages of the degassing. Instead of Büchner flasks, strong round-bottomed flasks may be used.
4. Rubber tubing with diameters of 9 mm. I.D. and 17 mm. O.D. was used.
5. An air leak cannot be employed to regulate the vacuum inside the reaction

flask since the catalyst becomes increasingly pyrophoric as the degassing progresses.

6. The average time required for the complete removal of the water from the catalyst varies from 4 to 12 hours. It is essential to evaporate the water slowly since much nickel may be lost if the water boils too vigorously. If the temperature of the bath should rise too high, the screw clamps are closed far enough to increase the pressure slightly in the apparatus. As soon as the bath has cooled to the required temperature, the clamps are reopened fully. The maximum practical temperature for the removal of the water was found to be 25–30° at pressures between 17 and 20 mm.

7. The pyridine used must be free of pyrrole since as little as 0.001% of pyrrole will markedly decrease the yield. The checkers found it most satisfactory to use spectroquality pyridine supplied by Matheson, Coleman and Bell. The submitters purified their pyridine by distillation from potassium hydroxide. To test for the presence of pyrrole, a 0.5-ml. sample of pyridine is diluted with 2.5 ml. of water, and 2 ml. of concentrated hydrochloric acid is added followed by 0.5 ml. of a 5% solution of *p*-dimethylaminobenzaldehyde in dilute hydrochloric acid (1:10 dilution of concentrated hydrochloric acid). If pyrrole is present, a red-purple color appears. Spectroquality pyridine gives a negative result in this test.

8. Excessive bumping will occur if the reaction mixture is heated too strongly.

9. A sintered-glass funnel (diameter 9 cm.) of medium porosity was used. The filtration is conveniently carried out under slightly reduced pressure, but care must be taken to keep any nickel on the funnel damp, as the catalyst is highly pyrophoric.

10. A relatively wide capillary (about 0.5 mm. I.D.) should be used to avoid blockages toward the end of the distillation.

11. The distillate contains, besides pyridine, small quantities of pyrrole, water, and 2,2'-bipyridine.

12. A petroleum fraction, b.p. 60–90° containing 5% of aromatics, was used throughout.

13. The petroleum-insoluble material is a nickel (II) complex containing 2,2'-bipyridine and 2,2'-pyrrolylpyridine.[4] About 1.5 g. of this compound is obtained.

14. The checkers used No. 2 grade neutral alumina (Woelm) in a column 3.5 × 20 cm. If a more active alumina is used, larger quantities of petroleum ether are needed for the elution.

15. Small quantities of 2,2',2''-tripyridine are removed by this recrystallization.

16. Similarly 3- and 4-alkylpyridines give the corresponding 5,5'-dialkyl-2,2'-bipyridines and 4,4'-dialkyl-2,2'-bipyridines, respectively, in good yield when treated with W7-J nickel.[5] Somewhat lower yields of 2,2'-biquinolines are obtained with quinolines.[6,7]

3. Discussion

2,2'-Bipyridine has been prepared by the action of ferric chloride,[8,9] iodine,[10] or a

nickel-alumina catalyst[10] on pyridine at temperatures ranging from 300° to 400°. It has also been obtained from the reaction of 2-bromopyridine and copper.[11] The present procedure is a modification of a previously published, general method.[3] The W7-J nickel catalyst was developed from the description of the W7 Raney nickel catalyst of Billica and Adkins.[12]

4. Merits of the Preparation

This procedure serves two purposes. It provides a synthesis for the important chelating reagent 2,2'-bipyridine, a substance of interest in several fields of chemistry, and it gives a preparation of an active, degassed Raney nickel catalyst.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 468

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alumina

petroleum ether

2,2',2"-tripyridine

W7-J nickel

2,2'-biquinolines

nickel-alumina

W7 Raney nickel

alcohol (64-17-5)

hydrochloric acid (7647-01-0)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

copper (7440-50-8)

nickel, Raney nickel (7440-02-0)

iodine (7553-56-2)

pyridine (110-86-1)

potassium hydroxide (1310-58-3)

ferric chloride (7705-08-0)

Pyrrole (109-97-7)

2-Bromopyridine (109-04-6)

nickel-aluminum, aluminum-nickel

nickel (II)

p-Dimethylaminobenzaldehyde (100-10-7)

2,2'-Bipyridine (366-18-7)

2,2'-pyrrolylpyridine

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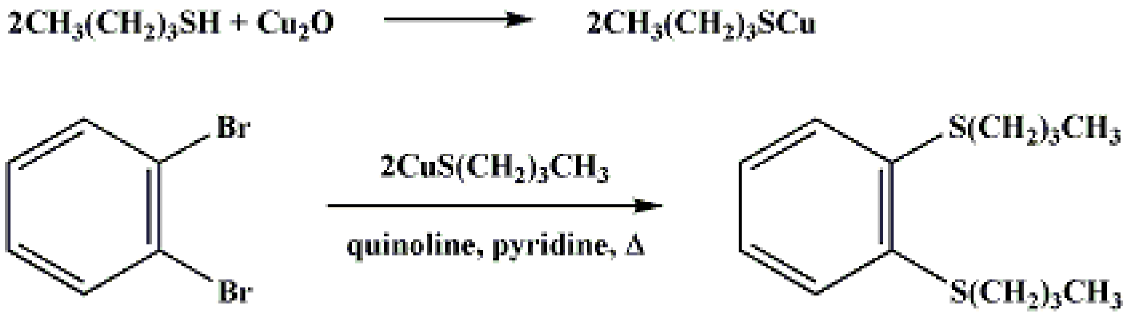
1,2-BIS(*n*-BUTYLTHIO)BENZENE

[Benzene, *o*-bis(butylthio)-]



Submitted by Roger Adams[1], Walter Reifschneider[2], and Aldo Ferretti[3].
Checked by William E. Parham, Wayland E. Noland, and James R. Throckmorton.

1. Procedure

A. *Cuprous n-butylmercaptide*. A mixture of 42.9 g. (0.30 mole) of freshly prepared cuprous oxide (Note 1), 61.3 g. (0.68 mole)of 1-butanethiol, and 750 ml. of 95% ethanol is heated under reflux with mechanical stirring (Note 2) until the orange or red color of the cuprous oxide is completely changed to the white color of the cuprous *n*-butylmercaptide (Note 3). The product is collected by filtration, washed several times with 95% ethanol, and dried in a vacuum. The yield is 91.6 g., essentially quantitative (Note 4).

B. *1,2-Bis(n-butylthio)benzene*. In a 1-l., round-bottomed, three-necked flask fitted with a reflux condenser, a mechanical stirrer, and a thermometer which reaches into the reaction mixture is placed a solution of 59.0 g. (0.25 mole) of *o*-dibromobenzene in a mixture of 250 ml. of quinoline and 80 ml. of pyridine. To this solution is added 84.0 g. (0.55 mole) of cuprous *n*-butylmercaptide, and the mixture is stirred and heated under reflux (Note 5) for 3.5 hours (Note 6). Heating is stopped and the reaction mixture is allowed to cool to about 100°. It is then poured into a stirred mixture of 1500 g. of ice and 400 ml. of concentrated hydrochloric acid; occasional stirring is continued for about 2 hours. The aqueous part is then decanted from the dark brown, gummy residue and is extracted twice with 400 ml. portions of ether. The ether extract is added to the residue, and the resulting mixture is stirred for about 5 minutes. The ether solution is then decanted from the residue and is filtered. The residue is extracted twice more with 400-ml. portions of ether (Note 7). The combined ether extract is washed twice with 100-ml. portions of 10% hydrochloric acid, once with water, and twice with 100-ml. portions of concentrated ammonia (Note 8). After a final wash with water, the ether solution is dried over anhydrous potassium carbonate. The potassium carbonate is collected on a filter, and the ether is removed from the filtrate by

distillation. The remaining brown oil is distilled in vacuum, giving a pale orange oil, b. p. 123–124°/0.3 mm., n_D^{25} 1.5684. The yield is 46.5–56.0 g. (73–87%) (Note 9).

2. Notes

1. Cuprous oxide was prepared according to the procedure of King.[4] A good grade of commercial cuprous oxide may also be used, but the time required to complete the conversion into mercaptide may be considerably longer (see (Note 3)).
2. It is not necessary to carry out the reaction under nitrogen, but it is advisable to close the condenser with a cotton plug or with a capillary tube to limit the entrance of air.
3. When freshly prepared cuprous oxide is used, a period of about 12 hours is generally sufficient. For commercial grade cuprous oxide the time required varies between 8 and 150 hours, depending on the reactivity of the cuprous oxide.
4. The checkers obtained a yield of 97%. The submitters and checkers have found that both larger and smaller runs can be carried out without difficulty or reduction in yield.
5. The pot temperature should rise during the reaction from about 150° at the beginning of reflux to about 170° at the end of the reaction time. Pot temperatures lower than 150° and higher than 180° result in lower yields.
6. Approximately 10 minutes after the mixture starts to boil a homogeneous solution is obtained.
7. If the last ether extract is not almost colorless, one more extraction of the residue with ether should be carried out.
8. If the ammonia layer is dark blue at the second extraction, extraction with ammonia should be continued until only a pale blue extract results.
9. The present procedure has also been used by the submitters to prepare the following thioethers: 1,4-bis-(*n*-butylthio)benzene, pale yellow oil, b.p. 142°/0.5 mm., n_D^{20} 1.5726, from *p*-dibromobenzene and cuprous *n*-butylmercaptide (yield 68–74%); 1,2-bis(phenylthio)benzene, white crystals, m.p. 42.5–44.5°, b. p. 190°/1 mm., from *o*-dibromobenzene and cuprous phenylmercaptide (see below) (yield 79–83%), or from *o*-dichlorobenzene (see below) and cuprous phenylmercaptide (yield 58–71%); 1,4-bis(phenylthio)benzene, white crystals, m.p. 82–83°, from *p*-dibromobenzene and cuprous phenylmercaptide (yield 80–84%), or from *p*-dichlorobenzene (see below) and cuprous phenylmercaptide (yield 59–72%).[5] The same method can be applied to the preparation of many other thioethers.
Cuprous phenylmercaptide is prepared from cuprous oxide and benzenethiol according to the procedure given for cuprous *n*-butylmercaptide. A heating period of only 2 hours (when freshly prepared cuprous oxide is used), however, is required to obtain the yellow compound. Chloro compounds can be used instead of bromo compounds for the reaction with cuprous phenylmercaptide.

However, a higher reaction temperature (210–220°) and a longer reaction time (24 hours) is required. The necessary pot temperature is obtained by using a mixture of 350 ml. of quinoline and 8 ml. of pyridine as solvents. It is also advantageous to use a larger excess of cuprous phenylmercaptide (121 g., 0.69 mole).
Aromatic chloro compounds cannot be used for reactions with aliphatic cuprous mercaptides.

3. Discussion

1,2-Bis(*n*-butylthio)benzene and 1,4-bis(*n*-butylthio)benzene have been prepared from the corresponding dibromobenzene and cuprous *n*-butylmercaptide, using a mixture of quinoline and pyridine as solvent.[6,5] 1,2-Bis(phenylthio)benzene and 1,4-bis (phenylthio)benzene have been prepared from the corresponding dichloro- or dibromobenzenes and cuprous phenylmercaptide, using a mixture of quinoline and pyridine as solvent.[6] 1,4-Bis(phenylthio)benzene has also been prepared from *p*-dibromobenzene or *p*-bromophenyl phenyl sulfide and lead phenylmercaptide[7] and from diazotized 4-aminophenyl phenyl sulfide and sodium phenylmercaptide.[8]

4. Merits of Preparation

As indicated (Note 9), the present procedure can be adapted for the preparation of a wide range of aryl and vinyl sulfides.[5] This, in combination with the cleavage reaction described for the preparation of 1,2-dimercaptobenzene (p. 419), provides a convenient and general method for the preparation of aryl mercaptans.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 419

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Appendix

Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ether (60-29-7)

nitrogen (7727-37-9)

pyridine (110-86-1)

cuprous oxide

Quinoline (91-22-5)

Benzenethiol (108-98-5)

1-butanethiol (109-79-5)

1,2-bis(phenylthio)benzene

phenylmercaptide (139-66-2)

1,4-bis(phenylthio)benzene

dibromobenzene, o-dibromobenzene (583-53-9)

4-aminophenyl phenyl sulfide (1135-14-4)

1,2-Dimercaptobenzene (17534-15-5)

cuprous phenylmercaptide (34012-88-9)

o-dichlorobenzene (95-50-1)

p-dibromobenzene (106-37-6)

p-dichlorobenzene (106-46-7)

1,2-BIS(n-BUTYLTHIO)BENZENE, Benzene, o-bis(butylthio)- (53663-38-0)

cuprous n-butylmercaptide

1,4-bis-(n-butylthio)benzene, 1,4-bis(n-butylthio)benzene

p-bromophenyl phenyl sulfide

lead phenylmercaptide

sodium phenylmercaptide

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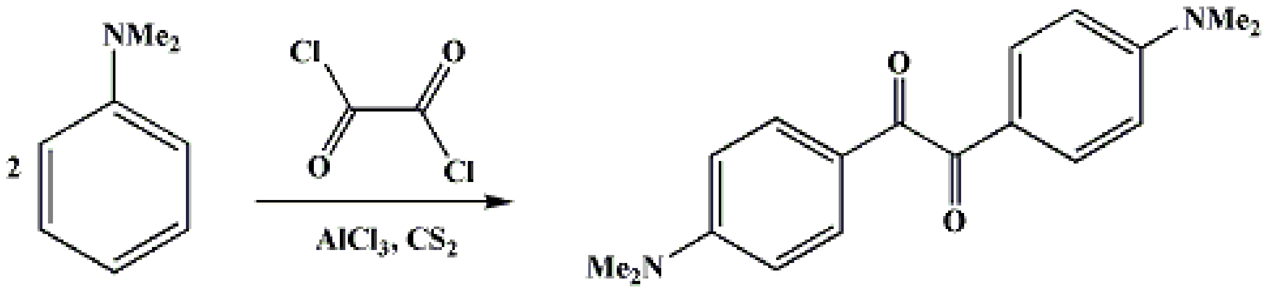
Organic Syntheses, CV 5, 111

4,4'-BIS(DIMETHYLAMINO)BENZIL

[Benzil, 4,4'-bis(dimethylamino)-]



Submitted by Celal Tüzün, Michael Ogliaruso, and Ernest I. Becker[1].
Checked by B. C. McKusick and R. J. Shozda.

1. Procedure

In a 3-l. three-necked flask equipped with an efficient mechanical stirrer of high torque (Note 1), a reflux condenser with a calcium chloride drying tube, a thermometer, and a dropping funnel are placed 133 g. (1.00 mole) of anhydrous aluminum chloride and 200 ml. of dry carbon disulfide. The mixture is cooled in an ice bath and stirred while 182 g. (1.50 moles) of N,N-dimethylaniline (Note 2) is added through the dropping funnel during a period of 15 minutes. The dropping funnel is rinsed with 20 ml. of carbon disulfide which is then run into the flask. Any aluminum chloride sticking to the walls of the flask is now scraped into the mixture, which is an easily stirred slurry of a white solid in a light-green liquid.

The reaction mixture is cooled to 5–10° in an ice-salt bath (Note 3), and, with continued stirring, a solution of 31.7 g. (21.3 ml., 0.250 mole) of oxalyl chloride in 200 ml. of dry carbon disulfide is added through the dropping funnel in the course of 20 minutes. After the addition is complete, the thick black reaction mixture is allowed to warm to room temperature, refluxed for 1 hour, and then cooled to 0–5° in an ice bath. The mixture is stirred throughout these steps. One hundred grams of chipped ice is added with stirring, followed by 400 ml. of cold water. Steam is then passed into the flask until the carbon disulfide and unreacted dimethylaniline are removed, and the green-black aluminum complex is decomposed to a mixture of a green solid and a blue solid; this requires 1–2 hours (Note 4). The mixture is cooled to 50°, and the solid, which is principally 4,4'-bis(dimethylamino)benzil, is collected on a Büchner funnel. In order to remove the major part of the impurity, which is somewhat soluble in water, the solid is slurried in 200 ml. of water at 50°, and the slurry is filtered. This process is repeated twice, and the crude benzil, now a green solid, is washed successively on the funnel with 200 ml. of water at 50° and with 100 ml. of cold methanol. After being dried in air, it weighs 44–55 g. and melts at 191–196°.

The crude benzil is dissolved in 500 ml. of chloroform. To remove the impurity that

remains (Note 5), the solution is shaken with three 400-ml. portions of 6% aqueous hydrogen peroxide solution containing 1.0 g. of sodium hydroxide in each portion, and finally with 500 ml. of water. The aqueous layers are combined, warmed to drive off dissolved chloroform, and filtered to separate about 1.5 g. of a yellow-green solid, which is dissolved in the chloroform solution.

The chloroform layer is distilled to dryness and the residue is dissolved in 1.5 l. of acetone under reflux. The hot acetone solution is filtered and then allowed to cool in a refrigerator. Yellow 4,4'-bis(dimethylamino)benzil crystallizes from the acetone solution. It is separated by filtration and washed with 100 ml. of cold methanol. After being dried in air, it weighs 28–31 g. (38–42%); m.p. 200–202°; $\lambda_{max}^{CH_3OH}$ 371 m•(ε 44,700) (Note 6).

The acetone filtrate is concentrated to 700 ml. and cooled to 0–5°. An additional 4–8 g. (6–11%) of slightly less pure benzil, m.p. 198–201°, crystallizes from solution (Note 7).

2. Notes

1. A magnetic stirrer is unsatisfactory. The submitters used a glass-blade stirrer at 300 r.p.m. The stirrer shaft must be rigidly attached to the motor because the reaction mixture becomes very thick during the addition of oxalyl chloride.
2. Eastman Kodak white label compounds used without further purification are satisfactory starting materials.
3. Cooling below –10° should be avoided because the reaction stops at that temperature and large amounts of oxalyl chloride accumulate in the flask. If this mixture is then allowed to come to room temperature, a vigorous reaction that may get out of control will take place. It is probable that, at reaction temperatures about 10°, the yield of 4,4'-bis(dimethylamino)benzil is less and some Crystal Violet is formed as an impurity, for it has been reported that aluminum chloride effects the conversion of N,N-dimethylaniline and oxalyl chloride to Crystal Violet in 92–95% yield when the reaction is allowed to proceed without cooling.[2]
4. The submitters recommend that the following purification procedure be used from this point for the preparation of 4,4'-bis(diethylamino)benzil (72% yield) and 4,4'-bis(di-*n*-propylamino)benzil (58% yield). The procedure has also been used as an alternative to the one given for 4,4'-bis(dimethylamino)benzil.
One liter of water is added, making the total volume about 2 l., and, after the solution has been cooled to room temperature, it is extracted with 1 l. of chloroform and then with 150 ml. of chloroform. The combined dark-blue extracts are washed with 550 ml. of 8.5% hydrochloric acid, then with 200 ml. of water and dried over anhydrous sodium sulfate. The chloroform solution is distilled until the volume is 250 ml., and it is then passed through an 8.5 × 25-cm. column (300 g.) of Alcoa F-20 alumina. The adsorbate is eluted with 1 l. of chloroform. The eluate is evaporated to a volume of 250 ml., washed with 500 ml. of 10% sodium hydroxide solution then with 100 ml. of water, and distilled to essential dryness. The residual crude, yellow, semi-solid product is stirred and brought to a boil with 250 ml. of ethyl acetate and then allowed to cool to room temperature while

stirring. Filtration affords 39–41 g. (52–55%) 4,4'-bis(dimethylamino)benzil, m.p. 201–203°. Concentration of the mother liquor to 50 ml. gives, after cooling, an additional 3.5–4.5 g. of product, m.p. 175–180°. Recrystallization of 10 g. of the combined products from 120–150 ml. of benzene gives 9.1–9.3 g. of yellow crystals, m.p. 202–203°.

5. The checkers found that at least part of the colored impurity is Crystal Violet. Alkaline hydrogen peroxide is reported to cleave Crystal Violet to N,N-dimethylaniline and Michler's ketone.[3]

6. The product is sometimes pale green because of traces of impurities, but it is nevertheless very pure, for repeated recrystallization does not change ε_{max}.

7. Addition of 1 l. of cold water to the acetone filtrate from which the second crop of benzil is separated causes about 5 g. of impure benzil to precipitate. This may be added to the crude benzil of a subsequent run prior to the treatment with hydrogen peroxide and alkali.

3. Discussion

4,4'-Bis(dimethylamino)benzil has been made previously by heating a mixture of oxalyl chloride and N,N-dimethylaniline under a pressure of 300 atmospheres of carbon monoxide in a steel pressure vessel at 100°.[4] The present method is simpler and gives better yields. As 4-dimethylaminobenzaldehyde cannot be converted to the corresponding benzoin,[5] this common route to benzils cannot be used to prepare 4,4'-bis(dimethylamino)benzil.

The present procedure is reported by the submitters to be a general way of making 4,4'-bis(dialkylamino)benzils and, with a somewhat modified purification scheme (Note 4), has been used by them to prepare 4,4'-bis(diethylamino)benzil from N,N-diethylaniline and 4,4'-bis(dipropylamino)benzil from N,N-dipropylaniline.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 1114
- Org. Syn. Coll. Vol. 5, 1135

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ethyl acetate (141-78-6)

methanol (67-56-1)

sodium hydroxide (1310-73-2)

carbon monoxide (630-08-0)

chloroform (67-66-3)

sodium sulfate (7757-82-6)

aluminum (7429-90-5)

acetone (67-64-1)

aluminum chloride (3495-54-3)

Benzil (134-81-6)

Benzoin (119-53-9)

carbon disulfide (75-15-0)

hydrogen peroxide (7722-84-1)

dimethylaniline, N,N-dimethylaniline (121-69-7)

N,N-diethylaniline (91-66-7)

oxalyl chloride (79-37-8)

4-dimethylaminobenzaldehyde (100-10-7)

N,N-dipropylaniline (2217-07-4)

4,4'-Bis(dimethylamino)benzil, Benzil, 4,4'-bis(dimethylamino)- (17078-27-2)

4,4'-bis(diethylamino)benzil

4,4'-bis(di-n-propylamino)benzil, 4,4'-bis(dipropylamino)benzil

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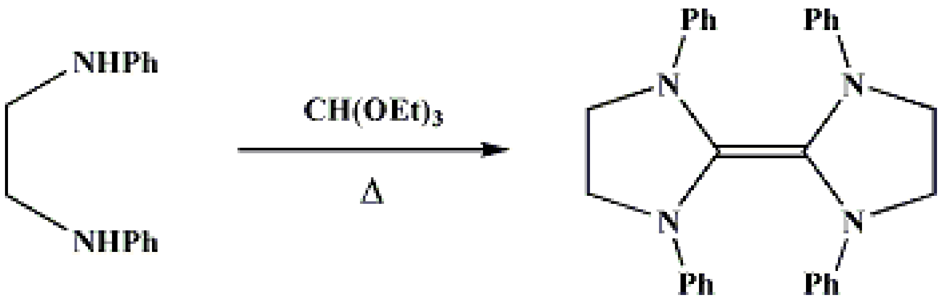
BIS(1,3-DIPHENYLIMIDAZOLIDINYLIDENE-2)

[$\Delta^{2,2'}$-Bis(1,3-diphenylimidazolidine)]



Submitted by H.-W. Wanzlick[1]
Checked by D. J. LaFollette and Ronald Breslow.

1. Procedure

In a 250-ml. round-bottomed flask equipped with a gas-inlet tube and reflux condenser 20 g. (0.094 mole) of N,N'-diphenylethylenediamine (1,2-dianilinoethane) (Note 1) and 100 ml. of purified triethyl orthoformate (Note 2) are heated by an oil bath under nitrogen (Note 3) for 5 hours. The oil bath is maintained between 190° and 200°, and water is allowed to stand in the condenser. The water in the condenser begins to boil slowly, and the alcohol which is produced is allowed to escape (Note 4). The reaction product which crystallizes during the reaction is filtered after cooling and washed with ether. There is obtained 19–20 g. (91–95%) of product, m.p. 285° (dec.) (Note 5).

2. Notes

1. 1,2-Dianilinoethane, containing water of crystallization, is best dried by melting under vacuum.
2. Commercial material, distilled.
3. The nitrogen is dried by passing it through concentrated sulfuric acid. It must be nearly oxygen-free; otherwise 1,3-diphenylimidazolidinone-2 is formed, and its removal by recrystallization results in a decreased yield.
4. An air condenser may also be employed.
5. The melting range depends on the rate of decomposition during heating. The checkers observed that in an evacuated capillary there is darkening from 270° to 290°, and fairly sharp melting at 299–300°. The product is autoxidizable and is best stored under dry nitrogen. Preparations which have oxidized on standing may be purified by digesting and washing with methylene chloride.

3. Discussion

This amino olefin was first prepared by thermal elimination of chloroform from 1,3-

diphenyl-2-trichlormethylimidazolidine,[2] and later by the procedure described here.[3,4] It can also be made by treatment of 1,3-diphenylimidazolinium salts with strong bases.[5,6]

4. Merits of the Preparation

The procedure described is the simplest one known. All other methods also employ 1,2-dianilinoethane as starting material. This method, however, converts it directly into the amino olefin in one step.

The preparative value of this compound lies in the surprising fact that bis(1,3-diphenylimidazolidinylidene-2) behaves in many reactions (*e.g.*, with aromatic aldehydes,[2,7] and with carbon acids[2,7,8,9]) as if it dissociated to form a "nucleophilic carbene." The hydrolytic cleavage of these derived imidazolidine derivatives makes possible the preparation of formyl compounds, so that the amino olefin can be considered as a potential carbonylation reagent. In many reactions it is not necessary to isolate the reagent, as it may be produced *in situ*.[10] It should be pointed out, however, that the reaction of the amino olefin with aldehydes and carbon acids does not actually involve prior dissociation to the carbene, but it is convenient, from a preparative point of view, to describe it in these terms.[6]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 162

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Bis(1,3-diphenylimidazolidinylidene-2)

$\Delta^{2,2'}$-Bis(1,3-diphenylimidazolidine)

sulfuric acid (7664-93-9)

ether (60-29-7)

chloroform (67-66-3)

nitrogen (7727-37-9)

triethyl orthoformate (122-51-0)

methylene chloride (75-09-2)

carbene (2465-56-7)

1,2-dianilinoethane, N,N'-diphenylethylenediamine (150-61-8)

1,3-diphenylimidazolidinone-2

1,3-diphenyl-2-trichlormethylimidazolidine

1,3-diphenylimidazolinium

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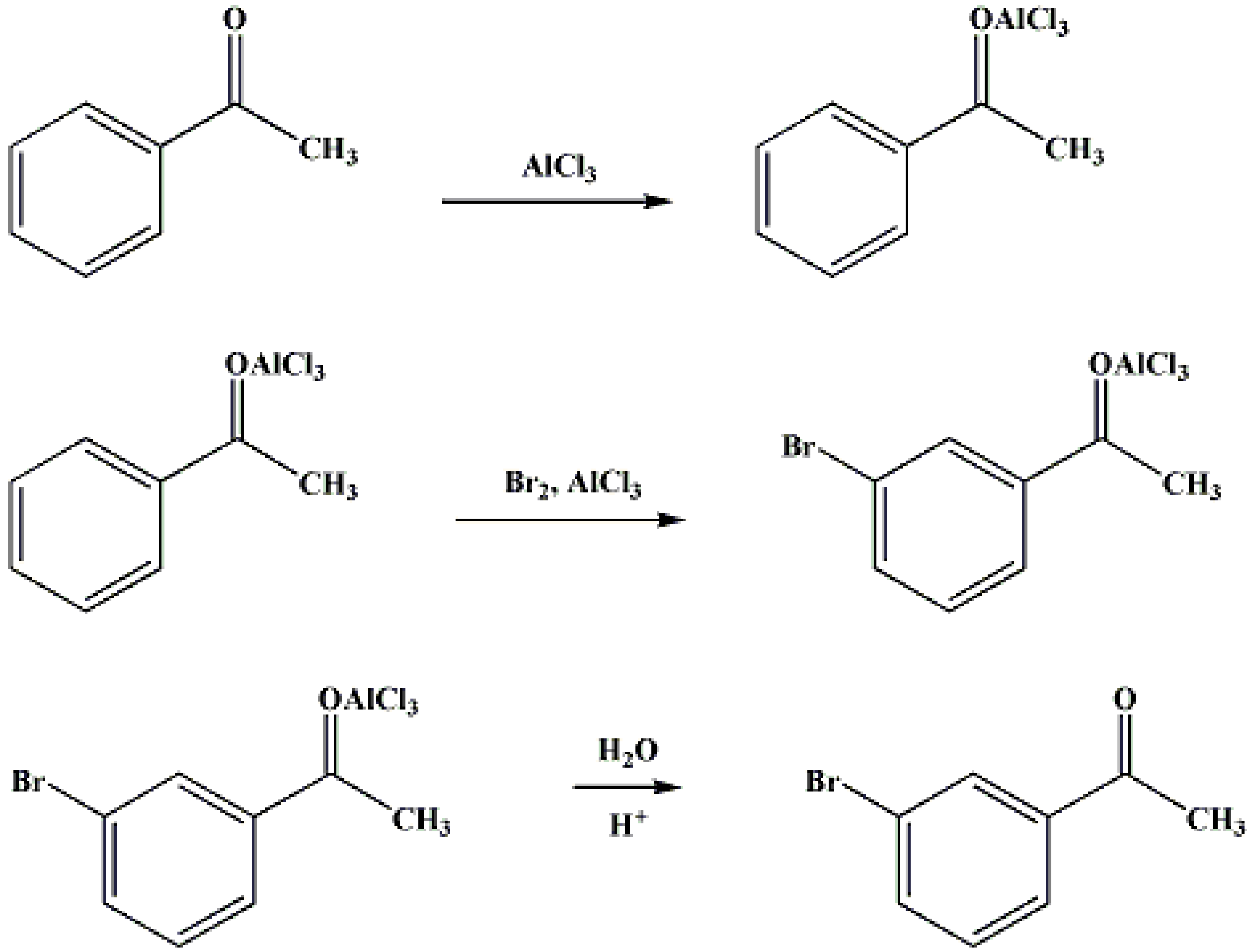
3-BROMOACETOPHENONE

[Acetophenone, 3-bromo-]



Submitted by D. E. Pearson, H. W. Pope, and W. W. Hargrove[1].
Checked by B. C. McKusick and D. W. Wiley.

1. Procedure

The apparatus consists of a 1-l. three-necked flask equipped with a condenser, a dropping funnel, and a stirrer terminating in a stiff, crescent-shaped Teflon polytetrafluoroethylene paddle. The stirrer motor must have good torque (Note 1). The assembled apparatus, which is protected from moisture by means of drying tubes in the condenser and funnel, is preferably predried. About 216–224 g. (1.62–1.68 moles) of powdered anhydrous aluminum chloride is added to the apparatus with as little exposure to the moisture of the air as possible (Note 2). While the free-flowing catalyst is stirred (Note 3), 81 g. (0.67 mole) of acetophenone is added from the dropping funnel in a slow stream over a period of 20–30 minutes. Considerable heat is evolved, and, if the drops of ketone are not dispersed, darkening or charring occurs. When about one-third of the acetophenone has been added, the mixture becomes a viscous ball-like mass that is difficult to stir. Turning of the stirrer by hand or more rapid addition of

ketone is necessary at this point. The addition of ketone, however, should not be so rapid as to produce a temperature above 180°. Near the end of the addition, the mass becomes molten and can be stirred easily without being either heated or cooled. The molten mass, in which the acetophenone is complexed with aluminum chloride, ranges in color from tan to brown.

Bromine (128 g., 0.80 mole) is added dropwise to the well-stirred mixture over a period of 40 minutes (Note 4). After all the bromine has been added, the molten mixture is stirred at 80–85° on a steam bath for 1 hour, or until it solidifies if that happens first (Note 5). The complex is added in portions to a well-stirred mixture of 1.3 l. of cracked ice and 100 ml. of concentrated hydrochloric acid in a 2-l. beaker (Note 6). Part of the cold aqueous layer is added to the reaction flask to decompose whatever part of the reaction mixture remains there, and the resulting mixture is added to the beaker. The dark oil that settles out is extracted from the mixture with four 150-ml. portions of ether. The extracts are combined, washed consecutively with 100 ml. of water and 100 ml. of 5% aqueous sodium bicarbonate solution, dried with anhydrous sodium sulfate, and transferred to a short-necked distillation flask. The ether is removed by distillation at atmospheric pressure, and crude 3-bromoacetophenone is stripped from a few grams of heavy dark residue by distillation at reduced pressure. The colorless distillate is carefully fractionated in a column 20 cm. long and 1.5 cm. in diameter that is filled with Carborundum or Heli-Pak filling. The combined middle fractions of constant refractive index are taken as 3-bromoacetophenone; weight, 94–100 g. (70–75%); b.p. 75–76°/0.5 mm.; n_D^{25} 1.5738–1.5742; m.p. 7–8° (Note 7) and (Note 8).

2. Notes

1. Among satisfactory motors are the Sargent Cone Drive and the Waco.
2. Exposure of the aluminum chloride to air is conveniently avoided by introducing the entire contents of two 4-ounce bottles of anhydrous resublimed aluminum chloride of the Baker and Adamson Company directly into the reaction flask.
3. If the paddle width is so small as to leave isolated, unagitated portions of aluminum chloride, it should be moved near the surface to disperse the ketone rapidly. If the ketone is not dispersed, condensation to dypnone occurs. Tars found in the stripping process are believed to originate from improper addition of the ketone to the aluminum chloride.
4. The rate of addition is regulated by the rate of evolution of hydrogen bromide. The yield of product is essentially the same whether the reaction mixture is held at 80–85° or at room temperature.
5. If the reaction mixture does not solidify during the heating, it is well to work it up at once while it can still be poured from the flask. Otherwise the work-up can be postponed to the next day. If the reaction mixture is too difficult to remove from the flask, the acid-ice slurry can be added *all at once* to the reaction flask immersed in ice. The vigorous surface decomposition is thus partly quenched. However, the cake is seldom difficult to remove unless

polyhalogenation has occurred.
6. The acid prevents the formation of insoluble aluminum salts that make separation of ether-water layers difficult. It is helpful in this regard to stir the mixture of water, ketone, and acid for an hour or so before extracting the ketone with ether.
7. The present procedure has been used by the submitters to prepare the following 3-bromoacetophenones and benzaldehydes in the indicated yields:[2] 3-bromopropiophenone, m.p. 40–41°, 60%; 3-bromo-4-methylacetophenone, m.p. 42–43°, 56%; 3,4-dibromoacetophenone, m.p. 89–90°, 55%; 3-bromo-4-*tert*-butylacetophenone, b.p. 92°/0.1 mm., 30%; 3,5-dibromo-4-methylacetophenone, m.p. 102–103°, 57%; 3-bromobenzaldehyde, b.p. 105–106°/2 mm., 59%; 3-bromo-4-tolualdehyde, m.p. 48–49°, 44%.
8. The same procedure can be used to prepare 3-chloroacetophenones and benzaldehydes. The apparatus is modified by replacing the dropping funnel with a gas-inlet tube that permits chlorine to be introduced under the surface of the molten complex of acetophenone and aluminum chloride. For a run with 81 g. (0.67 mole) of acetophenone, 31 ml. (48 g., 0.67 mole) of liquid chlorine is condensed in a trap cooled with solid carbon dioxide and acetone. The gas is passed consecutively through a safety trap, a bubble counter containing concentrated sulfuric acid, and the inlet tube into the stirred complex. The rate of addition is controlled by gradually lowering the cooling bath surrounding the liquid chlorine trap. The internal temperature of the reaction mixture rises just above room temperature and the color of the complex changes from light brown to deep red-brown. The addition chlorine is complete in 10–14 hours; with a faster rate of addition, some chlorine escapes. Stirring is continued for another hour, and the reaction mixture is worked up. The submitters have prepared the following in this way:[2] 3-chloroacetophenone, b.p. 61–63°/0.5 mm., 54%; 3-chlorobenzaldehyde, b.p. 93–96°/15 mm., 43%; 2,3,5,6-tetrachloro-4-methylacetophenone, m.p. 98.5–99.5°, 67%.

3. Discussion

Nuclear halogenation of acetophenone depends on formation of the aluminum chloride complex. If less than one equivalent of aluminum chloride is used, side-chain halogenation occurs.[3] 3-Bromoacetophenone has been prepared from 3-aminoacetophenone by the Sandmeyer reaction.[4,5] The synthesis described here has been taken from work of the submitters,[2] who have used it to prepare many 3-bromo- and 3-chloroacetophenones and benzaldehydes, as well as more highly halogenated ones (Note 7) and (Note 8).

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

3-Bromoacetophenone

Acetophenone, 3-bromo-

3-bromoacetophenones and benzaldehydes

3-bromo-4-methylacetophenone

3,4-dibromoacetophenone

3-bromo-4-tert-butylacetophenone

3,5-dibromo-4-methylacetophenone

3-chloroacetophenones and benzaldehydes

3-chloroacetophenone

2,3,5,6-tetrachloro-4-methylacetophenone

3-aminoacetophenone

3-bromo- and 3-chloroacetophenones and benzaldehydes

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium bicarbonate (144-55-8)

hydrogen bromide (10035-10-6)

bromine (7726-95-6)

sodium sulfate (7757-82-6)

carbon dioxide (124-38-9)

acetone (67-64-1)

Acetophenone (98-86-2)

aluminum chloride (3495-54-3)

chlorine (7782-50-5)

3-bromopropiophenone

3-bromobenzaldehyde (3132-99-8)

3-bromo-4-tolualdehyde

3-chlorobenzaldehyde (587-04-2)

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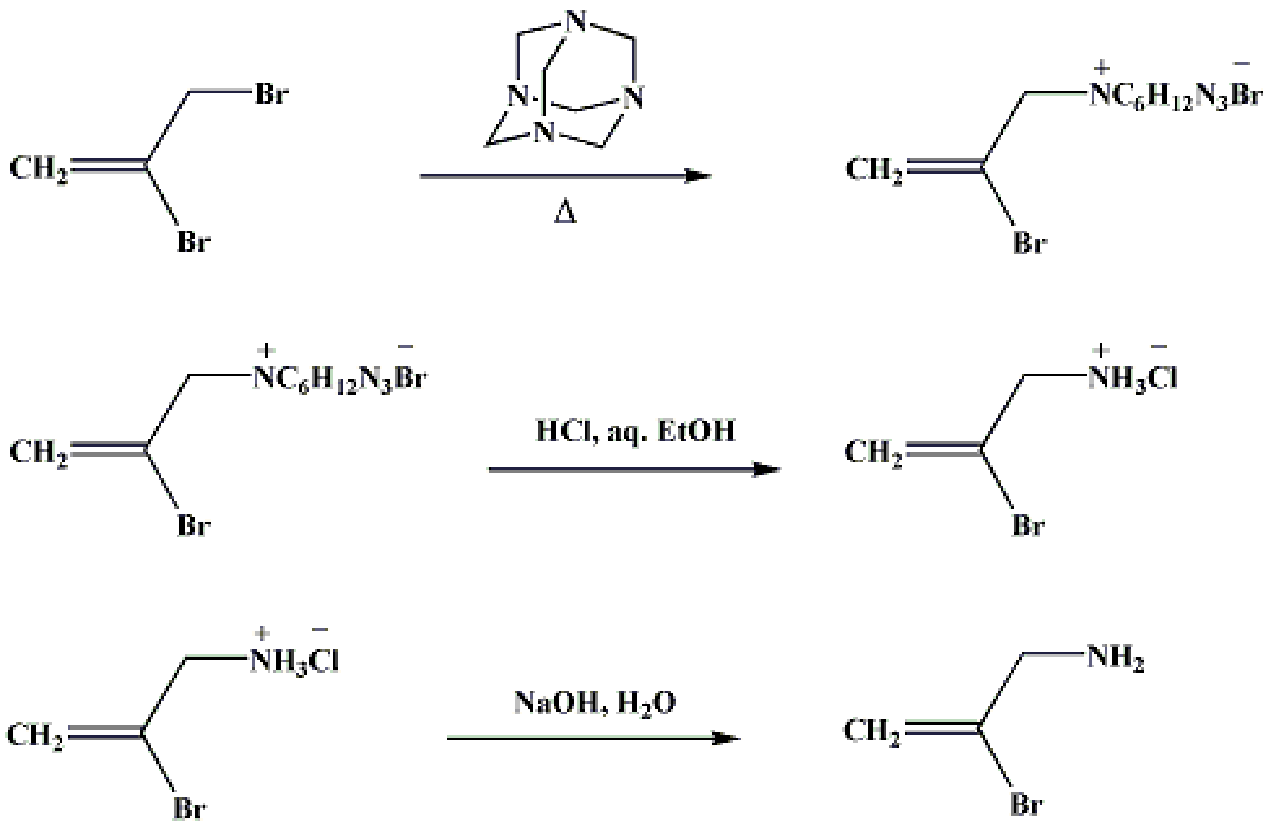
2-BROMOALLYLAMINE

[Allylamine, 2-bromo-]



Submitted by Albert T. Bottini, Vasu Dev, and Jane Klinck[1].
Checked by A. S. Pagano and W. D. Emmons.

1. Procedure

Caution! Contact with 2-bromoallylamine can cause severe eye and skin irritation. This preparation should be carried out in a good hood, and the operator should wear protective goggles and rubber gloves.

A. *2-Bromoallylhexaminium bromide*. A 2-l. three-necked flask fitted with a Hershberg stirrer,[2] a dropping funnel, and a condenser is charged with a solution of 154 g. (1.10 moles) of hexamethylenetetramine (Note 1) in 1250 ml. of chloroform. The solution is stirred and heated under reflux while 200 g. (1.00 mole) of 2,3-dibromopropene (Note 2) is added dropwise over a period of 1 hour. Precipitation of the product is noted soon after the first addition of 2,3-dibromopropene. After the addition is complete, the reaction mixture is stirred under reflux for 3 hours and allowed to stand overnight. The mixture is cooled in an ice bath, and the salt is collected by suction filtration. After air-drying, the crude yellow 2-bromoallylhexaminium bromide weighs 292–308 g. (86–91%) and melts at 183–186°.

B. *2-Bromoallylamine*. Crude 2-bromoallylhexaminium bromide (204 g., 0.60 mole) is dissolved in a warm solution prepared from 400 ml. of water, 2 l. of ethanol, and 480 ml. (5.8 moles) of 12*N* hydrochloric acid. A white precipitate of ammonium chloride forms within an hour. The reaction mixture is allowed to stand for 24 hours, and the precipitate is removed by suction filtration. The mother liquor is concentrated to a volume of 600 ml. (Note 3), and the precipitate (Note 4) is removed by suction filtration. The mother liquor is evaporated to dryness (Note 5), and the residue is dissolved in 300 ml. of water. The solution is cooled in an ice bath and made strongly alkaline (pH 13) with 6*N* sodium hydroxide solution.

The two-phase mixture is placed in a separatory funnel, and the heavy red-brown oil is separated. The aqueous phase is extracted with 100 ml. of ether. The oil and the ether extract are combined, washed with 50 ml. of saturated sodium chloride, and dried over potassium carbonate. The drying agent is removed by filtration, and the filtrate is distilled. Colorless 2-bromoallylamine is collected at 65–68°/100 mm.; weight 49–59 g. (59–72%); n_D^{25} 1.5075–1.5085 (Note 6).

2. Notes

1. The submitters used hexamethylenetetramine obtained from Matheson, Coleman and Bell.
2. The 2,3-dibromopropene was obtained from Columbia Organic Chemicals Co., Columbia, South Carolina, and was redistilled before use. The preparation of 2,3-dibromopropene is described in an earlier volume of this series.[3]
3. The submitters divided the mother liquor into 6 equal portions and concentrated each to a volume of 100 ml. at a pressure of 25 mm. in a 1-l. round-bottomed flask on a rotary film evaporator. The rotary film evaporator used was obtained from Cenco Scientific Co., Santa Clara, California.
4. The precipitate is ammonium chloride that contains virtually no 2-bromoallylamine hydrochloride.
5. The submitters used a rotary film evaporator to evaporate the mother liquor at a pressure of 25 mm. in a water bath heated to 90°.
6. 2-Bromoallylamine discolors slowly even when stored at 0° in a dark container. The refractometer to be used for determination of the refractive index should be placed in a good hood.

3. Discussion

2-Bromoallylamine has been prepared by heating N-(2-bromoallyl)-phthalimide with hydrazine in methanol;[4] by treatment of 2,3-dibromopropylamine hydrochloride with excess alcoholic potassium hydroxide;[5] by treatment of 1,2,3-tribromopropane with alcoholic ammonia at 100°;[6] and by the present procedure.[7]

4. Merits of the Preparation

This method gives better yields than other methods of preparation of 2-bromoallylamine, and it is the most convenient method for the preparation of large quantities of the compound. The procedure illustrates a reaction, the so-called Delépine reaction, that has been used for the preparation of many primary aliphatic amines.[8,9,10,11,12,13] It is especially useful in the preparation of derivatives of phenacylamine.[14,15,16] A number of primary aliphatic amines have been prepared by this method without isolation of the intermediate hexaminium salt.[11] Several preparations of aliphatic aldehydes via the hexaminium salt have been described in earlier volumes of this series.[17]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

2-Bromoallylhexaminium bromide

ethanol (64-17-5)

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

methanol (67-56-1)

ether (60-29-7)

ammonium chloride (12125-02-9)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium chloride (7647-14-5)

potassium hydroxide (1310-58-3)

2,3-Dibromopropene (513-31-5)

1,2,3-Tribromopropane (96-11-7)

hydrazine (302-01-2)

hexamethylenetetramine (100-97-0)

2-Bromoallylamine, Allylamine, 2-bromo- (6943-51-7)

2-bromoallylamine hydrochloride

N-(2-bromoallyl)-phthalimide

2,3-dibromopropylamine hydrochloride

phenacylamine

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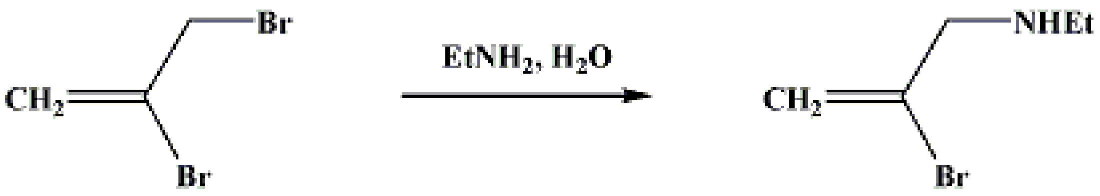
N-(2-BROMOALLYL)ETHYLAMINE

[Allylamine, 2-bromo-N-ethyl-]



Submitted by Albert T. Bottini and Robert E. Olsen[1].
Checked by Thomas H. Lowry and E. J. Corey.

1. Procedure

Caution! This preparation should be carried out in a hood to avoid exposure to ethylamine, 2,3-Dibromopropene, and the product. 2,3-Dibromopropene is a strong lachrymator. The operator should wear rubber gloves and protective goggles because some 2-haloallylamines have caused severe skin and eye irritation.

A 1-l. three-necked flask is fitted with a sealed mechanical stirrer, a dropping funnel, and a dry ice condenser charged with an ice-salt mixture (Note 1). Three hundred milliliters (240 g., 3.7 moles) of aqueous 70% ethylamine solution (Note 2) is placed in the flask, the stirrer is started, and 200 g. (1.00 mole) of 2,3-dibromopropene (Note 3) is added dropwise over a period of 1 hour. After the addition is complete, the reaction mixture is stirred for 3 hours. Ether (300 ml.) is added, and the mixture is cooled in an ice bath. Sodium hydroxide (100 g.) is added with stirring and cooling. The cold mixture is transferred to a separatory funnel, and the phases are separated. The organic layer is dried in two stages over 25-g. portions of sodium hydroxide. The organic layer and the small amount of water that separates during the second stage of drying are decanted into a separatory funnel, and the phases are separated. Most of the ether and unreacted ethylamine are removed from the organic layer by distillation through a 250-mm. × 13-mm. column packed with glass helices, and the residue is distilled through the same column at reduced pressure under nitrogen to give 115–128 g. (70–78%) of N-(2-bromoallyl)ethylamine; b.p. 53–55° (27 mm.), 79–81° (75 mm.) (Note 4); n^{25}D 1.4765–1.4770.

2. Notes

1. The checkers used an inner-spiral water condenser. The cooling water was chilled to about 0° by prior passage through a short copper coil immersed in ice.
2. The aqueous 70% ethylamine solution used was the practical grade obtained from Eastman Organic Chemicals.

3. The 2,3-dibromopropene used was obtained from Columbia Organic Chemicals Co., Columbia, South Carolina, and was redistilled before use. The preparation of 2,3-dibromopropene is described in an earlier volume of this series.[2]

4. The reported boiling point of N-(2-bromoallyl)ethylamine is 148–153°.[3] It is strongly recommended that the product and other 2-haloallylamines be distilled at reduced pressure under nitrogen, for the submitters have noted two instances when a 2-haloallylamine polymerized with considerable evolution of heat during slow distillation at atmospheric pressure.

3. Discussion

This method is essentially that described by Pollard and Parcell.[3] No other procedure appears to have been used to prepare N-(2-bromoallyl)ethylamine. A number of N-(2-haloallyl)alkylamines have been prepared by treatment of a 2,3-dihalopropene with a primary alkylamine in water,[3,4] ether,[3,4] or benzene.[5]

4. Merits of the Preparation

The method described here has been used for the preparation of a number of N-(2-haloallyl)alkylamines from a water-soluble amine and the corresponding 2,3-dihalopropene.[3,4]

Treatment of an N-(2-bromoallyl)alkylamine with sodium amide in liquid ammonia yields the N-alkylallenimine together with a small amount of the N-alkylpropargylamine.[3,4,5,6,7] Similar treatment of an N-(2-chloroallyl)alkylamine yields only the N-alkylpropargylamine.[4,6]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 541

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Appendix

Compounds Referenced (Chemical Abstracts Registry Number)

ammonia (7664-41-7)

Benzene (71-43-2)

ether (60-29-7)

sodium hydroxide (1310-73-2)

nitrogen (7727-37-9)

copper (7440-50-8)

2,3-Dibromopropene (513-31-5)

sodium amide (7782-92-5)

ethylamine (75-04-7)

N-(2-Bromoallyl)ethylamine, Allylamine, 2-bromo-N-ethyl- (871-23-8)

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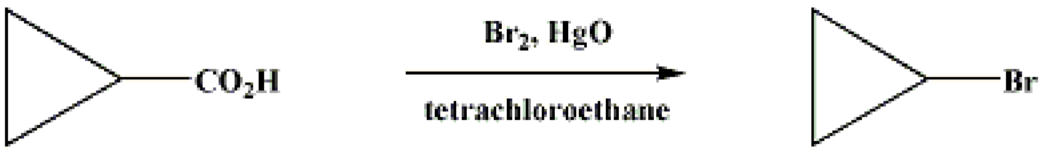
BROMOCYCLOPROPANE

[Cyclopropane, bromo-]



Submitted by John S. Meek and David T. Osuga[1].
Checked by F. S. Fawcett and B. C. McKusick.

1. Procedure

Twenty-four grams (0.11 mole) of red mercuric oxide (Note 1) and 60 ml. of freshly distilled 1,1,2,2-tetrachloroethane are placed in a 250-ml. three-necked flask equipped with a dropping funnel, a reflux condenser, and a stirrer. A solution of 32.2 g. (0.20 mole) of bromine and 17.2 g. (0.20 mole) of cyclopropanecarboxylic acid in 50 ml. of tetrachloroethane is added dropwise to the stirred suspension of mercuric oxide over a period of 45 minutes, the flask being kept in a water bath at 30–35° (Note 2). The mixture is stirred after the addition of the reactants until the evolution of carbon dioxide ceases.

The flask is then cooled in ice water, and the contents are filtered with as little suction as possible (Note 3). The filter cake is pressed dry and washed with three 15-ml. portions of tetrachloroethane first used to rinse out the flask. The combined filtrates are dried with a little calcium chloride. Sometimes the solution contains a little bromine; it is removed by adding allyl alcohol dropwise until the bromine color is discharged (usually 0.5–1.0 ml. suffices).

The solution is decanted into a 200-ml. round-bottomed flask containing a carborundum chip. The material is distilled through a 20-cm. column of glass helices or a 30-cm. spinning-band column. The fore-run boiling below 75°/760 mm. is bromocyclopropane pure enough for most purposes; weight 9.8–11.2 g. (41–46%); n_D^{25} 1.455–1.459; d_4^{26} 1.506 (Note 4). Redistillation of this product gives pure bromocyclopropane, b.p. 69°/760 mm., n_D^{25} 1.4570, with but slight loss (Note 5).

2. Notes

1. The mercuric oxide used was Mallinckrodt or Baker powdered red mercuric oxide, analytical reagent grade. Old mercuric oxide gives variable results and may lower the yield. The 1,1,2,2-tetrachloroethane used was a technical grade and was distilled to make sure no low-boiling impurities were present. Reagent-grade solvent has been used without distillation. The vapors of this chlorinated

hydrocarbon are toxic, and its distillation as well as the reaction should be carried out in a hood. Suitable cyclopropanecarboxylic acid[2] is obtainable from Aldrich Chemical Company.

2. The reaction starts spontaneously and is mildly exothermic. Moderating the temperature by use of a water bath diminishes the amount of bromine and product carried off by the carbon dioxide evolved. The reaction can be followed by use of a tetrachloroethane bubbler, and at the end of the reaction the solvent in the bubbler can be used to wash the mercuric bromide. The checkers followed the reaction with a wet test meter presaturated with carbon dioxide; 52–60% of the theoretical amount of carbon dioxide was evolved.

3. The checkers used a sintered glass pressure filter (Corning Glass Works, Cat. No. 34020) rather than a suction filter in order to minimize evaporation losses. An ordinary water aspirator can cause the mixture to boil at room temperature. The flask and filter can be cleaned readily with a little acetone, which dissolves mercuric bromide rapidly.

4. Once the boiling point starts to rise, it goes up quite rapidly. The fractions collected between 75° and 90° contain a little product and can be reworked if a second distillation is carried out.

5. After publication of this procedure, the submitters increased the yield to 53–65% by the following modification. A Barrett distilling receiver and thermometer are added to the described apparatus. A mixture of 60 ml. of undistilled technical 1,1,2,2-tetrachloroethane, 27.5 g. (0.125 mole) of mercuric oxide, and 21.5 g. (0.25 mole) of cyclopropane-carboxylic acid is heated to remove 10 ml. of solvent and water; during the distillation the mercuric oxide dissolves to form a solution of mercuric cyclopropanecarboxylate. The solution is cooled to about 70°, the distilling receiver is removed, and 40 g. (0.25 mole) of bromine is added dropwise with swirling over a period of 15–20 minutes. Mercuric bromide starts to precipitate when 50–75% of the bromine has been added and may cause frothing if the last of the bromine is added too rapidly. The evolution of carbon dioxide tapers off and ceases about 15 minutes after addition is complete; the reaction temperature is about 55° at this point. Any bromine color is discharged with allyl alcohol as described above. The condenser is replaced by one of the distillation columns specified above, and the reaction mixture is distilled without filtration. Stirring helps, but is not essential, for the finely divided mercuric bromide does not cause bumping. The yield of bromocyclopropane having the properties given above is 16–17 g. (53–56%).

3. Discussion

Bromocyclopropane has been prepared by the Hunsdiecker reaction by adding silver cyclopropanecarboxylate to bromine in dichlorodifluoromethane at −29° (53% yield) or in tetrachloroethane at −20° to −25° (15–20% yield).[3] Decomposition of the peroxide of cyclopropanecarboxylic acid in the presence of carbon tetrabromide gave bromocyclopropane in 43% yield.[4] An attempt to prepare the bromide via the von

Braun reaction was unsuccessful.[3] Ten percent yields are reported for the photobromination of cyclopropane[5] and the photochemical rearrangement of allyl bromide.[6] Treatment of 1,1,3-tribromopropane with methyllithium prepared from methyl bromide furnishes a 60–65% yield of bromocyclopropane.

4. Merits of the Preparation

The present procedure is substantially simpler and quicker than the best previous procedure[3] based on using cyclopropanecarboxylic acid, which requires 4 days instead of 4 hours. It is also safer, for no explosions have been encountered; whereas care must be taken to prevent explosion of the intermediate hypobromite when the Hunsdiecker method is used,[3] and one detonation has been reported.[7]

Although the treatment of 1,1,3-tribromobutane with methyllithium is a safe procedure offering an attractive yield, it suffers from the fact that the tribromide is not commercially available while cyclopropanecarboxylic acid is.

A recent illustration of the generality of this method for preparing alkyl bromides from acids is provided by an *Organic Syntheses* procedure for 1-bromo-3-chlorocyclobutane.[8] To aid in isolating higher boiling or solid products, solvents such as carbon tetrachloride and cyclohexane can be used.[9] In preparing a solid, mercuric bromide can be removed by extraction with 5% potassium iodide. It should also be noted that mercuric bromide can be converted back to mercuric oxide easily with alkali

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 179

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

red mercuric oxide

peroxide of cyclopropanecarboxylic acid

calcium chloride (10043-52-4)

bromine (7726-95-6)

Allyl bromide (106-95-6)

Allyl alcohol (107-18-6)

carbon tetrachloride (56-23-5)

potassium iodide (7681-11-0)

carbon dioxide (124-38-9)

mercuric oxide (21908-53-2)

cyclohexane (110-82-7)

acetone (67-64-1)

methyl bromide (74-83-9)

cyclopropane (75-19-4)

carbon tetrabromide (558-13-4)

tetrachloroethane (630-20-6)

mercuric bromide (7789-47-1)

Cyclopropanecarboxylic acid, cyclopropane-carboxylic acid (1759-53-1)

Methyllithium (917-54-4)

Bromocyclopropane, Cyclopropane, bromo- (4333-56-6)

1,1,2,2-tetrachloroethane (79-34-5)

mercuric cyclopropanecarboxylate

silver cyclopropanecarboxylate

dichlorodifluoromethane (75-71-8)

1,1,3-tribromopropane

1,1,3-tribromobutane

1-Bromo-3-chlorocyclobutane (4935-03-9)

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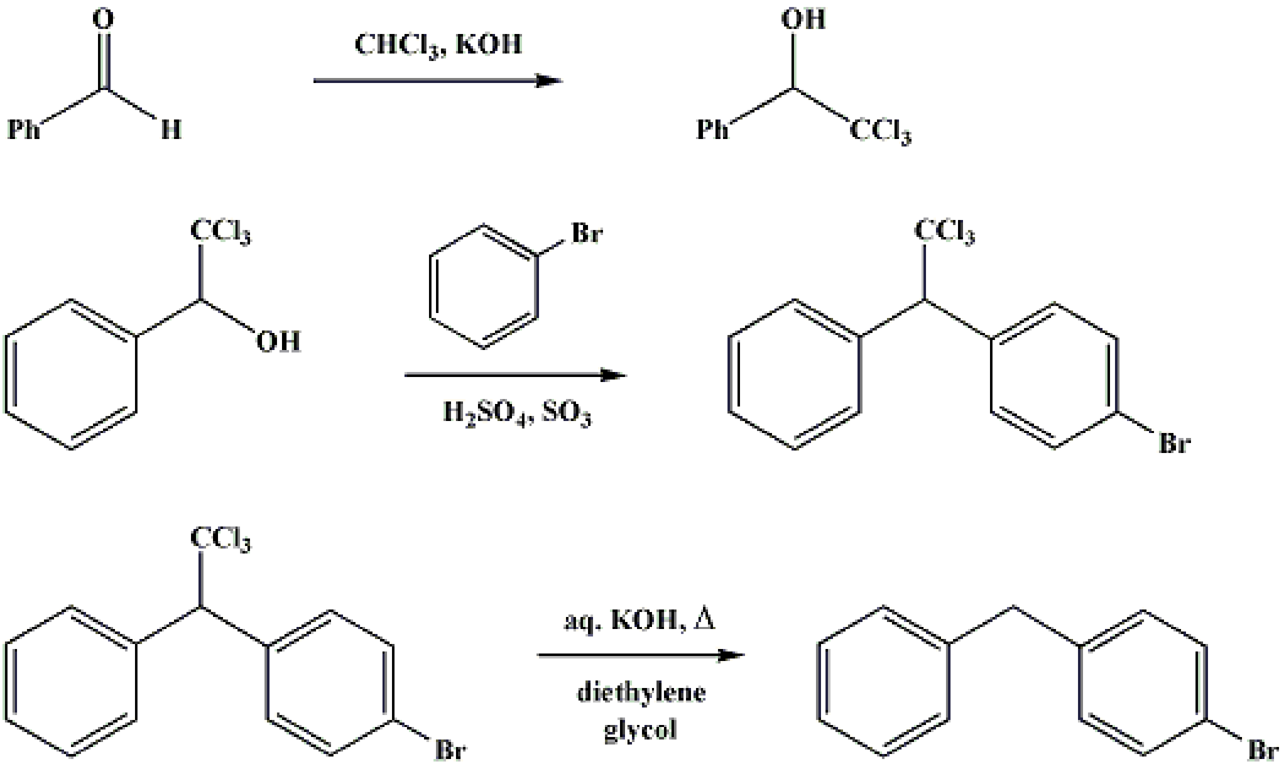
p-BROMODIPHENYLMETHANE

[Methane, (*p*-bromophenyl)phenyl-]



Submitted by A. B. Galun[1] and A. Kalir[2].
Checked by R. Breslow and H. T. Bozimo.

1. Procedure

A. *1-Phenyl-2,2,2-trichloroethanol*. In a 1-l. round-bottomed-flask fitted with a mechanical stirrer, a thermometer, and a powder funnel is placed a solution of 212 g. (2.00 moles) of freshly distilled benzaldehyde in 400 g. (270 ml., 3.35 moles) of chloroform. The mixture is cooled in an ice bath, and 123 g. of commercial powdered potassium hydroxide is added with stirring at such a rate that the temperature of the solution does not exceed 45° (1–1.5 hours). The reaction mixture is stirred and kept at 40–50° for an additional hour and then poured into a solution of 60 ml. of sulfuric acid in 3 l. of water. The resulting two-phase mixture is transferred to a separatory funnel and extracted with three 250-ml. portions of chloroform (a small amount of insoluble, black resinous material is discarded). The combined organic layers are washed with three 100-ml. portions of aqueous 10% sodium carbonate, dried over anhydrous magnesium sulfate, and filtered into a 1-l. flask. The solvent is removed under reduced pressure on a hot water bath. The residue is transferred to a 250-ml. flask and distilled under reduced pressure to give 1-phenyl-2,2,2-trichloroethanol, b.p. 155–165° (26 mm.), 90–100° (0.5 mm.) (Note 1) and (Note 2). The yield is 170–180 g. (38–40%).

B. *1-p-Bromophenyl-1-phenyl-2,2,2-trichloroethane*. In a 500-ml. round-bottomed flask fitted with a mechanical stirrer, a dropping funnel, and a thermometer are placed 136 g. (0.60 mole) of 1-phenyl-2,2,2-trichloroethanol and 120 g. (81 ml., 0.77 mole) of bromobenzene. The flask is cooled in an ice-water bath, and a mixture of 120 ml. of concentrated sulfuric acid and 50 ml. of

oleum (20% SO_3) is added with stirring at such a rate that the temperature of the reaction mixture does not exceed 10° (*ca.* 45 minutes) (Note 3). The mixture is stirred for another 30 minutes at 10° and for 4–5 hours at room temperature. It is then poured with manual stirring onto 1 kg. of cracked ice, and the mixture is allowed to stand overnight. The precipitate (Note 4) is filtered, washed with water, and recrystallized from 300 ml. of ethanol (Note 5). The yield is 129–162 g. (59–74%), m.p. 95–96° (Note 6).

C. *p-Bromodiphenylmethane*. A 2-l. three-necked flask fitted with a distillation condenser, a thermometer, and an efficient mechanical stirrer is charged with 1.1 l. of diethylene glycol (Note 7) and a solution of 190 g. of potassium hydroxide in 100 ml. of water. The mixture is stirred, and water is distilled until the internal temperature reaches 180°. The resulting solution is allowed to cool to 100° or below, and 146 g. (0.40 mole) of 1-*p*-bromophenyl-1-phenyl-2,2,2-trichloroethane (Note 8) is added. The condenser is set for reflux, and the mixture is stirred and heated to boiling for 5 hours (Note 9). The hot solution is then poured onto 3 kg. of cracked ice, and the mixture is allowed to stand overnight. The oily layer is separated and dissolved in ether (any insoluble material is discarded), and the aqueous layer is extracted with 250 ml. of ether. The combined ethereal solution and extracts are dried over calcium chloride and filtered. The ether is removed under reduced pressure on a hot water bath. The product is distilled under reduced pressure; b.p. 120–130° (3 mm.), 155–163° (13 mm.) (Note 10), $n^{24}\text{D}$ 1.6028, d_{24}^{24} 1.342. The yield is 74–79 g. (75–80%) (Note 11).

2. Notes

1. The purpose of the distillation is to separate the product from tars. Therefore no fractionation is required, and the distillation may be carried out rapidly.
2. The carbinol, which has a tendency to supercool, may crystallize overnight; m.p. 38°.
3. Solid material is sometimes deposited on the walls of the reaction flask.
4. In some cases the organic layer separates as an oil; it is then obtained in crystalline form by trituration with 200 ml. of cold methanol, which dissolves the excess of bromobenzene.
5. Wet material may require larger amounts of ethanol.
6. Trituration of the crude precipitate with methanol gives a 90% yield of material, m.p. 90–93°.
7. Eastman Organic Chemicals white label 2,2-oxydiethanol was used.
8. The material should be thoroughly freed of alcohol, preferably over phosphorus pentoxide under reduced pressure, before use. Even traces of alcohol may reduce the yield to 60%.
9. The temperature of the refluxing solution should be above 165°. Efficient stirring is essential; otherwise the precipitating potassium carbonate entrains much material, causing reduction of yield.
10. Good fractionation is not required.
11. Runs on a fourfold scale give the same yield.

3. Discussion

The procedure for the preparation of 1-phenyl-2,2,2-trichloroethanol is based on the work of Bergmann, Ginsburg, and Lavie.[3] 1-Phenyl-2,2,2-trichloroethanol has also been prepared from phenylmagnesium bromide and chloral.[4]

p-Bromodiphenylmethane has been reported as a product of the reduction of *p*-

bromobenzophenone with hydriodic acid and red phosphorus in a sealed tube at 160°.[5] The present method is a modification of the synthesis published by Galun, Kaluszyner, and Bergmann.[6]

4. Merits of the Preparation

In this method inexpensive, commercially available chemicals are used as starting materials. The operations are simple, the yields acceptable, and the final products are free of isomers.

This procedure is especially suited for preparing variously substituted diarylmethanes.[6] The 1,1-diaryl-2,2,2-trichloroethanes may be converted to the corresponding benzophenones via the 1,1-diaryl-2,2-dichloroethylenes[7] and to 1,1-diarylacetic acids.[8]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

red phosphorus

ethanol (64-17-5)

calcium chloride (10043-52-4)

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

methanol (67-56-1)

ether (60-29-7)

chloroform (67-66-3)

sodium carbonate (497-19-8)

benzaldehyde (100-52-7)

potassium hydroxide (1310-58-3)

bromobenzene (108-86-1)

hydriodic acid (10034-85-2)

Phenylmagnesium bromide (100-58-3)

magnesium sulfate (7487-88-9)

chloral (75-87-6)

diethylene glycol, 2,2-oxydiethanol (111-46-6)

1-Phenyl-2,2,2-trichloroethanol (2000-43-3)

phosphorus pentoxide (1314-56-3)

p-Bromodiphenylmethane, Methane, (p-bromophenyl)phenyl- (2116-36-1)

1-p-Bromophenyl-1-phenyl-2,2,2-trichloroethane (39211-93-3)

p-bromobenzophenone (90-90-4)

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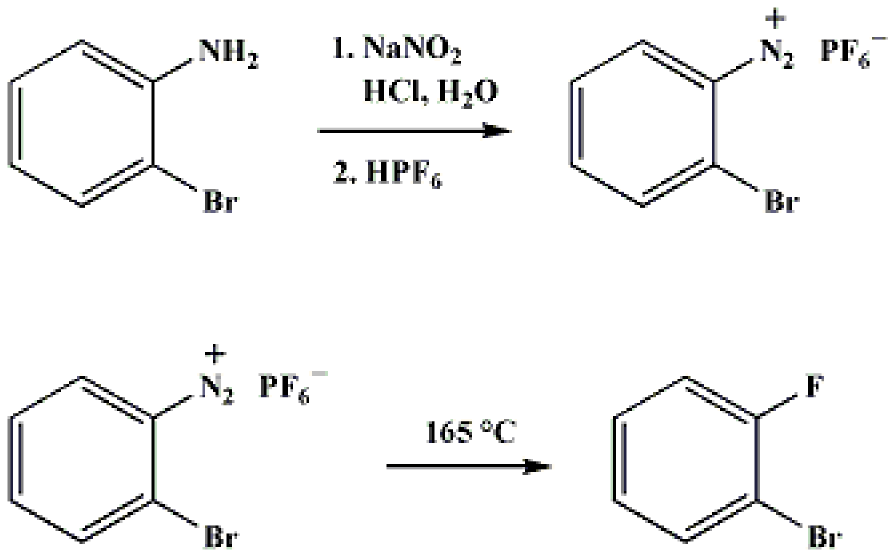
1-BROMO-2-FLUOROBENZENE

[Benzene, 1-bromo-2-fluoro-]



Submitted by K. G. Rutherford and W. Redmond[1].
Checked by M. Paulshock and B. C. McKusick.

1. Procedure

A. *o-Bromobenzenediazonium hexafluorophosphate*. A solution of 95 ml. of 12*N* hydrochloric acid in 650 ml. of water is added with stirring to 60 g. of *o*-bromoaniline (0.35 mole; (Note 1)) in a 2-l. three-necked flask equipped with stirrer and thermometer. Solution is effected by heating the mixture on a steam bath (Note 2). A solution of 29 g. (0.42 mole) of sodium nitrite in 75 ml. of water is added with stirring while the mixture is maintained at –5° to –10° by means of a bath of ice and salt or of dry ice and acetone. At the end of the addition there is an excess of nitrous acid, which can be detected with starch iodide paper. Seventy-four milliliters (134 g., 0.60 mole) of 65% hexafluorophosphoric acid (Note 3) is added in one portion, with vigorous stirring, to the cold solution of the diazonium salt. Cooling and slow stirring are continued for an additional 30 minutes, and the precipitated diazonium hexafluorophosphate is then collected on a Büchner funnel. The diazonium salt is washed on the funnel with 300 ml. of cold water and with a solution of 80 ml. of methanol in 320 ml. of ether (Note 4). The salt is partly dried by drawing air through the funnel for 2 hours. It is then transferred to a pile of several filter papers, powdered with a spatula, and dried at about 25°/1 mm. for at least 12 hours. The dried *o*-bromobenzenediazonium hexafluorophosphate is cream-colored; weight 108–111 g. (94–97%); m.p. 151–156° (dec.) (Note 5).

B. *1-Bromo-2-fluorobenzene*. *Caution! This step should be carried out in a hood*

because the PF_5 evolved on thermal decomposition of the diazonium salt is poisonous. The apparatus consists of a 1-l., three-necked, round-bottomed flask equipped with a thermometer, a condenser, a magnetic stirrer (optional), and a 250-ml. Erlenmeyer flask that is attached by means of a short rubber Gooch connecting tube. The dry powdered hexafluorophosphate salt is placed in the Erlenmeyer flask, and 300 ml. of heavy mineral oil is placed in the round-bottomed flask. The mineral oil is heated to 165–170° by means of an oil bath or electric heating mantle and maintained at this temperature while the salt is added rapidly in portions over a period of 30 minutes. The flask is cooled rapidly to room temperature, the side flask is removed, and 400 ml. of 10% aqueous sodium carbonate is added slowly through the condenser. The mixture is steam-distilled until no more oil is visible in the distillate.

The oil, which is heavier than water, is separated, and the aqueous layer is extracted with three 50-ml. portions of methylene chloride. The oil and extracts are combined, dried over anhydrous sodium sulfate, and distilled from a Claisen flask with an indented neck. Colorless 1-bromo-2-fluorobenzene is collected at 58–59°/17 mm. or 156–157°/760 mm.; weight 45–47 g. (73–75% based on *o*-bromoaniline); n_D^{25} 1.5320–1.5325.

2. Notes

1. *o*-Bromoaniline obtained from Eastman Kodak and used without redistillation is satisfactory.
2. The amine is dissolved to ensure its complete conversion to the hydrochloride. The amine hydrochloride may partly crystallize as the solution is cooled, but it redissolves as diazotization proceeds.
3. The 65% hexafluorophosphoric acid (density 1.81) was obtained from the Ozark-Mahoning Company, Tulsa, Oklahoma. A graduated polypropylene (Nalgene®) cylinder was used to contain the measured quantity of the acid. Rubber gloves should be worn as a precautionary measure against burns. Working in a hood prevents any contact of exposed parts of the body with fumes. *In the event of accidental contact of the acid with the skin, the affected place should be immediately washed well with running water and then treated with a paste of magnesium oxide and glycerol*[2] *or soaked in ice water.*
4. The methanol-ether filtrate has a slight yellow color. It is not known what impurity is removed by this solvent pair. However, the submitters found that this treatment improved the yield of several aryl fluorides prepared according to the present procedure.
5. The checkers had *o*-bromobenzenediazonium hexafluoro-phosphate examined in laboratories of the Du Pont Co. Explosives Department to see if it could be detonated. It was found sensitive to neither shock nor static electricity, and to decompose but not detonate when rapidly heated to 250°. Hence it probably does not present an explosion hazard, but it should be kept away from heat, especially if in a closed container.

3. Discussion

1-Bromo-2-fluorobenzene has been prepared in 37% yield by the Schiemann reaction from *o*-bromoaniline, nitrous acid, and fluoboric acid.[3,4] The present procedure[5] is a modification of the Schiemann reaction.

4. Merits of the Preparation

This procedure is a general way of converting arylamines to aryl fluorides, for it has been used to make fifteen other aryl fluorides. It generally gives better yields than the Schiemann reaction.

1-Bromo-2-fluorobenzene is used to prepare the highly reactive intermediate, benzyne.[6]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

fluoboric acid

hydrochloric acid (7647-01-0)

benzyne (71-43-2)

methanol (67-56-1)

ether (60-29-7)

glycerol (56-81-5)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

sodium nitrite (7632-00-0)

nitrous acid (7782-77-6)

methylene chloride (75-09-2)

magnesium oxide

1-Bromo-2-fluorobenzene, Benzene, 1-bromo-2-fluoro- (1072-85-1)

hexafluorophosphoric acid (16940-81-1)

o-bromoaniline (615-36-1)

o-Bromobenzenediazonium hexafluorophosphate, o-bromobenzenediazonium hexafluoro-phosphate

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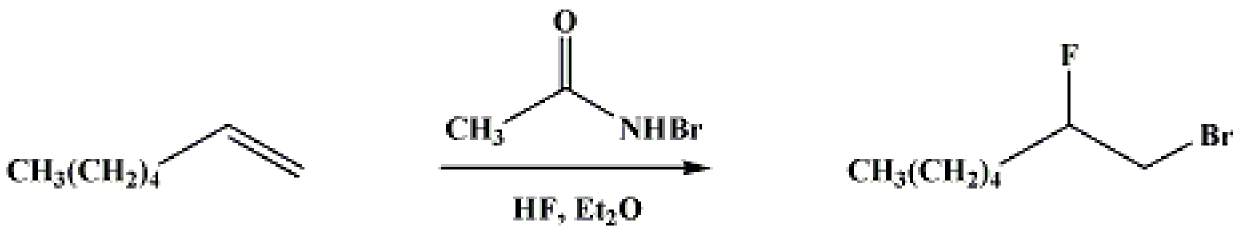
1-BROMO-2-FLUOROHEPTANE

[Heptane, 1-bromo-2-fluoro-]



Submitted by F. H. Dean, J. H. Amin, and F. L. M. Pattison[1].
Checked by P. B. Sargeant and B. C. McKusick.

1. Procedure

Caution! Hydrogen fluoride is very hazardous. All operations must be carried out in a hood, and the precautions outlined in (Note 1) should be followed.

A 1-l. polyethylene bottle is fitted with a three-holed rubber stopper. Three lengths of 0.25-in. (6-mm.) stiff polyethylene tubing extend through the stopper into the bottle. One length of tubing serves as an inlet tube for dry nitrogen, which is monitored by first bubbling through mineral oil. The second tube, the gas-outlet tube, carries a polyethylene drying tube packed with indicating Drierite®. These tubes extend only about 2 cm. into the bottle. The third tube serves as an inlet for anhydrous hydrogen fluoride and extends halfway into the bottle; it is connected to a hydrogen fluoride cylinder by a short length of Tygon® tubing secured to the cylinder outlet by copper wire. The bottle contains a Teflon®-covered magnetic stirring bar.

The bottle is flushed with dry nitrogen, and a slow stream of nitrogen passes through the bottle during all subsequent operations to ensure the exclusion of atmospheric moisture (Note 2). N-Bromoacetamide (80 g., 0.58 mole) is added (Note 3). The bottle is cooled in a mixture of dry ice and acetone, and 250 ml. of anhydrous ether is added with efficient magnetic stirring. About 100 g. (100 ml., 5 moles) of anhydrous hydrogen fluoride is allowed to condense into the bottle with magnetic stirring (Note 4). This requires about 2 hours.

1-Heptene (49 g., 0.50 mole) (Note 3) is mixed with 50 ml. of anhydrous ether. The solution is added during 20 minutes through what was originally the nitrogen inlet; the hydrogen fluoride inlet now serves as the nitrogen inlet. The reaction mixture is stirred in the dry ice bath for an additional 4 hours. The dry ice bath is replaced by an ice bath, and the mixture is stirred for 40 minutes. It is then allowed to stand overnight in a mixture of dry ice and acetone in a Dewar flask.

A solution of 690 g. (5.0 moles) of potassium carbonate in 2 l. of distilled water is prepared in a 4-l. polyethylene beaker or pail, and 500 g. of crushed ice and 300 ml. of ether are added. The cold reaction mixture is cautiously added to the carbonate solution with stirring. The pH of the aqueous layer becomes about 9. The ether layer is separated, and the aqueous layer is extracted with three 200-ml. portions of ether. The ether solutions are combined and washed with three 100-ml. portions of water. The ether solution is dried over anhydrous sodium sulfate, and the ether is removed by distillation. The oily residue is fractionated through a 15-cm. Vigreux column under reduced pressure. There is a fore-run of about 0.5 ml., and then 59–75 g. (60–77%) of 1-bromo-2-fluoroheptane is collected at 70–78° (15 mm.); n^{25}D 1.4408–1.4420. According to vapor phase chromatography, it is about 90% pure (Note 5).

2. Notes

1. Because of the hazardous nature of anhydrous hydrogen fluoride, *adequate precautions should be taken to protect the head, eyes, and skin.* Use of rubber gloves, an apron, and a plastic face mask is strongly recommended. All operations should be carried out in a hood. After completion of the reaction, all equipment should be washed with liberal quantities of water. A bottle containing magnesium oxide paste in glycerin should be available in case of emergency. *Note! Burns caused by hydrogen fluoride may not be noticed for several hours, by which time serious tissue damage may have occurred.*
The checkers recommend that, if hydrogen fluoride comes in contact with the skin, the contacted area be thoroughly washed with water and then immersed in ice water while the patient is taken to a physician.
2. Moisture or inefficient stirring reduces the yield considerably.
3. Satisfactory sources of chemicals are: N-bromoacetamide, Arapahoe Chemicals, Boulder, Colorado; 1-heptene, Aldrich Chemical Co.; hydrogen fluoride, Matheson Co.
4. The amount of hydrogen fluoride is not critical. The amount of hydrogen fluoride may be estimated by condensing in enough to increase the volume of the reaction mixture by 100 ml.
5. According to vapor phase chromatography in a 6-ft. column at 150° over silicone grease, the product contains about 8% of one impurity and 2% of another. It is sufficiently pure for conversion to 2-fluoroheptanoic acid.[2]

3. Discussion

1-Bromo-2-fluoroheptane[3] has been prepared only by the present procedure, which is similar to one described by Bowers and co-workers.[4]

4. Merits of the Preparation

The method is general for forming *vic*-bromofluorides, which in turn are useful

intermediates; this is exemplified in their conversion to 2-fluoroalkanoic acids.[2] The procedure can be applied, with minor modification, to many types of alkenes.[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 580
- Org. Syn. Coll. Vol. 5, 1135

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

potassium carbonate (584-08-7)

ether (60-29-7)

glycerin (56-81-5)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

hydrogen fluoride (7664-39-3)

copper (7440-50-8)

acetone (67-64-1)

magnesium oxide

N-Bromoacetamide (79-15-2)

1-Bromo-2-fluoroheptane, Heptane, 1-bromo-2-fluoro- (1786-32-9)

1-Heptene (592-76-7)

2-Fluoroheptanoic acid (1578-58-1)

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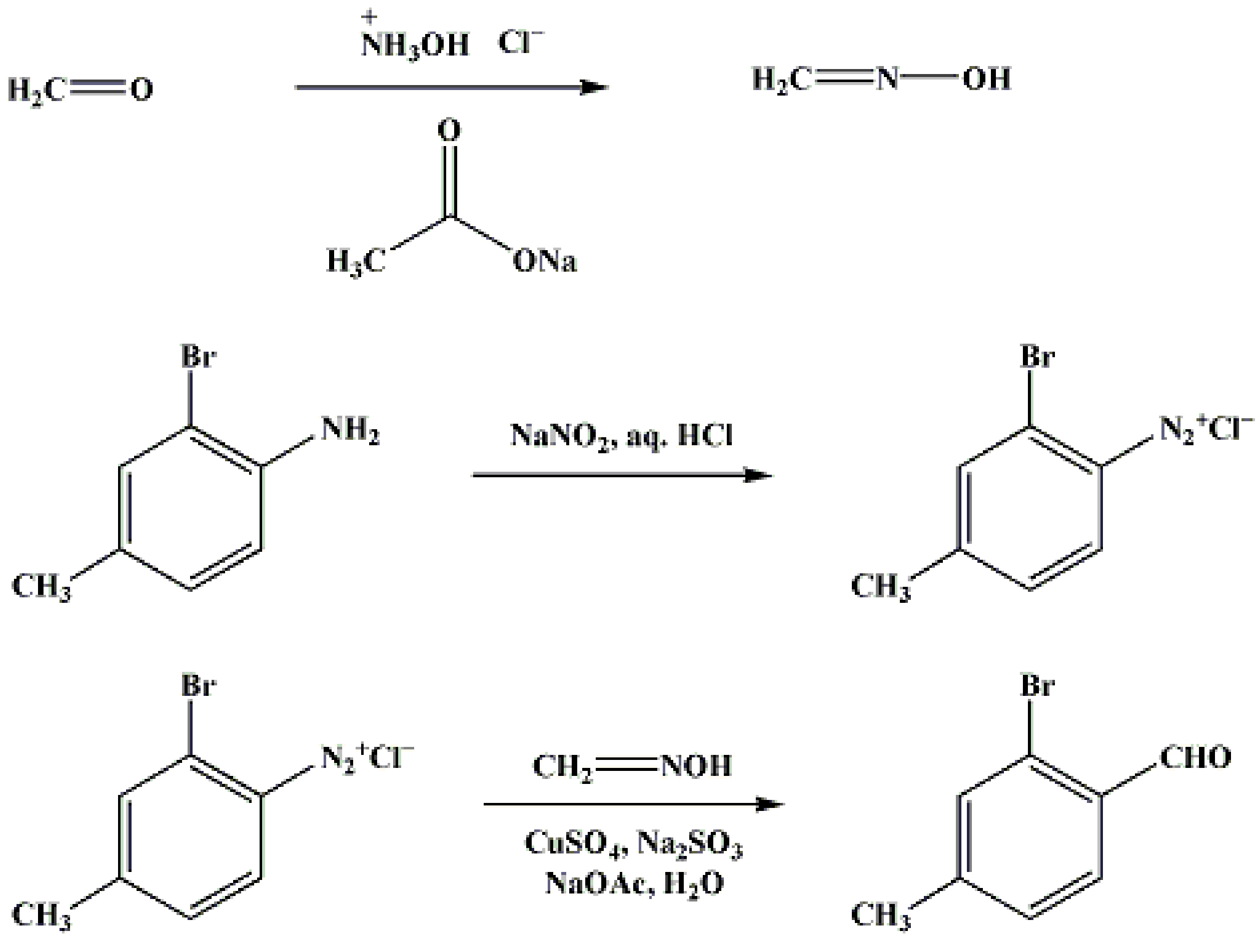
2-BROMO-4-METHYLBENZALDEHYDE

[*p*-Tolualdehyde, 2-bromo-]



Submitted by S. D. Jolad and S. Rajagopalan[1].
Checked by A. G. Szabo and Peter Yates.

1. Procedure

A. *Formaldoxime*. A mixture of 11.5 g. (0.38 mole) of paraformaldehyde and 26.3 g. (0.38 mole) of hydroxylamine hydrochloride in 170 ml. of water is heated until a clear solution is obtained. Then there is added 51 g. (0.38 mole) of hydrated sodium acetate, and the mixture is boiled gently under reflux for 15 minutes to give a 10% solution of formaldoxime.

B. *2-Bromo-4-methylbenzenediazonium chloride*. A mixture of 46.0 g. (0.25 mole) of 2-bromo-4-methylaniline[2] and 50 ml. of water is placed in a 1-l. three-necked flask equipped with an efficient stirrer, a dropping funnel, and a thermometer. The stirrer is started, and 57 ml. of concentrated hydrochloric acid is added slowly. The mixture is cooled to room temperature, 100 g. of ice is added, and the temperature of the mixture

is maintained at –5° to +5° by means of an ice-salt bath. To the stirred mixture there is added, dropwise, a solution of 17.5 g. (0.25 mole) of sodium nitrite in 25 ml. of water. After completion of the addition, the stirring is continued for a period of 15 minutes. The stirred solution of the diazonium salt is made neutral to Congo red by the addition of a solution of hydrated sodium acetate (22 g.) in water (35 ml.) (Note 1).

C. *2-Bromo-4-methylbenzaldehyde*. A 3-l. three-necked flask is equipped with an efficient stirrer, a dropping funnel (Note 2), and a thermometer. The aqueous 10% formaldoxime prepared in step A is placed in the flask, and to it are added 6.5 g. (0.026 mole) of hydrated cupric sulfate, 1.0 g. (0.0079 mole) of sodium sulfite, and a solution of 160 g. of hydrated sodium acetate in 180 ml. of water. The solution is maintained at 10–15° by means of a cold-water bath and stirred vigorously. The neutral diazonium salt solution prepared in step B is slowly introduced below the surface of the formaldoxime solution (Note 3) and (Note 4). After the addition of the diazonium salt solution is complete, the stirring is continued for an additional hour and then the mixture is treated with 230 ml. of concentrated hydrochloric acid. The stirrer and the dropping funnel are replaced by stoppers, and the mixture is gently heated under reflux for 2 hours. The flask is set up for steam distillation, and the reaction product is steam-distilled. The distillate is saturated with sodium chloride, extracted with three 150-ml. portions of ether, and the ethereal extracts are washed successively with three 20-ml. portions of a saturated sodium chloride solution, three 20-ml. portions of an aqueous 10% sodium bicarbonate solution, and again with three 20-ml. portions of a saturated sodium chloride solution.

The ether is distilled and to the residue there is added, with cooling, 90 ml. of an aqueous 40% sodium metabisulfite solution, previously heated to 60°. The mixture is shaken for 1 hour and allowed to stand overnight. The solid addition product is filtered, washed twice with ether, and then suspended in 200 ml. of water in a 500-ml. flask, and 40 ml. of concentrated sulfuric acid is slowly added with cooling. The mixture is gently boiled under reflux for 2 hours, cooled, and extracted with three 100-ml. portions of ether. The ethereal extract is washed with three 15-ml. portions of a saturated sodium chloride solution and dried over anhydrous sodium sulfate. The ether is evaporated, and the product is distilled under reduced pressure. 2-Bromo-4-methylbenzaldehyde distills at 114–115° (5 mm.) as a colorless oil, yield 17.5–22.5 g. (35–45%), which crystallizes in the receiver, m.p. 30–31°.

2. Notes

1. Exact neutralization of the diazonium salt solution is necessary in order to minimize coupling.
2. The stem of the dropping funnel should extend a little below the surface of the solution in the three-necked flask.
3. Addition of the diazonium salt solution sometimes results in the formation of a pasty mass which prevents further stirring; the mixture is then allowed to stand for a further period of 1 hour.
4. The checkers found it preferable to transfer the diazonium salt solution by

siphoning under slight nitrogen pressure.

3. Discussion

The preparation of this aldehyde is based on the reaction due to Beech[3] for the conversion of an aromatic amine to the corresponding aldehyde and has been described earlier by Jolad and Rajagopal.[4]

4. Merits of the Preparation

This method of preparation of a halobenzaldehyde is of wide application and has been used for the preparation of the following substituted benzaldehydes: 2-bromo-5-methyl-,[4] 2,3-dichloro- and 2,4-dichloro-,[5] 2-chloro-4-methyl-,[6] 2-methyl-4-bromo- and 3-methyl-4-bromo-,[7] 2-methyl-5-chloro- and 2-methyl-5-bromo-,[8] *p*-iodo-, *p*-fluoro-, 2-iodo-4-methyl-, and 6-iodo-3-methyl-.[9]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium metabisulfite

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium acetate (127-09-3)

sodium sulfite (7757-83-7)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

cupric sulfate (7758-98-7)

sodium nitrite (7632-00-0)

2-bromo-4-methylaniline (583-68-6)

Hydroxylamine hydrochloride (5470-11-1)

formaldoxime (75-17-2)

2-Bromo-4-methylbenzaldehyde, p-Tolualdehyde, 2-bromo- (824-54-4)

2-Bromo-4-methylbenzenediazonium chloride

paraformaldehyde (30525-89-4)

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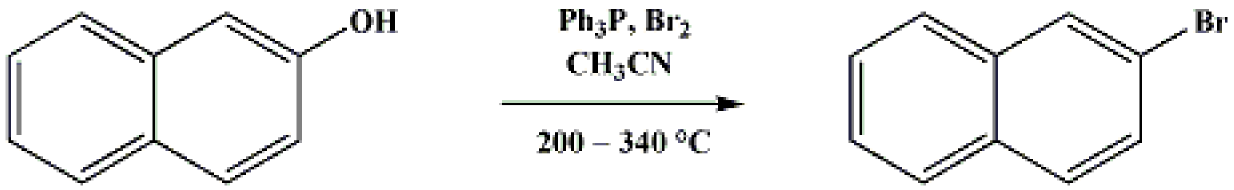
2-BROMONAPHTHALENE

[Naphthalene, 2-bromo-]



Submitted by J. P. Schaefer, Jerry Higgins, and P. K. Shenoy[1].
Checked by James P. Nelson, Wayland E. Noland, and William E. Parham.

1. Procedure

A 500 ml., three-necked, round-bottomed flask is equipped with a Trubore stirrer, a pressure-compensating dropping funnel, and a reflux condenser with drying tube. The flask is charged with 144 g. of triphenylphosphine (0.55 mole) (Note 1) and 125 ml. of acetonitrile (Note 2) and (Note 3). The solution is stirred and cooled in an ice bath and 88 g. of bromine is added dropwise over a period of 20–30 minutes (Note 4). After the addition of the bromine (Note 5) is complete, the ice bath is removed and 72 g. (0.50 mole) of β-naphthol (Note 6) in 100 ml. of acetonitrile (Note 7) is added in one portion and the reaction mixture is heated to 60–70° for at least 30 minutes (Note 8). The flask is now fitted for a simple distillation, stirring is discontinued, and the acetonitrile is distilled (Note 9) under aspirator pressure until the oil bath temperature reaches 110° (Note 10). After all the acetonitrile has been removed, the condenser is replaced by a short, large glass tube (Note 11) connected to a 500-ml. flask half-filled with water, and the oil bath is replaced by a Wood's metal bath. The bath temperature is now raised to 200–220° and kept at this temperature until all the solid has melted (Note 12). The mixture is stirred and the bath temperature is raised to 340° (Note 13) and held at this temperature until evolution of hydrogen bromide ceases (approximately 20–30 minutes). The Wood's metal bath is removed and the reaction mixture is cooled to approximately 100° and then poured into a 1-l. beaker and cooled to room temperature. Pentane (300 ml.) (Note 14) is added and the solid is broken into a fine precipitate (Note 15). The solid is filtered by suction and washed thoroughly with two 300-ml. portions of pentane. The pentane filtrates are combined, washed with 200 ml. of 20% sodium hydroxide, and dried over anhydrous magnesium sulfate. The pentane extract is then passed through a 25 mm. diameter column filled to 35 cm. in depth with alumina; distillation of the pentane at reduced pressure gives 72–81 g. (70–78%) (Note 16) of 2-bromonaphthalene, a white solid melting at 45–50° (reported:[2] 55–56.4°) (Note 17), (Note 18).

2. Notes

1. Triphenylphosphine was obtained from M and T Chemicals Inc. and was used without further purification.
2. The acetonitrile was *cautiously* distilled from phosphorus pentoxide. The solid phosphorus pentoxide may cause bumping during the distillation of the acetonitrile. This can be avoided if the solution is stirred during the distillation.
3. The triphenylphosphine is only partially dissolved.
4. The temperature is kept below 40° and the reaction mixture thoroughly stirred during this addition.
5. If a small amount of free bromine remains, as evidenced by color, then a sufficient amount of triphenylphosphine is added to take up the bromine.
6. Practical grade β-naphthol was obtained from Matheson Coleman and Bell and distilled at atmospheric pressure before use.
7. Warming the acetonitrile is necessary to dissolve the β-naphthol.
8. All the precipitate dissolves at this point. The checkers heated the mixture for 2 hours. The solids appeared to dissolve; then there was some reprecipitation. All solids had not dissolved after 2 hours at 70°.
9. The checkers encountered severe bumping during distillation of the acetonitrile. The acetonitrile may be removed with only moderate bumping if no external heat is applied.
10. The checkers did not remove all the acetonitrile at 110°, a factor which contributed to foaming later (Note 12).
11. If a tube smaller than inch in diameter is used, it may become plugged later in the reaction.
12. If temperature is higher than 220°, initial foaming may become troublesome. The checkers heated the solid to 240–270°, since melting did not occur at 200–220°; foaming was encountered.
13. Evolution of hydrogen bromide begins at about 280°.
14. The checkers used petroleum ether (b.p. 65–67°).
15. The checkers obtained a somewhat tarry precipitate.
16. The submitters obtained 85–87 g. (82–86% yield).
17. The checkers' product retained solvent. The product was heated for a short period at 120° (20 mm.) and a crystalline solid, free of solvent, was obtained.
18. Purity was checked by analytical vapor phase chromatography (98–99%). This product can be used for most reactions without further purification. If further purification is desired, 2-bromonaphthalene can be recrystallized from aqueous methanol (95% recovery) to give a product melting at 53–55°.

3. Discussion

2-Bromonaphthalene has been prepared from 2-aminonaphthalene by the reaction of mercuric bromide with the diazonaphthalene.[2,3] The reaction described in this preparation appears to be fairly general and provides a useful alternative method for introducing bromine into the aromatic nucleus. Using conditions similar to those outlined, the following have been prepared from the corresponding aryl alcohols:[4,5] α-

bromonaphthalene (72%), 3-bromopyridine (76%), 2-bromopyridine (61%), 8-bromoquinoline (48)%, *o*-bromotoluene (72%), *p*-chlorobromobenzene (90%), *p*-nitrobromobenzene (60%), and *p*-methoxybromobenzene (59%). The use of the triphenylphosphinehalogen complex to convert alcohols to alkylhalides is described elsewhere in this series.[6]

This preparation is referenced from:

- Org. Syn. 76, 12

References and Notes

1. Department of Chemistry, The University of Arizona, Tucson, Arizona.
2. M. S. Newman and P. H. Wise, *J. Am. Chem. Soc.*, **63**, 2847 (1941).
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5. G. A. Wiley, R. L. Hershkowitz, B. M. Rein, and B. C. Chung, *J. Am. Chem. Soc.*, **86**, 964 (1964).
6. J. P. Schaefer, J. G. Higgins, and P. K. Shenoy, this volume, p. 249.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

methanol (67-56-1)

acetonitrile (75-05-8)

sodium hydroxide (1310-73-2)

hydrogen bromide (10035-10-6)

bromine (7726-95-6)

β-naphthol (135-19-3)

α-Bromonaphthalene (90-11-9)

Naphthalene, 2-bromo-, 2-Bromonaphthalene (580-13-2)

Pentane (109-66-0)

magnesium sulfate (7487-88-9)

mercuric bromide (7789-47-1)

o-Bromotoluene (95-46-5)

2-Bromopyridine (109-04-6)

3-bromopyridine (626-55-1)

triphenylphosphine (603-35-0)

2-aminonaphthalene (91-59-8)

diazonaphthalene

8-bromoquinoline (16567-18-3)

p-methoxybromobenzene (104-92-7)

p-chlorobromobenzene (106-39-8)

phosphorus pentoxide (1314-56-3)

p-nitrobromobenzene (586-78-7)

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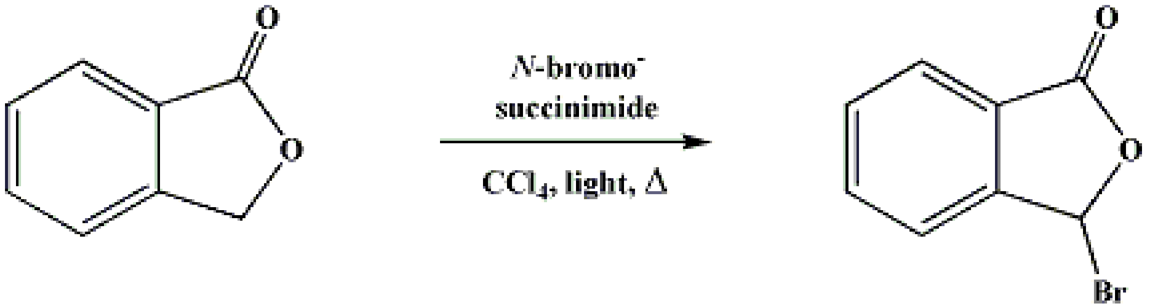
3-BROMOPHTHALIDE

[1(3H)-Isobenzofuranone, 3-bromo-]



Submitted by I. A. Koten and Robert J. Sauer[1].
Checked by R. C. Juola, Marjorie C. Caserio, and John D. Roberts.

1. Procedure

Ten grams (0.075 mole) of phthalide (Note 1), 13.3 g. (0.075 mole) of N-bromosuccinimide (Note 1), and 200 ml. of dry carbon tetrachloride (Note 1) are refluxed for 30 minutes in a 500-ml. flask carrying a reflux condenser equipped with a drying tube containing Drierite. The reaction mixture is exposed to the light of an ordinary 100-watt unfrosted light bulb placed 6–8 in. from the flask. The end of the reaction is indicated by the disappearance of N-bromosuccinimide from the bottom of the flask and accumulation of succinimide at the top of the reaction mixture. The succinimide is removed by filtration and the filtrate concentrated under atmospheric pressure to 15–20 ml. Cooling of this concentrate followed by filtration gives 12–13 g. (75–81%) of crude 3-bromophthalide, m.p. 74–80°. The crude material, when recrystallized from cyclohexane, gives colorless plates, m.p. 78–80° (Note 2),(Note 3),(Note 4).

2. Notes

1. The phthalide used was obtained from Aldrich Chemical Co. It was also prepared by the method of Gardner and Naylor, *Org. Syntheses Coll. Vol.* **2**, 526 (1943). The N-bromosuccinimide was obtained from Arapahoe Chemicals, Inc. The carbon tetrachloride used is dried over Drierite and filtered or distilled.
2. About 150 ml. of cyclohexane is necessary to recrystallize 12–13 g. of product, and the temperature of the solvent should be kept below 70° to avoid oiling of undissolved material. The recovery is 11–12 g.
3. When pure 3-bromophthalide is allowed to stand, its melting point is depressed, owing apparently to some decomposition. It may, therefore, be desirable to prepare the compound in smaller quantities than specified here. A sample of 3-bromophthalide, prepared by using 20 g. of phthalide and 26.6 g. of

N-bromosuccinimide, amounted to 29.8 g. (93.4%) of crude product. Hydrolysis of the crude material[2] gave phthalaldehydic acid, m.p. 96–98°.

4. Since one of the checkers developed a serious allergy to 3-bromophthalide, suitable precautions should be taken to avoid its inhalation and contact with the skin.

3. Discussion

3-Bromophthalide has previously been prepared by direct bromination of phthalide over a period of 10–13 hours in yields of 82–83%.[2] The procedure above, a modification of the Wohl-Ziegler method, appears to be preferable since it may be completed in 3–4 hours, is applicable to the preparation of small samples, and gives comparable yields.

References and Notes

1. Department of Chemistry, North Central College, Naperville, Ill. This work was supported by a grant from Research Corporation of New York City.
2. R. L. Shriner and F. J. Wolf, *Org. Syntheses*, Coll. Vol. **3**, 737 (1955).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Drierite

carbon tetrachloride (56-23-5)

cyclohexane (110-82-7)

Succinimide (123-56-8)

Phthalaldehydic acid (119-67-5)

Phthalide (87-41-2)

N-bromosuccinimide (128-08-5)

3-BROMOPHTHALIDE, 1(3H)-Isobenzofuranone, 3-bromo- (6940-49-4)

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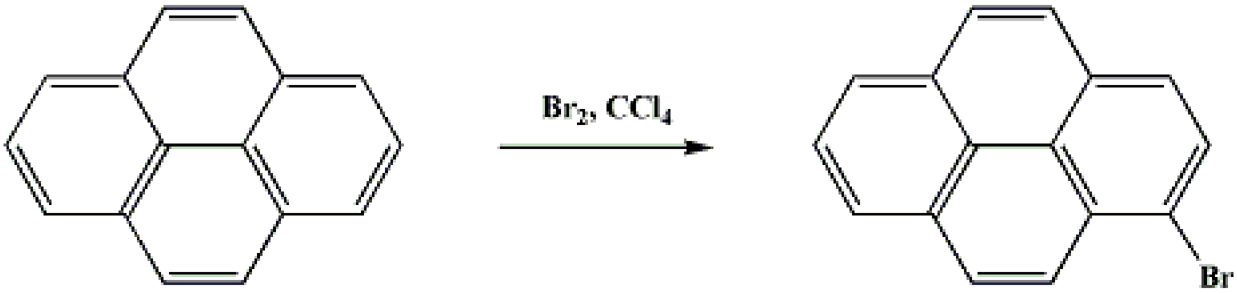
3-BROMOPYRENE

[Pyrene, 1-bromo-]



Submitted by W. H. Gumprecht[1]
Checked by Melvin S. Newman and Stephen Havlicek.

1. Procedure

Caution! Many pyrenes are carcinogens. Contact of the skin with these materials should be avoided.

In a 500-ml., three-necked, round-bottomed flask fitted with a stirrer, a reflux condenser, and a dropping funnel are placed 8.08 g. (0.040 mole) of pyrene (Note 1) and 80 ml. of carbon tetrachloride (Note 2). A solution of 2.0 ml. of bromine (6.24 g., 0.039 mole) (Note 3) in 30 ml. of carbon tetrachloride is added dropwise over a period of 2–3 hours. The resulting orange solution is stirred overnight, washed with three 100-ml. portions of water, and dried over anhydrous calcium chloride. The solvent is removed under reduced pressure, the pale yellow solid residue is dissolved in 10 ml. of benzene, and the benzene solution is treated with a small amount of activated carbon. The filtrate is diluted with 120 ml. of absolute ethanol, and the solution is distilled until about 80–90 ml. of solvent remains and then cooled. The bromopyrene crystallizes as pale yellow flakes, m.p. 93–95°. Additional material of similar melting point is obtained from the mother liquor on concentration. The total yield is 8.5–9.5 g. (78–86%) (Note 4). On recrystallization from benzene-alcohol a colorless product, m. p. 94.5–95.5°, is obtained with little loss.

2. Notes

1. Pyrene, m.p. 151–153°, obtained from Chemicals Division, Union Carbide Chemicals Corp., was used by the submitter. A commercial pyrene obtained from Germany was used by the checkers.
2. A C.P. solvent was used.
3. Reagent grade material was used. Excess bromine is to be avoided, as dibromopyrene can be formed.[2]

4. The submitter has run this preparation on 80 g. of pyrene with no change in yield.

3. Discussion

This procedure is described by Lock;[2] a modification using a small amount of phenol has been published.[3] The patent literature discloses the use of a tertiary amine, such as pyridine, and its combination with other solvents for the monobromination of pyrene with elemental bromine.[4] Brominating agents, such as N-bromosuccinimide[5] and N-bromohydantoins,[6] have also been used.

4. Merits of the Preparation

3-Bromopyrene is a precursor of 3-hydroxypyrene.[7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 632

References and Notes

1. Contribution No. 334 from the Organic Chemicals Department, E. I. du Pont de Nemours and Company, Wilmington, Delaware 19899.
2. G. Lock, *Ber.*, **70**, 926 (1937).
3. H. Hock and F. Ernst, *Ber.*, **92**, 2732 (1959).
4. A. Wolfram and W. Schnurr, U.S. Patent 2,094,227 (1937) [*C.A.*, **31**, 8550 (1937)].
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7. W. H. Gumprecht, this volume, p. 632.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

calcium chloride (10043-52-4)

Benzene (71-43-2)

phenol, benzene-alcohol (108-95-2)

bromine (7726-95-6)

carbon tetrachloride (56-23-5)

carbon (7782-42-5)

pyridine (110-86-1)

pyrene (129-00-0)

N-bromosuccinimide (128-08-5)

3-Bromopyrene, Pyrene, 1-bromo-, bromopyrene (1714-29-0)

dibromopyrene

3-Hydroxypyrene (5315-79-7)

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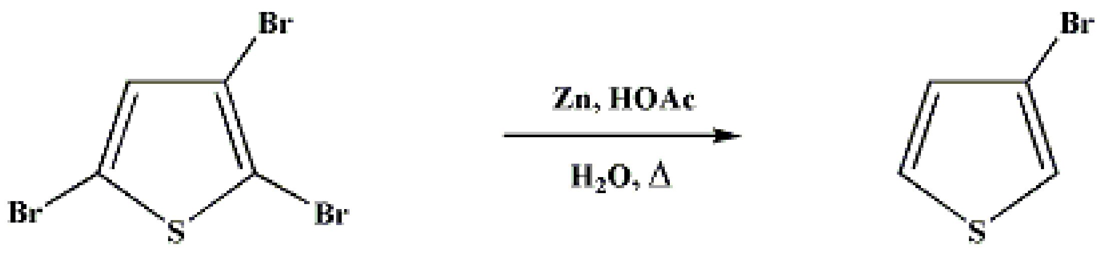
3-BROMOTHIOPHENE

[Thiophene, 3-bromo-]



Submitted by S. Gronowitz and T. Raznikiewicz[1].
Checked by Max Tishler, Arthur J. Zambito, and Ronald B. Jobson.

1. Procedure

A 5-l., three-necked, round-bottomed flask is equipped with an efficient stirrer (Note 1), a reflux condenser, and a dropping funnel. Water (1850 ml.) is added, stirring is begun and continued throughout the procedure, and 783 g. (12.0 moles) of zinc dust (Note 2) and 700 ml. of acetic acid are added. The mixture is heated to reflux, the heating mantle is removed, and 1283 g. (4.00 moles) of 2,3,5-tribromothiophene (Note 3) is added dropwise at such a rate that the mixture continues to reflux. The addition is complete in about 70 minutes. Heat is applied, and the mixture is refluxed for 3 hours. A condenser is arranged for downward distillation, and the mixture is distilled until no more organic substance distills with the water (Note 4). The heavier organic layer is separated, washed successively with 50 ml. of 10% sodium carbonate solution and 100 ml. of water, dried over calcium chloride (Note 5), and fractionated through a vacuummantled Dufton column (Note 6). A 19-g. fore-run, b.p. 78–159°, consists mainly of thiophene and 3-bromothiophene. 3-Bromothiophene is collected at 159–160°; n^{20}D 1.5919–1.5928; weight 580–585 g. (89–90%) (Note 7) and (Note 8).

2. Notes

1. The submitters used a Teflon® paddle-type stirrer sealed with rubber tubing lubricated by glycerol and driven by a powerful motor. The checkers used a Trubore® stirrer.
2. Mallinckrodt zinc powder (analytical reagent grade) is used.
3. 2,3,5-Tribromothiophene is conveniently prepared by the method of Troyanowsky.[2] Thiophene (1125 g., 13.4 moles) and 450 ml. of chloroform are charged into a 5-l. three-necked flask equipped with a stirrer, a dropping funnel, and an outlet for the hydrogen bromide evolved. The flask is in a deep pan through which cold tap water passes. Bromine (6480 g., 40.6 moles) is added dropwise to the stirred mixture over a period of 10 hours. After the mixture has

stood overnight, it is heated at 50° for several hours, washed with 2*N* sodium hydroxide solution, refluxed for 7 hours with a solution of 800 g. of potassium hydroxide in 1.5 l. of 95% ethanol, and poured into water. The organic layer is separated, washed with water, dried over calcium chloride, and fractionated to give 3200–3650 g. (75–85%) of 2,3,5-tribromothiophene; b.p. 123–124° (9 mm.); m.p. 25–27°.

4. About half of the volume is distilled over. The temperature of the vapor rises during the distillation from 95° to 101°.

5. The checkers washed the drying agent with ether and combined the wash with the filtrate.

6. A Dufton column was not available to the checkers. In its place a 2.5-cm. × 38-cm. column packed with glass helices was used. This column was heated by a 4.5-cm. concentric glass jacket wrapped with Nichrome ribbon. A 6.5-cm. concentric glass jacket surrounded the whole column and served to insulate it.

7. In several experiments on one-fifth the scale, the yields were 89–92%.

8. Infrared analysis shows that the 3-bromothiophene contains about 0.5% of 2-bromothiophene, as measured by 2-bromothiophene's characteristic absorption peak at 10.26 •. The traces of this lower-boiling isomer can easily be removed by fractionation through a more efficient column.

3. Discussion

The procedure described is a modification of that described by Gronowitz.[3] 3-Bromothiophene has been obtained more tediously and in lower yields by removal of the α-bromines of 2,3,5-tribromothiophene through the Grignard entrainment method[4] with ethyl bromide as the auxiliary halide, or by halogen-metal interconversion with *n*-butyllithium[5] followed by hydrolysis of the organometallic compounds. It has also been obtained from 4,5-dibromo-2-thiophenecarboxylic acid through simultaneous debromination and decarboxylation.[6]

4. Merits of the Preparation

3-Bromothiophene is a key intermediate for the synthesis of 3-substituted thiophenes.[7]

References and Notes

1. Department of Organic Chemistry, Chemical Institute, University of Uppsala, Sweden.
2. C. Troyanowsky, *Bull. Soc. Chim. France*, 1424 (1955).
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6. R. Motoyama, S. Nishimura, E. Imoto, Y. Murakami, K. Hari, and J. Ogawa, *Nippon Kagaku Zasshi*, **78**, 950 (1957).
7. S. Gronowitz, *Arkiv Kemi*, **13**, 295 (1959).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

calcium chloride (10043-52-4)

acetic acid (64-19-7)

ether (60-29-7)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

glycerol (56-81-5)

hydrogen bromide (10035-10-6)

sodium carbonate (497-19-8)

bromine (7726-95-6)

Ethyl bromide (74-96-4)

potassium hydroxide (1310-58-3)

zinc, zinc powder (7440-66-6)

Thiophene (110-02-1)

n-butyllithium (109-72-8)

2-Bromothiophene (1003-09-4)

3-Bromothiophene, Thiophene, 3-bromo- (872-31-1)

2,3,5-tribromothiophene

4,5-dibromo-2-thiophenecarboxylic acid (7311-68-4)

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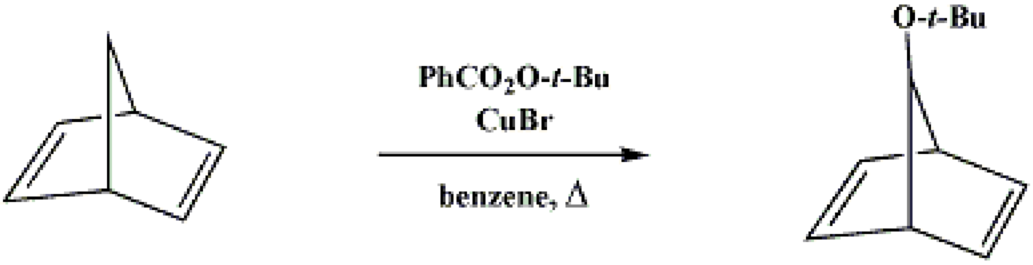
7-*t*-BUTOXYNORBORNADIENE

[2,5-Norbornadiene, 7-*tert*-butoxy-]



Submitted by Paul R. Story and Susan R. Fahrenholtz[1].
Checked by Eric Block and E. J. Corey.

1. Procedure

A 2-l. three-necked flask, fitted with stirrer, condenser, dropping funnel, and an arrangement for maintenance of an inert atmosphere, is charged with a mixture of 300 g. (3.26 moles) of norbornadiene (Note 1) and 0.650 g. (4.53 mmoles) of cuprous bromide (Note 2) in 500 ml. of benzene (Note 3). Dry nitrogen is introduced continuously, and, after the flask contents are brought to reflux, 245 g. (1.26 mole) of *t*-butyl perbenzoate (Note 4), dissolved in 100 ml. of benzene, is added over approximately 1 hour to the stirred mixture. The solution immediately becomes blue or blue-green. The modest heat of reaction requires the application of some heat throughout the reaction period in order to maintain reflux. After the addition is completed, the solution is heated at the reflux temperature for an additional 30 minutes (*Caution! (Note 5)*).

The mixture is cooled to room temperature, transferred to a 4-l. separatory funnel, and washed with three 300-ml. portions of saturated brine, to remove copper salts, and three 300-ml. portions of 10% aqueous sodium hydroxide, to remove benzoic acid (Note 6). The benzene solution is then washed with 150 ml. of brine and is dried over anhydrous sodium sulfate.

The dried solution is transferred to a 2-l. flask fitted with a Claisen head attached to a 30-cm. Vigreux column. Benzene is removed fairly rapidly at about 200 mm. so that the benzene boils at 45–50° (Note 7). After removal of most of the benzene, the pressure is slowly lowered to 10–15 mm.; a negligible amount of fore-run is obtained before the product begins to distil at about 65° at 15 mm. The product is collected until the temperature reaches 80–85° at the same pressure (Note 8). The yield of 7-*t*-butyoxynorbornadiene is 42–51 g. (20–25%,, based on *t*-butyl perbenzoate) (Note 9). Gas-phase chromatographic analysis of the product shows it to be about 95% pure. Greater purity can be obtained, if required, by fractionation through a spinning band column; the pure product is collected at 70–72° (14 mm.) (Note 10).

2. Notes

1. Norbornadiene as supplied by Shell Chemical Co. is used without further purification. Distillation of the norbornadiene immediately before use gives no change in yield of 7-*t*-butoxynorbornadiene.
2. The cuprous bromide was used as obtained from E. H. Sargent Co. One instance of an ineffective batch of cuprous bromide from another source has been reported to the submitters. Cuprous bromide is only slightly soluble in the benzene solution. Greater amounts of catalyst have no effect on the yield of product.
3. Baker and Adamson or Merck reagent grade benzene was used.
4. *t*-Butyl perbenzoate was used as received from Lucidol Division of Wallace and Tiernan Co., Buffalo, New York.
5. Normally, after this time, the *t*-butyl perbenzoate is completely reacted. It is advisable, however, to check for its presence because distillation of a crude product containing some perester can lead to an explosion. *t*-Butyl perbenzoate absorbs strongly in the infrared at 5.65–5.70 •, and examination of the infrared spectrum of the benzene solution is a sufficiently sensitive test. No difficulty has ever been encountered during reactions with norbornadiene. However, unreacted *t*-butyl perbenzoate has caused a minor explosion with another, less reactive olefin.
6. Unless the copper salts are removed first, the basic wash frequently produces a thick emulsion which requires considerable time to settle.
7. The benzene is removed at reduced pressure to minimize heating of the product which consists chiefly of high-boiling esters. The last trace of benzene and norbornadiene is removed at a lower pressure.
8. 7-*t*-Butoxynorbornadiene is collected over this wide temperature range since the last portion of the distillate is super-heated because of the large quantity of high-boiling materials remaining in the pot. No other reaction products boil in the same range, and GPC analysis has shown the last fraction of distillate to be nearly as pure as the middle cut.
9. This reaction has been conducted under a variety of conditions, but the yield of 7-*t*-butoxynorbornadiene has never been less than 20% or greater than 26%.
10. Infrared (•, CCl_4): 6.48 (w), 7.20 (m), 7.35 (s), 7.61 (m), 9.05 (s), 13.7 (s). The absorptions at 6.48 (double-bond stretch) and 13.7 (*cis* double bond C-H out-of-plane deformation) are very characteristic of the norbornadiene nucleus. N.m.r. spectrum (CCl_4): τ = 3.56 (m), 3.70 (m), 6.77 (m), 6.38 (m), 8.94 (s).

3. Discussion

The only method reported[2] for the preparation of 7-*t*-butoxynorbornadiene is that described here. The general reaction of *t*-butyl perbenzoate with various olefins has been described by many investigators.[3] When benzoyl peroxide is used in place of *t*-butyl perbenzoate under similar conditions, 7-benzoxynorbornadiene is obtained in

38% yield; it is said to be more easily hydrolyzed to the alcohol than 7-*t*-butoxynorbornadiene.[4]

4. Merits of the Preparation

7-*t*-Butoxynorbornadiene provides a convenient route to 7-substituted norbornenes and norbornadienes including *anti*-7-norbornenol,[2] 7-norbornadienyl acetate,[2] 7-norbornadienol,[2] 7-chloronorbornadiene,[5] 7-methylnorbornadiene,[6] and 7-phenylnorbornadiene.[6] These compounds are useful in studies of the nature of chemical bonding.[5,7]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

brine

t-butyl perbenzoate

Benzene (71-43-2)

sodium hydroxide (1310-73-2)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

Benzoic acid (65-85-0)

cuprous bromide (7787-70-4)

benzoyl peroxide (94-36-0)

norbornadiene

7-benzoxynorbornadiene

7-norbornadienyl acetate

7-norbornadienol

7-chloronorbornadiene

7-methylnorbornadiene

7-phenylnorbornadiene

7-t-BUTOXYNORBORNADIENE, 2,5-Norbornadiene, 7-tert-butoxy- (877-06-5)

anti-7-norbornenol

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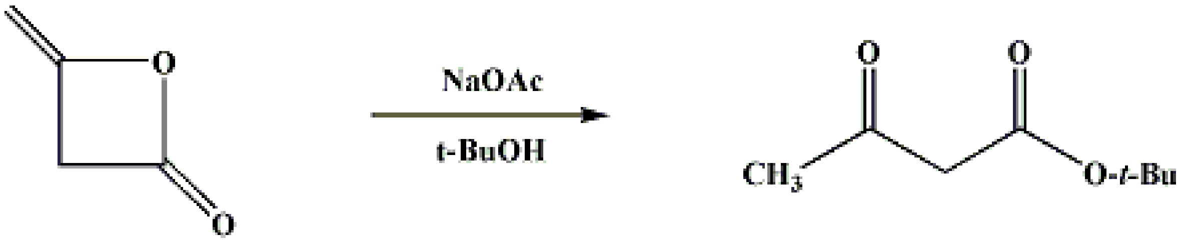
t-BUTYL ACETOACETATE

[Acetoacetic acid, *tert*-butyl ester]



Submitted by Sven-Olov Lawesson, Susanne Gronwall, and Rune Sandberg[1].
Checked by William G. Dauben and Richard Ellis.

1. Procedure

Caution! This preparation should be conducted in a hood to avoid exposure to diketene, which is toxic and which may irritate mucous tissues such as those of the eyes; the use of safety goggles is recommended.

A 500-ml. three-necked flask is equipped with a sealed mechanical stirrer, a dropping funnel, and a two-armed addition tube, one arm of which bears a reflux condenser and the other arm of which is fitted with a thermometer. *t*-Butyl alcohol (79 g., 1.07 moles) (Note 1) is added to the flask and the thermometer arranged so that its bulb is immersed in the liquid but out of the path of the stirrer. The flask is heated by means of an electric mantle until the temperature of the liquid is 80–85°, and the mantle then is removed. Anhydrous sodium acetate (0.4 g., 4.8 mmoles) is added with stirring, and then 96 g. (1.14 moles) of diketene (Note 2) is added dropwise over a period of 2.5 hours. The temperature of the solution drops to 60–70° during the first 15 minutes and then increases slowly to 110–115°. When all the diketene is added, the reaction subsides and, after the resulting brown-black solution is stirred for an additional 30 minutes, the product is distilled immediately under reduced pressure through a short column. After a small fore-run, the yield of *t*-butyl acetoacetate, b.p. 85°/20 mm. (Note 3), n_D^{20} 1.4200–1.4203, is 127–135 g. (75–80%) (Note 4).

2. Notes

1. Eastman Kodak white label grade is used without further purification.
2. The submitters used material directly as supplied by Dr. Theodor Schuchardt and Co., Munich, Germany. The checkers used material directly as supplied by Aldrich Chemical Co., Milwaukee, Wisconsin.
3. The still residue is dehydroacetic acid.
4. In a run five times the size described, the submitters report that the reaction goes in the same manner and in 85–92% yield.

3. Discussion

t-Butyl acetoacetate has been prepared by self-condensation of *t*-butylacetate.[2,3] The described procedure is based upon the method of Treibs and Hintermieier.[4]

The present preparation employs a method of considerable scope and is illustrative of a general method of preparing esters of acetoacetic acid; it gives much better yields, is considerably less laborious than other methods for the preparation of *t*-butyl acetoacetate, and appears to be the most convenient as starting materials are easily accessible. The title compound is of specific interest since the *t*-butoxy carbonyl group may be removed simply by heating the compound with catalytic amounts of *p*-toluenesulfonic acid. For instance, a new method has been developed for the preparation of acyloins by introducing the benzoyloxy group into *t*-butyl acetoacetate, followed by *t*-butoxy carbonyl-elimination and hydrolysis.[5] Using a similar technique and starting from *t*-butyl acetoacetate, levulinic esters,[6] δ-ketonitriles,[7] 1-methylcyclohexene-1-on-3,[8] α,β-unsaturated ketones,[9] and piperiton and related compounds[10] have been prepared.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 179

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium acetate (127-09-3)

diketene (674-82-8)

Dehydroacetic acid (520-45-6)

t-butyl alcohol (75-65-0)

acetoacetic acid (541-50-4)

p-toluenesulfonic acid (104-15-4)

t-BUTYL ACETOACETATE, Acetoacetic acid, tert-butyl ester (1694-31-1)

t-butylacetate

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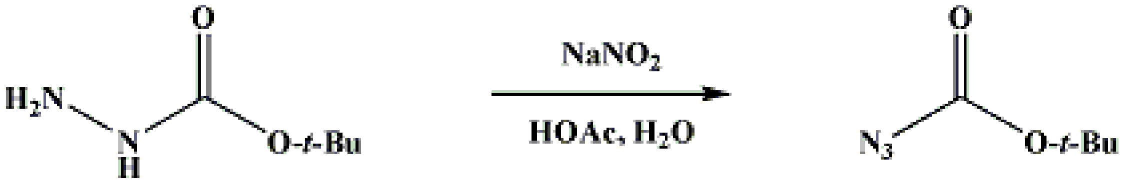
Organic Syntheses, *CV 5, 157*

t-BUTYL AZIDOFORMATE

[Formic acid, azido-, *tert*-butyl ester]



Submitted by Louis A. Carpino, Barbara A. Carpino, Paul J. Crowley, Chester A. Giza, and Paul H. Terry[1].
Checked by Virgil Boekelheide and S. J. Cross.

1. Procedure

In a 1-l. round-bottomed flask fitted with a mechanical stirrer are placed 82 g. (0.62 mole) of *t*-butyl carbazate,[2] 72 g. of glacial acetic acid, and 100 ml. of water. The solution is cooled in an ice bath, and 47.0 g. (0.68 mole) of solid sodium nitrite is added over a period of 40–50 minutes, the temperature being kept at 10–15° (Note 1). The mixture is allowed to stand in the ice bath for 30 minutes, 100 ml. of water is added, and the floating oil is extracted into four 40-ml. portions of ether. The combined ether extracts are washed twice with 50-ml. portions of water and with 40-ml. portions of 1*M* sodium bicarbonate solution until no longer acidic (about three washings are required). The solution is dried over magnesium sulfate, and the ether is removed by distillation from a water bath maintained at 40–45°; water aspirator pressure of 140–150 mm. is used. The pressure is then lowered to 70 mm., and the water bath temperature is raised to 90–95°. The azide is distilled (*Caution! (Note 2)*) using a Claisen flask and is collected at 73–74° (70 mm.), n^{24}D 1.4227, after a few drops of fore-run. The yield is 57–72.8 g. (64–82%) (Note 3) and (Note 4).

2. Notes

1. The sodium nitrite may be added as a concentrated aqueous solution.
2. It is recommended that the distillation be carried out behind a safety shield. The submitters have distilled this compound several hundred times without incident under the conditions given on a scale up to 300–400 g. per run. On the other hand, Prof. P. G. Katsoyannis (University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania) has reported that an explosion took place in the receiving flask while the compound was being distilled under conditions previously used without incident. The reason for the explosion could not be traced. According to Prof. R. Schwyzer (Ciba, Ltd., Basel, Switzerland) tests at a Swiss Federal Institute showed that the compound could not be exploded by mere heating: it simply decomposes. For explosion, one must apply a primary

explosive such as lead azide or silver azide. An attempt by the submitters to distil the azide at atmospheric pressure resulted in vigorous carbonization, but no explosion occurred. In view of the potential hazard some investigators prefer not to distil the azide; they use the crude material after removal of solvent. High yields of carbo-*t*-butoxy derivatives may be obtained in this way.
3. When freshly distilled, the azide is water-white. When the azide is allowed to stand for several weeks, it slowly develops a light yellow color; however, this does not appear to affect its reactivity as an acylating agent.[3]
4. The azide should be handled with adequate ventilation. Careless inhalation of the substance was accompanied by development of a painful throbbing headache or a sensation of giddiness or both. These effects disappeared within several hours upon exposure to fresh air.

3. Discussion

t-Butyl azidoformate has been prepared by a variety of procedures,[3,4,5,6,7,8,9,10,11,12] of which the present procedure and that described elsewhere in this series[12] appear most satisfactory.

Because of the instability of *t*-butyl chloroformate a number of carbonic acid derivatives have been prepared and studied as reagents for the introduction of the carbo-*t*-butoxy group. A listing of these reagents and references to their preparation may be found in reference [13]. In spite of some disadvantages the most widely used reagent is still *t*-butyl azidoformate, although *t*-butyl 2,4,5-trichlorophenyl-carbonate appears to be another potentially useful reagent. *t*-Butyl azidoformate is a convenient reagent for the acylation of amines, hydrazines, and similar compounds.[3]

The acylation product of hydroxylamine, *t*-butyl N-hydroxycarbamate,[5] is a valuable intermediate in the synthesis of O-substituted hydroxylamines such as O-acyl- and O-sulfonylhydroxylamines, many of which are valuable aminating agents and have not be obtained in any other way.[14,15]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 160
- Org. Syn. Coll. Vol. 6, 199
- Org. Syn. Coll. Vol. 6, 203
- Org. Syn. Coll. Vol. 6, 207
- Org. Syn. Coll. Vol. 6, 418
- Org. Syn. Coll. Vol. 7, 70

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

acetic acid (64-19-7)

ether (60-29-7)

sodium bicarbonate (144-55-8)

sodium nitrite (7632-00-0)

hydroxylamine (7803-49-8)

magnesium sulfate (7487-88-9)

silver azide

t-BUTYL AZIDOFORMATE, Formic acid, azido-, tert-butyl ester (1070-19-5)

t-butyl N-hydroxycarbamate (36016-38-3)

t-butyl carbazate (870-46-2)

t-butyl chloroformate

t-butyl 2,4,5-trichlorophenyl-carbonate (16965-08-5)

lead azide

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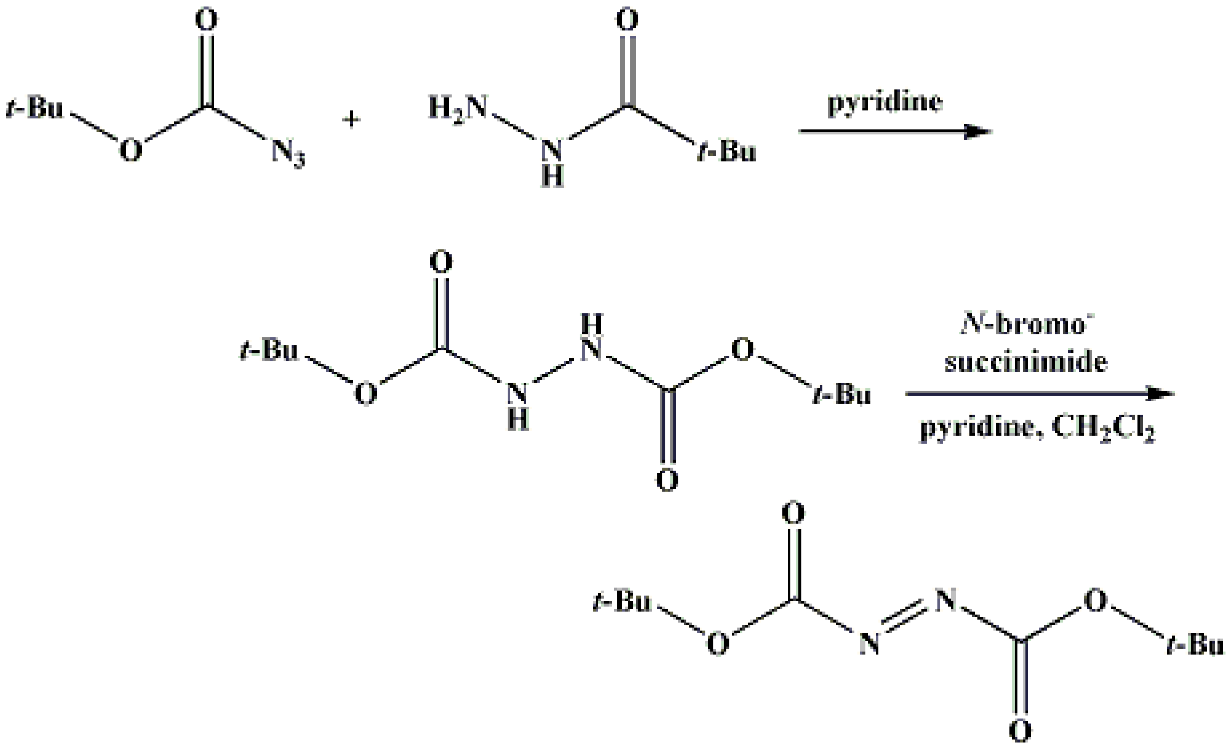
Organic Syntheses, *CV 5, 160*

t-BUTYL AZODIFORMATE

[Formic acid, azodi-, di-*tert*-butyl ester]



Submitted by Louis A. Carpino and Paul J. Crowley[1].
Checked by Virgil Boekelheide and S. J. Cross.

1. Procedure

A. *t-Butyl hydrazodiformate*. A solution of 28.6 g. (0.2 mole) of *t*-butyl azidoformate[2] and 26.4 g. (0.2 mole) of *t*-butyl carbazate[3] in 60 ml. of pyridine (Note 1) is allowed to stand at room temperature for 1 week and is then diluted with 500 ml. of water. The snow-white microcrystalline powder that separates is removed by filtration and is washed with two 50-ml. portions of water. The yield of air-dried hydrazide, m.p. 124–126°, is 35.5–37 g. (77–80%). The product is pure enough for most applications but may be purified by recrystallization from a 1:1 mixture of benzene and ligroin (60–90°) from which it separates as small white needles, m.p. 124–125.5°. The recovery is 92%.

B. *t-Butyl azodiformate*. In a 500-ml. Erlenmeyer flask is placed a solution of 23.2 g. (0.1 mole) of crude *t*-butyl hydrazodiformate (m.p. 124–126°) in 175 ml. of methylene chloride and 7.9 g. (0.1 mole) of pyridine (Note 1). The solution is cooled by a stream of running tap water while 18.2 g. (0.102 mole) (Note 2) of N-bromosuccinimide (Note 1) is added during 6–7 minutes with swirling. The resulting solution is allowed to stand at room temperature for 5 minutes and is washed with two 100-ml. portions of

water followed by one 100-ml. portion of 10% sodium hydroxide. The solution is dried for 30 minutes over magnesium sulfate, filtered into a large evaporating dish, and allowed to evaporate. The yellow-orange crystalline residue, m.p. 90–91.5°, which amounts to 20.7–21.8 g. (90–94.5%), is recrystallized by covering the dry solid with 35–40 ml. of petroleum ether (b.p. 30–60°) and adding ligroin (b.p. 60–90°) to the boiling solution until the solid dissolves. *t*-Butyl azodiformate, 19.8–20.0 g., m.p. 90.7–92°, separates from the cooled solution as large lemon-yellow crystals. Evaporation of the filtrate gives an additional amount of yellow solid which is recrystallized as before, yielding 0.4–0.7 g. of pure material, m.p. 90–92°. The total yield is 20.2–20.7 g. (88–90%).

2. Notes

1. The pyridine was a pure product, b.p. 113–115°, obtained from Mallinckrodt Chemical Company and used as supplied. The methylene chloride (technical grade) and N-bromosuccinimide (practical grade) were obtained from the Matheson Company and used as received.
2. Unless a 2% excess of N-bromosuccinimide is used, the azo compound is contaminated by an impurity, possibly the original hydrazo compound, which separates along with the desired product in the form of long, easily distinguished needles. The two substances cannot be separated by crystallization from ligroin.

3. Discussion

t-Butyl hydrazodiformate has been prepared by acylation of *t*-butyl carbazate by means of *t*-butyl azidoformate[4] or *t*-butyl cyanoformate.[5] *t*-Butyl azodiformate has been prepared only by oxidation of the hydrazo compound.[6]

4. Merits of the Preparation

The potassium salt of *t*-butyl hydrazodiformate can be easily alkylated and thus used in the synthesis of acyclic and cyclic 1,2-disubstituted hydrazines.[7]

Ethyl azodiformate is a well-known and useful dienophile in the Diels-Alder reaction.[8] *t*-Butyl azodiformate behaves similarly, although it is somewhat less reactive.[6] *t*-Butyl azodiformate does, however, provide products with ester groups that are easily cleaved. Monosubstituted hydrazines may be prepared by the addition of Grignard reagents to azoformates followed by cleavage.[6]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ligroin

petroleum ether

Benzene (71-43-2)

sodium hydroxide (1310-73-2)

pyridine (110-86-1)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

N-bromosuccinimide (128-08-5)

Ethyl azodiformate

t-BUTYL AZIDOFORMATE (1070-19-5)

t-butyl carbazate (870-46-2)

t-BUTYL AZODIFORMATE (870-50-8)

Formic acid, azodi-, di-tert-butyl ester

t-butyl hydrazodiformate

t-butyl cyanoformate

potassium salt of t-butyl hydrazodiformate

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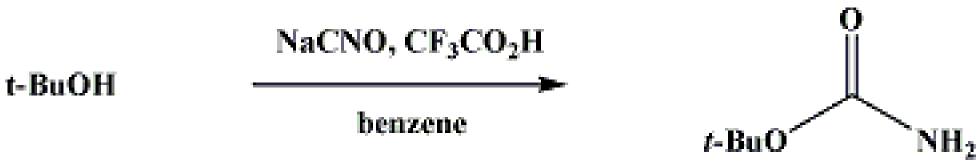
t-BUTYL CARBAMATE

[Carbamic acid, *tert*-butyl ester]



Submitted by Bernard Loev, Minerva F. Kormendy, and Marjorie M. Goodman[1].
Checked by David C. Armbruster and William D. Emmons.

1. Procedure

Caution! Because of the acrid nature of trifluoroacetic acid and the possibility of the evolution of toxic fumes the reaction should be carried out in a hood.

A solution of 14.8 g. (0.20 mole) of *t*-butyl alcohol in 125 ml. of benzene (Note 1) is placed in a 500-ml. three-necked flask equipped with a stirrer, a thermometer, and an addition funnel, and 26.0 g. (0.40 mole) of sodium cyanate (Note 2) is added. The suspension is stirred as *slowly* as possible (*ca.* 120 r.p.m.; (Note 3)) while 48.0 g. (31.2 ml., 0.42 mole) of trifluoroacetic acid is added dropwise at a rapid rate. The temperature slowly rises to about 37° after three-quarters of the trifluoroacetic acid has been added (*ca.* 7 minutes). At this point (Note 4) the mixture is cooled to 33–35° by brief immersion in an ice-water bath, then the addition is continued. When the addition of the acid is completed (10–12 minutes total time), the temperature slowly rises to 40° and then gradually subsides. Slow stirring is continued overnight (Note 5) at room temperature.

The mixture is treated with 35 ml. of water (Note 6) and stirred vigorously for a few minutes. The benzene layer is decanted, and the aqueous slurry is rinsed with two 125-ml. portions of benzene (Note 7). The combined organic extracts are washed once with 100 ml. of aqueous 5% sodium hydroxide (Note 8) and with 100 ml. of water, dried over anhydrous magnesium sulfate, and filtered. The solvent is removed by distillation under reduced pressure, preferably on a rotary evaporator, from a water bath kept at 30° (Note 9) to give 17.7–22.0 g. (76–94%) of *t*-butyl carbamate as white needles, m.p. 104–109° (Note 10). The product may be recrystallized from hexane (Note 11); m.p. 107–109° (Note 12).

2. Notes

1. The reagents should not be dried, as traces of moisture catalyze the reaction.

The choice of solvent for this type of reaction markedly affects the yield; for most alcohols the use of benzene or methylene chloride gives yields superior to those obtained in other solvents.
2. Sodium cyanate *cannot* be replaced by other cyanates (potassium, ammonium, etc.), for the yields are then drastically lowered.
3. Vigorous agitation markedly lowers the yield; stirring rates of 40–120 r.p.m. are optimum.
4. The temperature may rise to 40°; within the range 20–50° the temperature has little effect on the yield.
5. A contact time of 3–4 hours is sufficient, but it is convenient to stir the reaction mixture overnight. The yield is slightly higher after this additional time.
6. Only a limited amount of water is added at this point because *t*-butyl carbamate has some solubility in the resulting aqueous slurry. With water-insoluble carbamates the amount of water added is immaterial.
7. The checkers found that quantitative recovery of the benzene layer by decantation was impossible, so that in the final benzene rinse the mixture was poured into a graduated cylinder, and the benzene layer was quantitatively removed by a syringe.
8. The alkaline wash serves to hydrolyze a small amount of *t*-butyl N-trifluoroacetylcarbamate which occasionally forms. It is not clear why this by-product forms on some occasions but not on others under apparently identical conditions. The checkers found in every case that upon standing the alkaline wash deposited 1–2 g. (after drying) of white crystals which was shown to be identical with the *t*-butyl carbamate obtained as the main crop. This amount is included in the yield.
9. Most carbamates, including those of high molecular weight, are volatile. They are generally thermally unstable until they are purified.
10. The melting range varies markedly with the rate of heating, the temperature at which the sample is put into the bath, the solvent used, and the crystal form of the product. The compound at this stage is analytically pure and gives a single spot on thin-layer chromatography.
11. The carbamate may also be recrystallized from water in somewhat lower recovery. With either solvent, extensive heating should be avoided since a considerable amount of product is lost by volatilization. The checkers found that a relatively large volume of hexane was required for recrystallization and therefore used a 1:1 benzene-hexane or 1:1 benzene-ligroin solvent system for the recrystallization.
12. The reported melting points range from 108° to 110°.[2,3,4,5]

3. Discussion

Although numerous methods are known for the synthesis of carbamates of primary and secondary alcohols,[6] they are not satisfactory for the preparation of carbamates of tertiary alcohols.[7,8] *t*-Butyl carbamate was first obtained by reaction of sodium *t*-butoxide with phosgene and thionyl chloride at −60°, followed by reaction with

concentrated aqueous ammonia; the overall yield was less than 20%.[2] This procedure, however, was found to be unsuitable for the preparation of carbamates of other tertiary alcohols.[8] Carbamates have been prepared by the reaction of phenyl chloroformate (prepared from phenol and phosgene at −60°) with a tertiary alcohol in pyridine, followed by treatment with liquid ammonia.[8] A variation of this procedure involves hydrazinolysis of phenyl *t*-butyl carbonate, prepared as described above, conversion to the azide, and ammonolysis.[3,4] *t*-Butyl carbamate has also been prepared by a four-step procedure that starts with the preparation of *t*-butyl ethyl oxalate from ethoxalyl chloride. This mixed ester was converted to *t*-butyl oxamate, which was dehydrated to *t*-butyl cyanoformate, and this was treated with ammonia.[4]

The carbamates of tertiary acetylenic alcohols have also been made by reaction of these alcohols with sodium cyanate in trifluoroacetic acid.[9] The yields by this procedure are significantly lower than those obtained by the present modification, which is essentially that described by Loev and Kormendy.[5]

4. Merits of the Preparation

This one-step procedure is a convenient and general method for the preparation of carbamates. It is substantially simpler, quicker, and safer than the multistep methods hitherto used for the preparation of carbamates of tertiary alcohols. This procedure is applicable to the preparation of carbamates of primary, secondary, and tertiary alcohols and mercaptans, polyhydric alcohols, acetylenic alcohols, phenols, and oximes. It has also been extended to the preparation of carbamyl derivatives (*i.e.*, ureas) of inert (non-basic) amines.[10]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

benzene-ligroin

ethoxalyl chloride

ammonia (7664-41-7)

Benzene (71-43-2)

sodium hydroxide (1310-73-2)

thionyl chloride (7719-09-7)

phenol (108-95-2)

pyridine (110-86-1)

phosgene (75-44-5)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

benzene-hexane (1077-16-3)

hexane (110-54-3)

sodium cyanate (917-61-3)

t-butyl alcohol (75-65-0)

trifluoroacetic acid (76-05-1)

phenyl chloroformate (1885-14-9)

phenyl t-butyl carbonate (6627-89-0)

sodium t-butoxide (865-48-5)

t-butyl cyanoformate

t-BUTYL CARBAMATE, Carbamic acid, tert-butyl ester (4248-19-5)

t-butyl N-trifluoroacetylcarbamate

t-butyl ethyl oxalate

t-butyl oxamate

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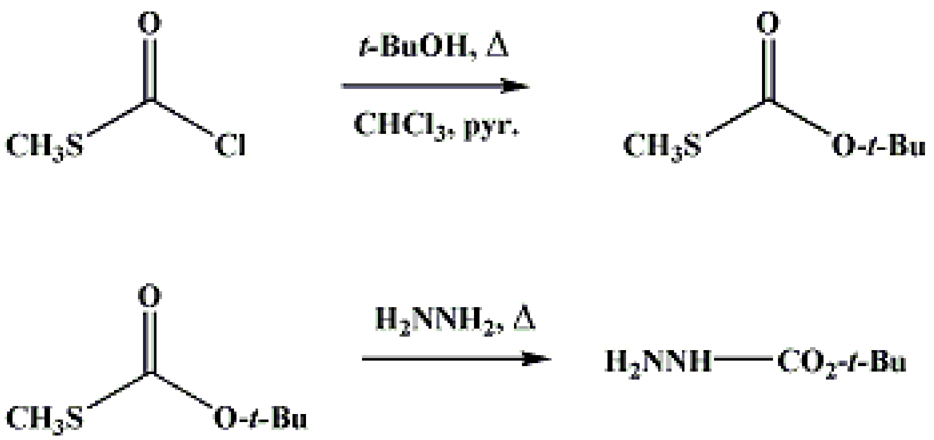
Organic Syntheses, CV 5, 166

t-BUTYL CARBAZATE

[Carbazic acid, *tert*-butyl ester]

[Method I]



Submitted by Louis A. Carpino, David Collins, Siegfried Göwecke, Joe Mayo, S. D. Thatte, and Fred Tibbetts[1].
Checked by Fred G. H. Lee and Virgil Boekelheide.

1. Procedure

Caution! Methyl chlorothiolformate has an obnoxious odor. All operations should be conducted in a well-ventilated hood.

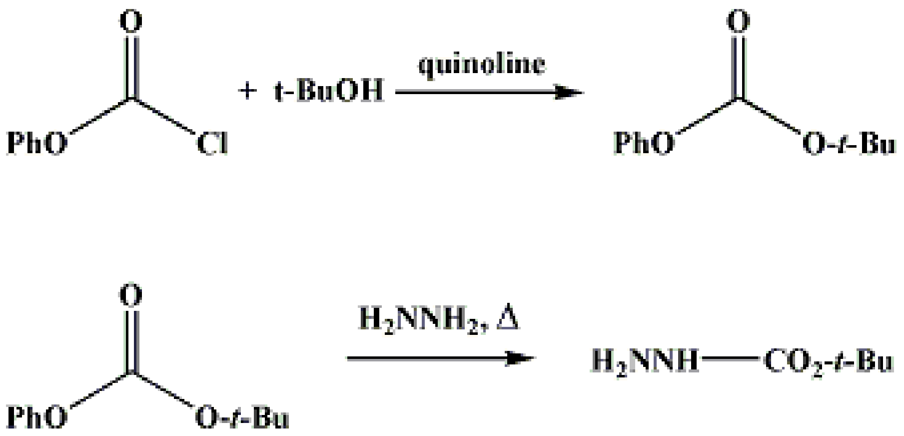
A. *t-Butyl S-methylthiolcarbonate*. In a 5-l. round-bottomed flask, fitted with mechanical stirrer, reflux condenser, and dropping funnel are placed 430 ml. (422 g., 5.33 moles) of pyridine, 508 ml. (395 g., 5.33 moles) of *t*-butyl alcohol, and 1.6 l. of chloroform (Note 1). The solution is stirred while 536 g. (4.85 moles) of methyl chlorothiolformate (Note 2) is added dropwise over a period of 30–40 minutes, and the solution is then stirred and heated at the reflux temperature for 24 hours. The resulting solution is divided into three equal portions of about 1 l., and each portion is washed in a 2-l. separatory funnel with two 500-ml. portions of water, three 275-ml. portions of 5% hydrochloric acid, and finally with 350 ml. of 1*M* sodium bicarbonate solution. The combined chloroform solutions are dried over anhydrous magnesium sulfate for 5 hours, and the solvent is removed by distillation from a water bath at atmospheric pressure followed by the use of a water aspirator. Distillation (Note 3) of the residue from a 1-l. Claisen flask by means of a water or oil bath gives 419–497 g. (58–69%) of a colorless liquid, b.p. 62–65° (24 mm.), n^{25}D 1.4525. This product is sufficiently pure for use in the preparation below but may be purified by distillation through a 30-cm. helices-packed column which gives 375–447 g. (52–62%) of the ester, b.p. 60–63° (24 mm.).

B. *t-Butyl carbazate*. In a 2-l. round-bottomed flask set up in a hood and fitted with an efficient mechanical stirrer and a reflux condenser are placed 500 g. (3.47 moles) of *t*-butyl S-methylthiolcarbonate and 186 g. (3.71 moles) of 64% hydrazine solution (Note 4). The contents of the flask are heated in an oil bath at 105–110° (external temperature) with mechanical stirring for 24 hours under a reflux condenser. The resulting mixture is diluted with 650 ml. of methylene dichloride, and anhydrous magnesium sulfate is added until the aqueous layer becomes nearly solid and nonflowing. The upper layer is decanted and dried over fresh anhydrous magnesium sulfate and the solvent removed by distillation from a water bath, the last portions being removed with the aid of a water aspirator. The residual liquid solidifies on cooling and stirring to give 322–385 g. (72–86%) of a snow-white solid, m.p. 37–40°. This product is pure enough for most purposes but can be purified by distillation, a 1-l. Claisen flask with a water or oil bath at 80° being used. After 1 or 2 drops of fore-run the carbazate is collected at 55–57° (0.4 mm.). The oil solidifies on cooling to give 312–358 g. (70–80%) of snow-white crystalline solid, m.p. 40–42° (Note 5).

2. Notes

1. The pyridine was a pure product, b.p. 113–115°, obtained from the Mallinckrodt Chemical Company. *t*-Butyl alcohol, m.p. 24.5–25.5°, and chloroform (U.S.P. or reagent grade) were obtained from the Matheson Company. All reagents were used as supplied.
2. The methyl chlorothiolformate, b.p. 110–111°, was used as supplied by the Stauffer Chemical Company.
3. This distillation is accompanied by foaming which is very difficult to prevent. The checkers recommend carrying out the distillation in two separate batches to allow greater free space in the distillation flask.
4. Hydrazine hydrate (64% hydrazine) was used as supplied by the Fairmount Chemical Company.
5. Further purification can be effected by recrystallization with 90% recovery from a 50-50 mixture of low- (b.p. 30–60°) and high-boiling (b.p. 60–70°) ligroin. This procedure gives white needles, m.p. 41–42°.

[Method II]



Submitted by Louis A. Carpino, Barbara A. Carpino, Chester A. Giza, Robert W. Murray, Arthur A. Santilli, and Paul H. Terry[1].
Checked by Virgil Boekelheide and S. J. Cross.

1. Procedure

A. *t-Butyl phenyl carbonate*. In a 2-l. round-bottomed flask fitted with thermometer, dropping funnel, and mechanical stirrer are placed 248 g. (3.35 moles) of *t*-butyl alcohol, 430 g. (3.33 moles) of quinoline, and 500 ml. of methylene dichloride (Note 1). The solution is stirred while 520 g. (3.32 moles) of phenyl chloroformate (Note 2) is added dropwise over a period of 4 hours. During the addition the temperature is maintained at 28–31° (Note 3) by cooling the flask, as needed, by a stream of tap water. The solution is allowed to stand overnight and is then treated with 800 ml. of water to dissolve the precipitated quinoline hydrochloride (Note 4). The mixture is shaken well in a separatory funnel; the organic layer is separated and washed with two 200-ml. portions of water and three or four 200-ml. portions of 5% hydrochloric acid. After the extract has dried over anhydrous magnesium sulfate for 5 hours, the solvent is removed by distillation, a water aspirator being used to remove the last portions of the methylene dichloride. Distillation of the residue from a 1-l. Claisen flask by means of an air bath maintained at 125–135° gives 460–495 g. (71–76%) (Note 5) of a colorless oil, b.p. 74–78° (0.5 mm.), n^{24}_D 1.4832. This product is sufficiently pure for use in the preparation below.

B. *t-Butyl carbazate*. In a 1-l. Erlenmeyer flask are placed 388.4 g. (2.0 moles) of phenyl *t*-butyl carbonate and 120.2 g. (2.4 moles) of a 64% hydrazine solution (Note 6). The mixture is swirled by hand and heated on a hot plate. When the internal temperature reaches 75–80°, it then rises rapidly and spontaneously to 104–110°, the two layers forming a clear solution. The solution is allowed to cool overnight. The mixture is then diluted with 500 ml. of ether and transferred to a separatory funnel in which it is shaken vigorously for about 10 minutes with a solution prepared from 160 g. (4.0 moles) of sodium hydroxide and 1.2 l. of water. The resulting two layers are placed in a 2-l. continuous extractor and extracted for 48 hours with ether. The ether solution is dried over magnesium sulfate, and the ether is removed by distillation from a water bath. The last portions of ether are removed with the aid of a water aspirator. The residual oil is then distilled using a Claisen flask with an air bath maintained at 115–125°. After 1 or 2 drops of fore-run the carbazate is collected at 61–65° (1.2 mm.), n^{24}_D 1.4518. The yield is 235–256 g. (89–97%) (Note 7).

2. Notes

1. The *t*-butyl alcohol and methylene dichloride were used directly as received from the Matheson Company. The quinoline was a practical grade material (Eastman Kodak Company) which was redistilled [b.p. 100–102° (25 mm.)].

2. Phenyl chloroformate was prepared by the method of Strain *et al.*,[2] except

that methylene dichloride or chloroform was used in place of benzene as the solvent. The yield was 85–95% [b.p. 74–76° (15 mm.), $n^{24}D$ 1.5125]. The checkers used commercial phenyl chloroformate (Eastman Kodak).

3. The reaction may be run without cooling by adding the acid chloride at a rate to maintain the temperature at 39–43°. On the scale indicated this requires about 5 hours. The yield is substantially the same, although more high-boiling material is formed.

4. Occasionally the quinoline hydrochloride does not separate; this does not affect the yield, however. If it is desired to recover the quinoline, the salt may be filtered at this point, dissolved in water, and converted to the free base.

5. The carbonate decomposes on attempted distillation of large amounts at water aspirator pressure (20–25 mm.).

6. Hydrazine hydrate (64% hydrazine) was used as supplied by the Olin-Mathieson Company.

7. The carbazate is sufficiently pure for most applications and is conveniently handled as a liquid. When the product is cooled in an ice box, it crystallizes as a waxy mass; such samples remain tacky after several recrystallizations from petroleum ether, however. A pure sample may be obtained by extracting an ether solution of the carbazate with dilute sodium hydroxide to remove any phenol, followed by distillation and recrystallization of the product from petroleum ether (b.p. 30–60°). White needles are obtained which melt at 41–42°.

3. Discussion

t-Butyl S-methylthiolcarbonate has been prepared from sodium *t*-butoxide, carbonyl sulfide, and methyl iodide[3] and from methyl chlorothiolformate and *t*-butyl alcohol.[4] *t*-Butyl phenyl carbonate has been prepared from phenyl chloroformate and *t*-butyl alcohol.[5,6]

t-Butyl carbazate has been prepared by reaction of hydrazine with *t*-butyl phenyl carbonate,[5,6] *t*-butyl S-methylthiolcarbonate,[3] *t*-butyl-*p*-nitrophenyl carbonate,[7] and N-*t*-butyloxycarbonylimidazole.[8]

4. Merits of the Preparation

Method I is easily adapted to larger-scale operation and provides a product which crystallizes readily. Method II provides a product which is difficult to crystallize; however, the procedure obviates the use of methyl chlorothiolformate and affords higher yields of product.

t-Butyl carbazate is a useful reagent for preparing 1,1-disubstituted hydrazines.[6] In turn, the 1,1-disubstituted hydrazines can undergo an elimination of nitrogen followed by radical coupling of the two substituent groups. This reaction is promoted either by direct oxidation of the 1,1-disubstituted hydrazine[9,10,11] or by base-catalyzed

elimination of benzenesulfinic acid from the corresponding benzenesulfonhydrazide.[6] For example, 1,1-dibenzyl-2-benzenesulfonhydrazide is converted to bibenzyl in 85% yield.

t-Butyl carbazate is also a key intermediate in the synthesis of *t*-butyl azidoformate,[5,6,12] *t*-butyl hydrazodiformate,[6] *t*-butyl azodiformate,[13] and *t*-butyl N-hydroxycarbamate,[12,14] all of which are valuable synthetic intermediates.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 157
- Org. Syn. Coll. Vol. 5, 160

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether (60-29-7)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium bicarbonate (144-55-8)

phenol (108-95-2)

nitrogen (7727-37-9)

pyridine (110-86-1)

Methyl iodide (74-88-4)

hydrazine hydrate (7803-57-8)

Quinoline (91-22-5)

hydrazine (302-01-2)

methylene dichloride (75-09-2)

magnesium sulfate (7487-88-9)

bibenzyl (103-29-7)

benzenesulfonhydrazide (80-17-1)

t-butyl alcohol (75-65-0)

phenyl chloroformate (1885-14-9)

Methyl chlorothiolformate (18369-83-0)

quinoline hydrochloride (530-64-3)

benzenesulfinic acid (618-41-7)

1,1-dibenzyl-2-benzenesulfonhydrazide

t-BUTYL AZIDOFORMATE (1070-19-5)

phenyl t-butyl carbonate, t-Butyl phenyl carbonate (6627-89-0)

t-butyl N-hydroxycarbamate (36016-38-3)

t-butyl carbazate, Carbazic acid, tert-butyl ester (870-46-2)

t-BUTYL AZODIFORMATE (870-50-8)

t-butyl hydrazodiformate

t-Butyl S-methylthiolcarbonate (29518-83-0)

sodium t-butoxide, carbonyl sulfide

N-t-butyloxycarbonylimidazole (49761-82-2)

t-butyl-p-nitrophenyl carbonate

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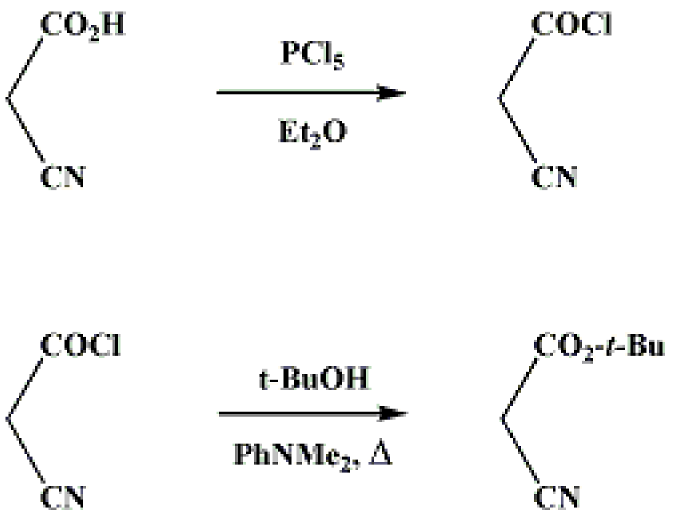
Organic Syntheses, *CV 5*, 171

t-BUTYL CYANOACETATE

[Cyanoacetic acid, *tert*-butyl ester]



Submitted by Robert E. Ireland and Michael Chaykovsky[1].
Checked by Max Tishler and Arthur J. Zambito.

1. Procedure

In a 5-l., three-necked, round-bottomed flask equipped with a rubber- or mercury-sealed mechanical stirrer and a reflux condenser carrying a drying tube are placed 340 g. (4 moles) of cyanoacetic acid (Note 1) and 2 l. of anhydrous ether. To the stirred solution, 834 g. (4 moles) of phosphorus pentachloride is added in portions through the third neck of the flask, which is sealed between additions. The mixture is cooled occasionally with an ice bath to prevent excessive refluxing, and, after the addition is complete, stirring is continued for 0.5 hour or until the phosphorus pentachloride dissolves completely. The reflux condenser is removed and replaced with apparatus for downward distillation (Note 2), and the ether is distilled from a water bath at 50–60° (Note 3), after which most of the phosphorus oxychloride is removed at reduced pressure (20–25 mm. with a bath temperature of 55–65°) (Note 4), the receiver being cooled in an ice-salt bath. The red, oily residue is dissolved in 200 ml. of benzene and the benzene and residual phosphorus oxychloride distilled under reduced pressure. This operation is repeated with 200 ml. of fresh benzene to ensure complete removal of phosphorus oxychloride (Note 5). The residue is then cooled to room temperature (Note 6) and is transferred to a 500-ml. pressure-equalized dropping funnel for immediate use in the following step.

The same 5-l. flask used in the preceding step is used again, without washing; it is fitted with a reflux condenser carrying a drying tube, a sealed mechanical stirrer, and the dropping funnel containing the acid chloride. In the flask are placed 296 g. (4 moles) of dry *t*-butyl alcohol (Note 7) and 484 g. (4 moles) of dimethylaniline in 600

ml. of anhydrous ether (Note 8). The acid chloride is added dropwise to the stirred solution, the mixture being cooled occasionally with an ice bath to prevent excessive refluxing. After the addition is complete, the reaction mixture is refluxed for 2 hours and then stirred gently at room temperature for 15 hours. Two liters of water is added with stirring, and the mixture is filtered with suction through a Büchner funnel fitted with a matting of glass wool (Note 9). The matting is washed with three 250-ml. portions of ether (Note 10). After separation of the combined ethereal layers, the aqueous layer is extracted twice with 250-ml. portions of ether. The combined ether solutions are washed with successive portions of 2*N* sulfuric acid (a total of 1 l.) until free of dimethylaniline, then with two 200-ml. portions of 2*N* sodium carbonate solution, and dried over sodium carbonate. After removal of the ether by distillation, the residue is transferred to an alkali-washed flask and distilled at reduced pressure through a 20-cm. alkali-washed Vigreux column (Note 11). The yield of colorless product is 355–378 g. (63–67%) boiling at 67–68°/1.5mm. (90°/10 mm., 54–56°/0.3 mm), n_D^{20} = 1.4198.

2. Notes

1. Cyanoacetic acid of 98% purity, obtained from Kay-Fries Chemicals, Inc., was used.
2. A Claisen head with a condenser leading into a flask with a suction arm connected to a drying tube is suitable. Ground-glass joints are recommended.
3. A large bucket containing water and placed on a steam bath serves as a suitable water bath. The temperature is easily controlled between the limits mentioned.
4. The ether is removed from the receiving flask before the phosphorus oxychloride is distilled. A drying tube should be placed between the suction arm of the flask and the water pump, which serves as the source of suction. The reaction mixture may be stirred during the distillation of the oxychloride, or the stirrer may be removed and replaced with a capillary ebulliator tube to which is attached a ballon filled with dry nitrogen.
5. The checkers found that the distillation with benzene ensures a more complete removal of phosphorus oxychloride which, if still present, interferes in the subsequent step and a lower yield of product results.
6. The submitters found that on several occasions, when the residue was not cooled before transfer, it began to generate considerable heat while standing in the dropping funnel and resulted in the total carbonization of the acid chloride.
7. The submitters dried the *t*-butyl alcohol by refluxing it over calcium hydride overnight and distillation in a moisture-free apparatus. The checkers found that stirring the *t*-butyl alcohol at 60–70° over calcium hydride for several hours and then distilling the alcohol, using an air condenser, is a satisfactory procedure. When the *t*-butyl alcohol is refluxed, the alcohol vapors condense and solidify (m.p. 24–25°) in the reflux condenser and cause clogging.
8. These reagents should be weighed out beforehand in order to prevent delay in commencing with this step.
9. The filtration removes some tarry resinous material which would otherwise

interfere in the separation of the layers. The checkers found that unless the filtrate is recycled through the same matting several times, to remove practically all the tarry residue, the separation of layers and the subsequent extractions prove troublesome owing mainly to emulsion formation.
10. The checkers found that a considerable amount of product is withheld by the residue on the glass-wool matting. The product is extracted by placing the matting in a beaker, stirring with ether, and filtering. This procedure is repeated twice, and the ether extracts are combined with the original filtrate.
11. The distilling flask and Vigreux column to be used should be washed with 25% aqueous sodium hydroxide solution, rinsed three times with water, and then dried. Alternatively, about 1 g. of anhydrous potassium carbonate may be added to the residue before distillation.

3. Discussion

t-Butyl cyanoacetate has been prepared from *t*-butyl bromoacetate and potassium cyanide in methanol[2] and from *t*-butyl chloroacetate and potassium cyanide in methyl Cellosolve.[3] The present method is an adaptation of that of Beech and Pigott[4] and is similar to the *Organic Syntheses* preparation of *t*-butyl acetate.[5]

4. Merits of Preparation

The present preparation employs a method of considerable scope which gives much better yields and is considerably less laborious than other methods for the preparation of *t*-butyl cyanoacetate. The compound is of specific interest since, for example, it may be used in any reaction where ethyl cyanoacetate is used (condensation reactions, etc.), but it has the added advantage that the carbo-*t*-butoxy group, which may serve in conjunction with the α-cyano group to activate the α-hydrogens (for cyanoethylations, etc.), may be later removed simply by pyrolysis of the compound.[6]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

Benzene (71-43-2)

methanol (67-56-1)

ether (60-29-7)

sodium hydroxide (1310-73-2)

phosphorus pentachloride (10026-13-8)

sodium carbonate (497-19-8)

nitrogen (7727-37-9)

potassium cyanide (151-50-8)

Phosphorus Oxychloride (21295-50-1)

Ethyl cyanoacetate (105-56-6)

cyanoacetic acid (372-09-8)

dimethylaniline (121-69-7)

methyl Cellosolve (109-86-4)

t-butyl alcohol (75-65-0)

calcium hydride (7789-78-8)

t-butyl acetate (540-88-5)

t-butyl chloroacetate (107-59-5)

t-butyl bromoacetate (5292-43-3)

t-BUTYL CYANOACETATE, Cyanoacetic acid, tert-butyl ester (1116-98-9)

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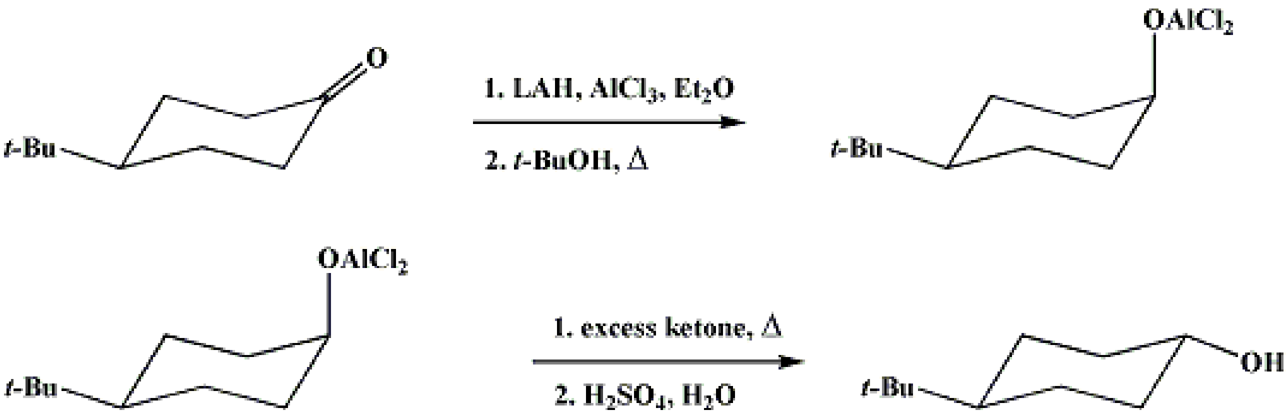
Organic Syntheses, CV 5, 175

trans-4-*t*-BUTYLCYCLOHEXANOL

[Cyclohexanol, 4-*t*-butyl, *trans*-]



Submitted by E. L. Eliel, R. J. L. Martin, and D. Nasipuri[1].
Checked by E. J. Corey and Barbara Kaski.

1. Procedure

In a 3-l. three-necked flask, equipped with a mercury-sealed Hershberg stirrer, a dropping funnel, and a reflux condenser protected with a calcium chloride tube, is placed 67 g. (0.5 mole) of powdered anhydrous aluminum chloride. The flask is cooled in an ice bath, 500 ml. of dry ether is slowly added from the dropping funnel, and the mixture is stirred for a few minutes. Meanwhile 5.5 g. of powdered lithium aluminum hydride (Note 1) is placed in a 1-l. flask fitted with a condenser, and 140 ml. of dry ether is added slowly from the top of the condenser with caution while the flask is kept cooled in ice. The mixture is gently refluxed for 30 minutes to effect, as far as possible, solution of the hydride. It is then cooled, and the resulting slurry (which consists of a suspension of lithium aluminum hydride in its solution) is transferred to the dropping funnel of the previous setup and is added to the ethereal solution of aluminum chloride with stirring within 10 minutes. After the addition is complete, the reaction mixture is stirred for an additional 30 minutes without cooling to complete the formation of the "mixed hydride."

A solution of 77.2 g. (0.5 mole) of 4-*t*-butylcyclohexanone (Note 2) in 500 ml. of dry ether is then placed in the dropping funnel and slowly added to the "mixed hydride" solution without much cooling so that gentle refluxing is maintained (Note 3) After addition of the ketone over a period of 45–60 minutes the reaction mixture is refluxed for 2 hours more to complete the reduction. The excess hydride is destroyed by the addition of 10 ml. of dry *t*-butanol, and the mixture is refluxed for an additional 30 minutes. 4-*t*-Butylcyclohexanone (3 g.) in 20 ml. of dry ether is then added to the reaction mixture, which is refluxed for 4 hours more and allowed to stand overnight (Note 4), (Note 5). The reaction mixture is cooled in an ice bath and decomposed by successive additions of 100 ml. of water and 250 ml. of 10% aqueous sulfuric acid. The ethereal layer is separated and the aqueous layer extracted once with 150 ml. of ether. The combined ether extracts are washed once with water and dried over anhydrous magnesium sulfate. The extract is filtered from magnesium sulfate and the ether removed by distillation on a steam bath. The residue, weighing 85–87 g., solidifies in the flask and on gas chromatographic analysis (see (Note 5)) is found to contain 96% *trans* alcohol, 0.8% *cis* alcohol, and 3.2% ketone.

The crude white product is dissolved in 150 ml. of hot petroleum ether (b.p. 60–70°). On cooling, it

forms a solid cake which is transferred to a Buchner funnel and rinsed with small portions of cooled petroleum ether. The yield of product, m.p. 75–78° (Note 6), is 57–61 g. (73–78%). It has an approximate composition of 99.3% *trans* alcohol, 0.3% *cis* alcohol, and 0.4% ketone. A further crop of 12 g. is obtained by concentration of the mother liquor. It contains less than 1% of the *cis* alcohol and the ketone and is sufficiently pure for most preparative purposes (Note 7).

2. Notes

1. The lithium aluminum hydride was obtained from Metal Hydrides Incorporated and was more than 95% pure. For calculation of the quantity of hydride required it was assumed that the purity was 95%.
2. 4-*t*-Butylcyclohexanone was supplied by the Dow Chemical Company.
3. The continuance of gentle refluxing as the last portion of the ketone is added assures that there is an excess of "mixed hydride" present.
4. It is not necessary to allow the reaction mixture to stand overnight, and it may be decomposed at this stage without any loss in purity.
5. At this stage the attainment of equilibrium can be checked by removing a 5-ml. aliquot from the reaction product and working it up in the same way as described in the preparation. The product is then analyzed by gas-liquid chromatography using a 20% Carbowax 20M on firebrick column at 150°. The features to note in the chromatogram are almost complete absence (less than 1%) of the *cis* isomer (second peak, disregarding initial solvent and *t*-butanol peaks) and the presence of some 4-*t*-butylcyclohexanone (first peak). The *trans* isomer constitutes the third peak with longest retention time.
6. The melting point of a highly purified sample[2] of *trans* alcohol is 82.5–83°.
7. Since the alcohol has a relatively high solubility in petroleum ether, the yield from the crystallization depends on the volume of solvent used. However, by concentrating the mother liquor the overall yield from the first and second crops of crystals varies from 74% to 94%.

3. Discussion

4-*t*-Butylcyclohexanol has been prepared from *p*-*t*-butylphenol by reduction under a variety of conditions.[3,4] Winstein and Holness[5] prepared the pure *trans* alcohol from the commercial alcohol by repeated crystallization of the acid phthalate followed by saponification of the pure *trans* ester. Eliel and Ro[6] obtained 4-*t*-butylcyclohexanol containing 91% of the *trans* isomer by lithium aluminum hydride reduction of the ketone. Hückel and Kurz[7] reduced *p*-*t*-butylphenol with platinum oxide in acetic acid and then separated the isomers by column chromatography.

4. Merits of the Preparation

The procedure employs a readily available starting material and produces the pure *trans* isomer in high yield. The method described is an improvement on that used by Eliel and Rerick[2] in that it is not necessary to use a clear solution of lithium aluminum hydride in ether for the preparation of the "mixed hydride." It is not necessary to know the precise amount of lithium aluminum hydride used so long as a slight excess is present. The excess hydride is destroyed by adding *t*-butanol; the excess *t*-butanol has no effect on the subsequent equilibration and purification. The equilibration of the 4-*t*-butylcyclohexanol is effected by adding a small amount of 4-*t*-butylcyclohexanone.

The method is useful in the preparation of other equatorial alcohols.[2,8]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

ether (60-29-7)

platinum oxide

aluminum chloride (3495-54-3)

magnesium sulfate (7487-88-9)

lithium aluminum hydride (16853-85-3)

t-butanol (75-65-0)

4-t-butylcyclohexanone (98-53-3)

trans-4-t-BUTYLCYCLOHEXANOL, Cyclohexanol, 4-t-butyl, trans- (21862-63-5)

4-t-Butylcyclohexanol (98-52-2)

p-t-butylphenol (98-54-4)

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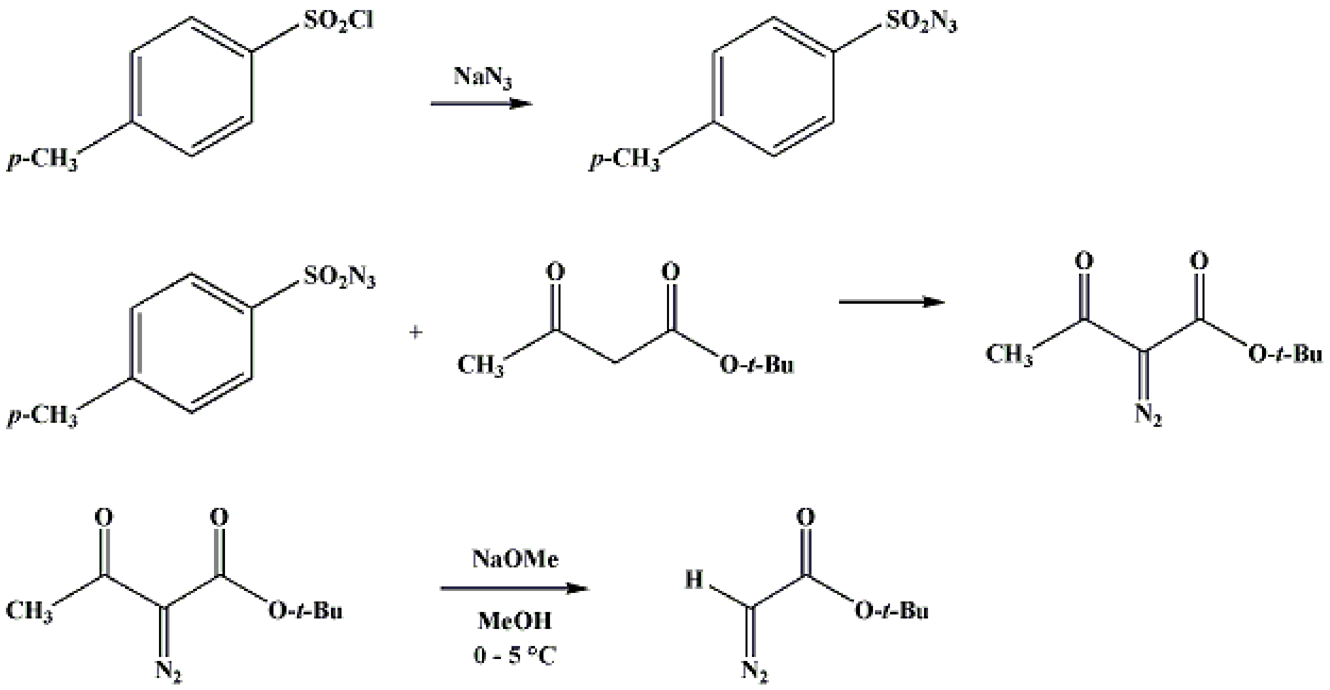
Organic Syntheses, CV 5, 179

t-BUTYL DIAZOACETATE

[Acetic acid, diazo-, *tert*-butyl ester]



Submitted by Manfred Regitz, Jürgen Hocker, and Annemarie Liedhegener[1].
Checked by C. John Blankley and Herbert O. House.

1. Procedure

Caution! Diazoacetic esters are toxic and potentially explosive and must be handled with caution. This preparation should be carried out in a hood, and the distillation of t-butyl diazoacetate should be conducted behind a safety shield.

A. *p-Toluenesulfonyl azide*.[2,3] A solution of 71.5 g. (1.10 moles) of sodium azide (Note 1) in 200 ml. of water is placed in a 2-l. Erlenmeyer flask and diluted with 400 ml. of 90% aqueous ethanol (Note 2). To this solution is added with stirring a warm (45°) solution of 190.5 g. (1.00 mole) of *p*-toluenesulfonyl chloride (Note 3) in 1 l. of 99% ethanol (Note 2). During this addition, sodium chloride separates, and the reaction mixture has been stirred at room temperature for 2.5 hours, most of the solvent is removed at 35° (15 mm.) with a rotary evaporator (Note 4). The residue is mixed with 1.2 l. of water in a separatory funnel, and the oily *p*-toluenesulfonyl azide is separated. This oil is washed with two 100-ml. portions of water and dried over anhydrous sodium sulfate. Filtration with suction gives 160–170 g. (81–86%, based on *p*-toluenesulfonyl chloride) of pure, colorless *p*-toluenesulfonyl azide which completely crystallizes on standing at 5°.

B. *t-Butyl α-diazoacetoacetate*. In a 2-l., wide-mouthed, Erlenmeyer flask are placed 118.5 g. (0.75 mole) of *t*-butyl acetoacetate (Note 5), 1 l. of anhydrous acetonitrile, and 75.8 g. (0.75 mole) of previously distilled triethylamine (b. p. 88.5–90.5°). The temperature of the mixture is adjusted to 20°, and 148 g. (0.75 mole) of *p*-toluenesulfonyl azide is added dropwise with vigorous stirring over 10–15 minutes. The addition causes the reaction mixture to warm to 38–40° and assume a yellow color. After the mixture has been stirred at room temperature for 2.5 hours, the solvent is evaporated at 35° (12 mm.). The partially crystalline residue is triturated with 1 l. of ether, and the mixture, including the insoluble residue, is placed in a 2-l. separatory funnel. The mixture is washed successively with a solution of 45 g. of potassium hydroxide in 500 ml. of water, a solution of 7.5 g. of potassium hydroxide in 250 ml. of water, and 250 ml. of water (Note 6). The yellow-orange ethereal phase is dried over anhydrous sodium sulfate, and the solvent is evaporated at 35° (15 mm.) until the residue has attained a constant weight. The yellow-orange diazo ester weighs 130–135 g. (94–98%) (Note 7).

C. *t-Butyl diazoacetate*. Into a 1-l. three-necked flask fitted with a stirrer, a dropping funnel, and a thermometer is placed a solution of 92.6 (0.50 mole) of *t*-butyl α-diazoacetoacetate in 150 ml. of methanol. After this solution has been cooled to 2–3° in an ice bath, a solution of sodium methoxide, prepared from 11.5 g. (0.50 g. atom) of sodium and 150 ml. of methanol, is added dropwise with stirring at such a rate that the reaction mixture remains within the temperature range 0–5° (about 30 minutes is required for the addition). After the addition is completed, the mixture is stirred in the ice bath for an additional 30 minutes. The red reaction solution is poured into 1 l. of ice water, and the resulting mixture is extracted with 500 ml. of ether. The aqueous phase is saturated with sodium chloride and extracted with two 500-ml. portions of ether (Note 8). The combined ethereal extracts are washed with 500 ml. of water and dried over anhydrous sodium sulfate. After the mixture has been filtered and the residue has been washed with ether, the bulk of the solvent is removed from the combined ethereal filtrates at 30° and water aspirator pressure with a rotary evaporator (Note 9). The remaining ether is removed by distillation under slightly reduced pressure while the stillpot is heated with a water bath at 50°. The residual red oil is distilled. (*Caution! See above.*) (Note 10). After a small forerun the diazo ester distills during which time the temperature of the water bath is raised from 60° to 75°. The yield is 48–50 g. (68–70%) of yellow-orange liquid, b.p. 51–53° (12 mm.), n^{20}D 1.4551, R_f = 0.56 (chloroform) (Note 11).

2. Notes

1. The submitters used sodium azide obtained from Dr. F. Raschig, GmbH, 67 Ludwigshafen, Rhein, Germany. The checkers used material from Eastman Organic Chemicals.
2. The checkers found 95% ethanol denatured with methanol to be a satisfactory substitute.
3. The submitters used *p*-toluenesulfonyl chloride obtained from Badische Anilin- und Soda-Fabrik, 67 Ludwigshafen, Rhein, Germany. Very impure *p*-toluenesulfonyl chloride can be purified by recrystallization from ether. The checkers used material from Matheson, Coleman and Bell without further purification.
4. In order to prevent foaming, the concentration is begun with the water bath at *ca.* 10°, and the bath is warmed slowly to 35°.
5. *t*-Butyl acetoacetate may be prepared from *t*-butyl alcohol and diketene.[4] The checkers obtained this material from Eastman Chemical Products, Inc.
6. Acidification of the aqueous potassium hydroxide phase with 6*N* hydrochloric acid gives *p*-toluenesulfonamide. After being dried at 85° (50 mm.) the sample weighs 110–120 g. (86–94%) and melts at 132–134°.
7. If desired, the α-diazo β-keto ester can be purified by a low-temperature crystallization. The diazo ester (10 g.) is cooled to −70° to −75° in a dry ice-acetone bath, and crystallization is initiated by rubbing. *(Caution! The rubbing should not be continued after crystallization has been initiated.)* This material is treated with 5 ml. of anhydrous ether which has been previously cooled, and the mixture is filtered with suction. The residue from the filtration is placed in a flask, and the residual ether is removed by evaporation at 35° (15 mm.) to give 5–6 g. of the yellow diazo ester.[5]
8. If the ethereal phase contains a small amount of insoluble material, the mixture should be filtered to avoid difficulty in separating the phases.
9. The distillate is light yellow and contains some *t*-butyl diazoacetate.
10. This distillation has been conducted with the usual precaution (safety glasses, safety shield) with no explosions up to the present time.
11. The thin-layer chromatogram was obtained on "DC-Fertiplatte Merck Kieselgel F_{254}" purchased from E. Merck A. G., 61 Darmstadt, Germany, Employing an Eastman Chromatoplate K301R1 (silica without indicator) with chloroform as eluent, the checkers found an R_f value of 0.72.

3. Discussion

t-Butyl diazoacetate has been prepared by the present method, by alkaline decomposition of *t*-butyl N-nitroso-N-acetylglycinate,[6] and by diazotization of *t*-butyl glycinate.[7]

4. Merits of the Preparation

The transformation of an active CH compound into the corresponding diazo derivative with *p*-toluenesulfonyl azide has been designated a "diazo transfer reaction"[8] and possesses a variety of preparative uses. The method has been

useful for the syntheses of diazo derivatives of cyclopentadiene,[3,9] 1,3-dicarbonyl compounds,[5,10,11] 1,3-disulfonyl compounds,[12] 1,3-ketosulfonyl compounds,[13,14,15] 1,3-ketophosphono compounds,[16] 1,3-ketophosphinyl compounds,[17] ketones,[18,19,20,21] carboxylic acid esters[18,21] and β-keto imines.[22] Further reaction of these diazo intermediates can lead to zao compounds,[11,13] 1,2,3-triazoles,[22,23] 1,2,3-thiadiazoles,[24] and pyrazolinones.[25] This and related diazo transfer reactions have been reviewed.[26]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 258
- Org. Syn. Coll. Vol. 6, 389
- Org. Syn. Coll. Vol. 6, 414
- Org. Syn. Coll. Vol. 7, 438
- Org. Syn. Coll. Vol. 9, 400
- Org. Syn. Coll. Vol. 9, 422

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

methanol (67-56-1)

ether (60-29-7)

acetonitrile (75-05-8)

chloroform (67-66-3)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

diketene (674-82-8)

sodium methoxide (124-41-4)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

sodium azide (26628-22-8)

triethylamine (121-44-8)

CYCLOPENTADIENE (542-92-7)

t-butyl alcohol (75-65-0)

t-butyl diazoacetate, Acetic acid, diazo-, tert-butyl ester (35059-50-8)

p-Toluenesulfonyl chloride (98-59-9)

p-toluenesulfonyl azide (941-55-9)

p-toluenesulfonamide (70-55-3)

t-BUTYL ACETOACETATE (1694-31-1)

t-butyl α-diazoacetoacetate (13298-76-5)

t-butyl glycinate (6456-74-2)

t-butyl N-nitroso-N-acetylglycinate

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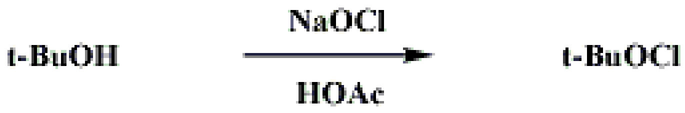
Organic Syntheses, *CV 5*, *184*

t-BUTYL HYPOCHLORITE



Submitted by M. J. Mintz[1] and C. Walling[2].
Checked by Lois A. Ablin and Henry E. Baumgrten.

1. Procedure

Caution! This preparation should be carried out in a hood to avoid exposure to the hypochlorite produced. To avoid vigorous decomposition the product should be handled only in dim light and should not be heated above its boiling point or be exposed to rubber.

In a 1-l. Erlenmeyer or round-bottomed flask equipped with a mechanical stirrer is placed 500 ml. of a commercial household bleach solution (Note 1). The flask is placed in a pail of ice and rapidly stirred until the temperature drops below 10°. At this point the lights in the vicinity of the apparatus should be turned off (Note 2). A solution of *t*-butyl alcohol (37 ml., 0.39 mole) and glacial acetic acid (24.5 ml., 0.43 mole) (Note 3) is added in a single portion to the rapidly stirred bleach solution, and stirring is continued for about 3 minutes (Note 4).

The entire reaction mixture is poured into a 1-l. separatory funnel. The lower aqueous layer (Note 5) is discarded, and the oily yellow organic layer is washed first with a 50-ml. portion of 10% aqueous sodium carbonate and then with 50 ml. of water. The product is dried over 1 g. of calcium chloride and filtered. The yield of *t*-butyl hypochlorite, 99–100% pure, is 29.6–34 g. (70–80%) (Note 1), (Note 6). The product can be stored conveniently in a freezer or refrigerator over calcium chloride in amber glass bottles (Note 7).

2. Notes

1. Both the submitters and checkers used the commercial household bleach solution, Clorox (Proctor and Gamble Co.). This solution is stated to be 5.25% sodium hypochlorite (NaOCl). The submitters found it to be 0.75–0.80*M* by iodometric titration for total oxidant (assumed to be NaOCl). Thus 500 ml. of this solution would contain 0.375–0.400 mole of NaOCl. The checkers found that as little as 440 ml. of fresh Purex (Purex Corp., Ltd., stated to be 6% sodium hypochlorite) gave the stated yield. However, samples from different bottles from one case of "Purex" gave consistently lower yields, 57–70%. Probably the lower yield was due to a lowering of the hypochlorite concentration on standing. The submitters and checkers recommend either discarding bleach solution over

6 months old or checking the titer before use. Presumably other household bleaches will give comparable results with possible small variations in yield.
2. Whereas the inorganic hypochlorite is rather stable to photodecomposition, *t*-butyl hypochlorite is much more readily decomposed. It is not necessary to work in a totally darkened room, but the incidence of strong light should be avoided—both for reasons of safety and to ensure that hypochlorite of high purity will be isolated.
3. The *t*-butyl alcohol was a commercial product obtained from Matheson Coleman and Bell, and the glacial acetic acid a commercial product obtained from Union Carbide.
4. The submitters have carried out runs using up to 4 l. of the commercial bleach solution (3 moles)—as the largest scale conveniently run in the laboratory—and found no change in the reaction behaviour.
5. The checkers observed that the aqueous layer was colorless when Clorox was used and was yellow when Purex was used.
6. The purity of the hypochlorite may be determined by iodometric titration. This titration is run conveniently by weighing out a small portion of the hypochlorite (<0.5 g.) in a 4-ml. vial and then dropping the vial and its contents into an iodine flask containing 20 ml. of glacial acetic acid, 10 l. of water, and 3 g. of potassium iodide. The titration is then conducted in the usual fashion.
7. The product isolated by this procedure is sufficiently pure for almost any purpose. It was found that distillation did not change the product purity and often led to product of lower purity.

3. Discussion

t-Butyl hypochlorite has been prepared by treatment of an alkaline solution of *t*-butyl alcohol with chlorine,[3,4,5,6,7] and a recent warning[8,9] cautions against allowing the temperature to rise above 20° during this reaction. *t*-Butyl hypochlorite has been prepared in solution by shaking a solution of the alcohol in carbon tetrachloride,[10] fluorotrichloromethane (Freon 11), and other solvents[11] with aqueous hypochlorous acid. It has also been prepared by the action of chlorine on an aqueous *t*-butyl alcohol suspension of calcium carbonate,[12] and by the action of chlorine monoxide on a carbon tetrachloride solution of the alcohol.[13]

The procedure described here has previously been reported by Mintz[14] and was adapted from work by Geneste and Kergomard,[15] Kergomard,[16] Sumner,[17] and Clark.[18] It eliminates the dangers in working with a compressed gas (chlorine) and the danger from explosion due to poor temperature control during the addition of chlorine.[3,8,9] The availability and low cost of the commercial bleach solution (NaOCl), the simplicity of the equipment needed, the short time involved, and the high purity of the *t*-butyl hypochlorite produced confer additional merit on this preparation. The submitters have also prepared benzyldimethylcarbinyl hypochlorite, cumyl

hypochlorite, and isopropyl hypochlorite by this procedure. The checkers have used essentially the same procedure (with twice as much sodium hypochlorite solution and acetic acid) to prepare N,N-dichloro-*t*-butylamine.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 208
- Org. Syn. Coll. Vol. 5, 909
- Org. Syn. Coll. Vol. 6, 581
- Org. Syn. Coll. Vol. 6, 601

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

calcium chloride (10043-52-4)

acetic acid (64-19-7)

sodium carbonate (497-19-8)

carbon tetrachloride (56-23-5)

potassium iodide (7681-11-0)

calcium carbonate (471-34-1)

chlorine (7782-50-5)

hypochlorous acid (7790-92-3)

sodium hypochlorite, NaOCl (7681-52-9)

fluorotrichloromethane (75-69-4)

t-butyl alcohol (75-65-0)

chlorine monoxide

t-BUTYL HYPOCHLORITE (507-40-4)

N,N-dichloro-t-butylamine

benzyldimethylcarbinyl hypochlorite

cumyl hypochlorite

isopropyl hypochlorite

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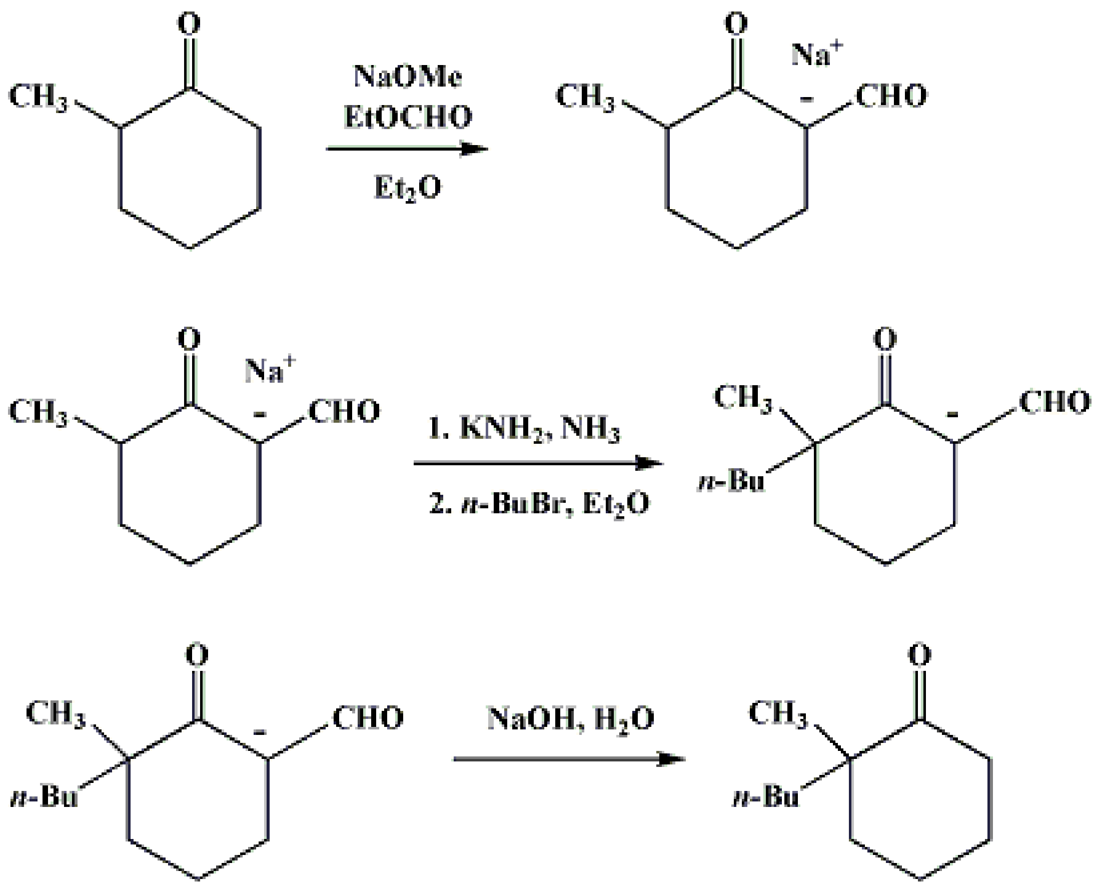
Organic Syntheses, CV 5, 187

2-*n*-BUTYL-2-METHYLCYCLOHEXANONE

[Cyclohexanone, 2-butyl-2-methyl-]



Submitted by S. Boatman, T. M. Harris, and C. R. Hauser[1].
Checked by William G. Dauben, Michael H. Mcgann, and Noel Vietemeyer.

1. Procedure

Caution! This preparation should be carried out in a hood to avoid exposure to ammonia.

In a 3-l. three-necked flask fitted with a calcium chloride drying tube, a nitrogen-inlet tube, and a sealed mechanical stirrer are placed 54.0 g. (1.00 mole) of commercial, anhydrous sodium methoxide (Note 1) and 2 l. of anhydrous ether. The flask is purged with dry nitrogen and cooled in an ice bath. The inlet tube is replaced by an addition funnel containing a solution of 123 g. (1.10 moles) of 2-methylcyclohexanone (Note 2) and 81.4 g. (1.10 moles) of ethyl formate (Note 3). The solution is added rapidly, dropwise, and at the end of the addition the funnel is replaced by the nitrogen-inlet tube. After 15 minutes the ice bath is removed, and the mixture is stirred for 12 hours at room temperature. The thick suspension is filtered by suction, and the filter cake is

washed with anhydrous ether, care being taken to protect the product from atmospheric moisture (Note 4). The solid salt is dried in a vacuum oven at *ca.* 70°, powdered (Note 5), and stored in a tightly capped bottle. Sodio-2-formyl-6-methylcyclohexanone, a cream-colored powder, is obtained in 80–85% (130–138 g.) yield (Note 6).

In a 1-l. three-necked flask equipped with a dry ice-acetone condenser and a sealed mechanical stirrer is placed 700 ml. of commercial, anhydrous, liquid ammonia. To the stirred ammonia is added a small piece of potassium metal. *(Caution! Care should be exercised in handling potassium metal, since it is extremely reactive and it ignites on contact with water, atmospheric moisture, or alcohol. It should be manipulated under toluene or xylene, and blotted with filter paper before addition.)* After the appearance of a blue color a few crystals of ferric nitrate hydrate (*ca.* 0.1 g.) are added, followed by small pieces of freshly cut potassium metal until 7.0 g. (0.18 g. atom) has been added. After all the potassium has been converted to the amide (Note 7), 24.9 g. (0.154 mole) of sodio-2-formyl-6-methylcyclohexanone is added carefully through a powder funnel (Note 8). After 1 hour a solution of 28.2 g. (0.21 mole) of *n*-butyl bromide (Note 9) in 50 ml. of anhydrous ether is added dropwise from an addition funnel. The mixture is stirred for 3 hours, and then the dry ice-acetone condenser is replaced by a water condenser. A steam bath is placed under the flask, and the ammonia is evaporated (*Caution!*) as 400 ml. of anhydrous ether is added. When the ammonia has been removed and the ether has refluxed for 5 minutes, 100 g. of ice is added, followed by 300 ml. of water. When the solid has dissolved, the layers are separated, and the ethereal layer is extracted twice with cold water. The combined aqueous extracts are placed in a 1-l. round-bottomed flask, and 6.4 g. of sodium hydroxide is added. The flask is warmed briefly to remove dissolved ether from the solution. The flask is equipped with an efficient condenser, and the mixture is refluxed until an enol test is no longer obtained (6–8 hours) (Note 10) and (Note 11). The mixture is cooled and extracted with three 200-ml. portions of ether. The combined ethereal extracts are washed with dilute hydrochloric acid and dried over anhydrous magnesium sulfate. The ether is evaporated, and the residue is distilled under reduced pressure to give 14–19 g. (54–74%) of 2-*n*-butyl-2-methylcyclohexanone, b.p. 116–118° (20 mm.) (Note 12).

2. Notes

1. Sodium methoxide was obtained from Matheson, Coleman and Bell. The best results were obtained with material from freshly opened bottles.
2. Eastman Organic Chemicals "Eastman grade" 2-methylcyclohexanone was distilled; b.p. 56° (20 mm.).
3. Eastman Organic Chemicals practical grade ethyl formate was shaken for 30 minutes with anhydrous sodium carbonate and for 30 minutes with anhydrous magnesium sulfate, and distilled; b.p. 54°.
4. A rubber dam was fastened tightly over the top of the Buchner funnel by

means of rubber bands. It was pulled down onto the surface of the filter cake by the vacuum.

5. The solid should be powdered to allow complete formation of the dianion in the following reaction. This is most readily accomplished if the solid is ground before it is completely dry (*i.e.*, when it appears to be dry but is still cool). The fine powder is then replaced in the oven to complete the drying.

6. The checkers, working at one-quarter scale, obtained a yield of 86–88%.

7. Conversion is indicated by discharge of the deep blue color. This generally requires about 20 minutes. When conversion is completed, the stirrer should be speeded up or the contents of the flask swirled so that potassium splattered on the upper part of the flask is converted to amide; this should be done until all traces of blue color are gone.

8. The escaping ammonia will blow away some of the fine powder unless this is done carefully.

9. Eastman Organic Chemicals "Eastman grade" *n*-butyl bromide was distilled; b.p. 101–102°.

10. The enol test is performed with about 0.5 ml. of solution, which is neutralized with dilute hydrochloric acid and treated with 3–5 drops of 10% ethanolic ferric chloride. A reddish brown color denotes the presence of unhydrolyzed formyl ketone.

11. An alternative procedure is steam distillation of the basic, aqueous solution until no further organic material distills. This may be done either instead of, or after, the refluxing of the aqueous solution. The steam distillate is extracted with ether, and the ether is removed by distillation.

12. A higher-boiling fraction consisting of 2-formyl-6-*n*-butyl-6-methylcyclohexanone, b.p. 201–203° (20 mm.), is obtained if hydrolysis is not complete.

3. Discussion

This procedure is an adaptation of one described by Boatman, Harris, and Hauser.[2]

4. Merits of the Preparation

The present method affords 2-*n*-butyl-2-methylcyclohexanone uncontaminated by the isomeric 2-*n*-butyl-6-methylcyclohexanone.

2,2-Dimethylcyclohexanone and 2-benzyl-2-methylcyclohexanone have been prepared similarly in yields of 60% and 55%, respectively.[2] The procedure has been extended to the synthesis of 9-methyl-, 9-*n*-butyl-, and 9-benzyl-1-decalone from the dianion of 2-formyl-1-decalone in yields of 55%, 48%, and 58% respectively.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 611

References and Notes

1. Department of Chemistry, Duke University, Durham, North Carolina 27706.
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

9-methyl-, 9-n-butyl-, and 9-benzyl-1-decalone

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium carbonate (497-19-8)

n-butyl bromide (109-65-9)

nitrogen (7727-37-9)

sodium methoxide (124-41-4)

toluene (108-88-3)

ferric chloride (7705-08-0)

potassium (7440-09-7)

xylene (106-42-3)

ethyl formate (109-94-4)

magnesium sulfate (7487-88-9)

2-methylcyclohexanone (583-60-8)

ferric nitrate hydrate

Sodio-2-formyl-6-methylcyclohexanone

2,2-Dimethylcyclohexanone (1193-47-1)

2-Benzyl-2-methylcyclohexanone (1206-21-9)

2-formyl-1-decalone

2-n-BUTYL-2-METHYLCYCLOHEXANONE, Cyclohexanone, 2-butyl-2-methyl- (1197-78-0)

2-formyl-6-n-butyl-6-methylcyclohexanone

2-n-butyl-6-methylcyclohexanone

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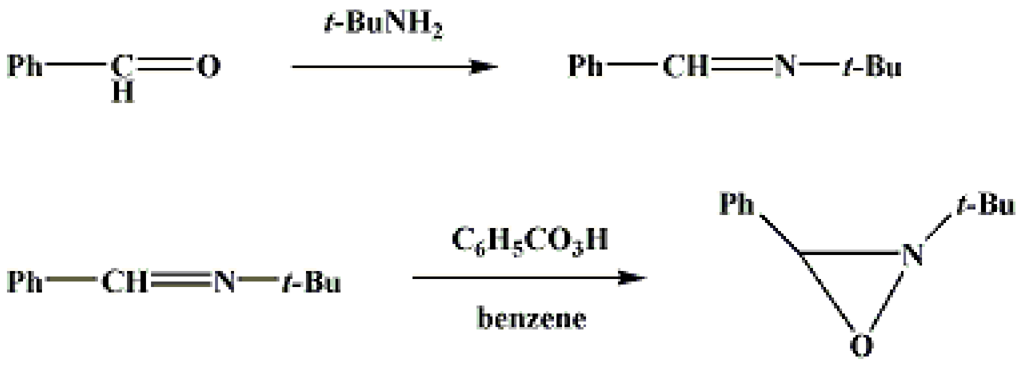
2-*t*-BUTYL-3-PHENYLOXAZIRANE

[Oxaziridine, 2-*t*-butyl-3-phenyl-]



Submitted by W. D. Emmons and A. S. Pagano[1].
Checked by G. Ryan and Ronald Breslow.

1. Procedure

Caution! The preparation and distillation of the oxazirane, like that of any active oxygen compound, should be carried out behind a safety screen.

A. *N-t-butylbenzaldimine*. A 1-l. three-necked flask equipped with stirrer, thermometer, and condenser for downward distillation is charged with 109.5 g. (1.5 moles) of *t*-butylamine (Note 1). Benzaldehyde (106 g., 1.0 mole) is then added in four increments to the stirred solution over a 20-minute period. A mild exotherm is noted which raises the temperature to 40–50°. Benzene (150 ml.) is then added and the solution is heated until distillation commences. Solvent (a mixture of amine, water, and benzene) is removed by distillation until a pot temperature of 110° is reached. The product mixture is then cooled to room temperature, dried over magnesium sulfate, and stripped free of solvent at aspirator pressure. Distillation of the yellow liquid so obtained yields 120–151 g. (78–94%) of colorless N-*t*-butylbenzaldimine, b.p. 59–63° (1 mm.), $n^{26}D$ 1.5174, $n^{20}D$ (Note 2).

B. *2-t-Butyl-3-phenyloxazirane*. A 1-l. three-necked flask equipped with an addition funnel, stirrer, and condenser is charged with 68.0 g. (0.422 mole) of N-*t*-buylbenzaldimine (Note 3) and 50 ml. of benzene. The stirred solution is cooled in an ice bath and a solution of 61 g. (0.445 mole) of perbenzoic acid in 315 ml. of benzene is added dropwise over a 40-minute period. After one additional hour the stirrer is stopped, and the reaction mixture is allowed to stand overnight with the concurrent melting of the ice bath. The light blue benzene solution is then filtered to remove the precipitated benzoic acid and is washed sequentially with three 100-ml. portions of sodium carbonate, 100 ml. of 5% hydrochloric acid, 100 ml. of saturated sodium bisulfite solution, and finally with 100 ml. of water. The solution is dried over

magnesium sulfate, and the solvent is evaporated at room temperature (Note 4) at aspirator pressure. There is obtained 46–60 g. (60–78%) of crude oxazirane, n^{26}D 1.5065. This product assays 96–98% purity by iodimetric titration (Note 5) and is sufficiently pure for many purposes. Distillation of the crude product through a short Vigreux column yields, after a few drops of forerun, 42–55 g. (56–74%) of pure oxazirane, n^{26}D 1.5062, n^{20}D 1.5144, b.p. 55–58° (0.05 mm.), 74–76° (0.2 mm.). Iodimetric assay of this product indicates a purity of 99–100%.

2. Notes

1. Eastman Kodak white label reactants are satisfactory. The benzaldehyde should be freshly distilled before use.
2. The checkers handled and stored this material under nitrogen.
3. The charge of N-*t*-butylbenzaldimine is adjusted according to the amount of perbenzoic acid available. The perbenzoic acid in benzene is prepared by the procedure of Silbert, Siegel, and Swern,[2] and a 5% excess of this reagent is employed in the oxidation. In one attempt with commercial *m*-chloroperbenzoic acid instead, the checkers obtained only a 34% yield of oxazirane.
4. A rotary evaporator is very convenient for this operation.
5. A 0.200–0.300 g. sample of the oxazirane is weighed into a stoppered flask to which is added 15 ml. of glacial acetic acid and 2 ml. of saturated aqueous sodium iodide solution. After 5–10 minutes 25 ml. of deionized water is added, and the liberated iodine is titrated with 0.1*N* sodium thiosulfate with freshly prepared starch as indicator. Each milliliter of thiosulfate solution is equivalent to 0.00885 g. of 2-*t*-butyl-3-phenyloxazirane.

3. Discussion

This procedure is an adaptation of that described by Emmons for the preparation of oxaziranes from imines using peracetic acid.[3] Other procedures which may be more useful for oxazirane preparation in specific instances are the oxidation of imines with *m*-chloroperbenzoic acid[4] and the reaction of aldehydes or ketones with hydroxylamine *O*-sulfonic acid in alkaline solution.[5] 2-*t*-Butyl-3-phenyloxazirane has also been prepared by photolysis of α-phenyl-N-*t*-butylnitrone[6] (a general reaction of considerable theoretical interest since it represents direct conversion of electromagnetic energy to chemical energy) and in low yields by ozonolysis of N-*t*-butylbenzaldimine.[7]

Oxaziranes are in a real sense active oxygen compounds and exhibit many reactions grossly analogous to those of organic peroxides. Thus they undergo one electron transfer reaction with ferrous salts and on pyrolysis they are converted to amides. Oxaziranes are also useful synthetic intermediates since in appropriate cases they may be isomerized to aromatic nitrones which are a convenient source of N-alkylhydroxylamines.[3] The reaction of oxaziranes with peracids also provides a source

of nitrosoalkanes and is in many instances the method of choice for preparation of these compounds.[8]

References and Notes

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2. L. S. Silbert, E. Siegel, and D. Swern, this volume, p. 904.
3. W. D. Emmons, *J. Am. Chem. Soc.*, **79**, 5739 (1957).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

sodium carbonate (497-19-8)

sodium thiosulfate (7772-98-7)

nitrogen (7727-37-9)

Benzoic acid (65-85-0)

sodium bisulfite (7631-90-5)

benzaldehyde (100-52-7)

iodine (7553-56-2)

sodium iodide (7681-82-5)

magnesium sulfate (7487-88-9)

peracetic acid (79-21-0)

hydroxylamine O-sulfonic acid (2950-43-8)

Perbenzoic acid (93-59-4)

t-butylamine (75-64-9)

m-Chloroperbenzoic acid (937-14-4)

Oxaziridine, 2-t-butyl-3-phenyl-, 2-t-butyl-3-phenyloxazirane (7731-34-2)

N-t-butylbenzaldimine (6852-58-0)

α-phenyl-N-t-butylnitrone

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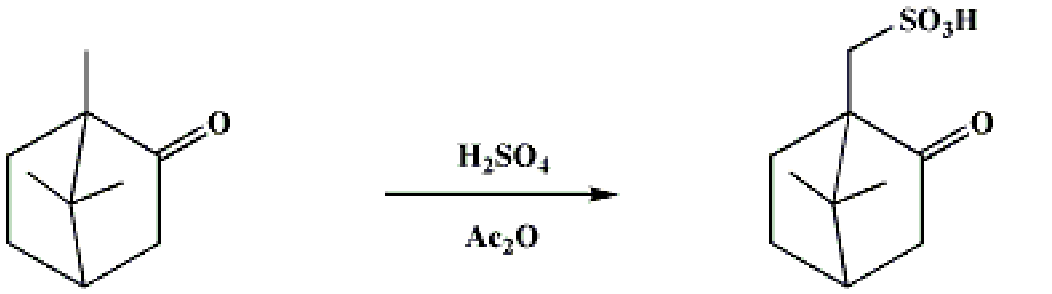
Organic Syntheses, *CV 5, 194*

D,L-10-CAMPHORSULFONIC ACID (REYCHLER'S ACID)



dl - camphor　　　　　　　　*dl* - camphorsulfonic acid

Submitted by Paul D. Bartlett and L. H. Knox[1].
Checked by John D. Roberts and Dinshaw Patel.

1. Procedure

In a 3-l., three-necked, round-bottomed flask fitted with a powerful slow-speed stirrer having a Teflon® blade, a 500-ml. dropping funnel, and a thermometer arranged to dip into the liquid is placed 588 g. (366 ml., 6 moles) of concentrated sulfuric acid. The flask is surrounded by an ice-salt mixture, the stirrer started, and 1216 g. (1170 ml., 12 moles) of acetic anhydride (Note 1) is added at such a rate that the temperature does not rise above 20° (Note 2). The separatory funnel is removed and 912 g. (6 moles) of coarsely powdered D,L-camphor is added (Note 3). The flask is then closed with a stopper and stirring is continued until the camphor is dissolved. The stirrer is replaced by a stopper, the ice bath allowed to melt, and the mixture left to stand for 36 hours (Note 4). The camphorsulfonic acid is collected on a suction filter and washed with ether (Note 5). After being dried in a vacuum desiccator at room temperature, the nearly white crystalline product weighs 530–580 g. (38–42%). It melts at 202–203° with rapid decomposition and is relatively pure (Note 6).

2. Notes

1. If the acetic anhydride is of a good commercial grade, it need not be redistilled.
2. When the temperature is allowed to rise above 20°, the acetic-sulfuric anhydride mixture acquires a yellow to orange color from which discolored crystals are subsequently deposited. The addition, which must be slow at first, requires 1–1.5 hours depending on the efficiency of the cooling bath.
3. The camphor employed is of the synthetic variety supplied by Howe and French, Boston. If an optically active product is desired, active natural camphor may be used.
4. The yields vary with the length of the crystallization period. After 16 hours

the yield is 470 g. (34%). When the crystallization period is extended to 2 weeks, the yield is 615–655 g. (44–47%).
5. The checkers found the product to be very hygroscopic, in fact deliquescent, in a reasonably humid atmosphere. In such circumstances, it was preferable to decant the mother liquor from the crystals in the flask and to wash the solid by stirring it up with four 250-ml. portions of anhydrous ether, each washing being removed by decantation. The well-drained residual solid can then be transferred to a crystallizing dish and the ether removed by pumping under reduced pressure before the final drying in a vacuum desiccator over sulfuric acid.
6. The product can be purified with some loss by recrystallization from glacial acetic acid. About 60 g. of crude product dissolves in 90 ml. of acetic acid at 105° and gives a recovery of about 40 g. of purified material.

3. Discussion

The procedure described is that of Reychler.[2]

4. Merits of the Preparation

D,L-10-Camphorsulfonic acid is used for the preparation of the corresponding chloride (p. 196). The optically active acid has been used widely for the resolution of basic compounds into optical antipodes.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 196

References and Notes

1. Converse Memorial Laboratory, Harvard University, Cambridge, Massachusetts. Preparation was submitted November 1, 1939.
2. A. Reychler, *Bull. Soc. Chim.*, [3] **19**, 120 (1898); H. E. Armstrong and T. M. Lowry, *J. Chem. Soc.*, **1441** (1902); B. Rewald, *Ber.*, **42**, 3136 (1909); F. Girault, *J. Pharm. Chim.*, [8] **20**, 207 (1934) [*C. A.*, **29**, 144 (1935)]; Y. Asahina and K. Yamguti, *Proc. Imp. Acad.* (Tokyo), **13**, 38 (1937) [*C. A.*, **31**, 4305 (1937)]; R. Poggi and A. Polverini, *Ann. Chim. Appl.*, **30**, 284 (1940) [*C. A.*, **35**, 1395 (1941)]; R. Poggi and A. Pasquarelli, *Ann. Chem. Appl.*, **37**, 321 (1947) [*C. A.*, **42**, 8788 (1948)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

REYCHLER'S ACID

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

ether (60-29-7)

acetic anhydride (108-24-7)

camphor (21368-68-3)

10-CAMPHORSULFONIC ACID, camphorsulfonic acid, D,L-10-CAMPHORSULFONIC ACID (5872-08-2)

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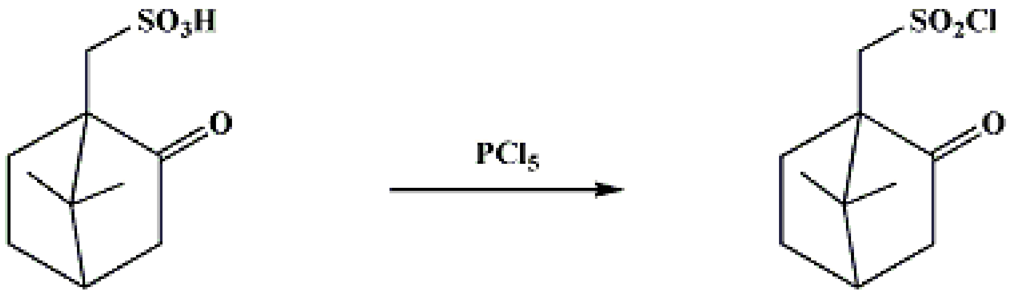
Organic Syntheses, CV 5, 196

D,L-10-CAMPHORSULFONYL CHLORIDE



Submitted by Paul D. Bartlett and L. H. Knox[1].
Checked by John D. Roberts

1. Procedure

In a 2-l., three-necked, round-bottomed flask (Note 1) fitted with a sealed stirrer having a Teflon® blade and, on the two side necks, with gas-outlet tubes connected by rubber or plastic tubing to an efficient hydrogen chloride absorption trap (Note 2), 464 g. (2 moles) of D,L-10-camphorsulfonic acid (Note 3) is mixed with 416 g. (2 moles) of phosphorus pentachloride (Note 4). The flask is immersed in ice water and, as soon as the mixture has liquefied sufficiently, the stirrer is started but must be run slowly at first because of lumps. When the vigorous reaction has subsided, the cooling bath is removed and stirring continued until the chloride is completely dissolved (Note 5). The mixture is then allowed to stand for 3 or 4 hours. It is poured (*Hood!*) onto 500 g. of crushed ice contained in a 2-l. beaker. This mixture is immediately poured into a second beaker containing a similar quantity of crushed ice. The mixture is then poured back and forth between the two beakers until all evidence of reaction has disappeared (Note 6). The fine white product is collected on a suction filter and washed several times with cold water. The yield is essentially quantitative (500 g.) of moist sulfonyl chloride which is pure enough to be used for the preparation of D,L-ketopinic acid (p. 55). When carefully dried, the crude material has m.p. 81–83° (Note 7) and (Note 8) and may be preserved in a desiccator.

2. Notes

1. The checker found it expedient to carry on the reaction in a 2-l. Pyrex® reaction kettle (Corning 6947), the large closure making the initial mixing of the solid reactant and the removal of the product much simpler.
2. The type of trap described in *Org. Syntheses*, Coll. Vol. **2**, p.4, is particularly useful.
3. The D,L-10-camphorsulfonic acid employed is the unrecrystallized product described on p. 194.
4. The initial mixing is conveniently made by turning the stirrer back and forth by hand.

5. The mixture does not usually become a clear solution because the product begins to crystallize. It is not difficult, however, to recognize yellow lumps of unreacted phosphorus pentachloride.

6. 10-Camphorsulfonyl chloride is rather rapidly hydrolyzed by warm water. The procedure here provides for complete hydrolysis of phosphorus oxychloride and excess phosphorus pentachloride without local heating and loss of product due to hydrolysis. For best results, the whole hydrolysis operation should be carried out quickly and steadily. It is well to have additional quantities of crushed ice on hand because the mixture may become quite hot if all of the ice added initially melts.

7. If the crude moist sulfonyl chloride is to be preserved, it must be thoroughly and reasonably rapidly dried. The checker found it very convenient to use a "freeze-drying" apparatus to remove the bulk of the moisture.

8. The submitters report that crystallization of the crude product from ligroin produces material of m.p. 83–84°. The sulfonyl chloride from (+)-camphorsulfonic acid has m.p. 67–68°.

3. Discussion

The procedure described here is adapted from that of Reychler.[2] The chloride may also be made from treatment of the acid with thionyl chloride.[3]

4. Merits of the Preparation

D,L-10-Camphorsulfonyl chloride may be oxidized to ketopinic acid (p. 690). The optically active forms of the sulfonyl chloride are useful for resolving alcohols and amines into optical antipodes.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 194
- Org. Syn. Coll. Vol. 5, 689
- Org. Syn. Coll. Vol. 5, 877

References and Notes

1. Converse Memorial Laboratory, Harvard University, Cambridge, Massachusetts. Preparation was submitted November 1, 1939.
2. A. Reychler, *Bull. Soc. Chim.*, [3] **19**, 120 (1898).
3. S. Smiles and T. P. Hilditch, *J. Chem. Soc.*, **91**, 519 (1907); H. Sutherland and R. L. Shriner, *J. Am. Chem. Soc.*, **58**, 62 (1936); J. Read and R. A. Storey, *J. Chem. Soc.*, 2761 (1930).

Appendix

Compounds Referenced (Chemical Abstracts Registry Number)

ligroin

D,L-ketopinic acid

ketopinic acid

phosphorus pentachloride (10026-13-8)

thionyl chloride (7719-09-7)

Phosphorus Oxychloride (21295-50-1)

D,L-10-CAMPHORSULFONIC ACID (5872-08-2)

10-CAMPHORSULFONYL CHLORIDE, D,L-10-CAMPHORSULFONYL CHLORIDE (6994-93-0)

(+)-camphorsulfonic acid (3144-16-9)

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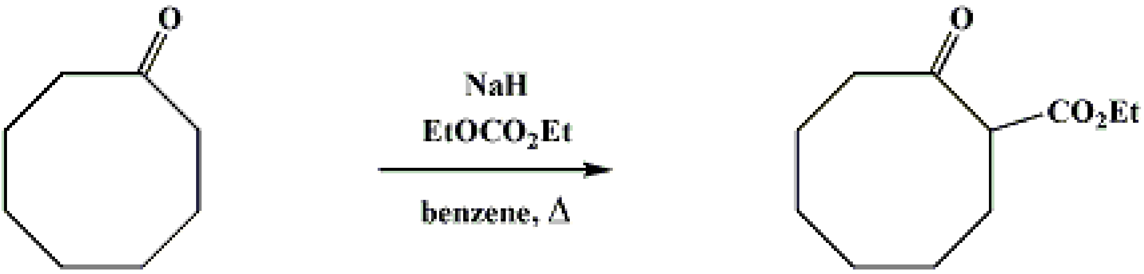
Organic Syntheses, CV 5, 198

2-CARBETHOXYCYCLOOCTANONE

[2-Oxocyclooctanecarboxylic acid, ethyl ester]



Submitted by A. Paul Krapcho, Joseph Diamanti, Charles Cayen, and Richard Bingham[1].
Checked by William G. Dauben and Charles Dale Poulter.

1. Procedure

A 2-l. two-necked, round-bottomed flask equipped with a magnetic stirrer (Note 1) is fitted with a 250-ml. pressure-equalizing constant-rate dropping funnel and a condenser, the top of which is connected to a mercury trap to prevent the entrance of air during the reaction and for the detection of gas evolution. The dropping funnel is removed, and 35 g. (0.85 mole) of sodium hydride dispersed in mineral oil is added (Note 2). The mineral oil is removed by washing the dispersion four times with 100-ml. portions of benzene (Note 3). The benzene is removed with a pipet after the sodium hydride is allowed to settle (Note 4).

After most of the mineral oil has been removed, 400 ml. of benzene is added to the sodium hydride, followed by 71 g. (0.6 mole) of diethyl carbonate (Note 5). This mixture is heated to reflux, and a solution of 38 g. (0.3 mole) of cyclooctanone (Note 6) in 100 ml. of benzene is added dropwise from the dropping funnel over a period of 3–4 hours. After the addition is complete, this mixture is allowed to reflux until the evolution of hydrogen ceases (15–20 minutes).

When the reaction mixture has cooled to room temperature, 60 ml. of glacial acetic acid is added dropwise, and a heavy, pasty solid separates. Ice-cold water (about 200 ml.) is added dropwise, and the stirring is continued until all the solid material has gone into solution (Note 7). The benzene layer is separated, and the aqueous layer is extracted three times using 100-ml. portions of benzene. The combined benzene extracts are washed three times with 100-ml. portions of cold water. The benzene is removed by distillation at atmospheric pressure, and the excess diethyl carbonate is removed under water-pump pressure with gentle heating. The residual material is transferred to a 100-ml. distillation flask, and the fraction boiling at 85–87° (0.1 mm.) is collected. The yield of 2-carbethoxycyclooctanone is 54–56 g. (91–94%), $n^{25}\text{D}$

1.4795–1.4800.

2. Notes

1. The checkers found that the agitation of the reaction mixture required later in this reaction is better achieved by use of a sealed mechanical stirrer.
2. The sodium hydride was obtained as a 58.6% dispersion in mineral oil from Metal Hydrides, Inc., Beverly, Massachusetts.
3. The benzene (Fisher certified reagent, thiophene free) was dried over potassium hydroxide and distilled from sodium metal.
4. By this procedure about 80–85% of the mineral oil was removed. Because some sodium hydride is lost in the pipetting procedure, an excess is initially employed.
5. The product supplied by Matheson, Coleman and Bell was used as received. Lower yields were obtained when a molar equivalent of diethyl carbonate was utilized, possibly because of self-condensation of the ketone.
6. The cyclooctanone was obtained from the Aldrich Chemical Co. and was utilized as received.
7. At this point the aqueous layer should be acidic, or more acetic acid should be added.

3. Discussion

The reaction of cyclooctanone with diethyl oxalate, followed by decarbonylation of the resulting glyoxylate, has been reported to yield 32% of 2-carbethoxycyclooctanone.[2] The reaction of cyclooctanone with sodium amide in ether, followed by the addition of diethyl carbonate, provided the product in 70% yield.[3]

The preparation of several medium- and large-sized 2-carbomethoxycycloalkanones has been accomplished by treatment of the cycloalkanone with sodium triphenylmethyl, followed by carbonation with dry ice, and esterification with diazomethane.[4] The yields are good but the procedure is laborious. The synthesis of 2-carbomethoxycyclooctanone via the Dieckmann cyclization of dimethyl azelate with sodium hydride yields 48% of this product when the procedure is carried out over a 9-day period.[5]

4. Merits of the Preparation

The reaction described is of general synthetic utility for the preparation of a variety of cyclic β-keto esters from the corresponding ketones. Using this procedure the 2-carbethoxycycloalkanones have been prepared from cyclononanone, cyclodecanone, and cyclododecanone in yields of 85%, 95%, and 90%, respectively. The procedure is simpler and gives much higher yields than other synthetic routes to these systems.

This procedure has been patterned after the method by which the carbethoxy group is

introduced into a few alicyclic ketones[6] and several cyclic ketones. Cyclohexanone has been reported to yield 50% of 2-carbethoxycyclohexanone when treated with sodium hydride and diethyl carbonate using ether as the solvent.[7] The preparation of 2-carbethoxycycloheptanone using potassium *t*-butoxide and diethyl carbonate in benzene has been reported in 40% yield.[8] Jacob and Dev report an 80% yield of the latter compound using sodium hydride as the base.[9]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 221

References and Notes

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4. V. Prelog, L. Ruzicka, P. Barman, and L. Frenkiel, *Helv. Chim. Acta*, **31**, 92 (1948) [*C. A.*, **42**, 4180 (1948)].
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium triphenylmethyl

acetic acid (64-19-7)

Benzene (71-43-2)

ether (60-29-7)

hydrogen (1333-74-0)

Cyclohexanone (108-94-1)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

Thiophene (110-02-1)

Diazomethane (334-88-3)

sodium amide (7782-92-5)

2-carbethoxycyclohexanone (1655-07-8)

diethyl carbonate (105-58-8)

sodium hydride (7646-69-7)

diethyl oxalate (95-92-1)

Cyclodecanone (1502-06-3)

cyclononanone (3350-30-9)

2-Carbethoxycyclooctanone, 2-Oxocyclooctanecarboxylic acid, ethyl ester (4017-56-5)

Cyclooctanone (502-49-8)

2-carbomethoxycyclooctanone

dimethyl azelate (1732-10-1)

cyclododecanone (830-13-7)

2-carbethoxycycloheptanone (774-05-0)

potassium t-butoxide (865-47-4)

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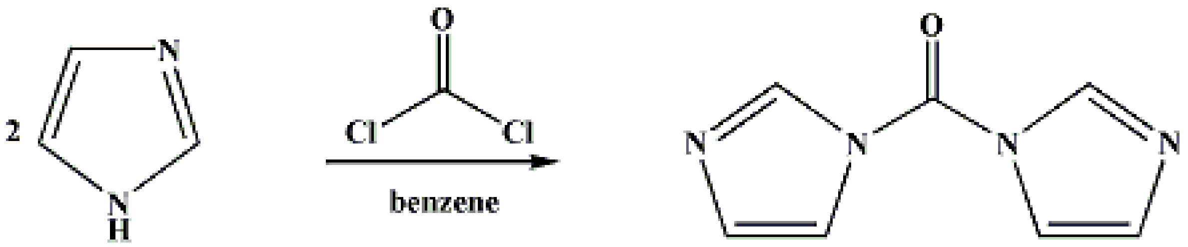
Organic Syntheses, CV 5, 201

1,1'-CARBONYLDIIMIDAZOLE

[Imidazole, 1,1'-carbonyldi-]



Submitted by Heinz A. Staab and Kurt Wendel[1].
Checked by A. C. Mackay and Peter Yates.

1. Procedure

Caution! This preparation must be carried out in a hood to avoid exposure to phosgene.

Anhydrous benzene (*ca.* 200 ml.) (Note 1) is poured into a calibrated, 500-ml., standard-taper dropping funnel equipped with a gas-inlet tube containing a fritted-glass filter; the dropping funnel is stoppered and weighed accurately. The funnel is protected with a calcium chloride tube, and 15–20 g. of phosgene is introduced at room temperature over a period of *ca.* 1 hour; this quantity corresponds to an increase in volume of 12–16 ml. (Note 2). The calcium chloride tube is removed, and the funnel is immediately restoppered and reweighed (Note 3). The amount of imidazole corresponding to the increase in weight observed (*e.g.*, 16.55 g., 0.167 mole, of phosgene) is calculated on the basis of a phosgene:imidazole molar ratio of 1:4 (Note 4). The funnel is placed on a 1-l., three-necked, round-bottomed flask, that contains a solution of the imidazole (here, 45.60 g., 0.669 mole) in 500 ml. of anhydrous tetrahydrofuran (Note 5) and is equipped with a sealed mechanical stirrer and a calcium chloride tube. The flask is cooled with cold water, and the solution of phosgene in benzene is added with stirring from the dropping funnel over a period of 15–30 minutes. The reaction mixture is stirred for an additional 15 minutes and then allowed to stand for 1 hour at room temperature. The precipitate of imidazolium chloride is removed by suction filtration with exclusion of atmospheric moisture by the use of a standard-taper fritted-glass filter funnel (Note 6). The filtrate is evaporated to dryness under reduced pressure on a water bath at 40–50° (Note 7). The yield of colorless crystalline 1,1'-carbonyldiimidazole is 80–94% (here, 24.8 g.; 91%). The product obtained in this way sinters at 110° and melts between 112° and 117° (here, 114–115°). This material can be used without further purification for most reactions, *e.g.*, ester, peptide, and aldehyde syntheses[2] (Note 8). The purity of a product of m.p.

113–117° was 98±2%.[3] The quality and yield of 1,1'-carbonyldiimidazole are not reduced when the scale is doubled.

1,1'-Carbonyldiimidazole may be kept for a long period of time in either a desiccator over phosphorus pentoxide or in a sealed tube. It is hydrolyzed by water to give carbon dioxide and imidazole.

2. Notes

1. The benzene is heated under reflux over sodium with benzophenone until a permanent blue coloration develops and then is distilled with exclusion of atmospheric moisture.
2. Use of a calibrated dropping funnel permits approximate estimation of the amount of phosgene absorbed; a volume increase of 1 ml. corresponds to about 1.3 g. of phosgene. The stream of phosgene is led through a wash bottle containing concentrated sulfuric acid and should not be too fast in order to avoid loss of solvent by evaporation.
3. The checkers used a fritted-glass inlet tube and drying tube incorporated in a standard-taper adapter that fitted the neck of the dropping funnel. Owing to small losses of solution on withdrawal of the adapter, the weight of phosgene was slightly underestimated.
4. Technical grade imidazole (from Badishe Anilin- und Soda-Fabrik, Ludwigshafen, Rhein, Germany) was recrystallized from benzene containing 1.0–1.5% ethanol; m.p. 90°. The checkers used imidazole obtained from Aldrich Chemical Co without further purification.
5. Technical grade tetrahydrofuran was predried for a few days over sodium hydroxide. It was then heated under reflux over sodium wire with benzophenone until it developed a permanent blue color and distilled with exclusion of atmospheric moisture. *[Caution! See p. 976 of this volume for a warning regarding purification of tetrahydrofuran.]*
6. By working quickly, the imidazolium chloride may be removed by suction filtration through a Buchner funnel. However, the precipitate should not be freed of solvent completely because imidazolium chloride is extremely hygroscopic. If the moist precipitate is washed with 50–100 ml. of anhydrous tetrahydrofuran, the yield of 1,1'-carbonyldiimidazole may be slightly increased; however, there is some danger of the introduction of too much moisture into the reaction solution.
7. The checkers used an antifoaming head for the solvent evaporation.
8. In order to obtain a purer product the crude material may be recrystallized from hot anhydrous tetrahydrofuran with careful exclusion of moisture. After this operation the yield is reduced to 65–75%; the m.p. is then between 114° and 118°; *e.g.*, recrystallization of 24.8 g. (91%) of 1,1'-carbonyldiimidazole from 60 ml. of anhydrous tetrahydrofuran yielded 19.9 g.. (73%); m.p. 116–118°.

3. Discussion

1,1'-Carbonyldiimidazole has been prepared by the reaction of imidazole and phosgene in anhydrous benzene and anhydrous tetrahydrofuran.[3,4,5] It has also been obtained by the reaction of 1-(trimethylsilyl)imidazole and phosgene in anhydrous benzene,[6] but that method offers no advantages that justify the more extensive preparative effort required.

4. Merits of the Preparation

1,1'-Carbonyldiimidazole has been used for the preparation of such compounds as esters, anhydrides, amides peptides, ketones, ethers, and isocyanates.[2] The present procedure provides a convenient method for its preparation in good yield.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 560

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

sulfuric acid (7664-93-9)

Benzene (71-43-2)

sodium hydroxide (1310-73-2)

carbon dioxide (124-38-9)

Benzophenone (119-61-9)

sodium (13966-32-0)

phosgene (75-44-5)

Tetrahydrofuran (109-99-9)

Imidazole (288-32-4)

imidazolium chloride

1-(trimethylsilyl)imidazole (18156-74-6)

phosphorus pentoxide (1314-56-3)

1,1'-Carbonyldiimidazole, Imidazole, 1,1'-carbonyldi- (530-62-1)

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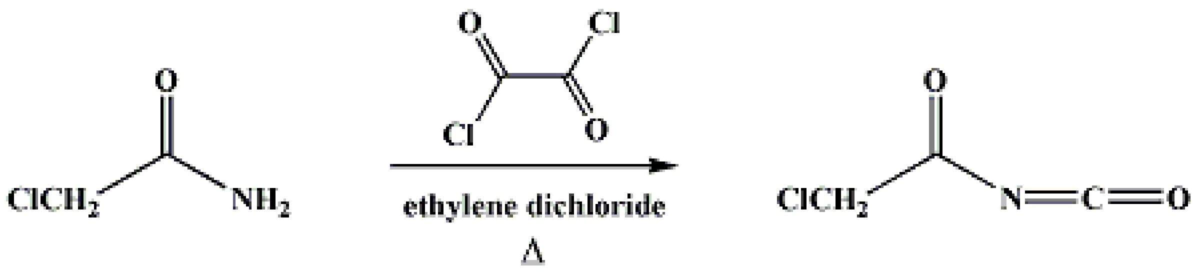
Organic Syntheses, CV 5, 204

α-CHLOROACETYL ISOCYANATE

[Isocyanic acid, anhydride with chloroacetic acid]



Submitted by A. John Speziale and Lowell R. Smith[1].
Checked by Leif A. Hoffmann and V. Boekelheide.

1. Procedure

In a 250-ml. round-bottomed flask fitted with a magnetic stirrer (Note 1), a thermometer, and a condenser carrying a calcium chloride tube (Note 2) are placed 46.7 g. (0.5 mole) of α-chloroacetamide (Note 3) and 100 ml. of ethylene dichloride. The mixture is chilled in an ice bath to about 2° and stirred while 76.2 g. (0.6 mole) of oxalyl chloride (Note 4) is added all at once. The mixture is removed from the ice bath, stirred for 1 hour, and then heated to reflux at 83° with stirring for 5 hours (Note 5). The solution is chilled in an ice bath to 0–10°, the condenser is replaced by a 120-mm. distillation column packed with glass helices, and the solvent is removed at 70 mm. pressure with stirring. The ice bath is removed after the solvent boils without foaming and is replaced by a heating mantle or oil bath. Distillation gives 39 g. (65%) of α-chloroacetyl isocyanate, b.p. 68–70° (70 mm.), as a colorless oil, $n^{25}\text{D}$ 1.4565.

2. Notes

1. For larger-scale preparations mechanical stirring is recommended.
2. Moisture must be rigorously excluded from the reaction mixture and the product.
3. The α-chloroacetamide was obtained from Eastman Kodak Co. and used without purification.
4. The oxalyl chloride was obtained from Aldrich Chemical Co. and used without purification. Oxalyl chloride vapor is irritating and toxic, and therefore manipulations must be carried out in a hood.
5. Because a large amount of hydrogen chloride is evolved, the reaction must be carried out in a hood.

3. Discussion

The only preparation reported for α-chloroacetyl isocyanate is that described by the submitters.[2]

4. Merits of the Preparation

The procedure may be adapted for the preparation of other acyl isocyanates (*i.e.*, dichloroacetyl, trichloroacetyl, phenylacetyl, diphenylacetyl, benzoyl, etc.) and is generally more convenient than the reaction of acid chlorides with silver cyanate.[3] [4] Acyl isocyanates react with amines, alcohols, and mercaptans to yield acyl ureas, carbamates, and thiocarbamates, and have been show to undergo a variety of interesting reactions.[5]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Isocyanic acid, anhydride with chloroacetic acid

hydrogen chloride (7647-01-0)

ethylene dichloride (107-06-2)

α-chloroacetamide (79-07-2)

oxalyl chloride (79-37-8)

α-Chloroacetyl isocyanate (4461-30-7)

silver cyanate (3315-16-0)

dichloroacetyl isocyanate

trichloroacetyl isocyanate

phenylacetyl isocyanate

diphenylacetyl isocyanate

benzoyl isocyanate

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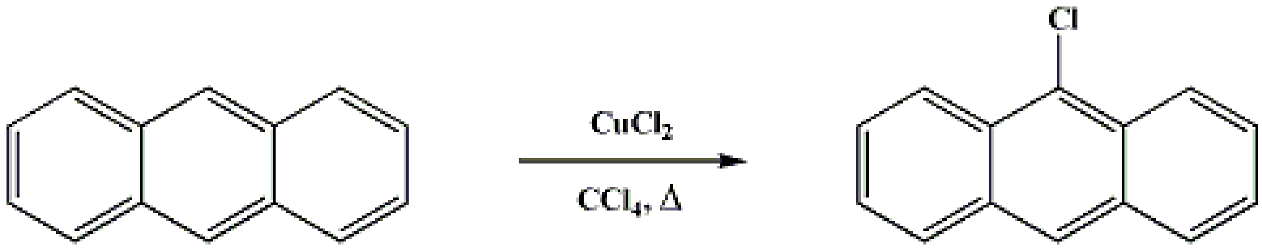
Organic Syntheses, CV 5, 206

9-CHLOROANTHRACENE

[Anthracene, 9-chloro-]



Submitted by D. C. Nonhebel[1]
Checked by R. B. Greenwald and E. J. Corey.

1. Procedure

In a dry, 1-l., two-necked flask, equipped with a mechanical stirrer and a reflux condenser fitted with a drying tube, are placed 17.8 g. (0.100 mole) of anthracene (Note 1), 27.2 g. (0.202 mole) of anhydrous cupric chloride (Note 2), and 500 ml. of carbon tetrachloride (Note 3). The reaction mixture is stirred and heated under reflux for 18–24 hours. The brown cupric chloride is gradually converted to white cuprous chloride, and hydrogen chloride is gradually evolved. At the end of the reaction the cuprous chloride is removed by filtration, and the carbon tetrachloride solution is passed through a 35-mm. Chromatographic column filled with 200 g. of alumina (Note 4). The column is eluted with 400 ml. of carbon tetrachloride. The combined eluates are evaporated to dryness to give 19–21 g. (89–99%) of 9-chloroanthracene as a lemon-yellow solid, m.p. 102–104° (Note 5). Crystallization of the product from petroleum ether (b.p. 60–80°) gives 16–17 g. (75–80%) of 9-chloroanthracene as yellow needles, m.p. 104–106°.

2. Notes

1. Anthracene, B. D. H. (blue fluorescence), was used. Traces of ethylene glycol, glycerol, ethanol, or water considerably retard the reaction and lead to unsatisfactory results.
2. Anhydrous cupric chloride is dried in an oven at 110–120° for several hours and stored in a desiccator or over phosphorus pentoxide before use.
3. Chlorobenzene or *sym*-tetrachlorethane may be used instead of carbon tetrachloride as solvent, in which case the reaction is complete as soon as the mixture has reached reflux. The product is liable to be contaminated by a small amount of 9,10-dichloroanthracene.
4. Merck alumina or Spence Type H alumina was used.
5. The 9-chloroanthracene at this stage usually contains a small amount of unreacted anthracene.

3. Discussion

9-Chloroanthracene has been prepared by the action of chlorine,[2] *t*-butyl hypochlorite,[3] 1,3-dichloro-5,5-dimethylhydantoin,[4] or phosphorus pentachloride[5] on anthracene. The present method is a one-step synthesis giving a high yield of 9-chloroanthracene from readily available starting materials.

The method outlined can be applied to the preparation in better than 90% yield of the 10-chloro derivatives of 9-alkyl-,[6] 9-aryl-,[6] and 9-halogenoanthracenes.[7] For the less reactive substrates chlorobenzene should be used as solvent. This is the only satisfactory procedure for the preparation of 9-bromo-10-chloroanthracene.[7] Other methods of chlorination lead to mixtures of the desired compound and 9,10-dichloroanthracene. Pyrene can likewise be converted to 1-chloropyrene (90% yield).[8] Analogous procedures with cupric bromide lead to the brominated compounds in similar high yields.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

sym-tetrachlorethane

ethanol (64-17-5)

hydrogen chloride (7647-01-0)

phosphorus pentachloride (10026-13-8)

glycerol (56-81-5)

carbon tetrachloride (56-23-5)

chlorobenzene (108-90-7)

chlorine (7782-50-5)

ethylene glycol (107-21-1)

cuprous chloride (7758-89-6)

cupric chloride (7758-89-6)

anthracene (120-12-7)

cupric bromide (7789-45-9)

pyrene (129-00-0)

9-Chloroanthracene, Anthracene, 9-chloro- (716-53-0)

9,10-dichloroanthracene (605-48-1)

1,3-dichloro-5,5-dimethylhydantoin (118-52-5)

9-bromo-10-chloroanthracene

1-chloropyrene (34244-14-9)

phosphorus pentoxide (1314-56-3)

t-BUTYL HYPOCHLORITE (507-40-4)

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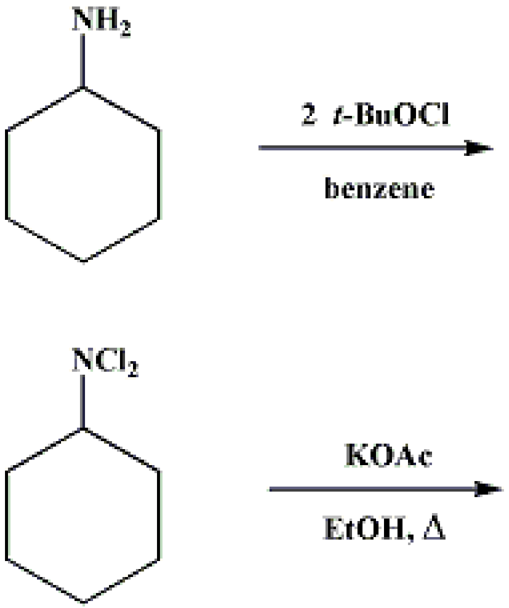
Organic Syntheses, CV 5, 208

N-CHLOROCYCLOHEXYLIDENEIMINE

[Cyclohexanimine, N-chloro-]



Submitted by G. H. Alt[1] and W. S. Knowles[2].
Checked by P. M. Burke and Peter Yates.

1. Procedure

A. *N,N-Dichlorocyclohexylamine* (Note 1). In a 300-ml. three-necked flask fitted with stirrer, addition funnel, thermometer, and calcium chloride tube are placed 9.92 g. (0.10 mole) of cyclohexylamine (Note 2) and 50 ml. of dry benzene (Note 3), and the mixture is cooled to 0–5° by an ice bath. A solution of 24 g. (0.22 mole) of *t*-butyl hypochlorite[3]. [4] in 50 ml. of dry benzene is added dropwise at such a rate that the temperature of the mixture does not exceed 10°. The mixture is allowed to come to room temperature and is then stirred for 1 hour, giving a solution of N,N-dichlorocyclohexylamine suitable for use in the next step.

B. *N-Chlorocyclohexylideneimine*. In a 500-ml. three-necked flask fitted with stirrer, addition funnel, thermometer, and reflux condenser fitted with a calcium chloride tube are placed 15 g. (0.15 mole) of potassium acetate (Note 4) and 100 ml. of absolute ethanol. The mixture is heated to reflux temperature, and, when the potassium acetate has dissolved, the N,N-dichlorocyclohexylamine solution is added at such a rate as to maintain reflux (Note 5). The reaction mixture is heated under reflux for an additional 3 hours, during which time potassium chloride precipitates. The mixture is cooled to room temperature, 200 ml. of ether and 100 ml. of water are added, and the resulting mixture is transferred to a 1-l. separatory funnel. The aqueous layer is separated and discarded. The ethereal layer is washed with three 100-ml. portions of water, three 50-

ml. portions of 2*N* hydrochloric acid, and an additional three 100-ml. portions of water, the washings being discarded. The ethereal solution is dried over anhydrous calcium sulfate, and the solvent is removed at room temperature with a rotary evaporator and water aspirator. The residue is transferred to a 25-ml. distilling flask and fractionally distilled at reduced pressure through a short, vacuum-jacketed Vigreux column equipped with a Claisen type still head and a condenser through which ice water is circulated (Note 6). N-Chlorocyclohexylideneimine, b.p. 53–54° (3 mm.) (*Caution! (Note 7)*), n^{25}_{D} 1.506, is obtained in 48–69% yield (6.3–9.1 g.) (Note 8).

2. Notes

1. This method is essentially that of Baumgarten and Petersen.[5]
2. Eastman Organic Chemicals cyclohexylamine, white label grade, was redistilled prior to use.
3. Dried by azeotropic distillation; the first 10% of distillate is discarded.
4. Baker and Adamson, reagent grade.
5. The checkers found it preferable to maintain some external heating; otherwise the rate of addition had to be very rapid to maintain reflux.
6. Ice water is essential, and cooling of the receiver is recommended; otherwise considerable losses by evaporation occur.
7. The pot temperature should not be allowed to rise above 70° (the submitters used a hot-water bath at 75°), as a fume-off which may proceed with explosive violence is likely to occur. A nitrogen bubbler may be used to eliminate bumping. The distillation should be carried out behind a safety shield.
8. The compound decomposes slowly even under refrigeration and should be used within 24 hours of preparation. Analytically pure material, b.p. 36° (1.5 mm.), may be obtained by redistillation.

3. Discussion

N-Chlorocyclohexylideneimine has been prepared by the treatment of N,N-dichlorocyclohexylamine with triethylamine,[6] potassium hydroxide,[6] or potassium acetate[7] and by reaction of chloramine with cyclohexanone[8] or *N*-cyclohexylideneaniline.[9]

4. Merits of the Preparation

This method, which is an adaptation of that of Alt and Knowles,[7] obviates the need to isolate the N,N-dichlorocyclohexylamine.

N-Chlorocyclohexylideneimine is of theoretical interest, being isoelectronic with the oxime tosylate. On treatment with 1 mole of base the imine undergoes a Neber-type rearrangement to the α-amino ketone[7] and has been shown to be an intermediate in the

rearrangement of N,N-dichlorocyclohexylamine to 2-aminocyclohexanone.[5,7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 909

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether (60-29-7)

Cyclohexanone (108-94-1)

calcium sulfate (7778-18-9)

potassium hydroxide (1310-58-3)

potassium chloride (7447-40-7)

potassium acetate (127-08-2)

cyclohexylamine (108-91-8)

chloramine (10599-90-3)

triethylamine (121-44-8)

N-CHLOROCYCLOHEXYLIDENEIMINE, Cyclohexanimine, N-chloro- (6681-70-5)

N,N-dichlorocyclohexylamine

oxime tosylate

2-aminocyclohexanone

t-BUTYL HYPOCHLORITE (507-40-4)

N-cyclohexylideneaniline

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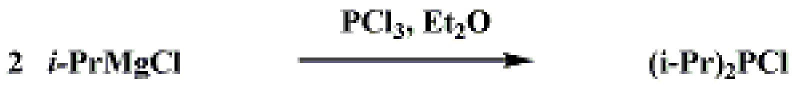
Organic Syntheses, *CV 5*, *211*

CHLORODIISOPROPYLPHOSPHINE

[Phosphinous chloride, diisopropyl-]



Submitted by W. Voskuil and J. F. Arens[1].
Checked by Hugh D. Olmstead, James E. Oliver, and Herbert O. House.

1. Procedure

Caution! Because of the sensitivity of the reagents and product to moisture and oxygen, all manipulations must be performed in an anhydrous, inert atmosphere (Note 1).

A 500-ml., four-necked, round-bottomed flask is equipped with an efficient stirrer, a reflux condenser, a 250-ml. dropping funnel, and a low-temperature thermometer (Note 2). In the flask are placed 34.4 g. (21.8 ml., 0.25 mole) of phosphorus trichloride (Note 3) and 150 ml. of anhydrous ether. A solution of 0.50 mole of isopropylmagnesium chloride in about 150 ml. of ether (Note 4) and (Note 5) is placed in the dropping funnel.

The flask is cooled in a dry ice-acetone bath, and the Grignard reagent solution is added dropwise with rapid stirring at such a rate that the temperature of the reaction mixture remains between −25° and −30° with a bath temperature of −45°; this addition requires about 1.5 hours. After the addition has been completed, the cooling bath is removed, and the mixture is allowed to warm to room temperature. Finally, the reaction mixture is heated to reflux with continuous stirring for 30 minutes.

After the reaction mixture has cooled to room temperature, it is filtered with suction (Note 6) and (Note 7), and the residual salts are washed thoroughly with three 100-ml. portions of anhydrous ether. The combined ethereal filtrates are concentrated under reduced pressure at room temperature, and the residual liquid is fractionally distilled through a 15-cm. Vigreux column. After a small forerun has been collected, the product is obtained as a clear, colorless liquid, b.p. 46–47° (10 mm.), n^{20}_D 1.4752 (Note 8). The yield is 21–23 g. (55–60%); practically no residue remains in the distillation pot.

2. Notes

1. The submitters used nitrogen purified by passage through B.T.S. catalyst (B. A.S.F., Ludwigshafen, Germany). The checkers used commercial prepurified nitrogen without further treatment.

2. The checkers used a three-necked flask, one neck of which was fitted with an adapter to accommodate the thermometer. They also used a pressure-equalizing dropping funnel so that a static nitrogen atmosphere several millimeters above atmospheric pressure could be maintained in the flask.
3. The submitters used Merck reagent grade phosphorus trichloride. The checkers used material from Baker and Adamson.
4. It is essential to use the Grignard reagent prepared from isopropyl chloride. From phosphorus trichloride and isopropylmagnesium bromide, bromodiisopropylphosphine is obtained because of a halogen exchange reaction between the initially formed chlorophosphine and magnesium bromide. The checkers used both the Grignard reagent prepared from isopropyl chloride and a commercial solution of isopropylmagnesium chloride available from Matheson, Coleman and Bell.
5. The concentration of the Grignard reagent should be estimated by titration. If an excess or less than the stoichiometric amount of the organometallic reagent is added, the yield is lower and the product is less pure. The checkers found the titration procedure of Watson and Eastham[2] to be most convenient. In a typical titration, performed under a nitrogen atmosphere, a 5.00-ml. aliquot of the Grignard reagent was added to a solution of about 2 mg. of *o*-phenanthroline in 10 ml. of anhydrous benzene. The resulting purple solution was titrated with a standard solution (0.999*M*) of *sec*-butyl alcohol in xylene until the purple color of the *o*-phenanthroline-Grignard reagent charge transfer complex was just discharged. In this procedure the number of millimoles of *sec*-butyl alcohol added is equal to the number of millimoles of alkylmagnesium chloride present in the aliquot of Grignard reagent.
6. The checkers performed this filtration and subsequent washing of the precipitate by replacing the dropping funnel in the reaction flask by a sintered-glass filter stick. A slight positive nitrogen pressure was applied in the reaction flask, and the pressure was reduced in the flask that served as a receiver for the filtrate passing through the sintered-glass filter.
7. The checkers found it necessary to dislodge and break up the cake of magnesium salts that formed on the walls of the reaction flask. If this precaution was not observed, a substantial amount of product occluded in the salt cake was not recovered during the washing process.
8. The checkers verified the absence of dichloroalkylphosphine and trialkylphosphine contaminants in this product by obtaining acceptable elemental analytical results and by measuring the mass spectrum of the product, which exhibits a molecular ion peak at m/e 152 (^{35}Cl) with abundant fragment peaks at m/e 110, 43, and 41.

3. Discussion

Chlorodiisopropylphosphine has been prepared by the reduction of the diisopropyltrichlorophosphorus-aluminum chloride complex with antimony;[3,4] this is a general method and the reduction can be performed with other reagents.[5] Other

general methods for the preparation of chlorodialkylphosphines are reaction of dialkylphosphines with phosgene[6,7] and the cleavage of N,N-dialkylaminodialkylphosphines with hydrogen chloride[8,9,10] or phosphorus trichloride.[11]

4. Merits of the Preparation

Chlorodialkylphosphines are important synthetic intermediates in organophosphorus chemistry. In the chemical literature there is a widespread view that the simple one-step Grignard method is not suitable for the preparation of these compounds because of dominant trisubstitution and the formation of difficultly separable mixtures.[12] Although this is true for the *n*-alkyl compounds, the present preparation demonstrates that in the case of branched primary alkyl compounds and secondary and tertiary alkyl compounds the method can be very convenient and can give pure products. The submitters have prepared[13] chlorodiisobutylphosphine (45–50%), chlorodi-*sec*-butylphosphine (75–80%), chlorodi-*t*-butylphosphine (65–70%), and chlorodicyclohexylphosphine (60–65%) in analogous manner.

With *t*-butylmagnesium chloride the substitution of only one chlorine atom of the phosphorus trichloride is possible, giving dichloro-*t*-butylphosphine (65–70%).

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 775
- Org. Syn. Coll. Vol. 6, 762
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

diisopropyltrichlorophosphorus-aluminum chloride complex

hydrogen chloride (7647-01-0)

Benzene (71-43-2)

ether (60-29-7)

oxygen (7782-44-7)

nitrogen (7727-37-9)

chlorine (7782-50-5)

phosgene (75-44-5)

phosphorus trichloride (7719-12-2)

magnesium bromide (7789-48-2)

xylene (106-42-3)

antimony (7440-36-0)

isopropylmagnesium bromide (920-39-8)

isopropylmagnesium chloride (1068-55-9)

Chlorodiisopropylphosphine, Phosphinous chloride, diisopropyl- (40244-90-4)

isopropyl chloride (75-29-6)

bromodiisopropylphosphine

chlorophosphine

phenanthroline

chlorodiisobutylphosphine

chlorodicyclohexylphosphine (16523-54-9)

sec-butyl alcohol (78-92-2)

t-butylmagnesium chloride (677-22-5)

chlorodi-sec-butylphosphine

chlorodi-t-butylphosphine (13716-10-4)

dichloro-t-butylphosphine (25979-07-1)

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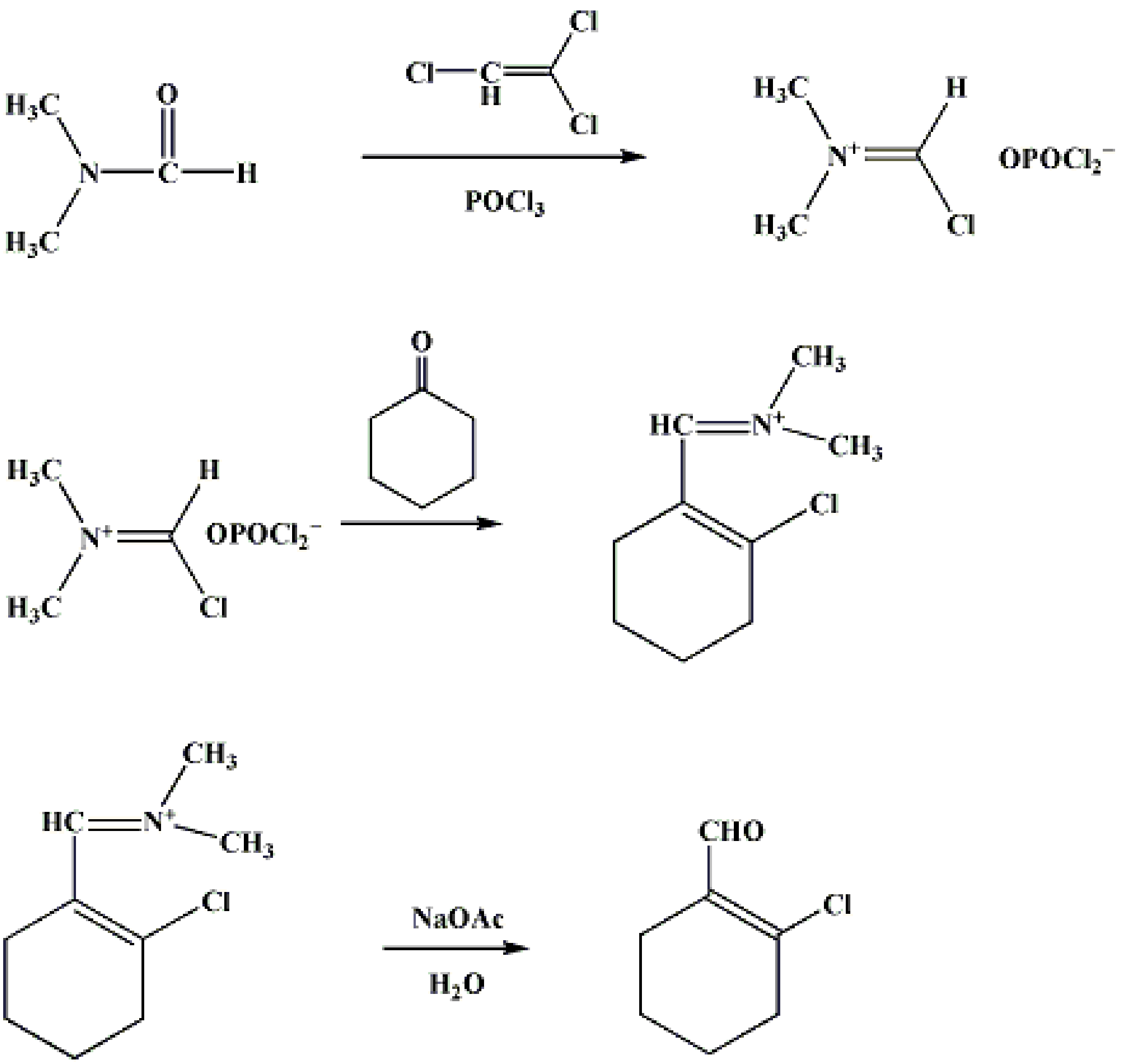
Organic Syntheses, CV 5, 215

2-CHLORO-1-FORMYL-1-CYCLOHEXENE

[2-Chloro-1-cyclohexenealdehyde]



Submitted by L. A. Paquette[1], B. A. Johnson[2], and F. M. Hinga[2].
Checked by William E. Parham and Robert W. Grady.

1. Procedure

To a 12-l. three-necked flask (Note 1) fitted with a stirrer, thermometer, reflux condenser, dropping funnel, nitrogen inlet, and calcium chloride drying tube are added 310 g. (4.24 moles) of dimethylformamide and 800 ml. of trichloroethylene (Note 2). The stirred solution is cooled to 5° with an external ice bath, and the system is blanketed with nitrogen (Note 3). Phosphorus oxychloride (460 g., 3.0 moles) is added during approximately 1 hour through the dropping funnel, the temperature of the

stirred reaction mixture being maintained below 10°. The mixture is then allowed to warm to room temperature.

A solution of 320 g. (3.26 moles) of cyclohexanone in 800 ml. of trichloroethylene is prepared and is added to the stirred reaction mixture at such a rate that the temperature does not rise above 60° (Note 4). When the addition is completed, the mixture is heated at 55–60° for 3 hours.

The solution is cooled to below 35° by use of an ice bath, and a solution of 1.2 kg. of anhydrous sodium acetate in 2.8 l. of water is cautiously added through the dropping funnel (Note 5) and (Note 6). The organic layer is separated and is washed twice with 1.5-l. portions of saturated aqueous salt solutions and once with 1.5 l. of deoxygenated water. The organic solution is dried over anhydrous sodium sulfate.

To the dried solution is added 10 g. of anhydrous sodium acetate. The solvent is evaporated under reduced pressure on a water bath heated to 50–60° (Note 7). The concentrate is distilled under nitrogen through a 14-in. vacuum-jacketed Vigreux column. The distillate is collected in receivers containing 1 g. of anhydrous sodium acetate per 100 ml. of flask capacity (Note 8). There is obtained 230–320 g. (53–74%) of colorless liquid, b.p. 86–88° (10 mm.), n^{20}D 1.5198 (Note 9) and (Note 10).

2. Notes

1. The checkers carried out this procedure using a 5-l. flask and employed five-twelfths of the quantities of reagents specified.
2. Du Pont extraction grade of trichloroethylene was employed throughout the course of this work.
3. A nitrogen atmosphere is maintained over the reaction mixture and the product at all times when possible.
4. Approximately 1.5 hours is required to complete the addition.
5. The temperature is maintained below 35° during this addition, which is of approximately 1-hour duration.
6. The resulting two-phase mixture appears to be stable and may be allowed to stand overnight or for several days at room temperature.
7. The concentrate may be conveniently stored at –45° or below before distillation.
8. The aldehyde is quite unstable and tends to decompose with some violence on standing at room temperature. However, when treated with 1 g. of anhydrous sodium acetate per 100 ml. of distilled product, the compound has remained stable for 2 weeks when stored in this condition at room temperature. It may be stored quite indefinitely in this condition at –45°.
9. Gas chromatography is a convenient method of monitoring the distillation. Early fractions contain trichloroethylene and an unidentified reaction by-product.
10. The product obtained by the checkers was pale yellow in color. The color was not removed by redistillation.

3. Discussion

2-Chloro-1-formyl-1-cyclohexene has been prepared only by the action of phosphorus oxychloride (or phosgene) and dimethylformamide on cyclohexanone.[3,4,5] 2-Bromo-1-formyl-1-cyclohexene has been synthesized by a method analogous to the above by the use of phosphorus oxybromide or phosphorus tribromide.[6]

4. Merits of the Preparation

The described procedure is useful for the conversion of ketones to chloroalkene aldehydes. Methyl ethyl ketone,[3,4] phenyl ethyl ketone,[3,4] cyclobutanone,[7] cyclopentanone,[3,4,5] cyclooöctanone,[3,4,5] α-tetralone,[5] and benzosuberone[5] are illustrative of the wide variety of ketones which have been so treated. The yields are reported generally to be 65–80%.

The chlorovinyl aldehydes, although still a relatively new class of compounds, show great promise as useful synthetic intermediates.[5,7,8]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 76

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium acetate (127-09-3)

Cyclohexanone (108-94-1)

sodium sulfate (7757-82-6)

phosphorus tribromide (7789-60-8)

nitrogen (7727-37-9)

Phosphorus Oxychloride (21295-50-1)

phosgene (75-44-5)

Cyclopentanone (120-92-3)

phosphorus oxybromide

phenyl ethyl ketone (93-55-0)

methyl ethyl ketone (78-93-3)

α-Tetralone (529-34-0)

dimethylformamide (68-12-2)

trichloroethylene (79-01-6)

Cyclooctanone (502-49-8)

2-Chloro-1-formyl-1-cyclohexene, 2-Chloro-1-cyclohexenealdehyde (1680-73-5)

2-Bromo-1-formyl-1-cyclohexene

Cyclobutanone (1191-95-3)

benzosuberone (826-73-3)

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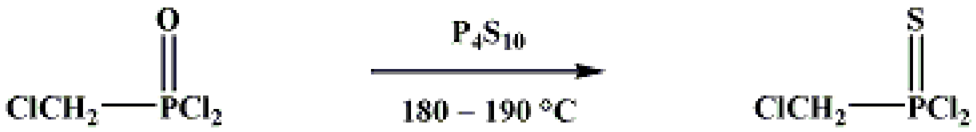
Organic Syntheses, CV 5, 218

CHLOROMETHYLPHOSPHONOTHIOIC DICHLORIDE



Submitted by R. Schmutzler[1]
Checked by M. D. Hurwitz and W. D. Emmons.

1. Procedure

A 500-ml. three-necked flask is provided with a mechanical stirrer, thermometer, and reflux condenser equipped with a drying tube. The flask is flushed with dry nitrogen and charged under nitrogen with 502 g. (3 moles) of chloromethylphosphonic dichloride (Note 1) and 160 g. (0.36 mole) of tetraphosphorus decasulfide (Note 2). The reaction mixture is heated under reflux with stirring for 6 hours, the liquid temperature being 180–190° (Note 3). The nearly black reaction mixture is then allowed to cool to room temperature and is distilled under reduced pressure. Material distilling between 70° (40 mm.) and 150° (20 mm.) is collected (Note 4). The yield is 364–396 g. (66–72%). There is no impurity in the material thus obtained which is detectable by gas chromatography (Note 5). The product may be redistilled if desired, although in most cases this is superfluous; b.p. 64–65° (10 mm.); n^{25}D 1.5730–1.5741 (Note 6). The P^{31} n.m.r. spectrum of the product shows a peak at −74.2 p.p.m. relative to external phosphoric acid.

2. Notes

1. Chloromethylphosphonic dichloride is used as obtained from Stauffer Chemical Co. Alternatively it may be prepared from the reaction of phosphorus trichloride with paraformaldehyde.[2]
2. Technical tetraphosphorus decasulfide (Stauffer Chemical Co.) is employed. The product is weighed under nitrogen protection.
3. In order to prevent contact of the boiling reaction mixture with air, nitrogen is passed through a T-tube on top of the drying tube on the reflux condenser.
4. Toward the end of the distillation a thick residue is formed, and this makes the distillation difficult. After the contents of the distillation flask are cooled to room temperature, this residue may be disposed of by careful continuous rinsing with water under a well-ventilated hood.
5. An F&M 500 Program-Temperature Unit (8 ft., 20% silicon rubber on 60–80 Super Support) was used for the VPC work: program 11°/min., flow 55 ml/min. Chloromethylphosphonothioic dichloride and chloromethylphosphonic

dichloride, a potential impurity, are separated cleanly under these conditions.

6. Literature[3] values are: b.p. 89° (30 mm.), $n^{25}D$ 1.5741, d^{25}_{25} 1.5891.

3. Discussion

Chloromethylphosphonothioic dichloride has been prepared by the reaction of chloromethylphosphonic dichloride with tetraphosphorus decasulfide[3,4,5] or with thiophosphoryl chloride under autogenous pressure.[3,5]

4. Merits of the Preparation

The reaction of chloromethylphosphonic dichloride with tetraphosphorus decasulfide[3,4,5] or with thiophosphoryl chloride[3] are the only methods of preparation for this compound reported. The method is applicable more generally, and the syntheses of methyl-, trichloromethyl-, ethyl-, propyl-, cyclohexyl-, phenyl-, and *p*-chlorophenylphosphonothioic dichloride from the corresponding phosphonic dichlorides have been reported.[4,5] Phosphinic chlorides of varying structures could also be converted to the corresponding thiono compounds by comparable procedures.[4,5] The present method is preferable to the thiophosphoryl chloride procedure[3,5] in that does not require working under pressure.

Chloromethylphosphonothioic dichloride is a reactive and useful intermediate in organophosphorus chemistry.[3,4,6] Of special interest is its desulfurization by trivalent phosphorus compounds such as phenylphosphonous dichloride leading to the formation of chloromethlphosphonous dichloride.[3]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

tetraphosphorus decasulfide

chloromethlphosphonous dichloride

nitrogen (7727-37-9)

phosphoric acid (7664-38-2)

phosphorus trichloride (7719-12-2)

phenylphosphonous dichloride (644-97-3)

Chloromethylphosphonothioic dichloride (1983-27-3)

chloromethylphosphonic dichloride (1983-26-2)

silicon

thiophosphoryl chloride (3982-91-0)

p-chlorophenylphosphonothioic dichloride

paraformaldehyde (30525-89-4)

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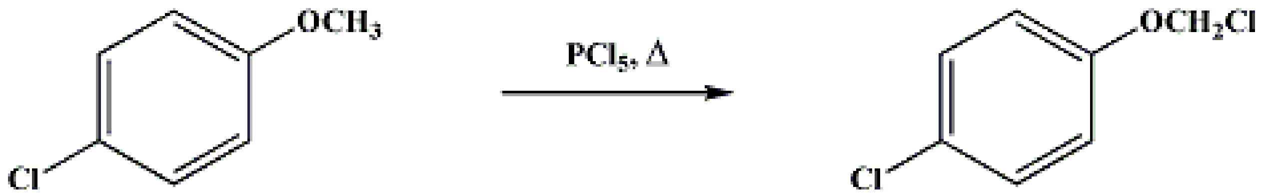
Organic Syntheses, *CV 5*, *221*

p-CHLOROPHENOXYMETHYL CHLORIDE

[Anisole, *p*-*a*-dichloro-]



Submitted by H. Gross and W. Bürger[1].
Checked by J. Longanbach and K. B. Wiberg.

1. Procedure

This preparation must be carried out in efficient hood.

A 250-ml. round-bottomed flask with a side arm is equipped with a distillation head and condenser. The receiving flask is attached to the condenser with an adapter, and the exit from the flask goes to a bubble counter containing high-boiling petroleum ether. A thermometer is inserted in the side arm of the distillation flask, and it reaches to the bottom. With exclusion of moisture, 147 g. (0.704 mole) of phosphorus pentachloride and 100 g. (0.704 mole) of *p*-chloroanisole are added to the flask. The flask is heated in an oil bath; the reaction begins when the inside temperature reaches 120° and occurs rapidly at 140°. The temperature is raised to 160° over a period of 2 hours, thereby distilling the phosphorus trichloride (Note 1). After the gas evolution subsides, the reaction mixture is heated to 175° for a short time. About 73–75 g. of phosphorus trichloride is collected.

The residue is distilled through a 30-cm. column packed with glass beads giving 10 g. of a fraction, b.p. 85–105° (10 mm.), containing mainly *p*-chloroanisole, and 85–99 g. (68–80%) of *p*-chlorophenoxymethyl chloride, b.p. 105–108° (10 mm.), $n^{23}\text{D}$ = 1.5496, m.p. 28–29° (Note 2), (Note 3). The n.m.r. spectrum [CCl_4, $(CH_3)_4Si$ reference] had bands at δ 5.6 (*s*, 2H) and 6.6–7.3 p.p.m.

2. Notes

1. Some phosphorus pentachloride may solidify in the upper part of the condenser. This may be removed by rotating the condenser.

2. The literature values are b.p. 120–124 (18 mm.), m.p. 29–30°.[2]

3. Gas chromatography analysis using a silicone gum column indicated the product to be 97% pure.

3. Discussion

Aryloxymethyl chlorides may be prepared by the reaction of sodium aryloxymethanesulfonates with phosphorus pentachloride.[2,3] The chlorination of anisole does not, as previously reported,[4] give phenoxymethyl chloride, but rather a mixture of *p*- and *o*-chloroanisoles.[5] Similarly, anisole and other unsubstituted methyl aryl ethers undergo ring chlorination with phosphorus pentachloride and chlorine,[6] whereas ring-chlorinated anisoles, such as *p*-chloroanisole, undergo chlorination at the methyl group with chlorine at 190–195° in the presence of a catalytic amount of phosphorus pentachloride.[6] Ring-nitrated aryloxymethyl chlorides may be obtained by the aluminum chloride-catalyzed decarbonylation of the corresponding aryloxyacetyl chlorides.[7,8]

The present method is simple, proceeds easily and in good yield to give a single product. It is applicable to other cases, such as the preparation of 2,4-dichlorophenoxymethyl chloride (89–92%). The chlorination of *p*-chloroanisole with chlorine and phosphorus pentachloride gives considerable amounts of *p*-chlorophenoxydichloromethane which is difficult to separate from the desired compound by distillation.

The reaction of chloromethyl aryl ethers with nucleophilic reagents has been described by Barber *et al.*[2] Thus, by reaction with thiourea, potassium thiocyanate, or sodium cyanide, there are obtained aryloxyalkylisothiouronium salts, aryloxyalkyl thiocyanates, and aryloxyalkylacetonitriles, respectively.[2] With silver sulfonates the sulfonic acid esters of aryloxymethanols may be obtained.[8] The reaction of chloromethyl aryl ethers with butyllithium leads to an aryloxycarbene which on reaction with olefins gives aryloxycyclopropanes.[3] The ethers react with triphenylphosphine and a base to give phenoxymethylene ylides which are useful in converting carbonyl compounds to aromatic enol ethers.[9] The reaction of the chloro ethers with trialkylphosphites gives aryloxymethanephosphonates.[10] Most of these reactions have been studied with phenoxymethyl chloride and the *p*-methyl derivative; they also proceed well and in good yield with the readily obtainable *p*-chlorophenoxymethyl chloride.[10]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

phosphorus pentachloride (10026-13-8)

sodium cyanide (143-33-9)

Anisole (100-66-3)

chlorine (7782-50-5)

phosphorus trichloride (7719-12-2)

potassium thiocyanate (333-20-0)

thiourea (62-56-6)

butyllithium (109-72-8)

p-chloroanisole (623-12-1)

triphenylphosphine (603-35-0)

phenoxymethyl chloride

2,4-dichlorophenoxymethyl chloride

p-Chlorophenoxymethyl chloride, Anisole, p-a-dichloro- (21151-56-4)

p-chlorophenoxydichloromethane

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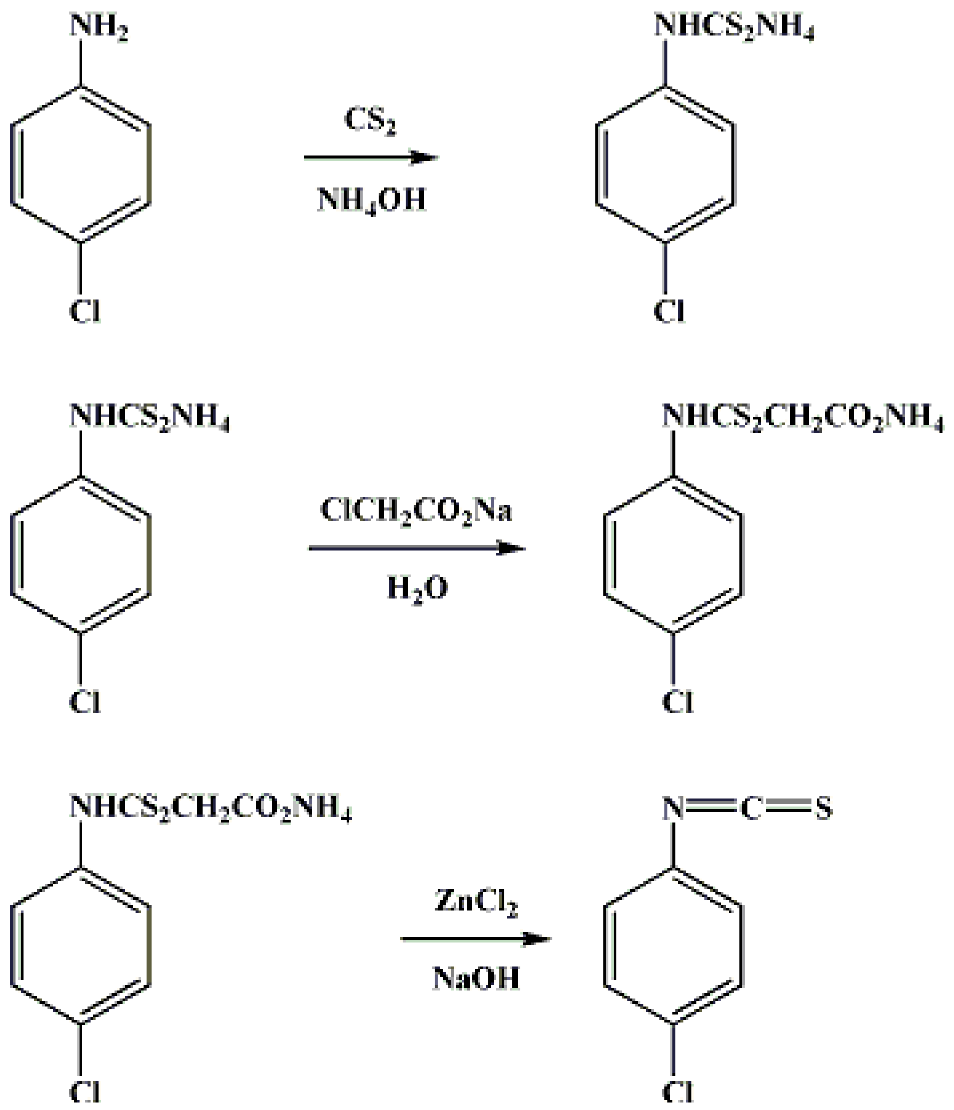
Organic Syntheses, *CV 5, 223*

p-CHLOROPHENYL ISOTHIOCYANATE

[Isothiocyanic acid, *p*-chlorophenyl ester]



Submitted by G. J. M. van der Kerk, C. W. Pluygers, and G. de Vries[1].
Checked by W. S. Wadsworth, Jr. and William D. Emmons.

1. Procedure

Caution! p-Chlorophenyl isothiocyanate may cause severe dermatitis if allowed to come in contact with the skin. This preparation should be carried out in a good hood, and rubber gloves should be worn throughout.

In a 250-ml. round-bottomed flask fitted with mechanical stirrer, reflux condenser, and thermometer are placed 38.3 g. (0.30 mole) of *p*-chloroaniline (Note 1), 41 ml. (0.6 mole) of concentrated aqueous ammonia (sp. gr. 0.9), and 21 ml. (0.35 mole) of

carbon disulfide. The mixture is stirred vigorously, and when it is heated to 30° the reaction starts. The temperature is maintained at 30–35° by external cooling (Note 2). The reaction mixture turns into a deep-red turbid solution within a few minutes, and then suddenly a heavy yellow precipitate of ammonium *p*-chlorophenyldithiocarbamate separates. To the mixture 15 ml. of water is added, and stirring is continued for 1 hour. The mixture is filtered with suction, and the residue is washed with two 30-ml. portions of a 3% aqueous solution of ammonium chloride and with two 15-ml. portions of 96% ethanol.

The ammonium *p*-chlorophenyldithiocarbamate obtained is transferred immediately to a 1-l. beaker fitted with an efficient mechanical stirrer. Water (250 ml.) is added, and the temperature is raised to 30°. A solution of 28.4 g. (0.30 mole) of chloroacetic acid in 30 ml. of water is neutralized with sodium carbonate [18.6 g. (0.15 mole) of $Na_2CO_3 \cdot H_2O$ in 70 ml. of water] and is added to the well-stirred dithiocarbamate suspension over a 10-minute period (Note 3). In the beginning the suspension gradually becomes less viscous, but at the end of the addition it rapidly turns into a creamy mass. Another 250 ml. of water is added to facilitate stirring, which is continued for 1 hour after the addition at about 30°.

The creamy suspension is allowed to cool to room temperature, and the electrodes of a pH meter are inserted (Note 4). A solution of 20.5 g. (0.15 mole) of zinc chloride (Note 5) in 75 ml. of water is added dropwise with vigorous stirring over a period of 45 minutes, while the pH is maintained at 7 by the simultaneous dropwise addition of a 4*N* aqueous solution of sodium hydroxide (Note 6). The mixture is stirred for 1 hour and is then filtered with suction; the solid product is dried under reduced pressure over phosphorus pentoxide. The dry material is slurried with 200 ml. of petroleum ether (b.p. 30–60°), and the solvent is decanted. This process is repeated five times, and the combined extract is evaporated at reduced pressure. The yield of almost pure *p*-chlorophenyl isothiocyanate, obtained as a readily crystallizing oil with a pleasant anise-like odor, is 33–35 g. (65–68%), m.p. 44–45°. The product can be recrystallized from the minimum amount of ethanol at 50°.

2. Notes

1. A commercial grade (Eastman Organic Chemicals, white label) of *p*-chloroaniline was used without further purification.
2. The reaction is conveniently started by dipping the flask in a hot-water bath. The reaction temperature is easily maintained by occasional dipping of the flask in a cold-water bath.
3. Any free chloroacetic acid leads to the formation of N-*p*-chlorophenylrhodanine.
4. A Beckman pH meter (Model N) was used.
5. The anhydrous zinc chloride used was obtained from Baker and Adamson, reagent grade.
6. The pH must not drop below 7, although a slightly higher pH does no harm;

addition of the zinc chloride in a shorter time lowers the yield.

3. Discussion

The procedure given here is essentially that described previously by the submitters.[2] *p*-Chlorophenyl isothiocyanate has been prepared from *sym*-di-*p*-chlorophenyl thiourea with iodine in alcoholic solution,[3] from ammonium *p*-chlorophenyldithiocarbamate and lead nitrate[4] [cf. also *Org. Syntheses*, Coll. Vol. **1** 447 (1932)], by the action of thiophosgene on *p*-chloroaniline[5] and from *p*-chloroaniline with thiocarbonyl tetrachloride in the presence of stannous chloride.[6]

4. Merits of the Preparation

The present method has the advantage that the whole process can be carried out in aqueous medium at low temperatures. The procedure is also attractive because of the reagents used and the relatively simple isolation procedure employed. The only restriction observed is that the formation of the aromatic dithiocarbamate must be possible.

Other isothiocyanates obtained by this method are: phenyl isothiocyanate (65%), *p*-phenylene diisothiocyanate (71%), *p*-acetylaminophenyl isothiocyanate (73%), *p*-ethoxyphenyl isothiocyanate (64%), and *p*-bromophenyl isothiocyanate (55%).

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

sym-di-p-chlorophenyl thiourea

ethanol (64-17-5)

ammonia (7664-41-7)

ammonium chloride (12125-02-9)

sodium hydroxide (1310-73-2)

sodium carbonate (497-19-8)

stannous chloride

chloroacetic acid (79-11-8)

iodine (7553-56-2)

lead nitrate (10099-74-8)

carbon disulfide (75-15-0)

zinc chloride (7646-85-7)

Thiophosgene (463-71-8)

PHENYL ISOTHIOCYANATE (103-72-0)

p-Chlorophenyl isothiocyanate, Isothiocyanic acid, p-chlorophenyl ester (2131-55-7)

thiocarbonyl tetrachloride

p-chloroaniline (106-47-8)

phosphorus pentoxide (1314-56-3)

ammonium p-chlorophenyldithiocarbamate

p-bromophenyl isothiocyanate (1985-12-2)

N-p-chlorophenylrhodanine

p-phenylene diisothiocyanate (4044-65-9)

p-acetylaminophenyl isothiocyanate

p-ethoxyphenyl isothiocyanate (3460-49-9)

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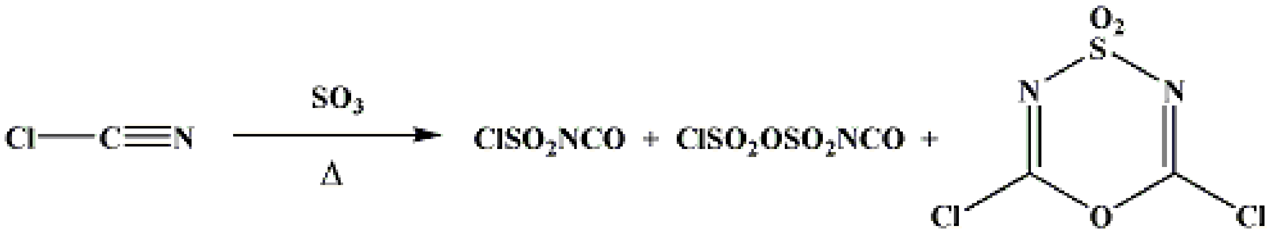
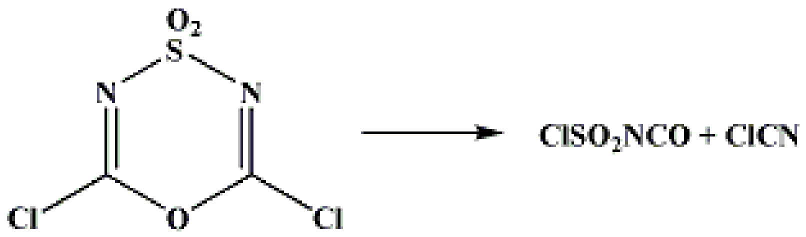
CHLOROSULFONYL ISOCYANATE

[Isocyanic acid, anhydride with chlorosulfonic acid]





Submitted by Roderich Graf[1]
Checked by Jerome F. Levy and William D. Emmons.

1. Procedure

Caution! Cyanogen chloride is extremely toxic. Sulfur trioxide and chlorosulfonyl isocyanate are highly corrosive materials. This preparation should be carried out in an efficient hood, and rubber gloves should be worn throughout.

A 200-ml. four-necked flask is fitted with a mechanical stirrer (Note 1), a thermometer, a Claisen-type adapter bearing a dry ice reflux condenser and a dropping funnel, and a gas-inlet tube consisting of a length of 6-mm. glass tubing extending almost to the bottom of the flask. This gas-inlet tube is connected through a stopcock to a safety trap and then to a cylinder of cyanogen chloride (Note 2). The dropping funnel, protected with a calcium chloride drying tube, is charged with 64 g. (0.80 mole) of liquid sulfur trioxide (Note 3). The outlet from the dry ice condenser is connected to a trap cooled in dry ice.

The flask is charged with approximately 36.9 g. (0.60 mole) of cyanogen chloride while being cooled in a dry ice-methylene chloride slush bath (Note 4). The flask is allowed to warm to –5° to melt the cyanogen chloride, and then the liquid sulfur trioxide is added over a period of 0.75–1.25 hours. The reaction is very exothermic. During the addition the temperature is gradually decreased from –5° to –15° (Note 5). After addition is completed, the reaction mixture is checked for unreacted sulfur trioxide by adding approximately 1–2 g. of cyanogen chloride and noting if a temperature rise takes place. If necessary, this test is

repeated until no more unreacted sulfur trioxide is left. The reaction mixture at this point is a pulpy, stirrable mass containing some chlorosulfonyl isocyanate, some chloropyrosulfonyl isocyanate, and much precipitated 2,6-dichloro-1,4,3,5-oxathiadiazine-4, 4-dioxide (Note 6).

The adapter bearing the dry ice condenser and dropping funnel is removed and replaced by a 16 cm. × 2 cm. distillation column packed with glass helices (Note 7) and connected to an efficient air-cooled condenser. The condenser has a 100-ml. receiver and is connected to a trap cooled in dry ice and protected by a drying tube to condense unreacted cyanogen chloride. The reaction flask is heated for about 1 hour while the temperature is gradually increased to 110–115°. At this point, cyanogen chloride is bubbled into the reaction mixture at the rate of about 0.010 mole/min (Note 8). The temperature of the flask is raised to 120–130°, whereupon chlorosulfonyl isocyanate begins to distil at a head temperature of 90–105°. When the distillation rate begins to slacken, and after most of the contents of the flask has distilled, the temperature of the flask is raised to 130–150°. When the residue in the flask is only 3–5 ml., the cyanogen chloride flow is discontinued and the distillation is stopped. This part of the reaction (from the start of the cyanogen chloride feed) requires about 0.4–0.6 mole of cyanogen chloride and takes about 0.75–1 hour.

The crude product, which may contain dissolved cyanogen chloride, is redistilled at a pressure of 100 mm. through the helices-packed column. Heating is done very slowly at first to allow the unreacted cyanogen chloride to distil and be condensed in the dry ice trap. The product is collected at 54–56° (100 mm.); d_4^{20} 1.626, weight 67.7–69.9 g. (60–62%) (Note 9),(Note 10),(Note 11).

2. Notes

1. The lubricant for the ground-glass sleeve of the stirrer may be silicone oil or mineral oil; however, Teflon® oil is preferred. Glycerin should not be used.
2. The checkers used cyanogen chloride supplied in a metal cylinder by the American Cyanamid Co., Bound Brook, New Jersey. The submitter prepared cyanogen chloride beforehand[2] and either charged it as a liquid or allowed it to distil in as is required later in the reaction.[3]
3. The checkers used Sulfan®, a stabilized liquid form of sulfur trioxide which is commercially available from Baker and Adamson, General Chemical Division, Allied Chemical Corp., Morristown, New Jersey. The submitter distilled sulfur trioxide from 65% oleum directly into the reaction flask, a procedure which is described elsewhere.[3]
4. Chlorosulfonyl isocyanate reacts violently with water. For safety reasons, therefore, it is recommended that either air or dry ice mixtures be used for all cooling condensers and cooling baths. The dry ice may be mixed with methylene chloride. Acetone is not recommended, as chlorosulfonyl isocyanate may react with it.
5. Too much cooling in the early stages of the reaction may cause the cyanogen chloride to crystallize. Furthermore, if the reaction mixture is cooled to substantially lower than –15°, *e.g.*, to –30° or –40°, the rate of reaction will decrease to the extent that there is danger of an uncontrollable delayed reaction.

6. At this point the reaction mixture may be stored protected from atmospheric moisture for an unlimited length of time before converting it to chlorosulfonyl isocyanate.
7. It is highly desirable to heat the distillation column with an electrical heating tape to compensate for heat loss. A 6 ft. × in., 288-watt heating tape available from Briscoe Manufacturing Co., Columbus, Ohio, was used by the checkers. This should not be necessary when the reaction is conducted on a larger scale.
8. A flowmeter calibrated for use with air was used. Although this introduces some degree of error, it is adequate for the preparation.
9. The submitter conducted the reaction on ten times the scale indicated here and obtained yields of 88–93%. The checkers, however, on a scale of 0.80 mole, reproducibly obtained the lower yields indicated.
10. For storage over a short time, glass bottles sealed with rubber stoppers that are covered with polyethylene sheet are adequate. Ground-glass stoppers, even if thoroughly coated with silicone grease, will soon become frozen. For storage over moderate periods of time (several weeks) low-pressure polyethylene may be used. If traces of sulfur trioxide are present, the walls of the polyethylene vessel will soon become black; if more than 2% of cyanogen chloride is present, the polyethylene is attacked without a change in color, and its surface is converted to a crumbly mass. For storage over a long period of time, Teflon® FEP bottles available from the Nalge Co., Inc., Rochester, New York, or sealed-glass ampoules may be used.
11. Chlorosulfonyl isocyanate is a colorless, fluid liquid which fumes slightly in moist air. The vapors have a tussive effect. The compound shows an extraordinarily violent, almost explosive-like reaction with water. The contact of a small amount of the compound with the skin has no deleterious effect if it is rapidly removed by rinsing with plenty of water. Contacts which last longer than a few seconds may result in severe burns. Cotton fabrics will char immediately on contact with the compound and produce a dense smoke. A specific toxic effect other than the purely cauterizing effect of the compound has not been observed by the submitter during the past 10 years.

3. Discussion

The present procedure corresponds to the method described earlier by Graf.[3]

4. Merits of the Preparation

The cycloaddition of chlorosulfonyl isocyanate to olefins, followed by removal of the N-sulfonyl chloride group of the resulting β-lactam-N-sulfonyl chloride, offers a convenient synthesis of a large number of β-lactams unsubstituted on nitrogen.[4,5,6] Also produced in the reaction with olefins are unsaturated carboxamide-N-sulfonyl chlorides, which, like the β-lactam-N-sulfonyl chlorides, may be worked up in various ways to give a variety of products.[5,6] The reagent has also been added to 1,3-dienes,[7] cycloheptatriene,[8] and acetylenes.[9] Photochemical reactions with olefins have also been reported.[10] Chlorosulfonyl isocyanate reacts with aldehydes, *e.g.*, benzaldehyde, to give imine-N-sulfonyl chlorides which will undergo cycloaddition reactions with ketene or dimethyl ketene to give, after removal of the sulfonyl chloride group, β-lactams also.[5]

Compounds containing active hydrogens react with chlorosulfonyl isocyanate first at the isocyanate group to give N-substituted sulfamyl chlorides which may react further with more active hydrogen compound at the sulfonyl chloride group.[3,7,8,9,10]

The reactions of chlorosulfonyl isocyanate have been reviewed.[11,12]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 673
- Org. Syn. Coll. Vol. 6, 304
- Org. Syn. Coll. Vol. 6, 465
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Isocyanic acid, anhydride

chloropyrosulfonyl isocyanate

chlorosulfonic acid (7790-94-5)

sulfur trioxide (7446-11-9)

glycerin (56-81-5)

nitrogen (7727-37-9)

benzaldehyde (100-52-7)

acetone (67-64-1)

Ketene (463-51-4)

methylene chloride (75-09-2)

cyanogen chloride (506-77-4)

dimethyl ketene (598-26-5)

CHLOROSULFONYL ISOCYANATE (1189-71-5)

2,6-dichloro-1,4,3,5-oxathiadiazine-4, 4-dioxide

cycloheptatriene (544-25-2)

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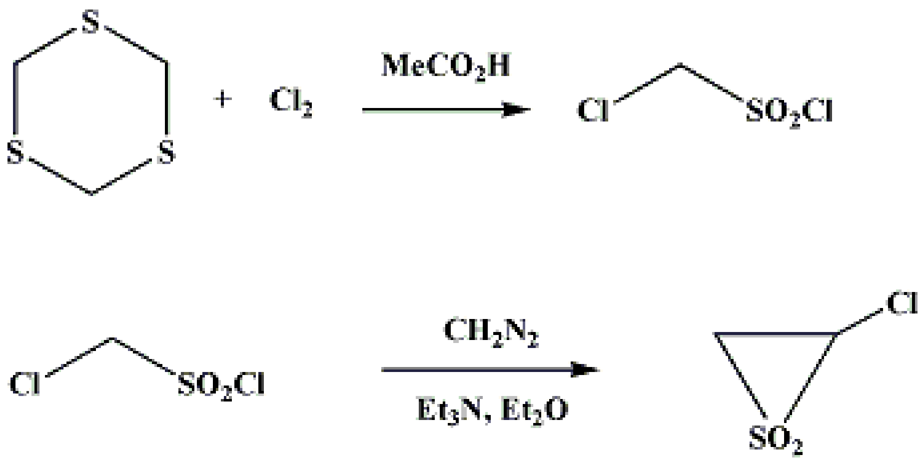
2-CHLOROTHIIRANE 1,1-DIOXIDE

[Thiirane, 2-chloro-, 1,1-dioxide]



Submitted by Leo A. Paquette and Lawrence S. Wittenbrook[1].
Checked by John J. Miller and William D. Emmons.

1. Procedure

Caution! Because of the toxic nature of chlorine and diazomethane and the lachrymatory properties of chloromethanesulfonyl chloride, both steps of this preparation should be carried out in a well-ventilated hood. Diazomethane is also explosive; follow the directions for its handling given in earlier volumes.[2,3]

A. *Chloromethanesulfonyl chloride*. A slurry of 210 g. (1.52 moles) of *s*-trithiane (Note 1) in a mixture of 1 l. of glacial acetic acid and 210 ml. of water is prepared in a 2-l., three-necked, round-bottomed flask equipped with an efficient mechanical stirrer, a thermometer, a coarsely fritted gas inlet tube (Note 2). and an exit tube by which excess fumes are carried to the rear of the hood. The flask is immersed in an ice bath, and the stirrer is started. A stream of chlorine is introduced at such a rate (Note 3) that the temperature of the mixture is maintained between 40° and 50° by the mildly exothermic reaction. After 1–2 hours a yellow solution results. To this solution is added 300 ml. of water, at which point the temperature rises to *ca*. 60°.

Chlorine is again introduced, and the stirred reaction mixture is cooled to maintain the temperature initially in the vicinity of 40°. During 3 hours the temperature slowly returns to that of the surroundings, and the stream of chlorine is stopped. The yellow solution is allowed to stand overnight at room temperature and is then transferred to a 4-l. Erlenmeyer flask and diluted with 1.5 l. of ice water. The flask is stoppered and placed in a refrigerator for 2–3 hours. The aqueous phase is decanted from the denser, organic layer that has separated (Note 4) and is extracted with four 300-ml. portions of

methylene chloride. The methylene chloride extracts are combined with the original organic layer, dried over anhydrous magnesium sulfate, filtered, and evaporated on a rotary evaporator at 20–30°. The material that remains is distilled through a 15-cm. Vigreux column. Chloromethanesulfonyl chloride is collected as a colorless, lachrymatory liquid, b.p. 80–81° (25 mm.), n^{26}D 1.4840–1.4850; yield 135–220 g. (20–32%) (Note 5).

B. *2-Chlorothiirane 1,1-dioxide*. In a 500-ml., three-necked, round-bottomed flask fitted with an efficient mechanical stirrer, a thermometer, and two pressure-equalizing addition funnels is placed an ethereal solution of 4.6 g. (0.11 mole) of diazomethane (Note 6). The system is blanked with nitrogen, the stirrer is started, and the solution is cooled to −10° with an ice-methanol bath. A solution of 14.9 g. (0.100 mole) of chloromethanesulfonyl chloride in 40 ml. of ether and a solution of 10.0 g. (0.099 mole) of triethylamine in 40 ml. of ether are simultaneously added dropwise from the two addition funnels. The addition requires about 45 minutes. The insoluble triethylamine hydrochloride is separated by filtration and washed with 25 ml. of cold ether. The combined filtrate and washings are evaporated at reduced pressure below 25° to give white crystalline 2-chlorothiirane 1,1-dioxide, m.p. 49–51° (Note 7); yield 10.0–10.5 g.. (80–84%). The product may be further purified by recrystallization from ether-hexane at –70°; m.p. 53–54° (8.9 g. after two recrystallizations) (Note 8) and (Note 9).

2. Notes

1. *s*-Trithiane obtained from Eastman Organic Chemicals was used without further purification.
2. The gas inlet tube must be sufficiently long to allow the chlorine to enter near the bottom of the flask, and sufficiently coarse to prevent the pores from becoming clogged by the suspended *s*-trithiane. A 6-mm. glass tube with a slightly constricted orifice has been found to be equally satisfactory.
3. The rate of addition of chlorine appears to be important. With rates adequate to maintain the temperature between 40° and 50°, addition times of 1–2 hours are required.
4. This separation is most conveniently achieved by first decanting as much water as possible from the 4-l. Erlenmeyer flask. The remaining mixture is then placed in a 4-l. separatory funnel, and the lower layer is collected. The separatory funnel is then used in the ensuing extractions.
5. The yield is based on the assumption that 3 molecules of chloromethanesulfonyl chloride arise from each molecule of *s*-trithiane. The checkers obtained a yellow product which had to be redistilled to provide material with the reported refractive index.
6. The ethereal diazomethane is prepared by the method of Arndt.[4] The checkers employed undistilled material as described in (Note 3) of the preparation cited.
7. Use of undistilled diazomethane solution gives a less pure product, m.p. 38–42°, which can be recrystallized as described.

8. The characteristic infrared maxima of 2-chlorothiirane 1,1-dioxide (Nujol) occur at 3.24, 7.53, and 8.56 •. Its n.m.r. spectrum ($CDCl_3$) shows a doublet of doublets at δ 3.17 (J = 9.5 and 5.5 Hz), a triplet at δ 3.75 (J = 9.5 Hz), and a doublet of doublets at δ 4.85 (J = 9.5 and 5.5 Hz).

9. A characteristic property of thiirane 1,1-dioxides is the ease with which such molecules fragment into sulfur dioxide and the related olefin on standing for several hours at room temperature. The title compound is no exception; however, the rate of decomposition may be reduced substantially by storage under an inert atmosphere in a freezing compartment (*ca.* −5°). Under such conditions the product may be kept for many months.

3. Discussion

2-Halothiirane 1,1-dioxides are known to be intermediates in the Ramberg-Bäcklund rearrangement of α,α-dihalo sulfones.[5,6,7,8] These three-membered cyclic sulfones are not isolable from such reactions, however, because they are not stable under the conditions of the rearrangement and they undergo further transformations. The present procedure represents the only means presently available for the preparation of halogen-substituted thiirane dioxides.[5,6,9] The addition of halosulfenes to diazoalkanes is a convenient and general synthesis which may be extended to the preparation of a variety of thiirane 1,1-dioxides with relative ease.[10]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

acetic acid (64-19-7)

ether (60-29-7)

sulfur dioxide (7446-09-5)

nitrogen (7727-37-9)

chlorine (7782-50-5)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

Diazomethane (334-88-3)

hexane (110-54-3)

triethylamine (121-44-8)

Triethylamine hydrochloride (554-68-7)

2-Chlorothiirane 1,1-dioxide, Thiirane, 2-chloro-, 1,1-dioxide (10038-13-8)

chloromethanesulfonyl chloride (3518-65-8)

s-trithiane (291-21-4)

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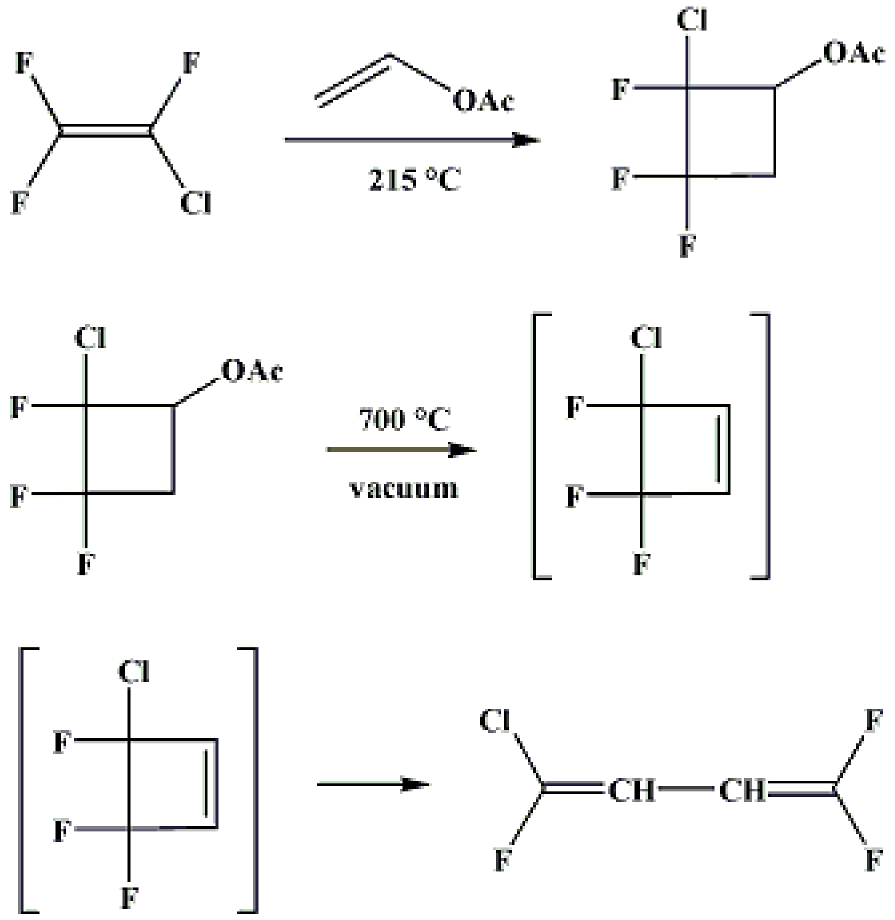
1-CHLORO-1,4,4-TRIFLUOROBUTADIENE

[Butadiene, 1-chloro-1,4,4-trifluoro-]



Submitted by R. E. Putnam, B. C. Anderson, and W. H. Sharkey[1].
Checked by R. D. Birkenmeyer, M. A. Rebenstorf, and F. Kagan[2].

1. Procedure

A. *2-Chloro-2,3,3-trifluorocyclobutyl acetate* (Note 1). A mixture of 1.0 g. of hydroquinone, 3 drops of a terpene inhibitor (Note 2), and 140 g. (1.63 moles) of inhibited redistilled vinyl acetate (Note 3) is placed in a 400-ml. high-pressure shaker tube lined with stainless steel (Note 4). The shaker tube is closed, cooled in a mixture of solid carbon dioxide and acetone, evacuated, and charged with 47 g. (0.40 mole) of chlorotrifluoroethylene (Note 5). The shaker tube is heated with agitation to 215° in a period of about 1 hour and is then heated at 215° for 3 hours. The shaker tube is cooled to room temperature and is bled slowly to remove excess chlorotrifluoroethylene. The black, viscous reaction mixture (Note 6) is transferred to a distillation flask and heated on a steam bath. After a fore-run of dichlorohexafluorocyclobutane and vinyl acetate is collected at atmospheric pressure, a receiver cooled in solid carbon dioxide and

acetone is attached, and crude 2-chloro-2,3,3-trifluorocyclobutyl acetate is rapidly distilled by gradually reducing the pressure to about 10 mm. (Note 7). Redistillation through a 30-cm. column packed with glass helices provides 22–30 g. (27–37%) (Note 8) of the acetate, b.p. 60–65°/100 mm., n_D^{25} 1.3916–1.3921.

B. *1-Chloro-1,4,4-trifluorobutadiene*. The apparatus is similar to that described in a previous volume.[3] It consists of a "Vycor" glass reaction tube, 60 cm. long by 25 mm. outside diameter, mounted vertically in an electric furnace about 35 cm. long (Note 9). Attached to the top of the tube is a graduated dropping funnel. A thermocouple well extending to the center of the heated section is inserted through the bottom of the tube. The heated section of the tube is packed with quartz tubing (8 mm. outside diameter), cut into 0.5-cm. lengths, and held in place by indentations in the tube. Ten centimeters from the bottom of the tube is a side arm leading successively to two traps cooled with solid carbon dioxide and acetone, an inlet tube for nitrogen, a manometer, and a vacuum pump.

The system is evacuated to a pressure of 5–10 mm., and the tube is heated to 700°, measured at the center of the heated zone. 2-Chloro-2,3,3-trifluorocyclobutyl acetate is admitted at the rate of 10–20 g. per hour. From 70 g. (0.35 mole) of the cyclobutyl acetate there is obtained 62–68 g. of mixed solid and liquid condensate (Note 10). Fractionation through a 30-cm. column packed with glass helices affords 30–35 g. (60–70%) of 1-chloro-1,4,4-trifluorobutadiene (Note 11), b.p. 50–51°, n_D^{25} 1.3870; 18–22 g. of acetic acid; and 7–18 g. of recovered 2-chloro-2,3,3-trifluorocyclobutyl acetate (Note 12).

2. Notes

1. The exact structure of the cyclobutane is not known. Any of the possible isomers would undergo pyrolysis to give 1-chloro-1,4,4-trifluorobutadiene. 2-Chloro-2,3,3-trifluorocyclobutyl acetate is now favored as the structure of the cycloadduct rather than 3-chloro-2,2,3-trifluorocyclobutyl acetate as originally proposed.[4] The basis for this preference is mass spectral data. Ions of *m/e* 64 $[(CF_2{=}CH_2)^+$, relative abundance 1.2%] and 138 $[(CFCl{=}CHOCOCH_3)^+$, relative abundance 0.96%] were much more abundant than ions of *m/e* 80 $[(CFCl{=}CH_2)^+$, relative abundance 0.10%] and 122 $[(CF_2{=}CHOCOCH_3)^+$, relative abundance 0.026%].
2. The purpose of the terpene is to inhibit polymerization of the fluoroölefin. Terpenes that are effective include dipentene and terpinolene.
3. Ordinary commercial-grade vinyl acetate is redistilled. One gram of hydroquinone per 100 g. of vinyl acetate is added to inhibit polymerization of the latter, which is then stored at 0–4° until needed.
4. A shaker tube equipped with a 1200-atm. rupture-disk assembly was used by the submitters. The checkers used a 1270-ml. stainless steel rocking autoclave fitted with a thermocouple well that extended into the reaction mixture and a stainless steel 5000-p.s.i. rupture disk. The agitation rate was 58 cycles per

second. Attempts to use a magnetically stirred autoclave were unsuccessful.
5. Chlorotrifluoroethylene is available in 1-lb. and 5-lb. cylinders from the Matheson Company, East Rutherford, New Jersey.
6. The checkers found the reaction mixture to be dark but not viscous. In experiments in which a magnetically stirred autoclave was used, dark viscous reaction mixtures were obtained, but no product.
Difficulties encountered by the checkers when they used a magnetically stirred autoclave led the submitters to re-examine the reaction. It was found that certain batches of vinyl acetate gave very poor yields. In these cases, 27–37% yields were obtained by heating to 175° in 1 hour followed by heating at 175° for 16 hours.
7. The quantity of fore-run depends on the amount of polymerization of vinyl acetate. Distillation of the product through a packed column goes more smoothly, with less heat having to be applied to the distillation flask, if the product has been separated from high-boiling material by a quick preliminary distillation.
8. Up to 25% by weight of the product is ethylidene diacetate. The diacetate can be detected by gas chromatographic analysis using a column of the diglyceride of 6,6,6-trifluorohexanoic acid on firebrick at 120°.[5] The checkers obtained yields ranging from 24% in a 0.75-scale experiment to 47% on a three-fold increase in scale.
9. A standard tube furnace such as the 120-volt "Multiple Unit" electric furnace manufactured by the Hevi Duty Electric Company was used.
10. Care must be taken to prevent plugging of the first cold trap by solid acetic acid because the back-pressure produced leads to greatly reduced yields and appreciable carbonization. Should plugging occur, the cooling bath is removed and the plug is melted with warm acetone. Some diene will distil into the second trap during this process.
11. 1-Chloro-1,4,4-trifluorobutadiene is a mixture of equal amounts of *cis* and *trans* isomers. This has been demonstrated by gas chromatographic analysis of the mixture on a packed column of high efficiency using Dow-Corning silicone 703 oil or 200 oil on firebrick, or on a capillary gas chromatographic column using squalane as the partitioning liquid.
12. The checkers did not isolate any recovered 2-chloro-2,3,3-trifluorocyclobutyl acetate.

3. Discussion

The procedure for chlorotrifluorocyclobutyl acetate[4] is a modification of one used by Coffman, Barrick, Cramer, and Raasch[6] for the preparation of tetrafluorocyclobutanes from tetrafluoroethylene.

The method for the pyrolysis of chlorotrifluorocyclobutyl acetate to chlorotrifluorobutadiene is that of Anderson, Putnam, and Sharkey.[4]

4. Merits of the Preparation

The synthesis of 2-chloro-2,3,3-trifluorocyclobutyl acetate illustrates a general method of preparing cyclobutanes by heating chlorotrifluoroethylene, tetrafluoroethylene, and other highly fluorinated ethylenes with alkenes. The reaction has recently been reviewed.[7] Chlorotrifluoroethylene has been shown to form cyclobutanes in this way with acrylonitrile,[8] vinylidene chloride,[9] phenylacetylene,[10] and methyl propiolate.[4] A far greater number of cyclobutanes have been prepared from tetrafluoroethylene and alkenes;[6,7] *when tetrafluoroethylene is used, care must be exercised because of the danger of explosion.* The fluorinated cyclobutanes can be converted to a variety of cyclobutanes, cyclobutenes, and butadienes.

The synthesis of chlorotrifluorobutadiene illustrates a general method that has been used to make tetrafluorobutadiene[4,11] and substituted fluorodienes.[4,11,12] The same procedure can be used to transform fluorocyclobutenes and chlorofluorocyclobutenes to the isomeric dienes; 2-methyl-1,1,4,4-tetrafluorobutadiene, 2-chloro-1,1,4,4-tetrafluorobutadiene, and 1-chloro-1,4,4-trifluoro-2-phenylbutadiene have been made thus.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 28

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

terpene

diglyceride of 6,6,6-trifluorohexanoic acid

acetic acid (64-19-7)

hydroquinone (123-31-9)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

acetone (67-64-1)

Phenylacetylene (536-74-3)

acrylonitrile (107-13-1)

vinyl acetate (108-05-4)

Chlorotrifluoroethylene (79-38-9)

ethylidene diacetate (542-10-9)

cyclobutane (287-23-0)

1-Chloro-1,4,4-trifluorobutadiene, Butadiene, 1-chloro-1,4,4-trifluoro- (764-14-7)

dichlorohexafluorocyclobutane

2-Chloro-2,3,3-trifluorocyclobutyl acetate

cyclobutyl acetate

3-chloro-2,2,3-trifluorocyclobutyl acetate

squalane (111-01-3)

chlorotrifluorocyclobutyl acetate

tetrafluoroethylene (9002-84-0)

chlorotrifluorobutadiene

vinylidene chloride (75-35-4)

methyl propiolate (922-67-8)

tetrafluorobutadiene

2-methyl-1,1,4,4-tetrafluorobutadiene

2-chloro-1,1,4,4-tetrafluorobutadiene

1-chloro-1,4,4-trifluoro-2-phenylbutadiene

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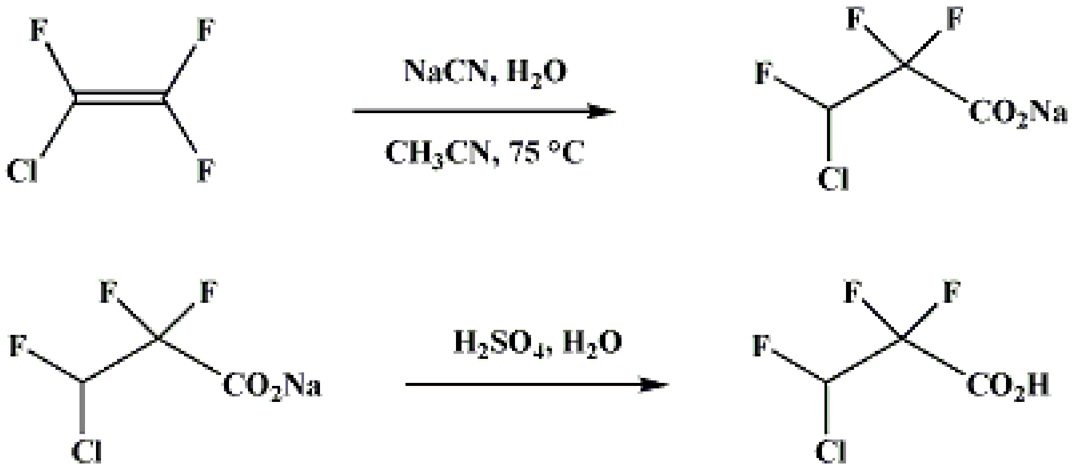
Organic Syntheses, CV 5, 239

3-CHLORO-2,2,3-TRIFLUOROPROPIONIC ACID

[Propionic acid, 3-chloro-2,2,3-trifluoro-]



Submitted by D. C. England and L. R. Melby[1].
Checked by Max Tishler and W. J. Jones.

1. Procedure

Caution! This is a strongly exothermic reaction. The reaction should be carried out in a hood. A protective shield should be placed between the operator and the reaction bottle.

A modified Parr low-pressure hydrogenation apparatus is used for this preparation.[2] The bottle is fitted with a two-holed rubber stopper through which is passed a thermocouple well made of 5-mm. glass tubing and a gooseneck made of 8-mm. heavy-walled glass tubing. The thermocouple well extends into the bottle within about 2 cm. of the bottom. The gooseneck extends 1 cm. into the bottle, and the other end is connected directly to a manifold system with heavy-walled pressure tubing using screw clamps. Also attached to the manifold system through needle valves are a vacuum line, a storage cylinder of chlorotrifluoroethylene, a pressure gauge, and a bleed line.

The bottle is charged with 52 g. (1.0 mole) of 95% sodium cyanide, 100 ml. of water, and 100 ml. of acetonitrile, giving a two-phase liquid system. After the bottle is clamped in the metal cage of the shaking apparatus, the bottle is evacuated and filled to a gauge pressure of 10 lb. (0.68 atm.) with chlorotrifluoroethylene. This procedure is repeated twice to purge the system of air. Finally, the bottle is pressured to 40 lb. (2.7 atm.), chlorotrifluoroethylene leaving the valve open to maintain this pressure (Note 1). The thermocouple is fitted into place and shaking is started. The temperature steadily increases, and in 10–15 minutes it is about 75° and rising more rapidly. It is kept at 75–80° by cooling and/or slowing the rate of chlorotrifluoroethylene addition.

Caution! Careful control of the reaction is mandatory. If the reaction rate cannot be controlled, it is imperative to shut the gas addition valve and to stop the agitation immediately. Cooling is accomplished by packing ice inside the wire cage holding the bottle and/or pouring ice water on the bottle. When cooling is used, it is possible to complete the reaction in 1 hour. When the rate of chlorotrifluoroethylene absorption is negligible and the temperature is about 30°, pressure is released through the bleed line and the bottle is removed. The gain in weight is 130–135 g. (about 1.1 moles).

The product is a dark-colored solution which is poured slowly into sulfuric acid (100 ml. of concentrated sulfuric acid in 100 ml. of water) with cooling (Note 2). *This operation should be conducted in a hood because some hydrogen cyanide may be evolved from unreacted sodium cyanide.* The mixture is then extracted four times with 100-ml. portions of ether (Note 3). The first 100 ml. of ether yields about 260 ml. of organic material, and succeeding portions about 95 ml. each. The extract is dried over about 20 g. of magnesium sulfate and distilled (Note 4). After removal of low-boiling materials, there is obtained 124–128 g. (76–79%) of crude 3-chloro-2,2,3-trifluoropropionic acid, b.p. 70–85°/30 mm.; the bulk of this fraction distills at 83°/30 mm., n_D^{25} 1.3708–1.3717. This product is of sufficient purity for most purposes (Note 5). About 25–30 g. of high-boiling residue remains which is chiefly chlorotrifluoropropionamide (Note 6).

2. Notes

1. The chlorotrifluoroethylene cylinder is fitted with a pressure-reduction valve which is set at a maximum pressure of 40 lb. (2.7 atm.).
2. The amount of product was not changed by cooling, but the acidification reaction is very exothermic and cooling is necessary before extraction with ether.
3. The checkers encountered troublesome emulsions in the extraction step. It was found helpful to filter the acidified reaction mixture through a sintered-glass funnel before ether extraction.
4. A precision distillation column is not necessary. The submitters have used an 80-cm. spinning-band column with a 10 mm. inside diameter or a 25-cm. helix-packed column of about 10 mm. inside diameter.
5. The neutral equivalent of this material is 169–173 (theory is 162.5). It is readily purified by mixing it thoroughly with 10% of its weight of phosphorus pentoxide and redistilling. The purified acid boils at 82–83°/30 mm. (159–160°/760 mm.), n_D^{25} 1.3695, N.E. 163.5. Recovery from the crude is 92%.
6. The higher-boiling material is largely 3-chloro-2,2,3-trifluoropropionamide, and some fractions crystallize at room temperature. The amide can be purified by redistillation, b.p. 111–112°/30 mm. (198–200°/760 mm.) or recrystallization from carbon tetrachloride. The pure amide melts at 41–42°. The amount of amide formed is not changed by running the above charge at a lower temperature. However, when the amount of water is reduced to 50 ml. and the temperature kept below 50°, the yield of crude acid is 38% and of amide, 21%. When the same charge is run at 80° maximum temperature, the yield of crude acid is 78% and of amide, 7%.

3. Discussion

3-Chloro-2,2,3-trifluoropropionic acid has been prepared by permanganate oxidation of 3-chloro-2,2,3-trifluoropropanol[3] which is one of the telomerization products of chlorotrifluoroethylene with methanol. The present procedure is a modification of one reported earlier[4] and is undoubtedly the method of choice for making propionic acids containing 2–4 fluorine atoms, i.e., 2,2,3,3-tetrafluoropropionic acid, 3,3-dichloro-2,2-difluoropropionic acid, and 3-bromo-2,2,3-trifluoropropionic acid. When preparing 2,2,3,3-tetrafluoropropionic acid from tetrafluoroethylene, it is desirable to use an additional 50 ml. of acetonitrile and externally applied heat to initiate the reaction.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

methanol (67-56-1)

ether (60-29-7)

acetonitrile (75-05-8)

sodium cyanide (143-33-9)

hydrogen cyanide (74-90-8)

carbon tetrachloride (56-23-5)

magnesium sulfate (7487-88-9)

Chlorotrifluoroethylene (79-38-9)

tetrafluoroethylene (9002-84-0)

3-Chloro-2,2,3-trifluoropropionic acid, Propionic acid, 3-chloro-2,2,3-trifluoro- (425-97-8)

chlorotrifluoropropionamide, 3-chloro-2,2,3-trifluoropropionamide

3-chloro-2,2,3-trifluoropropanol

3-bromo-2,2,3-trifluoropropionic acid

2,2,3,3-tetrafluoropropionic acid (756-09-2)

phosphorus pentoxide (1314-56-3)

3,3-dichloro-2,2-difluoropropionic acid

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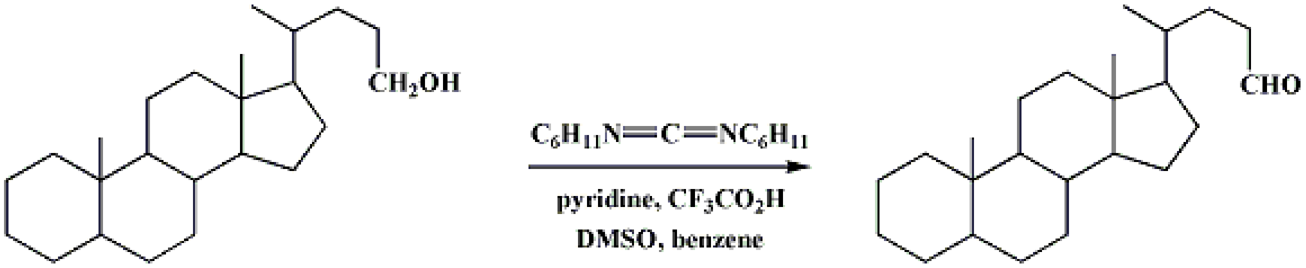
Organic Syntheses, CV 5, 242

CHOLANE-24-AL



Submitted by John G. Moffatt[1]
Checked by Robert Fairweather and Ronald Breslow.

1. Procedure

Cholane-24-ol (1.033 g., 3 mmoles) (Note 1) is dissolved by gentle warming in 10 ml. of anhydrous benzene (Note 2) in a 50-ml. flask, and 10 ml. of rigorously dried dimethyl sulfoxide (Note 3) is added. To the clear solution are added 0.24 ml. (3.0 mmoles) of anhydrous pyridine (Note 4), 0.12 ml. (1.5 mmoles) of distilled trifluoroacetic acid, and 1.85 g. (9 mmoles) of dicyclohexylcarbodiimide (Note 5), in that order. The flask is tightly stoppered and left at room temperature for 18 hours (Note 6). Benzene (30 ml.) is then added, and the crystalline dicyclohexylurea is removed by filtration (Note 7) and washed with benzene. The combined filtrates and washings are extracted three times with 50-ml. portions of water (Note 8) to remove the dimethyl sulfoxide. The organic layer is dried with sodium sulfate and evaporated to dryness under reduced pressure. There is obtained 2.12 g. of syrup which partially crystallizes. Thin-layer chromatography of this material (Note 9) shows a very intense spot of cholane-24-al, traces of starting material, and two compounds near the solvent front as well as excess carbodiimide (Note 9).

The crude product is dissolved in benzene-hexane (1:1) and applied to a column containing 125 g. of silicic acid (Note 10). Elution with the same solvent gives traces (less than 5 mg. each) of the two fast-moving components in fractions 2 and 4 (125-ml. fractions) and chromatographically pure cholane-24-al in fractions 5–8 (Note 11). Evaporation of the pooled fractions yields 870 mg. (84%) of the pure crystalline aldehyde, m.p. 102–104°. Recrystallization from 5 ml. of acetone raises the melting point to 103–104° (Note 12).

The compound gives a crystalline 2,4-dinitrophenylhydrazone, m.p. 163–164°, from ethanol.

2. Notes

1. Available from Aldrich Chemical Company.
2. Dried by storage over calcium hydride.
3. Dried by distillation under reduced pressure and storage for several days over Linde Molecular Sieves Type 4A.
4. Dried by distillation from, and storage over, calcium hydride.
5. The dry, crystalline material may be obtained from Aldrich Chemical Company. If the reagent is at all oily at room temperature, it should be distilled under reduced pressure, b.p. 140° (5 mm.).
6. Crystalline dicyclohexylurea (m.p. 234°) starts to separate after a short time. The checkers found a decrease in yield if this is allowed to run longer; a yield of 54% was found in a 22-hour reaction time.
7. Roughly 0.6–0.8 g. of the urea is usually obtained, m.p. 232–234°. The excess dicyclohexylcarbodiimide remains in the benzene. The oxidation is generally less satisfactory if less than 2.5 molar equivalents of carbodiimide is used.
8. Some further dicyclohexylurea tends to separate at the interface during the first extraction, and a clean separation of the layers near the interface is aided by mild centrifugation.
9. On Merck Silica G using benzene as the solvent and 5% ammonium molybdate in 10% sulfuric acid

followed by brief heating at 150° to develop the spots. Under these conditions cholane-24-al has an R_f of 0.76 while cholane-24-ol has R_f 0.19; dicyclohexylcarbodiimide streaks between 0.3 and 0.5.

10. Merck silica gel with 0.05–0.20 mm. particles obtained from Brinkman Instruments Inc. and packed in a 3-cm. diameter column under benzene-hexane (1:1).

11. The fractions were examined by thin-layer chromatography of 25–50 •l. aliquots as in (Note 9). The checkers found that cholane-24-al is found in fractions 4–7.

12. The compound is very soluble in most organic solvents. In order to get a high recovery, it is necessary to complete the crystallization in the deep freeze. From aqueous ethanol the aldehyde crystallized in high yield as the hemihydrate, m.p. 95°.

3. Discussion

Cholane-24-al has not been previously synthesized by other methods.

4. Merits of the Preparation

The oxidation reaction described is a very general one that may be used for the preparation of both aldehydes and ketones[2] in high yield. The reaction conditions are extremely mild and only slightly acidic, thus allowing the preparation of otherwise very unstable compounds.[2] Of particular merit is the fact that the oxidation of primary alcohols stops selectively at the aldehyde and gives no traces of acidic products. Among the many different acids that have been examined as the proton source for this type of reaction,[2] pyridinium trifluoroacetate consistently gives the best results.

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

sulfuric acid (7664-93-9)

Benzene (71-43-2)

sodium sulfate (7757-82-6)

acetone (67-64-1)

pyridine (110-86-1)

benzene-hexane (1077-16-3)

dimethyl sulfoxide (67-68-5)

calcium hydride (7789-78-8)

trifluoroacetic acid (76-05-1)

CHOLANE-24-AL (26606-02-0)

Cholane-24-ol

dicyclohexylcarbodiimide (538-75-0)

dicyclohexylurea

ammonium molybdate (13106-76-8)

pyridinium trifluoroacetate (464-05-1)

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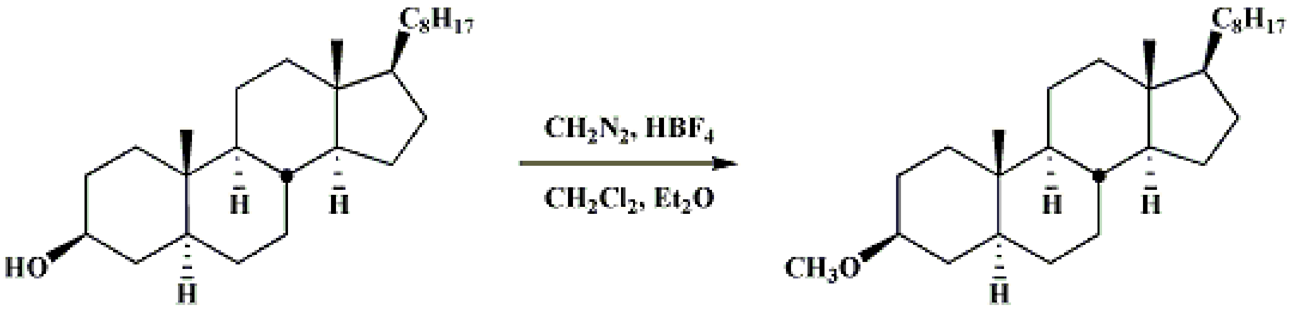
Organic Syntheses, *CV 5, 245*

CHOLESTANYL METHYL ETHER

[Cholestane, 3β-methoxy-]



Submitted by M. Neeman[1,2] and William S. Johnson[1].
Checked by F. Kaplan and John D. Roberts.

1. Procedure

To a solution of 0.200 g. (0.515 mmole) of dry dihydrocholesterol (Note 1) in 10 ml. of methylene chloride contained in a 50-ml. Erlenmeyer flask is added 0.3 ml. of a catalyst stock solution containing 0.0016 ml. (0.018 mmole) of concentrated fluoboric acid (Note 2) in 3:1 anhydrous diethyl ether-methylene chloride (Note 3). The solution is swirled, and a 0.45*M* solution of diazomethane (Note 4) in dry methylene chloride is added from a buret (Note 5) at a rate of about 2 ml. per minute. The yellow color of diazomethane disappears rapidly on contact with the reaction mixture and nitrogen is vigorously evolved. When about 3 ml. of diazomethane solution has been added, the reaction becomes sluggish. The yellow color persists for several minutes after the total amount of 3.9 ml. of diazomethane solution (1.76 mmoles) has been added (Note 6). After 1 hour the reaction mixture is filtered to remove a small amount of amorphous polymethylene, which is washed with methylene chloride. The washings are combined with the methylene chloride solution, washed with 5 ml. of saturated aqueous sodium bicarbonate, with three 5-ml. portions of water, and dried over anhydrous sodium sulfate. The solvent is removed on a steam bath in a stream of nitrogen and finally at reduced pressure. The crystalline residue of 0.207 g. (Note 7) is recrystallized in a 10-ml. conical flask from 1 ml. of acetone. When the flask has cooled to room temperature, 0.5 ml. of methanol is added, and the flask is chilled to +2° for 2 hours. The crystals are collected on a tared Hirsch funnel of 40-mm. diameter, washed on the funnel with two 0.5-ml. portions of ice-cold methanol, and dried for 2 hours at 40°/2 mm. The first crop of cholestanyl methyl ether thus obtained forms large colorless glistening plates, m.p. 85.5–86° (Note 8). An additional 0.002 g. of pure methyl ether adheres to the flask and spatula and is collected by washing with acetone. The total first crop material (0.197 g.) represents a 95% yield of methyl ether (Note 9).

2. Notes

1. Satisfactory material of melting point 143–143.5° is prepared as already described,[3] and dried for 2 hours at 110°/2 mm.
2. Commercial 50% fluoboric acid is evaporated at 50–60°/5 mm. to afford a residue of about 11*N* total acidity, which is satisfactory for use as a catalyst.
3. The catalyst stock solution should be freshly prepared by placing 19 ml. of anhydrous diethyl ether in a 25-ml. volumetric flask cooled to 0° and adding 0.133 ml. of concentrated

fluoboric acid (Note 2). The volume is made up to 25 ml. with methylene chloride.
4. Diazomethane solution in dry methylene chloride may be prepared from N-nitroso-N-methyl-N'-nitroguanidine by a procedure based on McKay's method.[4 5] Methylene chloride is substituted for diethyl ether used in the original procedure. A satisfactory solution of diazomethane is obtained, without distilling, by separating the methylene chloride layer from the reaction mixture, drying it for 2 hours over potassium hydroxide pellets, and decanting through a funnel plugged loosely with cotton. The diazomethane solution is kept in a loosely stoppered test tube immersed in a Dewar flask containing Dry Ice during the drying period and prior to use. *All handling of the highly toxic diazomethane should be done in an efficiently exhausted hood.* Attention is called to other precautions;[6] see also pp. 16.htm–17. Rigorous drying and exclusion of moisture are not necessary. The concentration of diazomethane solutions is determined by analysis,[6] using about 0.12 g. of benzoic acid per milliliter of solution and assuming a concentration of about 0.8*M* as in McKay's method.[5] Solutions approximately 0.45*M* are obtained by appropriate dilution.
5. Burets with ground-glass stopcocks should not be used, as leaking is caused by polymethylene formed preferentially on the ground surfaces. A buret such as "Ultramax F and P," having a stopcock of plastic material, is satisfactory. The buret should be filled immediately before commencement of the reaction to keep the diazomethane solution cool and thus to minimize polymerization. The technique used is very similar to that of a titration, and a number of methylations of prepared batches can be quickly performed with one filling of the buret.
6. Addition of a drop of catalyst stock solution after addition of diazomethane solution is complete causes rapid disappearance of the yellow color. The yield is not affected.
7. The crude reaction product is slightly yellow and has a very faint ammoniacal odor. It may be dissolved in acetone; on slow evaporation to dryness, the solution leaves large glistening transparent plates of good-quality cholestanyl methyl ether, m.p. 83–85°.
8. All melting points are corrected for stem exposure. Reported[7] melting point 83°.
9. The mother liquor may be evaporated to dryness and the slightly colored residue recrystallized in a 3-ml. conical flask from 6 drops of 1:1 acetone-methanol. The resulting large plates are easily transferred to a small Hirsch funnel and washed with 5 drops of methanol. This second crop of colorless methyl ether amounts to 0.010 g., m.p. 78.5–79.5°.

3. Discussion

Cholestanyl methyl ether has been prepared by catalytic hydrogenation of cholesteryl methyl ether[7,8] and of cholest-4-en-3-one in methanolic hydrobromic acid,[8] and by methylation of cholestanol with methyl iodide in the presence of "activated" silver oxide and sodium hydroxide.[9] The reported[10] formation of cholestanyl methyl ether from *epi*cholestanol in 96% yield by refluxing with "molecular" potassium in benzene and subsequent treatment with methyl iodide stands unconfirmed.[11] Methanolysis of *epi*cholestanyl tosylate afforded a 23% yield of cholestanyl methyl ether.[12] The procedure described here,[13] with slight changes in the molar proportions of the reactants, also gave a 98% yield of *epi*cholestanyl methyl ether from *epi*cholestanol, and a 95% yield of cholesteryl methyl ether from cholesterol.

4. Merits of Preparation

The present procedure is illustrative of the utility of the general method for preparation of methyl ethers from diazomethane and alcohols with fluoboric acid as catalyst.[13]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

fluoboric acid

polymethylene

epicholestanol

epicholestanyl methyl ether

epicholestanyl tosylate

Benzene (71-43-2)

methanol (67-56-1)

diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

silver oxide (20667-12-3)

HYDROBROMIC ACID (10035-10-6)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

Benzoic acid (65-85-0)

acetone (67-64-1)

potassium hydroxide pellets (1310-58-3)

potassium (7440-09-7)

Methyl iodide (74-88-4)

methylene chloride (75-09-2)

Dihydrocholesterol, cholestanol (80-97-7)

Cholesterol (57-88-5)

Diazomethane (334-88-3)

acetone-methanol (590-90-9)

Cholest-4-en-3-one (601-57-0)

N-nitroso-N-methyl-N'-nitroguanidine (674-81-7)

Cholestanyl methyl ether (1981-90-4)

Cholestane, 3β-methoxy-

diethyl ether-methylene chloride

cholesteryl methyl ether

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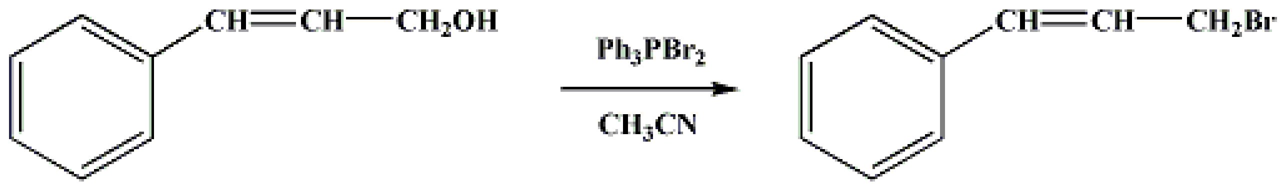
Organic Syntheses, *CV 5, 249*

CINNAMYL BROMIDE

[Benzene, 3-bromopropenyl-]



Submitted by John P. Schaefer, J. G. Higgins, and P. K. Shenoy[1].
Checked by R. Breslow and J. T. Groves.

1. Procedure

A 1-l., three-necked, round-bottomed flask equipped with a Trubore stirrer, a pressure-equalizing dropping funnel, and a reflux condenser with a drying tube is charged with 350 ml. of acetonitrile (Note 1) and 106.4 g. (0.41 mole) of triphenylphosphine (Note 2). The flask is cooled in an ice-water bath (Note 3), and 64 g. (0.40 mole) of bromine is added dropwise over a period of *ca.* 15–20 minutes (Note 4) and (Note 5). The ice-water bath is removed, and a solution of 54 g. (0.40 mole) of cinnamyl alcohol in 50 ml. of acetonitrile is added in portions over a period of 5–10 minutes with continued stirring (Note 6). The solvent is removed by distillation with the use of a water aspirator (30–40 mm.) and an oil bath until the bath temperature reaches 120°. The water aspirator is replaced by a vacuum pump and the water-cooled condenser with an air condenser, and the distillation is continued with rapid stirring (Note 7), (Note 8), and (Note 9). Most of the product (Note 10) distills at 91–98° (2–4 mm.), and about 59 g. of product crystallizes in the receiving flask (63–75% yield) (Note 11).

The product is dissolved in 200 ml. of ether, and the solution is washed with 75 ml. of saturated aqueous sodium carbonate, dried over anhydrous magnesium sulfate, and distilled to give 47–56 g. (60–71%) of product, b.p. 66–68° (0.07 mm.), 84–86° (0.8 mm.); m.p. 29°.

2. Notes

1. The acetonitrile was distilled from phosphorus pentoxide.
2. Triphenylphosphine was obtained from M and T Chemicals, Inc., and used without further purification.
3. The triphenylphosphine is only partially dissolved.
4. If a slight excess of bromine persists after addition, a small amount of triphenylphosphine should be added until the color of bromine disappears.
5. The solid triphenylphosphine disappears, but at the same time the adduct, $(C_6H_5)_3PBr_2$, precipitates as a white solid.
6. This addition is mildly exothermic, and the temperature rises to 50–60°. All the

precipitate should dissolve at this point; warming by external heat may be necessary.
7. To protect the vacuum pump from damage a dry ice-acetone trap and two liquid nitrogen traps are necessary to condense and solidify the hydrogen bromide evolved.
8. The receiving flask is placed in an ice-water bath.
9. The distillation is continued until the triphenylphosphine oxide solidifies and no more product distills. The oil bath is maintained at 130–140° during the distillation.
10. Some product is carried over by the hydrogen bromide in the initial stages of the distillation.
11. When this distillation was replaced by a procedure in which the acetonitrile was removed with a rotary evaporator and steam bath, and the product was extracted from the triphenylphosphine oxide with small portions of acetonitrile totaling *ca.* 250 ml., the checkers obtained an improved yield (79%) of cinnamyl bromide.

3. Discussion

Cinnamyl bromide has been prepared from cinnamyl alcohol by the action of hydrogen bromide in cold acetic acid[2] and of phosphorus tribromide in boiling benzene.[3] It has also been prepared by the action of N-bromosuccinimide on 3-phenylpropene[4] and on 1-phenylpropene.[5]

4. Merits of the Preparation

The method described is general for converting alcohols to alkyl halides and is stereospecific.[6]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 142

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

acetic acid (64-19-7)

Benzene (71-43-2)

ether (60-29-7)

acetonitrile (75-05-8)

hydrogen bromide (10035-10-6)

sodium carbonate (497-19-8)

bromine (7726-95-6)

phosphorus tribromide (7789-60-8)

1-phenylpropene

magnesium sulfate (7487-88-9)

cinnamyl alcohol (104-54-1)

N-bromosuccinimide (128-08-5)

3-phenylpropene (300-57-2)

triphenylphosphine (603-35-0)

Cinnamyl bromide, Benzene, 3-bromopropenyl- (4392-24-9)

triphenylphosphine oxide (791-28-6)

phosphorus pentoxide (1314-56-3)

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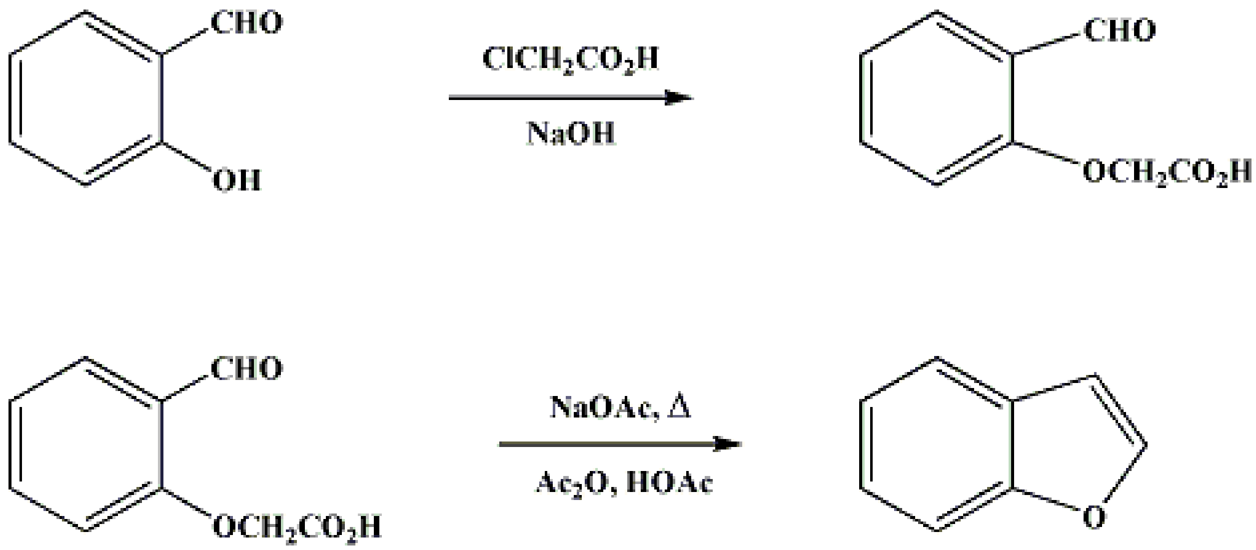
Organic Syntheses, CV 5, 251

COUMARONE

[Benzofuran]



Submitted by Albert W. Burgstahler and Leonard R. Worden[1].
Checked by Wayland E. Noland, William E. Parham, and Carol Wong.

1. Procedure

A. *o-Formylphenoxyacetic acid*. A solution of 80.0 g. (2 moles) of sodium hydroxide pellets in 200 ml. of distilled water is added to a mixture of 106 ml. (122 g., 1 mole) of salicylaldehyde (Note 1), 94.5 g. (1 mole) of chloroacetic acid (Note 1) and (Note 2), and 800 ml. of water. The mixture is stirred slowly and heated to boiling. The resulting black solution (Note 3) is heated under reflux for 3 hours (Note 4). The solution is acidified with 190 ml. of concentrated hydrochloric acid (sp. gr. 1.19) and is steam-distilled to remove unchanged salicylaldehyde (40.0–40.5 g.) (Note 5). The residual acidic mixture is cooled to 20°, and the precipitated product is collected on a Büchner funnel and rinsed with water. The light tan solid when dry weighs 99–100 g. (82–83% based on recovered salicylaldehyde), m.p. 130.5–133.0° (Note 6).

B. *Coumarone*. A mixture of 90.0 g. (0.5 mole) of crude (Note 7), dry *o*-formylphenoxyacetic acid, 180 g. of anhydrous, powdered sodium acetate, 450 ml. of acetic anhydride, and 450 ml. of glacial acetic acid (Note 8) in a 2-l. flask is heated under gentle reflux with stirring for 8 hours. The hot black solution (total volume *ca.* 1.2 l.) (Note 3) is poured into 2.5 l. of ice water and extracted with one 600-ml. portion of ether (Note 9). The ether layer is washed with one 600-ml. portion of water and then with several portions of cold dilute 5% sodium hydroxide solution (Note 10) until the aqueous layer is basic. The ether layer is washed successively with water and saturated sodium chloride solution and is partially dried over anhydrous granular

sodium sulfate. The ether is removed at water-bath temperature and the product is distilled, b.p. 166.5–168.0° (735 mm.) or 97.5–99.0° (80 mm.). The water-white benzofuran weighs 37.5–40.0 g. (63.5–67.8%, 52–56% overall from salicylaldehyde), n^{20}_D 1.5672; λ_{max} 245 (log ε 4.08), 275 (3.45), and 282 m• (3.48).

2. Notes

1. Matheson, Coleman and Bell practical grade material was used.
2. The yield is not increased by use of bromoacetic acid or 2 moles of chloroacetic acid and an additional mole of sodium hydroxide.
3. At no time did the checkers observe a black solution. The color of the solution changed from yellow to red-brown.
4. The yield is not increased by longer reflux periods.
5. Removal of unchanged salicylaldehyde by steam distillation (followed conveniently by testing the distillate with 2,4-dinitrophenylhydrazine reagent) provides a product sufficiently pure for use in the next step. Also, the recovered salicylaldehyde can be used again without further purification.
6. Three crystallizations of 36 g. of the crude *o*-formylphenoxyacetic acid from 360 ml. of water with 10 g. of activated carbon give 18 g. of glistening colorless plates, m.p. 133.0°–133.5°.
7. Use of purified *o*-formylphenoxyacetic acid increases the yield in this step by only 11%.
8. If no acetic acid is used, benzofuran is formed in only 30–31% yield, and coumarilic acid, m.p. 194–196°, is isolated in about 45% yield.
9. An additional extraction does not increase the yield appreciably.
10. About 250 ml. of this solution is required.

3. Discussion

o-Formylphenoxyacetic acid has been prepared previously in 46% yield by alkylation of salicylaldehyde with chloroacetic acid[2,3] and in unspecified yield by alkylation with ethyl bromoacetate followed by hydrolysis.[4]

Benzofuran is found in coal tar.[5] It has been prepared in 40–46% overall yield from coumarin by bromination, conversion of the resulting 3,4-dibromocoumarin to coumarilic acid, and then decarboxylation,[6] and also by passage of coumarin vapor through an iron tube at 860°.[7] The method given here is a variation of that described by Rössing,[2] who omitted the addition of acetic acid (see (Note 8) above). Benzofuran also has been prepared by the cyclization of ω-chloro-*o*-hydroxystyrene[8] or phenoxyacetaldehyde[9] in unspecified low yields and by the cyclization of phenoxyacetaldehyde diethyl acetal in 9% yield.[10] High-temperature catalytic dehydrocyclization of *o*-ethylphenol affords benzofuran in as much as 59% yield after

recycling unchanged *o*-ethylphenol.[11]

4. Merits of the Preparation

Although the high-temperature catalytic dehydrocyclization of *o*-ethylphenol[11] gives benzofuran in fair yield, these conditions are not convenient in the laboratory and cannot be applied easily to functionally substituted *o*-formylphenoxyacetic acids. The other methods of preparation give unsatisfactory yields, are unnecessarily lengthy, or require expensive starting materials. The method of Rössing,[2] on which the present procedure is based, gives good yields in its original form only in the case of *o*-acylphenoxyacetic acids; *o*-formylphenoxyacetic acids give principally the corresponding coumarilic acids. Often these can be decarboxylated only in very poor yield.[12] In the preparation described here, benzofuran is obtained directly in fair overall yield from readily available and inexpensive starting materials without the necessity of a separate decarboxylation step.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

o-acylphenoxyacetic acids

o-formylphenoxyacetic acids

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ether (60-29-7)

acetic anhydride (108-24-7)

sodium acetate (127-09-3)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

chloroacetic acid (79-11-8)

carbon (7782-42-5)

Salicylaldehyde (90-02-8)

2,4-Dinitrophenylhydrazine (119-26-6)

Bromoacetic acid (79-08-3)

Ethyl bromoacetate (105-36-2)

coumarin

3,4-dibromocoumarin (55077-11-7)

Coumarone, Benzofuran (271-89-6)

phenoxyacetaldehyde (2120-70-9)

phenoxyacetaldehyde diethyl acetal

o-Formylphenoxyacetic acid (6280-80-4)

ω-chloro-o-hydroxystyrene

o-ethylphenol (90-00-6)

Coumarilic acid (496-41-3)

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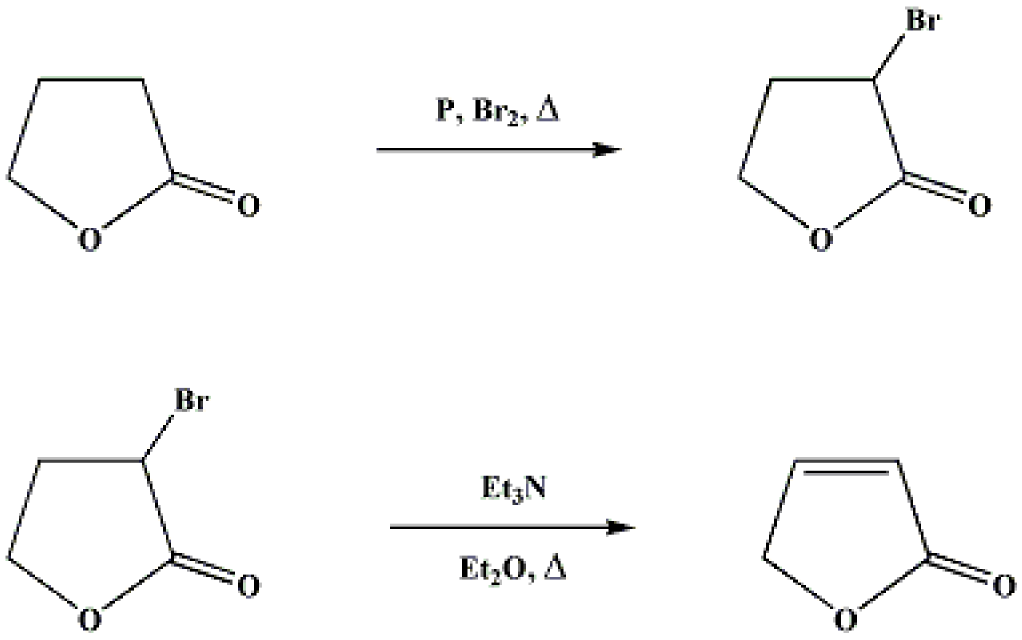
γ-CROTONOLACTONE

[$\Delta^{\alpha,\beta}$-Butenolide]



Submitted by Charles C. Price and Joseph M. Judge[1].
Checked by Richard F. Atkinson and E. J. Corey.

1. Procedure

Caution! Contact with α-bromo-γ-butyrolactone can cause severe eye and skin irritation. This preparation should be carried out in a good hood, and the operator should wear protective goggles and rubber gloves.

A. *α-Bromo-γ-butyrolactone*. In a 1-l., three-necked, round-bottomed flask equipped with a dropping funnel, sealed stirrer, and an efficient reflux condenser (Note 1) are placed 100 g. (1.16 moles) of redistilled γ-butyrolactone and 13.4 g. (0.43 g. atom) of red phosphorus. Over a half-hour interval, 195 g. (66.5 ml., 1.22 moles) of bromine is added, the mixture being stirred moderately and cooled by an ice bath.

This mixture is heated to 70° and an additional 195 g. (66.5 ml., 1.22 moles) of bromine added over a half-hour interval. After the bromine addition, the temperature is raised to 80° and the mixture held at that temperature for 3 hours. Air is blown into the cooled reaction until the excess bromine and hydrogen bromide are removed (Note 1). This process usually requires one hour (Note 2).

The aerated reaction mixture is heated to 80° and 25 ml. of water is added cautiously, with stirring. A vigorous reaction ensues, and upon cessation of the reaction an additional 300 ml. of water is added.

The reaction mixture of two layers and some solid residue is heated under reflux for 4 hours. Upon cooling, two layers again appear. The product is extracted with two portions of ether (200 ml. each), and the extracts are dried over magnesium sulfate (Note 3). *Care should be taken since the α-bromolactone is a vesicant.*

The dried crude material is distilled, b.p. 125–127° (13 mm.), n^{25}D 1.5030, yield 105 g. (55%).

B. $\Delta^{\alpha,\beta}$-*Butenolide*. In a 500-ml. three-necked flask fitted with a mechanical stirrer, a reflux condenser, and a 250-ml. dropping funnel containing a solution of 61 g. (84.5 ml., 0.6 mole) of triethylamine in 70 ml. of dry diethyl ether, a solution of 83 g. (0.5 mole) of α-bromo-γ-butyrolactone and 200 ml. of dry diethyl ether is heated to reflux, with stirring. The amine solution is added, slowly, during 5 hours and the stirring under reflux continued for an additional 24 hours. The brown precipitate (40 g.) is removed by filtration. Most of the solvent is removed from the filtrate by evaporation, and the additional precipitate (8 g.) is removed. This precipitate is predominantly triethylamine hydrobromide. The liquid residue is distilled under reduced pressure and the $\Delta^{\alpha,\beta}$-butenolide is collected at 107–109° (24 mm.); yield 25 g. (60%, 33% overall), m.p. 5°[2,3,4] (Note 4).

2. Notes

1. A trap to catch the resulting bromine-hydrogen bromide vapors is desirable.
2. Plieninger[5] reports that the product at this stage is α,γ-dibromobutyryl bromide.
3. Extraction with ether is necessary to separate the bromolactone efficiently.
4. The infrared spectrum of γ-crotonolactone shows two bands in the carbonyl region at 5.60 and 5.71 • in carbon tetrachloride (5%) [shifted to 5.61 and 5.71 •. in chloroform (5%)] and carbon-carbon stretching absorption at 6.23 •. The nuclear magnetic resonance spectrum shows olefinic peaks centered at 2.15τ (pair of triplets) and 3.85τ (pair of triplets), each due to one proton, and a two-proton triplet centered at 5.03τ (in CCl_4).
In the ultraviolet, γ-crotonolactone shows end absorption at 205 m• (ε *ca.* 11,000) and no maximum at higher wavelength.
Oxidation of this product by potassium permanganate affords 2,3-dihydroxy-4-butyrolactone.[2]

3. Discussion

The original preparation of γ-crotonolactone by Lespieau involved a five-step sequence from epichlorohydrin and sodium cyanide.[2] A recent detailed study of this procedure reported an overall yield of 25% for the lactone.[3] Glattfeld[4] used a shorter route from glycerol chlorohydrin and sodium cyanide; hydrolysis and distillation of

the intermediate dihydroxy acid yielded γ-crotonolactone in 23% yield and β-hydroxy-γ-butyrolactone in 28% yield.[4] The formation of γ-crotonolactone in 15% yield has also been reported from pyrolysis of 2,5-diacetoxy-2,5-dihydrofuran at 480–500°.[6] The lactone has been prepared in 37% overall yield from propynol by carboxylation and hydrogenation.[7]

The formation of α-bromo-γ-butyrolactone has been reported in 70% yield by uncatalyzed reaction of bromine at 160–170°,[8] as well as by the catalyzed procedure used here.[3]

4. Merits of the Preparation

γ-Crotonolactone is the simplest example of the butenolide ring system, which occurs in many natural products. In view of the availability of butyrolactone, the present procedure represents the most convenient method of synthesis of the unsaturated lactone.

The dehydrohalogenation by a tertiary amine illustrates the utility of such amines for dehydrohalogenations which produce a double bond normally activated for attack by many bases.[9]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

bromolactone

$\Delta^{\alpha,\beta}$-Butenolide

α-bromolactone

bromine-hydrogen bromide

glycerol chlorohydrin

ether, diethyl ether (60-29-7)

chloroform (67-66-3)

Epichlorohydrin (106-89-8)

potassium permanganate (7722-64-7)

sodium cyanide (143-33-9)

hydrogen bromide (10035-10-6)

bromine (7726-95-6)

PHOSPHORUS (7723-14-0)

carbon tetrachloride (56-23-5)

magnesium sulfate (7487-88-9)

triethylamine (121-44-8)

γ-butyrolactone, Butyrolactone (96-48-0)

γ-Crotonolactone (497-23-4)

α-Bromo-γ-butyrolactone (5061-21-2)

triethylamine hydrobromide (636-70-4)

α,γ-dibromobutyryl bromide

2,3-dihydroxy-4-butyrolactone (15667-21-7)

β-hydroxy-γ-butyrolactone (7331-52-4)

2,5-diacetoxy-2,5-dihydrofuran

propynol

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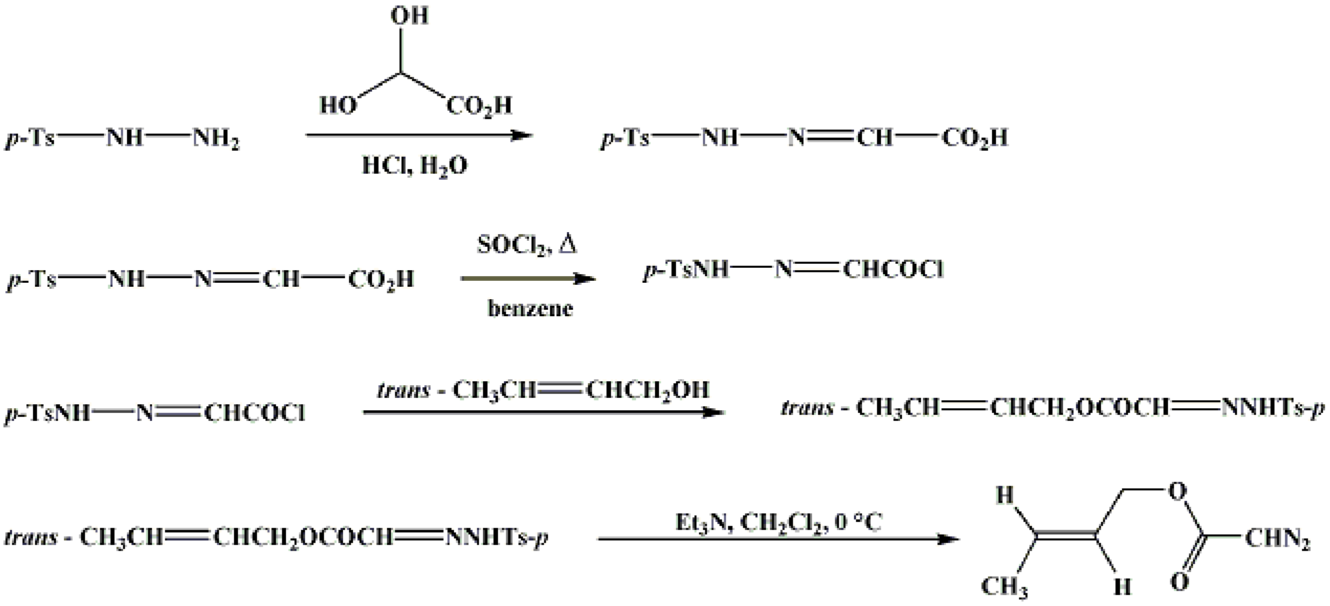
CROTYL DIAZOACETATE

[Acetic acid, diazo-, *trans*-2-butenyl ester]



Submitted by C. John Blankley, Frederick J. Sauter, and Herbert O. House[1].
Checked by J. H. Ham and R. E. Ireland.

1. Procedure

A. *Glyoxylic acid p-toluenesulfonylhydrazone*. A solution of 46.3 g. (0.50 mole) of 80% glyoxylic acid (Note 1) in 500 ml. of water is placed in a 1-l. Erlenmeyer flask and warmed on a steam bath to approximately 60°. This solution is then treated with a warm (approximately 60°) solution of 93.1 g. (0.50 mole) of *p*-toluenesulfonylhydrazide (Note 2) in 250 ml. (0.63 mole) of aqueous 2.5*M* hydrochloric acid. The resulting mixture is heated on a steam bath with continuous stirring until all the hydrazone, which initially separates as an oil, has solidified (about 5 minutes is required). After the reaction mixture has been allowed cool to room temperature and then allowed to stand in a refrigerator overnight, the crude *p*-toluenesulfonylhydrazone is collected on a filter, washed with cold water, and allowed to dry for 2 days (Note 3). The crude product (110–116 g., m.p. 145–149° dec.) is dissolved in 400 ml. of boiling ethyl acetate, filtered to remove any insoluble material, and then diluted with 800 ml. of carbon tetrachloride and allowed to cool. After the mixture has been allowed to stand overnight in a refrigerator, the *p*-toluenesulfonylhydrazone is collected and washed with cold mixture of ethyl acetate and carbon tetrachloride (1:2 by volume). The yield is 92.4–98.5 g. (76–81%) of the hydrazone as white crystals, m.p. 148–154° dec. (Note 4).

B. *The p-toluenesulfonylhydrazone of glyoxylic acid chloride*. *Caution! Since hydrogen chloride and sulfur dioxide are liberated during this reaction, it should be conducted in a hood.* To a suspension of 50.2 g. (0.21 mole) of glyoxylic acid *p*-toluenesulfonylhydrazone in 250 ml. of benzene is added 30 ml. (49 g. or 0.42 mole) of thionyl chloride (Note 5). The reaction mixture is heated under reflux with stirring until vigorous gas evolution has ceased and most of the suspended solid has dissolved (about 1.5–2.5 hours is required (Note 6)). The reaction mixture is then cooled immediately (Note 6) and filtered through a Celite mat on a sintered-glass funnel. After the filtrate has been concentrated to dryness under reduced pressure, the residual solid is mixed with 40–50 ml. of anhydrous benzene, warmed, and the solid mass is broken up to give a fine suspension. This suspension is cooled and filtered with suction. The crystalline product is washed quickly with two portions of cold benzene to remove most of the residual colored impurities, and then the remaining crude acid chloride is transferred to a flask for recrystallization.

The combined benzene filtrates from this initial washing procedure are concentrated under reduced pressure, and the washing procedure with benzene is repeated to give a second crop of the crude acid chloride which is transferred to a flask for recrystallization.

For recrystallization each crop of the crude acid chloride is dissolved in a minimum volume of boiling anhydrous benzene (about 100 ml. is required for the first crop) and petroleum ether (b.p. 30–60°; about 50 ml. is required for the

first crop) is added to the hot solution. Crystallization begins on cooling. After the mixture has cooled to room temperature, it is allowed to stand overnight at room temperature and the acid chloride is collected on a filter and washed with a small portion of cold benzene. The yield of recrystallized acid chloride from the first crop of crude acid chloride is 27.6–33.4 g. (50–61%) of pale yellow prisms, m.p. 101–112° (Note 4). The product obtained from crystallization of the second crop of acid chloride amounts to 3.3–3.6 g. (6–7%), m.p. 104–108°.

C. *Crotyl diazoacetate*. A solution of 10.0 g. (0.038 mole) of the *p*-toluenesulfonylhydrazone of glyoxylic acid chloride in 100 ml. of methylene chloride is cooled in an ice bath. Crotyl alcohol (2.80 g. or 0.038 mole) (Note 7) is added to this cold solution, and then a solution of 7.80 g. (0.077 mole) of redistilled triethylamine (b.p. 88.5–90.5°) in 25 ml. of methylene chloride is added to the cold reaction mixture dropwise and with stirring over a 20-minute period. During the addition a yellow color develops in the reaction mixture and some solid separates near the end of the addition period. The resulting mixture is stirred at 0° for 1 hour and then the solvent is removed at 25° under reduced pressure with a rotary evaporator. A solution of the residual dark orange liquid in approximately 200 ml. of benzene is thoroughly mixed with 100 g. of Florisil (Note 8) and then filtered. The residual Florisil, which has adsorbed the bulk of the dark colored by-products, is washed with two or three additional portions of benzene of such size that the total volume of the combined benzene filtrates is 400–500 ml. This yellow benzene solution of the diazoester is concentrated under reduced pressure at 25° with a rotary evaporator, and the residual yellow liquid is distilled under reduced pressure. *(Caution! This distillation should be conducted in a hood behind a safety shield)* (Note 9). The diazo ester is collected as 2.20–2.94 g. (42–55%) of yellow liquid, b.p. 30–33° (0.15 mm)., n^{24}D 1.4853 — 1.4856 (Note 10).

2. Notes

1. The submitters used a practical grade of material containing 80% glyoxylic acid purchased from Eastman Organic Chemicals.

2. The submitters used *p*-toluenesulfonylhydrazide prepared as described in *Organic Syntheses*.[2] This material may be purchased from Eastman Organic Chemicals.

3. Difficulty was encountered in the subsequently described recrystallization if the crude product was not dry.

4. The broad melting range is presumably due to the presence of a mixture of stereoisomers.

5. If the thionyl chloride is not taken from a freshly opened bottle, it should be redistilled before use.

6. The heating period is critical to the success of this reaction. After a heating period of 45–90 minutes the initially white suspension begins to turn yellow and the color gradually deepens as heating is continued. The correct heating period is normally reached about 10 minutes after vigorous gas evolution ceases; at this time the color of the reaction mixture is yellow-orange to orange. At this point the mixture is not clear, but relatively little suspended material separates when the stirrer is stopped for a short period. If heating is stopped too soon, a large amount of acid is lost during the filtration and the product is difficult to crystallize. If heating is continued too long, the product is contaminated with a brown-colored impurity and is difficult to crystallize.

7. The submitters used material purchased from the Aldrich Chemical Company.

8. This material was purchased from Fisher Scientific Company.

9. Although this distillation has been performed repeatedly without incident, the product is potentially explosive and the operator should take suitable precautions including surrounding the distillation apparatus with a hood and a safety shield and wearing an effective face shield.

10. A pot residue amounting to 2–3 g. of orange liquid remains at the end of this distillation.

3. Discussion

Crotyl diazoacetate has been prepared by the procedure described here[3] and by the reaction of diazomethane with crotyl chloroformate.[3] The lower homolog, allyl diazoacetate, has been prepared by the reaction of allyl glycinate with nitrous acid[4] and by the successive conversion of allyl chloroacetate to the corresponding azide, iminophosphorane, and, finally, the diazo ester.[5]

Other methods for the preparation of diazoacetic acid esters include the diazotization of glycine esters,[6] the thermal or base-catalyzed decomposition of N-acyl-N-nitrosoglycine esters,[7] the base-catalyzed cleavage of α-diazo-β-keto acetates,[8] the reaction of carboalkoxymethylenephosphoranes with arylsulfonyl azides,[9] the acid-catalyzed decomposition of acetic esters with α-aryl-triazene substituents,[10] and the reaction of chloroformate esters with diazomethane.[3,11] The present procedure is unique in that a diazoacetic ester may be prepared in one step by reaction of the desired alcohol with a relatively stable, solid acylating agent which may be prepared in quantity and stored (in a desiccator). Consequently, the method is of particular value for alcohols which are not readily available or for alcohols containing other functional groups which would be incompatible with the reaction conditions required in other

diazoacetate syntheses.

Although the present procedure illustrates the formation of the diazoacetic ester without isolation of the intermediate ester of glyoxylic acid *p*-toluenesulfonylhydrazone, the two geometric isomers of this hydrazone can be isolated if only one molar equivalent of triethylamine is used in the reaction of the acid chloride with the alcohol.[3] The extremely mild conditions required for the further conversion of these hydrazones to the diazo esters should be noted. Other methods for decomposing arylsulfonyl-hydrazones to form diazocarbonyl compounds have included aqueous sodium hydroxide,[12] sodium hydride in dimethoxyethane at 60°,[13] and aluminum oxide in methylene chloride or ethyl acetate.[14] Although the latter method competes in mildness and convenience with the procedure described here, it was found not to be applicable to the preparation of aliphatic diazoesters such as ethyl 2-diazopropionate. Hence the conditions used in the present procedure may offer a useful complement to the last-mentioned method when the appropriate arylsulfonylhydrazone is available.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 438

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

p-toluenesulfonylhydrazone

p-toluenesulfonylhydrazone of glyoxylic acid chloride

hydrogen chloride, hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ethyl acetate (141-78-6)

sodium hydroxide (1310-73-2)

thionyl chloride (7719-09-7)

sulfur dioxide (7446-09-5)

carbon tetrachloride (56-23-5)

nitrous acid (7782-77-6)

methylene chloride (75-09-2)

glyoxylic acid (298-12-4)

Diazomethane (334-88-3)

aluminum oxide (1344-28-1)

sodium hydride (7646-69-7)

triethylamine (121-44-8)

dimethoxyethane (534-15-6)

Crotyl diazoacetate, Acetic acid, diazo-, trans-2-butenyl ester (14746-03-3)

Crotyl alcohol

crotyl chloroformate

allyl diazoacetate

allyl glycinate

allyl chloroacetate (2916-14-5)

ethyl 2-diazopropionate

p-Toluenesulfonylhydrazide (1576-35-8)

Glyoxylic acid p-toluenesulfonylhydrazone (14661-68-8)

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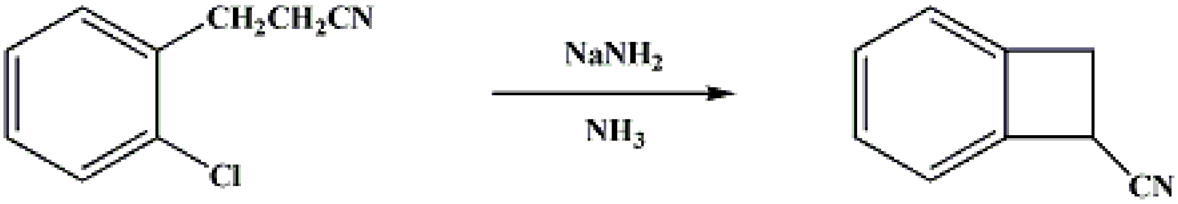
Organic Syntheses, *CV 5*, *263*

1-CYANOBENZOCYCLOBUTENE

[Bicyclo[4.2.0]octa-1,3,5-triene-7-carbonitrile]



Submitted by J. A. Skorcz and F. E. Kaminski[1].
Checked by V. Z. Williams and K. B. Wiberg.

1. Procedure

A 2-l. three-necked flask is thoroughly dried and fitted with a large dry-ice condenser, a mechanical stirrer, a nitrogen inlet, and a powder funnel in an efficient hood. With nitrogen flowing through the system, 62.5 g. (1.60 moles) of commercial sodium amide (Note 1) is added rapidly. *(Caution! Sodium amide is corrosive and readily decomposes in the presence of moisture.)* The funnel is replaced by a gas-inlet tube, the condenser is filled with a mixture of dry ice and acetone, and *ca.* 400 ml. of liquid ammonia is introduced from a cylinder. The gas-inlet tube is replaced by an addition funnel, stirring is commenced, and 66.3 g. (0.400 mole) of *o*-chlorohydrocinnamonitrile (Note 2) is added over a 10-minute period. The last traces of the nitrile are washed into the flask with small amounts of anhydrous ether.

The dark green reaction mixture is stirred vigorously for 3 hours and then is treated carefully with 96 g. (1.2 moles) of solid ammonium nitrate (Note 3). All the fittings are removed from the flask, and the ammonia is allowed to evaporate (Note 4). Water (300 ml.) is added cautiously to the residue. *(Caution! Traces of undecomposed sodium amide may adhere to the upper walls of the flask.)* The organic layer is taken up in two 160-ml. portions of chloroform, and the solutions are combined and washed twice with 100 ml. of 5% hydrochloric acid and once with 100 ml. of water. *(Caution! The extraction procedure and subsequent chloroform distillation should be conducted in a hood because some hydrogen cyanide is usually evolved.)* The chloroform solution is dried over anhydrous sodium sulfate, and the chloroform is removed by distillation. The residual liquid is distilled under reduced pressure through an insulated, 5-in. Vigreux column. The forerun, b.p. 95–100° (3 mm.), weighs *ca.* 1 g.; the product boils at 100–101° (3 mm.); $n^{25}D$ 1.5451. The yield of 1-cyanobenzocyclobutene is 33–34 g. (64–66%) (Note 5) and (Note 6).

2. Notes

1. The sodium amide was obtained from Farchan Research Laboratories and was approximately 90% pure.
2. The submitters prepared *o*-chlorohydrocinnamonitrile by the following procedure. Ethyl cyanoacetate (3040 g., 27 moles) was added to a solution of 140 g. (6.1 g. atoms) of sodium in 4 l. of absolute ethanol, followed by 970 g. (6 moles) of *o*-α-dichlorotoluene (Eastman Organic Chemicals), to afford 890 g. (63%) of ethyl 2-(*o*-chlorobenzyl)cyanoacetate,[2] b.p. 117–123° (0.03 mm.). Hydrolysis of this material in 2 l. of 10% aqueous sodium hydroxide at room temperature gave a quantitative yield (790 g.) of 2-(*o*-chlorobenzyl)cyanoacetic acid, m.p. 129–132° without recrystallization. Decarboxylation of 750 g. of the acid in 750 ml. of refluxing dimethylformamide gave 550 g. (93%) of *o*-chlorohydrocinnamonitrile,[3] b.p. 82–85° (0.3 mm.), n^{25}_{D} 1.5362. The checkers carried out this preparation starting with 8 moles of ethyl cyanoacetate and obtained comparable yields.
3. Other ammonium salts, such as ammonium chloride, are equally satisfactory.
4. Overnight evaporation at room temperature is convenient.
5. The submitters carried out the reaction on 1-molar and 3-molar scales and obtained yields of 62–64% and 67%, respectively.
6. This procedure has also been used to obtain 1-cyano-5-methoxybenzocyclobutene from 2-bromo-4-methoxyhydrocinnamonitrile.[4]

3. Discussion

1-Cyanobenzocyclobutene has been prepared from sodium cyanide and 1-bromobenzocyclobutene,[5] formed by reaction of benzocyclobutene with N-bromosuccinimide,[6] and by ring closure of *o*-chlorohydrocinnamonitrile with potassium amide in liquid ammonia.[7] The present procedure is a modification of the latter method and was previously described by one of the submitters.[8]

4. Merits of the Preparation

Cyclization by addition of a side-chain carbanion to an aryne bond has been proposed as the method of choice for synthesis of the versatile 1-substituted benzocyclobutene system.[7] This general procedure now has been modified to permit convenient large-scale preparations utilizing a commercially available base, a minimum amount of liquid ammonia, and distillation for isolation of the product.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ether (60-29-7)

ammonium chloride (12125-02-9)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium cyanide (143-33-9)

hydrogen cyanide (74-90-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

acetone (67-64-1)

sodium (13966-32-0)

Ethyl cyanoacetate (105-56-6)

ammonium nitrate

sodium amide (7782-92-5)

dimethylformamide (68-12-2)

N-bromosuccinimide (128-08-5)

potassium amide

1-Cyanobenzocyclobutene

Bicyclo[4.2.0]octa-1,3,5-triene-7-carbonitrile (6809-91-2)

o-α-dichlorotoluene (611-19-8)

1-cyano-5-methoxybenzocyclobutene

2-bromo-4-methoxyhydrocinnamonitrile

1-bromobenzocyclobutene

benzocyclobutene

o-chlorohydrocinnamonitrile (7315-17-5)

ethyl 2-(o-chlorobenzyl)cyanoacetate

2-(o-chlorobenzyl)cyanoacetic acid

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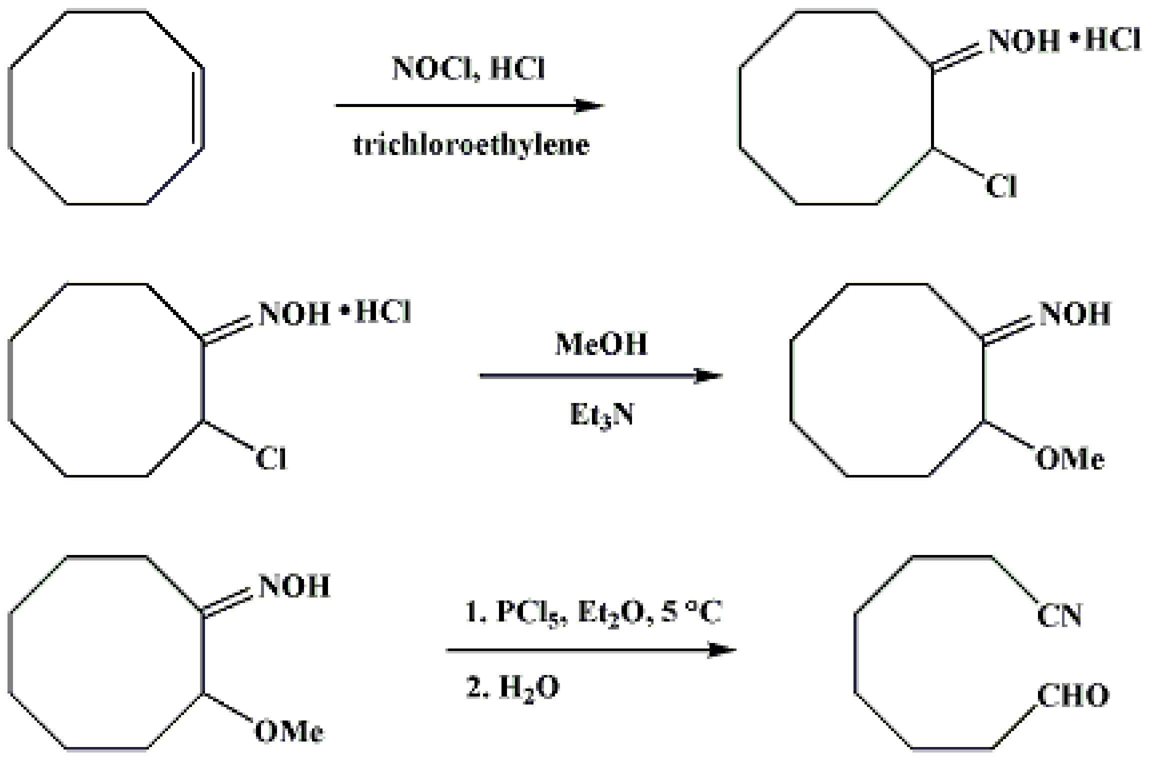
Organic Syntheses, CV 5, 266

7-CYANOHEPTANAL

[Heptanal, 7-cyano-]



Submitted by Masaji Ohno, Norio Naruse, and Isao Terasawa[1].
Checked by E. J. Corey and I. Vlattas.

1. Procedure

A. *2-Chlorocyclooctanone oxime hydrochloride*. In a 2-l. three-necked, round-bottomed flask, fitted with a mechanical stirrer, a gas inlet tube, and a tube fitted with a thermometer and a calcium chloride tube, is placed 55 g. (0.50 mole) of freshly distilled cyclooctene and 600 ml. of trichloroethylene. The solution is cooled with ice water to 5°, and 36 g. (0.55 mole) of nitrosyl chloride (Note 1) and excess of hydrogen chloride gas (about 400–600 ml. per minute) are bubbled into the solution, keeping the reaction temperature between 5–10°. The solution gradually becomes light reddish brown. The addition of nitrosyl chloride should be carried out in about 1.5 hours. After completion of the addition of nitrosyl chloride, hydrogen chloride gas is bubbled in for another 15 minutes. A light brown oily material is obtained after evaporation of the solvent under an aspirator pressure below 35° (Note 2) by using an efficient rotatory evaporator. On cooling this product in a refrigerator, 107.2 g. (*ca.* 100%) of crude 2-chlorocyclooctanone oxime hydrochloride is obtained as a solid.

B. *2-Methoxycyclooctanone oxime*. In a 500-ml., three-necked, round-bottomed flask,

fitted with a mechanical stirrer, a dropping funnel, and a reflux condenser equipped with a calcium chloride tube, is placed a solution of 53.5 g. (0.252 mole) of crude 2-chlorocyclooctanone oxime hydrochloride in 250 ml. of methanol. While cooling the vessel with running water, 60.7 g. of triethylamine (0.60 mole) is added dropwise during 40 minutes. The reaction temperature is kept below 50° and the reaction is continued for 30 minutes with stirring. After removal of methanol under reduced pressure using an efficient rotatory evaporator, a light brown semisolid is obtained; it is treated with 200 ml. of ether and 200 ml. of water to effect complete solution. The ether layer is separated and the aqueous layer is further extracted twice with ether. The combined ether solution is washed with saturated sodium chloride and dried over sodium sulfate. Removal of ether affords 42.8 g. of crude 2-methoxycyclooctanone oxime (Note 3) as a brown oil.

C. *Beckmann fission of 2-methoxycyclooctanone oxime*. In a 500-ml., three-necked, round-bottomed flask equipped with a mechanical stirrer, a dropping funnel, and a calcium chloride tube is placed a suspension of 62.5 g. (0.30 mole) of phosphorus pentachloride (Note 4) in 150 ml. of absolute ether, and the reaction vessel is cooled with ice. A solution of 42.8 g. of crude 2-methoxycyclooctanone oxime (0.25 mole) in 100 ml. of absolute ether is added over 30 minutes with vigorous stirring and the reaction is continued for 50 minutes at 5°. The reaction mixture, which becomes a transparent reddish brown solution (Note 5), is poured with mechanical stirring into 500 g. of ice in a 2-l. beaker. Stirring is continued for 1.5 hours at 5° (Note 6). The ether layer is separated and the aqueous layer is extracted with methylene chloride three times. The combined organic extracts are neutralized with dilute sodium carbonate solution and dried over sodium sulfate (Note 7). Removal of the solvent below 40° affords a reddish brown oil which is distilled to give 29.6 g. (85.2%) of 7-cyanoheptanal (Note 8), b.p. 109–115° (0.3 mm.) $n^{26}\text{D} = 1.4456$. The 2,4-dinitrophenylhydrazone has m.p. 74–75° after recrystallization from ethanol.

2. Notes

1. Solid nitrosyl chloride stored in a dry-ice box is quickly melted by warming, and as rapidly as possible the liquid nitrosyl chloride is weighed into a flask contained in a hood. Nitrosyl chloride is simply allowed to volatilize into the reaction from this flask under ambient conditions; rapid addition of nitrosyl chloride causes a decrease of the yield of α-chlorooxime. It may sometimes be necessary to control the rate of addition by cooling the nitrosyl chloride container with ice water.
2. 2-Chlorocyclooctanone oxime hydrochloride is unstable to heat. Therefore the temperature during removal of methanol should be kept below 35°.

3. The methanol-triethylamine reagent is superior to the previously used[2] methanolic sodium methoxide, and the crude 2-methoxycyclooctanone oxime thus obtained can be used for the Beckmann fission reaction without further purification. However, it is easily purified by distillation, b.p. 101° (0.7 mm.).

4. Thionyl chloride can also be used as the reagent for the Beckmann fission.
5. A very small amount of excess of phosphorus pentachloride is sometimes observed at the bottom of the reaction vessel.
6. If necessary, the temperature is kept at 5–10° by adding ice occasionally.
7. If the solution is acidic, the yield of ω-cyanoaldehyde is diminished by the occurrence of aldo condensation.
8. Although this distilled product, a pale yellow oil, is pure enough to use for most purposes, pure 7-cyanoheptanal, a colorless oil, is obtained by redistillation, b.p. 85–87° (0.013 mm.), n^{26}D 1.4451.

3. Discussion

The only preparation reported for 7-cyanoheptanal is that described by the submitters.[3] The present procedure starting from 2-methoxycyclooctanone oxime is superior to modifications employing 2-alkylamino- or 2-ethylthiocyclooctanone oxime in the Beckmann cleavage step.

ω-Cyanoaldehydes are not easily accessible by other routes but are interesting synthetic intermediates,[4] since the two terminal function groups are in different oxidation states which readily allow separate modification or elaboration.[5,6] The general applicability of the method described herein allows the synthesis of a wide variety of ω-cyanoaldehydes from available cycloolefins.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

2,4-dinitrophenylhydrazone

α-chlorooxime

ethanol (64-17-5)

hydrogen chloride (7647-01-0)

methanol (67-56-1)

ether (60-29-7)

phosphorus pentachloride (10026-13-8)

thionyl chloride (7719-09-7)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

sodium methoxide (124-41-4)

methylene chloride (75-09-2)

nitrosyl chloride (2696-92-6)

trichloroethylene (79-01-6)

triethylamine (121-44-8)

7-Cyanoheptanal, Heptanal, 7-cyano- (13050-09-4)

cyclooctene

2-Chlorocyclooctanone oxime hydrochloride

2-Methoxycyclooctanone oxime (10499-36-2)

2-ethylthiocyclooctanone oxime

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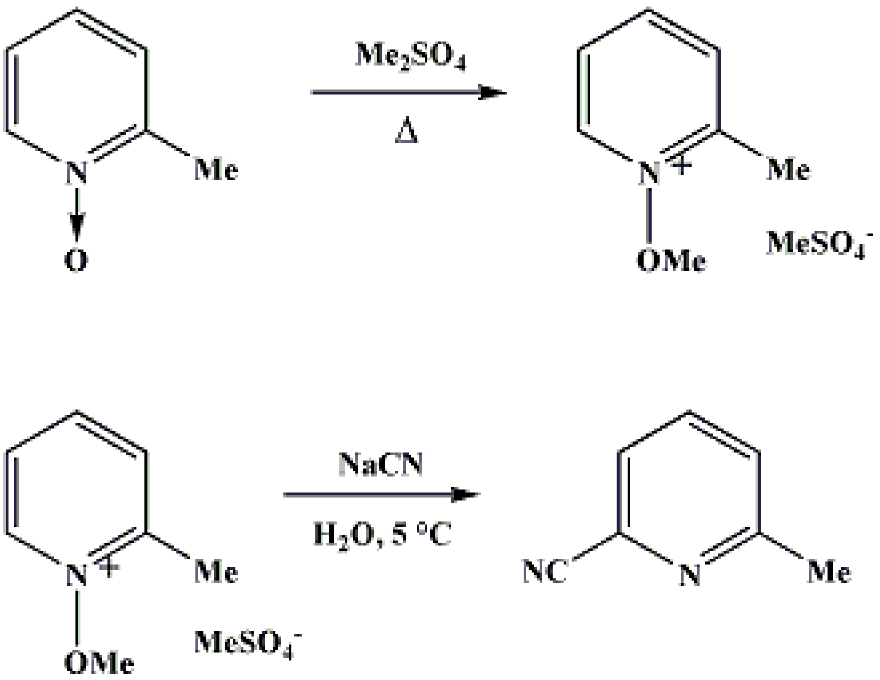
2-CYANO-6-METHYLPYRIDINE

[6-Methylpicolinonitrile]



Submitted by Wayne E. Feely, George Evanega, and Ellington M. Beavers[1].
Checked by William E. Parham, Stuart W. Fenton, and William W. Henderson.

1. Procedure

Caution! All the operations should be carried out in a well-ventilated hood because of the toxic natures of dimethyl sulfate, hydrogen cyanide, and cyanide solutions.

A. *1-Methoxy-2-methylpyridinium methyl sulfate*. In a 1-l. three-necked flask equipped with a Hirshberg stirrer, a thermometer which extends deep into the flask, and a 250-ml. pressure-equalizing, dropping funnel fitted with a calcium chloride drying tube is placed 109 g. (1.0 mole) of dry powdered 2-picoline-1-oxide (Note 1). The stirrer is started at a slow rate, and 126 g. (1.0 mole) of dimethyl sulfate (Note 2) is added dropwise at a rate such that the temperature of the reaction mixture slowly rises to between 80° and 90° and remains in this range throughout the addition (Note 3). When the addition is about two-thirds complete, gentle heating with a steam bath is necessary to maintain this temperature. After complete addition (about 1 hour), the mixture is heated for an additional 2 hours on a steam bath at 90–100°. The molten salt is then poured into a large evaporating dish and placed in a vacuum desiccator under partial vacuum to cool. The salt is obtained as a white crystalline mass in essentially quantitative yield (235 g.) (Note 4) and (Note 5).

B. *2-Cyano-6-methylpyridine*. In a 2-l., three-necked, round-bottomed flask equipped

with a Hershberg stirrer, a 500-ml. pressure-equalizing, dropping funnel without a stopper, and a thermometer-gas inlet adapter (Note 6) fitted with a thermometer which reaches deep into the flask is placed a solution of 147 g. (3.0 mole) of sodium cyanide dissolved in 400 ml. of water. The stirrer is started and the apparatus is flushed with prepurified nitrogen for 1 hour (Note 7). The solution in the flask is then cooled to 0° with an ice bath, and a solution of 235 g. (1.0 mole) of 1-methoxy-2-methylpyridinium methyl sulfate dissolved in 300 ml. of water is added dropwise over a period of 2 hours. The dropping funnel and the thermometer-adapter are then quickly removed and replaced by stoppers, and the flask is allowed to stand in a refrigerator overnight (12–16 hours). The flask, containing needles of the crude nitrile (Note 8), is removed from the refrigerator and the contents stirred at room temperature for 6 hours. After addition of 200 ml. of chloroform, the contents of the flask are transferred to a large separatory funnel and the layers separated. Extraction of the aqueous phase is repeated twice with 100-ml. portions of chloroform, and the combined extracts are dried over anhydrous magnesium sulfate. After removal of the drying agent by filtration, the filtrate is concentrated on a steam bath to remove chloroform, and the residual crude cyanopicoline (90–110 g.) is transferred, while hot, to a distilling flask. Distillation under reduced pressure (30 mm.) (Note 9) gives three fractions: Fraction I, b.p. 99–106°, weighs 15–20 g.; Fraction II, b.p. 106–124°, weighs 5–10 g.; and Fraction III, b.p. 125–131°, weighs 60–70 g. (Note 10). Fraction III is dissolved in 1 l. of hot 10% ethyl alcohol, treated with 0.5 g. of activated carbon, filtered, and the filtrate is allowed to cool slowly to room temperature. The 2-cyano-6-methylpyridine separates as white prismatic needles, m.p. 71–73°, and weighs 48–54 g. (40–46% based on 2-picoline-1-oxide) (Note 11) and (Note 12).

2. Notes

1. The preparation of 2-picoline-1-oxide is described by Boekelheide and Linn.[2] The oxide is hygroscopic, and best results are obtained if it is redistilled just before use. The submitters used 2-picoline-1-oxide, obtained from the Reilly Tar and Chemical Company, Indianapolis, Indiana, which was freshly redistilled and boiled at 118–120°/10 mm.
2. Eastman Kodak Company practical grade was used. Dimethyl sulfate is toxic and must be handled with caution. Provision should be made for containing the contents should breakage occur. Ammonia is a specific antidote for dimethyl sufate and should be at hand to destroy any accidentally spilled.
3. The submitters have observed that, when 1-methoxypyridinium methyl sulfate salts are heated above about 140–150°, violent explosions usually result.
4. The salt is very hygroscopic. Aqueous solutions of the salt slowly hydrolyze upon standing to di(1-methoxy-2-methylpyridinium) sulfate but may be used in the subsequent step without adverse effects.
5. The salt may be recrystallized from anhydrous acetone, giving colorless prisms, m.p. 67–70°.[3]
6. A thermometer adapted with a gas-addition tube may be purchased from Ace

Glass Inc., Vineland, New Jersey (Cat. No. 5266).
7. The presence of small amounts of air during the formation of the nitrile rapidly darkens the reaction mixture.
8. The crude 2-cyano-6-methylpyridine which has separated (40–50 g.) may be recrystallized from dilute ethyl alcohol to yield 35–45 g. of pure product.
9. The distillation is conveniently performed in a Claisen flask with a fractionating side arm. The checkers used a heat lamp to prevent solidification of product in the condenser.
10. Fraction **I**, b.p. 99–106°/30 mm., is mostly 4-cyano-2-methylpyridine and is best purified by redistillation.[4] Fraction **II**, b.p. 106–125°/30 mm., contains a mixture of the two nitriles and may be further purified by redistillation.
11. Physical constants reported for 2-cyano-6-methylpyridine are b.p. 135–136°/38 mm.,[5] m.p. 69–71°,[5] m.p. 72–74°.[6,7]
12. This general method has been used to prepare 2- and 4-cyanopyridine from pyridine-1-oxide in 32% and 49% yields, respectively; 2-cyano-4,6-dimethylpyridine (73%) from 4,6-dimethylpyridine-1-oxide; 2-cyanoquinoline (93%) from quinoline-1-oxide; and 1-cyanoisoquinoline (95%) from isoquinoline-2-oxide.[3]

3. Discussion

The present method is essentially that given by Feely and Beavers.[3] 2-Cyano-6-methylpyridine also has been prepared by the fusion of sodium 6-methylpyridine-2-sulfonate with potassium cyanide.[5] In addition, this nitrile has been prepared from 2-chloro-6-methylpyridine[6] (no yield stated) and from a catalytic reaction of 2,6-lutidine with air and ammonia in low yield.[6,7]

4. Merits of Preparation

This preparation describes a convenient and general method for preparing cyano derivatives of pyridine, quinoline, and isoquinoline from the corresponding, and readily available, amine oxides.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 303
- Org. Syn. Coll. Vol. 5, 370

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

2- and 4-cyanopyridine

ethyl alcohol (64-17-5)

ammonia (7664-41-7)

chloroform (67-66-3)

sodium cyanide (143-33-9)

hydrogen cyanide (74-90-8)

nitrogen (7727-37-9)

cyanide (57-12-5)

potassium cyanide (151-50-8)

dimethyl sulfate (77-78-1)

acetone (67-64-1)

carbon (7782-42-5)

pyridine (110-86-1)

Quinoline (91-22-5)

magnesium sulfate (7487-88-9)

2,6-Lutidine (108-48-5)

isoquinoline (119-65-3)

pyridine-1-oxide (694-59-7)

2-Cyano-6-methylpyridine, 6-Methylpicolinonitrile (1620-75-3)

2-picoline-1-oxide (931-19-1)

1-Methoxy-2-methylpyridinium methyl sulfate (55369-05-6)

cyanopicoline

1-methoxypyridinium methyl sulfate

di(1-methoxy-2-methylpyridinium) sulfate

4-cyano-2-methylpyridine (2214-53-1)

2-cyano-4,6-dimethylpyridine

4,6-dimethylpyridine-1-oxide

2-cyanoquinoline (1436-43-7)

quinoline-1-oxide (1613-37-2)

1-cyanoisoquinoline (1198-30-7)

isoquinoline-2-oxide (1532-72-5)

sodium 6-methylpyridine-2-sulfonate

2-chloro-6-methylpyridine (18368-63-3)

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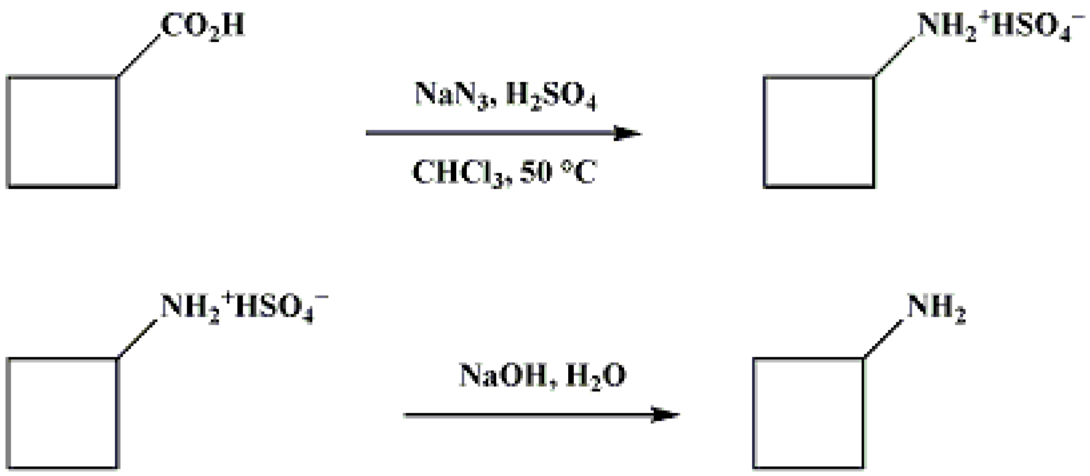
CYCLOBUTYLAMINE



Submitted by Newton W. Werner and Joseph Casanova, Jr.[1].
Checked by Donald Barth and Kenneth B. Wiberg.

1. Procedure

Caution! The reaction should be carried out in a good hood because hydrazoic acid is very toxic. Care should also be taken in handling sodium azide.

In a 1-l. three-necked, round-bottomed flask equipped with a mechanical stirrer, reflux condenser, and powder funnel are placed 180 ml. of reagent grade chloroform, 16.0 g. (0.16 mole) of cyclobutanecarboxylic acid (Note 1), and 48 ml. of concentrated sulfuric acid. The flask is heated in an oil bath to 45–50°, and 20.0 g. (0.31 mole) of sodium azide (Note 2) is added over a period of 1.5 hours (Note 3). After the addition of sodium azide is complete, the reaction mixture is heated at 50° for 1.5 hours. The flask is cooled in an ice bath, and approximately 200 g. of crushed ice is added slowly. A solution of 100 g. of sodium hydroxide in 200 ml. of water is prepared, cooled to room temperature, and then added slowly to the reaction mixture until the pH of the mixture is approximately 12–13. The mixture is poured into a 2-l. three-necked, round-bottomed flask, the flask is set up for steam distillation, and about 2 l. of distillate is collected in a cooled receiver containing 90 ml. of 3*N* hydrochloric acid (Note 4). The water and chloroform are removed by distillation under reduced pressure (Note 5), and the amine hydrochloride is transferred to a 50 ml. round-bottomed flask with a few milliliters of water. A straight condenser is connected to the flask, and the flask is cooled in an ice bath. A slush is prepared by grinding potassium hydroxide pellets in a mortar and then adding a minimum volume of water. The slush is added in portions through the top of the condenser. After the mixture has become sufficiently basic, the amine appears as a separate phase. More potassium hydroxide pellets are added to dry the amine phase. The condenser is replaced by a heated, vacuum-jacketed Vigreux column equipped with a soda-lime tube, and the fraction having a boiling point of 79–

83° is collected. The distillate is dried over potassium hydroxide pellets for 2 days. The liquid is decanted into a distilling flask containing a few potassium hydroxide pellets and distilled through the apparatus described above to give 7–9 g. (60–80%) of cyclobutylamine, b.p. 80.5–81.5°, n^{25}_{D} 1.4356 (Note 6), (Note 7).

2. Notes

1. Cyclobutanecarboxylic acid was purchased from the Aldrich Chemical Co., Milwaukee, Wisconsin. A synthesis of the acid is described in *Org. Syntheses*, Coll. Vol. **3**, 213 (1955).
2. Eastman practical grade was used.
3. The sodium azide is added at such a rate that a gentle reflux of vapors in the powder funnel is maintained. After somewhat more than the theoretical amount of azide has been added, the rate of addition may be much more rapid.
4. The distillation should be carried out carefully at first until all the chloroform has distilled. A distilling adapter dipping just below the surface of the acid solution should be used in order to minimize loss of cyclobutylamine. Care must be taken that the basic solution in the distillation flask which still contains sodium azide does not come in contact with the hydrochloric acid solution in the receiver.
5. A water aspirator is sufficient.
6. Contact of the amine with the atmosphere should be avoided since the amine reacts with carbon dioxide.
7. The purity of the product was checked by vapor phase chromatography on a polyethylene glycol on Teflon column at 72°, 15 p.s.i., and a flow rate of 102 ml. of helium per minute. The sample appeared to be homogeneous, but, since the amine tails badly on the column, it is not possible to detect the presence of a small amount of water (less than 3%).
An n.m.r. spectrum of cyclobutylamine in carbon tetrachloride showed no resonance signals at less than 1 p.p.m. from tetramethylsilane. This suggests that no cyclopropylcarbinylamine was formed by rearrangement during the reaction.

3. Discussion

The preparation of cyclobutylamine from cyclobutanecarboxylic acid and hydrazoic acid has been reported previously.[2,3] Cyclobutylamine has also been prepared by the Hofmann-type rearrangement of cyclobutanecarboxamide.[4,5,6,7] More recently it has been prepared in 82–87% overall yield from cyclobutanecarboxamide by oxidative rearrangement with lead tetraacetate or iodosobenzene diacetate.[8]

4. Merits of the Preparation

This procedure permits the synthesis of cyclobutylamine from cyclobutanecarboxylic acid in one step and in high yield. The procedures involving the Hofmann

rearrangement[4,5,6,7] require the preparation of the amide from the acid and afford lower yields of the amine.

The interest in the synthesis of compounds containing the cyclobutyl ring system is due to the observation that reactions which are thought to proceed through cationic intermediates give rise to rearrangement products. For example, deamination of cyclobutylamine in aqueous solution gives cyclopropylcarbinol and allylcarbinol as well as cyclobutanol.[9] Recent investigations have been concerned with the exact nature of these cationic intermediates.[10,11]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrazoic acid

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

carbon tetrachloride (56-23-5)

amine hydrochloride

carbon dioxide (124-38-9)

potassium hydroxide (1310-58-3)

sodium azide (26628-22-8)

Cyclobutanecarboxylic acid (3721-95-7)

helium (7440-59-7)

tetramethylsilane (75-76-3)

Cyclobutylamine (2516-34-9)

cyclopropylcarbinylamine (2516-47-4)

Cyclobutanecarboxamide (1503-98-6)

Iodosobenzene diacetate (3240-34-4)

cyclobutyl (4548-06-5)

cyclopropylcarbinol (2516-33-8)

allylcarbinol (627-27-0)

Cyclobutanol (2919-23-5)

lead tetraacetate

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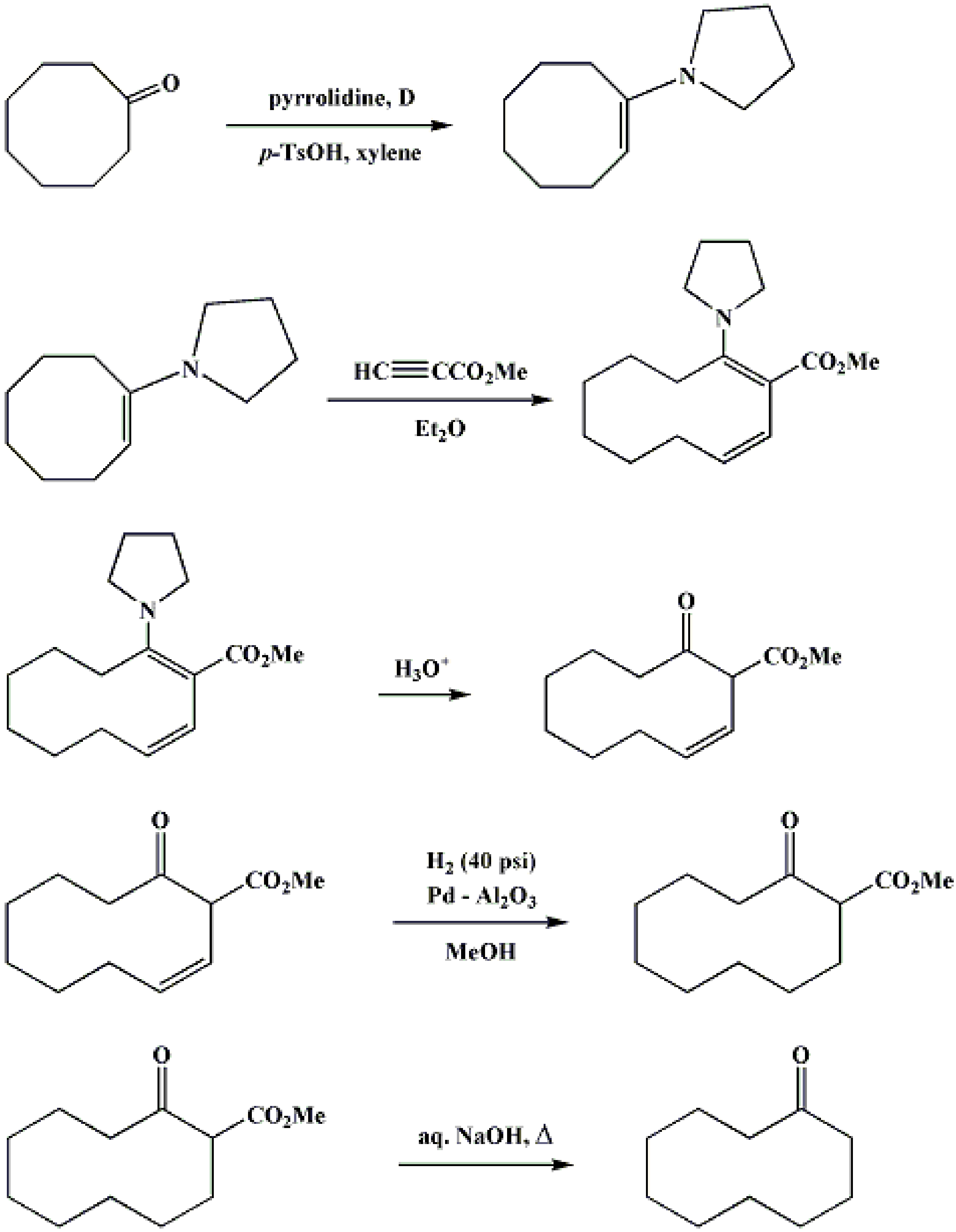
Organic Syntheses, CV 5, 277

CYCLODECANONE



Submitted by R. D. Burpitt and J. G. Thweatt[1].
Checked by William G. Dauben, Michael H. McGann, and Noel Vietmeyer.

1. Procedure

To a 500-ml. round-bottomed flask fitted with a 25- to 30-cm. column packed with glass helices to which is attached a water separator[2] filled with hexane (Note 1) are added 126 g. (1.00 mole) of cyclooctanone (Note 2), 100 g. (1.4 moles) of pyrrolidine, 100 ml. of xylene, and 0.5 g. of *p*-toluenesulfonic acid. The solution is heated under reflux until the separation of water ceases (Note 3). The water separator is replaced by a distillation head, and the reaction mixture is distilled through the column under reduced pressure to remove solvent and unreacted starting materials. When the head temperature reaches 50° (1 mm.), distillation is stopped, and the residue of almost pure N-(1-cycloocten-1-yl)pyrrolidine (152–161 g.) is used in the next step without further purification (Note 4).

The crude enamine is dissolved in 450 ml. of ether, and the solution is transferred to a 1-l. three-necked flask equipped with a sealed stirrer, a 250-ml. dropping funnel, and a two-necked adapter fitted with a calcium chloride tube and a thermometer immersed in the solution. A solution of 71–76 g. (0.85–0.90 mole) (Note 5) of methyl propiolate *(Caution! Methyl propiolate is a severe lachrymator and should be handled only in the hood.)* in 150 ml. of ether is added dropwise. During the addition the temperature of the mixture is maintained at 25–30° by periodic cooling of the reaction flask in a dry ice-acetone bath. When the addition is almost complete, a white solid begins to separate. The mixture is stirred at 25–30° for an additional hour, cooled to 0°, and filtered to remove the solid. This is dissolved in 700 ml. of 6% hydrochloric acid (Note 6), the acidic solution is warmed at 55–60° for 1 hour, and the mixture is cooled and extracted with two 100-ml. portions of ether. The ether is removed on a steam bath, and the residue of crude methyl 10-oxocyclodec-2-ene-1-carboxylate is dissolved in 300 ml. of methanol and hydrogenated over 5 g. of 5% palladium-on-alumina catalyst at 40 p.s.i. pressure and room temperature.

The catalyst is filtered, 200 g. (155 ml.) of 25% aqueous sodium hydroxide is added to the filtrate, and the mixture is heated under reflux for 1 hour. The condenser is replaced by a short Vigreux column and distillation head, and the heating is continued until most of the methanol has distilled. The two-phase residue is cooled and extracted with two 100-ml. portions of ether. The ether is removed on a steam bath, and the residue is distilled through a 20-cm. Vigreux column to yield 68–77 g. (44–50%) of cyclodecanone, b.p. 94–98° (10 mm.), m.p. 20–22° (Note 7).

2. Notes

1. If hexane is not used in the trap, an excessive amount of pyrrolidine is lost in the aqueous layer.
2. Cyclooctanone from Aldrich Chemical Co., methyl propiolate from Farchan Research Laboratories, and pyrrolidine from Eastman Organic Chemicals were used as received.
3. The reaction is usually complete after 3–6 hours at reflux. Owing to dissolved pyrrolidine, the aqueous layer amounts to 35–45 ml., and thus its volume is not a

good measure of the extent of reaction.
4. Pure N-(1-cycloocten-1-yl)pyrrolidine, b.p. 76–78° (1 mm.), may be isolated by distillation through a Vigreux column.
5. The amount used should be adjusted to be equimolar with the amount of crude enamine.
6. This solid intermediate is reasonably stable to storage under nitrogen; however, the yield in the acid hydrolysis step is better when freshly prepared material is hydrolyzed immediately.
7. The same reaction sequence may be used to convert cyclododecanone to cyclotetradecanone. Preparation of the pyrrolidine enamine of cyclododecanone requires 2–3 days at reflux, and reaction of the enamine with methyl propiolate is best carried out in refluxing hexane. The enamine-propiolate reaction may also be used to convert cycloheptanone to cyclononanone. In this case the procedure must be modified to provide for partial hydrogenation of the intermediate amino ester without prior hydrolysis.[3] The reduced intermediate is saponified as described in the present procedure.

3. Discussion

Cyclodecanone has been obtained together with other products in the pyrolysis of the thorium or yttrium salts of nonanedioic acid.[4] It has also been prepared by reduction of sebacoin with zinc and hydrochloric acid,[5,6] by dehydration of sebacoin followed by catalytic hydrogenation,[7] by ring enlargement of cyclononanone with diazomethane[8,9] and of cyclooctanone with diazomethane in the presence of a Lewis acid catalyst,[9] by hydroboration of 1,2-cyclodecadiene followed by oxidation of the organoborane,[10] and by the present procedure.[3]

4. Merits of the Preparation

The chief merits of this preparation are its simplicity and the high purity of the product. Although the synthesis involves several steps, each step is a simple operation, and all intermediates may be used in the subsequent steps without purification. The purity of even the crude product is high, and any impurities which may be present are readily removed by a simple distillation.

The overall yield of cyclodecanone is comparable to the overall yield obtained by conversion of dimethyl sebacate to sebacoin[11] and subsequent reduction to cyclodecanone.[6] In addition, the present procedure does not require the use of a high-speed stirrer, the rigorous exclusion of air, and the high dilution that are necessary in preparing sebacoin.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Sebacoin

palladium-on-alumina

enamine-propiolate

thorium or yttrium salts of nonanedioic acid

hydrochloric acid (7647-01-0)

methanol (67-56-1)

ether (60-29-7)

sodium hydroxide (1310-73-2)

nitrogen (7727-37-9)

zinc (7440-66-6)

xylene (106-42-3)

Diazomethane (334-88-3)

pyrrolidine (123-75-1)

hexane (110-54-3)

Cyclodecanone (1502-06-3)

cyclononanone (3350-30-9)

Cycloheptanone (502-42-1)

dimethyl sebacate (106-79-6)

Cyclooctanone (502-49-8)

cyclododecanone (830-13-7)

methyl propiolate (922-67-8)

N-(1-cycloocten-1-yl)pyrrolidine

methyl 10-oxocyclodec-2-ene-1-carboxylate

cyclotetradecanone (3603-99-4)

pyrrolidine enamine

1,2-cyclodecadiene

p-toluenesulfonic acid (104-15-4)

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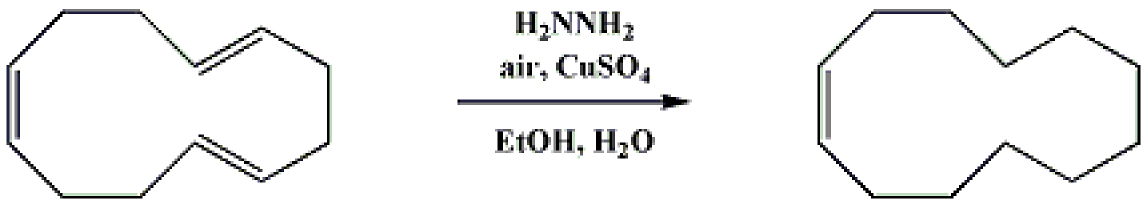
Organic Syntheses, *CV 5*, *281*

cis-CYCLODODECENE



Submitted by Masaji Ohno and Masaru Okamoto[1].
Checked by Frederick J. Sauter and Herbert O. House.

1. Procedure

In a 2-l., three-necked, round-bottomed flask equipped with a mechanical stirrer, an efficient condenser, and an air inlet tube (Note 1) are placed 60.0 g. (0.370 mole) of *cis,trans,trans*-1,5,9-cyclododecatriene (Note 2), 224.4 g. (7.00 moles) of 95% hydrazine (Note 3), 350 ml. of 95% ethanol, and 3.0 g. (0.012 mole) of copper(II) sulfate pentahydrate (Note 4). Air is bubbled through the reaction mixture (Note 5) with vigorous stirring for 8–12 hours or longer until the reaction mixture contains primarily the desired *cis*-monoolefin (Note 6). During the early stages in the reaction a considerable amount of heat is generated and the temperature of the reaction mixture rises to 50–60°.[2]

When the reaction has progressed to the desired stage (Note 6), the flow of air is stopped and the mixture is filtered. After the filtrate has been extracted with two 350-ml. portions of petroleum ether (b.p. 30–60°), the combined hydrocarbon extracts are washed successively with two 100-ml. portions of 2*N* hydrochloric acid and three 100-ml. portions of water. The petroleum ether is distilled from the solution, heated in a water bath, through a 60-cm. Vigreux column, and the residual liquid is distilled under reduced pressure. The fraction, b.p. 64–65° (1.0 mm.) or 132–134° (35 mm.), is collected as 39.5–52.0 g. (64–85%) of colorless liquid, n^{25}_{D} 1.4846–1.4850. This distillation fraction contains (Note 6) 80–90% of the *cis*-cyclododecene (51–76%) accompanied by 10–20% of a mixture of cyclododecane and *cis,trans*-1,5-cyclododecadiene (Note 7). If desired, the *cis*-cyclododecene may be further purified by preparative chromatography or separation of the silver nitrate-olefin addition complex (Note 8).

2. Notes

1. An air inlet tube with a sintered-glass disk or cylinder at the end immersed in the solution is recommended.
2. The submitters used material available from Hüls Company in Germany. This material was contaminated with 1–3% of the more easily reduced *trans,trans,trans*-1,5,9-cyclododecatriene. The checkers purchased the starting triene from

Aldrich Chemical Company, Inc. The gas chromatogram (see (Note 6)) of this material exhibited no peak corresponding to the all-*trans*-triene, an indication that less than 1% of this contaminant was present.

3. The submitters had specified the use of either hydrazine hydrate (aqueous 85% hydrazine) or aqueous 80% hydrazine. The checkers observed only partial reduction of the triene and intermediate diene under these conditions, apparently because sufficient water was present in the reaction mixture to prevent adequate partitioning of the olefins between the hydrocarbon layer and the aqueous ethanolic layer containing the diimide. The checkers avoided this difficulty by use of hydrazine containing less than 5% water (95+ % hydrazine) available from Olin Mathieson Chemical Company or from Eastman Organic Chemicals. This difficulty could probably also be avoided by use of absolute ethanol rather than 95% ethanol.

4. Copper(II) acetate can also be used.

5. The rate of air flow, measured with a precalibrated mercury flow meter in the gas inlet tube, was adjusted to 400–450 ml. per minute.

6. In order to stop the reaction when the amount of monoolefinic product in the reaction mixture is highest, aliquots of the reaction mixture are removed at intervals and analyzed by infrared spectrometry or by gas chromatography. In the infrared spectrum the relative intensities of bands at 965 cm.$^{-1}$ (*trans*-CH=CH) and 702 cm.$^{-1}$ (*cis*-CH=CH) are observed in successive aliquots. The reaction is stopped when the band at 965 cm.$^{-1}$, attributable to the *trans* double bonds of the starting triene, has almost completely disappeared and the band at 702 cm.$^{-1}$ (*cis*-olefin) remains.

Gas chromatographic analyses are obtained at about 120° with a 2 m. × 7 mm. column packed with a suspension of 5% (by weight) of silver nitrate and 15% (by weight) of Carbowax 6000 (polyethylene glycol) on either Chromosorb P or Celite 545. With this column the relative retention times of the various possible components in the reaction mixture are: cyclododecane, 1.00; *trans,trans,trans*-1,5,9-cyclododecatriene, 1.20; *trans*-cyclododecene, 1.13; *cis*-cyclododecene, 1.33; *cis,trans*-1,5-cyclododecadiene, 1.51; *cis,trans-trans*-1,5,9-cyclododecatriene, 1.72. The reaction should be stopped when the rate of reduction of *cis,trans*-1,5-cyclododecadiene to *cis*-cyclododecene has become approximately equal to the rate of conversion of the *cis*-monoolefin to cyclododecane.

7. The submitters reported obtaining a product after a 60–72 hour reaction period which contained 91%–95% of the *cis*-monoolefin and 5–9% of cyclododecane with no *trans*-monoolefin being detected. The checkers found the maximum amount of *cis*-monoolefin was present in the reaction mixture after a reaction period of 8–12 hours. At this time the resulting distilled product had the approximate composition: cyclododecane, 8%; *trans*-cyclododecene, 3%; *cis*-cyclododecene, 80%; and *cis,trans*-1,5-cyclododecadiene, 9%. The use of longer reaction times resulted in the further reduction of the *cis*-monoolefin to cyclododecane more rapidly than it was produced from the residual *cis,trans*-diene.

8. The conversion of the *cis*-monoolefin to its silver nitrate complex[3] was accomplished by adding 1.66 g. (0.010 mole) of the distilled reaction product to a solution of 1.70 g. (0.010 mole) of silver nitrate in 50 ml. of boiling methanol. The resulting solution, when cooled, deposited the complex as white needles, m. p. 79° dec.; recrystallization from methanol separated 1.0 g. of the complex, m. p. 80° dec. After this complex had been partitioned between water and ether, the ether phase was separated, dried over magnesium sulfate, and concentrated. Distillation of the residual liquid in a short path still separated 0.45 g. of the pure (Note 6) *cis*-cyclodecene, b.p. 70° (1.0 mm.), $n^{25}D$ 1.4852.

3. Discussion

Cyclododecene may be prepared from 1,5,9-cyclododecatriene by the catalytic reduction with Raney nickel and hydrogen diluted with nitrogen,[4] with nickel sulfide on alumina,[5] with cobalt, iron, or nickel in the presence of thiophene,[6] with palladium on charcoal,[7] with palladium chloride in the presence of water,[8] with palladium on barium sulfate,[9] with cobalt acetate in the presence of cobalt carbonyl,[10] and with cobalt carbonyl and tri-*n*-butyl phosphine.[11] It may also be obtained from the triene by reduction with lithium and ethylamine,[12] by disproportionation,[13,14] by epoxidation followed by isomerization to a ketone and Wolff-Kishner reduction,[15] and from cyclododecanone by the reaction of its hydrazone with sodium hydride.[16]

These methods generally afford a mixture of *cis*- and *trans*-cyclododecene. *cis*-Cyclododecene has also been prepared by the reduction of cyclododecyne with Lindlar catalyst,[17,3] and from 1,5-cyclododecadiene[18] or from 1,2-dichlorocyclododecane.[19] The *cis*-olefin is usually obtained as a minor product from the Hofmann degradation of cyclododecyltrimethylammonium hydroxide[17] and from the pyrolysis of cyclododecyl acetate.

The procedure described is based on the selective reduction with diimide described by Ohno and Okamoto[2] and by Nozaki and Noyori.[20] It illustrates the generation of diimide from the air oxidation of hydrazine and the use of diimide for the selective reduction of the *trans* double bond in *cis,trans,trans*-1,5,9-cyclododecatriene, the product of trimerization of butadiene.[21]

The use of diimide provides a particularly convenient and general method for the selective reduction of *trans* double bonds of medium ring systems.[22] The *cis*-cyclododecene produced in this selective reduction is thermodynamically less stable than the corresponding *trans*-isomer.[23]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alumina

petroleum ether

cis-monoolefin

silver nitrate-olefin

trans-monoolefin

cis-olefin

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

methanol (67-56-1)

ether (60-29-7)

hydrogen (1333-74-0)

iron (7439-89-6)

silver nitrate (7761-88-8)

nitrogen (7727-37-9)

nickel, Raney nickel (7440-02-0)

barium sulfate (7727-43-7)

charcoal (7782-42-5)

palladium (7440-05-3)

Copper(II) acetate (142-71-2)

hydrazine hydrate (7803-57-8)

hydrazine (302-01-2)

palladium chloride

Thiophene (110-02-1)

lithium (7439-93-2)

magnesium sulfate (7487-88-9)

butadiene (106-99-0)

copper(II) sulfate pentahydrate (7758-99-8)

sodium hydride (7646-69-7)

cobalt (7440-48-4)

ethylamine (75-04-7)

cyclododecanone (830-13-7)

cyclododecane (294-62-2)

Cyclododecene, cis- and trans-cyclododecene (1501-82-2)

1,5,9-cyclododecatriene

nickel sulfide

cobalt acetate

cobalt carbonyl

cyclododecyne (1129-90-4)

1,5-cyclododecadiene

1,2-dichlorocyclododecane

cyclododecyltrimethylammonium hydroxide

cyclododecyl acetate

tri-n-butyl phosphine (998-40-3)

trans-Cyclododecene (1486-75-5)

cis-Cyclododecene (1129-89-1)

cis,trans,trans-1,5,9-cyclododecatriene, cis,trans-trans-1,5,9-cyclododecatriene

cis,trans-1,5-cyclododecadiene

trans,trans,trans-1,5,9-cyclododecatriene (676-22-2)

cis-cyclodecene

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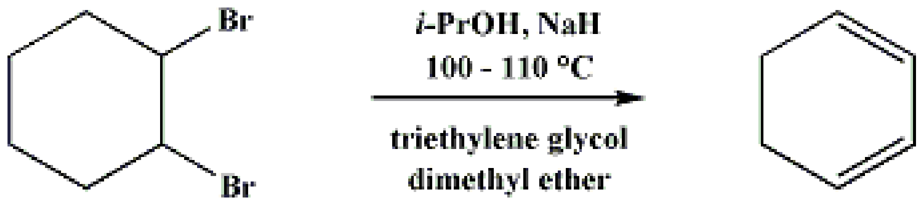
Organic Syntheses, CV 5, 285

1,3-CYCLOHEXADIENE



Submitted by John P. Schaefer and Leland Endres[1].
Checked by R. J. Crawford and Peter Yates.

1. Procedure

In a 3-l. three-necked, round-bottomed flask fitted with a mechanical stirrer and set up for a simple vacuum distillation are placed 500 ml. of triethylene glycol dimethyl ether (Note 1) and 300 ml. of isopropyl alcohol. Mechanical stirring is started, and 53.5 g. (2.23 moles) of sodium hydride in a mineral oil suspension is added in small portions. After the addition is complete, the remaining neck of the flask is fitted with a Y-tube to which is connected a two-holed rubber stopper containing a thermometer which reaches into the flask below the liquid level and a piece of glass tubing which is connected to a nitrogen tank. A pressure-equalizing dropping funnel containing 242 g. (1.00 mole) of 1,2-dibromocyclohexane (Note 2) is placed in the other arm of the Y-tube.

The temperature of the reaction flask is raised to 100–110°, and the receiving flask is cooled in a dry ice-isopropyl alcohol bath as a rapid stream of nitrogen is passed through the system. After most of the isopropyl alcohol has been removed by distillation (Note 3), the receiver is changed, and the system is evacuated by a water aspirator (Note 4). Dropwise addition of 1,2-dibromocyclohexane is begun, and the rate of addition is adjusted so that the temperature of the reaction mixture is maintained at 100–110° without external heating. The addition requires about 30 minutes; the reaction is terminated when distillation becomes very slow.

The distillate is washed four times with 200-ml. portions of water, and the organic layer is dried with anhydrous magnesium sulfate. The yield of 1,3-cyclohexadiene is 56 g. (70%) (Note 5). The diene can be separated from higher-boiling contaminants by a simple distillation at atmospheric pressure under nitrogen; b.p. 78–80°, yield 28–32 g. (35–40%) (Note 6).

2. Notes

1. 1,2-Bis(methoxyethoxy)ethane (triethylene glycol dimethyl ether) was obtained from Matheson, Coleman and Bell and used without further purification.

2. The 1,2-dibromocyclohexane was prepared by the method of Snyder and Brooks.[2] If the cyclohexene is cooled to *ca.* –30° with a dry ice-isopropyl alcohol bath and the bromine is not diluted, it is possible to run this preparation on a threefold scale in one-third of the recorded time. The product was always purified by the recommended procedure.
3. If the flow of nitrogen is rapid, the distillation can be completed in about 1 hour; otherwise the distillation is very slow.
4. A dry ice-isopropyl alcohol trap was inserted before the aspirator to catch any uncondensed product. The checkers also inserted a manometer between this trap and the aspirator, and maintained the pressure during the reaction at 130–170 mm. by careful adjustment of the regulator valve of the nitrogen cylinder.
5. If the temperature rises too high or the vacuum is not sufficient to flash out the diene as it forms, the product will be contaminated with small amounts of cyclohexene, benzene, and 1,4-cyclohexadiene.
6. The checkers found that distillation without the use of a nitrogen atmosphere gave 43–44 g. (54–55%) of product, b.p. 80–83°, of excellent purity as shown by n.m.r. spectroscopy.

3. Discussion

1,3-Cyclohexadiene has been prepared by dehydration of cyclohexen-3-ol,[3] by pyrolysis at 540° of the diacetate of cyclohexane-1,2-diol,[4] by dehydrobromination with quinoline of 3-bromocyclohexene,[5] by treating the ethyl ether of cyclohexen-3-ol with potassium bisulfate,[6,7] by heating cyclohexene oxide with phthalic anhydride,[8] by treating cyclohexane-1,2-diol with concentrated sulfuric acid,[9] by treatment of 1,2-dibromocyclohexane with tributylamine,[10] with sodium hydroxide in ethylene glycol,[10] and with quinoline,[6] and by treatment of 3,6-dibromo-cyclohexene with sodium.[6]

4. Merits of the Preparation

Because of its convenience and simplicity this procedure is the method of choice for laboratory preparation of 1,3-cyclohexadiene. This olefin is an intermediate of some importance because it offers a route via the Diels-Alder reaction to a variety of bicyclic compounds.[4,7,10]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 5

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

diacetate of cyclohexane-1,2-diol

quinoline of 3-bromocyclohexene

sulfuric acid (7664-93-9)

Benzene (71-43-2)

sodium hydroxide (1310-73-2)

Cyclohexene (110-83-8)

bromine (7726-95-6)

nitrogen (7727-37-9)

phthalic anhydride (85-44-9)

potassium bisulfate (7646-93-7)

sodium (13966-32-0)

isopropyl alcohol (67-63-0)

ethylene glycol (107-21-1)

Cyclohexene oxide (286-20-4)

Quinoline (91-22-5)

magnesium sulfate (7487-88-9)

1,2-Dibromocyclohexane (5401-62-7)

cyclohexane-1,2-diol

sodium hydride (7646-69-7)

1,3-Cyclohexadiene (592-57-4)

triethylene glycol dimethyl ether, 1,2-Bis(methoxyethoxy)ethane (112-49-2)

1,4-cyclohexadiene

cyclohexen-3-ol

tributylamine (102-82-9)

3,6-dibromo-cyclohexene

ethyl ether of cyclohexen-3-ol

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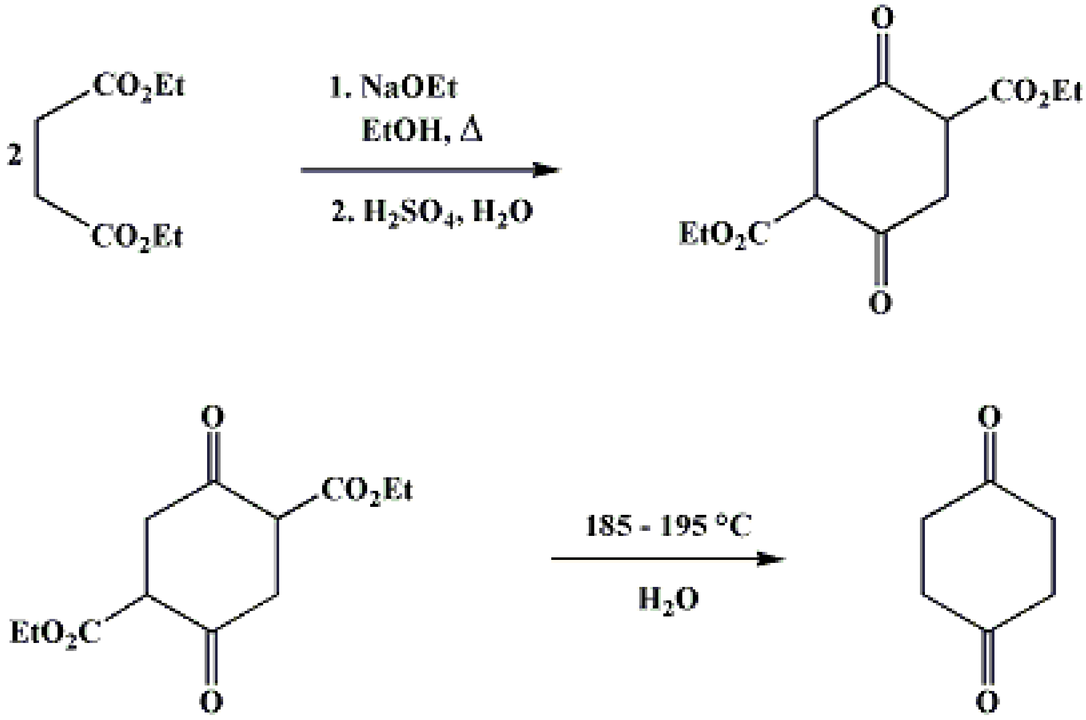
Organic Syntheses, CV 5, 288

1,4-CYCLOHEXANEDIONE



Submitted by Arnold T. Nielsen and Wayne R. Carpenter[1].
Checked by William G. Dauben and E. John Deviny.

1. Procedure

A. *2,5-Dicarbethoxy-1,4-cyclohexanedione*. A solution of sodium ethoxide is prepared by adding small pieces of sodium (92 g., 4 g. atoms) as rapidly as possible to 900 ml. of commercial absolute ethanol contained in a 3-l., three-necked, round-bottomed flask equipped with two stoppers and a reflux condenser fitted with a drying tube packed with calcium chloride and soda lime. The reaction is completed by heating the mixture under reflux for 3–4 hours (Note 1). To the hot solution is added diethyl succinate (348.4 g., 2 moles) (Note 2) in one portion *(Caution! Exothermic reaction)*, and the mixture is heated under reflux by maintaining the original bath temperature for 24 hours. A thick pink-colored precipitate is formed almost immediately and remains throughout the reaction.

At the end of the 24-hour period, the ethanol is removed under reduced pressure on a steam bath. A 2*N* sulfuric acid solution (2 l.) is added to the warm residue, and the mixture is stirred vigorously for 3–4 hours (Note 3). The solid is removed by suction filtration and washed several times with water. The air-dried product is a pale-buff powder weighing 180–190 g., m.p. 126–128°. The solid is added to 1.5 l. of ethyl acetate, the mixture is heated to boiling and is filtered rapidly while hot (Note 4). The filtrate is chilled, and it yields cream to pink-cream colored crystals of 2,5-dicarbethoxy-1,4-cyclohexanedione, 160–168 g., m.p. 126.5–128.5°. The filtrate is

concentrated to one-tenth of its original volume in order to obtain a second crop of crystals, 5–7 g., m.p. 121–125°. The total yield is 165–175 g. (64–68%).

B. *1,4-Cyclohexanedione*. The purified 2,5-dicarbethoxy-1,4-cyclohexanedione (170 g., 0.66 mole) (Note 5) and 170 ml. of water are placed in a glass liner (vented) of a steel pressure vessel of 1.5-l. capacity (fitted with a pressure-release valve). The vessel is sealed, heated as rapidly as possible to 185–195°, and kept at this temperature for 10–15 minutes (Note 6). The reaction vessel is immediately removed from the heater, placed in a large tub of ice water, and cooled to room temperature. The gas pressure then is carefully released. The resulting yellow to orange liquid is transferred to a distillation flask with the aid of a minimum volume of ethanol, and most of the water and ethanol is removed under reduced pressure by means of a rotary evaporator. The flask is attached to a short heated column fitted with a short air condenser. The remainder of the water and ethanol is removed under reduced pressure, and the 1,4-cyclohexanedione is distilled, b.p. 130–133° (20 mm.). The product solidifies to a white to pale-yellow solid, m.p. 77–79°, yield 60–66 g. (81–89% yield from 2,5-dicarbethoxy-1,4-cyclohexanedione). The compound may be conveniently recrystallized from carbon tetrachloride (7 ml. per gram of dione); the purified product is obtained as white plates, m.p. 77–79° (90% recovery).

2. Notes

1. A heating bath containing a liquid heat exchanger such as hydrogenated cottonseed oil should be used. Employment of an electric heating mantle may cause extreme charring in the later stages of the reaction.
2. The diethyl succinate was obtained from Eastman Organic Chemicals and used without purification.
3. The lumps of the sodium salt of 2,5-dicarbethoxy-1,4-cyclohexanedione should be completely reacted before the filtration step. If desired, the mixture may be stirred overnight at this point. The checkers found that in some runs a rock-like precipitate persisted on the bottom of the flask, and it had to be broken up manually by using a spatula with care.
4. A large fluted filter paper and a heated funnel are recommended for the filtration. The dark insoluble material which is removed by this process quickly fills the pores of the filter paper; more than one filter paper may be required. If a large amount of material remains in the filter, the material should be treated with additional ethyl acetate, the mixture filtered, and the filtrate combined with the first filtrate.
5. Use of unpurified ester results in a much lower yield of 1,4-cyclohexanedione.
6. An electrically heated pressure bomb, 4.5 in. in diameter, of 1.5-l. capacity, was employed (American Instrument Company, Model E 1143, cold-tested to 23,000 p.s.i.). About 90 minutes was required to raise the temperature from 25° to 185°.

3. Discussion

2,5-Dicarbethoxy-1,4-cyclohexanedione has been prepared by the self-condensation of diethyl succinate by use of sodium or sodium ethoxide catalyst (with or without a solvent)[2,3,4,5,6,7,8,9,10] and by reaction of ethyl 4-bromo-3-ketobutanoate[11] or ethyl 4-chloro-3-ketobutanoate[12,13] with sodium ethoxide in ethanol.

1,4-Cyclohexanedione has been prepared by hydrolysis and decarboxylation of 2,5-dicarbethoxy-1,4-cyclohexanedione by using concentrated sulfuric acid,[14] aqueous alcoholic phosphoric acid,[15] or water at 195–200°,[7,8,16] and by peroxyvanadic acid oxidation of cyclohexanone.[17]

4. Merits of the Preparation

The present procedure is simpler than others previously described and gives equally good yields. It is easily adapted to the preparation of large quantities of either the diester or the diketone. It can be extended to the preparation of various alkylated 1,4-cyclohexanediones[18] and bicyclic diketodicarboxylic esters such as diethyl bicyclo [2.2.2]octane-2,5-dione-1,4-dicarboxylate.[19,20] 1,4-Cyclohexanedione is a useful intermediate for the preparation of 1,4-substituted cyclohexanes such as the dioxime,[21] diamine,[22] 1,4-dichloro-1,4-dinitrosocyclohexane,[23] and 1,4-dinitrocyclohexane.[24] It is also the precursor of 7,7,8,8-tetracyanoquinodimethan.[25]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium salt of 2,5-dicarbethoxy-1,4-cyclohexanedione

ethanol (64-17-5)

sulfuric acid (7664-93-9)

ethyl acetate (141-78-6)

Cyclohexanone (108-94-1)

carbon tetrachloride (56-23-5)

sodium (13966-32-0)

phosphoric acid (7664-38-2)

sodium ethoxide (141-52-6)

ethyl 4-bromo-3-ketobutanoate

Diethyl succinate (123-25-1)

1,4-Cyclohexanedione (637-88-7)

2,5-dicarbethoxy-1,4-cyclohexanedione (787-07-5)

ethyl 4-chloro-3-ketobutanoate (638-07-3)

peroxyvanadic acid

diethyl bicyclo[2.2.2]octane-2,5-dione-1,4-dicarboxylate

1,4-dichloro-1,4-dinitrosocyclohexane

1,4-dinitrocyclohexane

7,7,8,8-tetracyanoquinodimethan

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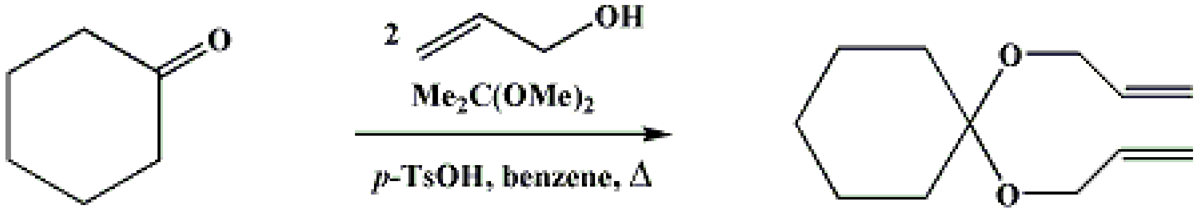
CYCLOHEXANONE DIALLYL ACETAL



Submitted by W. L. Howard and N. B. Lorette[1].
Checked by E. J. Corey and R. A. E. Winter.

1. Procedure

A solution of 294 g. (3 moles) of cyclohexanone, 343 g. (3.3 moles) of acetone dimethyl acetal, 418 g. (7.2 moles) of allyl alcohol, 1 l. of benzene, and 0.2 g. of *p*-toluenesulfonic acid monohydrate (Note 1) is distilled using a good fractionating column until the acetone and the benzene-methanol azeotrope are completely removed (Note 2). The solution is cooled below the boiling point, and a solution of 0.5 g. of sodium methoxide in 20 ml. of methanol is added all at once with stirring (Note 3). Distillation is resumed, and unreacted allyl alcohol and benzene are removed at atmospheric pressure and then at reduced pressure (Note 4). Distillation is continued at a pressure in the range 5–20 mm. to remove forerun (on the order of 100 ml.) (Note 5). The cyclohexanone diallyl acetal, b.p. 84°/5 mm., 98°/10 mm., 114°/20 mm., n_D^{25} 1.4600, is then collected. The yield is 382–435 g. (65–74%). A small amount of higher-boiling residue remains.

2. Notes

1. Commercial acetone dimethyl acetal and allyl alcohol from The Dow Chemical Company and cyclohexanone from Eastman Kodak Company were used without further treatment.
2. These reaction products distil within a narrow range. The head temperature was maintained in the range 56–59°. About 750 ml. of distillate is collected, depending on the efficiency of fractionation. The combined amount of methanol and acetone may be estimated by washing an aliquot of the distillate with 2 volumes of water and taking the difference between the original volume and that of the residual benzene as the volume of methanol-acetone. Usually this is about 450 ml. The distillation should be as rapid as possible to avoid the formation of by-product 2-allylcyclohexanone. A 1.9 × 120 cm. vacuum-jacketed, silvered column packed with 0.25-in. glass helices and fitted with a vapor-dividing head controlled by a timed relay was used.
The checkers used a 1.3 × 92 cm. vacuum-jacketed, silvered column packed with 0.25-in. glass ring chains. With this column it was necessary to carry out

the distillation of benzene-acetone-methanol using reflux ratios varying from 2:1 initially to 11:1 at the conclusion. The use of a shorter column is not satisfactory.
3. Other soluble, non-volatile bases may be used to neutralize the acid. The reactants may be kept at room temperature safely after addition of base.
4. An azeotrope of benzene and allyl alcohol distils at about 77°, followed by benzene. When the temperature in the boiling flask reaches 120–130°, the pressure is reduced and the remaining benzene is taken to a cold trap.
5. The forerun contains some acetone diallyl acetal and about 35–40 g. of 2-allylcyclohexanone, b.p. 78°/10 mm.

3. Discussion

Cyclohexanone diallyl acetal has been prepared from cyclohexanone and allyl orthosilicate[2] and by the above procedure.[3]

4. Merits of Preparation

The preparation given here is operable for a large number of ketone acetals, including those formed from both primary and secondary alcohols and from alcohols and ketones containing other functional groups which are stable under the conditions used.[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 25
- Org. Syn. Coll. Vol. 8, 578

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

benzene-methanol azeotrope

Benzene (71-43-2)

methanol (67-56-1)

Cyclohexanone (108-94-1)

Allyl alcohol (107-18-6)

acetone (67-64-1)

sodium methoxide (124-41-4)

2-Allylcyclohexanone (94-66-6)

methanol-acetone (590-90-9)

acetone dimethyl acetal (77-76-9)

Cyclohexanone diallyl acetal (53608-84-7)

benzene-acetone-methanol

acetone diallyl acetal

allyl orthosilicate

p-toluenesulfonic acid monohydrate (6192-52-5)

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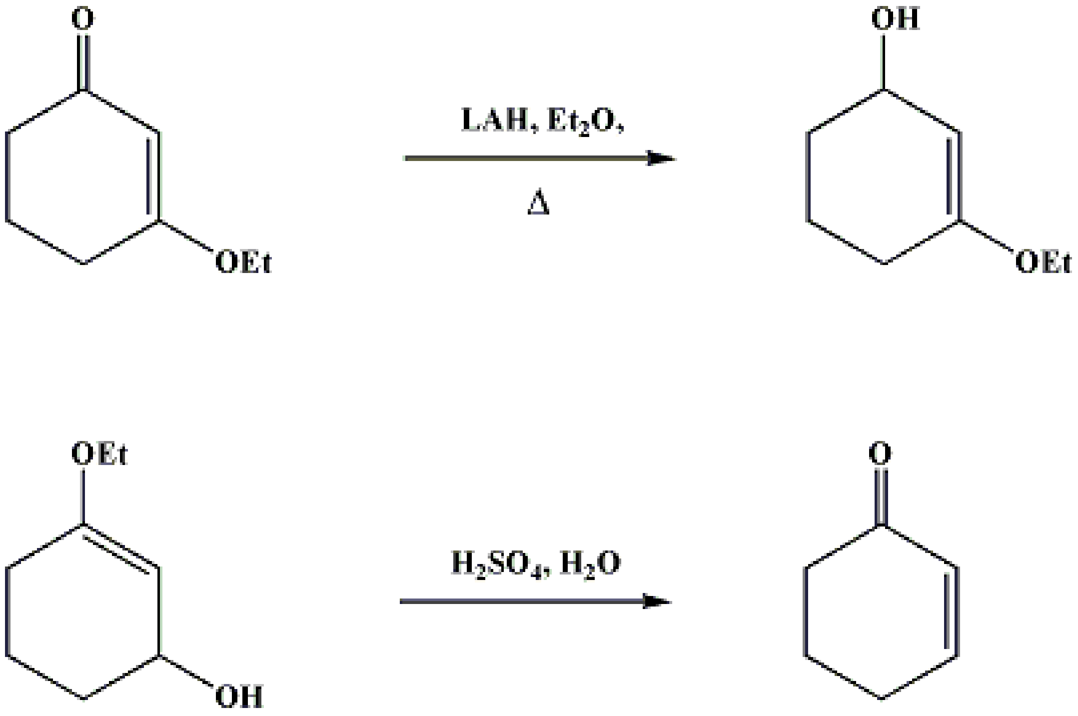
2-CYCLOHEXENONE



Submitted by Walter F. Gannon and Herbert O. House[1].
Checked by William E. Parham, Allan M. Huffman, George J. Meisters, and Wayland E. Noland.

1. Procedure

In a dry 500-ml. three-necked flask, equipped with a reflux condenser, a mechanical stirrer, and a dropping funnel and protected from atmospheric moisture with drying tubes, are placed 6.0 g. (0.16 mole) of lithium aluminum hydride and 200 ml. of anhydrous ether. A solution of 43 g. (0.307 mole) of 3-ethoxy-2-cyclohexenone (Note 1) in 50 ml. of anhydrous ether is added, dropwise and with stirring, to the reaction flask at a rate which maintains gentle refluxing of the solvent (Note 2). After the addition is complete, the reaction solution is boiled under reflux for an additional 30 minutes and then allowed to cool. The complex is hydrolyzed and the excess lithium aluminum hydride is destroyed by the cautious addition, dropwise and with stirring, of 15 ml. of water (Note 3). The resulting reaction mixture is poured into 500 ml. of cold aqueous 10% sulfuric acid. The ether layer which forms is separated, and the residual aqueous phase is extracted with three 300-ml. portions of ether. The combined ether solutions are washed successively with one 100-ml. portion of water and one 100-ml. portion of saturated, aqueous sodium bicarbonate solution and then dried over magnesium sulfate. The ether is removed by distillation through a 50-cm. Vigreux column, and the residue is distilled under reduced pressure through a 40-cm. spinning-band column (Note 4). The yield of 2-cyclohexenone (Note 5), b.p. 56–57.5°/10 mm.

or 96–97°/72 mm., n_D^{27} 1.4858, is 18.2–22.1 g. (62–75%).

2. Notes

1. The preparation of 3-ethoxy-2-cyclohexenone is described elsewhere in this volume.[2] (It has been reported that 3-isobutoxy-2-cyclohexenone can be prepared in somewhat higher yield than the 3-ethoxy compound by the same procedure and that the 3-isobutoxy compound is just as useful for the present preparation (private communication from D. A. H. Taylor).
2. This addition requires approximately 1.5 hours.
3. The addition of water is accompanied by foaming, and care must be taken to avoid excessive loss of the solvent.
4. The 2-cyclohexenone obtained by an ordinary distillation at this point is contaminated with lower-boiling impurities (see (Note 5)), primarily ether and ethanol.
5. The purity of the 2-cyclohexenone may be assayed by gas chromatography on an 8 mm. × 215 cm. column heated to 125° and packed with di-(2-ethylhexyl) sebacate suspended on ground firebrick. This method of analysis indicates that the 3-cyclohexenone in the product amounts to no more than 3%. The fore-run from this fractional distillation contains substantial amounts of 2-cyclohexenone accompanied by ether, ethanol, and minor amounts of other lower-boiling impurities. Additional quantities of pure 2-cyclohexenone can be recovered by redistillation of this fore-run. The preparation of 2-cyclohexenone has been run on twice the scale described with no loss in yield. The ultraviolet spectrum of an ethanol solution of the 2-cyclohexenone obtained has a maximum at 226 m• (ε = 10,400).

3. Discussion

2-Cyclohexenone has been prepared by dehydrohalogenation of 2-bromocyclohexanone,[3,4] by the hydrolysis and oxidation of 3-chlorocyclohexene,[5] by the dehydration of α-hydroxycyclohexanone,[6] by the oxidation of cyclohexene with chromic acid[7] or hydrogen peroxide in the presence of a vanadium catalyst,[8] by the addition of acrolein to ethyl acetoacetate followed by cyclization, hydrolysis, and decarboxylation,[9] by the reduction of N,N-dimethylaniline with sodium and ethanol in liquid ammonia followed by hydrolysis,[10] by the reduction of anisole with lithium in liquid ammonia,[11] and by the reduction of 3-alkoxy-2-cyclohexanones with lithium aluminum hydride followed by acid-catalyzed hydrolysis and rearrangement.[12]

The procedure described illustrates a general method for the preparation of α,β-unsaturated aldehydes and ketones from the enol ethers of β-dicarbonyl compounds.[12,13,14]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 539
- Org. Syn. Coll. Vol. 6, 679

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

sulfuric acid (7664-93-9)

ammonia (7664-41-7)

ether (60-29-7)

Acrolein (107-02-8)

sodium bicarbonate (144-55-8)

Cyclohexene (110-83-8)

Anisole (100-66-3)

sodium (13966-32-0)

chromic acid (7738-94-5)

hydrogen peroxide (7722-84-1)

N,N-dimethylaniline (121-69-7)

Ethyl acetoacetate (141-97-9)

lithium (7439-93-2)

magnesium sulfate (7487-88-9)

Vanadium (7440-62-2)

lithium aluminum hydride (16853-85-3)

2-bromocyclohexanone

α-hydroxycyclohexanone

2-Cyclohexenone (930-68-7)

3-Ethoxy-2-cyclohexenone (5323-87-5)

3-isobutoxy-2-cyclohexenone

3-cyclohexenone

3-chlorocyclohexene

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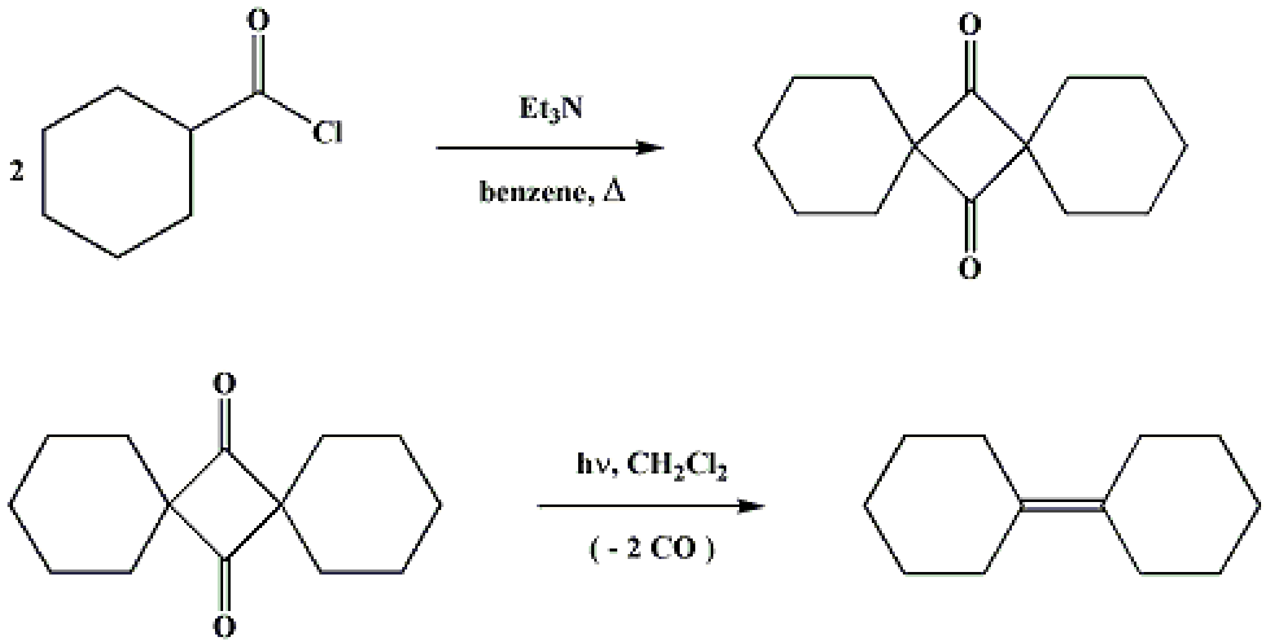
CYCLOHEXYLIDENECYCLOHEXANE

[Bicyclohexylidene]



Submitted by Nicholas J. Turro[1], Peter A. Leermakers[2], and George F. Vesley[2].
Checked by Alex G. Fallis and Peter Yates.

1. Procedure

A. *Dispiro[5.1.5.1]tetradecane-7,14-dione*. Cyclohexanecarbonyl chloride (Note 1) (30.0 g., 0.205 mole) and 250 ml. of dry benzene are placed in a three-necked, round-bottomed flask equipped with a stirrer, condenser, and dropping funnel. A nitrogen atmosphere is maintained in the system. Dry triethylamine (35.0 g., 0.35 mole) is slowly added, and the mixture is heated under reflux overnight. The amine hydrochloride is then filtered, and the filtrate is washed with dilute hydrochloric acid and with water. Solvent is removed on a steam bath, and the residue is recrystallized from ligroin-ethanol; yield 11–13 g. (49–58%), m.p. 161–62°.

B. *Cyclohexylidenecyclohexane*. In a Hanovia 450-watt immersion photochemical reactor (Note 2), equipped with a side arm attachment to monitor gas evolution, is placed 15 g. (0.068 mole) of dispiro[5.1.5.1]tetradecane-7,14-dione dissolved in 150 ml. of methylene chloride. The sample is irradiated, and carbon monoxide starts to evolve rapidly after a few minutes. Irradiation is continued until gas evolution has ceased, usually about 8–10 hours (Note 3). After the irradiation most of the solvent is removed on a steam bath. The residual oil is transferred to a sublimator. The sublimator, with the cold finger removed, is placed in a vacuum desiccator, and the system is evacuated to remove any remaining methylene chloride. The semisolid residue is then sublimed at 45° (1 mm.) to yield 7 g. (63%) of crude cyclohexylidenecyclohexane. The product after recrystallization from

methanol weighs 5.5 g. (49%), m.p. 53–54°.

2. Notes

1. Cyclohexanecarbonyl chloride was obtained from Eastman Organic Chemicals.

2. The reactor, manufactured by the Hanovia Division of Engelhard Industries, consists of a water-jacketed Vycor well through which a stream of water is continuously passed. Since wavelengths shorter than 3000 Å are not needed, the immersion well may be made of Pyrex instead. Within the well is a No. 679A-36 450-watt medium-pressure mercury lamp, also manufactured by Hanovia, and a cylindrical Pyrex filter which surrounds the lamp. The well is placed in an appropriately shaped flask containing the solution to be irradiated. The flask is essentially cylindrical and is equipped with a side arm near the top through which gas can escape and be bubbled through a container of water. The flask is so designed that the liquid level is above the top of the lamp. The reaction vessel is quite similar to that shown in fig. 1.htm (p. 65).

The same synthesis could be carried out in an ordinary flask using one or two sunlamps or sunlight, but the irradiation time would necessarily be much longer.

3. The system should be relatively free of oxygen during irradiation. Oxygen apparently combines with a photochemical intermediate to form cyclohexanone.[3] Under the conditions recommended in the procedure, oxygen is prevented from entering the system by the water trap which also serves as a monitor for gas evolution.

3. Discussion

Ethyl 1-bromocyclohexanecarboxylate, when treated with magnesium in anhydrous ether-benzene with subsequent addition of cyclohexanone, yields ethyl 1-(1-hydroxycyclohexyl) cyclohexanecarboxylate. Dehydration and saponification give rise to 1-(1-cyclohexenyl) cyclohexanecarboxylic acid, which upon decarboxylation at 195° yields cyclohexylidenecyclohexane in 8% overall yield, m.p. 54°.[4] This olefin has also been prepared by the debromination of 1,1'-dibromobicyclohexyl with zinc in acetic acid.[5]

The preparation of the dispiro[5.1.5.1]tetradecane-7,14-dione intermediate is essentially that of Walborsky and Buchman.[6]

4. Merits of the Preparation

The most obvious features of this synthesis are its simplicity and overall yield, which appear to be superior to those of any other published report. An important merit lies in the generality of the reaction, and the fact that it is an example of a reasonably large-scale photochemical preparation. Tetramethylethylene is readily produced from commercially available tetramethyl-1,3-cyclobutanedione by an identical route.[7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 470

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ligroin-ethanol

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

methanol (67-56-1)

ether (60-29-7)

carbon monoxide (630-08-0)

magnesium (7439-95-4)

Cyclohexanone (108-94-1)

oxygen (7782-44-7)

nitrogen (7727-37-9)

zinc (7440-66-6)

methylene chloride (75-09-2)

tetramethylethylene (563-79-1)

tetramethyl-1,3-cyclobutanedione (933-52-8)

triethylamine (121-44-8)

cyclohexanecarbonyl chloride (2719-27-9)

Cyclohexylidenecyclohexane, Bicyclohexylidene (4233-18-5)

Dispiro[5.1.5.1]tetradecane-7,14-dione (950-21-0)

Ethyl 1-bromocyclohexanecarboxylate

ethyl 1-(1-hydroxycyclohexyl)cyclohexanecarboxylate

1-(1-cyclohexenyl)cyclohexanecarboxylic acid

1,1'-dibromobicyclohexyl

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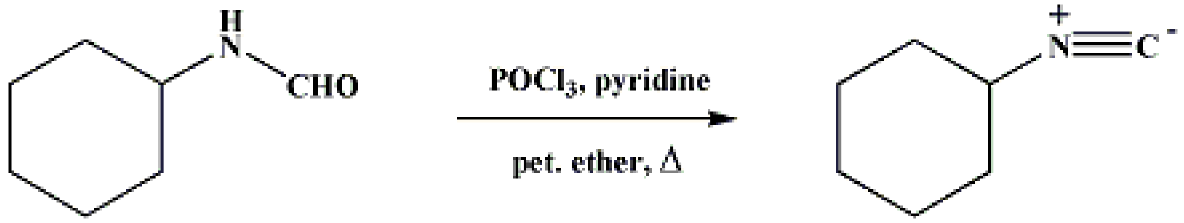
CYCLOHEXYL ISOCYANIDE



Submitted by Ivar Ugi, Rudolf Meyr, Martin Lipinski, Ferdinand Bodesheim, and Friedrich Rosendahl[1].
Checked by B. C. McKusick and M. E. Hermes.

1. Procedure

Caution! Isocyanides should be prepared in a hood since they have pungent odors and some are known to be toxic.

A solution consisting of 127 g. (1.00 mole) of N-cyclohexylformamide (Note 1), 500 ml. (490 g., 6.2 moles) of pyridine, and 300 ml. of petroleum ether (b.p. 40–60° or 30–60°) is charged into a 2-l., three-necked, round-bottomed flask equipped with a Hershberg stirrer,[2] dropping funnel, reflux condenser, and thermometer. The flask is immersed in an ice bath, and 92 g. (0.60 mole) of phosphorous oxychloride is added from the dropping funnel to the stirred mixture in the course of 30–40 minutes. The mixture is stirred under reflux for 10 minutes after all the phosphorus oxychloride is added. The mixture is then cooled to 0–5°; this converts it to a heavy slurry. Ice water (800 ml.) is gradually added with stirring, and stirring of the cold mixture is continued until all solid material has dissolved. The organic phase is separated in a separatory funnel. The aqueous phase is extracted with three 60-ml. portions of petroleum ether, and the extracts are combined with the organic phase, which is then extracted with three 100-ml. portions of water, dried over 20 g. of magnesium sulfate, and distilled through a 40-cm. vacuum-jacketed Vigreux column (Note 2). The petroleum ether is rapidly removed under slightly reduced pressure from a bath at a temperature not exceeding 50–60°. Cyclohexyl isocyanide, a colorless foul-smelling liquid (Note 3), is collected at 56–58° /11 mm.; weight 73–79 g. (67–72%); n_D^{25} 1.4488–1.4501.

2. Notes

1. The checkers prepared N-cyclohexylformamide by slowly adding 260 g. (3.52 moles) of ethyl formate with stirring to 396 g. (4.00 moles) of cyclohexylamine in a flask immersed in an ice bath. After the exothermic reaction ceased, the solution was refluxed for 2 hours and distilled through a 25-cm. Vigreux column to give 403 g. (90%) of N-cyclohexylformamide, b.p. 137–138° /10 mm., n_D^{25}

1.4849.[3]

2. The checkers used a 50-cm. spinning-band column.[4] In order to minimize resinification of the cyclohexyl isocyanide, distillation should be as rapid as possible and the temperature in the still pot should not exceed 90°.

3. The disagreeable odor of cyclohexyl isocyanide can be removed from the equipment used in this preparation by washing it with 5% methanolic sulfuric acid solution.

3. Discussion

A variety of methods has been employed in the synthesis of cyclohexyl isocyanide[5] but the dehydration of N-cyclohexylformamide is the most favorable method.

Of the numerous dehydrating agent/base systems which have been used in the preparation of isonitriles, the phosgene/tertiary amine system seems to afford the best yields. Examples of the phosgene procedure may be found in reference [5]. The disadvantage of phosgene is its extreme toxicity and the difficulty with which it is handled by the novice. The present procedure is therefore the best combination of convenience and safety for the preparation of aliphatic isocyanides boiling above ethyl isocyanide. (Methyl and ethyl isocyanides may be prepared by using high-boiling amines like quinoline.) It has been applied to the synthesis of the following isocyanides:[5] isopropyl (38%), *n*-butyl (61%), *t*-butyl (68%), and benzyl (56%). In preparing isopropyl isocyanide or *t*-butyl isocyanide, the petroleum ether should be of boiling point 30–35°, as otherwise it is difficult to separate these low-boiling isocyanides in the indicated yield, and, even then, substantial amounts of isocyanide are found in the petroleum ether fraction.

Aromatic isocyanides can also be prepared conveniently by the dehydration of the corresponding formamides by phosphorous oxychloride, but much better results are obtained if the reaction is done in the presence of potassium *t*-butoxide rather than pyridine.[6] The preparation of methyl isocyanide by the dehydration of N-methylformamide with *p*-toluenesulfonyl chloride and quinoline is described elsewhere in this volume.[7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 772
- Org. Syn. Coll. Vol. 5, 1060
- Org. Syn. Coll. Vol. 6, 232
- Org. Syn. Coll. Vol. 7, 27

8

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

Methyl and ethyl isocyanides

sulfuric acid (7664-93-9)

Phosphorus Oxychloride (21295-50-1)

pyridine (110-86-1)

phosgene (75-44-5)

ethyl formate (109-94-4)

Quinoline (91-22-5)

benzyl (2154-56-5)

n-Butyl (2492-36-6)

magnesium sulfate (7487-88-9)

cyclohexylamine (108-91-8)

isopropyl (2025-55-0)

Ethyl isocyanide (624-79-3)

t-Butyl (1605-73-8)

Cyclohexyl isocyanide (931-53-3)

N-cyclohexylformamide (766-93-8)

phosphorous oxychloride

isopropyl isocyanide (598-45-8)

Methyl isocyanide (593-75-9)

N-methylformamide (123-39-7)

p-Toluenesulfonyl chloride (98-59-9)

t-butyl isocyanide (7188-38-7)

potassium t-butoxide (865-47-4)

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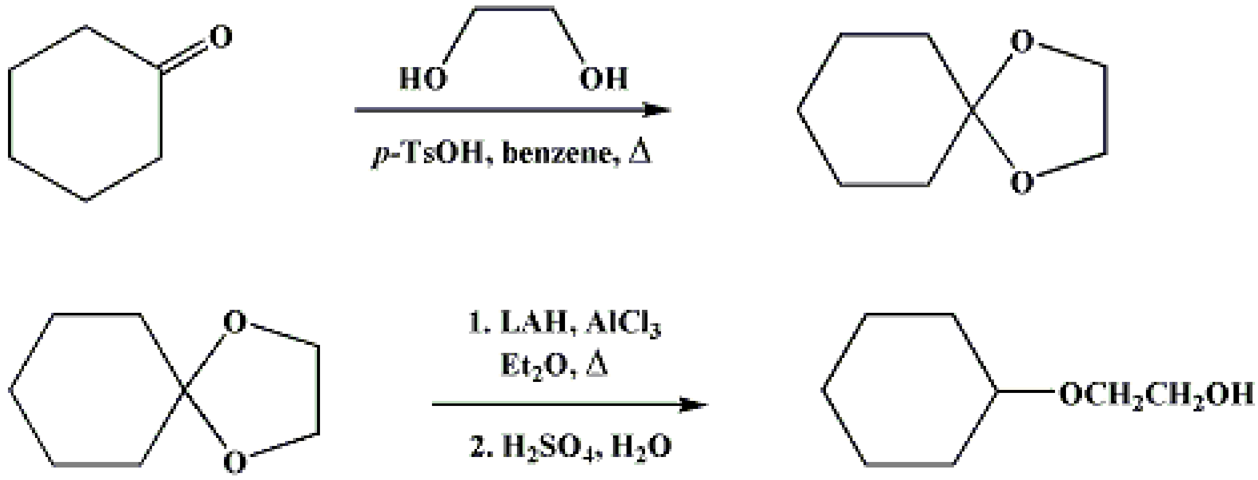
Organic Syntheses, CV 5, 303

2-CYCLOHEXYLOXYETHANOL

[Ethanol, 2-(cyclohexyloxy)-]



Submitted by Ronald A. Daignault and E. L. Eliel[1].
Checked by J. R. Edman and B. C. McKusick.

1. Procedure

A. *1,4-Dioxaspiro[4.5]decane*. A 1-l. round-bottomed flask is charged with 118 g. (1.20 moles) of cyclohexanone, 82 g. (1.32 moles) of 1,2-ethanediol, 250 ml. of reagent grade benzene, and 0.05 g. of *p*-toluenesulfonic acid monohydrate. The flask is attached to a water separator[2] under a reflux condenser fitted with a drying tube. A heating mantle is placed under the flask, and the reaction mixture is refluxed until close to the theoretical amount of water (21.6 ml.) has collected in the trap; this requires about 6 hours. The reaction mixture is cooled to room temperature, extracted successively with 200 ml. of 10% sodium hydroxide solution and five 100-ml. portions of water, dried over anhydrous potassium carbonate, and distilled through a 20-cm. Vigreux column. 1,4-Dioxaspiro[4.5]decane is obtained as a colorless liquid, b.p. 65–67° (13 mm.), weight 128–145 g. (75–85%), n^{25}D 1.4565–1.4575.

B. *2-Cyclohexyloxyethanol*. A well-dried, 3-l. three-necked, round-bottomed flask is equipped with a stirrer, a pressure-equalizing dropping funnel, and a condenser to whose top is attached a calcium chloride drying tube. The flask is charged with 242 g. (1.81 moles) of anhydrous aluminum chloride powder and is immersed in an ice-salt bath. Anhydrous ether (25–50 ml.) is added dropwise through the dropping funnel, stirring is begun as soon as possible, and an additional 450–475 ml. of ether is added rapidly (total volume of ether added: 500 ml.). The mixture is stirred for approximately 30 minutes and becomes a light gray solution. During this period a mixture of 16.7 g. (0.44 mole) of lithium aluminum hydride and 500 ml. of anhydrous ether is vigorously stirred in a 1-l. round-bottomed flask under a nitrogen atmosphere (Note 1). The

resulting suspension is added to the ethereal aluminum chloride solution through the dropping funnel. The resulting mixture, a gray slurry, is stirred for at least 30 minutes.

A solution of 125 g. (0.88 mole) of 1,4-dioxaspiro[4.5]decane in 200 ml. of anhydrous ether is added at a rate to cause gentle refluxing. The ice-salt bath is replaced by a steam bath, and the reaction mixture is refluxed for 3 hours. The calcium chloride drying tube is removed, and the steam bath is replaced by an ice bath. The excess hydride is carefully destroyed by adding water dropwise until hydrogen is no longer evolved; about 12 ml. of water is needed. This is followed by the more rapid addition of 1 l. of 10% sulfuric acid and then 400 ml. of water. This combination dissolves all the inorganic salts formed and results in the formation of two clear layers. The ether layer is separated in a 3-l. separatory funnel, and the aqueous layer is extracted with three 200-ml. portions of ether. The combined ethereal extracts are washed successively with 200 ml. of saturated sodium bicarbonate solution and 200 ml. of saturated brine. The ethereal solution is dried overnight over anhydrous potassium carbonate, filtered through a fluted filter paper, and concentrated by distillation on a steam bath. The residue, a pale yellow liquid weighing about 130 g., is distilled through a 20-cm. Vigreux column under reduced pressure. 2-Cyclohexyloxyethanol is obtained as a colorless liquid, b.p. 96–98° (13 mm.), weight 105–119 g. (83–94%), n^{25}_{D} 1.4600–1.4610.

2. Notes

1. Most of the lithium aluminum hydride is in solution, but some is in suspension. When the humidity is below 35%, lithium aluminum hydride can be weighed in air; otherwise the weighing should be done in a dry box. Although some workers pulverize lithium aluminum hydride before dissolving or suspending it in a liquid, *the checkers recommend that this not be done because it has led to several explosions in their laboratory*. The present procedure gives a fine suspension that generally passes through the stopcock of the dropping funnel without plugging it. A wooden stick or copper wire should be in readiness to clear the stopcock if it plugs up.
Twice the theoretical amount of lithium aluminum hydride is used, but this is necessary for the best yields.

3. Discussion

The method of preparing 1,4-dioxaspiro[4.5]decane is that of Salmi.[3] The methods used by Lorette and Howard[4] to prepare ketals are convenient for preparing 1,4-dioxaspiro[4.5]decane.

The present method of preparing 2-cyclohexyloxyethanol has been described before,[5] but on a smaller scale. Other β-hydroxy ethers[5] and β-hydroxy thio ethers[6] can be prepared by the same method. Hydrogenolysis of the C-O bond in acetals has also

been reported[7] with diisobutylaluminum hydride; for example, 2-cyclohexyloxyethanol was obtained in 91% yield in this manner.

2-Cyclohexyloxyethanol has also been prepared by reduction of cyclohexyloxyacetic acid with lithium aluminum hydride[8] and by decomposition of cyclohexanone methanesulfonylhydrazone with sodium in ethylene glycol.[9]

4. Merits of the Preparation

The method described is more convenient than earlier methods of preparing 2-cyclohexyloxyethanol. It may be adapted to the preparation of other β-hydroxyethyl and γ-hydroxypropyl ethers[5] and the corresponding thio ethers.[6,10] Although ketals are resistant to reduction by lithium aluminum hydride alone, the presence of a Lewis acid facilitates C-O cleavage, presumably via an oxocarbonium ion,[11] as the procedure demonstrates.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

brine

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

Benzene (71-43-2)

ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

Cyclohexanone (108-94-1)

nitrogen (7727-37-9)

copper (7440-50-8)

aluminum chloride, aluminum chloride powder (3495-54-3)

sodium (13966-32-0)

ethylene glycol, 1,2-ethanediol (107-21-1)

lithium aluminum hydride (16853-85-3)

diisobutylaluminum hydride (1191-15-7)

2-Cyclohexyloxyethanol, Ethanol, 2-(cyclohexyloxy)- (1817-88-5)

1,4-Dioxaspiro[4.5]decane (177-10-6)

cyclohexyloxyacetic acid

cyclohexanone methanesulfonylhydrazone

p-toluenesulfonic acid monohydrate (6192-52-5)

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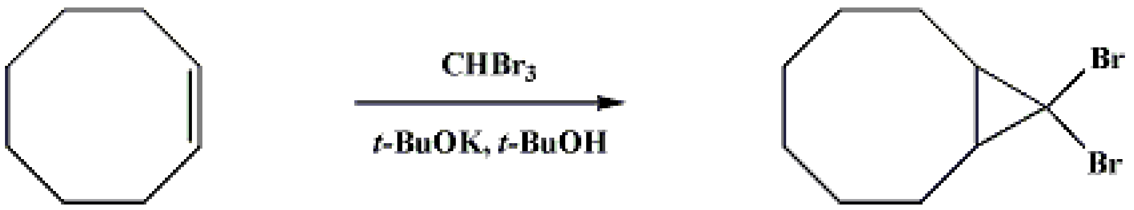
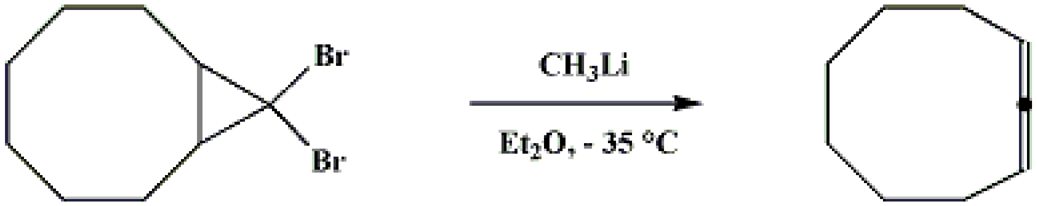
Organic Syntheses, CV 5, 306

1,2-CYCLONONADIENE





Submitted by L. Skattebøl and S. Solomon[1].
Checked by L. S. Keller and K. B. Wiberg.

1. Procedure

A. *9,9-Dibromobicyclo[6.1.0]nonane*. A dry 3-l. three-necked flask is fitted with a glass stopper, stirrer, and condenser. The flask is kept under a positive nitrogen pressure by means of a gas-trap arrangement connected to the top of the condenser (Note 1). The flask is quickly charged with 2 l. of anhydrous *t*-butyl alcohol (Note 2) and 73 g. (1.87 g. atoms) of potassium metal. *(Caution! See earlier volume[2] for handling of this metal.)* The flow of nitrogen is stopped and the mixture is stirred and boiled under reflux until the potassium has reacted, hydrogen being liberated through the trap. The condenser is arranged for distillation by means of an adapter. The glass stopper is replaced by a pressure-equalized dropping funnel with the nitrogen inlet connected to the top. About 1.5 l. of *t*-butyl alcohol (Note 3) is then distilled into a predried flask under an atmosphere of nitrogen. A water pump is then connected, the nitrogen inlet is closed, and the distillation is continued under reduced pressure while the three-necked flask is gradually heated to 150° in an oil bath. Finally, the water pump is replaced by an oil pump and the white remaining solid is heated at 150° under a pressure of 0.1–1 mm. for 2 hours. The connection to the vacuum system is closed, the oil bath removed, and nitrogen again introduced. The condenser with adapter is replaced by a glass stopper, and the flask is cooled in an ice-salt bath.

Freshly distilled *cis*-cyclooctene, 178 g. (214 ml., 1.62 moles) (Note 4) and 200 ml. of sodium-dried pentane (Note 5) are introduced to the flask, and the dropping funnel is charged with 420 g. (148 ml., 1.66 moles) of bromoform (Note 6). The bromoform is added dropwise to the stirred slurry over a period of 6–7 hours, the color of the reaction mixture changing gradually from light yellow to brown. When the addition is

complete, the reaction mixture is allowed to warm to room temperature and left stirring overnight. Water (400 ml.) is added to the reaction mixture followed by enough 10% aqueous hydrochloric acid to neutralize the slightly basic solution. The reaction mixture is transferred to a separatory funnel and the organic layer is separated. The aqueous layer is extracted with three 50-ml. portions of pentane, and the combined pentane solutions are washed with three 50-ml. portions of water. The pentane solution is dried over anhydrous magnesium sulfate, filtered, and stripped of solvent on a rotary evaporator. Distillation of the residue yields 237–299 g. (52–65%) of 9,9-dibromobicyclo[6.1.0]nonane, b.p. 62° (0.04 mm.), n^{23}D 1.5493–1.5507 (Note 7).

B. *1,2-Cyclononadiene*. A dry 2-l. three-necked flask is equipped with mechanical stirrer, pressure-equalized dropping funnel, and a nitrogen inlet tube connected to a gas-trap arrangement (Note 1). To the flask are added 187 g. (116 ml., 0.66 mole) of 9,9-dibromobicyclo[6.1.0]nonane and 100 ml. of anhydrous ether. The dropping funnel is charged with 450 ml. of 1.9*M* ether solution of methyllithium (0.85 mole) (Note 8). The flask is cooled by means of an acetone-dry ice bath maintained at −30° to −40°, and the methyllithium is added dropwise with stirring during 1 hour (Note 9). After the addition is complete, the reaction mixture is stirred for 30 minutes, and excess lithium reagent is decomposed by dropwise addition of 100 ml. of water. An additional 400 ml. of water is then added, and the ether layer is separated. The aqueous layer is extracted with three 30-ml. portions of ether. The combined ether solutions are washed with 30-ml. portions of water until neutral and dried over magnesium sulfate. The latter is filtered and the ether is distilled through a 40-cm Vigreux column. Distillation of the residue (Note 10) yields 66–73 g. (81–91%) of 1,2-cyclononadiene, b.p. 62–63° (16 mm.), n^{20}D 1.5060 (Note 11).

2. Notes

1. A suitable gas-trap has been described.[3] Mercury can conveniently be replaced by paraffin oil.
2. Reagent grade *t*-butyl alcohol distilled from calcium hydride was used.
3. The *t*-butyl alcohol thus recovered can be used for a second preparation without further purification.
4. *cis*-Cyclooctene was obtained from Columbia Organic Chemicals or Aldrich Chemical Co. It was distilled from sodium and a fraction, b.p. 81–82° (95 mm.), n^{25}D 1.4682, was used. Gas chromatography showed 98% purity, the impurity being mainly cyclooctane.
5. Pentane is added as a diluent in order to obtain an easily stirred slurry. Amounts varying from 100 to 250 ml. per mole of olefin have been used with no appreciable change in yield of product.
6. Reagent grade bromoform was used without further purification.
7. The submitters have also used commercially available dry potassium *t*-butoxide with varying success in this reaction; with a sample purchased from M.

S.A. Research Corporation a 65% yield of product was obtained. The submitters reported a 65–76% yield range for this step.
8. An ethereal solution of methyllithium was either prepared from lithium metal and methyl bromide or purchased from Alfa Inorganics, Inc. Concentrations of 0.5–2*M* were used with no change in result.
9. Solid methyllithium and lithium halide occasionally separate out on the tip of the dropping funnel, probably owing to the low temperature, and this may cause plugging. It can be avoided by using a faster rate of addition.
10. The submitters used a 40-cm. spinning band column. Owing to polymerization of the product, the checkers obtained consistently low yields when this column was used. Distillation through a 40-cm. Vigreux column gave the indicated yield without a significant decrease in product purity.
11. The product is more than 99% pure as shown by gas chromatography.

3. Discussion

Cyclic allenes have previously been obtained only admixed with the isomeric acetylenes.[4] The present two-step synthesis is a practical method for the preparation of cyclic allenes, and at the same time it describes a general method for the preparation of allenes.[5,6] It is based on the original work of Doering and co-workers.[7] Examples of the reaction sequence above are known in which allenes are not produced,[8] or they represent only a part of the reaction products.[9] A one-step synthesis of 1,2-cyclononadiene has been reported.[10]

R-(+)-1,2-Cyclononadiene and S-(–)-1,2-cyclononadiene have been prepared from R-(–)- and S-(+)-*trans*-cyclooctene, respectively.[11] Optically active 1,2-cyclononadiene has also been obtained when the reaction of the dibromo bicyclo intermediate with methyllithium is carried out in the presence of an optically active amine.[12] Reduction of 1,2-cyclononadiene with sodium in liquid ammonia gives *cis*-cyclononadiene in almost quantitative yield.[13]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium-dried pentane

S-(−)-1,2-cyclononadiene

R-(−)- and S-(+)-trans-cyclooctene

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ether (60-29-7)

hydrogen (1333-74-0)

nitrogen (7727-37-9)

mercury (7439-97-6)

sodium (13966-32-0)

methyl bromide (74-83-9)

potassium (7440-09-7)

Pentane (109-66-0)

bromoform (75-25-2)

lithium (7439-93-2)

magnesium sulfate (7487-88-9)

Methyllithium (917-54-4)

t-butyl alcohol (75-65-0)

calcium hydride (7789-78-8)

1,2-Cyclononadiene, R-(+)-1,2-Cyclononadiene (1123-11-1)

9,9-Dibromobicyclo[6.1.0]nonane (1196-95-8)

cyclooctane (292-64-8)

potassium t-butoxide (865-47-4)

cis-cyclooctene (931-87-3)

cis-cyclononadiene

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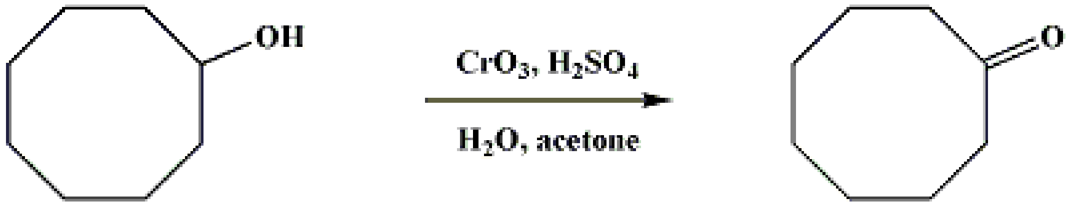
Organic Syntheses, CV 5, 310

CYCLOÖCTANONE



Submitted by E. J. Eisenbraun[1]
Checked by E. J. Corey and Ernest Hamanaka.

1. Procedure

The chromic acid oxidizing reagent is prepared by dissolving 67 g. of chromium trioxide in 125 ml. of distilled water. To this solution is added 58 ml. of concentrated sulfuric acid (sp. gr. 1.84), and the salts which precipitate are dissolved by addition of a minimum quantity of distilled water; the total volume of the solution usually does not exceed 225 ml.

A solution of 64 g. (0.5 mole) of cycloöctanol (Note 1) in 1.25 l. of acetone (Note 1) is added to a 2-l. three-necked flask fitted with a long-stem dropping funnel, a thermometer, and a powerful mechanical stirrer (Note 2). The vigorously agitated solution is cooled in a water bath to about 20°. The chromic acid oxidizing reagent is added from the dropping funnel as a slow stream, and the rate of addition is adjusted so that the temperature of the reaction mixture does not rise above 35° (Note 3). The addition is continued until the characteristic orange color of the reagent persists for about 20 minutes (Note 4) and (Note 5). The volume of reagent added is about 120 ml.

The stirrer is removed, the mixture is decanted into a 2-l. round-bottomed flask, and the residual green salts are rinsed with two 70-ml. portions of acetone. The rinsings are added to the main acetone solution and additional oxidizing agent is added, if necessary, to ensure complete reaction. The stirrer is replaced and isopropyl alcohol is added dropwise until the excess chromic acid is destroyed (Note 6). In small portions and with caution there is added 63 g. of sodium bicarbonate, and the suspension is stirred vigorously until the pH of the reaction mixture tests neutral (Note 7). The suspension is filtered and the filter cake is washed with 25 ml. of acetone. The filtrate is concentrated by distillation through a 75-cm. length of Vigreux column until the pot temperature rises to 80° and a water film begins to develop in the lower portions of the distillation column (Note 8). The cooled pot residue (about 110 ml.) is transferred to a 1-l. separatory funnel, 500 ml. of saturated sodium chloride solution is added, and the mixture is extracted with two 150-ml. portions of ether. The ether extracts are combined, washed with a total of 25 ml. water in several portions, dried over anhydrous magnesium sulfate, filtered, and the ether distilled at atmospheric pressure. The pot residue is distilled under reduced pressure, b.p. 76–77° (10 mm.) (Note 9).

The yield of cycloöctanone is 58–60 g. (92–96%), m.p. 40–42°.

An additional 2.2 g. (4%) of cycloöctanone may be obtained by addition of 250 ml. of water to the green salts formed during the reaction (Note 10), extraction of the mixture with ether, distillation of the ether, and addition of 12 ml. of acetone. To the acetone solution there is added sufficient chromic acid oxidizing reagent to permit the orange color of the reagent to persist (Note 11), and the mixture is processed as above.

2. Notes

1. Cycloöctanol is available from Aldrich Chemical Company, Inc. A redistilled solvent grade of acetone is satisfactory.
2. The submitter has also carried out this preparation starting from 2 moles of cycloöctanol. An 8-l. Pyrex® bottle, Corning No. 1595, is ideally suited for this scale. A round-bottomed flask is less desirable because it is necessary to see into the reaction vessel. Vigorous stirring is essential; a Lightnin Model L stirrer fitted with two 2-in., three-blade propellers is adequate for the larger-scale run. A cold-water bath for the 8-l. bottle may be conveniently constructed from an open-top 5-gallon solvent can by cutting a 1.5-cm. hole 5 cm. from the bottom and a 2.8-cm. hole 5 cm. from the top. These holes are respectively fitted with a rubber inlet tube (11/16 in. O.D. by 3/8 in. I.D.) and a rubber outlet tube (1 in. O.D. by 1 in. I.D.). The rubber tubing fits directly in the holes without adapter or nipples.
3. The temperature is kept below 35° to avoid the use of a condenser.
4. The characteristic end point orange color can be demonstrated by addition of a slight excess of the chromic acid oxidizing reagent to a few milliliters of acetone containing a few drops of isopropyl alcohol.
5. The course of the reaction can conveniently be followed by gas chromatography. A sample of the reaction mixture is withdrawn at intervals, neutralized with solid sodium bicarbonate, dried over magnesium sulfate, and injected directly into a gas chromatography column consisting of 15% phenyldiethanolamine succinate (PDEAS) substrate coated on 60/80 mesh, acid-washed fire brick contained in a in. by 5 ft. spiral-shaped copper tube. A Wilkens Instrument and Research, Inc., gas chromatography apparatus, Model A-90-P, operating at column temperature of 155°, 80 ml. per min. helium flow, was used. Complete separation of peaks (5.9 minutes for cycloöctanone, 7.0 minutes for cycloöctanol) is observed, and the reaction is considered complete when a peak for cycloöctanol can no longer be observed in the gas chromatogram.
6. The reaction mixture must be slightly acidic for the oxidation to proceed. On one occasion it was necessary to add a few drops of sulfuric acid to consume the oxidizing agent completely.
7. Calcium carbonate has also been used to remove residual acid.
8. If additional runs are contemplated, the recovered acetone may be used again.
9. A heat lamp may be used to prevent solidification during distillation.

10. The chromium salts formed during the oxidation are quite sticky and tend to occlude product as well as starting material.
11. The material freed from the chromium salts should be checked for completeness of reaction by gas chromatographic analysis to ensure the absence of starting material.

3. Discussion

Cycloöctanone has been prepared by distilling the calcium and thorium salts of azelaic acid,[2] by heating azelaic acid with barium oxide in the presence of iron,[3] by the action of nitrous acid on 1-(aminomethyl)-cycloheptanol,[4] by Dieckman cyclization of azelaic acid dimethyl ester[4] and diethyl ester,[5] and by ring expansion of cycloheptanone with diazomethane.[6,7]

4. Merits of the Preparation

This preparation illustrates a general and convenient way of oxidizing secondary alcohols to ketones in high yield. This procedure, usually called the Jones oxidation or oxidation by use of the Jones reagent,[8] offers the advantage of almost instantaneous oxidation of the alcohol under mild conditions. The reagent rarely attacks unsaturated centers; using this procedure an 81% yield of 2-cyclohexenone can be obtained from 2-cyclohexenol. The present example illustrates how this reagent can be utilized for a large-scale preparation. The major limitation of the reaction is the low solvent power of acetone. Another example of the Jones oxidation is given on p. 863 of this volume.

An attractive alternative to the Jones oxidation is oxidation with chromic acid in the two-phase system, water-ether, the details of which were reported recently.[9] By this procedure cyclooctanone was obtained in 93% yield (as determined by gas-liquid chromatography). Although the yield of isolated yields of ketones from other secondary alcohols were very good, particularly when a 100% excess of chromic acid was used at 0°.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 866
- Org. Syn. Coll. Vol. 7, 177
- Org. Syn. Coll. Vol. 7, 402

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

calcium and thorium salts of azelaic acid

sulfuric acid (7664-93-9)

ether (60-29-7)

sodium bicarbonate (144-55-8)

iron (7439-89-6)

sodium chloride (7647-14-5)

barium oxide

nitrous acid (7782-77-6)

calcium carbonate (471-34-1)

acetone (67-64-1)

isopropyl alcohol (67-63-0)

chromic acid (7738-94-5)

Azelaic acid (123-99-9)

magnesium sulfate (7487-88-9)

chromium trioxide (1333-82-0)

Diazomethane (334-88-3)

Cycloheptanone (502-42-1)

helium (7440-59-7)

Cyclooctanone (502-49-8)

azelaic acid dimethyl ester (1732-10-1)

2-cyclohexenol

2-Cyclohexenone (930-68-7)

phenyldiethanolamine succinate

1-(aminomethyl)-cycloheptanol

cyclooctanol

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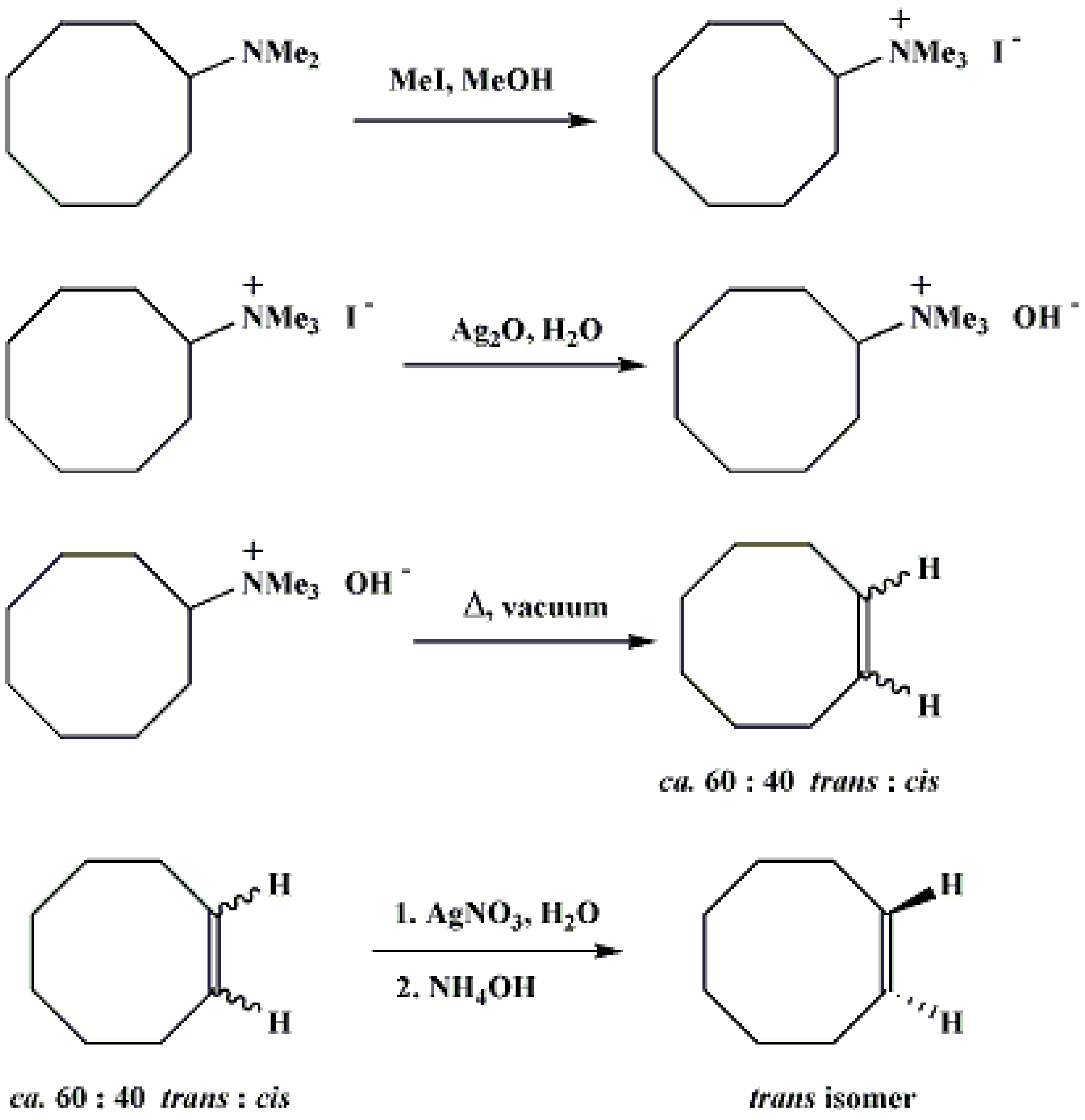
Organic Syntheses, CV 5, 315

trans-CYCLOOCTENE



Submitted by Arthur C. Cope[1] and Robert D. Bach[2].
Checked by A. DeMeijere and K. B. Wiberg.

1. Procedure

A. *N,N,N-Trimethylcyclooctylammonium iodide*. To a 2-l., three-necked, round-bottomed flask equipped with a stirrer, condenser, drying tube, and pressure-equalizing dropping funnel are added 155.3 g. (1 mole) of N,N-dimethylcyclooctylamine (Note 1) and 700 ml. of reagent grade methanol. To the stirred solution is added 170.3 g. (1.2 moles) of iodomethane (Note 2) dropwise over a 30-minute period. The flask is cooled intermittently with an ice bath to keep the reaction temperature at approximately 25° (Note 3). After 1 hour the bath is removed and the reaction mixture is allowed to stir at 25° for an additional 3 hours.

The light yellow solution is transferred to a 2-l. round-bottomed flask, and the solvent is removed under reduced pressure (Note 4) with slight warming. The solid product is triturated with 500 ml. of diethyl ether, filtered, and washed with three 200-ml. portions of diethyl ether. The white solid (291–296 g.) is dried under reduced pressure, m.p. 269–270° dec. (Note 5).

B. *N,N,N-Trimethylcyclooctylammonium hydroxide*. To a 1-l. round-bottomed flask equipped with a stirrer are added 100 g. (0.34 mole) of N,N,N-trimethylcyclooctylammonium iodide, 76 g. of silver oxide (Note 6), and 350 ml. of distilled water. The suspension is stirred at room temperature for 5 hours and is filtered through a Buchner funnel. The filter cake is washed with four 35-ml. portions of distilled water. The light yellow filtrate is transferred to a 1-l. round-bottomed flask and the volume is reduced to approximately 90 ml. employing a rotary evaporator and a 40° water bath. The viscous N,N,N-trimethylcyclooctylammonium hydroxide solution is transferred (Note 7) to a 200-ml. dropping funnel, with a pressure-equalizing side arm, for use in the next step in the synthesis (Note 8).

C. *trans-Cyclooctene*. A 500-ml., three-necked, round-bottomed flask is equipped with a nitrogen inlet capillary tube (Note 9), a short (10–20 cm.) unpacked column (Note 10), and a pressure-equalizing dropping funnel. The round-bottomed flask is connected by the unpacked column to a 100-ml. trap cooled in an ice bath. This trap is then connected to a 200-ml. trap cooled in dry ice-acetone (Note 11). The flask is heated in an oil bath to 110–125°, and the apparatus is evacuated to a pressure of *ca.* 10 mm. under a constant sweep of nitrogen. The hydroxide solution is added dropwise at approximately the rate of decomposition of the quaternary ammonium hydroxide (Note 12).

The combined distillates from the cold traps are allowed to come to room temperature (Note 13) and are placed in a 1-l. separatory funnel with 200 ml. of 5% hydrochloric acid solution. The mixture of *cis*- and *trans*-cyclooctenes (Note 14) is extracted with 200 ml. of *n*-pentane and subsequently with two 50-ml. portions of *n*-pentane. The *n*-pentane extracts are combined and washed with 170 ml. of 5% sodium bicarbonate solution.

To a 1-l. separatory funnel is added *ca.* 500 ml. of 20% aqueous silver nitrate solution (100 g. of Mallinckrodt C.P. crystals to *ca.* 500 ml. of water). The pentane solution is added to the separatory funnel in five approximately equal portions, with intermittent shaking until all the silver nitrate complex has gone into solution (Note 15).

The silver nitrate solution is extracted as described above with three portions of *n*-pentane to remove *cis*-cyclooctene (Note 16). The aqueous silver nitrate solution is added slowly to 300 ml. of concentrated ammonium hydroxide containing cracked ice. The hydrocarbon that separates is extracted with 300 ml. of *n*-pentane as described above and the pentane solution is dried over anhydrous magnesium sulfate and the pentane distilled through a 23 × 250 mm. column packed with glass beads.

The product is distilled under reduced pressure through a short (8 cm.) Vigreux column (Note 17) and has b.p. 75° (78 mm.), 44° (23 mm.), $n^{25}D$ = 1.4741, d_4^{25} = 0.8456. The yield of pure *trans*-cyclooctene is 15.0 – 15.3 g. (40%) (Note 18), (Note 19), (Note 20), (Note 21).

2. Notes

1. Cyclooctylamine was purchased from Aldrich Chemical Co. It was converted to N,N-dimethylcyclooctylamine in 74% yield using a procedure analogous to that for β-phenylethyldimethylamine.[3]
2. Fischer reagent grade methanol and Eastman Organic Chemicals iodomethane were used.
3. The molar ratio of iodomethane to N,N-dimethylcyclooctylamine may be reduced if precautions are taken to prevent loss of iodomethane due to vaporization.
4. It is convenient to use a rotary evaporator for removal of the solvents.
5. After one recrystallization from an acetone-methanol mixture, the compound melts at 273–275° dec. The compound is sufficiently pure for the next step in the synthesis without recrystallization.
6. Mallinckrodt purified silver oxide powder was used. The reaction flask should be protected from direct sunlight with a suitable wrapping.
7. The flask may be rinsed with a minimum of water and transferred to the dropping funnel. The total volume of hydroxide solution at this point should not exceed 100 ml.
8. The conversion of the quaternary ammonium iodide to the hydroxide may also be carried out using a strongly basic ion exchange resin.[4]
9. The decomposition should be carried out under a constant sweep of nitrogen. The nitrogen may be introduced through the pressure-equalizing dropping funnel if that is more convenient.
10. The unpacked column should be wrapped with a heating tape, or Nichrome heating wire, and kept at *ca.* 110° throughout the decomposition.
11. The reaction is stopped and the trap, cooled in dry ice-acetone, is emptied when the reaction is *ca.* one half finished to prevent plugging by ice. Most of the olefinic products are found in the first trap. The second trap contains mostly trimethylamine and water.
12. About 3 hours is required to add the hydroxide solution. The rate of addition may be increased, but considerable foaming occurs during the decomposition, and caution should be taken that the hydroxide does not foam over into the traps.
13. This part of the experiment should be carried out in a hood because trimethylamine is evolved.
14. The decomposition of N,N,N-trimethylcyclooctylammonium hydroxide forms a mixture of *cis*- and *trans*-cyclooctenes which contains *ca.* 60% of the *trans*- and 40% of the *cis*-isomer (see (Note 19)). The mixture is separated by extraction of the *trans*-isomer with aqueous silver nitrate.[5]

15. If the pentane solution is added to the silver nitrate solution too rapidly, the *trans*-cyclooctene forms a dark precipitate that is difficult to get into solution. This situation can, however, be remedied by the addition of more silver nitrate solution and continued shaking.
16. The pentane is removed and *ca.* 11 g. of *cis*-cyclooctene is obtained on distillation, b.p. 65° (59 mm.); $n^{25}D$ = 1.4684.
17. Considerable foaming occurs during distillation of *trans*-cyclooctene. The distillation may therefore be facilitated by use of a distilling adapter with a foam trap. The distilling adapter (5225) may be purchased from Ace Glass Incorporated, Vineland, New Jersey. The bath temperature should be kept below 100° owing to the possibility of isomerization to *cis*-olefin and polymerization.[6] The distillation should be carried out as rapidly as possible because the condensed product evaporates under prolonged exposure to reduced pressure.
18. The submitters carried out this preparation on a 1.0-mole scale and obtained 49–51 g. (45–46%) of *trans*-cyclooctene.
19. The purity of the *trans*-cyclooctene may be determined by infrared spectroscopy[5] or by gas chromatography using an NMPN (3-nitro-3-methylpimelonitrile) column.[7] A low injection port temperature is desirable (<200°).
20. *trans*-Cyclooctene is stable for at least 1 year if kept under refrigeration and if a free radical inhibitor is used (*e.g.* di-*t*-butyl-resorcinol). The compound has a very disagreeable odor.
21. Since this procedure was submitted the submitter has found that higher overall yields of *trans*-cyclooctene may be obtained from a stirred suspension of trimethylcyclooctylammonium iodide in anhydrous dimethyl sulfoxide using commercially available (sublimed) potassium *t*-butoxide as the base at 25°. The *cis/trans* ratio under these conditions is 1/4.6 (private communication from R. D. Bach).

3. Discussion

trans-Cyclooctene has been prepared by the Hofmann elimination of N,N,N-trimethylcyclooctylammonium hydroxide,[5,8] the present method; by the treatment of N,N,N-trimethylcyclooctylammonium bromide with phenyllithium, methyllithium, and potassium amide:[9] and by the treatment of *trans*-1,2-cyclooctene thiocarbonate with triisooctyl phosphite.[10]

This procedure illustrates a general method for preparing olefins by the elimination of an amine and a β-hydrogen atom.[11] The present method is more convenient for adaptation to large-scale laboratory preparation than is the Wittig modification, which utilizes liquid ammonia; both methods give essentially the same overall yield of *trans*-cyclooctene.

The preparation of olefins *via* their thiocarbonate[10] is a stereo-specific elimination reaction which may be used to advantage when a mixture of *cis*- and *trans*-olefins is difficult to separate. However, all the reagents required to prepare the thiocarbonate are not readily available.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

methanol (67-56-1)

diethyl ether (60-29-7)

sodium bicarbonate (144-55-8)

silver oxide, silver oxide powder (20667-12-3)

silver nitrate (7761-88-8)

nitrogen (7727-37-9)

ammonium hydroxide (1336-21-6)

iodomethane (74-88-4)

Pentane, n-PENTANE (109-66-0)

Trimethylamine (75-50-3)

Phenyllithium (591-51-5)

magnesium sulfate (7487-88-9)

acetone-methanol (590-90-9)

potassium amide

β-PHENYLETHYLDIMETHYLAMINE (1126-71-2)

Methyllithium (917-54-4)

dimethyl sulfoxide (67-68-5)

N,N-dimethylcyclooctylamine

N,N,N-trimethylcyclooctylammonium iodide, trimethylcyclooctylammonium iodide

N,N,N-trimethylcyclooctylammonium hydroxide

Cyclooctylamine (5452-37-9)

3-nitro-3-methylpimelonitrile

N,N,N-trimethylcyclooctylammonium bromide

triisooctyl phosphite

potassium t-butoxide (865-47-4)

cis-cyclooctene (931-87-3)

trans-Cyclooctene (931-89-5)

di-t-butyl-resorcinol

trans-1,2-cyclooctene thiocarbonate

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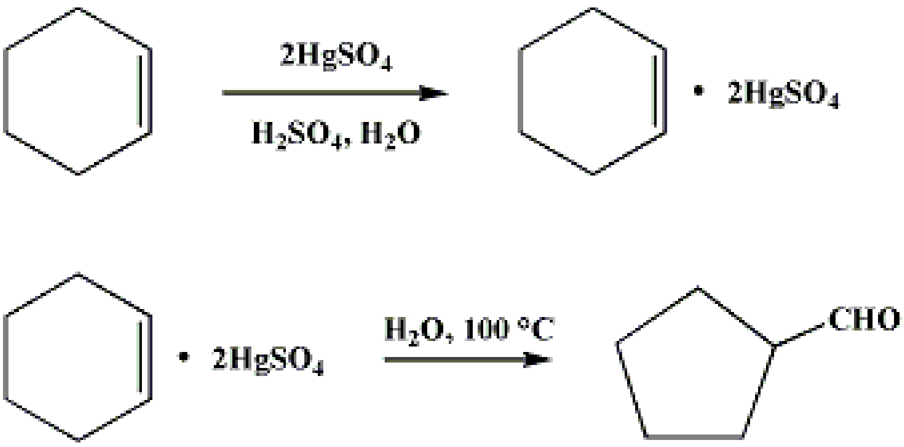
Organic Syntheses, *CV 5*, *320*

CYCLOPENTANECARBOXALDEHYDE



Submitted by Oliver Grummitt, John Liska, and Gerhard Greull[1].
Checked by William E. Parham and Gerald E. Stokker.

1. Procedure

In a 5-l. three-necked flask fitted with reflux condenser, mechanical stirrer, thermometer, and nitrogen gas inlet is placed a solution of 80.0 g. (43.5 ml., 0.82 mole) of concentrated sulfuric acid in 3 l. of water. The solution is stirred under nitrogen, and 740.0 g. (2.49 moles) of reagent mercuric sulfate is added to form a suspension of deep-yellow, basic mercuric sulfate. The mixture is stirred and heated to 55° under nitrogen, and 82.0 g. (101 ml., 1.0 mole) of cyclohexene (Note 1) is added at once. A temperature of 55–65° (Note 2) is maintained for 1 hour. During this time the color of the reaction mixture changes from a deep yellow to the cream color of the cyclohexene-mercuric sulfate complex.

At the end of 1 hour the condenser is set for distillation. The temperature of the reaction mixture is raised (Note 3), the mixture is stirred while a slow current of nitrogen is continued, and 300 ml. of a mixture of crude cyclopentanecarboxaldehyde and water is distilled over a period of approximately 2 hours. The crude product is removed in a separatory funnel from the aqueous layer, which is extracted with three 50-ml. portions of ether. The extracts are combined with the product and dried over anhydrous sodium sulfate. The solution is filtered into a 250-ml. Claisen flask set for vacuum distillation, the pressure is gradually reduced to 100 mm. to distil ether, and the cyclopentanecarboxyaldehyde is distilled rapidly (Note 4) at 74–78° (100 mm.). The yield of aldehyde (n^{20}D 1.4420–1.4428) is 45–52 g. (46–53%).

Unless the aldehyde is to be used immediately, it is stored in a brown bottle at 0° after the addition of 0.1 g. of hydroquinone and a blanket of nitrogen (Note 5).

2. Notes

1. Cyclohexene from an unopened bottle or freshly distilled material (b.p. 82–84°) is used.
2. This is the optimal temperature range to form the cyclohexene-mercuric sulfate complex.[2,3]
3. The complex undergoes oxidation-reduction at about 100° to give cyclopentanecarboxyaldehyde, mercurous sulfate, and some mercury. If desired, the mercury products can be regenerated to mercuric sulfate. However, approximately 40–140 g. of mercuric sulfate will be lost in the various filtrates in the recovery operation. Best current practice dictates that these filtrates be collected and disposed of as toxic chemicals. Concentration of the filtrates is not advisable since acetone, nitric acid, and sulfuric acid are present along with the mercury compounds. If the mercuric sulfate is not regenerated, the water and sludge of mercurous sulfate and mercury, which remain after the distillation of cyclopentanecarboxyaldehyde, should be disposed of with due regard to its toxic nature.
The regeneration procedure is as follows:
The water and sludge of mercurous sulfate and mercury, which remain after the distillation of cyclopentanecarboxyaldehyde, are filtered with suction, washed with three 100-ml. portions of boiling water, three 100-ml. portions of acetone, and finally with three 100-ml. portions of boiling water. The gray-black solid is sucked dry.
To the solid in a 3-l. Erlenmeyer flask is added 270 ml. of water, then 90 g. (65 ml., 1.0 mole) of concentrated nitric acid *slowly* (*Hood!*). The contents of the flask are swirled and allowed to stand until frothing and evolution of reddish brown oxides of nitrogen subsides. Dow-Corning Antifoam A helps to control frothing.
The mixture is heated *cautiously* on a hot plate to avoid excess frothing. When the frothing has almost subsided, additional concentrated nitric acid is added, 90 g. (65 ml., 1.0 mole) at a time, with swirling and intermittent heating to control the vigorous reaction. The solid changes from gray-black to a cream color after six 90-g. portions of concentrated nitric acid have been used.
Six hundred milliliters of concentrated nitric acid is then added with heating to form a clear, deep-orange solution of mercuric nitrate. This mixture is allowed to cool and is then filtered with suction through sintered glass to remove a small amount of solid.
Four hundred and sixty grams (250 ml., 4.7 moles) of concentrated sulfuric acid is added to the filtrate to precipitate mercuric sulfate. The mixture is boiled under the hood for 1 hour, cooled to 10–25°, and filtered with suction through sintered glass.
The solid mercuric sulfate is washed with three 100-ml. portions of approximately 40% aqueous sulfuric acid solution (110 ml. of concentrated sulfuric acid mixed with 300 ml. of water). The solid is sucked dry, transferred to an evaporating dish, broken up, and dried in the hood under a heat lamp.
The yield of recovered mercuric sulfate is 600–700 g. This material plus fresh mercuric sulfate to give 740 g. can be used in a subsequent preparation of

cyclopentanecarboxaldehyde without affecting the yield.
4. Cyclopentanecarboxyaldehyde may trimerize if heating is prolonged; hence a fast, simple distillation is done. When the distillation residue is cooled, a solid may appear. This solid can be distilled above 78° (100 mm.) as a clear liquid which solidifies when allowed to stand. Recrystallization of this material from 95% ethanol gives a white solid melting at 122–124°. This product was shown to be cyclopentanecarboxaldehyde trimer by a mixed melting-point determination with trimer prepared from cyclopentanecarboxyaldehyde and 85% phosphoric acid.[4]
5. During storage there is a slow formation of cyclopentanecarboxaldehyde trimer.

3. Discussion

Cyclopentanecarboxaldehyde has been prepared by the procedure described above;[2,3] by the reaction of aqueous nitric acid and mercuric nitrate with cyclohexene;[5] by the action of magnesium bromide etherate[6] or thoria[7] on cyclohexene oxide; by the dehydration of *trans*-1,2-cyclohexanediol over alumina mixed with glass helices;[8] by the dehydration of divinyl glycol over alumina followed by reduction;[9] by the reaction of cyclopentene with a solution of $[HFe(CO)_4]^-$ under a carbon monoxide atmosphere;[10] and by the reaction of cyclopentadiene with dicobalt octacarbonyl under a hydrogen and carbon monoxide atmosphere.[11]

4. Merits of the Preparation

This procedure uses readily available starting materials and in one operational step generally gives higher yields of cyclopentanecarboxaldehyde than other preparations described in the literature. Because mercuric sulfate is an expensive reactant, a method of regenerating the mercury products is given. Cyclopentanecarboxaldehyde is a useful intermediate for many cyclopentane derivatives.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

oxides of nitrogen

alumina

thoria

dicobalt octacarbonyl

Cyclohexene-mercuric sulfate complex

$[HFe(CO)_4]^-$

ethanol (64-17-5)

sulfuric acid (7664-93-9)

ether (60-29-7)

hydrogen (1333-74-0)

carbon monoxide (630-08-0)

hydroquinone (123-31-9)

nitric acid (7697-37-2)

Cyclohexene (110-83-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

mercury (7439-97-6)

acetone (67-64-1)

phosphoric acid (7664-38-2)

Cyclohexene oxide (286-20-4)

mercuric sulfate (7783-35-9)

mercuric nitrate

Cyclopentene (142-29-0)

divinyl glycol (764-78-3)

CYCLOPENTADIENE (542-92-7)

Cyclopentanecarboxaldehyde, cyclopentanecarboxyaldehyde (872-53-7)

mercurous sulfate (7783-36-0)

magnesium bromide etherate

trans-1,2-Cyclohexanediol (1460-57-7)

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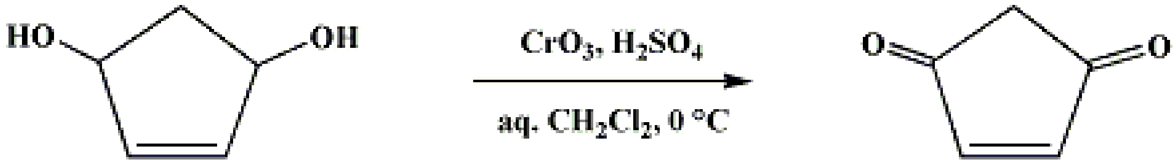
Organic Syntheses, CV 5, 324

2-CYCLOPENTENE-1,4-DIONE



Submitted by Gary H. Rasmusson[1], Herbert O. House[1], Edward F. Zaweski[2], and Charles H. DePuy[2].
Checked by William G. Dauben, Philip E. Eaton, and Richard Schneider.

1. Procedure

In a 2-l. three-necked flask equipped with a thermometer, a mechanical stirrer, and a dropping funnel (Note 1) is placed a mixture of 45.1 g. (0.45 mole) of a dihydroxycyclopentene mixture (Note 2), 200 ml. of water, and 300 ml. of methylene chloride. After this mixture has been cooled to –5° to 0° by means of an external cooling bath (Note 3), the addition of a solution of 100 g. (1.0 mole) of chromium trioxide and 160 ml. of concentrated sulfuric acid in 450 ml. of water is begun. The solution of the oxidant is added dropwise, and with stirring, at such a rate that the temperature of the reaction mixture remains between –5° and 0°. After the addition is complete (Note 4), the mixture is stirred at –5° to 0° for 1 hour and then 200 ml. of chloroform is added. The resulting mixture is stirred for 10 minutes, the organic layer is separated, and then the aqueous layer is extracted with two 200-ml. portions of a mixture (1:1 by volume) of chloroform and methylene chloride. The combined organic extracts are washed with 100 ml. of water, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure at room temperature. The yield of 2-cyclopentene-1,4-dione (Note 5), which crystallizes as yellow plates melting at 30.0–32°, is 17–22 g. (39–50% based on the dihydroxycyclopentene mixture) (Note 6).

2. Notes

1. All glassware must be washed with acid before use.
2. The dihydroxycyclopentene mixture was prepared from cyclopentene and peracetic acid.[3] The mixture contains approximately 70% of 2-cyclopentene-1,4-diol.
3. The submitters found a cooling bath composed of a Dry Ice and methanol-water mixture (1:3 by volume) to be convenient.
4. At this point in the preparation, an excess of the oxidant should be present. The presence of excess oxidant may be established by diluting 2 drops of the aqueous phase from the reaction mixture with 2 ml. of water and then adding 1 drop of a 0.4% solution of sodium diphenylaminesulfonate in water. A deepening in color is observed if excess oxidant is present.

5. This product is sufficiently pure for most applications. Further purification may be achieved either by sublimation of the product at 30–40°/0.1 mm. or by recrystallization of the dione from diethyl ether at Dry Ice temperatures. The dione decomposes rapidly at temperatures above 40°. An ethanol solution of pure dione, m.p. 35–36°, exhibits a maximum in the ultraviolet at 222 m• (log ε 4.16).
6. Starting with pure 2-cyclopentene-1,4-diol, the submitters obtained the dione in 67–79% yield.

3. Discussion

2-Cyclopentene-1,4-dione has been prepared by oxidation of 2-cyclopentene-1,4-diol with chromium trioxide in aqueous acetic acid[4,5] or in aqueous acetone,[4] and with silver chromate.[6] The present method eliminates the tedious removal of large amounts of acetic acid and gives a higher yield.

4. Merits of Preparation

2-Cyclopentene-1,4-dione is a very reactive dienophile in the Diels-Alder reaction and thus provides access to a variety of compounds containing the reactive β-dicarbonyl grouping in a five-membered ring.[4] Also, its multiple functionality makes it a versatile starting material for other types of reactions as well.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 414

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

diethyl ether (60-29-7)

chloroform (67-66-3)

acetone (67-64-1)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

chromium trioxide (1333-82-0)

Cyclopentene (142-29-0)

peracetic acid (79-21-0)

2-Cyclopentene-1,4-dione (930-60-9)

Dihydroxycyclopentene

2-cyclopentene-1,4-diol (4157-01-1)

sodium diphenylaminesulfonate

silver chromate (7784-01-2)

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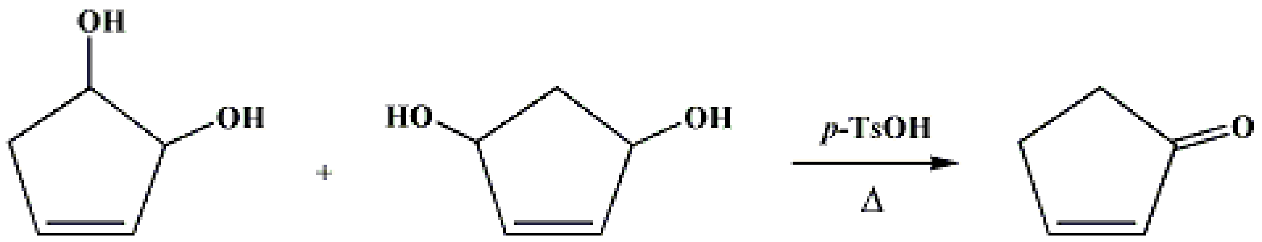
2-CYCLOPENTENONE

[2-Cyclopentene-1-one]



Submitted by Charles H. DePuy and K. L. Eilers[1].
Checked by William G. Dauben, Robert A. Flath, and Gilbert H. Berezin.

1. Procedure

In a 250-ml. round-bottomed flask fitted for vacuum distillation with a short path distilling head (Note 1), a condenser, and a 250-ml. receiving flask is placed 100 g. (1.0 mole) of a mixture of cyclopentenediols.[2] A few Carborundum boiling chips are added. The receiver is cooled in ice and the mixture heated to 50–55° (Note 2). At this time, the flask is opened momentarily and 1–2 g. of *p*-toluenesulfonic acid monohydrate is added. The flask is immediately closed and the pressure is reduced to 10–15 mm. Careful heating is continued, and a mixture of 2-cyclopentenone and water begins to distil with the temperature in the distilling head rising from 45° to 60° (Note 3). The temperature of the flask is gradually increased as necessary to maintain a reasonably rapid distillation rate.

The reaction is complete when approximately 10% of the original material remains in the distilling flask. The distillation normally requires 30–60 minutes.

The distillate, containing 2-cyclopentenone, water and varying amounts of cyclopentenediols, is dissolved in 150 ml. of methylene chloride and dried over anhydrous sodium sulfate. The solvent is carefully removed through a Vigreux column and the residue purified by distillation. After a forerun (b.p. 50–150°), there is collected 44–49 g. (53–60%) of pure 2-cyclopentenone, b.p. 151–154°. Cyclopentenediols may be recovered from the pot residue by distillation at 0.1 mm. The forerun contains appreciable amounts of cyclopentenone and should be added to a succeeding preparation before final distillation.

2. Notes

1. The distilling head should be short and unobstructed, for any attempt at fractionation at this stage leads to resinification of the 2-cyclopentenone by the acid. No capillary bleed is used, since the product is extremely sensitive to oxygen.

2. The submitters have found a 250-watt infrared heat lamp controlled by a Variac to be the most convenient source of heat. Occasionally, the reaction may become rapid and exothermic, and it is important to remove the heat source as quickly as possible. If an oil bath is used, the temperature is gradually increased until it approaches 150° at the end of the reaction.
3. If the temperature of the distillate rises much above 60° at this pressure, considerable amounts of diols co-distil and the yield of 2-cyclopentenone is diminished. If a reasonably rapid distillation does not occur with a head temperature below 60°, an additional gram of acid should be added after lowering the temperature of the distillation flask below 50°.

3. Discussion

Previous preparations of 2-cyclopentenone have involved the elimination of HCl from 2-chlorocyclopentanone[3] or its ketal.[4] The oxidation of 3-chloro-[5] or 3-hydroxycyclopentene[6] has been utilized as well as the direct oxidation of cyclopentene with H_2O_2.[7] Cyclopentenone has also been prepared from 1-dicyclopentadienol.[8]

4. Merits of Preparation

The α,β-unsaturated ketone system in 2-cyclopentenone makes possible a wide variety of reactions of the Michael and Diels-Alder type. Thus 2-cyclopentenone is a versatile starting material for preparing compounds containing a five-membered ring. The availability of the dihydroxycyclopentene mixture (p. 414) makes the present procedure the method of choice for its preparation.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 414
- Org. Syn. Coll. Vol. 7, 271

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

H_2O_2

1-dicyclopentadienol

HCl (7647-01-0)

sodium sulfate (7757-82-6)

oxygen (7782-44-7)

methylene chloride (75-09-2)

Cyclopentene (142-29-0)

2-Cyclopentenone, 2-Cyclopentene-1-one, cyclopentenone (930-30-3)

2-chlorocyclopentanone (694-28-0)

p-toluenesulfonic acid monohydrate (6192-52-5)

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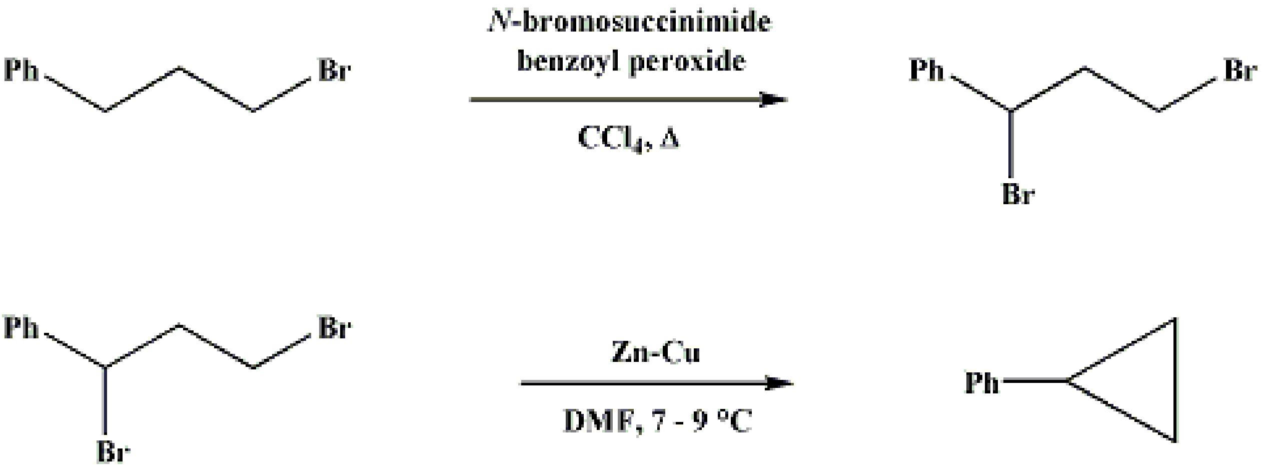
CYCLOPROPYLBENZENE

[Benzene, cyclopropyl-]



Submitted by Thomas F. Corbin, Roger C. Hahn[1], and Harold Shechter[2].
Checked by William G. Dauben and Paul Laug.

1. Procedure

Caution! N-Bromosuccinimide is a skin irritant.

A. *1,3-Dibromo-1-phenylpropane*. In a 3-l. three-necked flask fitted with a sealed stirrer and two efficient reflux condensers are placed 199 g. (1.0 mole) of 1-bromo-3-phenylpropane (Note 1), 187 g. (1.05 moles) of N-bromosuccinimide (Note 2), 3 g. of benzoyl peroxide, and 1.2 l. of carbon tetrachloride. The mixture is heated cautiously with a flame to reflux until a spontaneous reaction starts; ice-bath cooling is then applied if necessary (Note 3). When the spontaneous reaction subsides, the stirring is stopped; if more than a negligible amount of N-bromosuccinimide remains in the bottom of the flask (succinimide rises to the surface of the solvent), heating and stirring are continued until an evolution of hydrogen bromide is noted. The mixture is cooled, and the solids are removed by suction filtration and washed with carbon tetrachloride. The washings are combined with the original filtrate, and the bulk of the carbon tetrachloride is removed (Note 4) by distillation at water aspirator pressure and a bath temperature of 40–50° (Note 5). The remainder of the solvent is removed at the same bath temperature and at 0.1 mm. pressure (Note 6). The orange-yellow residue (nearly 100% of the theoretical yield of 1,3-dibromo-1-phenylpropane) is used without further purification (Note 7) in the next step.

B. *Cyclopropylbenzene*. In a 1-l. three-necked flask equipped with a stirrer and a thermometer extending into the flask but free from the stirrer are placed 500 ml. of redistilled dimethylformamide and zinc-copper couple prepared from 131 g. (2 g. atoms)

of zinc (Note 8). The mixture is cooled to 7° in an ice bath, and 1,3-dibromo-1-phenylpropane is added to the stirred mixture at a rate sufficient to maintain the reaction temperature at 7–9° (Note 9). The mixture is stirred for 30 minutes after the addition is completed, poured into 1 l. of water, and then steam-distilled until the condensate is homogeneous or 1 l. of water has been collected. The organic layer is separated from the distillate, and the aqueous layer is extracted with three 100-ml. portions of ether. The combined organic portions are washed with four 50-ml. portions of water and dried over anhydrous potassium carbonate. The ether is removed by distillation at atmospheric pressure at water bath temperature. The residue is distilled to give 88–100 g. (75–85%) of cyclopropylbenzene, b.p. 170–175° (Note 10), n^{26}D 1.5306–1.5318.

2. Notes

1. The 1-bromo-3-phenylpropane was obtained from Columbia Organic Chemicals Co., Inc., Columbia, South Carolina, and from Aldrich Chemical Co., Inc., Milwaukee, Wisconsin. Redistillation of the commercial material does not noticeably affect yields.
2. N-Bromosuccinimide was obtained from Arapahoe Chemicals, Inc., Boulder, Colorado, and from Coleman and Bell, Norwood, Ohio. The material utilized by the checkers was shown to be 98.6% pure by iodometric analyses.
3. This reaction may become vigorously exothermic; two condensers and a highly mobile setup, allowing quick (5 seconds) removal of heat and application of cooling, are then necessary to contain it. *Caution* must be taken to control but not stop the reaction.
4. Any bromine present at this point is entrained by the carbon tetrachloride; the separated carbon tetrachloride may be purified by shaking with a small quantity of sodium bisulfite, drying over anhydrous potassium carbonate, and distilling.
5. Higher bath temperatures cause darkening of the residue with evolution of hydrogen bromide.
6. An efficient dry ice trap is essential to protect the vacuum pump.
7. Attempts to distil the residue usually cause evolution of large amounts of hydrogen bromide.
8. Zinc powder, obtainable from Mallinckrodt Chemical Works, St. Louis, Missouri, and Merck and Co., Rahway, New Jersey, is placed in a beaker and is washed consecutively and *rapidly* (10 seconds) with three 100-ml. portions of 3% hydrochloric acid, two 100-ml. portions of water, two 200-ml. portions of 2% aqueous copper sulfate (until blue color disappears), two 200-ml. portions of water, two 100-ml. portions of acetone, two 100-ml. portions of dimethylformamide, and is washed into the reaction vessel with dimethylformamide. This procedure is a modification of one described by Hennion and Sheehan.[3]
9. This *highly exothermic* reaction often has an induction period the end of which is characterized by a rapid temperature rise dependent on the amount of dibromide already added. At the first sign of reaction (*watch the thermometer closely*), addition of dibromide should be stopped and should be resumed only after the temperature has stopped rising. Careful purification of the dimethylformamide

appears to minimize the induction period.
10. Analysis of this product by gas liquid chromatography (QF-1 coated column, 130°) showed it to be >98.5% pure. The boiling point of a sample collected by chromatography was 169–171°.

3. Discussion

Cyclopropylbenzene has been prepared by decomposition of 5-phenylpyrazoline,[4] addition of hydrogen bromide to cinnamyl bromide followed by cyclization with zinc,[5] decarboxylation of 1-phenylcyclopropanecarboxylic acid,[6] reaction of magnesium with 3-bromo-3-phenyl methyl ether followed by decomposition of the intermediate Grignard reagent,[7] reaction of styrene with methylene iodide and zinc-copper couple,[8] reaction of sodium amide with 3-phenylpropyltrimethylammonium iodide in liquid ammonia,[9] decarbonylation of 1-phenylcyclopropanecarboxaldehyde,[10] and reaction of sodium hydroxide with (1-phenylcyclopropyl)-diphenylphosphine oxide.[11]

4. Merits of the Preparation

Because of the unique properties of the cyclopropane ring, cyclopropylbenzene is a compound of considerable interest. Only one of the alternative methods[9] for the preparation of this compound has been reported to give more than 32% yield; the procedure described affords an olefin-free product without a relatively laborious purification process. By its utilization of readily available starting materials, and by its applicability to the preparation of large quantities of product, this method of synthesis provides easy access to many cyclopropylbenzene derivatives.[12]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

3-bromo-3-phenyl methyl ether

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ether (60-29-7)

sodium hydroxide (1310-73-2)

magnesium (7439-95-4)

hydrogen bromide (10035-10-6)

bromine (7726-95-6)

carbon tetrachloride (56-23-5)

copper sulfate (7758-98-7)

sodium bisulfite (7631-90-5)

acetone (67-64-1)

zinc, zinc powder (7440-66-6)

Methylene iodide (75-11-6)

styrene (100-42-5)

benzoyl peroxide (94-36-0)

zinc-copper

sodium amide (7782-92-5)

dimethylformamide (68-12-2)

N-bromosuccinimide (128-08-5)

Cinnamyl bromide (4392-24-9)

Cyclopropylbenzene, Benzene, cyclopropyl- (873-49-4)

1-bromo-3-phenylpropane (637-59-2)

1,3-Dibromo-1-phenylpropane (17714-42-0)

5-phenylpyrazoline

1-phenylcyclopropanecarboxylic acid (6120-95-2)

3-phenylpropyltrimethylammonium iodide (2125-48-6)

1-phenylcyclopropanecarboxaldehyde

(1-phenylcyclopropyl)-diphenylphosphine oxide

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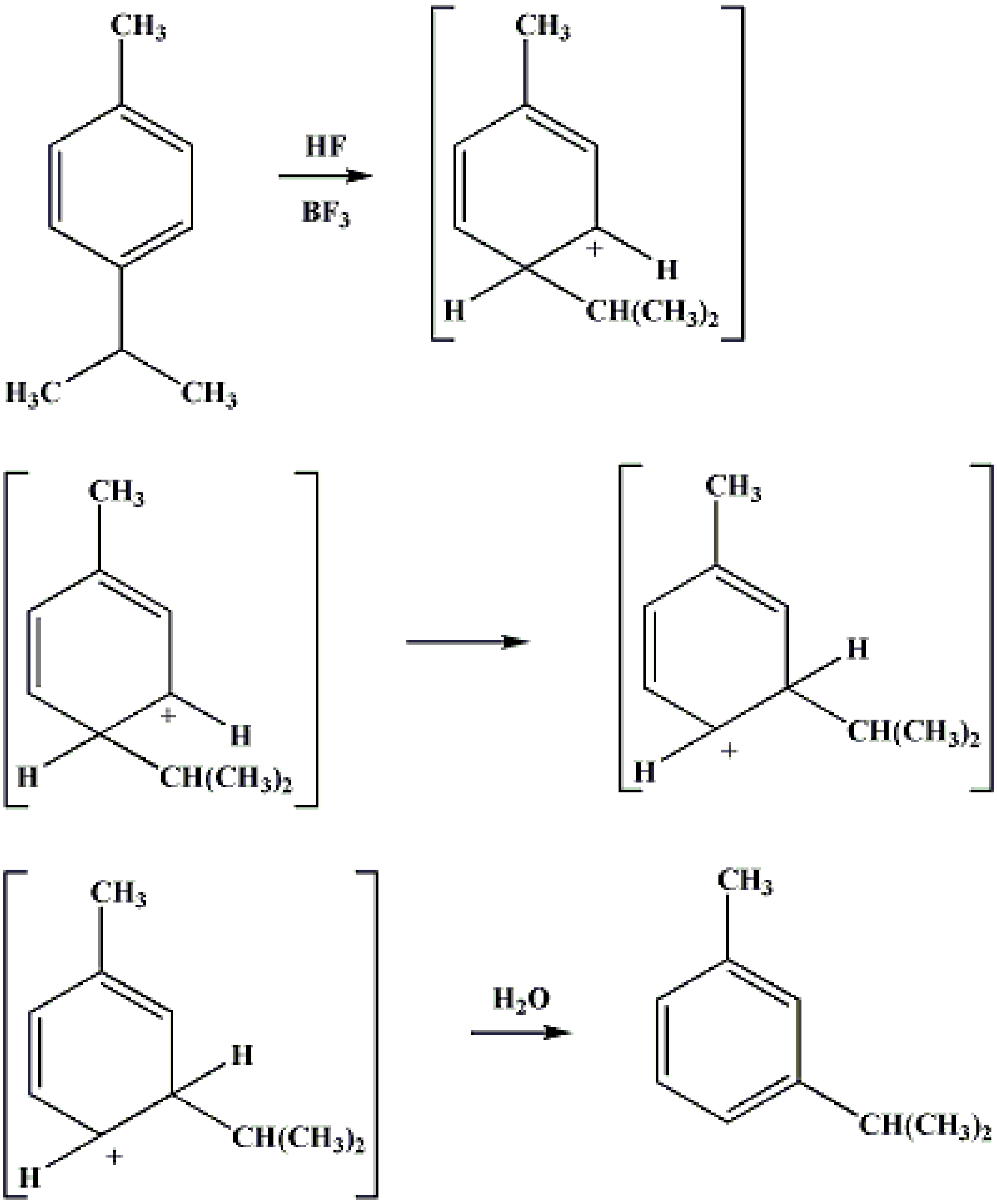
m-CYMENE

[*m*-Isopropyltoluene]



Submitted by D. E. Pearson, Robert D. Wysong, and J. M. Finkel[1].
Checked by Richard A. Haggard and W. D. Emmons.

1. Procedure

Caution! It is necessary to carry out the entire operation including the workup in a well-ventilated hood. Rubber gloves and safety glasses should be worn (Note 1).

Anhydrous hydrogen fluoride (135 ml., approx. 7 moles) is liquefied by passing the gas through an 8-ft. spiral of -in. I.D. copper tubing surrounded by an isopropyl alcohol-dry ice bath (Note 2). The liquid is delivered to a 500-ml. polyethylene squeeze bottle (Note 3) containing a magnetic stirring bar via a polyethylene tube inserted through the screw cap of the bottle. The squeeze bottle is contained in a 2-l. beaker and is surrounded by powdered dry ice (Note 4). After the hydrogen fluoride is collected, the cap and delivery tube are removed, and *p*-cymene (terpene-free, 67 g., 0.5 mole), precooled to −50° to −60°, just above the slush point, is added to the hydrogen fluoride. The cap and polyethylene tube assembly is now attached to deliver boron trifluoride. The delivery tube in this case dips below the surface of the hydrogen fluoride, the bottom layer. Boron trifluoride is bubbled through while the mixture is efficiently stirred with a magnetic stirrer (Note 5). A light orange color develops immediately, and the two layers become one in about 30 minutes (Note 6). Additional powdered dry ice must be added to the beaker during the boron trifluoride addition. The volume of the complex increases about 25%. After homogeneity is effected (in 30 minutes), a somewhat slower stream of boron trifluoride is added for an additional 30 minutes (Note 7). The delivery tube is replaced by a cap on the polyethylene bottle, the drying tube is removed, and the original side-arm tube is lowered to the bottom of the container. The cold reaction mixture is squirted, by squeezing the bottle, in a continuous small stream into a 4-l. beaker half-filled with cracked ice, vigorously hand-stirred. The bottle is rinsed, and the contents of the beaker are placed in a large separatory funnel. The upper colorless layer is separated, and the aqueous phase is extracted 3 times with 50-ml. portions of hexane. The combined organic layers are washed with three 50-ml. portions of water and dried overnight with anhydrous sodium sulfate under refrigeration (Note 8). The hexane solution at this point contains *m*-cymene with about 8% disproportionation impurities including toluene. The solution is fractionated through a 1-ft. helices-packed column, with the *m*-cymene at boiling point 173–176°, 50–54 g. (75–80%) being collected (Note 9).

2. Notes

1. In the event of accidental contact of hydrogen fluoride with the skin, the affected area must be washed immediately and thoroughly with cold water. Additional treatment has been described.[2]

2. If one half the given quantity of hydrogen fluoride is used, all other factors being kept the same, the *m*-cymene formed contains as much as 5% of *p*-cymene.

3. A Nalgene "15–500" polyethylene bottle (Nalge Co., Rochester, New York) was used. The side arm coming off the shoulder of the bottle is kept well above the liquid level, the constricted tip removed, and the end of the tube connected to a drying tube containing clay plate chips impregnated with concentrated sulfuric acid.

A squeeze bottle can be simply made from a 500-ml. narrow-mouthed polyethylene bottle and polyethylene tubing. Holes in the bottle cap and shoulder are made with a sharp cork borer of the appropriate size to ensure a

tight fit with the inserted tubing.

4. A polyethylene or copper foil loop 1 in. wide is placed between the squeeze bottle and the side of the beaker in such a position as to exclude the dry ice from the space and to provide a window to permit one to see that the liquid hydrogen fluoride fills the bottle to a premarked level. The frost on the beaker must be scraped off to allow inspection through the window.

5. The stirring motor is housed in a polyethylene bag to protect it from acid fumes.

6. Larger quantities of boron trifluoride are evolved from the drying tube at this point. During the first 30 minutes, boron trifluoride is added at a rate which gives a slow emanation of fuming vapor from the drying tube. The checkers found that the product was contaminated by *p*-cymene when inefficient stirring and slow boron trifluoride addition rates were employed (Note 7).

7. The checkers used a flowmeter to monitor boron trifluoride addition and found that an indicated addition rate of 1800 ml./min. (calibrated with air) for the first 5 minutes followed by an average rate of 600 ml./min. gave homogeneity in the prescribed time. A rate of 150 ml./min. was used for the second 30 minutes.

8. All glassware is rinsed with water immediately after use to prevent etching.

9. The product is analyzed by vapor phase chromatography using a 6-ft., -in. O.D. copper tube, packed with 5% Bentone-34 (Wilkins Instrument Co.) and 0.5% XF-1150 (General Electric Silicone Products) on Diatoport-S (80–100 mesh) (F and M Co.); flow rate of helium 60 ml./min., oven temperature 85°. This column separates *m*-cymene (retention time 12 minutes) from *p*-cymene (retention time 10 minutes) but does not resolve the *ortho* isomer. The purity of the distilled *m*-cymene is above 98%.

3. Discussion

m-Cymene has been prepared from the Grignard reagent of *m*-bromotoluene and acetone followed by conversion of the carbinol to the chloride and reduction with sodium in liquid ammonia.[3] It also has been prepared from *m*-toluoyl chloride and excess methylmagnesium bromide followed by catalytic reduction of the olefin formed.[4] The best set of physical properties for the isomeric cymenes appears to be that of Birch and co-workers.[4] Many examples of Friedel-Crafts alkylation of toluene with propylene are described; apparently the best of them gives a 90% yield of cymenes containing 65–70% *m*-cymene.[5]

The method of preparation in this procedure is adapted from that of McCauley and Lien by which they obtained *m*-cymene in unstated yields.[6] The procedure has been altered to operate at –78° rather than –20°.

4. Merits of the Preparation

Aromatic hydrocarbons substituted by alkyl groups other than methyl are notorious for their tendency to disproportionate in Friedel-Crafts reactions. This tendency has previously limited the application of the isomerization of *para*-(or *ortho*-) dialkylbenzenes to the corresponding *meta* compounds. At the lower temperature of the present modification, disproportionation can be minimized.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

ammonia (7664-41-7)

propylene (115-07-1)

sodium sulfate (7757-82-6)

hydrogen fluoride (7664-39-3)

acetone (67-64-1)

toluene (108-88-3)

sodium (13966-32-0)

methyl (2229-07-4)

p-cymene (99-87-6)

boron trifluoride (7637-07-2)

methylmagnesium bromide (75-16-1)

hexane (110-54-3)

helium (7440-59-7)

m-Bromotoluene (591-17-3)

m-toluoyl chloride (1711-06-4)

m-Cymene, m-Isopropyltoluene (535-77-3)

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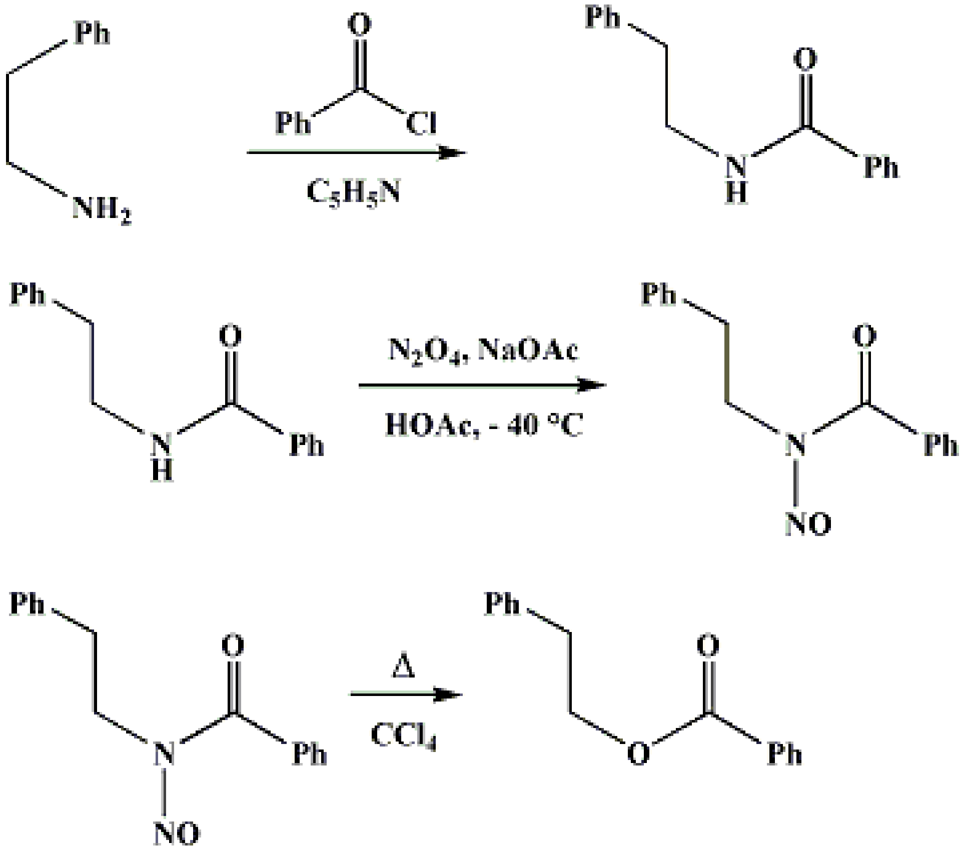
Organic Syntheses, *CV 5*, *336*

DEAMINATION OF AMINES. 2-PHENYLETHYL BENZOATE VIA THE NITROSOAMIDE DECOMPOSITION

[Benzoic acid, 2-phenylethyl ester]



Submitted by Emil White[1]
Checked by William G. Dauben and William C. Schwarzel.

1. Procedure

Caution! Dinitrogen tetroxide is extremely toxic and should only be handled in an excellent hood.

A. *N-(2-Phenylethyl)benzamide*. To a solution of 12.1 g. (0.10 mole) of 2-phenylethylamine and 7.9 g. (0.10 mole) of pyridine in a 250-ml. Erlenmeyer flask immersed in an ice bath is added, slowly with stirring, 15.5 g. (0.11 mole) of benzoyl chloride. The resulting crystalline mixture is extracted with chloroform and the chloroform solution washed with water, 5% hydrochloric acid, 5% sodium hydroxide, water, and dried. The solvent is removed under reduced pressure to yield 20–22 g. (89–98%) of the crude amide, m.p. 100–110°, which is of sufficient purity for use in the next step. If desired, however, the crude product may be recrystallized from 95%

ethanol, m.p. 115–116°.

B. *N-Nitroso-N-(2-phenylethyl)benzamide*. A solution of 10.4 g. (0.046 mole) of the crude N-(2-phenylethyl)benzamide, 7.36 g. (0.09 mole) of anhydrous sodium acetate, and 50 ml. of glacial acetic acid is placed in a 250-ml. Erlenmeyer flask equipped with a drying tube, and the mixture is cooled to the crystallization point of the acetic acid (Note 1). A solution of dinitrogen tetroxide (Note 2), (Note 3) in glacial acetic acid (85 ml. of a solution approximately 1*M* in N_2O_4) is then added with stirring. The reaction mixture is allowed to warm to about 15° (15 minutes), and then it is poured into a mixture of ice and water. The yellow solid nitroso derivative is dissolved in 75 ml. of carbon tetrachloride, and this solution is washed with 5% sodium bicarbonate, water, and dried. The solution is used directly in the next step.

If the nitroso derivative is desired, the yellow solid is separated by filtration, washed with water, 5% sodium bicarbonate solution, water, and dried under reduced pressure at room temperature. The solid is recrystallized from ether to give yellow needles of pure nitrosoamide; yield 7.5 g. (64%), m.p. 57–58° (dec.).

C. *2-Phenylethyl benzoate*. The carbon tetrachloride solution of N-nitroso-N-(2-phenylethyl)benzamide (Note 4) and 0.1 g. of sodium carbonate (Note 5) are placed in a 200-ml. round-bottomed flask equipped with a condenser, and the mixture is heated under reflux for 24 hours. The evolution of nitrogen ceases, and the yellow color of the nitrosoamide weakens or disappears near the end of this period. The solution is washed with 5% sodium hydroxide solution, water, and dried. The solvent is removed under reduced pressure and the 2-phenylethyl benzoate distilled; b.p. 139–142° (1 mm.), yield 5.8–6.1 g. [56–59% based on N-(2-phenylethyl)benzamide].

2. Notes

1. Carbon tetrachloride, methylene chloride, and other solvents may be used in this reaction. In these cases it is profitable to cool the reaction mixture to –40° or lower and then allow the mixture to warm to 10° after the dinitrogen tetroxide has been added.
2. Dinitrogen tetroxide (nitrogen dioxide) is available from the Matheson Company, Inc., East Rutherford, New Jersey.
3. Dinitrogen tetroxide is a *poisonous gas* and should only be handled in a well-ventilated hood. The boiling point of dinitrogen tetroxide is 21°, and it is convenient to condense a given volume (or weight, density = 1.5 g./ml. at 0°) from a cylinder of dinitrogen tetroxide and to pour the liquid into the required amount of solvent, or into the reaction mixture directly at temperatures below *ca.* –20°. Impure dinitrogen tetroxide, which is green because of the presence of lower oxides of nitrogen, may also be used.
4. Any nonreactive solvent may be used, but excessive temperatures favor the concurrent elimination reaction.
5. The sodium carbonate may be omitted if it is desired to titrate the acid formed in the reaction. The carbonate prevents denitrosation (observed in a few cases).

3. Discussion

The nitrosation of amides may also be carried out with nitrosyl chloride.[2] Related methods of deamination of aliphatic amines are the triazene[3] and nitrous acid methods.[4]

4. Merits of the Preparation

Dinitrogen tetroxide is the most versatile of the nitrosating reagents and, in addition, it is readily available. The nitrosoamide method of deamination gives far superior yields and much less skeletal isomerization than the nitrous acid method (which is essentially limited to aqueous media), and it leads to a greater retention of optical activity than the triazene method.[3] In general, the nitrosoamide decomposition proceeds with retention of configuration.[5,6]

The method outlined here works well for amides of primary carbinamines. For amides of secondary carbinamines, lower temperatures must be used for the nitrosation step (0°), and solvents such as methylene chloride are used in place of the acetic acid (the amide need not be completely soluble in the solvent); the procedure of White and Aufdermarsh[5] used for a trimethylacetamide is recommended in such a case. Nitrosoamides of tertiary carbinamines are very unstable, and the "salt method" of preparation is suggested for these compounds.[6]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

dinitrogen tetroxide

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ether (60-29-7)

sodium acetate (127-09-3)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium bicarbonate (144-55-8)

sodium carbonate (497-19-8)

carbon tetrachloride (56-23-5)

nitrogen (7727-37-9)

benzoyl chloride (98-88-4)

pyridine (110-86-1)

nitrogen dioxide (10102-44-0)

methylene chloride (75-09-2)

nitrosyl chloride (2696-92-6)

2-phenylethylamine (64-04-0)

trimethylacetamide (758-96-3)

triazene

2-Phenylethyl benzoate, Benzoic acid, 2-phenylethyl ester (94-47-3)

N-(2-Phenylethyl)benzamide (3278-14-6)

N-Nitroso-N-(2-phenylethyl)benzamide

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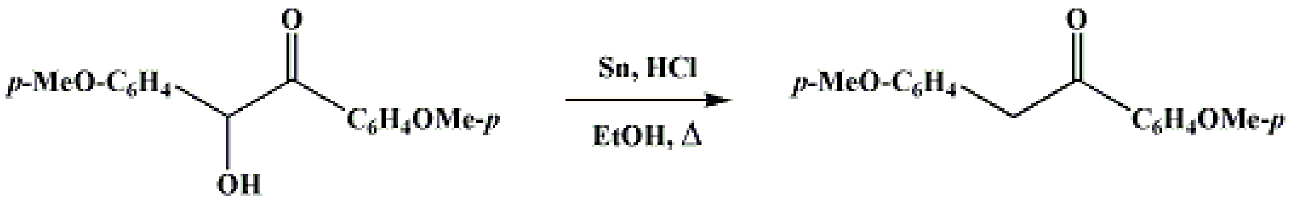
Organic Syntheses, CV 5, 339

DEOXYANISOIN

[Acetophenone, 4'-methoxy-2-(*p*-methoxyphenyl)-]



Submitted by P. H. Carter, J. Cymerman Craig, Ruth E. Lack, and M. Moyle[1].
Checked by Max Tishler and E. M. Chamberlin.

1. Procedure

A 500-ml. round-bottomed flask, equipped with a reflux condenser, is charged with 40 g. (0.33 mole) of powdered tin (Note 1) and (Note 2), 52 g. (0.19 mole) of anisoin (Note 3), 52 ml. of concentrated hydrochloric acid (Note 4), and 60 ml. of 95% alcohol. After the mixture is refluxed for 24 hours (Note 5), the boiling solution is decanted from undissolved tin, cooled to 0°, and the white crystals are filtered by suction. The filtrate is heated to boiling and then used to wash the tin by decantation. The combined washings are cooled to 0°, and the crystalline solid is collected by suction filtration. Recrystallization of the combined solids from 450 ml. of boiling 95% ethanol (Note 6) and (Note 7) gives, on cooling to 0°, colorless crystals of deoxyanisoin melting at 108–111°. The yield is 42–45 g. (86–92%).

2. Notes

1. A reduction in the amount of tin lowers the yield. Best results are obtained using powdered tin of between 100 and 200 mesh size. Use of tin coarser than 100 mesh results in the presence of unchanged anisoin, while tin finer than 200 mesh tends to conglomerate, causing lower yields. The checkers used tin obtained from E. H. Sargent Co., Chicago, labeled 200 mesh.
2. No advantage is gained by using amalgamated tin.
3. This procedure is generally applicable to the preparation of symmetrical deoxybenzoins. The submitters have prepared (*a*) deoxybenzoin (m.p. 56–58°) in 80–84% yield from 53 g. of benzoin (0.25 mole), 53 ml. of concentrated hydrochloric acid, 50 ml. of 95% alcohol, and 53 g. of powdered tin (0.44 mole), recrystallizing from 160 ml. of boiling 95% alcohol and cooling to 0°; (*b*) deoxypiperoin (m.p. and mixed m.p. 112–114°) in 89% yield from 14.3 g. of piperoin (0.048 mole), 13 ml. of concentrated hydrochloric acid, 30 ml. of 95% alcohol, and 10 g. of powdered tin (0.083 mole), recrystallizing from 140 ml. of boiling 95% alcohol and cooling to 0°.
4. A reduction in the amount of hydrochloric acid lowers the yield.
5. Lower yields are obtained by using reflux periods of 16 or 18 hours.
6. The checkers recommend washing the product with cold 95% alcohol; otherwise the product tends to discolor on standing.
7. Addition of water to the filtrate does not yield any further crystalline products.

3. Discussion

The synthesis of deoxybenzoin from phenacetyl chloride and benzene by the Friedel-Crafts reaction has been described.[2] For symmetrically substituted deoxybenzoins, direct reduction of the readily accessible benzoin is a more convenient method. Reduction of benzoin by zinc dust and acetic acid,[3] and by hydrochloric acid and granulated tin[4,5] or amalgamated powdered tin[6] has been reported. The present method is based on a publication of the authors.[7]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Deoxyanisoin

anisoin

deoxypiperoin

piperoin

phenacetyl chloride

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

tin (7440-31-5)

Benzoin (119-53-9)

zinc (7440-66-6)

deoxybenzoin (451-40-1)

Acetophenone, 4'-methoxy-2-(p-methoxyphenyl)- (120-44-5)

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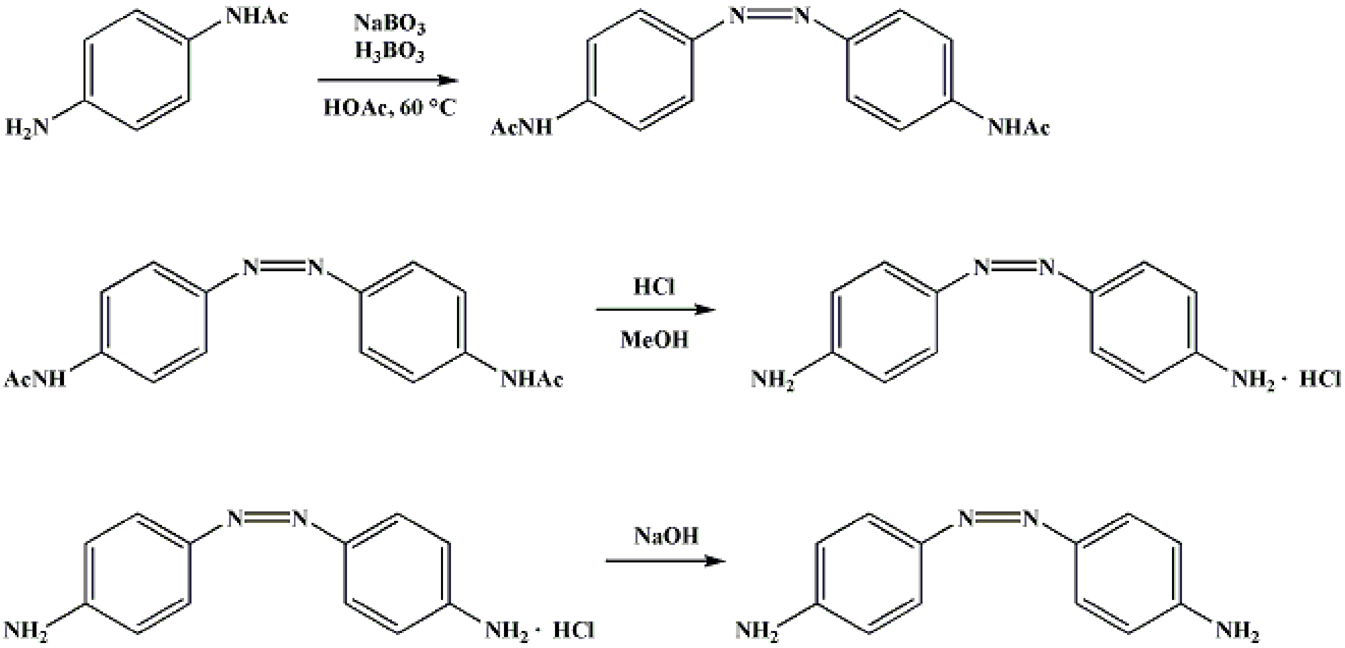
Organic Syntheses, CV 5, 341

4,4'-DIAMINOAZOBENZENE

[Aniline, 4,4'-azodi-]



Submitted by Pasco Santurri, Frederick Robbins, and Robert Stubbings[1].
Checked by Max Tishler, Earl M. Chamberlin, and William Harrison.

1. Procedure

In a 1-l. three-necked round-bottomed flask equipped with an efficient stirrer, a reflux condenser, and a thermometer (Note 1) are placed 500 ml. of glacial acetic acid (Note 2), 29.0 g. (0.19 mole) of *p*-aminoacetanilide (Note 3), 40 g. (0.26 mole) of sodium perborate tetrahydrate, and 10 g. (0.16 mole) of boric acid. The mixture is heated with stirring to 50–60° and held at this temperature for 6 hours. Initially the solids dissolve but, after heating for approximately 40 minutes, the product begins to separate. At the end of the reaction period, the mixture is cooled to room temperature and the yellow product is collected on a Büchner funnel. It is washed with water until the washings are neutral to pH paper (Note 4) and then dried in an oven at 110°. The yield of 4,4'-bis(acetamido)azobenzene, m.p. 288–293° (dec.), is 16.5 g. (57.7%). It is used as such for the hydrolysis step (Note 5).

In a 500-ml. round-bottomed flask equipped with a reflux condenser and a magnetic stirrer (Note 6) are placed 150 ml. of methanol, 150 ml. of 6*N* hydrochloric acid, and the total yield of 4,4'-bis(acetamido)azobenzene. The mixture is heated under reflux for 1.5 hours. The reaction mixture is cooled and the violet solid collected on a Büchner funnel (Note 7). The damp product is suspended in 500 ml. of water in a 1-l. beaker equipped with a stirrer, and the mixture is slowly neutralized by the addition of 2.5*N* sodium hydroxide. In the course of the neutralization, the salt dissolves and the free base separates. The 4,4'-diaminoazobenzene is collected on a Büchner funnel, washed with water, and dried under reduced pressure. The yield of yellow product, m.p. 238–241° (dec.), is 11–12 g. The over-all yield from *p*-aminoacetanilide is 52–56%.

2. Notes

1. The submitters carried out the reaction in a 1-l. beaker. The checkers found that considerable evaporation of acetic acid occurs when a beaker is used.
2. The use of dilute acetic acid decreases the yield.
3. Technical grade *p*-aminoacetanilide (m.p. 158–160°) obtained from Eastman Kodak Company (T-13) was used.
4. If the product is not washed well, the dried material will turn violet, indicating unreacted *p*-aminoacetanilide.
5. Witt and Kopetschni[2] report a melting point of 295–296° (dec.). This compound may be recrystallized from glacial acetic acid or ethanol.
6. The submitters did not stir the hydrolysis mixture. The checkers found that, if stirring was omitted, bumping occurred during the reflux period.
7. This product is probably the monohydrochloride salt. The dihydrochloride is reported to be red.[3]

3. Discussion

4,4'-Diaminoazobenzene was reported by Nietzki[4] to have been prepared by diazotizing *p*-nitroaniline and coupling the product with aniline. The resulting 4-nitrodiazoaminobenzene[5] is rearranged and the nitro group reduced. The submitters tried several times to carry out this procedure but were unsuccessful. 4,4'-Diaminoazobenzene has been prepared by the oxidation of *p*-nitroaniline with potassium persulfate[6] followed by the reduction of the nitro groups.[7]

The general method used by the submitters has been reported by others[8] for the preparation of other azo compounds.

4. Use of 4,4'-Diaminoazobenzene

The product is useful as a model compound for studies of the chemistry of derivatives of colored diamines. Specifically, the submitters used the compound for the preparation of colored diisocyanates.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

methanol (67-56-1)

aniline (62-53-3)

sodium hydroxide (1310-73-2)

potassium persulfate (7727-21-1)

boric acid (10043-35-3)

sodium perborate tetrahydrate (10486-00-7)

4-nitrodiazoaminobenzene

p-nitroaniline (100-01-6)

p-aminoacetanilide (122-80-5)

4,4'-Diaminoazobenzene, Aniline, 4,4'-azodi- (538-41-0)

4,4'-bis(acetamido)azobenzene (15446-39-6)

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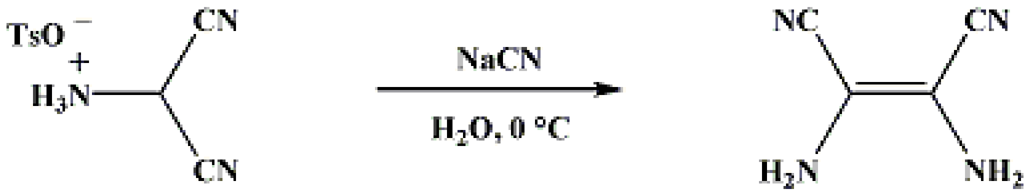
DIAMINOMALEONITRILE (HYDROGEN CYANIDE TETRAMER)

[Maleonitrile, diamino-]



Submitted by J. P. Ferris and R. A. Sanchez[1].
Checked by O. W. Webster and R. E. Benson.

1. Procedure

Caution! The preparation should be carried out in a hood because hydrogen cyanide may be evolved.

To a cooled (0°), stirred suspension of 10.0 g. (0.0395 mole) of aminomalononitrile *p*-toluenesulfonate[2] in 20 ml. of water is added 10.0 g. (0.204 mole) of sodium cyanide in 30 ml. of ice water. One minute (Note 1) after the addition of the sodium cyanide the precipitated product is collected by filtration and washed with 20 ml. of ice water. The solid is immediately dissolved (Note 1) in 30 ml. of boiling isobutyl alcohol, and the solution is stirred with 0.4 g. of Darco activated carbon (Note 2) The mixture is filtered rapidly through 10 g. of Celite filter aid, and the filter cake is washed with 10 ml. of hot isobutyl alcohol. The product that crystallizes on cooling is collected by filtration and washed with 10 ml. of isobutyl alcohol to give 0.95–1.1 g. (22–26%) of white needles, m.p. 181–183° (dec.).

2. Notes

1. The product darkens on long standing.
2. Hydrogen cyanide tetramer is strongly adsorbed on activated carbon; no more than the recommended amount of carbon should be used, and it should be added carefully to avoid frothing.

3. Discussion

The present procedure is a modification of the original synthesis.[3] Hydrogen cyanide tetramer can be prepared directly from hydrogen cyanide.[4]

4. Merits of the Preparation

This is a convenient laboratory preparation of hydrogen cyanide tetramer that avoids the hazards in using hydrogen cyanide itself. Hydrogen cyanide tetramer is a useful intermediate for the synthesis of heterocycles such as imidazoles[5,6] and thiadiazoles.[7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 32

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

DIAMINOMALEONITRILE (HYDROGEN CYANIDE TETRAMER)

Hydrogen cyanide tetramer

sodium cyanide (143-33-9)

hydrogen cyanide (74-90-8)

carbon (7782-42-5)

isobutyl alcohol (78-83-1)

Maleonitrile, diamino- (1187-42-4)

Aminomalononitrile p-toluenesulfonate (5098-14-6)

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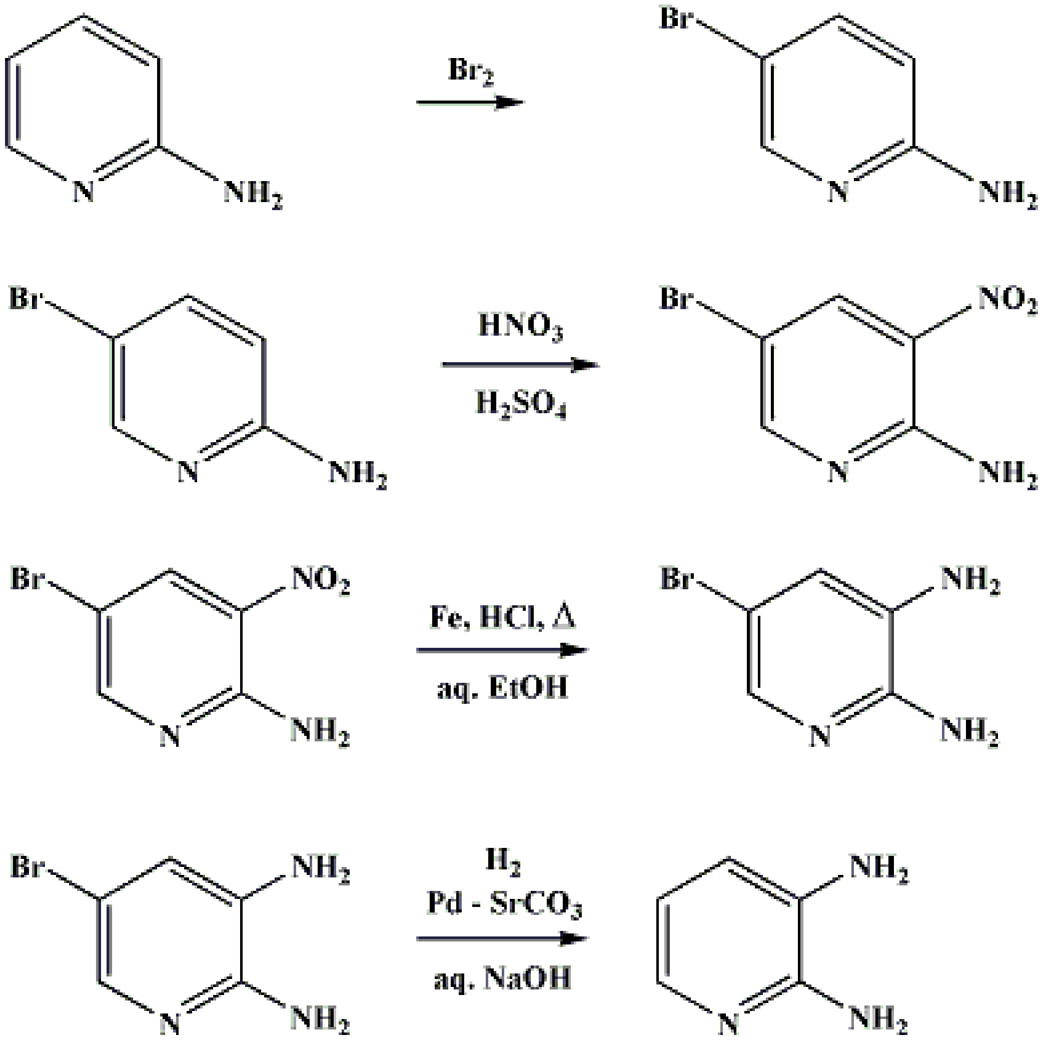
2,3-DIAMINOPYRIDINE

[Pyridine, 2,3-diamino-]



Submitted by B. A. Fox[1] and T. L. Threlfall[2].
Checked by Max Tishler, G. A. Stein, G. Lindberg, and M. Ryder.

1. Procedure

Caution! The bromination and nitration steps should be carried out in a well-ventilated hood.

A. *2-Amino-5-bromopyridine.* In a 2-l. three-necked flask equipped with stirrer, dropping funnel, and condenser is placed a solution of 282 g. (3.0 moles) of 2-aminopyridine (Note 1) in 500 ml. of acetic acid. The solution is cooled to below 20° by immersion in an ice bath, and 480 g. (154 ml., 3.0 moles) of bromine dissolved in 300 ml. of acetic acid is added dropwise with vigorous stirring over a period of 1 hour. Initially the temperature is maintained below 20°, but after about half the bromine

solution has been added it is allowed to rise to 50° to delay as long as possible the separation of the hydrobromide of 2-amino-5-bromopyridine. At 50° the hydrobromide usually begins to crystallize when about three-quarters of the bromine has been added. When addition of bromine is completed, the mixture is stirred for 1 hour and is then diluted with 750 ml. of water to dissolve the hydrobromide. The contents of the flask are transferred to a 5-l. beaker and are neutralized, with stirring and cooling, by the addition of 1.2 l. of 40% sodium hydroxide solution.

The precipitated 2-amino-5-bromopyridine, contaminated with some 2-amino-3,5-dibromopyridine, is collected by filtration and, after washing with water until the washings are free of ionic bromide, is dried at 110° (Note 2). The 2-amino-3,5-dibromopyridine is removed from the product by washing with three 500-ml. portions (Note 3) of hot petroleum ether (b.p. 60–80°). The yield of 2-amino-5-bromopyridine, m.p. 132–135°, sufficiently pure for use in the next stage, is 320–347 g. (62–67%) (Note 4) and (Note 5).

B. *2-Amino-5-bromo-3-nitropyridine.* A 1-l. three-necked flask immersed in an ice bath and equipped with stirrer, dropping funnel, condenser, and thermometer is charged with 500 ml. of sulfuric acid (sp. gr. 1.84), and 86.5 g. (0.5 mole) of 2-amino-5-bromopyridine is added at such a rate that the temperature does not exceed 5°. Twenty-six milliliters (39 g., 0.57 mole) of 95% nitric acid is added dropwise with stirring at 0°, and the mixture is stirred at 0° for 1 hour, at room temperature for 1 hour, and at 50–60° for 1 hour. The contents of the flask are cooled and poured onto 5 l. of ice and neutralized with 1350 ml. of 40% sodium hydroxide solution. The yellow precipitate of 2-amino-5-bromo-3-nitropyridine is collected by filtration and washed with water until the washings are free of sulfate, slightly acidulated water being used at the end to prevent colloidal break-through. The product is dried at room temperature to constant weight. The yield of 2-amino-5-bromo-3-nitropyridine, m.p. 204–208°, sufficiently pure for the next stage, is 85–93 g. (78–85%) (Note 6) and (Note 7).

C. *2,3-Diamino-5-bromopyridine* (Note 8). A 100-ml. flask fitted with a reflux condenser is charged with 10.9 g. (0.05 mole) of 2-amino-5-bromo-3-nitropyridine, 30 g. of reduced iron, 40 ml. of 95% ethanol, 10 ml. of water, and 0.5 ml. of concentrated hydrochloric acid (Note 9) and (Note 10). The mixture is heated on a steam bath (Note 11) for 1 hour, and at the end of this period the iron is removed by filtration and is washed three times with 10-ml. portions of hot 95% ethanol. The filtrate and washings are evaporated to dryness, and the dark residue is recrystallized from 50 ml. of water, 1 g. of activated carbon being used and the mixture being filtered while hot. The charcoal is washed with hot ethanol to avoid losses. 2,3-Diamino-5-bromopyridine crystallizes as colorless needles, m.p. 163°. The yield is 6.5–7.1 g. (69–76%).

D. *2,3-Diaminopyridine* (Note 12). In an apparatus for catalytic hydrogenation (Note 13) 56.4 g. (0.3 mole) of 2,3-diamino-5-bromopyridine suspended in 300 ml. of 4% sodium hydroxide solution is shaken with hydrogen in the presence of 1.0 g. of 5% palladized strontium carbonate (Note 14). When absorption of hydrogen is completed,

the catalyst is removed by filtration, and, after saturation with potassium carbonate (about 330 g. is required), the resulting slushy mixture is extracted continuously with ether until all the precipitate completely disappears (usually about 18 hours, but this depends on the efficiency of the extraction apparatus). The ether is removed by distillation, and the residue of crude 2,3-diaminopyridine is recrystallized from benzene (about 600 ml. is required) using 3 g. of activated charcoal and filtering rapidly through a preheated Büchner funnel. The yield of 2,3-diaminopyridine, obtained as colorless needles, m.p. 115–116°, pK_a 6.84, is 25.5–28.0 g. (78–86%) (Note 15).

2. Notes

1. The checkers used a pure grade of 2-aminopyridine (m.p. 58–60°) obtained from Matheson, Coleman and Bell.
2. The checkers dried their product at room temperature to constant weight in order to avoid loss of product due to its high volatility at 110°. It was found that 95% of an aliquot had sublimed during drying for 24 hours at 110° and atmospheric pressure. The residue analyzed high in bromine, indicating that the monobromo derivative is more volatile than the dibromo derivative.
3. The checkers washed their crude product by first refluxing its suspension in 600 ml. of petroleum ether (b.p. 60–71°) for about 20 minutes. The product, obtained by filtration, was slurry-washed on the funnel with two 600-ml. portions of boiling petroleum ether followed by air-drying to constant weight.
4. The checkers' yield, for reasons outlined in (Note 2), were appreciably higher. In two runs using one-half the quantities of reactants they obtained 211 g. and 224 g. (81–86%), of product, m.p. 132–133.5° and 133.5–135°, respectively; water content (K.F.) in both products was 0.2%.
5. If required, the 2-amino-5-bromopyridine may be recrystallized from benzene as colorless prisms, m.p. 137°.
6. The checkers' yield was 85.3 g. (78.2%), m.p. 202–204°.
7. Pure 2-amino-5-bromo-3-nitropyridine, yellow needles, m.p. 210°, may be obtained by recrystallizing the product from ethyl methyl ketone.
8. The method is essentially that of Petrow and Saper.[3]
9. Attempts to reduce larger quantities of the amino-nitro compound by this method usually give lower yields. For larger quantities several reductions may be carried out simultaneously, and the filtrates may be combined for isolation of the diamine.
10. The checkers reduced a double batch and obtained 12.8 g. (68%), m.p. 159.5–160°. In this run, heating time was doubled and charcoal was extracted repeatedly (by recycling mother liquors) to assure complete extraction.
11. The checkers employed a mechanical stirrer.
12. This is essentially the procedure of Leese and Rydon.[4]
13. The apparatus described in *Org. Syntheses*, Coll. Vol. **1**, 61 (1941), or a commercial equivalent of it, is suitable.
14. The palladized strontium carbonate is prepared as follows. Suspend 33 g. of

strontium carbonate in 350 ml. of water at 70°. Add 2 g. of palladium chloride dissolved in 10 ml. of concentrated hydrochloric acid, and stir the mixture at 70° for 15 minutes. Filter the mixture, wash the product thoroughly with hot water, and dry the product at 110°.
15. The checkers' yields were 74.8%–84.7% of analytically pure material giving a negative Beilstein test.

3. Discussion

2,3-Diaminopyridine has been prepared by reduction of 2-amino-3-nitropyridine with iron and aqueous acidified ethanol,[3] tin and hydrochloric acid,[5] or stannous chloride and hydrochloric acid,[5] by catalytic reduction of 3-amino-2-nitropyridine,[6] by reduction of 3-amino-2-nitropyridine,[7] 2-amino-5-chloro-3-nitropyridine,[8] or 2-amino-5-bromo-3-nitropyridine[4] with sodium hydroxide solution and an aluminum nickel alloy, and by catalytic reduction of 2-amino-5-bromo-3-nitropyridine.[4] Amination of 3-aminopyridine with sodamide[9] and of 3-amino-2-chloropyridine with concentrated aqueous ammonia[10] have also been employed.

4. Merits of the Preparation

By this method of preparation 2,3-diaminopyridine is obtained in 26–43% yield from the readily available 2-aminopyridine. The intermediates 2-amino-5-bromopyridine and 2-amino-5-bromo-3-nitropyridine are prepared in higher yields than previously recorded.

Methods of preparation of 2,3-diaminopyridine which involve the reduction of 2-amino-3-nitropyridine are laborious. The material is obtained in yields of less than 10% by nitration of 2-aminopyridine, and its separation from 2-amino-5-nitropyridine, which is the major product of the nitration, is tedious and inconvenient. Reduction of amino-nitro or amino-halo-nitro compounds with sodium hydroxide solution and an aluminum nickel alloy gives variable yields of an inferior product, and the method can be used only for preparing comparatively small quantities of 2,3-diaminopyridine. Catalytic reduction of 3-amino-2-nitropyridine gives a good yield of 2,3-diaminopyridine, but preparation of the amino-nitro compound is a difficult and time-consuming process. The method of Schickh, Binz, and Schulz,[10] which involves chlorination of 3-aminopyridine to 3-amino-2-chloropyridine and amination of the latter by heating for 20 hours at 130° with concentrated aqueous ammonia, suffers from the disadvantage that 3-aminopyridine is less readily available than is 2-aminopyridine. Furthermore the yields obtained in the amination stage are somewhat erratic, and the yields obtained by the submitters never approached the 57% reported.

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

palladized strontium carbonate

ethanol (64-17-5)

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ammonia (7664-41-7)

Benzene (71-43-2)

ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

iron (7439-89-6)

nitric acid (7697-37-2)

bromide (24959-67-9)

bromine (7726-95-6)

tin (7440-31-5)

stannous chloride

carbon (7782-42-5)

2-aminopyridine (504-29-0)

palladium chloride

ethyl methyl ketone (78-93-3)

sodamide (7782-92-5)

3-Aminopyridine (462-08-8)

strontium carbonate (1633-05-2)

3-amino-2-chloropyridine (6298-19-7)

2,3-Diaminopyridine, Pyridine, 2,3-diamino- (452-58-4)

2-Amino-5-bromopyridine (1072-97-5)

2-amino-3,5-dibromopyridine (35486-42-1)

2-Amino-5-bromo-3-nitropyridine (6945-68-2)

2,3-Diamino-5-bromopyridine (38875-53-5)

2-amino-3-nitropyridine (4214-75-9)

3-amino-2-nitropyridine (13269-19-7)

2-amino-5-chloro-3-nitropyridine

2-amino-5-nitropyridine (4214-76-0)

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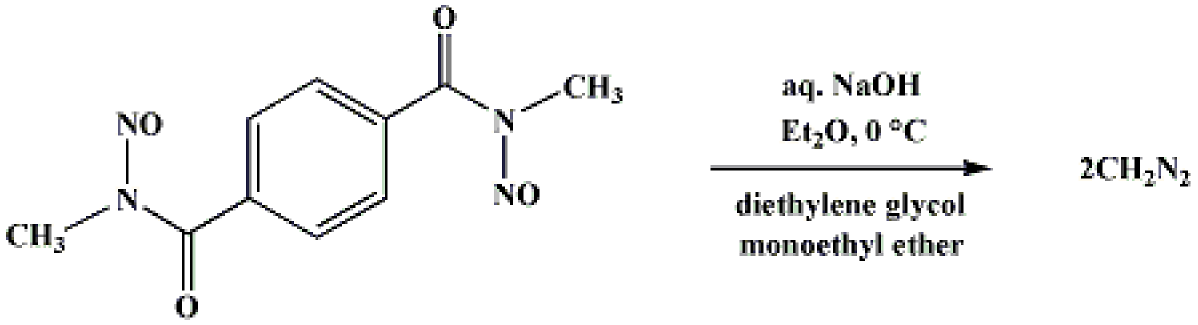
Organic Syntheses, CV 5, 351

DIAZOMETHANE

[Methane, diazo-]



Submitted by James A. Moore and Donald E. Reed[1].
Checked by D. J. Pasto and E. J. Corey.

1. Procedure

Caution! Diazomethane is toxic and explosive. The operation must be carried out in a good hood with an adequate shield (Note 1).

An efficient condenser (60 cm. or longer) is fitted with an adapter to which is sealed a length of 9-mm. tubing extending nearly to the bottom of a 5-l. round-bottomed flask, which serves as the distillation receiver (Note 2) and (Note 3). The adapter should be connected to the receiver with a two-hole stopper carrying a drying tube if anhydrous diazomethane is desired. The receiver is placed in a well-mixed ice-salt mixture, and sufficient anhydrous ether (about 200 ml.) is added to cover the tip of the adapter.

In a 5-l. round-bottomed flask are placed 3 l. of U.S.P. solvent grade ether, 450 ml. of diethylene glycol monoethyl ether (Note 4), and 0.6 l. of 30% aqueous sodium hydroxide solution (Note 5). The mixture is chilled in an ice-salt bath to 0° (Note 6), and 180 g. (0.5 mole) of N,N'-dimethyl-N,N'-dinitrosoterephthalamide (70% in mineral oil) (Note 7) is added in one portion. The flask is immediately transferred to a heating mantle and connected by a gooseneck to the condenser. The yellow color of diazomethane appears in the receiver almost immediately. About 2 l. of ether is distilled in 2–2.5 hours (Note 8); the distilling ether is practically colorless at this point. The tip of the adapter should be kept just below the surface of the distillate during the distillation. The distillate contains 0.76–0.86 mole (76–86%) (Note 9) and (Note 10) of diazomethane as determined by titration.[2] When the apparatus has been protected with a drying tube, the diazomethane is suitable for reaction with an acid chloride without further drying.

2. Notes

1. Diazomethane is not only toxic but also potentially explosive. Hence one should wear heavy gloves and goggles and work behind a safety screen or a hood door with safety glass, as is recommended in the preparation of diazomethane described by De Boer and Backer.[3] As is also recommended there, ground joints and sharp surfaces should be avoided. Thus all glass tubes should be carefully fire-polished, connections should be made with rubber stoppers, and separatory funnels should be avoided, as should etched or scratched flasks. Furthermore, at least one explosion of diazomethane has been observed at the moment crystals (sharp edges!) suddenly separated from a supersaturated solution. Stirring by means of a Teflon-coated magnetic stirrer is greatly to be preferred to swirling the reaction mixture by hand, for there has been at least one case of a chemist whose hand was injured by an explosion during the preparation of diazomethane in a hand-swirled reaction vessel.

It is imperative that diazomethane solutions not be exposed to direct sunlight or placed near a strong artificial light because light is thought to have been responsible for some of the explosions that have been encountered with diazomethane. Particular caution should be exercised when an organic solvent boiling higher than ether is used. Because such a solvent has a lower vapor pressure than ether, the concentration of diazomethane in the vapor above the reaction mixture is greater and an explosion is more apt to occur.

Most diazomethane explosions occur during its distillation. Hence diazomethane should not be distilled unless the need justifies it. An ether solution of diazomethane satisfactory for many uses can be prepared as described by Arndt,[2] where nitrosomethylurea is added to a mixture of ether and 50% aqueous potassium hydroxide and the ether solution of diazomethane is subsequently decanted from the aqueous layer and dried over potassium hydroxide pellets (not sharp-edged sticks!). When distilled diazomethane is required, the alternative procedure of De Boer and Backer[3] is particularly good because at no time is much diazomethane present in the distilling flask.

Both the toxicity and explosion hazards associated with diazomethane are discussed by Gutsche.[4]

2. If it is desired to determine the yield of diazomethane by titration, the receiver should be calibrated so that the volume of the distillate can be measured without the necessity of transferring to a graduated vessel.

3. The submitters have used equipment having all connections made with ungreased 29 / 42 ground-glass joints. This is contrary to previously recommended practice (Note 1). The submitters feel that ground-glass joints do not represent an added hazard, and that their use expedites the completion of consecutive runs. In the course of many preparations, however, a film of polymethylene was found to accumulate on the joints and prevent a tight fit. This film can be removed by a brief treatment with hot concentrated alkali and vigorous rubbing.

In some forty preparations made by the submitters, one explosion occurred which was attributed to the cracking of the adapter tube during the distillation.

The adapter and the drying tube were disintegrated, but the receiver and the contents of the distilling flask were not affected, indicating a local detonation that was not sustained.
The checkers did not use glassware with ground-glass joints. New unmarked flasks and condenser were used which were connected together with fire-polished glass tubing and rubber stoppers.
4. Practical grade 2-(2-ethoxyethoxy)ethanol (Matheson, Coleman and Bell) can be used without further treatment. In a few preparations, the submitters encountered difficulty with the formation of a very stiff gel of disodium terephthalate in the flask during distillation. In one case, this difficulty was traced to the use of an old bottle of 2-(2-ethoxyethoxy)ethanol from another source.
This relatively large volume of cosolvent was found to give optimum yields. The submitters have found that the evolution of diazomethane from a stirred suspension of the reagent in ether and 40% aqueous sodium hydroxide is extremely slow and incomplete.
5. The use of more concentrated solutions of potassium hydroxide gave somewhat lower yields.
6. *Caution! It is extremely important that the flask contents be cooled to at least 0°. The reaction is rapid and a considerable amount of diazomethane is generated at this temperature.*
7. This material is available from Eastman Organic Chemicals and Aldrich Chemical Company. It is also available from E. I. du Pont de Nemours and Company, who use the trade name Nitrosan for it. The 30% white mineral oil acts as a stabilizer. The material may be stored indefinitely at room temperature. It sometimes turns green on long standing, but this does not affect the yield of diazomethane (private communication from B. C. McKusick).
8. The yield of diazomethane is slightly lower if the distillation is carried out more slowly.
9. The average yield in some thirty runs was over 80%; yields as high as 95% have been obtained. It is probable that a second receiver in series would permit the recovery of a small additional amount of diazomethane.
10. The checkers decomposed the small amount of diazomethane remaining in the reaction flask by careful addition of 100 ml. of acetic acid before disposal.

3. Discussion

Diazomethane has been prepared by the action of base o nitrosomethylurea,[2] nitrosomethylurethane,[5] N-nitroso-β-methylaminoisobutyl methyl ketone,[6] *p*-tolylsulfonylmethylnitrosamide,[3] and N-nitroso-N-methyl-N'-nitroguanidine.[7 8]

4. Merits of Preparation

The great advantages of the present method are the availability, moderate cost, and high stability of the nitrosamide, and the suitability for large-scale preparations. The

procedure is rapid and simple, and the yields are consistently higher than in any other method tried by the submitters.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 231
- Org. Syn. Coll. Vol. 5, 877
- Org. Syn. Coll. Vol. 5, 1099
- Org. Syn. Coll. Vol. 6, 386
- Org. Syn. Coll. Vol. 6, 432
- Org. Syn. Coll. Vol. 6, 613
- Org. Syn. Coll. Vol. 7, 438
- Org. Syn. Coll. Vol. 8, 612

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6. C. E. Redemann, F. O. Rice, R. Roberts, and H. P. Ward, *Org. Syntheses*, Coll. Vol. **3**, 244 (1955).
7. A. F. McKay, *J. Am. Chem. Soc.*, **70**, 1974 (1948);
8. A. F. McKay et al., *Can. J. Research*, **28B**, 683 (1950).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

acetic acid (64-19-7)

ether (60-29-7)

sodium hydroxide (1310-73-2)

potassium hydroxide, potassium hydroxide pellets (1310-58-3)

Diazomethane, Methane, diazo- (334-88-3)

Nitrosomethylurea

Nitrosomethylurethane

N-Nitroso-β-methylaminoisobutyl methyl ketone (16339-21-2)

N-nitroso-N-methyl-N'-nitroguanidine (674-81-7)

N,N'-dimethyl-N,N'-dinitrosoterephthalamide

diethylene glycol monoethyl ether, 2-(2-ethoxyethoxy)ethanol (111-90-0)

disodium terephthalate (15596-76-6)

p-Tolylsulfonylmethylnitrosamide

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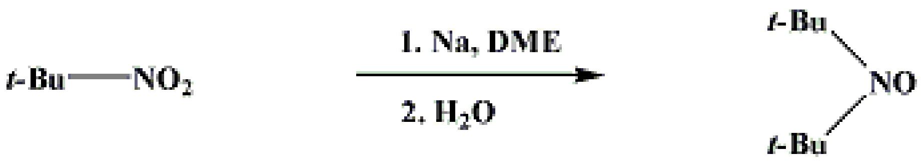
DI-*t*-BUTYL NITROXIDE

[Nitroxide, di-*tert*-butyl]



Submitted by A. K. Hoffmann, A. M. Feldman, E. Gelblum, and A. Henderson[1].
Checked by R. A. Haggard and William D. Emmons.

1. Procedure

(Note 1)
Thirteen hundred milliliters of 1,2-dimethoxyethane (glyme) is distilled from lithium aluminum hydride *(Caution! Under no circumstances should distillation be carried to dryness since explosive decomposition of the residual hydride may occur.)* (Note 2) directly into a 2-l., nitrogen-flushed, three-necked, Morton flask equipped with a nitrogen inlet, an outlet, and a high-speed stirrer with a stainless steel propeller-type blade. The flask is charged with 89.7 g. (0.87 mole) of *t*-nitrobutane (Note 3) and 19.9 g. (0.87 g. atom) of sodium cut into pea-sized pieces (Note 4). The stirrer is started and initially operated at a speed just adequate to draw some of the sodium through the blade. The onset of reaction is signaled when the solution is pale lavender and the sodium surface is clearly etched and colored bright gold (Note 5). The temperature of the reaction mixture is maintained at 25–30° (Note 6) by directing an air blast at the sides of the flask and by controlling the rate at which sodium is drawn through the blades of the stirrer. As the reaction progresses, colorless solid is formed, and at the end of the reaction (*ca.* 24 hours) the reaction mixture consists of solid and a colorless glyme solution. Most of the glyme is removed by evaporation under reduced pressure at room temperature with a water bath at 20–25° to leave a thick, colorless slurry. To the slurry under nitrogen (Note 7) is added 270 ml. of water, and the reddish brown organic layer is separated. The aqueous layer (Note 8) is extracted with several portions of pentane until the extract is colorless. The organic layer and pentane extracts are combined, cooled to 0°, and washed rapidly and thoroughly with two 70-ml. portions of ice-cold 0.25*N* hydrochloric acid to remove hydroxylamine impurities (Note 9). The pentane solution of the product is washed immediately with 70 ml. of cold water followed by 70 ml. of cold, aqueous 0.2*N* sodium hydroxide. The combined, cold, aqueous acidic washings are extracted with small portions of pentane until colorless. This pentane extract is used to extract the aqueous sodium hydroxide layer and is then washed with water and combined with the initial pentane extract.

The pentane solution is dried over anhydrous magnesium sulfate and fractionated with an efficient spinning-band column (Note 10). After foreruns of pentane and glyme containing *t*-nitrosobutane are removed (Note 11), 26–27 g. (42–43%) of red di-*t*-butyl nitroxide, b.p. 59–60° (11 mm.), is obtained.

2. Notes

1. The submitters obtained similar results using a preparative scale 7.5 times that described here; yield 36%.
2. The 1,2-dimethoxyethane (Ansul Chemical Co.) was predried for several days over calcium hydride, filtered, and stored over lithium aluminum hydride prior to its distillation at atmospheric pressure immediately before use. For a larger-scale preparation it is expeditious to distil simultaneously from two 5-l. flasks rather than from a single large one. Under these conditions, distillation of the glyme can be completed in 8–10 hours.
3. The *t*-nitrobutane employed was prepared by the procedure of Kornblum, Clutter, and Jones.[2] This method is essentially the same as that previously reported in *Organic Syntheses.*[3]
4. Throughout all transfers, air must be rigorously excluded from the flask by the nitrogen blanket.
5. When great care has not been taken to ensure the absence of moisture, induction times as long as several minutes are observed before the onset of reaction.
6. The temperature of the reaction mixture must never be allowed to exceed 30°; above this temperature drastic diminution of yield occurs.
7. A nitrogen blanket is used here to prevent ignition of hydrogen resulting from traces of unreacted sodium.
8. At this point during one run the checkers obtained a considerable amount of water-insoluble, colorless solid; however, the product yield was not changed.
9. It is essential to keep the reaction mixture and acid cold since otherwise substantial decomposition of product results.
10. The pot temperature should not exceed 100° until the di-*t*-butyl nitroxide fraction is collected.
11. In several runs it was noted that, despite the acid extraction, small amounts of N,N-di-*t*-butylhydroxylamine crystallized in the cooler parts of the fractionating column head. In such cases, repetition of the acid extraction procedure is required before fractionation.

3. Discussion

The procedure described is that of Hoffmann, Feldman, Gelblum, and Hodgson[4] and is the only one known at this time for the preparation of substantial amounts of di-*t*-butyl nitroxide.

4. Merits of the Preparation

The method is specific for the preparation of di-*t*-butyl nitroxide, a liquid member of a group of stable free radicals useful for the inhibition of a variety of reactions proceeding by radical chain mechanisms as well as for providing standards for e.s.r. measurements.

References and Notes

1. American Cyanamid Company, Stamford Research Laboratories, 1937 West Main Street, Stamford, Connecticut 06904.
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3. N. Kornblum and W. J. Jones, this volume, p. 845.
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

t-nitrobutane

glyme

t-nitrosobutane

hydrochloric acid (7647-01-0)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

nitrogen (7727-37-9)

sodium (13966-32-0)

Pentane (109-66-0)

magnesium sulfate (7487-88-9)

lithium aluminum hydride (16853-85-3)

calcium hydride (7789-78-8)

1,2-dimethoxyethane (110-71-4)

DI-t-BUTYL NITROXIDE, Nitroxide, di-tert-butyl (2406-25-9)

N,N-di-t-butylhydroxylamine

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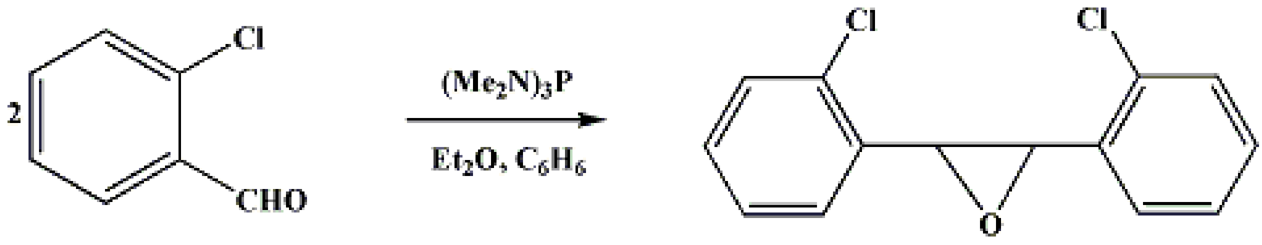
2,2'-DICHLORO-α,α'-EPOXYBIBENZYL

[Bibenzyl, α,α'-epoxy-, 2,2'-dichloro-]



Submitted by V. Mark[1]
Checked by G. A. Frank and W. D. Emmons.

1. Procedure

To a solution of *o*-chlorobenzaldehyde (56.2 g., 0.4 mole) (Note 1) in 50 ml. of benzene in a 250-ml. three-necked flask equipped with a stirrer, thermometer, dropping funnel, and reflux condenser, there is added a solution of hexamethylphosphorous triamide (37.9 g., 0.232 mole) in 20 ml. of dry ether[2] at such a rate that the temperature remains between 24° and 36°. The ensuing exothermic reaction is controlled readily by immersing the flask in a water bath (Note 2). After completion of the addition, which requires 30–50 minutes, the clear solution is maintained at 50° for 15 minutes. The solvent is removed on a rotary evaporator, and the oily residue is triturated with 100 ml. of water and then with 150 ml. of pentane. At this point only a small portion of the product is left undissolved (Note 3). The aqueous layer is extracted with 150 ml. of pentane (Note 4). The combined pentane solution is washed with two 100-ml. portions of water and concentrated to dryness to give 46–50 g. of a light yellow solid. Recrystallization from 100 ml. of methanol yields 37.5–43.1 g. of white crystals (71–81%), composed of a mixture of the *trans* epoxide (about 50–55%) and the *cis* epoxide (about 45–50%) (Note 5), (Note 6), (Note 7).

2. Notes

1. The commercial product was distilled before use. The checkers found the undistilled material equally satisfactory.
2. The solvent can be omitted, but more efficient cooling is then required to control the reaction.
3. Pentane dissolves the epoxide and water dissolves the co-product, hexamethylphosphoric triamide. The insoluble, thick, yellow syrup sometimes found is the betaine 1:1 adduct of the aldehyde and amide.[3] The checkers found no insoluble portion in their preparations.
4. Filtration through a sintered-glass funnel readily breaks up the emulsion which is formed occasionally.

5. The simplest and most accurate way to determine the composition of the product is by proton n.m.r. spectroscopy. The ratio of the oxirane hydrogen atoms (*cis* 4.48 p.p.m. and *trans* 3.97 p.p.m. downfield from internal tetramethylsilane reference, determined in carbon tetrachloride or deuteriochloroform solution)[3] gives directly the ratio of the isomers. Infrared spectroscopy, although it readily distinguishes between the isomers, gives a less accurate quantitative relationship.
6. Chromatography over silica gel (60–200 mesh), using benzene as eluent, yields pure *trans*-epoxide (m.p. 76–77°; δ 4.08) in the first fractions, and the *cis*-epoxide (m.p. 94–95°, after recrystallization from hexane; δ 4.56) in the last fractions. The assignment was also confirmed by analysis of the ^{13}C-satellite bands (*cis*, J(^{13}C-H) 181, J(H-H) 4.4, and *trans*, J(^{13}C-H) 182, J(H-H) 1.9 Hz.). In all of the cases studied the *trans* epoxide was eluted first and had lower δ and J(H-H) values than its *cis* isomer.
7. Hexaethylphosphorous triamide[2] may be substituted for the methyl homolog without adverse effect on the quality and yield of the product.

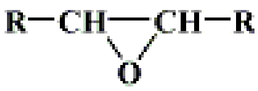
3. Discussion

2,2'-Dichloro-α,α'-epoxybibenzyl has been prepared only by the present procedure.[3]

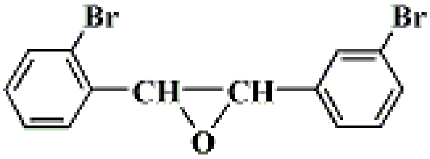
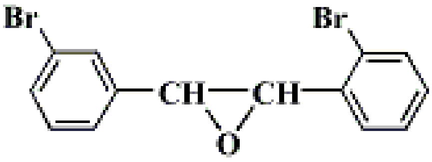
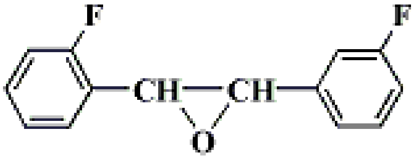
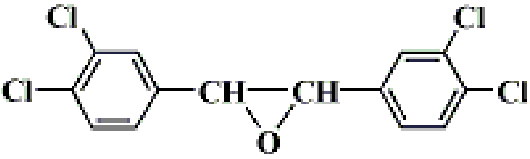
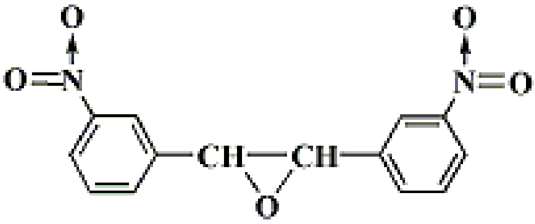
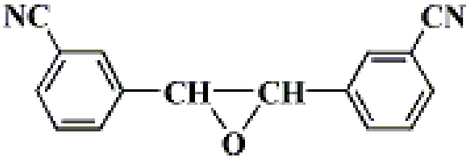
4. Merits of the Preparation

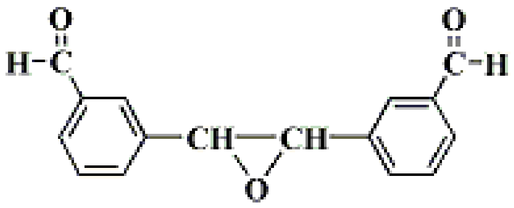
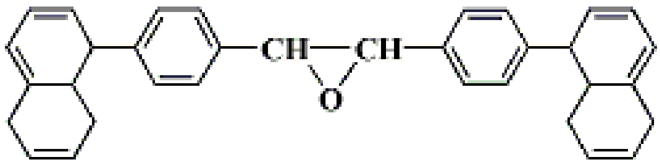
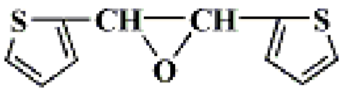
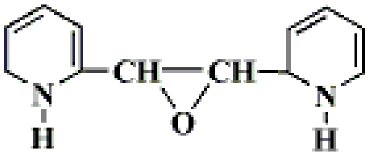
The reaction of aldehydes with hexaalkylphosphorous triamides to yield the corresponding epoxides is a synthetic procedure of considerable scope (Table I) and represents a new and simple, one-step method of forming symmetrical and unsymmetrical epoxides.[3] In contrast to the most widely used epoxide synthesis, *i.e.*, from olefins with peroxides or peracids, the present procedure may be used to obtain epoxides having structural features (*e.g.*, thiophene or pyridine rings) which would not survive the more drastic peroxide route. The procedure does not, however, afford stereochemically unique products. The yields of the epoxides from the corresponding aldehydes are usually high, and new members of the underpopulated class of aromatic and heterocyclic epoxides become readily accessible. Application of this method to certain aromatic dialdehydes yielded the first examples of cyclic aromatic epoxides.[4]

TABLE I SYNTHESIS OFSYMMETRICALEXPOXIDES



		Composition	
R	%Yield	%*trans*	%*cis*

 *o*-Bromophenyl	90–95	59	41
 *m*-Bromophenyl	45–50	72[a]	28
 *o*-Fluorophenyl	90–95	60	40
 3,4-Dichlorophenyl	88–95	60	40
 *m*-Nitrophenyl	75–80	74[b]	26
 *p*-Cyanophenyl	90–95	57	43

 *p*-Formylphenyl	75–80	53	47
 1-Naphthyl	83–87	53	47
 2-Thienyl[c]	60–65	53	47
 2-Pyridyl	85–90	75[d]	25

[a] M.p. 84–86°.

[b] M.p. 156–158°.

[c] Hexaethylphosphorous triamide was used.

[d] M.p. 95–97°.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 602

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Benzene (71-43-2)

methanol (67-56-1)

ether (60-29-7)

carbon tetrachloride (56-23-5)

Pentane (109-66-0)

hexane (110-54-3)

tetramethylsilane (75-76-3)

Hexamethylphosphorous triamide (1608-26-0)

hexamethylphosphoric triamide (680-31-9)

betaine (107-43-7)

deuteriochloroform (865-49-6)

Hexaethylphosphorous triamide (2283-11-6)

o-chlorobenzaldehyde (89-98-5)

2,2'-Dichloro-α,α'-epoxybibenzyl, Bibenzyl, α,α'-epoxy-, 2,2'-dichloro- (53608-92-7)

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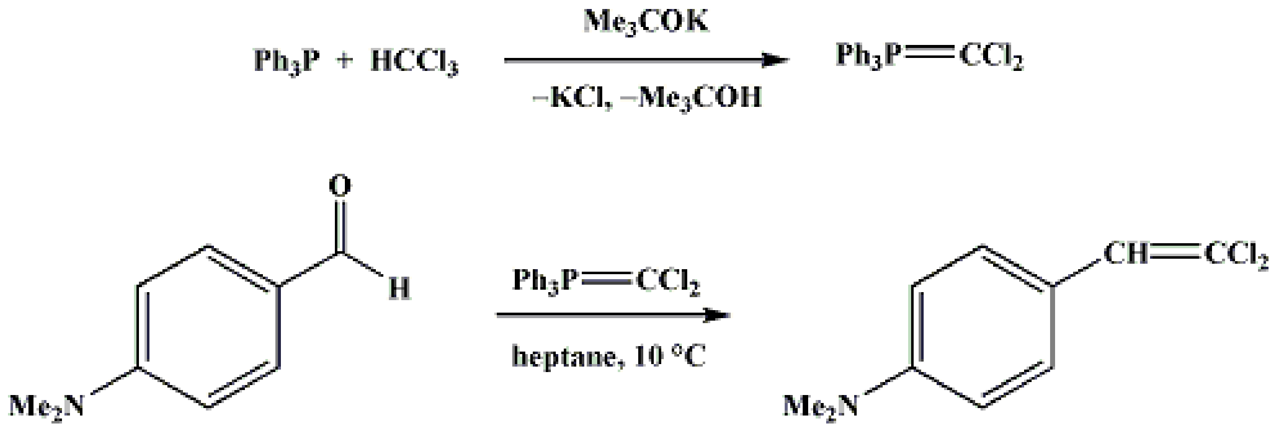
Organic Syntheses, CV 5, 361

DICHLOROMETHYLENETRIPHENYLPHOSPHORANE AND β,β-DICHLORO-*p*-DIMETHYLAMINOSTYRENE

[Phosphorane, (dichloromethylene) triphenyl-1]



Submitted by A. J. Speziale, K. W. Ratts, and D. E. Bissing[1].
Checked by William E. Parham and L. Dean Edwards.

1. Procedure

A. *Potassium t-butoxide*. To 500 ml. of *t*-butyl alcohol (Note 1) in a 3-l. three-necked flask equipped with an efficient sealed stirrer, a nitrogen inlet (Note 2), a 500-ml. dropping funnel with a pressure-equalizing side tube (Note 3), and a reflux condenser there is added 20 g. (0.5 g. atom) of clean potassium metal. After the potassium has reacted, the condenser is replaced by a 12-in. distillation column and the excess *t*-butyl alcohol is removed by distillation until crystals begin to form in the solution. There is added 2 l. of dry heptane and the distillation is continued until the head temperature reaches 98° (Note 4) and (Note 5). The residual mixture is adjusted to a 1.5-l. volume by addition of dry heptane and the resulting slurry of potassium *t*-butoxide in heptane is cooled to 0–5° in an ice bath (Note 6).

B. *Dichloromethylenetriphenylphosphorane*. In one portion 131 g. (0.5 mole) of triphenylphosphine (Note 7) is added to the cooled suspension of potassium *t*-butoxide in heptane, and to the well-stirred mixture a solution of 59.5 g. (0.5 mole) of chloroform in 500 ml. of dry heptane is added dropwise over a period of 1 hour, maintaining the temperature below 5° and an atmosphere of purified nitrogen. The resulting stirred suspension is concentrated to a 750-ml. volume at reduced pressure and at 15–20° (Note 8).

C. β,β-*Dichloro-p-dimethylaminostyrene*. To the heptane suspension of the phosphorane there is added over a period of 30 minutes 74.5 g. (0.5 mole) of *p*-dimethylaminobenzaldehyde in six equal portions; the reaction temperature is maintained below 10°. The mixture is stirred for 2 hours in an ice bath, for an additional 5 hours at room temperature, and is then allowed to stand overnight. The precipitated phosphine

oxide is filtered and the solvent is removed from the filtrate at 45–50° using a rotary evaporator. The resulting brown solid is recrystallized from methanol to yield 74–85 g. (68–79%) of crude olefin, m.p. 56–60°. The major impurity is unreacted triphenylphosphine.

The crude product is dissolved in absolute ethanol (10 ml. per gram of material), and a saturated solution of mercuric chloride (1 g. per 5 g. of crude olefin) in absolute ethanol is added (Note 9). The precipitate is filtered (Note 10) and washed with absolute ethanol. The filtrate is concentrated to half of its original volume (Note 11) and cooled in an ice bath. The yield of olefin is 42–60 g. (39–56%), m.p. 71–72°.

2. Notes

1. The *t*-butyl alcohol should be distilled from metallic sodium before use, care being taken to exclude moisture.
2. The nitrogen was purified by passing it through two wash bottles containing Fieser's solution[2] and single wash bottles containing concentrated sulfuric acid and solid anhydrous calcium chloride, respectively.
3. If available, it is more convenient to use a flask which also accommodates a thermometer extending into the reaction mixture.
4. It may be necessary to add more heptane during the distillation, as the slurry of potassium *t*-butoxide in heptane becomes very difficult to stir if the total volume is less than 1 liter.
5. About 2 hours is required for removal of all the excess *t*-butyl alcohol.
6. The potassium *t*-butoxide prepared in this manner is a 1:1 complex with *t*-butyl alcohol; neutralization equivalent calculated for $(CH_3)_3COH{\cdot}(CH_3)_3COK$, 186. Found: 184, 182. The complex can be isolated by simply removing the solvent at 20–25 mm. pressure on a steam bath. It can be stored for several months under a nitrogen atmosphere.
7. Triphenylphosphine was used as supplied by Eastman Organic Chemicals.
8. It is desirable to remove the *t*-butyl alcohol formed during the generation of dichlorocarbene because the *t*-butyl alcohol reacts with the phosphorane, thus lowering the yield of olefin. The evaporation is best accomplished with a vacuum pump (*e.g.*, a Langdon pump) since the removal of *t*-butyl alcohol and heptane by water aspiration is very slow at this temperature. It is imperative that this step be accomplished as rapidly as possible and that the temperature be maintained below 20°. Although the suspension of phosphorane in heptane can be stored overnight under a nitrogen atmosphere, it is better to use it immediately.
9. Mercuric chloride forms with triphenylphosphine a double salt which is insoluble in ethanol.
10. It is necessary to use a fine or ultra-fine sintered-glass funnel or Whatman No. 1 filter paper because the precipitate is finely divided.
11. The checkers obtained better results by reducing the volume to one-third the original volume.

3. Discussion

Dichloromethylenetriphenylphosphorane has been prepared by the direct reaction of triphenylphosphine with carbon tetrachloride.[3] 1,1-Dichloroethylenes have been prepared by dehydrochlorination of 1,1,1-trichloro compounds[4,5,6] or by specialized methods applicable only to specific compounds.[7,8]

4. Merits of the Preparation

The procedure described illustrates a general method for the preparation of 1,1-dichloroethylenes. Dichloromethylenetriphenylphosphorane has been treated with a variety of aldehydes and ketones including *p*-nitrobenzaldehyde, 2,6-dichlorobenzaldehyde, cinnamaldehyde, lauraldehyde, acetaldehyde, cyclohexanone, and benzophenone to give the corresponding 1,1-dichloroethylene in good yield.[9]

Chlorofluoromethylenetriphenylphosphorane has been utilized in an extension of this method to prepare chlorofluoroethylenes.[10]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Phosphorane, (dichloromethylene) triphenyl-1

ethanol (64-17-5)

acetaldehyde (75-07-0)

methanol (67-56-1)

chloroform (67-66-3)

Cyclohexanone (108-94-1)

carbon tetrachloride (56-23-5)

nitrogen (7727-37-9)

Benzophenone (119-61-9)

sodium (13966-32-0)

mercuric chloride (7487-94-7)

potassium (7440-09-7)

cinnamaldehyde

p-Nitrobenzaldehyde (555-16-8)

heptane (142-82-5)

2,6-Dichlorobenzaldehyde (83-38-5)

t-butyl alcohol (75-65-0)

p-Dimethylaminobenzaldehyde (100-10-7)

triphenylphosphine (603-35-0)

Dichloromethylenetriphenylphosphorane (6779-08-4)

β,β-DICHLORO-p-DIMETHYLAMINOSTYRENE (6798-58-9)

phosphine oxide

Chlorofluoromethylenetriphenylphosphorane

potassium t-butoxide (865-47-4)

lauraldehyde (112-54-9)

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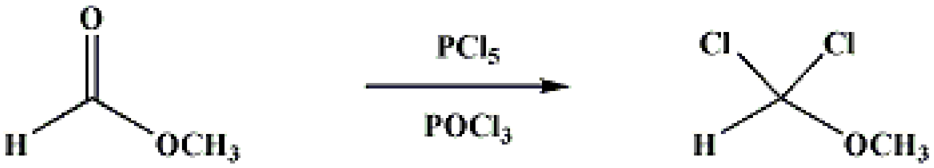
DICHLOROMETHYL METHYL ETHER



Submitted by H. Gross, A. Rieche, E. Höft, and E. Beyer[1].
Checked by G. N. Taylor and K. B. Wiberg.

1. Procedure

In a 2-l. three-necked flask equipped with a stirrer, a reflux condenser, and a dropping funnel (Note 1) 832 g. (4.0 moles) of phosphorus pentachloride is stirred with 250 ml. of phosphorus oxychloride (Note 2). To this is added with stirring 264 g. (272 ml., 4.4 moles) of methyl formate (Note 3). During the addition the reaction vessel is cooled in an ice bath to maintain a reaction temperature of 10–20°. The addition requires about 1.75 hours. When the addition is complete, the solution is stirred at a temperature under 30° until all the phosphorus pentachloride has dissolved (about 1 hour). Then the stirrer is removed, the reflux condenser is replaced by a distilling head, and the reaction mixture is distilled under a pressure of 80–120 mm. with a bath temperature of 50–65° (Note 4). During the distillation the receiver is cooled to −10° to −20° by an ice-salt bath.

The material which is collected is redistilled through a 90-cm. vacuum-jacketed column packed with glass beads (5 mm.) using a 1:10 reflux ratio. The fraction, b.p. 80–100°, is redistilled through the same column to give 353–386 g. (77–84%) of dichloromethyl methyl ether, b.p. 82–85.5°, n^{20}_{D} 1.4303 (Note 5).

2. Notes

1. The reflux condenser and dropping funnel must be provided with calcium chloride tubes.
2. Phosphorus oxychloride serves only as a suspension medium for phosphorus pentachloride and makes possible a homogeneous reaction. The phosphorus oxychloride obtained during workup may be recycled in this preparation.
3. Commercial methyl formate was dried over sodium sulfate and used without special purification.
4. If it is not first distilled under reduced pressure, extensive decomposition will occur during fractional distillation.
5. The product must be protected from moisture when stored.

3. Discussion

Dichloromethyl methyl ether has been prepared by the chlorination of chlorodimethyl ether in the liquid[2,3,4] or gas phase,[5] by the reaction of chlorodimethyl ether with sulfuryl chloride and benzoyl peroxide,[6,7] and by the treatment of methyl formate with phosphorus pentachloride.[8,9,10]

4. Merits of the Preparation

Dichloromethyl methyl ether may be employed preparatively in various ways. Thus it effects the replacement of carbonyl and hydroxyl oxygens by chlorine,[11] and may be used in the preparation of α-acetochlorosugars[12] and acid chlorides, particularly those derived from acetylated monocarboxylic acid sugars[12,13] and acetylated amino acids.[14] In addition, the *ortho* derivatives of formic acid may be prepared from dichloromethyl methyl ether.[15] With aromatic compounds, dichloromethyl methyl ether reacts under Friedel-Crafts conditions followed by hydrolysis to give the corresponding aromatic aldehydes.[10,16,17]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 49
- Org. Syn. Coll. Vol. 7, 467

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

phosphorus pentachloride (10026-13-8)

sodium sulfate (7757-82-6)

formic acid (64-18-6)

Phosphorus Oxychloride (21295-50-1)

sulfuryl chloride (7791-25-5)

methyl formate (107-31-3)

chlorodimethyl ether (107-30-2)

benzoyl peroxide (94-36-0)

Dichloromethyl methyl ether (4885-02-3)

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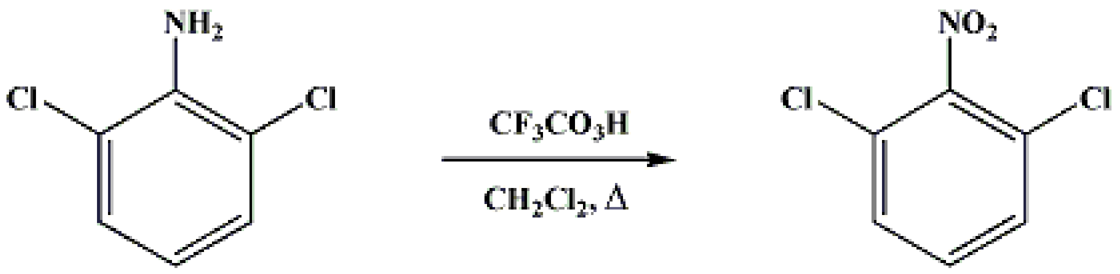
Organic Syntheses, CV 5, 367

2,6-DICHLORONITROBENZENE

[Benzene, 1,3-dichloro-2-nitro-]



Submitted by A. S. Pagano and W. D. Emmons[1].
Checked by V. Z. Williams, Jr. and K. B. Wiberg.

1. Procedure

Caution! The preparation and handling of peroxytrifluoroacetic acid should be carried out behind a safety screen. Precautions to be observed with 90% hydrogen peroxide are described in (Note 3) and should be carefully followed.

A 300-ml. three-necked flask equipped with a Trubore stirrer, dropping funnel, and reflux condenser protected with a calcium chloride drying tube is charged with 100 ml. of methylene chloride (Note 1). To this solvent is added without stirring 5.4 ml. (0.20 mole) of 90% hydrogen peroxide (Note 2), (Note 3), (Note 4), (Note 5). The hydrogen peroxide is not miscible with the solvent and separates as the lower layer at the bottom of the flask. The flask is then cooled in an ice bath, and the stirrer is started. To this cold solution over a 20-minute period is added 34.0 ml. (0.24 mole) of trifluoroacetic anhydride. After addition is complete, the ice bath is removed and the solution is stirred at room temperature for 30 minutes.

A solution is then prepared from 8.1 g. (0.05 mole) of 2,6-dichloroaniline (Note 6) and 80 ml. of methylene chloride. This solution is added dropwise over a 30-minute period to the previously prepared peroxytrifluoroacetic acid reagent (Note 7). During this addition the exothermic reaction causes the mixture to reflux. After addition is complete, the mixture is heated under reflux for 1 hour. It is then cooled and poured into 150 ml. of cold water. The organic layer is separated, washed with 100 ml. of water, with two 100-ml. portions of 10% sodium carbonate solution (Note 8), and finally with 50 ml. of water. The organic extract is treated with activated charcoal and anhydrous magnesium sulfate. After standing overnight, the volatile solvent is removed at aspirator pressure with the aid of a warm water bath. There is obtained 8.6–8.8 g. (89–92%) of yellow 2,6-dichloronitrobenzene, m.p. 63–68°. The product is recrystallized from a minimum volume (12–15 ml.) of ethanol and washed on the filter with 10 ml. of cold ethanol to give 5.7–7.0 g. (59–73%) of a slightly off-white

product, m.p. 69–70° (reported,[2] 70.5°).

2. Notes

1. Reagent grade methylene chloride was used without further purification.
2. Available from Becco Chemical Division, Food, Machinery and Chemical Co., Buffalo, New York.
3. The precautions to be observed with 90% hydrogen peroxide have been described in detail.[3] In essence, it is important to prevent contact of this reagent with any easily oxidizable substrate such as wood, alcohols, and sugars and with heavy metal salts since these substances catalyze its decomposition. Storage of hydrogen peroxide in the laboratory should be arranged in such a way that, even if the bottle containing the reagent breaks, the hydrogen peroxide will not come into contact with any material of this kind. Small samples of 90% hydrogen peroxide are regularly shipped in vented glass bottles provided with a protective outside metal container, and it is desirable to use this container while storing the reagent in the laboratory. In the event that spillage of the reagent occurs, dilution with at least several volumes of water is recommended. In weighing out 90% hydrogen peroxide it is good practice never to return excess reagent to the stock bottle; rather, it should be diluted with water and discarded to avoid any possibility that the stock bottle will be contaminated.
4. It is convenient to measure out the hydrogen peroxide by a 10-ml. graduate or by a 10-ml. pipet actuated by a glass syringe connected via a ground-glass joint.
5. The procedure described here for the preparation of peroxytrifluoroacetic acid in methylene chloride has been carried out by the submitters several hundred times without incident and is believed to be the best available. However, it has been pointed out that suspensions of 90% hydrogen peroxide in methylene chloride can be detonated by impact under certain conditions.[4] Accordingly, the use of the recommended safety screen is imperative, and the preparation should not be scaled up without special precautions. The homogeneous solution of peroxytrifluroacetic acid, once obtained, is undoubtedly much safer to handle than the suspension of hydrogen peroxide in methylene chloride. The latter suspension is not transferred, however, and exists for only a brief time period during the preparation.
6. Available from Aldrich Chemical Company, Inc.
7. Addition of the peracid solution to the aniline invariably resulted in a poor-quality product in low yield.
8. The sodium carbonate extracts are quite dark.

3. Discussion

2,6-Dichloronitrobenzene has been prepared by deamination of 3,5-dichloro-4-nitroaniline[2] and of 2,4-dichloro-3-nitroaniline.[5] This procedure is an example of the rather general oxidation of anilines to nitrobenzenes with peroxytrifluoroacetic acid.[6,7]

Use of this reagent is frequently the method of choice for carrying out this transformation, and it is particularly suitable for oxidation of negatively substituted aromatic amines. Conversely, those aromatic amines, such as *p*-anisidine and β-naphthylamine, whose aromatic nuclei are unusually sensitive to electrophilic attack give intractable mixtures with this reagent.[6] This is not a serious limitation, however, and many of the nitrobenzenes which are available from this procedure have in the past required tedious multistep syntheses.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

sodium carbonate (497-19-8)

hydrogen peroxide (7722-84-1)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

2,6-Dichloroaniline (608-31-1)

2,6-Dichloronitrobenzene, Benzene, 1,3-dichloro-2-nitro- (601-88-7)

peroxytrifluoroacetic acid, peroxytrifluroacetic acid

β-naphthylamine (91-59-8)

trifluoroacetic anhydride (407-25-0)

3,5-dichloro-4-nitroaniline

2,4-dichloro-3-nitroaniline

p-anisidine (104-94-9)

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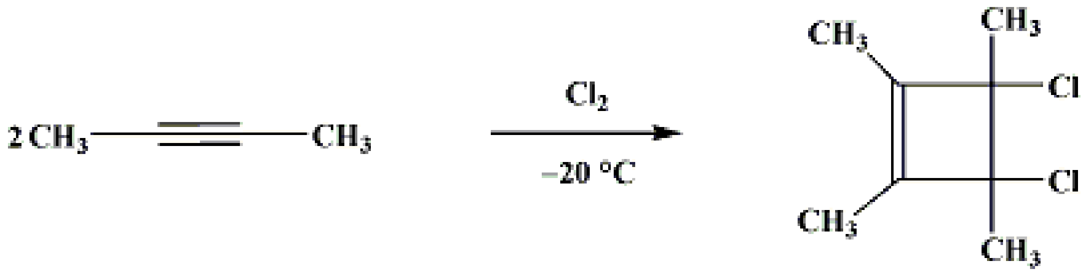
3,4-DICHLORO-1,2,3,4-TETRAMETHYLCYCLOBUTENE

[Cyclobutene, 1,2,3,4-tetramethyl-3,4-dichloro-]



Submitted by R. Criegee[1]
Checked by G. Brown and V. Boekelheide.

1. Procedure

A 400-ml. three-necked flask equipped with a mechanical stirrer, a gas dispersion tube, and a thermometer is charged with 216 g. (4 moles) of 2-butyne, 14 ml. of boron trifluoride etherate, and 1 ml. of water (Note 1). The mixture is stirred vigorously while the flask is partially immersed in a dry ice-acetone bath to maintain an internal temperature of −20°. Chlorine (195 g., 2.75 moles) is then added (Note 2) gradually over a period of 17–20 hours.

When all the chlorine has been added, the flask and contents (Note 3) are cooled to −78° and held at this temperature for 30 minutes. The white crystalline product which separates is collected on a sintered-glass funnel; 160–170 g. (45–48%) of crude crystals, m.p. 53–55°, is obtained. The crude product when stored at −20° takes on a reddish or blue color after a few days (Note 4).

Purification of the crude material is accomplished by dissolving it in petroleum ether (30–50°) or methylene chloride, shaking this solution three times with water, and passing the organic layer through a fluted filter paper. After the filtrate has been dried over anhydrous sodium sulfate, it is concentrated to a small volume and cooled to −78°. The perfectly white, crystalline product which separates is collected yielding 110–120 g. (30–33%) of crystals, m.p. 57–58° (Note 5).

2. Notes

1. The submitter reports that he and his colleagues have found since the procedure was submitted and checked that the yield and purity of the product is the same whether the preparation is carried out in the presence or absence of boron trifluoride etherate and water. Recommends that the 14 ml. of boron

trifluoride etherate and 1 ml. of water *not* be added.

2. The chlorine is most conveniently added by liquefying the required amount in a gas trap. The gas trap is placed in an empty Dewar flask and covered with glass wool. While the liquid chlorine slowly warms up, the resulting gaseous chlorine is passed through a sulfuric acid wash bottle into the reaction mixture. The addition generally takes 17–20 hours.

3. The final reaction mixture is slightly yellow, but at times it can be reddish. During the reaction some white crystalline product collects at the walls of the reaction vessel.

4. It is important to purify the crude product as soon as possible since it decomposes readily in the impure state. Once decomposition has set in, purification is difficult.

5. A still purer product is obtained if the dried petroleum ether solution is evaporated to dryness with a water aspirator and the residual crude product distilled through a Vigreux column. After a small fore-run, pure tetramethyl-3,4-dichlorocyclobutene distils at 59–60° at 12 mm. The product melts at 58° and is more stable at room temperature than the recrystallized but undistilled material.

3. Discussion

The method used is that of Criegee and Moschel.[2] Smirnow-Samkow[3] made the same substance by the reaction of 2-butyne with sulfuryl chloride in 10–15% yield.

4. Merits of the Preparation

3,4-Dichloro-1,2,3,4-tetramethylcyclobutene is an unusually versatile intermediate.[4] The tertiary and allylic chlorine atoms undergo ready solvolysis. With lithium aluminum hydride the chlorine atoms are replaced by hydrogen. The resulting *cis, trans*-tetramethylcyclobutenes are starting materials for numerous transformations, *e. g.*, thermolysis leads to stereoiisomeric tetramethylbutadienes.[5] Lithium amalgam in ether results in the formation of octamethyltricyclooctadiene. With nickel carbonyl the nickel chloride complex of tetramethylcyclobutadiene is formed.[6] Ammonia transforms the dichloride into tetramethylpyrrole.[7] Other reactions have been reported.[8]

This method of preparation is simpler, more reproducible, and gives considerably better yields than the original one of Smirnow-Samkow.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

octamethyltricyclooctadiene

nickel chloride complex of tetramethylcyclobutadiene

ammonia (7664-41-7)

ether (60-29-7)

sodium sulfate (7757-82-6)

sulfuryl chloride (7791-25-5)

chlorine (7782-50-5)

methylene chloride (75-09-2)

lithium (7439-93-2)

nickel carbonyl

lithium aluminum hydride (16853-85-3)

boron trifluoride etherate (109-63-7)

2-butyne (503-17-3)

3,4-Dichloro-1,2,3,4-tetramethylcyclobutene, Cyclobutene, 1,2,3,4-tetramethyl-3,4-dichloro-, tetramethyl-3,4-dichlorocyclobutene (1194-30-5)

tetramethylpyrrole (1003-90-3)

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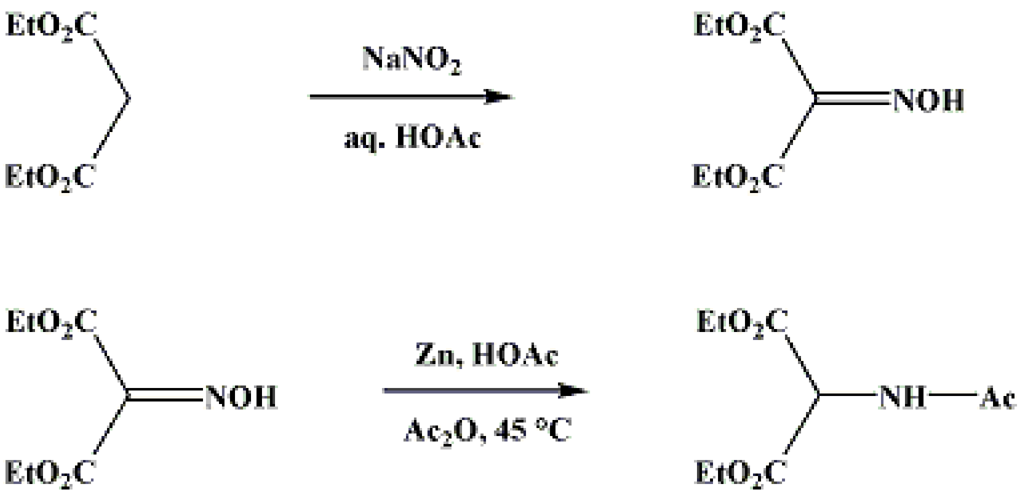
Organic Syntheses, CV 5, 373

DIETHYL ACETAMIDOMALONATE

[Malonic acid, acetamido-, diethyl ester]



Submitted by Arthur J. Zambito and Eugene E. Howe[1].
Checked by John C. Sheehan and Alma M. Boston.

1. Procedure

A. *Diethyl isonitrosomalonate*. In a 500-ml. three-necked, round-bottomed flask, equipped with a mechanical stirrer and thermometer, is placed 50 g. (47.4 ml., 0.312 mole) of diethyl malonate. The flask is cooled in an ice bath, and a mixture of 57 ml. of glacial acetic acid and 81 ml. of water is added with stirring. With the temperature at about 5°, a total of 65 g. of sodium nitrite (Note 1) (0.944 mole) is added in portions over a period of 1.5 hours, the temperature being maintained around 5° during the addition. After all the sodium nitrite is added, the ice bath is removed, and the stirring is continued for 4 hours (Note 2). During this time, the temperature reaches a maximum of 34–38° within 2 hours and falls to about 29° by the end of the stirring period. Gases which escape during the reaction (mostly oxides of nitrogen) are led to the hood.

The reaction mixture is transferred to a 300-ml. separatory funnel and is extracted with two 50-ml. portions of ether. The combined ethereal solution of diethyl isonitrosomalonate is used in the next step immediately or, if desired, may be used after storage in a refrigerator overnight (Note 3).

B. *Diethyl acetamidomalonate*. The solution of diethyl isonitrosomalonate described above, 86 g. (0.842 mole) of acetic anhydride, and 225 ml. (3.95 moles) of glacial acetic acid are placed in a 1-l., three-necked, round-bottomed flask fitted with a mechanical stirrer, a thermometer, and a dropping funnel. With vigorous stirring 78.5 g. (1.20 moles) of zinc dust is added in small portions over a period of 1.5 hours in

such a manner that the temperature of the reaction is maintained at 40–50°. The reaction is markedly exothermic during most of the zinc addition, and intermittent cooling (water bath) is required. After all the metal has been added, the mixture is stirred for an additional 30 minutes.

The reaction mixture is filtered with suction and the cake is washed thoroughly with two 200-ml. portions of glacial acetic acid (Note 4). The combined filtrate and washings are evaporated under reduced pressure on the steam bath until a thick oil, which generally partially crystallizes, remains. To purify the crude product, 100 ml. of water is added, and the flask is warmed on a steam bath until the solid melts. The mixture of water and oil is stirred rapidly in an ice bath, and diethyl acetamidomalonate crystallizes as a fine white product. After cooling in an ice bath for an additional hour, the product is collected by filtration, washed once with cold water, and dried in air at 50°. A second crop is obtained by concentrating the mother liquor under reduced pressure. The yield of diethyl acetamidomalonate, m.p. 95–97° (Note 5), is 52–53 g. (77–78%) based on malonic ester.

2. Notes

1. Owing to the instability of sodium nitrite solutions, the addition of the solid salt is preferred.
2. Prolonging the stirring to 24 hours has no effect on the yield of diethyl acetamidomalonate.
3. No attempt has been made to purify diethyl isonitrosomalonate. This product has been known to explode during distillation.
4. The zinc cake is very heavy and may be washed by slurrying on a sintered-glass funnel or, if a standard Büchner funnel is used, by removing and slurrying in a beaker.
5. The diethyl acetamidomalonate obtained is of high purity. If a product of inferior quality is obtained, it may be recrystallized from hot water, using 2.5 cc. per g. Upon cooling, the product separates first as an oil. With rapid stirring, it is converted to fine white crystals which are easily washed with cold water. Diethyl acetamidomalonate may be recrystallized in this manner with 97% recovery. The first crop amounts to 91% and the mother liquors may be concentrated to yield an additional 6%.

3. Discussion

Diethyl acetamidomalonate was first reported by Cherchez[2] in 1931, when in an attempt to carry out a carbon alkylation of diethyl aminomalonate with acetyl chloride he obtained a quantitative yield of diethyl acetamidomalonate. This method of preparation, however, is not practical since diethyl aminomalonate is unstable and is made in relatively poor yields.

Snyder and Smith[3] prepared diethyl acetamidomalonate in 40% yield by reduction of

diethyl isonitrosomalonate in ethanol over palladium on charcoal followed by direct acetylation of diethyl aminomalonate in the filtrate with acetic anhydride. Ghosh and Dutta[4] used zinc dust instead of palladium. A modification using Raney nickel is described by Akabori et al.[5] Shaw and Nolan[6] reported a 98% yield by conversion of diethyl oximinomalonate-sodium acetate complex.

4. Use of Diethyl Acetamidomalonate

Diethyl acetamidomalonate is useful in the synthesis of α-amino acids by alkylation, as, for example, histidine and tryptophan.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 376

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

oxides of nitrogen

diethyl oximinomalonate-sodium acetate complex

ethanol (64-17-5)

acetic acid (64-19-7)

ether (60-29-7)

acetic anhydride (108-24-7)

acetyl chloride (75-36-5)

sodium nitrite (7632-00-0)

Raney nickel (7440-02-0)

zinc (7440-66-6)

palladium (7440-05-3)

diethyl malonate (105-53-3)

histidine (71-00-1)

tryptophan (73-22-3)

Diethyl acetamidomalonate, Malonic acid, acetamido-, diethyl ester (1068-90-2)

diethyl isonitrosomalonate (6829-41-0)

diethyl aminomalonate (6829-40-9)

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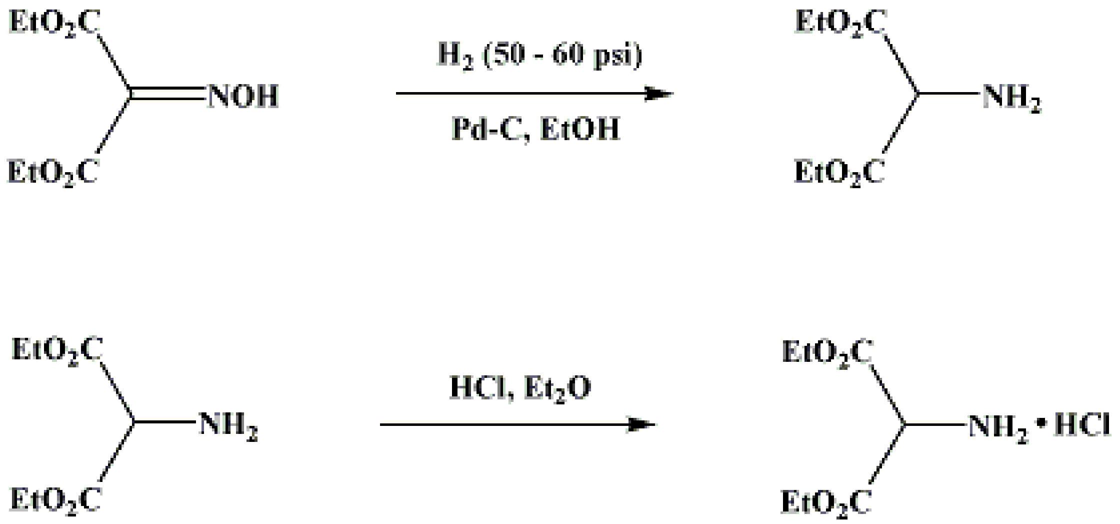
Organic Syntheses, *CV 5, 376*

DIETHYL AMINOMALONATE HYDROCHLORIDE

[Malonic acid, amino-, diethyl ester, hydrochloride]



Submitted by Walter H. Hartung, Jan H. R. Beaujon, and George Cocolas[1].
Checked by John C. Sheehan and Robert W. Parsons, Jr..

1. Procedure

A. *Diethyl aminomalonate*. An ethereal solution (about 150 ml.) of diethyl isonitrosomalonate prepared from 50 g. of diethyl malonate (Note 1) is washed with 80-ml. portions of 1% sodium bicarbonate solution until the final washing has a distinct yellow color (Note 2). The ethereal solution is dried over 40 g. of anhydrous sodium sulfate in a refrigerator overnight and then filtered into a tared round-bottomed flask. The solvent is removed under reduced pressure at a temperature below 30° (water bath). The weight of the residue in one case was 59.6 g. Assuming complete conversion of the 0.312 mole of diethyl malonate to diethyl isonitrosomalonate, a 0.1-mole aliquot (19.1 g.) of the residue is placed in a 500-ml. reduction bottle provided for the Parr Hydrogenator (Note 3). To this is added 100 ml. of absolute alcohol and 3 g. of 10% palladium-on-charcoal catalyst (Note 4). The bottle is placed in a hydrogenator, and the system is flushed three or four times with hydrogen. With the initial reading on the pressure gauge at 50–60 lb., the bottle is shaken until no further drop in pressure is observed (about 15 minutes).

The catalyst is removed by filtration, using an absolute alcohol wash, and the clear filtrate is concentrated under reduced pressure at a temperature below 50° (water bath). As diethyl aminomalonate is not so stable as its salts, the crude product is converted directly to diethyl aminomalonate hydrochloride (Note 5).

B. *Diethyl aminomalonate hydrochloride*. The crude diethyl aminomalonate is diluted

with 80 ml. of dry ether and filtered to remove a small amount of white solid. The filtrate is collected in a 250-ml. Erlenmeyer flask and cooled in an ice bath. Dry hydrogen chloride is passed just over the solution while it is being stirred mechanically (Note 6). The fine white crystals which precipitate are collected by suction filtration and washed three times with a total of 60 ml. of dry ether (Note 7). The filtrate and washings are treated again with hydrogen chloride, and a second crop of diethyl aminomalonate hydrochloride is collected and washed as before. This process is repeated until no further precipitation results from passing hydrogen chloride into the solution. A total of 16.5–17.4 g. (78–82% yield based on diethyl malonate) of diethyl aminomalonate hydrochloride, m.p. 162–163°, is obtained. Recrystallization from alcohol-ether affords a purer product, 164–165°.

2. Notes

1. It is convient to use the ether solution of diethyl isonitrosomalonate described by Zambito and Howe.[2]
2. About six washings are required. It may be necessary to add a total of 50 ml. of ether during the first three washings and 20 ml. during the final washing to facilitate breaking of the interphase emulsions. In each case, after partial separation of phases has occurred, ether is added and the separatory funnel is swirled gently until the interphase clears. The washing process requires about 1.5 hours.
3. As diethyl isonitrosomalonate may decompose with explosive violence on heating, further purification by distillation is not recommended.
According to the submitters, reductions using as much as 0.3 mole of diethyl isonitrosomalonate were carried out.
4. The checkers used 10% palladium-on-charcoal catalyst obtained from Baker and Company, Inc., 113 Astor Street, Newark, New Jersey.
5. According to the submitters, diethyl aminomalonate may be purified by distillation, b.p. 116–118°/12 mm. or 122–123°/16 mm.; n_D^{16} = 1.4353; d_{14}^{16} = 1.100.
6. Hydrogen chloride is dried by passage through a train of two gas washing bottles containing concentrated sulfuric acid. A 10-mm. tube through which the hydrogen chloride is passed is placed just over the stirring liquid, instead of under the surface, to prevent clogging of the tube by the bulky precipitate which is formed.
The checkers found magnetic stirring satisfactory. More ether may have to be added to prevent the heavy slurry from stopping the stirrer.
7. A medium-porosity sintered-glass funnel was used by the checkers.

3. Discussion

Diethyl isonitrosomalonate has been reduced catalytically, over palladium on charcoal,[3] Raney nickel,[4] and chemically by aluminum amalgam[5] or hydrogen

sulfide.[6]

4. Use of Diethyl Aminomalonate Hydrochloride

Diethyl aminomalonate is a useful intermediate, lending itself to N-acylation;[3,7] the N-acyl derivatives may be alkylated by procedures as established for syntheses via malonic ester.

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

palladium-on-charcoal

palladium on charcoal

sulfuric acid (7664-93-9)

hydrogen chloride (7647-01-0)

ether (60-29-7)

hydrogen (1333-74-0)

sodium bicarbonate (144-55-8)

hydrogen sulfide (7783-06-4)

sodium sulfate (7757-82-6)

aluminum (7429-90-5)

Raney nickel (7440-02-0)

diethyl malonate (105-53-3)

diethyl isonitrosomalonate (6829-41-0)

diethyl aminomalonate (6829-40-9)

Diethyl aminomalonate hydrochloride, Malonic acid, amino-, diethyl ester,

hydrochloride (13433-00-6)

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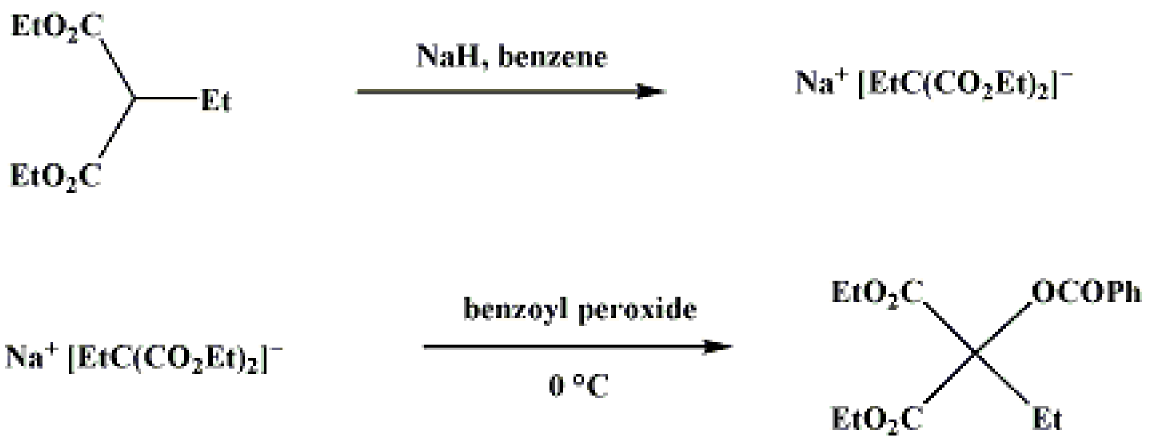
DIETHYL [O-BENZOYL]ETHYLTARTRONATE

[Malonic acid, ethylhydroxy-, diethyl ester, benzoate]



Submitted by E. H. Larsen and S.-O. Lawesson[1].
Checked by M. R. Michalewich and William D. Emmons.

1. Procedure

Caution! This reaction should be carried out behind a safety screen. The solvent removal and product distillation steps should also be carried out behind a screen to minimize trouble if the product is contaminated with undetected peroxides. Benzoyl peroxide should be handled with caution because it is impact-sensitive.

To a 1-l., three-necked, round-bottomed flask is added 7.2 g. (0.15 mole) of a 50% dispersion of sodium hydride in mineral oil (Note 1). The sodium hydride is washed several times by decantation with dry ether and is then covered with 300 ml. of dry benzene (Note 2). The flask is equipped with dropping funnel, stirrer, and reflux condenser. Diethyl ethylmalonate (28.2 g., 0.15 mole) (Note 1) is added dropwise over a 5-minute period, and the reaction mixture is stirred for 2 hours until a clear solution forms. The solution is cooled in an ice bath, and 24.2 g. (0.1 mole) of benzoyl peroxide (Note 3) in 300 ml. of dry benzene is added dropwise over a 1-hour period with continuous stirring. After another 30 minutes, a peroxide test (Note 4) is made to ensure that all the peroxide has reacted.

The porridge-like mixture is then poured into 300 ml. of water and vigorously shaken in a 1-l. separatory funnel. The benzene phase is separated, and the water phase is extracted three times with 100-ml. portions of ether. The combined extracts are washed until neutral and are dried over anhydrous sodium sulfate. The volatile solvents are evaporated at aspirator pressure, and the residue (Note 5) is distilled through a short Vigreux column. After a fore-run of diethyl ethylmalonate 23.3–24.1 g. (75–78%) of diethyl [O-benzoyl]ethyltartronate is obtained, b.p. 132° (0.1 mm.);

$n^{20}D$ 1.4885.

2. Notes

1. The sodium hydride is obtained from Metal Hydrides Inc., Beverly, Massachusetts; the diethyl ethylmalonate from Eastman Organic Chemicals.
2. Reagent grade benzene was dried over calcium hydride prior to use.
3. The benzoyl peroxide is recrystallized from chloroform and methanol at room temperature. The checkers used the 96% purity commercial grade available from the Lucidol Division of Wallace and Tiernan without further purification.
4. A few drops of the reaction mixture are added to a dilute solution of sodium iodide in glacial acetic acid; if a brown ring is not formed, all peroxides have reacted.
5. A peroxide test on the residue is recommended before the distillation is begun.

3. Discussion

The present procedure is essentially that described by one of the submitters.[2]

4. Merits of the Preparation

The reaction described is of considerable general utility for the preparation of benzoyloxy derivatives of β-carbonyl compounds. Thus O-benzoyl tartronates have been prepared, from which routes to diethyl tartronates and tartronic acids have been developed.[2] Ethyl benzoyloxy cyanoacetates have similarly been prepared and are of potential interest in connection with the chemistry of amino acid precursors.[3] Similarly the benzoyloxy group has been introduced into β-keto esters[4,5] and β-diketones.[6] Also a new method for the preparation of acyloins was found.[5] An extension of the method has led to certain types of benzoyloxy γ-keto esters[7] and benzoyloxy δ-ketonitriles.[8] The method has been reviewed.[9]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Ethyl benzoyloxy cyanoacetates

benzoyloxy γ-keto esters

benzoyloxy δ-ketonitriles

acetic acid (64-19-7)

Benzene (71-43-2)

methanol (67-56-1)

ether (60-29-7)

chloroform (67-66-3)

sodium sulfate (7757-82-6)

sodium iodide (7681-82-5)

benzoyl peroxide (94-36-0)

sodium hydride (7646-69-7)

diethyl ethylmalonate (133-13-1)

calcium hydride (7789-78-8)

DIETHYL [O-BENZOYL]ETHYLTARTRONATE

Malonic acid, ethylhydroxy-, diethyl ester, benzoate (6259-78-5)

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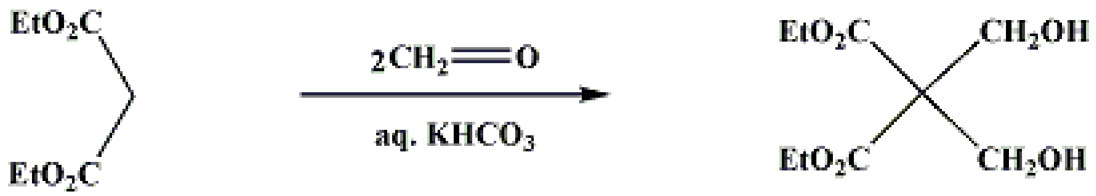
DIETHYL BIS(HYDROXYMETHYL)MALONATE

[Malonic acid, bis(hydroxymethyl)-, diethyl ester]



Submitted by Paul Block, Jr.[1]
Checked by Melvin S. Newman and Reinhardt Stein.

1. Procedure

Formaldehyde solution equivalent to 60 g. of formaldehyde (2 moles) (Note 1) and 8 g. of potassium bicarbonate (small crystals) are placed in an 800-ml. beaker standing in a water bath at 20° in a hood. Mechanical stirring is started and 160 g. (1 mole) of diethyl malonate (Note 2) is added dropwise during about 40–50 min., at such a rate that the temperature of the reaction mixture is held at 25–30°. Stirring is continued for 1 hour. The reaction mixture is transferred to a separatory funnel. A saturated solution of ammonium sulfate (320 ml.) (Note 3) is added and the mixture is extracted with 320 ml. of ether. The ethereal extract, dried for 1 hour with anhydrous sodium sulfate (20 g.), is filtered into a 1-l., three-necked flask through a fluted filter paper. The sodium sulfate and paper are washed with 50 ml. of anhydrous ether. The flask (fitted with a thermometer reaching to the bottom, a condenser set for downward distillation; third neck closed) is placed in a suitable heating bath (Note 4). Boiling chips are introduced and the ether is distilled until the temperature of the liquid has risen to 45–50°. The heating bath is then removed and the distillation assembly is replaced by a glass tube (about 4 mm. I.D.) reaching to the bottom of the flask and closed by a piece of rubber tubing and a screw clamp. An aspirator is now connected to the third neck of the flask. Vacuum is applied and volatile material is removed until the pressure falls to 20–30 mm. The temperature of the contents of the flask is brought to 40° and maintained there until crystallization begins and for an additional 30 minutes (Note 5). Isopropyl ether (500 ml.) (Note 6) is added. The mixture is warmed to 50° and swirled until the product (crystalline and oily) dissolves. The solution is transferred to an Erlenmeyer flask, and cooled in ice water with stirring until a thick suspension of crystals results. The suspension is refrigerated for 1 hour, filtered with suction (rubber dam), and the crystals are dried overnight at room temperature, and then in a vacuum desiccator over sulfuric acid. The yield of colorless crystals, m.p. 48–50°, is 158–166 g. (72–75%). This product may be recrystallized from isopropyl ether (3.5 volumes) with an 85% recovery to yield material with m.p. 50–52°. Melting points of 52–53° and 52° are reported.[2,3]

2. Notes

1. Exactly 3 ml. of formaldehyde solution is assayed by the method of U.S.P. XIII, and the result calculated to grams of formaldehyde per milliliter of solution.
2. The diethyl malonate used boiled over a 2° range.
3. Ammonium sulfate (175 g.) is added to 235 ml. of water, warmed until it is dissolved, and cooled.
4. A heating mantle or liquid bath may be used.
5. The screw clamp may be adjusted so that there will be a spattering on the upper, cool part of the flask, while the pressure is still maintained below 30 mm. Under these conditions, the initiation of crystallization is speeded.
6. A practical grade is adequate, but is should be peroxide-free.

3. Discussion

The only reported method of preparation of diethyl bis(hydroxymethyl)malonate is by the reaction described here.[2,3]

4. Use of Diethyl Bis(hydroxymethyl)malonate

Diethyl bis(hydroxymethyl)malonate is a useful intermediate for preparing substituted malonic esters, acrylic esters, and isobutyric esters.[2,4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 210
- Org. Syn. Coll. Vol. 7, 319
- Org. Syn. Coll. Vol. 8, 265

References and Notes

1. Department of Chemistry, University of Toledo, Toledo, Ohio.
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

ether (60-29-7)

formaldehyde (630-08-0)

sodium sulfate (7757-82-6)

diethyl malonate (105-53-3)

ammonium sulfate (7783-20-2)

isopropyl ether (108-20-3)

potassium bicarbonate (298-14-6)

Diethyl bis(hydroxymethyl)malonate, Malonic acid, bis(hydroxymethyl)-, diethyl ester (20605-01-0)

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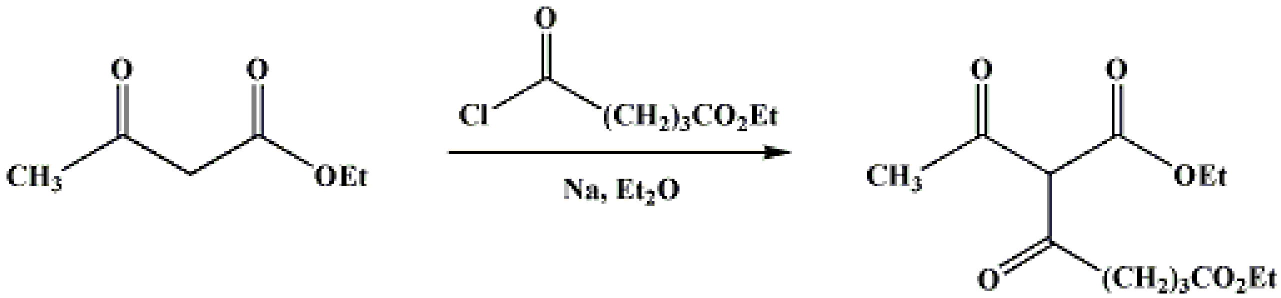
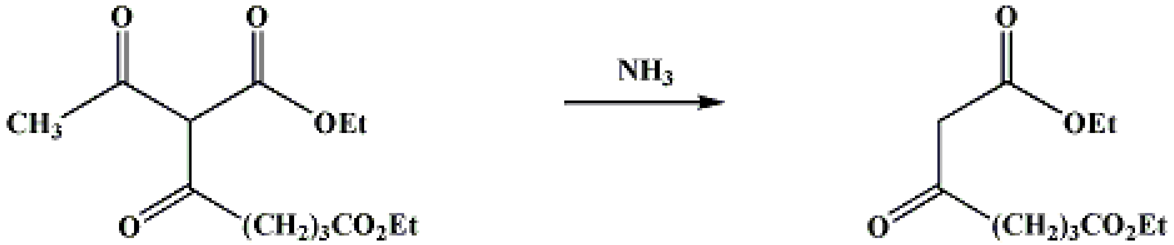
DIETHYL β-KETOPIMELATE

[Pimelic acid, β-oxo-, diethyl ester]





Submitted by Maya Guha and D. Nasipuri[1].
Checked by William G. Dauben and Richard Ellis.

1. Procedure

A. *Diethyl α-acetyl-β-ketopimelate*. In a 2-l. three-necked flask equipped with a mercury-sealed Hershberg stirrer, a dropping funnel, and a reflux condenser protected with a calcium chloride tube are placed 11.5 g. (0.5 g. atom) of finely powdered sodium (Note 1) and 500 ml. of dry ether. The flask is placed in an ice bath, and 65.0 g. (63.5 ml., 0.5 mole) of freshly distilled ethyl acetoacetate in 150 ml. of dry ether is slowly added from the dropping funnel with stirring (approximate time for addition is 30–40 minutes). The mixture is stirred overnight, then it is cooled in an ice bath, and 89.0 g. (0.5 mole) of γ-carbethoxybutyryl chloride (Note 2) in 200 ml. of dry ether is added gradually over the course of 1 hour. The reaction is first stirred overnight at room temperature, then gently refluxed by heating in a water bath for 30 minutes. The mixture is cooled in an ice bath, and a cold solution of 20 ml. of concentrated sulfuric acid in 300 ml. of water is added cautiously with vigorous stirring. The stirring is continued until two clear layers form when the stirring is stopped. The ethereal layer is separated and the aqueous layer extracted once with 100 ml. of ether. The two organic layers are combined, washed once with water, and dried over anhydrous sodium sulfate. After removal of the sodium sulfate by filtration, the solvent is removed by heating the ethereal solution on a water bath held at about 50–60°. The residual light-brown liquid is transferred to a 150 ml. Claisen flask and distilled under reduced pressure. The fraction boiling at 142–147°/0.4 mm. or 158–162°/2.5 mm. is collected (Note 3). The yield is 84–91 g. (61–66%), n_D^{28} 1.4649–1.4655.

B. *Diethyl β-ketopimelate*. In a 250-ml. distillation flask fitted with an inlet tube reaching near

the bottom of the flask and a soda-lime drying tube on the side-arm is placed a solution of 50 g. (0.18 mole) of diethyl α-acetyl-β-ketopimelate in 75 ml. of dry ether. The solution is cooled by placing the flask in an ice-salt bath, and then a slow stream of ammonia gas is passed through the inlet tube. The solution becomes turbid during the first few minutes and soon becomes clear again. The gas stream is continued for 45–50 minutes, and the yellow liquid is allowed to stand at room temperature overnight with due protection from atmospheric moisture. Most of the ether is then removed by passing a stream of dry air through the solution, and the residue is transferred to a separatory funnel with the aid of 50 ml. of ether. The ethereal solution is washed with three 70-ml. portions of cold 3*N* hydrochloric acid, each extraction being shaken vigorously for 10 minutes. The ethereal layer is set aside, and the acid washings are extracted twice with 50-ml. portions of ether. The combined ethereal extracts are washed once with water and dried over anhydrous sodium sulfate. After removal of the sodium sulfate by filtration, the solvent is removed by heating the solution on a water bath. The residue is transferred to a Claisen flask with a short Vigreux column, and the fraction boiling at 130–132°/0.5 mm. or 120–121°/0.2 mm. is collected (Note 4) and (Note 5). The yield is 21–25 g. (50–59%), n_D^{28} 1.4400, $n_D^{31.5}$ 1.4376, $n_D^{36.5}$ 1.4338.

2. Notes

1. Clean pieces of sodium are melted under xylene and powdered by vigorous shaking. When cold, the xylene is decanted and the sodium powder is washed by decantation with a few milliliters of dry ether and then washed into the reaction flask with dry ether.
2. The γ-carbethoxybutyryl chloride (b.p. 100–101°/5–6 mm. or 108–110°/15 mm.) was prepared by the method of Bachmann, Kushner, and Stevenson.[2]
3. The distillate contains mostly C-acyl ester with a little of O-acyl ester. Separation of these two esters by means of a carbonate solution in which only the C-acyl ester is soluble[3,4] is possible. This separation is unnecessary in the present procedure for the O-acyl derivative gives rise to ethyl acetoacetate during decomposition with ammonia. This low-boiling ester is removed during the distillation of diethyl β-ketopimelate.
4. A small fore-run, b.p. 60–80°/5 mm., is collected which gives a positive test with ferric chloride reagent. Presumably this fraction consists mostly of ethyl acetoacetate.
5. The checkers used an 18-in. Vigreux column with a heated jacket and observed a boiling point of 126–128°/2 mm.

3. Discussion

The described method of preparing diethyl β-ketopimelate is a modification of that described by Bouveault[5] and is essentially the same as that reported by Bardhan and Nasipuri.[6] This ester has also been prepared by condensation of γ-carbethoxybutyryl chloride with ethoxymagnesiummalonic ester and cleavage of the resulting acylated malonic ester by β-naphthalenesulfonic acid[7] or by acetic or propionic acids containing a trace of concentrated sulfuric acid.[8]

4. Merits of Preparation

The present method offers a more convenient synthesis with appreciably higher yields of diethyl β-ketopimelate. It is reported to be useful for the preparation of dimethyl β-

ketoadipate[3,9] and diethyl β-ketosuberate.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 359

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Ethoxymagnesiummalonic ester

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ether (60-29-7)

sodium sulfate (7757-82-6)

β-naphthalenesulfonic acid (120-18-3)

sodium (13966-32-0)

ferric chloride (7705-08-0)

xylene (106-42-3)

Ethyl acetoacetate (141-97-9)

Diethyl β-ketopimelate, Pimelic acid, β-oxo-, diethyl ester (40420-22-2)

γ-carbethoxybutyryl chloride (5205-39-0)

Diethyl α-acetyl-β-ketopimelate (61983-62-8)

dimethyl β-ketoadipate

diethyl β-ketosuberate

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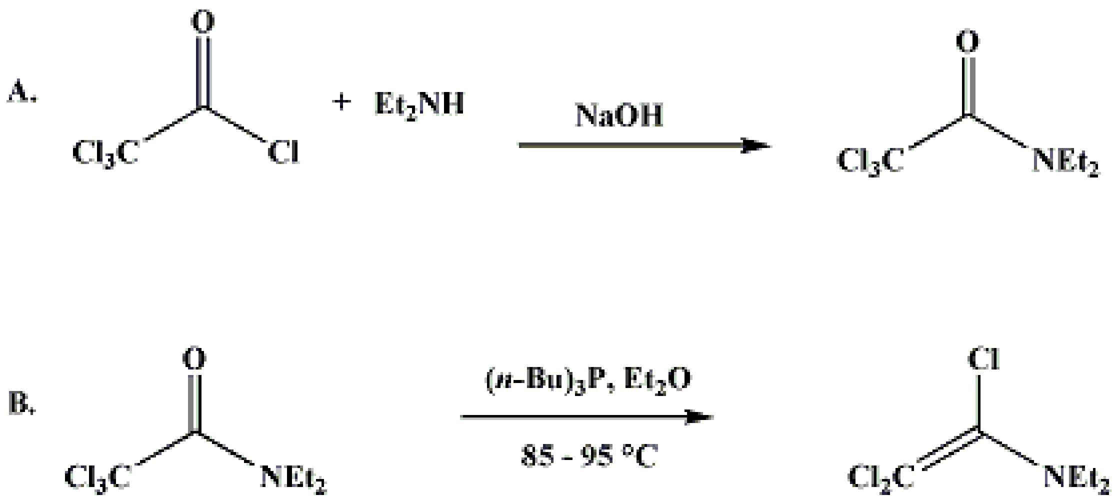
N,N-DIETHYL-1,2,2-TRICHLOROVINYLAMINE

[Vinylamine, 1,2,2-trichloro-N,N-diethyl-]



Submitted by A. J. Speziale and R. C. Freeman[1].
Checked by B. C. McKusick and H. D. Hartzler.

1. Procedure

A. *N,N-Diethyl-2,2,2-trichloroacetamide*. A 1-l. three-necked flask equipped with a stirrer and dropping funnel is charged with 73 g. (1.00 mole) of diethylamine, 500 ml. of ether, and a solution of 40 g. (1.00 mole) of sodium hydroxide in 160 ml. of water. The mixture is stirred and maintained at a temperature of –10° to –15° by a bath of Dry Ice and acetone while 200 g. (1.10 moles) of trichloroacetyl chloride is added in the course of 1 hour. The cooling bath is removed, the temperature is allowed to rise to 10°, and the organic layer is separated. The aqueous layer is extracted with two 50-ml. portions of ether. The ether extracts are combined, washed with 50 ml. of 5% hydrochloric acid, two 50-ml. portions of 5% sodium bicarbonate solution, and 50 ml. of water, and dried over magnesium sulfate. The ether is removed by distillation at atmospheric pressure. The residue is distilled through a short indented Claisen still head at reduced pressure. N,N-Diethyl-2,2,2-trichloroacetamide is collected at 77–79°/1.5 mm.; n_D^{25} 1.4902–1.4912; weight 183–200 g. (84–92%).

B. *N,N-Diethyl-1,2,2-trichlorovinylamine*. The reaction is carried out in a 500-ml. three-necked flask equipped with an efficient mechanical stirrer, a thermometer, a reflux condenser to which a drying tube containing calcium chloride is attached, and a 250-ml. dropping funnel with a pressure-equalizing tube. The flask is charged with 219 g. (2.00 moles) of N,N-diethyl-2,2,2-trichloroacetamide. A gas-inlet tube is attached to the dropping funnel, and dry nitrogen (Note 1) is passed through the apparatus for 5 minutes with stirring. The gas-inlet tube is removed briefly, 202 g. (2.00 moles) of tri-*n*-butylphosphine (Note 2) is placed in the dropping funnel, the gas-

inlet tube is replaced, and nitrogen is passed through the apparatus in a slow stream; the slow flow of nitrogen is continued all during the reaction. The phosphine is added at such a rate that a temperature of 85–90° is reached in 30 minutes (Note 3). The rate of addition is then slowed in order to maintain the temperature within this range. The total addition time is 45–55 minutes.

After all the phosphine has been added, the water bath is replaced by a heating mantle, and the reaction mixture is held at 85–95° for one additional hour and cooled to room temperature. The nitrogen-inlet tube, dropping funnel, and reflux condenser are removed, and the reaction flask is fitted with a 15 × 150-mm. Vigreux column for distillation under reduced pressure. The reaction mixture is then distilled (Note 4). The pot temperature rises from 94° to 150° during the distillation, and the crude N,N-diethyl-1,2,2-trichlorovinylamine, weight 151–164 g., is collected at 73–120°/8–11 mm. Redistillation of the crude vinylamine through a 20 × 400-mm. column packed with glass helices affords 140–150 g. (69–74%) of pure N,N-diethyl-1,2,2-trichlorovinylamine, b.p. 78–79°/18 mm., n_D^{25} 1.4857–1.4867 (Note 5) and (Note 6).

2. Notes

1. Tri-*n*-butylphosphine reacts exothermically with atmospheric oxygen to form tri-*n*-butylphosphine oxide.
2. Tri-*n*-butylphosphine obtainable from Westvaco Mineral Products, 161 East Forty-second St., New York City, can be used without further purification.
3. Because this reaction is very exothermic, the phosphine should be added cautiously.
4. The reaction and the initial distillation should be carried out on the same day.
5. As N,N-diethyl-1,2,2-trichlorovinylamine reacts rapidly with atmospheric moisture, it should be stored under nitrogen, preferably in a refrigerator.
6. If desired, the tri-*n*-butylphosphine oxide can be recovered by continuing the distillation. Crude tri-*n*-butylphosphine oxide distils at 115–118°/1–2 mm. (pot temperature 125–135°). The pure phosphine oxide[2] distils at 94–95°/0.03 mm.; m.p. 64.6–66.6°; yield 135–159 g. (62–73%). *Caution! The reaction mixture should not be distilled to dryness.* There should be a residue of about 40–50 ml.

3. Discussion

N,N-Diethyl-1,2,2-trichlorovinylamine has been prepared by the action of trimethyl, triethyl, or triisopropyl phosphite or triphenylphosphine on N,N-diethyl-2,2,2-trichloroacetamide.[3] These methods require a reaction temperature of 150–160° and several distillations in order to obtain a pure product. Consequently, the yields of the vinylamine are lower than by the present procedure.[3]

4. Merits of Procedure

The procedure has also been applied to the synthesis of N,N-dimethyl-1,2,2-

trichlorovinylamine from trichloroacetamide (60% yield),[3] and it probably is a general means of preparing N,N-dialkyl-1,2,2-trichlorovinylamines. The reaction is an unusual one involving reduction of the amide and halogen migration and is of theoretical interest.

N,N-Diethyl-1,2,2-trichlorovinylamine undergoes certain reactions which involve the 1-chlorine atom. Acids and alcohols are converted to their respective chlorides. Aniline converts the vinylamine to N,N-diethyl-N'-phenyl-2,2-dichloroacetamidine.[3]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

ether (60-29-7)

aniline (62-53-3)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

oxygen (7782-44-7)

nitrogen (7727-37-9)

diethylamine (109-89-7)

magnesium sulfate (7487-88-9)

trichloroacetamide (594-65-0)

phosphine (7723-14-0)

triisopropyl phosphite (116-17-6)

Triethyl phosphite (122-52-1)

triphenylphosphine (603-35-0)

phosphine oxide

N,N-Diethyl-1,2,2-trichlorovinylamine, Vinylamine, 1,2,2-trichloro-N,N-diethyl- (686-10-2)

trichloroacetyl chloride (76-02-8)

N,N-Diethyl-2,2,2-trichloroacetamide

vinylamine (593-67-9)

N,N-dimethyl-1,2,2-trichlorovinylamine

trimethyl phosphite (121-45-9)

tri-n-butylphosphine (998-40-3)

tri-n-butylphosphine oxide (814-29-9)

N,N-diethyl-N'-phenyl-2,2-dichloroacetamidine

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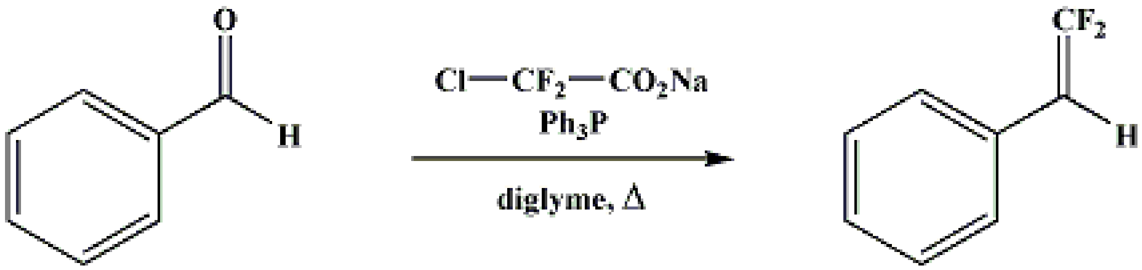
Organic Syntheses, CV 5, 390

β,β-DIFLUOROSTYRENE

[1,1-Difluoro-2-phenylethylene)]



Submitted by Samuel A. Fuqua[1], Warren G. Duncan[2], and Robert M. Silverstein[2].
Checked by John J. Miller, Herbert Aschkenasy, and William D. Emmons.

1. Procedure

In a 250-ml. two-necked flask fitted with a reflux condenser, a drying tube, a magnetic stirrer, and a heated dropping funnel with a pressure-equalizing side arm (Note 1) are placed 23.1 g. (0.088 mole) of triphenylphosphine, 8.5 g. (0.081 mole) of benzaldehyde, and 10 ml. of anhydrous 2,2'-dimethoxydiethyl ether (diglyme) (Note 2). A solution of 18.3 g. (0.12 mole) of dry sodium chlorodifluoroacetate (Note 3) is prepared by stirring the finely divided salt in 50 ml. of anhydrous diglyme at 70° for about 5 minutes. This warm solution is placed in the dropping funnel which is heated to 60°. The system is purged with dry nitrogen. The solution in the flask is stirred and heated in an oil bath held at 160°, while the contents of the dropping funnel are added dropwise over a period of 1.5–2 hours (Note 4). The diglyme and product are flash-distilled at 1 mm and a bath temperature of 100° into a receiver cooled with dry ice. The distillate is fractionated through a spinning-band column (18 in. × 6 mm. I.D.); the yield of product collected at a head temperature of 52–54° (40 mm.) is 7.6–8.9 g. (67–79%) (Note 5), n^{20}D 1.4939 (Note 6).

2. Notes

1. All glassware is oven-dried. The dropping funnel is wrapped with heating tape, and a thermometer is inserted between the funnel and the tape.
2. Triphenylphosphine is available from M and T Chemicals, Inc. Benzaldehyde is distilled immediately before use. Diglyme is refluxed for 4 hours over calcium hydride and distilled under reduced pressure.
3. Sodium chlorodifluoroacetate is prepared from chlorodifluoroacetic acid (K & K Laboratories) as follows: To a cooled, stirred solution of 60.7 g. (1.52 moles) of sodium hydroxide in 700 ml. of methanol is slowly added a solution of 198 g. (1.52 moles) of chlorodifluoroacetic acid in 300 ml. of methanol, the

temperature being kept below 40°. The methanol is removed under reduced pressure at 40°. The salt, which is pulverized and dried overnight at room temperature at 1 mm., is obtained in essentially quantitative yield. The salt is again dried in the same way immediately before use.

4. During the development of this procedure, evolution of carbon dioxide was monitored with a wet-test meter. At the bath temperature given (160°), sodium chlorodifluoroacetate eliminates carbon dioxide as rapidly as it is added over a period of 1.5–2 hours. If the bath temperature is allowed to drop, there is danger of buildup of sodium chlorodifluoroacetate followed by violent exothermic decomposition. Addition of the sodium chlorodifluoroacetate solution should not be started until the flask contents are equilibrated with the oil bath.

It is quite feasible to run the reaction at a bath temperature of 90–95° by adding all reagents to the flask initially; a quantitative evolution of carbon dioxide occurs over a period of about 18 hours. The reaction can also be carried out in refluxing 1,2-dimethoxyethane (Arapahoe Chemicals, Inc.) over a period of about 50 hours (yield 40–55%), or in triethylene glycol dimethyl ether (Ansul Chemical Company) at a bath temperature of 160° over a period of 2 hours (yield 64%).

5. The distilled product gave a single symmetrical peak on gas chromatography under the following conditions: 25% LAC on Chromosorb W, 6 ft. × in., 110°, helium flow 41 ml./min., elution time 14.2 minutes. The checkers used LB 5-50 on Fluoropak 80 and obtained a single peak. Gas chromatography of the flash distillate before fractionation showed an actual yield of 10.6 g. (95%). The product fumes in moist air, and some etching of glass containers was noted. This is presumably due to elimination of hydrogen fluoride. Samples in open glass containers deposit a small amount of solid on standing; the solid is probably a product of the glass-hydrogen fluoride reaction.

6. Care must be taken to clean and dry the refractometer prisms before and after use in order to prevent etching of the prisms.

3. Discussion

The literature preparation[3] of β,β-difluorostyrene consists of seven steps from sodium difluoroacetate, the last step involving pyrolysis at 600°; the overall yield was 5%.

4. Merits of the Preparation

The method described is a general synthesis for compounds containing the $-CH=CF_2$ moiety. There is no other simple general route to such compounds. Aromatic, aliphatic, and heterocyclic aldehydes to which this procedure has been applied are: *p*-fluorobenzaldehyde (65%), *p*-methoxybenzaldehyde (60%), heptanal (43–51%), and furfural (75%).[4] The method is also applicable to ketones[5] and to α-perfluoroketones.[6] Substitution of lithium chlorodifluoroacetate for the sodium salt has been advocated.[7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 949

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

2,2'-dimethoxydiethyl ether (diglyme)

methanol (67-56-1)

sodium hydroxide (1310-73-2)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

hydrogen fluoride (7664-39-3)

benzaldehyde (100-52-7)

Furfural (98-01-1)

Heptanal (111-71-7)

calcium hydride (7789-78-8)

1,2-dimethoxyethane (110-71-4)

helium (7440-59-7)

triphenylphosphine (603-35-0)

triethylene glycol dimethyl ether (112-49-2)

1,1-Difluoro-2-phenylethylene, β,β-Difluorostyrene (405-42-5)

sodium chlorodifluoroacetate (1895-39-2)

chlorodifluoroacetic acid (76-04-0)

sodium difluoroacetate

lithium chlorodifluoroacetate

p-methoxybenzaldehyde (123-11-5)

p-fluorobenzaldehyde (459-57-4)

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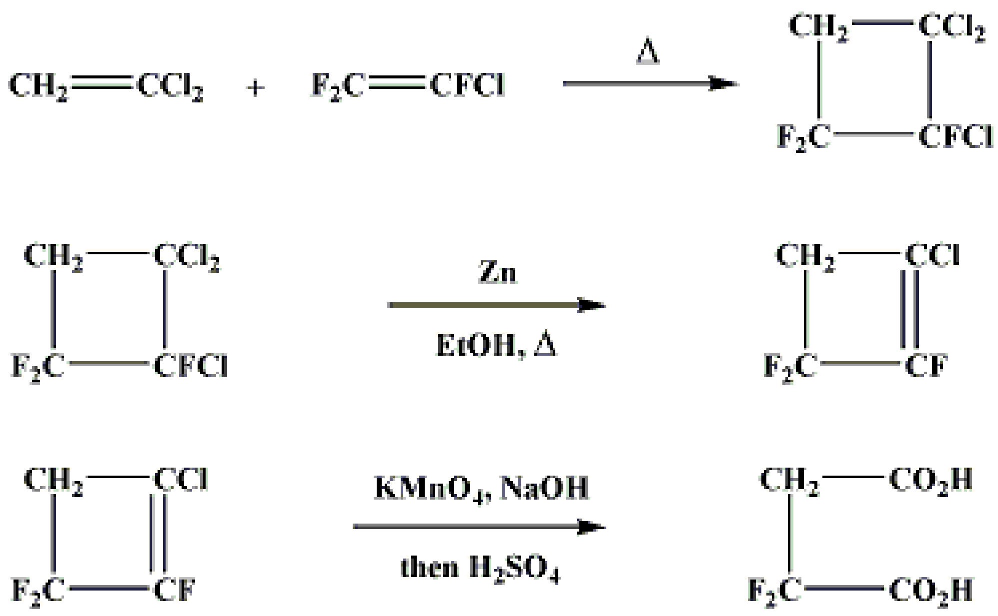
2,2-DIFLUOROSUCCINIC ACID

[Succinic acid, 2,2-difluoro-]



Submitted by M. S. Raasch and J. E. Castle[1].
Checked by R. H. Uloth and R. R. Covington[2].

1. Procedure

Caution! In the absence of toxicity data, the fluorine compounds should all be treated as though they were toxic materials.

A. *1,1,2-Trichloro-2,3,3-trifluorocyclobutane*. In a 1-l. rocker bomb are placed 350 g. (3.6 moles) of 1,1-dichloroethylene (Note 1) are 1 g. of hydroquinone. The bomb is cooled in a mixture of Dry Ice and acetone and evacuated. The vacuum is released with nitrogen and the bomb is again evacuated. The bomb is then charged with 300 g. (2.6 moles) of chlorotrifluoroethylene (Note 1) from a cylinder. The bomb is heated at 180° for 7 hours behind a barricade (Note 2) and is then cooled, vented, and unloaded. The solid polymer (about 45 g.) is removed by filtration and is rinsed with 50 ml. of ether. The combined filtrate and rinse are concentrated and then distilled through a 30-cm. packed column to give 242–262 g. (44–48%) of 1,1,2-trichloro-2,3,3-trifluorocyclobutane, b.p. 120–121°, n_D^{25} 1.4139–1.4141.

B. *1-Chloro-2,3,3-trifluorocyclobutene*. A 1-l. three-necked flask fitted with mercury-sealed stirrer, dropping funnel, reflux condenser, and heater is charged with 150 ml. of absolute ethyl alcohol and 76 g. (1 mole) of 95% zinc dust. The alcohol is heated to boiling, and 235 g. (1.1 moles) of 1,1,2-trichloro-2,3,3-trifluorocyclobutane is added

through the dropping funnel during 40 minutes. After the reaction has started, external heating is decreased. The mixture is heated under reflux for 1 hour after the end of the addition. It is then cooled below reflux temperature, 15 g. (0.2 mole) more of zinc powder is added, and the heating under reflux is continued for 30 minutes more. The mixture is again cooled below reflux temperature, and a simple still head arranged for downward distillation is attached in place of the condenser. Distillation is carried out until 165 ml. of distillate has been collected. The still head reaches a temperature of about 90°. The distillate is washed with two 250-ml. portions of water and dried by shaking gently for 5 minutes with 5 g. of 8-mesh calcium chloride. The product is decanted from the calcium chloride and distilled through a 30-cm. packed column to give 107–113 g. (68–72%) of 1-chloro-2,3,3-trifluorocyclobutene, b.p. 52–53°, n_D^{25} 1.3614–1.3619.

C. *2,2-Difluorosuccinic acid*. In a 3-l. three-necked flask fitted with stirrer, thermometer, and dropping funnel, 80 g. (2 moles) of sodium hydroxide is dissolved in 2 l. of water and 158 g. (1 mole) of potassium permanganate is then added. The mixture is cooled to 15–20° with an ice-salt bath, and 107 g. (0.75 mole) of 1-chloro-2,3,3-trifluorocyclobutene is added through the dropping funnel during 1 hour while the permanganate solution is stirred and maintained at 15–20°. After the solution has been stirred for 2 hours more at this temperature, the manganese dioxide is removed by filtration and rinsed with three 300-ml. portions of water. The combined filtrate and washings are concentrated to a volume of 500 ml. by evaporation on a steam bath (Note 3). The solution is then cooled and 85 ml. of concentrated sulfuric acid is added slowly with stirring. The cold solution is extracted with four 250-ml. portions of ether (Note 4). Drying of the ether extract is accomplished by agitating it for 5 minutes with 30 g. of anhydrous magnesium sulfate. When the drying agent has been removed by filtration and rinsed with ether, the filtrate and the ether washings are combined and concentrated to give 91–97 g. (79–84%) of 2,2-difluorosuccinic acid. The acid is recrystallized by dissolving it in hot nitromethane (1.25 ml. per g.), filtering the solution through a layer of filter aid if necessary, and cooling the solution to 3°. The crystals are collected by suction filtration and rinsed with 30 ml. of cold nitromethane. After drying, this gives 85–92 g. (74–80%) of 2,2-difluorosuccinic acid, m.p. 144–146°.

2. Notes

1. The checkers employed 1,1-dichloroethylene supplied by Dow Chemical Co., Midland, Michigan, and chlorotrifluoroethylene supplied by the Matheson Company, Joliet, Illinois.
2. This reaction has been carried out many times without incident in a 1-l. stainless-steel rocker bomb. A pressure gauge was attached during two runs and recorded a maximum of 750 p.s.i. However, an attempt in another laboratory to scale up the reaction using a 3-l. autoclave resulted in a bulged vessel. Uncontrolled polymerization may be hazardous.
3. Evaporation may be carried out in porcelain or glass dishes, but the fluoride

present will cause some etching.
4. The amounts removed in the third and fourth extractions are about 5.4 g. and 1.5 g., respectively.

3. Discussion

The procedure described is the method of Raasch[3,4] and is the only one published so far.

4. Merits of Preparation

The first step illustrates a very general reaction, the addition of fluoroalkenes to alkenes to give fluorocyclobutanes.[5] The subsequent steps illustrate the synthetic possibilities of fluorocyclobutanes as intermediates. 1,1,2-Trichloro-2,3,3-trifluorocyclobutane may also be converted into chlorotrifluorosuccinic acid, trifluorosuccinic acid, fluoromaleic acid, fluorofumaric acid, difluoromaleic acid, and difluorofumaric acid.[4,6]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethyl alcohol (64-17-5)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

ether (60-29-7)

sodium hydroxide (1310-73-2)

hydroquinone (123-31-9)

potassium permanganate (7722-64-7)

nitrogen (7727-37-9)

acetone (67-64-1)

zinc, zinc powder (7440-66-6)

manganese dioxide (1313-13-9)

Nitromethane (75-52-5)

magnesium sulfate (7487-88-9)

Chlorotrifluoroethylene (79-38-9)

Fluorine (7782-41-4)

fluoride (16984-48-8)

1,1-dichloroethylene (75-35-4)

2,2-Difluorosuccinic acid, Succinic acid, 2,2-difluoro- (665-31-6)

1,1,2-Trichloro-2,3,3-trifluorocyclobutane (697-17-6)

1-Chloro-2,3,3-trifluorocyclobutene (694-62-2)

difluorofumaric acid

chlorotrifluorosuccinic acid

trifluorosuccinic acid

fluoromaleic acid

fluorofumaric acid

difluoromaleic acid

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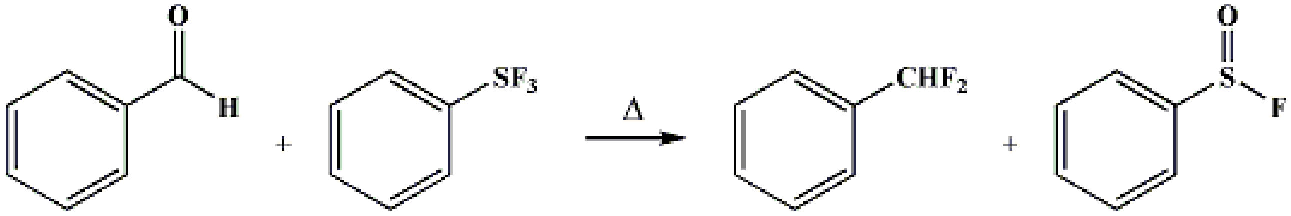
Organic Syntheses, CV 5, 396

α,α-DIFLUOROTOLUENE AND BENZENESULFINYL FLUORIDE

[Toluene, α,α-difluoro-]



Submitted by William A. Sheppard[1]
Checked by E. S. Glazer and John D. Roberts.

1. Procedure

Caution! Phenylsulfur trifluoride is toxic, and this reaction should be carried out in a good hood. The reagent should not be allowed to come in contact with the skin.

Phenylsulfur trifluoride[2] (16.6 g., 0.10 mole) is placed in a two-necked 50-ml. flask equipped with a dropping funnel and connected to a dry distillation column (Note 1). The flask is heated to 50–70° in an oil bath, and 10.6 g. (0.10 mole) of benzaldehyde is added in small portions over 30 minutes. A mild exothermic reaction occurs. After the addition is completed, the reaction flask is heated to 100° with an oil bath, and the pressure on the column is reduced until α,α-difluorotoluene distills. The major portion of product distills at 68° (80 mm.), but a small final cut, b.p. 45° (15 mm.), is obtained. The yield of α,α-difluorotoluene is 9.2–10.2 g. (71–80%) (Note 2). The pressure is reduced and the distillation is continued. An intermediate cut of 1–2 g., b.p. 45° (15 mm.) to 60° (2.5 mm.), is discarded, and benzenesulfinyl fluoride, 11.7–13.2 g. (81–91%), b.p. 60° (2.5 mm.), is collected. Since the benzenesulfinyl fluoride slowly attacks glass and may be unstable to storage at room temperature, it is recommended that this product be stored at –80°.

2. Notes

1. A 45-cm. spinning band column was employed by the submitter, but any distillation column with a low holdup may be used. Since the products have widely different boiling points, careful fractionation during distillation is not needed. Because the phenylsulfur trifluoride and benzenesulfinyl fluoride slowly attack glass, all equipment should be rinsed with water and acetone *immediately* after use to minimize etching.
2. The product attacks glass slowly on standing, and a moderate increase in pressure takes place. The product can be stored for a period of several days in a polyethylene bottle, but it is best to prepare the material shortly before use. If prolonged storage is required, a stainless steel cylinder or a bottle fabricated from Teflon® polytetrafluoroethylene resin is suggested.

3. Discussion

α,α-Difluorotoluene has been prepared by the reaction of α,α-dichlorotoluene with antimony (III) fluoride,[3] by the hydrogenation of α-chloro-α,α-difluorotoluene,[4] by the action of sulfur

tetrafluoride on benzaldehyde,[5] and by the present method.[6,7]

4. Merits of the Preparation

Sulfur tetrafluoride provides an inexpensive method for selectively converting a carbonyl to a difluoromethyl group. However, the reactions involving sulfur tetrafluoride, in general, require pressure equipment constructed of fluorine-resistant material such as "Hastelloy-C" bombs.[8] Phenylsulfur trifluoride may be used to advantage for the same reaction, where small amounts are involved, since the reaction may be run at atmospheric pressure in glass, polyethylene, or metal containers.

Although the sulfur trifluoride compounds are generally useful as selective agents for conversion of carbonyl and carboxyl groups to difluoromethylene and trifluoromethyl groups, variations in reaction conditions are often necessary.[7] Thus the reaction of aromatic ketones requires heating at 150°. Since the reaction with aliphatic aldehydes and ketones is exothermic, it is advantageous to run it in a solvent such as methylene chloride or acetonitrile containing a small amount of sodium fluoride powder (with ketones an induction period of several hours may be observed). Reactions with carboxylic acids should be carried out in a container resistant to hydrogen fluoride, and they require heating at 120° to 150°.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 959

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

polytetrafluoroethylene

acetonitrile (75-05-8)

hydrogen fluoride (7664-39-3)

benzaldehyde (100-52-7)

acetone (67-64-1)

methylene chloride (75-09-2)

α,α-dichlorotoluene (98-87-3)

sodium fluoride (7681-49-4)

BENZENESULFINYL FLUORIDE

Phenylsulfur trifluoride (672-36-6)

antimony (III) fluoride

sulfur tetrafluoride (7783-60-0)

sulfur trifluoride

α,α-Difluorotoluene, Toluene, α,α-difluoro- (455-31-2)

α-chloro-α,α-difluorotoluene

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9,10-DIHYDROANTHRACENE

[Anthracene, 9,10-dihydro-]

Submitted by K. C. Bass[1]
Checked by Virgil Boekelheide and S. T. Young.

1. Procedure

In a 2-l., three-necked, round-bottomed flask fitted with a rubber-tube sealed mechanical glass stirrer, a reflux condenser (Note 1), and a thermometer reaching to the bottom of the flask are placed 50 g. (0.28 mole) of anthracene (Note 2) and 750 ml. of commerical absolute ethanol. The suspension obtained is stirred and heated (Note 3) to 50°, and 75 g. (3.25 g. atom) of freshly cut sodium is added in quantities of about 10 g. each to the stirred mixture over a period of 5 minutes. The reaction mixture boils vigorously (Note 4) and stirring is continued for 15 minutes longer. The reaction mixture is then cooled and carefully diluted with 1 l. of water. The white-yellow solid which separates is a mixture of 9,10-dihydroanthracene and anthracene, and it is collected on a Büchner funnel, washed with 400 ml. of water, and dried in air.

The dry white-yellow solid is suspended in 500 ml. of commercial absolute ethanol in a 1-l., three-necked, round-bottomed flask fitted with a rubber-tube sealed mechanical glass stirrer, a reflux condenser (Note 1), and a thermometer reaching to the bottom of the flask. The suspension is stirred and heated (Note 3) to 50°, and 50 g. (2.17 g. atom) of freshly cut sodium is added in quantities of about 10 g. each to the stirred mixture over a period of 5 minutes. The reaction mixture boils vigorously (Note 4), and stirring is continued for an additional 15 minutes. The reaction mixture is then cooled and carefully diluted with 750 ml. of water. The white solid which separates is 9,10-dihydroanthracene, and it is collected on a Büchner funnel, washed with 300 ml. of water, and dried in air. It is recrystallized from ethanol (about 250–300 ml. of solvent is required), and the crystals are collected on a Büchner funnel, washed with 20 ml. of cold ethanol, and dried in air. The yield of dry 9,10-dihydroanthracene in the form of broad, colorless needles, m.p. 108–109°, is 38–40 g. (75–79%) (Note 5).

2. Notes

1. An efficient 12-in., double-surface, all-glass condenser should be used with an outlet tube carrying the evolved hydrogen into a good hood vent.

2. A purified grade of anthracene (blue fluorescence, m.p. 216°) should be used.
3. An electric heating mantle should be used. No free flames should be present anywhere near the reaction flask.
4. The reaction may be controlled by removing the heat source or slowing down the rate of stirring or both.
5. The 9,10-dihydroanthracene may be purified further by steam distillation from an aqueous suspension followed by recrystallization of the dried product from ethanol.

3. Discussion

The procedure described is adapted from the preparation outlined by Wieland.[2]

4. Merits of Preparation

9,10-Dihydroanthracene has been used as one of the hydrogen transfer reagents in a series of homolytic hydrogen transfer reactions by Braude, Jackman, and Linstead[3] and as a hydrogen donor for the hydrogenation of thiyl radicals to form thiols.[4]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

hydrogen (1333-74-0)

sodium (13966-32-0)

anthracene (120-12-7)

9,10-Dihydroanthracene, Anthracene, 9,10-dihydro- (613-31-0)

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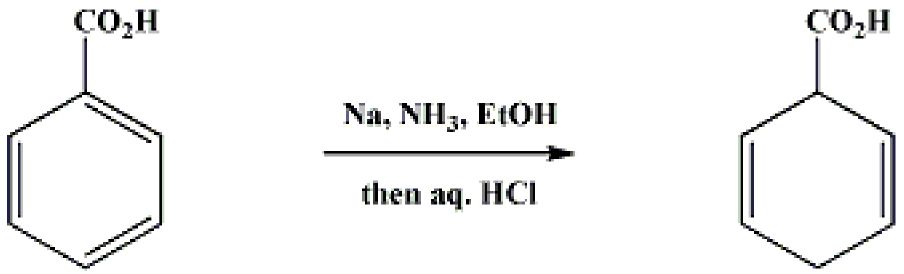
1,4-DIHYDROBENZOIC ACID

[2,5-Cyclohexadiene-1-carboxylic acid]



Submitted by M. E. Kuehne and B. F. Lambert[1].
Checked by Louise Kuda and V. Boekelheide.

1. Procedure

Ten grams (0.082 mole) of benzoic acid is added to 100 ml. of anhydrous ethanol in a 2-l. three-necked flask equipped with a mechanical stirrer and with loose cotton plugs in the side necks. After the benzoic acid has dissolved, 600 ml. of liquid ammonia (Note 1) is added to the stirred solution. Then 6.2 g. (0.27 g. atom) of sodium is added in small pieces. When about one-third of the sodium has been added, the white sodium salt of the acid precipitates, and there is strong foaming of the reaction mixture. After all the sodium has been consumed, as evidenced by the disappearance of the blue color, 14.6 g. (0.27 mole) of ammonium chloride is added cautiously. The mixture is stirred for an additional hour and then allowed to stand until the ammonia has evaporated.

The residue is dissolved in 300 ml. of water. The solution is poured onto 200 g. of ice and acidified to a pH of about 4 by addition of 75 ml. of 10% hydrochloric acid. The resulting mixture is extracted with four 100-ml. portions of peroxide-free ether, and the combined extracts are washed with 50 ml. of a saturated aqueous solution of sodium chloride and dried over 2 g. of anhydrous magnesium sulfate (Note 2). The ether solution is separated from the drying agent and concentrated at room temperature under reduced pressure. The residual oil is distilled from a 25-ml. Claisen flask with an indented neck. 1,4-Dihydrobenzoic acid is obtained as a colorless oil; weight 9.0–9.7 g. (89–95%); b.p. 80–98°/0.01 mm.; n_D^{24} 1.5011. This material is sufficiently pure for most purposes. However, by a careful redistillation, a small fore-run (b.p. 80–90°/0.01 mm.; n_D^{24} 1.5000) can be separated, and the remainder of the material (b.p. 91–97°/0.01 mm.; n_D^{24} 1.5019) solidifies on cooling; m.p. 15–17° (Note 3). It is stored under nitrogen in a closed vessel (Note 4).

2. Notes

1. Arrangements for cooling or condensing the ammonia can be made, but are not necessary. Most simply, the liquid ammonia can be passed directly from a cylinder into the reaction vessel through heavy rubber tubing.
2. 1,4-Dihydrobenzoic acid has a very penetrating, repulsive odor, and care should be taken to avoid contamination of hands or clothing.
3. Samples of the 1,4-dihydrobenzoic acid, after both the first and the second distillations, are transparent in the ultraviolet region between 220 m• and 300 m•, indicating the absence of benzoic acid or conjugated dihydrobenzoic acids. The refractive index cited in Reference [2] is in error.
4. In the presence of air, 1,4-dihydrobenzoic acid slowly gives benzoic acid and hydrogen peroxide.[3]

3. Discussion

Apparently, 1,4-dihydrobenzoic acid has been prepared only by the Birch reduction of benzoic acid, as illustrated by the present procedure.[3,2]

4. Merits of the Preparation

This procedure is illustrative of the general method of reduction of aromatic compounds by alkali metals in liquid ammonia known as the Birch reduction. The theoretical and preparative aspects of the Birch reduction have been discussed in excellent reviews,[4,5,6] and there is another example of a Birch reduction in *Organic Syntheses.*[7] Of particular interest in the present procedure is the effect of having a group that forms a stable anion with the alkali metal. For both simple aromatic acids and amides, a Birch reduction gives the corresponding 1,4-dihydro derivative. The same is true when *o*-alkyl or *o*-methoxyl groups are present. However, with *p*-alkyl or *m*-methoxyl substituents, the corresponding tetrahydro derivatives are formed. *p*-Methoxyl or *p*-acetamino groups, which can form stable anionic fragments, are lost during such reductions.

The following examples may be cited to illustrate these generalizations. *p*-Toluic acid under conditions of the Birch reduction essentially as given in this procedure yields mainly 1,2,3,4-tetrahydro-*p*-toluic acid (*cis* and *trans*) plus minor amounts of 1,4-dihydro-*p*-toluic acid (*cis* and *trans*).[2] *o*-Toluic acid gives 1,4-dihydro-*o*-toluic acid in 73% yield;[8] *m*-methoxybenzoic acid gives 1,4,5,6-tetrahydro-3-methoxybenzoic acid in 32% yield;[9] *o*-methoxybenzoic acid gives crude 1,4-dihydro-2-methoxybenzoic acid in 80% yield;[10] 3,4,5-trimethoxybenzoic acid gives 1,4-dihydro-3,5-dimethoxybenzoic acid in 87% yield;[2] 4-acetaminobenzoic acid gives 1,4-dihydrobenzoic acid in 75% yield;[2] benzamide gives 1,4-dihydrobenzamide in 69% yield;[2] *m*-methoxybenzamide gives 1,4-dihydro-3-methoxybenzamide in 30% yield;[2] 3,4,5-trimethoxybenzamide

gives 1,4-dihydro-3,5-dimethoxybenzamide in 73% yield;[2] and 3,5-dimethoxybenzamide gives 1,4-dihydro-3,5-dimethoxybenzamide in 59% yield.[2] Thus the present example of the Birch reduction illustrates a useful and general synthetic method for preparing dihydro aromatic derivatives.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ammonium chloride (12125-02-9)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

Benzoic acid (65-85-0)

benzamide (55-21-0)

sodium (13966-32-0)

hydrogen peroxide (7722-84-1)

3,4,5-trimethoxybenzoic acid (118-41-2)

acetamino

magnesium sulfate (7487-88-9)

methoxyl (2143-68-2)

p-Toluic acid (99-94-5)

1,4-Dihydrobenzoic acid, 2,5-Cyclohexadiene-1-carboxylic acid (4794-04-1)

1,4,5,6-tetrahydro-3-methoxybenzoic acid

1,4-dihydro-2-methoxybenzoic acid

1,4-dihydro-3,5-dimethoxybenzoic acid

4-acetaminobenzoic acid (556-08-1)

1,4-dihydrobenzamide

1,4-dihydro-3-methoxybenzamide

3,4,5-trimethoxybenzamide (3086-62-2)

1,4-dihydro-3,5-dimethoxybenzamide

3,5-dimethoxybenzamide (17213-58-0)

o-Toluic acid (118-90-1)

o-methoxybenzoic acid (579-75-9)

m-methoxybenzoic acid (586-38-9)

1,2,3,4-tetrahydro-p-toluic acid

1,4-dihydro-p-toluic acid

1,4-dihydro-o-toluic acid

m-methoxybenzamide (5813-86-5)

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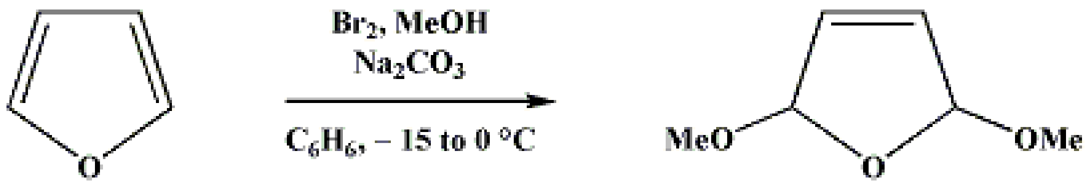
2,5-DIHYDRO-2,5-DIMETHOXYFURAN

[Furan, 2,5-dihydro-2,5-dimethoxy-]



Submitted by D. M. Burness[1]
Checked by Alan E. Black and Henry E. Baumgarten.

1. Procedure

In a 3-l., three-necked flask equipped with a stirrer, thermometer, drying tube filled with Drierite, and a dropping funnel are placed 500 ml. of methanol, 500 ml. of benzene, 380 g. of anhydrous sodium carbonate, and 155 ml. (2.15 moles) of distilled furan (Note 1). The slurry is cooled to < –5° with a dry ice-acetone bath (maintained at –10 to –15° during the addition), and an ice-cold solution of 106 ml. (2.0 moles) of bromine in 1.0 l. of methanol (Note 2) is added dropwise or at such a rate as to maintain a reaction temperature of 0 to –5°. This requires about one hour; the mixture is stirred for an additional 2 hours at < 0° and filtered. The solids collected are washed in the funnel with two 100-ml. portions of benzene. The filtrate is stirred for 30 minutes with 100 g. of anhydrous magnesium sulfate and refiltered. The solvent is removed at reduced pressure (Note 3) to a volume of about 300 ml. Filtration and washing with benzene is repeated (Note 4), the filtrate is stirred for 15–20 minutes with anhydrous potassium carbonate, filtered, and distilled through a short packed column to give 195–205 g. (75–79%) of a clear oil, b.p. 80–82° (50 mm.), n_D^{25} 1.4333 (Note 5) and (Note 6).

2. Notes

1. The furan was distilled from anhydrous potassium carbonate. Use of undistilled furan gives a lower yield (8–10%).
2. The methanol is cooled to about 0° before adding the bromine, and the solution is kept cold during the addition.
3. An aspirator, water bath, and short packed column are used, and distillation is continued until the temperature of the distillate begins to rise about 30°. Good stirring is needed here to prevent bumping and local superheating. The pot temperature never exceeds 25–30°.
4. If an additional 500 ml. of methanol is used in lieu of the recommended 500 ml. of benzene, a small, heavier second phase, consisting mostly of methanol, water, and salts, may separate at this point. This is removed before drying the

filtrate. Later, in the early stages of distillation of the product, if drying has not been thorough enough, water may appear in the distillate. This necessitates further drying, preferably by azeotroping with benzene.

The checkers observed a separation into two layers in some runs even in the absence of added methanol. The layers were filtered together and any solids in the funnel were washed with two 100-ml. portions of benzene. The combined filtrates were dried with a second 100 g. of anhydrous magnesium carbonate.

5. The product from this procedure is yellow, due to maleic dialdehyde, and occasionally gives a positive Beilstein test for bromine, although its purity is better than 99.5% by glpc. A colorless product is reported[2] to be obtained by treatment with sodium methoxide before the final distillation. Activated alumina treatment of the distillate is also effective.

6. If the product is not used promptly a peroxidation inhibitor should be used. *t*-Butyl catechol (0.01%) is recommended.[2]

3. Discussion

Numerous 2,5-dialkoxy-2,5-dihydrofurans have been prepared by electrolytic oxidation of furan and substituted furans in alcoholic ammonium bromide[3,4,5] or by bromine[6,7] or chlorine[8] oxidation in the appropriate alcohol. The present method is a modification of the halogen oxidation procedures cited. It is more convenient and gives better yields (5%) than with chlorine, and halogen-containing byproducts are eliminated in the distillation.

The 2,5-dialkoxy-2,5-dihydrofurans are cyclic acetals of unsaturated dicarbonyl compounds and as such serve as sources thereof. They are also valuable intermediates in the synthesis of numerous types of heterocyclic compounds including those of the tropinone series.[3]

Hydrogenation of the described product to tetrahydro-2,5-dimethoxyfuran is best accomplished with Raney nickel catalyst at 80–100° and 1700–2000 p.s.i. in 45–60 minutes.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 716

9

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alumina

potassium carbonate (584-08-7)

Benzene (71-43-2)

methanol (67-56-1)

ammonium bromide (12124-97-9)

sodium carbonate (497-19-8)

bromine (7726-95-6)

Raney nickel (7440-02-0)

sodium methoxide (124-41-4)

chlorine (7782-50-5)

Furan (110-00-9)

magnesium sulfate (7487-88-9)

2,5-Dihydro-2,5-dimethoxyfuran, Furan, 2,5-dihydro-2,5-dimethoxy- (332-77-4)

magnesium carbonate

maleic dialdehyde

tropinone (532-24-1)

tetrahydro-2,5-dimethoxyfuran (696-59-3)

t-Butyl catechol

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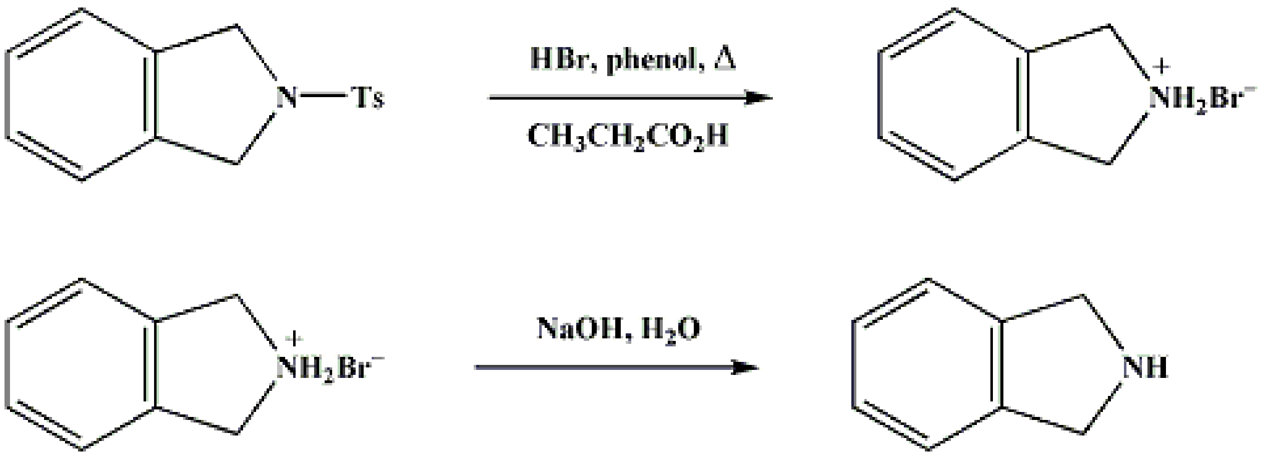
Organic Syntheses, CV 5, 406

1,3-DIHYDROISOINDOLE

[Isoindoline]



Submitted by J. Bornstein, J. E. Shields, and A. P. Boisselle[1].
Checked by William G. Dauben and Harold B. Morris.

1. Procedure

In a 1-l. round-bottomed flask are placed 36.0 g. (0.132 mole) of 2-(*p*-tolylsulfonyl) dihydroisoindole,[2] 36.0 g. (0.38 mole) of phenol, 270 ml. of 48% hydrobromic acid (Note 1), and 45 ml. of propionic acid. A few boiling chips are added, and the flask is fitted with a reflux condenser in the top of which is placed a T-tube connected to a source of low-pressure nitrogen and to a mercury bubbler. The mixture is heated under reflux for 2 hours in an atmosphere of nitrogen. The deeply colored reaction mixture is cooled to room temperature, transferred to a 1-l. separatory funnel, and washed with two 200-ml. portions of ether (Note 2). The aqueous phase is then added dropwise over a 1-hour period to a vigorously stirred (Note 3) solution of 200 g. of sodium hydroxide in 600 ml. of water in a 2-l. Erlenmeyer flask immersed in an ice bath. The solution is transferred to a 3-l. separatory funnel and extracted with five 300-ml. portions of ether. The ethereal extracts are combined, dried over anhydrous potassium carbonate (Note 4), and filtered. The solvent is distilled, and the dark residual oil is transferred to a distillation flask and distilled through a low-holdup, semimicro column (Note 5). After removal of 1 or 2 drops of forerun, colorless 1,3-dihydroisoindole is collected at 96–97° (10 mm.) or 55–56° (2 mm.), n^{25}D 1.5686, d_4^{20} 1.081. The yield is 9.9–11.2 g. (63–71%) (Note 6).

2. Notes

1. The hydrobromic acid should be colorless. Reagent grade 47–49% hydrobromic acid, obtained from J. T. Baker Chemical Co., was used as supplied. A technical grade of the constant-boiling acid is suitable if purified by distillation from

stannous chloride.

2. Detection of the water-ether interface may prove trouble-some; backlighting of the separatory funnel by an intense light source is recommended. The same volume of ether must be used for each washing, even when the preparation is carried out on a smaller scale, *e.g.*, one-half or one-third the scale described here.

3. Stirring is most conveniently accomplished with a magnetic stirrer.

4. Washing of the ethereal extract with water decreases the yield of product.

5. The submitters used a 7 × 300-mm. externally heated column packed with a helix of Chromel wire and fitted with a partial reflux head.[3]

6. Since the product slowly darkens on exposure to air, it should be stored under nitrogen in a refrigerator. The compound solidifies on cooling; m.p. 16.0–16.5°. Nuclear magnetic resonance spectrum (neat, tetramethylsilane internal standard): singlets at δ 7.00 (aromatic protons), 3.93 (CH_2), and 2.24 p.p.m. (NH).

3. Discussion

1,3-Dihydroisoindole has been prepared from phthalimide by electrolytic reduction[4] and by reduction with lithium aluminium hydride.[5] Other methods that have been used are reduction of 1-chlorophthalazine with zinc and hydrochloric acid[6] and hydrogenolysis of 2-benzyl-1,3-dihydroisoindole.[7] The present method is essentially that of Bornstein, Lashua, and Boisselle.[8]

4. Merits of the Preparation

This procedure illustrates a general method for the preparation of amines by reductive cleavage of sulfonamides by hydrobromic acid in the presence of phenol.[9] The present synthesis makes 1,3-dihydroisoindole readily accessible and is superior in certain respects to the other two practical methods of preparation. Thus the method here described is shorter and gives a higher overall yield than the three-step synthesis of Neumeyer,[7] and obviates the special apparatus and careful control required by the electrochemical process of Dunet, Rollet, and Willemart.[4]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium hydroxide (1310-73-2)

phenol (108-95-2)

propionic acid (79-09-4)

HYDROBROMIC ACID (10035-10-6)

nitrogen (7727-37-9)

stannous chloride

zinc (7440-66-6)

Phthalimide (85-41-6)

lithium aluminium hydride (16853-85-3)

1,3-Dihydroisoindole, Isoindoline (496-12-8)

1-chlorophthalazine

2-benzyl-1,3-dihydroisoindole (35180-14-4)

2-(p-Tolylsulfonyl)dihydroisoindole (32372-83-1)

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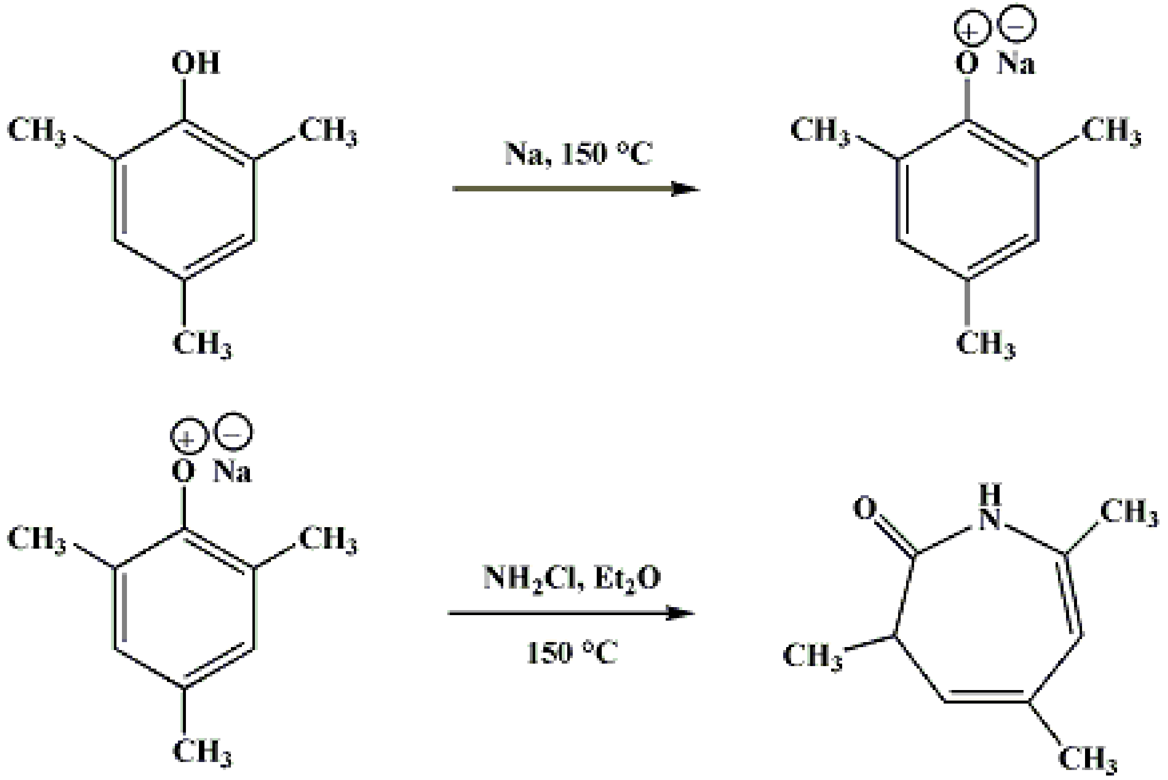
1,3-DIHYDRO-3,5,7-TRIMETHYL-2H-AZEPIN-2-ONE

[2H-Azepin-2-one, 1,3-dihydro-3,5,7-trimethyl-]



Submitted by Leo A. Paquette[1]
Checked by Klaus Herbig and B. C. McKusick.

1. Procedure

Caution! Because obnoxious fumes are liberated during the reaction with chloramine, the apparatus should be set up in a well-ventilated hood.

Five hundred forty-five grams (4.00 moles) of 2,4,6-trimethylphenol (Note 1) is placed in a 1-l. three-necked flask fitted with mechanical stirrer, thermometer, 90-cm. Vigreux column, and dropping funnel (not of the pressure-equalizing variety). The Vigreux column must extend sufficiently into the top of a well-ventilated hood to entrain effectively the fumes that will be generated later in the operation. The phenol is melted with the aid of an external oil bath or Glascol® heating mantle and heated to about 100°. The heating bath is removed, and 27.6 g. (1.20 g. atoms) of sodium in cubes about 1 cm. on a side or smaller is added to the stirred mixture at such a rate that the temperature does not exceed 150–160°. The molten mass gradually becomes dark red in color as the sodium dissolves. While the addition and solution of the sodium is proceeding, a cold solution of about 0.25 mole of chloramine in 250 ml. of ether is prepared (Note 2).

When all the sodium has dissolved, the phenoxide-phenol mixture is heated to 150°. With the oil bath or heating mantle still surrounding the flask, *and with a protective shield between the reaction vessel and the operator* (Note 3), the cold ethereal chloramine solution is added with rapid stirring in a thin stream from the dropping funnel at such a rate that the temperature of the reaction mixture does not drop below 125°. Best results are obtained if the thin stream of ether solution can be added directly to the molten mass without first touching the walls of the flask.

When the addition is completed, the heat source is removed and the dark-colored contents are allowed to cool until another 0.25 mole of ethereal chloramine has been prepared and is ready for use; a wait of 1.5–2 hours between chloramine additions is convenient but not essential to the success of the experiment. The cooled reaction mixture is then reheated to 150°, and the process is repeated. This sequence is repeated until a total of four 0.25-mole portions of chloramine are added.

The reaction mixture is allowed to cool. The dropping funnel, thermometer, and Vigreux column are replaced with a stopper and short-path distillation head. The mixture is stirred while the excess phenol is removed by distillation at water-aspirator pressure; b.p. 105–110° (14 mm.). When the temperature begins to rise above 110° (14 mm.), the distillation is stopped and the residue is allowed to cool (Note 4).

Water (500 ml.) and 500 ml. of ether are added to the residue, and the mixture is well stirred. The mixture is transferred to a 2-l. separatory funnel, and the two layers are carefully separated. The aqueous layer is extracted with two additional 250-ml. portions of ether. The combined organic layers are washed twice with 5% sodium hydroxide solution and then with water, dried over anhydrous magnesium sulfate, filtered, and evaporated on a rotary evaporator. The dark residue is transferred to a distillation flask and distilled through a 30-cm. Vigreux column to yield a crystalline fraction, b.p. 130–155° (13 mm.) (Note 5). Recrystallization of this distillate from ligroin gives 68–80 g. (45–53%, based on chloramine added) of 1,3-dihydro-3,5,7-trimethyl-2H-azepin-2-one as a fluffy white solid, m.p. 131–132°.

2. Notes

1. Suitable material is obtainable from the Aldrich Chemical Co., Milwaukee, Wisconsin.
2. The ethereal chloramine solution is conveniently prepared in this quantity according to the precise directions of Coleman and Johnson.[2] It is essential to the success of this reaction that their procedure be followed exactly.
3. The protective shield is recommended despite the fact that no fire or explosion has been observed in well over fifty such experiments by the submitter.
4. The phenol recovered at this stage is reusable in subsequent preparations.
5. It is not always necessary to distil the residue. The checkers obtained a tan crystalline residue that was recrystallized from about 2 l. of heptane to give 68 g. of colorless azepinone, m.p. 130–132°. An additional 12 g. of the azepinone

with the same appearance and melting point was obtained by concentrating and cooling the heptane filtrate.

3. Discussion

1,3-Dihydro-2H-azepin-2-one has been prepared in a lengthy five-step sequence by Vogel and Erb.[3] The present method,[4] the reaction of sodium 2,6-dialkylphenoxides with chloramine, easily affords the corresponding dihydroazepinones in good yield.

4. Merits of the Preparation

This reaction can be generally applied with equal success to other 2,6-dialkylphenols,[4] many of which are commercially available. Although the procedure cannot be extended to phenol or *o*-monosubstituted phenols (aminophenols result[5]), it represents a facile synthetic method for obtaining a ring system heretofore relatively unavailable. The dihydroazepinones in turn are excellent starting materials for the preparation of other novel heterocyclic systems such as 2,3-dihydro-1H-azepines,[6] 2-substituted-3H-azepines,[7] and derivatives of 2-azabicyclo[3.2.0]hept-6-ene.[8]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ligroin

ether (60-29-7)

sodium hydroxide (1310-73-2)

phenol (108-95-2)

sodium (13966-32-0)

magnesium sulfate (7487-88-9)

heptane (142-82-5)

chloramine (10599-90-3)

1,3-DIHYDRO-3,5,7-TRIMETHYL-2H-AZEPIN-2-ONE, 2H-Azepin-2-one, 1,3-dihydro-3,5,7-trimethyl- (936-85-6)

2,4,6-trimethylphenol (527-60-6)

1,3-Dihydro-2H-azepin-2-one

2-azabicyclo[3.2.0]hept-6-ene

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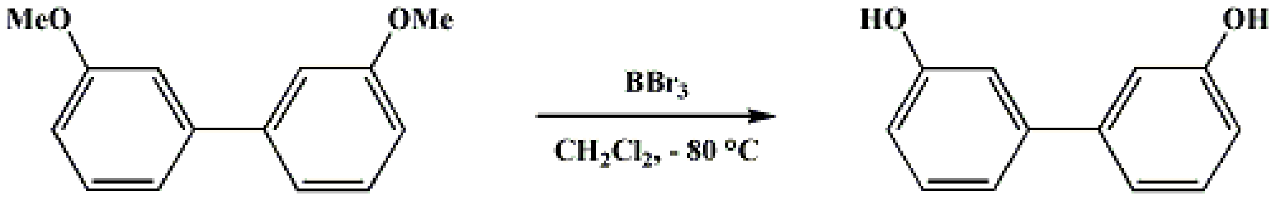
3,3'-DIHYDROXYBIPHENYL

[m,m'-Biphenol]



Submitted by J. F. W. McOmie and D. E. West[1].
Checked by J. E. Hiatt and K. B. Wiberg.

1. Procedure

3,3'-Dimethoxybiphenyl[2] (8 g., 0.037 mole) is dissolved in 120 ml. of methylene chloride in a 250-ml. conical flask, and the flask is placed in an acetone-dry ice bath at –80°. The flask is fitted with an air condenser. A solution of 15.9 g. (6.0 ml., 0.063 mole) of boron tribromide (Note 1), (Note 2) in 40 ml. of methylene chloride (Note 3), (Note 4) is added carefully to the stirred solution through the condenser. When the addition is complete, a calcium chloride tube is fitted to the top of the air condenser in order to protect the reaction mixture from moisture. As the solution of boron tribromide is added, a white precipitate is formed. The reaction mixture is allowed to attain room temperature overnight with stirring, when a clear, brownish yellow solution is obtained. The reaction mixture is then hydrolyzed by careful shaking with 130 ml. of water, thus precipitating a white solid which is dissolved by the addition of 500 ml. of ether. The organic layer is separated and extracted with 240 ml. of 2*N* sodium hydroxide; the alkaline extract is neutralized with dilute hydrochloric acid, extracted with 300 ml. of ether, and the ether extract is dried over anhydrous magnesium sulfate. On removal of the ether under reduced pressure, a brownish yellow oil remains which soon crystallizes to give an off-white solid; this is recrystallized twice from hot benzene, the first time with the addition of charcoal, and gives 3,3'-dihydroxybiphenyl as white needles with a pinkish tint, m.p. 126–127° (Note 5). The yield is 5.4–6.0 g. (77–86%).

2. Notes

1. Boron tribromide of 99.9% purity, from Koch-Light Laboratories Ltd., Colnbrook, Bucks, England, was used.
2. Boron tribromide is a heavy, colorless liquid (*d* = 2.6) when pure but begins to decompose on exposure to light, liberating free bromine. It fumes vigorously in air, being rapidly hydrolyzed to boric acid, with the evolution of considerable heat.
3. Demethylation reactions proceed equally well using dry *n*-pentane or dry methylene chloride as the solvent for both the ether and the boron tribromide; methylene chloride, having by far the more powerful solvent action, is to be preferred.
4. When making up the solution of boron tribromide in methylene chloride, it has been found best to stand the vessel containing the solvent in an acetone-dry ice bath at –80° and to add the required amount (it is difficult to measure accurately) to the methylene

chloride as rapidly as possible.

5. In order to obtain a perfectly white product, recrystallization from water is necessary;[3,4] prismatic needles several centimeters long are obtained. The compound is moderately soluble in boiling water and slightly soluble in cold water.

3. Discussion

The above preparation of 3,3'-dihydroxybiphenyl is a good example of the utility of boron tribromide for the cleavage of aryl methyl ethers; it is based on the method of McOmie, Watts, and West.[5] 3,3'-Dihydroxybiphenyl has been prepared previously by diazotization[3] of 3,3'-diaminobiphenyl and subsequent boiling with water, by the fusion of biphenyl-3,3'-disulfonic acid with potassium hydroxide,[6] and by heating 3,3'-dimethoxybiphenyl with hydriodic acid.[4]

Almost all the methods previously employed[7] for the demethylation of aromatic methyl ethers have involved fairly high temperatures, *e.g.*, hydrogen halides in water or acetic acid at reflux temperature, whereas the present method is effective at, or well below, room temperature although in a few cases it has been found necessary to boil the solution (b.p. of methylene chloride, 40°). Boron tribromide does not effect cleavage of methylenedioxy groups nor of diphenyl ethers. It can be used for the demethylation of aryl methyl ethers in the presence of many functional groups without affecting these.[5] It is especially valuable for the demethylation of iodinated ethers[5] and of methoxy biphenylenes[8] where the usual reagents are either ineffective or else cause decomposition. Boron tribromide was the reagent of choice for the final (demethylation) step in the synthesis of the naturally occurring macrolide, Zearalenone.[9]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

m,m'-Biphenol

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

ether (60-29-7)

sodium hydroxide (1310-73-2)

bromine (7726-95-6)

potassium hydroxide (1310-58-3)

hydriodic acid (10034-85-2)

n-PENTANE (109-66-0)

methylene chloride (75-09-2)

boric acid (10043-35-3)

magnesium sulfate (7487-88-9)

boron tribromide (10294-33-4)

3,3'-DIMETHOXYBIPHENYL (6161-50-8)

3,3'-dihydroxybiphenyl (612-76-0)

3,3'-diaminobiphenyl

biphenyl-3,3'-disulfonic acid

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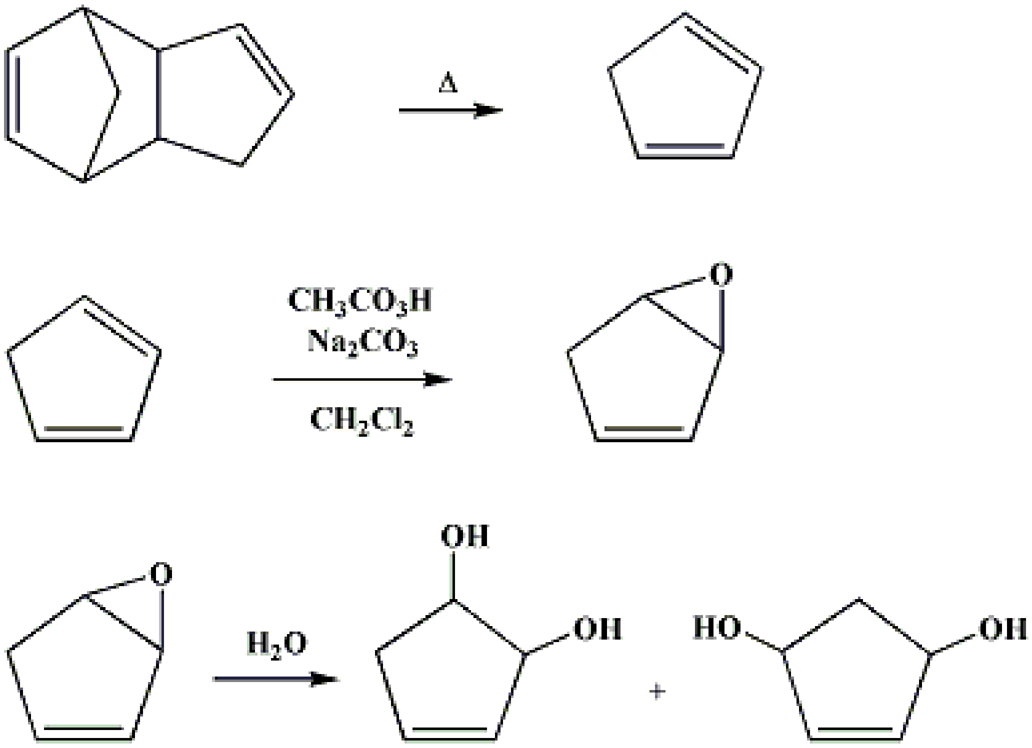
DIHYDROXYCYCLOPENTENE

[Cyclopentenediol]



Submitted by M. Korach, D. R. Nielsen, and W. H. Rideout[1].
Checked by William G. Dauben and Clifton Ashcraft.

1. Procedure

Caution! Reactions run with peracetic acid should be conducted with due regard to the properties of this reagent (Note 1).

In a 1-l. three-necked flask equipped with a dropping funnel, a thermometer, and an efficient fractionation column fitted with either a vapor- or liquid-splitting head (Note 2) is placed 400 ml. of mineral oil. The oil is heated to 240–270° and dicyclopentadiene (Note 3) is added at the rate of 5–10 ml. per minute. The reflux ratio and the rate of addition of dicyclopentadiene are adjusted to maintain the distillation head temperature at 40°. The cyclopentadiene is collected in a Dry Ice-acetone receiver (Note 4).

In a 1-l. three-necked flask fitted with a sealed stirrer, a thermometer, and a connecting tube with parallel side arm to which is attached an addition funnel and a reflux condenser are placed 56 g. (0.81 mole) of 96% cyclopentadiene, 106 g. (1.0 mole) of anhydrous sodium carbonate, and 500 ml. of methylene chloride. A solution of 2 g. of

sodium acetate in 76 g. of 40% peracetic acid (0.40 mole) (Note 5) is added, with stirring, over a period of 30–45 minutes, and the temperature is maintained at 20° by intermittent external cooling. The resulting mixture is stirred for an additional hour at room temperature (Note 6). The solid in the reaction is removed by suction filtration, and the filter cake is washed three times with 75 ml. of methylene chloride. The combined filtrate and washings are added, with rapid stirring, over a period of 1 hour, to 250 ml. of cold distilled water (maintained at 5–10° by external cooling) contained in a 2-l. three-necked flask fitted with a condenser, a sealed stirrer, and an addition funnel (Note 7). The stirring is continued for 1 hour as the temperature is allowed to rise to room temperature, the layers are separated, and the lower methylene chloride layer is extracted twice with 25 ml. of distilled water. The aqueous extracts are combined with the aqueous phase obtained from the hydrolysis reaction, and the combined solution is distilled at approximately 30 mm. pressure to remove the water (Note 8). The residue is distilled at reduced pressure to give 26–28 g. of colorless oil, b.p. 82–105°/1 mm. (Note 9). The yield of mixed cyclopentenediols is 65–70% based on the quantity of peracetic acid used.

The mixed cyclopentenediols can be separated by distillation through a 60-cm. spinning band column. The yield of pure 3-cyclopentene-1,2-diol, b.p. 65–68°/1 mm., n_D^{26} 1.4941–1.4951, is 4.5–5.5 g., and the yield of pure 2-cyclopentene-1,4-diol, b.p. 92–95°/1 mm., n_D^{26} 1.5000–1.5010, is 17–20 g. (Note 10).

2. Notes

1. When peracetic acid is used in organic synthesis the following precautions are recommended by the FMC Corporation, Inorganic Chemicals Division (Bulletins 4 and 69). All laboratory reactions and subsequent operations should be run behind a safety shield. The peracetic acid should be added to the organic material, never the reverse, and the rate of addition should be slow enough so that the peracid reacts as rapidly as it is added and no unreacted excess is allowed to build up. The reaction mixture should be stirred efficiently while the peracid is being added, and cooling facilities should be provided since most of the reactions of peracetic acid are exothermic. New or unfamiliar reactions, particularly those run at high temperatures, should be tried first on a very small scale. Reactions products should never be recovered from the final reaction mixture by distillation until all residual active oxygen compounds have been destroyed. This includes the hydrogen peroxide present in commercial 40% peracetic acid as well as the unreacted peracid. Decomposition may be readily accomplished by catalystic quantities of activated carbon or ferric sulfate added at 25–50°. The course of the decomposition may be followed by the titration described in (Note 5). (See also Note 1, p. 904).
A serious accident has occurred when the reaction described in this procedure was run on a scale ten times that described and some of the above precautions were not observed (G. Benoy, private communication).
2. The checkers used a 1 × 24 in. column packed with glass helices.
3. Commercially available dicyclopentadiene of 95% or 70% purity may be

used. The higher-purity material yields a less colored product.

4. Any ice present in the product can be removed by filtration of the cyclopentadiene through glass wool. Cyclopentadiene can be stored at Dry Ice temperatures in a tightly capped bottle for several weeks without serious loss due to dimerization. Purification of a stored sample can be effected by distillation through a short Vigreux column at 10–30 mm. pressure and collection of the product in a receiver cooled by a Dry Ice-acetone bath until the temperature in the distilling flask rises to 10°. The distillate contains approximately the same concentration of cyclopentadiene as the freshly purified material (95–96%).

5. Peracetic acid (40%) is available commercially. Since the epoxycyclopentene reacts rapidly with water, it is desirable to keep the water content of the peracetic acid solution as low as possible. This is the reason for the use of the concentrated peracetic acid solution.

The peracetic acid content of the reagent may be determined by adding an aliquot to an equal volume of ice and water and titrating first with ceric sulfate solution until the orange color of the ceric ion remains (to eliminate hydrogen peroxide) and then adding potassium iodide and titrating with standard sodium thiosulfate solution.

6. The extent of peracetic acid consumption can be determined by titration of an aliquot as described in (Note 4).

7. Distilled epoxycyclopentene can be hydrolyzed under identical conditions. However, distillation of the crude epoxide has occasionally resulted in a rapid, highly exothermic reaction when the pot temperature rises above 60°. The safest method for isolating the epoxide from the crude product is to remove the methylene chloride by distillation at atmospheric pressure until the pot temperature reaches 50°, then strip off crude epoxycyclopentene at reduced pressure and at a temperature below 50°. The apparatus should be shielded and the temperature in the distillation flask should be monitored. The crude distillate of epoxide and methylene chloride can be safely redistilled at 75–100 mm. pressure.

8. A rotatory evaporator has been found to be quite suitable for the rapid removal of water.

9. In some cases the distillate is yellow. The color can be removed by redistillation in the presence of 0.1% anhydrous sodium carbonate.

10. The purity of the distillation fractions can be determined by gas-liquid chromatography, using a 5 ft. × in. column containing 20% Carbowax at a temperature of 200°.

3. Discussion

Cyclopentenediol isomers have previously been prepared by hydrolysis of acetates produced by reaction of dibromocyclopentene with potassium acetate in acetic acid;[2] by reaction of cyclopentene with selenium dioxide in acetic anhydride;[3] or by reaction

of cyclopentadiene with phenyl iodosoacetate,[4] with lead tetraacetate,[5] or with peracetic acid in the absence of base.[6] Preparation of cyclopentenediol without intermediate formation of acetates has been accomplished by reaction of cyclopentadiene with hydrogen peroxide in the presence of osmium tetroxide in *tert*-butanol,[7] and by reaction of cyclopentadiene with peracetic acid in a methylene chloride suspension of anhydrous sodium carbonate, followed by hydrolysis of the resulting epoxycyclopentene.[8]

4. Merits of Preparation

The present method of preparation utilizes inexpensive, readily available, non-toxic reagents, is less laborious than previous methods, produces an easily purified product, and results in improved yields (65–70% vs. 10–50% for the older methods). It is a useful starting material for a variety of compounds as illustrated by the preparations of 2-cyclopentenone (p. 326) and 2-cyclopentene-1, 4-dione (p. 324).

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 60
- Org. Syn. Coll. Vol. 5, 324
- Org. Syn. Coll. Vol. 5, 326
- Org. Syn. Coll. Vol. 5, 1088
- Org. Syn. Coll. Vol. 6, 145
- Org. Syn. Coll. Vol. 7, 339
- Org. Syn. Coll. Vol. 8, 13
- Org. Syn. Coll. Vol. 8, 298
- Org. Syn. Coll. Vol. 9, 132
- Org. Syn. Coll. Vol. 9, 136

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

acetic acid (64-19-7)

acetic anhydride (108-24-7)

sodium acetate (127-09-3)

sodium carbonate (497-19-8)

potassium iodide (7681-11-0)

sodium thiosulfate (7772-98-7)

carbon (7782-42-5)

selenium dioxide (7446-08-4)

hydrogen peroxide (7722-84-1)

methylene chloride (75-09-2)

Cyclopentene (142-29-0)

potassium acetate (127-08-2)

peracetic acid (79-21-0)

osmium tetroxide (20816-12-0)

phenyl iodosoacetate

CYCLOPENTADIENE (542-92-7)

dicyclopentadiene

tert-butanol (75-65-0)

2-cyclopentene-1, 4-dione (930-60-9)

Dihydroxycyclopentene, Cyclopentenediol

2-cyclopentene-1,4-diol (4157-01-1)

2-Cyclopentenone (930-30-3)

3-cyclopentene-1,2-diol

ferric sulfate (10028-22-5)

epoxycyclopentene

ceric sulfate (13590-82-4)

dibromocyclopentene

lead tetraacetate

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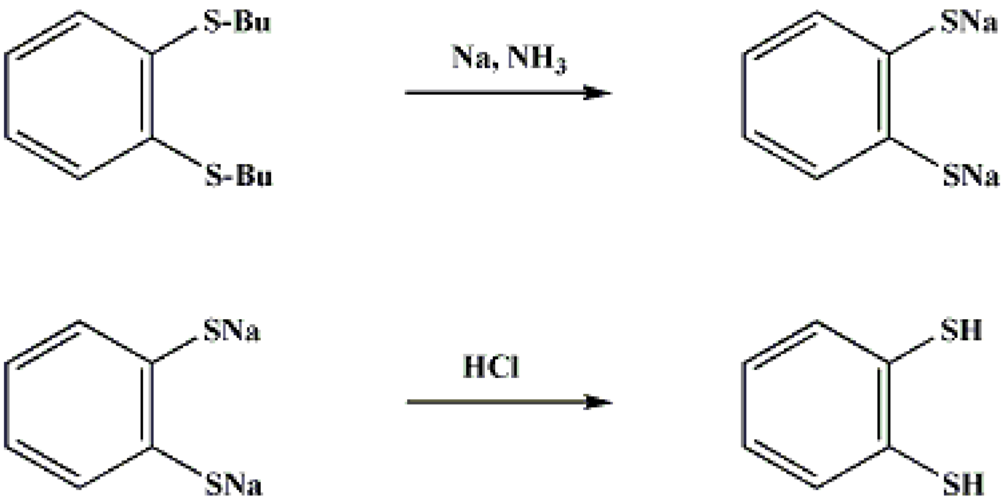
Organic Syntheses, CV 5, 419

1,2-DIMERCAPTOBENZENE

[*o*-Benzenedithiol]



Submitted by Aldo Ferretti[1]
Checked by William E. Parham, Wayland E. Noland, and James R. Throckmorton.

1. Procedure

A 200-ml. two-necked flask is fitted with an efficient Dry Ice-isopropyl alcohol condenser connected to a soda-lime tube, a magnetic stirrer, and a gas inlet tube. Isopropyl alcohol and Dry Ice are added to the condenser while the flask and condenser are flushed with dry nitrogen. The flask is immersed in a Dry Ice-isopropyl alcohol bath, and a vigorous stream of dry ammonia is introduced into the system. When about 80 ml. of liquid ammonia is condensed, the gas inlet tube is replaced with a ground-glass stopper. The cooling bath is removed, stirring is started, and 5.1 g. (0.020 mole) of 1,2-bis(*n*-butylthio) benzene (Note 1) is quickly introduced (Note 2).

Sodium is now added in small pieces; the solution is allowed to decolorize before each successive piece is added. A water bath is placed occasionally under the flask to ensure continuous ebullition of ammonia. The blue color will persist for at least 15 minutes after 1.6 g. (0.070 g. atom) of sodium has been added. The excess sodium is then destroyed by *cautious* addition of 6 g. (0.11 mole) of ammonium chloride, with stirring. Cooling and stirring are stopped, and a slow stream of argon is passed in for a period of about 12–15 hours. The white solid residue is transferred to a beaker, and 300 g. of ice water is added, together with sufficient pellets of sodium hydroxide to make the solution alkaline. The alkaline solution is then extracted twice with ether and the ether extracts discarded. The solution is then acidified to Congo red with cold 1:1 (by volume) hydrochloric acid and extracted three times with ether. The ether extracts are combined, washed with water, and dried over anhydrous sodium sulfate. The ether

is evaporated and the 1,2-dimercaptobenzene is distilled under reduced pressure under an atmosphere of nitrogen, giving a product which boils at 95°/5 mm. and usually solidifies after distillation (Note 3). The yield is 1.6–2.4 g. (56–85%) (Note 4).

2. Notes

1. The preparation of 1,2-bis(*n*-butylthio) benzene is described elsewhere in this volume.[2]
2. 1,2-Bis(*n*-butylthio)benzene is only slightly soluble in liquid ammonia. Stirring must be very efficient during the addition and subsequently during the reaction to prevent the drops of 1,2-bis(*n*-butylthio)benzene from collecting as a solid mass. If this happens, the time necessary for completion of the reaction, and the quantity of sodium necessary for dealkylation, must be increased. The checkers found that the 1,2-bis(*n*-butylthio)benzene invariably collected as several solid masses and that it was always necessary to add additional sodium, about 0.9 g.
3. The reported melting point is 27–28°.[3]
4. The reported yield is 2.0 g. (70%) of an oil, b.p. 102°/6.5 mm..[3] A similar procedure has been used by the submitter to prepare 1,4-dimercaptobenzene, 2,5-dimercaptotoluene, 1,3,5-trimercaptobenzene, 2,4,6-trimercaptomesitylene, and 4,4'-dimercaptobiphenyl.[3]

3. Discussion

The present procedure is that of Adams and Ferretti.[3] Another method is the reduction of 1,2-benzenedisulfonyl chloride with zinc powder.[4] In a third method[5] a 2-aminomercaptobenzene is diazotized and converted to an intermediate xanthate and then to the corresponding mercaptosulfonic acid. The latter can be converted to the dimercaptan either by: (1) oxidation to a disulfonic acid, conversion to the disulfonyl chloride, and reduction to the dimercaptan, or (2) mild oxidation to the corresponding disulfide, conversion to the sulfonyl chloride disulfide, and reduction to the dimercaptan.

4. Merits of the Preparation

The present procedure, when combined with the accompanying preparation of aryl sulfides (p. 107), provides a convenient and general method for preparing aryl mercaptans from aromatic halides.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 107

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ether (60-29-7)

ammonium chloride (12125-02-9)

sodium hydroxide (1310-73-2)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

zinc powder (7440-66-6)

sodium (13966-32-0)

isopropyl alcohol (67-63-0)

1,2-Dimercaptobenzene, o-Benzenedithiol (17534-15-5)

argon (7440-37-1)

1,4-dimercaptobenzene (25212-74-2)

2,5-dimercaptotoluene

1,3,5-trimercaptobenzene

2,4,6-trimercaptomesitylene

1,2-benzenedisulfonyl chloride (6461-76-3)

2-aminomercaptobenzene

1,2-BIS(n-BUTYLTHIO)BENZENE, 1,2-bis(n-butylthio) benzene (53663-38-0)

4,4'-dimercaptobiphenyl

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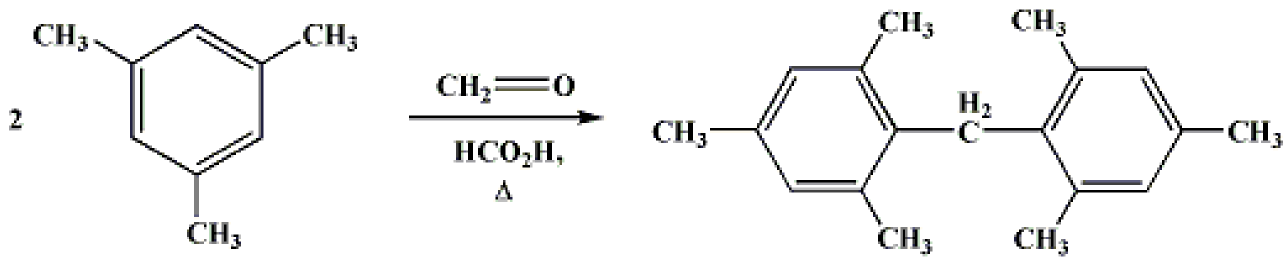
Organic Syntheses, CV 5, 422

DIMESITYLMETHANE

[Methane, dimesityl-]



Submitted by John H. Cornell, Jr. and Morton H. Gollis[1].
Checked by William E. Parham and James Togeas.

1. Procedure

Into a 5-l. round-bottomed flask fitted with stirrer, thermometer, and reflux condenser are introduced 165 g. (5 moles) of 91% paraformaldehyde (Note 1) and 1250 g. (24 moles) of 88% formic acid (Note 2). The mixture is heated to 80° with stirring and is stirred until the paraformaldehyde has dissolved. To the stirred mixture is rapidly added 1.8 kg. (15 moles) of mesitylene and the whole heated under reflux for 6 hours (Note 3).

On cooling to room temperature, a large mass of dirty-yellow crystals separates. The liquid layers are decanted from the yellow solid, and the aqueous (lower) layer is separated and discarded. The solid is washed in the reaction flask by stirring with 500 ml. of benzene. This slurry of solid in benzene is filtered and the solid sucked dry on a Büchner funnel. This filtrate is combined with the upper organic layer from the original reaction mixture, and the combined benzene solution is washed with 500 ml. of water, 500 ml. of 2–3% aqueous sodium carbonate (Note 4), and 200 ml. of saturated sodium chloride solution. Benzene and water are removed from this solution by distillation at atmospheric pressure. The still residue is cooled to room temperature, and precipitated solid is removed by filtration and added to the large crop of solid from the original reaction mixture. The combined solids are washed twice with 300 ml. of water, once with 400 ml. of 2–3% aqueous sodium carbonate, and once with 300–400 ml. of water and sucked dry on a Büchner funnel.

The yield is 779 g. of crude dimesitylmethane (62% of theoretical) melting at 128.5–131°, uncor.; its purity as determined by vapor-phase chromatography is 99.9 mole per cent (Note 5).

2. Notes

1. The checkers used 150 g. (5 moles) of paraformaldehyde obtained from Eastman Organic Chemicals.
2. Contact with formic acid and inhalation of its vapors should be avoided.
3. When a smaller ratio of mesitylene to formaldehyde was used, a considerable amount of polymeric residue was formed and the yield was very much reduced.
4. It is advisable to add the sodium carbonate solution cautiously and with good agitation to avoid a violent evolution of carbon dioxide.

5. The crude product is pure enough for most purposes. However, for catalytic reduction to bis(2,4,6-trimethylcyclohexyl)methane, the residual acid must be removed by dissolving the solid in hot benzene and stirring or shaking with dilute aqueous sodium carbonate solution until the washings are basic; this is followed by a water wash and drying.
The solid can be recrystallized from boiling benzene and precipitated with about 0.15 part of boiling methanol to give white platelets (68%), m.p. 133–135°, plus a second, less pure crop (22%) melting at 128–133°. Reported for dimesitylmethane,[2] m.p. 134.4–135.4°, b. p. 212–213°/21 mm.
The reaction has been scaled up tenfold using a 50-l. flask without changes in procedure and in the same yield.

3. Discussion

Substituted diarylmethanes have been prepared from formaldehyde and a variety of its derivatives. Sulfuric acid is a common catalyst.[2,3] The procedure described is based on the general method of Gordon, May, and Lee.[4] Formic acid is preferable to sulfuric acid as a catalyst because it is capable of acting as a solvent as well, thus eliminating troublesome emulsions. Side reactions such as sulfonation are avoided.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

Benzene (71-43-2)

methanol (67-56-1)

formaldehyde (630-08-0)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

formic acid (64-18-6)

carbon dioxide (124-38-9)

Mesitylene (108-67-8)

Dimesitylmethane, Methane, dimesityl- (733-07-3)

bis(2,4,6-trimethylcyclohexyl)methane

paraformaldehyde (30525-89-4)

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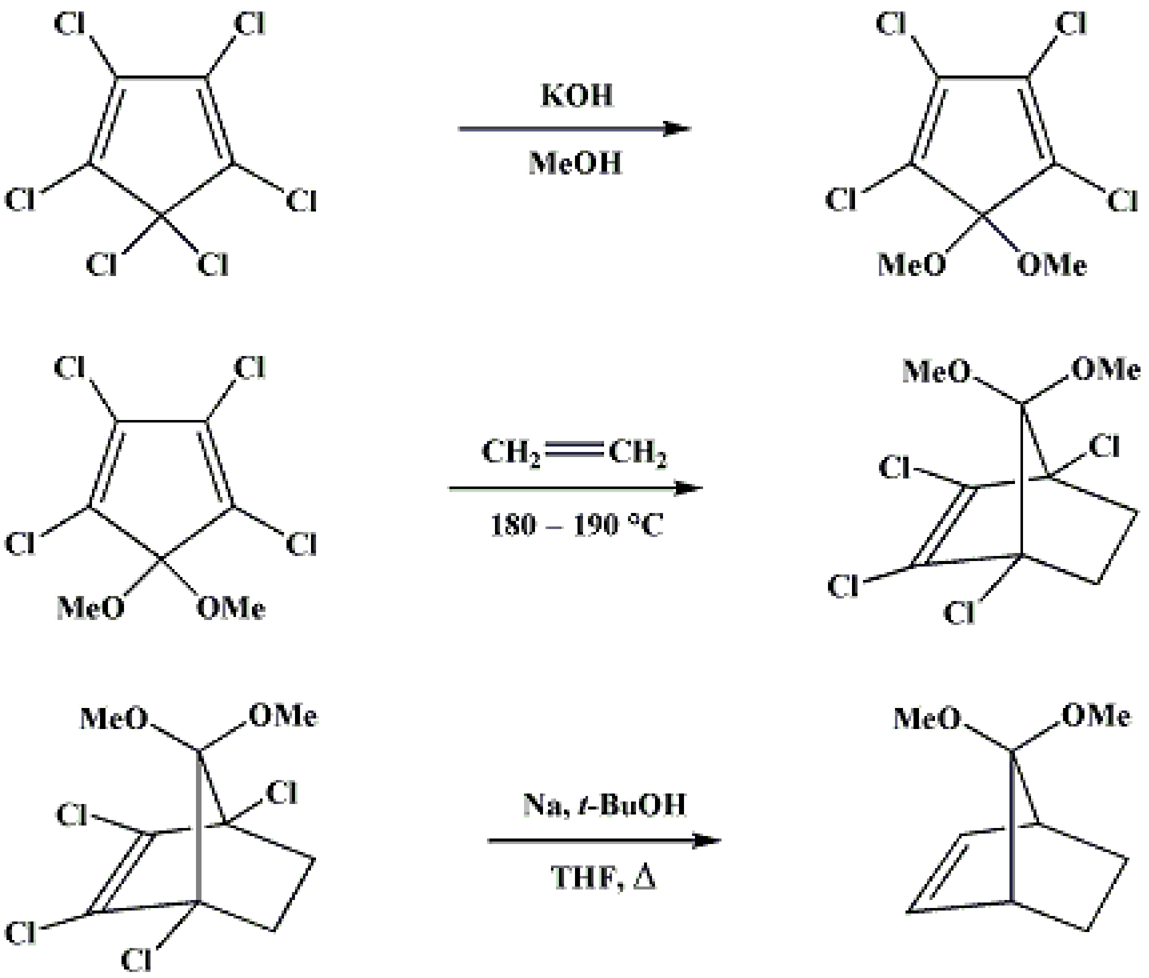
Organic Syntheses, CV 5, 424

7,7-DIMETHOXYBICYCLO[2.2.1]HEPTENE

[2-Norbornen-7-one dimethyl acetal]



Submitted by P. G. Gassman and J. L. Marshall[1].
Checked by William G. Dauben and James L. Chitwood.

1. Procedure

Caution! Most polychlorinated compounds show some toxicity. These compounds should be handled in a hood.

A. *5,5-Dimethoxy-1,2,3,4-tetrachlorocyclopentadiene*. In a 3-l. three-necked flask fitted with a condenser (Note 1), an addition funnel, and a mechanical stirrer (Note 2) are placed 254 g. (0.93 mole) of hexachlorocyclopentadiene (Note 3) and 800 ml. of methanol (Note 4). The stirrer is started, and a solution of 120 g. (2.14 moles) of potassium hydroxide in 600 ml. of methanol is added dropwise over a period of 2 hours (Note 5). The reaction mixture is stirred for an additional 2 hours and then poured over 3 l. of chopped ice. After the ice has melted, the mixture is extracted with

three 250-ml. portions of dichloromethane. The combined extracts are dried over anhydrous magnesium sulfate and concentrated to a yellow syrup on a rotary evaporator (Note 6). The residue is distilled through a 12-in. vacuum-jacketed Vigreux column to yield 187–189 g. (76–77%) of 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene as a viscous, yellow-tinted oil, b.p. 79–84° (0.6 mm.) (Note 7).

B. *7,7-Dimethoxy-1,2,3,4-tetrachlorobicyclo[2.2.1]hept-2-ene*. A large Pyrex gas washing bottle with fritted-glass inlet (Note 8) is fitted with a condenser and a drying tube. In the bottle is placed 189 g. (0.72 mole) of 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene, and a slow stream of nitrogen and ethylene is passed through the fritted-glass inlet (Note 9). The bottle is heated to 180–190° by means of an oil bath. The color of the liquid changes from yellow to reddish brown as ethylene is bubbled through the reaction mixture at this temperature for 6 hours (Note 10). The reaction mixture is cooled and distilled through a 12-in. vacuum-jacketed Vigreux column to yield 155–165 g. (73–78%) of a yellow syrup, b.p. 70–75° (0.15 mm.) (Note 11).

C. *7,7-Dimethoxybicyclo[2.2.1]heptene*. A 3-l. three-necked flask is equipped with a sealed Hershberg stirrer,[2] a condenser fitted with a nitrogen inlet to maintain a slight positive pressure, and a pressure-equalizing dropping funnel. The flask is placed in a heating mantle, and into it are placed 1.5 l. of tetrahydrofuran, 130 g. (5.7 g. atoms) of sodium chopped into 5-mm. cubes, and 190 ml. (150 g., 2.0 moles) of *t*-butyl alcohol. This mixture is stirred vigorously and brought to gentle reflux (Note 12). As soon as refluxing occurs, 106 g. (0.36 mole) of 7,7-dimethoxy-1,2,3,4-tetrachlorobicyclo[2.2.1]hept-2-ene is added dropwise over a 2-hour period (Note 13). The mixture is heated under reflux for 38 hours, cooled to room temperature, and filtered through a wire screen to remove the unreacted sodium. The dark filtrate is refiltered by suction through Celite in a Buchner funnel (Note 14). The filtrate is mixed with 2 l. of chopped ice and 500 ml. of ether. The aqueous phase is separated (Note 15), and the organic phase is washed with 500-ml. portions of saturated aqueous sodium chloride until the washings are clear. The ethereal solution is dried over anhydrous magnesium sulfate and concentrated to a dark oil by removal of the ether by fractional distillation. The oil is fractionally distilled through a 6-in. Vigreux column to yield 17–24 g. (31–43%) of colorless liquid, b.p. 58–68° (17 mm.), n^{25}D 1.4598 (Note 16) and (Note 17).

2. Notes

1. If the directions are carefully followed, the condenser will not be utilized since it serves mainly as a safety device in case the reaction should become too exothermic.

2. A Hershberg nichrome wire stirrer[2] is well suited for this reaction.

3. The hexachlorocyclopentadiene was used as obtained from Matheson, Coleman and Bell.

4. Commercial grade methanol was used.
5. This reaction mixture should not be cooled initially because an uncontrollable exothermic reaction will occur if a large concentration of alkoxide builds up.
6. Concentration at 100° (30 mm.) is necessary for removal of most of the dichloromethane.
7. The submitters have obtained an 86% yield of product, b.p. 79–91° (0.6 mm.). They have also found that the reaction may be scaled up fivefold if 4 hours is taken for the addition of the methanolic base. No danger exists if the temperature is maintained between 50° and 60°.
8. Pyrex gas washing bottle, Corning No. 31750, was used.
9. The checkers found that best results were obtained when the slowest detectable nitrogen flow was used with a fairly rapid ethylene flow (about 1 in. of foam in the gas washing bottle at the reaction temperature).
10. The course of the reaction is readily followed by n.m.r. spectroscopy. The spectrum of the starting material has a singlet at δ 3.30 p.p.m., whereas that of the product has two singlets at δ 3.50 and 3.55 p.p.m. The time required for complete reaction depends on the flow rate of ethylene and nitrogen. The reaction should be allowed to continue until all the starting material is consumed.
11. The distillation should be conducted carefully since the yield in the next step depends on the purity of the material used.
12. Occasionally the pieces of sodium may start to fuse together. This difficulty may be avoided by bringing the mixture to a gentle reflux and stirring vigorously. Once the addition of the chlorinated compound is started, fusing of the sodium ceases. When the reaction is finished, the sodium pieces often fuse into a single large chunk.
13. Unless the reaction mixture is heated *before* the addition process is started, there may be an initial induction period that may cause the reaction to become extremely vigorous once the mixture heats to reflux temperature.
14. The checkers found this last filtration to be a very time-consuming and cumbersome operation. They found it preferable to omit it; they cautiously added methanol[3] to decompose any traces of sodium and poured the resulting solution directly onto the chopped ice.
15. In the separation of the organic and aqueous phases it is often initially very difficult to discern the phase separation because of the dark color of the reaction mixture. The submitters found that, if the phase separation cannot be detected under ordinary light, it can usually be seen by the use of an ultraviolet scanning lamp.
16. The submitters report that 65% yields of product, b.p. 61–71° (18 mm.), can be obtained by workers with experience with this reaction.
17. The product is rather volatile, and care should be taken in its handling and storing.

3. Discussion

The procedures described for the preparation of 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene and 7,7-dimethoxy-1,2,3,4-tetrachlorobicyclo[2.2.1]hept-2-

ene are essentially those of Newcomer and McBee[4] and of Hoch,[5] respectively. The dechlorination is a modification of an analogous dechlorination carried out by Bruck, Thompson, and Winstein.[3] The overall procedure is that of Gassman and Pape.[6]

4. Merits of the Preparation

The reactions include an unusual Diels-Alder reaction and a very useful synthetic method, the dechlorination of polychlorinated compounds. At the present time this procedure is the best one available for the removal of chlorine from an organic molecule. The end product, 7,7-dimethoxybicyclo[2.2.1]heptene, is an interesting and useful intermediate in bicyclic chemistry; it has a reactive double bond and a protected carbonyl group in the 7-position.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 91
- Org. Syn. Coll. Vol. 6, 82

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

methanol (67-56-1)

ether (60-29-7)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

chlorine (7782-50-5)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

ethylene (9002-88-4)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

t-butyl alcohol (75-65-0)

7,7-Dimethoxybicyclo[2.2.1]heptene, 2-Norbornen-7-one dimethyl acetal (875-04-7)

hexachlorocyclopentadiene

5,5-Dimethoxy-1,2,3,4-tetrachlorocyclopentadiene (2207-27-4)

7,7-dimethoxy-1,2,3,4-tetrachlorobicyclo[2.2.1]hept-2-ene (19448-78-3)

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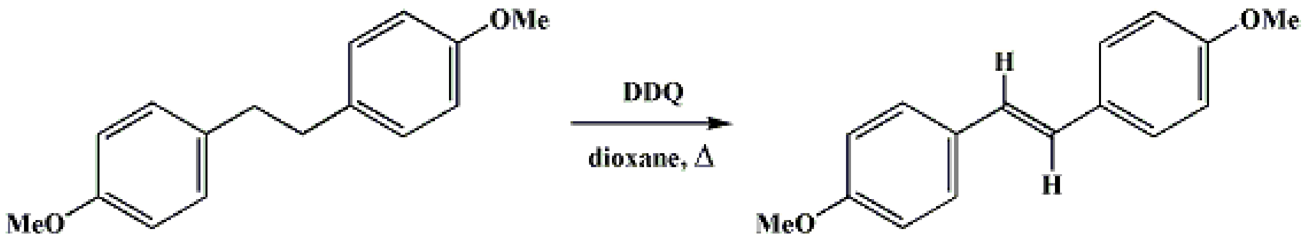
Organic Syntheses, *CV 5*, *428*

trans-4,4'-DIMETHOXYSTILBENE

[*trans*-Stilbene, 4,4'-dimethoxy-]



Submitted by J. W. A. Findlay and A. B. Turner[1].
Checked by R. E. Ireland and G. Brown.

1. Procedure

A solution of 100 mg. (0.41 mmole) of 4,4'-dimethoxybibenzyl (Note 1) in 1.5 ml. of anhydrous dioxane (Note 2) was placed in a 10-ml. round-bottomed flask. To this was added 103 mg. (0.45 mmole) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ; (Note 3)) dissolved in 1.5 ml. of anhydrous dioxane. The flask was fitted with a reflux condenser and heated in an oil bath at 105° for 18 hours. The solution, which was initially deep green, became pale yellow as the hydroquinone crystallized out. The mixture was cooled, and the solid was filtered off. It was washed with 1 ml. of warm benzene followed by 6 ml. of warm chloroform (Note 4), and dried at 100° to give 95 mg. (91%) of pure 2,3-dichloro-5,6-dicyanohydroquinone (Note 5). The filtrate and washings were combined and evaporated under reduced pressure. The semisolid residue was dissolved in 5 ml. of ethyl acetate and passed through a short column of neutral alumina (2.0 g.; (Note 6)). The column was eluted with 100 ml. of ethyl acetate (Note 7). Evaporation of the solvent under reduced pressure left the crude product, which was recrystallized from 35 ml. of ethanol to give 82–84 mg. (83–85%) of *trans*-4,4'-dimethoxystilbene as colorless plates, m.p. 212–213.5°.

2. Notes

1. The starting bibenzyl was prepared from *p*-methoxybenzyl chloride by a modified Wurtz reaction.[2] The checkers found the procedure described by Buu-Hoï and Lavit[2] inadequate and used the copper(I) chloride-catalyzed coupling of *p*-methoxybenzylmagnesium chloride in its place.
2. Dioxane was purified by the method of Vogel[3] and stored over molecular sieves.
3. DDQ was obtained from Koch-Light Laboratories, Ltd. It can be recrystallized from benzene if required.
4. Washing with chloroform is necessary to dissolve some of the stilbene which crystallizes out with hydroquinone. In many reactions, washing the hydroquinone with hot benzene is sufficient, as the dehydrogenation products crystallize to a limited extent from dioxane.
5. The amount of precipitated hydroquinone is a convenient measure of the extent of hydrogen transfer. DDQ is readily regenerated in good yield from the hydroquinone by oxidation with nitric acid.[4]
6. Woelm neutral alumina, activity grade 1.
7. The volume of ethyl acetate required to elute the product can be reduced considerably for more soluble products.

3. Discussion

DDQ was first introduced for the dehydrogenation of hydroaromatic compounds, such as tetralin and bibenzyl, which yield naphthalene and stilbene, respectively.[5] A benzene ring or an olefinic bond provides sufficient activation, although it is sometimes difficult to force the reaction to completion. This highpotential quinone has since found wide application,[6] particularly in the steroid field, and its scope has been extended by the dehydrogenation of carbonyl compounds (ketones and lactones) and alcohols. DDQ is also useful for preparing stable cations and radicals. These reactions are commonly carried out in refluxing benzene or dioxane, and the procedure described here is a general one. An alternative workup procedure involves washing with alkali.

A number of compounds react rapidly with DDQ at room temperature. They include allylic and benzylic alcohols, which can thus be selectively oxidized, and enols and phenols,[7] which undergo coupling reactions or dehydrogenation, depending on their structure. Rapid reaction with DDQ is also often observed in compounds containing activated tertiary hydrogen atoms.[8] The workup described here can be used in all these cases.

A number of side products can arise with this quinone. They include Diels-Alder adducts (DDQ is a powerful dienophile) and Michael adducts derived from the hydroquinone.

General methods for the preparation of *trans*-stilbenes have been covered previously.[9] 4,4'-Dimethoxystilbene has been prepared from deoxyanisoin and *n*-propylmagnesium iodide,[10] by treatment of thiophenol with 2-bromo-1, 1-di-*p*-methoxyphenylethane,[11] and by the action of nitrous acid on the corresponding amine.[12]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Deoxyanisoin

DDQ

ethanol (64-17-5)

Benzene (71-43-2)

ethyl acetate (141-78-6)

hydrogen (1333-74-0)

chloroform (67-66-3)

hydroquinone (123-31-9)

nitric acid (7697-37-2)

nitrous acid (7782-77-6)

Naphthalene (91-20-3)

copper(I) chloride (7758-89-6)

Thiophenol (108-98-5)

Tetralin (119-64-2)

dioxane (5703-46-8)

stilbene

bibenzyl (103-29-7)

2,3-dichloro-5,6-dicyano-1,4-benzoquinone

2,3-dichloro-5,6-dicyanohydroquinone

p-methoxybenzyl chloride (824-94-2)

p-methoxybenzylmagnesium chloride

n-propylmagnesium iodide

2-bromo-1, 1-di-p-methoxyphenylethane

trans-4,4'-Dimethoxystilbene, trans-Stilbene, 4,4'-dimethoxy- (15638-14-9)

4,4'-dimethoxybibenzyl

4,4'-Dimethoxystilbene

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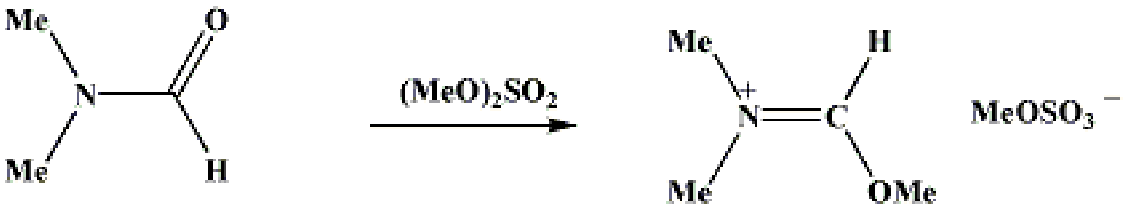
Organic Syntheses, CV 5, 431

6-(DIMETHYLAMINO)FULVENE



Submitted by K. Hafner, K. H. Vöpel, G. Ploss, and C. König[1].
Checked by S. S. Olin and Ronald Breslow.

1. Procedure

A. *N,N-Dimethylformamide-dimethyl sulfate complex*. In a 500-ml. four-necked flask equipped with mechanical stirrer, reflux condenser with calcium chloride drying tube, dropping funnel, and thermometer is placed 73 g. (1.0 mole) of dimethylformamide, and 126 g. (1.0 mole) of dimethyl sulfate is added dropwise with stirring at 50–60° (Note 1). After the addition is complete, the mixture is heated for another 2 hours at 70–80°. The dimethylformamide complex forms as a viscous, colorless or pale yellow ether-insoluble oil.

B. *6-(Dimethylamino)fulvene*. A 1-l. four-necked flask is equipped with mechanical stirrer, dropping funnel with calcium chloride drying tube, thermometer, and nitrogen delivery apparatus (Note 2). The flask is flushed with dry nitrogen, and in it is placed 1.0 mole of cyclopentadienylsodium[2] in 700 ml. of tetrahydrofuran (Note 3). The dimethylformamide-dimethyl sulfate complex prepared above is transferred to the dropping funnel and added slowly with stirring under nitrogen to the cyclopentadienylsodium at −10° (ice-salt bath). During the addition the temperature is kept below −5°. After the addition is complete, the mixture is stirred at 20° for 2 hours. The solution is filtered (with suction) from the precipitated sodium methyl sulfate, which is washed with another 200 ml. of tetrahydrofuran, and the combined tetrahydrofuran solutions are concentrated under reduced pressure. The residue is a dark brown oil which solidifies on cooling.

The crude product is crystallized after treatment with activated carbon from *ca.* 1.5 l. of petroleum ether (b.p. 60–80°) or 800 ml. of cyclohexane. From the orange-yellow

solution 84 g. (69%) of 6-(dimethylamino)fulvene separates in yellow leaflets, m.p. 67–68° (Note 4). Concentration of the filtrate and further recrystallization of the residue from petroleum ether or cyclohexane gives an additional 8 g. of product. The combined yield is 92 g. (76%).

2. Notes

1. Dimethylformamide and dimethyl sulfate must be purified by distillation in the absence of moisture.

2. The nitrogen delivery apparatus has been completely described.[2]

3. Air and moisture must be carefully excluded from the reactants during the course of this preparation.

4. 6-(Dimethylamino)fulvene is light-sensitive and is stored in brown bottles.

3. Discussion

N,N-Dimethylaminoethoxymethylium fluoborate[3] can be used instead of N,N-dimethylaminomethoxymethylium methyl sulfate[4] to prepare 6-(dimethylamino) fulvene.[5] The same fulvene is also obtained from the condensation of cyclopentadiene with diethoxy(dimethylamino) methane.[6]

4. Merits of the Preparation

This procedure illustrates formylation by N,N-dimethylaminomethoxymethylium methyl sulfate, a compound which can be produced readily by reaction of easily available materials. 6-(Dimethylamino)fulvene is a useful intermediate for the synthesis of various fused-ring nonbenzenoid aromatic compounds.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

N,N-Dimethylformamide-dimethyl sulfate complex

dimethylformamide-dimethyl sulfate complex

N,N-dimethylaminomethoxymethylium methyl sulfate

nitrogen (7727-37-9)

dimethyl sulfate (77-78-1)

sodium methyl sulfate (512-42-5)

cyclohexane (110-82-7)

carbon (7782-42-5)

Tetrahydrofuran (109-99-9)

dimethylformamide (68-12-2)

CYCLOPENTADIENE (542-92-7)

6-(Dimethylamino)fulvene (696-68-4)

cyclopentadienylsodium

N,N-Dimethylaminoethoxymethylium fluoborate

diethoxy(dimethylamino) methane (1188-33-6)

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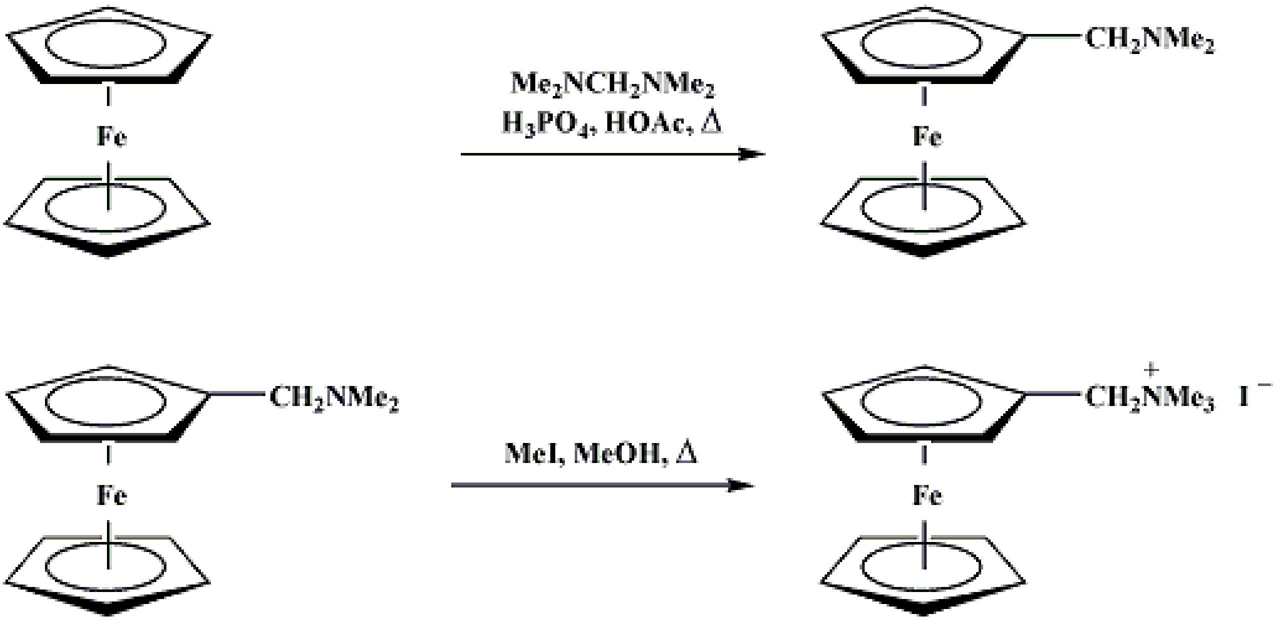
Organic Syntheses, CV 5, 434

N,N-DIMETHYLAMINOMETHYLFERROCENE METHIODIDE

[Iron, cyclopentadienyl[(dimethylaminomethyl)cyclopentadienyl]-, methiodid]



Submitted by Daniel Lednicer and Charles R. Hauser[1].
Checked by B. C. McKusick, W. A. Sheppard, R. D. Vest, and H. F. Mower.

1. Procedure

Caution! Bis(dimethylamino) methane is a potent lachrymator, so it should be handled only in a hood.

Ferrocene (46.4 g., 0.250 mole) (Note 1) is added to a well-stirred solution of 43.2 g. (0.422 mole) of bis(dimethylamino)-methane (Note 2) and 43.2 g. of phosphoric acid in 400 ml. of acetic acid in a 2-l. three-necked round-bottomed flask equipped with a condenser, a nitrogen inlet, and a mechanical stirrer (Note 3). The resulting suspension is heated on a steam bath under a slow stream of nitrogen (Note 4) for 5 hours (Note 5). The reaction mixture, a dark-amber solution, is allowed to cool to room temperature and is diluted with 550 ml. of water. The unreacted ferrocene is removed by extracting the solution with three 325-ml. portions of ether. The aqueous solution is then cooled in ice water and made alkaline by the addition of 245 g. of sodium hydroxide pellets. The tertiary amine separates from the alkaline solution as an oil in the presence of some black tar (Note 6). The mixture is extracted with three 500-ml. portions of ether. The organic solution is washed with water and dried over sodium sulfate. Crude dimethylaminomethylferrocene is obtained as a dark-red mobile liquid when the solvent is removed at the water pump (Note 7).

To a gently swirled solution of the crude amine in 54 ml. of methanol is added 54 ml. (123 g., 0.87 mole) of methyl iodide. The solution is heated on a steam bath for 5 minutes and cooled to

room temperature, and 800 ml. of ether is added. The methiodide, which separates as an oil, crystallizes on being scratched. The solid is collected on a Büchner funnel, washed with ether, and dried at 20–50 mm. for several hours at room temperature to yield 65–78 g. (68–81%; (Note 8)) of N,N-dimethylaminomethylferrocene methiodide as an orange powder, m.p. 200° (dec.) (Note 9).

2. Notes

1. The ferrocene may be prepared by Wilkinson's procedures[2] or it may be purchased from Matheson, Coleman and Bell, East Rutherford, New Jersey, and other companies.
2. The amine, under the name N,N,N',N'-tetramethylmethylenediamine, may be purchased from Ames Laboratories, South Norwalk, Connecticut. The checkers prepared it by the following procedure. A solution of 60.7 g. (0.75 mole) of 37% aqueous formaldehyde solution is placed in an 800-ml. beaker equipped with a mechanical stirrer and thermometer, and cooled in an ice bath. Two hundred seventy-one grams (1.50 moles) of a 25% aqueous solution of dimethylamine is added to this solution at a rate such that the reaction temperature is kept below 15°. The solution is stirred for 30 minutes after the addition is complete, and potassium hydroxide pellets (approximately 150 g.) are added in portions until the reaction mixture separates into two layers. The upper layer is separated, dried over potassium hydroxide pellets overnight, and distilled to give 59–64 g. (77–83%) of bis (dimethylamino) methane, b.p. 83–84°.[3]
3. The mixing of the amine and acids is exothermic. It is necessary to add the amine dropwise to the solution of acids with stirring and cooling in an ice bath.
4. Since ferrocene and many of its derivatives are easily oxidized by air in the presence of acids, nitrogen is passed in at a rate sufficient to exclude air from the system.
5. It was found that the reaction is essentially complete after 5 hours. Further heating does not affect the yield.
6. The checkers found that the solution turned into a gel after the addition of sodium hydroxide. They obtained satisfactory results by adding 200 ml. of water to the gel, which made it fluid enough to be extractable with ether.
7. Distillation of the tertiary amine before methiodide formation does not significantly affect the yield or purity of the quaternary salt. The amine boils at 91–92°/0.45 mm.
8. The submitters report yields as high as 89%.
9. The melting point of this compound is ill-defined by reason of considerable darkening and shrinking that start at 175°. The product thus obtained is sufficiently pure for use in further reactions.[4]

3. Discussion

This procedure is based on the method of Lindsay and Hauser[3] as modified slightly by Osgerby and Pauson.[5] N,N-dimethylaminomethylferrocene methiodide has also been prepared by heating formylferrocene with dimethylamine and hydrogen in the presence of Raney nickel catalyst to give dimethylaminomethylferrocene, which was quaternized with methyl iodide.[6]

Essentially the present procedure converted 1-methylindole to 1-methyl-3-(N,N-dimethylaminomethyl)indole[7] and α-methylstyrene to α-(N,N-dimethylaminoethyl)styrene.[8]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 578
- Org. Syn. Coll. Vol. 5, 621

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Ferrocene

N,N-Dimethylaminomethylferrocene methiodide

Iron, cyclopentadienyl[(dimethylaminomethyl)cyclopentadienyl]-, methiodid

dimethylaminomethylferrocene

formylferrocene

acetic acid (64-19-7)

methanol (67-56-1)

ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

formaldehyde (630-08-0)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

Raney nickel (7440-02-0)

potassium hydroxide (1310-58-3)

phosphoric acid (7664-38-2)

Methyl iodide (74-88-4)

dimethylamine (124-40-3)

α-methylstyrene (98-83-9)

Bis(dimethylamino) methane, bis (dimethylamino) methane, bis(dimethylamino)-methane, N,N,N',N'-tetramethylmethylenediamine (51-80-9)

1-Methylindole (603-76-9)

1-methyl-3-(N,N-dimethylaminomethyl)indole

α-(N,N-dimethylaminoethyl)styrene

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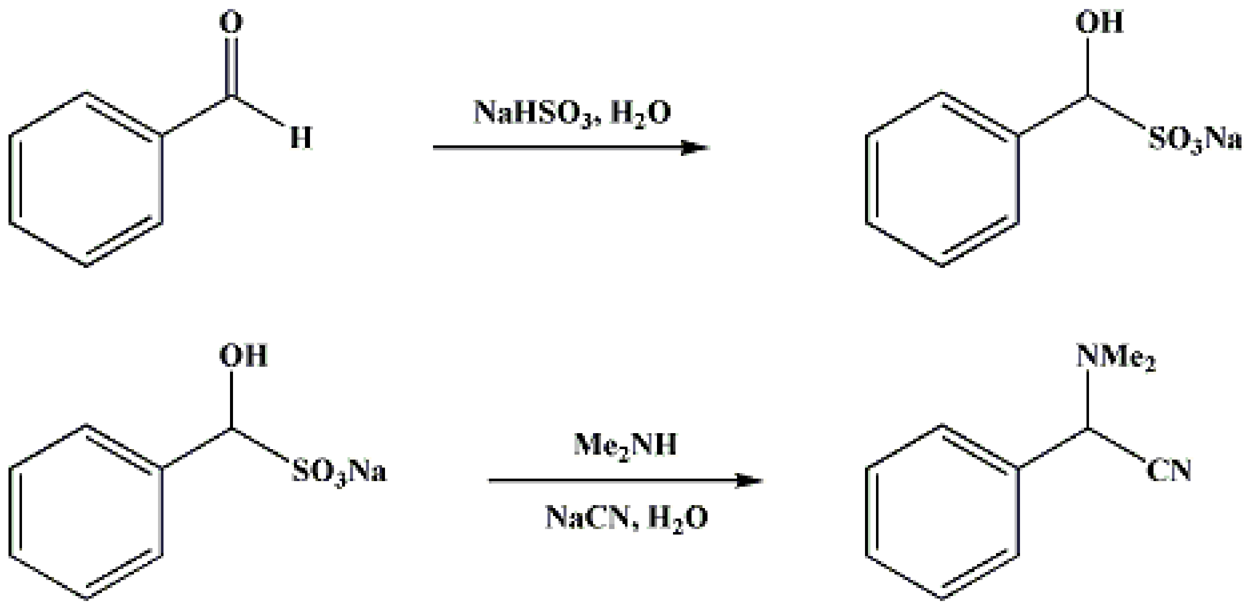
Organic Syntheses, CV 5, 437

α-(N,N-DIMETHYLAMINO)PHENYLACETONITRILE

[Glycinonitrile, N,N-dimethyl-2-phenyl-]



Submitted by Harold M. Taylor and Charles R. Hauser[1].
Checked by W. Bruce Kover and John D. Roberts.

1. Procedure

A mixture of 1.5 l. of water and 624 g. (6.00 moles) of sodium bisulfite in a 5-l. beaker equipped with a mechanical stirrer is stirred until solution is complete. Benzaldehyde (Note 1) (636 g., 6.00 moles) is added and the mixture is stirred for 20 minutes, during which time a slurry of the benzaldehyde-bisulfite addition product is formed. A 25% aqueous solution of dimethylamine (1100 g.) containing 275 g. (6.13 moles) of the amine is run in, and stirring is continued as most of the addition compound dissolves. The beaker is immersed in an ice bath, and 294 g. (6.00 moles) of sodium cyanide *(Caution! Toxic)* is added over a period of 20–25 minutes.

The ice bath is removed after addition of the sodium cyanide, and the mixture is stirred for 4 hours. The organic layer is separated, and the aqueous layer is extracted with three 500-ml. portions of ether. The combined ethereal extracts and organic layer are washed with two 100-ml. portions of cold water and dried over anhydrous magnesium sulfate. The ethereal solution is filtered, and the ether is removed at atmospheric pressure. The residue is transferred to a vacuum distillation system and distilled under reduced pressure *(Caution! See (Note 2))*. The yield of α-(N,N-dimethylamino) phenylacetonitrile boiling at 88–90°/1.9–2.1 mm. is 842–844 g. (87–88%) (Note 3) and (Note 4).

2. Notes

1. Eastman Kodak benzaldehyde (white label grade) was used without further purification.
2. Occasionally the odor of hydrogen cyanide can be detected during the distillation, even when a trap filled with sodium hydroxide pellets precedes the usual trap cooled in dry ice and acetone to protect the pump. For safety, the vacuum pump should be placed in a hood, or provision should be made for the pump exhaust to be vented into a hood or out-of-doors during the distillation.
3. Anhydrous dimethylamine has been used by the submitters in a slightly different procedure to give yields up to 95% of the theory.
4. The checkers carried out the preparation with one-half of the specified quantities without any decrease in the yield.

3. Discussion

The procedure described above is a modification of that of Hauser, Taylor, and Ledford[2] and of Luten[3] which avoids use of anhydrous dimethylamine. It is related to the procedure of Goodson and Christopher[4] that employs benzaldehyde, aqueous dimethylamine hydrochloride, and potassium cyanide.

The product can also be prepared from benzaldehyde, dimethylamine, and potassium cyanide in cold acetic acid and aqueous ethanol.[5]

4. Merits of the Preparation

The method can be used to prepare a number of α-aminonitriles from aliphatic or aromatic aldehydes and ketones and secondary aliphatic amines.[6]

The nitrile group of α-(N,N-dimethylamino)phenylacetonitrile can generally be replaced by an alkyl or aryl group of a Grignard reagent to form the corresponding tertiary amines.[4,7] The α-hydrogen of the aminonitrile can be alkylated,[2,7] and the resulting alkylation product can be converted to enamines[2] or to ketones.[7]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

acetic acid (64-19-7)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium cyanide (143-33-9)

hydrogen cyanide (74-90-8)

potassium cyanide (151-50-8)

sodium bisulfite (7631-90-5)

benzaldehyde (100-52-7)

acetone (67-64-1)

dimethylamine hydrochloride (506-59-2)

magnesium sulfate (7487-88-9)

dimethylamine (124-40-3)

Glycinonitrile, N,N-dimethyl-2-phenyl-, α-(N,N-DIMETHYLAMINO)PHENYLACETONITRILE (30123-97-8)

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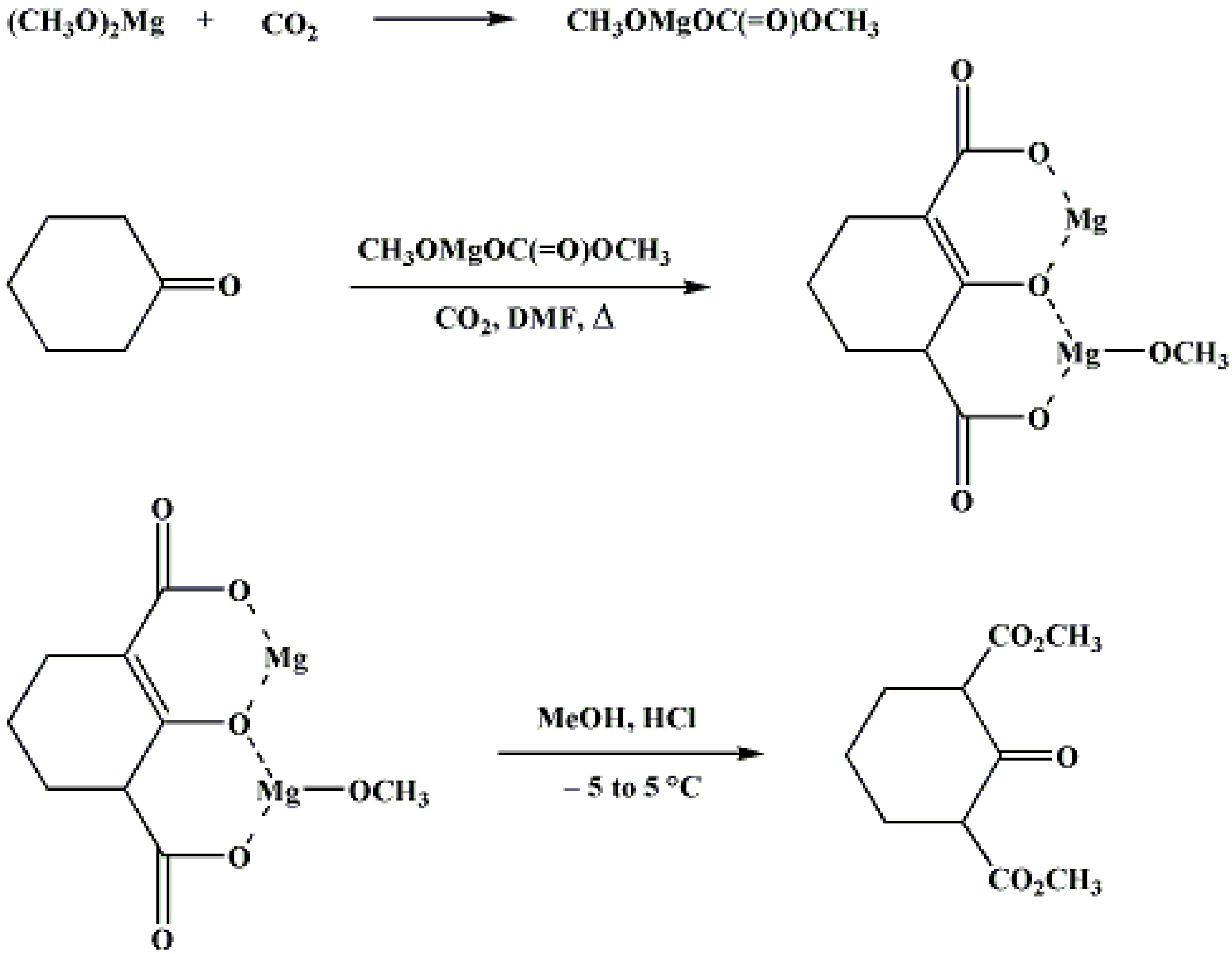
Organic Syntheses, CV 5, 439

DIMETHYL CYCLOHEXANONE-2,6-DICARBOXYLATE

[Cyclohexanone-2,6-dicarboxylic acid, dimethyl ester]



Submitted by S. N. Balasubrahmanyam and M. Balasubramanian[1].
Checked by Frederick J. Sauter and Herbert O. House.

1. Procedure

Caution! Since hydrogen is liberated in the first step of this reaction, it should be conducted in a hood. A dry 2-l. three-necked flask is fitted with a Trubore mechanical stirrer, an Allihn condenser, and a 1-l. pressure-equalizing dropping funnel, the top of which is fitted with a gas inlet tube. After 40.0 g. (1.64 g. atoms) of clean, dry magnesium ribbon (Note 1) has been placed in the flask, the system is flushed with nitrogen and 600 ml. of anhydrous methanol (Note 2) is added. As soon as the vigorous reaction begins, the nitrogen flow is stopped; if necessary, the reaction may be moderated by external cooling with wet towels. When the hydrogen evolution has ceased, a slow stream of nitrogen is passed through the reaction system and the condenser is replaced by a total condensation-partial take-off distillation head. The nitrogen flow is stopped, and the bulk of the methanol is distilled from the solution under reduced pressure (Note 3) with stirring while

the reaction flask is heated to 50–55° with a water bath. This distillation is stopped when stirring of the pasty suspension of magnesium methoxide is no longer practical. Nitrogen is readmitted to the system, and the outlet from the distillation head is attached to a small trap containing mineral oil so that the volume of gas escaping from the reaction system can be estimated. Anhydrous dimethylformamide (700 ml.; (Note 4)) is added to the reaction flask, and the resulting suspension is stirred vigorously while a stream of anhydrous carbon dioxide (Note 5) is passed into the reaction vessel through the gas inlet tube attached to the dropping funnel. The dissolution of the carbon dioxide is accompanied by an exothermic reaction with the suspended magnesium methoxide to form a solution. When the absorption of carbon dioxide has stopped (Note 6), the colorless solution is heated with a mantle under a slow stream of anhydrous carbon dioxide gas until the temperature of the liquid distilling from the flask reaches 140°, indicating that the residual methanol has been removed from the reaction mixture. The flow of carbon dioxide is stopped, and a slow stream of nitrogen is passed through the system while the resulting solution (Note 7) is cooled below 100° with a water bath. Cyclohexanone (20.0 g., 0.204 mole) (Note 8) is added to the reaction mixture, and the solution is heated under reflux for 2 hours while a slow stream of nitrogen (2–3 bubbles per second) is passed over the reaction mixture. The resulting solution is cooled first to room temperature with a water bath and then to –5° with a dry ice-acetone bath (Note 9).

Meanwhile, 700 ml. of anhydrous methanol is placed in a 2-l. flask fitted with a gas inlet tube extending approximately 5 mm. below the surface of the methanol and a calcium chloride tube to protect the contents of the flask from atmospheric moisture. The methanol is cooled with an external cooling bath prepared from ice and calcium chloride (Note 10) and saturated with anhydrous hydrogen chloride (Note 10) (290–300 g. of hydrogen chloride is required). This solution is transferred to the dropping funnel by means of a gooseneck adapter and the methanolic hydrogen chloride solution is then added, dropwise and with stirring, to the reaction flask, the temperature of the reaction being maintained at 0° ± 5° by means of a cooling bath. This addition is accompanied by the vigorous evolution of carbon dioxide and the separation of a white solid. After the addition is complete, the reaction mixture is allowed to stand overnight at room temperature and then the bulk of the methanol is removed from the solution by distillation under reduced pressure with stirring. During the distillation the temperature of the reaction mixture is kept below 55°. The remaining suspension is poured into a 4-l. beaker containing 1 kg. of crushed ice. The crude product separates as shiny white flakes which are collected on a filter and washed with water. A small second crop of the crude material may be obtained by cooling the aqueous filtrates to 0° overnight. The total crude product (25–26 g.) is dissolved in 250 ml. of boiling methanol, and this solution is concentrated to 125–150 ml. and allowed to cool. The keto diester separates as flat white needles, m.p. 128–132° (Note 11), yield 19.3–19.7 g. (44–45%). Concentration of the mother liquors affords an additional 2.2– 2.5 g. of crude product, m.p. 122–128° (Note 11).

2. Notes

1. Magnesium ribbon is conveniently cleaned by immersion in aqueous 10% hydrochloric acid, rinsing the ribbon with distilled water and with acetone, and

drying it in an oven at 120°.

2. To ensure a rapid reaction with the magnesium, the methanol should be heated to reflux over magnesium methoxide for 12 hours and then distilled and transferred to the reaction vessel with a siphon or a large pipet. If necessary, a crystal of iodine may be added to initiate the reaction of methanol with magnesium.

3. If a water aspirator is used, a calcium chloride tube or tower should be included in the line connecting the distillation head and the aspirator.

4. The dimethylformamide may be purified by distillation at atmospheric pressure. The checkers distilled material purchased from the J. T. Baker Company and used the fraction collected at 153–155°.

5. Carbon dioxide obtained from a cylinder of the compressed gas was passed through a tube packed with calcium chloride and either activated silica gel or Drierite (containing an indicator) to remove water.

6. If the gas flow is turned off while carbon dioxide is still being absorbed, the pressure inside the flask falls below atmospheric pressure. This pressure change is readily observed with the mineral oil-filled trap fitted to the gas exit tube of the system.

7. The submitters found that this solution of methyl magnesium carbonate in dimethylformamide could be stored for long periods in a well-stoppered bottle without loss of potency.

8. The checkers employed cyclohexanone purchased from Eastman Organic Chemicals and distilled before use, b.p. 155–157°. The ratio of cyclohexanone to methylmagnesium carbonate is fairly critical; a proportion of ketone larger than the ratio 1:8 ketone:magnesium salt specified yields a pasty product presumably contaminated with monocarboxylated material. A smaller proportion of ketone lowers the yield.

9. The checkers measured the temperature of this solution by sliding a thermometer through the distillation head so that the thermometer bulb was immersed in the reaction mixture.

10. The checkers used a cooling bath prepared from ice and sodium chloride and dried the hydrogen chloride obtained from a compressed-gas cylinder by passing the gas through a trap filled with concentrated sulfuric acid.

11. The submitters reported that the addition of eight volumes of warm (35°) water to a warm solution of the keto diester in ten volumes of methanol followed by gradual cooling to 0° separated, on one occasion, a product, m.p. 142–143°, which was presumably one pure isomer. The checkers found that the product recrystallized readily from methanol, aqueous methanol, or benzene in good crystalline form but invariably with a wide melting range (129–136°) which varied with the rate of heating. It would appear that the checkers invariably obtained the product as a mixture of two or more of the three readily interconvertible forms: keto *cis*-diester, keto *trans*-diester, and enol diester. The thin-layer chromatogram of the recrystallized product, determined on a plate coated with silica gel and eluted with a mixture of carbon tetrachloride and ethyl acetate (1:1 v/v), indicated the absence of monocarbomethoxycyclohexanone in the product. Also, the elemental composition of the product and the mass spectrum of the product are consistent with the idea that the product contains only stereoisomeric and tautomeric forms. The mass spectrum exhibits a molecular ion peak at *m/e* 214 with abundant fragment peaks at *m/e* 182,

154, 126, 95, 67, and 55 but exhibits a peak of relatively low abundance at *m/e* 156, the mass of the molecular ion derived from 2-carbomethoxycyclohexanone. An ethanol solution of the recrystallized keto diester product initially exhibits an ultraviolet maximum at 255 m• with a molecular extinction coefficient within the range 6000–11,000; on the addition of excess sodium hydroxide the ultraviolet maximum is shifted to 287.5 m• (ε 12,600). A chloroform solution of the recrystallized product has infrared absorption at 1750 (strong), 1712 (medium), 1675 (weak), and 1610 (weak) cm.$^{-1}$; an ethanol solution of the product, when treated with ferric chloride, gives no immediate color, but a brown color develops after the solution is allowed to stand for 10 to 20 minutes. These observations suggest that the crystalline product obtained in this preparation is primarily a mixture of the *cis*- and *trans*-isomers of the keto tautomer.

3. Discussion

Dimethyl cyclohexanone-2, 6-dicarboxylate has been prepared by the alkylation of dimethyl acetonedicarboxylate with trimethylene dibromide[2] and by the carboxylation of cyclohexanone.[3] The present preparation gives a general procedure for carboxylation of active methylene compounds.[3,4,5,6] The method has been used for carboxylation of methylene groups activated by ketones,[3,4,5] nitro groups,[3,4] and certain amide functions.[6] The success of the procedure is attributed to the formation of a magnesium enolate which is stabilized by chelation with an adjacent carboxylate anion.[4,6] In certain cases[3,6] the magnesium enolate has been alkylated in the original reaction mixture, thereby avoiding the necessity for isolating an intermediate ester. Although the present example illustrates the fact that when two equivalent active methylene groups are present both positions may be carboxylated, the submitters were unsuccessful in obtaining a pure keto diester when the procedure was applied to cyclopentanone.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Drierite

activated silica gel

ethanol (64-17-5)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrogen chloride, hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ethyl acetate (141-78-6)

methanol (67-56-1)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

magnesium, magnesium ribbon (7439-95-4)

Cyclohexanone (108-94-1)

sodium chloride (7647-14-5)

trimethylene dibromide (109-64-8)

carbon tetrachloride (56-23-5)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

iodine (7553-56-2)

acetone (67-64-1)

ferric chloride (7705-08-0)

Cyclopentanone (120-92-3)

magnesium methoxide

methylene (2465-56-7)

dimethylformamide (68-12-2)

Dimethyl cyclohexanone-2,6-dicarboxylate, Cyclohexanone-2,6-dicarboxylic acid, dimethyl ester, Dimethyl cyclohexanone-2, 6-dicarboxylate (25928-05-6)

methyl magnesium carbonate

methylmagnesium carbonate

monocarbomethoxycyclohexanone, 2-carbomethoxycyclohexanone (41302-34-5)

dimethyl acetonedicarboxylate

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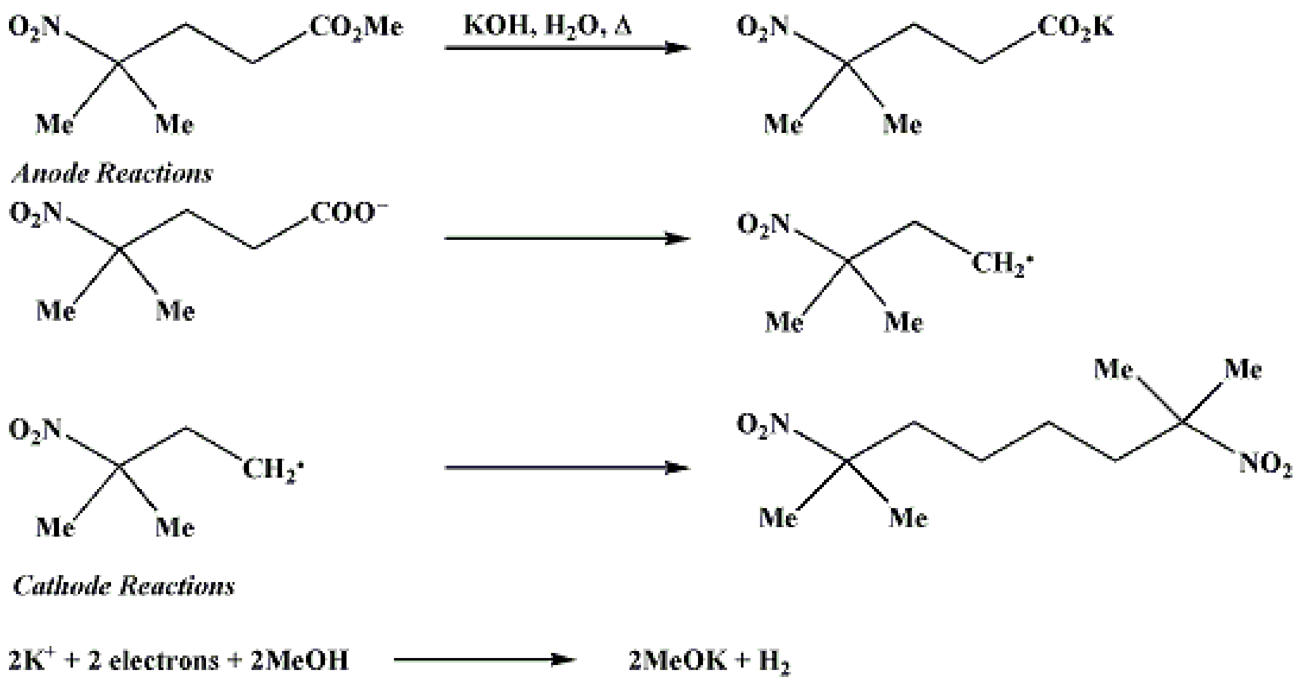
Organic Syntheses, CV 5, 445

2,7-DIMETHYL-2,7-DINITROÖCTANE

[Octane, 2,7-dimethyl-2,7-dinitro-]



Submitted by W. H. Sharkey and C. M. Langkammerer[1].
Checked by Masaaki Takahashi, Marjorie C. Caserio, and John D. Roberts.

1. Procedure

A. *4-Methyl-4-nitrovaleric acid*. In a 2-l. three-necked flask equipped with a stirrer and reflux condenser is placed a solution prepared from 118 g. (1.78 moles) of 85% potassium hydroxide pellets and 500 ml. of water. A thermometer may be so placed in the third neck that the bulb extends below the surface of the solution. To this solution is added 300 g. (1.71 moles) of methyl 4-methyl-4-nitrovalerate.[2] The mixture is stirred and gently heated (Note 1) and (Note 2). After hydrolysis has started, as indicated by changes in appearance of the hazy reaction mixture, the external source of heat is removed. The reaction is complete when the cloudy mixture has changed to a clear solution. This requires about 20–25 minutes (Note 3).

The reaction mixture is cooled to room temperature, and a saturated solution of potassium permanganate is added in an amount sufficient for a violet color to persist for about 1 minute before turning green (Note 4). About 100–110 ml. is required. Manganese dioxide is removed by filtration, and the filtrate is extracted with methylene chloride to remove non-acidic organic material. The aqueous layer is acidified with 18% hydrochloric acid, whereupon a pale yellow or green oil separates as a bottom layer. The oil is removed, and the aqueous layer is washed with methylene chloride. The washings are added to the oil, and the combined product is dried with anhydrous magnesium sulfate. Methylene chloride is removed by distillation, and the residual oil is distilled under reduced pressure through a 6-in. Vigreux column (Note 5). The fraction boiling at 125–135° (0.9–1.5 mm.) amounts to 217–225 g. (79–82%) and is a colorless oil that crystallizes on standing or when seeded to give a solid with a melting point of approximately 35–45°. This fraction is redistilled through a 24-in. spinning-band column and gives 166–180 g. (60–65%) of colorless 4-methyl-4-

nitrovaleric acid, b.p. 122–124°/0.70–0.90 mm., m.p. 45–46° (Note 6).

B. *2,7-Dimethyl-2,7-dinitroöctane*. A 200-mm. desiccator is adapted for use as an electrolysis cell. A lid is prepared from a glass plate ground to fit the desiccator; holes are bored in the lid to accommodate electrodes, a thermometer, and a stirrer, and to provide an opening for making additions to the cathode compartment. The cathode (Note 7) is placed in a porous ceramic cup having outside dimensions 4 in. deep, 6 in. long, and 2 in. wide (Note 8). This cup is placed on the glazed ceramic plate of the desiccator under the holes cut in the lid for the cathode and for making additions. The glazed ceramic plate is notched so that it can be slipped down over the supports in the bottom of the desiccator. The notches should be large enough for the ceramic plate to be about halfway between its normal position and the bottom of the desiccator (Note 9). The cathode is a 26-gauge stainless-steel plate 3 in. square (Note 10), and the anode consists of two platinum plates each 0.01 in. thick and 3 in. square (Note 11) placed as close as possible, one on either side, to the ceramic cup without touching the sides of the cup.

A solution made by dissolving 161 g. (1 mole) of 4-methyl-4-nitrovaleric acid and 33.0 g. (0.5 mole) of potassium hydroxide in 2.7 l. of methanol is added to the cell. The ceramic cup is filled with 200 ml. of 2*N* potassium hydroxide in methanol. The cell contents are cooled to 20° (Note 12), and current is passed through the solution (Note 13). When the current is turned on, vigorous evolution of hydrogen takes place inside the porous cup. Potassium hydroxide (2*N*) in methanol is added as needed to maintain the original volume inside the cup (Note 14). Carbon dioxide is evolved at the anodes. After about 5 hours, white crystals of the dinitroöctane form in the anode solution. As electrolysis proceeds, the resistance of the cell increases, and after several hours the cell is operated at 3–5 amperes and 60–80 volts. If a current of 3–5 amperes cannot be maintained, it is desirable to add 2*N* potassium hydroxide in methanol to the anode compartment (Note 15) and (Note 16). After 8 hours of operation, the current is shut off, the ceramic cup removed and cleaned, and the anode solution cooled to about −30°. The anode solution is filtered to remove crystals of 2,7-dimethyl-2,7-dinitroöctane. The yield of dry product, m.p. 98–100°, amounts to 50–65.5 g. (43–56%), which is sufficiently pure for most uses (Note 17). One recrystallization from methanol (Note 18) gives pure 2,7-dimethyl-2,7-dinitroöctane, m.p. 100–101° (lit.[3] 101.5–102°).

2. Notes

1. If stirring is not used, hydrolysis does not start until the reaction mixture is heated almost to the reflux temperature. Under these conditions the reaction, which is exothermic, proceeds so rapidly that the reflux condenser is flooded.
2. Although no explosions have yet occurred, it is advisable to conduct this reaction behind a shield. The hydrolysis, once started, proceeds quite rapidly.
3. The time required varies with the initial temperature of the hydrolysis solution. With warm solutions, e.g., freshly made potassium hydroxide solution, external heating is not needed. With such a solution, the checkers found that a cloudy mixture having an initial internal temperature of 40° became clear within 2–5 minutes of mixing and during this time the temperature rose to 70°. Stirring was continued for 20 minutes to ensure complete hydrolysis.
4. Addition of potassium permanganate removes colored impurities that otherwise persist through subsequent distillations of the acid. The maximum concentration of potassium permanganate in water at room temperature is about 5%. It may be more convenient to use a concentrated solution of sodium permanganate, which is very soluble in water. However, the end point is difficult to observe with sodium permanganate.
5. During this first distillation, nitrogen oxides are evolved in appreciable amounts. It is suggested this operation be done behind a shield in a well-ventilated area. A trap cooled with a mixture of solid carbon dioxide and acetone or with liquid air should be inserted between the

column and the vacuum pump. Pumps used in this distillation did not appear to suffer corrosion damage. A dry oil was used and changed after each distillation.
6. It may be necessary in this second distillation to apply a source of heat to the fraction-collecting system to prevent crystallization of the product prior to entry of the distillate into the receivers.
7. The cathode is the electrode connected to the negative terminal of the current source.
8. A satisfactory alumina cup may be purchased from the Norton Company, Worcester, Mass., Catalog No. 44805, RA-98.
9. This is necessary because the top of the porous cup must be below the lip of the desiccator. The volume of the desiccator up to the top of the porous cup should be 4 l.
10. The considerable heat generated inside the cup leads to rapid evaporation of the methanol with which the cup is filled. The cell can be operated by constant replenishment of methanol. However, loss of methanol can be minimized by use of a water-cooled cathode. Such an electrode is conveniently prepared from two 3-in.-square stainless-steel plates and a strip of stainless steel about 0.25 in. wide, which are welded to form a stainless-steel box. Nipples serving as water inlet and outlet are welded to the top of the box.
11. The 3-in.-square platinum plates are welded to a heavy platinum wire that protrudes through one of the holes cut in the glass lid. Heavy copper wire (No. 10) is used to connect the electrodes to the source of current.
12. This temperature is easily maintained by surrounding the cell with a methanol bath cooled with solid carbon dioxide. About 100 lb. of solid carbon dioxide is required for 8 hours' operation. Yields are severely reduced if the methanol is allowed to boil. Temperatures lower than 20° can be used but are less satisfactory.
13. The initial current is usually 6–8 amperes at 50–60 volts. The resistance of the cell constantly changes because of depletion of electrolyte and deposition of potassium methoxide in the pores of the ceramic cup. The preferred source of current is a rectifier capable of delivering 10–15 amperes at 30–90 volts. Lead storage batteries connected in series are also satisfactory but require frequent recharging.
14. In a typical run, 30 ml. of 2*N* potassium hydroxide in methanol was added at the end of each hour of operation. Total addition was 210 ml.
15. The amount added must be less than that required to bring the pH to 7. When the pH of the anode solution is greater than 7, undesirable reactions occur.
16. The checkers found that after 5.5 hours the current dropped below 3 amperes at 75 volts. Addition of 25 ml. of 2*N* potassium hydroxide in methanol to the anode solution increased the current to 6 amperes. Subsequent additions of 10–15 ml. of base were made approximately every 30 minutes. The total volume of base added was 80 ml.
17. Some unchanged 4-methyl-4-nitrovaleric acid can be recovered from the spent electrolysis solution by alkaline extraction followed by acidification and distillation of the water-insoluble oil. However, under ordinary circumstances, recovery of this material is not worth the effort expended.
18. About 500 ml. of refluxing methanol and 58 g. of crude product afford about 53 g. (95% recovery) of recrystallized material.

3. Discussion

2,7-Dimethyl-2,7-dinitroöctane has been prepared by nitration of 2,7-dimethyloctane.[3]

4. Merits of Preparation

Kolbe electrolysis is generally useful for the formation of hydrocarbons from monocarboxylic acids and for the preparation of many difunctional compounds as well. A specific illustration is the synthesis of esters of long-chain dicarboxylic acids from monoesters of appropriate dicarboxylic acids (see p. 463). A number of these syntheses are discussed by Fichter.[4] In the present preparation,

a two-compartment cell is employed to avoid, or at least greatly reduce, undesired reduction of the nitro group at the cathode. It seems likely that the procedure could be adapted to the preparation of other difunctional compounds containing groups that are easily reduced.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

methanol (67-56-1)

hydrogen (1333-74-0)

potassium permanganate (7722-64-7)

carbon dioxide (124-38-9)

acetone (67-64-1)

potassium hydroxide (1310-58-3)

manganese dioxide (1313-13-9)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

potassium methoxide (865-33-8)

2,7-dimethyloctane (1072-16-8)

methyl 4-methyl-4-nitrovalerate (16507-02-1)

Octane, 2,7-dimethyl-2,7-dinitro-, 2,7-Dimethyl-2,7-dinitrooctane (53684-51-8)

4-Methyl-4-nitrovaleric acid (32827-16-0)

sodium permanganate (10101-50-5)

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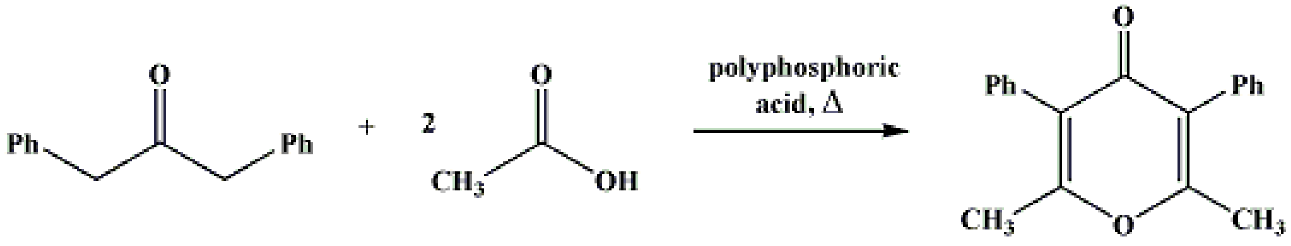
2,6-DIMETHYL-3,5-DIPHENYL-4*H*-PYRAN-4-ONE

[4*H*-Pyran-4-one, 2,6-dimethyl-3,5-diphenyl-]



Submitted by Thomas L. Emmick and Robert L. Letsinger[1].
Checked by Donald J. MacGregor and Peter Yates.

1. Procedure

A mixture of 400 g. of polyphosphoric acid and 250 ml. of glacial acetic acid is heated to reflux in a 2-l. round-bottomed flask equipped with a stirrer, reflux condenser, and thermometer. Dibenzyl ketone (42.0 g., 0.200 mole) (Note 1) is then added, and the reaction mixture is heated at reflux (130–135°) for 1.5 hours. The solution is cooled to 30° in an ice water bath, and 1 l. of water is added slowly with stirring. The brown precipitate which forms is collected by filtration, washed with 1 l. of water, and dissolved in 1 l. of hot benzene. The hot benzene solution is treated with 2 g. of activated carbon, filtered hot through a pad of diatomaceous earth, dried with 10 g. of magnesium sulfate, decanted from the magnesium sulfate, and concentrated to 500 ml. On addition of 450 ml. of hexane and cooling to 5–10°, tan crystals of the crude pyranone separate. Filtration affords 25–27 g. (45–49%) of product melting at 202–206°. For purification this material is dissolved in 500 ml. of hot benzene, treated with 1 g. of activated carbon as before, and precipitated from solution by the addition of 250 ml. of hexane and cooling of the mixture to 5–10°. On filtration 19–21 g. (34–38%) of 2,6-dimethyl-3,5-diphenyl-4*H*-pyran-4-one is obtained. This material melts sharply at 207–209° (Note 2). An additional quantity (3–4 g., 5–7%) of somewhat less pure product (m.p. 204–206°) may be recovered by evaporation of the filtrate and recrystallization of the residue from 200 ml. of benzene-hexane (50% benzene by volume).

2. Notes

1. For this preparation Matheson, Coleman and Bell practical grade dibenzyl ketone was recrystallized once from anhydrous ether at −70°. It melted at 33–34°. Practical grade dibenzyl ketone may be used directly; however, the yield of the pyranone is somewhat lower.
2. The corrected melting point is 209.5–210.0°. Melting points were obtained with a Fisher-Johns apparatus. The recrystallized sample retained a pale tan shade.

3. Discussion

This procedure is a modification of that of Letsinger and Jamison.[2] The pyranone has also been prepared by treatment of dibenzyl ketone with acetic anhydride-perchloric acid or acetyl chloride-aluminum chloride.[3]

4. Merits of the Preparation

This procedure represents a simple and unique route to certain pyran-4-ones. The reaction can be applied also to benzyl methyl ketone and diethyl ketone; the corresponding pyran-4-ones are obtained in yields of 48% and 26%, respectively.

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

polyphosphoric acid

acetic acid (64-19-7)

Benzene (71-43-2)

ether (60-29-7)

carbon (7782-42-5)

benzyl methyl ketone (103-79-7)

magnesium sulfate (7487-88-9)

dibenzyl ketone (102-04-5)

diethyl ketone (96-22-0)

benzene-hexane (1077-16-3)

hexane (110-54-3)

2,6-Dimethyl-3,5-diphenyl-4H-pyran-4-one, 4H-Pyran-4-one, 2,6-dimethyl-3,5-diphenyl- (33731-54-3)

acetic anhydride-perchloric acid

acetyl chloride-aluminum chloride

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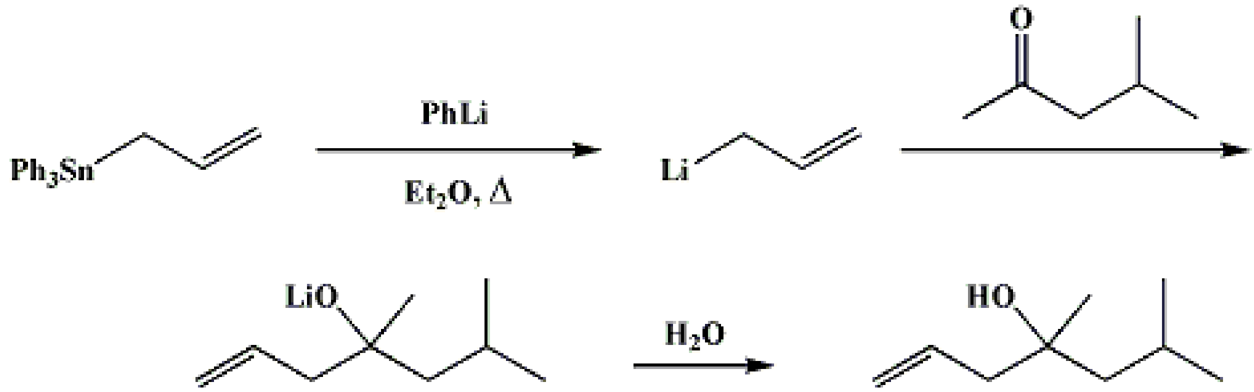
4,6-DIMETHYL-1-HEPTEN-4-OL

[1-Hepten-4-ol, 4,6-dimethyl-]



Submitted by Dietmar Seyferth and Michael A. Weiner[1].
Checked by Melvin S. Newman and Clifford Y. Peery.

1. Procedure

Caution! See. p. 976.

A solution of 50 g (0.127 mole) of allyltriphenyltin (Note 1) and (Note 2) in 200 ml. of diethyl ether (Note 3) is prepared in a 1-l. three-necked flask fitted with a reflux condenser, a motor-driven glass sleeve-type stirrer, nitrogen-inlet tube, and a 250-ml. dropping funnel with pressure-equalizing side arm. After the system has been flushed thoroughly with prepurified nitrogen, 113 ml. of a 1.13*N* solution of phenyllithium (0.127 mole) in diethyl ether (Note 4) is added rapidly to the stirred allyltriphenyltin solution. Precipitation of tetraphenyltin occurs immediately, and the reaction mixture is stirred for 30 minutes in an atmosphere of prepurified nitrogen. Through the dropping funnel is then added 12.0 g. (0.12 mole) of 4-methyl-2-pentanone (Note 5) in 25 ml. of diethyl ether at such a rate that moderate reflux is maintained. Subsequently the reaction mixture is refluxed for 1 hour, allowed to cool to room temperature, and hydrolyzed by adding 100 ml. of distilled water (Note 6). The solid tetraphenyltin is filtered (53.5 g. = 98% yield), and the filtrate is transferred to a separatory funnel. The aqueous layer is separated and extracted with three 30-ml. portions of ether. The ethereal extracts and the organic layer are combined and dried over anhydrous magnesium sulfate. After removal of the ether by distillation at atmospheric pressure, the residue is filtered through a sintered-glass funnel into a 250-ml. distilling flask and fractionally distilled at reduced pressure using a vacuum-jacketed Vigreux column equipped with a still head of the total-condensing, partial-takeoff type. 4,6-Dimethyl-1-hepten-4-ol, b.p. 70–71°/20 mm., n_D^{20} 1.4403, is obtained in 70–75% yield (12.0–12.8 g.) (Note 7).

2. Notes

1. Allyltriphenyltin is prepared as follows. To a 3-l. three-necked flask fitted with a reflux condenser, a motor-driven stirrer, nitrogen-inlet tube, and a 1-l. dropping funnel with pressure-equalizing side arm are added 50 g. (2.1 g. atom) of magnesium turnings and 800 ml. of diethyl ether (Mallinckrodt reagent grade). The dropping funnel is charged with a solution of 120 g. (1.0 mole) of allyl bromide (Eastman Kodak white label) and 250 g. (0.65 mole) of triphenyltin chloride (Metal Thermit Corporation) in 600 ml. of tetrahydrofuran (Electrochemicals Department, E. I. du Pont de Nemours and Company, Inc.) which has been freshly distilled from lithium aluminium hydride. This solution is added to the vigorously stirred, refluxing magnesium suspension during 7 hours. After the addition is complete, 500 ml. of dry benzene is added and the reaction mixture is refluxed overnight at 60°. It is then hydrolyzed by careful addition of 150 ml. of a saturated ammonium chloride solution. The organic phase is decanted from the solids, and the latter are washed twice with ether. The combined organic layer and ethereal extracts are evaporated at reduced pressure with the aid of a rotary evaporator. The solid residue is recrystallized from 350 ml. of ligroin. The yield of product, m.p. 73–74°, is 190–205 g. (75–80%). Allyltriphenyltin can also be prepared by using the reaction of preformed allylmagnesium bromide with triphenyltin chloride.[2] However, the submitters prefer the simpler procedure described above for large-scale preparations of allyltin compounds.

2. Tetraallyltin, triallylphenyltin, and diallyldiphenyltin may be used in place of allyltriphenyltin.

3. The diethyl ether used is Mallinckrodt reagent grade and is distilled from lithium aluminum hydride before use.

4. Ethereal phenyllithium, prepared from lithium and bromobenzene,[3] may be standardized by adding an aliquot to water and titrating with standard sulfuric acid.

5. The 4-methyl-2-pentanone used is Eastman Kodak white label grade.

6. The first few milliliters of water should be added dropwise.

7. The reported[4] physical constants for 4,6-dimethyl-1-hepten-4-ol are b.p. 68–69°/20 mm., n_D^{20} 1.4402.

3. Discussion

This procedure is essentially that reported previously.[5] 4,6-Dimethyl-1-hepten-4-ol has also been prepared by the reaction between allylmagnesium bromide and 4-methyl-2-pentanone,[4] by the treatment of magnesium with a mixture of allyl bromide and 4-methyl-2-pentanone,[6,7] and by the treatment of zinc with a mixture of allyl iodide and 4-methyl-2-pentanone.[8]

4. Merits of Preparation

The present synthesis of 4,6-dimethyl-1-hepten-4-ol is an example of the preparation and use of allyllithium. The same general procedure may be used to prepare vinyllithium from ether solutions of any of the compounds $(CH_2{=}CH)_nSn(C_6H_5)_{4-n}$ (n = 1–4),[9] and benzyllithium from any of the $(C_6H_5CH_2)_nSn(C_6H_5)_{4-n}$ (n=1–4) compounds.[10]

Allyllithium is of particular value in the preparation of allylmetal derivatives.[5] Allyllithium may also be prepared by transmetalation between phenyllithium and tetraallyltin[11] or by cleavage of allyl phenyl ether with lithium in tetrahydrofuran.[12]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ligroin

sulfuric acid (7664-93-9)

Benzene (71-43-2)

ether, diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

magnesium (7439-95-4)

Allyl bromide (106-95-6)

nitrogen (7727-37-9)

allyl iodide (556-56-9)

zinc (7440-66-6)

bromobenzene (108-86-1)

4-methyl-2-pentanone (108-10-1)

Phenyllithium (591-51-5)

lithium (7439-93-2)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride, lithium aluminium hydride (16853-85-3)

Allylmagnesium bromide (1730-25-2)

4,6-Dimethyl-1-hepten-4-ol, 1-Hepten-4-ol, 4,6-dimethyl- (32189-75-6)

Allyltriphenyltin (76-63-1)

tetraphenyltin (595-90-4)

triphenyltin chloride (639-58-7)

Tetraallyltin (7393-43-3)

triallylphenyltin

diallyldiphenyltin (10074-32-5)

Allyllithium

vinyllithium (917-57-7)

benzyllithium

allyl phenyl ether (1746-13-0)

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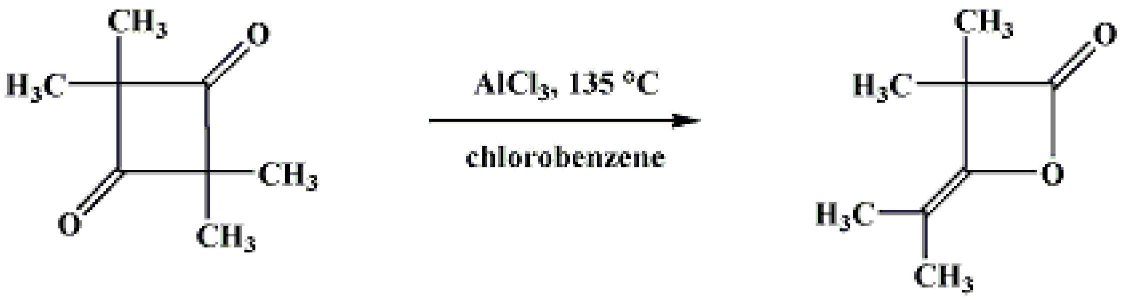
DIMETHYLKETENE β-LACTONE DIMER

[3-Pentenoic acid, 3-hydroxy-2,2,4-trimethyl-, β-lactone]



Submitted by Robert H. Hasek[1], R. Donald Clark[1], and Gerald L. Mayberry[2].
Checked by V. Boekelheide, J. Witte, and G. Singer.

1. Procedure

Caution! Dimethylketene β-lactone dimer is a mild but deceptively persistent lachrymator.

In a 500-ml. three-necked flask equipped with a thermometer, a mechanical stirrer, and a reflux condenser are placed 200 g. (1.43 moles) of tetramethyl-1,3-cyclobutanedione (Note 1) and 50 g. of chlorobenzene (Note 2). The mixture is heated to 135° with stirring while a total of 1.8 g. of reagent grade anhydrous aluminum chloride is added in 0.3-g. portions over a 3-hour period (Note 3). After the addition is complete, heating is continued for an additional 5 hours (Note 4).

The reaction mixture is then cooled to 35–40° and poured into a stirred solution of 230 g. of sodium chloride and 6.0 g. of sodium acetate in 600 ml. of water at 40°. The mixture is stirred for 15 minutes and then is transferred to a separatory funnel; the layers are separated, and the lower, aqueous layer is discarded. The crude product is distilled at reduced pressure through a stainless steel spinning-band column (Note 5). The yield of the β-lactone dimer of dimethylketene is 122–132 g. (61–67%); b.p. 69–71.5° (14 mm.) (Note 6). The product may be redistilled and the fraction boiling at 119.5–120° (150 mm.), n^{20}D 1.4380, collected.

2. Notes

1. Tetramethyl-1,3-cyclobutanedione is available from Eastman Organic Chemicals. It melts at 115–116° and is typically 99% pure by vapor-phase chromatography.
2. More highly chlorinated aromatic solvents such as 1,2,4-trichlorobenzene can be used with similar results.

3. No special drying precautions are required; however, traces of water can be conveniently removed before the catalyst is added by distilling a small portion of the solvent until cloudiness disappears. The checkers found that the distillation of part of the solvent as indicated was necessary in order to obtain satisfactory yields. When the catalyst is added incrementally, no appreciable exotherm is observed.
4. The isomerization is usually complete in 5 hours and can easily be followed by vapor-phase chromatography. (Heating periods up to 20 hours are not detrimental. The only failure among numerous preparations occurred when tetramethyl-1,3-cyclobutanedione contaminated with 4% of isobutyric acid was used. In case of partial conversion after 5 hours, additional increments (0.5 g.) of aluminum chloride should be added to complete the reaction.
5. The product may be distilled directly from the crude reaction mixture after addition of sodium acetate. The results are similar.
6. The distilled product is 99% pure by vapor-phase chromatography.

3. Discussion

The β-lactone dimer of dimethylketene can be prepared by pyrolysis of its polyester, which is formed by the base-catalyzed polymerization of dimethylketene.[3,4,5] In addition to the rearrangement of the normal dimer described above,[6] the direct dimerization of dimethylketene in the presence of aluminum chloride[3] or trialkyl phosphites[7] leads to the β-lactone dimer.

4. Merits of the Preparation

The β-lactone dimer of dimethylketene reacts with alcohols, phenols, mercaptans, and amines to form derivatives of 2,2,4-trimethyl-3-oxovaleric acid.[3] In this respect it is a more powerful acylating reagent than the normal dimer, tetramethyl-1,3-cyclobutanedione. The preparation of 2,2,4-trimethyl-3-oxovaleranilide, for example, is accomplished easily with the lactone dimer, but is extremely difficult with the normal dimer.[8]

In the presence of catalytic amounts of sodium methoxide, dimethylketene β-lactone dimer is polymerized at moderate temperature to a polyester.[3] At higher temperatures (above 100°), disproportionation to the cyclic trimer, hexamethyl-1.3,5-cyclohexanetrione, takes place.[9] Addition of a stoichiometric amount of sodium methoxide to the lactone dimer generates the sodium enolate of methyl 2,2,4-trimethyl-3-oxovalerate. This reaction provides a convenient entry into certain ester anion chemistry that formerly required the use of a strong base like tritylsodium.[10]

Although these reactions can be duplicated in most cases with the normal dimer of dimethylketene,[11] the more reactive lactone dimer is the preferred reagent. The liquid form of this dimer is convenient to handle. A distinct difference in behavior of the

dimethylketene dimers is noted when they are pyrolyzed. The normal dimer is dissociated at 600° to dimethylketene,[12] but the lactone dimer is decarboxylated almost quantitatively at 450° to tetramethylallene.[13]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 1103

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Dimethylketene β-lactone dimer

β-lactone dimer of dimethylketene

sodium enolate of methyl 2,2,4-trimethyl-3-oxovalerate

sodium acetate (127-09-3)

sodium chloride (7647-14-5)

sodium methoxide (124-41-4)

chlorobenzene (108-90-7)

aluminum chloride (3495-54-3)

tritylsodium (4303-71-3)

isobutyric acid (79-31-2)

1,2,4-trichlorobenzene (120-82-1)

tetramethyl-1,3-cyclobutanedione (933-52-8)

Dimethylketene (598-26-5)

3-Pentenoic acid, 3-hydroxy-2,2,4-trimethyl-, β-lactone (3173-79-3)

2,2,4-trimethyl-3-oxovaleranilide

hexamethyl-1.3,5-cyclohexanetrione (778-18-7)

tetramethylallene (1000-87-9)

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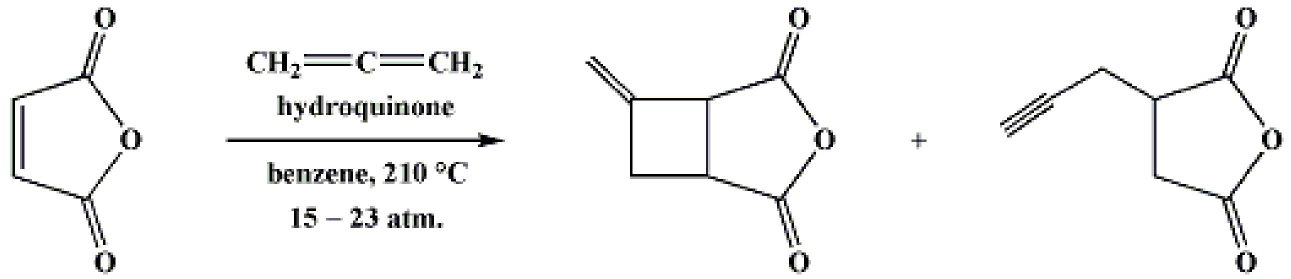
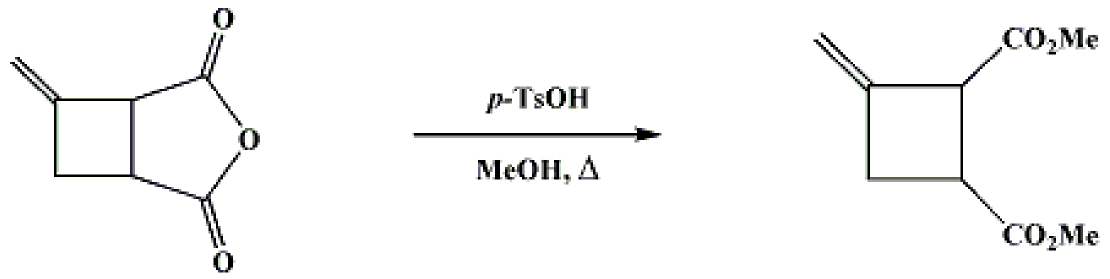
Organic Syntheses, *CV 5, 459*

DIMETHYL 3-METHYLENECYCLOBUTANE-1,2-DICARBOXYLATE

[3-Methylenecyclobutane-1,2-dicarboxylic acid, dimethyl ester]





Submitted by H. B. Stevenson, H. N. Cripps, and J. K. Williams[1].
Checked by R. D. Birkenmeyer, W. E. Russey, and F. Kagan[2].

1. Procedure

A. *3-Methylenecyclobutane-1,2-dicarboxylic anhydride*. A 2-l. stainless steel autoclave equipped with stirrer, pressure gauge, and thermocouple is charged with 500 g. (5.1 moles) of maleic anhydride, 645 ml. of benzene, and 0.25 g. of hydroquinone. The autoclave is closed, cooled to –70° with stirring, and evacuated to a pressure of about 20 mm. Allene[3] (100 g., 2.5 moles) (Note 1) is sucked into the autoclave, and the mixture is heated with stirring for 8–10 hours at 200–210°. During this time, the pressure drops from 23 atm. to 15 atm. The vessel is cooled to 25°, and unreacted allene (6–13 g.) is vented into a cold trap (Note 2). The benzene solution is decanted, and about 500 ml. of acetone is added to the autoclave and stirred until the dark viscous residue goes into solution. The benzene and acetone solutions are combined, filtered, and distilled through a 19-mm. × 1.8-m. Nester spinning-band still.[4] When the pot temperature reaches 170°, the pressure is reduced to 40 mm., and up to 250 g. of maleic anhydride, b.p. 110–115°/40 mm., is recovered. Finally 119 g. of crude anhydride mixture, b.p. 70–125°/3 mm. (Note 3), is collected.

The crude anhydride is carefully fractionated through a 13-mm. × 1.2-m. Nester still at a pressure of 25 mm. (Note 4) and a reflux ratio of at least 10:1. After a fore-run of maleic anhydride, b.p. 50–100°/25 mm., and a small intermediate fraction, there is obtained 75–90 g. (22–26%) of 3-methylenecyclobutane-1,2-dicarboxylic anhydride; b.p. 155–159°/25 mm.; n_D^{25} 1.4935–1.4952 (Note 5). This material is of sufficient purity for most uses, but it contains approximately 2–5%

of propargylsuccinic anhydride. Redistillation through the Nester still gives 65–80 g.. (19–23%) of 3-methylenecyclobutane-1,2-dicarboxylic anhydride; b.p. 155°/25 mm.; n_D^{25} 1.4946–1.4955.

By continuing the distillation after removal of the cyclobutane anhydride, there is obtained 25–30 g. (7–9%) of propargylsuccinic anhydride; b.p. 162–168°/25 mm.; m.p. 63–68°. The melting point is raised to 69–70° by one recrystallization from 100 ml. of benzene (80% recovery of purified product).

B. *Dimethyl 3-methylenecyclobutane-1,2-dicarboxylate*. One liter of methanol is added cautiously with occasional shaking to 276 g. (2.00 moles) of 3-methylenecyclobutane-1,2-dicarboxylic anhydride (n_D^{25} 1.4946–1.4955; (Note 6)) and 5 g. of *p*-toluenesulfonic acid in a 2-l. three-necked flask fitted with a thermometer, a condenser, and a dropping funnel. Refluxing starts after about two-thirds of the methanol has been added. The remainder is added at a rate that maintains vigorous boiling. The solution is refluxed for 30–40 hours with the pot temperature increasing from 67° to 68° (Note 7). The mixture is cooled to 15°, and methanol and water are removed by distillation under reduced pressure at temperatures below 15°, using a large receiver cooled with a mixture of solid carbon dioxide and acetone. When the pressure goes below 1 mm., the temperature is increased to 50° until the distillation is completed. One liter of methanol (Note 8) is added to the residue, and the solution is heated under reflux for an additional 30–40 hours, during which time the pot temperature increases from 67° to 67.5°. The solution is cooled to 15°, 1.7 g. of finely powdered anhydrous sodium carbonate is added to neutralize the *p*-toluenesulfonic acid, and the methanol and water are removed as before. Crude dimethyl 3-methylenecyclobutane-1,2-dicarboxylate is distilled rapidly at 65–85°/1 mm. through a 30-cm. Vigreux column (Note 9). The ester can be purified by redistillation through a 13-mm. × 1.2-m. Nester still, with the main fraction boiling at 134–137°/25 mm.; weight 297–338 g. (81–92%); n_D^{25} 1.4624–1.4630.

2. Notes

1. Freshly distilled allene should be used. It should be free of 2-chloropropene, usually present in allene prepared by zinc dehalogenation of 2,3-dichloropropene,[3] to avoid formation of chlorine-containing products that liberate hydrogen chloride on distillation.
2. The impurities present in the original allene are concentrated in the recovered material. If recovered allene is to be reused, it should be fractionated first.
3. The checkers isolated 167 g. of crude anhydride mixture boiling at 70–125°/3 mm. The large tarry residue contains allene polymers and small amounts of 1,2,3,4,5,6,7,8-octahydronaphthalene-2,3,6,7-tetracarboxylic dianhydride, which can be recovered by diluting the residue with benzene and filtering.
4. Pot temperatures above 175°, which result from use of pressures above 25 mm., cause formation of high-boiling by-products.
5. Collection of the product fraction should begin after a few milliliters of an intermediate fraction has been collected at 155°/25 mm. This material has a low index of refraction.
6. The checkers found that the use of anhydride with n_D^{25} 1.4937–1.4945 led to a product with a low index of refraction (n_D^{25} 1.4616).
7. The temperature rises because of disappearance of methanol by conversion to the methyl ester. Attainment of equilibrium is signified by the pot temperature reaching a constant temperature.
8. The second treatment with methanol increases the yield from 60% to 90%.
9. Rapid distillation from the neutralized catalyst results in much smaller loss of ester than

is encountered in the more usual procedure that includes washing with water and drying.

3. Discussion

The procedure used is essentially that described by Cripps, Williams, and Sharkey.[5] The anhydride has been prepared in a similar manner by Alder and Ackermann.[6] No other methods have been described for the preparation of these materials.

4. Merits of the Preparation

The first step of this procedure illustrates a general reaction, the addition of allenes to alkenes to form methylenecyclobutanes. The reaction has been reviewed recently.[7]

Since 3-methylenecyclobutane-1,2-dicarboxylic anhydride is easily converted to 3-methyl-2-cyclobutene-1,2-dicarboxylic acid,[8] it is an intermediate to a variety of cyclobutenes. The dimethyl ester of 3-methylenecyclobutane-1,2-dicarboxylic acid is also a versatile compound; on pyrolysis it gives the substituted allene, methyl butadienoate,[9] and on treatment with amines it gives a cyclobutene, dimethyl 3-methyl-2-cyclobutene-1,2-dicarboxylate.[8]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 734

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

cyclobutene, dimethyl 3-methyl-2-cyclobutene-1,2-dicarboxylate

hydrogen chloride (7647-01-0)

Benzene (71-43-2)

methanol (67-56-1)

hydroquinone (123-31-9)

sodium carbonate (497-19-8)

carbon dioxide (124-38-9)

acetone (67-64-1)

2,3-dichloropropene (78-88-6)

Allene (463-49-0)

maleic anhydride (108-31-6)

2-chloropropene (557-98-2)

Dimethyl 3-methylenecyclobutane-1,2-dicarboxylate, 3-Methylenecyclobutane-1,2-dicarboxylic acid, dimethyl ester, dimethyl ester of 3-methylenecyclobutane-1,2-dicarboxylic acid (53684-52-9)

3-Methylenecyclobutane-1,2-dicarboxylic anhydride

propargylsuccinic anhydride

1,2,3,4,5,6,7,8-octahydronaphthalene-2,3,6,7-tetracarboxylic dianhydride

3-methyl-2-cyclobutene-1,2-dicarboxylic acid

Methyl butadienoate (18913-35-4)

p-toluenesulfonic acid (104-15-4)

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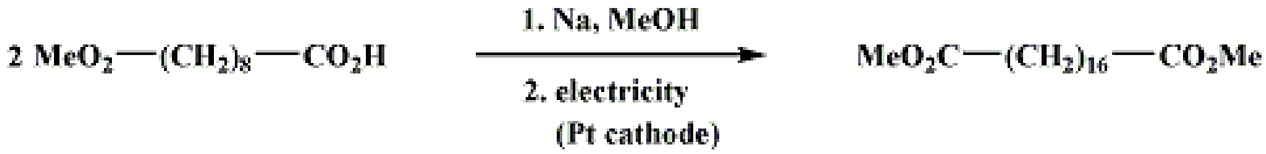
DIMETHYL OCTADECANEDIOATE

[Octadecanedioic acid, dimethyl ester]



Submitted by Sherlock Swann, Jr. and W. E. Garrison, Jr.[1].
Checked by James Cason, John A. Carlson, and Stanley Wood.

1. Procedure

To 500 ml. of absolute methanol (Note 1) in a 1-l. electrolytic (tall form) beaker is added 1.1 g. (0.05 g. atom) of clean sodium metal. After solution of the sodium, 216 g. (1.0 mole) of methyl hydrogen sebacate (Note 2) is dissolved in the sodium methoxide solution. A magnetic stirring bar is placed in the beaker which is then fitted with a large neoprene stopper (Note 3) holding a platinum sheet anode, 12 cm.^{2} in area; and two platinum sheet cathodes, approximately 5.3 cm.^{2} in area, spaced equidistantly on either side of the anode at a distance of approximately 1.5 cm. (Note 4). The stopper is also provided with a stoppered entry tube and an efficient reflux condenser (Note 5).

The electrodes are connected to a suitable variable source of direct current (Note 6), the magnetic stirrer is started, and a potential of about 50 volts is applied. This results in a current flow of 1–2 amperes. The solution soon comes to boiling; the voltage is then regulated so that a rapid reflux is maintained (Note 7).

Completion of the run, after 30–40 hours, is indicated when a few drops of the solution show an alkaline reaction to phenolphthalein. No harm is done if the electrolysis is carried a few hours beyond this point; however, after excessively long periods, formation of polymeric material lowers the yield and renders purification of the product rather troublesome.

Upon completion of the reaction (Note 8) the solution is acidified with acetic acid, and the solvent removed under reduced pressure. The residue is dissolved in about 1.4 l. of ether and filtered into a 2-l. separatory funnel through fluted paper. After the ether solution has been washed with two 300-ml. portions of 5% aqueous sodium bicarbonate solution (Note 9), the ether is removed on a steam bath. The residue is dissolved in about 1.5 l. of warm methanol, and the solution is allowed to cool to room temperature. The crystallized product is collected by suction filtration on a Büchner funnel and pressed well. The product is rather waxy and is best washed by transferring it to a beaker and stirring thoroughly with about 150 ml. of cold methanol. The white crystals are then collected and pressed well again. If the filtrate is colored, the crystals are washed again with a smaller quantity of methanol. The combined filtrate and washings are

concentrated to one-half the original volume and chilled in ice to yield a few grams of additional product of the same melting point. The combined lots are dried in a vacuum desiccator. The yield amounts to 116–126 g. (68–74%) of white, microcrystalline dimethyl octadecanedioate, m.p. 57–58°.

2. Notes

1. Analytical reagent absolute methanol is sufficiently pure for this purpose.
2. The methyl hydrogen sebacate used by the submitters was prepared by the method described by Pattison and co-workers,[2] which is a modification of the method described in *Organic Syntheses*, Coll. Vol. **2**, 276 (1943), for ethyl hydrogen sebacate. The methyl rather than the ethyl ester is preferred because of the greater ease of purification of methyl hydrogen sebacate and dimethyl octadecanedioate. The checkers prepared methyl hydrogen sebacate by the convenient procedure which has been described for methyl hydrogen hendecanedioate.[3] Absence of diacid in the half ester is imperative, for each molecule of diacid (in low concentration) will couple with two molecules of half ester.
3. A rubber stopper will suffice, but neoprene is more durable.
4. Convenient dimensions are 3 × 4 cm. for the anode, and 2.3 × 2.3 cm. for the cathode. The bottom of the anode should extend to about 3 cm. from the bottom of the beaker, and the centers of the cathodes should be lined up with the center of the anode. The submitters and checkers used 0.002-in. platinum sheet. Thinner material is easily distorted by the action of the stirrer and may thus develop a short circuit. Platinum wire may be attached to the sheet by heating both parts to redness and hammering them together. The wire may then be sealed in a piece of Pyrex tubing, which is passed through a properly located hole in the stopper, and mercury is used to make contact with the lead-in wire.[4]
In a run one-half the size here described, the checkers obtained similar results by using the same geometry of electrodes with the same concentrations of reactants in a 700-ml. tall-form beaker, with one-half the electrolysis time.
5. It is most convenient to insert a 24/40 outer joint in the stopper to accommodate the condenser. A 14/20 outer joint makes a convenient entry tube for withdrawing samples in order to determine when alkalinity has been reached. This joint must be stoppered during the electrolysis, which is under reflux.
6. A variable field d-c motor generator was used by the submitters. In lieu of such equipment, the checkers used a 120-volt d-c source with a heavy-duty resistor in the circuit. Occasionally, a film of polymeric material may form on the anode and reduce the current flow. This condition may be corrected by reversing the current flow for a period of 5–10 seconds. A suitable control circuit is diagrammed in f. htmig. 1.

Fig. 1

Fig. 1

7. It is usually necessary to increase the applied voltage toward the end of the

electrolysis in order to keep the current flow at a high rate. The submitters usually finished the electrolysis at 140 volts; however, the checkers found that a limit of 120 volts resulted in no significant delay in completion of the electrolysis.
8. The electrodes should be removed promptly from the warm reaction mixture, for the solution sets to a solid mass on cooling. It is most convenient to proceed with work-up of the warm solution.
9. An insignificant amount of half ester is recovered by acidification of the bicarbonate washings, followed by extraction with ether.

3. Discussion

Dimethyl and diethyl octadecanedioate have been prepared by the electrolysis of the sodium or potassium salts of methyl or ethyl hydrogen sebacate in water[5] or in methanol.[6]

4. Merits of Preparation

The advantages of this preparation of dimethyl octadecanedioate over that described earlier[5] are purity of product, no foaming of the electrolyte, higher yields, and elimination of the use of large quantities of the salt of the acid ester as supporting electrolyte. The procedure is regarded as near the optimum for a Kolbe electrolysis.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 445
- Org. Syn. Coll. Vol. 7, 181

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Dimethyl and diethyl octadecanedioate

sodium or potassium salts of methyl or ethyl hydrogen sebacate

acetic acid (64-19-7)

methanol (67-56-1)

ether (60-29-7)

sodium bicarbonate (144-55-8)

mercury (7439-97-6)

sodium methoxide (124-41-4)

sodium (13966-32-0)

phenolphthalein (77-09-8)

Ethyl hydrogen sebacate (693-55-0)

methyl hydrogen sebacate (818-88-2)

Methyl hydrogen hendecanedioate (3927-60-4)

Dimethyl octadecanedioate, Octadecanedioic acid, dimethyl ester (1472-93-1)

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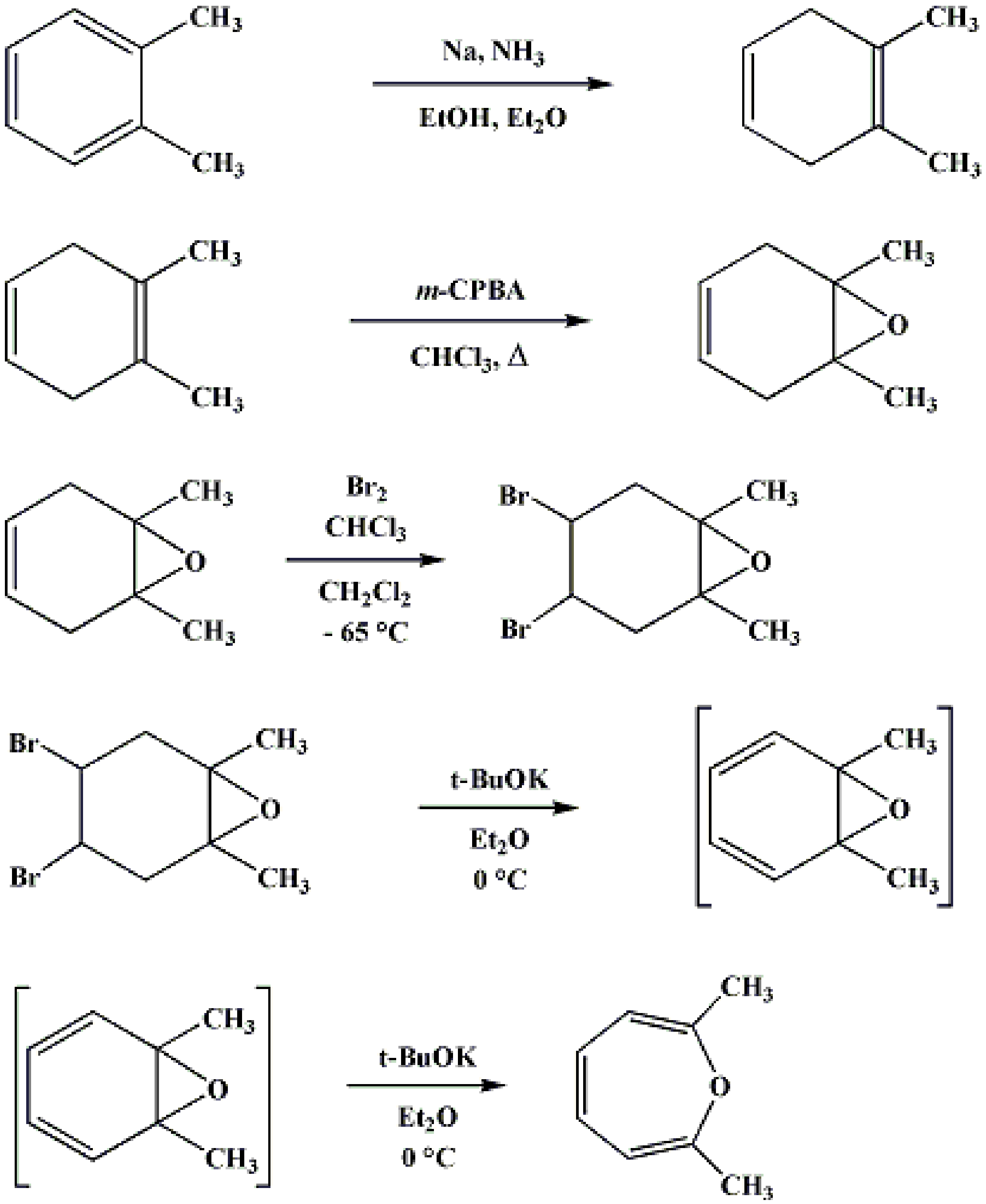
2,7-DIMETHYLOXEPIN

[Oxepin, 2,7-dimethyl-]



Submitted by L. A. Paquette and J. H. Barrett[1].
Checked by Jon Malmin and Ronald Breslow.

1. Procedure

A. *1,2-Dimethyl-1,4-cyclohexadiene*. *Caution! This step should be conducted in a hood to avoid exposure to ammonia fumes.* A 5-l. three-necked flask, cooled in a dry

ice-isopropyl alcohol bath, is fitted with an efficient stirrer and a dry ice condenser. The flask is charged with approximately 2.5 l. of liquid ammonia, the stirrer is started, and 450 g. of anhydrous diethyl ether, 460 g. (10 moles) of absolute ethanol, and 318.5 g. (3.0 moles) of *o*-xylene (Note 1) are added slowly in that order (Note 2). Then 207 g. (9.0 g. atoms) of sodium is added in small pieces over a 5-hour period (Note 3). The ammonia is allowed to evaporate overnight. The flask is now equipped with a reflux condenser, and approximately 800 ml. of ice water is slowly added with stirring to dissolve the salts (Note 4). The two layers which form are separated and the upper organic layer is washed three times with 800-ml. portions of water and dried over anhydrous magnesium sulfate. The liquid is separated from the drying agent and is distilled through a 20-cm. Vigreux column. The fraction boiling at 70–72° (48 mm.) is collected and weighs 250–300 g. (77–92%). The 1,2-dimethyl-1,4-cyclohexadiene is sufficiently pure for the epoxidation reaction (Note 5).

B. *1,2-Dimethyl-1,2-epoxycyclohex-4-ene*. A 2-l. three-necked flask equipped with an efficient stirrer, a reflux condenser, and a dropping funnel is charged with 41 g. (0.38 mole) of 1,2-dimethyl-1,4-cyclohexadine. Over a period of 2 hours 80 g. (0.46 mole of 85% assay) of *m*-chloroperbenzoic acid (Note 6) dissolved in 1 l. of chloroform is added with vigorous stirring. The mixture is heated to reflux on a steam bath for 3 hours and kept overnight. The contents of the flask are cooled in an ice bath and the precipitated *m*-chlorobenzoic acid is removed by filtration. The organic layer is washed with 25 ml. of 20% sodium bisulfite solution, three 100-ml. portions of 10% sodium bicarbonate solution (Note 7), and 100 ml. of saturated sodium chloride solution, in that order. The organic layer is dried over anhydrous magnesium sulfate, filtered, concentrated under reduced pressure, and distilled through a 30-cm. glass bead-packed column (Note 8) to afford 32.3–36.8 g. (68–78%) of the epoxide, b.p. 55–57° (15 mm.); n^{20}_D 1.4642–1.4650 (Note 9).

C. *4,5-Dibromo-1,2-dimethyl-1,2-epoxycyclohexane*. Into a 1-l. three-necked flask fitted with an efficient stirrer, an alcohol thermometer, a dropping funnel, and a drying tube are placed 32 g. (0.26 mole) of the epoxide and 500 ml. of an anhydrous chloroform-methylene chloride mixture (1:1). The solution is cooled to –65° and 34 g. (0.21 mole) of bromine in 50 ml. of the same solvent is added dropwise while maintaining the temperature below –60° (Note 10). When the addition is complete, the reaction mixture is stirred for 30 minutes and the solvent is removed at room temperature under reduced pressure. The resulting oil (or solid) is recrystallized from a minimum amount of *n*-hexane to give 47–51 g. (80–86%) of lustrous white needles, m. p. 82–83°.

D. *2,7-Dimethyloxepin.* In a 1-l. three-necked flask fitted as above, except that the dropping funnel is replaced by a 125-ml. Erlenmeyer flask connected to the reaction flask by means of Gooch tubing, is placed a solution of 42.1 g. (0.15 mole) of the purified dibromoepoxide in 500 ml. of anhydrous ether. The solution is cooled to 0° and 33.2 g. (0.30 mole) of potassium *t*-butoxide (Note 11) is added portionwise through the Gooch tubing over a period of 1 hour while maintaining the temperature

below 5°. The resulting mixture is stirred for 30 minutes and filtered. The ether is removed under reduced pressure, and the residual liquid is distilled to give 9.7–12.2 g. (52–67%) of 2,7-dimethyloxepin as an orange oil, b.p. 49–50° (15 mm). n^{27}D 1.5010 (Note 12).

2. Notes

1. Eastman Organic Chemicals, white label grade, was used without further purification.
2. It is advisable to precool these reagents before their addition to minimize excessive boiling of the liquid ammonia.
3. Only five or six pieces of sodium should be added at one time in order to avoid an almost uncontrollable exothermic reaction. The solution turns blue and then white as the sodium is consumed. When the solution turns white, another portion of sodium may be added. The last 50 g. of sodium may be added without waiting between portions because the reaction is much slower at this point.
4. Because dissolution of the salts is a highly exothermic process, the water should be added slowly. A stream of nitrogen may be passed through the reaction during the addition of the water to ensure that no fire is started by bits of sodium that may be adhering to the upper walls of the flask.
5. The product is readily analyzed by vapor phase chromatography. Since the only impurity is *o*-xylene (conversions range from 80% to 100%), the percentage of reduction product was calculated from the gas chromatogram and this value was used to determine the amount of *m*-chloroperbenzoic acid to be used in the epoxidation.
6. *m*-Chloroperbenzoic acid was obtained from Aldrich Chemical Company, Milwaukee, Wisconsin.
7. The separatory funnel must be vented frequently because of the large volume of carbon dioxide liberated at this point.
8. It appears necessary to effectively remove the residual *o*-xylene during this distillation in order that it not interfere (by liberation of hydrogen bromide) with the subsequent bromination of the epoxide. The checkers used a spinning-band column for this distillation.
9. The submitters worked at four times this scale with similar yields and purity.
10. Best yields are obtained if the bromination mixture is never allowed to become orange in color. If a calculated amount of bromine is added to the epoxide, the yields of dibromide are greatly diminished.
11. Potassium *t*-butoxide may be obtained from MSA Research Corporation, Callery, Pennsylvania.
12. 2,7-Dimethyloxepin is stable for long periods when stored under nitrogen at 0–5°.

3. Discussion

The procedure described is patterned after the method suggested by Vogel, Schubart,

and Böll,[2] and it illustrates a general method of preparing oxepins. Furthermore, the first step represents an example of the Birch reduction of an aromatic hydrocarbon.[3] The second step is illustrative of the selective epoxidation of a diene system.[3]

Oxepins themselves are interesting examples of cyclic conjugated molecules with 4*n* π-electrons.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 200

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

1,2-dimethyl-1,4-cyclohexadine

ethanol (64-17-5)

ammonia (7664-41-7)

ether, diethyl ether (60-29-7)

chloroform (67-66-3)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

hydrogen bromide (10035-10-6)

bromine (7726-95-6)

nitrogen (7727-37-9)

sodium bisulfite (7631-90-5)

carbon dioxide (124-38-9)

sodium (13966-32-0)

magnesium sulfate (7487-88-9)

chloroform-methylene chloride (76-01-7)

n-hexane (110-54-3)

2,7-Dimethyloxepin, Oxepin, 2,7-dimethyl- (1487-99-6)

1,2-Dimethyl-1,4-cyclohexadiene (17351-28-9)

m-Chloroperbenzoic acid (937-14-4)

o-Xylene (95-47-6)

potassium t-butoxide (865-47-4)

m-chlorobenzoic acid (535-80-8)

1,2-Dimethyl-1,2-epoxycyclohex-4-ene (57338-10-0)

4,5-Dibromo-1,2-dimethyl-1,2-epoxycyclohexane

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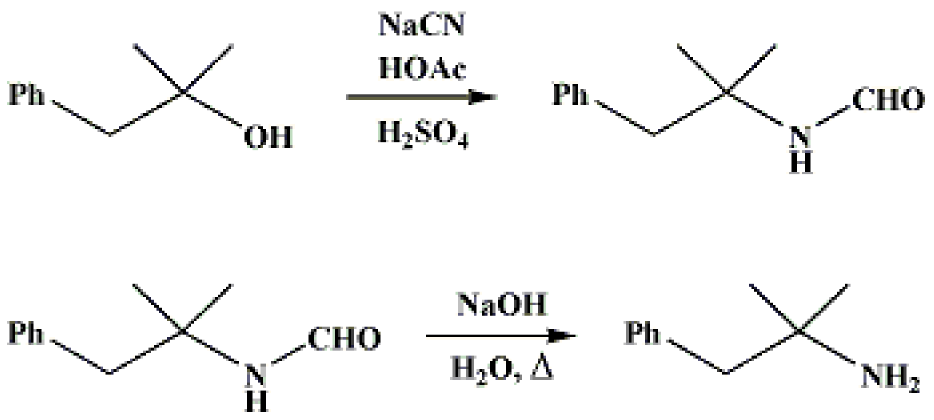
α,α-DIMETHYL-β-PHENETHYLAMINE

[Phenethylamine, α,α-dimethyl]



Submitted by John J. Ritter[1] and Joseph Kalish[2].
Checked by William G. Dauben and Alan Krubiner.

1. Procedure

Caution! This preparation should be conducted in a hood because poisonous hydrogen cyanide may be evolved.

A. *N-Formyl-α,α-dimethyl-β-phenethylamine*. To a 2-l., three-necked, round-bottomed flask fitted with a sealed stirrer carrying a crescent-shaped blade, a thermometer, an addition funnel, and a reflux condenser connected to a trap containing 20% sodium hydroxide solution is added 500 ml. of glacial acetic acid (Note 1). The contents of the flask are cooled to 20° by means of an ice bath, the addition funnel is temporarily replaced by a stopper, and to the stirred acetic acid is added 110 g. (2 moles) of 95% sodium cyanide in small portions. The temperature of the mixture is maintained around 20°, and the addition requires about 20 minutes (Note 2). The addition funnel is replaced, and a previously prepared and cooled solution of 500 g. (272 ml., 4.9 moles) of concentrated sulfuric acid in 250 ml. of glacial acetic acid is added slowly, with stirring, the temperature of the mixture being kept at about 20° by means of an ice bath (Note 3). The ice bath is removed, and 300 g. (2 moles) of α,α-dimethyl-β-phenethyl alcohol (Note 4) is added over a 20-minute period during which the temperature of the mixture rises slowly to 35–45°. The reaction mixture is stirred for an additional 90 minutes (Note 5) and allowed to stand overnight. The amber-colored mixture containing some solid sodium sulfate is aerated with nitrogen for 2 hours *(Caution! In a hood)*, poured into 3 l. of ice water, and the supernatant oil separated. The aqueous phase is neutralized with sodium carbonate and extracted with 600 ml. of ether. The ethereal extract is combined with the original oily supernatant, neutralized with sodium carbonate, and dried over anhydrous sodium sulfate. The solvent is

removed under reduced pressure, and the residue is distilled to yield 230–248 g. (65–70%) of product, b.p. 137–141° (2 mm.). Redistillation of the ether-containing fore-run yields up to an additional 14 g. of material.

B. *α,α-Dimethyl-β-phenethylamine*. In a 3-l., three-necked, round-bottomed flask equipped with a reflux condenser and a sealed stirrer are placed 246 g. (1.39 moles) of N-formyl-α,α-dimethyl-β-phenethylamine and 2.1 l. of 20% sodium hydroxide solution. The mixture is heated under reflux with vigorous stirring for 2.5 hours or until a test portion of the oily layer dissolves completely in cold 5% hydrochloric acid. The reaction mixture is cooled, 750 ml. of benzene is added, the mixture is stirred, and the benzene layer is separated. The benzene solution is shaken with a saturated sodium chloride solution, the benzene removed by distillation at atmospheric pressure, and the product distilled at reduced pressure to yield 155–165 g. (75–80%) of α,α-dimethyl-β-phenethylamine, b.p. 80–82° (10 mm.).

2. Notes

1. The reaction may be conducted in other solvents (e.g., dibutyl ether) or in the absence of solvent with some alteration in the order of mixing the reagents. The submitters find for this and a large number of similar preparations that acetic acid generally is most convenient.
2. Most of the sodium cyanide does not dissolve.
3. Care must be taken during the first part of the addition because the reaction is very exothermic.
4. Methallylbenzene or isobutenylbenzene may be used in place of the carbinol with practically identical results.
5. The temperature may continue to rise during the initial portion of this period, but it is controlled by means of an ice bath to limit the temperature of the mixture to 45–50°.

3. Discussion

α,α-Dimethyl-β-phenethylamine has been prepared from benzaldehyde and 2-nitropropane[3] and from isobutyrophenone by a series of steps involving alkylation with benzyl bromide, alkali cleavage, and Hofmann bromamide degradation.[4]

4. Merits of the Preparation

The present method is shorter and less laborious than previously described methods, and it gives better yields of material. The method, now known as the Ritter reaction, is one of considerable scope,[5] having been used with fair to excellent success with many tertiary alcohols or the corresponding alkenes, with benzyl alcohol, and with some secondary alcohols. It has also been used with alkanes, alkadienes, alicyclic and spiro alcohols, alkyl chlorides, glycols, aldehydes, chlorohydrins, N-methylolamides, ethers, carboxylic acids, esters, ketones, and ketoximes. The Ritter reaction has been

reviewed.[5] Another example of this reaction is given elsewhere in this volume.[6]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 73

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium cyanide (143-33-9)

sodium chloride (7647-14-5)

hydrogen cyanide (74-90-8)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

benzaldehyde (100-52-7)

Benzyl alcohol (100-51-6)

dibutyl ether (142-96-1)

benzyl bromide (100-39-0)

2-nitropropane (79-46-9)

Phenethylamine, α,α-dimethyl, α,α-Dimethyl-β-phenethylamine (122-09-8)

Methallylbenzene (3290-53-7)

isobutenylbenzene (768-49-0)

isobutyrophenone (611-70-1)

α,α-dimethyl-β-phenethyl alcohol (100-86-7)

N-Formyl-α,α-dimethyl-β-phenethylamine (52117-13-2)

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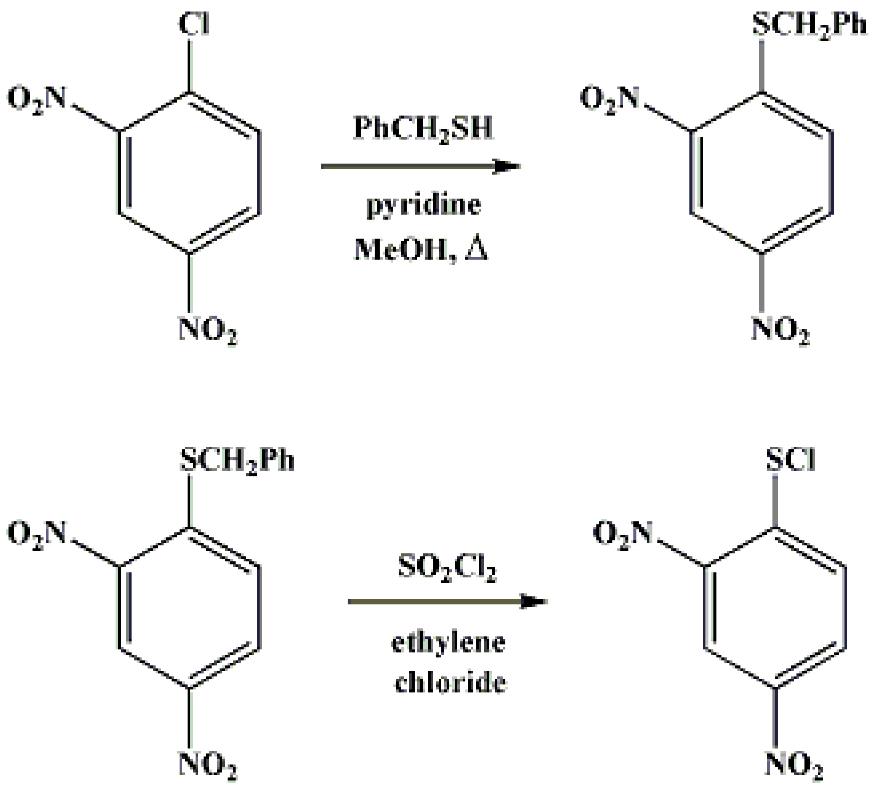
2,4-DINITROBENZENESULFENYL CHLORIDE

[Benzenesulfenyl chloride, 2,4-dinitro-]



Submitted by Norman Kharasch and Robert B. Langford[1].
Checked by D. C. Dittmer and B. C. McKusick.

1. Procedure

Caution! Both steps should be carried out in a good hood.

A. *2,4-Dinitrophenyl benzyl sulfide*. The apparatus consists of a 1-l., three-necked, round-bottomed flask equipped with a sealed mechanical stirrer and a reflux condenser. In it are placed 202 g. (1.00 mole) of 2,4-dinitrochlorobenzene (m.p. 50–52°) *(Caution! A skin irritant),* 400 ml. of methanol, 124 g. (1.00 mole) of benzyl mercaptan, and 87 g. (85 ml., 1.10 moles) of pyridine. The mixture is heated at the reflux temperature with stirring for 16 hours or more (Note 1) and cooled to 0°. The 2,4-dinitrophenyl benzyl sulfide that precipitates is separated by filtration, washed with two 250-ml. portions of ice-cold methanol, and dried at 60–80°. The sulfide, a yellow crystalline solid that melts at 128–129°, weighs 235–250 g. (81–86%) (Note 2). It may be used in the next step without further purification.

B. *2,4-Dinitrobenzenesulfenyl chloride*. Dry 2,4-dinitrophenyl benzyl sulfide (232 g., 0.80 mole) and 400 ml. of dry ethylene chloride are placed in a 2-l., one-necked, round-

bottomed flask equipped with a stirrer (Note 3). Sulfuryl chloride (119 g., 0.88 mole) (Note 4) is added to the resulting suspension at room temperature. A mildly exothermic reaction causes the solid to dissolve quickly, usually within 1 to 2 minutes, with a temperature rise of 10–15° (Note 5). The resulting clear yellow solution is concentrated to an oil by heating under aspirator vacuum on a steam bath (Note 6). *(Caution! Do not heat with gas or electricity because the product, like many nitro compounds, can explode if overheated.)* The residual oil is cooled to 50–60°, and 3–4 volumes of dry petroleum ether (b.p. 30–60°) are added with vigorous handswirling. The oil quickly crystallizes. The mixture is cooled to room temperature and filtered to separate 2,4-dinitrobenzenesulfenyl chloride as a yellow crystalline solid. The sulfenyl chloride is washed well with dry petroleum ether and dried at 60–80° (Note 7); weight 150–170 g. (80–90%); m.p. 95–96° (Note 8), (Note 9).

2. Notes

1. After 2 or 3 hours, solid product usually appears in the reaction mixture.
2. When practical grade 2,4-dinitrochlorobenzene (m.p. 46–47°) is substituted, a product of equally good quality (m.p. 128–129°) is obtained, but the yield is only 70–75%.
3. All materials and equipment used in Step B of this procedure must be completely dry to avoid loss of product by hydrolysis. The checkers found, however, that the reaction may be carried out open to the air without loss of yield.
4. Practical grade sulfuryl chloride, obtained from Matheson, Coleman and Bell, gives satisfactory results.
5. The 2,4-dinitrophenyl benzyl sulfide normally undergoes cleavage at room temperature without the addition of a catalyst. If the reaction does not occur spontaneously, the mixture may be warmed gently and/or one drop of dry pyridine may be added to initiate the reaction.
6. Rotary or other distillation equipment with metal parts should not be used in concentrating the reaction mixture because not only will the corrosive vapors damage the equipment, but also the resulting metal salts will discolor and partially decompose the product. The solution should not be heated any longer than is necessary to concentrate it; excessive heating gives a darkcolored product.
7. The product should not be dried longer than is necessary for it to reach constant weight, or there may be partial decomposition.
8. The product obtained by this procedure is pure enough for most purposes. Its melt, however, is faintly cloudy. A product of high purity, giving a clear melt, can be obtained by recrystallization from about 15 ml. of dry carbon tetrachloride per gram of sulfenyl chloride. When stored in a sealed brown bottle with a plastic cap (no metal!), the sulfenyl chloride is stable for years.
9. 2,4-Dinitrobenzenesulfenyl bromide may be similarly prepared by refluxing 2,4-dinitrophenyl benzyl sulfide with the equivalent amount of bromine in 5 parts of dry carbon tetrachloride. As it is less stable than the chloride, losing bromine if overheated, it should be concentrated on a 40° water bath under

vacuum. When worked up in the same manner as the chloride, the product usually contains some *bis*-(2,4-dinitrophenyl) disulfide. Because the disulfide is insoluble in carbon tetrachloride, the sulfenyl bromide may be readily purified by recrystallization; yield 75–80%, m.p. 102–104°.

3. Discussion

2,4-Dinitrophenyl benzyl sulfide has been prepared by the reaction of benzyl chloride with 2,4-dinitrothiophenol[2] or *bis*-(2,4-dinitrophenyl) disulfide[3] and by the condensation of 2,4-dinitrochlorobenzene with benzyl mercaptan.[4]

2,4-Dinitrobenzenesulfenyl chloride has been obtained by the chlorinolysis of 2,4-dinitrophenyl thiolbenzoate,[5] 2,4-dinitrothiophenol,[6] or *bis*-(2,4-dinitrophenyl) disulfide,[7,8] and by the present procedure.[9]

4. Merits of the Preparation

2,4-Dinitrobenzenesulfenyl chloride is a versatile analytical reagent for the characterization of a wide variety of organic compounds, including alcohols, mercaptans, ketones, olefins, amines, aromatic compounds, olefin oxides, and hydroxysteroids. Review articles summarize these applications.[10,11]

The chlorinolysis of 2,4-dinitrophenyl benzyl sulfide gives a good yield of product which is satisfactory for most purposes without recrystallization. Only simple equipment and inexpensive materials are needed, only 2 or 3 hours of the operator's time are required, and the entire procedure can be completed within 24 hours.

The best previous method of preparation, the chlorinolysis of *bis*-(2,4-dinitrophenyl) disulfide by sulfuryl chloride in the presence of pyridine,[8] requires much more time and effort with results that are uncertain, even for experienced operators.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

sulfenyl chloride

sulfenyl bromide

methanol (67-56-1)

bromine (7726-95-6)

carbon tetrachloride (56-23-5)

ethylene chloride (107-06-2)

sulfuryl chloride (7791-25-5)

pyridine (110-86-1)

benzyl chloride (100-44-7)

2,4-dinitrochlorobenzene (97-00-7)

2,4-Dinitrobenzenesulfenyl chloride, Benzenesulfenyl chloride, 2,4-dinitro- (528-76-7)

benzyl mercaptan (100-53-8)

2,4-Dinitrophenyl benzyl sulfide (7343-61-5)

2,4-Dinitrobenzenesulfenyl bromide

2,4-dinitrothiophenol

2,4-dinitrophenyl thiolbenzoate

bis-(2,4-dinitrophenyl) disulfide (2217-55-2)

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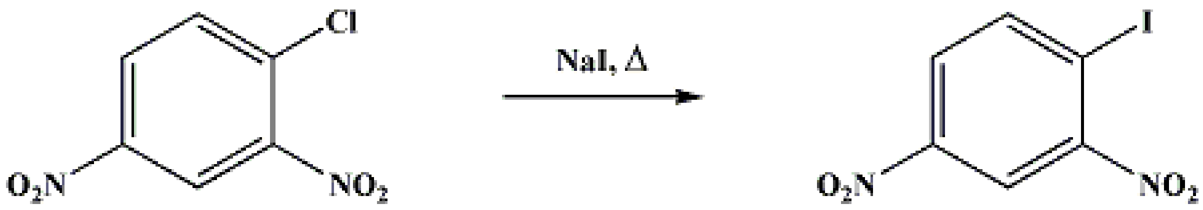
2,4-DINITROIODOBENZENE

[Benzene, 1-iodo-2,4-dinitro-]



Submitted by J. F. Bunnett and R. M. Conner[1].
Checked by Virgil Boekelheide and James S. Todd.

1. Procedure

Caution! 2,4-Dinitrochlorobenzene causes sever skin irritation to some individuals. Sensitive persons are advised to wear rubber gloves.

To 200 ml. of redistilled technical grade dimethylformamide (Note 1) in a 1-l. round-bottomed flask are added 150 g. (1 mole) of sodium iodide (Note 2) and 40.5 g. (0.2 mole) of 2,4-dinitrochlorobenzene (Note 3). The flask is fitted with a reflux condenser, and the red-brown mixture is refluxed for 15 minutes over a free flame arranged to impinge somewhat off-center (Note 4).

The hot reaction mixture is poured with stirring over about 0.75 l. of crushed ice in a 2-l. beaker. The beaker is filled with water, and the mixture is stirred to dissolve inorganic salts (Note 5). The insoluble red-brown solid is collected on a suction filter. This crude product, even while damp, is transferred to a 2-l. round-bottomed flask, and 500 ml. of a mixture of 75% (375 ml.) of petroleum ether (b.p. 90–100°) and 25% (125 ml.) of benzene is added. The flask is provided with a reflux condenser, and the mixture is heated at reflux for 15 minutes by means of an electric mantle (Note 6). The resulting solution is decanted into a second 2-l. flask, leaving in the first flask some water and a red-brown solid residue. To the slightly cooled liquor in the second flask is added cautiously 7 g. of powdered activated carbon. The carbon is dispersed by swirling, and the mixture is heated for an additional 5 minutes. The mixture is then filtered through a fluted filter into a 1-l. Erlenmeyer flask. This flask is stoppered and chilled to cause crystallization of the product (Note 7).

The product is collected on a suction filter. The yield of air-dried product, as yellow-orange crystals, m.p. 87–89°, is 38–42 g. (65–71%) (Note 8). A purer, lemon-yellow product, m.p. 88.5–90°, is obtained by an additional recrystallization from 1 l. of petroleum ether (b.p. 90–100°) with use of carbon; the yield after this second crystallization is 28–34 g. (48–58%).

2. Notes

1. Dimethylformamide is available from E. I. du Pont de Nemours and Co., Inc., Wilmington, Delaware.
2. Reagent grade sodium iodide was used.
3. Eastman Kodak white label 2,4-dinitrochlorobenzene, which had a light tan color, was used without further purification.
4. The burner should be so arranged that the flame impinges upon the side of the flask in such a way as to dissolve the sodium iodide from the top downward. The flask should be shaken or swirled frequently during the onset of boiling. A small amount of white solid remains undissolved even at reflux.
5. At this point there may be a lumpy, dark-brown material mixed with the orange-brown crude precipitated product. There appears to be no need to break up the lumps.
6. Alternatively, the flask can be heated on an efficient steam bath with swirling until the crude product melts. After an additional 15 minutes of heating, the solution can be decanted as described.
7. The submitters placed the flasks of warm filtrate in the refrigerator for storage overnight or in a freezing cabinet at –20° for at least 1 hour.
8. From a run of five times the scale described, the submitters obtained 219 g. (71%) of an orange-yellow crystalline product, m.p. 88–90°.

3. Discussion

2,4-Dinitroiodobenzene has been prepared by the nitration of *o*- or *p*-nitroiodobenzene,[2] by treatment of 2,4-dinitrobenzenediazonium sulfate with potassium iodide,[3] and by the reaction of sodium iodide with 2,4-dinitrochlorobenzene in refluxing ethylene glycol.[4] The present procedure is a modification[5] of the last-mentioned one.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 904

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

o- or p-nitroiodobenzene

Benzene (71-43-2)

potassium iodide (7681-11-0)

carbon, activated carbon (7782-42-5)

ethylene glycol (107-21-1)

sodium iodide (7681-82-5)

2,4-dinitrochlorobenzene (97-00-7)

dimethylformamide (68-12-2)

2,4-Dinitroiodobenzene, Benzene, 1-iodo-2,4-dinitro- (709-49-9)

2,4-dinitrobenzenediazonium sulfate

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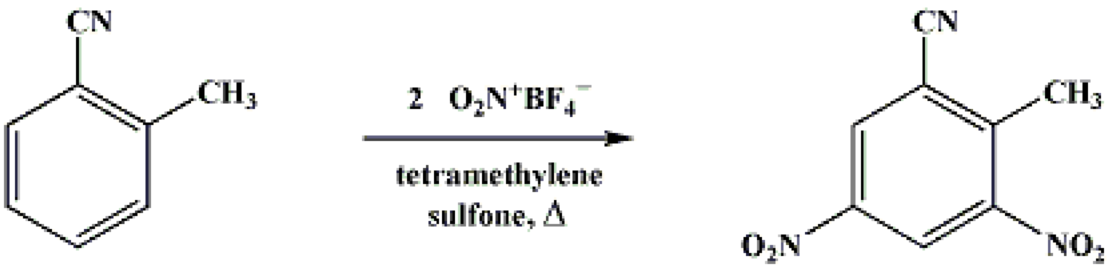
3,5-DINITRO-*o*-TOLUNITRILE

[Benzonitrile, 2-methyl-3,5-dinitro-]

$$HNO_3 + HF + 2BF_3 \longrightarrow O_2N^+BF_4^-$$



Submitted by George A. Olah[1] and Stephen J. Kuhn[2].
Checked by J. Lazar and B. C. McKusick.

1. Procedure

A. *Nitronium tetrafluoroborate* (Note 1). *Caution! Hydrogen fluoride is very hazardous. Caution is also called for in the use of boron trifluoride. All operations must be carried out in a hood, and the precautions outlined in (Note 2) should be followed.* A 1-l. three-necked polyolefin flask (Note 3) is provided with a short inlet tube for nitrogen, a long inlet tube for gaseous boron trifluoride, a drying tube, and a magnetic stirring bar (Note 4). The flask is immersed in an ice-salt bath and flushed with dry nitrogen. Under a gentle stream of nitrogen and with stirring, the flask is charged with 400 ml. of methylene chloride, 41 ml. (65.5 g., 1.00 mole) of red fuming nitric acid (95%), and 22 ml. (22 g., 1.10 moles) of cold, liquid, anhydrous hydrogen fluoride (Note 5).

Gaseous boron trifluoride (136 g., 2.00 moles) from a cylinder mounted on a scale is bubbled into the stirred, cooled reaction mixture (Note 6). The first mole is passed in rather quickly (in about 10 minutes). When approximately 1 mole has been absorbed, copious white fumes begin to appear at the exit, and the rate of flow is diminished so that it takes about 1 hour to pass in the second mole; even at this slow rate, there is considerable fuming at the exit. After all the boron trifluoride has been introduced, the mixture is allowed to stand in the cooling bath under a slow stream of nitrogen for 1.5 hours. The mixture is swirled, and the suspended product is separated from the supernatant liquid by means of a medium-porosity, sintered-glass Buchner funnel (Note 7). The gooey solid remaining in the flask is transferred to the funnel with the aid of two 50-ml. portions of nitromethane. The solid on the funnel, nitronium tetrafluoroborate, is washed successively with two 100-ml. portions of nitromethane

and two 100-ml. portions of methylene chloride. In order to protect the salt from atmospheric moisture during the washing procedure, suction is always stopped while the salt is still moist. The moist salt is transferred to a round-bottomed flask and dried by evaporating the solvent (Note 8). At the end of the procedure the flask can be gently heated to 40–50° (Note 9). The yield of colorless nitronium tetrafluoroborate is 85–106 g. (64–80%) (Note 10), (Note 11), (Note 12). It is stored in a wide-mouthed polyolefin bottle with a screw cap. The edge of the cap is sealed with paraffin wax after it is screwed on.

B. *3,5-Dinitro-o-tolunitrile*. A 500-ml. four-necked flask is equipped with a mechanical stirrer, a dropping funnel, a thermometer and an inlet for dry nitrogen (Note 13). It is baked thoroughly by means of a Bunsen flame and allowed to cool to room temperature with a slow stream of dry nitrogen passing through it. The flask is charge, preferably in a dry box, with 335 g. of tetramethylene sulfone (Note 14) and 73.1 g. (0.55 mole) of nitronium tetrafluoroborate. The thermometer is adjusted so that the bulb is immersed in the liquid. The reaction mixture is stirred well and kept at 10–20° by means of an ice bath while 58.5 g. (0.50 mole) of freshly distilled *o*-tolunitrile[3] is added dropwise. The nitronium tetrafluoroborate only partially dissolves in the tetramethylene sulfone (Note 15), but through good stirring a homogeneous suspension can be obtained. As the dissolved nitronium salt reacts with the nitrile, more and more salt dissolves until all of it is in solution. The addition of *o*-tolunitrile requires 25–35 minutes.

After the addition is complete, the cooling bath is removed and stirring is continued for 15 minutes at 35°. The dropping funnel is removed, 74.5 g. (0.56 mole) of nitronium tetrafluoroborate is added, and the opening of the flask is closed with a glass stopper. The well-stirred reaction mixture is heated by an electric heating mantle to 100° in 15 minutes and kept at 100–115° for 1 hour. The reaction mixture is allowed to cool to room temperature with continued stirring and is then poured into 800 g. of ice water. Crude 3,5-dinitro-*o*-tolunitrile separates on top of the aqueous mixture as a dark oil that solidifies after standing a few minutes. The solid is collected on a Buchner funnel. It is triturated on the funnel with five 50-ml. portions of cold water and with 40 ml. of ice-cold ethanol. After being dried in a vacuum desiccator, the crude nitrile weighs 75–84 g., m.p. 60–65°. Recrystallization from about 110 ml. of hot methanol gives 50–55 g. (48–53%) of 3,5-dinitro-*o*-tolunitrile, m.p. 82–84° (Note 16).

2. Notes

1. Nitronium tetrafluoroborate is commercially available from the Ozark-Mahoning Co., Tulsa, Oklahoma.
2. *Because of the hazardous nature of anhydrous hydrogen fluoride, adequate precautions should be taken to protect the head, eyes, and skin.* Rubber gloves, an apron, and a plastic face mask are strongly recommended. All operations should be carried out in a hood. If hydrogen fluoride comes in contact with the

skin, the contacted area should be thoroughly washed with water and then immersed in ice water while the patient is taken to a physician. After completion of the reaction, all equipment should be washed with liberal quantities of water. *Note! Burns caused by hydrogen fluoride may not be noticed for several hours, by which time serious tissue damage may have occurred.*

3. All operations involving liquid hydrogen fluoride must be carried out with equipment resisting hydrogen fluoride (fused silica, polyolefin, etc.).

4. An egg-shaped stirrer seems to work best. As the reaction proceeds, the precipitating nitronium tetrafluoroborate prevents the stirring bar from operating. This is not serious if the reaction mixture is shaken occasionally.

5. It is convenient to condense anhydrous hydrogen fluoride, b.p. 19.5°, from a cylinder into a small calibrated polyolefin flask immersed in a mixture of dry ice and acetone. As hydrogen fluoride is very hygroscopic, it should be carefully protected from atmospheric moisture, preferably by maintaining an atmosphere of dry nitrogen over it, otherwise by means of a drying tube. The hydrogen fluoride is then simply poured into the reaction flask.

6. The temperature of the reaction is not critical, but the reaction is slower at higher temperatures because of the lower solubility of boron trifluoride in the solvent.

7. Since free hydrogen fluoride is no longer present, filtration can be carried out with glass or porcelain equipment. However, commercially available polyolefin Buchner funnels and filter flasks are preferred.

8. Kel-F grease is recommended for ground-glass joints. Nitronium tetrafluoroborate slowly attacks silicone stopcock grease, causing air to enter the flask.

9. Nitronium tetrafluoroborate is thermally stable up to 170°. Above this temperature it starts to dissociate into nitryl fluoride and boron trifluoride.

10. Nitronium tetrafluoroborate is very hygroscopic. It is stable as long as it is anhydrous, but it is decomposed by moisture, and all transfers should be in a dry box. Its purity can be checked by conventional elemental analysis. However, because of the hygroscopic nature of the salt, the submitters have found it convenient to use neutron activation analysis (B, F, N, O) of samples sealed into polyolefin sample holders. Lange's method[4] for the determination of BF_4^- as the nitron salt gives good results but requires considerable care to achieve reproducibility.

11. The last part of the procedure can be used to purify nitronium tetrafluoroborate that has picked up water on standing. The impure salt is washed twice with nitromethane, twice with methylene chloride, and is dried under reduced pressure.

12. Nitronium tetrafluoroborate slowly attacks polyethylene and polypropylene, but apparatus made of these materials will last for several preparations of the salt.

13. The entire operation should be carried out in an atmosphere of dry nitrogen. If dry nitrogen is not available, rigorously anhydrous conditions should be maintained with the help of a drying tube.

14. Tetramethylene sulfone is commercially available from the Shell Chemical Company and the Phillips Petroleum Company.
15. A saturated solution at 25° contains 7 g. of nitronium tetrafluoroborate per 100 g. of tetramethylene sulfone.
16. This is pure enough for most purposes. An analytical sample melted at 86.5–88.4°.

3. Discussion

Nitronium tetrafluoroborate has been prepared by interaction of nitric acid, hydrogen fluoride, and boron fluoride in nitromethane.[5] However, mixtures of nitric acid and nitromethane are extremely explosive.[6,7] The present modification of the procedure, in which the medium is methylene chloride instead of nitromethane, was developed to avoid this hazard. It has not been published before.

The preparation of 3,5-dinitro-*o*-tolunitrile is based on previously published work.[8] The nitration of *o*-tolunitrile using fuming nitric acid has been reported by Candea and Macovski.[9]

4. Merits of the Preparation

Nitration of aromatic rings by nitronium tetrafluoroborate is a general method. Fifty-seven arenes, haloarenes, nitroarenes, arenecarboxylic esters, arenecarbonyl halides, and arenecarbonitriles have been nitrated in high yield by this reagent.[8] The method is particularly convenient for nitrating aromatic compounds susceptible to acid-catalyzed hydrolysis. For example, although mononitration of arenecarbonitriles is easily accomplished by conventional nitrating agents, dinitration is not. The reason is that the forcing conditions required for dinitration (strongly acid media and higher temperatures) bring about hydrolysis (and oxidation) of the nitrile group. In contrast, nitrations with nitronium tetrafluoroborate can be carried out in nonaqueous acid-free systems, where the only acid originates from proton elimination during nitration. In the basic solvent used, this acid concentration generally is not sufficient to cause any detectable hydrolysis (or oxidation).

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

BF_4

polyethylene

polypropylene

ethanol (64-17-5)

methanol (67-56-1)

nitric acid (7697-37-2)

nitrogen (7727-37-9)

hydrogen fluoride (7664-39-3)

acetone (67-64-1)

Nitromethane (75-52-5)

methylene chloride (75-09-2)

o-Tolunitrile (529-19-1)

boron fluoride, boron trifluoride (7637-07-2)

Benzonitrile, 2-methyl-3,5-dinitro-, 3,5-Dinitro-o-tolunitrile (948-31-2)

nitronium tetrafluoroborate

tetramethylene sulfone (126-33-0)

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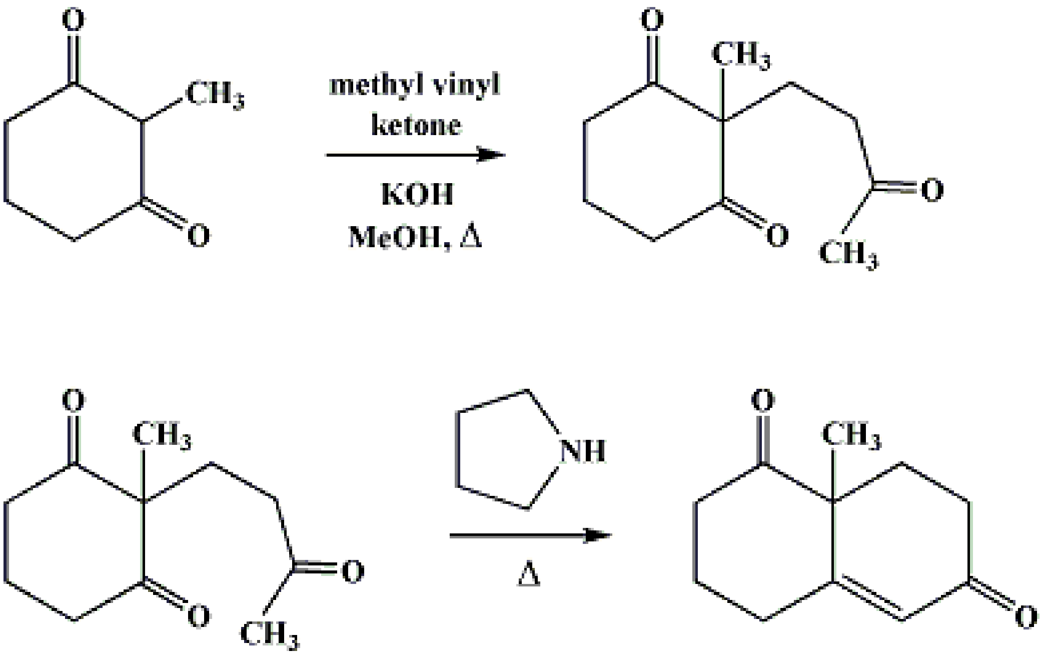
Organic Syntheses, CV 5, 486

1,6-DIOXO-8a-METHYL-1,2,3,4,6,7,8,8a-OCTAHYDRONAPHTHALENE

[1,6-Naphthalenedione, 1,2,3,4,6,7,8,8a-octahydro-8a-methyl-]



Submitted by S. Ramachandran and Melvin S. Newman[1].
Checked by Max Tishler, G. A. Stein, and G. Lindberg.

1. Procedure

A mixture of 63.1 g. (0.5 mole) of 2-methyl-1,3-cyclohexanedione (Note 1), 52.6 g. (0.75 mole) of methyl vinyl ketone (Note 2), about 0.25 g. (3 pellets) of potassium hydroxide, and 250 ml. of absolute methanol is placed in a 500-ml. round-bottomed flask fitted with a reflux condenser and a drying tube (Note 3). The mixture is heated under reflux for 3 hours, and the dione gradually goes into solution. At the end of this period, methanol and the excess methyl vinyl ketone are removed by distillation under reduced pressure (Note 4) and (Note 5). The residual liquid is dissolved in 250 ml. of benzene, a Dean-Stark phase-separating head is attached, and 20 ml. of solvent is removed by distillation at atmospheric pressure to remove traces of water and methanol. The solution is cooled well below the boiling point, 3 ml. of pyrrolidine is added (Note 6) and the mixture held at reflux for about 30 minutes, during which time about 9 ml. of water collects in the trap. Refluxing is continued for an additional 15 minutes after the separation of water ceases. The water collected is removed, and then 50 ml. of solvent is distilled. The reddish reaction mixture is cooled to room temperature and diluted with 150 ml. of ether. This solution is washed with 100 ml. of distilled water containing 15 ml. of 10% hydrochloric acid and 100 ml. of water. The

aqueous extracts are extracted with 50 ml. of ether (Note 7), and the combined organic layers are washed with three 100-ml. portions of water, then with saturated salt solution and dried over magnesium sulfate. The solvents are then removed, and on distillation of the residue (82–85 g.) (Note 8) at 0.5–1.0 mm. (Note 9) the material, b. p. 117–145°, is collected and diluted with 5 ml. of ether. The distillate is placed overnight in a refrigerator, the resulting crystals are then collected by rapid filtration and washed with about 25 ml. of cold ether (Note 10) and (Note 11). The first crop of diketone weighs 50–53 g. and is colorless. The combined mother liquors are redistilled to obtain a further 4–6 g. of crystalline product. A yield of 56–58 g. (63–65% based on dione) of 1,6-dioxo-8a-methyl-1,2,3,4,6,7,8,8a-octahydronaphthalene, m.p. 47–50°, suitable for most other purposes, is obtained (Note 12).

2. Notes

1. The 2-methyl-1,3-cyclohexanedione was prepared by the method described by Mekler et al., this volume, p. 743.
2. Technical grade methyl vinyl ketone supplied by Matheson, Coleman and Bell Co., Cincinnati, Ohio, was used without further purification.
3. The checkers found that stirring during reflux and concentration and in the cyclization step was advantageous.
4. The submitters report that the intermediate 2-methyl-2-(3'-oxobutyl)-1,3-cyclohexanedione can be isolated in 85% yield[2] at this point if desired.
5. The checkers removed methanol and methyl vinyl ketone at 650 mm. pressure with a water bath at 70°.
6. On adding pyrrolidine an exothermic reaction occurs rapidly. Cooling is needed to prevent too rapid a reaction. The submitters report that piperidine may be used in place of pyrrolidine.
7. The checkers extracted the aqueous extracts twice with 75-ml. portions of ether.
8. The checkers found the residual weights to amount to 87–100 g.
9. The checkers used a saddle-packed 5-in. column and found b.p. 137–150°/0.6–0.7 mm.; 123–150°/0.2–0.5 mm.; and 132–141°/0.5–0.8 mm.
10. A successful crystallization yields relatively large crystals which may be rapidly filtered and washed with ether with little loss. If fine crystals are obtained, it is preferable to redissolve and allow the material to crystallize again.
11. Because of the high solubility in ether (1 g. per 2.5 ml. at room temperature), the checkers washed the product with hexane (b.p. 60–71°).
12. Purer product, m.p. 48.6–50.0°, may be obtained by crystallization from ether.

3. Discussion

1,6-Dioxo-8a-methyl-1,2,3,4,6,7,8,8a-octahydronaphthalene has been obtained through the reaction of 2-methyl-1,3-cyclohexanedione with acetonedicarboxylic acid and formaldehyde,[3] 4-diethylamino-2-butanone methiodide,[3] pyridine and 4-

diethylamino-2-butanone,[4] triethylamine and 4-diethylamino-2-butanone,[5] and by cyclization of 2-methyl-2-(3-oxobutyl)-1,3-cyclohexanedione using either aluminum *tert*-butoxide or piperidine phosphate as catalyst.[6,7]

4. Merits of Preparation

1,6-Dioxo-8a-methyl-1,2,3,4,6,7,8,8a-octahydronaphthalene has been employed as an intermediate in the synthesis of terpenes[8,9] and in the projected synthesis of steroids.[4,10]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 368

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

methanol (67-56-1)

ether (60-29-7)

Acetonedicarboxylic acid

formaldehyde (630-08-0)

pyridine (110-86-1)

potassium hydroxide (1310-58-3)

piperidine (110-89-4)

magnesium sulfate (7487-88-9)

pyrrolidine (123-75-1)

hexane (110-54-3)

methyl vinyl ketone (78-94-4)

triethylamine (121-44-8)

4-diethylamino-2-butanone (3299-38-5)

1,6-DIOXO-8a-METHYL-1,2,3,4,6,7,8,8a-OCTAHYDRONAPHTHALENE, 1,6-Naphthalenedione, 1,2,3,4,6,7,8,8a-octahydro-8a-methyl- (20007-72-1)

2-Methyl-1,3-cyclohexanedione (1193-55-1)

2-Methyl-2-(3-oxobutyl)-1,3-cyclohexanedione (5073-65-4)

piperidine phosphate

ALUMINUM tert-BUTOXIDE

4-diethylamino-2-butanone methiodide

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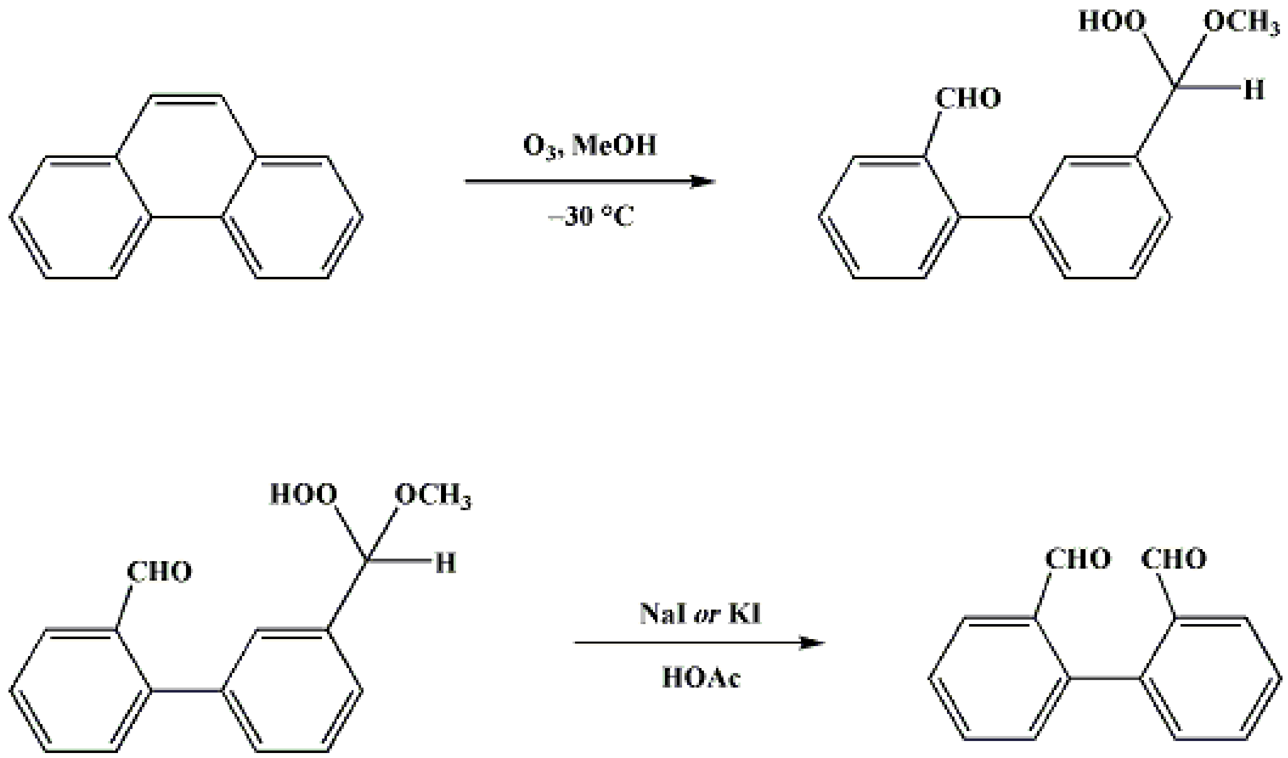
Organic Syntheses, CV 5, 489

DIPHENALDEHYDE

[Biphenyl, 2,2'-diformyl-]



Submitted by Philip S. Bailey and Ronald E. Erickson[1].
Checked by Marjorie C. Caserio and John D. Roberts.

1. Procedure

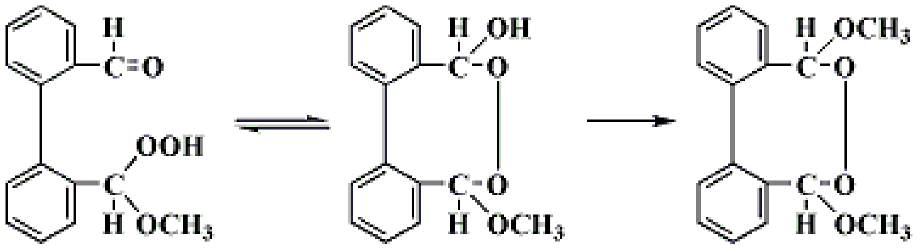
A finely divided suspension (Note 1) and (Note 2) of 10.0 g. (0.056 mole) of phenanthrene (Note 3) in 200 ml. of dry methanol (Note 4) is placed in a standard ozonolysis vessel (Note 5). The reaction mixture is cooled in a Dewar flask by an acetone-Dry Ice mixture to about −30° (Note 6) and (Note 7), and ozone (Note 8) is passed through at a rate of about 20 l. per hour (Note 9) until all the phenanthrene has reacted (Note 10).

To the cooled reaction mixture are added 25–30 g. (roughly 1.5 times the theoretical 0.112 mole) of sodium or potassium iodide and 30 ml. of glacial acetic acid (Note 11). After the addition, the reaction mixture is allowed to stand at room temperature for 30 minutes to 1 hour. The released iodine is reduced with 10% sodium thiosulfate solution, after which the reaction mixture is placed immediately under an air blast (Note 12). As the methanol evaporates, the product begins to crystallize (Note 13). The crystallization should be well advanced by the time most of the methanol has evaporated. Water is then added, and the solid is removed by filtration and dried. The yield of crude product, softening at about 54° and melting at 59–62°, is 9.2–11.4 g. (78–96%). The crude product may be recrystallized by dissolving it in the minimal amount (40–50 ml.) of dry ether and slowly adding about 150 ml. of ligroin (Note 14). Small crystals separate halfway through the addition, and crystallization is completed by cooling the mixture in an acetone-Dry Ice bath. An 80–90% recovery of pale yellow crystals melting at 62–63° is obtained. A second recrystallization from 70% aqueous ethanol gives nearly colorless crystals melting at

62.5–63.5° (Note 15).

2. Notes

1. This is produced by dissolving the phenanthrene in the refluxing solvent and cooling rapidly.
2. The finely divided suspension is necessary in order for the phenanthrene to go into solution and react readily during the ozonolysis.
3. Eastman white label 599, m.p. 99–100°, was used.
4. Commercial methanol reagent containing 0.1% or less of water is satisfactory.
5. The usual long, cylindrical, gas-absorption-type vessel with an inlet tube extending to near the bottom is satisfactory.[2] The total volume of the vessel should be at least twice that of the reaction solution. More elaborate reaction vessels equipped with a stirrer[3] are very useful in reactions such as this in which the reactant is suspended in the solvent. However, the commercially available vessels of this type are not large enough for the reaction mixture described here.
6. The temperature of the reaction mixture should not be allowed to rise above −20°, because at higher temperatures ozone tends to react with the solvent and the reactions shown below also occur. Compound III is not readily reduced to the dialdehyde.
7. Compound II may precipitate during ozonolysis at −30° or below. This is in no way detrimental.
8. A Welsbach T23 ozonator was used by the submitters. Oxygen dried by a Pittsburg Laboratory-Lectrodryer to a dew point of −60° was passed through the ozonator, which was set to produce a 5–6% by weight concentration of ozone.[4] Following the ozonation flask were a potassium iodide trap and a wet-test meter.[4] The checkers used a simple ozonator capable of producing 3.8% by weight of ozone at a flow rate of 20 l. per hour from oxygen dried by passage through a 30-cm. column of silica gel.



I II III

9. The rate should be sufficiently great to cause considerable agitation of the suspended phenanthrene. As the reaction proceeds, the reaction vessel should be shaken frequently in order to maintain good contact between the phenanthrene and ozone. For smaller runs a reaction vessel that includes a stirrer is advantageous (Note 5).
The checkers found it convenient to use leads of Tygon tubing of sufficient length to allow the reaction flask to be withdrawn at intervals from the Dewar flask and shaken manually.
10. Unreacted ozone starts passing through to the potassium iodide trap toward the end of the reaction. However, it is best to continue the reaction until all the suspended phenanthrene has disappeared. This usually requires a total of 1.1–1.3 mole-equivalents of ozone. Unless all the phenanthrene has reacted, difficulty is encountered in the crystallization and/or recrystallization of the dialdehyde.
11. The reduction may be carried out in the ozonolysis flask, or the reaction mixture may be transferred first to an Erlenmeyer flask or beaker. The iodide and acetic acid should be

added simultaneously. The reaction of peroxides with iodide ion is exothermic. The temperature of the reaction mixture should be kept below –20° while the sodium iodide and acetic acid are added, after which it may be allowed to rise slowly to room temperature.
12. It seems to be detrimental to the crystallization and recrystallization of the product to postpone the evaporation of the reaction mixture, probably because the product becomes contaminated with sulfur if the reduced reaction mixture is allowed to stand.
13. Sometimes difficulty is encountered in starting the crystallization, since the product may separate as a yellow oil. It is helpful to induce crystallization by rubbing the sides of the vessel with a stirring rod and seeding the solution with any crystals that form on the sides of the vessel during the evaporation.
14. The ligroin used was Skellysolve B.
15. About 30 ml. of warm absolute ethanol readily dissolves 8–9 g. of product. Addition of 15 ml. of water and cooling effect crystallization with about 90% recovery of product.

3. Discussion

Previously, diphenaldehyde has been made by the Ullman coupling of *o*-iodobenzaldehyde,[5,6] by bromination of *o,o'*-bitolyl and hydrolysis of the resulting tetrabromo compound,[7] and by lithium aluminium hydride reduction of the N-methylanilide of diphenic acid.[8] These methods involve more steps and give poorer yields than ozonolysis of phenanthrene.

The present method is based on the earlier described ozonolysis of phenanthrene in methanol.[9] The reduction of the peroxidic reaction mixture with trimethyl phosphite to give diphenaldehyde, isolated as the di-*p*-nitrophenylhydrazone, in quantitative yield has been described recently.[10] The disadvantage of this method is that the dialdehyde cannot be isolated in the free state in high yield. Diphenaldehyde has also been obtained by sodium iodide reduction of peroxidic products from ozonolysis of phenanthrene in solvents that do not react[2] with the zwitterion intermediate.[11,12] The yields are inferior to those obtained by the present method. The aldehyde has been obtained in 91% yield using dimethyl sulfide as the reducing agent.[13] An 81% yield of diphenaldehyde has been obtained from the ozonolsis in acqueous *t*-butyl alcohol followed by distillation of the solvent at pH 7.5.[14] Hydrogen peroxide is a by-product.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 493
- Org. Syn. Coll. Vol. 6, 43
- Org. Syn. Coll. Vol. 7, 168

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ligroin

Diphenaldehyde

N-methylanilide of diphenic acid

di-p-nitrophenylhydrazone

ethanol (64-17-5)

acetic acid (64-19-7)

methanol (67-56-1)

ether (60-29-7)

oxygen (7782-44-7)

potassium iodide (7681-11-0)

sodium thiosulfate (7772-98-7)

sulfur (7704-34-9)

iodine (7553-56-2)

sodium (13966-32-0)

hydrogen peroxide (7722-84-1)

sodium iodide (7681-82-5)

ozone (10028-15-6)

iodide (20461-54-5)

dimethyl sulfide (75-18-3)

phenanthrene (85-01-8)

lithium aluminium hydride (16853-85-3)

t-butyl alcohol (75-65-0)

trimethyl phosphite (121-45-9)

Biphenyl, 2,2'-diformyl- (1210-05-5)

o-iodobenzaldehyde (26260-02-6)

o,o'-bitolyl (612-75-9)

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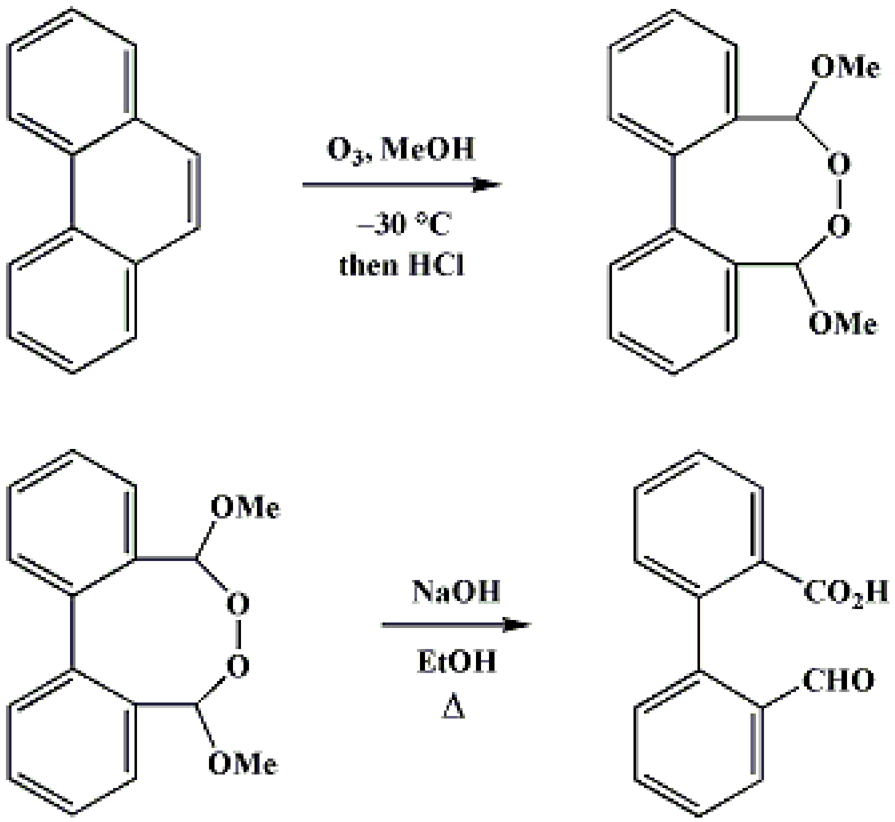
Organic Syntheses, CV 5, 493

DIPHENALDEHYDIC ACID

[2-Biphenylcarboxylic acid, 2'-formyl-]



Submitted by Philip S. Bailey and Ronald E. Erickson[1].
Checked by Carole L. Olson and John D. Roberts.

1. Procedure

A. *3,8-Dimethoxy-4,5,6,7-dibenzo-1,2-dioxacyclooctane*. The ozonolysis of 10 g. (0.0562 mole) of phenanthrene in dry methanol is carried out as described in the diphenaldehyde preparation (p. 489). The reaction mixture is not reduced, however, but is acidified with 1–3 drops of concentrated hydrochloric acid (Note 1) and allowed to stand at room temperature for an hour and then in the refrigerator for several hours or overnight. Suction filtration yields 11.5–12.5 g. (75–82%) of crystals melting at 178–181°. Trituration with methyl ethyl ketone gives a 90–95% recovery of colorless crystals melting at 180–181° (Note 2).

B. *Diphenaldehydic acid*. A mixture of 10 g. (0.0368 mole) of 3,8-dimethoxy-4,5,6,7-dibenzo-1,2-dioxacycloöctane, 50 ml. of 10% sodium hydroxide solution, and 200 ml. of 95% ethyl alcohol is heated under reflux for 15 minutes, during which time the solid dissolves (Note 3). The solution is cooled, acidified with concentrated hydrochloric acid, and diluted to the cloud point with water. Crystallization is induced

by rubbing the side of the vessel with a stirring rod (Note 4). More water is then added slowly until crystallization is complete. Filtration yields 6.7–7.3 g. (81–88%) of colorless to yellowish crystals melting at 130–132°. Recrystallization from 100 ml. of 1:1 methanol-water gives an 80–95% recovery of diphenaldehydic acid melting at 134–135° (Note 5), (Note 6), and (Note 7).

2. Notes

1. The acid catalyzes formation of the dimethoxy compound from the initial ozonolysis products (see Note 6 of the diphenaldehyde preparation, p. 490). Compound I forms only slowly in the absence of the hydrochloric acid.
2. The trituration is carried out at room temperature, but the mixture is cooled before filtering. The product can be recrystallized from methyl ethyl ketone, but this requires large volumes of the solvent and is unnecessary.
3. After solution has occurred, 1 ml. of the solution is acidified and tested with sodium or potassium iodide. If no iodine is released, the reaction is complete.
4. If the solution resists crystallization, it can be evaporated one-half or tow-thirds of its volume and cooled further. The checkers found that, if product was allowed to oil out and solidify, the subsequent purification was rendered more difficult.
5. Often recrystallization is unnecessary since the first crystalline product melts at 134–135°. The yields then are 81–84%.
6. If sodium hydroxide is omitted in this preparation and the reaction mixture is refluxed until it no longer gives a positive peroxide test with iodide ion (Note 3) (about 2 hours), the product is the methyl ester of diphenaldehydic acid in 91–98% yield (m.p. 50–51°).[2]
7. If, in the reaction mixture described, twice the volume of 10% sodium hydroxide solution and 25 ml. of 30% hydrogen peroxide are employed and the reaction mixture is refluxed until it no longer gives a positive peroxide test with iodide ion (about 30 minutes to 1 hour), the product is diphenic acid (m.p. 220–223°) in 73–85% yield.

3. Discussion

The method here described is based on the reported ozonolysis of phenanthrene in methanol, followed by conversion of the initial ozonolysis product to diphenaldehyde (p. 489), diphenaldehydic acid, methyl diphenaldehydate (Note 6), and diphenic acid (Note 7).[2] Diphenaldehydic acid has previously been made in low yields by oxidative decomposition of the monohydrazide of diphenic acid.[3,4] The presently described method is far superior, not only in yield, but also in simplicity.

Diphenic acid has been prepared by the reduction of diazotized anthranilic acid with cuprous ion,[5] Ullman coupling of potassium *o*-bromobenzoate,[6] and oxidation of phenanthrene or phenanthrenequinone with various oxidizing agents.[7] The latter

methods have been reviewed recently.[7] The ozonolysis method has also been carried out in solvents[8] that do not react with the zwitterion intermediate.[9]

Of the various routes to diphenic acid, the present method and the peracetic acid oxidation of phenanthrene[7] seem to be the simplest. The yields are equally good.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Diphenic acid

Diphenaldehyde

Diphenaldehydic acid

methyl ester of diphenaldehydic acid

methyl diphenaldehydate

ethyl alcohol (64-17-5)

hydrochloric acid (7647-01-0)

methanol (67-56-1)

sodium hydroxide (1310-73-2)

potassium iodide (7681-11-0)

iodine (7553-56-2)

sodium (13966-32-0)

hydrogen peroxide (7722-84-1)

Anthranilic Acid (118-92-3)

phenanthrenequinone (84-11-7)

methyl ethyl ketone (78-93-3)

phenanthrene (85-01-8)

peracetic acid (79-21-0)

potassium o-bromobenzoate

3,8-Dimethoxy-4,5,6,7-dibenzo-1,2-dioxacyclooctane (6623-54-7)

2-Biphenylcarboxylic acid, 2'-formyl- (6720-26-9)

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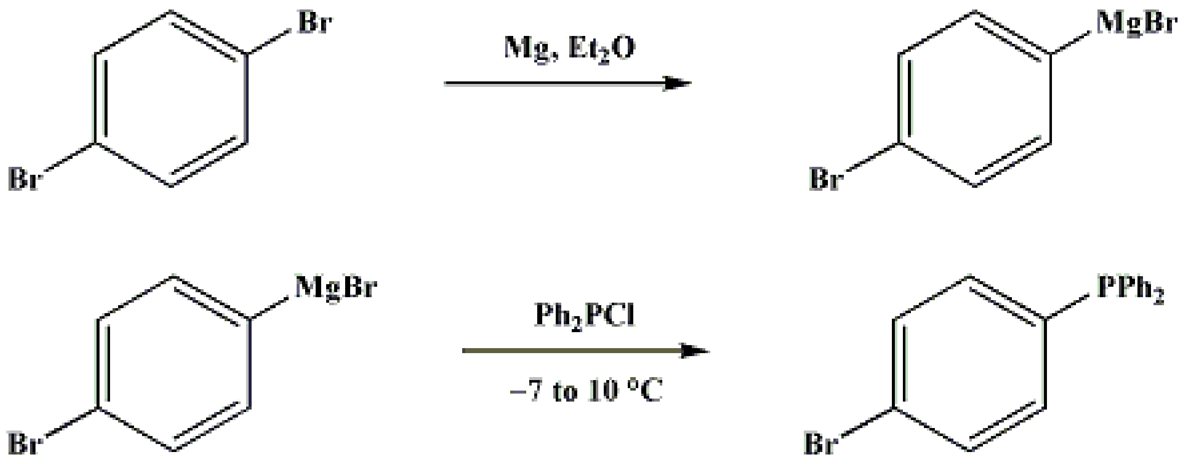
Organic Syntheses, CV 5, 496

DIPHENYL-*p*-BROMOPHENYLPHOSPHINE

[Phosphine, (*p*-bromophenyl)diphenyl]



Submitted by G. P. Schiemenz[1]
Checked by V. Z. Williams, Jr. and K. B. Wiberg.

1. Procedure

A dry 1-l. round-bottomed flask with five outlets is equipped with a sealed stirrer, a 500-ml. dropping funnel, a reflux condenser attached to a calcium chloride tube, an inlet for dry nitrogen (a weak stream of which is maintained through all the reaction until the hydrolysis step), and a thermometer reaching close to the bottom. In the flask are placed 9.0 g. (0.38 g. atom) of magnesium turnings, a crystal of iodine, and about 25 ml. of dry ether. With stirring, about 15 ml. of a solution of 88.5 g. (0.38 mole) of *p*-dibromobenzene (Note 1) in 500 ml. of dry ether (Note 2) is added at once. When the reaction has started, the remaining ether solution is added at a rate which maintains rapid refluxing. After the *p*-dibromobenzene has been added, the mixture is stirred at room temperature for 1.5 hours.

The mixture is then cooled by means of an ice-sodium chloride bath. When the internal temperatures has reached –7°, a solution of 71.8 g. (0.33 mole) of chlorodiphenylphosphine (Note 3) in 100 ml. of dry ether is added at such a rate that the internal temperature does not exceed +10°. The addition requires about 1.25 hours. The cooling bath is then removed and stirring continued for 1.5 hours. The flask is then again immersed in an icesodium chloride bath, and 150 ml. of a cold saturated aqueous ammonium chloride solution is added slowly. The ether is decanted and the remainder acidified with hydrochloric acid and extracted three times with 125 ml. of benzene each (Note 4). From the combined ether and benzene solutions, the solvents are evaporated and the residue is distilled at reduced pressure. After the low-boiling material, some *p*-dibromobenzene distills and crystallizes in the distillation bridge. At 2×10^{-2} mm., heating is continued until the phosphine reaches the stillhead. At this

stage the distillation is interrupted, the stillhead and condenser containing *p*-dibromobenzene replaced by a clean, short distillation bridge without condenser, and the phosphine distilled at 2×10^{-2} to 10^{-3} mm., no forerun being taken (Note 5). The main bulk distills at 180–185° (2×10^{-2} mm.). The colorless, oily distillate begins to crystallize in the receiving flask during or shortly after the distillation (Note 6) and weighs 81–83 g. (73–77% yield) (Note 7), m.p. 64–71°. This material is sufficiently pure for further reactions, *e.g.*, Grignard reaction. A sample may be recrystallized from methanol to give colorless needles, m.p. 79–80°.

2. Notes

1. A commercial product, m.p. 88–89°, was used without purification.
2. The *p*-dibromobenzene may be dissolved by heating the ether to reflux. If substantially less ether is used, part of the compound will crystallize out at room temperature.
3. A commercial product from Aldrich Chemical Company was used without purification.
4. When a larger excess of Grignard reagent was used, a polymer insoluble in either phase was observed.
5. Dividing the distillate into a forerun and a constant-boiling main fraction did not improve the melting point of the latter, 66 g. (62%) of phosphine being obtained. The forerun likewise consisted mainly of the phosphine.
6. The distillation apparatus should be taken apart and to a hard glass which blocks the joints and can hardly be removed from the flask.
7. No improvement of the yield was obtained when a 50% excess of Grignard reagent was used.

3. Discussion

This preparation[2] is an example of the general and versatile synthesis of *t*-phosphines of Michaelis[3] which, however, is usually not applicable for aromatic phosphines substituted with –M substituents. The synthesis is an interesting case of the Grignard reaction in that it includes the addition of a Grignard reagent to an "inorganic" single bond and makes use of the mono-Grignard reagent of a dihalogen compound with two equivalent halogen atoms. Similarly, from the mono-Grignard reagents of *m*-dibromobenzene in ether[4] and of *p*-dichlorobenzene in tetrahydrofuran,[5] diphenyl-*m*-bromophenyl-[4] and diphenyl-*p*-chlorophenylphosphine[2] were prepared in yields of 58 and 84%, respectively.

A slightly higher yield of diphenyl-*p*-bromophenylphosphine has been reported using more expensive reagents (tetrahydrofuran and butyllithium rather than ether and magnesium turnings).[6] An alternative route consists of a Friedel-Crafts type of reaction of bromobenzene with phosphorus trichloride and reaction of the resulting dichloro-*p*-bromophenylphosphine with phenylmagnesium bromide. The submitter

found this sequence less convenient, and the overall yield is given as only 21%.[7,8,9] In addition, this path fails for the *meta* isomer, and with other substituents the first step yields a mixture of isomers.[11] On the other hand, some phosphines containing – *M* substituents were prepared by making use of the second step.[12,13] A more facile synthesis of such phosphines starts from the title compound[2] or its *meta* isomer,[4] the key step being a second Grignard reaction with subsequent carbonation to give the diphenylphosphinobenzoic acids[2,4] which are also accessible by several other, apparently less convenient and more expensive, routes.[8,12,13,14,15] *p*-Diphenylphosphinobenzoic acid has been used in place of triphenylphosphine in a modification of the Wittig olefination, giving rise to a phosphine oxide which is scarcely soluble in organic solvents and easily soluble in aqueous carbonate solution, and therefore facilitates separation of the olefin from the phosphine oxide.[10]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

methanol (67-56-1)

ether (60-29-7)

ammonium chloride (12125-02-9)

magnesium turnings (7439-95-4)

nitrogen (7727-37-9)

iodine (7553-56-2)

bromobenzene (108-86-1)

phosphorus trichloride (7719-12-2)

Phenylmagnesium bromide (100-58-3)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

triphenylphosphine (603-35-0)

phosphine oxide

chlorodiphenylphosphine (1079-66-9)

p-dibromobenzene (106-37-6)

p-dichlorobenzene (106-46-7)

m-dibromobenzene (108-36-1)

Diphenyl-p-bromophenylphosphine, Phosphine, (p-bromophenyl)diphenyl (734-59-8)

diphenyl-m-bromophenyl-

diphenyl-p-chlorophenylphosphine

dichloro-p-bromophenylphosphine

p-Diphenylphosphinobenzoic acid (2129-31-9)

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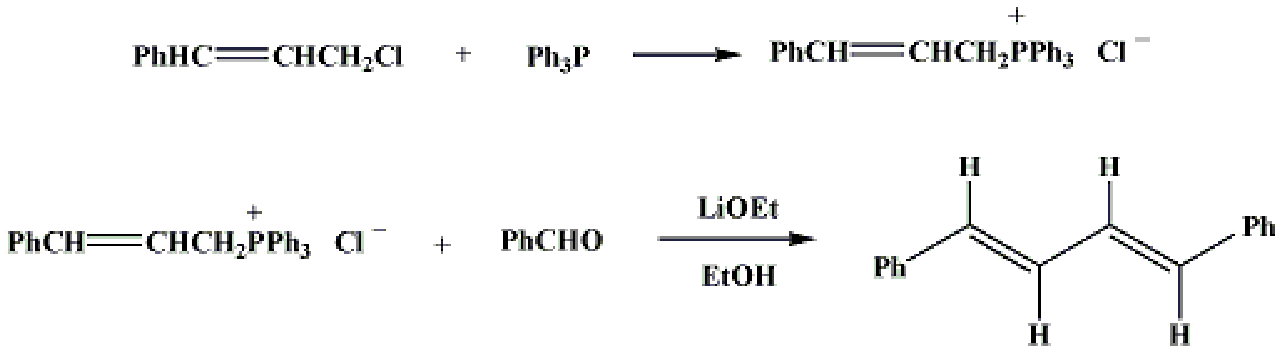
1,4-DIPHENYL-1,3-BUTADIENE

[1,3-Butadiene,1,4-diphenyl-]



Submitted by Richard N. McDonald and Tod W. Campbell[1].
Checked by M. S. Newman, R. Marshall, and W. N. White.

1. Procedure

A. *Triphenylcinnamylphosphonium chloride*. A mixture of 40 g. (0.26 mole) of (3-chloropropenyl) benzene (Note 1) and 92 g. (0.35 mole) of triphenylphosphine (Note 2) in 500 ml. of xylene is heated at reflux for 12 hours with stirring. The mixture is allowed to cool to about 60°, and the colorless crystalline product is filtered, washed with 100 ml. of xylene, and dried in a vacuum oven at about 20 mm. pressure and 60° to constant weight. The yield is 99–101 g. (91–93%), m.p. 224–226° (Note 3).

B. *1,4-Diphenylbutadiene*. To a solution of 60.0 g. (0.145 mole) of triphenylcinnamylphosphonium chloride and 16.4 g. (0.155 mole) of benzaldehyde in 200 ml. of ethanol (Note 4) is added 760 ml. of 0.2*M* lithium ethoxide in ethanol (Note 5) and (Note 6). After allowing this mixture to stand 30 minutes, 700 ml. of water is added (Note 7) and the colorless crystals are filtered, washed with 150 ml. of 60% ethanol, and dried in the vacuum oven at 65°. The yield of crystalline product, m.p. 153–156°, is 17.9–19.9 g. (60–67%) (Note 8). The product is the *trans-trans* isomer and is pure enough for most purposes (Note 9). Recrystallization from cyclohexane gives a product with m.p. 154–156°.

2. Notes

1. Eastman Organic Chemicals, white label grade, used without purification.
2. Commercial triphenylphosphine was used without further purification. Metal and Thermit Corp., Rahway, New Jersey, now offers this reagent for sale at a modest price.
3. The phosphonium salt can be recrystallized to analytical purity by dissolving in a small amount of boiling ethanol, adding ether at the boil until cloudy, and allowing the salt to crystallize in a refrigerator.
4. Commercial anhydrous ethanol was used throughout without further purification.
5. The lithium ethoxide solution is prepared by dissolving 1.40 g. of lithium wire in 1 l. of anhydrous ethanol.
6. A transient orange color is immediately formed, and it is replaced by crystallization of

the product in about 1 minute.
7. Triphenylphosphine oxide is soluble in 60% aqueous ethanol; therefore it remains in the filtrate and affords no difficulty.
8. The yield can probably be increased by carrying out the reaction in an ether solvent with an alkyllithium as base, but the simplicity and relative ease of the conditions described appear to make the possible yield advantage secondary.
9. This procedure has been applied successfully to the synthesis of substituted bistyryls, i. e., 1-(*p*-tolyl)-4-phenylbutadiene (76%), 1-(4-methoxyphenyl)-4-phenylbutadiene (63%), and 1-(4-acetamidophenyl)-4-phenylbutadiene (61%), by using the corresponding substituted benzaldehydes.

3. Discussion

1,4-Diphenylbutadiene has been obtained from phenylacetic acid and cinnamaldehyde with lead oxide,[2] by the dehydrogenation of 1,4-diphenyl-2-butene with butyllithium,[3] and by the coupling reaction of benzenediazonium chloride and cinnamylideneacetic acid.[4] The present method[5] gives better yields than those previously reported, is adaptable to the preparation of a variety of substituted bistyryls, and is relatively easy to carry out.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

ether (60-29-7)

lead oxide

benzenediazonium chloride

cyclohexane (110-82-7)

benzaldehyde (100-52-7)

Phenylacetic acid (103-82-2)

xylene (106-42-3)

cinnamaldehyde

Lithium wire (7439-93-2)

1,4-Diphenylbutadiene, 1,4-Diphenyl-1,3-butadiene, 1,3-Butadiene,1,4-diphenyl- (886-65-7)

butyllithium (109-72-8)

triphenylphosphine (603-35-0)

triphenylphosphine oxide (791-28-6)

(3-chloropropenyl) benzene (21087-29-6)

triphenylcinnamylphosphonium chloride

lithium ethoxide

1-(4-methoxyphenyl)-4-phenylbutadiene

1-(4-acetamidophenyl)-4-phenylbutadiene

1,4-diphenyl-2-butene

cinnamylideneacetic acid

1-(p-tolyl)-4-phenylbutadiene

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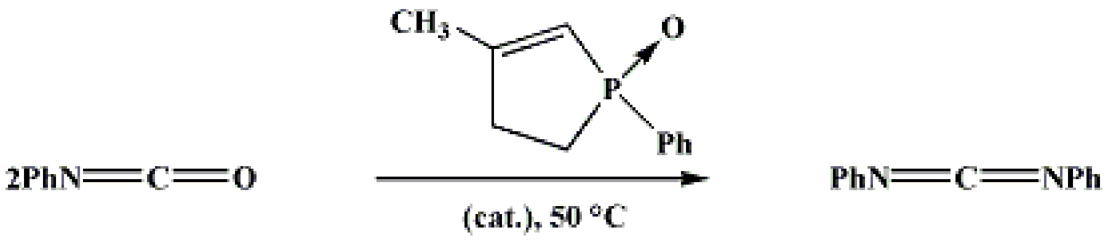
DIPHENYLCARBODIIMIDE

[Carbodiimide, diphenyl-
Method I]



Submitted by T. W. Campbell[1] and J. J. Monagle.
Checked by W. S. Wadsworth and W. D. Emmons.

1. Procedure

A 250-ml. four-necked flask is fitted with a sealed mechanical stirrer, a condenser protected by a drying tube, a thermometer, and a gas inlet. The flask is swept with a slow stream of nitrogen (Note 1) and dried by flaming. One hundred milliliters (108 g., 0.91 mole) of phenyl isocyanate (Note 2) is pipetted into the flask. One gram (0.052 mole) of 3-methyl-1-phenylphospholene 1-oxide[2] is added (Note 3), and the reaction mixture is heated at 50° under nitrogen for 2.5 hours (Note 4); at this point only a faint test for carbon dioxide is obtained when the off-gas is passed through saturated calcium hydroxide solution. The reaction mixture is cooled and rapidly transferred to a Claisen flask. Distillation yields 72–82 g. (82–93%) of diphenylcarbodiimide, obtained as a clear water-white oil, b.p. 110–112°/0.2 mm., n_D^{25} 1.6360–1.6362 (Note 5).

2. Notes

1. Commercial nitrogen is dried by passage through concentrated sulfuric acid.
2. Best results were obtained with material obtained from Eastman Kodak Company. Either freshly distilled material or material from a freshly opened bottle may be used. Material obtained from several other sources gave variable results even after redistillation.
3. Since the phosphine oxides are very hygroscopic and the reaction rate is sensitive to traces of moisture, the catalyst can be conveniently stored and added to the reaction mixture in long-necked, thin-walled glass ampoules. The catalyst may be dried by distillation (b.p. 168–170°/1.4 mm.) into a receiver containing the inverted ampoules. When sufficient catalyst has distilled to fill the ampoules, nitrogen is bled into the receiver, forcing the catalyst into the ampoules. An ampoule about 15 mm. in diameter will hold about 1 g. of catalyst. A small air space should be left to facilitate crushing the ampoule.

4. Use of more catalyst or higher temperature leads to an increasingly vigorous evolution of carbon dioxide.

5. Diphenylcarbodiimide can be stored for several weeks at 0°. At room temperature it gradually solidifies to a mixture of trimer and polymer. The monomer can be separated from the solid by vacuum distillation.

3. Discussion

Carbodiimides have been prepared by desulfurization of thioureas by metal oxides,[3] by sodium hypochlorite,[4] or by ethyl chloroformate in the presence of a tertiary amine;[5] by halogenation of ureas or thioureas followed by dehydrohalogenation of the N,N'-disubstituted carbamic chloride;[6] and by dehydration of disubstituted ureas using *p*-toluenesulfonyl chloride and pyridine.[7] The method described above is a modification of that of Campbell and Verbanc.[8]

This method may be applied to the synthesis of a variety of aryl and alkyl carbodiimides.[9] Other catalysts may also be used,[10] but the especially active one described here is the one most easily obtained. The method is superior to other methods reported in that it provides pure products under very simple and mild conditions, allows the use of readily available isocyanates with or without the use of solvent, and offers extremely easy work-up.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 504

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

phosphine oxides

tertiary amine

sulfuric acid (7664-93-9)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

pyridine (110-86-1)

calcium hydroxide

sodium hypochlorite (7681-52-9)

ethyl chloroformate (541-41-3)

phenyl isocyanate (103-71-9)

carbamic chloride

Diphenylcarbodiimide, Carbodiimide, diphenyl- (622-16-2)

3-Methyl-1-phenylphospholene 1-oxide (707-61-9)

p-Toluenesulfonyl chloride (98-59-9)

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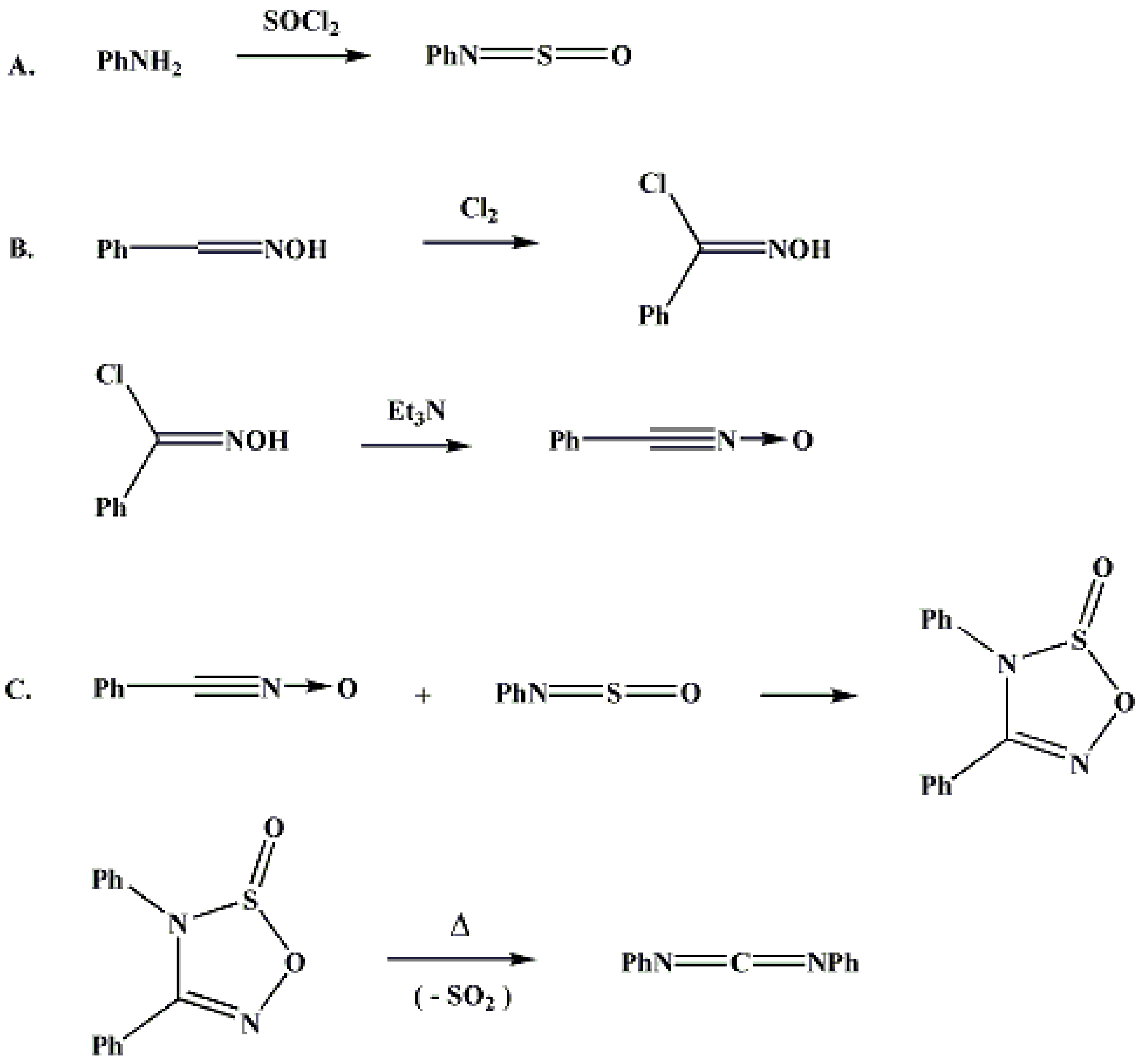
Organic Syntheses, CV 5, 504

DIPHENYLCARBODIIMIDE

[Carbodiimide, diphenyl
Method II]



Submitted by S. Rajagopalan, B. G. Advani, and C. N. Talaty[1].
Checked by A. Eschenmoser, R. Scheffold, and P. Mayer.

1. Procedure

Caution! All the following operations should be carried out in a well-ventilated hood.

A. *N-Sulfinylaniline* (Note 1). A solution of 82.5 g. (0.69 mole) of pure thionyl chloride (Note 2) in 100 ml. of anhydrous benzene is added slowly to a solution of 46.5 g. (0.5 mole) of freshly distilled aniline in 250 ml. of anhydrous benzene contained in a 1-l.

round-bottomed flask, with swirling and occasional cooling in an ice bath (if necessary). An immediate precipitation of aniline hydrochloride occurs. After the addition of the thionyl chloride solution is complete, the mixture is heated to reflux, protected from moisture, on a heating mantle until a clear solution is obtained (2–5 hours). The solvent and excess thionyl chloride are evaporated under reduced pressure (Note 3) at 50° and the residual brownish yellow liquid is distilled under vacuum to yield 63–65 g. (91–94%) of yellow N-sulfinylaniline, b.p. 88–95° (17–20 mm.), $n^{21}D$ 1.6253.

B. *Benzohydroxamoyl chloride* (Note 4). A four-necked flask equipped with a rubber-sealed stirrer, a thermometer, an inlet tube, and an outlet tube attached to a calcium chloride tube (Note 5) and containing a solution of 50 g. (0.41 mole) of benzaldoxime (Note 6) in 450 ml. of pure chloroform (Note 7) is cooled in a dry ice-acetone bath (Note 8). When the temperature of the solution reaches −2°, stirring is started and a stream of chlorine gas (Note 9) is passed through at such a rate as to maintain the temperature below 2°. After 1 hour the passage of chlorine is stopped and the greenish yellow solution is transferred to a 1-l. round-bottomed flask which is then connected to an aspirator to remove most of the dissolved chlorine. The light yellow solution thus obtained is stripped of the solvent at 40° under reduced pressure (Note 3). The almost colorless residual liquid is dissolved in 150 ml. of petroleum ether (b.p. 40–60°) and cooled, with scratching, in a dry ice-acetone bath, whereupon a colorless crystalline solid starts separating. The cooling is continued for 30 minutes and the solid is then filtered, washed with 50 ml. of cold petroleum ether (b.p. 40–60°), pressed to remove most of the adhering mother liquor, and dried over a filter paper. The yield of benzohydroxamoyl chloride, m.p. 48–52°, which is pure enough (Note 10) for the next step, is 33–38 g. (51–59%).

C. *Diphenylcarbodiimide* (Note 11). A solution of 15.6 g. (0.1 mole) of benzohydroxamoyl chloride in 300 ml. of anhydrous benzene contained in a 500-ml. wide-mouthed Erlenmeyer flask is cooled to 5°, agitated vigorously, and treated with 10.1 g. (0.1 mole) of freshly distilled triethylamine added in one portion. The mixture is shaken continuously for 3 minutes while being cooled in an ice bath and then filtered rapidly through a Buchner funnel into a filter flask cooled in an ice bath. The residue is washed with 50 ml. of anhydrous benzene, pressed to remove as much of the adhering solution as possible, dried in an oven at 60°, and weighed (Note 12). The yield of the triethylamine hydrochloride, m.p. 254–256°, is 13.4–13.6 g. (97–99%).

The combined filtrates containing benzonitrile oxide are transferred to a 1-l. round-bottomed flask, treated immediately with 13.9 g. (0.1 mole) of N-sulfinylaniline added in one portion, with swirling, and set aside protected from moisture, while the temperature reaches a maximum of 33–34° (usually 15 minutes). The mixture is then heated to reflux, protected from moisture, in a temperature-controlled oil bath for 3–5 hours. Continuous evolution of sulfur dioxide takes place during this period at the end of which the mixture is cooled and evaporated under reduced pressure (Note 3) at 70–80° to remove the solvent. The residual dark brown liquid is transferred to a 50-ml., pear-shaped distilling flask (Note 13) and heated, protected from moisture, at 110° for 30 minutes to complete the decomposition. It is then cooled and distilled under high vacuum (Note 14).

Unchanged N-sulfinylaniline (2.0–2.5 g.) distills over at 45–50° (0.1–0.2 mm.). A second fraction (1.2–1.5 g.) is collected until the temperature reaches 112° (Note 15); then diphenyl carbodiimide is collected at 114–117° (0.1–0.2 mm.) as a clear yellow liquid; yield 10.5–10.8 g. (54–56%) (Note 16); $n^{23}D$ 1.6355; $\nu_{max.}^{CHCl_3}$ 2140 cm.$^{-1}$ (very strong), 2110 cm.$^{-1}$ (medium), and 1480 cm.$^{-1}$ (medium) (Note 17).

2. Notes

1. This method is essentially that described by Kresze and co-workers[2] which is a modification of the original procedure of Michaelis.[3]
2. The yield of the product depends on the purity of the thionyl chloride. Thionyl chloride obtained from Riedel-Haen (Hannover, West Germany) was used as such.
3. A rotary evaporator equipped with a constant-temperature water bath is ideal for this purpose.
4. This method is essentially that of Werner and Buss.[4]
5. The calcium chloride tube is, in turn, attached to a rubber tube which is either led out of a ventilator or connected to a water pump through which water is adjusted to flow gently.
6. Purum grade α-benzaldoxime, m.p. 32°, obtained from Fluka AG (Buchs, Switzerland) was used most of the time. When out of stock, it was prepared in the usual manner and distilled before use.
7. Chloroform distilled over phosphorus pentoxide was used.
8. An ice-salt mixture is not adequate to regulate the temperature, as it rises steeply when chlorine is let in.
9. It is better to lead the gas through a drying tower containing small lumps of calcium chloride before passing it through the reaction mixture.
10. Although it is not necessary, the product can be recrystallized from petroleum ether (b.p. 40–60°) without much loss. The melting point of the recrystallized product is 51–52°.
11. This is a modification of the new general method for the preparation of carbodiimides by the thermolysis of 5-substituted 4-aryl-1,2,3,5-thiaoxadiazole-1-oxides described recently by Rajagopalan and Advani,[5] whereby the 4,5-diphenyl-1,2,3,5-thiaoxadiazole-1-oxide, which is formed in this reaction, is not isolated but decomposed *in situ*.
12. The drying and weighing of triethylamine hydrochloride should be carried out only after N-sulfinylaniline has been added to the solution of benzonitrile oxide, as otherwise the latter, not being very stable in the free state, would dimerize resulting in the reduction in yield of the carbodiimide.
13. At this point it is best to use the flask that is going to be employed subsequently for the distillation of the carbodiimide to avoid unnecessary loss in transferring from one flask to the other.
14. The temperature of the bath used in this distillation should not exceed 160°. A short-path distillation apparatus should be used.
15. Most of this fraction is comprised of diphenylcarbodiimide.
16. The yield, on the basis of average recovered N-sulfinylaniline, is 64–66%.

17. The infrared spectrum was determined in a Perkin-Elmer Infracord 337 spectrophotometer.

3. Discussion

Diphenylcarbodiimide can be prepared by the removal of the elements of hydrogen sulfide from N,N'-diphenylthiourea by mercuric oxide,[6] lead oxide,[7] sodium hypochlorite,[8] or phosgene;[9] by heating phenylisocyanate in a sealed tube[10] or in the presence of catalysts such as phospholenes[11] or phosphonates;[12] by the pyrolysis of N,N', N''-triphenylguanidine,[13] 3-phenyl-4-phenylimino-1,3-thiazetidin-2-one (carbonythiocarbanilide),[14] and 1,5-diphenyl tetrazole;[15] and by heating phenylisocyanide dichloride with aniline hydrochloride in an inert solvent.[16]

Although this procedure offers no advantage over that of Hünig, Lehmann, and Grimmer,[7] it effectively illustrates a new method for the synthesis of symmetrical and unsymmetrical carbodiimides.[5] The generality of this procedure is limited only by the number of substituted benzohydroxamoyl chlorides that can be made without difficulty, as a variety of N-sulfinylamines is easily accessible.[2]

N-Sulfinylaniline, the procedure for the preparation of which is described in Part A, is a versatile intermediate in the synthesis of heterocyclic compounds.[2,5,17] Benzohydroxamoyl chloride, the method for the preparation of which is given in Part B, is the precursor of the highly reactive benzonitrile oxide, the diverse dipolar addition reactions of which have been thoroughly investigated.[18] A wide array of heterocyclic compounds can be prepared starting with benzonitrile oxide.[18]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 787

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

Benzohydroxamoyl chloride

phospholenes

N,N',N"-triphenylguanidine

carbonythiocarbanilide

benzohydroxamoyl chlorides

N-sulfinylamines

calcium chloride (10043-52-4)

Benzene (71-43-2)

aniline (62-53-3)

thionyl chloride (7719-09-7)

chloroform (67-66-3)

lead oxide

hydrogen sulfide (7783-06-4)

sulfur dioxide (7446-09-5)

aniline hydrochloride (142-04-1)

mercuric oxide (21908-53-2)

chlorine (7782-50-5)

phosgene (75-44-5)

sodium hypochlorite (7681-52-9)

N,N'-diphenylthiourea (102-08-9)

phenylisocyanate (103-71-9)

triethylamine (121-44-8)

Triethylamine hydrochloride (554-68-7)

carbodiimide

Diphenylcarbodiimide, Carbodiimide, diphenyl, diphenyl carbodiimide (622-16-2)

N-Sulfinylaniline (1122-83-4)

benzaldoxime, α-benzaldoxime

benzonitrile oxide (873-67-6)

4,5-diphenyl-1,2,3,5-thiaoxadiazole-1-oxide

3-phenyl-4-phenylimino-1,3-thiazetidin-2-one

1,5-diphenyl tetrazole (7477-73-8)

phenylisocyanide dichloride

phosphorus pentoxide (1314-56-3)

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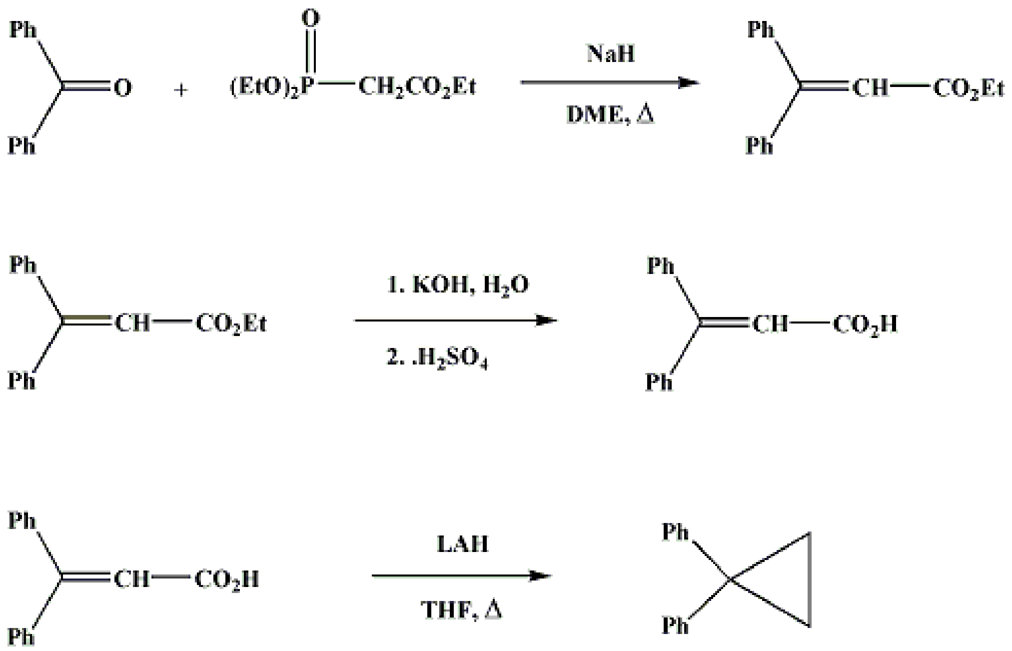
Organic Syntheses, CV 5, 509

1,1-DIPHENYLCYCLOPROPANE

[Cyclopropane, 1,1-diphenyl-]



Submitted by M. J. Jorgenson and A. F. Thacher[1].
Checked by John J. Miller and William D. Emmons.

1. Procedure

A. *β-Phenylcinnamic acid*. A suspension of 8.8 g. (0.20 mole) of a 55.1% sodium hydride dispersion in mineral oil (Note 1) and 300 ml. of 1,2-dimethoxyethane (Note 2) are added to a dry, 1-l., three-necked flask equipped with a stirrer, a condenser with drying tube, and a pressure-equalizing dropping funnel. The flask is immersed in an ice bath, and 44.8 g. (0.20 mole) of triethyl phosphonoacetate (Note 3) is added through the dropping funnel over a 20-minute period. After the addition the solution is stirred at room temperature for 30 minutes, and then 36.4 g. (0.20 mole) of benzophenone is added in one portion. The solution is heated at reflux for 4 days. The two-phase reaction mixture is cooled, and the flask is filled with water. The ester is extracted from the solution with three 100-ml. portions of ether. The ethereal extracts are combined, dried over anhydrous sodium sulfate, and evaporated to as small a volume as possible on the steam bath. The resulting mixture of ester and unreacted benzophenone is added to 140 ml. of water, 45 ml. of dioxane, and 26.4 g. (0.40 mole) of 85% potassium hydroxide in a 500-ml. one-necked flask, and the mixture is refluxed overnight (17 hours). The solution is cooled and extracted with 50 ml. of ether to remove benzophenone and any unhydrolyzed ester. The aqueous fraction is acidified with 10*N* sulfuric acid, and the resulting solid product is isolated by filtration, washed with two 50-ml. portions of water, and dried. Recrystallization from 200 ml. of benzene gives 28.3–33.9 g. (63–75%) of β-phenylcinnamic acid, m.p. 161–163° (Note 4) and (Note 5).

B. *1,1-Diphenylcyclopropane*. A 500-ml. three-necked flask is equipped with a nitrogen-inlet tube, a condenser, and a dropping funnel. The flask is charged with 100 ml. of dry tetrahydrofuran (Note 6) and 5.13 g. (0.135 mole) of lithium aluminum hydride (Note 1), and the system is purged with dry nitrogen. To the stirred solution is added dropwise over a period of 15–20 minutes a solution of 20 g. (0.089 mole) of β-phenylcinnamic acid (Note 7) in 100 ml. of tetrahydrofuran. The addition results in an exothermic reaction which causes the solution to reflux. The refluxing is allowed to subside after addition is complete, and then the mixture is carefully reheated to reflux. A mild exotherm occurs a few minutes after reflux is reached. This is easily controlled by removing the heat source or by cooling with ice. After the occurrence of this exothermic reaction, which is accompanied by a color change from rust to deep red, the mixture is heated at the reflux temperature for an additional 2 hours. The mixture is then cooled in an ice bath, and sufficient 10% sulfuric acid (*ca.* 5 ml.) is carefully *(Caution! Vigorous evolution of hydrogen.)* added dropwise to destroy excess lithium aluminum hydride. Another 100 ml. of 10% sulfuric acid is added after decomposition of the hydride is complete to dissolve the aluminum salts (Note 8). The acidified solution is worked up immediately (Note 9) by dilution with 200 ml. of water and extraction with one 100-ml. portion and three 50-ml. portions of ether. The combined ethereal extracts are washed with

three 50-ml. portions of saturated aqueous sodium bicarbonate. The bicarbonate extracts are combined and washed with 50 ml. of ether, and all the ethereal extracts are combined. The ethereal solution is dried over anhydrous sodium sulfate, and the ether is removed at atmospheric pressure. The residue is distilled under reduced pressure to give 10.0–10.7 g. (57–62%) of diphenylcyclopropane (Note 10), b.p. 132–134° (10 mm.), $n^{20}D$ 1.590.

2. Notes

1. Sodium hydride dispersions in mineral oil and lithium aluminum hydride are available from Metal Hydrides, Inc.
2. Before use, 1,2-dimethoxyethane (ethylene glycol dimethyl ether) was partially dried over anhydrous calcium chloride and then distilled from lithium aluminum hydride. It was stored over sodium ribbon.
3. Triethyl phosphonoacetate is available from Aldrich Chemical Co.
4. About half of the solid is insoluble in the hot benzene and is removed by filtration.
5. The submitters obtained 28.2 g. (63%) of β-phenylcinnamic acid, m.p. 162–163°.
6. Tetrahydrofuran is best dried according to the procedure described on page 976 of this volume. *(Caution! Note warning of danger in drying tetrahydrofuran containing peroxides.)* The checkers employed a peroxide-free grade of anhydrous tetrahydrofuran which is available from Fisher Scientific Co.
7. In the preparation of other phenylcyclopropanes by this method, esters rather than acids were employed. Use of the ester in the present preparation gave a poor yield of product. Since the acid can easily be purified, its use here is also more expedient.
8. The checkers found this amount of acid insufficient to dissolve all of the salts, and an additional 5 ml. of concentrated sulfuric acid was added.
9. In general it has been found that yields of cyclopropanes are lowered if the acidic solutions are permitted to stand before workup.
10. Fractionation is not essential because the main contaminant is high-boiling polymer. The checkers obtained two fractions: b.p. 138–142° (11 mm.), 10.0–10.2 g., 99% pure by vapor-phase chromatography; and b.p. 142–148° (11 mm.), 0.6–0.9 g., 96% pure.

3. Discussion

1,1-Diphenylcyclopropane has been prepared in 24% yield by the Simmons-Smith reaction,[2] in 78% yield by treatment of 3,3-diphenylpropyltrimethylammonium iodide with sodium or potassium amide,[3] in 61% yield by reaction of 1,1-diphenylethylene with dimethylsulfonium methylide,[4] and in unspecified yields from 1,1-diphenylethylene by reaction with diazomethane followed by pyrolysis of the resulting pyrazoline or by reaction with ethyl diazoacetate followed by distillation of the corresponding acid over calcium oxide.[5]

β-Phenylcinnamic acid has been prepared previously by a variety of methods, the best of which appear to be the dehydration of ethyl β-hydroxy-β,β-diphenylpropionate by treatment with sodium acetate in acetic acid[6] and the reaction of 1,1-diphenylethylene with oxalyl chloride.[7]

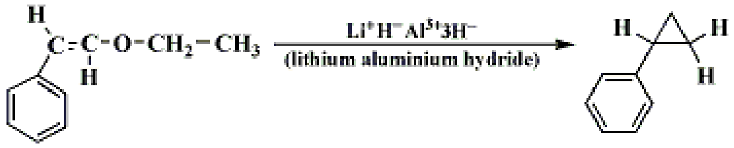
4. Merits of the Preparation

This procedure illustrates a general method for the preparation of phenylcyclopropanes from cinnamic acids, esters, aldehydes, or alcohols.[8] It complements the Simmons-Smith reaction as a general method for the preparation of such cyclopropanes. It offers advantages over the Simmons-Smith method in cases in which electron-withdrawing substituents in the benzene ring or steric crowding around the double bond lead to low yields in the Simmons-Smith reaction. Also, in the case of possible stereo-isomerism in the starting material or product, the present method leads stereospecifically to a single cyclopropane. It has the disadvantage that reducible substituents on the benzene ring do not survive the reductive treatment. The present method is an exceptionally simple, one-step preparative process employing starting materials that are commercially available, or readily accessible from aldehydes and ketones via the phosphono ester addition procedure of Wadsworth and Emmons.[9] Cyclopropane formation is particularly facile when electron-withdrawing substituents are present on the aromatic ring or when the β-position is substituted by another aryl group. Alkyl substitution on the double bond also facilitates cyclopropane formation. The exames recorded in Table I illustrate these effects. An excess of dride is necessary for producing good yields of cyclopropanes.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 372

TABLE I PREPARATION OF PHENYLCYCLOPROPANES FROM CINNAMIC ESTERS

Substituents	Solvent	Reflux Time, Hours	Yield of Cyclopropane, %
R = C_6H_5, R' = CH_3 Ar = C_6H_5	Tetrahydrofuran	10	78
R = R' = CH_3 Ar = *m*-$CF_3C_6H_4$	Tetrahydrofuran	10	54
R = R' = CH_3 Ar = C_6H_5	Dimethoxyethane	48	52
R = R' = H Ar = C_6H_5[a] 	Dimethoxyethane	320	66[b]
R = R' = CH_3 Ar = 3,4-$Cl_2C_6H_3$	Tetrahydrofuran	1	45[b]

[a] Aldehyde rather than ester was employed; the yield was 28% after 3 days.

[b] From Reference [8].

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium or potassium amide

phenylcyclopropanes

cinnamic acids

cyclopropanes

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

Benzene (71-43-2)

ether (60-29-7)

sodium acetate (127-09-3)

hydrogen (1333-74-0)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

potassium hydroxide (1310-58-3)

Benzophenone (119-61-9)

calcium oxide

1,1-Diphenylethylene (530-48-3)

cyclopropane (75-19-4)

dioxane (5703-46-8)

Diazomethane (334-88-3)

ethyl diazoacetate (623-73-4)

Tetrahydrofuran (109-99-9)

oxalyl chloride (79-37-8)

lithium aluminum hydride (16853-85-3)

sodium hydride (7646-69-7)

hydride

ethylene glycol dimethyl ether, 1,2-dimethoxyethane (110-71-4)

dimethoxyethane (534-15-6)

1,1-Diphenylcyclopropane, Cyclopropane, 1,1-diphenyl-, diphenylcyclopropane (3282-18-6)

triethyl phosphonoacetate (867-13-0)

β-Phenylcinnamic acid (606-84-8)

3,3-diphenylpropyltrimethylammonium iodide

dimethylsulfonium methylide

pyrazoline

Ethyl β-hydroxy-β,β-diphenylpropionate (894-18-8)

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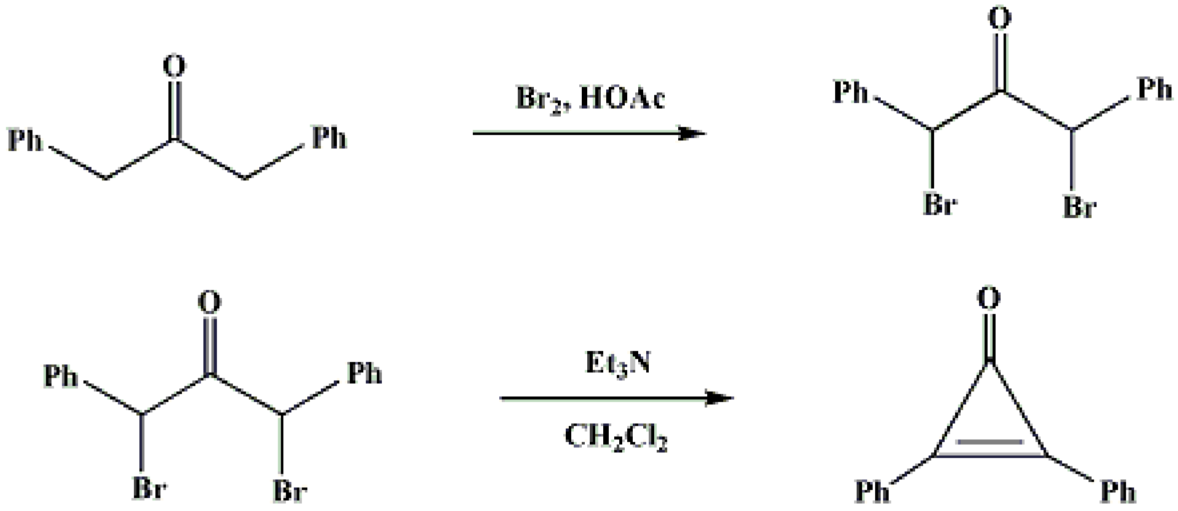
Organic Syntheses, CV 5, 514

DIPHENYLCYCLOPROPENONE



Submitted by R. Breslow and J. Posner[1].
Checked by E. J. Corey and M. F. Semmelhack.

1. Procedure

Caution! See (Note 1).

A. *α,α'-Dibromodibenzyl ketone*. To a solution of 70 g. (0.33 mole) of commercial dibenzyl ketone in 250 ml. of glacial acetic acid in a 2-l. one-necked flask fitted with a magnetic stirrer a solution of 110 g. (0.67 mole) of bromine in 500 ml. of acetic acid is added through a dropping funnel over a 15-minute period. After addition is complete, the mixture is stirred for an additional 5 minutes and is then poured into 1 l. of water. Solid sodium sulfite is added in small portions until the initial yellow color of the solution is discharged, and the mixture is allowed to stand for 1 hour. The slightly yellow dibromoketone is then collected by filtration and air-dried. Recrystallization from 1 l. of ligroin yields 97 g. of white needles, m.p. 79–87°; an additional 11 g., m.p. 79–83°, is obtained by concentrating the mother liquors, and the two crops are combined (Note 1).

B. *Diphenylcyclopropenone*. A solution of 100 ml. of triethylamine (Note 2) in 250 ml. of methylene chloride is magnetically stirred in a 2-l. one-necked flask while 108 g. (0.29 mole) of the above dibromoketone in 500 ml. of methylene chloride is added dropwise over 1 hour. The mixture is stirred for an additional 30 minutes and then extracted with two 150-ml. portions of 3*N* hydrochloric acid; the aqueous extracts are discarded. The red organic solution is transferred to a 2-l. Erlenmeyer flask and cooled in an ice bath. While this solution is swirled, a cold solution of 50 ml. of concentrated sulfuric acid in 25 ml. of water is slowly added. A slightly pink precipitate of diphenylcyclopropenone bisulfate gradually separates (Note 3). This is collected on a

sintered-glass funnel and washed with two 100-ml. portions of methylene chloride. The solid is then returned to the flask (Note 4) along with 250 ml. of methylene chloride and 500 ml. of water, and 5 g. of solid sodium carbonate is added in small portions. The organic layers is collected and the aqueous solution extracted with two 150-ml. portions of methylene chloride. The combined organic layers are dried over magnesium sulfate and evaporated to dryness. The impure diphenylcyclopropenone is recrystallized by repeated extraction with boiling cyclohexane (total 1.5 l.), the solution being decanted in each case from a reddish oily impurity. On cooling, the solution deposits 29 g. of white crystals, and an additional 1 g. can be obtained by concentrating the mother liquors to 150 ml. The combined 30 g., m.p. 119–120°, represents an overall yield of 44% based on dibenzylketone.

2. Notes

1. Care should be taken to prevent either the dibromoketone or the cyclopropenone from coming into contact with the skin, as allergic reactions have been observed in several cases. The use of gloves is recommended especially for the bromoketone. The latter product has a wide melting range because it is a mixture of the *meso*- and *d*,*l*-compounds.
2. For best results the commercial triethylamine (Matheson, b.p. 89–90°) should be purified to remove primary and secondary amines and water, either by distillation from acetic anhydride and then from barium oxide, or by reaction with phenylisocyanate.[2,3]
3. If the white solid fails to separate after 15–30 minutes, concentrated sulfuric acid is added in 4-ml. portions to the cooled solution with swirling until the white solid appears.
4. Since some of the white solid adheres to the walls of the flask, it is convenient to use the same flask for the neutralization after rinsing it with methylene chloride.

3. Discussion

Diphenylcyclopropenone has also been prepared by the action of phenylchlorocarbene on phenylketene acetal[4] and by the reaction of dihalocarbene with diphenylacetylene.[5] The present procedure[6] is the most convenient on a preparative scale.

4. Merits of the Preparation

Diphenylcyclopropenone is the first stable molecule prepared which has a carbonyl group in a three-membered ring. In a very real sense the compound has aromatic character and is fairly stable.[4] An interesting cycloaddition reaction of enamines with diphenylcyclopropenone has been reported.[7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 991
- Org. Syn. Coll. Vol. 7, 319

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

acetic anhydride (108-24-7)

sodium sulfite (7757-83-7)

sodium carbonate (497-19-8)

bromine (7726-95-6)

barium oxide

cyclohexane (110-82-7)

methylene chloride (75-09-2)

phenylisocyanate (103-71-9)

magnesium sulfate (7487-88-9)

dibenzyl ketone, dibenzylketone (102-04-5)

Diphenylacetylene (501-65-5)

dibromoketone, bromoketone (593-95-3)

triethylamine (121-44-8)

Diphenylcyclopropenone (886-38-4)

diphenylcyclopropenone bisulfate

cyclopropenone (2961-80-0)

phenylchlorocarbene

phenylketene acetal

α,α'-Dibromodibenzyl ketone (958-79-2)

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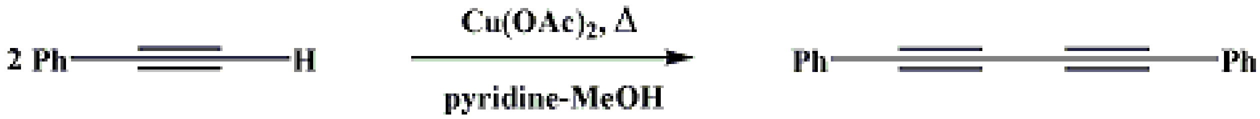
Organic Syntheses, CV 5, 517

DIPHENYLDIACETYLENE

[Butadiyne, diphenyl-]



Submitted by I. D. Campbell and G. Eglinton[1].
Checked by Joanne Groves and Virgil Boekelheide.

1. Procedure

To a saturated solution of 5.5 g. (0.028 mole) of finely powdered cupric acetate monohydrate (Note 1) in 20 ml. of a 1:1 by volume pyridine-methanol mixture (Note 2), (Note 3), (Note 4), and (Note 5) contained in a 50-ml. round-bottomed flask fitted with a reflux condenser is added 2.0 g. (0.0196 mole) of phenylacetylene (Note 6). The deep-blue suspension becomes green when heated under reflux. After 1 hour of heating, the solution is cooled (Note 7) and added dropwise to 60 ml. of 18*N* sulfuric acid, with stirring and external cooling in an ice-salt freezing mixture (Note 8). The resulting white suspension is extracted with three 25-ml. portions of ether, and the combined ethereal extracts are washed with 15 ml. of aqueous ethanolic silver nitrate solution (Note 9) to remove any unchanged phenylacetylene. The ether solution is then washed twice with water and dried over anhydrous magnesium sulfate. When the dried ether solution is concentrated under reduced pressure, a brown oil (1.81 g.) remains which solidifies on cooling.

The crude solid is purified by dissolving it in 50 ml. of petroleum ether (b.p. 40–60°) and introducing it on a short alumina column (15 g., Brockmann Activity 1 or an equivalent chromatographic alumina). The column is then eluted with 300 ml. of a 1:9 mixture of ether-petroleum ether (b.p. 40–60°). Concentration of the eluate leaves a solid which is recrystallized from aqueous ethanol to give 1.4–1.6 g. (70–80%) of diphenyldiacetylene as large colorless needles, m.p. 87–88° (Note 10).

2. Notes

1. Commercially available crystalline cupric acetate monohydrate was used. A large excess of cupric acetate does not improve the yield. Small catalytic amounts can be used if the cupric salt is continually regenerated by passage of oxygen through the reaction mixture, but the procedure is much slower.
2. A good grade of commercial pyridine was used. The reaction can also be carried out under anhydrous conditions (anhydrous cupric acetate, anhydrous methanol); then the pyridine is distilled from potassium hydroxide pellets. The

yields are similar, and, in fact, water may be added as co-solvent if desired. The solubility of anhydrous cupric acetate is ca. 2.3 g. per 100 ml. of pyridine, and that of the hydrate is ca. 1.6 g. per 100 ml. of pyridine. The solubility is much improved by the addition of methanol (solubility ca. 8.6 g. per 100 ml. of a 1:1 mixture of pyridine-methanol).

For high-dilution experiments, for example, the cyclization of α,ω-diynes, about 4 volumes of ether per volume of reagent solution can be added as entraining solvent without precipitation of the copper salt. A lower reaction temperature results.

3. Commercial grade methanol was used. Methanol is best avoided in experiments involving esters, as methanolysis has been encountered.[2]

4. It is apparently not essential that all the cupric acetate be in solution. Large volumes of solvent ensure complete solution but are inconvenient during isolation of the product.

5. Other solvent systems have been investigated. A base appears to be essential to remove the acetic acid formed; otherwise insoluble yellow precipitates of the cuprous derivative are obtained, which are only slowly oxidized to the required product.

6. Redistilled commercial phenylacetylene, titrating as 98% with silver nitrate-sodium hydroxide,[3] was used.

7. The reaction can be followed by adding an aliquot to ethanolic silver nitrate solution (Note 9). The reaction is complete when no precipitate of the silver derivative is obtained. Also the disappearance of the infrared absorption band at 3300 cm.$^{-1}$ (3.03 •) (ethynyl *v*CH) can be followed with carbon tetrachloride extracts of aliquots.

An 89% yield of diphenyldiacetylene was obtained when the reaction was allowed to proceed for 24 hours at room temperature (20°).

8. This is more convenient than removing the pyridine and the methanol by distillation.

9. The reagent is made by dissolving 3.5 g. of silver nitrate in 5 ml. of water and adding 10 ml. of ethanol.

10. The product may be contaminated by traces of the corresponding eneyne, *trans*-1,4-diphenyl-but-1-en-3-yne, formed by Straus coupling.[4] This compound, however, has an ultraviolet absorption spectrum which differs markedly from that of diphenylbutadiyne.[5]

3. Discussion

This compound has been prepared by air oxidation of the preformed cuprous salt[6] and through use of aqueous cuprous chloride-ammonium chloride and an oxidant (e.g., oxygen).[3] More recently the compound has been prepared in 95% yield by oxidation of phenylacetylene in pyridine solution containing cuprous chloride[7] and in 97% yield by oxidation in tetramethylenediamine solution containing 5 mole percent cuprous

chloride.[8] These and other coupling procedures have been reviewed.[9,10,11]

4. Merits of the Preparation

The reaction, "Glaser oxidative coupling," is a general one,[9] but this particular technique is recommended for the more water-insoluble ethynyl compounds, and also for the cyclization of α,ω-diynes,[2,12] where controlled dilution is required.

The cupric acetate-pyridine reagent provides a homogenous and basic reaction medium. The yields are high, and there is seldom precipitation of the cuprous derivative which may slow down the cuprous chloride-oxygen procedure.[3]

The rate of oxidative coupling is said to decrease with decreasing acidity of the ethynyl hydrogen.[13] Thus oct-1-yne underwent only limited reaction after being heated with the reagent under reflux for 24 hours.

It is to be noted that cupric acetate has been used to oxidize other systems, for example, α-ketols, phenols, thiols, and nitroalkanes.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

ethanol (64-17-5)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

methanol (67-56-1)

ether (60-29-7)

ammonium chloride (12125-02-9)

sodium hydroxide (1310-73-2)

silver nitrate (7761-88-8)

oxygen (7782-44-7)

carbon tetrachloride (56-23-5)

pyridine (110-86-1)

potassium hydroxide (1310-58-3)

cuprous chloride (7758-89-6)

cupric acetate (142-71-2)

Phenylacetylene (536-74-3)

magnesium sulfate (7487-88-9)

cupric acetate monohydrate (6046-93-1)

Diphenyldiacetylene, Butadiyne, diphenyl-, diphenylbutadiyne (886-66-8)

tetramethylenediamine (110-60-1)

oct-1-yne (629-05-0)

trans-1,4-diphenyl-but-1-en-3-yne

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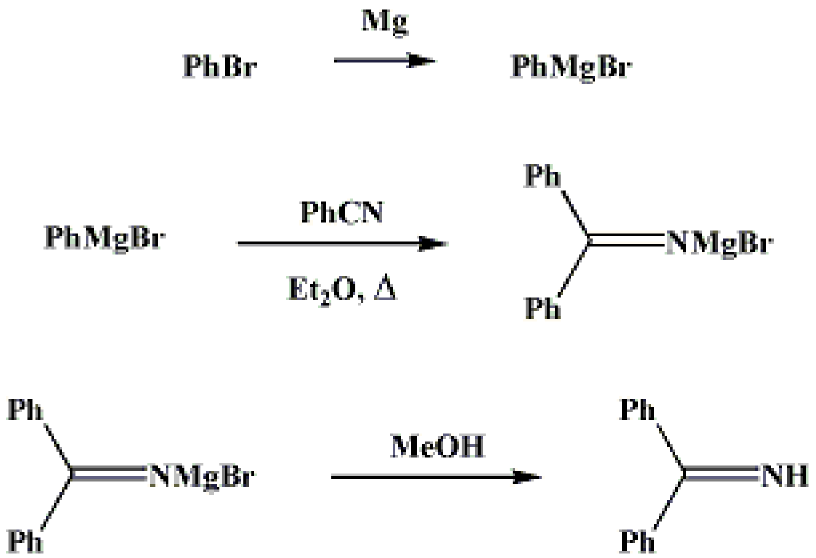
Organic Syntheses, CV 5, 520

DIPHENYL KETIMINE

[Diphenylmethylenimine]



Submitted by P. L. Pickard[1] and T. L. Tolbert[2].
Checked by C. L. Dickinson, H. D. Hartzler, and B. C. McKusick.

1. Procedure

The apparatus consists of a 1-l. three-necked flask equipped with a mechanical stirrer, a 250-ml. dropping funnel, and a Friedrichs reflux condenser fitted with a calcium chloride drying tube. Magnesium turnings (13.4 g., 0.55 g. atom) and 200 ml. of anhydrous diethyl ether are put in the flask (Note 1). Slow stirring is started, and 4 ml. of bromobenzene (Note 2) is added from the funnel. After reaction has started (Note 3), the stirring rate is increased, and moderate reflux is maintained by addition of 80.5 g. of bromobenzene (making a total of 86 g. or 0.55 mole) in 100 ml. of ether. The solution is refluxed for 30–45 minutes after the addition and is cooled to room temperature. Stirring is continued while a solution of 51.5 g. (0.50 mole) of benzonitrile (Note 2) in 100 ml. of ether is added slowly enough (Note 4) to maintain only a gentle reflux. On completion of the addition, the reaction, mixture of pale-yellow liquid and white solid is refluxed with stirring for 4–6 hours. The stirred mixture is cooled to room temperature, and the Grignard-nitrile complex is decomposed by cautious addition of 120 ml. (3 moles) of anhydrous methanol (Note 5).

On completion of the methanol addition, the mixture is stirred for 30 minutes and filtered. Low-boiling material is stripped from the filtrate, and the residue is distilled through a 45-cm. Vigreux column at reduced pressure. There is a fore-run, b.p. 120–127° (3.5 mm.), that weighs about 5 g. Then 55–73 g. (61–81%) of diphenyl ketimine is collected at 127–128° (3.5 mm.) or 151–152° (8 mm.); n^{20}_{D} 1.6180–1.6191 (Note

6). The product should be stored under nitrogen to prevent yellowing.

2. Notes

1. Freshly opened commercial (Baker and Adamson) anhydrous ether is suitable. The checkers found it more convenient to use commercial phenylmagnesium bromide than to prepare it. They obtained 80 g. (88%) of the ketimine by charging the flask with 175 ml. (0.525 mole) of 3*N* phenylmagnesium bromide (Arapahoe Chemicals, Boulder, Colorado), then adding 51.5 g. of benzonitrile as described.
2. Both bromobenzene and benzonitrile (white label grade, Eastman Kodak Company) were distilled before use.
3. If the reaction does not start spontaneously, a crystal of iodine may be added and the mixture may be warmed.
4. Care should be taken to prevent a buildup of unreacted nitrile that could result in uncontrolled reaction.
5. The methanol should be added as fast as possible. A quantity of gummy material will form as the decomposition progresses, but with continued addition of methanol it will be rapidly converted to crystalline methoxymagnesium bromide.
6. Gas chromatographic analysis of the product from three consecutive preparations showed less than 0.1% impurity. Similar results were obtained on 0.005-ml. samples in an F. and M. 202 Temperature Programed Gas Chromatograph using two columns: a 12-foot column of 10% HiVac grease and 5% Marlex-50 on 100–140 mesh Gas Chrom A, at a constant temperature of 275°, with a helium flow rate of 120 ml. per minute; and a 20-foot column of 20% GE-SE 30 on 100–140 mesh Gas Chrom A, programed at 3.3° per minute from 250° to 300°, with a helium flow rate of 120 ml. per minute.

3. Discussion

This procedure is a modification of the method employed by Moureu and Mignonac,[3] who first reported the preparation of ketimines via Grignard-nitrile complexes. The use of methanol in the decomposition step results in higher yields and extends the method to the less stable ketimines.[4] The preparation of diphenyl ketimine by the thermal decomposition of benzophenone oxime has been described in *Organic Syntheses.*[5]

4. Merits of the Preparation

The procedure is general and is often the best way to make ketimines.

References and Notes

1. Celanese Chemical Company, Clarkwood, Texas.

2. Chemstrand Research Center, Inc., Durham, North Carolina.
3. C. Moureu and G. Mignonac, *Compt. Rend.*, **156**, 1801 (1913).
4. P. L. Pickard and T. L. Tolbert, *J. Org. Chem.*, **26**, 4886 (1961).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

benzonitrile (100-47-0)

magnesium turnings (7439-95-4)

nitrogen (7727-37-9)

iodine (7553-56-2)

bromobenzene (108-86-1)

Phenylmagnesium bromide (100-58-3)

Benzophenone oxime (574-66-3)

Diphenylmethylenimine, Diphenyl ketimine (1013-88-3)

helium (7440-59-7)

methoxymagnesium bromide

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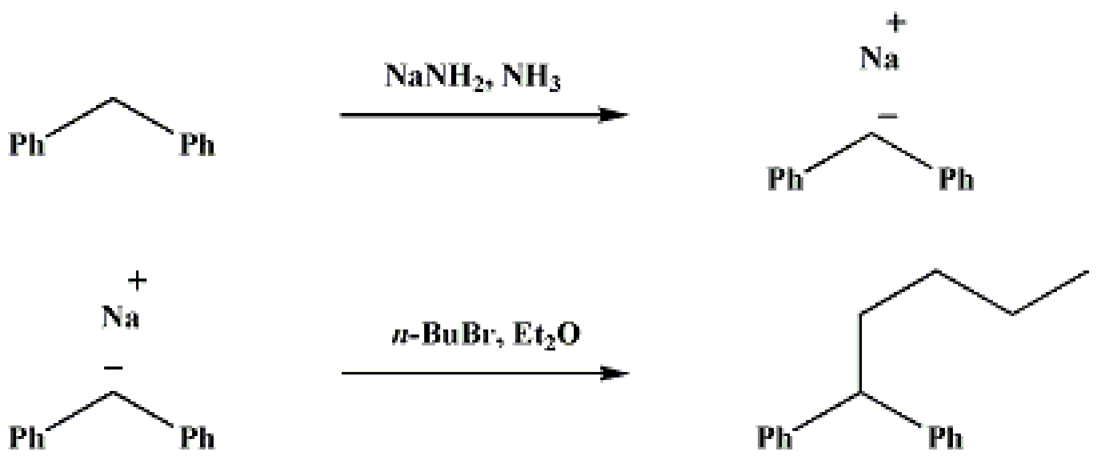
Organic Syntheses, CV 5, 523

1,1-DIPHENYLPENTANE

[Pentane, 1,1-diphenyl-]



Submitted by William S. Murphy, Phillip J. Hamrick, and Charles R. Hauser[1].
Checked by Prithipal Singh and Peter Yates.

1. Procedure

Caution! This preparation should be carried out in a hood to avoid exposure to ammonia.

A suspension of sodium amide (0.275 mole) (Note 1) in liquid ammonia is prepared in the following manner in a 1-l. three-necked flask equipped with an air condenser (Note 2), a sealed mechanical stirrer, and a dropping funnel. Commercial anhydrous liquid ammonia (600 ml.) is introduced by pouring from an Erlenmeyer flask (Note 3). To the stirred liquid ammonia is added a small piece of sodium. After the appearance of a permanent blue color (Note 4) a few crystals of ferric nitrate hydrate (*ca.* 0.1 g.) are added, followed by small pieces of freshly cut sodium (Note 5) until 6.32 g. (0.275 g. atom) has been added. After all the sodium is converted to the amide (Note 6), 42.0 g. (0.250 mole) of diphenylmethane (Note 7) in 20 ml. of anhydrous ether is added (Note 8). The deep red suspension is stirred for 15 minutes. *n*-Butyl bromide (37.6 g., 0.274 mole) (Note 7) in 20 ml. of anhydrous ether is then added dropwise with stirring. The ammonia is allowed to evaporate (Note 9) from the resulting gray suspension. Water (100 ml.) is added carefully (Note 10), then 100 ml. of ether. The ethereal layer is separated, and the aqueous layer is extracted with two further 100-ml. portions of ether. The combined ethereal extracts are dried over Drierite and filtered, and the solvent is removed. The resulting liquid (54.5 g., 97%) is essentially pure 1,1-diphenylpentane (Note 11) and (Note 12) The liquid is distilled with the use of a Claisen distillation head without a fractionating column. The fraction, b.p. 138–139° (1.5 mm.), n^{26}D 1.5501, weighs 51.6 g. (92%) (Note 13).

2. Notes

1. A 10% excess of sodium amide and *n*-butyl bromide with respect to diphenylmethane was adopted.
2. The checkers used a dry-ice condenser in place of the air condenser.
3. Dry commercial liquid ammonia is conveniently transferred from the cylinder via an Erlenmeyer flask without cooling and without the use of a condenser.
4. A permanent blue color may not remain after the addition of one pellet of sodium because of the presence of traces of moisture. Another pellet is added if necessary.
5. Sodium is cut into small pellets in the atmosphere but weighed under dry benzene or toluene.
6. Conversion is indicated by the discharge of the blue color (*ca.* 30 minutes). The addition of another portion of ferric nitrate hydrate will catalyze the conversion.
7. Freshly distilled diphenylmethane and *n*-butyl bromide were used.
8. The checkers found it important to add the diphenylmethane slowly (*ca.* 20 minutes); fast addition caused the reaction to get out of control.
9. The ammonia is allowed to evaporate overnight. A steam bath may be employed with care to facilitate the evaporation.
10. In the event of the presence of traces of unreacted sodium on the flask, water is added initially with special care.
11. The purity of the 1,1-diphenylpentane is attested by vapor-phase chromatography on a 5-ft. column of 10% Apiezon L on Celite at 200°.
12. Although 1,1-diphenylpentane undergoes air oxidation,[2] it appears to be stable in a stoppered flask under an inert atmosphere.
13. The checkers observed b.p. 127–129° (1.5 mm.).

3. Discussion

This procedure is an adaptation of one described by Hauser and Hamrick.[3] 1,1-Diphenylpentane has been prepared by the catalytic hydrogenation of 1,1-diphenyl-l-pentene[4,5,6] and in low yield from the reaction of diphenylmethyl bromide with di-*n*-butylmercury.[7] More recently 1,1-diphenylpentane was prepared by allowing lithium diphenylmethide to react with tri-*n*-butyl orthophosphate.[8]

4. Merits of the Preparation

This procedure illustrates a process which is general for 1,1-diphenyl substituted hydrocarbons. Diphenylmethane has been alkylated[3] with benzyl chloride, benzhydryl chloride, α-phenylethyl chloride, β-phenylethyl chloride, isopropyl chloride, 2-ethylbutyl bromide, and *n*-octyl bromide in yields of 99, 96, 97, 88, 86, 96, and 99%, respectively.

The present method is superior to earlier ones in that it is shorter, the chemicals are readily available, and high yields are obtained. The Gilman method[8] affords a 74% yield but a longer reaction time (1–2 days) and less readily available starting materials make it less convenient.

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Drierite

lithium diphenylmethide

ammonia (7664-41-7)

Benzene (71-43-2)

ether (60-29-7)

n-butyl bromide (109-65-9)

n-octyl bromide (111-83-1)

toluene (108-88-3)

sodium (13966-32-0)

Diphenylmethane (101-81-5)

benzyl chloride (100-44-7)

β-phenylethyl chloride (622-24-2)

sodium amide (7782-92-5)

diphenylmethyl bromide (776-74-9)

ferric nitrate hydrate

benzhydryl chloride (90-99-3)

isopropyl chloride (75-29-6)

1,1-Diphenylpentane, Pentane, 1,1-diphenyl- (1726-12-1)

1,1-diphenyl-l-pentene

α-phenylethyl chloride (672-65-1)

di-n-butylmercury (629-35-6)

tri-n-butyl orthophosphate (126-73-8)

2-ethylbutyl bromide (3814-34-4)

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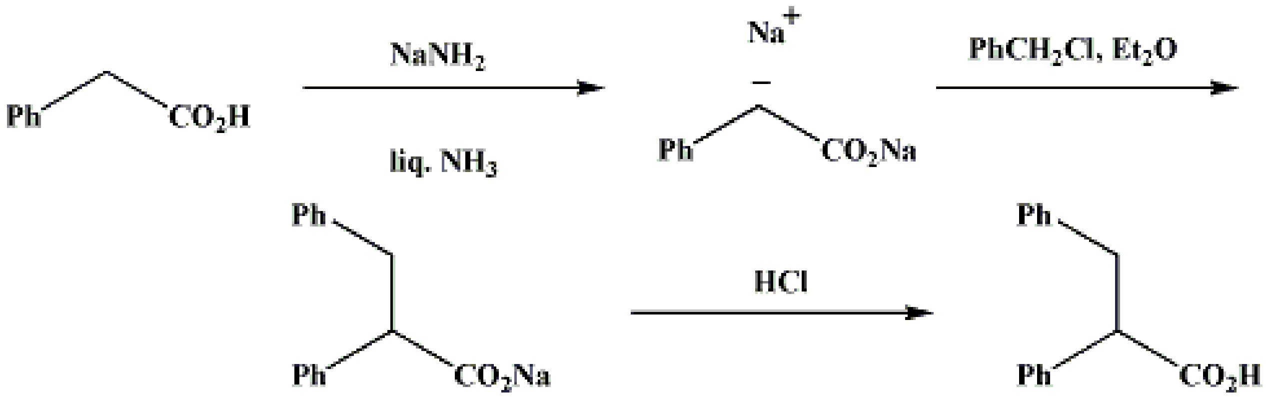
Organic Syntheses, *CV 5, 526*

α,β-DIPHENYLPROPIONIC ACID

[Propionic acid, 2,3-diphenyl-]



Submitted by Charles R. Hauser and W. R. Dunnavant[1].
Checked by Virgil Boekelheide and P. Warrick.

1. Procedure

Caution! This preparation should be carried out in a hood to avoid exposure to ammonia.

A solution of sodium amide (0.226 mole) in liquid ammonia is prepared in a 1-l. three-necked flask equipped with a condenser, a ball-sealed mechanical stirrer, and a dropping funnel. Commercial anhydrous liquid ammonia (500 ml.) is introduced from a cylinder through an inlet tube. To the stirred ammonia is added a small piece of sodium. After the appearance of a blue color, a few crystals of ferric nitrate hydrate (about 0.25 g.) are added, followed by small pieces of freshly cut sodium until 5.2 g. has been added. After all the sodium has been converted to the amide (Note 1), 14.2 g. (0.104 mole) of phenylacetic acid (Note 2) is added and the dark-green suspension is stirred for 15 minutes. To the green suspension is added rapidly 13.2 g. (0.104 mole) of benzyl chloride (Note 3) in 25 ml. of anhydrous ether, and the mixture is then stirred for 1 hour. The mixture is then evaporated to near dryness on a steam bath, 200 ml. of ether added, and evaporation to dryness effected. Another 200 ml. of ether is added, followed by evaporation to dryness. The resulting solid is then dissolved in 300 ml. of water and washed with three 200-ml. portions of ether. The aqueous solution is filtered through a layer of Celite to remove the slight brown coloration, and the filtrate is acidified with hydrochloric acid. A colorless oil forms which, when cooled for a few minutes in an ice bath, becomes a white crystalline solid. This is collected by filtration and washed with three 100-ml. portions of hot water (Note 4) and dried. The yield of crude α,β-diphenylpropionic acid, m.p. 92.0–93.5°, is 19.85 g. (84.5–88%). The crude solid is recrystallized from 60 ml. of petroleum ether (60–90°) to yield 18.80 g. (80–84%) (Note 5) of α,β-diphenylpropionic acid, m.p. 95.5–96.5° (Note 6) and (Note 7).

2. Notes

1. Conversion is indicated by the disappearance of any blue color. This generally requires about 20 minutes.
2. Phenylacetic acid as supplied by the Eastman Kodak Company was used without purification.
3. Eastman Kodak Company "Practical Grade" benzyl chloride was distilled before use, the fraction with b.p. 63–64°/12 mm. being used.
4. The hot water effectively removes unreacted phenylacetic acid, m.p. 76.7°, the presence of which hinders the purification of the product. The water should be hot but not boiling, since α,β-diphenylpropionic acid has some solubility in boiling water and may be recrystallized from water.
5. An identical preparation using potassium amide instead of sodium amide gave α,β-diphenylpropionic acid in 57% yield.
6. Miller and Rohde[2] report that α,β-diphenylpropionic acid exists in three crystalline modifications melting at 82°, 88–89°, and 95–96°. Although the product obtained by the submitters melted at 95.5–96.5°, corresponding to the high-melting form, the sample obtained by the checkers melted sharply at 88–89° corresponding to the crystalline form of intermediate melting point.
7. Under comparable conditions the corresponding alkylations of phenylacetic acid with α-phenylethyl chloride and benzhydryl chloride have been effected to form α,β-diphenylbutyric acid and α,β,β-triphenylpropionic acid in yields of 74% and 51%, respectively.[3]

3. Discussion

This procedure is an adaption of one described by Hauser and Chambers.[3] Previous preparations include the benzylation of diethyl phenylmalonate followed by hydrolysis,[4] the benzylation of phenylacetonitrile followed by hydrolysis,[5,6] the benzylation of phenylacetic acid through the Ivanov reagent,[7] and the reduction of α-phenylcinnamic acid using sodium amalgam.[2]

The present procedure illustrates the use of dianions for alkylation and gives α,β-diphenylpropionic acid more conveniently and in better yield than previous preparations.

The alkylation of ethyl phenylacetate is also described in this volume (see p. 559). The submitters of this alternative procedure reported that it gave an 85% yield of ethyl α,β-diphenylpropionate.

References and Notes

1. Department of Chemistry, Duke University, Durham, North Carolina. Work supported by the Office of Ordnance Research.
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ether (60-29-7)

sodium (13966-32-0)

benzyl chloride (100-44-7)

phenylacetonitrile (140-29-4)

Phenylacetic acid (103-82-2)

Ethyl phenylacetate (101-97-3)

diethyl phenylmalonate (83-13-6)

sodium amide (7782-92-5)

potassium amide

ferric nitrate hydrate

α-Phenylcinnamic acid (3368-16-9)

benzhydryl chloride (90-99-3)

α,β,β-Triphenylpropionic acid (53663-24-4)

α-phenylethyl chloride (672-65-1)

α,β-DIPHENYLPROPIONIC ACID, Propionic acid, 2,3-diphenyl- (3333-15-1)

α,β-diphenylbutyric acid

ethyl α,β-diphenylpropionate

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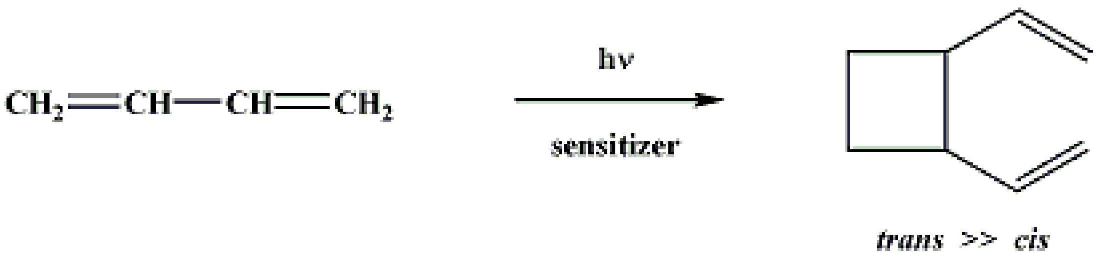
Organic Syntheses, *CV 5, 528*

cis- AND *trans*-1,2-DIVINYLCYCLOBUTANE



Submitted by Charles D. DeBoer[1], Nicholas J. Turro[2], and George S. Hammond[1].
Checked by William G. Dauben and James H. Smith.

1. Procedure

Caution! This reaction should be carried out in an explosion-proof room behind a safety shield because it involves a glass vessel under pressure.

A reaction vessel as shown in f.htmig. 1 is made from Pyrex tubing (Note 1). The vessel is evacuated and the stopcock closed. A 500-ml. round-bottomed, two-necked flask equipped with a gas inlet and a cold finger condenser containing dry ice is charged with 1 g. of *finely powdered* 4,4'-bis(dimethylamino)benzophenone (Michler's ketone) (Note 2), (Note 3). A butadiene tank is connected to the gas inlet, and about 250 ml. (160 g., 3.0 moles) of butadiene is collected in the flask (Note 4). The butadiene is cooled to dry ice temperature. The reaction vessel is immersed to the filling level shown in f.htmig. 1 in a slurry of dry ice and acetone. A 4-in. length of Tygon tubing is attached between the inlet of the reaction vessel and one neck of the flask containing the butadiene. The other neck of the flask is stoppered, and the flask is tipped to fill the connecting tube and the neck of the stopcock with butadiene. At the same time the stopcock is opened. The flask is shaken to ensure that the suspended Michler's ketone will be swept into the reaction vessel by the butadiene. After the vessel is filled with butadiene the stopcock is closed, the connecting tube removed, and the vessel transferred to a Dewar flask filled with liquid nitrogen. When the butadiene is frozen, the vessel is evacuated with a high-vacuum pump and sealed off below the stopcock with a torch (Note 5). The reaction vessel is fitted with cooling water hoses and a 450-watt Hanovia medium-pressure mercury arc lamp, and then the butadiene is allowed to thaw and come to room temperature (Note 6). The mixture is irradiated for 72 hours, the water jacket dried, and the vessel weighed (*Caution!* (Note 6). The reaction vessel is then frozen in a Dewar flask containing a dry ice-acetone mixture, and the seal is cautiously broken. The cooling bath is removed, and the reactor is allowed to come to room temperature. The reaction mixture is removed, the vessel cleaned (Note 7), and weighed again to determine the amount of starting

material. The reaction mixture is distilled and the fraction boiling between 109° and 111° (uncor.) is collected (Note 8). The yield is 96–104 g. (60–65%) of 99% pure (by gas chromatography) *trans*-1,2-divinylcyclobutane, n^{25}D 1.4429–1.4431, the impurities being butadiene and 1,5-cyclooctadiene (Note 9).

Fig. 1. *A*, 4-mm. stopcock; *B*, thickened for easy sealing; *C*, water inlet; *D*, water outlet; *E*, this seal can be replaced by a ground glass joint for higher-boiling materials than butadiene; *F*, filling level; *G*, the cooling water tube indicated by the dotted lines will permit a higher flow rate if shaped as an oval or rectangle; *H*, reaction well; *I*, lamp well; *J*, cooling water jacket.

Fig. 1. A, 4-mm. stopcock; B, thickened for easy sealing; C, water inlet; D, water outlet; E, this seal can be replaced by a ground glass joint for higher-boiling materials than butadiene; F, filling level; G, the cooling water tube indicated by the dotted lines will permit a higher flow rate if shaped as an oval or rectangle; H, reaction well; I, lamp well; J, cooling water jacket.

2. Notes

1. A reaction vessel, as shown in f.htmig. 1, is useful for many photochemical reactions because virtually all the light produced can be captured by the reagents. It can be constructed from either Pyrex or quartz tubing, depending on the absorption spectra of the reagents.
2. The choice of a sensitizer for butadiene dimerization depends on three things: the energy of the triplet-singlet transition, the intersystem crossing efficiency, and the absorption spectrum of the sensitizer.[3] Michler's ketone has a sufficiently high triplet energy to transfer energy at a diffusion-controlled rate to both *cis* and *trans* forms of butadiene, thus reducing the yield of 4-vinylcyclohexene produced.[4] Furthermore it has a high intersystem crossing efficiency and a high extinction coefficient at 3660 Å, which is the most intense line from a medium-pressure mercury arc lamp. For photochemical reactions where energy transfer is not diffusion-controlled, the lifetime of the triplet may be an important factor in the choice.
3. The amount of sensitizer is not critical since only enough is needed to absorb all the light. One gram of Michler's ketone will not be totally dissolved in 250

ml. of butadiene, but will be totally dissolved after the reaction is finished. Michler's ketone as obtained from Eastman Organic Chemicals was used without purification.

4. 1,3-Butadiene obtained from Matheson, Coleman and Bell was used without purification.

5. The butadiene should not be degassed by freeze-thaw cycles, because the presence of a small amount of oxygen reduces the amount of polymer formed on the walls of the vessel.

6. All experimental manipulations with the reaction vessel while it is sealed and under pressure should be carried out behind a safety shield.

7. The polymer can be conveniently removed by filling the flask two-thirds full with concentrated nitric acid and warming gently on a steam bath in a hood behind a safety shield.

8. The *cis*-1,2-divinylcyclobutane in the reaction mixture rearranges rapidly under reflux to the higher-boiling 1,5-cyclooctadiene.

9. If *cis*-1,2-divinylcyclobutane is desired, it can be isolated in 7–8% yield from the reaction mixture by preparative gas chromatography with the Beckman Megachrom instrument, using columns packed with Apiezon J.

3. Discussion

The *trans* isomer of 1,2-divinylcyclobutane may be isolated in low yield from the mixture formed by thermal dimerization of butadiene.[5] The *cis* isomer has been prepared by a sequence of reactions.[6]

4. Merits of the Preparation

Essentially the same procedure may be used to produce mixtures of cyclodimers from isoprene,[4] 1,3-cyclopentadiene,[4] and 1,3-cyclohexadiene.[7] Separation of all products is somewhat difficult in most cases but has always been possible by preparative vapor phase chromatography. Despite the problems that may be involved in separation of desired products in some instances, photocyclization frequently is the method of choice for preparation of 1,2-dialkenylcyclobutanes if they can be made major products of photoreactions. Starting materials are readily available, and the preparations are easily carried out on the scale described. There is little doubt that the method is the best for preparation of *trans*-1,2-divinylcyclobutane.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 962
- Org. Syn. 76, 275

References and Notes

1. Contribution No. 3131 from the Gates and Crellin Laboratories of Chemistry, California Institute of Technology, Pasadena, California.
2. Department of Chemistry, Columbia University, New York, New York.
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

cis and trans forms of butadiene

trans isomer of 1,2-divinylcyclobutane

1,2-dialkenylcyclobutanes

nitric acid (7697-37-2)

oxygen (7782-44-7)

nitrogen (7727-37-9)

acetone (67-64-1)

1,3-Butadiene, butadiene (106-99-0)

ISOPRENE (78-79-5)

1,3-cyclopentadiene (542-92-7)

1,3-Cyclohexadiene (592-57-4)

1,5-cyclooctadiene

4-vinylcyclohexene

trans-1,2-divinylcyclobutane (6553-48-6)

cis-1,2-divinylcyclobutane (16177-46-1)

4,4'-bis(dimethylamino)benzophenone

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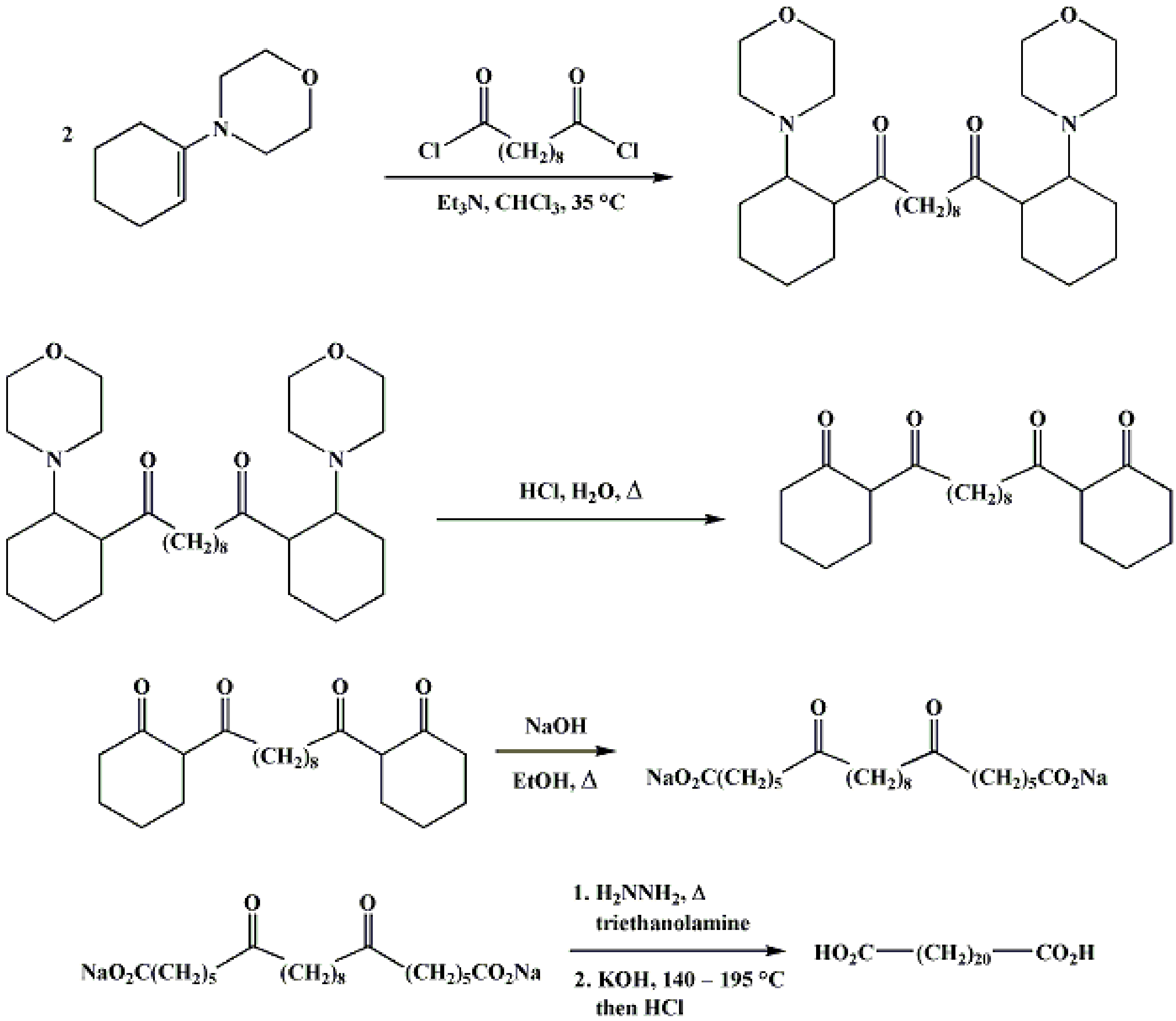
Organic Syntheses, CV 5, 533

DOCOSANEDIOIC ACID



Submitted by S. Hünig, E. Lücke, and W. Brenninger[1].
Checked by F. E. Mumford, E. A. LaLancette, W. J. Middleton, and B. C. McKusick.

1. Procedure

A. *2,2'-Sebacoyldicyclohexanone*. A solution of 167 g. (1.00 mole) of 1-morpholino-1-cyclohexene[2] and 101 g. (139 ml., 1.00 mole) of anhydrous triethylamine in 500 ml. of dry chloroform (Note 1) is put in a 5-l., three-necked, round-bottomed flask equipped with a mechanical stirrer, a dropping funnel, and a reflux condenser. Tubes of calcium chloride are inserted in the open ends of the dropping funnel and reflux condenser. The reaction flask is immersed in a water bath at 35°, and a solution of 120 g. (0.50 mole) of sebacoyl chloride (Note 2) in 200 ml. of dry chloroform is added to the well-stirred reaction mixture over a period of about 1.5 hours. The reaction mixture gradually assumes an orange to red color, and a solid precipitates. The reaction mixture is stirred for an additional 3 hours at 35°, 500 ml. of 20% hydrochloric acid is added, and the mixture is boiled under reflux for 5 hours with vigorous stirring. The reaction mixture is cooled to room temperature, and the chloroform layer is separated and extracted with six 150-ml. portions of water. The washings and the aqueous phase are combined, adjusted to a pH of 5–6 with 25% sodium hydroxide solution, and extracted with five 100-ml. portions of chloroform. The chloroform extracts are combined with the chloroform layer, and the chloroform is removed by distillation on a steam bath. The residue gradually congeals to an oily solid on standing at room temperature under a pressure of 10–50 mm. The yield of crude 2,2'-sebacoyldicyclohexanone is 181–192 g. (100–106%) (Note 3).

B. *Disodium 7,16-diketodocosanedioate*. A mixture of 120 g. (3.00 moles) of sodium hydroxide and 1.4 l. of commercial absolute ethanol is refluxed with mechanical stirring in a 5-l. round-bottomed flask until all the sodium hydroxide is dissolved (about 2 hours). The solution is cooled to room temperature, and a warm solution of the crude 2,2'-sebacoyldicyclohexanone from Step A in 300 ml. of absolute ethanol is added. The mixture is brought to a boil on a water bath or steam bath in the course of about 15 minutes and is then refluxed for 1 hour. Colorless disodium 7,16-diketodocosanedioate separates during the heating. The reaction mixture, now a thick mush, is cooled to room temperature, and the salt is collected on a 25-cm. Büchner funnel and pressed as dry as possible, preferably with the aid of a rubber dam. The moist salt is suspended in 1 l. of absolute ethanol with mechanical stirring and is then collected on the Büchner funnel as before. After being dried in air, the crude colorless disodium 7,16-diketodocosanedioate weighs 248–255 g. (112–115%, based on 1-morpholino-1-cyclohexene). It is pure enough for the following reduction to docosanedioic acid (Note 4).

C. *Docosanedioic acid*. All the crude disodium 7,16-diketodocosanedioate of Step B is added to 1 l. of triethanolamine in a 5-l. round-bottomed flask equipped with a reflux condenser, a thermometer, a mechanical stirrer, and a deep oil bath. The mixture is heated under reflux until all the salt dissolves (about 15 minutes). The solution is cooled to 130°, 610 ml. (10 moles) of 82% hydrazine hydrate is added through the reflux condenser, and the mixture is refluxed for 4 hours (Note 5).

Potassium hydroxide (168 g., 3.0 moles) is dissolved in 400 ml. of triethanolamine by heating the mixture to boiling in a 1-l. Erlenmeyer flask (about 15 minutes is required). At the end of the reflux period, the hot reaction mixture is transferred to a good hood if it is not already in one, the condenser is removed, and the hot potassium hydroxide solution is added cautiously but rapidly to the stirred reaction mixture (Note 6). The open reaction mixture is at least two-thirds immersed in the oil bath to help prevent foaming over and is heated strongly and rapidly in order to drive off water and excess hydrazine hydrate. After 2–3 hours the temperature inside the flask reaches about 140°, and decomposition of the bis-hydrazone begins, with evolution of nitrogen and considerable foaming. Foaming over is prevented by judicious regulation of the heating, good stirring, and occasional addition of a little silicone oil, which is a good antifoaming agent (Note 7). The temperature is raised as rapidly as possible to 195° (about 2 hours is needed) and held at this temperature for 6 hours. The final oil bath temperature is 200–220°.

The reaction mixture is cooled to about 100° (Note 5), washed out of the flask with 5 l. of hot water (Note 8), and acidified to a pH between 2 and 3 with 1.4 l. of 12*N* hydrochloric acid. The mixture is cooled to room temperature, and the docosanedioic acid that has precipitated is collected on a 25-cm. Büchner funnel and pressed as dry as possible (Note 9). The filter cake is suspended in 5 l. of water with mechanical stirring and collected on the Büchner funnel as before. The moist filter cake is dissolved in 700 ml. of hot 2-methoxyethanol, the hot solution is filtrate through a fluted paper in a heated funnel, and the filtrate is gradually cooled to 0–5°. The docosanedioic acid that crystallizes out is separated on a Büchner funnel, pressed as dry as possible, and suspended in 500 ml. of 95% ethanol with mechanical stirring. The acid is collected on a Büchner funnel, washed with a little 95% ethanol, dried in air, and pulverized. The colorless docosanedioic acid thus obtained weighs 127–133 g. (69–72%, based on 1-morpholino-1-cyclohexene) and is nearly pure; m.p. 124–126°; neutralization equivalent 181–184 (calculated, 185) (Note 10) and (Note 11).

2. Notes

1. Satisfactory chloroform is obtained by washing 2 l. of commercial chloroform with two 100-ml. portions of 2*N* sodium carbonate solution and two 200-ml. portions of water and distilling it until no more water codistils and the boiling point is 61°. The material remaining in the distillation pot is used without distillation.
2. Satisfactory sebacoyl chloride can be purchased from the Eastman Kodak Co., Rochester, New York. The submitters prepared it as follows. A mixture of 150 g. (0.74 mole) of sebacic acid and 150 ml. of thionyl chloride is heated in a water bath at 60°. The acid gradually goes into solution with evolution of sulfur dioxide and hydrogen chloride. When gas evolution ceases, the mixture is distilled as rapidly as possible under reduced pressure. The yield of sebacoyl chloride, b.p. 171–175°/15 mm., is about 140 g. (79%). *Caution! Toward the end of the distillation, spontaneous decomposition of the residue with formation of a voluminous black foam frequently occurs.*
3. The tetraketone can be obtained in a pure form by recrystallizing it first from ether with the addition of decolorizing carbon and then from *n*-butanol; yield 50–58%; m.p. 68–72°.
4. The submitters obtained pure 7,16-diketodocosanedioic acid by the following procedure. A solution of 300 ml. of 12*N* hydrochloric acid in 3 l. of water is stirred into a warm solution of 250 g. of the crude disodium

7,16-diketodocosanedioate in 3 l. of water. The resultant suspension of the diketo acid is boiled for a few minutes to make the acid easier to filter, then cooled to room temperature and collected on a Büchner funnel. The filter cake is suspended in 3 l. of water with mechanical stirring and collected on a Büchner funnel, and this procedure is repeated. The moist well-pressed filter cake is recrystallized from 600 ml. of 2-methoxyethanol. The recrystallized acid is suspended in 500 ml. of 95% ethanol, separated on a Büchner funnel, and dried in air. About 120 g. (61%) of pure 7,16-diketodocosanedioic acid is obtained; m.p. 127–129°; equivalent weight 196 (-CO_2H), 200

$$(>C=O)$$

(calculated, 199).

5. One may interrupt the procedure at this point and allow the mixture to stand overnight at room temperature.
6. It is essential for good results that the procedure not be interrupted from the time that the potassium hydroxide solution is added until the time that the 6-hour heating at 195° is completed.
7. Additional security against foaming over is provided by a glass tube that projects into the neck of the flask and is attached to a water pump. The checkers found it helpful to use a Hershberg stirrer with two wire blades; the upper blade was adjusted so that its ends extended above the surface of the reaction mixture and into the foam.
8. The aqueous mixture is not clear because the sodium salt is sparingly soluble in water.
9. The precipitate can be more rapidly separated by means of a centrifuge.
10. Very pure docosanedioic acid can be obtained by another recrystallization from about 450 ml. of 2-methoxyethanol. The recrystallized acid is collected on a Büchner funnel, and the well-pressed filter cake is suspended in 200 ml. of 95% ethanol, refiltered, and dried in air; weight 112 g. (61%); m.p. 126–127°; neutralization equivalent, 185–187.
11. The checkers found it slightly more convenient to recrystallize the moist crude docosanedioic acid from 1 l. of methyl ethyl ketone. The hot solution is filtered and cooled, and the acid is collected on a Büchner funnel, washed with methyl ethyl ketone, and dried in air.

3. Discussion

Docosanedioic acid has been prepared by Wolff-Kishner reduction of 6,17-diketodocosanedioic acid, formed by reaction of the half-ester acid chloride of adipic acid with the αω-cadmium derivative of decane (%26 overall yield).[3] Reduction of ω-[5-(ω-carboxy-*n*-octyl)-2-thenoyl]caprylic acid by the Wolff-Kishner method, followed by simultaneous reduction and desulfurization with Raney nickel of the 2,5-bis(*w*-carboxyoctyl)thiophene produced, is reported to yield docosanedioic acid in 68% overall yield.[4] Other routes to docosanedioic acid include electrolysis of the monomethyl ester of dodecanedioic acid (43% yield);[5] oxidative coupling of 10-undecynoic acid to docosa-10,12-diynedioic acid (90% yield) and reduction of this intermediate with a palladium catalyst;[6] and reaction of α,ω-diiodoeicosane with potassium cyanide followed by hydrolysis of the dinitrile produced.[7]

The present method of making docosanedioic acid has been described by Hünig and Lücke.[8] The Wolff-Kishner reduction of the diketonic intermediate is an application of the modification of Gardner, Rand, and Haynes.[9]

4. Merits of the Preparation

The present procedure has been used to convert suberoyl chloride to eicosanedioic acid (44%), and it is probably a general method for increasing by twelve carbon atoms the chain length of dicarboxylic acids whose chain length is eight or more carbon atoms.[8] A variant of the method, in the first step of which the ester chloride of a dicarboxylic acid is condensed with 1-morpholino-1-cyclohexene, has also been used to prepare dicarboxylic acids. Thus the mono-ester acid chloride of succinic acid has been converted to sebacic acid (48%), that of suberic acid to tetradecanedioic acid (34%), and that of sebacic acid to hexadecanedioic acid (32%).[8] A general method of increasing the chain length of a carboxylic acid by six carbon atoms is to employ a monoacyl chloride in the present procedure; overall yields of acids from nonanoic to tetracosanoic are 42–48%.[10] 1-Morpholino-1-cyclopentene[11] can be used in the same sort of syntheses as 1-morpholino-1-cyclohexene; thus, by starting with it and lauroyl chloride, heptadecanoic acid can be obtained in 60% yield.[12] Similarly, an enamine of cyclododecanone has been used to lengthen the chain of monocarboxylic acids by twelve carbon atoms, and of dicarboxylic acids by twenty-four; for

instance, stearic acid has been converted to triacontanoic acid (70%), and suberic acid to pentatricontanedioic acid (40%).[13]

How to decide whether the enamine method or some other method is better for preparing a given mono- or dicarboxylic acid is discussed in two papers.[8,10]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 808

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

αω-cadmium derivative of decane

Raney nickel of the 2,5-bis(w-carboxyoctyl)thiophene

ethanol (64-17-5)

hydrogen chloride, hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium hydroxide (1310-73-2)

thionyl chloride (7719-09-7)

chloroform (67-66-3)

Adipic acid (124-04-9)

sodium carbonate (497-19-8)

sulfur dioxide (7446-09-5)

nitrogen (7727-37-9)

potassium cyanide (151-50-8)

Succinic acid (110-15-6)

n-butanol (71-36-3)

decolorizing carbon (7782-42-5)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

palladium (7440-05-3)

hydrazine hydrate (7803-57-8)

methyl ethyl ketone (78-93-3)

sebacic acid (111-20-6)

stearic acid (57-11-4)

lauroyl chloride (112-16-3)

2-methoxyethanol (109-86-4)

suberic acid (505-48-6)

suberoyl chloride (10027-07-3)

triethylamine (121-44-8)

1-Morpholino-1-cyclohexene (670-80-4)

10-Undecynoic acid (2777-65-3)

cyclododecanone (830-13-7)

Docosanedioic acid (505-56-6)

2,2'-Sebacoyldicyclohexanone (17343-93-0)

sebacoyl chloride (111-19-3)

disodium 7,16-diketodocosanedioate (134507-60-1)

triethanolamine (102-71-6)

7,16-diketodocosanedioic acid

6,17-diketodocosanedioic acid

dodecanedioic acid (693-23-2)

docosa-10,12-diynedioic acid (28393-02-4)

eicosanedioic acid (2424-92-2)

tetradecanedioic acid (821-38-5)

hexadecanedioic acid (505-54-4)

1-Morpholino-1-cyclopentene

triacontanoic acid (506-50-3)

pentatricontanedioic acid

ω-[5-(ω-carboxy-n-octyl)-2-thenoyl]caprylic acid

Heptadecanoic acid (506-12-7)

α,ω-diiodoeicosane

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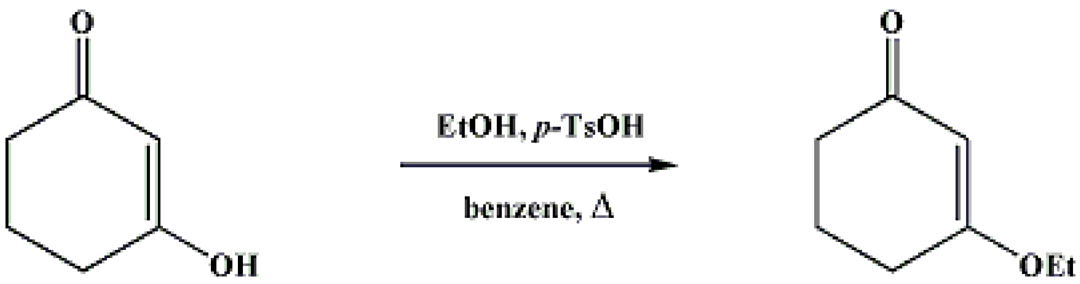
Organic Syntheses, CV 5, 539

3-ETHOXY-2-CYCLOHEXENONE

[Dihydroresorcinol monoethyl ether]



Submitted by Walter F. Gannon and Herbert O. House[1].
Checked by William E. Parham, Wayland E. Noland, George Meisters, and Allan M. Huffman.

1. Procedure

In a 2-l. flask fitted with a total-reflux, variable-take-off distillation head is placed a solution of 53 g. (0.472 mole) of dihydroresorcinol (Note 1), 2.3 g. of *p*-toluenesulfonic acid monohydrate and 250 ml. of absolute ethanol in 900 ml. of benzene. The mixture is heated to boiling and the azeotrope composed of benzene, alcohol, and water is removed at the rate of 100 ml. per hour. When the temperature of the distilling vapor reaches 78° (Note 2), the distillation is stopped and the residual solution is washed with four 100-ml. portions of 10% aqueous sodium hydroxide which have been saturated with sodium chloride. The resulting organic solution is washed with successive 50-ml. portions of water until the aqueous washings are neutral and then concentrated under reduced pressure. The residual liquid is distilled under reduced pressure. The yield of 3-ethoxy-2-cyclohexenone (Note 3), b.p. 66–68.5°/0.4 mm. or 115–121°/11 mm., n_D^{29} 1.5015, is 46.6–49.9 g. (70–75%).

2. Notes

1. The preparation of dihydroresorcinol was described in an earlier volume of this series.[2]
2. This distillation requires 6–8 hours.
3. The product may be analyzed by gas chromatography on an 8 mm. × 215 cm. column heated to 220–240° and packed with Dow-Corning Silicone Fluid No. 550 suspended on 50–80 mesh ground firebrick. The chromatogram obtained with this column exhibits a single major peak. The ultraviolet spectrum of an ethanol solution of the product has a maxium at 250 m• (ε = 17,200).

3. Discussion

3-Ethoxy-2-cyclohexenone has been prepared by reaction of the silver salt of dihydroresorcinol with ethyl iodide[3] and by the reaction of dihydroresorcinol with ethyl orthoformate, ethanol and sulfuric acid.[4] The acid-catalyzed reaction of dihydroresorcinol with ethanol in benzene solution utilized in this preparation is patterned after the procedure of Frank and Hall.[4,5]

This procedure can also be used to prepare other 2-alkoxy-2-cyclohexenones. For example, it has been reported that 2-isobutoxy-2-cyclohexenone can be prepared easily in high yield (91%) from dihydroresorcinol and isobutyl alcohol.[6] The use of isobutyl alcohol[7] often gives better yields of enol ethers.[8,9]

4. Use of 3-Ethoxy-2-cyclohexenone

The 3-alkoxy-2-cyclohexenones are useful intermediates in the synthesis of certain cyclohexenones. The reduction of 3-ethoxy-2-cyclohexenone with lithium aluminum hydride followed by hydrolysis and dehydration of the reduction product yields 2-cyclohexenone.[10] Similarly, the reaction of 3-alkoxy-2-cyclohexenones with organometallic reagents followed by hydrolysis and dehydration of the addition product affords a variety of 3-substituted 2-cyclohexenones.[3,5,6,8]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 294
- Org. Syn. Coll. Vol. 6, 679
- Org. Syn. Coll. Vol. 7, 208

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

sulfuric acid (7664-93-9)

Benzene (71-43-2)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

Ethyl orthoformate

isobutyl alcohol (78-83-1)

Ethyl iodide (75-03-6)

lithium aluminum hydride (16853-85-3)

Dihydroresorcinol

2-Cyclohexenone (930-68-7)

3-Ethoxy-2-cyclohexenone, Dihydroresorcinol monoethyl ether (5323-87-5)

2-isobutoxy-2-cyclohexenone

p-toluenesulfonic acid monohydrate (6192-52-5)

silver salt of dihydroresorcinol

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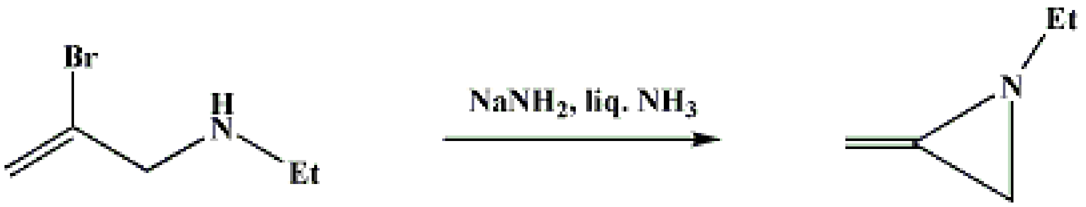
Organic Syntheses, CV 5, 541

N-ETHYLALLENIMINE

[Aziridine, 1-ethyl-2-methylene-]



Submitted by Albert T. Bottini and Robert E. Olsen[1].
Checked by Thomas H. Lowry and E. J. Corey.

1. Procedure

Caution! This preparation should be carried out in a good hood to avoid exposure to ammonia. The operator should wear rubber gloves and protective goggles because 2-haloallylamines and ethylenimines can cause severe skin and eye irritation.

A 2-l. three-necked flask is fitted with a sealed mechanical stirrer, a gas-inlet tube, and a dry ice condenser protected from the air by a soda-lime drying tube (Note 1). The system is flushed thoroughly with dry ammonia, and 32.8 g. (0.84 mole) of sodium amide (Note 2) is added to the flask. The system is again flushed with ammonia, the condenser is provided with dry ice covered by acetone, and 1.2 l. of liquid ammonia is condensed in the flask. The gas-inlet tube is replaced with a dropping funnel, the stirrer is started, and 118 g. (0.72 mole) of N-(2-bromoallyl)ethylamine[2] is added dropwise in 20–30 minutes; during the addition, the ammonia boils vigorously, and the color of the slurry changes from gray to black. Stirring is continued for 3 hours, and the dry ice is then allowed to evaporate. The condenser is provided with an ice-salt mixture, and the ammonia is allowed to evaporate until the volume is reduced to about 800 ml. (Note 3). Ethanol-free ether (200 ml.) is added rapidly through the dropping funnel, and the reaction is stopped by the slow, dropwise addition (Caution!) of 5 ml. of water. The ammonia is allowed to evaporate overnight. Water (150 ml.) and 100 ml. of ether are added to the residue, and the mixture is stirred for 2 minutes in order to dissolve the precipitated salts. The resulting mixture, which consists of aqueous and ethereal solutions, is separated, and the aqueous phase is extracted with 75 ml. of ether. The ether solutions are combined, dried over sodium hydroxide (Note 4), and distilled through an *efficient* low-holdup column (Note 5). The fraction with b.p. 77–80°, n^{25}D 1.4260–1.4268, which is 96–97% N-ethylallenimine (Note 6), weighs 30–34 g. (48–55%). Pure (>99.5%) N-ethylallenimine has b.p. 77–79°, n^{25}D 1.4281–1.4284 (Note 7) and (Note 8).

2. Notes

1. The glassware should be dried in an oven before use, and water must be rigorously excluded from the reaction mixture.
2. The sodium amide was obtained from Roberts Chemical Co., Nitro, West Virginia.
3. About 1.5–2.5 hours is required; stirring is continued and ice is prevented from forming on the outside of the flask. The checkers used an inner-spiral condenser cooled by ice water.
4. The ether solution and fractions taken during the subsequent distillation may be assayed by gas-liquid partition chromatography on a 0.8-cm. × 200-cm. column heated at 120° and packed with nonyl phthalate supported on ground firebrick.
5. The submitters concentrated the dry ether solution to a volume of 80–100 ml. by distillation through a 1.0-cm. × 40-cm. column packed with glass helices and equipped with a total-reflux head. *p*-Xylene (10 ml.) was added to the residue, and this solution was fractionated through a 0.8-cm. × 30-cm. Podbielniak-type column fitted with a total-reflux head. The submitters recommend that, during distillation of the concentrated solution, a slow stream of nitrogen be passed through the boiling liquid to minimize the formation of dark, tarry products. The checkers used a 1-cm. × 100-cm. spinning-band column (Nester and Faust Co.) for the distillation of N-ethylallenimine and were able to obtain material of 99% purity (Note 7) directly.
6. This fraction is 2–3% ether, 96–97% N-ethylallenimine, and 1–2% N-ethylpropargylamine. The product from the reaction consists of 80–90% N-ethylallenimine and 10–20% N-ethylpropargylamine. N-Ethylpropargylamine has b.p. 100–102° (760 mm.), $n^{25}\mathrm{D}$ 1.4314–1.4316.
7. The submitters obtained essentially pure (>99.5%) N-ethylallenimine by redistilling 30 g. or more of the 96–97% pure product through the Podbielniak column and rejecting the first 10–20% and the last 20% of the distillate. The yield of pure N-ethylallenimine is 18–21 g. (30–35%). Pure N-ethylallenimine has also been obtained in comparable yields by (*a*) distilling the combined concentrated solution from the equivalent of three runs through a 1.3-cm. × 100-cm. column packed with glass helices and equipped with a total-reflux head, and (*b*) treating the crude distillate with lithium aluminum hydride as described for the purification of N-propylallenimine.[3]
8. Samples of pure N-ethylallenimine and other allenimines have been stored at 0° for well over a year with no significant deterioration. *Caution! N-Alkylallenimines, even as dilute solutions in aqueous ethanol, are rapidly destroyed by acid.*[4,5] Therefore concentrated solutions of N-alkylallenimines should not be allowed to come in contact with acid because of the possibilities of violent decomposition.

3. Discussion

The method described is essentially that of Pollard and Parcell.[4] N-Ethylallenimine has been prepared by treating N-(2-bromoallyl)ethylamine in liquid ammonia with sodium amide,[4,6] lithium amide,[6] or potassium amide.[6]

4. Merits of the Preparation

This is a general method for making N-alkylallenimines, and the following ones have been made in this way: N-methyl-,[6] N-propyl-,[6] N-isopropyl-,[4] N-butyl-,[4] N-hexyl-,[6] and N-(3,5,5-trimethylhexyl)-.[4] N-*t*-Butylallenimine[6] and 1-(1-allenimino)-2-hydroxy-3-butene[7] have also been prepared by this method, but with sodium amide/2-bromoallylamine mole ratios of 1.75 and 2.1, respectively. This method has been used for the preparation of pure N-alkylpropargylamines from 2-chloroallylamines.[6,7] The optimum sodium amide/2-chloroallylamine ratio for the preparation of N-alkylpropargylamines is 2.1.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 124

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

ammonia (7664-41-7)

ether (60-29-7)

sodium hydroxide (1310-73-2)

nitrogen (7727-37-9)

acetone (67-64-1)

p-xylene (106-42-3)

sodium amide (7782-92-5)

lithium aluminum hydride (16853-85-3)

lithium amide (7782-89-0)

potassium amide

2-Bromoallylamine (6943-51-7)

N-(2-Bromoallyl)ethylamine (871-23-8)

N-Ethylallenimine

Aziridine, 1-ethyl-2-methylene- (872-39-9)

nonyl phthalate (24539-59-1)

N-ethylpropargylamine

N-propylallenimine

1-(1-allenimino)-2-hydroxy-3-butene

N-t-Butylallenimine

2-chloroallylamine

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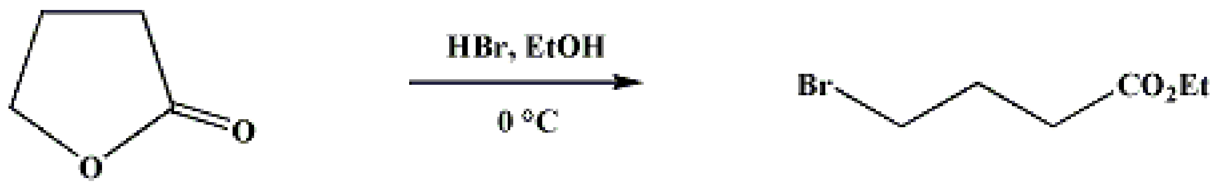
Organic Syntheses, CV 5, 545

ETHYL γ-BROMOBUTYRATE

[Butyric acid, γ-bromo-, ethyl ester]



Submitted by J. Lavety and G. R. Proctor[1].
Checked by Ian Morrison and Virgil Boekelheide.

1. Procedure

A solution of 200 g. (2.33 moles) of γ-butyrolactone (Note 1) in 375 ml. of absolute ethanol is cooled to 0° in an ice bath while a stream of dry hydrogen bromide (Note 2) is introduced. The passage of gas is discontinued 1 hour after hydrogen bromide is seen to pass through the reaction mixture unchanged (Note 3).

The alcoholic solution of the product is kept for 24 hours at 0° and then poured into 1 l. of ice-cold water. The oily layer is separated, and the aqueous layer is extracted with two 100-ml. portions of ethyl bromide (Note 4). The combined oil and extracts is washed with ice-cold 2% potassium hydroxide solution, then with very dilute hydrochloric acid, and finally with water. The organic layer is dried over sodium sulfate, the solvent is removed under reduced pressure, and the residual crude ester is purified by distillation. The yield of ethyl γ-bromobutyrate, obtained as a colorless oil, b.p. 97–99° (25 mm.), n^{25}D 1.4543, is 350–380 g. (77–84%) (Note 5) and (Note 6).

2. Notes

1. Technical grade γ-butyrolactone was employed.
2. The hydrogen bromide is made by burning together hydrogen and bromine.

The apparatus is essentially that described previously.[2,3] The submitters found that standard ground-glass fittings can be used throughout, connected where necessary by Neoprene® tubing. The combustion tube is made by "butt-joining" two ground-glass sockets. The checkers used commercial hydrogen bromide from a cylinder which was connected to the reaction flask through a safety trap.
3. The time varies from 6 to 8 hours, and the increase in weight from 450 g. to 480 g. Using the commercial hydrogen bromide, the checkers found the time for saturation to be 3.5–4 hours.
4. The aqueous layer may be kept and used again in repeating the reaction.
5. In smaller runs, yields as high as 95% have been obtained.[4]

6. The product is best stored in dark bottles at 0°.

3. Discussion

The ester has been made from the corresponding acid which was obtained from the nitrile,[5] but the present method is the more practicable.[4,6] This procedure is an adaptation of the method used for the preparation of ethyl 2-bromocyclopentaneacetate.[7]

4. Merits of the Preparation

This is a procedure for preparing ethyl γ-bromobutyrate in good yield. Ethyl γ-bromobutyrate is used for adding chains of four carbons and has been particularly useful in syntheses of benzazepines.[3,6,8,9]

References and Notes

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6. J. T. Braunholtz and F. G. Mann, *J. Chem. Soc.*, 3383 (1958).
7. R. P. Linstead and E. M. Meade, *J. Chem. Soc.*, 943 (1934).
8. G. R. Proctor, *J. Chem. Soc.*, 3989 (1961).
9. B. D. Astill and V. Boekelheide, *J. Am. Chem. Soc.*, **77**, 4080 (1955).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

hydrogen (1333-74-0)

hydrogen bromide (10035-10-6)

bromine (7726-95-6)

Ethyl bromide (74-96-4)

sodium sulfate (7757-82-6)

potassium hydroxide (1310-58-3)

γ-butyrolactone (96-48-0)

Ethyl γ-bromobutyrate, Butyric acid, γ-bromo-, ethyl ester (2969-81-5)

ethyl 2-bromocyclopentaneacetate

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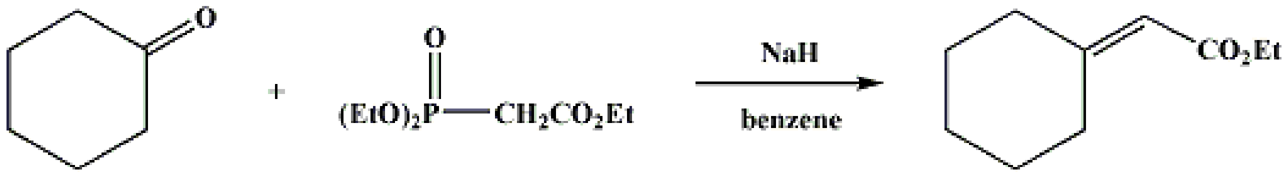
Organic Syntheses, CV 5, 547

ETHYL CYCLOHEXYLIDENEACETATE

[Δ¹-α-Cyclohexaneacetic acid, ethyl ester]



Submitted by W. S. Wadsworth, Jr. and William D. Emmons[1].
Checked by William E. Parham, R. M. Dodson, W. L. Salo, and J. N. Wemple.

1. Procedure

A dry, 500-ml., three-necked flask equipped with stirrer, thermometer, condenser, and dropping funnel is purged with dry nitrogen and charged with 16 g. (0.33 mole) of a 50% dispersion of sodium hydride in mineral oil (Note 1) and 100 ml. of dry benzene (Note 2). To this stirred mixture is added dropwise over a 45–50 minute period 74.7 g. (0.33 mole) of triethyl phosphonoacetate (Note 3). During the addition period the temperature is maintained at 30–35°, and cooling is employed if necessary (Note 4). Vigorous evolution of hydrogen is noted during this portion of the reaction. After addition of triethyl phosphonoacetate is completed, the mixture is stirred for 1 hour at room temperature to ensure complete reaction (Note 5). To this nearly clear solution is added dropwise over a 30–40 minute period 32.7 g. (0.33 mole) of cyclohexanone (Note 6). During the addition the temperature is maintained at 20–30° by appropriate cooling with an ice bath. After approximately one-half of the ketone is added, a gummy precipitate of sodium diethyl phosphate forms, which in some instances makes agitation difficult. The mixture is then heated at 60–65° for 15 minutes, during which time it is stirred without difficulty. The resulting product is cooled to 15–20°, and the mother liquor is decanted from the precipitate. This gummy precipitate is washed well by mixing it at 60° with several 25-ml. portions of benzene and decanting at 20° (Note 7). Benzene is distilled from the combined mother and wash liquors at atmospheric pressure. The product is distilled through a 20-cm. Vigreux column, and the mineral oil remains as pot residue after distillation is completed. Ethyl cyclohexylideneacetate (37–43 g., 67–77% yield) is collected at 48–49° (0.02 mm.), n^{25}D 1.4755 (Note 8).

2. Notes

1. Sodium hydride, 50–51% in mineral oil, was supplied by Metal Hydrides Inc., Beverly, Massachusetts.
2. Reagent grade benzene is filtered from sodium hydride just before use.
3. Triethylphosphonoacetate may be obtained from the Aldrich Chemical Company and is distilled before use; b.p. 140° (10 mm.).
4. Temperatures above 40–50° are detrimental to the anion and must be avoided.
5. Approximately the stoichiometric quantity of hydrogen (7.4 l.) is evolved during preparation of the anion.
6. The cyclohexanone was obtained from Eastman Organic Chemicals and redistilled before use.
7. The submitters obtained the yields indicated by washing the gummy precipitate with two

25-ml. portions of benzene; the checkers observed that additional extraction at this point is required, and they recommend extraction with a total of four 25-ml. portions of warm benzene.

8. If an excess of sodium hydride has been used, the product contains varying amounts of the β,γ-isomer, ethyl cyclohexenylacetate. To ensure against the occurrence of this side reaction, a 5–10% excess of the phosphonate ester can be used.

3. Discussion

Esters of cyclohexylideneacetic acid have been prepared by the Reformatsky reaction followed by acylation and pyrolysis,[2] a laborious procedure giving low yields. The phosphonate carbanion procedure would appear to be the method of choice for preparation of these esters.

4. Merits of the Preparation

The phosphonate carbanion method is generally applicable to the synthesis of a wide variety of olefins.[3] The synthesis complements the Wittig reaction in that the latter procedure is often unsatisfactory for preparation of olefins having an electron-with-drawing group adjacent to the double bond.[4] Generally, any ketone or aldehyde can be used in the phosphonate carbanion synthesis, and yields of olefins comparable to that obtained with cyclohexanone are obtained. Although a variety of alkyl phosphonates can be employed, the present procedure is specific for phosphonates containing an electron-withdrawing group. The synthesis can be performed at room temperature or below, and product isolation is facilitated by simplified removal of the by-products, virtues which make this procedure of practical value.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 509
- Org. Syn. Coll. Vol. 5, 642

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Δ^1-α-Cyclohexaneacetic acid, ethyl ester

Benzene (71-43-2)

hydrogen (1333-74-0)

Cyclohexanone (108-94-1)

nitrogen (7727-37-9)

sodium hydride (7646-69-7)

cyclohexylideneacetic acid

triethyl phosphonoacetate (867-13-0)

Ethyl cyclohexylideneacetate (1552-92-7)

sodium diethyl phosphate

Triethylphosphonoacetate

ethyl cyclohexenylacetate

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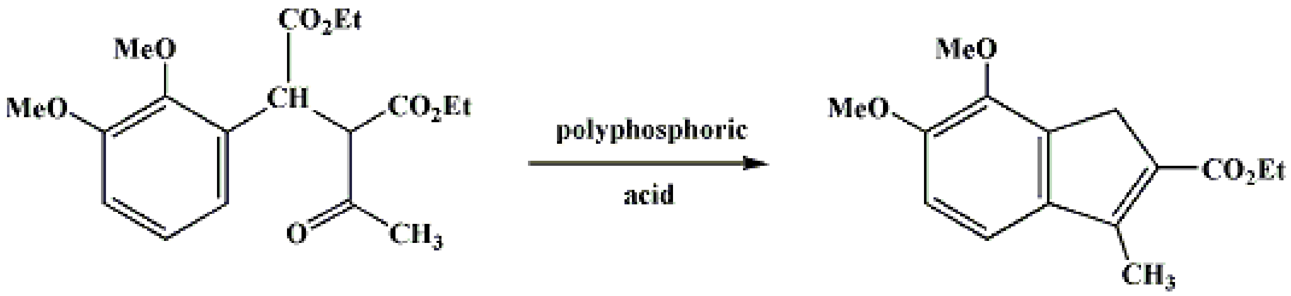
Organic Syntheses, CV 5, 550

ETHYL 6,7-DIMETHOXY-3-METHYLINDENE-2-CARBOXYLATE

[Indene, 6,7-dimethoxy-3-methyl-2-carbethoxy-]



Submitted by John Koo[1]
Checked by John C. Sheehan and J. Iannicelli.

1. Procedure

To 300 g. of polyphosphoric acid (Note 1) precooled to 5° is added 28 g. (0.1 mole) of ethyl α-acetyl-β-(2,3-dimethoxyphenyl)-propionate[2] contained in a 400-ml. beaker. The mixture is stirred thoroughly (Note 2) with a strong spatula for 15 minutes. The temperature, which is around 10° at the beginning, increases rapidly and is kept between 20° and 25° by occasionally cooling the beaker in an ice-water bath (Note 3). The deep-yellow reaction paste is then poured immediately into 600 ml. of ice water with thorough stirring and trituration (Note 4), and the beaker is rinsed with small portions of cold water. The product, which separates from the cold water as a colorless precipitate, is extracted with several portions of chloroform (first with 400 ml., then twice with 200 ml., and finally with 100 ml. of this solvent). The combined chloroform extracts are washed successively with 100 ml. of cold water, then once with 100 ml., twice with 50 ml. of 10% sodium bicarbonate solution (Note 5), and finally with 50 ml. of cold water. The chloroform solution is dried over magnesium sulfate and filtered. The chloroform is removed by distillation on a steam bath first at atmospheric pressure and finally under reduced pressure. The residual pale-yellow oil soon solidifies and is practically pure. The yield of ethyl 6,7-dimethoxy-3-methylindene-2-carboxylate is 21.5–22.5 g. (82–86%), m.p. 81–83° (Note 6).

2. Notes

1. Obtained from Victor Chemical Works, Chicago, Illinois.
2. Since the mixture is so viscous, continuous and vigorous hand stirring is necessary.
3. After the reaction starts, the temperature should be checked every few minutes and kept between 20° and 25°, which is the most favorable temperature.
4. Careful stirring and trituration are necessary to ensure the complete decomposition of every drop of the yellow paste.
5. According to the submitter, acidification of the combined sodium bicarbonate washings with 10% hydrochloric acid yields a colorless precipitate of 6,7-dimethoxy-3-methylindene-2-carboxylic acid, which is collected by filtration, washed, and dried; yield, 3.4–3.9 g. (14–16%); m.p. 216–218°.
6. Recrystallization from 75 ml. of 60% ethanol gives a 90% recovery of colorless long

needles, m.p. 83–85°.

3. Discussion

The method described here is based on the analogous preparation of some other indenes.[3]

References and Notes

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3. J. Koo, *J. Am. Chem. Soc.*, **75**, 1891 (1953).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

polyphosphoric acid

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

chloroform (67-66-3)

sodium bicarbonate (144-55-8)

magnesium sulfate (7487-88-9)

ETHYL α-ACETYL-β-(2,3-DIMETHOXYPHENYL)-PROPIONATE (53608-80-3)

Ethyl 6,7-dimethoxy-3-methylindene-2-carboxylate, Indene, 6,7-dimethoxy-3-methyl-2-carbethoxy- (5415-54-3)

6,7-dimethoxy-3-methylindene-2-carboxylic acid

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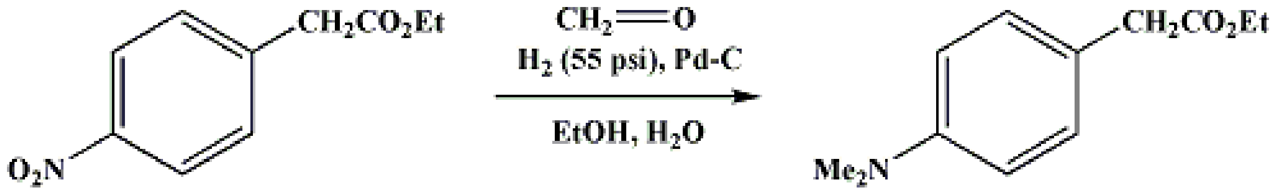
Organic Syntheses, *CV 5*, *552*

ETHYL *p*-DIMETHYLAMINOPHENYLACETATE

[Acetic acid, *p*-dimethylaminophenyl-, ethyl ester]



Submitted by Michael G. Romanelli and Ernest I. Becker[1].
Checked by Roy A. Sikstrom, Douglas R. Johnson, William E. Parham, and Wayland E. Noland.

1. Procedure

In a 400-ml. Parr bottle are placed 41.8 g. (0.20 mole) of ethyl *p*-nitrophenylacetate, 40 ml. of 40% aqueous formaldehyde solution, 200 ml. of 95% ethanol, and 2.0 g. of 10% palladium on charcoal (Note 1). The bottle is then placed on a Parr hydrogenation apparatus. The sample is evacuated and filled with hydrogen, this process being repeated three times. The tank and bottle are then filled with hydrogen to 55 p.s.i. The shaker is started, and the hydrogenation is allowed to proceed until the pressure drop corresponds to 1.0 mole of hydrogen (Note 2), (Note 3). The time required for hydrogenation is approximately 2.5 hours (Note 4). After venting the hydrogen from the bottle safely (Note 1), the ethanol solution is filtered and the catalyst washed carefully (Note 5) with 20 ml. of ethanol.

The filtrate is transferred to a flask which is placed on a rotary evaporator. The ethanol is then removed under reduced pressure on a steam bath. Using ether as a washing solvent, the residue is transferred to a small distilling flask and the ether distilled. The ethyl *p*-dimethylaminophenylacetate is then distilled (Note 6), (Note 7) at reduced pressure, affording 27.7–31.8 g. (67–77%) of colorless product, b.p. 122–124° (0.4 mm.), $n^{23}{}_D$ 1.5358.

2. Notes

1. Care must be taken in weighing out and transferring the catalyst as it can ignite mixtures of air and flammable vapors. The operation of the Parr apparatus and appropriate safety precautions in its use have been described in detail.[2]
2. The hydrogenation is exothermic, and care must be taken in order to prevent the reaction from getting out of control. The submitters have not experienced this difficulty, but exothermic hydrogenations require supervision.
3. With the apparatus used, a pressure drop of 85 lb. corresponds to 1.0 mole of hydrogen. Either the particular apparatus used can be calibrated or the hydrogenation allowed to proceed until the pressure ceases to drop.[2]
4. The time required for the hydrogenation will depend on several factors, such as the

speed of shaking, activity and particle size of the catalyst. In the experiments run on ethyl *p*-nitrophenylacetate the submitters have found that the time required varied from about 2 to 4 hours.

5. The filtration was by suction. The catalyst must not be allowed to dry out with a stream of air passing through it, as it can then readily ignite.

6. Before the actual distillation could be carried out, the flask was heated to approximately 95° and the residual formaldehyde removed at the aspirator. Only after the formaldehyde was removed could the pressure be reduced to that required for the distillation.

7. The checkers observed that rather rapid decomposition of the product occurs unless precautions were taken. A short path distillation using a 50-ml. distilling flask equipped with a capillary nitrogen bubbler was employed.

3. Discussion

Ethyl *p*-dimethylaminophenylacetate has been previously prepared in this laboratory by Fischer esterification of *p*-dimethylaminophenylacetic acid, the acid in turn being prepared by the reductive hydrolysis of *p*-dimethylaminomandelonitrile.[3]

4. Merits of the Preparation

Besides being a convenient preparation for ethyl *p*-dimethylaminophenylacetate, the procedure for reductive alkylation can be generalized.[4,5] Table I lists the results obtained by the submitters.

TABLE I
REDUCTIVE ALKYLATION OF NITRO COMPOUNDS

Nitro Compound	% Yield
p-Nitrophenylacetic acid	84–91
p-Nitrobenzoic acid	87
m-Nitrobenzoic acid	95
p-Nitrotoluene	90
o-Nitrotoluene	76

References and Notes

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Appendix

Compounds Referenced (Chemical Abstracts Registry Number)

palladium on charcoal

ethanol (64-17-5)

ether (60-29-7)

hydrogen (1333-74-0)

formaldehyde (630-08-0)

nitrogen (7727-37-9)

o-nitrotoluene (88-72-2)

m-Nitrobenzoic acid (121-92-6)

p-NITROBENZOIC ACID (62-23-7)

p-Nitrophenylacetic acid (104-03-0)

p-nitrotoluene (99-99-0)

Ethyl p-dimethylaminophenylacetate, Acetic acid, p-dimethylaminophenyl-, ethyl ester (17078-29-4)

ethyl p-nitrophenylacetate (5445-26-1)

p-dimethylaminophenylacetic acid (17078-28-3)

p-dimethylaminomandelonitrile

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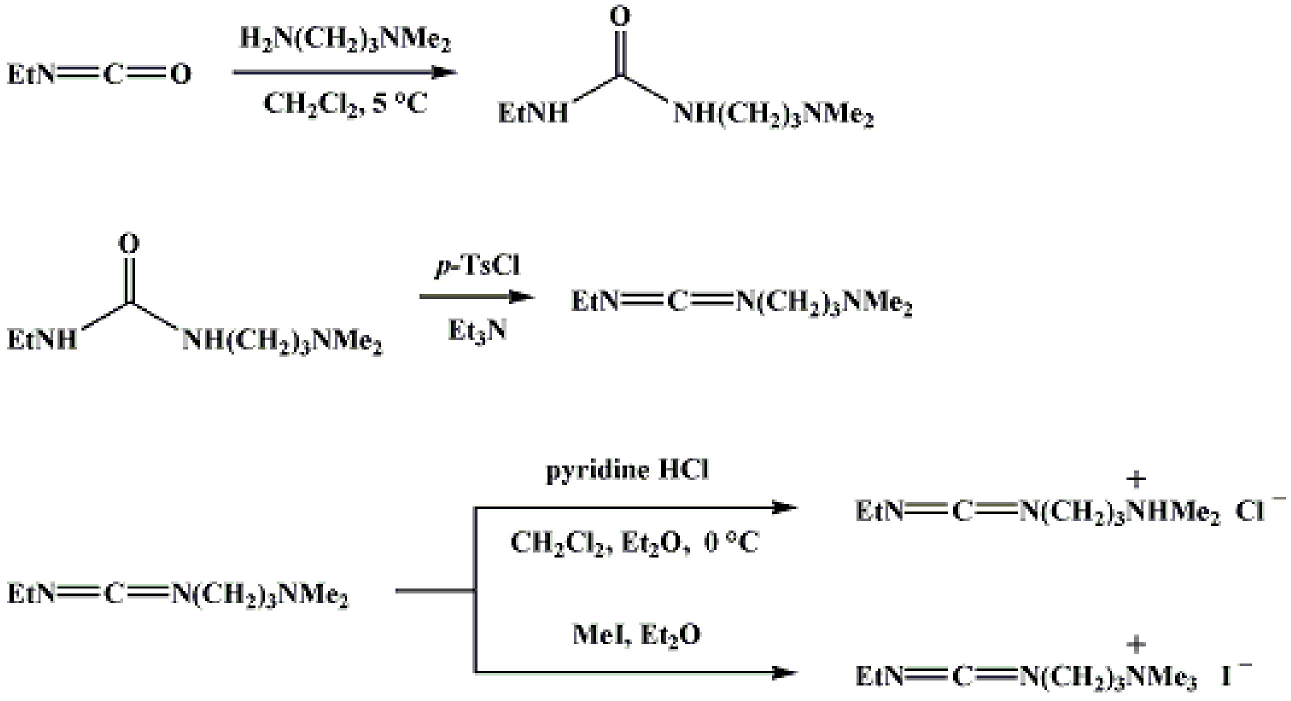
Organic Syntheses, CV 5, 555

1-ETHYL-3-(3-DIMETHYLAMINO)PROPYLCARBODIIMIDE HYDROCHLORIDE AND METHIODIDE

[Carbodiimide, [3-(dimethylamino)propyl]ethyl-, hydrochloride and Ammonium iodide, [3-[[(ethylimino)methylene]amino]propyl]trimethyl-]



Submitted by John C. Sheehan and Philip A. Cruickshank[1].
Checked by E. J. Corey and Jerome E. Anderson.

1. Procedure

A. *1-Ethyl-3-(3-dimethylamino)propylcarbodiimide*. A solution of 100 g. (1.41 moles) of ethyl isocyanate (Note 1) in 750 ml. of methylene chloride is prepared in a 5-l. three-necked flask equipped with a mechanical stirrer, an immersion thermometer, and a 500-ml., pressure-equalizing, addition funnel (Note 2). The flask and its contents are cooled to 5° in an ice bath, and a solution of 144 g. (1.41 moles) of N,N-dimethyl-1,3-propanediamine in 250 ml. of methylene chloride is added through the addition funnel at a rate such that the reaction temperature does not exceed 10° (Note 3). On completion of this addition 500 ml. of triethylamine is added to the flask, and a solution of 300 g. (1.6 moles) of *p*-toluenesulfonyl chloride in 300 ml. of methylene chloride is placed in the addition funnel and added to the reaction mixture, again at a rate such that the temperature does not exceed 10° (Note 4). After completion of the second addition, the ice bath is replaced with a heating mantle and the addition funnel with a reflux condenser; the reaction mixture is then heated under gentle reflux for 3 hours. Anhydrous sodium carbonate (400 g.) is added to the cooled reaction mixture, followed by 3.5 l. of ice water. The mixture is stirred vigorously for 30 minutes, after which the phases are allowed to separate, and the lower, organic phase is drawn off through a tube into a 2-l. suction flask. The aqueous phase is then extracted with three 500-ml. portions of methylene chloride (Note 5). The original methylene chloride phase and the extracts are combined and dried over anhydrous magnesium sulfate. The solvents are removed under reduced pressure, and the dark brown residue is distilled under reduced pressure through a

15-cm. Vigreux column to give 1-ethyl-3-(3-dimethylamino)propylcarbodiimide, b.p. 52–55° (0.3–0.4 mm.), n^{25}D 1.4591. The yield is 110–118 g. (50–54%) (Note 6).

B. *1-Ethyl-3-(3-dimethylamino)propylcarbodiimide hydrochloride*. A suspension of 34.6 g. (0.300 mole) of pyridine hydrochloride (Note 7) in 280 ml. of methylene chloride is prepared in a 1-l. Erlenmeyer flask. To this is slowly added 46.5 g. (0.300 mole) of 1-ethyl-3-(3-dimethylamino) propylcarbodiimide. The resulting solution is diluted with anhydrous ether (Note 8) and stored at 0–5° for 16–20 hours. The crystalline product is collected by filtration in a *dry* atmosphere (Note 9), washed with a little anhydrous ether, and dried under reduced pressure over phosphorus pentoxide. The yield is 50.5–55.5 g. (88–96.5%), m.p. 104–109° (Note 10) and (Note 11). This material is sufficiently pure for most purposes.

C. *1-Ethyl-3-(3-dimethylamino)propylcarbodiimide methiodide*. A solution of 30.0 g. (0.193 mole) of 1-ethyl-3-(3-dimethylamino)propylcarbodiimide in 750 ml. of anhydrous ether is prepared in a 2-l. Erlenmeyer flask. To this is slowly added from an addition funnel a solution of 30.0 g. (0.21 mole) of methyl iodide in 100 ml. of ether. The mixture is stored in the dark for 48 hours, after which the crystalline product is collected by filtration, washed with ether, and dried. The product, m.p. 94–95°, weighs 50.5–52.5 g. (88–91.5%) (Note 12).

2. Notes

1. Available from Eastman Organic Chemicals.
2. The assembled apparatus was dried at 120° for 18 hours.
3. The addition time was *ca.* 2 hours.
4. The addition time was *ca.* 3 hours.
5. Extractions were carried out in the reaction flask; after separation, the lower, methylene chloride phase was drawn off by suction.
6. The submitters, working on a twofold scale, obtained a yield of 60–65%.
7. Pyridine hydrochloride is extremely hygroscopic; the material used must be the anhydrous crystalline form.
8. Vigorous boiling of solvent occurs during addition of the carbodiimide and during spontaneous crystallization of the product. Approximately 250 ml. of ether was used.
9. The product is hygroscopic and care must be taken to protect it from atmospheric moisture at all times.
10. A sample of analytical purity had m.p. 113.5–114.5°.
11. The submitters, working on a 4.5-fold scale, obtained 92% of product, m.p. 108–112°.
12. The submitters, working on a twofold scale, obtained 95.5% of product, m.p. 93–95°, after one recrystallization from chloroform-ether.

3. Discussion

This procedure for the preparation of 1-ethyl-3-(3-dimethylamino)propylcarbodiimide and its salts is a modification of one that has been published.[2] Unsymmetrical carbodiimides have also been prepared by desulfurization of the corresponding thioureas with mercuric oxide[3] or by dehydration of the corresponding ureas with *p*-toluenesulfonyl chloride in pyridine.[4] Unsymmetrical 1,3-disubstituted ureas are best prepared by the reaction of isocyanates with primary or secondary amines[5] or by the action of carbamoyl chlorides on primary or secondary amines.[6]

4. Merits of the Preparation

Carbodiimides are, in general, useful compounds for effecting certain dehydrative condensations, *e. g.*, in the formation of amides, esters, and anhydrides. These two crystalline water-soluble carbodiimides are especially useful in the synthesis of peptides and in the modification of proteins. The excess of reagent and the co-product (the corresponding urea) are easily separated from products with limited solubility in water. The hydrochloride is best employed in nonaqueous solvents (methylene chloride, acetonitrile, dimethylformamide). The methiodide is relatively stable in neutral aqueous systems, and thus is recommended for those media.

Preparation of carbodiimides by dehydration of the corresponding ureas is of general applicability and is well adapted to the laboratory preparation of substantial quantities. The intermediates for this particular preparation are commercially available at moderate cost.

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

1-Ethyl-3-(3-dimethylamino)propylcarbodiimide hydrochloride and methiodide

ether (60-29-7)

acetonitrile (75-05-8)

chloroform (67-66-3)

sodium carbonate (497-19-8)

mercuric oxide (21908-53-2)

pyridine (110-86-1)

Methyl iodide (74-88-4)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

pyridine hydrochloride (628-13-7)

dimethylformamide (68-12-2)

triethylamine (121-44-8)

1-Ethyl-3-(3-dimethylamino)propylcarbodiimide (1892-57-5)

Carbodiimide, [3-(dimethylamino)propyl]ethyl-, hydrochloride, 1-Ethyl-3-(3-dimethylamino) propylcarbodiimide hydrochloride (25952-53-8)

Ammonium iodide, [3-[[(ethylimino)methylene]amino]propyl]trimethyl-

ethyl isocyanate (109-90-0)

N,N-dimethyl-1,3-propanediamine (109-55-7)

p-Toluenesulfonyl chloride (98-59-9)

phosphorus pentoxide (1314-56-3)

1-Ethyl-3-(3-dimethylamino)propylcarbodiimide methiodide (22572-40-3)

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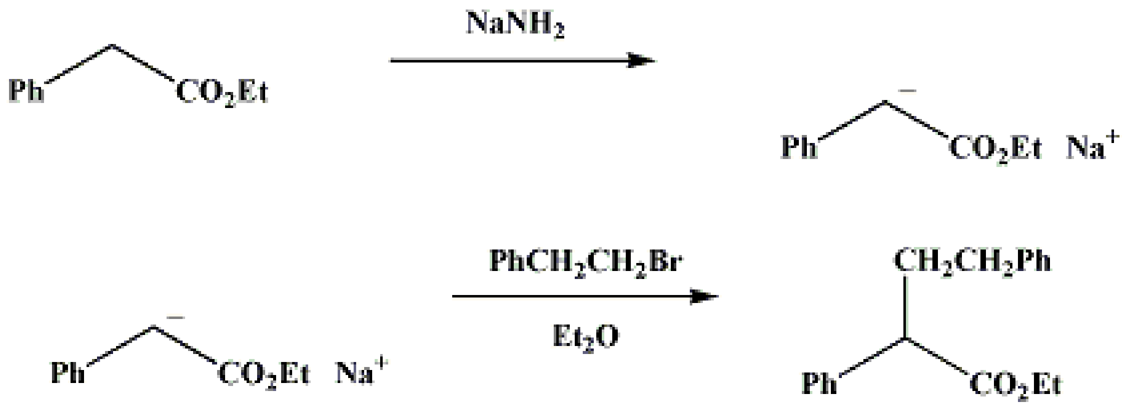
Organic Syntheses, *CV 5*, 559

ETHYL 2,4-DIPHENYLBUTANOATE

[Butyric acid, 2,4-diphenyl-, ethyl ester]



Submitted by Edwin M. Kaiser, William G. Kenyon, and Charles R. Hauser[1].
Checked by Joseph G. Pfeiffer and Kenneth B. Wiberg.

1. Procedure

Caution! This preparation should be carried out in a hood to avoid exposure to ammonia.

A suspension of sodium amide[2] (0.1 mole) in liquid ammonia is prepared in a 500-ml. three-necked, round-bottomed flask fitted with a West condenser, a ball and socket glass mechanical stirrer (Note 1), and a dropping funnel. In the preparation of this reagent a small piece of clean sodium metal is added to 350 ml. of commercial anhydrous liquid ammonia. After the appearance of a blue color, a few crystals of hydrated ferric nitrate are added, whereupon the blue color is discharged. The remainder of the 2.3 g. (0.1 mole) of sodium (Note 2) is then rapidly added as small pieces. After all the sodium has been converted to sodium amide (Note 3), a solution of 16.4 g. (0.1 mole) of ethyl phenylacetate (Note 4) in 35 ml. of anhydrous ethyl ether is added dropwise over a 2-minute period, and the mixture is stirred for 20 minutes. To the dark green suspension is added over an 8-minute period a solution of 18.5 g. (0.1 mole) of (2-bromoethyl) benzene (Note 4) dissolved in 35 ml. of anhydrous ethyl ether. The mixture is stirred for 3 hours and is then neutralized by the addition of 5.35 g. (0.1 mole) of ammonium chloride. After addition of 150 ml. of dry ethyl ether, the ammonia is evaporated with stirring by use of a warm water bath (Note 5). The mixture is then cooled to 0° by an ice bath and hydrolyzed by the dropwise addition of 100 ml. of 3*N* hydrochloric acid. After stirring for 15 minutes, the mixture is allowed to warm to room temperature, and the layers are separated. The aqueous layer is extracted with two 50-ml. portions of ethyl ether. The combined ether extracts are then washed with two 50-ml. portions of saturated aqueous sodium bicarbonate followed by

two 50-ml. portions of saturated sodium chloride. Drying is accomplished over magnesium sulfate. After filtration and solvent removal, the crude product is purified by vacuum distillation to give 20.6–21.8 g. (77–81%) of ethyl 2,4-diphenylbutanoate, b.p. 168–169° (3.5 mm.). Vapor phase chromatography shows the presence of one peak (Note 6).

2. Notes

1. Stirrers with Teflon paddles should not be used.
2. The sodium was weighed in toluene and then rinsed in anhydrous ethyl ether.
3. Conversion is indicated by the discharge of the blue color.
4. Ethyl phenylacetate and (2-bromoethyl)benzene as supplied by Eastman Organic Chemicals were used without further purification.
5. Alternatively, the ammonia may be evaporated after the ammonium chloride and ethyl ether have been added by allowing the flask to stand overnight with stirring.
6. A 5-ft. Apiezon L column at 225° was used.

3. Discussion

The procedure described is a modification of that given by Kenyon, Meyer, and Hauser.[3] No other methods appear to have been used to prepare ethyl 2,4-diphenylbutanoate. A number of alkylations of ethyl phenylacetate have previously been effected with alkyl halides by means of other basic reagents, but the yields generally have not been very satisfactory.[4,5]

4. Merits of the Preparation

The method described is successfully used for the alkylation and aralkylation of ethyl and *t*-butyl phenylacetate.[3] The alkylation of ethyl phenylacetate with methyl iodide, *n*-butyl bromide, benzyl chloride, and α-phenylethyl chloride affords the corresponding pure monoalkylation products in 69%, 91%, 85%, and 70% (*erythro* isomer) yields, respectively. The alkylation of *t*-butyl phenylacetate with methyl iodide, *n*-butyl bromide, α-phenylethyl chloride, and β-phenylethyl bromide gives the corresponding pure monoalkylated products in 83%, 86%, 72–73%, and 76% yields, respectively.

Certain of the monoalkylated ethyl phenylacetates have been further alkylated with alkyl and aralkyl halides to produce the corresponding disubstituted phenylacetic esters.[6] Ethyl 2-phenylpropanoate has been alkylated by methyl iodide to give pure ethyl 2-methyl-2-phenylpropanoate in 81% yield. Similarly, the alkylations of ethyl 2-phenylhexanoate with methyl iodide, *n*-butyl bromide, and benzyl chloride gave the corresponding pure dialkylated products in 73%, 92%, and 72% yields, respectively.

Butylation of ethyl phenylacetate, *t*-butyl phenylacetate, and ethyl 2-phenylhexanoate has also been accomplished with *n*-butyl bromide and sodium hydride in refluxing

monoglyme in 64%, 66%, and 56% yields, respectively.[6] In contrast to the sodium amide reactions above, however, careful fractionation of the crude products was required to obtain pure products.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 526

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethyl and t-butyl phenylacetate

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ether, ethyl ether (60-29-7)

ammonium chloride (12125-02-9)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

n-butyl bromide (109-65-9)

toluene (108-88-3)

sodium (13966-32-0)

benzyl chloride (100-44-7)

Methyl iodide (74-88-4)

Ethyl phenylacetate (101-97-3)

magnesium sulfate (7487-88-9)

β-phenylethyl bromide, (2-bromoethyl)benzene, (2-bromoethyl) benzene (103-63-9)

sodium amide (7782-92-5)

ferric nitrate

sodium hydride (7646-69-7)

α-phenylethyl chloride (672-65-1)

Ethyl 2,4-diphenylbutanoate, Butyric acid, 2,4-diphenyl-, ethyl ester (53608-81-4)

Ethyl 2-phenylpropanoate

ethyl 2-methyl-2-phenylpropanoate

ethyl 2-phenylhexanoate

t-butyl phenylacetate

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Organic Syntheses, CV 5, 562

ETHYLENE SULFIDE

Submitted by Scott Searles, Eugene F. Lutz, High R. Hays, and Harley E. Mortensen[1].
Checked by Melvin S. Newman and Bernard C. Ream.

1. Procedure

Into a 500-ml., two-necked, round-bottomed flask equipped with a thermometer (Note 1) and leading to a condenser equipped with a distillation head and a receiver is placed 145 g. (1.5 mole) of potassium thiocyanate (Note 2). The system is evacuated to about 1 mm., and the flask is heated with a free flame until the temperature of the molten salt is in the 165–175° range (Note 3). After the flask has been heated for 15 minutes, it is cooled to room temperature and 88 g. (1.0 mole) of ethylene carbonate (Note 4) is added. The apparatus is reconnected and the receiver protected with a calcium chloride tube.

The reaction flask is slowly heated by means of a sand bath, and the receiver is cooled in a Dry Ice-acetone bath. When the temperature in the fused potassium thiocyanate layer reaches 95°, reaction occurs. Ethylene sulfide distils and is collected in the receiver. Heating is continued for about 3 hours at 95–99° (Note 6). The distillate amounts to 41–45 g. (68–75%) (Note 7) and is sufficiently pure to be used directly (Note 8).

2. Notes

1. The thermometer may be inserted through a neoprene stopper in one neck or into a suitably designed thermometer well.
2. J. T. Baker's analytical grade was used.
3. The purpose of this operation is to ensure dryness, as potassium thiocyanate is hygroscopic. The presence of even small amounts of water is detrimental to the yield. The initially colorless salt melts to a blue liquid. On cooling, this solidifies to a colorless solid.
It has been reported that this procedure is more easily reproduced when the potassium thiocyanate is heated to *ca.* 100–110° at 0.1 mm. so that the salt does not melt, and a larger surface is available for reaction (Nelson N. Schwartz, private communication).
4. Ethylene carbonate obtained from the Eastman Kodak Company or the Jefferson Chemical Company was vacuum distilled and the fraction, b.p.

125°/10 mm., was used.
5. It has been reported that an oil bath may be used to provide greater uniformity of heating (Nelson N. Schwartz, private communication).
6. Differences in the rate of heating and time of heating cause small changes in the yield of ethylene sulfide obtained. If the time of heating is reduced and the rate of heating increased, the yield drops somewhat. For many purposes the saving in time offsets the higher yield obtained under optimum conditions. The submitters have obtained yields in the 81–87% range.
7. This product can be stored at room temperature for several weeks without polymerization. On distillation, pure ethylene sulfide, b.p. 54.0–54.5°, n_D^{20} 1.4960, is obtained.
8. For example, this product is suitable for reaction with amines.[2]

3. Discussion

Ethylene sulfide has been prepared by the reaction of ethylene oxide with aqueous potassium thiocyanate;[2,3] by the reaction of 2-chloroethyl mercaptan with aqueous sodium bicarbonate;[4] by the reactions of 2-chloroethylthiocyanate[5] and 1,2-dithiocyanoethane[6] with alcoholic sodium sulfide; and by the thermal decomposition of monothiolethylene carbonate.[7]

4. Merits of Preparation

The advantage of the present procedure is the easy availability at low expense of the starting material, ethylene carbonate.[8] Its advantages over the other methods are high yields and degree of purity of the product, combined with greater simplicity of procedure.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

monothiolethylene carbonate

sodium bicarbonate (144-55-8)

Ethylene oxide (75-21-8)

sodium sulfide (1313-82-2)

potassium thiocyanate (333-20-0)

Ethylene sulfide (420-12-2)

ethylene carbonate (96-49-1)

2-chloroethyl mercaptan

2-chloroethylthiocyanate (928-57-4)

1,2-dithiocyanoethane

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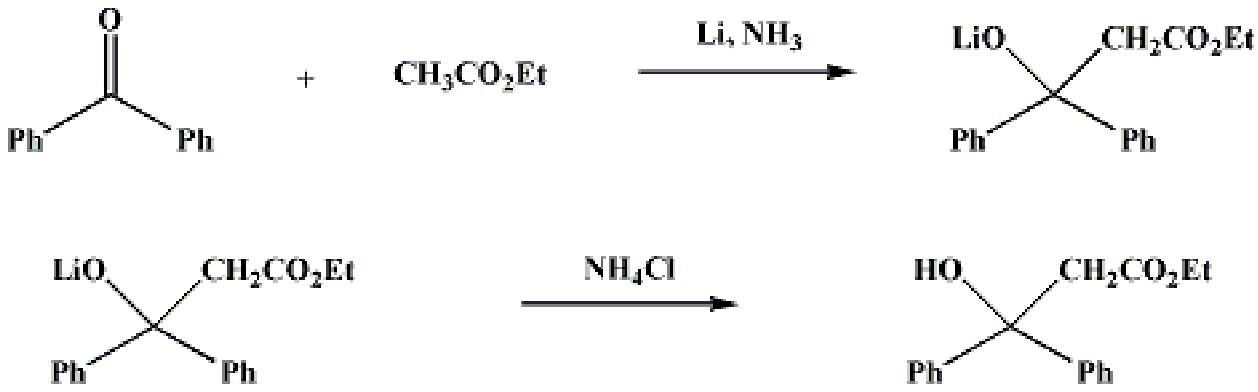
Organic Syntheses, CV 5, 564

ETHYL β-HYDROXY-β,β-DIPHENYLPROPIONATE

[Hydracrylic acid, 3,3-diphenyl, ethyl ester]



Submitted by W. R. Dunnavant and Charles R. Hauser[1].
Checked by William E. Parham and J. E. Burcsu.

1. Procedure

Caution! This preparation should be carried out in a hood to avoid exposure to ammonia.

A Suspension of lithium amide (0.25 mole) (Note 1) in liquid ammonia is prepared in a 1-l. three-necked flask equipped with a condenser, a ball-sealed mechanical stirrer, and a dropping funnel. In the preparation of this reagent commercial anhydrous liquid ammonia (500 ml.) is introduced from a cylinder through an inlet tube. To the stirred ammonia is added a small piece of clean lithium metal. After the appearance of a blue color a few crystals of ferric nitrate hydrate (about 0.25 g.) are added, followed by small pieces of freshly cut lithium metal (Note 2) until 1.73 g. has been added. After all the lithium has been converted to the amide (Note 3), 17.6 g. (0.2 mole) of ethyl acetate (Note 4) is added, and the gray suspension is stirred for about 30 seconds. To the gray suspension is added 36.4 g. (0.2 mole) of benzophenone (Note 4) dissolved in 100 ml. of anhydrous ether. The mixture is stirred for 30 minutes and is then neutralized by the addition of 13.4 g. (0.25 mole) of ammonium chloride. The liquid ammonia is then removed by use of a steam bath while 200–300 ml. of ether is being added (Note 5). When the ammonia has been removed, 200 ml. of cold water is added. The ether layer is separated, and the aqueous layer is further extracted with two 100-ml. portions of ether. The combined ether extract is dried over magnesium sulfate and filtered, and the solvent is evaporated. The residue is dissolved in 50 ml. of hot 95% ethanol, treated with Norit®, filtered, and allowed to cool. The yield of ethyl β-hydroxy-β,β-diphenylpropionate, obtained as colorless, needle-like crystals melting at 85–86°, is 40.5–45.5 g. (75–84%). The filtrate, on reduction in volume and cooling,

yields small amounts of benzophenone, m.p. 46–47°.

2. Notes

1. This preparation may be accomplished by using one molecular equivalent of lithium amide; special reaction procedures must be employed, however, and the yields are not reproducible.[2] The preparation may also be accomplished (with reduced yield) by using sodium amide, but only under special reaction conditions.[3]
2. The lithium wire or ribbon is cut in about 0.25-g. pieces, stored under kerosene, and blotted with filter paper before addition.
3. Conversion is indicated by the discharge of the blue color.
4. Ethyl acetate and benzophenone as supplied by the Eastman Kodak Company were used without further purification.
5. The checkers added ether and permitted the ammonia to evaporate overnight. If a steam bath is employed, care must be exercised to prevent charring of the product.

3. Discussion

This procedure is an adaptation of ones described by Dunnavant and Hauser.[2,4] Ethyl β-hydroxy-β,β-diphenylpropionate has been prepared previously using the Reformatsky reaction by condensing ethyl α-bromoacetate with benzophenone by means of zinc metal.[5]

4. Merits of the Preparation

This procedure illustrates the use of lithio esters for the preparation of β-hydroxy esters. Isopropyl and *t*-butyl β-hydroxy-β,β-diphenylpropionate may be prepared in approximately 80% yields by using isopropyl or *t*-butyl acetates in place of ethyl acetate.[2] This procedure is generally more convenient than the Reformatsky reaction for the preparation of such esters. Under similar conditions ethyl acetate may conveniently be condensed with various aldehydes or ketones to give the corresponding β-hydroxy esters.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 509

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Isopropyl and t-butyl β-hydroxy-β,β-diphenylpropionate

isopropyl or t-butyl acetates

ethanol (64-17-5)

ammonia (7664-41-7)

ethyl acetate (141-78-6)

ether (60-29-7)

ammonium chloride (12125-02-9)

Norit (7782-42-5)

Benzophenone (119-61-9)

zinc (7440-66-6)

lithium (7439-93-2)

magnesium sulfate (7487-88-9)

ethyl α-bromoacetate (105-36-2)

sodium amide (7782-92-5)

lithium amide (7782-89-0)

ferric nitrate hydrate

Ethyl β-hydroxy-β,β-diphenylpropionate, Hydracrylic acid, 3,3-diphenyl, ethyl ester (894-18-8)

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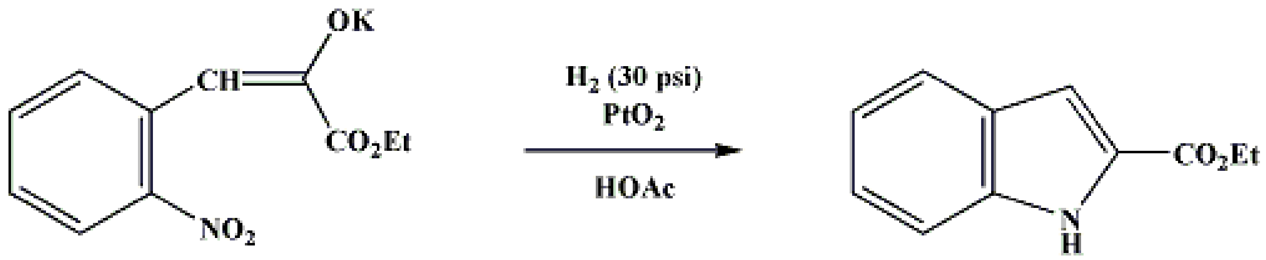
Organic Syntheses, *CV 5*, *567*

ETHYL INDOLE-2-CARBOXYLATE

[Indole-2-carboxylic acid, ethyl ester]



Submitted by Wayland E. Noland and Frederic J. Baude[1].
Checked by E. J. Corey and Ronald J. McCaully.

1. Procedure

A. *Potassium salt of ethyl o-nitrophenylpyruvate*. Anhydrous ether (300 ml.) is placed in a 5-l., three-necked, round-bottomed flask fitted with a 500-ml. dropping funnel, a motor-driven stirrer (with seal), and a reflux condenser protected with a calcium chloride tube. Freshly cut potassium (39.1 g., 1.00 g. atom) is added. *Caution! Follow the precautions for handling potassium described in an earlier volume.*[2]

A slow stream of dry nitrogen is passed through the flask above the surface of the stirred liquid, and a mixture of 250 ml. of commercial absolute ethanol and 200 ml. of anhydrous ether is added from the dropping funnel just fast enough to maintain mild boiling. When all the potassium has dissolved (Note 1), the nitrogen is shut off. The solution is allowed to cool to room temperature, and 2.5 l. of anhydrous ether is added. Diethyl oxalate (146 g., 1.00 mole) is added with stirring, followed after 10 minutes by 137 g. (1.00 mole) of *o*-nitrotoluene. Stirring is discontinued after an additional 10 minutes, and the mixture is poured, with the aid of a connecting tube, into a 5-l. Erlenmeyer flask. The flask is stoppered and set aside for at least 24 hours. The lumpy deep-purple potassium salt of ethyl *o*-nitrophenylpyruvate is separated by filtration (Note 2) and washed with anhydrous ether until the filtrate remains colorless. The yield of the air-dried salt is 204–215 g. (74–78%).

B. *Ethyl indole-2-carboxylate*. Thirty grams (0.109 mole) of the potassium salt is placed in a 400-ml. hydrogenation bottle and dissolved by addition of 200 ml. of glacial acetic acid, producing a yellow, opaque solution (Note 3). Platinum catalyst[3] (0.20 g.) is added, the bottle is placed in a Parr low-pressure hydrogenation apparatus, and the system is flushed several

times with hydrogen. With the initial reading on the pressure gauge about 30 p.s.i., the bottle is shaken until hydrogen uptake ceases and then for an additional 1–2 hours (Note 4). The catalyst is removed by filtration and washed with glacial acetic acid. The filtrate is placed in a 4-l. beaker, and 3 l. of water is added slowly with stirring. Ethyl indole-2-carboxylate precipitates as a yellow solid. It is separated by filtration, washed with five 100-ml. portions of water, and dried over calcium chloride in a desiccator. It weighs 13.2–13.6 g. (64–66%; 47–51% based on *o*-nitrotoluene); m.p. 118–124°.

The dried ether can be further purified by treatment with charcoal and recrystallization from a mixture of methylene chloride and light petroleum ether (b.p. 60–68°). This gives 11.3–11.7 g. (41–44% based on *o*-nitrotoluene) of ethyl indole-2-carboxylate in the form of white needles, m.p. 122.5–124° (Note 5).

2. Notes

1. Complete solution of the potassium takes 1.5–2 hours with stirring and 2.5–3 hours without stirring.
2. Salt that sticks to the sides of the Erlenmeyer flask may be loosened with a piece of 10-mm. glass tubing that has not been fire-polished.
3. On addition of the acetic acid, a small amount of black solid settles out, but this dissolves when the solution is swirled for several minutes. The potassium salt of ethyl *o*-nitrophenylpyruvate, although it undergoes no apparent change in color, does not keep indefinitely in the dry state. After 3 weeks of storage at room temperature, the salt still produced a yellow solution when dissolved in acetic acid, but, after 3 months of storage, the dry salt produced a deep-red solution from which an oil, rather than crystalline ester, was obtained after catalytic hydrogenation.
4. The hydrogen pressure-drop corresponds to 0.325–0.335 mole (99–102%). When the hydrogen pressure drops below about 15 p.s.i., the hydrogen should be replenished in the reservoir tank to bring the pressure back up to about 30 p.s.i. The checkers found a reduction period of 4–6 hours sufficient; the submitters routinely used a 24-hour reduction period.
5. The reported melting points[4,5,6,7,8,9,10,11,12,13] range from 119°[6] to 125–126°.[7,8]

3. Discussion

The potassium salt of ethyl *o*-nitrophenylpyruvate is prepared essentially according to the method of Wislicenus and Thoma.[14] However, the isolation of ethyl *o*-nitrophenylpyruvate has been eliminated by liberating the ester from its potassium salt in the acetic acid used as solvent for the hydrogenation. Catalytic hydrogenation of the ester is carried out essentially by the procedure of Brehm.[5]

Ethyl *o*-nitrophenylpyruvate[4,14] and *o*-nitrophenylpyruvic acid[14,15,16,17,18,19,20,21] have been prepared by condensation of *o*-nitrotoluene with diethyl oxalate in the presence of potassium ethoxide,[4,14] sodium ethoxide,[15,16,17,18,19,20] or sodium methoxide.[21] Sodium ethoxide is less reactive, however, and cannot be substituted successfully for potassium ethoxide in the present procedure, as it gives a very poor yield and poor quality of precipitated sodium salt. With sodium ethoxide the reaction does not appear to go to completion even under the conditions of refluxing ethanol usually employed,[15,16,17,18,19,20,21] which are considerably more severe than

the room temperature conditions employed with potassium ethoxide in the present procedure. *o*-Nitrophenylpyruvic acid has also been prepared by hydrochloric acid hydrolysis of *o*-nitro-α-acetaminocinnamic azlactone.[4]

Ethyl indole-2-carboxylate[5,13] and the corresponding carboxylic acid[4,17,19,22,23] have been prepared by reductive cyclization of ethyl *o*-nitrophenylpyruvate and *o*-nitrophenylpyruvic acid, both in the presence of reducing agents such as zinc and acetic acid,[4,13] ferrous sulfate and ammonium hydroxide,[17,19,23] and sodium hydrosulfite,[17,22] and by platinum-catalyzed hydrogenation.[5] The ethyl ester has also been prepared by esterification[9,19] of the acid in the presence of sulfuric[6] and hydrochloric[12] acid catalysts, by the Fischer indole synthesis from ethyl pyruvate phenylhydrazone catalyzed by polyphosphoric acid,[11] sulfuric acid and acetic acid,[11,17] or zinc chloride,[24,25,26] and by stannous chloride reduction of ethyl 1-hydroxyindole-2-carboxylate.[7] Indole-2-carboxylic acid has also been prepared by the Fischer indole synthesis from pyruvic acid phenylhydrazone catalyzed by zinc chloride,[24] by the Madelung synthesis from potassium oxalyl-*o*-toluidine,[27] by zinc and acetic acid reduction of 1-hydroxy- and 1-methoxyindole-2-carboxylic acids,[28] by cyclizative demethanolation of *o*-amino-α-methoxycinnamic acid,[29] by reductive cyclization and hydrolysis of *o*-nitrobenzalrhodanine,[12] by alkaline hydrolysis and decarboxylation of dimethyl indole-2,3-dicarboxylate,[30] and by fusion of 2-methylindole with potassium hydroxide in the presence of air.[31]

4. Merits of the Preparation

The procedure employs the least expensive commercially available starting materials and requires the minimum number of reaction steps.

Alkaline hydrolysis of ethyl indole-2-carboxylate yields indole-2-carboxylic acid,[4,5,7,11,24,25] which can be decarboxylated to indole by heating at 230°.[24,25] The acid or its ester serves as a readily accessible indole capable of electrophilic substitution at the 3-position,[6,22] and as a precursor for the synthesis of indole-2-acylamino derivatives of interest as model compounds in the study of alkaloid synthesis[5,23,32] and as a degradation product of the mold metabolite, gliotoxin.[4,33,34,35] Reduction of the ester with lithium aluminum hydride yields indole-2-methanol,[5] which can be oxidized to indole-2-carboxaldehyde by potassium permanganate in acetone.[10] Reduction of the acid chloride with lithium aluminum tri-*tert*-butoxy hydride[36] is a convenient synthesis of indole-2-carboxaldehyde.[37]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

polyphosphoric acid

Potassium salt of ethyl o-nitrophenylpyruvate

o-nitro-α-acetaminocinnamic azlactone

potassium oxalyl-o-toluidine

lithium aluminum tri-tert-butoxy hydride

ethanol (64-17-5)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ether (60-29-7)

hydrogen (1333-74-0)

potassium permanganate (7722-64-7)

nitrogen (7727-37-9)

sodium hydrosulfite (7775-14-6)

stannous chloride

ferrous sulfate (13463-43-9)

platinum (7440-06-4)

acetone (67-64-1)

sodium methoxide (124-41-4)

potassium hydroxide (1310-58-3)

zinc (7440-66-6)

sodium ethoxide (141-52-6)

zinc chloride (7646-85-7)

ammonium hydroxide (1336-21-6)

potassium (7440-09-7)

methylene chloride (75-09-2)

o-nitrotoluene (88-72-2)

potassium ethoxide (917-58-8)

lithium aluminum hydride (16853-85-3)

Indole (120-72-9)

indole-2-carboxylic acid (1477-50-5)

2-Methylindole (95-20-5)

diethyl oxalate (95-92-1)

Ethyl indole-2-carboxylate, Indole-2-carboxylic acid, ethyl ester (3770-50-1)

ethyl o-nitrophenylpyruvate

ethyl pyruvate phenylhydrazone

ethyl 1-hydroxyindole-2-carboxylate

pyruvic acid phenylhydrazone

dimethyl indole-2,3-dicarboxylate (54781-93-0)

indole-2-methanol

indole-2-carboxaldehyde

o-nitrophenylpyruvic acid (5461-32-5)

o-amino-α-methoxycinnamic acid

o-nitrobenzalrhodanine

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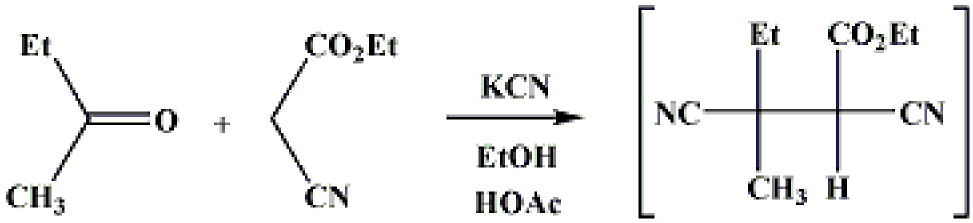
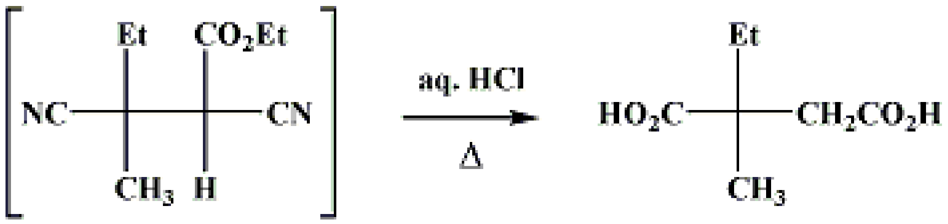
Organic Syntheses, CV 5, 572

α-ETHYL-α-METHYLSUCCINIC ACID

[Succinic acid, α-ethyl-α-methyl-]





Submitted by F. S. Prout, V. N. Aguilar, F. H. Girard, D. D. Lee, and J. P. Shoffner[1].
Checked by William G. Dauben and Dale L. Whalen.

1. Procedure

Potassium cyanide (71.6 g., 1.1 moles, U.S.P.) and 100 ml. of 95% ethanol are placed in a 2-l. round-bottomed flask having a ground joint and arranged with a Hershberg stirrer[2] (Note 1). A solution of 113 g. (106 ml., 1 mole) of ethyl cyanoacetate, 79 g. (98 ml., 1.1 moles) of 2-butanone, and 66 ml. of glacial acetic acid is added to the stirred solution over a period of 1 hour. The mixture is stirred for an additional hour, the stirrer is removed, and the mixture is allowed to stand at room temperature for 7 days (Note 2).

Concentrated hydrochloric acid (500 ml.) is added to the semisolid reaction mixture, a reflux condenser is placed on the flask, and the mixture is heated under vigorous reflux for a period of 4 hours (Note 3). An additional 500 ml. of hydrochloric acid is added, and the boiling under reflux is continued for an additional 4 hours.

The cooled reaction mixture is extracted (Note 4) with four portions of ether (400 ml., 250 ml., 200 ml., 200 ml.) (Note 5) The ether extracts are filtered and combined, and about two-thirds of the ether is distilled. The ethereal solution is transferred to a 500-ml. Erlenmeyer flask, and the remaining ether is removed. The residue (about 160 g.) is dissolved in 200 ml. of 24% hydrochloric acid (1 part water, 2 parts concentrated hydrochloric acid) and the solution distilled until the boiling point reaches 108° (Note

6) The solution is cooled and allowed to stand at 5° for about 20 hours. The product is collected by vacuum filtration and dried in a vacuum desiccator containing both concentrated sulfuric acid and potassium hydroxide pellets. The yield of α-ethyl-α-methylsuccinic acid is 65–75 g. (41–47%), m.p. 91–97°. Concentration of the mother liquor to 125 ml. gives an additional 8–9 g. of acid, m.p. 85–91° (Note 7).

2. Notes

1. The reaction can be run in an open flask because only a small amount of gas escapes. See (Note 3). Sodium cyanide can be substituted for potassium cyanide if 2 g. of β-alanine is also employed as a catalyst.
2. Heating the reaction for shorter periods gave erratic results. At this point the semisolid mixture can be diluted with 200 ml. of water, extracted with benzene, and the benzene extract fractionally distilled to give ethyl 2,3-dicyano-3-methylpentanoate, b.p. 146.0–147.5° (2.5 mm.), n^{27}D 1.4429 (highly purified ester has b.p. 138.5–141.5° (2 mm.), n^{25}D 1.4432). The overall yield of α-ethyl-α-methylsuccinic acid is decreased by about 5% when the dicyano intermediate is isolated.
3. During the reflux period, gases are continuously evolved; these apparently are hydrogen chloride, carbon dioxide, ethyl acetate, and possibly ethyl chloride. The reaction should be run in a hood, or the gases should be trapped.[3]
4. If no layer separates on addition of the ether, add 200 ml. of water.
5. This extraction, designed to remove organic acids from inorganic salts, may also be effected with a lighter-than-water Kutscher-Steudel extractor.[4]
6. The distillate consists of low-boiling solvents.
7. The acid can be purified further by dissolving 50 g. of it in 100 ml. of benzene. The solution is filtered, diluted with 100 ml. of hexane, and cooled to 5°. The yield of acid is 45.0 g., m.p. 97–102° (lit.[5] m.p. 101–102°).

3. Discussion

The one-step condensation to convert 2-butanone, ethyl cyanoacetate, and hydrocyanic acid to ethyl 2,3-dicyano-3-methylpentanoate is a modification of the procedure described by Smith and Horowitz[5] in which pyridine acetate was employed as the catalyst. Higson and Thorp[6] employed a two-step procedure in which butanone was converted to its cyanohydrin, which in turn was condensed with ethyl cyanoacetate.

α-Ethyl-α-methylsuccinic acid also has been prepared by the sulfuric acid hydrolysis of ethyl α-ethyl-α-methyl-β-carbethoxysuccinate,[7] the action of 80% sulfuric acid on 1-ethoxy-3-ethyl-3-methyl-1,2-cyclopropanedioic acid,[8] and the dichromate oxidation of β-ethyl-β-methylbutyrolactone.[9]

4. Merits of the Preparation

This procedure illustrates a process which should be general for many α,α-disubstituted succinic acids. It is more convenient than those previously employed because the reaction sequence is carried out in one step.

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrogen chloride, hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

ethyl acetate (141-78-6)

ether (60-29-7)

sodium cyanide (143-33-9)

hydrocyanic acid (74-90-8)

potassium cyanide (151-50-8)

carbon dioxide (124-38-9)

potassium hydroxide (1310-58-3)

Ethyl cyanoacetate (105-56-6)

β-Alanine (107-95-9)

butanone, 2-butanone (78-93-3)

hexane (110-54-3)

ethyl chloride (75-00-3)

α-Ethyl-α-methylsuccinic acid, Succinic acid, α-ethyl-α-methyl- (631-31-2)

ethyl 2,3-dicyano-3-methylpentanoate

pyridine acetate

ethyl α-ethyl-α-methyl-β-carbethoxysuccinate

1-ethoxy-3-ethyl-3-methyl-1,2-cyclopropanedioic acid

β-ethyl-β-methylbutyrolactone

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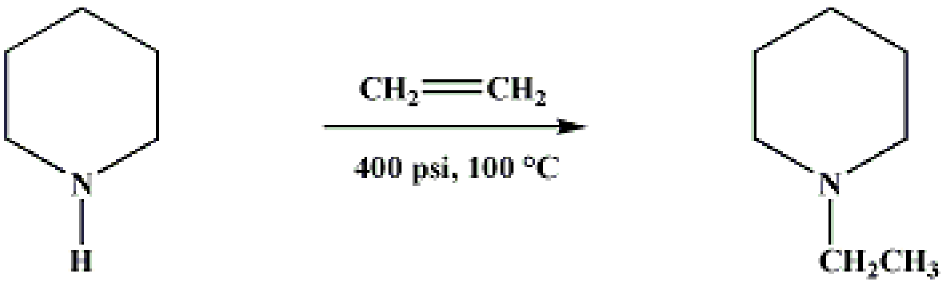
Organic Syntheses, CV 5, 575

N-ETHYLPIPERIDINE

[Piperidine, 1-ethyl-]



Submitted by J. Wollensak and R. D. Closson[1].
Checked by C. D. Ver Nooy and B. C. McKusick.

1. Procedure

A 1-l. three-necked flask equipped with a reflux condenser, an inlet for dry nitrogen, and a mechanical stirrer is flushed with dry nitrogen. It is then charged with 340 g. (4.00 moles) of piperidine (Note 1) 4.4 g. (0.19 g. atom) of sodium, and 5.0 g. (5.1 ml., 0.063 mole) of pyridine (Note 2). While a slow stream of nitrogen continues to pass through the flask, the solution is heated under reflux with high-speed stirring for approximately 10 minutes. During this time most of the sodium reacts without evolution of hydrogen, and the dispersion darkens. The dispersion, which contains some finely divided solids, is cooled and transferred to a 2-l. stirred autoclave (Note 3) under nitrogen. An additional 85 g. (1.00 mole) of piperidine is used to wash the last portions of the dispersion into the autoclave.

The autoclave is pressured with ethylene (Note 2) to 400 lb./in.^{2} with stirring (Note 4). It is then heated to 100° with stirring, which causes the pressure to rise to about 555 lb./in.^{2}. It is maintained at 100° with stirring until a gradual drop in pressure ceases; this usually takes about 2.5 hours, but it may take as long as 10 hours (Note 5). The autoclave is cooled to room temperature, and the excess ethylene is vented. The reaction mixture is transferred to a 1-l. round-bottomed flask, the autoclave is rinsed with 100 ml. of methanol that is added to the flask, and the mixture is fractionated through a 90-cm. column packed with glass helices. After a fore-cut of 50–100 g. distilling at 55–129°, 434–468 g. (77–83%) of N-ethylpiperidine is collected; b.p. 129–130.5°; n_D^{20} 1.443–1.444 (Note 6).

2. Notes

1. Piperidine obtained from Eastman Kodak was fractionated through a 90-cm. column packed with glass helices, and the fraction distilling at 105° was used

for this work. This material contained approximately 0.36 wt.% of pyridine as indicated by vapor phase chromatography and ultraviolet analysis.

2. Sodium from Ethyl Corporation, pyridine from Eastman Kodak, and C.P. ethylene from Matheson are suitable.

3. The kind of stirrer is not important. The submitters obtained similar results with a three-blade propeller turning at 600 r.p.m. and a paddle stirrer turning at 78 r.p.m. They believe that a rocking autoclave could be substituted for a stirred one.

4. Over half the ethylene pressured into the autoclave dissolves in the piperidine. It is essential to agitate the piperidine during the pressuring operation so that the piperidine will become saturated with ethylene, for otherwise there will not be enough ethylene for the reaction.

5. The checkers found that it shortened the reaction time appreciably to repressure the autoclave to 400–500 lb./in.^{2} whenever the pressure dropped below 350 lb./in.^{2}

6. The checkers got the same results using half the quantities of reactants in a 1-l. stirred autoclave.

3. Discussion

The described procedure is essentially the method of Closson, Kolka, and Ligett.[2] Since N-ethylpiperidine was first prepared by Cahours by reaction of piperidine with ethyl iodide,[3] a large number of synthetic methods have been used for its preparation. Reductive alkylation of pyridine with ethanol over Langenback or Raney nickel catalyst gives N-ethylpiperidine in high yield.[4] The compound may similarly be prepared by catalytic hydrogenation of N-ethylpyridinium chloride with platinum oxide as catalyst[5] and by the alkylation of piperidine using ethanol and Raney nickel catalyst under hydrogenating conditions.[6] Other methods that have been used are electrolytic reduction of N-ethylglutarimide,[7] interaction of pentamethylene oxide and ethylamine at high temperature over aluminum oxide,[8] interaction of ethylamine and 1,5-dibromopentane,[9] and reduction of 1-acetylpiperidine with lithium aluminum hydride.[10]

4. Merits of the Preparation

The procedure is illustrative of a general method of ethylating amines, wherein one reacts the amine with ethylene using an alkali-metal salt of the amine as catalyst.[2] Di-*n*-butylamine and *n*-hexylamine have been thus ethylated at 130–160°, aniline, *o*-toluidine, and N-methylaniline at 240–275°. In general, higher olefins add to amines only sluggishly.[2]

References and Notes

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2. R. D. Closson, J. P. Napolitano, G. G. Ecke, and A. J. Kolka, *J. Org. Chem.*, **22**, 646 (1957); R. D. Closson, A. J. Kolka, and W. B. Ligett, U.S. Patent 2,750,417 (1956).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Ethyl Corporation

ethanol (64-17-5)

methanol (67-56-1)

aniline (62-53-3)

hydrogen (1333-74-0)

nitrogen (7727-37-9)

platinum oxide

Raney nickel (7440-02-0)

pyridine (110-86-1)

sodium (13966-32-0)

piperidine (110-89-4)

1,5-dibromopentane (111-24-0)

ethylene (9002-88-4)

pentamethylene oxide (142-68-7)

Ethyl iodide (75-03-6)

aluminum oxide (1344-28-1)

N-Methylaniline (100-61-8)

lithium aluminum hydride (16853-85-3)

ethylamine (75-04-7)

di-n-butylamine (111-92-2)

N-Ethylpiperidine, Piperidine, 1-ethyl- (766-09-6)

N-ethylpyridinium chloride

N-ethylglutarimide

1-acetylpiperidine (618-42-8)

o-toluidine (95-53-4)

n-hexylamine (111-26-2)

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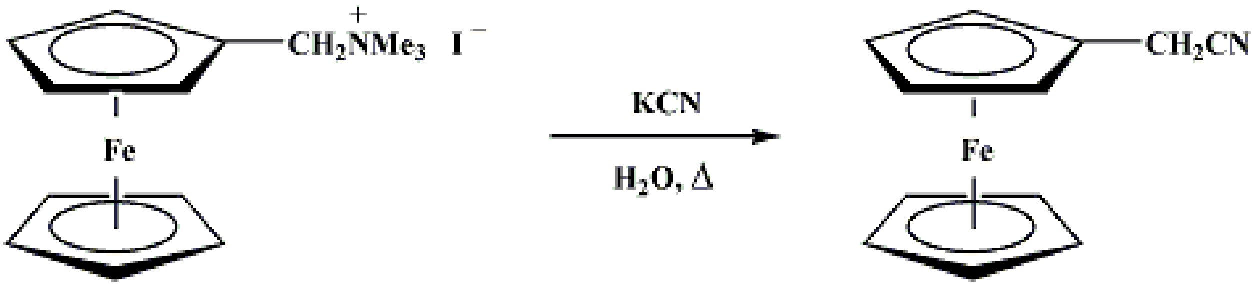
Organic Syntheses, CV 5, 578

FERROCENYLACETONITRILE

[Iron, [(cyanomethyl)cyclopentadienyl]cyclopentadienyl]



Submitted by Daniel Lednicer and Charles R. Hauser[1].
Checked by B. C. McKusick and R. D. Vest.

1. Procedure

Caution! This preparation should be carried out in a hood since trimethylamine is evolved.

A solution of 57 g. (0.88 mole) of potassium cyanide in 570 ml. of water is placed in a 1-l. three-necked flask equipped with a stirrer and a reflux condenser. Fifty-eight grams (0.15 mole) of N,N-dimethylaminomethylferrocene methiodide[2] is added and the mixture is heated to boiling with good stirring. As the mixture is brought to boiling, the solid goes into solution. Within a few minutes of the onset of boiling, evolution of trimethylamine begins and a steam-volatile oil starts to separate from the solution. The reaction mixture is boiled vigorously with stirring for 2 hours and then is allowed to cool to room temperature. During the cooling the oil that has separated solidifies.

The solid is separated by filtration and the filtrate is extracted with three 150-ml. portions of ether. *(Caution! Gloves should be worn when handling this solution because of the large amount of cyanide it contains.)* The solid is dissolved in ether and this solution is combined with the extracts. The combined ethereal solutions are washed with water and dried over 5 g. of sodium sulfate. Removal of the solvent by distillation leaves crude ferrocenylacetonitrile as a solid or as an oil that crystallizes on being scratched. The nitrile is dissolved in about 200 ml. of boiling technical grade hexane. The hot solution is decanted from a small amount of insoluble black tar and is cooled to room temperature. Ferrocenylacetonitrile is deposited as bright yellow crystals, m.p. 79–82° (Note 1). The yield of the nitrile is 24–26 g. (71–77%) (Note 2).

2. Notes

1. The pure nitrile melts at 81–83° after further recrystallization from hexane.[3]
2. The yield is directly dependent on the quality of the methiodide employed.

Yields as high as 95% have been obtained.[3]

3. Discussion

This method is that described by Lednicer, Lindsay, and Hauser.[3] No other procedure appears to have been employed to prepare this compound.

Essentially the present procedure converted 1-methylgramine to 1-methyl-3-indoleacetonitrile,[4] but it failed to convert benzyldimethylphenylammonium chloride to phenylacetonitrile.[5]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

N,N-Dimethylaminomethylferrocene methiodide

Ferrocenylacetonitrile

ether (60-29-7)

sodium sulfate (7757-82-6)

potassium cyanide (151-50-8)

phenylacetonitrile (140-29-4)

Trimethylamine (75-50-3)

hexane (110-54-3)

1-methylgramine

1-methyl-3-indoleacetonitrile

benzyldimethylphenylammonium chloride

Iron, [(cyanomethyl)cyclopentadienyl]cyclopentadienyl

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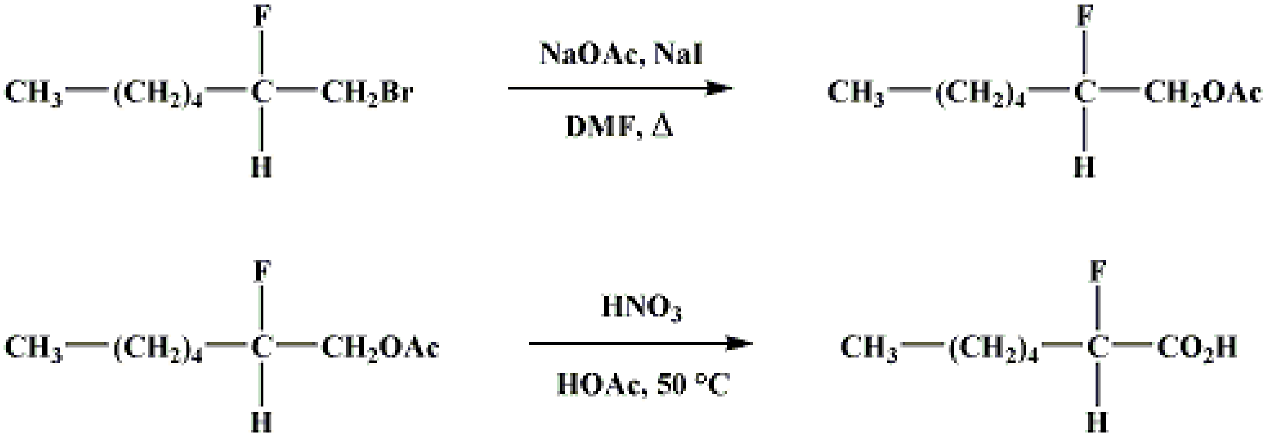
Organic Syntheses, CV 5, 580

2-FLUOROHEPTANOIC ACID

[Heptanoic acid, 2-fluoro-]



Submitted by F. H. Dean, J. H. Amin, and F. L. M. Pattison[1].
Checked by Michelle Moran and B. C. McKusick.

1. Procedure

A. *2-Fluoroheptyl acetate*. A 1-l. two-necked flask is fitted with a thermometer reaching close to the bottom and a reflux condenser that has a calcium chloride tube in its end. It is charged with 29.6 g. (0.150 mole) of 1-bromo-2-fluoroheptane,[2] 22.5 g. (0.150 mole) of dry sodium iodide, 24.6 g. (0.30 mole) of anhydrous sodium acetate, and 600 ml. of dimethylformamide previously dried over anhydrous calcium sulfate. The mixture is stirred by a magnetic bar for 40 hours while being maintained at 120–130° by means of an electric heating mantle. The mixture is cooled to room temperature, diluted with 750 ml. of water, and extracted with 900 ml. of ether. The aqueous layer is extracted with two 150-ml. portions of ether, and the combined ether extracts are washed with five 150-ml. portions of water (Note 1). The ethereal solution is dried over anhydrous sodium sulfate. The ether is removed by distillation, and the residue is transferred to a Claisen flask with a 15-cm. indented neck. Fractionation under reduced pressure gives, after a small fore-run, 16.6–20.6 g. (63–78%) of 2-fluoroheptyl acetate, b.p. 83–87° (10 mm.), n^{25}D 1.4101.

B. *2-Fluoroheptanoic acid (Note 2)*. A 250-ml. two-necked flask is fitted with a thermometer and a condenser that has an outlet tube to carry oxides of nitrogen to a gas absorption trap[3] or the back of a hood. It is charged with 17.6 g. (0.100 mole) of 2-fluoroheptyl acetate, 50 ml. of glacial acetic acid, and 60 ml. of 16 *N* nitric acid. The mixture is heated at 48–50° for 25 hours by means of an electric heating mantle. It is diluted with 500 ml. of water and crushed ice and extracted with one 300-ml. portion and five 100-ml. portions of ether (Note 3). The combined ether extracts are added carefully to a slurry of 125 g. of sodium bicarbonate in 500 ml. of water in a 2-l. beaker. The aqueous alkaline solution is extracted with two 100-ml. portions of ether, which are discarded. The aqueous solution is neutralized to a pH of approximately 4 with about 300 ml. of 10%

hydrochloric acid and is extracted with one 300-ml. portion and five 100-ml. portions of ether. The combined extracts are washed with four 100-ml. portions of water to remove traces of acetic acid and dried over anhydrous sodium sulfate. The ether is removed by distillation, leaving 12–13.5 g. of crude 2-fluoroheptanoic acid that soon solidifies. It is purified by distillation under reduced pressure through a short Claisen still-head with a short condenser that can be heated by steam, a burner, or a heat lamp when the acid solidifies in it. 2-Fluoroheptanoic acid, b.p. 62–64° (0.15 mm.), 78–80° (0.7 mm.), is obtained as a moist, waxy, pale yellow solid that smells faintly of acetic acid. After being dried on a porous plate, it is odorless and nearly colorless; weight 11.5–12.5 g. (78–84%), m.p. 38–39°.

2. Notes

1. Thorough washing with water is necessary to remove residual dimethylformamide.
2. 2-Fluoroheptanoic acid required no more than the usual precautions accorded organic compounds, for it and its precursors have LD_{50}>100 mg./kg. in mice. The relatively low toxicity of this and other 2-fluoroalkanoic acids is in contrast to the high toxicity of the ω-fluoro acids $F(CH_2)_nCOOH$ with *n* an odd number (if *n* = 5, LD_{50} = 1.3 mg./kg. in mice).[4]
3. The solubility of the fluoro acid in water is sufficient to require thorough ether extraction.

3. Discussion

2-Fluoroheptanoic acid[5] has been prepared only by the present procedure.

4. Merits of the Preparation

Bromofluorination[2] followed by the present procedure is a general way to convert 1-alkenes to 2-fluoroalkanoic acids; similar results have been obtained with ethylene, propylene, 1-butene, 1-hexene, 1-octene, 1-decene, and methyl 10-undecenoate.[5] It is an easy and convenient way to make 2-fluoroalkanoic acids, for it requires only conventional apparatus and readily available intermediates.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 136

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

oxides of nitrogen

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ether (60-29-7)

sodium acetate (127-09-3)

sodium bicarbonate (144-55-8)

propylene (115-07-1)

nitric acid (7697-37-2)

sodium sulfate (7757-82-6)

calcium sulfate (7778-18-9)

ethylene (9002-88-4)

1-butene (106-98-9)

sodium iodide (7681-82-5)

dimethylformamide (68-12-2)

1-hexene (592-41-6)

1-Bromo-2-fluoroheptane (1786-32-9)

2-Fluoroheptanoic acid, Heptanoic acid, 2-fluoro- (1578-58-1)

2-Fluoroheptyl acetate (1786-44-3)

methyl 10-undecenoate (111-81-9)

1-octene (111-66-0)

1-decene (872-05-9)

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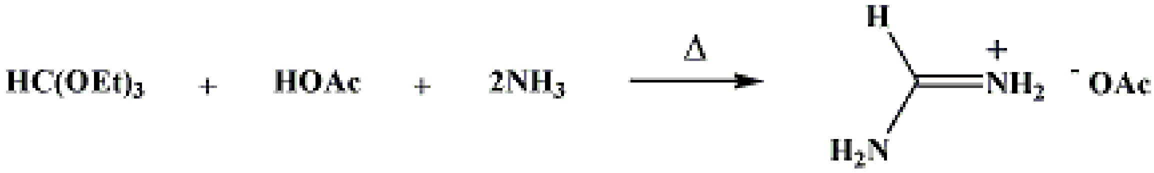
FORMAMIDINE ACETATE



Submitted by Edward C. Taylor, Wendell A. Ehrhart, and M. Kawanisi[1].
Checked by John J. Miller and William D. Emmons.

1. Procedure

In a 500-ml. three-necked flask equipped with a reflux condenser, a gas-inlet tube (Note 1) reaching to the bottom of the flask, a thermometer, and a magnetic stirrer is placed a mixture of 90.0 g. of triethyl orthoformate (Note 2) and 49.2 g. of glacial acetic acid. The flask is immersed in an oil bath maintained at 125–130° (Note 3). When the internal temperature of the mixture reaches 115°, a moderate stream of ammonia is introduced. As the temperature decreases gradually, vigorous refluxing is observed (Note 4). Formamidine acetate starts to crystallize from the boiling mixture after 20–30 minutes. The ammonia flow is continued until no further decrease in temperature is observed (Note 5). The mixture is cooled to room temperature, the precipitate collected by filtration and washed thoroughly with 50 ml. of absolute ethanol. The yield of colorless formamidine acetate is 53.0–55.8 g. (83.8–88.2%), m.p. 162–164° (Note 6). Evaporation of the mother liquor under reduced pressure followed by chilling gives a small additional amount of product (1.0–2.2 g.) (Note 7).

2. Notes

1. An open-end gas-inlet tube should be used rather than a fritted glass inlet because the latter becomes clogged.
2. Commercial triethyl orthoformate, b.p. 50–52° (20 mm.) (Matheson, Coleman and Bell) is used without further purification. It has been reported that it is essential to this procedure that the triethyl orthoformate be slightly wet. Commercial triethyl orthoformate as available in the USA appears to fulfill this requirement, but the anhydrous reagent fails to react. If anhydrous triethyl orthoformate is used, 3 drops of water should be added to ensure a slightly wet reagent (private communication from P. R. H. Speakman).
3. If the temperature is higher than 140°, the product is colored and the yield is lower.
4. This temperature decrease serves as a useful indication of the progress of the reaction.
5. The final temperature of the reaction mixture is usually 72–73°. Total working time is 60–70 minutes.

6. Recrystallization from ethanol does not change the melting point.
7. This material is usually slightly colored and not so pure as the first crop.

3. Discussion

This method is a modification of the procedure described by Taylor and Ehrhart.[2] Formamidine has previously been prepared (as its hydrochloride) from hydrogen cyanide via the formimino ether, which is then treated with ammonia,[3] or by desulfurization of thiourea in the presence of ammonium chloride.[4] The methosulfate salt of formamidine has been reported to be formed by reaction of formamide with dimethyl sulfate.[5]

4. Merits of the Procedure

Because formamidine hydrochloride is extremely deliquescent, considerable care must be exercised in its preparation if satisfactory results are to be achieved. Furthermore, formamidine hydrochloride cannot be used directly in most condensation reactions; it must be treated first with a mole of base to liberate free formamidine. The same restriction applies to the methosulfate salt of formamidine; in addition, complications in synthesis may be anticipated in this latter case because methyl hydrogen sulfate itself is an effective methylating agent.[6]

By contrast, formamidine acetate is not hygroscopic and no particular care need be taken to protect it from atmospheric moisture. Furthermore, formamidine acetate can be used directly without prior treatment with base in syntheses requiring free formamidine.[2,7,8,9,10] Finally, this preparation of formamidine is by far the simplest and most convenient yet reported; it obviates the necessity of using either toxic (hydrogen cyanide) or cumbersome (Raney nickel) reagents, and the method can be adapted to the preparation of N,N'-disubstituted formamidines by substitution of primary amines for ammonia.[11]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

methosulfate salt of formamidine

ethanol (64-17-5)

acetic acid (64-19-7)

ammonia (7664-41-7)

ammonium chloride (12125-02-9)

formamide (75-12-7)

hydrogen cyanide (74-90-8)

dimethyl sulfate (77-78-1)

Raney nickel (7440-02-0)

methyl hydrogen sulfate (75-93-4)

triethyl orthoformate (122-51-0)

thiourea (62-56-6)

Formamidine acetate (3473-63-0)

Formamidine

formimino ether

formamidine hydrochloride

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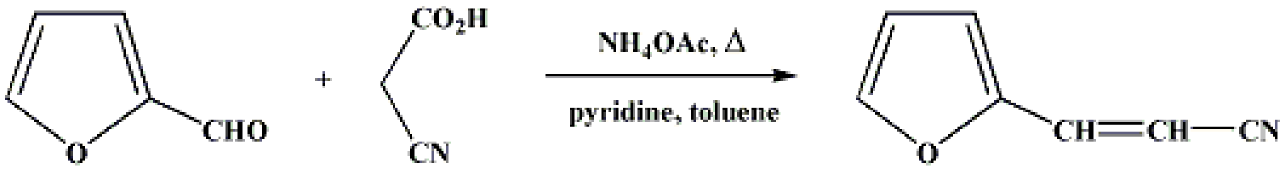
Organic Syntheses, CV 5, 585

3-(2-FURYL)ACRYLONITRILE

[2-Furanacrylonitrile]



Submitted by John M. Patterson[1]
Checked by Melvin S. Newman and Herbert Boden.

1. Procedure

A mixture of 105.6 g. (1.1 moles) of freshly distilled furfural, 87.0 g. (1.0 mole) of 98% cyanoacetic acid (Note 1), 3.0 g. of ammonium acetate, 200 ml. of toluene, and 110 ml. of pyridine is placed in a 1-l. round-bottomed flask equipped with a Stark and Dean water trap and reflux condenser. The mixture is boiled under reflux for 2 days. The theoretical quantity of water is collected in the trap within 1 hour. Upon completion of the reflux period, the solvent is removed under reduced pressure by heating on a water bath. The residue, distilled through a 15-cm. Vigreux column at 11 mm. pressure, yields 88.6–93.3 g. (74.5–78%) of colorless liquid boiling at 95–97°, n_D^{25} 1.5823–1.5825.

2. Notes

1. Cyanoacetic acid was obtained from Distillation Products Industries, Rochester, New York, and used without further purification.

3. Discussion

The method described is a modification of the procedure used by Ghosez[2] to synthesize cinnamonitrile. 3-(2-Furyl)acrylonitrile has been prepared by catalytic condensation of furfural with acetonitrile in the vapor phase at 320°,[3] by dehydration of the corresponding amide over phosphorus pentachloride,[4] and by decarboxylation of 3-(2-furyl)-2-cyanoacrylic acid.[5]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ammonium acetate (631-61-8)

acetonitrile (75-05-8)

phosphorus pentachloride (10026-13-8)

pyridine (110-86-1)

toluene (108-88-3)

cyanoacetic acid (372-09-8)

Furfural (98-01-1)

3-(2-Furyl)acrylonitrile, 2-Furanacrylonitrile (7187-01-1)

Cinnamonitrile (4360-47-8)

3-(2-furyl)-2-cyanoacrylic acid

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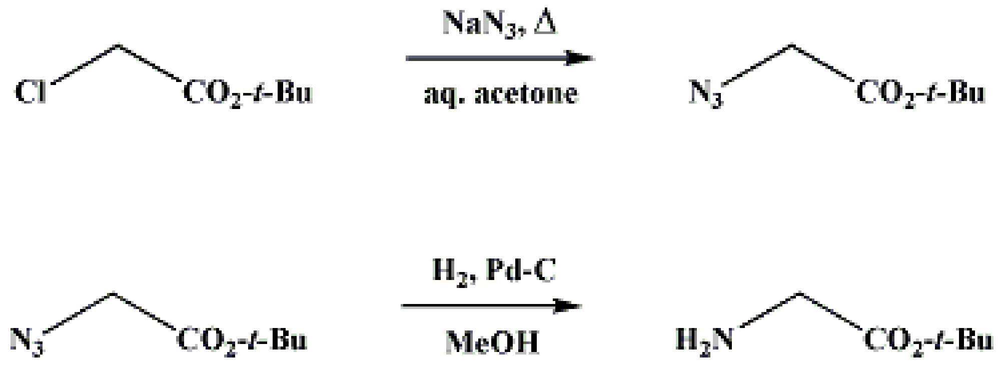
Organic Syntheses, CV 5, 586

GLYCINE *t*-BUTYL ESTER



Submitted by A. T. Moore and H. N. Rydon[1].
Checked by William G. Dauben and John A. Hennings.

1. Procedure

A. *t-Butyl azidoacetate*. In a 300-ml. round-bottomed flask fitted with a reflux condenser are placed 30 g. (0.2 mole) of *t*-butyl chloroacetate (Note 1), 24 g. (0.37 mole) of sodium azide, and 90 ml. of 60% (v./v.) acetone-water. The heterogeneous mixture (two liquid phases and a solid phase) is heated under reflux on a steam bath for 18 hours, the acetone distilled, and 15 ml. of water added (Note 2). The mixture is transferred to a separatory funnel, the layers separated, and the lower aqueous layer extracted twice with 25-ml. portions of ether. The ethereal extracts are added to the original upper layer, and the solution is dried over anhydrous sodium sulfate. The ether is distilled, and the residual oil is fractionated under reduced pressure (Note 3), the fraction boiling from 33–41° (1 mm.) being collected; yield 29 g. (92%), $n^{20}{}_D$ 1.4356 (Note 4).

B. *Glycine t-butyl ester*. In the center neck of a 500-ml. suction filtration flask is placed a gas-inlet tube which is connected to a nitrogen cylinder, and on the side arm of the flask there is attached an exit tube leading to a suitable ventilation duct. The flask is placed on a magnetic stirrer, and a solution of 28.9 g. (0.18 mole) of *t*-butyl azidoacetate in 150 ml. of methanol and 0.7 g. of 5% palladium-on-charcoal catalyst is added to the flask. A stream of nitrogen is swept over the surface of the stirred suspension for 5 minutes, the nitrogen cylinder is replaced by a hydrogen cylinder, and hydrogen is passed over the magnetically stirred mixture for 10 hours. The hydrogen is displaced from the flask by a sweeping with nitrogen, the catalyst is removed by filtration and is washed with 5 ml. of methanol. The filtrate is transferred to a 500-ml. Erlenmeyer flask, 15 g. (0.18 mole) of phosphorous acid is added, and the mixture is warmed gently to dissolve the phosphorous acid. The solution is cooled to room temperature (Note 5), 150 ml. of ether is added slowly, and the solution is cooled at 0° for 12 hours. The precipitated glycine *t*-butyl ester phosphite is filtered, washed with

ether, and dried in a vacuum oven at 70°, yield 29–32 g. (75–82%), m.p. 144–147° (dec.) (Note 6) and (Note 7).

To 50 ml. of a well-cooled 6*N* sodium hydroxide solution is added, with stirring, 32 g. (0.15 mole) of the phosphite salt. The stirring is continued until all the solid has dissolved. The solution is transferred to a 125-ml. separatory funnel, extracted with three 20-ml. portions of ether, and the combined extracts dried over anhydrous sodium sulfate. The drying agent is removed by filtration, the solvent removed under reduced pressure, and the glycine *t*-butyl ester distilled, b.p. 65–67° (20 mm.), n^{20}_D 1.4237, yield 14 g. (72%, based on phosphite salt). The overall yield from *t*-butyl chloroacetate is 50–55%.

2. Notes

1. The *t*-butyl chloroacetate was prepared from chloroacetyl chloride and *t*-butanol following the procedure of Baker.[2]
2. The water is added to dissolve any inorganic salts which are still not in solution.
3. Owing to the possibly explosive nature of the ester, the distillation was conducted behind a safety screen, using a water bath for the heat source and keeping the pressure as low as convenient.
4. The submitters reported a boiling point of 63–64° (5–6 mm.), n^{20}_D 1.4348. The literature values are b.p. 72–73° (13 mm.) and n^{25}_D 1.4332.[3] The submitters also report that the reaction has been run safely on a 200-g. scale.
5. If the mixture sets solid upon cooling, the lumps of phosphite salt should be broken up during the addition of the ether.
6. The crystallization of the crude product from methanol-isopropyl ether gave pure phosphite salt, m.p. 154–157° (dec.).
7. Some *t*-butyl azidoacetate can be recovered by evaporation of the mother liquor. After removal of the methanol from the filtrate, the residual oil is dissolved in ether, washed with distilled water, the ether removed, and the residue fractionally distilled under reduced pressure (using proper precautions).

3. Discussion

This method is a modification of that developed by Vollmar and Dunn.[3] Glycine *t*-butyl ester also has been prepared by the acid-catalyzed addition of *N*-benzyloxycarbonylglycine to isobutene, followed by catalytic hydrogenolysis of the resulting N-benzyloxycarbonylglycine *t*-butyl ester.[4] The esters of other amino acids have been prepared directly by the isobutene method.[5]

4. Merits of the Preparation

Glycine *t*-butyl ester is a valuable intermediate for the preparation of peptides of

glycine, since the labile *t*-butyl group can readily be removed by acid under conditions which do not affect the blocked amino grouping. The present method using *t*-butyl chloroacetate is superior to that using the bromo derivative,[3] since chloride is cheaper to prepare, less lachrymatory and more easily separated, by fractional distillation, from the *t*-butyl azidoacetate. The method is also less cumbersome than the procedure using isobutene.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

methanol (67-56-1)

ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

acetone (67-64-1)

palladium (7440-05-3)

chloroacetyl chloride (79-04-9)

Glycine (513-29-1)

sodium azide (26628-22-8)

phosphorous acid (13598-36-2)

isobutene (9003-27-4)

N-benzyloxycarbonylglycine (1138-80-3)

t-butanol (75-65-0)

methanol-isopropyl ether (598-53-8)

t-butyl chloroacetate (107-59-5)

GLYCINE t-BUTYL ESTER (6456-74-2)

t-butyl azidoacetate (6367-36-8)

glycine t-butyl ester phosphite

N-benzyloxycarbonylglycine t-butyl ester

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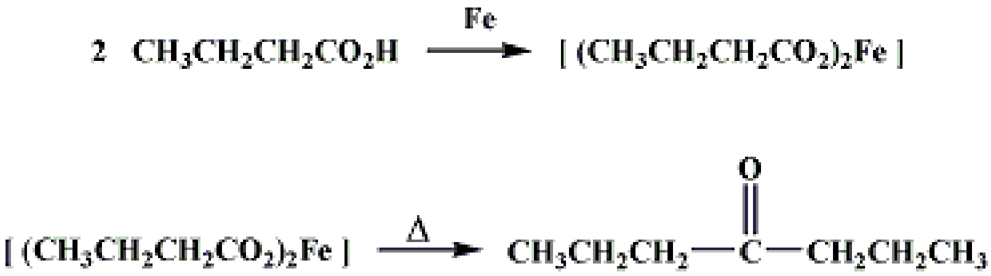
Organic Syntheses, *CV 5*, *589*

4-HEPTANONE



Submitted by Robert Davis, Charles Granito, and Harry P. Schultz[1].
Checked by William G. Dauben and Richard J. Shavitz.

1. Procedure

A mixture of 370 ml. (4 moles) of *n*-butyric acid (Note 1) and 123 g. (2.2 moles) of hydrogen-reduced iron powder (Note 2) is refluxed for 5 hours in a 1-l. flask equipped with a condenser (Note 3). The apparatus is converted for downward distillation while an atmosphere of nitrogen is maintained. The nitrogen sweep is then stopped, the flask is strongly heated, and the entire distillate collected.

The crude product is washed with two 20-ml. portions of 10% sodium hydroxide solution and with one 20-ml. portion of water. The 4-heptanone is dried over 5 g. of anhydrous sodium sulfate, filtered, and distilled. The yield of 4-heptanone, b.p. 142–144°, n^{25}D 1.4031–1.4036, is 157–171 g. (69–75%).

2. Notes

1. *n*-Butyric acid, b.p. 162–164°, from Eastman Organic Chemicals was redistilled before use.
2. Hydrogen-reduced iron powder from Fisher Scientific Company was used.
3. Severe foaming may force brief cessations of heating during the first hour. Boric acid (0.1 g.) somewhat diminishes the extent of foaming.

3. Discussion

The present procedure is that of Davis and Schultz.[2] 4-Heptanone has also been synthesized by virtually every general method known and listed for ketones in "Chemistry of Carbon Compounds," including liquid or vapor phase decarboxylation of *n*-butyric acid or its salts, oxidation of 4-heptanol, and hydration of 3-heptyne.[3]

4. Merits of the Preparation

This method is illustrative of a general method of preparing simple ketones from

normal aliphatic carboxylic acids. It is especially useful because the starting materials are easily accessible, the yields good, and the procedure very simple.

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium hydroxide (1310-73-2)

iron powder (7439-89-6)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

n-butyric acid (107-92-6)

boric acid (10043-35-3)

4-Heptanone (123-19-3)

4-heptanol (589-55-9)

3-heptyne (2586-89-2)

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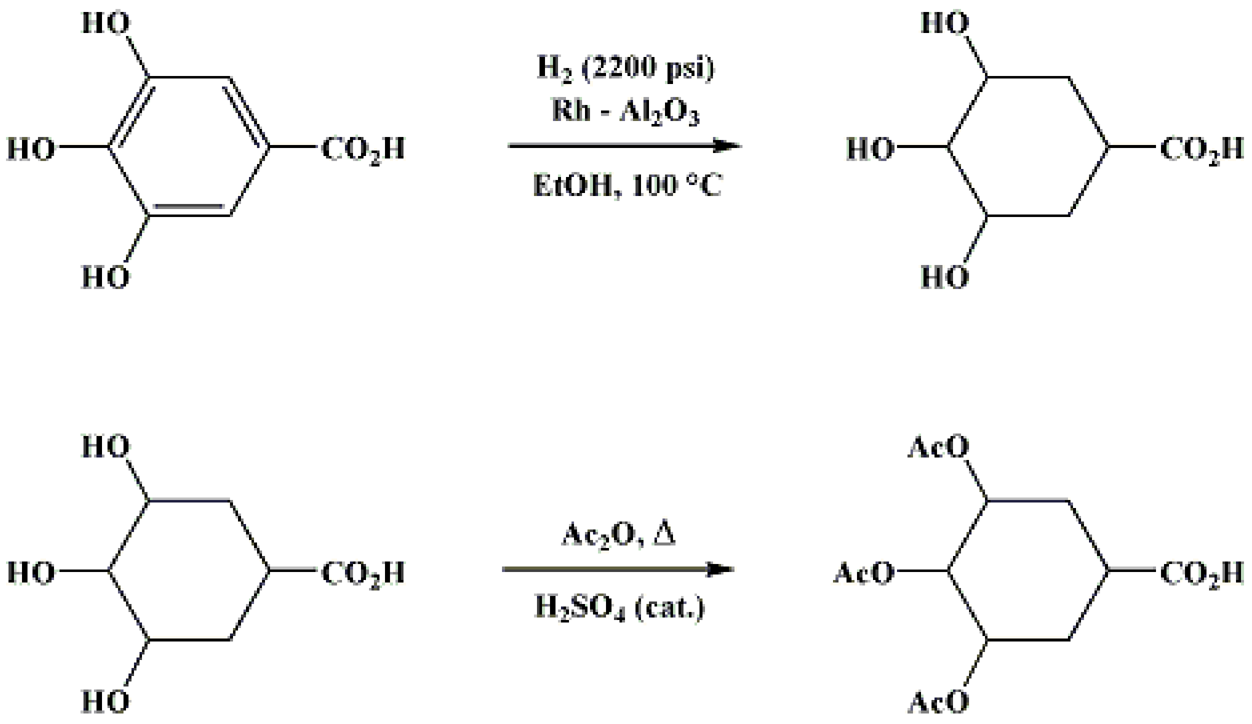
Organic Syntheses, *CV 5*, *591*

HEXAHYDROGALLIC ACID AND HEXAHYDROGALLIC ACID TRIACETATE

[Cyclohexanecarboxylic acid, 3,4,5-triol and triacetate]



Submitted by Albert W. Burgstahler and Zoe J. Bithos[1].
Checked by R. P. Lutz and John D. Roberts.

1. Procedure

A. *Hexahydrogallic acid*. A solution of 50 g. (0.266 mole) of recrystallized gallic acid monohydrate (Note 1) in 225 ml. of 95% ethanol (Note 2) is placed in a 1-l. high-pressure hydrogenation bomb (Note 3) with 8 g. of 5% rhodium-alumina catalyst (Note 4). The bomb is then closed, hydrogen admitted at full tank pressure (2200 lb., (Note 5)), and the temperature raised to 90–100° (Note 6) while agitation is commenced. When the hydrogen uptake is complete (8–12 hours), heating is discontinued and the bomb is allowed to cool. The residual hydrogen is bled off, and the contents of the bomb are rinsed out with two 40-ml. portions of warm distilled water and then heated to boiling on the steam bath for 5 minutes to dissolve any product which has crystallized on the catalyst. After removal of the catalyst by suction filtration (Note 7), the colorless filtrate (Note 8) is concentrated on the steam bath under reduced pressure (preferably using a rotary evaporator). The viscous residue which may have begun to deposit crystals is diluted with 75–100 ml. of ethyl acetate and the product allowed to crystallize at 0° for several hours or overnight. The product is collected on a 9-cm. Büchner funnel and washed with 75 ml. of cold 3:1 ethyl

acetate-absolute ethanol and finally with 100 ml. of 30–40° petroleum ether. When dry, it weighs 21–24 g. (45–51%); an additional 2–4 g. can usually be obtained by concentration of the mother liquors and crystallization from ethyl acetate. Recrystallization is achieved by dissolution of the combined products in the minimum amount of boiling water (Note 9), suction filtration if necessary to remove suspended matter (Note 10), addition of hot ethanol to bring the volume of the solution to about 110 ml., and finally addition of about 35 ml. of acetone, sufficient to produce a faint cloudiness. The solution is allowed to cool slowly to room temperature and is then stored at 0° overnight. The fine, colorless crystals are collected on a 7-cm. Büchner funnel and washed with 80 ml. of cold 5:3 absolute ethanol-acetone, then with 100 ml. of 30–40° petroleum ether. The product when dry weighs 18–20 g. (38–43%). The yield may be increased somewhat by concentration of the combined mother liquor and washings, and treatment as before with ethanol and acetone. The melting point is not a useful criterion of purity, since the hexahydrogallic acid decomposes on heating (Note 11). The product is apparently substantially the all-*cis* isomer.[2]

B. *Hexahydrogallic acid triacetate*. A suspension of 10 g. (0.057 mole) of the dry, recrystallized hexahydrogallic acid in 40 ml. of acetic anhydride is treated with 1 drop of concentrated sulfuric acid, which initiates the reaction (Note 12). Most of the solid then goes into solution with some evolution of heat. The reaction is completed on a steam bath for 30 minutes. The acetic acid and most of the excess anhydride are then removed on the steam bath under reduced pressure with the aid of an oil pump. Twenty-five milliliters of water is added, and the mixture is shaken and heated on the steam bath for 10 minutes in order to hydrolyze residual acetic anhydride and the mixed anhydride of the product and acetic acid. Most of the solvent is then removed under reduced pressure on the steam bath; the product usually crystallizes during this process. About 15 ml. of water is added, and the mixture is heated on the steam bath until the solids dissolve. The solution is first allowed to cool slowly to room temperature and then stored at 0° for several hours to complete crystallization. The colorless crystals are collected, washed rapidly with 10–15 ml. of cold water, and dried at 60° or in a vacuum desiccator at room temperature. The yield is 15–17 g., m.p. 152–154°. The product may be recrystallized by dissolution in 25–30 ml. of hot acetone and addition of 50 ml. of 30–40° petroleum ether. The colorless crystalline granules are collected by suction filtration and washed with a small amount of 2:1 petroleum ether(30–40°)-acetone. The recrystallized product when dried amounts to 13.5–14.5 g. (78–84%), m.p. 155–156° (Note 13).

2. Notes

1. Gallic acid is conveniently recrystallized from water (heated to boiling, then cooled to 0°) with treatment with decolorizing carbon if necessary.
2. Absolute alcohol leads to partial esterification of the product; a higher percentage of water deactivates the catalyst.
3. A glass liner may be helpful in preventing poisoning of the catalyst. Stainless-steel vessels usually require one run to "condition" the surfaces before the

reported yields can be obtained.
4. The catalyst is available from Englehardt Industries, Inc., Chemical Division, Newark, New Jersey. The activity appears to vary slightly with different lots. Other catalysts, such as palladium, platinum, and ruthenium on various supports, or Raney nickel, were found to be much less satisfactory or completely ineffective.
5. Pressures lower than 1800 lb. usually lead to incomplete reduction.
6. Reduction is inconveniently slow at lower temperatures; temperatures higher than 125° tend to favor esterification and other by-product formation.
7. The recovered catalyst (along with fresh catalyst) can be reused several times for further reductions.
8. The ferric chloride test is negative, and the filtrate remains colorless when hydrogenation is complete. A deep blue color (due to the presence of gallic acid or dihydro products) appears when it is not, but the hexahydro acid can usually be isolated in good yield in spite of this.
9. A hot plate equipped with a magnetic stirrer is especially convenient for this operation.
10. Any excess water used to transfer the solution or to wash the filter must be evaporated; otherwise the recovery is smaller.
11. Decomposition usually begins at about 190°, with melting at 198–200°. Melting points as high as 203–204° have been observed by the submitters and checkers. The purity of successively recrystallized products may be compared by immersing the samples enclosed in capillary tubes of uniform dimensions in a melting-point bath maintained at a constant temperature of 200° and noting the times required for complete melting.
12. Acetylation in pyridine is comparatively less satisfactory and considerably more inconvenient.
13. Using a Kofler melting-point block fitted with a microscope, the checkers observed a crystal transition at about 140° with final, moderately sharp, melting at 157–158°.

3. Discussion

The all-*cis* diasteroisomer of hexahydrogallic acid has been prepared from gallic acid in 13–19% over-all yield by a two-stage reduction, first with Raney nickel in basic solution to form the somewhat difficultly isolated dihydro intermediate, and then with a platinum catalyst to complete the reduction.[3] The present procedure is based on a published preparation.[2]

The acetylation procedure described here is based on that which has already been published.[3]

4. Merits of Preparation

The direct reduction of gallic acid described here illustrates the virtue of the rhodium-on-alumina catalyst to achieve the perhydrogenation of polyhydroxylated aromatic compounds with minimal attendant hydrogenolysis. A closely related hydrogenation,

that of pyrogallol, to yield a dihydro intermediate,[3] and also the direct reduction of pyrogallol with palladium-on-strontium carbonate to afford the all *cis*-pyrogallitol (1,2,3-cyclohexanetriol) have been reported.[4]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

Cyclohexanecarboxylic acid, 3,4,5-triol and triacetate

rhodium-alumina

ethyl acetate-absolute ethanol

hexahydro acid

rhodium-on-alumina

palladium-on-strontium carbonate

ethanol (64-17-5)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

ethyl acetate (141-78-6)

acetic anhydride (108-24-7)

hydrogen (1333-74-0)

platinum (7440-06-4)

nickel (7440-02-0)

acetone (67-64-1)

carbon (7782-42-5)

pyridine (110-86-1)

palladium (7440-05-3)

ferric chloride (7705-08-0)

gallic acid (149-91-7)

pyrogallol (87-66-1)

HEXAHYDROGALLIC ACID (53796-39-7)

HEXAHYDROGALLIC ACID TRIACETATE (53796-40-0)

gallic acid monohydrate (5995-86-8)

ruthenium (7440-18-8)

1,2,3-cyclohexanetriol (6286-43-7)

cis-pyrogallitol

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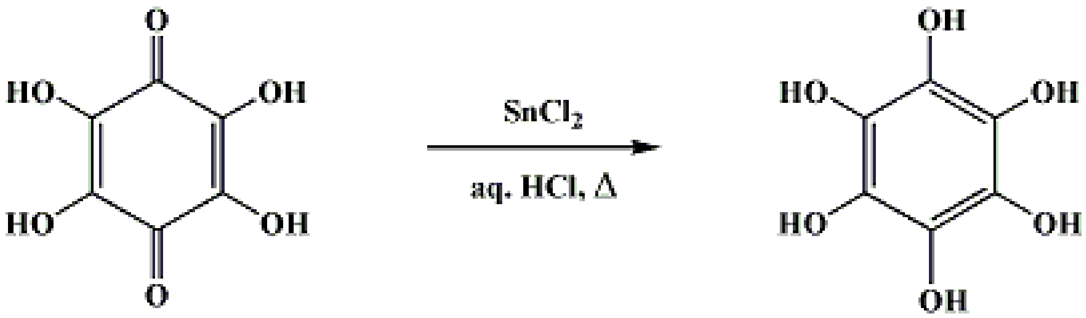
Organic Syntheses, *CV 5, 595*

HEXAHYDROXYBENZENE

[Benzenehexol]



Submitted by A. J. Fatiadi and W. F. Sager[1].
Checked by B. C. McKusick and J. K. Williams.

1. Procedure

One hundred grams (0.44 mole) of stannous chloride dihydrate is added to a boiling solution of 10 g. (0.058 mole) of tetrahydroxyquinone[2] in 200 ml. of 2.4*N* hydrochloric acid contained in a 1.5-l. beaker. The initial deep-red color disappears, and grayish crystals of hexahydroxybenzene precipitate. Two hundred fifty milliliters of 12*N* hydrochloric acid is added, and the mixture is heated to boiling with constant stirring. The beaker is removed from the hot plate, an additional 600 ml. of 12*N* hydrochloric acid is added, and the solution is cooled in a refrigerator. The hexahydroxybenzene is collected on a Büchner funnel fitted with a sintered-glass disk (Note 1) and sucked dry.

The crude hexahydroxybenzene is dissolved in 450 ml. of hot 2.4*N* hydrochloric acid containing 3 g. of hydrated stannous chloride and 1 g. of decolorizing carbon. The solution is filtered while hot, and the carbon is rinsed with 75 ml. of boiling water that is combined with the filtrate. One liter of 12*N* hydrochloric acid is added, and the mixture is cooled in a refrigerator. The snow-white crystals of hexahydroxybenzene that separate are collected under carbon dioxide or nitrogen (Note 2) on a Büchner funnel fitted with a sintered-glass disk. The hexahydroxybenzene is washed with 100 ml. of a cold 1:1 mixture of ethanol and 12*N* hydrochloric acid and dried in a vacuum desiccator over sodium hydroxide pellets; yield 7.1–7.8 g. (70–77%). It fails to melt on a hot plate at 310° (Note 3).

2. Notes

1. Filter paper cannot be used because it is attacked by strong hydrochloric acid.
2. By rapid manipulation it is possible to obtain a product of fair quality. The

moist product is susceptible to air oxidation, as is shown by a development of pink coloration on the crystals. The filtration is best carried out under a blanket of carbon dioxide or nitrogen obtained by inverting a funnel attached to a source of carbon dioxide or nitrogen over the Büchner funnel.
3. The decomposition point of hexahydroxybenzene is not a good criterion of purity. If the product is light in color, there can be no significant amount of oxidized material in it, for even traces of tetrahydroxyquinone cause intense coloration. Decomposition of a sample with nitric acid followed by evaporation and ignition of the residue should give a negligible amount of tin oxide. The product can be characterized as the hexaacetate, m.p. 202–203°, by treating it with acetic anhydride and sodium acetate.[3]

3. Discussion

The present procedure is a modification of the procedure of Anderson and Wallis.[4] Hexahydroxybenzene can also be prepared by acidic hydrolysis of potassium carbonyl[3] or by nitration and oxidation of diacetyl hydroquinone.[5]

4. Merits of the Procedure

This is the most convenient synthesis of hexahydroxybenzene, and the present procedure gives better yields than reported by Anderson and Wallis.[4] Hexahydroxybenzene is of interest as the most highly hydroxylated member of the polyhydroxybenzene family.

It has been used as a source of the biologically important *myo*-inositol[6,7] (1235/46 isomer) by hydrogenation over palladium and of *cis*-inositol (123456 isomer) by hydrogenation over palladium-on-carbon.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 1011

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Appendix

Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

acetic anhydride (108-24-7)

sodium acetate (127-09-3)

sodium hydroxide pellets (1310-73-2)

nitric acid (7697-37-2)

nitrogen (7727-37-9)

stannous chloride

carbon dioxide (124-38-9)

decolorizing carbon, carbon (7782-42-5)

palladium (7440-05-3)

stannous chloride dihydrate (10025-69-1)

Hexahydroxybenzene, Benzenehexol (608-80-0)

Tetrahydroxyquinone (319-89-1)

tin oxide

potassium carbonyl

diacetyl hydroquinone

myo-inositol (87-89-8)

cis-inositol

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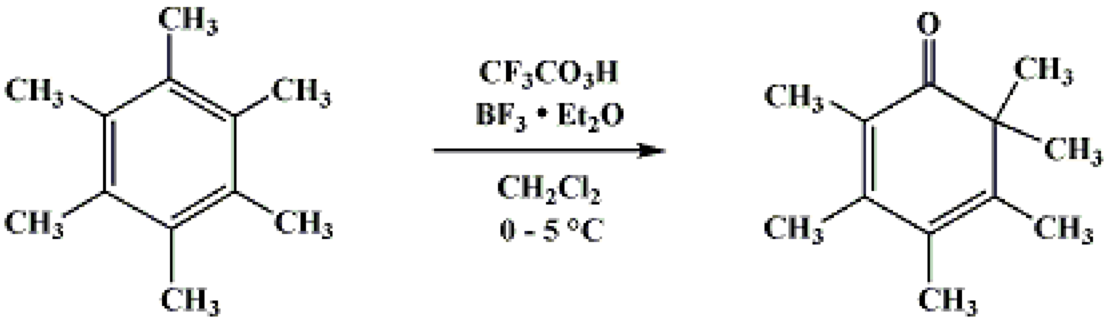
Organic Syntheses, CV 5, 598

2,3,4,5,6,6-HEXAMETHYL-2,4-CYCLOHEXADIEN-1-ONE

[2,4-Cyclohexadien-1-one, 2,3,4,5,6,6-hexamethyl-]



Submitted by Harold Hart, Richard M. Lange, and Peter M. Collins[1].
Checked by A. S. Pagano and William D. Emmons.

1. Procedure

Caution! The preparation and handling of peroxytrifluoroacetic acid should be carried out behind a safety screen. Precautions to be observed with 90% hydrogen peroxide are described in (Note 3) and should be followed carefully.

To a 300-ml. three-necked flask equipped with a glass Trubore stirrer and two loose-fitting ground-glass stoppers are added 46.2 g. (0.22 mole) of trifluoroacetic anhydride and 50 ml. of methylene chloride (Note 1). The stirred solution is cooled in an ice bath, and 5.40 ml. (0.20 mole) of 90% hydrogen peroxide is added from a 10-ml. graduated cylinder in *ca.* 1-ml. portions over a period of 10 minutes (Note 2),(Note 3), and (Note 4). When the mixture has become homogeneous, it is allowed to warm to room temperature for a few minutes and is then cooled once more in an ice bath to 0°.

A solution of 24.2 g. (0.15 mole) of hexamethylbenzene in 300 ml. of distilled methylene chloride is prepared in a 1-l. three-necked flask equipped with two ice-jacketed addition funnels (Note 5) and a thermometer. The solution is cooled to 5° in an ice-ethanol bath and is agitated by a magnetic stirrer. The cold peroxytrifluoroacetic acid solution is added at a constant rate to the hexamethylbenzene solution from one of the ice-jacketed addition funnels at the same time that 63.3 ml. of technical (48%) boron trifluoride etherate is added from the second addition funnel. The additions require *ca.* 45 minutes, and as far as possible they should be completed at the same time. During this period the temperature of the reaction mixture is maintained between 0° and 5° (Note 6) and (Note 7).

The mixture is stirred at 0–5° for 1 hour after addition is complete and then is

hydrolyzed with 100 ml. of water, which is added quickly. The reaction mixture is extracted consecutively with two 100-ml. portions of water, three 100-ml. portions of saturated aqueous sodium bicarbonate, one 75-ml. portion of aqueous 5% sodium hydroxide, and two 75-ml. portions of water. The organic phase is dried over anhydrous magnesium sulfate, and the solvent is removed on a rotary evaporator. The residue, a mobile yellow oil, is distilled through a 6-in. Vigreux column under reduced pressure to give pure (Note 8) 2,3,4,5,6,6-hexamethyl-2,4-cyclohexadien-1-one, b.p. 85–87° (1.0 mm.). The yield is 22–24 g. (82–90%) (Note 9) and (Note 10).

2. Notes

1. Excess anhydride is used to remove water introduced during the addition of 90% hydrogen peroxide.
2. Available from FMC Corp., Inorganic Chemicals Division, 808 Gwynne Building, Cincinnati 2, Ohio.
3. The precautions to be observed with 90% hydrogen peroxide have been described in detail.[2] In essence it is important to prevent contact of this reagent with any easily oxidizable substrates, such as wood, alcohols, and sugars and with heavy-metal salts, since the latter catalyze its decomposition. Storage of hydrogen peroxide in the laboratory should be arranged in such a way that, even if the bottle containing the reagent breaks, the hydrogen peroxide does not come into contact with any materials of this kind. Small samples of 90% hydrogen peroxide are regularly shipped in vented glass bottles provided with a protective outside metal container, and it is desirable to use this container while storing the reagent in the laboratory. If spillage of the reagent occurs, dilution with at least several volumes of water is recommended. In weighing out 90% hydrogen peroxide it is good practice never to return excess reagent to the stock bottle; rather it should be diluted with water and discarded to avoid any possibility that the stock bottle will be contaminated.
4. The hydrogen peroxide may be added in one portion, but then an appreciable exotherm is noted.
5. A simple procedure for the construction of a jacketed addition funnel has been described.[3]
6. Boron trifluoride gas may be used in place of the etherate. In this case a fritted-glass gas-dispersion tube that extends below the liquid surface replaces the second addition funnel. Boron trifluoride gas (0.20 mole, 4.48 l.) is passed through the solution as the peroxytrifluoroacetic acid is added. The boron trifluoride may be metered into the mixture through a calibrated flowmeter containing carbon tetrachloride as the indicator liquid. Alternatively, a premeasured quantity of boron trifluoride may be displaced by carbon tetrachloride from a gas bulb. The yield is approximately the same regardless of the source of boron trifluoride.
7. If boron trifluoride is omitted as a reactant, the yield falls to about 67%.
8. This material should be at least 98% pure by vapor-phase chromatography

(SE-30 column at 180–200°). It usually crystallizes if stored in a refrigerator. Unreacted hexamethylbenzene, present if insufficient oxidant is used, can best be removed by column chromatography on alumina with pentane as eluant.

9. The reaction can be used to prepare hexaethyl-2,4-cyclohexadienone, m.p. 44–45°, in 82% yield from hexaethylbenzene and 3,4,6,6-tetramethyl-2,4-cyclohexadienone from durene in over 80% yield.

10. One can use a solution of 90% hydrogen peroxide (*Caution!* see (Note 3) in acetic-sulfuric acid as the oxidant in place of peroxytrifluoroacetic acid-boron trifluoride. The reaction is less exothermic, therefore easier to control. The generality of the procedure for other polyalkylbenzenes has not been tested. A typical procedure is as follows: To a well-stirred slurry of 100 g. (0.618 mole) of hexamethylbenzene in 200 ml. of methylene chloride, 400 ml. of glacial acetic acid, and 300 ml. of concentrated sulfuric acid maintained at 0–10° there is added, during 30 minutes, a solution of 28 ml. (0.75 mole) of 90% hydrogen peroxide in 45 ml. of glacial acetic acid and 30 ml. of concentrated sulfuric acid. After addition, the mixture is stirred at 0° for 4 hours before workup, which is essentially as described in the original procedure. The yield of hexamethyl-2,4-cyclohexadienone is 95 g. (88%). The procedure is derived from that of Hart, Collins, and Warning[4] (private communication from H. Hart).

3. Discussion

The method described is that of Waring and Hart.[5] Dienones of this type have not been available by any previously described synthetic route.

4. Merits of the Preparation

Dienones of this class are useful starting materials for the preparation of bicyclic compounds via Diels-Alder reactions[5] and for the synthesis of small ring compounds.[6] The 2,4-dienone can be converted quantitatively to the 2,5-isomer by treatment with fuming sulfuric acid and subsequent hydrolysis.[7] The oxidation procedure is also applicable to the conversion of mesitylene to mesitol or of isodurene to isodurenol,[8] and can be used to convert tetramethylethylene quantitatively and directly to pinacolone.[9] A review which includes references to many applications of the procedure described here is available.[10]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

acetic-sulfuric acid

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

carbon tetrachloride (56-23-5)

Pinacolone (75-97-8)

hydrogen peroxide (7722-84-1)

Mesitylene (108-67-8)

Pentane (109-66-0)

methylene chloride (75-09-2)

tetramethylethylene (563-79-1)

magnesium sulfate (7487-88-9)

Durene (95-93-2)

Hexamethylbenzene (87-85-4)

Isodurene (527-53-7)

boron trifluoride (7637-07-2)

boron trifluoride etherate (109-63-7)

peroxytrifluoroacetic acid

trifluoroacetic anhydride (407-25-0)

mesitol (527-60-6)

2,3,4,5,6,6-Hexamethyl-2,4-cyclohexadien-1-one, 2,4-Cyclohexadien-1-one, 2,3,4,5,6,6-hexamethyl-, hexamethyl-2,4-cyclohexadienone (3854-96-4)

hexaethyl-2,4-cyclohexadienone

hexaethylbenzene (604-88-6)

3,4,6,6-tetramethyl-2,4-cyclohexadienone

peroxytrifluoroacetic acid-boron trifluoride

isodurenol

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Organic Syntheses, CV 5, 602

HEXAMETHYLPHOSPHOROUS TRIAMIDE

[Phosphorous triamide, hexamethyl-]

Submitted by V. Mark[1]
Checked by G. A. Frank and W. D. Emmons.

1. Procedure

A solution of phosphorus trichloride (137.3 g., 1.0 mole) in 1.5 l. of dry ether (Note 1) is added to a 3-l., three-necked, round-bottomed flask equipped with an efficient stirrer, thermometer, a gas-inlet tube (Note 2), and a reflux condenser vented through a nitrogen reservoir (a T-tube under slight positive nitrogen pressure) into a well-functioning hood (Note 3). The flask is cooled in an ice bath to 0–5°, and an excess of anhydrous dimethylamine (Note 4) is introduced at such a rate that the temperature does not exceed 15° The addition requires about 3–4 hours. At the end of this period the flask contains the white stirrable slurry of the amine hydrochloride and the ethereal solution of the phosphorous triamide (Note 5). The reaction mixture is allowed to warm to room temperature overnight while still being protected by nitrogen. Filtration of the slurry and thorough washing of the filter cake with three 100-ml. portions of dry ether afford dimethylamine hydrochloride, quantitatively (Note 6). The clear filtrate is concentrated on a rotary evaporator connected to a water aspirator in a bath not exceeding 40° to give 152–154 g. (94–95%) of hexamethylphosphorous triamide as a light yellow oil. The product can be purified by distillation at atmospheric pressure, b. p. 162–4°, or under reduced pressure, b.p. 49–51° (12 mm.), n^{25}D 1.4636 (Note 7). Hexamethylphosphorous triamide is best stored in a nitrogen atmosphere (Note 8).

2. Notes

1. An equal volume of a hydrocarbon solvent (pentane, hexane, benzene) can be substituted for ether without affecting the yield of the triamide.
2. The lower part of the gas-inlet tube, which reaches below the surface of the liquid, should be wide enough that it will not be clogged by the amine hydrochloride. A 12-mm. I.D. glass tube was found satisfactory.
3. Carbon dioxide is not satisfactory because it reacts with hexamethylphosphorous triamide.
4. Available from the Matheson Company. The checkers used Rohm & Haas anhydrous dimethylamine.
5. The water extract of the clear solution should give, after acidification with dilute nitric acid, no white precipitate with silver nitrate. When free of chloride

ion, the water extract gives only a dark coloration or precipitate.
6. The use of a large (9.5 cm. in diameter, 8 cm. high or larger), coarse grade, sintered-glass funnel, which permits the slurrying and thorough rinsing of the filter cake, is recommended. Since the conversion of the phosphorous trichloride to the triamide is quantitative, the major cause of lower yields is the retainment of the liquid product by the salt cake.
7. As a safety precaution the exposure of the hot material in the flask to air should be avoided. The checkers recovered 134 g. (82%) of distillate from 153 g. of crude product.
8. Essentially the same procedure can be used to obtain the higher alkyl homologs of hexamethylphosphorous triamide. Since the higher dialkylamines are liquid at room temperature, the gas-inlet tube is replaced by an addition funnel. Alternatively, the mode of addition may be reversed (*i.e.*, phosphorus trichloride may be added to the amine) without affecting the subsequent workup or yield. The higher homologs of hexamethylphosphorous triamide such as the ethyl, *n*-propyl, and *n*-butyl can also be prepared in 95–100% conversion when a slight excess (5–10%) of the amine is employed.

3. Discussion

The described procedure is a modification of the method of Carmody and Zletz[2] and of Burg and Slota.[3] The higher homologs were reported by Stuebe and Lankelma.[4]

4. Merits of the Preparation

This is a general method of preparing hexaalkylphosphorous triamides from the corresponding dialkylamines. The procedure is simple, and the yields are high. Hexaalkylphosphorous triamides are powerful nucleophiles.[5] This feature can be used in a rather unique way to synthesize epoxides directly from aldehydes.[5,6] More recently the methyl and ethyl derivatives have been used in desulfurization reactions to prepare thiolactones[7] and thietanes.[8]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 358
- Org. Syn. Coll. Vol. 9, 711

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Benzene (71-43-2)

ether (60-29-7)

nitric acid (7697-37-2)

silver nitrate (7761-88-8)

nitrogen (7727-37-9)

amine hydrochloride

carbon dioxide (124-38-9)

phosphorus trichloride, phosphorous trichloride (7719-12-2)

Pentane (109-66-0)

dimethylamine hydrochloride (506-59-2)

chloride ion

dimethylamine (124-40-3)

hexane (110-54-3)

Hexamethylphosphorous triamide, Phosphorous triamide, hexamethyl- (1608-26-0)

phosphorous triamide

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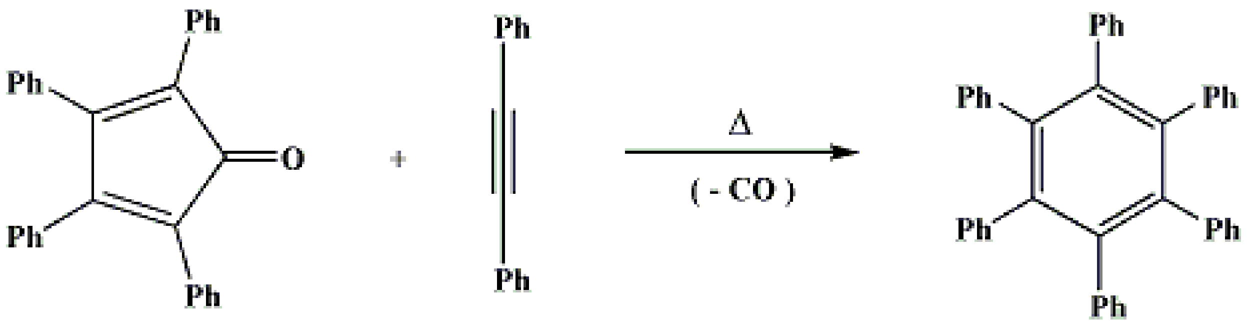
Organic Syntheses, CV 5, 604

HEXAPHENYLBENZENE

[Benzene, hexaphenyl-]



Submitted by Louis F. Fieser[1]
Checked by Chester E. Ramey and V. Boekelheide.

1. Procedure

A 100-ml., round-bottomed, ground-glass flask containing 40 g. of benzophenone is heated over a free flame to melt the bulk of the solid, and then 8.0 g. of tetraphenylcyclopentadienone (0.021 mole) (Note 1) and 8.0 g. of diphenylacetylene (0.043 mole) (Note 2) are introduced through a paper cone so that no material lodges on the neck or walls. An air condenser is attached, and the mixture is heated over a microburner so that it refluxes briskly but without flooding the condenser (the temperature of the liquid phase is 301–303°). Carbon monoxide is evolved, the purple color begins to fade in 15–20 minutes, and the color changes to a reddish brown in 25–30 minutes. When no further lightening in color is observed (after about 45 minutes), the burner is removed and 8 ml. of diphenyl ether is added to prevent subsequent solidification of the benzophenone. The crystals that separate are brought into solution by reheating, and the solution is let stand for crystallization at room temperature. The product is collected and washed free of brown solvent with benzene to give 9.4 g. (84%) of colorless plates, m.p. 454–456° (sealed capillary) (Note 3). A satisfactory solvent for recrystallization is diphenyl ether, using 7 ml. per gram of product.

2. Notes

1. A synthesis of tetraphenylcyclopentadienone is described in *Org. Syntheses*, Coll. Vol. **3**, 806 (1955). However, the following procedure is more convenient. A 250-ml. Erlenmeyer flask is charged with 21 g. of benzil, 21 g. of dibenzyl ketone (Eastman Organic Chemicals, practical grade), and 100 ml. of triethylene glycol, a thermometer is introduced, and the mixture is heated over a free flame until the solid has dissolved. A 10-ml. portion of a 40% solution of benzyltrimethylammonium hydroxide in methanol is made ready, the temperature of the reaction mixture is adjusted to 100°, the basic catalyst is

added, and the mixture is swirled once for mixing and let stand. Within 15–20 seconds the liquid sets to a stiff paste of purple crystals and the temperature rises to 115°. After the temperature has dropped to 80°, the mixture is cooled, thinned by stirring in 50 ml. of methanol, and the product is collected and washed with methanol until the filtrate is purple, not brown. The yield of product, m.p. 219–220°, is 35.5 g. (93%). Recrystallization can be accomplished with 92% recovery by dissolving the ketone in triethylene glycol (10 ml./gram) at 220°.

2. Improvements in the preparation and dehydrohalogenation of *meso*-stilbene dibromide [*Org. Syntheses*, Coll. Vol. **3**, 350 (1955)] are as follows. *trans*-Stilbene (20 g.) is heated with 400 ml. of acetic acid on the steam bath until dissolved, 40 g. of pyridinium bromide perbromide is added, and the mixture is heated on the steam bath and swirled for 5 minutes. *meso*-Stilbene dibromide separates at once in pearly white plates. The mixture is cooled to room temperature, and the product is collected and washed with methanol. The yield of dibromide, m.p. 236–237°, is 32.4 g. (86%). A 250-ml., round-bottomed, ground-glass flask is charged with 32.4 g. of the dibromide, 65 g. of potassium hydroxide pellets, and 130 ml. of triethylene glycol. A 15 × 125 mm. test tube containing enough of the same solvent to cover the bulb of a thermometer is inserted in the flask. The flask is supported in a clamp, which is used as a handle for swirling the flask over a free flame to mix the contents and bring the temperature to 160°, when potassium bromide begins to separate. By intermittent heating and swirling the mixture is kept at 160–170° for 5 minutes more to complete the reaction. The test tube is then removed, dipped into 500 ml. of water in a beaker, and the adhering organic material is rinsed into the beaker with 95% ethanol. The hot reaction mixture is poured into the beaker, and the flask is rinsed alternately with water and with ethanol. After cooling, the crude product is collected, washed with water, and air-dried (16.5 g.). The brown solution of this material in 50 ml. of 95% ethanol is filtered from a little dark residue, reheated, and let stand for crystallization. A first crop of diphenylacetylene (11.8 g.) separates in large colorless spars, m.p. 61.5–62.5°. Concentration of the mother liquor yield an additional 2.4 g. of crystals, m.p. 58–59°.

The checkers used diphenylacetylene provided by Aldrich Chemicals.

3. The melting point is determined conveniently with a Mel-Temp apparatus and a 90–510° thermometer designed for use with it (Laboratory Devices, Post Office Box 68, Cambridge 39, Massachusetts). An evacuated capillary containing a sample is sealed close to the sample to prevent sublimation, and repeated determinations are made with the same sample. The figure 456° is the average of two determinations of the temperature of melting; 454° is the average of two observations of the point of solidification. When the amount of diphenylacetylene was reduced to 1.2 times the theory, the yield was the same but the melting point was 450–452°.

3. Discussion

Hexaphenylbenzene has been prepared by heating tetraphenylcyclopentadienone and

diphenylacetylene without solvent[2] and by trimerization of diphenylacetylene with bis-(benzonitrile)-palladium chloride and other catalysts.[3]

4. Merits of the Preparation

Hexaphenylbenzene can be prepared satisfactorily by strong heating of a mixture of 0.5 g. each of tetraphenylcyclopentadienone and diphenylacetylene in a test tube, but the method is unsatisfactory on a larger scale because of the high melting point of the product and the poor heat transfer in a flask. The present procedure demonstrates use of benzophenone as solvent for a Diels-Alder reaction requiring a temperature of about 300°. When the reaction is completed, addition of a small amount of diphenyl ether lowers the melting point of benzophenone sufficiently to prevent this solvent from solidifying.

Other solvents tried and the liquid temperatures of the refluxing mixtures are: stearic acid (340–365°), di-*n*-butyl phthalate (320–325°), phenyl salicylate (290°). The first two solvents are unsatisfactory because of side reactions consuming some of the tetraphenylcyclopentadienone, the third because the addition reaction is too slow.

(Note 1) describes an improvement in the preparation of the starting dienone involving use of a medium of higher solvent power and higher boiling point than ethanol and of a basic catalyst more convenient than potassium hydroxide because it is miscible with the solvent employed. (Note 2) reports two improvements in the preparation of diphenylacetylene. The yield in the conversion of *trans*-stilbene to the *meso* dibromide is increased by use of the highly stereoselective reagent pyridinium bromide perbromide. In the dehydrohalogenation step the reaction time is reduced substantially and the yield increased by use of a high-boiling alcohol in place of ethanol.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

pyridinium bromide perbromide

meso dibromide

ethanol (64-17-5)

acetic acid (64-19-7)

Benzene (71-43-2)

methanol (67-56-1)

carbon monoxide (630-08-0)

Benzil (134-81-6)

potassium hydroxide, potassium hydroxide pellets (1310-58-3)

Benzophenone (119-61-9)

potassium bromide (7758-02-3)

phenyl salicylate (118-55-8)

stearic acid (57-11-4)

dibenzyl ketone (102-04-5)

diphenyl ether (101-84-8)

Diphenylacetylene (501-65-5)

benzyltrimethylammonium hydroxide (100-85-6)

Tetraphenylcyclopentadienone (479-33-4)

triethylene glycol (112-27-6)

Hexaphenylbenzene, Benzene, hexaphenyl- (992-04-1)

bis-(benzonitrile)-palladium chloride

trans-Stilbene (103-30-0)

meso-stilbene dibromide

di-n-butyl phthalate (84-74-2)

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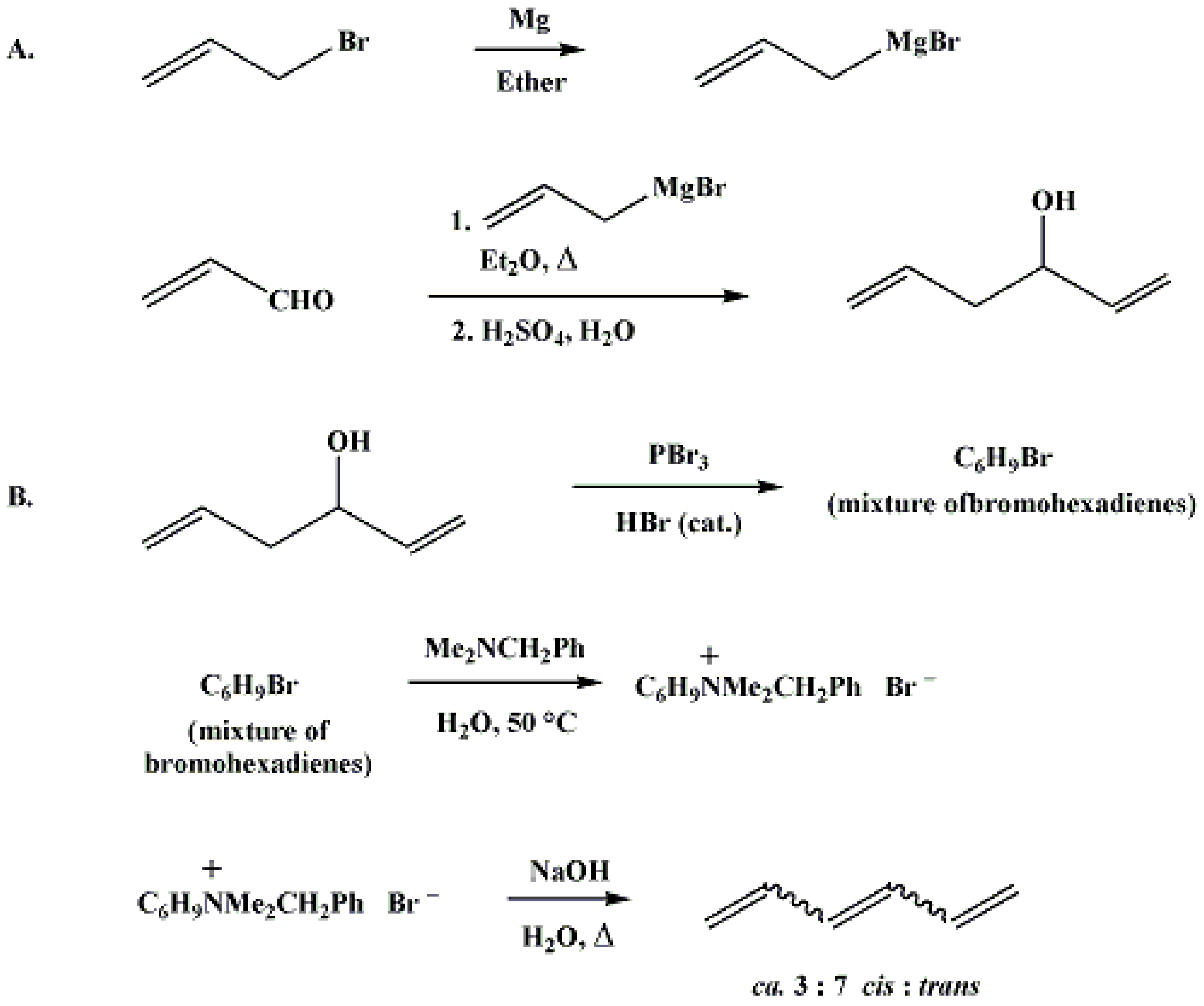
Organic Syntheses, CV 5, 608

1,3,5-HEXATRIENE



Submitted by Jesse C. H. Hwa and Homer Sims[1].
Checked by Virgil Boekelheide and E. A. Caress.

1. Procedure

A. *1,5-Hexadien-3-ol* (Note 1). In a 5-l. three-necked flask fitted with a stirrer, a dropping funnel and an ice-water condenser are placed 153.0 g. (6.28 g. atoms) of magnesium turnings, 360 ml. of anhydrous ether (Note 2), and a few crystals of iodine. A solution of 351.0 g. (2.90 moles) of allyl bromide (Note 3) in 2.6 l. of ether is added in small portions until the reaction begins, and then at such a rate as to maintain gentle refluxing of the ether. The addition requires about 3 hours, after which the reaction mixture is refluxed on a steam bath for an additional hour. Acrolein (Note 4) (104.0 g., 1.86 moles) is added during 2 hours, and this causes gentle refluxing. After an additional hour at room temperature the reaction mixture is poured slowly into 2 l. of ice water. The precipitate is dissolved by adding slowly a solution of 120 ml. of concentrated sulfuric acid (sp. gr. 1.84) in 400 ml. of water (Note 5). The organic layer is separated and the water layer extracted with three 200-

ml. portions of ether. The combined oil and ether extracts are dried over 8–10 g. of anhydrous magnesium sulfate. After removal of the ether, the residue is distilled through a 6-in. column packed with glass helices to yield 104–108 g. (57–59%, based on acrolein) of 1,5-hexadien-3-ol; b.p. 62–65/50 mm., n_D^{25} 1.4440.

B. *1,3,5-Hexatriene*. In a 500-ml., three-necked, round-bottomed flask fitted with a mechanical stirrer, a thermometer, and a graduated dropping funnel are placed 114 g. (0.42 mole) of phosphorus tribromide (Note 6) and 2 drops of 48% hydrobromic acid. As the contents of the flask are stirred and maintained at 10–15° by means of an ice-water bath, 98 g. (1.00 mole) of 1,5-hexadien-3-ol is added in the course of 1.5 to 1.75 hours. The mixture is allowed to stir at 10–15° for 40 minutes and then to stand at room temperature overnight. The flask is cooled in an ice-salt bath for 20 minutes, and the upper organic layer is decanted from the residue while still cold. The organic layer is successively washed with three 40-ml. portions each of ice water, 5% sodium bicarbonate, and water. The crude bromohexadiene weighs 147–153 g. (91–95%) (Note 7).

In an assembly similar to that used for the previous reaction, 90 g. (0.67 mole) of dimethylbenzylamine (Note 8), 0.13 g. of hydroquinone, and 500 ml. of water are stirred and heated at 50°. The crude bromohexadiene (107 g., 0.67 mole) is added in the course of 20–40 minutes, and stirring and heating are maintained at 50° for 2–2.5 more hours. The flask is then fitted for downward distillation, and the mixture is distilled at about 40–50° and 30 mm. until no more oil distils with the water. A total of 133–200 ml. of distillate is collected. This is discarded.

A solution of sodium hydroxide (106 g., 2.7 moles) in 535 ml. of water is placed in a 2-l. flask equipped with a sealed mechanical stirrer and an outlet arranged for downward distillation into an ice-cooled receiver. The aqueous solution of the quaternary bromide is added dropwise to the boiling solution of sodium hydroxide during a period of 2.5–4 hours (Note 9). The hexatriene and dimethylbenzylamine which form are distilled with the water. Distillation is continued for 10–15 minutes after the final addition of quaternary bromide solution. The clear upper layer of the distillate is separated, cooled to 5–10°, washed with three 170-ml. portions each of cold 2*N* hydrochloric acid and water, and dried over anhydrous sodium sulfate. The oil is then distilled, a spinning-band column being used to give 32.0–34.0 g.. (54–60%) of 1,3,5-hexatriene; b.p. 80–80.5°, n_D^{20} 1.5103–1.5119 (Note 10).

2. Notes

1. This method is essentially that of Butz, Butz, and Gaddis[2] except for modified charge ratios to increase the output per batch at some sacrifice in per cent yield.
2. Baker and Adamson, reagent grade.
3. Matheson, Coleman and Bell, b.p. 70–71°.
4. Shell Chemical Co., commercial grade, inhibited.
5. When the magnesium complex is dissolved, the solution may be decanted from the excess magnesium metal.
6. Dow Chemical Co., practical grade.
7. The moist crude bromohexadiene is quaternized in water without further purification. The submitters report that, if desired, the crude mixture may be dried

over anhydrous calcium chloride and fractionally distilled through a 10-in. stainless-steel-packed column at reduced pressure. Crude bromohexadiene (220–230 g.) from 147 g. (1.50 moles) of 1,5-hexadiene-3-ol was found to give the fractions listed in Table I. The yield of the total distillate is 174.9 g. of which fractions 1–4 amount to 155.7 g. (64.5%). The 1-bromo isomer has been reported in the literature,[3,4] and the infrared spectrum suggests that fraction 1 is 3-bromo-1,5-hexadiene. Both isomers when treated separately in this procedure yield hexatriene.

TABLE I

Fraction	Wt., g.	B.P./mm.	n_D^{20}	Product
1	43.2	55–56°/34	1.4829	3-Bromo-1,5-hexadiene
2	31.7	57–72°/34	1.4923	Mixture of the 3- and 1-bromo isomers
3	70.7	72–73°/36	1.4981	1-Bromo-2,5-hexadiene
4	10.1	56–59°/18	1.4996	Mostly 1-bromo-2,5-hexadiene
5	19.2	64–103°/14	1.5196	—

8. The amine should be freshly distilled.
9. This time, although not critical, was chosen to prevent accumulation of unreacted quaternary base or of hexatriene in the reaction vessel.
10. The faintly yellow product obtained before distillation is quite pure. The infrared absorption spectra of the liquid before and after distillation are identical and have, in addition to all the bands shown in the published spectrum of Woods and Schwartzman,[5] weak absorption bands, notably at 820, 989, 1187, and 1452 cm^{-1}. The differences between the two spectra are due to various ratios of *cis* and *trans* isomers in these hexatriene samples. The ratio of *cis*- to *trans*-1,3,5-hexatriene in this preparation is estimated at 3:7. This is based on studies using vapor-phase chromatography, ultraviolet absorption spectra, and refractive indices.[6] The hexatriene is stored under nitrogen at –5°. Although no visible change is observed after 1 week of storage, the liquid is partially polymerized to the consistency of glycol after 3 weeks. Hexatriene can be removed from the thin syrup by distillation at 40 mm., and when redistilled at atmospheric pressure under nitrogen has b.p. 80.5°, n_D^{20} 1.5101. Its infrared absorption spectrum is then identical with that of freshly prepared hexatriene.

3. Discussion

1,3,5-Hexatriene has been prepared by many workers. The more successful methods are the catalytic pyrolyses (alumina, 260–325°) of 1,3-hexadien-5-ol[5,7,8] and 2,4-hexadien-1-ol.[9] Other methods which give hexatriene of questionable purity or involve less convenient laboratory methods are dehydration of 1,5-hexadien-3-ol by sodium bisulfate at 170°,[10] or by phthalic anhydride at 160–200°,[2] and by catalytic hydrogenation of divinylacetylene.[11] Additional methods are listed in footnote [5]. The present procedure is a practical laboratory method of preparing pure hexatriene in satisfactory yields.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium hydroxide (1310-73-2)

Acrolein (107-02-8)

hydroquinone (123-31-9)

sodium bicarbonate (144-55-8)

magnesium, magnesium turnings (7439-95-4)

HYDROBROMIC ACID (10035-10-6)

Allyl bromide (106-95-6)

sodium sulfate (7757-82-6)

phosphorus tribromide (7789-60-8)

nitrogen (7727-37-9)

phthalic anhydride (85-44-9)

iodine (7553-56-2)

sodium bisulfate (7681-38-1)

magnesium sulfate (7487-88-9)

dimethylbenzylamine (103-83-3)

1,3,5-Hexatriene, hexatriene (2235-12-3)

1,5-Hexadien-3-ol, 1,5-hexadiene-3-ol (924-41-4)

bromohexadiene

3-Bromo-1,5-hexadiene

1-Bromo-2,5-hexadiene

1,3-hexadien-5-ol

2,4-hexadien-1-ol (17102-64-6)

divinylacetylene (31014-03-6)

trans-1,3,5-hexatriene

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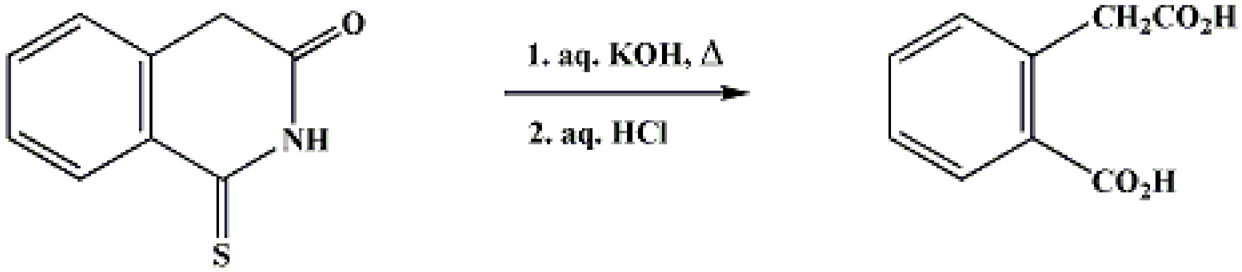
Organic Syntheses, CV 5, 612

HOMOPHTHALIC ACID



Submitted by P. A. S. Smith and R. O. Kan[1].
Checked by Melvin S. Newman and Bernard Darre.

1. Procedure

Ten grams (0.056 mole) of 2*a*-thiohomophthalimide[2] and a solution of 30 g. of potassium hydroxide in 125 ml. of water are placed in a 300-ml., one-necked, round-bottomed flask (Note 1). The mixture is refluxed for 48 hours, filtered, and acidified with 12*N* hydrochloric acid. The solid that forms on cooling is collected by filtration and recrystallized from a mixture of 25 ml. of water and as much acetic acid (about 7 ml.) as necessary to dissolve the solid in the boiling solution, with addition of a little activated carbon. The yield of homophthalic acid, m.p. 181° (Note 2), is 6.1–7.5 g. (60–73%) (Note 3).

2. Notes

1. Because base can attack glass vessels, possibly introducing difficultly removable silicates into the reaction mixture, a copper flask is recommended for routine operations.
2. The melting point depends on the rate of heating. When the solid is heated slowly, the melting range can be as low as 172–174°.
3. An alternative procedure involves 3 days of refluxing in a mixture of 75 ml. of glacial acetic acid, 50 ml. of 12*N* hydrochloric acid, and 30 ml. of water. The product separates on cooling in a slightly lower yield (48%).

3. Discussion

Homophthalic acid may be obtained by the oxidation of indene,[3,4] the reduction of phthalonic acid,[5,6] and the hydrolysis of *o*-carboxyphenylacetonitrile.[7] Other methods are listed in an earlier volume.[3]

4. Merits of the Preparation

This is a general method for converting 2*a*-thiohomophthalimides to homophthalic acids. Since 2*a*-thiohomophthalimides are readily obtained from phenylacetyl chlorides,[2] this is a convenient method for preparing homophthalic acids.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 1051

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

phthalonic acid

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

carbon (7782-42-5)

potassium hydroxide (1310-58-3)

indene (95-13-6)

Homophthalic acid (89-51-0)

thiohomophthalimide

o-CARBOXYPHENYLACETONITRILE (6627-91-4)

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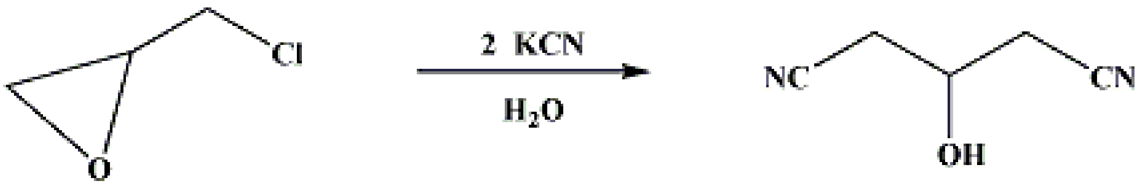
Organic Syntheses, CV 5, 614

3-HYDROXYGLUTARONITRILE

[Glutaronitrile, 3-hydroxy-]



Submitted by F. Johnson and J. P. Panella[1].
Checked by A. G. Anastassiou and B. C. McKusick.

1. Procedure

A mixture of 493 g. (2.00 moles) of magnesium sulfate heptahydrate and 700 ml. of tap water is stirred for 5 minutes and filtered into a 2-l. three-necked flask equipped with a mechanical stirrer and an alcohol thermometer that dips into the solution. The flask is immersed in a cooling bath (Note 1), the stirrer is started, and the solution is cooled to 10°. To the solution is added, in one portion, 143 g. (2.20 moles) of potassium cyanide *(Caution! Toxic)*, and stirring is continued for 45 minutes at 8–12° (Note 2). The solution is maintained at this temperature while 102 g. (1.10 moles) of epichlorohydrin (Note 3) is added dropwise with stirring over a period of 1 hour (Note 4). The mixture is allowed to come to room temperature and is stirred for an additional 24 hours at this temperature.

The dark red-brown reaction mixture is stirred and extracted continuously with 1 l. of ethyl acetate for 48 hours (Note 5). The extract is dried over anhydrous magnesium sulfate for 18 hours (Note 6), filtered, and the filtrate is concentrated under reduced pressure on a steam bath. The residual dark-brown oil (about 90 g.) is distilled from a Claisen flask; the distillation must be rapid to minimize decomposition. About 20 g. of fore-run consisting of 4-chloro-3-hydroxybutyronitrile and 4-hydroxycrotononitrile is collected at 90–115° (0.4 mm.). 3-Hydroxyglutaronitrile is collected at 155–160° (0.4 mm.), yield 65–75 g. (54–62%), n^{23}D 1.4634. This pale yellow distillate is sufficiently pure for most purposes. Further purification can be effected with only 3–5% loss by distillation of the material through a 15-cm. Vigreux column and collection of the portion boiling at 154–156° (0.2 mm.), n^{23}D 1.4632 (Note 7).

2. Notes

1. The bath contained a mixture of trichloroethylene and solid carbon dioxide kept at –20°.
2. At this point the mixture has an opaque milky-white appearance caused by precipitation of a little magnesium hydroxide.

3. Epichlorohydrin (white label brand) supplied by Eastman Organic Chemicals was used without further purification.
4. The reaction is exothermic. If the temperature of the reaction mixture is allowed to rise above 30°, the reaction is likely to get out of control.
5. The checkers found that a stirred extractor[2] was much more efficient than an unstirred one for this operation.
6. This extensive drying period is necessary to allow precipitation of traces of basic salts that have been carried over during the extraction procedure. Failure to remove these salts results in extensive decomposition of the product during the distillation step.
7. The submitters have obtained the same yield working on 10 times this scale.

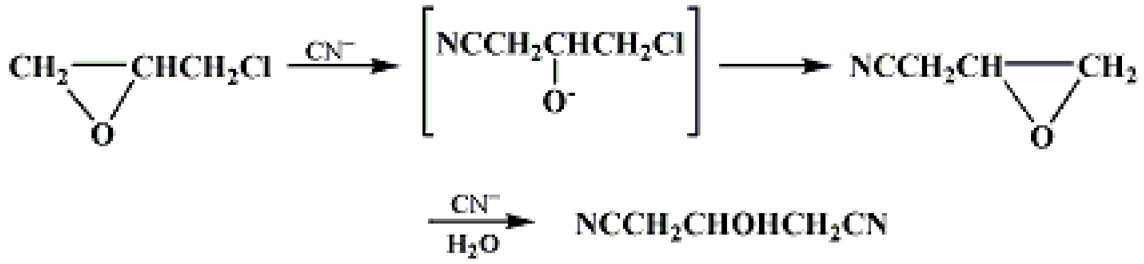
3. Discussion

3-Hydroxyglutaronitrile has been prepared by the action of potassium cyanide on 1,3-dichloro-2-propanol[3,4,5] or on 4-chloro-3-hydroxybutyronitrile.[6,7] More recently it has been prepared from epichlorohydrin using essentially the present method.[8]

4. Discussion

This is a much more convenient and satisfactory synthesis of 3-hydroxyglutaronitrile than earlier ones.[3,4,5,6,7] The method can be applied to other epichlorohydrins; 2-methylepichlorohydrin and 2-ethylepichlorohydrin have been converted to the corresponding hydroxydinitriles in 71% and 77% yields, respectively.[8] The hydroxydinitriles undergo cyclizations to heterocyclic compounds not easily prepared in other ways. Thus hydrogen bromide at 0° converts 3-hydroxyglutaronitrile to 2-amino-6-bromopyridine in 70% yield.[9]

The reaction probably proceeds as follows:[8]



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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

2-methylepichlorohydrin

2-ethylepichlorohydrin

ethyl acetate (141-78-6)

Epichlorohydrin (106-89-8)

hydrogen bromide (10035-10-6)

potassium cyanide (151-50-8)

carbon dioxide (124-38-9)

magnesium hydroxide

1,3-dichloro-2-propanol (96-23-1)

magnesium sulfate (7487-88-9)

trichloroethylene (79-01-6)

3-Hydroxyglutaronitrile, Glutaronitrile, 3-hydroxy- (13880-89-2)

magnesium sulfate heptahydrate (10034-99-8)

4-chloro-3-hydroxybutyronitrile

4-hydroxycrotononitrile

2-amino-6-bromopyridine

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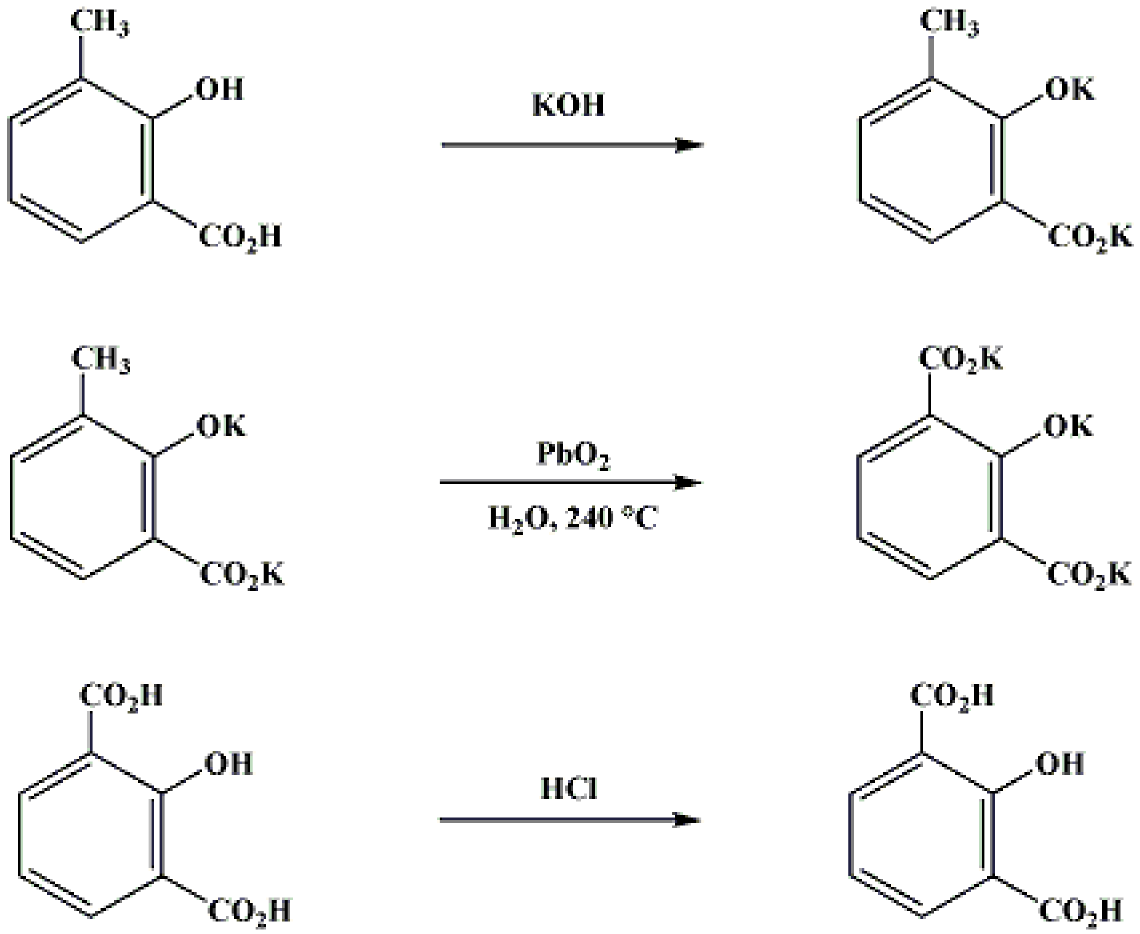
Organic Syntheses, *CV 5*, *617*

2-HYDROXYISOPHTHALIC ACID

[Isophthalic acid, 2-hydroxy-]



Submitted by David Todd[1] and A. E. Martell[2].
Checked by B. C. McKusick and S. Andreades.

1. Procedure

In an 800-ml. stainless-steel flanged beaker are placed 240 g. of potassium hydroxide pellets and 50 ml. of water. When the mush has cooled, 40.0 g. (0.263 mole) of 2-hydroxy-3-methylbenzoic acid (Note 1) is added, and the slurry is stirred with a long glass rod. The beaker is placed firmly in a clamp (Note 2) and set in a cold oil bath (Note 3) in a hood, and 240 g. (1.00 mole) of lead dioxide is stirred in all at once (Note 4). The oil bath is now heated by a flame, and when the bath temperature reaches 200° steady manual stirring by means of the glass rod is begun. *(Caution! Goggles and a rubber glove should be worn to protect eyes and the stirring hand against spattering.)* The temperature is raised, with steady stirring, until the bath reaches 238–240°, when the flame is moderated to maintain this bath temperature. Several minutes after 240° is reached, the mixture boils steadily and the lumpy brown mass turns quickly to a bright-orange melt containing heavy crystals of lead monoxide. The bath is held at 240° for

another 15 minutes. It is then brought briefly to 250°, the flame is removed, and the beaker is lifted out of the bath.

About 5 minutes later, the liquid contents of the beaker are poured cautiously into a 2-l. glass beaker, and this is tipped and rotated slowly so as to spread the congealing mass in a thin film on the beaker walls. When the material in the beakers has cooled, a total of 1 l. of water is poured into the beakers and the water is stirred well for at least 1 hour (Note 5). The cold suspension is filtered with suction to separate 200–210 g. of an insoluble mixture of lead monoxide and red lead, which is washed on the filter with six 50-ml. portions of water.

The alkaline filtrate and washings are combined and partially neutralized by the addition of 150–175 ml. of concentrated hydrochloric acid. Sufficient sodium sulfide solution is added to precipitate all the lead ion present (Note 6). The suspension is brought to a gentle boil to coagulate the lead sulfide, allowed to cool somewhat, and filtered with suction. The filtrate is placed in a 2-l. beaker set in an ice bath and acidified *(Caution! in the hood)* with about 150 ml. of concentrated hydrochloric acid to precipitate crude 2-hydroxyisophthalic acid monohydrate (Note 7). The suspension is cooled to 0–5° and filtered to separate the crude acid, which weighs 35–49 g. after being dried in a vacuum oven at 110°/50–150 mm. for 5 hours (Note 8).

In order to remove 1–3 g. of contaminating 2-hydroxy-3-methylbenzoic acid, the crude acid is ground in a mortar and refluxed briefly with 100 ml. of chloroform, and the suspension is filtered hot (Note 9). The separated solid is dried in air and added to 1 l. of boiling water. The mixture is boiled gently for 15 minutes and filtered by gravity to remove a small amount of gray sludge. The clear light-orange filtrate rapidly deposits needles of 2-hydroxyisophthalic acid monohydrate. After cooling to 0–5°, the acid is collected and dried at 110°/50–150 mm. for 20 hours. The anhydrous acid, which ranges in color from pale pink to tan, weighs 22–29 g. (46–61%) (Note 10) and melts at 243–255°, depending on the rate of heating and the apparatus used.

2. Notes

1. Eastman Kodak technical grade material is satisfactory.
2. A convenient clamp can be fashioned by bending a loop at the end of a 40-cm. length of iron rod 6 mm. (in.) in diameter so that the beaker can just slip up to its flange through the loop. A pinch clamp is used to hold the flange firmly to the loop.
3. The checkers used a bath wax (flash point 325°) supplied by the Fisher Scientific Co. The operation should be carried out in a hood because fumes from oil baths at high temperatures are injurious to health. A fire extinguisher should be close at hand in case the oil bath catches fire. A high-boiling silicone heat exchange oil, although more expensive, would be less of a fire hazard. Alternatively, a sodium nitrite-sodium nitrate-potassium nitrate mixture such as "Hitec" heat transfer salt sold by the du Pont Company (useful range 150–450°) can be used. Such baths will not burn, but they have the disadvantage of being oxidizing agents, so precautions should be taken not to let any organic material

get into them lest a flash oxidation accompanied by spattering of hot salt take place. Hot salt baths should be well shielded to guard against spattering.
4. If the calculated amount (190 g.) of lead dioxide is used, the yield is lowered by about 20%.
5. At least an hour's contact with water is necessary in order to dislodge all the solid from the walls.
6. The amount of sodium sulfide nonahydrate needed varies from 12 to 25 g. from one run to another.
7. The acid is precipitated from aqueous solution as the monohydrate, which is soluble in cold dilute hydrochloric acid to the extent of about 6 g. per l.
8. An additional 3–5 g. (6–10%) of crude product can be obtained by concentrating the filtrate to about 800 ml., cooling the concentrate to 0°, and filtering the solid that separates. This solid must be washed well with cold water to remove coprecipitated potassium chloride.
9. The starting material is moderately soluble in hot chloroform, while 2-hydroxyisophthalic acid is quite insoluble. Fractional crystallization from water, an alternative method suggested for the separation of starting material,[3] has been found by the submitters to be unsuccessful.
10. An additional 2–5 g.. (4–10%) of product can be obtained by concentrating the filtrate to one-third its volume, adding 25 ml. of concentrated hydrochloric acid, cooling the mixture, separating crude acid by filtration, and recrystallizing the acid from water.

3. Discussion

2-Hydroxyisophthalic acid has been prepared by oxidizing 2-hydroxy-3-methylbenzoic acid with lead dioxide,[3,4,5] by cleaving the ether group of 2-methoxyisophthalic acid with hydriodic acid,[6] and by hydrolyzing 2-iodoisophthalic acid with alcoholic sodium hydroxide.[7]

The lead dioxide-alkali method has also been applied successfully by Graebe and Kraft[4] to the three cresols, the three toluic acids, and 2,4-dimethylphenol. For the preparation of 2-hydroxyisophthalic acid, it is the only one-step method that starts from readily obtainable materials.

In general, this method is a one-step procedure for the oxidation of a cresol type of molecule to the corresponding phenolic acid. The vigorous reaction conditions clearly limit the type of functional groups that may be present in the molecule. There is no evidence that the reaction has been applied to polynuclear or heterocyclic alkylphenols.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

red lead

hydrochloric acid (7647-01-0)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

lead monoxide

potassium hydroxide pellets (1310-58-3)

hydriodic acid (10034-85-2)

sodium sulfide (1313-82-2)

potassium chloride (7447-40-7)

sodium sulfide nonahydrate (1313-84-4)

2-Hydroxyisophthalic acid, Isophthalic acid, 2-hydroxy- (606-19-9)

2-hydroxy-3-methylbenzoic acid (83-40-9)

2-hydroxyisophthalic acid monohydrate

sodium nitrite-sodium nitrate-potassium nitrate

2-methoxyisophthalic acid (1951-38-8)

2-iodoisophthalic acid

2,4-dimethylphenol (105-67-9)

lead dioxide

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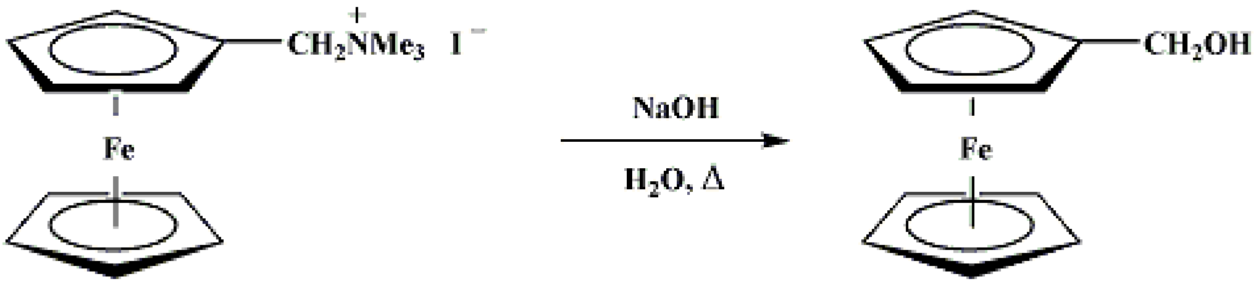
Organic Syntheses, CV 5, 621

HYDROXYMETHYLFERROCENE

[Iron, cyclopentadienyl[(hydroxymethyl)cyclopentadienyl]-]



Submitted by Daniel Lednicer, T. Arthur Mashburn, Jr., and Charles R. Hauser[1].
Checked by B. C. McKusick, H. F. Mower, and G. N. Sausen.

1. Procedure

Caution! This preparation should be conducted in a hood because trimethylamine is evolved.

A solution of 10.0 g. (0.25 mole) of sodium hydroxide in 250 ml. of water is prepared in a 1-l. round-bottomed flask equipped with a reflux condenser and a mechanical stirrer. Twenty-five grams (0.065 mole) of N,N-dimethylaminomethylferrocene methiodide[2] is added to the solution. The resulting suspension is heated to reflux temperature with stirring. At this point the solid is in solution. Within 5 minutes oil starts to separate from the solution and trimethylamine starts to come off. At the end of 3.5 hours, at which time the evolution of the amine has virtually ceased, the reaction mixture is allowed to cool to room temperature. The oil generally crystallizes during the cooling. The mixture is stirred with 150 ml. of ether until the oil or solid is all dissolved in the ether. The ether layer is separated in a separatory funnel and the aqueous layer is extracted with two additional 150-ml. portions of ether. The combined ether extracts are washed once with water and dried over sodium sulfate.

The oil that remains when the solvent is removed from the extract crystallizes when cooled to room temperature. This orange solid is recrystallized from 150 ml. of hexane (Note 1) to yield 9.5–12.5 g. (68–89%) of hydroxymethylferrocene, m.p. 74–76°. One more recrystallization from the same solvent affords 8.2–11.0 g. (59–79%) (Note 2) of good-quality alcohol as golden needles, m.p. 76–78° (Note 3).

2. Notes

1. Eastman Kodak Company practical grade hexane is suitable.
2. The yield of this reaction is directly dependent on the purity of the quaternary salt employed. If the salt is prepared from redistilled N,N-

dimethylaminomethylferrocene, the yield of alcohol may be as high as 90%.[3]
3. The pure alcohol melts at 81–82°.

3. Discussion

Hydroxymethylferrocene has been made by condensing ferrocene with N-methylformanilide to give ferrocenecarboxaldehyde, and reducing the latter with lithium aluminum hydride,[4] sodium borohydride,[5] or formaldehyde and alkali.[5] The present procedure is based on the method of Lindsay and Hauser.[3] A similar procedure has been used to convert gramine methiodide to 3-hydroxymethylindole,[6] and the method could probably be used to prepare other hydroxymethyl aromatic compounds.

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Ferrocene

N,N-Dimethylaminomethylferrocene methiodide

Hydroxymethylferrocene

N,N-dimethylaminomethylferrocene

ferrocenecarboxaldehyde

ether (60-29-7)

sodium hydroxide (1310-73-2)

formaldehyde (630-08-0)

sodium sulfate (7757-82-6)

Trimethylamine (75-50-3)

lithium aluminum hydride (16853-85-3)

N-methylformanilide (93-61-8)

hexane (110-54-3)

sodium borohydride (16940-66-2)

gramine methiodide

3-hydroxymethylindole (700-06-1)

Iron, cyclopentadienyl[(hydroxymethyl)cyclopentadienyl]-

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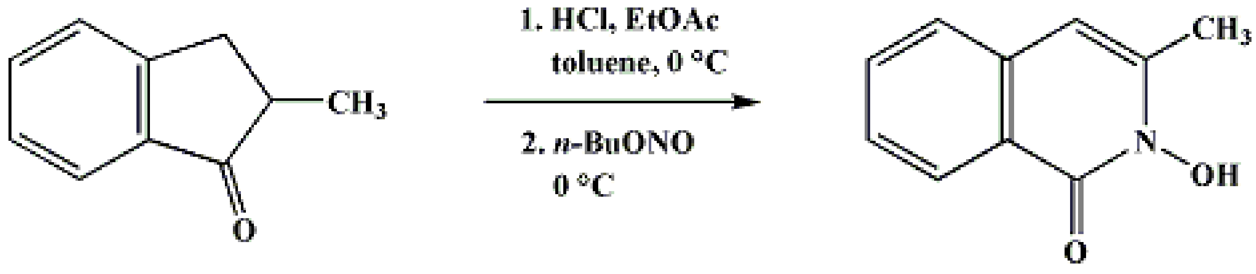
Organic Syntheses, CV 5, 623

2-HYDROXY-3-METHYLISOCARBOSTYRIL

[Isocarbostyril, 2-hydroxy-3-methyl-]



Submitted by Emil J. Moriconi and Francis J. Creegan[1].
Checked by Barbara A. Alexander, Hermann Ertl, T. Hoekemeijer, and Peter Yates.

1. Procedure

A solution of 8.0 g. (7.5 ml., 0.055 mole) of 2-methyl-1-indanone (Note 1) in 100 ml. of toluene is prepared in a 500-ml., three-necked, round-bottomed flask equipped with a thermometer, a dropping funnel, and a magnetic stirrer. The flask is immersed in a freezing mixture of sodium chloride and ice. When the solution temperature reaches 0°, 70 ml. (0.21 mole) of 3*N* hydrochloric acid in ethyl acetate (Note 2) is added slowly (Note 3). To this mixture 8.0 ml. (0.068 mole) of freshly prepared *n*-butyl nitrite (Note 4) in 25 ml. of toluene is added with stirring over a 10-minute period (Note 5). The mixture is stirred for 1 hour at 0° and for an additional hour at room temperature. The two layers are separated, and the upper layer (toluene) is concentrated to one-half volume. Both solutions are refrigerated at –20° for 4 days. The precipitated orange product is collected by filtration from each layer. Further concentration of each filtrate under reduced pressure to one-half volume gives additional crude product (Note 6).

The various fractions are combined, washed with 20 ml. of cold ether, and dried. Recrystallization from methylene chloride-ether (Note 7) gives 6.0–6.6 g. (62–69%) of 2-hydroxy-3-methylisocarbostyril as light orange plates, m.p. 175–180°. Sublimation of this material at 100–110° (0.5 mm.) gives a white product, m.p. 182–184°, with softening at 174° (Note 7).

2. Notes

1. The 2-methyl-1-indanone, b.p. 65–66° (0.6 mm.) [lit.[2] b.p. 120° (15 mm.)], was prepared by the following method, described by Colonge and Weinstein.[2] To 15.0 g. (0.50 mole) of paraformaldehyde (Eastman Organic Chemicals) and

100 g. (0.75 mole) of propiophenone (Eastman Organic Chemicals) in a 250-ml. Erlenmeyer flask, 10 ml. of 1*N* alcoholic potassium hydroxide solution was added with stirring. After a few minutes a clear solution formed, and the temperature rose to 35° and then fell slowly. The yellow solution was stirred for 5.5 hours at room temperature, during which time the solution became turbid. The turbid solution was poured into 150 ml. of water, and the mixture was acidified with concentrated hydrochloric acid (Congo red indicator).

The mixture was extracted with two 150-ml. portions of benzene, and the combined organic extracts were washed with two 150-ml. portions of water, two 150-ml. portions of 10% aqueous sodium carbonate, and two 150-ml. portions of water. The benzene extracts were dried over anhydrous sodium sulfate, and the solvent was removed. The yellow residue was distilled under reduced pressure to give a forerun consisting of 45 g. (0.34 mole) of unconsumed propiophenone followed by 32–36 g. (39–44%) of 3-hydroxy-2-methylpropiophenone, b.p. 108–110° (0.55 mm.) [lit.[2] b.p. 158–162° (17 mm.)]; infrared band (neat) at 5.94 • (C=O).

3-Hydroxy-2-methylpropiophenone (30 g., 0.183 mole) was added slowly to 150 ml. of concentrated sulfuric acid with stirring. The temperature rose and the solution turned dark brown. The temperature remained at 80° for 10 minutes and then slowly fell. After 1 hour the dark solution was poured onto 200 g. of cracked ice. The mixture was extracted with two 100-ml. portions of ether. The ethereal solution was washed with two 100-ml. portions of water, two 100-ml. portions of saturated aqueous sodium bicarbonate, and again with two 100-ml. portions of water. It was dried over anhydrous potassium carbonate, and the solvent was removed. The residue was distilled to give 18–19 g. (67–71%) of a pale yellow liquid, b.p. 65–66° (0.6 mm.) [lit[2]. b.p. 120° (15 mm.)], n^{20}20D 1.5510 (lit.[2] n^{23}D 1.5511); infrared band (neat) at 5.80 • (C=O).

2. Prepared by dissolving 17.5 ml. of 12*N* hydrochloric acid in 52.5 ml. of ethyl acetate.

3. Two phases are obtained; this heterogenous mixture is vigorously stirred during the addition of *n*-butyl nitrite.

4. The *n*-butyl nitrite must be refrigerated after preparation[3] and used as soon as possible thereafter. The use of commercially available *n*-butyl nitrite invariably led to lower yields of the isocarbostyril.

5. With lower hydrochloric acid concentration and reversal of the mode of addition, *i.e.*, acid to indanone-nitrite mixture, the intermediate 2-methyl-2-nitroso-1-indanone may also be isolated as its dimer. This can be isomerized to the isocarbostyril rapidly in refluxing methanolic sodium methoxide and more slowly in concentrated hydrochloric acid.[4]

6. To determine whether all the isocarbostyril has been isolated from the filtrates, a small aliquot of the filtrate is treated with excess aqueous ferric chloride. The appearance of a deep purple color indicates the necessity for further concentration under reduced pressure and precipitation of product.

7. The checkers used methylene chloride alone as the solvent for recrystallization; sublimation gave a product, m.p. 178–180°.

3. Discussion

2-Hydroxy-3-methylisocarbostyril has been prepared by the present method,[4] and in 12–15% yield by the ozonization of 3-methylisoquinoline-2-oxide.[5]

4. Merits of the Preparation

This simple, one-step ring expansion is the only available method for the preparation of 2-hydroxy-3-alkylisocarbostyrils in good yield from the corresponding 2-alkyl-1-indanones. Table I lists five new hydroxyisocarbostyrils prepared in this manner.

TABLE I SYNTHESES OF 2-HYDROXY-3-ALKYLISOCARBOSTYRILS

2-Alkyl Substituent	Yield, %	M.P., °C
Ethyl	65	154–155
Propyl	64	139–141
Isopropyl	49	107–108
Butyl	45	108–109
t-Butyl	20	104–106

Direct reduction of the 2-hydroxy-3-alkylisocarbostyrils gives 3-alkylisocarbostyrils and provides a useful synthesis of these compounds.

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ethyl acetate (141-78-6)

ether (60-29-7)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

sodium methoxide (124-41-4)

potassium hydroxide (1310-58-3)

toluene (108-88-3)

ferric chloride (7705-08-0)

n-butyl nitrite (544-16-1)

methylene chloride (75-09-2)

Propiophenone (93-55-0)

2-Hydroxy-3-methylisocarbostyril, Isocarbostyril, 2-hydroxy-3-methyl- (7114-79-6)

2-methyl-1-indanone (17496-14-9)

3-hydroxy-2-methylpropiophenone (3338-15-6)

2-methyl-2-nitroso-1-indanone

3-methylisoquinoline-2-oxide

paraformaldehyde (30525-89-4)

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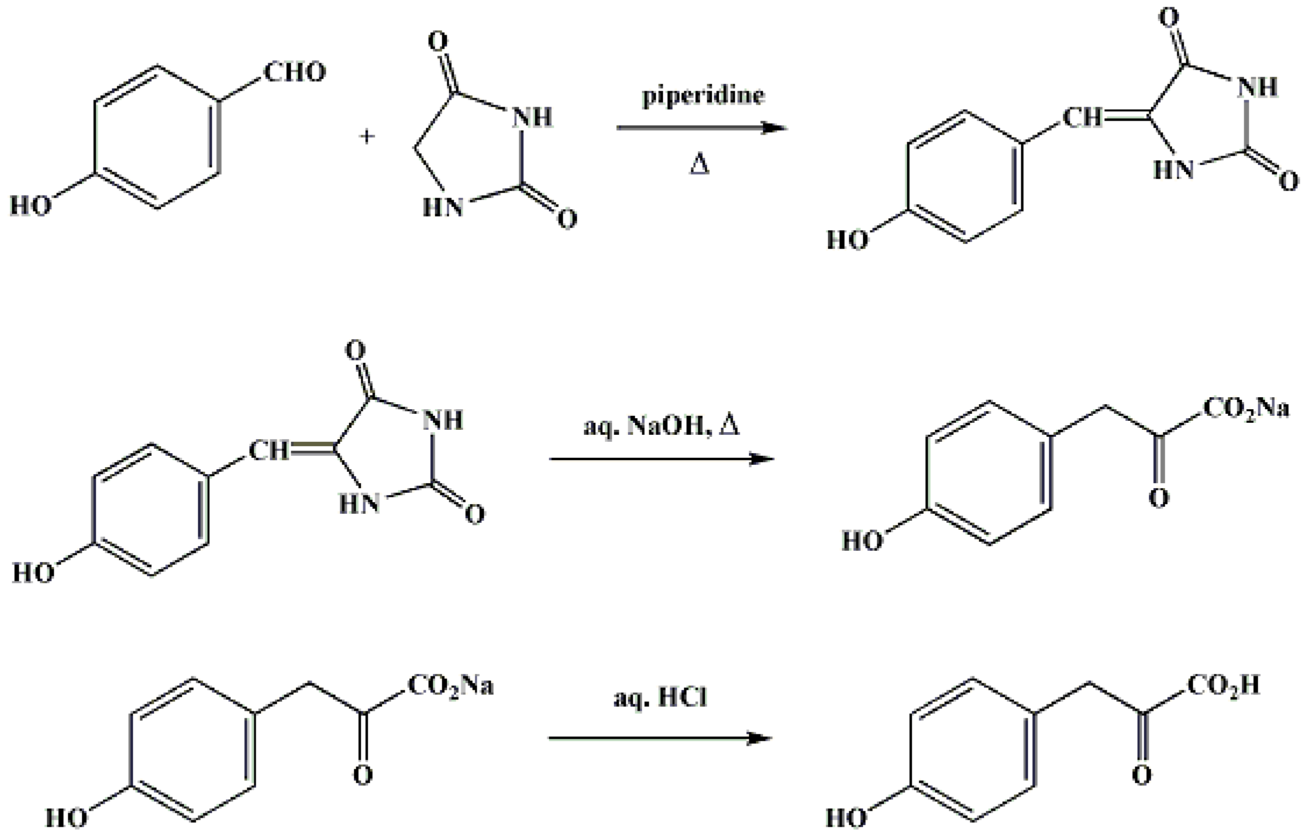
Organic Syntheses, CV 5, 627

p-HYDROXYPHENYLPYRUVIC ACID

[Pyruvic acid, *p*-hydroxyphenyl-]



Submitted by Gerhard Billek[1]
Checked by Max Tishler and Arthur J. Zambito.

1. Procedure

A. *5-(p-Hydroxybenzal)hydantoin*. An intimate mixture of 6.11 g. (0.050 mole) of *p*-hydroxybenzaldehyde (Note 1) and 5.5 g. (0.055 mole) of hydantoin (Note 2) is placed in a 250-ml. round-bottomed flask. Dry piperidine (10 ml.) is added, a reflux condenser protected by a calcium chloride tube is fitted to the flask, and the flask is immersed in an oil bath so that the level of the reaction mixture is the same as the oil level of the bath. The oil bath is heated slowly to 130° and is held at this temperature for 30 minutes; foaming and gentle boiling occur. The reaction mixture is cooled, and 200 ml. of water at about 60° is added. The contents of the flask are stirred by means of a glass rod until a clear red solution is obtained (Note 3). Any traces of tarry material are removed by filtration. The solution is cooled to room temperature, transferred to an Erlenmeyer flask, and acidified by dropwise addition of 20 ml. of 12*N* hydrochloric acid. The mixture stands at room temperature a few hours, and then the yellow precipitate of 5-(*p*-hydroxybenzal)hydantoin is collected on a Büchner funnel and washed thoroughly with cold water (Note 4). After being dried in a vacuum desiccator over potassium hydroxide, the crude hydantoin weighs 8.5–8.8 g. (83–86%). It melts at 310–315° (dec.) and is sufficiently pure for the next step and other preparative purposes (Note 5).

B. *p-Hydroxyphenylpyruvic acid*. Crude 5-(*p*-hydroxybenzal)hydantoin (8.5 g., 0.042 mole) and a few chips of porous plate are placed in a 500-ml., three-necked, round-bottomed flask fitted with a reflux condenser, a dropping funnel, and a gas-inlet tube (Note 6). A slow stream of oxygen-free nitrogen (Note 7) is introduced. As soon as the air has been swept out of the apparatus, 240 ml. of 20% aqueous

sodium hydroxide solution (w/v) is added through the dropping funnel. The mixture is boiled for 3 hours in an oil bath at 170–180° (Note 8). The 5-(*p*-hydroxybenzal)hydantoin dissolves rapidly, and a clear orange solution is obtained that becomes less deeply colored during the reaction. The reaction mixture is cooled by replacing the oil bath by a bath of cold water. Without interrupting the stream of nitrogen, 100 ml. of 12*N* hydrochloric acid is added through the dropping funnel at such a rate that foaming and heating of the mixture are not excessive. The flask is disconnected, and 5 g. of sodium bicarbonate is dissolved in the mixture (Note 9).

The liquid is transferred to a continuous extractor (Note 10) and extracted with ether until the supernatant layer of ether remains colorless (about 2 hours). The ethereal extract is discarded (Note 11). The aqueous solution is transferred to a 1-l. beaker and acidified by the cautious addition of 60 ml. of 12*N* hydrochloric acid (Note 12). The solution is returned to the extractor, which is attached to a tared round-bottomed flask. The solution is extracted with ether until no more *p*-hydroxyphenylpyruvic acid is obtained (Note 13). The undried ether solution is evaporated to dryness on a boiling water bath to give crude *p*-hydroxyphenylpyruvic acid as a pale-yellow crystalline mass. The mass is broken up with a spatula, and the flask is kept over potassium hydroxide in a vacuum desiccator until its weight is constant. The yield of crude acid is 6.9–7.2 g. (92–96%). It melts at 210–215° (dec.) (Note 14).

Twelve milliliters of water for each gram of the crude acid (83–86 ml.) is added to the flask, which is then attached to a reflux condenser and immersed in an oil bath at 150°. After 10–20 minutes of boiling, a clear pale-yellow solution is obtained. This is filtered through a fluted filter into an Erlenmeyer flask. After crystallization has started, 8.3–8.6 ml. of 12*N* hydrochloric acid (1.2 ml. of acid for each gram of crude acid) is added, and the mixture is allowed to cool slowly to room temperature, during which period it is occasionally agitated. Crystallization is completed by keeping the flask in a refrigerator for at least 10 hours. The product is separated by suction filtration and washed with a small amount of ice water. The purified *p*-hydroxyphenylpyruvic acid weighs 4.4–4.7 g. (59–63%) and melts at 216–218° (dec.) (Note 14) and (Note 15).

2. Notes

1. The *p*-hydroxybenzaldehyde used was a commercial product (practical grade) melting at 114–117°.
2. Hydantoin can be prepared in a variety of ways, notably from glycine[2] or ethyl aminoacetate[3] and potassium cyanate. The checkers used Eastman Kodak "white label" hydantoin.
3. Because of the viscous nature of the reaction mixture, which sometimes shows a tendency to crystallize, this is a slow process, but a mechanical stirrer is not required.
4. The checkers found that three or four cold-water washes are sufficient to wash the precipitate to neutral pH.
5. Further purification may be achieved by crystallization from acetic acid (50 ml. per g.). A product melting at 315° (dec.) is obtained.
6. The inlet tube, preferably in the center neck, is placed in such a way that it nearly touches the bottom of the flask. Thereby nitrogen bubbles effect some agitation of the reaction mixture and prevent bumping of the boiling solution.
7. *p*-Hydroxyphenylpyruvic acid is rapidly oxidized in alkaline solution. Commercially available compressed nitrogen may be used if the gas is further purified by passage through an alkaline solution of pyrogallol (45 g. of pyrogallol dissolved in 300 ml. of 50% sodium hydroxide solution).
8. This should be done in a hood because ammonia is evolved.
9. The purpose of the first extraction is to remove phenolic impurities. Care should be taken to adjust to the proper pH range (6–7). At this pH the solution changes in color from orange to yellow. A small amount of a flocculent precipitate is formed, but, to avoid longer contact of the solution with air, it is not filtered off.

10. A convenient type of extractor is described in *Organic Syntheses*.[4] The submitter improved the efficiency of the extractor by stirring the aqueous phase with a magnetic stirrer. The inner tube had no filter on the lower end of it and was suspended so that this end was about 1 cm. above the magnetic stirring bar. Tests show that magnetic stirring of the aqueous phase increases the speed of extraction by a factor of 2 to 3. It is convenient to use an extractor of such size that the same apparatus can be used for both extractions. A greater volume of solution must be handled in the second extraction than in the first because of the addition of hydrochloric acid.

11. Evaporating the ethereal solution yields not more than 0.3 g. of brown tarry material consisting mostly of impure *p*-hydroxybenzaldehyde.

12. Carbon dioxide and fumes of ether are evolved during the addition of the acid. The solution is stirred by means of a glass rod until the foaming ceases.

13. This is a slow process, and the extraction time depends on the type of extractor used. With stirring as described in (Note 10), practically quantitative extraction of *p*-hydroxyphenylpyruvic acid can be achieved within 6 hours. Extremely long extraction times may cause decomposition of the product.

14. The checkers observed a decomposition point of 198–202° for the crude acid, 211–214° for the purified acid.

15. A second crystallization from 10 parts of water raises the melting point of the acid to 220°. Any prolonged contact of the hot solution with air will cause some decomposition, notably the formation of traces of *p*-hydroxybenzaldehyde. The checkers preferred crystallization from 10 parts of glacial acetic acid and 10 parts of 12*N* hydrochloric acid,[5] from which solvent a white product was recovered in 75% yield; m.p. 220° (dec.).

The purity of the *p*-hydroxyphenylpyruvic acid may be checked by paper chromatography. By the ascending method on Schleicher and Schüll paper No. 2043b and *n*-butanol-acetic acid-water (4:1:1) as solvent, the following R_f values are obtained: *p*-hydroxyphenylpyruvic acid, 0.71; *p*-hydroxybenzaldehyde, 0.85. Sprays: 2,4-dinitrophenylhydrazine (0.2% in 2*N* hydrochloric acid) and Folin-Denis reagent.[6]

3. Discussion

p-Hydroxyphenylpyruvic acid has been prepared by alkaline hydrolysis of the azlactone of α-benzoylamino-*p*-acetoxycinnamic acid[7] and by a two-step hydrolysis of the azlactone of α-acetamino-*p*-acetoxycinnamic acid.[8] *p*-Hydroxyphenylpyruvic acid has also been prepared by alkaline hydrolysis of 5-(*p*-hydroxybenzal)-3-phenylhydantoin.[9] The procedure described here is adapted from published directions for the preparation of *p*-hydroxyphenylpyruvic-3-C^{14} acid.[5] 5-(*p*-Hydroxybenzal)hydantoin is prepared according to the method of Boyd and Robson.[10]

4. Merits of the Preparation

p-Hydroxyphenylpyruvic acid plays an important role in the biogenesis of compounds with a phenylpropane skeleton, and it has been used as substrate in several enzyme studies. Published procedures for its preparation are unsatisfactory in many ways. The alkaline hydrolysis of the azlactone of α-benzoylamino-*p*-acetoxycinnamic acid[7] makes necessary a tedious separation of the resulting benzoic acid, and the yield is only 34% based on *p*-hydroxybenzaldehyde. The hydrolysis of 5-(*p*-hydroxybenzal)-3-phenylhydantoin[9] requires a separation of phenylurea. Finally, the two-step cleavage of the azlactone of α-acetamino-*p*-acetoxycinnamic acid[8] does not proceed easily, and impure products are obtained. In applying this procedure to the synthesis of a carboxyl-labeled *p*-hydroxyphenylpyruvic acid, the overall yield was only 9%.[11] It must be kept in mind that any prolonged isolation procedure will cause some decomposition of this sensitive compound.

The method of preparing *p*-hydroxyphenylpyruvic acid presented here has the advantage that only volatile by-products, ammonia and carbon dioxide, are formed. Therefore the compound can be obtained in high purity and good yield. There are no difficulties in decreasing the amounts of starting materials to the millimole scale, as shown by the application of this procedure to the preparation of labeled *p*-hydroxyphenylpyruvic acid.[5]

Finally, this method is of general utility, for alkaline cleavage of analogously substituted hydantoins has given a series of substituted phenylpyruvic acids.[12]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 614
- Org. Syn. Coll. Vol. 6, 78
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

oxygen-free nitrogen

p-hydroxyphenylpyruvic-3-C^{14} acid

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ammonia (7664-41-7)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

potassium hydroxide (1310-58-3)

piperidine (110-89-4)

Glycine (513-29-1)

Phenylurea (64-10-8)

potassium cyanate (590-28-3)

phenylpropane (103-65-1)

2,4-Dinitrophenylhydrazine (119-26-6)

pyrogallol (87-66-1)

hydantoin (461-72-3)

ethyl aminoacetate (459-73-4)

p-hydroxybenzaldehyde (123-08-0)

p-Hydroxyphenylpyruvic acid, Pyruvic acid, p-hydroxyphenyl- (156-39-8)

5-(p-Hydroxybenzal)hydantoin (80171-33-1)

α-benzoylamino-p-acetoxycinnamic acid

α-acetamino-p-acetoxycinnamic acid

5-(p-hydroxybenzal)-3-phenylhydantoin

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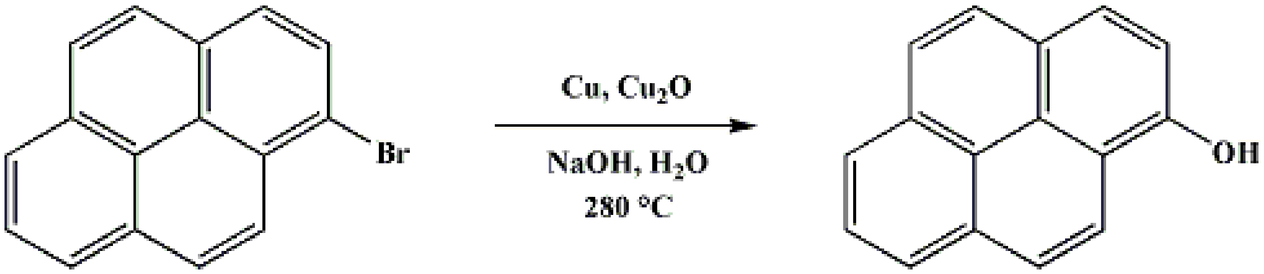
Organic Syntheses, CV 5, 632

3-HYDROXYPYRENE

[1-Pyrenol]



Submitted by W. H. Gumprecht[1]
Checked by William G. Dauben, John R. Wiseman, and Michael H. McGann.

1. Procedure

Caution! Many pyrene derivatives are carcinogens. Contact of the skin with these materials should be avoided.

In a 100-ml. pressure vessel (Note 1) are placed 14.0 g. (0.050 mole) of 3-bromopyrene (Note 2), 0.5 g. of copper bronze powder (Note 3), 1.5 g. of cuprous oxide (Note 4), and 60 ml. of 10% aqueous sodium hydroxide (Note 5). The vessel is sealed, heated rapidly with shaking to 275–280°, and maintained at this temperature for 3 hours. The vessel is allowed to cool and is opened, and the contents are poured into a 500-ml. beaker containing 200 ml. of water (Note 6). The mixture is filtered, and the filter cake is washed with water until the washings become neutral to pH paper. The combined filtrate and washings, which show a blue fluorescence, are made acid to Congo red paper with 20% aqueous sulfuric acid. The precipitate is collected by filtration, washed free of acid with water, and dried in an oven at 100° to give *ca.* 9 g. of a gray solid.

The solid is boiled under reflux with *ca.* 175 ml. of benzene for 1 hour, and the benzene-insoluble material is removed from the hot mixture by filtration through a medium-grade sintered-glass funnel (Note 7). Small portions of activated alumina are added to the hot filtrate until a strong green fluorescence develops; 20–25 g. is needed (Note 8). The mixture is boiled (Note 9) under reflux for 15 minutes and filtered hot. On concentration and cooling, the fluorescent, lemon-yellow filtrate yields 3-hydroxypyrene as light yellow needles, m.p. 179–181°. An additional quantity of equally pure product is obtained by further concentration of the mother liquor. The total yield is 5.5–6.0 g. (50–55%) (Note 10).

2. Notes

1. Stainless steel and Hastelloy-C vessels were used with equivalent results.
2. This material, m.p. 93–95°, is readily prepared in high yields (78–86%) from

commercial pyrene by the method of the submitter,[2] who used pyrene, m.p. 151–153°, obtained from Chemicals Division, Union Carbide Corp.
3. Copper bronze, type 3310, obtained from U.S. Bronze Powder Works, Inc., Flemington, New Jersey, was used. The use of some grades of copper powder leads to a considerably lower yield.
4. Technical grade cuprous oxide obtained from Baker and Adamson Products, General Chemical Division, Allied Chemical Corp., was used.
5. The amount of sodium hydroxide used does not affect the yield, provided that it is present in a quantity well in excess of that required by the stoichiometry.
6. The sodium salt of 3-hydroxypyrene is somewhat insoluble in the reaction mixture. Dilution before filtration ensures its removal from the copper residues.
7. The funnel should be preheated to prevent crystallization of the product in its pores. The filtration process can be accelerated by scraping the muddy cake from the funnel surface.
8. The use of a larger quantity reduces the yield with no significant improvement in quality.
9. The presence of the alumina causes the mixture to bump violently. Agitation of the boiling mixture with a magnetically driven stirring bar helps to alleviate this problem. The vessel should be securely clamped.
10. The submitter obtained 25–29 g. (57–67%) of product when the reaction was run with 56.2 g. (0.20 mole) of the bromide in a 400-ml. pressure vessel.

3. Discussion

This procedure is based on the method of Smith, Opie, Wawzonek, and Prichard[3] for the preparation of 2,3,6-trimethylphenol. 3-Hydroxypyrene has been prepared by fusion of pyrene-3-sulfonic acid with sodium hydroxide[4] and by desulfonation of 3-hydroxypyrene-5,8,10-trisulfonic acid with hot, dilute sulfuric acid.[5]

4. Merits of the Preparation

It has been shown[6] that two mechanisms, elimination-addition (benzyne) and S_N2 displacement, are operative in the liquid-phase hydrolysis of halogenated aromatic compounds. The formation of isomeric phenols as a result of the availability of the benzyne route makes the reaction of limited synthetic value. The incorporation of the copper-cuprous oxide system suppresses reaction via the benzyne route, so that the present method has general utility for the preparation of isomer-free phenols. For example, *p*-cresol is the only cresol formed from *p*-bromotoluene under the conditions of this preparation.

The methods previously reported for the preparation of 3-hydroxypyrene have been found to be unsatisfactory, because of both very poor yields and difficulties in operation.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 147

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alumina

copper bronze

copper bronze powder

sulfuric acid (7664-93-9)

Benzene, benzyne (71-43-2)

sodium hydroxide (1310-73-2)

bromide (24959-67-9)

copper, copper powder (7440-50-8)

cuprous oxide

cresol (95-48-7)

pyrene (129-00-0)

3-Bromopyrene (1714-29-0)

3-Hydroxypyrene, 1-Pyrenol (5315-79-7)

2,3,6-trimethylphenol (2416-94-6)

pyrene-3-sulfonic acid (26651-23-0)

3-hydroxypyrene-5,8,10-trisulfonic acid

copper-cuprous oxide

p-Bromotoluene (106-38-7)

p-CRESOL (106-44-5)

sodium salt of 3-hydroxypyrene

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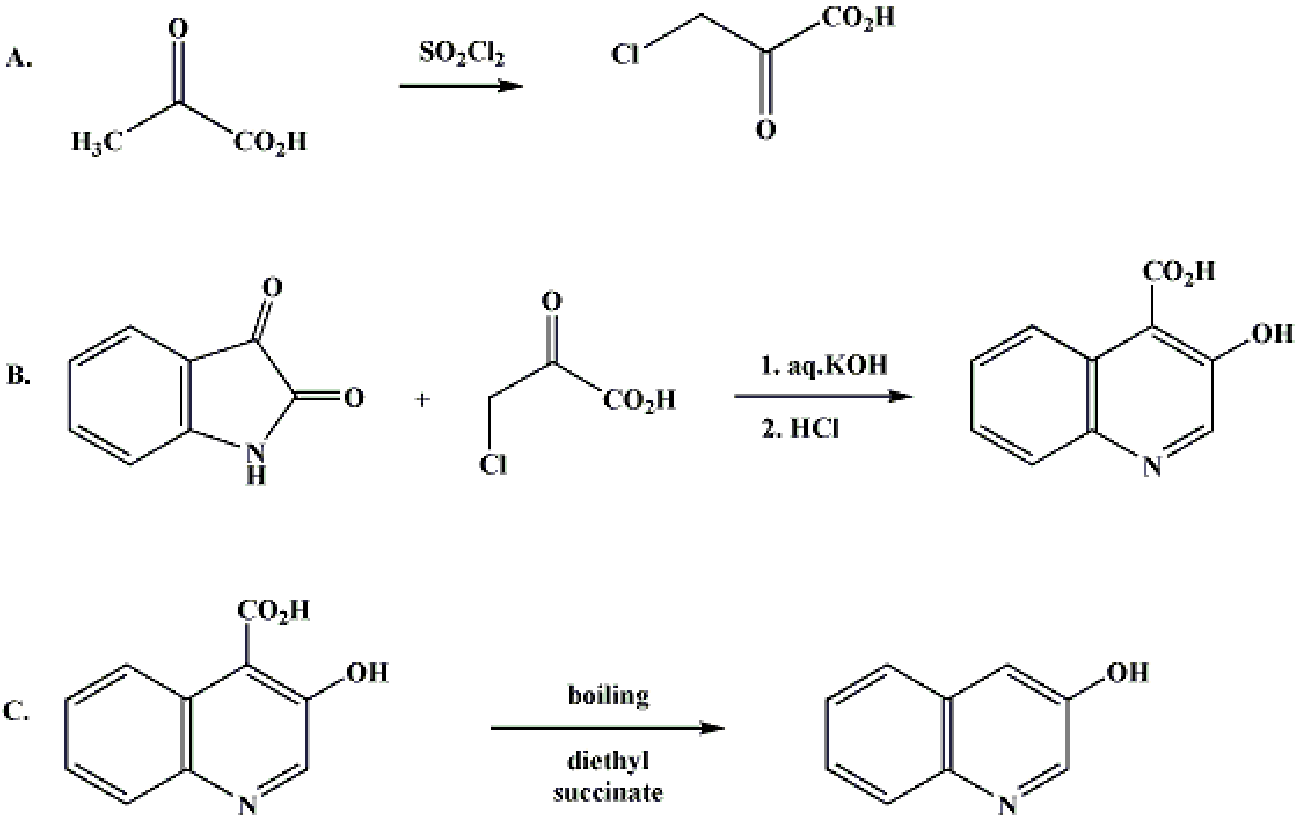
Organic Syntheses, CV 5, 635

3-HYDROXYQUINOLINE

[3-Quinolinol]



Submitted by Edward J. Cragoe, Jr. and Charles M. Robb[1].
Checked by James Cason and James D. Willett.

1. Procedure

Caution! The preparation of chloropyruvic acid should be carried out in a fume hood, as should the purification of 3-hydroxycinchoninic acid and its decarboxylation.

A. *Chloropyruvic acid*. In a 1-l. four-necked flask (Note 1) fitted with a sealed mechanical stirrer, dropping funnel, thermometer, and reflux condenser protected with a calcium chloride tube is placed 249 g. (2.83 moles) of pyruvic acid (Note 2). The stirrer is started and 394 g. (2.92 moles) of sulfuryl chloride (Note 3) is added dropwise over a period of 2 hours. During the addition the temperature is maintained at 25–30° by cooling with a water bath.

The mixture is stirred at room temperature for an additional 60 hours (Note 4), during which time the calcium chloride tube may become spent and need replacement. The viscous, light-yellow liquid product is transferred to a large crystallizing dish and dried in a vacuum desiccator over soda-lime for about 24 hours (Note 5).

The yield of light-yellow chloropyruvic acid is 333–340 g. (96–98%) (Note 6).

B. *3-Hydroxycinchoninic acid*. A 3-l., four-necked flask (Note 1) is equipped with a sealed mechanical stirrer, gas inlet tube, gas outlet consisting of a 1-mm. capillary (Note 7), and thermometer. The flask is charged with a freshly prepared solution containing 448 g. (8 moles) of reagent grade (85% minimum

assay) potassium hydroxide and 900 ml. of water. The solution (hot from dissolution of potassium hydroxide) is stirred and 147 g. (1 mole) of isatin (Note 8) is introduced. The solid quickly dissolves to give an orange-yellow solution.

After replacement of the gas outlet the flask is flushed with nitrogen, and a nitrogen atmosphere is maintained during the remaining operations (Note 9). The temperature is maintained at 20–25° by cooling when necessary. The solution is stirred vigorously as 168.5 g. (1.375 moles) of chloropyruvic acid (part A) is added gradually over a period of 2 hours (Note 10). After stirring has been continued for an additional hour, the introduction of nitrogen and the stirring are terminated, the flask is stoppered, and the mixture is allowed to stand at room temperature for 6 days.

At the end of the standing period the reaction mixture is cooled with stirring and maintained at 15–18°. A solution containing 34 g. of sodium bisulfite in 60 ml. of water (Note 11) is added, and the mixture is made acid to Congo red paper by the dropwise addition of reagent grade concentrated hydrochloric acid (Note 12) (approximately 480 ml.). The yellow product that precipitates is separated by suction filtration on a large (at least 15-cm.) Büchner (or sintered-glass) funnel and washed with water saturated with sulfur dioxide. Drainage of the filter cake, whose consistency is that of putty, is slow. Pressing with a large cork or use of a rubber dam is helpful. The pressed solid is suspended in 1.3 l. of water previously saturated with sulfur dioxide, and the mixture is mechanically stirred for 30 minutes.

After the product has been collected as before, the filter cake is pressed well, suspended in 800 ml. of water, and dissolved by stirring and adding the minimum quantity of reagent grade concentrated aqueous ammonia (approximately 60 ml.). A small amount of insoluble material is removed by filtration. A saturated solution of 8 g. of sodium bisulfite is added to the filtrate. The orange-yellow solution is stirred mechanically and made acid to Congo red paper by the dropwise addition of reagent grade concentrated hydrochloric acid (approximately 80 ml.).

The product is again collected by filtration, washed with water, resuspended in 225 ml. of water, collected, and pressed as dry as possible. The filter cake is thoroughly dispersed in 160 ml. of absolute alcohol, then filtered, air-dried, and finally dried in a vacuum desiccator over concentrated sulfuric acid. The bright-yellow solid is pulverized and redried. The yield is 115–135 g. (60–71%). When this product is inserted in a bath preheated to 210° and the temperature is increased at a rate of 1° per 10 seconds, decomposition with evolution of gas occurs at 219–220° (cor.) (Note 13).

C. *3-Hydroxyquinoline*. A 1-l. beaker is fitted with a thermometer and mechanical stirrer and clamped firmly on an efficient electric heater (Note 14). Diethyl succinate (400 ml.) (Note 15) is placed in the beaker and heated to boiling (215–220°) with stirring. 3-Hydroxycinchoninic acid (part B) (94.6 g., 0.5 mole) is added in portions to the boiling solution by means of a metal spoon or Scoopula. Care is taken to prevent too vigorous evolution of carbon dioxide. The addition requires 2–3 minutes, during which time a temperature drop is noted unless good heating is maintained.

Stirring and boiling are continued until complete solution is effected. This requires about 6 minutes (Note 16). The stirrer is withdrawn and the beaker is removed from the hot plate for a few minutes. Finally, the solution is stirred and cooled first in a warm water bath and then in an ice bath. After 30 minutes the gray-brown solid is collected by suction filtration and washed with hexane. The product is suspended in 250 ml. of hexane, filtered, and washed with hexane. After drying, the crude gray-colored 3-hydroxyquinoline weighs 57–63 g. (79–87%), m.p. 175–191° (cor.).

The crude product is suspended in 190 ml. of water and dissolved by the addition of the minimum quantity (31–35 ml.) of concentrated hydrochloric acid. The solution is filtered in order to remove a small amount of insoluble material. The filtrate is treated with decolorizing carbon (about 3.5 g.), allowed to stand for 30 minutes, and filtered. The filtrate from the charcoal is stirred and treated dropwise with concentrated aqueous ammonia (25–29 ml.) until precipitation is complete. The precipitate is removed by filtration, washed with water (two 30-ml. portions), and dried. The yield at this

stage is 48–55 g. of material melting at 185–195° (cor.).

The reprecipitated product is pulverized, dissolved in a boiling mixture of methanol (about 420 ml.) and water (about 360 ml.), and treated with decolorizing charcoal for about 10 minutes. The boiling mixture is filtered through a fluted filter paper placed on a large Pyrex funnel resting on a wide-mouthed Erlenmeyer flask containing a little boiling solvent of the same composition. The filtrate is concentrated to incipient precipitation (about 600 ml. volume) and allowed to cool. After drying, the yield of tan-colored crystalline 3-hydroxyquinoline is 44–47 g. (61–65%), m.p. 199–200° (cor.) (Note 17).

2. Notes

1. If suitable dual outlets are used, a three-necked flask is satisfactory.
2. Pyruvic acid from Matheson, Coleman and Bell was distilled just before use. Material boiling at 46–47° at 4 mm. was employed.
3. Technical grade sulfuryl chloride from Matheson, Coleman and Bell was found satisfactory.
4. The stirring prevents foaming and promotes the evolution of the gases.
5. It is advisable to change the desiccant at least once during the drying period.
6. The chloropyruvic acid prepared in this manner is satisfactory for use in the next reaction without purification. If often crystallizes to form a waxy solid or semisolid which is quite hygroscopic. The pure anhydrous material is reported[2] to melt at 45°, while the monohydrate obtained by other methods[3,4,5] melts at 57–58°. The chloropyruvic acid is normally used immediately, but it has been stored successfully in a desiccator at room temperature for a few days or for longer periods in an airtight container in the refrigerator. Material which has been stored for long periods gives poorer yields in the Pfitzinger reaction (part B) than that which has been freshly prepared.
7. When solids are added to the flask, the gas outlet is replaced by a powder funnel and nitrogen flow is increased slightly. If a separatory funnel is used (cf. (Note 10)), a dual outlet is needed.
8. Commercial isatin from Eastman Kodak or Matheson, Coleman and Bell has been used, but poorer yields are obtained (about 10% less) than when purified material is employed. Purification by reprecipitation[6] or by recrystallization from glacial acetic acid[6] is equally satisfactory.
9. Maintaining an atmosphere of nitrogen minimizes the darkening of the reaction mixture due to air oxidation.
10. If the chloropyruvic acid remains essentially as a viscous liquid, it may be introduced via a dropping funnel containing a large-bore stopcock. If the material has set up to a waxy solid, it must be introduced in portions through a powder funnel.
11. If no precautions are observed, the reaction mixture rapidly darkens after acidification when exposed to air. The sulfur dioxide generated upon acidification of the sodium bisulfite largely prevents this discoloration; however, the precipitated product should be collected *without delay* of more than a few hours. The sulfur dioxide used in the wash water also protects the product.
12. At about the midpoint in the addition of acid, frothing tends to raise the precipitate out of the flask. Addition of a 1-ml. portion of ether controls the frothing. A second portion of ether may be required later, but the frothing subsides as the addition proceeds.
13. 3-Hydroxycinchoninic acid of this purity is adequate for decarboxylation. A sample recrystallized from dimethylformamide or 5*N* hydrochloric acid decomposes at 224° when observed as described before.
14. It is advantageous to use a mechanical stirrer, but successful reactions have been carried out using manual stirring. A run in which no stirring was employed gave acceptable results.
15. Commercial diethyl succinate from Carbide and Carbon Chemicals Co. or from Eastman Organic Chemicals was found satisfactory. Nitrobenzene has been used successfully a number of times; however, it is considered a less desirable solvent to handle.
16. The heating time is kept to a minimum in order to reduce the darkening of the solution, which increases as the heating time is extended.
17. Once recrystallized, 3-hydroxyquinoline is pure enough for most purposes. One or two more

recrystallizations are required to produce white crystals, m.p. 201–202° (cor.).

3. Discussion

The method of synthesis described for chloropyruvic acid is essentially that reported.[2] This procedure affords the product in excellent yields from readily available materials by a short, convenient route. Other less acceptable methods involve chlorination of pyruvic acid with sulfur dichloride[7] or hypochlorous acid[8] and the treatment of ethyl chloro(1-hydroxyheptyl)- or (α-hydroxybenzyl) oxalacetate γ-lactone with 50% hydrochloric acid.[3,4,5]

The procedure described for the preparation of 3-hydroxycinchoninic acid is adapted from that reported.[9] This synthesis is successful when bromopyruvic acid or its ethyl ester is substituted for chloropyruvic acid.[9] The reaction of isatin with chloropyruvic acid to produce 3-hydroxycinchoninic acid has been reported;[10] however, no details or physical properties were given. This method offers a decided advantage over the method involving diazotization of the difficultly accessible 3-aminocinchoninic acid.[11]

Until recent years the only syntheses of 3-hydroxyquinoline involved multistep processes, the last step of which consisted of the conversion of 3-aminoquinoline to 3-hydroxyquinoline via the diazonium salt.[12,13,14] Small quantities of quinoline have been oxidized to 3-hydroxyquinoline in low yields by using oxygen in the presence of ascorbic acid, ethylenediaminetetraacetic acid, ferrous sulfate, and phosphate buffer.[15] The decarboxylation of 3-hydroxycinchoninic acid in boiling nitrobenzene has been reported.[9,11] The procedure described involves a simplified modification of this method.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

soda-lime

ethyl chloro(1-hydroxyheptyl)- or (α-hydroxybenzyl)oxalacetate γ-lactone

alcohol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ammonia (7664-41-7)

methanol (67-56-1)

ether (60-29-7)

sulfur dioxide (7446-09-5)

oxygen (7782-44-7)

nitrogen (7727-37-9)

ferrous sulfate (13463-43-9)

sodium bisulfite (7631-90-5)

carbon dioxide (124-38-9)

decolorizing carbon (7782-42-5)

sulfuryl chloride (7791-25-5)

potassium hydroxide (1310-58-3)

Nitrobenzene (98-95-3)

hypochlorous acid (7790-92-3)

Quinoline (91-22-5)

Isatin (91-56-5)

Pyruvic acid (127-17-3)

sulfur dichloride (10545-99-0)

dimethylformamide (68-12-2)

hexane (110-54-3)

Diethyl succinate (123-25-1)

phosphate

3-Hydroxyquinoline, 3-Quinolinol (580-18-7)

Chloropyruvic acid (3681-17-2)

3-Hydroxycinchoninic acid (118-13-8)

bromopyruvic acid (1113-59-3)

3-aminocinchoninic acid

3-aminoquinoline (580-17-6)

ethylenediaminetetraacetic acid (60-00-4)

ascorbic acid

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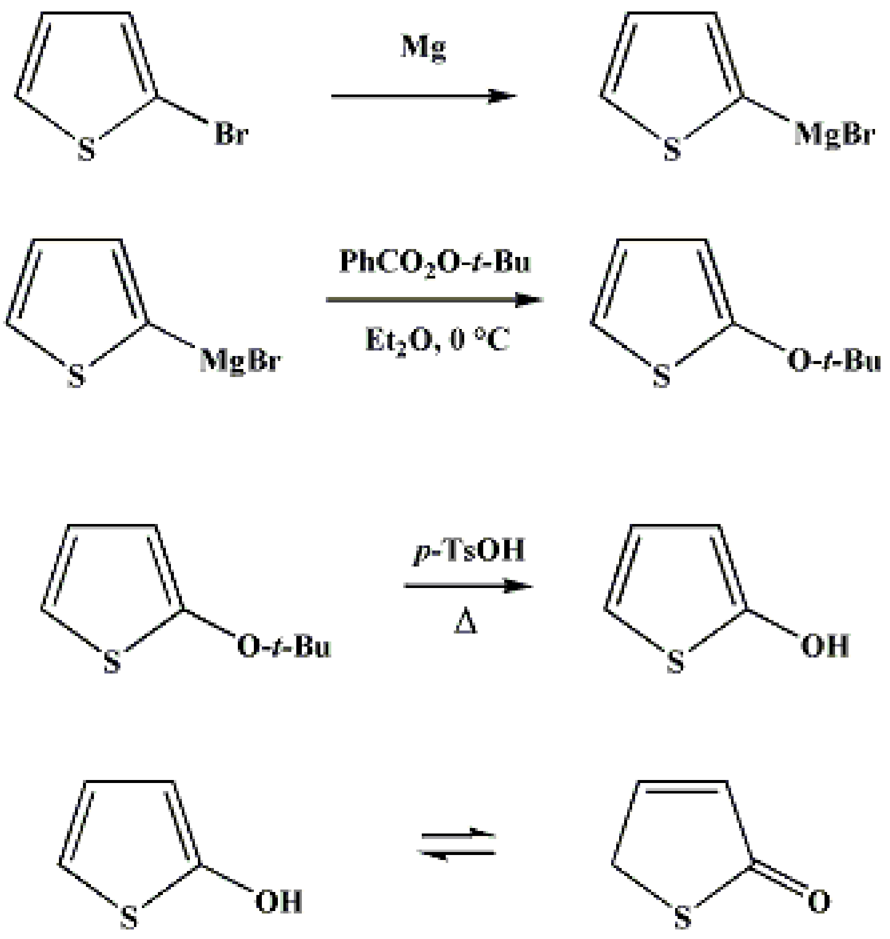
Organic Syntheses, CV 5, 642

2-HYDROXYTHIOPHENE

[Thiophene-2-ol and 2(5H)-thiophenone]



Submitted by C. Frisell and S.-O. Lawesson[1].
Checked by R. M. Scribner, C. G. McKay, and B. C. McKusick.

1. Procedure

A. *2-t-Butoxythiophene*. A dry 1-l. three-necked flask is fitted with a mechanical stirrer (Note 1), a reflux condenser having a take-off attachment, and a 250-ml. dropping funnel with a pressure-equalizing side tube.[2] A nitrogen-inlet tube is connected to the top of the condenser, and a T-tube branch of this is led to a mercury valve. The latter consists of a U-tube the bend of which is just filled with mercury.

Ten grams (0.41 g. atom) of magnesium turnings (Note 2) is placed in the flask and covered with 200 ml. of dry ether. Ten milliliters of a solution of 65.2 g. (0.40 mole) of 2-bromothiophene in 60 ml. of dry ether is added, the Grignard reaction is started by gently warming the reaction flask, and the remainder of the solution is added dropwise during 45 minutes. The mixture is stirred for 3.5 hours, the last 15 minutes under reflux. The Grignard reagent is cooled to 0–5° by immersing the flask in ice

water. *t*-Butyl perbenzoate (62 g., 56 ml., 0.32 mole) (Note 3) in 100 ml. of dry ether is added dropwise during 45 minutes to the stirred ice-cooled mixture. The reaction mixture is stirred overnight, poured into ice water, and acidified with concentrated hydrochloric acid. The two phases are separated, and the water phase is twice extracted with ether. The combined ether solutions are extracted with three 60-ml. portions of 2*N* sodium hydroxide solution (Note 4), washed until neutral with water, dried over anhydrous sodium sulfate, and transferred to a distillation flask equipped with a Vigreux column. *Caution! The ether extract should not be distilled unless a test shows that peroxides are absent (Note 5).* The ether is distilled off at atmospheric pressure, and the residual oil is distilled under reduced pressure to give 35–38 g. (70–76%) of 2-*t*-butoxythiophene, b.p. 64–66°/13 mm., n_D^{20} 1.4991.

B. *2-Hydroxythiophene*. The 2-*t*-butoxythiophene obtained in Step A is placed in a distillation flask equipped with a short Vigreux column and a capillary inlet for nitrogen, and 0.1 g. of *p*-toluenesulfonic acid is added. The apparatus is placed in an oil bath at 155°. Decomposition begins immediately. After 5–10 minutes the oil bath is removed, and the distillation assembly is connected to a water pump (Note 6). 2-Hydroxythiophene is distilled under reduced pressure, nitrogen gas being drawn through the capillary during the whole procedure (Note 7). 2-Hydroxythiophene is collected at 91–93°/13 mm.; yield 20–23 g. (89–94%); n_D^{20} 1.5613 (Note 8).

2. Notes

1. Although a mercury seal is preferable, a rubber tube lubricated with glycerol is an adequate seal.
2. Common laboratory magnesium is as satisfactory as extremely pure sublimed magnesium.
3. *t*-Butyl perbenzoate is supplied by Lucidol Division, Wallace and Tiernan, Inc., Buffalo, New York, and Light and Co., Colnbrook, Bucks, England.
4. Acidification of the basic solution gives 29–32 g. (80–88%) of benzoic acid if the reaction has proceeded properly.
5. To make a peroxide test, place a few milligrams of sodium iodide, a trace of ferric chloride, and 2–3 ml. of glacial acetic acid in a test tube and carefully add 1–2 ml. of the ether solution. When unconsumed perbenzoate is present, a yellow ring is immediately formed between the two phases. *If this test indicates the presence of peroxide, the extract should not be concentrated and distilled until it has been extracted first with a solution of potassium iodide in acetic acid to remove peroxide and then with aqueous sodium thiosulfate to remove iodine*.
6. The decomposition is considered to be complete when the pressure is constant.
7. 2-Hydroxythiophene resinifies on prolonged exposure to air.
8. It has recently been shown that 2-hydroxythiophene exists mainly as 2(5H)-thiophenone at room temperature.[3]

3. Discussion

The procedure described is essentially that of Lawesson and Frisell.[4] 2-Hydroxythiophene has been prepared in low yields by Hurd and Kreuz[5] from 2-thienylmagnesium bromide and oxygen in the presence of excess isopropylmagnesium bromide.

4. Merits of the Preparation

The first step of the procedure illustrates a general way of preparing aryl *t*-butyl ethers.[4,6] The second step is the best way to prepare 2-hydroxythiophene, inasmuch as the yield is good and *t*-butyl perbenzoate is a readily available perester that is relatively stable. The same procedure has been used to convert several other haloaromatic compounds to hydroxyaromatic compounds in good yield[4] and is probably quite general.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

t-butyl perbenzoate

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ether (60-29-7)

sodium hydroxide (1310-73-2)

glycerol (56-81-5)

magnesium, magnesium turnings (7439-95-4)

sodium sulfate (7757-82-6)

oxygen (7782-44-7)

potassium iodide (7681-11-0)

sodium thiosulfate (7772-98-7)

nitrogen (7727-37-9)

Benzoic acid (65-85-0)

mercury (7439-97-6)

iodine (7553-56-2)

ferric chloride (7705-08-0)

sodium iodide (7681-82-5)

isopropylmagnesium bromide (920-39-8)

2-Bromothiophene (1003-09-4)

2-thienylmagnesium bromide

t-Butyl (1605-73-8)

2-Hydroxythiophene, Thiophene-2-ol (17236-58-7)

2(5H)-thiophenone

p-toluenesulfonic acid (104-15-4)

2-t-butoxythiophene (23290-55-3)

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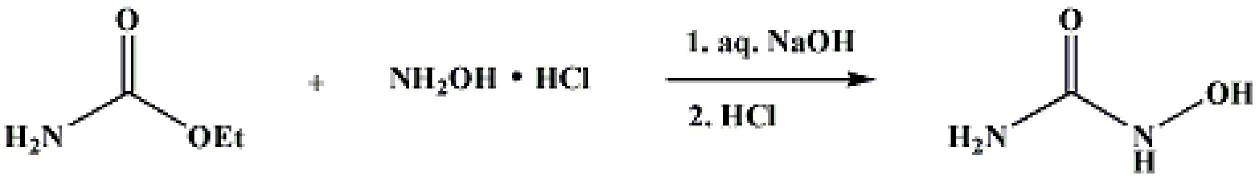
Organic Syntheses, CV 5, 645

HYDROXYUREA

[Urea, hydroxy-]



Submitted by R. Deghenghi[1]
Checked by Melvin S. Newman and John Eberwein.

1. Procedure

To a solution of 20.8 g. (0.3 mole) of hydroxylamine hydrochloride and 20.6 g. (0.5 mole) of sodium hydroxide (98%) in 100 ml. of water is added 22.26 g. (0.25 mole) of ethyl carbamate. After 3 days at room temperature the solution is cooled in an ice bath and carefully neutralized with concentrated hydrochloric acid (Note 1). If necessary (Note 2), the solution is filtered and then extracted with ether; the aqueous phase is evaporated on a water bath under reduced pressure as rapidly as possible at a temperature not above 50–60°.

The dry residue is extracted by boiling with 100 ml. of absolute ethanol, and the solution is filtered through a heated funnel. On cooling, a first crop (6–8 g.) of hydroxyurea crystallizes.

The saline residue on the filter is extracted once again with 50 ml. of boiling absolute ethanol. On concentrating the filtrate from the second extraction and the mother liquor from the first crystallizate to a small volume, a second crop (4–6 g.) of product is obtained. The yield of the hydroxyurea is 10–14 g. (53–73%) of white crystals, m.p. 137–141° (dec.).

The product may be purified by recrystallization of 10 g. from 150 ml. of absolute ethanol. The rate of solution is slow (15–30 minutes is required), and the yield of hydroxyurea, m.p. 139–141° (dec.), is about 8 g. (Note 3).

2. Notes

1. Neutralization to phenolphthalein is satisfactory, but a glass electrode might give better results. Hydroxyurea is decomposed very rapidly in aqueous acidic medium, whereas its metallic salts (sodium or the copper complex salts) are stable.
2. Insoluble matter is sometimes present if a commercial grade of reactants is employed.
3. It is preferable to store the crystals in a cool, dry place. Some decomposition

may occur after a few weeks.

3. Discussion

The improved method herein described is adapted from the procedure of Runti and Deghenghi.[2] Hydroxyurea has been prepared from potassium cyanate and hydroxylamine hydrochloride.[3,4,5] A lower melting isomeric substance, m.p. 71°, has been described.[4,5,6] The structure $NH_2CO_2NH_2$ has been proposed[5,6] for this low-melting substance.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium hydroxide (1310-73-2)

Hydroxylamine hydrochloride (5470-11-1)

phenolphthalein (77-09-8)

potassium cyanate (590-28-3)

ethyl carbamate (51-79-6)

Hydroxyurea, Urea, hydroxy- (127-07-1)

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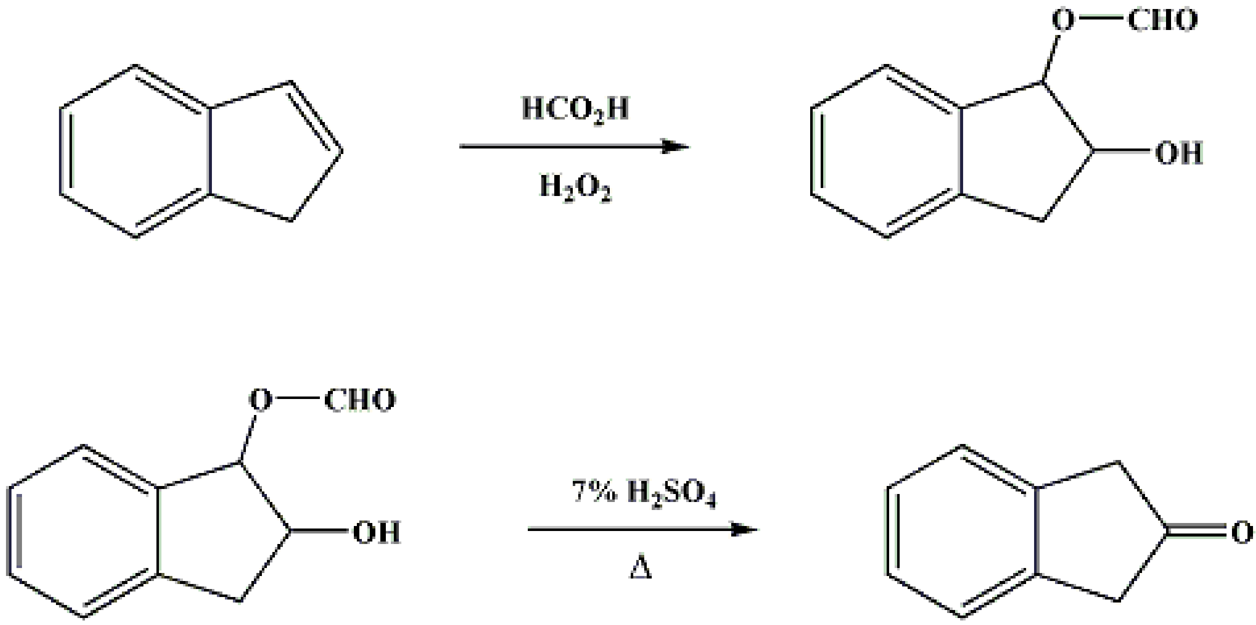
Organic Syntheses, CV 5, 647

2-INDANONE



Submitted by J. E. Horan and R. W. Schiessler[1].
Checked by William E. Parham, Wayland E. Noland, and Abdel-Moneim M. Makky.

1. Procedure

In a 2-l. three-necked flask fitted with stirrer, dropping funnel, and thermometer are placed 700 ml. of formic acid (88%) and 140 ml. of hydrogen peroxide (30%, 1.37 moles). While the temperature is kept at 35–40° (Note 1), 116.2 g. (117.3 ml., 1.00 mole) of indene (98%) (Note 2) is added dropwise, with stirring, over a period of 2 hours. An additional 100 ml. of formic acid is used to rinse the last of the indene from the dropping funnel into the reaction flask. The reaction solution is stirred at room temperature for 7 hours to ensure complete reaction (Note 3). The solution is transferred to a 2- or 3-l. Claisen flask, and the formic acid is removed under aspirator pressure (b. p. 35–40°/20–30 mm.), care being taken to maintain the boiler temperature below 60° (Note 4). The residue, after being cooled to room temperature, is a yellowish brown crystalline solid (Note 5), the color being due to contamination by a small amount of brownish oil.

In a 5-l. flask fitted with a long condenser (about 40 cm.) connected to an ice-cooled receiver is placed 2 l. of 7% (by volume) sulfuric acid. The solution is heated to boiling, and the crude monoformate of 1,2-indanediol is added. Steam is introduced and the mixture is steam distilled, while external heat is applied with a flame in order to maintain the boiler contents at a constant volume of 2 l. The steam distillation is carried out at the rate of about 1 l. per hour until 5–6 l. of distillate have been collected and the 2-indanone has stopped distilling (Note 6). The dark-brown oily residue becomes semisolid at room temperature.

The cold distillate is filtered with suction, and the white crystalline solid is sucked thoroughly dry on the filter (Note 7). The crystals are dried further in a vacuum desiccator (at about 1 mm.) at room temperature or below for about 12 hours. The melting point of the 2-indanone is 57–58° (Note 8). The yield is 90–107 g. (69–81%).

2. Notes

1. This is the best temperature at which to control the reaction. At higher temperatures, the reaction becomes too vigorous. The stirrer must be sufficiently powerful to thoroughly mix the phases or a very low yield will result. A Hershberg stirrer has been found to be very effective in this preparation (private communication from H. E. Baumgarten).

2. The indene ($n_D^{25.5}$ 1.5698, b.p. 74–76°/24 mm.) was obtained from Rütgerswerke, A. G., West Germany, through Terra Chemicals, Inc., 500 Fifth Avenue, New York 36, N. Y. It was faintly yellow, but was used without distillation, since distillation, although it removed the yellow color, did not change the refractive index. When Matheson, Coleman and Bell technical grade indene was used (redistilled, $n_D^{25.5}$ 1.5606, b.p. 177–179°), a 45% yield of 2-indanone was obtained.

3. The reaction mixture can be left overnight at this point with no adverse effect upon yield.

4. A higher temperature should be avoided at the start to prevent boilover, and later to reduce side reactions and eliminate danger from possible residual peroxides.

5. The reaction can be interrupted at this point and the formate ester stored for several weeks, if desired.

6. The rate of flow of cooling water through the condenser must be regulated so that the condenser does not become clogged with 2-indanone. The end point of the distillation can be recognized by lack of turbidity in the condensate or of solidification in the condenser when cold water is passed rapidly through the condenser.

7. The steam distillate, with the 2-indanone under water, can be kept for as long as a week in the refrigerator. In the dry state, 2-indanone is unstable to air at room temperature but can be kept in a closed vessel for several days at room temperature and for longer periods (several weeks or more) in a refrigerator.

8. The ultraviolet spectrum in the 300–350 m• region showed that less than 1% of 1-indanone was present. If the 2-indanone darkens on standing, it can be repurified by steam distillation or by crystallization from ethanol.

3. Discussion

2-Indanone was first prepared by distillation of the calcium salt of *o*-phenylenediacetic acid[2,3] and, more recently, by the action of acetic anhydride on its potassium salt.[4] It has been obtained by the dilute sulfuric acid-catalyzed hydrolysis and decarboxylation of 2-iminoindan-1-carboxylate[5] and ethyl 2-indanone-1-carboxylate.[6] 2-Indanone is

commonly obtained by acid-catalyzed dehydration of an indene glycol,[7,8] as illustrated in this preparation. Indene glycol has been obtained from indene via the bromohydrin.[9,10,11,12] The most recent preparation of 2-indanone is by Curtius degradation of 2-indenecarboxylic acid.[13]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

calcium salt of o-phenylenediacetic acid

ethanol (64-17-5)

sulfuric acid (7664-93-9)

acetic anhydride (108-24-7)

formic acid (64-18-6)

hydrogen peroxide (7722-84-1)

1-Indanone (83-33-0)

indene (95-13-6)

2-Indanone (615-13-4)

monoformate

1,2-indanediol

2-iminoindan-1-carboxylate

ethyl 2-indanone-1-carboxylate

indene glycol

2-indenecarboxylic acid

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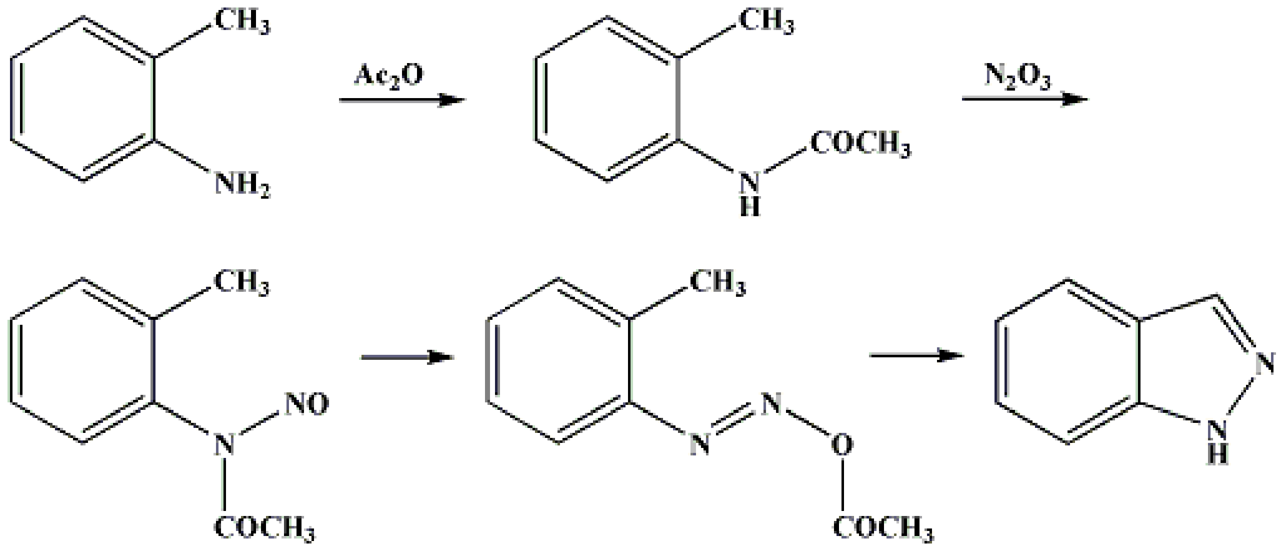
Organic Syntheses, CV 5, 650

INDAZOLE

[Benzopyrazole]



Submitted by Rolf Huisgen and Klaus Bast[1].
Checked by W. E. Parham, Wayland E. Noland, and John W. Drenckpohl.

1. Procedure

Ninety grams (90.2 ml., 0.839 mole) of *o*-toluidine is slowly added to a mixture of 90 ml. of glacial acetic acid and 180 ml. (1.90 mole) of acetic anhydride contained in a 750-ml. two-necked flask equipped with a thermometer and a two-hole cork stopper for a gas inlet tube (Note 1). Acetylation occurs with evolution of heat. The mixture is cooled in an ice bath (Note 2) and nitrosated by rapid admission of a stream of nitrous gases (Note 3). The nitrous gases are obtained by the action of nitric acid (density 1.47) on sodium nitrite (Note 4). Technical grade, large-grain sodium nitrite (180 g.) is placed in a 1-l. suction flask to which a dropping funnel is fitted by means of a rubber stopper (Note 5). The acid (a total of about 250 ml. is used) is added dropwise from the dropping funnel. The rate of the gas evolution should be such that the temperature of the reaction mixture is kept between +1° and +4° (Note 6). The gas is passed through a wash bottle (with inlet and outlet positions reversed) containing some glass wool and positioned between the generating flask and the reaction flask. After about 6 hours the nitrosation is complete, and the solution exhibits a permanent black-green color due to excess N_2O_3 (Note 7).

The solution of N-nitroso-*o*-acetotoluidide is poured onto a mixture of 400 g. of ice and 200 ml. of ice water in a beaker, covered loosely with a watch glass, and allowed to stand in an ice bath for 2 hours. The oil which separates is transferred to a separatory funnel and extracted by shaking with several portions of benzene (total volume 500 ml.). The combined extract is washed with three 100-ml. portions of ice water and, after shaking with 30 ml. of methanol to remove remaining acetic anhydride, is allowed to stand, lightly covered, in an ice bath for 1 hour. Next, the mixture is washed with three 100-ml. portions of ice water, and the cold benzene solution is allowed to stand, loosely covered, over calcium chloride in the refrigerator

overnight (Note 8). The brown solution is decanted from the drying agent into a 3-l. Erlenmeyer flask, and the calcium chloride is washed (by decantation) with 800 ml. of benzene. The combined benzene layer and washings are warmed to 35° in a large water bath and maintained at this temperature for 1 hour (internal temperature, (Note 9)(Note 10)), and then at 40–45° for 7 hours. These temperatures must be strictly adhered to; otherwise overheating can occur (Note 11).

After the completion of the decomposition, the solution is boiled for a short time by heating on a steam bath. The cooled solution is transferred to a separatory funnel and extracted with 200 ml. of 2*N* hydrochloric acid and then with three 50-ml. portions of 5*N* hydrochloric acid. The combined acid extracts are treated with excess ammonia, at which point the indazole precipitates. The mixture is kept in the refrigerator for 2 hours, and the solid is then collected on a Büchner funnel, washed with water, placed in a beaker covered with a piece of paper, and dried overnight at 100–105°. The yield of crude, light brown indazole, m.p. 144–147°, is 36–46 g. (36–47%) (Note 12). For purification, vacuum distillation in a Claisen flask, modified for distillation of solids, is suitable. This gives 33–43 g. of colorless indazole (b.p. 167–176°/40–50 mm.) with a melting point of 148° (Note 13).

2. Notes

1. The inlet tube should not be too narrow and should dip far enough into the reaction mixture to permit agitation of the reaction mixture by the gas stream.
2. Crystallization of *o*-acetotoluidide sometimes occurs at this stage and is allowed to go to completion. This is indicated by a decrease in the evolution of heat of crystallization. Addition of nitrous acid is not begun until the reaction mixture has reached 3°.
3. No harm is done by the separation of *o*-acetotoluidide, which sometimes occurs at this point.
4. The acid (density 1.47) is obtained by diluting 200 ml. of fuming nitric acid with 70 ml. of concentrated nitric acid.
The amount of N_2O_3 in the nitrous gases depends on the density of the nitric acid used. Density 1.40 corresponds to 13 vol. % N_2O_3 or its equivalent. Density 1.43 corresponds to 23 vol. % N_2O_3 or its equivalent. Density 1.45 corresponds to 41 vol. % N_2O_3 or its equivalent. Density 1.47 corresponds to 78 vol. % N_2O_3 or its equivalent.
5. The stopper is covered with a thin layer of paraffin. At the rubber tubing connections, the ends of the glass tubes should be in contact.
6. This is accomplished with an ice bath (without added salt).
7. Should the gas evolution become sluggish after 3–4 hours, the generator may be replaced by a new one containing one-half as much sodium nitrite.
8. It is necessary to begin the preparation early in the morning in order to bring it to this stage in one day.
9. If the water bath is heated by a hot plate controlled by a thermoregulator, it is only necessary to set the temperature at the thermoregulator.
10. At the beginning, the internal temperature is about 5–10° higher than the bath temperature because of the exothermic character of the indazole formation.
11. The use of a large bath simplifies dissipation of the heat of reaction.
12. The submitters regularly obtained yields as high as 55–61% of crude indazole and 52–58% of pure indazole.

13. This pressure range is used in order to give a boiling point sufficiently above the melting point of the indazole.

3. Discussion

The preceding method is that of Huisgen and Nakaten[2] and is based on the preparation of indazole (ca. 40% yield) from N-nitroso-*o*-benzotoluidide discovered by Jacobson and Huber.[3] Mechanistic studies[2] showed this reaction to be an intramolecular azo coupling with an initial acyl shift as the determining step. The yield of indazole from N-nitroso-*o*-benzotoluidide can be made almost quantitative.[2] Since the low solubility of *o*-benzotoluidide makes large quantities of acetic acid and acetic anhydride necessary, the method using the N-acetyl compound described here is more convenient.

With respect to time and cost, this method is superior to the five-step synthesis[4] from anthranilic acid. Older literature sources have been cited in an earlier volume of *Organic Syntheses*.[4] Indazole has also been prepared recently by the reaction of 2-hydroxymethylenecyclohexanone with hydrazine and dehydrogenation of the 5,6,7,8-tetrahydro derivative.[5]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

N_2O_3

N-nitroso-o-benzotoluidide

o-benzotoluidide

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ammonia (7664-41-7)

Benzene (71-43-2)

methanol (67-56-1)

acetic anhydride (108-24-7)

nitric acid (7697-37-2)

sodium nitrite (7632-00-0)

nitrous acid (7782-77-6)

Anthranilic Acid (118-92-3)

hydrazine (302-01-2)

Indazole, Benzopyrazole (271-44-3)

2-Hydroxymethylenecyclohexanone (823-45-0)

o-toluidine (95-53-4)

o-acetotoluidide (120-66-1)

N-nitroso-o-acetotoluidide

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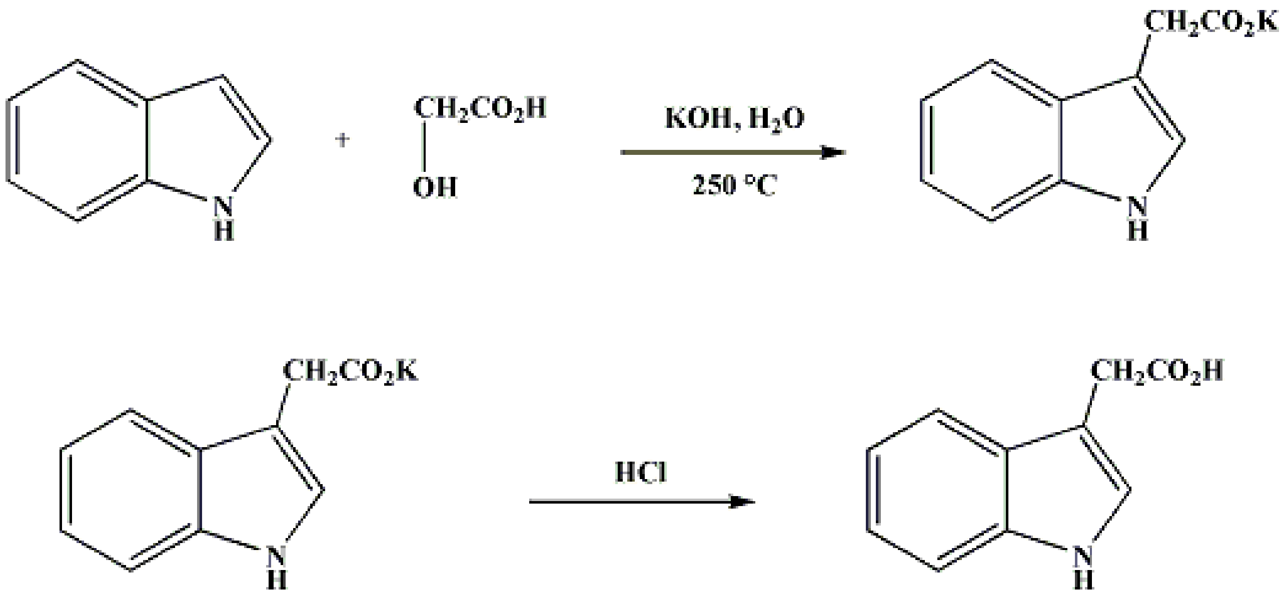
Organic Syntheses, CV 5, 654

INDOLE-3-ACETIC ACID



Submitted by Herbert E. Johnson and Donald G. Crosby[1].
Checked by W. W. Prichard and B. C. McKusick.

1. Procedure

A 3-l. stainless steel, rocking autoclave (Note 1) is charged with 270 g. (4.1 moles) of 85% potassium hydroxide and 351 g. (3.00 moles) of indole (Note 2), and then 360 g. (3.3 moles) of 70% aqueous glycolic acid is added gradually (Note 3). The autoclave is closed and rocked at 250° for about 18 hours (Note 4). The reaction mixture is cooled to below 50°, 500 ml. of water is added, and the autoclave is rocked at 100° for 30 minutes to dissolve the potassium indole-3-acetate. The aqueous solution is cooled to 25° and removed from the autoclave, the autoclave is rinsed out well with water, and water is added until the total volume of solution is 3 l. The solution is extracted with 500 ml. of ether (Note 5). The aqueous phase is acidified at 20–30° with 12*N* hydrochloric acid and then is cooled to 10° (Note 6). The indole-3-acetic acid that precipitates is collected on a Büchner funnel, washed with copious amounts of cold water, and dried in air or a vacuum desiccator out of direct light (Note 7); weight 455–490 g. (87–93%); m. p. 163–165° (dec.).

The indole-3-acetic acid, which is cream-colored, is of high purity. If further purification is desired, it may be done conveniently by recrystallization from water. One liter of water is used for 30 g. of acid, with 10 g. of decolorizing carbon added. Recovery is about 22 g. of a nearly colorless product, m.p. 164–166° (dec.).

2. Notes

1. A stirred autoclave is just as satisfactory. The scale is not critical, for the checkers got equally good results on one-third the scale; they used a 1-l. rocking autoclave.
2. Indole from the Union Carbide Olefins Company, Institute, West Virginia, is satisfactory.
3. If the reactants are added in this order, with the glycolic acid being introduced over a 5–

10 minute period, there is no violent heating because the heat of neutralization is used to melt the indole. An equivalent amount of anhydrous glycolic acid may be used, but this offers no special advantage.
4. These limits are not critical, but they are probably optimum. Reaction times of 24–30 hours are not particularly detrimental, and high yields of product can be obtained within 12 hours. The temperature can range from 230° to 270° with but slight effect on the yield of product.
5. This extraction may be omitted. It does, however, remove traces of neutral material and consequently gives a product with greater color stability.
6. This operation is most conveniently conducted in a flask equipped with a stirrer.
7. The product dries slowly, and several days in air or 24 hours in a vacuum desiccator is usually required. Considerable coloration will result if this is done in direct light. Drying in a heated oven or removing the water as a benzene azeotrope is not satisfactory because of some decarboxylation to skatole. The product should be stored in a dark bottle away from direct sunlight.

3. Discussion

Indole-3-acetic acid has been prepared by the Fischer indole synthesis,[2] by hydrolysis of indoleacetonitrile,[3] from the reaction of gramine-type compounds with cyanide ion under conditions which hydrolyze the nitrile,[4] by the reaction of indole with ethyl diazoacetate followed by hydrolysis,[5] through oxidation of indolepyruvic acid,[6] and by ultraviolet irradiation of tryptophan.[7]

4. Merits of the Preparation

This is the most convenient method of preparing indole-3-acetic acid if an agitated autoclave is available. The method can be used to prepare other indole-3-acetic acids from α-hydroxy acids. For example, α-methylindole-3-acetic acid has been prepared by condensing indole with lactic acid.

Indole-3-acetic acid is a natural plant auxin and is used as a control in research on plant growth.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether (60-29-7)

decolorizing carbon (7782-42-5)

potassium hydroxide (1310-58-3)

lactic acid (50-21-5)

ethyl diazoacetate (623-73-4)

glycolic acid (79-14-1)

tryptophan (73-22-3)

Indole (120-72-9)

Indole-3-acetic acid (87-51-4)

potassium indole-3-acetate (2338-19-4)

indoleacetonitrile

indolepyruvic acid

α-methylindole-3-acetic acid

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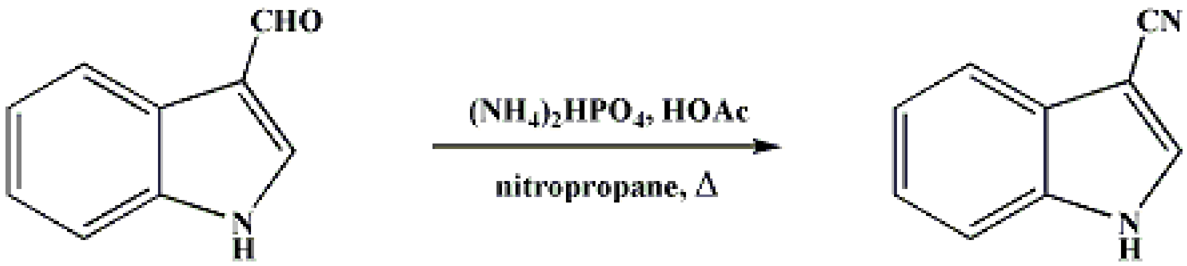
Organic Syntheses, CV 5, 656

INDOLE-3-CARBONITRILE



Submitted by H. M. Blatter, H. Lukaszewski, and G. de Stevens[1].
Checked by Wayland E. Noland and Kent R. Rush.

1. Procedure

A mixture of 1.44 g. (0.0099 mole) of indole-3-carboxaldehyde,[2] 7.0 g. (0.053 mole) of diammonium hydrogen phosphate, 30 g. (30 ml., 0.34 mole) of 1-nitropropane, and 10 ml. of glacial acetic acid is refluxed for 12.5 hours. During the reflux period the pale-yellow mixture becomes dark red. The volatile reactants and solvent are removed under reduced pressure, and an excess of water is then added to the dark residue. After a short time, crude indole-3-carbonitrile precipitates rapidly. It is separated by filtration and dried under reduced pressure; weight 1.20–1.34 g. (85–95%). Crystallization from acetone-hexane, with decolorization by activated carbon, yields 0.68–0.89 g. (48–63%) of fairly pure indole-3-carbonitrile, m.p. 179.5–182.5° (Note 1).

2. Notes

1. The checkers obtained pure indole-3-carbonitrile, m.p. 182–184°, by subliming the product at a pressure of 1.5 mm. (bath temperature 165–170°) and recrystallizing the sublimate from a mixture of acetone and light petroleum ether. The recovery was 84%.

3. Discussion

Indole-3-carbonitrile has been prepared by the dehydration of indole-3-carboxaldehyde oxime,[3,4,5] indole-3-glyoxalic acid oxime,[4,6] or indole-3-carboxamide;[3] by the action of cyanogen chloride on indolylmagnesium iodide;[6] by the reaction of isoamyl formate with *o*-aminobenzyl cyanide in the presence of metallic sodium;[7,8] by mild basic hydrolysis of 1-acetylindole-3-carbonitrile;[7] and by the present method.[9]

4. Merits of the Preparation

This synthetic process is applicable to the preparation of other aromatic nitriles from aldehydes. The submitters have used it to prepare 5-bromoindole-3-carbonitrile, 7-azaindole-3-carbonitrile, *p*-chlorobenzonitrile, 3,4,5-trimethoxybenzonitrile, and *p*-N, N-dimethylaminobenzonitrile.[9] There are several advantages to its use. They include (*a*) readily available and inexpensive reagents, (*b*) a simple, time-saving procedure, and (*c*) fair to good yields of nitrile obtained by a *one-step* method.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

acetic acid (64-19-7)

acetone (67-64-1)

carbon (7782-42-5)

sodium (13966-32-0)

cyanogen chloride (506-77-4)

Indole-3-carboxaldehyde (487-89-8)

isoamyl formate (110-45-2)

Indole-3-carbonitrile (5457-28-3)

diammonium hydrogen phosphate (7783-28-0)

1-nitropropane (108-03-2)

acetone-hexane (821-55-6)

indole-3-carboxaldehyde oxime (2592-05-4)

indole-3-glyoxalic acid oxime

indole-3-carboxamide

indolylmagnesium iodide

1-acetylindole-3-carbonitrile

5-bromoindole-3-carbonitrile

7-azaindole-3-carbonitrile

3,4,5-trimethoxybenzonitrile (1885-35-4)

p-chlorobenzonitrile (623-03-0)

o-aminobenzyl cyanide (2973-50-4)

p-N,N-dimethylaminobenzonitrile (1197-19-9)

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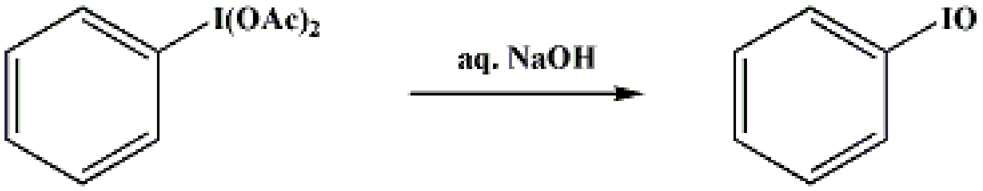
Organic Syntheses, CV 5, 658

IODOSOBENZENE

[Benzene, iodoso-]



Submitted by H. Saltzman and J. G. Sharefkin[1].
Checked by Melvin S. Newman and Narinder Gill.

1. Procedure

Caution! This compound explodes if heated to 210°.

Finely ground iodosobenzene diacetate[2] (32.2 g., 0.10 mole) is placed in a 250-ml. beaker, and 150 ml. of 3*N* sodium hydroxide is added over a 5-minute period with vigorous stirring. The lumps of solid that form are triturated with a stirring rod or spatula for 15 minutes, and the reaction mixture stands for an additional 45 minutes to complete the reaction. One hundred milliliters of water is added, the mixture is stirred vigorously, and the crude, solid iodosobenzene is collected on a Büchner funnel. The wet solid is returned to the beaker and triturated in 200 ml. of water. The solid is again collected on the Büchner funnel, washed there with 200 ml. of water, and dried by maintaining suction. Final purification is effected by triturating the dried solid in 75 ml. of chloroform in a beaker. The iodosobenzene is separated by filtration (Note 1) and air-dried; weight 18.7–20.5 g. (85–93%); m.p. 210° *(Caution! Explodes!)*. Iodometric titration[3] shows the product to be more than 99% pure (Note 2).

2. Notes

1. The filtrate yields unreacted diacetate on evaporation.
2. The purity of the iodosobenzene depends on the purity of the diacetate used.

3. Discussion

Iodosobenzene has been prepared by the action of sodium or potassium hydroxide solution on iodobenzene dichloride[3,4] and by addition of water to the dichloride.[5]

4. Merits of the Preparation

This method of preparing iodosobenzene is preferable to older ones based on

iodosobenzene dichloride because iodosobenzene diacetate[2] is more stable and more conveniently prepared than the dichloride[3] and the overall yield is greater (75% versus 54%).

The procedure seems to be a general way of preparing iodosoarenes with electron-donating substituents, for the submitters have used it to obtain good yields of *o*-, *m*- and *p*-iodosotoluene, 2- and 4-iodoso-*m*-xylene, 2-iodoso-*p*-xylene, *o*-iodosophenetole, and 4-iodosobiphenyl.

Iodosoarenes are useful in the preparation of iodonium salts, $Ar_2I^+X^-$.[6]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 660

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

o-, m- and p-iodosotoluene

2- and 4-iodoso-m-xylene

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

iodobenzene dichloride (2401-21-0)

Iodosobenzene, Benzene, iodoso- (536-80-1)

Iodosobenzene diacetate (3240-34-4)

iodosobenzene dichloride

4-iodosobiphenyl

2-iodoso-p-xylene

o-iodosophenetole

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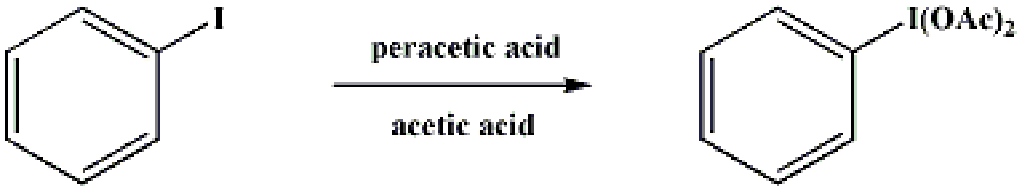
IODOSOBENZENE DIACETATE

[Benzene, iodoso-, diacetate]



Submitted by J. G. Sharefkin and H. Saltzman[1].
Checked by J. Diekmann and B. C. McKusick.

1. Procedure

Caution! Avoid inhaling the vapor of peracetic acid or allowing the liquid to come into contact with the skin. The reaction is best carried out in a hood (Note 1).

The apparatus consists of a 200-ml. beaker equipped with a magnetic stirrer or any other type suitable for stirring a small volume of liquid. The flask is charged with 20.4 g. (0.10 mole) of iodobenzene[2] and is immersed in a water bath maintained at 30° (Note 2). Thirty-six grams (31 ml., 0.24 mole) of commercial 40% peracetic acid (Note 3) is added dropwise to the well-stirred iodobenzene over a period of 30–40 minutes. Stirring is continued for another 20 minutes at a bath temperature of 30°, during which time a homogeneous yellow solution is formed. Crystallization of iodosobenzene diacetate may begin during this period.

The beaker is chilled in an ice bath for 1 hour. The crystalline diacetate that separates is collected on a Büchner funnel and washed with three 20-ml. portions of cold water. After drying for 30 minutes on the funnel with suction, the diacetate is dried overnight in a vacuum desiccator containing calcium chloride (Note 4). The dried diacetate weighs 26.7–29.3 g. (83–91%) and melts at 158–159° with decomposition. The purity of the diacetate, determined by the titration method of Lucas, Kennedy, and Formo,[3] is 97–98%, which is good enough for most purposes. The purity can be increased to 99–100% by a recrystallization from 5*M* acetic acid.

2. Notes

1. Rubber gloves should be worn when handling vessels containing peracetic acid, for traces of the liquid can cause severe irritation. Skin that has come into contact with peracetic acid should be washed immediately and treated with sodium bicarbonate. Details for the safe handling of peracetic acid are found in Bulletin 4 supplied by Buffalo Electrochemical Corp.

2. Appreciable amounts of iodoxybenzene are formed if the temperature of the bath is allowed to go above 30° or if the addition of peracetic acid is faster than indicated.
3. Satisfactory 40% peracetic acid is obtainable from Buffalo Electrochemical Corp., Food Machinery and Chemical Corp., Buffalo, New York. The specifications given by the manufacturer for its composition are: peracetic acid, 40%; hydrogen peroxide, 5%; acetic acid, 39%; sulfuric acid, 1%; water, 15%. Its density is 1.15 g. per ml.
A fresh sample of this 40% peracetic acid contains about 1.54 equivalents, or 0.77 mole, of peroxide per 100 ml. of solution, corresponding to 1.34 equivalents per 100 g. The concentration can be determined by treating the peroxide solution with potassium iodide and titrating the liberated iodine with standard sodium thiosulfate. The concentration of peroxide in peracetic acid decreases somewhat on long standing and should be checked before the peracetic acid is used. The yield of diacetate is lowered if the concentration of the peroxide is less than 1.0 equivalent per 100 g. of peracetic acid. The total amount of peroxide used should be 2.4 moles, or 4.8 equivalents, for each mole of iodobenzene.
4. The surface of the diacetate may become yellow during the drying, but this does not affect its usefulness for most purposes.

3. Discussion

Willgerodt[4] prepared iodosobenzene diacetate by adding chlorine to iodobenzene and hydrolyzing the dichloride to iodosobenzene, which was then reacted with acetic acid. Pausacker[5] used this method to synthesize a number of analogs but found it inferior to his modification of the method of Böeseken and Schneider[6] in which iodobenzene is treated with 30% hydrogen peroxide and acetic anhydride. Arbusov[7] obtained the diacetate in 79% yield by the action of a mixture of peracetic and acetic acids on iodobenzene. Quantitative yields of the diacetate have been claimed for the reaction of iodobenzene dichloride with lead tetraacetate in glacial acetic acid containing 10% acetic anhydride, followed by precipitation of the lead as the chloride.[8]

4. Merits of the Preparation

Iodosobenzene diacetate is best prepared by the action of peracetic acid and acetic acid on iodobenzene. The present procedure is superior to earlier ones[5,6,7,8] because it uses inexpensive, commercially available peracetic acid, is faster, and gives higher yields. The procedure seems general for aryl iodides with electron-releasing substituents, for the submitters have obtained good yields of diacetates from *o*-, *m*- and *p*-iodotoluene, 2- and 4-iodo-*m*-xylene, 2-iodo-*p*-xylene, *o*-iodophenetole, and 4-iodobiphenyl.

Iodosobenzene diacetate is used as a reagent for the preparation of glycol diacetates

from olefins,[9] for the oxidation of aromatic amines to corresponding azo compounds,[10] for the ring acetylation of N-arylacetamides,[11] for oxidation of some phenols to phenyl ethers,[12] and as a coupling agent in the preparation of iodonium salts.[13] Its hydrolysis to iodosobenzene constitutes the best synthesis of that compound.[14]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 658
- Org. Syn. Coll. Vol. 5, 665
- Org. Syn. Coll. Vol. 8, 132

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

o-, m- and p-iodotoluene

2- and 4-iodo-m-xylene

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

acetic anhydride (108-24-7)

sodium bicarbonate (144-55-8)

potassium iodide (7681-11-0)

sodium thiosulfate (7772-98-7)

iodine (7553-56-2)

chlorine (7782-50-5)

hydrogen peroxide, peroxide (7722-84-1)

Iodobenzene (591-50-4)

iodobenzene dichloride (2401-21-0)

peracetic acid (79-21-0)

Iodosobenzene (536-80-1)

Iodoxybenzene (696-33-3)

Iodosobenzene diacetate, Benzene, iodoso-, diacetate (3240-34-4)

4-iodobiphenyl (1591-31-7)

2-Iodo-p-xylene (1122-42-5)

o-iodophenetole (614-73-3)

lead tetraacetate

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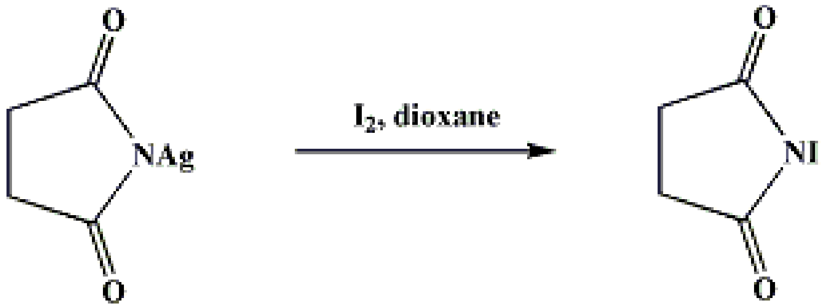
Organic Syntheses, CV 5, 663

N-IODOSUCCINIMIDE

[Succinimide, N-iodo-]



Submitted by W. R. Benson[1], E. T. McBee[2], and L. Rand[2].
Checked by B. C. McKusick and T. J. Kealy.

1. Procedure

Twenty grams (0.079 mole) of iodine and 90 ml. of dried dioxane (Note 1) are placed in a wide-mouthed, screw-cap, brown bottle of 150–200 ml. capacity. Most of the iodine dissolves. Eighteen grams (0.087 mole) of thoroughly dried N-silver succinimide (Note 2) is added, and the bottle is shaken vigorously for several minutes. The mixture is occasionally shaken in the course of an hour and then is warmed in a water bath at 50° for 5 minutes. It is now filtered hot through a Büchner funnel into a 500-ml. filter flask well wrapped with black paper or aluminum foil. The silver iodide that is collected is washed with a 10-ml. portion of warm dioxane. Carbon tetrachloride (200 ml.) is added to the combined filtrates in the filter flask, and the solution is chilled overnight at –8° to –20°. N-Iodosuccinimide separates as colorless crystals. It is collected on a Büchner funnel with as little exposure to light as possible, washed with 25 ml. of carbon tetrachloride, and dried with suction. After being dried overnight in the dark at 25° (1 mm.) the N-iodosuccinimide weighs 14.3–15.1 g. (81–85% yield) and melts with decomposition at 193–199° (Note 3).

2. Notes

1. The dioxane is purified only by the use of sodium strips and distillation.[3] The checkers used a newly opened bottle of "Spectroquality Reagent" dioxane (Matheson, Coleman and Bell) without further treatment.

2. N-Silver succinimide was prepared by the method of Djerassi and Lenk.[4] The checkers rapidly added a solution of 64 g. (1.6 moles) of sodium hydroxide in 300 ml. of water dropwise to a stirred solution of 249 g. (1.47 moles) of silver nitrate in 700 ml. of water at room temperature. The silver oxide that formed was separated on a Büchner funnel and washed with water. The moist oxide was

added in one portion to a boiling solution of 133 g. (1.34 moles) of succinimide in 4 l. of water. The reaction vessel was wrapped with aluminum foil in order to exclude as much light as possible. After 45 minutes, the suspension was filtered through a heated Büchner funnel into a filter flask also wrapped with aluminum foil. The filtrate was allowed to stand at room temperature overnight, during which time N-silver succinimide crystallized. The N-silver succinimide was separated on a Büchner funnel, dried in air under suction, and ground to a powder. After being dried in a vacuum oven for 1 hour at 110°, it weighed 128 g. (47%). N-Silver succinimide should be stored in a brown bottle.
3. This material is pure enough to use in the preparation of α-iodoketones. The checkers found that, after one recrystallization from a mixture of dioxane and carbon tetrachloride, the N-iodosuccinimide melted with decomposition at 195–200°. Pure N-iodosuccinimide is reported to melt at 200–201°.[4]

3. Discussion

N-Iodosuccinimide has been prepared by the action of iodine on N-silver succinimide,[4,5] and by the action of iodine monochloride on the sodium salt of succinimide.[6] The present procedure is essentially that of Djerassi and Lenk,[4] with the modification that dioxane is the reaction medium instead of acetone; dioxane gives a better yield without formation of a lachrymatory by-product.

4. Merits of Preparation

N-Iodosuccinimide reacts with enol acetates derived from ketones to give α-iodoketones, and the reaction has found application in the steroid field.[4,6] The iodination of the enol acetates seems to proceed by an ionic mechanism, and preliminary work indicates that N-iodosuccinimide is not capable of at least some of the radical-chain iodinations analogous to radical-chain brominations brought about by N-bromosuccinimide.[4] N-Iodosuccinimide has also been used for the iodination of purine nucleosides[7] and of fluorenone.[8] Iodination of 2-hydroxy-3-(β-alkylvinyl)-1,4-naphthoquinones results in an unusual replacement of a vinyl hydrogen.[9]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 226

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

N-silver succinimide

sodium hydroxide (1310-73-2)

silver oxide (20667-12-3)

silver nitrate (7761-88-8)

carbon tetrachloride (56-23-5)

iodine (7553-56-2)

acetone (67-64-1)

sodium (13966-32-0)

Succinimide (123-56-8)

dioxane (5703-46-8)

iodine monochloride (7790-99-0)

N-bromosuccinimide (128-08-5)

fluorenone (486-25-9)

silver iodide (7783-96-2)

N-Iodosuccinimide, Succinimide, N-iodo- (516-12-1)

sodium salt of succinimide

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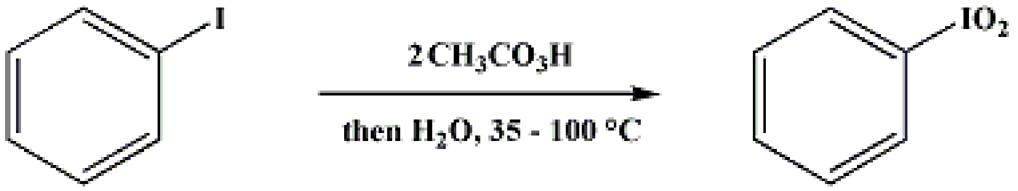
Organic Syntheses, CV 5, 665

IODOXYBENZENE

[Benzene, iodoxy-]



Submitted by J. G. Sharefkin and H. Saltzman[1].
Checked by E. J. Corey and C. P. Lillya.

1. Procedure

Caution! Avoid inhaling the vapor of peracetic acid or allowing the liquid to come into contact with the skin. The reaction is best carried out in a hood (Note 1). Iodoxybenzene explodes if heated to 230°.

A 500-ml. three-necked flask fitted with reflux condenser, stirrer, and dropping funnel and containing 20.4 g. (0.10 mole) of iodobenzene[2] is immersed in an oil bath maintained at 35°. Seventy-five grams (65 ml., 0.50 mole) of commercial 40% peracetic acid (Note 1) is added with vigorous stirring over a 30-minute period. Solid may begin to form before all the peracetic acid has been added, but, although this may slow down the stirring, it does not decrease the yield or cause a rise in temperature.

After all the peracetic acid has been added, the reaction mixture is diluted with 80 ml. of water and heated from 35° to 100° over a 20-minute period (Note 2). It is then kept at 100° for 45 minutes. The flask is cooled to 0–5° in an ice bath, and the solid iodoxybenzene is collected on a Büchner funnel and air-dried with suction for 1 hour. Additional material is obtained by concentrating the filtrate to one-fourth of its volume *(Caution! (Note 3)).* The two crops of crude iodoxybenzene are combined and dried overnight in a desiccator; weight 19.6–20.5 g.; m.p. 230° *(Caution! Explodes!).* Iodometric titration[3] shows the purity to be about 94% (Note 4).

Purification of the crude iodoxybenzene is effected by grinding it to a powder in a mortar, macerating it with 70 ml. of chloroform, and separating the solid by filtration. The chloroform extraction is repeated and the solid is dried; weight 17–19 g. (72–80%); purity 99.0–99.9% by iodometric titration.[3]

2. Notes

1. For a source and the specifications of 40% peracetic acid and precautions in

handling it, see Note 3 and Note1 under the preparation of iodosobenzene diacetate, p. 661.
2. If the temperature of the bath is not raised slowly, foaming is difficult to control. Although the gradual rise in temperature causes considerable foaming, the reaction mixture remains within the flask.
3. The filtrate must not be evaporated to dryness because iodoxybenzene explodes when heated.
4. The major by-products in this reaction are iodobenzene and iodosobenzene diacetate. An excess of 20 ml. of peracetic acid over the 65 ml. recommended results in an increase in the amount of iodobenzene. Both impurities are removed from the product by washing with chloroform.

3. Discussion

Iodoxybenzene has been prepared by the disproportionation of iodosobenzene,[4,5,6] by oxidation of iodosobenzene with hypochlorous acid or bleaching powder,[7] and by oxidation of iodobenzene with hypochlorous acid or with sodium hydroxide and bromine.[8] Other oxidizing agents used with iodobenzene include air,[3] chlorine in pyridine,[9] Caro's acid,[10,11] concentrated chloric acid,[12] and peracetic acid solution.[13] Hypochlorite oxidation of iodobenzene dichloride has also been employed.[14]

4. Merits of the Preparation

This one-step method of preparing iodoxybenzene is preferable to earlier methods because it is simpler and the yield is substantially higher. The procedure seems general for iodoxyarenes, at least those with electron-releasing substituents, for the submitters have used it to obtain good yields of *o*-, *m*- and *p*-iodoxytoluene, 2- and 4-iodoxy-*m*-xylene, 2-iodoxy-*p*-xylene, *o*-iodoxyphenetole, 4-iodoxybiphenyl, and *o*-iodoxybenzoic acid.

Iodoxyarenes are useful in the preparation of iodonium salts, $Ar_2I^+X^-$.[15]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

o-, m- and p-iodoxytoluene

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

bromine (7726-95-6)

pyridine (110-86-1)

chlorine (7782-50-5)

chloric acid (7790-93-4)

hypochlorous acid (7790-92-3)

Iodobenzene (591-50-4)

iodobenzene dichloride (2401-21-0)

peracetic acid (79-21-0)

Iodonium

Iodosobenzene (536-80-1)

Iodoxybenzene, Benzene, iodoxy- (696-33-3)

Iodosobenzene diacetate (3240-34-4)

4-iodoxybiphenyl

4-iodoxy-m-xylene

2-iodoxy-p-xylene

o-iodoxyphenetole

o-iodoxybenzoic acid

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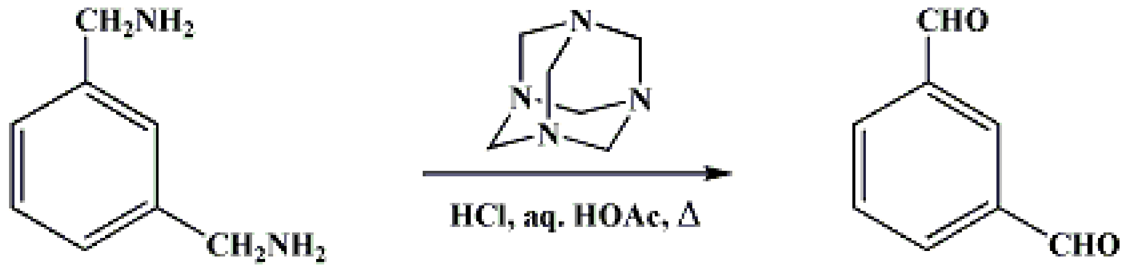
Organic Syntheses, CV 5, 668

ISOPHTHALALDEHYDE



Submitted by J. H. Ackerman and A. R. Surrey[1].
Checked by Kenneth H. Brown, Wayland E. Noland, and William E. Parham.

1. Procedure

A solution of 272 g. (261 ml., 2.00 moles) of α,α'-diamino-*m*-xylene (Note 1), 1.00 kg. (7.1 moles) of hexamethylenetetramine, 480 ml. of concentrated hydrochloric acid, and 3.2 l. of 50% aqueous acetic acid in a 12-l. flask is stirred and heated at the reflux temperature for 2.5 hours. The hot amber reaction mixture is then poured into a large battery jar in a well-ventilated hood, and a solution prepared from 298 g. of sodium hydroxide and 3.85 l. of water is added slowly with stirring (Note 2). The mixture is covered and allowed to stand overnight at about 5°. The product, which separates as long needles, is collected, washed on a Buchner funnel with 100 ml. of cold water, and then dried to constant weight under vacuum (Note 3) over calcium chloride. There is obtained 158–166 g. (59–62%) of almost colorless needles of isophthalaldehyde, m.p. 88–90° (Note 4).

2. Notes

1. α,α'-Diamino-*m*-xylene was obtained from California Chemical Company and Aldrich Chemical Company.
2. The sodium hydroxide solution is added to neutralize most of the acetic acid present. Better yields are obtained using this neutralization procedure than by merely cooling the reaction mixture.
3. The checkers observed that house vacuum removed only 50% of the water after 48 hours.
4. One lot of α,α'-diamino-*m*-xylene from Aldrich Chemical Company gave the isophthalaldehyde as pale pink, long needles, m.p. 88–90°. When 12.0 g. of this material was recrystallized from 500 ml. of water, there was obtained 10.9 g. (91%) of pale cream, long needles, m.p. 89–91°.

3. Discussion

The procedure described is a modification of the general procedure of Angyal[2] for the

preparation of aldehydes from benzylamines by the Sommelet reaction. Isophthalaldehyde has been prepared from *m*-xylene by preparation of the tetrachloro derivative and hydrolysis,[3] from isophthaloyl chloride by the Rosenmund reaction,[4] from α,α'-dibromo-*m*-xylene by the Sommelet reaction,[5] and from isophthaloyl chloride by reduction with lithium tri-*t*-butoxyaluminumhydride.[6]

4. Merits of the Preparation

Isophthalaldehyde is a valuable intermediate. Although the yields obtained by some of the other reported methods of preparation are better than the yield obtained here, the availability of starting material and the simplicity of reaction make this method attractive.

This appears to be the first reported case of the Sommelet reaction starting with a diamine.

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

sodium hydroxide (1310-73-2)

hexamethylenetetramine (100-97-0)

Isophthalaldehyde (626-19-7)

isophthaloyl chloride (99-63-8)

lithium tri-t-butoxyaluminumhydride

m-xylene (108-38-3)

α,α'-diamino-m-xylene

α,α'-dibromo-m-xylene

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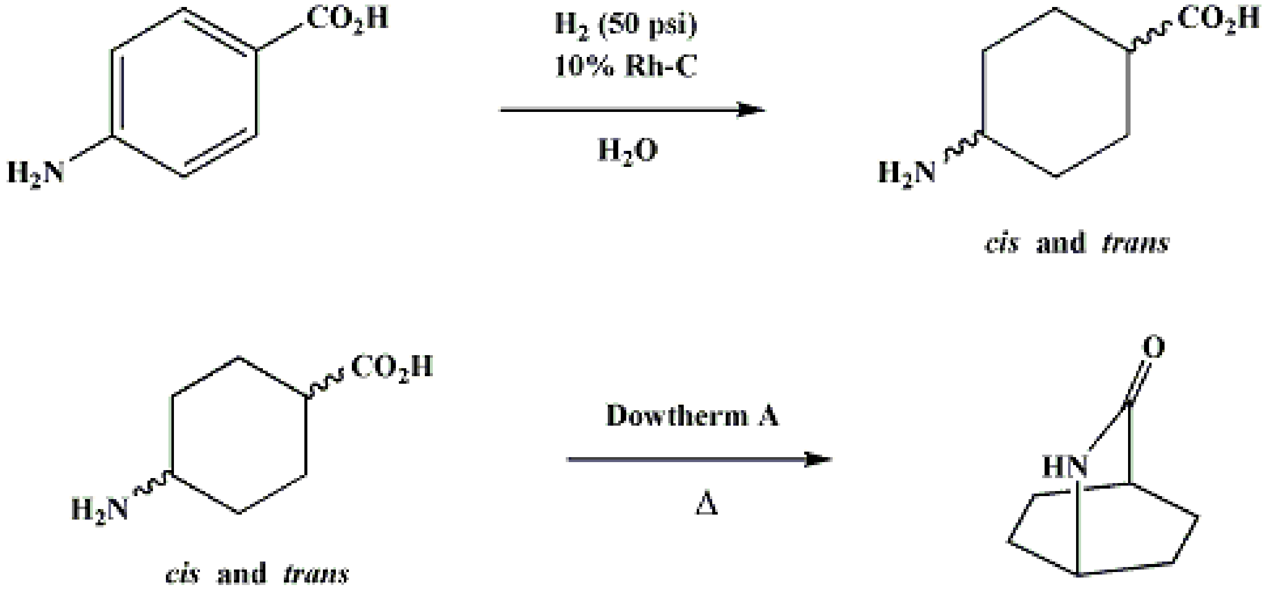
Organic Syntheses, CV 5, 670

3-ISOQUINUCLIDONE

[2-Azabicyclo[2.2.2]octan-3-one]



Submitted by W. M. Pearlman[1]
Checked by Peter Campbell and Ronald Breslow.

1. Procedure

A. *cis- and trans-4-Aminocyclohexanecarboxylic acid*. A mixture of 27.4 g. (0.20 mole) of *p*-aminobenzoic acid (Note 1), 200 ml. of water, and 2 g. of 10% rhodium-0.1% palladium on carbon catalyst (Note 2) is placed in a pressure bottle and hydrogenated at 50 p.s.i. When 0.6 mole of hydrogen has been absorbed (Note 3), the mixture is filtered and concentrated under reduced pressure until crystals start to form (Note 4). The mixture is diluted with 200 ml. of dimethylformamide and cooled to 5°, filtered, washed with dimethylformamide, then methanol, and dried, giving 19.4–20.3 g. (68–71%) of *cis*- and *trans*-4-aminocyclohexanecarboxylic acid, m.p. 292–296° (Note 5).

B. *3-Isoquinuclidone*. A mixture of 4.53 g. of *cis*- and *trans*-4-aminocyclohexanecarboxylic acid and 30 ml. of Dowtherm A (Note 6) is heated as rapidly as possible to reflux temperature. Heating is continued for 20 minutes during which time the water formed is allowed to distill away; at the end of this time, solution has taken place. The solution is allowed to cool to room temperature and is diluted with 100 ml. of isooctane. The solution is extracted three times with 50-ml. portions of water. The combined water extracts are treated with charcoal, filtered, and concentrated to dryness under reduced pressure. The residue is crystallized from cyclohexane giving 3.20–3.33 g. (81–84%) of 3-isoquinuclidone, m.p. 197–198° (Note 5).

2. Notes

1. Purchased from B. L. Lemke and Co., Inc., 199 Main Street, Lodi, New Jersey. The checkers used material from Eastman Organic Chemicals Department.
2. A mixture of 5.26 g. of rhodium chloride trihydrate, 0.34 g. of palladium chloride, 18 g. of carbon (Darco G-60), and 200 ml. of water is rapidly stirred and heated to 80°. Lithium hydroxide hydrate (2.7 g.) dissolved in 10 ml. of water is added all at once and the heating stopped. The mixture is stirred overnight, filtered, and washed with 100 ml. of 0.5 v/v% aqueous acetic acid. The product is dried under reduced pressure at 65°, giving 20.6–21 g. of the catalyst. One gram of this catalyst consumes 0.0022–0.0028 mole of hydrogen in aqueous suspension.[2]
3. The checkers found that the reduction requires 4–5 days, whereas the submitter reported the reaction requires 24 hours. Fresh catalyst is added whenever the rate of hydrogen uptake significantly decreases. When fresh catalyst is added to the reaction vessel, it is important that it first be wet with solvent and that the hydrogen be well evacuated. Opening the mixture to the atmosphere without careful evacuation will produce a hydrogen-oxygen mixture which may explode on contact with fresh catalyst.
4. It is necessary to concentrate the solution to one-fifth volume before crystals form.
5. The submitters report the preparation scaled up by fifty-fold with similar yields and purities.
6. Purchased from Dow Chemical Co., Midland, Michigan.

3. Discussion

Ferber and Brückner[3] reduced *p*-aminobenzoic acid using Adams catalyst (PtO_2) at atmospheric pressure, and Schneider and Dillman[4] reduced *p*-aminobenzoic acid using 10% ruthenium on carbon at 140 atm. and 70°. 3-Isoquinuclidone has been prepared, by the previously mentioned investigators,[3,4] by heating the dry 4-aminocyclohexane carboxylic acid at elevated temperatures.

The described method of preparation of 3-isoquinuclidone has the following advantages: The isolation of the *cis* form of 4-aminocyclohexane carboxylic acid is not required in order to obtain a good yield; the amount of 3-isoquinuclidone that can be prepared at a time is limited only by the size of available equipment; the yield is excellent and the workup is easy and straightforward.

3-Isoquinuclidone has been found to be an excellent substitute for camphor for molecular weight determinations.[2]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

3-ISOQUINUCLIDONE

10% rhodium-0.1% palladium on carbon

acetic acid (64-19-7)

methanol (67-56-1)

hydrogen (1333-74-0)

cyclohexane (110-82-7)

carbon (7782-42-5)

palladium chloride

hydrogen-oxygen (7732-18-5)

camphor (21368-68-3)

dimethylformamide (68-12-2)

ruthenium on carbon (7440-18-8)

2-Azabicyclo[2.2.2]octan-3-one (3306-69-2)

4-aminocyclohexane carboxylic acid, cis- and trans-4-Aminocyclohexanecarboxylic acid (1776-53-0)

isooctane (592-27-8)

rhodium chloride trihydrate (20765-98-4)

Lithium hydroxide hydrate (1310-66-3)

p-aminobenzoic acid (150-13-0)

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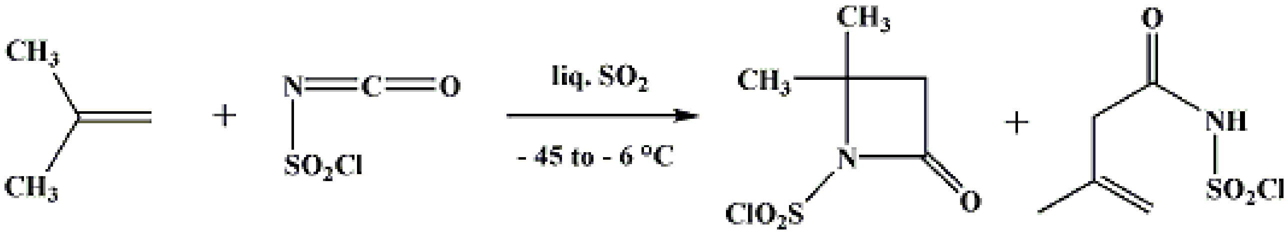
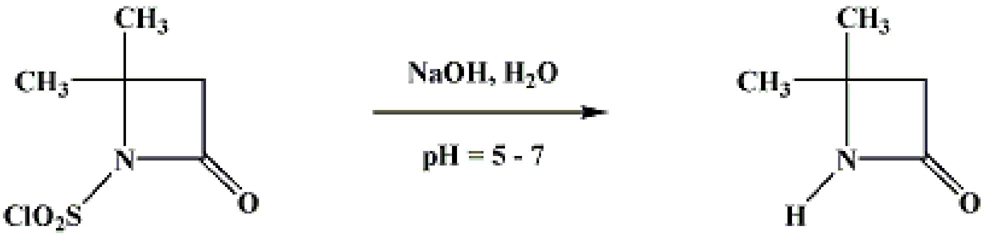
Organic Syntheses, *CV 5, 673*

β-ISOVALEROLACTAM-N-SULFONYL CHLORIDE AND β-ISOVALEROLACTAM

[2-Azetidinone-4,4-dimethyl-1-sulfonyl chloride and 2-azetidinone-4,4-dimethyl]





Submitted by Roderich Graf[1]
Checked by Jerome F. Levy and William D. Emmons.

1. Procedure

Caution! Chlorosulfonyl isocyanate is highly corrosive and may be contaminated with cyanogen chloride. This preparation should be carried out in a good hood, and rubber gloves should be worn.

A. *β-Isovalerolactam-N-sulfonyl chloride*. A 200-ml. four-necked flask fitted with a mechanical stirrer, a dry ice-jacketed dropping funnel (Note 1), and a thermometer is cooled with a dry ice-methylene chloride slush bath while 67 ml. of sulfur dioxide (Note 2) is condensed into the flask. Both the dry ice condenser and the dropping funnel are protected with drying tubes containing anhydrous calcium sulfate. With the liquid sulfur dioxide at –20°, the flask is charged with 0.3 g. of finely powdered potassium chloride (Note 3) and 47.1 g. (0.33 mole) of chlorosulfonyl isocyanate.[2] Then 19.5 g. (0.35 mole) of isobutylene, previously condensed in a cold trap, is added to the dropping funnel. The temperature of the flask is lowered to –40° to –50°, and isobutylene is added dropwise over a 20-minute period (Note 4), (Note 5). After the isobutylene addition is completed, the cooling bath under the flask is removed, and the reaction mixture is allowed to warm up until the solvent begins to reflux (approximately –6°). The colorless contents of the flask are then poured into 125 ml. of water contained in a 400-ml. beaker over a period of 1 minute with vigorous agitation provided by a mechanically driven paddle stirrer. Sulfur dioxide is evolved while β-isovalerolactam-N-sulfonyl chloride precipitates as a gritty, crystalline, white solid (Note 6). The major portion of dissolved sulfur dioxide is removed by impinging a vigorous stream of air on the surface of the liquid in the beaker until the temperature of the mixture rises again after

falling to 0–4°. The precipitate is removed by suction filtration and is washed three times with 33-ml. portions of ice water. The yield of moist product containing 10–20% water is 52–56 g. (Note 7). The product in this form is more suitable for subsequent conversion to the free β-lactam than if it is anhydrous or in a more coarsely crystalline form.

To prepare the anhydrous compound, the solid is dissolved in methylene chloride, whereupon the water separates as the upper phase. The organic layer is dried over anhydrous sodium sulfate, and the solvent is removed under reduced pressure at room temperature to give a colorless, crystalline mass, m.p. 75–77°. Small amounts of the pure compound may be obtained in the form of long needles by recrystallization from ether, m.p. 77–78°. The yield is 43–46 g. (65–70%) in anhydrous form (Note 8).

B. *β-Isovalerolactam*. A 200-ml. beaker is provided with a combination pH electrode, a mechanically driven paddle stirrer, a thermometer, and a syringe or dropping funnel (Note 9). An amount of water just sufficient for immersion of the pH electrode (20 ml.) is introduced, and with vigorous stirring the first portion (about one quarter) of the 52–56 g. (about 0.20–0.22 mole) of moist β-isovalerolactam-N-sulfonyl chloride is added. The liberated acid is neutralized by dropwise addition of approximately 10*N* sodium hydroxide solution (Note 10) to maintain the pH of the mixture between 2 and 8, and preferably in the range 5–7 (Note 11). The temperature is kept at 20–25° with cooling supplied by an ice bath as necessary. More lactam-N-sulfonyl chloride is added as the hydrolysis proceeds.

Hydrolysis is very sluggish at first, especially if anhydrous or coarsely crystalline sulfonyl chloride is used. Hydrolysis of the first one quarter to one half of the sulfonyl chloride requires 1–3 hours, and by that time the increasing salt concentration of the solution will cause the separation of the β-lactam as a second liquid phase. The sulfonyl chloride is significantly more soluble in this water-containing lactam phase, and as a result the rate of hydrolysis increases markedly (Note 12). Hydrolysis of the remainder of the sulfonyl chloride can be completed in about 30 minutes to 1 hour. The pH is adjusted finally to 7, and the mixture is cooled to 10° while being repeatedly seeded with sodium sulfate decahydrate. This converts all the precipitated sodium sulfate to the decahydrate (Note 13), and the β-lactam which originally separated in oily form is dissolved. The sodium sulfate decahydrate is removed by suction filtration and is washed with 90 ml. of chloroform. Small portions of the chloroform washings are then used for repeated extraction of the lactam from the salt solution. The extracts are combined, dried over anhydrous potassium carbonate, and distilled through an 8-in. Vigreux column. Most of the chloroform is removed by distillation at atmospheric pressure, and the product is distilled under reduced pressure, b.p. 70° (1.0 mm.), n^{25}D 1.4475, freezing point 14.7° (Note 14), weight 16.7–17.3 g. (51–53% overall from chlorosulfonyl isocyanate). The product is 99.8% pure by vapor phase chromatographic analysis.

2. Notes

1. A jacket which is suitable for holding dry ice may be made easily for use with a cylindrical dropping funnel. The neck and bottom of a narrow-mouthed polyethylene bottle are cut off, and two or three vertical slits are made at the narrow end to allow it to slip over the body of the dropping funnel and rest on the stop-cock barrel. The size of the dropping funnel will determine the size of polyethylene container to be used.
2. The checkers used anhydrous sulfur dioxide supplied in cylinders by the Matheson Co., Inc., East Rutherford, New Jersey, without further purification. Traces of moisture will not interfere with the reaction, and it is sufficient if the liquid sulfur dioxide is clear and colorless. If necessary, however, the gaseous sulfur dioxide may be dried with anhydrous calcium chloride before condensing it.

3. Addition of potassium chloride may be omitted if the chlorosulfonyl isocyanate is free of sulfur trioxide. Otherwise, traces of sulfur trioxide will give rise to a yellow or brown coloration of the reaction mixture and to formation of small amounts of by-products which, because of their emulsifying activity, may interfere with further processing.

4. The reaction may also be carried out at higher temperatures, *e.g.*, at −10°, with simultaneous addition of gaseous isobutylene over a prolonged period of time. This, however, results in a reaction product of lower purity than is obtained by the present procedure.

5. The reaction is exothermic, and the rate of addition should be controlled to keep the temperature within the limits indicated.

6. The cycloaddition reaction is accompanied by another reaction giving about 30% of 3-methyl-3-butenamide-N-sulfonyl chloride which is readily hydrolyzed during the aqueous work-up. The β-lactam-N-sulfonyl chloride which is the major product of the reaction is relatively stable to hydrolysis under the conditions of its isolation.

7. The product may be stored for several days before its conversion to the free β-lactam in a polyethylene bag placed in a refrigerator or preferably under dry ice in a Dewar flask.

8. The cycloaddition reaction can also be carried out with ether as solvent, especially in small batches.[3]

9. For hydrolysis of a much larger quantity of material, a four-necked flask may be employed instead of a beaker.

10. Three moles of sodium hydroxide solution is used per mole of sulfonyl chloride. The use of base of known concentration provides a means of following the hydrolysis as well as determining the true amount of product present for calculating the yield in Part A.

11. At high pH (>10–11) saponification of the sulfonyl chloride to the sodium salt of 3-amino-3-methylbutyric acid-N-sulfonic acid will predominate, and at too low a pH (*e.g.*, pH of 0) hydrolysis to 3-hydroxy-3-methylbutyramide will prevail.

12. Care should be taken that the sulfonyl chloride is not added too rapidly, as the increased hydrolysis rate at this point will not permit adequate control of temperature and pH if a large amount of sulfonyl chloride is present. For repeat preparations a portion of the reaction mixture from a preceding batch may be introduced to achieve a more rapid hydrolysis rate sooner in the reaction. For the first preparation there are ways of increasing the initial rate of hydrolysis, or shortening the time interval before the transition from low to higher hydrolysis rate occurs. These are use of sodium sulfate solution instead of pure water, addition of a few tenths of a gram of potassium iodide, or addition of a small amount (1 ml.) of methylene chloride. However, these steps are not necessary if a reasonable amount of patience is exercised.

13. If seeding with sodium sulfate decahydrate is omitted, the unstable heptahydrate may crystallize.

14. The freezing point given was determined by the checkers as the temperature of a solid-melt equilibrium for a sample of 99.8% purity. The submitter reports the melting point at 15.3° after recrystallization from isopropyl ether and redistillation.

3. Discussion

The only methods reported[3] for the preparation of 4,4-dimethyl-2-azetidinone-1-sulfonyl chloride and 4,4-dimethyl-2-azetidinone are those described here.

Conversion of β-lactam-N-sulfonyl chlorides to the free lactams may also be accomplished by means of reducing agents,[3,4] and for β-lactam-N-sulfonyl chlorides which are hydrolytically more stable than the one in the present example this represents a method to be preferred over pH-

controlled hydrolysis.[3] The N-sulfonyl chlorides are reduced to N-sulfinic acids which spontaneously decompose to β-lactams and sulfur dioxide. Among the reducing agents which may be used are thiophenol, hydrogen sulfide, zinc dust, iron power, iodide ion, and sodium sulfite.[4] Iodide ion need be used only in catalytic amounts, as the liberated iodine is reduced again to iodide ion by the sulfur dioxide split off.

4. Merits of the Preparation

This procedure illustrates a general method for preparing aliphatic and, in certain cases, aromatic β-lactams containing a free NH group and substituted in either the 4 position or in both the 3 and 4 positions of the 2-azetidinone ring. The major byproduct of the cycloaddition step is a β,γ-unsaturated carboxamide-N-sulfonyl chloride which, in the case of certain aromatic olefins, may predominate. Reactions of both β-lactam-N-sulfonyl chlorides and the β,γ-unsaturated carboxamide-N-sulfonyl chlorides have been tabulated.[3]

Recently additional examples of the synthesis of 3,4-disubstituted 2-azetidinones have been reported[5,6] as well as a kinetic study of the reaction of chlorosulfonyl isocyanate with olefins.[7]

β-Lactams substituted only in the 3 position cannot be prepared by the present procedure, since the lactam formed has the nitrogen of the chlorosulfonyl isocyanate attached to the more highly substituted carbon atom of the olefinic double bond in Markownikoff fashion. 2-Azetidinones substituted in the 3 position only have been prepared by Grignard reagent-catalyzed cyclizations of esters of appropriately substituted β-amino acids.[8,9]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 226
- Org. Syn. Coll. Vol. 5, 598

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

2-azetidinone-4,4-dimethyl

calcium chloride (10043-52-4)

potassium carbonate (584-08-7)

ether (60-29-7)

sodium sulfite (7757-83-7)

sodium hydroxide (1310-73-2)

sulfur trioxide (7446-11-9)

chloroform (67-66-3)

iron (7439-89-6)

hydrogen sulfide (7783-06-4)

sulfur dioxide (7446-09-5)

sodium sulfate (7757-82-6)

potassium iodide (7681-11-0)

nitrogen (7727-37-9)

iodine (7553-56-2)

carbon (7782-42-5)

zinc (7440-66-6)

methylene chloride (75-09-2)

Thiophenol (108-98-5)

potassium chloride (7447-40-7)

cyanogen chloride (506-77-4)

isobutylene (9003-27-4)

isopropyl ether (108-20-3)

sodium sulfate decahydrate (7727-73-3)

CHLOROSULFONYL ISOCYANATE (1189-71-5)

β-Isovalerolactam-N-sulfonyl chloride, 4,4-dimethyl-2-azetidinone-1-sulfonyl chloride (17174-96-8)

β-Isovalerolactam, 4,4-dimethyl-2-azetidinone (4879-95-2)

2-Azetidinone-4,4-dimethyl-1-sulfonyl chloride

3-methyl-3-butenamide-N-sulfonyl chloride

3-hydroxy-3-methylbutyramide

2-azetidinone (930-21-2)

sodium salt of 3-amino-3-methylbutyric acid-N-sulfonic acid

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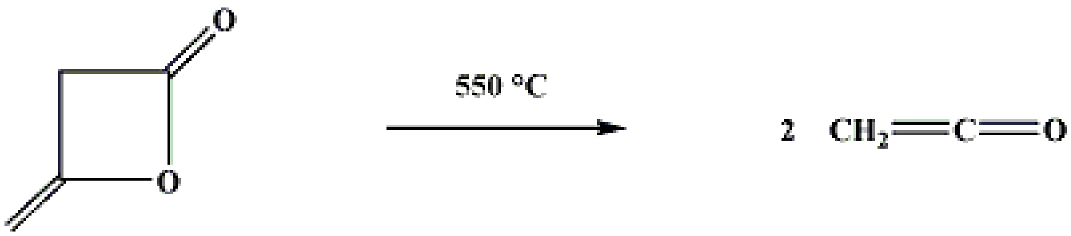
Organic Syntheses, CV 5, 679

KETENE



Submitted by S. Andreades and H. D. Carlson[1].
Checked by R. David Clark, James J. Fuerholzer, and Hentry E. Baumgarten.

1. Procedure

Caution! Ketene (b.p. –41°) is a poisonous gas of the same order of toxicity as phosgene. All operations with ketene should be carried out in an efficient hood.

The pyrolysis apparatus consists of a vertical, electrically-heated Vycor® tube (25 mm. I.D.) packed with 6-mm. lengths of Pyrex® tubing (10 mm. O.D.) and mounted in an electric furnace about 45 cm. long (Note 1) and (Note 2). Attached to the top is a 100-ml. dropping funnel with a pressure-equalizing side arm[2] that has an inlet for nitrogen (Note 3). A thermocouple well inside the tube holds a movable thermocouple and extends to the bottom of the heated section (Note 4). The bottom of the reactor is fitted to a 500-ml. side-arm flask packed in ice. The side arm leads to two traps in series cooled in ice and to a final trap cooled in a bath of dry ice and acetone (Note 5).

The hottest part of the tube, which is near the middle of the heated section, is maintained at 550° ± 10° while dry oxygen-free nitrogen is passed successively through a flowmeter and the tube at about 150 ml. per hr. for at least 30 minutes (Note 6). The dropping funnel is charged with 56 g. (0.67 mole) of diketene (Note 7) and (Note 8), which is then introduced into the hot tube at a rate of about 0.5 ml. per min. while the nitrogen flow continues. Essentially pure ketene (Note 9), yield 26–31 g. (46–55%) (Note 10), collects in the dry-ice trap as a colorless or nearly colorless liquid. The ketene is distilled directly from this trap for use in reactions.

If the ketene is not to be used at once, drying tubes should be attached to the trap, which should then be stored at –80°. Ketene can be kept for as long as 2 weeks in this way, although some transformation to high-boiling material occurs (Note 11). However, pure ketene can be readily obtained from a partially decomposed mixture by simple distillation from the trap (Note 11) and (Note 12). *Caution! Do not store ketene under pressure, as an explosion may result.*

2. Notes

1. The furnace used by the submitters and checkers was an 1870-watt hinged type manufactured by the Hevi-Duty Electric Company, Milwaukee, Wisconsin; length 18 in.; inside diameter 2 3/8; in.; catalog No. M-2018. With the packing described, the total surface area in the packed tube is about 2000 cm.^{2} In addition to this setup the checkers used a similar tube (20 mm. inside diameter) packed with 1/8;-in. I.D. single-turn Pyrex® glass helices and inserted in a 550-watt furnace manufactured by the Hoskins Mfg. Co., Detroit, Michigan; length 12 in.; inside diameter 1 in.; catalog No. FD303A.
2. To prevent heat loss from the ends of the furnace opening, the ends are packed with Pyrex® glass wool or Fiberglas® insulation PF-105. In addition, the checkers capped each end of the furnace with a plate constructed from -in. Transite® sheet in which a hole just large enough for a loose sliding fit on the tube had been bored. The plate at the bottom of the furnace was held in place with a rubber stopper also bored to fit the tube, and the plate at the top of the furnace was held in place with an iron ring attached to the ring stand supporting the funnel.
3. The lower part of the barrel of the dropping funnel should be bent in such a way as to offset it from the path of the thermocouple to permit adjustment of the latter. The checkers used a 8-mm. glass tube bent for offset and fitted at the upper end with a nitrogen inlet and a standard-taper ground joint to permit attachment of funnels of various sizes.
4. Attachment of dropping funnel and thermocouple well to the pyrolysis tube may be made with a rubber stopper suitably bored.
5. The first two traps may be packed loosely with glass wool to prevent mechanically entrained impurities (or aerosol) from passing through into the final trap. Omission of the glass wool may allow as much as 0.5–1.0 g. of colored material to be collected in the product. However, this colored impurity is easily removed by simple distillation. The checkers cooled the two traps in ice-ethanol.
6. The checkers passed the nitrogen through a gas absorption bottle filled to a depth of 10 cm. with concentrated sulfuric acid which had been calibrated roughly for flow rate. The rate of flow used was one bubble per 7 seconds (*ca.* 145 ml. per hr.) for the larger furnace, and one bubble per 10 seconds (*ca.* 100 ml. per hr.) for the smaller furnace.
7. Suitable diketene can be obtained from the Aldrich Chemical Company, Milwaukee, Wisconsin. If at all colored, this material should be distilled or sublimed before pyrolysis, for use of colored material may lead to a colored product. Distillation is easily carried out through use of the apparatus illustrated in f.htmig. 1. The impure diketene is placed in flask *A* and is cooled in ice and stirred with a magnetic stirrer. The Dewar trap is filled with dry ice and ethanol. Evacuation of the system with a vacuum pump is begun very carefully with appropriate upward adjustment of the pressure if necessary to prevent bumping and splashing. After the initial degassing and removal of low-boiling materials, the diketene distils smoothly (at 0.1–1.0 mm. pressure), collecting as a white solid on the cold surface of the Dewar trap. After the distillation is completed, the apparatus is partially disassembled and the dry ice and ethanol are poured

out. As the diketene melts, it flows into flask *B*. The diketene should be stored under nitrogen in tightly stoppered brown bottles in a refrigerator or, better, below its freezing point of −6.5°, as otherwise it may slowly decompose.

Fig. 1. Low-temperature distillation or evaporation apparatus. When solids are being collected, the Dewar flask bottom should be as indicated by the broken line.

Fig. 1. Low-temperature distillation or evaporation apparatus. When solids are being collected, the Dewar flask bottom should be as indicated by the broken line.

8. Equally good results have been obtained with charges one-fourth to twice that of the present procedure.
9. The ketene obtained by simple distillation from the final trap is essentially pure. The purity can be determined by passing a weighed sample into 1*N* sodium hydroxide solution and titrating for excess base. The checkers found it very difficult to avoid entirely the collection of minute traces of high-boiling colored impurities with the ketene . However, these impurities were easily removed by simple distillation of the ketene , just before use, from the original trap into a clean trap by warming the former in ice water and cooling the latter in dry ice and ethanol.
10. The checkers' yields were 54–66% for the larger furnace and 58–78% for the smaller furnace. The yield was found to be somewhat dependent on the rate of addition, with the rate specified in the procedure giving a good yield in a reasonable length of time. The checkers used an addition rate of 0.25–0.30 ml. per min. for the smaller furnace to obtain the yields cited.
11. Major impurities that collect on standing are all high-boiling, *e.g.*, diketene, b.p. 127°, and dehydroacetic acid, b.p. 270°. If the ketene has been stored long enough to allow a considerable portion of higher-boiling materials to accumulate, it is desirable to insert a trap cooled in an ice bath between the ketene-containing trap and the reaction vessel in order to minimize mechanical entrainment of the impurities. Repeated warming of the container to remove portions of the ketene naturally hastens transformation of the ketene to high-boiling materials.
12. The carbonaceous material that is deposited inside the pyrolysis tube is easily removed by passing a stream of oxygen through at about 550° after a thorough flushing with nitrogen.
13. The submitters no longer consider this method to be the most convenient one for preparing laboratory quantities of ketene . It has been supplanted at the Du Pont Experimental Station by pyrolysis of acetic anhydride according to the procedure of Fisher, MacLean, and Schnizer.[3] It is recommended that the wires of the preheater be glass-covered, since polymerization of the ketene at −78° seemed to occur frequently when bare wires were used, possibly because of

catalysis by trace amounts of metal. Using this procedure 55 g. (1.31 moles) of ketene per hour could be produced (private communication, J. B. Sieja and H. D. Carson).

3. Discussion

Ketene can be generated conveniently by pyrolysis of acetone in a hot tube[4] or over a hot wire in a "ketene lamp,"[5] or by pyrolysis of diketene in a hot tube,[6,7] or by pyrolysis of acetic anhydride.[3] Other methods of preparation have been summarized.[4] It has been shown that diketene cracks quite cleanly to ketene ,[7,8] although some allene and carbon dioxide are formed at the same time.[8]

4. Merits of the Preparation

The most convenient procedures for the preparation of ketene are the present one and the pyrolyses of acetone[5] or acetic ahnydride.[3] The acetone procedure gives ketene at a relatively fast rate (0.45 mole per hour), but it takes considerable adjustment to get optimum conditions, and trouble is sometimes caused by the wire getting coated with carbon. Furthermore, because the efficiency of a given wire coil varies with time, passing through a maximum, frequent calibration of the apparatus is necessary. The acetic anhydride method is even faster (1.31 moles per hour) and uses a readily available chemical. It appears to be the method of choice at this time. The diketene procedure described here is relatively simple and reliable; however, it is relatively slow (0.2 mole per hour) and requires a somewhat less readily available starting material.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 28

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Appendix

Compounds Referenced (Chemical Abstracts Registry Number)

acetic ahnydride

acetic anhydride (108-24-7)

carbon dioxide (124-38-9)

acetone (67-64-1)

diketene (674-82-8)

phosgene (75-44-5)

Ketene (463-51-4)

Allene (463-49-0)

Dehydroacetic acid (520-45-6)

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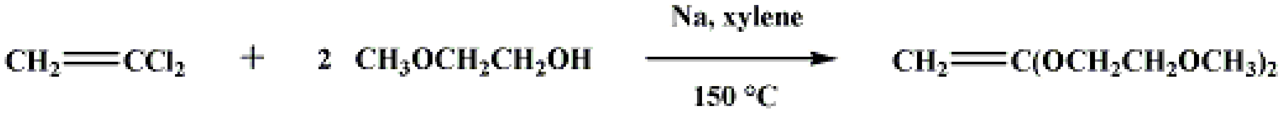
Organic Syntheses, CV 5, 684

KETENE DI(2-METHOXYETHYL) ACETAL

[Ketene bis(2-methoxyethyl) acetal]



Submitted by William C. Kuryla and John E. Hyre[1].
Checked by Earl M. Levi and Peter Yates.

1. Procedure

In a dry 1-l. five-necked flask equipped with a mechanical stirrer, a reflux condenser (Note 1), a thermometer, a nitrogen inlet, and a stoppered port (Note 2) are placed 152 g. (2.00 moles) of 2-methoxyethanol (Note 3) and 50 g. of xylene (Note 4). A constant dry nitrogen purge is maintained on the apparatus throughout the following operations (Note 5). Metallic sodium (46.0 g., 2.00 moles) is added in small chunks through the stoppered port to the stirred reaction mixture over a 2-hour period at a temperature of 130–150°. After all the sodium has reacted (Note 6), heating is discontinued, and 120 g. (1.24 moles) of vinylidene chloride (Note 7) is added dropwise to the stirred reaction mixture over a 20-minute period. During the addition of vinylidene chloride the reaction mixture becomes dark, and its temperature increases rapidly from an initial 140° to a maximum of 170–175°. It then decreases as addition continues, and concomitant precipitation of sodium chloride is noted. Stirring is continued for an additional 10 minutes after completion of the addition of vinylidene chloride. Anhydrous diethyl ether (100 ml.) is slowly added, serving both to reduce the viscosity and to cool the reaction mixture to about 60°. This mixture is then filtered through a medium-grade fritted-glass funnel, and the sodium chloride cake is washed with several 20-ml. portions of fresh ether (Note 8).

The ethereal filtrate and washings are distilled under reduced pressure (Note 9) with the use of a 6-in. Vigreux column, and pure ketene di(2-methoxyethyl) acetal (Note 10) is obtained; b.p. 81–84° (2.0 mm.), $n^{25}D$ 1.4411, yield 98–132 g. (56–75%). The infrared spectrum of the product shows a very strong C=C absorption band at 1640 cm.$^{-1}$.

2. Notes

1. A dry ice type of condenser has been found to be the most satisfactory because of the low boiling point (32°) of the vinylidene chloride. An efficient water-cooled condenser is satisfactory, however.
2. An addition funnel is fitted in this port after the sodium addition is complete.
3. 2-Methoxyethanol (methyl Cellosolve) from Union Carbide Corporation, Chemicals Division, was used.
4. Xylene (analytical reagent grade) from Mallinckrodt Chemical Works was distilled from sodium before use.
5. This is essential to avoid both the excessive oxidation of the reactants and the danger of a sodium-sparked fire.
6. Small amounts of metallic sodium, such as a few *very* small spheres floating in the

reaction mass, are tolerable as long as dry nitrogen is being continuously passed through the reaction flask. A slow nitrogen purge is also maintained on the apparatus during the addition of the vinylidene chloride. The checkers found that appreciable amounts of sodium remained unconsumed after 3.5 hours; they added more 2-methoxyethanol (10–12 g.) to complete the reaction (significant loss of this reagent appeared to occur from the port during addition of the sodium).

7. Vinylidene chloride (inhibited grade) from Dow Chemical Company was used.

8. The sodium chloride cake is washed with as many 20-ml. portions of ether as are required to make the filtrate essentially colorless (usually four or five).

9. The diethyl ether is collected directly into traps cooled in dry ice-acetone.

10. The directions of McElvain and Kundiger[2] regarding the storage of ketene acetals should be followed. The submitters have found that storage at 0°, in a bottle which was previously washed with a hot concentrated caustic solution, is satisfactory.

3. Discussion

Ketene di(2-methoxyethyl) acetal has been obtained by the present method with the use of diethylene glycol dimethyl ether as solvent.[3] Other methods for the preparation of ketene acetals include the dehydrohalogenation of a halo acetal with potassium *t*-butoxide[2,4] and the reaction of an α-bromo orthoester with metallic sodium.[5]

4. Merits of the Preparation

This synthetic process is applicable to the preparation of other ketene acetal derivatives of β-alkoxy alcohols. Examples include the ketene acetal derivatives of tetrahydrofurfuryl alcohol and 1-methoxy-2-propanol.[3] There are a number of advantages in its use, including a simple, time-saving procedure, readily available and inexpensive reagents, and good yields of ketene acetal obtained by a *one-step* method.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ketene acetal derivatives of tetrahydrofurfuryl alcohol and 1-methoxy-2-propanol

ether, diethyl ether (60-29-7)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

sodium (13966-32-0)

xylene (106-42-3)

methyl Cellosolve, 2-methoxyethanol (109-86-4)

diethylene glycol dimethyl ether (111-96-6)

vinylidene chloride (75-35-4)

KETENE DI(2-METHOXYETHYL) ACETAL, Ketene bis(2-methoxyethyl) acetal (5130-02-9)

potassium t-butoxide (865-47-4)

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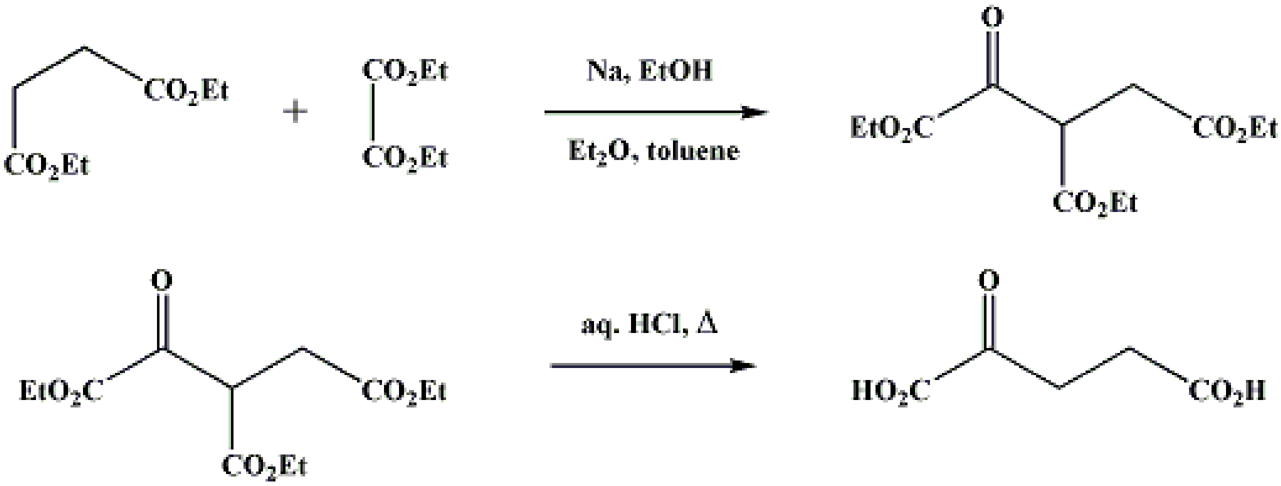
Organic Syntheses, CV 5, 687

α-KETOGLUTARIC ACID

[Glutaric acid, 2-oxo-]



Submitted by E. M. Bottorff and L. L. Moore[1].
Checked by William G. Dauben and Robert M. Coates.

1. Procedure

A. *Triethyl oxalylsuccinate*. In a 2-l. three-necked flask equipped with a sealed stirrer and a reflux condenser bearing a calcium chloride drying tube is placed 356 ml. (276 g., 6.00 moles) of anhydrous ethanol (Note 1). Sodium (23 g., 1.0 g. atom) is added in small portions at a rate sufficient to keep the ethanol boiling. External heating is required to dissolve the last portions of the metal. After all the sodium has dissolved, the excess ethanol is removed by distillation at atmospheric pressure; as the mixture becomes pasty, dry toluene is added in sufficient amounts to permit stirring and to prevent splattering of the salt. Distillation and addition of toluene is continued until all the ethanol is removed and the contents of the flask reach a temperature of 105° (Note 2). The sodium ethoxide slurry is cooled to room temperature and 650 ml. of anhydrous ether is added, followed by 146 g. (1.00 mole) of diethyl oxalate. To the yellow solution there is added 174 g. (1.00 mole) of diethyl succinate, and the mixture is allowed to stand at room temperature for at least 12 hours.

The mixture is hydrolyzed by the addition of 500 ml. of water with stirring. The layers are separated, the ether layer is washed with 150 ml. of water, and the ether layer is discarded. The combined aqueous layers are acidified with 100 ml. of 12*N* hydrochloric acid, and the layers are separated. The aqueous layer is extracted with three 150-ml. portions of ether, which are added to the oily layer. The ethereal solution is dried over anhydrous magnesium sulfate, and the ether is removed by evaporation under water-pump pressure at a bath temperature of 35–45°. Triethyl oxalylsuccinate, a yellow oil weighing 235–250 g. (86–91%), remains in the flask (Note 3).

B. *α-Ketoglutaric acid*. A mixture of 225 g. (0.82 mole) of triethyl oxalylsuccinate, 330 ml. of 12*N* hydrochloric acid, and 660 ml. of water is heated under reflux for 4 hours, and the mixture is distilled to dryness under reduced pressure at a bath temperature of 60–70° (Note 4). The liquid residue, which solidifies readily on standing, is warmed with 200 ml. of nitroethane on a

steam bath until it is in solution. The warm solution is filtered, the funnel is washed with 40 ml. of nitroethane, and the filtrate is stirred at 0–10° for 5 hours. α-Ketoglutaric acid is separated by filtration and dried at 90° under reduced pressure for 4 hours. It is obtained as a tan solid; weight 88–99 g. (73–83%); m.p. 103–110° (Note 5).

2. Notes

1. Commercial absolute ethanol is dried by heating with sodium and diethyl succinate and is then distilled directly into the reaction flask.
2. If the toluene method to remove all the ethanol is not used, the yield is lower by 5–10%.
3. Triethyl oxalylsuccinate begins to decompose at 84° at 760 mm. It cannot be distilled without decomposition even at a pressure of 1 mm.
4. The color of the α-ketoglutaric acid is darker if the pot temperature goes much above 90° during the evaporation and recrystallization.
5. The product is pure enough for most purposes. Further recrystallization from nitroethane does not improve the melting point.

3. Discussion

The present procedure is a modification of one reported in an earlier volume of *Organic Syntheses*.[2] The methods used to prepare triethyl oxalylsuccinate and α-ketoglutaric acid are summarized in that volume.

4. Merits of the Preparation

The advantages of this procedure over the earlier version are the use of sodium ethoxide instead of potassium ethoxide and better reproducibility.

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ether (60-29-7)

toluene (108-88-3)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

magnesium sulfate (7487-88-9)

potassium ethoxide (917-58-8)

α-Ketoglutaric acid, Glutaric acid, 2-oxo- (328-50-7)

Diethyl succinate (123-25-1)

diethyl oxalate (95-92-1)

nitroethane (79-24-3)

Triethyl oxalylsuccinate

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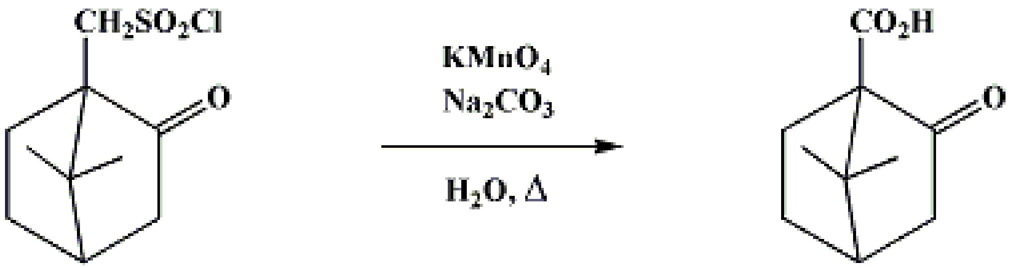
Organic Syntheses, CV 5, 689

DL-KETOPINIC ACID

[1-Apocamphanecarboxylic acid, 2-oxo-]



Submitted by Paul D. Bartlett and L. H. Knox[1].
Checked by John D. Roberts

1. Procedure

A 4-l. beaker containing a solution of 100 g. (0.95 mole) of anhydrous sodium carbonate in 900 ml. of water is placed on a steam bath, provision being made for efficient mechanical stirring. The stirrer is started and, when the solution is hot, one-third of a solution of 100 g. (0.63 mole) of potassium permanganate in 600 ml. of hot water is added all at once, followed by a 34-g. portion of DL-10-camphorsulfonyl chloride (Note 1). After an interval of 5–10 minutes, half the remaining permanganate is poured in, followed by 33 g. of the chloride. After a similar interval, the remaining permanganate solution and a final 33-g. portion of the chloride are added and heating is continued for an hour.

The excess permanganate is destroyed by adding a few milliliters of an acidified solution of sodium sulfite. The reaction mixture is cooled and made strongly acidic by cautious addition (foaming may occur) of 20% sulfuric acid. The mixture is heated, and the precipitated manganese dioxide is dissolved by stirring in powdered sodium sulfite (usually 70–80 g. is required). The resulting solution is cooled and extracted with one 200-ml., two 150-ml., and one 100-ml. portions of ether. The combined ether extracts are dried over anhydrous sodium sulfate and the bulk of the ether removed by distillation from a steam bath. The residue is evaporated in a crystallizing dish (Note 2). The crude acid (38–45 g.) is recrystallized from hot water. Considerable oiling may occur and 250–400 ml. of water is usually required to give complete solution. The yield of recrystallized acid is 28–32 g. (38–43%), m.p. 233–234° (Note 3).

2. Notes

1. The camphorsulfonyl chloride is the crude product obtained as described on p. 196. If it is not carefully dried, it should be oxidized reasonably promptly after its preparation. The oxidation is conveniently carried out in 100-g.

portions. Several reactions can easily be carried out in parallel.
2. The checker found it convenient to use a rotary evaporator at this point.
3. An additional small crop of crystals may be obtained by concentration of the mother liquor. The checker observed m.p. 240–242°.

3. Discussion

DL-Ketopinic acid has been prepared by oxidation of bornyl chloride with nitric acid at 20°[2] or with perbenzoic acid in acetic acid;[3] from 10,10-dinitrocamphan-2-ol[4] or apocamphan-2-ol-1-carboxylic acid[5] with alkaline permanganate; and from the oxidation of 10-camphorchlorosulfoxide, obtained from 10-camphorsulfonyl chloride by the action of pyridine, with potassium permanganate.[6] The present procedure represents a simplification of the latter and gives as high an overall yield.[7]

4. Merits of the Preparation

Ketopinic acid is of interest as a β-keto acid which fails to decarboxylate readily.[8] It may be converted to apocamphane-1-carboxylic acid.[7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 196

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

DL-Ketopinic acid

D,L-ketopinic acid

ketopinic acid

1-Apocamphanecarboxylic acid, 2-oxo-

apocamphan-2-ol-1-carboxylic acid

10-camphorchlorosulfoxide

apocamphane-1-carboxylic acid

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

ether (60-29-7)

sodium sulfite (7757-83-7)

nitric acid (7697-37-2)

potassium permanganate (7722-64-7)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

pyridine (110-86-1)

manganese dioxide (1313-13-9)

Perbenzoic acid (93-59-4)

10-CAMPHORSULFONYL CHLORIDE, camphorsulfonyl chloride, DL-10-Camphorsulfonyl chloride (6994-93-0)

10,10-dinitrocamphan-2-ol

bornyl chloride (464-41-5)

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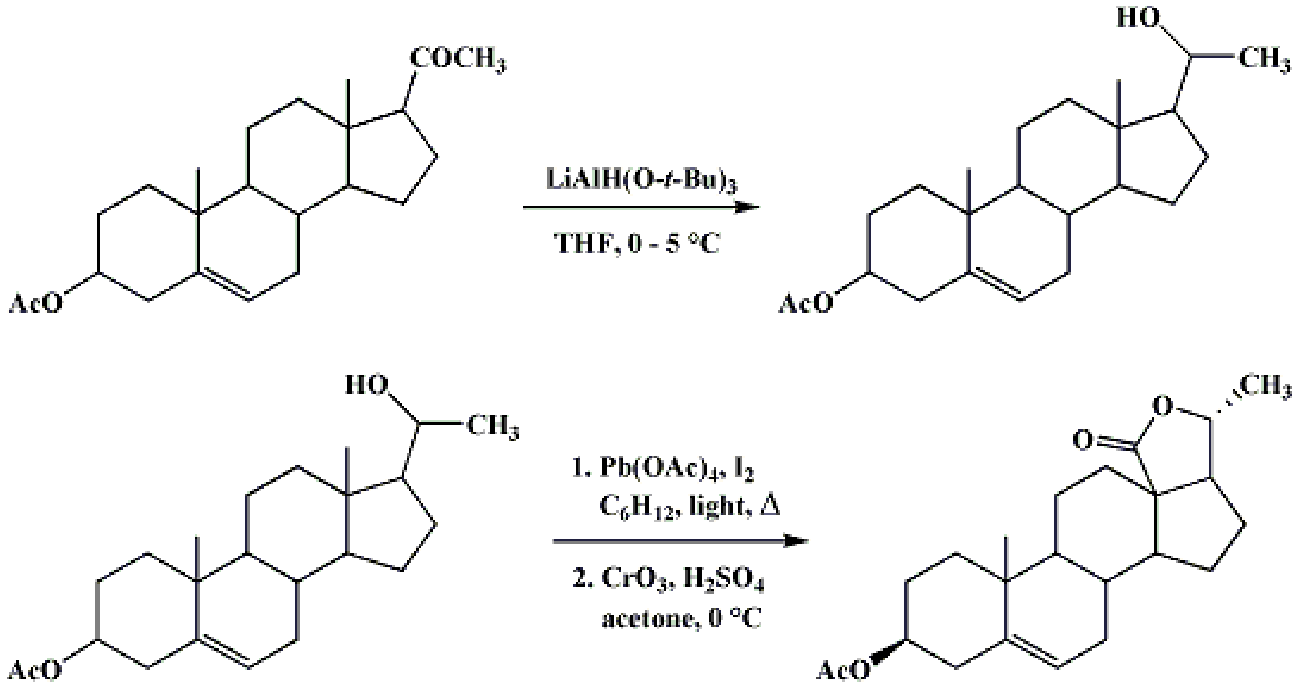
Organic Syntheses, CV 5, 692

18,20-LACTONE OF 3β-ACETOXY-20β-HYDROXY-5-PREGNENE-18-OIC ACID

[Pregn-5-en-18-oic acid, 3β,20β-dihydroxy, 18,20-lactone, 3-acetate]



Submitted by K. Heusler, P. Wieland, and Ch. Meystre[1].
Checked by E. J. Corey and William E. Russey.

1. Procedure

A. *3β-Acetoxy-20β-hydroxy-5-pregnene*. In a 2-l. five-necked flask fitted with a mechanical stirrer, 250-ml. dropping funnel, thermometer, nitrogen-inlet tube, and reflux condenser with calcium chloride tube is placed 750 ml. of anhydrous tetrahydrofuran (Note 1). The vessel is flushed with nitrogen, and 101.6 g. (0.4 mole) of lithium aluminum tri-*t*-butoxyhydride[2] (Note 2) is added. The suspension is cooled to about 2°, and 71.7 g. (0.2 mole) of pregnenolone acetate (Note 3) is added in one portion while stirring, the particles adhering to the wall of the flask being rinsed into the solution with an additional 50 ml. of tetrahydrofuran. The reaction mixture is stirred at 0–5° for 6 hours. A solution of 100 g. of ammonium sulfate in 150 ml. of water is added, with stirring, over a 15–20 minute period through the dropping funnel, the temperature of the reaction mixture being kept below 10° by efficient cooling with ice. A considerable quantity of hydrogen is evolved. There is added 20 g. of filter aid (Celite® or Hyflo Supercel®), the mixture is stirred for another 30 minutes, and it is finally filtered with suction through a layer of filter aid. The reaction vessel is rinsed and the filter residue thoroughly washed with 1.5 l. of tetrahydrofuran (Note 4). The filtrate is evaporated to dryness under reduced pressure. The crystalline residue is dissolved in 750 ml. of hot acetone, filtered (if necessary), and the solution is concentrated to a volume of about 200 ml. (crystallization may begin during this evaporation). The flask is kept overnight at 0° to −10° and the product isolated by suction filtration. The crystals are washed with 75 ml. of ice-cold acetone and dried at 60°. The yield of the product is 54–57 g. (75–79%), m.p. 161–164°,[3] $[\alpha]^{25}D$ −74° (*c* 1.0, $CHCl_3$) (Note 5).

B. 3β-*Acetoxy-18-iodo- and 18-hydroxy-18,20*β-*oxido-5-pregnene*. In a 5-l. three-necked flask fitted

with a mechanical stirrer, a thermometer, and a reflux condenser are placed 3 l. of cyclohexane (Note 6), 180 g. (*ca.* 0.37 mole) of commercial lead tetraacetate containing approximately 10% acetic acid (Note 7), 24 g. (0.095 mole) of iodine and 30 g. (0.083 mole) of 3β-acetoxy-20β-hydroxy-5-pregnene. The reaction mixture is stirred and heated to the boiling point by irradiation with a 1000-watt lamp (Note 8) from underneath. When the iodine color has disappeared (usually after about 60–90 minutes) (Note 9), the reaction mixture is cooled to room temperature, filtered with suction, and the filter residue with 600 ml. of cyclohexane. The filtrate is washed with two 500-ml. portions of 5% sodium thiosulfate solution and then with water. The combined aqueous solutions are extracted once with 500 ml. of ether. To the combined organic layers is added 6 ml. of pyridine, the solution is dried over sodium sulfate, filtered (Note 10), and the solvent evaporated under reduced pressure at a bath temperature of 35–40° (preferably by using a rotary evaporator). About 60 g. of an oily residue (Note 11), which is immediately oxidized (Note 12), is obtained.

C. *Oxidation to the 18,20-lactone of* 3β-*acetoxy-20*β-*hydroxy-5-pregnene-18-oic acid*. The above residue is dissolved in 600 ml. of acetone (Note 13), the solution is transferred to a 3-l. three-necked flask with a rigid mechanical stirrer, a dropping funnel, and a thermometer; the evaporation flask is rinsed with an additional 120 ml. of acetone. The solution is cooled to 0° to +5°, and 38.4 ml. of a chromic acid solution[4] (prepared by mixing 13.3 g. of chromium trioxide and 11.5 ml. of concentrated sulfuric acid and carefully diluting the mixture to 50.0 ml. with water while cooling) is slowly added within 10 minutes from the dropping funnel. The mixture is stirred (Note 14) for another 30 minutes at 0° to +5°, and a solution of 270 g. of crystalline sodium acetate in 780 ml. of water is added. The dark green solution is transferred to a separatory funnel, and it is extracted once with 2.4 l. and once with 600 ml. of benzene. Each extract is washed twice with 600 ml. of half-saturated sodium chloride solution, dried over sodium sulfate, and the solvent is evaporated under reduced pressure. The combined semisolid residue (48–50 g.) is triturated with 50 ml. of ether and kept overnight at 0° to –10°. The crude product is filtered, and the filter residue is washed with pentane. The yield of crystalline lactone is 14–16 g. (45–52% based on pure 3β-acetoxy-20β-hydroxy-5-pregnene). For further purification the product is dissolved in 200 ml. of hot acetone, if necessary 250 mg. of charcoal is added, the mixture is brought to the boiling point on a steam bath, filtered through a layer of filter aid, and the filter residue is washed with warm acetone. The solution is concentrated on the steam bath to a volume of about 90 ml. During this operation, crystallization begins. Then 150 ml. of hexane is added. the mixture is again concentrated to a volume of about 50–80 ml. with swirling, and finally kept at 0° overnight. A first crop of 12.0–13.5 g. (39–43%) of pure lactone, m.p. 201–206°, is obtained, $[\alpha]^{25}_D$ –44° to –45° (*c* 1.0, $CHCl_3$). Concentration of the mother liquor yields a second crop of 0.3–2.7 g. of less pure lactone.

2. Notes

1. Tetrahydrofuran freshly distilled from lithium aluminum hydride should be used. A commercial product with a peroxide content giving a positive iodine test must be treated with about 0.3% of cuprous chloride (boiling for 30 minutes and distillation) before the addition of the hydride. *[Caution! See p. 976.]*
2. Obtained from Metal Hydrides Inc., Beverly, Massachusetts.
3. A commercial product, m.p. 142.5–148.5°; $[\alpha]^{20}_D$ +141.5° (*c* 1.003, $CHCl_3$) was used.
4. Tetrahydrofuran free of peroxide, distilled from cuprous chloride, may be used. *[Caution! See p. 976.]*

5. The first crop of the product contains only a trace of the 20α-epimer.[3] The main portion of this compound is found in the mother liquor. Use of the material of a second crop for the subsequent steps is not recommended. The residue of the mother liquor can, however, be

reoxidized to pregnenolone acetate by the method described in step C. By crystallization of the oxidation product of the mother liquor residue from methanol, 13–14 g. of pure pregnenolone acetate can be recovered.

6. Commercial product, redistilled. Small amounts of cyclohexene do not interfere.

7. Obtained from Fluka A. G., Buchs, S. G., Switzerland, and Arapahoe Chemical Co., Boulder, Colorado. Dry lead tetraacetate may also be used.

8. An ordinary 1000-watt lamp was used for heating as well as irradiation. The light reduces the induction period and accelerates the reaction. It is important that the solution be at reflux during the irradiation; an aluminum foil tent may be used to prevent excessive loss of energy from the light/heat source. In smaller runs the intensity of the light should be reduced accordingly (see (Note 9)).

9. The disappearance of the iodine color is not indicative of the end of the reaction, since lead tetraacetate itself reacts with iodine under the reaction conditions giving lead diacetate, carbon dioxide, and methyl iodide. Under intense irradiation the decolorization can take place very quickly. In this case the rate of the decomposition of lead tetraacetate becomes comparable to the rate of the desired hypoiodite reaction, and the intermediate 18-iodo-20-alcohol will accumulate. The latter compound is oxidized by chromic acid to the 18-iodo-20-ketone. If an accumulation of the iodo alcohol is observed, a weaker light source or a larger excess of lead tetraacetate and iodine should be used to bring the reaction to completion.

10. The filtrate contains labile iodine derivatives which in light and at room temperature give off iodine. If the solution is not concentrated immediately, it should be kept at 0° in the dark; but it should be processed within less than 4 hours because of the instability of the hemiacetal-type intermediate.

11. The oil contains considerable amounts of derivatives formed by reaction with the solvent, *e. g.*, cyclohexanol acetate, bicyclohexyl, and a number of high-boiling, iodine-containing substances. These by-products are removed only after oxidation.

12. It is important to oxidize the product as soon as possible because the crude 18,20-hemiacetal is unstable. In solution, in the presence of traces of acid, bimolecular anhydro products are formed which are stable to chromic acid oxidation and greatly diminish the yield of lactone.

13. Commercial acetone, boiled with 0.05% potassium permanganate for about 2 hours and distilled from potassium carbonate, was used.

14. The chromium sulfate tends to aggregate in large lumps. The stirrer should therefore be rigid and at least an inch away from the bottom of the flask.

3. Discussion

The preparation of the title lactone has been described by a multistep synthesis from holarrhimine.[5 6] The method described in detail above is essentially an application of the "hypoiodite reaction" published by Ch. Meystre and co-workers.[7] These authors also describe the isolation of the intermediate hemiacetal in pure form. Saturated lactones epimeric at C-20 have also been obtained by chromic acid oxidation of 18,20-dihydroxy compounds[8] which were in turn prepared by treatment of 20-hydroxypregnanes with lead tetraacetate, acetolysis of the resulting 18,20β-oxides, and hydrolysis. Saturated lactones of the 20α- and 20β-series were also obtained by photolysis of the corresponding 20-nitrites, hydrolysis, and oxidation.[9]

4. Merits of the Preparation

For the substitution of the angular methyl groups in steroids five methods are known: (a) homolysis of N-chloramines [Löffler-Freytag reaction[10] (only C-18)]; (b) oxidation of alcohols with lead

tetraacetate;[11] (c) photolysis of nitrite esters;[12] (d) homolysis of hypochlorites;[13] (e) the "hypoiodite reaction."[14]

Of these methods the hypoiodite cleavage appears to be the simplest and most efficient one. It leads directly to compounds which are oxidized at the angular C-18 substituent to the aldehyde stage. In common with method (b), it has the advantage that an alcohol can be used directly as starting material, which under the reaction conditions is transformed into a derivative which is then homolytically cleaved; but, in contrast to method (b), the hypoiodite method is much less susceptible to steric effects, 20β-alcohols being oxidized almost as efficiently as 20α-alcohols. Methods (a), (c), and (d) require the formation of reactive derivatives in a separate step before homolysis. No special apparatus or special light source is needed for the hypoiodite reaction. Further applications and the scope of the reaction are discussed elsewhere.[15]

The lactone described can be used as starting material for the preparation of a number of 18-oxygenated steroids. Hydrolysis and Oppenauer oxidation[6,7] leads to the 18,20-lactone of 3-oxo-20β-hydroxy-4-pregnene-18-oic acid. This lactone is a suitable starting material for the preparation of 18-hydroxy- and 18-oxoprogesterone.[16] On the other hand, microbiological oxidation leads to the corresponding 11α-hydroxylactone[17] which is a suitable starting material for the preparation of aldosterone.[18]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 529
- Org. Syn. Coll. Vol. 5, 976

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

18,20-LACTONE OF 3β-ACETOXY-20β-HYDROXY-5-PREGNENE-18-OIC ACID

lithium aluminum tri-t-butoxyhydride

3β-Acetoxy-18-iodo- and 18-hydroxy-18,20β-oxido-5-pregnene

18,20-lactone of 3-oxo-20β-hydroxy-4-pregnene-18-oic acid

18-hydroxy- and 18-oxoprogesterone

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

Benzene (71-43-2)

methanol (67-56-1)

ether (60-29-7)

sodium acetate (127-09-3)

hydrogen (1333-74-0)

potassium permanganate (7722-64-7)

Cyclohexene (110-83-8)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

sodium thiosulfate (7772-98-7)

nitrogen (7727-37-9)

aluminum (7429-90-5)

carbon dioxide (124-38-9)

cyclohexane (110-82-7)

iodine (7553-56-2)

acetone (67-64-1)

pyridine (110-86-1)

lead diacetate

chromic acid (7738-94-5)

cuprous chloride (7758-89-6)

Methyl iodide (74-88-4)

ammonium sulfate (7783-20-2)

Pentane (109-66-0)

chromium sulfate (15244-38-9)

chromium trioxide (1333-82-0)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

hexane (110-54-3)

pregnenolone acetate

Pregn-5-en-18-oic acid, 3β,20β-dihydroxy, 18,20-lactone, 3-acetate

3β-Acetoxy-20β-hydroxy-5-pregnene (14553-79-8)

cyclohexanol acetate (622-45-7)

bicyclohexyl (92-51-3)

aldosterone

lead tetraacetate

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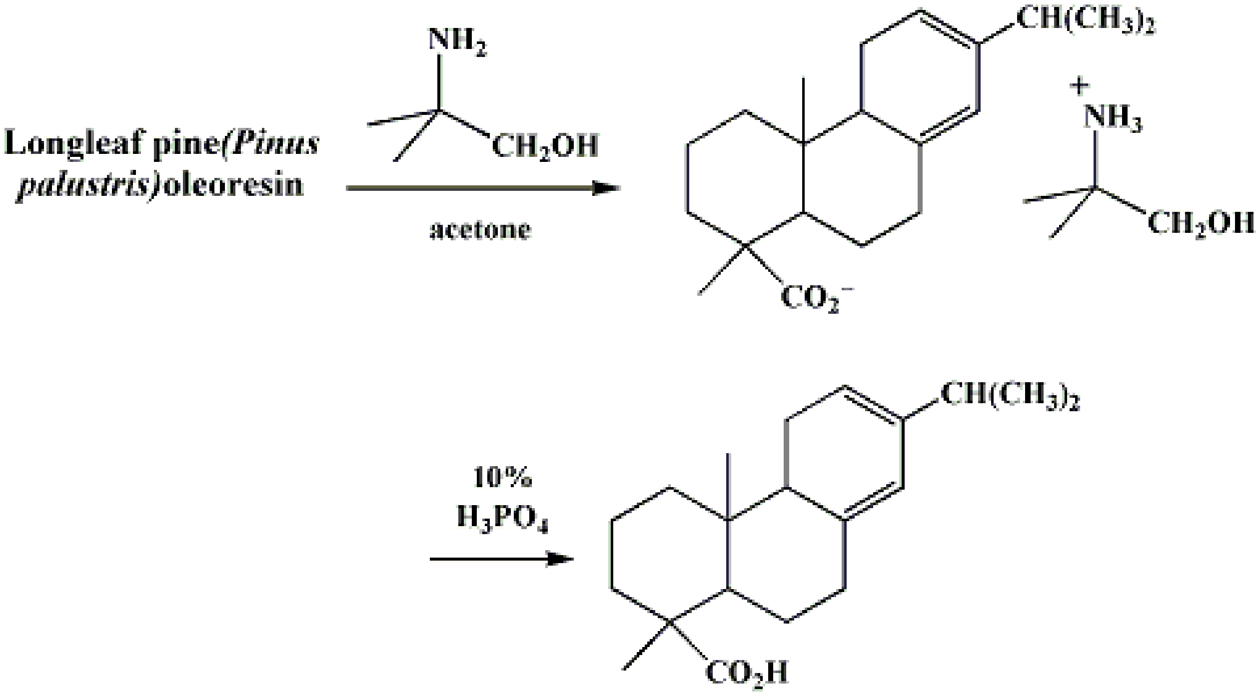
Organic Syntheses, CV 5, 699

LEVOPIMARIC ACID



Submitted by Winston D. Lloyd and Glen W. Hedrick[1].
Checked by William G. Dauben and Robert M. Coates.

1. Procedure

Pine oleoresin [1 kg. containing 260 g. (0.86 mole) of levopimaric acid] (Note 1) and (Note 2) is dissolved in 2 l. of acetone in a 4-l. beaker. A solution of 200 g. (2.2 moles) of 2-amino-2-methyl-1-propanol (Note 3) in 200 ml. of acetone is added as rapidly as possible with stirring. The pasty precipitate which forms almost immediately is collected by suction filtration and is pressed as dry as possible using a rubber dam (Note 4). The crude moist precipitate is returned to a 2-l. beaker and is dissolved in the minimum volume (1 l.) of boiling methanol. The methanolic solution is cooled to 5° in a refrigerator and stirred occasionally to expedite crystallization. When the crystallization is completed, the solid is collected by suction filtration. The precipitate is redissolved in a minimum volume of boiling methanol (1 l.) (Note 5), the solution concentrated to two-thirds its original volume (Note 6), cooled to 5°, and the amine salt allowed to crystallize. The solid is filtered by suction, and the filter cake is air-dried to yield 68–78 g. (20–23% of the available levopimaric acid) of the 2-amino-2-methyl-1-propanol salt of levopimaric acid, $[\alpha]^{25}D$ –202° (Note 7) and (Note 8). The recrystallization is repeated; approximately 0.8 l. of boiling methanol is used and then concentrated, the yield of amine salt is 41–46 g. (12–14% of the available levopimaric acid), $[\alpha]^{25}D$ –210° (Note 9).

In a 1-l. separatory funnel there are first placed 400 ml. of ether and 75 ml. of 10%

phosphoric acid (Note 10), and then the above amine salt is added (Note 11). The mixture is shaken vigorously for a few minutes, an additional 50 ml. of 10% phosphoric acid added, and the vigorous shaking continued until all the solid has disappeared. The ether layer is separated, washed twice with 100-ml. portions of water, and dried over anhydrous sodium sulfate. The drying agent is separated by filtration, the ether is removed at room temperature under reduced pressure using a rotary evaporator, and the residue dissolved in 40–60 ml. of boiling ethanol. The levopimaric acid is collected by suction filtration, yield 26–31 g. (10–12%), m.p. 147–150°, $[\alpha]^{25}D$ –265° (Note 12), (Note 13), and (Note 14).

2. Notes

1. The longleaf pine (*Pinus palustris*) oleoresin used was analyzed by the method of Lloyd and Hedrick[2] and was found to contain a total resin acid content of 660 g. The oleoresin used by the checkers was obtained from Shelton Naval Stores Co., Valdosta, Georgia. The oleoresin can also be obtained from the following sources: K. S. Varn and Co., Hoboken, Georgia; The Langdale Co., Valdosta, Georgia; Vidalia Gum Turpentine Co., Vidalia, Georgia; Stallworth Pine Products Co., Mobile, Alabama; Filtered Rosin Products Company, Baxley, Georgia; Taylor-Lowenstein and Co., Mobile, Alabama; and Nelio Chemicals, Inc., Jacksonville, Florida.
2. If any woody material remains undissolved, it should be removed by filtration of the acetone solution.
3. The 2-amino-2-methyl-1-propanol, m.p. 25–29°, N.E. 88.5–99.0, was obtained from the Commercial Solvents Corporation and was used without further purification. The checkers obtained their material from Matheson Coleman and Bell Co.
4. The use of a rubber dam is essential in this step to effect the separation of the residual acetone. It is also beneficial to use a rubber dam in the other suction filtrations in this process.
5. If a clear solution is not obtained, the undissolved material should be removed by filtration.
6. Concentration of the solution at this point gives a major improvement in yield. Crystallization does not occur during this concentration step unless the solution is seeded.
7. All rotations were taken with a 2% methanolic solution.
8. If the rotation is –210° or more negative, the next recrystallization may be omitted and the levopimaric acid generated directly.
9. The maximum observed rotation for the 2-amino-2-methyl-1-propanol salt of levopimaric acid is $[\alpha]^{24}D$ –218°.[3] Methanol and ethanol solutions give the same specific rotations, but methanol is the preferred solvent because the time required to effect solution in ethanol is longer. If pure levopimaric acid, m.p. 151–153°, $[\alpha]^{24}D$ –276° is desired, the salt with –210° rotation should be dissolved in 8 parts of boiling methanol, the solution concentrated to the point of incipient crystallization, cooled, and filtered. The yield in this recrystallization is about 70%.
10. The submitters find phosphoric acid more convenient than boric acid[3] or acetic

acid.[4] Acid isomerization to abietic acid[3,5] did not occur under the conditions used here.

11. After an induction period of approximately 1 week, the amine salt begins to be oxidized by air and the salt should be converted to levopimaric acid as soon as possible after it has been isolated.

12. The checkers found that their material with $[\alpha]^{25}D$ –260° had a melting point at 125–150°. The melting point is very sensitive to impurities, and a few percent of impurities can lower it drastically.

13. The yields obtained using this procedure can vary with the source of the oleoresin; the submitters report a yield of 29–34% of levopimaric acid.

14. Using slash pine (*Pinus elliotti*) oleoresin containing approximately 16% of levopimaric acid,[6,7] the submitters found yields consistently less than their reported 29–34%. Pine "scrape," a material which crystallizes on the surface of the pine tree, has been used in a similar process[4] but gives highly variable yields and, owing to interference by oxidation products, may fail to give the desired material. To avoid the deleterious effects of oxidized materials, the use of fresh oleoresin is recommended.

3. Discussion

The described process of isolating levopimaric acid is based on the method of Summers, Lloyd, and Hedrick.[8] The procedure, a modification of the process devised by Harris and Sanderson[3] and Loeblich, Baldwin, O'Connor, and Lawrence,[4] is more convenient and gives improved yields.

4. Merits of the Preparation

In pine oleoresin, many resin acids occur. This procedure illustrates how, by the use of a specific amine, it is possible to get a specific precipitation of one resin acid from a mixture of acids.

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Appendix

Compounds Referenced (Chemical Abstracts Registry Number)

LEVOPIMARIC ACID

2-amino-2-methyl-1-propanol salt of levopimaric acid

ethanol (64-17-5)

acetic acid (64-19-7)

methanol (67-56-1)

ether (60-29-7)

sodium sulfate (7757-82-6)

acetone (67-64-1)

phosphoric acid (7664-38-2)

boric acid (10043-35-3)

2-amino-2-methyl-1-propanol (124-68-5)

ABIETIC ACID (514-10-3)

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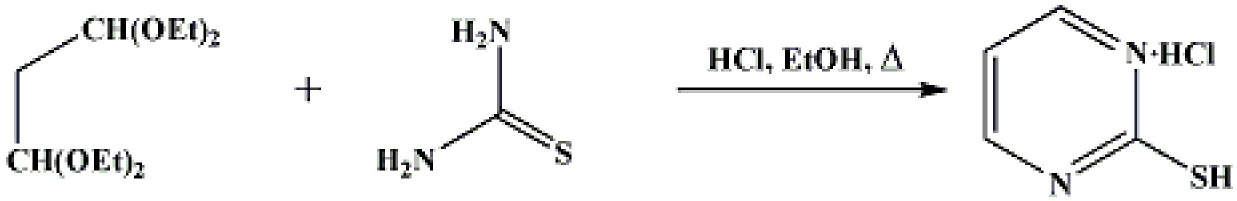
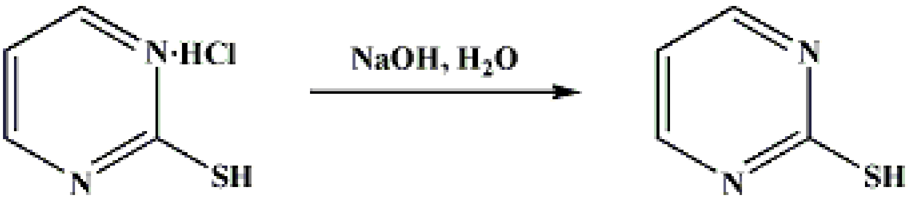
2-MERCAPTOPYRIMIDINE

[2-Pyrimidinethiol]





Submitted by Donald G. Crosby, Robert V. Berthold, and Herbert E. Johnson[1].
Checked by B. Bellin, J. L. Gibbs, and V. Boekelheide.

1. Procedure

A. *2-Mercaptopyrimidine hydrochloride*. Thiourea (61 g., 0.80 mole) and 600 ml. of ethyl alcohol (Note 1) are placed in a 2-l. three-necked flask equipped with a sealed mechanical stirrer, a reflux condenser, and a stopper. The stirrer is started, and 200 ml. of concentrated hydrochloric acid is added in one portion through the open neck. After several minutes, when the warm mixture has become homogeneous, 176 g. (0.80 mole) of commercial-grade 1,1,3,3-tetraethyoxypropane (Note 2) is added rapidly, the open neck is stoppered, and the yellow solution is boiled for about 1 hour with continuous stirring. During this period the reaction mixture darkens in color and the product separates (Note 3).

The reaction mixture is chilled to about 10° by immersing it in an ice bath for about 30 minutes, and the yellow crystalline precipitate is collected on a Büchner funnel. It is then washed with 100 ml. of cold alcohol and air-dried at room temperature. The yield of 2-mercaptopyrimidine hydrochloride is 71–76 g. (60–64%). The product is pure enough for most purposes (Note 4), but it may be recrystallized by dissolving it in 12*N* hydrochloric acid (10 ml. per gram of solid) at about 75°, filtering the hot solution through glass wool or a sintered glass filter, chilling the filtrate in ice, and collecting the golden-yellow crystals on a sintered glass filter. Recovery is 60–65% (Note 5).

B. *2-Mercaptopyrimidine*. Crude 2-mercaptopyrimidine hydrochloride (25 g., 0.17 mole) is suspended in 50 ml. of water in a beaker and stirred rapidly while a 20% aqueous solution of sodium hydroxide (about 27 ml.) is added until the pH of the

mixture is 7–8 (Note 6). The precipitated solid is collected on a Büchner funnel and washed on the funnel with 50 ml. of cold water. The damp product is dissolved by heating it in a mixture of 300 ml. of water and 300 ml. of alcohol on the steam bath, and the hot solution is filtered through a fluted paper and allowed to cool slowly to room temperature. The crystals of 2-mercaptopyrimidine are collected, washed with about 50 ml. of the aqueous alcohol, and dried either at room temperature overnight or for several hours in an oven at 110°. The yield is 15–16 g. (80–85%) of yellow needles, m.p. 218–219° (sealed tube).

2. Notes

1. Either commercial absolute alcohol or the 95% grade may be used.
2. 1,1,3,3-Tetraethoxypropane is available from Kay-Fries Chemicals, Inc., New York 16, New York, or from Distillation Products Industries, Rochester 3, New York, and may be used without further purification.
3. Longer boiling does not affect the yield but causes the product to be somewhat dark-colored. A shorter heating period or lack of mechanical stirring decreases the yield.
4. Electrometric titration shows the purity to be at least 95%. The product does not melt below 300°.
5. If concentrated sulfuric acid is substituted for the hydrochloric acid in the procedure, 2-mercaptopyrimidine bisulfate is obtained in about 50% yield. Recrystallization from aqueous acetic acid provides the bisulfate as yellow needles, m.p. 186–186.5°. (*Anal.* Calcd. for $C_4H_6N_2O_4S_2$: C, 22.9; H, 2.9. Found: C, 23.1; H, 2.9.)
6. pH indicator paper may be used, or the solution may be made weakly basic to litmus. Excess base dissolves the product and should be avoided.

3. Discussion

The synthesis of 2-substituted pyrimidines from 1,3-dicarbonyl compounds and urea derivatives was first described by Evans[2] and was later improved by Hunt, McOmie, and Sayer[3] for the preparation of 2-mercapto-4,6-dimethylpyrimidine. Burness[4] employed 3-ketobutyraldehyde acetal in this procedure to give 2-mercapto-4-methylpyrimidine. 2-Mercaptopyrimidine has been prepared from 1,1,3,3-tetraethoxypropane and thiourea by variations of this basic method[3,5,6] as well as by the reaction of 2-chloropyrimidine with thiourea[7] or sodium hydrosulfide.[8]

4. Merits of the Preparation

This preparation describes a convenient and general method of synthesis of substituted pyrimidines from compounds containing a β-dicarbonyl group, either intact or as the corresponding ketal. The usefulness of the 2-mercaptopyrimidines is enhanced by the ease of removal of the mercapto group by desulfurization[9] or oxidation[10] and its

replacement by other functional groups.[10]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

1,1,3,3-tetraethyoxypropane

2-mercaptopyrimidines

ethyl alcohol, alcohol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

sodium hydroxide (1310-73-2)

urea (57-13-6)

thiourea (62-56-6)

sodium hydrosulfide

2-Chloropyrimidine (1722-12-9)

2-Mercaptopyrimidine, 2-Pyrimidinethiol (1450-85-7)

2-mercaptopyrimidine hydrochloride

1,1,3,3-Tetraethoxypropane (122-31-6)

2-mercaptopyrimidine bisulfate

2-mercapto-4,6-dimethylpyrimidine (22325-27-5)

3-ketobutyraldehyde acetal

2-mercapto-4-methylpyrimidine

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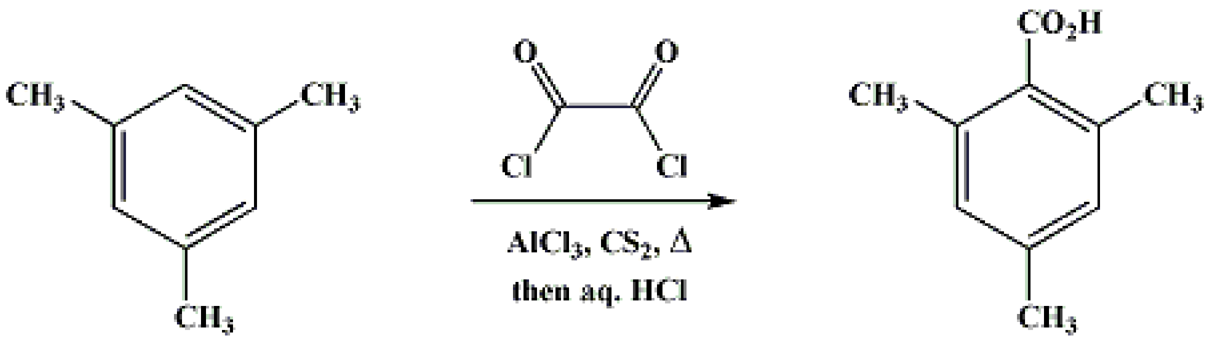
MESITOIC ACID

[Benzoic acid, 2,4,6-trimethyl-]



Submitted by Phillip E. Sokol[1]
Checked by Melvin S. Newman and Vern G. DeVries.

1. Procedure

Caution! The reaction should be carried out in a hood because carbon monoxide is evolved.

The apparatus consists of a 2-l. three-necked flask fitted with a sealed stirrer, a 500-ml. addition funnel, and a condenser protected by a drying tube connected to an alkaline trap. In it are placed 146 g. (1.10 moles) of anhydrous aluminum chloride (Note 1) and 700 ml. of dry carbon disulfide. The suspension is cooled to 10–15° in an ice bath, and 139 g. (1.10 moles) of oxalyl chloride (Note 2) is added dropwise with stirring over a 30-minute period. After this addition the reaction mixture is stirred for 15 minutes. A solution of 120 g. (1.00 mole) of mesitylene (Note 3) in 200 ml. of dry carbon disulfide is added dropwise with stirring over a 1-hour period to the mixture, the temperature being maintained at 10–15°. Hydrogen chloride evolution is observed after about 5 minutes, and a red complex soon forms.

After the addition is completed, the reaction mixture is refluxed for 1 hour and is then poured very cautiously with manual stirring onto a mixture of 2 kg. of crushed ice and 300 ml. of 12*N* hydrochloric acid in a 4-l. beaker. The mixture thus formed is extracted with three 250-ml. portions of carbon tetrachloride. The combined organic extracts are washed with two 500-ml. portions of water, and the acid is then extracted with 500 ml. of ice-cold 10% sodium hydroxide solution. The aqueous extract is then slowly added to 250 ml. of 6*N* hydrochloric acid. The suspension is cooled, and the mesitoic acid is separated by filtration, washed thoroughly with water, and dried. The colorless crude acid (m.p. 149–150°) weighs 106–124 g. (65–76%) (Note 4) and is sufficiently pure for most purposes (Note 5).

2. Notes

1. Good results have been obtained with several different varieties of anhydrous aluminum chloride.
2. High-purity commercial oxalyl chloride was used without further purification.
3. Commercial mesitylene of high purity (99+%) was used.
4. Similar yields were obtained when experiments were run on a 0.10-mole scale.
5. For recrystallization, 10 g. of crude acid is dissolved in 20 ml. of 45% methanol at reflux. About 9.5 g. of mesitoic acid, m.p. 153–154°. (uncor.),[2] is obtained.

3. Discussion

Mesitoic acid has been prepared by carbonation of mesitylmagnesium bromide;[2,3,4] by hydrolysis of its amide prepared by condensation of mesitylene with carbamyl chloride under the influence of aluminum chloride;[5] by oxidation of isodurene with dilute nitric acid;[6,7] by distillation of 2,4,6-trimethylmandelic acid (low yield);[8] by dry distillation of 2,4,6-trimethylphenylglyoxylic acid;[9] by oxidation of the latter with potassium permanganate;[10] and by treating 2,4,6-trimethylphenylglyoxylic acid with concentrated sulfuric acid in the cold[11] or with heating.[12]

4. Merits of the Preparation

The method described in this preparation of mesitoic acid avoids the preparation of bromomesitylene,[13] and the yield of acid is essentially the same as that from the two-step synthesis.[2,13] This procedure appears to be general and can be used to prepare such acids as α- and β-naphthoic acids,[14] cumenecarboxylic acid, 2,5-dimethylbenzoic acid, and durenecarboxylic acid. Carboxylic acids could not be obtained from benzothiophene, veratrole, *p*-dimethoxybenzene, and ferrocene under the conditions of this reaction. Although there has been no exhaustive study, this procedure is probably applicable to a variety of aromatic compounds, especially alkylated aromatics. Aromatic compounds which readily undergo oxidation, *e.g.*, ferrocene, catechol, and hydroquinone, do not lend themselves to this method.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 420

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Ferrocene

sulfuric acid (7664-93-9)

hydrogen chloride, hydrochloric acid (7647-01-0)

methanol (67-56-1)

sodium hydroxide (1310-73-2)

carbon monoxide (630-08-0)

hydroquinone (123-31-9)

nitric acid (7697-37-2)

potassium permanganate (7722-64-7)

carbon tetrachloride (56-23-5)

aluminum chloride (3495-54-3)

carbon disulfide (75-15-0)

Catechol (120-80-9)

Mesitylene (108-67-8)

Bromomesitylene (27129-86-8)

Isodurene (527-53-7)

carbamyl chloride

veratrole (91-16-7)

oxalyl chloride (79-37-8)

2,4,6-trimethylphenylglyoxylic acid (3112-46-7)

mesitylmagnesium bromide

Mesitoic acid, Benzoic acid, 2,4,6-trimethyl- (480-63-7)

2,4,6-trimethylmandelic acid

p-dimethoxybenzene (150-78-7)

durenecarboxylic acid

benzothiophene (95-15-8)

cumenecarboxylic acid

2,5-dimethylbenzoic acid (610-72-0)

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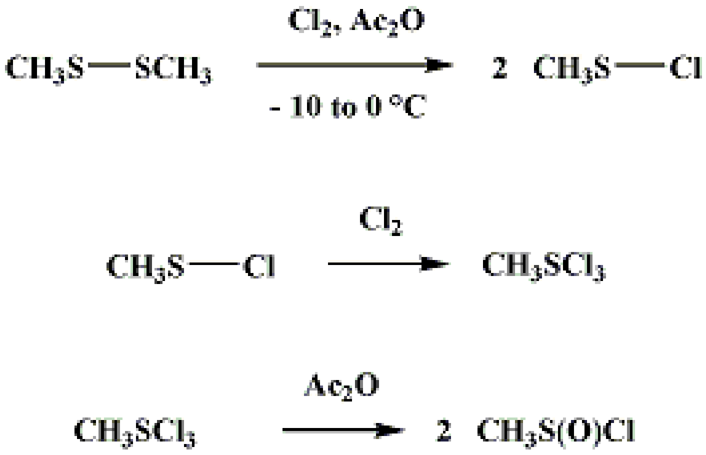
Organic Syntheses, *CV 5, 709*

METHANESULFINYL CHLORIDE

[Method I]



Submitted by Irwin B. Douglass and Richard V. Norton[1].
Checked by R. D. Thompson and Henry E. Baumgarten.

1. Procedure

In a 500-ml., three-necked flask, fitted with an efficient sealed stirrer, a gas inlet tube extending within 1 in. of the reaction mixture but not below its surface, a gas outlet tube connected to a calcium chloride tube, and a low-temperature thermometer to register the temperature of the reaction mixture, are placed 23.55 g. (0.25 mole) of freshly distilled methyl disulfide (Note 1) and 51.05 g. (0.5 mole) of acetic anhydride (Note 2). The reaction flask is then partially immersed in a bath of acetone cooled by dry ice until the internal temperature has reached 0° to −10°. The temperature is maintained within these limits throughout the reaction (Note 3). The reaction is best carried out in a well-ventilated hood.

Chlorine is passed into the well-stirred mixture at such a rate that the temperature is controlled between 0° and −10°. The progress of the reaction can be followed by color changes. At first the mixture turns yellow, then reddish as methanesulfenyl chloride (CH_3SCl) accumulates but gradually the color fades, and the mixture may become colorless. The addition of chlorine is terminated when a faint greenish-yellow color indicates an excess of chlorine (Note 4).

The reaction mixture is then transferred (Note 5) with a few fresh chips of porous plate to a distilling flask having a thermometer well, and the flask is fitted to a 12- to 18-in. Vigreux column and vacuum distillation apparatus. The fraction collector of the latter is connected through a trap cooled in an acetone-dry ice bath and a safety trap to a water pump. The cold trap must have sufficient capacity to contain, without backing up, all the acetyl chloride formed in the reaction.

The pressure is gradually decreased without heating the flask. The excess chlorine rapidly escapes and at 15 mm. the acetyl chloride boils smoothly below 0°. No heat is applied until most of the acetyl chloride has been removed (Note 6). Heat is then gradually increased until at 47–48° (15 mm.) the methanesulfinyl chloride distills as a nearly colorless liquid with n_D^{25} 1.500 (lit.[2] n_D^{25} 1.5038). Its nmr spectrum shows a single peak at δ 3.33 ppm with no sign of a singlet at δ 3.64 ppm, the frequency characteristic of methanesulfonyl chloride. The yield is 41–42 g. (83–86%) (Note 7).

[Method II]

$$CH_3SSCH_3 + 3Cl_2 \longrightarrow 2CH_3SCl_3$$

$$CH_3SCl_3 + CH_3CO_2H \longrightarrow CH_3SOCl + CH_3COCl + HCl$$

Submitted by Irwin B. Douglass and Basil Said Farah[1].
Checked by Melvin S. Newman, J. T. Golden, and W. N. White..

1. Procedure

In a 1-l. three-necked flask, fitted with an efficient sealed stirrer, a gas inlet tube extending within 1 in. of the reaction mixture but not below its surface, and a gas outlet tube leading through a trap cooled in a dry ice-acetone bath to a hydrogen chloride absorption system (Note 8), are placed 94.2 g. (1 mole) of methyl disulfide (Note 9) and 120 g. (2 moles) of glacial acetic acid. The reaction flask is then surrounded by a bath of acetone cooled by dry ice until the internal temperature has reached 0° to −10°. The temperature is maintained within these limits throughout the reaction (Note 10) except that, toward the end, the temperature should be kept at −10° to −15° to minimize the escape of hydrogen chloride which might carry with it unreacted chlorine. The entire reaction is best carried out in a well-ventilated hood.

Three moles of chlorine (212.7 g.) is condensed in a tared flask cooled by a dry ice-acetone bath (Note 11). This flask is then connected to the gas inlet tube of the chlorination apparatus, and the cooling bath surrounding the chlorine container is removed. After about 2 hours the chlorine has all been absorbed by the reaction mixture (Note 12).

When the last of the chlorine has been added, the cooling bath is removed and, while vigorous stirring is continued (Note 13), the reaction mixture is allowed slowly to warm to room temperature. During this period there is a vigorous evolution of hydrogen chloride. The flask is finally warmed to 35° to facilitate the escape of more hydrogen chloride.

The reaction mixture and contents of the cold trap and then transferred (Note 14) to a 500-ml. distilling flask attached through a short fractionating column to a water-cooled condenser which is connected in series to a receiver, a trap cooled in a dry ice-acetone

bath, and a hydrogen chloride absorption trap which may later be attached to a water pump. The mixture is then distilled until the pot temperature reaches 100° and practically all of the acetyl chloride has been driven over.

The residue, consisting chiefly of methanesulfinyl chloride, is then cooled immediately to 20° or lower and transferred to a 250-ml. flask and distilled through the same equipment under reduced pressure to remove the remaining acetyl chloride and other lower-boiling impurities. As the pot temperature begins to rise, a yellow intermediate fraction is collected very slowly until the distillate and pot temperatures are within 3° of each other (Note 15). At this point the distillation is temporarily discontinued while the accumulated acetyl chloride (Note 16) is removed from the cold trap and the receiver for the main product is attached. On resuming distillation the main product should come over within a 5° boiling range, and the distillation and pot temperature should remain within 2° of each other until the major part of the product has distilled. The yield is 161–177 g. (82–92%) of straw-colored or yellow product boiling at 55–59° (40 mm.) and having n_D^{25} 1.500–1.501 (Note 7).

2. Notes

1. The submitters used methyl disulfide obtained from the Crown Zellerback Corporation, Chemical Products Division, Camas, Washington, which was dried and redistilled. The fraction boiling at 108–109° was used. The checkers used methyl disulfide obtained from the Aldrich Chemical Co., Inc.

2. The success of the reaction is closely related to having stoichiometric quantities of reagents. An excess of disulfide will produce a colored product due to the presence of methanesulfenyl chloride or products from the decomposition of methylsulfur trichloride. An excess of acetic anhydride will give a problem of purification during distillation, or if chlorine is also in excess, will lead to the formation of methanesulfonyl chloride.[3]

3. The reaction of acetic anhydride with methylsulfur trichloride is temperature dependent. If the chlorination is carried out at too low a temperature (>–20°), solid methylsulfur trichloride separates as white crystals which may cause the reaction mixture to become semi-solid. At 0° to –10°, however, no solid trichloride is observed.

4. At the colorless stage, the weight of the reaction mixture indicates that a stoichiometric quantity of chlorine has been added. In some preparations, a colorless condition is not achieved and one depends on the color of excess chlorine to indicate the end of the reaction. Excess chlorine does not seem to affect the quality of the product. An alternative to depending on the color change to determine the end of the reaction is to condense the calculated weight of chlorine in a tube and allow it to evaporate quantitatively into the reaction mixture.

5. Because of the unpleasant nature of methanesulfinyl chloride, acetyl chloride, and chlorine, the transfer should be made in the hood.

6. It is not necessary to empty the acetyl chloride from the cold trap until after

the distillation is complete. Great care must be taken, however, to provide an intervening safety trap so that no water from the pump can back up into the trap holding the acetyl chloride.

7. Pure methanesulfinyl chloride boils at 48° (22 mm.) and 59° (42 mm.) and has n_D^{25} 1.5038, d_4^0 1.4044 and d_4^{25} 1.3706. On standing at room temperature, it slowly decomposes with the liberation of hydrogen chloride. It should not be stored for a long period in a tightly sealed container.

8. The hydrogen chloride absorption system must be of such design that there is no possibility for water to suck back into the reaction flask after a sudden surge of escaping hydrogen chloride.

9. The methyl disulfide was obtained from the Crown Zellerbach Corporation, Chemical Products Division, Camas, Washington, and redistilled. The 108–109° boiling fraction was used.

10. Crystalline acetic acid separates at first but redissolves as the reaction progresses.

11. The flask should be full of chlorine gas when the tare weight is taken. The success of this preparation depends in large measure on the use of stoichiometric quantities of all reagents. An excess or deficiency of any one will lead to an impure product and will greatly complicate the problem of purification.[2]

12. The white solid which collects inside the upper part of the flask is methylsulfur trichloride. This must be washed down with the cold reaction mixture before the flask warms to room temperature. The progress of the chlorination is accompanied by definite color changes. When one-third of the chlorine has been added, the reaction mixture is a deep reddish orange color which gradually fades as more chlorine is added until at the end the color should be a pale golden yellow or light straw color.

13. Vigorous stirring is necessary to prevent loss of material through too rapid escape of hydrogen chloride.

14. Since both methanesulfinyl and acetyl chlorides are unpleasant materials and the reaction mixture still contains much hydrogen chloride, all transfers should be made in the hood.

15. The difference between the distillation and pot temperature is closely related to the success of this preparation. If the specified weights of reactants and temperatures are employed a 3° temperature difference should be reached before the yellow intermediate fraction, probably containing methanesulfenyl chloride, chloromethanesulfenyl chloride, and acetic acid, has attained a volume of 10 ml. Toward the end of the distillation the pot temperature may begin to rise owing to the presence in the residue of methanesulfonyl chloride (b.p. 63°/20 mm., 72°/31 mm., 82°/48 mm.), methyl methanethiolsulfonate (b.p. 115°/15 mm.) or both. The residue at the end of the distillation should amount to less than 10 ml.

16. The acetyl chloride obtained is yellow in color, probably because of the presence of the sulfenyl chlorides mentioned above. The addition of cyclohexene will discharge the color (although a darker color develops later) and redistillation then yields a stable water-clear product. The yield of acetyl chloride varies from 60% to 85%, depending on the care with which liquids are

transferred and the vapors are trapped. The amount of sulfinyl chloride which may be recovered by redistilling the acetyl chloride fraction does not justify the time required.

3. Discussion

Alkanesulfinyl chlorides have been prepared by the action of thionyl chloride on alkanesulfinic acids[4,5] and by solvolysis of alkylsulfur trichlorides with water, alcohols, and organic acids.[2] Method II is an earlier procedure of the submitters,[6] which appears to be general for the preparation of sulfinyl chlorides in either the aliphatic or the aromatic series and is based on an improvement in the solvolysis method whereby the use of inert solvent is eliminated and the reaction is carried out in a one-phase system. In the submitters' laboratory this procedure has been supplanted by Method I which is superior to any of those previously employed in that the reaction is carried out in a homogeneous medium without the formation of hydrogen chloride gas. An adaptation of the present method is to chlorinate a mixture of a thiolester and acetic anhydride.[7] The latter modification is especially effective in the preparation of α-toluenesulfinyl chloride.

The present method seems to be general for the preparation of most sulfinyl chlorides in either the aliphatic or aromatic series. Benzyl and *t*-butyl disulfides, however, do not yield sulfinyl chlorides by this method because chlorine appears to cleave the carbon-sulfur rather than the sulfur-sulfur bonds.

Sulfinyl chlorides are highly reactive and unstable compounds. Methanesulfinyl chloride, at room temperature, disproportionates into methanesulfonyl and methanesulfenyl chlorides. It should *not* be stored in a sealed container at room temperature for a long period.[8] *Aromatic sulfinyl chlorides should not be distilled* because they have been known to explode on heating. They can, however, be prepared by the present method.

4. Uses of Methanesulfinyl Chloride

The utility of methanesulfinyl chloride lies in its great activity as a chemical intermediate. Through its ready hydrolysis, it serves as a convenient source of methanesulfinic acid. It reacts at low temperatures with aromatic amines to form sulfinamides, and with alcohols to form sulfinate esters. When it is hydrolyzed in the presence of an equimolar quantity of a sulfenyl chloride, a triolsulfonate ester is produced.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfinyl chloride

hydrogen chloride (7647-01-0)

acetic acid (64-19-7)

acetic anhydride (108-24-7)

acetyl chloride (75-36-5)

thionyl chloride (7719-09-7)

Cyclohexene (110-83-8)

chlorine (7782-50-5)

Methanesulfonyl chloride (124-63-0)

methyl disulfide (624-92-0)

Methanesulfinyl chloride (676-85-7)

methanesulfenyl chloride (5813-48-9)

methylsulfur trichloride

methyl methanethiolsulfonate (2949-92-0)

α-toluenesulfinyl chloride

methanesulfinic acid

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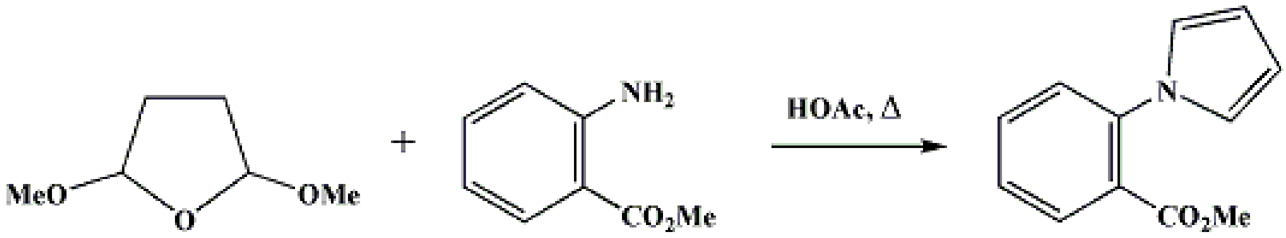
Organic Syntheses, CV 5, 716

1-(2-METHOXYCARBONYLPHENYL)PYRROLE

[Pyrrole, 1-(2-methoxycarbonylphenyl)-]



Submitted by A. D. Josey[1]
Checked by William G. Dauben and Juraj Hostynek.

1. Procedure

A solution of 90 g. (0.59 mole) of methyl anthranilate (Note 1) in 265 ml. of glacial acetic acid is placed in a 1-l. round-bottomed flask equipped with a reflux condenser and a magnetic stirrer. The stirrer is started, and 78 g. (0.59 mole) of 2,5-dimethoxytetrahydrofuran (Note 2) is added during 10–15 minutes (Note 3). The solution is heated under reflux for 1 hour, during which time the solution turns deep red to black in color. The heating is discontinued, the condenser is replaced with a Vigreux column, and the acetic acid is removed by distillation at aspirator pressure. The dark residue is distilled under reduced pressure through a 25-cm. column packed with glass helices, and 84–96 g. (70–80%) of slightly yellow 1-(2-methoxycarbonylphenyl)pyrrole is collected, b.p. 90–95° (2 mm.), n^{25}D 1.5729.

2. Notes

1. Methyl anthranilate from Eastman Kodak Company was used without further purification.
2. 2,5-Dimethoxytetrahydrofuran from Eastman Kodak Company was used without further purification. This material also can be prepared by catalytic hydrogenation[2] of 2,5-dihydro-2,5-dimethoxyfuran.[3]
3. The submitter reports that much heat is liberated during the addition; the checkers did not find the reaction to be markedly exothermic.

3. Discussion

1-(2-Methoxycarbonylphenyl)pyrrole has not been prepared previously. An attempt to prepare the material via the mucic acid pyrrole synthesis using methyl anthranilate was unsuccessful.[4]

4. Merits of the Preparation

The condensation of primary amines with 2,5-dialkoxytetrahydrofurans to give in one step N-substituted pyrroles is applicable to a variety of substituted aliphatic and aromatic amines.[5] The method, largely developed by Clauson-Kaas and associates, has the advantages of simplicity, mild conditions, and generally excellent yields from readily available starting materials.

The submitter has used the method to prepare the corresponding 1-pyrrolyl derivatives[6] from the

following amines in the indicated yields: ethyl β-aminobutyrate 88%, methyl β-aminoglutarate 87%, β-aminopropionitrile 58%, and 2,5-diamino-3,4-dicyanothiophene 22%.

On saponification 1-(2-methoxycarbonylphenyl)pyrrole yields 1-(2-carboxyphenyl)pyrrole, m.p. 106–107°, which on reaction with polyphosphoric acid at 70° is cyclized to 9-keto-9H-pyrrole-(1,2-*a*)indole in 28–32% yield. Through the choice of the appropriate amine and acetal components, the substituted 1-(2-methoxycarbonylphenyl)pyrroles become readily available intermediates in the preparation of a variety of derivatives of the pyrrolo(1,2-*a*)indole ring system.

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

polyphosphoric

9-keto-9H-pyrrole-(1,2-a)indole

acetic acid (64-19-7)

Pyrrole (109-97-7)

mucic acid

β-Aminopropionitrile (151-18-8)

2,5-Diamino-3,4-dicyanothiophene (17989-89-8)

2,5-Dihydro-2,5-dimethoxyfuran (332-77-4)

2,5-dimethoxytetrahydrofuran (696-59-3)

1-(2-Methoxycarbonylphenyl)pyrrole, Pyrrole, 1-(2-methoxycarbonylphenyl)- (10333-67-2)

methyl anthranilate (134-20-3)

ethyl β-aminobutyrate (5303-65-1)

methyl β-aminoglutarate

1-(2-carboxyphenyl)pyrrole (10333-68-3)

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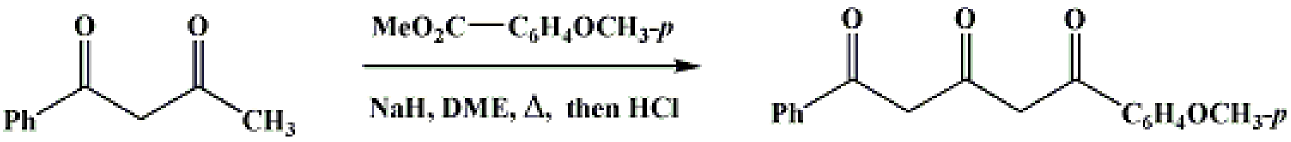
Organic Syntheses, *CV 5, 718*

1-(*p*-METHOXYPHENYL)-5-PHENYL-1,3,5-PENTANETRIONE

[1,3,5-Pentanetrione, 1-(*p*-methoxyphenyl)-5-phenyl-]



Submitted by Marion L. Miles, Thomas M. Harris, and Charles R. Hauser[1].
Checked by Victor Nelson, Wayland E. Noland, and William E. Parham.

1. Procedure

Caution! Sodium hydride causes severe burns if brought into contact with the skin and, in the dry state, is pyrophoric. Since hydrogen is evolved during the course of the reaction, the necessary precautions against fire and explosion should be taken.

A 1-l. three-necked flask is fitted with a sealed mechanical stirrer, an addition funnel with a pressure-equalizing side arm, and a reflux condenser with a gas take-off at the upper end. The gas take-off is connected by means of rubber tubing to one arm of a glass Y-tube. The other arm of the Y-tube is connected to a source of dry nitrogen gas. The bottom of the Y-tube is immersed just beneath the surface of a little 1,2-dimethoxyethane (monoglyme) contained in a small beaker.

The flask is swept with a stream of dry nitrogen. Monoglyme (100 ml.) (Note 1) and sodium hydride (6 g., 0.25 mole) (Note 2) are placed in the flask. A solution of 8.1 g. (0.050 mole) of benzoylacetone (Note 3) and 12.5 g. (0.075 mole) of methyl anisate (Note 4) in 100 ml. of monoglyme is placed in the addition funnel. The funnel is stoppered, and the nitrogen flow rate is adjusted so that approximately 10 bubbles per minute are emitted from the bottom of the Y-tube. The sodium hydride slurry is stirred and heated on the steam bath. When reflux is obtained, the solution of benzoylacetone and methyl anisate is added slowly so that hydrogen evolution is maintained at a controllable rate. The reaction mixture is kept at the reflux temperature for 6 hours.

The reaction mixture is then cooled to room temperature, the reflux condenser is replaced with a distillation condenser equipped with a vacuum take-off, and most of the solvent is removed under reduced pressure (*ca.* 100 mm.) until a thick paste is obtained. The mixture is then cooled in an ice water bath, and 150 ml. of ether is added. Cold water (200 ml.) is placed in the addition funnel, and initially the water is added dropwise *(Caution! Vigorous evolution of hydrogen)* until the excess sodium hydride is destroyed; then the remainder of the water is added more rapidly (Note 5).

The reaction mixture is poured into a 1-l. separatory funnel, and the aqueous layer is removed. The ether layer is extracted with two 100-ml. portions of water and then with 100 ml. of aqueous 1% sodium hydroxide. The extracts are combined with the original aqueous layer, and the resulting solution is washed once with 100 ml. of fresh ether. Crushed ice (100 g.) is added to the solution, followed by 30 ml. of 12*N* hydrochloric acid. The product, which precipitates at this point, is removed by filtration, washed with water, and recrystallized from 450 ml. (Note 6) of 95% ethanol. The yield of 1-(*p*-methoxyphenyl)-5-phenyl-1,3,5-pentanetrione is 11.4–12.8 g. (77–86%) (Note 7), m.p. 120–121.5°.

2. Notes

1. Eastman Kodak (Eastman grade) 1,2-dimethoxyethane was dried for 24 hours over calcium hydride, distilled from sodium metal, and then stored over calcium hydride.
2. The submitters used sodium hydride obtained as a 50% dispersion in mineral oil from Ventron Corp. This material was used as received.
3. The benzoylacetone was obtained from Eastman Kodak (Eastman grade), m.p. 57–58°.
4. Eastman Kodak (Eastman grade) methyl anisate was used without further purification.
5. The checkers observed that the thick brown oil, which separates as the water is added, may partially solidify when stored overnight. The solid was melted on a steam bath, placed in the separatory funnel, and processed with the rest of the reaction mixture as described.
6. The checkers used 480 ml. of 95% ethanol.
7. The checkers found that the product retained as much as 2 g. of ethanol after 20 minutes of air drying. The product was dried to constant weight.

3. Discussion

The method described is that of Miles, Harris, and Hauser[2] and is an improvement over the earlier procedure of Hauser and co-workers.[3,4] In the earlier method the dianion of benzoylacetone, formed by the action of alkali amide in liquid ammonia, was treated with methyl anisate to yield 1-(*p*-methoxyphenyl)-5-phenyl-1,3,5-pentanetrione (61% based on the ester). This compound has also been prepared by the base-catalyzed ring opening of 2-(*p*-methoxyphenyl)-6-phenyl-4-pyrone; however, no yield is reported.[5]

4. Merits of the Preparation

This procedure appears to be fairly general for the aroylation of β-diketones to give 1,3,5-triketones. Using this method, the submitters[2] have aroylated benzoylacetone with methyl benzoate (87%), methyl *p*-chlorobenzoate (78%), and ethyl nicotinate (69%). Also, acetylacetone has been monobenzoylated with methyl benzoate to form 1-phenyl-1,3,5-hexanetrione in 75% yield or dibenzoylated with the same ester to form 1,7-diphenyl-1,3,5,7-heptanetetraone in 56% yield.[6] Symmetrical 1,5-diaryl-1,3,5-pentanetriones can be conveniently prepared by a similar procedure[2] from acetone and two equivalents of the appropriate aromatic ester; for example, 1,5-diphenyl-1,3,5-pentanetrione and 1,5-di(*p*-methoxyphenyl)-1,3,5-pentanetrione are formed in yields of 82% and 77%, respectively.

1,3,5-Triketones are useful intermediates in the preparation of 4-pyrones, 4-pyridones,[3,4] and other cyclic products.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 721

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

1,2-dimethoxyethane (monoglyme)

Monoglyme

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

nitrogen (7727-37-9)

acetone (67-64-1)

sodium (13966-32-0)

methyl benzoate (93-58-3)

Acetylacetone (123-54-6)

benzoylacetone (93-91-4)

sodium hydride (7646-69-7)

calcium hydride (7789-78-8)

1,2-dimethoxyethane (110-71-4)

methyl anisate (121-98-2)

ethyl nicotinate (614-18-6)

1-phenyl-1,3,5-hexanetrione

1,7-diphenyl-1,3,5,7-heptanetetraone

1,5-diphenyl-1,3,5-pentanetrione (1467-40-9)

1-(p-Methoxyphenyl)-5-phenyl-1,3,5-pentanetrione, 1,3,5-Pentanetrione, 1-(p-methoxyphenyl)-5-phenyl- (1678-17-7)

2-(p-Methoxyphenyl)-6-phenyl-4-pyrone (14116-43-9)

methyl p-chlorobenzoate (1126-46-1)

1,5-di(p-methoxyphenyl)-1,3,5-pentanetrione

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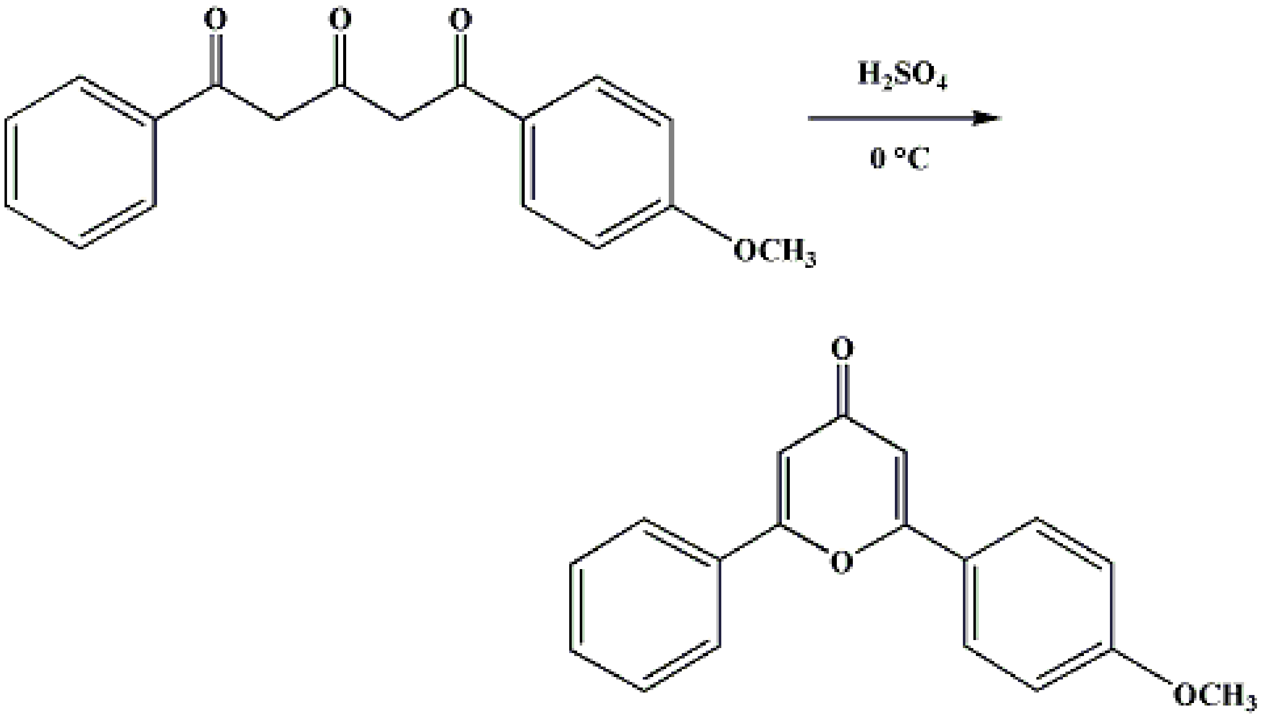
Organic Syntheses, CV 5, 721

2-(*p*-METHOXYPHENYL)-6-PHENYL-4-PYRONE

[4H-Pyran-4-one, 2-(*p*-methoxyphenyl)-6-phenyl-]



Submitted by Marion L. Miles and Charles R. Hauser[1].
Checked by Victor Nelson, Wayland E. Noland, and William E. Parham.

1. Procedure

In a 50-ml. Erlenmeyer flask is placed 10 ml. of concentrated (36*N*) sulfuric acid (Note 1), and the flask is then immersed in an ice water bath. When the temperature of the acid reaches 0°, 2.96 g. (0.010 mole) of 1-(*p*-methoxyphenyl)-5-phenyl-1,3,5-pentanetrione (Note 2) is added in small portions. As each portion is added, the flask is swirled until the triketone dissolves. After the addition is completed, the solution is kept at 0° for 1 hour and then poured into 500 ml. of cold water. To the resulting slurry is added solid sodium bicarbonate until a pH of 7–8 (Note 3) is obtained. The mixture is filtered, and the filter cake is washed with cold water and then recrystallized from 15 ml. of 95% ethanol to give 2.46–2.72 g. (88–98%) of 2-(*p*-methoxyphenyl)-6-phenyl-4-pyrone, m.p. 161–163°.

2. Notes

1. Regular commercial grade of concentrated sulfuric acid (sp. gr. 1.84) obtained from the General Chemical Division of Allied Chemical Corporation was used.
2. For the preparation of this compound see this volume, p. 718.
3. This pyrone has a tendency to form a salt in aqueous sulfuric acid. The

submitters used "Hydrion" paper to check the pH.

3. Discussion

The method is an adaptation of the procedure of Light and Hauser.[2] 2-(*p*-Methoxyphenyl)-6-phenyl-4-pyrone has been prepared in 50% yield by a Claisen-type acylation of *p*-methoxyacetophenone with ethyl phenylpropiolate accompanied by cyclization.[3]

4. Merits of the Preparation

This procedure offers an extremely simple and fairly general method for the preparation of 2,6-disubstituted 4-pyrones. Pyrones which have been prepared[2] by this procedure are: 2-methyl-6-phenyl-4-pyrone (60%), 2-(*p*-chlorophenyl)-6-methyl-4-pyrone (90%), 2,6-diphenyl-4-pyrone (91%), 2-(*p*-chlorophenyl)-6-phenyl-4-pyrone (90%), 2-phenyl-6-(3-pyridyl)-4-pyrone (91%), 5,6,7,8-tetrahydroflavone (76%), 4'-methoxy-5,6,7,8-tetrahydroflavone (70%), cyclopenteno[*b*]-6-(*p*-methoxyphenyl)-4-pyrone (59%), and flavone (63%).

References and Notes

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3. G. Soliman and I. E. El-Kholy, *J. Chem. Soc.*, 1755 (1954).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

cyclopenteno[b]-6-(p-methoxyphenyl)-4-pyrone

ethanol (64-17-5)

sulfuric acid (7664-93-9)

sodium bicarbonate (144-55-8)

ethyl phenylpropiolate (2216-94-6)

Flavone (525-82-6)

2-methyl-6-phenyl-4-pyrone

2,6-diphenyl-4-pyrone

2-phenyl-6-(3-pyridyl)-4-pyrone

5,6,7,8-tetrahydroflavone

p-Methoxyacetophenone (100-06-1)

1-(p-Methoxyphenyl)-5-phenyl-1,3,5-pentanetrione (1678-17-7)

2-(p-Methoxyphenyl)-6-phenyl-4-pyrone, 4H-Pyran-4-one, 2-(p-methoxyphenyl)-6-phenyl- (14116-43-9)

2-(p-chlorophenyl)-6-methyl-4-pyrone

2-(p-chlorophenyl)-6-phenyl-4-pyrone

4'-methoxy-5,6,7,8-tetrahydroflavone

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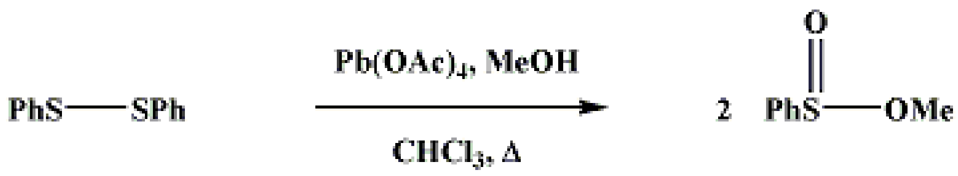
METHYL BENZENESULFINATE

[Benzenesulfinic acid, methyl ester]



Submitted by Lamar Field[1] and J. Michael Locke[2].
Checked by John J. Miller and William D. Emmons.

1. Procedure

Caution! Care should be taken to keep methyl benzenesulfinate off the skin (Note 1).

In a 5-l., three-necked, round-bottomed flask equipped with a sealed mechanical stirrer and a reflux condenser carrying a drying tube are placed 54.6 g. (0.25 mole) of diphenyl disulfide (Note 2), 450 ml. of chloroform (Note 3), and 450 ml. of methanol. To the stirred solution at the reflux temperature is added 443.4 g. (1.00 mole) of lead tetraacetate (Note 4) in 2 l. of chloroform during 8 hours. Owing to formation of lead dioxide, the initially yellow solution becomes dark brown during the addition. The mixture is kept at the reflux temperature overnight (about 12 hours), after which 2 l. of chloroform is removed by distillation at atmospheric pressure (Note 5). The mixture then is cooled to room temperature, and 330 ml. of distilled water is added with stirring to decompose any excess lead tetraacetate. Lead dioxide is removed by filtration of the entire mixture using a Celite®-coated filter paper. The chloroform layer is washed with distilled water until the washings are free of lead ions (Note 6). The chloroform solution is dried over anhydrous magnesium sulfate and, after separation of the drying agent, is concentrated by means of a rotating-flask evaporator. The oily yellow residue is left overnight under vacuum (about 0.1 mm.) to remove any traces of hexachloroethane (Note 7). Distillation is effected through a 15-cm. Vigreux column under reduced pressure (Note 8). The yield of methyl benzenesulfinate is 48.6–53 g. (62–68%), b.p. 59–60° (0.04 mm.), 76–78° (0.45 mm.); n^{25}D 1.5410–1.5428, reported n^{20}D 1.5400,[3] 1.5440.[4]

2. Notes

1. The checkers experienced an extreme and prolonged burning sensation on contact.
2. Diphenyl disulfide, supplied by Distillation Products Industries, Rochester 3, New York, was used as received.
3. Reagent grade chloroform is satisfactory.

4. Used as received from Arapahoe Chemicals, Inc., Boulder, Colorado. This product, usually about 85–96% lead tetraacetate moist with acetic acid, is stored at about 5°. The molar amount specified is based on occasional iodometric titration (Arapahoe brochure) as follows:[5] An accurately weighed sample of about 0.5 g. is dissolved in 5 ml. of glacial acetic acid with gentle warming, and 100 ml. of an aqueous solution of 12 g. of anhydrous sodium acetate and 1 g. of potassium iodide is added. After several minutes, with occasional swirling, the flask wall is rinsed with water. Liberated iodine is titrated with 0.1*N* sodium thiosulfate to a starch end point. The percent of lead tetraacetate is calculated from the formula 22.17 (milliliters of thiosulfate) (normality of thiosulfate)/(weight of sample).
The submitters recommend that the lead tetraacetate be added in eight separate portions of 0.125 mole of lead tetraacetate, each in 250 ml. of chloroform, because the solution of lead tetraacetate decomposes on standing.
5. This can be done conveniently by removing the reflux condenser and replacing it with apparatus for downward distillation.
6. A solution of sodium sulfide can be used to test for the presence of lead ions in the wash liquors. The checkers found that the yield can be improved somewhat by extraction of the initial water layer with chloroform.
7. The small amount of hexachloroethane produced during the reaction presumably is formed from chloroform by a free radical process.
8. The residue after distillation is diphenyl disulfide. It may be recovered by recrystallization from ethanol. The methyl benzenesulfinate may be pale yellow when first distilled, but if so it becomes colorless on standing. If possible, a spinning-band column should be used for distillation, and distillation should be as rapid as possible; use of a 47-cm. spinning-band column gave analytically pure ester, n^{25}_D 1.5436 (cf. Field and co-workers).[6]

3. Discussion

Methyl benzenesulfinate has been prepared by the three-stage process of reduction of benzenesulfonyl chloride to benzenesulfinic acid, conversion of the acid to benzenesulfinyl chloride, and esterification of the chloride with methanol.[3,7] It has been prepared also by ozonolysis of methyl benzenesulfenate.[4] Alkane- and arenesulfinate esters have been prepared from thiols or disulfides by the following sequence: conversion to a sulfinyl chloride by treatment with chlorine, reaction with the appropriate alcohol, treatment with an amine to remove any sulfonyl chloride, and distillation of the sulfinate.[8] The present procedure is based on one reported by Field, Hoelzel, and Locke.[6]

4. Merits of the Preparation

This procedure affords a one-step synthesis of aromatic sulfinic esters from readily available starting materials. It is successful with a variety of types of aromatic sulfinic

esters.[6] The method is rather unattractive for aliphatic disulfides, however, because the nature of by-products formed makes rigorous purification of the sulfinic esters impracticable.[9]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

acetic acid (64-19-7)

methanol (67-56-1)

sodium acetate (127-09-3)

chloroform (67-66-3)

potassium iodide (7681-11-0)

sodium thiosulfate (7772-98-7)

iodine (7553-56-2)

Benzenesulfonyl chloride (98-09-9)

chlorine (7782-50-5)

sodium sulfide (1313-82-2)

magnesium sulfate (7487-88-9)

benzenesulfinic acid (618-41-7)

Methyl benzenesulfinate, Benzenesulfinic acid, methyl ester (670-98-4)

diphenyl disulfide (882-33-7)

hexachloroethane (67-72-1)

benzenesulfinyl chloride (4972-29-6)

methyl benzenesulfenate

lead dioxide

lead tetraacetate

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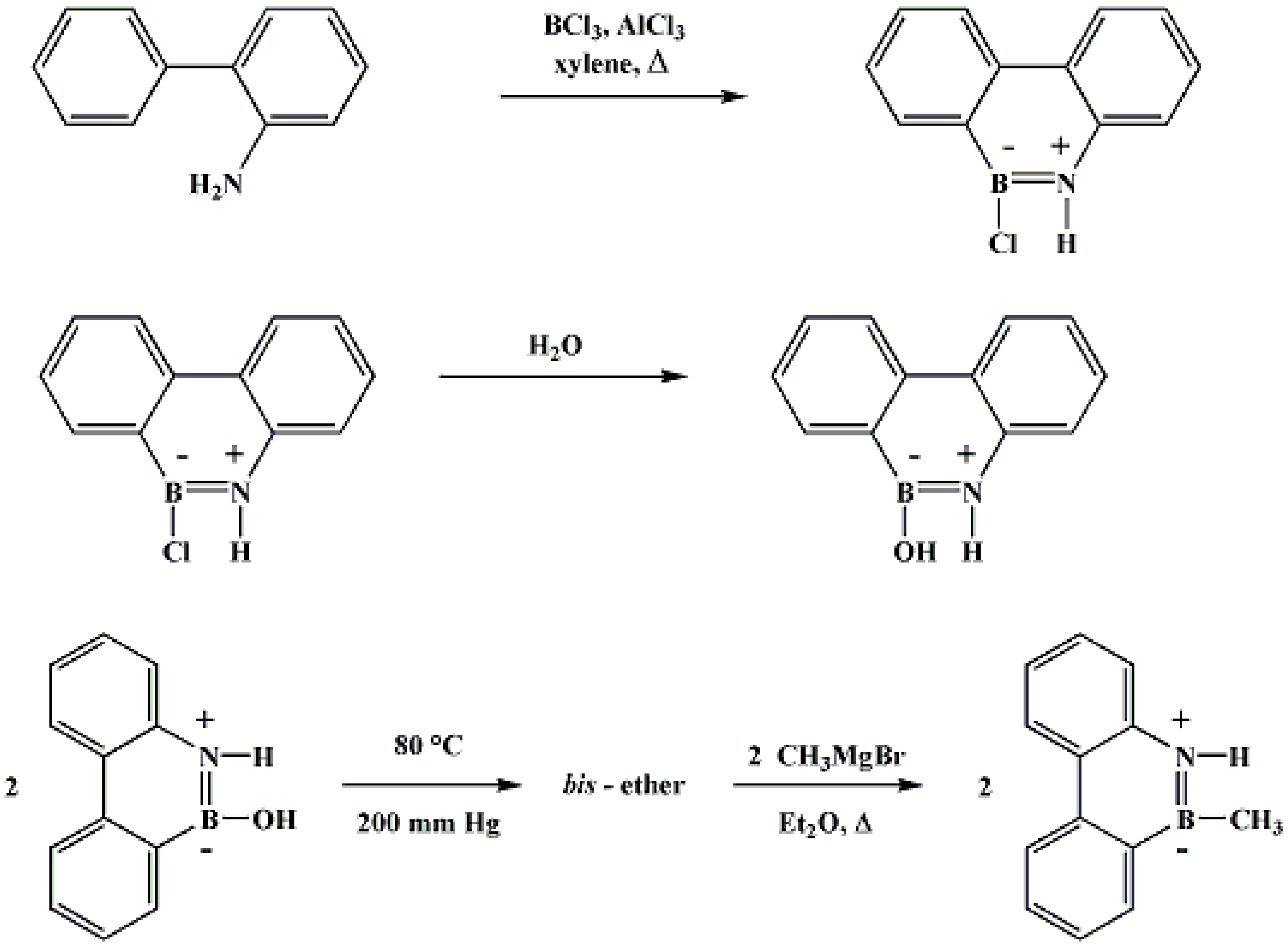
Organic Syntheses, CV 5, 727

10-METHYL-10,9-BORAZAROPHENANTHRENE

[Dibenz[c,e][1,2]azaborine, 5,6-dihydro-6-methyl-]



Submitted by M. J. S. Dewar, R. B. K. Dewar, and Z. L. F. Gaibel[1].
Checked by Jack A. Snyder and B. C. McKusick.

1. Procedure

A. *Bis(10,9-borazarophenanthryl) ether*. *Caution! All the operations involving boron trichloride should be carried out in a good hood.*

A solution of 250 g. (1.48 moles) of 2-aminobiphenyl (Note 1) in 2.0 l. of dry xylene (Note 2) is placed in a 5-l. four-necked flask equipped with a 500-ml. pressure-equalized dropping funnel, a reflux condenser fitted with a drying tube loosely packed with calcium chloride, a thermometer, and a mechanical stirrer. A solution of 250 g. (174 ml., 2.14 moles) of boron trichloride in 250 ml. of very cold xylene is placed in the dropping funnel (Note 3).

The boron trichloride solution is added dropwise to the stirred amine solution over a period of 30 minutes; a thick precipitate forms as the first third of the solution is added, but it gradually dissolves, and the reaction mixture is a clear, dark amber solution at the end of the addition. The mixture is heated under reflux for 1 hour; the temperature of the mixture gradually rises from 110° to 140° as hydrogen chloride and boron chloride are evolved (Note 4). The mixture is cooled to about 100°, the dropping funnel is replaced by a powder funnel, and 15 g. of anhydrous aluminum

chloride is cautiously added. The funnel is replaced by a well-greased stopper (Note 5), and the mixture is heated under reflux for 2 hours. The mixture is cooled slightly, and an additional 5 g. of aluminum chloride is added. The reaction mixture is heated under reflux at least 16 hours, and then the reflux condenser is replaced by a Claisen head leading to a water condenser and receiver. About 80% of the solvent (1.6–1.7 l.) is distilled with vigorous stirring.

A dropping funnel with a pressure-equalizing arm is inserted in place of the stopper, and 2.5 l. of distilled water is added from it with vigorous stirring. The reaction with water is extremely exothermic at first, and the first 30 ml. of water is added not faster than 1 drop per second. The mixture is steam-distilled with heating and vigorous stirring until the head temperature reaches 100°. A fresh receiver is attached, and the distillation is continued until the distillate no longer smells of xylene; this is usually after about 300 ml. of distillate has been collected in the receiving vessel (Note 6). If necessary, water is added from time to time to maintain the liquid level in the flask. The flask is cooled to room temperature with vigorous stirring (Note 7), and crystalline 10-hydroxy-10,9-borazarophenanthrene separates. The solid is collected by suction filtration, washed with about 750 ml. of water, and dried overnight at 75–80° in an oven under reduced pressure (200 mm. or below). Dehydration to bis(10,9-borazarophenanthryl) ether usually takes place during the drying. The ether, a tan solid, weighs 221–250 g. (80–91%) (Note 8).

B. *10-Methyl-10,9-borazarophenanthrene*. The tan bis(10,9-borazarophenanthryl) ether from the previous step is transferred to a dry, 5-l., four-necked flask equipped with a mechanical stirrer, a nitrogen inlet, a 1-l. pressure-equalized dropping funnel, a thermometer, and a very efficient reflux condenser with a drying tube packed with silica gel at the top (Note 9). A 3.2-l. portion of anhydrous ether is placed in the flask, and the mechanical stirrer is started. The flask is cooled in an ice bath, and 700 ml. (2.1 moles) of 3*M* methylmagnesium bromide solution in ether (Note 10) is added dropwise through the funnel during 1 hour. The reaction mixture is heated under reflux overnight. The mixture is cautiously and slowly poured into 1 l. of ice water and then cautiously acidified with 385 ml. (10% excess) of 6*N* hydrochloric acid. The ether layer is separated, and the water layer is extracted with five 400-ml. portions of ether. The combined ether fractions are washed with 200 ml. of saturated sodium bicarbonate solution; the sodium bicarbonate solution is washed with 300 ml. of ether, which is added to the other ether fractions.

The combined ether fractions are dried over 50 g. of magnesium sulfate, the ether is removed at reduced pressure, and the residue is dried overnight at 60° (10 mm.). The resulting slightly oily, crystalline, brown solid is a mixture of 10-methyl-10,9-borazarophenanthrene, bis(10,9-borazarophenanthryl) ether, and tars; weight about 220 g.; m.p. 92–98°. The methyl derivative is isolated by continuous chromatography over about 500 g. of Merck basic alumina (chromatography grade) in the apparatus shown in f.htmig. 1 (Note 11). The crude product is placed on top of the alumina, 4 l. of petroleum ether (b.p. 30–60°) is poured into the flask, and the extractor is operated for 30–35 hours. 10-Methyl-10,9-borazarophenanthrene gradually crystallizes as fine needles on the walls of the flask.

Fig. 1. *A*, 5-l. three-necked flask with electric heating mantle; *B*, alumina column 45 cm. × 3.8 cm. (Merck basic alumina); *C*, polyethylene tubing; *D*, condenser (see (Note 11)).

Fig. 1. A, 5-l. three-necked flask with electric heating mantle; B, alumina column 45 cm. × 3.8 cm. (Merck basic alumina); C, polyethylene tubing; D, condenser (see).

The flask is cooled to room temperature, all solvents are allowed to drain from the column, and 120–150 g. of colorless product, m.p. 99–101°, is separated by filtration and washed with petroleum ether. A second crop, weight 25–40 g.,m.p. 98.5–101.0°, is obtained by concentrating the combined filtrates to about 250 ml. and cooling the concentrate to room temperature. The crops of 10-methyl-10,9-borazarophenanthrene are combined; weight 155–182 g. (54–65% based on 2-aminobiphenyl). The product is sufficiently pure for many purposes. A purer product, m.p. 103–104°,[2] may be obtained by recrystallization from petroleum ether (b.p. 35°) (Note 12).

2. Notes

1. A technical grade of 2-aminobiphenyl obtainable from Columbia Organic Chemicals Co. is satisfactory. This black material contains the carcinogenic 4-isomer; it should therefore be handled carefully to avoid contact with the skin. Purification of the amine by vacuum distillation removes the black impurities but does not improve either the yield or the quality of the final product.
2. The xylene is dried over sodium wire or sodium-lead alloy before use.
3. Boron trichloride boils at 13°. To prepare the solution, the submitters poured liquid boron trichloride into a tared beaker containing dry xylene until the weight increased by 250 g. The beaker was in a methanol-ice bath.
The checkers placed 250 ml. of dry xylene in a 500-ml. round-bottomed flask marked with a line corresponding to a volume of 424 ml. and with a gas inlet above the line. A cold finger containing a mixture of dry ice and methanol was attached to the flask, which was immersed in the same mixture. Gaseous boron trichloride (Matheson Co.) was passed in until the flask was filled to the 424-ml. line, and the cold solution was transferred to the dropping funnel.
4. During the most vigorous evolution of gas it is advisable to replace the drying tube by a tube leading to the back of the hood or to a gas absorption trap.
5. Unless the stopper is well greased, the aluminum chloride will cement it to the flask.
6. The purpose of the steam distillation is to remove all the xylene. If the crystals are collected prematurely, the last traces of xylene are hard to remove.
7. If the mixture is not vigorously stirred while cooling, an intractable cake forms at the bottom of the flask.
8. The product may be bis(10,9-borazarophenanthryl) ether, 10-hydroxy-10,9-borazarophenanthrene, or a mixture. The melting point of either product varies widely with the method of determination. The checkers placed analytical samples in a bath at 125° with the temperature rising 9–12° per minute and observed m.p. 154–159° for the ether, m.p. 133° (with frothing) for the hydroxy compound. The infrared spectrum of the hydroxy compound has a band at 2.83 • that is lacking in the spectrum of the ether. According to the submitters, either the ether or the hydroxy compound can be used in step B. The checkers used only the ether.
The tan product is almost pure. Extraction with petroleum ether (b.p. 60–70°) in a Soxhlet gives white crystals.
9. A West condenser and a Friedrich condenser in tandem are recommended.
10. The methylmagnesium bromide solution is obtainable from Arapahoe Chemicals, Inc., Boulder, Colorado.
11. This procedure may prove useful in other cases where impurities are strongly adsorbed on alumina; it avoids the use of enormous volumes of solvent. The heating mantle is controlled by a Variac, set so that the liquid level remains constant. The plastic tubing should not be of Tygon®, since this is attacked by the solvent; polyethylene tubing is suitable. An efficient condenser is essential; the use of a West condenser and a Friedrich condenser in tandem is recommended. A similar but more complicated apparatus is described by Meier and

Fletschinger.[3]
12. Some unreacted bis(10,9-borazarophenanthryl) ether can be recovered from the column by extraction with methanol.

3. Discussion

10-Chloro-10,9-borazarophenanthrene has been obtained only by Friedel-Crafts cyclization of the adduct from 2-aminobiphenyl and boron trichloride;[2] the procedure described here is an improvement on the original process,[2] in which no solvent was used.

10-Methyl-10,9-borazarophenanthrene has been obtained by the action of methylmagnesium halides on 10-chloro-10,9-borazarophenanthrene[2] or bis(10,9-borazarophenanthryl) ether.[4] The former preparation was satisfactory when pure 2-aminobiphenyl was available, but existing grades lead to products containing intractable impurities, presumably derived from the 4-isomer. These impurities are eliminated during the hydrolysis to 10-hydroxy-10,9-borazarophenanthrene.

4. Merits of the Preparation

10,9-Borazarophenanthrene was the first representative of a new class of heteroaromatic compounds containing boron atoms in six-membered aromatic rings.[4] These compounds are of a different order of stability from previously known types of organoboron compounds, being chemically similar to "normal" aromatics, and their discovery has opened up a new field of aromatic chemistry. The procedure indicated here has been used to prepare a large number of related aromatic systems.

The cyclization can be carried out with halogenated amines, and substitution products of the new ring systems can also be obtained in the conventional way, by nitration, etc. Similar compounds can be prepared directly by using arylboron dichlorides in place of boron trichloride in the procedure indicated above. The parent borazarene derivatives, with hydrogen attached to boron, can be made from the B-hydroxy compounds with lithium aluminum hydride in the presence of aluminum chloride.[4,5] N-Alkyl derivatives can be made either by using N-alkyl derivatives of the aminobiphenyls as starting materials, or by N-alkylation of the unsubstituted compounds via their N-lithio derivatives.[5] Apart from their inherent interest, compounds of this type can serve as intermediates in various syntheses. Thus benzocinnolines and 2,2'-dihydroxybiphenyls can be obtained from derivatives of 2-aminobiphenyl.[5,6,7]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alumina

petroleum ether

10-Methyl-10,9-borazarophenanthrene

Dibenz[c,e][1,2]azaborine, 5,6-dihydro-6-methyl-

Bis(10,9-borazarophenanthryl) ether

10-hydroxy-10,9-borazarophenanthrene

sodium-lead alloy

10-Chloro-10,9-borazarophenanthrene

10,9-Borazarophenanthrene

hydrogen chloride, hydrochloric acid (7647-01-0)

methanol (67-56-1)

ether (60-29-7)

hydrogen (1333-74-0)

sodium bicarbonate (144-55-8)

aluminum chloride (3495-54-3)

sodium (13966-32-0)

xylene (106-42-3)

magnesium sulfate (7487-88-9)

boron (7440-42-8)

methylmagnesium bromide (75-16-1)

lithium aluminum hydride (16853-85-3)

boron trichloride (10294-34-5)

2-aminobiphenyl (90-41-5)

boron chloride (20583-55-5)

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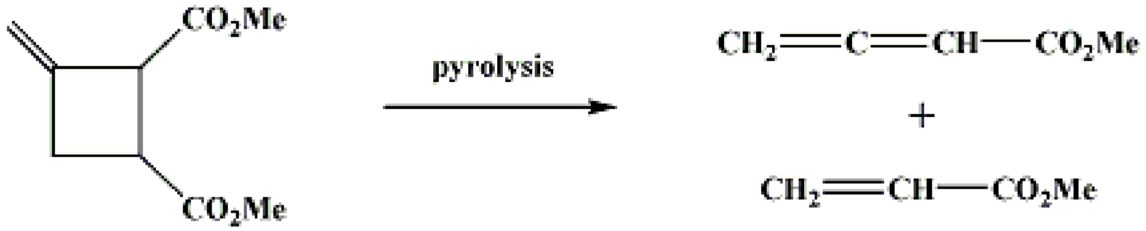
Organic Syntheses, CV 5, 734

METHYL BUTADIENOATE

[Butadienoic acid, methyl ester]



Submitted by H. B. Stevenson and W. H. Sharkey[1].
Checked by R. D. Birkenmeyer, W. E. Russey, and F. Kagan[2].

1. Procedure

A "Vycor" tube 550 mm. long and 25 mm. in outside diameter is packed for 500 mm. of its length with 6-mm. × 6-mm. quartz rings and mounted vertically so that the upper section is encased in a tube furnace 150 mm. long and the lower section is encased in a tube furnace 300 mm. long. The upper furnace, which serves as a preheater, is monitored by a thermocouple placed between the tube and the furnace heating elements. The temperature of the lower furnace is monitored by a thermocouple located in the center of the lower packed section. The upper end of the pyrolysis tube is fitted with a Y-tube carrying the thermocouple well and a graduated addition funnel with a pressure-equalizing arm. The lower end is attached through one 500-ml. trap and two 200-ml. traps, each immersed in a mixture of solid carbon dioxide and acetone, to a regulated vacuum source. One gram of hydroquinone is placed in the first trap.

The pyrolysis tube is flushed with nitrogen, the lower section is heated to 600° and the upper section to 300° (Note 1), and the pressure is regulated at 25 mm. Then 184 g. (1.00 mole) (Note 2) of dimethyl 3-methylenecyclobutane-1,2-dicarboxylate[3] is admitted over a period of 3 hours (Note 3). The product, which amounts to 172–177 g., collects in the traps. It is distilled through a 13-mm. × 1.2-m. Nester spinning-band still.[4] First there is 41–47 g. (48–55%) of methyl acrylate, n_D^{25} 1.4010, b.p. 34–36°/150 mm., then 39–43 g. (40–44%) of methyl butadienoate, n_D^{25} 1.4635 (Note 4), b.p. 59–60°/52 mm. or 48–49°/26 mm. By continuing the distillation, 20–30 g. of starting material, b.p. 125–150°/25 mm., can be recovered.

2. Notes

1. The temperature of the lower section is quite critical and should be maintained within the range 590–610°. However, the preheater section is needed only to volatilize the ester, so any temperature between 200° and 400° is

satisfactory.
2. Since an estimated 3–5 g. of carbon is deposited in the tube during the pyrolysis, it is advisable to pyrolyze only 1 mole of ester at a time and to burn out the carbon with a slow stream of air at 600° between pyrolyses.
3. The space velocity is approximately 125 l. of standard gas per l. of free space per hour, and the contact time is approximately 0.3 second.
4. The checkers used a 10-mm. × 0.76-m. Nester spinning band still and obtained material having n_D^{25} 1.4620 that could not be purified by redistillation. Analysis by vapor-phase chromatography (silicone gum rubber, 20% w/w on firebrick, 120-cm. × 6-mm. outside diameter column at 125°) showed this material to be 95% methyl butadienoate contaminated by small amounts of two other materials.

3. Discussion

The method used is described by Drysdale, Stevenson, and Sharkey.[5] The methyl ester of butadienoic acid has not been described previously, but the free acid contaminated by 2-butynoic acid has been prepared by Wotiz, Matthews, and Lieb[6] by carbonation of propargylmagnesium bromide. Ethyl butadienoate has been prepared by Eglinton, Jones, Mansfield, and Whiting[7] by alkali-catalyzed isomerization of ethyl 3-butynoate prepared from 3-butynol by chromic acid oxidation and esterification.

4. Merits of the Preparation

This procedure gives a product free of acetylenic groups. It illustrates the synthesis of an olefinic compound by cracking a cyclobutane into two fragments.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 459
- Org. Syn. Coll. Vol. 9, 28

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydroquinone (123-31-9)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

acetone (67-64-1)

carbon (7782-42-5)

chromic acid (7738-94-5)

methyl (2229-07-4)

methyl acrylate (96-33-3)

cyclobutane (287-23-0)

Dimethyl 3-methylenecyclobutane-1,2-dicarboxylate (53684-52-9)

Methyl butadienoate, Butadienoic acid, methyl ester (18913-35-4)

butadienoic acid

2-butynoic acid (590-93-2)

propargylmagnesium bromide

Ethyl butadienoate

ethyl 3-butynoate

3-butynol (927-74-2)

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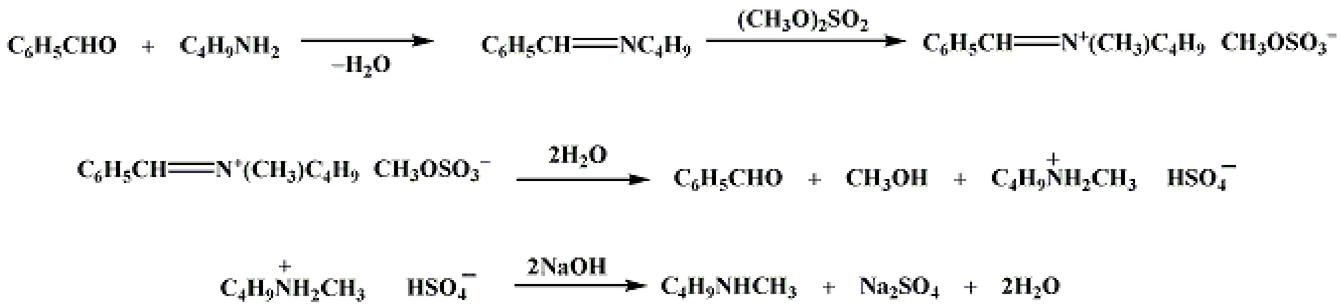
Organic Syntheses, *CV 5, 736*

N-METHYLBUTYLAMINE

[Butylamine, N-methyl-]



Submitted by John J. Lucier, Arlo D. Harris, and Philip S. Korosec[1].
Checked by Max Tishler and M. Bennett.

1. Procedure

A 1-l. round-bottomed flask fitted with a reflux condenser bearing a soda-lime drying tube is successively charged with 100ml. of anhydrous benzene, 36.6 g. (0.50 mole) of *n*-butylamine, and 63.7 g. (61 ml., 0.60 mole) of benzaldehyde (Note 1). The mixture is heated under reflux for 30 minutes (Note 2). The condenser is replaced by a Claisen distillation head, and the mixture is distilled until the temperature reaches 100° (Note 3). The residue, which is mostly N-benzylidenebutylamine, is cooled, and the distillation head is replaced by the reflux condenser bearing a soda-lime drying tube.

A solution of 75.6 g. (57 ml., 0.60 mole) of dimethyl sulfate (*Toxic! (Note 4)*) in 200 ml. of anhydrous benzene is added through the condenser with intermittent swirling (Note 2). The mixture is then heated *gently*. After a short period (about 10 minutes) the reaction becomes mildly vigorous, and the heating is stopped (Note 5). The ebullition subsides after about 10 minutes. The mixture is heated under reflux for 30 minutes. It is then steam-distilled until the distillate becomes clear; about 500 ml. of distillate is collected (Note 6). The residue is cooled in an ice bath, and 60 g. (1.5 moles) of sodium hydroxide is added with continuous swirling. The layers are separated, and the amine layer is dried for several hours over 5 g. of sodium hydroxide. The amine layer is separated, dried over a second 5-g. portion of sodium hydroxide (Note 7), and distilled from a 50-ml. Claisen flask containing 2 g. of sodium hydroxide. N-Methylbutylamine is collected at 86–90° (745 mm.); weight 19.6–23.0 g. (45–53%); n^{20}D 1.4010–1.4020. The product contains 3–5% of impurity according to vapor-phase chromatographic analysis.

2. Notes

1. The benzaldehyde and *n*-butylamine were obtained from the Eastman Kodak Company (white label grade). The benzaldehyde was used without further purification. The *n*-butylamine was redistilled before use.
The checkers dried benzene over sodium-lead alloy (dri-Na, Baker). Its water content was less than 0.1 mg. per ml. by Karl Fischer titration.
2. The checkers stirred the mixture with a magnetic stirrer.
3. This distillation is carried out to remove the water formed by the first reaction. No more water comes over after the temperature reaches 100°. Toward the end of distillation, slight bumping may occur.
4. The dimethyl sulfate was purchased from Matheson, Coleman and Bell and was used without further purification. Both the liquid and the vapors of dimethyl sulfate are *toxic*, and the compound must be handled with care.
5. An ice bath should be kept ready to restrain the reaction if necessary.
6. In a simpler alternative to steam distillation, 200 ml. of water is added to the benzene solution, and the mixture is vigorously stirred under gentle reflux for 20 minutes. The mixture is cooled to room temperature. The aqueous layer is separated, extracted with 100 ml. of ether to remove traces of benzaldehyde, and then treated with 60 g. of sodium hydroxide as in the present procedure.[2]
7. If a larger portion of sodium hydroxide is used, a semisolid mass is formed from which the product can be separated only with difficulty.

3. Discussion

Unsymmetrical secondary aliphatic amines have been prepared by reaction of alkyl halides with benzylidene amines and subsequent hydrolysis;[3,4] by reaction of alkyl halides with alkyl amines;[5] by reduction of amine-aldehyde adducts;[6,7,8] and

by dealkylation of tertiary amines with dibenzoyl peroxide.[9]

In the present procedure, the method of Decker and Becker[3] has been modified by substitution of a dialkyl sulfate for the corresponding alkyl halide.

4. Merits of the Preparation

The procedure is a general one for the preparation of unsymmetrical aliphatic amines, for the submitters have used it to obtain good yields of N-methylpentylamine, N-methylhexylamine, N-methylheptylamine, N-ethylbutylamine, N-ethylpentylamine, and N-ethylheptylamine.

Compared to the procedure of Decker and Becker[3] and that of Wawzonek, McKillip, and Peterson in this volume,[4] the present procedure has the advantages of being simpler and using cheaper alkylating agents. It tends to give lower yields and less pure products than the procedure of Wawzonek, McKillip, and Peterson.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 758

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Benzene (71-43-2)

ether (60-29-7)

sodium hydroxide (1310-73-2)

dimethyl sulfate (77-78-1)

benzaldehyde (100-52-7)

dibenzoyl peroxide (94-36-0)

n-butylamine (109-73-9)

sodium-lead

N-Methylbutylamine, Butylamine, N-methyl- (110-68-9)

N-benzylidenebutylamine

amine-aldehyde (14332-28-6)

N-methylpentylamine (25419-06-1)

N-methylhexylamine (35161-70-7)

N-methylheptylamine (36343-05-2)

N-ethylbutylamine (13360-63-9)

N-ethylpentylamine

N-ethylheptylamine

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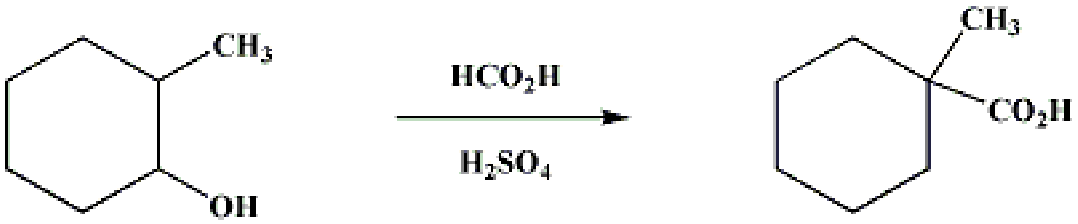
Organic Syntheses, CV 5, 739

1-METHYLCYCLOHEXANECARBOXYLIC ACID

[Cyclohexanecarboxylic acid, 1-methyl-]



Submitted by W. Haaf[1]
Checked by D. M. Gale and B. C. McKusick.

1. Procedure

Caution! Because carbon monoxide is evolved, the reaction should be carried out in a good hood.

Two hundred seventy milliliters (497 g., 4.86 moles) of 96% sulfuric acid (Note 1) is poured into a 1-l. three-necked flask equipped with a paddle stirrer driven by a powerful motor, a dropping funnel with a gas by-pass, and a thermometer that dips into the acid. The reaction mixture is stirred *vigorously* (Note 2) and maintained at 15–20° by means of a cooling bath as 3 ml. of 98–100% formic acid (Note 3) is added dropwise. Under the same conditions, a solution of 28.5 g. (0.25 mole) of 2-methylcyclohexanol (Note 4) in 46 g. (1.00 mole) of 98–100% formic acid is added in the course of 1 hour. The reaction mixture foams during the additions. The mixture, which is a very light cream color, is stirred for 1 hour at 15–20° and then is poured with stirring onto 1 kg. of crushed ice in a 4-l. beaker. The carboxylic acid separates as a white solid.

The acid is taken up in 200 ml. of hexane (Note 5), the hexane layer is separated, and the aqueous layer is extracted with two 150-ml. portions of hexane. The combined hexane solutions are extracted twice with a mixture of 175 ml. of 1.4*N* potassium hydroxide solution and 50 g. of crushed ice. The two alkaline solutions are combined and extracted with 100 ml. of hexane to remove traces of neutral oil, and then acidified to pH 2 with 12*N* hydrochloric acid (about 35 ml.). The liberated carboxylic acid is taken up in 150 ml. of hexane. The aqueous layer is extracted with 100 ml. of hexane, and the combined hexane layers are washed with 75 ml. of water and dried over 3 g. of anhydrous magnesium sulfate. The hexane is evaporated by warming the solution at 30–60° (15–30 mm.) overnight. The residue is 33–36 g. (93–101%) of colorless 1-methylcyclohexanecarboxylic acid, m.p. 34–36°, that is pure enough for most purposes. Distillation from a 100-ml. Claisen flask (Note 6) gives 31.5–33.5 g. (89–

94%) of the acid, b.p. 132–140° (19 mm.), 79–81° (0.5 mm.); m.p. 38–39°.

2. Notes

1. Three moles of 99–100% sulfuric acid may be used in place of the 96% sulfuric acid.
2. With slow stirring there is a higher concentration of carbon monoxide and hence less rearrangement. For example, cyclohexanol in a slowly stirred reaction mixture gave 75% cyclohexanecarboxylic acid and 14% 1-methylcyclopentanecarboxylic acid; with rapid stirring the corresponding yields were 8% and 61%.[2]
3. Technical grade 85% formic acid can be substituted for 98–100% formic acid if the decrease in sulfuric acid concentration that would result is compensated for by a suitable increase in the amount of sulfuric acid charged.
4. The checkers used "*o*-Methylcyclohexanol," available from K & K Laboratories, Jamaica, New York. They redistilled it before use; b.p. 70–80° (20 mm.), $n^{25}D$ 1.4617. 3- or 4-Methylcyclohexanol can be used in place of 2-methylcyclohexanol, or mixtures of the three can be used.
5. Normal hexane, commercial grade, from the Phillips Petroleum Co., Bartlesville, Oklahoma, was used. Other organic solvents, such as benzene, are satisfactory.
6. The checkers used a 30-cm. spinning-band column for the distillation.

3. Discussion

1-Methylcyclohexanecarboxylic acid can be prepared by carbonation of the Grignard reagent from 1-chloro-1-methylcyclohexane[3] or by Friedel-Crafts condensation of 1-chloro-1-methylcyclohexane with methyl 2-furancarboxylate followed by saponification and oxidation.[4] It can also be prepared by successive hydrogenation and saponification of the Diels-Alder adduct from butadiene and methyl methacrylate,[5] by oxidation of 1-methyl-1-acetylcyclohexane with nitric acid[6] or sodium hypobromite,[7] and by the present method of synthesis.[8]

4. Merits of the Preparation

Carboxylation by formic acid is a rapid and simple method of preparing many tertiary carboxylic acids.[8] It can be applied to primary, secondary, and tertiary alcohols as well as to olefins and other compounds equivalent to the alcohols under the reaction conditions. The reaction often proceeds with rearrangement of the carbon skeleton. The scope of the reaction is indicated by Table I, which lists 13 alcohols to which the reaction has been applied.

TABLE I CARBONYLATION OF ALCOHOLS TO ACIDS

Alcohol		Acids Formed[a]	Yield of RCO_2H, %[b]
1- or 2-Butanol	100	2-Methylbutyric acid	36 or 43
t-Butyl alcohol	95	Trimethylacetic acid	75
1- or 2-Pentanol	80	2,2-Dimethylbutyric acid	76 or 81
	20	C_{11} acids	
2-Methyl-2-butanol	10	Trimethylacetic acid	73
	42	2,2-Dimethylbutyric acid	
	12	C_7 acids	
	36	C_{11} acids	
2,3,3-Trimethyl-2-butanol	100	2,2,3,3-Tetramethylbutyric acid	88
2,2-Dimethyl-1-propanol	100	2,2-Dimethylbutyric acid	83
Cyclopentanol	63	Cyclopentanecarboxylic acid	26
	37	*cis*-9-Decalincarboxylic acid	
Cyclohexanol	80	1-Methylcyclopentanecarboxylic acid	78
	9	Cyclohexanecarboxylic acid	
	11	C_{13} acids	
Cycloheptanol	100	1-Methylcyclohexanecarboxylic acid	91
2-Decalol	80	*cis*-9-Decalincarboxylic acid	95
	20	*trans*-9-Decalincarboxylic acid	
1-Hydroxyadamantane	100	1-Adamantanecarboxylic acid[11,9]	95

[a] The number before each acid is its volume percent in the mixture of carboxylic acids formed.

[b] Total yield of all carboxylic acids formed.

In a related reaction, saturated hydrocarbons with a tertiary hydrogen are carboxylated by a mixture of formic acid, *t*-butyl alcohol, and sulfuric acid.[10,11]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 20

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

3- or 4-Methylcyclohexanol

1- or 2-Butanol

1- or 2-Pentanol

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

carbon monoxide (630-08-0)

nitric acid (7697-37-2)

Cyclohexanol (108-93-0)

formic acid (64-18-6)

potassium hydroxide (1310-58-3)

2-Methylbutyric acid (600-07-7)

Cyclohexanecarboxylic acid (98-89-5)

Trimethylacetic acid (75-98-9)

sodium hypobromite

magnesium sulfate (7487-88-9)

butadiene (106-99-0)

cyclopentanol (96-41-3)

2-Methyl-2-butanol (75-85-4)

hexane (110-54-3)

2-methylcyclohexanol (583-59-5)

t-butyl alcohol (75-65-0)

cyclopentanecarboxylic acid (3400-45-1)

1-Adamantanecarboxylic acid (828-51-3)

1-Hydroxyadamantane (768-95-6)

2,2-Dimethylbutyric acid (595-37-9)

1-Methylcyclohexanecarboxylic acid, Cyclohexanecarboxylic acid, 1-methyl- (1123-25-7)

1-methylcyclopentanecarboxylic acid (5217-05-0)

1-chloro-1-methylcyclohexane (931-78-2)

methyl 2-furancarboxylate (611-13-2)

methyl methacrylate (80-62-6)

1-methyl-1-acetylcyclohexane

2,2,3,3-Tetramethylbutyric acid

2,2-Dimethyl-1-propanol (75-84-3)

Cycloheptanol (502-41-0)

2-Decalol (825-51-4)

cis-9-Decalincarboxylic acid

trans-9-Decalincarboxylic acid

2,3,3-Trimethyl-2-butanol

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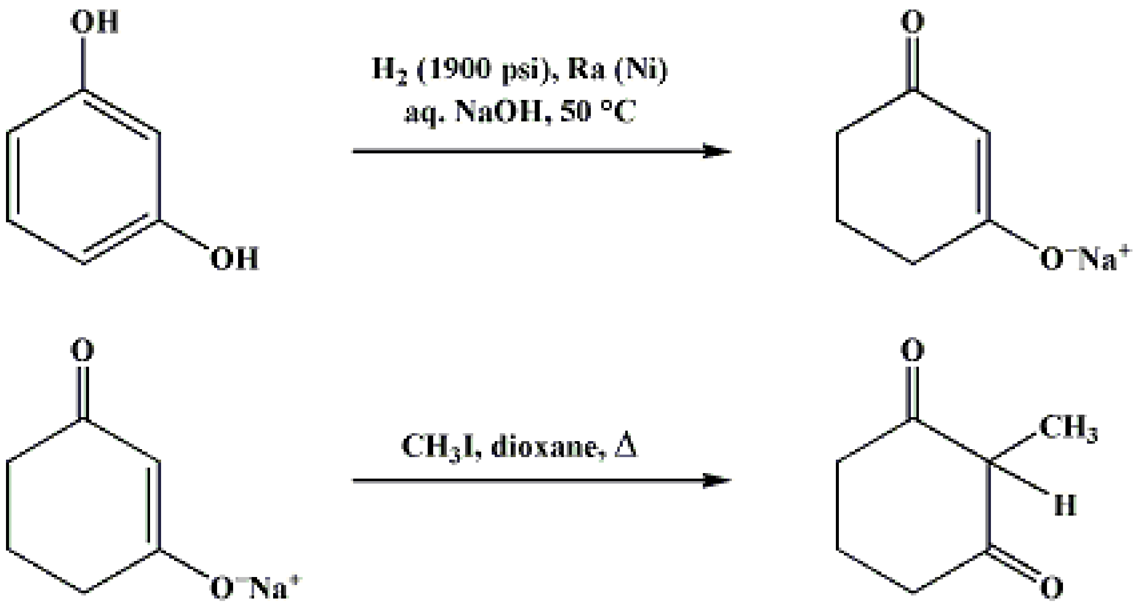
Organic Syntheses, CV 5, 743

2-METHYL-1,3-CYCLOHEXANEDIONE

[1,3-Cyclohexanedione, 2-methyl-]



Submitted by A. B. Mekler, S. Ramachandran, S. Swaminathan, and Melvin S. Newman[1].
Checked by Max Tishler, A. J. Zambito, and W. B. Wright.

1. Procedure

A freshly prepared solution of 96.0 g. (2.4 moles) of sodium hydroxide, 335 ml. of water, and 220.2 g. (2.0 moles) (Note 1) of resorcinol (Note 2) is placed in a 1.3-l. hydrogenation bomb together with 40.0 g. of finely powdered nickel catalyst (Note 3). The hydrogenation is carried out under an initial pressure of about 1900 lb. of hydrogen with agitation. The reaction is slightly exothermic, and gentle heating is applied to maintain a temperature of 45–50° (Note 4). The hydrogenation is continued until about a 10% excess of the theoretical amount of hydrogen (2.0 moles) has been absorbed (Note 5). At this point, the agitation is stopped, and the bomb is cooled to room temperature. The reaction mixture is poured into a 1-l. beaker, and the catalyst is removed by filtration with the aid of three 50-ml. portions of water for the combined operations. The filtrate and washings are transferred to a 2-l. round-bottomed flask and treated with 33.5 ml. of concentrated hydrochloric acid (for partial neutralization), 145 ml. of dioxane, and 335 g. (2.4 moles) of methyl iodide (Note 6). The reaction mixture is refluxed for a total of 12–14 hours. After 7 or 8 hours, an additional 33.5 g. (0.24 mole) of methyl iodide is added. The system is cooled several hours in an ice bath, and the 2-methyl-1,3-cyclohexanedione which crystallizes is collected by filtration (Note 7), washed with four 200-ml. portions of cold water (Note 8), and then dried in an oven at 110°. The initial crop of dione, m.p. 206–208° dec., weighs 138–142 g. (54–

56%). The mother liquors are concentrated under reduced pressure to one-half of their original volume and are then cooled in an ice-salt bath to yield an additional 7–11 g. (3–5%) of slightly yellow dione which melts at 200–204° dec.

The 2-methyl-1,3-cyclohexanedione thus obtained (Note 9) can be purified by recrystallization from 95% ethanol, using about 20 ml. of ethanol for each 5 g. of product to give colorless crystals, m.p. 208–210° dec., with only minor loss of material.

2. Notes

1. The submitters have carried out runs with as much as 990 g. (9.0 moles) of resorcinol.
2. Both Merck resorcinol U.S.P. powder and resorcinol of practical grade give satisfactory results.
3. Many different nickel catalysts have been used: e.g., Grade 0140T1/8 Harshaw Chemical Co., Cleveland 6, Ohio; reduced Universal Oil Products hydrogenation catalyst pellets which are pulverized just before use; and Raney nickel catalyst W-2. Before using the Raney nickel, care must be taken to free it of aluminum by careful washing with 5% sodium hydroxide solution, followed by thorough rinsing with distilled water (private communication from Dr. Richard Weiss, van Ameringen-Haebler, Inc., New York 19, N. Y.). The checkers prepared Raney nickel catalyst W-2 according to the procedure in *Org. Syntheses*, Coll. Vol. **3**, 181 (1955).
4. The temperature should not exceed 50°; at higher temperatures complex condensation products result.
5. The length of time required for the hydrogenation varies with the size of the run and the activity of the catalyst. For a 9-mole run the hydrogenation usually proceeds for 10–12 hours before external heating is needed to bring the temperature into the 45–50° range. The system is periodically recharged with hydrogen to maintain a pressure of about 1800 lb. Reduction is continued until a total of 9.0 moles of hydrogen has been absorbed. Absorption of the calculated amount of hydrogen serves as the criterion for stopping the hydrogenation. For the 2.0-mole run described, 4–5 hours are needed.
6. The conversion of resorcinol to 2-methyl-1,3-cyclohexanedione can be effected by first isolating the dihydroresorcinol[2] and subjecting it to the methylation reaction. However, this procedure is more laborious and the yield is no better.
7. The checkers found that filtration through a coarse sintered-glass funnel is rapid and better-quality product is obtained. When a medium-porosity sintered-glass funnel or Büchner funnel is used, the filtration is exceedingly slow and may even stop owing to a small amount of gelatinous impurity which is present.
8. If all the sodium iodide is not removed by the washings with water, the product tends to become yellow.
9. This product is sufficiently pure for use in conversion to 1,6-dioxo-8a-methyl-1,2,3,4,6,7,8,8a-octahydronaphthalene.[3,4]

3. Discussion

2-Methyl-1,3-cyclohexanedione has been prepared by cyclization of ethyl 5-oxoheptanoate[5] and methyl 5-oxoheptanoate[3] with sodium ethoxide and sodium methoxide, respectively, and by methylation of dihydroresorcinol[2] employing sodium methoxide in methanol,[3,6] potassium hydroxide in aqueous methanol,[7] potassium methoxide in methanol,[8] potassium hydroxide in aqueous acetone,[9] potassium carbonate in aqueous acetone,[4] or sodium ethoxide in ethanol.[10] The present method is essentially that of Stetter,[7] except that the unnecessary isolation of the intermediary dihydroresorcinol is omitted, and this greatly enhances the ease of preparation.

4. Merits of Preparation

2-Methyl-1,3-cyclohexanedione has been used as starting material for the syntheses of several polycyclic compounds for projected syntheses of steroids and terpenoids.[11,12,13] It has also been used to prepare 1,6-diketo-8a-methyl-1,2,3,4,6,7,8,8a-octahydronaphthalene.[3,4,14,15]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 486
- Org. Syn. Coll. Vol. 7, 368
- Org. Syn. Coll. Vol. 8, 312

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

methanol (67-56-1)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

aluminum (7429-90-5)

nickel, Raney nickel (7440-02-0)

acetone (67-64-1)

sodium methoxide (124-41-4)

potassium hydroxide (1310-58-3)

sodium ethoxide (141-52-6)

Methyl iodide (74-88-4)

sodium iodide (7681-82-5)

resorcinol (108-46-3)

dioxane (5703-46-8)

potassium methoxide (865-33-8)

Dihydroresorcinol

1,6-DIOXO-8a-METHYL-1,2,3,4,6,7,8,8a-OCTAHYDRONAPHTHALENE, 1,6-diketo-8a-methyl-1,2,3,4,6,7,8,8a-octahydronaphthalene (20007-72-1)

2-Methyl-1,3-cyclohexanedione, 1,3-Cyclohexanedione, 2-methyl- (1193-55-1)

ethyl 5-oxoheptanoate

methyl 5-oxoheptanoate

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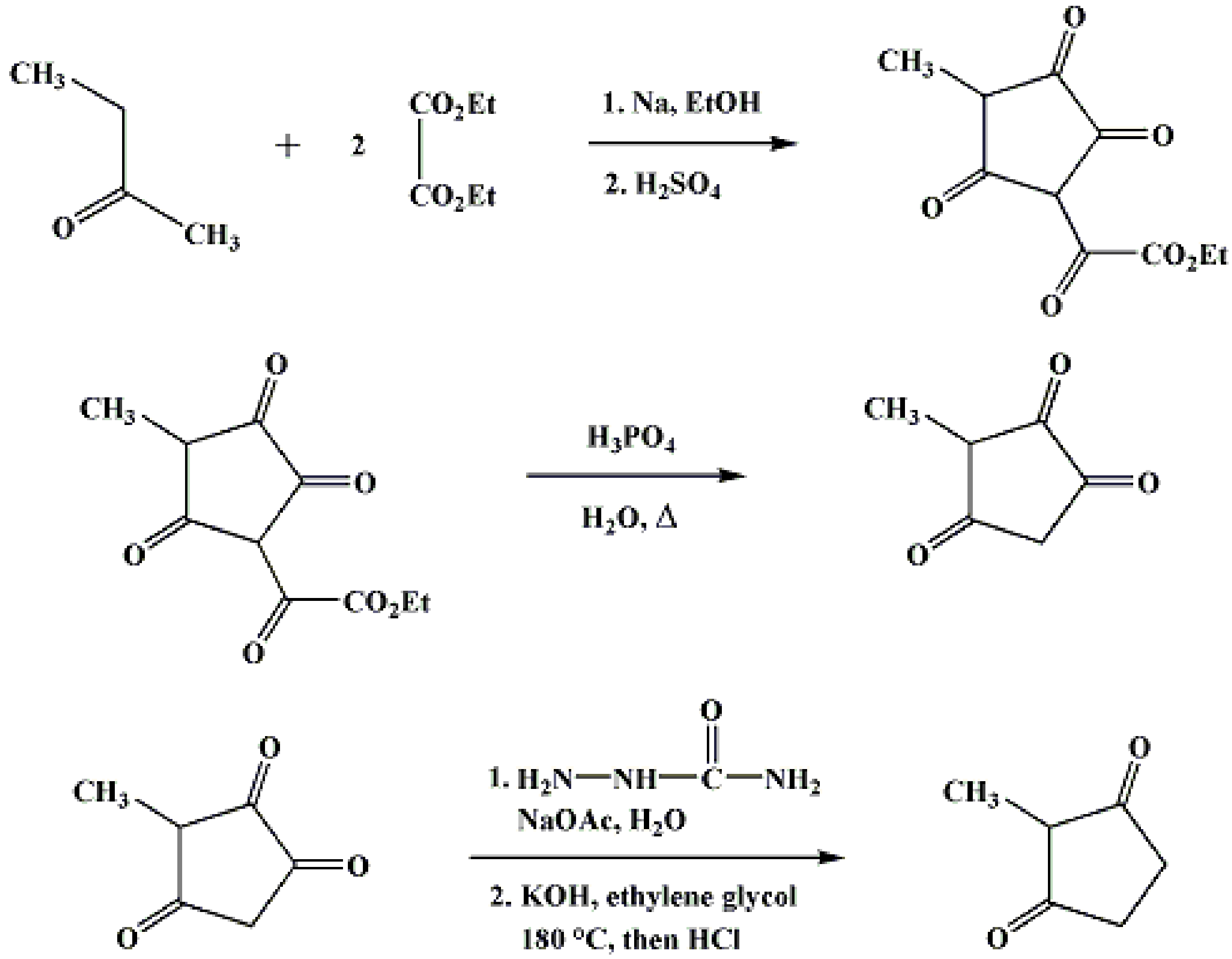
Organic Syntheses, CV 5, 747

2-METHYLCYCLOPENTANE-1,3-DIONE

[1,3-Cyclopentanedione, 2-methyl-]



Submitted by Joseph P. John, S. Swaminathan, and P. S. Venkataramani[1].
Checked by J. A. Berezowsky and Peter Yates.

1. Procedure

A. *2-Methyl-4-ethoxalylcyclopentane-1,3,5-trione*. A solution of sodium ethoxide is prepared in a 2-l. three-necked, round-bottomed flask fitted with a mercury-sealed stirrer, a reflux condenser carrying a drying tube, and a stopper by the addition of 69.0 g. (3 moles) of sodium to 950 ml. of absolute ethanol. The solution is cooled to 0–5° in an ice bath and stirred. The stopper is replaced by a dropping funnel, and a cold mixture (5–15°) of 108 g. (1.50 moles) of freshly distilled 2-butanone and 482 g. (3.30 moles) of diethyl oxalate (Note 1) is added gradually over a period of 30 minutes. After the addition is complete, the thick, orange-red mixture is allowed to warm with continued stirring to room temperature, heated under reflux for 30 minutes, and cooled again to 0° in an ice bath. The mixture is decomposed by stirring with 165 ml. of sulfuric acid (1:1 by volume) added in portions. The sodium sulfate formed is filtered by suction and washed with

ethanol (150–200 ml.) (Note 2). The washings and filtrate are combined and concentrated by evaporation at room temperature for 3–4 days in two wide-mouthed (6-in.) 1-l. crystallizing basins (Note 3). The yellowish brown product which accumulates by slow crystallization is collected by filtration, washed with small quantities of ice-cold water, and dried in air. The crude product weighs 140–150 g. Further evaporative concentration of the mother liquor followed by cooling furnishes an additional 40–50 g. of the keto ester, bringing the total yield to 180–200 g. (53–59%) (Note 2). This crude material (m.p. 120–130°) is used in the next step. A pure sample can be obtained by crystallization from ethyl acetate after treatment with Norit activated carbon, m.p. 160–162°.

B. *2-Methylcyclopentane-1,3,5-trione hydrate*. A mixture of 200 g. (0.89 mole) of the keto ester prepared above, 910 ml. of water, and 100 ml. of 85% phosphoric acid is heated under reflux for 4 hours and then cooled in an ice-salt bath to −5°. The trione mixed with oxalic acid separates and is collected by filtration and dried under reduced pressure. The dried material is extracted with boiling ether (250–300 ml.) under reflux, and the ethereal extract is separated from the undissolved oxalic acid. The original aqueous filtrate is also extracted with ether in a continuous extractor. The two extracts are combined, and ether is removed by distillation. The crude trione separates as a dark brown solid and is crystallized from *ca.* 250 ml. of hot water. The once-crystallized, faintly yellow product weighs 95–105 g. (74–82%), m.p. 70–74°. This product is used in the next step without further purification. A better specimen, m.p. 77–78°, which is almost colorless, can be obtained by recrystallization from hot water after treatment with Norit activated carbon.

C. *2-Methylcyclopentane-1,3,5-trione 5-semicarbazone*. The above trione hydrate (144 g., 1.00 mole) is dissolved in a mixture of 500 ml. of water and 1 l. of ethanol. A solution of 150 g. of sodium acetate in 200 ml. of water is added with stirring to raise the pH to 5–5.5, and the precipitate formed (Note 4) is filtered and washed with a little water (*ca.* 25 ml.). The filtrate is transferred to a 4-l. beaker and warmed to 45° on a water bath. Heating is then stopped, and a solution of 112 g. (1.00 mole) of semicarbazide hydrochloride and 150 g. of sodium acetate in 250 ml. of water is added dropwise from a dropping funnel with vigorous stirring during the course of 1.5 hours (Note 5). The stirring is continued for an additional hour, and the cream-colored monosemicarbazone is collected by filtration, washed with a little aqueous ethanol, and dried at 100°. The dried material weighs 110–120 g. (60–66%) and does not melt below 300°.

D. *2-Methylcyclopentane-1,3-dione*. In a 2-l. three-necked flask equipped with a reflux condenser and a stirrer are placed 115 g. (2.00 moles) of potassium hydroxide pellets and 1150 ml. of ethylene glycol. The flask is immersed in an oil bath which is heated to 130°. To the stirred mixture is added 12 ml. of water followed by 115 g. (0.628 mole) of the semicarbazone prepared above, added in portions over 30–40 minutes through the third neck of the flask, which is kept stoppered between additions. After the addition is complete, the bath temperature is raised to 150° and kept at this temperature for 30 minutes and then raised again to 180–185°. After 2 hours at 180–185° the reaction mixture is cooled, and the ethylene glycol is removed under reduced pressure (preferably below 4 mm.) (Note 6). The dry residue remaining is dissolved in 200–225 ml. of water, and the solution is cooled and carefully (Note 7) made acidic to Congo red with concentrated hydrochloric acid. The crude dione, which separates as a brown solid, is

collected by filtration and crystallized from a mixture of 250 ml. of water and 200 ml. of ethanol after treatment with Norit activated carbon. The almost colorless crystalline product weighs 40–44 g., m.p. 206–207°. The mother liquor is concentrated to furnish an additional 10–12 g. of product, m.p. 204–205°. The crops are combined and recrystallized as before to give 42–47 g. (60–67%) of colorless dione, m.p. 211–212°.

2. Notes

1. Eastman Organic Chemicals or B.D.H. Laboratory reagent grade diethyl oxalate was used.
2. The checkers washed the sodium sulfate with 500 ml. of ethanol. They obtained 202–213 g. (60–63%) of product, m.p. 140–155°.
3. The combined filtrate and washings may be concentrated to about 350 ml. under reduced pressure with a bath temperature not exceeding 40° and then worked up as described. However, the final yield of the keto ester is decreased to 120–140 g.
4. This pale yellow precipitate weighs 20–30 g. and is rejected.
5. The conditions described for the preparation of the semicarbazone are critical and should be strictly observed. Otherwise, the yield of the product in the subsequent Wolff-Kishner reduction is decreased.
6. The checkers found that it is important to remove the ethylene glycol immediately upon completion of the reaction; in a run in which the reaction mixture was allowed to stand overnight, a drastic reduction in the yield of product was observed.
7. There is considerable evolution of carbon dioxide and consequent frothing during acidification. Care must be exercised so that the contents of the flask do not spill over.

3. Discussion

2-Methylcyclopentane-1,3-dione has been prepared in 15% yield by the catalytic reduction of 2-methylcyclopentane-1,3,5-trione over platinum.[2] The present method is based on the original procedure[3] of Panouse and Sannie with improvements as effected by Boyce and Whitehurst[4] and the submitters.[5]

4. Merits of the Preparation

2-Methylcyclopentane-1,3-dione has found increasing use as an intermediate in the synthesis of steroids.[6,7,8,9,10,11,12] The method described is the only practicable method available for the preparation of 2-methylcyclopentane-1,3-dione in large amounts.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 774
- Org. Syn. Coll. Vol. 9, 570

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

2-Methyl-4-ethoxalylcyclopentane-1,3,5-trione

keto ester

trione hydrate

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

ether (60-29-7)

sodium acetate (127-09-3)

sodium sulfate (7757-82-6)

Oxalic acid (144-62-7)

carbon dioxide (124-38-9)

platinum (7440-06-4)

carbon, Norit (7782-42-5)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

phosphoric acid (7664-38-2)

sodium ethoxide (141-52-6)

ethylene glycol (107-21-1)

2-butanone (78-93-3)

diethyl oxalate (95-92-1)

semicarbazide hydrochloride (563-41-7)

2-Methylcyclopentane-1,3-dione, 1,3-Cyclopentanedione, 2-methyl- (765-69-5)

2-methylcyclopentane-1,3,5-trione (4505-54-8)

2-Methylcyclopentane-1,3,5-trione hydrate

2-Methylcyclopentane-1,3,5-trione 5-semicarbazone

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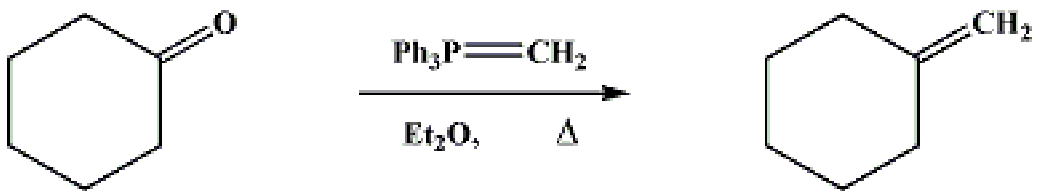
Organic Syntheses, CV 5, 751

METHYLENECYCLOHEXANE

[Cyclohexane, methylene-]



Submitted by George Wittig and U. Schoellkopf[1].
Checked by John D. Roberts and Martin Vogel.

1. Procedure

A. *Triphenylmethylphosphonium bromide*. A solution of 55 g. (0.21 mole) of triphenylphosphine dissolved in 45 ml. of dry benzene is placed in a pressure bottle, the bottle is cooled in an ice-salt mixture, and 28 g. (0.29 mole) of previously condensed methyl bromide is added (Note 1). The bottle is sealed, allowed to stand at room temperature for 2 days, and is reopened. The white solid is collected by means of suction filtration with the aid of about 500 ml. of hot benzene and is dried in a vacuum oven at 100° over phosphorus pentoxide. The yield is 74 g. (99%), m.p. 232–233°.

B. *Methylenecyclohexane* (Note 2). A 500-ml. three-necked round-bottomed flask is fitted with a reflux condenser, an addition funnel, a mechanical stirrer, and a gas inlet tube. A gentle flow of nitrogen through the apparatus is maintained throughout the reaction. An ethereal solution of *n*-butyllithium[2] (0.10 mole, about 100 ml., depending on the concentration of the solution) and 200 ml. of anhydrous ether is added to the flask. The solution is stirred and 35.7 g. (0.10 mole) of triphenylmethylphosphonium bromide is added cautiously over a 5-minute period (Note 3). The solution is stirred for 4 hours at room temperature (Note 4).

Freshly distilled cyclohexanone (10.8 g., 0.11 mole) is now added dropwise. The solution becomes colorless and a white precipitate separates. The mixture is heated under reflux over-night, allowed to cool to room temperature, and the precipitate is removed by suction filtration. The precipitate is washed with 100 ml. of ether, and the combined ethereal filtrates are extracted with 100-ml. portions of water until neutral and then dried over calcium chloride. The ether is carefully distilled through an 80-cm. column packed with glass helices. Fractionation of the residue remaining after removal

of the ether through an efficient, low-holdup column (Note 5) gives 3.4–3.8 g. (35–40%) of pure methylenecyclohexane, b.p. 99–101°/740 mm., n_D^{25} 1.4470 (Note 6).

2. Notes

1. Eastman Kodak Co. white label triphenylphosphine and Matheson Co. methyl bromide were used. Triphenylphosphine is available from the Metal and Thermit Corp., Rahway, New Jersey.
2. Since this procedure was first published in this series the use of methylsulfinyl carbanion (as the base) in dimethyl sulfoxide (as solvent) has been found to give better results in many examples than the base-solvent pair described here.[3] The Wittig reaction appears to proceed more rapidly in dimethyl sulfoxide and the yields of olefin are frequently superior. For purposes of comparison with the present procedure the procedure of Greenwald, Chaykovsky, and Corey[3] was repeated several times with the following deviations from the published procedure. Triphenylmethylphosphonium bromide from two different batches was purchased from the Aldrich Chemical Co., Inc. This material contained a small amount (*ca.* 1–2 percent) of benzene (as indicated by nmr analysis). Drying as described in part A reduced the benzene content to less than 1 percent. The apparatus was set up and the purification of cyclohexanone and dimethylsulfoxide was carried out as described in the preparation of methylenecyclohexane oxide (this volume, p. 755). With these modifications the procedure resembled that described by Monson.[4] In several experiments the *apparent* yields (75–94%) of methylenecyclohexane clustered about the 8.10 g. (84.2%) reported by Greenwald, Chaykovsky, and Corey;[3] however, analysis by nmr and glpc showed that the product was a mixture of methylenecyclohexane and benzene in the ratio of 4 to 1. Methylenecyclohexane and benzene may be separated quite easily by distillation (using a spinning-band column) or by preparative gas chromatography on any of several columns (SE-30, di-2-ethylhexyl sebacate, silver nitrate-ethylene glycol). Thus, the *true* yield of methylenecyclohexane was 60–78%. This is a substantial improvement over the yield obtained by the present procedure. The source of the benzene was not determined. Using different batches of the various reagents did not alter the results. Omitting the washing of the sodium hydride with *n*-pentane resulted in a 50–60% reduction in apparent yield (private communication from D. G. McMahan and H. E. Baumgarten).
3. If the triphenylmethylphosphonium bromide is added too rapidly, the evolution of butane causes excessive frothing of the solution.
4. The small amount of precipitate in the orange solution is not unreacted starting material but triphenylphosphinemethylene.
5. The checkers used a 6 × 350 mm. spinning-band column with a total reflux variable take-off head. The band was spun at 1100 r.p.m.
6. The methylenecyclohexane was analyzed by vapor-phase chromatography

and found to be better than 99% pure.

3. Discussion

The procedure is a modification of that published.[5] Methylenecyclohexane has been prepared by the pyrolysis of N,N-dimethyl-1-methylcyclohexylamine oxide, N,N,N-trimethyl-1-methylcyclohexylammonium hydroxide, N,N-dimethylcyclohexylmethylamine oxide, and N,N,N-trimethylcyclohexylmethylammonium hydroxide.[6] It has also been obtained from the pyrolysis of cyclohexylmethyl acetate[7] and of cyclohexylideneacetic acid[8] and from the dehydrohalogenation of cyclohexylmethyl iodide.[9]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

calcium chloride (10043-52-4)

Benzene (71-43-2)

ether (60-29-7)

Cyclohexanone (108-94-1)

silver nitrate (7761-88-8)

nitrogen (7727-37-9)

ethylene glycol (107-21-1)

methyl bromide (74-83-9)

n-PENTANE (109-66-0)

butane (106-97-8)

n-butyllithium (109-72-8)

sodium hydride (7646-69-7)

dimethyl sulfoxide, dimethylsulfoxide (67-68-5)

Methylenecyclohexane, Cyclohexane, methylene- (1192-37-6)

cyclohexylmethyl iodide

cyclohexylideneacetic acid

triphenylphosphinemethylene

N,N-Dimethylcyclohexylmethylamine oxide

triphenylphosphine (603-35-0)

di-2-ethylhexyl sebacate (122-62-3)

triphenylmethylphosphonium bromide (1779-49-3)

Methylenecyclohexane oxide (185-70-6)

N,N-dimethyl-1-methylcyclohexylamine oxide

N,N,N-trimethyl-1-methylcyclohexylammonium hydroxide

N,N,N-trimethylcyclohexylmethylammonium hydroxide

cyclohexylmethyl acetate

phosphorus pentoxide (1314-56-3)

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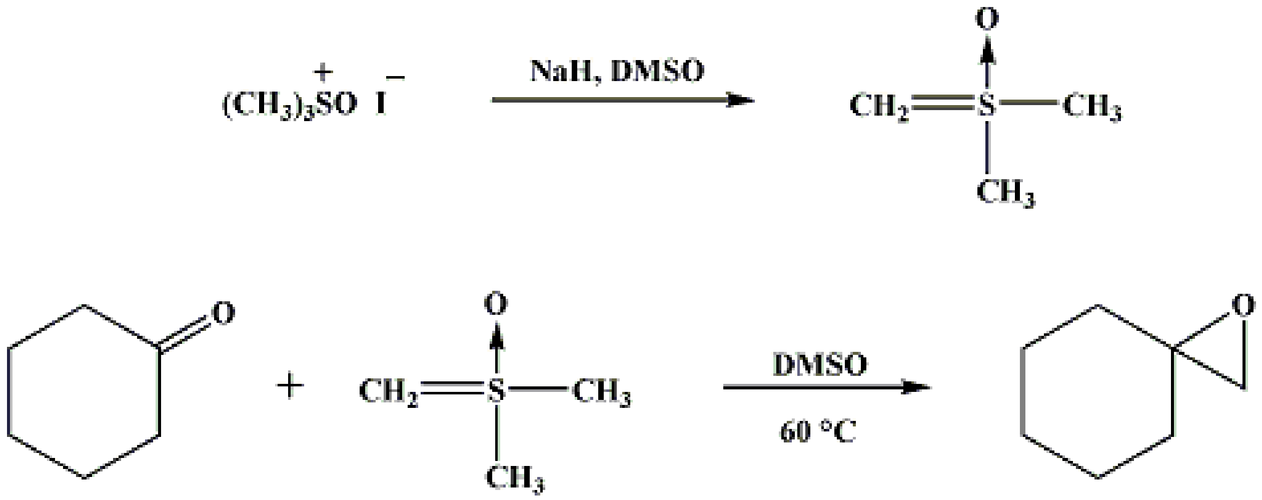
Organic Syntheses, CV 5, 755

METHYLENECYCLOHEXANE OXIDE

[Octane, 1-oxaspiro[2.5]-]



Submitted by E. J. Corey[1] and Michael Chaykovsky[2].
Checked by William Washburn and Ronald Breslow.

1. Procedure

A. *Dimethyloxosulfonium methylide* (Note 1). In a 500-ml., three-necked, round-bottomed flask with a magnetic stirrer (Note 2) are placed 8.8 g. (0.22 mole) of sodium hydride (60% oil dispersion) (Note 3) and 150 ml. of petroleum ether (30–60°). The suspension is stirred, the hydride allowed to settle, the petroleum ether decanted (Note 4), and 250 ml. of dry dimethyl sulfoxide (Note 5) is added. The flask is immediately fitted with an inlet and outlet for nitrogen and a piece of Gooch tubing connected to a 125-ml. Erlenmeyer flask containing 50.6 g. (0.23 mole) of trimethyloxosulfonium iodide (Note 6). A gentle stream of dry nitrogen is then continuously passed through the system. With stirring, the oxosulfonium iodide is added, in portions, over a period of 15 minutes (Note 7) and stirring is then continued for an additional 30 minutes (Note 8).

B. *Methylenecyclohexane oxide*. The Gooch tubing is removed from the reaction flask and immediately replaced with a sealed, pressure-compensated dropping funnel containing 19.6 g. (0.2 mole) of cyclohexanone (Note 9), which is then added to the reaction mixture over a 5-minute period. After stirring for 15 minutes, the reaction mixture is heated to 55–60° for 30 minutes with an oil bath and then poured into 500 ml. of cold water and extracted with three 100-ml. portions of ether. The combined ether extracts are washed with 100 ml. of water, then with 50 ml. of saturated aqueous salt solution, dried over anhydrous sodium sulfate, and the ether is distilled at atmospheric pressure through a 20-cm. Vigreux column. The almost colorless residue is transferred to a 50-ml. round-bottomed flask and distilled under reduced pressure

through a 5-cm. Vigreux column to yield 15–17 g. (67–76%) of the oxide as a colorless liquid, b.p. 61–62° (39 mm.); n^{23}D 1.4485 (Note 10). The n.m.r. spectrum ($CDCl_3$; $(CH_3)_4Si$ internal standard) showed a band at δ 1.58 (10H) and a sharp singlet at δ 2.53 (2H).

2. Notes

1. The reaction should be carried out in a well-ventilated hood because hydrogen is evolved.
2. The submitters used a mechanical stirrer, but the checkers found that the more convenient magnetic stirrer works as well.
3. The submitters used Alfa Inorganics Inc. sodium hydride dispersion.
4. The petroleum ether removes most of the oil from the hydride dispersion.
5. Matheson, Coleman and Bell anhydrous dimethyl sulfoxide was stirred over powdered calcium hydride overnight and then distilled under reduced pressure, b. p. 64–65° (4 mm.). Dimethyl sulfoxide should not be distilled at temperatures above 90° since at these higher temperatures appreciable disproportionation occurs producing dimethyl sulfone and dimethyl sulfide, the latter of which contaminates the distilled solvent.
6. Trimethyloxosulfonium iodide was purchased from Aldrich Chemical Co. and was recrystallized from water, crushed, and dried in a desiccator over phosphorus pentoxide before use. The salt may be prepared by reaction of dimethyl sulfoxide with excess methyl iodide.[3]
7. The reaction is only mildly exothermic. No cooling is necessary.
8. After this time the evolution of hydrogen is essentially complete.
9. Eastman Kodak white label cyclohexanone was used without further purification.
10. Reported physical constants are b.p. 62–63° (37 mm.), n^{20}D 1.4470;[4] b.p. 66–68° (50 mm.) n^{20}D 1.4506.[5]

3. Discussion

Methylenecyclohexane oxide has been prepared by the oxidation of methylenecyclohexane with benzonitrile-hydrogen peroxide or with peracetic acid;[5] by treatment of 1-chlorocyclohexylmethanol with aqueous potassium hydroxide;[6] and by the reaction of dimethylsulfonium methylide with cyclohexanone.[7]

This reaction illustrates a general method for the conversion of ketones and aldehydes[8] into oxiranes using the methylene-transfer reagent dimethyloxosulfonium methylide. The yields of oxiranes are usually high, and the crude products, in most cases, are of sufficient purity to be used in subsequent reactions (*e.g.*, rearrangement to aldehydes) without further purification.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 751

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

ether (60-29-7)

hydrogen (1333-74-0)

benzonitrile (100-47-0)

Cyclohexanone (108-94-1)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

potassium hydroxide (1310-58-3)

hydrogen peroxide (7722-84-1)

Methyl iodide (74-88-4)

dimethyl sulfide (75-18-3)

peracetic acid (79-21-0)

sodium hydride (7646-69-7)

dimethyl sulfoxide (67-68-5)

calcium hydride (7789-78-8)

Methylenecyclohexane (1192-37-6)

dimethylsulfonium methylide

Methylenecyclohexane oxide, Octane, 1-oxaspiro[2.5]- (185-70-6)

trimethyloxosulfonium iodide (1774-47-6)

dimethyl sulfone (67-71-0)

1-chlorocyclohexylmethanol

dimethyloxosulfonium methylide

phosphorus pentoxide (1314-56-3)

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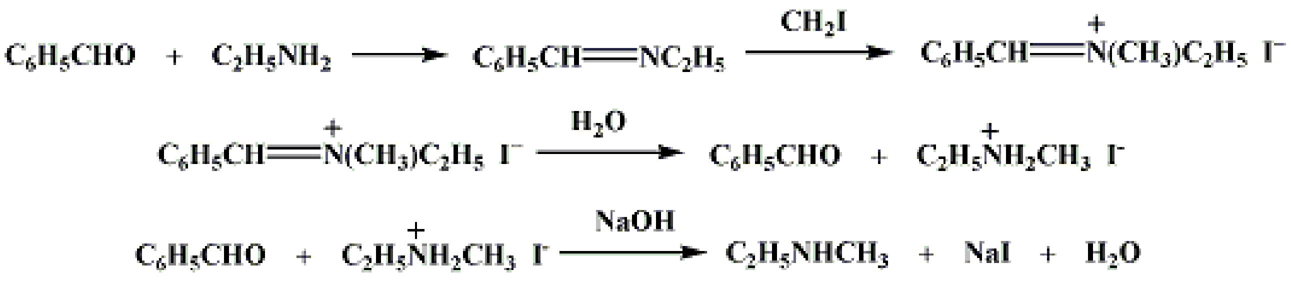
Organic Syntheses, CV 5, 758

N-METHYLETHYLAMINE

[Ethylamine, N-methyl-]



Submitted by S. Wawzonek, W. McKillip, and C. J. Peterson[1].
Checked by J. K. Williams, H. E. Winberg, C. L. Dickinson, and B. C. McKusick.

1. Procedure

A. *N-Benzylideneethylamine*. Benzaldehyde (466 g., 4.40 moles) is placed in a 2-l. three-necked flask equipped with a mechanical stirrer and a thermometer. The flask is cooled to 5° in an ice bath, and 200 g. (4.44 moles) of anhydrous ethylamine (Note 1) is added to the stirred benzaldehyde at such a rate that the temperature remains below 15°; about 50 minutes is required for the addition. The mixture is stirred for an additional 30 minutes at room temperature and allowed to stand for 1 hour.

The condenser is arranged for downward distillation, and the water is removed from the product by codistillation with 200 ml. of benzene. The residue, N-benzylideneethylamine, is purified by distillation through a 25-cm. Fenske column; b.p. 52–53° (4.5 mm.); n^{23}D 1.5400; weight 470–523 g. (80–89%) (Note 2).

B. *N-Methylethylamine* N-Benzylideneethylamine. (133 g., 1.00 mole) is heated with 156 g. (1.10 moles) of methyl iodide (Note 3) in a 300-ml. pressure bomb at 100° for 24 hours (Note 4). The bomb is cooled to 50° (Note 5), and the dark, viscous oil is poured into a 1-l. beaker containing 200 ml. of water. The bomb is rinsed with three 50-ml. portions of water, and the washings are combined with the main solution. The resulting mixture is heated with manual stirring on a steam bath for 20 minutes and then cooled in an ice bath to room temperature. The resulting mixture is extracted with two 75-ml. portions of ether (Note 6). The ether layer is washed with two 50-ml. portions of water, and the washings are combined with the main aqueous layer, which is then heated at 100° on a steam bath for 20 minutes to remove traces of ether.

For the liberation of N-methylethylamine, a 1-l. Claisen flask is equipped with a 250-ml. separatory funnel and an efficient condenser for distillation. The receiver is cooled with a mixture of acetone and dry ice (Note 7). A solution of 100 g. (2.5 moles) of sodium hydroxide in 100 ml. of water is added to the flask and kept at about 100° by heating on a steam bath. The aqueous solution of N-methylethylamine hydriodide is added to this solution through the separatory funnel in the course of 1.5 hours. After the addition is complete, the final solution is heated for an additional 30 minutes. Crude N-methylethylamine, b.p. 30–70°, collects in the cooled receiver. It is purified by distillation from 25 g. of solid potassium hydroxide in a 250-ml. modified Claisen flask fitted with a 25-cm. Fenske column and a receiver cooled by dry ice and acetone. N-Methylethylamine is collected at 34–35°; weight 49–55 g. (83–93%); n^{25}D 1.3830.

2. Notes

1. The ethylamine is cooled to 5° to prevent loss by evaporation. Addition is made directly from the bottle with intermittent cooling in an ice bath.
2. The aldimine need not be distilled but can be used directly in the next step.
3. Dimethyl sulfate, when substituted for the methyl iodide, reacts vigorously with the aldimine at ice-bath temperatures and gives a 49% yield of N-methylethylamine together with considerable tar.
4. Four times these amounts have been used for N-methylbutylamine with equal success.
5. The pressure bomb is opened while still warm (50°). If the bomb is allowed to cool below this temperature, the product solidifies and removal becomes a problem.
6. The benzaldehyde may be recovered after removal of the ether.
7. Because of the low boiling point of N-methylethylamine, there must be efficient cooling or a portion of the product will be lost.

3. Discussion

This procedure is a modification of the method used for N-methylallylamine.[2]

N-Methylethylamine has been prepared by heating ethylamine with methyl iodide in alcohol at 100°;[3] by the hydrolysis of N-methyl-N-ethylarenesulfonamides,[4,5] *p*-nitroso-N-methyl-N-ethylaniline,[6] or methylethylbenzhydrylidene ammonium iodide;[7] by catalytic hydrogenation of ethyl isocyanate or ethyl isocyanide;[8] and by the reduction of ethyl isocyanate by lithium aluminum hydride,[9] of N-methylacetisoaldoxime by sodium amalgam and acetic acid,[10] or of a nitromethane/ethylmagnesium bromide adduct by zinc and hydrochloric acid.[11]

4. Merits of the Preparation

This preparation illustrates a general method for the synthesis of N-methylalkylamines. The submitters have used it to prepare N-methylbutylamine (Note 4) and N-methylallylamine, and the checkers have used it to prepare N-methylisopropylamine (80%), N-methylisobutylamine (67%), N-methyl-*tert*-butylamine (52%), and N-methyl-2-methoxyethylamine (55%). Secondary amines are useful as starting materials for the synthesis of 1,1-disubstituted hydrazines and asymmetric amine imides.

The method gives better yields, utilizes more readily available starting materials, and is much less laborious than the hydrolysis of N-methyl-N-alkylarenesulfonamides and *p*-nitroso-N, N-dialkylanilines, or the lithium aluminum hydride reduction of alkyl isocyanates. Compared to the closely related procedure of Lucier, Harris, and Korosec,[12] in which the N-benzylidenealkylamine is treated with dialkyl sulfate at atmospheric pressure, the present procedure tends to give higher yields and purer products, but it is less convenient because of the need for a pressure vessel.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 736

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

N-methylacetisoaldoxime

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

ether (60-29-7)

sodium hydroxide (1310-73-2)

dimethyl sulfate (77-78-1)

benzaldehyde (100-52-7)

acetone (67-64-1)

potassium hydroxide (1310-58-3)

zinc (7440-66-6)

sodium (13966-32-0)

Methyl iodide (74-88-4)

lithium aluminum hydride (16853-85-3)

Ethyl isocyanide (624-79-3)

ethylamine (75-04-7)

ethyl isocyanate (109-90-0)

N-Methylbutylamine (110-68-9)

N-Methylethylamine, Ethylamine, N-methyl- (624-78-2)

N-Benzylideneethylamine (6852-54-6)

N-methylethylamine hydriodide

N-methylallylamine (627-37-2)

methylethylbenzhydrylidene ammonium iodide

N-methylisopropylamine (4747-21-1)

N-methylisobutylamine (625-43-4)

N-methyl-2-methoxyethylamine (38256-93-8)

p-nitroso-N-methyl-N-ethylaniline

N-methyl-tert-butylamine (14610-37-8)

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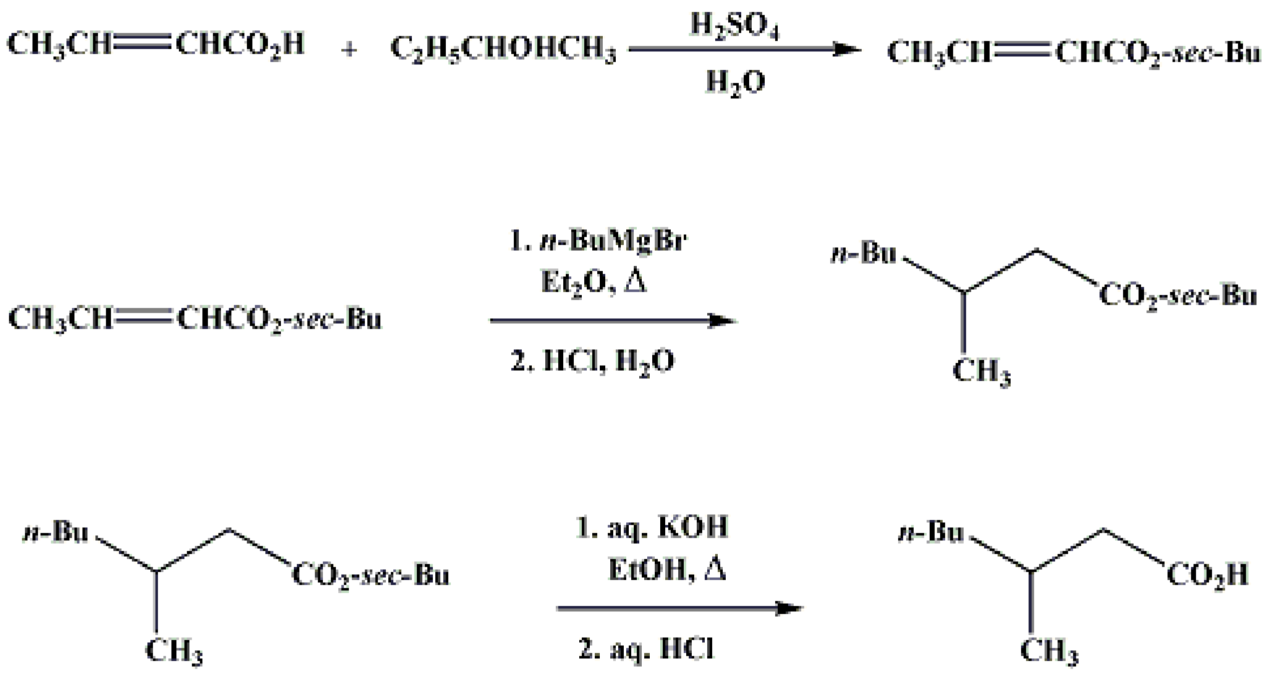
3-METHYLHEPTANOIC ACID

[Heptanoic acid, 3-methyl-]



Submitted by Jon Munch-Petersen[1]
Checked by Melvin S. Newman and Donald E. Harsh.

1. Procedure

A. *sec-Butyl crotonate*. In a 2-l. round-bottomed flask are placed 258 g. (3 moles) of crotonic acid (Note 1), 370 g. (5 moles) of *sec*-butyl alcohol in which has been dissolved 6–7 ml. of concentrated sulfuric acid, and 300 ml. of benzene. A few boiling chips are added, and the flask is fitted with a suitable water separator (Note 2) in the top of which is placed a reflux condenser. The mixture is heated under reflux for about 12 hours or until no further separation of aqueous phase occurs. About 65 ml. of water is collected. The cooled reaction mixture is diluted with 200 ml. of ether, washed with 10% sodium carbonate solution until neutral to litmus, washed with saturated sodium chloride solution, and finally dried over magnesium sulfate. The solvent is distilled, and the ester is fractionated under reduced pressure through a small column. The yield of *sec*-butyl crotonate, b.p. 74–75°/30 mm. or 83–84°/45 mm., n_D^{25} 1.4261, is 360–390 g. (85–90%) (Note 3).

B. *3-Methylheptanoic acid*. In a 2-l. three-necked flask fitted with a mercury-sealed stirrer, a reflux condenser carrying a calcium chloride tube, and a dropping funnel are placed 25.0 g. (1.04 g. atoms) of magnesium turnings. The flask is heated to about 100° for a few minutes and then cooled to room temperature. A solution of 178 g. (1.30 moles) of *n*-butyl bromide in 300 ml. of dry ether is prepared; and of this solution about

10 ml., together with 30 ml. of dry ether, is run into the flask. The reaction is started by heating to reflux for a few seconds, the stirrer is started, and the remainder of the bromide solution is added at such a rate as to maintain constant reflux (about 1 hour).

After the addition has been completed, the solution is heated under reflux for 10–15 minutes. The flask is now surrounded by an ice and water bath, and stirring is continued for 15 minutes (Note 4). From a graduated dropping funnel, a solution of 56.8 g. (0.4 mole) of *sec*-butyl crotonate (Note 5) in 400 ml. of dry ether is then added dropwise during a period of about 3 hours (Note 6) while the reaction mixture is effectively stirred and cooled in the ice bath. After the addition of the ester solution is complete, the reaction mixture is stirred in the ice bath for an additional 15 minutes. The ice bath is then removed, and stirring of the grayish brown solution is continued at room temperature for 1 hour.

In a 3-l. Erlenmeyer flask are placed about 500 g. of crushed ice, 110 ml. (1.3 equivalents) of concentrated hydrochloric acid, and 100 ml. of ether. This mixture is vigorously swirled and shaken while the Grignard reaction mixture is cautiously added in small portions. More ice is added to the Erlenmeyer flask as required to keep the temperature near 0°. The resulting mixture is poured into a separatory funnel and shaken thoroughly. The water layer is separated and extracted three times with 100 ml. of ether. The combined ether solutions are washed with 100 ml. of saturated sodium bicarbonate solution, and then with 100 ml. of water. The solution is dried over anhydrous magnesium sulfate, and the ether distilled on a water bath. The residue is fractionated at reduced pressure through a modified Claisen flask to yield 54–62 g. (68–78%) (Note 4) of *sec*-butyl 3-methylheptanoate, b.p. 92–93°/9 mm., n_D^{25} 1.4190.

A solution of 40 g. (0.2 mole) of *sec*-butyl 3-methylheptanoate in 100 ml. of ethanol containing 18.5 g. (0.3 mole) of potassium hydroxide and 20 ml. of water is heated under reflux for 30 minutes (Note 7) and (Note 8). The cooled solution is diluted with 200 ml. of water and acidified by the addition of 60 ml. of concentrated hydrochloric acid. The organic acid is extracted with three 100-ml. portions of 1:1 benzene-ether, and the combined benzene-ether extracts are washed with 50 ml. of saturated sodium chloride solution. The resulting solution is filtered by gravity through a bed of anhydrous magnesium sulfate. After removal of solvents by distillation, 26–27 g. (90–94%) of 3-methylheptanoic acid, b.p. 116–117°/10 mm., n_D^{25} 1.4242, is obtained by distillation in a modified Claisen flask (Note 9).

2. Notes

1. Eastman Organic Chemicals practical grade of crotonic acid (containing 10% water) was used by the checkers without further purification.

2. The water separator preferred by the submitter is that described by Wideqvist,[2] but any continuous water separator which will return the benzene to the reaction mixture may be used, e.g., the modified Dean-Stark water separator.[3]

3. By essentially the same procedure the submitter has prepared the following *sec*-butyl esters: *sec*-butyl acrylate, b.p. 127–129°, n_D^{20} 1.4158; *sec*-butyl

methacrylate, b.p. 59–62°/34 mm., n_D^{25} 1.4161; *sec*-butyl tiglate, b.p. 84.5°/27 mm., n_D^{25} 1.4332; *sec*-butyl β,β-dimethylacrylate, b.p. 68–70°/13 mm., n_D^{25} 1.4379; *sec*-butyl cinnamate, b.p. 122°/2 mm., n_D^{25} 1.5382. With *sec*-butyl acrylate and methacrylate, 2–3% of hydroquinone should be added to the reaction mixtures and 0.1% of hydroquinone to the esters if stored at room temperature.

4. Recent investigations[4] by the submitter have shown that the yield of *sec*-butyl 3-methylheptanoate is improved to 80–85% if 1.4 g. (1.4 mole% with respect to the Grignard reagent) of cuprous chloride (commercial grade, analytically pure) is added in seven portions during the course of the addition of the ester.

5. Ethyl crotonate may be used with the same yield (70%) of addition product if cuprous chloride is present during the addition[5] (Note 4). Methyl crotonate under these conditions yields methyl α,γ-di-(2-hexyl)-acetoacetate [methyl 2-(2'-hexyl)-3-keto-5-methylonanoate], b.p. 135°/2.5 mm., n_D^{25} 1.4419, in 67% yield.[6]

6. The large excess of Grignard reagent, the dilution of the ester, and the slow addition are essential features of the procedure. If these conditions are not fulfilled the yields drop considerably, and a greater amount of high-boiling residue, di-*sec*-butyl α-(2-hexyl)-β-methylglutarate, b.p. 145°/1.5 mm., n_D^{25} 1.4400, is formed.[6] When the reaction is run on a 0.2-mole scale the addition time of the ester may be reduced to 1.5 hours.

7. In the case of the analogous products obtained by the addition reactions with *sec*-butyl tiglate (Note 9) considerably more drastic conditions are necessary in order to secure complete saponification. The submitter generally employs reflux for 6–8 hours with 35 g. (0.6 mole) of potassium hydroxide dissolved in 250 ml. of 95% ethanol.

8. An alternative procedure is used by the submitter from this point to the final distillation of solvent and ester: The condenser is then set for downward distillation, and about 40 ml. of alcohol is distilled. Then 100 ml. of water is added, and an additional 100 ml. of alcohol and water is distilled. The cooled residue is diluted with 200 ml. of water and the solution freed of insoluble organic material by washing three times with 50 ml. of ether. After acidification with 40 ml. of concentrated hydrochloric acid, the organic layer is extracted with three 50-ml. portions of ether. The combined ether extracts are washed with water and dried over anhydrous magnesium sulfate.

9. The submitter has, by either cuprous chloride-catalyzed or uncatalyzed reactions, prepared a variety of 3-methyl-substituted fatty acids from the adducts of *sec*-butyl crotonate and other Grignard reagents.[4,5,6,7,8,9] The uncatalyzed reaction has also been used with *sec*-butyl tiglate to obtain 2,3-dimethyl-substituted fatty acids.[7]

3. Discussion

3-Methylheptanoic acid has been prepared by mixed electrolysis of β-methylglutaric acid monomethyl ester and butyric acid, followed by saponification of the methyl ester,[10] and

by the malonic ester synthesis from 2-bromohexane.[11] The present method[7] has the advantage of avoiding the use of secondary bromides, which are often difficult to secure entirely pure.[12]

4. Merits of Procedure

The reactions here described are of considerable general utility for the preparation of a variety of fatty acids from the addition products of Grignard reagents and α,β-unsaturated esters.[4,5,6,7,8,9,13]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether (60-29-7)

hydroquinone (123-31-9)

sodium bicarbonate (144-55-8)

magnesium turnings (7439-95-4)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

n-butyl bromide (109-65-9)

potassium hydroxide (1310-58-3)

butyric acid (107-92-6)

cuprous chloride (7758-89-6)

methyl (2229-07-4)

magnesium sulfate (7487-88-9)

crotonic acid (3724-65-0)

ethyl crotonate (623-70-1)

methyl crotonate (623-43-8)

β-methylglutaric acid monomethyl ester

sec-butyl alcohol (78-92-2)

3-Methylheptanoic acid, Heptanoic acid, 3-methyl- (59614-85-6)

methacrylate

methyl α,γ-di-(2-hexyl)-acetoacetate

2-bromohexane (3377-86-4)

sec-Butyl crotonate (10371-45-6)

sec-butyl 3-methylheptanoate (16253-72-8)

sec-butyl acrylate (2998-08-5)

sec-butyl methacrylate (2998-18-7)

sec-butyl tiglate

sec-butyl β,β-dimethylacrylate

sec-butyl cinnamate

di-sec-butyl α-(2-hexyl)-β-methylglutarate

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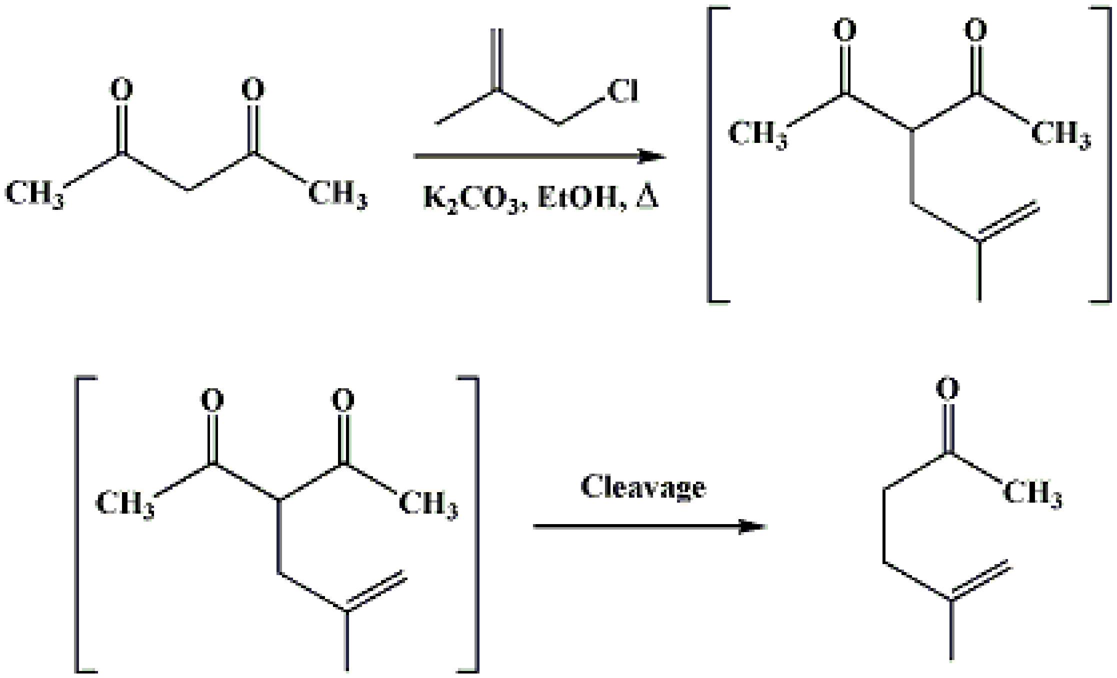
Organic Syntheses, CV 5, 767

5-METHYL-5-HEXEN-2-ONE

[5-Methylene-2-hexanone]



Submitted by Sandra Boatman and Charles R. Hauser[1].
Checked by E. J. Corey and William E. Russey.

1. Procedure

In a 1-l. round-bottomed flask equipped with a condenser are placed 78.0 g. (0.56 mole) of commercial anhydrous potassium carbonate, 45.0 g. (0.50 mole) of methallyl chloride (Note 1), 55.0 g. (0.55 mole) of 2,4-pentanedione (Note 1), and 300 ml. of anhydrous ethanol (Note 2). The mixture is refluxed on a steam bath for 16 hours. The condenser is replaced by a distilling head and condenser, and about 200 ml. of ethanol is distilled from the mixture (Note 3). Ice water (600 ml.) is added to dissolve the salts, and the mixture is extracted three times with ether. The combined ether extracts are washed twice with 100 ml. of saturated sodium chloride solution, dried for 30 minutes over anhydrous magnesium sulfate, and filtered; the solvent is evaporated. The residue is distilled through a 6-in. Vigreux column using an oil bath maintained at 190° to give 26–29 g. (47–52%) of the product, b.p. 145–155° (Note 4), (Note 5).

2. Notes

1. Eastman Organic Chemicals practical grade methallyl chloride was distilled (b.p. 70–71°); Union Carbide Chemicals Co. 2,4-pentanedione was distilled (b. p. 134.5–135.5°).

2. Commercial grade absolute ethanol was dried over Linde 3A molecular sieves.
3. At this point most of the ethyl acetate, which is formed as a by-product of the reaction, also is removed.
4. The checkers used a 2-ft. spinning-band column at 200 mm. and observed b.p. 110–111.5°.
5. In the distillation residue (5.7–6.3 g.) remain other byproducts, presumably 1,1-dimethallyl-2-propanone, 3-methallyl-2,4-pentanedione, and 3,3-dimethallyl-2,4-pentanedione (indicated by vapor phase chromatography). The checkers carried out v.p.c. analyses using an 8-ft. column of 5% silicone oil XE-60 on Diatoport S at 100° for analysis of the distillate and 175° for analysis of the residue.

3. Discussion

5-Methyl-5-hexen-2-one has been prepared by alkylation of acetoacetic ester with methallyl chloride, followed by cleavage; the overall yield in the two steps was 51%.[2]

4. Merits of the Preparation

The present procedure, which is characterized by its extreme simplicity, has been employed to prepare various ketones of type RCH_2COCH_3 from 2,4-pentanedione,[3] as indicated in Table I.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 275

TABLE I ALKYLATION AND CLEAVAGE OF 2,4-PENTANEDIONE

Alkyl Halide	Ketone	% Yield
Benzyl chloride	4-Phenyl-2-butanone	73
o-Bromobenzyl bromide	4-(*o*-Bromophenyl)-2-butanone	75
m-Bromobenzyl bromide	4-(*m*-Bromophenyl)-2-butanone	78
o-Chlorobenzyl chloride	4-(*o*-Chlorophenyl)-2-butanone	78
m-Chlorobenzyl bromide	4-(*m*-Chlorophenyl)-2-butanone	65
p-Chlorobenzyl bromide	4-(*p*-Chlorophenyl)-2-butanone	62
m-Fluorobenzyl chloride	4-(*m*-Fluorophenyl)-2-butanone	60
m-Nitrobenzyl chloride	4-(*m*-Nitrophenyl)-2-butanone	65
α-Chloromethylnaphthalen	4-(α-Naphthyl)-2-butanone	61
Phenacyl chloride	1-Phenyl-1,4-pentanedione	55
n-Butyl iodide	2-Heptanone	60

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

potassium carbonate (584-08-7)

ethyl acetate (141-78-6)

ether (60-29-7)

sodium chloride (7647-14-5)

benzyl chloride (100-44-7)

2-Heptanone (110-43-0)

magnesium sulfate (7487-88-9)

2,4-pentanedione (123-54-6)

phenacyl chloride (532-27-4)

α-Chloromethylnaphthalen (86-52-2)

methallyl chloride (563-47-3)

o-Chlorobenzyl chloride (611-19-8)

5-Methyl-5-hexen-2-one, 5-Methylene-2-hexanone (3240-09-3)

3,3-dimethallyl-2,4-pentanedione

4-Phenyl-2-butanone (2550-26-7)

4-(α-Naphthyl)-2-butanone

1-Phenyl-1,4-pentanedione (583-05-1)

4-(p-Chlorophenyl)-2-butanone (3506-75-0)

n-Butyl iodide (542-69-8)

p-chlorobenzyl bromide (622-95-7)

o-Bromobenzyl bromide (3433-80-5)

4-(o-Bromophenyl)-2-butanone

m-Bromobenzyl bromide (823-78-9)

4-(m-Bromophenyl)-2-butanone

4-(o-Chlorophenyl)-2-butanone

m-Chlorobenzyl bromide (766-80-3)

4-(m-Chlorophenyl)-2-butanone

m-Fluorobenzyl chloride (456-42-8)

4-(m-Fluorophenyl)-2-butanone

m-Nitrobenzyl chloride (619-23-8)

4-(m-Nitrophenyl)-2-butanone

1,1-dimethallyl-2-propanone

3-methallyl-2,4-pentanedione

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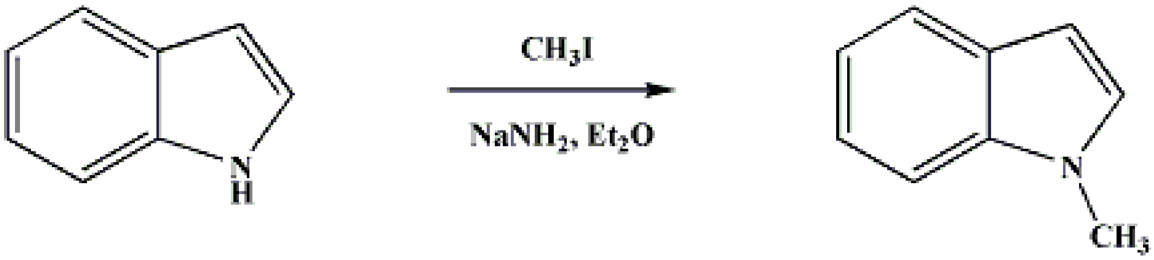
Organic Syntheses, *CV 5*, *769*

1-METHYLINDOLE

[Indole, 1-methyl-]



Submitted by K. T. Potts and J. E. Saxton[1].
Checked by W. E. Parham, Wayland E. Noland, and Bryce A. Cunningham.

1. Procedure

Caution! Ammonia gas is an extreme irritant and can cause serious burns to the eyes, etc. It is necessary to carry out the entire reaction under a well-ventilated hood.

In a 1-l. three-necked flask fitted with a motor stirrer (Note 1), gas inlet tube, dropping funnel, and a wide-bore soda-lime tube are placed 400–500 ml. of liquid ammonia and 0.1 g. of ferric nitrate nonahydrate (Note 2).

In small portions, just sufficient to maintain the blue color, 5.0 g. (0.22 gram atom) of clean, metallic sodium is added with vigorous stirring. After dissolution is complete (Note 3), a solution of 23.4 g. (0.20 mole) of indole (Note 4) in 50 ml. of anhydrous ether is added slowly and then, after an additional 10 minutes, a solution of 31.2 g. (0.22 mole) of methyl iodide in an equal volume of anhydrous ether is added dropwise. Stirring is continued for a further 15 minutes. The ammonia is allowed to evaporate (Note 5), 100 ml. of water is added, followed by 100 ml. of ether. The ether layer is separated, the aqueous phase extracted with an additional 20 ml. of ether, and the combined ether extracts washed with three 15 ml.-portions of water (Note 6) and dried over anhydrous sodium sulfate. The solvent is removed at atmospheric pressure, and the crude oil ($n_D^{18.5°}$ 1.6078) is purified by distillation under reduced pressure. 1-Methylindole is obtained as a colorless oil, b.p. 133°/26 mm., $n_D^{18.5°}$ 1.6082. In several runs the yield is 22.3–24.9 g. (85–95%).

2. Notes

1. Any sealed mechanical stirrer may be used. Those of the Hershberg[2] type were found particularly efficient during the formation of the sodium amide.

2. It was found most advantageous to run in the liquid ammonia from the commercial cylinder, laid on the floor with the foot raised slightly, and connected to the gas inlet tube with rubber tubing approximately 1 cm. in diameter. The large excess of liquid ammonia used obviates the need of a dry iceacetone cooling bath and permits a reasonably rapid formation of sodium amide.
3. This occurs when the blue color has disappeared. The formation of the light gray sodium amide is usually complete within 20 minutes and may be observed by washing a portion of the outside of the flask with a little alcohol.
4. A commercial grade of indole is satisfactory.
5. The checkers removed the ammonia by distillation (water aspirator).
6. The checkers extracted with two 50-ml. portions of ether and three 50-ml. portions of water.

3. Discussion

1-Methylindole has been prepared from the *as*-methylphenylhydrazone of pyruvic acid,[3] by the action of sodium amide or sodium hydride on indole followed by methyl iodide at elevated temperatures,[4,5] by treatment of indole with methyl *p*-toluenesulfonate and anhydrous sodium carbonate in boiling xylene,[6] and by the action of methyl sulfate on indole previously treated with sodium amide in liquid ammonia.[7] The present method is essentially that of Potts and Saxton.[8]

1-Methylindole has also been prepared by lithium aluminum hydride reduction of 1-methylindoxyl.[9] Compounds giving rise to NH absorption in the infrared (indole, skatole) can be completely removed[10] by refluxing the crude 1-methylindole over sodium for 2 days and then distilling the unreacted 1-methylindole from the sodio derivatives and tarry decomposition products.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 104
- Org. Syn. Coll. Vol. 6, 106

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

as-methylphenylhydrazone of pyruvic acid

1-methylindoxyl

ammonia (7664-41-7)

ether (60-29-7)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

sodium (13966-32-0)

xylene (106-42-3)

Methyl iodide (74-88-4)

methyl sulfate (75-93-4)

sodium amide (7782-92-5)

lithium aluminum hydride (16853-85-3)

sodium hydride (7646-69-7)

Indole (120-72-9)

skatole (83-34-1)

1-Methylindole, Indole, 1-methyl- (603-76-9)

ferric nitrate nonahydrate

Methyl p-toluenesulfonate (80-48-8)

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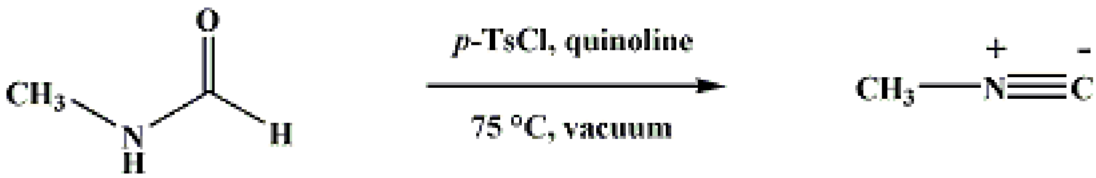
Organic Syntheses, CV 5, 772

METHYL ISOCYANIDE



Submitted by R. E. Schuster, James E. Scott, and Joseph Casanova, Jr.[1].
Checked by John A. Dupont and William D. Emmons.

1. Procedure

Caution! Methyl isocyanide should be prepared in a good hood since it is toxic and has a very unpleasant odor. The reaction and subsequent distillation of the product should be conducted behind safety shields (Note 1).

In a 2-l. four-necked flask (Note 2) equipped with a 250-ml. pressure-equalizing dropping funnel, a sealed mechanical stirrer, a thermometer, and a receiver trap (Note 3) are placed 1034 g. (8.0 moles) of quinoline and 572 g. (3.0 moles) of *p*-toluenesulfonyl chloride (Note 4). The solution is heated to 75° by an oil bath and the system evacuated to a pressure of 15 mm. The receiver is cooled in a bath of liquid nitrogen (Note 5). While the solution is vigorously stirred and maintained at this temperature, 118 g. (2.0 moles) of N-methylformamide (Note 4) is added dropwise to maintain a smooth distillation rate. The addition is complete in 45–60 minutes.

The material which collects in the receiver is distilled through a 15-cm. Vigreux column at atmospheric pressure. Methyl isocyanide, a colorless, vile-smelling liquid, is collected at 59–60°; weight 57–61 g. (69–74%) (Note 6). Analysis by gas liquid chromatography indicates that the purity exceeds 99% (Note 7).

2. Notes

1. An explosion involving methyl isocyanide has been reported.[2] For this reason, prudence dictates the use of adequate shielding in all heating operations.
2. A three-necked flask may be used by employing a suitable adapter on one of the necks. The checkers used a standard wide-bore, 75-degree side-arm adapter fitted with a long-stemmed thermometer extending into the reaction solution. A Trubore® stirrer equipped with a semicircular Teflon® paddle was also used.
3. A vapor trap having a wide-bore inlet tube and the appropriate condensate capacity is used. The checkers used a 4.8 cm. × 30.0 cm. trap having a 2.0 cm. × 18.0 cm. inlet tube. Best results are obtained when the trap is connected directly to the flask or the adapter (see (Note 2)) by a wide-bore tube. Ground-glass joints should be used throughout the apparatus.

4. All materials were obtained from Eastman Kodak Company. Quinoline, practical grade, b.p. 72–74° (0.2 mm.), was freshly distilled from zinc dust. If undistilled quinoline is employed, a major contaminant, which appears to be methyl isocyanate, will be formed. "White label" *p*-toluenesulfonyl chloride and N-methylformamide were used without further purification.
5. The checkers found that a bath of dry ice and acetone worked equally well.
6. A single transfer under high vacuum afforded a product of identical purity. The major contaminants appear to be small amounts of high-boiling starting materials.
7. When a 2-m. polypropylene glycol on firebrick column at 75° is used, the retention volume of methyl isocyanide is 55 cc. of helium. Because of an unknown factor in conditioning the column, it is advisable to perform at least two consecutive analyses.
The checkers employed a 5-ft. 20% Carbowax 20 M (terminated with terephthalic acid) on Chromosorb W (acid washed) column at 60°. Methyl isocyanide showed a retention volume of 300 cc. of helium. Only traces of lower-boiling impurities were observed.

3. Discussion

Methyl isocyanide has been prepared chiefly by minor modifications of the original method of Gautier,[3] which is the alkylation of silver cyanide by an alkyl halide.

4. Merits of the Preparation

The excellent procedures for dehydration of N-alkyl- and N-arylformamides developed by Hertler and Corey[4] and by Ugi and co-workers[5] are unsuccessful with low-molecular-weight isocyanides. This common failure is probably due to poor efficiency in extraction of these very polar substances from water. The present method also has been successfully employed for the preparation of smaller quantities of methyl (50%), ethyl (45%), *s*-butyl (35%) and cyclobutyl (24%) isocyanides.[6] The procedure is less laborious than that reported earlier for ethyl isocyanide.[7] For comments on procedures for the preparation of the higher alkyl isocyanides see p. 300 of this volume and reference [8].

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 300
- Org. Syn. Coll. Vol. 5, 1060
- Org. Syn. Coll. Vol. 6, 232
- Org. Syn. Coll. Vol. 7, 27

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

polypropylene glycol

nitrogen (7727-37-9)

zinc (7440-66-6)

Quinoline (91-22-5)

silver cyanide (506-64-9)

Terephthalic acid (100-21-0)

Ethyl isocyanide (624-79-3)

helium (7440-59-7)

Methyl isocyanide (593-75-9)

N-methylformamide (123-39-7)

methyl isocyanate (624-83-9)

p-Toluenesulfonyl chloride (98-59-9)

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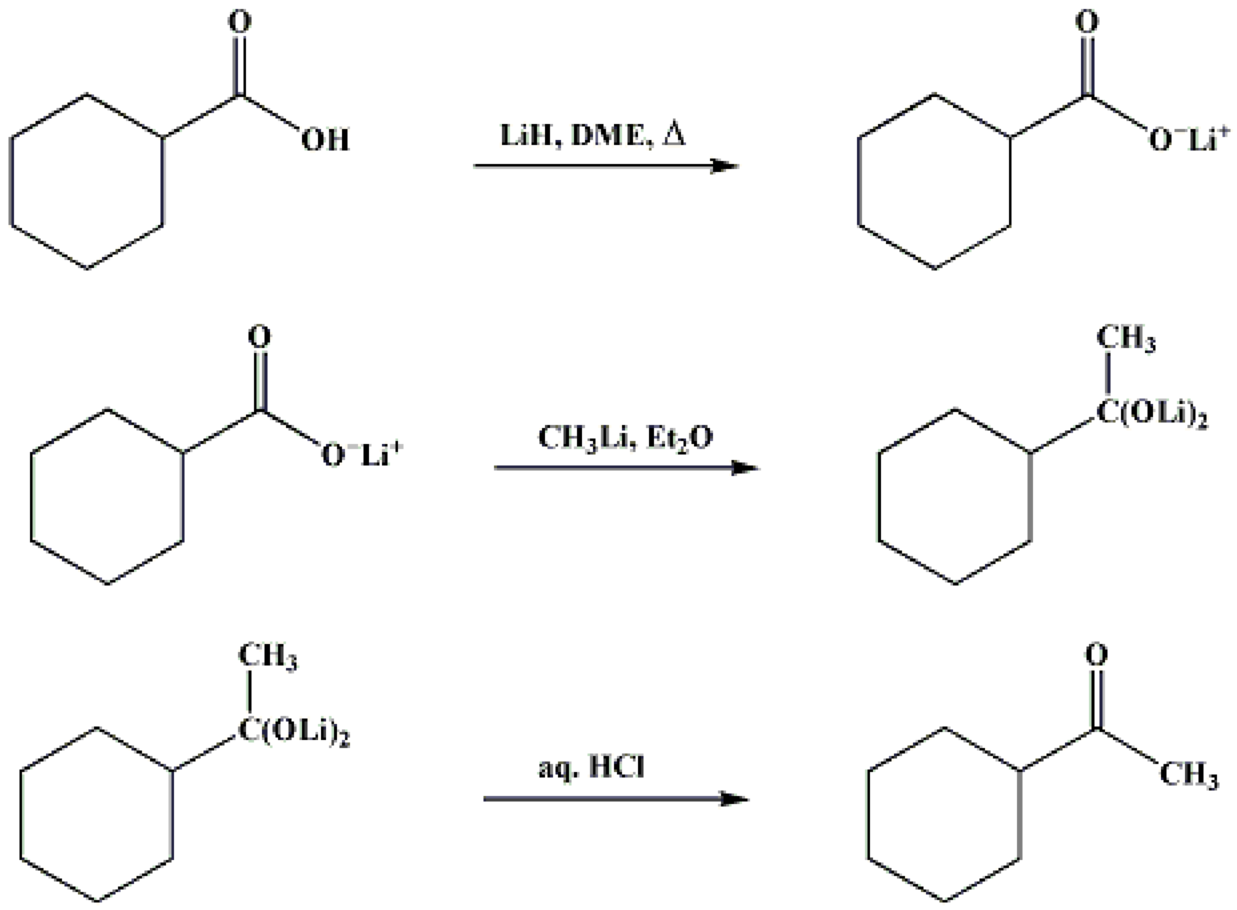
Organic Syntheses, CV 5, 775

METHYL KETONES FROM CARBOXYLIC ACIDS: CYCLOHEXYL METHYL KETONE

[Ketone, cyclohexyl methyl]



Submitted by Thomas M. Bare and Herbert O. House[1].
Checked by A. De Meijere and K. B. Wiberg.

1. Procedure

Caution! Since hydrogen is liberated in the first step of this reaction, it should be conducted in a hood. A dry, 500-ml., three-necked flask is fitted with a reflux condenser, a pressure-equalizing dropping funnel, a mechanical stirrer, and an inlet tube to maintain a static nitrogen atmosphere in the reaction vessel throughout the reaction. In the flask are placed 1.39 g. (0.174 mole) of powdered lithium hydride (Note 1) and 100 ml. of anhydrous 1,2-dimethoxyethane (Note 2). While this suspension is stirred vigorously, a solution of 19.25 g. (0.150 mole) of cyclohexanecarboxylic acid (Note 3) in 100 ml. of anhydrous 1,2-dimethoxyethane (Note 2) is added dropwise over a 10-minute period. The resulting mixture is heated to reflux with stirring for 2.5 hours, at which time hydrogen evolution and the formation of lithium cyclohexanecarboxylate are complete. After the resulting suspension has

been cooled to approximately 10° with an ice bath, it is stirred vigorously while 123 ml. of an ethereal solution containing 0.170 mole of methyllithium (Note 4) is added dropwise over a 30-minute period. After the addition is complete, the ice bath is removed and the resulting suspension is stirred at room temperature for 2 hours. The dropping funnel is removed from the reaction flask and replaced by a rubber septum fitted with a 4-mm. O.D. glass tube of suitable dimensions to permit the reaction mixture to be siphoned from the reaction flask when a slight positive nitrogen pressure is present in the flask.

The fine suspension in the reaction flask is agitated and siphoned into a vigorously stirred mixture of 27 ml. (0.32 mole) (Note 5) of concentrated hydrochloric acid and 400 ml. of water. The reaction flask is rinsed with an additional 100 ml. of ether which is also added to the aqueous solution. After the resulting mixture has been saturated with sodium chloride, the organic phase is separated and the alkaline (Note 5) aqueous phase is extracted with three 150-ml. portions of ether. When the combined organic solutions have been dried over magnesium sulfate, the bulk of the ether is distilled from the mixture through a 40-cm. Vigreux column (Note 6) and then the residual ether and the 1,2-dimethoxyethane are distilled from the mixture through a 10-cm. Vigreux column. Distillation of the residual pale yellow liquid separates 17.1–17.7 g. (91–94%) of the methyl ketone as a colorless liquid, b.p. 57–60° (8 mm.), n^{26}D 1.4488–1.4489 (Note 7).

2. Notes

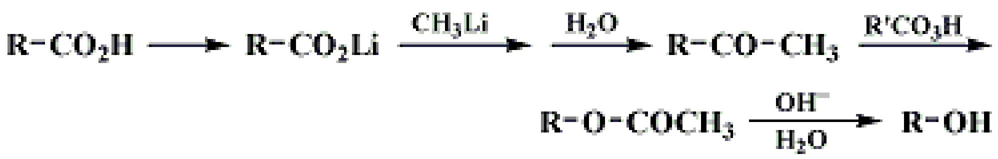
1. Lithium hydride of suitable quality may be purchased from Alfa Inorganics, Inc., 8 Congress Street, Beverly, Massachusetts 01915.
2. Commercial 1,2-dimethoxyethane, b.p. 85–86°, purchased from Eastman Organic Chemicals, was distilled from lithium aluminum hydride before use.
3. The cyclohexanecarboxylic acid, m.p. 31–32°, purchased from Aldrich Chemical Company was used without further purification.
4. An ethereal solution which was 1.38*M* in methyllithium was purchased from Foote Mineral Company. The concentration of methyllithium in ethereal solutions may be conveniently determined by a procedure described elsewhere[2,3] in which the lithium reagent is titrated with *sec*-butyl alcohol, utilizing the charge transfer complex formed from bipyridyl or *o*-phenanthroline and the lithium reagent as an indicator.
5. The quantity of hydrochloric acid used is normally insufficient to neutralize all the lithium hydroxide produced when the reaction mixture is quenched in the aqueous solution. As a result, any unchanged cyclohexanecarboxylic acid will be present as its lithium salt and will remain in the aqueous phase.
6. The product is sufficiently volatile that use of a rotary evaporator or an open flask to distill the bulk of the ether and 1,2-dimethoxyethane from this solution may result in loss of a significant fraction of the product.
7. The product may be analyzed by use of a gas chromatography column packed with either LAC-728 (diethylene glycol succinate) or Carbowax 20M suspended

on Chromosorb P. Using a 2.5-m. LAC-728 column heated to 100°, the submitters found retention times of 9.4 and 13.0 minutes for cyclohexyl methyl ketone and cyclohexyldimethylcarbinol. Less than 1% of the carbinol by-product was present.

3. Discussion

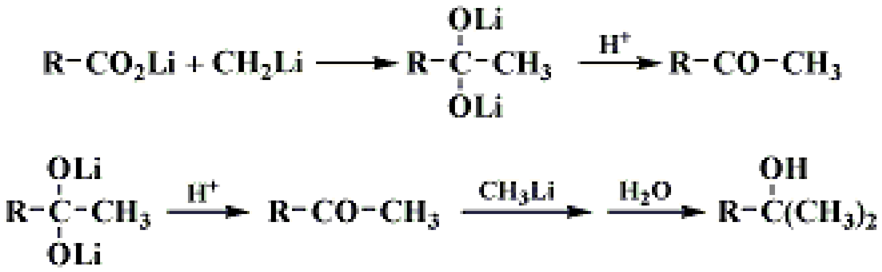
Apart from the reaction of cyclohexanecarboxylic acid with methyllithium,[4] cyclohexyl methyl ketone has been prepared by the reaction of cyclohexylmagnesium halides with acetyl chloride or acetic anhydride[5,6,7] and by the reaction of methylmagnesium iodide with cyclohexanecarboxylic acid chloride.[8] Other preparative methods include the aluminum chloride-catalyzed acetylation of cyclohexene in the presence of cyclohexane,[9] the oxidation of cyclohexylmethylcarbinol,[10,11] the decarboxylation and rearrangement of the glycidic ester derived from cyclohexanone and *t*-butyl α-chloropropionate,[12] and the catalytic hydrogenation of 1-acetylcyclohexene.[13,14]

This preparation illustrates the procedure for reaction of organolithium reagents with the lithium salts of carboxylic acids to form ketones.[15] The reaction is generally applicable to alkyl, vinyl, and aryl organolithium reagents and carboxylic acid salts which do not contain other interfering functional groups. However, the reaction has been most often used with methyllithium for the preparation of methyl ketones. The reaction is known to effect the *stereospecific* conversion of a carboxylic acid to methyl ketone and, consequently, is a useful part of the sequence illustrated in the accompanying equations for interrelating the stereochemistry of alcohols and carboxylic acids.[16,17]



The reaction is believed to proceed by the indicated conversion of a lithium carboxylate to the dilithium salt[18] which is stable at room temperature in the absence of proton-donating solvents or reactants. However, the rapidity with which this dilithium salt is decomposed to a ketone in the presence of proton donors, accompanied by the rapidity of the subsequent reaction of the ketone with more methyllithium, can lead to a common side reaction in which an alkyldimethyl carbinol is formed. Both of the aforementioned reactions appear to be fast compared with 0.01 second usually required to disperse components with the conventional mixing techniques. This side reaction can be almost entirely avoided by taking precautions to minimize the possibility that high *local concentrations* of the geminal dialkoxide and the lithium reagent are present when a proton donor is added during either the reaction or the *subsequent quenching*. It is frequently possible to obtain only relatively small

amounts of the alcohol by-product by the dropwise addition *with vigorous mixing* of 2 equivalents of the organolithium reagent *to* a solution of the carboxylic acid. During this procedure it is not uncommon for the lithium carboxylate to separate during the addition of the first mole of organolithium reagent and then to react and redissolve as the second equivalent of organolithium reagent is added. The reverse procedure, adding the acid to a solution of the organolithium reagent, appears always to produce substantial amounts of the alcohol by-product. The procedure used in this preparation illustrates how this mixing problem may be avoided by the initial conversion of the carboxylic acid to its lithium salt with lithium hydride. In all cases it is important not to add a large excess of organolithium reagent and to add the final reaction mixture to the aqueous quenching bath slowly and with vigorous stirring if the formation of substantial amounts of alcohol by-product is to be avoided.



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Appendix

Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

ether (60-29-7)

acetic anhydride (108-24-7)

hydrogen (1333-74-0)

acetyl chloride (75-36-5)

Cyclohexanone (108-94-1)

Cyclohexene (110-83-8)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

cyclohexane (110-82-7)

methylmagnesium iodide (917-64-6)

Cyclohexanecarboxylic acid (98-89-5)

lithium (7439-93-2)

magnesium sulfate (7487-88-9)

1-Acetylcyclohexene (932-66-1)

lithium aluminum hydride (16853-85-3)

Methyllithium (917-54-4)

cyclohexanecarboxylic acid chloride (2719-27-9)

1,2-dimethoxyethane (110-71-4)

phenanthroline

sec-butyl alcohol (78-92-2)

Cyclohexyl methyl ketone, Ketone, cyclohexyl methyl (823-76-7)

lithium hydride (7580-67-8)

lithium cyclohexanecarboxylate

bipyridyl (366-18-7)

lithium hydroxide (1310-65-2)

cyclohexyldimethylcarbinol

cyclohexylmethylcarbinol (4442-79-9)

lithium carboxylate

t-butyl α-chloropropionate (40058-88-6)

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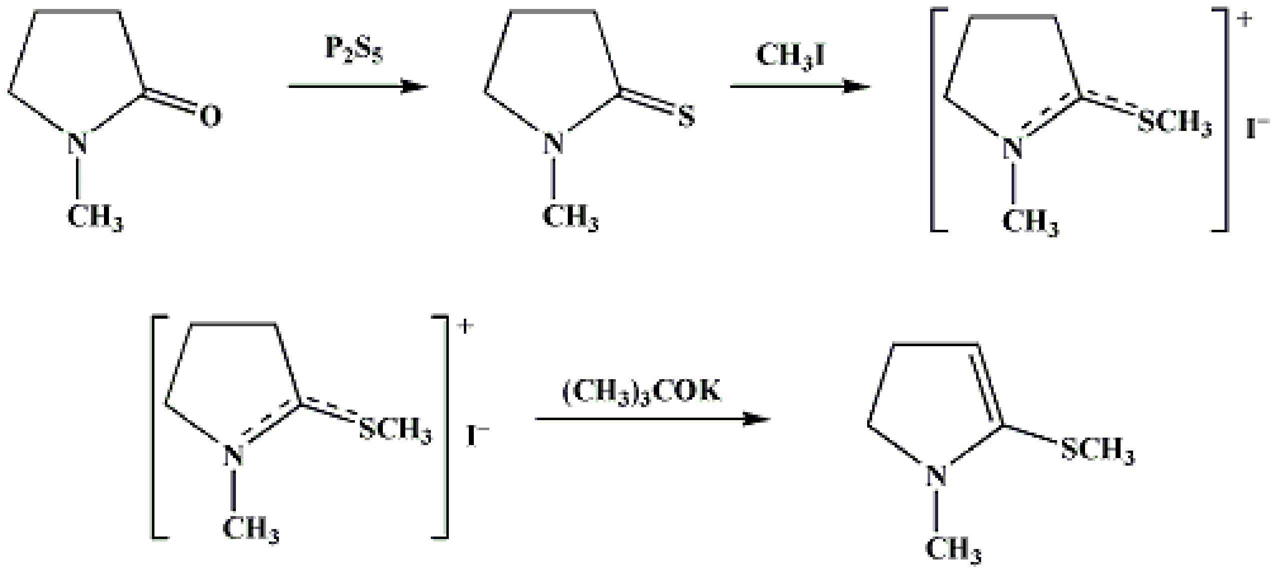
Organic Syntheses, *CV 5*, 780

2-METHYLMERCAPTO-N-METHYL-Δ2-PYRROLINE

[2-Pyrroline, 1-methyl-2-methylthio-]



Submitted by R. Gompper and W. Elser[1].
Checked by Hermann Ertl, Ian D. Rae, and Peter Yates.

1. Procedure

Caution! Hydrogen sulfide is very poisonous. Procedure A should be conducted in a hood.

A. *N-Methyl-2-pyrrolidinethione*. Phosphorus pentasulfide (667 g., 3.00 moles) is suspended in 600 ml. of carbon disulfide in a 2-l. three-necked flask equipped with a mechanical stirrer with a segment-shaped paddle, an efficient reflux condenser, and a dropping funnel. N-Methyl-2-pyrrolidinone (300 g., 3.03 moles) is added in large portions from the dropping funnel with vigorous stirring. The reaction mixture warms up considerably and, after addition of about two-thirds of the amide, becomes so viscous that further stirring is impossible. The addition of the remainder is carried out without stirring at a rate such that the solution boils gently. The semisolid, yellow-brown mixture is boiled under reflux on a water bath for a further 10 hours.

The carbon disulfide is decanted, and 200–300 ml. of water is added to the contents of the flask. Initially the mixture reacts slowly, but after some time the reaction becomes so vigorous that it is necessary to pour off the water (Note 1) and (Note 2). The addition of water, followed by its removal when the reaction becomes very vigorous, is repeated until decomposition is complete. The combined aqueous solutions are extracted several times with chloroform, and the combined extracts are dried over anhydrous sodium sulfate. Distillation of the solvent gives a dark brown liquid residue which is distilled under reduced pressure to give 310.3 g. (89%) of the thioamide as a yellow liquid, b.p. 133–135° (12 mm.) (Note 3).

B. *2-Methylmercapto-N-methyl-Δ ^{1}-pyrrolinium iodide*. N-Methyl-2-pyrrolidinethione (310

g., 2.69 moles) is dissolved with stirring in 1.1 l. of anhydrous ether in a 2-l. three-necked flask equipped with a mechanical stirrer, a reflux condenser fitted with a drying tube, and a dropping funnel. To this solution is added *ca.* 5 g. of the product as seed crystals (Note 4) to prevent initial deposition of the iodide as an oil that suddenly crystallizes with considerable evolution of heat. Methyl iodide (520 g., 3.66 moles) is then added rather rapidly. The solution becomes turbid after a short time, and separation of the salt begins with heat evolution. After 12 hours the hygroscopic, crystalline paste is filtered and dried in a desiccator; yield 663 g. (96%).

This product can be used without further purification. Crystallization from mixtures of acetonitrile and ether gives colorless, felted needles, m.p. 118–120° (dec.) (Note 5).

C. *2-Methylmercapto-N-methyl-Δ 2-pyrroline*. 2-Methylmercapto-N-methyl-Δ 1-pyrrolinium iodide (662 g., 2.57 moles) is suspended in 1.25 l. of anhydrous ether in a 4-l. three-necked flask equipped with a mechanical stirrer and a reflux condenser with a segment-shaped paddle. Potassium *t*-butoxide (448 g., 4.0 moles) is added in one batch to this suspension with vigorous stirring. The mixture warms up a little, and later the solid becomes fine-grained and more mobile as a result of separation of potassium iodide. After being stirred for 1.5 hours at room temperature, the mixture is treated with 1.8 l. of anhydrous ether and boiled under reflux on a water bath for 5 hours.

The flask is cooled in an ice bath, and the precipitate is filtered onto a large Buchner funnel and washed well with ether (Note 6). Ether is distilled from the yellow-brown filtrate at atmospheric pressure, and *t*-butyl alcohol is distilled under reduced pressure at 40°. Distillation of the residue through a 10-cm. Vigreux column at the water aspirator gives, after a small forerun (*ca.* 20 ml.), the product as a colorless liquid, b.p. 70–73° (10–12 mm.); yield 268 g. (81%) (Note 7), (Note 8), and (Note 9). This becomes brown on standing.

Repeated fractional distillation gives a product of analytical purity (Note 10), b.p. 65–68° (8–10 mm.), n^{25}_D 1.5222 (Note 11); yield 62%. This is an extremely disagreeable, musty liquid which on standing in the atmosphere warms up slightly and immediately turns red.

2. Notes

1. The large amount of hydrogen sulfide produced is destroyed by passage into two wash bottles containing concentrated aqueous potassium hydroxide.
2. It is also possible to moderate the reaction by the addition of chloroform.
3. The checkers, working at quarter scale, obtained 84–87% of product, b.p. 131–133° (11 mm.), 139–142° (14–15 mm.).
4. This can be prepared readily in a test tube by addition of methyl iodide to a solution of the thioamide in ether.
5. *Anal.* Calcd. for $C_6H_{12}INS$: I, 49.36. Found: 49.34.
6. The precipitate may be so fine-grained that the filtrate is initially turbid; the turbid filtrate is then filtered again through the Buchner funnel containing the precipitate.
7. This fraction is followed by tailings (12 g.), b.p. 74–75° (10–12 mm.).
8. The checkers, working at quarter scale, obtained 75% of product, b.p. 68–71° (13 mm.), followed by tailings, b.p. 71–74° (13 mm.).
9. This product is contaminated with N-methyl-2-pyrrolidinone, which does not impair its usefulness for most further reactions.

10. *Anal.* Calcd. for $C_6H_{11}NS$: C, 55.76; H, 8.58; N, 10.84; S, 24.82. Found: C, 55.60; H, 9.08; N, 10.84, S, 24.66.
11. The checkers found that the refractive index of the pyrroline increases rapidly on exposure to air, impairing its usefulness as a criterion of purity.

3. Discussion

The method described for the preparation of N-methyl-2-pyrrolidinethione is very similar to that of Peak and Stansfield[2] for the preparation of 4-thioacetylmorpholine. N-Methyl-2-pyrrolidinethione has also been prepared by the reaction of 2-chloro-N-methyl-Δ^1-pyrrolinium chloride with hydrogen sulfide [yield 83%; b.p. 144–145° (15 mm.)][3] and by heating N-methyl-2-pyrrolidinone with 2 equivalents of phosphorus pentasulfide in xylene [yield not reported; b.p. 125–132° (10 mm.)].[4] General procedures for the preparation of N, N-disubstituted thioamides have been reviewed.[5,6]

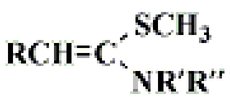
The method described for the preparation of 2-methylmercapto-N-methyl-Δ^1-pyrrolinium iodide is based on the general procedure of several authors.[2,7,8,9] Its preparation has not been described previously; the corresponding methyl sulfate has been obtained as a noncrystalline, viscous mass.[4,10]

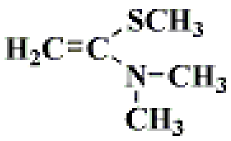
2-Methylmercapto-N-methyl-Δ^2-pyrroline has been prepared by the present method only.[11,12]

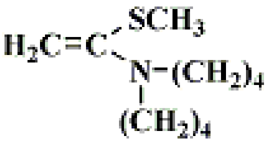
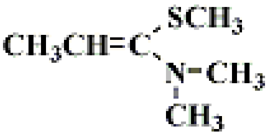
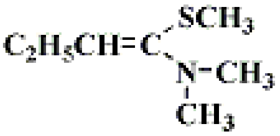
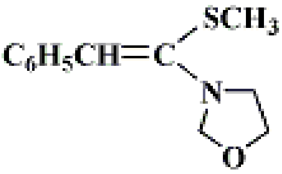
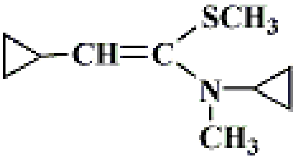
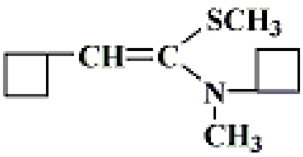
4. Merits of the Preparation

The procedure illustrates a general method for the preparation of ketene S,N-acetals via thioamides and their crystalline quaternary iodides; some other examples are shown in Table I. 2,2-Dialkyl-substituted ketene S,N-acetals cannot be prepared by this method because the nature of the products makes rigorous purification impractical. Ketene S,N-acetals are useful starting materials for many syntheses.[11,13,14,15]

TABLE I Preparation of Ketene S,N-Acetals



R	R'	R"	B.P., °C.	Yield of Crude Product, % (Purity, %)[a]
H	CH_3	CH_3	 31–32 (11 mm.)	77 (92–96)[b]

H	$(CH_2)_4$		 79–81 (10 mm.)	60 (72–88)
CH_3	CH_3	CH_3	 38–40 (10 mm.)	68 (88)
C_2H_5	CH_3	CH_3	 56 (11 mm.)	74 (92)
C_6H_5	$(CH_2)_2O(CH_2)_2$[c]		 114–120 (10^{-3} mm.)[d]	81
$(CH_2)_3$		CH_3	 75–76 (12 mm.)	69–73 (94)
$(CH_2)_4$		CH_3	 86–87.5 (12 mm.)	82 (94)

[a] Determined by gas chromatography; products distilled through a spinning-band column were 94–99% pure.

[b] Yield of pure product, 52%.

[c] M. A. T. Rogers, *J. Chem. Soc.*, 3350 (1950).

[d] M.p. 44–45° (ex ethanol).

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

2-Methylmercapto-N-methyl-Δ^2-pyrroline

2-Methylmercapto-N-methyl-Δ^1-pyrrolinium iodide

2-Methylmercapto-N-methyl-Δ^2-pyrroline

2-chloro-N-methyl-Δ^1-pyrrolinium chloride

2-methylmercapto-N-methyl-Δ^1-pyrrolinium iodide

ethanol (64-17-5)

ether (60-29-7)

acetonitrile (75-05-8)

chloroform (67-66-3)

hydrogen sulfide (7783-06-4)

sodium sulfate (7757-82-6)

potassium iodide (7681-11-0)

potassium hydroxide (1310-58-3)

carbon disulfide (75-15-0)

xylene (106-42-3)

Methyl iodide (74-88-4)

methyl sulfate (75-93-4)

phosphorus pentasulfide

t-butyl alcohol (75-65-0)

PYRROLINE

2-Pyrroline, 1-methyl-2-methylthio- (25355-52-6)

N-Methyl-2-pyrrolidinone (872-50-4)

N-Methyl-2-pyrrolidinethione (10441-57-3)

4-thioacetylmorpholine

potassium t-butoxide (865-47-4)

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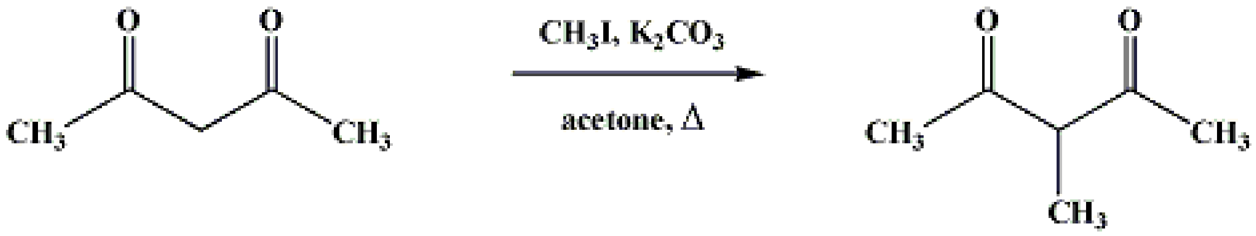
Organic Syntheses, *CV 5*, *785*

3-METHYLPENTANE-2,4-DIONE

[2,4-Pentanedione, 3-methyl-]



Submitted by A. W. Johnson, E. Markham, and R. Price[1].
Checked by Virgil Boekelheide and M. Kunstmann.

1. Procedure

A mixture of 65.2 g. (0.65 mole) of pentane-2,4-dione, 113 g. (0.80 mole) of methyl iodide, 84 g. of anhydrous potassium carbonate (Note 1), and 125 ml. of acetone is placed in a 500-ml. round-bottomed flask fitted with a reflux condenser and a calcium chloride guard tube. The mixture is heated under reflux for 20 hours and is then allowed to cool. The insoluble material is removed by filtration and washed with acetone (Note 2). The combined filtrate and acetone washings are concentrated on the steam bath (Note 3), and the residual oil is distilled. There is collected 56-57 g. (75-77%) of a colorless oil, b.p. 170–172°/760 mm.., n_D^{24} 1.4378 (Note 4).

2. Notes

1. The potassium carbonate is dried at 100° for 2 hours before use.
2. Thorough washing of the inorganic residues is essential and requires about 200 ml. of acetone.
3. During removal of the acetone, potassium iodide is deposited and it is advisable to decant the crude 3-methylpentane-2,4-dione from this material before distillation.
4. It has been reported by A. M. Roe and J. B. Harbride (private communication) that this procedure yields a product containing 20–25% of 3,3-dimethylpentane-2,4-dione as shown by gas chromatography. The amount of the dialkylation product is said to be reduced to 5–10% when the reflux period is shortened from 20 to 4.5 hours. The impurity is not readily removed, but it does not interfere with the preparation of 2,3,4,5-tetramethylpyrrole [this volume, p. 1022].
The same authors report that the work-up of the reaction may be improved by adding 250 ml. of petroleum ether (b.p. 40–60°) to the cold reaction mixture before filtering, and washing the solids with a 1:1 mixture of acetone and petroleum ether. With this change it is not necessary to decant the product from the precipitated potassium iodide as recommended in (Note 3).

3. Discussion

3-Methylpentane-2,4-dione has been prepared by the reaction of the sodium derivative of pentane-2,4-dione with methyl iodide in a sealed tube at 140°,[2] and from the sodium[3] and potassium[4] derivatives of pentane-2,4-dione and methyl iodide in alcoholic solution. It has also been prepared by the reaction of methyl iodide and pentane-2,4-dione in the presence of potassium carbonate in alcoholic or ethereal solution[5] and in acetone solution,[6,7] and by heating 2-aminopenten-4-one with methyl iodide at 100°.[8] The present modification affords improved yields.

4. Merits of Preparation

The method presented here has also been used for the preparation of 3-ethyl- and 3-isopropylpentane-2,4-diones and is probably of general applicability in the preparation of 3-alkylpentane-2,4-diones.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 1022

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

sodium derivative of pentane-2,4-dione

3-ethyl- and 3-isopropylpentane-2,4-diones

potassium carbonate (584-08-7)

potassium iodide (7681-11-0)

acetone (67-64-1)

sodium (13966-32-0)

potassium (7440-09-7)

Methyl iodide (74-88-4)

pentane-2,4-dione (123-54-6)

2,3,4,5-Tetramethylpyrrole (1003-90-3)

3-Methylpentane-2,4-dione, 2,4-Pentanedione, 3-methyl- (815-57-6)

3,3-dimethylpentane-2,4-dione (3142-58-3)

2-aminopenten-4-one

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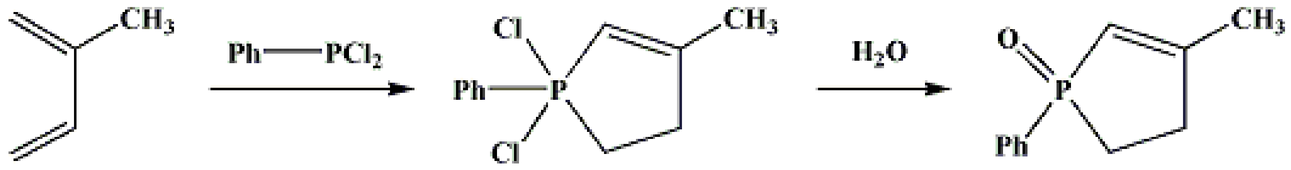
Organic Syntheses, *CV 5*, *787*

3-METHYL-1-PHENYLPHOSPHOLENE OXIDE

[Phospholene, 3-methyl-1-phenyl-, 1-oxide]



Submitted by W. B. McCormack[1]
Checked by S. N. Lewis and W. D. Emmons.

1. Procedure

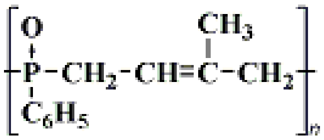
A. *3-Methyl-1-phenylphospholene 1,1-dichloride*. A dry 1-l. suction flask (Note 1) is charged with 179 g. (1.00 mole) of dichlorophenylphosphine (n_D^{28} 1.592; (Note 2)), 300 ml. (about 204 g., 3.0 moles) of commercial isoprene (Note 3), and 2.0 g. of Ionol® (Note 4). The flask is then stoppered, the side arm is sealed with tubing and a clamp, and the homogeneous solution is allowed to sit at room temperature in the back of a hood for 5–7 days. White solid is usually apparent within 2–4 hours, and after the reaction period the liquid phase is full of a white crystalline adduct, 1,1-dichloro-1-phenyl-3-methyl-1-phospha-3-cyclopentene The granular adduct is crushed, slurried with petroleum ether, collected on a sintered glass Büchner funnel, and washed with petroleum ether; exposure to moisture of the air is minimized by covering the funnel with a clock glass (Note 5).

B. *3-Methyl-1-phenylphosphacyclopentene 1-oxide*. The adduct is hydrolyzed by stirring it into 700 ml. of ice water, and stirring is continued until essentially all of it is in solution (Note 6). The total amount of acid in the solution is determined by titrating an aliquot, and the solution is nearly neutralized by slow addition of about 93% of the theoretical amount of 30% sodium hydroxide with good stirring and sufficient ice to keep the temperature below 25°. The solution generally contains about 1.62 equivalents of acid, which calls for 150 ml. (1.50 equivalents) of 30% sodium hydroxide. The pH is then adjusted to 6.5 with sodium bicarbonate solution (Note 7). After saturation of the aqueous solution with sodium chloride, the product is extracted with three 250-ml. portions of chloroform. The chloroform extracts are combined, dried briefly over calcium sulfate, filtered, and concentrated at atmospheric pressure until the temperature of the liquid in the distillation flask is 130°. The residual liquid is fractionated through a 30-cm. packed column. A water aspirator is used initially to strip small amounts of low boilers at 100° (Note 8), and then a mechanical pump is used. There is a fore-shot of a partially solidifying oil, weight 2-3 g., b.p. 163–168°/0.6–0.7 mm. Then 110–120 g. (57–63%) of 3-methyl-1-phenyl-1-phospha-3-cyclopentene 1-oxide, b.p. 173–174°/0.7 mm., is collected. It is a viscous liquid of a very pale yellow color that solidifies to a white solid, m.p. 60–65° (Note 9). A small amount of residue remains (Note 10).

2. Notes

1. A suction flask provides a strong-walled reactor that is conveniently stored for the reaction period.
2. Commercial material (currently from Stauffer Chemical Company, Special Chemicals Division) is suitable after distillation.

3. Shell Chemical material (92% minimum purity) was used. It was noted by the checkers that redistilled isoprene gave slightly better yields. The excess isoprene serves both as a solvent and for mass action. Moreover, dichlorophenylphosphine tends to dissolve in the product, and excess isoprene, by extracting the solid, promotes completion of reaction.
4. Ionol® is a commercial antioxidant, 2,6-di-*tert*-butyl-*p*-cresol, manufactured by Shell Chemical Corp. Inhibitors appear to minimize formation of polymeric side products, although with isoprene the effect is often small.
5. Sometimes, as with less pure reagents or on heating, a viscous oil, red to dark in color, will form instead of a white solid. At other times the solid is rather gummy. In these cases, mixing with petroleum ether as much as possible and decanting must suffice.
6. On occasion, gelatinous material is apparent; in time it usually dissolves or swells greatly.
7. The product is relatively sensitive to basic conditions, showing both polymerization and addition of water. Therefore alkaline conditions must be avoided. Neutralization serves to convert monophenylphosphinic acid (formed by hydrolysis of unreacted, unextracted dichlorophenylphosphine) to the monosodium salt, thereby preventing its subsequent extraction from water along with the phosphine oxide.
8. The crude mixtures all have strong odors of aromatic phosphines. Some of this odor presumably arises from disproportionation of monophenylphosphinic acid to phenylphosphine. It is recommended that manipulations be carried out with rubber gloves to prevent transfer of these rather durable odors to the skin, and that all equipment be washed with a bleach such as Clorox® before it is taken from the hood.
9. The distilled product can be used as a catalyst, although it usually has a relatively strong phenylphosphine odor. It is quite deliquescent, and it has not been satisfactorily recrystallized. If rigorous purification and deodorization are desired, the product is dissolved in water, a small amount of hydrogen peroxide is added to oxidize the phosphines, the solution is reneutralized, saturated with salt, and extracted with chloroform, and the product is refractionated. One cycle is normally enough. Pure product is essentially odorless, very hygroscopic, and soluble in polar solvents.
10. This residue is mostly the linear copolymer of nearly 1:1 composition. On occasion it can be present in substantial amounts, especially if higher temperatures are used to increase the reaction rate.



3. Discussion

3-Methyl-1-phenylphosphacyclopentene 1-oxide has been prepared only as described here.[2]

4. Merits of the Preparation

The reaction given here has been described before as a general reaction,[2] and there can be a wide variety of alkyl, aryl, and halo substituents on the diene and phosphorus. Dibromophosphines are appreciably more reactive than dichlorophosphines. If a free-radical catalyst is used instead of an inhibitor, the copolymers can be made in good yield.[3] The 1,4-addition of dichlorophosphines to 1,3-dienes is of theoretical interest because of its analogy to the well-known 1,4-addition of sulfur dioxide to 1,3-dienes.

The unsaturated cyclic phosphine oxides are active catalysts for the conversion of aryl isocyanates

to carbodiimides.[4] The polymeric material[3] and the saturated cyclic phosphine oxides[5] are also catalysts but are less active. The unsaturated cyclic phosphine oxides show properties analogous to those of the unsaturated cyclic sulfones from dienes and sulfur dioxide in that the double bond is quite reactive to basic reagents and relatively resistant to acidic reagents. Physically these cyclic phosphine oxides are stable to over 300°, are very powerful hydrogen bond acceptors, and are excellent solvents for polar materials.

The most recent review[6] summarizes the chemistry of these materials.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 501

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

Ionol

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

sulfur dioxide (7446-09-5)

PHOSPHORUS (7723-14-0)

calcium sulfate (7778-18-9)

hydrogen peroxide (7722-84-1)

phosphine (7723-14-0)

ISOPRENE (78-79-5)

dichlorophenylphosphine (644-97-3)

phosphine oxide

3-Methyl-1-phenylphospholene oxide, Phospholene, 3-methyl-1-phenyl-, 1-oxide, 3-Methyl-1-phenylphosphacyclopentene 1-oxide (707-61-9)

3-methyl-1-phenyl-1-phospha-3-cyclopentene 1-oxide

monophenylphosphinic acid (121-70-0)

phenylphosphine (638-21-1)

2,6-di-tert-butyl-p-cresol (128-37-0)

3-Methyl-1-phenylphospholene 1,1-dichloride (17154-12-0)

1,1-dichloro-1-phenyl-3-methyl-1-phospha-3-cyclopentene

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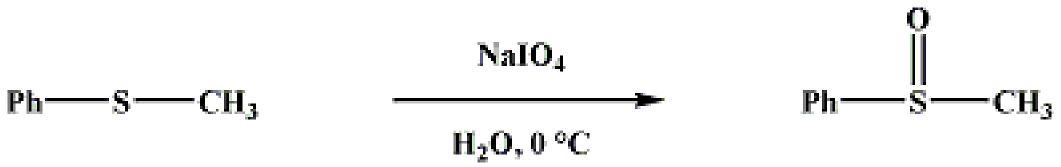
Organic Syntheses, CV 5, 791

METHYL PHENYL SULFOXIDE



Submitted by Carl R. Johnson and Jeffrey E. Keiser[1].
Checked by Wayland E. Noland, Leonard J. Czuba, and William E. Parham.

1. Procedure

In a 500-ml. round-bottomed flask equipped with a magnetic stirrer are placed 22.5 g. (0.105 mole) of powdered sodium metaperiodate and 210 ml. of water. The mixture is stirred and cooled in an ice bath (Note 1), and 12.4 g. (0.100 mole) of thioanisole (Note 2) is added. The reaction mixture is stirred for 15 hours at ice-bath temperature and is then filtered through a Büchner funnel. The filter cake of sodium iodate is washed with three 30-ml. portions of methylene chloride. The water-methylene chloride filtrate is transferred to a separatory funnel, the lower methylene chloride layer is removed, and the water layer is extracted with three 100-ml. portions of methylene chloride. The combined methylene chloride extracts are treated with activated carbon (Note 3) and dried over anhydrous sodium sulfate (Note 4). The solvent is removed at reduced pressure to yield 13.6–13.9 g. of a slightly yellow oil (Note 5) which crystallizes on cooling. The crude sulfoxide is transferred to a 25-ml. distillation flask with the aid of a small amount of methylene chloride. After removal of the solvent, a pinch of activated carbon is added to the distillation flask (Note 6). Simple vacuum distillation (Note 7) of the crude product through a short path still affords 12.7–12.8 g. (91%) of pure methyl phenyl sulfoxide, b.p. 78–79° (0.1 mm.), m. p. 33–34° (Note 8) and (Note 9).

2. Notes

1. The periodate oxidation of aryl sulfides to sulfoxides may be carried out at room temperature; however, an ice bath is necessary to prevent overoxidation of dialkyl sulfides.
2. Thioanisole (methyl phenyl sulfide) supplied by Aldrich Chemical Company, Milwaukee, Wisconsin, was used without further purification.
3. The checkers used 1 g. of activated carbon.
4. The checkers used 3–5 g. of sodium sulfate.
5. Gas-phase chromatography shows this crude material to be sulfide-free sulfoxide containing a small amount of methylene chloride.
6. The simple technique of adding a pinch of activated carbon to the distillation pot affords a more nearly colorless distillate.

7. No fore-run is observed other than a small amount of methylene chloride which does not condense. The pot is taken nearly to dryness.
8. Methyl phenyl sulfoxide is extremely hygroscopic. The melting point is best taken by rapid transfer of the easily supercooled oil to a melting-point capillary by means of a finely drawn pipet. The sealed capillary is then cooled to effect crystallization of the sulfoxide.
9. This procedure, with slight modifications depending on the physical properties of the sulfide and sulfoxide in question, has been used to prepare a variety of sulfoxides as illustrated by examples provided in Table I. In the case of very insoluble sulfides, co-solvents such as methanol or dioxane may be employed. Very soluble sulfoxides are best isolated by continuous extraction with chloroform or methylene chloride.

TABLE I PREPARATION OFSULFOXIDES

Products	Yields, %	M.P. [B.P.], °C.
Methyl 4-ketopentyl sulfoxide	98	22.5–23.5 [99–101 (0.12 mm.)]
Thian 1-oxide	99	67–68
1,4-Oxathian 1-oxide	83	46–47
Bis(2-diethylaminoethyl)sulfoxide	85	Dipicrate 146–148
Acetoxymethyl methyl sulfoxide	72	[85–90 (0.1 mm.)]
1-Benzylsulfinyl-2-propanone	89	126.0–126.5
Phenylsulfinylacetic acid	99	118.0–119.5
Benzyl sulfoxide	96	135–136
Ethyl sulfoxide	65	[45–47 (0.15 mm.)]
Ethyl phenyl sulfoxide	93	[101–102 (1.5 mm.)]

3. Discussion

Methyl phenyl sulfoxide has also been prepared from thioanisole by the action of hydrogen peroxide,[2,3] lead tetraacetate,[4] and dinitrogen tetroxide,[5,6] and from methanesulfinyl chloride and benzene with anhydrous aluminum chloride.[7]

4. Merits of the Preparation

The present procedure is a specific example of the method generalized by Leonard and Johnson.[8] The method employs extremely mild reaction conditions and affords high yields of sulfoxides (Note 9) free of contamination by sulfides or sulfones. Sodium periodate is easily and safely handled; however, the higher cost of this reagent in comparison to certain other oxidants, *e.g.*, hydrogen peroxide, may prohibit its use in large-scale reactions.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

dinitrogen tetroxide

Benzene (71-43-2)

methanol (67-56-1)

chloroform (67-66-3)

sodium sulfate (7757-82-6)

carbon (7782-42-5)

aluminum chloride (3495-54-3)

hydrogen peroxide (7722-84-1)

methylene chloride (75-09-2)

dioxane (5703-46-8)

Methanesulfinyl chloride (676-85-7)

Methyl phenyl sulfoxide (1193-82-4)

sodium metaperiodate, Sodium periodate (7790-28-5)

thioanisole, methyl phenyl sulfide (100-68-5)

water-methylene chloride

Methyl 4-ketopentyl sulfoxide

Thian 1-oxide

1,4-Oxathian 1-oxide

Bis(2-diethylaminoethyl)sulfoxide

Acetoxymethyl methyl sulfoxide

1-Benzylsulfinyl-2-propanone

Phenylsulfinylacetic acid

Benzyl sulfoxide (621-08-9)

Ethyl sulfoxide (70-29-1)

Ethyl phenyl sulfoxide (4170-80-3)

lead tetraacetate

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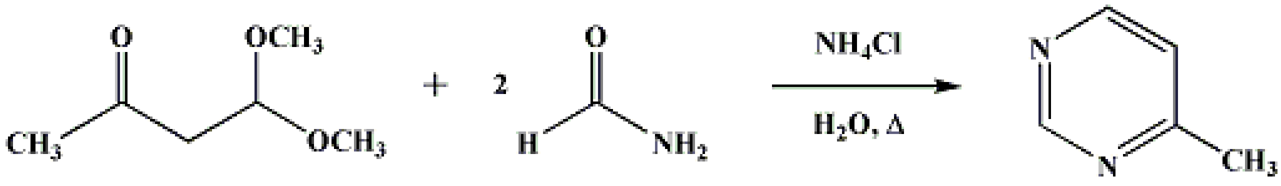
Organic Syntheses, CV 5, 794

4-METHYLPYRIMIDINE

[Pyrimidine, 4-methyl-]



Submitted by H. Bredereck[1]
Checked by Max Tishler, G. A. Stein, W. F. Jankowski, and J. ten Broeke.

1. Procedure

A 2-l. three-necked flask is equipped with a stirrer, a thermometer, an addition funnel, and a wide-bore reflux condenser (Note 1). A second condenser set downward for distillation is connected to the top of the reflux condenser by means of a head provided with a thermometer well. The thermometer well should be positioned in the connecting head in such a manner that the thermometer gives the temperature at the head of the reflux condenser. *Caution! The flask should be in a hood so that the carbon monoxide evolved cannot be a hazard.*

The three-necked flask is charged with 750 ml. of formamide, 25 ml. of water, and 50 g. of ammonium chloride (Note 2). The mixture is heated to 180–190° in an oil bath, and 400 g. (3.02 moles) of 4,4-dimethoxy-2-butanone (Note 3) is added dropwise with stirring over the course of 6 hours (Note 4). The flow of cooling water in the reflux condenser should be adjusted to a rate such that the methanol and methyl formate formed during the reaction distil out (Note 5). After all the acetal has been added, heating is continued for 1 hour (Note 6). The mixture is allowed to cool and is poured into 1 l. of 1*N* sodium hydroxide. The resultant solution is extracted with chloroform in a liquid-liquid extractor for 24 hours. The chloroform is separated, dried over sodium sulfate, and removed by distillation through a short column on a steam bath.

The residue is distilled under reduced pressure, and all the distillate boiling at 60–80°/15 mm. is collected (Note 7) and (Note 8). Pure 4-methylpyrimidine is obtained by redistillation through a short column at atmospheric pressure; b.p. 140–142°; n_D^{25} 1.4936; weight 153–180 g. (54–63%).

2. Notes

1. A wide-bore condenser is employed to prevent clogging of the tube by ammonium salts that may sublime from the reaction mixture (Note 5). A Liebig condenser is most suitable because it can be cleaned from the top with a rod or wire during the reaction.
2. An acidic salt must be present so that the acetal bonds will be hydrolyzed. Other salts, such as ammonium formate, may be substituted for ammonium chloride.
3. 4,4-Dimethoxy-2-butanone from Chemische Werke Huls, Huls, Germany, was used by the submitter. The checkers used 4,4-dimethoxy-2-butanone (practical grade) from Eastman Organic Chemicals Co., Rochester, New York; it was 95% pure by vapor-phase

chromatography.
4. The checkers found that, during the course of the addition, the internal temperature fell from 190° to 140°.
5. The checkers found that, if the temperature at the head of the reflux condenser is kept at 50–55°, no ammonium salts collect in the condenser and, therefore, there is no problem of clogging.
6. The checkers found that the temperature of the reaction mixture remains at 140° during the additional hour of heating.
7. It is advisable to carry out a vacuum distillation prior to the final distillation because the tarry residues obtained by distillation at atmospheric pressure retain a considerable amount of product.
8. The checkers collected their product at 50–70°/30 mm.

3. Discussion

4-Methylpyrimidine has been obtained by the present method[2] and by a three-step method that begins with the condensation of acetoacetic ester with urea to give 2,6-dihydroxy-4-methylpyrimidine; the latter is treated with phosphorus oxychloride to give 2,6-dichloro-4-methylpyrimidine, which is reduced by zinc dust and water[3] or by catalytic hydrogenolysis.[4]

4. Merits of the Preparation

The present one-step procedure for making 4-methylpyrimidine is simpler and easier than the three-step method used in the past. The present procedure and modifications of it have been used to make a variety of 4- and 4,6-substituted pyrimidines.[2,5]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

methanol (67-56-1)

ammonium chloride (12125-02-9)

formamide (75-12-7)

sodium hydroxide (1310-73-2)

carbon monoxide (630-08-0)

chloroform (67-66-3)

sodium sulfate (7757-82-6)

Phosphorus Oxychloride (21295-50-1)

zinc (7440-66-6)

urea (57-13-6)

methyl formate (107-31-3)

ammonium formate (540-69-2)

4,4-dimethoxy-2-butanone (5436-21-5)

2,6-dichloro-4-methylpyrimidine (5424-21-5)

4-Methylpyrimidine, Pyrimidine, 4-methyl- (3438-46-8)

2,6-dihydroxy-4-methylpyrimidine

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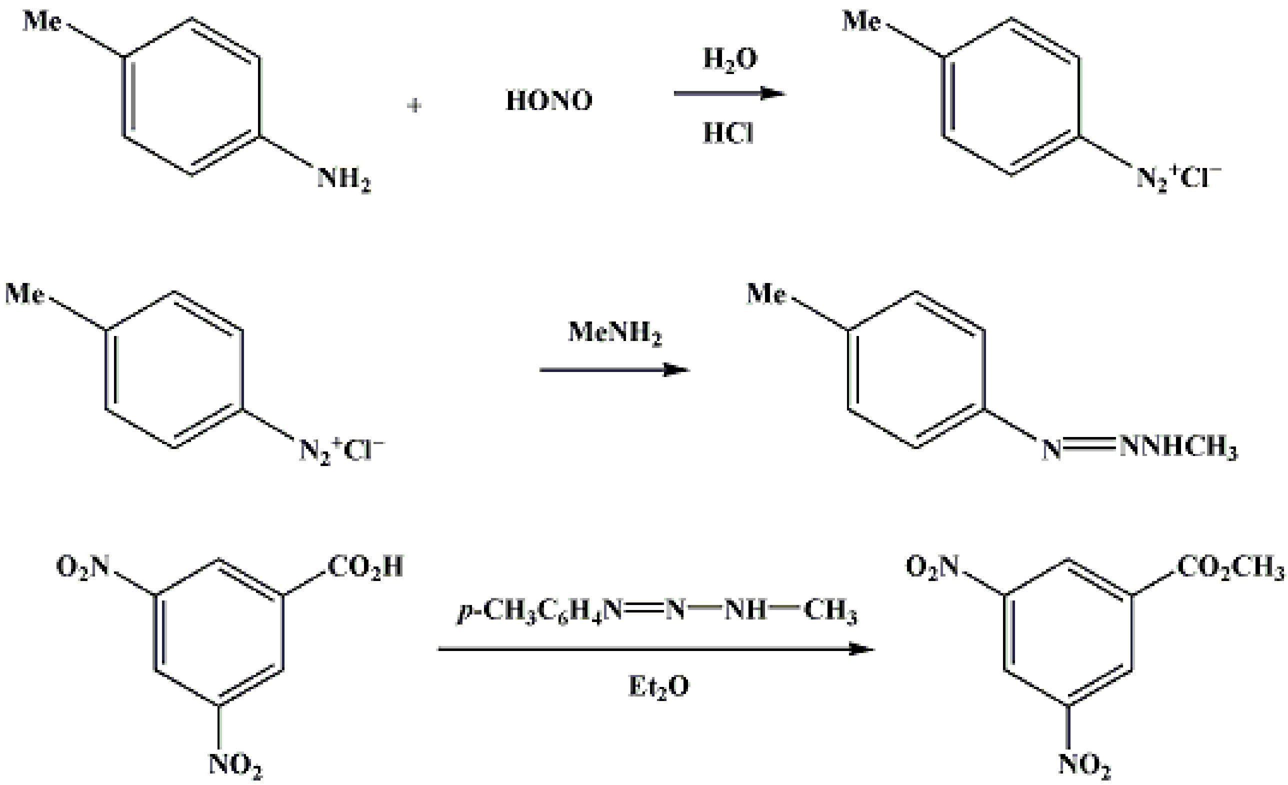
Organic Syntheses, CV 5, 797

1-METHYL-3-*p*-TOLYLTRIAZENE AND ITS USE IN THE ESTERIFICATION OF ACIDS

[Triazene, 1-methyl-3-*p*-tolyl-]



Submitted by E. H. White, A. A. Baum, and D. E. Eitel[1].
Checked by I. Katz and R. Breslow.

1. Procedure

A. *1-Methyl-3-p-tolyltriazene*. *p*-Toluidine (50.2 g., 0.47 mole) is added to a 2-l. flask equipped with a 200-ml. dropping funnel and an efficient stirrer, and the flask is immersed in an ice-salt bath at *ca.* −10°. A solution of 46.8 g. (0.55 mole) of potassium nitrite in 150 ml. of water is placed in the dropping funnel, and a mixture of 250 g. of crushed ice and 140 ml. of concentrated hydrochloric acid is added to the *p*-toluidine with stirring. The potassium nitrite solution is slowly added with continued stirring during 1–2 hours until a positive starch-potassium iodide test is obtained (Note 1), and the mixture is stirred for an additional hour to ensure the reaction of all the toluidine.

The solution of *p*-toluenediazonium chloride is then brought to pH 6.8–7.2 at 0° with cold, concentrated, aqueous sodium carbonate, whereupon the solution becomes red to orange in color and a small amount of red material settles out. The cold, neutral solution is transferred to a dropping funnel and added slowly to a vigorously stirred mixture of 150 g. of sodium carbonate, 300 ml. of 30–35% aqueous methylamine (Note 2), and 100 g. of crushed ice in a 3-l. flask. The reaction mixture is kept at *ca.* −10° during the addition, which requires about 45 minutes (Note 3). The solution is extracted with three 1-l. portions of ether. The ethereal extracts are dried with anhydrous sodium sulfate and evaporated on a rotary evaporator at room temperature to give 65 g. of crude 1-

methy1-3-*p*-tolyltriazene (Note 4). This is placed in a water-cooled sublimer, and the triazene is sublimed at 50° (1 mm.) *(Caution! See (Note 5))*; 43.3 g. (0.29 mole, 62%) of a yellow, crystalline sublimate, m.p. 77–80°, is obtained (Note 6). The sublimate can be recrystallized from hexane to give the triazene as white needles, m.p. 80.5–81.5°. More conveniently, it is dissolved in the minimum amount of ether, and the solution is diluted with 2 volumes of hexane and cooled to 0° to give flat plates with a slightly yellow cast; m.p. 79–81°. The yield of pure triazene is 33–37 g. (47–53%) (Note 7).

B. *Esterification of 3,5-dinitrobenzoic acid with 1-methyl-3-p-tolyltriazene* (Note 8). A solution of 1-methyl-3-*p*-tolyltriazene (1.05 g., 7.0 mmoles) in 10 ml. of ether is placed in a 100-ml. flask equipped with a 100-ml. dropping funnel (Note 9). A solution of 1.50 g. (7.1 mmoles) of 3,5-dinitrobenzoic acid in 25 ml. of ether is placed in the dropping funnel and is slowly added to the triazene solution; the contents of the flask are gently swirled from time to time. During the addition, nitrogen is evolved, and the solution becomes red in color. After the nitrogen evolution has ceased (*ca.* 1 hour), the ethereal solution is transferred to a separatory funnel and washed with 5*N* hydrochloric acid to remove toluidine (Note 10). It is then washed with 5% aqueous sodium carbonate and dried over anhydrous sodium sulfate. Evaporation of the ether yields methyl 3,5-dinitrobenzoate (1.11–1.42 g., 70–90%) as light tan crystals, m.p. 106–107.5° (Note 11). Recrystallization from ether yields small, flat plates, m.p. 107–107.5°.

2. Notes

1. The individual tests with starch-potassium iodide paper should be made 1–2 minutes after the addition of potassium nitrite has been stopped.
2. The checkers used 40% aqueous methylamine supplied by Matheson, Coleman and Bell.
3. The reaction is over when a drop of solution no longer gives a red color with a solution of β-naphthol in aqueous sodium carbonate.
4. The chief impurity is 1,5-di-*p*-tolyl-3-methyl-1,4-pentazadiene (m.p. 148°). This can be removed by fractional crystallization, but it is easier to sublime the triazene from the reaction mixture.
5. Care should be exercised during the sublimation, which should be conducted behind an appropriate shield. During the sublimation of an analog of 1-methyl-3-*p*-tolyltriazene, 1-benzyl-3-*p*-tolyltriazene, a violent explosion has occurred. In order to achieve effective sublimation, a temperature of 90–100° was required, and this elevated temperature may have been a factor in causing the explosion (private communication from D. W. Hutchinson).
6. The sublimate contains a trace of 1,3-di-*p*-tolyltriazene, as shown by thin-layer chromatography. Recrystallization yields the pure 1-methyl-3-*p*-tolyltriazene.
7. This procedure works well only with water-soluble amines. A procedure has been given elsewhere for the preparation of triazenes of water-insoluble amines.[2]
8. The ethyl, propyl, butyl, and other esters may be prepared similarly from the corresponding triazenes.
9. Many solvents may be used for this reaction; the reaction rate, however, is greater in nonpolar solvents. Less color develops in the reaction mixture if the system is flushed with nitrogen at this point.
10. The triazenes of secondary carbinamines also yield some N-alkyltoluidine.[3] Colored impurities normally enter the aqueous phase at this point in the work-up.
11. The infrared spectrum of this material is essentially identical with that of the pure, recrystallized ester.

3. Discussion

1-Methyl-3-*p*-tolyltriazene has been prepared by the reaction of methylmagnesium bromide with *p*-tolyl azide,[4], and, in unspecified yield, by the addition of methylamine to *p*-toluenediazonium chloride.[5]

4. Merits of the Preparation

This procedure represents the most convenient synthesis of 1-methyl-3-*p*-tolyltriazene. Triazenes with more complex alkyl groups may be prepared from the corresponding amine[2] or Grignard reagent.[4]

The alkylation of acids with triazenes is superior to alkylation with diazomethane and other diazoalkanes in that the triazenes are crystalline, stable materials which are easy to prepare and store. Alkylations with triazenes are unlikely to be accompanied by side reactions, such as addition to strained or conjugated double bonds, which are frequently observed in alkylations with diazoalkanes.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ester

1-methy1-3-p-tolyltriazene

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

β-naphthol (135-19-3)

methylamine (74-89-5)

potassium nitrite (7758-09-0)

Diazomethane (334-88-3)

methylmagnesium bromide (75-16-1)

3,5-Dinitrobenzoic acid (99-34-3)

toluidine, p-toluidine (106-49-0)

hexane (110-54-3)

triazene

1-Methyl-3-p-tolyltriazene, Triazene, 1-methyl-3-p-tolyl- (21124-13-0)

Methyl 3,5-dinitrobenzoate (2702-58-1)

p-toluenediazonium chloride

1,5-di-p-tolyl-3-methyl-1,4-pentazadiene (41798-81-6)

1-benzyl-3-p-tolyltriazene

1,3-di-p-tolyltriazene

p-tolyl azide (2101-86-2)

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Organic Syntheses, CV 5, 801

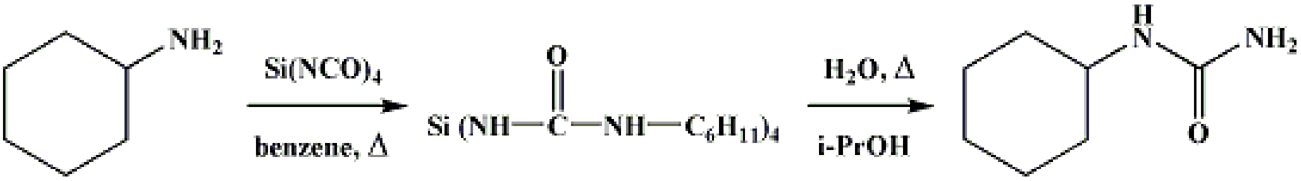
N-MONO- AND N,N-DISUBSTITUTED UREAS AND THIOUREAS

Submitted by Roy G. Neville[1] and John J. McGee[2].
Checked by William E. Parham and J. Kent Rinehart.

1. Procedure

METHOD I
CYCLOHEXYLUREA

[Urea, cyclohexyl-]

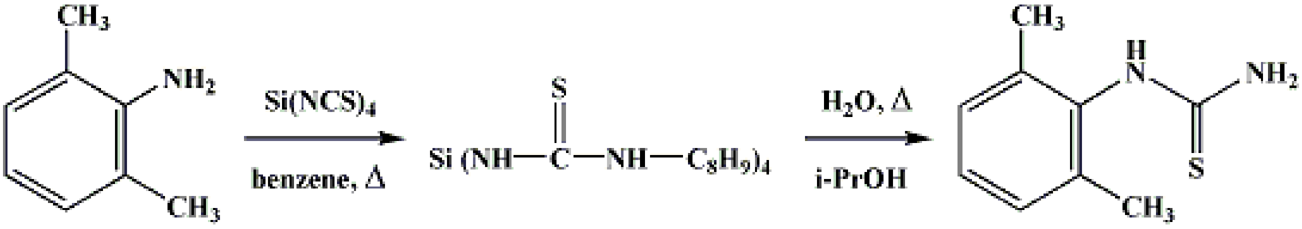


A solution of cyclohexylamine (39.7 g., 0.4 mole) (Note 1) in 100 ml. of anhydrous benzene (Note 2) is added slowly to a stirred solution (Note 3) of silicon tetraisocyanate (19.6 g., 0.1 mole) (Note 4) in 150 ml. of anhydrous benzene contained in a 1-l. round-bottomed flask. After the exothermic reaction has subsided, the mixture is heated at the reflux temperature for 30 minutes; the benzene is then removed using a rotary evaporator. Dilute isopropyl alcohol (200 ml.) (Note 5) is added to the residue, and the resulting mixture is heated at the reflux temperature for 30 minutes. The hot mixture is filtered through a 0.5-in. layer of Celite® contained in a coarse-grade sintered-glass funnel (Note 6). The gelationous silica is washed with two 75-ml. portions of acetone and is then pressed and drained. The combined filtrates are evaporated to dryness on a steam bath (Note 7). The crude cyclohexylurea (m.p. 185–191°, 55.0 g., 97% yield) is recrystallized from 220 ml. of isopropyl alcohol (Note 8) to give 37 g. (65%) of product, m.p. 192–193°. Concentration of the mother liquor affords about 9 g. (16%) of additional product which is less pure (m.p. 189–192°) (Note 9).

1. Procedure

METHOD II
2,6-DIMETHYLPHENYLTHIOUREA

[Urea, 1-(2,6-dimethylphenyl)-2-thio-]



Silicon tetraisothiocyanate (26.0 g., 0.10 mole) (Note 10) is finely ground under 100 ml. of anhydrous benzene, and the mixture is quickly transferred to a 1-l. round-bottomed flask. The mortar and pestle are washed with two 25-ml. portions of anhydrous benzene, and the washings are added

to the flask. A solution of 2,6-dimethylaniline (48.5 g., 0.4 mole) (Note 1) in 100 ml. of anhydrous benzene is added to the well-stirred mixture. The reaction is mildly exothermic. The mixture is heated at the reflux temperature for 30 minutes, and the benzene is then removed using a rotary evaporator. Dilute isopropyl alcohol (200 ml.) (Note 5) is added to the residue, and the resulting mixture is heated at the reflux temperature for 30 minutes. The mixture is then processed in exactly the same manner as described above for the preparation of cyclohexylurea. The crude 2,6-dimethylphenylthiourea (m.p. 193–197°, 71.3 g., 99% yield) is recrystallized from 280 ml. of isopropyl alcohol (Note 8) to give 50 g. (72%) of product, m.p. 201–202°. Concentration of the mother liquor affords 11 g.. (15%) of less pure product, m.p. 197–199° (Note 11).

2. Notes

1. Cyclohexylamine and 2,6-dimethylaniline were obtained from Eastman Organic Chemicals and were redistilled prior to use.
2. Benzene was dried over sodium wire.
3. The mixture becomes viscous; however, a good magnetic stirrer is adequate. The checkers found it convenient to decrease the viscosity of the mixture by increasing the volume of benzene from 100 ml. to 150–300 ml.
4. Silicon tetraisocyanate is prepared from silicon tetrachloride and silver cyanate or lead cyanate.[3,4]
5. Dilute isopropyl alcohol is prepared by mixing the alcohol (180 ml.) with water (20 ml.). The use of more than about 10% water in the alcohol results in an intractable mass of gelatinous silica from which it is very difficult to separate a good yield of the urea.
6. As gelatinous silica clogs the filter when too strong a suction is applied, it is best to carry out the filtration using very gentle suction. Only when almost all the liquid has passed through the filter is strong suction applied. The checkers used Hyflo Supercel® as the filter aid, and a 600-ml. coarse-grade sintered-glass funnel.
7. An open dish or a rotary evaporator is satisfactory.
8. Isopropyl alcohol is a good solvent to employ for recrystallizing most ureas; however, occasionally a mixture of alcohol and benzene or pure benzene is superior.
9. This material is of sufficient purity for most purposes. If a purer product is required, the first crop of the cyclohexylurea (37 g.) is recrystallized from 135 ml. of isopropyl alcohol to yield 23 g. of product, m.p. 195.5–196.0°
10. Silicon tetraisothiocyanate is prepared from silicon tetrachloride and silver thiocyanate[5,6] or, preferably, ammonium thiocyanate.[6,7] The silicon tetraisothiocyanate used by the checkers was slightly yellow; however, this did not affect the yield of product.
11. This material is of sufficient purity for most purposes. If purer material is required, the first crop of 2,6-dimethylphenylthiourea (50 g.) is recrystallized from 250 ml. of isopropyl alcohol to yield 41 g. of product, m.p. 203.5–204.0°.

3. Discussion

Cyclohexylurea has been prepared by the reaction of cyclohexyl isocyanate with gaseous ammonia[8] or ammonium hydroxide,[9] by thermal decomposition of cyclohexyl allophanamide,[10] by treating cyclohexylamine hydrochloride with an aqueous solution of potassium cyanate,[11] by heating nitrosomethylurea with cyclohexylamine,[12] and by heating an ethanolic solution of cyclohexylamine and 3,5-dimethyl-1-carbamylpyrazole.[13]

2,6-Dimethylphenylthiourea has been synthesized by allowing 2,6-dimethylaniline hydrochloride to react with ammonium thiocyanate.[14]

4. Merits of the Preparation

These procedures are generally applicable to aliphatic, alicyclic, aralkyl, aromatic, and heterocyclic primary or secondary amines. The reactions fail or give poor yields with sterically hindered amines such as 2-trifluoromethylaniline, 2,6-dibromoaniline, and diphenylamine. In general, however, excellent (95–100%) yields of N-mono- or N,N-disubstituted ureas or thioureas can be obtained by employing these versatile reactions which are, in most cases, superior to and supplement the methods conventionally employed for the synthesis of ureas and thioureas.[15] Because of the rapidity, ease, and excellent yields of these reactions, silicon tetraisocyanate and tetraisothiocyanate (both of which are readily prepared[4,6]) are likely to become standard reagents for the preparation of N-mono- and N,N-disubstituted ureas and thioureas. The submitters have employed these reagents to prepare large-scale (O.4*M*) amounts of the following compounds (yields in parentheses): benzylurea, m.p. 148° (96%);[16] phenylurea, m.p. 147° (95%);[17] *t*-butylurea, m.p. 182° (95%);[18] N-(2-benzothiazolyl) urea, m.p. >350° (95%);[19,20] dibenzylthiourea, m.p. 140° (95%);[21] *t*-butylthiourea, m.p. 168° (98%).[22] In addition, the scope and limitation of the reactions of silicon tetraisocyanate and tetraisothiocyanate have been investigated with more than fifty alkyl, aralkyl, aromatic, and heterocyclic primary and secondary amines.[23,24]

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Appendix

Compounds Referenced (Chemical Abstracts Registry Number)

N-MONO- AND N,N-DISUBSTITUTED UREAS AND THIOUREAS

silicon tetraisocyanate and tetraisothiocyanate

ammonia (7664-41-7)

Benzene (71-43-2)

ammonium thiocyanate (1762-95-4)

acetone (67-64-1)

sodium (13966-32-0)

isopropyl alcohol (67-63-0)

ammonium hydroxide (1336-21-6)

Phenylurea (64-10-8)

potassium cyanate (590-28-3)

diphenylamine (122-39-4)

Nitrosomethylurea

cyclohexylamine (108-91-8)

2,6-Dibromoaniline (608-30-0)

silver cyanate (3315-16-0)

Cyclohexylurea, Urea, cyclohexyl- (698-90-8)

silicon tetraisocyanate (3410-77-3)

Urea, 1-(2,6-dimethylphenyl)-2-thio-, 2,6-Dimethylphenylthiourea (6396-76-5)

Silicon tetraisothiocyanate (6544-02-1)

2,6-dimethylaniline (87-62-7)

silicon tetrachloride (10026-04-7)

silver thiocyanate (1701-93-5)

cyclohexyl isocyanate (3173-53-3)

cyclohexyl allophanamide

cyclohexylamine hydrochloride (4998-76-9)

3,5-dimethyl-1-carbamylpyrazole (934-48-5)

2,6-dimethylaniline hydrochloride (21436-98-6)

2-trifluoromethylaniline (88-17-5)

benzylurea (538-32-9)

N-(2-benzothiazolyl)urea

dibenzylthiourea

t-butylurea (1118-12-3)

t-butylthiourea (7204-48-0)

lead cyanate

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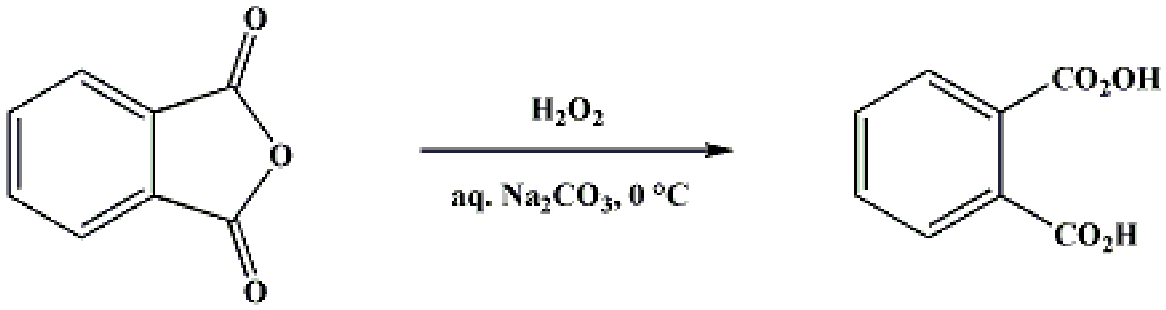
Organic Syntheses, CV 5, 805

MONOPERPHTHALIC ACID

[Phthalic monoperoxy acid]



Submitted by George B. Payne[1]
Checked by K. Nagarajan and John D. Roberts.

1. Procedure

In a 1-l. round-bottomed flask equipped with a mechanical stirrer and cooled in an ice-salt bath is placed a solution of 62 g. (0.5 mole) of sodium carbonate monohydrate in 250 ml. of water. This is cooled to 0°, and 69 g. (63 ml., 0.6 mole) of 30% hydrogen peroxide (Note 1) is added in one portion. With the temperature at –5 to 0°, 74 g. (0.5 mole) of phthalic anhydride (Note 1) which has been pulverized to pass a 14-mesh sieve is added (Note 2).

The reaction mixture is stirred vigorously at –5 to 0° for 30 minutes, then the resulting solution or suspension (Note 3) is poured into a 2-l. separatory funnel, shaken with 350 ml. of ether (Note 4), and carefully acidified with an ice-cold solution of 30 ml. of concentrated sulfuric acid in 150 ml. of water. The liberated monoperphthalic acid is extracted into the ether and removed completely from the water by extraction with two more 150-ml. portions of ether. The combined ether extracts are washed with two 200-ml. portions of 40% ammonium sulfate solution and dried overnight in a refrigerator over 50 g. of anhydrous magnesium sulfate.

The peracid content is determined by adding 30 ml. of 20% potassium iodide solution to 2 ml. of the peracid solution and, after 10 minutes, titrating the liberated iodine with 0.1 *N* thiosulfate. The yield is 71–78 g. (78–86% based on phthalic anhydride).

If crystalline monoperphthalic acid is desired, it may be prepared as described earlier.[2]

2. Notes

1. Commercial phthalic anhydride and hydrogen peroxide, both of reagent grade, are used.

2. Fieser and Fieser[3] recommend that the phthalic acid be recrystallized from benzene rather than pulverized.
3. The sodium salt of monoperphthalic acid may precipitate during the reaction.
4. The ether may be used, along with a *small amount* of cold water, to effect a quantitative transfer of the suspension from reaction vessel to separatory funnel.

3. Discussion

Monoperphthalic acid has been prepared by hydrolysis of phthalyl peroxide with sodium hydroxide,[4] by reaction of phthalic anhydride with excess alkaline peroxide solution,[5] by reaction of phthalic anhydride with hydrogen peroxide,[6] and by stirring phthalic anhydride with mildly alkaline peroxide.[7] The method described here is a slight modification of the last procedure.

The methods of preparation, properties, analysis, and safe handling of monoperphthalic acid have been reviewed.[8]

4. Merits of Preparation

The Böhme procedure[2,5] for preparing perphthalic acid from phthalic anhydride and hydrogen peroxide is sensitive to slight variations in the experimental conditions.[6,7] The present method gives reproducible yields with quite short reaction times.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Monoperphthalic acid

Phthalic monoperoxy acid

sodium salt of monoperphthalic acid

sulfuric acid (7664-93-9)

Benzene (71-43-2)

ether (60-29-7)

sodium hydroxide (1310-73-2)

potassium iodide (7681-11-0)

phthalic anhydride (85-44-9)

iodine (7553-56-2)

hydrogen peroxide (7722-84-1)

ammonium sulfate (7783-20-2)

phthalic acid (88-99-3)

magnesium sulfate (7487-88-9)

phthalyl peroxide

sodium carbonate monohydrate (5968-11-6)

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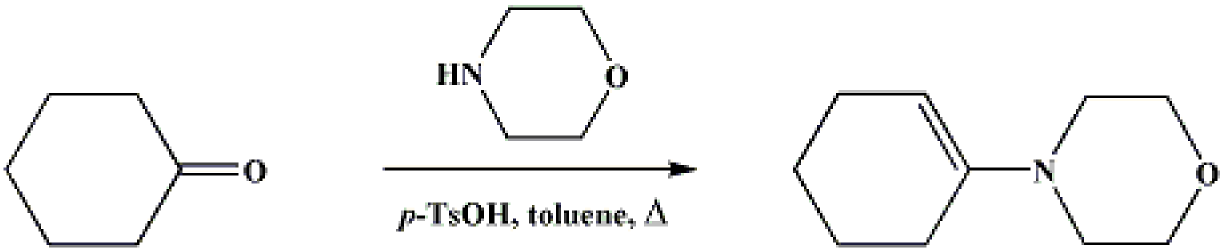
1-MORPHOLINO-1-CYCLOHEXENE

[Morpholine, 4-(1-cyclohexenyl)-]



Submitted by S. Hünig, E. Lücke, and W. Brenninger[1].
Checked by B. C. McKusick and F. E. Mumford.

1. Procedure

A solution of 147 g. (1.50 moles) of cyclohexanone, 157 g. (1.80 moles) of morpholine (Note 1), and 1.5 g. of *p*-toluenesulfonic acid in 300 ml. of toluene is heated to boiling in a 1-l. round-bottomed flask to which is attached a water separator[2] under a reflux condenser. The separation of water begins at once and ceases after 4 or 5 hours. An indented Claisen stillhead is attached to the flask, and the reaction mixture is distilled. Most of the toluene is removed at atmospheric pressure. 1-Morpholino-1-cyclohexene is collected as a colorless liquid at 118–120°/10 mm.; n_D^{25} 1.5122–1.5129 (Note 2). It weighs 180–200 g. (72–80%).

2. Notes

1. An excess of morpholine is required because the water that separates during the reaction always contains a considerable amount of it in solution.
2. 1-Morpholino-1-cyclohexene is very easily hydrolyzed. Accordingly one must be careful to keep moisture out. On long standing in a refrigerator, the compound generally becomes somewhat yellowish, but this does not affect its usefulness in subsequent reactions.

3. Discussion

The procedure is that of Hünig, Benzing and Lücke.[3] It is based on earlier work on the preparation of enamines.[4,5]

4. Merits of Preparation

This is a general method of preparing enamines from a secondary aliphatic amine and cyclohexanone or cyclopentanone. Acylation of such enamines is the first step in a general procedure for increasing the chain length of a carboxylic acid by 5 or 6 carbon

atoms and of a dicarboxylic acid by 10 or 12 carbon atoms.[6] Alkylation of enamines of cyclohexanones by alkyl halides[5,7] or electrophilic olefins,[8] followed by hydrolysis, is a good route to α-monoalkylcyclohexanones. The chemistry of enamines has been reviewed.[9]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 533
- Org. Syn. Coll. Vol. 5, 869

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Cyclohexanone (108-94-1)

carbon (7782-42-5)

toluene (108-88-3)

Cyclopentanone (120-92-3)

morpholine (110-91-8)

1-Morpholino-1-cyclohexene, Morpholine, 4-(1-cyclohexenyl)- (670-80-4)

p-toluenesulfonic acid (104-15-4)

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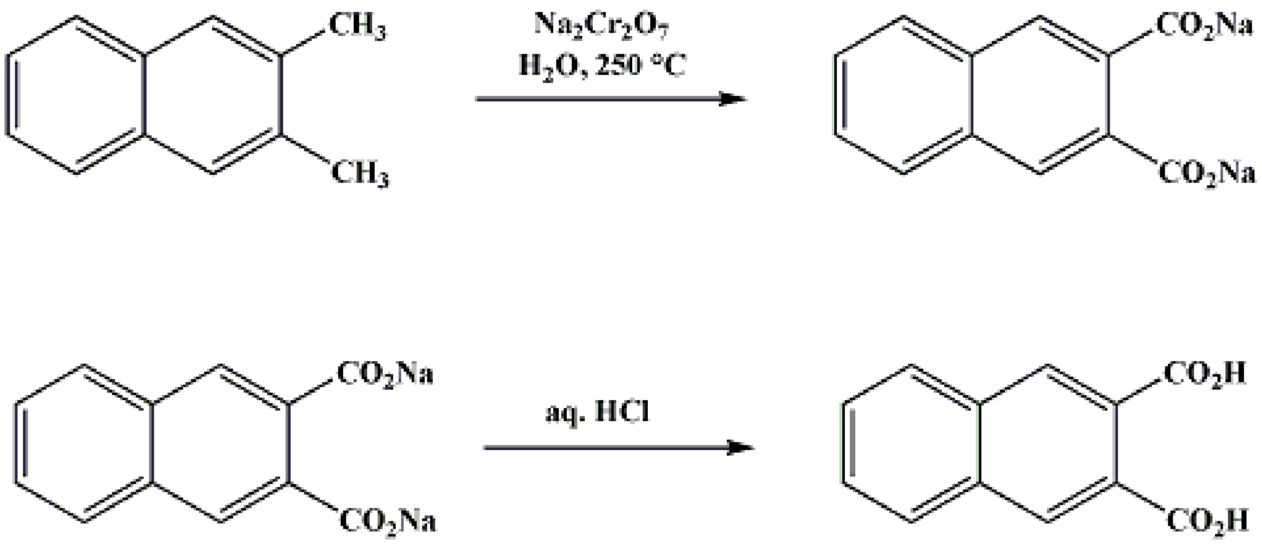
2,3-NAPHTHALENEDICARBOXYLIC ACID



Submitted by Lester Friedman[1]
Checked by G. A. Boswell and B. C. McKusick.

1. Procedure

An autoclave (Note 1) is charged with 200 g. (1.28 moles) of 2,3-dimethylnaphthalene (Note 2), 940 g. (3.14 moles, 23% excess) of sodium dichromate dihydrate, and 1.8 l. of water. The autoclave is closed, heated to 250°, and shaken continuously at this temperature for 18 hours. The autoclave is cooled with continued agitation (Note 3), the pressure is released, and the autoclave is opened. The contents are transferred to a large vessel (Note 4). To effect complete transfer, the autoclave is rinsed with several 500-ml. portions of hot water. Green hydrated chromium oxide in the reaction mixture is separated on a large Büchner funnel and washed with warm water until the filtrate is colorless. The combined filtrates (7–8 l.) are acidified with 1.3 l. of 6*N* hydrochloric acid. The acidified mixture is allowed to cool to room temperature overnight. The 2,3-naphthalenedicarboxylic acid that has precipitated is collected on a large Büchner funnel, washed with water until the filtrate is colorless, and dried to constant weight in a vacuum oven at 50°/20 mm. or by long standing in air. The 2,3-naphthalenedicarboxylic acid is a white powder; m.p. 239–241°; weight 240–256 g. (87–93%).

2. Notes

1. An autoclave fitted for stirring or shaking is essential for good yields. The submitter used a hydrogenation autoclave of the type supplied by the American Instrument Company, catalog No. 406-21, having a capacity of 3.2 l. The autoclave is shaken by means of a "Bomb Shaker" in which it is placed. If a stirred autoclave or "Magne-Dash" is used, the reaction time can be shortened to 3–5 hours. At 250° the gauge pressure is about 600 lb./in.^{2}. The checkers' yield was 92% in a shaker tube, but only 75% in a rocker tube; the latter yield was raised to

82% by extending the reaction time to 40 hours.
This oxidation does not poison the autoclave for subsequent hydrogenations.
2. Material produced by Ruetgerswerke A. G. is satisfactory. This can be obtained in the United States from Terra Chemicals Inc., New York, New York; Aldrich Chemical Co., Milwaukee 10, Wisconsin; and K and K Laboratories Inc., Jamaica 33, New York.
3. It is convenient to empty the autoclave while the contents are still warm.
4. Commercially available 10-quart polyethylene pails are very satisfactory.

3. Discussion

2,3-Naphthalenedicarboxylic acid has been prepared by the present method[2] and by hydrolysis of 3-cyano-2-naphthoic acid, which is obtainable from 3-amino-2-naphthoic acid by the Sandmeyer reaction.[3]

4. Merits of the Preparation

This procedure illustrates a general method for the preparation of aromatic carboxylic acids by oxidation of the corresponding alkylarenes.[2] For example, 2-naphthoic acid (360 g., 93% yield; m.p. 184–185°) was obtained from 2-methylnaphthalene (320 g., 2.25 moles), sodium dichromate (975 g., 3.26 moles, 45% excess), and water (1.8 l.).

2,3-Naphthalenedicarboxylic acid is useful in the synthesis of linear polyacenes,[3] 3-halo-2-naphthoic acids,[4] and 3-amino-2-naphthoic acid.[4]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

sodium dichromate (7789-12-0)

2-Naphthoic acid (93-09-4)

2-methylnaphthalene (91-57-6)

sodium dichromate dihydrate (10588-01-9)

3-Amino-2-naphthoic acid (5959-52-4)

chromium oxide (1308-38-9)

2,3-Naphthalenedicarboxylic acid (2169-87-1)

2,3-dimethylnaphthalene (581-40-8)

3-cyano-2-naphthoic acid

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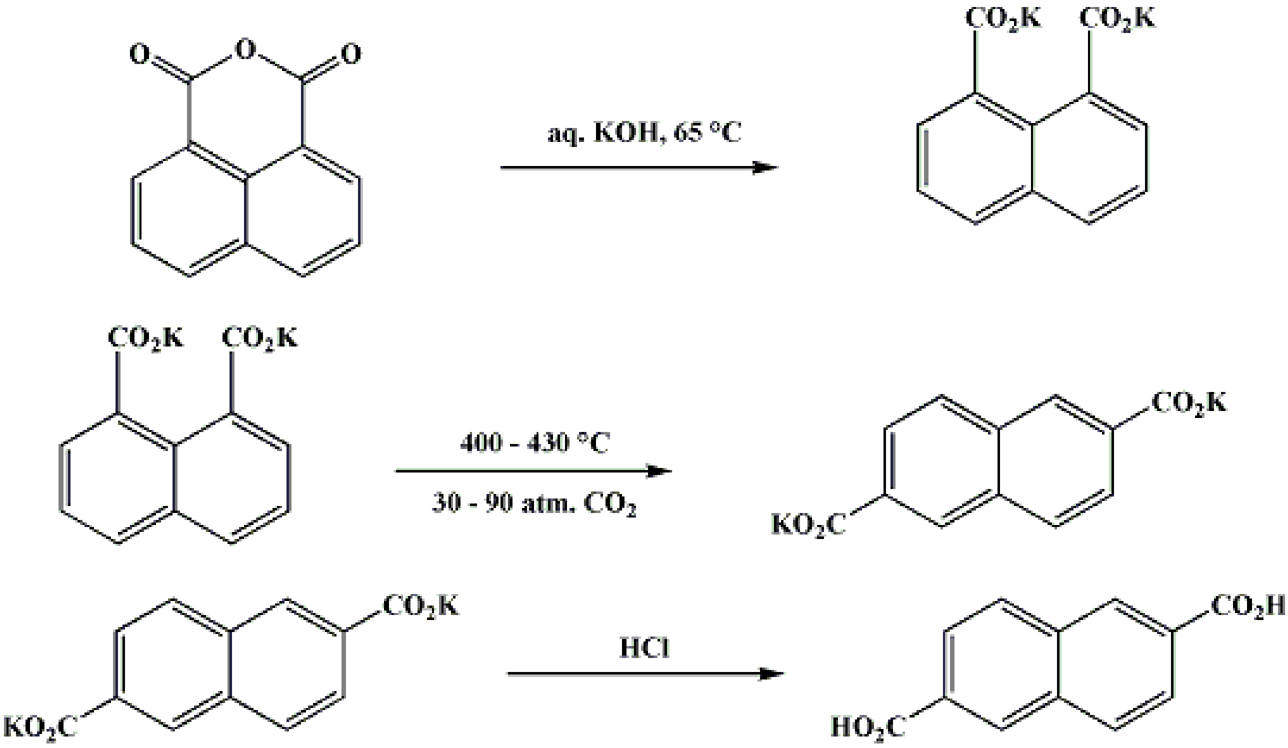
Organic Syntheses, CV 5, 813

2,6-NAPHTHALENEDICARBOXYLIC ACID



Submitted by Bernhard Raecke and Hubert Schirp[1].
Checked by B. C. McKusick and P. E. Aldrich.

1. Procedure

A solution of 66.5 g. (1.01 moles) of 85% potassium hydroxide in 300 ml. of water in an 800-ml. beaker is heated to 60–70°, and 100 g. (0.505 mole) of commercial 1,8-naphthalic anhydride (Note 1) is stirred in. The pH of the resultant deep-brown solution is adjusted to a value of 7 (Note 2) with 6*N* hydrochloric acid and 3*N* potassium hydroxide. It is treated with 10 g. of decolorizing carbon and filtered. This operation is repeated. The filtrate is concentrated in a 1.5-l. beaker on a steam bath to about 180 ml. The concentrate is cooled to room temperature, 800 ml. of methanol is added with vigorous stirring by hand, and the mixture is cooled to 0–5°. The precipitated dipotassium naphthalate is separated by filtration, washed with 150 ml. of methanol, and dried in a vacuum oven at 150°/150 mm. The dried cream-colored salt weighs 130–135 g. (88–92%).

A mixture of 100 g. of dipotassium naphthalate and 4 g. of anhydrous cadmium chloride[2] is ground in a ball mill for 4 hours. The mixture is placed in a 0.5-l. autoclave (Note 3) and (Note 4) that can be rocked, rolled, or shaken. The autoclave is evacuated, for oxygen lowers the yield of the product. The autoclave is then filled with carbon dioxide to a pressure of about 30 atm. The agitated autoclave is heated to an internal temperature of 400–430° in the course of 1–2 hours and is maintained at this temperature for 1.5 hours. The pressure rises to about 90 atm. in the course of the heating (Note 4).

The autoclave is cooled to room temperature, and the carbon dioxide is bled off. The solid reaction product is taken from the autoclave, pulverized, and dissolved in 1 l. of water at 50–60°. Ten grams of decolorizing carbon is added, and the mixture is stirred well and filtered to remove cadmium salts and carbon. The filtrate is heated to 80–90° and acidified with concentrated hydrochloric acid to pH 1 (Note 5). 2,6-Naphthalenedicarboxylic acid precipitates. It is separated from the hot mixture by

filtration. It is then suspended in 500 ml. of water at 90–95° (Note 5), separated by filtration, and washed successively with 300 ml. of water, 300 ml. of 50% ethanol, and 300 ml. of 90% ethanol. After being dried at 100–150°/150 mm. in a vacuum oven, the 2,6-naphthalenedicarboxylic acid weighs 42–45 g. (57–61%). It decomposes on a heated block at 310–313°.

2. Notes

1. Suitable 1,8-naphthalic anhydride, m.p. 274–275°, is obtainable from Coaltar Chemicals Corp., 420 Lexington Ave., New York, N. Y.
2. Bromothymol blue or commercial universal indicator pH paper (graduated in 0.2-pH units) may be used as external indicators.
3. A 150-ml. shaking Hastelloy-C autoclave, manufactured by the Haynes Stellite Division of Union Carbide Co., Kokomo, Indiana, was used by the checkers. The approximate composition of the alloy is: Cr, 15.5–17.5%; Mo, 16–18%; Fe, 4.5–7%; W, 3.7–4.75%; and the remainder, Ni. Because their autoclave had only three-tenths the capacity of that used by the submitters, the checkers used three-tenths the quantities of materials given here.
4. The line to the pressure gauge tends to become clogged during the reaction.
5. Heat conduction in the heavy slurry that is formed is poor, and bumping may occur if the mixture is overheated. Efficient mechanical stirring aids this operation.

3. Discussion

2,6-Naphthalenedicarboxylic acid has been prepared by fusing dipotassium 2,6-naphthalenedisulfonate with potassium cyanide to give the corresponding dinitrile, which is hydrolyzed;[3] by oxidation of 2-methyl-6-acetylnaphthalene with dilute nitric acid at 200°;[4] by the thermal disproportionation of potassium α- or β-naphthoate to dipotassium 2,6-naphthalenedicarboxylate and naphthalene;[5] and by the present method.[6] The present method is much more convenient than earlier methods, if a suitable autoclave is available.

The present method for preparing aromatic dicarboxylic acids has been used to convert phthalic or isophthalic acid to terephthalic acid (90–95%); 2,2'-biphenyldicarboxylic acid to 4,4'-biphenyldicarboxylic acid; 3,4-pyrroledicarboxylic acid to 2,5-pyrroledicarboxylic acid; and 2,3-pyridinedicarboxylic acid to 2,5-pyridinedicarboxylic acid.[7] A closely related method for preparing aromatic dicarboxylic acids is the thermal disproportionation of the potassium salt of an aromatic monocarboxylic acid to an equimolar mixture of the corresponding aromatic hydrocarbon and the dipotassium salt of an aromatic dicarboxylic acid. The disproportionation method has been used to convert benzoic acid to terephthalic acid (90–95%); pyridinecarboxylic acids to 2,5-pyridinedicarboxylic acid (30–50%); 2-furoic acid to 2,5-furandicarboxylic acid; 2-thiophenecarboxylic acid to 2,5-thiophenedicarboxylic acid; and 2-quinolinecarboxylic acid to 2,4-quinolinedicarboxylic acid.[7] One or the other of these two methods is often the best way to make otherwise inaccessible aromatic dicarboxylic acids. The two methods were recently reviewed.[7]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Bromothymol blue

potassium α- or β-naphthoate

phthalic or isophthalic acid

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

methanol (67-56-1)

nitric acid (7697-37-2)

oxygen (7782-44-7)

potassium cyanide (151-50-8)

Benzoic acid (65-85-0)

carbon dioxide (124-38-9)

carbon (7782-42-5)

potassium hydroxide (1310-58-3)

Naphthalene (91-20-3)

2-Furoic acid (88-14-2)

cadmium chloride (10108-64-2)

Terephthalic acid (100-21-0)

2,6-Naphthalenedicarboxylic acid (1141-38-4)

1,8-naphthalic anhydride (81-84-5)

dipotassium naphthalate

dipotassium 2,6-naphthalenedisulfonate

2-methyl-6-acetylnaphthalene

dipotassium 2,6-naphthalenedicarboxylate

3,4-pyrroledicarboxylic acid

2,5-pyrroledicarboxylic acid

2,3-pyridinedicarboxylic acid (89-00-9)

2,5-pyridinedicarboxylic acid (100-26-5)

2,5-furandicarboxylic acid (3238-40-2)

2-thiophenecarboxylic acid (527-72-0)

2,5-thiophenedicarboxylic acid (4282-31-9)

2-quinolinecarboxylic acid (93-10-7)

2,4-quinolinedicarboxylic acid

2,2'-biphenyldicarboxylic acid (482-05-3)

4,4'-biphenyldicarboxylic acid

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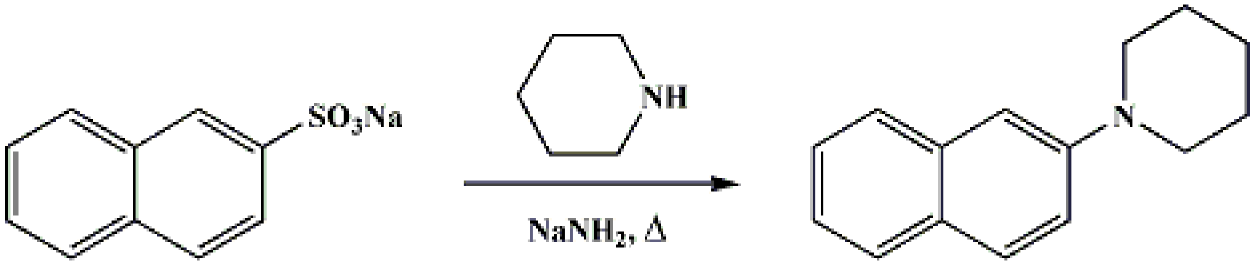
Organic Syntheses, CV 5, 816

N-β-NAPHTHYLPIPERIDINE

[Piperidine, 1-(2-naphthyl)-]



Submitted by J. F. Bunnett, T. K. Brotherton, and S. M. Williamson[1].
Checked by Virgil Boekelheide and F. Lind.

1. Procedure

A dry 1-l. three-necked round-bottomed flask is fitted in the center neck with a sweep-blade stirrer whose shaft passes through an airtight bearing (Note 1). One side neck is fitted with a condenser topped by a soda-lime drying tube, and the other is fitted with a solid stopper. In the flask are placed 75 ml. of piperidine (Note 2) and 15.6 g. (0.4 mole) of sodium amide (Note 3), and the mixture is heated at reflux (Note 4) for 15 minutes with good stirring. The mixture is cooled just below reflux temperature, and 46 g. (0.2 mole) of sodium β-naphthalenesulfonate (Note 5) is added, followed by an additional 75 ml. of piperidine. The mixture is then heated at reflux for 12 hours with stirring.

To the cooled reaction mixture, 200 ml. of water is added carefully with stirring. Potassium carbonate is added with continued stirring until the water layer is saturated; the mixture is now transferred to a separatory funnel and extracted three times with 60-ml. portions of ether. The combined ether extracts are dried over solid sodium hydroxide and are then transferred to a simple distillation apparatus. Distillation is commenced with a steam bath as source of heat; when most of the ether has been removed, the steam bath is replaced by a flame. Distillation is continued until most of the piperidine (b.p. 106°) has been removed. The cooled residue in the distillation flask is recrystallized from petroleum ether (boiling range 30–60°) with the use of charcoal. There is obtained 30.0 g. (71%) of N-β-naphthylpiperidine as tan crystals, m.p. 52–56°. An additional recrystallization from the same solvent gives crystals, m.p. 56–58°, with about 10% loss in weight (Note 6).

2. Notes

1. The submitters used a ball-joint bearing. A mercury seal or a Trubore bearing should also suffice.

2. Commercial piperidine was purified by 6 hours' refluxing with sodium metal followed by distillation from sodium.
3. Sodium amide from Farchan Research Laboratories, Cleveland, Ohio, was used.
4. The submitters used an electric heating mantle as a source of heat.
5. Sodium β-naphthalenesulfonate, technical grade, from Matheson, Coleman and Bell was dried in an oven and then used directly.
6. The melting point of pure β-naphthylpiperidine is 58–58.5°.[2,3] By the same procedure the submitters have obtained N-phenylpiperidine (94%) from sodium benzenesulfonate and N-α-naphthylpiperidine (23%) from sodium α-naphthalenesulfonate.

3. Discussion

N-β-Naphthylpiperidine has been prepared by the condensation of β-bromonaphthalene[2,3] or of β-naphthol[4] with piperidine at elevated temperatures; from the action of 1,5-dibromopentane on β-naphthylamine;[5] and from the action of the sodium amidepiperidine reagent on each of the eight monohalonaphthalenes[3,6] or on methyl β-naphthyl sulfone.[6] The present procedure is adapted from that of Brotherton and Bunnett.[7]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

β-naphthylpiperidine

sodium amidepiperidine

potassium carbonate (584-08-7)

ether (60-29-7)

sodium hydroxide (1310-73-2)

β-naphthol (135-19-3)

Sodium Benzenesulfonate (515-42-4)

sodium (13966-32-0)

piperidine (110-89-4)

1,5-dibromopentane (111-24-0)

β-bromonaphthalene (580-13-2)

sodium α-naphthalenesulfonate (130-14-3)

sodium β-naphthalenesulfonate (532-02-5)

sodium amide (7782-92-5)

N-phenylpiperidine (4096-20-2)

β-naphthylamine (91-59-8)

N-β-Naphthylpiperidine, Piperidine, 1-(2-naphthyl)- (5465-85-0)

N-α-naphthylpiperidine

methyl β-naphthyl sulfone

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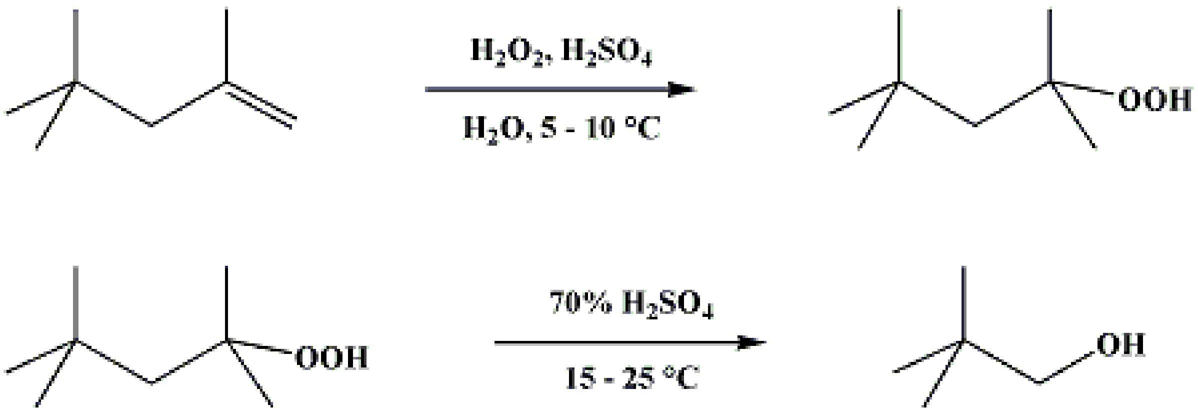
Organic Syntheses, CV 5, 818

NEOPENTYL ALCOHOL

[2,2-Dimethyl-1-propanol]



Submitted by Joseph Hoffman[1]
Checked by John D. Roberts and J. Eric Nordlander.

1. Procedure

A. *Preparation of hydroperoxide*. In a 2-l. three-necked round-bottomed flask, equipped with a mechanical stirrer (Note 1), a dropping funnel, and a thermometer, is placed 800 g. of 30% hydrogen peroxide (Note 2). The flask is surrounded by an ice bath and rapid stirring is started. In the meantime, 800 g. of 95–96% sulfuric acid is added to 310 g. of cracked ice and the solution is cooled to 10°. When the temperature of the hydrogen peroxide reaches 5–10°, the cold sulfuric acid is added slowly from the dropping funnel during a period of about 20 minutes (Note 3). The temperature of the solution should not exceed 20° during the addition. Commercial diisobutylene (224.4 g., 2 moles) is now added over a period of 5–10 minutes. The ice bath is removed and replaced by a water bath maintained at approximately 25° (Note 4). Vigorous agitation is maintained for 24 hours (Note 5). At the end of this time, mixing is discontinued, the mixture is transferred to a 2-l. separatory funnel and the two layers are allowed to separate (Note 6).

B. *Decomposition of hydroperoxide*. The upper organic layer (240–250 g.) is removed (Note 7) and added with vigorous stirring to 500 g. of 70% sulfuric acid in a 1-l. three-necked round-bottomed flask fitted with thermometer, stirrer, and dropping funnel and surrounded by an ice bath. The reaction temperature is maintained at 15–25° during addition, which requires 65–75 minutes (Note 8). Stirring is continued for 30 minutes at 5–10°, and then the reaction mixture is allowed to stand (0.5–3 hours) until the two layers are completely separated. The mixture is now transferred to a 1-l. separatory funnel and allowed to stand for about 15 minutes, after which time the lower layer is drawn off into 1 l. of water. The resulting mixture is distilled from a 3-l. flask without fractionation. The distillation is complete when 50–100 ml. of water has been

collected (Note 9). The upper organic layer from the distillate (180–190 g.) is removed and dried over anhydrous magnesium sulfate (Note 10). The dried organic layer is filtered with the aid of a small amount of ether and distilled through an efficient fractionating column. The fraction which boils at 111–113° is collected (Note 11) and (Note 12). The yield is 60–70 g. (34–40% of theory, based upon the diisobutylene).

2. Notes

1. A heavy nichrome wire twisted into 4 loops (similar to an egg beater) was found to be very satisfactory. The two ends of the wire, extending several inches beyond the loops, were pushed into a piece of glass tubing for the stirrer shaft.
2. If the hydrogen peroxide is slightly below 30%, enough should be used to give the amount called for. The acid concentration should be maintained by increasing the sulfuric acid proportionately.
3. The hydrogen peroxide-sulfuric acid solution consists of approximately 12.5% hydrogen peroxide and 40% sulfuric acid.
4. Good results have been obtained in the temperature range 23–27°. Although the heat given off during the reaction is not great and is spread over a long period of time, the reaction vessel must nevertheless be surrounded by a water bath. If the room temperature is in the range indicated, no further regulation of the water bath temperature is required.
5. It is necessary to provide rapid and vigorous stirring in order to obtain good results.
6. The aqueous layer now contains approximately 8% hydrogen peroxide. This layer may be reused by adjusting the hydrogen peroxide percentage to 12.5 by use of either 30% or 50% hydrogen peroxide. The sulfuric acid must be readjusted to 40%. Approximately 1.9 kg. of aqueous layer is required for 2 moles of diisobutylene.
7. The submitter states that the procedure may be interrupted at this point by washing the organic layer free of acid with a saturated solution of sodium bicarbonate and that the hydroperoxide concentrate will keep for a long time, especially if refrigerated.
8. Care should be taken in decomposing the hydroperoxide. If the temperature is kept too low, decomposition takes place too slowly and hydroperoxide may accumulate. Heat is liberated during the decomposition, and after each small addition the temperature will rise. At the start, small amounts of hydroperoxide are added until the temperature rises above 15°; the rate is then adjusted to keep the temperature in the range 15–25°. The rise in temperature after each small addition is the best evidence that decomposition is actually taking place.
9. The submitter states that, when the distillation is essentially complete, there is a tendency for the residue to foam; this should be watched for and the heat should be turned back to avoid carryover into the distillate. The checkers did not experience any difficulties of this sort.
10. The checkers found that the commercial grade of "dried" magnesium sulfate was not completely effective and, even after three treatments with fresh drying agent, the subsequent distillation afforded an azeotrope of neopentyl alcohol and

water of b.p. 80–85°. The organic layer of the azeotrope had to be separated from the water, dried, and redistilled to give the stated total yields.
11. The fraction between 95° and 110° should be taken off at a high reflux ratio; toward the end of the distillation the reflux ratio should again be increased. Most of the product comes over at 113°.
12. Pure neopentyl alcohol melts at about 55°. From time to time it will be necessary to circulate hot water through the take-off condenser in order to facilitate removal of the alcohol.

3. Discussion

Neopentyl alcohol has been made by lithium aluminum hydride reduction of trimethylacetic acid[2] and by treating *tert*-butylmagnesium chloride with methyl formate.[3]

The preparation of neopentyl alcohol from diisobutylene herein described represents an example of acid-catalyzed addition of hydrogen peroxide to a branched olefin, followed by an acid-catalyzed rearrangement of the tertiary hydroperoxide formed. In addition to neopentyl alcohol, there are formed acetone and also small amounts of methanol and methyl neopentyl ketone by an alternative rearrangement of the hydroperoxide.

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

diisobutylene

sulfuric acid (7664-93-9)

methanol (67-56-1)

ether (60-29-7)

sodium bicarbonate (144-55-8)

acetone (67-64-1)

hydrogen peroxide (7722-84-1)

methyl formate (107-31-3)

Trimethylacetic acid (75-98-9)

magnesium sulfate (7487-88-9)

lithium aluminum hydride (16853-85-3)

hydroperoxide

2,2-Dimethyl-1-propanol, Neopentyl alcohol (75-84-3)

hydrogen peroxide-sulfuric acid

methyl neopentyl ketone (590-50-1)

tert-butylmagnesium chloride (677-22-5)

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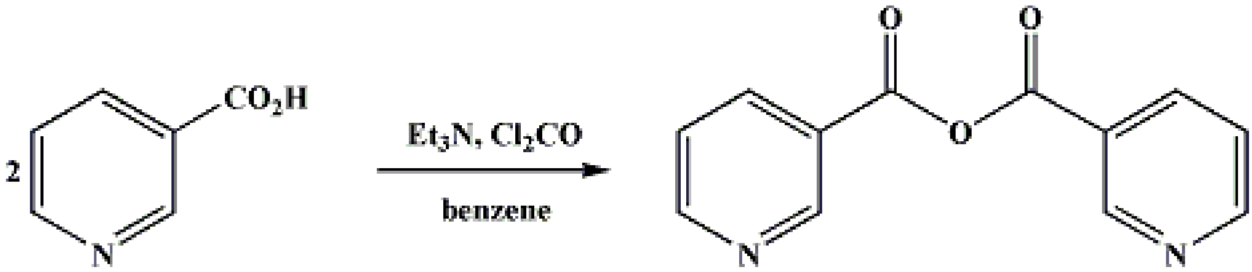
NICOTINIC ANHYDRIDE



Submitted by Heinrich Rinderknecht and Morris Gutenstein[1].
Checked by Walter K. Sosey, Wayland E. Noland, and William E. Parham.

1. Procedure

Nicotinic acid (10 g., 0.081 mole) (Note 1) and anhydrous benzene (275 ml.) (Note 2) are placed in a 500-ml. three-necked, round-bottomed flask (Note 3) fitted with a sealed Hershberg stirrer, a dropping funnel with a pressure-equalizing tube, and a stillhead connected to a condenser. In order to remove traces of moisture introduced with the nicotinic acid the mixture is heated until about 75 ml. of benzene has distilled. The stillhead is replaced by a Claisen head fitted with a thermometer and a calcium chloride tube, and the mixture is cooled to 5° by stirring in an ice bath. To the cold suspension of nicotinic acid is added all at once 8.65 g. (0.086 mole, 5% excess) of triethylamine (Note 4). The resulting clear solution is stirred with continued cooling while 34 g. of a 12.5% solution of phosgene (0.043 mole, 5% excess) in benzene (Note 5) is added through the dropping funnel. The rate of addition is regulated so that the temperature of the reaction mixture does not exceed 7°. Triethylamine hydrochloride precipitates immediately. After the addition of phosgene the mixture is stirred at room temperature for 45 minutes, heated to the boiling point, and filtered under slightly reduced pressure (Note 6) while hot. The triethylamine hydrochloride cake (Note 7) is washed on the filter with three 25-ml. portions of warm benzene (60°). The combined filtrate and washes are transferred to a 500-ml. round-bottomed flask and evaporated to dryness on a rotary evaporator at low temperature and pressure. The dry residue is simmered with 75 ml. of anhydrous benzene (Note 2), and the mixture is filtered while hot. The triethylamine hydrochloride cake (Note 7) is washed with two 5-ml. portions of cold benzene, and the filtrate and washes are allowed to stand at 20° for 2–3 hours. The crystalline product is collected on a filter, washed with two 4-ml. portions of cold anhydrous benzene, and dried in a vacuum. The yield of nicotinic anhydride, m.p. 122–125° (Note 8), is 6.25 g. (68%). The combined filtrate and washes are evaporated to dryness on a rotary evaporator. The residue is simmered with 175 ml. of a mixture of benzene and cyclohexane (2:3) (Note 2), and a small amount of insoluble material is removed by filtration of the hot mixture (Note 6). The filtrate is stored at 5° for 18 hours (Note 9); the crystalline deposit is collected, washed with 3 ml. of cold benzene-cyclohexane mixture, and dried in a vacuum. An additional 2.4 g. (25%) of colorless

product, m.p. 122–123°, is thus obtained. The total yield of nicotinic anhydride is 8.05–8.65 g. (87–93%).

2. Notes

1. Nicotinic acid supplied by Matheson, Coleman and Bell yielded a colorless anhydride; U.S.P. grade material gave a slightly buff-colored product.
2. Benzene and cyclohexane are freshly distilled and stored over sodium wire or calcium hydride.
3. Nicotinic anhydride is extremely sensitive to moisture; all glassware is therefore dried overnight in an oven at 200° before use.
4. Triethylamine is freshly distilled and stored over potassium hydroxide pellets.
5. A 12.5% solution of phosgene in benzene is available from Matheson, Coleman and Bell.
6. It is essential to carry out filtration under only slightly reduced pressure in order to minimize evaporation, cooling, and crystallization in the filter plate and funnel.
7. The yield of triethylamine hydrochloride obtained in this and subsequent extractions amounts to over 96% of that expected.
8. Melting points were determined in capillary tubes and are corrected. Reported:[2] 123–126°.
9. Rigorously anhydrous conditions are essential throughout this procedure and the flask must be air-tight.

3. Discussion

The present method is that described by Rinderknecht and Ma.[3] It is equally applicable to a variety of other heterocyclic, aromatic, and aliphatic anhydrides.[4,5] Nicotinic anhydride was first prepared by reaction of nicotinoyl chloride with sodium nicotinate,[6,7] and more recently by reaction of potassium nicotinate with oxalyl chloride in anhydrous benzene.[2]

4. Merits of the Preparation

The present method of preparing anhydrides is distinguished from other procedures by its simplicity and high yield. It avoids the two-phase reaction systems of older methods and the need for often inaccessible and highly sensitive acid chlorides. The only nongaseous by-product, triethylamine hydrochloride, is readily removed from the reaction mixture and leaves, in nearly quantitative yield, a solution of product suitable for further reaction or isolation.

References and Notes

1. Contribution No. 3176 from the Gates and Crellin Laboratories of Chemistry,

California Institute of Technology, Pasadena, California. This work was supported by grant No. HD-00347 from the National Institute of Child Health and Human Development.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

benzene-cyclohexane

Benzene (71-43-2)

cyclohexane (110-82-7)

potassium hydroxide (1310-58-3)

phosgene (75-44-5)

Nicotinic acid (59-67-6)

oxalyl chloride (79-37-8)

triethylamine (121-44-8)

Triethylamine hydrochloride (554-68-7)

Nicotinic anhydride (16837-38-0)

nicotinoyl chloride

sodium nicotinate (54-86-4)

potassium nicotinate (16518-17-5)

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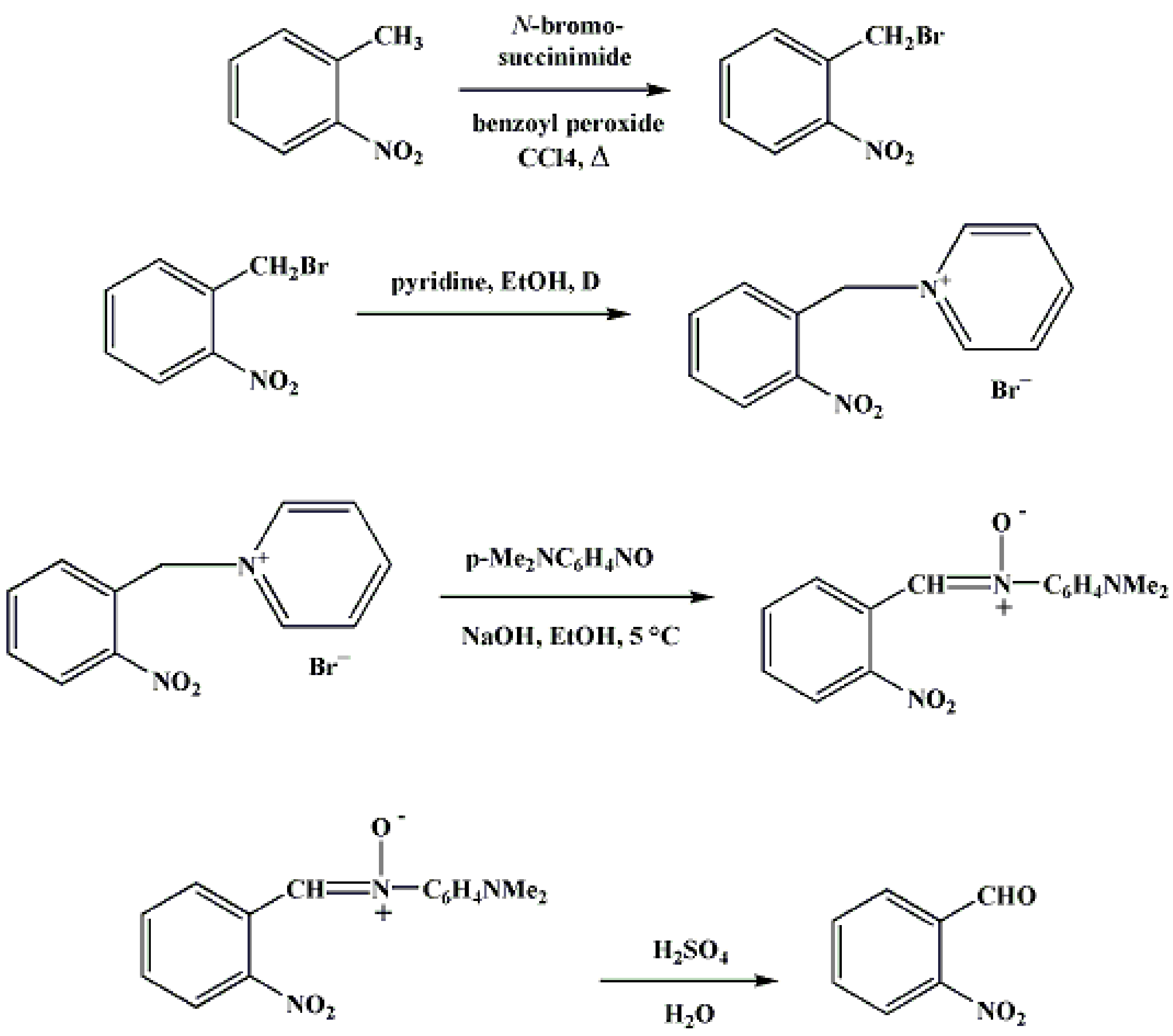
o-NITROBENZALDEHYDE

[Benzaldehyde, *o*-nitro-]



Submitted by A. Kalir[1]
Checked by John H. Sellstedt, Wayland E. Noland, and William E. Parham.

1. Procedure

A. *o-Nitrobenzylpyridinium bromide*. A 1-l. flask fitted with a reflux condenser is charged with 102 g. (0.744 mole) of *o*-nitrotoluene, 120 g. (0.675 mole) of N-bromosuccinimide, 1.0 g. of benzoyl peroxide, and 450 ml. of dry carbon tetrachloride. The mixture is heated under reflux until, after the refluxing is temporarily interrupted, all the solid is seen to float on the surface (usually 6–8 hours suffices).

The hot mixture is filtered with suction into a 1-l. round-bottomed flask through a Büchner-type sintered glass funnel provided with a ground joint (Note 1). The solid on the funnel is washed successively with two 50-ml. portions of hot carbon tetrachloride. The solvent is removed from the filtrate under reduced pressure on a water bath (Note 2). The flask is then fitted with a reflux

condenser, and 400 ml. of commercial absolute ethanol and 65 ml. (0.81 mole) of good grade pyridine (Note 3) are added to the residue.

The solution is heated at the reflux temperature for 45 minutes and immediately transferred to a wide-mouthed Erlenmeyer flask. Crystallization begins at once, and, after the mixture is cooled, the crystals of nearly pure *o*-nitrobenzylpyridinium bromide are collected, washed with cold ethanol, and used in the next step (Note 4).

B. *N-(p-Dimethylaminophenyl)-α-(o-nitrophenyl)nitrone*. The wet *o*-nitrobenzylpyridinium bromide, together with 100 g. (0.536 mole) of *p*-nitrosodimethylaniline hydrochloride (Note 5) and 800 ml. of ethanol are introduced into a 2-l. three-necked flask equipped with an efficient stirrer, thermometer, and a dropping funnel, and immersed in an ice-salt bath. The stirrer is started, and a solution of 54 g. (1.35 mole) of sodium hydroxide in 500 ml. of water is added at 0–5° (Note 6). The color changes gradually from yellow to green, brown, and orange. The stirring is continued at 5–10° over a period of 1 hour. At the end of this time 500 ml. of ice-cold water is added to the flask, and the orange N-(*p*-dimethylaminophenyl)-α-(*o*-nitrophenyl)nitrone is collected on a large Büchner funnel, pressed well, and washed with cold water. The nitrone is used in the next step without further purification (Note 7).

C. *o-Nitrobenzaldehyde*. The wet crude nitrone is placed in a 3-l. beaker. A solution of approximately 6*N* sulfuric acid (Note 8), (Note 9) is then added, and the mixture is hand-stirred with a spatula or a glass rod. Crushed ice is added after 10 minutes, and the crude solid *o*-nitrobenzaldehyde is filtered, washed successively with dilute sodium bicarbonate solution and water, and dried over calcium chloride in a desiccator.

The light brown material is best purified by distillation under reduced pressure. The yellow aldehyde is collected at 120–140° (3 mm.) (Note 10) and melts at 41–44°. This material weighs 48–54 g. (47–53% overall yield based on N-bromosuccinimide) and is sufficiently pure for most uses (Note 11), (Note 12).

2. Notes

1. Suction filtration is necessary. The filtration is conveniently carried out through a regular Büchner funnel connected through a rubber stopper to a 1-l. suction flask. *Since o-nitrobenzyl bromide is a powerful lachrymator, the filtration should be carried out in a fume hood.*
2. The checkers used a rotary evaporator.
3. The checkers used Merck Reagent A.C.S. grade pyridine.
4. The yield of air-dried *o*-nitrobenzylpyridinium bromide is 125–135 g. (63–68%). The product melts at 206–208° (cor.).
5. Freshly prepared *p*-nitrosodimethylaniline hydrochloride[2] was used without further purification.
6. Sometimes a difficulty in stirring is encountered, and 100–200 ml. of ethanol should be added to the reaction mixture. The checkers found that the reaction mixture became a very thick paste which was quite difficult to stir. Use of a sturdy Hershberg stirrer is recommended.
7. The wet material contains about 55–65% of water. When the product is dried in a vacuum desiccator and recrystallized from ethyl acetate or acetone, it melts at 130–134°.
8. The solution is prepared by careful addition of 170 ml. of concentrated sulfuric acid to 850 ml. of water.

9. Hydrochloric acid (15%) can be substituted for sulfuric acid with equal results.
10. The checkers collected the product at 97–99° (1 mm.).
11. Very pure material can be obtained by dissolving *o*-nitrobenzaldehyde in toluene and precipitating with petroleum ether, according to earlier instructions.[3]
12. The same yields are obtained when the scale of this preparation is doubled.

3. Discussion

o-Nitrobenzaldehyde has been prepared by numerous methods.[3] The best-known and most widely used route involves the oxidation of *o*-nitrotoluene by chromium trioxide in acetic anhydrideacetic acid solution.[3] The present preparation is an example of the Kröhnke reaction.[4] It is adapted from the published directions for the synthesis of a series of halo- and nitrobenzaldehydes.[5]

4. Merits of the Preparation

The present procedure is a general method for preparing aromatic and heterocyclic aldehydes. It is of particular value in the synthesis of *o*-nitrobenzaldehydes in 100–200 g. lots. The benzaldehydes are useful starting materials for cinnamic acids, β-nitrostyrenes, etc. The manipulations are simple, the yields are reproducible, and the intermediates can be easily isolated and purified. The intermediates themselves have many synthetic uses.

The submitter has prepared the fluoro-*o*-nitrobenzaldehydes shown in Table I by application of this method.[6]

TABLE I
FLUORO-*o*-NITROBENZALDEHYDES

Position of Fluorine	M. P. of Fluoro-2-nitrobenzylpyridinium Bromide, °C	M. P. of N-(*p*-dimethylaminophenyl)- α-(fluoro-*o*-nitrophenyl) nitrone, °C	M. P. of Aldehyde, °C	Overall Yield, %
4	200–201	164–165	32–33	55–62
5	189–190	155–156	93–95	45–55
6	202–204	151–152	62–63	59–66

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

ethanol (64-17-5)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

carbon tetrachloride (56-23-5)

acetone (67-64-1)

pyridine (110-86-1)

toluene (108-88-3)

o-nitrotoluene (88-72-2)

benzoyl peroxide (94-36-0)

chromium trioxide (1333-82-0)

o-Nitrobenzaldehyde, Benzaldehyde, o-nitro- (552-89-6)

N-bromosuccinimide (128-08-5)

nitrone

o-nitrobenzyl bromide (3958-60-9)

acetic anhydrideacetic acid

p-Nitrosodimethylaniline hydrochloride (42344-05-8)

o-Nitrobenzylpyridinium bromide (13664-80-7)

N-(p-Dimethylaminophenyl)-α-(o-nitrophenyl)nitrone (13664-79-4)

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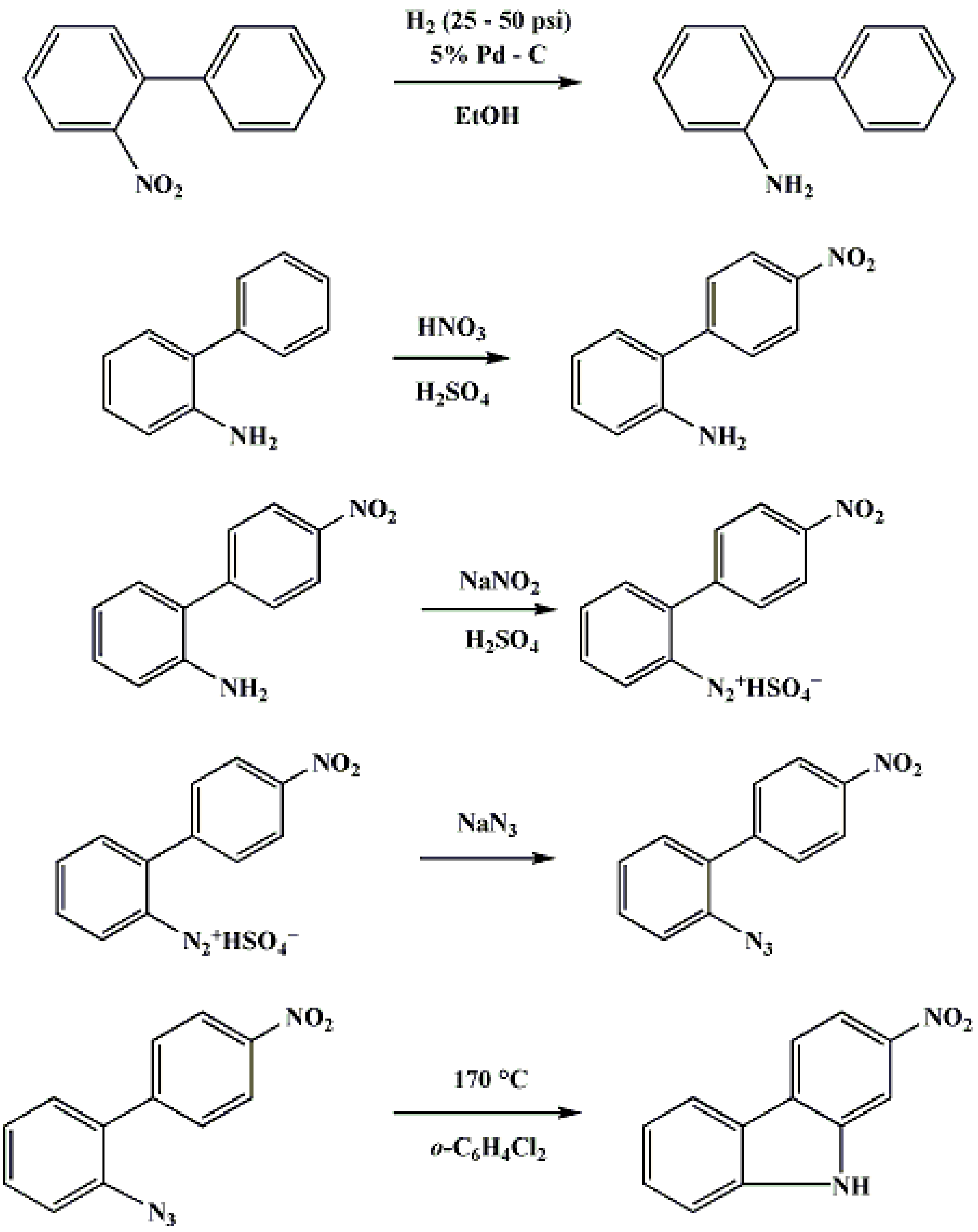
Organic Syntheses, CV 5, 829

2-NITROCARBAZOLE

[Carbazole, 2-nitro]



Submitted by G. David Mendenhall and Peter A. S. Smith[1].
Checked by Howard A. Harris and Kenneth B. Wiberg.

1. Procedure

A. *o-Aminobiphenyl*. A Parr bottle is charged with 60 g. (0.30 mole) of *o*-nitrobiphenyl (Note 1), 3 g. of 5% palladium-on-carbon catalyst (Note 2), and 200 ml. of 95% ethanol. The mixture is shaken with hydrogen under 25–50 p.s.i. until the gas is no longer absorbed (about 70 minutes), the catalyst is filtered from the hot solution and washed with 20 ml. of ethanol, and the filtrates are poured in a thin stream into 1 l. of ice water contained in a 2-l. Erlenmeyer flask (Note 3). After standing for 20 minutes the white solid is filtered with suction, pressed to remove excess water, and allowed to dry in air. The yield of essentially pure *o*-aminobiphenyl is 48–51 g. (94–100%), m.p. 43–45.5°.

B. *o-Amino-p'-nitrobiphenyl*. Concentrated sulfuric acid (400 ml.) is placed in a 1-l. round-bottomed flask fitted with a mechanical stirrer and a thermometer. Stirring is begun, and 45.0 g. (0.27 mole) of powdered *o*-aminobiphenyl is added all at once through a powder funnel. When the amine has dissolved, the flask is placed in an ice-salt bath and its contents cooled to a temperature between 0° and −5°. A mixture of 30 ml. of concentrated sulfuric acid and 11.0 ml. of fuming nitric acid (density 1.5) is then added dropwise from a separatory funnel while the temperature is kept below 0°. The addition requires about an hour, and stirring is continued 45 minutes longer. The liquid is poured onto 1.5 kg. of ice in a 4-l. beaker and treated carefully until neutral with a solution of 580 g. (14.5 moles) of sodium hydroxide in 1.5 l. of water cooled to room temperature. The resultant hot suspension of product is allowed to cool nearly to room temperature, filtered with suction, and the orange solid is washed with 500 ml. of water. The crude material is pressed free of excess water and recrystallized from 850–1000 ml. of 95% ethanol (Note 4), giving 32–42 g. (56–74%) of orange needles, m.p. 156–158.5°.

C. *o-Azido-p'-nitrobiphenyl*. Water (100 ml.) is placed in a 1-l. round-bottomed flask equipped with a thermometer and an efficient mechanical stirrer. With stirring, 30 ml. of concentrated sulfuric acid is added, followed by 32.1 g. (0.15 mole) of recrystallized *o*-amino-*p'*-nitrobiphenyl. When all the amine has been converted to the white sulfate, 50 ml. more of water is added and the suspension is cooled to 0–5° in an ice-salt bath. A solution of 11 g. (0.16 mole) of sodium nitrite in 30 ml. of water is added dropwise over a period of 15 minutes (Note 5), and the mixture is stirred for 45 minutes longer. A thick precipitate of the sparingly soluble diazonium salt may have separated from the initially clear solution by this time. With strong stirring, a solution of 12 g. (0.17 mole) of sodium azide in 40 ml. of water is run in (Note 6), and stirring is continued for 40 minutes longer. The thick white solid is filtered with suction and washed with 200 ml. of water. After pressing free of excess water, the material is allowed to dry in air in a dark place. The yield of gray-white azide is 35.5–36 g. (99–100%), m.p. 91.5–92.5° (Note 7).

D. *2-Nitrocarbazole*. In a 2-l. round-bottomed flask fitted with a mechanical stirrer, a thermometer, and a short air condenser are placed 35.5 g. (0.15 mole) of powdered *o*-azido-*p'*-nitrobiphenyl and 1 l. of *o*-dichlorobenzene (Note 8). The stirred mixture is

heated above 170° for 1 hour by means of a heating mantle, allowed to cool to room temperature, and chilled in a refrigerator (5°) for several hours. The crude product is filtered with suction, washed with 40 ml. of light petroleum, and sucked dry on the filter. There results 26–28 g. of yellow-brown crystals, m.p. 171.5–174°. The filtrate is distilled under aspirator pressure to a volume of 150–200 ml. and chilled as before, to yield an additional 2–3 g., m.p. 171–174°. The total yield is 28–30 g. (89–96%). The combined crops are dissolved in 400–450 ml. of boiling 95% ethanol with 3–4 g. of Norit® to remove impurities and filtered through a preheated Büchner funnel. The filtrate on cooling deposits bright yellow needles of product, which are filtered after standing at 5° for several hours. This crop weighs 23–25 g., m.p. 174–175.5°. Concentration of the mother liquor to a small volume (50–70 ml.) and chilling gives a second crop of lesser purity, 1–2 g., m.p. 172–175°. The total yield of recrystallized material is 24–26.5 g. (77–85%), and the overall yield from *o*-nitrobiphenyl is 40–63%.

2. Notes

1. An Eastman Kodak technical grade of *o*-nitrobiphenyl was used by the submitters. This is no longer available, and the checkers used the material supplied by K and K Laboratories. Both *o*-amino- and *o*-nitrobiphenyl are available from the Aldrich Chemical Company.
2. The Baker Co. catalyst was used.
3. This carcinogen is more easily handled in a flask than in a beaker. Contact with the skin obviously should be avoided.
4. Recrystallization is best accomplished by adding the compound to boiling ethanol and filtering. Prolonged heating should be avoided, as the substance gradually decomposes in hot solvent.
5. The sodium nitrite solution must be added carefully in order to avoid loss of material due to vigorous foaming.
6. This operation should be carried out in a hood to avoid the unpleasant effects of exposure to hydrogen azide vapors.
7. The compound may be recrystallized from a large volume of ethanol, but no increase in yield was noted using recrystallized material in the next step.
8. Eastman Kodak *o*-dichlorobenzene of 95% purity was used. Olefin-free kerosene or decalin may be substituted for the solvent, keeping the reaction temperature between 170° and 190°.

3. Discussion

o-Aminobiphenyl has been prepared by the reduction of the corresponding nitro compound with zinc and acetic acid,[2] zinc and hydrochloric acid,[3] iron and hydrochloric acid,[4] sodium bisulfite under pressure,[5] or hydrazine and palladium;[6] by the Hofmann reaction on *o*-phenylbenzamide;[7] and by pyrolysis of diazoaminobenzene.[8,9]

o-Amino-*p*'-nitrobiphenyl has been made by the nitration of *o*-aminobiphenyl with

ethyl nitrate;[10] by hydrolysis of the corresponding acetamide derivative;[11,12] and by partial reduction of *o*, *p*'-dinitrobiphenyl with sodium bisulfite under pressure.[5]

2-Nitrocarbazole has been prepared by the dehydrogenation of 2-nitro-1,2,3,4-tetrahydrocarbazole with chloranil,[13] by the deamination of 2-nitro-3-aminocarbazole,[14] and by the thermal decomposition of *o*-azido-*p*'-nitrobiphenyl.[15] The procedure given here is a slight modification of the last-mentioned method.

4. Merits of the Preparation

The decomposition of *o*-azidobiphenyls is a convenient and general synthesis for a variety of carbazoles in good yield,[15] especially those not available through direct substitution of carbazole itself. Many of the required intermediates can be prepared from *o*-aminobiphenyl by substitution reactions. The method is also applicable to the preparation of analogs of the carbazole system in which a heterocyclic ring replaces a benzene ring, to the preparation of indoles, and to certain analogous aliphatic systems.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

palladium-on-carbon

light petroleum

o-amino- and o-nitrobiphenyl

chloranil

o-azidobiphenyls

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

iron (7439-89-6)

nitric acid (7697-37-2)

sodium nitrite (7632-00-0)

sodium bisulfite (7631-90-5)

zinc (7440-66-6)

palladium (7440-05-3)

hydrazine (302-01-2)

sodium azide (26628-22-8)

carbazole (86-74-8)

Diazoaminobenzene (136-35-6)

ethyl nitrate (625-58-1)

decalin (91-17-8)

hydrogen azide

o-Aminobiphenyl (90-41-5)

2-Nitrocarbazole, Carbazole, 2-nitro (14191-22-1)

2-nitro-1,2,3,4-tetrahydrocarbazole

2-nitro-3-aminocarbazole

o-dichlorobenzene (95-50-1)

o-nitrobiphenyl (86-00-0)

o-phenylbenzamide

o-Azido-p'-nitrobiphenyl (14191-25-4)

o-Amino-p'-nitrobiphenyl (6272-52-2)

o, p'-dinitrobiphenyl

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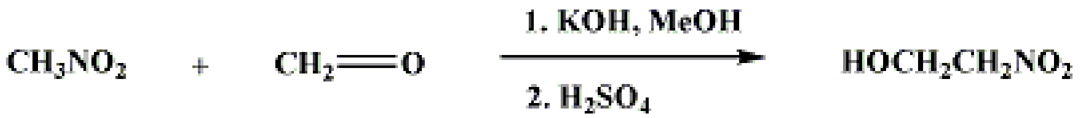
Organic Syntheses, CV 5, 833

2-NITROETHANOL

[Ethanol, 2-nitro-]



Submitted by Wayland E. Noland[1]
Checked by Melvin S. Newman and Surjan S. Rawalay.

1. Procedure

In a 5-l., three-necked, round-bottomed flask fitted with a 30-ml. dropping funnel, mechanical stirrer, and thermometer extending down into the liquid is placed a suspension of paraformaldehyde (trioxymethylene, 125 g., 4.16 moles) in freshly distilled (Note 1) nitromethane (2.5 l., 46.6 moles). The suspension is stirred vigorously, and 3*N* methanolic potassium hydroxide solution is added dropwise from the dropping funnel until, at an apparent pH of 6–8, but closer to pH 8 (pH paper), the paraformaldehyde begins to dissolve and the suspension assumes a clearer appearance. About 10 ml. of the alkaline solution is required, and the addition takes about 10 minutes. About 15–20 minutes after addition of the alkaline solution is complete, the paraformaldehyde dissolves completely. Shortly thereafter, the solution temperature reaches a maximum of 13–14 degrees above room temperature and then slowly drops. Stirring is continued 1 hour after addition of the alkaline solution is complete.

Stirring is continued while the added alkali is *completely* neutralized by adding concentrated (36*N*) sulfuric acid (1 ml.) dropwise from a medicine dropper over a period of about 3 minutes until an apparent pH of about 4 is reached (Note 2). The solution is then stirred for an hour, during which time the pH should not change (Note 3).

The precipitated potassium sulfate is filtered by passing the solution through a 12-cm. Büchner funnel. The light-yellow or yellowish green filtrate is transferred to a 5-l., one-necked, round-bottomed flask fitted with a Claisen head containing a capillary ebulliator tube and a thermometer, and connected to a water-cooled condenser. The condenser is connected through a vacuum adapter to a 3-l., one-necked, round-bottomed flask, cooled in ice, to act as a receiver. About 2.3 l. of pure, unchanged nitromethane is removed by distillation at aspirator pressure and a water-bath temperature of 40–50°. The distillation takes about 6–7 hours.

The golden-yellow residue (315–365 g.) is transferred to a 1-l., one-necked, round-bottomed flask containing an equal weight of diphenyl ether (Note 4). The flask is fitted with a Claisen head containing a capillary ebulliator tube and a thermometer, and connected to a water-cooled condenser. The condenser is connected to a 3- or 4-

port fraction cutter fitted with 100–500 ml., one-necked, round-bottomed flasks, at least one of which is 500 ml. or larger to accommodate the main fraction (Note 5). The mixture is distilled under the vacuum of a good pump. The fore-run, b.p. 29–33° at about 0.10 mm., consisting of nitromethane (about 56 ml.), can be distilled at a water-bath temperature of 32–79° and usually passes directly into the Dry Ice trap protecting the vacuum pump. The temperature then rises as 2-nitroethanol and diphenyl ether codistil. The main fraction, a two-phase distillate initially richer in 2-nitroethanol than diphenyl ether, gradually changes in composition until the proportion of 2-nitroethanol becomes negligible. The main fraction of 410–425 g., b.p. 54–57° at about 0.10 mm. (or 64–66° at about 0.4 mm.), collects at a water-bath temperature of 79–88°. Care should be taken to prevent clogging of the condenser or fraction cutter with solid diphenyl ether (m.p. 27°). The distillation is continued until the proportion of 2-nitroethanol (lower layer) observed in the distillate becomes negligible, and the temperature suddenly starts to rise. At this point heating is stopped, *but the residue is cooled to room temperature or below before the vacuum is broken* (Note 6).

The two-phase main fraction of the distillate is placed in a 500-ml. separatory funnel and the lower layer of crude 2-nitroethanol (185–200 g., 146–158 ml., n_D^{25} 1.4493–1.4513, containing about 92–94 mole % 2-nitroethanol) is drawn off. The 2-nitroethanol is then extracted in a 500-ml. separatory funnel with an equal volume of light petroleum ether (b.p. 60–68°, such as Skellysolve B) or hexane, and the colorless lower layer of 2-nitroethanol (174–188 g., 46–49%, n_D^{25} 1.4432–1.4433, containing about 98 mole % 2-nitroethanol) is drawn off (Note 7) and (Note 8). The product turns light yellow after standing for a day or more.

2. Notes

1. Commercial nitromethane is sometimes quite acidic, and much more methanolic potassium hydroxide is required to initiate the reaction when such material is used. For safety, the nitromethane should be distilled at aspirator pressure instead of atmospheric pressure.
2. Sulfuric acid *must* be used in an amount slightly *more* than enough exactly to neutralize the alkali, and not just sufficient to make the reaction acidic. Otherwise, the metal salts of nitromethane can form explosive fulminates upon heating.
3. This is a suitable point at which to interrupt the experiment overnight.
4. 2-Nitroethanol prepared by the formaldehyde-nitromethane method should not be distilled without use of diphenyl ether as a heat-dispersing agent. The residue, consisting of di- and tri-condensation products of formaldehyde with nitromethane, when hot and concentrated, and particularly when the vacuum is broken and air is let in on the hot distillation residue, is very likely to undergo a flash detonation, or at least a fume-off which may proceed with explosive violence. Use of diphenyl ether is a wise safety precaution in the distillation of 2-nitroethanol made by other methods as well.
5. If a fraction cutter is not used, the residue should be cooled to room

temperature each time before the vacuum is broken.

6. The large amount of diphenyl ether (80–125 g.) left as the upper layer in the distilling flask has served the useful purpose, by its mass and volatility, of preventing superheating of the residue and subsequent violent decomposition, as described in (Note 4).

7. This procedure has been carried out 30 times by students in the advanced organic laboratory course at the University of Minnesota. The extreme ranges of yields obtained were 32–52%, and the median yield was 46%.

8. The 2-nitroethanol obtained by this procedure is quite satisfactory for synthetic purposes, such as the preparation of nitroethylene. The small amount of light petroleum ether dissolved in the 2-nitroethanol can easily be removed under reduced pressure. Most of the remaining diphenyl ether can be removed by one redistillation under vacuum, since the fore-run is relatively rich in diphenyl ether. The main fraction has n_D^{25} 1.4425–1.4431. Although vacuum redistillation of 2-nitroethanol which has been freed by the present procedure from higher condensation products of formaldehyde with nitromethane is relatively safe, it is recommended that the procedure be carried out behind a safety shield or a barricade.

3. Discussion

The present procedure is that of Controulis, Rebstock, and Crooks,[2] modified to include the diphenyl ether purification method of Roy.[3] 2-Nitroethanol has been prepared by condensation of formaldehyde (usually employed in the solid form as paraformaldehyde) with a large excess of nitromethane in the presence of an alkali catalyst,[2,4,5,6] as illustrated by the present procedure, or in the presence of a strongly basic ion-exchange resin.[7] Dimethoxymethane has also served as a source of formaldehyde in a reaction catalyzed by a mixture of acidic and basic ion-exchange resins.[8] 2-Nitroethanol has also been prepared by the action of silver nitrite on 2-iodoethanol (ethylene iodohydrin);[9,10,11,12] by selective catalytic hydrogenation over 5% palladium on barium sulfate in pyridine solution of halogenated derivatives, including 2-chloro-2-nitroethanol, 2,2-dichloro-2-nitroethanol, and 2-bromo-2-nitroethanol;[13] by the action of fuming nitric acid on ethylene;[14] and by the action of dinitrogen tetroxide on ethylene in the presence of oxygen[15,16,17,18,19] or nitric oxide,[20] or in carbon tetrachloride solution.[21] The preparation of 2-nitroethanol from ethylene oxide by the action of aqueous solutions of barium,[22] calcium,[22] magnesium,[23] or zinc[22] nitrite, or by the action of sodium nitrite and carbon dioxide,[24] has also been reported. The submitter has been unable to prepare 2-nitroethanol from ethylene oxide using the procedures described for barium[6] or sodium nitrite; his observation with respect to barium nitrite has been confirmed in another laboratory.[25] More recently, the preparation of 2-nitroethanol in 50% yield has been reported by

adding ethylene oxide to aqueous sodium nitrite at 20° under nitrogen in the presence of a nitrite scavenger, such as sodium hydrosulfite or phloroglucinol, at a pH of 7.1–7.3 controlled by the addition of phosphoric acid.[26] The action of dinitrogen tetroxide on ethylene oxide in chloroform solution has been reported to yield 2-nitroethyl nitrate, from which 2-nitroethanol could be obtained by alkaline saponification.[27] This report has since been refuted with the finding that the initial product is the mononitrite mononitrate ester of ethylene glycol, which saponifies to ethylene glycol mononitrate and diethylene glycol mononitrate.[28]

4. Merits of Preparation

The present procedure has the advantage of using inexpensive, commercially available starting materials, combined with an apparently safe method of isolating the product. 2-Nitroethanol is particularly valuable as a synthetic intermediate for the preparation of nitroethylene. Nitroethylene is conveniently prepared by heating 2-nitroethanol with phthalic anhydride and allowing the nitroethylene to distil under reduced pressure.[29,30]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

trioxymethylene

dinitrogen tetroxide

methanolic potassium hydroxide

mononitrate ester of ethylene glycol

sulfuric acid (7664-93-9)

formaldehyde (630-08-0)

chloroform (67-66-3)

potassium sulfate (37222-66-5)

magnesium (7439-95-4)

nitric acid (7697-37-2)

oxygen (7782-44-7)

carbon tetrachloride (56-23-5)

nitrogen (7727-37-9)

sodium nitrite (7632-00-0)

mononitrite (14797-65-0)

sodium hydrosulfite (7775-14-6)

carbon dioxide (124-38-9)

phthalic anhydride (85-44-9)

barium sulfate (7727-43-7)

pyridine (110-86-1)

potassium hydroxide (1310-58-3)

zinc (7440-66-6)

calcium (7440-70-2)

phosphoric acid (7664-38-2)

palladium (7440-05-3)

Ethylene oxide (75-21-8)

ethylene (9002-88-4)

nitric oxide

barium (7440-39-3)

Dimethoxymethane (109-87-5)

Nitromethane (75-52-5)

Phloroglucinol (108-73-6)

silver nitrite (7783-99-5)

diphenyl ether (101-84-8)

hexane (110-54-3)

2-Nitroethanol, Ethanol, 2-nitro- (625-48-9)

nitroethylene (3638-64-0)

2-iodoethanol, ethylene iodohydrin (624-76-0)

2-chloro-2-nitroethanol

2,2-dichloro-2-nitroethanol

barium nitrite

2-nitroethyl nitrate (4528-34-1)

ethylene glycol mononitrate

diethylene glycol mononitrate

2-bromo-2-nitroethanol

paraformaldehyde (30525-89-4)

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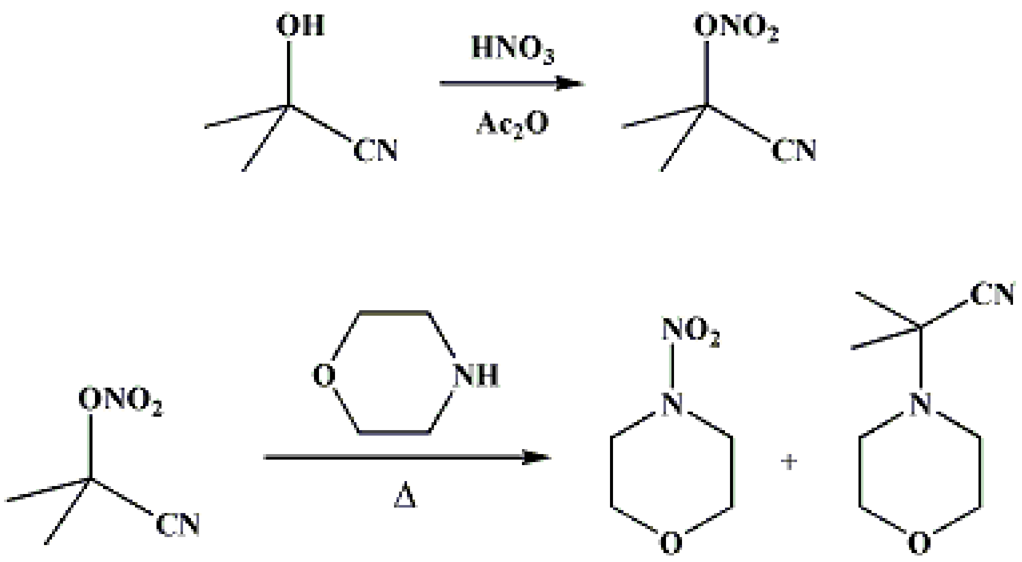
Organic Syntheses, CV 5, 839

N-NITROMORPHOLINE

[Morpholine, 4-nitro-]



Submitted by Jeremiah P. Freeman and Inella G. Shepard[1].
Checked by C. G. Bottomley and B. C. McKusick.

1. Procedure

Caution! The nitrating mixture consisting of fuming nitric acid and acetic anhydride is an extremely active one, and combinations of it and organic materials are potentially explosive. The nitration should be carried out behind adequate safety shields. Acetone cyanohydrin nitrate is moderately explosive (Note 6) and all operations with it, but particularly its distillation, should be carried out behind safety shields.

A. *Acetone cyanohydrin nitrate*. White fuming nitric acid (106 ml., 158 g., 2.3 moles) (Note 1) is added dropwise to 380 ml. (408 g., 4.00 moles) of acetic anhydride at 3–5° contained in a 2-l. three-necked flask fitted with a stirrer, a thermometer, and a dropping funnel and immersed in an ice bath. After the addition, which requires 45 minutes, the mixture is stirred at 5° for 15 minutes (Note 2). Acetone cyanohydrin (92 ml., 85 g., 1.00 mole (Note 3) is added dropwise to the mixture at 5–10° over a 45-minute period. After the addition, the ice bath is removed and the mixture is allowed to warm to room temperature and is stirred there for 30 minutes. It is then poured into 600 g. of ice and water, and the resulting mixture is stirred for 90 minutes to dissolve the acetic anhydride.

The mixture is extracted with four 100-ml. portions of methylene chloride. The extracts are combined, washed successively with 100 ml. of water and four 100-ml. portions of 5% sodium carbonate solution (Note 4), and dried over anhydrous

magnesium sulfate. The methylene chloride is removed by evaporation at 30–40° under the pressure of a water aspirator, and the residue is distilled through a 30-cm. Vigreux column to yield 85–90 g. (65–69%) (Note 5) of acetone cyanohydrin nitrate (Note 6); b.p. 62–65°/10 mm.; n_D^{20} 1.4170–1.4175 (Note 7).

B. *N-Nitromorpholine*. Morpholine (34.8 g., 0.40 mole) and 26 g. (0.20 mole) of acetone cyanohydrin nitrate are mixed in a 50-ml. round-bottomed flask equipped with a thermometer well. A condenser is attached, and the mixture is heated slowly. At about 60° an exotherm ensues that raises the temperature of the mixture to 110°. The mixture is allowed to cool to 80° and maintained there for 1 hour. It is poured into 200 ml. of 10% hydrochloric acid *Caution! Do in a hood! (Note 8))* and extracted with three 100-ml. portions of methylene chloride (Note 9). The extracts are combined, washed successively with two 100-ml. portions of water, 100 ml. of 10% hydrochloric acid, and 100 ml. of water, and dried over anhydrous magnesium sulfate. The solvent is removed by evaporation on a water aspirator at room temperature to yield a pale-yellow oil (Note 10).

The oil is dissolved in 80 ml. of absolute ethanol. The solution is cooled to 0–5°, causing white crystals of N-nitromorpholine to precipitate; weight 15–17 g. (57–64%); m.p. 52–54° (Note 11).

2. Notes

1. This is 90% nitric acid, d. 1.48–1.50. In order to remove dissolved nitrogen oxides from it, 0.5 g. of urea is added and the mixture is air-sparged for 20 minutes. The acid should be colorless before it is added to the acetic anhydride.
2. The nitrating mixture should be colorless at this point. If it is not, 0.5 g. of urea should be added and the mixture air-sparged until colorless.
3. Suitable acetone cyanohydrin can be purchased from the Rohm and Haas Co. and other commercial sources, or it can be prepared as described in *Organic Syntheses*.[2]
4. Washing with the carbonate solution should be continued until the organic layer is free of acid. Traces of acid may cause extensive decomposition during the distillation.
5. Similar yields were observed in preparations on three times this scale.
6. Acetone cyanohydrin nitrate should be regarded as a moderately explosive material and should be handled carefully and distilled behind a safety shield. For purposes of comparison, the drop-weight sensitivities on the Olin-Mathieson drop-weight tester of three materials are: propyl nitrate, 10 kg.-cm.; acetone cyanohydrin nitrate, 40 kg.-cm; nitromethane, 60 kg.-cm.
7. The product obtained from this distillation usually contains small amounts of acetone cyanohydrin acetate, as evidenced by an ester carbonyl band at 1740 cm.$^{-1}$ in its infrared spectrum. This material does not interfere with the nitration reactions of the reagent. It may be removed by fractionation through a more efficient column.

8. This operation should be carried out in a good hood because hydrogen cyanide is evolved at this point.

9. The aqueous solution contains α-morpholinoisobutyronitrile in the form of its hydrochloride. It is formed by condensation of morpholine with the acetone and hydrogen cyanide formed in the nitration reaction. It is because of this side reaction that the excess amine is employed.

10. Occasionally this oil solidifies after removal of the last traces of solvent; in these instances it is necessary to warm the ethanol slightly to effect solution.

11. In nitrating amines other than morpholine, particularly on a larger scale, it may be desirable to carry out the reaction in acetonitrile to control the temperature better.[3]

3. Discussion

N-Nitromorpholine has been prepared by the oxidation of N-nitrosomorpholine with peroxytrifluoroacetic acid,[4] by the chloride ion-catalyzed reaction of nitric acid with morpholine,[5] by the action of nitric acid and acetic anhydride on N-formylmorpholine,[6] by the reaction of dinitrogen pentoxide with morpholine,[7] and by alkaline nitration of morpholine with acetone cyanohydrin nitrate.[3]

4. Merits of the Preparation

This synthesis of N-nitromorpholine is representative of a rather general reaction for the preparation of both primary and secondary nitramines.[3] It represents the simplest process for obtaining both types of compounds. The reaction is unique in that a nitration is carried out under neutral or alkaline conditions. Acetone cyanohydrin nitrate may also be used for the nitration of many active methylene compounds.[8]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

acetic anhydride (108-24-7)

acetonitrile (75-05-8)

nitric acid (7697-37-2)

hydrogen cyanide (74-90-8)

sodium carbonate (497-19-8)

nitrogen (7727-37-9)

acetone (67-64-1)

urea (57-13-6)

Nitromethane (75-52-5)

methylene chloride (75-09-2)

Acetone cyanohydrin (75-86-5)

magnesium sulfate (7487-88-9)

morpholine (110-91-8)

Acetone cyanohydrin nitrate (40561-27-1)

peroxytrifluoroacetic acid

N-Nitromorpholine, Morpholine, 4-nitro- (4164-32-3)

propyl nitrate (627-13-4)

acetone cyanohydrin acetate

α-morpholinoisobutyronitrile

N-nitrosomorpholine (59-89-2)

N-formyl-morpholine (4394-85-8)

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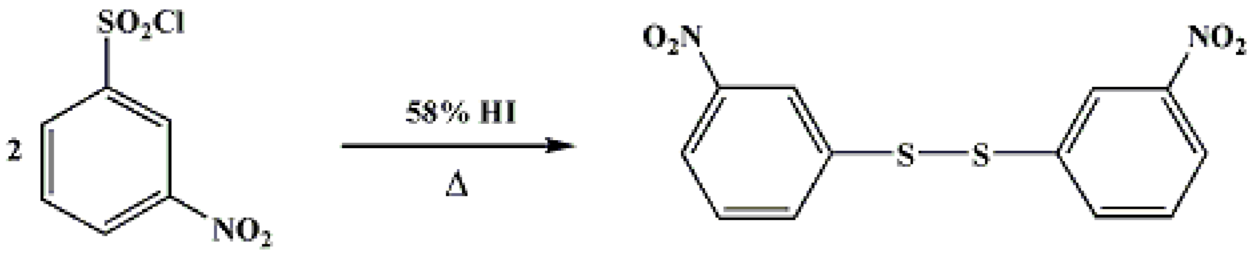
Organic Syntheses, CV 5, 843

m-NITROPHENYL DISULFIDE

[Disulfide, bis-(*m*-nitrophenyl)]



Submitted by W. A. Sheppard[1]
Checked by John D. Roberts and W. H. Graham.

1. Procedure

A 5-l. three-necked round-bottomed flask equipped with a reflux condenser, a sealed mechanical stirrer, and a dropping funnel is set up in a hood and charged with 333 g. (1.50 moles) of *m*-nitrobenzenesulfonyl chloride (Note 1). The stirrer is started and 1033 ml. (7.5 moles) of 55–58% hydriodic acid (Note 2) is rapidly added dropwise over a period of 30–45 minutes (Note 3). After the addition is complete, the reaction mixture is stirred and refluxed on a steam bath for 3 hours. It is then cooled to room temperature, and the dropping funnel is replaced with an open powder funnel. Solid sodium bisulfite powder (Note 4) is added in portions until all the iodine has been reduced, and the reaction mixture is a suspension of pale yellow *m*-nitrophenyl disulfide in an almost colorless solution. The reaction mixture is filtered through a coarse-grade sintered-glass funnel to separate the disulfide, which is washed thoroughly with warm water to remove all inorganic salts. There is obtained 210–221 g. (91–96%) of crude *m*-nitrophenyl disulfide, m.p. 81–83°. This material is purified by dissolving it in approximately 800 ml. of boiling acetone, which is filtered hot and cooled to give 170–183 g. (74–79%) of the disulfide in the form of pale yellow prisms, m.p. 82–83°. By concentration of the mother liquor an additional 30–40 g. (13–17%) of disulfide, m.p. 82–83°, is obtained, so that the total yield of satisfactory product is 200–210 g. (86–91%).

2. Notes

1. Eastman Kodak white label *m*-nitrobenzenesulfonyl chloride was used.
2. Reagent grade hydriodic acid was generally employed, but material of lower purity may be used without decreasing the yield. The calculated amount of 45–47% hydriodic acid may also be employed[2] with only a slight diminution in yield.
3. The reaction of the hydriodic acid with *m*-nitrobenzenesulfonyl chloride is

mildly exothermic, and iodine crystals precipitate as the reaction proceeds.
4. Approximately 3 lb. of sodium bisulfite is required to reduce the iodine. Technical grade bisulfite may be used satisfactorily. Caution should be observed in adding the bisulfite, since evolution of sulfur dioxide can cause excessive foaming. This foaming occurs a short time after each addition and is most noticeable when the iodine is almost neutralized. Iodine and product clinging to the upper walls of the flask and in the condenser may be conveniently rinsed into the reaction mixture with a stream of water from a wash bottle.

3. Discussion

The described method of preparation of *m*-nitrophenyl disulfide is essentially that of Foss and co-workers[2] and is a modification of that reported by Ekbom.[3] The disulfide has been prepared by reaction of potassium ethyl xanthate with *m*-nitrobenzenediazonium chloride solution, followed by hydrolysis to yield the mercaptan, which is subsequently oxidized with potassium ferrocyanide or dilute nitric acid to the disulfide.[4]

The usual method of preparing aromatic disulfides is to treat an aryl halide with Na_2S_2.[5] However, this method is limited to compounds where the halogen is strongly activated by electronegative groups (for example, *o*- or *p*-nitrochlorobenzene). The reaction of diazonium salts with xanthate is unsatisfactory for large-scale preparations because dilute solutions must be employed to reduce the hazard of explosion. Aromatic sulfonyl chlorides (not containing nitro groups) are also reduced with zinc and mineral acid to mercaptans,[6] which must be subsequently oxidized to the disulfide. The present method has been used to prepare nitronaphthalene disulfides,[7,8] naphthalene disulfide, and phenyl disulfide[8] and should be applicable to the preparation of any symmetrical aromatic disulfides containing substituents stable to hydriodic acid.

4. Use of *m*-Nitrophenyl Disulfide

The disulfides are useful intermediates in the preparation of sulfenyl chlorides.[2,9]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

o- or p-nitrochlorobenzene

nitric acid (7697-37-2)

sulfur dioxide (7446-09-5)

sodium bisulfite, sodium bisulfite powder (7631-90-5)

iodine (7553-56-2)

acetone (67-64-1)

zinc (7440-66-6)

hydriodic acid (10034-85-2)

potassium ferrocyanide

potassium ethyl xanthate (140-89-6)

xanthate

phenyl disulfide (882-33-7)

naphthalene disulfide

m-nitrobenzenediazonium chloride

m-Nitrophenyl disulfide, Disulfide, bis-(m-nitrophenyl) (537-91-7)

m-nitrobenzenesulfonyl chloride (121-51-7)

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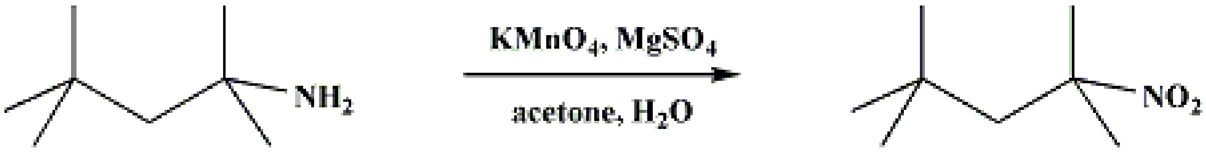
Organic Syntheses, CV 5, 845

4-NITRO-2,2,4-TRIMETHYLPENTANE

[Pentane, 2,2,4-trimethyl-4-nitro-]



Submitted by Nathan Kornblum and Willard J. Jones[1].
Checked by William G. Dauben and Paul R. Resnick.

1. Procedure

A solution of 25.8 g. (0.20 mole) of 4-amino-2,2,4-trimethylpentane (*tert*-octylamine) (Note 1) in 500 ml. of C.P. acetone is placed in a 1-l. three-necked flask equipped with a "Tru-Bore" stirrer and a thermometer and is diluted with a solution of 30 g. of magnesium sulfate (Note 2) in 125 ml. of water. Potassium permanganate (190 g., 1.20 moles) is added to the well-stirred reaction mixture in small portions over a period of about 30 minutes (Note 3). During the addition the temperature of the mixture is maintained at 25–30° (Note 4), and the mixture is stirred for an additional 48 hours at this same temperature (Note 5). The reaction mixture is stirred under water-aspirator vacuum at an internal temperature of about 30° until most of the acetone is removed (Note 6). The resulting viscous mixture is steam-distilled; approximately 500 ml. of water and a pale-blue organic layer are collected. The distillate is extracted with pentane, the extract is dried over anhydrous sodium sulfate, and the pentane is removed by distillation at atmospheric pressure. The residue is distilled through a column (Note 7) at reduced pressure to give 22–26 g. (69–82%) of colorless 4-nitro-2,2,4-trimethylpentane, b.p. 53–54°/3 mm., n_D^{28} 1.4314, m.p. 23.5–23.7°.

2. Notes

1. The *tert*-octylamine employed was redistilled commercial-grade material, b.p. 140°/760 mm., n_D^{20} 1.4240.
2. The magnesium sulfate was purified dried powder of J. T. Baker Chemical Co. This is approximately 70% magnesium sulfate and 30% water.
3. Good agitation prevents the permanganate from caking on the bottom of the flask. The formation of a cake results in local overheating and consumption of the permanganate as mentioned in (Note 4).
4. If a constant-temperature bath is not available, a bucket of water, initially at 25°, serves to dissipate the heat of reaction. At higher temperatures the potassium permanganate is rapidly consumed, presumably by reaction with the acetone.

5. At the end of the reaction time there was no unreacted amine as shown by the following test: A 10-ml. aliquot was filtered through "Supercel" to remove the manganese dioxide, and the filtrate was added to a mixture of 25 ml. of benzene and 25 ml. of water. Extraction of the benzene layer with 10% hydrochloric acid, followed by the addition of sodium hydroxide, gave no oil layer or characteristic odor of the free amine.
6. If agitation becomes difficult during the concentration, 100 ml. of water can be added to give a more fluid mixture.
7. A 60-cm. × 1-cm. externally heated column packed with 4-mm. glass helices and equipped with a total-reflux variable take-off head was used.

3. Discussion

The procedure described is that of Kornblum, Clutter, and Jones.[2] 4-Nitro-2,2,4-trimethylpentane has been prepared previously, in low yield, by allowing isoöctane to react with concentrated nitric acid in a sealed tube at elevated temperature.[3]

4. Merits of the Preparation

This is a general method of preparing trialkylnitromethanes from the corresponding (trialkylmethyl) amines.[2,4] Table I lists seven prepared in this way. The procedure is simple and reliable, and the yields of product are high. Other methods give mixtures of products and low yields of nitro compounds and are inconvenient to perform.

TABLE I SYNTHESIS OFTRIALKYLNITROMETHANES, R_3CNO_2

Nitro Compound	Yield, %
2-Nitro-2-methylpropane	83
2-Nitro-2,3-dimethylbutane	71
2-Nitro-2,4-dimethylpentane	82
1-Nitro-1-methylcyclopentane	72
1-Nitro-1-methylcyclohexane	73
1-Nitro-1,4-dimethylcyclohexane	70
1,8-Dinitro-*p*-methane	61

[a] This oxidation was carried out in water.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 355
- Org. Syn. Coll. Vol. 6, 803

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

1,8-Dinitro-p-methane

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

sodium hydroxide (1310-73-2)

nitric acid (7697-37-2)

potassium permanganate (7722-64-7)

sodium sulfate (7757-82-6)

acetone (67-64-1)

manganese dioxide (1313-13-9)

Pentane (109-66-0)

magnesium sulfate (7487-88-9)

1-Nitro-1-methylcyclohexane

4-Nitro-2,2,4-trimethylpentane, Pentane, 2,2,4-trimethyl-4-nitro- (5342-78-9)

4-amino-2,2,4-trimethylpentane (107-45-9)

2-Nitro-2-methylpropane (594-70-7)

2-Nitro-2,3-dimethylbutane

2-Nitro-2,4-dimethylpentane

1-Nitro-1-methylcyclopentane (30168-50-4)

1-Nitro-1,4-dimethylcyclohexane

tert-octylamine

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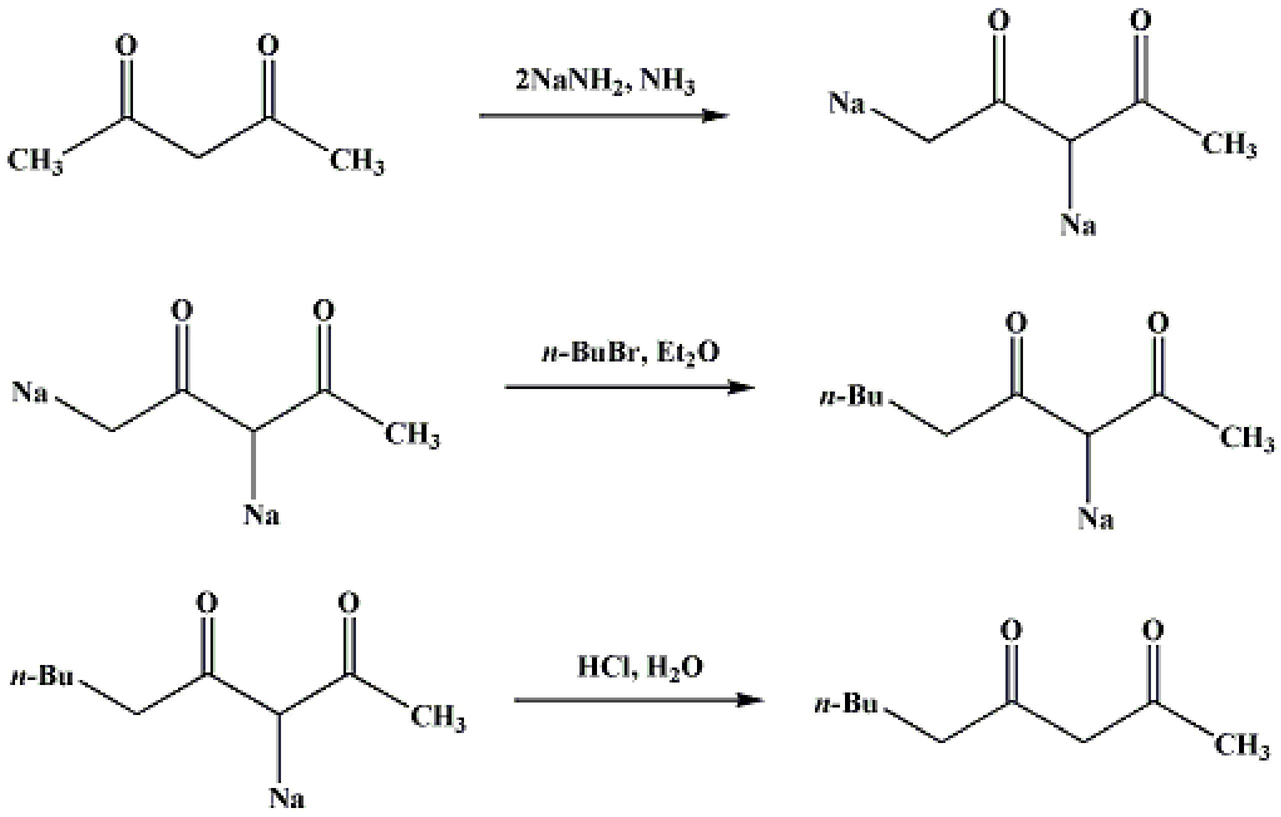
Organic Syntheses, *CV 5, 848*

2,4-NONANEDIONE



Submitted by K. Gerald Hampton, Thomas M. Harris, and Charles R. Hauser[1].
Checked by Eugene Gosselink and Peter Yates.

1. Procedure

Caution! This preparation should be carried out in a hood to avoid exposure to ammonia.

A suspension of sodium amide (1.10 moles) in liquid ammonia is prepared in a 1-l. three-necked flask equipped with an air condenser (Note 1), a ball-sealed mechanical stirrer, and a glass stopper. In the preparation of this reagent commercial anhydrous liquid ammonia (800 ml.) is introduced from a cylinder through an inlet tube. To the stirred ammonia is added a small piece of sodium. After the appearance of a blue color a few crystals of ferric nitrate hydrate (about 0.25 g.) are added, followed by small pieces of freshly cut sodium until 25.3 g. (1.10 moles) has been added. After the sodium amide formation is complete (Note 2), the glass stopper is replaced by a pressure-equalizing dropping funnel containing 60.0 g. (0.600 mole) of 2,4-pentanedione (Note 3) in 40 ml. of anhydrous ether. The top of the addition funnel is fitted with a nitrogen inlet tube. The reaction flask is immersed at least 3 in. into a dry ice-acetone bath (Note 4), and simultaneously the slow introduction of dry nitrogen through the inlet tube is begun. After the reaction mixture is thoroughly cooled (about 20 minutes), 2,4-pentanedione is added intermittently in small portions (Note 4) over 10 minutes. The cooling bath is removed. After 20 minutes the nitrogen purge is stopped, and 68.5 g. (0.500 mole) of 1-bromobutane (Note 5) in 40 ml. of anhydrous ether is introduced dropwise during 10–20 minutes. The addition funnel is rinsed with a small volume of anhydrous ether,

which is added to the reaction mixture. After 30 minutes 400 ml. of anhydrous ether is added, and the ammonia is removed by cautious heating on the steam bath. Crushed ice (200 g.) is added causing a thick slurry to form. Next a mixture of 60 ml. of concentrated hydrochloric acid and 10 g. of crushed ice is added. The reaction mixture is stirred until all solids are dissolved and then is transferred to a separatory funnel, the flask being washed with a little ether and dilute hydrochloric acid. The ethereal layer is separated, and the aqueous layer (Note 6) is further extracted three times with 100-ml. portions of ether. The combined ethereal extracts are dried over anhydrous magnesium sulfate. After filtration and removal of the solvent the residue is distilled through a 12-in. Vigreux column to give 63.0–63.6 g. (81–82%) of 2,4-nonanedione, b.p. 100–103° (19 mm.), as a colorless liquid (Note 7).

2. Notes

1. The checkers used a dry ice condenser during the introduction of ammonia to the reaction flask and replaced it with an air condenser before the addition of sodium.
2. Conversion to sodium amide is indicated by the disappearance of the blue color. This generally requires about 20 minutes.
3. Eastman Organic Chemicals 2,4-pentanedione was dried over potassium carbonate and distilled before use, the fraction boiling at 133–135° at atmospheric pressure being used.
4. The addition of 2,4-pentanedione to liquid ammonia is a highly exothermic process. Also, ammonia vapor reacts with the β-diketone to produce an insoluble ammonium salt, which tends to clog the tip of the addition funnel. Cooling the reaction mixture in dry ice-acetone reduces the vigor of the reaction and minimizes the clogging of the addition funnel. The 2,4-pentanedione should be added in spurts which fall on the surface of the reaction mixture rather than on the wall of the flask.
5. Eastman Organic Chemicals 1-bromobutane was used without purification.
6. The aqueous layer should be acidic to litmus paper. If it is basic, indicating that the ammonia was not completely removed from the reaction mixture, more hydrochloric acid should be added until an acidic test is obtained.
7. A small forerun of 2,4-pentanedione, b.p. 32–100° (19 mm.), is obtained. The purity of the product may be demonstrated by gas chromatography on a 2-ft. column packed with silicone gum rubber (F and M Scientific Co., Avondale, Pennsylvania) programmed linearly from 100° to 300°. The chromatogram obtained is a single sharp peak. The three conceivable impurities, 2,4-pentanedione, 3-butyl-2,4-pentanedione, and 6,8-tridecanedione, would have been observed under these conditions if they had been present.

3. Discussion

The method described is that of Hampton, Harris, and Hauser[2] and is an improvement over the earlier procedures[3,4] of Hauser and co-workers, which employed potassium amide. 2,4-Nonanedione has been prepared by the condensation of ethyl caproate with acetone in the presence of sodium hydride (54–80%),[5,6] and by the acylation of ethyl acetoacetate followed by cleavage and decarboxylation (51%).[7] Other preparations include the acetylation of 2-heptanone with ethyl acetate and sodium amide (61%),[8] the acetylation of 1-heptyne with

acetic anhydride and boron fluoride (42%),[9] and the sulfuric acid-catalyzed hydration of 3-nonyn-2-one.[10] Low yields (6–7%) of 2,4-nonanedione were obtained by the acetylation of 2-heptanone with acetic anhydride and boron fluoride,[11] and by the pyrolysis of the enol acetates of 2-heptanone.[12] The last two methods afforded substantial amounts of the isomeric 3-butyl-2,4-pentanedione.

4. Merits of the Preparation

This procedure represents a novel, convenient, and fairly general method for preparing higher β-diketones. By this method the submitters have alkylated 2,4-pentanedione at the 1-position with methyl iodide to give 2,4-hexanedione (59–65%) and with *n*-octyl bromide to give 2,4-tridecanedione (66–79%).[2] Alkylation at the 3-position is not observed, and little or no 1,5-dialkylation occurs. By similar procedures employing potassium amide, 2,4-pentanedione has been alkylated with benzyl chloride,[3,4] allyl bromide,[4] *n*-heptyl bromide,[4] and isopropyl bromide.[4] Numerous other β-diketones have been alkylated similarly. They include benzoylacetone,[3] 6-phenyl-2,4-hexanedione,[4,13] 2-acetylclopentanone,[13] 2-acetylcyclohexanone,[13] and 2,4-tridecanedione.[4] In contrast to 2,4-pentanedione, these β-diketones may be added readily to the liquid ammonia solution without employing a dry ice cooling bath.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

2-acetylclopentanone

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ethyl acetate (141-78-6)

ether (60-29-7)

acetic anhydride (108-24-7)

1-bromobutane (109-65-9)

n-octyl bromide (111-83-1)

Isopropyl bromide (75-26-3)

nitrogen (7727-37-9)

acetone (67-64-1)

sodium (13966-32-0)

benzyl chloride (100-44-7)

Methyl iodide (74-88-4)

Ethyl acetoacetate (141-97-9)

ethyl caproate (123-66-0)

2-Heptanone (110-43-0)

1-heptyne (628-71-7)

magnesium sulfate (7487-88-9)

Ammonium (14798-03-9)

boron fluoride (7637-07-2)

n-heptyl bromide (629-04-9)

sodium amide (7782-92-5)

2,4-pentanedione (123-54-6)

benzoylacetone (93-91-4)

sodium hydride (7646-69-7)

potassium amide

ferric nitrate hydrate

2,4-Nonanedione (6175-23-1)

6,8-tridecanedione

3-nonyn-2-one

3-Butyl-2,4-pentanedione (1540-36-9)

2,4-hexanedione (3002-24-2)

2,4-tridecanedione

6-phenyl-2,4-hexanedione

2-acetylcyclohexanone (874-23-7)

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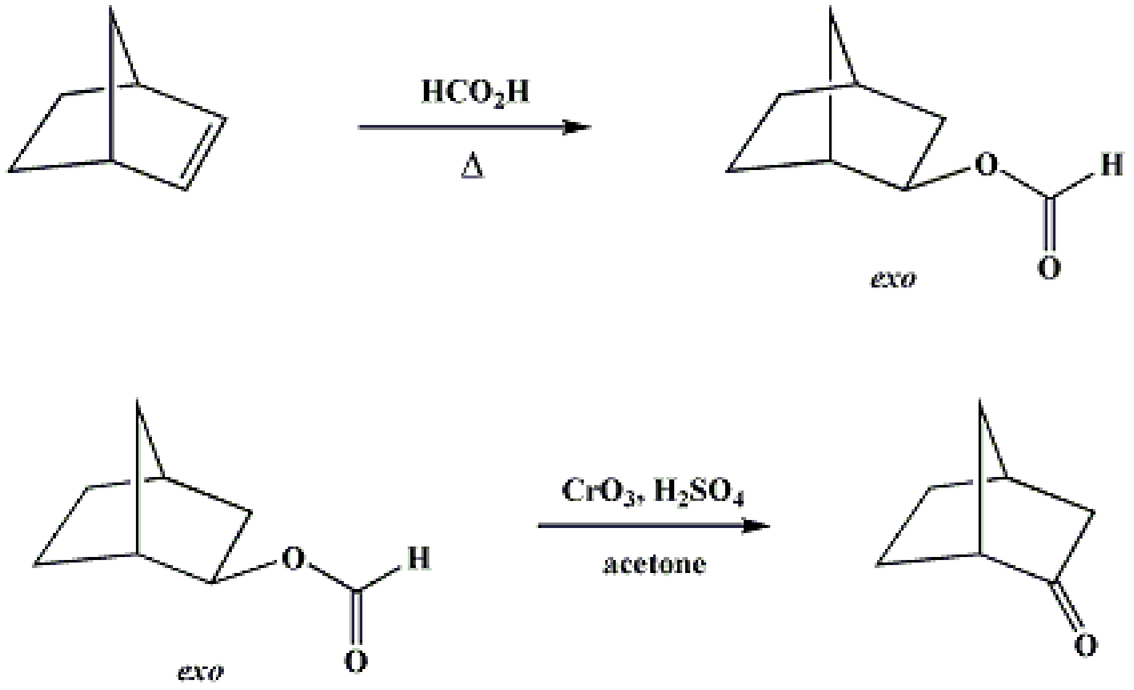
Organic Syntheses, CV 5, 852

2-NORBORNANONE

[Norcamphor]



Submitted by Donald C. Kleinfelter and Paul von R. Schleyer[1].
Checked by William E. Parham, Wayland E. Noland, and Lynette E. Christensen.

1. Procedure

A. *2-exo-Norbornyl formate*. Approximately 800 g. (17.4 4 moles) of 98–100% formic acid (Note 1) is added to 400 g. (4.25 moles) of nobornene (Note 2) in a 2-l. round-bottomed flask equipped with a condenser, and the mixture is boiled under reflux for 4 hours (Note 3). The dark solution is cooled and the flask arranged for distillation using a 30-cm. Vigreux column. The excess formic acid is removed under reduced pressure (b.p. 26–30°/21–30 mm.). Distillation of the residue then gives a forerun of about 100 ml. of a mixture of formic acid and ester followed by about 485 g. of 2-*exo*-norbornyl formate, a colorless oil, b.p. 65–67°/14–16 mm. n_D^{25} 1.4594–1.4597. Another 55–65 g. of ester is obtained by adding water to the forerun, extracting with 30–60° petroleum ether, washing the extracts with dilute sodium carbonate solution, drying over sodium sulfate, and distilling. The total yield is 540–550 g. (90.5–92.5%) (Note 4).

B. *2-Norbornanone*. A solution of 510 g. (3.64 moles) of 2-*exo*-norbornyl formate in 1.5 l. of reagent grade acetone is contained in a 5-l. three-necked flask equipped with a thermometer, stirrer, and dropping funnel containing 8*N* chromic acid solution (Note

5). The flask is cooled with an ice bath and the oxidant is added at a rate such that the reaction temperature is maintained at 20–30°. Approximately 1870 ml. of oxidant solution is required, completion of the reaction being shown by the persistence of the brownish orange color. A slight excess of oxidant is added, and the solution is stirred overnight at room temperature. Solid sodium bisulfite is added in portions to reduce the excess oxidant.

The reaction mixture is poured into a large separatory funnel. The dark green chromic sulfate sludge, which has formed during the course of the reaction, is separated either by decantation and washing or by drawing it off from the bottom of the funnel. The acetone solution is washed three times with 200–250 ml. portions of an aqueous saturated potassium carbonate solution and finally is dried over anhydrous potassium carbonate. The acetone is removed by distillation through a 30-cm. Vigreux column at atmospheric pressure; benzene may be added near the end to assist in the removal of water by azeotropic distillation. When it is observed that the distillation of solvent is complete and the considerably hotter vapors of product begin to ascend the column, the condenser is removed from the top and replaced by an adapter and collection flask immersed in ice water. The adapter is heated and maintained above 100° by a free flame until the product begins to distil (Note 6). 2-Norbornanone, 335–350 g. (83–87%), distils at 170–173° and crystallizes immediately in the collection flask. The crystals melt at 90–91° (Note 7) and are sufficiently pure for most preparative purpose (Note 8).

2. Notes

1. Baker and Adamson 98–100% formic acid was used.
2. Prepared as described in *Org. Syntheses*, Coll. Vol. **4**, 738 (1963).
3. Norbornene is not soluble in cold formic acid; initially there are two layers. As heat is applied to the flask, solution occurs and the reaction becomes quite exothermic. It is recommended that a splash trap be mounted at the top of the condenser and that an ice bath be nearby in case the refluxing becomes too rapid. *Caution! Formic acid causes severe burns!*
4. Quite pure 2-*exo*-norborneol, m.p. 127–128°, can be prepared by saponification of 2-*exo*-norbornyl formate in an aqueous ethanolic solution of potassium hydroxide. The product can be isolated in about 85% yield by distillation and boils at 178–179°.
5. The 8*N* chromic acid solution[2] is prepared by dissolving 534 g. of chromium trioxide in ice water, adding 444 ml. of conc. sulfuric acid carefully, and diluting to 2 l. with water.
6. The product solidifies readily. Care should be taken to prevent clogging of the adapter. Once begun, there is no difficulty if the distillation proceeds smoothly to completion.
7. The melting points given in the literature vary from 90–91° (Ref. [3]) to 95.5° (Ref. [4]). Pure 2-norbornanone, m.p. 97.2–98.0°, may be made by regeneration from its semicarbazone derivative, m.p. 196.5–197.6°.

8. Gas chromatographic analysis shows this material to have a purity of about 96%. Besides a small amount of water (up to 0.5%) there are two minor impurities. Neither 2-*exo*-norbornyl formate nor 2-*exo*-norbornyl is present, however. Oxidation of 2-*exo*-norbornanol with chromic acid, under a variety of conditions, gives 2-norbornanone contaminated with some starting material.

3. Discussion

2-Norbornanone is generally prepared from the Diels-Alder adduct of cyclopentadiene and vinyl acetate by hydrogenation, saponification, and oxidation with chromic acid in acetic acid solution.[5] The present procedure, which gives higher over-all yields in fewer steps, makes use of the superior solvent, acetone, for mild chromic acid oxidations[2] and of the observation that formate esters of secondary alcohols can be oxidized directly to ketones.[6]

4. Merits of Preparation

2-Norbornanone is a useful starting material for various bicyclic derivatives of theoretical interest. The present procedure provides a convenient method for its preparation and illustrates a general method for the oxidation of formate esters to ketones.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 845

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

nobornene

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

Benzene (71-43-2)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

formic acid (64-18-6)

sodium bisulfite (7631-90-5)

acetone (67-64-1)

potassium hydroxide (1310-58-3)

chromic acid (7738-94-5)

chromic sulfate (15244-38-9)

chromium trioxide (1333-82-0)

vinyl acetate (108-05-4)

CYCLOPENTADIENE (542-92-7)

Norbornene

2-Norbornanone, Norcamphor (497-38-1)

2-exo-norbornyl (30967-37-4)

2-exo-Norbornyl formate (41498-71-9)

2-exo-norborneol, 2-exo-norbornanol (1632-68-4)

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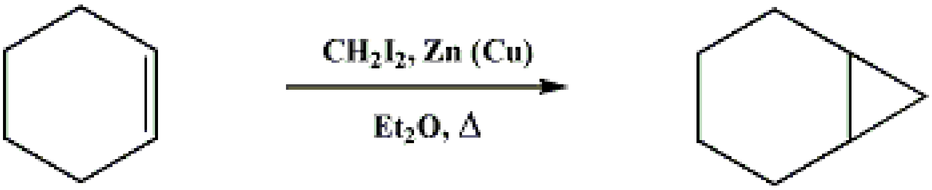
Organic Syntheses, CV 5, 855

NORCARANE

[Bicyclo[4.1.0]heptane]



Submitted by R. D. Smith and H. E. Simmons[1].
Checked by William E. Parham and M. D. Bhavsar.

1. Procedure

A. *Zinc-copper couple*. In a 500-ml. Erlenmeyer flask fitted with a magnetic stirrer are placed 49.2 g. (0.75 g. atom) of zinc powder (Note 1) and 40 ml. of 3% hydrochloric acid. The mixture is stirred rapidly for 1 minute, then the supernatant liquid is decanted. In a similar manner, the zinc powder is washed successively with three additional 40-ml. portions of 3% hydrochloric acid, five 100-ml. portions of distilled water, two 75-ml. portions of 2% aqueous copper sulfate solution, five 100-ml. portions of distilled water, four 100-ml. portions of absolute ethanol, and five 100-ml. portions of absolute ether (Note 2). The couple is finally transferred to a Büchner funnel, washed with additional anhydrous ether, covered tightly with a rubber dam, and suction-dried until it reaches room temperature. The zinc-copper couple is stored overnight in a vacuum desiccator over phosphorus pentoxide and is then ready for use in the preparation of norcarane (Note 3).

B. *Norcarane*. In a 500-ml. round-bottomed flask fitted with a magnetic stirrer and a reflux condenser protected by a drying tube filled with Drierite are placed 46.8 g. (0.72 g. atom) of zinc-copper couple and 250 ml. of anhydrous ether. A crystal of iodine is added, and the mixture is stirred until the brown color has disappeared (Note 4). A mixture of 53.3 g. (0.65 mole) of cyclohexene and 190 g. (0.71 mole) of methylene iodide is added in one portion (Note 5). The reaction mixture is then heated under gentle reflux with stirring. After 30–45 minutes, a mildly exothermic reaction occurs which may require cessation of external heating. After the exothermic reaction has subsided (approximately 30 minutes), the mixture is stirred under reflux for 15 hours. At the end of this time, most of the gray couple has been converted to finely divided copper. The ether solution is decanted (Note 6) from the copper and unreacted couple, which are then washed with two 30-ml. portions of ether. The washes are combined with the bulk of the solution and shaken with two 100-ml. portions of saturated ammonium chloride solution (Note 7), 100 ml. of saturated sodium bicarbonate solution, and 100 ml. of water. The ether solution is dried over anhydrous magnesium

sulfate and filtered. The ether is distilled through a 20 × 2-cm. column packed with glass helices. The residue is distilled through a 45-cm. spinning-band column[2] to give 35–36 g. (56–58%) of norcarane, b.p. 116–117°, n_D^{25} 1.4546 (Note 8).

2. Notes

1. Mallinckrodt A. R. zinc dust was found satisfactory for this preparation. The checkers used Merck zinc dust but found it necessary to start with 51 g. of zinc in order to obtain sufficient couple for the next step.
2. The washings with hydrochloric acid should be done rapidly to avoid adsorption of bubbles of hydrogen on the zinc which make subsequent washings more difficult. The use of a magnetic stirrer greatly facilitates the washings. The absolute ethanol and absolute ether washings are decanted directly on a Büchner funnel to prevent loss of the couple.
3. This method of preparing zinc-copper couple is essentially that of Shank and Shechter.[3] An equally active couple can be prepared by reduction of cupric oxide in the presence of zinc powder.[4] Mallinckrodt A. R. wire-form cupric oxide (30 g.) is ground to a powder in a mortar and mixed with 240 g. of Mallinckrodt A. R. zinc dust. The mixture is placed in a Vycor combustion boat lined with copper foil, and a thermocouple is imbedded in the powder. The boat is placed in a Vycor tube heated by a muffle furnace. A mixed gas (hydrogen, 65 l. per hour; nitrogen, 25 l. per hour) is passed through the tube while the temperature is raised to 500° during 4 hours. The mixture is kept at 500° for 30 minutes, and the tube is then allowed to cool to room temperature in a hydrogen atmosphere. The zinc-copper couple is obtained as dark gray lumps, which are ground to a fine powder in a mortar before use. In some instances, there is also found in the mixture a small amount of material which has apparently melted and agglomerated during heating. This shiny, metallic material is easily separated from the powdered couple and is not used in the preparation of norcarane.
4. The addition of iodine appears to promote the subsequent reaction of the zinc-copper couple with methylene iodide.
5. Commercial cyclohexene (Eastman Kodak) was distilled and passed over a column of activated alumina just before use. Methylene iodide (Matheson, Coleman and Bell) was distilled under reduced pressure, b.p. 50–51°/7 mm., and was stored in a brown bottle over iron wire.
6. The checkers filtered the solution because the finely divided copper and unreacted couple did not settle completely.
7. Care must be taken when adding the ammonium chloride solution to the ether solution since considerable heat is generated.
8. About 10–12 g. of cyclohexene, b.p. 82–84°, is recovered. The intermediate fraction, b.p. 84–116°, amounts to 1.5–2.5 g., and 10–12 g. of a dark residue remains in the still pot.

3. Discussion

This method is generally applicable to the stereospecific synthesis of cyclopropane derivatives from a large variety of substituted olefins.[4]

Three methods have been employed to generate iodomethylzinc iodide, the intermediate active in cyclopropanation: (1)reaction of methylene iodide with a zinc-copper couple in an ether solvent;[4] (2) reaction of diazomethane with zinc iodide in an ether solvent;[5] (3) reaction of methylene iodide with diethylzinc in ether or hydrocarbon solvents.[6] Method (1) has been used more extensively to prepare cyclopropanes from olefins because it is generally the simplest, most convenient, and most economical variation when applicable.[7] An active zinc-copper couple has been reported that is easily prepared and is recommended for the cyclopropanation reaction.[8]

Norcarane has been prepared by the reduction of 7,7-dichloronorcarane with sodium and alcohol,[9] and by the light-catalyzed reaction of diazomethane with cyclohexene.[9] The reaction of cyclohexene with methylene iodide and zinc-copper couple represents the most convenient preparation of norcarane which is of high purity.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 327
- Org. Syn. Coll. Vol. 8, 274

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

zinc-copper couple

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ether (60-29-7)

ammonium chloride (12125-02-9)

hydrogen (1333-74-0)

sodium bicarbonate (144-55-8)

Cyclohexene (110-83-8)

nitrogen (7727-37-9)

copper sulfate (7758-98-7)

copper (7440-50-8)

iodine (7553-56-2)

zinc, zinc powder (7440-66-6)

sodium (13966-32-0)

cupric oxide (1317-38-0)

Methylene iodide (75-11-6)

diethylzinc (557-20-0)

cyclopropane (75-19-4)

magnesium sulfate (7487-88-9)

Diazomethane (334-88-3)

zinc iodide

Norcarane, Bicyclo[4.1.0]heptane (286-08-8)

iodomethylzinc iodide

7,7-dichloronorcarane (823-69-8)

phosphorus pentoxide (1314-56-3)

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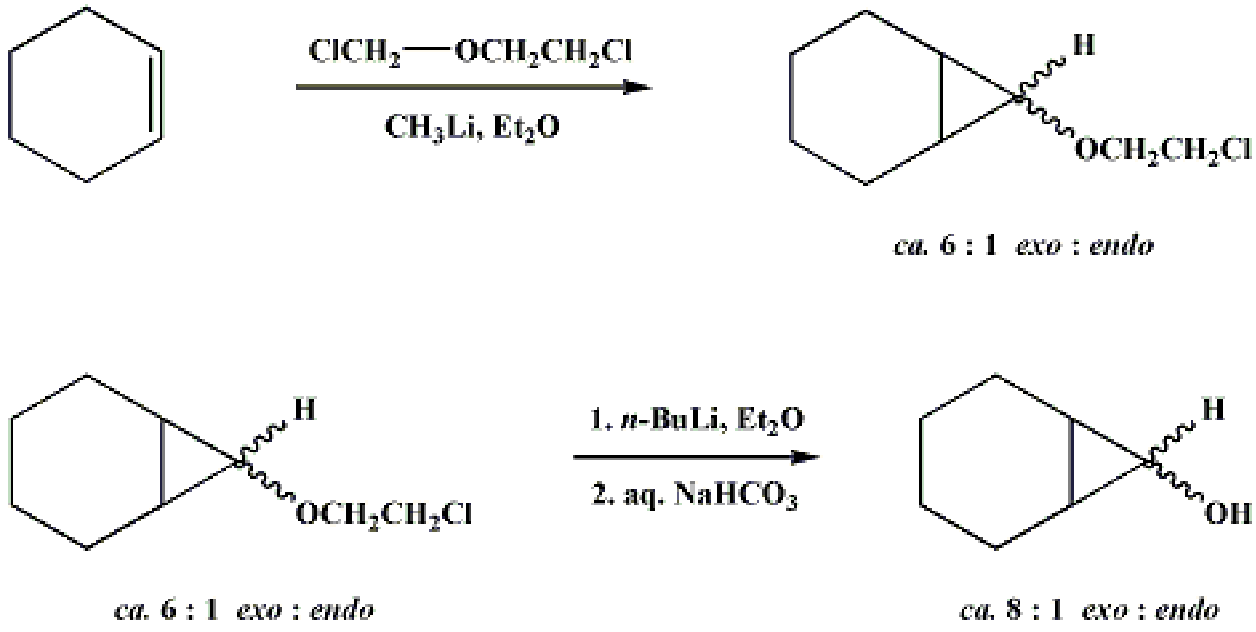
Organic Syntheses, CV 5, 859

exo/endo-7-NORCARANOL



Submitted by U. Schöllkopf, J. Paust, and M. R. Patsch[1].
Checked by William G. Dauben, Michael H. McGann, and Noel Vietmeyer.

1. Procedure

A. *exo/endo-7-(2-Chloroethoxy)bicyclo[4.1.0]heptane*. A 2-l., three-necked, round-bottomed flask is equipped with a sealed stirrer, a pressure-equalizing dropping funnel, and a condenser fitted with a nitrogen-inlet tube (Note 1). The flask is flushed with dry nitrogen, and to it are added 500 ml. of cyclohexene (Note 2) and 49.0 g. (0.300 mole) of dichloromethyl 2-chloroethyl ether (Note 3). To the stirred solution at room temperature is added dropwise 430 ml. (0.47 mole) of a 1.1*N* ethereal solution of methyllithium (Note 4) at a rate adequate to maintain gentle reflux of the ether; the addition requires *ca.* 4 hours (Note 5). The reaction mixture is poured into 1.5 l. of ice water, the aqueous layer is separated, and the organic layer is extracted with four 300-ml. portions of water and dried over anhydrous sodium sulfate. The solvents are removed by distillation through a 10-cm. Vigreux column (Note 6), and the residue is distilled under reduced pressure to yield 21–29 g. (40–56%) of *exo/endo*-7-(2-chloroethoxy)bicyclo[4.1.0]heptane, b.p. 98–101° (10 mm.). This material is sufficiently pure for the next step (Note 7).

B. *exo/endo-7-Norcaranol*. A 500-ml. three-necked flask equipped with a magnetic stirrer, a pressure-equalizing dropping funnel, and a condenser fitted with a nitrogen-inlet tube (Note 1) is flushed with nitrogen, and a solution of 20.0 g. (0.115 mole) of *exo/endo*-7-(2-chloroethoxy)bicyclo[4.1.0]heptane in 150 ml. of dry ether is added. To this solution is added dropwise at room temperature 280 ml. (0.45 mole) of a 1.6*N*

solution of *n*-butyllithium in hexane over a 30- to 45-minute period (Note 5). The mixture is poured into 800 ml. of ice-cold, saturated, aqueous sodium bicarbonate, and the aqueous phase is separated and extracted with four 150-ml. portions of ether. The organic solutions are combined and dried over anhydrous sodium sulfate, and the solvents are removed by distillation through a 10-cm. Vigreux column at a maximum bath temperature of 65°. The residue is distilled under reduced pressure to yield 11.6–12.3 g. (90–95%) of *exo/endo*-7-norcaranol, b.p. 80–85° (10 mm.) (Note 8) and (Note 9).

2. Notes

1. The nitrogen-inlet system described by Johnson and Schneider[2] is satisfactory.
2. The cyclohexene was dried over potassium hydroxide pellets and distilled from sodium before use.
3. The checkers prepared this ether in the following manner. 2-Ethoxy-1,3-dioxolane was prepared in 82% yield from ethylene glycol and ethyl orthoformate and treated with acetyl chloride to give 2-chloroethyl formate by the procedures of Baganz and Domaschke;[3] the overall yield was 56–60%. The formate was converted to dichloromethyl 2-chloroethyl ether with phosphorus pentachloride by the procedure of Gross, Rieche, and Höft,[4] and the product was distilled through a 10-cm. column containing glass helices; b.p. 107–111° (110 mm.); yield 85%.
4. The methyllithium must be prepared from methyl iodide because the presence of the iodide anion is essential. The submitters prepared methyl lithium in the following manner. Methyliodide (425.7 g., 3.00 moles) was added with stirring to 48 g. (7.0 g. atoms) of lithium in 2.5 l. of ether under nitrogen at a rate adequate to maintain gentle reflux of the ether. After 24 hours the solution of methyllithium was decanted into a storage vessel filled with nitrogen. The concentration was estimated in the usual way by hydrolysis of an aliquot and titration with 0.1*N* hydrochloric acid.
5. The addition of the organolithium solution is continued until a positive Gilman test[5] is obtained.
6. Isopropyl 2-chloroethyl ether, b.p. 118–121°, is formed in variable amounts as a by-product.
7. The *exo/endo* ratio is 6:1; the *exo* and *endo* isomers show characteristic triplets in their n.m.r. spectra at δ 2.9 and 3.1 p.p.m., respectively.
8. The *exo/endo* ratio is 8:1; the *exo* and *endo* isomers show characteristic triplets in their n.m.r. spectra at δ 3.0 and 3.25 p.p.m., respectively.
9. In some runs, *exo*-7-norcaranol, m.p. 57–58°, crystallized in the condenser or in the receiver.

3. Discussion

This method for the preparation of *exo/endo*-7-norcaranol is an adaptation of that described by Schöllkopf, Paust, Al-Azrak, and Schumacher.[6] The method has been used by the submitters for the preparation of the following cyclopropanols: *exo/endo*-6-hydroxybiclo[3.1.0]hexane, *exo/endo*-8-hydroxybicyclo[5.1.0] octane, *exo/endo*-9-hydroxybicyclo[6.1.0]nonane, 2,2-dimethylcyclopropanol, 2,2,3,3-tetramethylcyclopropanol, *trans*-2,3-dimethylcyclopropanol, *cis*-2,3-dimethyl-*cis/trans*-cyclopropanol, *cis/trans*-2,2,3-trimethylcyclopropanol, and *cis/trans*-2-phenylcyclopropanol.

The principal disadvantage of this procedure is that the olefin must be used in at least three- to fourfold excess in order to obtain reasonable yields. In case of rare olefins, or of olefins containing groups such as the carbonyl group which add organolithium compounds, other methods[7,8] might be more advantageous. The method is also limited to the preparation of secondary cyclopropanols.

The most satisfactory procedure for obtaining cyclopropanol itself is that of Cottle[7,9] which is also recommended for the synthesis of 1-arylcyclopropanols.[7] 1-Alkylcyclopropanols are best prepared via the corresponding acetates which are obtained by the method of Freeman[10] that involves thermolysis of a 3-acetoxy-1-pyrazolin. According to DePuy,[7] cyclopropyl acetates are best cleaved to cyclopropanols by methyllithium. However, the preparation of cyclopropyl acetates is somewhat laborious. It usually involves reactions of an olefin with ethyl diazotate—in this step the olefin must be used in excess, too—followed by a Baeyer-Villiger rearrangement of the corresponding methyl cyclopropyl ketone.[7]

The cyclopropanols, the study of whose chemistry is still in its early stages,[7,8] show promise as useful synthetic intermediates. The chemistry of their derivatives should aid in the understanding of the nature of nucleophilic substitution on three-membered rings.[7,8,11]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 346

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

exo/endo-6-hydroxybiclo[3.1.0]hexane

hydrochloric acid (7647-01-0)

ether (60-29-7)

phosphorus pentachloride (10026-13-8)

acetyl chloride (75-36-5)

sodium bicarbonate (144-55-8)

Cyclohexene (110-83-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

potassium hydroxide pellets (1310-58-3)

sodium (13966-32-0)

ethylene glycol (107-21-1)

Methyl iodide, Methyliodide (74-88-4)

Ethyl orthoformate

lithium (7439-93-2)

n-butyllithium (109-72-8)

hexane (110-54-3)

Methyllithium, methyl lithium (917-54-4)

dichloromethyl 2-chloroethyl ether (13830-34-7)

2-Ethoxy-1,3-dioxolane

2-chloroethyl formate

Isopropyl 2-chloroethyl ether

2,2-dimethylcyclopropanol

2,2,3,3-tetramethylcyclopropanol

cyclopropanol (16545-68-9)

3-acetoxy-1-pyrazolin

exo/endo-7-Norcaranol, exo-7-norcaranol (13830-44-9)

exo/endo-7-(2-Chloroethoxy)bicyclo[4.1.0]heptane

exo/endo-8-hydroxybicyclo[5.1.0] octane

exo/endo-9-hydroxybicyclo[6.1.0]nonane

trans-2,3-dimethylcyclopropanol

cis-2,3-dimethyl-cis/trans-cyclopropanol

cis/trans-2,2,3-trimethylcyclopropanol

cis/trans-2-phenylcyclopropanol

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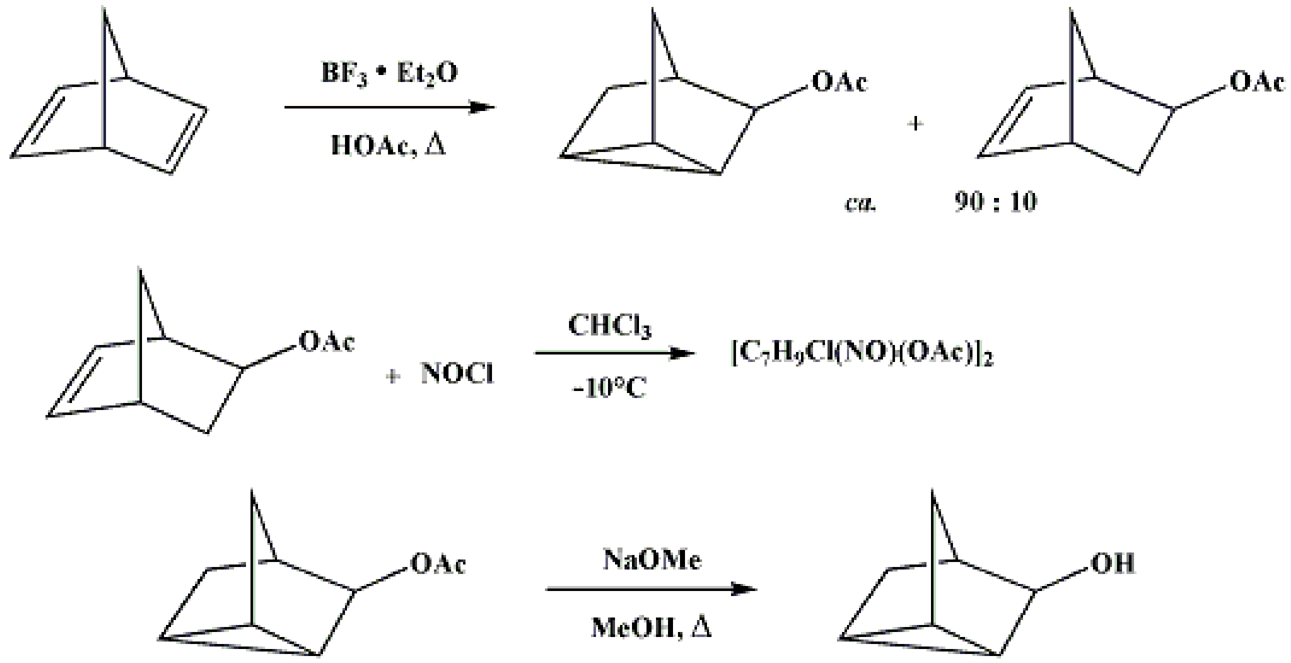
Organic Syntheses, CV 5, 863

NORTRICYCLANOL

[Tricyclo[2.2.1.0^{2,6}]heptan-3-ol]



Submitted by J. Meinwald, J. Crandall, and W. E. Hymans[1].
Checked by J. R. Roland and B. C. McKusick.

1. Procedure

A. *Nortricyclyl acetate*. A mixture of 156 g. (1.70 moles) of bicyclo[2.2.1]hepta-2,5-diene (Note 1), 105 g. (100 ml., 1.75 moles) of glacial acetic acid, and 3 ml. of boron trifluoride etherate (Note 2) is placed in a 500-ml. flask attached to a condenser equipped with a drying tube. The mixture is heated on a steam bath for 6 hours, cooled to room temperature, and diluted with 250 ml. of ether. The ethereal solution is washed successively with two 50-ml. portions of 3*N* ammonia and 50 ml. of water and dried over magnesium sulfate. The ether is removed by distillation through a short column of glass helices, and the dark residue is distilled under reduced pressure to give about 200 g. of a mixture of nortricyclyl acetate and bicyclo[2.2.1]hepta-5-en-2-yl acetate as a colorless liquid, b.p. 85–95° (15 mm.) (Note 3).

The acetate mixture is dissolved in 500 ml. of chloroform (analytical reagent grade) in a 2-l. Erlenmeyer flask equipped with a thermometer and a gas-inlet tube and located in a good hood. *Caution! All operations using nitrosyl chloride should be performed in a good hood.* The solution is cooled to –10° in an ice-salt bath, and nitrosyl chloride (Note 4) is bubbled into the solution with swirling at –10° ± 3° until the color of the solution changes through bright green to a brownish green that indicates excess nitrosyl chloride. A white precipitate begins to form at this point. There is added 500 ml. of 30–60° petroleum ether, and the mixture is cooled at –10° ± 3° for an additional 15 minutes. The precipitated nitrosyl chloride adduct (Note 5) is collected by suction filtration *(Caution! Hood)*. The filtrate is washed successively with two 200-ml. portions of saturated sodium carbonate solution and 500 ml. of saturated sodium chloride and dried over magnesium sulfate. The solvent is removed through a short column of glass helices, and the dark

residue is distilled under reduced pressure *(Caution! (Note 6))* to give 132–167 g. (52–66%) of nortricyclyl acetate as a faintly green liquid, b.p. 83–85° (13 mm.), n^{25}D 1.4673–1.4681 (Note 7).

B. *Nortricyclanol*. The nortricyclyl acetate obtained above is added to a solution of 0.5 g. of sodium in 500 ml. of anhydrous methanol (analytical grade reagent). The solution is heated on a steam bath, and the methanol is slowly distilled through a short column packed with glass helices (Note 8). The residue is cooled, diluted with 250 ml. of 30–60° petroleum ether, and the solution is washed with two 50-ml. portions of water and dried over magnesium sulfate. The solvent is removed by distillation through a short column packed with glass helices, finally at 25° and water-pump pressure. The crude product, which solidifies on cooling, is sublimed at 80° (2 mm.) to yield 84–107 g. (45–57% based on bicycloheptadiene; (Note 9)) of nortricyclanol, m.p. 108–110°. It is pure enough for most purposes. A slightly purer product is obtained by resublimation (Note 10).

2. Notes

1. Bicycloheptadiene supplied by Shell Chemical Corporation can usually be used without purification. If the material is cloudy or contains a precipitate, it should be distilled before being used.
2. The purified grade of Eastman Organic Chemicals is satisfactory. After the procedure had been checked, the submitters found that the use of only 1 ml. of this reagent gave the specified yield more consistently.
3. The exact proportion of unsaturated acetate varies slightly but is typically 10–15% as determined by vapor-phase chromatography.
4. Nitrosyl chloride from the Matheson Company is satisfactory.
5. The adduct may be recrystallized from chloroform to give a white crystalline product, m.p. 152–153°.
6. The hot residue decomposes vigorously with the evolution of irritating gases when opened to the atmosphere. Consequently, the distillation flask should be cooled to room temperature before breaking the vacuum.
7. Vapor-phase chromatographic analysis of this product showed less than 1% of isomeric material.
8. The checkers used a 1.3-cm. × 25-cm. column of helices and removed the solvent over a period of about 5 hours.
9. The yield of nortricyclanol from nortricyclyl acetate is 82–95%.
10. Vapor-phase chromatography shows no detectable impurities under conditions where <1% of isomeric material would be easily visible. A melting point of 108–109° has been reported.[2]

3. Discussion

The addition of carboxylic acids to bicyclo[2.2.1]hepta-2,5-diene has been described by several authors;[3 4 5 6] the method described here is a modification of these procedures. Nortricyclanol has been prepared by the hydration of bicyclo[2.2.1]hepta-2,5-diene[7] and the solvolysis of nortricyclyl[2] and bicyclo[2.2.1]hept-2-en-5-yl[8] halides, as well as by the saponification[3], [9] and transesterification[5] of the corresponding esters. The described conversion of the acetate to the alcohol is patterned after a similar procedure of Hall.[5]

4. Merits of the Preparation

The present preparation affords high-purity nortricyclanol in good yield without the necessity of

tedious purification. It illustrates a convenient way to convert olefins to alcohols and to remove olefinic impurities from alcohols. Nortricyclanol is of current interest in studies of highly strained ring systems. It is readily oxidized to nortricyclanone.[10]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 310
- Org. Syn. Coll. Vol. 5, 866
- Org. Syn. Coll. Vol. 8, 350

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

Nortricyclyl acetate

Nortricyclanol

Nortricyclanone

acetic acid (64-19-7)

ammonia (7664-41-7)

methanol (67-56-1)

ether (60-29-7)

chloroform (67-66-3)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

sodium (13966-32-0)

nitrosyl chloride (2696-92-6)

magnesium sulfate (7487-88-9)

boron trifluoride etherate (109-63-7)

bicyclo[2.2.1]hepta-2,5-diene

Tricyclo[2.2.1.0^{2,6}]heptan-3-ol (695-04-5)

bicyclo[2.2.1]hepta-5-en-2-yl acetate

bicycloheptadiene

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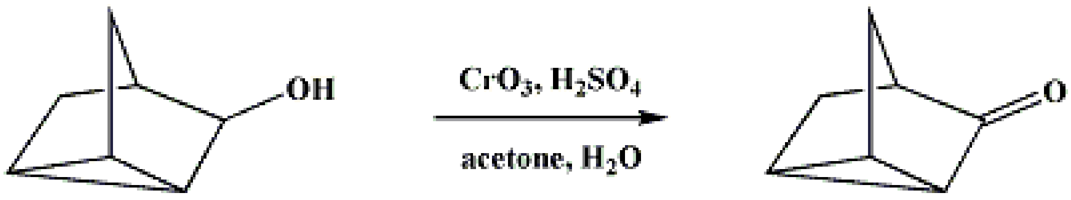
Organic Syntheses, CV 5, 866

NORTRICYCLANONE

[Tricyclo[2.2.1.0^{2,6}]heptan-3-one]



Submitted by J. Meinwald, J. Crandall, and W. E. Hymans[1].
Checked by J. R. Roland and B. C. McKusick.

1. Procedure

The oxidation reagent is prepared by dissolving 70 g. (0.70 mole) of chromium trioxide in 100 ml. of water in a 500-ml. beaker. The beaker is immersed in an ice bath, and 112 g. (61 ml., 1.10 moles) of concentrated (18*M*) sulfuric acid followed by 200 ml. of water is added cautiously with manual stirring. The solution is cooled to 0–5°.

A solution of 110 g. (1.00 mole) of nortricyclanol (Note 1) in 600 ml. of acetone (analytical reagent grade) is cooled to 0–5° in a 2-l. three-necked flask immersed in an ice bath and equipped with an efficient mechanical stirrer, a thermometer, and a dropping funnel with a pressure-equalizing arm. The cooled oxidation reagent prepared above is poured into the dropping funnel, and the reagent is added with vigorous stirring, at a rate to maintain the temperature of the reaction mixture at about 20°. The stirring is continued for 3 hours after the addition is completed.

Sodium bisulfite is added in small portions until the brown color of chromic acid is gone from the upper layer of the two-phase mixture. The top layer is decanted, and the dense, green, lower layer is extracted with 200 ml. of 30–60° petroleum ether. Combination of this extract with the original upper layer causes a separation into two phases. The lower phase is drawn off and added to the original lower phase, which is then extracted with there 200-ml. portions of 30–60° petroleum ether (Note 2). The extracts are combined, washed successively with two 50-ml. portions of saturated sodium chloride, two 50-ml. portions of saturated sodium bicarbonate solution, and 50 ml. of saturated sodium chloride solution, and dried over magnesium sulfate. The solvent is removed by distillation through a short column containing glass helices, and the residue is distilled under reduced pressure to give 85–95 g. (79–88%) of nortricyclanone, b.p. 103–105° (77 mm.), n^{26}D 1.4873 (Note 3) and (Note 4).

2. Notes

1. The preparation of nortricyclanol is described in this volume, p. 863. The

crude, unsublimed nortricyclanol is a satisfactory starting material.
2. Sufficient time between extraction and separation of layers must be allowed, for the organic layer separates slowly from the thick aqueous phase.
3. The product was shown to contain <1% of the starting material and no other detectable impurity by vapor-phase chromatographic analysis.
4. The reported[2] properties of this material are b.p. 78–79° (24 mm.), $n^{25}D$ 1.4878.

3. Discussion

Nortricyclanone has been prepared by oxidation of nortricyclanol using chromic acid in acetic acid[2,3] and using a modified Oppenauer reaction.[4] The present procedure is based on the Jones modification[5] of chromic acid oxidations.

4. Merits of the Preparation

This preparation illustrates a general and convenient way of oxidizing secondary alcohols to ketones. The novel feature of the reaction is represented by acetone solvent which affects markedly the properties of the oxidizing agent. The reaction is very rapid (if not instantaneous), and the yields are high, the reagent rarely attacking unsaturated centers. The procedure is applicable to acetylenic carbinols, allyl and other unsaturated alcohols, and saturated carbinols. The main limitation is the low solvent power of acetone. Another example of the Jones oxidation is given on p. 310 of this volume.

An attractive alternative to the Jones oxidation is oxidation with chromic acid in the two-phase system, water-ether, the details of which were reported recently;[6] however, this method has not been applied to the preparation of nortricyclanone.

The preparation illustrates the utility of the reaction in preparing the highly strained and reactive nortricyclanone, a compound of current interest in studies of strained ring systems.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 863
- Org. Syn. Coll. Vol. 6, 1033

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

Nortricyclanol

Nortricyclanone

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

ether (60-29-7)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

sodium bisulfite (7631-90-5)

acetone (67-64-1)

chromic acid (7738-94-5)

magnesium sulfate (7487-88-9)

chromium trioxide (1333-82-0)

Tricyclo[2.2.1.0^{2,6}]heptan-3-one (695-05-6)

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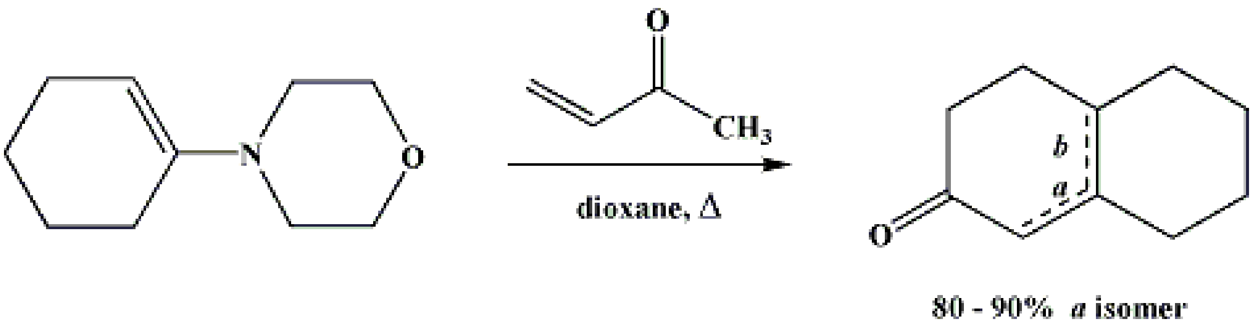
Organic Syntheses, CV 5, 869

$\Delta^{1(9)}$-OCTALONE-2

[2(3H)-Naphthalenone, 4,4a,5,6,7,8-hexahydro-]



Submitted by Robert L. Augustine and Joseph A. Caputo[1].
Checked by William G. Dauben and Jeffrey N. Labovitz.

1. Procedure

A. *$\Delta^{1(9)}$-Octalone-2* and *$\Delta^{9(10)}$-octalone-2*. In a 2-l., three-necked, round-bottomed flask equipped with a sealed stirrer, a condenser, and a dropping funnel is placed a solution of 102 g. (0.61 mole) of 1-morpholino-1-cyclohexene[2] (Note 1) in 600 ml. of purified dioxane (Note 2) and (Note 3). To this stirred solution is added 45 g. (0.64 mole) of freshly distilled methyl vinyl ketone at such a rate that the addition requires approximately 1 hour. The resulting solution is heated under reflux for 4 hours, after which time 750 ml. of water is added, and the heating under reflux is continued for an additional 10–12 hours. The solution is cooled to room temperature and poured into 1 l. of water. The resulting mixture is extracted four times with 500-ml. portions of ether. The combined ether extracts are washed three times with 250-ml. portions of 3*N* hydrochloric acid, twice with 100-ml. portions of a saturated aqueous sodium bicarbonate solution, once with a 250-ml. portion of water, once with a 200-ml. portion of a saturated aqueous sodium chloride solution, and dried over anhydrous magnesium sulfate. The mixture is filtered, the ethereal filtrate evaporated, and the residual octalones distilled through a short column. The yield is 54–59 g. (59–65%) of an octalone mixture (Note 4), b.p. 75–78° (0.2 mm.), 101–103° (2 mm.).

B. *$\Delta^{1(9)}$-Octalone-2*. A solution of 35 g. (0.23 mole) of the above octalone mixture in 200 ml. of 60–110° petroleum ether is cooled to –80° in an acetone-dry ice bath and kept at this temperature for 1 hour. The crystalline $\Delta^{1(9)}$-octalone-2 is filtered by suction through a jacketed sintered-glass funnel kept at –80°. The residue is washed with 100 ml. of cold petroleum ether, removed from the funnel, and recrystallized a second time in the same way. After the second recrystallization the white crystals are removed from the funnel, allowed to melt by warning to room temperature, and distilled. The yield of purified $\Delta^{1(9)}$-octalone-2 (Note 5), b.p. 143–145° (15 mm.), is 20–25 g. (34–46% based on starting enamine). The petroleum ether mother liquors can be distilled to yield a

fraction boiling at 143–145° (15 mm.) which is enriched in $\Delta^{9(10)}$-octalone-2.

2. Notes

1. The enamine should be utilized as soon as possible after distillation.
2. A suitably purified dioxane can be obtained by distillation of reagent grade dioxane from lithium aluminum hydride.
3. Absolute ethanol and dry benzene are also useful solvents for enamine reactions. In this instance, however, the use of these solvents results in a lower yield of octalones.
4. The octalone mixture contains 10–20% of the $\Delta^{9(10)}$-isomer. This mixture may be used as such for many purposes.
5. The purified octalone still contains 1–3% of the $\Delta^{9(10)}$-isomer which cannot be removed even on further crystallization.

3. Discussion

The method of preparation used here is styled after the general procedure described for the reaction of enamines with electrophilic olefins.[3] $\Delta^{1(9)}$-Octolone-2 also has been prepared by condensation of 4-diethylamino-2-butanone with cyclohexanone; by condensation of 2-diethylaminomethylcyclohexanone with ethyl acetoacetate;[4] by condensation of methyl vinyl ketone with cyclohexanone;[5] by condensation of 4-oxo-1,1-dimethylpiperidinium salts with 2-carbethoxycyclohexanone;[6] by the oxidation of α-decalones;[7] and by the reduction of 6-methoxytetralin.[8]

4. Merits of the Preparation

The present procedure is a general method for the preparation of monoalkylated ketones from enamines of aldehydes and ketones with electrophilic olefins.[3] There are many advantages in this method of alkylation. Generally only monoalkylation occurs, even when such reactive species as acrylonitrile are used; and, when a cyclic ketone like 2-methylcyclohexanone is used, reaction occurs only at the lesser substituted center. In a general base-catalyzed reaction, substitution occurs on the more substituted center.

Another advantage of this method is that no catalyst is needed for the addition reaction; this means that the base-catalyzed polymerization of the electrophilic olefin (*i.e.*, α,β-unsaturated ketones, esters, etc.) is not normally a factor to contend with, as it is in the usual base-catalyzed reactions of the Michael type. It also means that the carbonyl compound is not subject to aldol condensation which often is the predominant reaction in base-catalyzed reactions. An unsaturated aldehyde can be used only in a Michael addition reaction when the enamine method is employed.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 619

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

$\Delta^{9(10)}$-octalone-2

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether (60-29-7)

sodium bicarbonate (144-55-8)

Cyclohexanone (108-94-1)

sodium chloride (7647-14-5)

Ethyl acetoacetate (141-97-9)

magnesium sulfate (7487-88-9)

dioxane (5703-46-8)

2-carbethoxycyclohexanone (1655-07-8)

acrylonitrile (107-13-1)

lithium aluminum hydride (16853-85-3)

methyl vinyl ketone (78-94-4)

2-methylcyclohexanone (583-60-8)

4-diethylamino-2-butanone (3299-38-5)

1-Morpholino-1-cyclohexene (670-80-4)

2(3H)-Naphthalenone, 4,4a,5,6,7,8-hexahydro-, $\Delta^{1(9)}$-Octalone-2, $\Delta^{1(9)}$-Octolone-2 (1196-55-0)

2-diethylaminomethylcyclohexanone

6-methoxytetralin (1730-48-9)

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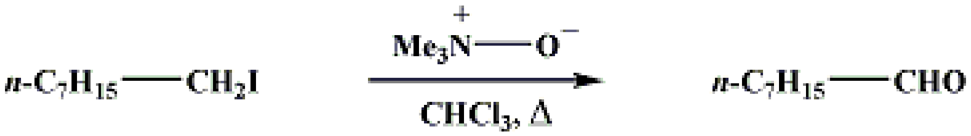
Organic Syntheses, CV 5, 872

OCTANAL



Submitted by Volker Franzen[1]
Checked by Claibourne Smith and V. Boekelheide.

1. Procedure

To a solution of 30 g. (0.4 mole) of anhydrous trimethylamine oxide (Note 1) in 100 ml. of dry chloroform placed in a 250-ml. three-necked, round-bottomed flask fitted with a reflux condenser, a stirrer, and a dropping funnel with protection against moisture is added 48.0 g. (0.2 mole) of *n*-octyl iodide (Note 2) dropwise with stirring. At the beginning of the addition the flask is warmed to 40–50° on a steam bath to initiate the reaction. The start of the reaction can be recognized by the evolution of heat, and the rate of addition can then be adjusted to maintain the temperature around 50°. Overall the addition requires about 20–30 minutes. When addition is complete, the solution is boiled under reflux for another 20 minutes. Then the solution is cooled, and 110 ml. of 2*N* aqueous sulfuric acid solution is added with stirring. The chloroform layer is separated and washed successively with water, 2*N* aqueous sodium carbonate solution, and again with water. After the chloroform solution has been dried over sodium sulfate, it is concentrated under reduced pressure, and then the residue is distilled. The first distillation (Note 3) is carried out at atmospheric pressure and gives 12.0–12.5 g. of a crude oil, b.p. 155–165°. Redistillation using a simple Vigreux column gives 10.6–11.0 g. (41.5–43%) of a colorless oil, b.p. 69–71° (19 mm.), n^{26}_{D} 1.4167.

2. Notes

1. Trimethylamine oxide is normally available as a hydrate, and for the present preparation it is necessary to convert it to its anhydrous form. A convenient way of doing this is as follows. A solution of 45.0 g. of trimethylamine oxide dihydrate (supplied by Beacon Chemicals) is dissolved in 300 ml. of warm dimethyl-formamide and placed in a three-necked flask set up for distillation. At atmospheric pressure the flask is heated and solvent distilled off until the boiling point reaches 152–153°. Then the pressure is reduced using a water aspirator, and the remainder of the solvent is distilled. At the end of the distillation the temperature of the bath is slowly raised to 120°. The residual anhydrous trimethylamine oxide (30 g.) can be dissolved in 100 ml. of chloroform and may remain in the same flask for use in the present preparation.
2. In place of *n*-octyl iodide other derivatives such as *n*-octyl bromide, *n*-octyl *p*-

toluenesulfonate, and *n*-octyl chlorosulfonate can be substituted; the submitter reports that the yields of octanal in these cases are comparable.
3. At this stage the product is a waxy semisolid, presumably a trimer or polymer of octanal, and the higher temperature of an atmospheric distillation is needed to generate the monomeric octanal.

3. Discussion

Octanal has been prepared by the reduction of caprylonitrile with hydrogen chloride and stannous chloride,[2] by the passage of a mixture of caprylic acid and formic acid over titanium dioxide[3] or manganous oxide,[4] by dehydrogenation of 1-octanol over copper,[5] and by oxidation of 1-octanol.[6]

4. Merits of the Preparation

The conversion of alkyl halides to aldehydes is a synthetic step of broad utility. Earlier procedures for such conversions involving the use of dimethyl sulfoxide[7] or pyridine N-oxide[8] have worked best with activated alkyl halides, although Kornblum has described a modification of the dimethyl sulfoxide procedure for use with ordinary aliphatic halides.[9] The present procedure using trimethylamine oxide avoids some of the complicating side reactions of pyridine N-oxide and is useful with ordinary aliphatic halides.[10,11]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

hydrogen chloride (7647-01-0)

chloroform (67-66-3)

sodium carbonate (497-19-8)

n-octyl bromide (111-83-1)

sodium sulfate (7757-82-6)

formic acid (64-18-6)

stannous chloride

copper (7440-50-8)

1-Octanol (111-87-5)

caprylic acid (124-07-2)

n-octyl iodide (629-27-6)

manganous oxide

titanium dioxide

dimethyl-formamide (68-12-2)

dimethyl sulfoxide (67-68-5)

Pyridine N-oxide (694-59-7)

OCTANAL (124-13-0)

trimethylamine oxide (1184-78-7)

trimethylamine oxide dihydrate (62637-93-8)

caprylonitrile (124-12-9)

n-octyl p-toluenesulfonate (3386-35-4)

n-octyl chlorosulfonate

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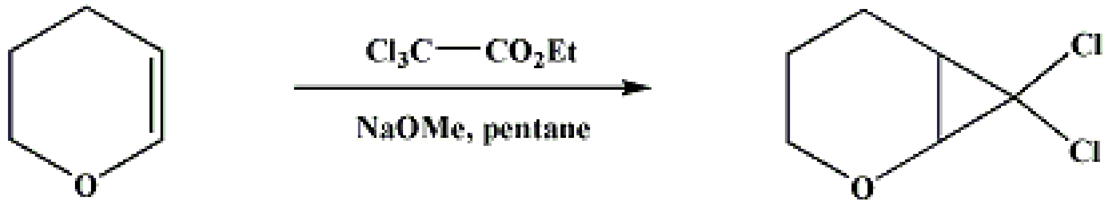
Organic Syntheses, CV 5, 874

2-OXA-7,7-DICHLORONORCARANE

[7,7-Dichloro-2-oxabicyclo[4.1.0]heptane]



Submitted by William E. Parham, Edward E. Schweizer, and Sigmund A. Mierzwa Jr[1].
Checked by William G. Dauben and Richard Ellis.

1. Procedure

In a 1-l. three-necked flask (Note 1) is placed 50 g. (0.92 mole) of sodium methoxide (Note 2) and (Note 3). The flask is temporarily stoppered and then fitted with a nitrogen inlet tube, a sealed stirrer, and a 250-ml. pressure-equalized dropping funnel carrying a calcium chloride tube.

The dropping funnel is removed, and 67.4 g. (0.8 mole) of dihydropyran (Note 4) and 600 ml. of dry, olefin-free pentane (Note 5) are added successively. The light-yellow solution is stirred for 15 minutes in an ice-water bath, and then 164.8 g. (0.86 mole) of ethyl trichloracetate (Note 6) is added from the dropping funnel over a period of 3–4 minutes. The dropping funnel is removed and replaced by a calcium chloride tube.

The reaction mixture is stirred for 6 hours (Note 7) at the ice-bath temperature and then is allowed to warm to room temperature overnight while the stirring is continued. During this period the color of the mixture changes from yellow-orange to brown.

Water (200 ml.) is added, the mixture is transferred to a 2-l. separatory funnel and shaken. The layers are separated and the aqueous layer is extracted twice with 100-ml. portions of petroleum ether (b.p. 60–68°). The organic layers are combined and dried over anhydrous magnesium sulfate.

The solvent is removed at a maximum water-bath temperature of 60° and a minimum pressure of 30 mm. (Note 8). The residual liquid is distilled through a 25-cm. Vigreux column, and the fraction boiling at 74–76/8 mm. is collected (Note 9). The yield of 2-oxa-7,7-dichloronorcarane is 91–100 g. (68–75%), n_D^{25} 1.4974–1.4983.

2. Notes

1. All the glassware used is dried in an oven at 120°. The reaction vessel is arranged so that all the steps prior to hydrolysis are carried out under a constant

positive pressure of dry nitrogen.

2. The sodium methoxide was obtained from Matheson, Coleman and Bell Co. The submitters carried out all operations with this reagent in a dry-box under a stream of dry nitrogen. Sodium ethoxide and potassium *tert*-butoxide have been successfully substituted for sodium methoxide;[2] the choice of sodium methoxide is here principally one of convenience. With other olefins, the choice of alkoxide depends upon the boiling points of the dichlorocarbene adduct and the corresponding dialkyl carbonates.

3. The checkers did not use a dry-box but simply rapidly weighed the sodium methoxide on a balance which was constantly swept with a stream of dry nitrogen from a large inverted funnel and then transferred the solid directly to the reaction flask.

4. The dihydropyran (Matheson) is dried over sodium carbonate and distilled once prior to use.

5. Technical grade pentane (Eastman Kodak) is freed of olefins by five successive washes each with 100 ml. of concentrated sulfuric acid per liter of pentane. The olefin-free pentane is then washed with an equal amount of water, dried over magnesium sulfate, distilled, and stored over sodium wire.

6. Ethyl trichloracetate (Eastman Kodak) is distilled prior to use.

7. The nitrogen flow must be slow enough to prevent significant loss of the pentane by evaporation.

8. A rotary evaporator is a convenient apparatus for this operation.

9. Distillation at significantly higher pressures results in increased decomposition.

3. Discussion

The present procedure is that described by the submitters.[3]

4. Merits of the Preparation

The generation of dichlorocarbene for addition to olefins has been realized by the use of chloroform and alkali metal alkoxides[4,5] (preferably potassium *tert*-butoxide), sodium trichloroacetate,[6] buthyllithium and bromotrichloromethane,[7] phenyl (trichloromethyl)mercury,[8] and the reaction of an ester of trichloracetic acid with an alkali metal alkoxide.[2,3] The latter method, which is here illustrated by the preparation of 2-oxa-7,7-dichloronorcarane, and procedures using phenyl-(trichloromethyl) mercury generally give higher yields of adducts.

References and Notes

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7. W. T. Miller and C. S. Y. Kim, *J. Am. Chem. Soc.*, **81**, 5008 (1959).
8. D. Seyferth, J. M. Burlitch and J. K. Heeren, *J. Org. Chem.*, **27**, 1491 (1962); T. J. Logan, this volume, p. 969.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

2-Oxa-7,7-dichloronorcarane

buthyllithium

sulfuric acid (7664-93-9)

chloroform (67-66-3)

sodium carbonate (497-19-8)

nitrogen (7727-37-9)

sodium methoxide (124-41-4)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

Pentane (109-66-0)

magnesium sulfate (7487-88-9)

trichloracetic acid (76-03-9)

dihydropyran

ethyl trichloracetate (515-84-4)

7,7-Dichloro-2-oxabicyclo[4.1.0]heptane (7556-13-0)

sodium trichloroacetate (650-51-1)

bromotrichloromethane (75-62-7)

Phenyl(trichloromethyl)mercury, phenyl-(trichloromethyl)mercury (3294-57-3)

potassium tert-butoxide (865-47-4)

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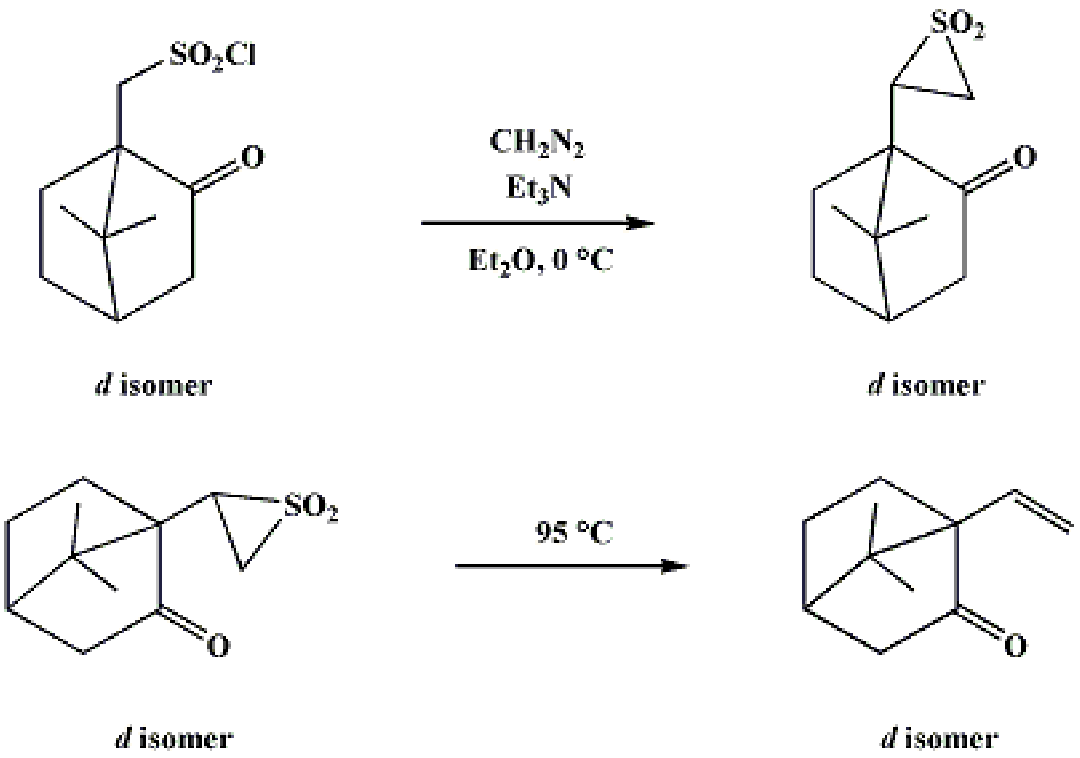
D-2-OXO-7,7-DIMETHYL-1-VINYLBICYCLO[2.2.1] HEPTANE

[2-Norbornanone, 7,7-dimethyl-1-vinyl-, D-]



Submitted by Nikolaus Fischer[1] and G. Opitz[2].
Checked by Hermann Ertl, Ian D. Rae, and Peter Yates.

1. Procedure

Caution! Diazomethane is both explosive and poisonous, and all operations involving its preparation and use must be carried out in a hood. Follow the directions for its handling given in earlier volumes.[3,4]

In a 500-ml. three-necked flask equipped with a mechanical stirrer, a dropping funnel, and a reflux condenser fitted with a potassium hydroxide drying tube are placed 7.0 g. (0.069 mole) of triethylamine (Note 1) and a solution of 3.15 g. (0.075 mole) of diazomethane in 200 ml. of ether (Note 2). The flask is cooled in an ice bath, and a solution of 13.0 g. (0.052 mole) of D-camphor-10-sulfonyl chloride (Note 3) in 75 ml. of anhydrous ether is added dropwise over a period of 1 hour. Triethylamine hydrochloride slowly precipitates. The reaction mixture is stirred for an additional 30 minutes and then concentrated to *ca.* 150 ml. under reduced pressure (water aspirator) with continued stirring to remove the excess of diazomethane. The mixture is filtered under reduced pressure; the precipitate is washed with 50 ml. of anhydrous ether,

giving 6.7 g. (94%) of triethylamine hydrochloride. The combined filtrate and washings are freed of solvent on a rotary evaporator at room temperature to give 10.7 g. (90%) of crude episulfone, m.p. 76–85° (dec.) (Note 4). This is used without purification in the next step; it can be purified by crystallization from a little methanol at −20°. This gives colorless episulfone, m.p. 83–85° (dec.), $[\alpha]^{24}D$ −6.72° (methanol, c = 3.20); infrared bands at 3070, 1300, and 1170 $cm.^{-1}$ (Note 5).

The crude episulfone (3.0 g.) is placed in a 10-ml. round-bottomed flask fitted with a reflux condenser and is heated at 95° for 30 minutes, when it decomposes with loss of sulfur dioxide. The reflux condenser is replaced with a distillation head (Note 6), and the yellow residue is distilled under reduced pressure (water aspirator). D-2-Oxo-7,7-dimethyl-1-vinylbicyclo[2.2.2]heptane (1.7 g., 71% based on sulfonyl chloride), b.p. 95–96° (10 mm.), distills at a bath temperature of 110–120°. Sublimation at 60° (0.01 mm.) gives the olefin as colorless, waxy crystals, m.p. 64–65°, $[\alpha]^{25}D$ +16.35° (methanol, c = 2.16); infrared band at 1650 $cm.^{-1}$.

2. Notes

1. The triethylamine was purified by treatment with naphthyl isocyanate and distilled; the distillate was stored over sodium wire.
2. The ethereal diazomethane was prepared from N-nitrosomethylurea and aqueous potassium hydroxide and dried over potassium hydroxide pellets for 2–3 hours. The solid potassium hydroxide was replaced once or twice to ensure complete dryness. The checkers used the procedure of Arndt[5] for this preparation and for the estimation of the diazomethane.
3. D-Camphor-10-sulfonyl chloride can be prepared from commercially available D-camphor-10-sulfonic acid and phosphorus pentachloride[6] or thionyl chloride.[7] The checkers used the following procedure. D-Camphor-10-sulfonic acid (50.0 g.) was added slowly to 50 g. of thionyl chloride. The mixture was boiled under reflux until homogeneous and then for a further 2 hours. The solution was cooled and poured onto *ca.* 500 g. of crushed ice. The crude product (51.1 g., 95%) was filtered and crystallized twice from hexane to give the sulfonyl chloride, m.p. 65–67.5°; yield, 35.5 g. (66%).
4. The checkers obtained higher yields (94–97%) of less pure material [m.p. 50–78° (dec.)].
5. The checkers observed that the episulfone decomposed slowly at room temperature and, on one occasion, during evaporation at 15°.
6. The checkers found it advisable to use an apparatus with a wide-bore side arm (18 mm.) without a condenser.

3. Discussion

The only method reported for the preparation of D-2-oxo-7,7-dimethyl-1-vinylbicyclo[2.2.1]heptane is that of the present procedure.[8,9]

4. Merits of the Preparation

The method is of general applicability[8,9] for the synthesis of olefins. Other sulfonyl chlorides, RCH_2SO_2Cl, have been used where R = H, C_2H_5, C_6H_5, and $C_6H_5CH_2$; other diazoalkanes that have been used are diazoethane and 1-diazo-2-methyl-propane.

In all cases the olefins form without double-bond migration. A review[9] of the method is available.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 231

References and Notes

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2. Chemisches Institut der Universität, Tübingen, Germany.
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8. G. Opitz and K. Fischer, *Angew. Chem.*, **77**, 41 (1965); *Angew. Chem. Intern. Ed. Engl.*, **4**, 70 (1965) [Correction: Compounds (**1f**) and (**2i**) were obtained from 1-diazo-2-methylpropane (R^2=H, R^3=$CH(CH_3)_2$) and not from 2-diazobutane (R^2=CH_3, R^3=C_2H_5)].
9. N. H. Fisher, *Synthesis*, 393 (1970).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

episulfone

D-2-Oxo-7,7-dimethyl-1-vinylbicyclo[2.2.2]heptane

methanol (67-56-1)

ether (60-29-7)

phosphorus pentachloride (10026-13-8)

thionyl chloride (7719-09-7)

sulfur dioxide (7446-09-5)

potassium hydroxide (1310-58-3)

sodium wire (13966-32-0)

Diazomethane (334-88-3)

N-nitrosomethylurea

hexane (110-54-3)

naphthyl isocyanate (86-84-0)

triethylamine (121-44-8)

Triethylamine hydrochloride (554-68-7)

D-camphor-10-sulfonyl chloride (6994-93-0)

D-2-Oxo-7,7-dimethyl-1-vinylbicyclo[2.2.1]heptane, 2-Norbornanone, 7,7-dimethyl-1-vinyl-, D- (53585-70-9)

diazoethane

1-diazo-2-methyl-propane

D-camphor-10-sulfonic acid (3144-16-9)

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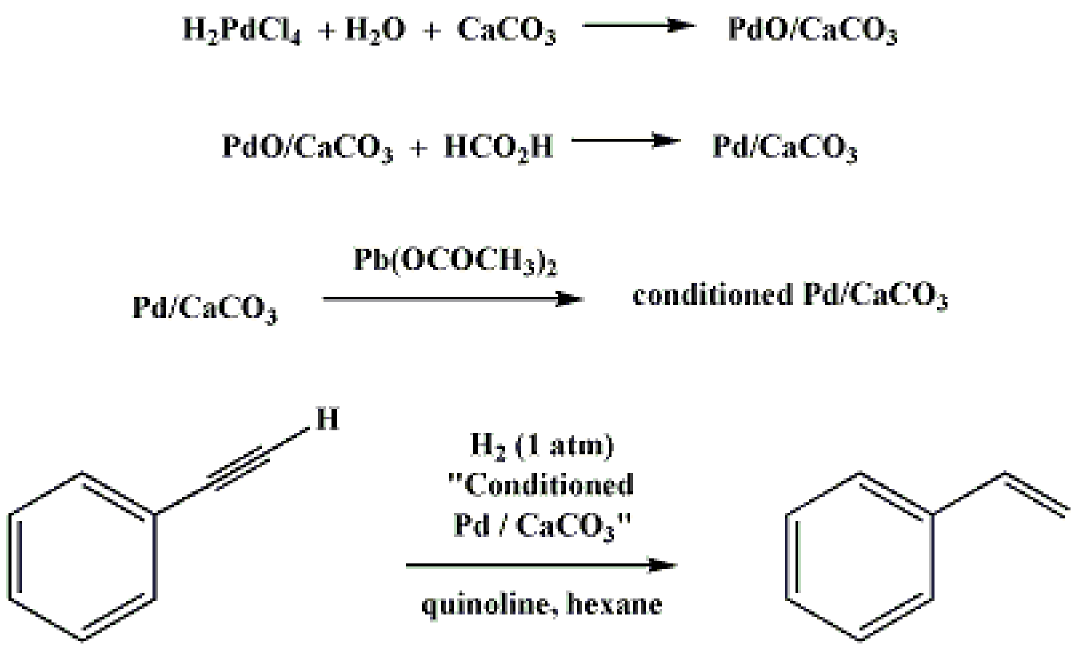
Organic Syntheses, CV 5, 880

PALLADIUM CATALYST FOR PARTIAL REDUCTION OF ACETYLENES[1]



Submitted by H. Lindlar and R. Dubuis[2].
Checked by F. N. Jones and B. C. McKusick.

1. Procedure

Palladous chloride (1.48 g., 0.0083 mole) (Note 1) is placed in a 10-ml. Erlenmeyer flask, and 3.6 ml. (0.043 mole) of 37% hydrochloric acid is added. The flask is shaken at about 30° until the palladous chloride is dissolved. The chloropalladous acid solution is transferred to a 150-ml. beaker with 45 ml. of distilled water (Note 2). The beaker is equipped with a pH meter and a magnetic or mechanical stirrer. The pH of the stirred solution is brought to 4.0–4.5 by slow addition of aqueous 3*N* sodium hydroxide from a buret. A precipitate may form at high local concentrations of sodium hydroxide, but it dissolves on further stirring. The solution is diluted to approximately 100 ml. in a graduated cylinder and placed in a 200-ml. or 250-ml., three-necked, round-bottomed flask equipped with a mechanical stirrer and a thermometer and partly immersed in a bath of oil or water. Precipitated calcium carbonate (18 g.) (Note 3) is added. The well-stirred suspension is heated to 75–85° and held at this temperature until all the palladium has precipitated, as indicated by loss of color from the solution; this takes about 15 minutes. With the mixture still at 75–85°, 6.0 ml. of sodium formate solution (about 0.7*N*) (Note 4) is added. During the addition CO_2 escapes and the catalyst turns from brown to gray; rapid stirring is essential to keep the mixture from foaming over. An additional 4.5 ml. of the sodium formate solution is added, and the reduction is completed by stirring the mixture at 75–85° for 40 minutes. The catalyst, which is now black, is separated on a 10-cm. Büchner funnel (Note 5) and

washed with eight 65-ml. portions of water.

The moist catalyst is placed in a 200-ml. or 250-ml. round-bottomed flask equipped as described above. Water (60 ml.) and 18 ml. of a 7.7% solution of lead acetate (Note 6) are added. The slurry is stirred and heated at 75–85° for 45 minutes. The catalyst is separated on a 10-cm. Büchner funnel, washed with four 50-ml. portions of water, sucked as dry as possible, and dried in an oven at 60–70° (Note 7). The dried catalyst, a dark gray powder, weighs 19–19.5 g. (Note 8).

To establish that the catalyst is active and selective, it is convenient to test it by quantitative hydrogenation of phenylacetylene to styrene. The reaction flask of a low-pressure hydrogenation apparatus (Note 9) is charged with 2.04 g. (0.0200 mole) of phenylacetylene, 0.10 g. of the palladium catalyst, 1.0 ml. of quinoline (Note 10), and 15 ml. of olefin-free petroleum ether (b.p. 80–105°) or hexane (Note 11). The apparatus is evacuated, and hydrogen is admitted to a pressure slightly above 1 atm. Stirring or shaking is started, causing rapid absorption of hydrogen. The hydrogen pressure is kept close to 1 atm. Absorption of the first 0.0200 mole of hydrogen requires 10–90 minutes, depending on the activity of the catalyst. Hydrogen absorption then abruptly slows but does not stop. In synthetic work it is desirable to stop the reaction soon after the required amount of hydrogen has been absorbed.

2. Notes

1. Palladium chloride, Engelhard, 60% Pd, was obtained from Engelhard Industries, 113 Astor Street, Newark 14, New Jersey.
2. All water used in the procedure should be distilled or deionized water or chlorine-free tap water.
3. A commercial grade of "precipitated" (not "powdered" or "prepared") calcium carbonate is satisfactory, if it can be filtered easily. The checkers used Fisher Catalog No. C-62 Calcium Carbonate, U.S.P. (Precipitated Chalk).
4. To prepare the sodium formate solution, a filtered solution of 15 g. (0.14 mole) of anhydrous sodium carbonate in 80 ml. of water is diluted to 120 ml. Approximately 4 ml. (4.9 g., 0.10 mole) of 99% formic acid (a commercial grade) is then added dropwise until the solution is weakly alkaline to phenolphthalein.
5. The checkers found a funnel with a fritted disk convenient. Thorough washing is essential.
6. The solution is prepared by dissolving 9.0 g. (0.024 mole) of a commercial grade of lead acetate, $Pb(OCOCH_3)_2 \cdot 3H_2O$, in 100 ml. of water.
7. The checkers dried the catalyst for 2 hours in a vacuum oven at 60° (1 mm.).
8. The catalyst has been stored for more than 3 years with no loss in activity.
9. The hydrogen pressure and the design of the apparatus are not critical; any apparatus in common use is satisfactory. The checkers used an apparatus having a magnetically stirred reaction flask as described by Wiberg.[3]
10. Less quinoline (as little as 5% of the weight of the catalyst) often suffices for

hydrogenations of this type. The submitters report that 2,2'-(ethylenedithio) diethanol (available from Fluka AG., Chemische Fabrik, CH-9470 Buchs, Switzerland) has proved to be more effective than quinoline in most selective hydrogenations. Between 1 and 10 parts per thousand calculated on the weight of the catalyst is usually sufficient (private communication from H. Lindlar and P. P. Gutmann).

11. Benzene, toluene, or acetone may be used as solvent for substances insoluble in paraffins. Alcohols are usually unsatisfactory media.

3. Discussion

The preparation of the catalyst is a slight modification of the original procedure.[4]

4. Merits of the Preparation

This form of palladium can be used for the hydrogenation of almost any triple bond to the double bond. Reduction of doubly substituted acetylenes gives *cis* olefins.

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

olefin-free petroleum ether

chloropalladous acid

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

sodium carbonate (497-19-8)

formic acid (64-18-6)

CO_2 (124-38-9)

calcium carbonate (471-34-1)

acetone (67-64-1)

toluene (108-88-3)

lead acetate

palladium (7440-05-3)

Quinoline (91-22-5)

sodium formate

phenolphthalein (77-09-8)

styrene (100-42-5)

Phenylacetylene (536-74-3)

palladous chloride, palladium chloride

hexane (110-54-3)

2,2'-(ethylenedithio) diethanol

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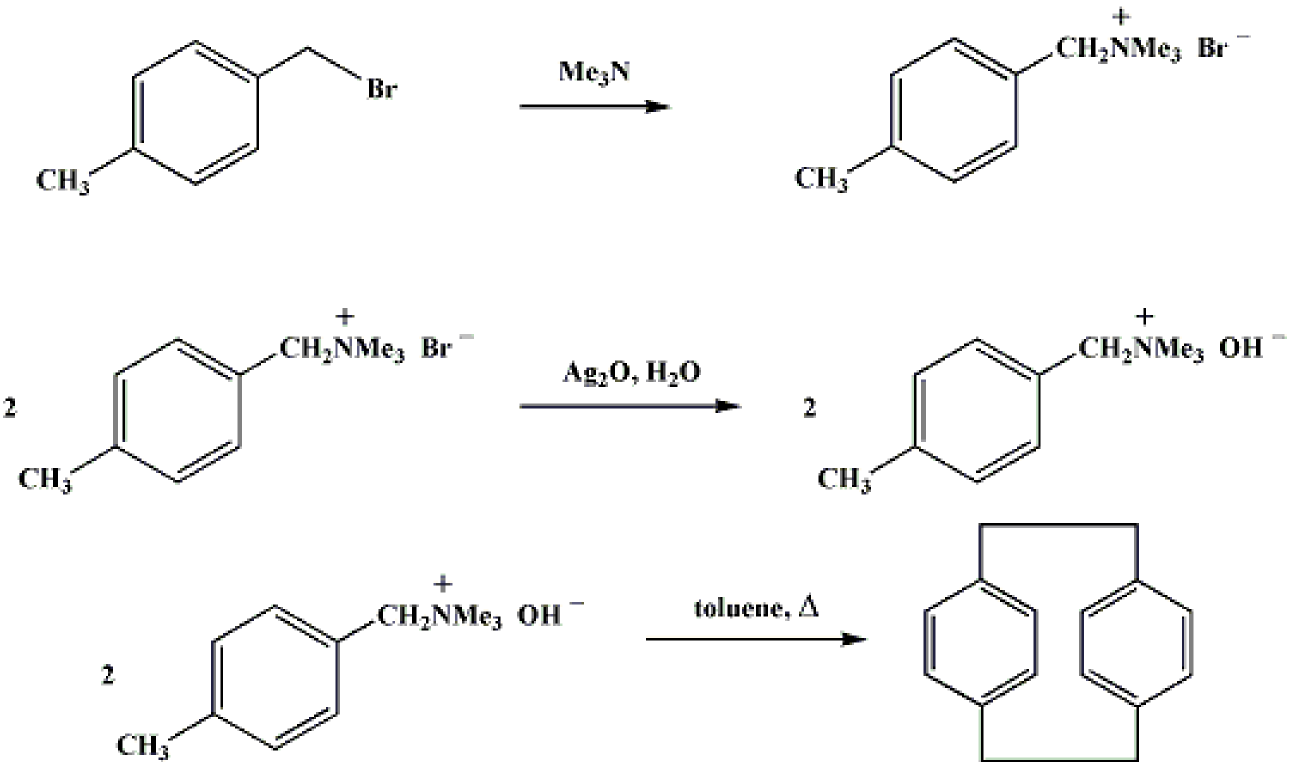
[2.2]PARACYCLOPHANE

[Tricyclo[8.2.2.2^{4,7}]hexadeca-4,6,10,12,13,15-hexaene]



Submitted by H. E. Winberg and F. S. Fawcett[1].
Checked by William E. Parham, Wayland E. Noland, and Thomas A. Chamberlin.

1. Procedure

Caution! This preparation should be conducted in a hood to avoid exposure to trimethylamine and to α-bromo-p-xylene.

A. *p-Methylbenzyltrimethylammonium bromide*. In a 1-l. three-necked flask equipped with a stirrer, a reflux condenser provided with a Drierite drying tube, and a gas inlet tube about 1 cm. above the surface of the liquid are placed 600 ml. of dry ether and 100 g. (0.54 mole) of α-bromo-*p*-xylene (Note 1). The flask is cooled in an ice-water bath with stirring. A dry, weighed trap is cooled in a mush of Dry Ice-acetone, and 50 g. (0.85 mole) of liquid trimethylamine is condensed into the trap. A boiling chip is added to the cold trimethylamine, the trap is connected to the gas inlet tube and is then removed from the cooling bath. The trimethylamine is allowed to distil into the flask during a period of 2 hours, during which time *p*-methylbenzyltrimethylammonium bromide separates as a white solid (Note 2). The resulting pasty mixture is allowed to stand overnight at room temperature. The bromide is collected on a Büchner funnel, the transfer being aided by re-use of the filtrate. The bromide is washed on the filter with 200 ml. of dry ether and dried in air to give 125–130 g. (95–99%) of product (Note 3).

B. *[2.2]Paracyclophane*. *p*-Methylbenzyltrimethylammonium bromide (24.4 g., 0.10 mole) is dissolved in 75 ml. of water. Silver oxide (23 g.) (Note 4) is added, and the mixture is stirred at

room temperature for 1.5 hours. The mixture is filtered, the solid is rinsed with 40 ml. of water, and the combined liquids are collected and then dried azeotropically as follows. A 500-ml. three-necked flask is equipped with a Tru-bore stirrer with a paddle of "Teflon" tetrafluoroethylene resin, a Dean-Stark water separator[2] attached to a reflux condenser, and a heating mantle. In the flask are placed 300 ml. of toluene, 0.5 g. of phenothiazine (Note 5), and the above aqueous solution containing the quaternary ammonium hydroxide. The mixture is stirred and heated under reflux during about 3 hours, the water being separated as it collects in the separator. When the water has been removed, decomposition occurs, as indicated by trimethylamine evolution and the separation of solid polymer. Heating and stirring are continued for 1.25 hours, after which time the evolution of trimethylamine has virtually ceased. The mixture is cooled, the solid is separated by filtration, and the somewhat gelatinous solid is extracted overnight in a Soxhlet apparatus (Note 6) employing the toluene used in the azeotropic drying step. After extraction there remains 5.7–6.7 g. of air-dried insoluble poly-*p*-xylylene. The toluene extract is concentrated to dryness under reduced pressure, and the solid residue is washed with three 10-ml. portions of acetone. Sublimation of the remaining solid at 0.5–1.0 mm. (temperature of oil bath 150–160°) gives a sublimate of 1.0–1.1 g. (10–11%; (Note 7)) of white, crystalline [2.2]paracyclophane, m.p. 284–287° (sealed capillary tube).

2. Notes

1. The α-bromo-*p*-xylene was obtained from Eastman Organic Chemicals; it melted at 35–36.5°.
2. A convenient, alternative procedure consists in slowly passing trimethylamine directly from a cylinder through a trap into the reaction mixture until an excess is present.
3. *p*-Methylbenzyltrimethylammonium bromide is not noticeably hygroscopic. The crude product, after it has been dried at 80° under reduced pressure over phosphorus pentoxide, melts at 197–199°. Recrystallization from absolute ethanol followed by similar drying gives crystals melting at 199–200°. Less thoroughly dried samples show lower and erratic melting points.
4. The silver oxide used may be the commercially available material or that freshly prepared by adding, with stirring, 8.8 g. of sodium hydroxide in 80 ml. of water to a solution of 34 g. of silver nitrate in 200 ml. of water. The precipitate is collected by filtration and washed with water to remove the bulk of the alkali. The wet cake is used directly for preparation of the quaternary hydroxide. The strongly basic quaternary hydroxide solution should be protected from excessive exposure to air because of carbon dioxide absorption.
5. The addition of a polymerization inhibitor appears to increase the amount of paracyclophane formed in the reaction.
6. The polymer is bulky when swollen by the toluene; a Soxhlet thimble 12 cm. long and 145 mm. in diameter is used. Additional toluene may be used in the extraction.
7. The checkers' yields are reported; the submitters report yields of 1.75–2.05 g. (17–19%).

3. Discussion

The above procedures are essentially those described by Winberg, Fawcett, Mochel, and Theobald.[3] Equally good results have been obtained starting with α-chloro-*p*-xylene, but the hygroscopic nature of *p*-methylbenzyltrimethylammonium chloride makes this intermediate less convenient to use than the bromide. [2.2]Paracyclophane has been isolated from the pyrolysis of *p*-xylene[4] and by dimerization of *p*-xylylene.[5] Paracyclophanes have been synthesized by intramolecular Wurtz reactions at high dilution.[6]

4. Merits of Preparation

This reaction, a 1,6-elimination of the Hofmann type, gives [2.2]paracyclophane from readily available starting materials without requiring complex equipment or manipulations, and, accordingly, it is probably the most convenient method of preparing [2.2]paracyclophane. This substance is of interest because of its unusual geometrical features.[6] The method is fairly general. Thus in addition to the hydrocarbon [2.2]paracyclophane, heterocyclophanes have been prepared by similar procedures.[3] The thiophene derivative, 5,5'-ethylene-1,2-bis-(2-thienyl)-ethane, has been made in 19% yield and the furan derivative, 5,5'-ethylene-1,2-bis-(2-furyl)-ethane, has been made in 72% yield. A monomeric intermediate, 2,5-dimethylene-2,5-dihydrofuran, was isolated in the latter case.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 485

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

[2.2]Paracyclophane

poly-p-xylylene

paracyclophane

ethanol (64-17-5)

ether (60-29-7)

sodium hydroxide (1310-73-2)

silver oxide (20667-12-3)

silver nitrate (7761-88-8)

carbon dioxide (124-38-9)

acetone (67-64-1)

toluene (108-88-3)

ammonium hydroxide (1336-21-6)

p-xylene (106-42-3)

Trimethylamine (75-50-3)

tetrafluoroethylene (9002-84-0)

α-bromo-p-xylene (104-81-4)

phenothiazine (92-84-2)

2,5-dimethylene-2,5-dihydrofuran

phosphorus pentoxide (1314-56-3)

α-chloro-p-xylene (104-82-5)

p-methylbenzyltrimethylammonium bromide

p-methylbenzyltrimethylammonium chloride

p-xylylene

Tricyclo[8.2.2.2^{4,7}]hexadeca-4,6,10,12,13,15-hexaene (1633-22-3)

5,5'-ethylene-1,2-bis-(2-thienyl)-ethane

5,5'-ethylene-1,2-bis-(2-furyl)-ethane

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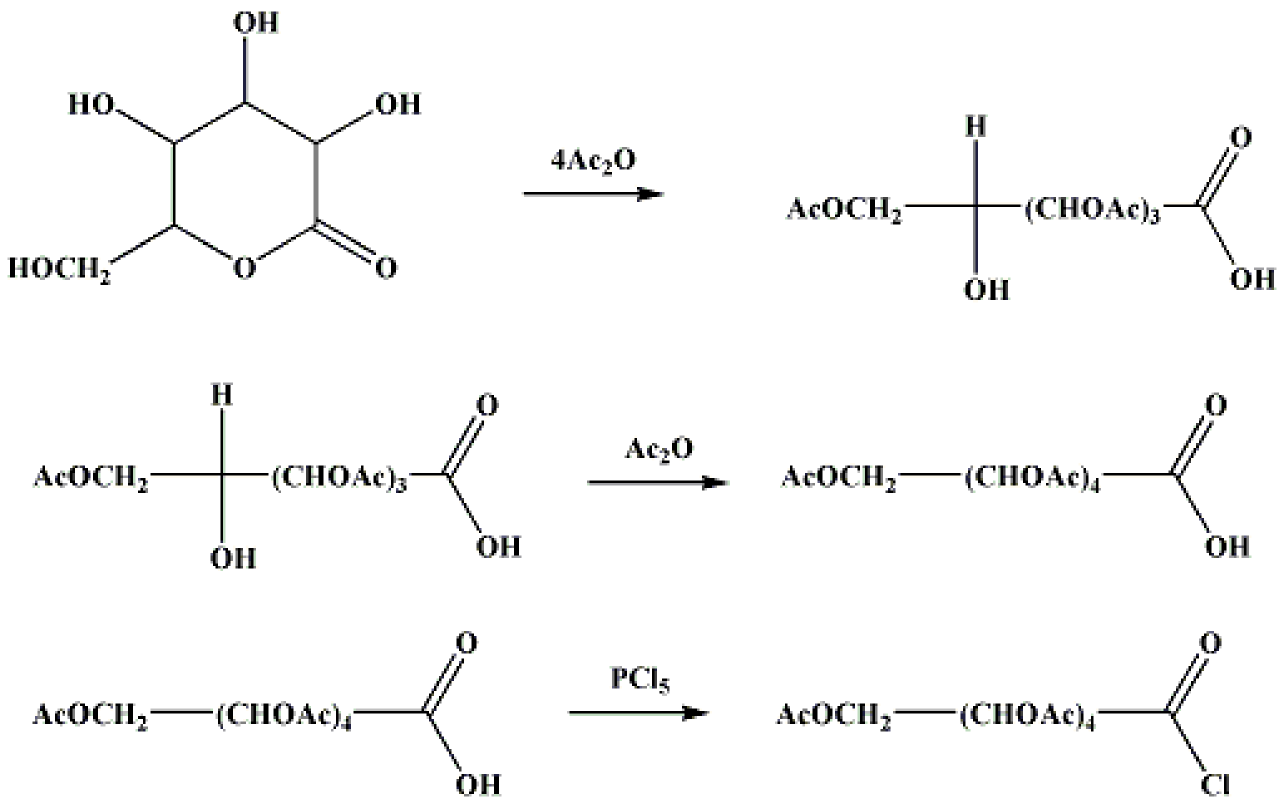
2,3,4,5,6-PENTA-O-ACETYL-D-GLUCONIC ACID AND 2,3,4,5,6-PENTA-O-ACETYL-D-GLUCONYL CHLORIDE

[Gluconic acid, pentaacetyl-,D-, and Gluconyl chloride, pentaacetyl-, D-]



Submitted by Charles E. Braun and Clinton D. Cook[1].
Checked by W. G. Woods, E. F. Silversmith, and John D. Roberts.

1. Procedure

A. *2,3,4,6-Tetra-O-acetyl-D-gluconic acid monohydrate.* Crushed, fused zinc chloride (20 g.) is shaken with 250 ml. of acetic anhydride in a 1-l. three-necked flask until most of the solid dissolves. The flask is then equipped with mechanical stirrer, thermometer reaching into the liquid, and a dropping funnel. As the flask is cooled in an ice bath, 50 g. (0.28 mole) of D-glucono-δ-lactone (Note 1) is added slowly with vigorous stirring. During the addition, the temperature should be kept below 65°. After an hour in the ice bath, the solution is kept at room temperature for 24 hours and is then poured into 1 l. of water and stirred until the hydrolysis of the acetic anhydride is complete (about an hour). The mixture is placed in a refrigerator until the product crystallizes completely (Note 2). The crude material is removed by filtration and washed with a small amount of ice water. The 2,3,4,6-tetra-O-acetyl-D-gluconic acid monohydrate thus obtained melts at 113–117°. The yield is 79–84 g. (74–79%).

B. *2,3,4,5,6-Penta-O-acetyl-D-gluconic acid.* Tetra-O-acetyl-D-gluconic acid monohydrate (50 g., 0.13 mole) is slowly added to a chilled (0–5°) solution of 18 g. of fused zinc chloride in 190 ml. of acetic anhydride contained in a 1-l. Erlenmeyer flask. The solution is kept in an ice

bath for an hour and then allowed to stand at room temperature for 24 hours. After dilution with 1 l. of water, the solution is extracted with four 100-ml. portions of chloroform. In order to remove the chloroform, 200 ml. is distilled, 250 ml of toluene is added, and 250 ml. of this solution is distilled. Another 250 ml. of toluene is then added and the volume is reduced to 300 ml. The product crystallizes on standing at 0° (Note 2). The solid is removed by filtration, washed with toluene and then with petroleum ether (b.p. 35–55°). A yield of 44–45 g. (83–84%) of anhydrous 2,3,4,5,6-penta-O-acetyl-D-gluconic acid, melting at 110–111°, is obtained; $[\alpha]_D^{23}$ +11.5° (c = 4.0 in ethanol-free chloroform).

C. *2,3,4,5,6-Penta-O-acetyl-D-gluconyl chloride.* Anhydrous 2,3,4,5,6-penta-O-acetyl-D-gluconic acid (25 g., 0.062 mole) is shaken with 185 ml. of anhydrous ethyl ether in a 1-l. round-bottomed flask until most of the solid dissolves. Then 15 g. (0.072 mole) of phosphorus pentachloride is added with shaking. The flask is fitted with a calcium chloride drying tube and stored overnight at room temperature. Any solid material is removed by filtration through a fritted-glass funnel into a 1-l. round-bottomed flask, and the ethereal solution is concentrated to about one-half volume under reduced pressure at room temperature. The concentrated solution is allowed to stand overnight at 0° or below. The mother liquor is decanted from the crystals, which are then broken up, transferred to a fritted-glass funnel, washed quickly with petroleum ether (b.p. 35–55°), and dried in a vacuum desiccator. The mother liquor is again concentrated to one-half its volume under reduced pressure and a second crop of crystals collected. The total yield of 2,3,4,5,6-penta-O-acetyl-D-gluconyl chloride, melting at 68–71° (Note 3), is 21–24 g. (80–92%), depending on the temperature of crystallization (Note 4) and (Note 5).

2. Notes

1. The D-glucono-δ-lactone (m.p. 153–155°; assay > 99%, Pfizer specification; water content < 0.2%, Karl Fischer titration) is obtained from Charles Pfizer & Co., Inc., 630 Flushing Avenue, Brooklyn 6, New York. Material having a water content greatly in excess of 0.2% may be dried for 48 hours at 100°. Drying at higher temperatures has in some samples produced decomposition. Independent experience with many preparations in the laboratories of one of the editors (Max Tishler, Merck Sharp & Dohme Research Laboratories) has indicated that drying is generally not necessary.
2. As long as 48 hours may be required.
3. The checkers found m.p. 69.5–74°.
4. Since 2,3,4,5,6-penta-O-acetyl-D-gluconyl chloride is appreciably soluble in ethyl ether at 0°, the yield can be improved by carrying out the crystallization at lower temperatures.
5. The submitters report $[\alpha]_D^{23°}$ = +2.2 (c = 4.0 in ethanol-free chloroform). The checkers found $[\alpha]_D^{25°}$ = +2.5°.

3. Discussion

The method followed for the preparation of the two acids is a modification of that of Major and Cook.[2] The preparation for penta-O-acetyl-D-gluconyl chloride is that of Braun and coworkers.[3] A slightly different technique has also been described.[4]

References and Notes

1. University of Vermont, Burlington, Vt.
2. R. T. Major and E. W. Cook, *J. Am. Chem. Soc.*, **58**, 2475, 2477 (1936).
3. C. E. Braun, S. H. Nichols, Jr., J. L. Cohen, and T. E. Aitken, *J. Am. Chem. Soc.*, **62**, 1619 (1940).
4. R. T. Major, and E. W. Cook, U.S. pat. 2,368,557 [*C.A.*, **40**, 3549 (1946)].

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

ethyl ether (60-29-7)

acetic anhydride (108-24-7)

phosphorus pentachloride (10026-13-8)

chloroform (67-66-3)

toluene (108-88-3)

zinc chloride (7646-85-7)

D-glucono-δ-lactone (90-80-2)

2,3,4,6-Tetra-O-acetyl-D-gluconic acid monohydrate

2,3,4,5,6-PENTA-O-ACETYL-D-GLUCONIC ACID (17430-71-6)

2,3,4,5,6-PENTA-O-ACETYL-D-GLUCONYL CHLORIDE, penta-O-acetyl-D-gluconyl chloride (53555-69-4)

Gluconic acid, pentaacetyl-,D-

Tetra-O-acetyl-D-gluconic acid monohydrate

Gluconyl chloride, pentaacetyl-, D-

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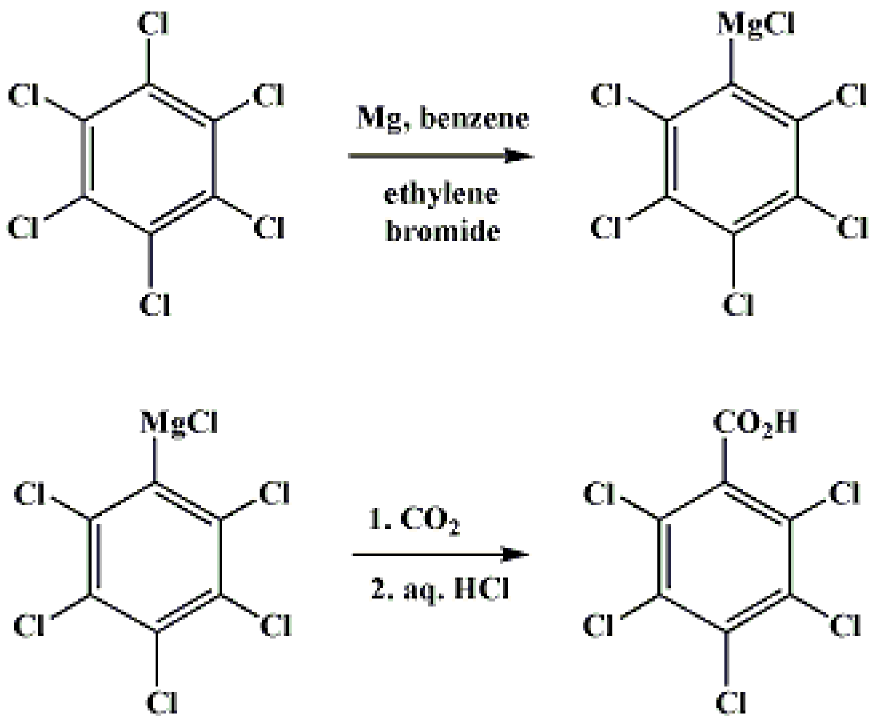
Organic Syntheses, CV 5, 890

PENTACHLOROBENZOIC ACID

[Benzoic acid, pentachloro-]



Submitted by D. E. Pearson and Dorotha Cowan[1].
Checked by Virgil Boekelheide and Fred G. H. Lee.

1. Procedure

Magnesium turnings (39 g., 1.6 g. atoms) and hexachlorobenzene (142.4 g., 0.5 mole, m.p. 228–229°) in 1 l. of dry ether are brought to gentle reflux in a 3-l. three-necked flask heated by a Glascol® mantle at 20 volts (Note 1). Ethylene bromide (188 g., 1.0 mole) in 200 ml. of dry benzene is added through a Hershberg funnel[2] over a period of 48 hours (about 1 drop/25 seconds) (Note 2). Efficient stirring is maintained throughout the period of addition, during which the reaction mixture turns dark brown and forms a precipitate. The mixture is cooled to room temperature, and carbon dioxide, generated from dry ice and dried by passage through anhydrous calcium chloride, is added under the surface of the stirred mixture for at least 3 hours and at such a rate as to minimize clogging of the entrance tube (Note 3). After this addition 10% aqueous hydrochloric acid is added slowly until the mixture is strongly acid. The ether and benzene are removed by distillation, and the crude pentachlorobenzoic acid left in the water is removed by filtration and is washed free of salts with water. The dark-brown damp acid is converted to the ammonium salt by repeated extraction with hot dilute ammonium hydroxide (1 part by volume of concentrated ammonium hydroxide and 2 parts of water) followed by decantation. The combined decanted

solutions are treated with Norit® while still hot, filtered, and then strongly acidified while still hot with concentrated hydrochloric acid. The precipitated acid is digested for at least several hours (Note 4). After the suspension has been cooled, the crude brown-colored acid is removed by filtration, washed with cold water, and air-dried to give 113 g. (77%) of product. The crude acid is recrystallized from 900 ml. of 50% aqueous methanol to yield 95 g. (65%) of tan-colored needles, m.p. 202–206° (Note 5).

2. Notes

1. The atomic proportions of magnesium are not related to the mole quantity of hexachlorobenzene in this or any other entrainment reaction. The excess magnesium (1.1 g. atoms in this case) is used to react with ethylene bromide and leave 0.5 g. atom of clean-surfaced magnesium. Ordinarily 1 mole of entrainment reagent is used per mole of "inert" halide, but for this preparation 2 moles of entrainment reagent per mole of halide gives a better yield.
2. Little attention is needed provided that the capillary tube is fitted properly. The capillary tube of the Hershberg dropping funnel should be about 4.5 in. long, and a Band S 24 platinum wire should be inserted to fit very snugly. Rather than a Hershberg funnel, a commercial constant addition funnel (Kontes Glass Co., Vineland, N.J.) can be used.
3. A T-tube in the carbon dioxide stream serves to bypass the gas if its rate of addition is too rapid. Also, the T-tube is large enough to permit the insertion of a plunger to dislodge particles within the mouth of the tube.
4. Without digestion the acid will contain appreciable amounts of the ammonium salt. In an alternative method of purification the crude acid is converted to the insoluble sodium salt. The sodium salt can be recrystallized from 95% ethanol to give flaky white crystals, m.p. 339–340°. Digestion of the sodium salt with 1 part of concentrated hydrochloric acid and 1 part of water yields the free acid. From 10 g. of crude acid, 7.3 g. of purified acid can be obtained from the sodium salt. The free acid is reported to crystallize well from toluene and light petroleum ether.[3]
5. The melting point is reported variously in the range from 199° to 208°.[4] The acid is colorless if purified by conversions through the sodium salt (Note 4), but the yield is lower.

3. Discussion

Pentachlorobenzoic acid has been prepared by oxidation of pentachlorotoluene with nitric acid and mercury,[3] by oxidation of pentachlorobenzaldehyde by potassium permanganate,[5] and by chlorination of tetrachlorophthalyl chloride[6] and of dichlorobenzoic acids.[7] Pentachlorobenzoic acid recently has been prepared by the exhaustive chlorination of benzoic acid in sulfuric acid containing iodine.[8] The present procedure has been adapted from that of Pearson, Cowan, and Beckler.[9]

4. Merits of the Preparation

Ethylene bromide has been demonstrated to be as efficient as ethyl bromide as an entrainment agent.[9] Its use is advantageous because a second Grignard reagent is not introduced in the reaction mixture—only magnesium bromide. An additional feature of this preparation and of most preparations involving entrainment agents is the slow rate of addition of the entrainer, which permits adequate time for the "inert" halide (in this preparation, hexachlorobenzene) to react on the bright, clean surfaces of the magnesium turnings.

Although pentachlorophenylmagnesium chloride can be made in tetrahydrofuran without the use of the entrainment method, the Grignard reagent in this solvent does not react with carbon dioxide to give pentachlorobenzoic acid in good yield.[10]

References and Notes

1. Department of Chemistry, Vanderbilt University, Nashville, Tennessee.
2. L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed., D. C. Heath, Boston, 1955, p. 265.
3. O. Silberrad, *J. Chem. Soc.*, **127**, 2684 (1925).
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6. A. Kirpal and H. Kunze, *Ber.*, **62**, 2105 (1929).
7. A. Claus and A. W. Bucher, *Ber.*, **20**, 1627 (1887).
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9. D. E. Pearson, Dorotha Cowan, and J. D. Beckler, *J. Org. Chem.*, **24**, 504 (1959).
10. H. E. Ramsden, A. E. Balint, W. R. Whitford, J. J. Walburn, and R. Cserr, *J. Org. Chem.*, **22**, 1202 (1957).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

ethanol (64-17-5)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

methanol (67-56-1)

ether (60-29-7)

magnesium, magnesium turnings (7439-95-4)

nitric acid (7697-37-2)

potassium permanganate (7722-64-7)

Ethyl bromide (74-96-4)

Benzoic acid (65-85-0)

mercury (7439-97-6)

carbon dioxide (124-38-9)

platinum wire (7440-06-4)

iodine (7553-56-2)

Norit (7782-42-5)

toluene (108-88-3)

ethylene bromide (106-93-4)

ammonium hydroxide (1336-21-6)

magnesium bromide (7789-48-2)

Tetrahydrofuran (109-99-9)

Pentachlorobenzoic acid, Benzoic acid, pentachloro- (1012-84-6)

hexachlorobenzene (118-74-1)

pentachlorotoluene (877-11-2)

pentachlorobenzaldehyde

tetrachlorophthalyl chloride

pentachlorophenylmagnesium chloride

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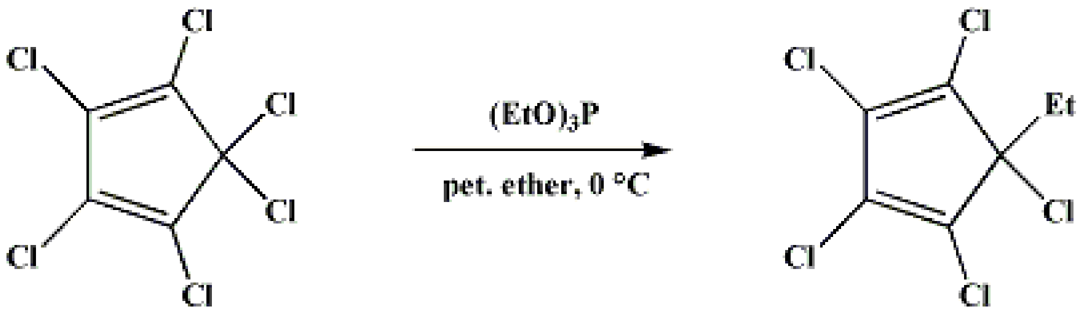
1,2,3,4,5-PENTACHLORO-5-ETHYLCYCLOPENTADIENE

[Cyclopentadiene, 1,2,3,4,5-pentachloro-5-ethyl-]



Submitted by V. Mark, R. E. Wann, and H. C. Godt, Jr.[1].
Checked by William E. Parham, Wayland E. Noland, and G. Paul Richter.

1. Procedure

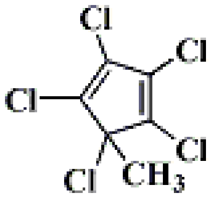
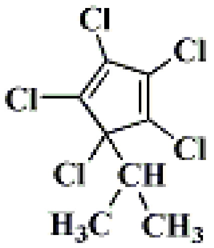
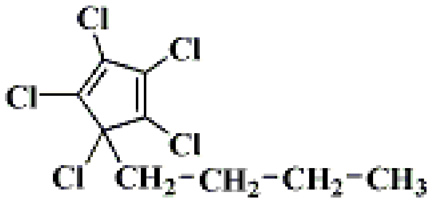
A solution of 183 g. (1.10 moles) of triethyl phosphite (Note 1) in 200 ml. of petroleum ether (b.p. 30–60°) is added to a 3-l., three-necked, round-bottomed flask equipped with a mechanical stirrer, a thermometer, a dropping funnel, and an air condenser; the open end of the condenser is connected to a drying tube filled with calcium sulfate or calcium chloride. The flask is immersed in a freezing mixture of sodium chloride and ice, and the stirrer is started. When the temperature of the phosphite solution reaches 0°, a solution of 273 g. (1.00 mole) of hexachlorocyclopentadiene (Note 2) in 100 ml. of petroleum ether (b.p. 30–60°) is added through the dropping funnel at such a rate that the temperature remains between 0° and 10°. The addition requires about 4–6 hours. After the addition is complete, the freezing mixture is removed, and the brown, clear solution is allowed to warm up to room temperature.

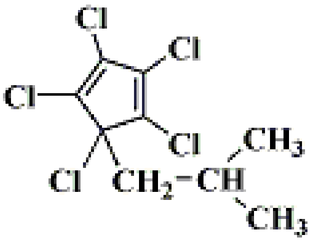
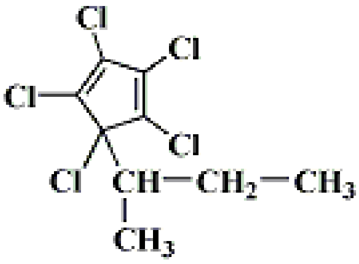
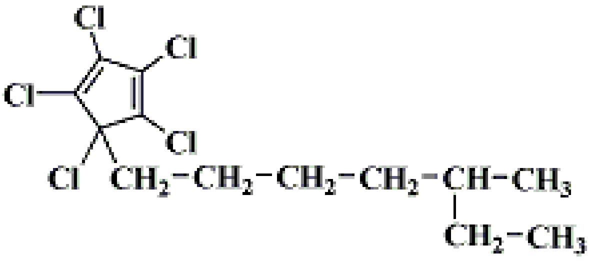
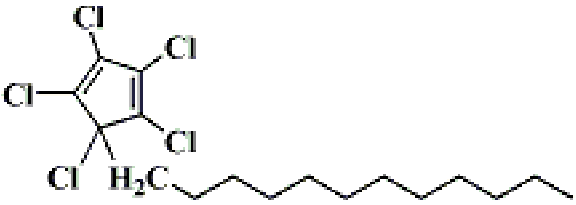
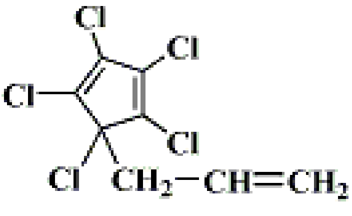
The air condenser is replaced by an efficient water condenser set downward for steam distillation. One liter of water is added in one portion to the stirred reaction mixture, and stirring is continued for 30 minutes (Note 3). The dropping funnel is replaced by a steam-inlet tube reaching into the liquid, and steam is passed through the mixture until first the petroleum ether, then, separately, the ethylpentachlorocyclopentadiene is completely removed. The diene is separated from the steam distillate as a pale-yellow heavy oil. The aqueous phase of the steam distillate is extracted with petroleum ether, and the extract is combined with the diene and dried over calcium sulfate (Note 4). The petroleum ether is removed by evaporation on a steam bath or through a water aspirator at room temperature, leaving 245–257 g. (92–96%) of 1,2,3,4,5-pentachloro-5-ethylcyclopentadiene as a pale-yellow oil, n_D^{25} 1.5387–1.5400. The diene can be distilled without appreciably lowering the yield; b.p. 51–53°/0.2 mm.; n_D^{25} 1.5398.

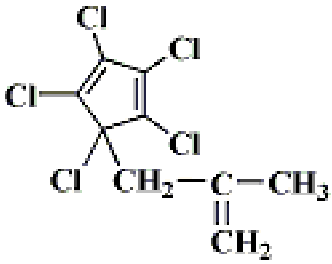
2. Notes

1. Triethyl phosphite can be obtained from Virginia Carolina Chemical Corp., Eastman Kodak Co., Aldrich Chemical Co., K and K Laboratories, and Matheson, Coleman and Bell. The presence of dialkyl hydrogen phosphite or trialkyl phosphate is not deleterious, but a correction for assay is required. Fractionation readily separates triethyl phosphite (b.p. 48–49°/11 mm.) from diethyl hydrogen phosphite (b.p. 72°/11 mm.) and triethyl phosphate (b.p. 90°/10 mm.). The presence of amines and amine hydrochlorides may seriously interfere with the alkylation, especially in the case of trimethyl phosphite (see Table I). The checkers redistilled triethyl phosphite obtained from Matheson, Coleman and Bell.

TABLE I SYNTHESIS OF 5-ALKYLPENTACHLOROCYCLOPENTADIENES, RC_5Cl_5

R[a]	Temperature, °C.[b]	B.P., °C./mm.	n_D^{25}	% Yield
Methyl 	20–22	45–47/0.3	1.5465	89
Isopropyl 	2–5	67–68/0.4	1.5397	95
Butyl 	5–10	72–74/0.3	1.5270	84

Isobutyl 	5–10	73–75/0.4	1.5254	72
sec-Butyl 	20–25	90–92/0.7	1.5370	89
2-Ethylhexyl 	5–10	105–107/0.3	1.5172	90
Dodecyl 	5–10	130–135/0.2	1.5043	78
Allyl 	20–22	63–65/0.5	1.5450	75

Methallyl 	25–40	80–83/0.5	1.5385	80

a All the trialkyl phosphites required for the preparations listed are available from the suppliers mentioned in (Note 1).

b Temperature range during the addition period.

2. A commercial product obtained from Matheson, Coleman and Bell was used.
3. Water hydrolyzes diethyl phosphorochloridate [chlorodiethoxyphosphorus (V) oxide] readily but does not affect the diene. Alternatively, the reaction mixture can be processed by fractionation. Evaporation of the petroleum ether and fractionation of the residue through a 25-cm. × 2.2-cm. column of glass helices yields 170 g. (98.5%) of diethyl phosphorochloridate, b.p. 34–36°/0.2 mm., n_D^{25} 1.4210–1.4250 (the refractive index indicates that it contains 5–10% of the title compound), and 240–255 g. (90–96%) of 1,2,3,4,5-pentachloro-5-ethylcyclopentadiene, b.p. 51–53°/0.2 mm., n_D^{25} 1.5398.
The reaction mixture can also be processed by chromatography. The crude reaction mixture is poured on a 90-cm. × 4.5-cm. column of alumina (e.g., Fisher "adsorption grade") and eluted with about 2 l. of technical-grade pentane. This yields a pale-yellow solution that is free of diethyl phosphorochloridate. Evaporation of the pentane gives 240–255 g. (90–96%) of 1,2,3,4,5-pentachloro-5-ethylcyclopentadiene.
4. Calcium chloride or sodium sulfate can also be used.

3. Discussion

1,2,3,4,5-Pentachloro-5-ethylcyclopentadiene has been prepared only by the present procedure.[2]

4. Merits of the Preparation

5-Alkyl-1,2,3,4,5-pentachlorocyclopentadienes are a novel class of compounds.[2] The alkylation of hexachlorocyclopentadiene by trialkyl phosphites is a synthetic procedure of considerable scope (Table I) and represents a new method of forming carbon-to-carbon bonds. The products, 5-alkylpentachlorocyclopentadienes, show the manifold reactions of the parent chlorocarbon and undergo a variety of substitution

and addition reactions, including Diels-Alder reactions.

References and Notes

1. Monsanto Chemical Co., Agricultural Chemicals Division, St. Louis, Missouri.
2. V. Mark, *Tetrahedron Lett.*, 296 (1961).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

calcium chloride (10043-52-4)

sodium chloride (7647-14-5)

allyl (1981-80-2)

sodium sulfate (7757-82-6)

calcium sulfate (7778-18-9)

methyl (2229-07-4)

Pentane (109-66-0)

butyl (2492-36-6)

isopropyl (2025-55-0)

2-ethylhexyl

Dodecyl

isobutyl (4630-45-9)

methallyl (15157-95-6)

Triethyl phosphite (122-52-1)

diethyl hydrogen phosphite (762-04-9)

hexachlorocyclopentadiene

trimethyl phosphite (121-45-9)

1,2,3,4,5-Pentachloro-5-ethylcyclopentadiene, Cyclopentadiene, 1,2,3,4,5-pentachloro-5-ethyl-, ethylpentachlorocyclopentadiene (16177-48-3)

triethyl phosphate (78-40-0)

diethyl phosphorochloridate (814-49-3)

chlorodiethoxyphosphorus (V) oxide

sec-butyl (2348-55-2)

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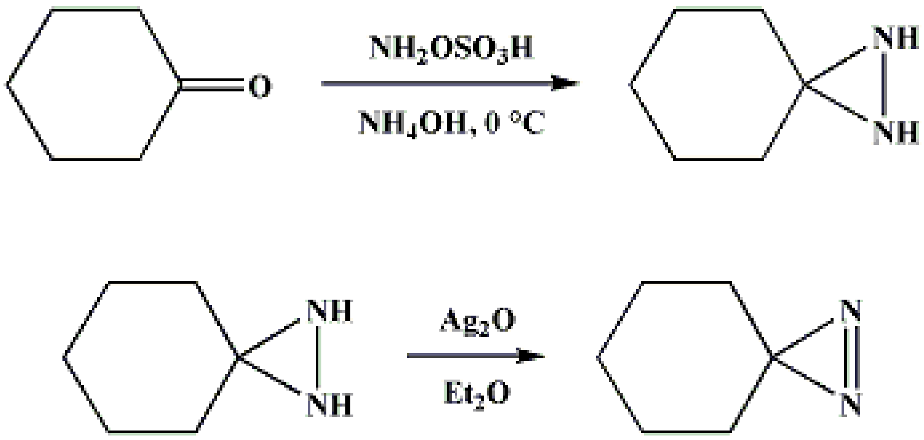
Organic Syntheses, CV 5, 897

3,3-PENTAMETHYLENEDIAZIRINE



Submitted by Ernst Schmitz and Roland Ohme[1].
Checked by E. J. Corey and Richard Glass.

1. Procedure

A. *3,3-Pentamethylenediaziridine*. A solution of 147 g. (1.5 moles) of cyclohexanone in 400 ml. of 15*N* aqueous ammonia (6.0 moles) in a 1-l. beaker is stirred mechanically and cooled to 0° with an ice-salt mixture. Maintaining the temperature of the solution between 0° and +10°, 124 g. (1.0 mole) of 90% hydroxylamine-O-sulfonic acid (Note 1) is added in portions of about 1 g. The addition requires about 1 hour, and the mixture is stirred for another hour at 0° and allowed to stand overnight at −15° in a refrigerator. The precipitated crystalline cake is filtered and pressed tight with a glass stopper. The solid is washed with 50-ml. portions of ice-cold ether, toluene, and finally ether. There is obtained 110–115 g. of product which is 70–90% pure (Note 2) and (Note 3). The product is divided into two portions, each of which is boiled briefly with a 50-ml. portion of toluene; the solutions are decanted from small salt residues and cooled to 0° for 2 hours. The precipitates are filtered with suction and washed with 50 ml. of ice-cold petroleum ether. The combined yield of 3,3-pentamethylenediaziridine is 68–78 g. (61–70%), m.p. 104–107°. The purity is 96–100% (Note 4).

B. *3,3-Pentamethylenediazirine*. *Caution! See (Note 5).* A solution of 34.0 g. (0.2 mole) of silver nitrate is 100 ml. of water is treated dropwise, with shaking, with 100 ml. of 2*N* sodium hydroxide. The precipitate is filtered with suction and washed thoroughly with water, methanol, and lastly ether. A mixture of 10.0 g. (0.089 mole) of 3,3-pentamethylenediaziridine (Note 5) and 220 ml. of ether is warmed, the resulting solution cooled to room temperature, and within a 5-minute period the silver oxide prepared above is added in small portions, with shaking, to the cooled solution. During the addition the reaction mixture is cooled with tap water and then is shaken without cooling until an aliquot does not liberate iodine from an acidified iodide solution; the reaction is normally complete in 30–60 minutes. The mixture is filtered

through a fluted filter, the solid residue washed with a small volume of ether, and the filtrate dried over potassium carbonate. The ether is distilled at a bath temperature of 45° through a 30-cm. Vigreux column. The last 20 ml. of the solvent is removed at a pressure of 30 mm. and a bath temperature of 10°. Using a protective shield, the residue is distilled at 33° (30 mm.) to yield 6.4–7.4 g. (65–75%) of 3,3-pentamethylenediazirine. In order to prevent decomposition of the product on storage, it is diluted with ether and kept in a refrigerator.

2. Notes

1. Hydroxylamine-O-sulfonic acid is prepared according to the method of Gösl and Meuwsen,[2] or of Matsuguma and Audrieth.[3] The material is available from Eastman Organic Chemicals.
Analysis of this substance, just prior to use, is carried out in the following manner. A sample is dissolved in water and treated with a solution of potassium iodide in 2*N* sulfuric acid. After 5 minutes the solution is titrated with thiosulfate solution; near the end of the titration the solution is boiled to ensure completeness of iodine liberation. Instead of the 90% product, a correspondingly greater amount of the 80% product can be employed.
2. For the analysis an ethanolic solution of the 3,3-pentamethylenediaziridine is treated with a solution of potassium iodide in 2*N* sulfuric acid. It liberates two equivalents of iodine instantaneously.
3. The crude product is recrystallized without additional drying; it undergoes partial decomposition on standing.
4. If subsequent treatment is not to be performed within a few days, it is recommended that the preparation be recrystallized a second time to obtain a stable product. Smaller amounts can be advantageously purified by vacuum sublimation.
5. It is recommended that the dehydrogenation be done with small amounts if the dehydrogenation product is to be isolated. Although decomposition was never observed with the preceding procedure, *diazirines should be handled with caution. Explosions were reported when working with 3-methyldiazirine[4] and 3-n-propyldiazirine[4] as well as when overheating pentamethylenediazirine.[5]* Most of the reactions of diazirines, especially the reaction with Grignard compounds,[5] can be done without purification of the diazirine.

3. Discussion

Diazirines have been prepared by dehydrogenation of diaziridines with mercuric oxide,[6] silver oxide,[5] or dichromate-sulfuric acid.[4] The present procedure corresponds to that of Schmitz and Ohme.[5] The procedure for the preparation of the 3,3-pentamethylenediaziridine has been reported by H. J. Abendroth.[7]

4. Merits of the Preparation

Diazirines are the cyclic isomers of the alphatic diazo compounds. Both the diaziridines and the diazirines are starting materials for the synthesis of alkyl hydrazines. 3,3-Pentamethylenediaziridine can be hydrolyzed quantitatively to hydrazine. Methylamine[8] may be substituted for ammonia in the procedure resulting in 1-methyl-3,3-pentamethylenediaziridine (m.p. 35–36°, yield 62% of theoretical) and then methyl hydrazine. Use of ethylenediamine leads to ethylene bis-hydrazine[9] via a bifunctional diaziridine (m.p. 143–144°, yield 48% of theoretical). Ammonia can also be replaced by *n*-propylamine[7] or cyclohexylamine[9]; cyclohexanone by acetone.

3,3-Pentamethylenediazirine and other diazirines easily add Grignard reagents to the N—N double bond. The reaction leads to N-alkyl diaziridines which can be hydrolyzed to alkyl hydrazines. Cyclohexylhydrazine (85% yield), *n*-propylhydrazine (88%), isopropylhydrazine (95%), and benzylhydrazine were prepared from 3,3-pentamethylenediazirine and the corresponding Grignard reagent.[10]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

ammonia (7664-41-7)

methanol (67-56-1)

ether (60-29-7)

sodium hydroxide (1310-73-2)

Cyclohexanone (108-94-1)

silver oxide (20667-12-3)

silver nitrate (7761-88-8)

potassium iodide (7681-11-0)

mercuric oxide (21908-53-2)

iodine (7553-56-2)

acetone (67-64-1)

toluene (108-88-3)

hydrazine (302-01-2)

methylamine (74-89-5)

cyclohexylamine (108-91-8)

methyl hydrazine (60-34-4)

ethylenediamine (107-15-3)

Hydroxylamine-O-sulfonic acid (2950-43-8)

3,3-Pentamethylenediazirine (930-82-5)

3,3-Pentamethylenediaziridine (185-79-5)

3-methyldiazirine

3-n-propyldiazirine

pentamethylenediazirine

1-methyl-3,3-pentamethylenediaziridine (61008-71-7)

ethylene bis-hydrazine

Cyclohexylhydrazine

isopropylhydrazine (2257-52-5)

benzylhydrazine (555-96-4)

n-propylamine (107-10-8)

n-propylhydrazine (5039-61-2)

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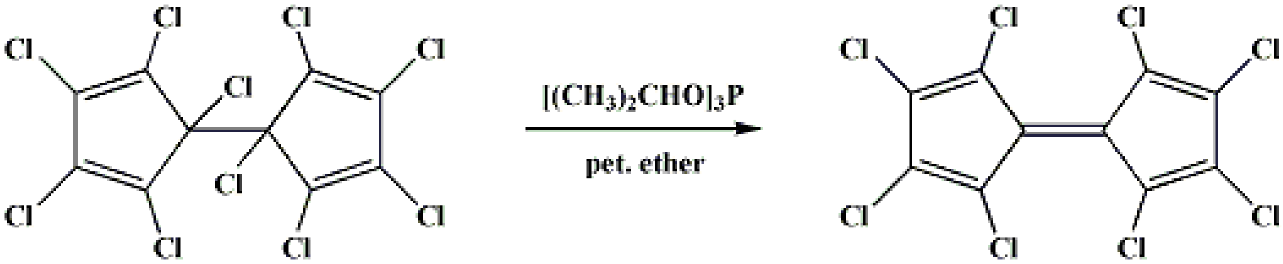
Organic Syntheses, CV 5, 901

PERCHLOROFULVALENE

[Bicyclopentadienylidene, octachloro-]



Submitted by V. Mark[1]
Checked by M. Rosenberger and Peter Yates.

1. Procedure

A slurry of 47.5 g. (0.100 mole) of decachlorobi-2,4-cyclopentadienyl (Note 1) in 200 ml. of petroleum ether (b.p. 30–60°) is prepared in a 1-l., three-necked, round-bottomed flask equipped with a Hershberg stirrer, thermometer, dropping funnel, and air condenser fitted with a drying tube. The reaction flask is immersed in a water bath at 20–24° and the stirrer is started. A solution of 25.2 g. (0.121 mole) of triisopropyl phosphite (Note 2) in 25 ml. of petroleum ether (b.p. 30–60°) is added from the dropping funnel at such a rate that the temperature of the mildly exothermic reaction remains between 20° and 25°. During the addition, which requires 50–80 minutes, the light yellow slurry of the starting material is converted to a dark blue slurry of perchlorofulvalene.

After the addition is completed, the reaction mixture is stirred for an additional period of 20 minutes. The crystalline product is filtered rapidly by suction through a sintered-glass funnel (Note 3) and rapidly washed with three 20-ml. portions of petroleum ether (b.p. 30–60°). After the last washing, the perchlorofulvalene is allowed to dry at room temperature. The yield of the dark bluish-violet, uniform crystals is 26–29 g. (65–72%). The chlorocarbon is of a high purity, as indicated by infrared and ultraviolet spectroscopy (Note 4); it can be recrystallized from benzene, cyclohexane, hexane, carbon tetrachloride, or methylene chloride without appreciable lowering of the yield.

2. Notes

1. Decachlorobi-2,4-cyclopentadienyl [bis-(pentachlorocyclopentadienyl)], m.p. 123–124°, can be obtained from Columbia Organic Chemicals Co., Inc., and Aldrich Chemical Co., Inc. The checkers used purified material, m.p. 124–126°, obtained by recrystallization of commercial material from hexane. They found that without prior purification of the commercial starting materials or correction for assay (cf. (Note 2)) the yield was reduced to 50%. The checked runs were carried out under nitrogen, but it was not determined whether this influenced the yield.
2. Triisopropyl phosphite can be obtained from Virginia Carolina Chemical Corporation, Eastman Organic Chemicals, Aldrich Chemical Company, Matheson Coleman and Bell, and K and K Laboratories. The presence of diisopropyl hydrogen phosphite or triisopropyl phosphate is not deleterious, but a correction for the assay is required. Fractionation readily

separates triisopropyl phosphite, b.p. 60–61° (10 mm.), from diisopropyl hydrogen phosphite, b.p. 70–71° (10 mm.), and triisopropyl phosphate, b.p. 95–96° (10 mm.). The checkers used a fraction, b.p. 85–88° (33 mm.) (cf. (Note 1)).
Alternatively, triethyl phosphite (available from the suppliers given above) can be substituted, in equivalent amount, for triisopropyl phosphite; the yield of perchlorofulvalene is 55–60%. The use of trimethyl phosphite gives lower yields (45–48%) and a less pure product.
3. The use of a large-size (500-ml.), coarse-grade, sintered-glass funnel permits rapid filtration and the washing of the filter cake directly in the funnel. Rapid removal of the co-product, diisopropyl phosphorochloridate, $(C_3H_7O)_2P(O)Cl$, from perchlorofulvalene is necessary in order to prevent its hydrolysis to petroleum ether-insoluble products.
4. Since perchlorofulvalene does not melt below its decomposition point around 200°, infrared and ultraviolet spectroscopic analyses provide the most satisfactory method of checking the purity of the product. The characteristic infrared maxima of perchlorofulvalene occur at 6.55, 7.56, 7.97, 8.10, 8.63, 10.37, 13.03, 14.24, and 14.53 •, and the ultraviolet and visible maxima at 386 m• (ε 35,800) and 590 m• (ε 505). The absence of decachlorobi-2,4-cyclopentadienyl in the product is indicated by the absence of its characteristic bands at 6.27, 12.35, and 14.83 •.

3. Discussion

The present procedure is that described by the submitter.[2] Perchlorofulvalene has also been obtained by the dechlorination of decachlorobi-2,4-cyclopentadienyl catalytically at 500° and 0.1 mm. in 57% yield,[3] or by a mixture of iron and ferric chloride in warm tetrahydrofuran in 14% yield[4] or by stannous chloride in refluxing acetone in 36% yield.[5,6]

4. Merits of the Preparation

Perchlorofulvalene and the more recently prepared perbromofulvalene[7] are the only stable compounds known at present in which the fulvalene system alone represents all the unsaturation. The current listing of a compound as "perchlorofulvalene" in various chemical catalogs is based on earlier work shown to be in error;[2] this compound has been shown to be a $C_{15}Cl_{12}$ chlorocarbon with a trindane skeleton.[2]

Perchlorofulvalene is a highly reactive chlorocarbon which undergoes a variety of reactions, including dimerization and oligomerization[8] and other addition reactions, including chlorination,[6] (2+4)-cycloadditions,[8] and reaction with nucleophiles.[8] It has a unique structure[9] which reflects a compromise between steric hindrance and conjugation. More recently its dipole moment[10] and nqr spectrum[11] have been determined.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

Benzene (71-43-2)

iron (7439-89-6)

carbon tetrachloride (56-23-5)

nitrogen (7727-37-9)

stannous chloride

cyclohexane (110-82-7)

acetone (67-64-1)

ferric chloride (7705-08-0)

methylene chloride (75-09-2)

Tetrahydrofuran (109-99-9)

hexane (110-54-3)

triisopropyl phosphite (116-17-6)

Triethyl phosphite (122-52-1)

diisopropyl hydrogen phosphite

trimethyl phosphite (121-45-9)

Perchlorofulvalene, Bicyclopentadienylidene, octachloro- (6298-65-3)

decachlorobi-2,4-cyclopentadienyl

triisopropyl phosphate

diisopropyl phosphorochloridate

perbromofulvalene

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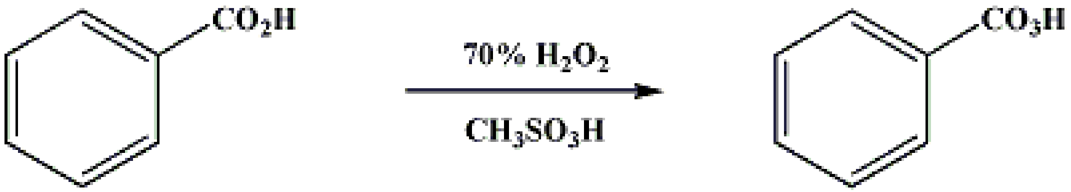
Organic Syntheses, CV 5, 904

PEROXYBENZOIC ACID



Submitted by Leonard S. Silbert, Elaine Siegel, and Daniel Swern[1].
Checked by A. S. Pagano and W. D. Emmons.

1. Procedure

Caution! All reactions in which 50% or more concentrated hydrogen peroxide is employed must be conducted behind a safety shield. Beakers are recommended as reaction vessels to permit rapid escape of gas and avoidance of pressure build-up in the event of a rapid decomposition. (See (Note 1))

Twenty-two grams (0.45 mole) of 70% hydrogen peroxide (Note 2) is added dropwise with efficient agitation to a slurry or partial solution of 36.6 g. (0.30 mole) of benzoic acid (Note 3) in 86.5 g. (0.90 mole) of methanesulfonic acid (Note 4) in a 500-ml. tall-form beaker. The reaction temperature is maintained at 25–30° by means of an ice-water bath. The reaction is exothermic during the hydrogen peroxide addition, which requires approximately 30 minutes. During this period the benzoic acid completely dissolves.

The solution is stirred for an additional 2 hours and is then cooled to 15°. Fifty grams of chopped ice and 75 ml. of ice-cold saturated ammonium sulfate solution are cautiously added in sequence while the temperature is maintained below 25° during the dilution (Note 5). The contents of the beaker are transferred to a separatory funnel, and the peroxybenzoic acid solution is extracted with three 50-ml. portions of benzene at room temperature (Note 6). The aqueous layer is discarded, and the combined benzene extracts are washed twice with 15 ml. of cold saturated ammonium sulfate solution to ensure complete removal of methanesulfonic acid and hydrogen peroxide, dried over anhydrous sodium sulfate, and filtered. Iodometric titration of an aliquot of the benzene solution (Note 7) indicates that the conversion of benzoic to peroxybenzoic acid is 85–90%. This solution can be used directly for epoxidation or other oxidation reactions without further treatment (Note 8).

2. Notes

1. For a summary of procedures to be followed in the safe handling of hydrogen peroxide and peroxy acids see reference 2, p. 90 and 478.

2. Hydrogen peroxide of this concentration can be obtained from various commercial sources. The submitters have also used 50% and 95% hydrogen peroxide instead of the 70% concentration. With 50% hydrogen peroxide, conversion to peroxybenzoic acid is only about 75%. With 95% peroxide, the reaction proceeds more rapidly and is slightly more exothermic, and conversions of benzoic acid to peroxybenzoic acid are about 90–95% instead of 85–90%. Little advantage is seen in using the more concentrated hydrogen peroxide in the preparation of peroxybenzoic acid except when a high yield of pure crystalline material is needed (Note 7).

3. Benzoic acid of analytical reagent grade is used.

4. Methanesulfonic acid, Eastman Chemicals, practical grade, is satisfactory.

5. Dilution of the methanesulfonic acid is exothermic. Since peroxybenzoic acid has an appreciable solubility in aqueous methanesulfonic acid, dilution and washing are conducted with minimal quantities of saturated ammonium sulfate solution.

6. In the first extraction, 90% of the available peroxybenzoic acid is extracted. The second extraction removes 7%, and the third 2%. The first benzene extract is an approximately 40% solution of peroxybenzoic acid (2.8*M*).

7. A 1-ml. or 2-ml. aliquot of the benzene solution of peroxybenzoic acid is pipetted into an iodine flask, the walls of the flask are rinsed with a small quantity of chloroform, and 15 ml. of acetic acid is added. Two milliliters of a saturated aqueous solution of analytical reagent grade sodium iodide is added. After a reaction period of about 5 minutes, 50–75 ml. of water is added, and the liberated iodine is titrated with 0.1*N* sodium thiosulfate solution (starch indicator). One milliliter of 0.1*N* sodium thiosulfate is equivalent to 0.00691 g. of peroxybenzoic acid.

The analytical method described is also used in following the consumption of peroxybenzoic acid or other peroxy acids during an oxidation reaction; it has also been used in determining the conversion of other carboxylic acids to peroxy acids when solvent extraction has been used in the isolation.

8. If a solvent other than benzene *must* be used in an oxidation reaction, peroxybenzoic acid can be isolated by evaporation of the benzene in an evaporating dish in the hood under a stream of nitrogen gas, or preferably in a rotary evaporator. Evaporation of the solvent from the peroxybenzoic acid solution is preferably conducted as rapidly as possible from a water bath at a temperature below 30°. *Caution! This operation must be carried out behind a good shield. A heavy explosion once occurred during such evaporation of a chloroform solution of perbenzoic acid.*[2] Owing to the volatility of peroxybenzoic acid, some is lost during solvent evaporation; overall recovery of peroxy acid is 70–90%. The crude peroxybenzoic acid obtained as a residue is a pale-yellow mushy solid or liquid if it still contains traces of benzene. The peroxy acid should be stored in a refrigerator if it is not used immediately. Analytically pure solid peroxybenzoic acid decomposes at the rate of about 2–3% per day at room temperature, but it can be stored for long periods in a

refrigerator without significant loss of active oxygen. Crude preparations lose active oxygen more rapidly. Pure peroxybenzoic acid can be obtained readily from peroxybenzoic acid of 90–95% purity by crystallization at –20° from *olefin-free* 3:1 petroleum ether/diethyl ether cosolvent. About 4.5 ml. per gram of crude peroxy acid is needed, and the solution should be seeded at about 5°. From 15 g. of crude peroxy acid, 9–10 g. of the pure acid, m.p. 41–42°, is obtained as long white needles. To obtain reaction products containing 90–95% peroxybenzoic acid, 95% hydrogen peroxide must be used in the preparation.

3. Discussion

The methods of preparation, properties, analysis, and safe handling of peroxybenzoic acid have been reviewed.[3] Numerous methods of preparing peroxy acids are described in the literature,[3,4] and many of them have been applied to the synthesis of peroxybenzoic acid. A common way of preparing it has been by the action of sodium methoxide on benzoyl peroxide followed by acidification.[4] The present method is adapted from one in a publication of the submitters.[5]

The preparation of *m*-chloroperoxybenzoic acid is described elsewhere in this series.[6]

4. Merits of the Preparation

The present procedure for peroxybenzoic acid is easier and more reliable than earlier ones. Thus that in an earlier volume of *Organic Syntheses*[4] has been found by the submitters to be difficult to reproduce, and yields are frequently low. The modified procedure of Kolthoff, Lee, and Mairs[7] is an improvement, but it is tedious and indirect.

There are other methods for converting aliphatic acids directly to peroxy acids, but this is the first that converts aromatic acids directly to peroxy acids. With suitable modifications it is applicable to a wide variety of aliphatic and aromatic peroxy acids.[5] The methyl ester may be used in place of highly insoluble acids. Water-insoluble peroxy acids such as *p*-nitroperoxybenzoic acid (an outstanding epoxidizing agent[8]), *p*-*tert*-butylperoxybenzoic acid, and peroxystearic acid require 90–95% hydrogen peroxide for best results; the procedure is essentially the same *except that greater precautions are necessary with hydrogen peroxide of such high strength.*[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 191
- Org. Syn. Coll. Vol. 5, 414
- Org. Syn. Coll. Vol. 5, 900

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

acetic acid (64-19-7)

Benzene (71-43-2)

diethyl ether (60-29-7)

chloroform (67-66-3)

sodium sulfate (7757-82-6)

oxygen (7782-44-7)

sodium thiosulfate (7772-98-7)

nitrogen (7727-37-9)

Benzoic acid (65-85-0)

iodine (7553-56-2)

sodium methoxide (124-41-4)

hydrogen peroxide, peroxide (7722-84-1)

sodium iodide (7681-82-5)

ammonium sulfate (7783-20-2)

benzoyl peroxide (94-36-0)

methanesulfonic acid (75-75-2)

Perbenzoic acid, Peroxybenzoic acid (93-59-4)

peroxystearic acid (5796-86-1)

p-nitroperoxybenzoic acid (943-39-5)

m-chloroperoxybenzoic acid (937-14-4)

p-tert-butylperoxybenzoic acid

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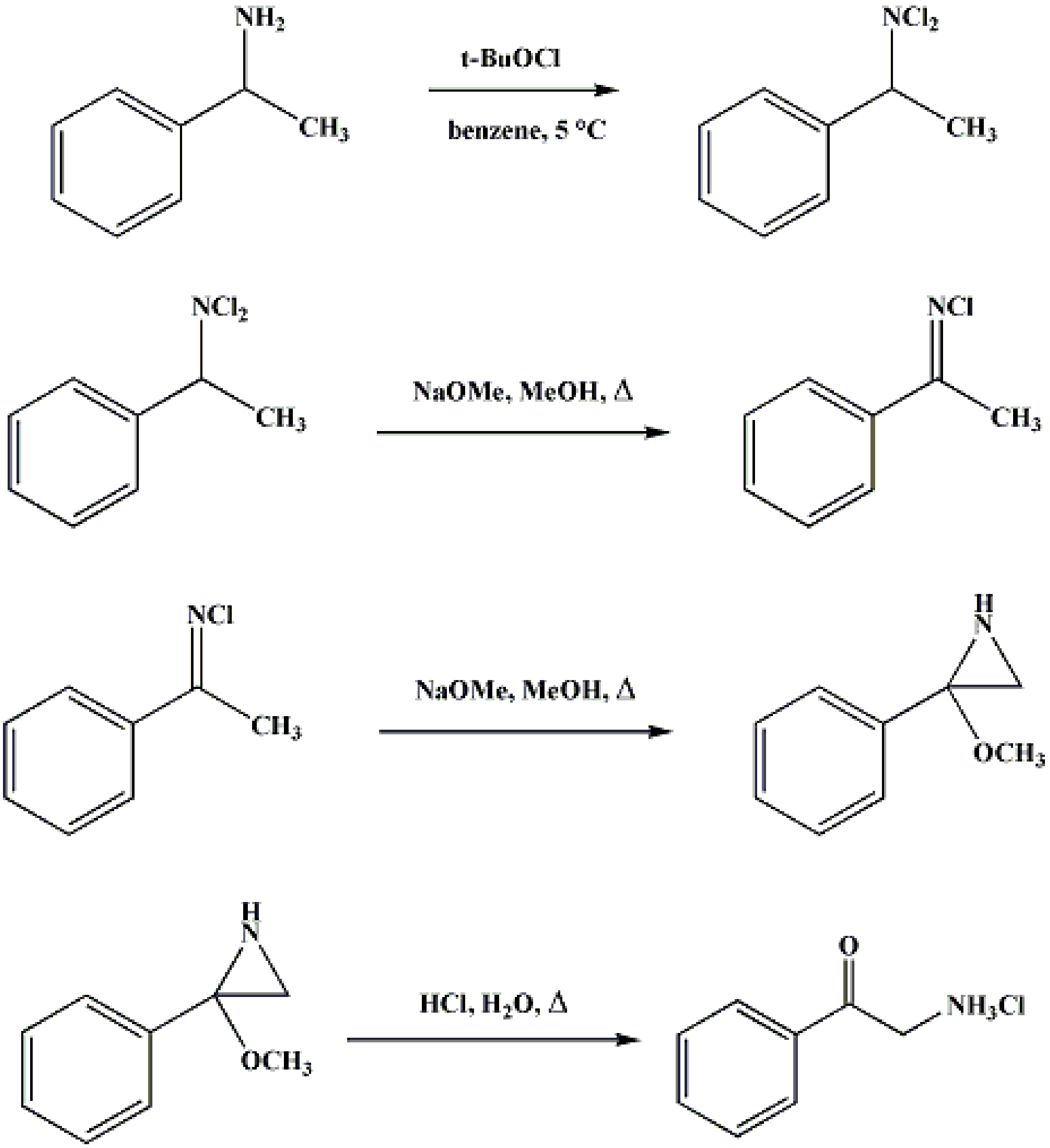
Organic Syntheses, CV 5, 909

PHENACYLAMINE HYDROCHLORIDE

[Acetophenone, 2-amino-, hydrochloride]



Submitted by Henry E. Baumgarten and James M. Petersen[1].
Checked by William E. Parham, Norman Newman, and R. M. Dodson..

1. Procedure

In a thoroughly dry 500-ml., three-necked, round-bottomed flask fitted with a mechanical stirrer, dropping funnel, and a Y-tube containing a calcium chloride drying

tube and a thermometer (Note 1) are placed 24.2 g. (26 ml., 0.20 mole) of α-phenylethylamine (Note 2) and 50 ml. of dry benzene (Note 3). The solution is cooled in an ice-salt bath to 5°, and a solution of 44.5 g. (50 ml., 0.41 mole) of *tert*-butyl hypochlorite[2] (Note 4) in 50 ml. of dry benzene (Note 3) is added at such a rate as to maintain the temperature below 10° (Note 5). After the addition of the *tert*-butyl hypochlorite solution is complete, the reaction mixture is stirred at room temperature 1–4 hours (Note 6).

The Y-tube is replaced by a reflux condenser fitted with a calcium chloride drying tube, and a freshly prepared solution of 13.8 g. (0.60 g. atom) of sodium in 140 ml. of anhydrous methanol (Note 7) is added to the benzene solution of N,N-dichloro-α-phenylethylamine at such a rate as to maintain gentle reflux (Note 8). After addition of the sodium methoxide is complete, the reaction mixture is heated under reflux until a test with acidified starch-iodide paper is negative (about 45–70 minutes) (Note 9). The reaction mixture is cooled in an ice-water bath, and the precipitated sodium chloride is removed by filtration through a Büchner funnel. The filter cake is washed with three 25-ml. portions of dry benzene. The combined filtrates are added very slowly with shaking or stirring *to* 150 ml. of 2*N* hydrochloric acid contained in a 1-l. beaker (Note 10). The layers are separated, and the benzene layer is extracted with three 50-ml. portions of 2*N* hydrochloric acid. The combined acid extracts are washed twice with 50-ml. portions of ether (Note 11). The ether extracts are discarded. The pale amber to yellow aqueous solution is evaporated to dryness at a temperature not greater than 40° (Note 12). The residue is transferred to a 1-l. round-bottomed flask fitted with a reflux condenser to which is added 400 ml. of isopropyl alcohol-hydrochloric acid solution (Note 13). The mixture is heated under reflux for at least 30 minutes and is filtered hot through a Büchner funnel. The residual solid is returned to the flask and extracted in the same manner with a 150-ml. portion of the isopropyl alcohol-hydrochloric acid solution. The solid residue (sodium chloride) is discarded (Note 14). The two extracts are cooled separately in the refrigerator overnight and then filtered on a Büchner funnel (Note 15). The nearly colorless crystals are washed on the filter with two 50-ml. portions of dry ether. Each of the filtrates is diluted with an equal volume of dry ether (400 ml. and 150 ml., respectively) and is allowed to stand in the refrigerator overnight. From these diluted filtrates additional crops of crystals are collected (Note 16). The combined yield of the three to four crops is 18.9–24.8 g. (55–72%), m.p. 185–186° dec. (Note 17) and (Note 18). Normally the product is sufficiently pure for use without further purification: however, the product may be recrystallized from isopropyl alcohol-hydrochloric acid solution (Note 12), using 100 ml. of the solution for each 6 g. of compound. The recovery is about 5.5 g. per 6.0 g. of crude product.

2. Notes

1. The submitters used apparatus with ground-glass joints and dried the various pieces in the oven at 120–140° overnight before use. The Y-tube was constructed from a 24/40 male joint by joining a short length of 8-mm. i.d. glass

tubing to the unground end of the joint in such a fashion as to permit insertion of a thermometer through the joint into the flask and then joining a second short piece of 8-mm. i.d. glass tubing in such a fashion as to permit attachment of a calcium chloride tube without interfering with the thermometer opening. If desired, a four-necked flask may be substituted for the Y-tube and three-necked flask.

2. The submitters used *dl*-α-phenylethylamine obtained either from the Eastman Kodak Company or Matheson, Coleman and Bell without further purification. The preparation of *dl*-α-phenylethylamine has been described previously in *Organic Syntheses.*[3,4]

3. Reagent grade dry benzene is dried by simple distillation, the first 10% of the distillate being discarded.

4. The submitters did not redistil the *tert*-butyl hypochlorite. If it is desired to avoid the use of *tert*-butyl hypochlorite, an equivalent quantity of dichloramine B (N,N-dichlorobenzenesulfonamide, Arapahoe Chemical Co., Boulder, Colorado) may be substituted. This material is soluble in benzene but the benzenesulfonamide is not; therefore the reaction mixture must be filtered just before the addition of the sodium methoxide solution. Using this technique, the submitters obtained 44–52% of phenacylamine hydrochloride.

5. The rate of addition is not critical, for the reaction is not especially exothermic. However, at even slightly elevated temperatures the N,N-dichloroamines may begin to decompose with the formation of undesired products; therefore the addition can be carried out as rapidly as desired within the specified temperature range. With a reasonable cooling efficiency this will be well below 30 minutes, but no harm will be done if a longer period is required.

6. The halogenation reaction appears to be quite rapid; therefore the time of stirring is not critical but probably should not be prolonged beyond 4 hours. The submitters used this time interval to prepare the sodium methoxide solution, and the actual time lapse depended upon the time required to prepare this solution. The solution of N,N-dichloro-α-phenylethylamine should be clear yellow after the stirring period. A turbid solution or one containing a precipitate usually indicates a poor sample of *tert*-butyl hypochlorite.

7. Commercial absolute methanol is dried by heating the material under reflux over magnesium turnings for 4 hours, followed by distillation into a dried receiver. Normally 1 g. of magnesium turnings per 100 ml. of absolute methanol will be sufficient. To allow for losses during the drying and distillation, the charge of methanol should be at least twice the amount required for the preparation.

It is advantageous to dry the methanol the day before the preparation is to be carried out and to store the dried methanol in a carefully sealed, *dry* flask or to allow the methanol-magnesium mixture to reflux overnight followed by distillation just prior to use.

The submitters used the inverse addition procedure for preparing the methanolic sodium methoxide, as follows. In a thoroughly dry 500-ml., three-necked, round-

bottomed flask fitted with a mechanical stirrer, dropping funnel, and a reflux condenser carrying a calcium chloride drying tube is placed 13.8 g. (0.60 g. atom) of sodium freshly cut into small pieces. To this is added slowly 140 ml. of anhydrous methanol at such a rate as to maintain vigorous reflux. If all the sodium does not dissolve during the addition of the methanol, the mixture may be heated on the steam bath until solution is effected or additional methanol (up to 25 ml.) may be added. The preparation of the solution of sodium methoxide requires about 30 minutes.

It may be advantageous to allow a slow stream of dry nitrogen to pass through the apparatus during the addition of the methanol. The submitters routinely omit this precaution and, as yet, have experienced no accidents or fires. For other precautions see Note 1, *Org. Syntheses*, Coll. Vol. **3**, 215 (1955).

8. The rate of addition probably is not critical but should not be allowed to proceed uncontrolled. The submitters added the sodium methoxide solution at such a rate as to cause vapors of the refluxing methanol to condense in the first 2–3 in. of the reflux condenser without application of external heating.

9. A positive test is the immediate formation of a dark violet or brown spot on starch-iodide paper moistened with 2*N* hydrochloric acid. A negative test may consist of a very faint beige color or complete absence of color.

10. The reverse mode of addition may lower the yield and introduce unwanted condensation products of the amino ketone, which is not stable in neutral or alkaline solution.

11. The procedure should be continued up to at least this point without stopping. After this operation the sequence may be interrupted at any time.

If the *tert*-butyl hypochlorite has been prepared in advance and if the methanol to be used has been allowed to reflux over magnesium overnight, the solvents can be distilled and the reaction carried to this point in an 8-hour day. However, it may be preferable to prepare the dry solvents the day before the reaction is to be run. The latter procedure appears to have little effect on the final yield provided that the solvents are stored in tightly sealed containers and transferred with due care.

12. The submitters strongly recommend the use of a rotating evaporator (such as the Flash-Evaporator, Laboratory Glass Supply Co., New York 31, N. Y.). with which the solution can be reduced to a syrup in about 4 hours. The further evaporation is facilitated by adding 100 ml. of commercial absolute ethanol at this point and continuing the evaporation. Total time for evaporation will be about 6 hours, and the product will be a crystalline mass. The extraction step may be carried out in the 2-l. flask normally used with the evaporator.

If a rotating evaporator is not available, the solution is poured into a large porcelain evaporating dish and is allowed to stand protected in the hood for several days. Toward the end of this time, the evaporation may be accelerated by the addition of 100 ml. of ethanol as described above. The checkers removed water by blowing air over the solution.

13. The isopropyl alcohol-hydrochloric acid solution contains 1 ml. of concentrated hydrochloric acid per 100 ml. of isopropyl alcohol. If the hydrochloric acid is omitted, the product will be impure and the yield greatly

reduced. Sodium chloride is not appreciably soluble in this solution.

14. The yield of sodium chloride is usually 33–35 g. (94–100%). It is often helpful to recover and weigh the sodium chloride before discarding it. An excess over the theoretical amount indicates incomplete extraction.

15. If the reflux period has been sufficiently long, little or no precipitate will be formed at this stage in the second extracting solution, which is used to ensure efficient extraction.

16. At this stage, crops of crystals may be formed in each solution.

17. Further treatment of the filtrate normally will yield little crystalline material.

18. The submitters report that, on the basis of experience in student preparation courses, the usual percentage yields for fairly capable technicians on their first trial are in the low fifties, and on subsequent trials in the sixties. Persons with exceptionally good laboratory technique may get even greater yields than those specified (up to 78%).

This procedure may be used for the preparation of a variety of α-amino ketones as is indicated in Table I, which summarizes most of the submitters' experience with this reaction. Principal deviations from the procedure will be in the time required for a negative starch-iodide test and the nature and amount of extraction and recrystallization solvent. *It is strongly recommended that any one using the reaction for the first time carry out the preparation on α-phenylethylamine before attempting to use it on other more valuable amines.*

TABLE I PREPARATION OF α-AMINO KETONES

Product	Approx. Reaction Time,[a] min.	Yields, %	Recryst. Solvent	M.P., °C.[b]
Hydrochloride of				
2-Aminocyclopentanone	180	34–36	*i*-PrOH	146–147
2-Aminocyclohexanone	25–45	49–73	*i*-PrOH	156
3-Amino-2-heptanone	210	50–75	*i*-PrOH	134–135
p-Bromophenacylamine	70	58–73	2*N* HCl	275
p-Chlorophenacylamine	80–90	49–60	EtOH	270–271
p-Methoxyphenacylamine	270	62–74	EtOH	200
p-Nitrophenacylamine	60	50–56	MeOH	243
p-Methylphenacylamine	80–90	70–72	*i*-PrOH	206–207
p-Phenylphenacylamine	80	54–71	2*N* HCL	185–186
α-Aminovalerophenone	30	65–66	*i*-PrOH-Et_2O	156.5–158

2-Amino-1-tetralone	100	63–70	*i*-PrOH	201–202
2-Amino-4,4-dimethyl-1-tetralone	300	61–65	*i*-PrOH	212–213
Desylamine (2-amino-2-phenylacetophenone)	30	45–46	*i*-PrOH	233–234
Phenacylamine	45–70	55–78	*i*-PrOH	185–186

*a*Time for negative starch-iodide test.

*b*Usually with decompsition.

3. Discussion

Phenacylamine hydrochloride has been prepared by (1) the hydrolysis of the quaternary salt obtained from phenacyl bromide and hexamethylenetetramine (the Delepine reaction),[5,6,7,8,9,10,11] (2) the hydrolysis of N-phenacylphthalimide (the Gabriel reaction),[12,13,14] (3) the reduction or catalytic hydrogenation of α-oximinoacetophenone,[10,15,16,17,18,19] (4) the reduction of α-nitroacetophenone,[20,21] (5) the catalytic hydrogenation of α-azidoacetophenone,[22] (6) the catalytic hydrogenation of α-benzylaminoacetophenone,[23] (7) the base-catalyzed rearrangement of the tosylate of acetophenone oxime (the Neber rearrangement),[24,25] (8) the base-catalyzed rearrangement of acetophenone dimethylhydrazone methiodide,[26] (9) the Friedel-Crafts acylation of benzene with glycyl chloride hydrochloride,[27] as well as by other procedures of uncertain preparative value. The present procedure is adapted from those of Baumgarten and Bower[19] and Baumgarten and Petersen.[28]

4. Merits of the Preparation

The present procedure is a specific example of a synthetic method of some generality. The procedure describes an example which is of considerable interest *per se* but, perhaps more importantly, which also serves as a model for the use of this procedure for the preparation of other α-amino ketones. In the submitters' laboratory, this specific procedure is used routinely for the training of persons who will be using this general technique or related techniques.[29]

Of the procedures cited in Section 3, procedures (1), (3), and (4) have been examined by the submitters for comparison with the present procedure. Of these, the present procedure and that based on the Delepine reaction (1) appeared to be the most satisfactory for preparative purposes. Yields by the two procedures were comparable; however, the Delepine reaction could be run somewhat more conveniently on a larger scale (provided that one was willing to accept a tedious extraction of the product from

the copious quantity of ammonium salts with which it is mixed). The Delepine reaction also makes a lesser demand on the skill and technique of the operator. On the other hand, attempts in the submitters' laboratory to extend the Delepine reaction to *sec*-bromides have been unsuccessful; therefore the Delepine reaction appears to lack the generality of the present procedure, which shares such generality, apparantly, with procedures (2), (3), (7), and (8). Furthermore, the Delepine reaction gives a mixture of phenacylamine hydrochloride and hydrobromide[5,10] (although the submitters have found that by careful fractional crystallization from isopropyl alcohol-hydrochloric acid solution about 50% of the pure hydrochloride can be obtained).

Under appropriate conditions each of the intermediates shown in the equation may be prepared. Suitable conditions for the preparation of many N-chloroimines are described in this volume.[30] In the event that this procedure is found unsuitable, the use of slightly more than one equivalent of sodium methoxide *at room temperature* may be an acceptable alternative.[31] Solutions of the methoxy aziridine may be obtained by carrying out the present procedure up to the point where the starch-iodide test is negative. In favorable examples the methoxy aziridines may be isolated.[31]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 121
- Org. Syn. Coll. Vol. 5, 208

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

isopropyl alcohol-hydrochloric acid

dichloramine B

tosylate of acetophenone oxime

ethanol (64-17-5)

hydrochloric acid, HCl (7647-01-0)

Benzene (71-43-2)

methanol (67-56-1)

ether (60-29-7)

magnesium, magnesium turnings (7439-95-4)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

sodium methoxide (124-41-4)

sodium (13966-32-0)

isopropyl alcohol (67-63-0)

hexamethylenetetramine (100-97-0)

Phenacyl bromide (70-11-1)

α-Phenylethylamine, dl-α-phenylethylamine (3886-69-9)

α-oximinoacetophenone

α-nitroacetophenone (614-21-1)

Benzenesulfonamide (98-10-2)

phenacylamine

2-aminocyclohexanone

Phenacylamine hydrochloride, Acetophenone, 2-amino-, hydrochloride (5468-37-1)

N,N-dichloro-α-phenylethylamine

N,N-dichlorobenzenesulfonamide (473-29-0)

methanol-magnesium

N-phenacylphthalimide

α-azidoacetophenone

α-benzylaminoacetophenone

acetophenone dimethylhydrazone methiodide

glycyl chloride hydrochloride

2-Aminocyclopentanone

3-Amino-2-heptanone

α-Aminovalerophenone

2-Amino-1-tetralone

2-Amino-4,4-dimethyl-1-tetralone

Desylamine, 2-amino-2-phenylacetophenone

methoxy aziridine

tert-Butyl hypochlorite (507-40-4)

p-Bromophenacylamine

p-Chlorophenacylamine

p-Methoxyphenacylamine

p-Nitrophenacylamine

p-Methylphenacylamine

p-Phenylphenacylamine

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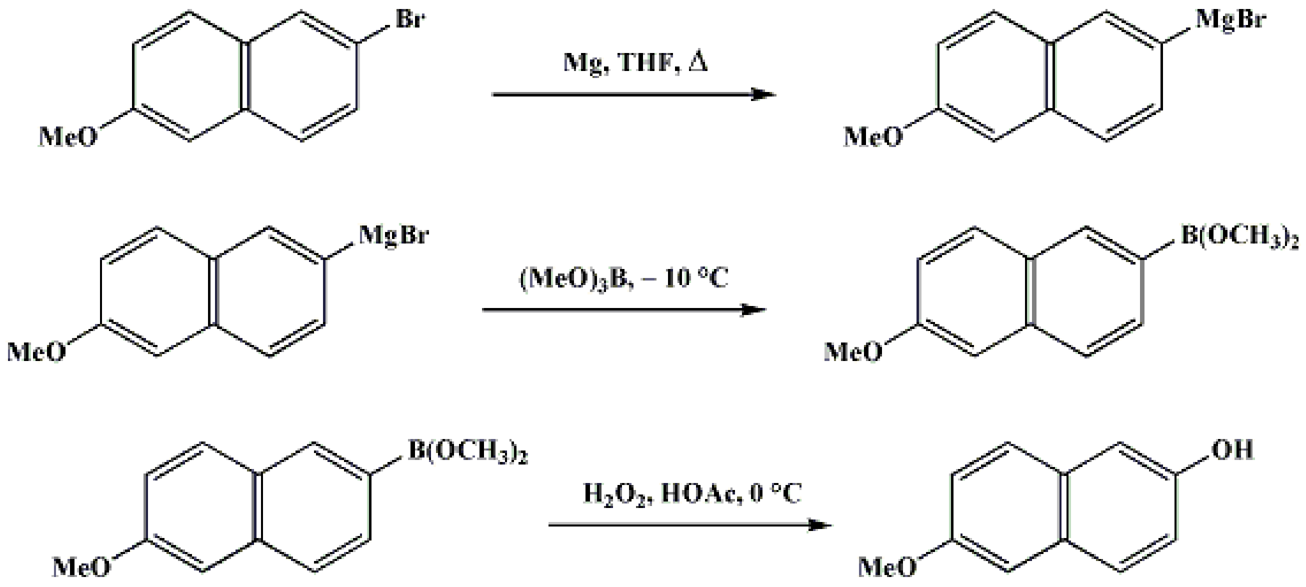
Organic Syntheses, CV 5, 918

PHENOLS: 6-METHOXY-2-NAPHTHOL

[2-Naphthol, 6-methoxy-]



Submitted by R. L. Kidwell, M. Murphy, and S. D. Darling[1].
Checked by R. E. Ireland, J. W. Tilley, and C. Kowalski.

1. Procedure

A 2-l. Three-necked flask equipped with a condenser and containing 27 g (1.1 mole) of magnesium is flame-dried and the atmosphere replaced with nitrogen. A 200-ml. portion of tetrahydrofuran (Note 1) is added along with several lumps, totaling about 95 g., of 6-bromo-2-methoxynaphthalene (Note 2) and a small crystal of iodine. The mixture is heated to reflux until the boiling becomes spontaneous. An additional 600 ml. of tetrahydrofuran is added with more of the bromide to maintain a vigorous reflux, until 237.4 g. (1 mole) of 6-bromo-2-methoxy-naphthalene has been added. After the spontaneous reflux has subsided, the dark solution is heated to reflux for 20minutes.

A 5-l. three-necked flask fitted with a paddle stirrer, a Claisen adapter containing a thermometer well and nitrogen inlet, and a dropping funnel is flame-dried and placed under nitrogen. Into the flask are introduced 125 ml. (1.1 mole) of trimethyl borate (Note 3) and 600 ml. of tetrahydrofuran. This solution is cooled to −10° with an all-encompassing ice-salt bath or a dry ice-carbon tetrachloride bath. The dropping funnel is charged with the Grignard solution which is added over 30 minutes to the borate solution while stirring rapidly and maintaining the temperature between −10° and −5°. A white sludge separates from the solution during the addition. After stirring for an additional 15 minutes, 86 ml. (1.5 mole) of chilled acetic acid (Note 4) is added all at once. This is followed by the addition of a cold solution of 112 ml. (1.1 mole) of 30% hydrogen peroxide in 100 ml. of water, dropwise over 15 minutes, while maintaining the temperature below 0° (Note 5) and stirring vigorously.

The mixture is allowed to warm up over 20 minutes and is poured into a 2-l. separatory funnel. The purplish solution is washed with a saturated ammonium sulfate solution (about 1.5 l) containing ferrous ammonium sulfate until the rust-brown ferric color is no longer produced. The organic layer is dried over magnesium sulfate and concentrated, leaving a dark solid. Purification of the solid by high-vacuum short path distillation gives 127–142 g. (73–81%) of a pinkish or tan-colored product, b.p. 148–150° (0.15 mm.), m.p. 145–147°. It may be further purified by sublimation, or recrystallization from benzene-hexane, m.p. 148–149°.

2. Notes

1. Reagent grade tetrahydrofuran (Mallinckrodt) has been used directly. The formation of the Grignard reagent starts readily and no precipitates are formed. Tetrahydrofuran obtained from the Quaker Oats Company in 1-gal. cans has also been used; the reaction, however, is slower to start, a cloudy precipitate is formed, and the yield is slightly lower. *[Caution! See P. 976]*

2. This starting material is obtained conveniently from the bromination [2] and methylation of 2-naphthol. The procedure is modified by not removing the tin salts.
After bromination of 144 g. (1 mole) of 2-naphthol, the hot solution is poured into water and filtered. The dry precipitate is mixed with a solution of 200 ml. of concentrated sulfuric acid in 500 ml. of technical methanol and heated to vigorous reflux for 4 hours. An oily layer separates during the heating period. The hot mixture is poured into 3 l. of ice and water, and the solids are removed by filtration. The moist solid is triturated with 1 l. of hot 5% sodium hydroxide. After chilling the mixture to solidify the oil, it is filtered and the product is washed and dried. The 6-methoxy-2-bromonaphthalene is purified by distillation, b.p. 114–118° (0.2 mm.). After distillation the product is most conveniently handled by remelting and pouring it into a mold to solidify. The overall yield is 173–208 g. (73–88%), m.p. 101.5–103°.
3. Commercial trimethyl borate contains an appreciable amount of methanol. It is removed by adding anhydrous lithium chloride [3] to the bottle and allowing the mixture to stand with occasional shaking. The upper layer is decanted off and fractionated, b.p. 68–69°. The product must be protected from moisture.
4. Water added at this point hydrolyzes the arylboronic ester extremely rapidly to 2-methoxynaphthalene.
5. The reaction is exothermic. Except for a darkening of the product, no apparent harm results if occasionally the temperature rises to 10–15°.

3. Discussion

The classic caustic fusion of sulfonic acid salts has been used for preparing 2,6-dinaphthol [4] and its derivatives. Other more recent procedures have employed the direct hydrolysis of aryl bromides [5] and the oxidation of aryl Grignard reagents.[6]

The indirect oxidation of an aryl Grignard reagent through a boronic ester nearly doubles the yield of phenol obtained by direct oxidation and decreases the reaction time. Tetrahydrofuran is the preferred solvent. It facilitates the dissolution of the bromide, which is relatively insoluble in diethyl ether, solvates the Grignard reagent, and renders the oxidation reaction homogeneous.

The preparation of 6-methoxy-2-naphthol is of particular interest as the starting point in many synthetic sequences. It is readily converted to 6-methoxy-2-tetralone through a Birch reduction.[7]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

methanol (67-56-1)

diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

magnesium (7439-95-4)

phenol (108-95-2)

nitrogen (7727-37-9)

2-naphthol (135-19-3)

iodine (7553-56-2)

hydrogen peroxide (7722-84-1)

ammonium sulfate (7783-20-2)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

ferrous ammonium sulfate (10045-89-3)

benzene-hexane (1077-16-3)

Lithium chloride (7447-41-8)

6-Methoxy-2-naphthol, 2-Naphthol, 6-methoxy- (5111-66-0)

6-bromo-2-methoxynaphthalene, 6-bromo-2-methoxy-naphthalene, 6-methoxy-2-bromonaphthalene (5111-65-9)

trimethyl borate (121-43-7)

6-methoxy-2-tetralone (2472-22-2)

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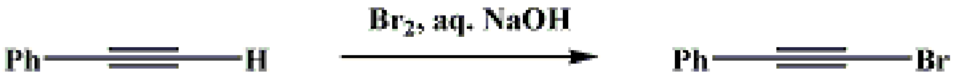
Organic Syntheses, CV 5, 921

PHENYLBROMOETHYNE

[Benzene, bromoethynyl]



Submitted by Sidney I. Miller, Gene R. Ziegler, and R. Wieleseck[1].
Checked by William E. Parham and James N. Wemple.

1. Procedure

To a 2-l. bottle equipped with a rubber stopper and immersed in a mixture of ice and water (slush) there is added a cold (about 0°) solution containing 300 g. (7.5 moles) of sodium hydroxide (Note 1) and 800 ml. of water. The mixture is swirled or stirred while 160 g. (2 moles) of bromine is added. Phenylacetylene (84 g., 0.82 mole) (Note 2) is then added to the yellow solution, and the resulting mixture is stoppered and shaken. The rubber stopper is wired down, the bottle is covered with opaque cloth or paper, and the bottle is then placed in a mechanical shaker for 60 hours at room temperature (Note 3).

The crude oil is then separated from the aqueous phase, dried with calcium chloride (Note 4). and fractionated (Note 5) at reduced pressure under nitrogen *(Caution! (Note 6))*. The distillation receiver should be cooled in an ice-salt or dry ice-acetone mixture. After a small fore-run of phenylacetylene, there is obtained 109–124 g. (73–83% yield) of water-white phenylbromoethyne, b.p. 40–41° (0.1 mm.) n^{25}D 1.6075 (Note 7).

2. Notes

1. Practical grade sodium hydroxide and bromine were used.
2. Commercially available phenylacetylene can be used. The checkers used material as obtained from Columbia Organic Chemicals co., Inc.
3. Vigorous shaking is essential. For this reaction rate = $k[C_6H_5 C$ ☐ $CH] [OBr^-] [OH^-]$ with $k = 7\ M^{-2}\ sec.^{-1}$ at 25°.[2] Since the solubility of phenylacetylene at 25° is 5.1×10^{-3} M in water (2.0×10^{-3} M in 2*M* sodium chloride), efficient mixing of the reagents is of paramount importance.[2] An ordinary motor-drive stirrer proved to be inadequate. Phenylbromoethyne gradually darkens when exposed to light or air. The product is best stored under nitrogen in a refrigerator and should be distilled within a few days of its preparation.
4. The checkers observed that the calcium chloride absorbs appreciable quantities of product. The crude oil was dissolved in peroxide-free ether (about 300 ml.) prior to drying with calcium chloride, or the calcium chloride was

extracted with several 50-ml. portions of dry ether after use. The ethereal extracts were concentrated under nitrogen and added to the product before distillation.

5. The checkers distilled the product from a flask equipped with a Claisen head but no column.

6. No air should be allowed to come in contact with the hot pot liquid during the distillation, for an exothermic reaction may occur; at best this may fill the apparatus with tarry material and the room with noxious fumes; at worst, pressure built up may destroy all or part of the apparatus. As a precaution, this distillation should be carried out behind a safety shield.

7. The checkers observed that the refractive index of a sample stored for 5 days in the refrigerator in a stoppered tube wrapped in aluminum foil and cloth changed from n^{25}_{D} 1.6074 to n^{25}_{D} 1.6082.

3. Discussion

Phenylbromoethyne has been prepared by base-catalyzed dehydrobromination of 1,1- or 1,2-dibromostyrene;[3] by the thermal decomposition of silver 1,2-dibromocinnamate;[3] from phenylethynylmagnesium Grignard reagent and bromine;[4,5] cyanogen bromide,[6] or benzenesulfonic anhydride;[7] from phenylethynylsodium and cyanogen bromide[5] or *p*-toluenesulfonylbromide[8]; from phenylethynylsilver and bromine in pyridine;[9] and from phenylethynyllithium and N-bromoimides.[10] The present method is a modification of one in which the hypobromite-phenylacetylene mixture is warmed for 1.5 hours in the presence of an emulsifying agent, 1% potassium stearate[11] or soap,[12] to give 88% yield of product.

4. Merits of the Preparation

The hypohalite route to 1-chloro-, 1-bromo-, or 1-iodoalkynes is both general and convenient. The purity of the reagents does not appear to be critical.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

peroxide-free ether

1,1- or 1,2-dibromostyrene

calcium chloride (10043-52-4)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

bromine (7726-95-6)

nitrogen (7727-37-9)

aluminum (7429-90-5)

pyridine (110-86-1)

Phenylacetylene (536-74-3)

Cyanogen bromide (506-68-3)

Phenylbromoethyne, Benzene, bromoethynyl (932-87-6)

silver 1,2-dibromocinnamate

phenylethynylmagnesium

benzenesulfonic anhydride (512-35-6)

phenylethynylsodium

phenylethynylsilver

phenylethynyllithium (4440-01-1)

potassium stearate

p-toluenesulfonylbromide

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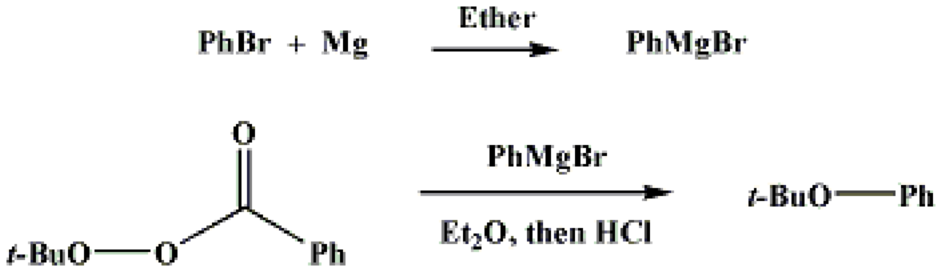
Organic Syntheses, CV 5, 924

PHENYL *t*-BUTYL ETHER

[Ether, *tert*-butyl phenyl]

[Method I]



Submitted by Christer Frisell and Sven-Olov Lawesson[1].
Checked by William G. Dauben and Gilbert H. Berezin..

1. Procedure

A 1-l., three-necked, round-bottomed flask equipped with a sealed mechanical stirrer, a reflux condenser, and a 500-ml. pressure-equalized dropping funnel is arranged for conducting a reaction in an atmosphere of nitrogen by fitting into the top of the condenser a T-tube attached to a low-pressure supply of nitrogen and to a mercury bubbler. The flask is dried by warming with a soft flame as a slow stream of nitrogen is passed through the system. In the cooled flask a solution of phenylmagnesium bromide is prepared from 13 g. (0.53 g. atom) of magnesium turnings, 79 g. (0.5 mole, 53.6 ml.) of bromobenzene, and 200 ml. of anhydrous ether.

After the preparation of phenylmagnesium bromide is complete, the ethereal solution is cooled in an ice bath and 200 ml. of anhydrous ether is added. A solution of 58.3 g. (0.3 mole, 56 ml.) of *t*-butyl perbenzoate (Note 1) in 120 ml. of anhydrous ether is added, dropwise, with stirring over a 30-minute period, and the stirring is continued for an additional 5 minutes.

The reaction mixture is poured carefully into a cold solution of 40 ml. of concentrated hydrochloric acid in 1 1. of water. The ethereal layer is separated, and the aqueous layer is extracted twice with 150-ml. portions of ether. The combined organic layers are extracted with three 25-ml. portions of 2*M* sodium hydroxide solution, washed with water until the washings are neutral, and then dried over anhydrous magnesium sulfate (Note 2) and (Note 3). The dried solution is concentrated and the product distilled under reduced pressure, b.p. 57–59°/7 mm. The yield of phenyl *t*-butyl ether is 35–38 g. (78–84%), n_D^{25} 1.4870–1.4880. This synthetic process is applicable to the preparation of other *t*-butyl ethers (Note 4).

2. Notes

1. *t*-Butyl perbenzoate is supplied by Lucidol Division, Wallace and Tiernan Inc., Buffalo 5, New York, or L. Light & Co., Ltd., Colnbrook, Bucks, England. The Lucidol product contains 98% *t*-butyl perbenzoate.
2. The ethereal solution should be tested for peroxides as follows: A few milligrams of sodium iodide, a trace of ferric chloride, and 3 ml. of glacial acetic acid are placed in a test tube and 2 ml. of the ether solution added carefully. When unconsumed perbenzoate is present, a yellow ring is formed immediately between the two phases. If a positive test is obtained, the acid and base treatments should be repeated.
3. By acidification of the sodium hydroxide solution, 29–32 g. of benzoic acid (80–90%) is obtained.
4. The same general method[2] has been used by the submitters to prepare *o*-tolyl *t*-butyl ether,[3] *m*-tolyl *t*-butyl ether,[3] benzyl *t*-butyl ether,[3] and *p*-anisyl *t*-butyl ether.

3. Discussion

The method presented is essentially that described by Lawesson and Yang.[4] Phenyl *t*-butyl ether has been prepared by acid-catalyzed condensation of isobutylene and phenol[5] by reaction of diphenyliodonium chloride with potassium *t*-butoxide,[6] and by the next procedure in this volume.[7]

4. Merits of Preparation

The synthesis of *t*-butyl ethers by the reaction of Grignard reagents with *t*-butyl perbenzoate appears to have considerable generality (Note 4), and the perester is a stable, readily available material.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 926

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

t-butyl perbenzoate

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ether (60-29-7)

sodium hydroxide (1310-73-2)

magnesium turnings (7439-95-4)

phenol (108-95-2)

nitrogen (7727-37-9)

Benzoic acid (65-85-0)

bromobenzene (108-86-1)

ferric chloride (7705-08-0)

Phenylmagnesium bromide (100-58-3)

sodium iodide (7681-82-5)

magnesium sulfate (7487-88-9)

isobutylene (9003-27-4)

diphenyliodonium chloride (1483-72-3)

potassium t-butoxide (865-47-4)

PHENYL t-BUTYL ETHER, Ether, tert-butyl phenyl (6669-13-2)

o-tolyl t-butyl ether (15359-96-3)

p-anisyl t-butyl ether (15360-00-6)

m-tolyl t-butyl ether

benzyl t-butyl ether

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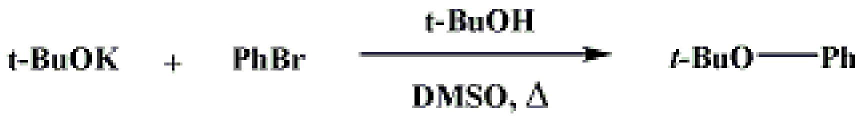
Organic Syntheses, CV 5, 926

PHENYL *t*-BUTYL ETHER

[Ether, *t*-butyl phenyl]

[Method II]



Submitted by Melville R. V. Sahyun and Donald J. Cram[1].
Checked by William G. Dauben and David J. Ellis.

1. Procedure

In a loosely stoppered 1-l. round-bottomed flask are placed 37.5 g. (48 ml.) of *t*-butyl alcohol, 150 ml. of dimethyl sulfoxide (Note 1), and a Teflon®-coated magnetic stirring bar. The solution is heated in an oil bath which is placed on a combination magnetic stirrer-hotplate. When the temperature of the mixture reaches 125–130°, 75 g. (0.67 mole) of alcohol-free potassium *t*-butoxide (Note 2) and (Note 3) is added, the stopper is replaced loosely, and the mixture is stirred. When all the potassium *t*-butoxide is in solution, the stopper is removed, 25 g. (0.159 mole, 17 ml.) of bromobenzene is added in one portion to the hot solution, and an air condenser fitted with a drying tube is *rapidly* placed on the flask. The solution immediately turns dark brown, and an extremely vigorous, exothermic reaction occurs. After 1 minute the reaction mixture is poured into 500 ml. of water. The aqueous solution is saturated with sodium chloride and extracted with four 200-ml. portions of ether (Note 4). The ether extract is washed with three 100-ml. portions of water and dried over anhydrous potassium carbonate. The ether is distilled at atmospheric pressure on a steam bath to leave 17–18 g. of crude phenyl *t*-butyl ether (Note 5). The brown oil is distilled to yield 10–11 g. (42–46%) of pure phenyl *t*-butyl ether, b.p. 45–46° (2 mm.), m.p. −17 to −16°, n^{25}_{D} 1.4860–1.4890 (Note 6). The ether may be hydrolyzed readily to phenol (Note 7).

2. Notes

1. "Baker Analyzed" dimethylsulfoxide, which is freshly opened and dry to Karl Fischer reagent, is used without further purification.
2. Commercial potassium *t*-butoxide is used directly as obtained from the Mine Safety Appliance Reserach Corp., Callery, Pennsylvania.
3. This amount of potassium *t*-butoxide is not soluble in the dimethylsulfoxide at a lower temperature. An excess of base over *t*-butyl alcohol is necessary to the reaction, and a high concentration of *t*-butyl alcohol (3.3*M*) considerably

improves the yield of product desired.
4. The aqueous residue from the extraction can be acidified and extracted to yield phenol which is purified by chromatography on a silica gel column, with an eluant solution composed of 95% pentane and 5% ether by volume. The purified phenol weighs 4.3 g. (29% of the theoretical amount) and is obtained as long needles.
5. The crude material also contains some polymeric material and traces of solvent. Gas chromatography indicates that the phenyl *t*-butyl ether is 60–70% pure at this point.
6. The checkers found their product to contain 0.5–1.0% bromobenzene. Careful redistillation is required to free the product of this impurity.
7. Phenyl *t*-butyl ether is swirled with 6*N* hydrochloric acid until solution is completed. The solution is then saturated with sodium chloride and extracted with ether to yield phenol, identifiable as the tribromide.

3. Discussion

The procedure described here is based on a method outlined by Cram, Rickborn, and Knox.[2] The method is not a general one for the preparation of a substituted phenyl *t*-butyl ether because an aryne intermediate is involved. It appears that aryl fluorides undergo direct substitution to yield unrearranged aryl *t*-butyl ethers. Alternative methods for preparation of these ethers are listed on page 924.

4. Merits of the Preparation

This reaction sequence illustrates how the rates of many basecatalyzed reactions can be enhanced greatly by substitution of dimethylsulfoxide for the usual hydroxylic solvents.[3] Other examples of the enhanced reactivity of anions in dimethylsulfoxide are found in Wolff-Kishner reductions and Cope elimination reactions.[5] The present reaction illustrates the generation of an aryne intermediate from bromobenzene.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 924
- Org. Syn. Coll. Vol. 6, 683
- Org. Syn. Coll. Vol. 6, 991

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alcohol-free potassium t-butoxide

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium chloride (7647-14-5)

bromobenzene (108-86-1)

Pentane (109-66-0)

dimethyl sulfoxide, dimethylsulfoxide (67-68-5)

t-butyl alcohol (75-65-0)

potassium t-butoxide (865-47-4)

PHENYL t-BUTYL ETHER, Ether, t-butyl phenyl (6669-13-2)

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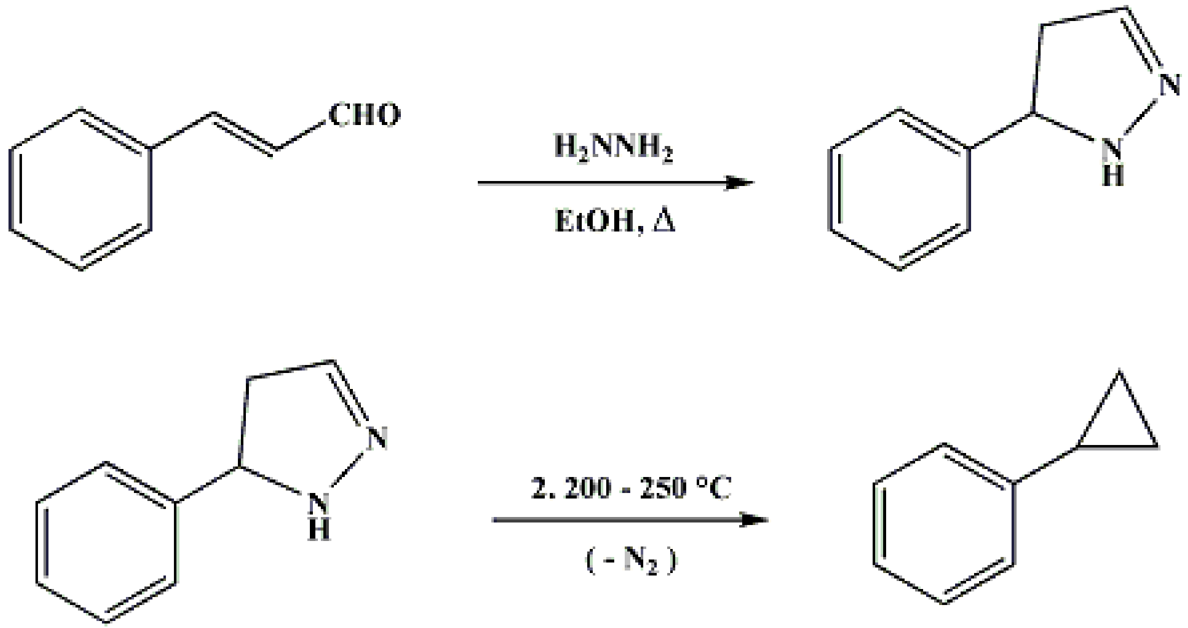
PHENYLCYCLOPROPANE

[Benzene, cyclopropyl-]



Submitted by R. J. Petersen and P. S. Skell[1].
Checked by Thomas R. Lynch and Peter Yates.

1. Procedure

Caution! This reaction should be carried out behind a safety screen.

A 1-l. three-necked flask is fitted with a reflux condenser, an addition funnel, and a thermometer. It is charged with 450 ml. of 95% ethanol, 230 ml. (236 g.) of 85% hydrazine hydrate (Note 1), and several porcelain boiling chips. The solution is brought to reflux with a heating mantle. Cinnamaldehyde (200 g., 1.51 moles) (Note 2) is added dropwise over a period of 45 minutes to the refluxing solution, while the mixture turns orange because of the formation of cinnamalazine in a side reaction (Note 3). After an additional 30 minutes at reflux, the flask is fitted with a simple takeoff head, and ethanol, water, and hydrazine hydrate are slowly removed by distillation. After approximately 3 hours the pot temperature rises to 200°, and phenylcyclopropane begins to codistil with the last of the hydrazine hydrate (Note 4). The distillate from this point is collected in a 250-ml. receiver, the main fraction coming over at 170-80°. When the pot temperature exceeds 250°, the decomposition is essentially complete (Note 5), (Note 6).

The crude, cloudy distillate (110–130 g.) is washed twice with 100-ml. portions of water and dried over anhydrous potassium carbonate. Distillation at reduced pressure, b.p. 60° (13 mm.), 79–80° (37 mm.), through a 12-in. Vigreux column gives

phenylcyclopropane pure enough for most purposes; yield 80–100 g. (45–56%), $n^{25}D$ 1.5309.

2. Notes

1. Matheson, Coleman and Bell technical grade 85% hydrazine hydrate was used.
2. Eastman Organic Chemicals cinnamaldehyde gave satisfactory results. If colorless crystals are present in the neck of the bottle or on the walls above the liquid, the cinnamaldehyde is seriously contaminated with cinnamic acid and should be distilled before use. A small amount of cinnamic acid apparently does not affect the yield of phenylcyclopropane.
3. Reversal of the addition procedure results in formation of cinnamalazine as a major product.
4. Earlier investigators employed strong bases (sodium hydroxide, potassium hydroxide) or platinum on asbestos to catalyze the decomposition of 5-phenylpyrazoline. These catalysts are not necessary and should be avoided because they also cause the reduction of cinnamalhydrazone to propenylbenzene. Phenylcyclopropane can be freed from propenylbenzene only with great difficulty.
5. The checkers found in a full-scale run that the pot temperature had to be raised to close to 250° before the onset of reaction, which was then very vigorous.
6. Pyrazoline vapors are known to be rather flammable. It is advisable, therefore, to cool the pyrolysis flask somewhat before dismantling the apparatus. The syrupy residue in the flask sets to a hard mass on cooling; it can be removed by heating under dimethylformamide on a steam bath overnight.

3. Discussion

Phenylcyclopropane has been prepared by the base-catalyzed decomposition of 5-phenylpyrazoline (33%),[2] by the reaction of 1,3-dibromo-1-phenylpropane with magnesium (68%),[3] and by the reaction of 3-phenylpropyltrimethylammonium iodide with sodium amide in liquid ammonia (80%).[4] However, the method frequently used at present is the reaction of styrene with the methylene iodide-zinc reagent (32%).[5]

4. Merits of the Preparation

The procedure outlined is much quicker and simpler than previous methods. Starting materials are readily available, and the preparation can be run on any scale in the length of a day. Because exclusion of a basic catalyst eliminates the Wolff-Kishner reduction of the cinnamalhydrazone, separation of the 5-phenylpyrazoline from cinnamalhydrazone, or of phenylcyclopropane from propenylbenzene, does not have to be effected. The present procedure can also be used to convert other ring-substituted

cinnamaldehydes to the corresponding arylcyclopropanes.

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

cinnamalazine

cinnamalhydrazone

ethanol (64-17-5)

potassium carbonate (584-08-7)

ammonia (7664-41-7)

sodium hydroxide (1310-73-2)

magnesium (7439-95-4)

platinum (7440-06-4)

potassium hydroxide (1310-58-3)

hydrazine hydrate (7803-57-8)

cinnamic acid (621-82-9)

cinnamaldehyde

styrene (100-42-5)

propenylbenzene

sodium amide (7782-92-5)

dimethylformamide (68-12-2)

Benzene, cyclopropyl-, Phenylcyclopropane (873-49-4)

1,3-Dibromo-1-phenylpropane (17714-42-0)

5-phenylpyrazoline

3-phenylpropyltrimethylammonium iodide (2125-48-6)

pyrazoline

methylene iodide-zinc

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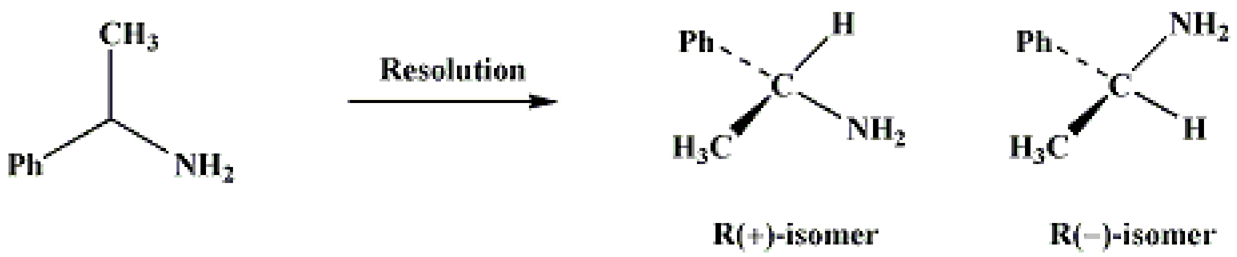
Organic Syntheses, CV 5, 932

R(+)- AND S(–)-α-PHENYLETHYLAMINE

[Benzylamine, α-methyl]



Submitted by Addison Ault[1]
Checked by Martin Gall, Elia J. Racah, and Herbert O. House.

1. Procedure

A. *(S)-(–)-α-Phenylethylamine*. A mixture of 31.25 g. (0.208 mole) of (+)-tartaric acid and 450 ml. of methanol is placed in a 1-l. Erlenmeyer flask and heated to boiling. To the hot solution is added, cautiously to avoid foaming, 25.0 g. (26.2 ml., 0.206 mole) of racemic α-phenylethylamine (Note 1) and the resulting solution is allowed to cool. Since crystallization occurs slowly, the solution should be allowed to stand at room temperature for approximately 24 hours. The (–)-amine (+)-hydrogen tartrate salt separates as white prismatic crystals (Note 2). The product (18.1–19.3 g.) should be collected on a filter and washed with a small volume of methanol. The combined mother liquor and methanol washings should be concentrated to a volume of 175 ml. with a rotary evaporator. The resulting mixture is then heated to boiling, and the solution is allowed to cool and stand at room temperature for approximately 24 hours. In this way an additional crop (2.0–3.8 g.) of the (–)-amine (+)-hydrogen tartrate salt may be separated as white prisms (Note 2). The combined methanolic mother liquors and washings from these crystallizations are concentrated to dryness on a rotary evaporator. The crude residual salt is used for the preparation of the (+)-amine.

The combined crops of crude (–)-amine (+)-hydrogen tartrate are pulverized in a mortar and redissolved in 450–500 ml. of boiling methanol. The resulting hot solution is concentrated to 350 ml. (Note 3) and then allowed to cool and stand for 24 hours. After the initial crop (14.3–16.2 g.) of pure (–)-amine (+)-hydrogen tartrate has been collected as white prisms (Note 2) (m.p. 179–182° dec.), the mother liquors and washings are concentrated to 75 ml. and again allowed to stand for 24 hours. In this way a second crop (2.9–3.6 g.) of the pure (–)-amine salt is obtained. The total yield of the pure (–)-amine salt is 17.9–19.1 g. (64–68%).

A mixture of the pure (–)-amine salt (17.9–19.1 g.) and 90 ml. of water is treated with 15 ml. of aqueous 50% sodium hydroxide and the resulting mixture is shaken with four 75-ml. portions of ether. After the combined ether extracts have been washed with

50 ml. of saturated aqueous sodium chloride and dried over magnesium sulfate, the bulk of the ether is distilled from the mixture through a 30-cm. Vigreux column and the residual liquid is distilled under reduced pressure. The (−)-amine is collected as 6.9–7.2 g. (55–58%) of colorless liquid, b.p. 94–95° (28 mm.), n^{25}D 1.5241–1.5244, [α]^{29}D − 39.4° (neat) (Note 4), (Note 5).

B. *(R)-(+)-α-Phenylethylamine*. The residual salts (approximately 35 g.) obtained by concentration of the methanolic mother liquors from the initial crystallization of the (−)-amine (+)-hydrogen tartarate are treated successively with 160 ml. of water and 25 ml. of aqueous 50% sodium hydroxide. After the resulting mixture has been extracted with ether, the extract is dried, concentrated, and distilled as previously described. The recovered amine amounts to 12.5–14.1 g. of colorless liquid, b.p. 79–80° (18 mm.), [α]^{28}D +23.8 to +24.7° (neat). From the weight and specific rotation data for this amine sample and the reported[2] specific rotation, [α]^{25}D +40.6° (neat), for the pure (+)-amine, the amount of excess (+)-amine present in the recovered amine sample is calculated. Typical values range from 0.06 to 0.07 mole of excess (+)-amine. A solution of this partially resolved amine in 90 ml. of 95% ethanol is heated to boiling and then treated with 180 ml. of an ethanolic solution containing a sufficient amount (0.03–0.035 mole) of concentrated sulfuric acid to convert the excess (+)-amine to its neutral sulfate salt (Note 6). The hot solution is allowed to cool to room temperature, and the crude (+)-amine sulfate which separates as white needles (7.8–9.3 g.) is collected on a filter and washed with 95% ethanol. The combined ethanolic mother liquors and washings are concentrated and allowed to cool to separate a second crop (1.2–1.4 g.) of the crude (+)-amine sulfate. The combined crops of (+)-amine sulfate are dissolved in a minimum volume (about 45 ml. of hot water), and the resulting hot solution is diluted with acetone until it is just saturated at the boiling point. After the solution has been allowed to cool to room temperature, the pure (+)-amine sulfate which separates as white needles, m.p. 240–265° dec. (5.0–6.1 g.) is collected on a filter and washed with cold 95% ethanol. The combined mother liquors and washings are concentrated to dryness, and the residual solid is recrystallized from aqueous acetone to separate additional crops (2.6–2.8 g.) of the pure (+)-amine sulfate. The total yield of the pure amine sulfate is 7.8–8.9 g. (45–51% on the basis of the starting α-phenylethylamine).

A mixture of the pure (+)-amine sulfate (7.8–8.9 g.) and 40 ml. of water is treated with 6.0 ml. of aqueous 50% sodium hydroxide and the resulting mixture is shaken with four 75-ml. portions of ether. The combined ether extracts are washed with 50 ml. of saturated aqueous sodium chloride, dried over magnesium sulfate, and concentrated by distillation of the ether through a 30-cm. Vigreux column. The residual liquid is distilled under reduced pressure to separate 5.1–5.5 g. (41–44%) of the (+)-amine as a colorless liquid, b.p. 85–86° (21 mm.), n^{25}D 1.5243–1.5248, [α]^{29}D +39.7° (neat) (Note 7).

2. Notes

1. A practical grade of racemic α-phenylethylamine supplied by Eastman Organic Chemicals is satisfactory. However, if the racemic amine is highly discolored, distillation before use is recommended.
2. Sometimes a salt separates in the form of white needles. The (–)-amine recovered from these needlelike crystals is not optically pure; $[\alpha]^{25}D$ –19° to –21° (neat). If the product separates either partially or completely as needlelike crystals during the crystallization, the mixture should be warmed until all the needlelike crystals have dissolved, and then the solution should be allowed to cool slowly. If possible, the solution should be seeded with the prismatic crystals. Separation of the prismatic and needlelike crystals can also be effected by taking advantage of the fact that the needles dissolve more rapidly than the prisms in warm methanol.
3. Because of the low rate of solution of the amine salt, the desired solution is obtained most rapidly by dissolving the salt in excess solvent and then concentrating the solution.
4. The literature value (d_4^{25} 0.9528)[2] for the density of α-phenylethylamine was used to calculate the specific rotation.
5. From the reported specific rotation value, $[\alpha]^{25}D$ –40.14° (neat),[3] $[\alpha]^{22}D$ –40.3° (neat),[4] the optical purity of this preparation is estimated to be 98%. The boiling point of this amine at atmospheric pressure is 186–187°.
6. For example, a 14.1-g. (0.116 mole) sample of amine, $[\alpha]^{28}D$ +23.8° (neat), was estimated to contain 0.0676 mole of excess (+)-amine. Therefore 3.52 g. (0.0345 mole) of concentrated sulfuric acid was added.
7. From the reported specific rotation value, $[\alpha]^{25}D$ +40.6° (neat),[2] the optical purity of this preparation is estimated to be 98%. The boiling point of this amine at atmospheric pressure is 186–187°.

3. Discussion

The method presented is based on the procedure of Theilaker and Winkler.[4] It makes use of (+)-tartaric acid, an inexpensive and readily available material, as the resolving agent and provides optically pure samples of both enantiomers of α-phenylethylamine.

Some other methods of resolution include the use of *l*-malic acid [(+)-form],[5] *l*- and *dl*-malic acids [(+)- and (–)-forms],[6] *l*-malic acid and *d*-tartaric acids [(+)- and (–)-forms],[7] *d*-α-bromocamphor-π-sulfonic acid [(–)-form],[8] *l*-quinic and *d*-tartaric acids [(+)- and (–)-forms],[9] 2,3,4,6-tetraacetyl-D-glucose [(+)-form],[10] and barium (–)-bornyl sulfate [(+)- and (–)-forms].[11]

The enantiomers of this amine are useful resolving agents. Some of the compounds which have been resolved with one of the optically active forms of α-phenylethylamine are: mandelic acid,[12] α-methylmandelic acid,[13] α-ethylmandelic acid,[14] 2-phenylpropionic acid,[15] 2-(*p*-nitrophenyl) propionic acid,[16] 2,3-dichloro-2-

methylpropionic acid,[17] 2-phenylbutyric acid,[15] 2-phenylvaleric acid,[18] 2-phenylcaproic acid,[18] α-methylhydrocinnamic acid,[19] β-methylhydrocinnamic acid,[20] benzylsuccinic acid,[21] N-formylphenylalanine,[22] N-acetyl-3,5-dibromotyrosine,[23] N-acetyltryptophan,[24] 6,6'-dinitrodiphenic acid,[25] and 3-methylcyclohexanone and β-methylcinnamaldehyde, via the amine bisulfite complexes.[26]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

R(+)- AND S(−)-α-PHENYLETHYLAMINE

racemic α-phenylethylamine

d-α-bromocamphor-π-sulfonic acid

barium (−)-bornyl sulfate

6,6'-dinitrodiphenic acid

(S)-(−)-α-Phenylethylamine

ethanol (64-17-5)

sulfuric acid (7664-93-9)

methanol (67-56-1)

ether (60-29-7)

sodium hydroxide (1310-73-2)

Mandelic acid (90-64-2)

sodium chloride (7647-14-5)

acetone (67-64-1)

(+)-tartaric acid (87-69-4)

magnesium sulfate (7487-88-9)

l-malic acid (617-48-1)

α-Phenylethylamine, Benzylamine, α-methyl (3886-69-9)

α-methylmandelic acid (515-30-0)

2-Phenylpropionic acid (492-37-5)

2,3,4,6-tetraacetyl-D-glucose

α-ethylmandelic acid

2,3-dichloro-2-methylpropionic acid (10411-52-6)

2-phenylbutyric acid (90-27-7)

2-phenylvaleric acid

2-phenylcaproic acid

α-methylhydrocinnamic acid (1009-67-2)

β-methylhydrocinnamic acid (4593-90-2)

benzylsuccinic acid (36092-42-9)

N-formylphenylalanine

N-acetyl-3,5-dibromotyrosine

N-acetyltryptophan (1218-34-4)

3-methylcyclohexanone (591-24-2)

β-methylcinnamaldehyde

2-(p-nitrophenyl) propionic acid (19910-33-9)

(R)-(+)-α-Phenylethylamine (2627-86-3)

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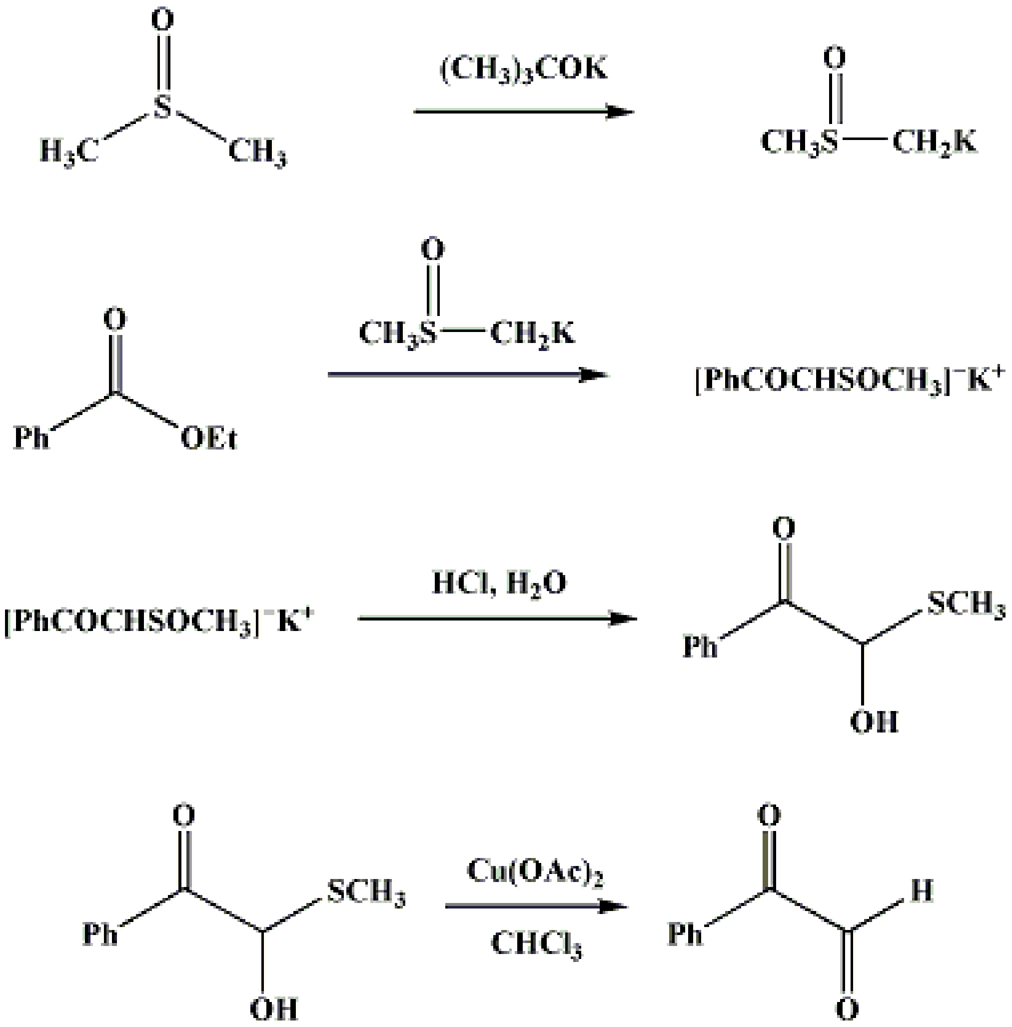
Organic Syntheses, CV 5, 937

PHENYLGLYOXAL

[Glyoxal, phenyl-]



Submitted by Gerard J. Mikol and Glen A. Russell[1].
Checked by William G. Dauben, Michael H. McGann, and Noel Vietmeyer.

1. Procedure

A. *Phenylglyoxal hemimercaptal*. In a 1-l. three-necked flask equipped with an all-glass mechanical stirrer, a 125-ml. dropping funnel, and a condenser fitted with a nitrogen-inlet tube are placed 90 ml. (99 g., 1.27 moles) of dry dimethyl sulfoxide (Note 1), 120 ml. of dry *t*-butyl alchohol (Note 1), and 57.4 g. (0.51 mole) of potassium *t*-butoxide (Note 2) and (Note 3). The mixture is warmed to 80°; when all the solid has dissolved, the heating is discontinued, and 72 ml. (75 g., 0.50 mole) of dry ethyl benzoate (Note 1) is added slowly from the dropping funnel. The reaction mixture is stirred at room temperature for 4 hours, and the solvent is removed at 80–90° under reduced pressure until the volume of the reaction mixture has been reduced to 150 ml. (Note 4). The residue is poured into 500 ml. of an ice-water slurry. The

resulting aqueous solution is extracted with three 100-ml. portions of ether, and the ethereal extracts are discarded (Note 5). The aqueous solution is acidified with a solution of 190 ml. of concentrated hydrochloric acid in 675 ml. of water, and the mixture is allowed to stand at room temperature for 30 hours. The pale yellow precipitate is removed by suction filtration, washed with 500 ml. of cold water, and air-dried to yield 69–74 g. (76–81%) of phenylglyoxal hemimercaptal, m.p. 103–105°.

B. *Phenylglyoxal*. The phenylglyoxal hemimercaptal prepared as described in procedure A (69–74 g.) is dissolved in 400 ml. of warm chloroform, and 60 g. (0.30 mole) of powdered cupric acetate monohydrate is added in one portion to the well-stirred solution. The mixture is stirred at room temperature for 1 hour; the solids are removed by suction filtration and washed with two 75-ml. portions of chloroform. The combined chloroform filtrate and washings are shaken in a separatory funnel with 75 ml. of water; 20 g. of powdered sodium carbonate is added in small portions to the funnel, and the chloroform solution is shaken with the neutralized aqueous solution. *(Caution! Carbon dioxide is evolved.)* The aqueous layer is separated and extracted with four 30-ml. portion of chloroform. The chloroform solutions are combined and dried with anhydrous magnesium sulfate, and the chloroform is removed under reduced pressure. The residue is fractionally distilled under reduced pressure to yield 43–49 g. (64–73%, based on ethyl benzoate) of anhydrous phenylglyoxal as a yellow liquid, b.p. 63–65° (0.5 mm.).

2. Notes

1. The presence of water results in very rapid saponification of ethyl benzoate. Dimethyl sulfoxide (Crown Zellerbach Corp.) may be dried by stirring with calcium hydride for 4–8 hours, followed by distillation under reduced pressure at 80–90° without filtration. Commercial *t*-butyl alcohol and ethyl benzoate are conveniently dried by stirring for 2–4 hours with calcium hydride followed by filtration.
2. Potassium *t*-butoxide was obtained from Mine Safety Appliances Corp.
3. The potassium salt of dimethyl sulfoxide can also be prepared in the following manner. In a 1-l. three-necked flask equipped with an all-glass mechanical stirrer, a 125-ml. dropping funnel containing 90 ml. of dry dimethyl sulfoxide (Note 1), and a Claisen distillation head and condenser is placed 425 ml. of dry *t*-butyl alcohol (Note 1). The system is flushed with dry nitrogen, and 20 g. (0.51 g. atom) of potassium is added (Note 6). The system is closed to the atmosphere by a mineral oil bubbler through which the evolved hydrogen escapes. The mixture is stirred at 80° until the potassium has dissolved. After cooling, the unreacted alcohol is removed by distillation under reduced pressure until a thick slurry of potassium *t*-butoxide remains (Note 7). The dimethyl sulfoxide is added from the dropping funnel, and the mixture is heated to 80–90° to dissolve all the solid. The solution is maintained at this temperature, and additional *t*-butyl alcohol is removed under reduced pressure until the volume of

the solution is reduced to 300 ml.

4. Since the volume of the solution at this point is critical, the reaction flask should be calibrated.

5. The aqueous solution can be used to prepare 2-(methylsulfinyl)acetophenone by the following procedure. The solution is acidified to pH 1–2 (Hydrion paper) by the slow addition of concentrated hydrochloric acid with vigorous stirring and is extracted immediately with two 100-ml. portions of chloroform. The chloroform extracts are combined, washed with 75 ml. of saturated aqueous sodium carbonate and two 75-ml. portions of water, and dried over anhydrous magnesium sulfate. The chloroform is removed under reduced pressure, and the resulting solid is pulverized, slurried with 100 ml. of ether, collected by filtration, and air-dried. The 2-(methylsulfinyl)acetophenone weighs 75–77 g. (82–85%); m.p. 85–86°. It can be converted to phenylglyoxal hemimercaptal by treatment with dilute hydrochloric acid in dimethyl sulfoxide solution at room temperature (2 ml. of dimethyl sulfoxide, 2 ml. of concentrated hydrochloric acid, and 15 ml. of water per gram of the keto sulfoxide). The solution is allowed to stand at room temperature for 30 hours, after which the phenylglyoxal hemimercaptal can be isolated as described in procedure A.

6. The potassium should be free of oxide and/or hydroxide to avoid subsequent saponification of ethyl benzoate.

7. A heating mantle may be used, but care must be taken to avoid decomposition on the walls of the flask due to overheating during the later stages of the distillation.

3. Discussion

Phenylglyoxal has been prepared from isonitrosoacetophenone via the bisulfite compound[2] and by treatment with nitrosyl sulfuric acid[3] or nitrous acid.[4] It has also been prepared by oxidation of benzoylcarbinol with cupric acetate,[5] by heating or aqueous hydrolysis of 2-acetoxy-2-bromoacetophenone,[6] by selenium dioxide oxidation of acetophenone,[7] by oxidation of phenacyl bromide with dimethyl sulfoxide,[8] by oxidative bromination of phenylglyoxal diethyl mercaptal,[9] and by treatment of 2,2-dibromoacetophenone with morpholine followed by acidic hydrolysis.[10] Excellent yields of phenylglyoxal hemihydrate can be obtained on a small scale by the hydrolysis of phenylglyoxal hemimercaptal with boiling dilute hydrochloric acid[11] or in one step from 2-(methylsulfinyl) acetophenone by hydrolysis with boiling 8% phosphoric acid.

4. Merits of the Preparation

This procedure provides a convenient synthesis of phenylglyoxal from readily available starting materials. In addition the method described appears to have general utility for the synthesis of glyoxals. It has been used for the synthesis of *p*-

tolylglyoxal, *p*-methoxyphenylglyoxal, *p*-bromophenylglyoxal, and cyclohexylglyoxal. Since β-keto sulfoxides are readily alkylated in basic solution to yield α-alkyl β-keto sulfoxides,[12] it would appear possible to extend the scope of the reaction to yield a variety of α-diketones.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Phenylglyoxal hemimercaptal

t-butyl alchohol

potassium salt of dimethyl sulfoxide

hydrochloric acid (7647-01-0)

ether (60-29-7)

hydrogen (1333-74-0)

chloroform (67-66-3)

sodium carbonate (497-19-8)

nitrogen (7727-37-9)

nitrous acid (7782-77-6)

carbon dioxide (124-38-9)

Acetophenone (98-86-2)

selenium dioxide (7446-08-4)

phosphoric acid (7664-38-2)

Phenylglyoxal, Glyoxal, phenyl- (1074-12-0)

potassium (7440-09-7)

cupric acetate (142-71-2)

ethyl benzoate (93-89-0)

nitrosyl sulfuric acid (7782-78-7)

magnesium sulfate (7487-88-9)

Phenacyl bromide (70-11-1)

isonitrosoacetophenone

benzoylcarbinol (582-24-1)

2-acetoxy-2-bromoacetophenone

cupric acetate monohydrate (6046-93-1)

morpholine (110-91-8)

2,2-dibromoacetophenone

dimethyl sulfoxide (67-68-5)

t-butyl alcohol (75-65-0)

calcium hydride (7789-78-8)

2-(methylsulfinyl)acetophenone, 2-(methylsulfinyl) acetophenone (26524-93-6)

phenylglyoxal diethyl mercaptal

cyclohexylglyoxal

potassium t-butoxide (865-47-4)

p-tolylglyoxal

p-methoxyphenylglyoxal

p-bromophenylglyoxal

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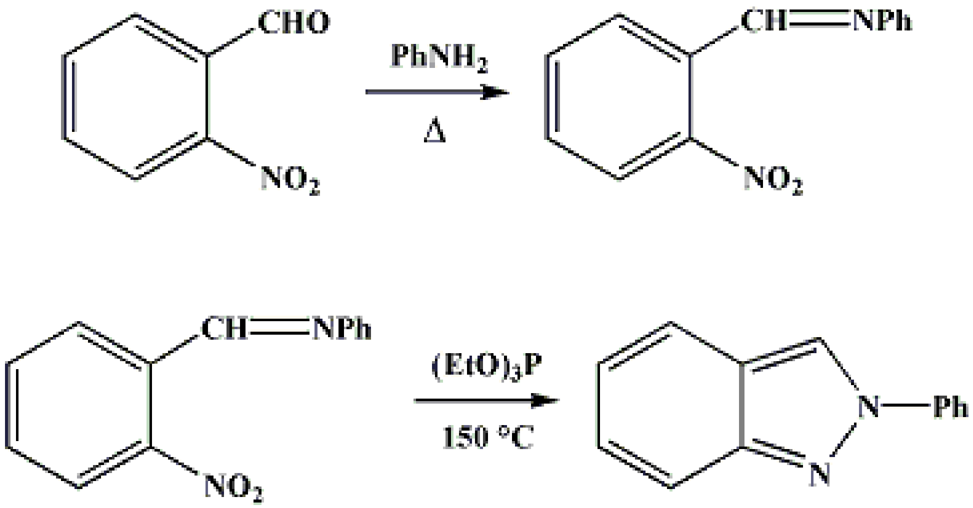
Organic Syntheses, CV 5, 941

2-PHENYLINDAZOLE

[2*H*-Indazole, 2-phenyl-]



Submitted by J. I. G. Cadogan and R. K. Mackie[1].
Checked by William G. Dauben, Harold B. Morris, and Kent E. Opheim.

1. Procedure

A. *o-Nitrobenzalaniline*. A mixture of 14 g. (0.15 mole) of aniline (Note 1) and 22.7 g. (0.15 mole) of *o*-nitrobenzaldehyde (Note 2) is heated in a 100-ml. round-bottomed flask on a water bath for 1 hour, allowed to cool, and dissolved in 100 ml. of ether. The ethereal solution is dried, and the ether is removed by distillation. The residue solidifies on standing (Note 3) and is recrystallized from 55 ml. of water-ethanol (1:8) to yield 29.4–31.8 g. (87–94%) of yellow *o*-nitrobenzalaniline, m.p. 64–66° (Note 4).

B. *2-Phenylindazole*. In a 200-ml. round-bottomed flask fitted with a condenser are mixed 50 g. (0.30 mole) of triethyl phosphite (Note 5) and 22.6 g. (0.10 mole) of *o*-nitrobenzalaniline. The apparatus is sealed from the atmosphere by means of a liquid paraffin bubbler that consists of a U-tube the bend of which is just filled with mineral oil. The apparatus is flushed with nitrogen, and the contents are kept under nitrogen during the reaction. The mixture is heated at 150° in an oil bath for 8 hours and cooled, and the condenser is replaced by a Claisen distillation head. Triethyl phosphite, b.p. 46–48° (10 mm.), and triethyl phosphate, b.p. 90–92° (10 mm.), are removed by distillation under reduced pressure; the volume of distillate is 48–50 ml. On cooling, the black residue solidifies. The flask is filled with glass wool, and the remaining phosphite and phosphate (1–3 g.) are removed by distillation at 30–50° (1 mm.). The residue of crude 2-phenylindazole is distilled at 10^{-4} mm.; b.p. 108–112°. The yield is 13–15 g. (67–78%) (Note 6) and (Note 7).

This product is crystallized from 75–100 ml. of ethanol-water (7:3) to yield pale yellow crystals, m.p. 81–82°. Additional material is obtained by dilution of the mother liquor with *ca.* 200 ml. of water and two crystallizations as before. The total yield is 10–12 g. (52–62%).

2. Notes

1. Aniline is purified by distillation from zinc dust.
2. The reagent as supplied by British Drug Houses or Eastman Organic Chemicals was used directly.
3. If the product does not solidify at room temperature, it should be cooled with dry ice.
4. *o*-Nitrobenzalaniline is very photosensitive and should be kept away from light as much as possible.
5. The reagent as supplied by Albright and Wilson, Ltd., or Matheson, Coleman and Bell was fractionally distilled from sodium and used within a few days of distillation.
6. A slightly purer sample may be obtained by chromatography on alumina. Elution with chloroform-benzene (1:4) gives a pale yellow solid which is purified further by crystallization from 70% ethanol.
7. The checkers found it more convenient to transfer the crude, black 2-phenylindazole to an apparatus for simple bulb-to-bulb distillation and not to retain the distillation head.

3. Discussion

The procedure given here is essentially that described previously by the submitters[2] and is based on the early work of Knoevenagel.[3] 2-Phenylindazole has been prepared by reduction of N-(*o*-nitrobenzyl)aniline with tin and hydrochloric acid,[4] by reduction of N-(*o*-nitrobenzyl)-N-nitrosoaniline with tin and hydrochloric acid,[5] by dehydration of 2-(phenylazo)benzyl alcohol,[6] by elimination of acetic acid from 2-(phenylazo)benzyl acetate,[7] by dehydrogenation of 3,3a,4,5,6,7-hexahydro-2-phenylindazole with sulfur,[8] and by thermal decomposition of *o*-azidobenzalaniline.[9]

4. Merits of the Preparation

Reductive cyclization of nitro compounds by triethyl phosphite is a general method for the preparation of a variety of nitrogen-containing heterocyclic systems. The submitters have synthesized the following ring systems by this method from the starting materials given in parentheses: 2-arylindoles (*o*-nitrostilbenes),[2] 2-arylindazoles (*o*-nitrobenzalanilines),[2] 2-arylbenzotriazoles (*o*-nitroazobenzenes),[2] carbazoles (*o*-nitrobiphenyls),[2] phenothiazines (*o*-nitrodiphenyl sulfides),[10,11] and anthranils (*o*-nitrophenyl ketones).[10]

The products are isolated in good yield in a one-stage synthesis from starting materials that are readily available in the main. An alternative method involves the decomposition of the corresponding azides.[9,12] These compounds are less readily available and are more hazardous to use than are the nitro compounds used in the present synthesis. This synthesis also gives better yields than the cyclization using ferrous oxalate,[12,13] which is performed under much harsher conditions. The present method of synthesis has been reviewed.[14]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alumina

chloroform-benzene

o-nitrostilbenes

o-nitrobenzalanilines

o-nitroazobenzenes

o-nitrobiphenyls

o-nitrodiphenyl sulfides

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ether (60-29-7)

aniline (62-53-3)

nitrogen (7727-37-9)

tin (7440-31-5)

sulfur (7704-34-9)

zinc (7440-66-6)

sodium (13966-32-0)

o-Nitrobenzaldehyde (552-89-6)

Triethyl phosphite (122-52-1)

triethyl phosphate (78-40-0)

2-PHENYLINDAZOLE, 2H-Indazole, 2-phenyl- (3682-71-1)

water-ethanol

2-(phenylazo)benzyl alcohol

2-(phenylazo)benzyl acetate

3,3a,4,5,6,7-hexahydro-2-phenylindazole

ferrous oxalate (516-03-0)

N-(o-nitrobenzyl)aniline

o-Nitrobenzalaniline (17064-77-6)

N-(o-nitrobenzyl)-N-nitrosoaniline

o-azidobenzalaniline

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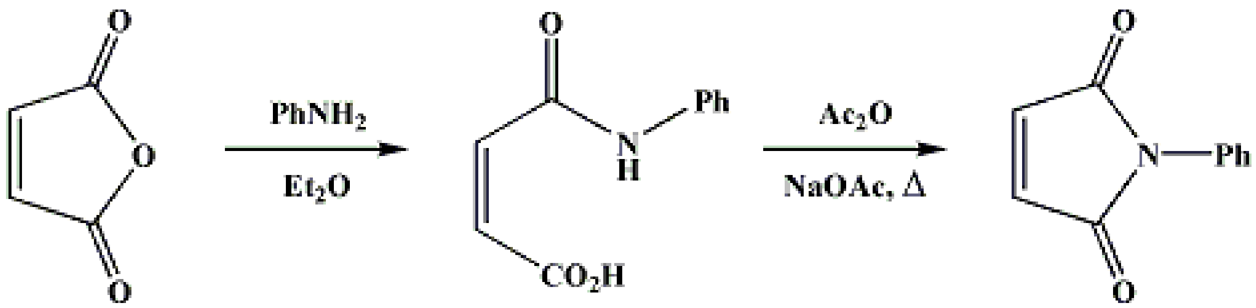
Organic Syntheses, CV 5, 944

N-PHENYLMALEIMIDE

[Maleimide, N-phenyl-]



Submitted by M. P. Cava, A. A. Deana, K. Muth, and M. J. Mitchell[1].
Checked by Carole L. Olson, Marjorie C. Caserio, and John D. Roberts.

1. Procedure

A. *Maleanilic acid*. In a 5-l. three-necked flask provided with a paddle-type stirrer, a reflux condenser, and a dropping funnel are placed 196 g. (2 moles) of maleic anhydride (Note 1) and 2.5 l. of ethyl ether (Note 2). The stirrer is started and, when all the maleic anhydride has dissolved, a solution of 182 ml. (186 g., 2 moles) of aniline (Note 3) in 200 ml. of ether (Note 2) is run in through the dropping funnel (Note 4). The resulting thick suspension is stirred at room temperature for 1 hour and is then cooled to 15–20° in an ice bath. The product is obtained by suction filtration. It is a fine, cream-colored powder, m.p. 201–202°, suitable for use in the next step without purification. The yield is 371–374 g. (97–98%).

B. *N-Phenylmaleimide*. In a 2-l. Erlenmeyer flask are placed 670 ml. of acetic anhydride (Note 5) and 65 g. of anhydrous sodium acetate. The maleanilic acid (316 g.), obtained as described above, is added, and the resulting suspension is dissolved by swirling and heating on a steam bath for 30 minutes (Note 6). The reaction mixture is cooled almost to room temperature in a cold water bath and is then poured into 1.3 l. of ice water. The precipitated product is removed by suction filtration, washed three times with 500-ml. portions of ice-cold water and once with 500 ml. of petroleum ether (b.p. 30–60°), and dried. The yield of crude N-phenylmaleimide is 214–238 g. (75–80%), m.p. 88–89°. Recrystallization from cyclohexane gives canary-yellow needles, m.p. 89–89.8° (Note 7).

2. Notes

1. Reagent grade maleic anhydride is used without purification.
2. Reagent grade anhydrous ether is used.
3. Reagent grade aniline is used without further purification.

4. The aniline solution may be run in as fast as is possible without flooding the condenser.
5. Carbide and Carbon or Baker's Analyzed technical grade acetic anhydride is used.
6. The sodium acetate fails to dissolve completely.
7. About 500 ml. of the refluxing solvent will dissolve some 58 g. of N-phenylmaleimide. The recovery of recrystallized material is approximately 93%.

3. Discussion

The procedure described here is based on a method outlined in U. S. patent 2,444,536.[2] N-Phenylmaleimide has also been prepared by the dry distillation of the aniline salt of malic acid,[3,4] by treating the aniline salt of malic acid with phosphorus pentoxide,[5] and by treating maleanilic acid with phosphorus trichloride or with phosphorus pentoxide.[6] Ring-substituted N-phenylmaleimides, viz., N-(*p*-methoxyphenyl)-, N-(*p*-ethoxyphenyl)-, and N-(*p*-nitrophenyl)maleimide, have been prepared by treatment of the appropriate maleanilic acids with acetic anhydride and fused potassium acetate.[7]

4. Merits of Preparation

N-Phenylmaleimide is an active dienophile in the Diels-Alder reaction and usually gives crystalline adducts.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 957

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

N-(p-methoxyphenyl

N-(p-ethoxyphenyl

ether, ethyl ether (60-29-7)

acetic anhydride (108-24-7)

sodium acetate (127-09-3)

aniline (62-53-3)

cyclohexane (110-82-7)

phosphorus trichloride (7719-12-2)

potassium acetate (127-08-2)

maleic anhydride (108-31-6)

N-Phenylmaleimide, Maleimide, N-phenyl- (941-69-5)

maleanilic acid (555-59-9)

phosphorus pentoxide (1314-56-3)

N-(p-nitrophenyl)maleimide (4338-06-1)

aniline salt of malic acid

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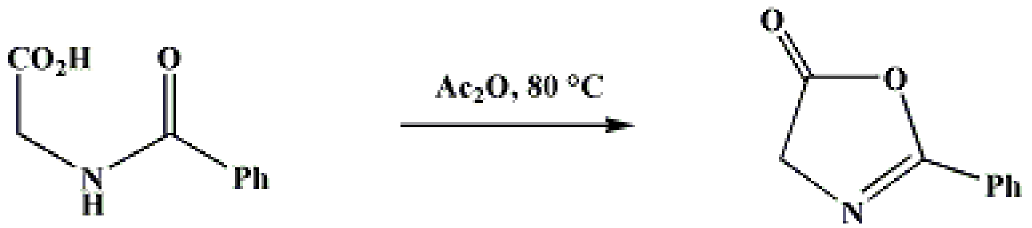
Organic Syntheses, CV 5, 946

2-PHENYL-5-OXAZOLONE

[2-Phenyl-2-oxazolin-5-one]



Submitted by G. E. VandenBerg[1], J. B. Harrison[2], H. E. Carter[2], and B. J. Magerlein[1].
Checked by William G. Dauben, Noel Vietmeyer, and Steven A. Schmidt.

1. Procedure

A mixture of 537 g. (3 moles) of hippuric acid (Note 1) and 1.6 l. (17 moles) of acetic anhydride is prepared in a 3-l. three-necked, round-bottomed flask fitted with a sealed stirrer, a reflux condenser with a drying tube, a thermometer, and a nitrogen inlet tube (Note 2).

In a nitrogen atmosphere the reaction mixture is heated to 80° *on a water bath* over a period of 40 minutes with stirring. The solids slowly dissolve, and a yellow-orange solution results (Note 3). The reaction mixture is cooled to 5°, and the reflux condenser is turned downward for distillation. The condenser is cooled with a circulating fluid maintained at –20° to –40° (Note 4). The receiver is immersed in dry ice and acetone. At 1–3 mm. pressure, 1.5 l. of distillate is collected while the distillation flask is kept in a water bath maintained at 50° (Note 5). A capillary tube is used to bubble nitrogen through the reaction mixture to ensure good agitation. The distillation residue is dissolved in 1 l. of *t*-butanol, the solution scratched to encourage crystallization, and it is refrigerated overnight. The crystals are collected by filtration (Note 2). The filter cake is washed with a minimum volume of *t*-butanol and then with Skellysolve B (Note 6) or hexane. The moist cake is slurried with Skellysolve B or hexane under a nitrogen atmosphere (Note 7), filtered, and dried to constant weight under vacuum at ambient temperature. The yield of light buff to yellow crystals, m.p. 89–92°, is 320–328 g. (66–68%).

2. Notes

1. The checkers ran the reaction on one-fifth scale.
2. Exposure to air produces a pink to red product of lower melting point and purity.
3. Temperature control is important in order to obtain a high yield of light-

colored product. Prolonged heating at 80° is to be avoided.
4. Acetone, cooled by passing through a copper coil placed in a dry ice-acetone bath, may be circulated through the condenser. If a temperature lower than −40° is used, the distillate will freeze in the condenser.
5. This distillate should be collected within about 1 hour, as longer distillation time diminishes the yield.
6. A saturated hydrocarbon fraction, b.p. 60–71°, available from, the Skelly Oil Company, Kansas City, Missouri.
7. Alternatively, the moist cake may be recrystallized by dissolving in hot *t*-butanol (about 800 ml.) and diluting with Skellysolve B. The yield is then about 40–50% and the melting point about the same as that of the reslurried product.

3. Discussion

This procedure is a modification of the original method of preparation of 2-phenyl-5-oxazolone[3] which has since appeared in the literature in various forms.[4,5,6] In addition to the use of acetic anhydride, the cyclization of hippuric acid to 2-phenyl-5-oxazolone has been described using phosphorus tribromide[7] and N,N'-dicyclohexylcarbodiimide.[8].

4. Merits of the Preparation

This procedure offers a reproducible method for the preparation of 2-phenyl-5-oxazolone, which is not commercially available. It illustrates that strict attention to detail often smooths out an erratic procedure. 2-Phenyl-5-oxazolone is, of course, an important intermediate in the synthesis of α-amino acids and related materials.[6]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

acetic anhydride (108-24-7)

phosphorus tribromide (7789-60-8)

nitrogen (7727-37-9)

acetone (67-64-1)

Hippuric acid (495-69-2)

hexane (110-54-3)

t-butanol (75-65-0)

N,N'-dicyclohexylcarbodiimide (538-75-0)

2-Phenyl-5-oxazolone, 2-Phenyl-2-oxazolin-5-one (1199-01-5)

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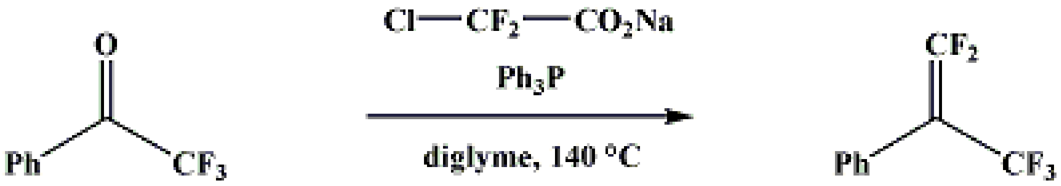
2-PHENYLPERFLUOROPROPENE

[Styrene, β,β-difluoro-α-(trifluoromethyl)-]



Submitted by Frank E. Herkes and Donald J. Burton[1].
Checked by W. C. Ripka and R. E. Benson.

1. Procedure

Caution! This compound is an analog of the toxic olefin, perfluoroisobutylene. Since its toxicity is unknown, proper care should be exercised in its handling.

A 1-l., three-necked, round-bottomed flask is equipped with a mechanical stirrer, a nitrogen-inlet tube, and a reflux condenser connected to a dry ice-trichloroethylene trap (Note 1) that is followed by a water trap to measure carbon dioxide evolution (Note 2). The flask is charged with 65.6 g. (0.250 mole) of triphenylphosphine (Note 3) and 43.5 g. (0.250 mole) of α,α,α-trifluoroacetophenone (Note 4) in 200 ml. of dry diglyme (Note 5). The solution is heated to a bath temperature of 140° under a nitrogen atmosphere, and the nitrogen-inlet tube is replaced by a pressure-equalizing dropping funnel (Note 6) containing a solution of 76.2 g. (0.500 mole) of sodium chlorodifluoroacetate (Note 7) in 150 ml. of dry diglyme. The solution of sodium chlorodifluoroacetate is added dropwise over a period of 1 hour (Note 8), and the reaction mixture is heated for an additional hour at 130–140° to ensure complete decarboxylation of the salt (Note 9). The colors of the reaction mixture are characteristic of ylid reactions, changing from a creamy white to a creamy orange and finally to a deep brown.

The reaction mixture is then cooled to room temperature under nitrogen. The cool mixture is steam distilled until 2 l. of distillate has been collected. The lower, organic layer is separated from the distillate, washed with cold water (Note 10) to remove diglyme, and dried over anhydrous calcium sulfate. Fractional distillation gives 26–31 g. (50–60%) of 2-phenylperfluoropropene, b.p. 58–59° (54 mm.), n^{20}D 1.4225 (Note 11) and (Note 12).

2. Notes

1. In addition to carbon dioxide, small amounts of fluoroformyl fluoride and

chloride are formed and swept out with the carbon dioxide.

2. The rate of decarboxylation can be followed qualitatively by collecting the liberated carbon dioxide over water, *e.g.*, by the use of a wet test meter.

3. Eastman Organic Chemicals white label triphenylphosphine was used directly.

4. Available from Pierce Chemical Co., Rockford, Illinois. The ketone can also be prepared conveniently from phenylmagnesium bromide and trifluoroacetic acid by the method of Dishart and Levine.[2]

5. Diglyme (Ansul Ether 141) was predried over calcium hydride and distilled under reduced pressure from lithium aluminum hydride; b.p. 62–63° (15 mm.).[3] The yield of olefin is dependent on the dryness of the solvent. The formation of 2-phenyl-2H-perfluoropropane is favored by the presence of water in the solvent.

6. A dropping funnel of the type described by Benson and McKusick[4] is satisfactory.

7. Sodium chlorodifluoroacetate is prepared in quantitative yield by careful neutralization of 130.5 g. (1.00 mole) of chlorodifluoroacetic acid (available from Allied Chemical Corp.) in 300 ml. of ether with 53.0 g. (0.500 mole) of anhydrous sodium carbonate, removal of the solvent and water under reduced pressure, and drying over phosphorus pentoxide in a vacuum desiccator. Studies have shown that the best yield of olefin is obtained when a 100% excess of salt is used.

8. The salt is added at a rate sufficient to cause a constant evolution of carbon dioxide. The reaction is slightly exothermic (*ca.* 10° temperature rise).

9. A total of 9460 ml. (72% STP) of carbon dioxide was collected.

10. Eight washings with 50-ml. portions of water were found to remove all the diglyme.

11. The submitters used an 18-in. spinning-band column. The product was shown to be >99.9% pure by gas-liquid chromatography on Carbowax 20M.

12. The checkers used a 40-cm. spinning-band column. The product, $n^{25}D$ 1.4237, was shown to be 98.9% pure by gas-liquid chromatography on a 6-ft. 20% fluorosilicone column. The retention time was 3.75 minutes with a flow rate of helium of 100 ml. per minute, and a column temperature of 125° with the injection port at 170°. The ^{19}F n.m.r. spectrum (56.4 MHz) consists of four lines of equal intensity centered at +3396 Hz from trichlorofluoromethane (internal) and two sets of two overlapping quartets centered at +4369 Hz and +4461 Hz, respectively. The integrated intensities of the three sets of fluorine resonances are 3:1:1.

3. Discussion

This procedure is a modification of the method previously reported by the submitters.[5] 2-Phenylperfluoropropene has been reported as a by-product of the thermal decomposition of 7,7-bis(trifluoromethyl)-1,3,5-cycloheptatriene; however, no experimental procedure was given.[6]

4. Merits of the Preparation

The procedure illustrates a fairly general method for the preparation of β-substituted perfluoroolefins. The method has been applied to the synthesis of 2-cyclohexyl- (70%), 2-benzyl- (61%), and 2-(*p*-fluorophenyl)perfluoropropenes (67%), and it is probably applicable to any α-trifluoromethyl ketone. Olefins containing a perfluoroalkyl group other than trifluoromethyl can be prepared by the same procedure by the substitution of lithium chlorodifluoroacetate for sodium chlorodifluoroacetate.[7] Other routes to β-substituted perfluoroolefins are not general or convenient. Routes to perfluoroolefins generally yield the α-substituted olefin rather than the β-substituted olefin.

This method can also be utilized as a general method for the preparation of olefins with terminal difluoromethylene groups from aldehydes.[8] Also, by the substitution of tributylphosphine for triphenylphosphine in this procedure, ketones other than those containing an α-perfluoroalkyl group can be converted to terminal difluoromethylene compounds.[9]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

fluoroformyl fluoride and chloride

Diglyme (Ansul Ether 141)

ether (60-29-7)

sodium carbonate (497-19-8)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

calcium sulfate (7778-18-9)

Phenylmagnesium bromide (100-58-3)

lithium aluminum hydride (16853-85-3)

calcium hydride (7789-78-8)

diglyme (111-96-6)

trifluoroacetic acid (76-05-1)

helium (7440-59-7)

triphenylphosphine (603-35-0)

sodium chlorodifluoroacetate (1895-39-2)

chlorodifluoroacetic acid (76-04-0)

lithium chlorodifluoroacetate

2-Phenylperfluoropropene, Styrene, β,β-difluoro-α-(trifluoromethyl)- (1979-51-7)

perfluoroisobutylene (382-21-8)

α,α,α-trifluoroacetophenone (434-45-7)

2-phenyl-2H-perfluoropropane

7,7-bis(trifluoromethyl)-1,3,5-cycloheptatriene

tributylphosphine (998-40-3)

phosphorus pentoxide (1314-56-3)

2-cyclohexyl-perfluoropropene

2-(p-fluorophenyl)perfluoropropene

2-benzyl-perfluoropropene

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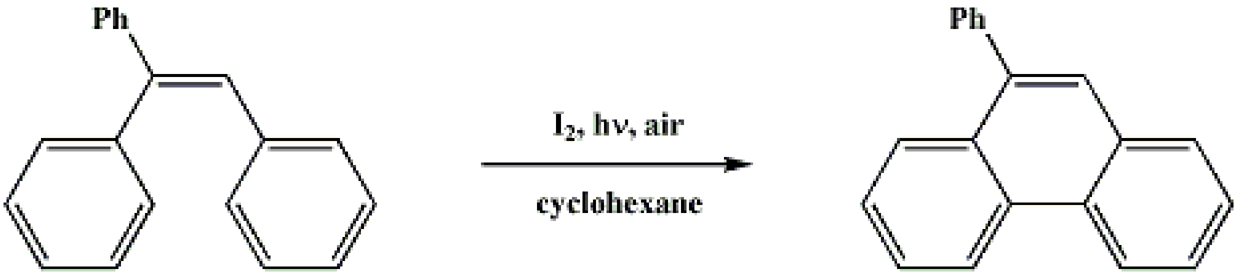
9-PHENYLPHENANTHRENE

[Phenanthrene, 9-phenyl-]



Submitted by Frank B. Mallory and Clelia S. Wood[1].
Checked by William G. Dauben and Donald N. Brattesani.

1. Procedure

A solution of 2.56 g. (0.01 mole) of triphenylethylene[2] (Note 1) and 0.127 g. (0.5 mmole) of iodine in 1 l. of cyclohexane (Note 2) is placed in a 1.5-l. beaker and stirred magnetically (Note 3). A Hanovia water-cooled 19433 Vycor immersion well fitted with a 200-watt 654A-36 mercury lamp (Note 4) and (Note 5) is inserted into the beaker, and the lamp is started (Note 6). The irradiation is continued for about 3 hours (Note 7).

The reaction mixture is transferred to a 2-l. round-bottomed flask, and the solvent is evaporated under reduced pressure (Note 8). The residue is dissolved in 50 ml. of warm cyclohexane (Note 2), and the solution (Note 9) is poured onto a column of alumina (Note 10) 1.8 cm. in diameter and 6–7 cm. in length. The round-bottomed flask is rinsed with three 10-ml. portions of cyclohexane, and the rinsings are poured onto the column. The column is eluted with additional cyclohexane (about 100 ml.) until no appreciable amount of 9-phenylphenanthrene is obtained in the eluate. The elution of any yellow material from the column should be avoided. The total eluate is evaporated to dryness under reduced pressure (Note 8), and the residue is recrystallized from 40–45 ml. of 95% ethanol to give 1.65–1.90 g. (65–75%) of 9-phenylphenanthrene, m.p. 103.5–104.5° (Note 11), (Note 12), and (Note 13).

2. Notes

1. The triphenylethylene used by the submitters had been recrystallized from absolute ethanol, and the material melted at 68.0–68.6°.
2. Eastman Organic Chemicals practical grade cyclohexane is distilled before use.
3. A 4-cm. Teflon®-coated stirring bar gives sufficiently effective stirring.

4. This unit is sold as a Hanovia Laboratory Photochemical Reactor by the Hanovia Lamp Division, Engelhardt Industries, Inc., 100 Chestnut Street, Newark 5, New Jersey.
5. A relatively inexpensive light source and probe can be made as described below and used in place of the Hanovia unit. A 100-watt General Electric H100A4/T or H100A38-4 mercury lamp, available from the Lamp Department, General Electric Co., Nela Park, Cleveland, Ohio, is modified by cutting away the outer glass envelope and by detaching the inner quartz bulb from the screw base on which it is mounted. The two electrical leads from the lamp are then connected, as shown in f.htmig. 2, by means of insulated wire to a suitable power supply such as a General Electric 9T64Y-3518 or 9T64Y-1019 transformer. The modified mercury lamp is then inserted in a 17-mm. I.D. quartz tube which is about 30 cm. long and is sealed on one end. This tube is made from Clear Fused Quartz tubing available from the Lamp Glass Department, General Electric Co., Nela Park, Cleveland 12, Ohio.

Fig. 2

Fig. 2

Irradiations with this type of light source are carried out using a 1-l. Erlenmeyer flask as the reaction vessel instead of a 1.5-l. beaker. The flask is placed in a cold-water bath that is supported on a magnetic stirrer. The bath can be made from a 10-qt. polyethylene bucket with a -in. hole bored about 1 in. from the top of the bucket and a piece of rubber tubing with a 5/8-in. bore and 1/8-in. wall inserted as a drain. A stream of 24° tap water run into the bucket at a flow rate of 5 l. per min. maintains the temperature of the reaction mixture below 33°.
6. Unfiltered light from mercury lamps is damaging to the eyes; suitable precautions, such as wearing appropriate glasses and surrounding the reaction vessel with aluminum foil, should be taken.
7. The irradiation time required depends on the type of light source used and can be determined by following the progress of the reaction by infrared spectroscopy. A 10-ml. aliquot is withdrawn from the reaction mixture and evaporated to dryness under reduced pressure; the residue is dissolved in 0.5 ml. of carbon tetrachloride, and the spectrum is obtained using 0.1-mm. sodium chloride cells. A new peak appears at 899 cm.$^{-1}$, and the ratio of the absorbance of the peak at 703 cm.$^{-1}$ to that of the peak at 727 cm.$^{-1}$ continuously decreases during the course of the reaction. Using these spectral criteria, the submitters judged the reaction to be complete after 4 hours of irradiation with the lamp described in (Note 5); however, the recrystallized products from 4-hour reactions melted about 0.4° lower than those from 5-hour reactions. The submitters found that varying the irradiation time from 4 hours to 8 hours had no significant effect on the yield of 9-phenylphenanthrene. The extent of the reaction can also be monitored by gas-liquid chromatography.
8. It is convenient to use a rotary evaporator and a water aspirator for this operation.
9. This solution may be purple in color owing to incomplete removal of iodine during the reduced-pressure evaporation.

10. The submitters used Merck 71707 aluminum oxide. The checkers used Woelm neutral alumina, Activity I.
11. A sample of 9-phenylphenanthrene that had been exhaustively purified by zone refining and by recrystallization melted at 104.1–104.7°. The melting point has been reported as 104–105°[3,4,5] and as 105–106°.[6,7]
12. Reactions carried out at higher concentrations or on larger scales give slightly lower yields of less pure material. To obtain larger amounts of the product, the submitters recommend irradiating in batches on the scale specified in the procedure and combining the reaction mixtures prior to the chromatographic purification.
13. Using the apparatus described in (Note 5), the submitters obtained 2.08–2.17 g. (82–85%) of 9-phenylphenanthrene.

3. Discussion

This preparation is based on a procedure published by the submitters.[8,9] 9-Phenylphenanthrene has been prepared previously by the reaction of phenyllithium with 9-chlorophenanthrene,[10] by the high-temperature dehydrogenation with palladium on charcoal of the Diels-Alder dimer of 1-phenyl-1,3-butadiene,[11] and by the acid-catalyzed cyclization of the alcohol formed from the reaction of 2-biphenylylmagnesium iodide and 2-phenoxyacetophenone.[3]

4. Merits of the Preparation

This preparation illustrates a reasonably general method for obtaining 1-, 3-, or 9-substituted phenanthrenes in good yields from the photocyclization of the corresponding *o*-, *p*-, or α-substituted stilbenes.[8,9] The submitters have obtained satisfactory results with bromo, chloro, fluoro, methoxy, methyl, phenyl, trifluoromethyl, and carboxyl substituents. α-Styrylnaphthalene gives chrysene, β-styrylnaphthalene gives benzo[*c*]phenanthrene, and 1,2-di-α-naphthylethylene gives picene.

The photocyclization has been found not to occur with stilbenes substituted with acetyl, dimethylamino, or nitro groups. Iodo substituents are replaced by hydrogen by photolysis in cyclohexane solution.[9,12] *m*-Substituted stilbenes give mixtures of 2- and 4-substituted phenanthrenes which generally are difficult to separate.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alumina

ethanol (64-17-5)

hydrogen (1333-74-0)

carbon tetrachloride (56-23-5)

cyclohexane (110-82-7)

iodine (7553-56-2)

palladium (7440-05-3)

Phenyllithium (591-51-5)

aluminum oxide (1344-28-1)

Triphenylethylene (58-72-0)

1-phenyl-1,3-butadiene (31915-94-3)

9-Phenylphenanthrene, Phenanthrene, 9-phenyl- (844-20-2)

9-chlorophenanthrene (947-72-8)

2-biphenylylmagnesium iodide

2-phenoxyacetophenone

α-Styrylnaphthalene

chrysene (218-01-9)

β-styrylnaphthalene

1,2-di-α-naphthylethylene

picene (213-46-7)

benzo[c]phenanthrene (195-19-7)

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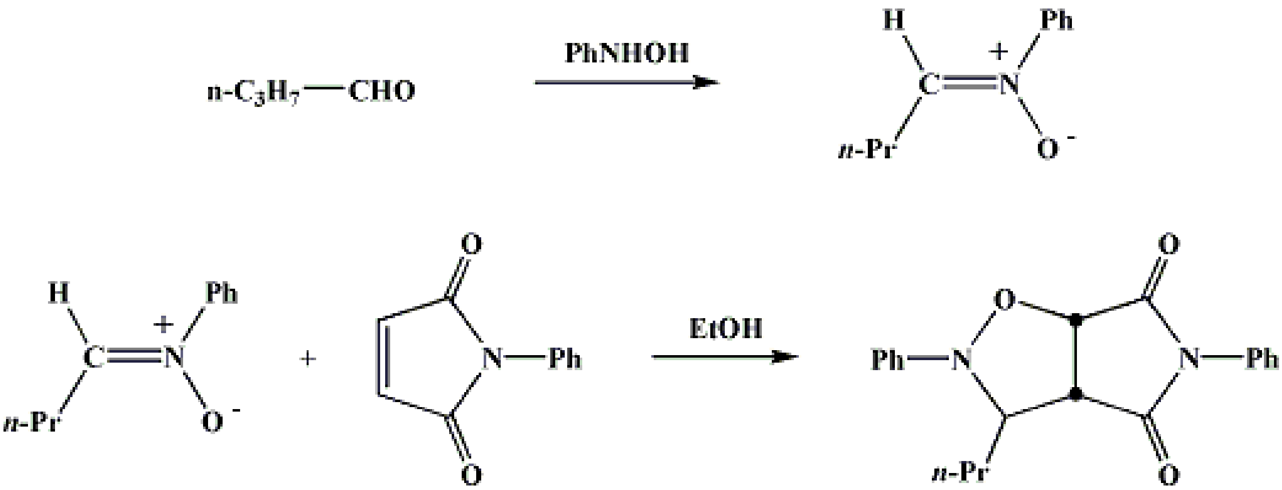
Organic Syntheses, CV 5, 957

2-PHENYL-3-*n*-PROPYLISOXAZOLIDINE-4,5-*cis*-DICARBOXYLIC ACID N-PHENYLIMIDE



Submitted by Ingrid Brüning, Rudolf Grashey, Hans Hauck, Rolf Huisgen, and Helmut Seidl[1].
Checked by Robert Eliason, Wayland E. Noland, and William E. Parham.

1. Procedure

N-Phenylhydroxylamine (11 g., 0.10 mole)[2] (Note 1) and N-phenylmaleimide (17.4 g., 0.10 mole)[3] are suspended in 40 ml. of ethanol contained in a 200-ml. Erlenmeyer flask. To the mixture is added immediately (Note 2) 8.98 g. (11.2 ml., 0.124 mole) of freshly distilled *n*-butyraldehyde. An exothermic reaction ensues, and the mixture spontaneously heats to the boiling point. A clear slightly yellow solution results which, upon cooling, deposits an almost colorless crystalline cake. The mixture is allowed to stand in the ice box for 1 day; it is then filtered through a Büchner funnel, and the crystals are washed twice with 25-ml. portions of ice-cold ethanol. The yield of air-dried product, m.p. 99–101°, is 31–32 g. (92–95%). For further purification the crude material is dissolved in 60 ml. of boiling ethanol on the steam bath, and the resulting solution is allowed to cool slowly to room temperature. If crystallization does not spontaneously begin in 5–10 minutes, it can then be induced by seeding. After being kept for 5 hours in the refrigerator, the solution is filtered and the colorless crystals are washed twice with 20-ml. portions of cold ethanol. The dried product weighs 29–30 g. An additional recrystallization of the air-dried product from 60 ml. of ethanol gives 26–27 g. (77–80%) of the pure isoxazolidine, m.p. 106.5–107.5°.

2. Notes

1. The phenylhydroxylamine should be free of sodium chloride. This can be easily removed by dissolution of the substance in benzene followed by filtration, and then addition of petroleum ether to precipitate the pure compound.
2. The checkers observed, in two runs, that when *n*-butyraldehyde is added after 10–15 minutes, the reaction is only mildly exothermic, and the white precipitate that forms does not dissolve. The infrared spectrum of the white crystalline product (19–20 g., m.p. 181–184° dec.) suggests that it may be the adduct of phenylhydroxylamine and N-

phenylmaleimide formed by addition of the N-H bond of the amine to the olefinic bond of the imide; however, the structure of the product was not further examined.

3. Discussion

The preparation of 2-phenyl-3-*n*-propylisoxazolidine-4,5-*cis*-dicarboxylic acid N-phenylimide from *n*-butyraldehyde, N-phenylhydroxylamine, and N-phenylmaleimide is new and is described by Hauck.[4] The intermediate, C-(*n*-propyl)-N-phenylnitrone, is an unstable compound and is difficult to purify. The procedure described avoids the isolation of the nitrone by adding it *in situ* to a suitable dipolarophile.

4. Merits of the Preparation

The present procedure serves as a model for the generation and use *in situ* of unstable nitrones in 1,3-dipolar cycloaddition reactions.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

2-PHENYL-3-n-PROPYLISOXAZOLIDINE-4,5-cis-DICARBOXYLIC ACID N-PHENYLIMIDE

ethanol (64-17-5)

Benzene (71-43-2)

sodium chloride (7647-14-5)

n-butyraldehyde (123-72-8)

Phenylhydroxylamine, N-Phenylhydroxylamine (100-65-2)

N-Phenylmaleimide (941-69-5)

C-(n-propyl)-N-phenylnitrone

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Organic Syntheses, CV 5, 959

PHENYLSULFUR TRIFLUORIDE

[Benzenesulfenyl trifluoride]

Submitted by William A. Sheppard[1]
Checked by E. S. Glazer and John D. Roberts.

1. Procedure

Caution! Phenylsulfur trifluoride and by-products (e.g., hydrogen fluoride from hydrolysis) are toxic, and all manipulations should be carried out in a good hood. Silver difluoride is a powerful oxidative fluorinating agent and reacts vigorously with many organic materials. These reagents should not be allowed to come in contact with the skin.

A 1-l., four-necked, round-bottomed flask equipped with reflux condenser, sealed stirrer, thermometer, and solid addition funnel[2] and protected from atmospheric moisture with a Drierite® guard tube is carefully dried and flushed with a dry inert gas (Note 1). The flask is charged with 453 g. (3.1 moles) of silver difluoride (Note 2) and 500 ml. of 1,1,2-trichloro-1,2,2-trifluoroethane (Note 3), and phenyl disulfide (100 g., 0.458 mole) (Note 4) is weighed into the solid addition funnel. The stirrer is started, and phenyl disulfide is added to the slurry in small portions. An exothermic reaction occurs, and after the addition of several portions the reaction mixture reaches a temperature of 40° (Note 5). By intermittent use of a cooling bath and by adjusting the rate of addition of the disulfide, the reaction temperature may be maintained between 35° and 40°. The addition of the phenyl disulfide requires 45–60 minutes. On completion of the addition the suspension of black silver difluoride has been converted to yellow silver monofluoride, and the exothermic reaction gradually subsides. The reaction mixture is stirred for an additional 15–30 minutes without external cooling and then quickly heated to reflux.

The reaction mixture is filtered hot through a fluted filter paper under a blanket of dry nitrogen into a dry, 1-l., round-bottomed flask. The residue of solid silver fluoride is washed with a total of 500 ml. of boiling 1,1,2-trichloro-1,2,2-trifluoroethane in portions (Note 6). The filtrates are combined and distilled through a short Vigreux column, an oil bath not heated over 70° being used (Note 7). The residue of phenylsulfur trifluoride is transferred to a 200-ml. round-bottomed flask and distilled, b.p. 47–48° (2.6 mm.), through a Claisen-type distillation column, discarding a small fore-run. The product is obtained in a yield of 84–92 g. (55–60%) as a colorless liquid,

m.p. –10° (Note 8). Since phenylsulfur trifluoride slowly attacks Pyrex® glass, it should be used immediately. It can be stored for several days in glass at –80° or in polyethylene, however, and may be stored indefinitely at room temperature in bottles of Teflon® polytetrafluoroethylene resin or aluminum (Note 9).

2. Notes

1. The equipment should be dried carefully by the techniques normally employed when preparing for a Grignard reaction. Dry nitrogen gas was normally employed to flush the apparatus, but any dry inert atmosphere, or dry air, could be employed.
2. A technical grade of silver difluoride (approximately 85%) is available from Harshaw Chemical Company. Better grades of silver difluoride are available and may be employed. It is important that the silver difluoride be a black powder. If the material is light brown and lumpy, a lower yield of product may be obtained. Normally, the contents of a 1-lb. can (approximately 435–470 g.) are employed.
3. 1,1,2-Trichloro-1,2,2-trifluoroethane (trademark "Freon-113"), b.p. 47°, is available from the Organic Chemicals Department, E. I. du Pont de Nemours and Company, Wilmington, Delaware.
4. Eastman's white label grade phenyl disulfide is suitable.
5. Caution must be exercised in the addition of the phenyl disulfide. There is a short induction period between the addition of disulfide and the exothermic reaction. If the disulfide is added too rapidly, a vigorous exothermic reaction, which is difficult to control, will result. The extensive use of a cooling bath should be avoided because the reaction rate is sufficiently slow at lower temperatures to allow buildup of reactants and the development of a vigorous, uncontrollable reaction.
6. Etching of the glass equipment is reduced to a minimum if all equipment used in the preparation and subsequent manipulation is rinsed with water and acetone *immediately* after use.
7. The Freon® solvent may be removed under reduced pressure in order to shorten the distillation time. Since phenylsulfur trifluoride attacks glass, the total time involved in the preparation and distillation in the glass equipment should be kept to a maximum of a few hours. It is recommended that the column be changed after distillation of the Freon®. If the preparation cannot be completed within a day, the Freon® solution of crude phenylsulfur trifluoride may be stored in polyethylene bottles overnight.
8. In contact with moisture of glass, phenylsulfur trifluoride develops pink, green, or bluish colors. A small amount of discoloration does not appear to affect the quality. Phenylsulfur trifluoride prepared in glass equipment always contains a few percent of phenylsulfinyl fluoride. The amount of this impurity depends on the care taken to exclude moisture during preparation and manipulation.
9. Phenylsulfur trifluoride slowly oozes through polyethylene bottles after storage for several days. However, a sample of phenylsulfur trifluoride has been

stored in a bottle of Teflon® for several years without decomposition. Storage in a dry atmosphere in a well-ventilated area is recommended.

3. Discussion

Phenylsulfur trifluoride has been prepared only by the present method.[3,4]

4. Merits of the Preparation

This procedure illustrates a fairly general method for the preparation of alkyl- and arylsulfur trifluorides. The method has also been applied to the synthesis of nitrophenyl-, tolyl-, and fluorobutylsulfur trifluorides,[3,4] and it is probably applicable to any disulfide that does not contain groups reactive with silver difluoride. 2,4-Dinitrophenyl- and perfluoroalkylsulfur trifluorides have been prepared by reaction of disulfides with fluorine or by electrolytic fluorination.[5,6] These other routes to sulfur trifluoride compounds are not general or convenient, and they often give low yields.

The sulfur trifluoride compounds are useful as selective agents for conversion of carbonyl and carboxyl groups to difluoromethylene[7] and trifluoromethyl groups,[3,4] respectively, and as intermediates for synthesis of arylsulfur pentafluorides.[3,8]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 396

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

nitrogen (7727-37-9)

hydrogen fluoride (7664-39-3)

Fluorine (7782-41-4)

silver fluoride, silver monofluoride (7775-41-9)

phenylsulfinyl fluoride

Phenylsulfur trifluoride (672-36-6)

phenyl disulfide (882-33-7)

Benzenesulfenyl trifluoride

Silver difluoride

1,1,2-trichloro-1,2,2-trifluoroethane (76-13-1)

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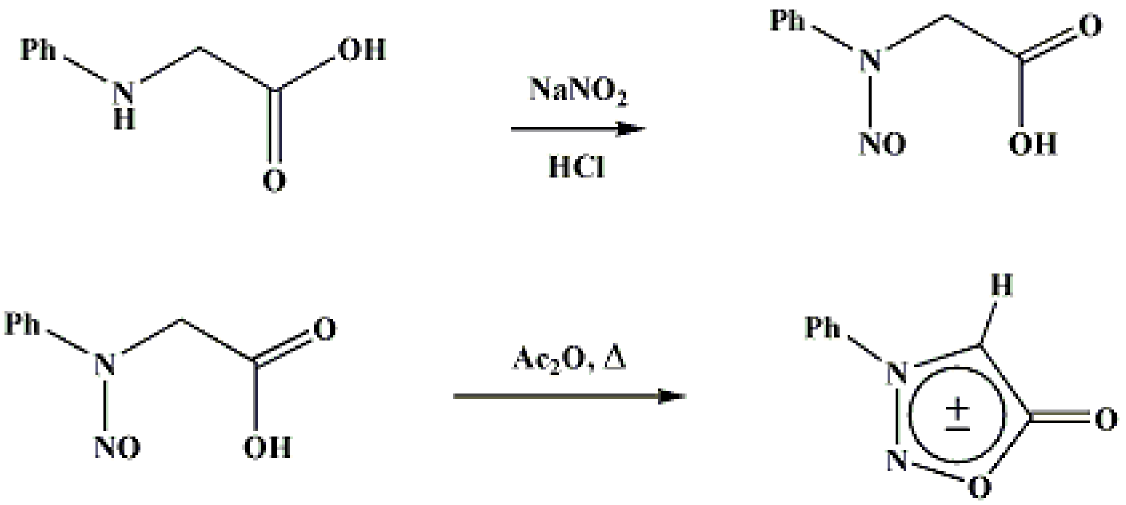
Organic Syntheses, CV 5, 962

3-PHENYLSYDNONE

[N-Phenylsydnone]



Submitted by Charles J. Thoman and Denys J. Voaden[1].
Checked by William E. Parham and Edward A. Walters.

1. Procedure

A. *N-Nitroso-N-phenylglycine*. One hundred grams (0.66 mole) of N-phenylglycine (Note 1) is suspended in 1.2 l. of water contained in a 3-l. beaker placed in an ice-salt bath and stirred until the temperature has dropped below 0°. A solution of 50 g. (0.72 mole) of sodium nitrite in 300 ml. of water is added dropwise over a period of 40 minutes at such a rate that the temperature never exceeds 0°. The red, almost clear solution (Note 2) is filtered as quickly as possible with suction, after which 3 g. of Norit® is added and allowed to stir with the cold solution for several minutes (Note 3). The mixture is again filtered with suction. Addition of 100 ml. of concentrated hydrochloric acid to the well-stirred solution produces, after about 30 seconds, a profusion of light, fluffy crystals. The suspension is stirred for 10 minutes and is then filtered with suction and washed twice with ice-cold water. The precipitate is best dried by leaving it on the suction funnel overnight. The resulting product melts at 103–104°, weighs 96–99 g. (80–83%) (Note 4), and is off-white in color. It can be used without recrystallization.

B. *3-Phenylsydnone*. The 99 g. (0.55 mole) of N-nitroso-N-phenylglycine is dissolved in 500 ml. of acetic anhydride in a 1-l. Erlenmeyer flask fitted with a reflux condenser topped by a drying tube. The deep-red solution is heated in a boiling water bath for 1.5 hours with magnetic stirring (Note 5) and is then allowed to cool to room temperature. The cool solution is poured slowly into 3 l. of cold water which is very well stirred (Note 6), white crystals separate almost immediately. After 5 minutes of stirring, the solid is filtered with suction, washed twice with ice-cold water, and dried on the funnel

with suction overnight. The dried product is cream-colored, weighs 74–75 g. (83–84%), and melts at 136–137° (Note 7). The overall yield for the two steps is 67–70%.

2. Notes

1. Eastman Organic Chemicals practical grade material, mud-brown in color, was used without purification.
2. Often a small amount of insoluble, dark-brown material remains in suspension. Filtration of this product is most difficult, since it tends to clog the filter paper. It seems advisable to change filter papers two or three times during the filtration, if necessary. This step usually requires from 30 minutes to 1.5 hours; however, the time can be shortened appreciably by the use of Hyflo Supercel®.
3. This Norit® treatment, when combined with the preceding filtration, does much to improve the purity of the N-nitroso-N-phenylglycine; though the yield of nitroso compound thereby is lowered, the yield of the sydnone is increased correspondingly and the sydnone is much purer.
4. Earl and Mackney[2] report a tan product (96.8% yield) melting at 102–103°. They did not use the preliminary filtration or Norit® treatment described above.
5. The usual method (Earl and Mackney[2]) has been to let the solution stand at room temperature for 24 hours. Control experiments proved, however, that the procedure described above gives comparable results.[3]
6. On rare occasions a small amount of insoluble material may be present in the cool solution; the solution can be poured into the water through a funnel fitted with a plug of glass wool.
7. Earl and Mackney[2] report a very light tan product, melting at 134–135°, in 73% yield. The product can be recrystallized from boiling water to give cream-colored needles, but this does not improve the purity of the product.

3. Discussion

This procedure is a modification of preparations of 3-phenylsydnone described earlier.[2,3] The dehydration of N-nitroso-N-phenylglycine has also been effected by the use of thionyl chloride and pyridine in dioxane,[4] thionyl chloride in ether,[4] trifluoroacetic anhydride in ether,[4] and diisopropylcarbodiimide in water;[5] or by reaction of the alkali metal salts of N-nitroso-N-phenylglycine with phosgene or benzenesulfonyl chloride in water[5] or with acetyl chloride in benzene.[4]

4. Merits of the Preparation

The present procedure makes possible the preparation of large quantities of very pure 3-phenylsydnone without recrystallization. The earlier procedure[2] produced a tan or brown product which lost its color only after several recrystallizations. Slight variations in this procedure can be used to prepare a variety of 3-substituted and 3,4-

disubstituted sydnones.

3-Phenylsydnone is the prototype of that class of mesoionic compounds called sydnones. On acidic hydrolysis it produces phenylhydrazine, whereas basic hydrolysis regenerates N-nitroso-N-phenylglycine. This sydnone undergoes a variety of electrophilic substitutions,[3,4,6,7,8,9,10,11,12,13,14,15,16,17,18,19] including mercuration[11,13,16] and formylation,[19] with an ease comparable to thiophene, and a number of "1,3-dipolar cycloadditions" with numerous alkenes,[15,18] alkynes,[17] and quinones[8] to form, with loss of carbon dioxide, a variety of pyrazole derivatives.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether (60-29-7)

acetic anhydride (108-24-7)

acetyl chloride (75-36-5)

thionyl chloride (7719-09-7)

sodium nitrite (7632-00-0)

Phenylhydrazine (100-63-0)

carbon dioxide (124-38-9)

Norit (7782-42-5)

Benzenesulfonyl chloride (98-09-9)

pyridine (110-86-1)

phosgene (75-44-5)

Thiophene (110-02-1)

dioxane (5703-46-8)

N-Nitroso-N-phenylglycine (6415-68-5)

N-phenylglycine (103-01-5)

trifluoroacetic anhydride (407-25-0)

diisopropylcarbodiimide (693-13-0)

3-Phenylsydnone, N-Phenylsydnone (120-06-9)

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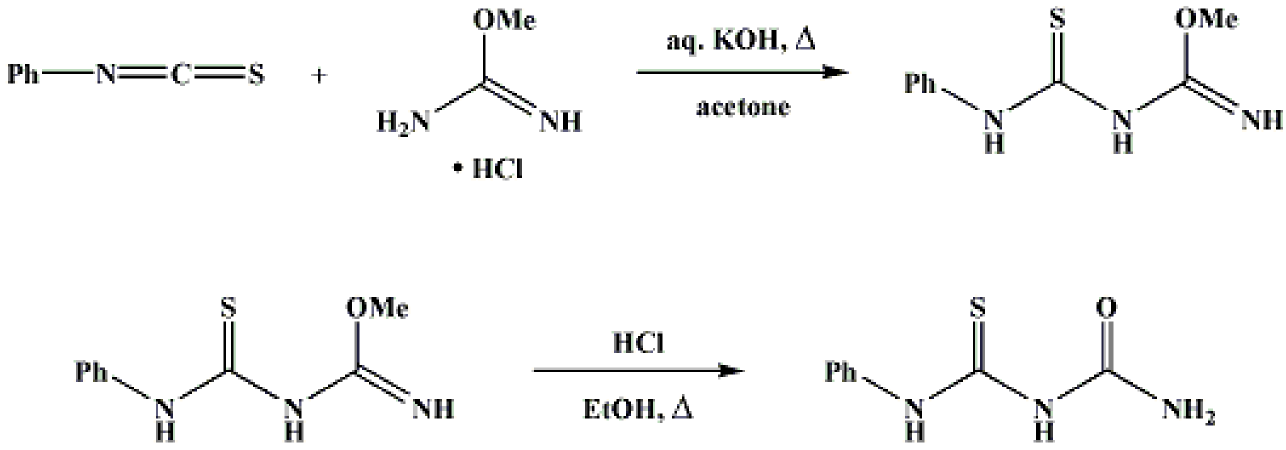
Organic Syntheses, CV 5, 966

1-PHENYL-2-THIOBIURET

[Biuret, 1-phenyl-2-thio-]



Submitted by Frederick Kurzer and W. Tertiuk[1].
Checked by James Cason and Francis J. Schmitz.

1. Procedure

A. *1-Phenyl-2-thio-4-methylisobiuret*. Into a 500-ml. three-necked flask fitted with a Hershberg stirrer[2] and reflux condenser are introduced a solution of 23.0 g. (0.35 mole) of 85% potassium hydroxide in 75 ml. of water, followed by 38.7 g. (0.35 mole) of methylisourea hydrochloride (Note 1). The clear liquid is diluted with 150 ml. of acetone, and the resulting suspension, containing finely divided crystalline solid, is treated with 27.0 g. (24 ml., 0.2 mole) of recently distilled phenyl isothiocyanate.

After the additions have been completed, the third neck of the flask is closed and the temperature of the stirred reaction mixture is raised to its boiling point during 15–20 minutes, then heating under reflux is continued for 10–15 minutes. The contents of the flask, which first change to a greenish yellow clear solution, then later separate into two phases, are kept well mixed by rapid stirring (Note 2). The flask is next disconnected, fitted with a stillhead, and the acetone is distilled rapidly at 25–35° under reduced pressure. The residual semicrystalline suspension, or two-phase mixture containing the crude product in the upper viscous layer, is carefully stirred onto 300–400 g. of crushed ice. This yields the crude isobiuret as a very pale-yellow granular solid, which is collected by suction filtration, washed with successive small portions of water, drained well, and allowed to dry at room temperature. The dry product is dissolved 120–150 ml. of boiling benzene. Small quantities of suspended yellow powdery material (and possibly droplets of water) are removed by gravity filtration through a heated funnel or by suction filtration through a preheated Büchner funnel. The clear yellow filtrate deposits large prismatic crystals of 1-phenyl-2-thio-4-methylisobiuret, which are collected by suction filtration at room temperature, washed with a little benzene, and air-dried. The yield of material having a melting point in the range of 122–128° is 27–31.5 g. (65–75%) (Note 3). Further small quantities (2–4 g.) of less pure material may be obtained by partial vacuum evaporation of the combined mother liquors and washings.

B. *1-Phenyl-2-thiobiuret*. A solution of 20.9 g. (0.1 mole) of 1-phenyl-2-thio-4-methylisobiuret in 200 ml. of hot absolute ethanol is treated with 40 ml. of concentrated hydrochloric acid, and the clear liquid is heated under reflux until to more methyl chloride is evolved (6–12 minutes, (Note

4)). The resulting solution is stirred into 2.1 of water, and the separated crystalline precipitate is collected after storage at 0° for at least 24 hours. The dried product is dissolve in boiling absolute ethanol (5–6 ml. per g.) then the hot solution is quickly filtered by light suction and diluted with half its volume of petroleum ether (b.p. 60–80°). The separated 1-phenyl-2-thiobiuret is collected by suction filtration after storage for 12 hours at room temperature, and rinsed with small portions of a mixture of equal volumes of ethanol and petroleum ether. The yield of product, m.p. 159–161° (Note 5), is 8.8–10.5 g. (45–54%) (Note 6).

2. Notes

1. Methylisourea hydrochloride is accessible from commercially available calcium cyanamide by the method described in *Organic Syntheses.*[3]
2. The reaction is complete when a withdrawn sample of the liquid, stirred on a watch-glass in an air current, solidifies rapidly and smells only very faintly of phenyl isothiocyanate.
3. This product, though still pale yellow, is suitable for most synthetic purposes. Colorless glass-like prisms of m.p. 128–130° (cor.) are obtainable on further crystallization from benzene.
4. The top of the condenser is fitted with a short vertical piece of hard-glass tubing at the mouth of which the escaping methyl chloride may be burned off. The completeness of the reaction is indicated when insufficient gas is evolved to support a *steady* flame. Methyl chloride will continue to diffuse out and produce a flickering flame when a match is held to the outlet. Prolonging the reaction time excessively reduces the yield.
5. Rather variable melting points have been reported for this compound, probably because the melting is accompanied by decomposition. In a bath heated at about 2° per minute, the checkers obtained capillary tube melting points for all samples in the range 149.5–152° (cor.).
6. The submitters report that partial evaporation of the mother liquors gives additional small quantities of low-melting fractions from which additional pure material may be obtained by further crystallizations. In contrast, the checkers obtained nearly one-half the yield in a second crop which had essentially the same melting point as the first crop. This somewhat different behavior may result from a difference in solvent characteristics of different samples of petroleum ether.

3. Discussion

1-Phenyl-2-thiobiuret has been prepared by the pyrolysis, at 75–90°, of 1-phenyl-2-thio-4-methylisobiuret hydrochloride,[4] and by the condensation of carbamyl isothiocyanate with aniline.[5] The method here described, which is based on the former method, is regarded as most convenient. A comprehensive review of syntheses of biurets, thiobiurets, and dithiobiurets is available.[6]

4. Merits of Preparation

This synthesis is generally applicable. For example, condensation of phenyl isothiocyanate and ethylisourea by the procedure above gives 70–80% yield of 1-phenyl-2-thio-4-ethylisobiuret,[4] which forms lustrous massive prisms, m.p. 98–99° (from benzene).

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

calcium cyanamide

1-Phenyl-2-thio-4-methylisobiuret

1-phenyl-2-thio-4-methylisobiuret hydrochloride

1-phenyl-2-thio-4-ethylisobiuret

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

aniline (62-53-3)

methyl chloride (74-87-3)

acetone (67-64-1)

potassium hydroxide (1310-58-3)

PHENYL ISOTHIOCYANATE (103-72-0)

1-Phenyl-2-thiobiuret, Biuret, 1-phenyl-2-thio- (53555-72-9)

Methylisourea hydrochloride

carbamyl isothiocyanate

ethylisourea

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Organic Syntheses, CV 5, 969

PHENYL(TRICHLOROMETHYL)MERCURY

Submitted by Ted J. Logan[1]
Checked by William E. Parham and John R. Potoski.

1. Procedure

Into a 250-ml. round-bottomed flask equipped with a magnetic stirrer and reflux condenser fitted with a drying tube containing Drierite® are placed 150 ml. of dimethoxyethane (Note 1), 27.8 g. (0.15 mole) of sodium trichloroacetate (Note 2), and 31.3 g. (0.1 mole) of phenylmercuric chloride. The stirred mixture (Note 3) is heated to reflux (85°) by use of a heating mantle. Carbon dioxide evolution, which begins shortly after heating is begun. is accompanied by the appearance of a precipitate of sodium chloride. The reactants are heated at the reflux temperature until no more carbon dioxide evolution is obvious (1 hour), then cooled to room temperature and poured into 500 ml. of water. The resulting mixture, consisting of a dense oil layer, a solid, and an aqueous layer, is extracted with four 50-ml. portions of diethyl ether. The combined ether layers are then washed with two 50-ml. portions of water, dried over anhydrous magnesium sulfate, filtered, and the solvent removed using a rotary evaporator. The resulting white solid, which weighs 44.8 g., is dissolved in 130 ml. of hot chloroform and fractionally crystallized. The first three fractions weigh 2.3 g. and are recovered phenylmercuric chloride. Successive reduction of solvent volume and further fractional crystallization provides 25.6 g. of product (65% yield), m.p. 110° (Note 4) and (Note 5).

2. Notes

1. The 1,2-dimethoxyethane (monoglyme) was purchased from Matheson Coleman and Bell and purified by distillation from lithium aluminum hydride. The use of unpurified solvent had little effect on the yield of product.
2. Sodium trichloroacetate may be purchased from the Dow Chemical Company (96.4% pure by Cl analysis) or prepared by neutralizing trichloroacetic acid (Matheson Coleman and Bell) with aqueous sodium hydroxide to the phenolphthalein end point. The product is dried under vacuum for 12 hours, sieved, then dried an additional 12 hours under vacuum, all at room temperature. The salt prepared by this method and used in this preparation was 98.5% pure, based on chlorine analysis, and can be stored indefinitely without decomposition. The submitter has obtained nearly identical yields of phenyltrichloromethylmercury from the commercial and from the prepared salts.
3. If all the reactants are stirred for several minutes at room temperature, they

dissolve to give a turbid solution. Stirring while heating then becomes unnecessary, except to promote more even heating, since the refluxing solvent and carbon dioxide evolution keep the precipitated sodium chloride in suspension.

4. Purity of the product was ascertained by quantitative X-ray fluorescence analysis for chlorine and mercury, which showed satisfactory agreement with calculated values. Compounds containing both mercury and chlorine are difficult to analyze by classical "wet" analytical procedures.

5. Yields as high as 77% have been obtained by this procedure. It is difficult to recover all the product from the mother liquor. The use of a 1:1 ratio of sodium trichloroacetate and phenylmercuric chloride gave yields of 39–45%, while a 1.25:1 ratio gave a 61% yield of product.

3. Discussion

This procedure is essentially identical with that previously published by the submitter.[2]

The pyrolysis of sodium trichloroacetate in 1,2-dimethoxyethane was originally described by Wagner.[3] Razuvaev later adapted this procedure to the synthesis of organomercurials, including the title compound.[4]

Phenyl(trichloromethyl)mercury has also been prepared by the reaction of phenylmercuric bromide with sodium methoxide and ethyl trichloroacetate[5] (62–71% yield); of phenylmercuric chloride with potassium *t*-butoxide and chloroform[6] (75% yield); of phenylmagnesium bromide with trichloromethylmercuric bromide[7] (24% yield); of trichloromethylmercuric bromide with diphenyldichlorotin (49%); and of trichloromethylmercuric bromide with phenylmagnesium bromide[8] (no yield given).

4. Merits of the Preparation

The main advantages of this procedure are simplicity of apparatus and technique, availability of reactants, ease of product isolation in good yield, and purity of product. The submitter has also used this method successfully for the preparation of trichloromethylmercuric chloride (from mercuric chloride), bis-(trichloromethyl) mercury (from a 2:1 ratio of sodium trichloroacetate to mercuric chloride or mercuric acetate), and trichloromethylmercuric bromide (from mercuric bromide).

Phenyl(trihalomethyl)mercurials, including the title compound, can be thermally decomposed in the presence of olefins to yield the corresponding dichlorocyclopropane derivatives.[2,9,10,11] Olefins such as tetrachloroethylene and ethylene, which give exceptionally low yields of dichlorocyclopropanes when treated with other reagents for generating dichlorocarbene ($:CCl_2$), give reasonable yields of dichlorocyclopropanes when heated with phenyltrichloromethylmercurials.[12]

These mercurials have also been employed in the preparation of dihalomethyl derivatives of carbon, silicon, and germanium,[13] in the conversion of carboxylic acids to dichloromethyl esters,[14] in the deoxygenation of pyridine N-oxide,[5] in the synthesis of diarylcyclopropenones from diaryl acetylenes,[15] and in numerous other applications. Leading references to these applications may be found in a recent review on the use of phenyl (trihalomethyl)mercury compounds as divalent carbon transfer reagents.[16]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 874
- Org. Syn. Coll. Vol. 6, 142

1718

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

1,2-dimethoxyethane (monoglyme)

ether, diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium chloride (7647-14-5)

mercuric acetate (1600-27-7)

mercury (7439-97-6)

carbon dioxide (124-38-9)

sodium methoxide (124-41-4)

carbon (7782-42-5)

chlorine (7782-50-5)

ethylene (9002-88-4)

mercuric chloride (7487-94-7)

Phenylmagnesium bromide (100-58-3)

phenylmercuric bromide

phenolphthalein (77-09-8)

magnesium sulfate (7487-88-9)

trichloroacetic acid (76-03-9)

tetrachloroethylene (127-18-4)

mercuric bromide (7789-47-1)

lithium aluminum hydride (16853-85-3)

1,2-dimethoxyethane (110-71-4)

dimethoxyethane (534-15-6)

ethyl trichloroacetate (515-84-4)

Pyridine N-oxide (694-59-7)

silicon

sodium trichloroacetate (650-51-1)

Phenyl(trichloromethyl)mercury, phenyltrichloromethylmercury (3294-57-3)

phenylmercuric chloride

trichloromethylmercuric bromide

diphenyldichlorotin (1135-99-5)

trichloromethylmercuric chloride

bis-(trichloromethyl)mercury

germanium

potassium t-butoxide (865-47-4)

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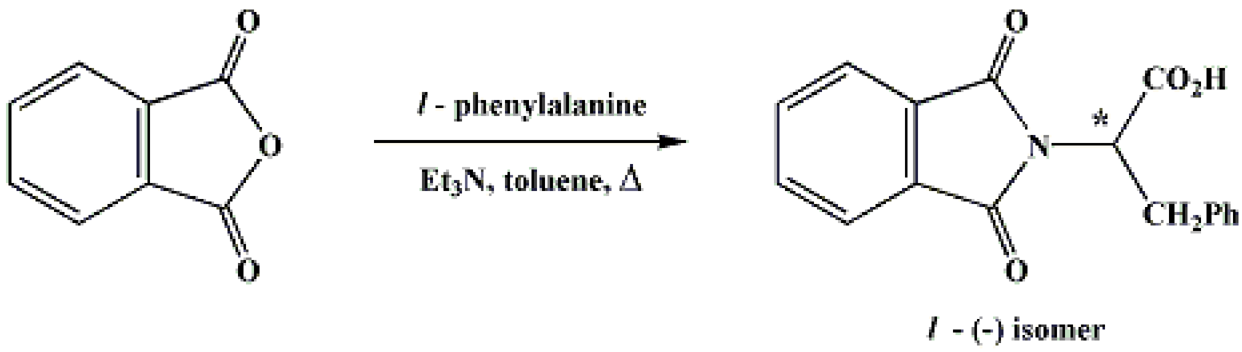
Organic Syntheses, CV 5, 973

N-PHTHALYL-L-β-PHENYLALANINE

[2-Isoindolineacetic acid, α-benzyl-1,3-dioxo-, L-]



Submitted by Ajay K. Bose[1]
Checked by Max Tishler and George A. Doldouras.

1. Procedure

In a 300-ml. flask fitted with a water separator and a reflux condenser are placed 16.5 g. (0.1 mole) of L-phenylalanine (Note 1), 14.8 g. (0.1 mole) of finely ground phthalic anhydride, 150 ml. of toluene, and 1.3 ml. of triethylamine. The flask is heated on an oil bath or with an electric mantle so as to maintain a vigorous reflux (Note 2). Separation of water is rapid at the beginning but becomes slower with time and is virtually over in 1.5 hours.

After 2 hours the water separator and the reflux condenser are disconnected, and volatile material is removed from the mixture under reduced pressure and on a steam bath (Note 3). The solid residue is stirred with 200 ml. of cold water and 2 ml. of hydrochloric acid until all the lumps are broken (Note 4).

The mixture is filtered under suction, and the product is washed with three 50-ml. portions of cold water. After drying in an air oven the product weighs 27–28 g. (91.5–95%) and consists of a white crystalline powder, m.p. 179–183°, $[\alpha]_D^{25}$ –198 to –200° (in alc.) (Note 5).

This product can be recrystallized by dissolving 10 g. in 20 ml. of hot ethyl alcohol (95%), adding 14 ml. of water, and allowing the solution to cool slowly so that no oiling out takes place. Colorless needles, m.p. 183–185°, $[\alpha]_D^{25}$ –211 to –217° (in alc.) (Note 6), are obtained (first crop, 7.5–8.5 g., 83–90% recovery; further quantities can be recovered from the mother liquor).

2. Notes

1. Material (supplied by Nutritional Biochemicals Corp., Cleveland, Ohio) of [α]

$^{25}_{D}$ −32° (c = 1.98 in water) was used.

2. An applicator stick (available from drug stores) can be used very conveniently to ensure smooth boiling. If a boiling chip is used, it should be colored (Carborundum, for example) to make its separation from the product convenient.

3. This evaporation during which a solid separates is very conveniently carried out in a rotary vacuum evaporator (manufactured by Rinco Instrument Co., Greenville, Illinois). An equally convenient alternative arrangement for solvent stripping that is in use in some laboratories is shown in f.htmig. 1. The splash-head *A* permits rapid removal of solvent under reduced pressure. Any solid carried beyond the flask *B* by spattering is arrested in *A* and can be washed down into *B* by introducing a low-boiling liquid like acetone through the port *C*. The side arm *D* permits continuous feeding into the "stripper." If the feed tube *E* is fitted with a plug of glass wool, the feed solution can be automatically filtered from suspended solids such as drying agents. Another advantage of this stripper is that a conveniently small collecting flask *B* can be used for a feed solution that is very dilute and large in volume.

Fig. 1. Solvent stripper.

Fig. 1. Solvent stripper.

4. The purity of the product depends largely on the efficient breaking up of all lumps and the subsequent washing.

5. This material gives satisfactory elemental analysis and can be used without purification for further reactions.

6. The checkers observed a rotation of −211 to −217°, as against −207 to −212° reported by the submitter; Sheehan, Chapman, and Roth[2] report −212°.

3. Discussion

N-Phthalyl-L-phenylalanine has been prepared by the fusion of L-alanine with phthalic anhydride.[2]

The present method, based on a recent publication,[3] ensures a low temperature of reaction which precludes racemization and is more convenient than the fusion method for large-scale operation.

The method described here can be applied to other amino acids and on a larger scale. Thus β-alanine on a 1.5-mole scale gave *N*-phthalyl-β-alanine in 96% yield and L-alanine gave N-phthalyl-L-alanine in 91% yield, and glycine ethyl ester hydrochloride (using more than one molar equivalent of triethylamine) gave the ethyl ester of N-phthalylglycine in 96% yield.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

N-Phthalyl-L-β-phenylalanine

N-Phthalyl-L-phenylalanine

N-phthalyl-β-alanine

N-phthalyl-L-alanine

ethyl ester of N-phthalylglycine

ethyl alcohol (64-17-5)

hydrochloric acid (7647-01-0)

L-alanine (56-41-7)

phthalic anhydride (85-44-9)

acetone (67-64-1)

toluene (108-88-3)

β-Alanine (107-95-9)

Glycine ethyl ester hydrochloride (623-33-6)

phenylalanine (63-91-2)

triethylamine (121-44-8)

2-Isoindolineacetic acid, α-benzyl-1,3-dioxo-, L-

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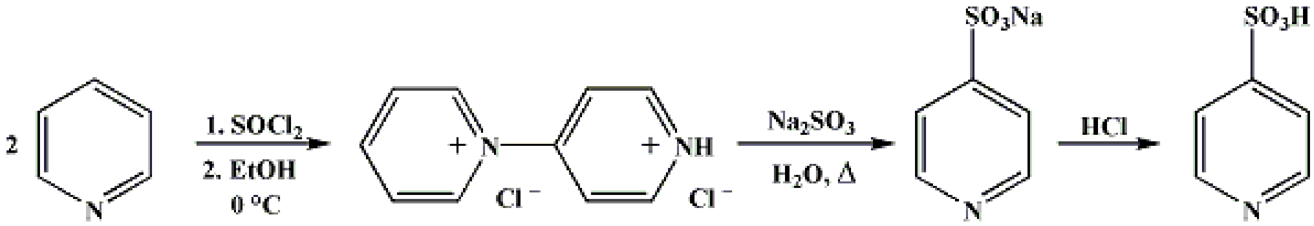
Organic Syntheses, CV 5, 977

4-PYRIDINESULFONIC ACID



Submitted by Russell F. Evans[1,2], Herbert C. Brown[1], and H. C. van der Plas[3].
Checked by James Cason and Taysir Jaouni.

1. Procedure

A. *N-(4-Pyridyl)pyridinium chloride hydrochloride*. In a 2-l. round-bottomed flask equipped with a ground joint (Note 2) is placed 395 g. (5.00 moles) of dry pyridine (Note 3). As this flask is cooled by swirling in a bath of cold water (Note 4), there is added during a few minutes 1190 g. (10.0 moles) of a good commercial grade of thionyl chloride (Note 1). After completion of the addition, the flask is protected by a drying tube, and the reaction mixture is allowed to stand at room temperature under a hood for 3 days. During this period, the color of the mixture changes from deep yellow through brown to black.

The flask is fitted with a Claisen head, and excess thionyl chloride is distilled at reduced pressure (water pump) and collected in a receiver cooled in a mixture of dry ice and acetone (Note 5). The flask is heated with a water bath that is slowly raised from room temperature to about 90°, then held at that temperature until no more distillation occurs and a black residue remains.

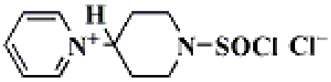
The black residue is cooled to 0°, and 100 ml. of ice-cold ethanol is added very cautiously to react with residual thionyl chloride. An additional 400 ml. of ice-cold ethanol is added, and the solid mass left at the bottom of the flask is broken up with the aid of a rod (Note 2). The resultant light-brown powder is collected by suction filtration, preferably on a sintered glass funnel, and washed with five 150-ml. portions of ethanol. The yield of crude N-(4-pyridyl)pyridinium chloride hydrochloride is 230–257 g. (40–45%). This product is very deliquescent and should be used immediately or stored over phosphorus pentoxide.

B. *4-Pyridinesulfonic acid*. A 115-g. (0.50 mole) quantity of N-(4-pyridyl)pyridinium chloride hydrochloride is dissolved in 750 ml. of water in a 2-l. round-bottomed flask, and 378 g. (1.50 moles) of solid sodium sulfite heptahydrate is added cautiously. After the evolution of sulfur dioxide has ceased, the solution is gently heated under reflux in a nitrogen atmosphere for 24 hours. After slight cooling, 20 g. of charcoal is added to the mixture, and it is heated under reflux for an additional hour. The resultant mixture is filtered through a fluted paper, the filtrate is evaporated to dryness on a steam bath under reduced pressure, and the residue is air-dried at 100–110° (Note 6). This solid is now continuously extracted with absolute ethanol for 24 hours in a Soxhlet apparatus. The alcohol is distilled from the extract on a steam bath, and the crude sodium 4-pyridinesulfonate is dissolved in about 160 ml. of hot water. After 320 ml. of 12*N* hydrochloric acid has been added with mixing, the solution is cooled to room temperature. The precipitate of sodium chloride is filtered, and the filtrate is evaporated to dryness under reduced pressure on a steam bath. Crystallization of the residue from 600 ml. of 70% aqueous ethanol yields 27–30 g. of colorless crystals of 4-pyridinesulfonic acid, m.p. 313–315° (dec.). Concentration of the mother liquor affords about 10 g. of additional product which is less pure. The total yield is 36–40 g. (45–50%) (Note 7). Recrystallization from 70% aqueous ethanol affords a purer specimen, m.p. 317–318° (dec.). (Note 8).

2. Notes

1. Although N-(4-pyridyl)pyridinium chloride hydrochloride is formed by reaction of pyridine with thionyl chloride, followed by treatment with ethanol, the intermediates involved in the reaction have not

been well established. It has been suggested[4,5] that 1 mole of thionyl chloride converts 2 moles of pyridine to the compound. This intermediate would be further oxidized by thionyl chloride and solvolyzed by ethanol to the pyridinium chloride hydrochloride. According to this reaction route, the stoichiometric ratio of pyridine to thionyl chloride for the overall process would be about 1:1. Varying ratios of thionyl chloride have been used[6,7,8] and varying yields of the product have been reported, ranging from 60% of crude product[7] to 48% of recrystallized product.[8] In one run in which the checkers used one-half the specified amount of thionyl chloride, the yield was unaffected. The submitters report yields in the range 58–62% by the procedure described here.



2. Thionyl chloride attacks rubber so rapidly that all-glass apparatus is highly desirable for this procedure. Since breaking up the residual product in a flask results in a high mortality of flasks, the checkers preferred a distilling vessel with a removable top of the type used with vacuum desiccators (e.g., Corning Glass Works, No. 3480).
3. Since moisture reacts with thionyl chloride to give hydrogen chloride, which forms the salt of pyridine and thus inactivates it, the pyridine should be dried over barium oxide for 24 hours, then distilled under anhydrous conditions shortly before use.
4. Provided that this addition is carried out rapidly, ingress of moisture is not significant, and more complicated apparatus is not recommended.
5. Since thionyl chloride ruins all rubber tubing with which it comes in contact, efficient cooling of the receiver is recommended.
6. Alternatively, to decrease the time required to complete drying at 100–110°, the moist solid residue may be triturated with chloroform and the chloroform distilled from the steam bath. The checkers used a vacuum oven for drying.
7. The submitters report yields in the range 63–70%.
8. Because the sulfonic acid melts with decomposition, the value observed for the melting point is highly dependent on the rate of heating of the sample.[9,10,11,12]

3. Discussion

The preparation of N-(4-pyridyl)pyridinium chloride hydrochloride follows the procedure of Koenigs and Greiner,[6] while the preparation of the sulfonic acid is a modification of a patent procedure.[13]

4-Pyridinesulfonic acid has been prepared by oxidation of 4-pyridinethiol with hydrogen peroxide in barium hydroxide solution,[9] with hydrogen peroxide in glacial acetic acid,[10] with nitric acid-chlorine or nitric acid-chlorine-hydrochloric acid mixtures,[11] and with nitric acid alone.[10,12,14] The latter reaction gives a mixture of 4-pyridinesulfonic acid and other products, e.g., di-4-pyridyl disulfide dinitrate, and this has led to some confusion in the literature.[10,11,12,14] 4-Pyridinesulfonic acid has also been obtained from its N-oxide derivative by reduction of the N-oxide group with iron and acetic acid[15] or catalytically.[16]

Sodium 4-pyridinesulfonate has been formed by the oxidation of 4-pyridinethiol with hydrogen peroxide in sodium hydroxide solution,[17,18] and from the reaction of 4-chloropyridine with aqueous sodium sulfite.[19] The salt has been converted to the free acid by treatment with a cation-exchange resin[10,11] or with sulfuric acid.[11]

4. Merits of the Preparation

This is the most convenient preparation of 4-pyridinesulfonic acid, a useful intermediate for the synthesis of various pyridine derivatives.

References and Notes

1. Department of Chemistry, Purdue University, Lafayette, Indiana.
2. National Chemical Laboratory, D.S.I.R., Teddington, Middlesex, England.
3. Landbouwhogeschool, Laboratorium voor Organische Chemie, Wageningen, Holland.
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

nitric acid-chlorine-hydrochloric acid

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrogen chloride, hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

sodium sulfite (7757-83-7)

sodium hydroxide (1310-73-2)

thionyl chloride (7719-09-7)

chloroform (67-66-3)

iron (7439-89-6)

nitric acid (7697-37-2)

sodium chloride (7647-14-5)

sulfur dioxide (7446-09-5)

barium oxide

nitrogen (7727-37-9)

acetone (67-64-1)

pyridine (110-86-1)

hydrogen peroxide (7722-84-1)

barium hydroxide (17194-00-2)

4-Pyridinesulfonic acid (5402-20-0)

N-(4-Pyridyl)pyridinium chloride hydrochloride (5421-92-1)

sodium sulfite heptahydrate

sodium 4-pyridinesulfonate

4-pyridinethiol (4556-23-4)

nitric acid-chlorine (14545-72-3)

4-chloropyridine (626-61-9)

phosphorus pentoxide (1314-56-3)

di-4-pyridyl disulfide dinitrate

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Organic Syntheses, CV 5, 982

α-PYRONE

[2-Oxo-1, 2H-pyrane-]

Submitted by Howard E. Zimmerman, Gary L. Grunewald, and Robert M. Paufler[1].
Checked by E. J. Corey, W. H. Pirkle, and M. J. Haddadin.

1. Procedure

(Note 1)
A 37.5-g. (0.266-mole) sample of coumalic acid (Note 2) is placed in a 30 × 10 cm. cylindrical flask attached horizontally to a 55 × 3 cm. oven-heated Vycor tube (Note 3) *loosely* packed with 20 g. of fine copper turnings (Note 4). Following the Vycor tube successively are two ice-cooled 50-ml. receivers and a dry ice trap. The latter is connected to an efficient vacuum pump (Note 5). The system is evacuated, and the Vycor tube is heated to 650–670°. Then the flask containing the coumalic acid is heated with a nichrome wound heating jacket to 180°, and the temperature is allowed to rise slowly to 215°. During this time coumalic acid sublimes into the Vycor tube and α-pyrone distills into the ice-cooled receivers. The pressure is held below 5 mm. (Note 6). The yield of pale yellow crude material is 18–19.3 g. (70–75%). Distillation affords 16.9–18 g. (66–70%) of colorless oily α-pyrone. b.p. 110° (26 mm.), n^{25}D 1.5270.

2. Notes

1. Since this procedure was checked, a method[1] has been developed which uses a vertical arrangement of the oven together with a powder sifter placed above the oven. This allows the use of less pure starting material but with reduced yields. Also, it allows more rapid throughput. It is required that the top portion of the tube be filled with porcelain Berl saddles onto which the powder is sifted. The saddles then pick up any tarry residue which might clog the pyrolysis tube.
2. Coumalic acid, m.p. 206–209°, was prepared by the method of Wiley and Smith[2] and recrystallized from methanol as described. Starting material prepared in this way still contains impurities but is satisfactory for the preparation of α-pyrone. A purer grade of colorless coumalic acid, m.p. 206–208.5°, may be obtained by further recrystallization and a subsequent

sublimation at 180–190° (0.5 mm.) (Precision Glass Macro Sublimator No. JM7410), and its use leads to higher yields of α-pyrone (80–85%) by the procedure given here. However, the losses of coumalic acid incurred in the purification (about 50%) and the time involved render this modification unprofitable. On the other hand, when unrecrystallized coumalic acid is used, the yields are generally somewhat lower (60–65%) and the results are slightly more variable.

3. The following apparatus was used by the submitters. The furnace was a Lindberg Model CF-1R High Temperature Combustion Furnace (Fisher Scientific Co. Catalog No. 10-467-1; E. H. Sargent Co. Catalog No. S-35955). This furnace has a hot zone of 8 3/4; in. and a maximum temperature of 1450°C. Because of the short heating length, the Vycor tube was packed with copper turnings over its entire length to prevent condensation of coumalic acid in the cooler parts of the tube. Glass wool insulation was used at both ends of the furnace to prevent heat loss.

The heater used for the sublimation vessel was made from a length of 15-cm. Pyrex tubing. The tube was covered partially with moistened asbestos fiber strips (*ca.* 1 mm. thick) which remain in place when dry. The tube was only partially covered with asbestos to allow visual inspection of the sublimation vessel. A sufficient length of nichrome wire (depending on the resistance of the wire) was wound over the asbestos base, and more asbestos was added over that already in place to hold the wire loops apart. During use, the open end was well stuffed with glass wool.

The sublimation vessel was made from 10-cm. Pyrex tubing sealed at one end and fitted with a standard taper 34/45 female joint at the other end.

The checkers used a Hoskins tube furnace, type FD303A (Central Scientific Co.), 17 in. long. The heater for the sublimation vessel was wound in two sections with heating wire in such a way that a decreasing temperature gradient in the direction of the pyrolysis oven was maintained. The open end of the heater was closed by an asbestos end plate which could be heated independently by a small nichrome coil.

4. Copper appears to function only as a surface heat transfer agent. Broken pieces of porous plate, for example, may also be used.

5. Better yields are obtained at low pressures (preferably below 5 mm.) because of more efficient sublimation of coumalic acid. The submitters report that a water aspirator could be used with crude (unrecrystallized) coumalic acid to avoid damage to the vacuum pump by untrapped corrosive vapors, and that yields of α-pyrone averaged 45% in this modification. The checkers used a mechanical pump with an efficient sodium hydroxide trap in all runs.

6. It is important that the melting of the coumalic acid be prevented during the sublimation process; hence maintenance of the lowest possible pressure is recommended. If the material in the sublimation vessel begins to melt, resinification occurs with no further sublimation and a correspondingly lower yield of product. The temperature of the sublimator should be maintained high enough to allow a maximum rate of sublimation of coumalic acid, but not so high as to cause melting. Increasing the scale of the preparation increases the

possibility of resinification of coumalic acid in the sublimator before complete reaction. However, the submitters have successfully carried out the preparation of α-pyrone on twice the scale described here using the same procedure and apparatus (except that the collection flasks were 100-ml. size). On the larger scale it is advisable to use pure sublimed coumalic acid. In the experience of the checkers, larger-scale runs are much less readily reproducible.

3. Discussion

α-Pyrone has previously been prepared in low yield by the pyrolysis of heavy metal salts of coumalic acid[3] and by the small-scale pyrolysis of α-pyrone-6-carboxylic acid over copper.[4]

4. Merits of the Preparation

This method affords α-pyrone in quantity and in good yield not achieved previously.[3] The compound has considerable possibilities in Diels-Alder reactions, such as a decarboxylative double diene synthesis.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 462
- Org. Syn. Coll. Vol. 9, 28

6

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

2-Oxo-1, 2H-pyrane-

methanol (67-56-1)

copper, copper turnings (7440-50-8)

Coumalic acid (500-05-0)

α-Pyrone (504-31-4)

α-pyrone-6-carboxylic acid

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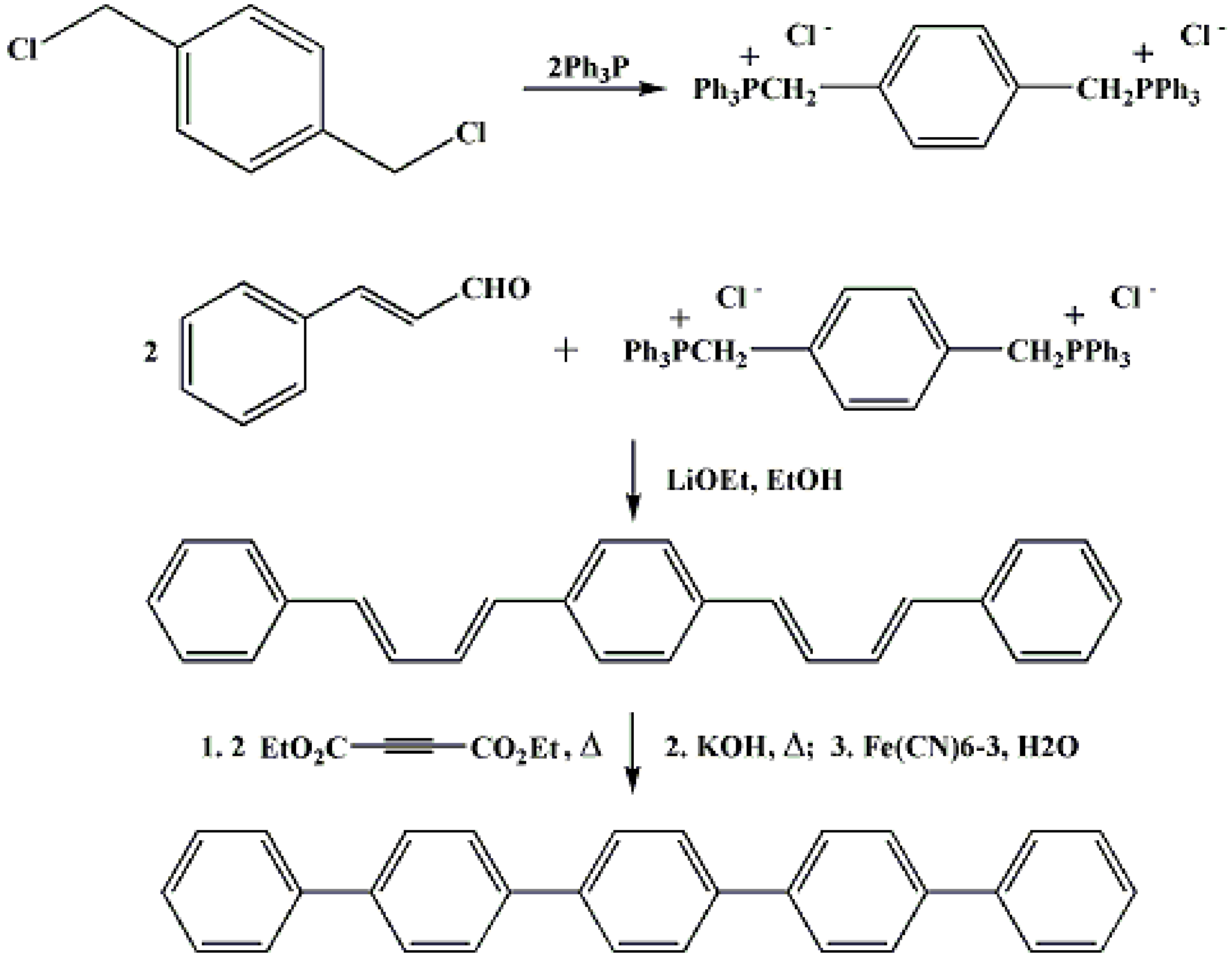
Organic Syntheses, CV 5, 985

p-QUINQUEPHENYL



Submitted by Tod W. Campbell and Richard N. McDonald[1].
Checked by Virgil Boekelheide and Richard E. Partch.

1. Procedure

A. *p-Xylylene-bis(triphenylphosphonium chloride)*. A mixture of 262 g. (1.0 mole) of triphenylphosphine (Note 1) and 84 g. (0.48 mole) of *p*-xylylene dichloride (Note 2) in 1 l. of dimethyl formamide is heated at reflux with stirring for 3 hours (Note 3). The mixture is then allowed to cool to room temperature with stirring, and the white crystalline solid is collected, washed with 100 ml. of dimethylformamide followed by 300 ml. of ether, and dried in a vacuum oven at 20 mm. pressure and 80°. The dry weight is 313–329 g. (93–98%).

B. *1,4-Bis-(4-phenylbutadienyl)benzene*. To a solution of 70 g. (0.10 mole) of *p*-xylylene-bis(triphenylphosphonium chloride) and 35 g. (0.26 mole) of cinnamaldehyde in 250 ml. of ethanol (Note 4) is added a solution of 0.25*M* lithium ethoxide in ethanol (Note 5). After being allowed to stand overnight at room temperature the yellow solid is collected by filtration, washed with 300 ml. of 60% ethanol, and dried in a vacuum oven

at 20 mm. and 70°. The dry weight is 29–32 g. (87–95%). The solid is then dissolved in the minimum amount (about 2 1.) of boiling xylene, treated with decolorizing charcoal, and filtered. The filtrate is reduced in volume to about 1.2 1. and digested at the boiling point with a trace of iodine for 3 hours (Note 6). After the solution has stood overnight at room temperature, the yellow plates are collected by filtration, washed with benzene, and dried in a vacuum oven at 20 mm. pressure at 70°. The weight of crystals, m.p. 285–287° (Note 7), is 23–25 g. (69–75%).

C. *p-Quinquephenyl*. A mixture of 3.40 g. (0.020 mole) of diethyl acetylenedicarboxylate[2] and 3.34 g. (0.010 mole) of 1,4-bis-(4-phenylbutadienyl) benzene is refluxed with 20 ml. of *o*-dichlorobenzene for 3 hours. It is allowed to cool to about 80°, then 100 ml. of ethanol and 5 g. of potassium hydroxide are added, and the mixture is refluxed for about 2 hours. The solvent is evaporated on a steam bath under a nitrogen atmosphere (Note 8), and the damp solid is extracted with 200 ml. of water. The intense yellow or yellow-orange aqueous layer is filtered, then extracted twice with 75-ml. portions of ether, charcoal is added and then filtered to separate water-insoluble matter. The filtrate is just neutralized with dilute hydrochloric acid (Note 9) and then made basic with 5 g. of sodium carbonate. To this is added a solution of 30 g. of potassium ferricyanide in 200 ml. of water. The mixture rapidly becomes milky and is allowed to stand overnight (Note 10). The suspended solid is centrifuged and washed with water twice by centrifugation. It is dried in a vacuum oven to give 3.1–4.2 g. of a green-tinged solid (Note 11). The combined material from five runs (18 g.) is sublimed to give 10 g. (52%) of pure quinquephenyl, m.p. 385–390°. This can be recrystallized from dimethylsulfoxide to give well-defined leaflets.

2. Notes

1. Commercial triphenylphosphine was used without further purification.
2. A sample of this compound was obtained from Hooker Electrochemical Co. and used without further purification.
3. The salt begins to precipitate after about 30 minutes.
4. Commercial anhydrous ethanol was used throughout.
5. Prepared by dissolving 1.74 g. of lithium wire in 1 1. of ethanol.
6. After the volume is reduced, a small crystal of iodine is added whereupon large yellow leaflets of product begin to separate.
7. The product can be recrystallized readily from dimethylformamide to give yellow leaflets, m.p. 290–293°. However, it is pure enough to be used in the next step. This synthesis has also been applied to the preparation of 1,4-bis-[4-(*p*-tolyl) butadienyl]benzene (100%), 1,4-bis-[4-(3-nitrophenyl)butadienyl]-benzene (56%), and 1,4-bis-(3-methyl-4-phenylbutadienyl)benzene (87%).
8. Nitrogen is used both for rapid removal of the solvent and to maintain an inert atmosphere.
9. The acid is added slowly with stirring until a trace of permanent precipitate is formed.
10. All the steps to this point can be completed in 1 day.

11. This procedure has been applied to the synthesis of 4,4''''-dimethylquinquephenyl and 2',3'''-dimethylquinquephenyl from 1,4-bis-[4-(*p*-tolyl)butadienyl]benzene and 1,4-bis-(3-methyl-4-phenylbutadienyl)benzene, respectively.

3. Discussion

1,4-Bis-(4-phenylbutadienyl)benzene has been obtained by condensation of cinnamaldehyde and *p*-phenylenediacetic acid with lead oxide.[3] *p*-Quinquephenyl has been prepared by the reaction of biphenyllithium with 1,4-cyclohexanedione, followed by dehydration and air oxidation of the dihydroquinquephenyl;[4] by the Gatterman coupling reaction of benzenediazonium formate with copper;[5] by the Ullmann coupling of 4-iodoterphenyl and 4-iodobiphenyl with silver;[5] by the catalytic reduction of *p*-di-bromobenzene;[6] and the Friedel-Crafts reaction of cyclohexene with terphenyl followed by dehydrogenation.[7] The procedure described represents the best route to both the 1,4-bis-(4-arylbutadienyl)benzenes and quinquephenyls that has been reported.[8] The details of the oxidative decarboxylation step for reactions of the type described here have been established by Fieser and Haddadin.[9]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether (60-29-7)

Cyclohexene (110-83-8)

lead oxide

sodium carbonate (497-19-8)

nitrogen (7727-37-9)

copper (7440-50-8)

iodine (7553-56-2)

potassium hydroxide (1310-58-3)

xylene (106-42-3)

cinnamaldehyde

silver (7440-22-4)

potassium ferricyanide (13746-66-2)

Lithium wire (7439-93-2)

dimethylformamide, dimethyl formamide (68-12-2)

p-phenylenediacetic acid (1205-91-0)

dimethylsulfoxide (67-68-5)

diethyl acetylenedicarboxylate (762-21-0)

triphenylphosphine (603-35-0)

1,4-Cyclohexanedione (637-88-7)

lithium ethoxide

4-iodobiphenyl (1591-31-7)

1,4-Bis-(4-phenylbutadienyl)benzene (10162-88-6)

quinquephenyl

1,4-bis-[4-(3-nitrophenyl)butadienyl]-benzene

1,4-bis-(3-methyl-4-phenylbutadienyl)benzene

biphenyllithium

dihydroquinquephenyl

benzenediazonium formate

4-iodoterphenyl

terphenyl (84-15-1)

o-dichlorobenzene (95-50-1)

p-di-bromobenzene (106-37-6)

p-Quinquephenyl (3073-05-0)

p-Xylylene-bis(triphenylphosphonium chloride) (1519-47-7)

p-xylylene dichloride (623-25-6)

1,4-bis-[4-(p-tolyl)butadienyl]benzene

4,4'''' dimethylquinquephenyl

2',3'''-dimethylquinquephenyl

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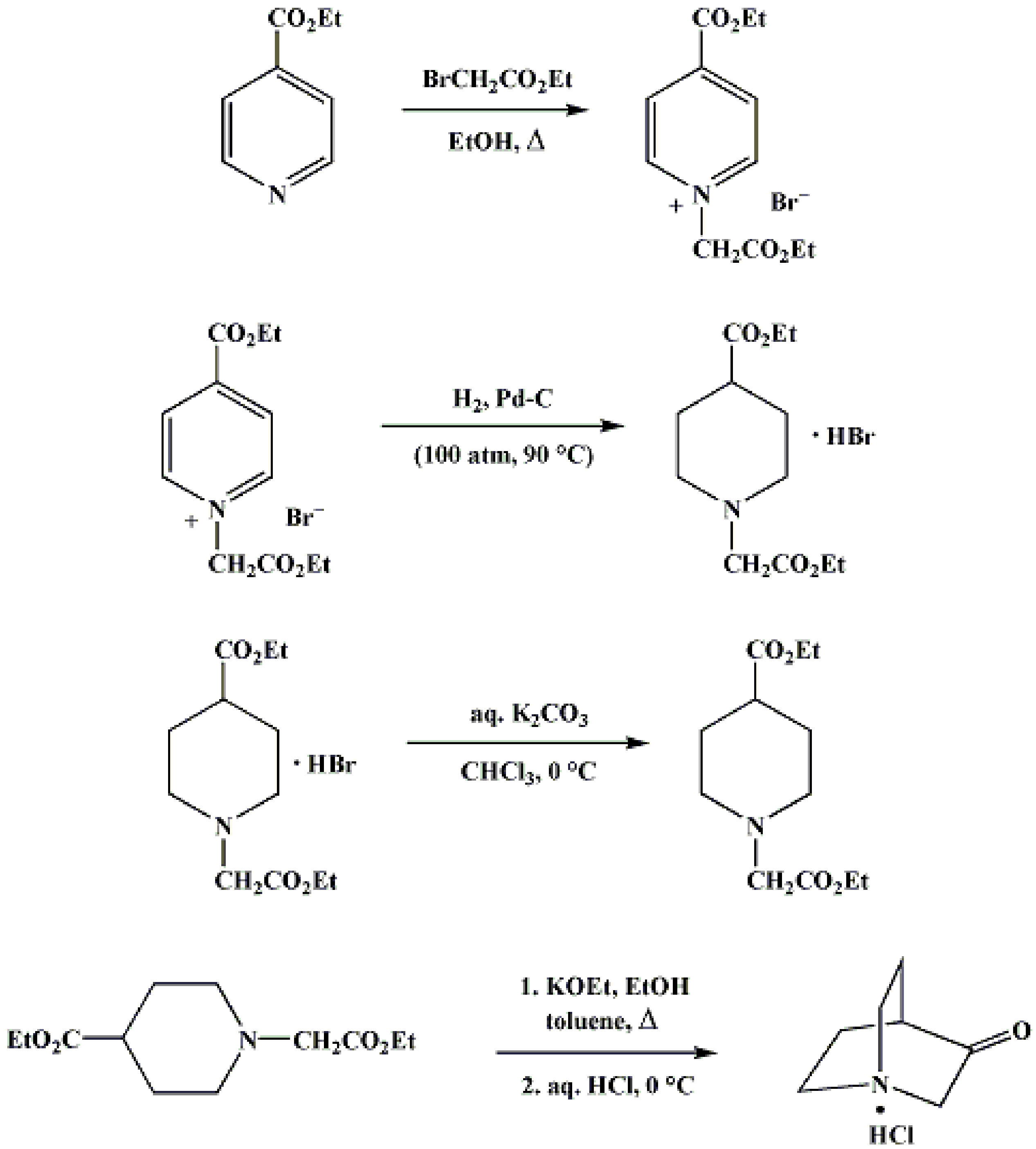
Organic Syntheses, *CV 5, 989*

3-QUINUCLIDONE HYDROCHLORIDE

[3-Quinuclidinone, hydrochloride]



Submitted by H. U. Daeniker and C. A. Grob[1].
Checked by E. Ciganek, W. R. Hertler, A. D. Josey, and B. C. McKusick.

1. Procedure

A. *1-Carbethoxymethyl-4-carbethoxypyridinium bromide*. A solution of 151 g. (1.00

mole) of ethyl isonicotinate (Note 1) and 167 g. (1.00 mole) of ethyl bromoacetate in 500 ml. of ethanol is allowed to stand overnight at room temperature in a 1-l. round-bottomed flask equipped with a reflux condenser (Note 2). The mixture is then heated at the reflux temperature for 4 hours. The resulting solution of 1-carbethoxymethyl-4-carbethoxypyridinium bromide is used directly for the next step (Note 3).

B. *1-Carbethoxymethyl-4-carbethoxypiperidine*. Fifteen grams of 10% palladium on charcoal[2] is added to the solution of the pyridinium bromide. The mixture is placed in an agitated 2-l. hydrogenation autoclave and hydrogenated at 90° under an initial pressure of 100 atm. (Note 4). Slightly more than the calculated amount of hydrogen (3 moles) is absorbed within 30–60 minutes. The mixture is cooled to 25°, and the catalyst is separated by filtration and washed with 100 ml. of ethanol. The filtrate is evaporated to dryness under water-aspirator vacuum at a bath temperature of 50–60°. The residue, semicrystalline 1-carbethoxymethyl-4-carbethoxypiperidine hydrobromide, is taken up in 500 ml. of ice-cold water. The solution is added to 500 ml. of chloroform in a 5-l. beaker immersed in an ice bath, and an ice-cold solution of 150 g. of potassium carbonate in 250 ml. of water is added gradually with stirring (Note 5). After the carbon dioxide evolution has subsided, the mixture is placed in a 2-l. separatory funnel and thoroughly shaken for some time. The lower, organic layer is drawn off and washed once with 200 ml. of water. The aqueous layers are combined and washed once with 500 ml. of chloroform. The two chloroform extracts are combined and dried over anhydrous sodium sulfate. After 1 hour the sodium sulfate is separated on a Büchner funnel and washed with two 200-ml. portions of chloroform. The chloroform is removed on a steam bath, and the resulting oily residue is distilled under high vacuum through a 20-cm. Vigreux column. A fore-run, weight 4–8 g., is collected below 110° (0.20 mm.). Then 156–190 g. (64–78%) of 1-carbethoxymethyl-4-carbethoxypiperidine is collected as a colorless oil, b.p. 111–113° (0.2 mm.), *d*15/15 1.057, n^{20}D 1.4585.

C. *3-Quinuclidone hydrochloride*. A 2-l. three-necked flask is fitted with a Hershberg stirrer, a pressure-equalizing addition funnel, and a condenser connected to a source of dry nitrogen. Absolute toluene (330 ml.) and 80 g. (2.05 g. atom) of potassium free of oxide crust are added. *(Caution! Directions[3] for the safe handling of potassium should be consulted.)* The air in the flask is replaced by an atmosphere of dry nitrogen that is maintained until the reaction mixture is decomposed. The flask is heated in an oil bath until the toluene begins to reflux gently. As soon as the potassium is molten, it is pulverized by vigorous stirring. One hundred twenty-five milliliters (98.6 g., 2.14 moles) of absolute ethanol (Note 6) is added through the addition funnel within 30 minutes while heating and stirring are continued. After disappearance of the potassium the temperature is raised to 130°, and a solution of 200 g. (0.822 mole) of 1-carbethoxymethyl-4-carbethoxypiperidine in 500 ml. of absolute toluene is added within 2 hours. The mixture is stirred and heated for an additional 3 hours.

The resulting solution is cooled to 0° and decomposed by careful addition of 500 ml. of 10*N* hydrochloric acid. The mixture is transferred to a separatory funnel, the aqueous phase is separated, and the toluene layer is extracted with two 250-ml. portions of 10*N*

hydrochloric acid. The aqueous extracts are combined and heated under reflux for 15 hours to effect decarboxylation. The hot, dark-colored solution is treated with 10 g. of activated charcoal, filtered, and evaporated to dryness under reduced pressure. The residue is washed into a separatory funnel with 300 ml. of water. The solution is treated with saturated aqueous potassium carbonate solution until it is alkaline to litmus; the carbonate solution must be added very carefully to prevent excessive foaming. Solid potassium carbonate is added until a thin slurry is obtained, and the slurry is extracted with four 400-ml. portions of ether. The combined ether extracts are dried for at least 60 minutes over calcined potassium carbonate and then filtered.

The ether is removed by distillation on a steam bath through a column filled with Raschig rings. The yellowish crystalline residue is treated with 150 g. of ice and 150 g. (130 ml.) of 10*N* hydrochloric acid, and the solution is evaporated to dryness under reduced pressure (Note 7). The crystalline residue is dissolved in the minimum amount of hot water (about 70 ml.), and boiling isopropyl alcohol (about 1.5 l.) is added until crystalline 3-quinuclidone hydrochloride begins to separate. The mixture is cooled to 0–5°, and the solid is separated by filtration, washed with acetone, and dried. The yield of 3-quinuclidone hydrochloride, m.p. 294–296° (sealed capillary) (Note 8), is 102–109 g. (77–82%).

2. Notes

1. The checkers used ethyl isonicotinate purchased from K and K Laboratories, Inc., Jamaica, New York, or prepared by esterification of isonicotinic acid as described by La Forge[4] for nicotinic acid.
2. The quaternization is slightly exothermic.
3. The quaternary salt may be isolated by evaporation of the solution and subsequent recrystallization of the residue from isopropyl alcohol; m.p. 159° (dec.). Calcd. for $C_{12}H_{16}BrNO_4$: C, 45.30; H, 5.07; Br, 25.12. Found: C, 45.41; H, 5.14; Br, 25.28.
4. The checkers found that hydrogenation proceeded rapidly and quite exothermically at a pressure of only 7 atm. at 90°. They used 10% palladium-on-carbon powder purchased from Engelhard Industries Inc., Newark, New Jersey.
5. The evolution of carbon dioxide causes considerable foaming. Losses are easily avoided if a 5-l. beaker is used.
6. Commercial absolute alcohol was further dried by treatment with magnesium and a little iodine with subsequent redistillation, as described by Lund and Bjerrum.[5]
7. In an alternative method of isolating crude quinuclidone hydrochloride, found by the checkers to give equally good results, the dried ether solution of quinuclidone is transferred to a 2-l. round-bottomed flask equipped with a stirrer, a gas-inlet tube, and a gas-exit tube. The flask is immersed in an ice bath, and gaseous hydrogen chloride is passed into the stirred solution until it begins to bubble out, indicating that the solution is saturated. The quinuclidone hydrochloride that precipitates is collected on a Büchner funnel, washed with

acetone, and dried in a vacuum desiccator. The product is then dissolved in hot water and precipitated with isopropyl alcohol as described in the procedure.
8. The melting point depends on the rate of heating and the apparatus used. The checkers observed m.p. 297–305°, 298–303°, and 301° under various conditions.

3. Discussion

Quinuclidone hydrochloride has been prepared by intramolecular condensation of 1-carbethoxymethyl-4-carbethoxypiperidine with potassium[6,7,8] or, as in the present procedure, with potassium ethoxide.[9] 1-Carbethoxymethyl-4-carbethoxypiperidine has been prepared by alkylating ethyl hexahydroisonicotinate with ethyl chloroacetate[6,8] or by the present method.[7]

4. Merits of the Preparation

This is the most convenient way to prepare quinuclidone hydrochloride. The second step illustrates the conversion of an N-alkylpyridinium salt to an N-alkylpiperidine. The third step illustrates the formation of a bicyclic system by the Dieckmann condensation.

Quinuclidone can be reduced to quinuclidine.[6] Depending on the availability of starting materials, either this reduction or the dehydrative cyclization of 4-(2-hydroxyethyl) piperidine[10] is the most convenient synthesis of quinuclidine.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

palladium on charcoal

palladium-on-carbon powder

alcohol, ethanol (64-17-5)

potassium carbonate (584-08-7)

hydrogen chloride, hydrochloric acid (7647-01-0)

ether (60-29-7)

hydrogen (1333-74-0)

chloroform (67-66-3)

magnesium (7439-95-4)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

iodine (7553-56-2)

acetone (67-64-1)

toluene (108-88-3)

isopropyl alcohol (67-63-0)

Ethyl chloroacetate (105-39-5)

potassium (7440-09-7)

Nicotinic acid (59-67-6)

potassium ethoxide (917-58-8)

Ethyl bromoacetate (105-36-2)

3-Quinuclidinone, hydrochloride, 3-Quinuclidone hydrochloride (1193-65-3)

ethyl isonicotinate (1570-45-2)

1-carbethoxymethyl-4-carbethoxypyridinium bromide

1-carbethoxymethyl-4-carbethoxypiperidine hydrobromide

1-carbethoxymethyl-4-carbethoxypiperidine (1838-39-7)

isonicotinic acid (55-22-1)

ethyl hexahydroisonicotinate (1126-09-6)

quinuclidine (100-76-5)

4-(2-hydroxyethyl)piperidine (622-26-4)

quinuclidone hydrochloride

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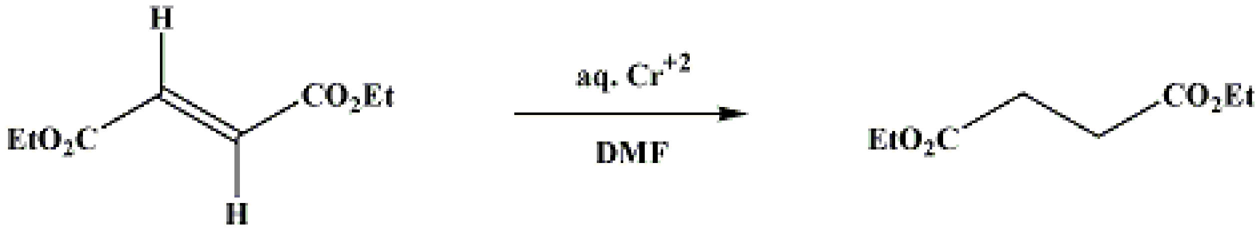
Organic Syntheses, CV 5, 993

REDUCTION OF CONJUGATED ALKENES WITH CHROMIUM(II) SULFATE: DIETHYL SUCCINATE

[Succinic acid, diethyl ester]

$$Cr_2(SO_4)_3 + Zn(Hg) \longrightarrow 2CrSO_4 + ZnSO_4$$



Submitted by A. Zurqiyah and C. E. Castro[1].
Checked by Frederick J. Sauter and Herbert O. House.

1. Procedure

A. *Chromium(II) sulfate solution.* A 3-l., three-necked flask fitted with a gastight mechanical stirrer and nitrogen inlet and outlet stopcocks is charged with 300 g. (*ca.* 0.55 mole) of hydrated chromium(III) sulfate (Note 1), 2 l. of distilled water, 75 g. (1.15 g. atoms) of mossy zinc (Note 2), and 4.0 ml. (54 g., 0.27 g. atom) of mercury (Note 3). After the flask has been flushed with nitrogen for 30 minutes, the mixture is warmed in a water bath to about 80° (Note 4) with stirring for 30 minutes under a nitrogen atmosphere to initiate reaction. Then the mixture is stirred at room temperature under a nitrogen atmosphere for an additional 30 hours, at which time the originally green reaction mixture has been converted to a clear, deep blue solution. While a nitrogen atmosphere is maintained over the reaction solution, the mechanical stirrer is removed and replaced with a nitrogen outlet (Note 5). The third neck of the reaction flask is fitted with a short adapter closed with a rubber septum (Note 6).

The solution is standardized by withdrawing 5.0-ml. aliquots into a hypodermic syringe (Note 6) fitted with a relatively wide-bore needle and flushed with nitrogen before use. The aliquots are quenched by injecting them into 10 ml. of aqueous 1*M* ferric chloride solution in an Erlenmeyer flask under a nitrogen atmosphere. After 2 minutes the flow of nitrogen is stopped, and the resulting solution is diluted with 50 ml. of water and titrated with 0.1*N* ceric sulfate to the ferrous ion-phenanthroline end point (Note 7). Solutions prepared in this fashion are usually 0.55*M* in chromium(II) species (Note 8) and are stable for years, if they are protected from reaction with oxygen.

B. *Reduction of diethyl fumarate.* A 1-l. three-necked flask is equipped with a

magnetic stirring bar, an addition funnel with a pressure-equalizing tube, a stopcock connected to a mercury trap, and a rubber septum (Note 9). The addition funnel is charged with a solution of 13.87 g. (0.080 mole) of diethyl fumarate (Note 10) in 137 ml. of dimethylformamide (Note 11). A nitrogen line is connected to the top of the addition funnel and the system is thoroughly flushed with nitrogen (Note 12). With a hypodermic syringe, 318 ml. (0.175 mole) of the previously described 0.55*M* chromium(II) sulfate solution (0.175 mole) is added to the reaction flask through the rubber septum. After the stirrer has been started, the diethyl fumarate solution is added rapidly. The solution immediately turns green and the reduction is complete in 10 minutes (Note 13). The resulting solution is diluted with 100 ml. of water and 30 g. of ammonium sulfate is added. The mixture is shaken with four 150-ml. portions of ether, and the combined ether extracts are washed with three 50-ml. portions of water and then dried over magnesium sulfate. After the ether has been removed by distillation through a 60-cm. Vigreux column, the residual liquid is distilled through a short Vigreux column to separate 12.4–13.2 g. (88–94%) of diethyl succinate (Note 14); b.p. 129° (44 mm), n^{23}D 1.4194.

2. Notes

1. Mallinckrodt analytical reagent, chromium(III) sulfate crystals, $Cr_2(SO_4)_3(H_2O)_x$, were employed. Repeated preparations with this substance have indicated its average formula weight to be 542.
2. Either Baker and Adamson or Mallinckrodt reagent grades of mossy zinc have been used interchangeably.
3. Distilled mercury was employed.
4. Warming is not always essential, but a more rapid reduction occurs routinely if the reaction is initiated by warming. In some cases a longer heating period may be required.
5. In order to maintain an oxygen-free atmosphere over the solution, it is essential that all standard taper joints be adequately lubricated and that the various joints be held together with rubber bands, wire, or springs.
6. Transfers are conveniently made by maintaining a slightly positive nitrogen pressure in the reaction vessel before the aliquots are removed and using an adapter consisting of a standard taper joint sealed to a wide-bore stopcock. The short length of glass tubing above the stopcock is fitted with a securely fastened rubber septum. The rubber septum above the stopcock is pierced with the hypodermic syringe, and then the stopcock is opened to place a slightly positive nitrogen pressure in the small septum-capped chamber. This procedure forces the plunger of the syringe out and sweeps any remaining oxygen from the syringe. The syringe plunger is replaced and the syringe needle is pushed below the surface of the solution. The internal nitrogen pressure forces liquid into the syringe until slightly more than the desired amount is obtained. The syringe is then withdrawn and inverted and the excess solution is expelled into an absorbent paper. Finally, the syringe containing the desired volume of solution is emptied into a reaction vessel under a nitrogen atmosphere.

7. The preparation of the indicator solution is described by Kolthoff and Sandell.[2] The red-brown to green end point is easily observed.
8. Solutions of higher or lower concentrations can be prepared by adjusting the amounts of reagents.
9. Though unnecessary for this reduction, it is more usually convenient for chromium(II) sulfate reductions to fit the rubber septum to a stopcock adapter of the type described in (Note 6).
10. Diethyl fumarate was purchased from either Eastman Organic Chemicals, Inc., or Aldrich Chemical Company and used without purification.
11. Baker reagent grade dimethylformamide was used without further purification.
12. The submitters recommend that the system be flushed with a slow stream of nitrogen for 30 minutes.
13. The kinetics of this reduction have been reported.[3] The reaction is easily followed by withdrawing aliquots and analyzing them for chromium(II) content.
14. Diethyl succinate is the sole product of the reduction. The yield reflects the efficiency of the workup. The distilled product gives a single sharp peak on gas chromatography employing a column packed with Carbowax 20M suspended on Chromosorb P. On this column the checkers found the retention times of diethyl fumarate and diethyl succinate to be 38.8 minutes and 43.6 minutes, respectively.

3. Discussion

Aqueous solutions of chromium(II) sulfate have been prepared from chromium(III) sulfate by reduction with zinc powder[3] and from potassium dichromate by reduction with amalgamated zinc and sulfuric acid.[4] Solid chromium(II) sulfate pentahydrate can be obtained from the reaction of highly purified chromium metal with concentrated sulfuric acid.[5] The present procedure is especially simple since it avoids filtration of zinc powder and avoids the acid present in the dichromate reduction.

Chromium(II) sulfate is a versatile reagent for the mild reduction of a variety of bonds. Thus aqueous dimethylformamide solutions of this reagent at room temperature couple benzylic halides,[3,6] reduce aliphatic monohalides to alkanes,[6] convert vicinal dihalides to olefins,[7] convert geminal halides to carbenoids,[8] reduce acetylenes to *trans*-olefins,[9] and reduce α,β-unsaturated esters, acids, and nitriles to the corresponding saturated derivatives.[10] These conditions also reduce aldehydes to alcohols.[7]

The reduction of diethyl fumarate described in this preparation illustrates the mildness of the reaction conditions for the reduction of acetylenes and α,β-unsaturated esters, acids, and nitriles.

The reduction of diethyl fumarate to diethyl succinate has also been effected with diethyl 1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate[11] and by catalytic

hydrogenation.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 821

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

amalgamated zinc

sulfuric acid (7664-93-9)

ether (60-29-7)

oxygen (7782-44-7)

nitrogen (7727-37-9)

mercury (7439-97-6)

zinc, zinc powder (7440-66-6)

ferric chloride (7705-08-0)

diethyl fumarate (623-91-6)

ammonium sulfate (7783-20-2)

potassium dichromate (7778-50-9)

chromium(III) sulfate (15244-38-9)

magnesium sulfate (7487-88-9)

chromium (7440-47-3)

diethyl 1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (1149-23-1)

dimethylformamide (68-12-2)

Diethyl succinate, Succinic acid, diethyl ester (123-25-1)

ceric sulfate (13590-82-4)

CHROMIUM(II) SULFATE

chromium(II)

chromium(II) sulfate pentahydrate

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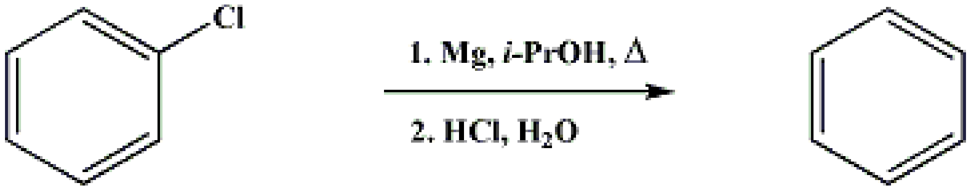
Organic Syntheses, CV 5, 998

REDUCTION OF ORGANIC HALIDES. CHLOROBENZENE TO BENZENE



Submitted by D. Bryce-Smith and B. J. Wakefield[1].
Checked by William G. Dauben and Louis E. Friedrich.

1. Procedure

To a 250-ml. round-bottomed flask fitted with a glass-blade stirrer, a pressure-equalizing dropping funnel, a thermometer and a reflux condenser equipped with a nitrogen bubbler (Note 1) are added 6.0 g. (0.25 mole) of magnesium powder (Note 2) 50 ml. of decahydronaphthalene (Note 3), and a crystal of iodine. The flask is swept with nitrogen, and a nitrogen atmosphere is maintained throughout the reaction. The mixture is heated to reflux without stirring, and from the dropping funnel there is added slowly one-fifth of a solution of 11.3 g. (0.1 mole) of chlorobenzene (Note 4) and 9.0 g. (0.15 mole) of dry 2-propanol. Reaction is almost immediately apparent in the region of the iodine crystal, and as the reaction becomes progressively more vigorous (*ca.* 15 minutes) the stirrer is started and the external heating is reduced (Note 5). The remainder of the chlorobenzene solution is added over a 30-minute period; this rate of addition causes the mixture to reflux gently without external heating. An additional 25 ml. of decahydronaphthalene is added to facilitate the stirring, and the mixture is heated under reflux for one additional hour.

To the cooled mixture 6*N* hydrochloric acid is added dropwise with stirring, until no solid remains. The organic layer is separated, washed four times with 30-ml. portions of water (Note 6), dried over powdered calcium chloride (Note 7), and distilled through a 1 × 15 cm. column packed with Fenske helices (Note 8). The yield of benzene is 5.5–6.5 g. (70–83%), b.p. 80–82°, n^{20}_D 1.5007. The fraction boiling at 82–180° contains no unreacted chlorobenzene (Note 9), (Note 10), (Note 11).

2. Notes

1. To minimize loss of volatile products such as benzene, it is advisable to employ a dry ice condenser on top of the conventional condenser.
2. Magnesium powder (Grade 4) from Magnesium Elektron, Inc., 610 Fifth Avenue, New York 20, New York, or from Magnesium Elektron Ltd., Manchester, England, was employed within six months of the date of its grinding by the manufacturer. The use of older or coarser material may lead to

lengthened induction periods, particularly when chlorides are used.
3. Freshly distilled decahydronaphthalene was used. With the more easily reduced halides, and where the boiling point of the neutral reduction product was close to that of decahydronapthalene, an excess of 2-propanol was used as the reaction medium. Other hydrocarbons and secondary or tertiary alcohols may be employed for convenience in particular reductions. Diethyl ether and tetrahydrofuran were not found to be generally suitable media.
4. The checkers found it necessary to distil the chlorobenzene just before use.
5. When there is no sustained reaction after 10 minutes, initiation can often be accomplished by the addition of another crystal of iodine (no stirring) and/or a small amount of an easily reduced halide such as 1-bromobutane.
6. These washings remove the bulk of the 2-propanol.
7. This drying also removes the last traces of 2-propanol.
8. The checkers used a Nester-Faust 44-cm. spinning-band column.
9. This procedure has been used to effect the following reductions at *ca.* 150°: bromobenzene to benzene (89%), iodobenzene to benzene (95%), 1-chlorobutane to *n*-butane (95%), 2-chloro-2-methylbutane to 2-methylbutane (32%), and isopropyl chloroacetate to isopropyl acetate (63%).
10. The following reductions have been carried out at 80° with the use of an excess of 2-propanol as the reaction medium (see (Note 3)): carbon tetrachloride to methane (47%), 1-bromonaphthalene to naphthalene (90%), β-bromostyrene to styrene (72%), *p*-bromoaniline to aniline (61%), *p*-bromophenol to phenol (66%), and monochloroacetone to acetone (30%).
11. Certain halides, notably fluorides, are comparatively inert under these reaction conditions. In such cases the *entrainment method* can be used, and reduction can be accomplished in the presence of a reactive halide such as 1-bromonaphthalene or 1-bromobutane. Also with certain halides, such as chlorocyclohexane, the tendency for dehydrohalogenation is diminished by the use of such entraining agents.
A typical example is the following reduction of chlorocyclohexane to cyclohexane. The general procedure is employed using 8.0 g. (0.33 mole) of magnesium powder in decahydronaphthalene (50 ml. + 20 ml.) and a solution of 6.0 g. (0.05 mole) of chlorocyclohexane, 10.4 g. (0.05 mole) of 1-bromonaphthalene, and 18 g. (0.3 mole) of 2-propanol. The product fraction, b. p. 78–80°, is a mixture of 3.5 g. (83%) of cyclohexane and 0.4 g. (10%) of cyclohexene. The olefin is removed by treatment with concentrated sulfuric acid in the usual manner.
Under the foregoing conditions, fluorocyclohexane gives cyclohexane (33%), and benzotrifluoride gives toluene (10%); fluorobenzene is inert.

3. Discussion

The present procedures are based on those briefly described by the submitters in conjunction with E. T. Blues,[2] and are based on the observation that magnesium does

not, under normal conditions, readily react with secondary and tertiary alcohols in the absence of a halogen or an organic halide; little or no hydrogen is evolved during the reduction. Magnesium reacts readily with primary alcohols, evolving hydrogen, and the system is much less active in the reduction of organic halides. 2-Propanol is recommended as a general-purpose alcoholic component, but other secondary and tertiary alcohols can also be employed.

4. Merits of the Preparation

Reduction with magnesium and 2-propanol provides a simple and effective procedure for the reduction of alkyl and aryl chlorides, bromides, and iodides; with an entraining agent some alkyl fluorides are attacked. Groups such as amino, phenolic hydroxyl, ester carbonyl, and ethylenic linkages have not interfered. Nitro compounds must be absent as they inhibit the reaction with magnesium. Many carbonyl compounds, for example, *p*-bromobenzophenone, undergo much simultaneous reduction of the carbonyl groups, but acetone was obtained in fair yield from chloroacetone.

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

diethyl ether (60-29-7)

aniline (62-53-3)

hydrogen (1333-74-0)

magnesium, magnesium powder (7439-95-4)

phenol (108-95-2)

Cyclohexene (110-83-8)

1-bromobutane (109-65-9)

carbon tetrachloride (56-23-5)

nitrogen (7727-37-9)

cyclohexane (110-82-7)

iodine (7553-56-2)

acetone (67-64-1)

methane (7782-42-5)

chlorobenzene (108-90-7)

toluene (108-88-3)

2-propanol (67-63-0)

bromobenzene (108-86-1)

1-bromonaphthalene (90-11-9)

Naphthalene (91-20-3)

1-chlorobutane (109-69-3)

chlorocyclohexane (542-18-7)

Iodobenzene (591-50-4)

styrene (100-42-5)

β-bromostyrene (103-64-0)

chloroacetone, monochloroacetone (78-95-5)

Fluorobenzene (462-06-6)

n-butane (106-97-8)

2-methylbutane (78-78-4)

Tetrahydrofuran (109-99-9)

decahydronaphthalene, decahydronapthalene (91-17-8)

2-chloro-2-methylbutane (594-36-5)

isopropyl chloroacetate (105-48-6)

isopropyl acetate (108-21-4)

fluorocyclohexane (372-46-3)

benzotrifluoride (98-08-8)

p-bromoaniline (106-40-1)

p-Bromophenol (106-41-2)

p-bromobenzophenone (90-90-4)

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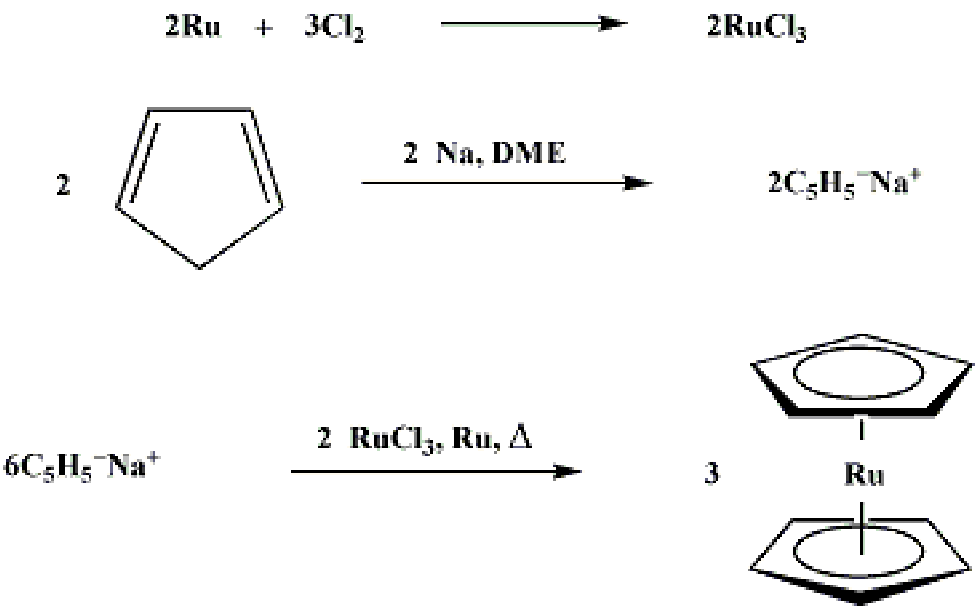
Organic Syntheses, CV 5, 1001

RUTHENOCENE

[Ruthenium, dicyclopentadienyl-]



Submitted by D. E. Bublitz, William E. McEwen, and Jacob Kleinberg[1].
Checked by Hans G. Essler and John H. Richards.

1. Procedure

A 500-ml. three-necked flask is equipped with a Trubore stirrer, reflux condenser, and a pressure-equalizing dropping funnel that carries an inlet for admission of nitrogen. The system is purged with nitrogen (Note 1), and 300 ml. of 1,2-dimethoxyethane (Note 2) is added, followed by 7.2 g. (0.312 g. atom) of sodium either as wire or freshly cut small pieces. The solution is stirred, and 31.0 ml. (0.376 mole) of cyclopentadiene (Note 3) is added dropwise. When the evolution of hydrogen has almost ceased, the mixture is maintained at slightly below the reflux temperature for 1–2 hours. In the event that all the sodium does not dissolve, the solution is cooled to room temperature, a few milliliters more of cyclopentadiene added, and the mixture heated again until dissolution of the sodium is complete.

A mixture of 14.6 g. (0.07 mole) of ruthenium trichloride and 2.4 g. (0.024 g. atom) of ruthenium metal (Note 4) is added, and the reaction mixture is heated and stirred under nitrogen for 80 hours (Note 5) at slightly below the reflux temperature. With the use of stirring, the solvent is removed at aspirator pressure, and the flask then refilled with nitrogen. The solid is transferred to a sublimator in a dry-box containing a nitrogen atmosphere (Note 6) and sublimed at 0.1 mm. pressure with a heating bath at 130° (Note 7). The sublimate is dissolved in benzene and passed through a 1 × 12-in. column of activated alumina. Evaporation of the benzene gives 12.2–15.1 g. (56–69%)

of ruthenocene, m.p. 199–200° (Note 8).

2. Notes

1. The submitters used prepurified nitrogen, obtained from Matheson Company, Inc., East Rutherford, New Jersey, without further purification. The checkers passed Linde (H. P. Dry) nitrogen successively through chromous chloride solution, solid potassium hydroxide, Ascarite, and solid phosphorus pentoxide.
2. 1,2-Dimethoxyethane is dried over sodium wire and then distilled under nitrogen from lithium aluminum hydride just before use.
3. For preparation of cyclopentadiene from the dimer, see G. Wilkinson, *Org. Syntheses*, Coll. Vol. **4**, 475 (1963). The dicyclopentadiene used as starting material was dried by passage through a 1 × 12-in. column of activated alumina prior to cracking.
4. Ruthenium trichloride was prepared by chlorination of powdered ruthenium at 650–700°[2] with the use of metal obtained from Goldsmith Bros. Smelting and Refining Co., 111. N. Wabash Ave., Chicago 2, Illinois. Complete chlorination could not be effected under these conditions, and on the average about 85% of the metal was converted to trichloride. Consequently, in all the preparations of ruthenocene, mixtures of trichloride and metal, as obtained from the chlorination reaction, were employed. The equations given for the preparation are idealized; the submitters believe that during the course of reaction the trichloride is gradually reduced to dichloride by ruthenium metal, and that it is the dichloride which reacts with sodium cyclopentadienide.
5. Somewhat lower yields than those reported are obtained when the reaction is carried out for a shorter period of time.
6. From this point on, the solid materials are pyrophoric, especially the residual solids from the sublimation process. However, the ruthenocene obtained by sublimation is not pyrophoric. The checkers found that careful addition of the sublimation residues to water under nitrogen destroys their pyrophoric character.
7. The checkers found the use of a Dry Ice-cooled sublimation finger advantageous.
8. The yield reported here is based on the total amount of ruthenium (both Ru^{III} and Ru^{0}) available for formation of ruthenocene. An additional quantity of ruthenocene may be obtained by extraction of the pyrophoric residue from the sublimation step with benzene in a Soxhlet extractor under a nitrogen atmosphere. The benzene solution is filtered through activated alumina, the solvent evaporated, and the residue sublimed.

3. Discussion

Ruthenocene has been prepared in 20% yields by reaction of cyclopentadienylmagnesium bromide with ruthenium(III) acetylacetonate.[3] More recently,[4] the compound has been made in 43–52% yield by treatment of sodium cyclopentadienide with ruthenium trichloride in tetrahydrofuran or 1,2-

dimethoxyethane.

4. Merits of the Preparation

Ruthenocene is an example of a stable π-bonded organometallic compound which undergoes substitution reactions similar to those displayed by ferrocene. Because ruthenocene has heretofore been relatively unavailable, its chemistry has not been extensively studied.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Ruthenocene

Ascarite

ruthenium(III) acetylacetonate

Benzene (71-43-2)

hydrogen (1333-74-0)

nitrogen (7727-37-9)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

chromous chloride (10049-05-5)

CYCLOPENTADIENE (542-92-7)

dicyclopentadiene

sodium cyclopentadienide (4984-82-1)

1,2-dimethoxyethane (110-71-4)

cyclopentadienylmagnesium bromide

ruthenium (7440-18-8)

Ruthenium, dicyclopentadienyl-

ruthenium trichloride (14898-67-0)

phosphorus pentoxide (1314-56-3)

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Organic Syntheses, CV 5, 1005

STYRYLPHOSPHONIC DICHLORIDE

[Phosphonic dichloride, styryl-]

Submitted by R. Schmutzler[1]
Checked by William G. Dauben and David A. Cox.

1. Procedure

The reaction is conducted in a 500-ml. three-necked flask equipped with a sealed mechanical stirrer, a dropping funnel, and a reflux condenser carrying a drying tube. The flask is flushed with dry nitrogen, and 104 g. (0.50 mole) of phosphorous pentachloride in 150 ml. of dry benzene is added. The mixture is cooled in an ice bath (Note 1) and stirred while a solution of 26 g. (0.25 mole) of styrene in 50 ml. of dry benzene is added through the dropping funnel during a period of 30 minutes. A dense crystalline solid begins to form immediately, and after the addition is completed the mixture is stirred for 30 minutes at room temperature. The dropping funnel is replaced by a gas-inlet tube which is connected to a cylinder of sulfur dioxide through a wash bottle containing concentrated sulfuric acid. Sulfur dioxide is bubbled through the stirred mixture until all the precipitate is dissolved. The mildly exothermic reaction is controlled by occasionally cooling the reactants with an ice bath. The benzene solvent is removed from the clear solution under reduced pressure, and the residue is distilled at reduced pressure from a Claisen flask with Vigreux indentations. The yield of styrylphosphonic dichloride is 49–52 g. (89–94%), b.p. 107–110° (0.2 mm.). The distillate solidifies during or after the distillation, m.p. 71–72°.

2. Notes

1. Care must be taken not to freeze the benzene before the styrene is added.

3. Discussion

Styrylphosphonic dichloride has been prepared by the addition of phosphorus pentachloride to styrene with subsequent reaction of the adduct with phosphorus pentoxide[2] or sulfur dioxide.[3,4]

4. Merits of the Preparation

The addition reaction of phosphorus pentachloride to styrene and its derivatives provides a convenient route to styrylphosphonic acids and their derivatives.[2,3,4,5,6,7] The styrene phosphorus pentachloride adduct also can be reduced with phosphorus to give the corresponding dichlorophosphine.[4,8]

The behavior of phosphorus pentachloride toward carbon-carbon multiple bonds has received considerable attention, and the procedure described represents but one example of a wide variety of derivatives of unsaturated phosphonic acids which are accessible. Indene was the first olefinic compound to be reacted with phosphorus pentachloride,[9] and the reaction of phosphorus

pentachloride with other unsaturated compounds has been described.[2,3,4,5,6,10,11,12,13] More recent examples include the reaction of phosphorus pentachloride with vinyl ethers[14,15,16] and vinyl thioethers,[17] providing access to β-alkoxy- and β-alkylmercaptovinylphosphonic and phosphonothioic acid derivatives.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

Benzene (71-43-2)

phosphorus pentachloride, phosphorous pentachloride (10026-13-8)

sulfur dioxide (7446-09-5)

PHOSPHORUS (7723-14-0)

nitrogen (7727-37-9)

styrene (100-42-5)

indene (95-13-6)

vinyl (2669-89-8)

Styrylphosphonic dichloride, Phosphonic dichloride, styryl- (4708-07-0)

styrene phosphorus pentachloride

dichlorophosphine

phosphorus pentoxide (1314-56-3)

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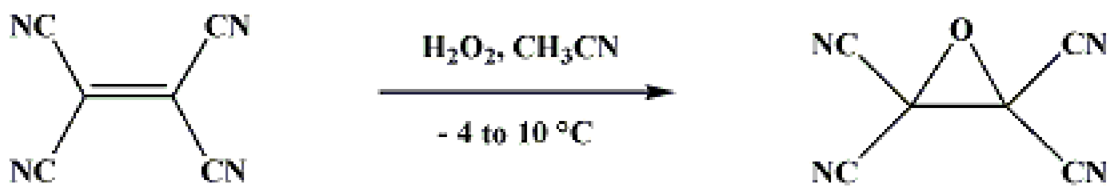
Organic Syntheses, *CV 5*, *1007*

TETRACYANOETHYLENE OXIDE

[Ethanetetracarbonitrile, 1,2-epoxy-]



Submitted by W. J. Linn[1]
Checked by A. Eschenmoser, W. Lusuardi, and R. Scheffold.

1. Procedure

Caution! Both tetracyanoethylene and tetracyanoethylene oxide slowly evolve hydrogen cyanide when exposed to water. Therefore all operations should be conducted in an efficient hood and contact with the skin should be avoided.

In a 500-ml. Erlenmeyer flask fitted with an efficient stirrer and thermometer are placed 25.6 g. (0.2 mole) of tetracyanoethylene (Note 1) and 150 ml. of acetonitrile (Note 2). The flask is surrounded by an ice-salt bath and the stirrer is started. When the temperature is about –4°, 21 ml. of 30% hydrogen peroxide is added from a buret at the rate of 3–5 ml. of per minute. The rate is adjusted to keep the temperature at 10–12° (Note 3). Near the end of the addition, the color of the reaction mixture changes from dark amber to pale yellow. When all the peroxide has been added, the reaction mixture is stirred with efficient cooling for 3–4 minutes. Without delay the solution is then poured slowly, with very rapid stirring, into a mixture of 500 ml. of water and approximately 250 g. of crushed ice contained in 2-l. beaker (Note 4). The solid is filtered rapidly by suction through a coarse, sintered-glass funnel and washed with 200 ml. of ice water. For best results the product is dried on the funnel with continuous suction for 3–4 hours and recrystallized from 1,2-dichloroethane (10 ml. per g.) (Note 5). The yield of nearly colorless needles melting at 177–178° (sealed capillary) is 17.1–19.6 g. (59–68%) (Note 6). The infrared spectrum of the oxide (Nujol mull) is simple and useful in product identification. In addition to the strong -C☐N absorption at 4.38•, there are bands at 7.68, 8.47, 8.66, 10.54, and 11.23•.

2. Notes

1. Tetracyanoethylene may be purchased from the Columbia Organic Chemicals Co., the Eastman Kodak Co., or prepared by the method of Carboni.[2] This procedure has been simplified in this laboratory as follows.[3]
To 450 ml. of cold water in the apparatus of Part A[2] there is added 99 g. (1.5

moles) of molten malononitrile followed by 250 g. of ice and 158 ml. (3.05 moles at 25°) of bromine. The bromine is added during 5–10 minutes, and during the addition enough ice (about 200 g.) is added to maintain the temperature at 10–15°. The mixture is stirred at 20° for 1 hour. A heavy layer of dibromomalononitrile is separated, and the aqueous layer is extracted with two 50-ml. portions of 1,2-dichloroethane. The dibromomalononitrile and the extracts are combined, dried over magnesium sulfate, and added to 750 ml. of dry 1,2-dichloroethane in the flask of Part B. Twenty grams of copper powder is added, and the mixture is heated to gentle reflux with stirring. An exothermic reaction generally occurs; when it subsides, or after about 10 minutes, a second 20-g. portion is added, and this process is continued until 120 g. has been added. The mixture is allowed to reflux a total of 4–6 hours. The solids are separated from the hot mixture using a fluted filter paper, which is washed with a little hot 1,2-dichloroethane. The filtrate is stored overnight at 0–5°. Nearly colorless tetracyanoethylene crystallizes out. It is separated on a Buchner funnel, washed with a little 1,2-dichloroethane, and dried in a vacuum desiccator; weight 29–38 g. (30–40%). The purity of the product is over 98% as judged by the ε_{max} [pure tetracyanoethylene has $\lambda_{max.}^{CH_2Cl_2}$ 277 m• (ε 12,050) 267 m• (ε 13,600)]. It is pure enough for most purposes including synthesis of the epoxide. If very pure material is needed, tetracyanoethylene can be recrystallized from 1,2-dichloroethane (15 ml. per g.) or sublimed at 130–140° at 1 mm.

2. Eastman Kodak Co. practical grade is sufficiently pure for the reaction.

3. The rate of addition of hydrogen peroxide is fairly fast initially but is slowed to maintain the indicated temperature. It is important to get the reaction over in a short time (5–7 minutes) for the best yield.

4. It is wise to use a mechanical or magnetic stirrer in order to induce rapid crystallization of the product. Prolonged contact of the product with water at this stage diminished the yield markedly. The presence of anions, *e.g.*, chloride, can lead to more rapid decomposition of the product, and it is best to use distilled water and ice prepared from distilled water at this point. If the oil cannot be induced to crystallize rapidly, more ice water should be added.

5. If it is necessary to interrupt the preparation before recrystallization, the product should be stored in a desiccator with continuous evacuation until it is absolutely dry.

6. This preparation has been carried out on a 4.2-mole scale using essentially the same procedure with only a slight diminution in yield. In larger runs the crude product may be more efficiently washed by rapidly resuspending the filter cake in fresh ice water, filtering, and drying. The only problem is that of drying the product rapidly. The drying can be hastened on a large scale by heating the mass on the funnel slightly with an infrared lamp.

3. Discussion

The usual method for epoxidation of an olefin with a peracid fails when the double bond is substituted with an electron-withdrawing group.[4] This difficulty has been circumvented in certain cases by the use of a very strong peracid; *i.e.*,

peroxytrifluoroacetic acid, in the presence of a buffer[5] or by the use of alkaline hydrogen peroxide.[6] In the latter case, the attack is by the hydroperoxide anion.[7] This method is normally not applicable to the synthesis of epoxynitriles because of the simultaneous conversion of the nitrile to an amide group.[8] However, the four nitrile groups of tetracyanoethylene so diminish the electron density at the double bond that it is attacked by hydrogen peroxide in the absence of any added base. There is no significant attack on the nitrile groups when the reaction is carried out rapidly in a mutual solvent for the olefin and peroxide.[9] Olefins that are somewhat less electrophilic, *e.g.*, phenyltricyanoethylene and diethyl 1,2-dicyanoethylene-1,2-dicarboxylate, can be epoxidized by essentially the same procedure using a catalytic amount of a mild base such as pyridine.[10]

Slight variations in the procedure described above have been used to prepare tetracyanoethylene oxide. Hydrogen peroxide in ether or *t*-butyl hydroperoxide in benzene[11] gives the epoxide in higher yield than the present method but requires large amounts of organic solvents and is not readily adaptable to large-scale preparations. An apparent contradiction of the opening statement above is the observation that tetracyanoethylene *can* be epoxidized with a peracid.[12] This is undoubtedly due to *nucleophilic* attack by the peracid or its anion on the electron-deficient double bond, a mechanism which cannot operate with olefins containing only one or two electronegative substituents. An example of this type of epoxidation is the preparation of 1,1-dicyano-2,2-bis(trifluoromethyl)ethylene oxide.[13]

Tetracyanoethylene oxide does not undergo reactions typical of epoxides of simple hydrocarbon olefins. Entirely new types of reactions are observed; *e.g.*, cleavage by nucleophilic reagents into the elements of dicyanomethylene and carbonyl cyanide[10] and cleavage of the carbon-carbon bond, followed by addition to a wide variety of olefins, acetylenes, and aromatic compounds.[14] For example, tetracyanoethylene oxide adds thermally to adjacent positions on the benzene ring to give 1,1,3,3-tetracyano-1,3,3a,7a-tetrahydroisobenzofuran.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Benzene (71-43-2)

acetonitrile (75-05-8)

hydrogen cyanide (74-90-8)

bromine (7726-95-6)

1,2-dichloroethane (107-06-2)

copper powder (7440-50-8)

pyridine (110-86-1)

hydrogen peroxide (7722-84-1)

magnesium sulfate (7487-88-9)

Malononitrile (109-77-3)

Tetracyanoethylene (670-54-2)

peroxytrifluoroacetic acid

dibromomalononitrile

hydroperoxide anion

Tetracyanoethylene oxide, Ethanetetracarbonitrile, 1,2-epoxy- (3189-43-3)

phenyltricyanoethylene

diethyl 1,2-dicyanoethylene-1,2-dicarboxylate

1,1-dicyano-2,2-bis(trifluoromethyl)ethylene oxide

dicyanomethylene

carbonyl cyanide (1115-12-4)

1,1,3,3-tetracyano-1,3,3a,7a-tetrahydroisobenzofuran

t-butyl hydroperoxide (75-91-2)

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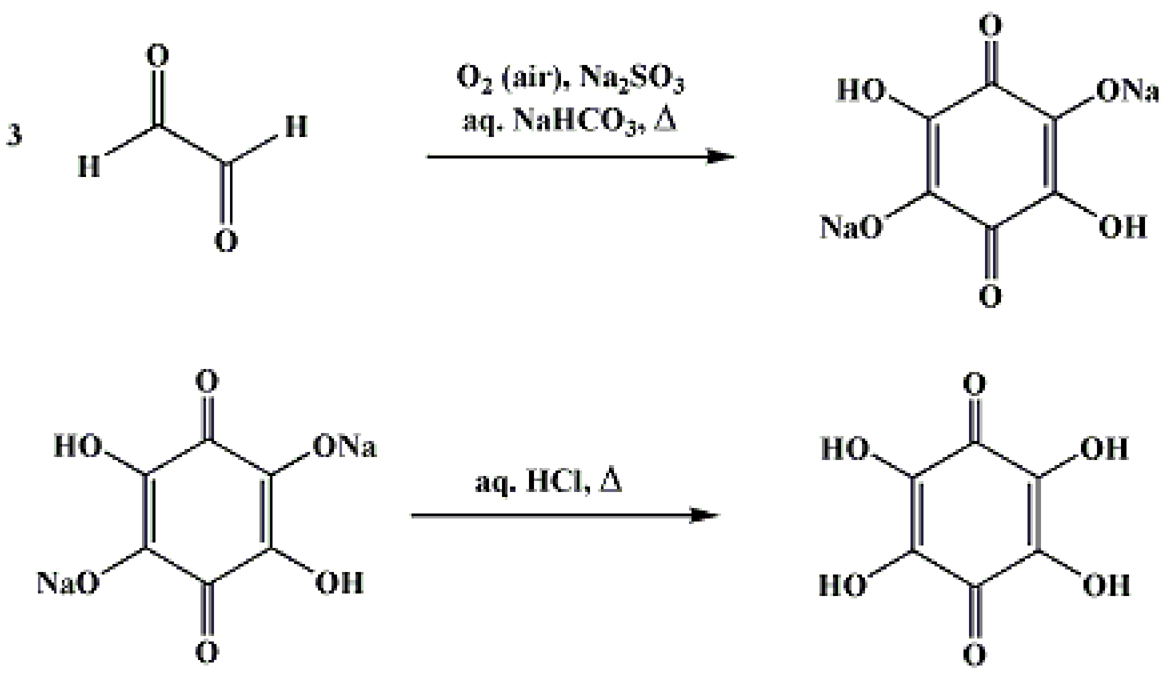
Organic Syntheses, CV 5, 1011

TETRAHYDROXYQUINONE

[Quinone, tetrahydroxy-]



Submitted by A. J. Fatiadi and W. F. Sager[1].
Checked by B. C. McKusick and J. K. Williams.

1. Procedure

A 5-l., three-necked round-bottomed flask is fitted with a thermometer, an air-inlet tube of 10-mm. diameter extending to within approximately 1 cm. of the bottom, and an outlet tube connected to an aspirator (Note 1). A solution of 400 g. (3.17 moles) of anhydrous sodium sulfite and 150 g. (1.79 moles) of anhydrous sodium bicarbonate (Note 2) in 3 l. of water is heated to 40–45° in the flask. Six hundred grams (480 ml., 3.11 moles) of 30% glyoxal solution (Note 3) is added, and a brisk stream of air is drawn through the solution for 1 hour without application of heat. Within a few minutes, greenish black crystals of the sodium salt of tetrahydroxyquinone begin to separate. The flask is warmed to between 80° and 90° over a period of an hour. The air current is then stopped, and the mixture is heated to incipient boiling and set aside for 30 minutes. It is then cooled to 50° (Note 4), and the sodium salt of tetrahydroxyquinone is separated by filtration and washed successively with 50 ml. of cold 15% sodium chloride solution, 50 ml. of cold 1:1 methanol-water, and 50 ml. of methanol. The air-dried salt weighs 20–21 g.

The salt is added to 250 ml. of 2*N* hydrochloric acid, and the mixture is heated to incipient boiling. The resultant solution is cooled in an ice bath, and the glistening black crystals of tetrahydroxyquinone that precipitate are collected on a Büchner

funnel and washed with ice water to give 11–15 g. (6.2–8.4%) of product. The quinone fails to melt on a hot plate at 320° (Note 5).

2. Notes

1. A tube of 10-mm. diameter is necessary to prevent the clogging of the outlet that occurs if tubing of smaller diameter is used.
2. Equivalent amounts of hydrated salt may be used.
3. Dow commercial grade 30% glyoxal solution is satisfactory.
4. It is not necessary to cool below this temperature since crystallization is essentially complete at 50°.
5. This material is pure enough for reduction to hexahydroxybenzene[2] and most other purposes. A purer product can be obtained by dissolving the crude tetrahydroxyquinone in acetone and adding petroleum ether of b.p. 60–80° to precipitate it.

3. Discussion

The procedure employed for tetrahydroxyquinone is based on an observation by Homolka.[3] Tetrahydroxyquinone may also be prepared by treatment of the glyoxal-bisulfite addition compound with sodium carbonate[3] or magnesium hydroxide and potassium cyanide[4] or by treatment of 50% glyoxal with sodium hydrosulfite.[5]

4. Merits of the Preparation

Tetrahydroxyquinone is of interest because of its application in analytical chemistry to the determination of barium and as a complexing agent for many ions.[6] Moreover, it serves as a convenient source not only of the reduction product hexahydroxybenzene[2] but also of the oxidation products rhodizonic acid and triquinoyl and of the product of catalytic reduction, *meso*-inositol.

This procedure serves as a particularly simple method for preparing tetrahydroxyquinone. The low yield is more than offset by the simplicity of the set-up, the ease of manipulation, and the low cost and ready availability of the starting materials.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 595

References and Notes

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3. B. Homolka, *Ber.*, **54**, 1393 (1921).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

hydrochloric acid (7647-01-0)

methanol (67-56-1)

glyoxal (107-22-2)

sodium sulfite (7757-83-7)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

potassium cyanide (151-50-8)

sodium hydrosulfite (7775-14-6)

acetone (67-64-1)

magnesium hydroxide

barium (7440-39-3)

Quinone (106-51-4)

glyoxal-bisulfite (18381-20-9)

Hexahydroxybenzene (608-80-0)

Tetrahydroxyquinone, Quinone, tetrahydroxy- (319-89-1)

rhodizonic acid

meso-inositol (87-89-8)

sodium salt of tetrahydroxyquinone

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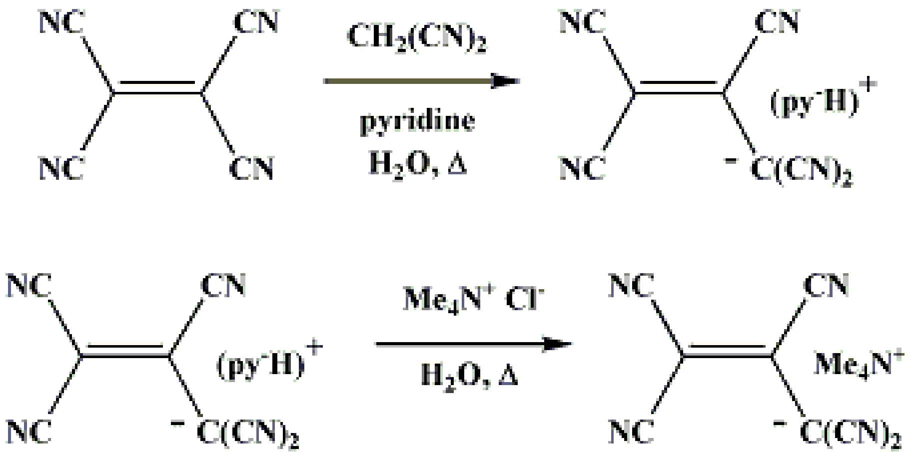
Organic Syntheses, *CV 5*, *1013*

TETRAMETHYLAMMONIUM 1,1,2,3,3-PENTACYANOPROPENIDE

[1-Propene-1,1,2,3,3-pentacarbonitrile, tetramethylammonium salt]



Submitted by W. J. Middleton and D. W. Wiley[1].
Checked by James Cason and William T. Miller.

1. Procedure

Caution! This reaction must be carried out in an efficient hood because large amounts of hydrogen cyanide are evolved. It is also recommended that tetracyanoethylene not be allowed to come into contact with the skin.

A solution of 6.6 g. (0.10 mole) of malononitrile (Note 1) in 8.7 g. (0.11 mole) of pyridine and 25 ml. of water is prepared in a 125-ml. Erlenmeyer flask and stirred mechanically (no stirrer seal required) as there is added rapidly in small portions a total of 12.8 g. (0.10 mole) of powdered recrystallized tetracyanoethylene (Note 2). The resulting mixture is warmed on a hot plate as stirring is continued until complete solution occurs (5–10 minutes, (Note 3)). The hot dark solution is poured into a swirled solution of 12.1 g. (0.11 mole) of tetramethylammonium chloride (Note 4) in 500 ml. of water. The resultant mixture is heated almost to boiling to give a dark-red solution, which is then allowed to cool spontaneously to room temperature. After final cooling in an ice bath, the orange needles of tetramethylammonium 1,1,2,3,3-pentacyanopropenide are collected by suction filtration and washed with two 100-ml. portions of cold water. This product is dissolved in 500 ml. of hot water, decolorized with about 5 g. of activated carbon, and allowed to crystallize as described above. The yield of bright yellow-orange needles, m.p. 314–315° (Note 5), is 19.5–20.5 g. (81–85%).

2. Notes

1. Malononitrile, m.p. 30–31°, obtained from Winthrop-Stearns Corp., New York, N. Y., is satisfactory.
2. Tetracyanoethylene is available from the Aldrich Chemical Company, Inc., or may be prepared by a simplified version of the procedure of Carboni.[2] In the simplified version, 99 g. of molten malononitrile is added to 450 ml. of cold water in the apparatus of Part A. This is followed by about 250 g. of ice and 158 ml. of bromine. The bromine is added during 5–10 minutes, and during the addition enough ice (about 200 g.) is added to maintain the temperature at 10–15°. The mixture is stirred at 20° for one hour. A heavy layer of dibromomalononitrile is separated, and the aqueous layer is extracted with two 50-ml. portions of 1,2-dichloroethane. The dibromomalononitrile and the extracts are combined, dried over magnesium sulfate, and added to 750 ml. of dry 1,2-dichloroethane in the flask of Part B. Twenty grams of copper power is added, and the mixture is heated to gentle reflux with stirring. An exothermic reaction generally occurs; when it subsides, or after about 10 minutes, a second 20-g. portion is added, and this process is continued until 120 g. has been added. The mixture is refluxed a total of 4-6 hours. The solids are separated from the hot mixture on a fluted filter, which is washed with a little hot 1,2-dichloroethane. The filtrate is stored overnight at 0–5°. Nearly colorless tetracyanoethylene crystallizes out. It is separated on a Büchner funnel, washed with a little 1,2-dichloroethane, and dried in a vacuum desiccator; weight 29–38 g. (30–40%). It is over 98% pure as judged by its ε_{max} (pure tetracyanoethylene has $\lambda_{max}^{CH_2Cl_2}$ 277 m• (ε 12,050), 267 m• (ε 13,600)). It is pure enough for most purposes, but can be sublimed at 1 mm. (bath 130–140°) if very pure material is needed (private communication from E. L. Martin and H. D. Carlson via B. C. McKusick).
3. The rate of solution depends upon the fineness of the tetracyanoethylene powder; however, solution should occur soon after the temperature reaches 60–70°.
4. A technical grade of tetramethylammonium chloride is satisfactory, provided old samples that have absorbed considerable water are not used.
5. In a heated block, the checkers observed melting points in the range 318–321°.

3. Discussion

Tetramethylammonium 1,1,2,3,3-pentacyanopropenide has been prepared by the base-catalyzed hydrolysis of tetracyanoethylene,[3] and by the present method, which is more economical of tetracyanoethylene.

4. Merits of Preparation

Tetramethylammonium 1,1,2,3,3-pentacyanopropenide is useful for preparation of pentacyanopropenide salts of other metal and quaternary ammonium cations by metathesis.[3] The free acid, which may be obtained by use of an ion-exchange resin,[3]

has an ionization constant comparable to that of a strong mineral acid ($pK_a < -8.5$; the anion is not detectably protonated in 12*M* sulfuric acid).[4]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

1-Propene-1,1,2,3,3-pentacarbonitrile, tetramethylammonium salt

copper power

sulfuric acid (7664-93-9)

hydrogen cyanide (74-90-8)

bromine (7726-95-6)

1,2-dichloroethane (107-06-2)

activated carbon (7782-42-5)

pyridine (110-86-1)

magnesium sulfate (7487-88-9)

Malononitrile (109-77-3)

Tetracyanoethylene (670-54-2)

dibromomalononitrile

Tetramethylammonium 1,1,2,3,3-pentacyanopropenide (53663-17-5)

tetramethylammonium chloride (75-57-0)

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Organic Syntheses, CV 5, 1016

TETRAMETHYLBIPHOSPHINE DISULFIDE

[Diphosphine, tetramethyl-, disulfide]

Submitted by G. W. Parshall[1]
Checked by W. S. Wadsworth and William D. Emmons.

1. Procedure

A 3-l. round-bottomed flask equipped with mechanical stirrer, condenser (surmounted by a drying tube), thermometer, and addition funnel is charged with 800 ml. of 3*M* methylmagnesium bromide solution (2.4 moles) (Note 1) and 600 ml. of anhydrous ether. The solution is stirred and cooled to 0–5° while a solution of 135 g. (83 ml., 0.80 mole) of thiophosphoryl chloride (Note 2) in 85 ml. of ether is added over a period of 3 hours. A thick white precipitate forms during the course of the addition. After completion of the addition, the reaction mixture is poured onto 500 g. of ice in a 4-l. beaker. Sulfuric acid (900 ml. of 10% solution) is added over a period of 20 minutes with gentle stirring. The mixture is filtered, and the white solid product is washed with 4 l. of water and recrystallized from 2 l. of ethanol. The product is dried over phosphorus pentoxide in a vacuum desiccator to give 50–55 g. (67–74%) of white crystalline tetramethylbiphosphine disulfide, m.p. 223–227° (Note 3). Evaporation of the mother liquor to a volume of 900 ml. gives an additional 3 g. of tetramethylbiphosphine disulfide, m.p. 222–225°.

2. Notes

1. A suitable 3*M* solution of methylmagnesium bromide in diethyl ether can be purchased from Arapahoe Chemical Co., Boulder, Colorado.
2. Although practical grade thiophosphoryl chloride obtained from Eastman Organic Chemicals will serve in this reaction, a much cleaner product is obtained if the thiophosphoryl chloride is redistilled (b.p. 122–123°).
3. Tetramethylbiphosphine disulfide melts sharply at 227° when pure, but the material obtained as described above is satisfactory for most reactions.

3. Discussion

Tetramethylbiphosphine disulfide has been prepared by reaction of methylmagnesium halides with thiophosphoryl chloride.[2,3,4]

4. Merits of the Preparation

Tetramethylbiphosphine disulfide is an extremely versatile intermediate for the preparation of compounds containing two methyl groups on phosphorus, for example, dimethylphosphine.[5] Most other methods for the preparation of such compounds give large amounts of mono- and trimethylated by-products. Tetramethylbiphosphine disulfide has been converted in high yields to dimethylphosphinic acid,[3,4] dimethylphosphinyl chloride,[4,6] dimethylchlorophosphine,[7] and dimethylthiophosphinic bromide.[8] Other tetraalkylbiphosphine disulfides have been converted to tetraalkylbiphosphines, dialkylthiophosphoryl bromides, and dialkylphosphinic anhydrides.[9] Addition of tetramethylbiphosphine disulfide to ethylene followed by desulfurization gives tetramethylethylenediphosphine, a powerful chelating agent.[10] Other alkyl Grignard reagents also react with thiophosphoryl chloride under the conditions of the present procedure to give the corresponding tetraalkylbiphosphine disulfides in high yield.[5,11]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 533

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Tetramethylbiphosphine disulfide

Diphosphine, tetramethyl-, disulfide

ethanol (64-17-5)

sulfuric acid (7664-93-9)

ether, diethyl ether (60-29-7)

PHOSPHORUS (7723-14-0)

ethylene (9002-88-4)

methylmagnesium bromide (75-16-1)

thiophosphoryl chloride (3982-91-0)

dimethylphosphine (676-59-5)

dimethylphosphinic acid (3283-12-3)

dimethylphosphinyl chloride (1111-92-8)

dimethylchlorophosphine (811-62-1)

dimethylthiophosphinic bromide (6839-93-6)

tetramethylethylenediphosphine

phosphorus pentoxide (1314-56-3)

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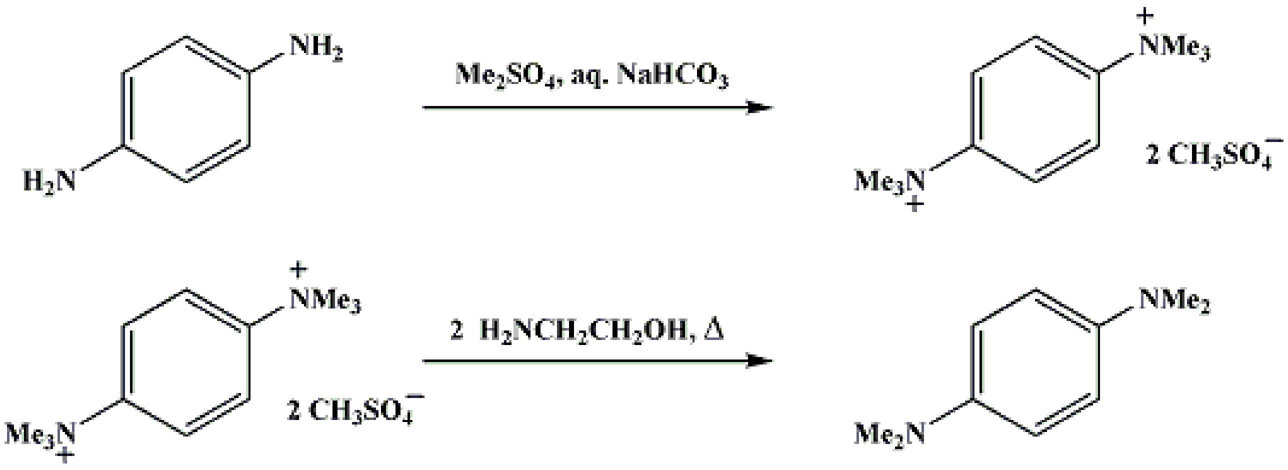
Organic Syntheses, CV 5, 1018

TETRAMETHYL-*p*-PHENYLENEDIAMINE

[*p*-Phenylenediamine, N,N,N'N'-tetramethyl]



Submitted by S. Hünig, H. Quast, W. Brenninger, and E. Frankenfield[1].
Checked by R. A. Schwartz and K. B. Wiberg.

1. Procedure

Caution! Tetramethyl-p-phenylenediamine may induce a painful dermatitis when brought into contact with the skin.[2] Suitable precautions should be taken to avoid such contact.

In a 2-l. three-necked flask fitted with a stirrer, thermometer, and pressure-compensated dropping funnel are placed 54 g. (0.5 mole) of powdered *p*-phenylenediamine (Note 1), 310 g. (3.7 mole) of sodium bicarbonate, and 250 ml. of water. The temperature of the solution is maintained at 18–22° using an ice bath while 320 ml. (3.4 mole) of dimethyl sulfate (Note 2) is added with stirring over a 30- to 50-minute period. Carbon dioxide is evolved vigorously and a transient purple color is developed; it changes to a brown tinge later on.

When the addition of dimethyl sulfate is complete, stirring is continued for 1 hour at 20–25°. Then the temperature is raised to 60–65° during 10 minutes (Note 3) and is kept at this value until the evolution of carbon dioxide ceases. After the addition of 250 ml. of cold water, the reaction flask is cooled rapidly in an ice bath and 100 ml. of ethanolamine (Note 4) is added. The resultant crystalline slurry is removed from the flask, and the apparatus is rearranged as indicated in (Note 5), using an upright condenser between the dropping funnel (Note 6) and the receiving flask.

To the reaction flask is added 200 ml. of ethanolamine, and it is heated to 140° with stirring. The slurry above is added in moderate portions over a 40- to 50-minute period (Note 7). When the heating bath is maintained at 230–240°, the addition of the slurry should provide an inner temperature at 120–140° as the water and oily product distill. After the addition is complete, the dropping funnel is rinsed with 100–150 ml. of water. As soon as the inner temperature has reached 160°, 50 ml. of ethanolamine is added and the temperature is maintained at 160–170° for 20 minutes. Water (50 ml.) is added through the dropping funnel to initiate a rapid steam distillation. Steam distillation is continued by the addition of 50-ml. portions of water at an inner temperature of 120–140° and a bath temperature of 230–240° until no more oil appears in the distillate (Note 8).

The oily product solidifies on cooling to about 20°, forming white lumps. After filtration by suction, the lumps are crushed, filtered, and washed four times with 50-ml. portions of ice water. Drying over silica gel in a vacuum gives 62–72 g. (82–88%) of white glistening scales, m.p. 51°.

2. Notes

1. A technical grade of *p*-phenylenediamine was used.
2. Dimethyl sulfate was distilled, b.p. 73–75° (13 mm.).
3. At this temperature the excess of dimethyl sulfate is destroyed.
4. Ethanolamine was distilled, b.p. 74–75° (13 mm.).
5. The apparatus shown in f.htmig. 1 is suitable for this step. It is essential that the condenser be very effective since the steam distillation is very rapid. If vapor is lost from the top of an internal coil condenser, cold towels placed on the outside of the condenser will provide additional cooling.

Fig. 1

Fig. 1

6. The dropping funnel should have a stopcock bore as large as possible.
7. Stirring and addition of only 40–50 ml. of the slurry into the dropping funnel should avoid obstruction of the stopcock. The use of a thin metal wire is sometimes helpful.
8. Transient blue colors in the distillate result from autoxidation. They do not, however, affect the purity of the final product.

3. Discussion

Tetramethyl-*p*-phenylenediamine has been obtained in low yield by the reaction of *p*-phenylenediamine with various alkylating agents such as methyl iodide,[3] methanol in the presence of hydrochloric acid at 170–200°,[4] or formaldehyde and formic acid.[5] In addition it has been prepared by methylating *p*-dimethylaminoaniline using methanol in the presence of hydrochloric acid at 170–200°,[6,7] followed by treatment of the resulting salts with aqueous ammonia at 180–190°.[7] In the most recent procedure, *p*-phenylenediamine was alkylated with sodium chloroacetate. Decarboxylation of the *p*-phenylenediaminetetraacetic acid at 180° gave 28% of tetramethyl-*p*-phenylenediamine based on the starting diamine.[8]

The present procedure[9] combines two general methods described earlier.[10,11] It is conveniently carried out and gives a substantially higher yield than previous methods. Dimethyl sulfate in the presence of aqueous sodium bicarbonate selectively methylates aromatic amines under mild conditions to give quaternary salts without affecting phenolic hydroxy groups present in the molecule. If the quaternization step is sterically hindered, the reaction stops at the tertiary amine stage.[10] Heterocyclic compounds may also be converted to quaternary salts in high yield, two or more methyl groups being introduced in one step.[12] The rate of reaction may conveniently be followed by observing the carbon dioxide evolution.

Dealkylation of quaternary ammonium salts using ethanolamine is more convenient than the use of aqueous ammonia in sealed tubes at high temperatures.[10] Ethanolamine may be replaced by other ethanolamines.[13] The reaction leads to preferential removal of methyl groups.

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

methanol (67-56-1)

formaldehyde (630-08-0)

sodium bicarbonate (144-55-8)

formic acid (64-18-6)

carbon dioxide (124-38-9)

dimethyl sulfate (77-78-1)

sodium chloroacetate (3926-62-3)

hydroxy (3352-57-6)

Methyl iodide (74-88-4)

ethanolamine (141-43-5)

Tetramethyl-p-phenylenediamine (3102-87-2)

p-dimethylaminoaniline (99-98-9)

p-phenylenediamine (106-50-3)

p-phenylenediaminetetraacetic acid (1099-02-1)

p-Phenylenediamine, N,N,N'N'-tetramethyl (100-22-1)

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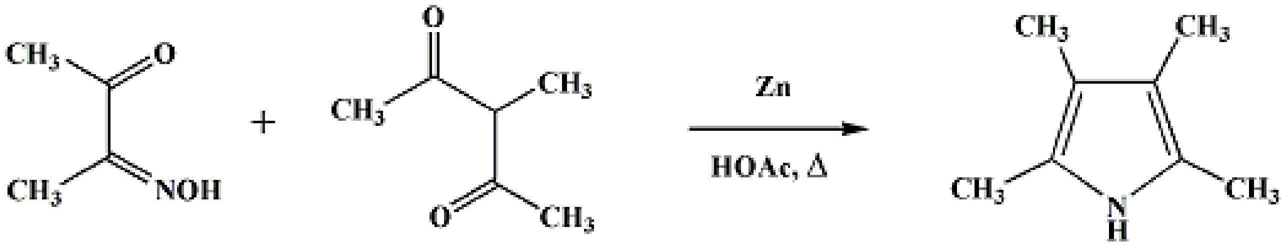
Organic Syntheses, CV 5, 1022

2,3,4,5-TETRAMETHYLPYRROLE

[Pyrrole, 2,3,4,5-tetramethyl-]



Submitted by A. W. Johnson and R. Price[1].
Checked by Virgil Boekelheide and M. Kunstmann.

1. Procedure

In a 2-l. three-necked flask fitted with a stirrer, thermometer, and reflux condenser are placed 250 ml. of glacial acetic acid, 54.5 g. (0.84 g. atom) of zinc dust, and 52.5 g. (0.46 mole) of 3-methylpentane-2,4-dione (Note 1). The contents of the flask are stirred vigorously (Note 2), and a solution of 42 g. (0.415 mole) of diacetyl monoxime[2] in 150 ml. of glacial acetic acid is added from a separatory funnel at a rate to maintain the temperature of the mixture at 65–70°. The addition takes 1 hour. When the addition is complete, the mixture is refluxed with stirring for an additional 30 minutes. The flask is then fitted for distillation with steam under nitrogen; 500 ml. of water is added and steam is introduced. Steam distillation (Note 3) is continued until no more tetramethylpyrrole comes over. This takes 1–2 hours and the distillate amounts to 1–2 l. The tetramethylpyrrole crystallizes from the steam distillate and is collected by filtration, washed with water, and dried over phosphorus pentoxide in a vacuum desiccator. There is obtained 15–18 g. of white plates, m.p. 110–111° (lit.,[3] m.p. 112°).

By neutralizing the filtrate with sodium hydroxide solution, a second crop of 4–5 g. of tetramethylpyrrole, m.p. 109–110°, is obtained. The total yield is 20.5–22.5 g. (40–44%) (Note 4).

2. Notes

1. 3-Methylpentane-2,4-dione is prepared by the methylation of acetylacetone.[4,5]
2. It is essential that the zinc dust be stirred effectively or the reaction may become violent.
3. Tetramethylpyrrole must be prevented from blocking the condenser. From time to time the condenser is cleared by turning off the coolant water.
4. 2,3,4,5-Tetramethylpyrrole is very readily oxidized in the air to a green resinous substance. If it is not used immediately, it should be stored under nitrogen or sealed in a glass vial under vacuum.

3. Discussion

2,3,4,5-Tetramethylpyrrole has been prepared by the action of sodium methoxide on 2,3,5-

trimethylpyrrole,[6] by the reduction of 2,3,5-trimethylpyrrole-4-aldehyde semicarbazone with sodium ethoxide,[7] by the reduction of 2,3,4-trimethylpyrrole-5-aldehyde with sodium ethoxide and hydrazine hydrate,[8] and by the reduction of 2,4-dimethylpyrrole-3,5-dicarboxylic acid with lithium aluminum hydride.[9] Direct ring synthesis by the condensation of 3-aminobutan-2-one and butan-2-one in alkaline solution gave very poor yields, the principal product being 2,3,5,6-tetramethylpyrazine.[3] The above modification of direct ring synthesis avoids this side reaction.[10]

4. Merits of Preparation

The present method possesses these advantages over those reported earlier:[5,6,7,8] it is less laborious, in that it is a single-stage preparation, and it gives a better over-all yield.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 785

References and Notes

1. Department of Chemistry, The University of Nottingham, Nottingham, England.
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

diacetyl monoxime

acetic acid (64-19-7)

sodium hydroxide (1310-73-2)

nitrogen (7727-37-9)

sodium methoxide (124-41-4)

zinc (7440-66-6)

sodium ethoxide (141-52-6)

hydrazine hydrate (7803-57-8)

butan-2-one (78-93-3)

Acetylacetone (123-54-6)

lithium aluminum hydride (16853-85-3)

tetramethylpyrrole, 2,3,4,5-Tetramethylpyrrole, Pyrrole, 2,3,4,5-tetramethyl- (1003-90-3)

3-Methylpentane-2,4-dione (815-57-6)

2,3,5-trimethylpyrrole

2,3,5-trimethylpyrrole-4-aldehyde semicarbazone

2,3,4-trimethylpyrrole-5-aldehyde

2,4-dimethylpyrrole-3,5-dicarboxylic acid

3-aminobutan-2-one

2,3,5,6-tetramethylpyrazine (1124-11-4)

phosphorus pentoxide (1314-56-3)

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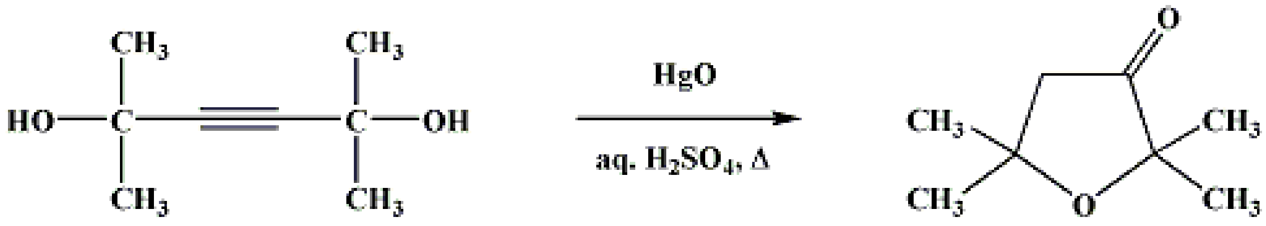
2,2,5,5-TETRAMETHYLTETRAHYDRO-3-KETOFURAN

[3(2)-Furanone, 4,5-dihydro-2,2,5,5-tetramethyl-]



Submitted by Melvin S. Newman and Walter R. Reichle[1].
Checked by Virgil Boekelheide and Graham Solomons.

1. Procedure

To the solution formed by dissolving 3 g. of mercuric oxide and 10 ml. of concentrated sulfuric acid (Note 1) in 1 l. of water is added 250 g. (1.76 moles) of 2,5-dimethyl-3-hexyne-2,5-diol (Note 2). The mixture is warmed with gentle swirling to dissolve the diol. At 80–90° the clear solution suddenly turns cloudy and the flask is immersed in a bath of water at about 20°. A colorless oil rises to the surface within a few minutes (Note 3).

The flask is then fitted for steam distillation, and 700–800 ml. of distillate is collected. After addition of 55 g. of sodium chloride to the distillate, the phases are separated in a 1-l. separatory funnel. The organic layer is dried by intermittent stirring with 25 g. of anhydrous magnesium sulfate for 6–10 hours.

The material is filtered and the residual solid washed twice with 50-ml. portions of low-boiling petroleum ether. The combined filtrates are concentrated and distilled through a short packed column to yield 190–205 g. (76–82%) of 2,2,5,5-tetramethyltetrahydro-3-ketofuran; b.p. 149–151°, n_D^{25} 1.4180.

2. Notes

1. Any other water-soluble mercury salt may be used.
2. Supplied by Air Reduction Chemical Company, 150 East 42nd Street, New York, N. Y.
3. The reaction is fairly exothermic. Cooling is advisable. An increase in acid and mercuric ion concentrations results in a faster reaction starting at a lower temperature.

3. Discussion

The procedure described is essentially that of Richet[2] which has been repeated.[3,4] The reaction is of interest since it provides a facile method of preparing tetrahydro-3-

furanones which are useful reagents for alkylation in the Friedel-Crafts reaction.[4]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

3(2)-Furanone, 4,5-dihydro-2,2,5,5-tetramethyl-

sulfuric acid (7664-93-9)

sodium chloride (7647-14-5)

mercuric oxide (21908-53-2)

magnesium sulfate (7487-88-9)

2,2,5,5-Tetramethyltetrahydro-3-ketofuran (5455-94-7)

2,5-dimethyl-3-hexyne-2,5-diol (142-30-3)

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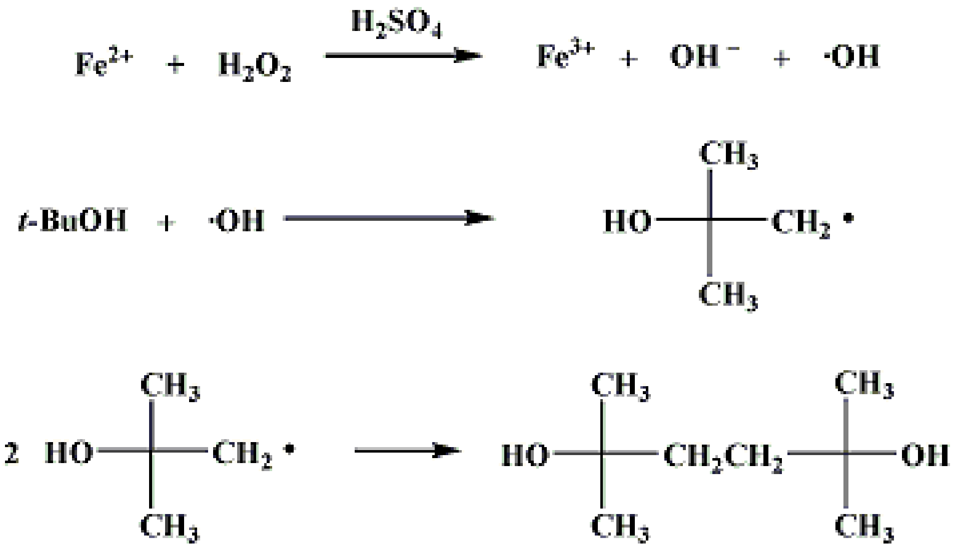
α,α,α',α'-TETRAMETHYLTETRAMETHYLENE GLYCOL

[2,5-Hexanediol, 2,5-dimethyl-]



Submitted by E. L. Jenner[1]
Checked by John D. Roberts and M. Panar.

1. Procedure

Tertiary butyl alcohol (900 ml., 702 g., 9.47 moles) is dissolved in a solution prepared by mixing 28 ml. (0.50 mole) of concentrated sulfuric acid with 1.5 l. of water in a 5-l. round-bottomed flask (Note 1) equipped with a thermometer, stirrer, gas inlet tube, and two addition burets. One buret is charged with 86 ml. (1 mole) of 11.6*M* hydrogen peroxide (Note 2), and the other with a solution of 278 g. (1 mole) of ferrous sulfate pentahydrate and 55.5 ml. (1 mole) of concentrated sulfuric acid in 570 ml. of water (Note 3). The reaction flask is swept out with nitrogen and cooled to 10° by means of an ice bath. Stirring is commenced and the two solutions are added simultaneously and equivalently over a period of 20 minutes. The temperature is held below 20°.

When the addition is completed, 50 ml. (1 mole) of 52% sodium hydroxide is added with stirring and cooling, and then 450 g. of anhydrous sodium sulfate (not all of the salt dissolves). The cold solution is transferred to a separatory funnel and the phases are separated. The organic layer is neutralized with 52% sodium hydroxide; approximately 20 ml. is required to bring the pH to 7. The aqueous layer, including the precipitated ferric hydroxide, is added to the aqueous portion of the reaction mixture and the whole is extracted with 400 ml. of *t*-butyl alcohol. This extract is similarly treated with 52% sodium hydroxide (about 5 ml. is required). The resulting aqueous layer is combined with the main aqueous fraction, which is again extracted with 400

ml. of *t*-butyl alcohol. This whole process is again repeated so that the organic phases comprise the three extracts and the phase which separated initially from the reaction mixture.

The four organic fractions are combined and distilled under reduced pressure. The distillation is continued until the temperature of the flask is about 70°/5 mm. in order to remove most of the *t*-butyl alcohol. The still residue is then extracted with 2 l. of ether and the extract is treated with decolorizing carbon and diatomaceous earth. Distillation of the ether at slightly reduced pressure from a water bath yields α,α,α',α'-tetramethyltetramethylene glycol as a pale yellow crystalline residue weighing 30–45 g. (41–62% yield based on hydrogen peroxide employed). The crude product is digested at room temperature in a mixture of 30 ml. of ether and 70 ml. of cyclohexane. The resulting slurry is filtered to yield 29–34 g. (40–46%; (Note 4)) of the glycol as a white crystalline solid, m.p. 87–88°. The product, which is pure enough for most purposes, can be further purified by recrystallization from ethyl acetate (1 g. in 4 ml.), cyclohexane (1 g. in 20 ml.), or water (1 g. in 2 ml.).

2. Notes

1. The flask should have creased sides and a conical indentation in the bottom and should be equipped with a high-speed, propeller-type stirrer rotated to force the liquid downwards. The stirrer should be constructed of glass because metals may interfere with the generation and utilization of the hydroxyl free radicals.
2. Commercial 35% hydrogen peroxide was employed. Any concentration from 5% to 50% may be used.
3. It is convenient to calibrate the burets so that the liquid is divided into 20 equal portions. Then, in the addition of the reagents, these calibrations aid in synchronizing the rates.
4. The submitter reports yields of 48–55%, which are slightly higher than those given here.

3. Discussion

α,α,α',α'-Tetramethyltetramethylene glycol has been prepared by the action of methylmagnesium bromide on acetonylacetone,[2,3,4] on ethyl levulinate,[5] and on ethyl succinate.[6,7] It has also been made by the hydrogenation of 2,5-dimethyl-3-hexyne-2,5-diol over nickel[8,9] and over platinum[10,11] and by the hydrogenation of 2,5-dihydroperoxy-2,5-dimethyl-3-hexyne.[12] Other methods of preparation include the autoxidation of 2,5-dimethylhexane[13] and the alkaline hydrolysis of 2,5-dibromo-2,5-dimethylhexane.[6] The present method, the hydroxyl- radical coupling of *t*-butyl alcohol,[14] is a one-step synthesis using readily available starting materials. A similar technique may be used to synthesize α,α,α',α'-tetramethyladipic acid from pivalic acid, α,α,α',α'-tetramethyltetramethylenediamine from *t*-butylamine, and α,α,α',α'-

tetramethyladiponitrile from pivalonitrile.[14]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

ethyl acetate (141-78-6)

ether (60-29-7)

sodium hydroxide (1310-73-2)

ethyl succinate

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

platinum (7440-06-4)

cyclohexane (110-82-7)

nickel (7440-02-0)

decolorizing carbon (7782-42-5)

hydrogen peroxide (7722-84-1)

Pivalic acid (75-98-9)

Acetonylacetone (110-13-4)

methylmagnesium bromide (75-16-1)

Tertiary butyl alcohol, t-butyl alcohol (75-65-0)

2,5-dimethyl-3-hexyne-2,5-diol (142-30-3)

2,5-Hexanediol, 2,5-dimethyl-, α,α,α',α'-Tetramethyltetramethylene glycol (110-03-2)

ferrous sulfate pentahydrate

ferric hydroxide (1309-33-7)

ethyl levulinate (539-88-8)

2,5-dihydroperoxy-2,5-dimethyl-3-hexyne (3491-36-9)

2,5-dimethylhexane (592-13-2)

2,5-dibromo-2,5-dimethylhexane

pivalonitrile (630-18-2)

t-butylamine (75-64-9)

α,α,α',α'-tetramethyladipic acid

α,α,α',α'-tetramethyltetramethylenediamine

α,α,α',α'-tetramethyladiponitrile

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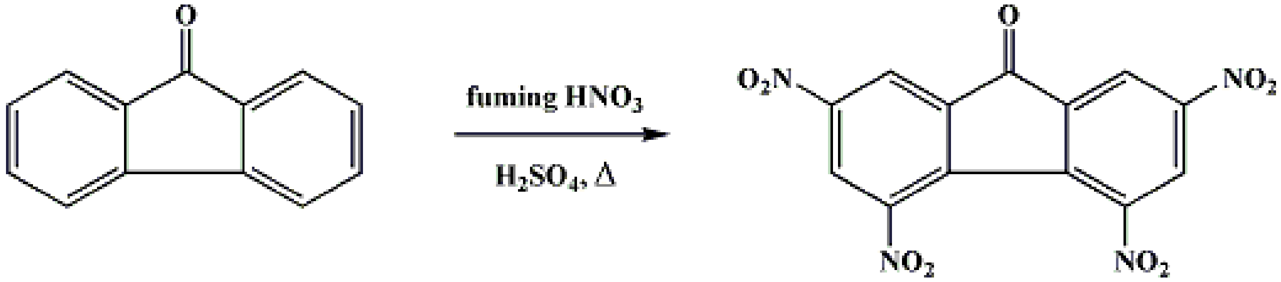
2,4,5,7-TETRANITROFLUORENONE

[9-Fluorenone, 2,4,5,7-tetranitro-]



Submitted by Melvin S. Newman and H. Boden[1].
Checked by William E. Parham, Peter Delvigs, and E. Leete.

1. Procedure

A 5-l. three-necked flask fitted with an all-glass addition funnel and two condensers is charged with 770 ml. of concentrated sulfuric acid and 1.3 l. of 90% fuming nitric acid (Note 1). The solution is heated under gentle reflux, and a solution of 73 g. (0.4 mole) of 9-fluorenone (Note 2) in 840 ml. of concentrated sulfuric acid (Note 3) is added from the dropping funnel over a 1-hour period. After the fluorenone addition is complete, a solution of 950 ml. of fuming nitric acid in 1120 ml. of concentrated sulfuric acid is added dropwise during 8.5 hours to the gently refluxing reaction mixture. The heating jacket is turned off and the solution is allowed to stand for 10 hours. The reaction mixture is poured into 5 gallons of water in two 5-gal. crocks (Note 4). The light yellow precipitate is washed with water, twice by decantation, filtered, washed several times with water and sucked dry, and finally is dried in a vacuum oven at 80° for 10 hours (Note 5). The yield of crude 2,4,5,7-tetranitrofluorenone, m.p. 249–253°, is 105–117 g. (72–80%). This solid is recrystallized from 1.6 l. of acetic acid containing 100 ml. of acetic anhydride. The hot solution is filtered through a fluted filter and cooled rapidly to yield 80–86 g. (51–54%) of 2,4,5,7-tetranitrofluorenone, m.p. 253.0–254.5° cor. (Note 6) and (Note 7).

2. Notes

1. Baker Analyzed reagent grade fuming nitric acid may be added to the sulfuric acid without special precautions, since the heat effect is not large.
2. Eastman white label 9-fluorenone, m.p. 82–84°, was used. The checkers used material, m.p. 83.5–84.5°, prepared from fluorene.[2]
3. The deep purple-brown solution may have to be warmed in order to dissolve all the fluorenone.
4. This operation must be carried out in the hood.
5. The product may be dried under reduced pressure over calcium chloride for several days.
6. Additional product amounting to 15–17% may be obtained by recrystallization of further crops from the mother liquor.
7. Tetranitrofluorenone crystallizes with 0.5 mole of acetic acid which is readily lost on heating under reduced pressure.

3. Discussion

The procedure described here is essentially that of Newman and Lutz.[3] 2,4,5,7-Tetranitrofluorenone has been prepared by nitration of fluorenone,[4] 2,4,7-trinitrofluorenone,[5,6] and 4,5-dinitrofluorenone.[6] The preparation by Schmidt et al.,[4,5] which supposedly yielded the 2,3,6,7-isomer, has been shown[6] to yield the 2,4,5,7-isomer.

4. Merits of Preparation

The complexes which 2,4,5,7-tetranitrofluorenone forms with aromatic compounds are in general higher melting and less soluble than are the corresponding complexes of 2,4,7-trinitrofluorenone.[3,7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 1031

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

acetic anhydride (108-24-7)

nitric acid (7697-37-2)

fluorene (86-73-7)

2,4,7-Trinitrofluorenone (129-79-3)

fluorenone, 9-fluorenone (486-25-9)

2,4,5,7-Tetranitrofluorenone, 9-Fluorenone, 2,4,5,7-tetranitro- (746-53-2)

Tetranitrofluorenone

4,5-dinitrofluorenone

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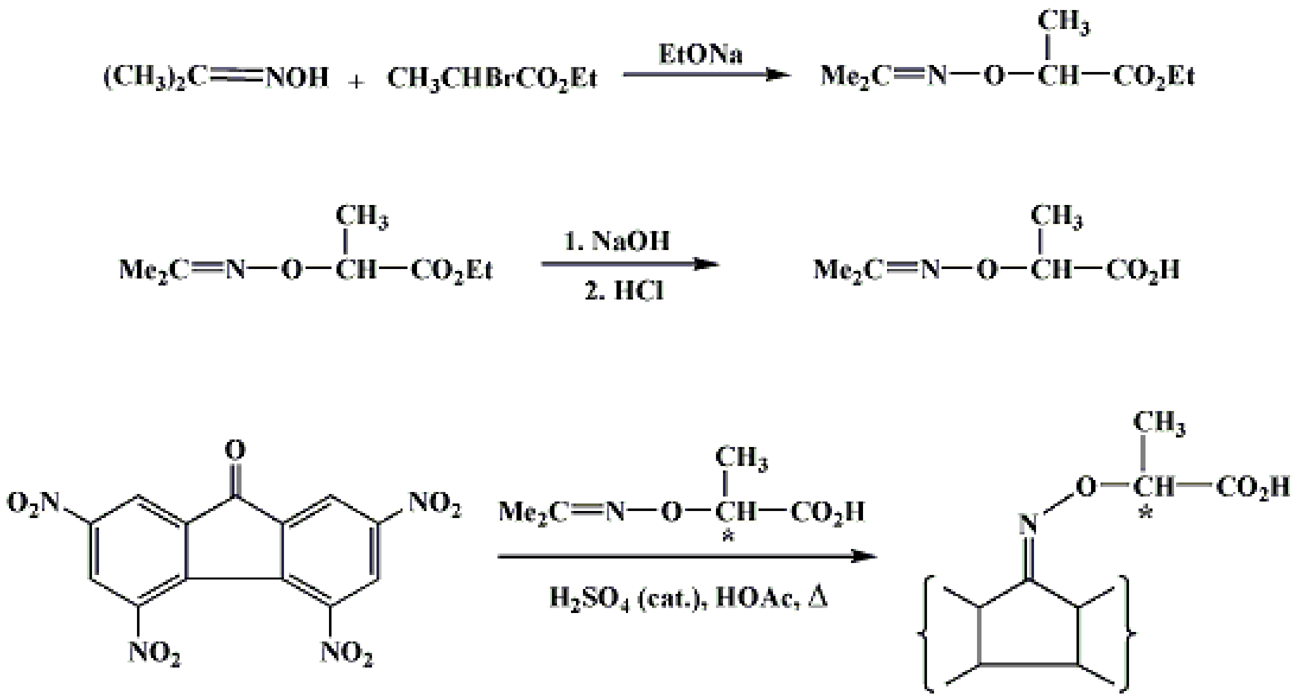
(+)- AND (−)-α-(2,4,5,7-TETRANITRO-9-FLUORENYLIDENEAMINOOXY)PROPIONIC ACID

[Propionic acid, 2-(2,4,5,7-tetranitrofluoren-9-ylideneaminooxy)-, (+)- and (−)-]



Submitted by Paul Block Jr[1] and Melvin S. Newman[2].
Checked by William G. Dauben, Milton E. Lorber, Carroll S. Montgomery, and Gary W. Shaffer.

1. Procedure

A. *Ethyl α-(isopropylideneaminooxy)propionate*. A 1-l. three-necked flask is equipped with a mechanical stirrer, a dropping funnel, and a thermometer that can be immersed in the contents of the flask. There is added to the flask 500 ml. of commercial absolute ethanol (Note 1) followed by 17.5 g. (0.76 g. atom) of sodium, which is added carefully in small portions. When a clear solution has been obtained, 55.0 g. (0.75 mole) of acetone oxime is added (Note 2). The flask is cooled in a water bath held at 5–10°, the stirrer is started, and 136 g. (0.75 mole) of ethyl α-bromopropionate (Note 3) is added during 20–30 minutes at a rate such that the temperature does not rise above 20°. The cooling bath is removed, and the stirring is continued until the contents of the flask reach room temperature.

After standing for 12 hours, the reaction mixture is filtered by gravity into a 1-l. round-bottomed flask, and the solid sodium bromide is washed with 50 ml. of ethanol. The combined filtrate and washings are concentrated to a volume of about 400 ml., and 250 ml. of water is added to the cooled concentrate. The mixture is extracted with 50 ml. of a 1:1 mixture of ether and benzene, and the aqueous layer is reextracted with 100 ml. of the same solvent mixture. The organic extracts are combined, washed with 100 ml. of water and 50 ml. of saturated aqueous sodium chloride, and filtered through a few grams of anhydrous magnesium sulfate. The solvent is removed on a rotary evaporator, and the residue is distilled to yield 71–77 g. (55–59%) of ethyl α-(isopropylideneaminooxy)propionate, b.p. 62–64° (4 mm.).

B. *d,l-α-(Isopropylideneaminooxy)propionic acid*. In a 1-l. three-necked flask fitted with a stirrer and a thermometer that can be immersed in the contents of the flask is placed 300 ml. of 5% aqueous sodium hydroxide (0.37 mole). The flask is heated on a water bath until the temperature of the solution reaches 70°, and 52 g. (0.30 mole) of ethyl α-(isopropylideneaminooxy)propionate is added. The mixture is stirred rapidly while the temperature is held at 70°; the stirring is continued for 20 minutes beyond the time necessary for the contents of the flask to become homogeneous (Note 4). The solution is cooled and acidified to Congo red paper with 5*N* hydrochloric acid, and 175 g. of ammonium sulfate is added. The mixture is extracted three times with a total of 300 ml. of a 1:1 mixture of ether and benzene. The combined extracts are dried rapidly over 5 g. of anhydrous magnesium sulfate and filtered (Note 5). The solvent is removed by distillation, and 160 ml. of petroleum ether (b.p. 30–60°) is added to the cooled residue. The resulting solution is placed in a refrigerator for several hours. The crystals that separate are removed by suction filtration and washed with a small volume of cold petroleum ether. The yield of colorless product is 35–37 g. (80–85%); m. p. 59–60.5° (Note 6).

C. (+)- and (–)-α-*(Isopropylideneaminooxy)propionic acid-(–)-ephedrine salts*. A solution of 36.6 g. (0.200 mole) of (–)-ephedrine monohydrate (Note 7) in 800 ml. of ethyl acetate containing 6% of ethanol (Note 8) is placed in a 2-l. beaker. *d,l*-α-(Isopropylideneaminooxy)propionic acid (29.0 g., 0.200 mole) is dissolved in this solution by stirring (Note 9). The beaker is covered securely with a rubber dam, cooled for a short period in an ice bath, placed in a refrigerator at 0–5°, and allowed to remain undisturbed for 8–16 hours after crystallization has begun (Note 10). The solid mass of crystals is filtered by suction, and the funnel is covered with a rubber dam to remove most of the solvent. The solid product is placed in a 500-ml. beaker, 250 ml. of ethyl acetate is added (Note 11), and the mixture is heated until all the solid has dissolved. The solution is cooled, placed in a refrigerator for several hours, and filtered; the crystalline precipitate is dried in air. The yield of the (–)-ephedrine-(+)-α-(isopropylideneaminooxy)propionic acid salt is 22–25 g. (71–81%); m.p. 115–119° (Note 12) and (Note 13); $[\alpha]^{20}D$ –4.2° (*c* 1.5, chloroform).

The combined filtrates are diluted with an equal volume of petroleum ether (b.p. 30–60°), placed in a refrigerator for 8–16 hours, and filtered. The solid product is recrystallized from ethyl acetate (10 ml. per gram of the salt). The yield of the monohydrate of the (–)-ephedrine-(–)-α-(isopropylideneaminooxy)propionic acid salt is 19–26 g. (58–79%); m.p. 88–90°; $[\alpha]^{20}D$ –57° (*c* 1.5, chloroform) (Note 13) and (Note 14).

D. (+)- *and (–)-*α-*(Isopropylideneaminooxy)propionic acid*. To a solution of 20 g. (0.064 mole) of the (–)-base-(+)-acid salt in 60 ml. of water is added 14 ml. (0.070 mole) of 5*N* hydrochloric acid. The solution is filtered to remove a slight insoluble residue and extracted with four 25-ml. portions of a 1:1 mixture of ether and benzene. The combined extracts are dried rapidly over 1–2 g. of anhydrous magnesium sulfate and filtered. The organic solvents are removed by distillation from a steam bath, the residue is dissolved in 75 ml. of petroleum ether (b.p. 30–60°), and the solution is allowed to stand in a refrigerator for 12 hours. The crystalline product (7.0–7.5 g.; m.p. 75–81°) is collected and dissolved in hot acetone (0.5 ml. per gram), and the solution is diluted with hexane (5 ml. per gram). The solution is placed in a refrigerator for 8–16 hours, and the crystalline (+)-α-(isopropylideneaminooxy)propionic acid (5.5–6.5 g.; 59–70%) that separates is collected; m.p. 83–85°; $[\alpha]^{20}D$ +32° (*c*. 1.6, water).

In a similar manner, from 20 g. (0.061 mole) of the monohydrate of the (–)-base-(–)-acid salt, there is obtained 6.4–6.7 g. (73–76%) of the (–)-acid, m.p. 83–85°, $[\alpha]^{20}D$ –29° (*c* 1.44, water), directly from the crystallization from petroleum ether. Subsequent recrystallization from acetone-hexane is normally not required.

E. (+)- *and (–)-α-(2,4,5,7-Tetranitro-9-fluorenylideneaminooxy)propionic acid (TAPA)*. To a solution of 5.5 g. (0.038 mole) of either optical antipode of α-(isopropylideneaminooxy)propionic acid in 85 ml. of 96% acetic acid in a 250-ml. round-bottomed flask are added 9.0 g. (0.025 mole) of 2,4,5,7-tetranitrofluorenone,[3] 0.30–0.35 ml. of concentrated sulfuric acid, and a few boiling chips. The flask is fitted with an air condenser (Note 15), and the contents are heated under reflux so that the condensing liquid nearly reaches the top of the condenser (Note 16). After 2 hours, 18 ml. of water is added to the hot solution, and crystallization is allowed to take place slowly, first at room temperature and finally for 12 hours in a refrigerator. The yellow crystalline acid is filtered and dissolved in 70 ml. of hot acetic acid. The solution is diluted while hot with 60 ml. of water, cooled rapidly with stirring, and kept at 0° for several hours. The optically active TAPA is filtered and air-dried away from direct sunlight until the odor of acetic acid is negligible. The crystals are then dried in an oven at 110° (Note 17) and protected from light by storage in a suitable container; yield 7.8–10.0 g. (70–90%). The TAPA from the (–)-acid has $[\alpha]^{25}_D$ +97° and that from the (+)-acid $[\alpha]^{25}_D$ –97° (Note 18).

2. Notes

1. Pure anhydrous ethanol[4] offers no advantage over commercial absolute ethanol.
2. "Eastman grade" acetone oxime was used as obtained from Eastman Organic Chemicals.
3. "Eastman grade" ethyl α-bromopropionate was used as obtained from Eastman Organic Chemicals.
4. Usually 10–20 minutes are required to obtain complete reaction.
5. If the solution is not entirely colorless, it should be shaken with a small amount of activated carbon and filtered before distillation.
6. The checkers found 53–56°; m.p. 57–61° has been reported.[5]
7. "Ephedrine alkaloid hydrous," Merck, was used. If anhydrous ephedrine is employed, only 33 g. should be used, and 3.6 g. (0.20 mole) of water should be added. Anhydrous conditions lead to incomplete resolution.
8. Commercial absolute ethanol (48 ml.) is pipetted into a 1-l. graduated cylinder and diluted with 800 ml. of ethyl acetate ("Eastman grade").
9. Both components are soluble in ethyl acetate at room temperature; the resulting salt is not. By dissolving the components sequentially, precipitation of the salt is generally avoided. Should the salt form, however, it must be dissolved by gentle heating.
10. Prolonged standing must be avoided as the deposition of the (–)-ephedrine-(–)-acid salt can occur.
11. Ethanol is not added to the ethyl acetate at this point.
12. Highly purified samples have m.p. 124.0–124.5°.
13. The two diastereoisomeric salts can be readily distinguished from each other. The (–)-ephedrine-(+)-acid salt is formed as cottony crystals that grow in the solution and eventually become a solid, white opaque mass. The monohydrate of the (–)-ephedrine-(–)-acid salt consists of clear, chunky crystals that grow from, and adhere to, the bottom and sides of the flask.
14. The water of hydration is lost on standing in a desiccator over phosphorus pentoxide; the melting point eventually reached is 109–110°.[6]
15. A 250 × 15-mm. glass tube is satisfactory.
16. The suspended tetranitrofluorenone dissolves completely in about 25 minutes; the vigorous heating is required to bring about the solution and reaction.
17. One mole of acetic acid of solvation is lost only slowly at room temperature; the solvated product has m.p. *ca.* 123°.[5] The submitters found that the air-dried material, on being dried at 110°, yielded essentially solvent-free compound, m.p. 201–203° (dec. with prior darkening).

The checkers found that at 110° the air-dried material melted, turned brown, and then resolidified. They also found that the material, on being dried at 70–80° (1 mm.) over potassium hydroxide pellets for several days, remained yellow but melted over a range 110–125°, resolidified, and remelted at 190–195°.
18. The checkers used material dried at 70–80° for their determination of the rotation and obtained values in agreement with those reported by the submitters.

3. Discussion

TAPA has been prepared only as described in this procedure.[5] α-(isopropylideneaminooxy)propionic acid has been prepared and resolved by the present procedure[6] and has been prepared directly from α-bromopropionic acid and resolved as the (–)-ephedrine salt by crystallization from hydrocarbon mixtures.[5]

4. Merits of the Preparation

The use of ethyl α-bromopropionate simplifies the preparation of α-(isopropylideneaminooxy) propionic acid. Resolution in ethyl acetate solution has proved less erratic than in the hydrocarbon solvents previously recommended,[5] and the isolation of both diastereoisomeric salts formed is facilitated. TAPA has found use in the resolution of polycyclic aromatic compounds that do not possess functional groups that would permit resolution by other methods.[5,7,8]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

(+)- AND (–)-α-(2,4,5,7-TETRANITRO-9-FLUORENYLIDENEAMINOOXY)PROPIONIC ACID

Propionic acid, 2-(2,4,5,7-tetranitrofluoren-9-ylideneaminooxy)-, (+)- and (–)-

(+)- and (–)-α-(Isopropylideneaminooxy)propionic acid-(–)-ephedrine salts

(–)-ephedrine monohydrate

(+)- and (–)-α-(Isopropylideneaminooxy)propionic acid

(+)- and (–)-α-(2,4,5,7-Tetranitro-9-fluorenylideneaminooxy)propionic acid (TAPA)

(–)-ephedrine

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

ethyl acetate (141-78-6)

ether (60-29-7)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium chloride (7647-14-5)

α-bromopropionic acid (598-72-1)

sodium bromide (7647-15-6)

acetone (67-64-1)

carbon (7782-42-5)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

ammonium sulfate (7783-20-2)

magnesium sulfate (7487-88-9)

monohydrate (7732-18-5)

ethyl α-bromopropionate (535-11-5)

hexane (110-54-3)

acetone-hexane (821-55-6)

2,4,5,7-Tetranitrofluorenone (746-53-2)

Tetranitrofluorenone

acetone oxime (127-06-0)

ethyl α-(isopropylideneaminooxy)propionate (54716-29-9)

d,l-α-(Isopropylideneaminooxy)propionic acid, α-(isopropylideneaminooxy)propionic acid, (+)-α-(isopropylideneaminooxy)propionic acid (5001-36-5)

Ephedrine (90-82-4)

phosphorus pentoxide (1314-56-3)

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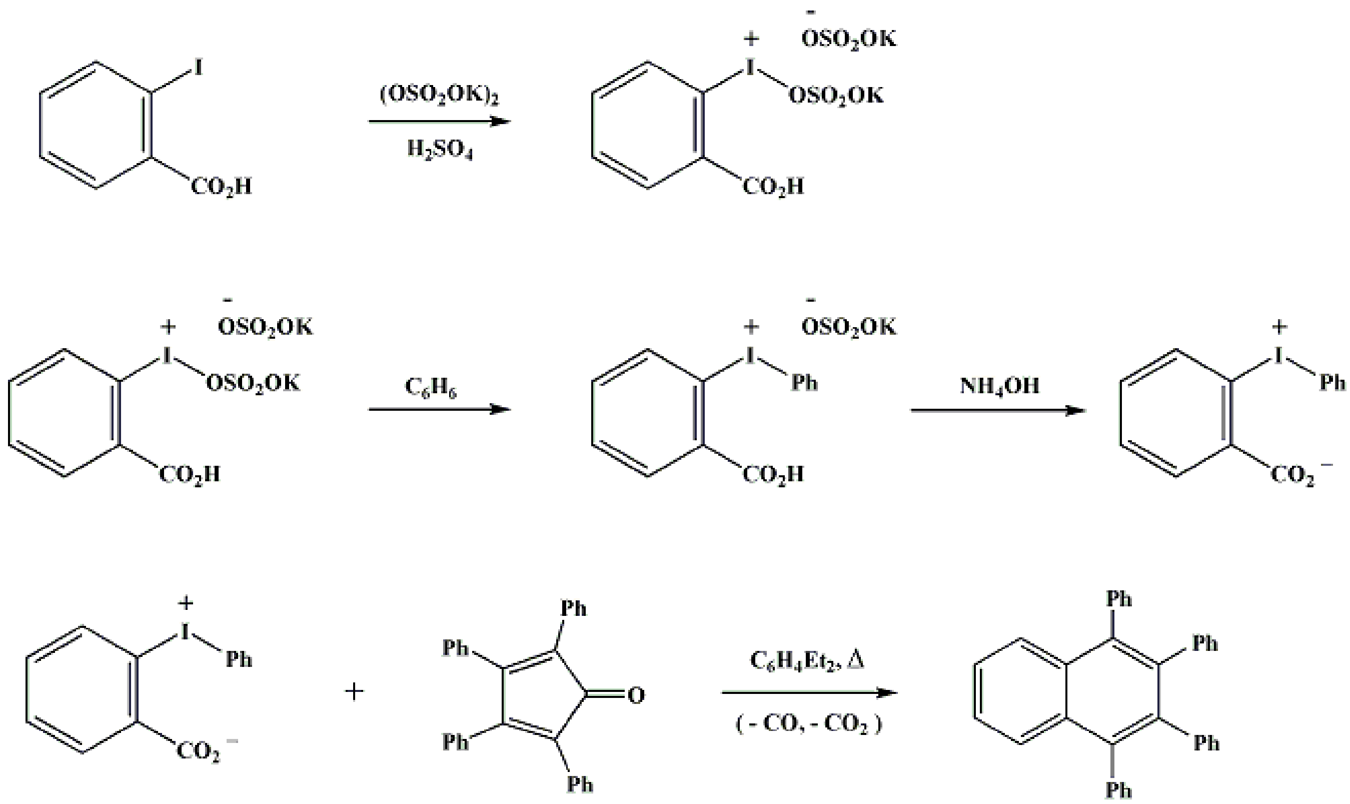
Organic Syntheses, CV 5, 1037

1,2,3,4-TETRAPHENYLNAPHTHALENE

[Naphthalene, 1,2,3,4-tetraphenyl-]



Submitted by Louis F. Fieser and Makhluf J. Haddadin[1].
Checked by Joyce M. Dunston and Peter Yates.

1. Procedure

A. *Diphenyliodonium-2-carboxylate*. An Erlenmeyer flask containing 80 ml. of concentrated sulfuric acid (Note 1) is placed in an ice bath to cool. To a 2-l. three-necked flask are added (Note 2) 20 g. (0.081 mole) of lump-free *o*-iodobenzoic acid (Note 3) and 26 g. (0.096 mole) of potassium persulfate (Note 4). The flask is cooled in an ice bath, the chilled sulfuric acid is added, and the flask is swirled in an ice bath for 4–5 minutes to produce an even suspension and to control the initial exothermal reaction. The flask is then removed from the ice bath and the time is noted. The reaction mixture foams somewhat and acquires a succession of colors. The flask is mounted in a pan of acetone, a mechanical stirrer with a curved Teflon® blade is placed in the center neck of the flask and operated slowly, and a 250-ml. separatory funnel is mounted into a side neck. Three flasks are put in an ice bath to cool: one containing 190 ml. of distilled water, another 230 ml. of 29% ammonium hydroxide, and another 400 ml. of methylene chloride.

After the oxidation has proceeded for 20 minutes, the acetone bath is brought to 10° by addition of crushed dry ice, and the solution is stirred for 2–3 minutes. There is added 20 ml. of thiophene-free benzene (17.6 g., 0.226 mole), and stirring at 10° is continued for 1 hour (Note 5). The temperature of the acetone bath is lowered to −15° by addition of crushed dry ice and the bath kept at this temperature while the chilled 190 ml. of distilled water is added with efficient stirring to precipitate the potassium bisulfate salt of diphenyliodonium-2-carboxylic acid. The 400 ml. of chilled methylene chloride (Note 6) is added, and a 100° thermometer is mounted in a side neck in such a way that the 15–25° section is visible. With efficient cooling (bath at −15°) and stirring, the 230 ml. of chilled 29% ammonium hydroxide (Note 7) is added at such a rate that the temperature of the reaction mixture remains between 15° and 25°. Approximately 10 minutes is required for the addition, and after the addition the aqueous layer should be alkaline to indicator paper (pH 9). The stirrer and the thermometer are removed and rinsed with water and methylene chloride. The bulk of the aqueous layer is decanted into a 500-ml. Erlenmeyer flask for temporary storage, and the reaction flask is emptied and rinsed into a 500-ml. separatory funnel. The pale tan lower methylene chloride layer is drained into a 1-l. Erlenmeyer flask, the decanted aqueous layer is added to the separatory funnel, and the combined aqueous layer is extracted with two 100-ml. portions of methylene chloride. The combined extract is dried over anhydrous sodium sulfate, filtered into a 1-l. Erlenmeyer flask, and the filtrate is evaporated on the steam bath until the product is left as a dry grayish cake. The cake is dislodged and broken up with a stainless steel spatula, and the bulk of the product is transferred to a paper. Material adhering to the flask and spatula is dissolved in boiling methylene chloride and the solution transferred to a tared 500-ml. flask and evaporated

to dryness. The solid product is added to the flask and the combined solid is brought to constant weight at steam-bath temperature and water-aspirator pressure. The yield of crude product is 23.3–24.4 g. (Note 8).

Boiling water (275 ml.) is poured into the flask, the product brought into solution at the boiling point, and 0.4 g. of Norit® is added carefully to the slightly cooled solution. The solution is again heated to boiling, filtered, and allowed to stand for crystallization overnight, eventually at 0°. The colorless prisms of diphenyliodonium-2-carboxylate monohydrate (Note 9) are collected and air-dried to constant weight at room temperature. The yield of product, m.p. 220–222° (dec.), is 20–22 g. (72–79%, (Note 10).

B. *1,2,3,4-Tetraphenylnaphthalene*. To a 100-ml. round-bottomed flask equipped with an 11-cm. water-cooled condenser (Note 11) there is added 60 ml. of diethylbenzene (*meta* and *para* mixture) (Note 12), and the flask is heated in a fume hood with the free flame of a microburner until refluxing liquid rises well into the condenser. If a cloudy zone of condensate appears at the top of the condenser, the moisture is removed with an applicator stick wrapped with absorbent cotton (Note 13). The same technique is used later for removal of water of hydration which appears in the early stages of the reaction and causes hissing and eruption if allowed to drop back into the flask (Note 14). The flame is removed and 10 g. (0.026 mole) of tetraphenylcyclopentadienone[2] (Note 2) and 11.8 g. (0.035 mole) of diphenyliodonium carboxylate monohydrate are added to the flask. The mixture is heated over a microburner at a rate such as to maintain vigorous gas evolution and gentle refluxing. The water of hydration is eliminated in 8–10 minutes. The flask is then fitted with a normal reflux condenser and the heating is continued. After 30 minutes considerable undissolved diphenyliodonium carboxylate can still be seen, under illumination, at the bottom of the flask. In another 5 minutes the color changes to transparent red, and in a minute or two longer the solution becomes pale amber. Refluxing is continued until no solid remains (10–15 minutes) (Note 15). The flask is then fitted for distillation, and 55 ml. of liquid (diethylbenzene and iodobenzene, b.p. 188°) is removed by distillation. The residue is cooled and dissolved in 25 ml. of dioxane. The solution is rinsed into a 125-ml. Erlenmeyer flask and diluted with 25 ml. of 95% ethanol. The solution is heated to boiling, and water (6–7 ml.) is added gradually until a few shiny prisms remain undissolved on boiling. Crystallization is allowed to proceed at room temperature and then for several hours at 0°. The precipitate is removed by filtration, and the mother liquor upon further standing deposits a small second crop of crystals (0.3 g., m.p. 1° low). The main product melts initially in the range 196–199°, solidifies on cooling, and remelts sharply at 203–204° (Note 16). The total yield is 9.2–10.2 g. (82–90%).

2. Notes

1. The amount of acid is half that called for in previous procedures.[3,4]
2. The solids are added using a powder funnel or a rolled-up piece of glazed paper to prevent material from lodging on the neck or walls.
3. Obtained from Eastman Organic Chemicals.
4. The fine granular material supplied by Fisher Scientific Co. is satisfactory; any lumps present should be crushed. Persulfate in the form of large prisms should be ground prior to use.
5. If the reactants are mixed at room temperature, a rapid temperature rise of about 7° is noted. The reaction can then be brought to completion by swirling at 50° for 5 minutes or at room temperature for 20 minutes, but the product contains considerable brown pigment.
6. The methylene chloride is added for efficient extraction of the product as it is liberated on neutralization. The product is more soluble in this solvent than in chloroform.[3,4]
7. Neutralization with sodium hydroxide[3,4] leads to troublesome separation of sodium salts.
8. This crude product contains a little solid which will not redissolve in an organic solvent and it is unsuitable for procedure B. The checkers used a 500-ml. filter flask with sealed side arm for the evaporation and drying operation.
9. *Anal.* Calcd. for $C_{13}H_{11}O_3I$ (342.13): C, 45.63; H, 3.24, I, 37.10. Found: C, 45.48; H, 3.19; I, 37.16.
10. Anhydrous material, m.p. 215–216° (dec.), can be obtained in quantitative yield by extracting 12 g. of the monohydrate in a Soxhlet extractor with 80 ml. of methylene chloride and evaporating to constant weight.
11. A convenient condenser is a water-cooled Ace Glass Bearing, No. 8244.
12. Obtained from Eastman Organic Chemicals, b.p. 175–181°. This solvent, in which the benzyne precursor is very sparingly soluble, seemed slightly superior to trimethylene glycol dimethyl ether (b.p. 222°) in which the solubility is considerably higher. *o*-Dichlorobenzene (b.p. 179°), a still better solvent for the dipolar salt, is less satisfactory than the ether. Diethyl oxalate (b.p. 184°) and N,N-dimethylacetamide (b.p. 195°) are unsatisfactory.
13. The checkers found it impossible to prevent water from dropping into the hot mixture and leading to its eruption through the top of the condenser. They found it convenient to eliminate the small condenser and use only a normal condenser where the prolonged reflux period is needed.
14. The yield was not improved by use of anhydrous material (Note 10).
15. Solid adhering to the walls of the flask can be dislodged by loosening the clamp supporting the flask and using the condenser as a lever to swirl the flask.
16. The double melting point has been observed in only one[5] of the previous studies. The initial melting point varies with the state of subdivision and is not a reliable index of purity. Several recrystallizations did not change the melting behavior or the remelt temperature. The checkers did not observe the double melting point with the product initially obtained, but did so with material recrystallized once.

3. Discussion

1,2,3,4-Tetraphenylnaphthalene has been isolated by Wittig and co-workers by generation of benzyne in the presence of excess tetraphenylcyclopentadienone as trapping agent. Yields of hydrocarbon isolated by chromatography and based upon the precursor are as follows: from *o*-fluorobromobenzene, 17%;[6] from either *o*-iodophenylmercuric iodide or bis-(*o*-iodophenyl)-mercury, 25%.[7] The hydrocarbon has also been obtained in low yield as one of two products resulting from the reaction of diphenylacetylene with triphenylchromium.[5] The present method is due to Le Goff,[4] who reports a 68% yield of hydrocarbon from diphenyliodonium-2-carboxylate. However, this investigator states in a private communication that he refluxed the benzyne precursor with a large excess of tetraphenylcyclopentadienone in diethylene glycol dimethyl ether and isolated the hydrocarbon by tedious hexane extraction and chromatography. In the experience of the submitters the solvent selected has too low a boiling point (161°) for efficient conversion.

4. Merits of the Preparation

The procedure demonstrates a safe and simple method for the generation of benzyne from a stable and easily prepared precursor and its use in the synthesis of a hitherto difficulty accessible hydrocarbon.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

potassium bisulfate salt of diphenyliodonium-2-carboxylic acid

ethanol (64-17-5)

sulfuric acid (7664-93-9)

Benzene, benzyne (71-43-2)

ether (60-29-7)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium sulfate (7757-82-6)

acetone (67-64-1)

Norit (7782-42-5)

ammonium hydroxide (1336-21-6)

Iodobenzene (591-50-4)

o-iodobenzoic acid (88-67-5)

methylene chloride (75-09-2)

potassium persulfate (7727-21-1)

dioxane (5703-46-8)

Diphenylacetylene (501-65-5)

hexane (110-54-3)

Tetraphenylcyclopentadienone (479-33-4)

diethyl oxalate (95-92-1)

diethylene glycol dimethyl ether (111-96-6)

diphenyliodonium-2-carboxylate, diphenyliodonium carboxylate (1488-42-2)

o-fluorobromobenzene (1072-85-1)

1,2,3,4-Tetraphenylnaphthalene, Naphthalene, 1,2,3,4-tetraphenyl- (751-38-2)

diphenyliodonium-2-carboxylate monohydrate, diphenyliodonium carboxylate monohydrate

diethylbenzene (135-01-3)

trimethylene glycol dimethyl ether (17081-21-9)

N,N-dimethylacetamide (127-19-5)

triphenylchromium

o-dichlorobenzene (95-50-1)

o-iodophenylmercuric iodide

bis-(o-iodophenyl)-mercury

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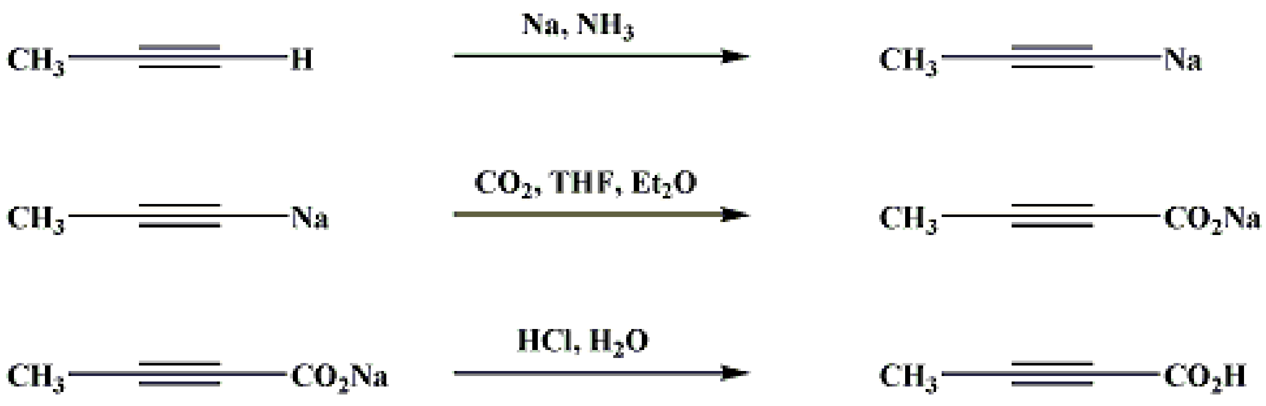
Organic Syntheses, CV 5, 1043

TETROLIC ACID

[2-Butynoic Acid]



Submitted by J. C. Kauer and M. Brown[1].
Checked by W. E. Parham, Wayland E. Noland, and Richard J. Sundberg.

1. Procedure

A 3-l., three-necked, round-bottomed flask is equipped with a glass paddle stirrer, a condenser containing a mixture of acetone and solid carbon dioxide, and a gas inlet tube. The outlet of the condenser is protected from the atmosphere by a T-tube through which a slow stream of nitrogen is passed. The flask is purged with nitrogen, and about 1.5 l. of anhydrous liquid ammonia is either poured or distilled into the flask. A small crushed crystal of ferric nitrate nonahydrate is added, followed by 23 g. (1 g. atom) of freshly cut sodium in small pieces (Note 1).

Methylacetylene (44–48 g., 1.1–1.2 mole) (Note 2) is bubbled in through the gas inlet tube with rapid stirring. Sodium methylacetylide precipitates as a flocculent gray solid. The solid carbon dioxide is removed from the condenser, and the ammonia is evaporated overnight under a slow stream of nitrogen. A hot water bath may be used to drive off residual ammonia. One liter of dry tetrahydrofuran (Note 3) and 500 ml. of anhydrous ether are added, and with rapid stirring a slow stream of anhydrous carbon dioxide from a cylinder is passed into the mixture (Note 4). After 8 hours the rate of absorption of carbon dioxide is very slow. Any solid caked on the inside walls of the flask should be scraped off with the glass paddle stirrer. A very slow flow of carbon dioxide is continued overnight (Note 5).

The solvent is removed as completely as possible by distillation on a steam bath under water-pump vacuum. Two hundred milliliters of water is added, and the solid is dissolved by swirling the flask (Note 6). The solution is filtered if suspended solid is present. The aqueous solution is extracted twice with 100-ml. portions of ether. The aqueous layer in a 1-l. Erlenmeyer flask is then cooled in ice, and a mixture of 70 ml. of concentrated hydrochloric acid and 200 g. of ice is added slowly with swirling. The acidified solution

is continuously extracted with 200 ml. (or more) of ether for 24–36 hours. The extract is evaporated in a stream of air or nitrogen to give tetrolic acid in the form of a mushy tan solid that is further dried in a vacuum desiccator over concentrated sulfuric acid for 2 days (Note 7). The product is a tan crystalline solid weighing 58–60 g. (69–71% based on sodium) and melting at 71–75°. It is purified further by addition to 700 ml. of boiling hexane. As soon as the tetrolic acid has dissolved, about 1 g. of activated carbon is added, and the solution is filtered through a heated funnel (Note 8). The filtrate is refrigerated (5°) overnight and 42–50 g. (50–59%) (Note 9) of tetrolic acid is collected in the form of white needles, m.p. 76–77°. A second recrystallization from hexane gives tetrolic acid melting at 76.5–77° (Note 10).

2. Notes

1. The first few pieces of sodium should be converted to sodium amide as evidenced by a color change from blue to gray. The rest of the sodium is then added over a period of 30 minutes.
2. An excess may be used if the purity of the methylacetylene is in doubt; however, a large excess will result in foaming when the liquid ammonia is later evaporated. Methylacetylene of satisfactory purity is available from the Matheson Company.
3. The tetrahydrofuran is distilled from sodium and stored under nitrogen.
4. When a flow rate of 70–100 ml. per minute is used, the internal temperature does not rise above 30° and most of the carbon dioxide is absorbed. A lower yield (50%) of product is obtained when carbon dioxide gas is generated by the slow evaporation of commercial solid carbon dioxide. *[Caution! See p. 976.]*
5. The reaction is complete when the addition of a small amount of the solid to a few drops of water yields a solution with a pH below 10.
6. Residual tetrahydrofuran may separate as a second (upper) phase. It is removed by the ether extraction.
7. To avoid spattering of the solid the desiccator is evacuated slowly. If drying is incomplete, an aqueous layer will be left in the hexane solution when the tetrolic acid is recrystallized.
8. Prolonged boiling should be avoided since some tetrolic acid is lost by volatilization.
9. The submitters obtained yields of tetrolic acid as high as 67.2 g. (80%).
10. In one run the submitters passed excess methylacetylene (1.6 moles) into a solution of sodium in liquid ammonia until the color turned from blue to white. No ferric nitrate was used. This somewhat shorter procedure yielded pure white sodium methylacetylide and did not diminish the yield of tetrolic acid. Excess methylacetylene is necessary because 0.5 mole is converted to propylene.

3. Discussion

Tetrolic acid has been prepared by treatment of acetoacetic ester with phosphorus pentachloride followed by dehydrochlorination of the reaction products;[2] by the base-

catalyzed isomerization of 3-butynoic acid;[3] and by the treatment of 4,4-dibromo-3-methyl-2-pyrazolin-5-one with alkali followed by acidification.[4]

It has also been prepared by the carbonation of sodium methylacetylide under pressure,[5,6] in ether suspension,[7] and in the dry state.[8]

4. Merits of Preparation

The virtue of the present method is its convenience, especially when pressure equipment is not available. This method is probably generally applicable to the synthesis of acetylenecarboxylic acids from terminal acetylenes. Thus phenylpropiolic acid was prepared from phenylacetylene in 51% yield by the present procedure.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

acetoacetic ester

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ether (60-29-7)

phosphorus pentachloride (10026-13-8)

propylene (115-07-1)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

carbon (7782-42-5)

sodium (13966-32-0)

Phenylacetylene (536-74-3)

Phenylpropiolic acid (637-44-5)

sodium amide (7782-92-5)

Tetrahydrofuran (109-99-9)

ferric nitrate

hexane (110-54-3)

methylacetylene (74-99-7)

2-butynoic acid, Tetrolic acid (590-93-2)

ferric nitrate nonahydrate

Sodium methylacetylide

3-butynoic acid (2345-51-9)

4,4-dibromo-3-methyl-2-pyrazolin-5-one

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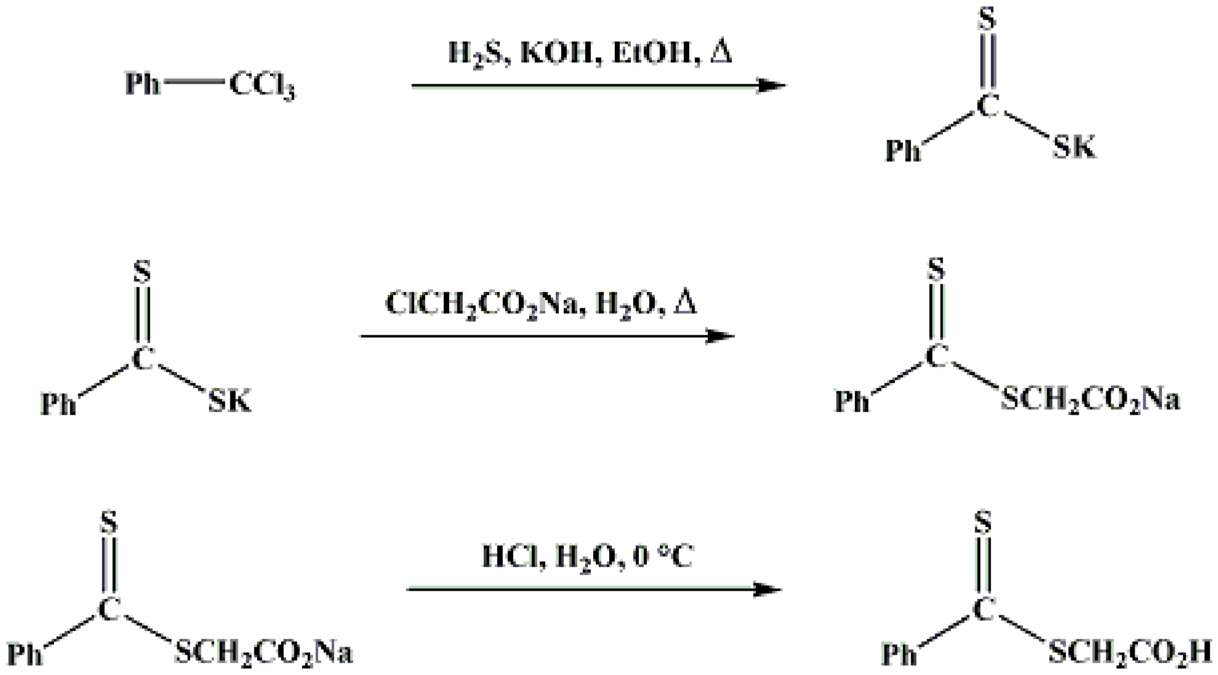
Organic Syntheses, CV 5, 1046

THIOBENZOYLTHIOGLYCOLIC ACID

[Benzoic acid, dithio-, carboxymethyl ester]



Submitted by Frederick Kurzer and Alexander Lawson[1].
Checked by Max Tishler, G. A. Stein, and W. F. Jankowski.

1. Procedure

A solution of alcoholic caustic potash, prepared by dissolving 59.3 g. of 85% potassium hydroxide (0.90 mole) in 400 ml. of absolute ethanol with warming, is divided into two equal portions, one of which is saturated with hydrogen sulfide at room temperature (Note 1). The recombined solutions are placed in a 1-l. three-necked flask fitted with a Hershberg stirrer (Note 2), a gas delivery tube (Note 3), and a reflux condenser carrying a dropping funnel (Note 4). The air is displaced from the apparatus by passing a stream of nitrogen through the stirred liquid (Note 5). The solution is warmed to approximately 45–50°, and 49 g. (35 ml., 0.25 mole) of benzotrichloride is added dropwise through the condenser from a dropping funnel at a rate to maintain the temperature of the reaction mixture at approximately 60°; this requires 1–1.5 hours (Note 6). The reaction mixture turns deep red soon after the addition is started. When all the benzotrichloride has been added, the stirred deep-red suspension is refluxed gently for 30 minutes. A solution of 33.1 g. (0.35 mole) of chloroacetic acid in 200 ml. of water, neutralized with 29.4 g. (0.35 mole) of solid sodium bicarbonate, is next rapidly added through the condenser, the stirred mixture heated to boiling as rapidly as possible and refluxed (Note 5) for 5 minutes.

The resulting brownish red suspension is added to 750–1000 g. of ice contained in a 2-

l. beaker (Note 7) and the turbid orange solution slowly acidified (to Congo red) with good stirring (Note 8) by the addition of approximately 50 ml. (Note 9) of concentrated hydrochloric acid. The deep-scarlet crystalline precipitate is collected at the pump after 30 minutes at 0° and rinsed with small quantities of water.

The air-dried product is crystallized by dissolving it in chloroform (approximately 120 ml.), followed by dilution of the filtered boiling liquid (Note 10) with hot petroleum ether (boiling range 60–80°, 60–80 ml.). The crystalline product, which separates rapidly, is collected at 0°, rinsed on the filter with a mixture of chloroform and petroleum ether (1:3), and dried. The yield of magnificent deep-scarlet lustrous prisms, m.p. 127–128°, varies between 28.9 and 30.4 g. (54–57% of the theoretical). Concentration of the combined filtrates and wash liquids under reduced pressure to a small volume (50–80 ml.) yields an additional small quantity (1.5–3.0 g., 3–6%) of material of satisfactory purity, m.p. 121–124°.

2. Notes

1. Saturation is complete when a slow stream of gas is passed through the solution during 2.5–3 hours. The initially turbid liquid generally clears and remains nearly colorless during this process.
The checkers on several occasions obtained a small amount of a flocculent precipitate that most probably was potassium carbonate.
2. The checkers used a Trubore stirrer with a Teflon paddle.
3. The delivery tube is fitted to allow the stream of nitrogen to enter as far under the surface of the liquid as possible without obstructing the operation of the stirring device.
4. The checkers used a pressure-equalizing dropping funnel.
5. The passage of nitrogen is continued throughout the experiment.
6. The exothermic nature of the reaction maintains the temperature of the mixture between 50° and 60°, depending upon the rate of the addition of the benzotrichloride.
7. The checkers used a 3-l., wide-necked, round-bottomed flask equipped with a mechanical stirrer.
8. Some unmelted ice should remain during the acidification, which is carried out slowly at 0°, to prevent the separation of the crude material in the form of an oil.
9. The checkers found that 25–30 ml. of concentrated hydrochloric acid was sufficient.
10. The submitters filtered the solution rapidly with suction through a preheated Büchner funnel. The checkers found that the product often crystallized too rapidly and plugged the filter. As a result, the crude product was dissolved in an excess of chloroform (160–175 ml.), then filtered, and the excess solvent evaporated before dilution with light petroleum ether. In some cases, no filtration was necessary because the chloroform solution was clear.

3. Discussion

Thiobenzoylthioglycolic acid has been prepared by the interaction of potassium dithiobenzoate and alkali chloroacetate.[2,3,4] The required intermediate, dithiobenzoic acid, has been obtained from phenylmagnesium bromide and carbon disulfide,[2,3,5] or by the condensation of benzaldehyde and hydrogen polysulfides,[2,6] or most conveniently by treatment of benzotrichloride with potassium hydrogen sulfide.[2,4,7] The last procedure has been adapted here to afford improved yields.

4. Merits of Preparation

Thiobenzoylthioglycolic acid is a useful thiobenzoylating agent,[2,3,4,8,9,10,11,12] and the resulting products find application for the synthesis of various heterocycles. These applications of thiobenzoylthioglycolic acid have recently been reviewed.[13]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

ethanol (64-17-5)

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

chloroform (67-66-3)

sodium bicarbonate (144-55-8)

hydrogen sulfide (7783-06-4)

nitrogen (7727-37-9)

benzaldehyde (100-52-7)

chloroacetic acid, chloroacetate (79-11-8)

potassium hydroxide (1310-58-3)

benzotrichloride (98-07-7)

carbon disulfide (75-15-0)

potassium hydrogen sulfide (1310-61-8)

Phenylmagnesium bromide (100-58-3)

Thiobenzoylthioglycolic acid

Benzoic acid, dithio-, carboxymethyl ester (942-91-6)

potassium dithiobenzoate

dithiobenzoic acid

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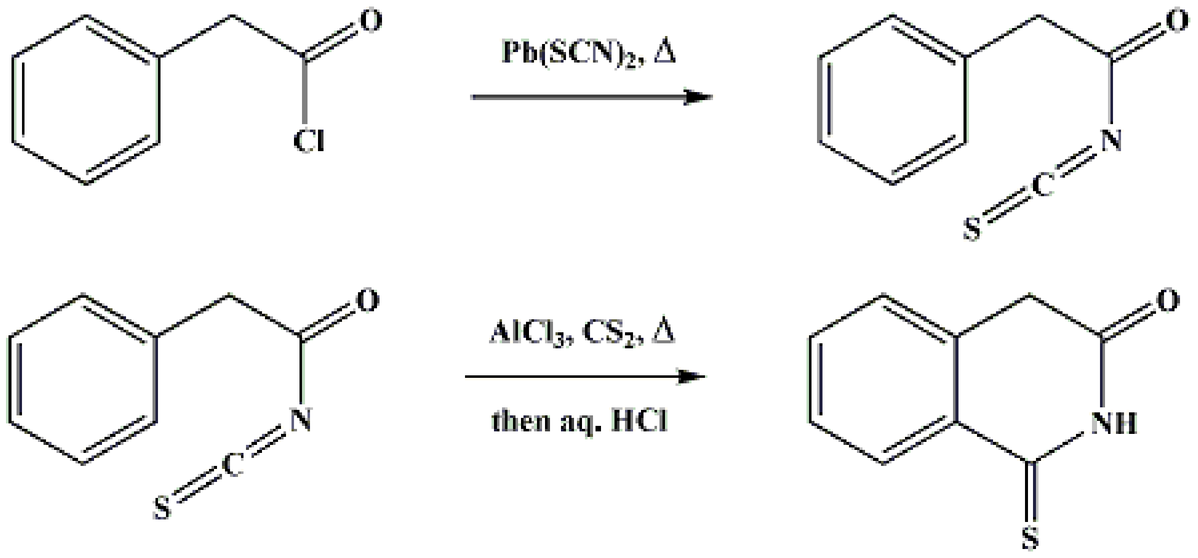
Organic Syntheses, CV 5, 1051

2*a*-THIOHOMOPHTHALIMIDE

[3(2H)-Isoquinolone, 1,4-dihydro-1-thioxo-]



Submitted by P. A. S. Smith and R. O. Kan[1].
Checked by Melvin S. Newman and R. L. Childers.

1. Procedure

A. *Phenylacetyl isothiocyanate*. Twenty-five grams (0.16 mole) of phenylacetyl chloride (Note 1), 100 ml. of benzene, and 53 g. (0.16 mole) of lead thiocyanate (Note 2) are placed in a 1-l., three-necked, round-bottomed flask equipped with a mechanical stirrer and a reflux condenser. The stirrer is started and the mixture is refluxed for 5 hours. A small amount of activated charcoal is added, and refluxing is continued for 5 minutes. The warm mixture is filtered through a Büchner funnel under suction (Note 3), and the solid on the filter is washed with two 50-ml. portions of benzene. The solvent is removed from the filtrate under reduced pressure, and the residue is distilled at once to yield 17.5–22.7 g. (61–79%) of phenylacetyl isothiocyanate, b.p. 83–91° at about 0.3 mm. It is a colorless liquid that rapidly darkens on standing (Note 4) and (Note 5).

B. *2a-Thiohomophthalimide*. In a 500-ml., three-necked, round-bottomed flask equipped with a mechanical stirrer, a reflux condenser, and a dropping funnel are placed 150 ml. of carbon disulfide (Note 6) and 29.3 g. (0.22 mole) of anhydrous powdered aluminum chloride. The stirrer is started, and 17.7 g. (0.10 mole) of phenylacetyl isothiocyanate is added dropwise at such a rate that the solvent refluxes gently. The total addition time is about 5 minutes. The mixture is refluxed gently for 2 hours (Note 7) and is cooled in an ice bath and treated with a solution of 10 ml. of 12*N* hydrochloric acid in 90 ml. of water; the addition is dropwise at first, more rapid later.

Stirring is continued at room temperature for another hour. Crude 2*a*-thiohomophthalimide is collected by filtration on a 10-cm. Büchner funnel and is pressed dry and subsequently dried thoroughly, either in a vacuum desiccator or in an oven at 40–45° *(Caution! (Note 8)*). A solution of the imide in 300 ml. of boiling glacial acetic acid is boiled a few minutes with a small amount of activated charcoal, and the hot solution is filtered through a large fluted filter as rapidly as possible to prevent premature crystallization on the filter. Orange-yellow crystals of 2*a*-homophthalimide precipitate when the filtrate is cooled. They are separated by filtration and dried in an oven or a vacuum desiccator; weight 9.2–13.3 g. (52–75%); m.p. 221–222°.

2. Notes

1. Eastman Kodak Company white label grade of phenylacetyl chloride was used, but equally good results are obtained with the crude acid chloride obtained by treating phenylacetic acid with an excess of thionyl chloride and removing the latter under reduced pressure.
2. Lead thiocyanate was made by stirring together a solution of 45 g. (1.37 moles) of lead nitrate in 360 ml. of boiling water with a solution of 266 g. (2.74 moles) of potassium thiocyanate in 140 ml. of boiling water. The mixture was cooled to room temperature, and 437 g. (99%) of lead thiocyanate was separated by filtration and air-dried.
3. If the filtrate is not clear, filtration should be repeated through the same filter.
4. When large quantities are used, the distillation should be performed in parts, for on prolonged heating phenylacetyl isothiocyanate decomposes with a heavy loss in yield.
5. The distillation should be carried out just before commencing Part B.
6. *sym*-Tetrachloroethane may be substituted for carbon disulfide. In this case 5 minutes of heating on a steam bath, or even no heating at all, gives satisfactory results, although the product is of slightly lower purity. The solvent may be removed quickly by steam distillation of the reaction mixture after addition of dilute acid, and the product is isolated by filtration of the slurry remaining in the flask.
7. The best heating device has been found to be an infrared lamp placed about 20 cm. from the vessel.
8. Drying at higher temperatures can be dangerous because of the low flash-point of carbon disulfide.

3. Discussion

The only reported method of preparation of 2*a*-thiohomophthalimide is by the reaction described here.[2]

4. Merits of the Preparation

This is a general method of converting arylcarbonyl and arylacetyl isothiocyanates to

the corresponding thioimides as the following examples show (percent yield and duration of the reaction follow each example): 6-methyl-1*a*-thiophthalimide[2] (45%, 4 days); 4,6-dimethyl-1*a*-thiophthalimide[2] (64%, 24 hours); 5-methyl-2*a*-thiohomophthalimide (42%, 4 hours); 4-methyl-2*a*-thiohomophthalimide (48%, 4 hours); 5-methoxy-2*a*-thiohomophthalimide (41%, 4 hours); 4-chloro-2-thiohomophthalimide (40%, 4 hours); 1*a*-phenyl-2*a*-thiohomophthalimide (40%, 30 minutes); 1*a*-thio-1,2-naphthalimide[2] (25%, 4 days); 2*a*-thio-1-homo-1,2-naphthalimide[2] (41%, 16 hours); thiophene-2*a*-thio-2,3-dicarboximide (12%, 24 hours).

The thioimides can be hydrolyzed to the corresponding dicarboxylic acids.[3] The thioimides can be converted to the corresponding imides, and thiohomophthalimides can be converted to phthalimides; both conversions are one-step processes.[4] Thus a variety of substituted phthalic and homophthalic acids and their derivatives are available from these thioimides.

Thiohomophthalimides can be reduced to tetrahydroisoquinolines.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 612

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sym-Tetrachloroethane

4-chloro-2-thiohomophthalimide

2a-thio-1-homo-1,2-naphthalimide

thiophene-2a-thio-2,3-dicarboximide

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

thionyl chloride (7719-09-7)

aluminum chloride (3495-54-3)

lead nitrate (10099-74-8)

Phenylacetic acid (103-82-2)

carbon disulfide (75-15-0)

potassium thiocyanate (333-20-0)

phenylacetyl chloride (103-80-0)

2a-homophthalimide

3(2H)-Isoquinolone, 1,4-dihydro-1-thioxo-, 2a-Thiohomophthalimide (938-38-5)

Phenylacetyl isothiocyanate (29313-32-4)

1a-thio-1,2-naphthalimide

lead thiocyanate

6-methyl-1a-thiophthalimide

4,6-dimethyl-1a-thiophthalimide

5-methyl-2a-thiohomophthalimide

4-methyl-2a-thiohomophthalimide

5-methoxy-2a-thiohomophthalimide

1a-phenyl-2a-thiohomophthalimide

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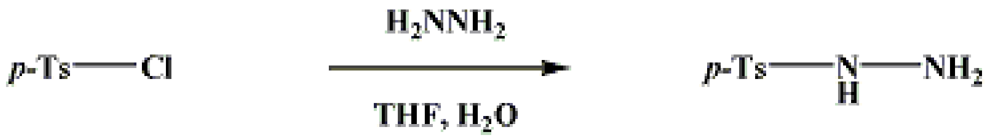
Organic Syntheses, CV 5, 1055

p-TOLUENESULFONYLHYDRAZIDE

[*p*-Toluenesulfonic acid, hydrazide]



Submitted by Lester Friedman, Robert L. Litle[1], and Walter R. Reichle.
Checked by Alan Black and Henry E. Baumgarten.

1. Procedure

Into a 1-l. round-bottomed three-necked flask fitted with a thermometer, a mechanical stirrer, and a dropping funnel are placed 200 g. (1.05 moles) of *p*-toluenesulfonyl chloride and 350 ml. of tetrahydrofuran (Note 1). The stirred mixture is cooled in an ice bath to 10–15°; then a solution of hydrazine in water (135 ml. of 85% hydrazine hydrate, 2.22 moles; (Note 2)) is added at such a rate that the temperature is maintained between 10° and 20° (Note 3). Stirring is continued for 15 minutes after the addition is complete. The reaction mixture is transferred to a separatory funnel. The lower layer is drawn off, and discarded. The upper tetrahydrofuran layer is filtered with suction through a bed of Celite to remove suspended particles and foreign matter (if any). The Celite is washed with a little tetrahydrofuran to remove any absorbed tosylhydrazide. The clear, colorless filtrates are stirred vigorously during the slow addition of two volumes of distilled water. *p*-Toluenesulfonylhydrazide separates as fluffy white crystalline needles (Note 4). The product is filtered through a Büchner funnel; washed several times with distilled water, and air-dried. A yield of 175–185 g. (91–94%) is obtained; m.p. 109–110° (Note 5).

2. Notes

1. According to the submitters, commercial tetrahydrofuran (DuPont) is washed several times with 40% aqueous sodium hydroxide to remove peroxides and organic stabilizers and then dried over solid sodium hydroxide. The clear supernatant liquid is used without further purification. This procedure is no longer regarded as being free from hazard as several serious accidents have occurred during attempts to purify tetrahydrofuran in this fashion. The checkers used a good grade of commercially available tetrahydrofuran taken from a freshly opened bottle (without washing or drying) as recommended in this volume (see p. 976).
2. The submitters diluted 74 ml. of 95% hydrazine with 74 ml. of water. The dilution of hydrazine with water is exothermic. Hydrazine hydrate (50–100%) may be substituted if the volume of water is adjusted so that the resulting

solution contains 50% hydrazine.
3. The addition is complete in 20–25 minutes.
4. Celite analytical filter aid, a product of the Johns-Manville Company, was used.
5. In some runs the checkers found it necessary to chill the mixture in the refrigerator for several hours or to stir the mixture in an ice bath until the product crystalized.
6. The product may be contaminated with trace amounts of N,N'-di-*p*-toluenesulfonylhydrazide. A more nearly pure product may be obtained by dissolving the crude product in hot methanol (4 ml. per gram of hydrazide), filtering through a bed of Celite, and reprecipitating the purified material by addition of 2 to 2.5 volumes of distilled water. This purification step is not necessary for most uses.
The submitters obtained the same yields with quantities as much as ten times those specified here.

3. Discussion

p-Toluenesulfonylhydrazide has been prepared by shaking 50% hydrazine hydrate and *p*-toluenesulfonyl chloride in benzene for several hours.[2,3] Ammonia has been used as an agent for removing the hydrogen chloride evolved.[4] The present procedure is a modification of one previously published in *Organic Syntheses.*[5]

A number of hydrazides have been prepared in comparable yields from their respective sulfonyl chlorides by the procedure cited.[5] These include *p*-bromobenzenesulfonylhydrazide, *p*-chlorobenzenesulfonylhydrazide, *p*-methoxybenzenesulfonylhydrazide, *m*-nitrobenzenesulfonylhydrazide, *p*-nitrobenzensulfonylhydrazide, *o*-nitrobenzenesulfonylhydrazide, benzenesulfonylhydrazide, and methanesulfonylhydrazide.

p-Toluenesulfonylhydrazide has been found to be an exceptionally useful reagent in the synthesis of diazo compounds, olefins, and acetylenes and in the generation of diimide, carbenes, and carbenoid intermediates. Examples are too numerous to cite here; however, leading references may be found in *Reagents for Organic Synthesis.*[6]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 258
- Org. Syn. Coll. Vol. 6, 62
- Org. Syn. Coll. Vol. 6, 172
- Org. Syn. Coll. Vol. 6, 293
- Org. Syn. Coll. Vol. 5, 976

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Celite

N,N'-di-p-toluenesulfonylhydrazide

hydrogen chloride (7647-01-0)

ammonia (7664-41-7)

Benzene (71-43-2)

methanol (67-56-1)

sodium hydroxide (1310-73-2)

hydrazine hydrate (7803-57-8)

hydrazine (302-01-2)

Tetrahydrofuran (109-99-9)

benzenesulfonylhydrazide (80-17-1)

tosylhydrazide

methanesulfonylhydrazide (10393-86-9)

p-Toluenesulfonyl chloride (98-59-9)

o-nitrobenzenesulfonylhydrazide (5906-99-0)

p-Toluenesulfonylhydrazide, p-Toluenesulfonic acid, hydrazide (1576-35-8)

p-bromobenzenesulfonylhydrazide

p-chlorobenzenesulfonylhydrazide

p-methoxybenzenesulfonylhydrazide (1950-68-1)

m-nitrobenzenesulfonylhydrazide

p-nitrobenzensulfonylhydrazide

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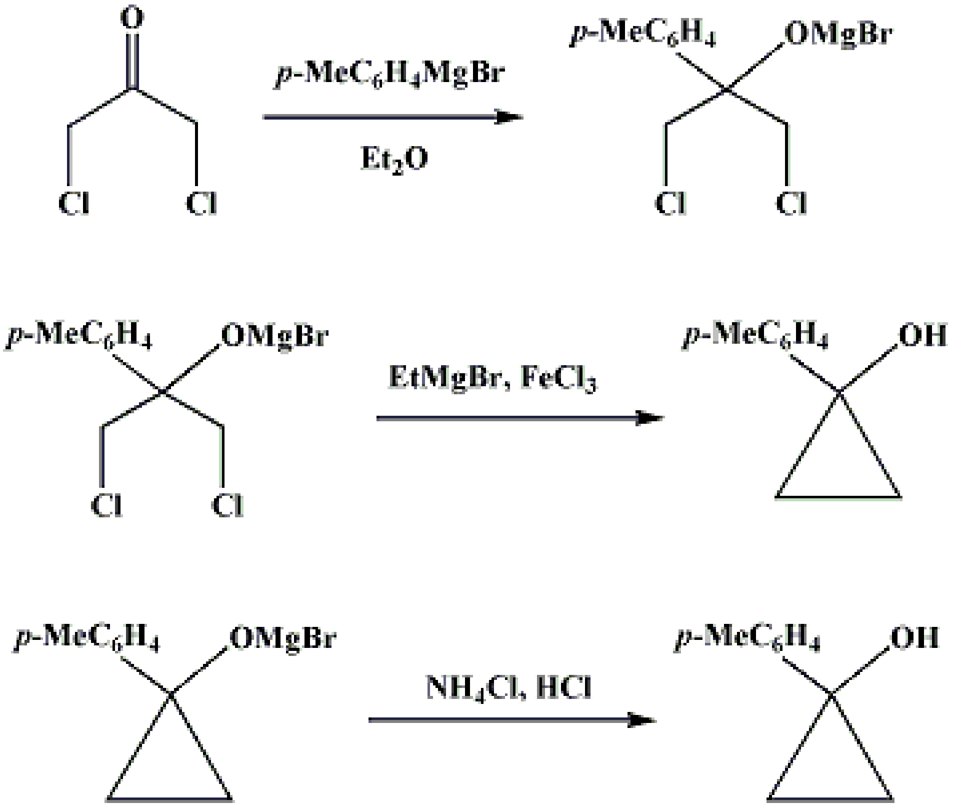
Organic Syntheses, CV 5, 1058

1-*p*-TOLYLCYCLOPROPANOL



Submitted by C. H. DePuy and R. A. Klein[1].
Checked by O. Aniline and K. B. Wiberg.

1. Procedure

In a dry 3-l. three-necked, round-bottomed flask fitted with an efficient reflux condenser, a stirrer, a Y-tube holding a 1-l. and a 250-ml. addition funnel, and protected from moisture by calcium chloride tubes is placed 5.76 g. (0.237 mole) of magnesium turnings barely covered by anhydrous ether. *p*-Bromotoluene (40 drops) and ethyl bromide (20 drops) are added, and the reaction starts immediately. *p*-Bromotoluene (35.0 g., 0.205 mole) in 200 ml. of anhydrous ether is added at such a rate that reflux is maintained. To the resultant solution of *p*-methylphenylmagnesium bromide is added, over a 1-hour period, a solution of 25.4 g. (0.200 mole) of dichloroacetone in 200 ml. of anhydrous ether.

At the same time, in a separate 2-l. three-necked, round-bottomed flask equipped with reflux condenser, stirrer, and addition funnel, ethylmagnesium bromide is prepared from 128.6 g. (1.18 moles) of ethyl bromide and 30 g. (1.23 moles) of magnesium in 800 ml. of anhydrous ether. When the reaction is complete, the addition funnel is replaced by a rubber stopper containing a short glass tube, and the reflux condenser is replaced by an exit tube lightly plugged with a small amount of glass wool. The Grignard reagent solution is forced, under mild nitrogen pressure, through the glass

wool plug into the 1-l. addition funnel (Note 1). In the 250-ml. addition funnel is placed a filtered solution of 2.5 g. (0.0154 mole) of anhydrous ferric chloride in 200 ml. of anhydrous ether. Stirring is resumed, and the two solutions are simultaneously added to the dichloroacetone-*p*-methylphenylmagnesium bromide solution over a 2-hour period (Note 2). Stirring is continued for an additional 14 hours under dry nitrogen.

The reaction mixture is added to a slurry of 1500 g. of ice and 600 ml. of 2*N* hydrochloric acid saturated with ammonium chloride. The ether layer is separated, and the aqueous layer is extracted three times with 200-ml. portions of ether. The combined organic layers are washed with three 200-ml. portions of water until a neutral reaction is obtained with litmus and the wash water is free of chloride. The solution is dried over anhydrous magnesium sulfate and stored in a refrigerator. After evaporation of the ether, the residue is distilled at a low pressure through a short Vigreux column (Note 3). The fraction, b.p. 70–78° (0.4 mm.) (oil bath 100–135°), is collected to give 15–17 g. (51–57%) of the crude carbinol which crystallizes upon standing in an ice box. The product is recrystallized from pentane (4 g. per g. of alcohol) in an ice-salt mixture to give the pure alcohol, m.p. 38–39°.

2. Notes

1. Since the ethyl Grignard reagent is used in large excess, no special precautions need to be taken in the transfer to prevent the loss of small amounts.
2. Large volumes of gas are generated, primarily ethane and ethylene, from the disproportionation of the ethyl radicals produced in the reaction of ethylmagnesium bromide with ferric chloride. The reaction should be carried out in an efficient hood, or else a tube should be run from the top of the reflux condenser to a hood.
3. 1-Arylcyclopropanols readily rearrange to propiophenones under the influence of acids and bases. In carrying out the distillation, care must be taken that the apparatus is clean and neutral.

3. Discussion

The method is that of DePuy and co-workers.[2] No other syntheses of 1-arylcyclopropanols have been reported.

4. Merits of the Preparation

The procedure can be adapted to the preparation, in comparable yield, of a variety of 1-substituted cyclopropanols, alkyl as well as aryl.

References and Notes

1. Department of Chemistry, University of Colorado, Boulder, Colorado.
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(1964).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

ether (60-29-7)

ammonium chloride (12125-02-9)

magnesium (7439-95-4)

Ethyl bromide (74-96-4)

nitrogen (7727-37-9)

ethylene (9002-88-4)

ferric chloride (7705-08-0)

dichloroacetone (513-88-2)

Pentane (109-66-0)

ethylmagnesium bromide (925-90-6)

magnesium sulfate (7487-88-9)

ethane (74-84-0)

p-Bromotoluene (106-38-7)

p-methylphenylmagnesium bromide (4294-57-9)

1-p-Tolylcyclopropanol (40122-37-0)

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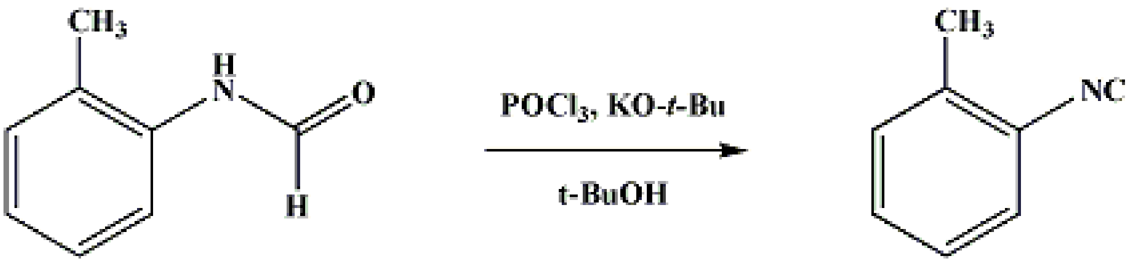
Organic Syntheses, CV 5, 1060

o-TOLYL ISOCYANIDE



Submitted by Ivar Ugi and Rudolf Meyr[1].
Checked by B. C. McKusick and O. W. Webster.

1. Procedure

Caution! Isocyanides should be prepared in a hood since they have pungent odors and some are known to be toxic.

The reaction is conducted in a 2-l. round-bottomed flask equipped with a dropping funnel, Hershberg stirrer, thermometer, and reflux condenser. A T-tube attached to a cylinder of dry nitrogen is inserted in the top of the condenser in order to keep the reaction mixture blanketed with nitrogen.

A suspension of potassium *tert*-butoxide is prepared by a slight modification of the procedure of Johnson and Schneider,[2] *particular attention being paid to the precautions they recommend for safe handling of potassium.* Dry *tert*-butyl alcohol (1250 ml.) is distilled directly into the reaction flask under nitrogen. One hundred grams (2.6 g. atoms) of potassium cut into about ten pieces is added. The stirred mixture spontaneously warms to the melting point of potassium (62°) in the course of 15–60 minutes, whereupon the metal disperses into droplets. As the potassium gradually dissolves, the temperature of the mixture rises to the boiling point of *tert*-butyl alcohol. The rate of solution of the potassium should be such that the *tert*-butyl alcohol refluxes gently, and this rate is regulated by the speed of stirring. If the boiling becomes too vigorous, the stirring is stopped completely, and if necessary the reaction vessel is cooled by immersion in a bath of cold oil kept in readiness for this purpose. Potassium *tert*-butoxide gradually precipitates, and the mixture is a thick suspension when all the potassium has reacted (Note 1).

N-*o*-Tolylformamide (135 g., 1.00 mole) (Note 2) is added to the hot stirred suspension, which becomes a clear solution within a few minutes. The solution is cooled to 10–20° by means of an ice bath and maintained at this temperature while 92 g. (0.60 mole) of phosphorus oxychloride is added to it with stirring over the course of 30–40 minutes. The reaction mixture is stirred at 30–35° for 1 hour and poured into an ice-cold stirred solution of 50 g. of sodium bicarbonate in 5 l. of water (Note 3). *o*-

Tolyl isocyanide precipitates as an oil. It is taken up in 300 ml. of petroleum ether (b. p. 40–60°), and the organic phase is separated in a separatory funnel. The aqueous phase is extracted with three 200-ml. portions of petroleum ether. The combined extracts are washed with 50 ml. of 5% sodium bicarbonate solution, dried over 50 g. of powdered potassium hydroxide, and distilled through a 30-cm. vacuum-jacketed Vigreux column. *o*-Tolyl isocyanide is collected as a colorless, vile-smelling liquid at 61–63°/10 mm.; n_D^{25} 1.5212–1.5222; weight 74–85 g. (63–73%) (Note 4).

2. Notes

1. In order to keep down the volume of the reaction mixture, less *tert*-butyl alcohol is used than is necessary to dissolve the potassium *tert*-butoxide.

2. The checkers prepared N-*o*-tolylformamide[3] as follows. A solution of 100 g. (0.94 mole) of *o*-toluidine and 82 ml. (100 g., 2.13 moles) of 98% formic acid in 300 ml. of toluene is refluxed under a condenser attached to a water separator.[4] After water stops collecting in the separator (about 3 hours), toluene and excess formic acid are removed by distillation under reduced pressure. The crude N-*o*-tolylformamide that remains is recrystallized from toluene to give 95–101 g. (75–80%) of N-*o*-tolylformamide, m.p. 60/61°. If a formamide that melts above the boiling point of *tert*-butyl alcohol is to be converted to an isocyanide by the present procedure, it should be finely pulverized.

3. *o*-Tolyl isocyanide is rather unstable, and in order to get a good yield one should work up the reaction mixture as quickly as possible and avoid unnecessary heating of the crude isocyanide. If the isocyanide is to be stored for a long time, it should be kept at the temperature of Dry Ice.

4. The equipment used in this preparation can be freed of the disagreeable odor of *o*-tolyl isocyanide by being washed with 5% methanolic sulfuric acid.

3. Discussion

o-Tolyl isocyanide has been prepared in 20% yield by the action of chloroform and potassium hydroxide on *o*-toluidine.[5] It has also been prepared by the dehydration of N-*o*-tolylformamide using the phosgene/tertiary amine system in good yield.[6] The present procedure is better than the carbylamine reaction[5] in terms of yield.

Although the use of pohsgene/tertiary amine systems is superior to the present procedure for production of isonitriles, the toxicity of phosgene and the difficulty with which it is handled by the inexperienced worker make it less convenient than the present procedure. For most purposes, this procedure illustrates the best way to prepare aryl isocyanides. It is quite general, having been used by Ugi and Meyr[7] to make the following isocyanides from the corresponding formamides: phenyl (56%), *p*-tolyl (66%), 2,6-dimethylphenyl (88%), mesityl (80%), *o*-chlorophenyl (43%), *p*-chlorophenyl (54%), 2-chloro-6-methylphenyl (87%), *p*-methoxyphenyl (64%), *p*-diethylaminophenyl (75%), *p*-nitrophenyl (41%), and 2-naphthyl (50%). Aliphatic

isonitriles are generally best prepared by a simpler procedure involving the action of phosphorus oxychloride on an N-alkylformamide in the presence of pyridine.[8]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 300
- Org. Syn. Coll. Vol. 5, 772
- Org. Syn. Coll. Vol. 6, 232

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

sulfuric acid (7664-93-9)

chloroform (67-66-3)

sodium bicarbonate (144-55-8)

formic acid (64-18-6)

nitrogen (7727-37-9)

Phosphorus Oxychloride (21295-50-1)

pyridine (110-86-1)

potassium hydroxide (1310-58-3)

toluene (108-88-3)

phosgene (75-44-5)

potassium (7440-09-7)

tert-butyl alcohol (75-65-0)

o-toluidine (95-53-4)

potassium tert-butoxide (865-47-4)

N-o-Tolylformamide (94-69-9)

o-Tolyl isocyanide (10468-64-1)

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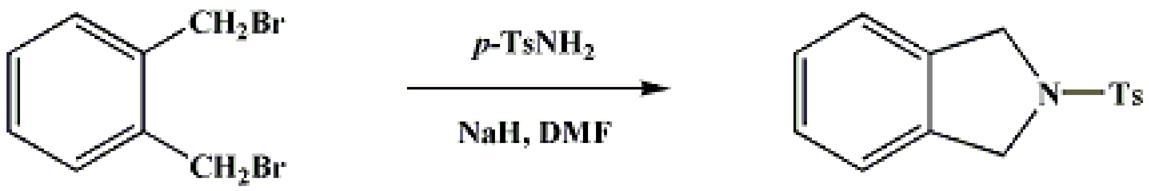
Organic Syntheses, CV 5, 1064

2-(*p*-TOLYLSULFONYL)DIHYDROISOINDOLE

[Isoindoline, 2-*p*-tolylsulfonyl-]



Submitted by J. Bornstein and J. E. Shields[1].
Checked by Rosetta McKinley and R. E. Benson.

1. Procedure

Caution! This reaction should be carried out in a good hood because hydrogen is evolved and o-xylylene dibromide is a powerful lachrymator (Note 6).

A 1-l. three-necked flask is fitted with an efficient stirrer (Note 1), thermometer, condenser, and a pressure-equalizing dropping funnel that carries an inlet for admission of dry nitrogen. The entire apparatus is dried by warming with a soft flame as a brisk stream of nitrogen is passed through the system. The flow of nitrogen is reduced to a slow stream, and in the cooled flask are placed 18.9 g. (0.42 mole) of 53% sodium hydride dispersed in mineral oil (Note 2) and 60 ml. of purified dimethylformamide (Note 3). The mixture is stirred at room temperature and a solution of 34.2 g. (0.20 mole) of *p*-toluenesulfonamide (Note 4) in 100 ml. of purified dimethylformamide is added dropwise over a period of 1 hour. The resulting suspension is stirred at room temperature for 1 hour and then at 60° for an additional hour (Note 5).

A solution of 52.8 g. (0.20 mole) of *o*-xylylene dibromide (Note 6) in 300 ml. of purified dimethylformamide is added dropwise with stirring at such a rate as to maintain a temperature of 60–70° (Note 7). Subsequently the reaction mixture is stirred at room temperature for 3 hours and then poured into 600 ml. of ice water in a 2-l. Erlenmeyer flask. After standing at room temperature overnight the product is collected by suction filtration, pressed on the funnel, and washed twice with 100-ml. portions of water. The crude product is air-dried on filter paper for 2–3 hours and is then dissolved in 1.2 l. of boiling 95% ethanol. The solution is filtered through a heated funnel, and the filtrate is refrigerated overnight. The crystals are collected on a Buchner funnel and washed on the funnel with 100 ml. of cold 95% ethanol. The product is dried over phosphorus pentoxide in a vacuum desiccator. The yield of white crystals of 2-(*p*-tolylsulfonyl)dihydroisoindole is 41–46 g. (75–84%), m.p. 174–175° (dec.).

2. Notes

1. Either a paddle-type sealed stirrer or a heavy-duty magnetic stirrer is suitable.
2. Sodium hydride was obtained from Metal Hydrides Division of Ventron Corporation, Beverly, Massachusetts.
3. Dimethylformamide, b.p. 152–154°, purchased from Matheson, Coleman and Bell, was stirred for 5 minutes with solid potassium hydroxide, decanted, shaken briefly with lime, filtered, and distilled.
4. Commercial *p*-toluenesulfonamide of high purity was recrystallized from water and dried over phosphorus pentoxide in a vacuum desiccator, m.p. 134–135°.
5. It is necessary to maintain vigorous stirring at this stage to prevent excessive foaming due to the evolution of hydrogen.
6. Precautions to be observed in handling *o*-xylylene dibromide are described in *Org. Syntheses*, Coll. Vol. **4**, 984 (1963). The dibromide was purchased from Eastman Organic Chemicals, recrystallized from 95% ethanol (3 ml./g.), and dried over potassium hydroxide in a vacuum desiccator, m.p. 89–91°.
7. Control of the temperature at this point is critical; a deeply colored product is obtained if the temperature is allowed to exceed 70°. The addition of the dibromide requires about 1 hour.

3. Discussion

2-(*p*-Tolylsulfonyl)dihydroisoindole has been prepared by alkylation of *p*-toluenesulfonamide with *o*-xylylene dibromide in the presence of sodium methoxide in ethanol.[2,3]

4. Merits of the Preparation

This is the most practical procedure for the preparation of 2-(*p*-tolylsulfonyl)dihydroisoindole. It is superior to earlier ones[2,3] because it is more convenient and affords considerably higher yields (*ca.* 80% versus *ca.* 45%).

The method illustrates the ability of the sodium hydridedimethylformamide system to effect the alkylation of aromatic sulfonamides under mild conditions and in good yield. The method appears to be fairly general. The submitters have prepared N,N-diethyl- and N,N-di-*n*-butyl-*p*-toluenesulfonamide as well as 2-(*p*-tolylsulfonyl)benz[*f*]isoindoline from 2,3-bis-(bromomethyl)naphthalene, and 1-(*p*-tolylsulfonyl)pyrrolidine from 1,4-dichlorobutane; the yield of purified product exceeded 75% in each case.

The reductive cleavage of 2-(*p*-tolylsulfonyl)dihydroisoindole to 1,3-dihydroisoindole constitutes the most convenient synthesis of this heterocyclic compound.[3] The sulfonamide is also useful in the synthesis of isoindole.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 406

References and Notes

1. Department of Chemistry, Boston College, Chestnut Hill, Massachusetts 02167.
2. G. W. Fenton and C. K. Ingold, *J. Chem. Soc.*, 3295 (1928).
3. J. Bornstein, S. C. Lashua, and A. P. Boisselle, *J. Org. Chem.*, **22**, 1255 (1957).
4. R. Kreher and J. Seubert, *Z. Naturforsch.*, **20b**, 75 (1965).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

N,N-diethyl- and N,N-di-n-butyl-p-toluenesulfonamide

ethanol (64-17-5)

hydrogen (1333-74-0)

nitrogen (7727-37-9)

sodium methoxide (124-41-4)

potassium hydroxide (1310-58-3)

1,4-dichlorobutane (110-56-5)

dimethylformamide (68-12-2)

sodium hydride (7646-69-7)

o-Xylylene dibromide (91-13-4)

1,3-Dihydroisoindole (496-12-8)

2,3-bis-(bromomethyl)naphthalene

isoindole

phosphorus pentoxide (1314-56-3)

p-toluenesulfonamide (70-55-3)

2-(p-Tolylsulfonyl)dihydroisoindole, Isoindoline, 2-p-tolylsulfonyl- (32372-83-1)

2-(p-tolylsulfonyl)benz[f]isoindoline

1-(p-tolylsulfonyl)pyrrolidine

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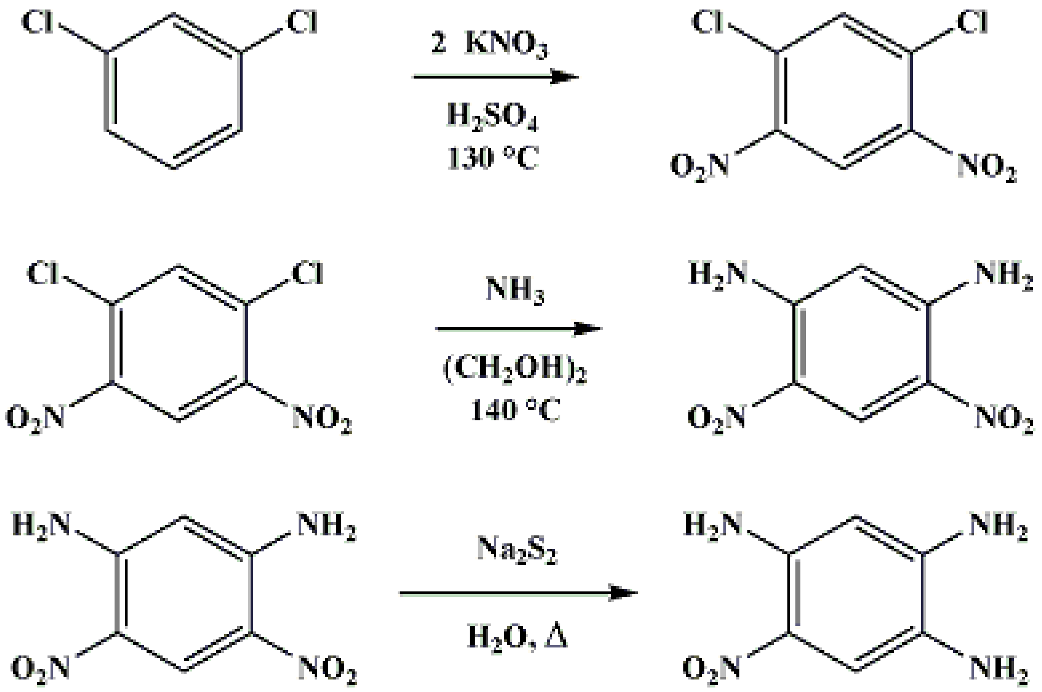
Organic Syntheses, CV 5, 1067

2,4,5-TRIAMINONITROBENZENE

[1,2,4-Benzenetriamine, 5-nitro-]



Submitted by J. H. Boyer and R. S. Buriks[1].
Checked by James Cason and Taysir M. Jaouni.

1. Procedure

A. *1,5-Dichloro-2,4-dinitrobenzene* *Caution!* (Note 1). To a well-stirred solution of 140 g. (1.386 moles) of potassium nitrate in 500 ml. of concentrated sulfuric acid is added 100.0 g. (0.680 mole) of *m*-dichlorobenzene in one portion. The temperature of the reaction mixture rises during a few minutes to 135–140°, then drops slowly to 125°. The stirred mixture is kept at 120–135° for an additional hour. After the reaction mixture has been cooled to about 90° it is poured over 1.5 kg. of crushed ice. The precipitated product is collected by suction filtration, drained well on the funnel, and dissolved in about 1 l. of boiling 95% ethanol. A small amount of insoluble impurity is removed by filtration of the hot solution by gravity through a fluted filter paper, and the product is allowed to crystallize in the refrigerator at about 0° (Note 2). The yield of yellow needles is 112–115 g. (70–71.5%), m.p. 103–104°.

B. *1,5-Diamino-2,4-dinitrobenzene* Ammonia gas from a tank is bubbled into a well-stirred, clear yellow solution of 60.0 g. (0.253 mole) of 1,5-dichloro-2,4-dinitrobenzene in 400 ml. of technical grade ethylene glycol (heated to 140°), at such a rate that the gas is just absorbed. Within 30 minutes the color of the solution changes through orange to deep red. About 1 hour after the start of the reaction an orange, crystalline precipitate begins to separate. Heating is continued for an additional 2

hours as a slow stream of ammonia gas is bubbled through the reaction mixture. Finally, the reaction mixture is cooled to room temperature, the product is collected by suction filtration, and the finely divided orange-brown crystals are washed with boiling water and boiling ethanol. The yield of dried product, m.p. 300° (subl.), is 44–48 g. (88–95.5%) (Note 3).

C. *2,4,5-Triaminonitrobenzene*. A well-stirred slurry (Note 4) of 22.5 g. (0.114 mole) of 1,5-diamino-2,4-dinitrobenzene in 150 ml. of water is heated (Note 4) to the boiling point under reflux in a 500-ml. three-necked flask. To this vigorously stirred mixture, a clear orange-red solution of sodium polysulfide (prepared by heating a mixture of 30.0 g. of sodium sulfide nonahydrate, 7.25 g. of sulfur, and 125 g. of water) is added dropwise during a period of 1.5 hours. After completion of the addition, reflux of the well-stirred reaction mixture is maintained for an additional 1.5 hours. The resultant deep red mixture is cooled to 0° and the total insoluble material is collected by suction filtration. This residue of product, sulfur, and some starting material is thoroughly extracted with five 200-ml. portions of boiling water. The combined hot extracts are filtered by gravity and cooled to room temperature to yield 9.5–10.0 g. (49.5–52%) of red needles, m.p. 200–207°, of 2,4,5-triaminonitrobenzene.

2. Notes

1. Unnecessary contact with dichlorodinitrobenzene should be avoided. It is a skin irritant and may cause severe blisters.
2. When a first crop of crystals was collected at room temperature and a second at 0°, the two lots exhibited the same melting point. When the filtrate from crystallization at 0° was concentrated to about 500 ml., the small crop of additional crystals had a much lower melting point.
3. The product is very slightly soluble in most solvents. It was used satisfactorily in the next step without further purification. Melting with sublimation occurs between 285° and 300°, depending on the rate of heating.
4. The submitters report that the best yield in this heterogeneous reaction depends upon particle size of the diaminodinitrobenzene and efficient stirring, and that the diamine should be thoroughly ground in a mortar before use. The checkers found that grinding had no effect on the yield if heating was in an oil bath. Heating with a flame or heating mantle caused some caking and charring on the bottom of the flask, even with rather efficient stirring, and in one run the bottom of the flask dropped out during the reaction.

3. Discussion

1,5-Dichloro-2,4-dinitrobenzene has been prepared from *m*-dichlorobenzene and nitric acid[2] or potassium nitrate[3] in the presence of sulfuric acid. 1,5-Diamino-2,4-dinitrobenzene has been prepared by the nitration of *m*-*bis*-acetamidobenzene followed by hydrolysis;[4] or from 1,5-dichloro-2,4-dinitrobenzene and alcoholic ammonia in a pressure bottle at 150° for 8 hours.[2,5] The preparation and characterization of

previously unknown 2,4,5-triaminonitrobenzene will be published elsewhere.

The present procedures represent simplified methods for obtaining the subject compounds and for accomplishing the illustrated conversions.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 27

References and Notes

1. Department of Chemistry, Tulane University, New Orleans, Louisiana.
2. R. Nietzki and A. Schedler, *Ber.*, **30**, 1666 (1897).
3. Footnote No. 7 in Th. Zincke, *Ann.*, **370**, 302 (1909) refers to this method used by Fries.
4. R. Nietzki and E. Hagenbach, *Ber.*, **20**, 328, 2114 (1887).
5. P. Ruggli and R. Fischer, *Helv. Chim. Acta*, **28**, 1270 (1945).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium polysulfide

ethanol (64-17-5)

sulfuric acid (7664-93-9)

ammonia (7664-41-7)

nitric acid (7697-37-2)

sulfur (7704-34-9)

ethylene glycol (107-21-1)

potassium nitrate (7757-79-1)

sodium sulfide nonahydrate (1313-84-4)

2,4,5-Triaminonitrobenzene, 1,2,4-Benzenetriamine, 5-nitro- (6635-35-4)

1,5-Dichloro-2,4-dinitrobenzene (3698-83-7)

1,5-Diamino-2,4-dinitrobenzene (4987-96-6)

dichlorodinitrobenzene

diaminodinitrobenzene

m-dichlorobenzene (541-73-1)

m-bis-acetamidobenzene (10268-78-7)

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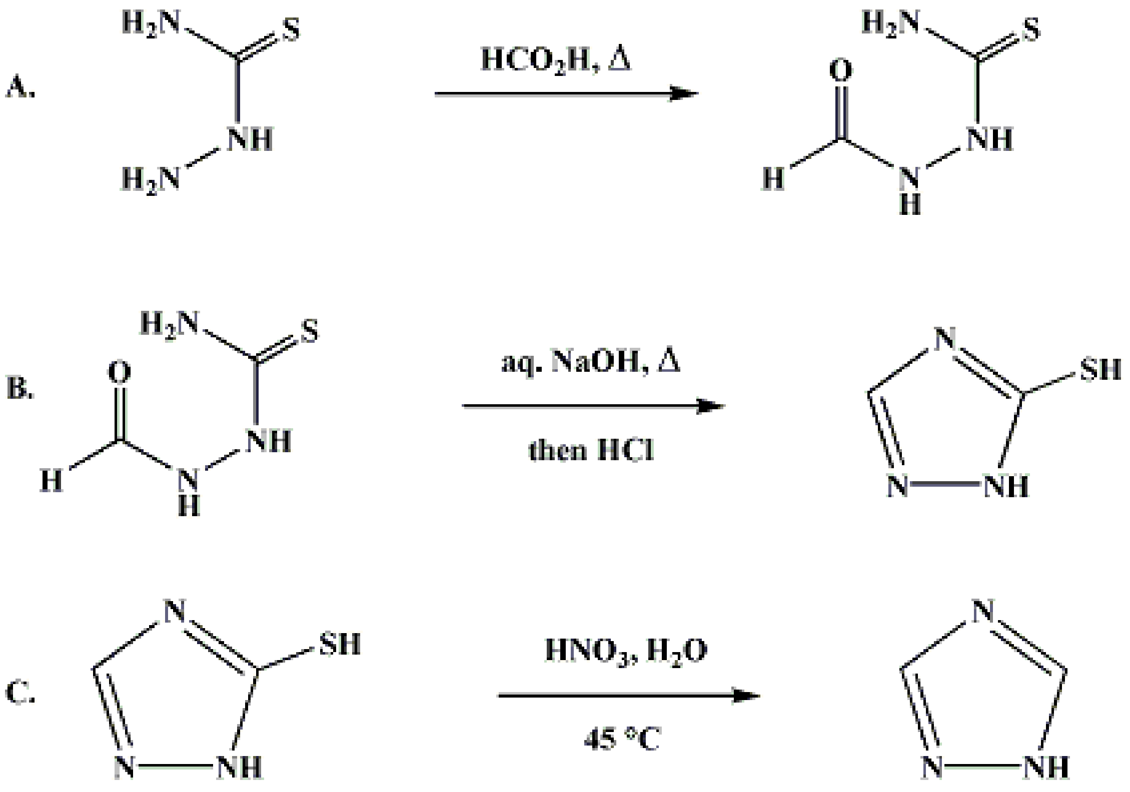
Organic Syntheses, CV 5, 1070

1,2,4-TRIAZOLE

[1H-1,2,4-Triazole]



Submitted by C. Ainsworth[1]
Checked by B. C. McKusick and B. C. Anderson.

1. Procedure

(Note 1)

A. *1-Formyl-3-thiosemicarbazide*. Four hundred milliliters of 90% formic acid contained in a 2-l. round-bottomed flask is heated on a steam bath for 15 minutes, and then 182 g. (2 moles) of colorless thiosemicarbazide (Note 2) is added. The mixture is swirled until the thiosemicarbazide dissolves. The heating is continued for 30 minutes, during which time crystalline 1-formyl-3-thiosemicarbazide usually separates. Boiling water (600 ml.) is added, and the milky solution that results is filtered through a fluted filter paper. After standing for 1 hour, the filtrate is cooled in an ice bath for 2 hours, and the 1-formyl-3-thiosemicarbazide that separates is collected by suction filtration and air-dried overnight. It weighs 170–192 g. (71–81%) and melts at 177–178° with decomposition.

B. *1,2,4-Triazole-3(5)-thiol*. A solution of 178.5 g. (1.5 moles) of 1-formyl-3-thiosemicarbazide and 60 g. (1.5 moles) of sodium hydroxide in 300 ml. of water in a 2-l. round-bottomed flask is heated on a steam bath for 1 hour. The solution is cooled

for 30 minutes in an ice bath and then is treated with 150 ml. of concentrated hydrochloric acid. The reaction mixture is cooled in an ice bath for 2 hours, and the 1,2,4-triazole-3(5)-thiol that precipitates is collected by suction filtration. The thiol is dissolved in 300 ml. of boiling water and the solution is filtered through a fluted filter paper. The filtrate is cooled in an ice bath for 1 hour, and the thiol is collected by suction filtration and air-dried overnight. The 1,2,4-triazole-3(5)-thiol weighs 108–123 g. (72–81%) and melts at 220–222°.

C. *1,2,4-Triazole*. *Caution! This preparation should be carried out in a ventilated hood to avoid exposure to noxious fumes.*

A mixture of 300 ml. of water, 150 ml. of concentrated nitric acid, and 0.2 g. of sodium nitrite (Note 3) is placed in a 2-l. three-necked flask equipped with a stirrer and a thermometer. The stirred mixture is warmed to 45°, and 2 g. of 1,2,4-triazole-3(5)-thiol is added. When oxidation starts, as indicated by the evolution of brown fumes of nitrogen dioxide and a rise in temperature, a bath of cold water is placed under the reaction flask to provide cooling and an additional 99 g. (total, 101 g.; 1 mole) of 1,2,4-triazole-3(5)-thiol is added in small portions over the course of 30–60 minutes. The rate of addition and the extent of cooling by the water bath are so regulated as to keep the temperature close to 45–47° all during the addition. The water bath is kept cold by the occasional addition of ice.

When the addition is completed, the bath is removed and stirring is continued for 1 hour while the reaction mixture gradually cools to room temperature. Sodium carbonate (100 g.) is added in portions, followed by the cautious addition of 60 g. of sodium bicarbonate (Note 4). The water is removed from the slightly basic solution by heating the solution in a 3-l. round-bottomed flask under reduced pressure on a steam bath. To aid in removing the last traces of water, 250 ml. of ethanol is added to the residue and the mixture is heated under reduced pressure on a steam bath until it appears dry (Note 5).

The residue is extracted twice with 600 ml. of boiling ethanol to separate the triazole from a large amount of inorganic salts. This extract is evaporated to dryness on a steam bath under reduced pressure, and the resulting residue is extracted with two 500-ml. portions of boiling ethyl acetate. The ethyl acetate extract is evaporated to dryness on a steam bath under reduced pressure. The crude 1,2,4-triazole remaining in the flask is dissolved by heating it with 50 ml. of absolute ethanol, and then 1 l. of benzene is added. The mixture is heated under reflux for 15 minutes, and the hot solution is filtered through a fluted filter paper. This extraction procedure is repeated. The two extracts are combined, cooled in an ice bath for 30 minutes, and filtered to remove colorless crystals of 1,2,4-triazole (m.p. 120–121°), weighing 28–30 g. after being dried in air. About 300 ml. of the filtrate is removed by slow distillation through a Claisen still-head to remove the bulk of the ethanol. The residual solution is cooled in an ice bath for 30 minutes and filtered to separate an additional 8–10 g. of colorless 1,2,4-triazole, m.p. 119–120°. The total weight of 1,2,4-triazole is 36–40 g. (52–58% yield).

2. Notes

1. This procedure is no longer regarded as the best available for the preparation of 1,2,4-triazole. See Discussion section.
2. The thiosemicarbazide must be of good quality or the yield and quality of 1-formyl-3-thiosemicarbazide will suffer. The thiosemicarbazide supplied by Olin Mathieson Chemical Corporation, obtained as a colorless free-flowing powder, can be used without purification.
3. The use of sodium nitrite helps to avoid an induction period.
4. A large flask is used to contain the vigorous effervescence that occurs upon the addition of carbonate. The final pH should be near 7.5, and it is reached after the addition of bicarbonate no longer causes bubbling.
5. Prolonged heating under reduced pressure should be avoided, since 1,2,4-triazole tends to sublime.

3. Discussion

1-Formyl-3-thiosemicarbazide has been prepared by the reaction of thiosemicarbazide and formic acid.[2]

1,2,4-Triazole-3(5)-thiol has been prepared by heating thiosemicarbazide and formic acid,[3] by heating 1-formyl-3-thiosemicarbazide,[3] and by heating 1,3,5-triazine and thiosemicarbazide.[4] The ring closure of 1-formyl-3-thiosemicarbazide using aqueous base was suggested by L. F. Audrieth and F. Hersman.

1,2,4-Triazole has been prepared by the oxidation of substituted 1,2,4-triazoles,[5] by the treatment of urazole with phosphorus pentasulfide,[6] by heating equimolar quantities of formylhydrazine and formamide,[7] by removal of the amino function of 4-amino-1,2,4-triazole,[8] by oxidation of 1,2,4-triazole-3(5)-thiol with hydrogen peroxide,[3] by decarboxylation of 1,2,4-triazole-3(5)-carboxylic acid,[9] by heating hydrazine salts with formamide,[10] by rapidly distilling hydrazine hydrate mixed with two molar equivalents of formamide,[11] by heating N,N'-diformylhydrazine with excess ammonia in an autoclave at 200° for 24 hours,[11] by the reaction of 1,3,5-triazine and hydrazine monohydrochloride,[12] and by the deamination of 3-amino-1,2,4-triazole with hypophosphorous acid.[13] In view of the availability of 3-amino-1,2,4-triazole in several grades and from several commercial sources, the last-cited procedure, that of Henry and Finnegan,[13] is considered to be preferable to that described here for the preparation of 1,2,4-triazole itself.[14] The Henry and Finnegan procedure has been found to be useful for the deamination of a wide variety of heteroaromatic amines.[15]

Modifications of the present procedure for the preparation of 1,2,4-triazole have been used to prepared 3-aryl-1,2,4-triazoles[16] and 3-alkyl-1,2,4-triazoles.[17]

References and Notes

1. The Lilly Research Laboratories, Indianapolis, Indiana.
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hypophosphorous acid

1,2,4-Triazole-3(5)-thiol

1,2,4-triazole-3(5)-carboxylic acid

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

Benzene (71-43-2)

ethyl acetate (141-78-6)

formamide (75-12-7)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

nitric acid (7697-37-2)

sodium carbonate (497-19-8)

formic acid (64-18-6)

sodium nitrite (7632-00-0)

hydrogen peroxide (7722-84-1)

nitrogen dioxide (10102-44-0)

hydrazine hydrate (7803-57-8)

phosphorus pentasulfide

3-amino-1,2,4-triazole (61-82-5)

4-Amino-1,2,4-triazole (584-13-4)

formylhydrazine (624-84-0)

1,2,4-Triazole, 1H-1,2,4-Triazole (288-88-0)

thiosemicarbazide (79-19-6)

1-Formyl-3-thiosemicarbazide (2302-84-3)

1,3,5-triazine (290-87-9)

urazole (3232-84-6)

hydrazine monohydrochloride (2644-70-4)

N,N'-diformylhydrazine

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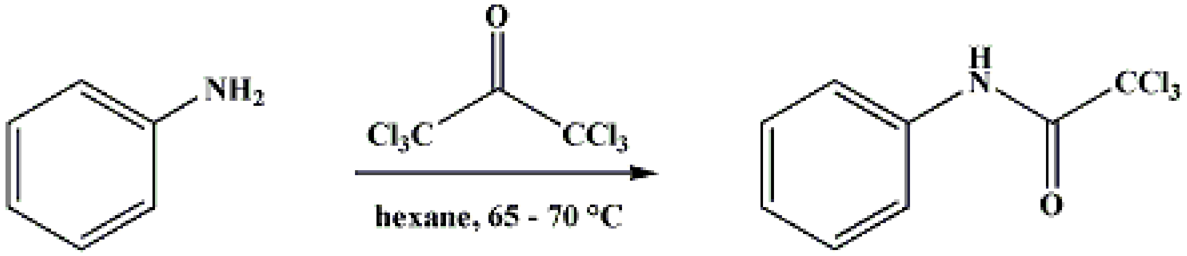
Organic Syntheses, CV 5, 1074

α,α,α-TRICHLOROACETANILIDE

[Acetanilide, α,α,α-trichloro-]



Submitted by Bernard Sukornick[1]
Checked by John D. Roberts and Eugene I. Snyder.

1. Procedure

Into a 1-l. three-necked flask, fitted with a mechanical stirrer, a reflux condenser, a thermometer (Note 1), and a dropping funnel, is placed a solution of 265 g. (1 mole) of hexachloroacetone (Note 2) in 400 ml. of hexane (Note 3). To the stirred solution is added, dropwise, 93 g. (1 mole) of aniline (Note 4) over a period of 35–40 minutes. During this time the temperature rises to about 55°. After the addition is complete, stirring is continued at 65–70° for 45 minutes.

The hot solution is poured into a 1-l. beaker and cooled to 0–5°. The solid is collected on a filter and air-dried; it weighs 208–218 g. (87–91%) and melts at 90–92°. One recrystallization from 400 ml. of 90% ethanol (Note 5) yields 160–165 g. (67–69%) (Note 6) of product melting at 92.5–93.0° (Note 7). A second crop of 9–16 g. (4–7%), m.p. 93.5–95.5°, can be obtained by concentrating the filtrate to 200 ml. and cooling (Note 8).

2. Notes

1. The thermometer and the reflux condenser are fitted to a two-necked adapter.
2. Commercial hexachloroacetone (Allied Chemical Corporation) was distilled and the fraction boiling at 93–97°/24 mm. was used.
3. Technical grade hexane suffices.
4. Technical grade aniline was purified by simple distillation and the light-yellow distillate was used directly.
5. The 90% ethanol was prepared by adding 22 ml. of water to 378 ml. of 95% ethanol.
6. The submitter reports a 76–81% yield of product melting at 94–96°.
7. The melting point is raised to 93.5–94.0° by carefully washing the product on a Büchner funnel with 50 ml. of iced 90% ethanol.

8. The submitter has applied this procedure successfully to several amines[2] (see Table I).

TABLE I

Amine	Yield of N-Trichloroacetylamine, %	M.p., °C*
3-Chloroaniline	93	101
4-Chloroaniline	97	125–127
2-Toluidine	83	98
3-Toluidine	79	102–103
4-Toluidine	70	115
4-Fluoroaniline	83	96
Benzidine	65	301 (dec.)
Benzylamine	84	87–90
2-Phenylethylamine	97	117–120
Ammonia	96	141
Dimethylamine	89	b.p. 110–111°/16 mm.
2-Aminothiazole	80	196–198 (dec.)

*All melting points are uncorrected.

3. Discussion

Trichloroacetanilide has been prepared from hexachloroacetone and aniline,[3] from trichloroacetyl chloride and aniline,[4] by the action of aniline magnesium iodide on ethyl trichloroacetate,[5] by heating N-phenyltrichloroacetimidyl chloride with dilute methanol,[6] and from trichloroacetic acid and aniline in the presence of phosphorus oxychloride[7] or dicyclohexylcarbodiimide,[8] and from trichloroacetyl diethyl phosphonate and aniline.[9]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

N-phenyltrichloroacetimidyl chloride

trichloroacetyl diethyl phosphonate

ethanol (64-17-5)

ammonia (7664-41-7)

methanol (67-56-1)

aniline (62-53-3)

Phosphorus Oxychloride (21295-50-1)

benzylamine (100-46-9)

benzidine (92-87-5)

trichloroacetic acid (76-03-9)

dimethylamine (124-40-3)

2-phenylethylamine (64-04-0)

4-Toluidine (106-49-0)

hexane (110-54-3)

ethyl trichloroacetate (515-84-4)

dicyclohexylcarbodiimide (538-75-0)

trichloroacetyl chloride (76-02-8)

α,α,α-Trichloroacetanilide, Trichloroacetanilide, Acetanilide, α,α,α-trichloro- (2563-97-5)

hexachloroacetone (116-16-5)

N-Trichloroacetylamine

3-Chloroaniline (108-42-9)

4-Chloroaniline (106-47-8)

2-Toluidine (95-53-4)

3-Toluidine (108-44-1)

4-Fluoroaniline (371-40-4)

2-Aminothiazole (96-50-4)

aniline magnesium iodide

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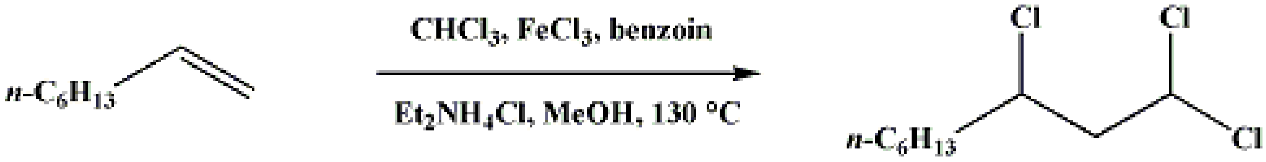
Organic Syntheses, CV 5, 1076

1,1,3-TRICHLORO-*n*-NONANE

[Nonane, 1,1,3-trichloro-]



Submitted by D. Vofsi and M. Asscher[1].
Checked by S. N. EGe and Peter Yates.

1. Procedure

A solution of 0.54 g. (2 mmoles) of ferric chloride hexahydrate and 0.33 g. (3 mmoles) of diethylammonium chloride (Note 1) in 5 g. of methanol is added to a solution of 11.2 g. (0.1 mole) of 1-octene (Note 2) and 0.42 g. (2 mmoles) of benzoin (Note 3) in 36 g. (0.3 mole) of chloroform (Note 4). The resulting homogeneous mixture is introduced into a Carius tube of about 100-ml. capacity. Air is displaced by dropping a few pieces of dry ice into the tube (Note 5). The tube is sealed (Note 6), heated to 130°, kept at that temperature for 15 hours, cooled to room temperature (Note 7), and opened. The contents of the tube are transferred to a separatory funnel, and the tube is rinsed with about 10 ml. of chloroform. The reaction mixture is washed with 40 ml. of water. The aqueous solution is extracted with 10 ml. of chloroform, and the extract is added to the original chloroform layer. Solvent is distilled at atmospheric pressure (bath temperature up to 130°). The distillation flask is allowed to cool, and distillation is continued at 25 mm. (bath temperature up to 120°) (Note 8). The flask is cooled again, and distillation is continued to dryness at 0.1 mm. (bath temperature up to 150°), giving crude 1,1,3-trichloro-*n*-nonane (19.4 g.) as a yellow oil, b.p. 60–85° (0.1 mm.), n^{25}D 1.4650. The purity of this product is 95% (Note 9), and the actual yield is 80%. Fractionation of this material through a 13-in. Vigreux column gives 15 g. (64%) of pure, colorless 1,1,3-trichloro-*n*-nonane, b.p. 61–62° (0.1 mm.), n^{25}D 1.4640 (Note 10) and (Note 11).

2. Notes

1. Pure diethylammonium chloride can be obtained from Fluka A. G., Buchs, S. G., Switzerland. If this salt is omitted, somewhat lower yields (about 75%) of adduct are obtained.
2. Phillips 1-octene of 99% minimum purity was used; however, it was freed of peroxide by percolating through acid-washed alumina.
3. Benzoin, Eastman Organic Chemicals, practical grade, can be used directly.
4. Reagent grade chloroform is used.
5. If air is not displaced before sealing, there is an induction period of about 1 hour.
6. The Carius tube has a short piece (about 4 in.) of heavy-walled tube (8-mm. external diameter) sealed to it. This greatly facilitates subsequent sealing and re-use

of the tube. The solution is introduced by means of a funnel with a drawn-out stem.
7. On cooling, the contents of the tube separate into two layers.
8. Occasionally a few drops, consisting mainly of unconverted 1-octene, are collected. The receiver then must be changed before the distillation at 0.1 mm. is continued.
9. The purity was determined by gas chromatography (1.5-m. column packed with 25% silicone oil on Chromosorb W, at 180°, and a flow rate of 60 ml. of helium per minute). The yellow color, which is due to traces of benzil, may be removed by diluting the product with three times its volume of pentane, percolating the solution through a column of about 30 g. of acid-washed alumina, washing the alumina with 50 ml. of pentane, and distilling the pentane at atmospheric pressure. The residue, which is colorless, boils at 61–63° (0.1 mm.), n^{25}D 1.4643; the recovery is 95%.
10. The checkers distilled the reaction product directly through a 4-in. Vigreux column to obtain 15.4–15.8 g. (66–68%) of colorless product, b.p. 95–97° (2.5 mm.), n^{25}D 1.4632.
11. The submitters have found that the reaction may be carried out on a much larger scale in an autoclave. The reaction must be run in a glass liner. As the hot reaction mixture is homogeneous, the autoclave may be heated while standing upright. The liner may be filled to three-quarters of its capacity.

3. Discussion

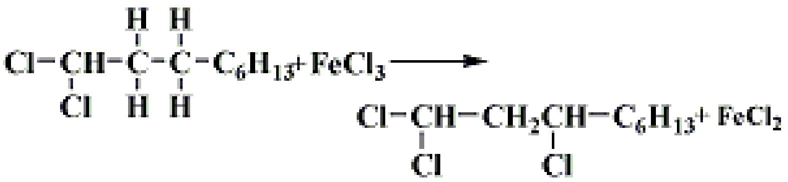
The method described, which is the only one available for the direct preparation of 1,1,3-trichloroalkanes, is applicable to aliphatic olefins and gives good yields, especially with terminal olefins.[2] With styrene or butadiene, yields are much lower.

4. Merits of the Preparation

1,1,3-Trichloroalkanes are potential starting materials for the preparation of unsaturated aldehydes.[3]

A similar method[2] can be used for the addition of carbon tetrachloride to nonpolymerizable olefins (*e.g.*, 1-octene, 2-octene, 1-butene, 2-butene); pure adducts are obtained in yields of over 90% if the components are allowed to react at 100° for 6 hours. Adducts of carbon tetrachloride with vinylic monomers (styrene, butadiene, acrylonitrile, methyl acrylate, etc.) can be prepared in good yields by substituting cupric chloride dihydrate in acetonitrile for ferric chloride hexahydrate and benzoin.

In ordinary homolytic reactions (as distinguished from the reaction described here), chloroform adds to the double bond in the sense $H\text{-}CCl_3$.[4] Bromodichloromethane adds in the sense $Br\text{-}CHCl_2$,[3] similar to the orientation of chloroform additions in the present method ($Cl\text{-}CHCl_2$). The present method has the advantage of giving high yields while using cheap reagents, and it is thought to proceed as shown in the following equations.



Carbon tetrachloride can be substituted for chloroform in this reaction when the cupric chloride modification described above is used.

References and Notes

1. Plastics Research Laboratory, Polymer Department, The Weizmann Institute of Science, Rehovoth, Israel.
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alumina

methanol (67-56-1)

acetonitrile (75-05-8)

chloroform (67-66-3)

carbon tetrachloride (56-23-5)

Benzil (134-81-6)

Benzoin (119-53-9)

1-butene (106-98-9)

cupric chloride (7758-89-6)

Pentane (109-66-0)

styrene (100-42-5)

methyl acrylate (96-33-3)

butadiene (106-99-0)

ferric chloride hexahydrate (10025-77-1)

acrylonitrile (107-13-1)

helium (7440-59-7)

Nonane, 1,1,3-trichloro-, 1,1,3-TRICHLORO-n-NONANE (10575-86-7)

diethylammonium chloride

1-octene (111-66-0)

cupric chloride dihydrate (10125-13-0)

Bromodichloromethane (75-27-4)

2-butene

2-octene (13389-42-9)

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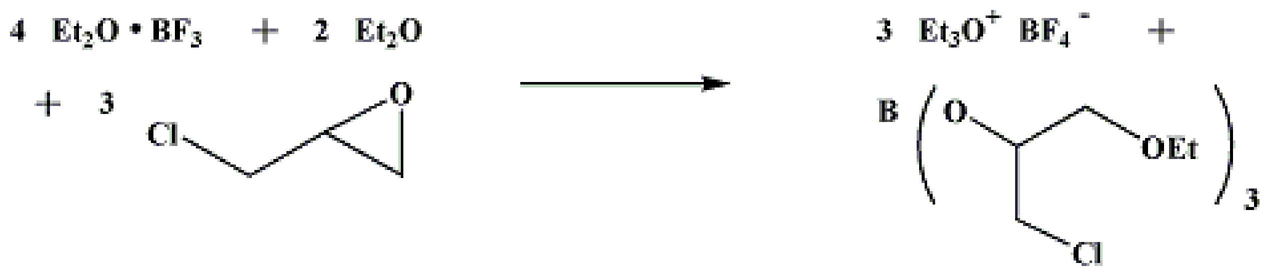
Organic Syntheses, CV 5, 1080

TRIETHYLOXONIUM FLUOBORATE

[Oxonium compounds, triethyloxonium tetrafluoroborate]



Submitted by H. Meerwein[1]
Checked by B. C. Anderson, O. H. Vogl, and B. C. McKusick.

1. Procedure

A 2-l. three-necked flask, a stirrer, a dropping funnel, and a condenser provided with a drying tube are dried in an oven at 110°, assembled while hot, and cooled in a stream of dry nitrogen. Sodium-dried ether (500 ml.) and 284 g. (252 ml., 2.00 moles) of freshly distilled boron fluoride etherate (Note 1) and (Note 2) are placed in the flask. Epichlorohydrin (140 g., 119 ml., 1.51 moles) is added dropwise to the stirred solution at a rate sufficient to maintain vigorous boiling (about 1 hour is needed). The mixture is refluxed an additional hour and allowed to stand at room temperature overnight. The stirrer is replaced by a filter stick, and the supernatant ether is withdrawn from the crystalline mass of triethyloxonium fluoborate; nitrogen is admitted through a bubbler during this operation to prevent atmospheric moisture from entering the flask. The crystals are washed with three 500-ml. portions of sodium-dried ether. The flask is transferred to a dry box, and triethyloxonium fluoborate is collected on a sintered-glass filter and bottled in a stream of dry nitrogen. The fluoborate is colorless; m.p. 91–92° (dec.), yield 244–272 g. (85–95%) (Note 3).

2. Notes

1. The checkers obtained boron fluoride etherate and epichlorohydrin from Eastman Organic Chemicals and redistilled each through a 23-cm. Vigreux column immediately before use.
2. It is convenient to measure the liquids with syringes using the densities: epichlorohydrin d_4^{25} 1.179; boron fluoride etherate, d_4^{25} 1.125.
3. Triethyloxonium fluoborate is very hygroscopic. It should be stored in a tightly closed screw-cap bottle at 0–5° and should be used within a few days of the time it is made. It should be weighed and transferred in a dry box. It can be stored indefinitely under ether or at –80°.

3. Discussion

The procedure used is essentially that described by Meerwein and co-workers.[2,3] The salt also has been prepared from ethyl fluoride and boron fluoride etherate, and from silver fluoborate, ethyl bromide, and ether.[4]

4. Merits of the Preparation

This simple procedure easily provides large amounts of triethyloxonium fluoborate. Triethyloxonium fluoborate readily ethylates such compounds as ethers, sulfides, nitriles, ketones, esters, and amides on oxygen, nitrogen, or sulfur to give onium fluoborates (often isolable) that can react with nucleophilic reagents to give useful products.[5] For example, dimethylformamide gives the imino ether fluoborate $[(CH_3)_2NCH\text{-}OC_2H_5]^+ BF_4^-$, which is converted to $(CH_3)_2NCH(OC_2H_5)_2$ by sodium ethoxide.[5] Since an imino ether fluoborate is easily hydrolyzed to the corresponding amine and ester, triethyloxonium fluoborate is a useful reagent for converting amides to amines under mild conditions.[6] Curphey provides a fuller discussion of the alkylating properties of trialkyloxonium fluoborates.[7]

If there is no advantage in ethylation over methylation, trimethyloxonium fluoborate[8] or trimethyloxonium 2,4,6-trinitrobenzenesulfonate[9] may be preferable alkylating agents; their preparation is more laborious, but they may be stored for a longer period of time.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 1096
- Org. Syn. Coll. Vol. 5, 1099
- Org. Syn. Coll. Vol. 6, 576
- Org. Syn. Coll. Vol. 6, 1019

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1. Deceased October 24, 1965; formerly at University of Marburg, Marburg, Germany.
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8. H. Meerwein, this volume, p. 1096.

9. G. K. Helmkamp and D. J. Pettitt, this volume, p. 1099.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Sodium-dried ether

epichlorohydrin d_4^{25}

BF_4^-

ether (60-29-7)

Epichlorohydrin (106-89-8)

Ethyl bromide (74-96-4)

oxygen (7782-44-7)

nitrogen (7727-37-9)

sulfur (7704-34-9)

sodium ethoxide (141-52-6)

dimethylformamide (68-12-2)

boron fluoride etherate (109-63-7)

Triethyloxonium fluoborate (368-39-8)

ethyl fluoride (353-36-6)

trimethyloxonium fluoborate (420-37-1)

Trimethyloxonium 2,4,6-trinitrobenzenesulfonate (13700-00-0)

silver fluoborate (14104-20-2)

Oxonium compounds, triethyloxonium tetrafluoroborate

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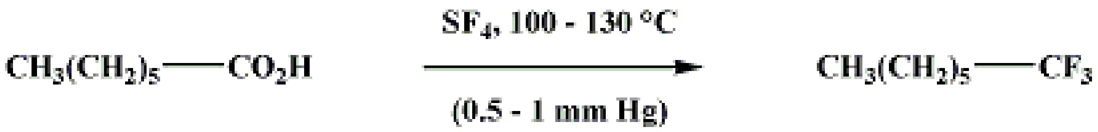
Organic Syntheses, CV 5, 1082

1,1,1-TRIFLUOROHEPTANE

[Heptane, 1,1,1-trifluoro-]



Submitted by W. R. Hasek[1]
Checked by John E. Baldwin and John D. Roberts.

1. Procedure

Caution! Sulfur tetrafluoride is toxic. This procedure should be carried out in a good hood. The pressure vessel should be heated in a well-ventilated area.

Twenty-six grams (0.20 mole) of heptanoic acid is placed in a 145-ml. pressure vessel lined with Hastelloy-C (Note 1). The air in the vessel is displaced with nitrogen, and the head of the vessel is secured in place. The vessel is cooled in a bath of acetone and solid carbon dioxide, and the nitrogen in the vessel is evacuated with a vacuum pump to a pressure of 0.5–1.0 mm. Sixty-five grams (95% pure, 0.57 mole) of sulfur tetrafluoride (Note 2) is transferred to the cold vessel. This is conveniently done by connecting a cylinder containing 65 g. of sulfur tetrafluoride to the pressure vessel by a length of copper tubing having a 1/16-in. bore and 1/8-in. outside diameter (Note 3).

The pressure vessel is heated with agitation at 100° for 4 hours and at 130° for 6 hours. The vessel is allowed to cool to room temperature and the volatile by-products [*Caution! Toxic!* (Note 4)] are vented. The crude, fuming, liquid product (Note 5) is poured into a stirred suspension of 10 g. of finely divided sodium fluoride in 60 ml. of pentane (Note 6), the mixture is filtered, and the filtrate is fractionated through a 6-in. Vigreux column. 1,1,1-Trifluoroheptane is collected at 100–101°/760 mm., n_D^{25} 1.3449. The yield is 21.7–24.6 g. (70–80%).

2. Notes

1. The pressure vessel should be lined with Hastelloy-C, stainless steel, or other metal resistant to attack by hydrogen fluoride, because the latter substance is a by-product of the reaction. The pressure vessel employed should be safe for use at 500 atm. pressure and should be equipped with a rupture disk rated at 500 atm. If the equipment available is rated for use only at lower pressure, the size of the charge should be reduced appropriately.
2. Directions for the synthesis of sulfur tetrafluoride by the action of sodium fluoride on sulfur dichloride in acetonitrile have been published,[2] and a more

detailed version of these directions appears in *Inorganic Syntheses*, **7**, 119 (1963).

3. It is also possible to connect the supply cylinder of sulfur tetrafluoride to the pressure vessel by a short length of butyl rubber vacuum tubing.

If the supply cylinder of sulfur tetrafluoride contains more than 65 g., it may be placed on a balance in order to determine when the required amount has been transferred to the pressure vessel.

4. Since the volatile gases include sulfur tetrafluoride and thionyl fluoride, which possess toxicities comparable to that of phosgene, caution must be exercised in their disposal. A suitable procedure is to condense the volatile gases in a trap cooled in a mixture of acetone and solid carbon dioxide, and then to allow this material to pass slowly through an empty polyethylene bottle, which serves as a safety trap, and into a stirred aqueous potassium hydroxide solution.

5. If it is found necessary to retain the crude product for any period of time before working it up, it may be conveniently stored in a polyethylene bottle or other container resistant to attack by hydrogen fluoride.

6. As indicated above, the crude product contains hydrogen fluoride. The sodium fluoride disposes of this by-product by the reaction NaF + HF $NaHF_2$. An alternative procedure is to pour the crude product into water and to separate the product by extraction with pentane.

3. Discussion

1,1,1-Trifluoroheptane has been prepared only by the action of sulfur tetrafluoride on heptanoic acid.[3]

4. Merits of Preparation

The described procedure is useful for the preparation of a wide variety of compounds containing trifluoromethyl groups from the corresponding carboxylic acids.[3] The yields are generally 60–90%. Some representative examples are listed in Table I. In the cases of the difunctional acids, only 0.1 mole of the compound should be used in the procedure.

TABLE I

Product	B.P., °C.	n_D^{25}
1,1,1-Trifluorododecane	92 (12 mm.)	1.3896
1,1,1-Trifluorohexadecane	107 (0.3 mm.)	1.4148
1,1,1-Trifluoro-3,5,5-trimethylhexane	121–122	1.3657
(4,4,4-Trifluorobutyl)cyclohexane	172–173	1.3987
1,1,1,10,10,10-Hexafluorodecane	183–184	1.3519
1,1,1,6,6,6-Hexafluoro-3-hexene	90–91	1.3131
p-Bis(trifluoromethyl)benzene	113–115	1.3767

2,4-Bis(trifluoromethyl)chlorobenzene	147	1.4130
p-Trifluoromethylnitrobenzene	(m.p. 41–43°)	

Carboxylic anhydrides and esters react with sulfur tetrafluoride to give the same products as the acids only at elevated temperatures, i.e., 200° to 300°.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 396

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

acetonitrile (75-05-8)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

hydrogen fluoride (7664-39-3)

acetone (67-64-1)

potassium hydroxide (1310-58-3)

phosgene (75-44-5)

Pentane (109-66-0)

sulfur dichloride (10545-99-0)

Heptanoic acid (111-14-8)

sodium fluoride (7681-49-4)

sulfur tetrafluoride (7783-60-0)

1,1,1-Trifluoroheptane, Heptane, 1,1,1-trifluoro- (693-09-4)

thionyl fluoride (7783-42-8)

1,1,1-Trifluorododecane

1,1,1-Trifluorohexadecane

1,1,1-Trifluoro-3,5,5-trimethylhexane

(4,4,4-Trifluorobutyl)cyclohexane

1,1,1,10,10,10-Hexafluorodecane

1,1,1,6,6,6-Hexafluoro-3-hexene

2,4-Bis(trifluoromethyl)chlorobenzene (327-76-4)

p-Bis(trifluoromethyl)benzene (433-19-2)

p-Trifluoromethylnitrobenzene (402-54-0)

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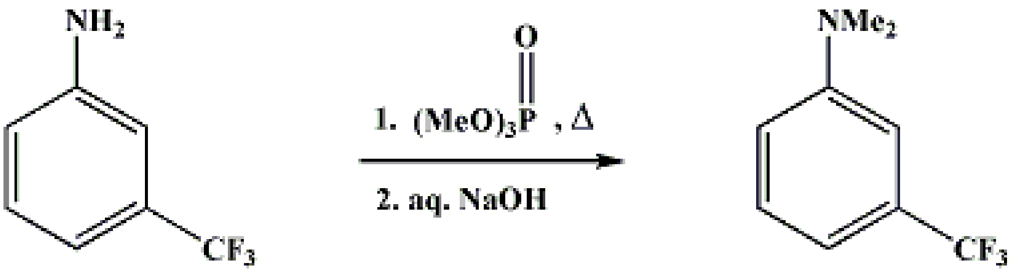
Organic Syntheses, CV 5, 1085

m-TRIFLUOROMETHYL-N,N-DIMETHYLANILINE

[*m*-Toluidine, α,α,α-trifluoro-N,N-dimethyl-]



Submitted by William A. Sheppard[1]
Checked by G. B. Bennett and K. B. Wiberg.

1. Procedure

A solution of 16.1 g. (0.100 mole) of *m*-trifluoromethylaniline (Note 1) and 14.3 g. (0.102 mole) of trimethyl phosphate (Note 2) is added to a 300-ml. round-bottomed flask with a side arm. The flask is equipped with a thermometer, magnetic stirrer, and air condenser topped by a water condenser under a nitrogen atmosphere. The stirred reaction mixture is gradually heated by an oil bath to approximately 150° over 30–60 minutes; at this point there is a mild exothermic reaction such that the temperature of the reaction reaches 160–170° and reflux starts (Note 3). After 2 hours at reflux (reaction temperature 145–150°) with oil-bath temperature maintained at 180–200°, the reaction mixture is cooled to room temperature.

A solution of 15 g. of sodium hydroxide in 100 ml. of water is added, and the mixture is stirred vigorously for 1.5 hours to hydrolyze the phosphate ester. The hydrolysis is initially mildly exothermic, and the reaction temperature increases to 50–70°. An additional 200 ml. of water is added. The product, which separates as an oil, is extracted with two 150-ml. portions of ether (Note 4). The combined ether extracts are dried for at least several hours over a mixture of anhydrous magnesium sulfate and sodium hydroxide pellets, filtered, and concentrated by distillation of the ether through a Vigreux column. The residue is distilled at reduced pressure. *m*-Trifluoromethyl-N,N-dimethylaniline is collected at 66–67° (4.5 mm.) and weighs 10.4–11.0 g. (55–58%); n^{24}D 1.4834–1.4828 (Note 5), (Note 6).

2. Notes

1. *m*-Trifluoromethylaniline (under the name *m*-aminobenzotrifluoride) obtained from Columbia Organic Chemicals Co., Inc., Columbia, South Carolina, was employed. The aniline is also available from Eastman Kodak under the name α,α,α-trifluoro-*m*-toluidine.

2. Trimethyl phosphate obtained from Columbia Organic Chemicals was employed. Although the phosphate ester is reported to be nontoxic under normal handling conditions,[2] use of a hood is recommended.
3. Separation of the reaction mixture into two phases can be observed if the stirrer is stopped for a short period at this point and is also noted on cooling after completion of reflux.
4. The phosphate salts sometimes precipitate before or during the extraction and should be removed by suction filtration to facilitate the extraction. Precipitation may be avoided by addition of larger volumes of water before extraction.
5. A very small forecut is discarded, and only a small amount of tarry residue remains in the pot after the distillation is complete. A spinning-band distillation column was employed by the submitter, but a simple Claisen head is considered adequate because of lack of by-products.
6. The product is free from secondary aniline product on the basis of infrared and n.m.r. proton analysis. If equimolar amounts of aniline and phosphate are employed, the product is obtained in a higher yield (12.3 g., 65%), but it contains a trace of *m*-trifluoromethyl-N-methylaniline as detected by infrared analysis. This secondary aniline is readily removed by heating the product to reflux with 1 ml. of acetic anhydride followed by redistillation. Use of a larger molar excess of trimethyl phosphate does not affect the purity but does decrease the yield significantly.

3. Discussion

The described method of dialkylation of anilines is essentially that of Billman and co-workers.[3,2] It has not previously been applied to *m*-trifluoromethylaniline. *m*-Trifluoromethyl-N,N-dimethylaniline has been prepared in 29% yield by alkylating *m*-trifluoromethylaniline with methyl iodide.[4]

The use of trialkyl phosphates for dialkylation of anilines has been found applicable to naphthylamines[2] and to a large number of anilines substituted in the ortho, meta, or para position by groups such as chloro, methoxy, and methyl[3] and in the meta position by fluoroalkyl (author's laboratory). The reaction has been used to introduce ethyl and *n*-butyl as well as methyl groups by employing the appropriate phosphate esters. The reported yields range from 50% to 95%.

This method has two major advantages over other alkylation procedures: much less manipulation and higher yields; and no troublesome by-products, such as monoalkylated or quaternary products. The Eschweiler-Clarke procedure[5] for alkylation of amines (formaldehyde-formic acid) also has these synthetic advantages for the aliphatic series but gives high molecular weight condensation products with anilines (anilines highly substituted in the ortho-para position may be employed successfully, but *m*-trifluoromethylaniline gives only a resin).

The phosphate method has not been synthetically useful for alkylation of anilines of

low basicity such as *p*-nitro-[2] or *p*-trifluoroaniline. Only monoalkylation occurs in introducing branched-chain alkyl groups such as isopropyl.[2] Use of this method for alkylation of aliphatic amines has not been reported.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 181

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ether (60-29-7)

acetic anhydride (108-24-7)

aniline (62-53-3)

sodium hydroxide (1310-73-2)

nitrogen (7727-37-9)

Methyl iodide (74-88-4)

formaldehyde-formic acid (298-12-4)

magnesium sulfate (7487-88-9)

trimethyl phosphate (512-56-1)

m-trifluoromethylaniline, m-aminobenzotrifluoride, α,α,α-Trifluoro-m-toluidine (98-16-8)

m-Trifluoromethyl-N,N-dimethylaniline, m-Toluidine, α,α,α-trifluoro-N,N-dimethyl- (329-00-0)

m-trifluoromethyl-N-methylaniline

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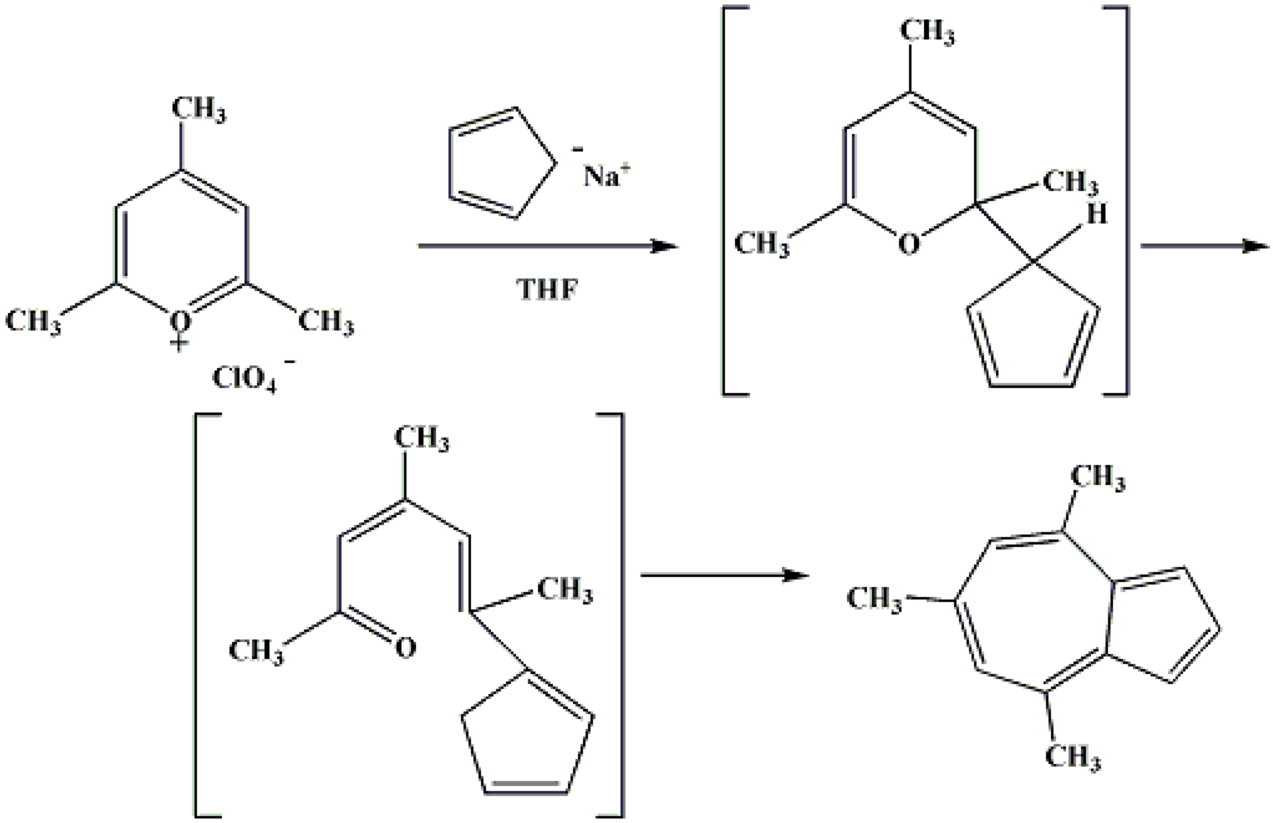
Organic Syntheses, CV 5, 1088

4,6,8-TRIMETHYLAZULENE

[Azulene, 4,6,8-trimethyl-]



Submitted by K. Hafner and H. Kaiser[1].
Checked by Karl Bangert and Virgil Boekelheide.

1. Procedure

A. *Cyclopentadienylsodium*. A 1-l. four-necked flask (or a three-necked flask with a Y-tube connection) is outfitted with a Trubore® stirrer, a pressure-equalizing dropping funnel, a thermometer reaching to the bottom of the flask, and a reflux condenser in whose outlet is placed a T-tube, one side of which leads to a bubble counter and the other is connected to a source of pure nitrogen. The system is flushed with nitrogen, and a suspension of 23 g. (1.0 mole) of sodium in 350 ml. of dry tetrahydrofuran (Note 1) and (Note 2) is prepared in the flask. There is then added dropwise with stirring 73.0 g. (1.1 moles) of freshly distilled cyclopentadiene (Note 3). As the exothermic reaction begins, evolution of hydrogen through the bubble counter can be observed immediately. The temperature of the reaction mixture should be kept below 35–40° by intermittent cooling of the flask with an ice bath. At the end of the reaction the color of the solution should be a pale rose; exposure to air causes a rapid change in color to dark brown (Note 4).

B. *4,6,8-Trimethylazulene*. *Caution! 2,4,6-Trimethylpyrylium perchlorate is explosive. Operations with it should be conducted behind a shield.* The arrangements of the reaction flask used in the preparation of cyclopentadienylsodium are now altered for the next step. While increasing the nitrogen flow rate strongly, the dropping funnel is removed and replaced by a

wide-mouthed powder funnel. The strong flow of pure nitrogen coming out of the flask and around the powder funnel prevents the atmosphere from diffusing into the flask to any appreciable extent. Then, with strong stirring of the reaction mixture, 142 g. (0.64 mole) of 2,4,6-trimethylpyrylium perchlorate *(Caution! Moistened with dry tetrahydrofuran, (Note 5))* is added in small portions through the powder funnel at such a rate that the immediate exothermic reaction which ensues maintains the temperature of the reaction mixture between 42° and, at most, 48°. The color of the reaction mixture turns purple immediately on addition of the 2,4,6-trimethylpyrylium perchlorate. Usually the addition requires about 1 hour; then the reaction mixture is stirred for an additional 20 minutes. The powder funnel is replaced with a stopper, the condenser is turned downward for distillation, and about 130 ml. of tetrahydrofuran is removed by distillation while stirring is continued. For the distillation the flask is heated on a steam bath, and the temperature of the reaction mixture at the end of the distillation is about 68–70°. The color of the distillate is a weak violet owing to the co-distillation of a small amount of 4,6,8-trimethylazulene. After the reaction mixture has cooled, it is transferred to a 3-l. separatory funnel and diluted, first with 75 ml. of methanol and then with 1 l. of water. This causes the separation of a dark violet oil which is taken up in 400 ml. of petroleum ether (b.p. 60–70°) and separated from the aqueous phase. The aqueous layer is extracted again with 200 ml. of fresh petroleum ether, and the combined petroleum ether extracts are washed five times with 175-ml. portions of water. Since a small quantity of a greasy by-product separates at the interface during the washing with water, the petroleum ether extract, after the final washing, is purified by passing it through a Büchner funnel lined with asbestos fibers as a filtering aid. After the filtrate has been dried over calcium chloride, the solution is concentrated under reduced pressure, and the residue is carefully freed of solvent by heating on a steam bath under reduced pressure for 4 hours.

The crude product is then transferred to an apparatus suitable for distillation of solids (Note 6), and this is joined to a high-vacuum system capable of a vacuum in the range of 10^{-5} mm. Distillation begins when the bath temperature reaches about 190°; a boiling point of around 120° is usually observed. When the distillate first begins to appear brown rather than violet, the distillation is stopped immediately (Note 7). The crystalline distillate (ca. 70 g.) is dissolved in 20 ml. of hot ethanol, filtered while hot, and allowed to cool. The solid (about 60 g. of crystals, m.p. 74–76°) is recrystallized from 20 ml. of ethanol to yield 47–53 g. (43–49%) of 4,6,8-trimethylazulene as dark-violet plates, m.p. 80–81° (Note 8).

2. Notes

1. The suspension of sodium is best prepared as follows. In a three-necked flask fitted with a ground-glass stopper, a reflux condenser, and a Vibromischer (available from A. G. für Chemie-Apparatebau, Zurich, Switzerland) are placed 150 ml. of toluene and 23 g. of sodium. When the toluene is boiling under reflux, the melted sodium is dispersed by the Vibromischer, and the flask is quickly cooled. Under nitrogen atmosphere the toluene is removed by decantation and is replaced by 350 ml. of dry tetrahydrofuran.
2. The dry tetrahydrofuran can be prepared by allowing tetrahydrofuran to stand over sodium, decanting, and distilling from lithium aluminum hydride. *(Caution! See p. 976.)*
3. For the preparation of cyclopentadiene from its dimer, see M. Korach, D. R. Nielsen, and W. H. Rideout, this volume, p. 414.
4. If desired, the cyclopentadienylsodium concentration in solution can be determined by withdrawing 1 ml. of solution, diluting this with 100 ml. of water, and titrating the resulting aqueous sodium hydroxide solution with 0.1*N* hydrochloric acid using methyl

red as an indicator.
5. The 2,4,6-trimethylpyrylium perchlorate, obtained and stored as described by Balaban and Nenitzescu[2] or by Hafner and Kaiser,[3] is used directly.
6. A round-bottomed, standard-taper flask with a Claisen head carrying an ebullition capillary and a thermometer and attached to a two-necked flask with one neck for vacuum takeoff is satisfactory. It is important that the setup allow for heating by either flame or infrared lamp to melt the solid distillate and prevent its clogging the vapor passage.
7. It is helpful to empty the brown tarry residue from the distillation flask while it is still hot. The flask can then be cleaned by using a sulfuric acid-chromic acid solution.
8. For purification of small amounts of 4,6,8-trimethylazulene it is advantageous to dissolve it in a small amount of methanol and treat the solution with activated carbon.

3. Discussion

This procedure is adapted from that described earlier by Hafner and Kaiser,[4] and apparently it is the only method that has been used for synthesizing 4,6,8-trimethylazulene.

4. Merits of the Preparation

This procedure illustrates a simple and general method for preparing azulenes. It is far more convenient and proceeds in much better yield than previous syntheses of azulenes involving dehydrogenation.[5] Also, it is superior to the alternative methods utilizing the monoanil of glutacondialdehyde[6] or pyridinium salts.[7,8] In fact, this procedure has made the azulenes a readily available class of compounds for study and use as starting materials. Illustrative of the latter are the recent syntheses of pentalene,[9] heptalene,[9] and *peri*-benzazulene derivatives.[10]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 431
- Org. Syn. Coll. Vol. 5, 1106
- Org. Syn. Coll. Vol. 5, 1135
- Org. Syn. Coll. Vol. 7, 339

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

Methyl Red

ethanol (64-17-5)

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

methanol (67-56-1)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

nitrogen (7727-37-9)

carbon (7782-42-5)

toluene (108-88-3)

sodium (13966-32-0)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

CYCLOPENTADIENE (542-92-7)

cyclopentadienylsodium

4,6,8-Trimethylazulene, Azulene, 4,6,8-trimethyl- (941-81-1)

2,4,6-Trimethylpyrylium perchlorate (940-93-2)

sulfuric acid-chromic acid

glutacondialdehyde

pentalene

heptalene

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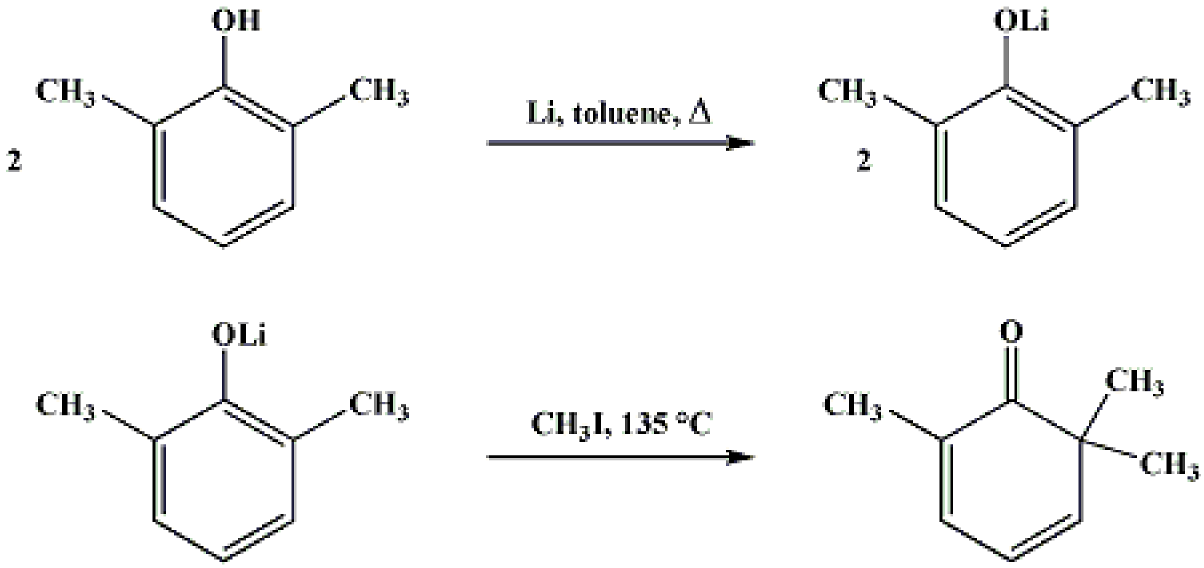
Organic Syntheses, CV 5, 1092

2,6,6-TRIMETHYL-2,4-CYCLOHEXADIENONE

[2,4-Cyclohexadiene-1-one, 2,6,6-trimethyl-]



Submitted by David Y. Curtin and Allan R. Stein[1].
Checked by William G. Dauben and Joel W. Rosenthal.

1. Procedure

A. *Lithium 2,6-dimethylphenoxide*. In a 300-ml. flask, equipped with a magnetic stirrer and a reflux condenser and flushed with nitrogen, are placed 150 ml. of toluene (freshly distilled from sodium), 1.40 g. (0.202 mole) of lithium metal (Note 1) and 25.0 g. (0.205 mole) of resublimed 2,6-dimethylphenol. The mixture is heated under reflux with stirring for 36 hours; a nitrogen atmosphere is maintained for the reflux period (Note 2). The condenser is replaced by a distillation head with a condenser set for distillation, and a distillation capillary is inserted in the thermometer joint. The bulk of the toluene is removed under nitrogen at reduced pressure (Note 3). The distillation head is rapidly removed, and the flask is flushed with nitrogen and closed by a stopper. The stoppered flask is transferred to a dry box flushed with nitrogen, the stopper removed, and the slurry in the flask filtered with suction through a 65-mm. sintered-glass funnel. The collected lithium salt is washed with three 75-ml. portions of hexane (freshly distilled from lithium aluminum hydride), and the white powder (Note 4) is dried at 100–150° and 0.5 mm. pressure to constant weight (3–10 hours is required). The yield of lithium 2,6-dimethylphenoxide as a fine white or light gray powder is 25.0–25.5 g. (98–100%) (Note 5) and (Note 6).

B. *2,6,6-Trimethyl-2,4-cyclohexadienone*. In a nitrogen-filled dry box, 25.0 g. of lithium 2,6-dimethylphenoxide (0.195 mole) is transferred to an oven-dried, thick-walled Pyrex® bomb tube (650 × 19 mm.). The bomb tube is stoppered with a rubber

stopper fitted with a drying tube, removed from the dry box, and 75 ml. of methyl iodide (170 g., 1.20 moles) (freshly distilled from calcium hydride) is quickly pipetted into the bomb under a dry nitrogen stream. The bomb is cooled in a dry-ice bath and sealed with an oxygen torch. After warming to room temperature, the bomb is shaken to disperse the salt cake and placed in a bomb furnace which has been preheated to 135° (Note 7).

After 36 hours the furnace is allowed to cool, the bomb is removed, cooled to dry-ice temperatures, and opened carefully as there may be residual pressure. The golden brown liquid is poured into a 200-ml. flask, and the methyl iodide is removed on a rotary evaporator *Caution! (Hood)*. The residue from the flask and the bomb is washed into a 500-ml. separatory funnel with 100 ml. each of ether and 1 : 1 solution of Claisen's alkali and water (Note 8). The funnel is shaken, and the alkali layer is removed. The ether layer is extracted four additional times with 100 ml. portions of the alkali (Note 9), washed twice with 75-ml. portions of water, once with saturated aqueous salt solution, and dried by filtration through anhydrous sodium sulfate into a 200-ml. round-bottomed flask. The ether is removed on a rotary evaporator, and the 23.0 g. of yellow oil remaining is allowed to stand at room temperature for 7–10 days to permit dimerization of the dienone (Note 10).

The 2,6-dimethylanisole is removed by vacuum distillation (nitrogen capillary bubbler) at 35–50° (0.75 mm. or less pressure). The solid dimerized product[2] in the residue is either recrystallized twice from the minimum amount of hot hexane or vacuum-distilled, b.p. 175° (25 mm.) (Note 11) followed by a single recrystallization from hexane.

The yield of purified 2,6,6-trimethyl-2,4-cyclohexadienone dimer (white needles, m.p. 119.5–121.0°) is 4.8–5.1 g. (18–19%) (Note 12), and the yield of 2,6-dimethyl anisole is 13.5–14.0 g. (51–53%).

The dienone monomer may be regenerated from its dimer as desired by heating the dimer above 170° for several minutes in a test tube and quenching, or by distillation at 25 mm. (Note 11) through a short condenser into a dry ice-acetone cooled receiver. The monomer may be stored for several days at dry-ice temperatures without appreciable dimerization.

2. Notes

1. The lithium should be added in the form of very small pieces. The pieces are most conveniently prepared as follows. Trim the oxide layer off a small block of lithium metal under mineral oil, grip it with tweezers and rinse the mineral oil off in a beaker of dry ether. Hold the block in the ether vapors momentarily to dry, and then plunge it into a tared beaker of mineral oil for weighing. Cut the block into strips with a sharp knife, remove the pieces one by one, and squeeze them into long flat ribbons with pliers which are frequently dipped into the mineral oil. Cut the ribbons into short sections over another beaker of dry ether,

swirl and transfer the pieces to a third beaker of ether to wash off the last traces of mineral oil before adding the lithium to the reaction flask.

2. A positive pressure of nitrogen is maintained by attachment of a mercury bubbler on the top of the reflux condenser.

3. If heating is desired to speed the toluene removal, a steam or an oil bath is used to prevent charring of the salt.

4. If the salt is lumpy, it is best to grind it into a fine powder in an agate mortar before washing it with the hexane. The fine powder is more easily washed and reacts more readily in the alkylation reaction.

5. The lithium phenoxide may be prepared in larger quantities and may be stored for some time sealed under nitrogen and protected from light by wrapping the flask with aluminum foil. Traces of water lead to a gummy salt, while traces of oxygen cause a purple coloration. Quite badly discolored salt has been used successfully in the alkylation procedure, but yields tend to be reduced by tar formation.

6. Titration of a portion of the salt with 0.1*N* hydrochloric acid to methyl orange end-point shows the salt to be 97–103% lithium 2,6-dimethylphenoxide.

7. The temperature used is not crucial, but the best yield is obtained in the 120–180° range. At higher temperatures considerable tar forms, while at lower temperatures dienone yields are sacrificed.[3]

8. Claisen's alkali is a solution of 350 g. of potassium hydroxide in 250 ml. of water made up to 1 liter with methanol.

9. About 4.5 g. or 18% of the starting 2,6-dimethylphenol may be recovered from the combined alkaline extracts by acidification with concentrated hydrochloric acid and extraction of the liberated phenol with ether.

10. The Diels-Alder dimerization of 2,6,6-trimethyl-2,4-cyclohexadienone to 1,4,6,6,9,9-hexamethyl-$\Delta^{3,11}$-tricyclo-[6.2.2.0 ^{2,7}]-dodecane-5,10-dione[2] facilitates its separation from the major alkylation product, 2,6-dimethylanisole.

11. In the distillation of the dienone it is necessary to maintain a pot temperature of 175–200° to reverse the dimerization (Note 10).

12. An additional 0.5–1.0 g. of the dienone dimer may be obtained by allowing the 2,6-dimethylanisole fraction to stand for several days and then redistilling it.

3. Discussion

This preparation of 2,6,6-trimethyl-2,4-cyclohexadienone is based upon the published procedure of the submitters,[2] and it is the only preparation of the 2-substituted-2,4-cyclohexadienones. The simpler 6,6-dimethyl-2,4-cyclohexadienone is more conveniently prepared by the method of Alder.[4]

4. Merits of the Preparation

The use of lithium in toluene for the preparation of alkali metal phenoxides appears to be the most convenient and least expensive procedure. The procedure also has the

merit of giving the salt as a finely divided powder.

The alkylation procedure can be used to prepare a wide variety of 2-substituted-2,4-cyclohexadienones,[2,3,5,6] which are useful starting materials. The compounds can serve either as dienes or dienophiles[7] in the Diels-Alder reaction and can be opened photochemically to yield substituted $\Delta^{3,5}$-hexadienoic acids.[8]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

methanol (67-56-1)

ether (60-29-7)

sodium sulfate (7757-82-6)

oxygen (7782-44-7)

nitrogen (7727-37-9)

aluminum (7429-90-5)

potassium hydroxide (1310-58-3)

toluene (108-88-3)

sodium (13966-32-0)

Methyl iodide (74-88-4)

lithium (7439-93-2)

lithium aluminum hydride (16853-85-3)

hexane (110-54-3)

calcium hydride (7789-78-8)

2,6-dimethylphenol (576-26-1)

2,6,6-Trimethyl-2,4-cyclohexadienone, 2,4-Cyclohexadiene-1-one, 2,6,6-trimethyl- (13487-30-4)

lithium 2,6-dimethylphenoxide

2,6-dimethylanisole, 2,6-dimethyl anisole (1004-66-6)

lithium phenoxide

tricyclo-[6.2.2.0 ^{2,7}]-dodecane-5,10-dione

6,6-dimethyl-2,4-cyclohexadienone

methyl orange (547-58-0)

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Organic Syntheses, CV 5, 1096

TRIMETHYLOXONIUM FLUOBORATE

[Oxonium compounds, trimethyloxonium tetrafluoroborate]

$$2\ Et_3O^+\ BF_4^- + 3\ Me_2O \xrightarrow{CH_2Cl_2} 2\ Me_3O^+\ BF_4^- + 3\ Et_2O$$

Submitted by H. Meerwein[1]
Checked by O. Vogl, B. C. Anderson, and B. C. McKusick.

1. Procedure

Freshly prepared triethyloxonium fluoborate[2] (170 g., 0.90 mole) is dissolved in 500 ml. of anhydrous methylene chloride in a 1-l. three-necked flask equipped with a stirrer, gas-inlet tube, and drying tube (Note 1). The reaction flask is immersed in an ice bath, the stirrer is started, and 138 g. (3.00 moles) of dry dimethyl ether is passed into the solution from a tared cylinder over a period of about 2 hours. The reaction mixture is allowed to stand overnight at room temperature. An hour after the addition of dimethyl ether is complete, trimethyloxonium fluoborate begins to separate. The initially liquid product solidifies slowly.

The stirrer is replaced by a filter stick, and the supernatant methylene chloride is withdrawn from the crystalline mass of trimethyloxonium fluoborate; nitrogen is admitted through a bubbler during this operation to prevent atmospheric moisture from entering the flask. The crystals are washed with three 100-ml. portions of anhydrous methylene chloride. The flask is transferred to a dry box, and trimethyloxonium fluoborate is collected on a sintered-glass filter, dried for 2 hours in a vacuum desiccator at 25° (1 mm.), and bottled in a stream of dry nitrogen. The fluoborate is colorless; yield 114–124 g. (86–94%). Rapidly heated in an open capillary tube, it sinters and darkens, with decomposition, at 141–143° (Note 3).

2. Notes

1. In order to obtain maximum yields, all operations must be carried out under rigorously dry conditions. The apparatus should be dried in an oven at 110°, assembled while hot, and cooled in a stream of dry nitrogen. The checkers dried the methylene chloride over PA 100 silica gel (12–28 mesh) obtained from Davison Chemical Co., Baltimore, Maryland.
2. Trimethyloxonium fluoborate is less hygroscopic and keeps better than triethyloxonium fluoborate, but it should be stored at 0–5° in a tightly closed screw-cap bottle.[2] So stored, it can be kept at least a few weeks.
3. The decomposition point varies widely, depending on rate of heating and apparatus. Professor S. H. Pine, California State College at Los Angeles, informed the checkers that he observed decomposition at 210–220°, with the salt

totally disappearing and $(CH_3)_2OBF_3$ forming on the wall of the capillary tube above the bath. This prompted the checkers to study the decomposition by differential thermal analysis. At a heating rate of 30°/min., there was an endotherm peak at 142°, with sample all gone by 200°. At 15°/min., the peak was at 155°, with sample all gone by 180°.

3. Discussion

The procedure used is essentially that described by Meerwein and co-workers.[3] The salt has also been prepared from the same reagents in a sealed tube.[4]

Curphey has described a convenient synthesis from boron trifluoride diethyl etherate, dimethyl ether, and epichlorohydrin.[5]

4. Merits of the Preparation

This facile preparation is suitable for preparation of large amounts of salt. Like triethyloxonium fluoborate,[2] trimethyloxonium fluoborate is a potent alkylating agent. In comparison with trimethyloxonium 2,4,6-trinitrobenzenesulfonate,[6] trimethyloxonium fluoborate is easier to make but does not keep quite as well on storage.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 1080
- Org. Syn. Coll. Vol. 5, 1099
- Org. Syn. Coll. Vol. 6, 1019

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1. Deceased October 24, 1965; formerly at University of Marburg, Marburg, Germany.
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6. G. K. Helmakamp and D. J. Pettitt, this volume, p. 1099.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Epichlorohydrin (106-89-8)

nitrogen (7727-37-9)

dimethyl ether (115-10-6)

methylene chloride (75-09-2)

boron trifluoride diethyl etherate (109-63-7)

Triethyloxonium fluoborate (368-39-8)

trimethyloxonium fluoborate (420-37-1)

Trimethyloxonium 2,4,6-trinitrobenzenesulfonate (13700-00-0)

Oxonium compounds, trimethyloxonium tetrafluoroborate

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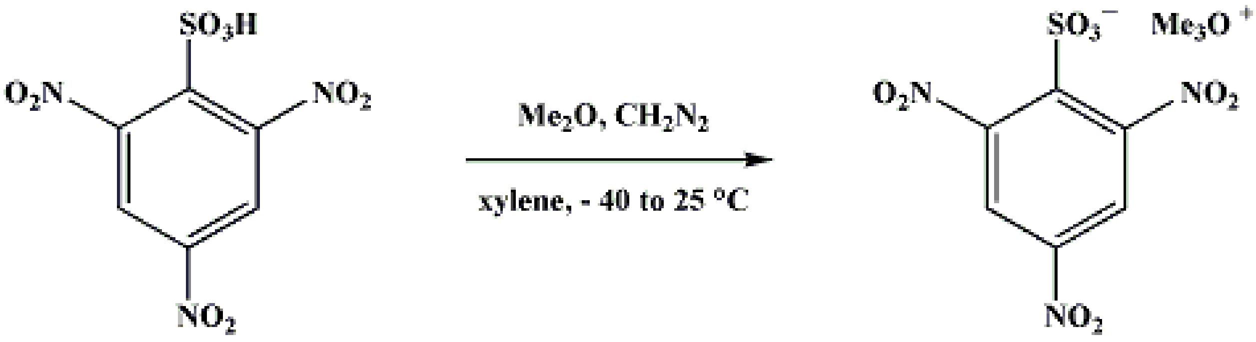
Organic Syntheses, CV 5, 1099

TRIMETHYLOXONIUM 2,4,6-TRINITROBENZENESULFONATE

[Oxonium compounds, trimethyloxonium 2,4,6-trinitrobenzenesulfonate]



Submitted by G. K. Helmkamp and D. J. Pettitt[1 2].
Checked by O. Vogl, B. C. Anderson, and B. C. McKusick.

1. Procedure

Caution! Diazomethane is hazardous. Follow the directions for safe handling of diazomethane given in earlier volumes.[3,4] All operations are carried out in a hood.

The apparatus is shown in f.htmig. 1. Two 500-ml. round-bottomed flasks *without standard-taper joints* (which could cause diazomethane to detonate) are used. The gas inlet *C* is connected to a cylinder of dimethyl ether. Gas inlet *C* is long enough to reach near the bottom of flask *A*, but tubing *D* extends only about halfway into flask *B*. A calcium chloride drying tube is attached to the gas outlet *E*. Flask *B* contains a Teflon®-covered stirring bar. The pieces of the apparatus are dried in an oven at 110°; well-dried apparatus is essential for a good yield.

Fig. 1.

Fig. 1.

A solution of diazomethane in 200 ml. of xylene is prepared from 15.0 g. (0.146 mole) of nitrosomethylurea[5] (Note 1). The diazomethane solution is decanted into flask *A*, and about 20 g. of potassium hydroxide pellets is added to the solution. The mixture is swirled for a few seconds to ensure removal of most of the water. About 4.2 g. (0.10 mole) of diazomethane is present. Flask *A* is then immersed in a water bath at 20–25°.

2,4,6-Trinitrobenzenesulfonic acid (14.7 g., 0.050 mole) (Note 2), previously dried for

at least 1 hour at 80–100° (1 mm.), is placed in flask *B*, which is then immersed to the level shown in fig. 2.htm in a bath of acetone maintained at –35° to –40° by addition of small amounts of dry ice (Note 3). About 200 ml. of dimethyl ether is rapidly poured from an ampoule into flask *B* (Note 3). Flasks *A* and *B* are connected as shown in fig. 2.htm, and magnetic stirring is started in flask *B*. When most of the sulfonic acid has dissolved, gaseous dimethyl ether is introduced through *C* at such a rate that a rapid stream of individual bubbles passes through the diazomethane solution in flask *A*. In the course of the reaction all the acid goes into soution and is replaced by a fluffy precipitate of the oxonium salt. The introduction of dimethyl ether is discontinued as soon as the supernatant solution in flask *B* turns yellow (Note 5) and (Note 6).

Flask *B* is separated from the apparatus but kept in the cooling bath, and 200 ml. of anhydrous ethyl acetate is added; addition is slow so as to avoid excessive boiling of the dimethyl ether (Note 7). The flask, with a tube of calcium chloride attached, is gradually brought to room temperature; most of the dimethyl ether evaporates during this operation. Crystalline trimethyloxonium 2,4,6-trinitrobenzenesulfonate is separated on a coarse sintered-glass funnel, washed with two 25-ml. portions of ethyl acetate and with 50 ml. of high-boiling petroleum ether, and dried over phosphorus pentoxide at 25° (<1 mm.) (Note 8); yield 12–14 g. (68–79%) (Note 9), m.p. 181–183° (Note 10).

2. Notes

1. Xylene is used as the solvent instead of diethyl ether because of its considerably lower vapor pressure.
2. 2,4,6-Trinitrobenzenesulfonic acid from Nutritional Bio-chemical Corp., Cleveland, Ohio, can be used without any purification other than drying. The checkers observed m.p. 174–177° for the dried acid.
The acid can be prepared from picryl chloride according to the method described by Golumbic, Fruton, and Bergmann,[6] but the following modifications are recommended: sodium metabisulfite should be used in place of sodium bisulfite; the crude sodium salt is not recrystallized but is converted directly to the acid by the addition of hydrochloric acid to its acetone solution; the product is recrystallized by dissolving it in a minimum amount of hot acetone, adding chloroform until crystallization starts, and cooling to about 0°. Two recrystallizations yield a product with m.p. 194–196°.
3. If the level of the cooling bath is too high, or if the bath temperature is less than –40°, unnecessary condensation of dimethyl ether occurs. If the level of the bath is too low, a brownish ring of decomposition product forms in the flask. Since the brown material is soluble in dimethyl ether and ethyl acetate, it does not contaminate the trimethyloxonium salt.
4. The submitters first transferred the dimethyl ether from a cylinder to an ampoule in order to avoid the accumulation of excess water. The ampoule should have a moderately wide mouth in order to facilitate rapid transfer of dimethyl ether.
The checkers made a mark on flask *B* corresponding to a volume of 220 ml.,

added the acid and stirrer, immersed the flask in liquid nitrogen, and passed in gaseous dimethyl ether from a cylinder until the volume of condensate reached the mark.
5. Diazomethane reacts with 2,4,6-trinitrobenzenesulfonic acid with ring opening similar to that observed with 1,3,5-trinitrobenzene.[7] Hence an excess of the reagent is to be avoided. The yellow color is not due to the presence of diazomethane itself. The reaction time is highly sensitive to the temperature of the xylene solution and to the flow rate of gaseous dimethyl ether. The reaction time is usually 20–40 minutes.
6. The excess diazomethane in flask A should be destroyed by adding a few drops of glacial acetic acid.
7. The ethyl acetate acts only as a high-boiling material that makes the subsequent vacuum filtration easier to control.
8. If the product is air-dried for more than a few seconds on the filter, it may pick up a significant amount of water. Most of the solvent that remains with the crystals should be removed under vacuum.
9. The product at this stage of purification is sufficiently pure for synthetic applications. As measured by the amount of dimethyl ether evolved on heating, its purity is about 95%.
10. On very rapid heating, the compound effervesces at about 120–130°. It then resolidifies and melts again at 181–183°, which is the melting point of methyl 2,4,6-trinitrobenzenesulfonate. At low heating rates, the effervescence may not be noticed.

3. Discussion

This method for the preparation of trimethyloxonium 2,4,6-trinitrobenzenesulfonate is an adaptation of that described by the submitters.[8] The salt can also be prepared from trimethyloxonium fluoborate by anion exchange.[8] Trimethyloxonium fluoborate[9] and hexachloroantimonate[10,11,12] have been prepared by other methods.

4. Merits of the Preparation

Like triethyloxonium fluoborate,[13] trimethyloxonium 2,4,6-trinitrobenzenesulfonate is a potent alkylating agent. Trimethyloxonium 2,4,6-trinitrobenzenesulfonate is nonhygroscopic and hence keeps better than trimethyloxonium fluoborate,[9] but it is more laborious to make.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 1080
- Org. Syn. Coll. Vol. 5, 1096
- Org. Syn. Coll. Vol. 6, 1019

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

sodium metabisulfite

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ethyl acetate (141-78-6)

diethyl ether (60-29-7)

chloroform (67-66-3)

nitrogen (7727-37-9)

sodium bisulfite (7631-90-5)

dimethyl ether (115-10-6)

acetone (67-64-1)

potassium hydroxide (1310-58-3)

xylene (106-42-3)

1,3,5-Trinitrobenzene (99-35-4)

Diazomethane (334-88-3)

Nitrosomethylurea

picryl chloride (88-88-0)

Triethyloxonium fluoborate (368-39-8)

trimethyloxonium fluoborate (420-37-1)

Trimethyloxonium 2,4,6-trinitrobenzenesulfonate (13700-00-0)

2,4,6-Trinitrobenzenesulfonic acid (2508-19-2)

methyl 2,4,6-trinitrobenzenesulfonate

hexachloroantimonate

phosphorus pentoxide (1314-56-3)

Oxonium compounds, trimethyloxonium 2,4,6-trinitrobenzenesulfonate

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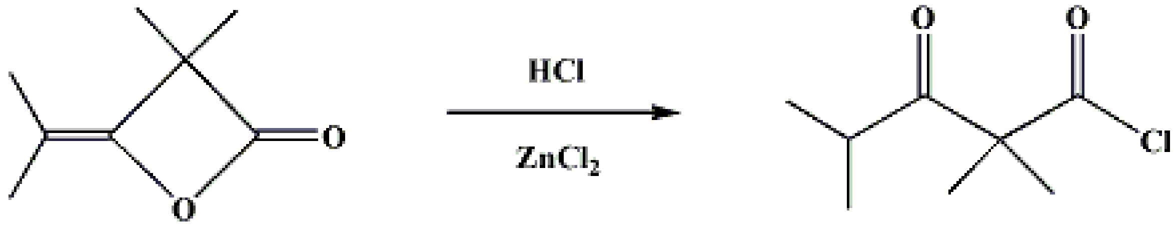
Organic Syntheses, CV 5, 1103

2,2,4-TRIMETHYL-3-OXOVALERYL CHLORIDE

[Valeryl chloride, 2,2,4-trimethyl-3-oxo-]



Submitted by Edward U. Elam, P. Glenn Gott, and Robert H. Hasek[1].
Checked by V. Boekelheide and G. Singer.

1. Procedure

Caution! The starting material in this preparation, 3-hydroxy-2,2,4-trimethyl-3-pentenoic acid β-lactone, is a mild but deceptively persistent lachrymator.

A mixture of 5 g. of anhydrous zinc chloride (Note 1) and 280 g. (2.00 moles) of 3-hydroxy-2,2,4-trimethyl-3-pentenoic acid β-lactone[2] is placed in a 500-ml. three-necked flask equipped with a sealed stirrer (Note 2), a coarse fritted-glass gas-dispersion thimble, a thermometer immersed in the liquid, and an air-cooled reflux condenser (Note 3). The outlet of the condenser is connected to a bubble counter filled with concentrated sulfuric acid; this in turn is vented to the atmosphere through a water scrubber. The flask is immersed in an ice bath, and stirring is started. When the temperature of the mixture is about 10°, anhydrous hydrogen chloride is introduced through the gas-dispersion tube at such a rate that a slow stream of bubbles escapes through the bubble counter. Gas absorption is slow at first, but after a few minutes the zinc chloride dissolves and the rate of gas absorption increases sharply. The temperature rises rapidly to 50–70° at the same time (Note 4). After about 10 minutes the temperature falls and the rate of gas absorption decreases. The ice bath is revmoed, and the addition of hydrogen chloride is continued for 30 minutes.

The reaction mixture is distilled rapidly under reduced pressure through a short Vigreux column (Note 5). The yield of crude product, b.p. 50–80° (5–10 mm.), n^{20}_D 1.4410–1.4416, is 310–330 g. (88–93%). This material is sufficiently pure for most purposes (Note 6). Fractionation through a 1 × 36-in. column packed with 8 × 8-mm. glass helices gives, after removal of a small amount of forerun, pure 2,2,4-trimethyl-3-oxovaleryl chloride, b.p. 86° (23 mm.), n^{20}_D 1.4418.

2. Notes

1. Reagent grade anhydrous zinc chloride from a freshly opened bottle may be used without special drying.
2. A glass or Teflon stirrer should be used.
3. An air-cooled condenser long enough to trap escaping spray is sufficient since the mixture is never hot enough to reflux.
4. Overheating of the mixture at this point or during the subsequent distillation causes decomposition of the crude acid chloride with formation of tarry by-products. This decomposition in the presence of zinc chloride is fairly rapid at temperatures above 100°.
5. Since hydrogen chloride is evolved in the early stages of this distillation, no effort is made to control the pressure. The vacuum pump is protected from the hydrogen chloride by insertion of a 1.5 × 15-in. glass tube packed with sodium hydroxide pellets in the vacuum line. The purpose of this distillation is to remove dissolved hydrogen chloride and the zinc chloride catalyst; it should be completed as rapidly as possible, under the best vacuum attainable, with no attempt at fractionation. The distillate may be fractionally distilled for further purification if desired. 2,2,4-Trimethyl-3-oxovaleryl chloride is stable at its normal boiling point, 190° (730 mm.), after the zinc chloride has been removed. Contact of the acid chloride with metals should be avoided.
6. The chlorine content of the crude product varied from 19.9% to 20.1% in successive experiments; saponification analysis indicated a purity above 97%.

3. Discussion

The procedure described is related to that for preparing acetoacetyl chloride from diketene and hydrogen chloride.[3]

4. Merits of the Preparation

Unlike acetoacetyl chloride, which decomposes at temperatures above −20°, 2,2,4-trimethyl-3-oxovaleryl chloride is stable at elevated temperatures. It may find use as an intermediate; for example, it can be used in the preparation of acid chlorides by an exchange reaction which is forced to completion by decarboxylation of the by-product, β-keto acid:

$$RCO_2H + (CH_3)_2CHCOC(CH_3)_2COCl \rightleftharpoons RCOCl + (CH_3)_2CHCOC(CH_3)_2CO_2H$$

$$(CH_3)_2CHCOC(CH_3)_2CO_2H \downarrow (CH_3)_2CHCOCH(CH_3)_2 + CO_2$$

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

hydrogen chloride (7647-01-0)

sodium hydroxide (1310-73-2)

diketene (674-82-8)

chlorine (7782-50-5)

zinc chloride (7646-85-7)

acetoacetyl chloride

3-hydroxy-2,2,4-trimethyl-3-pentenoic acid β-lactone (3173-79-3)

2,2,4-Trimethyl-3-oxovaleryl chloride, Valeryl chloride, 2,2,4-trimethyl-3-oxo- (10472-34-1)

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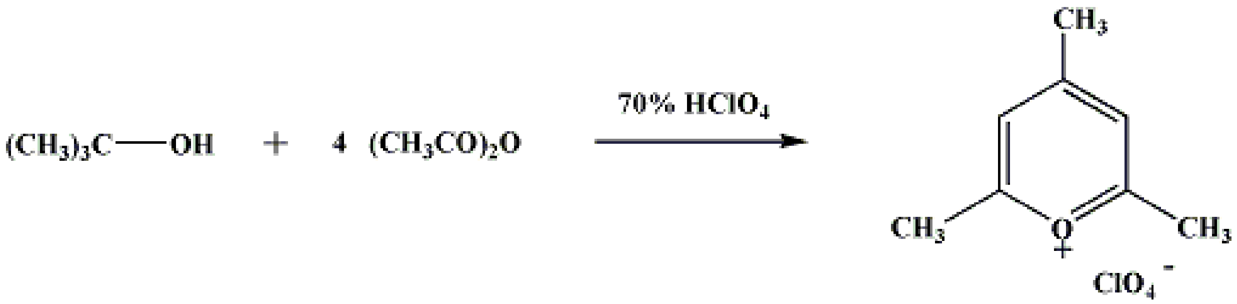
Organic Syntheses, CV 5, 1106

2,4,6-TRIMETHYLPYRYLIUM PERCHLORATE

[Method I]



Submitted by A. T. Balaban[1] and C. D. Nenitzescu[2].
Checked by Karl Bangert and Virgil Boekelheide.

1. Procedure

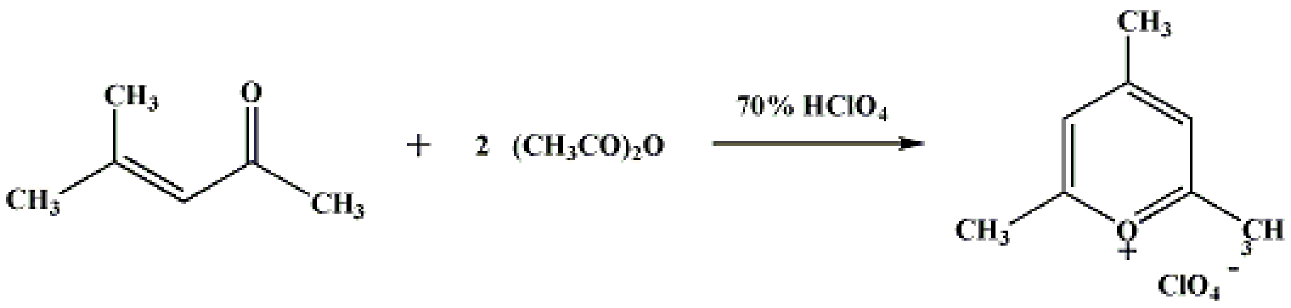
Caution! 2,4,6-Trimethylpyrylium perchlorate is explosive. Operations should be conducted behind a shield, and directions should be followed closely (see (Note 1) of Method I and Section 4 before carrying out these preparations).

In a 2-l. four-necked flask (or a three-necked flask with a Y-tube connection) outfitted with a stirrer, a short reflux condenser, a dropping funnel, and a thermometer reaching to the bottom of the flask, 148 g. (2.0 moles) of anhydrous *t*-butyl alcohol and 1020 g. (945 ml., 10.0 moles) of acetic anhydride are mixed with stirring and cooled to −10° by means of an ice-salt cooling bath. Then 250 g. (150 ml., 1.75 moles) of 70% perchloric acid is added rapidly from the dropping funnel to the stirred mixture over a period of 5–7 minutes (Note 2). With the first few drops a vigorous reaction begins which is manifested by evolution of fumes, coloration of the reaction mixture to orange and then reddish brown, and a rapid rise in temperature. When the temperature of the reaction mixture reaches 40–50°, crystals of 2,4,6-trimethylpyrylium perchlorate should begin to separate (Note 3); then the temperature is allowed to rise to 100°. The rate of perchloric acid introduction and the use of the cooling bath are then so controlled that the temperature of the reaction mixture is maintained between 100° and 105°. Toward the end of the addition the perchloric acid may be added quite rapidly and the desired temperature may still be maintained. After all the perchloric acid has been added, the cooling bath is removed and stirring of the mixture is continued. The temperature remains at about 90° for 10 or 15 minutes and then falls to about 75° after 30 minutes. The dark-brown stirred mixture is cooled once again until the temperature has fallen to 15°. The crystalline 2,4,6-trimethylpyrylium perchlorate, which has separated, is collected on a Büchner funnel and is washed on the funnel with a 1:1 mixture of acetic acid and ether and then washed twice with ether (Note 4). Suction is stopped before the crystals are dry. The product can be air-dried to give 195–210 g. (50–54%) of yellow crystals, m. p. 244° dec. (Note 1), (Note 5), and (Note 6). For storing or for use in the preparation of 4,6,8-trimethylazulene, however, it is best to place the product in a cork-stoppered flask and moisten it with dry tetrahydrofuran.

2. Notes

1. The impact sensitivity of 2,4,6-trimethylpyrylium perchlorate was examined by Dr. T. E. Stevens at the Redstone Arsenal Division of Rohm and Haas Co., and the compound was found to be slightly more sensitive to detonation by impact than the commercial explosive RDX. This point should be kept constantly in mind. When the crystals are handled as a slurry or are wet with solvent, the hazard is considerably reduced. On the other hand, the dry perchlorate should be handled with great care and should never be crushed, rubbed, or pushed through a narrow opening.
2. The specified order of mixing the three reagents is critical. If the reagent added to the solution of the other two is *t*-butyl alcohol or acetic anhydride, large amounts of triisobutylenes are formed, separating as a colorless upper layer.
3. The rate of perchloric acid introduction should be slow at first so that in the range of 40–50° crystals of the 2,4,6-trimethylpyrylium perchlorate will begin to appear. Then the rate of addition should be increased to maintain the temperature in the optimum range of 100–105°. If the temperature rises too rapidly, no crystals will appear and the yield will be somewhat lower. Then seeding is helpful.
4. If crystallization is not complete, dilution of the filtrate by the ether washings will cause separation of additional crystals. These are collected separately because they are finer and less pure. Concentration of filtrates is to be avoided because severe explosions[3] have been reported when solutions of perchloric acid in acetic acid were concentrated.
5. The product is of satisfactory purity for use in the 4,6,8-trimethylazulene preparation without further purification. Recrystallization of a small sample of the 2,4,6-trimethylpyrylium perchlorate from a seven-fold amount of hot water, containing a few drops of perchloric acid and some carbon black, gives colorless crystals, m.p. 245–247° dec. However, the recrystallization of larger amounts in this way presents some hazard and is not recommended. Concentration of filtrates should be avoided (see (Note 4)).
6. The preparation of 2,4,6-trimethylpyrylium perchlorate may be carried out on a much smaller scale, such as one-tenth, with only a small lowering of the yield.

[Method II]



Submitted by K. Hafner and H. Kaiser[4].
Checked by Virgil Boekelheide and H. Fleischer.

1. Procedure

Caution! 2,4,6-Trimethylpyrylium perchlorate is explosive. Operations should be conducted behind a shield, and directions should be followed closely (see (Note 1) of Method I and Section 4 before carrying out these preparations.)

In a 2-l. four-necked flask (or a three-necked flask with a Y-tube connector) equipped with a stirrer, a reflux condenser, a dropping funnel, and a thermometer extending nearly to the bottom of

the flask is placed 550 ml. (595 g., 5.83 moles) of acetic anhydride which is cooled to 0° with an ice-salt bath. Then 180 ml. (300 g., 2.09 moles) of a 70% solution of perchloric acid is added with stirring at a rate such that the temperature does not rise above 8° (Note 1). This step takes about 3 hours. The mixture is continually cooled and stirred, and 240 ml. (204 g., 2.09 moles) of mesityl oxide is then added slowly. The slow addition of 370 ml. (400 g., 3.92 moles) of acetic anhydride follows. The ice bath is then replaced by a water bath; the temperature of the reaction mixture will usually rise to 50–70° because of the heat liberated by the exothermic reaction, and the reaction mixture will turn dark. The reaction mixture is heated on a steam bath for 15 minutes to complete the reaction, and the mixture is then allowed to cool and stand at room temperature for 2 hours. The crystals, which have separated from the brown solution, are collected on a Büchner funnel and are washed on the funnel twice with 100-ml. portions of acetic acid, twice with 100-ml. portions of absolute ethanol, and twice with 100-ml. portions of absolute ether. This gives 250–260 g. (54–56%) of pale-yellow to light-brown crystals, m.p. 240° dec. (Note 2). For storage the crystals should be transferred, without drying, to an ordinary flask, moistened with dry tetrahydrofuran, and then kept in this state by stoppering the flask with an ordinary cork (Note 3).

2. Notes

1. Since the reaction is quite exothermic, the mixture must be well stirred to avoid developing any local hot spots which could lead to explosions. Although no difficulties were encountered in either the submitters' or checkers' laboratories, it is well to keep in mind that 2,4,6-trimethylpyrylium perchlorate is potentially hazardous; hence due precaution should be exercised at all times.
2. Although a small sample of 2,4,6-trimethylpyrylium perchlorate may with care be recrystallized from acetic acid to give white crystals, m.p. 245–247° dec., it is recommended that this not be done with larger quantities. The 2,4,6-trimethylpyrylium perchlorate is of satisfactory purity for use in the 4,6,8-trimethylazulene preparation without further purification.
3. The hazard of handling 2,4,6-trimethylpyrylium perchlorate is greatly reduced if the crystals are kept moist with a solvent such as tetrahydrofuran. The flask used for storage should be stoppered with a cork rather than a ground-glass stopper to avoid the possibility of initiating an explosion by the grinding action of the stopper.

3. Discussion

2,4,6-Trimethylpyrylium perchlorate has been prepared from 2,6-dimethylpyrone and methylmagnesium halides;[5] from mesityl oxide and sulfoacetic acid;[6] from mesityl oxide (or less satisfactorily from acetone) and a mixture of acetic anhydride and perchloric acid;[7] from mesityl oxide, acetyl chloride, and aluminum chloride;[8] and from *t*-butyl chloride, acetyl chloride, and aluminum chloride.[8] The procedure given under Method I is adapted from that reported by Balaban and Nenitzescu[9] and is similar to that of Praill and Whitear.[10] The procedure given under II is adapted from that reported by Hafner and Kaiser.[11] The methods of preparation have been reviewed.[12]

4. Merits of the Preparation

2,4,6-Trimethylpyrylium perchlorate is a very versatile and useful starting material. Thus its reaction with cyclopentadienylsodium has made 4,6,8-trimethylazulene[13] easily available for

general studies of the properties of azulenes[14] and for the synthesis of related compounds.[15] In addition, pyrylium salts are readily converted to a variety of pyridine derivatives,[9,16] 4H- and 2H-pyrans,[17] 2-acylfurans,[18,19] isoxazolines,[20] pyrazolines,[20] 1,2-diazepines,[20,21] 5-cyano-2,4-dien-1-ones,[22] and various benzene and naphthalene derivatives,[23] including derivatives of nitrobenzene[24] and phenol.[9,25,26] It is clear that its value as a starting material is such that it is receiving wide use.

In including this preparation in *Organic Syntheses*, it was felt that standard procedures which have been tested in more than one laboratory without difficulty and which attempt to point out as clearly as possible the potential hazards involved would serve a useful function for those who, despite the hazards, find this a necessary and important starting material.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 1088
- Org. Syn. Coll. Vol. 5, 1114
- Org. Syn. Coll. Vol. 5, 1135

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

carbon black

ethanol (64-17-5)

acetic acid (64-19-7)

ether (60-29-7)

acetic anhydride (108-24-7)

acetyl chloride (75-36-5)

phenol (108-95-2)

acetone (67-64-1)

aluminum chloride (3495-54-3)

Nitrobenzene (98-95-3)

t-butyl chloride (507-20-0)

Mesityl oxide (141-79-7)

Tetrahydrofuran (109-99-9)

t-butyl alcohol (75-65-0)

perchloric acid (7601-90-3)

cyclopentadienylsodium

4,6,8-Trimethylazulene (941-81-1)

2,4,6-Trimethylpyrylium perchlorate (940-93-2)

2,6-dimethylpyrone

sulfoacetic acid (123-43-3)

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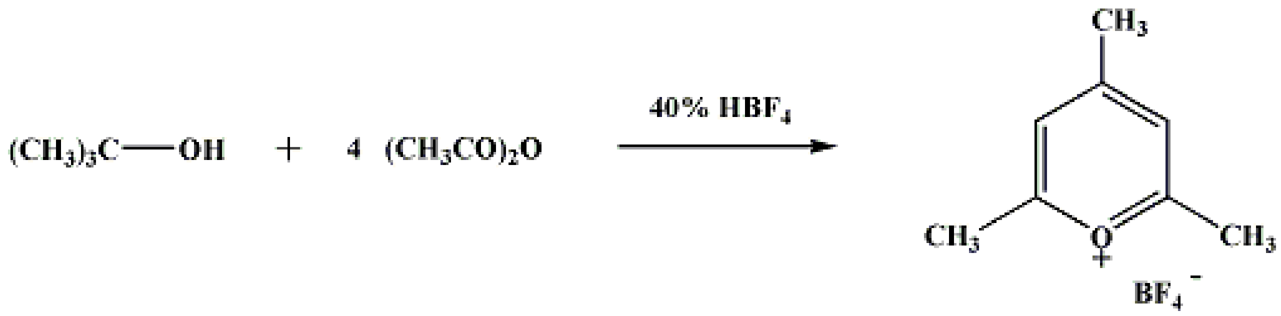
Organic Syntheses, CV 5, 1112

2,4,6-TRIMETHYLPYRYLIUM TETRAFLUOROBORATE



Submitted by A. T. Balaban and A. J. Boulton[1].
Checked by Dorothy G. McMahan and Henry E. Baumgarten.

1. Procedure

In a 250-ml. Erlenmeyer flask provided with a magnetic stirrer bar and a thermometer containing 50 ml. (54 g., 530 mmol.) of acetic anhydride and 4.0 ml. (3.1 g., 41 mmol.) of dry *t*-butyl alcohol, 7 ml. (39 mmol.) of 40% fluoroboric acid (Note 1) are added, initially very cautiously, and then in *ca.* 0.2-ml. portions until all has been added, at such a rate that the final temperature reaches *ca.* 100°. A dark yellow-brown color develops. The solution is allowed to cool spontaneously to 80°, and then is chilled to 5° in an ice bath. Separation of the salt begins and is completed by the addition of 100 ml. of ether. After filtration on a Büchner funnel the salt is washed with 30 ml. of ether, yielding 3.9–4.1 g. (47–50%) of a colorless or pale yellow product, m.p. 218–220° (decomp.) (Note 2). The crude product may be recrystallized from ethanol-methanol 1:1 (*ca.* 70–80 ml.) containing a few drops of fluoroboric acid, affording 3.4–3.5 g. (41–43%) of colorless prisms, m.p. 224–226° (decomp.) (Note 3).

2. Notes

1. The checkers used 6 ml. of 48% fluoroboric acid obtained from the Ozark Mahoning Co.
2. The checkers collected two crops of crystals, the second precipitating during the filtration of the first. The crude product was dried between filter papers overnight.
3. The yields reported are those of the checkers obtained with 48% fluoroboric acid and are about 30% higher than those (27–32%) reported by the submitters. Larger scale preparations (five or more times the quantities described here) have been carried out by the submitters. Such preparations require external cooling.

3. Discussion

See the Discussion section of 2,4,6-trimethylpyrilium trifluoromethanesulfonate.[2]

References and Notes

1. Institute of Atomic Physics, Bucharest, Rumania.

2. A. T. Balaban and A. J. Boulton, this volume, p. 1114.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

2,4,6-trimethylpyrilium trifluoromethanesulfonate

ether (60-29-7)

acetic anhydride (108-24-7)

ethanol-methanol (504-63-2)

t-butyl alcohol (75-65-0)

2,4,6-Trimethylpyrylium tetrafluoroborate (773-01-3)

fluoroboric acid (16872-11-0)

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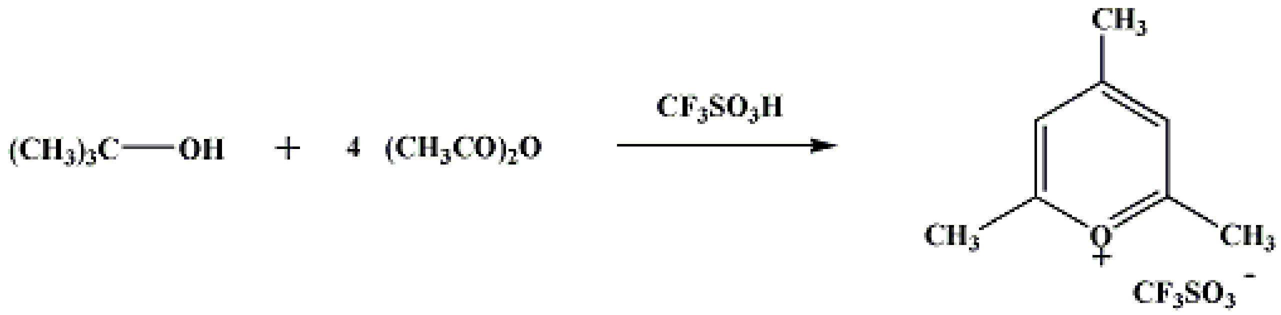
Organic Syntheses, CV 5, 1114

2,4,6-TRIMETHYLPYRYLIUM TRIFLUOROMETHANESULFONATE



Submitted by A. T. Balaban and A. J. Boulton[1].
Checked by Dorothy G. McMahan and Henry E. Baumgarten.

1. Procedure

In a 150-ml. Erlenmeyer flask are mixed 18 ml. (19.4 g., 192 mmol.) of acetic anhydride and 3.2 ml. (2.5 g., 34 mmol.) of anhydrous *t*-butyl alcohol. Two to three drops of trifluoromethanesulfonic acid (Note 1) is added and the mixture is swirled rapidly until the initial esterification reaction is complete (temperature stops rising). Further trifluoromethanesulfonic acid (total acid: 3.0 ml., 5.0 g. (33 mmol.)) is added in 0.1–0.2-ml. portions, over 10 minutes, with swirling and pausing between each addition until the temperature begins to fall. At the end of the addition the temperature is 60–70° (Note 2), and the solution is brown in color. It is allowed to stand for a further 5 minutes and then is cooled in ice. Anhydrous ether (100 ml.) is added, whereupon the pyrylium salt separates. The mixture is filtered with suction using a sintered glass funnel and the crude product is washed with a further 50 ml. of dry ether (Note 3), giving 3.6–3.8 g. (40–42%) of mustard colored to pale brown plates, m.p. 116–118° (Note 4).

The crude product is recrystallized from dioxane-acetic acid (7:1) or chloroform-carbon tetrachloride (2:1). The crystal form is very variable; needles, plates, or prisms may be formed, depending on the rate of formation, and the temperature. After recrystallization the 2,4,6-trimethylpyrilium trifluoromethane sulfonate melts at 119–120° (Note 5).

2. Notes

1. Trifuloromethanesulfonic acid may be obtained from Aldrich Chemical Company or Pierce Chemical Company.
2. If the reaction is conducted at a lower temperature (*ca.* 20°), a lighter solution and a more nearly pure product result, but the yield is much reduced (1–2 g., 11–22%). Allowing the temperature to rise above 70° gives a darker brown mixture, but with no improvement in yield.
3. The washing ether should be added before the crystals are exposed to the air, and the ether and crystals should be stirred to ensure thorough mixing. Otherwise a troublesome tar may separate. The product should be isolated within 2–3 hours of its precipitation, or it will be accompanied by black impurities which are slowly deposited by the mother

liquor, and are difficult to remove.
4. The checkers observed a variable range of melting points for the crude product, as broad as 108–113° and as sharp as 116–117°.
5. The checkers used chloroform-carbon tetrachloride for recrystallization and found that about 500 ml. of this mixture was required to dissolve the crude product and give a green colored solution. Their final yield after two recrystallations was 3.2–3.4 g. (36–38%), m.p. 118–119°.

3. Discussion

Although more expensive in materials, and so suitable mainly for small-scale work, the product does not have the explosive hazard of the corresponding perchlorate.[2] This advantage is shared with the tetrafluoroborate,[3] which, however, requires more acetic anhydride and may give poorer yields. The trifluoromethanesulfonate salt is also more soluble in organic solvents than the perchlorate or tetrafluoroborate (1 g. dissolves in 7 ml. of chloroform at 20°, and in 3 ml. at *ca.* 35°; it is also very soluble in alcohols and dichloromethane). For the usefulness of 2,4,6-trimethylpyrylium salts in general, see the notes pertaining to the perchlorate.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 1112

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

chloroform-carbon tetrachloride

2,4,6-trimethylpyrilium trifluoromethane sulfonate

acetic acid (64-19-7)

ether (60-29-7)

acetic anhydride (108-24-7)

chloroform (67-66-3)

carbon tetrachloride (56-23-5)

dichloromethane (75-09-2)

dioxane (5703-46-8)

t-butyl alcohol (75-65-0)

2,4,6-Trimethylpyrylium trifluoromethanesulfonate (40927-60-4)

trifluoromethanesulfonic acid (1493-13-6)

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Organic Syntheses, CV 5, 1116

TRIPHENYLALUMINUM

[Aluminum, triphenyl-]

$$3\ (C_6H_5)_2Hg + 2\ Al \xrightarrow{\text{xylene, }\Delta} 2\ (C_6H_5)_3Al + 3\ Hg$$

Submitted by T. A. Neely, William W. Schwarz, and Herbert W. Vaughan, Jr.[1].
Checked by R. D. Lipscomb and B. C. McKusick.

1. Procedure

Caution! Triphenylaluminum and its etherate undergo decomposition in the presence of air and moisture. Upon contact with water, vigorous heat evolution and sparking have been observed.

A 500-ml. one-necked flask with a side arm to admit nitrogen is fitted with a reflux condenser protected at the top by a T-tube through which nitrogen is slowly passed during the entire reaction (Note 1). In the flask there is placed 12 g. (0.44 g. atom) of aluminum wool (Note 2), and the system is thoroughly dried by flaming (Note 3) and then cooled to room temperature. A positive pressure of nitrogen is maintained in the system by admission of the gas through the side arm while the flask is detached from the condenser, stoppered, and transferred to a nitrogen-filled dry box. To the flask there is added 80 g. (0.23 mole) of diphenylmercury (Note 4) which is spread evenly on top of the aluminum wool, followed by 340 ml. of sodium-dried xylene. The flask is stoppered, returned to the condenser, and immersed in a preheated oil bath, which is maintained at 140–150°. The reaction mixture is allowed to reflux for 24 hours, the water drained from the condenser, and the top of the condenser is connected to a vacuum system through a trap cooled in dry ice. The xylene is distilled by gradually reducing the pressure to 20–30 mm. The flask is cooled to room temperature and nitrogen readmitted.

The flask is returned to the dry box, and the nearly dry solid that remains in it is transferred to an extraction thimble (123 mm. × 43 mm.) previously dried in a vacuum oven. The product is extracted in a dried Soxhlet apparatus (250 mm. × 50 mm.) with 250 ml. of dry ether (Note 5) in a carefully dried 300-ml. flask. The extraction is continued for 15–20 hours (Note 6), during which time white crystals of triphenylaluminum etherate form in the flask. The flask and its contents are placed in a dry box, the ether is decanted, and the crystals are washed several times by decantation with small portions of dry ether. The triphenylaluminum etherate is dried at 25° under reduced pressure; m.p. 126–130°. The ether of crystallization is removed by heating the etherate at 150° (0.1 mm.) for about 13 hours (Note 7). Pure triphenylaluminum, m. p. 229–232°, is obtained; yield 23–27 g. (59–70%).

2. Notes

1. All operations are conducted in an atmosphere of prepurified nitrogen or in a nitrogen-filled dry box. A positive nitrogen pressure is maintained in the flask during all transfers and additions. Prepurified nitrogen is available from Matheson Co., East Rutherford, New Jersey.
2. Suitable aluminum wool is available from Custom Scientific Instrument Inc., Kearney, New Jersey. It is thoroughly cleaned with both methylene chloride and ether and dried before use.
3. All glassware used in this preparation must be dry. Flaming out while purging with prepurified nitrogen is sufficient.
4. Suitable diphenylmercury is available from Orgmet, Hampstead, New Hampshire, or it can be prepared by the procedure of Gilman and Brown.[2]
5. A new container of anhydrous ether from Mallinckrodt Chemical Works or Merck and Co. is satisfactory.
6. At the end of the extraction the residual aluminum wool should be disposed of very carefully because it is in a highly reactive condition. As the ether evaporates, the aluminum wool oxidizes rapidly and becomes quite hot. In one run, 84% of the theoretical amount of metallic mercury was liberated during this oxidation.
The checkers evaporated the ether in a stream of nitrogen, then allowed air to diffuse in gradually through a small opening during 2 days. The residue was then inert.
7. During this operation the etherate melts, effervesces, and then solidifies. The etherate sublimes to a small extent; this can be counteracted by immersing the flask in an oil bath only part way during the first half of the heating, and finally immersing it to the bottom of its neck.

3. Discussion

The general procedure for this reaction, which was first reported by Friedel and Crafts,[3] is essentially that of Hilpert and Grüttner[4] as modified by Gilman and Marple.[5] Upon laboratory examination of these methods, only water-reactive gums and tars were isolated. Nesmeyanov and Novikova[6] reported the preparation of triphenylaluminum by a similar method, but worked on a test-tube scale and did not report a yield. Wittig and Wittenberg[7] prepared crystalline triphenylaluminum in 43% yield by the action of phenyllithium on aluminum chloride. In most of the procedures found, the triphenylaluminum was used in solution; hence crystalline material was not isolated.

When aluminum wool was substituted for strips of aluminum foil, a 20% yield of triphenylaluminum was obtained. This yield was increased to 70% by the extractive isolation described above. An alternative method of isolation and purification, that of

Krause and Polack,[8] was not attempted because of the lack of experimental detail and the complexity of the apparatus.

4. Merits of the Preparation

Triphenylaluminum is useful as a component of catalyst systems for ionic or coordination polymerization of vinyl compounds. This preparation of the material in solid form enables the purity of the compound to be easily determined. The availability of solid triphenylaluminum permits the user a choice of solvents for a reaction, and a variety of concentrations of the reagent. Storage and dispensation of the reagent are more convenient in the solid form.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium-dried xylene

ether (60-29-7)

nitrogen (7727-37-9)

aluminum (7429-90-5)

mercury (7439-97-6)

aluminum chloride (3495-54-3)

xylene (106-42-3)

Diphenylmercury (587-85-9)

methylene chloride (75-09-2)

Phenyllithium (591-51-5)

Triphenylaluminum, Aluminum, triphenyl- (841-76-9)

triphenylaluminum etherate

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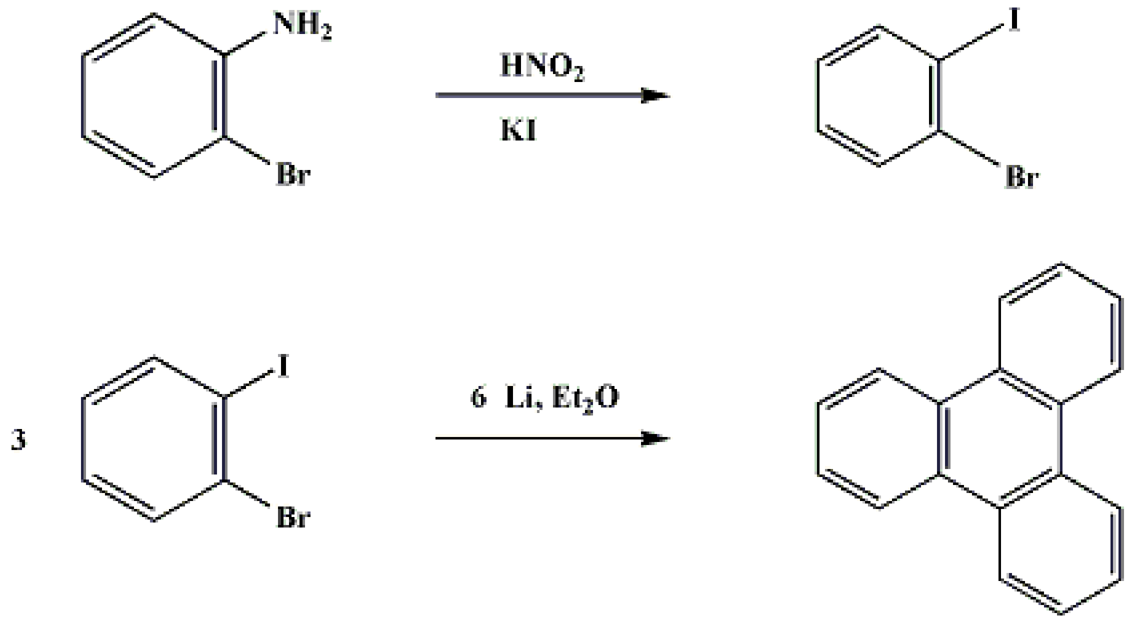
Organic Syntheses, CV 5, 1120

TRIPHENYLENE



Submitted by H. Heaney and I. T. Millar[1].
Checked by John D. Roberts and L. K. Montgomery.

1. Procedure

(Note 1)
In a 600-ml. beaker fitted with a thermometer and mechanical stirrer are placed 150 ml. of concentrated hydrochloric acid and 55 g. (0.32 mole) of *o*-bromoaniline. After brief stirring, 100 g. of ice is added and the beaker is surrounded by an ice-salt bath. The solution is then diazotized by the dropwise addition with stirring of a solution of 24.3 g. (0.35 mole) of sodium nitrite in 100 ml. of water, the temperature being kept at 0–5°.

After stirring the diazotized solution for 15 minutes, it is slowly poured through a glass-wool filter into a solution of 180 g. (3.4 moles) of potassium iodide in 600 ml. of water. After standing overnight, the heavy dark oil is separated, washed successively with 10% aqueous sodium hydroxide, water, 5% aqueous sodium bisulfite and water, and then dried over magnesium sulfate.

Distillation under reduced pressure gives *o*-bromoiodobenzene as a nearly colorless liquid, b.p. 120–121° at 15 mm. Yield 65–75 g. (72–83%).

A 1-l. flask is fitted with a reflux condenser, dropping funnel, and a sealed mechanical stirrer. A nitrogen atmosphere is maintained in the flask during the entire reaction period.

In the flask is placed 150 ml. of anhydrous ether, and 5.7 g. (4.1 atomic equivalents) of

lithium foil is then added (Note 2). A solution of 56.6 g. (0.2 mole) of *o*-bromoiodobenzene in 300 ml. of anhydrous ether is added dropwise (Note 3). When a vigorous reaction commences, the stirrer is started and the flask is cooled in ice water to maintain the temperature at about 10°. The reflux condenser is replaced by a thermometer, and the remainder of the *o*-bromoiodobenzene solution is added at a rate such that the temperature in the flask remains at about 10° (about 1.5 hours). When this addition is complete, 200 ml. of dry benzene is added; the mixture is stirred at 10° for 1 hour and finally at room temperature for 1 hour. The mixture is then poured through a glass-wool filter on 200 g. of ice.

The organic layer is separated, evaporated on a steam bath, and the dark semicrystalline residue is distilled with steam to remove biphenyl. The contents of the steam-distillation flask are then extracted with ether (Note 4), and the ethereal layer is separated, dried over magnesium sulfate, and percolated through a short column of chromatographic alumina (Note 5) and (Note 6). Evaporation of the ethereal solution gives crude triphenylene which is sublimed at 175–180° and 0.1 mm. pressure. After rejection of an initial sublimate of impure biphenyl, the sublimed material forms nearly colorless crystals, m.p. 186–194° (Note 7). Yield 8–9 g. (53–59%). It may be further purified by recrystallization from a mixture of methylene chloride and pentane yielding colorless crystals, m.p. 199° (Note 8).

2. Notes

1. Although the procedure described here is still a useful method of preparing triphenylene, it is in the opinion of the submitters no longer the best available. In their opinion a more nearly pure product and a higher yield (85%) may be obtained by the reaction of *o*-bromofluorobenzene and magnesium in tetrahydrofuran[2] (private communication from H. Heaney).
2. Slugs of lithium, coated with paraffin oil, are hammered into thin foil. They are washed free of oil with dry ether and cut by scissors into slips which are allowed to fall directly into the ether in the reaction flask.
3. By adding 10–20 ml. of the *o*-bromoiodobenzene solution to the metal before stirring is started, high local concentrations of the dihalo compound which initiate reaction are built up. An induction period of about 10 minutes is usually observed before the vigorous reaction commences.
4. The checkers found that, in view of the limited solubility of triphenylene in ether (about 1 g. per 100 ml.), care must be exercised in the extraction to ensure that all the product is removed.
5. The volume of ether solution must be reduced to approach the solubility limit of the triphenylene in ether before the chromatographic procedure.
6. The checkers used a 30-mm. (I.D.) chromatographic column charged with approximately 250 g. of activated (400° for 12 hours), acid-washed, chromatographic aluminum oxide (Merck and Co., Inc.).
7. The contaminant in the product of m.p. 186–194° is present in low concentration and is very probably *o*-terphenyl. It is characterized by an

absorption near 695 cm.$^{-1}$ in the infrared which is absent in the spectrum of pure triphenylene.

The submitters report that the purity of the product is rather dependent upon the purity of the lithium used and that results can vary from batch to batch. In addition, they state that side reactions may be catalyzed by traces of heavy metals, that the degree of vigor in the initial reaction may influence the purity of the product owing to local overheating, and that increase in scale of this reaction is deleterious.

8. The checkers carried out this recrystallization by dissolving triphenylene in a minimum of methylene chloride maintained at reflux. Pentane was slowly added to this solution; up to 90% recovery was achieved.

3. Discussion

Triphenylene has been prepared by self-condensation of cyclohexanone using sulfuric acid[3] or polyphosphoric acid[4] followed by dehydrogenation of the product, dodecahydrotriphenylene, using copper,[3] palladium-charcoal,[4] or selenium;[5] by electrolytic oxidation of cyclohexanone;[6] from chlorobenzene and sodium[7] or phenyllithium;[8] from 2-cyclohexyl-1-phenylcyclohexanol[9] or 2-(1-cyclohexene-1-yl)-1-phenylcyclohexanol[4,10] by dehydrogenation; from 9-phenanthryl magnesium bromide and succinic anhydride followed by reduction, cyclization, and dehydrogenation;[11] by the action of lithium on *o*-diiodobenzene[12] or magnesium on *o*-bromofluorobenzene,[2] and by the dehydrogenation of *o*-terphenyl.[13]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

polyphosphoric acid

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether (60-29-7)

sodium hydroxide (1310-73-2)

magnesium (7439-95-4)

Cyclohexanone (108-94-1)

potassium iodide (7681-11-0)

nitrogen (7727-37-9)

sodium nitrite (7632-00-0)

sodium bisulfite (7631-90-5)

copper (7440-50-8)

chlorobenzene (108-90-7)

sodium (13966-32-0)

palladium (7440-05-3)

Biphenyl (92-52-4)

Pentane (109-66-0)

methylene chloride (75-09-2)

Phenyllithium (591-51-5)

lithium (7439-93-2)

magnesium sulfate (7487-88-9)

Succinic anhydride (108-30-5)

selenium

aluminum oxide (1344-28-1)

Tetrahydrofuran (109-99-9)

9-phenanthryl magnesium bromide

o-bromofluorobenzene (1072-85-1)

o-terphenyl (84-15-1)

Triphenylene (217-59-4)

dodecahydrotriphenylene

2-cyclohexyl-1-phenylcyclohexanol

2-(1-cyclohexene-1-yl)-1-phenylcyclohexanol

o-bromoaniline (615-36-1)

o-bromoiodobenzene (583-55-1)

o-diiodobenzene (615-42-9)

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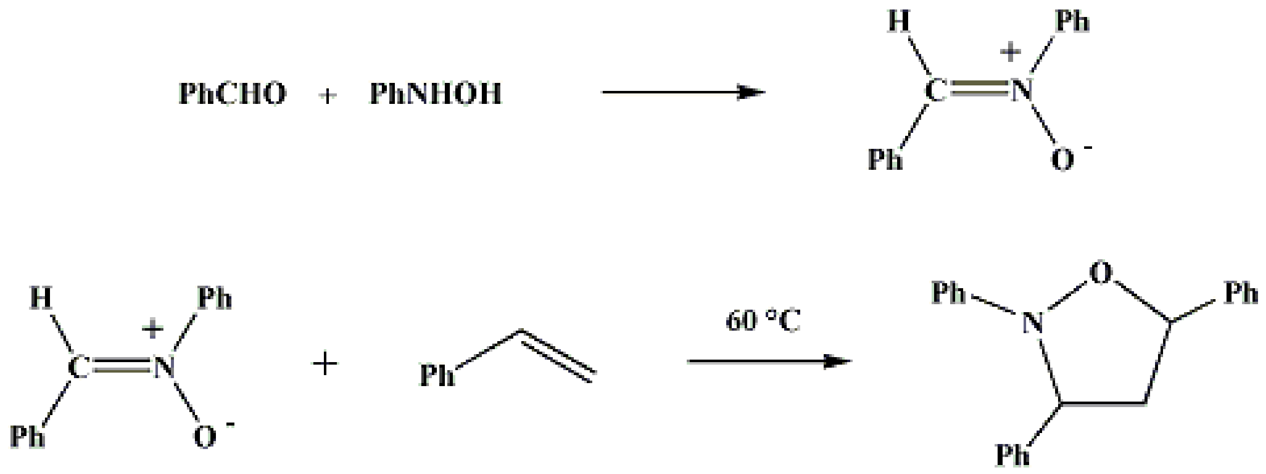
Organic Syntheses, CV 5, 1124

2,3,5-TRIPHENYLISOXAZOLIDINE

[Isoxazolidine, 2,3,5-triphenyl-]



Submitted by Ingrid Brüning, Rudolf Grashey, Hans Hauck, Rolf Huisgen, and Helmut Seidl[1].
Checked by George E. Davis, Wayland E. Noland, and William E. Parham.

1. Procedure

A. *N,α-Diphenylnitrone*. A solution of 27.3 g. (0.25 mole) of pure N-phenylhydroxylamine[2] (Note 1) in 50 ml. of ethanol is prepared in a 200-ml. Erlenmeyer flask by swirling a mixture of the two and warming it briefly to 40–60° (Note 2). To the clear, lightly colored solution is added 26.5 g. (25.3 ml., 0.25 mole) of freshly distilled benzaldehyde (exothermic reaction). The flask is stoppered and kept overnight at room temperature in the dark. The colorless needles of N,α-diphenylnitrone are collected on a Büchner funnel and washed once with 20 ml. of ethanol. There is obtained 42–43 g. (85–87%) of product (m.p. 111–113°), which can be further purified by dissolving the crude material in 80 ml. of ethanol and allowing the solution to cool for several hours in the ice box. In this manner there is produced 35–39 g. (71–79%) of pure crystalline nitrone, m.p. 113–114° (Note 3).

B. *2,3,5-Triphenylisoxazolidine*. In a 100-ml. two-necked flask provided with a reflux condenser and a gas-inlet tube are placed 20.0 g. (0.101 mole) of pure N,α-diphenylnitrone and 50 ml. (0.43 mole) of freshly distilled styrene (Note 4). The flask is heated at 60° for 40 hours a slow nitrogen stream. The mixture is then cooled, and most of the excess styrene is removed (Note 5) from the clear orange solution by heating at a bath temperature of 55° (12 mm.). The warm residue is poured into 40 ml. of petroleum ether (40–60°), whereupon the isoxazolidine crystallizes immediately (Note 6). The flask is rinsed twice with 20-ml. portions of petroleum ether, and the washings are combined with the product. The resulting mixture is cooled for 1 hour in the ice box, and the lightly colored crystals are collected on a Büchner funnel and washed with two

20-ml. portions of petroleum ether. The yield of crude air-dried isoxazolidine (m.p. 96–98°) is 28–30 g. (92–99%).

For further purification the product is dissolved in 40 ml. of methylene chloride in a 250-ml. Erlenmeyer flask. The solution is heated to boiling, and 30 ml. of methanol is added (Note 7). When the solution has cooled to room temperature, 70 ml. of methanol is added to complete the crystallization, and the solution is kept in the ice box for 3 hours. The colorless needles are collected by vacuum filtration and washed with two 30-ml. portions of cold methanol. There is obtained 23–25 g. (76–82%) of product which melts at 99–100° (Note 8),(Note 9),(Note 10).

2. Notes

1. The N-phenylhydroxylamine should be free of sodium chloride. This is easily attained by dissolution of the compound in benzene followed by filtration and then addition of petroleum ether to cause rapid crystallization.
2. On prolonged heating, N-phenylhydroxylamine begins to decompose.
3. The compound is light-sensitive and should be kept in a brown container.
4. The styrene should be redistilled and stabilized with 0.1% hydroquinone just prior to use; otherwise the final product will be contaminated with polystyrene. The checkers used approximately 60 ml. (0.52 mole) of styrene.
5. The checkers found that, if all the styrene is removed, the product may become too viscous to pour.
6. By this method the formation of a thick crustaceous material, which is difficult to pulverize or wash, is avoided.
7. In this way the boiling solution is kept clear.
8. From the mother liquor a second diastereoisomer can be isolated (m.p. 78.5–79.5°) in about 10% yield by fractional crystallization.
9. In an analogous manner several other isoxazolidines can be prepared. From the reaction of N,α-diphenylnitrone with 1,1-diphenylethylene, 2,3,5,5-tetraphenylisoxazolidine is obtained. As above, 10.0 g. (50.7 mmoles) of diphenylnitrone is heated under a nitrogen atmosphere for 24 hours at 85° with 15.3 g. (15.0 ml., 85.0 mmole) of 1,1-diphenylethylene.[3] The excess olefin is removed at 105–130° (bath temperature) under high vacuum (0.005 mm.). The yellow-gold viscous residue is dissolved by warming it in a mixture of 15 ml. of methylene chloride and 30 ml. of methanol; on cooling, crystallization commences. After 2 hours another 10 ml. of methanol is added, and the mixture is cooled overnight in the ice box. The colorless crystals are collected on a Büchner funnel and washed twice with 20-ml. portions of methanol. The yield of air-dried product (m.p. 113–115°) is 14–16 g. (73–84%). The compound can be further purified by adding methanol (30 ml.) to a boiling solution in methylene chloride (15 ml.). After the solution has cooled to room temperature, another 10 ml. of methanol is added; the mixture is kept in the ice box for several hours and then filtered. The pure compound melts at 115–116°, yield 13–15 g. (68–79%).
10. The preparation of the oily ethyl 2,3-diphenyl-5-methylisoxazolidine-4-carboxylate provides another example of this reaction. As in the procedure

described with styrene, 10.0 g. (50.7 mmoles) of N,α-diphenylnitrone is heated under nitrogen for 24 hours at 90–100° with 35.0 g. (38.0 ml., 307 mmoles) of ethyl crotonate. The excess olefin, b.p. 45° (12 mm.) is removed on the water pump, and the red-orange residue, while still warm, is transferred to a 50-ml. Claisen flask using acetone as a rinse. After removal of the solvent, 13–14 g. (82–88%) of the isoxazolidine is obtained as an orange oil by high-vacuum distillation at 163–173° (0.003 mm.). Redistillation of this material yields 2–3 g. of fore-run and a purer product obtained as a yellow oil, b.p. 165–170° (0.003 mm.), n^{20}_D 1.5602–1.5612.

3. Discussion

N,α-Diphenylnitrone was first obtained by Bamberger[4] from N-phenylhydroxylamine and benzaldehyde. The procedure described above is analogous to that of Wheeler and Gore.[5]

2,3,5-Triphenylisoxazolidine, 2,3,5,5-tetraphenylisoxazolidine, and ethyl 2,3-diphenyl-5-methylisoxazolidine-4-carboxylate have been prepared only by this method.[6]

4. Merits of the Preparation

The procedure described illustrates the use of 1,3-dipolar addition[7] of nitrones to olefins for the preparation of isoxazolidines. The preparations of 2,3,5,5-tetraphenylisoxazolidine and ethyl 2,3-diphenyl-5-methylisoxazolidine-4-carboxylate, as described in (Note 9) and (Note 10), respectively, indicate the versatility of the method.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

polystyrene

ethanol (64-17-5)

Benzene (71-43-2)

methanol (67-56-1)

hydroquinone (123-31-9)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

benzaldehyde (100-52-7)

acetone (67-64-1)

N-Phenylhydroxylamine (100-65-2)

1,1-Diphenylethylene (530-48-3)

methylene chloride (75-09-2)

styrene (100-42-5)

ethyl crotonate (623-70-1)

2,3,5-Triphenylisoxazolidine, Isoxazolidine, 2,3,5-triphenyl- (13787-96-7)

N,α-Diphenylnitrone (1137-96-8)

2,3,5,5-tetraphenylisoxazolidine (25116-92-1)

diphenylnitrone (59862-61-2)

ethyl 2,3-diphenyl-5-methylisoxazolidine-4-carboxylate (19744-10-6)

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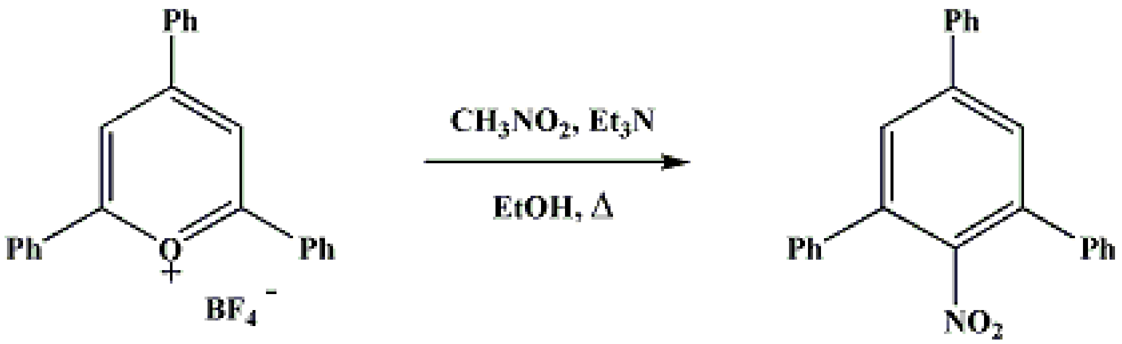
Organic Syntheses, CV 5, 1128

2,4,6-TRIPHENYLNITROBENZENE

[Benzene, 2-nitro-1,3,5-triphenyl-]



Submitted by K. Dimroth, A. Berndt, and C. Reichardt[1].
Checked by Saul Cherkofsky and Richard E. Benson.

1. Procedure

In a 1-l. three-necked flask equipped with a mechanical stirrer, a reflux condenser, and a dropping funnel are placed 119 g. (0.30 mole) of 2,4,6-triphenylpyrylium tetrafluoroborate (Note 1), 21 ml. (24 g., 0.39 mole) of nitromethane (Note 2), and 350 ml. of absolute ethanol (Note 3). Triethylamine (70 ml., 51 g.) (Note 4) is added rapidly from the dropping funnel to the well-stirred suspension. The reaction mixture becomes reddish brown immediately, and the solid dissolves. After all the triethylamine has been added, the mixture is heated under reflux for 3 hours, cooled, and allowed to stand overnight in a refrigerator. The crystalline product that separates is collected on a Buchner funnel and washed with two 50-ml. portions of ice-cold methanol. The product (75–80 g.; m.p. 142–144°) is recrystallized from 200–250 ml. of glacial acetic acid to yield 70–75 g. (67–71%) of 2,4,6-triphenylnitrobenzene as slightly yellow crystals, m.p. 144–145° (Note 5).

2. Notes

1. The preparation of 2,4,6-triphenylpyrylium tetrafluoroborate is described on p. 1135.
2. Nitromethane is dried over anhydrous calcium sulfate (Drierite) or calcium chloride for 1 day and distilled; the fraction with b.p. 101.5–102.5° is used.
3. Commercial absolute ethanol is used without additional drying.
4. Triethylamine is dried over sodium hydroxide pellets and distilled; the fraction with b.p. 89.5–90° is used.
5. The n.m.r. spectrum ($CDCI_3$) shows singlets at 7.45 p.p.m. (15 H) and 7.65 p.p.m. (2 H) (downfield from internal tetramethylsilane reference).

3. Discussion

2,4,6-Triphenylnitrobenzene may be prepared by direct nitration of 1,3,5-triphenylbenzene[2,3,4] and by the reaction of 2,4,6-triphenylpyrylium tetrafluoroborate with nitromethane.[5] The present procedure is an adaptation of the latter method.

This procedure illustrates a general method for converting substituted pyrylium salts to nitrobenzene derivatives. The reaction has been the subject of several reviews.[6,7,8] The yields are generally high, and under these conditions only a single product is formed, in contrast to the nitration of 1,3,5-triphenylbenzene. The preparation of 2,4,6-triphenylnitrobenzene from the corresponding pyrylium salt eliminates isomer separation problems, which are encountered when the direct nitration procedure is used. Also, labeled compounds can readily be prepared by this method.[9]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 1130

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

calcium sulfate (Drierite)

ethanol (64-17-5)

calcium chloride (10043-52-4)

acetic acid (64-19-7)

methanol (67-56-1)

sodium hydroxide pellets (1310-73-2)

Nitromethane (75-52-5)

triethylamine (121-44-8)

2,4,6-Triphenylnitrobenzene, Benzene, 2-nitro-1,3,5-triphenyl- (10368-47-5)

2,4,6-Triphenylpyrylium tetrafluoroborate (448-61-3)

1,3,5-triphenylbenzene (612-71-5)

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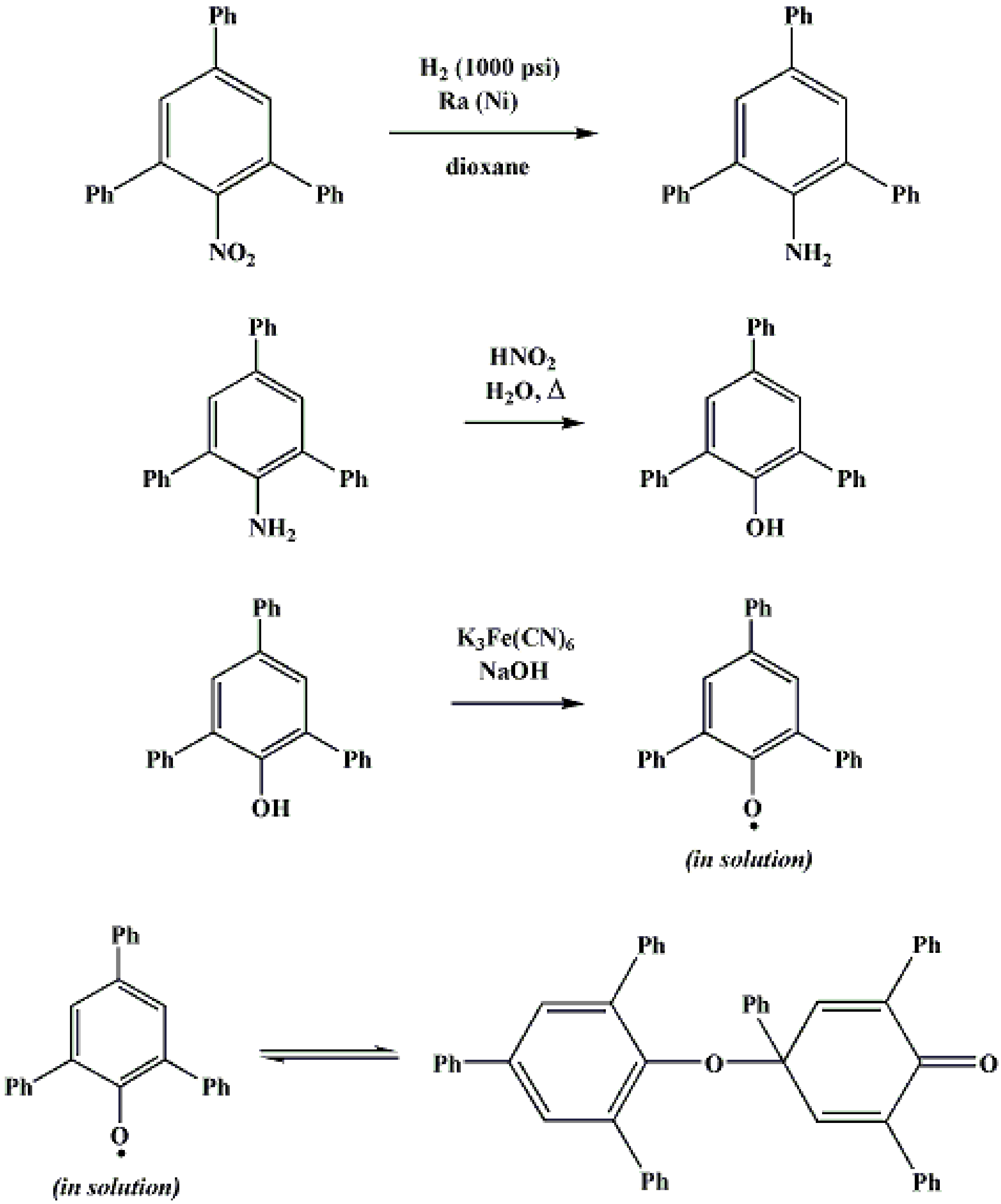
Organic Syntheses, CV 5, 1130

2,4,6-TRIPHENYLPHENOXYL

[Phenoxy, 2,4,6-triphenyl]



Submitted by K. Dimroth, A. Berndt, H. Perst, and C. Reichardt[1].
Checked by E. K. W. Wat and R. E. Benson.

1. Procedure

A. *2,4,6-Triphenylaniline*. To a filtered solution of 70 g. (0.20 mole) of 2,4,6-triphenylnitrobenzene (Note 1) in 500 ml. of dioxane (total volume *ca.* 540 ml.) in a 1-l. pressure vessel equipped with a magnetic stirrer is added 10 g. of Raney nickel catalyst (Note 2) that has been previously rinsed with absolute ethanol. The head and fittings are attached, and the vessel is connected to a hydrogen cylinder. The system is alternately evacuated to 40–50 mm. and pressured with hydrogen to 30–40 p.s.i. three times (Note 3). After a final evacuation, hydrogen is introduced into the vessel until the pressure reaches 1000 p.s.i. (*ca.* 70 atm.). The reaction is allowed to proceed overnight (*ca.* 25 hours) (Note 4), during which time 0.6 mole (13.5 l.) of hydrogen is absorbed. The vessel is vented and the catalyst is removed by filtration from the reaction mixture and is washed with 30 ml. of dioxane. The filtrates are combined, and the solvent is removed by distillation under reduced pressure using a rotary evaporator at 40–50° (50 mm.) to leave an oil which solidifies on trituration with a small portion of methanol. The product is collected on a Buchner funnel and washed twice with 40-ml. portions of ice-cold methanol. The remaining light yellow 2,4,6-triphenylaniline (m.p. 135–136°) weighs 60–63 g. (94–98%) (Note 5).

B. *2,4,6-Triphenylphenol*. To a 2-l. three-necked flask equipped with a mechanical stirrer, a dropping funnel, and a thermometer are added 32 g. (0.10 mole) of 2,4,6-triphenylaniline and 300 ml. of glacial acetic acid. Stirring is begun and the contents of the flask are brought into solution by heating to 70°. Concentrated sulfuric acid (90 ml., *d* 1.84) is added dropwise while the temperature is lowered concurrently from 70° to 20° by cooling. After the addition is completed, the mixture is cooled to 0° with an ice-salt bath, and a solution of 9 g. (0.13 mole) of sodium nitrite in 50 ml. of water is added over a period of 20–30 minutes with stirring, the reaction temperature being kept at 0–5°. The stirring is continued for 20 minutes after the sodium nitrite solution has been added, then 300 ml. of ice-cold water and 3 g. of urea or amidosulphonic acid are added in small portions. The yellow diazonium salt solution is filtered with suction into an ice-cold flask and is kept cold (at 0°) while the next step is carried out.

To a 2-l. three-necked flask equipped with a mechanical stirrer, a reflux condenser, and a dropping funnel is added a mixture of 600 ml. of water and 150 ml. of concentrated sulfuric acid (*d* 1.84). The acid solution is vigorously stirred and heated to boiling, and the cold diazonium salt solution is added at such a rate that the boiling is not interrupted (Note 6). The time required for this addition should not exceed 30 minutes. After the addition is completed, boiling is continued for 10 minutes and then the mixture is allowed to cool to room temperature with stirring. The product is collected on a Buchner funnel, washed, with water, and dried in a vacuum desiccator containing phosphorus pentoxide to give 28–32 g. of crude 2,4,6-triphenylphenol. After drying, the product is dissolved in *ca.* 200 ml. of benzene and filtered through a layer of 300 g. of alumina packed in a 30-mm. × 75-cm. chromatohgraphy column (Note 7). The product is eluted with benzene until about 500 ml. of eluate has been collected. The collected eluate is concentrated under reduced pressure using a rotary evaporator at 50 mm. pressure and 50° to yield light yellow crystals, which are recrystallized from glacial

acetic acid (10 g. of 2,4,6-triphenylphenol requires *ca.* 30–35 ml. of acetic acid). The pure, nearly colorless product (13–15 g., 39–47%) melts at 149–150°.

C. *2,4,6-Triphenylphenoxyl*. In a 1-l. separatory funnel is placed a filtered solution of 10 g. (31 moles) of 2,4,6-triphenylphenol in 300 ml. of ether. To this solution is added 60 ml. of a filtered, saturated solution of potassium hexacyanoferrate(III) in 2N sodium hydroxide solution (Note 8), and the resulting mixture is vigorously shaken for about 10 minutes. After a few minutes the dimer of 2,4,6-triphenylphenoxyl begins to separate in the form of pink crystals. The crystals are isolated by filtration, washed with several portions of water (Note 9) and twice with ether. After drying in a vacuum desiccator over phosphorus pentoxide while protecting from light, the product weighs 8–9 g. (81–91%) and melts at 145–150° to a red liquid (Note 10). The purity of the 2,4,6-triphenylphenoxyl dimer (which in solution attains a rapid equilibrium with its red monomer) is established by titration with a solution of hydroquinone in acetone (Note 11). The radical titer of a freshly prepared solution of the dimer in benzene or acetone should be 98–99%.

2. Notes

1. The preparation of 2,4,6-triphenylnitrobenzene is described in *Organic Syntheses*, this volume, p. 1128.
2. The submitters used Raney nickel catalyst from the Badische Anilin- & Sodafabrik AG, Ludwigshafen (Rhein). Germany.
3. The checkers used a stainless steel pressure vessel that was cooled to –60° and then evacuated to 1 mm. The cold system was purged with hydrogen three times, evacuated, and placed in the rocker assembly before pressuring it to 1000 p.s.i. with hydrogen.
4. The checkers used a rocking-motion autoclave and the reduction required 48 hours to complete.
5. The 2,4,6-triphenylaniline resulting from this procedure is sufficiently pure for use in the preparation of 2,4,6-triphenylphenol, but it may be recrystallized from 100 ml. of glacial acetic acid to give 50–55 g. (78–86%) of pure 2,4,6-triphenylaniline, m.p. 136–137°. On occasions a product with initial m.p. 121–122° is obtained which solidifies on further heating and then melts at 136–137°
6. Contact of the diazonium salt solution with the hot wall of the flask before decomposition in the solution should be avoided in order to prevent the formation of a brown resin.
7. The submitters used Aluminiumoxid WOELM neutral, Aktivitätsstufe I.
8. A saturated solution requires *ca.*/35 g. (110 mmoles) of potassium hexacyanoferrate(III) per 100 ml. of 2*N* sodium hydroxide solution at room temperature.
9. The final wash water must be free of potassium hexacyanoferrate(III). The checkers washed the product until the filtrates were colorless.
10. The product obtained is analytically pure: Calcd. for $C_{24}H_{17}O$: C, 89.69; H, 5.33; O, 4.98. Found: C, 89.94; H, 5.27; O, 5.00. The product is stable for several months when stored in the dark. The 2,4,6-triphenylphenoxyl dimer is

piezochromic; rubbing in a mortar produces a red color. Solutions of the colorless dimer in organic solvents are red owing to dissociation to the monomer radical.
11. The radical solution is titrated with 0.01*M* solution of analytically pure hydroquinone in pure acetone. The end point of the titration is marked by disappearance of the red color of the phenoxyl radical: 1 ml. of 0.01*M* hydroquinone solution is equivalent to 6.428 mg. of 2,4,6-triphenylphenoxyl dimer.

3. Discussion

The procedure for preparing 2,4,6-triphenylphenoxyl is based on the method described by Dimroth and co-workers.[2] This method represents the commonly used preparation of aroxyl radicals by oxidation of the corresponding phenol.[3] The chemistry of stable phenoxyl radicals has been reviewed.[4]

In solution the colorless 2,4,6-triphenylphenoxyl dimer attains a rapid equilibrium with its red monomer radical (dissociation constant in benzene 4×10^{-5} at 20°). The radical is surprisingly stable toward oxygen and can be stored in solution for a long time when it is protected from light. The stability of the 2,4,6-triphenylphenoxyl radical is ascribed to steric and mesomeric effects.[2,5] The e.s.r. spectrum[5] and an ENDOR-spectrum[6] of the radical are described.

The dimer belongs to the rare group of compounds which are piezochromic. Rubbing in a mortar produces a red color due to mechanical bond-breaking and dissociation into the red-colored monomer. The *p*-quinol structure of the 2,4,6-triphenylphenoxyl dimer has been confirmed by infrared studies of ^{18}O-labeled material[7] and by X-ray analysis of 3-bromo derivative.[8]

Other aroxyl radicals, especially those with *t*-butyl groups at the phenyl ring, are described by Cook[9] and by Müller.[10]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alumina

amidosulphonic acid

2,4,6-triphenylphenoxyl dimer

ethanol (64-17-5)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

Benzene (71-43-2)

methanol (67-56-1)

ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

hydroquinone (123-31-9)

oxygen (7782-44-7)

sodium nitrite (7632-00-0)

Raney nickel (7440-02-0)

acetone (67-64-1)

urea (57-13-6)

potassium hexacyanoferrate(III) (13746-66-2)

dioxane (5703-46-8)

2,4,6-Triphenylnitrobenzene (10368-47-5)

2,4,6-Triphenylphenoxyl, Phenoxy, 2,4,6-triphenyl (10384-15-3)

2,4,6-Triphenylaniline (6864-20-6)

2,4,6-Triphenylphenol (3140-01-0)

phosphorus pentoxide (1314-56-3)

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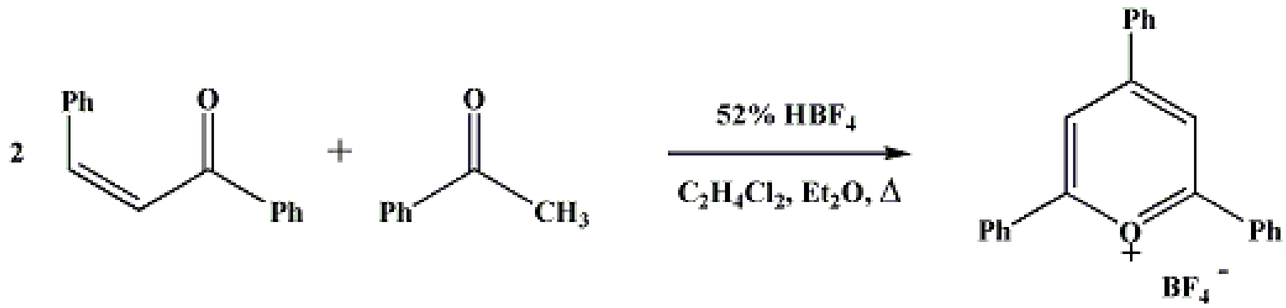
2,4,6-TRIPHENYLPYRYLIUM TETRAFLUOROBORATE

[Pyrylium tetrafluoroborate, 2,4,6-triphenyl-]



Submitted by K. Dimroth, C. Reichardt, and K. Vogel[1].
Checked by Saul Cerkofsky and Richard E. Benson.

1. Procedure

In a 1-l. four-necked flask (or a three-necked flask with a Y-tube connector) equipped with a mechanical stirrer, a reflux condenser, a dropping funnel, and a thermometer are placed 208 g. (1.00 mole) of benzalacetophenone (Note 1), 60 g. (58.5 ml., 0.50 mole) of acetophenone, and 350 ml. of 1,2-dichloroethane. The contents of the flask are warmed to 70–75°, and 160 ml. of a 52% ethereal solution of fluoboric acid (Note 2) is added from the funnel with stirring during 30 minutes. With the first addition the mixture becomes orange; subsequently the color changes to brownish yellow. After the addition is completed, the mixture is stirred and heated under reflux for 1 hour (Note 3). The fluorescent mixture is allowed to stand overnight in a refrigerator. The crystalline product that separates is collected on a Buchner funnel and washed well with ether. By addition of 250 ml. of ether (Note 4) to the mother liquor an additional quantity of 2,4,6-triphenylpyrylium tetrafluoroborate is obtained. A total yield of 125–135 g. (63–68%) of yellow crystals results; m.p. 218–225° (Note 5). The product can be recrystallized from 650–700 ml. of 1,2-dichloroethane, when it separates in the form of yellow needles, m.p. 251–257° (Note 6). The yield of product dried at 80° (10 mm.) for 3 hours is 102.5–107 g. (52–54%) (Note 6).

2. Notes

1. The preparation of benzalacetophenone is described in *Org. Syntheses*, Coll. Vol. **1**, 78 (1941).

2. Ethereal fluoboric acid can be prepared as follows: 19 ml. (19 g., 0.95 mole) of anhydrous hydrofluoric acid, b.p. 19.4° (760 mm.) [*Caution! Hydrofluoric acid in contact with the skin produces extremely painful burns. It is therefore necessary to use every precaution to protect exposed parts of the body, especially the hands and eyes. Cf. Org. Syntheses, Coll. Vol.* **2**, *295 (1943). Note 3; this volume, p. 136, Note 1*] is added in small portions with shaking or stirring to 126 ml. (142 g., 1.00 mole) of distilled boron trifluoride etherate, b.p. 126° (760 mm.), contained in a 500-ml. polyethylene flask that is cooled in an ice bath to 0°. The concentration of the resulting yellowish solution of fluoboric acid in ether is about 52% by weight (*ca.* 6.6 moles per l.).

3. Some boron trifluoride is evolved during the first part of the refluxing; it may be

disposed of by absorption in water in a gas trap [cf. *Org. Syntheses*, Coll. Vol. **2**, 3 (1943)].

4. The ether used for washing the product may be added to the filtrate.

5. The 2,4,6-triphenylpyrylium tetrafluoroborate resulting from this procedure is sufficiently pure for use in the preparation of 2,4,6-triphenylnitrobenzene.[2]

6. It is necessary to dry under reduced pressure in order to remove that portion of the solvent that is tightly held. *Anal.* Calcd. for $C_{23}H_{17}BF_4O$: C, 69.73; H, 4.33; B, 2.73; F, 19.18. Found: C, 69.38; H, 4.47; B, 3.07; F, 19.51. The n.m.r. spectrum (acetone-d_6) shows a singlet at 9.1 p.p.m. (2 H) and multiplets at 8.6 p.p.m. and 7.9 p.p.m. (15 H) (downfield from internal tetramethylsilane reference).

3. Discussion

The present procedure is an improved modification of that described by Balaban[3] for the corresponding perchlorate. 2,4,6-Triphenylpyrylium tetrafluoroborate has also been prepared from the corresponding tetrachloroferrate[4,5] with fluoboric acid,[5] from acetophenone and boron trifluoride,[6] and from acetophenone, benzaldehyde, and boron trifluoride etherate.[7] Additional methods for the preparation of pyrylium salts have been reviewed.[5,8,9,10,11,12,13,14]

2,4,6-Triphenylpyrylium tetrafluoroborate is a versatile and useful stable starting material. Its reaction with nitromethane under basic conditions has made 2,4,6-triphenylnitrobenzene easily available.[2,15] In addition, pyrylium salts are readily converted to a variety of pyridine derivatives[16,17,18] including alkyl- and arylpyridinium slats,[17,18] to thiopyrylium salts,[19] and to substituted azulenes.[20]

The chemistry and transformation of pyrylium salts have been reviewed.[5,8,9,10,11,21,14]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 1128

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

fluoboric acid

ether (60-29-7)

1,2-dichloroethane (107-06-2)

hydrofluoric acid (7664-39-3)

Benzalacetophenone (94-41-7)

benzaldehyde (100-52-7)

Acetophenone (98-86-2)

Nitromethane (75-52-5)

boron trifluoride (7637-07-2)

boron trifluoride etherate (109-63-7)

2,4,6-Triphenylnitrobenzene (10368-47-5)

2,4,6-Triphenylpyrylium tetrafluoroborate, Pyrylium tetrafluoroborate, 2,4,6-triphenyl- (448-61-3)

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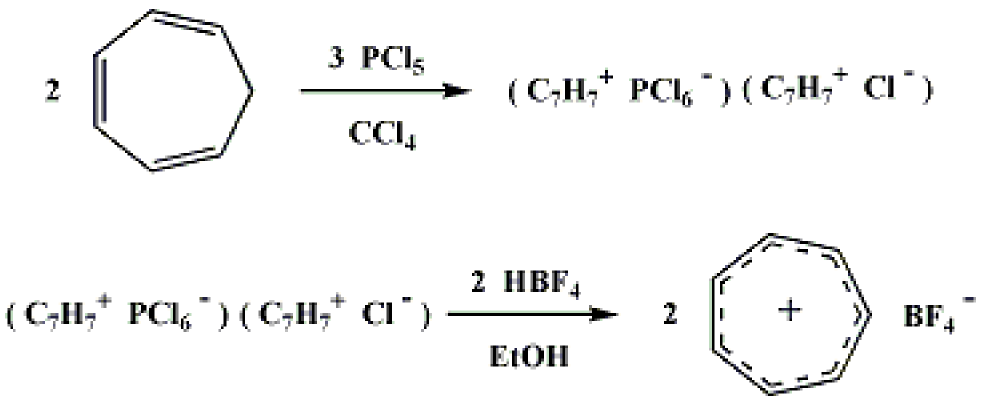
Organic Syntheses, CV 5, 1138

TROPYLIUM FLUOBORATE

[Cycloheptatrienocarbonium fluoborate]



Submitted by Kenneth Conrow[1]
Checked by D. W. Wiley and B. C. McKusick.

1. Procedure

A suspension of 100 g. (0.48 mole, 33% excess) of phosphorus pentachloride in 800 ml. of carbon tetrachloride is prepared in a 1-l. flask equipped with an efficient stirrer and an exit valve for the hydrogen chloride that is evolved (Note 1). Tropilidene (cycloheptatriene; 24.2 g. of 91% material; 0.24 mole) (Note 2) is added all at once, and the mixture is stirred for 3 hours at room temperature (Note 3).

Absolute ethanol (400 ml.) is vigorously stirred in a 1-l. wide-necked Erlenmeyer flask immersed in an ice bath (Note 4). The tropylium hexachlorophosphate-tropylium chloride double salt[2] is separated from the reaction mixture by suction filtration, washed briefly with fresh carbon tetrachloride, and transferred as rapidly as possible into the cold, well-stirred ethanol (Note 5). The salt dissolves rapidly and exothermally to give a reddish solution. Fifty milliliters (0.39 mole) of 50% aqueous fluoboric acid is added rapidly to the cold stirred solution (Note 6). The dense white precipitate of tropylium fluoborate that forms is separated by suction filtration, washed with a little cold ethanol and with ether, and air-dried at room temperature (Note 7); weight 34–38 g. (80–89%); decomposition point about 200°; $\lambda_{max}^{0.1N\ HCl}$ 218 m• (log ε 4.70), 274 m• (log ε 3.61). The product is 98–100% pure (Note 8) and (Note 9).

2. Notes

1. The use of a flask just large enough to hold the reaction mixture obviates the necessity for an inert atmosphere, for the evolving hydrogen chloride soon displaces the small amount of air over the reaction mixture.

2. Cycloheptatriene containing 9% toluene is available from the Shell Chemical Company, New York. Less pure cycloheptatriene, obtained by pyrolysis of bicycloheptadiene followed by a crude distillation, has been used successfully in this preparation. The quantity of the tropilidene/toluene mixture is adjusted in accord with its purity as estimated by vapor-phase chromatography on didecyl phthalate.

3. The mixture thickens rapidly. After about an hour, even an efficient stirrer often fails to stir the whole mixture, but after a time the mixture thins again and the reaction is completed without incident.

4. Stirring is most conveniently accomplished with a magnetic stirrer. A large plastic bucket is used to contain the ice used for cooling.

5. Exposure of this salt to the atmosphere causes discoloration that may persist in the final product. A slight discoloration at this stage does not appear to affect the quality of the final product. A rubber dam is helpful on days of high humidity.

6. Use of perchloric acid gives the perchlorate. However, the perchlorate is so dangerously explosive that its use should be avoided.[3]

7. Additional salt is precipitated by the addition of ether to the ethanolic filtrate, but the quantity is so small that this treatment is not worth while.

8. The product may be crystallized from a large volume of ethyl acetate or from acetonitrile-ethyl acetate. However, there is little reason to do this, for losses are heavy and the purity, as measured by ultraviolet spectroscopy, is hardly affected.

9. In a variation of this procedure that gives a nearly quantitative yield of good material, the intermediate salt is dissolved in 250 ml. of glacial acetic acid in a 2-l. beaker, and 100 g. of 50% fluoboric acid is added with stirring. When the evolution of gas has stopped, 1 l. of ethyl acetate is added to precipitate tropylium fluoborate. The fluoborate is separated by filtration, washed successively with ethyl acetate and ether, and dried in an oven at 40°.[4]

3. Discussion

This method is a modification of the method originally published by Kursanov and Vol'pin.[5] Tropylium salts have also been prepared by bromination-dehydrobromination of tropilidene,[6] and by the hydride-exchange reaction between tropilidene and triphenylmethyl carbonium ion.[7]

4. Merits of the Preparation

Tropylium salts are starting materials for the preparation of a wide range of substituted tropilidenes. The fluoborate is the salt of choice for work involving the tropylium ion because it is indefinitely stable, non-hygroscopic, and, unlike the perchlorate, non-explosive. Its preparation by this method avoids the use of triphenyl carbinol, which is an unnecessarily expensive reagent in the quantities required for tropylium ion preparation.

This preparation is referenced from:

- Org. Syn. 75, 210

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

fluoboric acid

Cycloheptatrienocarbonium fluoborate

tropylium hexachlorophosphate-tropylium chloride

acetonitrile-ethyl acetate

ethanol (64-17-5)

hydrogen chloride (7647-01-0)

acetic acid (64-19-7)

Tropilidene (71-43-2)

ethyl acetate (141-78-6)

ether (60-29-7)

phosphorus pentachloride (10026-13-8)

carbon tetrachloride (56-23-5)

toluene (108-88-3)

triphenyl carbinol (76-84-6)

perchloric acid (7601-90-3)

cycloheptatriene (544-25-2)

bicycloheptadiene

Tropylium fluoborate (27081-10-3)

didecyl phthalate (84-77-5)

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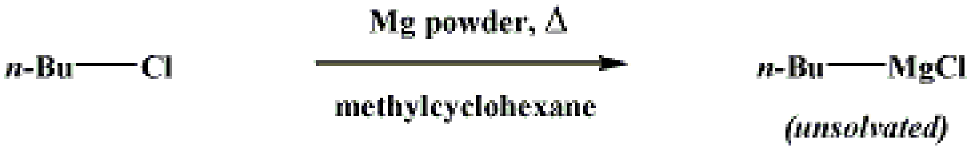
Organic Syntheses, CV 5, 1141

UNSOLVATED *n*-BUTYLMAGNESIUM CHLORIDE



Submitted by D. Bryce-Smith and E. T. Blues[1].
Checked by William E. Parham and Siemen Groen.

1. Procedure

In a 250-ml. round-bottomed flask fitted with a glass-link or Teflon, stirrer, thermometer, reflux condenser with outlet to an oil seal, dropping funnel, and inlet for nitrogen (Note 2), (Note 3) are placed 3.22 g. of magnesium powder (0.132 mole) (Note 4) having a particle size of 64–76 • (Note 5), (Note 6), and 60 ml. of methylcyclohexane (Note 7). The apparatus is flushed with nitrogen. A slow stream of nitrogen is introduced, and the methylcyclohexane is heated to reflux temperature (Note 8).

About one-fifth of a solution of 9.26 g. of 1-chlorobutane (0.1 mole) (Note 9), (Note 10) in 20 ml. of methylcyclohexane is added to the vigorously stirred refluxing mixture. Reaction commences (gray turbidity) within 2–8 minutes (Note 5), (Note 11), and the remainder of the halide solution is then added steadily over about 12 minutes to the heated mixture, the rate being adjusted so that the inner temperature of the refluxing mixture does not fall appreciably below 99–100°. Stirring and heating under reflux are continued for an additional 15 minutes. The resulting product contains approximately 0.073 mole (73% yield) of *n*-butylmagnesium chloride as determined either by hydrolysis to *n*-butane (Note 12), (Note 13) or by titration (Note 14).

2. Notes

1. The empirical formula of *n*-butylmagnesium chloride prepared in methylcyclohexane cannot readily be determined because of the virtual insolubility of the reagent in this medium. The reagent is somewhat more soluble in aromatic media such as toluene or isopropylbenzene, and, although the empirical formula of the solute may initially approach C_4H_9MgCl, there is a tendency for precipitation of magnesium chloride from solution. This process appears to be catalyzed by traces of alkoxides, which are liable to be formed after contact of oxygen with the solution. In practice, products will tend to contain less halogen than is required by the simple formula C_4H_9MgCl. The reagents are associated (see reference [2] for a fuller discussion).
2. The nitrogen used (British Oxygen Co., White Spot) contained about 10 p.p.

m. of oxygen and was dried by passage through a glass spiral cooled in acetone and solid carbon dioxide. For the most precise work, the submitters reduced the proportion of oxygen to about 0.1 p.p.m. by scrubbing the nitrogen with chromous chloride solution in a Nilox apparatus (Southern Analytical Ltd., Camberley, Surrey, England).

3. The apparatus should preferable be baked at 120° for several hours immediately before use. The uppermost region of condensing methylcyclohexane should not be cloudy; if it is, a few milliters should be allowed to distil.

4. The yield of *n*-butylmagnesium chloride is increased to 80% (analyzed by evolution of *n*-butane) if twice the stated amount of magnesium is used.

5. Magnesium powder (grade 4, Magnesium Elektron Ltd., Manchester, England) was used within 6 months of its grinding by the manufacturer, and was sieved to the stated particle size. The use of unsieved material often gives results nearly as good, but exact reproducibility is more difficult because of variations of the particle size distribution from sample to sample. In general, the more freshly ground the magnesium, the shorter are the induction periods before reaction and, to a limited extent, the higher are the yields of organomagnesium product.

6. Fresh magnesium turnings for Grignard reaction can be used if suitable powder is unavailable, but initiation of reaction is likely to be prolonged, and the subsequent addition of the halide solution should occupy at least 30 minutes, longer if possible.

7. Methylcyclohexane is purified by shaking with 3 portions of concentrated sulfuric acid, washing successively with water, sodium carbonate solution, and water, drying over calcium sulfate (Drierite), and distilling. The material boiling at 100–101° is used. Other nonsolvating media which can be used are toluene, xylenes, cumene, tetralin, light petroleum (b.p. 80°), decalin, and kerosene; aliphatic media are preferred, for reasons given in references [2], [3], and [4].

8. The rate of flow of nitrogen should be just sufficient to maintain a positive pressure in the apparatus. Too rapid a flow leads to loss of 1-chlorobutane.

9. 1-Chlorobutane is purified with sulfuric acid as for methylcyclohexane (Note 7), dried over calcium chloride, and fractionated. A middle fraction is collected.

10. The yield of product is increased to 81% (analyzed by evolution of *n*-butane) if 0.67 g. (0.0033 mole) of aluminum isopropoxide is added to the suspension of magnesium before addition of the halide solution. Alternatively, an equivalent amount of 2-propanol and iodine (giving 0.01 mole of C_3H_7OMgI) may be added. These modified procedures (particularly the second) also shorten the induction periods and render unnecessary any special drying of the reagents and apparatus and the use of fresh magnesium.

The products in such cases contain complexes between *n*-butylmagnesium chloride and the particular alkoxide employed. With the stated low proportions of alkoxides, these complexes broadly resemble the alkoxide-free materials, but increased proportions of the alkoxide component give complexes having

generally decreased chemical reactivity (see references [3] and [4]).

11. The reaction generally starts without addition of iodine as an initiator, but the use of a crystal of iodine (no stirring) may occasionally be necessary with "old" magnesium or insufficiently dried materials or apparatus. A slower rate of addition of 1-chlorobutane gives slightly higher yields; for example, addition over a period of 60 minutes gave yields of 82–87%.

12. The reflux condenser was connected by an adaptor and Teflon tube to a trap of known weight which was cooled by a mixture of acetone and solid carbon dioxide. The flow of nitrogen was stopped, and an excess of water (about 15 ml.) was added dropwise through the dropping funnel to the stirred reaction product. The resulting mixture was heated at the reflux temperature, and the butane was collected in the trap. The weight of butane, b.p. –1° to 0°, was 4.23–4.35 g. (73–76% yield).

13. The submitters have detected traces of *trans*-butene-2 and propylene among the gases (mainly *n*-butane and hydrogen) formed on hydrolysis.

14. Sufficient dry ether (approximately 100 ml.) is added to bring the organomagnesium products into solution. Aliquot portions of the solution are then added to a known volume of standard hydrochloric acid, and the excess acid is determined by titration with standard base. Yields determined in this way tend to be a few percent higher than those determined by collection of *n*-butane (Note 12).

3. Discussion

The method is an extension of the well-known Grignard synthesis in ethers to the use of nonsolvating media, and is a development of procedures previously reported.[2,3,4,5,6] A version of it has been employed with straight-chain primary alkyl chlorides, bromides, and iodides from C_2 to C_{14},[5,6,7] and in solvents (or an excess of the halide) which permit reaction temperatures above 120°, with simple aryl halides such as chlorobenzene and 1-chloronaphthalene. Branched-chain primary, secondary, and tertiary alkyl halides, allyl, vinyl, and benzyl halides either fail to react or give extensive side reactions. Better results are reported to be obtained in such cases with the use of catalytic quantities of a mixture of an alkoxide and an ether such as diethyl ether or tetrahydrofuran in a hydrocarbon medium, but the products are not, of course, completely unsolvated.[4]

4. Merits of the Preparation

Unsolvated organomagnesium compounds have been recommended for the synthesis of organometallic derivatives of mercury, boron, aluminum, silicon, germanium, tin, phosphorus, arsenic, and antimony[3,6,8] and have been used in procedures for the alkylation of aromatic rings and for the production of various polymerization catalysts.[4,6,9]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

calcium sulfate (Drierite)

light petroleum

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ether, diethyl ether (60-29-7)

hydrogen (1333-74-0)

magnesium, magnesium turnings, magnesium powder (7439-95-4)

propylene (115-07-1)

sodium carbonate (497-19-8)

PHOSPHORUS (7723-14-0)

oxygen (7782-44-7)

nitrogen (7727-37-9)

tin (7440-31-5)

aluminum (7429-90-5)

mercury (7439-97-6)

carbon dioxide (124-38-9)

iodine (7553-56-2)

acetone (67-64-1)

chlorobenzene (108-90-7)

toluene (108-88-3)

2-propanol (67-63-0)

aluminum isopropoxide

1-chlorobutane (109-69-3)

methylcyclohexane (108-87-2)

antimony (7440-36-0)

cumene, isopropylbenzene (98-82-8)

Tetralin (119-64-2)

boron (7440-42-8)

butane, n-butane (106-97-8)

magnesium chloride

Tetrahydrofuran (109-99-9)

arsenic

1-chloronaphthalene (90-13-1)

chromous chloride (10049-05-5)

decalin (91-17-8)

silicon

germanium

n-BUTYLMAGNESIUM CHLORIDE (693-04-9)

trans-butene-2 (624-64-6)

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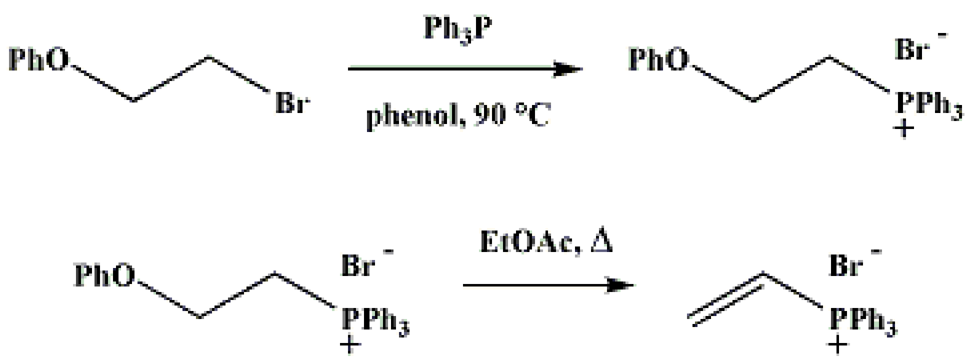
Organic Syntheses, CV 5, 1145

VINYL TRIPHENYLPHOSPHONIUM BROMIDE

[Phosphonium bromide, triphenylvinyl-]



Submitted by Edward E. Schweizer and Robert D. Bach[1].
Checked by François X. Garneau and Peter Yates.

1. Procedure

Caution! Because phenol and its solutions are corrosive, rubber gloves should be used in the following operations. The product, vinyl triphenylphosphonium bromide, has been found to induce a sneezing, allergic reaction and contact with it should be avoided.

In a 1-l. three-necked flask is placed 1 lb. of reagent grade phenol (Note 1), 100 g. (0.50 mole) of β-bromophenetole, and 131 g. (0.50 mole) of triphenylphosphine (Note 2). The flask is equipped with a sealed stirrer, a thermometer, and a reflux condenser fitted with a calcium chloride drying tube. The mixture is stirred and heated to 90° ± 3° (Note 3) and kept at this temperature for 48 hours.

The solution is cooled to room temperature and added slowly (during 45 minutes) from a dropping funnel to vigorously stirred anhydrous ether (3 l.) in a 4-l. beaker. Material that adheres to the sides of the beaker is scraped down with a long steel spatula, and the mixture is filtered by suction. The solid product is transferred into a second 3-l. portion of anhydrous ether, and the mixture is stirred vigorously for 15 minutes and filtered by suction. The product is washed with three 250-ml. portions of warm anhydrous ether.

The white crystalline residue of crude phenoxyethyltriphenylphosphonium bromide (Note 4) is placed in a 3-l. two-necked flask equipped with a sealed stirrer and a reflux condenser fitted with a calcium chloride drying tube. Reagent grade (Note 5) ethyl acetate (1.5 l.) is added, and the solution is stirred under reflux for 24 hours. The mixture is cooled to room temperature, and the ethyl acetate layer is decanted (or filtered if the salt is crystalline). This procedure is repeated until the filtered salt, vinyl

triphenylphosphonium bromide, melts at 186° and higher (Note 6).

After the final filtration the product is washed with two 100-ml. portions of ethyl acetate and two 100-ml. portions of anhydrous ether and dried for 24 hours at 80°. The dried, analytically pure vinyl triphenylphosphonium bromide, m.p. 186–190°, weighs 122–158 g. (66–86%).

2. Notes

1. The checkers found that it was important to use phenol free of colored impurities; in a run in which phenol, m.p. 39.5–41°, with a slight rose tinge was used the yield of product was reduced to 56%.
2. The β-bromophenetole was obtained from Aldrich Chemical Co.; the triphenylphosphine was obtained from M and T Chemicals, Inc., or Carlisle Chemical Works, Reading, Ohio, and recrystallized once from anhydrous ether (with filtration).
3. It is important that the temperature does not rise above 95°. There is a slight exotherm on initial heating that may necessitate the removal of the heating mantle in order to maintain a temperature below 95°.
4. Pure samples of this material may be obtained by using acetic acid as solvent instead of phenol.[2]
5. Because the vinyl salt reacts with ethanol, and decomposition of the phenoxyethyl precursor is inhibited by acetic acid,[2] reagent grade ethyl acetate is recommended.
6. Four treatments have always been necessary. The residue has always crystallized on cooling after the third treatment.

3. Discussion

The present procedure is that described by the submitters.[2] Vinyl triphenylphosphonium bromide has also been prepared by dehydrobromination of 2-bromoethyltriphenylphosphonium bromide, but no preparative details or yields have been disclosed.[3]

4. Merits of the Preparation

This salt has been used as a general reagent for the preparation of a large number of heterocyclic and carbocyclic systems.[4,5,6,7,8,9,10,11,12,13,14,15,16,17] A variety of salts of type $XCH_2CH_2P^+(C_6H_5)_3Br^-$ has been prepared from the vinyl salt by treatment with alcohols, thiophenol, and diethylamine.[2]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

acetic acid (64-19-7)

ethyl acetate (141-78-6)

ether (60-29-7)

phenol (108-95-2)

diethylamine (109-89-7)

β-bromophenetole (589-10-6)

Thiophenol (108-98-5)

triphenylphosphine (603-35-0)

Vinyl triphenylphosphonium bromide, Phosphonium bromide, triphenylvinyl- (5044-52-0)

phenoxyethyltriphenylphosphonium bromide

2-bromoethyltriphenylphosphonium bromide

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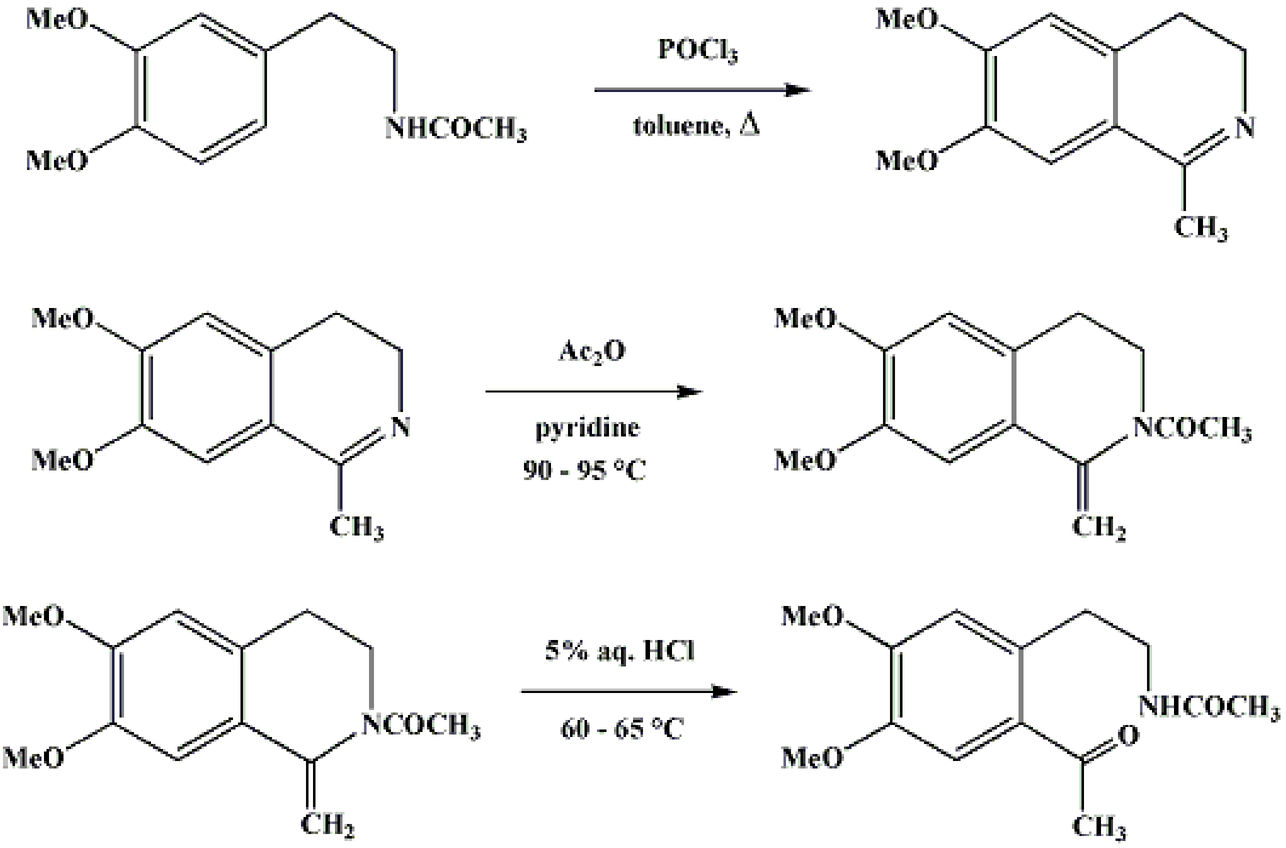
Organic Syntheses, CV 6, 1

ACYLAMIDOALKYL ACETOPHENONES FROM SUBSTITUTED PHENETHYLAMINES: 2-(2-ACETAMIDOETHYL)-4,5-DIMETHOXYACETOPHENONE

[Acetamide, *N*-[2-(2-acetyl-4,5-dimethoxyphenyl)ethyl]-]



Submitted by A. Brossi, L. A. Dolan, and S. Teitel[1].
Checked by Hiroshi Itazaki and Wataru Nagata.

1. Procedure

Caution! Part A should be conducted in a hood to avoid inhalation of hydrogen chloride fumes.

A. 6,7-*Dimethoxy*-1-*methyl*-3,4-*dihydroisoquinoline*. A 2-l., three-necked, round-bottomed flask equipped with a mechanical stirrer, a reflux condenser protected by a calcium chloride tube, and a pressure-equalizing dropping funnel is charged with 54.0 g. (0.243 mole) of *N*-acetylhomoveratrylamine (Note 1) and 275 ml. of dry toluene (Note 2). The mixture is stirred, warmed to 40°, and treated with 86.4 g. (52.5 ml., 0.572 mole) (Note 3) of phosphorus oxychloride (Note 4), which is added over 1 hour (Note 5). After addition, the reaction mixture is stirred at reflux for 2 hours, then cooled with an ice bath for 4 hours. The resulting crystals are collected by filtration and dried overnight at 50° in a vacuum oven, giving 79.0–79.5 g. (Note 6) of 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline dichlorophosphate, m.p. 148–152° (Note 7). This material is dissolved in 150 ml. of water (Note 8), and the solution is treated with 100 ml. of aqueous 40% sodium hydroxide (Note 9). The oil which separates is drawn off, and the aqueous

solution is washed with three 20-ml. portions of chloroform. These extracts and the oil are combined, washed with 15 ml. of water, and dried over anhydrous sodium sulfate. Removal of chloroform with a rotary evaporator provides 47.0–48.0 g. (95–96%) of product, which is used without purification in Part B (Note 10).

B. *2-Acetyl-6,7-dimethoxy-1-methylene-1,2,3,4-tetrahydroisoquinoline*. A 1-l., three-necked, round-bottomed flask equipped with a mechanical stirrer, a reflux condenser topped with a calcium chloride drying tube, and a thermometer is charged with 110 ml. of acetic anhydride, 110 ml. of pyridine, and 45.0 g. (0.220 mole) of the dihydroisoquinoline prepared in Part A. The reaction mixture is stirred and heated at 90–95° for 30 minutes, stored at room temperature overnight, and concentrated by distillation at 50° using a rotary evaporator. The residue is diluted with 20 ml. of ethyl acetate, and another evaporation under reduced pressure gives material that can be crystallized from 75 ml. of ethyl acetate to yield 38.5–41.0 g. (72–77%) of product m.p., 106–107° (Note 11).

C. 2-(2-*Acetamidoethyl*)-4,5-*dimethoxyacetophenone*. A slurry of 31.0 g. (0.125 mole) of the methylene derivative obtained in Part B and 75 ml. of 5% hydrochloric acid is stirred and warmed on a steam bath to 60–65°. As soon as all the solid has dissolved, the solution is cooled with an ice bath to 30° and basified by slowly adding a solution of 6.25 g. of potassium carbonate in 12.5 ml. of water (Note 12). The crystalline precipitate is collected by filtration, washed with three 12.5-ml. portions of water, and air-dried, yielding 30.5–32.0 g. (91–93%) of the acetophenone, m.p. 123–125° (Note 13).

2. Notes

1. *N*-Acetylhomoveratrylamine[2] was prepared by adding 190 ml. of acetic anhydride to a stirred solution of 300 g. (1.80 moles) of β-(3,4-dimethoxyphenyl)ethylamine (Aldrich Chemical Company, Inc.) in 150 ml. of pyridine at such a rate that the temperature is maintained at 90–95° (*ca.* 1.5 hours is required). After the solution had been stored at room temperature overnight, the volatile material was evaporated under reduced pressure, and the residue was crystallized from ethyl acetate to give 286–306 g. (78–83%) of acetylated product, m.p. 99–100°.
2. The checkers used reagent-grade toluene dried over Linde-type 5A molecular sieves.
3. The checkers obtained an identical result when the molar ratio of phosphorous oxychloride to substrate was reduced from 2.35 to 1.5.
4. The checkers obtained phosphorus oxychloride from Wako Pure Chemical Industries, Ltd., Japan and distilled it prior to use.
5. The reaction temperature increased gradually to reflux, at which time the rate of addition was adjusted to maintain reflux.
6. This weight varies with the amount of solvent remaining.
7. Analysis calculated for $C_{12}H_{15}O_2N \cdot HOPOCl_2$: C, 42.37; H, 4.74; N, 4.12; Cl, 20.85; P, 9.10. Found: C, 42.30; H, 4.92; N, 4.21; Cl, 19.08; P, 8.51. IR (KBr) $cm.^{-1}$: 2800, 1665, 1602, 1565, 1105; ^{1}H NMR (D_2O), δ (multiplicity, number of protons, assignment): 3.17 (s, 3H, N=CCH_3), 4.25 (s, 3H, OCH_3), 4.30 (s, 3H, OCH_3), 7.37 (s, 1H, aryl C*H*), 7.62 (s, 1H, aryl C*H*).
The submitters, working on a kilogram scale without purification of reagent or solvent and with no precaution against moisture, obtained 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline hydrochloride,[2] m.p. 202–203°, instead of the dichlorophosphate at this stage. The checkers obtained this hydrochloride by either treating the free base with

hydrochloric acid or recrystallizing the dichlorophosphate from methanol–ethyl acetate.

8. The crystals dissolve gradually in water and, since dissolution is exothermic due to decomposition of the dichlorophosphoric acid, ice cooling is desirable.

9. Ice is added during neutralization to keep the temperature below 30°.

10. A pure sample may be prepared by crystallization from ether: m.p. 105–107°; UV (C_2H_5OH) nm. max. (ε): 227 (24,000), 270 (7360), 307 (6640); UV (0.01 *N* hydrochloric acid) nm. max. (ε): 244 (17,250), 302 (8740), 352 (8440); IR (KBr) cm.$^{-1}$: 1650 (C=N).

11. UV (C_2H_5OH) nm. max. (ε): 220 (30,750), 267 (13,200), 304 (7080); UV (0.01 *N* hydrochloric acid) nm. max. (ε): 232 (23,500), 276 (9345), 305 (6120); IR (KBr) cm.$^{-1}$: 880–910 (C=CH_2). A dimorphic form melts at 100–102°. A mixture of this material and the 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline described in (Note 10) melted below 90°.

12. The rate of addition is dependent on the amount of foaming. Ice is added periodically to keep the temperature below 35°.

13. The product can be used without further purification. Recrystallization from water gave an analytical specimen, m.p. 126–127°; UV (95% C_2H_5OH) nm. max. (ε): 231 (24,100), 274 (8750), 304 (5500); infrared (KBr) cm.$^{-1}$: 1673, 1633; ^{1}H NMR ($CDCl_3$), δ (multiplicity, number of protons, assignment): 1.92 (s, 3H, *H*a), 2.60 (s, 3H, *H*b), 2.68–3.17 (m, 2H, *H*g), 3.30–3.68 (m, 2H, *H*h), 3.93 (s, 6H, *H*c and *H*d), 6.68–7.07 (broad, 1H, *H*i), 6.80 (s, 1H, *H*e), 7.22 (s, 1H, *H*f).

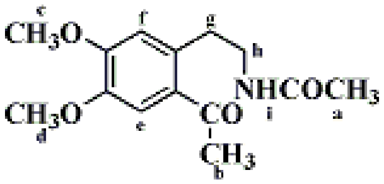
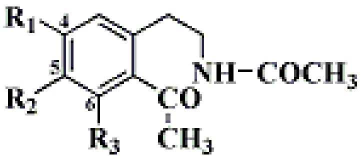
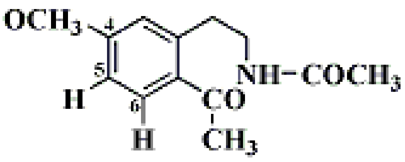
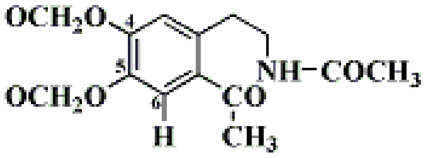
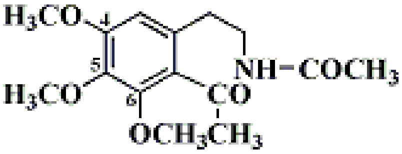


TABLE I

SUBSTITUTED ACETAMIDOETHYL ACETOPHENONES[3]

	Melting Point	Ultraviolet C_2H_2OH nm. max (ε)
R_1 = OCH_3, R_2 = R_3 = H		
	86°	221 (14,700), 269 (13,600)
R_1, R_2 = OCH_2O, R_3 = H		
	120°	230 (36,500), 273 (5200), 307 (5460)

$R_1 = R_2 = R_3 = OCH_3$

	58°	222 (14,700), 263 (16,250)

3. Discussion

This procedure provides a facile method for converting substituted 1-methyl-3,4-dihydroisoquinolines into the corresponding 2-(2-acetamidoethyl)acetophenones, which are useful intermediates in the synthesis of 1-(substituted phenethyl)-2-methyl-1,2,3,4-tetrahydroisoquinolines.[4,5] The sequence is uncomplicated and affords, in excellent yield, a product that requires no further purification. In addition to the examples in Table I, this method has been utilized for the synthesis of other substituted acetophenones,[4,3,6] as well as related benzophenones and a heptanophenone.[7] The latter two classes of compounds have also been obtained by ring opening of 2-ethyl-1-phenyl- or 2-ethyl-1-hexyl-6,7-dialkoxy-3,4-dihydroisoquinolinium iodides with benzoyl chloride.[8]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 268

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

2-(2-Acetamidoethyl)-4,5-dimethoxyacetophenone

2-(2-acetamidoethyl)acetophenones

1-(substituted phenethyl)-2-methyl-1,2,3,4-tetrahydroisoquinolines

potassium carbonate (584-08-7)

hydrogen chloride, hydrochloric acid, hydrochloride (7647-01-0)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether (60-29-7)

acetic anhydride (108-24-7)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium sulfate (7757-82-6)

Acetophenone (98-86-2)

benzoyl chloride (98-88-4)

Phosphorus Oxychloride (21295-50-1)

pyridine (110-86-1)

toluene (108-88-3)

methylene (2465-56-7)

β-(3,4-dimethoxyphenyl)ethylamine (120-20-7)

phosphorous oxychloride

6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline dichlorophosphate

dihydroisoquinoline

6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline hydrochloride

dichlorophosphate

dichlorophosphoric acid

6,7-Dimethoxy-1-methyl-3,4-dihydroisoquinoline (4721-98-6)

heptanophenone (1671-75-6)

Acetamide, N-[2-(2-acetyl-4,5-dimethoxyphenyl)ethyl]- (57621-03-1)

N-acetylhomoveratrylamine (6275-29-2)

2-Acetyl-6,7-dimethoxy-1-methylene-1,2,3,4-tetrahydroisoquinoline (57621-04-2)

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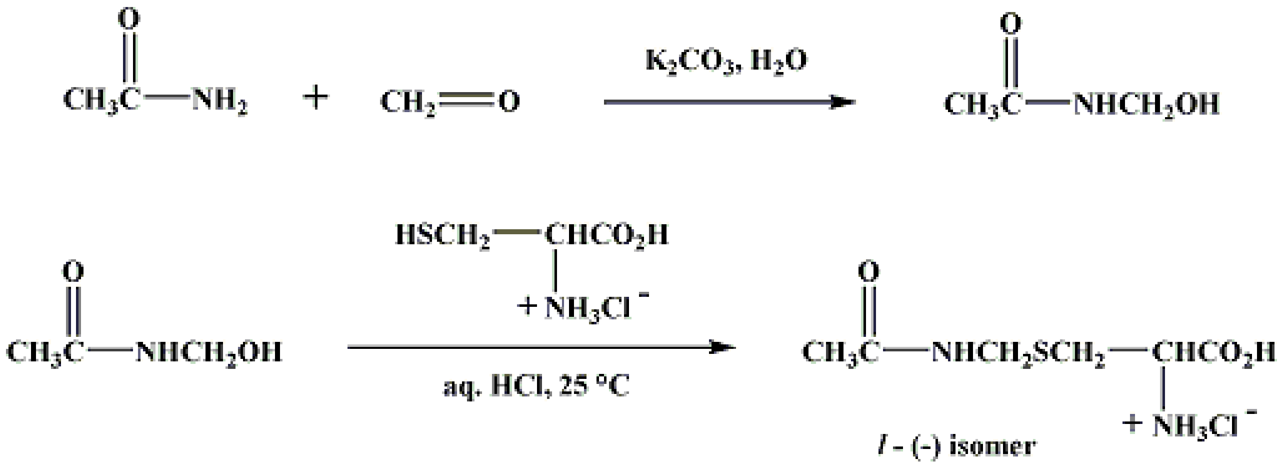
Organic Syntheses, CV 6, 5

THIOL PROTECTION WITH THE ACETAMIDOMETHYL GROUP: *S*-ACETAMIDOMETHYL-L-CYSTEINE HYDROCHLORIDE

[L-Cysteine, *S*-[(acetylamino)methyl]-, monohydrochloride]



Submitted by John D. Milkowski[1], Daniel F. Veber[2], and Ralph Hirschmann[1].
Checked by A. Pearce and G. Büchi.

1. Procedure

A. *N-(Hydroxymethyl)acetamide*. In a 2-l., round-bottomed flask, 100 g. (1.70 moles) of acetamide (Note 1) is added to a solution of 10 g. (0.072 mole) of anhydrous potassium carbonate in 137 g. (1.7 moles) of an aqueous 36–38% solution of formaldehyde (Note 2). The mixture is swirled, heated on a steam bath for 3 minutes, and allowed to stand overnight at room temperature. Several pieces of crushed dry ice are added (Note 3), after which the mixture is evaporated under reduced pressure with a heating bath kept below 40° (Note 4). A 128-g. portion of anhydrous sodium sulfate is added to the remaining colorless oil, which may have some precipitated salt suspended in it. After several hours the oil is dissolved in 1 l. of acetone, the suspended drying agent and salts are filtered, and the filtrate (Note 5) is dried further with additional anhydrous sodium sulfate. The suspension is filtered, and the clear filtrate is evaporated under reduced pressure. The yield of *N*-(hydroxymethyl)acetamide, a colorless hygroscopic oil at this point, is 148–151 g. (98–100%) (Note 6). The oily product, which may solidify (Note 7) on standing for several days, is used directly in step B.

B. *S-Acetamidomethyl-L-cysteine hydrochloride*. A 1-l., round-bottomed flask is charged with 127 g. (1.43 moles) of *N*-(hydroxymethyl)acetamide, 228 g. (1.30 moles) of L-cysteine hydrochloride monohydrate (Note 8), and 350 ml. of water. The resulting solution is swirled and cooled in an ice bath as 50 ml. of concentrated hydrochloric acid is slowly added (Note 9). The flask is flushed with nitrogen, capped with a nitrogen-filled balloon, and allowed to stand for 1–2 days at room temperature. The progress of the reaction is monitored by TLC (Note 10). When L-cysteine hydrochloride is no longer detectable, the solution is evaporated under reduced pressure at a bath temperature of *ca.* 40°. The remaining solid is suspended in a small

amount of absolute ethanol, and the mixture is again carefully evaporated to avoid bumping. This entrainment procedure with absolute ethanol is repeated several times to remove traces of water. The dry solid is dissolved in the minimum amount of methanol (Note 11), and anhydrous diethyl ether is added until the cloud point is reached. The cloudy solution is allowed to stand in a refrigerator at *ca.* 4–5° for 1 week, during which the crystalline mass is broken up several times. The white crystalline product is collected, washed with ether, and dried under reduced pressure, yielding 152–190 g. (51–64%) of *S*-acetamidomethyl-L-cysteine hydrochloride, dec. 159–163°, $[\alpha]_D^{25}$ –30.7° (*c* = 1, water) (Note 12),(Note 13),(Note 14).

2. Notes

1. The submitters obtained acetamide from Merck & Company, Inc. Acetamide was purchased by the checkers from the Fisher Scientific Company.
2. A 37% solution of formaldehyde in water is available from the Aldrich Chemical Company, Inc.
3. The submitters state that the failure to add dry ice at this point may result in greatly reduced yields. The purpose of the dry ice is presumably to lower the pH of the solution by converting potassium carbonate to potassium bicarbonate.
4. When the mixture was heated above 40° by the submitters, it became discolored and an insoluble precipitate was formed.
5. The filtrate may be cloudy.
6. Apparent yields in excess of the theoretical amount may be observed, owing to the presence of a small portion of water. The oily product may be dried at high vacuum over phosphorous pentoxide for several days.
7. A melting point of 50–52° is reported for *N*-(hydroxymethyl)acetamide.[3]
8. The submitters purchased L-cysteine hydrochloride monohydrate from Schwartz/Mann Division, Becton, Dickinson, and Company, Mountain View Avenue, Orangeburg, New York 10962. The checkers used material supplied by Aldrich Chemical Company, Inc.
9. The pH of the solution is *ca.* 0.5.
10. The balloon was removed briefly while aliquots were taken. The flask was flushed again with nitrogen and the balloon was then replaced. TLC analyses were carried out on glass plates coated with silica gel G purchased from Analtech, Newark, Delaware. With a 10:2:3 (v/v/v) solution of 1-butanol, acetic acid, and water as developing solvent, the R_f values for the product and L-cysteine hydrochloride are 0.19 and 0.25, respectively.
11. The submitters dissolved the solid in methanol at room temperature; however, the solid obtained by the checkers was not very soluble under these conditions. Consequently, the material was dissolved in approximately 2–3 l. of methanol by gentle warming on a steam bath.
12. The product obtained by the checkers had $[\alpha]_D^{25}$ –28° (*c* = 1, water); IR (Nujol) cm^{-1}: 1715 (C=O), 1580 (C=O); ^1H NMR (DCl in D_2O), δ (multiplicity, number of protons, assignment): 2.05 (s, 3H, CH_3), 3.2–3.4 (m, 2H, CH_2CH), 4.3–4.5 (m, 1H, CH_2CH), 4.39 (s, 2H, NCH_2S).
13. On several occasions the product isolated by the submitters was contaminated with L-cystine dihydrochloride, which was not easily removed by recrystallization. In this event the product was converted to the zwitterionic form and recrystallized in the following manner: The pH of a solution of the product in water was adjusted to 6 with aqueous 2.5 *N* potassium hydroxide, and the solution was evaporated to dryness under reduced

pressure at *ca.* 40°. The residue was dissolved in a minimum amount of hot water, and two volumes of 95% ethanol were added to precipitate *S*-acetamidomethyl-L-cysteine monohydrate, dec. 187°, $[\alpha]_{589}^{25}$ −42.5° (*c* = 1, water).

14. The following unchecked procedure for liberating L-cysteine from *S*-acetamidomethyl-L-cysteine was provided by the submitters as a model for removing the *S*-acetamidomethyl group from peptides. The pH of a solution of 96.1 mg. (0.500 mmole) of *S*-acetamidomethyl-L-cysteine in 10.0 ml. of water is adjusted to 4.0 with aqueous 0.25 *N* hydrochloric acid. The solution is stirred, 159.3 mg. (0.5000 mmole) of mercury(II) acetate is added, and the pH is readjusted to 4.0 by adding more 0.25 *N* hydrochloric acid. The resulting suspension is stirred for 1 hour at room temperature then diluted with an equal volume of water. Hydrogen sulfide gas is introduced to complete the precipitation of mercury from solution, the mixture is filtered, and the aqueous filtrate is evaporated to dryness under reduced pressure. TLC analysis on the residue as described in (Note 10) showed the presence of L-cysteine and the absence of *S*-acetamidomethyl-L-cysteine.

3. Discussion

The present procedure provides a convenient method for preparing *S*-acetamidomethyl-L-cysteine hydrochloride.[4] The zwitterionic form may be obtained readily from the hydrochloride by the procedure described in (Note 13), by ion-exchange chromatography,[5] or by precipitation from 2-propanol with pyridine.[6] *S*-Acetamidomethyl-L-cysteine has also been prepared from *N*-(hydroxymethyl)acetamide under anhydrous conditions in liquid hydrogen fluoride[4] and in trifluoroacetic acid.[7] The preparation of *N*-(hydroxymethyl)acetamide described in Part A is based on the procedure of Einhorn.[3]

The acetamidomethyl group serves as a useful thiol-protecting group for cysteine during peptide synthesis.[4,7,8,9] The protecting group is stable to the conditions generally prevailing in peptide synthesis, including not only typical solution and solid-phase procedures but also reactions carried out in liquid hydrogen fluoride.[4] Peptides containing *S*-acetamidomethyl-L-cysteine generally have good water solubility[8] and are not prone to racemization at the α-position of the cysteine residue.[4] The acetamidomethyl protecting group may be easily removed by reaction with either mercury(II) acetate at pH 4, as described in (Note 14), or iodine.[7,8] *S*-Acetamidomethylation of the cysteine residues of proteins may be accomplished in liquid hydrogen fluoride, and the group may be removed by reaction with mercury(II) ion.[4] The thiol group of β-mercaptopropionic acid has also been protected by formation of the *S*-acetamidomethyl derivative.[7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 252

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

phosphorous pentoxide

ethanol (64-17-5)

potassium carbonate (584-08-7)

hydrochloric acid, hydrochloride (7647-01-0)

Acetamide (60-35-5)

acetic acid (64-19-7)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

formaldehyde (630-08-0)

hydrogen sulfide (7783-06-4)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

mercury(II) acetate (1600-27-7)

mercury (7439-97-6)

hydrogen fluoride (7664-39-3)

1-butanol (71-36-3)

iodine (7553-56-2)

acetone (67-64-1)

pyridine (110-86-1)

potassium hydroxide (1310-58-3)

2-propanol (67-63-0)

potassium bicarbonate (298-14-6)

trifluoroacetic acid (76-05-1)

mercury(II) ion

L-cysteine hydrochloride (52-89-1)

L-cysteine hydrochloride monohydrate (7048-04-6)

L-cystine dihydrochloride (90350-38-2)

cysteine, L-cysteine (52-90-4)

β-mercaptopropionic acid (107-96-0)

L-Cysteine, S-[(acetylamino)methyl]-, monohydrochloride (28798-28-9)

N-(hydroxymethyl)acetamide (625-51-4)

S-Acetamidomethyl-L-cysteine hydrochloride

S-acetamidomethyl-L-cysteine monohydrate

S-acetamidomethyl-L-cysteine

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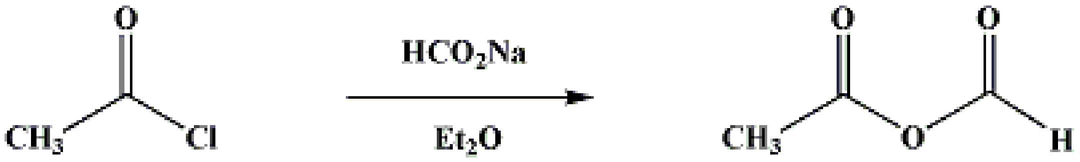
Organic Syntheses, *CV 6*, *8*

ACETIC FORMIC ANHYDRIDE

[Acetic acid, anhydride with formic acid]



Submitted by Lewis I. Krimen[1]
Checked by James Savage and Peter Yates.

1. Procedure

A dry, 2-l., three-necked, round-bottomed flask equipped with a stirrer, a thermometer, a reflux condenser fitted with a calcium chloride tube, and a dropping funnel is charged with 300 g. (4.41 moles) of sodium formate (Note 1) and 250 ml. of anhydrous diethyl ether (Note 2). To this stirred mixture is added 294 g. (266 ml., 3.75 moles) of acetyl chloride (Note 3) as rapidly as possible, while the temperature is maintained at 23–27° (Note 4). After the addition is complete, the mixture is stirred for 5.5 hours at 23–27° to ensure complete reaction. The mixture is then filtered with suction, the solid residue is rinsed with 100 ml. of ether, and the washings are added to the original filtrate (Note 5). The ether is removed by distillation at reduced pressure, and the residue is distilled, yielding 212 g. (64%) of colorless acetic formic anhydride, b.p. 27–28° (10 mm.), 38–38.5° (39 mm.); n_D^{20} 1.388 (Note 6).

2. Notes

1. Reagent grade sodium formate from J. T. Baker Chemical Co. was used; it was finely ground to ensure better contact. It is imperative that extreme care be taken to ensure anhydrous conditions throughout the procedure, since hydrolysis produces formic and acetic acids, which are very difficult to remove from the product. A slight excess of sodium formate ensures a product free of acetyl chloride.

2. Mallinckrodt AR grade ether was used without further drying by the submitter. The checkers, working at half scale, found it essential to dry the ether over sodium.

3. Acetyl chloride from Matheson, Coleman and Bell was used without further purification.

4. The addition of acetyl chloride is mildly exothermic; the exotherm can be controlled by slower addition or by the use of a cooling bath (20–24°). The addition is completed in *ca.* 5 minutes.

5. The filtration and subsequent ether rinse should be carried out quickly in order to keep the filtrate dry.

6. The acetic formic anhydride may be stored at 4° in a standard-taper, round-bottomed flask fitted with a polyethylene stopper. Moisture catalyzes the decomposition of the product to acetic acid, with the evolution of carbon monoxide. *The material must not be stored in sealed containers!*

7. The IR spectrum of neat acetic formic anhydride shows two bands in the carbonyl region at 1765 and 1791 cm.$^{-1}$ and carbon-oxygen-carbon stretching absorption at 1050 cm.$^{-1}$ (a band at 1180 cm.$^{-1}$ could also be due to C-O-C). The ^{1}H NMR spectrum (neat) shows a singlet at δ 2.25 (acetyl protons) and a singlet at δ 9.05 (formyl proton). If the product is not pure, the following peaks may also be observed: δ 2.05 (CH_3CO_2H), 2.20 [$(CH_3CO)_2O$], 2.68 (CH_3COCl), 8.05 ($HCOOH$), 8.85 [$(HCO)_2O$]. The spectrum of the product obtained by the checkers showed slight contamination with acetic anhydride and formic anhydride.

3. Discussion

Acetic formic anhydride has been prepared by the reaction of formic acid with acetic anhydride[2,3] and ketene,[4,5] and of acetyl chloride with sodium formate.[6] The present procedure is essentially that of Muramatsu.[6] It is simpler than others previously described, gives better yields, and is easily adapted to the preparation of large quantities, usually with an increase in yield. Acetic formic anhydride is a useful intermediate for the formylation of amines,[3,7] amino acids,[8,9] and alcohols,[2,10] for the synthesis of aldehydes from Grignard reagents,[11] and for the preparation of formyl fluoride.[12]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Acetic formic anhydride

Acetic acid, anhydride with formic acid

acetic acid (64-19-7)

ether, diethyl ether (60-29-7)

acetic anhydride (108-24-7)

carbon monoxide (630-08-0)

acetyl chloride (75-36-5)

formic acid (64-18-6)

sodium (13966-32-0)

sodium formate

formyl fluoride (1493-02-3)

FORMIC ANHYDRIDE

carbon-oxygen-carbon

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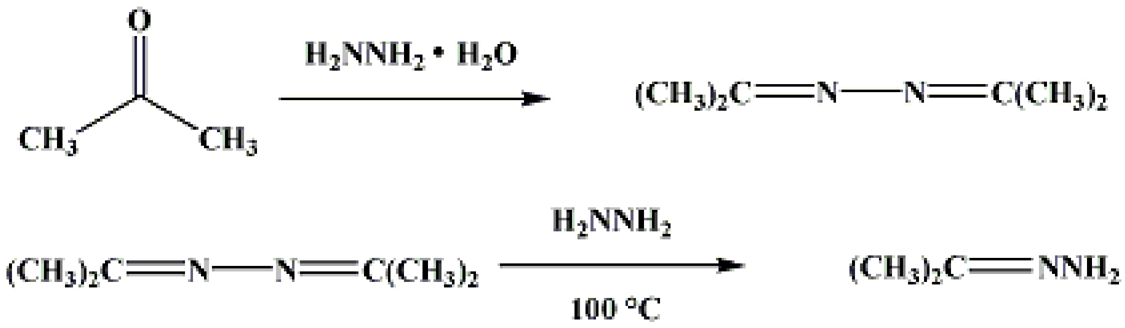
Organic Syntheses, *CV 6, 10*

ACETONE HYDRAZONE

[2-Propanone, hydrazone]



Submitted by A. C. Day[1] and M. C. Whiting[2].
Checked by G. Swift and W. D. Emmons.

1. Procedure

Caution! Hydrazine is toxic and should be handled in a hood. Anhydrous hydrazine is extremely reactive with oxidizing agents (including air) and should always be prepared and used behind a protective screen.

A. *Acetone azine*. A 500-ml., round-bottomed flask containing 145 g. (183 ml., 2.50 moles) of acetone (Note 1) is fitted with a mechanical stirrer (Note 2) and a dropping funnel and cooled in an ice bath. With vigorous stirring, 65.5 g. (1.31 moles) of 100% hydrazine hydrate (Note 1) is added at such a rate that the temperature is maintained below 35°. The addition takes 20–30 minutes. The mixture is stirred for an additional 10–15 minutes before 50 g. of potassium hydroxide pellets is added with vigorous stirring and continued cooling (Note 3). The upper liquid layer is separated and allowed to stand over 25 g. of potassium hydroxide pellets for 30 minutes, with occasional swirling (Note 4). After filtration, the liquid is further dried with two successive 12.5-g. portions of potassium hydroxide. Distillation gives 120–126 g. (86–90%) of almost colorless acetone azine, b.p. 128–131°, n_D^{22} 1.4538 (Note 5).

B. *Acetone hydrazone*. Anhydrous hydrazine is prepared by heating under reflux 100% hydrazine hydrate with an equal weight of sodium hydroxide pellets for 2 hours, followed by distillation in a slow stream of nitrogen introduced through a capillary leak. *(Caution! Distillation in air can lead to explosion.)* The distillate boils at 114–116° and the yield is 95–97% (Note 6).

A mixture of 112 g. (1.00 mole) of acetone azine and 32 g. (1.0 mole) of anhydrous hydrazine is placed in a 300-ml. round-bottomed flask fitted with a reflux air condenser and drying tube, and kept at 100° for 12–16 hours. *(Caution! This reaction*

and the subsequent distillation should be carried out behind a protective screen.) The crude product is then distilled rapidly through a water-cooled condenser, and the colorless fraction boiling at 122–126° is collected, n_D^{22} 1.4607 (Note 7), yielding 111–127 g. (77–88%, (Note 7) and (Note 8)) of essentially pure acetone hydrazone (Note 9).

2. Notes

1. The acetone and hydrazine hydrate were good-quality commercial products purified before use.
2. A Hershberg stirrer made of Nichrome wire is most efficient for aiding dissolution of the potassium hydroxide added after azine formation is complete.
3. The dissolution of the potassium hydroxide is strongly exothermic. A small proportion may remain undissolved.
4. A lower, aqueous phase may form at this stage, but the product is easily decanted from it.
5. The distillation gives a small forerun, b.p. 120–128°, containing hydrazine and acetone hydrazone. There is virtually no distillation residue. The submitters carried out the preparation of both acetone azine and acetone hydrazone on a fourfold scale with comparable results.
6. The purity is 95–98% by this method.[3] The purity is lower (85–95%) by an alternative procedure[4] which requires separation of the hydrazine and alkaline phases above 60°; with the latter method the submitters found that a frequent problem was the solidification of the lower phase in the separating funnel, and in one case *a very serious fire* occurred during the transfer of the hot (*ca.* 100°) mixture to the separating funnel.
7. The forerun contains hydrazine; material boiling above 126° contains much acetone azine. With a slow rate of distillation, disproportionation occurs and the yield of acetone hydrazone is reduced. If the forerun and material boiling above 126° are combined and reheated at 100° for 12–16 hours, they give more acetone hydrazone on redistillation. With further repetitions of this procedure, the yield is almost quantitative.
8. The highest yields were obtained in cases where the anhydrous hydrazine was treated with barium oxide for several hours before use.
9. The hydrazone should be used as soon as possible. If it is stored, care must be taken to exclude moisture, which catalyzes disproportionation to hydrazine and acetone azine.[5,6,7] Even in the absence of moisture it disproportionates slowly at room temperature and so should be redistilled immediately before use. Old samples can be regenerated fairly satisfactorily by reheating them for 12–16 hours at 100° before redistillation, but there is always some irreversible decomposition to high-boiling products during storage.

3. Discussion

The procedure for acetone azine is essentially that of Curtius and Thun.[5] The method

for acetone hydrazone is adapted from that of Staudinger and Gaule.[8] The hydrazone has been prepared directly from acetone and hydrazine, but this is much less satisfactory.[6]

Acetone hydrazone is produced in good yield by the method described, but an inferior product is obtained without the precautions noted. The compound is used for the preparation of 2-diazopropane.[8,9,10]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 161

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium hydroxide pellets (1310-73-2)

barium oxide

nitrogen (7727-37-9)

acetone (67-64-1)

potassium hydroxide, potassium hydroxide pellets (1310-58-3)

hydrazine hydrate (7803-57-8)

hydrazine (302-01-2)

Acetone hydrazone, 2-Propanone, hydrazone (5281-20-9)

Acetone azine (627-70-3)

2-Diazopropane (2684-60-8)

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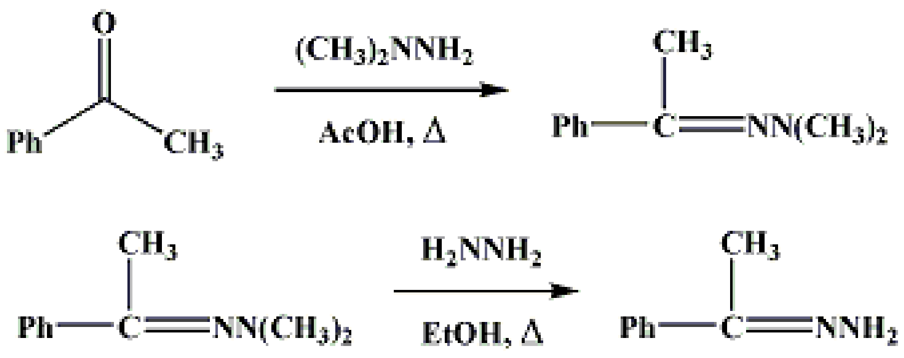
Organic Syntheses, *CV 6, 12*

PREPARATION OF HYDRAZONES: ACETOPHENONE HYDRAZONE

[Ethanone, 1-phenyl-, hydrazone]



Submitted by G. R. Newkome[1] and D. L. Fishel[2].
Checked by G. Swift and W. D. Emmons.

1. Procedure

Caution! Hydrazines are toxic and should be handled in a hood. Anhydrous hydrazine is extremely reactive with oxidizing agents (including air) and should always be used behind a protective screen.

A. *Acetophenone N,N-dimethylhydrazone*. A mixture of acetophenone (12.0 g., 0.100 mole), anhydrous *N,N*-dimethylhydrazine (18.0 g., 0.300 mole) (Note 1), absolute ethanol (25 ml.), and glacial acetic acid (1 ml.) (Note 2) is heated at reflux for 24 hours. During this period the colorless solution becomes bright yellow. The volatile reactants and solvent are removed under reduced pressure and the residual oil is fractionally distilled through a 10-cm. Vigreux column, giving a small forerun of unreacted acetophenone, b.p. 30–40° (0.15 mm.), followed by 14.6–15.2 g. (90–94%) of acetophenone *N,N*-dimethylhydrazone, b.p. 55–56° (0.15 mm.), n_D^{25} 1.5443 (Note 3) and (Note 4).

B. *Acetophenone hydrazone*. A mixture of acetophenone *N,N*-dimethylhydrazone (8.1 g., 0.050 mole) and anhydrous hydrazine (6.4 g., 0.20 mole) (Note 5) in absolute ethanol (15 ml.) is heated at reflux until the reaction mixture turns colorless (Note 6). The volatile materials are removed on a rotary evaporator without allowing the flask temperature to rise above 20° (Note 7). The colorless residual acetophenone hydrazone, which solidifies as the last traces of solvent are removed, weighs 6.5–6.6 g. (97–99%) and is sufficiently pure for most purposes, m.p. 24–25° (Note 8) and (Note 9).

2. Notes

1. Anhydrous *N,N*-dimethylhydrazine obtained from Matheson, Coleman and Bell is used directly. It can also be prepared by the method in *Org. Synth.*, **Coll. Vol. 2**, 213 (1943).
2. It is not necessary to use glacial acetic acid as a catalyst, but without it the reaction time required for completion is prolonged.
3. Physical constants previously reported:[3] b.p. 100.5–102° (10 mm.), n_D^{25} 1.5455.
4. This method has been used to prepare various *N,N*-dimethylhydrazones in 70–99% yield.[4]
5. A good commercial grade of anhydrous hydrazine (Eastman Organic Chemicals) is satisfactory.
6. The reaction time for complete conversion is usually less than 24 hours. A convenient "end point" is the visual color change from bright yellow to colorless or very pale yellow.
7. It is of utmost importance that the flask temperature during the removal of the volatile materials be kept below 20° to minimize possible azine formation by decomposition of the hydrazone.
8. The reported melting points are 16–20°,[5] 22°,[6] 24–25°,[4,7] and 26°.[7]
9. Acetophenone hydrazone can be stored at temperatures below 0° for indefinite periods of time.

3. Discussion

The formation of acetophenone hydrazone has been accomplished by heating acetophenone with hydrazine or hydrazine hydrate,[7,8,9,10] by heating acetophenone azine with anhydrous hydrazine,[6,11] by the reaction of α-dimethylaminoacetophenone with hydrazine,[5] and by the present method.[4]

This synthetic process is applicable to the preparation of most hydrazones from aldehydes and ketones. The two-step preparation offers several distinct advantages over the one-step method:[6,9] (1) The yield of both steps is high; (2) the product is not contaminated with azine; (3) the isolated product is pure enough to be used in subsequent reactions without further purification. This method excels in the preparation of unstable liquid or low-melting hydrazones over the common methods of preparation.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

acetic acid (64-19-7)

Acetophenone (98-86-2)

hydrazine hydrate (7803-57-8)

hydrazine (302-01-2)

N,N-dimethylhydrazine (57-14-7)

Acetophenone hydrazone, Ethanone, 1-phenyl-, hydrazone (13466-30-3)

acetophenone azine (729-43-1)

α-dimethylaminoacetophenone (3319-03-7)

Acetophenone N,N-dimethylhydrazone (13466-32-5)

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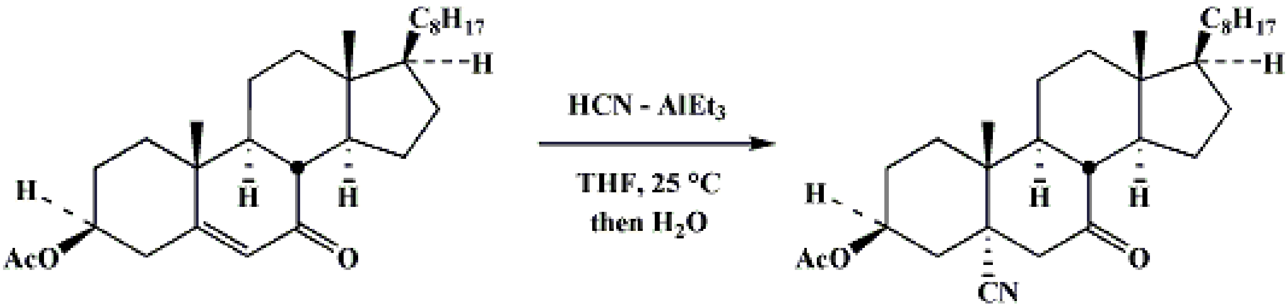
Organic Syntheses, CV 6, 14

3β-ACETOXY-5α-CYANOCHOLESTAN-7-ONE

[Cholestane-5-carbonitrile, 3-(acetyloxy)-7-oxo-, (3β, 5α)-]



Submitted by W. Nagata and M. Yoshioka[1].
Checked by Robert E. Ireland, Robert Czarny, and Conrad J. Kowalski.

1. Procedure

Caution! This preparation should be carried out in a good hood. Also, great care should be taken in handling neat triethylaluminum because it is pyrophoric—that is, it ignites spontaneously upon contact with air (Note 2).

Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A dry, 50-ml., three-necked, round-bottomed flask equipped with a gas-inlet tube for nitrogen, a magnetic stirring bar, and a serum stopper for the introduction of reagents is flushed with nitrogen, stoppered with a glass stopper, charged with 17 ml. of anhydrous tetrahydrofuran (Note 1), then immersed in an ice bath. Stirring is begun and 3.3 g. (3.9 ml., 0.028 mole) of triethylaluminum is introduced into the flask with a dry hypodermic syringe (Note 2), (Note 3). After 5–10 minutes, 4.8 ml. of a 3.57 *M* solution of hydrogen cyanide (0.017 mole) in anhydrous tetrahydrofuran (Note 4) is added with a dry hypodermic syringe. The stirring is continued for about 5–10 minutes.

A dry, 100-ml., three-necked, round-bottomed flask equipped with a gas-inlet tube for nitrogen, a magnetic stirring bar, and a serum stopper, as described above, is flushed with nitrogen. While the flask is being flushed, 2.50 g. (0.00565 mole) of 3β-acetoxycholest-5-en-7-one (Note 5) and 0.0521 ml. (0.00289 mole) of water (Note 6) are added to the reaction flask. The flask is stoppered with a glass stopper and charged with 17 ml. of anhydrous tetrahydrofuran. After the starting material has dissolved, the cold triethylaluminum-hydrogen cyanide solution is transferred to the reaction flask with a dry hypodermic syringe. The resulting pale yellow solution is stirred at room temperature under a positive nitrogen pressure. After 3 hours, a solution of 0.044 ml. (0.0024 mole) of water in 0.87 ml. of anhydrous tetrahydrofuran is added, and the solution is allowed to stir for an additional 4 hours.

The reaction mixture is poured slowly into a vigorously stirred solution of 28 ml. (0.28 mole) of concentrated hydrochloric acid and 350 ml. of ice water in a 1-l., three-necked, round-bottomed flask fitted with an efficient stirrer and immersed in an ice bath (Note 7), (Note 8). The mixture is

stirred for 20 minutes with ice cooling and extracted with three 200-ml. portions of a 3:1 (v/v) mixture of diethyl ether and dichloromethane. The extracts are washed with three 200-ml. portions of aqueous 2 *M* sodium hydroxide, two 200-ml. portions of water, and one 200-ml. portion of saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, and evaporated under reduced pressure (Note 9) and (Note 10). The crystalline residue, weighing 2.70 g., is recrystallized by dissolving it in 7.5–8 ml. of hot (almost boiling) benzene and adding 25 ml. of *n*-pentane (distilled) to the hot solution (Note 11). 3β-Acetoxy-5α-cyanocholestan-7-one is obtained as white crystals, m.p. 192.5–193.5°; the yield is 2.27–2.41 g. (86–91%). A second crop (50–170 mg.) can be obtained, m.p. 188.5–190° (Note 12); the total yield is 92–93% (Note 13) and (Note 14).

2. Notes

1. Prior to use the tetrahydrofuran was distilled from lithium aluminum hydride into a dry flask flushed with nitrogen and sealed with a serum stopper.

2. *Caution! Triethylaluminum is pyrophoric. Use safety glasses, gloves, and an apron. Use dry sand to extinguish fires.* The submitters note that a description of the properties and handling procedures for triethylaluminum are available from the Ethyl Corporation, Louisiana. The checkers used triethylaluminum in lecture bottles from Alpha Inorganics, Inc., and suggest the handling procedure described below. Since this procedure was submitted and checked, standardized solutions of triethylaluminum in various hydrocarbon solvents, which may be substituted for pure triethylaluminum, have become available from Texas Alkyls, Inc., a division of Stauffer Chemical Company.

a. *Checkers handling procedure*. f.htmigures 1 and 2.htm suggest the equipment to be used, and how to assemble it. The hose end fitting is connected to the stopcock with a piece of Teflon-lined tubing and fastened with copper wire. The stopcock should be well greased and held secure with a taut rubber band since it does have a tendency to pop out. The triethylaluminum may now be removed from the lecture bottle by the following procedure. A dry, three-necked flask equipped with serum stopper and gas-inlet tube is flushed thoroughly with nitrogen from a nitrogen bubbler. The triethylaluminum transfer apparatus is put into the open neck of the flask, the joint being well greased (the gas-inlet tube joint should also be greased). With the stopcock of the transfer apparatus *open* and well secured as suggested above, the tank valve is opened (usually one or two full turns) with a wrench. The flow of triethylaluminum may now be adjusted with the stopcock. When one obtains as much triethylaluminum as desired, the tank valve is closed, the transfer apparatus is allowed to drain, and the stopcock is closed. The transfer apparatus is removed from the flask which is quickly stoppered with a glass stopper while the flask is flushed with nitrogen. This flask of triethylaluminum can be stored in this manner for many weeks since this reagent is quite stable. The transfer apparatus, which may still contain some triethylaluminum, should be carefully removed, rinsed quickly with acetone, and cleaned with dilute hydrochloric acid.

Figure 1. Apparatus for collecting triethylaluminum from a lecture bottle.

Figure 1. Apparatus for collecting triethylaluminum from a lecture bottle.

Figure 2. Detailed construction of the stopcock for the apparatus shown in f.htmigure 1.

Figure 2. Detailed construction of the stopcock for the apparatus shown in Figure 1.

b. *Submitters handling procedure.* The submitters suggest another handling procedure especially useful for removing triethylaluminum from a lecture bottle having a clogged valve outlet. f.htmigure 3 shows the apparatus and how to transfer the material. With the cylinder clamped in upright position, remove the valve unit so that only the bottle remains. Quickly attach the adaptor to the opening of the bottle and apply a slow stream of nitrogen. Transfer the triethylaluminum into dry, nitrogen-flushed, 50-ml. ampoules using a 100- or 200-ml. Luer-lock hypodermic syringe with a needle, 43 cm. long and 2 mm. in diameter. Sweep the opening of the ampoule with nitrogen during the transfer. The syringe should be slightly greased, and the ampoules should be strong with a long, thick stem so that they can be resealed. The ampoules are sealed as soon as possible. The use of rubber caps is effective for temporary protection of the ampoules from air. The material in a 50-ml. ampoule can be divided in smaller ampoules using the apparatus shown in f.htmigure 4, which can be used also for transferring triethylaluminum from an ampoule to a reaction flask.

Figure 3. Apparatus for removing triethylaluminum from the lecture bottle.

Figure 3. Apparatus for removing triethylaluminum from the lecture bottle.

Figure 4. Apparatus for collecting aliquots of triethylaluminum.

Figure 4. Apparatus for collecting aliquots of triethylaluminum.

This procedure was not tested by the checkers. It has the advantage that one does not have to contend with a clogged lecture bottle, which in the checkers experience is best discarded. It has the disadvantage that one must handle large syringe-fulls of triethylaluminum and make several transfers without exposing the liquid to air. Caution must be exercised with either procedure.

3. Neat triethylaluminum may be replaced with a 10–25% stock solution of it in anhydrous tetrahydrofuran, decreasing the amount of solvent in the reaction flask. The stock solution is prepared using a graduated flask to measure the volume of the triethylaluminum and solvent, added appropriately. The stock solution is very stable and not pyrophoric.

4. The submitters have prepared hydrogen cyanide as directed in *Org. Synth.*, **Coll. Vol. 1**, 314, (1944). The checkers used a similar procedure described by Brauer.[2] The hydrogen cyanide was collected in a tared flask and diluted with anhydrous tetrahydrofuran to a previously marked volume. The flask was capped with two serum stoppers (the second put on in an inverted position) to ensure against leakage and stored in a freezer. Solutions such as these seem to be stable for several months when kept cold.

5. Checkers obtained the steroid from K & K Laboratories.

6. A small amount of water has been found to accelerate the reaction. In the absence of water, the reaction was about 80% complete after 7.5 hours. Despite the rate acceleration by water, the reaction mixture should be protected from moisture, because a larger amount of water than that specified retards the reaction, owing to decomposition of the

triethylaluminum.

7. This treatment is an exothermic reaction with evolution of gaseous ethane. The reaction mixture should be added in a slow stream, with good stirring, at such a rate that the content in the flask does not overflow. When the ice has melted, additional ice should be added.
8. The reaction mixture remaining on the wall of the reaction flask is treated with a small amount of cold, dilute hydrochloric acid and combined with the extraction mixture.
9. Acid treatment followed by alkaline washing of the extracts prevents possible hydrolysis of the acetoxyl and the cyano groups.
10. The submitters have performed the extraction and washing in a countercurrent manner using three 2-l. separatory funnels.
11. The recrystallization was carried out in a 40-ml. centrifuge tube. The recrystallization mixture, after cooling to room temperature, was cooled in a freezer and washed twice with 20-ml. portions of cold recrystallization solvent.
12. When the second crop is contaminated with a polar material (α-cyanohydrin of the product) as evidenced by a lower melting point (m.p. 160–170°) and TLC (Kiesel Gel GF, benzene-ethyl acetate, 4:1, $R_f = 0.2$), the residue from the mother liquor must be treated again with alkali before crystallization.
13. This procedure is applicable to smaller or larger scale preparations with some modification. In a smaller scale experiment, the submitters suggest using a stock solution of triethylaluminum (Note 3). In a larger scale preparation, to avoid using large syringes, it is possible to run the triethylaluminum into a dry, graduated, pressure-equalizing dropping funnel, in which case the triethylaluminum-hydrogen cyanide solution may be added to the reaction flask through a funnel instead of using a syringe.
14. The submitters used 5.76 g. of 3β-acetoxycholest-5-en-7-one and obtained 5.65 g. (92%) of the cyano ketone.

3. Discussion

3β-Hydroxy-5α-cyanocholestan-7-one has been prepared in 43% yield by the action of potassium cyanide and ammonium chloride[3] on 7-ketocholesterol at 100° for 33 hours.[4] The present method was developed by the submitters.[4]

This process is superior to classical hydrocyanation methods using an alkali metal cyanide[5] and to the improved method using potassium cyanide and ammonium chloride[3] with respect to reactivity, stereospecificity, and absence of side reactions. Also, the process is applicable to conjugate hydrocyanation of various α,β-unsaturated carbonyl and imino compounds,[4,6] cyanohydrin formation from less-reactive ketones,[4] and cleavage of epoxides to produce β-cyanohydrins,[7] the reaction conditions being varied depending on the substrate to be used. The present procedure is typical of hydrocyanation procedures using other organoaluminum compounds. Cyanotrimethylsilane reacts with α,β-unsaturated ketones in the presence of triethylaluminum to give trimethylsilyl enol ethers of β-cyano ketones.[8]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

hydrogen cyanide (74-90-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

potassium cyanide (151-50-8)

acetone (67-64-1)

n-PENTANE (109-66-0)

dichloromethane (75-09-2)

ethane (74-84-0)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

triethylaluminum (97-93-8)

3β-ACETOXY-5α-CYANOCHOLESTAN-7-ONE, Cholestane-5-carbonitrile, 3-(acetyloxy)-7-oxo-, (3β, 5α)- (2827-02-3)

3β-acetoxycholest-5-en-7-one

triethylaluminum-hydrogen cyanide

3β-Hydroxy-5α-cyanocholestan-7-one

7-ketocholesterol

Cyanotrimethylsilane (7677-24-9)

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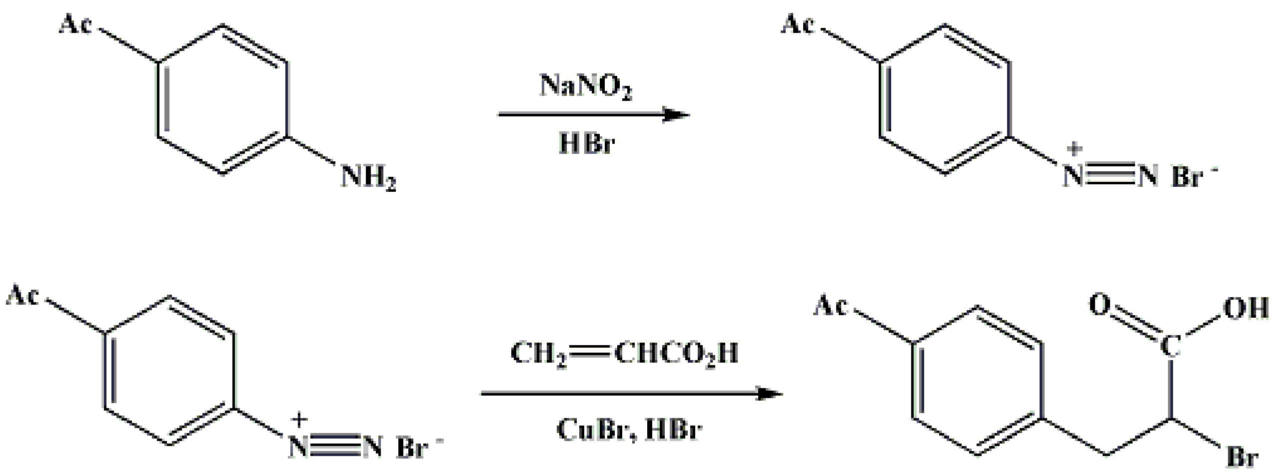
Organic Syntheses, CV 6, 21

p-ACETYL-α-BROMOHYDROCINNAMIC ACID

[Benzenepropanoic acid, 4-acetyl-α-bromo-]



Submitted by George H. Cleland[1]
Checked by Michael J. Umen and Herbert O. House.

1. Procedure

Caution! Since bromoacetone, a powerful lachrymator, is produced as a by-product in this preparation, the reaction should be performed in a hood.

A tared, 500-ml., two-necked, round-bottomed flask is equipped with a magnetic stirring bar, a thermometer, and an ice-filled cooling bath. A solution of 13.5 g. (0.100 mole) of 4-aminoacetophenone (Note 1) in 200 ml. of acetone is placed in the flask and stirred while 32 ml. (about 0.3 mole) of aqueous 48% hydrobromic acid is added. After the resulting solution has been cooled to 5–7°, it is stirred continuously while 20 ml. of an aqueous solution containing 6.90 g. (0.100 mole) of sodium nitrite is added rapidly (30 seconds) beneath the surface of the reaction solution with a hypodermic syringe or a long-stemmed dropping funnel. Stirring and cooling are continued until the exothermic reaction subsides (Note 2) and the reaction solution has cooled to 14–15°. After 106 g. (100 ml., 1.47 moles) of acrylic acid (Note 3) is added, the solution is again cooled to 14–15°, with stirring, before 0.10–0.11 g. (0.00069–0.00077 mole) of copper(I) bromide (Note 4) is added. Stirring is continued, during which time the solution darkens, and nitrogen evolution is observed; the temperature of the reaction mixture is kept below 33° by use of the external cooling bath. As soon as the evolution of nitrogen has ceased (usually 20 minutes is sufficient), the reaction solution is concentrated with a rotary evaporator, giving a mixture weighing about 120–130 g. The residual brown suspension is mixed with 5 g. of decolorizing charcoal and 200 ml. of water, and the resulting mixture is boiled for 3 minutes, and filtered while hot through a Büchner funnel containing Celite filter aid. The residue on the filter is washed with 100 ml. of boiling water, and the combined filtrates are diluted with 300 ml. of water. The resulting aqueous solution, from which the product begins to crystallize, is cooled in a water bath and then allowed to stand in a refrigerator (0–3°) for 24 hours to complete the crystallization of the crude product. The crystalline solid is collected on a filter, washed with two 100-ml. portions

of cold water, and dried in the air. The crude product, a pale yellow solid (19.1–22.2 g.), is recrystallized from 40 ml. of a 2:3 (v/v) formic acid-water mixture. The resulting crystals are collected on a filter, washed with 20 ml. of 2:3 (v/v) cold formic acid-water, and dried in the air, yielding 16.6–18.2 g. (61–67%) of white needles, m.p. 158–160°, which are sufficiently pure for most purposes. Three additional crystallizations from 20-ml. portions of 2:3 (v/v) formic acid-water give 15.2–16.0 g. (56–59%) (Note 5) of the pure *p*-acetyl-α-bromohydrocinnamic acid, m.p. 159–161° (Note 6).

2. Notes

1. Commercial grades of acetone and 4-aminoacetophenone (Matheson, Coleman and Bell or Aldrich Chemical Company, Inc.) were used without further purification.
2. The temperature of the reaction mixture rises to about 30° and then falls to 15° as stirring and cooling are continued. If this preparation were performed on a larger scale, it would probably be necessary to add the sodium nitrite solution over a longer period of time in order to control the temperature.
3. A freshly opened bottle of acrylic acid, obtained from Eastman Organic Chemicals, was used without further purification. The checkers encountered difficulty in attempting to use samples of acrylic acid that had been stored in partially filled bottles for long periods of time.
4. A reagent grade of copper(I) bromide, obtained from Fisher Scientific Company, was washed with acetone until the washings were colorless and then dried.
5. The combined filtrates from these recrystallizations can be concentrated to obtain an additional 1–2 g. of product.
6. The product has IR absorption (KBr) at 1735, 1645, and 1607 cm.$^{-1}$ with a UV maximum (95% C_2H_5OH solution) at 252.5 nm (ε 17,000). The sample has ^1H NMR peaks (CF_3CO_2H) at δ 2.78 (s, 3H, CH_3CO), 3.2–3.9 (m, 2H, benzylic CH_2), 4.60 (t, J = 7.5 Hz., 1H, C*H*Br), 7.47 (d, J = 9 Hz., 2H, aryl C*H*), and 8.10 (d, J = 9 Hz., 2H, aryl C*H*). The mass spectrum has weak molecular peaks at *m/e* 270 and 272 with the following relatively abundant fragment peaks: *m/e* (rel. int.), 191 (73), 175 (100), 131 (52), 103 (40), 77 (55), and 51 (43). The product gives a deep red color when treated with sodium nitroprusside and aqueous base; this color changes to dark blue upon acidification with acetic acid.

3. Discussion

This procedure has been used to prepare a variety of substituted α-bromohydrocinnamic acids;[2] *p*-acetyl-α-bromohydrocinnamic acid was prepared for the first time by this method. The method illustrates a typical application of the Meerwein reaction for the arylation of unsaturated substrates.[3] In this reaction a catalytic amount of a copper(I) salt is used to reduce an aryl diazonium salt forming an aryl radical and a copper(II) halide. Addition of the aryl radical to an unsaturated substrate forms an alkyl radical that is reoxidized by the copper(II) halide present forming an alkyl halide and regenerating the copper(I) salt catalyst. In this preparation, the product, an α-bromo acid, is formed in an acidic reaction mixture and dehydrohalogenation does not occur. However, dehydrohalogenation of the intermediate halide is often observed in analogous reactions performed under neutral or basic reaction conditions.[3] The use of the Meerwein reaction to form ultimately 1-(4-nitrophenyl)-1,3-butadiene by the addition of an intermediate aryl radical to 1,3-butadiene followed by

dehydrohalogenation of the initially formed alkyl halide is illustrated in *Organic Syntheses*.[4]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

4-aminoacetophenone

sodium nitroprusside

acetic acid (64-19-7)

HYDROBROMIC ACID (10035-10-6)

nitrogen (7727-37-9)

sodium nitrite (7632-00-0)

acetone (67-64-1)

Acrylic acid (9003-01-4)

copper(I) bromide (7787-70-4)

Bromoacetone (598-31-2)

1,3-Butadiene (106-99-0)

Benzenepropanoic acid, 4-acetyl-α-bromo-, p-Acetyl-α-bromohydrocinnamic acid (18910-19-5)

1-(4-nitrophenyl)-1,3-butadiene (20264-89-5)

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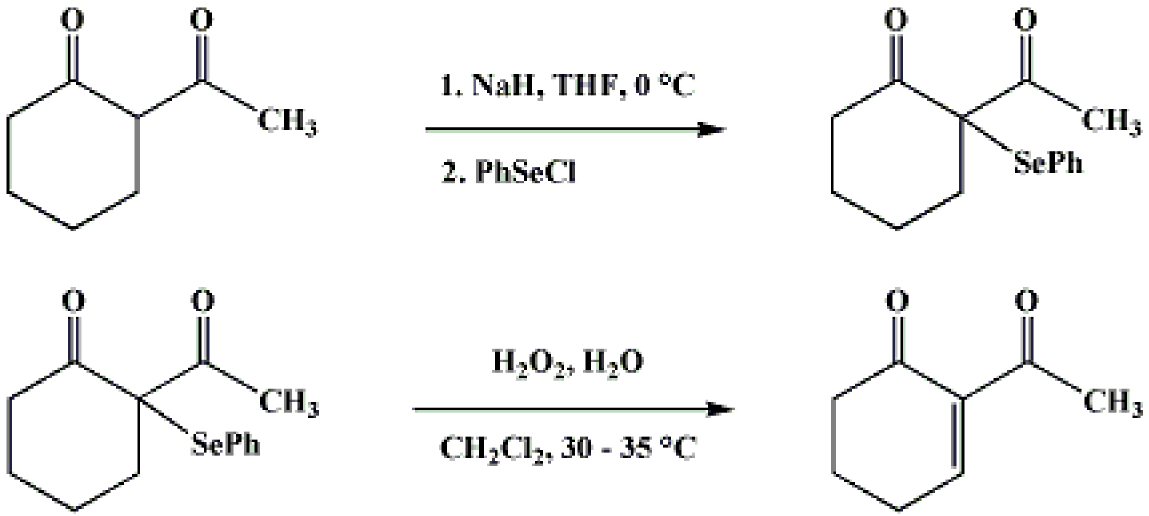
Organic Syntheses, CV 6, 23

α,β-DEHYDROGENATION OF β-DICARBONYL COMPOUNDS BY SELENOXIDE ELIMINATION: 2-ACETYL-2-CYCLOHEXEN-1-ONE

[2-Cyclohexen-1-one, 2-acetyl-]



Submitted by James M. Renga and Hans J. Reich[1].
Checked by Albert W. M. Lee and Robert V. Stevens.

1. Procedure

Caution! Most selenium compounds are toxic; consequently care should be exercised in handling them. The hydrogen peroxide oxidation of selenides is highly exothermic, acid-catalyzed, and autocatalytic. The procedure given for adding the hydrogen peroxide solution should be carefully followed.

A. *2-Acetyl-2-phenylselenocyclohexanone*. A 500-ml., three-necked, round-bottomed flask is fitted with a mechanical stirrer, a pressure-equalizing dropping funnel, and a combined inlet-outlet assembly connected to a nitrogen source and a bubbler. The flask is charged with 3.36 g. (0.140 mole) of sodium hydride (Note 1), the apparatus is flushed with nitrogen, and 100 ml. of tetrahydrofuran (Note 2) is added. The suspension is stirred and cooled in an ice bath under a static nitrogen atmosphere as a solution of 14.02 g. (0.100 mole) of 2-acetylcyclohexanone (Note 3) in 15 ml. of tetrahydrofuran is added over a 15-minute period. The formation of the sodium enolate is complete when hydrogen evolution ceases and a thick suspension has developed. Stirring and cooling are continued for 20 minutes, after which a solution of 20.1 g. (0.105 mole) of benzeneselenenyl chloride (Note 4) in 20 ml. of tetrahydrofuran is rapidly added. The contents of the flask are stirred at 0° for 15 minutes and poured into a beaker containing a magnetically stirred mixture of 200 ml. of 1:1 (v/v) diethyl ether-

pentane, 50 ml. of aqueous 7% sodium hydrogen carbonate, and 50 g. of ice. The layers are separated, and the aqueous layer is extracted with 50 ml. of 1:1 (v/v) ether–pentane. The combined organic extracts are washed with 50 ml. of saturated aqueous sodium chloride and dried by filtration through a cone of anhydrous sodium sulfate. Evaporation of the solvents under reduced pressure gives 29.2–30 g. of crude, solid 2-acetyl-2-phenylselenocyclohexanone which is used in Part B without purification (Note 5).

B. *2-Acetyl-2-cyclohexen-1-one*. A 500-ml., three-necked, round-bottomed flask equipped with a pressure-equalizing dropping funnel, a reflux condenser, a thermometer, and a magnetic stirring bar is charged with a solution of 29.2–30 g. (*ca.* 0.1 mole) of crude 2-acetyl-2-phenylselenocyclohexanone in 100 ml. of dichloromethane (Note 6). The solution is stirred at room temperature, and a 2–3 ml. portion from a solution of 23.8 g. of 30% hydrogen peroxide (7.14 g., 0.21 mole) (Note 7) in 20 ml. of water is added to initiate the oxidation (Caution! (Note 8)). After the exothermic reaction begins, the mixture is stirred and cooled in an ice–salt bath as necessary to keep the temperature between 30 and 35° while the remainder of the hydrogen peroxide solution is added. When the oxidation is complete (Note 9), the ice–salt bath is removed, and vigorous stirring is continued for 15 minutes at room temperature and 15 minutes at 0°. The chilled suspension of benzeneseleninic acid is filtered, and the filter cake is washed with 50 ml. of dichloromethane (Note 10). The dichloromethane layer from the filtrate is washed with 50 ml. of aqueous 7% sodium hydrogen carbonate, dried by filtration through a cone of anhydrous sodium sulfate, and evaporated, providing 12.8–13.7 g. of crude product (Note 11). Distillation in carefully washed glassware (Note 12) at 0.1 mm. using a Kügelrohr apparatus (Note 13) with an oven temperature of 50–55° gives 11.0–11.9 g. (79–85%) of 2-acetyl-2-cyclohexen-1-one (Note 14).

2. Notes

1. A 57% dispersion of sodium hydride in mineral oil was purchased from Alfa Division, Ventron Corporation. A 5.90-g. portion of the dispersion was placed in the reaction vessel and washed free of mineral oil with three 50-ml. portions of pentane by decanting the supernatant pentane after each washing. The pentane that remains in the flask is evaporated as the assembled apparatus is purged with nitrogen prior to adding the tetrahydrofuran.
2. Tetrahydrofuran was purified by the submitters by distillation from the sodium ketyl of benzophenone.
3. 2-Acetylcyclohexanone was used as supplied by Aldrich Chemical Company, Inc.
4. Benzeneselenenyl chloride was prepared by the procedure in *Org. Synth.*, **Coll. Vol. 6**, 533 (1988). A freshly prepared solution of 24.8 g. (0.105 mole) of benzeneselenenyl bromide[2] in 25 ml. of tetrahydrofuran may also be used.
5. The crude selenide is contaminated by volatile impurities including some 2-

acetylcyclohexanone which may be removed by sublimation at 50–60° to a cold finger cooled with dry ice, or by recrystallization from ether–pentane. The purified product melts at 72–73°; IR (CCl_4) cm^{-1}: 1693 strong, 1579 weak; ^1H NMR (CCl_4) δ (multiplicity, number of protons, assignment): 1.3–2.3 (m, 7H, ring protons), 2.30 (s, 3H, CH_3), 2.5–2.8 (m, 1H, CH_AH_BC=O), 7.28 (m, 5H, C_6H_5Se). The product was analyzed by the submitters. Analysis calculated for $C_{14}H_{16}O_2Se$: C, 56.96; H, 5.46. Found: C, 57.12; H, 5.48.

6. Dichloromethane was used without purification.

7. A 30% solution of hydrogen peroxide in water was purchased from Mallinckrodt Chemical Works. The reaction requires 2 molar equivalents of hydrogen peroxide, the first to oxidize the selenide to the selenoxide and the second to oxidize the elimination product, benzeneselenenic acid, to benzeneseleninic acid. The submitters recommend that the hydrogen peroxide solution be taken from a recently opened bottle, or titrated to verify its concentration.

8. The oxidation is autocatalytic, being catalyzed by the product, benzeneseleninic acid.[3] If the temperature drops significantly below 30°, the addition of hydrogen peroxide should be stopped, and the ice–salt bath should be removed to maintain the rate of oxidation and avoid an accumulation of hydrogen peroxide in the flask.

9. The yellow dichloromethane solution turns colorless, and a precipitate of benzeneseleninic acid appears.

10. The benzeneseleninic acid weighs 14.4–16 g. (73–82%) and melts at 123–124°. It may be reconverted to diphenyl diselenide by reduction with sodium thiosulfate[2] or sodium bisulfite.[4]

11. The enol content of the product at this point is less than 2%. If the unenolized enedione is desired, the following distillation should be omitted and the product used without purification to avoid further isomerization.

12. The glassware was cleaned in a sodium dichromate–sulfuric acid bath, washed with aqueous 10% ammonium hydroxide, and rinsed with water. The extent of enolization apparently depends on the care taken in washing the glassware and conducting the distillation.

13. Kügelrohr distillation ovens manufactured by Büchi Glasapparatfabrik are available from Brinckmann Instruments, Inc., Westbury, New York.

14. The product is contaminated by 5–15% of 2-acetylcyclohexanone, which was present in the crude selenide. This impurity may be avoided by purifying the selenide as described in (Note 5). The enol content of the product obtained by the submitters varied from 5 to 50%. At equilibrium the enol content is 84%. The spectral properties of the enedione are as follows: IR (CCl_4) $cm.^{-1}$: 1694 strong, 1602 weak; ^1H NMR (CCl_4), δ (multiplicity, coupling constant J in Hz., number of protons, assignment): 1.9–2.2 (m, 2H, $CH_2CH_2CH_2$), 2.35 (s, 3H, CH_3), 2.3–2.7 (m, 4H, $CH_2CH_2CH_2$), 7.56 (t, J = 4.3, H, CH_2CH=C). The enol form of the product exhibits the following ^1H NMR (CCl_4), δ (multiplicity,

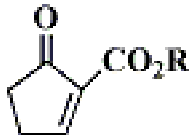
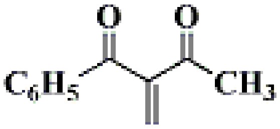
coupling constant *J* in Hz., number of protons, assignment): 2.07 (s, 3H, CH_3), 2.1–2.7 (m, 4H, CH_2CH_2), 5.55 (d of t, *J* = 4.5 and 10, 1H, CH_2CH=CH), 6.19 (d of t, *J* = 1.5 and 10, 1H, CH_2CH=C*H*), 15.8 (s, 1H, O*H*).

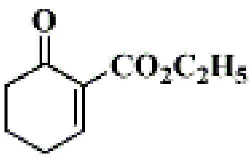
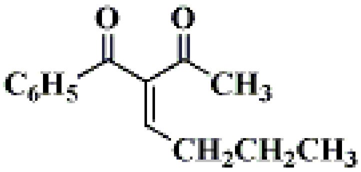
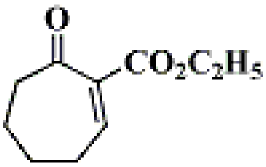
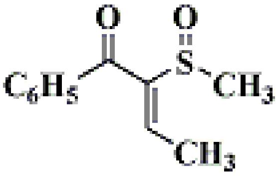
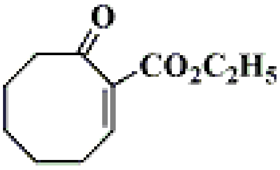
3. Discussion

The procedure described here serves to illustrate a new, general method for effecting the α,β-dehydrogenation of ketones,[2,5,6,7,8,9] aldehydes,[9] esters,[2,5,6,7,9] lactones,[9,10] nitriles,[11] sulfones, and related compounds.[2,12] The individual steps in the process are formation of an α-carbanion or enol derivative, phenylselenenylation with diphenyl diselenide or benzene selenenyl halides, oxidation of the resulting α-phenylseleno compound to the selenoxide, and thermal *syn*-elimination of benzeneselenenic acid. The advantages of this method include (*a*) the ease of introducing the α-phenylseleno group; (*b*) the rapid stoichiometric oxidation of the selenide with aqueous hydrogen peroxide at 25–35°, sodium metaperiodate in aqueous media, or ozone in dichloromethane at −78°; and (*c*) the fact that the elimination occurs at about room temperature under essentially neutral conditions.

The mild character of the reaction conditions is exemplified effectively here by the preparation of 2-acetyl-2-cyclohexen-1-one from 2-acetylcyclohexanone.[2] The crude product is initially isolated entirely in the less stable enedione form which is partially converted to the more stable enol form, 2-acetyl-1,3-cyclohexadien-1-ol,[13,14,15] during distillation at 45–55°. A series of α,β-unsaturated β-keto esters, β-diketones, and a β-keto sulfoxide have also been prepared in the unenolized form by this procedure (Table I).[2,5,6,7] In the case of the highly sensitive ethyl 5-oxo-1-cyclopentene-1-carboxylate, the hydrogen carbonate extraction must be omitted to avoid base-catalyzed decomposition during isolation.

TABLE I
α,β-UNSATURATEDβ-KETOESTERS, β-DIKETONES AND Aβ-KETOSULFOXIDEPREPARED BYSELENOXIDEELIMINATION

α,β-Unsaturated Product	Yield (%)[a]	α,β-UnsaturatedProduct	Yield (%)[a]
	81[b]		74

	89		89
	84		55
	89		

a Overall yield from β-keto ester, β-diketone, or β-keto sulfoxide. The scale was 0.01–0.005 mole.

b The starting β-keto ester and the product were 2:1 mixtures of ethyl and methyl esters.

The enolized form of 2-acetyl-2-cyclohexen-1-one has been synthesized in low yield by dehydrochlorination of 2-acetyl-2-chlorocyclohexanone in collidine at 180°[13,14] and by elimination of acetamide from *N*-(2-acetyl-3-oxo-1-cyclohexyl)acetamide at 120–140°.[15] The preparation of other α,β-unsaturated β-dicarbonyl compounds has been attempted with varying degrees of success. The dehydrogenation of 2-hydroxymethylene-3-keto steroids to 2-formyl-Δ^1-3-keto compounds with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone has been reported.[16] Ethyl 5-oxo-1-cyclopentene-1-carboxylate has been prepared by selenium dioxide oxidation of the parent β-keto ester.[17] α-Acetoxylation of 3-methyl- and 3-isopropyl-2,4-pentanedione with lead tetraacetate followed by acetate pyrolysis provided the α,β-unsaturated β-diketones.[18] Chlorination and dehydrochlorination of 2-acetylcycloheptanone gave an enolic tautomer of 2-acetyl-2-cyclohepten-1-one.[14] Numerous failures in attempts to synthesize these and other α,β-unsaturated β-dicarbonyl compounds by halogenation and dehydrohalogenation have been recorded as a consequence of competing Favorskii rearrangement, migration of halogen to the α'-position, and decomposition of the products from a combination of the high temperatures and basic conditions employed.[13,14,16,17,18,19] A number of α,β-unsaturated β-keto esters and β-diketones

have been prepared by intermolecular aldol condensations under Knoevenagel conditions,[20] aldol cyclization,[19,21] and Robinson annelation.[22] All these procedures lead to equilibrium mixtures of keto and enol forms.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium ketyl

3-methyl- and 3-isopropyl-2,4-pentanedione

Acetamide (60-35-5)

ether (60-29-7)

hydrogen (1333-74-0)

sodium hydrogen carbonate (144-55-8)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

sodium thiosulfate (7772-98-7)

nitrogen (7727-37-9)

sodium bisulfite (7631-90-5)

selenium dioxide (7446-08-4)

Benzophenone (119-61-9)

hydrogen peroxide (7722-84-1)

ammonium hydroxide (1336-21-6)

Pentane (109-66-0)

dichloromethane (75-09-2)

ozone (10028-15-6)

selenium

Tetrahydrofuran (109-99-9)

sodium hydride (7646-69-7)

hydrogen carbonate (463-79-6)

Diphenyl diselenide (1666-13-3)

collidine

2,3-dichloro-5,6-dicyano-1,4-benzoquinone

sodium metaperiodate (7790-28-5)

sulfoxide

2-acetylcyclohexanone (874-23-7)

2-Acetyl-2-cyclohexen-1-one, 2-Cyclohexen-1-one, 2-acetyl- (52784-38-0)

diethyl ether-pentane

2-acetyl-2-phenylselenocyclohexanone

benzeneseleninic acid (6996-92-5)

Benzeneselenenyl chloride (5707-04-0)

benzeneselenenyl bromide (34837-55-3)

2-acetyl-1,3-cyclohexadien-1-ol

ethyl 5-oxo-1-cyclopentene-1-carboxylate

2-acetyl-2-chlorocyclohexanone

2-acetylcycloheptanone

2-acetyl-2-cyclohepten-1-one

N-(2-acetyl-3-oxo-1-cyclohexyl)acetamide

lead tetraacetate

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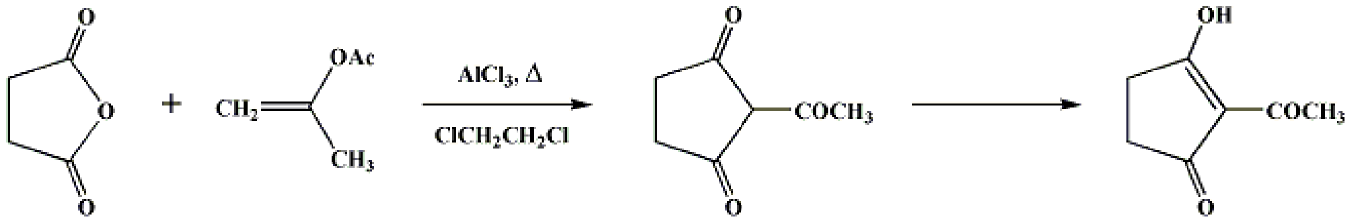
Organic Syntheses, CV 6, 28

2-ACETYL-1,3-CYCLOPENTANEDIONE

[2-Acetyl-3-hydroxy-2-cyclopenten-1-one, (Note 1)]



Submitted by Ferenc Merényi and Martin Nilsson[1].
Checked by E. J. Corey, Joel I. Shulman, and Lawrence Libit.

1. Procedure

Caution! Since hydrogen chloride is evolved in this reaction, it should be conducted in a hood.

A dry, 3-l., three-necked round-bottomed flask equipped with a sealed mechanical stirrer (all-glass or glass-Teflon), a reflux condenser fitted with a calcium chloride drying tube and a 100-ml. dropping funnel is charged with 50.0 g. (0.500 mole) of finely powdered succinic anhydride (Note 2), 133.4 g. (1.000 mole) of freshly crushed anhydrous aluminum chloride (Note 3), and 500 ml. of anhydrous 1,2-dichloroethane. The mixture is stirred vigorously at room temperature for about 2 hours to dissolve as much of the solid reactants as possible before 50.0 g. (0.500 mole) of isopropenyl acetate (Note 4) is added rapidly through the dropping funnel; the reaction starts immediately as indicated by a rise in temperature to about 60° to 70°. The mixture is refluxed for 15 minutes with continuous stirring. The hot reaction mixture, which contains a sticky oil, is poured into a stirred mixture of 200 ml. of 12 *M* hydrochloric acid and 1000 g. of crushed ice, and the reaction flask is rinsed with part of the acidic aqueous phase. When the dark mass has dissolved, 200 ml. of 12 *M* hydrochloric acid is added, and the mixture is stirred vigorously for about 3 hours (Note 5). The dichloroethane phase is separated, and the aqueous phase is extracted with eight 600-ml. portions of dichloromethane. The extracts are combined with the dichloroethane phase (Note 6) and extracted first with 600 ml. and then twice with 200-ml. portions of aqueous saturated sodium hydrogen carbonate solution. The combined sodium hydrogen carbonate extracts are washed with 200 ml. of dichloromethane and then cautiously acidified in a 3-l. beaker with 150 ml. of 12 *M* hydrochloric acid, with vigorous stirring. The acidic solution (Note 7) is extracted first with 600 ml. and then with four 400-ml. portions of dichloromethane. The bulk of the dichloromethane is removed by distillation at atmospheric pressure and water bath temperatures; however, the last 150 ml. of solvent is removed below room temperature under reduced pressure (about 20 mm.), leaving 24–27 g. of crude 2-acetyl-1,3-cyclopentanedione as a light brown solid, m.p. 68–71° (Note 8).

The crude product is purified by decolorization with charcoal and recrystallization from 100–150 ml. of diisopropyl ether, giving 19–21 g. (27–30%) of colorless needles, m.p. 70–72°. This material is sufficiently pure for most purposes. Further purification may be achieved by recrystallization from diisopropyl ether and/or sublimation at 60° (0.1 mm.) onto a cold-finger condenser, giving material melting at 73–74° (Note 9), (Note 10).

2. Notes

1. 2-Acetyl-1,3-cyclopentanedione is completely enolized in the solid state as well as in solution.[2] Indirect evidence indicates that the carbon-carbon double bond of the enol is within the ring.
2. The submitters used a practical grade of succinic anhydride obtained from Matheson, Coleman and Bell.
3. The submitters used anhydrous, sublimed aluminum chloride obtained from E. Merck AG, Darmstadt, Germany. The checkers used analytical reagent grade material obtained from Mallinckrodt Chemical Works.
4. The submitters used either a pure grade (more than 98.5%) of isopropenyl acetate or a practical grade (95–98%) from Fluka AG, Buchs SG, Switzerland. Generally, it was not essential to distill the material before use.
5. This treatment increases the amount of product which can be extracted from the aqueous solution.
6. Evaporation of the solvents at this stage gives an oily product which may be decolorized with charcoal and then recrystallized from diisopropyl ether to give 2-acetyl-1,3-cyclopentanedione, m.p. 68–71°. However, the extraction with sodium hydrogen carbonate is preferred.
7. Decolorization of the acidic aqueous solution with charcoal at this stage improves the quality of the product.
8. 2-Acetyl-1,3-cyclopentanedione is quite volatile and appreciable losses may occur if the evaporation of the concentrated solution is continued at elevated temperature.
9. Further amounts of 2-acetyl-1,3-cyclopentanedione can be obtained by continuous extraction of the original aqueous phase with dichloromethane. The submitters have obtained total yields of product as high as 41–43%. 2-Acetyl-1,3-cyclopentanedione is sparingly soluble in diethyl ether and is not extracted very efficiently from aqueous solution with ether.

10. 2-Acetyl-1,3-cyclopentanedione can be hydrolyzed to 1,3-cyclopentanedione.[3,4] The preferred method[4] is to keep a 0.1 *M* solution of 2-acetyl-1,3-cyclopentanedione in 0.1 *M* aqueous acetic acid at 100° for 24 hours. The solvent is then evaporated at 40° with a water pump and the yellow solid is recrystallized from butanone (with charcoal) to give 1,3-cyclopentanedione, m.p. 148–150°, in 65–80% yield.

3. Discussion

2-Acetyl-1,3-cyclopentanedione has been obtained in small amounts from the aluminum chloride-catalyzed reactions of vinyl acetate and succinyl chloride in 1,1,2,2-tetrachloroethane.[5] 2-Acetyl-1,3-cyclopentanediones have been prepared via Dieckmann condensation of 1,4-bis(ethoxycarbonyl)-3,5-hexanediones.[6] The present procedure is essentially that of Merényi and Nilsson[7] with some modifications.

The diacylation of isopropenyl acetate with anhydrides of dicarboxylic acids is applicable to the synthesis of several other cyclic β-triketones in moderate yield.[3,7] It has been used for the synthesis of 2-acetyl-1,3-cyclohexanedione (40% yield), 2-acetyl-4-methyl-1,3-cyclopentanedione (10% yield), 2-acetyl-4,4-dimethyl-1,3-cyclopentanedione (10% yield), 2-acetyl-5,5-dimethyl-1,3-cyclohexanedione (10% yield), 2-acetyl-1,3-cycloheptanedione (12% yield), and 2-acety-1,3-indanedione (25% yield). Maleic anhydrides under more drastic conditions give acetyl-1,3-cyclopent-4-enediones in yields from 5 to 12%.[8] The corresponding acylation of the enol acetate of 2-butanone with succinic anhydride has been used to prepare 2-methyl-1,3-cyclopentanedione, an important intermediate in steroid synthesis.[9,10]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

2-acety-1,3-indanedione

hydrogen chloride, hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ether, diethyl ether (60-29-7)

sodium hydrogen carbonate (144-55-8)

1,2-dichloroethane (107-06-2)

aluminum chloride (3495-54-3)

dichloromethane (75-09-2)

Succinic anhydride (108-30-5)

butanone (78-93-3)

succinyl chloride (543-20-4)

diisopropyl ether (108-20-3)

isopropenyl acetate (108-22-5)

vinyl acetate (108-05-4)

dichloroethane (75-34-3)

1,1,2,2-tetrachloroethane (79-34-5)

2-Methyl-1,3-cyclopentanedione (765-69-5)

2-Acetyl-1,3-cyclopentanedione (3859-39-0)

2-Acetyl-3-hydroxy-2-cyclopenten-1-one

1,3-cyclopentanedione (3859-41-4)

2-acetyl-1,3-cyclohexanedione (4056-73-9)

2-acetyl-4-methyl-1,3-cyclopentanedione

2-acetyl-4,4-dimethyl-1,3-cyclopentanedione

2-acetyl-5,5-dimethyl-1,3-cyclohexanedione

2-acetyl-1,3-cycloheptanedione

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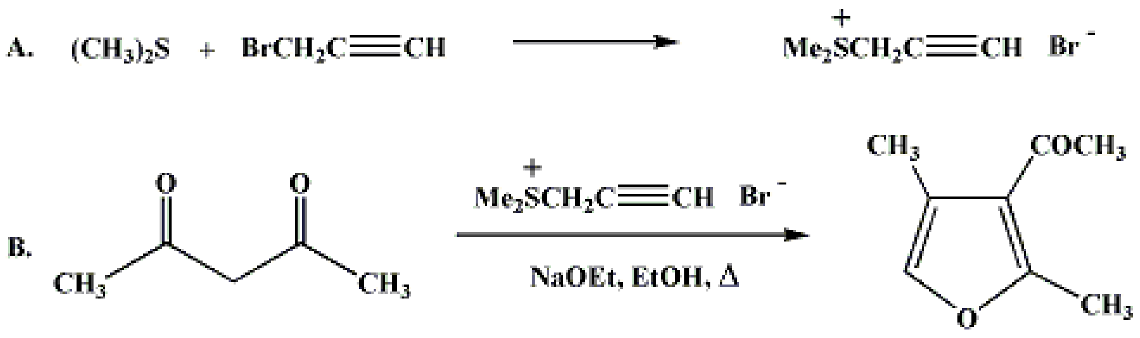
3-ACETYL-2,4-DIMETHYLFURAN

[Ethanone, 1-(2,4-dimethyl-3-furanyl)-]



Submitted by P. D. Howes and C. J. M. Stirling[1].
Checked by C. Reese, M. Uskokovic, and A. Brossi.

1. Procedure

Caution! These reactions should be performed in a hood because of the noxious odors.

A. *Dimethyl-2-propynylsulfonium bromide*. A mixture of 6.2 g. (0.10 mole) of dimethyl sulfide (Note 1), 11.9 g. (0.100 mole) of 3-bromopropyne (Note 2), and 10 ml. of acetonitrile (Note 3) is stirred magnetically for 20 hours (Note 4) in a darkened, 100-ml., round-bottomed flask (Note 5) fitted with a calcium chloride drying tube. The resulting white, crystalline mass is filtered with suction and washed with three 50-ml. portions of dry diethyl ether (Note 6), giving 16.4 g. (90%) of the sulfonium salt, m.p. 105–106°. This material may be used in the next step without purification but, if desired, it may be recrystallized from ethanol-ether (Note 7) with minimal loss, m.p. 109–110°.

B. *3-Acetyl-2,4-dimethylfuran*. To a solution of 8.7 g. (0.087 mole) of acetylacetone (Note 8) in 175 ml. of 0.5 *M* ethanolic sodium ethoxide (0.087 mole), contained in a 500-ml., round-bottomed flask, fitted with a condenser topped with a calcium chloride drying tube, is added a solution of 15.75 g. (0.0870 mole) of dimethyl-2-propynylsulfonium bromide in 150 ml. of ethanol (Note 9). The mixture is refluxed until the odor of dimethyl sulfide is no longer appreciable (Note 10). The reaction flask is then fitted with a 30-cm., helix-packed column, and by heating the flask with a water bath, ethanol is distilled through the column (Note 11). The residue is treated with 200 ml. of ether, and the suspension is filtered. Ether is distilled from the filtrate at atmospheric pressure, and the residue is distilled, giving 9.7 g. (81%) of 3-acetyl-2,4-dimethylfuran (Note 12) and (Note 13), b.p. 90–95° (12 mm.), n_D^{24} 1.4965.

2. Notes

1. Dimethyl sulfide was used as supplied by British Drug Houses.
2. 3-Bromopropyne, supplied by British Drug Houses, was distilled before use (b.p. 84–86°).
3. Acetonitrile (Matheson, Coleman and Bell, spectral grade) was used without further treatment.
4. The maximum yield was obtained after 20 hours. Shorter reaction times give slightly lower yields.
5. If a brown glass flask is unavailable, an ordinary flask wrapped with aluminum foil may be

used.

6. The ether was dried over sodium.

7. The salt was dissolved in 10 ml. of ethanol, 75 ml. of ether was added portion-wise, and the mixture was allowed to stand overnight at room temperature.

8. Acetylacetone, supplied by British Drug Houses, was distilled before use (b.p. 137°).

9. The ethanol was dried with magnesium ethoxide.[2]

10. About 6 hours is required on this scale.

11. Distillation through the packed column is essential to prevent loss of furan by co-distillation with ethanol.

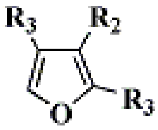
12. The product has IR absorption (neat) at 1690 $cm.^{-1}$ (ketone C=O and ^1H NMR peaks (CCl_4) at δ 2.20 (s, 3H, $COCH_3$), 2.40 (s, 3H, CH_3), 3.60 (s, 3H, CH_3), and 7.40 (s, 1H, furyl).

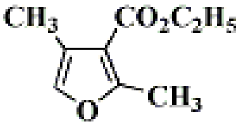
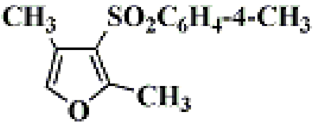
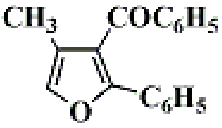
13. A convenient modification of this procedure gives the furan in 70–75% yield; the sulfonium salt is preformed in acetonitrile and, without isolation, the other reagents are added.

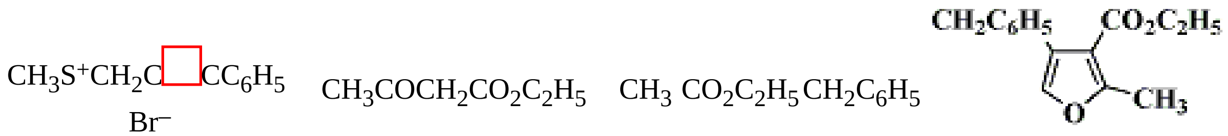
3. Discussion

This procedure illustrates a recently published,[3] simple, general method for the synthesis of substituted furans. The scope of the reaction is shown in Table I. Many variations of this procedure are clearly possible.

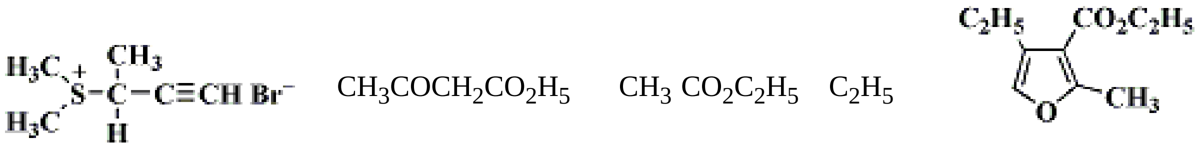
TABLE I
FURANS PREPARED VIA ACETYLENIC SULFONIUM SALTS



Sulfonium Salt	Addend	R_1	R_2	R_3	Yield, %[2]
$CH_3S^+CH_2C\equiv CH\ Br^-$	$CH_3COCH_2CO_2CO_2C_2H_5$	CH_3	$CO_2C_2H_5$	CH_3	 86
$CH_3S^+CH_2C\equiv CH\ Br^-$	$CH_3COCH_2SO_2C_6H_4$-4-CH_3	CH_3	$SO_2C_6H_4$-4-CH_3	CH_3	 78
$CH_3S^+CH_2C\equiv CH\ Br^-$	$C_6H_5COCH_2COC_6H_5$	C_6H_5	COC_6H_5	CH_3	 72



63



50

The method described has some features in common with the well-known, but apparently little-used, Feist-Benary furan synthesis,[4] which uses an α-haloketone in place of the sulfonium salt. Acetylenic bromides suitable for preparing the sulfonium salts are readily available by well-documented procedures involving acetylenic organometallic compounds.

The mechanism of furan formation by this route is determined by the structure of the sulfonium salt; the course, hence the end product, is governed by whether an α-substituent is present. This must be considered when syntheses based on this procedure are being planned. Plausible mechanisms for the reaction have been suggested.[3]

Direct treatment of propargyl halides with β-dicarbonyl compounds and subsequent treatment of the products with zinc carbonate yields 2,3,5-trisubstituted furans.[5]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

ether, diethyl ether (60-29-7)

acetonitrile (75-05-8)

Salt (7647-14-5)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

dimethyl sulfide (75-18-3)

Acetylacetone (123-54-6)

magnesium ethoxide (2414-98-4)

sulfonium

3-Acetyl-2,4-dimethylfuran, Ethanone, 1-(2,4-dimethyl-3-furanyl)- (32933-07-6)

3-bromopropyne (106-96-7)

dimethyl-2-propynylsulfonium bromide (23451-62-9)

zinc carbonate (3486-35-9)

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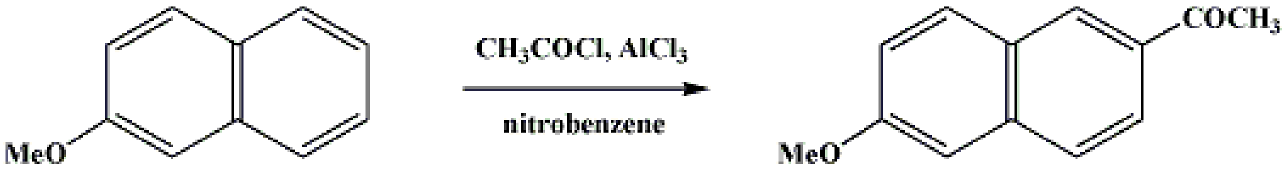
2-ACETYL-6-METHOXYNAPHTHALENE

[Ethanone, 1-(6-methoxy-2-naphthalenyl)-]



Submitted by L. Arsenijevic[1], V. Arsenijevic[1], A. Horeau[2], and J. Jacques[2].
Checked by David Walba and Robert E. Ireland.

1. Procedure

A 1-l., three-necked, round-bottomed flask is fitted with a mechanical stirrer and a thermometer; the third neck of the flask is fitted with a 50-ml., pressure-equalizing addition funnel, carrying a drying tube attached to a gas trap. The flask is charged with 200 ml. of dry nitrobenzene (Note 1), followed by 43 g. (0.32 mole) of anhydrous aluminum chloride. After the aluminum chloride has dissolved, 39.5 g. (0.250 mole) of finely ground 2-methoxynaphthalene (nerolin, (Note 2)) is added. An ice bath is used to cool the stirred solution to about 5° before 25 g. (23 ml., 0.32 mole) of redistilled acetyl chloride (Note 3) is added dropwise over a 15–20 minute period, with stirring and at a rate which holds the temperature between 10.5 and 13° (Note 4). After addition of the acetyl chloride is complete, the flask is kept immersed in the ice water while stirring is continued for 2 hours. The mixture is then allowed to stand at room temperature for at least 12 hours.

The reaction mixture is cooled in an ice bath, poured with stirring into a 600-ml. beaker containing 200 g. of crushed ice, and treated with 100 ml. of concentrated hydrochloric acid. The resulting two-phase mixture and 50 ml. of chloroform are transferred to a 1-l. separatory funnel (Note 5); the chloroform-nitrobenzene layer is separated and washed with three 100-ml. portions of water. The organic layer is transferred to a 2-l., round-bottomed flask, and steam-distilled. A fairly rapid flow of steam is used, and the distillation flask is heated in an oil bath at about 120°. After about 3 hours (3–4 l. of water) the distillation is stopped, and the residue in the flask is allowed to cool. Residual water in the flask is decanted from the solid organic material and extracted with chloroform. The solid residue in the flask is dissolved in 100 ml. of chloroform and separated from any water left in the flask, and the chloroform layers are combined and dried over anhydrous magnesium sulfate. The chloroform is removed on a rotary evaporator, and the solid residue, weighing 50–65 g. (still slightly wet with chloroform), is distilled under vacuum (Note 6). The receiving flask should be immersed in ice water, and the fraction boiling about 150–165° (0.02 mm.) is collected (Note 7).

The yellow distillate (*ca.* 40 g., m.p. 85–95°) is recrystallized from 75 ml. of methanol, cooled in an ice bath (Note 8) and filtered, yielding 22.5–24 g. (45–48%) of white, crystalline 2-acetyl-6-methoxynaphthalene (Note 9), m.p. 106.5–108° (lit. 104–105°).[3]

2. Notes

1. The nitrobenzene may be dried by distilling the first 10% and using the residue directly, or standing over anhydrous calcium chloride overnight and filtering.

2. 2-Methoxynaphthalene (Matheson, Coleman and Bell), m.p. 71.5–73°, was used without further purification.
3. Acetic anhydride may be used instead of acetyl chloride. However, it is then necessary to use two molecular equivalents of aluminum chloride per mole of anhydride and increase the amount of nitrobenzene by about 30%. About the same yield of ketone is obtained.
4. Temperature control is very important (see discussion).
5. The addition of chloroform is not always indispensable, but very useful to prevent emulsification and facilitate separation of the nitrobenzene layer. The reaction vessel and beaker are rinsed with this chloroform before it is added to the nitrobenzene layer. If an emulsion does form and phase separation becomes inconveniently slow, as much nitrobenzene as possible is withdrawn, and the emulsion and water layers are filtered by suction through a Celite cake wet with chloroform. The phases should then separate easily.
6. The material may be distilled from a two-bulb distillation flask as described in *Org. Synth.*, **Coll. Vol. 3**, 133 (1955), or from a small Claisen flask.
7. Care must be taken to prevent solidification and possible blocking in the condenser. A small burner may be used to keep the adapter just hot enough to melt the distillate.
8. If the methanol is cooled below 0°, the 1-acetyl isomer that is formed during the reaction will also crystallize with the product.
9. ^{1}H NMR ($CDCl_3$): δ 2.65 (s, 3H, $COCH_3$), 3.92 (s, 3H, OCH_3), 7.20 (m, 4H, Ar*H*), 7.80 (m, 1H, Ar*H*), 8.30 (m, 1H, Ar*H*).

3. Discussion

The procedure described herein is a modification of that of Haworth and Sheldrick,[3] the efficiency of which has been confirmed by many authors.[4,5,6,7,8,9,10] 2-Acetyl-6-methoxynaphthalene has also been prepared by the action of methylzinc iodide on 6-methoxy-2-naphthoyl chloride.[11]

In this reaction, nitrobenzene has an important function because it causes acylation to occur predominantly at the 6-position, whereas 1-acetyl-2-methoxynaphthalene is the principal product when carbon disulfide is used. The main feature of this procedure is the particular attention given to temperature control in order to obtain reliable results. It has been observed that the ratio of 6-acetylated to 1-acetylated nerolin is dependent on the temperature, the lower temperatures favoring 1-acetylation. Below 0° the yield of 6-acetylated product is only 3–10%; at higher temperatures the 6-acetylated product predominates, but an increased amount of tarry material is formed.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 175

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

nerolin

chloroform-nitrobenzene

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

methanol (67-56-1)

acetic anhydride (108-24-7)

acetyl chloride (75-36-5)

chloroform (67-66-3)

2-methoxynaphthalene (93-04-9)

aluminum chloride (3495-54-3)

Nitrobenzene (98-95-3)

carbon disulfide (75-15-0)

magnesium sulfate (7487-88-9)

methylzinc iodide

2-Acetyl-6-methoxynaphthalene, Ethanone, 1-(6-methoxy-2-naphthalenyl)- (3900-45-6)

6-methoxy-2-naphthoyl chloride

1-acetyl-2-methoxynaphthalene

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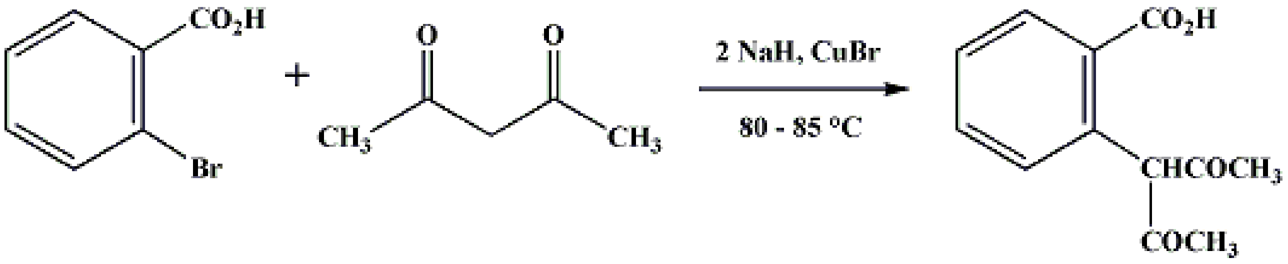
COPPER CATALYZED ARYLATION OF β-DICARBONYL COMPOUNDS: 2-(1-ACETYL-2-OXOPROPYL)BENZOIC ACID

[Benzoic acid, 2-(1-acetyl-2-oxopropyl)-]



Submitted by Alle Bruggink, Stephen J. Ray, and Alexander McKillop[1].
Checked by Sadao Hayashi and Wataru Nagata.

1. Procedure

A 250-ml., three-necked, round-bottomed flask equipped with a sealed-mechanical stirrer, a Claisen adapter fitted with a thermometer and a gas-inlet adapter, and a calcium chloride drying tube (Note 1) is charged with 150 ml. of acetylacetone (Note 2) and (Note 3), 25 g. (0.12 mole) of 2-bromobenzoic acid (Note 4), and 1.0 g. of copper(I) bromide (Note 5). The mixture is thoroughly purged with dry nitrogen and stirred rapidly while 9.0 g. (0.47 mole) of an 80% dispersion of sodium hydride in mineral oil (Note 6) is slowly added portionwise through the inlet protected by the calcium chloride drying tube. Addition of the first portions of the sodium hydride results in an immediate exothermic reaction, and the temperature of the mixture rises rapidly to 50–55°. The remainder of the sodium hydride is added at such a rate that the temperature remains within the 50–55° range; external cooling with a cold-water bath may be necessary (Note 7). After addition of the sodium hydride is complete (30–35 minutes), the flask is placed in a hot-water bath heated to 80–85°, and the reaction mixture is stirred and heated for 5 hours, during which time a slow stream of dry nitrogen is passed through the apparatus.

When the reaction mixture has cooled, the contents of the flask are poured into a 1-l. Erlenmeyer flask containing 400 ml. of distilled water. The reaction flask and stirrer are thoroughly washed with an additional 100 ml. of distilled water, with the washings added to the bulk of the reaction mixture. The aqueous mixture is allowed to stand at room temperature for 15 minutes to ensure completion of hydrolysis and precipitation of inorganic salts. After the salts are removed by filtration under reduced pressure (Note 8) and discarded, the filtrate is transferred to a 1-l. separatory funnel, and the excess acetylacetone is separated (Note 9). The aqueous phase is washed with five 100-ml. portions of diethyl ether (Note 9) and transferred to a 1-l. conical flask. Nitrogen is blown through the solution for 15 minutes to remove traces of ether (Note 10). The aqueous solution is then acidified to pH 3 with concentrated hydrochloric acid, with the flask being constantly swirled during addition of the acid, and the mixture is allowed to stand at room temperature for 30 minutes to ensure complete precipitation of the product. The crude material is collected by filtration under reduced pressure, washed with 25 ml. of distilled water, and dried under reduced pressure over phosphorus pentoxide, giving 21–22 g. (76–80%) of crude product, m. p. 138–145° (Note 11). Recrystallization from a mixture of 50 ml. of methanol and 100 ml. of

water gives 19.5–21 g. (71–76%) of pure material (Note 12) as colorless prisms, m.p. 142–144.5° (Note 11).

2. Notes

1. The checkers inserted a condenser between the flask and the drying tube to prevent acetylacetone from being carried away by the nitrogen stream.
2. The acetylacetone was washed with aqueous sodium hydrogen carbonate solution, dried over sodium sulfate, and distilled prior to use. The checkers used acetylacetone with a purity greater than 95%, purchased from Wako Pure Chemical Industries, Ltd., Japan, and purified by distillation prior to use.
3. The use of a large amount of acetylacetone as both reagent and solvent is essential to prevent precipitation of the sodium salts of acetylacetone and 2-bromobenzoic acid. If this happens, the whole reaction mixture rapidly solidifies, resulting in incomplete mixing and poor, irreproducible yields of the product.
4. Commercial 2-bromobenzoic acid, purchased from Aldrich Chemical Company, Inc., is a gray powder, m.p. 144–147°, and was purified as follows: the crude acid was dissolved in warm 2 *N* sodium hydroxide solution; the mixture was heated to reflux, treated with activated carbon, filtered, and cooled, and the filtrate was acidified with concentrated hydrochloric acid. The colorless solid that precipitated was collected by filtration under reduced pressure and recrystallized from aqueous methanol, giving pure 2-bromobenzoic acid as colorless needles, m.p. 148–150°. The checkers used 2-bromobenzoic acid of m.p. 151–151.5°, obtained from Wako Pure Chemical Industries, Ltd., Japan, without further purification. Their results were comparable to those of the submitters.
5. Copper(I) bromide was prepared according to *Org. Synth.*, **Coll. Vol. 3**, 186 (1955); the salt was dried under reduced pressure over phosphorus pentoxide prior to use. The checkers observed that good results could be realized by using a commercially available copper(I) bromide with a purity greater than 95% from Wako Pure Chemical Industries, Ltd., Japan, without purification.
6. The checkers used a 50% dispersion of sodium hydride in mineral oil, available from Wako Pure Chemical Industries, Ltd., Japan, and obtained results comparable to those of the submitters.
7. Cooling is normally required. It is important, however, to ensure that the temperature of the reaction mixture does not fall below 50°; otherwise efficient stirring becomes impossible.
8. The inorganic salts that precipitate at this stage are generally in a very finely divided form. A medium-sized Büchner funnel (11–15 cm.) or a small Büchner funnel (5–7.5 cm.) fitted with a Celite pad should be used to avoid slow filtration.
9. Acetylacetone can readily be recovered and recycled. The bulk of it, which is obtained at the separation step, is combined with the ether washings and dried over anhydrous sodium sulfate. The solvent is then removed by evaporation under reduced pressure and the residual crude acetylacetone is purified by distillation, giving 85–95 g. of pure acetylacetone.
10. Acidification without prior removal of the small amount of ether present in the aqueous solution results in precipitation of the product as an oily, semisolid mass that is difficult to filter.
11. Evolution of water is noticeable from *ca.* 130° upward; this is a result of lactone formation between the enolic hydroxyl group of the β-dicarbonyl unit and the aromatic carboxylic acid group.
12. The product, which exists entirely in the enolic form, has the following spectral data: UV (CH_3OH) nm. max. (ε): 227 (7760) and 287 (8190); IR (Nujol) cm^{-1}: 3300–2400, 1700–1690, 1305, 1270, 810, 770, 720, and 700; ^1H NMR ($CDCl_3$), δ (multiplicity, number of

protons, assignment): 1.82 (sharp s, 6H, 2CH_3), 7.2–8.2 (complex m, 4H, C_6H_4), 10.1 (broad s, 1H, COO*H*), and 16.3 (broad s, 1H, enolic O*H*).

3. Discussion

2-(1-Acetyl-2-oxopropyl)benzoic acid has been prepared by the copper-catalyzed arylation of acetylacetone with 2-bromobenzoic acid. Facile condensation of β-dicarbonyl compounds with 2-bromobenzoic acid was first demonstrated by Hurtley in 1929,[2] and reactions of this type have occasionally been employed with limited success in a number of natural product syntheses.[3] The reaction conditions originally employed for these condensations and subsequently adopted by all other workers involve the use of sodium ethoxide as base, ethanol as solvent, and copper powder as catalyst. Under these conditions, however, 2-ethoxybenzoic acid is obtained as a by-product in substantial amounts (25–35%), together with smaller amounts of unchanged 2-bromobenzoic acid (5–10%); furthermore, separation and purification of the desired α-(2-carboxyphenyl)-β-dicarbonyl product is often difficult and tedious.

The present method of preparation, described by Bruggink and McKillop,[4] has the particular advantages of high yield and manipulative simplicity, and avoids the problem inherent in Hurtley's procedure of separation of mixtures of carboxylic acids by fractional crystallization or column chromatography. The method has wide applicability with respect to both the β-dicarbonyl compound and the 2-bromobenzoic acid. The synthetic scope and limitations of this procedure for the direct arylation of β-dicarbonyl compounds have been fully defined with respect to a wide range of substituted 2-bromobenzoic acids and to certain other bromoaromatic and heteroaromatic carboxylic acids.[4]

References and Notes

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3. K. A. Cirigottis, E. Ritchie, and W. C. Taylor, *Aust. J. Chem.*, **27**, 2209 (1974).
4. A. Bruggink and A. McKillop, *Tetrahedron*, **31**, 2607 (1975).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium salts of acetylacetone and 2-bromobenzoic acid

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

methanol (67-56-1)

diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium hydrogen carbonate (144-55-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

copper (7440-50-8)

carbon (7782-42-5)

sodium ethoxide (141-52-6)

2-bromobenzoic acid (88-65-3)

copper(I) bromide (7787-70-4)

Acetylacetone (123-54-6)

sodium hydride (7646-69-7)

2-(1-Acetyl-2-oxopropyl)benzoic acid, Benzoic acid, 2-(1-acetyl-2-oxopropyl)- (52962-26-2)

2-ethoxybenzoic acid (134-11-2)

phosphorus pentoxide (1314-56-3)

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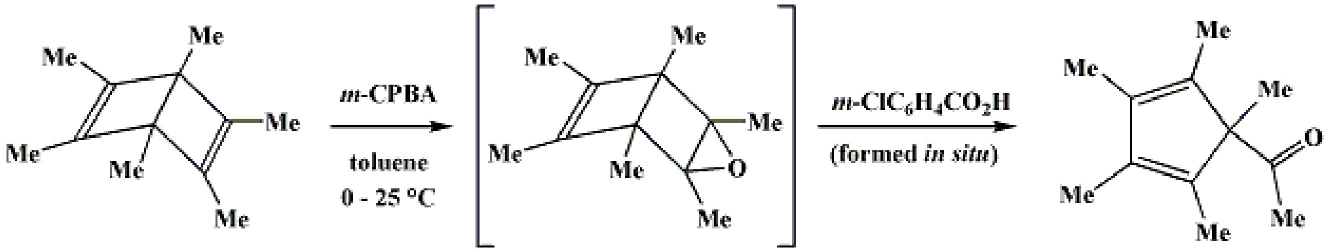
5-ACETYL-1,2,3,4,5-PENTAMETHYLCYCLOPENTADIENE

[Ethanone, 1-(1,2,3,4,5-pentamethyl-2,4-cyclopentadien-1-yl)-]



Submitted by R. B. King, W. M. Douglas, and A. Efraty[1].
Checked by J. X. McDermott, G. M. Whitesides, and G. Büchi.

1. Procedure

Caution! Explosive mixtures often result when peracids other than m-chloroperbenzoic acid are used in this reaction. No such problem has ever been encountered using m-chloroperbenzoic acid.

A 3-l., three-necked, round-bottomed flask is fitted with a nitrogen-inlet tube, a pressure-equalizing addition funnel, and an air-driven stirring apparatus. After the system has been thoroughly purged with nitrogen, it is charged with a solution of 100 g. (0.615 mole) of 1,2,3,4,5,6-hexamethylbicyclo[2.2.0]hexa-2,5-diene (Hexamethyldewarbenzene (Note 1)) in 200 ml. of toluene. The reaction mixture is cooled to 0° with a bath of ice water and stirred rapidly while a solution of 130 g. (0.640 mole) of 85% *m*-chloroperbenzoic acid (Note 2) in 1.5 l. of chloroform is added dropwise over 3–4 hours. Throughout the addition and for 4 hours following its completion the reaction mixture is kept at 0°, after which it is stirred at room temperature for 36 hours. The white precipitate that forms during the reaction (mainly *m*-chlorobenzoic acid) is removed by filtration through a 650-ml., sintered-glass funnel (porosity 10–15 •m), and the filter cake is washed with two 100-ml. portions of chloroform. Combination of the filtrates gives a chloroform–toluene solution, which is condensed on a rotary evaporator with the water bath at 35–40°. When all of the chloroform has been removed, the residual toluene solution is diluted with 500 ml. of pentane and refiltered. The filtrate is washed with four 200-ml. portions of 10% aqueous sodium hydroxide and two 250-ml. portions of water, dried over anhydrous magnesium sulfate, and evaporated to dryness on a rotary evaporator with the water bath at 50°. Traces of toluene are removed under high vacuum (0.02 mm.) at 25°, and the residue is distilled (Note 3). Collection of material boiling between 72° and 95° (4 mm.) gives about 50 g. of crude product, which is further purified by dissolving it in 50 ml. of pentane and cooling the pentane solution at −78° for several hours. The resulting white crystals are collected by filtration and dried, giving 31.3–37.5 g. (29–34%) of pure 5-acetyl-1,2,3,4,5-pentamethylcyclopentadiene, m.p. 54–56° (Note 4) and (Note 5).

2. Notes

1. 1,2,3,4,5,6-Hexamethylbicyclo[2.2.0]hexa-2,5-diene may be purchased from Columbia Organic Chemicals, Columbia, South Carolina, or Henley Chemical Company, New York, New York.
2. *m*-Chloroperbenzoic acid may be purchased from Columbia Organic Chemicals or the Aldrich Chemical Company, Inc., Milwaukee, Wisconsin.
3. Distillation was performed using a 30-cm., vacuum-jacketed column wrapped with heating tape and containing a spiral of wire (Nichrome or Chromel) in the center bore. The receiver portion of the assembly contained two flasks, one to collect the material that distilled below 72° and another for the desired fraction. An air-cooled condenser was used with this apparatus, since water cooling often causes the product to solidify and clog the condenser tube.
4. If the product is to be used for the preparation of metal carbonyl derivatives, further usable material may be obtained from the mother liquors. Removal of pentane on a rotary evaporator leaves a yellow–orange, viscous oil that is suitable for most preparative purposes.
If an extremely pure product is required, the crystalline material can be sublimed at 35–40° (0.01 mm.).
5. IR (cyclohexane) cm.$^{-1}$: 1703, 1340, 1190, 1090, 960, 760; ^{1}H NMR (CCl_4): δ (number of protons,

multiplicity): 1.0 (s, 3H), 1.5 (s, 3H), 1.7 (s, 6H), 1.9 (s, 6H).

3. Discussion

The present preparation of 5-acetyl-1,2,3,4,5-pentamethylcyclopentadiene is more reliable and convenient than that previously available.[2] This compound has been used to prepare many pentamethylcyclopentadienyl metal carbonyl derivatives[3] and is also a convenient source of pentamethylcyclopentadiene for use in preparing other $(Me_5Cp)_mML_n$ derivatives.[4,5]

References and Notes

1. Department of Chemistry, University of Georgia, Athens, Georgia 30602.
2. H. N. Junker, W. Schafer, and H. Niedenbruck, *Chem. Ber.*, **100**, 2508 (1967).
3. R. B. King and A. Efraty, *J. Am. Chem. Soc.*, **94**, 3773 (1972).
4. R. B. King and M. Bisnette, *J. Organomet. Chem.*, **8**, 287 (1967).
5. U. Burger, A. Delay, and F. Mazenod, *Helv. Chim. Acta*, **57**, 2106 (1974); D. Feitler and G. M. Whitesides, *Inorg. Chem.*, **15**, 466 (1976).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

nitrogen (7727-37-9)

toluene (108-88-3)

Pentane (109-66-0)

magnesium sulfate (7487-88-9)

5-Acetyl-1,2,3,4,5-pentamethylcyclopentadiene, Ethanone, 1-(1,2,3,4,5-pentamethyl-2,4-cyclopentadien-1-yl)- (15971-76-3)

1,2,3,4,5,6-hexamethylbicyclo[2.2.0]hexa-2,5-diene, Hexamethyldewarbenzene (7641-77-2)

pentamethylcyclopentadiene (4045-44-7)

m-Chloroperbenzoic acid (937-14-4)

m-chlorobenzoic acid (535-80-8)

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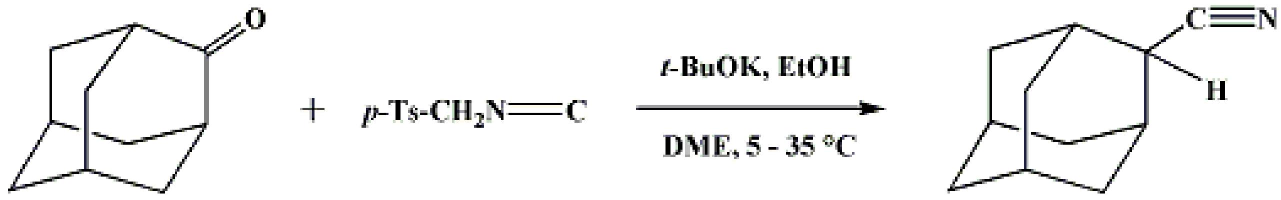
2-ADAMANTANECARBONITRILE

[Tricyclo[3.3.1.1^{3,7}]decane-2-carbonitrile]



Submitted by O. H. Oldenziel, J. Wildeman, and A. M. van Leusen[1].
Checked by Teresa Y. L. Chan and S. Masamune.

1. Procedure

A 500-ml., three-necked, round-bottomed flask equipped with a mechanical stirrer, a thermometer, and a calcium chloride drying tube is charged with 15.0 g. (0.100 mole) of adamantanone (Tricyclo[3.3.1.1^{3,7}]decan-2-one), (Note 1), 25.4 g. (0.130 mole) of *p*-tolylsulfonylmethyl isocyanide (Note 2), (Note 3), 10 ml. (0.17 mole) of absolute ethanol (Note 4), and 350 ml. of 1,2-dimethoxyethane (Note 5). The stirred solution is cooled in an ice bath to 5°, and 28 g. (0.25 mole) of potassium *tert*-butoxide is added in portions at such a rate that the temperature is kept between 5° and 10° (Note 6)(Note 7). After the addition is complete, the ice bath is removed and stirring is continued for 30 minutes. The reaction mixture is heated for 30 minutes at 35–40°, the stirred suspension is cooled to room temperature, and the precipitated potassium *p*-toluenesulfinate is removed by filtration. The precipitate is extracted with three 50-ml. portions of 1,2-dimethoxyethane, and the combined 1,2-dimethoxyethane solutions are concentrated to a volume of 25–35 ml. on a rotary evaporator. The concentrated solution is chromatographed (Note 8) through a short column of alumina using distilled petroleum ether (b. p. 40–60°) as the eluent. The combined fractions are refluxed for 15 minutes with 1 g. of activated carbon (Note 9). After removal of the carbon, the solution is concentrated to dryness in a rotary evaporator. The white solid residue is dried overnight in a vacuum desiccator over silica gel, yielding 13.5–14.5 g. (84–90%) of analytically pure 2-adamantanecarbonitrile, m.p. 170–177° (Note 10).

2. Notes

1. Commercial adamantanone (Aldrich Chemical Company, Inc.) was used; the synthesis of adamantanone is described in *Org. Synth.*, **Coll. Vol. 6**, 48 (1988).
2. The synthesis of *p*-tolylsulfonylmethyl isocyanide is described in *Org. Synth.*, **Coll. Vol. 6**, 987 (1988).[2] The light-brown compound, m.p. 111–114°, was used without further purification.
3. *p*-Tolylsulfonylmethylisocyanide was used in slight excess to effect complete conversion of the adamantanone, which otherwise is difficult to remove from the final product.
4. Commercial absolute ethanol was used.
5. Commercial 1,2-dimethoxyethane, "zur Synthese" quality, was purchased from E. Merck, Darmstadt.

6. Scoops of solid potassium *tert*-butoxide (purchased from E. Merck, Darmstadt, and specified to be at least 95% pure) were added over 20–30 minutes by temporarily removing the drying tube. At the beginning of the reaction much heat is evolved; therefore, the base should be added in small portions in order to keep the temperature below 10°. During the addition of the base, a precipitate is formed.

7. The reaction has also been carried out successfully with sodium ethoxide.[3]

8. The submitters recommend using a 5 cm. by 10 cm. column packed with 200 g. of neutral alumina (activity I) in petroleum ether (b.p. 40–60°), and eluting with 250-ml. of this solvent. The checkers have found that the elution may require more solvent depending on the amount of residual 1,2-dimethoxyethane: they recommend following the chromatography by GC analysis (see (Note 9)).

9. Treatment with activated carbon (purchased from J. T. Baker Chemical Company) can be omitted. In that case, removal of the solvent will provide 14–15 g. (87–93%) of a near-white product with a melting range of 160–180° (see (Note 10)). Despite this wide range, this material is over 99.8% pure, according to a GC analysis carried out at 190° on a 2-m. SE-30 column. This high degree of purity was confirmed on three different types of column.

10. Melting points of 2-adamantanecarbonitrile were determined in sealed tubes to prevent sublimation. Varying values were found for the melting point which apparently is not a very reliable indication of the purity of this compound. Occasionally, a value as high as 184–187° has been found by following the same procedure. Spectral properties of this product: IR ($CHCl_3$) $cm.^{-1}$: 2240 (CN); ^1H NMR ($CDCl_3$), δ (multiplicity, number of protons): 1.4–2.4 (m, 14H), 2.9 (m, 1H).

3. Discussion

The procedure described is an example of a more general synthetic method for the direct conversion of ketones into cyanides.[3,4,5,6] The reaction has been carried out successfully with acyclic and cyclic aliphatic ketones, including numerous steroidal ketones and aryl-alkyl ketones. The conversion of diaryl or highly hindered ketones such as camphor and β,β-dimethyl-α-tetralone requires the use of a more polar solvent. In those cases, the dimethoxyethane used in the present procedure should be replaced by dimethyl sulfoxide.[6] By introduction of a slight modification, the method applies to aldehydes also.,[7]

2-Adamantanecarbonitrile was prepared previously by a more laborious method,[8] also starting from adamantanone, in 46% overall yield.

The hydrolysis of 2-adamantanecarbonitrile with hydrogen bromide in acetic acid provides a useful route to 2-adamantanecarboxylic acid (m.p. 143–144°),[9] which the submitters obtained in 95% yield. Stetter and Tillmans[8] reported a yield of 62% starting with impure 2-adamantanecarbonitrile.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 334
- Org. Syn. Coll. Vol. 6, 987

References and Notes

1. Department of Organic Chemistry, Groningen University, Nijenborgh 16, 9747 RG Groningen, The Netherlands.
2. A. M. van Leusen, G. J. M. Boerma, R. B. Helmholdt, H. Siderius, and J. Strating, *Tetrahedron Lett.*, 2367 (1972); A. M. van Leusen, R. J. Bouma, and O. Possel, *Tetrahedron Lett.*, 3487 (1975).
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7. A. M. van Leusen and P. G. Oomkes, *Synth. Commun.*, **10**, 399 (1980).
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9. For other syntheses, see A. H. Alberts, H. Wynberg, and J. Strating, *Synth. Commun.*, **2**, 79 (1972) and D. Farcasiu, *Synthesis*, 615 (1972).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

petroleum ether

ethanol (64-17-5)

acetic acid (64-19-7)

hydrogen bromide (10035-10-6)

carbon (7782-42-5)

sodium ethoxide (141-52-6)

camphor (21368-68-3)

dimethyl sulfoxide (67-68-5)

1,2-dimethoxyethane (110-71-4)

dimethoxyethane (534-15-6)

2-ADAMANTANECARBONITRILE, Tricyclo[3.3.1.1^{3,7}]decane-2-carbonitrile (35856-00-9)

Adamantanone, Tricyclo[3.3.1.1^{3,7}]decan-2-one (700-58-3)

β,β-dimethyl-α-tetralone

2-adamantanecarboxylic acid (15897-81-1)

p-Tolylsulfonylmethyl isocyanide, p-Tolylsulfonylmethylisocyanide (36635-61-7)

potassium tert-butoxide (865-47-4)

potassium p-toluenesulfinate

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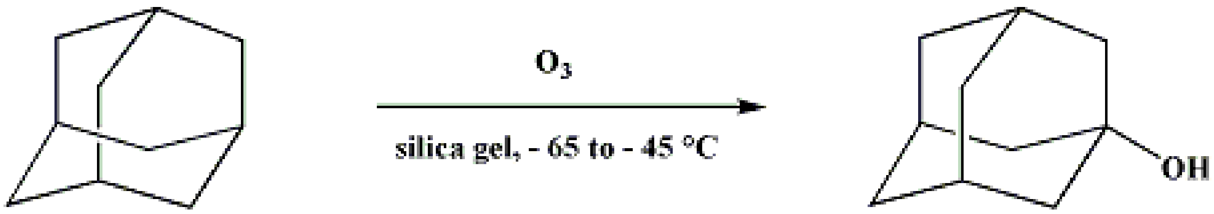
TERTIARY ALCOHOLS FROM HYDROCARBONS BY OZONATION ON SILICA GEL: 1-ADAMANTANOL

[Tricyclo[3.3.1.1^{3,7}]decan-1-ol]



Submitted by Zvi Cohen, Haim Varkony, Ehud Keinan, and Yehuda Mazur[1].
Checked by Frank E. Blaney and Robert M. Coates.

1. Procedure

Caution! Ozone is toxic and potentially explosive. This procedure should be carried out in an efficient hood and behind a suitable protective shield.

A solution of 6 g. (0.044 mole) of adamantane (Note 1) in 100 ml. of pentane and 500 g. of silica gel (Note 2) are placed in a 2-l., round-bottomed flask (Note 3). The pentane is removed by rotary evaporation at room temperature under reduced pressure (20 mm.), and the resulting dry silica gel is allowed to rotate for an additional 2 hours (Note 4). The adamantane–silica gel dispersion is poured through a powder funnel into the ozonation vessel (Note 5), which is then immersed in a 2-propanol–dry ice bath at −78°. A flow of oxygen is passed through the vessel at a rate of 1 l. per minute for 2 hours, after which the internal temperature reaches −60 to −65° (Note 6). The ozone generator (Note 7) is turned on, and the ozone–oxygen mixture is passed through the vessel for *ca.* 2 hours, causing the silica gel to become dark blue (Note 8) and (Note 9). The cooling bath is removed, and the vessel is allowed to warm to room temperature in the hood over a 3-hour period. The silica gel is transferred to a chromatography column, and the organic material is eluted with 3 l. of ethyl acetate. Evaporation of the solvent affords 6.1–6.4 g. of crude adamantanol (Note 10), which is dissolved in 200 ml. of 1:1 (v/v) dichloromethane–hexane by heating on a steam bath. The solution is filtered, concentrated to incipient crystallization and placed in a freezer at −20°. After a crop of fine, white needles (3.0–3.2 g.), m.p. 280–282° (sealed capillary), is collected, the mother liquor is concentrated and cooled to separate two additional crops, which give 2.2–2.6 g. and have melting point ranges of 270–274° to 275–280° (sealed capillary) (Note 11). The total yield of 1-adamantanol is 5.4–5.6 g. (81–84%) (Note 12).

2. Notes

1. Adamantane is available from Aldrich Chemical Company, Inc., and Fluka AG, Buchs, Switzerland.
2. Silica gel 60, with particle sizes ranging from 0.063 to 0.200 mm. (70–230 mesh), is suitable and may be purchased from Brinkmann Instruments, Inc., or E. Merck, Darmstadt, Germany. The submitters report that silica gel of this type normally contains *ca.* 5% water, which may be removed by drying at 300° for several hours, and that somewhat better yields are obtained when the silica gel is dried in this manner before use.
3. The submitters have found that the absorption of adamantane on silica gel may also be accomplished by mixing the dry solids in a closed flask for a few hours.
4. Heating should be avoided to prevent loss of some of the adamantane through sublimation.
5. The submitters have used both a tightly closed, 1-l. gas-washing bottle and the apparatus shown in f.htmigure 1 for ozonation vessels. They recommend that the glass joints not be greased. The apparatus used by the checkers consisted of a cylindrical, two-necked vessel having dimensions given in f.htmigure 1. One neck of the vessel was fitted with a Claisen distillation head and the other with a thermometer with its bulb positioned in the middle of the vessel. A bent gas-dispersion tube with an extra-coarse sintered-glass frit extending through the vertical branch of the Claisen head to within 2–3 mm. of the center of the bottom of the flask served as the gas inlet. The curved branch of the Claisen head was fitted with a drying tube and this functioned as the gas exit.

Figure 1.

Figure 1.

6. The checkers found that the maintenance of a flow of oxygen during the cooling period prevented clogging of the glass frit and a building up of pressure in the gas-inlet tube in their apparatus.
7. A Welsbach T-816 Ozonator purchased from the Welsbach Corporation, Philadelphia, Pennsylvania, was used. The oxygen stream was dried by passage through dry silica gel and molecular sieves and introduced into the ozonator with the operating voltage set at 115 V., the gas pressure at 8 p.s.i.g., and the gas flow rate at 1 l. per minute. The resulting ozone flow rate was 0.00245 mole per minute, as determined by titration of a potassium iodide trap. *Org. Synth.*, **Coll. Vol. 5**, 489 (1973)][2].
8. In the apparatus used by the checkers, the internal temperature was between −45° and −65° while ozone was being passed through the silica gel. The use of lower bath temperatures results in the adsorption of a greater quantity of ozone on the silica gel; consequently, shorter reaction times and higher conversions were realized. *However, since ozone liquifies at* −112°, *there is a serious danger of explosion.*

9. The ozone flow is stopped when the silica gel reaches a constant, dark blue color. The time required for saturating the silica gel with ozone depends on the type of silica gel used and on whether it has been dried (Note 2).

10. A GC analysis on the crude adamantanol was carried out by the checkers using a 1.8 m. × 3 mm. column packed with 5% silicone oil (SE-30) supported on Chromosorb W and the following column temperature program: hold at 120° for 6 minutes and then increase at *ca.* 8° per minute. The chromatogram of the product from one run showed a major peak at retention time of 10 minutes and three minor peaks with retention times of 11.2, 12, and 13.7 minutes and relative areas amounting to 1.5, 1.6, and 4% of the major peak, respectively. A GC analysis by the submitters with 5% diethylene glycol succinate supported on Chromosorb W as a stationary phase at 110–160° showed peaks for adamantan-1,3-diol and adamantanone, as by-products totaling 7%, in addition to the peak for 1-adamantanol.

11. A GC analysis by the checkers (see (Note 10)) on the material in the third crop from one run showed a major peak for 1-adamantanol and a second minor peak having an area *ca.* 12% of that of the major peak. In another run the area of the peak from this by-product in the third crop was less than 2% relative to that of 1-adamantanol.

12. A yield of 5.8 g. (87%), m.p. 280–282°, was obtained by the submitters. The IR, ^{1}H NMR, ^{13}C NMR, and mass spectra of the product were identical to those of an authentic sample of 1-adamantanol. A mixed melting point with an authentic sample of 1-adamantanol showed no depression.

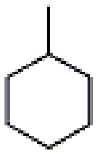
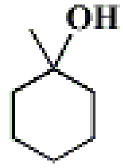
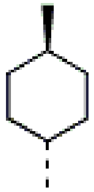
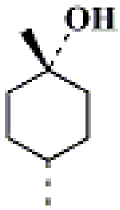
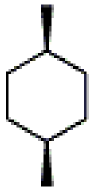
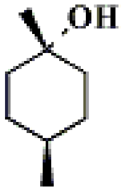
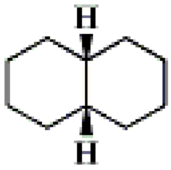
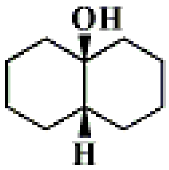
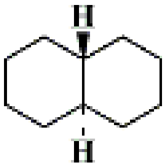
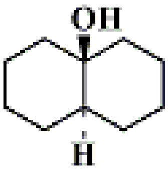
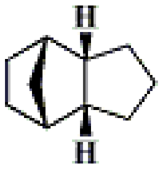
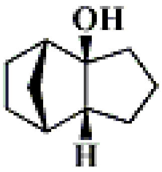
The spectral characteristics of the product are as follows: IR (KBr) cm.$^{-1}$ 3350 (OH), 1455, 1352, 1302, 1118, 1088; ^{1}H NMR ($CDCl_3$), δ (multiplicity, number of protons, assignment): 1.53 (s, 1H, O*H*), 1.55–1.80 (m, 12H, 6 CH_2), 2.17 (broad s, 3H, 3C*H*); ^{13}C NMR ($CDCl_3$), δ (assignment): 30.7 (3*C*H), 36.1 (3*C*H), 36.1 (3*C*H_2), 45.4 (3*C*H_2), 68.2 (*C*OH).

3. Discussion

This "dry ozonation" procedure is a general method for hydroxylation of tertiary carbon atoms in saturated compounds (Table I).[3,4,5,6] The substitution reaction occurs predominantly with retention of configuration. Thus, *cis*-decalin gives *cis*-1-decalol, whereas *cis*- and *trans*-1,4-dimethylcyclohexane afford *cis*- and *trans*-1,4-dimethylcyclohexanol, respectively. The amount of epimeric alcohol formed in these ozonation reactions is usually less than 1%. The tertiary alcohols may be further oxidized to diols by repeating the ozonation; however, the yields in these reactions are poorer. For instance, 1-adamantanol is oxidized to 1,3-adamantanediol in 43% yield. Secondary alcohols are converted to the corresponding ketone. This method has been employed for the hydroxylation of tertiary positions in saturated acetates and bromides.

TABLE I

PREPARATION OF TERTIARY ALCOHOLS FROM HYDROCARBONS WITH OZONE ON SILICA GEL

Hydrocarbon	Tertiary Alcohol	Conversion (%)	Yield (%)[a]
		>99.5	65[b]
		72	79[c]
		92	76[d]
		>99.5	99
		88	72[e]
		>99.5	90

a Based on the amount of hydrocarbon consumed, as determined by GC.

b A mixture of the three methyl cyclohexanones was also formed to the extent of 34%.

c The epimeric alcohol was also present to the extent of 0.6%.

d The epimeric alcohol was also present to the extent of 3.5%.

e trans-1-Decalone (10%) and *trans*-2-decalone (16%) were also formed.

Dry ozonation may be carried out according to the following alternative procedure: The ozone–oxygen mixture is passed through the silica gel at –45°C followed by removal of the excess ozone at the same temperature (–45°C) by passing an inert gas (nitrogen or argon) through the sample.

1-Adamantanol has been prepared by oxidation of adamantane with peroxyacetic acetic[7] and by hydrolysis of 1-bromoadamantane with silver nitrate[8] or hydrochloric acid.[9]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

silver nitrate (7761-88-8)

oxygen (7782-44-7)

nitrogen (7727-37-9)

methyl (2229-07-4)

Pentane (109-66-0)

dichloromethane (75-09-2)

ozone (10028-15-6)

hexane (110-54-3)

Adamantane (281-23-2)

1-Adamantanol, adamantanol, Tricyclo[3.3.1.1^{3,7}]decan-1-ol (768-95-6)

1-bromoadamantane (768-90-1)

argon (7440-37-1)

diethylene glycol succinate

Adamantanone (700-58-3)

adamantan-1,3-diol, 1,3-adamantanediol

cis-decalin

cis-1-decalol

e trans-1-Decalone (21370-71-8)

trans-2-decalone

cis- and trans-1,4-dimethylcyclohexane

cis- and trans-1,4-dimethylcyclohexanol

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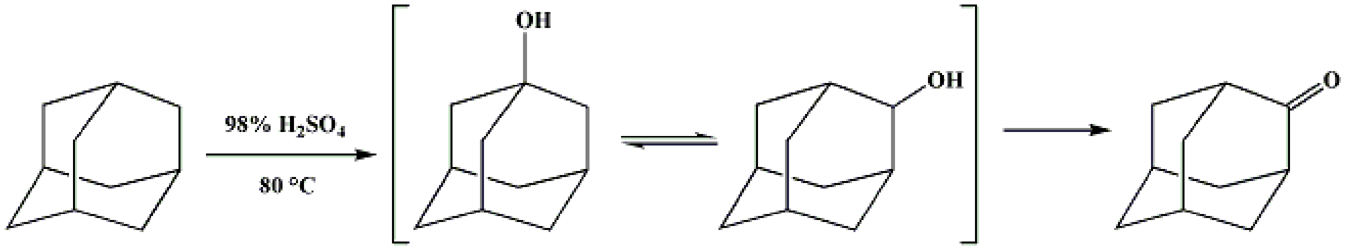
ADAMANTANONE

[Tricyclo[3.3.1.1^{3,7}]decanone]



Submitted by H. W. Geluk and V. G. Keizer[1].
Checked by L. Foley, W. Jackson, and A. Brossi.

1. Procedure

Caution! This procedure should be carried out in an efficient hood to avoid exposure to sulfur dioxide.

Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A 1-l., three-necked, round-bottomed flask equipped with an efficient mechanical stirrer (Note 1), a thermometer, and a vent (Note 2) is placed in a water bath and charged with 600 ml. of 98% sulfuric acid (Note 3). Powdered adamantane [*Org. Synth.*, **Coll. Vol. 5**, 16 (1973)], (100 g., 0.735 mole), is added in one portion to the stirred acid, and the mixture is heated rapidly (with the water bath) to an internal temperature of 70°. The internal temperature is then raised gradually to 80° over a 2-hour period (Note 4) while vigorous stirring is maintained (Note 5). After stirring at 80° is continued for an additional 2 hours, the temperature is raised to 82°. When almost all the adamantane is dissolved, the residual sublimed material is scraped and rinsed from the walls of the flask (Note 1) and (Note 6). When GC analysis indicates that 2–3% of adamantanol is present (Note 6), the hot reaction mixture is poured immediately onto 800 g. of crushed ice, giving a 1500-ml. suspension containing crude adamantanone.

A 750-ml. portion of this suspension of crude adamantanone is transferred to a 2-l., round-bottomed flask, equipped for steam distillation (Note 7) and (Note 8), which is placed in a heating mantle. The contents of the distillation flask are heated to 70°; the external heating is turned off (Note 9) and steam is introduced carefully through both inlet tubes (Note 10). The two layers of distillate are separated, and the aqueous layer is extracted with two 75-ml. portions of dichloromethane. This steam distillation procedure is then repeated with the second half of the suspension of crude adamantanone. The organic extracts are combined, washed with 100 ml. of aqueous, saturated sodium chloride, dried over anhydrous sodium sulfate, and evaporated under reduced pressure, yielding 52–53 g.. (47–48%) of adamantanone (Note 11), (Note 12), and (Note 13).

2. Notes

1. The stirrer should be placed just under the surface of the sulfuric acid. The flask should be filled to at least three-quarters of its volume so the sublimed material can be rinsed from the walls with vigorous stirring.
2. Sulfur dioxide generated during the reaction can escape through the third neck of the flask. This neck should be wide enough to prevent clogging by subliming adamantane.
3. The required amount of 98% sulfuric acid is prepared by adding 53 ml. of fuming sulfuric acid (65% free sulfur trioxide) to 530 ml. of 96% sulfuric acid, or by adding 120 ml. of fuming sulfuric acid (30–33% free sulfur trioxide) to 480 ml. of 96% sulfuric acid.
4. During this part of the reaction a vigorous evolution of sulfur dioxide takes place. Care should be taken to ensure that the internal temperature does not rise too fast to prevent an uncontrollable increase in the evolution of the sulfur dioxide.
5. An adamantane layer floating on the sulfuric acid, caused by ineffective stirring or too rapid evolution of sulfur dioxide, can lead to heavy foaming and subsequent losses. This layer, if formed, may be brought into contact with the reaction mixture by increasing the speed of the stirrer or by lowering the bath temperature to 65–70°.
6. At this stage the reaction should be monitored carefully by GC. For this purpose samples are taken periodically from the reaction mixture, poured onto ice, extracted with dichloromethane, washed with water, and subjected to GC. The submitters used an F and M Model 700 gas chromatograph equipped with a 2 m. by 3 mm. glass column, filled with 80/100 mesh Chromosorb-W-Hp impregnated with 9.5% Apiezon-L and 0.5% Carbowax-20 M, at 120° with a flame ionization detector and nitrogen as carrier gas. To obtain a good yield of a fairly pure product, the reaction should be stopped when the amount

of 1-adamantanol remaining is between 2% and 3%. Prolonged heating will give a further reduction in the 1-adamantanol content but it should be emphasized that concurrently the yield of the adamantanone will diminish rapidly.

7. The flask is fitted with two inlet tubes, one narrow and adjustable positioned above the surface of the adamantanone suspension, and the other reaching half-way between the bottom of the flask and the surface. Both tubes are connected to the steam supply. The flask is connected through a splash head and a short adapter to a 1-l., three-necked, round-bottomed flask equipped with two very efficient reflux condensers each stoppered with a wad of cotton. The receiving flask is charged with 100 ml. of benzene, which, during the course of the steam distillation, begins to reflux and rinses the adamantanone from the condensers. *Added in proof.* Because of the toxicity of benzene the submitters advise replacement of this solvent with ethyl acetate at this point and in (Note 8).

8. The checkers found that it is advisable to use superheated steam and also to distill each portion twice. Thus when the first receiving flask fills with distillate, it is replaced with a second 1-l., round-bottom flask charged with 100 ml. of benzene and distillation is resumed.

9. Prolonged external heating will stimulate the foaming. Insulation by the heating mantle is sufficient to prevent extensive steam condensation in the distilling flask.

10. The short inlet tube above the surface (Note 7) will break the foam and enable smooth removal of the adamantanone. When foaming is very heavy, steam is introduced only through this short inlet tube.

11. The checkers found that an additional 3 g. of adamantanone could be obtained by extracting the combined contents of the two distillation flasks with dichloromethane, removing the solvent under reduced pressure and steam-distilling the residue, resulting in a total yield of 55–56 g. (50–51%).

12. The product is 97–98% pure by GC (Note 6) and is satisfactory for most purposes. If desired, the adamantanone may be purified by either column chromatography (alumina, activity grade IV; eluent: ether) or by treatment with fuming sulfuric acid (20% free sulfur trioxide). For example, 8.0 g. of adamantanone is added portionwise to 40 ml. of ice-cold, fuming sulfuric acid, and the solution is heated to 40° and maintained at this temperature for one hour. After pouring the mixture onto ice, the adamantanone is recovered by extraction with dichloromethane.

13. The IR spectrum (KBr) shows a strong band at 1717 with minor peaks or shoulders at 1670, 1690, 1725, and 1740 cm.$^{-1}$; ^{1}H NMR ($CDCl_3$), δ 2.04 (broad s, 12H, 2C*H*, 5CH_2) and 2.55 (broad s, 2H, 2C*H*C=O).

3. Discussion

Adamantanone is a very versatile starting material for the preparation of adamantane derivatives, especially those substituted at secondary carbon atoms.

The preparative method presented is a slight modification of that reported by Geluk and co-workers,[2,3] who also give a detailed account of the several reactions of adamantane, 1-adamantanol, and 2-adamantanol that take place in sulfuric acid.[2,4] Adamantanone can be prepared essentially as described herein starting with 1-adamantanol instead of adamantane[2]—the yield is better (70%) and the reaction time is shorter, but adamantane is a more suitable starting material.

Adamantane can also be oxidized to adamantanone with ozone,[5] and the oxime can be made directly from adamantane by photoöximation.[6]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 41

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

Benzene (71-43-2)

ethyl acetate (141-78-6)

ether (60-29-7)

sulfur trioxide (7446-11-9)

sodium chloride (7647-14-5)

sulfur dioxide (7446-09-5)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

carbon (7782-42-5)

dichloromethane (75-09-2)

ozone (10028-15-6)

Adamantane (281-23-2)

1-Adamantanol, adamantanol (768-95-6)

Adamantanone, Tricyclo[3.3.1.1^{3,7}]decanone (700-58-3)

2-adamantanol (700-57-2)

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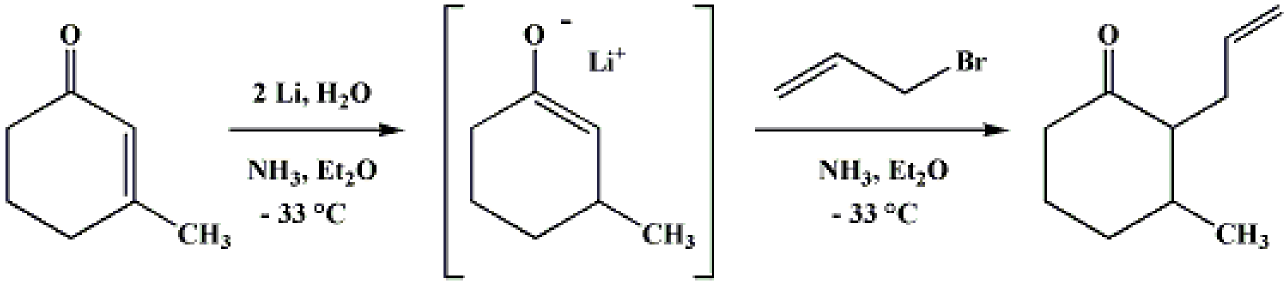
ENONE REDUCTION-ENOLATE ALKYLATION SEQUENCE: 2-ALLYL-3-METHYLCYCLOHEXANONE

[Cyclohexanone, 3-methyl-2-(3-propenyl)-]



Submitted by Drury Caine[1], Sam T. Chao[1], and Homer A. Smith[2].
Checked by Mark E. Jason and Kenneth B. Wiberg.

1. Procedure

Caution! Since liquid ammonia is to be used, this preparation should be carried out in a well-ventilated hood.

A 2-l., three-necked, round-bottomed flask is fitted with a mechanical stirrer (Note 1), a pressure-equalizing dropping funnel, and a two-necked Claisen adapter holding a Dewar condenser (in the offset neck) and an adapter with stopcock for introduction of ammonia (Note 2). The entire apparatus is flame-dried under a stream of nitrogen, which enters at the top of the Dewar condenser, and a positive pressure of nitrogen is maintained throughout the experiment (Note 3). After anhydrous ammonia (1 l.) is introduced into the flask in liquid form (Note 4), the condenser is filled with an acetone–dry ice slurry, and the inlet adapter is removed and replaced with a glass stopper. Stirring is begun, and the ammonia is dried by adding very small pieces of lithium (*ca.* 5 mg. each) until the blue color persists (Note 5). Stirring is continued throughout the following reaction sequence.

Freshly-cut lithium wire (2.77 g., 0.400 g.-atom) (Note 6) is introduced into the flask and allowed to dissolve for 20 minutes, before a solution of 20.0 g. (0.182 mole) of 3-methyl-2-cyclohexen-1-one (Note 7) and 3.27 g. (0.182 mole) of water in 400 ml. of anhydrous diethyl ether (Note 8) and (Note 9) is added dropwise over 60 minutes (Note 10). Ten minutes after completion of the addition, a solution of 65 g. (0.54 mole) of allyl bromide (Note 11) in 150 ml. of anhydrous ether is added from the dropping funnel in a stream over 60 seconds (Note 12). Five minutes later 30 g. of ammonium chloride is added as rapidly as possible. Stirring is discontinued, the Dewar condenser is removed, and the ammonia is allowed to evaporate. A mixture of 300 ml. of ether and 300 ml. of water is added, and the reaction mixture is transferred to a separatory funnel and shaken. After separation of the ether layer, the aqueous layer is saturated with sodium chloride and extracted with two 100-ml. portions of ether. The combined ether extracts are washed with 100 ml. of 5% hydrochloric acid and 100 ml. of aqueous saturated sodium chloride and dried over anhydrous magnesium sulfate. After filtration, ether is removed with a rotary evaporator. The residual oil is distilled through a 37-cm. column packed with 6-mm. Raschig rings and equipped with a resistance heater for thermal balance. There is a forerun, b.p. 74–80° (12 mm.), consisting principally of 3-methylcyclohexanone, before

12.3–13.6 g. (45–49%) (Note 13) of 2-allyl-3-methylcyclohexanone distils as a 20:1 mixture of *trans*- and *cis*-isomers, b.p. 99–102° (12 mm.), n_D^{24} 1.4680–1.4683 (Note 14).

2. Notes

1. A glass stirring shaft and blade should be employed.
2. An apparatus with four necks makes possible the introduction of solid reactants without removal of the condenser or dropping funnel.
3. An apparatus similar to that described in *Org. Synth.*, **Coll. Vol. 4**, 132 (1963). was used for maintaining a nitrogen atmosphere in the system. A positive nitrogen flow was maintained whenever the system was open.
4. Some commercial cylinders are provided with an eductor tube, which allows the extraction of liquid ammonia when the cylinder is upright. Cylinders not so equipped may be secured in a suitable wooden or metal cradle, constructed so that the outlet valve is inclined below the body of the cylinder. The checkers dried commercial ammonia with sodium in a separate flask, then distilled the ammonia into the reaction flask.
5. Although water was used as a proton donor in this preparation, drying of the liquid ammonia and ether was carried out so that the lithium–ammonia solution would not be exposed to water during preparation and so that the amount of water added could be accurately controlled.
6. Lithium wire, purchased from the Lithium Corporation of America, Inc., was cut in 2.5–5.0-cm pieces, washed free of the protective oil with ether, and weighed by transferring quickly to a tared beaker containing mineral oil. The lengths of wire were again washed in a beaker of ether and then held with forceps over an open neck of the reaction flask (positive nitrogen flow), cut with scissors into 3–4-mm. pieces, and allowed to fall directly into the flask.
7. 3-Methyl-2-cyclohexen-1-one, b.p. 76–78° (11 mm.), was purchased from Aldrich Chemical Company, Inc., or prepared according to the procedure of Cronyn and Riesser.[3]
8. Ether was heated to reflux over lithium aluminum hydride and distilled prior to use.
9. The three-component mixture required a few minutes of shaking to ensure the formation of a homogeneous solution. It is essential that the water be completely dissolved before the solution is used.
10. The deep blue solution of lithium in liquid ammonia generally turned pale blue at the end of the addition, and a white precipitate of the lithium enolate and/or lithium hydroxide could be seen.
11. Allyl bromide purchased from Eastman Organic Chemicals, Inc., was dried over calcium chloride and distilled, b.p. 69–70° (760 mm.), prior to use.
12. Since the ammonia boils vigorously during this addition, it is advisable to open one neck of the flask to avoid excessive pressure buildup.
13. The checkers obtained an additional 2–5 g. of 2-allyl-3-methylcyclohexanone by redistilling the column wash and the pot residue through a short-path distillation column, raising the total yield to 14.9–18.1 g. (54–66%).
14. IR (neat) cm.$^{-1}$: 1714 (C=O), 1641 (C=C); ^{1}H NMR (CCl_4), δ (number of protons, multiplicity): 0.82 and 1.10 (two d's, total of 3H, CH_3 of *cis*- and *trans*-isomers, respectively), 1.4–2.7 (m, 10H), 5.1 (two t's, total of 2H, -CH=CH_2), 5.8 (m, 1H, -CH=CH_2). The distillate was analyzed by GC on a 3 mm. by 2 m. column containing 10% Carbowax 20M on HMDS Chromosorb W (60–80 mesh). Using a column temperature of 104° and a carrier gas flow rate of 30 ml./minute, the retention times for the *trans*- and *cis*-isomers were 9.0 minutes and 11.2 minutes, respectively. The product contained greater than 98% of the mixture of *trans*- and *cis*-2-allyl-3-methylcyclohexanone.
A portion of the product was heated to reflux with methanolic sodium methoxide to convert it into the thermodynamic mixture of *trans*- (*ca.* 65%) and *cis*- (*ca.* 35%) isomers. Small

amounts of the isomers were collected by preparative GC using an 8 mm. by 1.7 m. column containing 15% Carbowax 20M on Chromosorb W, and each isomer exhibited the expected spectral and analytical properties. The same thermodynamic mixture of isomers was prepared independently by lithium–ammonia reduction[4] of 2-allyl-3-methylcyclo-2-hexen-1-one,[5] followed by equilibration with methanolic sodium methoxide.
Using the 3 mm. by 2m. column described above, a mixture of stereoisomers of 2-allyl-5-methylcyclohexanone, prepared by allylation of the enamine of 3-methylcyclohexanone,[6] showed peaks at retention times of 8.4 minutes (more stable isomer) and 9.6 minutes. A mixture of the two isomeric 2-allyl-3-methylcyclohexanones and the two isomeric 2-ally-5-methylcyclohexanones clearly exhibited four distinct peaks.

3. Discussion

Alternative preparations of 2-allyl-3-methylcyclohexanone include (a) lithium–ammonia reduction of 2-allyl-3-methyl-2-cyclohexen-1-one (see (Note 13)), which can be prepared by alkylation of 3-methyl-2-cyclohexen-1-one or by alkylation of ethyl 2-methyl-4-oxo-2-cyclohexene-1-carboxylate (Hagemann's ester), followed by hydrolysis and decarboxylation; and (b) conjugate addition of lithium dimethylcuprate to 2-cyclohexen-1-one followed by trapping of the enolate with allyl iodide[7] or allyl bromide[8] in an appropriate solvent.

The present procedure utilizes the enone reduction–enolate alkylation procedure discovered by Stork and co-workers[9] and provides a means of directing alkylation to relatively inaccessible α-positions of unsymmetrical ketones. This procedure has been applied to the synthesis of specifically alkylated steroidal ketones,[10] decalones,[9] hydrindanones,[9] and monocyclic[4] and acyclic ketones.[11] The method is successful because, unlike enolates with other alkali metal counterions, lithium enolates of unsymmetrical ketones undergo alkylation with relatively reactive alkylating agents more rapidly then they equilibrate to isomeric enolates by proton transfer.

The direct conversion of 3-methyl-2-cyclohexen-1-one into 2-allyl-3-methylcyclohexanone provides an interesting example of the utility of the reduction-alkylation procedure. Synthesis of this compound from 3-methylcyclohexanone would be difficult because the latter is converted mainly into 2-alkyl-5-methylcyclohexanones either by direct base-catalyzed alkylation[12] or by indirect methods such as alkylation of its enamine (see (Note 13)) or alkylation of the magnesium salt derived from its cyclohexylimine.[13]

The procedure may also be extended to other alkylating agents and enones. We have reported[4] that 2,3-dimethylcyclohexanone can be prepared by reduction–methylation of 3-methyl-2-cyclohexen-1-one and have found that 2-benzyl-3-methylcyclohexanone is obtained by substituting benzyl chloride for allyl bromide in a procedure similar to that described above, but employing a longer alkylation time.[14] In a related case, Conia and Berlin[15] have prepared 3-(3-butenyl)-2-methylcyclohexanone by reduction–methylation of 3-(3-butenyl)-2-cyclohexen-1-one.

High-boiling products found in this procedure and in similar experiments involving cyclohex-2-enone derivatives[4] probably result from bimolecular reduction processes.[16,17] 3-Methylcyclohexanone, which arises by protonation rather than alkylation of the enolate (and which made up *ca.* 12% of the volatile products), is probably the result of reaction of allyl bromide with liquid ammonia to form the acidic species allyl ammonium bromide.[4,11]

Unless a proton donor is added, the lithium–ammonia reduction of an enone leads to the lithium

enolate and lithium amide. The latter is a sufficiently strong base to rapidly convert the mono-alkylated ketone into its enolate (see f.htmigure 1), which can be further alkylated. The function of the added proton donor is to buffer the system by reaction with the lithium amide. *tert*-Butyl alcohol has been widely used as a proton donor in lithium–ammonia reductions,[4,9,11] but lithium *tert*-butoxide is also a sufficiently strong base to cause a significant amount of polyalkylation in easily ionizable system. In a procedure similar to that above but in which *tert*-butyl alcohol was substituted for water, and/or 2,2- 2,6-diallyl-3-methylcyclohexanone made up 15–20% of the volatile products. However, when water was used as the proton donor so that lithium hydroxide was the strongest base present during the alkylation step, the amount of diallyl product was 2% or less.

Figure 1.

Figure 1.

It is interesting that *trans*-2-allyl-3-methylcyclohexanone is by far the major product of this reduction–alkylation sequence, being formed in greater than the equilibrium ratio (see (Note 13)). The lithium enolate would be expected to exist in the two conformations shows in f.htmigure 2. The conformation having the methyl group quasiaxial may be quite important, because A[1,2]-strain may be significant when the methyl group is quasiequatorial.[18] Recent work on the alkylation of lithium enolates of cyclohexanone derivatives has revealed that the stereochemistry of the reaction is governed largely by steric factors within the reactants.[19,20] From examination of models of the two conformations shown above, it appears that steric interactions between the methyl group and the approaching alkylating agent would be minimized in either of the two possible transition states which lead to the *trans* product.

Figure 2.

Figure 2.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

trans- and cis-2-allyl-3-methylcyclohexanone

2,2- 2,6-diallyl-3-methylcyclohexanone

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ether, diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

sodium chloride (7647-14-5)

Allyl bromide (106-95-6)

nitrogen (7727-37-9)

allyl iodide (556-56-9)

sodium methoxide (124-41-4)

sodium (13966-32-0)

benzyl chloride (100-44-7)

lithium (7439-93-2)

magnesium sulfate (7487-88-9)

lithium aluminum hydride (16853-85-3)

lithium amide (7782-89-0)

tert-butyl alcohol (75-65-0)

2-cyclohexen-1-one (930-68-7)

lithium hydroxide (1310-65-2)

3-methylcyclohexanone (591-24-2)

2-Allyl-3-methylcyclohexanone, Cyclohexanone, 3-methyl-2-(3-propenyl)- (56620-95-2)

3-methyl-2-cyclohexen-1-one

2-allyl-5-methylcyclohexanone

2-allyl-3-methyl-2-cyclohexen-1-one, 2-allyl-3-methylcyclo-2-hexen-1-one

ethyl 2-methyl-4-oxo-2-cyclohexene-1-carboxylate

lithium dimethylcuprate

2,3-dimethylcyclohexanone

2-benzyl-3-methylcyclohexanone

3-(3-butenyl)-2-methylcyclohexanone

3-(3-butenyl)-2-cyclohexen-1-one

allyl ammonium bromide

lithium tert-butoxide (1907-33-1)

trans-2-allyl-3-methylcyclohexanone

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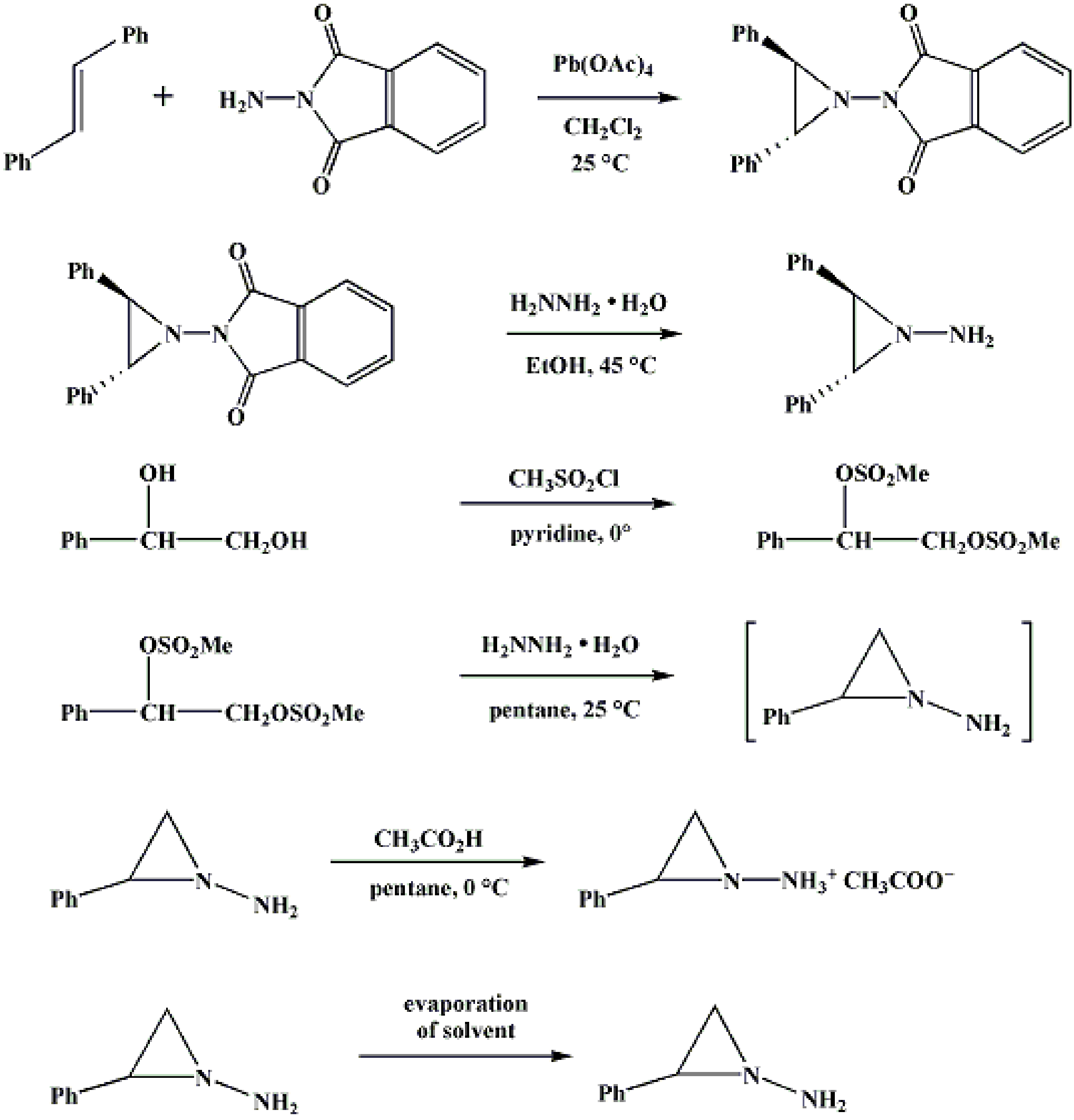
Organic Syntheses, CV 6, 56

PREPARATION OF *N*-AMINOAZIRIDINES: *trans*-1-AMINO-2,3-DIPHENYLAZIRIDINE, 1-AMINO-2-PHENYLAZIRIDINE, AND 1-AMINO-2-PHENYLAZIRIDINIUM ACETATE

[1-Aziridinamine, *trans*-(±)-2,3-diphenyl-, 1-aziridinamine, (±)-2-phenyl-, and 1-aziridinamine, monoacetate, (±)-2-phenyl-]



Submitted by Robert K. Müller, Renato Joos, Dorothee Felix, Jakob Schreiber, Claude Wintner, and A. Eschenmoser[1].
Checked by Robert E. Ireland, J. Kleckner, and David M. Walba.

1. Procedure

Caution! Steps B and D should be carried out in a hood behind a safety screen.

A. trans-2,3-*Diphenyl*-1-*phthalimidoaziridine* (Note 1). A 1-l., three-necked, round-bottomed flask equipped with an efficient mechanical stirrer is charged with a mixture of 19.5 g (0.120 mole) of *N*-aminophthalimide (Note 2), 108 g. (0.600 mole) of (*E*)-stilbene (Note 3), and 300 ml. of dichloromethane (Note 4). To the resulting suspension is added 60 g. (*ca.* 0.12 mole) of lead tetraäcetate (Note 5) over a period of 10 minutes, at room temperature with *vigorous* stirring. Stirring is continued for an additional 30 minutes, after which time the mixture is filtered through Celite®, which is washed twice with 50-ml. portions of dichloromethane. The combined filtrates are transferred to a 4-l. beaker, and 1.5 l. of pentane is added with gentle stirring and cooling in an ice bath. The yellow precipitate that forms after 15 minutes is suction filtered and redissolved in 200 ml. of dichloromethane. The solution obtained is swirled for 5 minutes with 20 g. of silica gel, filtered through Celite®, which is washed with two 100-ml. portions of dichloromethane. To this dichloromethane solution is added 1.5 l. of pentane, with cooling. The precipitate that forms after 0.5 hour is dried under vacuum (10 mm.) at room temperature for 5 hours, yielding 16–21 g. (39–51%) of product, m.p. 175°, which is of sufficient purity for use in the next step (Note 6).

B. trans-1-*Amino*-2,3-*diphenylaziridine* (Note 7). To a magnetically stirred suspension of 20.4 g. (0.0600 mole) of *trans*-2,3-diphenyl-1-phthalimidoaziridine in 150 ml. of 95% ethanol in a 500-ml., round-bottomed flask at room temperature is added 150 ml. (3 moles) (Note 8) of hydrazine hydrate (Note 9). The mixture is stirred for 40 minutes while maintaining the temperature at 43–45° (Note 10) with a thermostatted oil bath. The resulting cloudy yellow solution (Note 11) is cooled and filtered through Celite®. The filtrate is poured into a 2-l. separatory funnel containing 400 ml. of diethyl ether and 200 g. of ice, and shaken vigorously. The organic phase is separated and washed with three 200-ml. portions of ice-cold water, and the aqueous washings are reextracted with a 250-ml. portion of ether (Note 12). The combined ethereal extracts are dried over anhydrous potassium carbonate, filtered through Celite® if necessary, and concentrated to approximately 300 ml. on a rotary evaporator at room temperature. Addition of 400 ml. of pentane and overnight storage at −20° leads to crystallization of 7.9–9.5 g. (63–75%) of *trans*-1-amino-2,3-diphenylaziridine (Note 13) as colorless crystals, m.p. 93–94° (dec.) (Note 14). An additional 1.2–2.2 g.. (10–17%) is obtained by concentration of the mother liquor to 50–80 ml. and addition of approximately 50 ml. of pentane (Note 7).

C. *Styrene glycol dimesylate* (Note 15). A 300-ml., three-necked, round-bottomed flask equipped with a thermometer, an efficient stirrer (Note 16), and a dropping funnel is charged with a solution of 34.5 g. (0.250 mole) of styrene glycol (Note 17) in 90 ml. of pyridine (Note 18). The solution is cooled to −5° with an ice–salt bath, and 64.7 g. (43.7 ml., 0.560 mole) of methanesulfonyl chloride (Note 19) is added dropwise over a 1-hour period, while maintaining the temperature at or below 0° (Note 20). Stirring is continued for 4 hours at 2–4°, with the flask cooled with an ice-water bath. The reaction mixture is mixed thoroughly with 600 g. of ice, and the dimesylate precipitates. After careful acidification of the mixture with 6 *N* hydrochloric acid to approximately pH 3 (Note 21), the dimesylate is suction filtered, washed twice with 100-ml. portions of ice water, and pressed as dry as possible. This product, which is still moist, is transferred to a separatory funnel and is shaken well with 200 ml. of dichloromethane. The dichloromethane is separated, and the aqueous layer is extracted further with two 20-ml. portions of dichloromethane. The combined dichloromethane layers are dried over anhydrous magnesium sulfate, and 250–300 ml. of pentane is added to the solution, until crystallization just begins. After 2 hours in a deep freeze at −25°, the crystals are collected, washed with two 30-ml. portions of pentane precooled to 0°, and dried to constant weight in a vacuum desiccator (10 mm.) at room temperature, yielding 62–64 g. (84–86%) of white,

crystalline dimesylate, m.p. 93–94° (Note 15).

D. *Hydrazinolysis of styrene glycol dimesylate*. A 1-l., round-bottomed flask equipped with a magnetic stirring bar is charged with 50 ml. (1 mole) of hydrazine hydrate (Note 9). Finely powdered styrene glycol dimesylate (20 g., 0.068 mole), m.p. 93–94°, is then added with gentle stirring at room temperature. To the resulting slurry is slowly added 600 ml. of pentane. The stirring speed should be adjusted in such a manner that the two phases mix somewhat, but the dimesylate–hydrazine hydrate layer is not deposited on the upper walls of the flask. After 20–24 hours of stirring at room temperature two entirely clear layers can be observed upon the cessation of stirring (Note 22), indicating that the reaction is complete. The hydrazine hydrate is separated from the pentane and extracted with two 30-ml. portions of pentane. The combined pentane layers are filtered through cotton, which holds back any remaining droplets of hydrazine hydrate, into a 1-l., round-bottomed flask. At this point *Step E* is followed for 1-amino-2-phenylaziridine, and *Step F* for 1-amino-2-phenylaziridinium acetate.

E. *1-Amino-2-phenylaziridine* (Note 23). If the pentane solution from *Step D* is removed on a rotary evaporator at room temperature, 7.5–7.7 g.. (82–85%) of 1-amino-2-phenylaziridine, suitable for preparative use, is obtained. Kügelrohr distillation of this material on a 1–2 g. scale (0.01 mm./60–65° oven temperature) (Note 24) gives a recovery of over 90% (Note 23) and (Note 25).

F. *1-Amino-2-phenylaziridinium acetate* (Note 23). The pentane solution from *Step D* is stirred with a magnetic stirrer and cooled to 0°, and 3.9 ml. (0.068 mole) of acetic acid is measured. Three drops of acetic acid are added at first, and stirring is continued at 0° until the precipitation of white 1-amino-2-phenylaziridinium acetate begins. If necessary, crystallization is initiated by scratching with a glass rod or by addition of a seed crystal from a previous run. The remainder of the acetic acid is added over a 10-minute period, and stirring is continued for an additional 20 minutes, while maintaining the temperature at 0°. The salt is filtered, washed with 30 ml. of pentane precooled to 0°, and dried in a vacuum desiccator (10 mm.) at room temperature, yielding 10.0–10.5 g. (76–79%) (Note 26) of product, m.p. 69–70° (Note 27) which is suitable for preparative purposes. Recrystallization is possible; however, it must be carefully carried out to avoid the formation of a yellow product, whose melting point is lower than that of the crude product. A solution of 10 g. of 1-amino-2-phenylaziridinium acetate in 40 ml. of dichloromethane is prepared at a maximum temperature of 20–22°. The turbid solution is immediately filtered through Celite®, which is washed with two 10-ml. portions of dichloromethane. The resulting clear solution is treated with 200–250 ml. of pentane until crystallization just begins, and placed in a deep freeze at –25° for 2 hours. Filtration, washing with 30 ml. of pentane precooled to 0°, and drying as before, afford 9.2–9.3 g. of 1-amino-2-phenylaziridinium acetate, m.p. 70–72° (Note 23) and (Note 28).

2. Notes

1. *trans*-2,3-Diphenyl-1-phthalimidoaziridine is available from Fluka AG, CH-9470 Buchs.
2. *N*-Aminophthalimide is available from Fluka AG or may be prepared from phthalimide and hydrazine.[2] The quality is important; the m.p. should be 199–202° with subsequent resolidification of the melt due to thermal reaction. Recrystallization, if necessary, can be carried out in ethanol. The checkers observed that with one batch of recrystallized material, the solid never really did melt, but seemed to sinter at 200°.
3. Technical grade (*E*)-stilbene obtained from Fluka AG gives satisfactory results, although a better grade is preferable. The checkers used reagent grade material obtained from Aldrich Chemical Company, Inc.
4. This was distilled over phosphorus pentoxide.

5. "Purum" grade lead tetraäcetate, 85–90%, moistened with acetic acid, obtained from Fluka AG was used. The checkers used reagent grade material, moistened with acetic acid, purchased from Matheson, Coleman and Bell.
6. The yield of the reaction, while always at least 39%, is subject to fluctuation. The product may be contaminated with small amounts of (*E*)-stilbene and/or lead salts. The presence of (*E*)-stilbene can easily be monitored by TLC, using ready-prepared Silica Gel F_{254} plates available from E. Merck & Company, Darmstadt, Germany. The plates are developed with dichloromethane, and the spots detected under UV light. In runs of smaller scale, or if product of higher purity is desired, column chromatography on silica gel may replace the work-up described; the reaction mixture is filtered through Celite®, and the resulting solution is concentrated on a rotary evaporator. The residue is then chromatographed on 570 g. of silica gel. Eluting with dichloromethane gives the stilbene first, then small amounts of unidentified impurities, and finally the desired adduct in 70–73% yield.
7. *trans*-1-Amino-2,3-diphenylaziridine decomposes thermally, largely to (*E*)-stilbene and nitrogen. In the crystalline state it is stable for several hours at room temperature, and for several weeks (probably for several months) at –20°. It decomposes within 3 days at room temperature in aprotic solvents and much more rapidly in protic solvents.[3] Decomposition is still faster in the presence of traces of acids. The work-up described should be completed as quickly and as *precisely* as possible, and the product should be stored in a deep freeze if it is not to be used immediately. For the use of this reagent in the α,β-epoxyketone fragmentation, see references [3] and [4].
8. Use of lesser amounts of hydrazine hydrate or ethanol causes precipitation of the product as a pasty mass that dissolves only slowly in ether, thereby making the work-up difficult.
9. "Purum" grade hydrazine hydrate obtained from Fluka AG was used. The checkers used 99–100% hydrazine hydrate purchased from Matheson, Coleman and Bell.
10. The reaction temperature must be carefully controlled. At temperatures above 48° the yield is markedly reduced by decomposition of the product, and below 43° the reaction time is greatly lengthened.
11. The submitters report that if very pure *trans*-2,3-diphenyl-1-phthalimidoaziridine is used, no insoluble matter is present at this point, and filtration through Celite® is not necessary.
12. Before working up the reaction mixture, it is recommended to test whether the reaction is complete by TLC (Note 6). If (*E*)-stilbene is observed, the reaction should be interrupted immediately. The checkers found that the work-up was complicated by formation of emulsions; small quantities of brine were used to aid separation of the phases.
13. IR ($CHCl_3$) cm.$^{-1}$: 3340, 1603, 1495, 1450, 1085, 1070, 1030 (a weak band at 960 cm.$^{-1}$ is due to (*E*)-stilbene, as there is always some decomposition of the *trans*-1-amino-2,3-diphenylaziridine during the recording of the spectrum) (Note 7); ^{1}H NMR ($CDCl_3$), δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 3.10 (broad m, 2H, NH_2), 3.22 and 3.36 (AB q, 2H, *J* = 5), 7.1–7.6 (m, 10H). The nonequivalence of the two methine protons is due to slow inversion at nitrogen, and confirms the *trans*-2,3-substitution.
14. The melting-point tube is placed in the bath at 85° and heated rapidly.
15. A second crystallization from dichloromethane–pentane is sometimes necessary to achieve material having this melting point. Styrene glycol dimesylate must be stored in a refrigerator, since slow decomposition takes place at room temperature.
16. Toward the end of the reaction, the mixture becomes quite viscous. Unless the stirring assembly is capable of mixing material at the flask walls, homogeneous temperature control cannot be guaranteed.
17. Styrene glycol is available from Aldrich Chemical Company, Inc., or from Eastman Organic Chemicals. Alternatively, it may be prepared by hydrolysis of styrene oxide.[3] If the glycol melts at lower than 63°, it should be recrystallized before use.

18. Dried over potassium hydroxide and distilled.
19. "Purum" grade methanesulfonyl chloride supplied by Fluka AG or 98% pure material supplied by Eastman Organic Chemicals was used.
20. The addition rate is about 30 drops/minute. After about half of the methanesulfonyl chloride has been added, white crystals of pyridine hydrochloride begin to precipitate, and the solution becomes viscous (Note 16).
21. About 110–120 ml. of 6 *N* hydrochloric acid is needed. The temperature should not be allowed to rise above 5°.
22. The rate of the reaction is influenced by the speed of stirring. At slow speeds, 30 hours may be required for completion without any decrease in the final yield. The role of pentane is to continuously remove newly formed product from the hydrazine solvent.
23. 1-Amino-2-phenylaziridine decomposes at temperatures over 0°, and must therefore be stored in a deep freeze at −25°, at which temperature it is crystalline. 1-Amino-2-phenylaziridinium acetate is somewhat more stable, but it too decomposes within 2 days at room temperature. It can be kept unchanged in a deep freeze for months. For the use of these two reagents in the α,β-epoxyketone fragmentation, see references [3] and [4].
24. In order to minimize decomposition, the distillation should be carried out on small portions at the lowest possible temperature and pressure.
25. The distilled product has the following ^{1}H NMR spectrum ($CDCl_3$), δ (number of protons, assignment): 1.91, 1.98, and 2.06 (2H, AB part of ABX), 2.50, 2.58, 2.64, and 2.72 (1H, X part of ABX), 3.60 (2H, NH_2), 7.25 (5H). Undistilled material shows substantially the same spectrum.
26. By the addition of two further drops of acetic acid to the mother liquor, and overnight cooling at −25°, an additional 0.3–0.4 g. (2–3%) of product, m.p. 60–62°, can be isolated.
27. For the melting point determination the capillary is placed in the apparatus at 60°, and the temperature is raised 4°/minute.
28. Recrystallized 1-amino-2-phenylaziridinium acetate has the following ^{1}H NMR spectrum ($CDCl_3$), δ (number of protons, assignment): 1.95–2.20 (5H, AB part of ABX and CH_3 at δ 2.02), 2.67–2.95 (1H, X part of ABX), 6.50–6.70 (3H, NH_3) 7.0–7.4 (5H).

3. Discussion

trans-1-Amino-2,3-diphenylaziridine and 1-amino-2-phenylaziridine are reagents for the α,β-epoxyketone alkynone fragmentation,[3] an example of which is given in this volume.[4] An alternative preparation of 1-amino-2-phenylaziridine is the hydrazinolysis of 2-phenyl-1-phthalimidoaziridine.[3]

The lead tetraäcetate reaction between *N*-aminophthalimide and (*E*)-stilbene was first described by Rees,[5] and the hydrazinolysis of the addition product by Carpino.[6] The procedures described here incorporate their methods, with improvements. The dimesylate–hydrazine reaction was first described by Paulsen[7] in the carbohydrate series.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 679

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

ethanol (64-17-5)

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ether, diethyl ether (60-29-7)

nitrogen (7727-37-9)

pyridine (110-86-1)

potassium hydroxide (1310-58-3)

Phthalimide (85-41-6)

hydrazine hydrate (7803-57-8)

Pentane (109-66-0)

hydrazine (302-01-2)

dichloromethane (75-09-2)

Styrene oxide (96-09-3)

magnesium sulfate (7487-88-9)

pyridine hydrochloride (628-13-7)

stilbene

Methanesulfonyl chloride (124-63-0)

1-Amino-2-phenylaziridinium acetate (37079-43-9)

styrene glycol

Styrene glycol dimesylate (32837-95-9)

1-Amino-2-phenylaziridine, 1-aziridinamine, (±)-2-phenyl- (19615-20-4)

2-phenyl-1-phthalimidoaziridine

phosphorus pentoxide (1314-56-3)

(E)-stilbene (103-30-0)

trans-2,3-Diphenyl-1-phthalimidoaziridine (37079-32-6)

N-aminophthalimide (1875-48-5)

trans-1-Amino-2,3-diphenylaziridine, 1-Aziridinamine, trans-(±)-2,3-diphenyl- (28161-60-6)

lead tetraacetate

1-aziridinamine, monoacetate, (±)-2-phenyl-

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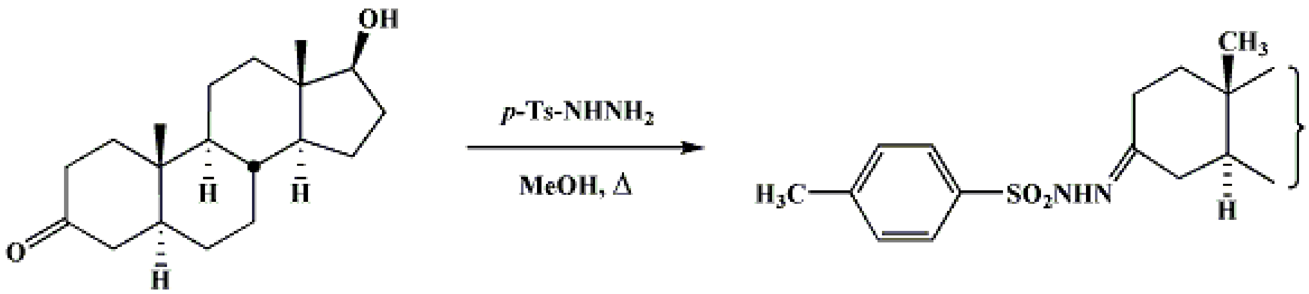
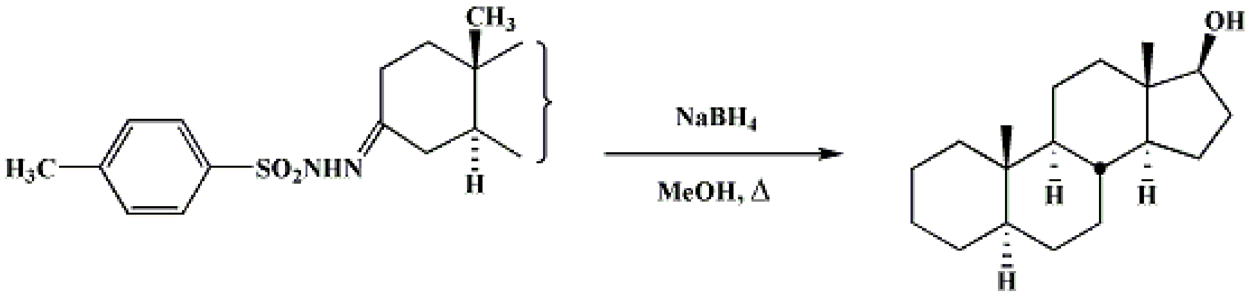
REDUCTION OF KETONES BY USE OF THE TOSYLHYDRAZONE DERIVATIVES: ANDROSTAN-17 β-OL

[Androstan-17-ol, (5α, 17β)-]





Submitted by L. Caglioti[1]
Checked by J. F. Moser and A. Eschenmoser.

1. Procedure

A 100-ml., round-bottomed flask equipped with a reflux condenser is charged with 1.00 g. (0.00345 mole) of 5α-androstan-17β-ol-3-one (Note 1), 0.90 g. (0.0048 mole) of tosylhydrazide (Note 2), and 70 ml. of methanol (Note 3). The mixture is heated under gentle reflux for 3 hours, then cooled to room temperature. To the solution is added 2.5 g. (0.075 mole) of sodium borohydride in small portions over one hour (Note 4) and the resulting mixture is heated under reflux for an additional 8 hours. The reaction mixture is cooled to room temperature before the solvent is removed under reduced pressure. The residue is dissolved in diethyl ether, transferred to a separatory funnel, and washed successively with water, dilute aqueous sodium carbonate, 2 *M* hydrochloric acid, and water. The ethereal solution is dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue, 0.95 g. of white crystals (Note 5), is dissolved in about 20 ml. of a 7:3 (v/v) mixture of cyclohexane-ethyl acetate and applied to a column packed with 60 g. of silica gel (Merck, 0.05–0.2 mm.). The column is eluted with the 7:3 (v/v) cyclohexane-ethyl acetate mixture and a 200-ml. fraction is collected. Evaporation of this fraction under reduced pressure affords 0.70–0.73 g. (73–76%) of pure 5α-androstan-17β-ol. Recrystallization from aqueous methanol provides 0.64 g. of analytically pure product, m.p. 161–163°.

2. Notes

1. 5α-Androstan-17β-ol-3-one was supplied by Aldrich Chemical Co., Inc.
2. Tosylhydrazide was supplied by Aldrich Chemical Co., Inc. Alternately, it may be prepared by a procedure described in *Org. Synth.*, **Coll. Vol. 5**, 1055 (1973).
3. Tetrahydrofuran serves equally well as a solvent. However, the quantity of sodium borohydride should be reduced to 1.0 g. and the isolation procedure modified in the following way. After the

solution has been refluxed for 8 hours, the reaction mixture is cooled and the excess sodium borohydride is decomposed by the slow addition of dilute hydrochloric acid. The resulting mixture is extracted with ether and the ethereal solution is washed as described.
4. Because of the ready decomposition of sodium borohydride in methanol, the solution is maintained at room temperature during the addition of the metal hydride.
5. The crude product is contaminated with a small amount of a more polar substance which is subsequently removed by chromatography.

3. Discussion

The preparation of 5α-androstan-17β-ol from 5α-androstan-17β-ol-3-one may be realized by classical methods such as the Wolff-Kishner or Clemmensen reduction.

This procedure illustrates a general method for the reduction of aldehyde and ketone functions to methylene groups under very mild conditions. Since strong acids and bases are not employed, this procedure is of particular importance for the reduction of ketones possessing an adjacent chiral center.[2,3] Moreover, the use of deuterated metal hydrides permits the preparation of labeled compounds.[4]

The reduction of the preformed tosylhydrazones with sodium borohydride may be effected in aprotic solvents, such as tetrahydrofuran or dioxane.[5] The use of lithium aluminium hydride in nonhydroxylic solvents permits the reduction of aromatic aldehydes and ketones.

References and Notes

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2. The reduction of the tosylhydrazone of (+)(*S*)-4-methyl-3-hexanone affords (+)(*S*)-3-methylhexane, optical purity 85%; L. Lardicci and C. Botteghi, private communication.
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

tosylhydrazone of (+)(S)-4-methyl-3-hexanone

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

cyclohexane (110-82-7)

dioxane (5703-46-8)

Tetrahydrofuran (109-99-9)

lithium aluminium hydride (16853-85-3)

sodium borohydride (16940-66-2)

tosylhydrazide

ANDROSTAN-17 β-OL

Androstan-17-ol, (5α, 17β)-, 5α-androstan-17β-ol (1225-43-0)

5α-androstan-17β-ol-3-one

(+)(S)-3-methylhexane

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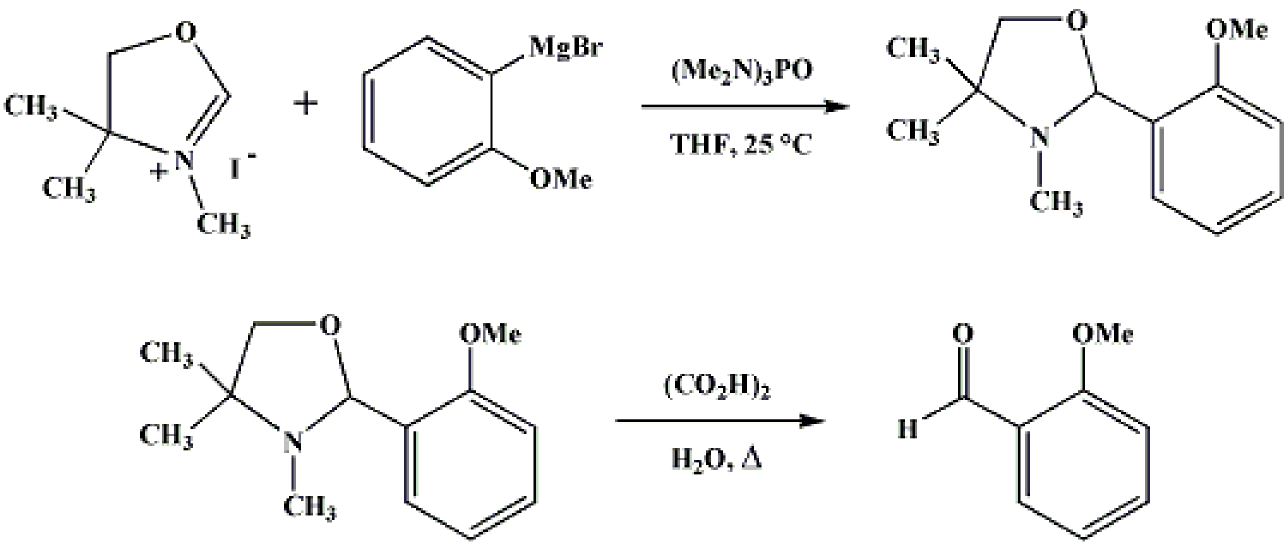
Organic Syntheses, *CV 6, 64*

ALDEHYDES FROM 4,4-DIMETHYL-2-OXAZOLINE AND GRIGNARD REAGENTS: *o*-ANISALDEHYDE

[Benzaldehyde, 2-methoxy-]



Submitted by R. S. Brinkmeyer, E. W. Collington, and A. I. Meyers[1].
Checked by R. E. Ireland and R. R. Schmidt, III.

1. Procedure

Caution! Hexamethylphosphoric triamide (HMPA) vapors have been reported to cause cancer in rats.[2] All operations with hexamethylphosphoric triamide should be performed in a good hood, and care should be taken to keep the liquid off the skin.

Methyl iodide, in high concentrations for short periods or in low concentrations for long periods, can cause serious toxic effects in the central nervous system. Accordingly, the American Conference of Governmental Industrial Hygienists[3] has set 5 p.p.m., a level which cannot be detected by smell, as the highest average concentration in air to which workers should be exposed for long periods. The preparation and use of methyl iodide should always be performed in a well-ventilated fume hood. Since the liquid can be absorbed through the skin, care should be taken to prevent contact.

A 1-l., three-necked, round-bottomed flask equipped with a 500-ml. dropping funnel (Note 1), a mechanical stirrer, and an argon inlet tube is charged with 80 g. (0.33 mole) of *N*,4,4-trimethyl-2-oxazolinium iodide (Note 2). The system is flushed with argon; 150 ml. of dry tetrahydrofuran (Note 3) is added, and the stirred suspension is cooled in an ice bath. Meanwhile, to a cooled solution of freshly prepared 2-methoxyphenylmagnesium bromide (0.414 mole) (Note 4) is added 150 g. (146 ml., 0.828 mole) of dry hexamethylphosphoric triamide (Note 5). This solution is then transferred under an argon atmosphere to the 500-ml. dropping funnel with the aid of an argon-pressurized siphon. The solution is slowly run into the cooled suspension, whereupon the methiodide salt dissolves. When the addition is complete, the reaction mixture is stirred at room temperature overnight.

The suspension is slowly poured into 600 ml. of saturated ammonium chloride solution which has previously been cooled to 10–15°, and the mixture is extracted with three 250-ml. portions of diethyl ether. Concentration of the combined extracts gives the crude addition product (Note 6), which is added to 200 ml. of ice-cold water and quickly acidified with cold 3 *N* hydrochloric acid. The acidic solution is rapidly extracted with 300 ml. of cold hexane, and the extract is discarded. The aqueous solution is then made basic by the addition of aqueous 20% sodium hydroxide solution (Note 7), and the mixture is extracted with three 250-ml. portions of ether. Concentration of the combined ethereal extracts affords 70–75 g. of crude oxazolidine (Note 8).

A 1-l., round-bottomed flask is charged with 72 g. of the crude oxazolidine in 600 ml. of water, and 201.6 g. (1.6 moles) of hydrated oxalic acid is added. The mixture is heated under reflux for 1 hour, cooled, treated with 600 ml. of water to dissolve precipitated oxalic acid, and extracted with three 100-ml. portions of ether. The combined ethereal extracts are washed with 50 ml. saturated sodium hydrogen carbonate, dried over anhydrous potassium carbonate, and concentrated, giving 30–35 g. of crude aldehyde. Distillation of this material at 70–75° (1.5 mm.) gives pure *o*-anisaldehyde (22.8–26.3 g.; 51–59%), m.p. 35.5–38° (Note 9).

2. Notes

1. The dropping funnel should be equipped so that the transfer of the Grignard reagent to it can be carried out under a positive nitrogen pressure.
2. 4,4-Dimethyl-2-oxazoline is commercially available from Columbia Organic Chemicals, 912 Drake Street, Columbia, South Carolina, or may be prepared as follows. A 250-ml., three-necked flask is charged with 89.14 g. (1.001 mole) of 2-amino-2-methylpropanol and cooled in an ice bath. The amine is carefully neutralized with 52.3 g. (1.25 mole) of 90.6% formic acid over a 1-hour period. A magnetic stirring bar is added, the flask is fitted with a short path distillation head, and the reaction mixture is placed in a silicon oil bath which is rapidly heated to 220–250°. The azeotropic mixture of water and oxazoline distills over a period of 2–4 hours and is collected in an ice-cooled flask containing ether. The aqueous layer is separated, saturated with sodium chloride, and extracted with three 50-ml. portions of ether. The combined ethereal extracts are dried over potassium carbonate and filtered. The ether is removed at 35–40° at atmospheric pressure, and 4,4-dimethyl-2-oxazoline is collected as the temperature rises above 85°, yielding 56.7–62.7 g. (57–63%) of a colorless mobile liquid, b.p. 99–100° (758 mm.).
The checkers found that if the azeotropic mixture is distilled more slowly from the reaction mixture at a pot temperature of 175–195°, the yield is greatly reduced and large amounts of polymeric material are formed.
N,4,4-Trimethyl-2-oxazolinium iodide is prepared by adding 49.5 g. (0.500 mole) of 4,4-dimethyl-2-oxazoline to an excess of cold methyl iodide (182 g., 78.2 ml., 1.28 moles) in a 500-ml. flask and stirring at room temperature under argon for 20 hours. The light brown solid is suction filtered and dissolved in 350 ml. of dry acetonitrile. The methiodide salt is precipitated by the addition of 750 ml. of dry ether to this acetonitrile solution. The purified salt is again suction filtered, and the white solid is washed with 250 ml. of dry ether and finally dried under vacuum, giving 96 g. (80%) of the methiodide, m.p. 215° (dec.). The salt can be stored in an inert atmosphere without deterioration.
3. Tetrahydrofuran was dried by distillation from lithium aluminium hydride. See *Org. Synth.*, **Coll. Vol. 5**, 976, 1973, for a warning concerning the purification of tetrahydrofuran.
4. 4.2-Methoxyphenylmagnesium bromide was prepared from 77.5 g. (0.414 mole, distilled from calcium hydride) of *o*-bromoanisole and 11 g. (0.46 g.-atom) of magnesium turnings in

100 ml. of dry tetrahydrofuran. The solution of this Grignard reagent is heated to reflux for 30 minutes prior to use.

5. Hexamethylphosphoric triamide was dried by distillation from calcium hydride.

6. If pure oxazoline is required, residual amounts of hexamethylphosphoric triamide can be removed by elution of the ethereal solution through silica gel (20–40 mesh).

7. Ice may be added to keep the mixture cool during the neutralization.

8. If this step is omitted, the *o*-anisaldehyde obtained after hydrolysis of the oxazolidine is contaminated with 5–10% *o*-bromoanisole.

9. *o*-Anisaldehyde is commercially available from Aldrich Chemical Co. and Eastman Organic Chemicals, Eastman Kodak Co.

3. Discussion

The conversion of a Grignard or an organolithium reagent to an aldehyde has been accomplished by a variety of reagents. The methods utilize such reagents as *N*-ethoxymethyleneaniline;[4] ethyl orthoformate;[4] 4-dimethylaminobenzaldehyde;[5] *N*,*N*-dimethylformamide;[6] a dihydroquinazolinium salt;[7] and, more recently, a *tert*-alkyl isonitrile.[8]

This procedure illustrates a general method for the preparation of aryl, benzyl, alkynyl, and vinyl aldehydes.[9] Table I gives the aldehydes which have been prepared from the corresponding Grignard reagents by conditions similar to those described here.

TABLE I
ALDEHYDES FROM *N*,4,4-TRIMETHYL-2-OXAZOLINIUM IODINE

Grignard Reagent	Aldehyde	Yield, %
C_6H_5MgBr	C_6H_5CHO	69
$C_6H_5CH_2MgCl$	$C_6H_5CH_2CHO$	87
$C_6H_5CH{=}CHMgBr$	$C_6H_5CH{=}CHCHO$	64
$C_6H_5C{\equiv}CMgBr$	$C_6H_5C{\equiv}CCHO$	51
$2\text{-}CH_3OC_6H_4MgBr$	$2\text{-}CH_3OC_6H_4CDO$	70[a]

a From 2-deuterio-*N*,4,4-trimethyl-2-oxazolinium iodide.

This method does not allow the formylation of aliphatic Grignard or organolithium reagents, since in these cases, the enhancement in base strength in the presence of hexamethylphosphoric triamide produces side reactions due to proton abstraction.

The present method is simple, proceeds easily and in good yield. The starting materials are readily available. The method is of particular value for the ready preparation of C-1 deuterated aldehydes using the 2-deuterio-*N*,4,4-trimethyl-2-oxazolinium iodide.[9] Also, since ^{14}C-labeled formic acid is routinely available, this provides easy access to isotopically labeled aldehydes.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

ether, diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

acetonitrile (75-05-8)

sodium hydroxide (1310-73-2)

sodium hydrogen carbonate (144-55-8)

magnesium (7439-95-4)

sodium chloride (7647-14-5)

formic acid (64-18-6)

Oxalic acid (144-62-7)

nitrogen (7727-37-9)

Methyl iodide (74-88-4)

Ethyl orthoformate

Tetrahydrofuran (109-99-9)

N-ethoxymethyleneaniline (6780-49-0)

lithium aluminium hydride (16853-85-3)

N,N-dimethylformamide (68-12-2)

2-amino-2-methylpropanol (124-68-5)

hexane (110-54-3)

oxazoline

calcium hydride (7789-78-8)

Benzaldehyde, 2-methoxy-, o-Anisaldehyde (135-02-4)

4-dimethylaminobenzaldehyde (100-10-7)

hexamethylphosphoric triamide (680-31-9)

argon (7440-37-1)

4,4-DIMETHYL-2-OXAZOLINE (30093-99-3)

2-methoxyphenylmagnesium bromide

oxazolidine

4.2-Methoxyphenylmagnesium bromide

o-bromoanisole (578-57-4)

N,4,4-trimethyl-2-oxazolinium iodide (30093-97-1)

2-deuterio-N,4,4-trimethyl-2-oxazolinium iodide

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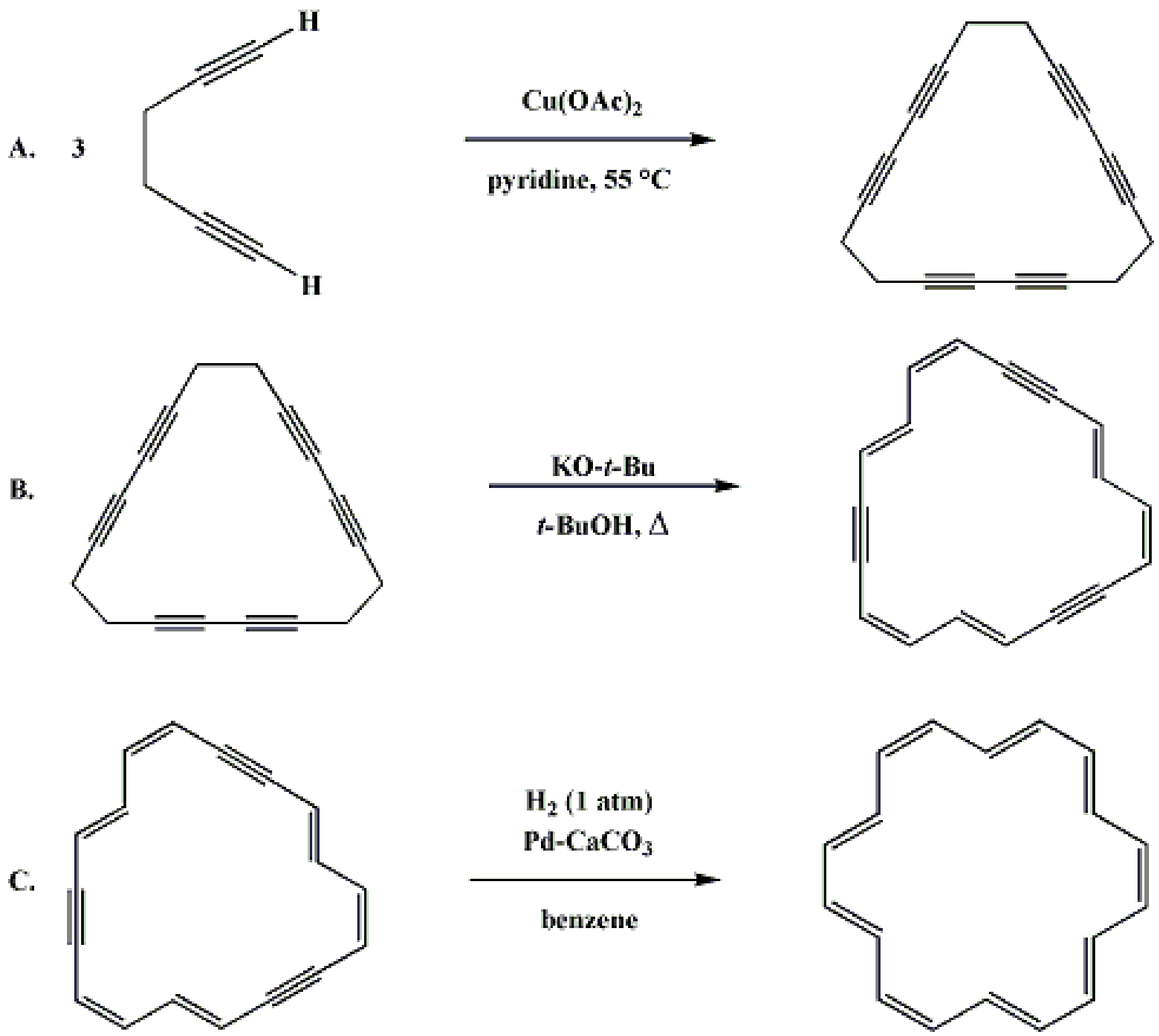
Organic Syntheses, CV 6, 68

[18]ANNULENE

[1,3,5,7,9,11,13,15,17-Cycloöctadecanonaene]



Submitted by K. Stöckel and F. Sondheimer[1].
Checked by R. C. Wheland, R. E. Benson, H. Ona, and S. Masamune.

1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and giove protection is required.

A. *Hexadehydro*[18]*annulene*. A 12-l., four-necked, round-bottomed flask provided with a stopcock at the bottom (f.htmigure 1) (Note 1) is fitted with a stirrer (Note 2), a reflux condenser, and a 500-ml. pressure-equalizing dropping funnel. The flask is placed in a

large metal vessel equipped with a hot–cold water inlet and a drain. The flask is charged with 600 g. (3.00 moles) of copper(II) acetate monohydrate (Note 3) and 3.8 l. of pyridine (Note 4). Stirring is begun and warm water is added to the metal vessel to heat the contents of the flask to 55 ± 1°, and the mixture is slowly stirred at this temperature for 1 hour. With vigorous stirring (approximately 600 r.p.m., (Note 4)), a solution of 50 g. (0.64 mole) of 1,5-hexadiyne (Note 5) in 400 ml. of pyridine (Note 6) is added over 30 minutes to the 55°, green suspension. The mixture is stirred vigorously at this temperature for an additional 2 hours before the warm water in the metal vessel is allowed to drain and is replaced with a mixture of ice and water. When the contents of the flask have cooled, the mixture is drawn off through the stopcock at the bottom of the flask and filtered through a 25-cm. Büchner funnel (Filtrate A). The green residue is transferred to a 5-l. beaker and 2.5 l. of 1:1 (v/v) benzene–diethyl ether is added. The mixture is stirred well, avoiding emulsion formation, and filtered (Filtrate B). The residue is similarly extracted with 2.5 l. of 1:1 (v/v) benzene–ether and filtered (Filtrate C). Each filtrate is kept separate.

Figure 1.

Figure 1.

Filtrate A is concentrated to approximately 200 ml. (Note 7) and added to Filtrate C. The resulting mixture is well agitated and filtered through a 25-cm. Büchner funnel. The residue is extracted twice in a similar manner with 500 ml. of 1:1 (v/v) benzene–ether. All the filtrates are now combined in the original 12-l. reaction vessel (Note 8) and washed successively with two 500-ml. portions of water, two 500-ml. portions of cold (0°), 2 *N* hydrochloric acid, and three 500 ml portions of water. The organic layer is dried for 2 hours over *ca.* 110 g. of magnesium sulfate (Note 9), filtered, and evaporated to dryness (Note 7), yielding approximately 16 g. of crude product.

B. *Tridehydro*[18]*annulene*. The dark brown residue from Part A and 800 ml. of benzene (Note 10) are added to a 2-l., round-bottomed flask fitted with a reflux condenser and a calcium chloride drying tube. The solid dissolves on heating to reflux, then the solution is allowed to cool briefly. The condenser is removed, and 800 ml. of a saturated solution of potassium *tert*-butoxide in *tert*-butyl alcohol (Note 11) and (Note 12) is rapidly added (Note 13). After the resulting solution is heated to reflux for 30 minutes, the hot mixture is transferred to the original 12-l. reaction vessel (Note 14), which contains approximately 2 l. of ice, and 1.5 l. of ether is added. The resulting mixture is stirred well then allowed to stand for a few minutes. The incompletely separated phases, in which is suspended a large amount of black solid, are filtered through a 25-cm. Büchner funnel. Whenever the filtration becomes slow, the black material on the filter paper is washed with ether, and the paper is replaced. The organic layer of the filtrate is separated, washed three times with 500-ml. portions of water, dried for 2 hours over *ca.* 100 g. of anhydrous magnesium sulfate (Note 9), filtered, and evaporated to dryness (Note 7) and (Note 15). The red-brown viscous residue is dissolved in 60 ml. of benzene (Note 10) and chromatographed on alumina.

One liter of 95:5 (v/v) pentane–ether (Note 16) is poured into a closed chromatography column (100 × 4.5 cm.), the bottom of which is protected by a small plug of cotton wool.

One kilogram of alumina (Note 17) is added in portions, with slow rotation by hand. The stopcock is opened, and the level of the supernatant liquid is allowed to fall to the top of the alumina. The benzene solution is now added with a long pipette and is allowed to seep in. The column is developed first with 1 l. of 95:5 (v/v) pentane–ether in order to wash out the benzene, then with 80:20 (v/v) pentane–ether. Two bands are observable on the column. The faster moving, light brown band consists of tridehydro[18]annulene (Note 18) and the slower moving, dark brown band consists of tetradehydro[24]annulene. When the first band is approximately 15 cm. from the bottom of the column, after approximately 4–6 l. of solvent have been eluted, 150-ml. fractions are collected, and the electronic spectrum of each fraction is determined. As soon as the maxima at 385 and 400 mm. characteristic of tridehydro[18]annulene appear (Note 19), the fractions are combined ("mixed fractions") until the first band is approximately 1 cm. from the bottom of the column. Essentially "pure" tridehydro[18]annulene (Note 18) is now eluted, and this material is collected until the second band is approximately 5 cm. from the bottom of the column. Smaller fractions (150 ml. each) are now collected again; the electronic spectrum of each fraction is determined, and those still showing maxima at 385 and 400 nm. are combined with the previously mentioned "mixed fractions." If required, the tetradehydro [24]annulene suitable for conversion to [24]annulene[2] can then be eluted with pentane–ether (70:30 to 50:50).

The electronic spectrum of the fractions containing the "pure" tridehydro[18]annulene exhibits the strongest absorption maximum (in benzene) at 342 nm. (ε 155,000)[3] and the spectroscopic yield, based on the molar extinction coefficient, is 1.17 g. (2.40% from 1,5-hexadiyne). The yield of tridehydro[18]annulene in the "mixed fractions," based on the 342 nm. maximum, is 0.27 g. (0.55%). The tridehydro[18]annulene is best stored in solution in the refrigerator.

C. [18]*Annulene*. In a 300-ml., conical flask fitted with a side arm (with a closed stopcock) and a 3.5-cm. Teflon®-coated magnetic stirring bar is placed 1 g. of a 10% palladium-on-calcium carbonate catalyst (Note 20) and 30 ml. of benzene (Note 10). The flask is attached to an atmospheric pressure hydrogenation apparatus, and the air in the system is replaced by hydrogen by evacuating the flask and refilling with hydrogen three times. The catalyst suspension is stirred until no more gas is absorbed. One-third (390 mg., determined spectroscopically) of the "pure" tridehydro[18]annulene solution described in Part B is evaporated to dryness (Note 7), and the resulting brown crystalline residue is dissolved in 30 ml. of benzene (Note 10). This solution is added to the hydrogenation flask through the side arm without stirring. The mixture is now stirred under a hydrogen atmosphere as rapidly as possible (*ca.* 600 r.p.m.) (Note 21) until 207 ml. (4.9 molar equivalents) of gas (22°, 740 mm.) are absorbed over *ca.* 5 minutes. The mixture is filtered through a sintered glass funnel, and the catalyst is washed with three 20-ml. portions of benzene.

This hydrogenation experiment is repeated twice with the remaining two-thirds of the "pure" tridehydro[18]annulene solution, and the combined filtrates from the three hydrogenations are evaporated to approximately 30 ml. (Note 7). The solution is then transferred with a pipette to a test tube (10 × 3 cm.) and concentrated to approximately 15 ml. at 40° with a stream of nitrogen. The dark green solution is diluted with 20 ml. of ether

and cooled in an ice bath for 30 minutes. The resulting red-brown crystals of [18]annulene are collected by filtration on a sintered glass funnel and washed with approximately 3 ml. of cold (–20°) ether. After drying in air for a few minutes this material weighs 114 mg. A second crop weighing 42 mg. is obtained by evaporation of the mother liquors to dryness (Note 7), followed by crystallization from 6 ml. of benzene and 20 ml. of ether. Both crops give a single spot on TLC (Note 22).

The [18]annulene mother liquors contain 181 mg. of unchanged tridehydro[18]annulene, as determined by the electronic spectrum (see Part B). They are combined with the "mixed fractions" described in Part B (containing 270 mg. of tridehydro[18]annulene), and the resulting solution is evaporated to dryness (Note 7). The residue is dissolved in 30 ml. of benzene and stirred with hydrogen and 1.0 g. of a 10% palladium-on-calcium carbonate catalyst (Note 20), as before, until 216 ml. (4.4 molar equivalents) of hydrogen (20°, 740 mm.) are absorbed. The catalyst is removed, and the filtrate is concentrated to approximately 6 ml., as described previously. After the addition of 20 ml. of ether and cooling in an ice bath, 112 mg. of [18]annulene is collected by filtration (Note 23). The purity of the product is confirmed by TLC (Note 22). The total yield of [18]annulene is 268 mg. (0.54% overall from 1,5-hexadiyne, (Note 24).

[18]Annulene is best stored in benzene–ether solution in the refrigerator. The crystals can also be kept for some time in the refrigerator, small crystals being less stable than large ones.[2] Material that has decomposed to some extent may be purified as follows. The substance (300 mg.) is broken up with a spatula and heated with 30 ml. of benzene, and the insoluble material is removed by filtration. The filtrate is poured onto a chromatography column (20 × 1.8 cm.), prepared with 35 g. of alumina (Note 17) and benzene. The column is washed with benzene until the eluate is colorless. Polymeric material is retained at the top of the column. The eluent is concentrated to approximately 6 ml., diluted with 20 ml. of ether, and cooled in an ice–salt bath. The resulting crystals of [18]annulene are collected on a sintered glass funnel, washed with 3 ml. of cold (–20°) ether, and dried in air for a few minutes.

2. Notes

1. The submitters used an ordinary 10-l., three-necked, round-bottomed flask.
2. A stirrer with one 11-cm., Teflon® blade was employed by the checkers. The submitters used a stirrer with two 7.5-cm. paddles, 9 cm. apart.
3. Copper(II) acetate monohydrate A. R. available from Fisons Scientific Apparatus Ltd. (Loughborough, England) was employed by the submitters. The checkers used both Baker Analytical Reagent and Fisher A.C.S. certified copper(II) acetate monohydrate. Small portions were finely ground with a mortar and pestle.
4. Vigorous stirring is important, since the yield of product appears to be reduced if the mixture is not stirred well.[4] The checkers used rates of 530–560 r.p.m.
5. 1,5-Hexadiyne was obtained from Farchan Research Laboratories and was distilled at atmospheric pressure (b.p. 84–85°) before use. It can be prepared as described by Raphael and Sondheimer.[5]
6. The submitters employed pyridine from BDH Chemicals Ltd. (Poole, England)

that was dried over solid potassium hydroxide for 24 hours, then distilled under slightly reduced pressure. The checkers used a similarly treated product.

7. All evaporations, unless otherwise stated, were carried out with a rotary evaporator under reduced pressure (water pump) in a water bath kept at about 40°. The checkers' water bath was maintained at 44–50°, and the evaporation required 4–5 hours rather than the 2 hours found by the submitters.

8. The submitters used a 10-l. separatory funnel.

9. Magnesium sulfate ("dried") from BDH Chemicals Ltd. (Poole, England) was used by the submitters. The checkers used anhydrous magnesium sulfate available from Fisher Scientific Company.

10. Benzene A. R. from Fisons Scientific Apparatus Ltd. (Loughborough, England) was employed by the submitters, and Fisher reagent grade benzene was used by the checkers.

11. The solution was obtained from 44 g. of potassium (Fisons Scientific Apparatus Ltd., Loughborough, England, submitters; Fisher Scientific Company, checkers) and 1 l. of *tert*-butyl alcohol (Note 12) by boiling under reflux under nitrogen, in the apparatus described by Vogel,[6] until all the metal had dissolved. The solution is kept well stoppered. If crystals of potassium *tert*-butoxide separate, they are dissolved by gentle heating before use.

12. *tert*-Butyl alcohol from May & Baker Ltd. of Dagenham, England, was dried by refluxing 1 l. of the alcohol with approximately 40 g. of sodium wire until about two-thirds of the metal had dissolved, and recovering the alcohol by distillation (see note 2.htm in Reference [4]). The checkers used *tert*-butyl alcohol available from Fisher Scientific Company and recommend conducting this purification on twofold scale.

13. An exothermic reaction was observed at this point. Too rapid addition of the *tert*-butoxide solution to the benzene solution will lead to loss of product by frothing.

14. The submitters used a 10-l. separatory funnel and shook the mixture after addition to the ice and ether.

15. It is important that all volatile solvents are removed, particularly *tert*-butyl alcohol, since its presence will interfere with the subsequent chromatography procedure. The checkers obtained approximately 9.0 g. of crude material.

16. The submitters used "pentane" petroleum spirit (b.p. 25–40°) available from Hopkin & Williams Ltd., Hadwell Heath, England, and anhydrous ether available from May & Baker Ltd., Dagenham, England. Both solvents were distilled over solid potassium hydroxide before use. The checkers purchased pentane from Phillips Petroleum Company and distilled it over solid potassium hydroxide. Anhydrous ether supplied by Mallinckrodt Chemical Works was used without further purification.

17. Aluminum oxide (neutral, activity grade I) available from M. Woelm, Eschwege, Germany, was deactivated by the addition of 7 ml. of water to 1 kg. of the adsorbent before use.

18. "Tridehydro[18]annulene" here and in the sequel refers to the symmetrical isomer shown in the formula, admixed with smaller quantities of an unsymmetrical isomer and tetradehydro[18]annulene.[7] These can be separated by chromatography on alumina coated with 20% silver nitrate, but this is unnecessary for the synthesis

of [18]annulene, since all three substances give this annulene on catalytic hydrogenation.[7]

19. For the full electronic spectra of tridehydro[18]annulene and tetradehydro[24]annulene in isoöctane, see reference [3].

20. The submitters used 10% palladium-on-calcium carbonate available from Fluka AG, Buchs, Switzerland. The checkers prepared the catalyst in a manner similar to that described by Busch and Stöve.[8] To a solution of calcium chloride (5.1 g.) in 60 ml. of water was added 4.8 g. of sodium carbonate. The precipitate was filtered, washed thoroughly with water, and then suspended in 30 ml. of water. To this calcium carbonate suspension was added with stirring a solution of 0.833 g. of palladium chloride in a few drops of 6 *N* hydrochloric acid. The catalyst mixture was then filtered through a sintered glass funnel, and the solid was washed with water until the chloride test (silver nitrate) became negative. After being washed with ethanol and ether, the catalyst was dried under reduced pressure.

21. Vigorous stirring is essential, since the yield of [18]annulene is reduced considerably if the mixture is stirred more slowly.[9]

22. TLC was performed on silica gel GF_{254} plates supplied by E. Merck AG, Darmstadt, Germany, using (92:4:4) pentane–cyclohexane–benzene. The electronic spectra in benzene were essentially identical to those previously reported,[2] and exhibit absorption maxima at 378 (ε 270,000), 414 (ε 8,600), 428 (6,700), and 455 nm. (26,200). ^{1}H NMR spectra of [18]annulene (tetrahydrofuran-d_8, vacuum-sealed) are temperature-dependent and show a singlet at 5.45 p.p.m. at 120° and two multiplets at 9.25 (12*H*) and –2.9 p.p.m. (6*H*) at –60°. The latter two signals merge just above room temperature.[10] The checkers observed the similar temperature dependence of ^{13}C NMR (tetrahydrofuran-d_8, 22.6 MHz) of the [18]annulene. Thus, proton-decoupled spectra show a singlet at 126 p.p.m. at 60° and two singlets at 128 and 121 p.p.m. at –70°. The rapid processes exchanging the inner and outer nuclei (both proton and ^{13}C) in solution are responsible for the above spectral behavior.

23. The submitters reported in their original procedure that some additional amounts of [18]annulene and tridehydro[18]annulene were obtained by chromatography of the mother liquors.

24. The yields described in Parts B and C are the average values of two runs performed by the checkers, and both runs proceeded with virtually identical results at every stage. The submitters obtained a 0.63% overall yield of [18]annulene from 1,5-hexadiyne.

3. Discussion

Only two general methods have been developed for the synthesis of the macrocyclic annulenes.[11] The first of these, developed by Sondheimer and co-workers, involves the oxidative coupling of a suitable terminal diacetylene to a macrocyclic polyacetylene of required ring size, using, typically, copper(II) acetate in pyridine. The cyclic compound is then transformed to a dehydroannulene, usually by prototropic rearrangement effected by potassium *tert*-butoxide. Finally, partial catalytic hydrogenation of the triple bonds to double bonds leads to the annulene.

The presently described procedure for the synthesis of [18]annulene, although the overall yield is low by the standard normally set for *Organic Syntheses,* illustrates the above general route leading to the theoretically important macrocyclic annulenes, and in this way [14]-, [16]-, [18]-, [20]-, [22]-, and [24]annulenes have been prepared in pure crystalline form.

[18]Annulene was the first macrocyclic annulene containing (4*n* + 2) π-electrons to be synthesized. The compound is of considerable interest, since it is the type of annulene that was predicted to be aromatic by Hückel.[12] It proved to be aromatic in practice, as evidenced from the ^{1}H NMR spectrum,[10,13] the X-ray crystallographic analysis,[14] and the fact that electrophilic substitution reactions could be effected.[15]

The method of synthesis is essentially that described by Sondheimer and Wolovsky[3] (preparation of tridehydro[18]annulene) and by Sondheimer, Wolovsky, and Amiel[2] (hydrogenation of tridehydro[18]annulene to [18]annulene). It has been simplified, since [18]annulene is now obtained from tridehydro[18]annulene without chromatography, and the whole procedure involves only one chromatographic separation. [18]Annulene has also been obtained by Figeys and Gelbcke[16] in 0.42% overall yield by a six-step sequence from propargyl alcohol via propargyl aldehyde, *meso*-1,5-hexadiyne-3,4-diol, *meso*-1,5-hexadiyne-3,4-diol ditosylate, *cis*-3-hexene-1,5-diyne, and 1,3,7,9,13,15-hexadehydro [18] annulene.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 251

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alumina

silica gel

1,3,7,9,13,15-hexadehydro [18]annulene

Hexadehydro[18]annulene

Tridehydro[18]annulene

tetradehydro[24]annulene

palladium-on-calcium carbonate

tetradehydro[18]annulene

ethanol (64-17-5)

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether, diethyl ether (60-29-7)

hydrogen (1333-74-0)

silver nitrate (7761-88-8)

sodium carbonate (497-19-8)

nitrogen (7727-37-9)

cyclohexane (110-82-7)

calcium carbonate (471-34-1)

pyridine (110-86-1)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

potassium (7440-09-7)

Copper(II) acetate (142-71-2)

Pentane (109-66-0)

palladium chloride

magnesium sulfate (7487-88-9)

aluminum oxide (1344-28-1)

copper(II) acetate monohydrate (6046-93-1)

tert-butyl alcohol (75-65-0)

propargyl aldehyde (624-67-9)

propargyl alcohol (107-19-7)

isooctane (592-27-8)

[18]Annulene, 1,3,5,7,9,11,13,15,17-Cyclooctadecanonaene (2040-73-5)

1,5-hexadiyne (628-16-0)

[24]annulene

potassium tert-butoxide (865-47-4)

tert-butoxide

meso-1,5-hexadiyne-3,4-diol

meso-1,5-hexadiyne-3,4-diol ditosylate

cis-3-hexene-1,5-diyne

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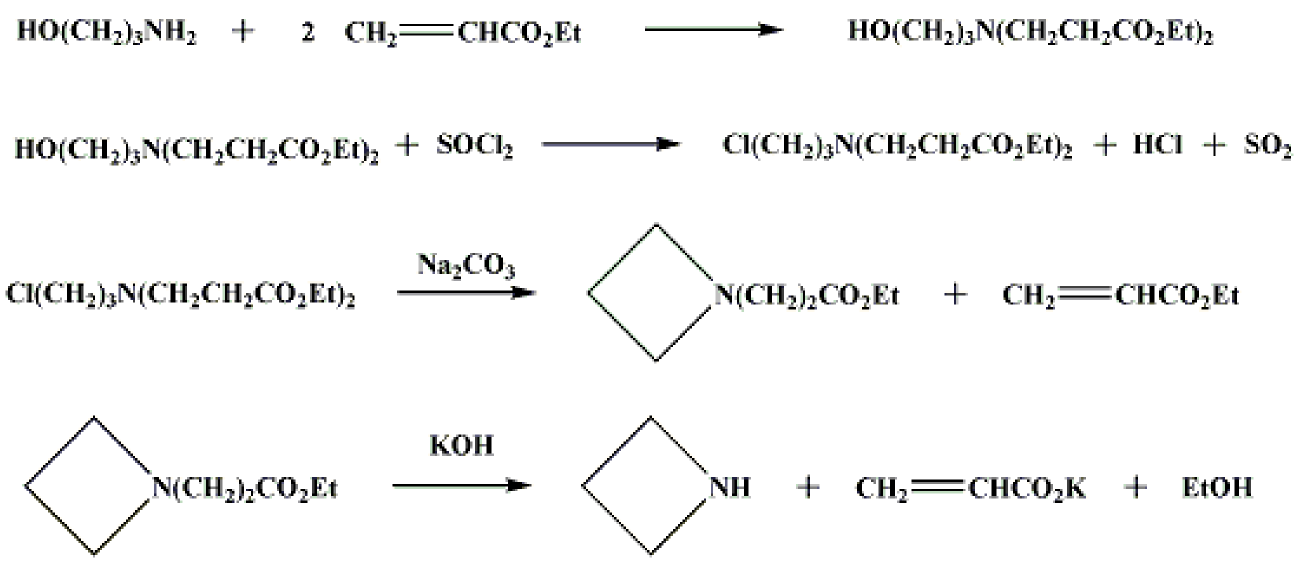
Organic Syntheses, CV 6, 75

AZETIDINE



Submitted by Donald H. Wadsworth[1]
Checked by F. Thoenen, E. Vogel, R. Hobi, and A. Eschenmoser.

1. Procedure

A. *Ethyl 3-(1-azetidinyl)propionate*. A solution of 150 g. (2.00 moles) of 3-amino-1-propanol in 500 g. (5.00 moles) of ethyl acrylate (Note 1) is refluxed for 2 hours in a 1-l., round-bottomed flask. Subsequent vacuum removal of the excess ethyl acrylate at steam temperature yields 548 g.. (99%) of crude diethyl 3-*N*-(3-hydroxypropyl)iminodipropionate. A stirred, cooled solution of this material (548 g.) in 1 l. of chloroform and 10 ml. of *N*,*N*-dimethylformamide is treated dropwise with 262 g. 2.20 moles) of thionyl chloride. By cooling with an ice bath and controlling the addition rate, the reaction temperature is maintained below 40° (Note 2). After the addition is complete, the reaction mixture is stirred for 30 minutes at room temperature and poured slowly into a slurry of 340 g. of sodium hydrogen carbonate in 1 l. of water (Note 3). The organic layer is separated (Note 4) and dried over sodium sulfate, and the solvent is removed under reduced pressure, below 50°, yielding 570 g. (97%) of crude diethyl 3-*N*-(3-chloropropyl)iminodipropionate. A mixture of 100 g. of this crude material, 200 g. of anhydrous, powdered sodium carbonate (Note 5), and 10.0 g. of pentaerythritol (Note 6) in 200 ml. of diethyl phthalate is placed in a 500-ml., round-bottomed flask fitted with a vacuum-distillation head and an effective stirrer. The system is evacuated through a trap of sufficient capacity to contain 50 ml. of liquid, and the product is distilled by heating the stirred suspension with a heating mantle at 10–15 mm. By proper adjustment of the heat source, the distillation temperature is maintained below 150°, minimizing codistillation of diethyl phthalate. The distillate is collected until the head temperature cannot be kept below 150°. Redistillation of the resulting crude product through a 4-in. Vigreux column yields 34.0 g. (57–68%) of ethyl 3-(1-azetidinyl)propionate, b.p. 86–87° (12 mm.), 99% pure by GC (Note 7).

B. *Azetidine*. A stirred mixture of 38 g. (0.68 mole) of potassium hydroxide pellets in 100 ml. of white mineral oil (Note 8) is heated to 140–150° in a four-necked, 500-ml., round-bottomed flask, fitted with an air-driven Hershberg stirrer, a thermometer, a dropping funnel, and a 6-in. Vigreux column fitted with a vacuum-distillation head. The flask is removed from the heat source, and 50 g. (0.32 mole) of purified ethyl 3-(1-azetidinyl)propionate is added dropwise at a rate sufficient to maintain the reaction temperature at 150° (Note 9). After addition is complete, the reaction mixture is heated to

200° at 50 mm. to remove all traces of ethanol (Note 10). The flask is fitted with a distillation head and a nitrogen bubbler, and the distillation is resumed at atmospheric pressure until azetidine distills (210° maximum pot temperature, (Note 11)). The resulting product (19.6 g., 85% purity) is dried over potassium hydroxide and redistilled through a short Vigreux column yielding 14.5–15.8 g. (80–87%) of purified azetidine, b.p. 62–63° (Note 12).

2. Notes

1. Eastman Organic Chemicals, practical grade, 3-amino-1-propanol, and ethyl acrylate were used. The checkers used 3-amino-1-propanol, Fluka purum.
2. If the reaction temperature is not controlled, a tarry by-product is formed. By dissolving the crude aminochloride in petroleum ether, the impurity is separated as an insoluble tar.
3. Considerable foaming occurs during neutralization, which is best accomplished in a 4-l. beaker with rapid stirring.
4. Any excess of insoluble salt should be filtered from the reaction mixture before the chloroform layer is separated. The checkers observed no insoluble salt at this point.
5. Baker and Adamson reagent grade sodium carbonate powder was used. The checkers found that the use of crystalline anhydrous sodium carbonate lowered the yield.
6. The presence of some hydroxylic material appears to be necessary to ensure reproducibility of this step, and the submitters have found empirically that pentaerythritol is very effective for this purpose.
7. The crude distillate can be used directly without intermediate isolation of ethyl 3-(1-azetidinyl)propionate to give a 50% yield of azetidine, assuming that all of the crude material was ethyl 3-(1-azetidinyl)propionate and running the reaction as described for the pure material.
8. Fisher Scientific Company Paraffin Oil, N.F., Saybolt Viscosity 125/135 and Mobil Oil Corp. S/V Industrial White Oil Number 320, Saybolt Viscosity 200/210 gave comparable results.
9. If the reaction does not start immediately, 5 ml. of ethanol may be added as an initiator.
10. Any ethanol that is not removed will contaminate the product. Although careful distillation will separate azetidine and ethanol, a considerable yield loss is encountered.
11. The submitters used a higher pot temperature (230–275°). The checkers, however, recommend the lower temperature to minimize losses of azetidine.
12. ^{1}H NMR ($CDCl_3$), δ 1.85 (s, 1H, N*H*), 2.0–2.6 (m, 2H, CH_2), 3.68 (t, *J* = 8 Hz., 2CH_2).

3. Discussion

Azetidine has been prepared by the following procedures: cyclization of 3-bromopropylamine with potassium hydroxide (low yield);[2] cleavage of 1-*p*-toluenesulfonylazetidine with sodium and refluxing 1-pentanol (85–100% yield)[3,4] or sodium and liquid ammonia (30% yield);[5] hydrogenolysis of 1-benzylazetidine (50%);[6] cyclization of diethyl 3-*N*-(3-chloropropyl)iminodipropenoate with sodium carbonate without solvent (60–70% yield).[7] A review of methods for preparing azetidine has been published.[8]

All other preparations of azetidine suffer either from low yields, arduous preparative procedures, or cumbersome purification operations. In this procedure, cyclization is accomplished in relatively concentrated solutions, and azetidine is obtained directly from the cleavage reaction in a state sufficiently pure for most applications. In addition, stable ethyl 3-(1-azetidinyl)propionate can be prepared in advance, and the air-sensitive azetidine can be formed readily as needed with a one-step procedure.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

diethyl 3-N-(3-hydroxypropyl)iminodipropionate

diethyl 3-N-(3-chloropropyl)iminodipropionate

diethyl 3-N-(3-chloropropyl)iminodipropenoate

ethanol (64-17-5)

ammonia (7664-41-7)

hydrogen (1333-74-0)

thionyl chloride (7719-09-7)

chloroform (67-66-3)

sodium hydrogen carbonate (144-55-8)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

ethyl acrylate (140-88-5)

Pentaerythritol (115-77-5)

1-pentanol (71-41-0)

N,N-dimethylformamide (68-12-2)

diethyl phthalate (84-66-2)

Azetidine (503-29-7)

3-amino-1-propanol (156-87-6)

ethyl 3-(1-azetidinyl)propionate (7730-42-9)

3-bromopropylamine (5003-71-4)

1-benzylazetidine

1-p-toluenesulfonylazetidine (7730-45-2)

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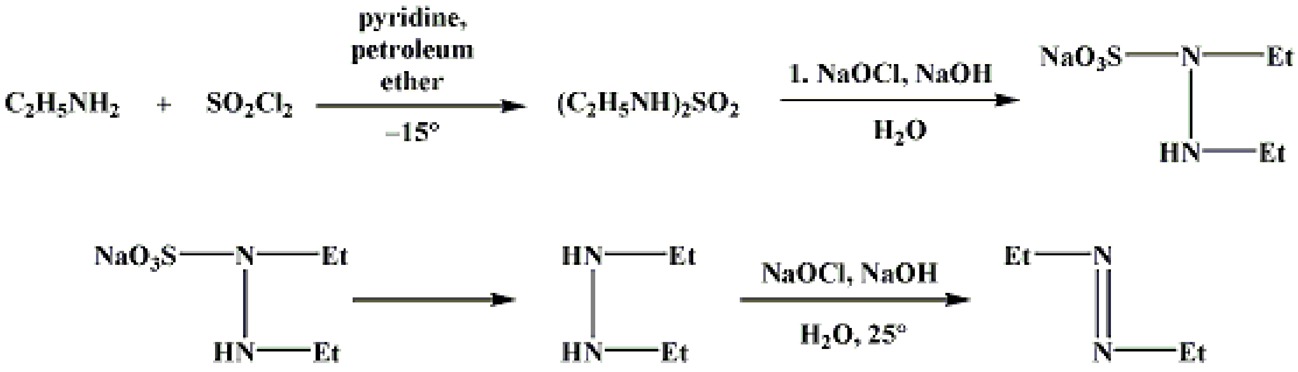
Organic Syntheses, CV 6, 78

AZOETHANE

[Diazene, diethyl]



Submitted by Roland Ohme, Helmut Preuschhof, and Hans-Ulrich Heyne[1].
Checked by Harvey W. Taylor and Henry E. Baumgarten.

1. Procedure

Caution! Azoalkanes have been reported to have carcinogenic properties.[2,3] Care should be taken to avoid inhalation of these substances and contact of them with the skin. It is advisable to prepare and handle these compounds in a good fume hood.

A. *N,N'-Diethylsulfamide*. A dry, 2-l., three-necked, round-bottomed flask fitted with a mechanical stirrer, a reflux condenser, a thermometer, and a dropping funnel, and protected from atmospheric moisture with calcium chloride drying tubes is charged with 500 ml. of petroleum ether, 100 g. (2.20 moles) of ethylamine, and 140 g. (1.76 moles) of pyridine (Note 1). The stirred mixture is cooled in an acetone–dry ice bath to –30° to –15°; a solution of 120 g. (0.889 mole) of sulfuryl chloride in 220 ml. of petroleum ether is added, dropwise and with stirring, to the reaction flask at such a rate that the temperature remains below –15°. After addition is complete, the reaction mixture is stirred at room temperature for one hour. The petroleum ether layer is separated and discarded. The dark semisolid residue is made acidic by addition of 6 *M* hydrochloric acid, and the acidic mixture is heated under reflux for 2 hours (Note 2). The resulting solution is extracted with diethyl ether in a continuous extractor (Note 3) until all of the diethylsulfamide has dissolved. The ether is evaporated using a rotary evaporator, yielding 58–61 g.. (44–45%) of crude *N,N'*-diethylsulfamide, m.p. 65–67°, (Note 4) which is of sufficient purity for use in the next step.

B. *Azoethane*. A 3-l., three-necked, round-bottomed flask fitted with a mechanical stirrer, a reflux condenser, a thermometer, and a dropping funnel is charged with 500 ml. of an aqueous 2 *M* solution of sodium hydroxide and 152 g. (1.00 mole) of *N,N'*-diethylsulfamide, which is brought into solution by warming the reaction flask. The reaction flask is cooled in a cold water bath before 715 ml. (1.0 mole) of aqueous 1.4 *M* sodium hypochlorite (Note 5) is added dropwise with stirring. After addition is complete, the reaction mixture is stirred for 15 minutes at room temperature. The mixture is brought to pH 1 by addition of 6 *M* hydrochloric acid and stirred for an additional 30 minutes at 60° (Note 6). The mixture is cooled to room temperature, then is brought to pH 14 by addition of aqueous 2 *M* sodium hydroxide (Note 7). Addition of 715 ml. (1.0 mole) of aqueous 1.4 *M* sodium hypochlorite solution causes the separation of azoethane as an oil, having a fruitlike odor. The mixture is extracted with three 100-ml. portions of toluene (Note 8). The combined extracts are dried over anhydrous sodium sulfate and distilled through a 50-cm. packed column, yielding 44–46 g. (51–54%) of azoethane, b.p. 58–59°,

n_D^{20} 1.3861 (Note 9).

2. Notes

1. The submitters dried the ethylamine and pyridine by distillation over potassium hydroxide pellets and used 600 ml. of petroleum ether, 113 g. (2.50 moles) of ethylamine, and 158 g. (2.00 moles) of pyridine to which was added 135 g. (1.00 mole) of sulfuryl chloride in 250 ml. of petroleum ether. In the United States ethylamine is sold in 100-g. quantities in sealed-glass vials (Eastman Organic Chemicals) or as the compressed gas in cylinders (Matheson Gas Products). The checkers used the contents of a freshly opened vial (without distillation) for each run, as a matter of convenience, and used either pentane or petroleum ether (b.p. 38–51°). Note that step B requires the product from at least two [submitters' scale *and yield* (Note 4)] or three (checkers' scale) step A runs. Step B can be run at half scale with the same percentage yield.

2. The purpose of this step is to hydrolyze any alkyl imido compound that may have formed from the further reaction of the sulfamide.[4]

3. A convenient continuous extractor has been described earlier in this series.[5]

4. After purification by dissolving the crude product in ether and precipitating with petroleum ether, *N,N'*-diethylsulfamide is obtained as shiny, white leaflets, m.p. 67°. The submitters reported a 54% yield of the purified product.

Under identical conditions using 78 g. (2.5 mole) of methylamine, 71 g. (57%) of *N,N'*-dimethylsulfamide, m.p. 76°, may be obtained as fine, white needles after recrystallization from benzene.

For sulfamides with larger alkyl groups (C_3 to C_6) the following procedure is preferred. A solution of 316 g. (4.00 moles) of pyridine in 400 ml. of chloroform is added dropwise, with cooling to –10° to –5°, to a stirred mixture of 135 g. (1.00 mole) of sulfuryl chloride and 500 ml. of chloroform. Maintaining a temperature of –5° to 0°, a solution of 2.5 moles of alkylamine in 600 ml. of chloroform is added to the reaction. After addition is complete the mixture is stirred for 30 minutes at room temperature, evaporated under reduced pressure to a thick brown liquid, and treated with 2 *M* hydrochloric acid until the pyridine dissolves. Cooling the acidic solution, the crystalline sulfamide precipitates and is filtered. Any dissolved sulfamide may be recovered by extraction of the filtrate with ether. The crude product may be purified by recrystallization from 50% ethanol.

The pyridine used in the submitters' procedures apparently reacts with the sulfuryl chloride to form an intermediate, quaternary pyridinium complex which undergoes aminolysis, yielding the sulfamide.[6] However, in many instances the pyridine may be replaced by an equivalent quantity of the primary alkylamine being used.[4,7] Using this variation the checkers obtained a 78% yield of *N,N'*-dicyclohexylsulfamide (compare with Table I). Moreover, in the reaction of 4-aminospiro (cyclohexane-1,9'-fluorene) with sulfuryl chloride no sulfamide could be isolated from reactions run in the presence of pyridine (or triethylamine); however, a 54% (purified) yield of *N,N'*-dispiro (cyclohexane-1,9'-fluorene)-4-ylsulfamide was obtained when 2.7 *equivalents* of the amine (relative to sulfuryl chloride) were used. Probably the failure of the mixed pyridine-alkylamine technique was the result of combined bulk of the pyridinium complex and the amine.

TABLE I
PREPARATION OF AZOALKANES

R	$RNHSO_2NHR$		R-N=N-R	
	m.p.	Yield, %	b.p.	Yield, %

n-C_3H_7	118°	69	113–115°	54
n-C_4H_9	126°	66	59–60° (18 mm.)	54
tert-C_4H_9	140–142°	68	109–110°	84
cyclo-C_6H_{11}	154°	59	m.p. 33–34°	80
4-NO_2-C_6H_4	197°	58	m.p. 216°	31

5. The sodium hypochlorite solution was prepared by passing chlorine, with stirring and cooling to 0–5°, into 1.5 l. of aqueous 1.4 *M* sodium hydroxide solution.
In some small-scale preparations of this type the checkers used commercial household bleach (Chlorox®, 5.25% NaOCl) and followed the course of the reaction by TLC. The yields appear to be somewhat lower than those obtained with sodium hypochlorite prepared as described above. The obvious attractive alternative, preparation of potassium hypochlorite as described elsewhere in this series,[8] apparently has not been tried.
6. In the preparation of 2,2'-azoisobutane and azocyclohexane the acid hydrolysis step is not necessary and the two moles of sodium hypochlorite may be added in one step.
7. In the preparation of azomethane a gas-inlet tube is used to pass nitrogen slowly through the reaction mixture, during the second oxidation stage while the temperature is raised to 60°. The reflux condenser is fitted with a drying tube filled with potassium hydroxide pellets connected via rubber hose to two dry ice-cooled cold traps connected in series and terminated with a second drying tube filled with potassium hydroxide pellets. The azomethane collects in the cold traps. Redistillation gives a 39% yield of azomethane, b.p. 1°.
8. For the homologous azoalkanes ether, pentane, or petroleum ether may be used for extraction. The extraction solvent may be added before the addition of hypochlorite.[6]
9. The checkers used a 60-cm. Vigreux column. Their product gave the following ^{1}H NMR spectrum ($CDCl_3$): δ 1.17 (q, *J* = 7 Hz., 2H, CH_2), 3.77 (t, *J* = 7Hz., 3H, CH_3).

3. Discussion

Azoalkanes have been prepared by oxidation of *N,N'*-dialkylhydrazines with copper(II) chloride[9] or with yellow mercury(II) oxide.[10,11] The dialkyl hydrazines are obtained by alkylation of *N,N'*-diformylhydrazine and subsequent hydrolysis,[9] by reduction of the corresponding azine with lithium aluminum hydride,[11] or by catalytic hydrogenation of the azine over a platinum catalyst.[10]

The present procedure may be used for the preparation of azoalkanes with alkyl, cycloalkyl, or aromatic substituents (Table I). Azoalkanes have been used as radical sources for inducing of radical reactions (*e. g.*, polymerization). The present procedure may also be used for the preparation of *N,N'*-dialkylhydrazines.[6] For this purpose only one equivalent of sodium hypochlorite solution is employed and the reaction mixture is worked up after its addition (yields: 60–95%).

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

Diazene, diethyl

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether, diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

mercury(II) oxide (21908-53-2)

platinum (7440-06-4)

sulfuryl chloride (7791-25-5)

pyridine (110-86-1)

chlorine (7782-50-5)

potassium hydroxide (1310-58-3)

toluene (108-88-3)

copper(II) chloride (7758-89-6)

Pentane (109-66-0)

sodium hypochlorite (7681-52-9)

methylamine (74-89-5)

potassium hypochlorite

lithium aluminum hydride (16853-85-3)

triethylamine (121-44-8)

ethylamine (75-04-7)

Azoethane (38534-43-9)

diethylsulfamide

azocyclohexane

azomethane

N,N'-diformylhydrazine

N,N'-Diethylsulfamide (6104-21-8)

N,N'-dimethylsulfamide

N,N'-dicyclohexylsulfamide

4-aminospiro(cyclohexane-1,9'-fluorene)

N,N'-dispiro(cyclohexane-1,9'-fluorene)-4-ylsulfamide

2,2'-azoisobutane

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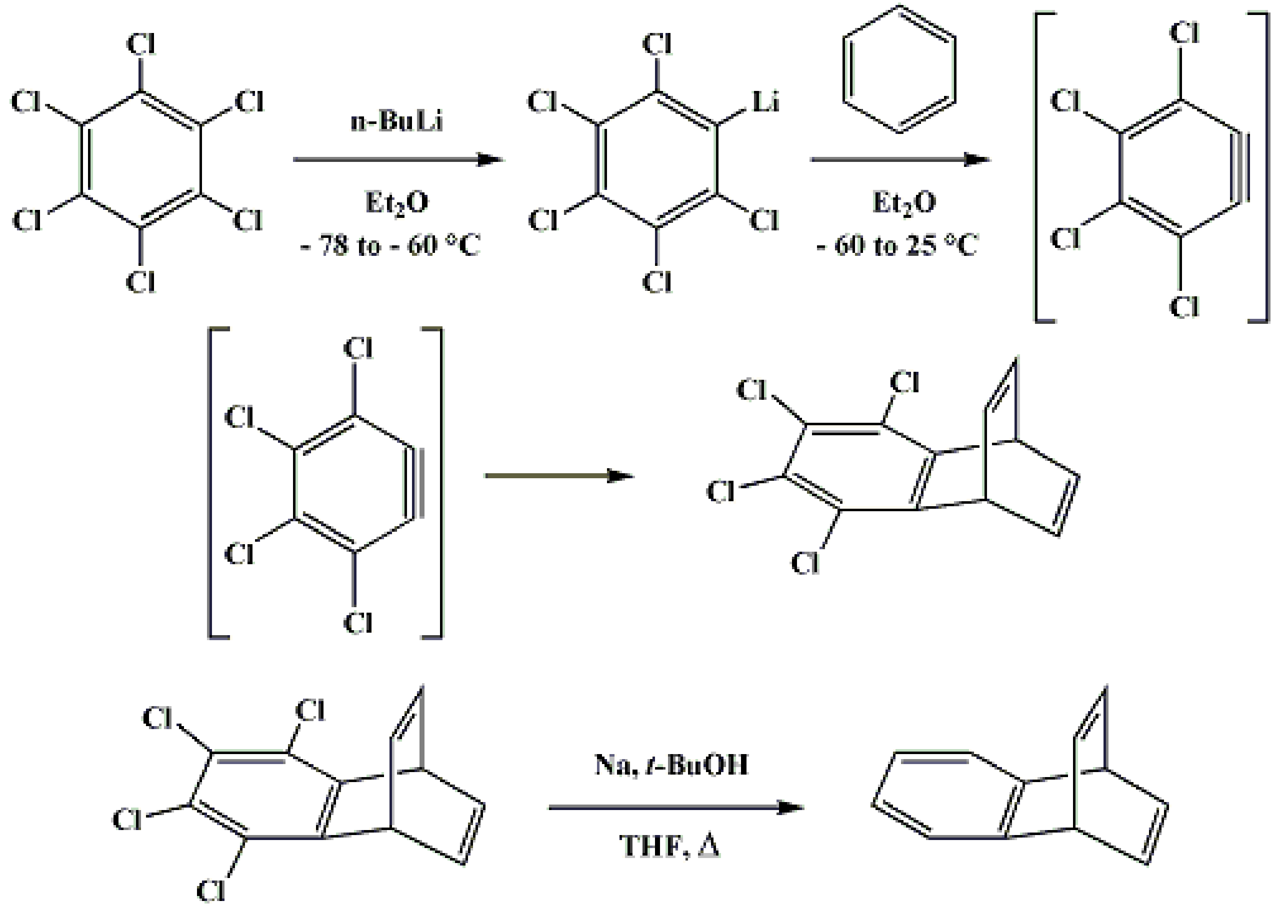
Organic Syntheses, CV 6, 82

DIELS-ALDER ADDITION OF PERCHLOROBENZYNE: BENZOBARRELENE

[1,4-Ethenonaphthalene, 1,4-dihydro]



Submitted by Neil J. Hales, Harry Heaney[1], John H. Hollinshead, and Pritpal Singh.
Checked by G. Crass, M. Pohmakotr, and D. Seebach.

1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A. *Tetrachlorobenzobarrelene*. A carefully dried, 5-l., three-necked, round-bottomed flask equipped with a large magnetic stirring bar, a low-temperature thermometer, a 500-ml., pressure-equalizing dropping funnel bearing a gas-inlet tube, and a Nujol bubbler (Note 1) is charged with 28.5 g. (0.100 mole) of hexachlorobenzene (Note 2). The apparatus is flushed with argon or nitrogen (Note 3) before 600 ml. of dry diethyl ether (Note 4) is added. The resulting suspension is stirred and cooled to –72° to –78° in a 4-l. acetone–dry ice bath. A solution of *n*-butyllithium (0.110 mole) in hexane (Note 5) is added over a 30-minute period such that the temperature does not exceed –70° (Note 6). The mixture is then allowed to

warm to –60° over an additional 1.5 hours. Four liters of dry, thiophene-free benzene (Note 4) is added to the pentachlorophenyllithium solution (Note 7) over a 1-hour interval, during which the temperature rises to *ca.* + 10° (Note 8). The mixture is allowed to warm slowly to room temperature over a period of at least 14 hours and then is heated at +30° for another 2 hours to ensure complete reaction (Note 9). A 10-g. portion of solid ammonium chloride is added, and 15 minutes later the contents of the flask are filtered through 20 g. of Celite. The volume of the filtrate is reduced to 75 ml. with a rotary evaporator, and 100 g. of alumina (Note 10) is added to the concentrate in a 250-ml. flask. The rotary evaporation is continued until the weight remains constant and a free-flowing consistency is attained. The material is placed on a column packed with 800 g. of alumina and eluted with low-boiling petroleum ether (Note 11). Fractions of *ca.* 200 ml. are collected and analyzed by GC or TLC ((Note 6)), with the appropriate fractions combined and evaporated, providing 16.9–17.5 g. (58–60%, (Note 12)) of essentially pure tetrachlorobenzobarrelene, m.p. 127–129° (Note 13).

B. *Benzobarrelene*. A dry, 1-l., three-necked, round-bottomed flask equipped with a magnetic stirring bar, a combined gas-inlet tube and rubber septum, a 500-ml., pressure-equalizing dropping funnel, and a reflux condenser connected to a Nujol bubbler is charged with 500 ml. of dry tetrahydrofuran (Note 14) and 17 g. (0.74 mole) of sodium wire having a diameter of *ca.* 0.5 mm. The mixture is stirred and heated at reflux under an atmosphere of argon or nitrogen while 50 ml. of freshly distilled *tert*-butyl alcohol is added. Immediately afterward a solution of 15 g. (0.051 mole) of tetrachlorobenzobarrelene in 200 ml. of tetrahydrofuran is added over a 15-minute period. After 4 hours under reflux (Note 15) the contents of the flask are cooled to room temperature and filtered through a plug of glass wool (Note 16) into a 2-l. beaker containing 50 ml. of methanol. After any remaining pieces of sodium have reacted with the methanol, 400 ml. of water is added, and the mixture is extracted with six 150-ml. portions of ether. The combined ether layers are washed with two 200-ml. portions of aqueous saturated sodium chloride, dried over magnesium sulfate, and evaporated with a rotary evaporator operated at water aspirator pressure and room temperature. The semicrystalline residue (7.3–8.1 g.) is mixed with 40 g. of alumina (Note 10) and swirled at room temperature under reduced pressure until it attains a free-flowing consistency. The material is then placed on a column packed with 600 g. of alumina and eluted with low-boiling petroleum ether (Note 11). Fractions of *ca.* 200 ml. are collected, evaporated, and assayed by GC (Note 15) and (Note 17). Combination of the appropriate fractions yields 5.9–6.8 g. (75–86%) of benzobarrelene, m.p. 62–64.5° (Note 18).

2. Notes

1. The dropping funnel must be arranged so that the drops fall directly into the solution and not onto the side of the flask. The checkers used a 4-l., four-necked flask equipped with a mechanical stirrer and a ground-glass stirring assembly, and carried out the reaction on four-fifths scale.
2. Technical-grade hexachlorobenzene was purchased by the submitters from BDH Chemicals, Ltd., and recrystallized twice from benzene: m.p. 227°. The submitters found that if the technical-grade material is used without purification, some insoluble material remains after the reaction with *n*-butyllithium, though the yield of tetrachlorobenzobarrelene is only slightly reduced. The checkers used 22.8 g. (0.0800 mole) of hexachlorobenzene of 98% purity, purchased as a fine powder from EGA-Chemie K. G., an affiliate of Aldrich Chemical Company, Inc., without further

purification.
3. The flushing operation was accomplished by replacing the bubbler with a stop-cock and alternately evacuating and filling the apparatus with inert gas three times. A slight outflow of inert gas should be maintained during all subsequent operations. When the flask is being cooled, it is necessary to increase the gas flow.
4. Dry ether and dry, thiophene-free benzene were prepared by the submitters according to procedures presented in reference [2].
5. *n*-Butyllithium as 1.5–3.0 *M* solutions in hexane is available from the following firms: Pfizer, Ltd., Sandwich, England; Metallgesellschaft, Frankfurt, Germany; Alfa Division, Ventron Corporation. The appropriate volume of the solution is transferred with a 50-ml. syringe to the dropping funnel with care being taken to exclude air. An excess of *n*-butyllithium above the 10% recommended here may lead to the formation of dilithiotetrachlorobenzene.
6. The reaction of *n*-butyllithium and hexachlorobenzene and, later, the formation of tetrachlorobenzobarrelene may be monitored by GC or TLC. Samples withdrawn from the reaction mixture with a syringe are injected into a small amount of water, and the organic layer is analyzed. GC was carried out by the submitters with flame ionization detection and 1.5 m. × 4 mm. (inside diameter) glass column packed with 3% silicone rubber (SE-30) supported on 80–100 mesh Gaschrom Q. With a column temperature of 150° and a nitrogen carrier gas flow rate of 45 ml. per minute, the retention times of pentachlorobenzene, hexachlorobenzene, and tetrachlorobenzobarrelene are *ca.* 2, 4, and 18 minutes, respectively. Normally trace amounts of hexachlorobenzene are still detectable at the end of the reaction with *n*-butyllithium. TLC was performed on silica gel with 5% ether in pentane as developing solvent. The R_f value of tetrachlorobenzobarrelene is less than that of chlorobenzenes.
7. A clear yellow solution is usually obtained at this stage; however, some suspended material may be present, particularly when technical grade hexachlorobenzene is used.
8. For proper temperature control the cooling bath should be free from excess amounts of dry ice. The benzene should be added in the following manner (volume of benzene added, period of addition, final temperature reached): 0.5 l., 15 minutes, *ca.* –20°; 0.5 l., 15 minutes, *ca.* –10°; 3.0 l., 30 minutes, *ca.* +10°.
9. The reaction is relatively slow at a laboratory temperature of 18–20° and may require as much as 40 hours to reach completion.
10. The submitters used Activity I (Brockmann) Camag alumina, which was purchased from Hopkins and Williams. The checkers used comparable material obtained from E. Merck, Darmstadt, Germany.
11. Low-boiling petroleum ether (b.p. 30–50° or 40–60°) was distilled from calcium chloride prior to use.
12. The submitters usually combined fractions 5–14 and obtained 18–19.5 g. (62–67%) of tetrachlorobenzobarrelene, m.p. 127–131°. The checkers, using a 3.5 cm. × 1 m. column for the chromatography, isolated 13.5–14 g. (58–60%) of product from fractions 10–25.
13. ^{1}H NMR ($CDCl_3$): δ (multiplicity, number of protons, assignment): 5.45 (m, 2H, bridgehead *H*), 6.95 (m, 4H, vinyl *H*). A melting point of 125° is reported in the literature.[3]
14. The tetrahydrofuran was freshly distilled from lithium aluminum hydride. For a warning regarding this method of purifying tetrahydrofuran, see *Org. Synth.*, **Coll. Vol. 5**, 976 (1973).

15. An aliquot may be removed at this stage and analyzed by either GC or TLC to ensure that the reaction is complete. Benzobarrelene has a retention time of *ca.* 5 minutes under the conditions stated in (Note 6), but with a column temperature of 104°. The completion of the reaction is also indicated by a purple coloration of the precipitated sodium chloride.

16. The glass wool removes the larger pieces of unreacted sodium and much of the purple sodium chloride.

17. The dimensions of the column used by the checkers were the same as those specified in (Note 12), and the product was obtained from fractions 10–20. The submitters evaporated the fractions with a rotary evaporator operated at water aspirator pressure and room temperature (*ca.* 20°); however, the checkers caution that the product sublimes very readily.

18. IR $cm.^{-1}$, strong peaks: 1460, 1325, 790, 750, 690, 660; ^1H NMR ($CDCl_3$): δ (multiplicity, number of protons, assignment): 4.9 (m, 2H, bridgehead *H*), 6.8–7.3 (m, 8H, aryl and vinyl *H*). The reported melting point is 65.5–66°.[4] From 20 g. of tetrachlorobenzobarrelene the submitters obtained 8.3–8.8 g. (79–83%) of benzobarrelene, m.p. 64–65°.

3. Discussion

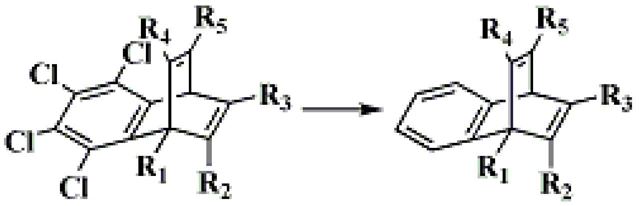
Although benzobarrelene has been used in a number of recent studies, the best available published synthesis[4] starts with the Diels-Alder reaction of β-naphthol and maleic anhydride, affording benzobarrelene in *ca.* 1% yield after five additional steps. Minor improvements allow small quantities of benzobarrelene to be prepared in an overall yield of *ca.* 10%.[5] The reaction of benzyne with benzene is relatively inefficient, giving benzobarrelene in *ca.* 2% yield.[6] When benzyne is generated by decomposition of benzenediazonium-2-carboxylate at high dilution in benzene, the yield of benzobarrelene is raised to 14%.[7] The reactions of benzyne with other aromatic substrates are equally inefficient.

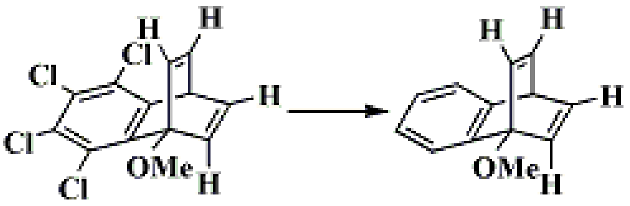
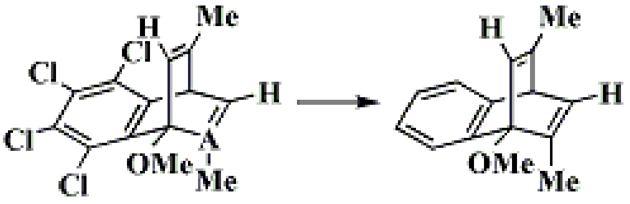
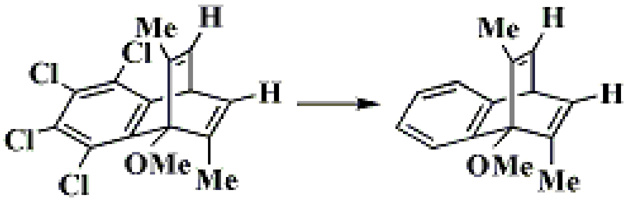
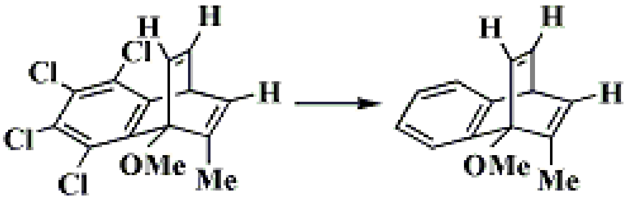
Tetrahalobenzynes, however, react with a variety of aromatic compounds to afford tetrahalobenzobarrelene derivatives in good yields, frequently in the range of 55 to 75%.[8] The dehalogenation of a variety of alkenyl chlorides with alkali metals in tetrahydrofuran containing *tert*-butyl alcohol[9] suggested this approach to the dechlorination of tetrachlorobenzobarrelenes.

The generation of pentachlorophenyllithium by the reaction of *n*-butyllithium with hexachlorobenzene has been reported previously by Rausch, Tibbetts, and Gordon.[10] The present procedure for the preparation of benzobarrelene is based on the submitters' previously published note.[11] By this method 10-g. quantities of benzobarrelene may be obtained in *ca.* 3 working days without the use of large-scale apparatus. The generality of the procedure is shown by the examples given in Table I.

TABLE I

PREPARATION OF SUBSTITUTED BENZOBARRELENES



Tetrachlorobenzobarrelenes	Yield of Benzobarrelenes (%)
R^1 = OMe; R^2 = R^3 = R^4 = R^5 = H 	100
R^1 = OMe; R^2 = R^5 = Me; R^3 = R^4 = H 	90
R^1 = OMe; R^2 = R^4 = Me; R^3 = R^5 = H 	95
R^1 = OMe; R^2 = Me; R^3 = R^4 = R^5 = H 	95

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alumina

petroleum ether

Tetrachlorobenzobarrelene

Benzobarrelene

Dry ether

calcium chloride (10043-52-4)

Benzene, benzyne (71-43-2)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

β-naphthol (135-19-3)

sodium (13966-32-0)

Pentane (109-66-0)

magnesium sulfate (7487-88-9)

n-butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

maleic anhydride (108-31-6)

lithium aluminum hydride (16853-85-3)

hexane (110-54-3)

tert-butyl alcohol (75-65-0)

Benzenediazonium-2-carboxylate (1608-42-0)

argon (7440-37-1)

hexachlorobenzene (118-74-1)

PERCHLOROBENZYNE (634-66-2)

1,4-Ethenonaphthalene, 1,4-dihydro (7322-47-6)

pentachlorophenyllithium

dilithiotetrachlorobenzene

pentachlorobenzene (608-93-5)

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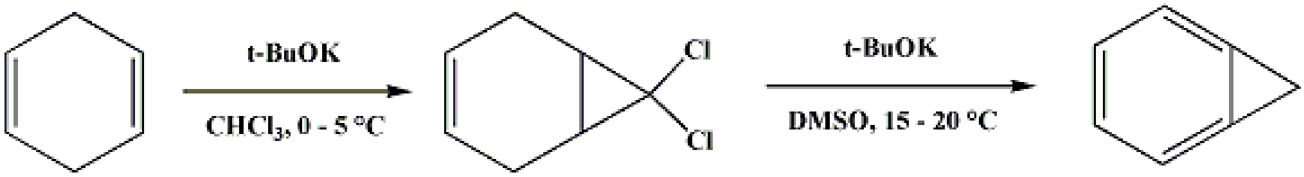
Organic Syntheses, CV 6, 87

BENZOCYCLOPROPENE

[Bicyclo [4.1.0]hepta-1,3,5-triene]



Submitted by W. E. Billups[1], A. J. Blakeney, and W. Y. Chow[1].
Checked by Nobuo Nakamura and S. Masamune.

1. Procedure

Caution! Benzocyclopropene is characterized by an extremely unpleasant (foul) odor, and use of a good hood is recommended for the preparation.

A. *7,7-Dichlorobicyclo[4.1.0]hept-3-ene*.[2] A 2-l., three-necked, round-bottomed flask is equipped with a sealed mechanical stirrer, a reflux condenser, and a pressure-equalizing dropping funnel. The system is flushed with nitrogen with a gas-inlet tube attached to the top of the condenser before 126 g. (1.123 moles) of potassium *tert*-butoxide (Note 1) and 1.2 l. of pentane are added. The stirred suspension is cooled to 0–5° with an ice bath and 90 g. (1.12 moles) of 1,4-cyclohexadiene (Note 2) is introduced rapidly through the dropping funnel; 135 g. (1.131 moles) of chloroform (Note 3) is then added dropwise over a period of 1.5–2 hours. The resulting mixture is stirred for an additional 30 minutes before 300 ml. of cold water is added to dissolve all of the precipitated salts. The organic phase is separated, and the aqueous phase is extracted with one 50-ml. portion of pentane. The extract is combined with the original pentane solution and dried over approximately 20 g. of anhydrous sodium sulfate. The solvent is removed on a rotary evaporator, and the product is distilled through a 15-cm. Vigreux column, giving 69–72 g. (38–39%) of 7,7-dichlorobicyclo [4.1.0]hept-3-ene, b.p. 50–51° (0.8 mm.) (Note 4).

B. *Benzocyclopropene*. A dry, three-necked, round-bottomed flask fitted with a sealed mechanical stirrer, a reflux condenser, and a pressure-equalizing dropping funnel is flushed with nitrogen and charged with 35.0 g (0.312 mole) of potassium *tert*-butoxide (Note 1), followed by 200 ml. of dimethyl sulfoxide (Note 5). The stirred mixture is cooled to 15–20° (Note 6) with an ice bath before 24.5 g. (0.154 mole) of 7,7-dichlorobicyclo[4.1.0]hept-3-ene is added over a 7-minute period. The bath is removed, the mixture stirred an additional 25 minutes, and the reaction quenched by first cooling the flask with an ice bath and then adding 180 ml. of ice water. The crude product is pumped directly into an acetone–dry ice cold trap through a glass vacuum take-off adapter. The *tert*-butyl alcohol and dimethyl sulfoxide are removed by washing the distillate once with 400 ml. of ice water (Note 7) and (Note 8). The benzocyclopropene that separates as the lower layer is distilled from 1 g. of anhydrous sodium sulfate, using the apparatus shown in f.htmigure 1. This procedure gives 4.35–5.48 g. (32–41%) of almost pure benzocyclopropene (Note 9).

Figure 1.

Figure 1.

2. Notes

1. Potassium *tert*-butoxide was used from a freshly opened bottle supplied by the MSA Research Corporation.
2. The checkers purchased 1,4-cyclohexadiene from Aldrich Chemical Company, Inc., and distilled it

prior to use.

3. Reagent grade chloroform was used without removal of stabilizer.

4. The product was shown to be approximately 95% pure by GC analysis, using a 180 cm. × 0.24 cm. column packed with UCW-98 and heated to 130°.

5. Dimethyl sulfoxide (supplied by the Aldrich Chemical Company, Inc.) was dried by distilling over calcium hydride at 5 mm.

6. Care should be taken not to freeze the dimethyl sulfoxide.

7. On one occasion the checkers observed that the mixture formed an emulsion and that centrifugation facilitated the separation of the layers.

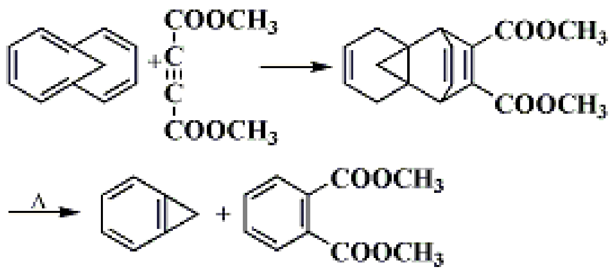
8. An alternative procedure is to extract the product into pentane.

9. The ^{1}H NMR spectrum shows that the product is approximately 95% pure. The major impurities are toluene and styrene. The product has the following spectral properties; IR (neat) $cm.^{-1}$: 1666, 1380, 1060, 735; ^{1}H NMR ($CDCl_3$), δ (number of protons): 3.17 (2H), 7.21 (4H); ^{13}C NMR ($CDCl_3$ δ: 18.56, 115.07, 125.86, 129.15; UV (cyclohexane) nm. max. (log ε): 263 (3.88), 268 (3.96), 276 (3.90).

3. Discussion

Fusion of the smallest cycloalkene, cyclopropene, to benzene would be expected to result in accommodation of the aromatic sextet with consequent bond length alteration in the aromatic ring. Benzocyclopropene thus arouses theoretical interest, and the high strain energy (approximately 68 kcal./mole)[3] associated with the compound suggests unusual chemical reactivity. Two review articles have appeared.[4,5]

The first successful synthesis of benzocyclopropene was reported by Vogel and coworkers[6] and is illustrated below. Though elegant, this method does require the prior, lengthy synthesis of the commercially unavailable 1,6-methano[10]annulene.[7]



The procedure described here[8] is a convenient two-step reaction which relies on the base-induced elimination-isomerization reactions of *gem*-dichlorocyclopropanes.[9,10,11,12,13,14,15,16] The reaction mechanism has been studied.[17] The principal advantage of this method is the availability of reagents.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 731

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

MSA Research Corporation

Benzene (71-43-2)

chloroform (67-66-3)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

toluene (108-88-3)

Pentane (109-66-0)

styrene (100-42-5)

dimethyl sulfoxide (67-68-5)

tert-butyl alcohol (75-65-0)

calcium hydride (7789-78-8)

1,4-cyclohexadiene

Benzocyclopropene

Bicyclo [4.1.0]hepta-1,3,5-triene (4646-69-9)

7,7-dichlorobicyclo[4.1.0]hept-3-ene (16554-84-0)

Cyclopropene (2781-85-3)

1,6-Methano[10]annulene (2443-46-1)

potassium tert-butoxide (865-47-4)

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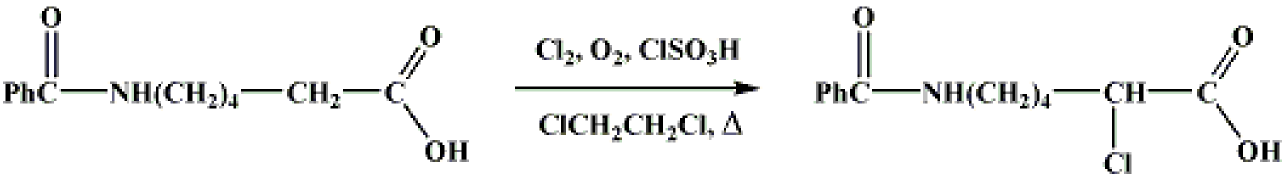
Organic Syntheses, CV 6, 90

α-CHLORINATION OF CARBOXYLIC ACIDS MEDIATED BY CHLOROSULFONIC ACID: ε-BENZOYLAMINO-α-CHLOROCAPROIC ACID

[Hexanoic acid, 6-benzoylamino-2-chloro-]



Submitted by Yoshiro Ogata, Toshiyuki Sugimoto, and Morio Inaishi[1].
Checked by Angela Hoppmann and George Büchi.

1. Procedure

Caution! Since chlorine is poisonous, this procedure should be conducted in an efficient hood. Chlorosulfonic acid is a strong skin irritant and should be handled with gloves and a protective face shield.

A 500-ml., four-necked, round-bottomed flask is equipped with an air-tight mechanical stirrer (Note 1), a gas dispersion tube with a porous glass frit, a Dimroth reflux condenser (Note 2), and a thermometer, making sure all joints are greased with silicone grease. The top of the condenser is connected to a series of three traps with polyvinyl chloride tubing (f.htmigure 1). The first trap is empty, and the other two contain aqueous 10 *N* sodium hydroxide. The gas dispersion tube extends to near the bottom of the flask, just above the stirrer blade, and is connected to a gas-mixing chamber having two inlet tubes, one for oxygen and the other for chlorine. The flask is charged with 47.1 g. (0.200 mole) of ε-benzoylaminocaproic acid (Note 3) and 200 ml. of 1,2-dichloroethane. The solution is stirred and heated to 60–70°, before 25.5 g. (0.219 mole) of chlorosulfonic acid (Note 4) is added gradually. A 2:1 (v/v) mixture of gaseous chloride and oxygen (Note 5) is bubbled into the flask for 3 hours while the contents are stirred and heated at reflux. The chlorine-oxygen gas flow is discontinued, and nitrogen is passed through the reaction mixture for 1 hour at 60–70° to remove chlorine remaining in solution. The flask is stoppered, allowed to stand for 1 hour at room temperature, and stored in a refrigerator for 12 hours. The supernatant liquid is removed, and *ca.* 800 ml. of aqueous 1 *N* sodium hydroxide is added to the solid remaining in the flask with ice cooling. Nitrogen is bubbled through the alkaline solution for 30 minutes to expel 1,2-dichloroethane. The solution is decolorized with 5 g. of activated carbon, mixed with *ca.* 400 g. of ice, and acidified to a pH of *ca.* 6 with 6 *N* hydrochloric acid. If available, a few seed crystals of ε-benzoylamino-α-chlorocaproic acid are added to the solution to facilitate crystallization. After 1 hour, more 6 *N* hydrochloric acid (Note 6) is added gradually until the pH is lowered to 1. An hour later the precipitate is filtered and washed thoroughly with 300 ml. of cold water until sulfate ion in the aqueous wash is no longer detectable with a test solution of barium chloride.

Figure 1.

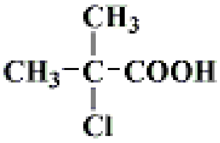
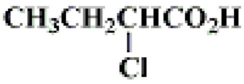
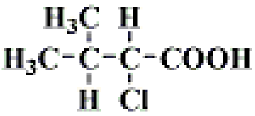
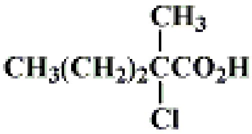
Figure 1.

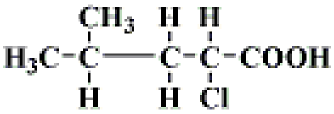
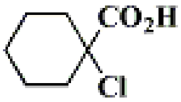
Drying under reduced pressure yields 39.1–43.1 g.. (72–80%) of crude, crystalline ε-benzoylamino-α-chlorocaproic acid, m.p. 138–140°. The product is dissolved in 320 ml. of hot 95% ethanol, 480 ml. of boiling water is added, and the resulting solution is allowed to cool slowly. The crystals are collected, washed with cold water, and dried, yielding 26.1–28.2 g. (48–52%) of pure ε-benzoylamino-α-chlorocaproic acid, m.p. 143–144° (Note 7).

2. Notes

1. Vigorous stirring action is necessary to disperse the heavy, viscous mixture. The use of a magnetic stirrer is not advisable since the mixture may separate into two layers. A mechanical stirrer with ground-glass shaft and bearing lubricated with 1,2-dichloroethane is recommended.
2. A Dimroth condenser has an internal, spiral cooling tube with the inlet and outlet both connected at the top. Spiral condensers of this type are available from Ace Glass Incorporated, Vineland, New Jersey 08360. A Dimroth condenser is recommended for use with refluxing liquids that boil up to 160°.[2] Since the points of sealing are situated above the zone with a high temperature gradient, the risk of cracking from thermal stress is minimized. The α-chlorination of aliphatic acids by this procedure is usually carried out at 110–140° (see Table I). The submitters circulated ice-cold water through the condenser.

TABLE I
α-CHLOROCARBOXYLICACIDSPREPARED BYCHLORINATION IN THEPRESENCE OFCHLOROSULFONICACID ANDOXYGEN[a]

Entry	α-Chloro Acid	Scale (mole)	Temperature (°)	Yield[b] (%)
1		0.45	120	75
2		0.45	120	82[c]
3		0.60	140	73
4		0.35	120	81

5		0.18	120	78
6		0.16	120	79[d]
7		0.23	110	73

[a]A 4:1:0.04 molar ratio of carboxylic acid, chlorosulfonic acid, and chloranil was used.
A 2:1 mixture of chlorine and oxygen was passed into the reaction for 3 hours.

[b]The yields were determined by gas chromatographic analysis after esterification of aliquots with sulfuric acid and methanol in 1,2-dichloroethane.

[c]β-Chloro acid was also formed in 1.6% yield.

[d]β-Chloro acid was also formed in 6.4% yield.

3. ε-Benzoylaminocaproic acid was prepared by the reaction of benzoyl chloride with ε-aminocaproic acid, as described in *Org. Synth.*, **Coll. Vol. 2**, 76 (1943).
4. Chlorosulfonic acid was purified by distillation before use, b.p. 86–88° (33 mm.).
5. The flow rates of the two gases are regulated by flow meters inserted in parallel between the gas-mixing chamber and the chlorine and oxygen tanks. Appropriate flow rates for chlorine and oxygen are 80–100 and 40–50 ml. per minute, respectively. The checkers purchased gas flow meters from Arthur H. Thomas Company, Philadelphia, Pennsylvania.
6. If the warm alkaline solution is acidified rapidly with 6 *N* hydrochloric acid, the product is likely to separate as an oil.
7. A melting point of 145–147° has been reported.[3] The submitters performed a high-pressure liquid chromatographic analysis on a 25 × 0.2 cm. column packed with porous, dichlorodimethylsilane-treated silica gel (Yanapak DMS). With 40:60 (v/v) methanol–water as carrier liquid and a flow rate of 80–100 ml. per hour, the product appeared as a single peak. IR (KBr) cm.$^{-1}$: 3360, 3040, 2920, 1700, 1600, 1550, 820, 770, 720, 690; ^{1}H NMR (dimethyl sulfoxide-d_6), δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 1.2–2.2 (m, 6H, $CH_2CH_2CH_2$), 3.0–3.4 (m, 2H, CH_2N), 4.40 (t, *J* = 7, 1H, CHCl), 7.2–7.9 (m, 5H, C_6H_5), 8.40 (broad t, *J* = 6, 1H, NH).

3. Discussion

The present procedure, a modification of one reported earlier by the submitters,[4] has been applied

to the α-chlorination of a series of aliphatic carboxylic acids (Table I).[5] In these reactions solvent (1,2-dichloroethane) was unnecessary, 0.25 molar equivalents of chlorosulfonic acid was sufficient, and higher temperatures in the range of 110–140° were employed. The α-chloro acids were converted efficiently to the corresponding methyl esters, for characterization, by reaction with methanol and a catalytic amount of concentrated sulfuric acid in 1,2-dichloroethane at reflux for 10 hours.[6] The methyl esters of the α-chloro acids shown in entries 3–6 have not been previously prepared.

Chlorosulfonic acid is particularly effective at mediating the α-chlorination of carboxylic acids, evidently owing to both its high acidity and its ability to render the reaction mixture more nearly homogeneous than other acidic catalysts. The function of oxygen is to scavenge free radicals, thereby suppressing the free radical chlorination at other positions of the carboxylic acid.[7] The chlorination of isovaleric acid (entry 3) in the absence of oxygen gives an appreciable amount of β-chloro acid. In the presence of oxygen only trace amounts (0–6.4%) of the β-chloro, or other isomers, were formed in the chlorinations shown in the table despite the tertiary hydrogens present in entries 3,5, and 6. This method, which uses chlorosulfonic acid and 1,2-dichloroethane, can be applied to α-bromination[8] and α-iodination[9] of carboxylic acids, where no radical trapper such as molecular oxygen is necessary.

ε-Benzoylamino-α-chlorocaproic acid has been previously prepared by chlorination of ε-benzoylaminocaproic acid with sulfuryl chloride in the presence of iodine.[3] The corresponding bromo analog has been obtained by reaction with bromine and red phosphorous and subsequent hydrolysis.[10,11] ε-Benzoylamino-α-halocaproic acid is an intermediate in the synthesis of *d,l*-lysine dihydrochloride.[3,12]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 119

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

red phosphorous

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

methanol (67-56-1)

sodium hydroxide (1310-73-2)

chlorosulfonic acid (7790-94-5)

bromine (7726-95-6)

oxygen (7782-44-7)

1,2-dichloroethane (107-06-2)

nitrogen (7727-37-9)

barium chloride (10361-37-2)

iodine (7553-56-2)

carbon (7782-42-5)

benzoyl chloride (98-88-4)

sulfuryl chloride (7791-25-5)

chlorine (7782-50-5)

ε-AMINOCAPROIC ACID (60-32-2)

ε-Benzoylaminocaproic acid (956-09-2)

isovaleric acid (503-74-2)

Hexanoic acid, 6-benzoylamino-2-chloro-, ε-Benzoylamino-α-chlorocaproic acid (5107-15-3)

chlorine-oxygen

carboxylic acid, chlorosulfonic

d,l-lysine dihydrochloride

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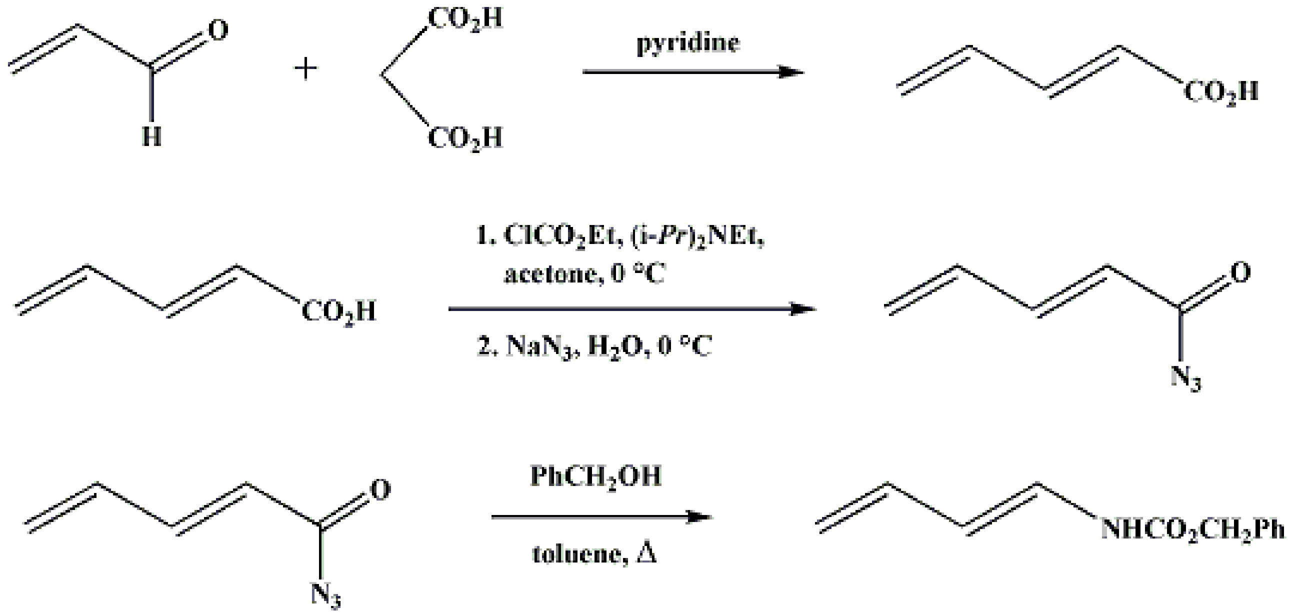
1-*N*-ACYLAMINO-1,3-DIENES FROM 2,4-PENTADIENOIC ACIDS BY THE CURTIUS REARRANGEMENT: BENZYL *trans*-1,3-BUTADIENE-1-CARBAMATE

[Carbamic acid, 1,3-butadienyl-, (*E*)-, phenylmethyl ester]



Submitted by Peter J. Jessup, C. Bruce Petty, Jan Roos, and Larry E. Overman[1].
Checked by Paul H. Liang and G. Büchi.

1. Procedure

A. trans-2,4-*Pentadienoic acid*. A 1-l., three-necked, round-bottomed flask is equipped with a mechanical stirrer, a condenser cooled with ice-cold water (Note 1) bearing a calcium chloride drying tube, and a powder funnel. The flask is charged with 206 g. (210 ml., 2.61 moles) of pyridine (Note 2), and with vigorous stirring 208 g. (2.00 moles) of powdered malonic acid (Note 3) is added in portions. The powder funnel is replaced by a 250-ml., pressure-equalizing dropping funnel containing 126 g. (150 ml., 2.25 moles) of acrolein (Note 4), which is added, with vigorous stirring, over a 30-minute period. The exothermic reaction begins immediately with evolution of carbon dioxide, and the gently refluxing mixture becomes homogeneous. After 1 hour, as carbon dioxide evolution ceases, the solution is poured onto 1 l. of ice in a 3-l. Erlenmeyer flask, and carefully acidified with 130 ml. of concentrated sulfuric acid. The aqueous layer is extracted with four 250-ml. portions of dichloromethane, and the organic extracts are dried over magnesium sulfate for *ca.* 10 minutes. The dichloromethane solution is concentrated to *ca.* 300 ml. on a rotary evaporator with the water bath at 20–30° and allowed to crystallize in a freezer at −10° for several hours. After a first crop, yielding 40–50 g. of product, m.p. 72–73°, is collected, three additional crops are taken following successive concentration of the mother liquor to 150, 70, and 30 ml. Dried under reduced pressure in the presence of phosphorous pentoxide, the four crops of off-white crystals total 82–90 g. (42–46%), m.p. 69–71° (Note 5).

B. *Benzyl* trans-1,3-*butadiene*-1-*carbamate*. *Caution! The following reaction should be carried out in a fume hood to avoid accidental exposure to toxic hydrazoic acid.*

A dry, 1-l., three-necked, round-bottomed flask is equipped with a magnetic stirring bar, a thermometer, and a 250-ml., pressure-equalizing dropping funnel bearing a nitrogen inlet. The flask is flushed with nitrogen and charged with 49 g. (0.50 mole) of *trans*-2,4-pentadienoic acid, 80 g. (0.62 mole) of *N,N*-diisopropylethylamine, and 300 ml. of acetone (Note 6). The resulting solution is stirred and cooled to 0° in an ice–salt bath. A solution of 55 g. (0.51 mole) of ethyl chloroformate in 150 ml. of acetone is added over 30 minutes while the temperature is maintained below 0° (Note 7). Stirring is continued for an additional 30 minutes at 0°, after which a chilled solution of 65 g. (1.0 mole) of sodium azide (Note 8) in 170 ml. of water is added over a 20-minute interval, keeping the temperature below 0°. The contents of the flask are stirred for an additional 10–15 minutes at 0° (Note 9) and poured into a 2-l. separatory funnel containing 500 ml. of ice-water. The acyl azide is isolated by extraction with six 250-ml. portions of toluene. The combined toluene extracts are dried over anhydrous magnesium sulfate for 20 minutes and concentrated to a volume of *ca.* 300 ml. on a rotary evaporator at a water bath temperature of 40–50° (Note 10). *Caution! The acyl azide is potentially explosive. The solution should not be evaporated to dryness.* While the toluene solution is being concentrated, a dry, 2-l., three-necked, round-bottomed flask equipped with a mechanical stirrer, a 500-ml. pressure-equalizing dropping funnel, a simple distillation head, and a heating mantle is charged with 43 g. (0.40 mole) of benzyl alcohol, 250 mg. of 4-*tert*-butylcatechol (Note 11), and 200 ml. of toluene. About 30 ml. of toulene is distilled from the flask to remove trace amounts of water, and the distillation head is replaced with a condenser fitted with a nitrogen inlet. The toluene solution is stirred and heated at a rapid reflux under a nitrogen atmosphere as the toluene solution of the acyl azide is added over 30 minutes. The disappearance of the acyl azide and isocyanate is followed by IR analysis (Note 12). Conversion to the carbamate is complete in 10–30 minutes, after which the solution is cooled rapidly to room temperature by immersing the flask in an ice bath. The toluene is rapidly removed on a rotary evaporator with the water bath at 40–50°, producing a yellow solid residue (Note 13) which is dissolved in 50 ml. of 95% ethanol and allowed to crystallize in a freezer at −25° for several hours. Two crops of pale yellow crystals, m.p. 69–72°, are isolated which total 39–46 g. after drying under reduced pressure. Concentration of the mother liquor affords an oily residue that is placed on a 6 × 80-cm. column packed with 500 g. of silica gel (Note 14) and eluted with 1:9 (v/v) ethyl acetate–hexane. An additional 11–12 g. of crystalline product is obtained from the chromatography, raising the total yield to 50–58 g. (49–57%) of nearly pure benzyl *trans*-1,3-butadiene-1-carbamate, a pale yellow solid, m.p. 70–73° (Note 15).

2. Notes

1. A water pump purchased from Little Giant Pump Company, Oklahoma City, Oklahoma, was used by the submitters to circulate ice-water through the condenser. The checkers used a dry ice condenser.
2. Reagent grade pyridine was stored over Linde type 4A molecular sieves for at least 24 hours before use.
3. Malonic acid was purchased from Aldrich Chemical Company, Inc. Most, but not all, of the malonic acid dissolves after 30 minutes. If pyridine is added to the malonic acid, a hard cake results.
4. Acrolein contaminated by 3% water was obtained by the submitters from Aldrich Chemical Company, Inc., and was purified by distillation from anhydrous calcium sulfate, b.p. 53°. The checkers used acrolein purchased from MC and B Manufacturing Chemists.
5. This material is of satisfactory purity for use in Part B. A thin-layer chromatogram on silica gel developed with 1:1 (v/v) ethyl acetate–hexane containing 1% acetic acid and visualized with 10% phosphomolybdic acid in ethanol as a spray reagent showed a major spot at $R_f = 0.4$ and a faint spot at 0.2. The crystalline acid may be stored for several months without significant decomposition. A melting point of 72° is reported[2] for *trans*-2,4-pentadienoic acid.

The spectral properties of the product are as follows: IR ($CHCl_3$) cm.$^{-1}$: 3200–2700 (OH), 1696 (C=O), 1640, 1600, 1280, 1010; ^{1}H NMR ($CDCl_3$), δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 5.1–5.8 (m, 2H, two *H* at C-5), 5.92 (d, *J* = 15, 1H, *H* at C-2), 6.2–6.8 (m, 1H, *H* at C-4), 7.37 (d of d, $J_{2,3}$ = 15, $J_{3,4}$ = 11, 1H, *H* at C-3), 12.0 (s, 1H, CO_2H).

6. *N,N*-Diisopropylethylamine was supplied by Aldrich Chemical Company, Inc., and purified by distillation from sodium hydride, b.p. 127°. Reagent grade acetone was stored over Linde type 4A molecular sieves for at least 24 hours before use.

7. Ethyl chloroformate obtained from Aldrich Chemical Company, Inc., was distilled, b.p. 93°. The progress of the reaction may be followed by ^{1}H NMR spectroscopy. Aliquots are partitioned between dichloromethane and water, the organic layer is concentrated, and the spectrum is recorded. A quartet from the ethoxy group of the mixed anhydride appears at δ 4.2. Ethyl chloroformate, which exhibits a quartet at δ 4.3, is removed in the concentration step.

8. Analytical reagent grade sodium azide purchased from Alfa Division, Ventron Corporation, or J. T. Baker Chemical Company was used as supplied.

9. The formation of the acyl azide may be followed by the growth of the 2130-cm.$^{-1}$ (-N=N=N) IR absorption of concentrated dichloromethane extracts of aliquots removed from the reaction.

10. The solution is concentrated for the purpose of removing residual ethanol. If this step is omitted, ethyl *trans*-1,3-butadiene-1-carbamate will be formed, contaminating the final product.

11. Reagent grade benzyl alcohol was purified by distillation, b.p. 205°. 4-*tert*-Butylcatechol purchased from Aldrich Chemical Company was sublimed at 50° (0.1 mm.) and recrystallized from hexane.

12. The acyl azide IR absorption occurs at 2130 cm.$^{-1}$ and the isocyanate at 2270 cm.$^{-1}$.

13. Impure samples of the product are particularly prone to decomposition. The purification steps should be carried out immediately.

14. Grade 60, activity III silica gel, purchased from W. R. Grace and Company, was used.

15. Material of this purity is suitable for most applications and may be stored in a freezer for several months with only slight decomposition. A thin-layer chromatogram on silica gel developed with 1:3 (v/v) ethyl acetate–hexane and visualized by UV fluorescence showed a single spot. Benzyl *trans*-1,3-butadiene-1-carbamate, like all *N*-acylamino-1,3-dienes, is quite acid sensitive and can, for example, be decomposed by traces of deuterium chloride in chloroform-*d*. A pure sample may be obtained by recrystallization from 1:20 (v/v) ethyl acetate–hexane, m.p. 74–75°; IR (Nujol) cm.$^{-1}$: 3300, 1692, 1625, 1515, 1230, 690; ^{1}H NMR ($CDCl_3$), δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 4.8–5.0 (m, 2H, two *H* at C-4), 5.15 (s, 2H, $CH_2C_6H_5$), 5.4–5.8 (m, 2H, *H* at C-2 and N*H*), 6.26 (apparent d of t, *J* = 10 and *J* = 17, 1H, *H* at C-3), 6.71 (broadened d, *J* = 9, 1H, *H* at C-1), 7.33 (s, 5H, C_6H_5); ^{13}C NMR ($CDCl_3$), δ (assignment): 67.5 ($CH_2C_6H_5$), 112.5 (*C*-2), 113.5 (*C*-4), 127.2 (*C*-1), 128.3 (*para*-C_6H_5), 128.4 (*meta*-C_6H_5), 128.7 (*ortho*-C_6H_5), 134.6 (*C*-3), 136.0 (*peri*-C_6H_5), 153.7 (*C*=O).

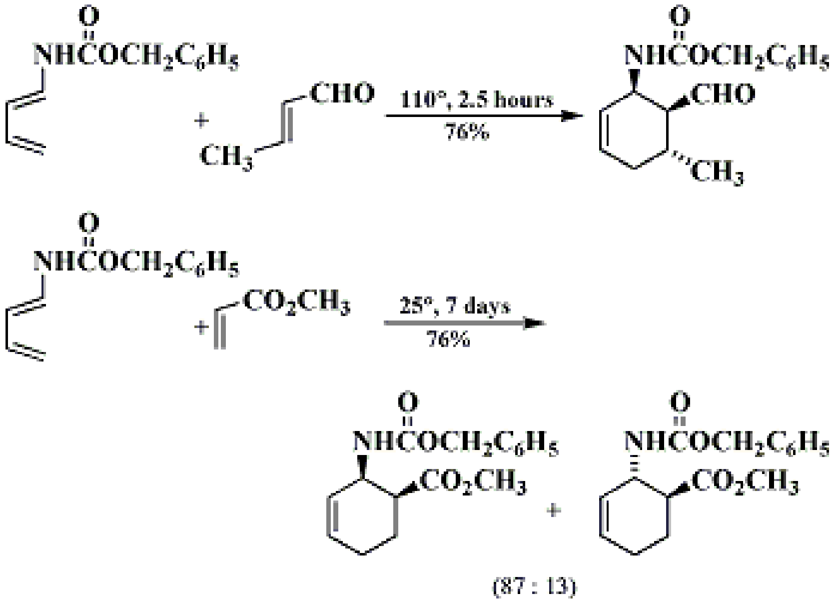
3. Discussion

This procedure illustrates a general method[3] for the preparation of *trans*-1-*N*-acylamino-1,3-butadienes from 2,4-pentadienoic acids. A number of 1,3-butadienyl and 1,3-pentadienyl carbamates, thiocarbamates, and ureas have been prepared by this procedure (Table I).[3] These dienamides are reasonably stable crystalline solids which, when pure, may be stored in a freezer for

several months with little decomposition. Since a variety of conjugated dienoic acids are readily accessible from Knoevenagel, Wittig, and related reactions,[4] 1-*N*-acylamino-1,3-butadienes with a diversity of carbon skeletons and heteroatom acyl substituents are potentially available by this method. Although this procedure describes the only known preparation of benzyl *trans*-1,3-butadiene-1-carbamate, a number of similar 1-*N*-acylamino-1,3-butadiene derivatives have been prepared by Curtius rearrangement of 2,4-hexadienoyl azide,[5] by Hofmann rearrangement of 2,4-hexadienamide,[6] by *N*-acylation of 1-*N*-alkylamino-1,3-butadiene anions generated from crotonaldehyde imines,[7] and by thermal rearrangement of trichloroacetimidic esters of acetylenic alcohols.[8]

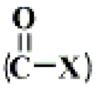
The Curtius rearrangement procedure described here is a modification of one reported by Weinstock.[9] The submitters have found this procedure to be considerably more reproducible when *N*,*N*-diisopropylethylamine is substituted for triethylamine. The procedure described for the preparation of *trans*-2,4-pentadienoic acid is a modification of an earlier one by Doebner.[10] The submitters have found this method to give reproducibly higher yields, and to be more convenient, than other commonly used procedures for preparing this material.[2,11] The use of dichloromethane as the extracting and crystallizing solvent greatly simplifies the isolation of polymer-free samples of the crystalline acid.

trans-1-*N*-Acylamino-1,3-butadienes are useful dienes in Diels-Alder reactions. They are the most convenient synthetic equivalents currently available for the parent 1-amino-1,3-butadienes. These electron-rich dienamides undergo Diels-Alder cycloaddition with remarkable ease and high regio- and stereoselectivity.[12,13] As illustrated below, they react readily with even relatively unreactive dienophiles such as methyl acrylate and *trans*-crotonaldehyde. A recent quantitative study[12] has confirmed the expectation of an increase in reactivity with increasing electron-donating ability of the acyl substituent of an acylaminobutadiene, although the effects observed are not large.



The choice of the acyl substituent X for Diels-Alder reactions of 1-*N*-acylamino-1,3-butadienes depends on the particular synthetic problem. The acyl substituent has a moderate effect on the cycloaddition reactivity of these dienes,[12] and also determines what amine unmasking procedures are required. As a result of their stability[12,13] and the variety of amine deprotection procedures available,[14] the diene carbamates are the components of choice in most cases. A particularly attractive aspect of the diene synthesis detailed here is the ability to "tailor" the amino-protecting

group (

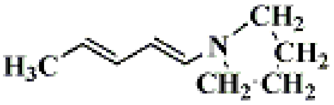


) for the application at hand. Benzyl *trans*-1,3-butadiene-1-carbamate has the amino group protected with the benzyloxycarbonyl group. The ability to remove this functionality by catalytic hydrogenation was an important design feature in a recent alkaloid synthesis[13] that utilized this diene.

TABLE I

PREPARATION OF *trans*-1-*N*-ACYLAMINO-1,3-BUTADIENES[3]

R	X	Procedure[a]	M.p. (°)	Yield (%)
H	$OCH_2C_6H_5$	A	74–75	53[b]
H	$OC(CH_3)_3$	A	67–68	59
CH_3	OCH_2CH_3	A	91–92	80
H	OCH_2CH_3	A	44–45	71[b]
CH_3	OC_6H_5	A	118–120	72

H	OC_6H_5	B[c]	118–119	66
		A		45
CH_3	$N(CH_2)_4$	B	164–165	77
		A		(10)[d]
H	$N(CH_2)_4$	B	163–164	44
CH_3	SC_6H_5	B	116–118	78
H	SC_6H_5	B	92–93	47

[a]Isocyanate trapped as formed at 100° (Procedure A) or isocyanate preformed at 110° and trapped at 25° (Procedure B).

[b]Mean yield of four runs. All other entries are non-optimized yields from one run.

[c]A few drops of triethylamine were added.

[d]Estimated from the ^1H NMR spectrum.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

phosphorous pentoxide

ethanol (64-17-5)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

ethyl acetate (141-78-6)

Acrolein (107-02-8)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

calcium sulfate (7778-18-9)

acetone (67-64-1)

pyridine (110-86-1)

toluene (108-88-3)

Benzyl alcohol (100-51-6)

sodium azide (26628-22-8)

dichloromethane (75-09-2)

Malonic acid (141-82-2)

ethyl chloroformate (541-41-3)

methyl acrylate (96-33-3)

magnesium sulfate (7487-88-9)

isocyanate

sodium hydride (7646-69-7)

hexane (110-54-3)

trans-crotonaldehyde (123-73-9)

triethylamine (121-44-8)

chloroform-d (865-49-6)

phosphomolybdic acid (51429-74-4)

deuterium chloride (7698-05-7)

2,4-hexadienoyl azide

2,4-hexadienamide

N,N-diisopropylethylamine (7087-68-5)

4-tert-butylcatechol (98-29-3)

Benzyl trans-1,3-butadiene-1-carbamate, Carbamic acid, 1,3-butadienyl-, (E)-, phenylmethyl ester (71616-72-3)

trans-2,4-Pentadienoic acid (21651-12-7)

ethyl trans-1,3-butadiene-1-carbamate

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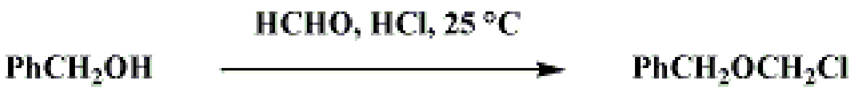
Organic Syntheses, CV 6, 101

BENZYL CHLOROMETHYL ETHER

[Benzene, (chloromethyoxy)methyl-]



Submitted by D. S. Connor[1,2], G. W. Klein[13], G. N. Taylor[14], R. K. Boeckman, Jr.[5], and J. B. Medwid[6].
Checked by E. M. Carreira, S. E. Denmark, and Robert M. Coates.

1. Procedure

Caution! Benzyl chloromethyl ether is a powerful alkylating agent and a potential carcinogen. Furthermore, it is a mild lachrymator and reacts with water and alcohols, forming hydrogen chloride. The procedure should be conducted in a hood, and inhalation and skin contact should be avoided.

A 1-l, three-necked flask equipped with an overhead mechanical stirrer with a Teflon paddle, gas-inlet tube, thermometer, and a calcium chloride drying tube (Note 1) is charged with 216 g. (2.00 moles) of benzyl alcohol (Note 2) and 66 g. (2.20 moles as CH_2O) of paraformaldehyde (Note 3). The resulting mixture is maintained at 20–25° with a water bath during addition of anhydrous hydrogen chloride (Note 4) at a moderate rate, with stirring (Note 5). After approximately 2 hours the reaction is complete, as judged by the appearance of two clear homogeneous phases (Note 6). The layers are separated, and the upper layer is diluted with 800 ml. of pentane and dried over anhydrous magnesium sulfate for 3 hours at 0°, with stirring. The drying agent is removed by filtration, 2–3 g. of anhydrous calcium chloride is added to the filtrate, and the solution is concentrated on a rotary evaporator (Note 7). The residual liquid, which is nearly pure benzyl chloromethyl ether, is decanted, affording 260 g. (83%) of crude product (Note 8). This crude benzyl chloromethyl ether, which is suitable for use in some applications, is stored over anhydrous calcium chloride at 0° under an inert atmosphere (Note 9) and (Note 10).

If further purification is desired, just prior to use the crude material (40 g.) may be distilled at approximately 3 mm from anhydrous calcium chloride (Note 11), affording very pure benzyl chloromethyl ether (35 g.), b.p. 70–71° (3 mm.) (Note 12) and (Note 13).

2. Notes

1. A Claisen adapter is utilized to accommodate both the thermometer and

calcium chloride drying tube.

2. Fisher Scientific reagent grade benzyl alcohol was freshly distilled prior to use.

3. Fisher Scientific reagent grade paraformaldehyde was used.

4. Anhydrous hydrogen chloride was obtained from Matheson Gas Products and dried by passing it through concentrated sulfuric acid.

5. The gas-inlet tube utilized was a Pasteur pipet; however, a fritted glass gas-dispersion tube could be utilized. Hydrogen chloride is introduced as a stream of fine bubbles; the rate of addition controls the reaction temperature.

6. To judge whether the reaction is complete, stirring is stopped and the phases are permitted to separate. ^{1}H NMR analysis of the upper phase ($CDCl_3$) showed that the reaction is complete and devoid of major side-products.

7. Decomposition was noted during concentration and distillation in the absence of anhydrous calcium chloride.

8. The checkers obtained 316.3–316.6 g. (101%).

9. The crude material is satisfactory for the *C*-alkylation of an ester enolate; little difference was noted when the crude material was substituted for distilled material.

10. The crude product exhibits singlets in the ^{1}H NMR (CCl_4) at δ 4.68 (2H), 5.41 (2H), and 7.29 (5H). Both ^{1}H NMR and GC analyses indicate a purity of greater than 90%. GC analysis was carried out at 155° with a 2 m. × 0.7 cm. column packed with silicone fluid No. 710 suspended on 60–80 mesh finebrick. The major impurities appear to be varying amounts of benzyl chloride and dibenzyl formal, by ^{1}H NMR analysis.

11. Complete decomposition occurs if distillation is attempted at atmospheric pressure. Minor to occasionally major decomposition occurs upon attempted distillation at reduced pressure in the absence of anhydrous calcium chloride, which retards the decomposition significantly.

12. The product gave satisfactory microanalytical data after one distillation. The reported physical constants for benzyl chloromethyl ether are b.p. 96–98° (9.5 mm.),[7] n_D^{20} 1.5264–1.5292.[8,9]

13. The checkers used a procedure identical to that described above at one-eighth scale to prepare bromomethyl ether, using hydrogen bromide. A quantitative yield of crude material was obtained and distilled, giving a 97% yield of pure benzyl bromomethyl ether, b.p. 55–57° (1 mm.), n_D^{20} 1.5547: ^{1}H NMR ($CDCl_3$): δ 4.67 (s, 2H), 5.66 (s, 2H), 7.30 (s, 5H). Analysis calculated for C_8H_9BrO (201.09): C, 47.79; H, 4.51; Br, 39.74. Found: C, 48.05; H, 4.68; Br, 40.05. This was found to be a superior alkylating agent.

3. Discussion

Benzyl chloromethyl ether is useful for introduction of a potential hydroxymethyl group in alkylation reactions. Hill and Keach[10] first used this method and found it convenient in barbiturate syntheses. Graham and McQuillin,[11] and Graham,

McQuillin, and Simpson[12] have extended the scope of the alkylation reaction to various ketone derivatives. They also have investigated the conditions for obtaining maximum *C*-alkylation and the stereochemistry of alkylation in various octalone systems.[11] Alkylation of ketones followed by sodium borohydride reduction and catalytic hydrogenolysis represents a convenient method for obtaining 1,3-diols.[11] Similarly, Wolff-Kishner reduction and catalytic hydrogenolysis give primary alcohols.[11] A procedure of this type has been used for obtaining bridgehead methanol derivatives of bicyclic compounds.[13] Alkylation of ester enolates, generated by lithium diisopropylamide, has been reported.[14]

Several other alkylations with benzyl chloromethyl ether using phosphorus compounds as nucleophiles have been reported.[8] Hydrolysis and alcoholysis reactions of the reagent[15] have been investigated, along with the addition of the chloroether to propylene in the presence of zinc chloride.[16] Alkylation of enamines with benzyl bromomethyl ether has been reported.[17]

Benzyl chloromethyl ether has been prepared from benzyl alcohol, aqueous formaldehyde solution, and hydrogen chloride.[9,10,18] Gaseous formaldehyde[9] and 1,3,5-trioxane[19] have also been used. This chloromethyl ether has also been prepared by the chlorination of benzyl methyl ether.[16] The present procedure is based on the first method, but avoids the use of a large excess of formaldehyde and provides a considerably simplified isolation procedure.

References and Notes

1. Work done at Department of Chemistry, Yale University, New Haven, Connecticut 06520.
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5. Department of Chemistry, University of Rochester, Rochester, New York 14627.
6. Department of Chemistry, Wayne State University, Detroit, Michigan 48202.
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Benzene, (chloromethyoxy)methyl-

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrogen chloride (7647-01-0)

formaldehyde (630-08-0)

propylene (115-07-1)

hydrogen bromide (10035-10-6)

benzyl chloride (100-44-7)

Benzyl alcohol (100-51-6)

zinc chloride (7646-85-7)

Pentane (109-66-0)

chloromethyl ether (542-88-1)

magnesium sulfate (7487-88-9)

benzyl methyl ether (538-86-3)

sodium borohydride (16940-66-2)

chloroether (7791-21-1)

Benzyl chloromethyl ether (3587-60-8)

dibenzyl formal

bromomethyl ether

benzyl bromomethyl ether

lithium diisopropylamide (4111-54-0)

1,3,5-trioxane (110-88-3)

paraformaldehyde (30525-89-4)

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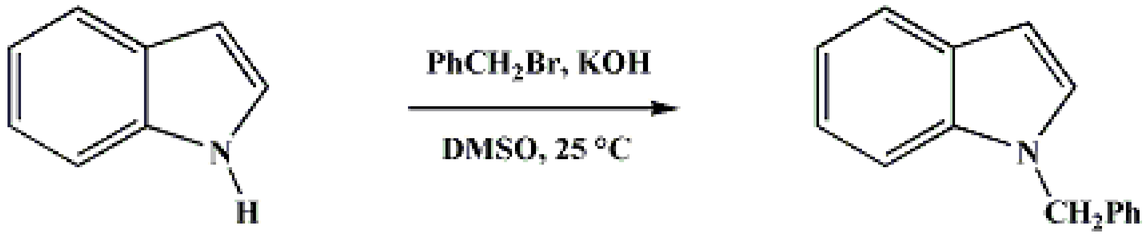
Organic Syntheses, CV 6, 104

1-BENZYLINDOLE

[1*H*-Indole, 1-(phenylmethyl)-]



Submitted by Harry Heaney[1] and Steven V. Ley.
Checked by A. Brossi, E. E. Garcia, and R. P. Schwartz.

1. Procedure

A 500-ml. Erlenmeyer flask equipped with a magnetic stirring bar is charged with 200 ml. of dimethyl sulfoxide (Note 1) and 26.0 g. (0.399 mole) of potassium hydroxide (Note 2). The mixture is stirred at room temperature for 5 minutes before 11.7 g. (0.100 mole) of indole (Note 3) is added. Stirring is continued for 45 minutes before 34.2 g. (0.200 mole) of benzyl bromide (Note 4) is added (Note 5). After being stirred for an additional 45 minutes the mixture is diluted with 200 ml. of water. The mixture is extracted with three 100-ml. portions of diethyl ether, and each ether layer is washed with three 50-ml. portions of water. The combined ether layers are dried over calcium chloride, and the solvent is removed at slightly reduced pressure (Note 6). The excess benzyl bromide is removed by distillation at approximately 15 mm., and the residue is distilled, yielding 17.5–18.4 g. (85–89%) of 1-benzylindole, b.p. 133–138° (0.3 mm.). The distillate crystallizes upon cooling and scratching; recrystallization from ethanol gives material melting at 42–43° (Note 7) and (Note 8).

2. Notes

1. The dimethyl sulfoxide used was not rigorously dried but should not contain an appreciable amount of water.
2. Freshly crushed 86% potassium hydroxide pellets were used.
3. A commercial grade of indole is satisfactory.
4. Reagent grade benzyl bromide was used without further purification.
5. Cooling with an ice–water bath moderates the exothermic reaction.
6. The submitters used a Büchi rotary evaporator (water aspirator).
7. The submitters have obtained yields as high as 20 g. (97%).
8. ^1H NMR ($CDCl_3$): 5.21 (s, 2H), 6.52 (d, J = 3.4 Hz., 1H), 7.0–7.4 (m, 9H), and 7.5–7.7 (m, 1H).

3. Discussion

Although the *N*-alkylation of pyrrole[2] and indole[3] has been reported on many occasions, a generally applicable, simple, high yield procedure was not available. Many simple procedures give mixtures of products because of the ambident nature of the anions; however, alkylation at nitrogen is usually predominant in strongly ionizing solvents. Recent methods include alkylations of indole in liquid ammonia,[4] *N,N*-dimethylformamide,[5] and hexamethylphosphoric triamide.[6]

The use of dimethyl sulfoxide as a dipolar aprotic solvent is well known;[7] the present method can be regarded as a model procedure and has been applied to the preparation of a number of *N*-*n*-alkyl pyrroles and *N*-*n*-alkyl indoles.[8] The yield of *N*-benzylindole is considerably higher than in previously reported preparations and is as good as that reported for the preparations of *N*-methylindole in liquid ammonia.[4] The present method is, however, less laborious and quicker. Very high yields are obtained using *n*-alkyl halides and moderately good yields with secondary alkyl halides. The reactions may be compared with those recently reported for pyrrylthallium[9]

The procedure has been much used for the alkylation of a variety of indoles,[10] including a modification using sodium methoxide in the methylation of tetrahydroalstonine.[11] The wide applicability of the method is indicated by the methylation of diarylamines such as 10,11-dihydro-5*H*-dibenzo[*b,f*]azepine.[12] An extension to the acylation of indoles has been reported using, for example, acetic anhydride-KOH in dimethyl sulfoxide.[13]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

pyrrylthallium

tetrahydroalstonine

acetic anhydride-KOH

ethanol (64-17-5)

calcium chloride (10043-52-4)

ammonia (7664-41-7)

ether, diethyl ether (60-29-7)

nitrogen (7727-37-9)

sodium methoxide (124-41-4)

potassium hydroxide (1310-58-3)

Pyrrole (109-97-7)

benzyl bromide (100-39-0)

N,N-dimethylformamide (68-12-2)

Indole, 1H-Indole (120-72-9)

dimethyl sulfoxide (67-68-5)

hexamethylphosphoric triamide (680-31-9)

N-methylindole (603-76-9)

1-Benzylindole, N-benzylindole (3377-71-7)

10,11-dihydro-5H-dibenzo[b,f]azepine (494-19-9)

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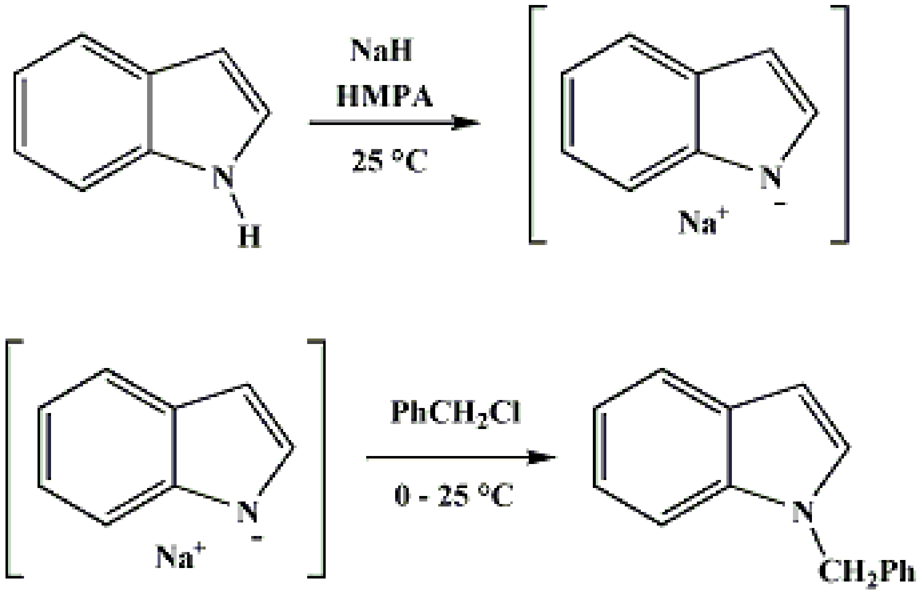
N-ALKYLINDOLES FROM THE ALKYLATION OF SODIUM INDOLIDE IN HEXAMETHYLPHOSPHORIC TRIAMIDE: 1-BENZYLINDOLE

[1*H*-Indole, 1-(phenylmethyl)-]



Submitted by George M. Rubottom[1] and John C. Chabala[2].
Checked by R. E. Ireland and James E. Kleckner.

1. Procedure

Caution! Hexamethylphosphoric triamide (HMPA) vapors have been reported to cause cancer in rats.[3] All operations with hexamethylphosphoric triamide should be performed in a good hood, and care should be taken to keep the liquid off the skin.

A 100-ml., three-necked flask fitted with a reflux condenser, a magnetic stirring bar, and a gas-inlet tube is charged with 2.34 g. (0.0200 mole) of indole (Note 1) and 15 ml. of hexamethylphosphoric triamide (Note 2) under a static atmosphere of argon. The flask is cooled to 0° with an ice bath, and 0.53 g. (0.022 mole) of sodium hydride is added to the stirred solution over a period of 10 minutes (Note 3). The resulting slurry is stirred for 5 hours at room temperature (Note 4) then cooled to 0° (ice bath) before 2.53 g. (2.30 ml., 0.0200 mole) of benzyl chloride (Note 5) is added as rapidly as possible to the stirred mixture. The mixture is stirred for 8–15 hours (overnight), during which time the ice in the ice bath melts, and the temperature of the reaction flask gradually rises to room temperature. The mixture is then diluted with 15 ml. of

water and extracted with three 25-ml. portions of diethyl ether. The combined ethereal extracts are washed with two 40-ml. portions of water and dried with anhydrous magnesium sulfate. After filtration the solvent is removed at reduced pressure, and 4.4 g. of crude 1-benzylindole is obtained as a liquid. After bulb-to-bulb distillation of this material in a Kügelrohr oven [120–130° (0.0025 mm.)], crystallization of the distillate from 15 ml. of hot ethanol affords 3.46–3.61 g. (83–87%) of 1-benzylindole. A second crop of 0.17–0.26 g. (4–6%) is obtained on concentration of the mother liquors to 6 ml. The total yield of 1-benzylindole, m.p. 43–44°, is 3.72–3.78 g. (90–91%) (Note 6) and (Note 7).

2. Notes

1. Commercial indole (Matheson, Coleman and Bell) was used with no further purification.
2. Commercial HMPA (Aldrich) was stored over Linde 4 A Molecular Sieves and used without further purification.
3. A batch of 0.93 g. of a 57% sodium hydride dispersion in mineral oil is washed with hexane to remove the mineral oil immediately prior to use. The slow addition in the cold minimizes the small amount of foaming caused by hydrogen evolution.
4. This stirring time insures complete formation of sodium indolide.
5. Commercial benzyl chloride (Matheson, Coleman and Bell) was used without further purification.
6. The recrystallized product has ^{1}H NMR absorptions ($CDCl_3$) at δ 5.21 (s, 2H), 6.52 (d, *J* = 3.4 Hz., 1H), 7.0–7.4 (m, 9H), and 7.5–7.7 (m, 1H).
7. 1-Benzylindole colors significantly in contact with air at room temperature (*ca.* 1 week), but keeps indefinitely under argon.

3. Discussion

Generally, the alkylation of sodium indolide, generated from indole and sodium amide in liquid ammonia, has been used for the preparation of *N*-alkylindoles.[4,5,6,7,8,9,10,11,12] The drawback to this method is the use of liquid ammonia. The procedure outlined here[13] overcomes this problem and affords pure *N*-alkylindoles in excellent yields. Further, the use of the hexamethylphosphoric triamide–sodium hydride system affords conditions leading to the formation of the *N*-alkylindoles with little or no side reaction leading to *C*-alkylated products.[13,14] Table I illustrates the generality of the method.

TABLE I
ALKYLATION OF INDOLE SODIUM WITH R-X IN HMPA SOLVENT

R-X	Yield of *N*-Alkylindole, %	b.p. or m.p.

CH_3I	94	b.p. 73–75°/2.4 mm. (Ref. [15], b. p. 70–75/2 mm.)
C_2H_5I	92	b.p. 83–86°/0.6 mm. (Ref. [16], b. p. 82–85°/0.7 mm.)
CH_2=$CHCH_2Br$	84	b.p. 72–73°/0.12 mm. (Ref. [7], b. p. 114–116°/6 mm.)
$C_6H_5CH_2Cl$	90–91	m.p. 43–44° (Ref. [6], m.p. 44°)

References and Notes

1. Department of Chemistry, University of Puerto Rico, Rio Piedras, Puerto Rico 00931. [Present address: Department of Chemistry, University of Idaho, Moscow, Idaho 83843.]
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

ammonia (7664-41-7)

diethyl ether (60-29-7)

hydrogen (1333-74-0)

benzyl chloride (100-44-7)

magnesium sulfate (7487-88-9)

sodium amide (7782-92-5)

sodium hydride (7646-69-7)

Indole (120-72-9)

hexane (110-54-3)

hexamethylphosphoric triamide (680-31-9)

argon (7440-37-1)

1-Benzylindole, 1H-Indole, 1-(phenylmethyl)- (3377-71-7)

SODIUM INDOLIDE

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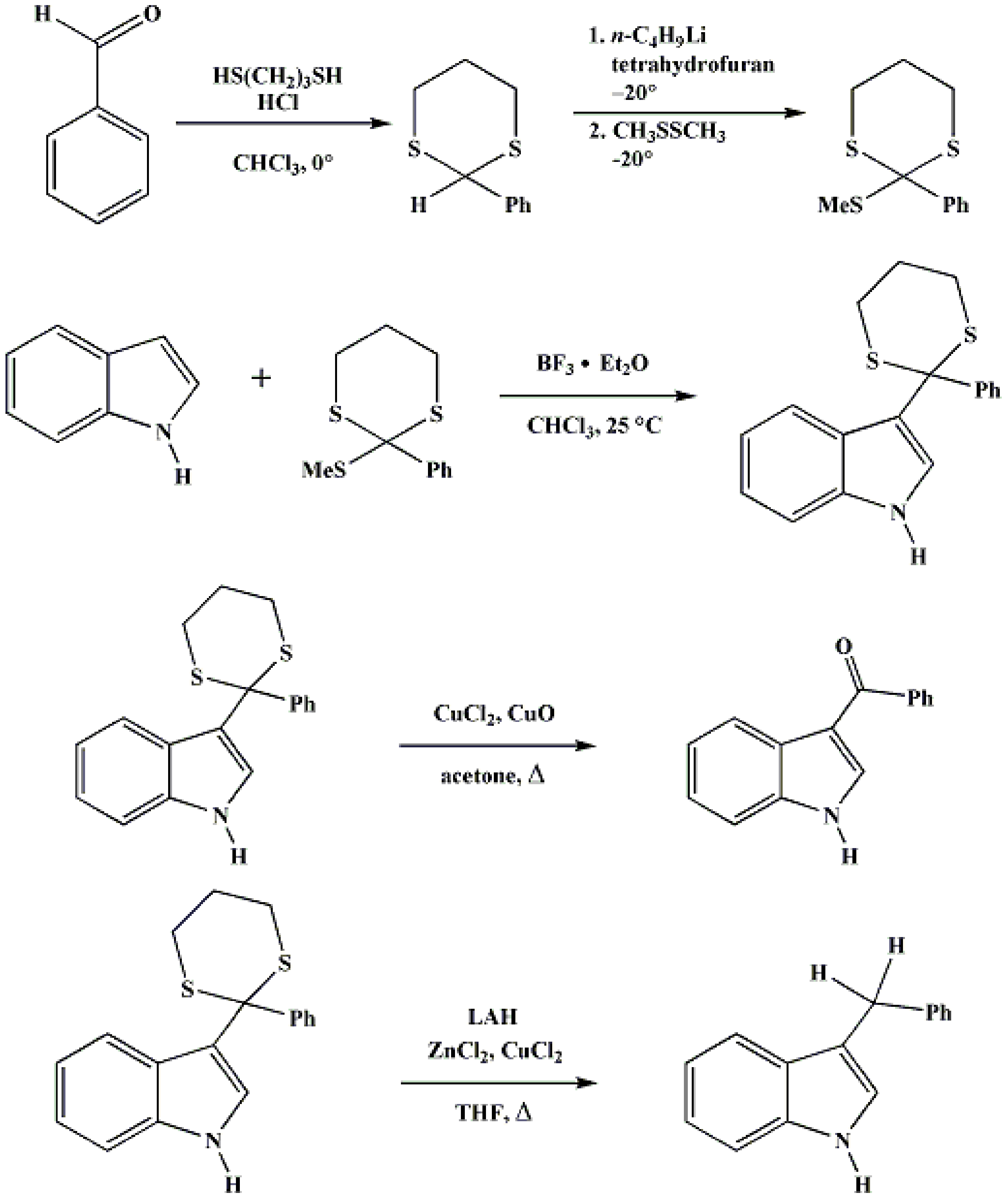
Organic Syntheses, CV 6, 109

3-ALKYLATED AND 3-ACYLATED INDOLES FROM A COMMON PRECURSOR: 3-BENZYLINDOLE AND 3-BENZOYLINDOLE

[1*H*-Indole, 3-(phenylmethyl)- and Methanone, 1*H*-indole-3-ylphenyl-]



Submitted by P. Stütz and P. A. Stadler[1].

Checked by M. Cushman and G. Büchi.

1. Procedure

Caution! The following reactions should be conducted in a well-ventilated hood, since in each step evil-smelling sulfur compounds are either used as starting materials or generated during the reaction.

A. *2-Phenyl-1,3-dithiane*. A 100 ml., two-necked, round-bottomed flask fitted with a gas-inlet tube and a drying tube containing glass wool is charged with 5.52 g. (5.28 ml., 0.0521 mole) of benzaldehyde, 5.6 g. (5.2 ml., 0.052 mole) of 1,3-propanedithiol, and 30 ml. of chloroform (Note 1). The flask is immersed in an ice bath, and a slow stream of hydrogen chloride gas is bubbled through the solution. When saturated (after *ca.* 5 minutes), the reaction mixture is left at room temperature for 30 minutes, then evaporated at reduced pressure. The oily residue (Note 2) is taken up in 50 ml. of methanol and vigorously agitated to induce crystallization. The crystals are collected by filtration, washed with ligroin, and air dried. By condensing the mother liquors, two more crops may be obtained, giving a total of 9.5–9.7 g. (93–95%) of 2-phenyl-1,3-dithiane, m.p. 69–70° (Note 3).

B. *2-Methylthio-2-phenyl-1,3-dithiane*. A 2-l., three-necked, round-bottomed flask is fitted with a mechanical stirrer, a gas inlet connected to a nitrogen source, and a pressure-equalizing dropping funnel. The apparatus is maintained under a positive pressure of nitrogen and carefully protected from moisture throughout the ensuing reaction. The flask is charged with 37.2 g. (0.190 mole) of 2-phenyl-1,3-dithiane and 600 ml. of anhydrous tetrahydrofuran, and 0.228 mole of *n*-butyllithium in hexane (Note 4) is placed in the funnel. With stirring, the flask is cooled with a –20° bath, and the *n*-butyllithium solution is run into the flask over a 10-minute period. Stirring and cooling are continued for 2 hours, after which a solution of 32.2 g. (30.4 ml., 0.342 mole) of dimethyl disulfide (Note 5) in 50 ml. of anhydrous tetrahydrofuran is added over a 10-minute period. The cooling bath is then removed, and as the solution is stirred at room temperature a fine, white precipitate forms.

When the reaction mixture has been at room temperature for 90 minutes, 300 ml. of saturated aqueous sodium chloride is added slowly, followed by 500 ml. of chloroform. The resulting aqueous layer is separated and washed with three 100-ml. portions of chloroform, and the combined chloroform solutions are dried with sodium sulfate and decolorized with activated carbon. Removal of chloroform with a rotary evaporator leaves an oily residue, which is readily crystallized from 100 ml. of methanol. The colorless crystals are collected by filtration and washed with petroleum ether, giving 33.5–35.3 g. (72–77%) of 2-methylthio-2-phenyl-1,3-dithiane, m.p. 76–78°. A second crop of crystalline product may be obtained from the mother liquors.

C. *3-(2-Phenyl-1,3-dithian-2-yl)-1H-indole*. A solution of 24.2 g. (0.102 mole) of 2-methylthio-2-phenyl-1,3-dithiane and 5.86 g. (0.0501 mole) of indole in 600 ml. of chloroform is placed in a 2-l., three-necked flask fitted with a mechanical stirrer and a 100-ml., pressure-equalizing dropping funnel. The reaction mixture is stirred vigorously as a solution of 25 ml. (about 0.2 mole) of boron trifluoride diethyl etherate (Note 6) in 50 ml. of chloroform is added over 10 minutes. An orange–brown, resinous precipitate forms as the slightly exothermic reaction proceeds. After an additional 10 minutes of stirring, a solution of 5.86 g. (0.0501 mole) of indole in 50 ml. of chloroform is added in one portion.

Stirring is continued for 2 hours at room temperature, and methanol is added until a clear solution is obtained (*ca.* 10 ml. of methanol is required, and some heat is generated). When the solution has cooled, it is washed successively with 200 ml. of aqueous 2 *N* potassium carbonate and 200 ml. of water. The aqueous phases are combined, washed with three 100-ml. portions of chloroform, and discarded. The organic phases are combined, dried over sodium sulfate, and decolorized with activated carbon. Concentration of the chloroform solution obtained provides three crops of pale yellow crystals, which are washed with 30% hexane in chloroform and dried for 2 hours at 80°/0.1 mm, yielding 22.3–25.4 g. (72–81%) of 3-(2-phenyl-1,3-dithian-2-yl)-1*H*-indole, m.p. 167–169° (Note 7). This material requires no further purification for use in Parts D or E.

D. 3-*Benzoylindole*. A 100-ml., three-necked flask fitted with a magnetic stirring bar, a condenser, and a pressure-equalizing dropping funnel is charged with 0.48 g. (0.0060 mole) of copper(II) oxide, 1.61 g. (0.0120 mole) of anhydrous copper(II) chloride (Note 8), and 40 ml. of acetone. The resulting suspension is brought to reflux with vigorous stirring, and a solution of 1.55 g. (0.00508 mole) of 3-(2-phenyl-1,3-dithian-2-yl)-1*H*-indole in 9 ml. of acetone and 1 ml. of *N,N*-dimethylformamide is added over 5 minutes. Reflux temperatures are maintained for 90 minutes, during which time the reaction mixture gradually turns yellow, then the mixture is cooled and filtered. The insoluble material is washed with three 20-ml. portions of hot 10% ethanol in dichloromethane, and the combined organic solutions are washed with 50 ml. of aqueous 2 *N* sodium carbonate (Note 9), dried over sodium sulfate, and filtered. Concentration of the filtrate to a small volume under reduced pressure gives a residue which gradually deposits crystals. Filtration provides 0.94–0.97 g. (85–88%) of pure 3-benzoylindole, m.p. 238–240°.

E. 3-*Benzylindole*. A suspension of 1.34 g. (0.0100 mole) of anhydrous copper(II) chloride (Note 8) and 2.72 g. (0.0200 mole) of anhydrous zinc chloride (Note 10) in 150 ml. of anhydrous tetrahydrofuran is prepared in a 500-ml., three-necked, round-bottomed flask fitted with a mechanical stirrer and a condenser connected to a nitrogen source. This mixture is stirred at room temperature and maintained under a nitrogen atmosphere while 3.04 g, (0.0800 mole) of lithium aluminum hydride is added cautiously in small portions (Note 11). The resulting exothermic reaction gives a black precipitate, which is stirred at room temperature for 45 minutes before 1.55 g. (0.00508 mole) of 3-(2-phenyl-1,3-dithian-2-yl)-1*H*-indole is added. Stirring is continued as the mixture is refluxed for 1 hour, cooled to room temperature, and quenched by careful dropwise addition of 10 ml. of water. The resulting slurry is diluted with 100 ml. of dichloromethane and filtered to remove inorganic salts, which are washed by digesting with three 50-ml. portions of refluxing dichloromethane. The combined filtrates are then washed with a solution of 4.0 g. (0.012 mole) of mercury(II) acetate in 100 ml. of water, dried over sodium sulfate, filtered, and concentrated on a rotary evaporator, leaving about 1.1 g. of a yellow crystalline residue. Bulb-to-bulb distillation at 145–155° (0.1 mm.) yields 0.74–0.85 g. (72–82%) of practically pure 3-benzylindole as pale yellow crystals, m.p. 102–105° (Note 12).

2. Notes

1. benzaldehyde and 1,3-propanedithiol were purchased from the Aldrich Chemical Company, Inc., and used without further purification. Exclusion of moisture during the reaction is advantageous but not essential.
2. The checkers obtained a crystalline residue, which was triturated with 10 ml. of

methanol and filtered.

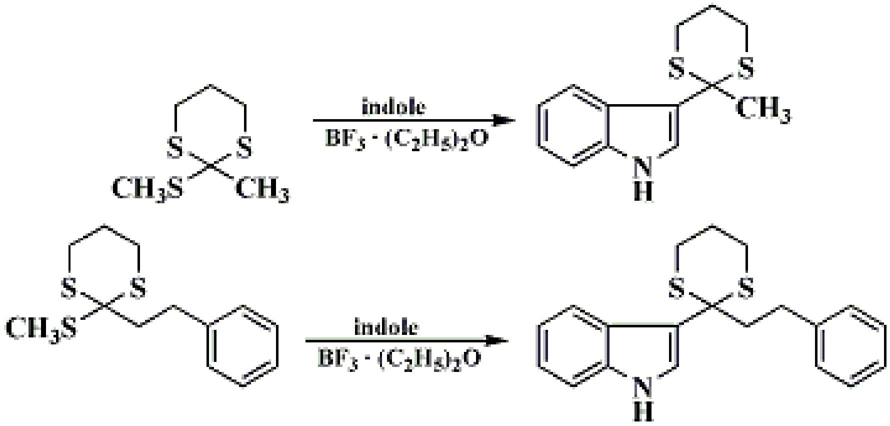
3. The method used is quite general for substituted 1,3-dithianes.[2] A different method is required for the preparation of 1,3-dithiane itself [*Org. Synth.*, **Coll. Vol. 6**, 556 (1988)].
4. The volume of solution required will depend on the concentration of *n*-butyllithium, which should be determined by titration prior to use. A convenient procedure utilizes 1,10-phenanthroline as an indicator; titration to the colorless end point with 2-butanol[3] in xylene gives organolithium concentration directly.[4] A method for transferring large volumes of *n*-butyllithium solution is outlined in *Org. Synth.*, **Coll. Vol. 6**, 979 (1988).
5. Dimethyl disulfide was obtained from the Aldrich Chemical Company, Inc., and used without further purification. The molar ratio used is the same as that in the original reference.[5]
6. Boron trifluoride etherate was purchased from either Fluka AG, Switzerland or Aldrich Chemical Company, Inc. The checkers distilled the commercial material from calcium hydride immediately prior to use.[6]
7. ^{1}H NMR ($CDCl_3$), δ (multiplicity, coupling constant *J* in Hz., number of protons): 1.5–2.2 (m, 2H), 2.7–3.0 (m, 4H), 7.0 (d, *J* = 2.5, 1H), 7.1–7.5 (m, 6H), 7.7–8.2 (m, 4H). A sample recrystallized from methanol–chloroform melted at 183–185°. The submitters also obtained pure product, m.p. 181–183°, after chromatography on basic alumina with 20% petroleum ether in dichloromethane as eluent.
8. Anhydrous copper(II) chloride was prepared by heating the dihydrate at 110° overnight.
9. This extraction must be performed gently, since violent agitation will give an emulsion.
10. Reagent grade anhydrous zinc chloride was obtained from Merck & Company, Inc.
11. Lithium aluminum hydride was obtained from Fluka AG or from Ventron Corporation. One convenient technique for the addition is to weigh the reagent into an Erlenmeyer flask, which is then connected to the reaction flask by a short piece of Gooch tubing. In this way the solid can be added in portions without exposing it to the atmosphere.
12. Various melting points are reported in the literature for 3-benzylindole: 96–98°,[7] 103°, and 107°.[8]

3. Discussion

There are other convenient methods for the preparation of 3-benzylindole[7,8] and 3-benzoylindole.[9] The present procedure, however, has two useful elements of flexibility: it produces both 3-alkyl- and 3-acylindoles from a single precursor, and it tolerates the presence of a wide variety of substituents.

The pivotal step in this sequence is an electrophilic substitution on indole. Although the use of 1,3-dithian-2-yl carbanions is well documented, it has been shown only recently that 1,3-dithian-2-yl carbenium ions can be used in a Friedel–Crafts type reaction. This was accomplished initially using 2-methoxy-1,3-dithiane or 2-methoxy-1,3-dithiolane and titanium tetrachloride as the Lewis acid catalyst.[10] 2-Substituted lysergic acid derivatives and 3-substituted indoles have been prepared under these conditions, but the method is limited in scope by the difficulties of preparing substituted 2-methoxy-1,3-dithianes. 1,3-Dithian-2-yl carbenium ions have also been prepared by protonation of ketene dithioacetals with trifluroacetic acid,[11] but this reaction cannot be used to introduce 1,3-dithiane moieties into indole.

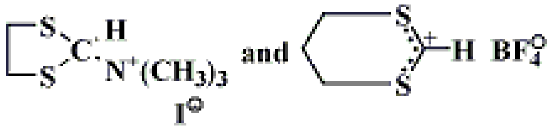
The procedure described herein is fairly general for indoles, and since 2-methylthio-1,3-dithianes are readily available,[3,5] it should prove versatile. Two further examples are as follows:



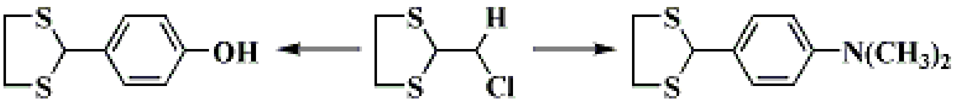
In attempting to extend the method to other activated aromatics, it was found that pyrroles give mixtures of 2-and 3-substituted products, and that naphthol ethers and benzo[b]thiophene fail to react.

The hydrolytic step (Part D) uses conditions described by Narasaka, Sakashita, and Mukaiyama.[12] It was necessary to modify the original stoichiometry, since the recommended molar ratio of substrate: copper(II) chloride: copper(II) oxide (1:2:4) gave only a 57% yield of 3-benzoylindole. The more generally known mercuric oxide-mercuric chloride hydrolysis[2] may also be used, and in the present case it gives a yield of about 90%. The reductive desulfurization of Part E, also based on the work of Mukaiyama,[13] is clearly superior to Raney nickel desulfurization, which gives only 35–45% of 3-benzylindole.

Some new reagents of the same general type, leading to intermediate carbocations of dithians, have been reported in the literature recently. Hiratani, Nakai, and Okawara synthesized 1,3-dithian-2-yltrimethylammonium iodide.[14] Corey and Walinsky[15] applied 1,3-dithian-2-yl fluoroborate, prepared by hydride ion exchange from 1,3-dithian and trityl fluoroborate,[16] to a new kind of electrophilic reaction for the preparation of cyclopentane derivatives.



Further, substantial progress leading to a generally applicable method is shown by the preparation of 2-chloro-1,3-dithiane and its application in electrophilic substitution reactions with reactive aromatic molecules like phenol and *N*,*N*-dimethylaniline.[17]



So far, however, no reagent of the dithianylcarbocation type has been found which allows electrophilic substitution reactions with unactivated aromatic molecules such as benzene.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

2-methoxy-1,3-dithianes

2-methylthio-1,3-dithianes

mercuric oxide-mercuric chloride

ethanol (64-17-5)

potassium carbonate (584-08-7)

hydrogen chloride (7647-01-0)

Benzene (71-43-2)

methanol (67-56-1)

chloroform (67-66-3)

phenol (108-95-2)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

naphthol (90-15-3)

sulfur (7704-34-9)

mercury(II) acetate (1600-27-7)

benzaldehyde (100-52-7)

Raney nickel (7440-02-0)

acetone (67-64-1)

carbon, activated carbon (7782-42-5)

zinc chloride (7646-85-7)

copper(II) chloride (7758-89-6)

xylene (106-42-3)

N,N-dimethylaniline (121-69-7)

copper(II) oxide (1317-38-0)

dichloromethane (75-09-2)

n-butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

N,N-dimethylformamide (68-12-2)

Indole (120-72-9)

hexane (110-54-3)

titanium tetrachloride (7550-45-0)

boron trifluoride etherate, boron trifluoride diethyl etherate (109-63-7)

calcium hydride (7789-78-8)

trifluroacetic acid (76-05-1)

dimethyl disulfide (624-92-0)

benzo[b]thiophene (95-15-8)

2-Butanol (78-92-2)

3-Benzoylindole, Methanone, 1H-indole-3-ylphenyl- (15224-25-6)

1,3-propanedithiol (109-80-8)

2-Phenyl-1,3-dithiane (5425-44-5)

2-methylthio-2-phenyl-1,3-dithiane (34858-82-7)

3-Benzylindole, 1H-Indole, 3-(phenylmethyl) (16886-10-5)

1,10-phenanthroline (66-71-7)

1,3-dithian-2-yl carbenium

2-methoxy-1,3-dithiane

2-methoxy-1,3-dithiolane

1,3-Dithiane, 1,3-dithian (505-23-7)

1,3-dithian-2-yltrimethylammonium iodide

1,3-dithian-2-yl fluoroborate

trityl fluoroborate

2-chloro-1,3-dithiane

3-(2-phenyl-1,3-dithian-2-yl)-1H-indole (57621-00-8)

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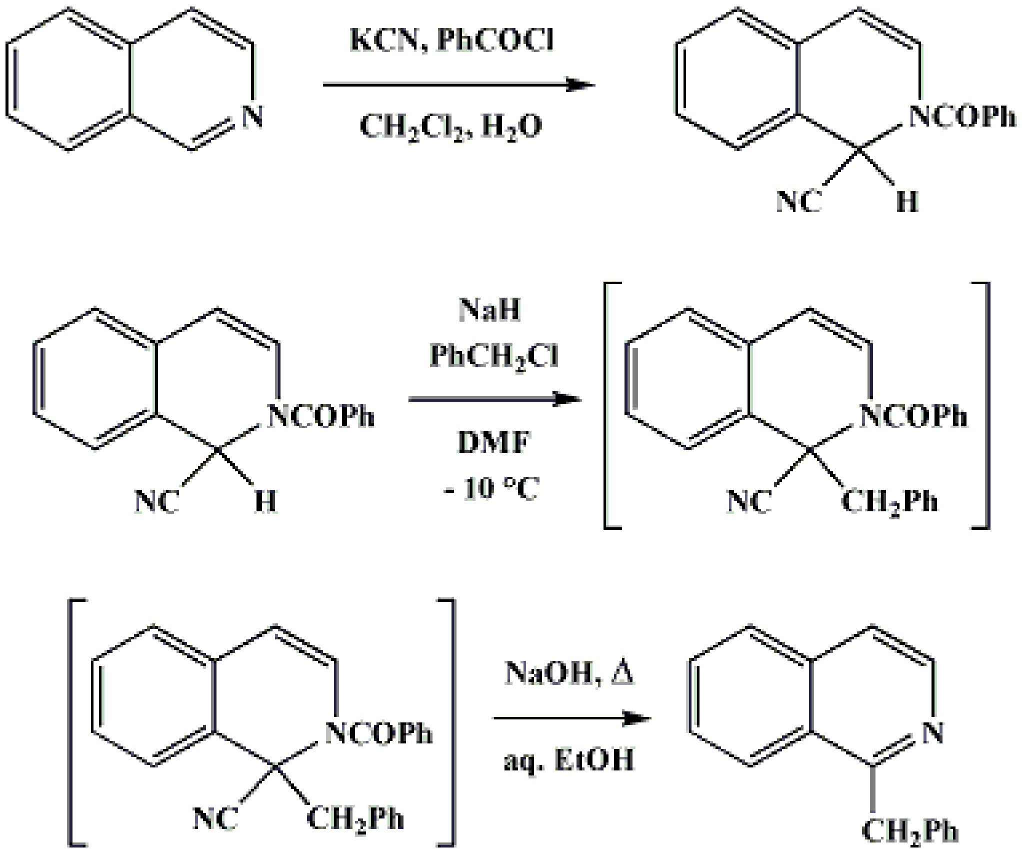
ALKYLATION OF ISOQUINOLINES *via* 2-BENZOYL-1,2-DIHYDROISOQUINALDONITRILES: 1-BENZYLISOQUINOLINE

[Isoquinoline, 1-(phenylmethyl)-]



Submitted by Barrie C. Uff[1], John R. Kershaw[1], and John L. Neumeyer[2].
Checked by A. Brossi, H. Bruderer, and J. Metzger.

1. Procedure

Caution! This reaction involves highly toxic cyanide salts. It may be carried out safely, however, if prudent laboratory procedures are practiced. In particular, cyanide residues should be collected and disposed of separately (Note 1), and the entire sequence should be performed in an efficient hood.

A. *2-Benzoyl-1,2-dihydroisoquinaldonitrile*. A 1-l., three-necked, round-bottomed flask fitted with a mechanical stirrer, a thermometer, and a 250-ml., pressure-equalizing dropping funnel is charged with 64.6 g. (0.499 mole) of freshly distilled isoquinoline (Note 2) in 400 ml. of dichloromethane and 97.7 g. (1.50 moles) of potassium cyanide (Note 2) in 200 ml. of water. The mixture is stirred vigorously as

126.5 g. (121 ml., 0.900 mole) of freshly distilled benzoyl chloride is added from the dropping funnel over 1 hour. As the addition proceeds, the temperature rises to 38°, and the dichloromethane comes to reflux. Stirring is continued for an additional 3 hours, and the resulting brown reaction mixture is filtered through 20 g. of Dicalite Speedex. After the insoluble material has been washed with 200 ml. of water and 200 ml. of dichloromethane, the filtrate and washings are transferred to a separatory funnel. The layers are separated (Note 1) and (Note 3), and the dichloromethane layer is washed successively with 300 ml. of water, three 200-ml. portions of 2 *N* hydrochloric acid, 200 ml. of water, three 200-ml. portions of aqueous 2 *N* sodium hydroxide, and 200 ml. of water (Note 1). After drying over anhydrous potassium carbonate, the dichloromethane solution is filtered and evaporated under reduced pressure, giving 108–110 g. of a pale brown solid. This crude product is dissolved in 200 ml. of boiling ethyl acetate, filtered, and set aside to cool. On standing, the Reissert compound crystallizes as cream rhombs, which are collected on a Büchner funnel and dried in a vacuum desiccator, giving 89.9 g. (69%) of 2-benzoyl-1,2-dihydroisoquinaldonitrile, m.p. 125–127° (Note 4) and (Note 5).

B. 1-*Benzylisoquinoline*. An 11.4-g. portion of 55% sodium hydride–mineral oil dispersion (Note 6) is washed free of oil by slurrying with two 40-ml. portions of dry hexane (Note 7) and decanting the liquid. The sodium hydride is transferred to a dry, 2-l., three-necked, round-bottomed flask fitted with a mechanical stirrer, a 500-ml., pressure-equalizing dropping funnel, and a nitrogen-inlet tube (Note 8). A slurry formed by adding 200 ml. of *N,N*-dimethylformamide (Note 9) is cooled to −10° with a methanol-ice bath. Stirring is begun, and a solution of 65.0 g. (0.250 mole) of 2-benzoyl-1,2-dihydroisoquinaldonitrile and 32 g. (29 ml., 0.25 mole) of benzyl chloride in 400 ml. of dry *N,N*-dimethylformamide is added dropwise over 1 hour. During addition the reaction mixture becomes dark, then fades to light brown. Ice is added as required to hold the bath temperature near −10° (Note 10).

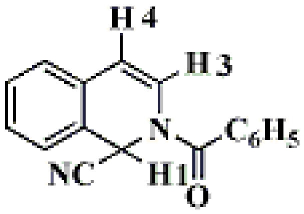
When the addition is complete, the reaction mixture is stirred overnight at room temperature, maintaining a nitrogen atmosphere. Excess sodium hydride is destroyed by slow addition of 10 ml. of water. The *N,N*-dimethylformamide is evaporated at 40° (0.01 mm.), and the residue is diluted with 800 ml. of toluene and 800 ml. of water. After thorough shaking, the mixture is transferred to a separatory funnel. The aqueous layer is discarded, and the toluene layer is washed with two 200-ml. portions of water, dried over anhydrous potassium carbonate, and filtered. Removal of toluene under reduced pressure leaves a yellow oil, which crystallizes on standing (Note 11).

This material is dissolved in 500 ml. of ethanol and transferred to a 2-l., round-bottomed flask. A solution of 200 g. of sodium hydroxide in 200 ml. of water is added, and the mixtured is refluxed for 2 hours. Ethanol is then removed by distillation, and the residue is shaken with 500 ml. of water and 800 ml. of toluene. The toluene layer is separated, washed with two 200-ml. portions of water, and then vigorously shaken with 600 ml. of 2 *N* hydrochloric acid. A portion of the 1-benzylisoquinoline hydrochloride precipitates at this point and is collected on a Büchner funnel and

washed with 200-ml. portions of water and toluene. The filtrate is then transferred to a separatory funnel, the acidic layer is separated, and the crystals from the Büchner funnel are suspended in this layer. After basifying the suspension with 50% aqueous sodium hydroxide, the oil that separates is extracted with three 200-ml. portions of dichloromethane. The combined dichloromethane layers are dried over anhydrous potassium carbonate, filtered, and evaporated under reduced pressure, leaving the crude product as a yellow oil. Distillation under reduced pressure yields 49.8 g. (91%) of pure 1-benzylisoquinoline as a pale yellow oil, b.p. 145–150° (0.01 mm.). The product solidifies on standing and may be crystallized from chloroform–hexane, giving colorless prisms, m.p. 54–55° (Note 12).

2. Notes

1. The original aqueous layer and the aqueous washings of the dichloromethane layer contain cyanide residues. These should be destroyed prior to disposal by making the solution strongly basic with sodium hydroxide and then adding, with stirring, a large excess of iron(II) sulfate. The resulting suspension should be boiled for several hours in the hood before disposal. This process converts cyanide to the nontoxic Prussian Blue [iron(III) ferrocyanide], which precipitates.
2. This product is supplied by Fluka AG, Buchs, Switzerland.
3. Any precipitate occurring during the washing procedure was removed by filtration through a small amount of Dicalite Speedex, obtained from Chemische Fabrik Schweizerhalle, Switzerland.
4. A further fraction of less pure material can be obtained by evaporating the filtrate to approximately 50 ml. and refrigerating the solution overnight.
5. The literature[3] gives m.p. 124–126°. IR (KBr)cm.$^{-1}$: 2240 very weak (-C N), 1658 strong (C=O), 1632 strong (C=C-N); ^{1}H NMR (8% w/w in $CDCl_3$, δ (multiplicity, coupling constant J in Hz., number of protons, assignment): 6.06 (d, $J_{3,4}$ = 7.8, 1H, H_4), 6.57 (broad s, 1H, H_1), 6.60 (d of d, $J_{3,4}$ = 7.8 and $J_{1,3}$ = 1, 1H, H_3), 7.0–7.7 (m, 9H, aromatic CH).



6. This product is supplied by Fluka AG, Buchs, Switzerland. The amount of dispersion used should provide 6.25 g. (0.260 mole) of pure sodium hydride. A small molar excess is used to allow for variation in the sodium hydride: oil ratio of commercial material.
7. The hexane was dried by filtration through alumina.
8. The apparatus was dried in an oven and assembled hot under a stream of dry, oxygen-free nitrogen. A nitrogen atmosphere was maintained throughout the

reaction, since oxygen reacts with the Reissert anion, giving 1-cyanoisoquinoline.[4] Commercial nitrogen was dried by bubbling through concentrated sulfuric acid and found to be sufficiently oxygen-free, requiring no special treatment.

9. *N,N*-Dimethylformamide was purchased from Merck, Darmstadt and dried over molecular sieves (Union Carbide, type 4A).

10. It is necessary to hold the reaction temperature below –5° in order to prevent 1,2-rearrangement of the Reissert anion to 1-benzoylisoquinoline.[5]

11. The intermediate 1-benzyl-2-benzoyl-1,2-dihydroisoquinaldonitrile can be crystallized from ethyl acetate–hexane, m.p. 130–131°. The compound has been described as an oil[5,6] and as a crystalline product, m.p. 129°.[7] IR (KBr) $cm.^{-1}$: 2236 weak (C N), 1669 strong (C=O), 1641 strong (C=C-N); ^1H NMR 8% w/w in $CDCl_3$), δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 3.48 and 3.78 (AB qtr, J = 13, 2H, $C_6H_5CH_2$), 5.54 (d, J = 8, 1H, H_4), 6.37 (d, J = 8, 1H, H_3), 6.75–7.8 (m, 14H, aromatic C*H*). Analysis calculated for $C_{24}H_{18}N_2O$: C, 82.26; H, 5.18; N, 7.99. Found: C, 82.08; H, 5.29; N, 7.89.

12. The literature gives m.p. 56°[8] IR (KBr) $cm.^{-1}$: 1621, 1601, 1585, 1560, 1500, 1493; ^1H (8% w/w in $CDCl_3$), δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 4.66 (s, 2H, CH_2), 7.1–8.25 (m, 10H, aromatic C*H*), 8.5 (d, J = 6, 1H, H_3).

3. Discussion

Other methods for the synthesis of 1-benzylisoquinolines include: (a) dehydrogenation of 1-benzyl-3,4-dihydroisoquinolines,[9,10] which in turn are produced in the BischlerNapieralski reaction by heating *N*-phenylacetyl-β-phenylethylamines with a dehydrating agent such as phosphorus pentoxide in xylene,[9,10] (b) the Pictet-Gams modification of (a), in which *N*-phenylacetyl-2-hydroxy-2-phenylethylamines are dehydrated with phorphorus pentoxide,[8,10,11,12] (c) thermal rearrangements of *N*-benzylisoquinolinium chlorides in the presence of copper,[13] and (d) addition of benzylmagnesium chloride to isoquinolines.[14] The first two methods are limited in scope by the accessibility of starting materials and the requirement that the aromatic ring carry an electron-donating substituent *para* to the point of closure for reasonable yields. The last two methods often lead to mixtures and have not been shown to be of general applicability.

The Reissert method[15]—conversion of an isoquinoline to a 2-benzoyl-1,2-dihydroisoquinaldonitrile (Reissert compound), alkylation, and hydrolysis—has enjoyed wide success in the synthesis of benzylisoquinoline and related alkaloids.[16,17] In particular, aporphines are prepared conveniently by converting isoquinolines to 1-(o-

nitrobenzyl)-isoquinolines *via* a Reissert sequence, followed by *N*-alkylation, reduction, and Pschorr cyclization.[17]

The present procedure illustrates two recent and highly useful modifications of the Reissert method. First, the Reissert compound is formed by the two-phase method of Popp and Blount.[18] This modification generally gives much higher yields for isoquinolines[19] and quinolines[20] than does the single (aqueous) phase method used previously,[21] succeeding in many cases where the aqueous method fails altogether. The aqueous method is generally less clean and has the disadvantage that both starting material and product are insoluble in water. A nonaqueous benzene–hydrogen cyanide method[22] has also been used for Reissert compound formation, but it has the obvious drawbacks associated with the use of hydrogen cyanide. Second, the Reissert anion is formed with sodium hydride–*N*,*N*-dimethylformamide. This modification, developed by the submitters[23] and independently by Popp and Wefer,[6,24] has several advantages over the earlier reagent, phenyllithium in ether,[5,21] in that the sodium hydride does not have to be specially prepared, and its strength is known without titration; cessation of hydrogen evolution indicates that carbanion generation is complete; and the use of *N*, *N*-dimethylformamide overcomes solubility problems often encountered because of the ether used in the earlier method.

It has been observed[25,26] that in lower yielding syntheses of Reissert compounds improvements can be obtained by the inclusion of a phase transfer catalyst such as benzyltrimethylammonium chloride, in 1–3% quantities by weight with respect to the weight of potassium cyanide. For example, methyl 1-cyano-1,2-dihydoisoquinoline-2-carboxylate forms in 69% yield in the presence of benzyltrimethylammonium chloride, but in only 24% in its absence.[25]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

1-benzylisoquinolines

1-benzyl-3,4-dihydroisoquinolines

N-phenylacetyl-β-phenylethylamines

N-phenylacetyl-2-hydroxy-2-phenylethylamines

phorphorus pentoxide

N-benzylisoquinolinium chlorides

isoquinolines

1-(o-nitrobenzyl)-isoquinolines

methyl 1-cyano-1,2-dihydoisoquinoline-2-carboxylate

ethanol (64-17-5)

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

hydrogen cyanide (74-90-8)

oxygen (7782-44-7)

nitrogen (7727-37-9)

potassium cyanide (151-50-8)

iron(II) sulfate (13463-43-9)

copper (7440-50-8)

benzoyl chloride (98-88-4)

toluene (108-88-3)

benzyl chloride (100-44-7)

benzylmagnesium chloride (6921-34-2)

xylene (106-42-3)

dichloromethane (75-09-2)

Phenyllithium (591-51-5)

N,N-dimethylformamide (68-12-2)

sodium hydride (7646-69-7)

hexane (110-54-3)

benzyltrimethylammonium chloride (56-93-9)

isoquinoline (119-65-3)

2-Benzoyl-1,2-dihydroisoquinaldonitrile (844-25-7)

1-Benzylisoquinoline, Isoquinoline, 1-(phenylmethyl)-, benzylisoquinoline (6907-59-1)

1-cyanoisoquinoline (1198-30-7)

1-benzylisoquinoline hydrochloride

iron(III) ferrocyanide

1-benzoylisoquinoline (16576-23-1)

phosphorus pentoxide (1314-56-3)

1-benzyl-2-benzoyl-1,2-dihydroisoquinaldonitrile

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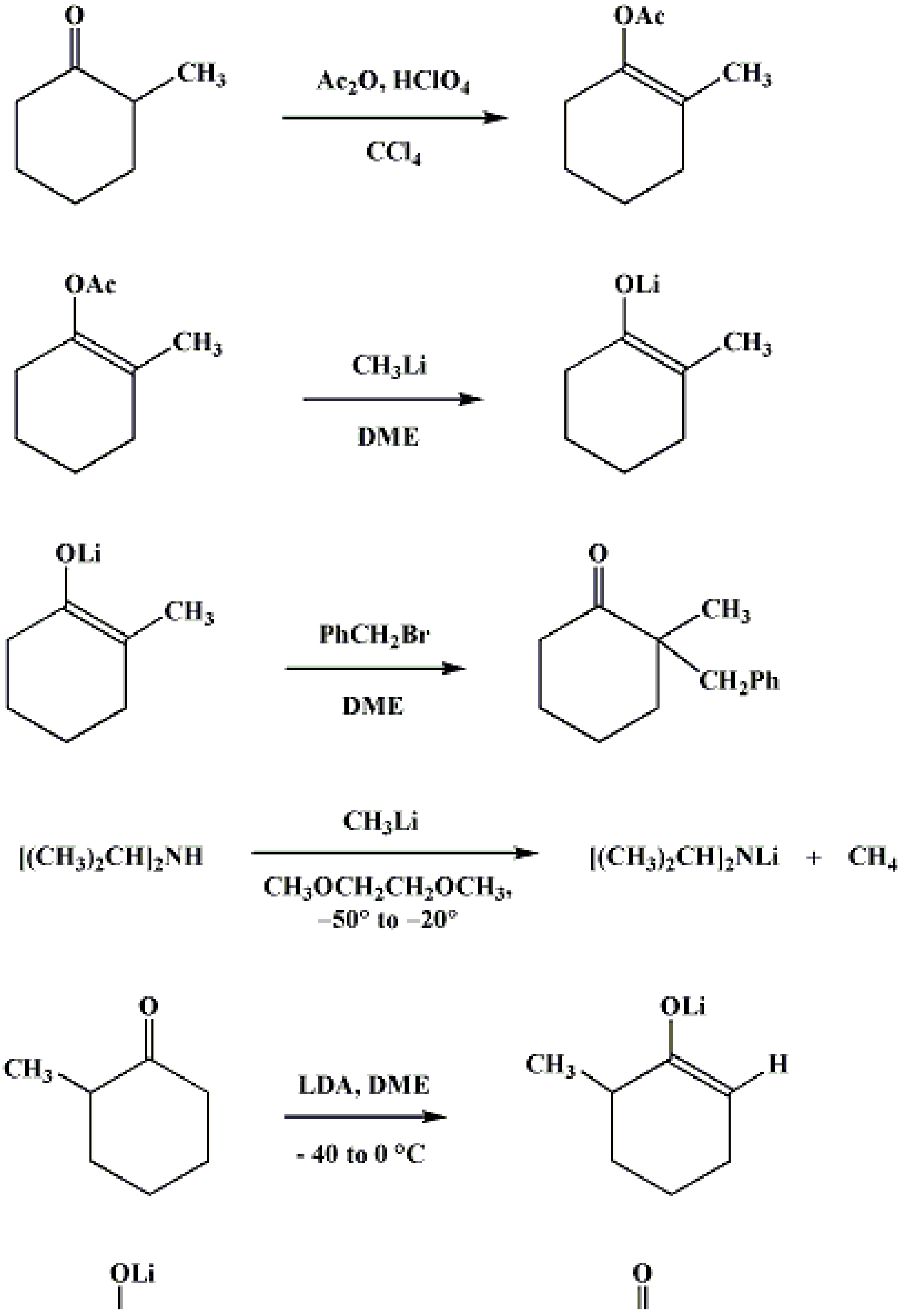
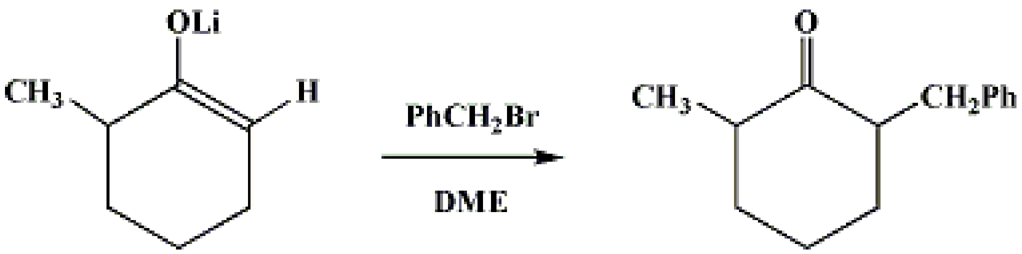
THE FORMATION AND ALKYLATION OF SPECIFIC ENOLATE ANIONS FROM AN UNSYMMETRICAL KETONE: 2-BENZYL-2-METHYLCYCLOHEXANONE AND 2-BENZYL-6-METHYLCYCLOHEXANONE

[Cyclohexanone, 2-methyl-2-(phenylmethyl)- and cyclohexanone, 2-methyl-6-(phenylmethyl)-]





Submitted by Martin Gall and Herbert O. House[1].
Checked by K. E. Wilson and S. Masamune.

1. Procedure

A. *2-Methyl-1-cyclohexen-1-yl acetate*. *Caution! Since mixtures of perchloric acid with small amounts of organic material can explode violently, the perchloric acid should always be the last component added to the reaction mixture.*

To a 1-l. flask are added 600 ml. of carbon tetrachloride, 270 g. (250 ml., 2.65 moles) of acetic anhydride, 56 g. (0.50 mole) of 2-methylcyclohexanone, and 0.34 ml. (0.002 mole) of 70% perchloric acid. The reaction flask is stoppered and allowed to stand at room temperature for 3 hours during which time the reaction solution becomes first yellow-orange and finally red in color. The reaction mixture is poured into a cold (0–5°) mixture of 400 ml. of saturated aqueous sodium hydrogen carbonate and 400 ml. of pentane contained in a 4-l. Erlenmeyer flask equipped with a mechanical stirrer. While the mixture is stirred vigorously at 0–5°, solid sodium hydrogen carbonate is added in 3–5 g. portions as rapidly as foaming of the reaction mixture will permit. The addition of solid sodium hydrogen carbonate is continued until the acetic acid has been neutralized and the aqueous phase remains slightly basic (pH 8). This neutralization requires approximately 400 g. of solid sodium hydrogen carbonate added in portions over a period of *ca.* 3 hours. As soon as the neutralization is complete (Note 1), the organic layer (the lower layer) is separated and the aqueous phase is extracted with three 200-ml. portions of pentane. The combined organic solutions are dried over anhydrous magnesium sulfate and concentrated by distilling the bulk of the pentane through a 30-cm. Vigreux column. The remaining solvents are removed with a rotary evaporator and the residual liquid is distilled (Note 2) under reduced pressure, yielding 66.6–70.9 g. (87–92%) of 2-methyl-1-cyclohexen-1-yl acetate, as a colorless liquid, b. p. 81–86° (18 mm.), n_D^{25} 1.4562–1.4572 (Note 3).

B. *2-Benzyl-2-methylcyclohexanone*. *Caution! Ethereal solutions of methyllithium in contact with atmospheric oxygen may catch fire spontaneously. Therefore any manipulations with this reagent must be carried out with the utmost care to avoid accidental spillage. Benzyl bromide is a powerful lachrymator. Steps B and C should be performed in an efficient fume hood.*

A 1-l., three-necked flask is equipped with a nitrogen-inlet tube fitted with a stopcock, a glass joint fitted with a rubber septum, a 125-ml., pressure-equalizing dropping

funnel, a thermometer, and a glass-covered magnetic stirring bar. After the apparatus has been dried in an oven, 20 mg. of 2,2'-bipyridyl is added to the flask and the apparatus is thoroughly flushed with anhydrous, oxygen-free nitrogen (Note 4). A static nitrogen atmosphere is maintained in the reaction vessel throughout subsequent operations involving organometallic reagents (Note 5). An ethereal solution containing 0.40 mole of methyllithium (Note 6) is added to the reaction vessel with a hypodermic syringe. The diethyl ether is removed by evacuating the apparatus while the solution is stirred and the flask is warmed with a water bath (40°) (Note 7). The reaction vessel is refilled with nitrogen and 400 ml. of 1,2-dimethoxyethane (b.p. 83°, freshly distilled from lithium aluminum hydride) is transferred to the reaction vessel with a hypodermic syringe or a stainless steel cannula. The resulting purple solution of methyllithium and the methyllithium bipyridyl charge-transfer complex is cooled to 0–10° before 29.3 g. (0.190 mole) of 2-methyl-1-cyclohexen-1-yl acetate is added, dropwise and with stirring, over a period of 35–45 minutes (Note 8) while the temperature of the reaction mixture is maintained at 0–10° with an ice bath. After the addition of the enol acetate, the reaction solution must still retain a light red-orange color indicating the presence of a small amount of excess methyllithium (Note 9). To this cold (10°) solution is added rapidly (10–15 seconds) and with stirring, 68.4 g. (0.400 mole) of freshly distilled benzyl bromide [b.p. 78–79° (12 mm.), n_D^{25} 1.5738]. The resulting yellow solution is stirred for 2–2.5 minutes (during which time the temperature of the reaction mixture rises from 10° to about 30°), poured into 500 ml. of cold (0–10°), saturated aqueous sodium hydrogen carbonate, and extracted with three 150-ml. portions of pentane. The combined organic extracts are dried over anhydrous magnesium sulfate and concentrated with a rotary evaporator. The residual liquid is fractionally distilled under reduced pressure, separating 31–41 g. of forerun fractions, b.p. 71–89° (20 mm.) and 41–87° (0.3 mm.) (Note 10), and 20.7–22.2 g. (54–58%) of 2-benzyl-2-methylcyclohexanone as a colorless to pale yellow liquid, b.p. 87–93° (0.3 mm.), n_D^{25} 1.5322–1.5344 (Note 11) and (Note 12).

C. *2-Benzyl-6-methylcyclohexanone*. *Caution! The same precaution as that described in part B should be exercised in this step.*

A 1-l., three-necked flask is equipped as described in part B. After the assembled apparatus has been dried in an oven, 45 mg. of 2,2'-bipyridyl is added to the flask and the apparatus is thoroughly flushed with anhydrous, oxygen-free nitrogen (Note 4). A static nitrogen atmosphere is maintained in the reaction vessel throughout subsequent operations involving organometallic reagents (Note 5). An ethereal solution containing 0.20 mole of methyllithium (Note 6) is added to the reaction flask with a hypodermic syringe. After the ether is removed under reduced pressure as described in part B (Note 7), the reaction vessel is refilled with nitrogen and 400 ml. of 1,2-dimethoxyethane (b.p. 83°, freshly distilled from lithium aluminum hydride) is added to the vessel with a hypodermic syringe or a stainless steel cannula. The resulting purple solution of methyllithium and the methyllithium-bipyridyl charge-transfer complex is cooled to –50° with a dry ice–methanol bath before 21.0 g. (29.2 ml., 0.208

mole) of diisopropylamine (b.p. 84–85°, freshly distilled from calcium hydride) is added with a hypodermic syringe, dropwise and with stirring. During this addition, which requires 2–3 minutes, the temperature of the reaction solution should not be allowed to rise above −20° (Note 12). The resulting reddish-purple solution of lithium diisopropylamide and the bipyridyl charge-transfer complex is stirred at −20° for 2–3 minutes before 50 ml. of a 1,2-dimethoxyethane solution containing 21.3 g. (0.190 mole) of 2-methylcyclohexanone is added, dropwise and with stirring. During this addition the temperature of the reaction solution should not be allowed to rise above 0° (Note 12). After the addition of the ketone, the solution of the lithium enolate must still retain a pale reddish-purple color indicating the presence of a slight excess of lithium diisopropylamide (Note 9) and (Note 13). The enolate solution is stirred and warmed to 30° with a water bath before 68.4 g. (0.400 mole) of freshly distilled benzyl bromide [b.p. 78–79° (12 mm.), n_D^{25} 1.5738] is added, rapidly and with vigorous stirring, from a hypodermic syringe. The temperature of the reaction mixture rises to about 50° within 2 minutes and then begins to fall. After a total reaction period of 6 minutes, the reaction mixture is poured into 500 ml. of cold (0–10°), saturated aqueous sodium hydrogen carbonate and extracted with three 150-ml. portions of pentane. The combined organic extracts are washed successively with two 100-ml. portions of 5% hydrochloric acid and 100 ml. of saturated aqueous sodium hydrogen carbonate, dried over anhydrous magnesium sulfate, and concentrated with a rotary evaporator. The residual yellow liquid is fractionally distilled under reduced pressure (Note 14), separating 31–32 g. of forerun fractions, b.p. 67–92° (20 mm.) and 40–91° (0.3 mm.) (Note 10), and 21.3–23.3 g. (58–61%) of crude 2-benzyl-6-methylcyclohexanone as a colorless liquid, b.p. 91–97° (0.3 mm.), n_D^{25} 1.5282–1.5360. The residue (10–11 g.) contains dibenzylated products. The crude reaction product contains (Note 11) and (Note 15) 2-benzyl-6-methylcyclohexanone (86–90%) and 2-benzyl-2-methylcyclohexanone (10–14%) accompanied in some cases by small amounts of *trans*-stilbene (Note 13).

To obtain the pure 2,6-isomer, the following procedure may be followed. A 200-ml. flask, equipped with a Teflon-covered magnetic stirring bar, dried in an oven, and flushed with nitrogen, is charged with 2.59 g. (0.0479 mole) of sodium methoxide (Note 16) and stoppered with a rubber septum. A static nitrogen atmosphere is maintained in the reaction vessel throughout the remainder of the reaction. Using a hypodermic syringe, 90 ml. of ether (freshly distilled from lithium aluminum hydride) is added to the flask. The resulting suspension is cooled with an ice bath before a mixture of the crude, distilled, alkylated product (about 21–23 g.) and 3.74 g. (0.0505 mole) of ethyl formate (Note 17) is added with a hypodermic syringe. The mixture is stirred for 10 minutes with ice-bath cooling. The bath is then removed and stirring is continued for an additional 50 minutes. The resulting yellow suspension is treated with 300 ml. of water and extracted with 250 ml. of ether. The ethereal extract is washed with 100 ml. of aqueous 1 *M* sodium hydroxide, dried over anhydrous magnesium sulfate, and concentrated with a rotary evaporator. The residual yellow liquid is distilled under reduced pressure, yielding 16.2–17.3 g. (overall yield 42–45%) of pure (Note 11) 2-benzyl-6-methylcyclohexanone as a colorless liquid, b.p. 95–100° (0.3

mm.), n_D^{25} 1.5299–1.5328.

2. Notes

1. Because the enol acetate is slowly hydrolyzed, even by neutral aqueous solutions, the reaction mixture should be neutralized and the organic product separated and dried as rapidly as is practical.
2. The glassware employed in the distillation should be washed first with ammonium hydroxide, then water, and dried in an oven before use to avoid the possibility of acid-catalyzed hydrolysis or rearrangement of the enol acetate during the distillation.
3. The submitters have been unsuccessful in finding a convenient GC column which will separate 2-methyl-1-cyclohexen-1-yl acetate from its double-bond isomer, 6-methyl-1-cyclohexen-1-yl acetate. However, the ^{1}H NMR spectrum (CCl_4) of the product exhibits a peak at δ 2.02 (singlet, CH_3CO) superimposed on a multiplet at δ 1.3–2.2 (vinyl CH_3 and aliphatic CH_2) and lacks absorption δ at 0.98 where 6-methyl-1-cyclohexen-1-yl acetate exhibits a doublet (J = 7 Hz.) attributable to the aliphatic methyl group.[2] Consequently, the product contains less than 5% of the unwanted double-bond isomer. The product exhibits IR absorption (CCl_4) at 1755 $cm.^{-1}$ (enol ester C=O) and 1705 $cm.^{-1}$ (C=C).
4. A good grade of commercial, prepurified nitrogen can be used without further purification. A suitable method for the purification of nitrogen is described in the literature.[3]
5. The apparatus illustrated in f.htmigure 1 is convenient both for evacuating the reaction vessel, refilling it with nitrogen, and also for maintaining a static atmosphere of nitrogen at slightly above atmospheric pressure in the reaction vessel.

Figure 1. Apparatus for either evacuating or supplying a nitrogen atmosphere to the reaction vessel.

Figure 1. Apparatus for either evacuating or supplying a nitrogen atmosphere to the reaction vessel.

6. A solution of methyllithium in ether was purchased from Alfa Inorganics, Inc. Directions for the preparation of methyllithium from methyl bromide are also available.[4] Solutions of methyllithium should be standardized immediately before use by the titration procedure of Watson and Eastham.[5] A standard 0.500 *M* solution of 2-butanol (b.p. 99–100°, freshly distilled from calcium hydride)[6] in *p*-xylene (b.p. 137–138°, freshly distilled from sodium) is prepared in a volumetric flask. A 25-ml. round-bottom flask, fitted with a rubber septum and a

glass-covered magnetic stirring bar, is dried in an oven. After 1–2 mg. of 2,2'-bipyridyl has been added to the flask, it is flushed with anhydrous, oxygen-free nitrogen by inserting hypodermic needles through the rubber septum to allow gas to enter and escape. The tip of a 10-ml. burette is forced through the rubber septum and a measured volume of the standard 2-butanol solution is added to the flask, followed by 2.50 ml. of methyllithium solution. The mixture is stirred and additional standard 2-butanol solution is added to the flask from the burette until the purple color of the methyllithium-bipyridyl complex is just discharged. For a 1.66 *M* solution of methyllithium, 8.30 ml. of the standard 2-butanol solution is required in this titration.

7. Since some lithium enolates are significantly less soluble and less reactive in ether than in 1,2-dimethoxyethane, the submitters recommend the general use of this simple procedure to remove the ether before the lithium enolate is generated.

8. Lithium enolates react relatively slowly with enol acetates to form *C*-acetylated products. Consequently, the enol acetate should be added slowly with efficient stirring so that high local concentrations of both the enolate anion and the enol acetate are avoided.

9. It is important that the indicator color, showing a small excess of strong base, not be discharged completely since the presence of any excess enol acetate or ketone will permit equilibration of the isomeric metal enolates. Consequently, the addition of this reactant is complete if further additions will discharge completely the color of the indicator.

10. The various fractions of the forerun were analyzed employing a GC column packed with silicone gum, No. XE-60, suspended on Chromosorb P and heated to 248°. The components found (retention times) were: benzyl bromide (9.0 minutes), 2-methylcyclohexanone (5.3 minutes), and, in some cases, bibenzyl (22.6 minutes). The bibenzyl, formed by reaction of the benzyl bromide with the excess methyllithium[7] was identified from the IR spectrum of a sample collected from the GC.

11. Using a 6-m. GC column packed with silicone gum, No. XE-60, suspended on Chromosorb P and heated to 240°, 2-benzyl-2-methylcyclohexanone (retention time 35.0 minutes) and 2-benzyl-6-methylcyclohexanone (retention time 33.2 minutes, *cis*- and *trans*-isomers not resolved) are partially resolved. However, the use of this analytical method to detect small amounts of one structural isomer in the presence of the other is not reliable. GC, however, can be used to determine the presence of any *trans*-stilbene (retention time 39.0 minutes) in the crude product.

The proportions of structurally isomeric benzylmethylcyclohexanones can be more accurately measured from the ^{1}H NMR spectra of the distilled monoalkylated products. Pure 2-benzyl-6-methylcyclohexanone (principally the more stable *cis*-isomer in which both substituents are equatorial) exhibits the following ^{1}H NMR (C_6D_6): δ 0.97 (d, J = 6.0 Hz., 3H, CH_3), 1.1–2.6 (m, 9H, aliphatic C*H* and one of the two nonequivalent benzylic protons), 2.9–3.5 (m with at least 5 lines, 1H, the second of the nonequivalent benzylic protons), and 7.0–7.3 (m, 5H, aryl C*H*). In CCl_4 the corresponding peaks are found at δ 0.97

(d, *J* = 6.0 Hz.), 1.1–2.7, 2.9–3.5, and 7.0–7.3; in this solvent a second weak doublet (*J* = 6.5 Hz.) is present at δ 1.04 and is attributable to the small amount of the less stable *trans*-2-benzyl-6-methylcyclohexanone (one equatorial to one axial substituent) present. The 2,6-isomer exhibits IR absorption (CCl_4) at 1710 cm.$^{-1}$ (C=O) and a series of weak (ε 202 to 335) UV maxima (95% C_2H_5OH) in the region 240–270 nm. The mass spectrum exhibits a molecular ion at *m/e* 202 with relatively abundant fragment peaks at *m/e* 159, 145, 117, 111, and 91 (base peak). Pure 2-benzyl-2-methylcyclohexanone has the following ^{1}H NMR absorptions (C_6D_6): δ 0.91 (s, 3H, CH_3), 1.2–1.7 (m, 6H, aliphatic C*H*), 2.1–2.4 (m, 2H, CH_2CO), 2.78 (s, 2H, benzylic CH_2), and 6.9–7.3 (m, 5H, aryl C*H*). In CCl_4 the corresponding peaks are found at 0.95, 1.4–2.0, 2.2–2.6, 2.78, and 6.9–7.3. This ketone has IR absorption (CCl_4) at 1710 cm.$^{-1}$ (C=O) and shows a series of weak (ε 140 to 284) UV maxima (95% C_2H_5OH) in the region 240–270 nm. The mass spectrum exhibits a molecular ion at *m/e* 202 with relatively abundant fragment peaks at *m/e* 159, 117, 92, 91 (base peak), 55, 44, 43, and 41. Mixtures of the 2,6- and 2,2-isomer, could be analyzed by measuring their ^{1}H NMR spectra in C_6D_6 and integrating the region δ 2.6–3.5. The peak at δ 2.78, attributable to both benzylic hydrogen atoms of the 2,2-isomer, is well resolved from the multiplet at δ 2.9–3.5, attributable to one of the two benzylic hydrogen atoms of the 2,6-isomer. Utilizing this method (which is in agreement with the less reliable value obtained by GC analysis), no 2,6-isomer is detected in the 2-benzyl-2-methylcyclohexanone prepared by the present procedure. The 2-benzyl-6-methylcyclohexanone product contains 10–14% of the 2,2-isomer.

12. At temperatures above 0°, 1,2-dimethoxyethane is slowly attacked by lithium diisopropylamide resulting in the protonation of the strong base.

13. If this precaution is not followed, partial or complete equilibration of the enolates will occur because of proton transfers between the enolates and the excess un-ionized ketone. In an experiment where a slight excess of ketone was added, the distilled, monoalkylated product (40% yield) contained 77% of the undesired 2,2-isomer and only 23% of the desired 2,6-isomer. However, it is also important in this preparation not to allow a large excess of lithium diisopropylamide to remain in the reaction mixture; this base reacts with benzyl bromide, forming *trans*-stilbene[8] which is difficult to separate from the reaction product.

14. During the early part of the distillation when a substantial amount of benzyl bromide is present, serious discoloration can be avoided by not heating the still pot above 140°. When the bulk of the benzyl bromide has been removed, the temperature of the still pot may be raised to 150–160° to facilitate distillation of the product.

15. The proportions of the desired 2,6-isomer and the unwanted 2,2-isomer in the alkylated product will vary depending on the rate and efficiency of mixing of the benzyl bromide with the lithium enolate. If the alkylation of the initially formed enolate could be effected without any enolate equilibration, less than 2%

of the unwanted 2,2-isomer would be expected.[9]
16. Sodium methoxide was purchased from Matheson, Coleman and Bell. Material from a freshly opened bottle was used without further purification.
17. Commercial ethyl formate (Eastman Organic Chemicals) was purified by stirring it successively over anhydrous sodium carbonate and over anhydrous magnesium sulfate. The material was distilled to separate pure ethyl formate, b. p. 54–54.5°.

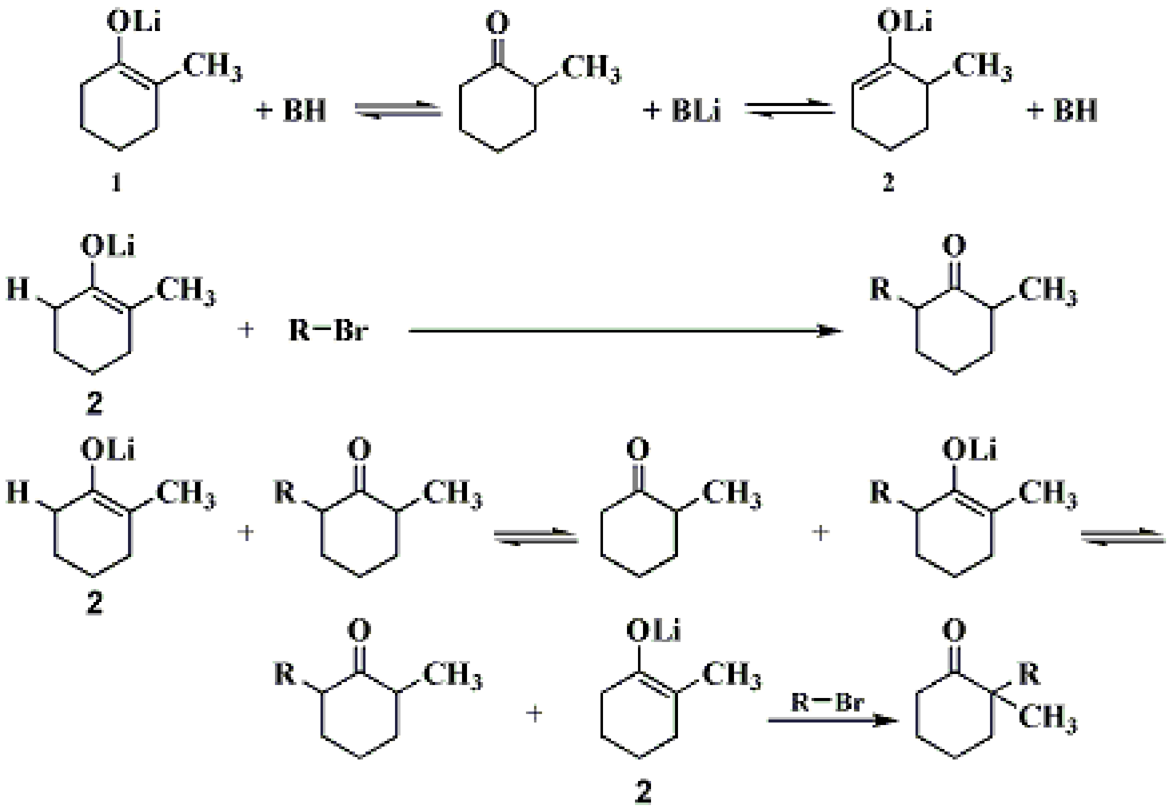
3. Discussion

2-Benzyl-6-methylcyclohexanone has been prepared by the hydrogenation of 2-benzylidene-6-methylcyclohexanone over a platinum or nickel catalyst,[10] and by the alkylation of the sodium enolate of 2-formyl-6-methylcyclohexanone with benzyl iodide followed by cleavage of the formyl group with aqueous base.[11] The 2,6-isomer was also obtained as a minor product (about 10% of the monoalkylated product) along with the major product, 2-benzyl-2-methylcyclohexanone by successive treatment of 2-methylcyclohexanone with sodium amide and then with benzyl chloride or benzyl bromide[12,13]. Reaction of the sodium enolate of 2-formyl-6-methylcyclohexanone with potassium amide in liquid ammonia formed the corresponding dianion which when first treated with 1 equiv. of benzyl chloride, then deformylated with aqueous base gave 2-benzyl-2-methylcyclohexanone[14].

These synthetic routes illustrate the classical methods which have been used for the alkylation of unsymmetrical ketones. Reaction of the ketone with a strong base such as sodium amide under conditions which permit equilibration of the enolates affords an equilibrium mixture of enolates, and subsequent reaction with an alkylating agent yields a mixture of monoalkylated products, as well as polyalkylated products. In the present case, the equilibrium mixture of metal enolates from 2-methylcyclohexanone contains 10–35% of the less highly substituted double bond isomer.[2,15,16] Consequently, the major alkylation product from this mixture is the 2,2-isomer. If the methylene group is protected with a blocking group, the resulting ketone is alkylated solely at the more highly substituted alpha carbon. Removal of the blocking group affords pure 2,2-isomer. Alternatively, an activating group such as a formyl group or a carboalkoxyl group can be introduced at the less highly substituted alpha carbon to permit selective alkylation at this position; the activating group is then removed.

An alternative solution to the problem of effecting the selective alkylation of an unsymmetrical ketone consists of generating a specific enolate under conditions where the enolate isomers do not equilibrate.[17] The methods which have been used to generate specific enolate anions include the reduction of enones[18,19] or α-haloketones[20,21] with metals, the reaction of organolithium reagents with enol silyl ethers[9,22,23] or enol esters,[17,23] and the kinetically controlled abstraction of the least hindered alpha proton from a ketone with a hindered base such as lithium

diisopropylamide.[9] The present procedures illustrate the last two methods. To prevent the equilibration of lithium enolates during their formation, care is taken that no proton-donor BH (such as an alcohol or the un-ionized ketone) is present. Although with attention to this precaution, either of the structurally isomeric enolate ions can be prepared and maintained in solution, this fact does not ensure a structurally specific alkylation. As the accompanying equations illustrate, once reaction of the enolate with the alkyl halide is initiated, the reaction mixture will necessarily contain an un-ionized ketone, namely the alkylated product, and equilibration of the enolate ions can occur. Consequently, a structurally specific alkylation of an enolate anion can be successful only if the alkylation reaction is more rapid than equilibration so that the starting enolate **2** is consumed by the alkylating agent before significant amounts of the unwanted enolate **1** have been formed. In practice, this criterion normally is fulfilled with very reactive alkylating agents such as methyl iodide. With less reactive alkylating agents such as benzyl bromide and *n*-alkyl iodides, some equilibration is usually observed.[23] The problem is aggravated when the alkylation involves the less stable and/or the less reactive enolate isomer (*e.g.*, **2**,). In the present procedures, relatively high concentrations of the enolate and the alkyl halide are employed to increase the alkylation rate and, consequently, decrease the proportion of the unwanted monoalkylation product which results from equilibration prior to alkylation. As is to be expected from the foregoing discussion, the alkylation of the enolate **1**, forming 2-benzyl-2-methylcyclohexanone, exhibits more structural specificity than the alkylation of the enolate **2**, forming 2-benzyl-6-methylcyclohexanone. The unwanted 2,2-isomer (10–14%) in this alkylation is removed by a well-known chemical separation procedure in which the 2,2-isomer is converted to its formyl derivative.[24,25]



This preparation is referenced from:

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- Org. Syn. Coll. Vol. 6, 762
- Org. Syn. Coll. Vol. 7, 172
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- Org. Syn. Coll. Vol. 7, 351
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25. The application of this procedure to the separation of the benzylmethylcyclohexanone isomers was developed by Michael J. Umen.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

methyllithium bipyridyl

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ammonia (7664-41-7)

ether, diethyl ether (60-29-7)

acetic anhydride (108-24-7)

sodium hydroxide (1310-73-2)

sodium hydrogen carbonate (144-55-8)

sodium carbonate (497-19-8)

oxygen (7782-44-7)

carbon tetrachloride (56-23-5)

nitrogen (7727-37-9)

platinum (7440-06-4)

nickel (7440-02-0)

sodium methoxide (124-41-4)

carbon (7782-42-5)

sodium (13966-32-0)

benzyl chloride (100-44-7)

methyl bromide (74-83-9)

ammonium hydroxide (1336-21-6)

p-xylene (106-42-3)

Methyl iodide (74-88-4)

ethyl formate (109-94-4)

Pentane (109-66-0)

magnesium sulfate (7487-88-9)

benzyl bromide (100-39-0)

sodium amide (7782-92-5)

lithium aluminum hydride (16853-85-3)

potassium amide

2-methylcyclohexanone (583-60-8)

bibenzyl (103-29-7)

Methyllithium (917-54-4)

perchloric acid (7601-90-3)

calcium hydride (7789-78-8)

1,2-dimethoxyethane (110-71-4)

2-Benzyl-2-methylcyclohexanone, benzylmethylcyclohexanone, Cyclohexanone, 2-methyl-2-(phenylmethyl)- (1206-21-9)

2-Butanol (78-92-2)

2,2'-bipyridyl (366-18-7)

lithium diisopropylamide (4111-54-0)

2-Benzyl-6-methylcyclohexanone, cyclohexanone, 2-methyl-6-(phenylmethyl)- (24785-76-0)

2-Methyl-1-cyclohexen-1-yl acetate (75411-49-3)

diisopropylamine (108-18-9)

6-methyl-1-cyclohexen-1-yl acetate

2-benzylidene-6-methylcyclohexanone

2-formyl-6-methylcyclohexanone

benzyl iodide (620-05-3)

trans-Stilbene (103-30-0)

trans-2-benzyl-6-methylcyclohexanone

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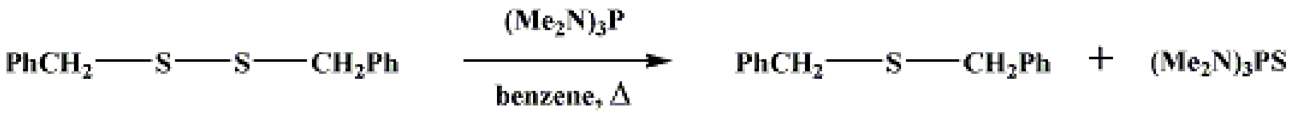
Organic Syntheses, CV 6, 130

SULFIDE SYNTHESIS: BENZYL SULFIDE

[Benzene, 1,1-[thiobis(methylene)]bis-]



Submitted by David N. Harpp[1] and Roger A. Smith.
Checked by Susan A. Vladuchick and William A. Sheppard.

1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A 100-ml., one-necked, round-bottomed flask equipped with a magnetic stirring bar and reflux condenser topped with a drying tube is charged with 3.92 g. (0.0240 mole) of freshly-distilled hexamethylphosphorous triamide (Note 2), 15 ml. of dry benzene (Note 3), and 4.93 g. (0.0200 mole) of benzyl disulfide (Note 4). The mixture is refluxed for 1 hour (Note 5) and (Note 6), during which time it may develop a slight yellow color. After cooling to room temperature, the solution is concentrated on a rotary evaporator (Note 7), and the residue is chromatographed over 75 g. of silica gel (Note 8). After eluting with 8:2 (v/v) hexane–chloroform at 3–4 ml. per minute (Note 9) and monitoring the eluant by GC (Note 10), an initial fraction containing no product is collected (typically 100 ml.). Successive fractions (*ca.* 1.45 1.) contain the product. These are combined and evaporated (Note 11); 20 ml. of absolute ethanol is added to the residue, and the mixture is heated on a steam bath for *ca.* 30 seconds to form a homogeneous solution. The solution is filtered hot through a Büchner funnel (medium-porosity fritted disk), which is washed with three 3-ml. portions of absolute ethanol. The solvent is then removed to constant weight of residue by rotary evaporation, yielding 4.15–4.27 g. (96.7–99.5%) of benzyl sulfide as a white solid or colorless oil that crystallizes on standing (cooling on dry ice for *ca.* 1 minute may be required), m.p. 46.5–47.5°. This product is of sufficient purity for most purposes (Note 12). Further elution of the column with 1.1 1. of chloroform (same flow rate as above) and removal of solvent by rotary evaporation afford 3.94–4.06 g. (101–104%) of crude (*ca.* 95% pure) tris(dimethylamino) phosphine sulfide (Note 13).

2. Notes

1. To avoid benzene, dry toluene or acetonitrile can be used as solvents following the same procedure.
2. The hexamethylphosphorous triamide was obtained from the Eastman Kodak Company, distilled under reduced pressure (water aspirator), yielding a clear, colorless oil, b.p. 46–48° (7 mm.) and stored under nitrogen (rubber septums should be avoided as they tend to deteriorate on prolonged contact with phosphine vapors). Hexamethylphosphorous triamide not freshly distilled often requires much longer reaction times. Since this chemical is an irritant, all operations with it should be performed in a well-ventilated hood. Hexamethylphosphoric triamide is classified as a carcinogen.[2] It should not be confused with hexamethylphosphorous triamide used in this preparation.

3. The benzene was dried over type 3Å molecular sieves. Use of a greater amount of solvent slows the reaction rate. The checker flamed the reaction flask under nitrogen and ran the reaction under a nitrogen atmosphere.

4. The benzyl disulfide was obtained from the Eastman Kodak Company. Some batches, not homogeneous by GC, were recrystallized from absolute ethanol (*ca.* 2.5 ml. per g.), yielding colorless crystals, m.p. 69–71° (lit.,[3] m.p. 70–71.5°).

5. The temperature of the oil bath is 100–105°; the reaction mixture is *ca.* 88°.

6. After 1 hour, the reaction is complete as monitored by GC on an Hewlett-Packard F&M 5751 research chromatograph (1.85 m. × 0.313 cm. stainless-steel column of 10% Apiezon L on Chromosorb W AW/DMCS; column temperature 250°). TLC was found to be of little use in monitoring the reaction, as the R_f values for benzyl disulfide and benzyl sulfide are virtually identical for a variety of solvent systems tried. ^{1}H NMR (C_6H_6) shows that these two compounds have coincidental chemical shifts for the benzylic protons: δ 3.4 (singlet).

A 20% excess of hexamethylphosphorous triamide was utilized to increase the reaction rate. When a 10% excess of the phosphine was used, the reaction was not quite complete (as monitored by GC) even after 3 hours. If the reaction is not allowed to go to completion, the chromatographed product will contain benzyl disulfide. Note that the desulfurization rate for hexaethylphosphorous triamide is comparable to that for hexamethylphosphorous triamide. However, the chromatographic separation following the reaction is much more efficient when hexamethylphosphorous triamide is used.

7. The pressure should be reduced gradually and cautiously to avoid the "bumping" often characteristic of benzene distillations.

8. To 75 g. of silica gel (see below) that has been freshly heated at 120–130° for 18 hours and cooled in a desiccator (see below) is added *ca.* 200 ml. of a 8:2 (v/v) hexane–chloroform mixture. The resulting slurry is stirred to remove air bubbles and added to a 26-mm. column (in which a flat base of glass wool and sand has been prepared) in one portion with tapping of the column. Any remaining silica gel is also added to the column by washing with more of the solvent mixture, resulting in a *ca.* 28-cm. column of silica gel. A sand layer is then carefully added to the top of the column, and the solvent is drained to the sand level. The reaction residue is placed on the column as is, and the reaction flask is rinsed with small portions of hexane–chloroform which are also loaded onto the column.

The volume of column packing used represents a length–width ratio of *ca.* 10:1. Since column efficiency improves as the length–width ratio is increased (for a given volume of packing), these approximate dimensions should be maintained. For example, when a length–width ratio of *ca.* 9:1 was applied (with the same amount of silica gel), there was not complete separation, and the yield of pure benzyl sulfide was less than optimum (93%).

The packing material is Silica Gel 60, Cat 7734 (70–230 mesh ASTM), for column chromatography, an EM Reagent of E. Merck, Darmstadt, available from Brinkmann Instruments Ltd. (Canada). Lower grades of silica gel such as the 60–120 mesh grade of BDH Chemicals Ltd. were found to be much less efficient, not effecting a complete separation of the compounds. The amount of Silica Gel 60 utilized and found to be most efficient was 75 g., or 8.5 g. of silica gel per g. of reaction mixture. The checkers used Mallinckrodt CC-7 Special (100–200 mesh) column packing, a flow rate of 8.5 ml. per minute, a 9:1 ratio of hexane–chloroform eluant and obtained a lower product yield (77%).

Eighteen hours at 120–130° was found to dry various batches of Silica Gel 60 to the same activity. The silica gel was cooled in a desiccator over 8-mesh Drierite available from Anachemia Chemicals Ltd. This procedure should be performed so that the silica gel is used immediately after cooling; otherwise, the activity will decrease with time even if the silica is left in the desiccator.

The solvent mixture of 8:2 (v/v) was found to be the most effective, with increased concentrations of chloroform not effecting a complete separation. The two solvents should

therefore be mixed thoroughly. Chloroform (A.C.S. grade) and an isomeric mixture of hexanes (A.C.S. grade) supplied by Fisher Scientific Company are quite suitable.
9. Increased flow rate resulted in a poorer chromatographic resolution.
10. The chromatography may be monitored by collection of 50-ml. fractions analyzed by GC (same conditions as in (Note 6)).
11. The residue will be a white solid or colorless oil.
12. The solidified residue is homogeneous by GC, and its IR and ^{1}H NMR spectra and GC are identical to those of recrystallized authentic benzyl sulfide. The product may be recrystallized from *ca.* 25 ml. of absolute ethanol to yield colorless plates, m.p. 47–48° (lit.,[4] m.p. 50°), which give a satisfactory combustion analysis.
13. This material has IR and ^{1}H NMR spectra identical to those of an authentic sample prepared by the procedure of Stuebe and Lankelma.[5]

3. Discussion

The disulfide linkage is found in a large number of natural products,[6,7,8,9] and chemical manipulations of this functionality are of considerable interest.[10,11,12,13,14] In contrast to desulfurization methods utilizing various phosphines[15,16,17,18] and phosphites,[19,20,21,22,23,24,25,26,27,28,29] aminophosphines have proved to be efficient desulfurizing agents for a variety of alkyl, aralkyl, alicyclic, and certain diaryl disulfides.[30] In addition, the reaction conditions are mild enough to be compatible with a variety of common functional groups. Hence, the desulfurization procedure given here for benzyl disulfide merely demonstrates the practibility of this method for which the synthetic scope and mechanism have already been developed.[30]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

Benzene (71-43-2)

acetonitrile (75-05-8)

chloroform (67-66-3)

nitrogen (7727-37-9)

toluene (108-88-3)

phosphine (7723-14-0)

hexane (110-54-3)

benzyl disulfide (150-60-7)

Hexamethylphosphorous triamide (1608-26-0)

hexamethylphosphoric triamide (680-31-9)

Hexaethylphosphorous triamide (2283-11-6)

Benzyl sulfide, Benzene, 1,1-[thiobis(methylene)]bis- (538-74-9)

tris(dimethylamino) phosphine sulfide (3732-82-9)

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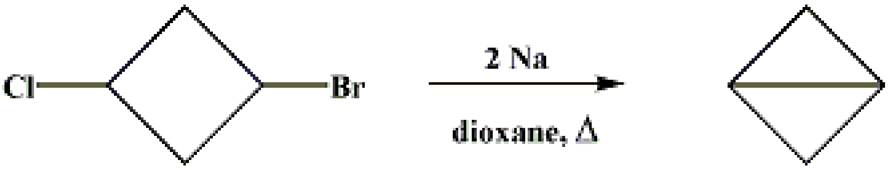
Organic Syntheses, CV 6, 133

BICYCLO[1.1.0]BUTANE

[Bicyclo[1.1.0]butane]



Submitted by Gary M. Lampman and James C. Aumiller[1].
Checked by R. A. Fenoglio and K. B. Wiberg.

1. Procedure

A 300-ml., three-necked, round-bottomed flask is equipped with a mechanical stirrer, a reflux condenser, and a pressure-equalizing addition funnel. The condenser is connected in series with two traps, immersed in liquid nitrogen, with the exit leading to a drying tube (Note 1). A line for dry nitrogen that has a T-tube joined to a U-tube containing mercury is connected to the top of the addition funnel (Note 2). To the flask are added 150 ml. of purified dioxane (Note 3) and 13.6 g. (0.591 g.-atom) of freshly cut sodium (Note 4). The mixture is heated to reflux, and the molten sodium is broken up with the stirrer. A solution of 20.0 g. (0.118 mole) of 1-bromo-3-chlorocyclobutane (Note 5) in 20 ml. of dioxane (Note 3) is added to the refluxing dioxane over a 1-hour period; refluxing is maintained for an additional 2 hours (Note 6) and (Note 7). The product in the traps is separated from any dioxane with the vacuum manifold system shown in f.htmigure 1 (Note 8). The two traps containing the product are cooled in liquid nitrogen and connected to one of the stopcocks on the manifold. A gas storage bulb (f.htmigure 2) is attached to the other stopcock. All the stopcocks are opened, and the system is evacuated. The stopcock to the pump is then closed, and the liquid nitrogen bath is removed from the traps and used to cool the gas storage bulb. The traps are warmed slightly, and the bicyclobutane condenses in the storage bulb, leaving the dioxane behind, yielding 5–6 g. (78–94%) (Note 9) of bicyclobutane.

Figure 1. Vacuum manifold.

Figure 1. Vacuum manifold.

Figure 2. Gas storage bulb.

Figure 2. Gas storage bulb.

2. Notes

1. Although the entire gaseous product is caught in the first trap, this trap tends

to plug during the reaction. Therefore, the second trap is used as a safety measure to collect the bicyclobutane as the first trap is thawed to open the system.

2. It is essential that a U-tube containing mercury is connected by a T-connector to the nitrogen inlet. The U-tube monitors the pressure on the system and acts as a safety valve in the event of a plugged trap. A slight positive pressure is maintained.

3. Reagent grade dioxane (2 l.) was heated to reflux with the sodium ketyl of benzophenone, prepared from 10 g. of benzophenone and 1 g. of sodium, until a deep blue solution results. If the color is not developed, another portion of benzophenone and sodium is added and heating continued until the color persists. The peroxide-free dioxane was distilled from the flask and used immediately.

4. The excess sodium allows the reaction to proceed at a greater rate and decomposes any peroxides remaining in the dioxane.

5. 1-Bromo-3-chlorocyclobutane was prepared as described in *Org. Synth.*, **Coll. Vol. 6**, 179 (1988).

6. The reflux rate and flow of nitrogen gas must be kept at a minimum to assure that the amount of dioxane carried over to the traps in liquid nitrogen is kept as small as possible.

7. This reflux time is a minimum since decreased yields were observed when the reflux time was shortened. There was no increase in yield when the refluxing time was increased to 4 hours.

8. The basic apparatus consists of a large diameter (about 25 mm.) glass tube to which are attached at least two stopcocks, a closed-end manometer, and a large stopcock, used to isolate the manifold from the vacuum pump.

9. The product, which is about 90% bicyclobutane and 10% cyclobutene, is sufficiently pure for most purposes. The purity of the product can be determined by GC analysis at room temperature, using a 275-cm.-long column containing 20% β,β'-oxydipropionitrile on Chromosorb W (45/60). The retention times are 2.7 and 3.8 minutes for cyclobutene and bicyclobutane, respectively. Bicyclobutane (b.p. 8°) can be stored temporarily in the gas storage bulb as a liquid in an acetone–dry ice bath or for longer periods of time in an ampoule, sealed under vacuum, and stored in a freezer.

3. Discussion

Bicyclobutane has been prepared by intramolecular addition of divalent carbon to an olefinic double bond,[2] irradiation of butadiene,[3] decomposition of cyclopropanecarboxaldehyde tosylhydrazone,[4] and deamination of cyclobutylamine and cyclopropylcarbinylamine.[5] The present procedure, based upon a published method,[6] gives the highest yield of the known methods and provides a process for making moderate quantities of material.

The procedure provides a good example of a high-yield intramolecular Wurtz reaction. Intermolecular Wurtz reactions normally do not give high yields of coupled products and are accompanied by formation of alkenes and alkanes corresponding to the alkyl halide.[7] In contrast, intramolecular reactions of 1,3-dihalides with metals such as sodium are important synthetic methods for making cyclopropane derivatives. Examples are the reactions of sodium with pentaerythrityl tetrabromide, giving spiropentane[8] and of sodium-potassium alloy with 1,3-dibromohexamethylcyclobutane, giving hexamethylbicyclo[1.1.0]butane.[9] If 1,3-dihalides are not used, the yields of cyclic compounds may be considerably reduced. Thus, 1,4-dibromobutane[10] and 3-(bromomethyl)cyclobutyl bromide[11] give very little cyclobutane and bicyclo[1.1.1]pentane, respectively.

Metals other than sodium may be considered for the reduction in intramolecular Wurtz reactions.[11] One of the most common of these is zinc under various reaction conditions. Examples of use of this reagent that have resulted in high yields of cyclopropane and derivatives of cyclopropane include cyclopropane from 1,3-dichloropropane,[12] spiropentane from pentaerythrityl tetrabromide in the presence of a chelating agent,[13] spiro[2.5]octane from 1,1-bis-(bromomethyl)cyclohexane,[14] and 1,1-dialkylcyclopropanes from 1,3-dibromo-2,2-dialkylpropanes.[14] However, 1-bromo-3-chlorocyclobutane yields no bicyclobutane on reaction with zinc,[6] even in the presence of a chelating agent.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 179

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium ketyl of benzophenone

nitrogen (7727-37-9)

mercury (7439-97-6)

Benzophenone (119-61-9)

zinc (7440-66-6)

sodium (13966-32-0)

cyclopropane (75-19-4)

1,3-dichloropropane (142-28-9)

dioxane (5703-46-8)

butadiene (106-99-0)

Pentaerythrityl tetrabromide (3229-00-3)

sodium-potassium

1,4-dibromobutane (110-52-1)

cyclobutane (287-23-0)

cyclobutene (822-35-5)

1-Bromo-3-chlorocyclobutane (4935-03-9)

Cyclobutylamine (2516-34-9)

cyclopropylcarbinylamine (2516-47-4)

Bicyclo[1.1.0]butane (157-33-5)

bicyclobutane

cyclopropanecarboxaldehyde tosylhydrazone

spiropentane (157-40-4)

1,3-dibromohexamethylcyclobutane

hexamethylbicyclo[1.1.0]butane

3-(bromomethyl)cyclobutyl bromide

bicyclo[1.1.1]pentane

spiro[2.5]octane (185-65-9)

1,1-bis-(bromomethyl)cyclohexane

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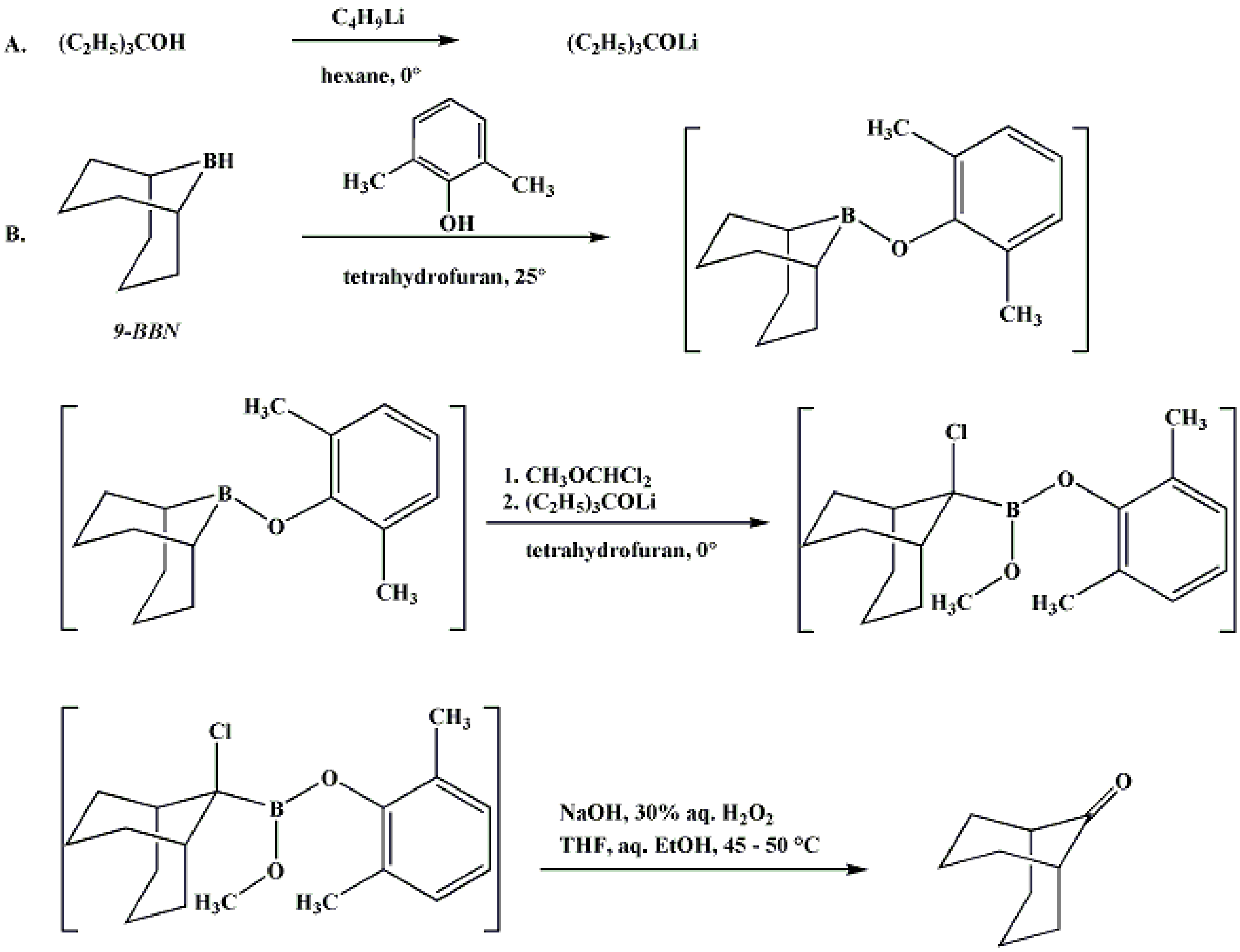
Organic Syntheses, CV 6, 137

BORANES IN FUNCTIONALIZATION OF DIENES TO CYCLIC KETONES: BICYCLO[3.3.1]NONAN-9-ONE



Submitted by Bruce A. Carlson[1] and Herbert C. Brown[2].
Checked by J. C. Bottaro and G. Büchi.

1. Procedure

Caution! The oxidation with 30% hydrogen peroxide in the last step of Part B may become vigorous and exothermic. No difficulties have been encountered under the conditions described; however, the oxidation should be carried out in a hood behind a protective shield.

A. *Lithium triethylcarboxide* (Solution **1**). A thoroughly dried, 1-l., three-necked, round-bottomed flask fitted with a septum inlet with serum cap, a reflux condenser, and a magnetic stirrer is purged with and maintained under an atmosphere of dry nitrogen. After a solution of 300 ml. of 1.67 *M n*-butyllithium (0.500 mole) in hexane (Note 1) is introduced into the flask by syringe (Note 2) and cooled to 0° in an ice bath, 58 g. (0.50 mole) of 3-ethyl-3-pentanol (Note 3) is added slowly, but constantly, by syringe (Note 4). At the end of addition the yellow tint of the *n*-butyllithium solution disappears. The alkoxide solution is standardized by hydrolysis of aliquots in water and by titration of the resulting lithium hydroxide with standard acid to a phenolphthalein end point (Note 5).

B. *Bicyclo[3.3.1]nonan-9-one* (2). A thoroughly dried, 3-l., three-necked, round-bottomed flask fitted with a serum cap and a magnetic stirrer under nitrogen is charged with 42.3 g. (0.347 mole) of 9-borabicyclo[3.3.1]nonane (9-BBN) (Note 6) before 500 ml. of anhydrous tetrahydrofuran (Note 7) is added using a double-ended syringe needle (Note 2). The flask is fitted with a dry, 500-ml., pressure-equalizing dropping funnel while the flask is purged with a rapid stream of dry nitrogen. The apparatus is maintained under a static pressure of nitrogen throughout the reaction. A solution of 42.3 g. (0.347 mole) of 2,6-dimethylphenol (Note 8) in 75 ml. of anhydrous tetrahydrofuran is added slowly by syringe, and the mixture is

stirred at room temperature for 3 hours. Once hydrogen evolution is complete (Note 9), 350 ml. of a 1.46 *M* solution of **1** in hexane is introduced into the dropping funnel after purging it with dry nitrogen. The clear solution in the flask is cooled to 0°, and 44 g. (35 ml., 0.38 mole) of dichloromethyl methyl ether (Note 10) is added. Solution **1** is then added slowly over approximately 30 minutes. The ice bath is removed, and the flask is warmed to room temperature for 90 minutes (Note 11). A heavy white precipitate of lithium chloride forms (Note 12), and the nitrogen atmosphere is no longer required. A solution of 300 ml. of 95% ethanol, 70 ml. of water, and 42 g. of sodium hydroxide is added, and the mixture is cooled to 0° with efficient stirring. Oxidation is carried out over a 40–45 minute period by the slow, dropwise addition of 70 ml. of 30% hydrogen peroxide (Note 13), while the temperature is maintained below 50° with a cooling bath. After addition the mixture is heated with stirring to 45–50° for 2 hours (Note 14) and then cooled to room temperature. Water (300 ml.) is added, and the aqueous phase is saturated with sodium chloride. The organic phase is separated and washed with 100 ml. of saturated aqueous sodium chloride. The solvents are removed on a rotary evaporator, and the resulting orange liquid is diluted with 500 ml. of pentane, which is then extracted with 250-ml. and 100-ml. portions of aqueous 3 *M* sodium hydroxide to remove 2,6-dimethylphenol. After washing with 100 ml. of saturated aqueous sodium chloride, the pentane is removed on a rotary evaporator. The 3-ethyl-3-pentanol is removed by distillation under a water aspirator vacuum, b.p. 54–56° (16 mm.) (Note 15). The resulting semisolid residue is dissolved in 200 ml. of pentane and filtered to remove the impurities. Ketone **2** is crystallized by cooling the filtrate to −78°. Ketone **2** is collected by suction filtration, washed with 50 ml. of −78° pentane (Note 16), and dried (Note 17), yielding 35–40 g. (78–83%) of pure ketone **2**, m.p. 154–156° (Note 18). Evaporation of the filtrate to *ca.* 50 ml. and cooling to −78° gives another 3–4 g. of ketone **2**, m.p. 149–154°. The total yield of bicyclo[3.3.1]nonan-9-one **(2)** is 38–44 g. (79–91%).

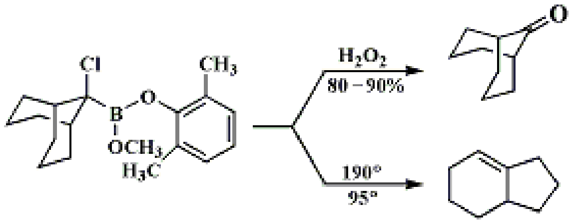
2. Notes

1. *n*-Butyllithium in hexane was obtained from Foote Mineral Company. The solution can be titrated for total alkyllithium by the procedure of Watson and Eastham,[3] and for total base by hydrolysis of aliquots and titration against standard acid prior to use. *n*-Butyllithium solution of good purity is essential for success of the reaction.
2. A double-ended syringe needle is most convenient for transfer of reagents and handling of air-sensitive solutions. Transfer is completed by applying nitrogen pressure. See references [4] and [5,6,7,8,9] for descriptions of this procedure and for general techniques for handling air-sensitive reagents.
3. 3-Ethyl-3-pentanol (triethylcarbinol) (98%) was purchased from Chemical Samples Company, 469 Kenny Road, Columbus, Ohio 43221, and used without further purification. It is also available from Aldrich Chemical Company, Inc.
4. Addition causes vigorous reaction with evolution of butane and heat. Redissolution of the butane in the solution may create a partial vacuum, causing air to be sucked back into the flask; the addition should be kept at such a rate to prevent this. The solution may reflux, but this causes no harm.
5. Alternatively, if only one use of the solution of lithium triethylcarboxide **(1)** is planned, the required amounts of butyllithium solution and 3-ethyl-3-pentanol may be reacted, and the resulting solution of lithium triethylcarboxide used without standardization.
6. 9-Borabicyclo[3.3.1]nonane (9-BBN) was purchased from Aldrich Chemical Company, Inc., and used directly. Alternatively, 9-BBN may be prepared by hydroboration of 1,5-cycloöctadiene.[5,6,7,8,9] *Caution! 9-BBN is air sensitive and can be pyrophoric.*
7. Tetrahydrofuran, containing less than 0.002% peroxides, supplied by the William A. Mosher, Ph.D. Company, 101 Townsend Road, Newark, Delaware 19711, was used directly. Tetrahydrofuran from other sources may require purification prior to use. Stirring with lithium aluminum hydride or sodium benzophenone ketyl, followed by distillation under an inert atmosphere, is the recommended procedure for removal of water and peroxides (see reference 4, p. 256).
8. 2,6-Dimethylphenol (99%), from Chemical Samples Company, was used without purification. It is also available from Aldrich Chemical Company, Inc.
9. Addition causes evolution of hydrogen and is carried out over *ca.* 10 minutes to prevent foaming. The undissolved 9-BBN rapidly goes into solution. Completion of the reaction may be measured by monitoring hydrogen evolution with a gas meter. The theoretical amount of hydrogen is 7.8 l. at STP.
10. Dichloromethyl methyl ether (98%) was purchased from Aldrich Chemical Company, Inc. (listed as α,α-dichloromethyl methyl ether) and used without purification. Better results can be obtained if the material is distilled under nitrogen prior to use. Unlike chloromethyl methyl ether and bis(chloromethyl) ether, dichloromethyl methyl ether is reported to have no significant carcinogenic activity;[10] however, as a precaution it should be handled carefully in a well-ventilated hood.
11. Longer reaction times (*e.g.*, allowing the reaction to stir overnight) will not affect the product.
12. The checkers observed no precipitate in their two runs. On occasion the submitters have also noted no lithium chloride precipitate during a run or sudden precipitation of the salt. Apparently the lithium chloride supersaturates on

these occasions.
13. The 30% hydrogen peroxide was obtained from Fisher Scientific Company.
14. Initial heating should be done cautiously in case an additional exotherm is experienced.
15. 3-Ethyl-3-pentanol may be removed rapidly by condensation into an acetone–dry ice cold trap.
16. The temperature of the solution should be kept as close as possible to −78° during filtration to prevent losses of the first crop of product. On humid days crystallization and filtration are best accomplished in a closed system to prevent excessive condensation of water.
17. The product has a high vapor pressure and sublimes readily. Care should be taken in drying so that losses of product are not incurred. Drying briefly in a vacuum desiccator over Drierite is recommended.
18. Literature,[11] m.p. 155–158.5°; the 2,4-dinitrophenylhydrazone was prepared by the standard procedure and recrystallized from ethyl acetate–ethanol to provide orange prisms, m.p. 190–191.2° lit.,[11] m.p. 191.8–192.3°.

3. Discussion

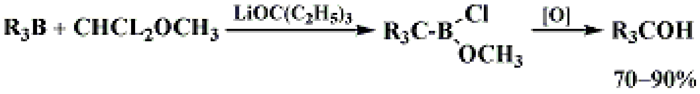
Dialkylborinic acids are conveniently prepared by the hydroboration of olefins with monochloroborane diethyl etherate[7] or, in some cases, by controlled hydroboration of two equivalents of olefin[7] with borane–tetrahydrofuran or borane–methyl sulfide complex followed by alcoholysis. The base-induced reaction of dichloromethyl methyl ether with borinic acid esters provides a route to a variety of ketones[12] and olefins.[13,14] The reaction presumably proceeds *via* generation of a haloalkoxy carbanion or carbene which reacts rapidly with the borinic acid ester, resulting in transfer of the alkyl groups from boron to carbon. The α-chloroboronic ester intermediate, thus generated, is exceptionally versatile. Oxidation results in the formation of the corresponding ketone in high yield,[12,15] whereas pyrolysis or solvolysis with aqueous silver nitrate[14] provides the internal olefin:



Lithium triethylcarboxide **(1)** is the base of choice for these conversions. The use of less hindered alkoxide or amide bases results in poorer yields. In this procedure 1.5–2.0 equivalents of base are required, although with more bulky alkyl groups attached to boron only 1 equivalent is necessary. The use of the more hindered 2,6-diisopropylphenol, forming the borinic ester, gives a 96% yield of the bicyclic ketone with only 1 equivalent of base; however, in the work-up procedure this phenol is more difficult to separate from the ketone.

Carbonylation of trialkylboranes in the presence of water[9] and the cyanation of thexyldialkylboranes[16] offer alternative routes to ketones from organoboranes. Neither procedure can utilize dialkylborinic esters in the synthesis and, thus, result in loss of one alkyl group. Carbonylation requires a moderate pressure of carbon monoxide in some cases, and the cyanation reaction involves the use of strongly electrophilic reagents; neither route has been used successfully in the preparation of bicyclo[3.3.1]nonan-9-one **(2)**. Previous synthetic routes to this interesting bicyclic ketone[17] have generally required numerous steps and resulted in low overall yields.[11,18] The best alternative procedure, which gives a 60% yield of the bicyclic ketone, involves reaction of nickel carbonyl with 1,5-cyclooctadiene.[19]

The base-induced reaction of dichloromethyl methyl ether with trialkyl- and triarylboranes also provides a powerful method for the preparation of the corresponding tertiary carbinols.[20,21] In this case, all three groups transfer readily from boron to carbon under mild conditions, and oxidation with alkaline hydrogen peroxide provides the tertiary alcohol.



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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

2,4-dinitrophenylhydrazone

sodium benzophenone ketyl

Lithium triethylcarboxide

bis(chloromethyl) ether, dichloromethyl methyl ether

ethanol (64-17-5)

ethyl acetate (141-78-6)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

carbon monoxide (630-08-0)

sodium chloride (7647-14-5)

silver nitrate (7761-88-8)

nitrogen (7727-37-9)

hydrogen peroxide (7722-84-1)

Pentane (109-66-0)

phenolphthalein (77-09-8)

chloromethyl methyl ether (107-30-2)

borane (7440-42-8)

methyl sulfide (75-18-3)

butane (106-97-8)

butyllithium, n-butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

nickel carbonyl

3-ethyl-3-pentanol, Triethylcarbinol (597-49-9)

lithium aluminum hydride (16853-85-3)

hexane (110-54-3)

Lithium chloride (7447-41-8)

Dichloromethyl methyl ether, α,α-dichloromethyl methyl ether (4885-02-3)

2,6-dimethylphenol (576-26-1)

1,5-cyclooctadiene

lithium hydroxide (1310-65-2)

Bicyclo[3.3.1]nonan-9-one (17931-55-4)

9-borabicyclo[3.3.1]nonane (280-64-8)

2,6-diisopropylphenol (2078-54-8)

bicyclo[3.3.1]nonane (280-65-9)

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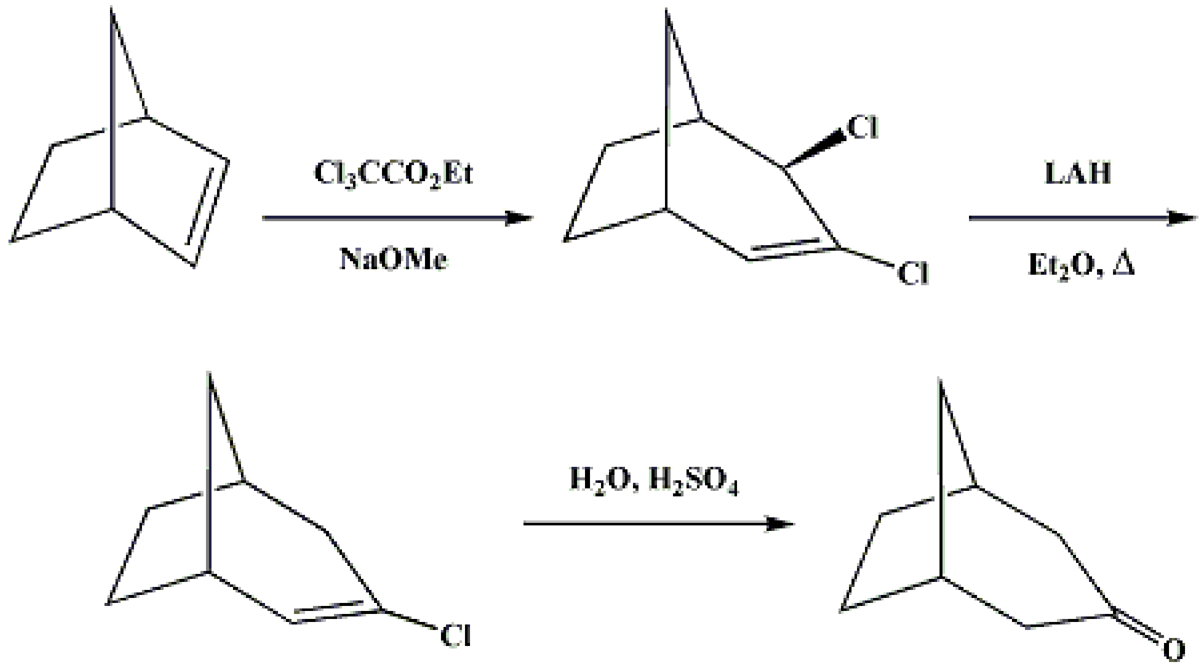
Organic Syntheses, CV 6, 142

BICYCLO[3.2.1]OCTAN-3-ONE

[Bicyclo[3.2.1]octan-3-one]



Submitted by C. W. Jefford[1 2], J. Gunsher[1], D. T. Hill[1], P. Brun[3], J. Le Gras[3], and B. Waegell[3].
Checked by R. W. Begland and R. E. Benson.

1. Procedure

A. exo-3,4-*Dichlorobicyclo*[3.2.1]*oct*-2-*ene.* A 1-l., four-necked, round bottomed flask is fitted with an efficient stirrer, a thermometer, a reflux condenser protected by a calcium chloride tube, and a 500-ml., stoppered, pressure-equalizing addition funnel. After the addition of a solution of 52.5 g. (0.558 mole) of norbornene (Note 1) in 400 ml. of petroleum ether ((Note 2), b.p. 45–60°) to the flask, 112 g. (2.06 moles) of sodium methoxide (Note 3) is added, and stirring is begun. The flask is immersed in an ice–salt mixture (Note 4) before 349 g. (1.82 moles) of ethyl trichloroacetate (Note 5) is placed in the addition funnel and allowed to drip slowly into the stirred mixture at a rate such that the temperature does not rise above 0° (Note 6). The addition requires about 4 hours, and the originally white reaction mixture becomes increasingly yellow in color. The mixture is stirred at a temperature below 0° for 4 hours (Note 6) before the temperature is allowed to rise gradually to room temperature overnight. The reaction mixture is poured onto 500 g. of crushed ice in 300 ml. of water. After the ice has melted, the organic layer is separated, and the aqueous layer is shaken with four 200-ml. portions of diethyl ether. The aqueous layer is neutralized with 10% hydrochloric acid and shaken again with two 200-ml. portions of ether. The original organic layer and the ether extractions are combined, washed with 300 ml. of a

saturated solution of sodium chloride, dried for 6 hours over 20 g. of anhydrous magnesium sulfate, filtered, and concentrated to about 200 ml. by distillation. The resulting product is distilled through a 20-cm. Vigreux column, giving 72.5–87.0 g. (74–88%) of *exo*-3,4-dichlorobicyclo[3.2.1]oct-2-ene as a colorless liquid, b.p. 72–73° (0.9 mm.), n_D^{25} 1.5333 (Note 7) and (Note 8).

B. *3-Chlorobicyclo*[3.2.1]*oct-2-ene.* A 2-l., three-necked, round-bottomed flask equipped with a stirrer, a reflux condenser protected by a calcium chloride tube, and a 500-ml., stoppered, pressure-equalizing addition funnel is charged with 350 ml. of dry ether and 15 g. (0.40 mole) of powdered lithium aluminum hydride (Note 9). The flask is placed in a mixture of ice and water, and 1050 ml. of dry tetrahydrofuran (Note 10) is added. Stirring is begun, and a solution of 39.5 g. (0.224 mole) of *exo*-3,4-dichlorobicyclo[3.2.1]oct-2-ene in 50 ml. of dry tetrahydrofuran (Note 10) is added dropwise from the addition funnel over a 30-minute period. After the addition is complete, the reaction mixture is heated under gentle reflux for 18 hours. The mixture is cooled to 0°, and the remaining lithium aluminum hydride is decomposed by the careful addition of wet ether, followed by the cautious dropwise addition of 10 ml. of water. The resulting mixture is poured onto 500 g. of crushed ice in 200 ml. of water. After the ice has melted, the organic layer is separated, and the aqueous layer is acidified to a pH of 5–6 with 10% hydrochloric acid, dissolving the lithium and aluminum salts present (Note 11). The aqueous solution is shaken five times with 200-ml. portions of ether. The organic layers are combined, washed with 200 ml. of a saturated solution of sodium chloride, and dried overnight over 20 g. of anhydrous magnesium sulfate. The ether and tetrahydrofuran are removed by distillation at atmospheric pressure, and the product is distilled through a 20-cm. Vigreux column, yielding 23.5–23.9 g. (74–75%) of 3-chlorobicyclo[3.2.1]oct-2-ene as a colorless oil, b. p. 76–77° (21 mm.), n_D^{20} 1.5072 (Note 12).

C. *Bicyclo*[3.2.1]*octan-3-one.* A magnetic stirring bar is placed in a 300-ml., round-bottomed flask and 100 ml. of concentrated sulfuric acid (Note 13) is added Stirring is begun, the flask is cooled in an ice bath, and 9.0 g. (0.63 mole) of 3-chlorobicyclo [3.2.1]oct-2-ene is added in one portion. The mixture is stirred, allowed to warm slowly over 4 hours to room temperature, then stirred overnight. The resulting solution is poured onto 200 g. of ice with stirring. After the ice has melted, the mixture is shaken with three 100-ml. portions of ether. The ether layers are combined, washed once with 50 ml. of water, and dried over 10 g. of magnesium sulfate. The ether is removed by careful distillation, and the crude product is sublimed at a bath temperature of 70° (15 mm.) directly onto a cold finger inserted into the flask. The crude product is twice sublimed, yielding 5.9–6.3 g. (75–81%) of bicyclo[3.2.1]octan-3-one, m.p. 137°, 98% pure by analysis (Note 14), (Note 15), and (Note 16).

2. Notes

1. Norbornene can be prepared by the Diels-Alder reaction of ethylene with dicyclopentadiene, as described in *Org. Synth.*, **Coll. Vol. 4**, 738 (1963). It can

be purchased from Matheson, Coleman and Bell or the Aldrich Chemical Company, Inc.
2. The petroleum ether used must be olefin-free.
3. The submitters used sodium methoxide available from Schuchardt, Ainmillerstrasse 25, 8-Munich 13, Germany. The checkers used product available from Matheson, Coleman and Bell.
4. An amount sufficient to fill a 5-l. container is recommended.
5. It is used as purchased from either Schuchardt or Eastman Organic Chemicals. It appears that when equimolar amounts of carbene precursor and olefin are used, the adduct is obtained in only 25% yield.[4]
6. Efficient stirring and maintenance of a low temperature are required if high yields are to be obtained.
7. For the final distillation the pressure is regulated with a manostat.
8. The IR spectrum (neat) shows absorption at 1645, 1450, 1305, 1223, 1052, 974, 959, 866, 796, and 750 cm.$^{-1}$. The ^{1}H NMR spectrum (CCl_4) shows absorption at δ 4.1 (d, *J* □ 3 Hz.), and 6.08 (d, *J* □ 4 Hz) attributable to the vinyl and allyl protons, respectively
9. This was purchased from Metal Hydrides, Inc., and is also obtainable from Schuchardt.
10. The checkers used reagent grade tetrahydrofuran (available from Fisher Scientific Company) from a freshly opened bottle. The submitters used tetrahydrofuran purified as described in the literature.[5] [See *Org. Synth.*, **Coll. Vol. 5**, 976 (1973) for a warning regarding the purification of tetrahydrofuran.]
11. A small amount of insoluble material may remain at this point. If it interferes with the extraction procedure it may be removed by filtration.
12. The IR spectrum (neat) shows absorption at 1635, 1440, 1038, 952, 841, 833, and 685 cm.$^{-1}$. The ^{1}H NMR spectrum (CCl_4) shows three major peaks between δ 2.0–2.8 and a doublet at 5.91 (*J* □ Hz., 1H, C*H*)
13. Sulfuric acid of specific gravity 1.84 is used.
14. The IR spectrum (Nujol) has an intense band at 1710 cm.$^{-1}$. The ^{1}H NMR spectrum ($CDCl_3$) has a broad peak at δ 1.7 (6H), a sharp peak at 2.35 (4H) and a broad peak at 2.55 (2H).
15. The GC data were obtained using 3 m. × 7 mm. column packed with nonacid-washed Chromosorb 45/60 W containing 15% 200M Apiezon silicone oil as the immobile phase.
16. The oxime has m.p. 96°. The ketone can be further purified *via* the semicarbazone derivative, which can be purified by crystallization and subsequently hydrolyzed by dilute hydrochloric acid.

3. Discussion

Studies by the submitters have indicated that the procedure reported here is the preferred method for the preparation of bicyclo[3.2.1]octan-3-one. It employs readily available, inexpensive reagents, and the overall yield is good. In addition, the method can be used for the synthesis of the relatively inaccessible, higher homologues of

bicyclo[2.2.2]oct-2-ene, as well as for derivatives of norbornene. Bicyclo[3.2.2]nonan-3-one and 1-methylbicyclo[3.2.1]octan-3-one have been prepared by a similar route[6] in 60% and 47% yields, respectively (based on adduct). However, the preferred procedure for the formation of the dichlorocarbene adduct of bicyclo[2.2.2]oct-2-ene is that of Seyferth, using phenyltrichloromethylmercury. Even in this case the overall yield is moderate (37%).

The present procedure is a refinement of existing methods,[6,7,8,9] an adaption of the method of Parham and Schweizer[10] that furnishes the carbene adduct in higher yield than other methods. The submitters' studies indicate that the procedure of Doering,[11] involving the interaction of chloroform with potassium *tert*-butoxide, is unsatisfactory since traces of *tert*-butyl alcohol present react with the rearranged adduct during the reduction step. In addition, the yields of adduct are poor (4–15%).[4] The method of Wagner,[12] utilizing the pyrolysis of sodium trichloroacetate, is easy to perform, but the yields of initial adduct are poor (13%). That of Seyferth,[13] involving the pyrolysis of phenyltrichloromethylmercury, gives the adduct in 45% yield. However, the higher cost and additional steps entailed in the preparation of the reagent, together with the hazards associated with mercury, detract from its use.

Other preparations leading to bicyclo[3.2.1]octan-3-one include the oxidation of the mixture of alcohols obtained by the action of nitrous acid on 2-aminomethylnorbornane,[14] the chromic acid oxidation of bicyclo[3.2.1]octane,[15] and the oxidative hydroboration of bicyclo[3.2.1]oct-2-ene.[16] These reactions lack preparative utility, and all have a common disadvantage of being accompanied by isomer formation.

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ether, diethyl ether (60-29-7)

chloroform (67-66-3)

sodium chloride (7647-14-5)

nitrous acid (7782-77-6)

mercury (7439-97-6)

sodium methoxide (124-41-4)

chromic acid (7738-94-5)

ethylene (9002-88-4)

magnesium sulfate (7487-88-9)

carbene (2465-56-7)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

dicyclopentadiene

tert-butyl alcohol (75-65-0)

ethyl trichloroacetate (515-84-4)

Norbornene

dichlorocarbene

sodium trichloroacetate (650-51-1)

phenyltrichloromethylmercury (3294-57-3)

Bicyclo[3.2.1]octan-3-one (14252-05-2)

3-Chlorobicyclo[3.2.1]oct-2-ene (35242-17-2)

bicyclo[2.2.2]oct-2-ene

1-methylbicyclo[3.2.1]octan-3-one

2-aminomethylnorbornane

bicyclo[3.2.1]octane (6221-55-2)

bicyclo[3.2.1]oct-2-ene

potassium tert-butoxide (865-47-4)

exo-3,4-dichlorobicyclo[3.2.1]oct-2-ene (2394-47-0)

Bicyclo[3.2.2]nonan-3-one

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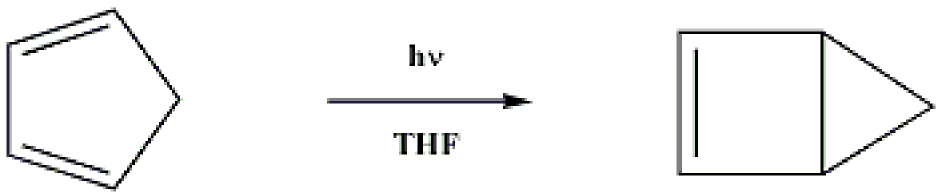
Organic Syntheses, CV 6, 145

BICYCLO[2.1.0]PENT-2-ENE



Submitted by A. Harry Andrist, John E. Baldwin[1], and Robert K. Pinschmidt, Jr..
Checked by Keith C. Bishop, III and Kenneth B. Wiberg.

1. Procedure

Caution! The photochemical reaction should be carried out under a light absorbent cover. The operator should wear goggles affording protection from ultraviolet light.

While still slightly warm from the drying oven, a photolysis vessel with a water-jacketed quartz immersion well (Note 1) (section *A* of f.htmigure 1) is charged with 500 ml. of anhydrous tetrahydrofuran (Note 2) and 10.0 ml. (8.05 g., 0.122 mole) of cyclopentadiene (Note 3). The solution is cooled in an ice bath and purged with dry nitrogen for 2 minutes. The vessel is then sealed, the lamp inserted, and the solution irradiated at 0° for 30 minutes. During this period, sections *B* and *C* (see diagram) are removed from the oven to cool slightly. While still warm, the bottom part of *C* is filled with 0.5 ml. of anhydrous tetrahydrofuran and approximately 25 •l. of triethylamine (Note 4), greased, and stoppered. The top parts of *B* and *C* are thoroughly greased and connected to the 24/40 T joint of *A*. The bottom of part *B* is filled rapidly with 200 ml. of an approximately 1 *M* solution of dimsyl anion (Note 5) in dimethyl sulfoxide. The bottom part of *C* is then connected and cooled in a 2-propanol–dry ice bath. The system is irradiated and subjected to a steady flow of nitrogen (approximately 400–500 ml./minute). After the first hour, this flow rate is reduced to 200–250 ml./minute for the remaining 4.5 hours. At the end of a total irradiation period of 6 hours, trap *C* is stoppered and stored at dry ice temperature. This trap contains 15–25 ml. of a 2–5% solution of bicyclopentene in tetrahydrofuran, (Note 6) contaminated with minor amounts (<15%) of tricyclo[2.1.0.0^{2,5}]pentane,[2] which is highly labile and difficult to separate.

Figure 1.

Figure 1.

2. Notes

1. The submitters used an unfiltered, Hanovia, 450-watt, medium-pressure

mercury vapor lamp (catalog No. 679A, Hanovia Lamp Division, Canrad Precision Industries, 100 Chestnut Street, Newark, N.J. 07105) and a reactor equipped with a nitrogen-inlet containing a glass frit, which enters the bottom of the reactor. All connections (Note 9) were glass with the exception of the rubber tubing between the second trap and the mercury bubbler. All glassware was soaked for 30 minutes in aqueous 30% ammonium hydroxide and oven-dried prior to use without further rinsing. Any polymer formed on the quartz immersion well during this preparation may be removed with nitric acid or with warm water and cleansing powder; if it is not removed, yields in subsequent preparations are significantly diminished.

2. Tetrahydrofuran (purchased from Mallinckrodt Chemical Works) was dried by distillation from lithium aluminum hydride, and stored over Linde 4A Molecular Sieves.

3. Cyclopentadiene was prepared [compare with *Org. Synth.*, **Coll. Vol. 4**, 473, Note 4 (1963) and **Coll. Vol. 5**, 414 (1973)] by heating dicyclopentadiene (purchased from Eastman Organic Chemicals) and a pinch of hydroquinone under a column of glass helices or a Vigreux column at 175° and collecting the distillate in a receiver cooled with a 2-propanol–dry ice bath. The monomer was dried over Linde 4A Molecular Sieves at −20° and could be stored at this temperature for several weeks without excessive dimerization.

4. Triethylamine (purchased from Matheson, Coleman and Bell) was dried over Linde 4A Molecular Sieves.

5. Dimsyl anion[3] was prepared from 10.2 g. (0.241 mole) (Note 10) of 56.8% sodium hydride, which was washed with pentane and vacuum dried, and 200 ml. of anhydrous dimethyl sulfoxide. The mixture was heated at 65–70° for about 50 minutes, until hydrogen evolution ceased. *Caution! This mixture should not be heated above 80° because of the possibility of explosive decomposition.*

6. Analysis and purification of the product solution is best accomplished by GC. The submitters used a 500 cm. by 0.6 cm. aluminum or polyethylene column packed with 21% β,β'-oxydipropionitrile on Chromosorb P with column, injector, and detector operated at 25° and a flow rate of 50 ml./minute. Under these conditions the retention times of bicyclopentene and cyclopentadiene were 3 and 5 minutes, respectively, beyond that of coinjected air. Tricyclopentane elutes in low yield with the bicyclopentene. Since bicyclopentene is extremely labile with respect to acid catalysis, any contact with water, hydroxylic solvents, and aprotic acids should be avoided (Note 11). Bicyclopentene stored at −78° in anhydrous tetrahydrofuran is stable indefinitely.

7. Decalin, benzene, 1,4-dioxane, and ethanol may be used as solvents for the photolysis. In an alternative procedure, volatile materials swept from the photolysis vessel are condensed in a dry ice trap. This cold mixture is added to a flask containing a magnetically stirred solution of dimsyl anion in dimethyl sulfoxide, and fractionation at reduced pressure provides a solution of bicyclopentene in tetrahydrofuran. In both variants additional bicyclopentene remains in the dilute reactor and trap solutions. It may be more fully recovered by using a modified distillation assembly composed of a gently warmed flask, a

distillation head with a dry ice condenser filled with ice, an ice-cooled receiver, and a 2-propanol-dry ice vapor trap prior to a vacuum pump. (A rotary evaporator with an ice-filled dry ice condenser also works.) The vacuum is adjusted to rapidly distill the high boiling solvent into the receiver and bicyclopentene past the condenser into the −78° trap. The final distillation should be from the dimsyl anion solution (mainly tetrahydrofuran distills here) to remove codistilled cyclopentadiene.

8. A purified, undiluted sample of bicyclopentene has been reported to explode.[4]

9. All of the connections must be well secured by sturdy rubber bands to avoid leakage caused by substantial back pressure that develops in the course of the reaction.

10. A higher base concentration or substitution of one or two gas-dispersion tubes leads to clogging of the inlet to the trap.

11. Two injections of 10 ml. of ammonia vapors greatly helps to eliminate decomposition on the column during GC collection.

3. Discussion

The present procedure, a modification of that previously reported,[5,6,7,8] permits the ready preparation of a cyclopentadiene-free solution of bicyclopentene on a synthetic scale. Until now, synthetic chemistry involving the use of bicyclopentene has been limited to preparations of bicyclopentane[5,8] and bicyclopentane-2,3-d_2,[8] which is more a reflection of the extraordinary care required in handling this unusually sensitive bicyclic alkene than a lack of interesting potential or useful reactivity.

Most cyclic and acyclic 1,3-dienes, such as cyclopentadiene, undergo photochemical ring-closure to cyclobutenes.[9] Bicyclo[2.1.0]pent-2-ene derivatives have also been prepared *via* photolysis of cyclopentadiene-5-*d*-, -d_6, and -1,5-$^{13}C_2$;[2,10] 1-, 2-, and 5-methylcyclopentadiene;[2,11] 5,5-dimethylcyclopentadiene;[12] 1,5-dimethyl- and 2,5-dimethyl-1,3-cyclopentadien-5-yl acetic acid;[13] 2,2-dimethylisoindene[14] and 2,3,5-tri-*tert*-butylcyclopentadienone.[15] Substituted thiophenes have been converted photochemically to 5-thia derivatives of bicyclopentene.[16]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 226

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

bicyclopentane-2,3-d_2

2,2-dimethylisoindene

ethanol (64-17-5)

ammonia (7664-41-7)

Benzene (71-43-2)

hydrogen (1333-74-0)

hydroquinone (123-31-9)

nitric acid (7697-37-2)

nitrogen (7727-37-9)

ammonium hydroxide (1336-21-6)

Pentane (109-66-0)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

sodium hydride (7646-69-7)

dimethyl sulfoxide (67-68-5)

triethylamine (121-44-8)

CYCLOPENTADIENE (542-92-7)

dicyclopentadiene

decalin (91-17-8)

Bicyclo[2.1.0]pent-2-ene (5164-35-2)

bicyclopentene

tricyclo[2.1.0.0^{2,5}]pentane

1,4-dioxane (123-91-1)

bicyclopentane (1636-39-1)

5-methylcyclopentadiene

5,5-dimethylcyclopentadiene

2,5-dimethyl-1,3-cyclopentadien-5-yl acetic acid

cyclopentadiene-5-d

2,3,5-tri-tert-butylcyclopentadienone

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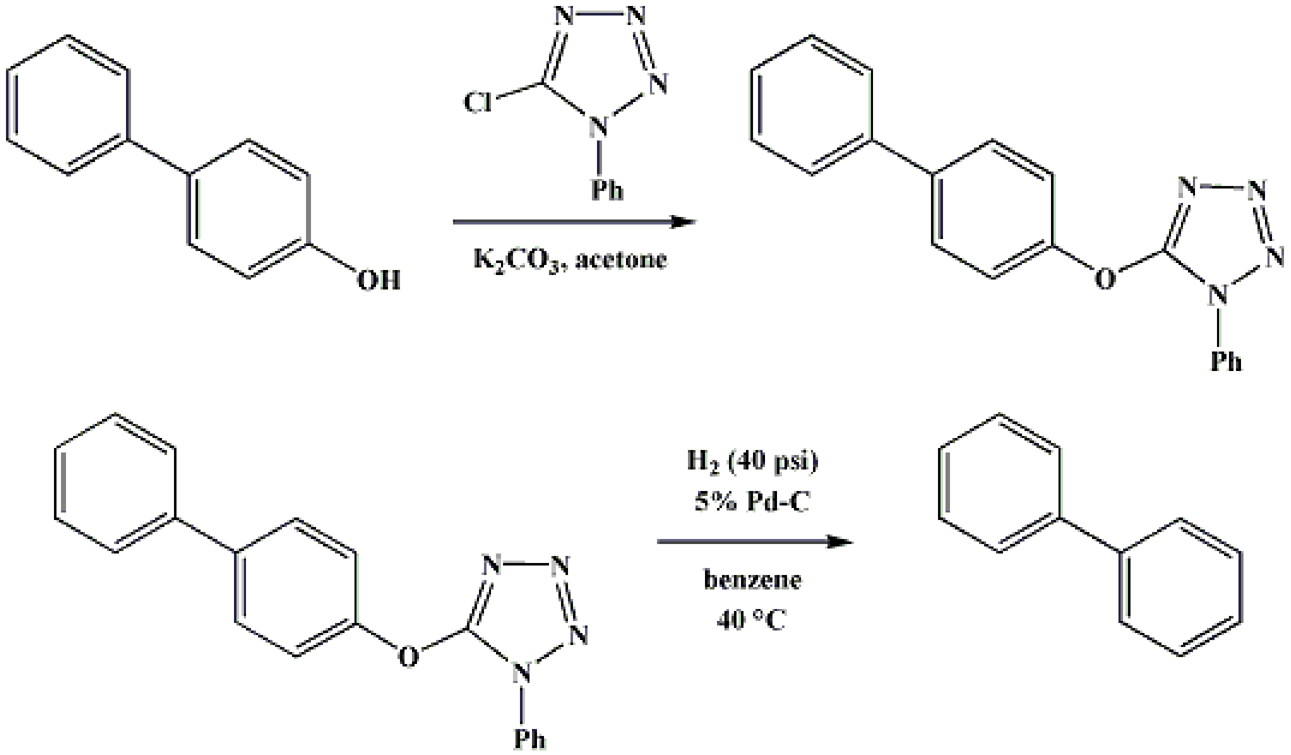
Organic Syntheses, *CV 6, 150*

DEHYDROXYLATION OF PHENOLS; HYDROGENOLYSIS OF PHENOLIC ETHERS: BIPHENYL



Submitted by Walter J. Musliner and John W. Gates Jr[1].
Checked by D. Robert Coulson and Richard E. Benson.

1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A. *4-(1-Phenyl-5-tetrazolyloxy)biphenyl*. A 1-l., round-bottomed flask fitted with an efficient condenser and a magnetic stirring bar is charged with 17 g. (0.10 mole) of 4-phenylphenol, 18.1 g. (0.100 mole) of 1-phenyl-5-chlorotetrazole (Note 1), 27.6 g. (0.200 mole) of anhydrous potassium carbonate, and 250 ml. of acetone. The mixture is stirred and heated under reflux for 18 hours (Note 2). Water (250 ml.) is added to the hot mixture producing a clear solution that is chilled in ice. After 1 hour, the solid is collected by filtration and dried in air, giving 32–33 g. of the crude product, m.p. 151–153°, which is then dissolved in 250 ml. of hot ethyl acetate. The solution is filtered while hot to remove a small amount of insoluble material and cooled on ice, yielding 25 g. of 4-(1-phenyl-5-tetrazolyloxy)biphenyl, as white crystals, m.p. 150–153°. An additional 2–3 g. of product is recovered from the filtrate by concentration to 125 ml. bringing the total yield to 27–28 g. (86–89%).

B. *Biphenyl*. Added to a solution of 10 g. (0.032 mole) of the product from Part A in 200 ml. of benzene is 2 g. of 5% palladium-on-charcoal, and the mixture is shaken with hydrogen in a Parr apparatus at 40 p.s.i. and 35–40° for 8 hours (Note 3). The mixture is filtered, and the insoluble residue is washed with three 100-ml. portions of hot ethanol (Note 4). The filtrates are combined,

and the solvent is removed with a rotary evaporator at 60° (12 mm.), leaving a solid residue, which is dissolved in 100 ml. of benzene. After adding 100 ml. of 10% aqueous sodium hydroxide the mixture is shaken, and the layers separated. The aqueous layer is extracted with 100 ml. of benzene, and the original benzene layer is washed with 100 ml. of water (Note 5). The benzene solutions are combined and dried over magnesium sulfate. Removal of the benzene by distillation yields 4.0–4.7 g. (82–96%) of biphenyl as a white powder, m.p. 68–70° (Note 6). The IR spectrum is identical with that of an authentic sample, and a purity of at least 99.5% was indicated by GC analysis.

2. Notes

1. 4-Phenylphenol and 1-phenyl-5-chlorotetrazole were obtained from Eastman Organic Chemicals.
2. A reflux period of 18 hours was chosen because it represents an overnight reaction time; the reaction is essentially completed in 8 to 10 hours.
3. The hydrogenolysis can also be carried out in ethanol or tetrahydrofuran. An amount of catalyst equivalent to 10–20% by weight of tetrazolyl ethers is most satisfactory for this reaction. Platinum oxide also catalyzes this hydrogenolysis.
4. A large portion of 1-phenyl-5-tetrazolone (and a small amount of biphenyl) remains mixed with and adsorbed to the catalyst and is removed by the ethanol treatment.
5. 1-Phenyl-5-tetrazolone can be recovered from the combined aqueous solutions by acidification with dilute hydrochloric acid. The yield is 4.2–4.7 g. (82–92%), m.p. 190–191°.
6. Benzoxazolyl ethers can also be used in this reaction sequence but an amount of catalyst equivalent to 20–40% by weight of ether is necessary in the hydrogenolysis step. 2-Chlorobenzoxazole is available from Eastman Organic Chemicals.

3. Discussion

The preparation is essentially that described by the submitters[2] and is cited as an example of this general procedure for replacement of phenolic hydroxyl groups by hydrogen.

The reaction sequence, which involves the conversion of the phenolic hydroxyl groups to a phenyltetrazolyl ether (see (Note 6)) followed by reduction to effect removal of the phenolic hydroxyl group, illustrates a mild, efficient, general, and convenient procedure. It has been applied successfully by the submitters[2] to a variety of substituted phenols, as shown in Table I.

TABLE I
HYDROGENOLYSIS OF PHENOLIC ETHERS

Substituted Phenol	Yield of Tetrazolyl Ether, %	Hydrogenolysis Time, hours	Hydrogenolysis Product	Hydrogenolysis Yield, %
Guaiacol	94	15	Anisole	86[a]
3-Methoxyphenol	95	16	Anisole	85[a]
4-Methoxyphenol	97	6	Anisole	83[a]
2-Phenylphenol	98	8	Biphenyl	82
4-Aminophenol	86	9	Aniline	46[b]

4-Carbethoxyphenol	91	16	Ethyl benzoate	89[a]
Thymol	93	15	*p*-Cymene	72[a]
1-Naphthol	88	7	Naphthalene	50
2-Naphthol	94	17	Naphthalene	65
4-Chlorophenol	92	18	Benzene[c]	70[a]

[a]Filtered solution analyzed directly by gas chromatography with toluene as internal standard.

[b]Isolated as the hydrochloride salt.

[c]From hydrogenolysis of carbon-chlorine bond.

Phenols having a variety of substituents including alkyl, alkoxyl, aryl, amino, and carbalkoxyl have been successfully converted to the desired product in good yield. The only limitation yet found is in the hydrogenolysis of the halogen–carbon bond. Thus 4-chlorophenol was converted to benzene using this procedure.

Other procedures include zinc-dust distillation, not generally useful except for exhaustive degradation of phenols to hydrocarbons, and various sodium and liquid ammonia cleavages of phenol ethers.[3,4,5,6,7] These latter reactions lack generality and are often unpredictable. They require conditions too harsh for certain aromatic substituents, and the yields are frequently low.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

palladium-on-charcoal

efficient condenser

ethanol (64-17-5)

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

Benzene (71-43-2)

ethyl acetate (141-78-6)

ether (60-29-7)

aniline (62-53-3)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

phenol (108-95-2)

1-Naphthol (90-15-3)

2-naphthol (135-19-3)

platinum oxide

Anisole (100-66-3)

acetone (67-64-1)

toluene (108-88-3)

sodium (13966-32-0)

Biphenyl (92-52-4)

Naphthalene (91-20-3)

Guaiacol (90-05-1)

ethyl benzoate (93-89-0)

thymol (89-83-8)

p-cymene (99-87-6)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

4-Carbethoxyphenol (120-47-8)

4-Methoxyphenol (150-76-5)

4-phenylphenol (92-69-3)

1-phenyl-5-chlorotetrazole (14210-25-4)

4-(1-Phenyl-5-tetrazolyloxy)biphenyl (17743-27-0)

1-phenyl-5-tetrazolone

2-Chlorobenzoxazole (615-18-9)

phenyltetrazolyl ether

Tetrazolyl Ether

3-Methoxyphenol (150-19-6)

2-Phenylphenol (90-43-7)

4-Aminophenol (123-30-8)

4-Chlorophenol (106-48-9)

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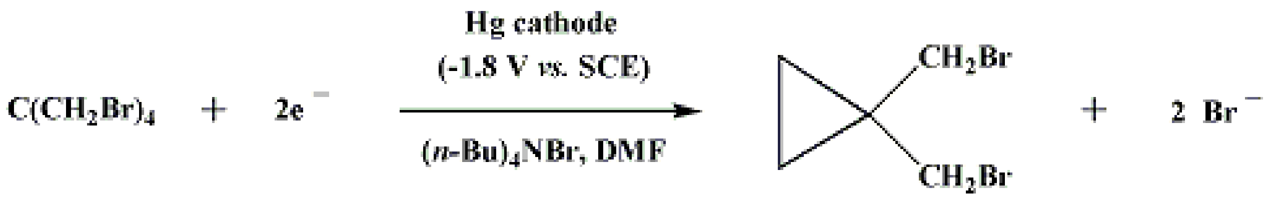
Organic Syntheses, CV 6, 153

CONTROLLED-POTENTIAL ELECTROLYTIC REDUCTION: 1,1-BIS(BROMOMETHYL) CYCLOPROPANE

[Cyclopropane, 1,1-bis(bromomethyl)-]



Submitted by M. R. Rifi[1]
Checked by Edith Feng and Herbert O. House.

1. Procedure

Caution! Since bromine is liberated during the electrolysis, the reaction should be conducted in a hood.

The electrolysis cell (Note 1) is assembled in a 1000-ml., flat-bottomed Pyrex reaction kettle. The Pyrex cover contains four standard taper outer joints in which are mounted: (1) a 11.5 × 2-cm.-diameter carbon rod (Note 2) surrounded by a 15 × 5.5-cm.-diameter, porous, porcelain cup (Note 3); (2) a 31-cm. × 8-mm.-diameter length of soda-lime glass tubing (Note 4) with a short length of 0.6-mm.-diameter platinum wire fused into the bottom: (3) a tee-tube fitted to hold a thermometer and to allow nitrogen to be passed into the reaction vessel: and (4) a saturated calomel reference electrode fitted with successive salt bridges containing aqueous 1 *M* sodium nitrate and 1.5 *M* tetraethylammonium tetrafluoroborate in *N,N*-dimethylformamide (Note 5). The cover is also equipped with a suitable clamp so that it may be fastened to the reaction kettle during the electrolysis.

A sufficient quantity of mercury (about 700 g.) is added to the reaction kettle to form a cathode pool 1-cm. deep, and a Teflon-covered magnetic stirring bar is placed on this mercury pool. A solution of 25.0 g. (0.0651 mole) of pentaerythrityl tetrabromide (Note 6) in 250 ml. of 0.2 *M* tetra-*n*-butylammonium bromide (Note 7) in *N,N*-dimethylformamide (Note 8) is added to the reaction vessel. An additional 175 ml. (Note 9) of 0.2 *M* tetra-*n*-butylammonium bromide (Note 7) in *N,N*-dimethylformamide (Note 8) is added to the porous porcelain cup surrounding the carbon-rod anode, and the cover is clamped to the reaction kettle. The glass tubing with a platinum wire contact sealed in the bottom is adjusted so that all of the exposed platinum is below the mercury surface (Note 10). The bottom of the porous porcelain cup should be a sufficient distance above the mercury pool so as not to interfere with the magnetic stirring bar. The salt bridge associated with the calomel reference electrode (Note 5) should be adjusted so that the

lower, porous Vycor plug is between 5 and 10 mm. above the surface of the mercury pool. Before the electrolysis is begun a 0.5-ml. aliquot of the reaction solution should be removed from the cathode compartment and analyzed polarographically (Note 11), and the electrical resistances between the cathode and anode and between the cathode and the reference electrode should be measured with a suitable resistance bridge (Note 12). If all electrical connections are satisfactory the cathode-anode resistance should be in the range 20–30 ohms and the cathode-reference resistance should be in the range 5000–15,000 ohms. The electrical leads from the anode and cathode should be connected with a direct current source whose potential may be conveniently adjusted from 0 to 40 volts with a continuous current output of at least 1 amp. A suitable d.c. voltmeter is mounted in parallel with the anode and cathode leads, and a d.c. ammeter, capable of measuring currents of 0 to 3 amps is placed in series in either of the two leads. Finally, a vacuum-tube d.c. voltmeter or some equivalent *high-impedance* (Note 13) potential measuring device is connected to measure the potential difference between the cathode and the reference electrode. The reaction kettle should be placed in a nonmagnetic bath, to which cooling water may be added if necessary and magnetic stirring started. A very slow stream of nitrogen (1–2 ml. per minute) is passed through the apparatus throughout the electrolysis (Note 14). The potential of the direct current source is adjusted, giving a potential difference of 1.7 to 1.8 volts between the cathode and the reference electrode (Note 15), and the current source is adjusted at 10–15 minute intervals to maintain this potential difference throughout the electrolysis. It is convenient to keep a record of time and the current passing through the cell so that the time when the theoretical amount of electricity (12,500 coulombs or 3.5 amp.-hours) has been passed through the cell can be estimated (Note 16). During the electrolysis the temperature of the catholyte solution is kept below 40° (Note 17) by the use of external cooling if necessary. When approximately the theoretical amount of electricity has been passed through the electrolysis cell ((Note 16), typically 4–6 hours), a 0.5-ml. aliquot is removed and analyzed polarographically (Note 11). The electrolysis is continued until the polarographic analysis (Note 11) indicates the consumption of practically all the pentaerythrityl tetrabromide.

The solutions are removed from the cathode and anode (Note 18) compartments and added to 200 ml. of water. The resulting mixture is extracted with four 150-ml. portions of pentane, and the combined pentane extracts are washed with water, dried over anhydrous sodium sulfate, and concentrated by distillation through a short Vigreux column (Note 19). The remaining pentane is removed by distillation and the residual yellow liquid is distilled under reduced pressure, yielding 6.9–8.5 g. (47–58%) of 1,1-bis-(bromomethyl)cyclopropane as a colorless liquid, b.p. 65–67° (5 mm.), n_D^{25} 1.5341–1.5347 (Note 20).

2. Notes

1. The electrolysis cell designed by the checkers is shown in f.htmigure 1. The adapters, which hold the reference electrode salt bridge (Note 5), the glass tube with the platinum contact, the tee tube for the nitrogen-inlet, and the thermometer are commercially available from Ace Glass, Inc., Vineland, New Jersey. The

adapter which supports the carbon rod anode and the surrounding porous porcelain cup was machined from a Teflon rod; the dimensions of the adapter used by the checkers are indicated in f.htmigure 2. Holes were drilled in the porcelain cup to permit fastening to the Teflon adapter with three stainless-steel machine screws. Electrical contact between the carbon anode and the wire to the external circuitry was achieved by drilling and tapping the end of the carbon rod for a small machine screw. The arrangement used for the remainder of the electrical circuit is indicated in f.htmigure 1.

Figure 1. Cell for controlled-potential electrolytic reduction.

Figure 1. Cell for controlled-potential electrolytic reduction.

Figure 2. Teflon anode support for the electrolysis cell. Unless otherwise stated, the dimensions are in centimeters.

Figure 2. Teflon anode support for the electrolysis cell. Unless otherwise stated, the dimensions are in centimeters.

2. Carbon rods of approximately the dimensions indicated are commercially available from welding supply companies.
3. A suitable porous porcelain cup (Coors 700, unglazed) may be purchased from the Arthur H. Thomas Company.
4. To obtain a satisfactory seal between the platinum and the glass, soda-lime glass rather than Pyrex glass should be employed. Before the platinum wire is sealed into the glass a length of copper wire should be silver soldered to the platinum to provide an accessible electrical lead at the top of the glass tubing.
5. Any commercial saturated calomel electrode of convenient dimensions may be employed. The arrangement of the salt bridges between the calomel electrode and the reaction solution is illustrated in f.htmigure 3. The Teflon tubing is available from Bolab, Inc., 359 Main Street, Reading, Massachusetts 01867, and the porous Vycor plugs are cut from lengths of 1/8-in.-diameter porous Vycor rod ("thirsty" glass or Corning Vycor No. 7930), available from the Electronic Parts Department, Corning Glass Works, Houghton Park, Corning, New York, 14830. The intermediate salt bridge containing aqueous sodium nitrate is used to prevent precipitation of the insoluble potassium tetrafluoroborate at the small fiber in the tip of the calomel electrode.[2] To minimize resistance in the long, lower, nonaqueous salt bridge, a concentrated (1.5 *M*) solution of tetraethylammonium tetrafluoroborate[3,4] in *N*,*N*-dimethylformamide is used with a length of platinum wire inside the tube. Tetraethylammonium tetrafluoroborate was prepared by mixing 5.3 g. (0.025 mole) of tetraethylammonium bromide (Eastman Organic Chemicals) and 3.6 ml. (*ca.* 0.026 mole) of aqueous 48–50% fluoroboric acid

(Allied Chemical Corporation) in 8 ml. of water. The resulting mixture was concentrated under reduced pressure, diluted with ether and filtered, yielding 4.6 g. (85%) of the crude tetrafluoroborate salt, m.p. 375–378° (dec.). Two recrystallizations from methanol-petroleum ether mixtures afforded 3.7 g. (69%) of the pure tetraethylammonium tetrafluoroborate as white needles, m.p. 377–378° (dec.) (after drying).

Figure 3. Reference electrode and salt bridges for controlled potential electrolysis.

Figure 3. Reference electrode and salt bridges for controlled potential electrolysis.

6. Crude pentaerythrityl tetrabromide, purchased from Columbia Organic Chemicals Company, Inc., was recrystallized from chloroform, yielding the tetrabromide as tan needles, m.p. 158–160°. Alternatively, this material may be obtained by the procedure described in *Org. Synth.*, **Coll. Vol. 4**, 753 (1963).

7. Tetra-*n*-butylammonium bromide, obtained from Eastman Organic Chemicals, was recrystallized from chloroform. The white prisms that separated were pulverized and dried under reduced pressure, giving the pure salt, m.p. 116–117.5°.

8. *N*,*N*-Dimethylformamide, obtained from Allied Chemical Corporation, was purified by distillation under reduced pressure, b.p. 39–41° (6 mm.).

9. Since the amount of solvent in the anode compartment is slowly depleted as the electrolysis proceeds, it is convenient to begin the electrolysis with the level of solution in the anode compartment about 9 cm. above the level of the solution in the cathode compartment. Alternatively, additional 0.2 *M* tetra-*n*-butylammonium bromide in *N*,*N*-dimethylformamide may be added to the anode compartment as the electrolysis proceeds.

10. To avoid competing liberation of hydrogen at the cathode, no platinum should be exposed to the catholyte solution.

11. The polarographic analysis is obtained at a dropping mercury electrode with any conventional three-electrode polarograph employing a saturated calomel electrode as the reference. The checkers added the 0.5-ml. aliquots of the reaction mixture to 10-ml. portions of 0.2 *M* tetra-*n*-butylammonium bromide (Note 7) in *N*,*N*-dimethylformamide (Note 8). The half-wave potentials ($E_{1/2}$ vs. sce) for the reduction of pentaerythrityl tetrabromide and 1,1-bis-(bromomethyl)cyclopropane are –1.71 (αn = 0.44) volts and –2.18 (αn = 0.31) volts, respectively.

12. The checkers measured these resistances with a Serfass Conductivity Bridge, Model RCM 15, employing a 1000-Hz. alternating current.

13. Since the resistance in the circuit containing the reference electrode is approximately 10,000 ohms, an accurate measure of the cathode-reference electrode potential can only be obtained by the use of a potential measuring device with an input impedance of at least 100,000 ohms. Although a vacuum-tube voltmeter (VTVM, typical imput impedance 11×10^6 ohms) is suitable for this purpose, a common multimeter (VOM, typical imput impedance 20,000 ohms per volt) *is not a satisfactory alternative.*

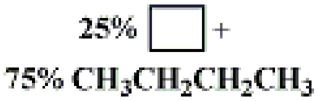
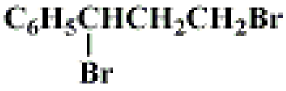
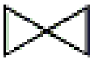
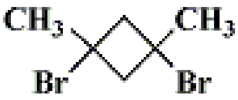
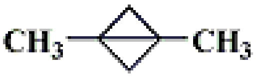
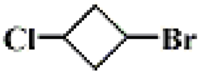
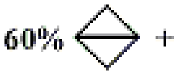
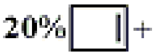
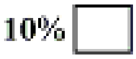
14. This slow stream of nitrogen passes through the hole about 2.5 cm. from the top of the porous cup surrounding the anode compartment and sweeps the bromine formed at the anode out the top of the apparatus through the hole in the center of the Teflon adapter.
15. If the cathode-reference potential is allowed to rise significantly above −1.8 volts, further reduction of the 1,1-bis-(bromomethyl)cyclopropane will occur. The submitter reports that the dibromide may be reduced to spiropentane in 39% yield by employing a cathode-reference potential of −2.0 volts to −2.2 volts.
16. The checkers found that about 1.3 times the theoretical amount of electricity was passed through the cell during the time required to consume the starting material. Presumably the excess electricity is consumed partially in the reduction of impurities (*e.g.*, oxygen) and partially in the further reduction of the dibromide to spiropentane (Note 15).
17. This temperature limit was selected to avoid the possible loss of solvent and the volatile product in the slow stream of nitrogen passed through the cell. Since the rate of the electrolytic reduction is increased with an increase in the reaction temperature, it is advantageous to maintain the temperature of the reaction solution in the range 35–40°.
18. Since some diffusion of the product from the cathode compartment to the anode compartment is probable, both solutions are subjected to the isolation procedure.
19. To avoid the possible loss of the volatile product, the pentane solvent should be removed by distillation through a 20–30-cm. Vigreux column rather than by distillation in a rotary evaporator.
20. On a GC column, packed with Apiezon M suspended on Chromosorb P and heated to 70°, the product exhibits a single peak with a retention time of 23.2 minutes. The sample exhibits IR absorption (CCl_4) at 3100, 3030, 2985, 1440, 1340, and 1235 cm.$^{-1}$ with ^{1}H NMR (CCl_4) singlets at δ 3.45 (CH_2Br) and 0.90 (cyclopropyl CH_2). The mass spectrum of the sample has abundant fragment peaks at *m/e* 149, 147, 67, 41, and 39.

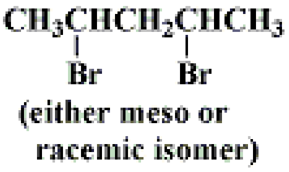
3. Discussion

1,1-Bis-(bromomethyl)cyclopropane has been obtained as one component in a mixture of isomeric bromides by reaction of methylenecyclobutane with bromine[5] and by reaction of cyclopropane-1,1-dimethanol with phosphorus tribromide.[6,7,8] The present method illustrates a general procedure for the preparation of cyclopropane and cyclobutane derivatives by the electrolytic reduction of 1,3- and 1,4-dihalides.[9,13,10,15,14,16,11,12] In at least some cases, this method is clearly superior to the reductive cyclizations of dihalides effected with metals or with chromium(II) salts. Examples of this reductive ring closure are provided in Table I. The reaction appears to give the best results when dibromides rather than dichlorides are used as starting materials and when an aprotic solvent such as *N,N*-dimethylformamide or acetonitrile is used. These electrolytic ring closures proceed by way of a stepwise reaction mechanism.[14]

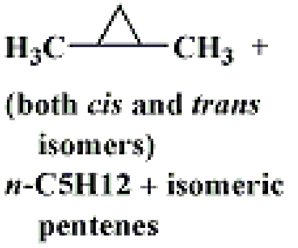
TABLE I

ELECTROLYTIC REDUCTIVE RING CLOSURE OF DIHALIDES

Dihalide	Product(s)	Yield, %	Ref.
$Br(CH_2)_3Br$	(only product)	60–80	13, 14
$Br(CH_2)_4Br$	 + 75% $CH_3CH_2CH_2CH_3$	—	13
$Br(CH_2)_5CH_3$	$CH_3(CH_2)_3CH_3$ (only product)	80	13
		70	15
		39	14
		55–94	13
	 +  + 	—	13



(either meso or racemic isomer)



(both *cis* and *trans* isomers) *n*-C_5H_{12} + isomeric pentenes

— 16

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

methanol (67-56-1)

ether (60-29-7)

hydrogen (1333-74-0)

acetonitrile (75-05-8)

chloroform (67-66-3)

bromine (7726-95-6)

sodium sulfate (7757-82-6)

oxygen (7782-44-7)

phosphorus tribromide (7789-60-8)

nitrogen (7727-37-9)

mercury (7439-97-6)

platinum (7440-06-4)

Pentane (109-66-0)

sodium nitrate

silver (7440-22-4)

Pentaerythrityl tetrabromide (3229-00-3)

N,N-dimethylformamide (68-12-2)

fluoroboric acid (16872-11-0)

spiropentane (157-40-4)

1,1-Bis(bromomethyl)cyclopropane, Cyclopropane, 1,1-bis(bromomethyl)-, 1,1-bis-(bromomethyl)cyclopropane (29086-41-7)

tetraethylammonium tetrafluoroborate (429-06-1)

potassium tetrafluoroborate (14075-53-7)

tetraethylammonium bromide (71-91-0)

Tetra-n-butylammonium bromide (1643-19-2)

methylenecyclobutane (1120-56-5)

cyclopropane-1,1-dimethanol

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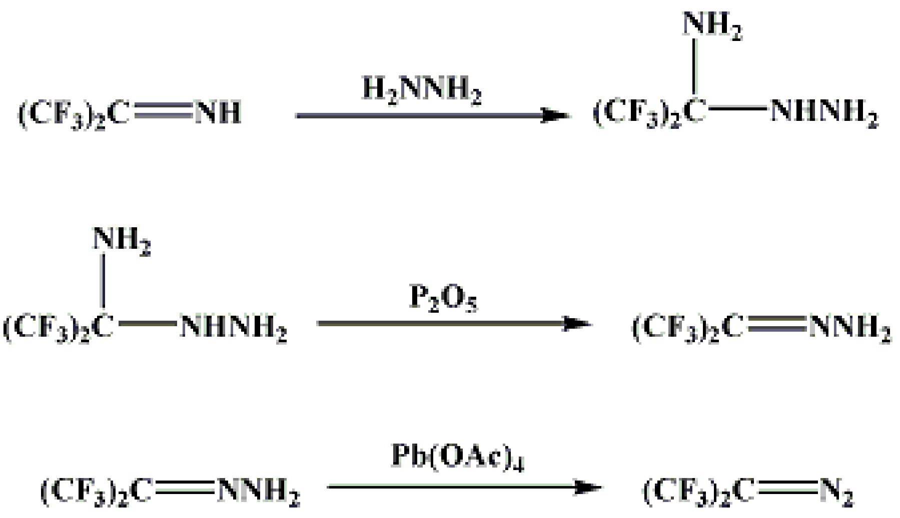
BIS(TRIFLUOROMETHYL)DIAZOMETHANE

[Propane, 2-diazo-1,1,1,3,3,3-hexafluoro-]



Submitted by W. J. Middleton[1] and D. M. Gale.
Checked by L. Scerbo and W. D. Emmons.

1. Procedure

Caution! This procedure should be carried out in a good hood and behind a shield to avoid exposure to the toxic compounds, hexafluoroacetone imine and hydrazine.

A. *Hexafluoroacetone hydrazone*. A 100-ml., three-necked, round-bottomed flask fitted with a thermometer, a gas-inlet tube, a Dewar condenser, and a magnetic stirring bar is charged with 16 g. (0.50 mole) of anhydrous hydrazine [*Org. Synth.*, **Coll. Vol. 6**, 10 (1988)] and cooled in an ice-methanol bath. The condenser is filled with a cooling mixture of ice and methanol, the magnetic stirrer is started, and 82.5 g. (0.500 mole) (Note 1) of hexafluoroacetone imine [*Org. Synth.*, **Coll. Vol. 6**, 664 (1988)] is slowly distilled into the flask through the gas-inlet tube, while the temperature is maintained below 10°. After the addition, which requires about 1 hour, the cooling bath is removed and the reaction mixture is allowed to warm to room temperature, then poured rapidly into a 500-ml., single-necked, round-bottomed flask containing 150 g. of phosphorus pentoxide. A spatula is used to partially mix the liquid with the phosphorus pentoxide (Note 2); the flask is quickly fitted with a simple still head with condenser and heated with a heating mantle until no further distillation occurs (Note 3). The crude distillate is redistilled through a 45-cm. spinning-band column, giving 48–53 g. (53–59% conversion) of hexafluoroacetone hydrazone as a colorless liquid, b. p. 95.5–96°, n_D^{25} 1.3298.

B. *Bis(trifluoromethyl)diazomethane*. A 1-l., three-necked, round-bottomed flask is

equipped with a sealed mechanical stirrer and a 100-ml., pressure-equalizing dropping funnel. The third neck is connected with pressure tubing to a 50-ml. capacity cold trap immersed in an acetone-dry ice cooling bath and protected from the atmosphere with a calcium chloride drying tube. The system is purged with nitrogen, and 375 ml. of benzonitrile and 120 g. (0.271 mole) of lead tetraäcetate (Note 4) are placed in the flask. Stirring is started and the flask is cooled with an ice bath before a solution of 45 g. (0.25 mole) of hexafluoroacetone hydrazone in 50 ml. of benzonitrile is added with the dropping funnel over a period of 1 hour. The ice bath is removed and the reaction mixture is stirred for an additional hour at room temperature. During this time some product collects in the cold trap. The remaining product is distilled into the trap at 10 mm. pressure by removing the drying tube and connecting the trap to a pump or aspirator (a small amount of acetic acid and other impurities can be removed by trap-to-trap distillation), yielding 20–21 ml. or 34–35 g. (76–79%) (Note 5) of bis (trifluoromethyl)diazomethane as a yellow liquid, b.p. 12–13°. The product is neither impact- nor static-sensitive (Note 6) and is stable to long storage at −78°; however, it partly decomposes with loss of nitrogen after several weeks at room temperature.

2. Notes

1. If it is inconvenient to distill the hexafluoroacetone imine directly from a cylinder, it may be condensed first in a calibrated cold trap cooled to −10°, then distilled from the trap into the reaction mixture. About 55 ml. of the imine, measured at −10°, corresponds to 0.5 mole.
2. *Caution! A spontaneous reaction may result if mixing is prolonged beyond 1 minute. Rubber gloves should be worn to avoid exposure to hydrazine vapors.*
3. About 14 g. (17%) of hexafluoroacetone imine can be recovered during the redistillation step if the receivers for both distillations are cooled to −10° or lower. The yield of the hydrazone is about 67% if the recovered imine is taken into account.
4. Since acetic acid does not interfere with this reaction, a grade of lead tetraäcetate that has been stabilized with acetic acid may be used.
5. The submitters have obtained yields as high as 90% on runs two times this scale.
6. *Caution! Toxicity data on this material are not available; therefore, it should be assumed to be as toxic as other diazo compounds and handled only in an efficient hood. Although it has been stored in stainless-steel cylinders at autogenous pressure and handled without incident, contact with reagents likely to initiate rapid evolution of nitrogen should be carried out with caution.*

3. Discussion

Bis(trifluoromethyl)diazomethane has been prepared by the nitrosation of 1,1,1,3,3,3-hexafluoroisopropylamine[2] and by the present procedure,[3] which gives higher yields. Bis(perfluoroethyl)diazomethane has also been prepared by an extension of this method.[2]

Bis(trifluoromethyl)diazomethane is a reactive, electrophilic compound, in that it forms adducts with nucleophiles such as amines and phosphines[3] and adds to olefins, acetylenes,[3] and thiocarbonyl compounds, forming heterocycles. It has been used as a source of bis(trifluoromethyl)carbene in reactions with benzene,[3] saturated hydrocarbons,[4] carbon disulfide,[5] and transition metal compounds,[6] and it undergoes a unique radical chain reaction with saturated hydrocarbons, giving hydrazone and azine adducts.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 392

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

1,1,1,3,3,3-hexafluoroisopropylamine

acetic acid (64-19-7)

Benzene (71-43-2)

methanol (67-56-1)

benzonitrile (100-47-0)

nitrogen (7727-37-9)

carbon disulfide (75-15-0)

hydrazine (302-01-2)

Bis(trifluoromethyl)diazomethane, Propane, 2-diazo-1,1,1,3,3,3-hexafluoro- (684-23-1)

Hexafluoroacetone imine (1645-75-6)

Hexafluoroacetone hydrazone (1588-41-6)

Bis(perfluoroethyl)diazomethane

bis(trifluoromethyl)carbene

phosphorus pentoxide (1314-56-3)

lead tetraacetate

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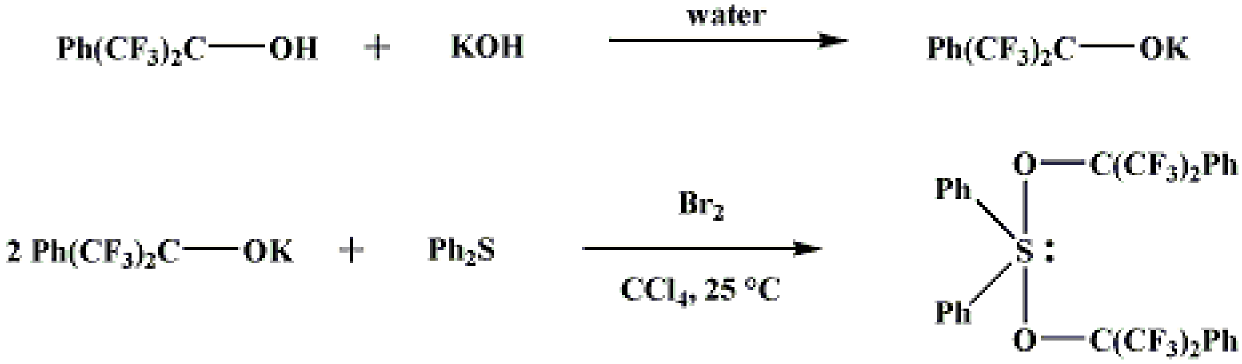
BIS[2,2,2-TRIFLUORO-1-PHENYL-1-(TRIFLUOROMETHYL) ETHOXY] DIPHENYL SULFURANE

[Sulfur, bis[α,α-bis(trifluoromethyl)benzenemethanolato]diphenyl-]



Submitted by J. C. Martin[1], R. J. Arhart, J. A. Franz, E. F. Perozzi, and L. J. Kaplan.
Checked by H. G. Corkins, C. J. Stark, and C. R. Johnson.

1. Procedure

A. *Potassium 1,1,1,3,3,3-hexafluoro-2-phenyl-2-propanolate*. A 500-ml., round-bottomed flask equipped for simple vacuum distillation is charged with a solution of 25.4 g. (0.390 mole) of 86% potassium hydroxide (Note 1) and (Note 2) in 50 ml. of water, to which is added 100.0 g. (0.4098 mole) of 1,1,1,3,3,3-hexafluoro-2-phenyl-2-propanol (Note 3). The colorless solution obtained is concentrated to a syrup by vacuum distillation at aspirator pressure. Further evacuation with a vacuum pump with heating to 140° results in a white solid; under the greater vacuum volatile substances can be collected in a trap immersed in an acetone-dry ice bath. The trap must be cleaned or be replaced several times during the first hour. After drying the white solid at 140° for 12 hours, the flask is transferred to a glove bag (Note 4) equipped with a mortar and pestle, a vacuum adapter, a powder funnel, a spatula, and a tared, 500-ml., round-bottomed flask. Under a dry nitrogen atmosphere the white solid is ground to a fine powder, transferred to the 500-ml. flask, and dried on a vacuum pump (10^{-2} mm.) to constant weight, yielding 107–109 g. (97–99%) of potassium 1,1,1,3,3,3-hexafluoro-2-phenyl-2-propanolate as a white powder.

B. *Bis[2,2,2-trifluoro-1-phenyl-1-(trifluoromethyl)ethoxy] diphenyl sulfurane*. Carbon tetrachloride is distilled directly from phosphorous pentoxide into a dry, 2-l., three-necked flask, fitted with stoppers, until 700 ml. is collected. The flask is quickly fitted with an adapter for use as a nitrogen-inlet, a mechanical stirrer, and an adapter for solid addition (Note 5) which is attached to the 500-ml. flask containing the potassium

alkoxide from Part A. A positive pressure of dry nitrogen is used to maintain inert atmosphere conditions. A white slurry is obtained when the powdered alkoxide is added at room temperature to the stirred carbon tetrachloride. Since all of the alkoxide does not transfer, the tared, 500-ml. flask is reweighed, and the amount added to the reaction vessel is determined by difference (Note 6). The adaptor used for solid addition is quickly exchanged for a septum.

To a stirred suspension of 105 g. (0.372 mole) of the alkoxide, 34.7 g. (31.0 ml., 0.186 mole) of diphenyl sulfide is added by syringe. Bromine, 29.9 g. (9.6 ml., 0.186 mole), is then added by syringe over a 5-minute period, giving a red-brown mixture which gradually fades to a pale yellow within 30 minutes. Stirring is continued at room temperature for 2.5 hours, leaving a pale-yellow solution and a copious precipitate of potassium bromide containing some potassium alkoxide.

A glove bag is equipped with a spatula, a tared, 1-l., single-necked round-bottomed flask, a 350-ml. Buchner funnel with filter paper, a 1-l. flask, a vacuum adapter, an aspirator hose (Note 7), and a flask containing 100 ml. of dry carbon tetrachloride. Filtration of the reaction mixture under a nitrogen atmosphere can be achieved by pouring the solution into the filter funnel *via* one neck of the three-necked flask, which is inserted through a hole in the glove bag. The potassium bromide is removed and washed with two 50-ml. portions of dry carbon tetrachloride. The filtrate is then transferred to the 1-l. flask, fitted with the vacuum adapter. After removal of the sulfurane solution from the glove bag (Note 8), the flask is quickly placed on a rotary evaporator (Note 9) and concentrated to a semisolid. Drying under reduced pressure (10^{-2} mm.) for 24 hours results in crude sulfurane (115–119 g., 93–96%) as slightly yellow crystals.

The flask containing the crude sulfurane is transferred to the nitrogen atmosphere of the glove bag which contains a powder funnel, a fluted filter paper, a 1-l., single-necked, round-bottomed flask, a 250-ml. graduated cylinder, a 1-l. flask containing 700 ml. of dry pentane (Note 10), and a 500-ml. flask containing 250 ml. of dry diethyl ether (Note 10). After dissolving the sulfurane in 150 ml. of ether, 500 ml. of pentane is added, giving a cloudy solution that clarifies when filtered directly into the 1-l. flask. The flask, is stoppered with the vacuum adapter and removed from the bag. At this time everything but the pentane is removed from the glove bag and the following items are added: a 600-ml., medium-frit sintered-glass funnel, a 1-l., single-necked, round-bottomed flask, a tared, 500-ml., single-necked round-bottomed flask, a vacuum adaptor, two spatulas, and a powder funnel. The sulfurane solution is concentrated to *ca.* 350 ml. at reduced pressure and a temperature not exceeding 40° (Note 9), using a magnetic stirrer to prevent bumping as the solvent is evaporated through the vacuum adapter. After a drying tube is connected to the adapter, the flask is cooled in an acetone–dry ice bath to induce crystallization; swirling the flask during the crystallization prevents crystals from adhering to the sides. When crystallization is complete, the flask is exchanged for the three-necked flask inserted into the side of the glove bag. Cooling in the acetone–dry ice bath is continued while the neck of the flask penetrates the glove bag. The crystals, collected in the sintered-glass funnel by

vacuum filtration, are washed with one 50-ml. portion of cold (−78°) pentane and transferred to the 500-ml. flask. After fitting with the vacuum adapter, the flask is removed from the bag and the crystals dried under reduced pressure (10^{-2} mm.) until the powdered, white sulfurane is at constant weight (76–79 g., 61–64%, m.p. 103–108°). Further crystallization from the mother liquors, after concentration by rotary evaporation to one-half the original volume, gives up to 7 g. of crude sulfurane (m.p. < 95°) for a total yield of 79–83 g. (63–67%) (Note 11). Recrystallization by the same method as above gives analytically pure material, m.p. 109.5–110.5°.

2. Notes

1. The submitters report no problems in running the entire procedure on four times the scale described here.
2. The use of potassium hydroxide rather than sodium hydroxide is dictated by solubility characteristics which make purification of the sodium alkoxide difficult.
3. The alcohol was obtained from PCR, Incorporated, or was prepared from hexafluoroacetone (E.I. du Pont de Nemours and Company), benzene, and aluminum chloride by the published[2] procedure.
4. Glove bags may be purchased from Instruments for Research and Industry, 108 Franklin Avenue, Cheltenham, Pennsylvania 19012. The 27 × 27 × 15 inch bag was found to be a convenient size for this procedure. The submitters performed all inert atmosphere operations in a dry box. All apparatus must be oven or flame dried prior to use.
5. This adapter consisted of two 24/40 joints connected with Gooch tubing.
6. The quantities of bromine and diphenyl sulfide must be adjusted according to the amount of alkoxide added.
7. A stopcock and a drying tube were inserted into the hose between the glove bag and the aspirator.
8. The other materials in the bag may be removed at this time, but the three-necked flask inserted through the side of the glove bag must not be removed.
9. During solvent removal or recrystallization, temperatures should be kept below 50° to avoid degradation of product quality.
10. Dry ether was obtained by distillation of reagent grade dry ether from sodium dispersion or by drying over three portions of sodium wire over a 48-hour period. Dry pentane was prepared by adding sodium wire directly to reagent grade solvent at least twice or by distilling it from a sodium dispersion.
11. Hexafluoro-2-phenyl-2-propanol may be recovered from mother liquors, recovered solvent, and the KBr salt cake by extracting the mixture with aqueous base. Neutralization of the aqueous phase gives the alcohol (13–23 g.), which is purified by distillation.

3. Discussion

This dialkoxy diphenyl sulfurane has been prepared by the reaction of diphenyl sulfide, 2,2,2-trifluoro-1-phenyl-1-(trifluoromethyl)ethyl hypochlorite, and potassium

1,1,1,3,3,3-hexafluoro-2-phenyl-2-propanolate[3] and by the reaction of diphenyl sulfide with 1 equivalent of chlorine and 2 equivalents of potassium 1,1,1,3,3,3-hexafluoro-2-phenyl-2-propanolate in ether.[4]

The present method offers several advantages over earlier methods. The use of carbon tetrachloride instead of ether as solvent avoids the intrusion of certain radical-chain reactions with the solvent which are observed with bromine and to a lesser degree with chlorine. In addition, the potassium bromide has a reduced solubility in carbon tetrachloride compared to ether, thus providing additional driving force for the reaction and ease of purification of product. The selection of bromine over chlorine as the oxidizing agent is made in consideration of the ease of handling the bromine by syringe compared to the greater number of operations and more complex apparatus required for chlorine.

Another dialkoxy diaryl sulfurane has been prepared[5] under conditions similar to those reported here, indicating that this reaction for sulfurane formation may have wide applicability.

The great reactivity of the sulfurane prepared by this procedure toward active hydrogen compounds, coupled with an indefinite shelf life in the absence of moisture, makes this compound a useful reagent for dehydrations,[6,7] amide cleavage reactions,[8] epoxide formation,[9] sulfilimine syntheses,[10] and certain oxidations and coupling reactions.

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

phosphorous pentoxide

Sulfur, bis[α,α-bis(trifluoromethyl)benzenemethanolato]diphenyl-

Benzene (71-43-2)

ether, diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

bromine (7726-95-6)

carbon tetrachloride (56-23-5)

nitrogen (7727-37-9)

aluminum chloride (3495-54-3)

chlorine (7782-50-5)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

potassium bromide (7758-02-3)

Pentane (109-66-0)

Diphenyl sulfide (139-66-2)

BIS[2,2,2-TRIFLUORO-1-PHENYL-1-(TRIFLUOROMETHYL) ETHOXY] DIPHENYL SULFURANE, Bis[2,2,2-trifluoro-1-phenyl-1-(trifluoromethyl)ethoxy] diphenyl sulfurane (32133-82-7)

1,1,1,3,3,3-hexafluoro-2-phenyl-2-propanol, Hexafluoro-2-phenyl-2-propanol (718-64-9)

potassium 1,1,1,3,3,3-hexafluoro-2-phenyl-2-propanolate

Hexafluoroacetone (684-16-2)

sulfilimine

2,2,2-trifluoro-1-phenyl-1-(trifluoromethyl)ethyl hypochlorite

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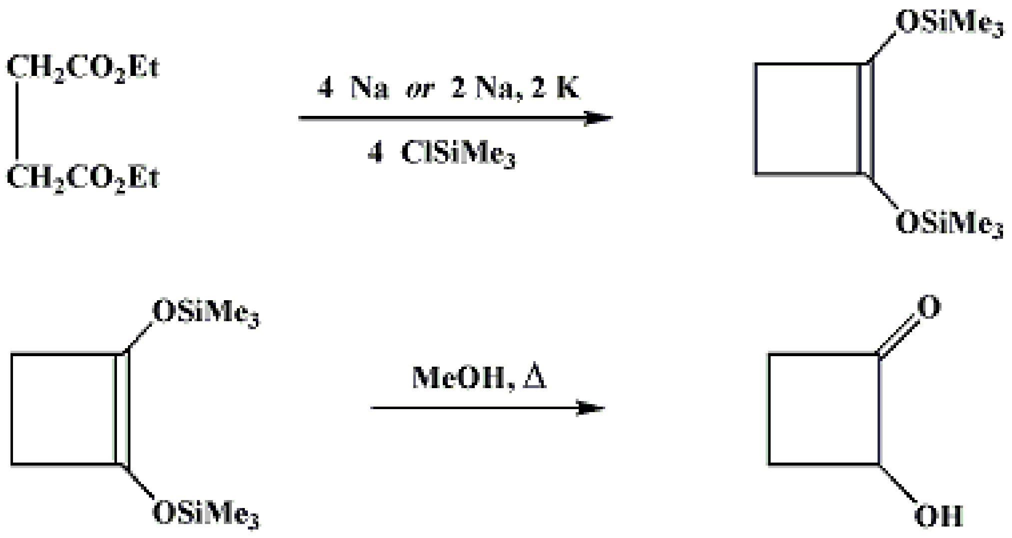
Organic Syntheses, CV 6, 167

ACYLOIN CONDENSATION IN WHICH CHLOROTRIMETHYLSILANE IS USED AS A TRAPPING AGENT: 1,2-BIS(TRIMETHYLSILYLOXY) CYCLOBUTENE AND 2-HYDROXYCYCLOBUTANONE

[Trimethylsilane, 1-cyclobuten-1,2-ylenedioxybis- and Cyclobutanone, 2-hydroxy-]



Submitted by Jordan J. Bloomfield[1] and Janice M. Nelke.
Checked by Z. Stojanac and Z. Valenta.

1. Procedure

Caution! See warnings concerning the use of impure chlorotrimethylsilane (Note 8) and finely dispersed alkali metals (Note 1),(Note 9),(Note 11) and (Note 19).

A. *1,2-Bis(trimethylsilyloxy)cyclobutene*. *Method* 1. A 1-l., three-necked, creased flask is fitted with a stirrer capable of forming a fine dispersion of molten sodium (Note 1), a reflux condenser, and a Hershberg addition funnel and maintained under an oxygen-free, nitrogen atmosphere. The flask is charged with 250–300 ml. of dry solvent (Note 2) and 9.6–9.8 g. (0.4 g.-atom) of freshly cut sodium (Note 3), (Note 4). The solvent is brought to gentle reflux, and the stirrer is operated at full speed until the sodium is fully dispersed (Note 5). The stirrer speed is then reduced (Note 6), and a mixture of 17.4 g. (0.100 mole) of diethyl succinate (Note 7) and 45–50 g. (0.4 mole) of chlorotrimethylsilane (Note 8) in 125 ml. of solvent is added over 1–3 hours. The reaction is exothermic, and a dark purple precipitate appears within a few minutes

(Note 9). The solvent is maintained at reflux during and after the addition (Note 10). After five hours of additional stirring, the contents of the flask are cooled and filtered through a 75-mm., coarse sintered-disk funnel in a nitrogen dry-box (Note 11). The precipitate is washed several times with anhydrous diethyl ether or petroleum ether.

The colorless to pale yellow filtrate is transferred to a distilling flask, the solvent is evaporated, and the residue is distilled under reduced pressure (Note 12). After a small forerun (0.5–1.0 g.), 18 g. (78%) of the product is obtained at 82–86° (10 mm.) as a colorless liquid, n_D^{25} 1.4331 (Note 13).

Method 2. The apparatus described above is charged with 4.8–5.0 g. (0.2 g.-atom) of clean sodium and 8.0–8.2 g. (0.2 g.-atom) of clean potassium (Note 3), (Note 4). The flask is heated with a heat gun, forming the low-melting alloy, and 300–350 ml. of anhydrous ether is added from a freshly opened can. The stirrer is operated at full speed until the alloy is dispersed, then at a slower speed for the remainder of the reaction (Note 5), (Note 6). A mixture of 17.4 g. (0.100 mole) of diethylsuccinate (Note 7), 44 g. (0.41 mole) of chlorotrimethylsilane (Note 8), and 125 ml. of anhydrous ether is added at a rate sufficient to keep the reaction under control (Note 14). The purple mixture is stirred for another 4–6 hours (Note 9), then filtered and washed as above in a nitrogen dry-box (Note 11). The product is distilled as above, collecting a forerun, 0.5–2 g. to 80° (10 mm.), and then the product at 82–86° (10 mm.) as a colorless liquid, 13.8–16.1 g. (60–70%), n_D^{25} 1.4323–1.4330 (Note 15), (Note 16),(Note 17),(Note 18),(Note 19).

B. *2-Hydroxycyclobutanone*. A 1-l., three-necked flask fitted with a magnetic stirring bar, a sintered-disk gas-inlet tube, a dropping funnel, and a reflux condenser is charged with 450 ml. of reagent grade methanol (Note 20). Dry, oxygen-free nitrogen is bubbled vigorously through the methanol for about 1 hour before 23 g. (0.10 mole) of freshly distilled (Note 21) 1,2-bis(trimethylsilyloxy)cyclobutene is transferred under nitrogen to the addition funnel and added dropwise to the stirred methanol. Stirring under a reduced nitrogen flow is continued for 24–30 hours (Note 22). The methanol and methoxytrimethylsilane are removed under reduced pressure, and the residual 2-hydroxycyclobutanone is distilled through a short-path still as a colorless liquid, b.p. 52–57° (0.1 mm.), 6.1–7.4 g. (71–86%), n_D^{25} 1.4613–1.4685 (Note 23),(Note 24), (Note 25).

2. Notes

1. Generally a "Stir-O-Vac" stirrer (available from Labline Instruments, Inc., Melrose Park, Ill.) is used. A Vibromixer type of stirrer is also satisfactory, especially when high-dilution conditions are required. Both were used in the submitter's laboratory in conjunction with a short condenser surrounding the stirrer shaft to prevent loss of solvent or reactants. The condenser is required in high-dilution procedures with the Vibromixer to protect the diaphragm from solvent vapor. A plain sleeve stirrer with a Teflon paddle was used by the

checkers, but the submitters warn that a Teflon paddle with highly dispersed metal, especially sodium-potassium alloy, is dangerous; explosions have been reported when Teflon and molten sodium are in contact. The submitters also emphasize that, because the large particle size can cause or lead to side reactions, a fine dispersion of metal is desirable, even with chlorotrimethylsilane.

2. Toluene is commonly used and can be dried with molecular sieves or directly distilled from calcium hydride into the reaction flask. Solvent stored over calcium hydride for several days is usually sufficiently dry to decant directly into the reaction flask, but distillation gives more consistent results. Any solvent with a boiling point sufficiently high to melt sodium is satisfactory. The submitters have also used methylcyclohexane and xylene in acyloin condensations. After the sodium is dispersed, the high-boiling solvent can be removed and replaced with anhydrous ether (as noted by the submitters) or can be retained and used in combination with ether (checkers).

3. The submitters routinely used a nitrogen dry-box to clean, cut, and weigh alkali metals. The checkers cut and weighed these metals under dry toluene.

4. An excess of metal is used because aromatic solvents are reduced to some extent, and it is easier than weighing out the exact amount.

5. One or two minutes of a "Stir-O-Vac" operated through a variable transformer at full voltage is required.

6. A setting of 30–40 volts on the variable transformer is used.

7. Diethyl succinate was obtained by the submitters from Eastman Organic Chemicals and used without purification. The checkers obtained the ester from British Drug Houses, Ltd., and distilled it at 100° (11 mm.). In general, it is preferable to distill or crystallize and dry all esters before attempting acyloin condensations.

8. Chlorotrimethylsilane, obtained from Eastman Organic Chemicals (submitters) and Aldrich Chemical Co. (checkers), was distilled from calcium hydride under nitrogen, then stored and weighed in a nitrogen dry-box. *Caution! It is particularly important that the chlorotrimethylsilane be distilled, preferably from calcium hydride, under nitrogen.* In at least one laboratory[2] the use of this reagent without prior purification led to explosions. Chlorotrimethylsilane may contain some dichlorodimethylsilane as an impurity, which hydrolyzes more readily than the monochlorosilane. Cautious treatment with a small amount of water, followed by distillation from calcium hydride, under nitrogen, removes this impurity. A further cautionary note concerning these reactions is also necessary. The explosions occurred in reactions run on a scale larger than 0.1 mole, using undistilled chlorotrimethylsilane and following a published procedure.[3] This procedure requires mixing all the reagents at 20–30° and gradually warming the mixture. When this procedure was applied to diethyl pentanedioate on a large scale, the reaction became uncontrollably exothermic at about 50°.[2] It is recommended that the ester and chlorosilane be added together, dropwise, at a rate sufficient to maintain the exothermic reaction. It is often unsafe with many esters to have a large amount of unreacted ester in the reaction

mixture at any time.

9. The purple color seems to be indicative of a satisfactory reduction. When the color is light or no color develops, the yield is usually poor. Sometimes no reaction occurs. In this instance it is best to discard all residues (*pyrophoric*) carefully and start over with scrupulous attention to the dryness of all apparatus and reagents.

10. This is the usual procedure. The submitters report that equally good results are obtained if all the dispersing solvent is replaced by ether and the reaction is run at room temperature. The checkers have found a slightly modified procedure in which refluxing toluene (90 ml.) is used for dispersion, anhydrous ether (250 ml.) is added without removal of toluene, additional ether (120 ml.) is used for addition of diethyl succinate and chlorotrimethylsilane, and the mixture is heated under reflux for 14 hours, to be particularly convenient and to give consistently high yields (77–86%). The checkers have also found that prior removal of toluene does not affect the yields, but simplifies final purification. With toluene as solvent, better results are usually obtained at or near reflux. The amount of time following completion of addition of the ester is not critical. (It may vary with the compound being reduced.) The submitters generally use 4–6 hours or overnight, whichever happens to be more convenient.

11. Since a slight excess of metal is used, some may be left over. The excess chlorosilane and the product are sensitive to moisture. To avoid unpleasantness due to the pyrophoric nature of finely divided alkali metal residues, to hydrolysis of product, or production of free acid from the excess silane the submitters *always* filtered the reaction mixture in a nitrogen dry-box. The checkers used simple sintered-glass funnel filtration under a stream of dry nitrogen.

12. The submitters used a 250-mm. vacuum-jacketed Vigreux column fitted with a variable take-off head. Any good column should be as satisfactory.

13. The yield varies from 65 to 86%, n_D^{25} 1.4322–1.4338; b.p. 58–59° (2 mm.); 68–70° (6 mm.); 82–86° (10 mm.); 88–92° (13–14 mm.). In twelve separate runs (in toluene, toluene-ether, or in ether), the checkers did not obtain a yield below 76%.

14. The reaction is exothermic. Two hours is more than enough time. Too vigorous a reaction can be controlled with an acetone–dry ice bath.

15. The yields given are those obtained by the checkers. For this particular reaction the submitters have found the product to be cleaner and the yields higher (78–93%) with sodium-potassium reduction. This is not necessarily a general observation inasmuch as other reactions can occur with the alloy.[4] The checkers found that a modification involving formation of the alloy in hot toluene (10 ml.), removal of most of the toluene with a stream of dry nitrogen, and dispersion of the alloy in ether led to somewhat better yields (81–85%). Because of convenience, safety, and yield reproducibility, they strongly favor Method 1.

16. The product can be examined for purity by ^1H NMR or by GC. The submitters have used XF-1150 columns successfully. Columns with polar sites will strip silyloxy groups from the bis(silyloxy) compounds and are

unsatisfactory.

17. Both Methods 1 and 2 have been successfully applied to a wide range of 1,2-diesters[5] and to a variety of other esters.[6] The use of a high-dilution cycle permits this procedure to be applied to medium- and large-ring acyloins with good to excellent results.

18. The product is stable if stored in a tightly screw-capped bottle. Prolonged exposure to moist air leads to decomposition. The submitters have stored samples for several years with no change in physical properties.

19. *Caution! Disposal of residues must be made with care. When excess metal, especially sodium-potassium alloy, is used, the residues can be pyrophoric!*

20. The submitters used a freshly opened bottle for each hydrolysis.

21. Use of freshly distilled bis(silyloxy) compound is critical in many cases, especially in this example. The yield and, more particularly, the quality of the product deteriorate with the age of the sample. Traces of acid should be avoided because even as little as one drop of chlorotrimethylsilane added to the reaction mixture produces a different product. The longer the reaction time in the presence of acid, the greater is the number of other products formed.

22. The reaction time can be reduced considerably by gentle reflux. It is advantageous to follow the reaction by GC (see (Note 16)) if heating is used, because prolonged reflux can lead to side reactions.

23. The wide range of refractive indices is related to the time interval between distillation and measurement. The longer one waits, the higher the refractive index. This is apparently due to rapid formation of dimer.

24. In the IR ($CHCl_3$), 2-hydroxycyclobutanone has a carbonyl band at 1780 cm^{-1}. Kept in nitrogen-filled screw-capped vials in the freezing compartment of a refrigerator, 2-hydroxycyclobutanone slowly but completely solidifies as its dimer. The IR spectrum (KBr) of the solid shows no carbonyl. However, a $CHCl_3$ solution of the solid does show the characteristic 1780 cm^{-1} band, indicating rapid equilibration with the monomer.

25. Air readily oxidizes 2-hydroxycyclobutanone; quantitative conversion to succinic acid occurs on standing in the open for several days.

3. Discussion

The discovery that chlorotrimethylsilane will react *in situ* with alcoholates and the acyloin enediolates[3,7,8,9] provided the opportunity to prepare a wide range of four-membered acyloins for the first time.[5] In addition, most acyloin reaction yields are improved, and some diesters, which were found to give Dieckmann condensation products as a result of the base formed concomitantly with the acyloin, can now be reductively cyclized in good yield.[6] The general reaction conditions given for the cyclization of diethyl succinate have been applied to synthesis of four- to eight-membered rings with very good results.[3,7,8,9] Likewise, when a high-dilution cycle is used, good to excellent cyclizations of eight- to fourteen-membered rings can be obtained. (Yields are 8, 72–85%; 9,68%; 10, 58–69%; 11,48%; 12,68%; 13,84% 14,67%.)[10]

For many reasons, use of the trapping agent is recommended as the most efficient method for running acyloin condensations. Among them are: (a) the work-up is very simple: filter and distill; (b) the bis(silyloxy)olefin is usually easier to store than the free acyloin and is readily purified by redistillation; (c) unwanted base-catalyzed side reactions during reduction are completely avoided; and (d) the bis(silyloxy)olefin can be easily converted directly into the diketone by treatment with 1 mole of bromine in carbon tetrachloride.[11,12,13] Other reactions are described in Rühlmann's review and in *Organic Reactions*.[14]

Bis(silyloxy)cyclobutenes are also subject to a variety of special reactions. Probably the most interesting is the observation that they readily undergo a ring-opening reaction leading to butadiene derivatives[5]. This reaction has already been used to prepare largering diketones from cyclic 1,2-diesters[15].

The synthesis of 2-hydroxycyclobutanone was chosen as a model for the use of a trapping agent because diethyl succinate is the most accessible of 1,2-diesters and the hydrolysis step for this compound is more difficult than most. Procedures developed for succinoin have been found broadly applicable in preparation of other sensitive acyloins.

This preparation is referenced from:

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- Org. Syn. Coll. Vol. 7, 95
- Org. Syn. Coll. Vol. 7, 112
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

methanol (67-56-1)

ether, diethyl ether (60-29-7)

bromine (7726-95-6)

carbon tetrachloride (56-23-5)

nitrogen (7727-37-9)

Succinic acid (110-15-6)

toluene (108-88-3)

sodium (13966-32-0)

potassium (7440-09-7)

xylene (106-42-3)

methylcyclohexane (108-87-2)

Diethyl succinate (123-25-1)

sodium-potassium

calcium hydride (7789-78-8)

CHLOROTRIMETHYLSILANE (75-77-4)

1,2-bis(trimethylsilyloxy)cyclobutene, Trimethylsilane, 1-cyclobuten-1,2-ylenedioxybis- (17082-61-0)

2-Hydroxycyclobutanone, Cyclobutanone, 2-hydroxy- (17082-63-2)

diethylsuccinate

methoxytrimethylsilane (1825-61-2)

dichlorodimethylsilane (75-78-5)

monochlorosilane (13465-78-6)

diethyl pentanedioate (818-38-2)

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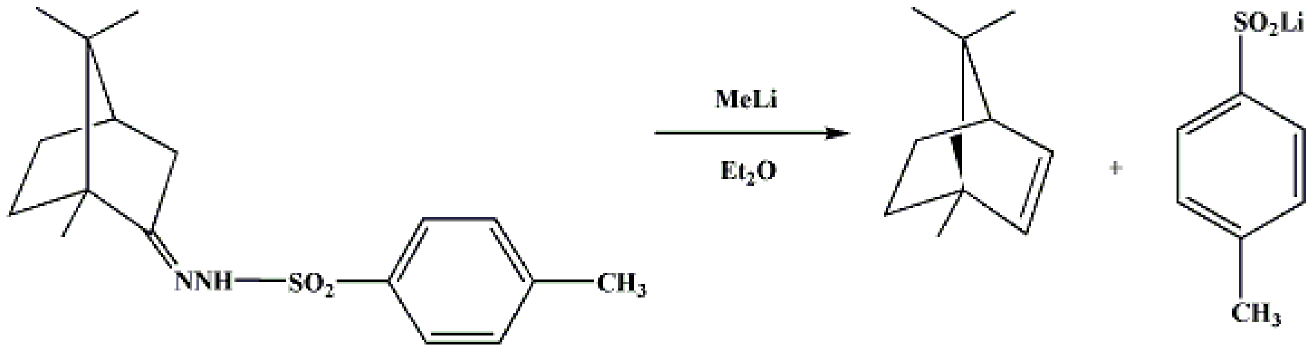
2-BORNENE

[1,7,7-Trimethylbicyclo[2.2.1]hept-2-ene]



Submitted by Robert H. Shapiro[1] and J. H. Duncan.
Checked by Robert Czarny and Robert E. Ireland.

1. Procedure

A dry, 1-l., three-necked flask equipped with a reflux condenser protected with a calcium sulfate drying tube, a 250-ml., pressure-equalizing dropping funnel, and a magnetic stirring bar is charged with 32 g. (0.10 mole) of camphor tosylhydrazone (Note 1) and 400 ml. of dry diethyl ether (Note 2). The flask is immersed in a cold-water bath (20–25°), and the contents are stirred magnetically. About 50 ml. of dry ether is placed in the dropping funnel, and the addition rate is set at 2–3 ml./minute (Note 3). After this addition 150 ml. of 1.6 *N* (0.24 mole) methyllithium (Note 4) in ether is added to the dropping funnel and dropped into the reaction flask over 1 hour (Note 5), while the cooling bath temperature is maintained at 20–25°. The yellow-orange solution is stirred for 8–9 hours, during which time lithium *p*-toluenesulfinate precipitates and the solution develops a deep red-orange color. A small amount of water is carefully added to destroy excess methyllithium before an additional 200 ml. is added. The layers are separated, the organic phase is washed with four 250-ml. portions of water, and the combined aqueous phases are shaken twice with 100-ml. portions of ether. After drying the combined ethereal extracts over anhydrous sodium sulfate, the volume of the solution is reduced to 50–60 ml. by distillation of the ether through a 25-cm. Vigreux column with gentle boiling on a steam bath. After 100 ml. of distilled pentane (Note 6) is added to the orange solution, the solvent is again gently boiled away, reducing the volume to 30–50 ml. The addition and removal of pentane is repeated two additional times to assure the complete removal of ether, and the final volume of the solution of 2-bornene is reduced to 30–40 ml. The solution is added to an 80 × 5 cm. chromatography column packed with 500 g. of alumina (Note 7), and the product is eluted with 750 ml. of pentane. After concentration of the eluate by distillation of the solvent through a Vigreux column, the residue is transferred to a 50-ml. flask and distilled through a U-tube with the aid of an oil bath and a heating lamp (Note 8). After collecting a forerun (pentane and 2-bornene), 8.5–8.8 g. (63–65%) of 2-bornene, m.p. 110–111° (lit.[2,3,4], 109–110°), is collected as colorless crystals in a cooled flask (Note 9). GC analysis[5] shows this product to be 98–99% pure, containing no camphene or tricyclene (Note 10).

2. Notes

1. Camphor tosylhydrazone[6] is prepared in the following manner. To a 1-l., one-necked, round-bottomed flask are added 44 g. (0.24 mole) of *p*-toluenesulfonylhydrazide [*Org. Synth.*, **Coll. Vol. 5**, 1055 (1973)], 31.6 g. (0.208 mole) of camphor, and 300 ml. of 95% ethanol. One milliliter of concentrated hydrochloric acid is added, the flask is fitted with a reflux condenser, and the solution is heated under reflux for 2 hours. The resulting solution is cooled in an ice bath; colorless needles are collected by suction filtration and dried in air (Note 11). Recrystallization from ethanol yields 50 g.

(73%) of pure camphor tosylhydrazone, m.p. 163–164°.

2. Anhydrous ether available from Mallinckrodt Chemical Works can be used without further drying.

3. This prevents clogging of the funnel during the subsequent addition of methyllithium solution.

4. Methyllithium available from either Foote Mineral Company or Alfa Inorganics, Inc., can be used without further purification. The checkers used 137 ml. of a 1.85 *M* solution.

5. During the first half of the addition each drop of methyllithium solution produces a yellow color that quickly disappears. The solution turns yellow during the second half of the addition and slowly becomes more intensely colored until it reaches red-orange near the end of the reaction period.

6. Since the solvent is never completely removed at any time prior to final distillation of the product, the accumulation of higher boiling hydrocarbons results if petroleum ether is used. As a result the forerun of the final distillation will be larger, and the yield of 2-bornene will be reduced. The pentane was distilled to assure the removal of any higher boiling impurities.

7. Neutral, reagent grade aluminum oxide available from Merck & Co., Inc., was used by the checkers.

8. When the temperature of the bath reaches 140–143°, the heating lamp is turned directly on the U-tube, and the receiver is changed to collect the 2-bornene.

9. The yield of the product is greatly reduced if the receiver is not cooled. A 2-propanol–dry ice bath was used.

10. On a 180 cm. × 32 mm. GC column containing 10% Apiezon L on Chromosorb P at 60° a synthetic mixture of 2-bornene (10.3 minutes), tricyclene (12.3 minutes), and camphene (15.5 minutes) was readily resolvable.

11. The product has m.p. 161–163° and can be used without further purification.

3. Discussion

2-Bornene has been prepared from the reaction of 2-bromobornane-3-carboxylic acid with aqueous sodium hydrogen carbonate,[7] by pyrolysis of isoborneol methyl xanthate,[8] and by the β-elimination of hydrogen chloride from bornyl chloride with sodium alkoxides in various solvents.[2,3,4]

This procedure appears to be general for the preparation, without rearrangement, of lesser substituted olefins. 2-Methylcyclohexanone tosylhydrazone gives 3-methylcyclohexene (98% yield by GC analysis).[9] Cholestan-6-one tosylhydrazone gives cholest-6-ene (95% isolated yield), androstan-17-one tosylhydrazone gives androst-16-ene (91% isolated yield),[9] and phenylacetone tosylhydrazone gives allylbenzene (70% yield by GC analysis, accompanied by the substitution product isobutylbenzene in 30% yield). Advantages of this procedure include its simplicity and the availability of carbonyl compounds as precursors. The reaction proceeds smoothly but more slowly at −25° and can be employed with heat-sensitive or volatile compounds in ordinary laboratory equipment.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 77

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alumina

isoborneol methyl xanthate

ethanol (64-17-5)

hydrogen chloride, hydrochloric acid (7647-01-0)

ether, diethyl ether (60-29-7)

sodium hydrogen carbonate (144-55-8)

sodium sulfate (7757-82-6)

Pentane (109-66-0)

aluminum oxide (1344-28-1)

camphor (21368-68-3)

Methyllithium (917-54-4)

allylbenzene (300-57-2)

2-Bornene, 1,7,7-Trimethylbicyclo[2.2.1]hept-2-ene (464-17-5)

camphor tosylhydrazone (10224-32-5)

camphene (565-00-4)

tricyclene (508-32-7)

2-bromobornane-3-carboxylic acid

bornyl chloride (464-41-5)

2-Methylcyclohexanone tosylhydrazone

3-Methylcyclohexene (591-48-0)

Cholestan-6-one tosylhydrazone

cholest-6-ene

androstan-17-one tosylhydrazone

androst-16-ene

phenylacetone tosylhydrazone

isobutylbenzene (538-93-2)

p-Toluenesulfonylhydrazide (1576-35-8)

lithium p-toluenesulfinate

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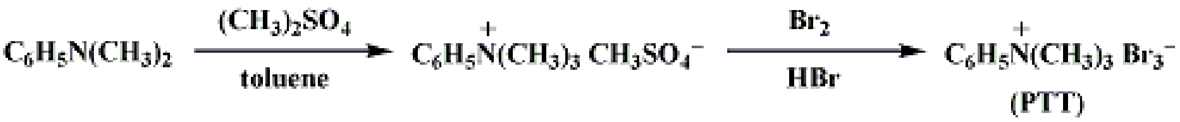
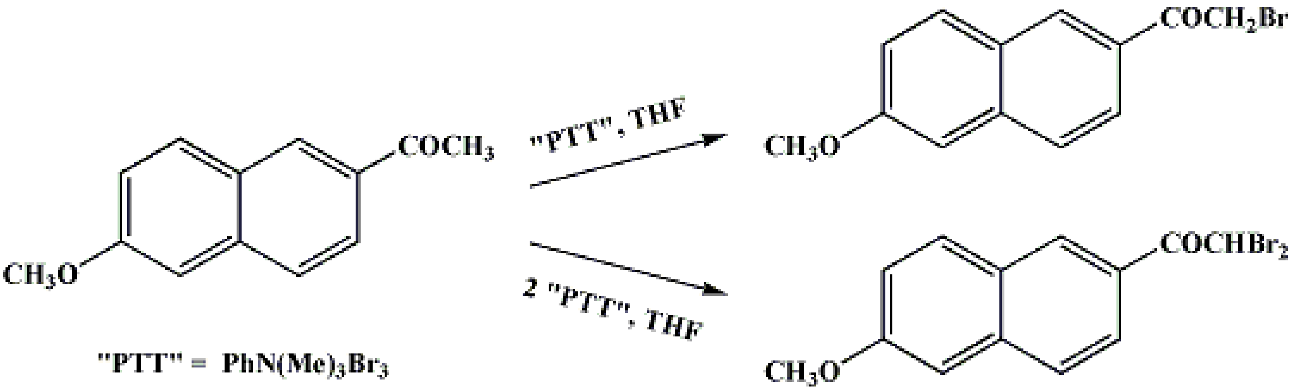
Organic Syntheses, CV 6, 175

SELECTIVE α-BROMINATION OF AN ARALKYL KETONE WITH PHENYLTRIMETHYLAMMONIUM TRIBROMIDE: 2-BROMOACETYL-6-METHOXYNAPHTHALENE AND 2,2-DIBROMOACETYL-6-METHOXYNAPHTHALENE

[Ethanone, 2-bromo-1-(6-methoxy-2-naphthalenyl)- and Ethanone, 2,2-dibromo-1-(6-methoxy-2-naphthalenyl)-]





Submitted by J. Jacques and A. Marquet[1].
Checked by David Walba and Robert E. Ireland.

1. Procedure

Caution! All operations should be carried out in a well-ventilated hood because dimethyl sulfate is highly toxic and the bromoketones are lachrymators and skin irritants.

A. *Phenyltrimethylammonium sulfomethylate*. A solution of 24.8 g. (25.9 ml., 0.205 mole) of freshly distilled *N,N*-dimethylaniline (Note 1) in 100 ml. of toluene (Note 2) is prepared in a 250-ml. Erlenmeyer flask equipped with a thermometer and a magnetic stirrer. The solution is stirred and heated to about 40°. Heating is stopped and 25 g. (19 ml., 0.20 mole) of distilled dimethyl sulfate (Note 3) is added with an addition funnel over 20 minutes. Within minutes, the colorless sulfomethylate starts to crystallize. The temperature which varies very little during the previous addition, rises slowly for one hour thereafter and approaches 50°. The reaction is allowed to proceed at ambient temperature for 1.5 hours after the addition is complete before it is heated on a steam bath for one hour. After cooling, the phenyltrimethylammonium sulfomethylate is filtered, washed with 20 ml. of dry toluene, and dried under vacuum, yielding 44–46.5 g. (89–94%) (Note 4).

B. *Phenyltrimethylammonium tribromide*. A solution of 10 g. (0.040 mole) of phenyltrimethylammonium sulfomethylate in 10 ml. of 48% hydrobromic acid diluted with 10 ml. of water is prepared in a 125-ml. Erlenmeyer flask equipped with a magnetic stirrer. Bromine (7.8 g., 2.5 ml., 0.049 mole) (Note 5) is added to the stirred solution from a dropping funnel over 20

minutes. An orange-yellow precipitate forms immediately, and the slurry is stirred at room temperature for 5–6 hours. The product, phenyltrimethylammonium tribromide (PTT), is filtered, washed with about 10 ml. of water, and air-dried under an efficient hood. The crude PTT, *ca.* 15 g., is recrystallized from 25 ml. of acetic acid, giving, after filtration and air-drying, 12.9–14.0 g. (86–93%) (Note 6) of orange crystals, m.p. 113–115°.

C. *2-Bromoacetyl-6-methoxynaphthalene*. To a solution of 1 g. (0.005 mole) of 2-acetyl-6-methoxynaphthalene [*Org. Synth.*, **Coll. Vol. 6**, 34 (1988)] in 10 ml. of anhydrous tetrahydrofuran (Note 7) contained in a 125-ml. Erlenmeyer flask is added 1.88 g. (0.00500 mole) of PTT in small portions over a 10 minute period. A white precipitate forms immediately and the solution becomes pale yellow. After 20 minutes, 50 ml. of cold water is added, and the crystalline precipitate (Note 8) is filtered and washed with 10 ml. of water. The crude, white 2-bromoacetyl-6-methoxynaphthalene (*ca.* 1.3 g., m.p. 100–105°) is recrystallized from 32 ml. of cyclohexane, yielding 1.1 g. (79%) of crystalline product, m.p. 107–109° (lit. 107–108°)[2] (Note 9) and (Note 10).

D. 2,2-*Dibromoacetyl*-6-*methoxynaphthalene*. To a solution of 1 g. (0.005 mole) of 2-acetyl-6-methoxynaphthalene [*Org. Synth.*, **Coll. Vol. 6**, 34 (1988)] in 10 ml. of anhydrous tetrahydrofuran (Note 7) contained in a 125-ml. Erlenmeyer flask is added 3.76 g. (0.0100 mole) of PTT in small portions over 10 minutes. A white precipitate forms and the solution becomes yellow over one hour. Cold water (50 ml.) is added, and the crystalline product (Note 8) is filtered and washed with 10 ml. of water. The crude 2,2-dibromoacetyl-6-methoxynaphthalene (*ca.* 1.7 g., m.p. 110–117°) is recrystallized from 15 ml. of ethanol, filtered, and washed with 2 ml. of ethanol, yielding 1.40–1.55 g. (78–87%) of slightly yellow product, m.p. 116.5–118° (lit. 118–119°)[3] (Note 9) and (Note 11).

2. Notes

1. Commercial *N,N*-dimethylaniline was redistilled, b.p. 78° (13 mm.).
2. Benzene can also be used, but toluene is preferable because of its lower toxicity.
3. Commercial dimethyl sulfate was distilled, b.p. 70° (13 mm.). A slight deficiency of dimethyl sulfate ensures the complete utilization of this toxic product.
4. This product is slightly hygroscopic, but no special precautions are required for handling.
5. Bromine (B & A, ACS Reagent Grade) was used without further purification.
6. The "active bromine" can be titrated according to the following procedure: about 300 mg. of PTT is dissolved in 50 ml. of acetic acid, 10 ml. of a 5% solution of potassium iodide in ethanol is added, and the liberated iodine is titrated with a 0.1 *N* solution of sodium thiosulfate. Percent "active bromine": calculated 42.5%; found 42.1–42.5%. The molecular weight of PTT is 375.96.
7. Tetrahydrofuran was purified and dried as previously described [*Org. Synth.*, **Coll. Vol. 5**, 976 (1973)]. PTT is remarkably soluble in tetrahydrofuran (630 g. per 1. at 20°). Under the same conditions, the solubility of the resulting phenyltrimethylammonium bromide is only 0.09 g. per 1.
8. If the product precipitates as an oil, mere standing at room temperature may cause it to crystallize. If not, the addition of *ca.* 3 ml. of tetrahydrofuran, followed by swirling will usually induce crystallization.
9. *This product, like other bromoketones, can be very irritating to exposed skin.*
10. ^{1}H NMR ($CDCl_3$): δ 3.94 (s, 3H, OCH_3), 4.54 (s, 2H, $COCH_2Br$), 7.20 (m, 4H, Ar*H*), 7.90 (m, 1H, Ar*H*), 8.21 (m, 1H, Ar*H*).
11. ^{1}H NMR ($CDCl_3$): δ 3.93 (s, 3H, OCH_3), 6.86 (s, 1H, $COCHBr_2$), 7.20 (m, 4H Ar*H*), 7.90 (m, 1H, Ar*H*), 8.50 (m, 1H, Ar*H*).

3. Discussion

Quaternary ammonium perhalogenides, being solid compounds, constitute convenient halogen sources. Of the different compounds studied and reported,[2] pyridine hydrobromide perbromide[4] is the most popular. Phenyltrimethylammonium tribromide (PTT), the utility of which was recognized by Marquet and Jacques,[5] has the advantage of high stability and ease of preparation. The procedure described herein is a modification of that of Vorländer and Siebert.[6]

When dissolved in tetrahydrofuran, PTT (like pyridine hydrobromide perbromide) is a source of Br_3^- ions, the properties of which are different from those of molecular bromine. In particular, it is much less electrophilic and less reactive toward aromatic rings and double bonds,[7] and is thus a selective brominating reagent for ketones[3] or ketals[3,8] when the molecule has double bonds or activated aromatic nuclei which would be attacked by bromine. The two examples of use of this reagent clearly differentiate between its reactivity from that of bromine. Reaction of bromine with 2-acetyl-6-methoxynaphthalene (in diethyl ether solution) gives a mixture of products, the main constituent of which results from ring bromination (2-acetyl-5-bromo-6-methoxynaphthalene).[9]

Many other examples have been described that illustrate the selectivity of PTT, not possible with bromine. Steroid and terpene α-bromoketones have been selectively obtained in molecules containing double bonds[3] or cyclopropane rings;[10,11,12] anisyl cyclohexyl ketone gives the α-bromoketone in very good yield with the aromatic ring remaining unattacked;[3] 5,7-dimethoxyflavanone can be brominated in good yield at the position alpha to the keto group, although the aromatic ring is activated by two methoxy groups.[13] A similar selectivity has been observed in the analogous case of 2-methyl-2-(2-benzyloxy-5-methoxyphenyl)cyclopentanone.[14] PTT has also been used for the selective bromination of 4-oxo-4,5,6,7-tetrahydrobenzofuran.[15]

Anhydrous tetrahydrofuran contributes to the selectivity of the reagent because of the stability of Br_3^- in this solvent. Moreover, tetrahydrofuran acts as a buffer by reaction with the liberated hydrobromic acid, which is why PTT in tetrahydrofuran can also be very useful if the substrate bears acid-sensitive functions. Acid-catalyzed epimerization can also be avoided: 2-bromobenzo[6.7]bicyclo[3.2.1]oct-6-en-3-one gives the diaxial 2,4-dibromoketone[16] and 3,4-dihydro-1-(*p*-tolylsulfonyl)benz[*c*,*d*]indol-5(1*H*)-one leads to the expected bromoketone, in spite of the tendency of this type of molecule to isomerize into the naphthalenoid system.[17] The importance of the solvent appears in the bromination of 1,5-cycloöctanedione: in tetrahydrofuran, the pure *cis-trans-cis* isomer is isolated,[18] whereas in dichloromethane, a mixture of two tetrabromo ketones is obtained.[19] It must be emphasized that anhydrous tetrahydrofuran must be used because small amounts of water can greatly retard the rate of bromination of ketones, with resulting decreased selectivity.

Other uses of this reagent have also been described. Tosylhydrazones undergo oxidation to tosylazoalkenes, using PTT followed by treatment with base; this reaction fails with molecular bromine, dioxane dibromide, or *N*-bromosuccinimide in a range of solvents.[20] PTT has also been recommended for the aromatization of 2-substituted-6-benzoyl-4,5-dihydro-6*H*-pyrrolo[3,2-*e*]-benzothiazoles.[21]

Recently, other bromination reagents containing Br_3^- have been described: pyrrolidone hydrotribromide,[22] 2-carboxyethyltriphenylphosphonium perbromide,[23] and Amberlyst A 26-Br_3^-.[24]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

3,4-dihydro-1-(p-tolylsulfonyl)benz[c,d]indol-5(1H)-one

phenyltrimethylammonium tribromide (PTT)

PTT

pyridine hydrobromide perbromide

2-carboxyethyltriphenylphosphonium perbromide

Amberlyst A 26

Br_3^-

ethanol (64-17-5)

acetic acid (64-19-7)

Benzene (71-43-2)

diethyl ether (60-29-7)

HYDROBROMIC ACID (10035-10-6)

bromine (7726-95-6)

potassium iodide (7681-11-0)

sodium thiosulfate (7772-98-7)

dimethyl sulfate (77-78-1)

cyclohexane (110-82-7)

iodine (7553-56-2)

toluene (108-88-3)

N,N-dimethylaniline (121-69-7)

dichloromethane (75-09-2)

Tetrahydrofuran (109-99-9)

N-bromosuccinimide (128-08-5)

2-Acetyl-6-methoxynaphthalene (3900-45-6)

PHENYLTRIMETHYLAMMONIUM TRIBROMIDE (4207-56-1)

2-Bromoacetyl-6-methoxynaphthalene

2,2-Dibromoacetyl-6-methoxynaphthalene

Ethanone, 2-bromo-1-(6-methoxy-2-naphthalenyl)- (10262-65-4)

Phenyltrimethylammonium sulfomethylate

phenyltrimethylammonium bromide (16056-11-4)

2-acetyl-5-bromo-6-methoxynaphthalene

anisyl cyclohexyl ketone

5,7-dimethoxyflavanone (1036-72-2)

2-methyl-2-(2-benzyloxy-5-methoxyphenyl)cyclopentanone

4-oxo-4,5,6,7-tetrahydrobenzofuran (16806-93-2)

2-bromobenzo[6.7]bicyclo[3.2.1]oct-6-en-3-one

pyrrolidone hydrotribromide

Dioxane dibromide

Ethanone, 2,2-dibromo-1-(6-methoxy-2-naphthalenyl)- (52997-56-5)

1,5-cyclooctanedione

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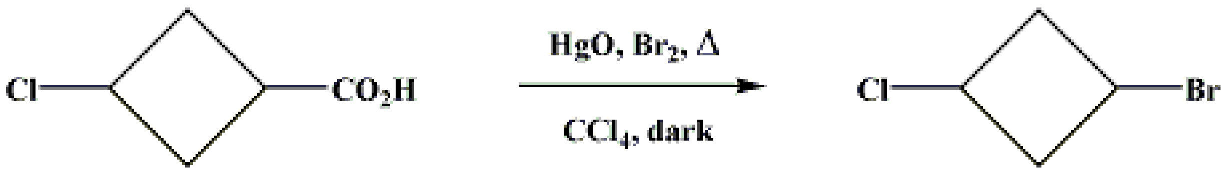
Organic Syntheses, CV 6, 179

MERCURY(II) OXIDE-MODIFIED HUNSDIECKER REACTION: 1-BROMO-3-CHLOROCYCLOBUTANE



Submitted by Gary M. Lampman and James C. Aumiller[1].
Checked by G. Nelson and K. B. Wiberg.

1. Procedure

In a 1-l., three-necked, round-bottomed flask, wrapped with aluminum foil to exclude light, and equipped with a mechanical stirrer, a reflux condenser, and an addition funnel, is suspended 37 g. (0.17 mole) of red mercury(II) oxide (Note 1) in 330 ml. of carbon tetrachloride (Note 2). To the flask is added 30.0 g. (0.227 mole) of 3-chlorocyclobutanecarboxylic acid (Note 3). With stirring, the mixture is heated to reflux before a solution of 40 g. (0.25 mole) of bromine in 180 ml. of carbon tetrachloride is added dropwise, but as fast as possible (4–7 minutes) without loss of bromine from the condenser (Note 4). After a short induction period, carbon dioxide is evolved at a rate of 150–200 bubbles per minute (Note 5). The solution is allowed to reflux for 25–30 minutes, until the rate of carbon dioxide evolution slows to about 5 bubbles per minute (Note 5). The mixture is cooled in an ice bath, and the precipitate is removed by filtration. The residue is washed with carbon tetrachloride, and the filtrates are combined. The solvent is removed by distillation using a modified Claisen distillation apparatus with a 6-cm. Vigreux column; vacuum distillation of the residual oil gives 13–17 g. (35–46%) of 1-bromo-3-chlorocyclobutane, b.p. 67–72° (45 mm.), n_D^{23} 1.5065 (Note 7) and (Note 8).

2. Notes

1. Purified product is available from J. T. Baker Chemical Company.
2. Reagent grade carbon tetrachloride was used.
3. 3-Chlorocyclobutanecarboxylic acid was prepared as described in *Org. Synth.*, **Coll. Vol. 6**, 271 (1988).
4. The heating bath should be maintained at about 120° to ensure that the solution continues to reflux while the bromine solution is added.
5. The gas evolution can be monitored by conducting the gas through rubber tubing from the condenser into a small amount of water where the bubbling can be observed. A small amount of bromine is lost because of entrainment by the gas.
6. There is no increase in yield on heating the mixture under reflux for 3 hours.

7. The submitters reported a 48–52% yield (18–20 g.) using the indicated scale, and a 35% yield when the reaction was carried out using twice the scale. The checkers obtained the product in 28–29% yield when the reaction was conducted on a scale 10 times that indicated.
8. The product was analyzed by GC at 130° on a Beckman GC-2 chromatograph equipped with a 180 cm. × 6 mm. column (Beckman 17449) containing 42/60 Johns-Manville C-22 firebrick coated with Dow-Corning 550 silicone oil. The retention times are 12 and 14 minutes for the *trans* and *cis* compounds, respectively.

3. Discussion

This procedure, a modified Hunsdiecker reaction based upon the method of Cristol and Firth,[2] results in moderate to high yields of bromides and iodides from aliphatic[2,3] and alicyclic carboxylic acids.[4,5,6] Carbon tetrachloride is most frequently used as the solvent, but others can be employed.[3,6] Attempts to prepare chlorides by the method have proved to be unsuccessful.[7]

The main advantage of this procedure over that of the standard method[8] is one of convenience. For example, the present method is a one-step reaction while the usual method is a two-step sequence involving an intermediate silver salt. In addition, the presence of water produced in the reaction apparently does not reduce the yield in the present method while water markedly reduces the yield in that involving the silver intermediate.

Some variations of the method have been used to prepare cyclopropyl and cyclobutyl halides. Simultaneous addition of bromine and 3-bromocyclobutanecarboxylic acid to the suspension of mercury(II) oxide gives 1,3-dibromocyclobutane in good yield.[7] Similarly, cyclopropanecarboxylic acid gives bromocyclopropane,[9] and 3-(bromomethyl)cyclobutanecarboxylic acid gives 1-bromo-3-(bromomethyl) cyclobutane.[10] In the latter reaction, it was found desirable to remove the water from the reaction as it is formed in order to obtain high yields. Another variation is the addition of a mixture of the acid and mercury (II) oxide to excess bromine in bromotrichloromethane.[6]

The conversion of 1-bromo-3-chlorocyclobutane to bicyclo[1.1.0]butane is described in *Organic Syntheses.*[11]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 126
- Org. Syn. Coll. Vol. 6, 133
- Org. Syn. Coll. Vol. 6, 271

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

bromine (7726-95-6)

carbon tetrachloride (56-23-5)

carbon dioxide (124-38-9)

mercury(II) oxide, mercury (II) oxide (21908-53-2)

Cyclopropanecarboxylic acid (1759-53-1)

Bromocyclopropane (4333-56-6)

1-Bromo-3-chlorocyclobutane (4935-03-9)

bromotrichloromethane (75-62-7)

Bicyclo[1.1.0]butane (157-33-5)

1-bromo-3-(bromomethyl)cyclobutane

3-Chlorocyclobutanecarboxylic acid (35207-71-7)

3-bromocyclobutanecarboxylic acid

1,3-dibromocyclobutane

3-(bromomethyl)cyclobutanecarboxylic acid

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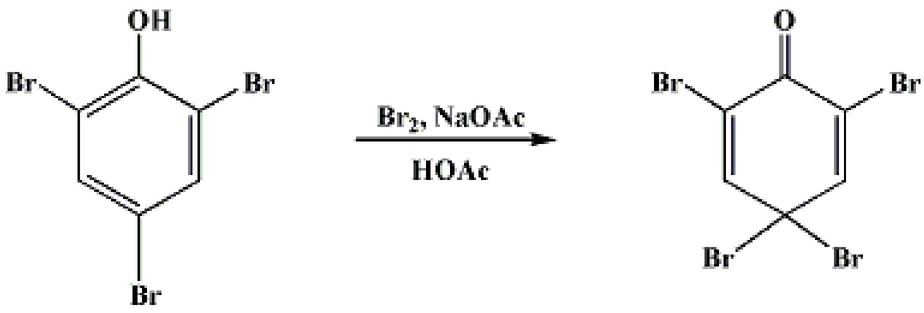
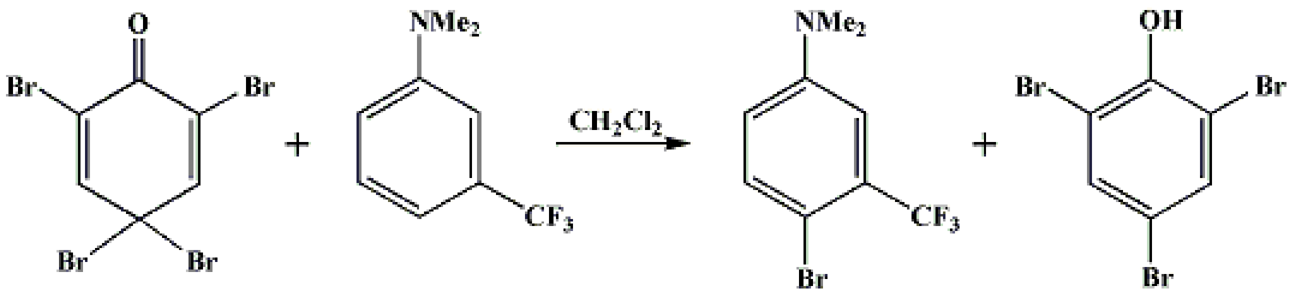
Organic Syntheses, CV 6, 181

para-BROMINATION OF AROMATIC AMINES: 4-BROMO-*N*, *N*-DIMETHYL-3-(TRIFLUOROMETHYL)ANILINE

[Benzenamine, 4-bromo-*N*,*N*-dimethyl-3-(trifluoromethyl)]





Submitted by G. J. Fox[1], G. Hallas[2], J. D. Hepworth[1], and K. N. Paskins[2].
Checked by J. D. Lock, Jr. and S. Masamune.

1. Procedure

Caution! The reaction should be conducted in a hood to avoid inhalation of bromine vapor.

A. 2,4,4,6-*Tetrabromo*-2,5-*cyclohexadien*-1-*one*. A mixture of 66.2 g. (0.200 mole) of 2,4,6-tribromophenol (Note 1), 27.2 g. (0.197 mole) of sodium acetate trihydrate, and 400 ml. of glacial acetic acid is placed in a 1-l. Erlenmeyer flask and warmed (*ca.* 70°) until a clear solution is obtained. The solution is magnetically stirred and cooled to room temperature to produce a finely divided suspension of the phenol, to which a solution of 32 g. (0.20 mole) of bromine in 200 ml. of glacial acetic acid is added dropwise over 1 hour (Note 2). The resulting mixture is kept at room temperature for 30 minutes, then poured onto 2 kg. of crushed ice. The yellow solid which separates is removed by suction filtration after the ice has melted, and the damp crystals are dissolved in the minimum of warm chloroform (Note 3). The upper aqueous layer is removed with a pipet fitted with a suction bulb. The dienone crystallizes from the chloroform solution upon cooling, yielding 50–55 g. (61–67%) of crystals, m.p. 125–130° (dec.), sufficiently pure for use in the next step (Note 4) and (Note 5).

B. 4-*Bromo*-N,N-*dimethyl*-3-(*trifluoromethyl*)*aniline*. A solution of 9.45 g. (0.0500 mole) of *N*,*N*-dimethyl-3-(trifluoromethyl)aniline (Note 6) in 200 ml. of dichloromethane is placed in a 500-ml. Erlenmeyer flask, cooled to −10°, and stirred magnetically as 20.5 g. (0.0500 mole) of finely powdered 2,4,4,6-tetrabromo-2,5-cyclohexadien-1-one is added in 0.5-g. portions. During this

addition the temperature of the mixture should be maintained between −10° and 0° (Note 7). The cooling bath is removed and the reaction mixture is allowed to warm to room temperature over a 30-minute period and extracted twice with 50 ml. of aqueous 2 *N* sodium hydroxide to remove 2,4,6-tribromophenol (Note 8). The organic layer is washed with 25 ml. of water and dried over anhydrous magnesium sulfate. Removal of the solvent yields 12–12.5 g. of crude 4-bromo-*N,N*-dimethyl-3-(trifluoromethyl)aniline. Distillation through an 8-cm. Vigreux column provides 11–12 g. (82–90%) of pure bromoamine, b.p. 134–136° (15 mm.), which solidifies, giving colorless crystals, m.p. 29–30° (Note 9) and (Note 10).

2. Notes

1. The submitters used reagent grade 2,4,6-tribromophenol. The checkers recrystallized the practical grade reagent purchased from Fisher Scientific Company. The solvent used was Skelly B, and the melting point of the phenol, after recrystallization, was 93–95°.
2. It is essential to maintain the temperature of the solution below 25° during the addition of the bromine solution. If external cooling is applied, initially with an ice-water bath, the addition can be completed within 20 minutes.
3. Some decomposition of the dienone is observed if the chloroform solution is vigorously refluxed for any length of time; bromine is evolved and there is a reduction in yield. Approximately 400 ml. of chloroform is needed to dissolve the dienone at approximately 60°. The checkers used 450 ml of the solvent.
4. The submitters used 0.5-molar quantities with no reduction in yield.
5. ^{1}H NMR (dioxane-d_8), δ (multiplicity): 7.98 (singlet).
6. The amine was prepared according to the procedure described in *Org. Synth.*, **Coll. Vol. 5**, 1085 (1973).
7. The reaction proceeds satisfactorily over a range between −30° and +20°. At lower temperatures, the reaction proceeds rather slowly.
8. 2,4,6-Tribromophenol may be recovered by acidification of the aqueous alkaline extracts and reused in the preparation of the tetrabromo-compound after crystallization from petroleum ether (b.p. 80–100°).
9. The product can be crystallized from petroleum ether (b.p. 30–40°).
10. ^{1}H NMR ($CDCl_3$), δ (multiplicity, number of protons, assignment): 2.94 (s, 6H, $2CH_3$), 6.7 (approximate d of d, 1H), 7.0 (approximate d, 1H), 7.5 (approximate d, 1H).

3. Discussion

4-Bromo-*N,N*-dimethyl-3-(trifluoromethyl)aniline has been prepared by the methylation of 4-bromo-3-(trifluoromethyl)aniline with trimethyl phosphate in 70–80% yield.[3] The present method, which effectively uses 3-(trifluoromethyl)aniline as starting material, offers advantages in cost, yield, and ease of purification.

Aromatic amines are usually polybrominated on treatment with bromine. Several mild brominating agents have been introduced in attempts to achieve partial bromination without the necessity of protecting and deprotecting the amino group, but these give variable results when applied to a large variety of amines. Dioxane dibromide[4] monobrominates tertiary aromatic amines, but gives poor yields with primary and secondary aryl amines. The use of *N*-bromosuccinimide[5,6] (1-bromo-2,5-pyrrolidinedione) leads to monobrominated compounds frequently contaminated with decomposition products.

The dienone, which is prepared essentially as described by Benedikt[7] and Caló,[8] monobrominates a

wide range of primary, secondary, and tertiary aromatic amines almost exclusively in the *para*-position. The procedure described is of general synthetic utility for the preparation of *para*-brominated aromatic and heteroaromatic amines in high yields and frequently in a high state of purity. The submitters have used this technique to *para*-brominate many compounds in quantities ranging from 0.01–0.1 mole, including the following (yields after one crystallization): aniline (92), *N*-methylaniline (94), *N*,*N*-dimethylaniline (91), *N*,*N*-diethylaniline (94), *o*-toluidine (88), *N*,2-dimethylaniline (91), *N*,*N*,2-trimethylaniline (90), *m*-toluidine (90), *N*,*N*,3-trimethylaniline (86), 2,3-dimethylaniline (91), 2,5-dimethylaniline (91), 3,5-dimethylaniline (81), 2-chloroaniline (86), 3-chloroaniline (86), 2-bromoaniline (78), 3-bromoaniline (82), 2-nitroaniline (91), 3-nitroaniline (85), *m*-phenylenediamine (82), *o*-anisidine (85), 3-methoxyaniline (58, 4-bromo; 30, 6-bromo), diphenylamine (90), 1-aminonaphthalene (86), 1-dimethylaminonaphthalene (84), 2-(trifluoromethyl)aniline (85), 2-aminopyridine (75), 2-dimethylaminopyridine (70), 3-dimethylaminopyridine (60),[9] 2-amino-6-methylpyridine (76). Where solubility of the amine in dichloromethane is low, chloroform may be used as solvent. For example, 2-aminopyrimidine gave 2-amino-5-bromopyrimidine (82%) in this manner, compared with 41% when the amine is brominated conventionally in aqueous solution.[10] In the case of anthranilic acid, 2-amino-5-bromobenzoic acid (82%) precipitated from the chloroform reaction medium. In addition to its use with amines, the dienone reagent monobrominates a variety of phenols,[11] and behaves as an oxidizing agent toward sulfides, converting them to sulfoxides.[12]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

acetic acid (64-19-7)

aniline (62-53-3)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

bromine (7726-95-6)

N,N-dimethylaniline (121-69-7)

Anthranilic Acid (118-92-3)

dichloromethane (75-09-2)

2-aminopyridine (504-29-0)

1-aminonaphthalene (134-32-7)

diphenylamine (122-39-4)

magnesium sulfate (7487-88-9)

2,4,6-tribromophenol (118-79-6)

N,N-diethylaniline (91-66-7)

N-Methylaniline (100-61-8)

N-bromosuccinimide, 1-bromo-2,5-pyrrolidinedione (128-08-5)

sodium acetate trihydrate (6131-90-4)

2-aminopyrimidine (109-12-6)

2-Nitroaniline (88-74-4)

2-(trifluoromethyl)aniline (88-17-5)

3-Chloroaniline (108-42-9)

o-toluidine (95-53-4)

m-toluidine (108-44-1)

trimethyl phosphate (512-56-1)

2,4,4,6-Tetrabromo-2,5-cyclohexadien-1-one (20244-61-5)

4-bromo-3-(trifluoromethyl)aniline (393-36-2)

3-(trifluoromethyl)aniline (98-16-8)

Dioxane dibromide

2,3-dimethylaniline (87-59-2)

2,5-dimethylaniline (95-78-3)

3,5-dimethylaniline (108-69-0)

2-chloroaniline (95-51-2)

2-bromoaniline (615-36-1)

3-bromoaniline (591-19-5)

3-nitroaniline (99-09-2)

3-methoxyaniline (536-90-3)

1-dimethylaminonaphthalene (86-56-6)

2-dimethylaminopyridine (5683-33-0)

3-dimethylaminopyridine

2-amino-6-methylpyridine (1824-81-3)

2-amino-5-bromopyrimidine (7752-82-1)

o-anisidine (90-04-0)

N,N-dimethyl-3-(trifluoromethyl)aniline (329-00-0)

4-Bromo-N,N-dimethyl-3-(trifluoromethyl)aniline, Benzenamine, 4-bromo-N,N-dimethyl-3-(trifluoromethyl) (51332-24-2)

N,2-dimethylaniline (611-21-2)

N,N,2-trimethylaniline (609-72-3)

N,N,3-trimethylaniline (121-72-2)

m-phenylenediamine (108-45-2)

2-amino-5-bromobenzoic acid (5794-88-7)

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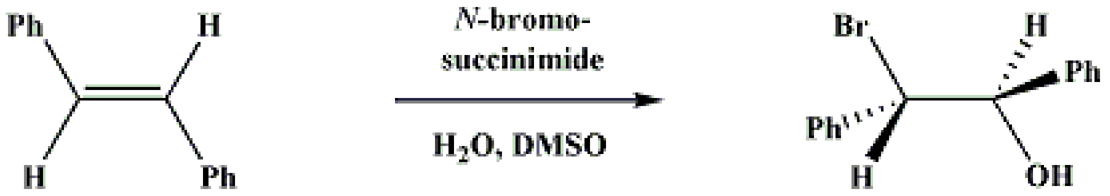
BROMOHYDRINS FROM ALKENES AND *N*-BROMOSUCCINIMIDE IN DIMETHYL SULFOXIDE: *erythro*-2-BROMO-1,2-DIPHENYLETHANOL

[Ethanol, 2-bromo-1,2-diphenyl-, *erythro*-]



Submitted by A. W. Langman and D. R. Dalton[1].
Checked by I. David Reingold and S. Masamune.

1. Procedure

A 500-ml., round-bottomed flask equipped with a magnetic stirring bar and a thermometer is charged with 18.0 g. (0.100 mole) of (*E*)-stilbene (Note 1), 5.0 ml. (0.28 mole) of water, and 300 ml. (4.23 moles) of dimethyl sulfoxide (Note 2). The resulting suspension is stirred for 5 minutes at room temperature (20–25°) (Note 3). Stirring is continued as 35.6 g. (0.200 mole) of *N*-bromosuccinimide (Note 4) is added in small portions over *ca.* 10 minutes. A yellow color appears when the first portion of *N*-bromosuccinimide is added, and by the time the addition is complete, the solution is bright orange. During the addition the temperature of the mixture rises to 50–55°, and all the (*E*)-stilbene dissolves. The contents of the flask are stirred for another 15 minutes and poured into 1 l. of ice water; the product separates immediately as a white solid (Note 5). The aqueous slurry is transferred to a separatory funnel with the aid of 50-ml. portions of water and diethyl ether, and extracted with four 200-ml. portions of ether. The combined ethereal extracts are washed with 250 ml. of water and 250 ml. of sodium chloride solution, dried over anhydrous magnesium sulfate, and evaporated with a rotary evaporator at a water bath temperature of *ca.* 30°. The pale yellow, crystalline residue is dissolved, to the extent possible, in 600 ml. of hot hexane, and the resulting suspension is filtered while hot, removing a small amount of an insoluble impurity. Cooling the filtrate provides colorless fibers of analytically pure *erythro*-2-bromo-1,2-diphenylethanol, m.p. 83–84° (Note 6); a second crop of crystals is obtained by concentrating the mother liquor to 200 ml. (Note 7). The combined yield is 22.0–24.9 g. (80–90%) (Note 8).

2. Notes

1. (*E*)-Stilbene, m.p. 123–126°, was purchased from Aldrich Chemical Company, Inc., and used as received. It is also available from J. T. Baker

Chemical Company and from Eastman Organic Chemicals.
2. Reagent grade dimethyl sulfoxide was used without purification. The amount of dimethyl sulfoxide can be varied. A large excess is employed in this case to facilitate dissolution of the stilbene.
3. The suspension may be warmed to dissolve the alkene more rapidly; (*E*)-stilbene dissolves completely at *ca.* 65°. If the suspension is warmed, it *must* be cooled below 30° before proceeding further to prevent a vigorous reaction when the *N*-bromosuccinimide is added. The submitters recommend that the warm suspension be cooled under an atmosphere of nitrogen. If a volatile alkene is used, the mixture should be cooled prior to and during the addition of *N*-bromosuccinimide to prevent losses by evaporation.
4. *N*-Bromosuccinimide purchased from Arapahoe Chemical Company was used without purification. If the purity of the *N*-bromosuccinimide is in doubt, it should be titrated before use by the standard iodide–thiosulfate method and purified, if necessary, by recrystallization from 10 times its weight of water.[2] Solutions of *N*-bromosuccinimide in dimethyl sulfoxide cannot be stored, since the solvent is oxidized by the brominating reagent.
5. The product does not appear to deteriorate if allowed to stand at this point.
6. The submitters recrystallized the product from 600 ml. of petroleum ether (b.p. 30–60°) and reported a melting point of 84–84.5° (lit., m.p. 84.5–85.5°[3] and 86°[4]).
7. The submitters found that the residue (2.8 g.) obtained upon evaporation of the mother liquor was largely *erythro*-2-bromo-1,2-diphenylethanol contaminated with a small amount of succinimide. Absorptions for the *threo* isomer could not be detected in the IR and ^{1}H NMR spectra of this material.
8. The product obtained by the checkers was analyzed. Analysis calculated for $C_{14}H_{13}BrO$: C, 60.67; H, 4.73. Found: C, 60.74; H, 4.77. The spectral properties of the product are as follows: IR (CCl_4) cm.$^{-1}$: 3610, 1500, 1460, 700; ^{1}H NMR ($CDCl_3$), δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 5.06 and 5.16 (AB doublet, *J* = 6.5, 2H, C*H*BrC*H*OH), 7.35 (m, 10H, aryl *H*).

3. Discussion

The present procedure affords a simple, general method for preparing bromohydrins from alkenes and avoids the heterogeneous solvent systems often used in such reactions. Labeling experiments have demonstrated that the oxygen from the dimethyl sulfoxide appears in the hydroxyl group of the bromohydrin;[5] therefore, the role of the water is to hydrolyze the intermediate β-bromodimethylsulfoxonium ion.

Many alkenes have been converted into their respective bromohydrins by this procedure, usually with high regio- and stereoselectivity (Table I).[5,6] Although the regioselectivity of the addition generally follows Markovnikov's rule, the opposite orientation is observed with alkenes bearing the bulky *tert*-butyl substituent (entries 7–

9). The reaction of conjugated dienes with *N*-bromosuccinimide in aqueous dimethyl sulfoxide also occurs in a regio- and stereoselective manner, leading exclusively to vicinal bromohydrins in high yield.[7]

TABLE I BROMOHYDRINS FROM ALKENES WITH *N*-BROMOSUCCINIMIDE IN AQUEOUS DIMETHYL SULFOXIDE

Entry	Alkene	Bromohydrin	Yield (%)[a]
1	(*Z*)-$C_6H_5CH{=}CHC_6H_5$	*threo*-$C_6H_5CH(OH)CH(Br)C_6H_5$	82
2	(*E*)-$C_6H_5CH{=}CHCH_3$	*erythro*-$C_6H_5CH(OH)CH(Br)CH_3$	92
3	(*Z*)-$C_6H_5CH{=}CHCH_3$	*threo*-$C_6H_5CH(OH)CH(Br)CH_3$	95
4	$C_6H_5CH{=}CH_2$	$C_6H_5CH(OH)CH_2Br$	76
5	C_6H_5-$C(CH_3){=}CH_2$	$C_6H_5C(CH_3)(OH)CH_2Br$	89
6	$C_6H_5CH_2CH{=}CH_2$	$C_6H_5CH_2CH(OH)CH_2Br$	83
7	(*E*)-$(CH_3)_3CCH{=}CHCH_3$	*erythro*-$(CH_3)_3CCH(Br)CH(OH)CH_3$	90
8	(*Z*)-$(CH_3)_3CCH{=}CHCH_3$	*threo*-$(CH_3)_3CCH(Br)CH(OH)CH_3$	90
9	$(CH_3)_3CCH{=}CH_2$	$(CH_3)_3CCH(Br)CH_2OH$	89
10	$(CH_3)_3CC(CH_3){=}CH_2$	$(CH_3)_3CC(CH_3)(OH)CH_2Br$	60[b]

[a]Average yield from two or more runs.

[b]Accompanied by 24% dibromide.

When electron-withdrawing groups are attached to the double bond, the reaction is strongly inhibited and may fail completely. In such cases, the bromide anion, produced by the reaction of dimethyl sulfoxide with *N*-bromosuccinimide, competes with the dimethyl sulfoxide for the bromonium (or bromo carbonium) ion intermediate. Thus, dibromide may accompany recovered alkene or any bromohydrin formed. Similarly, exogenous anions often compete with dimethyl sulfoxide for the cation.[6]

erythro-2-Bromo-1,2-diphenylethanol has been prepared by reaction of (*E*)-stilbene with *N*-bromoacetamide in buffered aqueous acetone,[3] by addition of hydrogen bromide to (*E*)-stilbene oxide,[4] and by reaction of (*E*)-stilbene with bromotrinitromethane in dimethyl sulfoxide followed by hydrolysis.[8]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

erythro-2-Bromo-1,2-diphenylethanol

Ethanol, 2-bromo-1,2-diphenyl-, erythro-

(Z)-$C_6H_5CH{=}CHC_6H_5$

threo-$C_6H_5CH(OH)CH(Br)C_6H_5$

(E)-$C_6H_5CH{=}CHCH_3$

erythro-$C_6H_5CH(OH)CH(Br)CH_3$

(Z)-$C_6H_5CH{=}CHCH_3$

threo-$C_6H_5CH(OH)CH(Br)CH_3$

$C_6H_5CH{=}CH_2$

$C_6H_5CH(OH)CH_2Br$

$C_6H_5\text{-}C(CH_3){=}CH_2$

$C_6H_5C(CH_3)(OH)CH_2Br$

$C_6H_5CH_2CH{=}CH_2$

$C_6H_5CH_2CH(OH)CH_2Br$

(E)-$(CH_3)_3CCH{=}CHCH_3$

erythro-$(CH_3)_3CCH(Br)CH(OH)CH_3$

(Z)-$(CH_3)_3CCH{=}CHCH_3$

threo-$(CH_3)_3CCH(Br)CH(OH)CH_3$

$(CH_3)_3CCH{=}CH_2$

$(CH_3)_3CCH(Br)CH_2OH$

$(CH_3)_3CC(CH_3)=CH_2$

$(CH_3)_3CC(CH_3)(OH)CH_2Br$

ether, diethyl ether (60-29-7)

sodium chloride (7647-14-5)

hydrogen bromide (10035-10-6)

oxygen (7782-44-7)

nitrogen (7727-37-9)

acetone (67-64-1)

magnesium sulfate (7487-88-9)

N-bromosuccinimide (128-08-5)

hexane (110-54-3)

N-Bromoacetamide (79-15-2)

dimethyl sulfoxide (67-68-5)

bromotrinitromethane (560-95-2)

(E)-stilbene (103-30-0)

(E)-stilbene oxide

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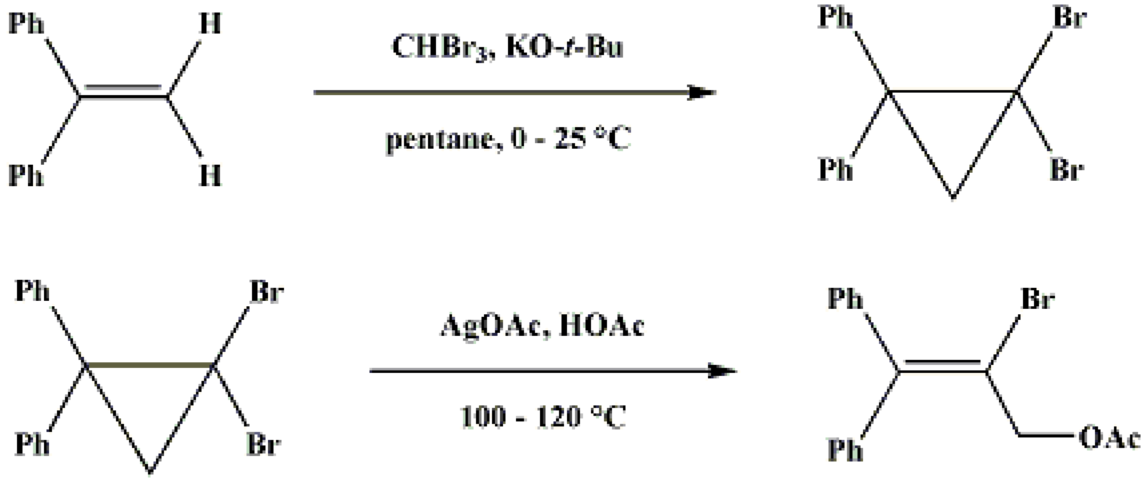
Organic Syntheses, CV 6, 187

CHAIN ELONGATION OF ALKENES *via gem-* DIHALOCYCLOPROPANES: 2-BROMO-3,3-DIPHENYL-2-PROPEN-1-YL ACETATE

[2-Propen-1-ol, 2-bromo-3,3-diphenyl-, acetate]



Submitted by Stanely R. Sandler[1]
Checked by D. W. Brooks and S. Masamune.

1. Procedure

A. *1,1-Dibromo-2,2-diphenylcyclopropane*. A 500-ml., three-necked, round-bottomed flask equipped with a mechanical stirrer, a dropping funnel, and a condenser fitted with a drying tube is flushed with dry nitrogen, then charged with 25.0 g. (0.139 mole) of 1,1-diphenylethylene (Note 1), 100 ml. of pentane, and 28 g. (0.25 mole) of potassium *tert*-butoxide (Note 2). The mixture is stirred and cooled to 0° before 66.0 g. (0.261 mole) of bromoform (Note 3) is added dropwise over 30–45 minutes. Stirring is continued for an additional 2–3 hours at room temperature, and 200 ml. of water is added. The yellowish insoluble product is filtered, dried, and digested with 300 ml. of refluxing 2-propanol for 30 minutes. After cooling, the product is filtered and washed with 100 ml. of 2-propanol, yielding 31–38 g. (63–78%) of colorless crystals, m.p. 151–152°.

B. *2-Bromo-3,3-diphenyl-2-propen-1-yl acetate*. A 250-ml. flask equipped with a condenser is charged with 17.6 g. (0.0500 mole) of 1,1-dibromo-2,2-diphenylcyclopropane, 12.5 g. (0.0748 mole) of silver acetate (Note 4), and 50 ml. of glacial acetic acid, then immersed in an oil bath at 100–120° for 24 hours (Note 5). After cooling, the mixture is diluted with 200 ml. of diethyl ether and filtered. The ethereal filtrate is washed with two 100-ml. portions of water, two 100-ml. portions of aqueous saturated sodium carbonate, and finally with two 100-ml. portions of water.

After drying over anhydrous sodium sulfate, the ether is removed on a rotary evaporator. Distillation of the resulting residue under reduced pressure yields 12.0 g. (72%) of the product, b.p. 142–145° (0.15 mm.), n_D^{22} 1.6020–1.6023 (Note 6).

2. Notes

1. 1,1-Diphenylethylene was purchased from Eastman Organic Chemicals.
2. Potassium *tert*-butoxide was supplied by Mine Safety Appliances (MSA) Research Corporation. See end of Discussion section below.
3. Bromoform was supplied by the Dow Chemical Company and used without further purification.
4. The silver acetate can be replaced by a mixture of sodium acetate and silver nitrate.
5. A 24-hour period may not be required but was found to be convenient.
6. UV (CH_3OH) nm. max. (log ε): 260 (3.94); ^1H NMR ($CDCl_3$), δ (multiplicity, number of protons): 2.08 (s, 3H), 4.87 (s, 2H), 7.3 (m, 10H).

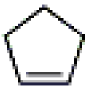
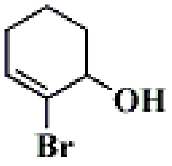
3. Discussion

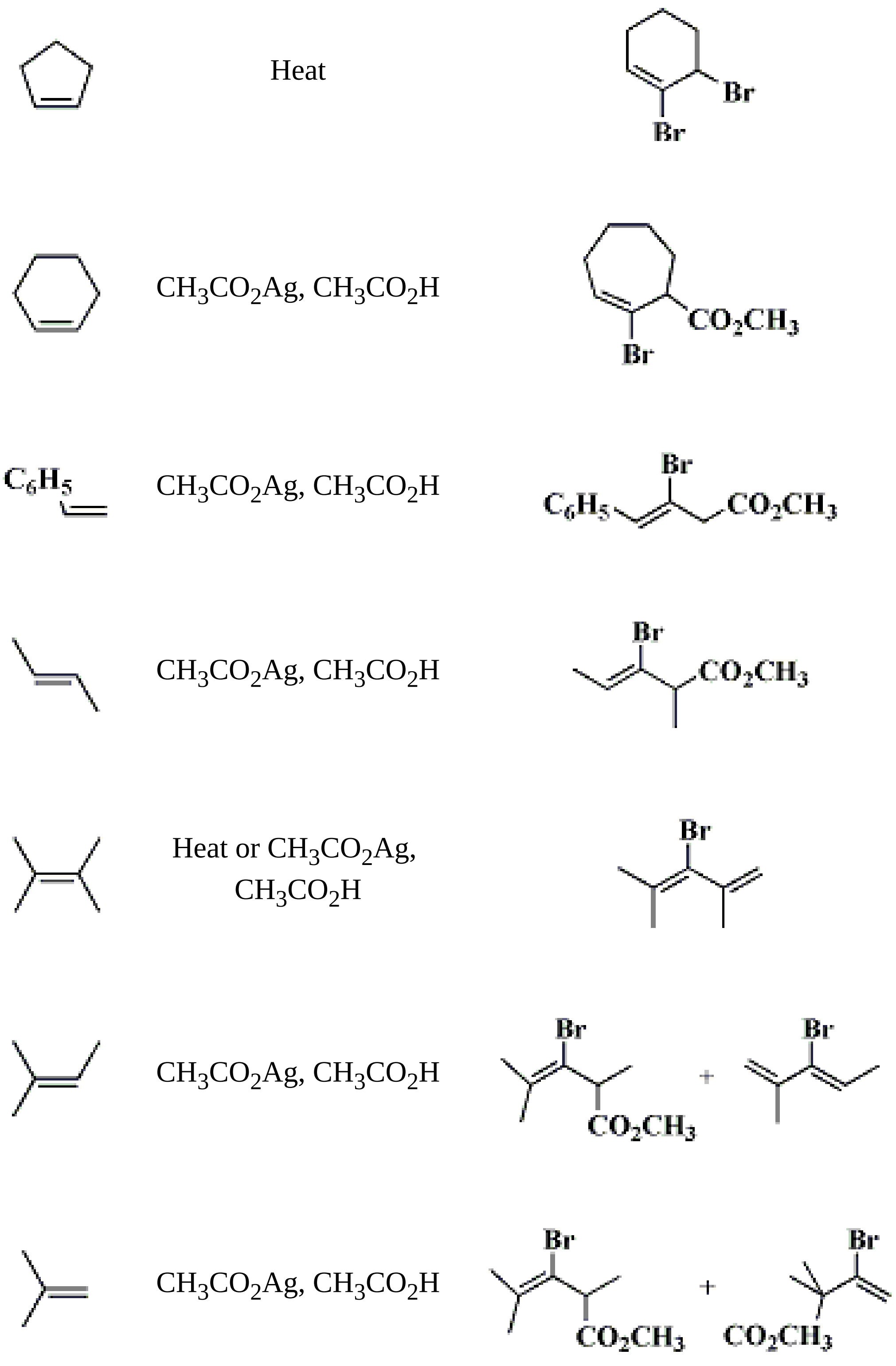
The present procedure is that of the submitter[2] and illustrates a general method for the chain extension of alkenes *via gem*-dihalocyclopropanes, earlier described by Skell and Sandler.[3] The reaction of dihalocyclopropanes with electrophilic reagents yields haloallylic derivatives,[2] the thermal reaction yields haloallylic halides or halodienes, and the reaction with magnesium, sodium, or lithium alkyl reagents yields allenes.[2] These reactions are summarized in f.htmigure 1, and examples are given in Table I.

Figure 1.

Figure 1.

TABLE I
CHAIN ELONGATION OF ALKENES *via gem*-DIBROMOCYCLOPROPANES

Alkene	Conditions for Dibromocyclopropane Opening	Product
	$AgNO_3$, H_2O	



This general method has been used by Parham and co-workers[4] to transform indenes into β-halonaphthalenes. The method is also useful for the conversion of pyrroles to β-substituted pyridines and of indoles to β-haloquinolines.[3] More recently, phase transfer agents have been used to aid the preparation of *gem*-dihalocyclopropanes by the reaction of olefins with haloforms, using aqueous sodium hydroxide.[5,6,7]

References and Notes

1. Borden, Inc., Chemical Division, Central Research Laboratory, Philadelphia, Pennsylvania 19124 [Present address: Pennwalt Corp., King of Prussia, Pennsylvania 19406].
2. S. R. Sandler, *J. Org. Chem.*, **32**, 3876 (1967) and references cited therein.
3. P. S. Skell and S. R. Sandler, *J. Am. Chem. Soc.*, **80**, 2024 (1958).
4. W. E. Parham and H. E. Reiff, *J. Am. Chem. Soc.*, **77**, 1177 (1955) and subsequent papers on the reaction of indenes with dihalocarbenes to yield β-halonaphthalenes.
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

H_2O

acetic acid (64-19-7)

ether, diethyl ether (60-29-7)

sodium acetate (127-09-3)

sodium hydroxide (1310-73-2)

silver nitrate (7761-88-8)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

2-propanol (67-63-0)

1,1-Diphenylethylene (530-48-3)

Pentane (109-66-0)

bromoform (75-25-2)

silver acetate (563-63-3)

2-BROMO-3,3-DIPHENYL-2-PROPEN-1-YL ACETATE, 2-Propen-1-ol, 2-bromo-3,3-diphenyl-, acetate (14310-15-7)

1,1-Dibromo-2,2-diphenylcyclopropane (17343-74-7)

potassium tert-butoxide (865-47-4)

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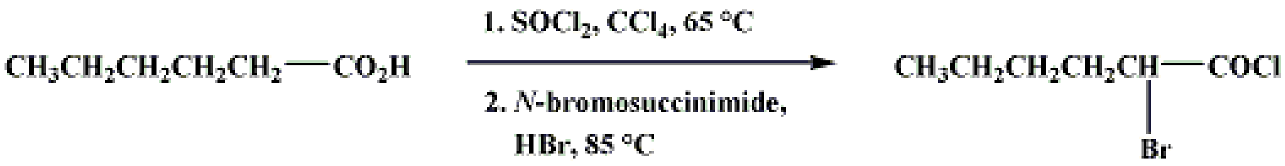
2-BROMOHEXANOYL CHLORIDE



Submitted by David N. Harpp, L. Q. Bao, Christopher Coyle, John G. Gleason, and Sharon Horovitch[1].
Checked by James E. Kleckner and Robert E. Ireland.

1. Procedure

Caution! This reaction should be conducted in a good hood since hydrogen chloride and bromine vapors are evolved.

A 200-ml., round-bottomed flask equipped with a magnetic stirring bar is charged with 11.6 g. (0.100 mole) of hexanoic acid (Note 1) and 10 ml. of carbon tetrachloride. After 46.9 g. (28.8 ml., 0.394 mole) of thionyl chloride (Note 2) is added to the solution, an efficient reflux condenser with an attached drying tube is fitted to the flask. The solution is stirred and heated with an oil bath at 65° for 30 minutes (Note 3). The flask is removed from the oil bath and cooled to room temperature. To the reaction mixture are added successively 21.4 g. (0.120 mole) of finely powdered *N*-bromosuccinimide (Note 4), 50 ml. of carbon tetrachloride, and 7 drops of 48% hydrogen bromide (Note 5). The flask is heated at 70° for 10 minutes (Note 6), before the temperature of the bath is increased to 85°, until the color of the reaction becomes light yellow (*ca.* 1.5 hours; (Note 7). The reaction mixture is cooled to room temperature, and the carbon tetrachloride and excess thionyl chloride are removed under reduced pressure (Note 8). The residue is suction filtered, the solid (Note 9) is washed several times with carbon tetrachloride (total 20 ml.) and the combined filtrate collected in a 50-ml. flask. The solvent is removed from the solution as before, and the residue is distilled into a dry ice-cooled receiver (short-path column), giving, after a small forerun, 16.1–17.1 g. (76–80%) of 2-bromohexanoyl chloride, b.p. 44–47° (1.5 mm.) as a clear, slightly yellow oil, n_D^{22} 1.4707. This material is of sufficient purity for most synthetic purposes (Note 10).

The yellow product (Note 11) is decolorized by dissolving it in an equal volume of carbon tetrachloride (*ca.* 12 ml.) and vigorously shaking the solution thus obtained with 1.5 ml. of freshly prepared aqueous 35% sodium thiosulfate. The two layers are completely separated after 5 minutes. The colorless bottom layer is drawn off into a 50-ml. Erlenmeyer flask. The top layer is extracted three times with 1.5 ml. of carbon tetrachloride. The combined carbon tetrachloride extracts are dried over 0.5 g. (Note 12) of anhydrous magnesium sulfate for 30 minutes. The solution is filtered into a 50-ml. anhydrous magnesium sulfate for 30 minutes. The solution is filtered into a 50-ml. distilling flask, and the magnesium sulfate is washed several times with carbon tetrachloride (total 5 ml.). The solvent is removed, and the colorless product is distilled as described above, affording 14.7–15.8 g. (69–74% overall, based on hexanoic acid; 88–92% for the decolorization step) of colorless 2-bromohexanoyl chloride, b.p. 45–47° (1.5 mm.), n_D^{22} 1.4706 (Note 13), d_4^{24} 1.4017 (Note 14) and (Note 15).

2. Notes

1. Practical grade hexanoic acid is obtainable from Matheson, Coleman and Bell. The submitters report slightly higher yields using purified grade hexanoic acid obtained from Fisher Scientific Company.
2. Thionyl chloride was obtained from Anachemia Chemicals Ltd., Fisher Scientific Company (reagent grade), or Matheson, Coleman and Bell. The first two were slightly yellow, and the latter was colorless; however, the yields of final product were identical with each brand. The excess thionyl chloride serves as a drying agent for the hexanoic acid and as a solvent for the *N*-bromosuccinimide, which is not very soluble in carbon tetrachloride.
3. ^{1}H NMR analysis indicates complete conversion to the acid chloride. This may be monitored by following the disappearance of the triplet (CH_2CO_2H) at δ 2.40 and the emergence of a new triplet (CH_2COCl) at δ 2.87.
4. *N*-Bromosuccinimide was obtained from Matheson, Coleman and Bell or Aldrich Chemical Company, Inc. Product yields were optimized using 20% excess, although only 5–10% yield reductions were noted using 5% excess reagent. Recrystallizing the reagent prior to use had no noticeable effect on the overall yield of product.
5. Aqueous 48% hydrogen bromide was obtained from Baker and Adamson. Without added hydrogen bromide, the reaction was much slower.
6. If the reaction was heated too rapidly to 85°, vigorous foaming resulted.
7. Initially the reaction mixture is dark red, and there is bromine vapor in the condenser. Toward the end of the reaction the color lightens considerably and after a short period (*ca.* 15 minutes) begins to darken again. The heat should be removed when this darkening commences. On standing, the yellow solution may also turn black, but the yield of the product is not noticeably affected. When the stirring is stopped, succinimide floats to the top of the solution. The reaction may be conveniently monitored by following the disappearance of the triplet (CH_2COCl) at δ 2.87 and appearance of a triplet ($CHBrCOCl$) at δ 4.54 in the ^{1}H NMR spectrum.
8. The evaporation of solvents under reduced pressure should be performed carefully with vigorous stirring at room temperature. An oil pump protected with a dry ice trap and equipped with a manometer is used. Initially the pressure should be adjusted to prevent excessive foaming; it is reduced progressively to approximately 5 mm.
9. About 10 g. of the solid (succinimide) is collected.
10. The IR and ^{1}H NMR spectra are identical with those of colorless, doubly distilled material; n_D^{22} 1.4706.
11. When the decolorization procedure was carried out before the first distillation, inconsistent yields were obtained. About 2.5 ml. of a dark viscous liquid (giving a violet solution on dilution in carbon tetrachloride) remained in the distillation flask.
12. When more drying agent was employed, the product yield was lower.
13. A central fraction had n_D^{22} 1.4704.
14. Analysis calculated for $C_6H_{10}BrClO$: C, 33.75; H, 4.72; Br, 37.42; Cl, 16.60. Found: C, 33.42; H, 4.77; Br, 37.29; Cl, 16.74. IR (NaCl) $cm.^{-1}$: 2955, 2925, 1785, 1470; ^{1}H NMR δ (multiplicity, number of protons): 0.94 (m, 3H), 1.43 (m, 4H), 2.10 (m, 2H), 4.54 (t, 1H), mass spectrum *m/e*: 179, 177 (M–Cl).
15. The corresponding α-bromo acid is prepared by the following procedure. A 500-ml., round-bottomed flask is charged with 10.28 g. (0.04826 mole) of 2-bromohexanoyl chloride and 92 ml. of acetone. The flask is fitted with a magnetic stirring bar, a thermometer, and a 200-ml. dropping funnel in which is placed 115 ml. of aqueous

saturated sodium hydrogen carbonate (*ca*. 0.115 mole). The flask is cooled to approximately 10°, while the base is added over a period of about 45 minutes. The mixture is acidified with concentrated hydrochloric acid. An organic layer forms at the top and is separated from the aqueous layer, which is extracted with three 30-ml. portions of chloroform. The combined organic extracts are dried over anhydrous magnesium sulfate and the solvent is removed under reduced pressure, giving 9.36 g. of crude 2-bromohexanoic acid as a colorless liquid. This product is 96% pure by GC analysis, using a Hewlett-Packard 5750 Research Chromatograph with a 1.8 m. 4% SE-30 column at 130°, and having a flow rate of 60 ml./minute. This product can be distilled through a short-path column, yielding, after an 11% forerun, 7.76 g. (83%) of 2-bromohexanoic acid, b.p. 64–66° (0.075 mm.), which shows one peak by GC analysis (as above). IR and ^{1}H NMR spectra are consistent with the structure.

3. Discussion

The α-bromination of acids (*via* the acid chloride) has been achieved by the Hell–Volhard–Zelinsky reaction or its variances,[2] however, this technique can involve reaction times of up to 2–3 days,[3] high reaction temperatures (>100°), copious evolution of hydrogen bromide, and variable yields. A recent procedure,[4] while affording good overall yields, involves several steps to achieve the transformation (alkylation, proton abstraction, bromination, deacylation and deësterification).

The submitters have found the *N*-bromosuccinimide procedure to be a very general reaction. Alkyl, alicyclic, aryl, and heterocyclic acetic acids have been brominated in 50–80% yield.[5] The reaction may be applied in the presence of labile benzylic hydrogens; for example, 3-phenylpropanoic acid gives exclusively 2-bromo-3-phenylpropanoyl chloride.[6] The procedure has several significant advantages; it is considerably faster than the known methods (overall reaction times of 2 hours are common),[7] the use of bromine is circumvented, and work-up is simplified considerably.

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrogen chloride, hydrochloric acid (7647-01-0)

thionyl chloride (7719-09-7)

chloroform (67-66-3)

sodium hydrogen carbonate (144-55-8)

hydrogen bromide (10035-10-6)

bromine (7726-95-6)

carbon tetrachloride (56-23-5)

sodium thiosulfate (7772-98-7)

2-Bromohexanoic acid (616-05-7)

acetone (67-64-1)

hexanoic acid (142-62-1)

3-phenylpropanoic acid (501-52-0)

Succinimide (123-56-8)

magnesium sulfate (7487-88-9)

N-bromosuccinimide (128-08-5)

2-Bromohexanoyl chloride (42768-46-7)

2-bromo-3-phenylpropanoyl chloride

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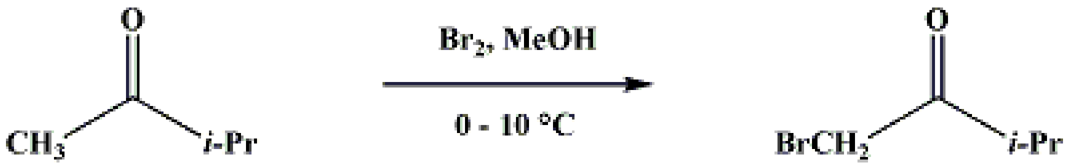
1-BROMO-3-METHYL-2-BUTANONE



Submitted by M. Gaudry and A. Marquet[1].
Checked by Diana Metzger and Richard E. Benson.

1. Procedure

Caution! This preparation must be carried out in an efficient hood. Bromomethyl ketones are highly lachrymatory and are skin irritants.

A 2-l., four-necked, round-bottomed flask equipped with a sealed mechanical stirrer, a thermometer, a reflux condenser fitted with a calcium chloride drying tube, and a 100-ml., pressure-equalizing dropping funnel is charged with 86.0 g. (105 ml., 1.00 mole) of 3-methyl-2-butanone (Note 1) and 600 ml. of anhydrous methanol (Note 2). The solution is stirred and cooled in an ice–salt bath to 0–5°, and 160 g. (54.6 ml., 1.00 mole) of bromine (Note 3) is added in a rapid, steady stream from the dropping funnel (Note 4). During this time, the temperature is allowed to rise but not permitted to exceed 10°. The reaction temperature is maintained at 10° during the remaining reaction time (Note 5). The red color of the solution fades gradually in about 45 minutes (Note 6), 300 ml. of water is then added (Note 7), and the mixture is stirred at room temperature overnight (Note 8).

To the solution is added 900 ml. of water, and the resulting mixture is washed with four 500-ml. portions of diethyl ether. The ether layers are combined, washed with 200 ml. of aqueous 10% potassium carbonate and then twice with 200-ml. portions of water (Note 9), and dried for 1 hour over 200 g. of anhydrous calcium chloride (Note 10). The solvent is removed on a rotary evaporator at room temperature, yielding 145–158 g. of crude product (Note 11). Distillation under reduced pressure through a Vigreux column gives 115–128 g. of a fraction, b.p. 83–86° (54 mm.), n_D^{22} 1.4620–1.4640, containing 95% of 1-bromo-3-methyl-2-butanone as established by ^1H NMR measurements (Note 11).

2. Notes

1. The checkers used 3-methyl-2-butanone purchased from Eastman Organic Chemicals. One sample that gave a positive test for peroxides was purified by passage through a column of alumina before distillation. The material was distilled routinely before use.

2. The methanol was distilled twice from magnesium turnings. Alternately, it was dried overnight over molecular sieves then distilled. The checkers also found freshly opened reagent methanol (purchased from Fisher Scientific Company) to be satisfactory.
3. The submitters used R. P. bromine obtained from Prolabo, Paris, without further purification. The checkers used bromine available from Fisher Scientific Company.
4. It is very important to add the bromine in a single portion. When it is added dropwise, a mixture containing significant amounts of 3-bromo-3-methyl-2-butanone is obtained.
5. The temperature must be controlled carefully, especially at the end of the addition when the reaction becomes more exothermic. If the solution becomes warm, a mixture of the two isomeric bromoketones is obtained.
6. If a slight excess of bromine has been added, a light yellow color remains after reaction of one equivalent since dibromination is very slow under these conditions.
7. The quantity of water added is such that the brominated products do not separate from the aqueous methanol.
8. The water is added in order to hydrolyze the α-bromodimethyl ketals produced during the reaction. The ease of hydrolysis of these bromoketals depends on the structure of the ketone. With acetylcyclohexane or acetylcyclopentane, stirring with water for 10 minutes is sufficient for complete hydrolysis. In contrast, with phenylacetone or methyl ethyl ketone, after dilution with water, the addition of 10 equivalents of concentrated sulfuric acid with respect to ketone and stirring for 15 hours at room temperature are necessary for complete hydrolysis.
9. The submitters state that the hydrobromic acid can also be neutralized before extraction by adding 75 g. of potassium carbonate (6 g. excess) in small portions.
10. Under these extraction conditions, the ether solution contains significant amounts of water and methanol which cannot be removed efficiently with anhydrous sodium sulfate.
11. In the crude product the ratio of 1-bromo-3-methyl-2-butanone to 3-bromo-3-methyl-2-butanone is estimated by ^{1}H NMR to be 95:5. The ^{1}H NMR properties of the two isomers are as follows; 1-bromo-3-methyl-2-butanone: ($CDCl_3$), δ (multiplicity, coupling constant J in Hz., number of protons, assignment): 1.17 (d, J = 6.9, 6H, 2CH_3), 3.02 (m, 1H, CH), 4.10 (s, 2H, CH_2); 3-bromo-3-methyl-2-butanone. ($CDCl_3$): δ (multiplicity, number of protons, assignment): 1.89 (s, 6H, 2CH_3), 2.46 (s, 3H, COCH_3).

3. Discussion

Pure isomeric, monobrominated ketones substituted at the less substituted or at the more substituted α-carbon are not readily accessible by direct bromination of unsymmetrical ketones since the reaction often leads to a mixture of products, with the

more substituted isomer usually predominating.[2] Radical bromination of unsymmetrical ketones in the presence of epoxides yields exclusively the monobromo ketone corresponding to bromination at the more substituted α-position.[3] The action of hydrobromic acid on diazo ketones has been, for a long time, the only method of preparing bromomethyl ketones.[4] Recently, some indirect routes involving halogenation of preformed isomeric enol silyl ethers[5] or enamines[6] have been described. The bromination of unsymmetrical ketals (e.g., dioxolanes or dimethyl ketals) occurs to a greater extent on the less substituted carbon atom, and this constitutes an efficient route to the corresponding α-bromo ketones.[7,8,9] Direct bromination of 2-substituted cyclohexanones[8] and various methyl ketones[10] in methanol leads to the same result.

This procedure, in contrast to methods mentioned above, has only one step and is readily adapted to large-scale preparative work. Furthermore, because dibromination is very slow in methanol, the crude reaction products contain only traces of dibromo ketones. This contrasts with the behavior in other solvents, such as ether or carbon tetrachloride, where larger amounts of dibromo ketones are always present, even when one equivalent of bromine is used. Methanol is thus recommended as a brominating solvent even when no orientation problem is involved. It should be noted that α-bromomethyl ketals are formed along with α-bromoketones and must be hydrolyzed during the workup (Note 8).[10]

The regiospecificity of bromination depends on the structure of the ketone.[10] This regiospecificity is very high for methyl ketones when the α'-position is tertiary, and not as high when it is secondary. For example, cyclohexyl methyl ketone and cyclopentyl methyl ketone lead to crude products containing 100 and 85%, respectively, of bromomethyl ketone, while 2-methylcyclohexanone, methyl ethyl ketone, and phenylacetone give 65,[8] 70,[10] and 40%,[10] respectively, of ketone brominated at the less substituted carbon. In these latter cases, bromination of the corresponding dimethyl ketal in methanol affords better yields of these bromo ketones.[10]

References and Notes

1. Organic Chemistry of Hormones Laboratory, College of France, Paris Cedex 05. [Present address: Laboratoire de Chimie Organique Biologique, Université Pierre et Marie Curie, Tour 44–45, 4 Place Jussieu, 75230 Paris Cedex 05, France.]
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

calcium chloride (10043-52-4)

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

methanol (67-56-1)

diethyl ether (60-29-7)

magnesium turnings (7439-95-4)

HYDROBROMIC ACID (10035-10-6)

bromine (7726-95-6)

sodium sulfate (7757-82-6)

carbon tetrachloride (56-23-5)

phenylacetone (103-79-7)

methyl ethyl ketone (78-93-3)

3-methyl-2-butanone (563-80-4)

2-methylcyclohexanone (583-60-8)

Cyclohexyl methyl ketone, acetylcyclohexane (823-76-7)

1-Bromo-3-methyl-2-butanone (19967-55-6)

3-bromo-3-methyl-2-butanone (2648-71-7)

acetylcyclopentane, cyclopentyl methyl ketone (6004-60-0)

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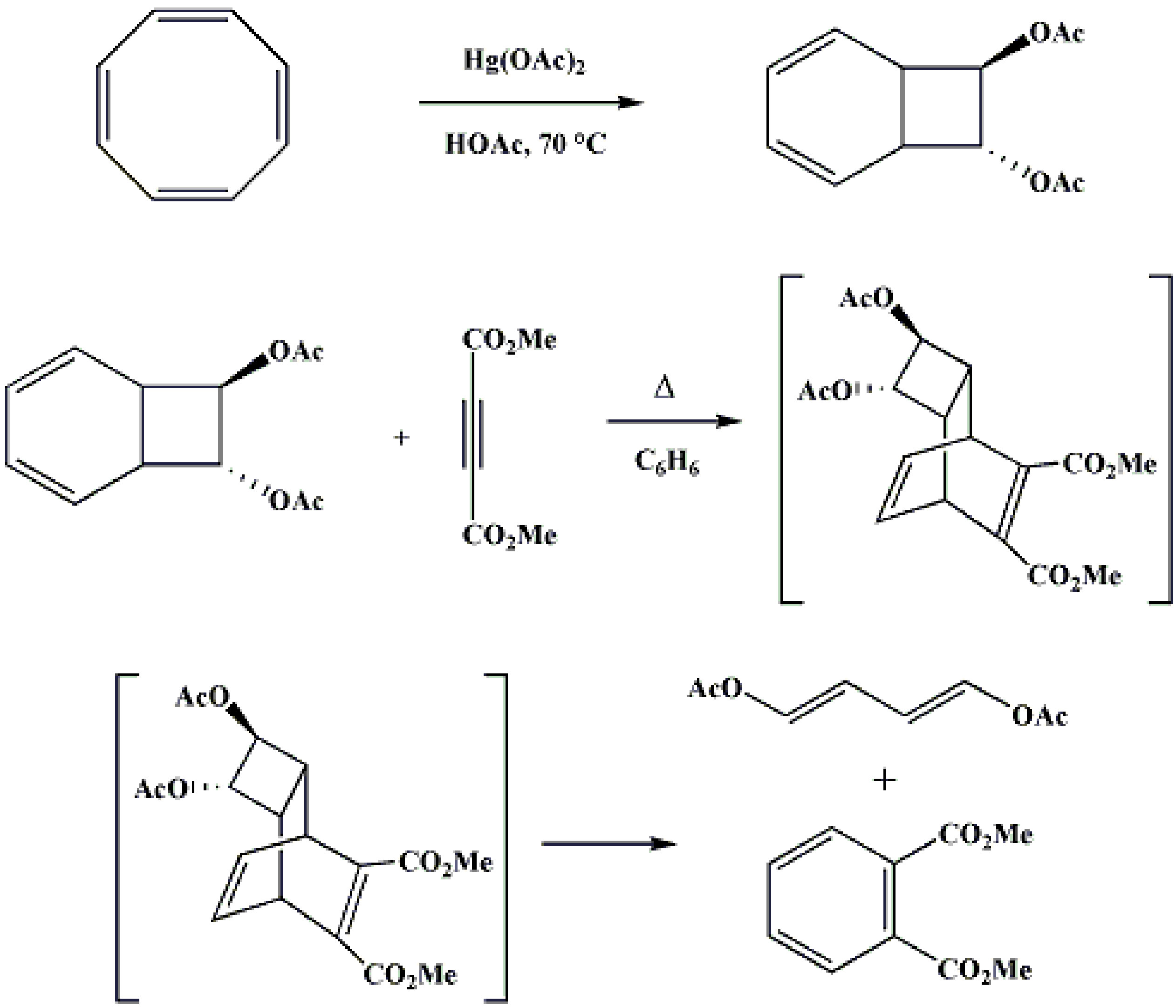
trans,trans-1,3-BUTADIENE-1,4-DIYL DIACETATE

[1,3-Butadiene-1,4-diol, diacetate, *E*,*E*-]



Submitted by Robert M. Carlson[1] and Richard K. Hill[2].
Checked by Jack M. Pal and Peter Yates.

1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A. trans-7,8-*Diacetoxybicyclo*[4.2.0]*octa*-2,4-*diene*. A 1-l., three-necked flask fitted with a reflux condenser, an efficient stirrer, and a thermometer dipping well into the solution is charged with a suspension of mercury(II) acetate (Note 1) (160 g., 0.502 mole) in glacial acetic acid (400 ml). While the suspension is stirred, 52.0 g. of cycloöctatetraene (0.500 mole) (Note 2) is added rapidly. The white addition compound that separates after 10–15

minutes is decomposed by careful heating of the reaction mixture at 70–75° for 2 hours (Note 3). While still warm, the mixture is poured through funnels containing glass wool plugs into two, 4-l. beakers, each containing 2 l. of water (Note 4). The mixture is allowed to stand for several hours, and the solid that separates is collected on a Büchner funnel and pressed as dry as possible on the funnel. The moist, yellow solid is spread out on a large piece of filter paper and allowed to dry overnight, yielding 83–86 g. (75–77.5%) of *trans*-7,8-diacetoxybicyclo[4.2.0]octa-2,4-diene, m.p. 52–55° (Note 5); it may be used in the next step without further purification (Note 6).

B. trans,trans-1,3-*Butadiene*-1,4-*diyl diacetate*. A solution of the diacetate (83.0 g., 0.373 mole) and dimethyl acetylenedicarboxylate [*Org. Synth.*, **Coll. Vol. 4**, 329 (1963); 54.0 g., 0.380 mole] in benzene (250 ml.) is placed in a 500-ml. flask and refluxed for 6 hours (Note 7). The solution is filtered to remove the remaining mercury and mercury salts, and the benzene is distilled under reduced pressure. The residual viscous yellow oil is distilled under reduced pressure (Note 8). A mixture of 1,3-butadiene-1,4-diyl diacetate and dimethyl phthalate is collected at 140–155° (18–20 mm.), bath temperature 170–200°, from which the diene crystallizes as colorless needles in the cooled receiver. The solid is broken up, washed onto a Büchner funnel with petroleum ether (b.p. 60–70°), pressed between sheets of filter paper to remove excess dimethyl phthalate, and recrystallized from *ca.* 1:2 acetone–petroleum ether (b.p. 60–70°) (Note 9), yielding 26–31 g. (41–49%) of *trans,trans*-1,3-butadiene-1,4-diyl diacetate, as colorless needles, m.p. 102–104° (Note 10),(Note 11), and (Note 12).

2. Notes

1. "Baker analyzed" mercury(II) acetate was used as obtained from J. T. Baker Chemical Company.
2. Cycloöctatetraene was used as obtained from Badische Anilin- und Soda-Fabrik, 67 Ludwigshafen, Rhein, Germany.
3. Temperatures in excess of 75° cause darkening of the reaction mixture. The submitters found that adequate temperature control could be maintained with a Bunsen flame; the checkers used a heating mantle.
4. This operation should be carried out in a well-ventilated hood. Scratching the sides of the beakers at the surface of the water promotes crystallization. The beakers are stirred occasionally to promote rapid crystallization and to minimize the formation of a solid cake on the bottom.
5. The checkers obtained 92–93 g. (83–84%); m.p. 58–61°.
6. Melting points of 61–62°, 61.4–62.5°, 64–65°, and 66° have been reported.[3,4,5] The diacetate may be recrystallized from aqueous acetic acid,[3,4,5] ligroin,[3] or ethanol.[4]
7. A longer reflux period, *e.g.*, overnight, did not affect the yield.
8. The submitters used a 500-ml. distilling flask with a 250-ml. distilling flask as receiver. The side arm of the distilling flask was extended, if necessary, with a Tygon joint into the bulb of the receiver. The receiver was cooled with a stream of cold water. The distillation was continued until about three-fourths of the material in the flask had distilled. The checkers used standard-taper glassware for the distillation and found it necessary to heat the distillation adapter with a microburner from time

to time in order to prevent plugging by solidified product. They continued the distillation until no further solid product distilled.
9. The checkers found that it was essential to conduct the recrystallization rapidly in order to obtain maximum yields.
10. The checkers obtained a yield of 40.8 g. (64%) when distillation of the product mixture was continued until no additional solid product distilled (*cf.* (Note 8) and (Note 9)).
11. A satisfactory alternative to recrystallization of the diene is the following. The crude solid is placed in a 100-ml. beaker containing 40–50 ml. of a 15% solution of acetone in petroleum ether (b.p. 60–70°). The lumps are broken up, and the colorless solid is filtered from the pale-yellow solution. A final wash with 20 ml. of ice-cold acetone leaves 31–32 g. of diene, m.p. 99–102°, pure enough for many purposes.
12. The IR and UV spectra of the product have been reported.[6]

3. Discussion

This method is essentially that described by Reppe, Schlichting, Klager, and Toepel,[3] although the correct structures were assigned by others.[4,7] 7,8-Diacetoxybicyclo[4.2.0]octa-2,4-diene has also been prepared by oxidation of cycloöctatetraene with lead tetraäcetate,[5] and by chlorination of cycloöctatetraene with sulfuryl chloride followed by displacement with potassium acetate.[3,7] The two other geometric isomers of the diene have been prepared by another method.[6] *trans,trans*-1,3-Butadiene-1,4-diyl diacetate is a reactive diene in the Diels-Alder reaction. It has been used as the starting material in stereospecific syntheses of conduritol-D[8] and shikimic acid,[9,10] and in simple, general methods of preparation of benzene derivatives, especially unsymmetrical biphenyls.[11,12]

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Appendix

Compounds Referenced (Chemical Abstracts Registry Number)

ligroin

petroleum ether

conduritol-D

ethanol (64-17-5)

acetic acid (64-19-7)

Benzene (71-43-2)

mercury(II) acetate (1600-27-7)

mercury (7439-97-6)

acetone (67-64-1)

sulfuryl chloride (7791-25-5)

potassium acetate (127-08-2)

Dimethyl acetylenedicarboxylate (762-42-5)

1,3-butadiene-1,4-diyl diacetate

dimethyl phthalate (131-11-3)

7,8-Diacetoxybicyclo[4.2.0]octa-2,4-diene

shikimic acid

cyclooctatetraene

trans,trans-1,3-BUTADIENE-1,4-DIYL DIACETATE

1,3-Butadiene-1,4-diol, diacetate, E,E- (15910-11-9)

trans-7,8-Diacetoxybicyclo[4.2.0]octa-2,4-diene (42301-50-8)

lead tetraacetate

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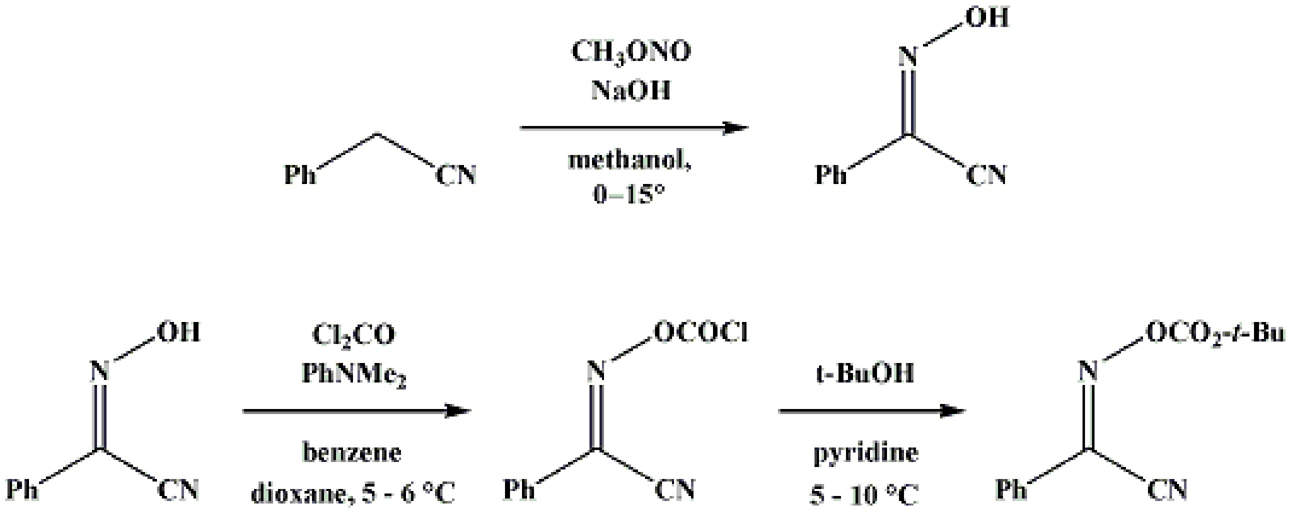
Organic Syntheses, CV 6, 199

A NEW REAGENT FOR *tert*-BUTOXYCARBONYLATION: 2-*tert*-BUTOXYCARBONYLOXYIMINO-2-PHENYLACETONITRILE

[Benzeneacetonitrile, α-[[[(1,1-dimethylethoxy)carbonyl]carbonyl]oxy]imino]-]



Submitted by Masumi Itoh, Daijiro Hagiwara, and Takashi Kamiya[1].
Checked by Hiroyuki Ishitobi, Teruji Tsuji, and Wataru Nagata.

1. Procedure

Caution! Phosgene is highly toxic. Part B should be performed in an efficient hood. Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A. *2-Hydroxyimino-2-phenylacetonitrile*. A 1-l., round-bottomed flask fitted with a mechanical stirrer, a calcium chloride drying tube, a thermometer, and a gas-inlet tube is charged with 117 g. (1.00 mole) of benzyl cyanide and a solution of 40.0 g. (1.00 mole) of sodium hydroxide in 300 ml. of methanol (Note 1). The resulting solution is stirred and cooled at 0° as methyl nitrite is introduced through the gas-inlet tube, which extends below the surface of the liquid. The methyl nitrite is generated by dropwise addition of a cold solution of 32 ml. of concentrated sulfuric acid in 65 ml. of water from a 100-ml., pressure-equalizing dropping funnel into a 300-ml. Erlenmeyer flask containing a suspension of 83 g. (1.2 moles) of sodium nitrite in 53 ml. of methanol and 50 ml. of water (Note 2). The rate of generation of methyl nitrite is adjusted so that the reaction temperature does not exceed 15°. After the addition is complete (Note 3), stirring is continued for another 2 hours, and the solvent is removed under reduced pressure with a rotary evaporator. The residue is dissolved in 500 ml. of water, and the resulting solution is washed with two 100-ml. portions of toluene. The aqueous layer is acidified with concentrated hydrochloric acid and cooled in an ice bath. The resulting precipitate is filtered, washed thoroughly with cold water, and dried, yielding 111–120 g. (76–82%) of 2-hydroxyimino-2-phenylacetonitrile, m.p. 119–124° (Note 4). This material is used in Part B without further purification.

B. 2-tert-*Butoxycarbonyloxyimino*-2-*Phenylacetonitrile*. A 200-ml., three-necked, round-bottomed flask equipped with a dropping funnel, a mechanical stirrer, a thermometer, and a calcium chloride drying tube is charged with a solution of 10.9 g. (0.110 mole) of phosgene (Note 5) in 30 ml. of benzene. The contents of the flask are stirred and cooled in an ice bath while a solution of 14.6 g. (0.100 mole) of 2-hydroxyimino-2-phenylacetonitrile and 13.2 g. (0.113 mole) of *N,N*-dimethylaniline in 5 ml. of dioxane and 80 ml. of benzene (Note 6) is added dropwise over 1 hour at 5–6°. Stirring is continued for 6 hours at the same temperature, after which the mixture is allowed to stand overnight in an ice bath. A solution of 11.1 g. (0.150 mole) of *tert*-butyl alcohol and 12.0 ml. (0.150 mole) of pyridine (Note 7) in 30 ml. of benzene (Note 6) is added over 1 hour as the mixture is stirred and cooled at 5–10°. Stirring is continued for an additional 6 hours while the reaction temperature is allowed to rise to room temperature. The reaction mixture is allowed to stand overnight (Note 8) and is then mixed with 50 ml. of water and 50 ml. of benzene. The organic layer is separated and washed successively with three 30-ml. portions of cold 1 *N* hydrochloric acid, 30 ml. of water, two 30-ml. portions of 5% sodium hydrogen carbonate solution, and two 30-ml. portions of water. Each of the aqueous washings is extracted with 30 ml. of benzene. The organic layers are combined, dried with magnesium sulfate, and concentrated to dryness under reduced pressure at a temperature lower than 35°. The crystalline residue is triturated with 20 ml. of aqueous 90% methanol. The solid is filtered, washed with 30 ml. of aqueous 90% methanol, and dried, giving 15.8–17.0 g. of crude product, m.p. 84–86° (Note 9). Recrystallization from methanol (Note 10) affords 14.6–15.7 g. (59–64%) of 2-*tert*-butoxycarbonyloxyimino-2-phenylacetonitrile as white needles or plates, m.p. 84–86° (Note 11).

2. Notes

1. The submitters used reagent grade solvents and reagents without further purification. The yield of 2-hydroxyimino-2-phenylacetonitrile was 76% when the checkers used technical grade benzyl cyanide purchased from Wako Pure Chemical Industries, Ltd., Osaka, Japan. The yield was improved to 81% with distilled material, b.p. 75–77° (3 mm.). Benzyl cyanide is also available from Aldrich Chemical Company, Inc.

2. This method for the preparation of methyl nitrite is described in *Org. Synth.*, **Coll. Vol. 2**, 363 (1943).

3. The addition of sulfuric acid requires *ca.* 1 hour. Occasional swirling of the Erlenmeyer flask is recommended for smooth generation of methyl nitrite.

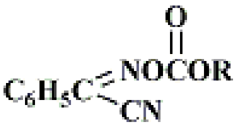
4. Material of this quality is satisfactory for most purposes; however, if further purification is necessary, it may be recrystallized from hot water, giving a solid that melts at 126–128°. The checkers obtained product melting at 104–116° and 104–117° in the first and second runs, respectively. Evidently the product is a mixture of *syn* and *anti* isomers, the ratio of which was different in the material obtained by the submitters and the checkers. This difference in the isomer ratio might be attributed to a slight variation of experimental conditions. The submitters later informed the checkers that the methanol was evaporated at 70–80°; the checkers removed the solvent at 35–40°. On partial recrystallization from hot water, the checkers isolated both the less soluble *anti* isomer, m.p. 127.5–129°, and the more soluble *syn* isomer, m.p. 97–99°. The melting points given in the literature for the *syn* and *anti* isomers are 129° and 99°, respectively.[2] The UV spectra (95% C_2H_5OH) of the *syn* and *anti* isomers show maxima at 274 nm. (log ε, 3.99) and 260 nm. (log ε, 4.05), respectively.

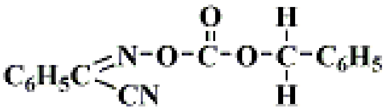
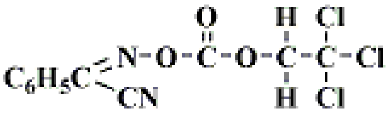
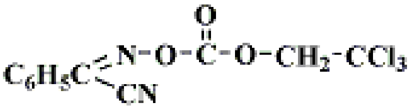
5. Phosgene may be replaced by a 0.5 molar equivalent of trichloromethyl chloroformate. This reagent may be purchased from Hodogaya Chemical Company, Ltd., Tokyo, Japan, or prepared by the procedure in *Org. Synth.*, **Coll. Vol. 6**, 715 (1988).

6. *N,N*-Dimethylaniline, pyridine, *tert*-butyl alcohol, and the solvents were dried with Linde

type 3A molecular sieves.
7. The use of a 0.5 molar excess of pyridine and *tert*-butyl alcohol is necessary in this case to obtain a satisfactory yield. However, when this procedure is applied to the preparation of other alkoxycarbonates (Table II), excess alcohol should be avoided since it may contaminate the product.

TABLE II
OTHER ALKOXYCARBONYLATING REAGENTS PREPARED FROM 2-HYDROXYIMINO-2-PHENYLACETONITRILE



R	Solvent for Recrystallization	M.p. (°)	Yield (%)
 $C_6H_5CH_2$-	ethyl acetate-hexane	73–75	62
 4-$CH_3OC_6H_4CH_2$-	ethyl acetate-hexane	112–113	36
 Cl_3CCH_2-	methanol	82–84	87

8. The yield was reduced to 46% in a run in which the product was isolated without the additional overnight reaction time.
9. The checkers obtained 12.8–13.0 g. (52–53%), m.p. 84–86°, in the first crop and 2.7–3.4 g. (11–14%), m.p. 52–62°, in the second crop. Recrystallization of the former from methanol gave 11.5 g. of crystals, m.p. 84–86°, suggesting that the first crop is a pure single isomer. A ^{1}H NMR spectrum ($CDCl_3$) of the second crop shows two singlets at δ 1.62 and 1.64 for the *tert*-butyl groups. Thus, this material is a mixture of *syn* and *anti* isomers. Both the first and second crops proved equally useful for *tert*-butoxycarbonylation of an amino acid.
10. Recrystallization from boiling methanol should be avoided owing to the thermal instability of the product.
11. IR (Nujol) cm.$^{-1}$: 1785 (C=O); ^{1}H NMR ($CDCl_3$), δ (multiplicity, number of protons, assignment): 1.62 (s, 9H, 3CH_3), 7.2–8.2 (m, 5H, C_6H_5). A TLC on silica gel (Merck precoated plate, 60 F_{254}) using UV detection and 10% methanol in chloroform as the developing solvent showed a major and a minor spot at an R_f value of 0.74 and 0.50,

respectively. The minor spot arises from 2-hydroxyimino-2-phenylacetonitrile formed by partial hydrolysis of the product on the silica gel.
The submitters recommend that the product be stored in a stoppered brown bottle in a refrigerator. Although the material can be kept at room temperature for several weeks without noticeable decomposition, gradual evolution of carbon dioxide occurs over a period of several months, with the attendant risk of explosion. However, storage in the presence of a small amount of silica gel as a drying agent extends the shelf life of the material to more than a year.

3. Discussion

2-Hydroxyimino-2-phenylacetonitrile has been prepared from benzyl cyanide by reaction with nitrous acid,[3] with isoamyl nitrite and sodium ethoxide,[4] and with butyl nitrite and hydrogen chloride.[2]

The *tert*-butoxycarbonyl group is one of the most important amino protecting groups in peptide synthesis. Many *tert*-butoxycarbonylating reagents[5,6] have been prepared as substitutes for *tert*-butyl azidoformate,[7] which is toxic, shock-sensitive, and relatively unreactive.[8] 2-*tert*-Butoxycarbonyloxyimino-2-phenylacetonitrile,[9,10] one such reagent, possesses the following advantages: (1) it is stable, highly reactive, and ready for use; (2) *tert*-butoxycarbonylation of an amino acid is usually complete within 4–5 hours at room temperature in the presence of a 0.5 molar excess of triethylamine in 50% aqueous dioxane (Table I); and (3) the by-product, 2-hydroxyimino-2-phenylacetonitrile, is easily and completely removed by extraction into an organic solvent, leaving the *tert*-butoxycarbonylamino acid salt in the aqueous phase. The present procedure is also applicable to preparation of other amino-protecting reagents (Table II).

TABLE I

PREPARATION OF *N-tert*-BUTOXYCARBONYL-PROTECTED AMINO ACIDS WITH 2-*tert*-BUTOXYCARBONYLOXYIMINO-2-PHENYLACETONITRILE[a]

Amino Acid	Solvent[b]	Time (hours)	Yield (%)
Glycine	A	2	87
Alanine	B	4	80
S-Benzyl cysteine	A	3	94
Glutamic acid	A	3	78
Leucine	A	3	72
Methione	A	3	82
Phenylalanine	A	2	65
Proline	C	1.5	88
Threonine	A	3	100
Asparagine	A	20	86

a The reactions were carried out with 0.010 mole of the amino acid, 0.011 mole of 2-*tert*-butoxycarbonyloxyimino-2-phenylacetonitrile, and 0.015 mole of triethylamine at 20–25°.

b The solvents were as follows: A, aqueous dioxane; B, aqueous acetone;
C, methanol–dioxane–water, 15:5:10.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 203
- Org. Syn. Coll. Vol. 6, 715

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

Benzeneacetonitrile, α-[[[(1,1-dimethylethoxy)carbonyl]carbonyl]oxy]imino]-

Methione

sulfuric acid (7664-93-9)

hydrogen chloride, hydrochloric acid (7647-01-0)

Benzene (71-43-2)

methanol (67-56-1)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium hydrogen carbonate (144-55-8)

alanine (56-41-7)

sodium nitrite (7632-00-0)

nitrous acid (7782-77-6)

carbon dioxide (124-38-9)

acetone (67-64-1)

pyridine (110-86-1)

toluene (108-88-3)

phosgene (75-44-5)

sodium ethoxide (141-52-6)

Benzyl cyanide (140-29-4)

Butyl nitrite (544-16-1)

N,N-dimethylaniline (121-69-7)

Glutamic Acid (56-86-0)

Glycine (513-29-1)

methyl nitrite (624-91-9)

magnesium sulfate (7487-88-9)

dioxane (5703-46-8)

Isoamyl nitrite (110-46-3)

phenylalanine (63-91-2)

proline (147-85-3)

asparagine (70-47-3)

leucine (61-90-5)

threonine (72-19-5)

triethylamine (121-44-8)

tert-butyl alcohol (75-65-0)

2-hydroxyimino-2-phenylacetonitrile (825-52-5)

Trichloromethyl chloroformate (503-38-8)

ethyl acetate-hexane (2639-63-6)

tert-Butyl azidoformate (1070-19-5)

2-tert-Butoxycarbonyloxyimino-2-phenylacetonitrile (58632-95-4)

S-Benzyl cysteine

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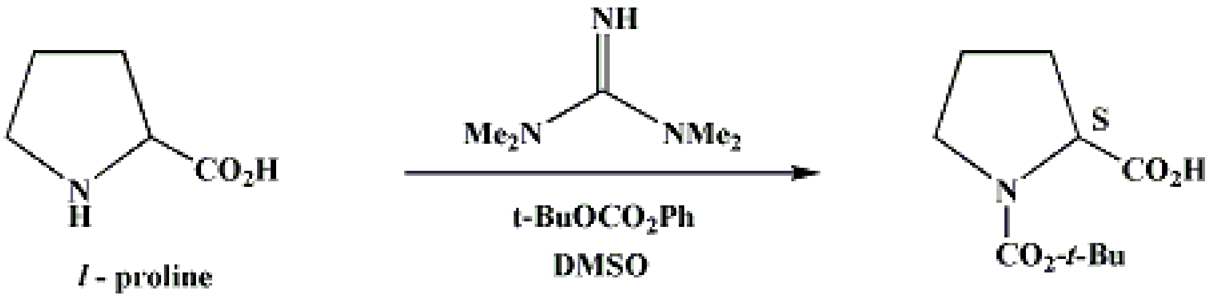
tert-BUTOXYCARBONYL-L-PROLINE

[1,2-Pyrrolidinedicarboxylic acid, 1-(1,1-dimethylethyl) ester, (*S*)-]



Submitted by Ulf Ragnarsson[1], Sune M. Karlsson, Bengt E. Sandberg, and Lars-Eric Larsson.
Checked by S. Wang and A. Brossi.

1. Procedure

A 1-l. Erlenmeyer flask (Note 1) equipped with a magnetic stirrer, and a thermometer is charged with 115 g. (1.00 mole) of L-proline (Note 2) and 500 ml. of dimethyl sulfoxide (Note 3). To the stirred suspension are added simultaneously, over 5 minutes, 115 g. (1.00 mole) of 1,1,3,3-tetramethylguanidine (Note 4) and 214 g. (1.10 moles) of *tert*-butyl phenyl carbonate (Note 5). The proline dissolves completely within a few minutes in an exothermic reaction, the temperature of which reaches a maximum of 50–52° after 10–15 minutes. After stirring for 3 hours, the clear reaction mixture is transferred to a 6-l. separatory funnel and shaken with 2.2 l. of water and 1.8 l. of diethyl ether (Note 6). The aqueous layer, after being washed with 500 ml. of ether, is acidified to pH 3.0 by the addition of 10% sulfuric acid (Note 7), which generally causes partial crystallization of the product. The acidic solution, including the solid, is extracted with three 600-ml. portions of a mixture of equal volumes of ethyl acetate and ether. The combined extracts are washed with three 25-ml. portions of water, dried over magnesium sulfate, filtered, and evaporated with a rotary evaporator at a bath temperature not exceeding 40°. After drying in a vacuum oven at 50°, the crude product weighs 202 g., m.p. 129–132°. It is recrystallized from 300 ml. of hot ethyl acetate, and clarified by filtration and the addition of 1 l. of petroleum ether (40–60°), yielding, after drying under vacuum at 50°, 179–193 g. (83–90%) of *tert*-butoxycarbonyl-L-proline, m.p. 132–134°, $[\alpha]_D^{25}$ –59.84° to –61.6° (*c* = 1, glacial acetic acid) (Note 8),(Note 9), and (Note 10).

2. Notes

1. A three-necked flask equipped with a U-tube may also be used for the reaction.

2. The submitters used L-proline obtained from Tanabe Seiyaku Company, Ltd., Osaka, Japan, and checked its purity by the method of Manning and Moore.[2] The L-proline used by the checkers was obtained from Ajinomoto Company, New York.

3. Dimethyl sulfoxide, Fisher Scientific Company, was used without further purification.

4. 1,1,3,3-Tetramethylguanidine, b.p. 159–160°, was used without further purification. The submitters obtained their material from Schuchardt, Munich, Germany, and the checkers obtained theirs from Pfaltz and Bauer, New York.

5. *tert*-Butyl phenyl carbonate furnished by Ega-Chemie KG, Steinheim, Germany, was used by the submitters. The checkers used material obtained from Aldrich Chemical Company, Inc.

6. The pH of the aqueous layer was 7.2. If the pH, as measured with a pH meter, is not between 7 and 8, it should be adjusted to within these limits by the addition of either 10% sulfuric acid or 1,1,3,3-tetramethylguanidine. The submitters worked up the reaction by the following alternate, but less convenient, method. The reaction mixture was poured into 1.25 l. of 1 *M* sodium hydrogen carbonate solution, 500 ml. of ether, and sufficient water (*ca.* 1 l.) to give two clear phases. The pH, which was 8.9, was adjusted to 8.0 by the addition, with stirring, of solid potassium hydrogen sulfate.

7. 10% Sulfuric acid (1.1 *M*) was prepared by diluting 25 ml. of concentrated sulfuric acid with 398 ml. of water. The submitters used solid potassium hydrogen sulfate for acidification to pH 3.0.

8. An additional 5 g. of product, m.p. 127–129°, may be obtained from the mother liquor

9. Some reported yields, melting points, and rotations are: 55%, 136–137°, and $[\alpha]_D^{25}$ −60.2° (2.011 in acetic acid)[3]; 96%, 134–136°, $[\alpha]_{578}^{18-25}$ −68.5° (c = 1, acetic acid)[4]; 95%, 132–134°, $[\alpha]_{578}$ −62.5° (acetic acid)[5]; 90%, 133–135°, $[\alpha]_D^{25}$ −60.4° (c = 2.2 in acetic acid)[6]; 93%, 134–135°, no rotation reported.[7]

10. ^{1}H NMR (dimethyl sulfoxide-d_6): δ 1.38 (s, 9H, 3CH_3), 1.92 (m, 4H, 2CH_2), 3.31 (t, 2H, CH_2N), 4.05 (t, 1H, C*H*N), 12.3 (s, 1H, CO_2H). Analysis calculated for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.51. Found: C, 55.81; H, 7.95; N, 6.44.

3. Discussion

Since their introduction by McKay and Albertson,[8] and Anderson and McGregor,[3] *tert*-butoxycarbonyl amino acids have been prepared by several different methods. The simplest procedure[6] requires working with large quantities of phosgene. Another very good method,[5] but one that has not found wide application, involves the use of *tert*-butoxycarbonylfluoride, which is not commercially available. At the present the most useful reagent has been *tert*-butoxycarbonylazide, for which good procedures[9,10] are available; the excellent method of Schnabel[4] and one more recently reported[7] are

based on this reagent. Of the procedures for the preparation of *tert*-butoxycarbonylazide, one,[9] which is readily adaptable for large-scale operations, involves three steps and the other,[10] a two-step process, is more suitable for small-scale work.

Our procedure[11] represents a simplification in that *tert*-butyl phenyl carbonate, which is used as a starting material, is the first intermediate in the three-step synthesis[9] of *tert*-butoxycarbonylazide. This reagent is easy to prepare in quantity and is commercially available in bulk (Note 5). Further, 1,1,3,3-tetramethylguanidine is inexpensive and the experimental operations are extremely simple.

Proline dissolves readily in dimethyl sulfoxide. Some other amino which are less soluble require longer reaction times and, in some instances, other solvents.[11] These details and the scope of the reaction are illustrated in Table I.

TABLE I

OTHER BOC[a] AMINO ACIDS SYNTHESIZED BY THIS PROCEDURE

Compound	Solvent	Temperature, °	Time, Hr.	Yield, %	Remarks
Boc-Ala[b]	DMSO[c]	25	40	58	
Boc-Ala[b]	DMSO[c]	40	40	79	
Boc-Asn[d]	DMSO[c]	25	66	70	2 equiv. TMG[e]
Boc-Asp[f]	DMSO[c]	25	18	89	2 equiv. TMG
Boc-Cys(Bzl)[g]	DMSO[c]	25	40	62	CHA salt[h]
Boc-Cys (Bzl)[g]	DMSO[c]	40	40	78	CHA salt
Boc-Gln[i]	DMSO[c]	50	48	62	2 equiv. TMG, DCHA salt,[j] continuous extraction with ethyl acetate
Boc-Glu[k]	DMSO[c]	25	2.5	80	2 equiv. TMG
Boc-Ile[l]	DMSO[c]	40	72	72	
Boc-Leu[m]	DMSO[c]	25	48	73	Calc. as hemihydrate
Boc-Met[n]	DMSO[c]	25	24	86	81% solid +5% DCHA salt
Boc-Phe[o]	DMSO[c]	25	40	81	DCHA salt
Boc-Phe[o]	DMSO[c]	25	96	88	DCHA salt
Boc-Phe[o]	DMSO[c]	40	18	81	DCHA salt

Boc-Phe[o]	DMSO[c]	25	48	59	DCHA salt
Boc-Phe[o]	D—W[q]	25	48	5	DCHA salt
Boc-Pro[r]	DMSO[c]	25	2.5	90	
Boc-Pro[r]	DMF[p]	25	2.5	92	
Boc-Pro[r]	D—W[q]	25	21	84	
Boc-Thr[s]	DMSO[c]	25	67	66	DCHA salt
Boc-Val[t]	DMSO[c]	25	71	77	2 equiv. TMG, 65% solid +12% DCHA salt

[a]*tert*-Butoxycarbonyl. [b]L-Alanine. [c]Dimethylsulfoxide. [d]L-Aspargine. [e]1,1,3,3-Tetramethylguanidine. [f]L-Aspartic acid. [g]S-Benzyl-L-cysteine. [h]Cyclohexylamine. [i]L-Glutamine. [j]Dicyclohexylamine. [k]L-Glutamic acid. [l]L-Isoleucine. [m]L-Leucine. [n]L-Methionine. [o]L-Phenylalanine. [p]Dimethylformamide. [q]Dioxane-water 1:1. [r]L-Prolone. [s]L-Threonine. [t]L-Valine.

More recently, a few additional reagents have been found useful for the synthesis of Boc-amino acids. Among these are *tert*-butyl-4,6-dimethylpyrimidyl-2-thiol carbonate,[12] di-*tert*-butyl dicarbonate,[13] 2-*tert*-butoxycarbonyloxyimino-2-phenylacetonitrile,[14] and *tert*-butyl α-methoxyvinyl carbonate.[15] With the advent of a relatively simple method for the preparation of carbonyl chloride fluoride[16] *tert*-butoxycarbonylfluoride[17] is now more readily available.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 199
- Org. Syn. Coll. Vol. 6, 207
- Org. Syn. Coll. Vol. 6, 418
- Org. Syn. Coll. Vol. 7, 70

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

ethyl acetate (141-78-6)

ether, diethyl ether (60-29-7)

sodium hydrogen carbonate (144-55-8)

alanine (56-41-7)

potassium hydrogen sulfate (7646-93-7)

phosgene (75-44-5)

Glutamic Acid (56-86-0)

magnesium sulfate (7487-88-9)

Methionine (63-68-3)

phenylalanine (63-91-2)

proline, L-proline (147-85-3)

isoleucine (73-32-5)

leucine (61-90-5)

threonine (72-19-5)

valine (72-18-4)

aspartic acid (56-84-8)

dimethyl sulfoxide (67-68-5)

cysteine (52-90-4)

1,1,3,3-tetramethylguanidine (80-70-6)

Butoxycarbonyl

Glutamine

tert-butoxycarbonylazide (1070-19-5)

2-tert-Butoxycarbonyloxyimino-2-phenylacetonitrile (58632-95-4)

tert-Butyl phenyl carbonate (6627-89-0)

Di-tert-butyl dicarbonate (24424-99-5)

1,2-Pyrrolidinedicarboxylic acid, 1-(1,1-dimethylethyl) ester, (S)-, tert-Butoxycarbonyl-L-proline (15761-39-4)

tert-butoxycarbonylfluoride

tert-butyl-4,6-dimethylpyrimidyl-2-thiol carbonate

tert-butyl α-methoxyvinyl carbonate

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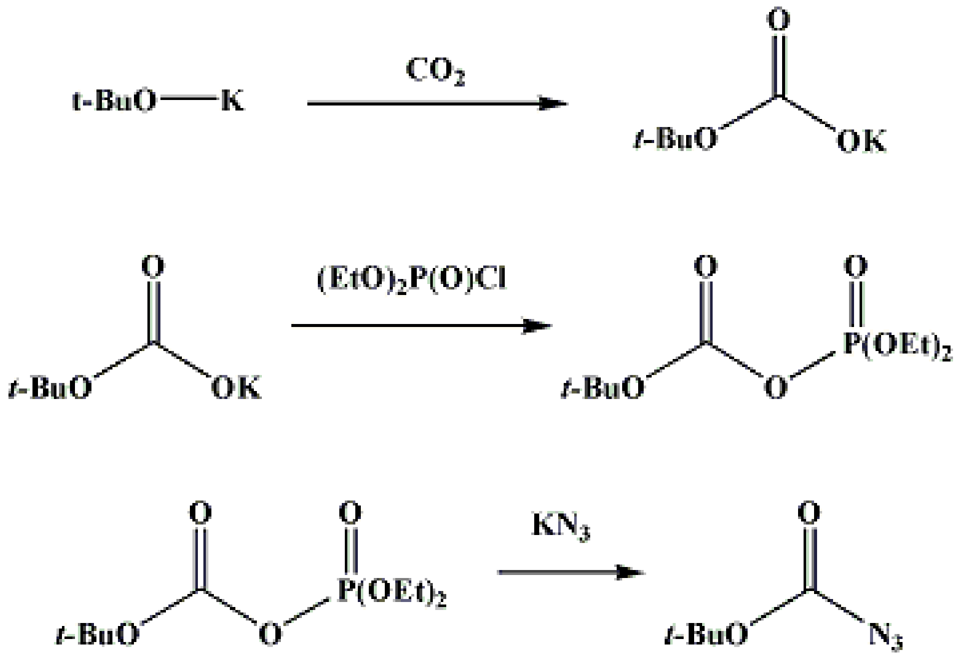
tert-BUTYL AZIDOFORMATE

[Carbonazidic acid, 1,1-dimethylethyl ester]



Submitted by Michael A. Insalaco and D. Stanley Tarbell[1].
Checked by Frederick J. Sauter, Walter J. Campbell, and Herbert O. House.

1. Procedure

Caution! Tests conducted by the Eastman Kodak Company have shown that tert-butyl azidoformate, also known as tert-butoxy carbonyl azide and t-BOC azide, is a thermally unstable, shock-sensitive compound (TNT equivalence: 45%).

A number of less-hazardous reagents that can be substituted for tert-butyl azidoformate in tert-butoxycarbonylation reactions are available, including 2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile (Aldrich Chemical Company), O-tert-butyl S-phenylthiocarbonate (Eastman Organic Chemicals), di-tert-butyl dicarbonate[2] and tert-butyl phenyl carbonate.[3]

A. tert-*Butylcarbonic diethylphosphoric anhydride*. A 500-ml., three-necked flask fitted with a mechanical stirrer, a pressure-equalizing dropping funnel, and a gas-inlet tube is dried in an oven, flushed with nitrogen, and allowed to cool while an atmosphere of nitrogen is maintained in the reaction vessel. To the flask are added successively 250 ml. of anhydrous tetrahydrofuran (Note 1) and 13.9 g. (0.124 mole) of alcohol-free potassium *tert*-butoxide (Note 2). After the mixture has been stirred for 10 min. under a nitrogen atmosphere to complete dissolution of the salt, the solution is

cooled in an ice bath, and a slow stream of anhydrous carbon dioxide (Note 3) is bubbled through the cold solution for 1.5 hours with continuous stirring. While cooling, stirring, and the flow of carbon dioxide are maintained, a solution of 20.6 g. (0.120 mole) of pure diethyl phosphorochloridate (Note 4) in 50 ml. of anhydrous tetrahydrofuran (Note 1) is added dropwise to the reaction mixture, and the cold reaction mixture is stirred for an additional 30 minutes under a carbon dioxide atmosphere. After the solvent has been removed from the reaction mixture by concentration with a rotary evaporator at room temperature, the residual mixture of anhydride and potassium chloride is diluted with 300 ml. of anhydrous diethyl ether and centrifuged, separating the insoluble salt. The salt is successively suspended in two 150-ml. portions of anhydrous ether and centrifuged to remove any remaining ether soluble product. The combined ether solutions are concentrated at room temperature with a rotary evaporator, leaving 25–28 g. (84–91%) of the crude anhydride, as a colorless to pale yellow liquid (Note 5), sufficiently pure for use in the next step.

B. *tert-Butyl azidoformate.* A 300-ml., three-necked flask fitted with a mechanical stirrer, a pressure-equalizing dropping funnel, and a gas-inlet tube is dried in an oven, flushed with nitrogen, and allowed to cool while a nitrogen atmosphere is maintained in the reaction vessel. To the flask are added 120 ml. of anhydrous dimethyl sulfoxide (Note 6) and 8.1 g (0.10 mole) of powdered potassium azide (Note 7). While a nitrogen atmosphere is maintained in the reaction vessel, the mixture is stirred for 30 minutes to dissolve the bulk of the potassium azide before 25.4 g. (0.100 mole) of *tert*-butylcarbonic diethylphosphoric anhydride is added dropwise with stirring. During this addition the temperature of the reaction mixture is maintained at approximately 25° with a water bath. The resulting solution is stirred at 20–25° for 1 hour; 120 ml. of water is then added dropwise while stirring and external cooling are maintained. The resulting mixture is extracted with three 120-ml. portions of pentane, and the combined pentane extracts are washed successively with 20 ml. of water and 20 ml. of saturated aqueous sodium chloride. After the pentane solution has been dried over magnesium sulfate, the pentane is removed at room temperature with a rotary evaporator. The residual crude product, 11–14 g. of a pale yellow liquid, is distilled under reduced pressure from a distilling flask heated in a water bath. *Caution! This distillation should be conducted in a hood behind a safety shield.* (Note 8). The product is collected as 7.2–9.3 g. (50–65%) of colorless liquid, b.p. 57–61° (40 mm.), n_D^{24} 1.4224–1.4230 (Note 9).

2. Notes

1. A reagent grade of tetrahydrofuran should be redistilled from lithium aluminum hydride immediately before use. In this distillation discontinue heating when the residue in the stillpot has reached a volume of 50–100 ml.
2. Alcohol-free potassium *tert*-butoxide, obtained from the MSA Research Corporation, Callery, Pennsylvania, should be weighed and transferred under anhydrous conditions.

3. The carbon dioxide, obtained from a cylinder or from a container packed with dry ice, should be passed through a drying tube packed with silica gel or anhydrous calcium sulfate.

4. The diethyl phosphorochloridate, available from Stauffer Chemical Company, New York, should be redistilled before use: b.p. 60° (2 mm.), n_D^{25} 1.4153.

5. IR (CCl_4), 1770 (C=O), 1255 and 1292 $cm.^{-1}$ (P=O); ^1H NMR (CCl_4), δ 1.38 (pair of t, $J_{H\text{-}H}$ = 6.6Hz., $J_{P\text{-}H}$ = 2.5 Hz., 6H, $2CH_2CH_3$), 1.53 [s, 9H, $C(CH_3)_3$], and 4.17 (pair of quadruplets, $J_{H\text{-}H}$ = 6.6 Hz., $J_{P\text{-}H}$ = 8.5 Hz., 4H, $2CH_2CH_3$).

6. An analytical grade of dimethyl sulfoxide obtained from J. T. Baker Co. or Matheson, Coleman and Bell was used. The checkers redistilled this solvent from calcium hydride before use; b.p. 83–85° (17 mm.).

7. A commercial grade of potassium azide, obtained from either Eastman Organic Chemicals or Alfa Inorganics, Inc., was purified by recrystallization from aqueous ethanol (1:2, v/v) as previously described.[4] The pure azide, obtained as white solid, m.p. 343° (dec.), was dried in an oven at 110° for 2 hours before use. In this preparation it is preferable to use the more soluble potassium azide rather than sodium azide.

8. Although this distillation has been conducted repeatedly without incident, azides are potentially explosive.[5] Consequently, the distillation should be conducted behind a safety shield and the operator should wear protective equipment. The distilling flask should be heated with a water bath to avoid the possibility of overheating the distillation residue.

9. IR (CCl_4), 2170, 2120 (azide), 1760, and 1735 $cm.^{-1}$ (C=O); ^1H NMR (CCl_4), δ 1.51, singlet, $(CH_3)_3$ C; mass spectrum, m/e (rel.int.), 115 (17), 100 (16), 59 (85), 57 (20), 56 (41), 44 (18), 43 (84), 41 (21), 39 (19), 29 (30), 28 (100), 27 (21).

3. Discussion

Although *tert*-butyl azidoformate, a useful reagent for the protection of primary and secondary amino groups[6,7,8,9] has been prepared previously from *tert*-butyl carbazate,[5] the present procedure[10] is more convenient. The intermediate carbonic phosphoric anhydride reacts with nucleophiles other than the azide ion; for example, reaction of this anhydride with amines yields the *tert*-butoxycarbonyl derivatives of amines.[10] Other carbonic phosphoric anhydrides have been prepared by procedures analogous to the method described here.[11]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 157
- Org. Syn. Coll. Vol. 5, 160
- Org. Syn. Coll. Vol. 6, 199
- Org. Syn. Coll. Vol. 6, 203

- Org. Syn. Coll. Vol. 6, 418
- Org. Syn. Coll. Vol. 7, 70

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

tert-Butylcarbonic diethylphosphoric anhydride

alcohol-free potassium tert-butoxide

ethanol (64-17-5)

ether, diethyl ether (60-29-7)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

calcium sulfate (7778-18-9)

Pentane (109-66-0)

sodium azide (26628-22-8)

potassium chloride (7447-40-7)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

dimethyl sulfoxide (67-68-5)

calcium hydride (7789-78-8)

diethyl phosphorochloridate (814-49-3)

Carbonazidic acid, 1,1-dimethylethyl ester, tert-Butyl azidoformate, tert-butoxy carbonyl azide, t-BOC azide (1070-19-5)

2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile (58632-95-4)

O-tert-butyl S-phenylthiocarbonate (36760-43-7)

tert-Butyl phenyl carbonate (6627-89-0)

potassium azide

Di-tert-butyl dicarbonate (24424-99-5)

tert-Butyl carbazate (870-46-2)

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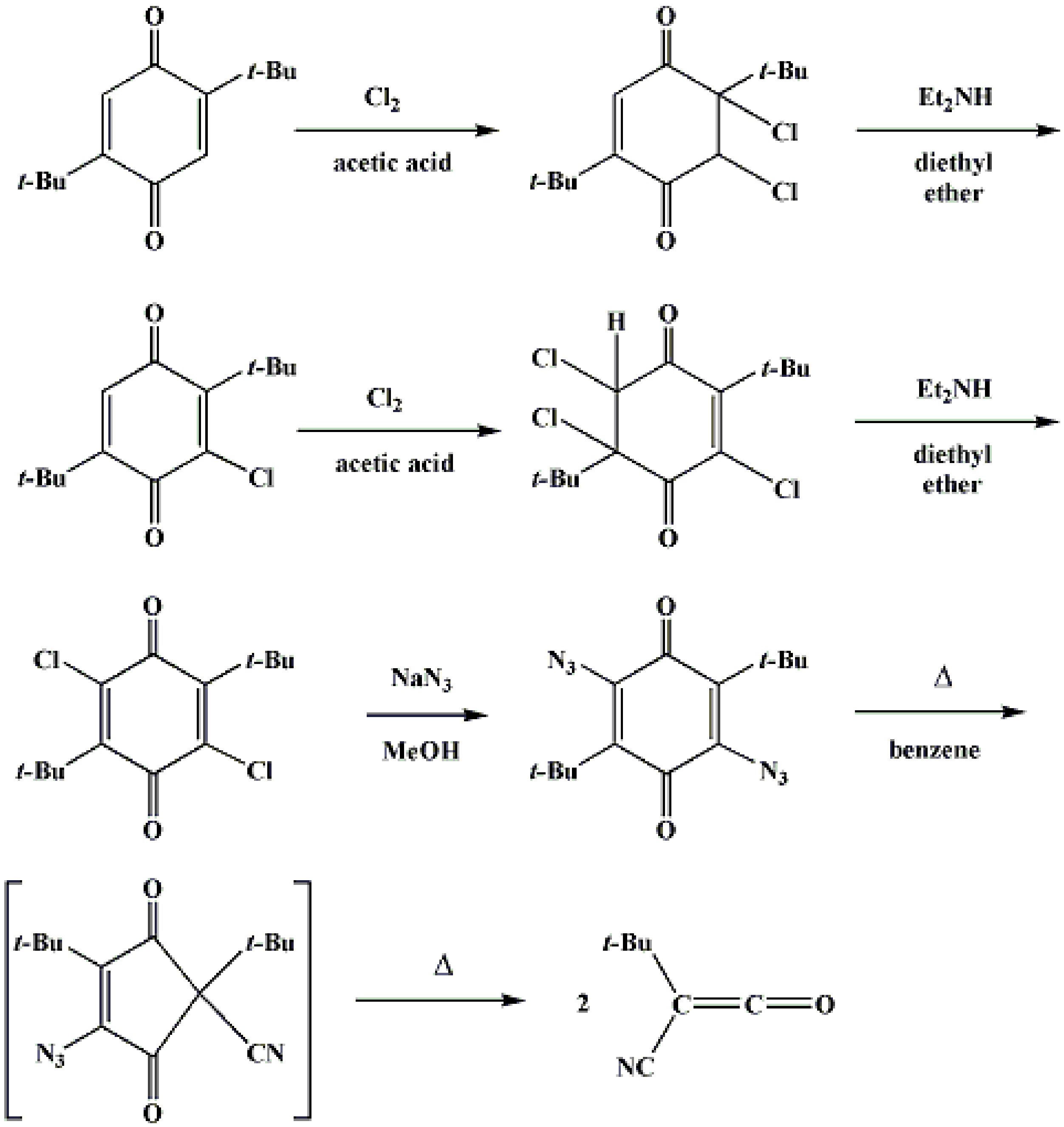
Organic Syntheses, CV 6, 210

tert-BUTYLCYANOKETENE

[Butanenitrile, 2-carbonyl-3,3-dimethyl-]



Submitted by Walter Weyler, Jr., Warren G. Duncan, Margo Beth Liewen, and Harold W. Moore[1].
Checked by B. E. Smart and R. E. Benson.

1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-

ventilated hood, and glove protection is required.

A. *2,5-Di-*tert*-butyl-5,6-dichloro-2-cyclohexene-1,4-dione.* A 2-l. Erlenmeyer flask is charged with 110 g. (0.500 mole) of 2,5-di-*tert*-butyl-1,4-benzoquinone (Note 1) and 500 ml. of glacial acetic acid. The reaction flask is equipped with an efficient magnetic stirring bar, and chlorine gas is introduced through a safety trap into the well-stirred mixture (Note 2). During the course of the reaction, which should be completed in 35–40 minutes (Note 3), the mixture becomes homogeneous and warms to about 60°. The mixture is flushed with nitrogen to expel excess chlorine. During this process the product crystallizes from the solution; precipitation is completed by cooling the reaction mixture to 20°. The mixture is filtered, and the product is washed with 1 l. of water and air dried, yielding 112 g. (77%) of 2,5-di-*tert*-butyl-5,6-dichloro-2-cyclohexene-1,4-dione, m.p. 125–129° (Note 4).

B. *3-Chloro-2,5-di-*tert*-butyl-1,4-benzoquinone.* A 2-l. Erlenmeyer flask is charged with a solution of 112 g. (0.385 mole) of 2,5-di-*tert*-butyl-5,6-dichloro-2-cyclohexene-1,4-dione in 800 ml. of diethyl ether. A solution of 28.4 g. (0.383 mole) of diethylamine in 50 ml. of ether is added in one portion to the vigorously swirled flask (Note 5). The reaction is instantaneous, resulting in a voluminous precipitate. The mixture is washed with two 1-l. portions of water, then with 500 ml. of aqueous saturated sodium chloride. The yellow ether solution is dried over anhydrous magnesium sulfate, filtered, and concentrated on a rotary evaporator, yielding 96–97 g. (98–99%) of 3-chloro-2,5-di-*tert*-butyl-1,4-benzoquinone as a yellow oil which is used without further purification (Note 6).

C. *2,5-Di-*tert*-butyl-3,5,6-trichloro-2-cyclohexene-1,4-dione*. A 2-l. Erlenmeyer flask is charged with a solution of 96.6 g. (0.379 mole) of crude 3-chloro-2,5-di-*tert*-butyl-1,4-benzoquinone in 500 ml. of glacial acetic acid. The reaction flask is equipped with an efficient magnetic stirring bar, and chlorine gas is introduced (Note 7). The reaction is complete in 4-5 hours (Note 8), at which time the solution is flushed with nitrogen to expel excess chlorine. Approximately 1 l. of water is added, and the resulting mixture is extracted with 300 ml. of dichloromethane. The dichloromethane solution is washed three times with water, dried over anhydrous magnesium sulfate, filtered, and concentrated on a rotary evaporator, yielding 116–117 g. (94%) of 2,5-di-*tert*-butyl-3,5,6-trichloro-2-cyclohexene-1,4-dione as a lemon yellow oil which is used directly in the next step (Note 9).

D. *2,5-Di-*tert*-butyl-3,6-dichloro-1,4-benezoquinone.* A 2-l. Erlenmeyer flask is charged with a solution of 116.6 g. (0.3582 mole) of 2,5-di-*tert*-butyl-3,5,6-trichloro-2-cyclohexene-1,4-dione in 800 ml. of ether. To the vigorously swirled solution is added, in one portion, 26.2 g. (0.359 mole) of diethylamine dissolved in *ca.* 50 ml. of ether. The reaction,which is instantaneous, results in a voluminous precipitate (Note 10). The reaction mixture is washed with two 1-l. portions of water and then with 500 ml. of aqueous saturated sodium chloride (Note 11). The ether solution is dried over anhydrous magnesium sulfate, filtered, and concentrated on a rotary evaporator. The crude product, a yellow semisolid (109 g.), is dissolved in 300 ml. of hot ethanol, then cooled first to room

temperature and finally to 0°. After crystallization has begun, the flask is left at –5° to –10° overnight. The product is filtered, washed with 85% ethanol, and air dried, yielding 62–70 g. (60–67%) of yellow crystalline 2,5-di-*tert*-butyl-3,6-dichloro-1,4-benzoquinone, m.p. 68–69° (Note 12) and (Note 13).

E. 3,6-*Diazoido*-2,5-*di*-tert-*butyl*-1,4-*benzoquinone.* A solution of 10 g. (0.035 mole) of 2,5-di-*tert*-butyl-3,6-dichloro-1,4-benzoquinone in 375 ml. of methanol is cooled to 5–15°. To the solution is added, over 1–2 minutes, a solution of 5 g. (0.08 mole) of sodium azide in 15 ml. of water. The initial yellow solution becomes orange during addition of the azide. The flask is then cooled to –5° to –10° for at least 4 hours. The product precipitates from the solution and is collected by filtration, yielding 8.3–8.8 g. (80–85%) of 3,6-diazido-2,5-di-*tert*-butyl-1,4-benzoquinone, m.p. 88.9–90° (dec.), which is recrystallized at room temperature by dissolving it in a minimum amount of chloroform, filtering, and adding 2 parts of 95% ethanol to the chloroform solution. The resulting solution is cooled to –5° to –10°; the crystalline precipitate is isolated (86% recovery) by filtration (Note 14), with no appreciable change in melting point (Note 15).

F. tert-*Butylcyanoketene.* Typically, the ketene is prepared by dissolving 1 g. (0.003 mole) of 3,6-diazido-2,5-di-*tert*-butyl-1,4-benzoquinone in 10–25 ml. of anhydrous benzene (Note 16). The solution is refluxed, and the disappearance of the starting material as well as the intermediate cyclopentenedione is followed by TLC (Note 17). When the cyclopentenedione is no longer detectable, after approximately 90 minutes, the heating is stopped. The solution contains *tert*-butylcyanoketene in amounts equivalent to at least a 95% yield (Note 18).

2. Notes

1. Practical grade 2,5-di-*tert*-butyl-1,4-benzoquinone of m.p. 151–154° obtained from Eastman Organic Chemicals was used. Chlorine available from Air Products and Chemicals, Inc., was used by the checkers.
2. A satisfactory way to introduce chlorine with minimal loss of the gas is to seal the reaction flask with a two-holed stopper equipped with a gas-inlet tube, reaching just above the surface of the reaction mixture, and an exit tube, connected to a U-tube filled with mineral oil which is used as a gas-flow indicator. Chlorine is introduced from the cylinder through a safety trap at such a rate as to maintain a small positive pressure in the reaction flask.
3. The reaction can be followed by ^{1}H NMR spectroscopy. The original absorption for the vinyl proton disappears and two new absorption peaks appear, one in the vinyl region (*ca.* δ 6.5, $CDCl_3$) and the other in the methine region of the spectrum. There are two products formed, presumably the *cis*- and *trans*-isomers, in the ratio of 95:5, respectively. The checkers also obtained the same yield when the reaction quantities were doubled.
4. An analytical sample has a m.p. of 127–129°. Additional product can be recovered from the mother liquor by addition of approximately 1 l. of water followed by filtration. The yield of this product is about 31 g. (21%). However, it contains about 20% of the minor isomer (Note 3) that is not dehydrohalogenated under the reaction conditions employed in the next step. The second crop can be

recrystallized from hot methanol, giving predominantly the desired isomer. In some preparations the submitters did not separate the minor product and observed no significant loss in yield in the subsequent steps. The spectral properties of the product are as follows; IR (Nujol) cm.$^{-1}$; 1700 (C=O), 1600 (C=C); ^{1}H NMR ($CDCl_3$), δ (multiplicity, number of protons, assignment): 1.28 [s, 9H, C(CH_3)$_3$], 1.37 (s, 9H, C(CH_3)$_3$], 4.75 (s, 1H, C*H*), 6.47 (s, 1H, =C*H*).

5. The reaction mixture warms slightly, resulting in the boiling of the ether. The large amount of diethylamine hydrochloride formed transforms the reaction mixture into a thick paste.

6. The spectral properties of the product are as follows; IR (Nujol) cm.$^{-1}$: 1680 (C=O), 1660 (C=C); ^{1}H NMR ($CDCl_3$), δ (multiplicity, number of protons, assignment): 1.30 [s, 9H, C(CH_3)$_3$], 1.46 [s, 9H, C(CH_3)$_3$], 6.59 (s, 1H, =C*H*).

7. The experimental setup in this reaction is exactly as that described in (Note 2).

8. The progress of the reaction is followed by ^{1}H NMR spectroscopy. When the absorption for the vinyl proton (*ca.* δ 6.6, $CDCl_3$) is completely absent, the reaction is stopped. Several minor products that were not identified are also formed in this step.

9. IR (Nujol) cm.$^{-1}$: 1710 (C=O); ^{1}H NMR ($CDCl_3$), δ (multiplicity, number of protons, assignment): 1.1–1.4 [m, 18H, 2C(CH_3)$_3$], 4.68 (s, 1H, C*H*), 4.87 (s, 1H, C*H*).

10. Comments given in (Note 5) apply here also.

11. The solution may have a brown tint, partially masking the yellow color of the quinone. The dark color is probably due to reaction of the diethylamine with the 2,5-di-*tert*-butyl-3,6-dichloro-1,4-benzoquinone.

12. The mother liquor and wash solution are combined and concentrated to 200 ml. on a rotary evaporator. Upon cooling, a second crop (15–18 g.) of product is obtained. This second crop was a semisolid material. The spectral properties of the crystalline product are as follows; IR (Nujol) cm.$^{-1}$: 1660 (C=O); ^{1}H NMR ($CDCl_3$), δ (multiplicity, assignment): 1.45 [s, C(CH_3)$_3$].

13. Theoretically there remains about 22% of product to be isolated. Some of this material can be recovered indirectly by converting it to the diazide. The submitters diluted the mother liquor, which contains at most 23 g. (0.079 mole) of 2,5-di-*tert*-butyl-3,6-dichloro-1,4-benzoquinone, with 500 ml. of methanol, and then added, with swirling, a solution of 10.4 g. (0.0160 mole) of sodium azide in 30 ml. of water over a 2-minute period, turning, the yellow solution orange. It is cooled to –5° to –10°, and the resulting orange precipitate is collected, yielding 12 g. of the diazide. The minimum yield is thus 88%.

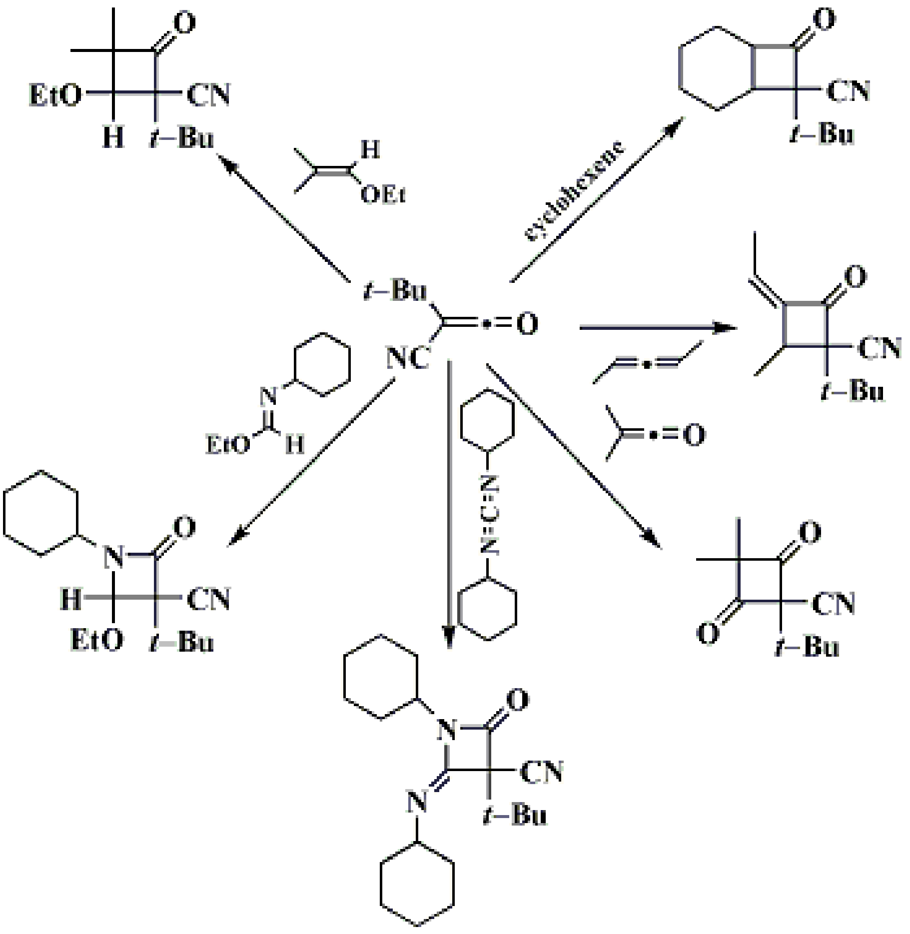
14. Water can be added to the mother liquor, and the mixture extracted with chloroform to increase the diazide yield to 95–98%. During the course of any purification method that might be employed the diazide should not be heated above 50° since decomposition occurs quite noticeably at that temperature. It is best to store the pure product below –5° in the dark since it undergoes a facile photochemical rearrangement to the cyclopentenedione.

15. IR (Nujol) cm.$^{-1}$: 2110 (N_3), 1640 (C=O); ^{1}H NMR ($CDCl_3$), δ (multiplicity, assignment): 1.31 [s, C(CH_3)$_3$].

16. The Discussion contains comments on the stability of *tert*-butylcyanoketene in various solvents.
17. TLC is carried out on silica gel using 1:1 (v/v) petroleum ether–chloroform as eluent. The cyclopentenedione has an R_f value about half that of the diazide, and can be detected with an UV lamp when silica gel containing fluorescent indicator is used. The ketene undoubtedly reacts with the hydroxyl groups of the silica gel and remains at the origin. The checkers found the reaction to be complete in 1.5–2 hours. The yield was established by the checkers to be ≥ 95% by ^{1}H NMR, by integration studies in the presence of an internal standard.
18. The submitters have not been successful in isolating *tert*-butylcyanoketene by any method. If the solvent is removed, the ketene polymerizes. The spectral properties of the product are as follows; IR (C_6H_6) cm.$^{-1}$: 2220 (C≡N), 2130 (C=C=O); ^{1}H NMR (C_6H_6), δ (multiplicity, assignment): 0.75 [s, C(CH_3)$_3$].

3. Discussion

In benzene at room temperature, *tert*-butylcyanoketene (TBCK) does not undergo rapid self-condensation;[2] however, it is quite reactive toward cycloaddition reactions with alkenes, allenes, ketenes, imines, and formimidates.[3] The mechanisms of a number of these cycloaddition reactions have been investigated and in some cases have been shown to involve the formation of a zwitterionic intermediate. Typical examples of TBCK cycloadditions are summarized in the formula below.



The ketene is less stable in nonaromatic hydrocarbon solvents than in aromatic solvents. For example, it has a half-life of greater than 7 days in benzene at 25°. On the other hand, in cyclohexane at the same temperature its half-life is only a few hours. All attempts to isolate *tert*-butylcyanoketene have failed. Either removal of the solvent or cooling the solution to low temperature (−70°) causes polymerization of the ketene, a very efficient process, giving a white solid polymer which appears to have repeating ketenimine units. This assignment is consistent with the very strong absorption at 2140 cm^{-1} in the IR spectrum.[4]

The method described here for the synthesis of *tert*-butylcyanoketene has marked advantages over other possible classical routes, *e.g.*, dehydrohalogenation of the corresponding acid chloride. The only other product formed is molecular nitrogen and no external catalyst, *e.g.*, triethylamine, is necessary. In fact, when *tert*-butylcyanoketene reacts with triethylamine, or when α-*tert*-butyl-α-cyanoacetyl chloride is subjected to dehydrohalogenation conditions, 1,3-di-*tert*-butyl-1,3-dicyanoallene is immediately formed and no ketene can be detected.

tert-Pentylcyanoketene can be prepared in an analogous fashion starting from the commercially available 2,5-di-*tert*-pentylbenzoquinone. This ketene seems to be very similar in stability and reactivity to the *tert*-butyl homolog. Other cyanoketenes which have been prepared from azidoquinones or related compounds include dicyano-, chlorocyano-, bromocyano-, iodocyano-, methylcyano-, and isopropylcyanoketene.[3] However, all of these must be generated *in situ* since they undergo rapid self-condensation in the absence of a ketenophile.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

3,6-Diazoido-2,5-di-tert-butyl-1,4-benzoquinone

ethanol (64-17-5)

acetic acid (64-19-7)

Benzene (71-43-2)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

chloroform (67-66-3)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

cyclohexane (110-82-7)

chlorine (7782-50-5)

diethylamine (109-89-7)

sodium azide (26628-22-8)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

diethylamine hydrochloride (660-68-4)

triethylamine (121-44-8)

Butanenitrile, 2-carbonyl-3,3-dimethyl-, tert-BUTYLCYANOKETENE (29342-22-1)

cyclopentenedione

isopropylcyanoketene

2,5-di-tert-butyl-1,4-benzoquinone

2,5-Di-tert-butyl-5,6-dichloro-2-cyclohexene-1,4-dione (33611-72-2)

3-Chloro-2,5-di-tert-butyl-1,4-benzoquinone (33611-70-0)

2,5-Di-tert-butyl-3,5,6-trichloro-2-cyclohexene-1,4-dione (117257-58-6)

2,5-Di-tert-butyl-3,6-dichloro-1,4-benzoquinone, 2,5-Di-tert-butyl-3,6-dichloro-1,4-benezoquinone (33611-73-3)

3,6-diazido-2,5-di-tert-butyl-1,4-benzoquinone (29342-21-0)

α-tert-butyl-α-cyanoacetyl chloride

1,3-di-tert-butyl-1,3-dicyanoallene

tert-Pentylcyanoketene

2,5-di-tert-pentylbenzoquinone

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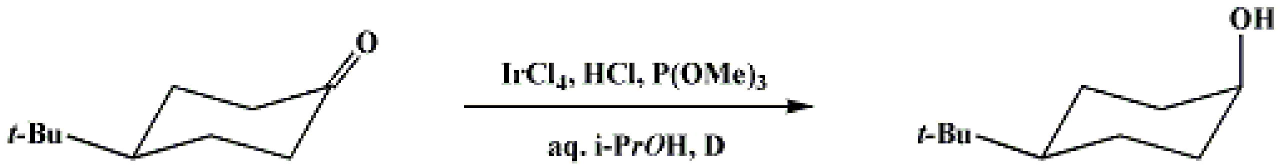
Organic Syntheses, CV 6, 215

cis-4-*tert*-BUTYLCYCLOHEXANOL

[Cyclohexanol, 4-(1,1-dimethylethyl)-, *cis*-]



Submitted by E. L. Eliel[1], T. W. Doyle, R. O. Hutchins[2], and E. C. Gilbert.
Checked by Mitchell Winnik and Ronald Breslow.

1. Procedure

To a solution of 4.0 g. (0.012 mole) of iridium tetrachloride (Note 1) in 4.5 ml. of concentrated hydrochloric acid is added 180 ml. of water followed by 52 g. (50 ml., 0.42 mole) of trimethyl phosphite (Note 2). This solution then is added to a solution of 30.8 g. (0.200 mole) of 4-*tert*-butylcyclohexanone (Note 3) in 635 ml. of 2-propanol contained in a 2-l. flask equipped with a reflux condenser. The solution is heated at reflux for 48 hours (Note 4), at which time the 2-propanol is removed with a rotary evaporator. The remaining solution is diluted with 250 ml. of water and extracted with four 150-ml. portions of diethyl ether. The combined ether extracts are washed with two 100-ml. portions of water, which are combined with the aqueous residue (Note 5), dried over magnesium sulfate or potassium carbonate, and concentrated on a rotary evaporator, yielding 29–31 g. (93–99%) of *cis*-4-*tert*-butylcyclohexanol as a white solid. Analysis of the crude product by GC shows it contains 95.8–96.2% *cis*-alcohol and 4.2–3.8% of the *trans* isomer with essentially no ketone remaining (Note 6). Recrystallization from 40% aqueous ethanol affords greater than 99% pure *cis*-alcohol, m.p. 82–83.5° after sublimation (Note 7).

2. Notes

1. Iridium tetrachloride was originally obtained from Platinum Chemicals, Inc., Box 565, Asbury Park, New Jersey 07712, or from Alfa Products, Thiokol/Ventron Division, P.O. Box 299, 152 Andover St., Danvers, Massachusetts 01923. More recently, the procedure has been repeated successfully with material obtained from Pfaltz and Bauer, Inc., a subsidiary of Aceto Chemical Co., Inc., 375 Fairfield Ave., Stamford, Connecticut 06902.
2. The order of mixing the catalyst components is required for good results, and the sequence described should be followed. Particular care should be taken *not* to add the trimethyl phosphite before the water, as the reaction between it and concentrated hydrochloric acid is extremely violent.
3. 4-*tert*-Butylcyclohexanone was obtained from Dow Chemical Company or Aldrich Chemical Co. Inc.
4. The reaction solution is often dark-colored at the beginning but lightens as reflux continues. The reflux time may be varied with the amount of ketone to be reduced. The completeness of the reaction may be followed by removing small aliquots, working up these samples as described in the text, and analyzing the product mixture by GC (see

(Note 6)).

5. The iridium catalyst used in this preparation may be regenerated by reducing the volume of the aqueous residue to about 200 ml. at diminished pressure. This solution is then used instead of the iridium tetrachloride and water called for in the procedure.

6. The product was analyzed by GC using a 9-ft. 20% Carbowax 20M on 45/60 Chromosorb W column at 150°. The order of increasing retention times is: ketone, *cis*-alcohol, *trans*-alcohol.

7. Recrystallization is best accomplished by dissolving the crude product in hot ethanol (approx. 35 ml. per 10 g.) followed by adding water (approx. 25 ml. per 10g.) and allowing the solution to cool slowly to 0°. The fluffy white needles are filtered using a sintered-glass funnel and dried over P_2O_5 at atmospheric pressure. Recooling the filtrate affords a second crop of product, for an overall yield of 75–87%.

3. Discussion

4-*tert*-Butylcyclohexanol has been prepared from *p*-*tert*-butylphenol by reduction under a variety of conditions.[3,4] Eliel and Ro[5] obtained *cis*-rich 4-*tert*-butylcyclohexanol by the reduction of 4-*tert*-butylcyclohexanone with hydrogen on platinum oxide in glacial acetic acid containing some hydrogen chloride; Sommerville and Theimer have similarly reduced *p*-*tert*-butylphenol with 5% rhodium on carbon.[6,7] They have also prepared *cis*-rich alcohol by fractional distillation of the *cis*-*trans* mixture over an equilibrating catalyst, such as aluminum isopropoxide in the presence of 4-*tert*-butylcyclohexanone.[6] Eliel and Nasipuri[8] have also obtained 4-*tert*-butylcyclohexanol containing 80–92% of the *cis* isomer by the reduction of 4-*tert*-butylcyclohexanone with isobornyloxyaluminum dichloride.

The present[9] procedure employs a readily available starting material and produces essentially pure *cis* isomer in good yield. In view of the fact that the catalyst may be reused several times with little loss in stereoselectivity, the expense of the iridium tetrachloride is not a serious impediment.

The method is useful in the preparation of other axial alcohols. Henbest[9] has reported the reductions of 3-*tert*-butylcyclohexanone, 3,3,5-trimethylcyclohexanone, and cholestanone to the axial alcohols by this procedure, although for the preparation of cholestan-3α-ol the procedure of Edward[10] is preferred by the checkers. Recently[11] 2,4,4-trimethylcyclohexanone has been reduced to the pure axial alcohol by this method in 90% yield.

Since this preparation was submitted, a number of reductions of 4-*tert*-butylcyclohexanone to the *cis* alcohol, with 93–100% selectivity, using various bulky, complex metal hydrides have been described: lithium tri-*sec*-butylborohydride (L-Selectride),[12,13] lithium trisiamylborohydride,[13,14,15] lithium tri-*trans*-2-methylcyclopentylborohydride,[14] lithium dimesitylborohydride,[16] lithium 2,6-di-*tert*-butylphenoxyneopentoxyaluminumhydride;[17] high (94–99%) selectivity is also attained by catalytic hydrogenation with various rhodium catalysts.[18,19] Hydrogenation over rhodium-on-carbon[18] (94% *cis*) followed by purification with liquid chromatography appears to be an attractive method, one which avoids the need for special reagents.

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

cis-rich 4-tert-butylcyclohexanol

lithium trisiamylborohydride

rhodium-on-carbon

ethanol (64-17-5)

potassium carbonate (584-08-7)

hydrogen chloride, hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ether, diethyl ether (60-29-7)

hydrogen (1333-74-0)

platinum oxide

carbon (7782-42-5)

2-propanol (67-63-0)

aluminum isopropoxide

magnesium sulfate (7487-88-9)

Cholestanone (566-88-1)

trimethyl phosphite (121-45-9)

iridium tetrachloride (10025-97-5)

iridium (7439-88-5)

rhodium (7440-16-6)

isobornyloxyaluminum dichloride

3,3,5-trimethylcyclohexanone (873-94-9)

cholestan-3α-ol

2,4,4-trimethylcyclohexanone

lithium dimesitylborohydride

4-tert-Butylcyclohexanone (98-53-3)

4-tert-Butylcyclohexanol (98-52-2)

p-tert-butylphenol (98-54-4)

cis-4-tert-Butylcyclohexanol, Cyclohexanol, 4-(1,1-dimethylethyl)-, cis- (937-05-3)

3-tert-butylcyclohexanone (936-99-2)

lithium tri-sec-butylborohydride

lithium tri-trans-2-methylcyclopentylborohydride

lithium 2,6-di-tert-butylphenoxyneopentoxyaluminumhydride

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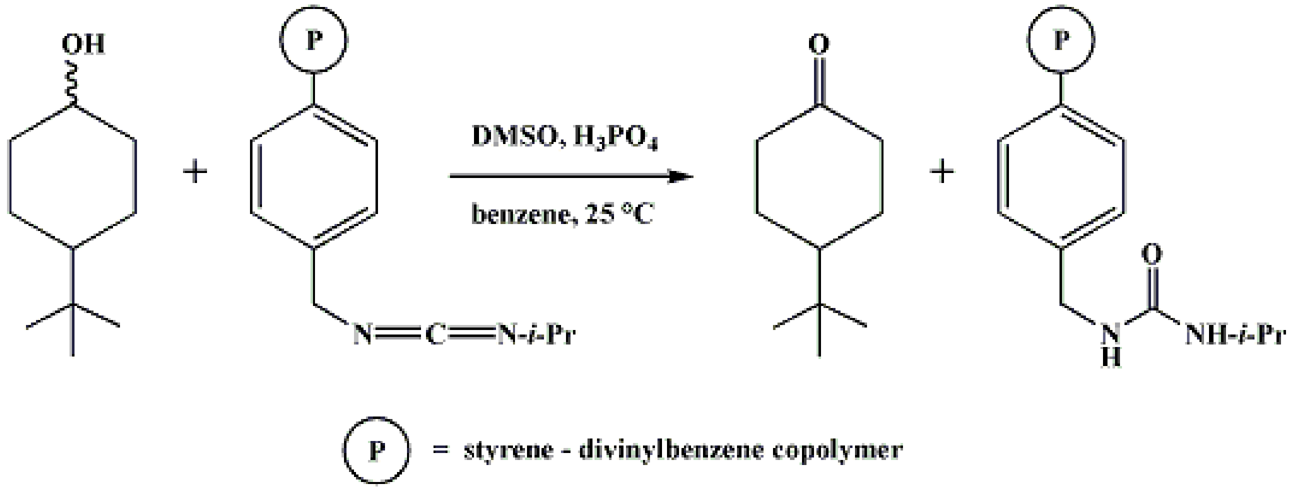
POLYMERIC CARBODIIMIDE. MOFFAT OXIDATION: 4-*tert*-BUTYLCYCLOHEXANONE

[Cyclohexanone, 4-(1,1-dimethylethyl)-]



Submitted by Ned M. Weinshenker[1], Chah M. Shen, and Jack Y. Wong.
Checked by A. Fukuzawa and S. Masamune.

1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required

A 250-ml., three-necked, round-bottomed flask equipped with a mechanical stirrer, a gas-inlet, and a stopper is charged with 540 mg. (0.00346 mole) of a mixture of *cis*- and *trans*-4-*tert*-butylcyclohexanols (Note 1), 50 ml. of anhydrous benzene (Note 2), and 25 ml. of anhydrous dimethyl sulfoxide (Note 3). While a slight positive pressure of argon is maintained in the system, 13.19 g. of carbodiimide resin (Note 4) is added, followed by 0.2 ml. of dimethyl sulfoxide (Note 3) containing 98 mg. (0.0010 mole) of anhydrous orthophosphoric acid (Note 5). The resulting mixture is stirred at room temperature for 3.5 days. The beads are then separated by filtration and washed with three 100-ml. portions of diethyl ether, and the combined filtrates are washed with five 100-ml. portions of water. After evaporation of the organic phase to dryness, the residue crystallizes, providing 446–450 mg. (83–84%) of crude 4-*tert*-butylcyclohexanone, m.p. 42–45° (Note 6). The deactivated carbodiimide resin can be regenerated by treatment with triethylamine and 4-toluenesulfonyl chloride (Note 4).

2. Notes

1. This mixture is available from Aldrich Chemical Company, Inc. The checkers used a 7:93 mixture of the *cis*- and *trans*-isomers, prepared by lithium aluminum hydride reduction of 4-*tert*-butylcyclohexanone and recrystallization of the crude product. The ketone was purchased from Aldrich Chemical Company, Inc.
2. Benzene was dried by distillation from sodium.

3. The submitters dried dimethyl sulfoxide over Linde-type 3A molecular sieves. The checkers distilled this reagent from calcium hydride at 10 mm. prior to use.
4. The amount of resin used contains about 0.012 mole of active carbodiimide. Methods for preparing this reagent, determining its carbodiimide content, and regenerating spent resin are described in *Org. Synth.*, **Coll. Vol. 6**, 951 (1988).
5. Anhydrous orthophosphoric acid was prepared according to the equation: $P_2O_5 + 3H_2O$
$2H_3PO_4$
The submitters added 5.88 ml. of 85% phosphoric acid to 3.98 g. of phosphorous pentoxide and heated the mixture for 15 minutes or until all of the solid had dissolved. The checkers placed 71.0 g. of phosphorous pentoxide in a flask, cooled it in ice, and cautiously added 27 ml. of water.
6. IR($CHCl_3$) cm.$^{-1}$: 1712 (C=O). GC analysis (10% Carbowax 20M, 3 mm. by 1.8 m., 180°) showed the crude product to be 97% pure. 4-*tert*-Butylcyclohexanone has been reported to melt at 49.5–51°.[2]

3. Discussion

The general procedure described here was originally published by the submitters.[3] Both ketones and aldehydes may be prepared, and this method is particularly effective when the mild conditions of the Moffat oxidation are required, but the dicyclohexylurea by-product formed with the usual reagents causes purification problems.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 951

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

phosphorous pentoxide

cis- and trans-4-tert-butylcyclohexanols

Benzene (71-43-2)

diethyl ether (60-29-7)

sodium (13966-32-0)

phosphoric acid, orthophosphoric acid (7664-38-2)

lithium aluminum hydride (16853-85-3)

dimethyl sulfoxide (67-68-5)

triethylamine (121-44-8)

calcium hydride (7789-78-8)

dicyclohexylurea

carbodiimide

argon (7440-37-1)

Cyclohexanone, 4-(1,1-dimethylethyl)-, 4-tert-Butylcyclohexanone (98-53-3)

4-toluenesulfonyl chloride (98-59-9)

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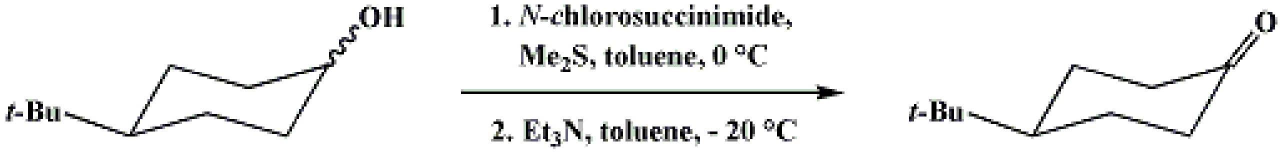
OXIDATION OF ALCOHOLS BY METHYL SULFIDE – *N*-CHLOROSUCCINIMIDE – TRIETHYLAMINE: 4-*tert*-BUTYLCYCLOHEXANONE

[Cyclohexanone, 4-(1,1-dimethylethyl)-]



Submitted by E. J. Corey[1], C. U. Kim[2], and P. F. Misco[2].
Checked by S. Yamamoto and W. Nagata.

1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A 1-l., three-necked, round-bottomed flask equipped with a mechanical stirrer (Note 1), a thermometer, a dropping funnel, and an argon-inlet tube is charged with 8.0 g. (0.060 mole) of *N*-chlorosuccinimide (Note 2) and (Note 3) and 200 ml. of toluene (Note 4). While a continuous positive argon pressure is maintained, the solution is stirred and cooled to 0°, and 6.0 ml. (0.10 mole) of methyl sulfide (Note 2) is added. A white precipitate appears immediately after addition of the sulfide. The mixture is cooled to –25° using a carbon tetrachloride-dry ice bath (Note 5), and a solution of 6.24 g. (0.0400 mole) of 4-*tert*-butylcyclohexanol (mixture of *cis*- and *trans*-) (Note 2) in 40 ml. of toluene is added dropwise over 5 minutes (Note 6). The stirring is continued for 2 hours at –25° ((Note 5)) before a solution of 6.0 g. (0.59 mole) of triethylamine (Note 2) in 10 ml. of toluene is added dropwise over 3 minutes (Note 7). The cooling bath is removed; after 5 minutes 400 ml. of diethyl ether is added (Note 8). The organic layer is washed with 100 ml. of 1% hydrochloric acid, then with two 100-ml. portions of water (Note 9), dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The residue is transferred to a 50-ml., round-bottomed flask and distilled bulb to bulb at 120° (25 mm.), yielding 5.54–5.72 g. (90–93%) of 4-*tert*-butylcyclohexanone, m.p. 41–45° (Note 10).

2. Notes

1. Efficient magnetic stirring could be used as well.
2. The submitters used *N*-chlorosuccinimide, 4-*tert*-butylcyclohexanol, methyl sulfide, and triethylamine, available from Aldrich Chemical Company, Inc., without further purification.
The checkers used *cis*- and *trans*-4-*tert*-butylcyclohexanol (36:64) obtained from E. Merck A G, Darmstadt, methyl sulfide obtained from Tokyo Kasei Kogyo Co., Ltd., and

triethylamine obtained from Wako Pure Chemical Industries, Ltd., without further purification.

3. The checkers observed that, when *N*-chlorosuccinimide of 93–95% purity, m.p. 128–132° (checked by iodometry), obtained from E. Merck A G, Darmstadt, was used without purification, the oxidation was incomplete, resulting in 93–94% yields of a product containing a 12–15% amount of the starting alcohol (a mixture of the *cis*- and *trans*-). The use of 98% pure *N*-chlorosuccinimide, m.p. 150–151° (recrystallized from benzene), resulted again in recovery of the alcohol in a considerable amount, mainly because of low solubility of the pure reagent in toluene. Therefore, the checkers modified slightly the earlier part of the procedure as follows: the 98% pure *N*-chlorosuccinimide (8.0 g., 0.06 mole) m.p. 150–151°, is dissolved in 400 ml. of toluene (twice as much as the volume used by the submitters) at 40°, and the solution is cooled to room temperature, stirred under nitrogen atmosphere, and cooled to 0–5°. Methyl sulfide (6 ml., 0.10 mole) is added at this temperature and, after addition, the reaction mixture is stirred for an additional 20 minutes at 0–3°, during which time white precipitate appeared.

4. Reagent grade toluene employed by the submitters was obtained from Mallinckrodt Chemical Works. The checkers used reagent grade toluene purchased from Wako Pure Chemical Industries, Ltd., and dried over molecular sieves (4 Å) before use. Regarding the volume of the toluene used by the checkers, see (Note 3).

5. The checkers observed that the internal temperature was –20° with this cooling mixture.

6. The checkers observed that the reaction was slightly exothermic as judged from an internal temperature rise of *ca.* 5°.

7. The checkers needed a little longer time (3–5 minutes) for this operation to maintain the internal temperature at –15 to –20°.

8. The checkers successively added 100 ml. 1% hydrochloric acid to the reaction mixture.

9. Vigorous shaking is necessary for complete removal of succinimide. The triethylamine hydrochloride is also removed in this step. The methyl sulfide codistils with the ether.

10. An authentic sample from Aldrich Chemical Company, Inc., had m.p. 45–50°. The product was analyzed by GC at 80° on F & M Research chromatograph model 1810 with 3% OV-17 column, which indicated the contamination of the product by 4-*tert*-butylcyclohexanol (<2%) and 4-*tert*-butylcyclohexylmethyl methylthiomethyl ether (<2%).[3] The submitters reported a yield of 6.0 g. (96%) of purity greater than 96%. The checkers recrystallized the product from petroleum ether (dissolved at room temperature and cooled to –20°) and obtained a pure product, m.p. 45–46° (88.5% recovery); IR ($CHCl_3$) cm^{-1}: 1712 (C=O); ^{1}H NMR ($CDCl_3$), δ (multiplicity, number of protons, assignment): 0.93 [s, 9H, $C(CH_3)_3$], 1.3–2.2 (m, 5H, CH_2CHCH_2), and 2.2–2.5 (m, 4H, CH_2COCH_2).

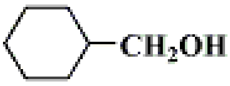
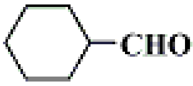
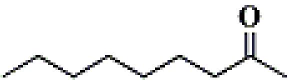
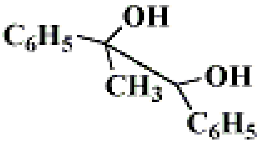
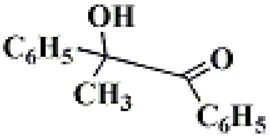
3. Discussion

The procedure described here is general for the oxidation of primary and secondary alcohols to carbonyl compounds,[3] but not for allylic and dibenzylic alcohols, which give halides in high yields.[4] The yields of carbonyl compounds are usually high, and the formation of methyl thiomethyl ether can be minimized in nonpolar media. Some examples are listed in Table I. The quantitative conversion of catechols to *o*-quinones using this oxidation procedure has been reported.[5] For oxidation of allylic and dibenzylic alcohols to the corresponding carbonyl

compounds, a dimethyl sulfoxide–chlorine reagent[6] is suitable.

TABLE I

OXIDATION OF PRIMARY AND SECONDARY ALCOHOLS[3]

Alcohol	Product	Yield (%)
$C_6H_5CH_2OH$	C_6H_5CHO	90
		96
		94
		91
		86[7]

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4. E. J. Corey, C. U. Kim, and M. Takeda, *Tetrahedron Lett.*, 4339 (1972).
5. J. P. Marino and A. Schwatz, *J. Chem. Soc., Chem. Commun.*, 812 (1974).
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7. E. J. Corey and C. U. Kim, *Tetrahedron Lett.*, 287 (1974).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

alcohol (64-17-5)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether, diethyl ether (60-29-7)

nitrogen (7727-37-9)

chlorine (7782-50-5)

toluene (108-88-3)

magnesium sulfate (7487-88-9)

methyl sulfide (75-18-3)

dimethyl sulfoxide (67-68-5)

triethylamine (121-44-8)

N-chlorosuccinimide (128-09-6)

Triethylamine hydrochloride (554-68-7)

argon (7440-37-1)

Cyclohexanone, 4-(1,1-dimethylethyl)-, 4-tert-Butylcyclohexanone (98-53-3)

trans-4-tert-Butylcyclohexanol (21862-63-5)

4-tert-Butylcyclohexanol (98-52-2)

cis-4-tert-Butylcyclohexanol (937-05-3)

4-tert-butylcyclohexylmethyl methylthiomethyl ether

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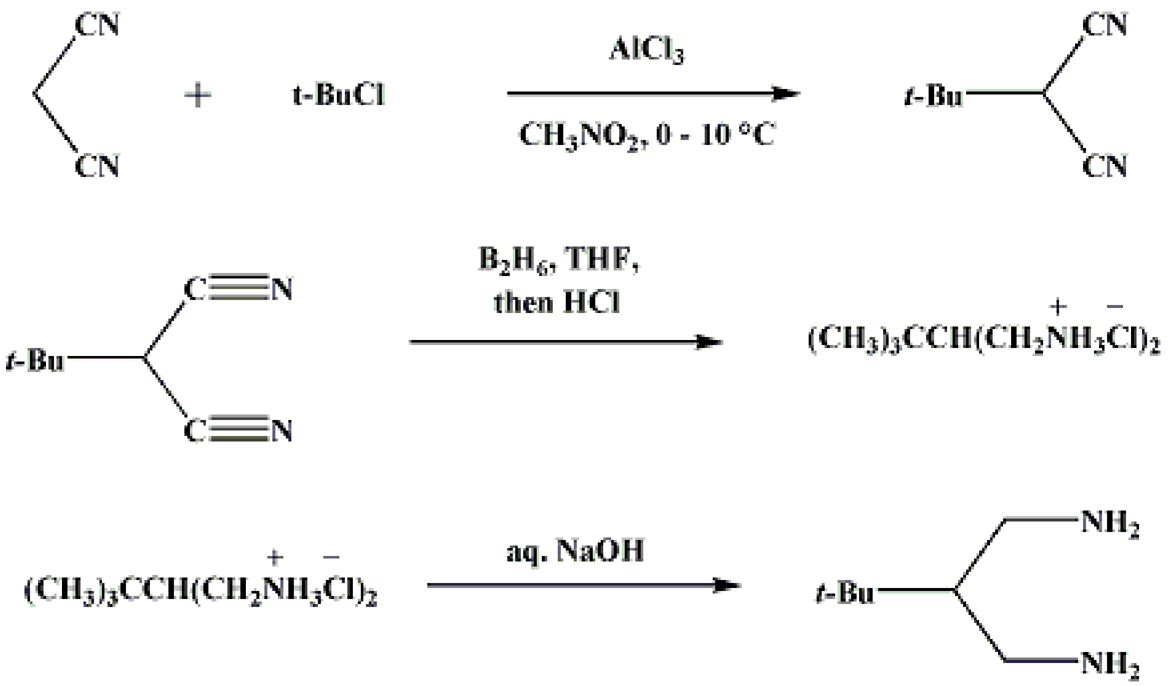
Organic Syntheses, CV 6, 223

2-*tert*-BUTYL-1,3-DIAMINOPROPANE

[1,3-Propanediamine, 2-(1,1-dimethylethyl)-]



Submitted by R. O. Hutchins[1] and B. E. Maryanoff.
Checked by Abraham Pinter and Ronald Breslow.

1. Procedure

A. tert-*Butylmalononitrile.* A dry, 2-l., three-necked flask equipped with a thermometer, mechanical stirrer, and a Claisen adapter fitted with a dropping funnel and condenser protected with a drying tube is charged with 200 ml. of nitromethane (Note 1). The flask is cooled to 0° in an ice–salt bath (Note 2), and anhydrous powdered aluminum chloride (90.0 g., 0.674 mole) is added, with slow stirring, through a powder funnel that temporarily replaces the thermometer. The temperature may rise to *ca.* 50° but quickly drops to 0°. A solution of 45.0 g. (0.682 mole) of malononitrile (Note 3) in 50 ml. of nitromethane is added through the dropping funnel at a rate such that the temperature is kept below 10° (approximately one hour). This is followed by slow, dropwise addition of a solution of 150 g. (1.62 moles) of *tert*-butyl chloride in 50 ml. of nitromethane at a rate such that the temperature is maintained below 10° (approximately 3–4 hours). The reaction mixture is stirred at 0–5° for 10 hours before 1 l. of saturated sodium hydrogen carbonate (*ca.* 80 g. in 1000 ml. of water) is added slowly and cautiously (still in the cold), keeping the temperature below 10°. The mixture is poured into a 3 or 4 l. beaker and solid sodium hydrogen carbonate (*ca.* 100 g.) is added in *small* portions, with stirring. The organic phase is separated, and the aqueous layer extracted with three half-volume portions of dichloromethane, which are concentrated on a rotary evaporator, combined with the organic phase, and

concentrated further. The resultant brown oil is subjected to steam distillation. The first fraction is collected using a cold water condenser until solidification is observed in the condenser, at which time warm water is passed through the condenser and the receiver is changed (Note 5). The product is collected until occasional passage of cold water through the condenser no longer causes apparent solidification. At this point, the receiver is changed again, and a third fraction (*ca.* 500 ml.) is collected. The middle fraction is cooled in ice and filtered with vacuum through a medium fritted glass funnel, yielding 48–50 g. of light-yellow product. Extraction of the filtrate with two half-volumes of diethyl ether followed by evaporation gives an additional small amount (*ca.* 2 g.) of product. Another small crop of product may be gleaned from the first and third steam distillation fractions by separating any organic phase, removing distillable material on a rotary evaporator, cooling, and filtering the resulting solid. The total combined yield of crude product is 54–58 g. (65–70%). Further purification is accomplished by careful sublimation at 80–90 mm. (*ca.* 85°), giving 52–56.5 g. (63–68%) of white, waxy dinitrile, m.p. 76–79° with softening at 71°.

B. *2-tert-Butyl-1,3-diaminopropane.* A dry, 500-ml., three-necked flask fitted with a magnetic stirrer, nitrogen inlet, dropping funnel, and condenser attached to an acetone gas trap (Note 6) is flushed with dry nitrogen for 30 minutes and charged with purified *tert*-butylmalononitrile (30.5 g., 0.250 mole), sodium borohydride (17.5 g., 98% assay, 0.453 mole), and 150 ml. of dry tetrahydrofuran (Note 1) A dry nitrogen atmosphere is maintained while boron trifluoride diethyl etherate (85.3 g., 0.600 mole) (Note 7) in 50 ml. of dry tetrahydrofuran is added dropwise, with slow magnetic stirring, at a rate that permits gentle reflux. The addition takes about 4 hours (Note 8). The mixture is stirred for an additional 90 minutes, hydrolyzed by the very cautious dropwise addition of 30 ml. of concentrated hydrochloric acid, and transferred to a 1-l. flask, with rinsing by 100 ml. of tetrahydrofuran. The solution is evaporated to dryness on a rotary evaporator, yielding a dry, white, solid mass, to which is added a small portion (*ca.* 10 ml.) of 125 ml. of aqueous 40% (w/w) sodium hydroxide. The mixture is triturated with a glass rod and warmed on a steam bath until a reaction begins; heat is generated, and white smoke is evolved. The reaction is controlled by cooling in an ice bath. When the reaction appears to have subsided at room temperature, the trituration is repeated cautiously until all 125 ml. of the hydroxide solution is added. The resulting mixture is warmed for 30 minutes on a steam bath, with occasional stirring, cooled, and filtered with vacuum. The solid material is washed with ten 20-ml. portion of ether. The filtrate is separated, and the aqueous phase is extracted with three 100-ml. portions of ether. The combined ethereal extracts and organic phase are dried over anhydrous sodium sulfate. The drying agent is filtered and washed with ether, and the filtrate concentrated on a rotary evaporator. The residue is fractionally distilled at reduced pressure through a short Vigreux column. After removal of residual solvent and collection of a small forerun, 11.5–15.5 g. (36–48%) of product is obtained, b.p. 92.5–95° (21 mm.), 96–98° (27 mm.), n_D^{28} 1.4570–1.4585. Analysis of the product by GC (OV-1 column) indicated the purity to be *ca.* 95% (Note 9).

2. Notes

1. Fisher Scientific Company certified reagent grade was used without further purification from a freshly opened bottle.
2. As a convenience, the reaction may be conducted in a refrigerated room, in which case it will be unnecessary to replenish the ice during the course of the reaction.
3. Malononitrile was obtained from Eastman Organic Chemicals and distilled prior to use, b.p. 80–82° (3 mm.).
4. The commercial material was distilled prior to use, b.p. 50–51°.
5. Passing warm water through the condenser prevents blockage by solid product; otherwise, pressure may build and force the joints apart. As an alternative, steam may be passed through the condenser periodically.
6. Impure diborane is a hazardous material and may combust explosively on contact with air. Therefore, precautions must be taken to prevent escape from the reaction.
7. The commercial material was distilled prior to use, b.p. 59–60° (20 mm.). The material employed should not be more than a few days old.
8. The duration of the reaction is important and should not be curtailed. For example, if one is operating on a one-tenth scale, the reaction should be heated at gentle reflux for an additional 3.5 hours after the addition (25 minutes).
9. A sample of the compound, collected by GC, gave the correct analyses for carbon, hydrogen, and nitrogen. Two solid derivatives were prepared in good yield and both gave correct analyses.

3. Discussion

This preparation illustrates the alkylation of malononitrile under acid-catalyzed conditions, and the use of diborane for the reduction of a dinitrile to a diamine. The procedure for the preparation of *tert*-butylmalononitrile has been outlined briefly by Boldt and co-workers.[2] The generation of diborane *in situ* and the general method for nitrile reduction is that described by Brown and co-workers.[3] Attempts to reduce the dinitrile to the diamine by other methods including catalytic hydrogenation (5% rhodium on alumina, 5 atm.), lithium aluminum hydride, and lithium aluminum hydride–aluminum chloride were singularly unsuccessful.

References and Notes

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3. H. C. Brown and B. C. Subba Rao, *J. Am. Chem. Soc.*, **82**, 681 (1960); and more recently, H. C. Brown, P. Heim, and N. M. Yoon, *J. Am. Chem. Soc.*, **92**, 1637 (1970).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

diborane

hydrochloric acid (7647-01-0)

ether, diethyl ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

sodium hydrogen carbonate (144-55-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

carbon (7782-42-5)

aluminum chloride (3495-54-3)

tert-Butyl chloride (507-20-0)

hydroxide (14280-30-9)

Nitromethane (75-52-5)

dichloromethane (75-09-2)

Malononitrile (109-77-3)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

boron trifluoride diethyl etherate (109-63-7)

sodium borohydride (16940-66-2)

rhodium (7440-16-6)

1,3-Propanediamine, 2-(1,1-dimethylethyl)-, 2-tert-Butyl-1,3-diaminopropane (56041-82-8)

tert-Butylmalononitrile (4210-60-0)

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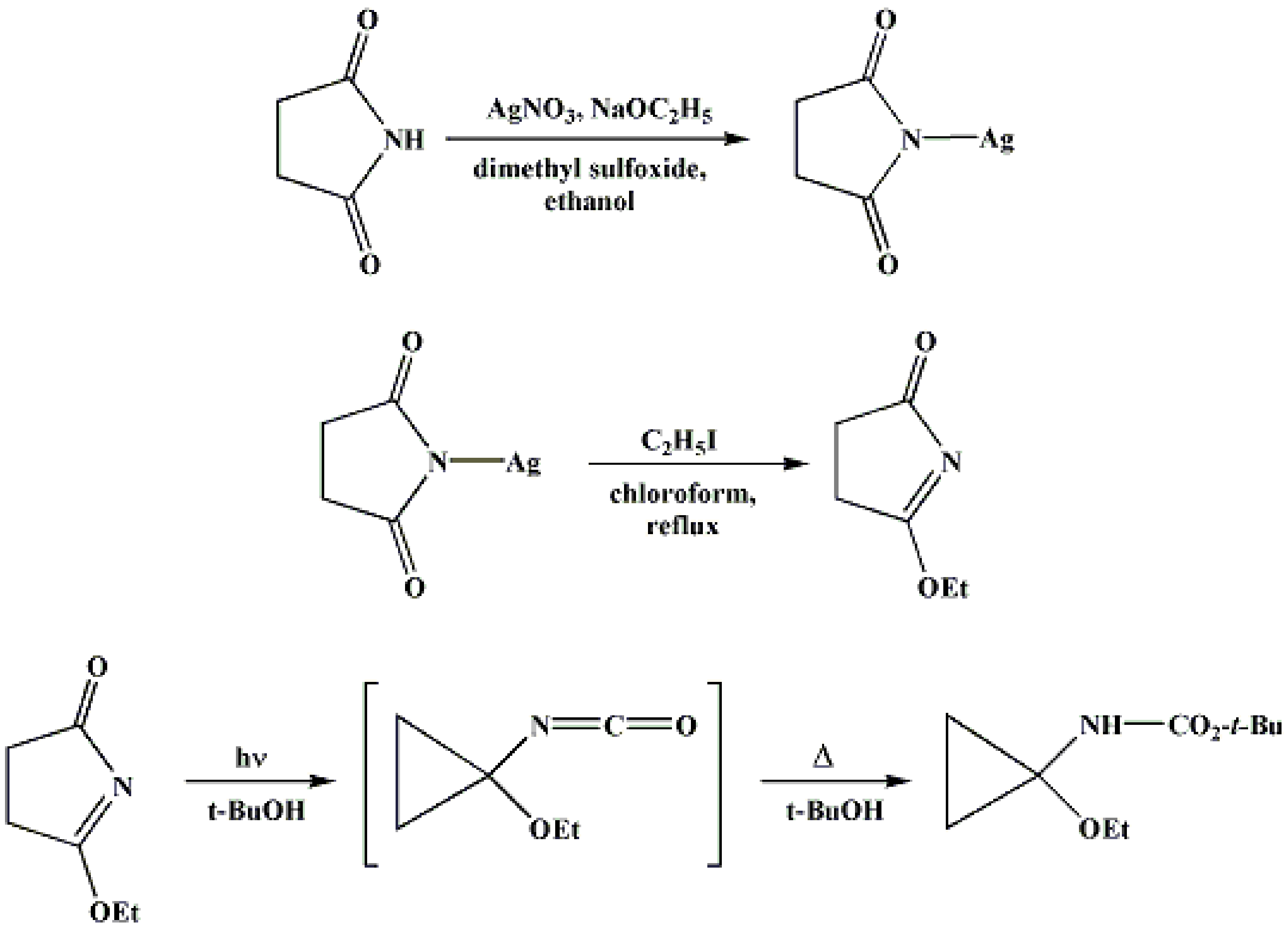
Organic Syntheses, CV 6, 226

PHOTOCHEMICAL RING CONTRACTION OF 2-ETHOXYPYRROLIN-5-ONES TO CYCLOPROPANONE DERIVATIVES: *tert*-BUTYL *N*-(1-ETHOXYCYCLOPROPYL) CARBAMATE

[Carbamic acid, (1-ethoxycyclopropyl)-, 1,1-dimethylethyl ester]



Submitted by Geoffrey C. Crockett and Tad H. Koch[1].
Checked by S. Boettger and M. F. Semmelhack.

1. Procedure

Caution! The photochemical reaction in Part C should be carried out behind a light-absorbent cover or shield. Protective goggles should be worn to avoid exposure of the eyes to ultraviolet light.

A. *Succinimide silver salt (Note 1).* A 3-l., two-necked, round-bottomed flask equipped with a mechanical stirrer and a pressure-equalizing dropping funnel is charged with a solution of 28.9 g. (0.292 mole) of succinimide (Note 2) in 1.2 l. of absolute ethanol (Note 3). A solution of 48.58 g. (0.2860 mole) of silver nitrate in 200 ml. of dimethyl sulfoxide (Note 4) is added in one portion. The resulting solution is stirred as 700 ml. (0.280 mole) of 0.400 *M* sodium ethoxide in ethanol (Note 5) and (Note 6) is added dropwise over 1.5 hours. The off-white silver salt begins to precipitate after *ca.* 140 ml. of the sodium ethoxide solution has been added. Stirring is continued for 45 minutes

after the addition is completed, and the reaction mixture is then stored in a refrigerator at *ca.* 5° overnight to complete the precipitation and aggregation of the product.

The precipitate is collected on filter paper (Note 7) in a Büchner funnel by vacuum filtration and washed with 100 ml. of absolute ethanol. The solid is slurried in three 75-ml. portions of distilled water (Note 8), 100 ml. of absolute ethanol, two 100-ml. portions of reagent grade acetone, and two 100-ml. portions of anhydrous ethyl ether. The filter cake is pressed dry in the funnel with suction using a piece of rubber dam, transferred to a tared, 500-ml., round-bottomed flask, and dried under reduced pressure (0.01 mm.) at room temperature for 24 hours (Note 9), yielding 51–54 g. (88–94%) of the silver salt of succinimide.

B. *2-Ethoxypyrrolin-5-one.* The flask containing 51–54 g. (0.25–0.26 mole) of succinimide silver salt is equipped with a magnetic stirring bar (Note 10), a heating mantle, and reflux condenser bearing a silica gel drying tube. The solid is suspended in 295 ml. of dry chloroform (Note 11), and 51.4 g. (26.4 ml., 0.330 mole) of ethyl iodide is added in one portion. The flask is covered with aluminum foil, and the mixture is stirred vigorously and heated under reflux for 48 hours. The mixture is cooled, the silver iodide is removed by vacuum filtration through Celite, and the filter cake is washed well with dry chloroform. The filtrate is concentrated by rotary evaporation to a mixture of a dark liquid and a white solid identified as succinimide. Anhydrous diethyl ether is added to dissolve the liquid, and the resulting suspension is filtered through a plug of glass wool, separating 7.7–11.5 g. of succinimide. The ether is removed from the filtrate by rotary evaporation at aspirator pressure, and the residual liquid is distilled under reduced pressure with a short-path distillation apparatus. The product is collected at 74–82° (0.01 mm.) as a faintly yellow oil which crystallizes in the freezer. The yield is 11.5–16.7 g. (32–46% based on sodium ethoxide in Part A) (Note 12) and (Note 13).

C. *tert-Butyl N-(1-ethoxycyclopropyl)carbamate.* A three-necked, cylindrical irradiation vessel is equipped with a magnetic stirring bar, a water-jacketed quartz immersion well, an inert gas-inlet, and a gas-exit tube connected to a bubbler (Note 14). The vessel is charged with 6.26 g. (0.0493 mole) of redistilled 2-ethoxypyrrolin-5-one (Note 20) and 180 ml. of dry *tert*-butyl alcohol (Note 15). The solution is stirred and degassed by bubbling nitrogen or argon through the gas-inlet tube for 15 minutes. The degassed solution is stirred and irradiated with ultraviolet light from a 450-watt, Hanovia, medium-pressure, mercury lamp filtered through a Vycor glass sleeve. During the irradiation an atmosphere of nitrogen or argon is maintained, and the lamp is cooled with warm water (35–40°) circulated through the cooling jacket of the immersion well. The progress of the irradiation is monitored by GC (Note 16). When 90% of the 2-ethoxypyrrolin-5-one has reacted, the irradiation is stopped. The solution (Note 17) is transferred to a 250-ml., round-bottomed flask equipped with a magnetic stirring bar and an air-cooled reflux condenser mounted with a T-shaped nitrogen inlet. Nitrogen is passed through the apparatus for 30 minutes, after which the solution is stirred and heated at reflux under a nitrogen atmosphere for 20 hours (Note 18). The solvent is removed by rotary evaporation, and the residual orange oil is refrigerated to induce crystallization. Sublimation of the solid at 35–40° (0.05 mm.) affords 5.5–6.3 g. (56–64%) of the carbamate as white needles, m.p. 38–40° (Note 19) and (Note 20).

2. Notes

1. In parts A and B care should be taken to minimize the exposure of silver-containing reactants and products to light.
2. Succinimide purchased from MC and B Manufacturing Chemists was used without purification.
3. Absolute ethanol from a commercial supplier was used.

4. A mixture of silver nitrate and dimethyl sulfoxide was stirred vigorously for *ca.* 1 hour to dissolve all of the salt. Reagent grade dimethyl sulfoxide was used without purification.
5. The sodium ethoxide solution was prepared from the reaction of 9.2 g. (0.40 mole) of sodium with 1 l. of absolute ethanol and is standardized by titration with aqueous 0.1 *N* hydrochloric acid. The appropriate volume of the solution to give 0.280 mole of base was used.
6. Slightly less than equivalent amounts of both silver nitrate and sodium ethoxide are used to minimize the formation of silver oxide which imparts a brown color to the product.
7. The submitters state that the use of a sintered-glass funnel may cause discoloration of the product. However, the checkers used a sintered glass funnel in one run with no adverse effect on the yield or purity of the product.
8. A considerable amount of sodium nitrate is present in the precipitate. Although the presence of sodium nitrate did not hinder small-scale alkylation reactions (*ca.* 250 mg.), the submitters recommend that it be removed in larger runs to facilitate the isolation and drying of the silver salt.
These washings are most easily done without removing the material from the filter. However, the solid must be slurried thoroughly in each portion of solvent, particularly with acetone and ether. Care must be taken to ensure that the filter paper is not lifted from the bottom of the funnel. The submitters accomplished this by holding the filter paper in the funnel with a ring of flexible polyvinyl chloride (inside diameter 0.64 cm.), the ends of which were joined by a small piece of rigid polyethylene tubing. The ring was expanded to fit snugly in the bottom of the funnel over the paper.
9. Silver salts may be unstable when heated. An explosion occurred while the silver salt of isatin was drying under reduced pressure at *ca.* 100°.
10. The checkers found that the heavy suspension could not be stirred effectively with a magnetic stirring bar and recommend that a mechanical stirrer be used.
11. Reagent grade chloroform was dried by filtering through alumina (50 g. per l. of solvent).
12. The checkers' data are given. The submitters recovered 4.7–11.4 g. of succinimide and collected 15.6–21.2 g. (44–60% based on sodium ethoxide in Part A) of product, b.p. 65–70° (0.05 mm.). Based on the amount of unrecovered succinimide, the yield of product obtained by the checkers and submitters was 49–61% and 68–69%, respectively. The product is best stored in a freezer. If sufficient care is taken to exclude moisture, 2-ethoxypyrrolin-5-one is stable indefinitely.
13. The product obtained by the submitters was contaminated with impurities amounting to *ca.* 10% which were primarily succinimide and *N*-ethylsuccinimide. Although this material was considered to be of satisfactory purity for use in Part C, further purification can be accomplished, if desired, by redistillation, giving product boiling at 72–74° (0.05 mm.). The checkers found it necessary to redistil the 2-ethoxypyrrolin-5-one to obtain product with the reported melting point in Part C (Note 20); IR (neat) $cm.^{-1}$: 2940, 1748, 1562; ^1H NMR ($CDCl_3$), δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 1.4 (t, $J = 7$, 3H, OCH_2CH_3), 2.4–3.0 (m, 4H, CH_2CH_2), 4.45 (q, $J = 7$, 2H, OCH_2CH_3); UV (cyclohexane) nm. max. (ε): 273 (55).
14. The irradiation apparatus was similar to one depicted in the procedure for bicyclo[2.1.0]pent-2-ene in *Org. Synth.*, **Coll. Vol. 6**, 145 (1988), Figure 2, Section A. The height and inside diameter of the irradiation vessel used by the submitters were approximately 35 cm. and 6.2 cm., respectively. Two short necks with **T** 14/20 outer joints were located on the shoulder of the vessel just below the **T** 60/50 center joint. One neck was capped with a rubber septum and the other was connected to the exit bubbler. The nitrogen inlet was a syringe needle passing through the septum and connected to a section of Teflon tubing that extended to the bottom of the vessel. The checkers used a similar 23 × 7.5 cm. irradiation vessel that had a fritted-glass inlet for argon situated at the base as shown in the figure referred to above. The solution was agitated during the irradiation by a continual flow of argon rather than by magnetic stirring.

The apparatus is dried in an oven at 140° overnight and cooled under nitrogen or argon prior to the irradiation. A Vycor filter sleeve and a 450-watt, medium-pressure mercury lamp are placed in the immersion well. The Vycor filter, the quartz immersion well (catalog No. 19434), the 450-watt mercury lamp (catalog No. 679A36), and the requisite transformer are all available from Hanovia Lamp Division, Canrad-Hanovia Inc., 100 Chestnut Street, Newark, New Jersey 07105.

15. Reagent grade *tert*-butyl alcohol was distilled from calcium hydride prior to use. The scale described is that used by the checkers. The submitters irradiated 4.0 g. (0.032 mole) of 2-ethoxypyrrolin-5-one in 115 ml. of dry *tert*-butyl alcohol.

16. The submitters used a 2.1 m. × 0.64 cm. column with 5% fluorosilicone (FS-1265) supported on Diatoport S as stationary phase. With a column temperature of 170° and a helium flow rate of 60 ml. per minute, 2-ethoxypyrrolin-5-one has a retention time of 2.2 minutes. The analysis was carried out at 160° by the checkers, using a column of 5% diethylene glycol succinate–Bentone34 supported on Diatoport S. The starting material had a retention time of 3.9 minutes under these conditions. Bentone34 is available from Applied Sciences Laboratory, Box 440, State College, Pennsylvania 16801.

17. At this point the product consisted mostly of the isocyanate, since the reaction with *tert*-butyl alcohol is relatively slow at 35–40°. If the photolysis is carried out in an aprotic solvent such as tetrahydrofuran, the isocyanate may be isolated.[2] However, care must be exercised to avoid losses of this rather volatile and moisture-sensitive compound.

18. The isocyanate is completely consumed at this time, as evidenced by the disappearance of the absorption band at 2250 $cm.^{-1}$ in the IR spectrum.

19. Alternatively, the product may be distilled at 40° (0.05 mm.). However, the distillate tends to crystallize in the condenser and plug the apparatus.

20. The checkers found that product with the reported melting point was obtained only when the starting 2-ethoxypyrrolin-5-one was redistilled carefully and was largely free of the *N*-ethyl isomer and succinimide. With 2-ethoxypyrrolin-5-one purified by a single distillation, the product was obtained as a gummy solid that was difficult to purify. Nevertheless, the IR and ^{1}H NMR spectra of this material were essentially identical to those of pure *tert*-butyl *N*-(1-ethoxycyclopropyl)carbamate. The submitters obtained 4.4–4.8 g. (70–76%) of carbamate, m. p. 40–42°, from 4.0 g. of 2-ethoxypyrrolin-5-one. The product has the following spectral characteristics: IR (neat) $cm.^{-1}$: 3333, 2940, 1754 (C=O); ^{1}H NMR ($CDCl_3$), δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 0.80–1.15 (m, 4H, cyclopropyl *H*), 1.13 (t, *J* = 7, 3H, OCH_2CH_3), 1.47 [s, 9H, $C(CH_3)_3$], 3.68 (q, *J* = 7, 2H, OCH_2CH_3), 5.75 (broad, 1H, N*H*).

3. Discussion

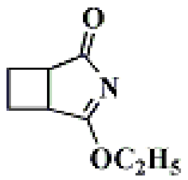
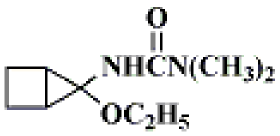
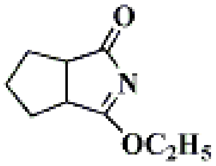
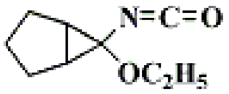
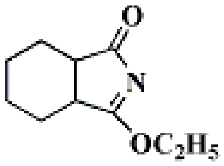
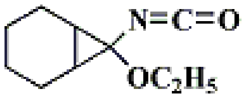
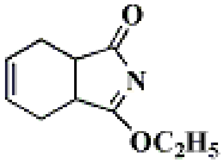
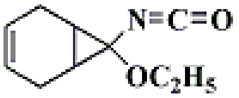
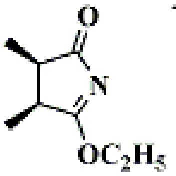
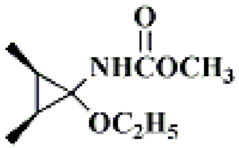
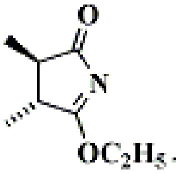
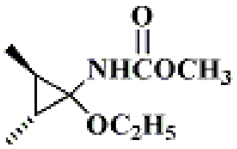
The procedure described here for the preparation of succinimide silver salt is a modification of one reported for the formation of the silver derivative of maleimide.[3] The alkylation step is modeled after the procedure of Comstock and Wheeler,[4] who prepared 2-ethoxypyrrolin-5-one in unspecified yield, and is an improvement over a later procedure developed in the laboratories of the submitters.[2] The general scheme has been successfully applied to the preparation of a variety of 2-ethoxypyrrolin-5-ones (Table I)[5,6,7] as well as 6-ethoxy- and 6-propoxy-4,5-dihydro-2(3*H*)-pyridone from the corresponding five- and six-membered cyclic imides.[2]

The photochemical rearrangement of substituted 2-ethoxypyrrolin-5-ones is a general reaction of synthetic utility and high stereoselectivity, which affords the corresponding 1-ethoxycyclopropyl isocyanates and their derivatives in useful yields (Table I).[6,7] The procedure reported here is the only

known preparation of *tert*-butyl *N*-(1-ethoxycyclopropyl)carbamate, a precursor of 1-aminocyclopropanol and 1-ethoxycyclopropylamine.[8] 1-Aminocyclopropanol has previously been prepared in low yield by the addition of ammonia to cyclopropanone.[8] The photorearrangement of 2-ethoxypyrrolin-5-one to *tert*-butyl *N*-(1-ethoxycyclopropyl)carbamate followed by hydrolysis to 1-aminocyclopropanol is a key step in the synthesis of the alkaloid coprine.[8] Cyclopropanone derivatives have been used as precursors for a variety of compounds[9] such as β-lactams,[10] cyclobutanones,[11] and cyclopropanols.[12]

TABLE I

PREPARATION AND IRRADIATION OF 2-ETHOXYPYRROLIN-5-ONES

2-Ethoxypyrrolin-5-one	Yield (%)	Photoproduct or Its Derivative	Yield (%)
	46[a]		43[b]
	59		76[b]
	89		64[b]
	74		53[b]
	88[c]		58[d]
			60

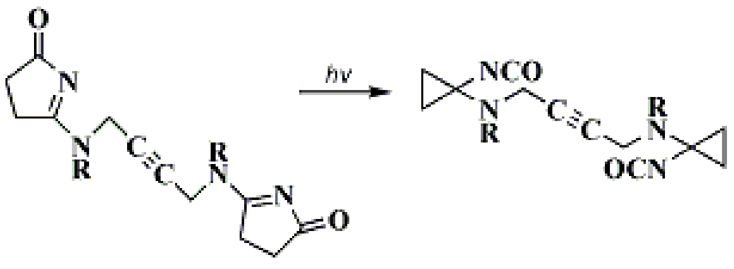
[a]The yield was 84% based on unrecovered imide.

[b]The product is a mixture of *endo*- and *exo*- isomers.

[c]The isomers were separated by preparative GC.

[d]The product is a mixture of *cis*- and *trans*- isomers.

2-Ethoxypyrrolin-5-one reacts with secondary amines, giving 2-aminopyrrolin-5-ones which photochemically rearrange to aminocyclopropyl isocyanates in 80–90% yield.[13] Furthermore, 1,4-bis[(pyrrolin-3-onyl)methylamino]-2-butyne photorearranges to 1,4-bis[(isocyanatocyclopropyl) methylamino]-2-butyne. This reaction is of potential use for photocrosslinking polyurethanes and polyureas.



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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

6-ethoxy- and 6-propoxy-4,5-dihydro-2(3H)-pyridone

Bentone[34]

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ether, ethyl ether, diethyl ether (60-29-7)

chloroform (67-66-3)

silver oxide (20667-12-3)

silver nitrate (7761-88-8)

nitrogen (7727-37-9)

aluminum (7429-90-5)

acetone (67-64-1)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

sodium nitrate

Succinimide (123-56-8)

Ethyl iodide (75-03-6)

Tetrahydrofuran (109-99-9)

dimethyl sulfoxide (67-68-5)

tert-butyl alcohol (75-65-0)

silver iodide (7783-96-2)

calcium hydride (7789-78-8)

helium (7440-59-7)

argon (7440-37-1)

diethylene glycol succinate

Bicyclo[2.1.0]pent-2-ene (5164-35-2)

CYCLOPROPANONE (5009-27-8)

Carbamic acid, (1-ethoxycyclopropyl)-, 1,1-dimethylethyl ester, tert-Butyl N-(1-ethoxycyclopropyl) carbamate (28750-48-3)

Succinimide silver salt, silver salt of succinimide

2-Ethoxypyrrolin-5-one (29473-56-1)

1-aminocyclopropanol

1-ethoxycyclopropylamine

1,4-bis[(pyrrolin-3-onyl)methylamino]-2-butyne

1,4-bis[(isocyanatocyclopropyl)methylamino]-2-butyne

N-ethylsuccinimide (2314-78-5)

silver salt of isatin

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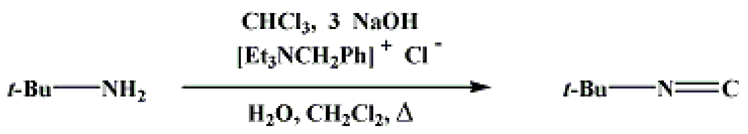
Organic Syntheses, CV 6, 232

PHASE-TRANSFER HOFMANN CARBYLAMINE REACTION: *tert*-BUTYL ISOCYANIDE

[Propane, 2-isocyano-2-methyl-]



Submitted by George W. Gokel[1] [2], Ronald P. Widera, and William P. Weber[1].
Checked by F. A. Souto-Bachiller, S. Masamune, Charles J. Talkowski, and William A. Sheppard.

1. Procedure

Caution! This preparation should be conducted in an efficient hood because of the evolution of carbon monoxide and the obnoxious odor of the isocyanide.[3]

A 2-l., round-bottomed flask equipped with a magnetic stirring bar, a reflux condenser, and a pressure-equalizing dropping funnel is charged with 300 ml. of water. Stirring is begun and 300 g. (7.50 moles) of sodium hydroxide are added in portions in order to maintain efficient stirring (Note 1). A mixture of 141.5 g. (203.3 ml., 1.938 moles) of *tert*-butylamine, 117.5 g. (78.86 ml., 0.9833 mole) of chloroform (Note 2), and 2 g. (0.009 mole) of benzyltriethylammonium chloride (Note 3) in 300 ml. of dichloromethane is added dropwise to the stirred, warm (*ca.* 45°) solution over a 30-minute period. The reaction mixture begins to reflux immediately (Note 4) and subsides within 2 hours; stirring is continued for an additional hour (Note 5). After the reaction mixture is diluted with 800 ml. of ice and water, the organic layer is separated and retained, and the aqueous layer is extracted with 100 ml. of dichloromethane. The dichloromethane solutions are combined and washed successively with 100 ml. of water and 100 ml. of aqueous 5% sodium chloride, and dried over anhydrous magnesium sulfate.

The drying agent is removed by filtration, and the filtrate is distilled under nitrogen through a spinning band column (Note 6) and (Note 7). The fraction, boiling at 92–93° (725 mm.), is collected, yielding 54.2–60.0 g. (66–73%, based on chloroform) of *tert*-butyl isocyanide (Note 8) and (Note 9).

2. Notes

1. Efficient stirring is required. A solution of 225 g. (5.62 moles) of sodium hydroxide in 225 ml. of water can be added to the stirred mixture of the organic substrates in dichloromethane if a more efficient mechanical stirrer is used. In the original procedure, the submitters noted an induction period of about 20 minutes which was found to vary somewhat with the stirring rate, stirring-bar size, and relative amount of phase-transfer catalyst. Three moles of base are required for the reaction: one to generate the carbene and two to react with the additional two moles of hydrochloric acid lost by the amine–carbene adduct in the isonitrile formation step. If less base is used, the excess hydrochloric acid reacts with the isonitrile by α-addition, and the yield is substantially reduced.
2. Chloroform, commercially available, normally contains 0.75% ethanol and was used as supplied.
3. Benzyltriethylammonium chloride is available from Eastman Organic Chemicals. The checkers prepared the salt in a state of high purity by a modification of a reported procedure.[4] A solution of 33.7 g. (0.334 mole) of triethylamine and 50.0 g. (0.395 mole) of benzyl chloride (both from Eastman Organic Chemicals) in 60 ml. of absolute ethanol was refluxed for 64 hours, cooled to room temperature, and treated with 300 ml. of ether. The precipitated ammonium salt was removed by filtration, redissolved in the minimum amount of hot acetone, and reprecipitated with ether.
4. The volatilities of both *tert*-butylamine and dichloromethane necessitate the use of an efficient condenser as a precaution, although the rate of reflux is generally not vigorous. In preparations where higher boiling amines are used, this precaution is less critical.
5. The submitters noted that a longer stirring period did not seem to affect the yield appreciably.
6. The bulk of the residual *tert*-butylamine is recovered.
7. A 60-cm., annular, Teflon®, spinning band, distillation column is recommended to achieve clean separation of solvent and unreacted reagent from product rather than a column packed with glass helices. For higher boiling isocyanides, separation of solvent and unreacted reagents may be effected by the use of a rotary evaporator, although the thermal instability of the isocyanides should be taken into consideration.
8. Yields higher than about 70% for any of these isonitrile preparations generally indicate incomplete fractionation. The purity of the product may be conveniently checked by ^1H NMR ($CDCl_3$) spectroscopy. The characteristic 1:1:1 triplet for β-hydrogen: ^{14}N coupling in *tert*-butyl isocyanide appears at δ 1.45. A small upfield peak usually indicates the presence

of unreacted amine. Other common contaminants are dichloromethane and chlorofrom. The purity may be determined more accurately by GC analysis on a 230 cm. by 0.6 cm. column packed with 10% SE-30 on Chromosorb G, 60–80 mesh, at 80°.

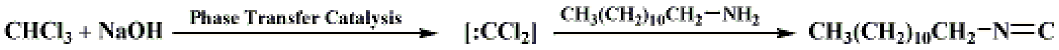
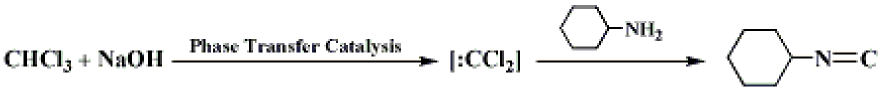
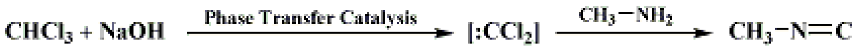
9. Glassware may be freed from the isocyanide odor by rinsing with a 1:10 mixture of concentrated hydrochloric acid and methanol.

3. Discussion

The present method utilizes dichlorocarbene generated by the phase-transfer method of Makosza[5] and Starks.[6] The submitters have routinely realized yields of pure distilled isocyanides in excess of 40%.[7] With less sterically hindered primary amines a 1:1 ratio of amine to chloroform gives satisfactory results. Furthermore, by modifying the procedure, methyl and ethyl isocyanides may be prepared directly from the corresponding aqueous amine solutions and bromoform.[8] These results are summarized in Table I.

TABLE I

PREPARATION OF ISOCYANIDES (RN=C) BY THE CARBYLAMINE REACTION[a]

	R	>Yield (%)	b.p. of RN=C
	$CH_3(CH_2)_2CH_2$-	60	40–42° (11 mm.)
	$C_6H_5CH_2$-	45	92–93° (11 mm.)
	$CH_3(CH_2)_{10}CH_2$-	41	115–118° (0.1 mm.)
	cyclo-C_6H_{11}-	48	67–72° (13 mm.)
	C_6H_5-	57	50–52° (11 mm.)
	CH_3-[b]	24	59–60° (760 mm.)
	CH_3CH_2-[b]	47	78–79° (760 mm.)

[a]Prepared by the phase-transfer method using chloroform and aqueous sodium hydroxide with the corresponding amines.[7]

[b]Bromoform substituted for chloroform for ease of fractionation.[8]

Various synthetic routes to isocyanides have been reported since their identification over 100 years ago.[9] Until now,[9,10] the useful synthetic procedures required a dehydration reaction.[11,10,12] Although the carbylamine reaction involving the dichlorocarbene intermediate is one of the early methods,[9] it had not been preparatively useful until the innovation of phase-transfer catalysis (PTC).[5,6]

The phase-transfer catalysis method has also been utilized effectively for addition of dichlorocarbene to olefins,[5] as well as for substitution and elimination reactions, oxidations, and reductions.[13] A later procedure in this volume is another example.[14]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 897
- Org. Syn. Coll. Vol. 6, 940
- Org. Syn. Coll. Vol. 6, 954
- Org. Syn. Coll. Vol. 7, 27

References and Notes

1. Department of Chemistry, University of Southern California, University Park, Los Angeles, California 90007. This work was supported in part by a grant from the National Science Foundation, grant number GP 40331X.
2. Present address: Department of Chemistry, University of Maryland, College Park, Maryland 20742.
3. Many isocyanides are reported to exhibit no appreciable toxicity to mammals. See J. A. Green II and P. T. Hoffmann in "Isonitrile Chemistry," I. Ugi, Ed., Academic Press, New York, 1971, p. 2. However, since certain isocyanides are highly toxic (*e.g.*, 1,4-diisocyanobutane), the checkers recommend that all isocyanides be handled with due caution.
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

chlorofrom

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

methanol (67-56-1)

ether (60-29-7)

sodium hydroxide (1310-73-2)

carbon monoxide (630-08-0)

chloroform (67-66-3)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

acetone (67-64-1)

benzyl chloride (100-44-7)

bromoform (75-25-2)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

triethylamine (121-44-8)

dichlorocarbene

Propane, 2-isocyano-2-methyl-, tert-Butyl isocyanide (7188-38-7)

1,4-diisocyanobutane

benzyltriethylammonium chloride (56-37-1)

tert-Butylamine (75-64-9)

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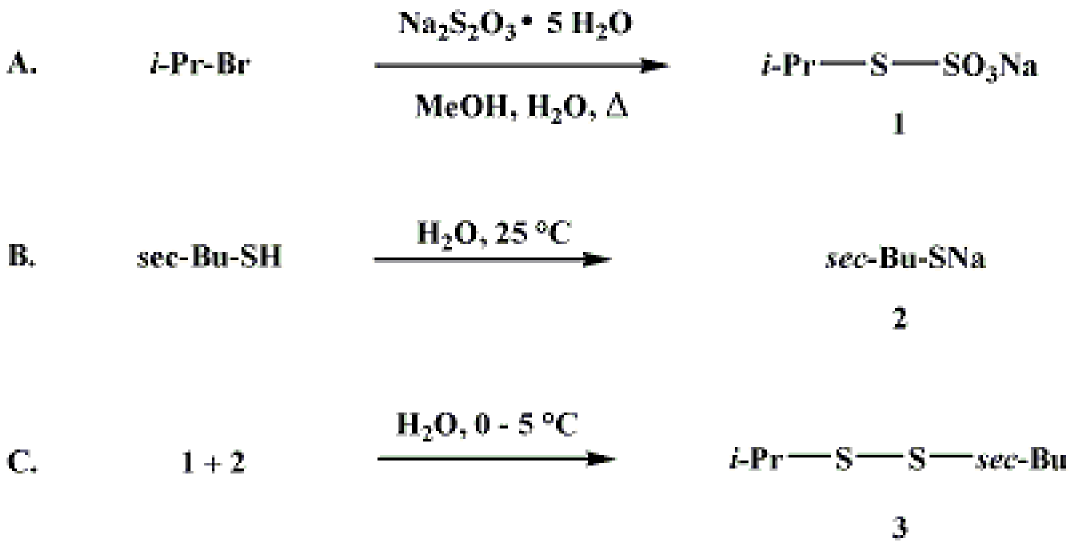
Organic Syntheses, CV 6, 235

SULFIDE SYNTHESIS IN PREPARATION OF UNSYMMETRICAL DIALKYL DISULFIDES: *sec*-BUTYL ISOPROPYL DISULFIDE

[Disulfide, 1-methylethyl 1-methylpropyl]



Submitted by M. E. Alonso[1] and H. Aragona.
Checked by Linda D.-L. Lu and S. Masamune.

1. Procedure

Caution! This procedure should be carried out in an efficient hood to prevent exposure to alkane thiols.

A. *Sodium isopropyl thiosulfate* **(1).** A 5-l., three-necked, round-bottomed flask equipped with a condenser, a 300-ml. dropping funnel, and a mechanical stirrer is charged with 123 g. (1.00 mole) of freshly distilled 2-bromopropane (Note 1) in 1.2 l. of methanol. Water is added slowly with stirring until a slight turbidity develops (Note 2). The stirred mixture is heated to reflux, and 310 g. (1.25 mole) of sodium thiosulfate pentahydrate (Note 3) in 250 ml. of water is added over a period of 30 minutes. The slightly yellow-tinted solution is heated for an additional 3.5–4.0 hours and allowed to cool to room temperature. The alcohol is removed with a rotary evaporator; the remaining milky solution is diluted with water to a total volume of about 1.2 l and extracted twice with hexane (Note 4). Discarding the organic layers, the aqueous solution of crude thiosulfate is cooled to 0° and stored.

B. *Sodium 2-butanethiolate* **(2).** A 500-ml., three-necked, round-bottomed flask equipped with a dropping funnel, a mechanical stirrer, and a gas-inlet is charged with

40 g. (1.0 mole) of sodium hydroxide in 100 ml. of water. Under an atmosphere of argon (Note 5), 90 g. (1.0 mole) of 2-butanethiol (Note 6) is added dropwise over a 2-hour period, with rapid stirring at room temperature (Note 7). Thiolate solution **2** becomes very viscous toward the end of the addition; it is diluted with 30 ml. of water and cooled to 0°.

C. *sec-Butyl isopropyl disulfide* **(3).** A 3-l., three-necked, round-bottomed flask equipped with a dropping funnel, a thermometer, and a mechanical stirrer is charged with the crude thiosulfate solution **1** and cooled to 0° with the aid of an ice-salt bath. The cold thiolate solution **2** is added rapidly, with vigorous stirring for 3 minutes, followed by 200 ml. of aqueous saturated sodium chloride (Note 8), and the mixture is warmed to 5°. Stirring is stopped after 10 minutes, counted from the start of the addition of the aqueous sodium chloride. The crude disulfide **3**, which separates as an oil, is removed, and the aqueous layer is extracted twice with 250-ml. portions of diethyl ether. The extracts are combined with the oil, washed twice with 150-ml. portions of water, dried briefly over granular calcium sulfate, and filtered through a glass-wool plug. Removal of the solvent leaves 125–133 g. of crude disulfide **3** (Note 9). Distillation of this material at 44.5–45° (1.25 mm.) gives 118–123 g. (73–75%) of pure disulfide **3** (Note 10).

2. Notes

1. The submitters used 2-bromopropane available from Aldrich Chemical Company, Inc. The checkers purchased the reagent from J. T. Baker Chemical Company.
2. The turbidity indicates saturation of alkyl halide. In this way both sodium thiosulfate and 2-bromopropane are nearly in a one-phase system, thus shortening significantly the heating period. Furthermore, competing hydrogen bromide elimination and acid-promoted decomposition of thiosulfate into sulfur and sulfur dioxide are minimized. The checkers added 300 ml. of water over a period of 90 minutes.
3. The submitters used sodium thiosulfate pentahydrate supplied by E. Merck A G, Darmstadt, and the checkers used A.C.S. reagent grade material available from Fisher Scientific Company.
4. This extraction is intended to remove traces of unreacted alkyl halide that might compete for the thiolate in the nucleophilic substitution (Step B).
5. The submitters performed this step in air, but the checkers found that use of an inert atmosphere resulted in a somewhat improved yield.
6. This reagent was purchased from Aldrich Chemical Company, Inc.
7. The submitters observed the separation of a pasty solid at this stage, added four 10-ml. portions of water during the addition of the thiol, and dissolved the entire solid with approximately 240 ml. of water. Sometimes, at this point, as much as 10% of the added thiol separated out as a floating oil. The presence of this thiol affects the course of the reaction, yielding symmetrical disulfides.[2] In this case the organic layer should be separated, added dropwise to an equivalent amount of sodium hydroxide dissolved in a minimum amount of water, and

mixed with the original thiolate solution.
8. The submitters found that the addition of sodium chloride facilitated the separation of the insoluble disulfide.
9. This material contained no less than 90% of disulfide **3** according to GC analysis (1.5-m. 5% SE-30 column).
10. The distilled disulfide **3** has the following ^1H NMR spectrum ($CDCl_3$), δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 1.00 (t, *J* = 7.0, 3H, CH_3CH_2), 1.31 (d, *J* = 7.0, 9H, $(CH_3)_2CH$ and CH_3CH), 1.62 (m, 2H, CH_2), 2.86 (sextuplet, *J* = 7.0, 1H, CH_3CHCH_2), 3.02 (septuplet, *J* = 7.0, 1H, CH_3CHCH_3).

3. Discussion

Unsymmetrical, dialkyl disulfides[3] can be prepared by several methods; three procedures appear to be generally applicable. First, the reaction of an *N*-(alkylthio)- or *N*-(arylthio)phthalimide with thiols[4] gives unsymmetrical disulfides in good yield; however, the synthesis of the thiophthalimide[5,6] requires the corresponding sulfenyl chloride, which is rather unstable and undergoes undesirable side reactions when α-protons are available.[7] Second, the adduct of a thiol and diethyl azodicarboxylate reacts with a thiol, giving unsymmetrical disulfides in high yield.[8] The adduct formation, however, is severely suppressed by steric hindrance in the alkyl portion of the thiol; secondary and tertiary thiols are normally unreactive.[9] Third, the reaction of sodium alkylthiosulfates[10] with thiolates provides unhindered, mixed disulfides in low to moderate yields,[11] and hindered compounds[12] in yields of 6–10%. A general and satisfactory synthetic procedure for hindered, unsymmetrical disulfides was not available at the time the present study was undertaken,[6] the probable reason being that the known methods utilize a sterically sensitive bimolecular attack by a nucleophilic form of sulfur onto a sulfur atom bearing a suitable leaving group. Forcing conditions usually lead to disproportionation[13] and polysulfide formation.[11] The availability and low cost of starting materials and the expeditious process involved in the "Bunte Salt" approach[10] provided a reasonable basis for modifying the existing procedure,[11] extending its applicability to bulky, unsymmetrical disulfides. Table I shows boiling points and distillate composition of a number of mixed disulfides prepared in up to 80% yield by the method presented here;[14] base-catalyzed disproportionation[13] and polymerization[11] appear to be minimized.

TABLE I
UNSYMMETRICAL DIALKYL DISULFIDES PREPARED BY THE THIOSULFATE PROCEDURE. DISTILLATION CONDITIONS AND COMPOSITION[a,b]

R	R'	bp, °C/ torr	yield (%)	RSSR' (%)	RSSR (%)	R'SSR' (%)
$(CH_3)_2CHCH_2$-	$(CH_3)_2CH$-	33–34/0.15	60	92	6	2
$(CH_3)_2CHCH_2$-	CH_3CH_2-	51/3	62	98		1
$(CH_3)_2CHCH_2$-	CH_3-	52/8.5	65	97		1.5
$(CH_3)_2CHCH_2$-	CH_2=$CHCH_2$	57.5/1.5	81	96	2	1.5
$(CH_3)_2CH$-	CH_3CH_2=	49/9	60	98	<1	*c*
$(CH_3)_2CH$-	CH_3-	37–38/11	72	98.5	<1	
$(CH_3)_2CH$-	CH_2=$CHCH_2$-	55.5/5	69	98.5		<1
$C_2H_5CH(CH_3)$-	$(CH_3)_2CH$-	40–41/0.2	73	96.5	3	*c*
$C_2H_5CH(CH_3)$-	CH_3CH_2-	47/1.5	64	98.5	<1	<1
$C_2H_5CH(CH_3)$-	CH_3-	46.5/6	71	99		
$C_2H_5CH(CH_3)$-	CH_2=$CHCH_2$-	51/1	71	98.5	<1	
$(CH_3)_3C$	$(CH_3)_2CH$	30–32/2	53	96.5	1	<1
$(CH_3)_3C$-	CH_3CH_2-	43–44/5	52	97	<1	2
$(CH_3)_3C$-	CH_3-	46/12	49	98.5	<1	<1
$(CH_3)_3C$-	CH_2=$CHCH_2$-	53/2	54	99		

[a]Determined by GC analysis on a 12-ft 5% SE-30 on Chromosorb G column.

[b]Satisfactory analytical data (±0.52% for C, H, S) were obtained for all compounds.

[c]Could not be separated by GC.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

methanol (67-56-1)

diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

hydrogen bromide (10035-10-6)

sulfur dioxide (7446-09-5)

2-bromopropane (75-26-3)

sodium thiosulfate (7772-98-7)

sulfur (7704-34-9)

calcium sulfate (7778-18-9)

diethyl azodicarboxylate (1972-28-7)

hexane (110-54-3)

argon (7440-37-1)

thiophthalimide

Disulfide, 1-methylethyl 1-methylpropyl, sec-Butyl isopropyl disulfide (67421-86-7)

sodium thiosulfate pentahydrate

2-butanethiol (513-53-1)

Sodium 2-butanethiolate

Sodium isopropyl thiosulfate

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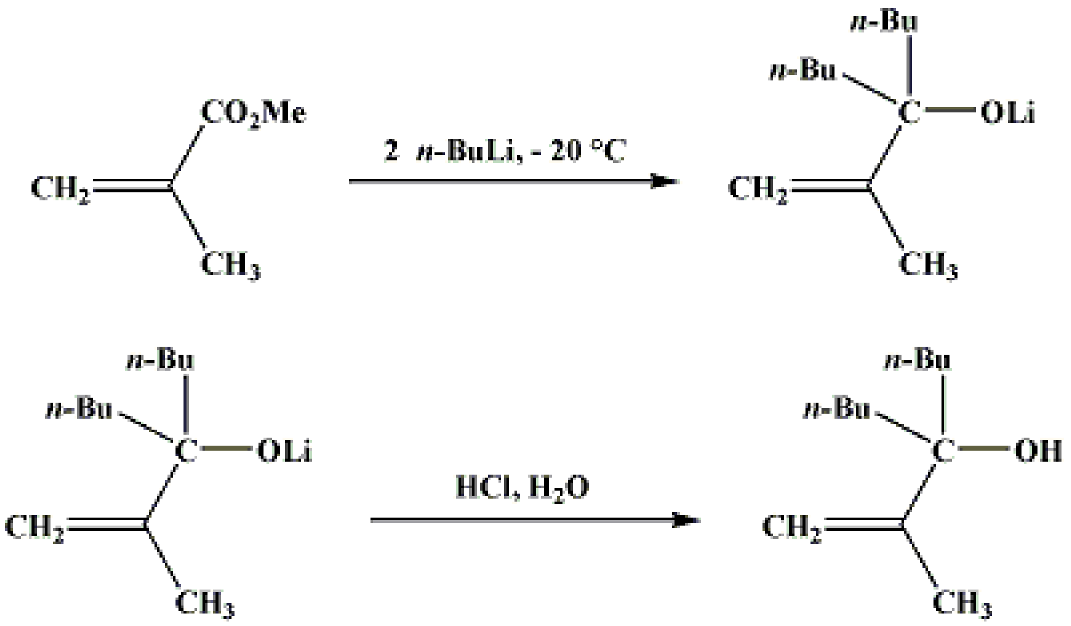
3-BUTYL-2-METHYLHEPT-1-EN-3-OL

[5-Nonanol, 5-(2-propenyl)-]

$$n\text{-}C_4H_9Br + 2\ Li \longrightarrow n\text{-}C_4H_9Li + LiBr$$



Submitted by P. J. Pearce[1], D. H. Richards, and N. F. Scilly.
Checked by N. Cohen, R. Lopresti, and A. Brossi.

1. Procedure

A 2-l., four-necked flask equipped with a sealed, Teflon-paddle stirrer, a mercury thermometer, a gas-inlet tube, and a dropping funnel is charged with 1.2 l. of anhydrous tetrahydrofuran (Note 1) and 50 g. (7.1 g.-atoms) of lithium pieces (Note 2) under an atmosphere of prepurified nitrogen. The stirred mixture is cooled to –20° with an acetone dry-ice bath and a mixture of 100 g. (1.00 mole) of methyl methacrylate (Note 3), and 411 g. (3.00 moles) of *n*-butyl bromide (Note 4) is added dropwise over a period of 3–4 hours. During this addition, an exothermic reaction ensues and is controlled at –20° (Note 5), and on completion of the addition, the vessel is maintained at this temperature, with stirring, for an additional 30 minutes. The contents of the flask are filtered with suction through a 70-mm.-diameter, slit-sieve Buchner funnel, without filter paper, to remove the excess lithium metal. The filtrate is concentrated on a rotary evaporator at aspirator pressure. The residual lithium alcoholate is hydrolyzed by the addition of 1 l. of 10% hydrochloric acid, with ice bath cooling. The liberated alcohol is extracted with two 400-ml. portions of diethyl ether, and the combined ether extracts are washed with two 400-ml. portions of water and dried over 100 g. of anhydrous magnesium sulfate. After suction filtration and removal

of the ether on a rotary evaporator at aspirator pressure, the crude alcohol is distilled under reduced pressure through a 40-cm. Vigreux column, yielding 147–158 g. (80–86%) of 3-butyl-2-methyl-1-hepten-3-ol, b.p. 80° (1mm.). The purity of the product, determined by GC analysis, is greater than 99%.

2. Notes

1. Reagent grade (stabilized) tetrahydrofuran was allowed to stand over molecular sieves for 24 hours, refluxed for 2 hours with sodium wire, and finally distilled and used within 48 hours. The checkers found that it was convenient simply to percolate the tetrahydrofuran, after preliminary drying over molecular sieves, through a column of grade I, neutral aluminum oxide, under nitrogen, directly into the reaction flask, until the required volume of solvent was collected.
2. A convenient form of lithium metal can be purchased from Associated Lead Manufacturers Ltd., 14 Gresham Street, London. A typical analysis shows a purity of 99.6%, and it can be obtained as 1.3-cm.-diameter rod coated with petroleum jelly. A comparable form of lithium metal can be purchased from Ventron Corporation, Chemicals Division, Beverly, Massachusetts. Preparation for use involves weighing, washing with petroleum ether (b.p. 40–60°), and cutting the rod by scissors so that the pieces fall into the reaction vessel. The rod is cut into pieces about 0.5 cm. long that have an average weight of 0.3 g. per piece. Since excess lithium is employed in this reaction, accurate weighing is unnecessary.
3. Reagent grade methyl methacrylate monomer was dried over powdered calcium hydride and freshly distilled before use. The checkers found that identical yields could be obtained when Matheson, Coleman and Bell Chromatoquality methyl methacrylate monomer was used as received with no purification.
4. Reagent grade *n*-butyl bromide (greater than 98% pure) was used after drying over molecular sieves.
5. The reaction is highly exothermic and the submitters have found that isothermal conditions are best maintained by using cooling equipment consisting of a cooling bath seated on a pneumatically operated labjack and controlled by a temperature sensor which is attached to the thermometer dipping into the reaction vessel. This equipment, known as Jack-o-matic, is supplied by Instruments for Research and Industry, Cheltenham, Pennsylvania.

3. Discussion

This method has general applicability in that the carbonyl compound may be an aldehyde, a ketone, or an ester.[2] Similarly, the halide may be chloride, bromide, or iodide, although yields are generally lower with iodides. Alkyl and aryl halides react with equal facility, and the alkyl halide may be primary, secondary, or tertiary. A few examples of the yields obtained with a variety of reagents are given in Table I (the yields quoted are obtained by GC analysis of the reaction mixture using an internal

standard).

TABLE I

Carbonyl Compound	Halide	Product	Yield %
Propionaldehyde	Ethyl bromide	3-Pentanol	90
Benzaldehyde	Chlorobenzene	Benzhydrol	100
Di-*n*-butyl ketone	*n*-Butyl bromide	Tri-*n*-butyl carbinol	91
Ethyl formate	*n*-Butyl bromide	5-Nonanol	91
Acrolein	Ethyl bromide	1-Penten-3-ol	90
Butyraldehyde	*sec*-Butyl bromide	3-Methyl-4-heptanol	89

For maximum yield, care must be taken to ensure that the rate of addition of the reagents is not excessive. If this occurs, the alkyllithium is generated in the presence of significant amounts of unchanged alkyl halide, and Wurtz condensation may be favored. The rate of formation of the alkyllithium is proportional to the surface area of the lithium metal; therefore, at a constant rate of addition, an increase in the lithium surface available for reaction will reduce the probability of Wurtz condensation.

Excess alkyl halide is required to compensate for these side reactions; commonly, only a 10–20% excess is used, rather than the 50% quoted in the method above. The yields given in the table are those obtained with 20% excess halide. The submitters have scaled up the reaction by a factor of 40 with no lowering of yield.

The technique is more efficient than the conventional Grignard reaction for three main reasons: (1) it is a one-stage process; (2) the yields are generally higher; and (3) the final product isolation is cleaner and more convenient.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

hydrochloric acid (7647-01-0)

ether, diethyl ether (60-29-7)

Acrolein (107-02-8)

n-butyl bromide (109-65-9)

Ethyl bromide (74-96-4)

sec-Butyl bromide (78-76-2)

Propionaldehyde (123-38-6)

nitrogen (7727-37-9)

benzaldehyde (100-52-7)

chlorobenzene (108-90-7)

sodium wire (13966-32-0)

butyraldehyde (123-72-8)

ethyl formate (109-94-4)

3-Pentanol (584-02-1)

lithium (7439-93-2)

magnesium sulfate (7487-88-9)

5-Nonanol (623-93-8)

aluminum oxide (1344-28-1)

Tetrahydrofuran (109-99-9)

benzhydrol (91-01-0)

calcium hydride (7789-78-8)

methyl methacrylate (80-62-6)

3-BUTYL-2-METHYLHEPT-1-EN-3-OL, 3-Butyl-2-methyl-1-hepten-3-ol

5-Nonanol, 5-(2-propenyl)- (76071-61-9)

1-Penten-3-ol (616-25-1)

3-Methyl-4-heptanol (1838-73-9)

di-n-butyl ketone (502-56-7)

tri-n-butyl carbinol (597-93-3)

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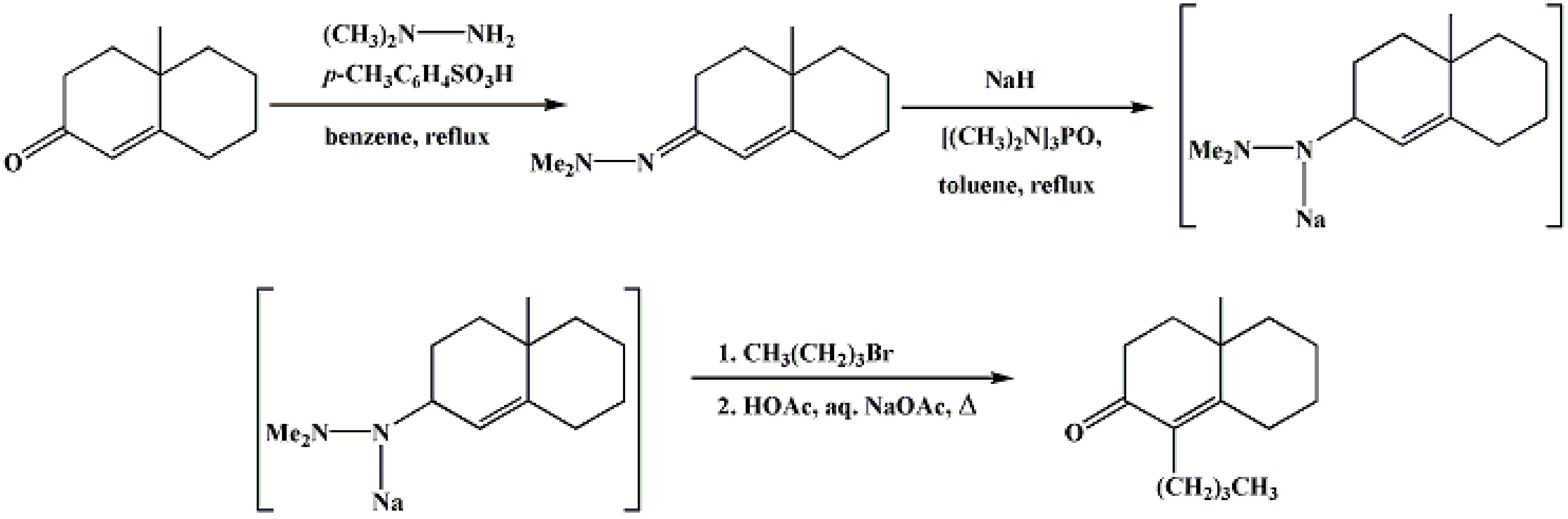
MONOALKYLATION OF α,β-UNSATURATED KETONES *via* METALLOENAMINES: 1-BUTYL-10-METHYL-$\Delta^{1(9)}$-2-OCTALONE

[2(3*H*)-Naphthalenone, 1-butyl-4,4a,5,6,7,8-hexahydro-4a-methyl-]



Submitted by G. Stork[1] and J. Benaim[2].
Checked by K. J. Bruza, R. K. Boeckman, and C. R. Johnson.

1. Procedure

Caution! Hexamethylphosphoric triamide vapors have been reported to cause cancer in rats.[3] All operations with hexamethylphosphoric triamide should be performed in a good hood, and care should be taken to keep the liquid off the skin.

Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should

be carried out in a well-ventilated hood, and glove protection is required.

A. 10-*Methyl*-$\Delta^{1(9)}$-2-*octalone* N,N-*dimethylhydrazone.* A 250-ml., round-bottomed flask equipped with a magnetic stirring bar and a Dean-Stark trap is maintained under a dry nitrogen atmosphere (Note 1) and charged with 7.4 g. (0.045 mole) of 10-methyl-$\Delta^{1(9)}$-2-octalone (Note 2), 9.0 g. (0.15 mole) of *N,N*-dimethylhydrazine, 150 ml. of dry benzene, and 0.02 g. of *p*-toluenesulfonic acid. This mixture is refluxed for 10–14 hours, after which time no additional water separates. Benzene and excess *N,N*-dimethylhydrazine are removed by simple distillation, and the residue is distilled under reduced pressure, giving 8.1 g. (87%) of the dimethylhydrazone as a pale-yellow liquid, b.p. 94–98° (0.2 mm.) (Note 3), (Note 4).

B. *1-Butyl-10-methyl-$\Delta^{1(9)}$-2-octalone.* A 250-ml., three-necked flask equipped with a magnetic stirring bar, a reflux condenser, a 50-ml., pressure-equalizing funnel, and a rubber septum is charged with 1.4 g. (0.032–0.035 mole) of 55–60% sodium hydride dispersion in mineral oil and put under a dry nitrogen atmosphere. The mineral oil is removed by washing the sodium hydride three or four times with 5-ml. portions of dry toluene (Note 5). A solution of 6.12 g. (0.0297 mole) of 10-methyl-$\Delta^{1(9)}$-2-octalone *N,N*-dimethylhydrazone in 100 ml. of dry toluene is placed in the flask, and 10 ml. of dry hexamethylphosphoric triamide is added. The rubber septum is replaced with a glass stopper. The solution is warmed with an oil bath to reflux the toluene; hydrogen evolution is observed. Reflux is maintained for 14–16 hours, during which time the solution becomes dark brown. The solution is then cooled to −10° and 4.5 g. (0.033 mole) of 1-bromobutane in 10 ml. of dry toluene is slowly added. The solution is warmed to 60° and maintained at that temperature for 4–5 hours. An abundant precipitate of sodium bromide is formed. The solution is cooled to 0°, and an acetate-buffer solution (Note 6) is added. The mixture is refluxed for 4–5 hours to complete the hydrolysis before it is cooled and decanted. The aqueous phase is extracted three times with 25-ml. portions of diethyl ether. The combined organic layers are successively washed with three 80- to 100-ml. portions of 10% hydrochloric acid, three 50-ml. portions of saturated sodium hydrogen carbonate, two 50-ml. portions of saturated sodium chloride, and then dried over sodium sulfate. The solvents are removed by rotary evaporation (Note 7). The residue is distilled under high vacuum using a short column. After a small forerun, 4.3–4.7 g. (65–72%) of pure 1-butyl-10-methyl-$\Delta^{1(9)}$-2-octalone, b.p. 84–92° (0.2 mm.), is obtained (Note 8).

2. Notes

1. A positive pressure of nitrogen is maintained using a mercury bubbler.

2. 10-Methyl-$\Delta^{1(9)}$-2-octalone, which can be prepared from 4-(diethylamino)-2-butanone, 2-methylcyclohexanone, and sodium,[4] has b. p. 65–70° (0.1 mm.) and n_D^{20} 1.523. IR (neat) cm.$^{-1}$: 1610, 1670; ^{1}H NMR (CCl_4), δ (assignment): 1.25 (CH_3), 5.6 (CH).

3. The hydrazone should be stored under dry nitrogen at −10°.

4. ^{1}H NMR (CCl_4), δ (multiplicity, assignment): 1.15 (s, CCH_3), 2.35 [s, $N(CH_3)_2$], 6.35 (40%) and 5.70 (60%) (s, CH of

diastereomeric hydrazones); IR (neat) cm.$^{-1}$: 1620, 1580; n_D^{20} 1.505.

5. A 5-ml. portion of dry toluene is introduced into the flask with a syringe, and sodium hydride dispersion is stirred for 1 minute before 4 ml. of the supernatant toluene is carefully removed from the flask with a syringe.

6. The buffer solution is prepared by dissolving 20 g. of anhydrous sodium acetate in a mixture of 40 ml. of acetic acid and 40 ml. of water.

7. At this point the submitters reported 7.07 g. of crude product; GC analysis on an SE-30 column at 200° showed 1–3% of 10-methyl-$\Delta^{1(9)}$-2-octalone and 85% of the desired alkylated product.

8. ^{1}H NMR (CCl_4), δ (multiplicity, assignment): 0.9 (t, CH_2CH_3), 1.2 (s, CCH_3); IR (neat) cm.$^{-1}$: 1660, 1600; n_D^{25} = 1.511.

3. Discussion

Alkylations of enamines of α,β-unsaturated ketones with alkyl halides often give very poor yields of *C*-alkylated products because of competing *N*-alkylation.[5,6] In the type of transformation illustrated here, direct alkylations of enamines are completely unsuccessful, even in cases where hindered enamines[7] are used. Generally, the metalloenamine method[8] can be applied with good success to the problem of monoalkylation of α,β-unsaturated ketones.[9]

Metalloenamines can be formed from *N*,*N*-dimethylhydrazones, as illustrated here, or from *N*-cyclohexylimines. Various strong bases have been used, including *n*-butyllithium, lithium diisopropylamide, sodium hydride, and lithium bis(trimethylsilyl) amide. The nature and sometimes the stoichiometry of the strong base used can be important. Poor yields of alkylated compounds are obtained with Grignard reagents, and in the case of *n*-butyllithium, excess base can result in the formation of significant amounts of kinetically controlled alkylation products (*e.g.*, alkylation at C-3 of 10-methyl-$\Delta^{1(9)}$-2-octalone). In the cases of octalones and steroid compounds (cholestenone, testosterone benzoate) it has been found that sodium hydride and lithium diisopropylamide gave the best yields of the desired alkylated compounds.[9]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

1-Butyl-10-methyl-$\Delta^{1(9)}$-2-octalone

10-Methyl-$\Delta^{1(9)}$-2-octalone N,N-dimethylhydrazone

10-methyl-$\Delta^{1(9)}$-2-octalone

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

diethyl ether (60-29-7)

sodium acetate (127-09-3)

hydrogen (1333-74-0)

sodium hydrogen carbonate (144-55-8)

sodium chloride (7647-14-5)

1-bromobutane (109-65-9)

sodium bromide (7647-15-6)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

toluene (108-88-3)

sodium (13966-32-0)

Cholestenone

N,N-dimethylhydrazine (57-14-7)

n-butyllithium (109-72-8)

sodium hydride (7646-69-7)

2-methylcyclohexanone (583-60-8)

4-(diethylamino)-2-butanone (3299-38-5)

hexamethylphosphoric triamide (680-31-9)

p-toluenesulfonic acid (104-15-4)

lithium diisopropylamide (4111-54-0)

lithium bis(trimethylsilyl) amide (4039-32-1)

testosterone benzoate

2(3H)-Naphthalenone, 1-butyl-4,4a,5,6,7,8-hexahydro-4a-methyl- (66252-93-5)

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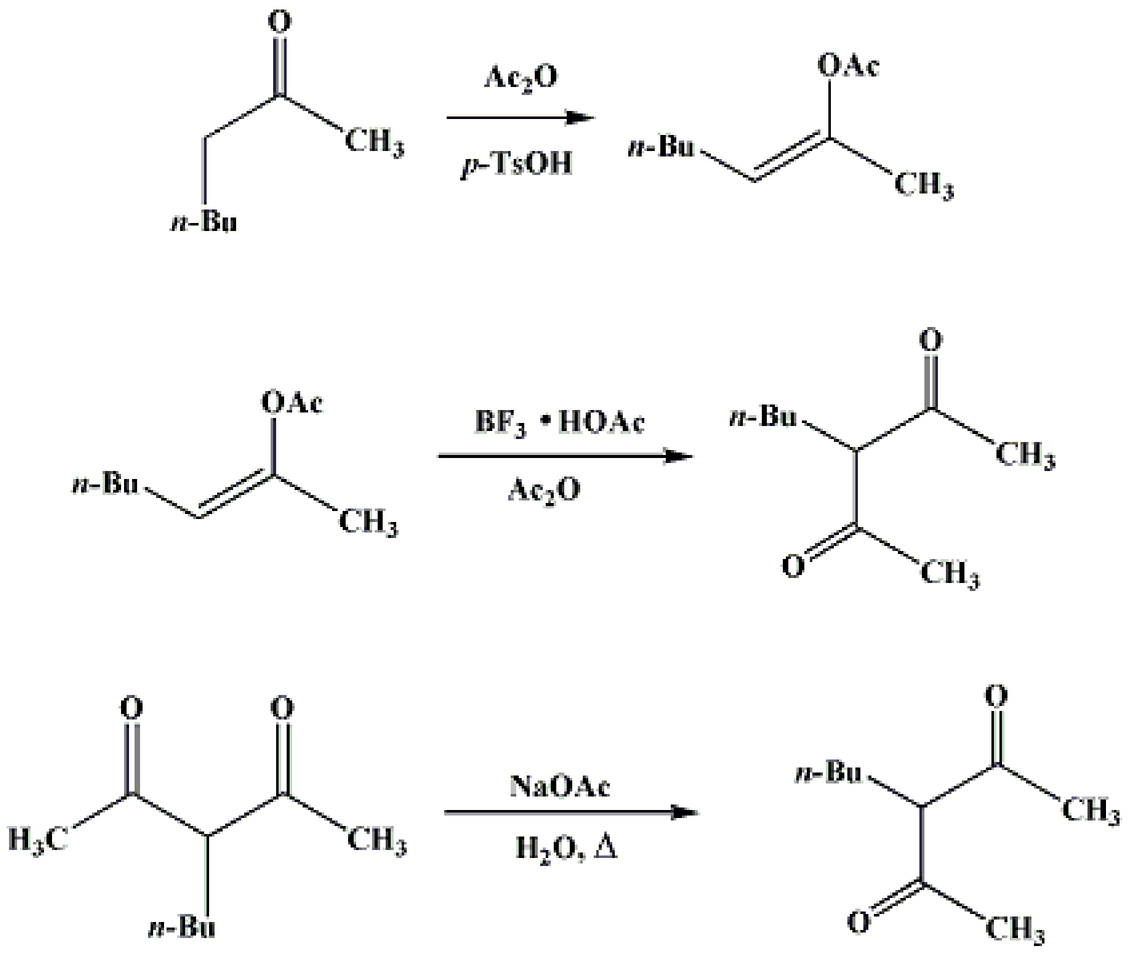
β-DIKETONES FROM METHYL ALKYL KETONES: 3-*n*-BUTYL-2,4-PENTANEDIONE



Submitted by Chung-Ling Mao[1] and Charles R. Hauser[12].
Checked by David G. Melillo and Herbert O. House.

1. Procedure

A mixture of 28.6 g. (0.251 mole) of 2-heptanone (Note 1), 51.0 g. (0.500 mole) of acetic anhydride (Note 2), and 1.9 g. (0.010 mole) of *p*-toluenesulfonic acid monohydrate (Note 3) contained in a stoppered 500-ml., round-bottomed flask, equipped with a magnetic stirrer, is stirred at room temperature for 30 minutes before 55 g. (0.43 mole) of the solid 1:1 boron trifluoride-acetic acid complex (Note 4) is added, resulting in the evolution of heat. The amber-colored solution is stirred in the stoppered flask at room temperature for 16–20 hours (Note 5), and a solution of 136 g. (1.00 mole) of sodium acetate trihydrate (Note 6) in 250 ml. of water is added. After the flask has been fitted with a reflux condenser, the reaction mixture is heated at reflux for 3 hours and cooled, and the product is extracted with three 100-ml. portions of petroleum ether (b.p. 30–60°). The combined organic extracts are washed successively with aqueous 5% sodium hydrogen carbonate and saturated aqueous

sodium chloride and dried over anhydrous calcium sulfate (Drierite). The solvent is removed with a rotary evaporator, and the residual oil is distilled, yielding 25–30 g. (64–77%) of 3-*n*-butyl-2,4-pentanedione as a colorless liquid, b.p; 84–86° (6 mm.), n_D^{25} 1.4422–1.4462 (Note 7).

2. Notes

1. 2-Heptanone, obtained from Eastman Organic Chemicals, was distilled before use, b.p. 145–147°.
2. Acetic anhydride purchased from Merck & Co., Inc., was fractionally distilled and the fraction, b.p. 139–141°, was used.
3. *p*-Toluenesulfonic acid monohydrate was obtained from Eastman Organic Chemicals and used without purification.
4. The submitters employed 75 g. (0.50 mole) of the liquid 1:2 boron trifluorideacetic acid complex obtained from Harshaw Chemical Company. Since the checkers were unable to obtain this complex from a commercial source, a solid 1:1 complex was prepared according to the literature.[3,4] A 2-l., three-necked flask fitted with a mechanical stirrer, a gas-outlet tube, and a gas-inlet tube extending to the bottom of the flask is charged with a solution of 230 ml. of acetic acid in 750 ml. of 1,2-dichloroethane. A stream of boron trifluoride gas is passed through the reaction flask while the solution is stirred and cooled with an ice bath. After approximately 1 hour, when the mixture is saturated, the addition of boron trifluoride is stopped and the insoluble 1:1 boron trifluoride-acetic acid complex is rapidly collected on a filter, washed with 200 ml. of 1,2-dichloroethane, and transferred to a dry, stoppered container. Since this solid complex tends to liquefy partially on storage, portions to be used in this preparation should be washed with 1,2-dichloroethane immediately prior to use. The amount of catalyst obtained is sufficient to perform this preparation several times.
5. A longer reaction time gives similar results.
6. Sodium acetate trihydrate was obtained from Eastman Organic Chemicals.
7. On a GC column packed with SE-30 silicone gum on Chromosorb P and heated to 150°, the product exhibits a single peak with a retention time of 12.3 minutes; under the same conditions the peak for 2-heptanone has a retention time of 4.4 minutes; The product, which is partially enolic, has IR bands (CCl_4) at 1725(sh), 1695, and 1605 cm.$^{-1}$ with a UV maximum (95% C_2H_5OH) at 288 nm. (ε 2560) and ^{1}H NMR peaks (CCl_4) at δ 0.7–2.0 (m, 9H, aliphatic C*H*), 2.10 (s, 6H, 2COCH_3), 3.57 (t, *J* = 7 Hz., 0.7H, COC*H*CO), and 16.50 (s, 0.3H, enolic O*H*). The mass spectrum exhibits a molecular ion at *m/e* 156 with abundant fragment peaks at *m/e* 100, 71, 58, 44, and 43 (base peak).

3. Discussion

This procedure for the acetylation of methyl alkyl ketones to β-diketones is a modification[5] of an earlier method, which used boron trifluoride gas as the catalyst.[6] 3-

n-Butyl-2,4-pentanedione has also been prepared by the acetylation of 2-heptanone catalyzed with boron trifluoride gas,[7] by the thermal rearrangement of the enol acetate of 2-heptanone,[7] and by the alkylation of the potassium enolate of 2,4-pentanedione with *n*-butyl bromide.[8]

In this procedure, the ketone is first converted to its enol acetate by reaction with acetic anhydride in the presence of a protic acid. Since enol acetylation is performed under equilibrating conditions, the more stable enol acetate, (usually the more highly substituted isomer) is produced. Acetylation of this enol acetate, catalyzed by boron trifluoride, usually leads to the formation of the enol acetate of a β-diketone, which is cleaved by boron trifluoride, forming acetyl fluoride and the borofluoride complex of the β-diketone. Thus, this procedure offers a convenient and general synthetic route to 3-substituted-2,4-pentanediones.[5] The acylation of 2-butanone to 3-methyl-2,4-pentanedione (48%); 2-pentanone to 3-ethyl-2,4-pentanedione (57%); phenylacetone to 3-phenyl-2,4-pentanedione (68%); and 3-methyl-2-butanone to 3,3-dimethyl-2,4-pentanedione (40–48%) have been reported by the submitters.

A similar acetylation procedure (without *p*-toluenesulfonic acid) has been employed to prepare other β-diketones.[5] For example, cyclohexanone was converted to 2-acetylcyclohexanone (73%); cyclopentanone yielded 2-acetylcyclopentanone (80%); 3-pentanone yielded 3-methyl-2,4-hexanedione (81%); dibenzyl ketone yielded 1,3-diphenyl-2,4-pentanedione (72%); and acetophenone gave benzoylacetone (70%).

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

1:1 boron trifluoride-acetic acid complex

boron trifluorideacetic acid complex

potassium enolate of 2,4-pentanedione

acetic acid (64-19-7)

acetic anhydride (108-24-7)

sodium hydrogen carbonate (144-55-8)

Cyclohexanone (108-94-1)

sodium chloride (7647-14-5)

n-butyl bromide (109-65-9)

1,2-dichloroethane (107-06-2)

calcium sulfate (7778-18-9)

Acetophenone (98-86-2)

Cyclopentanone (120-92-3)

2-Heptanone (110-43-0)

phenylacetone (103-79-7)

2-butanone (78-93-3)

boron trifluoride (7637-07-2)

dibenzyl ketone (102-04-5)

3-methyl-2-butanone (563-80-4)

3-pentanone (96-22-0)

benzoylacetone (93-91-4)

sodium acetate trihydrate (6131-90-4)

2-acetylcyclopentanone (1670-46-8)

3-methyl-2,4-pentanedione (815-57-6)

3,3-dimethyl-2,4-pentanedione (3142-58-3)

3-n-BUTYL-2,4-PENTANEDIONE (1540-36-9)

2-acetylcyclohexanone (874-23-7)

p-toluenesulfonic acid (104-15-4)

acetyl fluoride (557-99-3)

2-pentanone (107-87-9)

3-ethyl-2,4-pentanedione (1540-34-7)

3-phenyl-2,4-pentanedione (5910-25-8)

3-methyl-2,4-hexanedione

1,3-diphenyl-2,4-pentanedione (19588-08-0)

p-toluenesulfonic acid monohydrate (6192-52-5)

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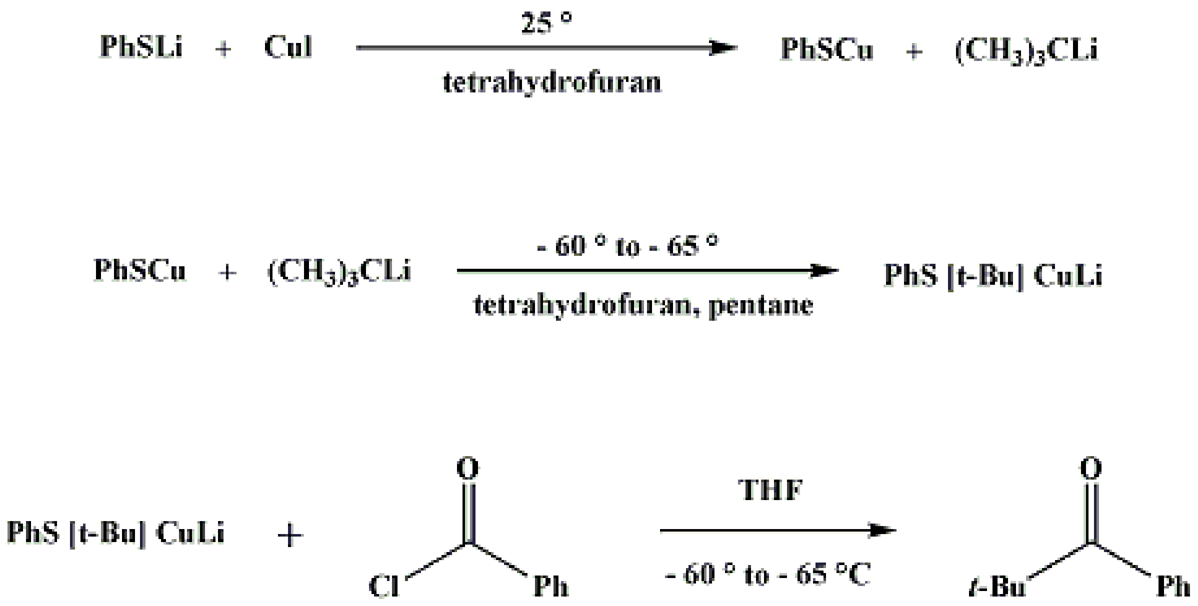
SECONDARY AND TERTIARY ALKYL KETONES FROM CARBOXYLIC ACID CHLORIDES AND LITHIUM PHENYLTHIO(ALKYL)CUPRATE REAGENTS: *tert*-BUTYL PHENYL KETONE

[1-Propanone, 2,2-dimethyl-1-phenyl]



Submitted by Gary H. Posner[1] and Charles E. Whitten.
Checked by Joyce M. Wilkins and Herbert O. House.

1. Procedure

Caution! Since the odor of the thiophenol (benzenethiol) used in this preparation is unpleasant, both steps of this preparation should be conducted in a hood and the glassware used should be washed before it is removed from the hood.

A. *Lithium phenylthio(tert-butyl)cuprate.* A dry, 200-ml., round-bottomed flask is fitted with a magnetic stirring bar and a 100-ml., pressure-equalizing dropping funnel, the top of which is connected to a nitrogen inlet. After the apparatus has been flushed with nitrogen, 50 ml. of 1.60 *M* (0.080 mole) *n*-butyllithium (Note 1) solution is placed in the flask and cooled with an ice bath. Under a nitrogen atmosphere, a solution of 8.81 g. (0.0801 mole) of freshly distilled thiophenol (Note 2) in 30 ml. of anhydrous tetrahydrofuran (Note 3) is added dropwise to the cooled, stirred solution. An aliquot of the resulting solution (Note 4) is standardized by quenching in water, followed by titration with 0.10 *N* hydrochloric acid to a green end point with a bromocresol indicator. The concentration of lithium thiophenoxide prepared in this manner is typically 1.0 *M*.

A dry, 250-ml., three-necked round-bottomed flask is equipped with a sealed mechanical

stirrer (Note 5), a glass stopper, and a rubber septum through which are inserted hypodermic needles used to evacuate the flask and to admit nitrogen. After the apparatus has been flushed with nitrogen, 4.19 g. (0.0220 mole) of purified copper(I) iodide (Note 6) is added, and while warming with a flame, the apparatus is evacuated, then refilled with nitrogen. After this procedure has been performed twice, the flask is allowed to cool, the stopper is replaced with a thermometer, and 45 ml. of anhydrous tetrahydrofuran is added (Note 3) with a hypodermic syringe. With continuous stirring, 22 ml. of 1.0 *M* (0.022 mole) lithium thiophenoxide solution is added with a syringe to the slurry of copper (I) iodide. After 5 minutes, the resulting yellow solution is cooled, with continuous stirring, to –65° with an acetone–dry ice cooling bath. Some copper(I) thiophenoxide usually separates from solution at *ca.* –45°. When the temperature of the mixture has reached *ca.* –65°, 13.6 ml. (0.0218 mole) of 1.60 *M tert*-butyllithium (Note 7) solution is added with a syringe to the stirred mixture at such a rate that the temperature of the mixture remains at –60° to –65°. The resulting cloudy yellow-orange solution of the cuprate reagent is stirred at –60° to –65° for 5 minutes (Note 8).

B. *tert-Butyl phenyl ketone.* With a syringe a solution of 2.81 g. (0.0200 mole) of freshly distilled benzoyl chloride (Note 9) in 15 ml. of anhydrous tetrahydrofuran (Note 3) is added dropwise, with stirring, to the cold solution (–60° to –65°) of the cuprate reagent. The resulting yellow-brown solution is stirred for 20 minutes (at –60° to –65°) and quenched by the addition, with a syringe, of 5 ml. of anhydrous methanol. The red-orange reaction mixture is allowed to warm to room temperature and then poured into 100 ml. of aqueous saturated ammonium chloride. The copious precipitate of copper(I) thiophenoxide is separated by suction filtration and washed thoroughly with several 50-ml. portions of diethyl ether. The combined filtrate is extracted with three 100-ml. portions of ether. The combined ethereal solution is washed with two 50-ml. portions of aqueous 1 *N* sodium hydroxide and with one 50-ml. portion of aqueous 2% sodium thiosulfate. Each of the aqueous washes is extracted in turn with a fresh 50-ml. portion of ether. The combined ethereal solution is dried with anhydrous magnesium sulfate, filtered, and concentrated by distillation through a short Vigreux column. The residual pale yellow liquid (Note 10) is distilled through a short column under reduced pressure, yielding 2.73–2.82 g. (84–87%) of *tert*-butyl phenyl ketone as a colorless liquid b.p. 105–106° (15 mm.), 114–115° (44 mm.), n_D^{20} 1.5092, n_D^{25} 1.5066 (Note 11).

2. Notes

1. Solutions containing approximately 1.6 *M* *n*-butyllithium in hexane were purchased either from Alfa Inorganics, Inc., or from Foote Mineral Company. The concentration of *n*-butyllithium in these solutions can be determined either by a double titration procedure[2] or by dilution with anhydrous tetrahydrofuran, followed by titration with 2-butanol[3] in the presence of a 2,2'-bipyridyl indicator [*Org. Synth.*, **Coll. Vol. 6** 121 (1988)]. In either case the total base concentration in the reagent is determined by titration with standard aqueous acid.
2. Thiophenol, purchased from Aldrich Chemical Company, Inc., was redistilled

before use; b.p. 65–66° (42 mm.).

3. Commercial anhydrous tetrahydrofuran was distilled from lithium aluminum hydride and stored under nitrogen.

4. The submitters report that this solution may be stored under nitrogen at 0° for several days without deterioration. Phenylthiocopper is now commercially available from the Alpha Division of the Ventron Corp., 152 Andover St., Danvers, Massachusetts 01923.

5. Although the submitters had recommended use of a magnetic stirring bar, the checkers encountered considerable difficulty in maintaining adequate stirring of the cold reaction mixture with a magnetic stirrer and recommend use of a sealed mechanical stirrer such as a Truebore® stirrer.

6. Copper(I) iodide, purchased from Fisher Scientific Company, was purified by continuous extraction with anhydrous tetrahydrofuran in a Soxhlet extractor for approximately 12 hours, to remove colored impurities. The residual copper(I) iodide was then dried under reduced pressure at 25° and stored under nitrogen in a desiccator.

7. A pentane solution of *tert*-butyllithium (purchased from either Alfa Inorganics, Inc., or Lithium Corporation of America, Inc.) was standardized by one of the previously described titration procedures (Note 1). If possible, it is desirable to use a freshly opened bottle of *tert*-butyllithium since previously used bottles of this reagent often contain lithium *tert*-butoxide, which will lead to formation of a contaminant in the final product (Note 10).

8. Although the submitters report that this reagent is stable at 0° (*i.e.*, still reactive toward benzoyl chloride) for periods of at least one hour under a nitrogen atmosphere,[3,4] the checkers repeatedly observed evidence of thermal decomposition when the solution was allowed to warm above –40°. This decomposition was indicated by the appearance of a red-brown coloration as the reagent was warmed to –40°; as the temperature was raised further to –25° and to 0°, the mixture progressively exhibited a darker brown color.

9. Benzoyl chloride (purchased from Eastman Organic Chemicals) was redistilled before use; b.p. 35–36° (0.5 mm.).

10. The checkers found that with previously opened bottles of *tert*-butyllithium, the crude product was often contaminated with *tert*-butyl benzoate (from lithium *tert*-butoxide; see (Note 7)). The presence of this impurity in the crude product may be detected either by the presence of an extra IR peak at 1720 cm.$^{-1}$ (conjugated ester), or by GC analysis. On a 1.3-m. GC column, packed with silicone fluid, No. SE-52, suspended on Chromosorb P and operated at 155°, the retention time of *tert*-butyl phenyl ketone was 4.4 minutes, and the retention times of potential impurities, methyl benzoate and *tert*-butyl benzoate were 2.4 minutes and 7.8 minutes, respectively. If a small amount of *tert*-butyl benzoate is present in the crude product, it is most easily removed by heating a mixture of the crude product with 1% by weight of *p*-toluenesulfonic acid on a steam bath for 10 minutes followed by partitioning the product between ether and aqueous sodium hydrogen carbonate. After the resulting ether solution has been dried and distilled, pure *tert*-butyl phenyl ketone is obtained.

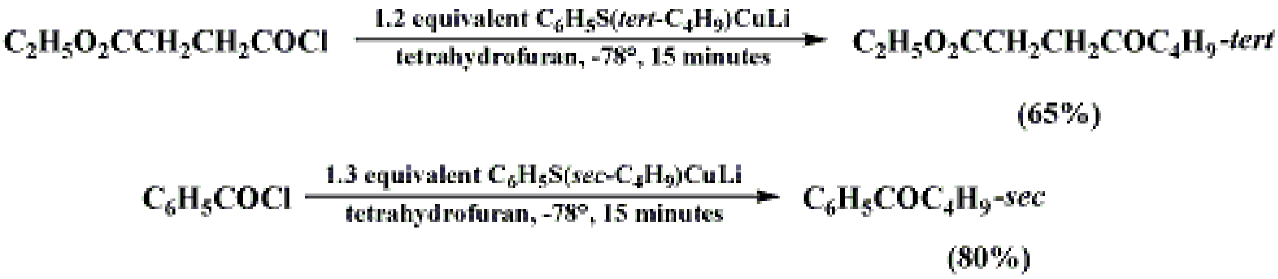
11. The product exhibits a single GC peak (see (Note 10)). The spectral properties of the product are as follows; IR (CCl_4) $cm.^{-1}$: 1680 (conjugated ketone), 1395 and 1370 [$C(CH_3)_3$]; ^1H NMR (CCl_4), δ(multiplicity, number of protons, assignment): 1.30 [s, 9H, $C(CH_3)_3$], 7.2–7.9 (m, 5H, C_6H_5); UV (95% C_2H_5OH) nm. max. (ε): 237 (7350) and 272 (620); mass spectrum *m/e* (relative intensity): 162 (M,45), 106 (28), 105 (100), 77 (63), 57 (40), 51 (23), and 41 (30). The physical constants reported for the product are: b.p. 103–104° (13 mm.).[5] n_D^{20} 1.5090.[6]

3. Discussion

tert-Butyl phenyl ketone has been prepared by the reactions of benzoic acid with *tert*-butyllithium,[7] of acetophenone with methyl iodide and base,[5,9] of benzaldehyde with *tert*-butylmagnesium chloride followed by oxidation,[10], and of 2,2-dimethylpropanoyl chloride with phenylmagnesium bromide.[11]

The procedure described here illustrates the preparation of mixed lithium arylhetero(alkyl) cuprate reagents and their reactions with carboxylic acid chlorides.[4] These mixed cuprate reagents also react with α,α'-dibromoketones,[12] primary alkyl halides,[4] and α,β-unsaturated ketones,[4] with selective transfer of the alkyl group.

Two limitations on the utility of organocopper reagents have often been the difficulty in using thermally unstable lithium *sec*- and especially *tert*-alkylcuprates[13] and the need for a large (*e.g.*, 300–500%) excess of an organocuprate to achieve complete conversion of substrate to product. Both of these limitations are circumvented by using lithium phenylthio(*tert*-alkyl)cuprates, which react with approximately equimolar amounts of carboxylic acid chlorides, forming the corresponding *tert*-alkyl ketones in high yield, even with the yield based on the transferred alkyl group. Furthermore, this alkyl group transfer can be achieved in the presence of other functional groups (*e.g.*, remote halogen or ester functionalities) in the carboxylic acid chloride substrate (Equation 1). Transfer of secondary alkyl groups can also be accomplished efficiently in this way (Equation 2).



The reaction of *tert*-alkyl Grignard reagents with carboxylic acid chlorides in the presence of a copper catalyst provides *tert*-alkyl ketones in substantially lower yields than those reported here.[4,14] The simplicity and mildness of experimental conditions and isolation procedure, the diversity of substrate structural type, and the functional group selectivity of these mixed organocuprate reagents render them very useful for conversion of carboxylic acid chlorides to the corresponding secondary and tertiary alkyl ketones.[15]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 137

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

sodium hydroxide (1310-73-2)

sodium hydrogen carbonate (144-55-8)

sodium thiosulfate (7772-98-7)

nitrogen (7727-37-9)

Benzoic acid (65-85-0)

copper (7440-50-8)

benzaldehyde (100-52-7)

Acetophenone (98-86-2)

benzoyl chloride (98-88-4)

Methyl iodide (74-88-4)

Phenylmagnesium bromide (100-58-3)

methyl benzoate (93-58-3)

Pentane (109-66-0)

Thiophenol, Benzenethiol (108-98-5)

copper(I) iodide (7681-65-4)

magnesium sulfate (7487-88-9)

bromocresol

butyllithium, n-butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

hexane (110-54-3)

2-Butanol (78-92-2)

2,2'-bipyridyl (366-18-7)

p-toluenesulfonic acid (104-15-4)

1-Propanone, 2,2-dimethyl-1-phenyl, tert-Butyl phenyl ketone (938-16-9)

lithium thiophenoxide

copper(I) thiophenoxide (34012-88-9)

Phenylthiocopper

2,2-dimethylpropanoyl chloride (3282-30-2)

tert-Butyllithium (594-19-4)

tert-butylmagnesium chloride (677-22-5)

lithium tert-butoxide (1907-33-1)

tert-butyl benzoate (774-65-2)

Lithium phenylthio(tert-butyl)cuprate

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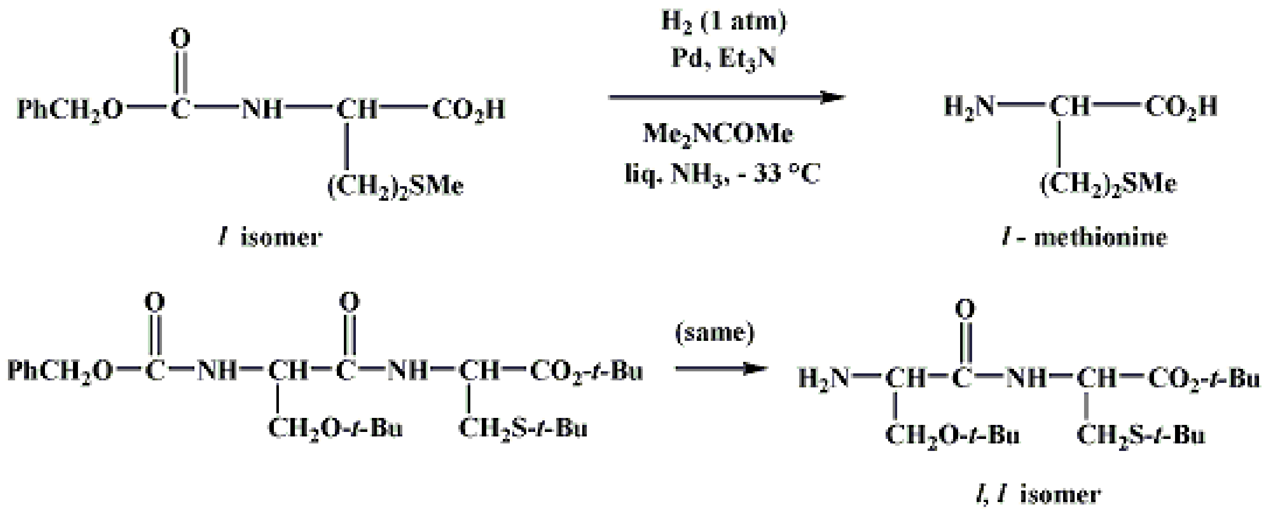
REMOVAL OF *N*α-BENZYLOXYCARBONYL GROUPS FROM SULFUR-CONTAINING PEPTIDES BY CATALYTIC HYDROGENATION IN LIQUID AMMONIA: *O-tert*-BUTYL-L-SERYL-*S-tert*-BUTYL-L-CYSTEINE *tert*-BUTYL ESTER



Submitted by Arthur M. Felix, Manuel H. Jimenz, and Johannes Meienhofer[1,2].
Checked by László Révész and G. Büchi.

1. Procedure

Caution! All operations described in these procedures must be carried out in a well-ventilated hood, since ammonia is highly toxic, hydrogen is extremely flammable, and palladium black is pyrophoric.

A. L-*Methionine.* A dry, 1-l., three-necked, round-bottomed flask is equipped with a dry ice reflux condenser (Note 1), a gas-inlet tube, and a magnetic stirring bar as illustrated in f.htmigure 1. The reaction vessel is immersed in an acetone–dry ice bath, and a total of 300 ml. of ammonia (Note 2) is passed through a drying tower containing potassium hydroxide pellets and collected in the flask. The bath is removed to permit the reaction to proceed at the boiling point of ammonia (–33°), and a gentle stream of dry nitrogen (Note 2) is bubbled into the flask. A solution of 0.708 g. (0.80250 mole) of *N*-benzyloxycarbonyl-L-methionine (Note 3) in 10 ml. of *N,N*-dimethylacetamide (Note 4), 1.02 g. (1.40 ml., 0.0101 mole) of triethylamine (Note 5), and 1.25 g. of freshly prepared palladium black (Note 6) are added. The nitrogen stream is discontinued and replaced by a stream of hydrogen (Note 2) that has been passed through a concentrated sulfuric acid scrubber. The mixture is stirred under reflux for 5.5 hours to effect hydrogenolysis (Note 1). The

hydrogen stream is discontinued, a flow of nitrogen is resumed, and the dry ice is removed from the reflux condenser, permitting rapid evaporation of ammonia (Note 7). The flask is attached to a rotary evaporator (Note 8), and the mixture is evaporated to dryness under reduced pressure. The residue is dissolved in water and filtered through a sintered funnel of medium porosity to remove the catalyst. The filtrate is evaporated to dryness, and the residue (354 mg., 95%) is crystallized from water–ethanol. The white crystalline product, after drying under reduced pressure at 25°, weighs 272–305 mg. (73–82%), m.p. 280–282° (dec.) (Note 9), $[\alpha]_D^{25}$ +23.1° (*c* = 1, aqueous 5 *N* hydrochloric acid) (Note 10).

Figure 1.

Figure 1.

B. O-tert-*Butyl*-L-*seryl*-S-tert-*butyl*-L-*cysteine* tert-*butyl ester*. A dry, 1-l., three-necked, round-bottomed flask is equipped with a dry ice reflux condenser (Note 1), a gas-inlet tube, and a magnetic stirring bar, as illustrated in f.htmigure 1. The reaction vessel is immersed in an acetone–dry ice bath, and a total of 300 ml. of ammonia (Note 2) is passed through a drying tower containing potassium hydroxide pellets and then collected in the flask. The bath is removed, and a gentle stream of nitrogen (Note 2) is bubbled into the flask. A solution of 200 mg. (0.392 mole) of N^{α}-benzyloxycarbonyl-*O*-*tert*-butyl-L-seryl-*S*-*tert*-butyl-L-cysteine *tert*-butyl ester (Note 11) in 4 ml. of *N*,*N*-dimethylacetamide (Note 4), 0.160 g. (0.220 ml., 0.00158 mole) of triethylamine (Note 5), and 200 mg. of palladium black freshly prepared from 333 mg. (0.00188 mole) of palladium(II) chloride (Note 6) are added. The nitrogen stream is discontinued and replaced by a stream of hydrogen (Note 2) that has been passed through a concentrated sulfuric acid scrubber. The mixture is stirred and hydrogenated at reflux temperature for 6 hours (Note 1). The hydrogen stream is discontinued, a stream of nitrogen is again passed into the flask, and the dry ice is removed from the reflux condenser to permit rapid evaporation of ammonia (Note 7). The flask is attached to a rotary evaporator (Note 8) and evaporated to dryness under reduced pressure. The residue is dissolved in 50 ml. of methanol (Note 12), and the suspension is filtered through a 5 × 25-mm. bed of Celite (Note 13) to remove the catalyst. The Celite bed is washed thoroughly with three 20-ml. portions of methanol. The filtrate is evaporated to dryness, and the residue is recrystallized from petroleum ether (b.p. 60–90°). The white crystalline product, after drying under reduced pressure at 25°, weighs 121–127 mg. (82–86%), m.p. 71–73° (Note 14), $[\alpha]_D^{25}$ –5.8° (*c* = 1, methanol) (Note 15).

2. Notes

1. The condenser is filled with crushed dry ice (no solvent). More dry ice is added periodically as necessary throughout Parts A and B.
2. Anhydrous ammonia, prepurified nitrogen, and prepurified hydrogen were all purchased from Matheson Gas Products.
3. *N*-Benzyloxycarbonyl-L-methionine was obtained from Bachem, Inc., 3132 Kashiwa Street, Torrance, California 90505.
4. Spectrophotometric-grade *N*,*N*-dimethylacetamide was purchased from Aldrich Chemical Company, Inc., and stored over molecular sieves.
5. Sequanal-grade triethylamine, obtained from Pierce Chemical Company, Rockford, Illinois, was distilled under nitrogen from ninhydrin, which was also purchased from Pierce Chemical Company.
6. The catalyst is prepared[4,5] with palladium(II) chloride and 97–100% formic acid, which were purchased from Engelhard Industries Division (Engelhard Minerals and Chemicals Corporation) and MC and B Manufacturing Chemists, respectively. A 10.4-ml. aliquot containing 2.08 g. (0.0117 mole) of palladium(II) chloride from a stock solution of palladium(II) chloride in 2 *N* hydrochloric acid (10 g. per 50 ml.) is added to 104

ml. of boiling water in a 600-ml. beaker. A 0.51-g. (0.42 ml., 0.011 mole) portion of formic acid and 33 ml. of aqueous 10% potassium hydroxide are added to the boiling solution. The pH of the resulting slightly alkaline solution (pH □ 8) is adjusted to 6–7 by adding formic acid, after which the mixture is allowed to boil for an additional 5 minutes. The catalyst is isolated by careful suction filtration. *Caution! The palladium catalyst is pyrophoric and must always be kept wet with water or methanol to prevent contact with air.*

To minimize the danger in handling palladium black, the submitters recommend that filtration, washing, and transfer of the catalyst be performed with a "syringe filter."[6] This device was fashioned from a 10-ml. Plastipak syringe, purchased from Becton-Dickinson and Company, Rutherford, New Jersey, by cutting off the tip at the end of the cylindrical barrel and forcing a tight-fitting, porous disk of polypropylene into its place. The use of this "syringe filter" permits the removal of most of the solvent and the safe transfer of the catalyst to the flask with little danger of ignition or moisture absorption.

The catalyst is washed thoroughly with 100 ml. of water and with 200 ml. of absolute methanol to remove all traces of water, after which it is transferred to the flask under nitrogen with a minimal amount of absolute methanol. To be effective the catalyst must be pyrophoric, and extreme care must be taken during this operation to prevent ignition of the methanol or ammonia. The catalyst must not be allowed to become dry or to collect on the wall of the flask above the surface of the liquid ammonia.

7. Evaporation of the ammonia generally requires several hours. Toward the end of the evaporation, it is advantageous to immerse the flask in an acetone bath, taking care to avoid bumping.

8. *N,N*-Dimethylacetamide remains in the flask and is removed by rotary evaporation under reduced pressure with a water bath kept at a temperature lower than 35°. The submitters recommend that the evaporation be carried out directly in the same three-necked flask by stoppering the two side arms and adjusting the angle of the rotary evaporator.

9. The melting point is corrected [lit.,[7] m.p. 280–281° (dec.)].

10. The literature[8] reports $[\alpha]_D^{25}$ +23.2° (c = 1, 5*N* hydrochloric acid). The product was analyzed by the submitters. Analysis calculated for $C_5H_{11}NO_2S$: C, 40.25; H, 7.43; N, 9.39; S, 21.49. Found: C, 40.14; H, 7.42; N, 9.50; S, 21.52. The product was homogeneous according to TLC on precoated silica gel G plates purchased from Analtech, Inc., Newark, Delaware, and developed with the following two solvent systems (solvents, volume ratios of solvents in the same order): 1-butanol–acetic acid–ethyl acetate–water, 1:1:1:1, R_f 0.49; 1-butanol-acetic acid-pyridine-water, 15:3:10:12, R_f 0.51.

11. The protected dipetide was prepared by the procedure described in the following paragraph using *N*-benzyloxycarbonyl-*O*-*tert*-butyl-L-serine purchased from Chemical Dynamics Corporation (P. O. Box 395, South Plainfield, New Jersey 07080), tetrahydrofuran distilled from lithium aluminum hydride [*Caution!* For a warning regarding this method for purifying tetrahydrofuran, see *Org. Synth.*, **Coll. Vol. 5**, 976 (1973)], and *N*-methylmorpholine distilled from ninhydrin. *S*-*tert*-Butyl-L-cysteine *tert*-butyl ester[9] was prepared as follows: To a suspension of 10 g. (0.082 mole) of L-cysteine in 75 ml. of dry dioxane in a 200-ml. pressure bottle cooled in an ice bath are added 10.0 ml. of concentrated sulfuric acid and 56 g. (95 ml., 1.0 mole) of isobutylene. The pressure bottle is stoppered and shaken at room temperature for 18 hours. The mixture is cooled to 0°, the pH is adjusted to 10 by adding 160 ml. of aqueous 2 *N* sodium hydroxide, and the product is extracted with three 100-ml. portions of diethyl ether. The ethereal solution is washed with three 80-ml. portions of aqueous 5% sodium hydrogen carbonate and three 80-ml. portions of water, dried over anhydrous magnesium sulfate, and concentrated to a volume of *ca.* 200 ml. The concentrate is stirred and cooled at 0° as 90.8 ml. (0.0908 mole) of 1 *M* hydrogen chloride in ether is added. The resulting mixture is stirred for several minutes, the precipitated hydrochloride is filtered, and the filter

cake is washed with ether. The white crystalline product weighs 18.1 g. (81%) and is used without further purification. The submitters caution that the hydrochloride sublimes under reduced pressure. Recrystallization from chloroform–petroleum ether affords an analytical sample, double m.p. 187° and 219–222°, $[\alpha]^{25}_{D}$ +5.85° (*c* = 1, methanol). Analysis calculated for $C_{11}H_{23}NO_2S\cdot HCl$: C, 48.96; H,8.96; N, 5.19; S, 11.88; Cl, 13.14. Found: C, 49.07; H, 9.25; N, 5.13; S, 12.06; Cl, 13.07. The free base is obtained by dissolving the hydrochloride in aqueous 10% sodium carbonate, extracting the mixture with ether, and evaporating the ethereal solution under reduced pressure.

A dry, three-necked, round-bottomed flask is equipped with a mechanical stirrer, a rubber septum, and a 200-ml., pressure-equalizing dropping funnel mounted with a T-shaped gas-inlet connected to both a nitrogen source and a bubbler serving as a gas exit. The flask is charged with a solution of 14.9 g. (0.0506 mole) of N^{α}-benzyloxycarbonyl-*O*-*tert*-butyl-L-serine in 100 ml. of tetrahydrofuran and purged with nitrogen. The solution is stirred and cooled at −15° as 5.12 g. (5.67 ml., 0.0506 mole) of *N*-methylmorpholine and 6.91 g. (6.61 ml., 0.0506 mole) of isobutyl chloroformate are added rapidly through the septum with syringes. One minute after the addition is completed, a precooled (−20°) solution of 11.8 g. (0.0506 mole) of *S*-*tert*-butyl-L-cysteine *tert*-butyl ester in 100 ml. of tetrahydrofuran is added dropwise at −15°. The contents of the flask are stirred for 1 hour at −15° and for 3 hours at room temperature. The mixture is then evaporated to dryness under reduced pressure and dissolved in 150 ml. of ethyl acetate. The solution is washed with three 50-ml. portions of each of the following: 5% sodium hydrogen carbonate in water, water, 1 *M* citric acid in water, and water. The ethyl acetate solution is then dried over anhydrous magnesium sulfate, the solvent is evaporated, and the remaining solid is recrystallized from ethyl acetate–petroleum ether (b.p. 35–60°). The white crystalline product, after drying under reduced pressure at 25°, weighs 25.5 g. (98.6%), m.p. 94.5–95°, $[\alpha]^{25}_{D}$ −2.47° (*c* = 1, methanol). TLC of the product on plates precoated with silica gel G and purchased from Analtech, Inc., Newark, Delaware, each showed a single spot when developed with the following three solvent systems (solvents, volume ratio of solvents in the same order): 1-butanol–acetic acid–ethyl acetate–water, 1:1:1:1, R_f 0.90; 1-butanol–acetic acid–water, 4:1:1, R_f 0.81; 1-butanol–acetic acid–pyridine–water, 15:3:10:12, R_f 0.81. Analysis calculated for $C_{26}H_{42}N_2O_6S$: C, 61.15; H, 8.29; N, 5,49; S, 6.28. Found: C, 61.15; H, 8.52; N, 5.42; S, 6.44.

12. Other solvents including *N*,*N*-dimethylformamide and water may also be used to dissolve the products.

13. In some cases the catalyst was not entirely removed, and the filtrate contained trace amounts of palladium. In those instances the submitters evaporated the filtrate to a small volume and repeated the filtration using a large bed of Celite.

14. The melting point was taken on a Reichert hot stage microscope. This instrument is available from William J. Hacker and Company, Inc., P.O. Box 646, West Caldwell, New Jersey 07006.

15. The recrystallized product was analyzed by the submitters. Analysis calculated for $C_{18}H_{36}N_2O_4S$: C, 57.41; H, 9.63; N, 7.43; S, 8.51. Found: C, 57.60; H, 9.66; N, 7.37; S, 8.25. TLC ((Note 10)) run by the submitters showed a single spot for the product in each of three following solvent systems (solvents, volume ratio of solvents in the same order): chloroform–methanol–acetic acid, 85:10:5, R_f 1-butanol–acetic acid–water, 4:1:1, R_f 0.58; 1-butanol–acetic acid–pyridine–water, 15:3:10:12, R_f 0.71.

3. Discussion

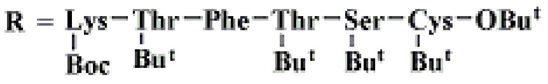
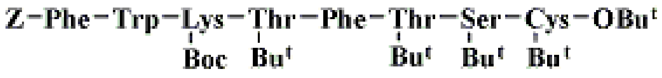
The protection of the amino terminus of a peptide with the benzyloxycarbonyl group combined with protection of the carboxyl terminus and all side-chain functions with *tert*-butyl-derived groups[10] enables totally selective liberation of the terminal amino function by catalytic hydrogenolysis. This combination of protecting groups is currently considered "ideal" for peptide synthesis,[11] except for the rather serious limitation that catalyst poisoning has

prevented its application to the preparation of peptides that contain cysteine, methionine, or other residues bearing divalent sulfur groups. The submitters have recently discovered[12] that catalyst poisoning is greatly diminished when liquid ammonia is used as solvent for palladium-catalyzed hydrogenation. This solvent enables quantitative cleavage of *N*α-behzyloxycarbonyl groups on many protected peptides bearing *S*-protected cysteine residues. The method has been used successfully in syntheses of oxytocin[13] and somatostatin.[3]

The present procedures illustrate this method with the regeneration of L-methionine and the preparation of the *tert*-butyl ester of *O*-*tert*-butyl-L-seryl-*S*-*tert*-butyl-L-cysteine[3] from their respective *N*α-benzyloxycarbonyl derivatives. No other procedures for the preparation of this protected dipeptide have been reported. These preparations and other peptide syntheses have served to establish the complete stability of the *S*-methyl substituent and various protecting groups including the *tert*-butyl ester (OBu^t), *tert*-butyl ether (Bu^t), *N*-*tert*-butyloxycarbonyl (Boc), *S*-*tert*-butyl (Bu^t), *S*-benzyl (Bzl), and *S*-acetamidomethyl (Acm) groups.[14] Table I summarizes the results of hydrogenations carried out with sulfur-containing peptides having chain lengths varying from 6 to 13 amino acid residues, demonstrating the stability of various protecting groups to this procedure for hydrogenolysis. In each case the Nα-benzyloxycarbonyl (Z) group was removed quantitatively and the *tert*-butyl based protecting groups were unaffected. As a result of these findings, sulfur-containing amino acids may now be used in peptide synthesis by the "ideal" combination of aminoterminal benzyloxycarbonyl protection with *tert*-butyl-type blocking groups on all other functions.

TABLE I

REMOVAL OF *N*α-BENZYLOXYCARBONYL GROUPS FROM SULFUR-CONTAINING PEPTIDES

Peptide  *a*	Amount (g.) (mmole.)	Dimethylacetamide (ml.)	Ammonia (ml.)	Triethylamine (mmole.)	Palladium (II) Chloride (g.)	Yield[b] (%)
	3.05 (2.54)	10.0	300	40	2.08	98
	0.418 (0.272)	3.0	35	4.0	0.227	81

Z–Phe–Phe–Trp–Lys(Boc)–Thr(Bu^t)–Phe–Thr(Bu^t)–Ser(Bu^t)–Cys(Bu^t)–OBu^t	0.263 (0.160)	3.5	30	4.0	0.133	91
Z–Asn–Phe–Phe–Trp–Lys(Boc)–Thr(Bu^t)–Phe–Thr(Bu^t)–Ser(Bu^t)–Cys(Bu^t)–OBu^t	0.305 (0.170)	3.0	60	4.7	0.532	100
Z–Lys(Boc)–Asn–Phe–Phe–Trp–Lys(Boc)–Thr(Bu^t)–Phe–Thr(Bu)–Ser(Bu^t)–Cys(Bu^t)–OBu^t	0.368 (0.182)	3.0	70	4.7	0.596	89
Z–Cys(Bu^t)–Lys(Boc)–Asn–Phe–Phe–Trp–Lys(Boc)–Thr(Bu^t)–Phe–Thr(Bu^t)–Ser(Bu^t)–Cys(Bu^t)–OBu^t	0.281 (0.129)	2.0	40	10.0	0.596	86
Z–Gly–Cys(Bu^t)–Lys(Boc)–Asn–Phe–Phe–Trp–Lys(Boc)–Thr(Bu^t)–Phe–Thr(Bu^t)–Ser(Bu^t)–Cys(Bu^t)–OBu^t	0.178 (0.080)	1.3	40	10.0	0.380	85

a Protecting group abbreviations are as follows: *N*-benzyloxycarbonyl (Z), *N*-*tert*-butyloxycarbonyl (Boc), *tert*-butyl ether (Bu^t), and *S*-*tert*-butyl (Bu^t).

b The reaction time was 5.0–6.0 hours in all entries.

Since the use of *N,N*-dimethylacetamide and triethylamine improved the rate and extent of cleavage of the *N*-benzyloxycarbonyl group in several difficult cases, these additives have been incorporated into the submitters' standard procedure and are included in the present procedures. Deprotection with this method has been carried out with as much as 25 g. of the protected peptide.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 137

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14. A procedure for *S*-acetamidomethylation is described in *Org. Synth.*, **Coll. Vol. 6**, 5 (1988).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

palladium black

N^{α}-benzyloxycarbonyl-O-tert-butyl-L-serine

sulfuric acid (7664-93-9)

hydrogen chloride, hydrochloric acid, hydrochloride (7647-01-0)

acetic acid (64-19-7)

ammonia (7664-41-7)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

citric acid (77-92-9)

chloroform (67-66-3)

sodium hydrogen carbonate (144-55-8)

sodium carbonate (497-19-8)

formic acid (64-18-6)

nitrogen (7727-37-9)

1-butanol (71-36-3)

pyridine (110-86-1)

potassium hydroxide (1310-58-3)

palladium (7440-05-3)

palladium(II) chloride

magnesium sulfate (7487-88-9)

dioxane (5703-46-8)

isobutylene (9003-27-4)

Methionine, L-Methionine (63-68-3)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

N,N-dimethylformamide (68-12-2)

benzyloxycarbonyl (Z)

triethylamine (121-44-8)

S-tert-Butyl (1605-73-8)

N,N-dimethylacetamide, Dimethylacetamide (127-19-5)

cysteine, L-cysteine (52-90-4)

ninhydrin (938-24-9)

isobutyl chloroformate (543-27-1)

N-methylmorpholine (109-02-4)

butyloxycarbonyl (Boc), tert-butyl ether

O-tert-Butyl-L-seryl-S-tert-butyl-L-cysteine tert-butyl ester, tert-butyl ester of O-tert-butyl-L-seryl-S-tert-butyl-L-cysteine (67942-95-4)

N-benzyloxycarbonyl-L-methionine

N$^{\alpha}$-benzyloxycarbonyl-O-tert-butyl-L-seryl-S-tert-butyl-L-cysteine tert-butyl ester

N-benzyloxycarbonyl-O-tert-butyl-L-serine

S-tert-Butyl-L-cysteine tert-butyl ester (45157-84-4)

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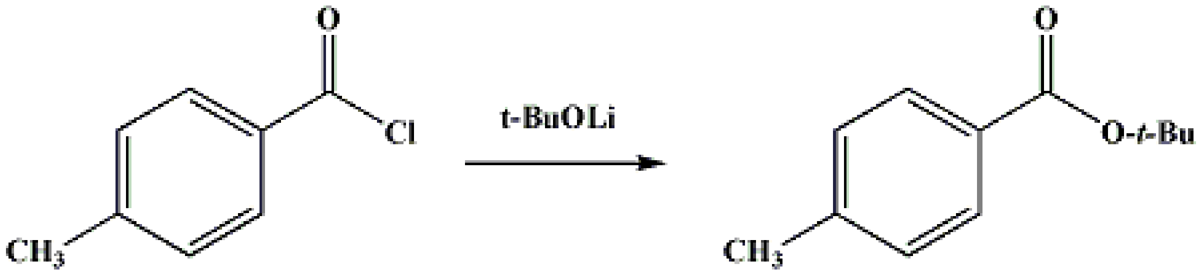
ESTERIFICATION OF HINDERED ALCOHOLS: *tert*-BUTYL *p*-TOLUATE

[Benzoic acid, 4-methyl-, 1,1-dimethylethyl ester]

$$n\text{-}C_4H_9Li + HOC(CH_3)_3 \longrightarrow LiOC(CH_3)_3 + n\text{-}C_4H_{10}$$



Submitted by G. P. Crowther[1], E. M. Kaiser[2], R. A. Woodruff[2], and C. R. Hauser[13].
Checked by A. Brossi, R. A. LeMahieu, and P. LaSalle.

1. Procedure

A 200-ml., one-necked, round-bottomed flask equipped with a Claisen adapter, a condenser, an addition funnel, and a magnetic stirring bar is charged with 50 ml. of *tert*-butyl alcohol (Note 1). Under nitrogen, 22.6 ml. of a 1.55 *M* solution (0.0350 mole) of *n*-butyllithium in hexane (Note 2) is added slowly from a syringe (Note 3), giving a turbid reaction mixture. A water bath is used to keep the mixture near room temperature. After stirring for 15 minutes, a solution of 5.42 g. (0.0351 mole) of *p*-toluoyl chloride (Note 4) in 25 ml. of anhydrous diethyl ether (Note 5) is added dropwise to the stirred mixture. The resulting yellow slurry is stirred at room temperature for 15 hours (Note 6). The yellow suspension (Note 7) is transferred with 100 ml. of ether to a separatory funnel and washed with three 25-ml. portions of saturated sodium chloride, and dried over magnesium sulfate. The ether is removed by distillation, and the residual oil distilled under reduced pressure, yielding a small forerun (0.10 g.) and 5.31–5.51 g. (79–82%) of *tert*-butyl *p*-toluate, b.p. 98–101° (4.2 mm.) (Note 8).

2. Notes

1. *tert*-Butyl alcohol (Eastman Organic Chemicals white label) was dried by distillation from calcium hydride.
2. The solution of 1.55 *M* *n*-butyllithium in hexane was obtained from Foote Mineral Company.

3. Formation of the lithium *tert*-butoxide in this manner is very exothermic and causes the hexane to boil during addition.

4. *p*-Toluoyl chloride was prepared by treating *p*-toluic acid (Eastman Organic Chemicals white label) with thionyl chloride (Eastman Organic Chemicals white label). The *p*-toluoyl chloride used was distilled, b.p. 48–49° (0.1 mm.).

5. Anhydrous ether was distilled from lithium aluminum hydride and stored over sodium ribbon prior to use.

6. In one instance an additional 75 ml. of anhydrous ether was added to make the slurry less viscous. The ester was obtained in the same yield in another run after stirring only 30 minutes.

7. Alternatively, the reaction mixture may be concentrated with a rotary evaporator, removing excess *tert*-butyl alcohol. Ether and water are added, and the mixture transferred to the separatory funnel; the yield of ester is unchanged.

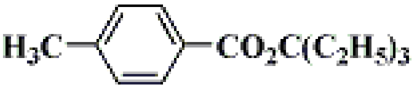
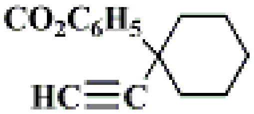
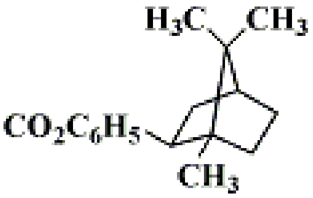
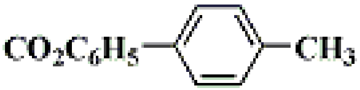
8. With the same procedure *tert*-butyl phenylacetate has been prepared in 47% yield.[4] When esters of less common alcohols were prepared, anhydrous ether was used as a solvent instead of excess alcohol, with equivalent amounts of alcohol, *n*-butyllithium, and acid chloride employed. Thus, the triethylcarbinol ester of *p*-toluic acid and the 2,2-diphenylethanol ester of benzoic acid have been prepared in 72 and 70% yields, respectively.

3. Discussion

The present procedure[4] is an especially effective method for the synthesis of esters of aromatic acids and hindered tertiary alcohols or of acid-labile alcohols such as 2,2-diphenylethanol. The yields are excellent, and the reaction procedure is simple. The method is illustrated by the preparation of *tert*-butyl *p*-toluate, a compound that could not be prepared by a conventional method[5] of esterification involving the acid chloride and *tert*-butyl alcohol in the presence of *N,N*-dimethylaniline. Examples of esters prepared by this method are illustrated in Table I.

TABLE I
ESTERS PREPARED BY ALKOXIDE METHODS

Ester	Yield, %	Ester	Yield, %
$C_6H_5CH_2CO_2C(CH_3)_3$	47[a]	$C_6H_5CO_2CH_2CH(C_6H_5)_2$	70[b]
		$C_6H_5CO_2C(CH_3)_3$	89[c]
		$C_6H_5CO_2CCH_3(C_2H_5)_2$	87[c]
		$C_6H_5CO_2C(C_2H_5)_3$	94[c]
		$C_6H_5CO_2CH(CH_3)(t\text{-}C_4H_9)$	76[c]

		$C_6H_5CO_2CH_2(t\text{-}C_4H_9)$	78[c]
	72[b]		70[c]
			69[c]
	91[c]		
	94[c]		85[d]
$(CH_3)_3CCO_2C(CH_3)_3$	64[c]		
$(CH_3)_3CCO_2C(C_2H_5)_3$	75[c]	$(i\text{-}C_3H_7)_2CHCO_2C(C_2H_5)_3$	88[e]
$C_6H_5CH{=}CHCO_2C(CH_3)_3$	88[c]	$(tC_4H_9)CH_2CO_2C(C_2H_5)_3$	86[e]
$C_6H_5CH_2CH_2CO_2C(CH_3)_3$	72[c]	$(tC_4H_9)_2CHCO_2C(C_2H_5)_3$	30[e]

a As described in the accompanying procedure.

b As described in the accompanying procedure except ether used as solvent (see (Note 8)).

c Prepared in refluxing tetrahydrofuran with 1.0 equivalent of appropriate alcohol, 1.1 equivalents of *n*-butyllithium, and 1.1 equivalents of acid chloride.[4]

d Prepared by adding an equivalent amount of *p*-toluenesulfonyl chloride to a suspension 2,2-diphenylethoxide in ether.[6]

e Prepared by adding 0.50 equivalent of acid chloride to an ether suspension of sodium triethylmethoxide, which was obtained from 0.52 equivalent of sodium amide and 0.55 equivalent of triethylcarbinol.[7]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

2,2-diphenylethoxide

ether, diethyl ether (60-29-7)

thionyl chloride (7719-09-7)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

sodium (13966-32-0)

N,N-dimethylaniline (121-69-7)

magnesium sulfate (7487-88-9)

sodium amide (7782-92-5)

butyllithium, n-butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

Triethylcarbinol (597-49-9)

lithium aluminum hydride (16853-85-3)

hexane (110-54-3)

p-Toluic acid (99-94-5)

tert-butyl alcohol (75-65-0)

calcium hydride (7789-78-8)

2,2-diphenylethanol (1883-32-5)

p-Toluenesulfonyl chloride (98-59-9)

Benzoic acid, 4-methyl-, 1,1-dimethylethyl ester, tert-Butyl p-toluate (13756-42-8)

sodium triethylmethoxide

tert-butyl phenylacetate

lithium tert-butoxide (1907-33-1)

p-toluoyl chloride (874-60-2)

triethylcarbinol ester of p-toluic acid

2,2-diphenylethanol ester of benzoic acid

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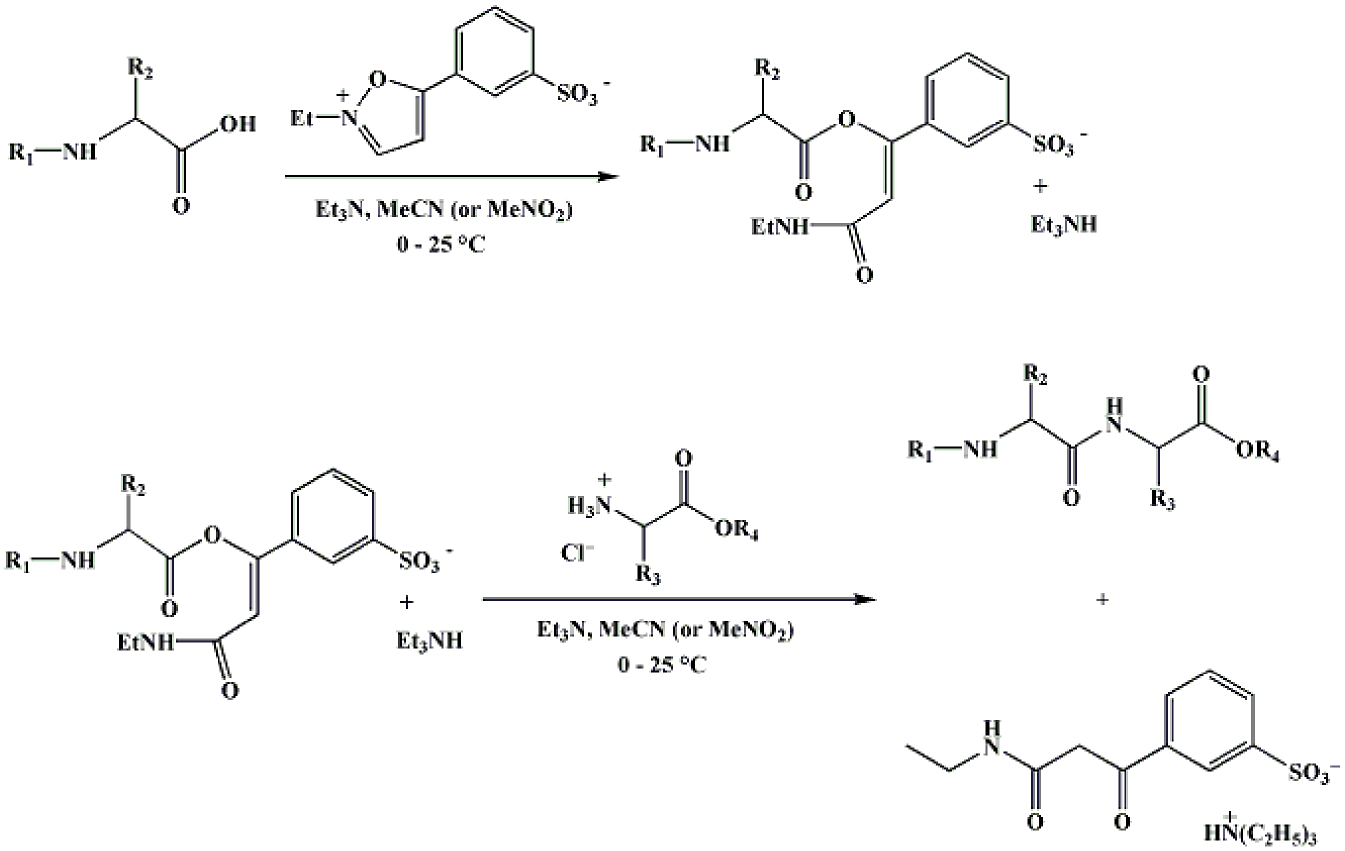
PEPTIDE SYNTHESES USING *N*-ETHYL-5-PHENYLISOXAZOLIUM-3'-SULFONATE: CARBOBENZOXY-L-ASPARAGINYL-L-LEUCINE METHYL ESTER AND *N*-CARBOBENZOXY-3-HYDROXY-L-PROLYLGLYCYLGLYCINE ETHYL ESTER

[L-Leucine, *N*-[N^2-[(phenylmethoxy)carbonyl]-L-asparginyl]-, methyl ester and Glycine, *N*-[3-hydroxy-1-[(phenylmethoxy)-carbonyl]-L-prolyl]-, ethyl ester]



Submitted by R. B. Woodward[1] and R. A. Olofson[2].
Checked by David L. Carroll, James C. Powers, and Herbert O. House.

1. Procedure

A. *Carbobenzyloxy-L-asparaginyl-L-leucine methyl ester.* A mixture of 2.024 g. (0.00800 mole) of *N*-ethyl-5-phenylisoxazolium-3'-sulfonate (Note 1) and 20 ml. of nitromethane (Note 2) is prepared in a 50-ml., glass-stoppered Erlenmeyer flask and stirred vigorously, at room temperature, with a magnetic stirrer (Note 3). A solution of 2.128 g. (0.00800 mole) of carbobenzyloxy-L-asparagine (Note 4) and 810 mg. (0.00802 mole) of triethylamine (Note 5) and (Note 6) in 15 ml. of nitromethane (Note 2)) is added. Stirring is continued until dissolution of the isoxazolium salt is practically complete, giving a pale yellow solution (*ca.* 8 minutes is required; (Note 3), before 1.452 g. (0.00800 mole) of L-leucine methyl ester hydrochloride (Note 7) is added, followed by a solution of 810 mg. (0.00802 mole) of triethylamine (Note 5) in 5 ml. of nitromethane (Note 2). The resulting mixture is stirred overnight at room temperature, during which time some solid may separate from the solution. The mixture is then transferred to a 100-ml., round-bottomed flask and concentrated with a rotary evaporator. The residue is triturated with warm (*ca.* 60°) aqueous 0.5% sodium hydrogen carbonate, and the resulting suspension is cooled and allowed to stand at 5° for at least 4 hours. The precipitate is collected on a filter, washed thoroughly with a total of 25 ml. of cold water, and dried, leaving 2.36–2.65 g. (75–84%) of the crude peptide, which melts within the range of 168–178°. Recrystallization from acetone–water provides 2.09–2.21 g. (66–70%) of pure carbobenzyloxy-L-asparaginyl-L-leucine methyl ester as fine, colorless crystals, m.p. 175–176.3°, $[\alpha]_D^{24}$ −27.7° (*c* 1.0, methanol) (Note 8).

B. N-*Carbobenzyloxy-3-hydroxy-L-prolylglycylglycine ethyl ester*. A mixture of 760 mg. (0.00300 mole) of *N*-ethyl-5-phenylisoxazolium-3'-sulfonate (Note 1) and 5 ml. of acetonitrile (Note 9) is prepared in a 25-ml., glass-stoppered Erlenmeyer flask. The mixture is cooled to 0° with an ice bath and stirred vigorously with a magnetic stirrer (Note 3). A solution of 796 mg.

(0.00300 mole) of *N*-carbobenzyloxy-3-hydroxy-L-proline (Note 10) and 304 mg. (0.00301 mole) of triethylamine (Note 5) and (Note 6) in 5 ml. of acetonitrile (Note 9) is added. The cold (0–5°) mixture is stirred vigorously until almost all of the isoxazolium salt has dissolved (*ca.* 1–1.5 hours; (Note 3)), then treated with 590 mg. (0.00300 mole) of glycylglycine ethyl ester hydrochloride (Note 11), followed by addition of a solution of 304 mg. (0.00301 mole) of triethylamine (Note 5) in 6 ml. of acetonitrile (Note 9). After this mixture has been stirred for 1 hour at 0–5°, the resulting pale yellow solution is allowed to warm to room temperature and stirred overnight. The reaction solution is then transferred to a 100-ml., round-bottomed flask and concentrated with a rotary evaporator. The residue is partitioned between 10 ml. of aqueous 1% sodium hydrogen carbonate and 50 ml. of ethyl acetate. After the phases are separated, the aqueous phase is extracted with three 10-ml. portions of ethyl acetate, and the combined organic extracts are dried over anhydrous sodium sulfate. The organic solution is concentrated with a rotary evaporator, the residual white crystalline solid is triturated with 20 ml. of water, and the resulting slurry is cooled to 5° and allowed to stand overnight in a refrigerator. Filtration of the cold mixture provides a solid, which is washed with a small amount of cold water and dried. The combined aqueous filtrates are concentrated with a rotary evaporator, and the residual solid is again triturated with 10 ml. of water, allowed to stand overnight at 5°, and filtered. The solids collected total 958–980 mg. (78–80%) of *N*-carbobenzyloxy-3-hydroxy-L-prolylglycylglycine ethyl ester, m.p. 145–146°, $[\alpha]_D^{24}$ −18.5° (*c* 1.0, ethanol) (Note 12).

2. Notes

1. This isoxazolium salt reagent is commonly known and sold as Woodward's Reagent K (see, for example: The Merck Index, 9th ed., 1976, entry 9715). This salt (10 g.) (obtained from the Aldrich Chemical Company, Inc.) was dissolved in 45 ml. of 1 *M* hydrochloric acid and reprecipitated by the slow addition with swirling of 400 ml. of acetone. The salt was collected, washed with 300 ml. of acetone, and dried overnight at 25° under reduced pressure (<1 mm.) to give a fluffy product, m.p. 206–208° (dec.). An isomeric salt, *N*-ethyl-5-phenylisoxazolium-4'-sulfonate, which may be obtained by the usual synthetic procedure,[3 4] is also useful in peptide synthesis.
2. An anhydrous spectral grade of nitromethane, obtained from Fisher Scientific Company, was used without purification.
3. Since the initially formed enol ester rearranges slowly to an imide,[5] the yield depends on the rate at which the isoxazolium salt reacts, and that rate is increased by vigorous stirring. The reaction time for the activation step is approximately 8 minutes in nitromethane at 25° and approximately 1 hour in acetonitrile at 0°. In reactions performed in acetonitrile, the checkers did not obtain complete solution. The reaction flask should be kept in a water bath to minimize heat transfer from the magnetic stirrer to the reaction mixture.
4. Carbobenzyloxy-L-asparagine (obtained from the Aldrich Chemical Company, Inc.) was recrystallized from acetone–water to give the pure acid, m.p. 162–163°.
5. Commercial triethylamine (obtained from Eastman Organic Chemicals), was distilled (b.p. 89–90°) from phosphorus pentoxide and stored under a nitrogen atmosphere. Since the presence of even a small excess of triethylamine is deleterious in these reactions, the quantities of this amine used should be measured by weight rather than volume.
6. The triethylamine salts of peptide acids are often relatively insoluble in acetonitrile or nitromethane; therefore, the supersaturated solution formed on mixing the amine and the acid should be added to this reaction mixture immediately, before crystallization occurs. If crystallization does occur, the mixture should be heated to dissolve the salt, cooled rapidly, and added to the reaction mixture immediately. If it is impossible to obtain a solution of the salt, the peptide acid and then the triethylamine solution may be added separately to the reaction mixture with only a small sacrifice in yield.
7. L-Leucine methyl ester hydrochloride (obtained from the Mann Research Laboratories, Inc.) was recrystallized from methanol–ether, m.p. 149–150°.
8. The reported[6] rotation for this product is $[\alpha]_D^{23}$ −26.3° (*c* 2.0, methanol). IR (KBr) $cm.^{-1}$: 3455, 3400, 3295 (amide NH stretching), 1737 (urethane and ester C=O), 1692 (amide C=O), 1647, 1535 (amide NH bending); ^{1}H NMR (dimethyl sulfoxide-d_6), δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 0.7–1.1 (m, 6H, 2CH_3), 1.4–1.8 (m, 3H, aliphatic C*H*), 2.3–2.7 (m, 2H, CH_2CO), 3.62 (s, 3H, OCH_3), 4.1–4.7 (m, 2H, 2 NC*H*CO), 5.03 (s, 2H, benzylic CH_2), 6.92 (broad, 1H, N*H*), 7.25 (broad, 2H, NH_2), 7.35 (s, 5H, aromatic *H*), 8.17 (broad d, *J* = 7, 1H, N*H*); mass spectrum *m/e* (relative intensity): 393 (M^+, 1), 316 (5), 210 (12), 177 (15), 108 (37), 91 (100), 86 (50), 43 (28).
9. Reagent grade acetonitrile (obtained from Eastman Organic Chemicals) was dried over Linde type 4A molecular sieves, decanted, and used without further purification.
10. *N*-Carbobenzyloxy-3-hydroxy-L-proline (purchased from either Mann Research Laboratories or Sigma Chemical Company) was recrystallized prior to use. The submitters recommend recrystallization from water, but the checkers found it easier to recrystallize the material from a mixture of ethyl acetate and petroleum ether (b.p. 30–60°). In either case, the checkers added a seed crystal to induce crystallization. The recrystallized product melted at 106–107°.
11. Glycylglycine ethyl ester hydrochloride (obtained from Nutritional Biochemicals Corporation) was recrystallized twice from mixtures of ethanol and ether to separate the pure salt, m.p. 181–182°.
12. The reported[7] rotation for this product (m.p. 144–145°) is $[\alpha]_D^{21}$ −11.1° (*c* 1.0, ethanol). The submitters report that the melting point of the product is not changed by recrystallization. IR ($CHCl_3$) cm^{-1}: 3390, 3295 (OH and NH stretching), 1730 (ester and urethane C=O), 1620 (broad, amide C=O), 1520 (broad, amide NH bending); ^{1}H NMR ($CDCl_3$), δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 1.2 (t, *J* = 7, 3H, OCH_2CH_3), 2.0–

2.4 (m, 3H, aliphatic C*H*), 3.5–4.7 (m, 10H, O*H* and aliphatic C*H*), 5.08 (s, 2H, benzylic CH_2), 7.30 (s, 5H, aromatic *H*), 7.6 (broad, 2H, 2N*H*); mass spectrum, *m/e* (relative intensity): 207 (6), 149 (17), 108 (93), 107 (64), 91 (18), 79 (100), 77 (55), 65 (13).

3. Discussion

These procedures illustrate the use of *N*-ethyl-5-phenylisoxazolium-3'-sulfonate as a reagent for peptide synthesis.[3,4,5] Procedure A is recommended for peptides not soluble in either organic solvents or water. Procedure B illustrates the formation of a peptide that is soluble both in organic solvents and in water. For peptides soluble in organic solvents and insoluble in water, the submitters recommend the use of Procedure B, except that the peptide product may be recovered directly from its solution in ethyl acetate after this organic solution has been washed successively with aqueous 5% sodium hydrogen carbonate, water, 1 *M* hydrochloric acid, and water. Table I summarizes the preparation of various peptides by these procedures. Additional complex examples from other laboratories are listed elsewhere.[4]

Since there are a number of excellent and extensive reviews of peptide chemistry,[8,9,10,11 12] no attempt will be made here to describe the known methods of peptide synthesis. Absolute comparisons of the procedure presented herein with other methods are impossible due to a number of factors: (a) the practice of many authors of reporting only yields of crude materials of unknown purity, (b) the necessities that prompt many experimenters to use a large excess of either the carboxyl component or the amine component in peptide synthesis, and (c) the difficulty of comparing this one-step synthesis of the amide bond with the ordinary two- and three-step syntheses (carboxyl activation, isolation of the free amine component from its hydrohalide, and aminolysis of the activated carboxyl group).

The method illustrated here does have, however, several excellent features.[13] The yields are very good even in the synthesis of asparaginyl and glutaminyl peptides, which are ordinarily very difficult to prepare in reasonable yield. Furthermore, all by-products are water-soluble and, therefore, easily removed from the product peptide derivative. One recrystallization, even under conditions of almost complete precipitation, usually suffices to yield pure material. A stringent test of this statement is the synthesis of carbobenzyl-oxyhydroxy-L-prolylglycylglycine ethyl ester, a peptide which is itself very soluble in water. The water solubility of the starting isoxazolium salt and of the by-products from coupling has also been useful in studies of the reaction of proteins with the isoxazolium salt in aqueous solution[14,15] and to effect intermolecular cross linking of polypeptides.[16] Finally, use of the isoxazolium salt procedure for activation of the carboxyl groups of serine, tyrosine, and threonine offers the advantage that protection of the hydroxyl groups is often unnecessary.[12] Among the disadvantages of this method of peptide synthesis are the high cost of the isoxazolium salt and the limitations in the choice of solvent.

TABLE I[3,4]

Peptide	Reaction Procedure	Yield
Z-(N^{ε}-Z)-Lys·Gly-OEt[Glycine, *N*-[N^2,N^6-bis-[(phenylmethoxy)carbonyl]-L-lysyl]-, ethyl ester]	B	95%
Z-Phe·Gly-OEt[Glycine, *N*-[*N*-[(phenylmethoxy)-carbonyl]-L-phenylalanyl]-, ethyl ester]	B	93%
Z-Phe·Leu-OMe[L-Leucine, *N*-[*N*-[(phenylmethoxy)-carbonyl]-L-phenylalanyl]-, methyl ester]	B	90%
Z-Met·Gly·Gly-OEt[Glycine, *N*-[*N*-[*N*-(phenylmethoxy)carbonyl]-L-methionyl] glycyl-, ethyl ester]	B	86%
Phth-Gly·Gly-OEt[Glycine, *N*-[(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)acetyl]-, ethyl ester]	B	88%
Z-Gly·Gly·Tyr-OMe[L-Tyrosine, *N*-[*N*-[*N*-[(phenylmethoxy)carbonyl]glycyl] glycyl]-, methyl ester]	B	84%
Z-Gly·DL-Phe·Gly-OEt[Glycine, *N*-[*N*-*N*-[(phenylmethoxy)carbonyl]glycyl-DL-phenelalanyl]-, ethyl ester]	A	89%
Z-Gly·Gly·Gly-OEt[Glycine, *N*-[*N*-[*N*-[(phenylmethoxy)carbonyl]glycyl]glycyl]-, ethyl ester]	A	91%
Z-Gly-NHBz[Carbamic acid, [2-oxo-2-[(phenylmethyl)amino]ethyl]-, phenylmethyl ester]	A	94%
Z-Asp·Gly-OEt [Glycine, *N*-[N^2-[(phenylmethoxy)carbonyl]-L-asparaginyl]-, ethyl ester]	A	80%
Z-Gln·Val-OMe[L-Valine, *N*-[N^2-[(phenylmethoxy)carbonyl]-Lglutaminyl]-, methyl ester]	A	77%
Z-Gln·Tyr-OMe[L-Tyrosine, *N*-[N^2-[(phenylmethoxy)carbonyl]-L-glutaminyl]-, methyl ester]	A	75%

In tests devised to determine the amount of racemization to be expected in peptide syntheses in which the carboxyl component is a di- or higher peptide, this method ranks below the racemization-resistant azide procedure but above almost all other standard methods. Using a very sensitive and accurate isotope dilution assay, 1% racemization was observed[17] in the formation of the Anderson test peptide (Z-Gly·Phe·Gly-OEt)[18] and 7% racemization was observed[17] in the formation of the Young test peptide (Bz-Leu·Gly·OEt)[19] under optimized conditions. (The Young test was designed to exaggerate racemization problems, thus permitting more accurate studies of the effects of reaction condition variations.)

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

L-Leucine, N-[N^2-[(phenylmethoxy)carbonyl]-L-asparginyl]-, methyl ester

Glycine, N-[N^2,N^6-bis-[(phenylmethoxy)carbonyl]-L-lysyl]-, ethyl ester

Glycine, N-[N-N-[(phenylmethoxy)carbonyl]glycyl-DL-phenelalanyl]-, ethyl ester

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether (60-29-7)

acetonitrile (75-05-8)

sodium hydrogen carbonate (144-55-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

acetone (67-64-1)

tyrosine (60-18-4)

Nitromethane (75-52-5)

serine (56-45-1)

threonine (72-19-5)

triethylamine (121-44-8)

L-leucine methyl ester hydrochloride

glycylglycine ethyl ester hydrochloride (2087-41-4)

phosphorus pentoxide (1314-56-3)

L-Tyrosine, N-[N-[N-[(phenylmethoxy)carbonyl]glycyl]glycyl]-, methyl ester

CARBOBENZOXY-L-ASPARAGINYL-L-LEUCINE METHYL ESTER, Carbobenzyloxy-L-asparaginyl-L-leucine methyl ester

N-Carbobenzyloxy-3-hydroxy-L-prolylglycylglycine ethyl ester, N-CARBOBENZOXY-3-HYDROXY-L-PROLYLGLYCYLGLYCINE ETHYL ESTER (57621-06-4)

N-ETHYL-5-PHENYLISOXAZOLIUM-3'-SULFONATE

Glycine, N-[3-hydroxy-1-[(phenylmethoxy)-carbonyl]-L-prolyl]-, ethyl ester

carbobenzyloxy-L-asparagine

N-carbobenzyloxy-3-hydroxy-L-proline

N-ethyl-5-phenylisoxazolium-4'-sulfonate

carbobenzyl-oxyhydroxy-L-prolylglycylglycine ethyl ester

Carbamic acid, [2-oxo-2-[(phenylmethyl)amino]ethyl]-, phenylmethyl ester

Glycine, N-[(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)acetyl]-, ethyl ester

Glycine, N-[N^2-[(phenylmethoxy)carbonyl]-L-asparaginyl]-, ethyl ester

Glycine, N-[N-[N-[(phenylmethoxy)carbonyl]glycyl]glycyl]-, ethyl ester

Glycine, N-[N-[(phenylmethoxy)-carbonyl]-L-phenylalanyl]-, ethyl ester

L-Valine, N-[N^2-[(phenylmethoxy)carbonyl]-Lglutaminyl]-, methyl ester

Glycine, N-[N-[N-(phenylmethoxy)carbonyl]-L-methionyl]glycyl-, ethyl ester

L-Leucine, N-[N-[(phenylmethoxy)-carbonyl]-L-phenylalanyl]-, methyl ester

L-Tyrosine, N-[N^2-[(phenylmethoxy)carbonyl]-L-glutaminyl]-, methyl ester

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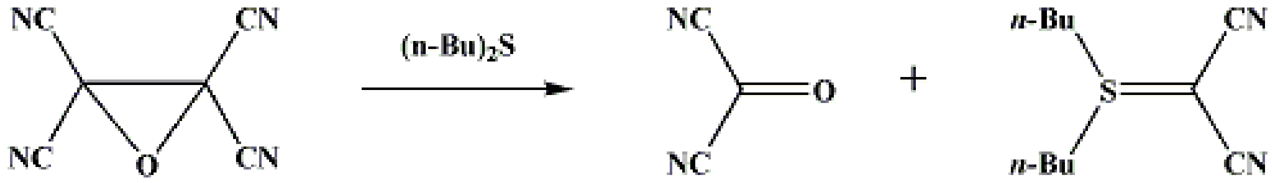
CARBONYL CYANIDE

[Propanedinitrile, oxo-]



Submitted by E. L. Martin[1]
Checked by R. Kottke and W. D. Emmons.

1. Procedure

Caution! Carbonyl cyanide and water react with explosive violence, forming hydrogen cyanide and carbon dioxide. This preparation should be carried out in a good hood with shielding, and rubber gloves should be worn.

A 500-ml., three-necked flask equipped with a magnetic stirring bar, a pressure-equalizing dropping funnel, a thermometer, and a 25-cm. Vigreux column attached to a trap cooled in an acetone–dry ice mixture is charged with 100 ml. of diethyl phthalate (Note 1) and 43 g. (0.30 mole) of tetracyanoethylene oxide (Note 2). The dropping funnel is charged with 44 g. (0.30 mole) of distilled *n*-butyl sulfide, the pressure is reduced to 5–20 mm. with a water aspirator, and the reaction flask is warmed with a 50° water bath. The *n*-butyl sulfide is added dropwise with stirring over 20–25 minutes, and the internal temperature is maintained at 50 ± 2° by controlling the temperature of the water bath. The reaction is exothermic at the start, but it is necessary to supply heat toward the end of the addition. The internal temperature is increased to 80° over 10–15 minutes after the sulfide has been added. The vacuum on the system is released by the introduction of nitrogen. The solid carbonyl cyanide that has collected in the trap is allowed to warm to room temperature under nitrogen, and 2 g. of tetracyanoethylene oxide (Note 3) and a boiling stone are added. The mixture is then warmed to 50°, and the product is distilled under reduced pressure (5–20 mm.) into a second trap cooled in an acetone–dry ice mixture. Another portion of tetracyanoethylene oxide (1 g.) is added to the distillate, and the carbonyl cyanide is distilled, again under reduced pressure (5–20 mm.), into a distillation flask cooled in acetone–dry ice mixture. Fractionation of the distillate through a 20-cm. column packed with glass helices gives 20.8–21.8 g. (86–91%) (Note 4) of faintly yellow carbonyl cyanide, b.p. 65–66° (Note 5), (Note 6), and (Note 7).

2. Notes

1. The diethyl phthalate is freed of traces of water and ethanol by distilling about 5% of it under reduced pressure, b.p. 185° (20 mm.) and then cooling the residue with protection from moisture. Moisture must be excluded because carbonyl cyanide reacts vigorously with water.

2. Tetracyanoethylene oxide was prepared as described in *Org. Synth.*, **Coll. Vol. 5**, 1007 (1973).
3. The distillate is treated with tetracyanoethylene oxide to remove the small amount of *n*-butyl sulfide that codistills with carbonyl cyanide.
4. The yield is based on the amount of tetracyanoethylene oxide initially charged.
5. There is very little if any low-boiling material when the reaction is carried out as described and care is taken to have the apparatus dry and exclude moisture.
6. GC analyses of various cuts indicate essentially pure carbonyl cyanide with traces of hydrogen cyanide and carbon dioxide. Both are hydrolysis products of carbonyl cyanide and probably are formed because of traces of moisture on the column.
7. Carbonyl cyanide has m.p. −38°, n_D^{19} 1.3923.[2]

3. Discussion

The procedure described is that of Linn, Webster, and Benson.[3] Carbonyl cyanide has previously been prepared by the pyrolysis of the diacetyl derivative of diisonitrosoacetone, a multistep process that suffers from low yield, lack of reproducibility, and risk of explosion.[2] The present procedure provides a convenient high-yield synthesis of carbonyl cyanide.

Carbonyl cyanide reacts with alcohols and phenols, giving cyanoformate esters;[4] with primary and secondary amines, giving cyanoformamides; with *N,N*-dimethylaniline, giving bis[4-(dimethylamino)phenyl]malononitrile; and with pyrrole, giving 2-(cyanoformyl)pyrrole.[5] With olefins of the type C=C-CH, products with structures C=CC-C(CN)$_2$OH, C=CC-COCN, and C=CC-C(CN)$_2$OCOCN are obtained, depending on the nature of the olefin and the reaction conditions.[6] Carbonyl cyanide also undergoes Diels-Alder reactions with some conjugated dienes, yielding dicyanodihydropyrans.[7]

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Appendix

Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

hydrogen cyanide (74-90-8)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

N,N-dimethylaniline (121-69-7)

Pyrrole (109-97-7)

diethyl phthalate (84-66-2)

Tetracyanoethylene oxide (3189-43-3)

carbonyl cyanide, Propanedinitrile, oxo- (1115-12-4)

diisonitrosoacetone

bis[4-(dimethylamino)phenyl]malononitrile

2-(cyanoformyl)pyrrole

n-butyl sulfide (544-40-1)

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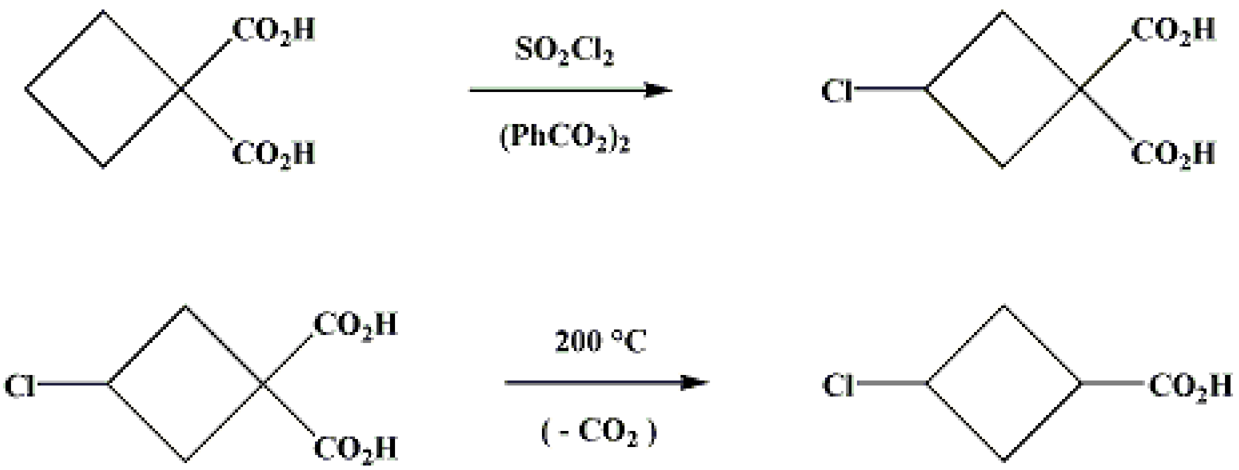
3-CHLOROCYCLOBUTANECARBOXYLIC ACID

[Cyclobutanecarboxylic acid, 3-chloro-]



Submitted by Gary M. Lampman and James C. Aumiller[1].
Checked by G. Nelson and K. B. Wiberg.

1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A 2-l., three-necked, round-bottomed flask equipped with a Trubore stirrer and paddle is charged with 172.8 g. (1.200 moles) of 1,1-cyclobutanedicarboxylic acid (Note 1) and 1500 ml. of benzene. The mixture is stirred and heated at reflux, and 200 ml. of benzene and benzene-water azeotrope is removed by distillation to ensure anhydrous conditions. The flask is then fitted with an addition funnel and a reflux condenser attached to a drying tube. Stirring and heating are continued, and over a 40-minute period, 170 g. (102 ml., 1.26 moles) of sulfuryl chloride (Note 2) is added from the funnel, while 4.0 g. of benzoyl peroxide (Note 3) is added simultaneously in small portions through the top of the condenser. After a short induction period, hydrogen chloride and sulfur dioxide are evolved. After the addition is complete, heating at reflux is maintained for 22 hours. The solid is dissolved after 1 hour, leaving a light brown solution. After the heating period is complete, the benzene is removed by distillation, and the residue is heated to 190–210° for 45 minutes to effect decarboxylation. The black residue is transferred to a small flask and distilled under vacuum through a 6-cm. Vigreux column. After a forerun of about 25–30 g. (Note 4), 65–79 g. (40–49%) of *cis*- and *trans*-3-chlorocyclobutanecarboxylic acid is collected as a light yellow liquid, b.p. 131–137° (15 mm.) n_D^{24} 1.4790 (Note 5). A black residue remains in the distillation flask.

2. Notes

1. Diethyl 1,1-cyclobutanedicarboxylate is prepared by the method in *Org. Synth.*, **Coll. Vol. 4**, 288 (1963). The diester is isolated in 55% yield, b.p. 111–114° (16 mm.). The diester can be saponified by the method in *Org. Synth.*, **Coll. Vol. 3**, 213 (1955), but omitting the barium chloride step, to give the diacid. This material upon recrystallization from ethyl acetate gives the diacid in high purity. The diacid may also be purchased from Aldrich Chemical Company, Inc.
2. Eastman Organic Chemicals or Matheson, Coleman and Bell practical grade material was distilled before use. Since hydrogen chloride and sulfur dioxide are evolved, the preparation should be carried out in an efficient hood.
3. Eastman Organic Chemicals white label material was used.
4. The forerun contains cyclobutanecarboxylic acid and 3-chlorocyclobutanecarboxylic acid, b.p. 100–130° (15 mm.) n_D^{24} 1.4623. The presence of cyclobutanecarboxylic acid indicates that some of the diacid was not chlorinated. Attempts were made to reduce the amount of unchlorinated product by increasing the amount of sulfuryl chloride. Instead, this increased the amount of a dichlorinated impurity which is difficult to separate from the desired product.
5. The product is analyzed by GC at 190° on a Beckman GC-2 chromatograph equipped with a 180 cm. × 6 mm. column (Beckman 17449) containing 42/60 Johns-Manville C-22 firebrick coated with Dow-Corning 550 silicone oil. The retention times are 8 and 9 minutes for the *trans*- and *cis*- compounds, respectively.

3. Discussion

3-Chlorocyclobutanecarboxylic acid has been prepared from the rather inaccessible 3-hydroxy-1,1-cyclobutanedicarboxylic acid.[2] The related 3-bromocyclobutanecarboxylic acid has also been prepared by an eight-step synthetic scheme.[3] The present method, based upon the procedure of Nevill, Frank, and Trepka,[4] affords the 3-chloro acid in high yield in one step. Thus this method provides a compound which cannot be easily made by other methods.

The use of sulfuryl chloride for free radical chlorination of aliphatic carboxylic acids gives mixtures of positional isomers;[5] however, with the cyclobutane ring, the attack is much more selective. The present method provides a procedure for free radical halogenation of a cyclobutane ring.

The conversion of 3-chlorocyclobutanecarboxylic acid to 1-bromo-3-chlorocyclobutane is described in *Organic Syntheses*.[6]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 179

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrogen chloride (7647-01-0)

Benzene (71-43-2)

ethyl acetate (141-78-6)

sulfur dioxide (7446-09-5)

barium chloride (10361-37-2)

sulfuryl chloride (7791-25-5)

benzoyl peroxide (94-36-0)

1,1-Cyclobutanedicarboxylic acid (5445-51-2)

Cyclobutanecarboxylic acid (3721-95-7)

Diethyl 1,1-cyclobutanedicarboxylate (3779-29-1)

cyclobutane (287-23-0)

1-Bromo-3-chlorocyclobutane (4935-03-9)

3-Chlorocyclobutanecarboxylic acid, Cyclobutanecarboxylic acid, 3-chloro-, cis- and trans-3-chlorocyclobutanecarboxylic acid (35207-71-7)

3-bromocyclobutanecarboxylic acid

3-hydroxy-1,1-cyclobutanedicarboxylic acid

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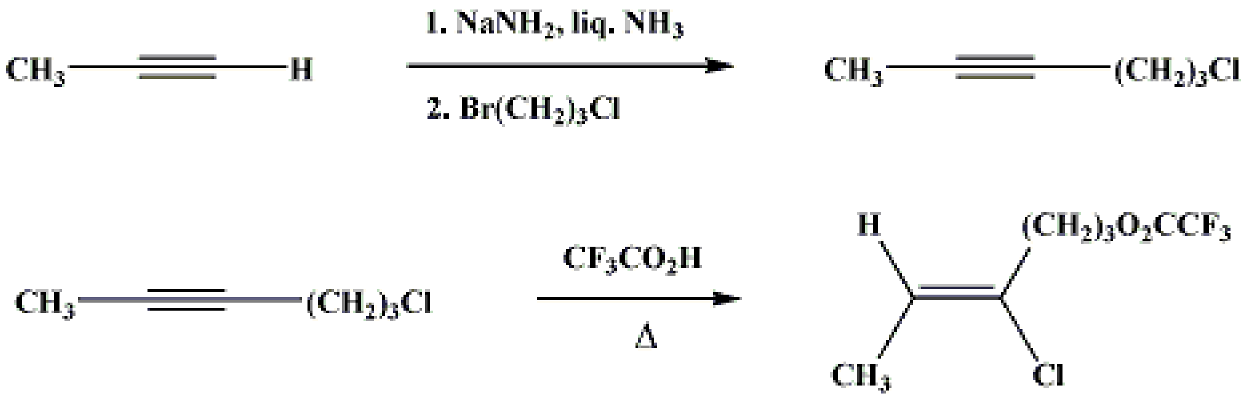
Organic Syntheses, CV 6, 273

(*Z*)-4-CHLORO-4-HEXENYL TRIFLUOROACETATE

[Acetic acid, trifluoro-, (*Z*)-4-chloro-4-hexenyl ester]



Submitted by P. E. Peterson and M. Dunham[1].
Checked by K.-C. Luk and G. Büchi.

1. Procedure

A. 6-*Chloro-2-hexyne*. A 2-l., three-necked, round-bottomed flask is equipped with a low-temperature condenser (Note 1), a gas-inlet, and a magnetic stirrer. Sodium hydroxide drying tubes are placed to precede the inlet and on the condenser. The system is purged with nitrogen, and approximately 650 ml. of anhydrous ammonia (Note 2) is condensed. Freshly cut sodium metal (20.2 g., 0.878 g.-atom) is added to the refluxing ammonia. After dissolution of the sodium (about 20 minutes is required), 0.2 g. of iron(III) nitrate is added. Two hours of stirring are allowed for conversion of the deep-blue solution of sodium in ammonia to sodium amide. The reaction mixture is cooled to –73° using an acetone-dry ice bath and 35.3 g. (50.0 ml., 0.882 mole) of precondensed propyne (Note 3), (Note 4), is added in portions over a 1-minute period through a glass funnel precooled in dry ice (Note 4). The mixture is stirred, with continued cooling for 15 minutes, and 153.5 g. (0.975 mole) of 1-bromo-3-chloropropane (Note 5) is added from an addition funnel over 20 minutes (Note 6). After 30 minutes of additional stirring, 250 ml. of diethyl ether is added to the flask, the dry ice bath is removed, and the ammonia is allowed to evaporate (Note 7). Water (200 ml.) is added to the reaction vessel, and the resulting solution is transferred to a 1-l. separatory funnel. The water layer is removed and extracted once with 100 ml. of ether. The combined ether extracts are treated with 6 *M* hydrochloric acid until the aqueous layer is acidic (approximately 20 ml. is required). The ether layer is separated and dried in three stages over magnesium sulfate. Removal of the solvent and distillation of the crude product through a 20-cm. Widmer column (Note 8) yields 49.4–56.0 g. of 6-chloro-2-hexyne, b.p. 58–64° (20 mm.), which contained some 1-bromo-3-chloropropane (to be removed in the next step). The corrected yield is 29–

31% (Note 9).

B. *4-Chloro-4-hexenyl trifluoroacetate*. A 500-ml., one-necked flask equipped with a magnetic stirrer is charged with 200 ml. of redistilled trifluoroacetic acid (Note 10) and 6-chloro-2-hexyne (0.16 mole, calculated from GC analysis) containing 1-bromo-3-chloropropane. The flask is fitted with a Friedrichs condenser, and the mixture is refluxed for 3 hours. The flask is transferred to a vacuum distillation apparatus; with the aid of an aspirator and a controlled leak, excess trifluoroacetic acid is removed under slightly reduced pressure, maintaining the pot temperature below 65° to prevent reactions of the acid with the double bond. The remaining trifluoroacetic acid is removed by pouring the product into 100 ml. of ice water and extracting with 100- and 50-ml. portions of dichloromethane. The organic extracts are brought to pH 7 with saturated sodium hydrogen carbonate (*ca.* 40 ml.). The resulting aqueous layer is extracted once with an additional 25 ml. of dichloromethane, and the combined dichloromethane extracts are dried in three stages by stirring over magnesium sulfate. The final stage is allowed to stand in a refrigerator for 24 hours. The solvent is removed by distillation through a 20-cm. Widmer column ((Note 8)) at atmospheric pressure. Distillation at reduced pressure gives 16.0–16.4 g. of 4-chloro-4-hexenyl trifluoroacetate, b.p. 86–89° (22 mm.) (Note 11), which contains trace amounts of 1-bromo-3-chloropropane (Note 12). On the basis of the alkyne present in the reactant the yield is 50–52%.

2. Notes

1. A cold finger condenser packed with dry ice and 2-propanol may be used. A Friedrichs condenser in combination with a circulating low-temperature bath (–70°) is more convenient.
2. Ammonia was purchased from Matheson Gas Products.
3. Propyne can be purchased from Linde Specialty Gases or Farchan Research Laboratories. Matheson Gas Products sells propyne also, but only in 100-lb. quantities.
4. The propyne (b.p. –23.2°) is precondensed to the mark in a volumetric flask cooled by acetone–dry ice. Evaporation of some propyne during addition will lead to a moderate molar excess of 1-bromo-3-chloropropane, regarded as desirable in preventing formation of diyne product.
5. 1-Bromo-3-chloropropane was purchased from Aldrich Chemical Company, Inc.
6. Sudden foaming occurred in a run involving insufficient cooling or overly rapid additions. Slow addition could lead to diyne product.
7. The checkers maintained the condenser at –5° during the evaporation to minimize loss of alkyne.
8. The submitters use a platinum spinning band apparatus for the distillation.
9. GC analysis at 79° using a flame detector in conjunction with a 183 × 0.32 cm. stainless-steel column containing Dow-Corning 550 fluid on silanized support gave peaks for 1-bromo-3-chloropropane (6.5 minutes) and 6-chloro-2-

hexyne (9.3 minutes) whose areas were shown to be proportional to the mole fractions. The latter were determined by integration of the expanded (50 Hz. sweep width) 100 MHz. ^{1}H NMR spectrum in the region of overlapping triplets near δ 3.6.

10. The checkers purchased trifluoroacetic acid from Aldrich Chemical Company, Inc., and distilled it from phosphorous pentoxide. The submitters point out that some trifluoroacetic anhydride, whose effects have not been fully investigated, is obtained under these conditions. The submitters prefer to use trifluoroacetic acid which has been distilled through a glass packed column without the use of a drying agent.

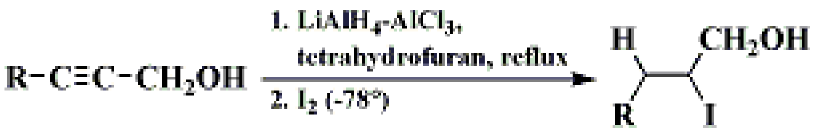
11. n_D^{25} 1.4025; ^{1}H NMR (CCl_4), δ (multiplicity, coupling constant *J* in Hz., number of protons): 1.70 (d, *J* = 7, 3H), 1.8–2.6 (m, 4H), 4.35 (t, *J* = 6, 2H), 5.58 (q, *J* = 7, 1H).

12. 1-Bromo-3-chloropropane, b.p. 46–55° (15 mm.) is well separated in the early fractions. GC analysis at 120° (*cf.* (Note 9)) gives peaks of proportional areas for 1-bromo-3-chlororopane (1.2 minutes), 4-chloro-4-hexenyl trifluoroacetate (2.3 minutes), and traces of 4-chloro-4-hexen-1-ol (2.5 minutes).

3. Discussion

The presence, in the 4-chloro-4-hexenyl trifluoroacetate, of small amounts of two *cis*–*trans* pairs of products of addition of trifluoroacetic acid to the triple bond without concomitant halogen shift remains speculative. In any event, these compounds would be removed as ketones upon hydrolysis[2] of the trifluoroacetate. Both the 4-chloro-4-hexenyl trifluoroacetate and the alcohol resulting from its hydrolysis have been shown to contain 9% of the (*E*) isomer.[2] In the present study, the hydrogen decoupled ^{13}C magnetic resonance spectra of the ester and alcohol were shown to contain peaks attributable to approximately 9% of (*E*) isomer.

Unsymmetrical *trans*-vinyl halides have been prepared from acetylenic alcohols by Corey and co-workers[3] [4] (as illustrated in the accompanying formulation) in connection with their synthesis of farnesol and *Cecropia* juvenile hormone. Several syntheses of vinyl halides (with identical R groups, *trans*) have been reported, including procedures involving halogenation and elimination,[5] addition of hydrochloric acid to alkynes,[6] and preparation from alkynes *via* vinyl alanes.[7] The synthesis of unsymmetrical *trans*-vinyl halides by 1,4-halogen shift reactions is exemplified by the procedure given here. Such compounds are potentially useful in the synthesis of compounds containing trisubstituted double bonds.[8]



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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

phosphorous pentoxide

1-bromo-3-chlororopane

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ether, diethyl ether (60-29-7)

hydrogen (1333-74-0)

sodium hydrogen carbonate (144-55-8)

nitrogen (7727-37-9)

sodium (13966-32-0)

2-propanol (67-63-0)

1-bromo-3-chloropropane (109-70-6)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

sodium amide (7782-92-5)

iron(III) nitrate

trifluoroacetic acid (76-05-1)

propyne (74-99-7)

trifluoroacetic anhydride (407-25-0)

6-chloro-2-hexyne (28077-73-8)

4-chloro-4-hexenyl trifluoroacetate

4-chloro-4-hexen-1-ol

trifluoroacetate

farnesol

(Z)-4-Chloro-4-hexenyl trifluoroacetate, Acetic acid, trifluoro-, (Z)-4-chloro-4-hexenyl ester (28077-77-2)

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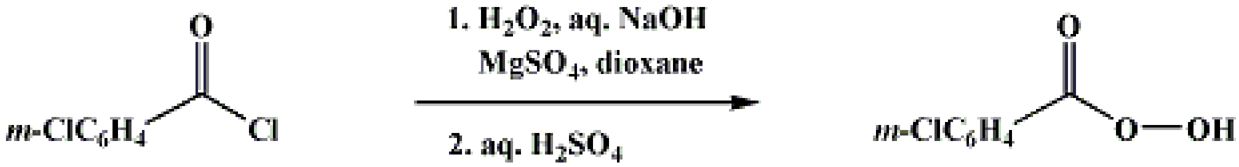
Organic Syntheses, CV 6, 276

m-CHLOROPERBENZOIC ACID

[Benzenecarboperoxoic acid, 3-chloro-]



Submitted by Richard N. McDonald[1], Richard N. Steppel, and James E. Dorsey.
Checked by William N. Washburn and Ronald Breslow.

1. Procedure

A 1-l. beaker (Note 1) equipped with a magnetic stirrer is charged with 1.5 g. of magnesium sulfate heptahydrate, 36 g. of sodium hydroxide, 360 ml. of water, 90 ml. of 30% hydrogen peroxide, and 450 ml. of dioxane. This mixture is cooled to 15° with an ice-water bath and by the addition of a small amount of ice to the mixture before 52.5 g. (0.300 mole) of *m*-chlorobenzoyl chloride (Note 2) is added in one portion while vigorous stirring is maintained. Small portions of ice are added to maintain the temperature below 25°. The reaction mixture is stirred at this temperature for 15 minutes, then transferred to a 3-l. separatory funnel. Cold, 20% sulfuric acid (900 ml.) (Note 3) is added to the separatory funnel, the mixture is shaken and separated, and the aqueous layer is extracted with four 200 ml. portions of cold dichloromethane (Note 4). The combined extracts are dried over anhydrous magnesium sulfate, and the dichloromethane is removed under reduced pressure *via* a short-path distillation (Note 5). After most of the solvent has been removed, a white pasty solid remains and the residual solvent is removed under full vacuum for an additional 2 hours or until a white, flaky powder remains. The product weighs approximately 51 g. Sodium thiosulfate analysis indicates 80–85% active oxygen present (Note 6).

2. Notes

1. The checkers used a Pyrex vessel; the submitters utilized a Nalgene beaker, because contact with the glass surface may catalyze the decomposition of the peracid.
2. The *m*-chlorobenzoyl chloride is prepared by refluxing *m*-chlorobenzoic acid, either commercial or recovered, with excess thionyl chloride. Distillation gives the *m*-chlorobenzoyl chloride in high yield, b.p. 112° (11 mm.).[2]
The recovery of the *m*-chlorobenzoic acid, the by-product from *m*-chloroperbenzoic acid oxidations, is facilitated by using dichloromethane as the solvent since the peracid is very soluble whereas the acid is quite insoluble.
3. The cold 20% sulfuric acid solution is made by adding concentrated sulfuric

acid (180 ml.) to crushed ice followed by the addition of more ice until the required volume is reached, *i.e.*, 900 ml. The acid solution is kept cold in an ice bath until required. The dichloromethane is also precooled before use.

4. Iodometric titration of the moist extracts indicates approximately 51 g. of *m*-chloroperbenzoic acid present. A 4.0-ml. aliquot of the solution requires approximately 20 ml. of a 0.1000 *N* solution of sodium thiosulfate. To prepare the sample, 10 ml. of 10% sodium iodide and 5 ml. of acetic acid are added to the 5-ml. aliquot, and the mixture is diluted to 50 ml. The dark red solution is titrated to a pale yellow. At this point 1 ml. of starch solution is added and the titration continued to the end point, *i.e.*, a change from dark blue to clear.

$$\text{Total weight of peracid} = \frac{N_{Na2S2O3} \cdot V_{Na2S2O3(ml.)} \cdot V_{total\ extract\ (l.)} \cdot 86.29}{V_{aliquot\ (ml.)}}$$

5. The dichloromethane solvent should be removed as rapidly as possible because contact with glass and heat cause decomposition of the peracid. A convenient method for the removal of the solvent involves a short-path vacuum distillation using a 2-l. distillation flask and trapping the solvent at dry ice or liquid nitrogen temperatures. The pressure should be reduced slowly at first and at least three traps used to minimize the amount of solvent introduced into the vacuum pump. Adjustment of a stopcock located between the first and second traps will help to control this problem. The distillation flask is placed in a water bath maintained between 25° and 35° so that the rate of solvent evaporation is quite rapid. Removal of the solvent over prolonged periods and drying of the solid peracid by excessive heating results in drastic losses of active oxygen. *m*-Chloroperbenzoic, once isolated, is stable over long periods of time when stored in polyethylene containers and refrigerated.

6. Iodometric titration of the solid product involves the use of 0.2-g. samples of the peracid and the procedure in (Note 4).

$$\text{Percent peracid} = \frac{N_{Na2S2O3} \cdot V_{Na2S2O3(ml.)} \cdot 0.8629}{\text{Weight of sample}}$$

3. Discussion

This method is an extension of the reported perhydrolysis of certain other acid chlorides and anhydrides.[3] Although *m*-chloroperbenzoic acid is commercially available, this preparation requires only a short reaction time and simple equipment, and it affords high yields of this relatively stable and useful peracid. The dichloromethane–dioxane extracts can be stored and used directly for many peroxidations, in which case the total preparation time should not exceed 2 hours.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 904
- Org. Syn. Coll. Vol. 6, 403

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Benzenecarboperoxoic acid, 3-chloro-

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

sodium hydroxide (1310-73-2)

thionyl chloride (7719-09-7)

oxygen (7782-44-7)

sodium thiosulfate (7772-98-7)

nitrogen (7727-37-9)

hydrogen peroxide (7722-84-1)

sodium iodide (7681-82-5)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

dioxane (5703-46-8)

magnesium sulfate heptahydrate (10034-99-8)

m-Chloroperbenzoic acid (937-14-4)

m-chlorobenzoic acid (535-80-8)

m-chlorobenzoyl chloride (618-46-2)

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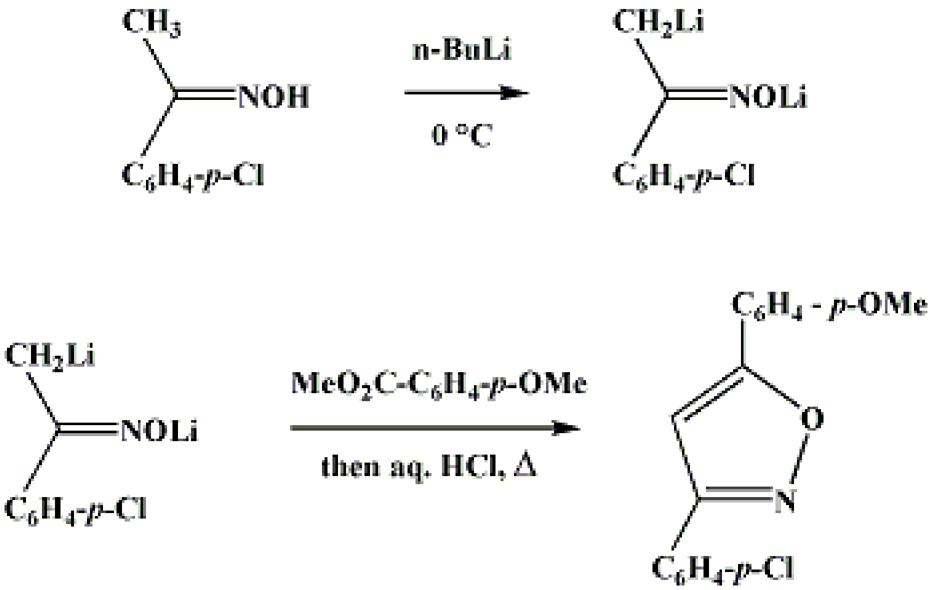
Organic Syntheses, CV 6, 278

3-(4-CHLOROPHENYL)-5-(4-METHOXYPHENYL) ISOXAZOLE

[Isoxazole, 3-(4-chlorophenyl)-5-(4-methoxyphenyl)-]



Submitted by Matilda Perkins, Charles F. Beam, Jr.[1], Morgan C. D. Dyer[2], and Charles R. Hauser[3].
Checked by H. W. Jacobson and R. E. Benson.

1. Procedure

Caution! This preparation should be carried out in an efficient hood.

A 2-l., three-necked, round-bottomed flask equipped with a magnetic stirring bar, a nitrogen-inlet tube, and a 250-ml. pressure-equalizing dropping funnel attached to a calcium chloride tube is charged with 16.96 g. (0.1000 mole) of 4-chloroacetophenone oxime (Note 1) and 500 ml. of anhydrous tetrahydrofuran (Note 2). The flask is stoppered (Note 3) and cooled in an ice-water bath (Note 4). In the dropping funnel is placed 140 ml. (0.22 mole) of 1.6 *M* *n*-butyllithium in hexane (Note 5), which is rapidly added dropwise to the stirred solution over a 12–15-minute period. The solution is stirred for 30 minutes after the addition is complete, and the addition funnel is replaced by a clean one (125-ml. capacity), fitted with a calcium chloride drying tube (Note 6). Cooling is continued, a solution of 8.31 g. (0.0501 mole) of methyl anisate (Note 7) and (Note 8) in 100 ml. of anhydrous tetrahydrofuran is added to the stirred mixture over a 6–10-minute period, and the resulting mixture is stirred for an additional 30 minutes (Note 9). At the end of this period, 300 ml. of 3 *N* hydrochloric acid is added. The nitrogen-inlet tube is removed and replaced by a reflux condenser, and the dropping funnel is replaced by a ground-glass stopper. The ice bath is

removed, and the mixture is heated under reflux for 1 hour. The flask is then cooled, and its contents are poured into a 2-l. Erlenmeyer flask, and solid sodium hydrogen carbonate is added to the mixture until neutralization is complete (Note 10).

The resulting mixture consists of an organic phase and a lower aqueous phase containing a small amount of insoluble material. The mixture is transferred to a 2-l. separatory funnel and the phases are separated. The aqueous phase is extracted with 100 ml. of tetrahydrofuran, which is combined with the original organic phase and concentrated to dryness on a rotary evaporator. Approximately 150 ml. of xylene is added to the flask and the contents of the flask are heated to reflux to remove any water present as the azeotrope. The resulting hot solution is filtered rapidly through a large Büchner funnel with light suction. The volume is reduced to approximately 100 ml., and the solution is cooled in an ice bath. The tan crystals which separate are collected in a Büchner funnel and washed with 10 ml. of ice-cold xylene. The crude product is recrystallized from 150 ml. of xylene (Note 11), yielding, after drying, 7.4–7.6 g. (52–53%) of 3-(4-chlorophenyl)-5-(4-methoxyphenyl)isoxazole, m.p. 175–176° (Note 12).

2. Notes

1. 4-Chloroacetophenone oxime was prepared by a modification of the method described by Shriner, Fuson, and Curtin.[4] A mixture of 100 g. (0.647 mole) of reagent grade 4-chloroacetophenone, 300 ml. of water, 200 ml. of aqueous 10% sodium hydroxide, 50 g. (0.72 mole) of hydroxylamine hydrochloride, and 500 ml. of ethanol is heated at reflux in a 2-l., round-bottomed flask for 2 hours. The crystals that separate on cooling in an ice bath are recovered by filtration and air dried. The product is added to approximately 1 l. of hexane, and the mixture is heated to reflux to remove any remaining water as the azeotrope. The resulting solution is cooled, yielding 70–74 g. (64–68%) of 4-chloroacetophenone oxime as white crystals, m.p. 96–97°.
2. Tetrahydrofuran was obtained from E. I. du Pont de Nemours and Company and distilled from lithium aluminum hydride or sodium-benzophenone immediately before use. The submitters used reagent grade tetrahydrofuran available from Matheson, Coleman and Bell.
3. Ground-glass stoppers proved most convenient.
4. The initial reaction of *n*-butyllithium (or lithium diisopropylamide) with the oxime is exothermic, and if the bath is not used, a slightly lower yield of colored product is obtained.
5. The concentration of the *n*-butyllithium obtained from Foote Mineral Company is generally close to the 1.6 *M* as quoted. An exact measurement of the volume (hypodermic syringe recommended) is not necessary, but a slight excess above the stoichiometrically required amount (0.20 mole) is needed. The submitters used *n*-butyllithium available from Lithium Corporation of America, Inc. A recent modification utilizes lithium diisopropylamide (0.33 mole) instead of *n*-butyllithium (0.22 mole).[5] A 0.33-mole sample of *n*-butyllithium is cooled

to 0° and blanketed with nitrogen. To this base is added 0.33 mole of diisopropylamine dissolved in 150 ml. of tetrahydrofuran.

6. The purpose of the exchange is to provide a clean funnel for the addition of the ester solution. If the funnel is not changed, the yield is slightly lower. When lithium diisopropylamide is used the ratio of the reagents is 2 oxime: 6 base: 2 ester.

7. The ratio of the reagents is 2 oxime:4 base: 1 ester and is consistent with similar procedures used for a modified Claisen condensation.[6] The yield is based on the ester. When a ratio of reagents of 1 oxime: 2 base: 1 ester was used, a yield of 21% based on the ester was obtained.

8. Methyl anisate was obtained from Eastman Organic Chemicals.

9. At least 30 minutes is required for an optimum yield of the isoxazole.

10. Care should be taken to add the sodium hydrogen carbonate in small amounts initially, in order to avoid excessive frothing. The mixture was tested with pH paper to establish complete neutralization.

11. The product can also be recrystallized from ethanol, but a substantially larger volume of solvent is required.

12. The product has the following spectral properties; IR (KBr) cm.$^{-1}$: 3103 and 3006 (aromatic C-H), 2955, 2925, and 2830 (aliphatic C-H stretching), 1257 and 1032 (aromatic methyl ether), 841 and 812 (C-H out-of-plane bending of isoxazole C_4-*H* and 4-substituted phenyl); ^{1}H NMR (trifluoroacetic acid), δ (multiplicity, number of protons, assignment): 3.98 (s, 3H, OCH_3), 7.00–7.27 (m, 1H, isoxazole C_4-*H*; and 2H, aryl *H*), and 7.42–7.97 (m, 6H, aryl *H*).

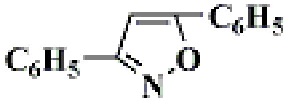
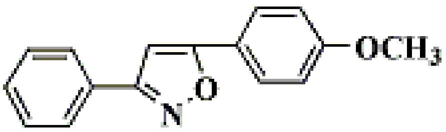
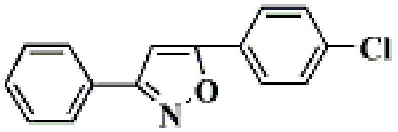
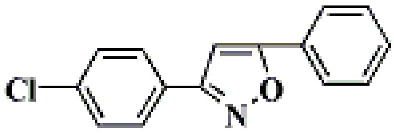
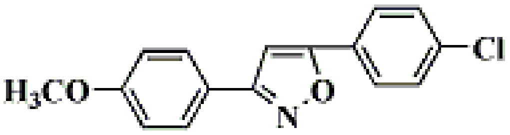
3. Discussion

This procedure has several advantages over previous methods. It provides a simple, direct route to unsymmetrically substituted isoxazoles in which the location of substituents is unequivocal. The method uses readily available starting materials and can be used for the synthesis of a variety of substituted isoxazoles in which the substituents are stable to *n*-butyllithium. Examples of products synthesized by this method[7] are given in Table I.

TABLE I

ISOXAZOLES DERIVED FROM OXIMES[7]

R_1	R_2	Yield[a] (%)

C_6H_5-	C_6H_5-		59
C_6H_5-	4-$CH_3OC_6H_4$-		51
C_6H_5-	4-ClC_6H_4-		59
4-ClC_6H_4-	C_6H_5-		65
4-$CH_3OC_6H_4$-	4-ClC_6H_4-		66[b]

[a]Yield obtained using 2.25 *M* *n*-butyllithium reagent.

[b]100% yield obtained using lithium diisopropylamide reagent.

3-(4-Chlorophenyl)-5-(4-methoxyphenyl)isoxazole has been prepared from the dilithio derivative of 4-chloroacetophenone oxime by three other methods: (a) reaction with anisonitrile (4-methoxybenzonitrile) followed by acid-catalyzed cyclization,[8] (b) reaction with *N*,*N*-dimethylbenzamide followed by acid-catalyzed cyclization,[9] and (c) condensation of the dilithio intermediate, prepared in an excess of lithium

diisopropylamide, with methyl 4-methoxybenzoate, followed by acid-catalyzed cyclization.[6] The condensation of dilithioöxime with aroyl chlorides, followed by acid-catalyzed cyclization, could result in 4-acylisoxazoles.[10]

The use of dilithio reagents for the preparation of heterocyclic systems has been extended to the synthesis of 2-isoxazolin-5-ones[11] by carboxylation of a dilithioöxime, followed by cyclization, and the synthesis of pyrazoles from dilithiophenylhydrazones and trilithiothiohydrazones.[12,13] If the dilithiophenylhydrazones are formed in an excess of lithium diisopropylamide, they can be treated with diethyl carbonate, followed by cyclization to give 2-pyrazolin-5-ones.[14] Dilithioöximes formed in an excess of lithium diisopropylamide can be condensed with electrophilic-nucleophilic reagents such as methyl anthranilate.[15]

References and Notes

1. Submitted from William Chandler Chemistry Laboratory, Lehigh University, Bethlehem, Pennsylvania 18015. [Present address: Department of Chemistry, Newberry College, Newberry, South Carolina 29108. Technical assistance by David C. Reames is acknowledged.]
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

4-chloroacetophenone oxime

4-chloroacetophenone

sodium-benzophenone

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

sodium hydroxide (1310-73-2)

sodium hydrogen carbonate (144-55-8)

nitrogen (7727-37-9)

xylene (106-42-3)

Hydroxylamine hydrochloride (5470-11-1)

n-butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

diethyl carbonate (105-58-8)

lithium aluminum hydride (16853-85-3)

hexane (110-54-3)

methyl anthranilate (134-20-3)

methyl anisate, methyl 4-methoxybenzoate (121-98-2)

lithium diisopropylamide (4111-54-0)

diisopropylamine (108-18-9)

3-(4-Chlorophenyl)-5-(4-methoxyphenyl)isoxazole, Isoxazole, 3-(4-chlorophenyl)-5-(4-methoxyphenyl)- (24097-19-6)

isoxazole (288-14-2)

anisonitrile, 4-methoxybenzonitrile (874-90-8)

N,N-dimethylbenzamide (611-74-5)

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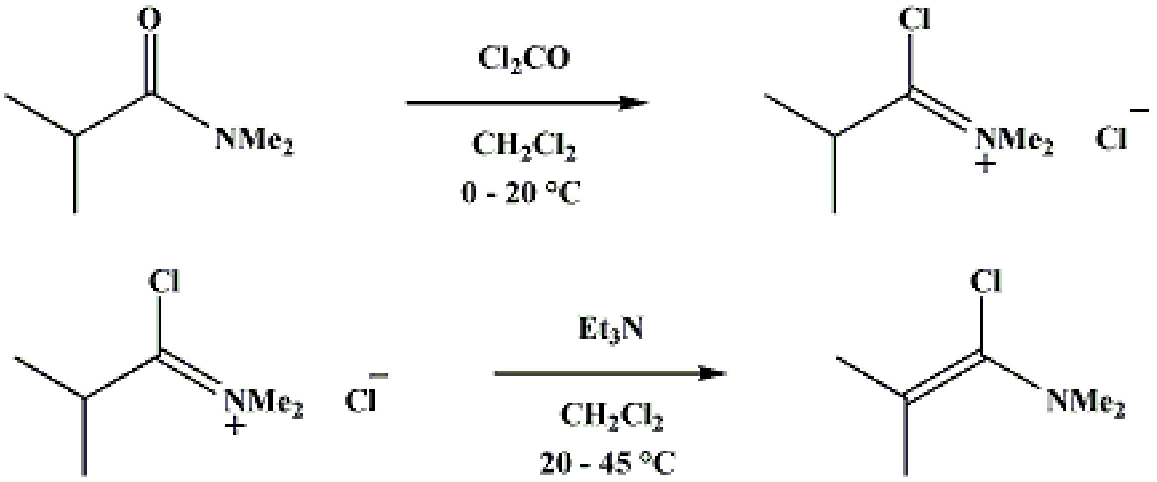
α-CHLORO ENAMINES, REACTIVE INTERMEDIATES FOR SYNTHESIS: 1-CHLORO-*N*,*N*,2-TRIMETHYLPROPENYLAMINE

[Propenylamine, 1-chloro-*N*,*N*,2-trimethyl-]



Submitted by B. Haveaux, A. Dekoker, M. Rens, A. R. Sidani, J. Toye, and L. Ghosez[1].
Checked by Masayuki Murakami, Mitsuru Yoshioka, and Wataru Nagata.

1. Procedure

Caution! Phosgene is highly toxic. This preparation should be carried out in a well-ventilated hood.

A. *1-Chloro-*N,N*,2-trimethylpropylideniminium chloride*. A 1-l., three-necked, round-bottomed flask is equipped with a magnetic stirring bar, a pressure-equalizing dropping funnel, an inlet tube connected to a graduated trap with a flexible polyethylene tube, and a dry-ice condenser connected to a series of three traps. The first and last traps in the series contain sulfuric acid and 10% potassium hydroxide, respectively, and the middle trap is left empty, as shown in f.htmigure 1. Phosgene (85–100 ml., 1.2–1.4 moles) (Note 1) is condensed in the graduated trap which is cooled in an acetone–dry ice bath. The flask is charged with 200 ml. of anhydrous dichloromethane (Note 2) and cooled in an ice–salt bath. The liquid phosgene is slowly poured into the flask (Note 3), the inlet tube is replaced with a thermometer, and a solution of 115 g. (1.00 mole) of freshly distilled *N*,*N*-dimethylisobutyramide (Note 4) in 150 ml. of anhydrous dichloromethane is added dropwise from the dropping funnel over 20 minutes. The temperature is maintained at 0° during this time and gradually raised to room temperature within *ca.* 1 hour. The gas evolution becomes vigorous, and the phosgene begins to boil. The reaction mixture, containing a

white precipitate, is left overnight at room temperature. The flask is prepared for distillation and connected to a water pump (Note 5), maintaining a slightly reduced pressure in the system. The excess phosgene and most of the solvent are removed by warming the flask in a water bath at *ca.* 50° and collected in an ice-cold receiver (Note 6). The white or pale-yellow solid remaining, 1-chloro-*N*,*N*,2-trimethylpropylideniminium chloride, is used directly in Part B.

Figure 1.

Figure 1.

B. *1-Chloro-*N,N*,2-trimethylpropenylamine*. The flask is equipped with a dropping funnel, a mechanical stirrer, and a reflux condenser protected from moisture with a sulfuric acid trap. The iminium chloride is suspended in 200 ml. of anhydrous dichloromethane, and 140 g. (1.39 moles) of triethylamine (Note 7) is slowly added to the mixture from the dropping funnel, with vigorous stirring, over 1 hour (Note 8). The temperature rises to 45°, and the solvent begins to reflux. The resulting suspension is stirred at room temperature for an additional 2 hours, after which 150 ml. of dry, low-boiling petroleum ether (Note 9) is added to complete the precipitation of triethylamine hydrochloride (Note 10). The mixture is quickly filtered under nitrogen (Note 11) into a 1-l., round-bottomed flask through an Iena sintered-glass filter. A 300-ml. portion of petroleum ether is used to wash the flask and the triethylamine hydrochloride on the filter. The solvent is removed by distillation under nitrogen. Further distillation through a Vigreux column under nitrogen gives 93–103 g. (69–77%) of 1-chloro-*N*,*N*,2-trimethylpropenylamine, b.p. 125–130° (760 mm.) (Note 12) and (Note 13). The compound is very sensitive to humidity and should be immediately stored in ampoules (Note 14).

2. Notes

1. The submitters used technical grade phosgene purchased from Gardner Cryogenics Europe N. V., 1800 Vilvoorde, Belgium.
2. Technical grade dichloromethane was dried by refluxing over phosphorus pentoxide for 24 hours and distilled.
3. Alternatively phosgene may be allowed to distill into the flask cooled in an acetone–dry ice bath. For this operation the inlet tube should extend to the bottom of the flask.
4. Following a procedure reported in the literature,[2] the checkers prepared *N*,*N*-dimethylisobutyramide, b.p. 67–68° (15 mm.), in 85% yield by treating reagent grade isobutyryl chloride with 2 molar equivalents of reagent grade dimethylamine in anhydrous ethyl ether at 0°. The reported boiling point for *N*,*N*-dimethylisobutyramide is 175–176° (744 mm.).[2] Isobutyryl chloride and dimethylamine were both purchased from Tokyo Kasei Kogyo Company Ltd., Tokyo, Japan. These two reagents are also available from Aldrich Chemical

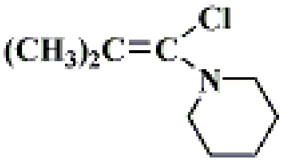
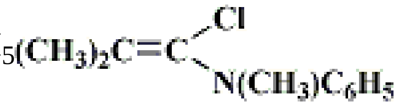
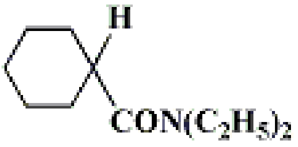
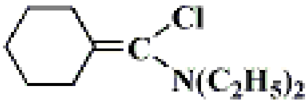
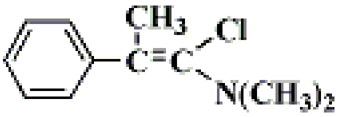
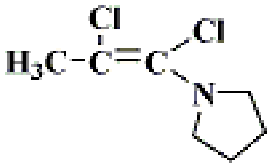
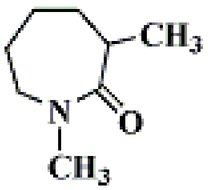
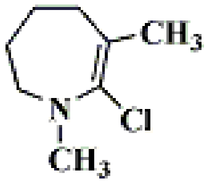
Company, Inc., and the Specialty Gas Division, J. T. Baker Chemical Company, respectively.
5. A phosphorus pentoxide tube is placed between the water pump and the distillation apparatus.
6. The submitters found that filling the flask with argon helped to reduce exposure to moisture in the air.
7. The submitters used Baker-grade triethylamine purchased from J. T. Baker Chemicals N.V., P.O. Box 1, Deventer, Holland, after distillation from potassium hydroxide.
8. The reaction is exothermic. The checkers found that the yield of the final product was raised from 57% in the first run to 71% in the second and third runs when the triethylamine was added at 30–34° with slight cooling. Another procedural change made by the checkers in Part A in these last two runs was that the dry ice condenser was kept in place for more than 8 hours after the addition of *N,N*-dimethylisobutyramide was completed. In the first run the condenser was removed after 20 minutes.
9. The submitters used technical petroleum ether, b.p. <70°, which was distilled from sodium wire.
10. Leaving the reaction mixture overnight before filtration did not affect the yield.
11. A slow stream of dry nitrogen was passed through an inverted funnel placed over the filtration apparatus.
12. The checkers collected several fractions during the distillation. Early fractions boiling at 100–125° (760 mm.) were shown to be a mixture of the product and triethylamine. The product from two runs carried out at one-half scale was collected in two main fractions amounting to 2.2–5.8 g., b.p. 125–130° (760 mm.), and 41.7–45.4 g., 130–134° (760 mm.). The total yield was 47.5–47.6 g. (71%), b.p. 125–134°. The submitters obtained 105–110 g. (78–82%), b.p. 129–130° (760 mm.).
13. The checkers obtained an analysis on the distilled product. Analysis calculated for $C_6H_{12}NCl$: C, 53.93; H, 9.05; N, 10.48; Cl, 26.54. Found: C, 54.51; H, 9.21; N, 10.69; Cl, 26.49. The spectral properties of the product are as follows: IR (CCl_4) $cm.^{-1}$: 1653, 1470, 1451, 1295, 1124, 1013; ^{1}H NMR (*ca.* 15% w/v in CCl_4), δ (multiplicity, number of protons, assignment): 1.73 (s, 3H, allylic CH_3), 1.79 (s, 3H, allylic CH_3), 2.37 (s, 6H, 2NCH_3); ^{1}H NMR (about 15% w/v in $CDCl_3$), δ (multiplicity, number of protons, assignment): 1.77 (s, 6H, two allylic CH_3) and 2.38 (s, 6H, 2NCH_3); mass spectrum (225°, 70 e.v.) *m/e* (relative intensity): 135 (M + 2, 24), 133 (M, 77), 98 (100), 83 (56), 82 (23), 72 (31), 44 (36), 42 (60).
14. The tubes should be sealed immediately to avoid hydrolysis. In spite of this precaution, a light precipitate is always formed.

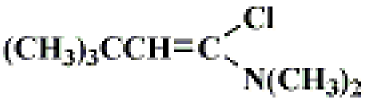
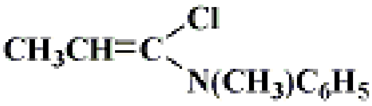
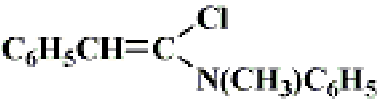
3. Discussion

1-Chloro-*N,N*,2-trimethylpropenylamine has been prepared by reaction of 2-methylpropenylidenebis(dimethylamine) with phosphorous trichloride or

dichlorophenylphosphine.[3] The present method[4] is far more convenient and general. The reagents are inexpensive, the amide reactants are readily available, and the procedure is applicable to the synthesis of various α-chloro enamines on a large scale with only minor modifications (Table I).[5]

TABLE I
SYNTHESIS OF α-CHLORO ENAMINES FROM AMIDES

Entry	Amide	α-Chloro Enamine	Yield(%)
1			85
2	$(CH_3)_2CHCON(CH_3)C_6H_5$		55–79
3			40
4	$C_6H_5CH(CH_3)CON(CH_3)_2$		76[a]
5			60–70[a]
6			75

7	$(CH_3)_3CCH_2CON(CH_3)_2$		65[a]
8	$CH_3CH_2CON(CH_3)C_6H_5$		45–62[a]
9	$C_6H_5CH_2CON(CH_3)C_6H_5$		45
10	$CH_3CON(CH_3)C_6H_5$		42

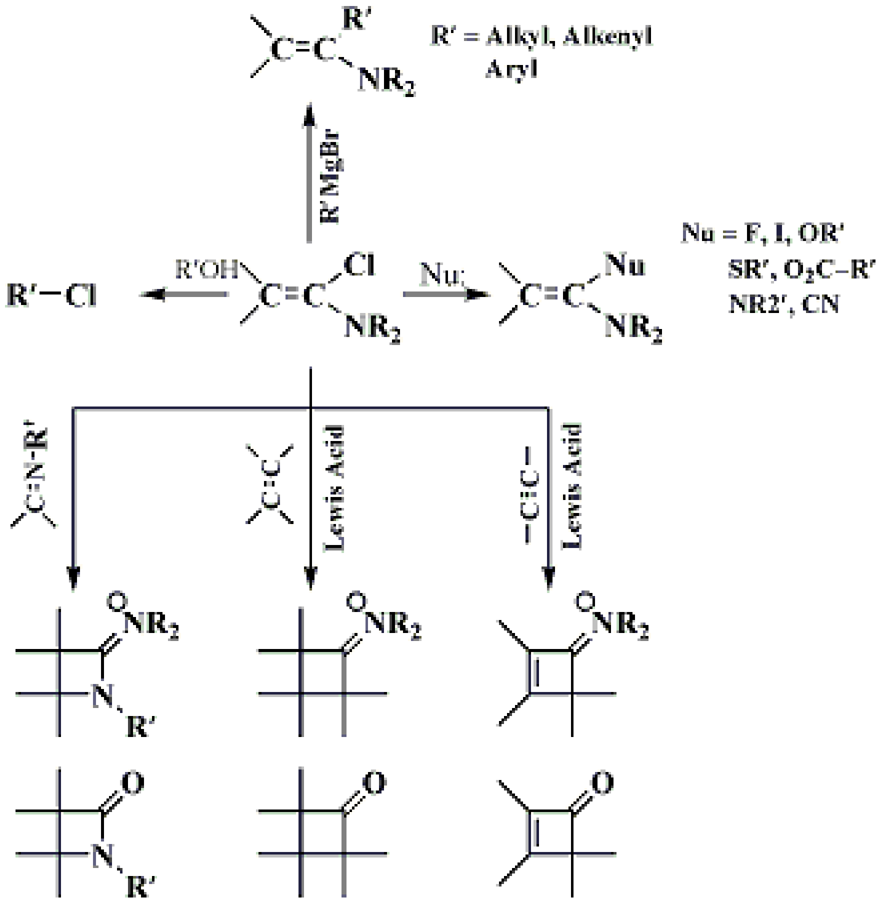
[a]The product is a mixture of *cis* and *trans* isomers.

The reaction of the more basic amides with phosgene is exothermic *(Caution!);* consequently the reaction mixture must be cooled in an ice bath. With the less reactive amides (*e.g.*, entries 2, 4, 5, and 8–10), however, the reaction often requires several days. It can be accelerated by the addition of catalytic amounts of *N,N*-dimethylformamide. With the monosubstituted acetamides or acetanilides, the solution must be saturated with gaseous hydrogen chloride before adding phosgene to avoid the formation of β-chlorocarbonyl α-chloro enamines resulting from elimination of hydrogen chloride and acylation of the α-chloro enamine with phosgene. The subsequent elimination reaction must be conducted with an excess of triethylamine in ethyl ether, carbon tetrachloride, or petroleum ether. Dichloromethane and chloroform are not suitable since these solvents promote the formation of condensation products to a considerable extent. With the exceptions of entries 7–10, α-chloroenamines derived from monosubstituted acetamides are unstable and should be kept in solution at concentrations below 1 *M*.

Most α-chloro enamines can be readily converted into the corresponding α-fluoro enamines by reaction with potassium or cesium fluoride.[6] The less stable α-iodo enamines are more conveniently prepared *in situ* from α-chloro enamines and potassium iodide. 1-Bromo-*N*,*N*,2-trimethylpropenylamine is easily obtained from the corresponding chloro compound and refluxing dibromomethane.[7] All α-haloenamines are highly hygroscopic and must be stored in sealed tubes.

α-Halo enamines are useful organic reagents that show versatile chemical behavior

and have great synthetic potential.[5] As enamines derived from carboxylic acid halides, they react with a variety of electrophilic reagents on C-2 to give, after hydrolysis, a carboxamide substituted at the α-position. Moreover, spontaneous or catalyzed ionization leads to keteniminium ions that are strongly electrophilic and add various nucleophilic reagents at C-1.[5,8,9,10] Keteniminium ions are also capable of undergoing [2 + 2]-cycloaddition reactions with olefins,[11] acetylenes,[12] and imines[13] extremely readily. 1-Halo-*N*,*N*,2-trimethylpropenylamines are also highly effective reagents for the replacement of hydroxyl groups by chlorine, bromine, and iodine under neutral conditions.[5,7] A summary of some of the reactions of α-chloro enamines follows.



This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 441

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

iminium chloride

2-methylpropenylidenebis(dimethylamine)

sulfuric acid (7664-93-9)

hydrogen chloride (7647-01-0)

ethyl ether (60-29-7)

chloroform (67-66-3)

carbon tetrachloride (56-23-5)

potassium iodide (7681-11-0)

nitrogen (7727-37-9)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

phosgene (75-44-5)

phosphorous trichloride (7719-12-2)

potassium (7440-09-7)

dibromomethane (74-95-3)

dichloromethane (75-09-2)

dimethylamine (124-40-3)

isobutyryl chloride (79-30-1)

N,N-dimethylformamide (68-12-2)

triethylamine (121-44-8)

Triethylamine hydrochloride (554-68-7)

dichlorophenylphosphine (644-97-3)

cesium fluoride (13400-13-0)

phosphorus pentoxide (1314-56-3)

1-Chloro-N,N,2-trimethylpropenylamine, Propenylamine, 1-chloro-N,N,2-trimethyl- (26189-59-3)

N,N-dimethylisobutyramide (21678-37-5)

1-Bromo-N,N,2-trimethylpropenylamine (73630-93-0)

1-Chloro-N,N,2-trimethylpropylideniminium chloride (52851-35-1)

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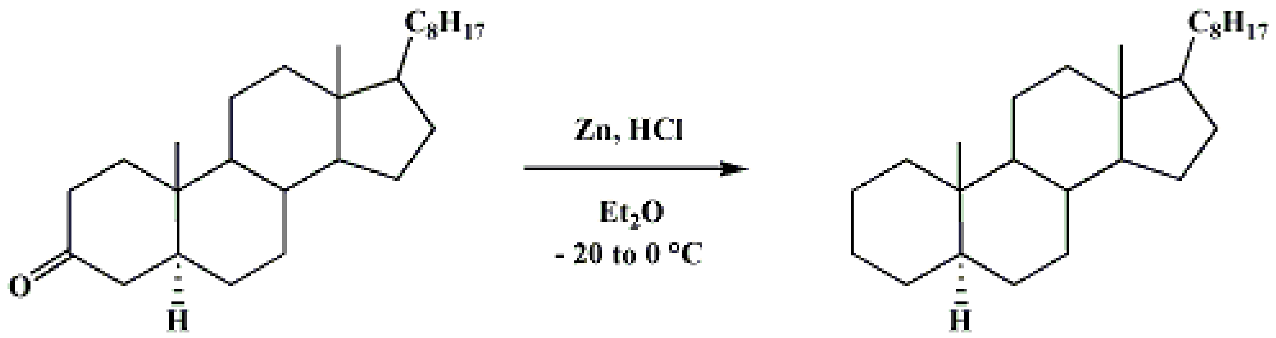
Organic Syntheses, *CV 6, 289*

MODIFIED CLEMMENSEN REDUCTION: CHOLESTANE



Submitted by Shosuke Yamamura[1], Masaaki Toda[2], and Yoshimasa Hirata[2].
Checked by A. Laurenzano, L. A. Dolan, and A. Brossi.

1. Procedure

A 500-ml., four-necked, round-bottomed flask (Note 1) equipped with a sealed mechanical stirrer (Note 2), a gas-inlet tube, a low-temperature thermometer, and a calcium chloride tube is charged with 250 ml. of dry diethyl ether. With an acetone–dry ice bath the temperature of the ether is lowered to −10 to −15° and maintained within this range while a slow stream (Note 3) of hydrogen chloride is introduced, with slow stirring, for about 45 minutes. The gas-inlet tube is replaced with a glass stopper, and 10.0 g. (0.0259 mole) of cholestan-3-one (Note 4) is added while the temperature of the stirred solution (Note 5) is kept below −15°. The reaction mixture is cooled to −20°, and 12.3 g. (0.188 g.-atom) of activated zinc (Note 6) is added over a 2–3 minute period. The temperature of the reaction mixture is allowed to rise to −5° (Note 7), and it is maintained between −4° and 0° (Note 8) for 2 hours. Stirring is not interrupted for the duration of the reaction. The mixture is finally cooled to −15° and poured slowly onto about 130 g. of crushed ice. The ethereal layer is separated, and the aqueous layer is extracted with 100 ml. of ether that had been used to rinse the reaction vessel. The ethereal solutions are combined, washed with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and filtered. The ether is distilled under reduced pressure with a 50° water bath, leaving 9.3–9.5 g. of a colorless, liquid residue that solidifies on cooling. This solid is dissolved in 30–40 ml. of *n*-hexane (Note 9). The solution is poured onto a 3.5 cm. by 17 cm. column of silica gel (Note 10) and eluted with 80–90 ml. of *n*-hexane. Distillation of the solvent under reduced pressure with a 50° water bath leaves 8.0–8.2 g. (82–84%) of cholestane (Note 11), which, after recrystallization from ethanol-ether (Note 12), yields 7.3–7.5 g. (76–77%) of product as plates m.p. 78–79° (lit., m.p. 80°)[3] (Note 13).

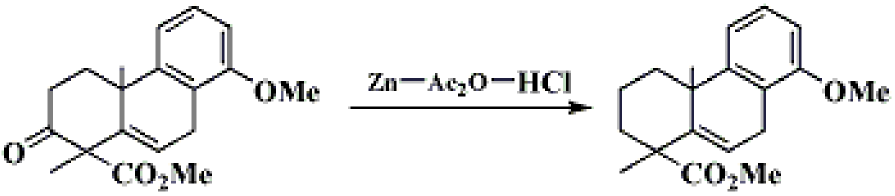
2. Notes

1. A standard, three-necked flask fitted with a Y-tube may be used.
2. An efficient magnetic stirrer may be substituted.

3. Approximately one bubble per second can be spot-checked periodically by connecting the calcium chloride tube to an oil-filled bubble counter.
4. Cholestan-3-one was prepared according to *Org. Synth.*, **Coll. Vol. 2**, 139 (1943); single spot on TLC with the system described in (Note 11).
5. The cholestanone does not dissolve completely at this low temperature, but the reaction is not affected.
6. The submitters prepared activated zinc by the following procedure. Commercial zinc powder (16 g.), special grade, *ca.* 300 mesh, obtained from either Kishida Chemical Company Ltd. or Hayashi Pure Chemical Company Ltd., is added with stirring to a 300-ml., round-bottomed flask containing 100 ml. of 2% hydrochloric acid. Vigorous stirring is continued until the surface of the zinc becomes bright (*ca.* 4 minutes). The aqueous solution is decanted, and the zinc powder in the flask is washed by decantation with four 200-ml. portions of distilled water. The activated zinc powder is transferred to a suction filter with 200 ml. of distilled water and washed successively with 50 ml. of ethanol, 100 ml. of acetone, and 50 ml. of dry ether. Filtration and washing should be done as rapidly as possible to minimize exposure of the activated zinc to air. The zinc is finally dried at 85–90° for 10 minutes in a vacuum oven (*ca.* 15 mm.), cooled, and used immediately; the yield is 13–14 g.
The checkers used this procedure with certified zinc powder, 325 mesh, obtained from Fisher Scientific Company.
7. This requires *ca.* 20 minutes.
8. The temperature is regulated by adding pieces of dry ice to the cooling bath as required. As the reduction proceeds, the solution separates into two phases.
9. The solution is decanted from any insoluble matter.
10. Silicic acid, 100 mesh (Mallinckrodt), was used.
11. This material melts at 78–79°. On TLC [silica, development with *n*-hexane, visualization with sulfuric acid-methanol (1:1) and heating] the product had R_f = 0.74. An impurity, R_f = 0.65, was present.
12. The cholestane is dissolved in 50 ml. of ether. Ether is distilled until the volume is 25 ml., 200 ml. of ethanol is added, and the mixture is refrigerated.
13. Recovery is 92%. Recrystallization has no effect on the quality of the product as judged by m.p. and TLC (Note 11).

3. Discussion

The well-known Clemmensen reduction[4] is a general method by which aralkyl ketones are readily converted to the corresponding hydrocarbons with amalgamated zinc and hydrochloric acid. It is not particularly effective, however, with alicyclic and aliphatic ketones. The procedure described herein provides a simple method of reducing a variety of ketones to their desoxy derivatives in high yields under much milder conditions (0°, 1–2 hours) than those normally used in the Clemmensen reaction.[4] This permits selective deoxygenation of ketones in polyfunctional molecules[5] containing groups such as cyano, amido, acetoxy, and carboalkoxy, which are stable under the mild reaction conditions. For example, the following reduction[6] has been carried out successfully by the modification of our procedure, using acetic anhydride as the solvent.[5]



Wide latitude is permitted in choosing the solvent for the reaction. Several organic solvents (tetrahydrofuran, benzene, *n*-hexane)[7] and particularly acetic anhydride[5,8] may be used instead of dry ether. α-Halo- and α-acetoxycholestanone[5] are converted to cholestane with Zn-HCl-Et_2O and also with Zn-HCl-Ac_2O.[7,8] These reduction systems, however, have given different results with α,β-unsaturated ketones.[9] With Zn-HCl-Et_2O, cholest-1-en-3-one gave cholestane in 88% yield, while cholest-4-en-3-one gave an 88% yield of a mixture of 1.2 parts of cholestane and 1 part of coprostane. By contrast, reaction of Zn-HCl-Ac_2O with cholest-1-en-3-one afforded a mixture of three compounds: cholestane (30–32%), 3-acetoxycholest-2-ene (10–24%), and cholestan-3-one (30–40%). Cholestan-3-one appears to be formed from the corresponding cyclopropanol acetate[10] during the work up. The mechanism of this reduction is probably similar to that of the Clemmensen reaction.[11]

References and Notes

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2. Chemical Institute, Nagoya University, Chikusa-ku, Nagoya, Japan.
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

hydrogen chloride, hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether, diethyl ether (60-29-7)

acetic anhydride (108-24-7)

sodium chloride (7647-14-5)

acetone (67-64-1)

zinc (7440-66-6)

magnesium sulfate (7487-88-9)

Cholestanone, cholestan-3-one (566-88-1)

Tetrahydrofuran (109-99-9)

n-hexane (110-54-3)

cholest-1-en-3-one

Cholest-4-en-3-one (601-57-0)

acetoxy

Cholestane, coprostane (481-21-0)

sulfuric acid-methanol

3-acetoxycholest-2-ene

cyclopropanol acetate

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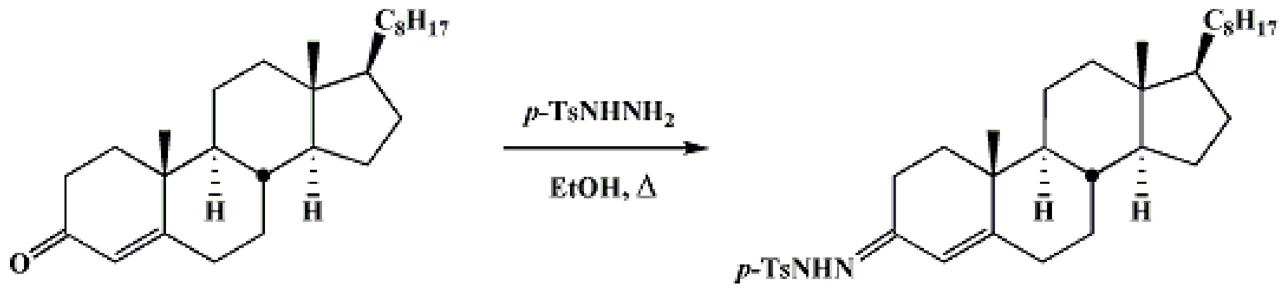
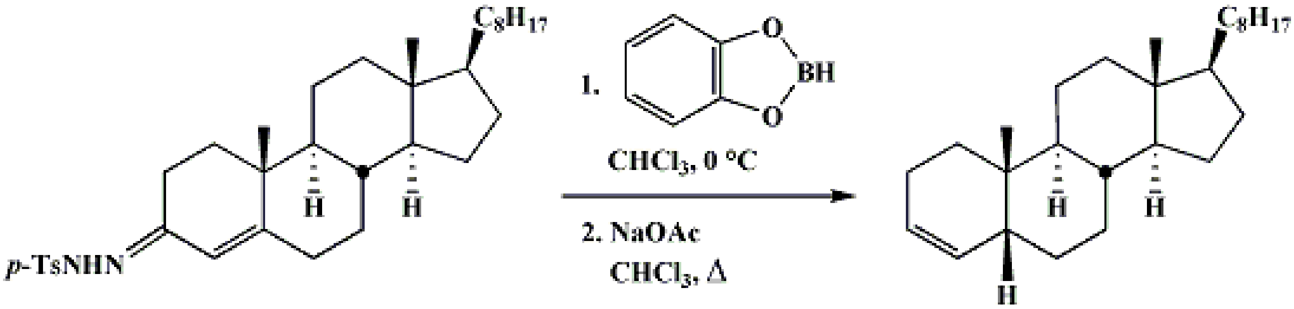
Organic Syntheses, CV 6, 293

CONJUGATE REDUCTION OF α,β-UNSATURATED *p*-TOLUENESULFONYLHYDRAZONES TO ALKENES WITH CATECHOLBORANE: 5β-CHOLEST-3-ENE

[Cholest-3-ene, (5β)-]





Submitted by George W. Kabalka[1], Robert Hutchins[2], Nicholas R. Natale[2], Dominic T. C. Yang[3], and Vicky Broach[3].
Checked by Steven J. Brickner and Martin F. Semmelhack.

1. Procedure

A. *Cholest-4-en-3-one p-toluenesulfonylhydrazone*. A 100-ml., round-bottomed flask equipped with a magnetic stirring bar and a reflux condenser is charged with 10.19 g. (0.0265 mole) of cholest-4-en-3-one (Note 1), 5.53 g. (0.0297 mole) of *p*-toluenesulfonylhydrazide (Note 1), and 17 ml. of 95% ethanol. The solution is stirred and heated at reflux for 10 minutes and allowed to cool to room temperature. The precipitated solid is collected by filtration and recrystallized from 95% ethanol, affording 13.1–13.3 g (89–91%) of cholest-4-en-3-one *p*-toluenesulfonylhydrazone, m.p. 139–141° (Note 2), in two crops.

B. 5β-*Cholest*-3-*ene*. A dry, 100-ml., two-necked, round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and a reflux condenser connected to a mercury bubbler (Note 3) is charged with 4.98 g. (0.00950 mole) of cholest-4-en-3-one *p*-toluenesulfonylhydrazone and 20 ml. of chloroform, and the apparatus is evacuated with an aspirator and filled with nitrogen three times. The solution is stirred and cooled at 0° as 1.29 g. (1.21 ml., 0.0108 mole) of catecholborane (Note 4) is injected through the septum into the flask. Stirring and cooling are continued for 2 hours, after which 2.5 g. (0.018 mole) of sodium acetate trihydrate and 20 ml. of chloroform are added. The mixture is allowed to warm to room temperature over *ca.* 30 minutes, heated under reflux for 1 hour, cooled to room temperature, and filtered. The solid material is washed with 50 ml. of chloroform, and the combined filtrates are evaporated under reduced pressure. The remaining oil is purified by

chromatography on a 5 × 50 cm. column packed with 200 g. of alumina (Note 5). The column is eluted with hexane and 200-ml. fractions are collected. Evaporation of the second 200-ml. fraction affords 2.76–2.95 g. (83–88%) of 5β-cholest-3-ene as a colorless oil which eventually crystallizes on standing, m.p. 48–50°, $[\alpha]_D^{24}$ = 19.6° (*c* = 63, chloroform) (Note 6).

2. Notes

1. Cholest-4-en-3-one and *p*-toluenesulfonylhydrazide are available from Aldrich Chemical Company, Inc. Procedures for the preparation of cholest-4-en-3-one and *p*-toluenesulfonylhydrazide are described in *Org. Synth.*, **Coll. Vol. 4**, 192, 195 (1963) and **Coll. Vol. 5**, 1055 (1973). The checkers used 5.70 g. of *p*-toluenesulfonylhydrazide, the purity of which was 97%.

2. The reported[4] melting point is 139–142°.

3. Nitrogen is introduced *via* a syringe needle that pierces the septum. A positive pressure of nitrogen is maintained in the apparatus during the following operations.

4. Catecholborane with a purity of 95% was purchased from Aldrich Chemical Company, Inc.

5. Activity grade I, neutral alumina was supplied by Brinckmann Instruments, Inc., Westbury, New York. The checkers used a 3 × 30 cm. column.

6. A TLC analysis was carried out by the submitters on a precoated silica gel plate (type Q6) purchased from Quantum Industries, 341 Kaplan Drive, Fairfield, New Jersey 07006. The chromatogram was developed with cyclohexane and showed a single spot for the product after visualization by charring with concentrated sulfuric acid. 5β-Cholest-3-ene is reported[5] to melt at 48–49°. The spectral properties of the product are as follows: IR ($CHCl_3$) $cm.^{-1}$: 2926, 1658, 1465, 831, 758, 678; ^1H NMR ($CDCl_3$), δ (multiplicity, number of protons, assignment): 0.66 (s, 3H, C-18 CH_3), 0.82 (s, 3H, CH_3), 0.92 (s, 3H, CH_3), 0.94 (s, 3H, C-19 CH_3), 5.2–5.7 (m, 2H, vinyl *H*); mass spectrum *m/e*: 370 (M+).
The submitters prepared the dibromide derivative, 3α,4β-dibromo-5β-cholestane, m.p. 98–99°. The melting point of the dibromide is reported as 98–100°.[6] The mass spectrum of the dibromide exhibits three molecular ions at *m/e* (relative intensity, assignment): 532 (25%, $C_{27}H_{46}^{81}Br^{81}Br$), 530 (50%, $C_{27}H_{46}^{79}Br^{81}Br$), 528 (25%, $C_{27}H_{46}^{79}Br^{79}Br$).

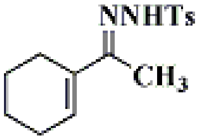
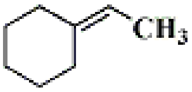
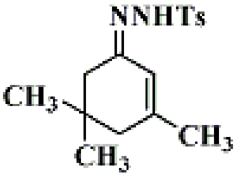
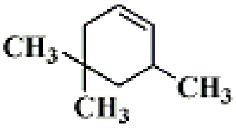
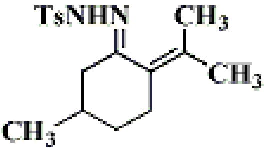
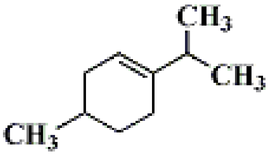
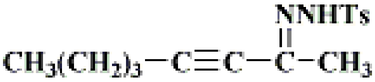
3. Discussion

The reduction of *p*-toluenesulfonylhydrazone derivatives of α,β-unsaturated ketones and aldehydes with aluminum[7] or boron hydride reagents[8,9,10,11] effects a formal "conjugate" hydride transfer and produces alkenes in which the double bond has migrated to the position between the α-carbon and the carbonyl carbon. The mechanism of the reaction is presumed to involve initial reduction of the C=N double bond, elimination of *p*-toluenesufinate, forming an allyl diazene, and concerted fragmentation of the diazene with 1,5-hydrogen transfer. One or both of the last two steps may take place during a subsequent hydrolysis. The reductions have been carried out with excess lithium aluminum hydride in tetrahydrofuran,[7] with catecholborane in chloroform at 0° followed by hydrolysis at *ca.* 60° (Procedure A),[8] with sodium cyanoborohydride in 1:1 (v/v) *N,N*-dimethylformamide–sulfolane acidified with concentrated hydrochloric acid at 100–105° (Procedure B),[9,10] and with sodium borohydride in acetic acid at 70° (Procedure C).[11] A selection of examples of these reductions is given in Table I.

TABLE I

CONJUGATE REDUCTION OF α,β-UNSATURATED *p*-TOLUENESULFONYLHYDRAZONES

TOALKENES

p-Toluenesulfonylhydrazone[a,b]	Alkene[b]	Procedure[c]	Yield (%)
	$C_6H_5CH_2CH{=}CHCH_3$	A B C	72[d] 54 54
	$C_6H_5CH_2CH{=}CH_2$	A B C	53[d] 98[d] 42–56
	$(CH_3)_2CH\text{-}CH{=}CHCH_3$	A	65[d]
		A B C	77[d] 79 61–72
		A B C	66[e] 4[d,f] 18
		B C	70 51
	$CH_3(CH_2)_3\text{-}CH{=}C{=}CH\text{-}CH_3$	A	64
	$CH_3\text{-}CH{=}C{=}CH\text{-}C_6H_5$	A	75

[a] The abbreviation Ts stands for *p*-toluenesulfonyl.

[b] The *p*-toluenesulfonylhydrazones and alkenes with acyclic disubstituted double bonds are the *E* isomers.

[c] See text for descriptions of the procedures.

[d] Yield determined by GC.

[e] Yield determined by ^{1}H NMR spectroscopy.

[f] The cycloalkane was also formed in 32% yield.

This method provides a convenient synthesis of alkenes with the double bond in a relatively unstable position. Thus, reduction of the *p*-toluenesulfonylhydrazones of α,β-unsaturated aryl ketones and conjugated dienones gives rise to nonconjugated olefins. Unsaturated ketones with endocyclic double bonds produce olefins with double bonds in the exocyclic position. The reduction of *p*-toluenesulfonylhydrazones of conjugated alkynones furnishes a simple synthesis of 1,3-disubstituted allenes.[12,13]

The present procedure illustrates this method with the preparation of 5β-cholest-3-ene by reduction of cholest-4-en-3-one *p*-toluenesulfonylhydrazone, using catecholborane as the reducing agent.[8,14] The advantages of catecholborane include its high solubility in common aprotic and nonpolar solvents, the low temperatures required for the reduction (0–25°), and the generally mild conditions used. Although the sodium cyanoborohydride and sodium borohydride procedures require higher temperatures, the use of polar solvents and protic conditions offers a valuable complement to the nonpolar, aprotic medium employed in the catecholborane procedure. However, the reduction of cholest-4-en-3-one *p*-toluenesulfonylhydrazone with sodium cyanoborohydride (Procedure B) gave a 71% yield of a mixture consisting of 5β-cholest-3-ene (32.5%), 5β-cholestane (30.5%), 5α-cholestane (30.5%), and 5α-cholest-3-ene (6.5%).[15]

5β-Cholest-3-ene has been prepared previously by deamination of 5β-cholestan-3β-yl amine,[16] by reduction of a mixture of 4β-bromo-5β-cholestan-3α-ol and its 3β epimer with zinc in acetic acid,[5] and as component of a mixture of cholestenes by Wolff-Kishner reduction of cholest-4-en-3-one.[6]

References and Notes

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2. Department of Chemistry, Drexel University, Philadelphia, Pennsylvania 19104.
3. Department of Chemistry, University of Arkansas at Little Rock, Little Rock, Arkansas 72204.
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

p-toluenesulfonylhydrazones

p-toluenesufinate

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

chloroform (67-66-3)

nitrogen (7727-37-9)

aluminum (7429-90-5)

cyclohexane (110-82-7)

zinc (7440-66-6)

boron hydride (7440-42-8)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

N,N-dimethylformamide (68-12-2)

sodium acetate trihydrate (6131-90-4)

hexane (110-54-3)

Cholest-4-en-3-one (601-57-0)

sodium borohydride (16940-66-2)

sulfolane (126-33-0)

CATECHOLBORANE (274-07-7)

5β-Cholest-3-ene, Cholest-3-ene, (5β)- (13901-20-7)

3α,4β-dibromo-5β-cholestane

allyl diazene

diazene (3618-05-1)

sodium cyanoborohydride (25895-60-7)

5β-cholestane

5α-cholestane

5α-cholest-3-ene

5β-cholestan-3β-yl amine

4β-bromo-5β-cholestan-3α-ol

cyanoborohydride

p-toluenesulfonyl

p-Toluenesulfonylhydrazide (1576-35-8)

Cholest-4-en-3-one p-toluenesulfonylhydrazone (21301-41-7)

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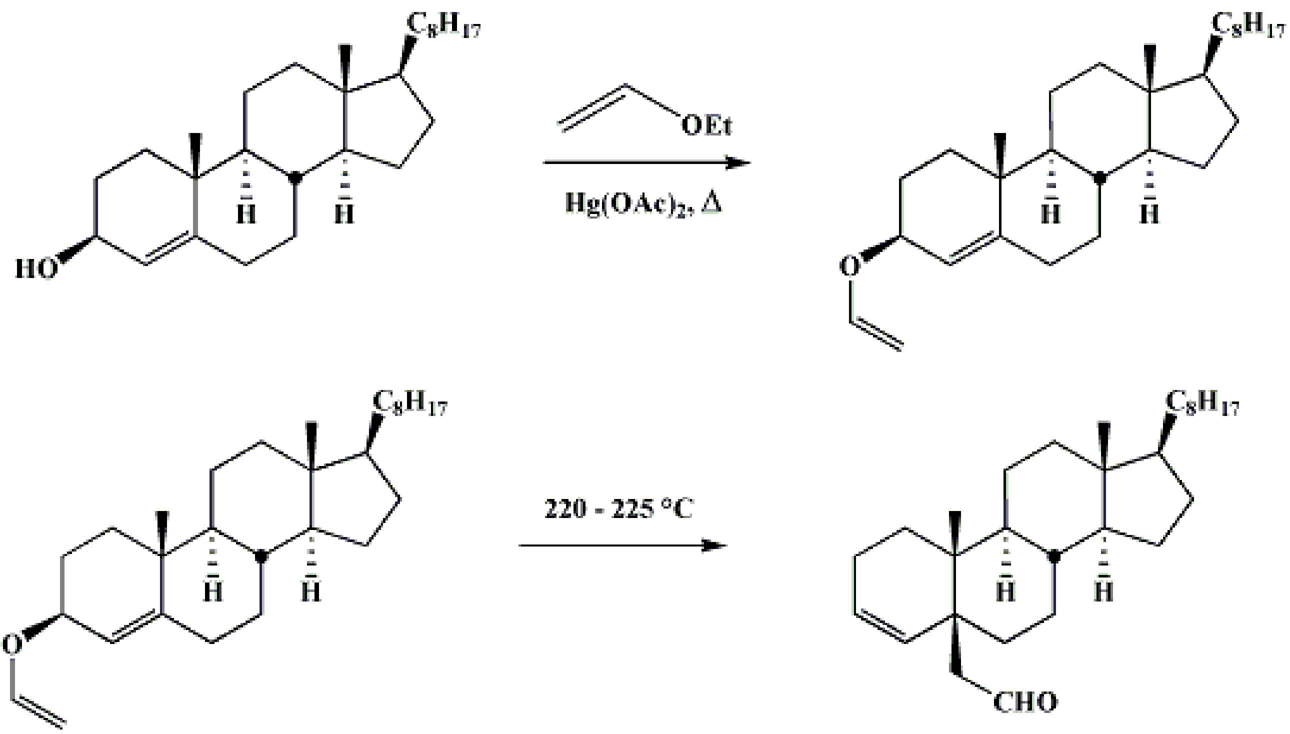
5β-CHOLEST-3-ENE-5-ACETALDEHYDE

[Cholest-3-ene-5-acetaldehyde, (5β)-]



Submitted by R. E. Ireland[1] and D. J. Dawson.
Checked by W. Pawlak and G. Büchi.

1. Procedure

A 50-ml., round-bottomed flask equipped with a magnetic stirring bar and a 20-ml. calibration mark (Note 1) is charged with 970 mg. (2.51 mmoles) of cholest-4-en-3β-ol (Note 2). Ethyl vinyl ether is distilled into the flask to the 20-ml. mark (Note 3). The mixture is stirred to effect solution before 820 mg. (2.55 mmoles) of mercury(II) acetate (Note 4) is added to the reaction mixture. The flask is fitted with a reflux condenser connected to a gas-inlet tube and flushed with argon. The reaction mixture is then stirred and heated (Note 5) at reflux under a positive argon pressure for 17 hours. After the solution has cooled to room temperature, 0.062 ml. (1.1 mmoles) of glacial acetic acid (Note 6) is added, and stirring is continued for 3 hours. The reaction mixture is poured into a preshaken mixture of 150 ml. of petroleum ether (Note 7) and 50 ml. of 5% aqueous potassium hydroxide. The aqueous phase is extracted with 50 ml. of petroleum ether, and the combined extracts are washed with three 50-ml. portions of a 20% aqueous sodium chloride, dried over anhydrous sodium carbonate, filtered and evaporated at reduced pressure (Note 8), giving 1.11 g. of an oil which, upon filtration through 5 g. of silica gel (Note 9) with 200 ml. of petroleum ether, affords 0.81 g. of the cholestenyl vinyl ether as a clear, colorless oil. If desired, crystallization of this oil from 10 ml. of acetone will give 0.74 g. (71%) of the vinyl ether as colorless prisms, m.p. 55–56.5° (Note 10).

Alternatively, the crude vinyl ether (0.81 g.) is transferred with petroleum ether into a 50-ml., round-bottomed flask fitted with a long gas-inlet tube. After the petroleum ether is removed at reduced pressure (Note 8), the flask is filled with argon and heated (Note 11) under a positive argon pressure at 220–225° for 5 hours; little or no bubbling should occur. After cooling, the oil is chromatographed

on 75 g. of silica gel using 10% diethyl ether in petroleum ether as the elution solvent (Note 7), (Note 9), (Note 12). The first 175 ml. of eluant contains side products and is discarded; elution with another 175 ml. of the solvent gives 0.45–0.55 g. (50–53% overall yield from cholest-4-en-3β-ol) of 5β-cholest-3-ene-5-acetaldehyde as white prisms, m.p. 66.5–68° (Note 10).

2. Notes

1. This flask must be cleaned with hot chromic acid solution and then, along with *all* other glassware used in this preparation, soaked in a base solution, rinsed with distilled water, and over dried. Thermal rearrangement of the intermediate vinyl ether in a new (untreated) flask resulted in elimination.

2. Cholest-4-en-3β-ol can be prepared by the procedure of Burgstahler and Nordin.[2] A melting point below 130° indicates that the material is contaminated with some of the 3α-hydroxy isomer. The material used above melted at 130.5–131° (from ethanol).

3. Eastman practical grade ethyl vinyl ether was dried over anhydrous sodium carbonate, distilled (b.p. 36°) from sodium wire, and then redistilled from calcium hydride (b.p. 36°) into the reaction flask after a 5-ml. forerun is discarded.

4. Matheson, Coleman and Bell mercury(II) acetate was partially dissolved in hot absolute ethano containing 0.02% glacial acetic acid ((Note 6)) and filtered by suction. The filtrate was cooled, and the white plates of mercury(II) acetate were collected by suction filtration and stored under vacuum.

5. An oil bath at 50–55° was found to be satisfactory.

6. DuPont 99.7% acetic acid was used without purification.

7. Baker petroleum ether (b.p. 30–60°) was used.

8. The solvent was removed by rotary evaporation followed by vacuum (0.01 mm.) drying for 1 hour.

9. Merck silica gel (0.05–0.2 mm., 70–325 mesh ASTM) was used. The filtration column (1.4 × 7 cm.) is prepared in the same way as one used for chromatography, only one (200-ml.) fraction is collected. Use of alumina for the filtration gives variable results.

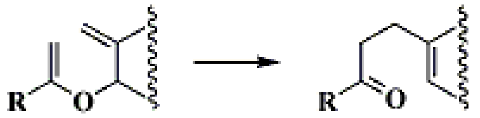
10. Burgstahler and Nordin report the melting point for the vinyl ether as 56–57°, and for the aldehyde, 66–69°.[2]

11. A Kügelrohr oven was used.

12. Mallinckrodt anhydrous ether was used. The chromatography column was 2.7 × 27 cm.

3. Discussion

The Claisen rearrangement[3] has been adapted in recent years to provide a viable synthetic sequence for the preparation of functional groups other than aldehydes and ketones. Ester[4] and amide[5] syntheses have been reported which proceed through the Claisen intermediate (**A**). The Claisen rearrangement has also been used to generate *trans*-trisubstituted double bonds stereoselectively,[4,6,7,8,9] angularly-functionalized derivatives,[10] substituted cyclohexenes,[11] acids,[12] and furans.[7]



R = —H, —Alkyl —Aryl —OR', —NR$_2$', —OSiR$_3$',

A

The procedure given above is an excellent example of the utilization of the Claisen rearrangement to

generate an angularly functionalized steroid. The vinyl ether and aldehyde were originally prepared by Burgstahler and Nordin.[2] This procedure combines variations employed by Ireland and co-workers and, in addition, introduces the use of silica gel for the purification of the vinyl ether, thereby improving the reproducibility of the procedure.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

ethanol (64-17-5)

acetic acid (64-19-7)

ether, diethyl ether (60-29-7)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

mercury(II) acetate (1600-27-7)

acetone (67-64-1)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

chromic acid (7738-94-5)

ethyl vinyl ether (109-92-2)

calcium hydride (7789-78-8)

argon (7440-37-1)

5β-Cholest-3-ene-5-acetaldehyde, Cholest-3-ene-5-acetaldehyde, (5β)- (56101-55-4)

cholest-4-en-3β-ol

cholestenyl vinyl ether

vinyl ether (109-93-3)

ethano

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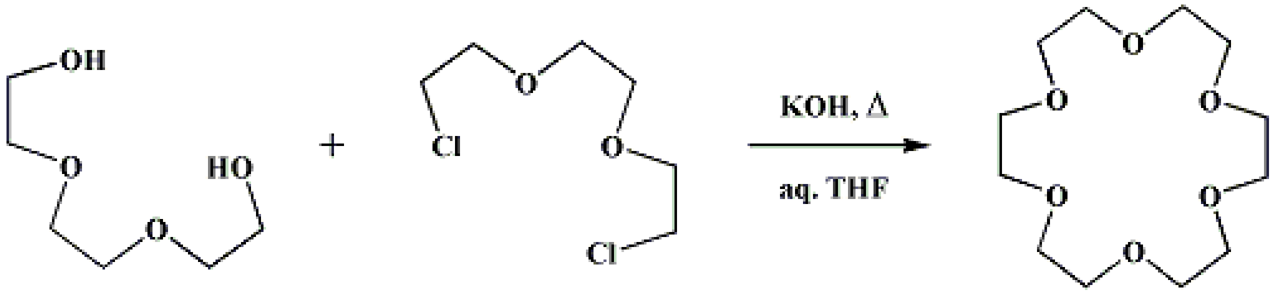
Organic Syntheses, CV 6, 301

18-CROWN-6

[1,4,7,10,13,16-Hexaoxacycloöctadecane]



Submitted by George W. Gokel[1], Donald J. Cram[2], Charles L. Liotta[3], Henry P. Harris[3], and Fred L. Cook[3].
Checked by E. A. Noe, M. Raban, and C. R. Johnson.

1. Procedure

Caution! Crown ethers may be toxic.[4] Due care should be exercised in the preparation and handling of 18-crown-6. An explosion has been reported during the thermal decomposition of the crude 18-crown-6-potassium salt complex; see (Note 8).

A 3-l., three-necked flask equipped with a mechanical stirrer, a reflux condenser, and an addition funnel is charged with 112.5 g. (100.0 ml., 0.7492 mole) of triethylene glycol and 600 ml. of tetrahydrofuran (Note 1). Stirring is begun and a 60% potassium hydroxide solution, prepared by dissolving 109 g. (1.65 moles) of 85% potassium hydroxide in 70 ml. water, is added (Note 2). The solution warms slightly. After about 15 minutes of vigorous stirring (the solution begins to develop color and gradually becomes rust brown; (Note 3)), a solution of 140.3 g. (0.7503 mole) of 1,2-bis(2-chloroethoxy)ethane (Note 4) in 100 ml. of tetrahydrofuran is added in a stream. After the addition is complete, the solution is heated at reflux and stirred vigorously for 18–24 hours. The solution is allowed to cool and the bulk of the tetrahydrofuran is evaporated under reduced pressure (Note 5). The resulting thick, brown slurry is diluted with 500 ml. of dichloromethane and filtered through a glass frit. The salts removed by filtration are washed with more dichloromethane to remove absorbed crown and the combined organic solution is dried over anhydrous magnesium sulfate (Note 6), filtered, evaporated to minimum volume (aspirator vacuum), and distilled under high vacuum using a simple distillation head. The distillation should be carried out at the lowest possible pressure; a typical fraction contains 76–87 g. (38–44%) of crude 18-crown-6 and is collected over 100–167° (0.2 mm.) (Note 7),(Note 8),(Note 9).

To 50 g. of the crude 18-crown-6 in a 250-ml. Erlenmeyer flask is added 100 ml. of acetonitrile. A magnetic stirring bar is added, and the flask is equipped with a calcium chloride drying tube. The resulting slurry is heated on a hot plate to effect solution. The solution is stirred vigorously as it is allowed to cool to ambient temperature; fine white crystals of crown-acetonitrile complex are deposited. The flask is allowed to stand in a

freezer for 24–48 hours and is finally cooled in a –30° bath to precipitate as much of the complex as possible. The solid is collected by rapid filtration (Note 10) and washed once with a small amount of cold acetonitrile. The hygroscopic crystals are transferred to a 200-ml., round-bottomed flask equipped with a magnetic stirring bar and a vacuum takeoff. The acetonitrile is removed from the complex under high vacuum (0.1–0.5 mm.), with gentle heating (35°), over 2–3 hours. The pure colorless crown (28–33 g., 56–66%) (Note 11) crystallizes on standing, m.p. 38–39.5° (Note 12).

2. Notes

1. The tetrahydrofuran may be used directly without drying or purification.
2. The potassium hydroxide may be added to the water in one portion, but the resulting base solution should be allowed to cool to nearly room temperature before adding to the reaction mixture. If the potassium hydroxide solution is cooled much below ambient temperature, the potassium hydroxide begins to separate; hot potassium hydroxide solution could cause the tetrahydrofuran solution to boil.
3. The rate of darkening is related to the temperature of the solution and, if warm potassium hydroxide solution is used, the color will develop somewhat more rapidly. Differences in the rate of darkening do not appear to affect the yield or purity of product.
4. 1,2-Bis(2-chloroethoxy)ethane is available from Eastman Organic Chemicals.
5. As much water as possible should be removed during evaporation so that the salts will filter more readily and the solution can be dried more easily.
6. Drying agents containing complexable cations, such as K^+ or Na^+, should be avoided.
7. There is generally a forerun (room temperature to *ca.* 100°) the size of which varies according to the vigor of the previous evaporation steps (see (Note 5)).
8. In a large batch preparation of 18-crown-6 an explosion has been reported as a result of difficulties occurring during this distillation step.[5] In this instance the head temperature rose to near 200°. When the system was vented to the atmosphere at this temperature an explosion occurred, apparently the result of autoignition of 1,4-dioxane vapors. Dioxane is reported to undergo autoignition in air at temperatures in excess of 180°. It is recommended that the head and pot be allowed to cool and then be vented with a nitrogen atmosphere.
9. The material obtained in the distillation cut contains both alcoholic and vinylic impurities. The crown may be purified by a second, more careful distillation followed by recrystallization, sublimation or by chromatography in addition to the method described here (see Discussion).
10. The filtration should be conducted in a dry-box or by using an inverted funnel-nitrogen flow, whichever is more convenient.
11. The yield of pure crown depends somewhat on the purity of the crude material used. Additional crown may be obtained by combining mother liquors and repeating the distillation and complex formation process.
12. The ^{1}H NMR spectrum (CCl_4) exhibits a singlet at δ 3.56.

3. Discussion

The compound known as 18-crown-6 is one of the simplest and most useful of the

macrocyclic polyethers. Its synthesis in low yield was first reported by Pedersen.[5] Greene[6] and Dale and Kristiansen[7] have reported syntheses of the title compound from triethylene glycol and triethylene glycol di-*p*-toluenesulfonate. Both of these procedures use strong base and anhydrous conditions and achieve purification by more or less classical methods. The combination of distillation and formation of the acetonitrile complex affords crown of high purity without lengthy chromatography or sublimation.[8,9]

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9. Acknowledgment is made to E. P. Kyba (University of Texas) for noting that this crown can be distilled and to E. R. Wonchoba (Du Pont Co.) for helpful comments.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

acetonitrile (75-05-8)

nitrogen (7727-37-9)

potassium hydroxide (1310-58-3)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

dioxane (5703-46-8)

Tetrahydrofuran (109-99-9)

triethylene glycol (112-27-6)

1,4-dioxane (123-91-1)

18-Crown-6, 1,4,7,10,13,16-Hexaoxacyclooctadecane (17455-13-9)

18-crown-6-potassium

1,2-bis(2-chloroethoxy)ethane (112-26-5)

triethylene glycol di-p-toluenesulfonate (19249-03-7)

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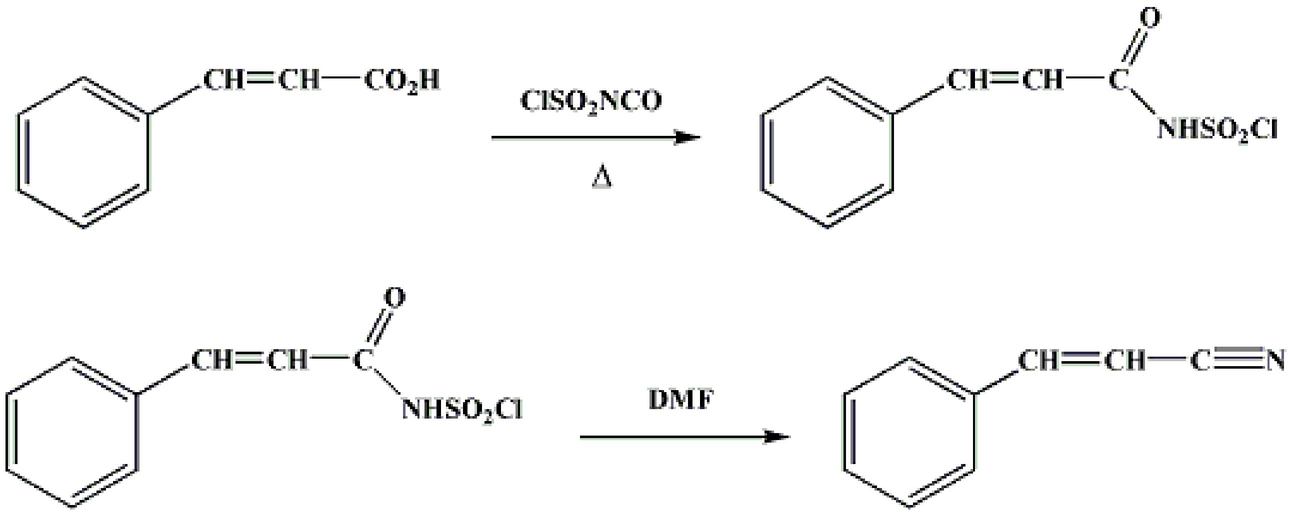
Organic Syntheses, CV 6, 304

CINNAMONITRILE

[2-Propenenitrile, 3-phenyl-]



Submitted by G. Lohaus[1]
Checked by Frank J. Weigert and Richard E. Benson.

1. Procedure

Caution! Chlorosulfonyl isocyanate is a highly corrosive, irritating compound. This reaction should be carried out in an efficient hood.

A 2-l., four-necked flask equipped with a stirrer, thermometer, dropping funnel, and reflux condenser is charged with 296 g. (2.00 moles) of cinnamic acid and 600 ml. of dichloromethane. The mixture is heated to reflux and a solution of 290 g. (2.05 moles) of chlorosulfonyl isocyanate (Note 1) in 100 ml. of dichloromethane is added dropwise, with stirring, over a period of 45 minutes. After a few minutes the solution becomes clear and, after about one-half of the isocyanate has been added, the carboxylic acid amide *N*-sulfonyl chloride begins to precipitate. At the end of the addition, the reaction mixture is heated for an hour to complete the evolution of carbon dioxide (Note 2). *N,N*-Dimethylformamide (300 g., 4.11 moles) (Note 3) is added, with stirring, over a 15-minute period, while cooling with ice to an internal temperature of 15–20°. The reaction mixture is stirred for an additional 15 minutes and then poured onto *ca.* 800 g. of ice. After the ice has melted, the resulting layers are separated and the aqueous phase is extracted once with 100 ml. of dichloromethane. The organic phases are combined and extracted six times with 100-ml. portions of water to remove most of the *N,N*-dimethylformamide (Note 4). The resulting organic solution is dried for 2 hours with 50 g. of potassium carbonate, decanted from the drying agent, and concentrated by distillation at atmospheric pressure. The resulting oil is distilled through a 10-cm. Vigreux column (Note 5) to give 197–225 g. (78–87%) of cinnamonitrile, b.p. 92–94° (1 mm.), n_D^{25} 1.5998 (Note 6). Its ^1H NMR spectrum (60 MHz., CCl_4, 36°) δ, (multiplicity, coupling constant *J* in Hz., number of protons): 5.79 (d, *J* = 17, 1H), 7.29 (d, *J* = 17, 1H), 7.35 (s, 5H).

2. Notes

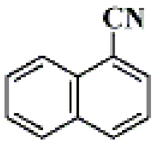
1. Chlorousulfonyl isocyanate, *Org. Synth.,* **Coll. Vol. 5**, 226 (1973), is available from

Farbwerke Hoechst AG. The checkers found it necessary to distill the product before use.
2. The rate of evolution of carbon dioxide can be followed easily with a bubble counter attached to the reflux condenser.
3. Other amides also can be used, but *N,N*-dimethylformamide generally is preferred because of its volatility, high solvating ability, and miscibility with water.
4. The checkers found that, if the mixture at this point was allowed to stand overnight, a crystalline product separated that was identified as the *N,N*-dimethylformamide–sulfur trioxide complex.
5. The presence of a crystalline residue at the end of the distillation prevents the use of a spinning band column.
6. GC indicates the purity to be greater than 99.9%. A column containing Chromosorb W/DMCS/AW with 10% Triton X 305 as the stationary phase is used.

3. Discussion

This reaction illustrates a broadly applicable method for converting carboxylic acids to the corresponding nitriles.[2] It avoids the necessity for conversion of the acid to the amide, followed by dehydration with vigorous reagents such as phosphorus pentachloride or phosphorus oxychloride. The reaction is characterized by easy workup, generally good yields, and by mild reaction conditions that permit certain functional groups that may be present to remain unchanged. For example, the half ethyl easter of succinic acid is converted to the corresponding nitrile in 72% yield with this procedure. Aliphatic unsaturation may be present; thus, 2,4-hexadienenitrile is obtained from 2,4-hexadienoic acid in 76% yield. The reaction is operable with chlorine-containg acids, and an aromatic acid has been converted to the nitrile with this procedure. The results are summarized in Table I.[2].

TABLE I
NitrilesDerived fromCorrespondingAcid

Nitrile	Yield, %
cyclo-$C_6H_{11}CN$	78
$ClCH_2CH_2CN$	66
$(CH_3)_3CCN$	68
$CH_3CH{=}CHCH{=}CHCN$	76
$C_6H_5CH_2CN$	84
$C_2H_5OCOCH_2CH_2CN$	72
$NC\text{-}(CH_2)_8CN$	86
	63

Other specific procedures for the synthesis of cinnamonitrile include the dehydration of cinnamamide with phosphorus pentachloride[3] or phosphorus oxychloride,[4] the dehydration of cinnamaldehyde oxime with acetic anhydride,[5] and the dehydrochlorination of α-chloro-β-phenylpropionitrile with quinoline,[6,7] *N,N*-diethylaniline,[8] or triethylamine.[9]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

N-sulfonyl chloride

Chlorousulfonyl isocyanate

potassium carbonate (584-08-7)

acetic anhydride (108-24-7)

phosphorus pentachloride (10026-13-8)

sulfur trioxide (7446-11-9)

carbon dioxide (124-38-9)

Succinic acid (110-15-6)

Phosphorus Oxychloride (21295-50-1)

cinnamic acid (621-82-9)

Quinoline (91-22-5)

dichloromethane (75-09-2)

N,N-diethylaniline (91-66-7)

isocyanate

N,N-dimethylformamide (68-12-2)

2,4-hexadienoic acid (110-44-1)

triethylamine (121-44-8)

CHLOROSULFONYL ISOCYANATE (1189-71-5)

Cinnamonitrile, 2-Propenenitrile, 3-phenyl- (4360-47-8)

2,4-hexadienenitrile

cinnamamide

cinnamaldehyde oxime

α-chloro-β-phenylpropionitrile

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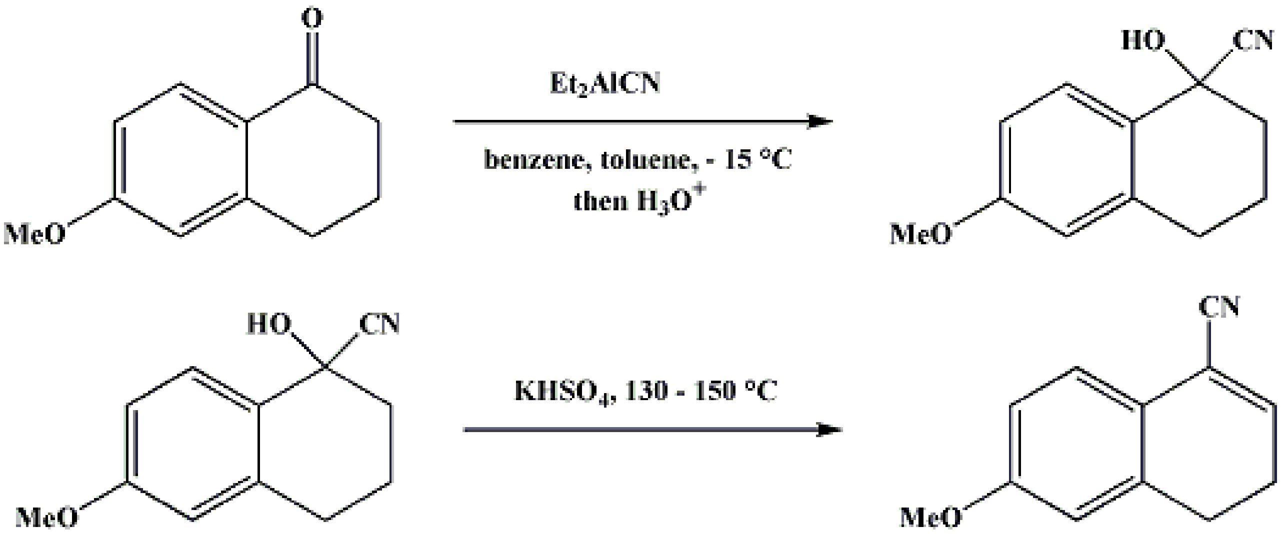
Organic Syntheses, CV 6, 307

PREPARATION OF CYANO COMPOUNDS USING ALKYLALUMINUM INTERMEDIATES: 1-CYANO-6-METHOXY-3,4-DIHYDRONAPHTHALENE

[Naphthalenecarbonitrille, 3,4-dihydro-6-methoxy-]



Submitted by W. Nagata[1], M. Yoshioka, and M. Murakami.
Checked by R. Wong, C. Kowalski, R. Czarny, and R. E. Ireland.

1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A 200-ml., two-necked round-bottomed flask charged with 6.15 g. (0.0347 mole) of 6-methoxy-1-tetralone (Note 1) and a 100 ml., round-bottomed flask are flushed with nitrogen, and each of the flasks is fitted with an adaptor with a side arm connected to a nitrogen bubbler system and then charged with 30 ml. of anhydrous toluene. The 200-ml. flask is cooled to –20° to –25° (bath temperature) (Note 2). Into the 100-ml. flask is introduced 60 ml. (0.07 mole) of a 13% solution of diethylaluminum cyanide in benzene (Note 3) with a hypodermic syringe, and this flask is cooled with ice water. The cooled diethylaluminum cyanide solution is added to the cold solution of 6-methoxytetralone with a hypodermic syringe and the resulting mixture, after being swirled, is kept at –15° for 80 minutes under nitrogen. The stopper of the flask is replaced by a glass tube which has one end extending to the bottom of the reaction flask and the other end mounted in a neck of a 2-l., three-necked flask, equipped with an efficient stirrer and containning a cold (–70°) mixture of 250 ml. of methanol and 150 ml. of concentrated hydrochloric acid as shown in f. htmigure 1. The reaction mixture is added through the glass tube to the vigorously stirred acid mixture by applying a positive nitrogen pressure to the reaction flask (Note 4). After the bulk of the reaction mixture is added, about 50 ml. of a cold mixture of methanol and hydrochloric acid is added to the reaction flask and this mixture is transferred to the 2-l. flask in the same way, as described above. Stirring is continued for one hour, and the resulting mixture is poured into a

mixture of 200 ml. of concentrated hydrochloric acid and 1 l. of ice water (Note 5) and extracted with three 500-ml. portions of dichloromethane. The combined organic phases are washed once with 1.5 l. of water, dried over anhydrous sodium sulfate, and evaporated from a flask containing 55 mg. of *p*-toluenesulfonic acid monohydrate (Note 6). using a rotary evaporator at a temperature below 40°.

Figure 1. Apparatus for acid treatment of the reaction mixture.

Figure 1. Apparatus for acid treatment of the reaction mixture.

The residue, obtained as a pale yellow oil, weighs approximately 7.4 g. and consists of 1-cyano-1-hydroxy-6-methoxytetralin and a small amount of unchanged 6-methoxy-1-tetralone. The oil is transferred to a 10-ml. Claisen flask, a small amount of a mixture of dichloromethane and diethyl ether being used to complete the transfer. Two hundred milligrams of powdered potassium hydrogen sulfate is added, and the flask is heated at 130° under reduced pressure (5 mm.) for 30 minutes. The pressure is then reduced to 0.01 mm. and the temperature is raised to about 150°, collecting all the distillate [b.p. 113–117° (0.01 mm.)] in a 50-ml. flask. The viscous distillate (including material adhering to the distillation apparatus), weighs 6.0–6.2 g. and yields 4.91–5.05 g. (76–78%) of product, m.p. 50–51.5°, after two or three crystallizations from methanol. The residue from the mother liquors (1.0–1.3 g.) is adsorbed on a column of 100 times its weight of silica gel (70–325 mesh), and the column is eluted with approximately 1 l. of 40% ether in petroleum ether (b.p. 30–60°). The first 200 ml. of eluent is discarded, and 510–550 mg. of the product is eluted in the next 250 ml. of eluent. Crystallization of this material from an ether–petroleum ether (b.p. 30–60°) mixture affords an additional 460–500 mg. (7.0–7.8%) of pure product, m.p. 50.5–51.5°. The total yield of the unsaturated nitrile is 5.41–5.51 g. (83.8–85.5%). (Note 7). The final 500 ml. fraction from chromatography contains 330–660 mg. (5.4–10.7%) of the starting material, m.p. 77–78°.

2. Notes

1. 6-Methoxy-1-tetralone is available from K & K Laboratories, New York, although the submitters used a material, m.p. 77–80°, produced by Osaka Yuki Gosei K. K., Nishinomiya-shi, Japan.
2. Crystals of 6-metoxy-1-tetralone may separate from the solution on cooling, but redissolve upon addition of the cooled diethylaluminum cyanide solution.
3. For the preparation of diethylaluminum cyanide, see *Org. Synth.*, **Coll. Vol. 6**, 436 (1988). Both the submitters and the checkers employed a crude reagent solution rather than a solution prepared from distilled diethylaluminum cyanide. A 1–2 *M* solution of diethylaluminum cyanide in benzene is commercially available from Alfa Products, Ventron Corporation, Danvers, Massachusetts.
4. Application of the nitrogen pressure may be made conveniently by capping the outlet of the mercury bubbler.
5. The two-step decomposition is effective for preventing reconversion of the cyanohydrin into the starting ketone.
6. The cyanohydrin initially formed is unstable and readily reconverted to the starting 6-methoxy-1-tetralone on evaporation of the extracts unless the solution is kept slightly acidic by addition of a trace amount of *p*-toluenesulfonic acid monohydrate. As this acid is relatively insoluble in dichloromethane, it should be added directly to the flask used for

evaporation of the solvent.
7. Preferably, the product should be stored in an oxygen-free atmosphere. Samples not stored in an inert atmosphere have deteriorated to dark-brown masses within several months, whereas no appreciable change has been observed in a sample stored for 2 years in an ampoule filled with argon.

3. Discussion

The present method developed by the submitters[2] is the only practical process for the preparation of 1-cyano-6-methoxy-3,4-dihydronaphthalene. Birch and Robinson[3] have reported that 6-methoxy-1-tetralone did not react with hydrogen cyanide or sodium acetylide.

This process presents a procedure applicable to the preparation of cyanohydrins from relatively unreactive ketones and aldehydes. 1-Cyano-6-methoxy-3,4-dihydronaphthalene is useful as an intermediate in the synthesis of polycyclic compounds.

Cyanotrimethylsilane[4] is useful for the preparation of trimethylsilyl ethers of cyanohydrins, obtained from ketones, aldehydes, α,β-unsaturated ketones, and quinones.[5]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

Naphthalenecarbonitrille, 3,4-dihydro-6-methoxy-

6-metoxy-1-tetralone

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

hydrogen cyanide (74-90-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

potassium hydrogen sulfate (7646-93-7)

toluene (108-88-3)

dichloromethane (75-09-2)

sodium acetylide

argon (7440-37-1)

Cyanotrimethylsilane (7677-24-9)

6-methoxy-1-tetralone, 6-methoxytetralone (1078-19-9)

Diethylaluminum cyanide (5804-85-3)

1-cyano-1-hydroxy-6-methoxytetralin

1-Cyano-6-methoxy-3,4-dihydronaphthalene (6398-50-1)

p-toluenesulfonic acid monohydrate (6192-52-5)

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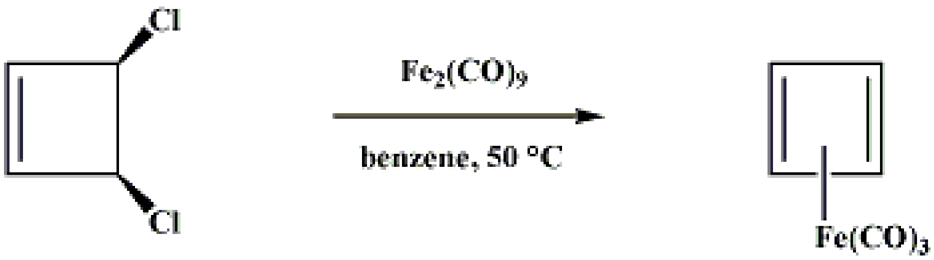
Organic Syntheses, CV 6, 310

CYCLOBUTADIENEIRON TRICARBONYL

[Iron, tricarbonyl (η^4-1,3-cyclobutadiene)-]



Submitted by R. Pettit[1] and J. Henery.
Checked by J. Napierski and R. Breslow.

1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

In a well-ventilated hood a 500-ml., three-necked flask is immersed in an oil bath and fitted with a condenser and a mechanical stirrer; a T-piece is inserted through a rubber stopper placed in the top of the condenser. One lead of the T-piece is connected to a nitrogen supply and the other to a gas bubbler. *cis*-3,4-Dichlorocyclobutene [*Org. Synth.*, **Coll. Vol. 6**, 422 (1988)], 20 g. (0.16 mole), and 125 ml. of anhydrous benzene are added to the flask, and the apparatus is flushed with nitrogen. Diiron nonacarbonyl, 25 g. (Note 1) is then added, the flow of N_2 is stopped, and the mixture is heated to 50–55°, with stirring. After about 15 minutes the initial rapid evolution of carbon monoxide becomes greatly diminished and an additional 8 g. of the nonacarbonyl is added; additional 8-g. quantities are added at intervals (approximately 15 minutes), governed by the rate of carbon monoxide evolution. The addition is continued until no more carbon monoxide is liberated (Note 2), and the reaction mixture is stirred at 50° for an additional hour. Approximately 140 g. of diiron nonacarbonyl is required for the complete conversion of the dichlorocyclobutene, the total reaction time being about 6 hours.

The contents of the flask are then filtered with suction through Filtercel and the residue, while kept in the Buchner funnel, is thoroughly washed with pentane until the washings are colorless (Note 3). The pentane and much of the benzene are evaporated from the combined filtrates with a water aspirator.

The residual liquid is transferred to a flask equipped with an efficient fractionating column and distilled under reduced pressure. Benzene is removed first, followed by

considerable quantities of iron pentacarbonyl (b.p. 20°, 30 mm.); when the diiron nonacarbonyl has been removed, the pressure is reduced further and cyclobutadieneiron tricarbonyl[2] is collected as a pale yellow oil, b.p. 47° (3 mm.), yielding 13.8–14.4 g. (45–46% based on dichlorocyclobutene), (Note 4).

2. Notes

1. Diiron nonacarbonyl is readily available through photolysis of iron pentacarbonyl.[3]
2. The conversion of the dichlorocyclobutene to cyclobutadieneiron tricarbonyl can be conveniently monitored by GC. On a 5 ft. × 1/8 in. column of 20% Carbowax on Chromosorb W, under conditions where the retention time of dichlorocyclobutene is 2.6 minutes, the retention time of cyclobutadieneiron tricarbonyl is 2.4 minutes.
3. The brown insoluble residue is frequently pyrophoric if it is allowed to dry; it should be immediately wetted with water before it is disposed of.
4. In some preparations the last portion of the distillate of the complex may be dark green in color. This color is due to trace amounts of $Fe_3(CO)_{12}$. If desired, this can be readily removed by chromatography over alumina. The submitters report a similar yield on three times the scale.

3. Discussion

Cyclobutadieneiron tricarbonyl may also be produced by the reaction of 3,4-dichlorocyclobutene with disodium irontetracarbonyl[4] and by irradiation of α-pyrone followed by treatment with diiron nonacarbonyl.[4] The method outlined here is the most convenient, especially when considerable quantities (10 g. or more) of cyclobutadieneiron tricarbonyl are required. The analogous reaction of derivatives of 3,4-dihalocyclobutenes with diiron nonacarbonyl affords the corresponding cyclobutadieneiron tricarbonyl complexes. Cyclobutadieneiron tricarbonyl can be oxidized to generate cyclobutadiene *in situ*.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 1002

6

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Cyclobutadieneiron tricarbonyl

(η^4-1,3-cyclobutadiene)-

Diiron nonacarbonyl

disodium irontetracarbonyl

Benzene (71-43-2)

carbon monoxide (630-08-0)

nitrogen (7727-37-9)

Pentane (109-66-0)

iron pentacarbonyl

α-Pyrone (504-31-4)

Iron, tricarbonyl

nonacarbonyl

dichlorocyclobutene

3,4-dichlorocyclobutene

cis-3,4-Dichlorocyclobutene (2957-95-1)

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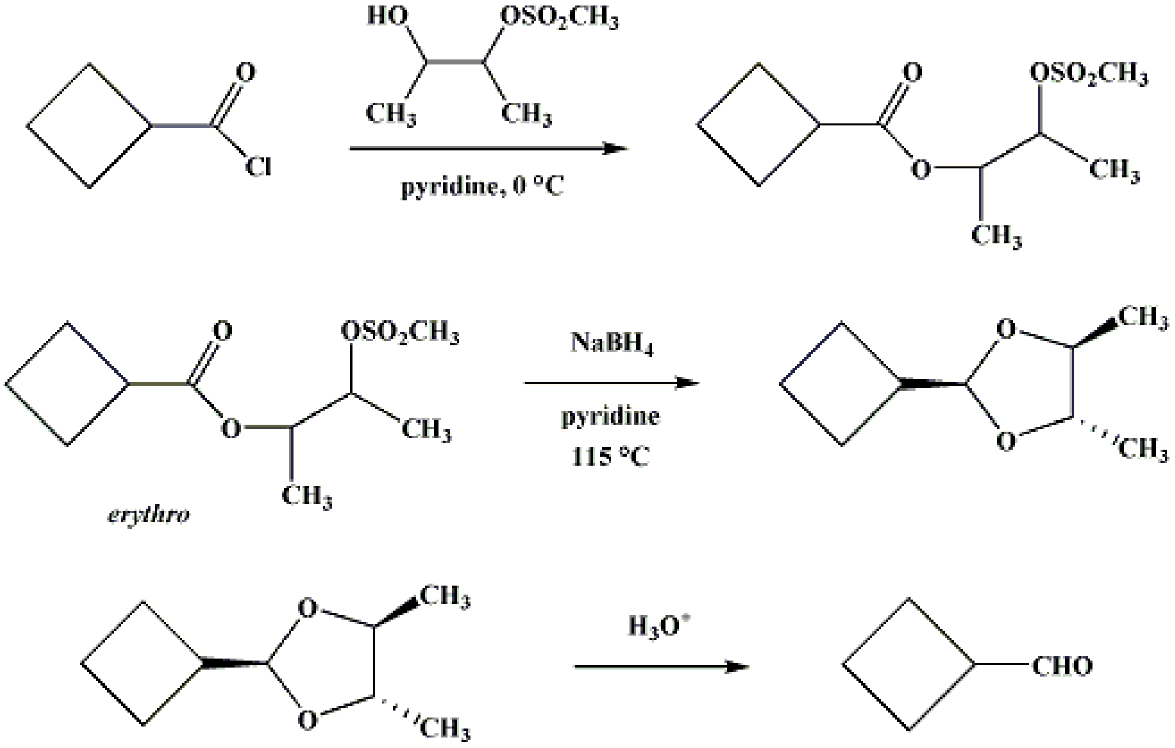
Organic Syntheses, CV 6, 312

ALDEHYDES FROM ACID CHLORIDES BY REDUCTION OF ESTER-MESYLATES WITH SODIUM BOROHYDRIDE: CYCLOBUTANECARBOXALDEHYDE



Submitted by M. Ross Johnson and Bruce Rickborn[1].
Checked by Saul C. Cherkofsky and Richard E. Benson.

1. Procedure

A. erythro-2,3-*Butanediol monomesylate*. A 2-l., round-bottomed flask is equipped with a 1-l. dropping funnel attached to a calcium chloride drying tube. A magnetic stirring bar is placed in the flask and a solution of 48.0 g. (0.500 mole) of methanesulfonic acid (Note 1) in 500 ml. of anhydrous diethyl ether is added. Stirring is begun, and the flask is cooled in an ice-water bath while a solution of 37 g. (0.52 mole) of *trans*-2-butene oxide (Note 2) and (Note 3) in 500 ml. of anhydrous ether is added over a period of 3–4 hours (Note 4). After 6 hours the cooling bath is removed and the mixture is stirred an additional 12 hours. The ether and any excess epoxide are removed with a rotary evaporator at 25° and water aspirator pressure, giving 83–84 g. (99–100%) of *erythro*-2,3-butanediol monomesylate as a clear, colorless, somewhat viscous liquid (Note 5).

B. erythro-3-*Methanesulfonyloxy*-2-*butyl cyclobutanecarboxylate*. A 500-ml., round-bottomed flask, cooled in an ice-water bath, equipped with a 50-ml. dropping funnel and a magnetic stirring bar is charged with 35.3 g. (0.210 mole) of *erytho*-2,3-butanediol monomesylate and 150 ml. of dry pyridine. Stirring is begun, and 23.7 g. (0.200 mole) of cyclobutanecarboxylic acid chloride (Note 6) is added over a period of 1 hour. The cooling bath is removed, and stirring is continued for 8 hours. The mixture is added to 500 ml. of ether, and the resulting solution washed with three 250-ml. portions of 3 *N* sulfuric acid. The pyridine-free solution is washed with 250 ml. of a saturated sodium hydrogen carbonate solution and then with 250 ml. of water. The ether solution is dried over 2 g. of anhydrous magnesium sulfate. The solvent is removed with a rotary evaporator at 25°, giving 45.1–48.0 g. (90–96%) of *erythro*-3-methanesulfonyloxy-2-butyl cyclobutanecarboxylate as a pale yellow, viscous liquid (Note 7).

C. *2-Cyclobutyl-cis-4-trans-5-dimethyl-1,3-dioxolane*. A 2-l., three-necked, round-bottomed flask is equipped with a mechanical stirrer, a 125-ml. dropping funnel, and a condenser attached to a nitrogen line with a bubbler device to permit maintenance of a positive pressure of nitrogen. Anhydrous pyridine (650 ml.) and 5 g. (0.1 mole) of sodium borohydride (Note 8) are added to the flask, stirring is begun, and the mixture is heated at reflux. A solution of 25 g. (0.10 mole) of *erythro*-3-methanesulfonyloxy-2-butyl cyclobutanecarboxylate in 50 ml. of anhydrous pyridine is added from the dropping funnel over a period of 30 minutes, and heating at reflux is continued for 8 hours. After cooling, 50 ml. of water is added (some heat is evolved), and the mixture is transferred to a 4-l. separatory funnel with 1 l. of pentane (Note 9), and 700 ml. of cold 3 *N* sulfuric acid saturated with sodium chloride. The aqueous layer is separated and washed with two 250-ml. portions of pentane. The pentane extractions are combined and washed with three 500-ml. portions of 3 *N* sulfuric acid saturated with sodium chloride and finally with 500 ml. of saturated sodium hydrogen carbonate. The pentane solution is dried over 1 g. of anhydrous potassium carbonate and evaporated on a steam bath. The product is distilled through a short Vigreux column, yielding 6.7–7.6 g. (43–49% (Note 10)) of 2-cyclobutyl-*cis*-4-*trans*-5-dimethyl-1,3-dioxolane, b.p. 79–83° (22 mm.) (Note 11).

D. *Cyclobutanecarboxaldehyde.* A 1-l., round-bottomed flask equipped with a magnetic stirring bar and a 60-cm. glass helix-packed column is charged with 600 ml. of 3 *N* sulfuric acid, 200 ml. of *N,N*-dimethylformamide (Note 12), and 20 g. (0.13 mole) of 2-cyclobutyl-*cis*-4-*trans*-5-dimethyl-1,3-dioxolane. The mixture is heated to gentle reflux, and cyclobutanecarboxaldehyde is collected as a steam distillate, b.p. 86°. After the distillation of the oil has ceased, the product is transferred to a separatory funnel, and the lower layer of water is discarded. The oil is dissolved in 25 ml. of ether and dried over anhydrous sodium sulfate. The product is distilled through a small Vigreux column. After removal of the ether, 6.2–6.7 g. (58–63%) of cyclobutanecarboxaldehyde is collected, b.p. 56–59° (120 mm.) (Note 13).

2. Notes

1. Methanesulfonic acid was obtained from Aldrich Chemical Company, Inc., and distilled prior to use. The fraction collected at 140° (0.2 mm.) was used.
2. *trans*-2-Butene oxide was prepared by appropriate modification of the procedure in *Org. Synth.*, **Coll. Vol. 4**, 860 (1963). A 2-l., four-necked, round-bottomed flask fitted with a mechanical stirrer, a 1-l. dropping funnel, an acetone–dry ice condenser, and a thermometer is charged with 1 l. of 1,1,2,2-tetrachloroethane. The condenser is packed with dry ice and acetone, and the flask is cooled in a methanol-ice bath to −15°. *trans*-2-Butene (153 g., 2.73 moles) (Phillips Petroleum Company, 99%) is distilled into the flask from a tared, chilled trap. Six hundred milliliters of 40% peracetic acid (FMC Corporation), to which has been added 30 g. sodium acetate to neutralize the sulfuric acid present, is added to the stirred solution from the dropping funnel over a period of 2 hours. The mixture is stirred at −15° for another hour, then allowed to warm to room temperature. The mixture is poured into 1 l. of ice-cold water. The organic layer is separated, washed first with 10% sodium carbonate solution, then with water, dried over magnesium sulfate, and filtered. Distillation of the filtrate through a 75-cm. spinning-band column gives 133 g. (68%) of *trans*-2-butene oxide as a colorless oil, b.p. 52.5–55°.
3. A slight excess of *trans*-2-butene oxide is used to assure complete utilization of methanesulfonic acid. The checkers' experiments indicated that a 15% excess of the epoxide substantially reduced the amount of unreacted methane–sulfonic acid present in the product and did not appear to interfere with the succeeding steps of this procedure.
4. This order of addition and dilution is required to avoid dimerization or polymerization of the epoxide.
5. No attempt was made to purify this compound further. It had a very characteristic ^{1}H NMR spectrum ($CDCl_3$, external tetramethylsilane reference): δ 1.22 (d, *J* = 7.5 Hz., 3H), 1.37 (d, *J* = 7.5 Hz., 3H), 3.1 (s, 3H), 3.4 (s, O*H*, position variable), 4.0 (d of q, *J* = 4.0, 7.5 Hz., 1H), and 4.78 (d of q, *J* = 4.0, 7.5 Hz., 1H). A sample stored for several weeks at room temperature showed no change in its spectrum.
6. Cyclobutanecarboxylic acid chloride was obtained from Aldrich Chemical Company, Inc., and

distilled prior to use. The acid chloride can be prepared by the reaction of thionyl chloride with the corresponding acid (available from Aldrich) by the general procedure in *Org. Synth.*, **Coll. Vol. 1**, 147 (1941). The preparation of cyclobutanecarboxylic acid has been described in *Org. Synth.*, **Coll. Vol. 3**, 213 (1955) and elsewhere.[2]

7. The ^{1}H NMR spectrum ($CDCl_3$, external tetramethylsilane reference): δ 1.27 (d, *J* = 6.5 Hz., 3H), 1.41 (d, *J* = 6.5 Hz., 3H), 2.18 (m, 6H), 3.10 (s, 3H), superimposed on 3.2 (m, 1H)k, and 5.0 (m, 2H). IR ($CDCl_3$): 1725 cm.$^{-1}$.

8. Commercial material from Matheson, Coleman and Bell and recrystallized reagent gave comparable results. The yield is decreased by use of less than 1 mole of sodium borohydride per mole of mesylate.

9. Either purified pentane or Spectranalyzed pentane available from Fisher Scientific Company was used.

10. The submitter reports yields of 10–11 g. (64–71%). The checker obtained the dioxolane in 57% yield on conducting the experiment on a sixfold scale.

11. The ^{1}H NMR spectrum (neat, external tetramethylsilane reference) δ 1.1 (two overlapping d, *J* = 6 Hz., 6H), 1.7–2.0 (m, 6H), 2.1–2.6 (m, 1H), 3.2–3.8 (m, 2H), and 4.94 (d, *J* = 5 Hz., 1H).

12. This proportion of water to *N*,*N*-dimethylformamide is needed to assure solubility (hence facile reaction) of the acetal on heating at reflux.

13. The ^{1}H NMR spectrum (neat, external tetramethylsilane reference): δ 1.4–2.4 (m, 6H), 2.6–3.2 (m, 1H), and 9.8 (d, *J* ≈ 1.5 Hz., 1H); IR (CCl_4); 1730 cm.$^{-1}$ (C=O).

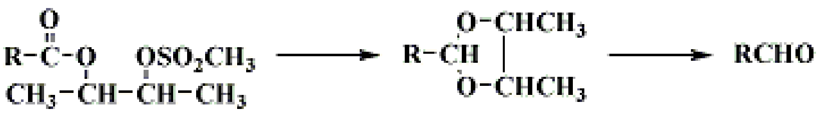
3. Discussion

Cyclobutanecarboxaldehyde has been prepared in very low yield by the Rosenmund reduction procedure.[3] A 46% yield of the 2,4-dinitrophenylhydrazone derivative has also been reported, with the aldehyde formed as an intermediate, in the reaction of the acid chloride and lithium tri-*t*-butoxyaluminum hydride at −78° in diglyme.[4]

Methods now available for the reduction of carboxylic acid derivatives to aldehydes require careful control of conditions to avoid overreduction or underreduction. The procedure described here is particularly convenient in that the acetal, not subject to further reduction, is formed directly in the reducing medium.

The scope of the reaction is indicated in Table I. An interesting aspect of the reaction is that the rate of the borohydride reduction step appears to be relatively insensitive to the substitutent R. It is suggested that the reaction occurs with formation of an intermediate acyloxonium ion, which is rapidly converted to acetal by reaction with the borohydride ion. Pyridine–borane has been shown to be the other product of this reaction; yield studies also indicate that only one hydride per borohydride ion is used efficiently in the formation of acetal.

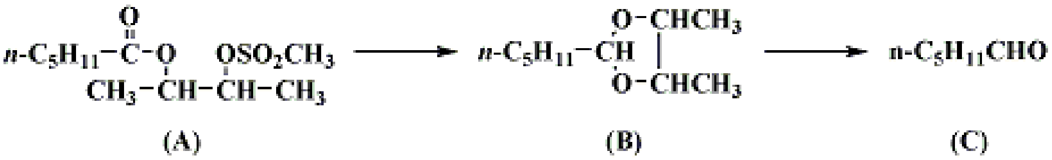
TABLE I
ALDEHYDES FROMESTER-MESYLATES



(A) (B) (C)

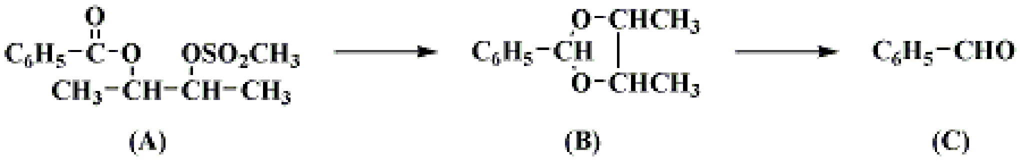
Ester-Mesylates (A), R =	Acetal (B) Yield, %[a]	Aldehyde (C) Yield, %[a]

n-C_5H_{11}-



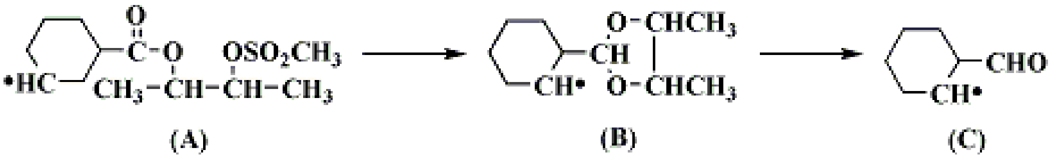
63 78

C_6H_5-



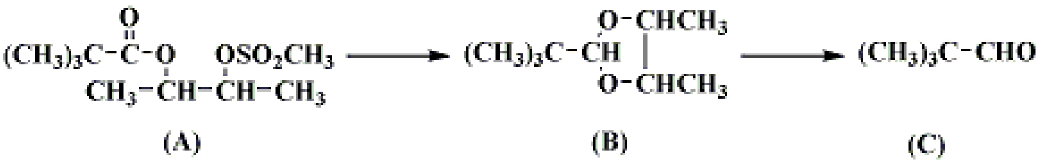
64 89

cyclo-C_6H_{11}-



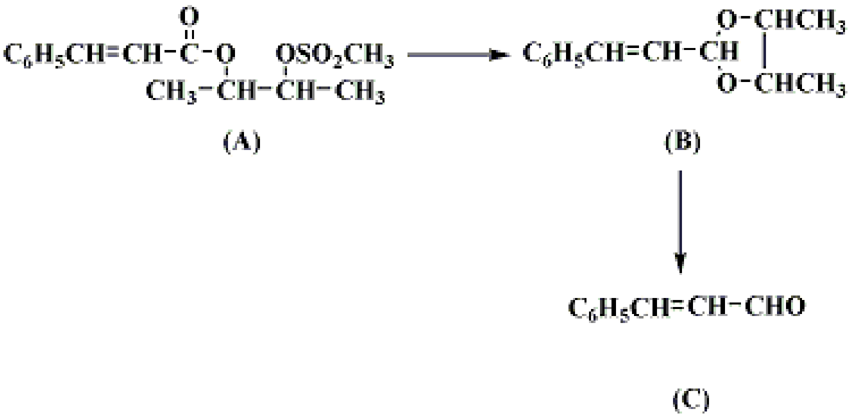
75 93

$(CH_3)_3C$-

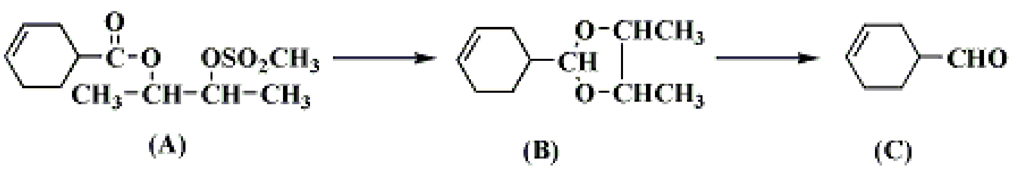


77 50[b]

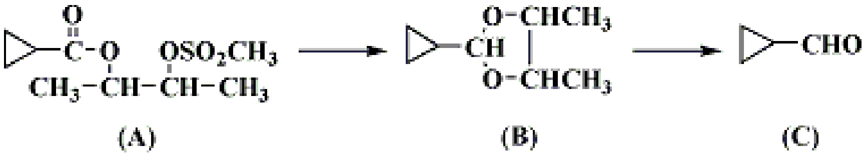
$C_6H_5CH=CH$-



62 87[c,d]



67 81[c]

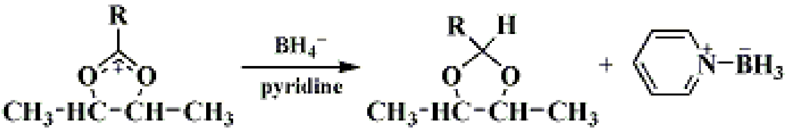
cyclo-C_3H_5- 	72	81

a Yield of distilled product; in several instances numerous runs were made, and the lowest yield is given.

b This acetal hydrolyzes quite slowly, and the relatively low yield of pivalaldehyde appears to be associated with this observation.

c Yields determined by GC analysis only.

d Fifteen percent of this product is the dihydro derivative, that is, the acetal of 3-phenylpropanal.



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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

erythro-3-Methanesulfonyloxy-2-butyl cyclobutanecarboxylate

erythro-2,3-Butanediol monomesylate

erytho-2,3-butanediol monomesylate

acetal of 3-phenylpropanal

ACETAL (105-57-7)

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

ether, diethyl ether (60-29-7)

sodium acetate (127-09-3)

thionyl chloride (7719-09-7)

sodium hydrogen carbonate (144-55-8)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

acetone (67-64-1)

pyridine (110-86-1)

Pentane (109-66-0)

magnesium sulfate (7487-88-9)

borane (7440-42-8)

N,N-dimethylformamide (68-12-2)

Cyclobutanecarboxylic acid (3721-95-7)

peracetic acid (79-21-0)

methanesulfonic acid, mesylate (75-75-2)

sodium borohydride (16940-66-2)

1,1,2,2-tetrachloroethane (79-34-5)

Cyclobutanecarboxaldehyde (2987-17-9)

cyclobutanecarboxylic acid chloride (5006-22-4)

dioxolane (646-06-0)

pivalaldehyde (630-19-3)

lithium tri-t-butoxyaluminum hydride

trans-2-Butene (624-64-6)

trans-2-butene oxide (21490-63-1)

2-Cyclobutyl-cis-4-trans-5-dimethyl-1,3-dioxolane (36416-29-2)

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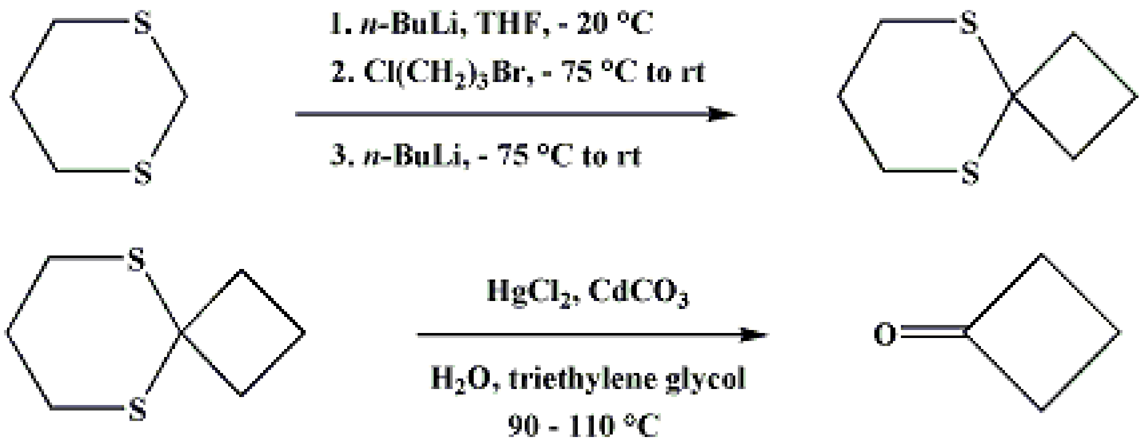
Organic Syntheses, CV 6, 316

CYCLIC KETONES FROM 1,3-DITHIANE: CYCLOBUTANONE



Submitted by D. Seebach[1] and A. K. Beck.
Checked by Jose F. Pazos and Richard E. Benson.

1. Procedure

A. 5,9-*Dithiaspiro*[3.5]*nonane*. A dry, 2-l., one-necked, round-bottomed flask containing a magnetic stirring bar (Note 1) is flushed with dry nitrogen (Note 2), and 1.25 l. of dry tetrahydrofuran (Note 3) and 50 g. (0.42 mole) of 1,3-dithiane (Note 4) are added. The flask is quickly equipped with a three-way stopcock bearing a standard tapered joint, a rubber septum, and a nitrogen inlet, as shown in f.htmigure 1 (Note 5). The solution is stirred with an efficient magnetic stirrer and cooled to an external temperature of –20° with a methanol–dry ice bath. A 3% excess (total of 0.43 mole) of 1.5–2.5 *M* *n*-butyllithium in *n*-hexane (Note 6) is added through the rubber septum with a syringe. The bath temperature is kept between −10° and –20° for 2 hours before the temperature of the bath is reduced to –75° (Note 7) and 65.5 g. (44.5 ml., 0.417 mole) of 1-bromo-3-chloropropane (Note 8) is added with a syringe over 10 minutes. The temperature of the bath is raised to –30° over a 2-hour period by gradually replacing the cold methanol with warm methanol. The bath is removed and stirring is continued until the reaction flask is at room temperature (Note 9). The flask is again cooled to –75° (Note 7) and 0.44 mole of *n*-butyllithium in *n*-hexane (Note 6) is added with a syringe over 10 minutes. After the addition is complete, the temperature of the reaction flask is allowed to rise to room temperature overnight (Note 10). The solvent is removed from the product with a rotary evaporator at 50° and aspirator pressure. Water (300 ml.) and diethyl ether (500 ml.) are added to the product in the flask, the ether layer is separated, and the aqueous layer is washed again with 500 ml. of ether. The organic layers are combined, washed with 200 ml. of water, and dried over 10 g. of anhydrous potassium carbonate. The ether is removed by distillation to yield about 75 g. of crude product. Distillation through a packed column gives 44–57 g. (65–84%)

of 5,9-dithiaspiro[3.5]nonane, b.p. 65–75° (1 mm.), n_{D}^{20} 1.5700. This product is of sufficient purity for use in Part B (Note 11).

Figure 1.

Figure 1.

B. *Cyclobutanone*. A 2-l., three-necked flask is fitted with an efficient mechanical stirrer and a water-cooled condenser assembled for downward distillation to which is attached a 250-ml. receiver with a side arm. Two cold traps are attached consecutively to the distillation apparatus as shown in f.htmigure 2 (Note 12). The receiver is immersed in an ice-water bath, and the traps are immersed in dry ice and acetone. To the flask is added 45 g. (0.28 mole) of 5,9-dithiaspiro[3.5]nonane, 900 ml. of triethylene glycol, and 150 ml. of water. Stirring is begun, and 163 g. (0.600 mole) of mercury(II) chloride (Note 13) and 51.5 g. (0.300 mole) of cadmium carbonate (Note 13) are added. A nitrogen-inlet tube reaching to the bottom of the flask is inserted into the third neck of the flask, and nitrogen is introduced at approximately 50 ml. per minute. The reaction flask is heated to 90° in an oil bath, and the temperature is slowly increased to 110° over a 2–3 hour period. Water and cyclobutanone are carried into the receivers. The water in the receiving flask is saturated with sodium chloride, and the resulting solution is transferred to a separatory funnel. The flask is rinsed with 25 ml. of dichloromethane, and this solution is used for an initial washing of the aqueous solution. The aqueous solution is shaken three additional times with 25-ml. portions of 12chloromethane. The dichloromethane solutions are combined and added to the traps to dissolve cyclobutanone. The resulting solution is transferred to a 250-ml. flask, the traps are rinsed with a small amount of dichloromethane, and the rinse is combined with the original solution. The organic solution is dried over 5 g. of anhydrous sodium sulfate, filtered, and the solvent is removed by distillation through a 20-cm., helix-packed, vacuum-insulated column. The product is transferred to a 25-ml. flask, 5 ml. of mesitylene is added, and the product is distilled through a spinning-band column. The fraction boiling at 95–100° is collected, yielding 12–15.8 g. (60–81%) (Note 14) of cyclobutanone.

Figure 2.

Figure 2.

2. Notes

1. Efficient stirring is required throughout the reaction.
2. If available, argon is preferable to nitrogen because of its higher density.
3. The checkers used reagent grade tetrahydrofuran (available from Fisher Scientific Company) from a freshly opened bottle. The submitters used tetrahydrofuran purified by distillation from lithium aluminum hydride. See

Org. Synth., **Coll. Vol. 5**, 976 (1973), for warning regarding purification of tetrahydrofuran.

4. 1,3-Dithiane was prepared as described in *Org. Synth.*, **Coll. Vol. 6**, 556 (1988), and sublimed prior to use.

5. During the entire reaction sequence a positive pressure of approximately 50 mm. of nitrogen is maintained against the atmosphere with a mercury bubbler.

6. The titer of the solution should be determined prior to use. The checkers used product available from Foote Mineral Company.

7. Only a slight excess of dry ice should be added.

8. Available from Eastman Organic Chemicals. The product was distilled prior to use, b.p. 140–142°.

9. Approximately 2 hours is required.

10. The submitters have found that the ring closure reaction is essentially complete by the time the temperature reaches −20°.

11. GC analysis using a column containing 20% silicone DC 200 on Gas Chrom Z at 160° showed the product to be 96% pure.

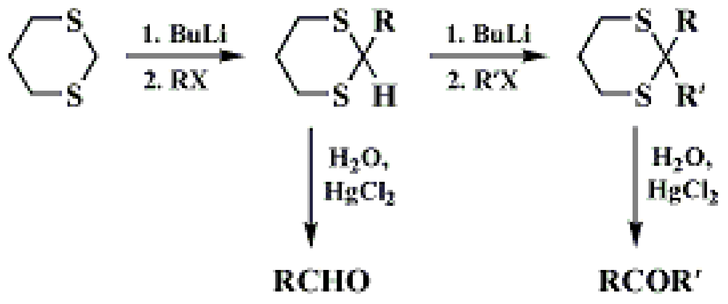
12. The traps are attached in a reverse manner. The diameter of the inner tubing is 1.5 cm.

13. Anhydrous practical grade reagents were used.

14. The IR spectrum (neat) shows strong absorption at 1775 cm.$^{-1}$. The purity of the product is greater than 95% as established by GC on a 4-ft. column containing 20% silicone DC 200 on Gas Chrom Z at 50°. The ^{1}H NMR spectrum (CCl_4) shows a pentet at δ 1.83 (J = 8 Hz.) and a triplet at 3.01 (J = 8 Hz.) in a ratio 1:2, respectively.

3. Discussion

The best large-scale preparation of cyclobutanone is the reaction of diazomethane with ketene.[2] It requires a ketene generator and necessitates handling large quantities of the potentially hazardous diazo compound. A more frequently used method for the preparation of cyclobutanone starts with pentaerythritol, the final step being the oxidative degradation of methylenecyclobutane,[4,3], which can also be prepared from other precursors.[5] A general survey of all methods used to obtain cyclobutanone has been published.[6,7]



The procedure described here is an example of the use of the dithiane method[8] for the preparation of ketones. The reactions appear to be general, and the yields are

satisfactory. The dithiane method can be successfully applied to the synthesis of rings containing up to seven carbon atoms with a slight modification[9,10] of the procedure above. The synthesis of larger rings may require high dilution methods.[9]

Aldehydes and open-chain ketones are also available from dithiane.[9] Carbonyl compounds with high optical activity[9] have been synthesized, including those that undergo facile racemization. An extensive review covering all applications of this reaction up to June 1969 has been authored by one of the submitters.[9] Methods and limitations for the preparation of silyl ketones[11] (R_3SiCOR) and germanyl ketones (R_3GeCOR) have been described.[12]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 320
- Org. Syn. Coll. Vol. 6, 324
- Org. Syn. Coll. Vol. 6, 542
- Org. Syn. Coll. Vol. 6, 869
- Org. Syn. Coll. Vol. 7, 114
- Org. Syn. Coll. Vol. 7, 153

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

potassium carbonate (584-08-7)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

acetone (67-64-1)

1-bromo-3-chloropropane (109-70-6)

mercury(II) chloride (7487-94-7)

Mesitylene (108-67-8)

dichloromethane (75-09-2)

Pentaerythritol (115-77-5)

Diazomethane (334-88-3)

butyllithium, n-butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

n-hexane (110-54-3)

triethylene glycol (112-27-6)

dithiane (505-20-4)

Cyclobutanone (1191-95-3)

argon (7440-37-1)

1,3-Dithiane (505-23-7)

methylenecyclobutane (1120-56-5)

5,9-dithiaspiro[3.5]nonane (15077-16-4)

cadmium carbonate (513-78-0)

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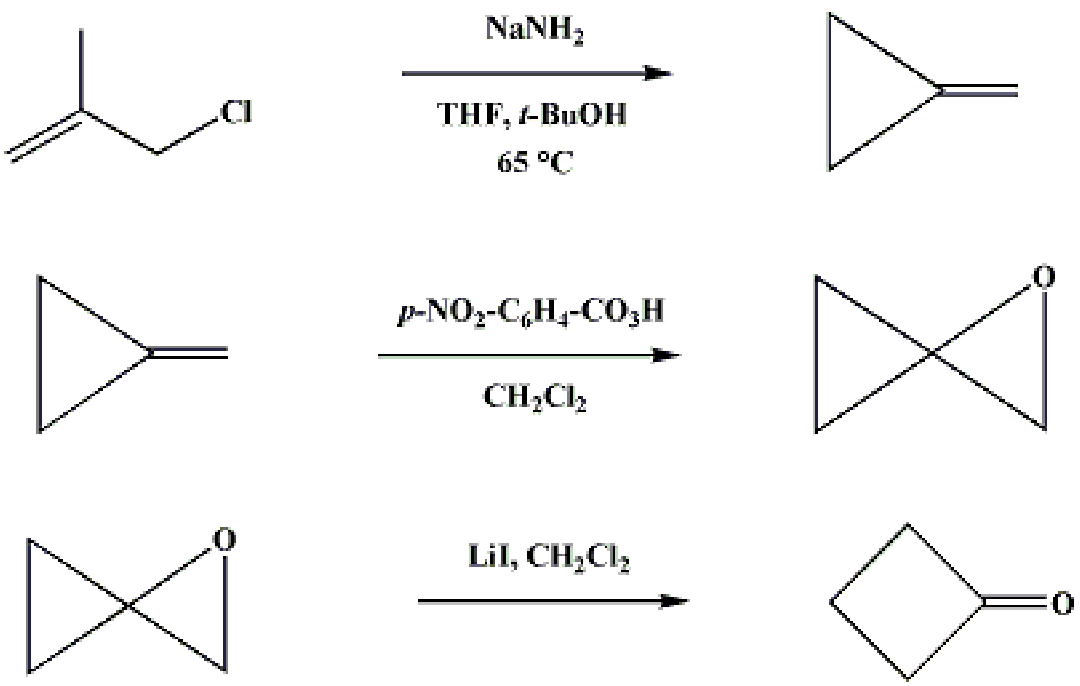
Organic Syntheses, CV 6, 320

CYCLOBUTANONE FROM METHYLENECYCLOPROPANE *via* OXASPIROPENTANE



Submitted by J. R. Salaun, J. Champion, and J. M. Conia[1].
Checked by Z. Stojanac and Z. Valenta.

1. Procedure

Caution! The preparation of methylenecyclopropane must be carried out in an efficient hood because ammonia is evolved. Oxaspiropentanes have been widely used as useful synthetic intermediates and appear to be quite stable; nevertheless, in view of the nature of the compounds, it is recommended that the preparation and handling of oxaspiropentane be carried out behind a safety screen.

A. *Methylenecyclopropane* (Note 1). A dry, 3-l., three-necked, round-bottomed flask with ground-glass fittings is equipped with a sealed stirrer (Note 2) driven by a heavy-duty motor, an efficient condenser fitted with a silica gel drying tube, and a 500-ml., pressure-equalizing dropping funnel connected to a nitrogen inlet. The flask is charged with 450 g. (11.5 moles) of sodium amide (Note 3) and 750 ml. of anhydrous tetrahydrofuran (Note 4), and the dropping funnel with a solution of 283.5 g. (3.831 moles) of anhydrous *tert*-butyl alcohol (Note 5) in 300 ml. of anhydrous tetrahydrofuran While the sodium amide suspension is stirred vigorously under a nitrogen atmosphere, the solution of *tert*-butyl alcohol is added dropwise at room temperature over 3 hours. The stirred mixture is heated to 45°, with an oil bath, for 2

hours, at which point it may be necessary to add additional tetrahydrofuran (Note 6). The outlet of the condenser is connected with an adapter to a 250-ml. gas washing bottle containing 100 ml. of 5 *N* sulfuric acid, to eliminate evolved ammonia (Note 7). A silica gel drying tube (15 cm. long) joins the gas washing bottle to a 300-ml. cold trap protected from the atmosphere with a calcium chloride drying tube and cooled in a methanol–dry-ice bath maintained at −80° (Note 8). A solution of 228 g. (2.52 moles) of 3-chloro-2-methyl-1-propene (Note 9) in 500 ml. of dry tetrahydrofuran is added to the stirred basic mixture, which is then heated to 65° over a period of approximately 8 hours; a light nitrogen stream is used to carry the methylenecyclopropane into the cold trap. After the addition is complete, the reaction mixture is stirred and heated to 65° for 3 more hours (Note 10). The trap flask contains 58 g. (43%) of methylenecyclopropane (Note 11).

B. *Oxaspiropentane*. A 3-l., three-necked, round-bottomed flask equipped with a sealed stirrer, a thermometer, and an efficient condenser cooled by methanol–dry ice (Note 12) is charged with 450 ml. of dichloromethane and 200 g. (1.09 moles) of 4-nitroperbenzoic acid (Note 13). The mixture is stirred and cooled to −50° by immersion of the flask in a methanol–dry-ice bath before 58 g. (1.1 moles) of methylenecyclopropane is distilled directly into the flask with a gas-inlet tube reaching to the bottom of the flask. The cooling bath is removed so that the temperature gradually rises; at about 0° the exothermic reaction starts. The temperature is maintained below 20° by occasional immersion of the flask in an ice–water bath; the methylenecyclopropane is allowed to reflux slowly (Note 14). After refluxing stops, the mixture is stirred overnight at room temperature. The 4-nitrobenzoic acid is removed by filtration and washed twice with 100-ml. portions of dichloromethane. The combined organic layers, which still contain about 10% of the total amount of 4-nitrobenzoic acid, are distilled at room temperature under reduced pressure (15 mm.) to eliminate the acid completely (Note 15). The distillate is concentrated to *ca.* 200 ml. of dichloromethane by distillation through a 15-cm., helix-packed, vacuum-insulated column, at a maximum oil bath temperature of 60° (Note 16).

C. *Cyclobutanone* (Note 16). The resulting solution of oxaspiropentane (35%) in 200 ml. dichloromethane is added dropwise at room temperature to a magnetically stirred solution containing 5–10 mg. of lithium iodide in 50 ml. of dichloromethane (Note 17), (Note 18), at such a rate as to maintain gentle reflux of the solvent. After the addition, when the reaction mixture returns to room temperature, the transformation into cyclobutanone is complete. The dichloromethane solution is washed with 20 ml. of saturated aqueous sodium thiosulfate and 20 ml. of water, dried over magnesium sulfate, and concentrated by distillation of the solvent through a 15-cm., helix-packed, vacuum-insulated column. The residual liquid consists of cyclobutanone (95%) and 3-buten-2-one and 2-methylpropenal (5%).[2] A final distillation at 760 mm. through a 50-cm., stainless-steel spinning band column yields 41 g. (64% from methylenecyclopropane) of pure cyclobutanone, b.p. 100–101° (Note 19), (Note 20).

2. Notes

1. The procedure described for the synthesis of methylenecyclopropane is patterned after the method reported by Caubere and Coudert.[3] Methylenecyclopropane is also available from the stepwise method described by Köster and co-workers.[4]
2. The checkers used a stirrer for vacuum work (Teflon bearing, Fisher Scientific Company). The submitters used a mercury-sealed stirrer.
3. The submitters used sodium amide (obtained from Fluka A G as small lumps under kerosene) which was washed with anhydrous tetrahydrofuran and ground with a mill. The checkers used freshly opened and recently purchased cans of sodium amide powder (Fisher Scientific Company); older reagent gave unsatisfactory results.
4. Tetrahydrofuran is purified by distillation from lithium aluminium hydride after 48 hours of refluxing over potassium hydroxide (see *Org. Synth.*, **Coll. Vol. 5**, 976 (1973).
5. *tert*-Butyl alcohol was refluxed overnight over calcium hydride and distilled.
6. The checkers obtained a heavy slurry at this stage which became heavier during addition of 3-chloro-2-methyl-1-propene. They found it necessary to dilute with more tetrahydrofuran (about 450 ml. for the scale given in the procedure) before the allyl chloride was added.
7. It is advisable to insert a safety bottle to avoid any run-back of sulfuric acid into the reaction flask. The gas washing bottle must be cooled by immersion in a large water bath (15°); the sulfuric acid solution is replaced by a fresh 5 *N* solution when neutralized by evolved ammonia (checked by phenolphthalein).
8. Methylenecyclopropane, b.p. 11° (760 mm.), is volatile at room temperature; all adapter fittings must be carefully checked. The checkers recommend the use of two cold traps in series.
9. 3-Chloro-2-methyl-1-propene (methallyl chloride) is available from Fluka A G and Eastman Organic Chemicals. The chloride, b.p. 72° (760 mm.), was distilled before use.
10. In the checkers' hands, at least 24 hours was needed to produce the bulk of methylenecyclopropane; small amounts of the product condenser during an additional 24-hour period.
11. The yield is determined by weighing the cold trap before and after distillation of methylenecyclopropane. Any small amounts of tetrahydrofuran carried into the methylenecyclopropane trap are eliminated in a subsequent distillation. By ^{1}H NMR analysis the checkers found that no tetrahydrofuran reached the cold traps; the spectrum (CD_2Cl_2) shows a triplet at δ 1.00 and a quintuplet at δ 5.35 in the ratio 4:2.
12. *Caution! The yield isolated from this reaction depends on the efficiency of this condenser; the epoxidation is exothermic and methylenecyclopropane is volatile.*
13. The 4-nitroperoxybenzoic acid (technical, 77–85%) may be obtained from

the Aldrich Chemical Co., Inc., or Fluka A. G. (or from its U.S. representative, Tridom Chemical Inc.), or may be prepared from 4-nitrobenzoic acid.[5] The oxidation of methylenecyclopropane to oxaspiropentane has been reported to proceed in the same manner, in 48% yield, with the less expensive reagent *m*-chloroperbenzoic acid (MCPBA).[2]

14. Cooling below 0° stops the reaction.

15. A short-path distillation apparatus is used, the distillate (oxaspiropentane plus dichloromethane) being trapped in a receiver placed in a methanol–dry-ice bath cooled to –80°. The checkers found it useful to drive out last traces of product by adding several milliliters of dichloromethane to the residual thick paste and distilling. The ^1H NMR spectrum (CD_2Cl_2) shows an octet at δ 0.85 and a singlet at δ 3.00 in the ratio 4:2.

16. If the oil bath temperature reaches 80°, the residue consists of cyclobutanone (75%) and oxaspiropentane (25%). Distillation of this residue at 97–103° (760 mm.) yields cyclobutanone and oxaspiropentane; however, as reported[2] oxaspiropentane can be distilled at low temperature (36°) in vacuum (20 mm) without rearrangement.

17. *Caution! Addition of lithium iodide (catalytic amount) to a dichloromethane solution containing more than 30% oxaspiropentane leads to a very vigorous reaction.*

18. Dichloromethane from the previous distillation is used.

19. The purity of cyclobutanone was checked by GC on a 3.6-m. column containing 20% silicone SE-30 on chromosorb W at 65°. The IR spectrum (neat) shows carbonyl absorption at 1779 cm.$^{-1}$; the ^1H NMR spectrum (CCl_4) shows a multiplet at δ 2.00 and a triplet at δ 3.05 in the ratio 1:2.

20. The checkers obtained yields of 61–64% on smaller-scale runs (10 g. of cyclobutanone).

3. Discussion

This method for the preparation of cyclobutanone *via* oxaspiropentane is an adaptation of that reported by Salaün and Conia.[6] Although cyclobutanone has been known now for over 75 years,[7] renewed interest in the potential of this small ring compound has led to several recently reported syntheses. The earlier syntheses of this compound consist of the reaction of the hazardous diazomethane with ketene[8] and the oxidative degradation[9] or the ozonization of methylenecyclobutane.[10] Recent syntheses involve the dithiane method of Corey and Seebach,[11,12] the solvolytic cyclization of 3-butyn-1-yl trifluoromethanesulfonate,[13] the ring enlargement of protected cyclopropanone cyanohydrin[14] and of 1-(phenylthio)cyclopropanemethanol,[15] and finally, the cyclodialkylation of tosylmethyl isocyanide.[16] These methods are most or less laborious, time-consuming, and based on expensive starting materials. Most of them

present the disadvantage of producing an aqueous solution of the highly water-miscible and volatile cyclobutanone (b.p. 100°C).

The availability of methylenecyclopropane, its facile oxidation to oxaspiropentane, and the lithium iodide-induced ring enlargement to cyclobutanone described here remains the best laboratory scale preparation of cyclobutanone. Furthermore, this rearrangement of oxaspiropentanes appears to be general for the preparation of substituted cyclobutanones.[2,17]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 114

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

m-chloroperbenzoic acid (MCPBA)

Oxaspiropentanes

4-nitroperbenzoic acid

sulfuric acid (7664-93-9)

ammonia (7664-41-7)

sodium thiosulfate (7772-98-7)

nitrogen (7727-37-9)

allyl chloride (107-05-1)

dichloromethane (75-09-2)

phenolphthalein (77-09-8)

magnesium sulfate (7487-88-9)

Diazomethane (334-88-3)

sodium amide (7782-92-5)

Tetrahydrofuran (109-99-9)

lithium aluminium hydride (16853-85-3)

3-buten-2-one (78-94-4)

2-methylpropenal (78-85-3)

tert-butyl alcohol (75-65-0)

calcium hydride (7789-78-8)

methallyl chloride, 3-chloro-2-methyl-1-propene (563-47-3)

lithium iodide (10377-51-2)

Cyclobutanone (1191-95-3)

methylenecyclobutane (1120-56-5)

Methylenecyclopropane (6142-73-0)

Oxaspiropentane (157-41-5)

4-nitrobenzoic acid (62-23-7)

4-nitroperoxybenzoic acid (943-39-5)

3-Butyn-1-yl trifluoromethanesulfonate (32264-79-2)

cyclopropanone cyanohydrin

1-(phenylthio)cyclopropanemethanol

tosylmethyl isocyanide (36635-61-7)

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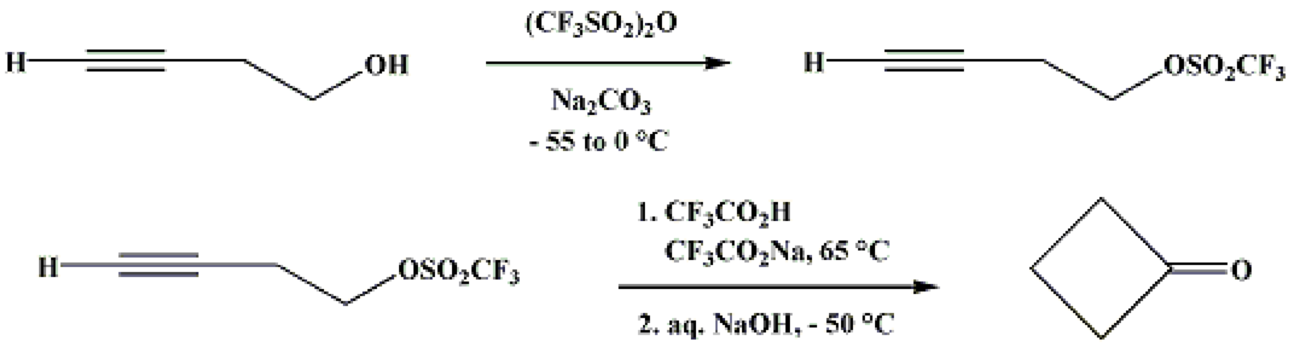
Organic Syntheses, CV 6, 324

CYCLOBUTANONE *via* SOLVOLYTIC CYCLIZATION



Submitted by M. Hanack[1], T. Dehesch, K. Hummel, and A. Nierth.
Checked by H. Ona, B. A. Boire, and S. Masamune.

1. Procedure

A. *3-Butyn-1-yl trifluoromethanesulfonate*. A 500-ml., three-necked flask is fitted with a mechanical stirrer, a pressure-equalizing dropping funnel, and a stopper. The system is flushed with nitrogen through a gas-inlet tube attached to the top of the funnel. To 150 ml. of dry dichloromethane (Note 1) in the flask is added 75 g. (0.27 mole) of trifluoromethanesulfonic anhydride (Note 2), and the solution is cooled to –40°. After addition of 14.5 g. (0.175 mole) of finely powdered anhydrous sodium carbonate (Note 3), 15g. (0.21 mole) of 3-butyn-1-ol (Note 4) is added dropwise over a 20-minute period to the well-stirred reaction mixture maintained at –40° to –55°. Stirring is continued at –30° for 2 hours, at 0° for another hour, and finally the reaction is quenched by dropwise addition of 50 ml. of water. The organic layer is separated, dried over anhydrous sodium sulfate, filtered and concentrated with a rotary evaporator, the temperature of the water bath not exceeding 25° The resulting residue is placed in a flask directly connected with a liquid nitrogen trap and distilled at 1 mm. The fractions boiling in the range from 40° to 50° are sufficiently pure for use in the next step. The yield of the sulfonate is 38.94 g. (90%) (Note 5) and (Note 6).

B. *Cyclobutanone*. A 500-ml., thick-walled ampoule is charged with 210 g. (137 ml.) of trifluoroacetic acid, 11.5 g. (0.0846 mole) of sodium trifluoroacetate (Note 7), and 17 g. (0.084 mole) of 3-butyn-1-yl trifluoromethanesulfonate, in this order. A magnetic stirring bar is added, and the ampoule is sealed. The stirred reaction mixture is immersed in a constant temperature bath kept at 65° (±2°) for 1 week. The ampoule is cooled slowly to –50° with a methanol–dry-ice bath (Note 8) and opened. With the aid of 200 ml. of diethyl ether the reaction mixture is transferred to a 1-l. Erlenmeyer flask to which 74 g. (1.83 mole) of sodium hydroxide in 150 ml. of water is added carefully. During the addition the flask is immersed in the bath, maintained at approximately –50° (Note 8). After the ethereal layer is separated, the aqueous layer is saturated with sodium chloride and extracted twice with ether. The original organic layer and ethereal extracts are combined, dried over anhydrous sodium sulfate, and directly distilled into a liquid nitrogen trap. The total condensate in the trap is placed in a distillation flask attached to a 40-cm. Vigreux column and a condenser cooled to –40° with a circulating cold bath (Note 9). After the ether is distilled, all volatile materials are collected by raising the bath to 130°, yielding 1.84–2.05 g. (31–36%) of cyclobutanone. The purity of the product is greater than 95% by ^{1}H NMR, the only impurity being diethyl ether (Note 10), (Note 11).

2. Notes

1. The submitters treated dichloromethane first with sulfuric acid, then with sodium hydroxide, and distilled it before use. The checkers used reagent grade solvent, supplied by Fisher Scientific Company, stored overnight over 4A Molecular Sieves.
2. The submitters prepared the anhydride, following basically the procedure described by Burdon, Farazmand, Stacey, and Tatlow.[2] Trifluoromethanesulfonic acid (32.1 g., 0.214 mole) (supplied by Minnesota Mining and Manufacturing Company) maintained at 0°, is treated with 25 g. of phosphorus pentoxide in three portions. The resulting anhydride is distilled by gradually heating the reaction mixture to a bath temperature of 110° over a 1-hour period. The fractions boiling at 80–100° (760 mm.) are collected and redistilled from approximately 8 g. of phosphorus pentoxide until the distillate no longer fumes on exposure to air. Normally three distillations are necessary. The presence of the trifluoromethanesulfonic acid can be detected by dipping a glass rod into the distillate and waving the wet rod in the air. The anhydride, in contrast, does not fume. The final yield of the product is 25 g. (83%), b.p. 84°. The checkers purchased the anhydride from Pierce Chemical Company and used it without further purification.
3. Anhydrous sodium carbonate was ground into fine powder and dried in vacuum at 200° for 4 hours.
4. In one experiment the checkers used 3-butyn-1-ol available from Aldrich Chemical Company, Inc., and found that its purity was satisfactory. In other experiments, both the submitters and the checkers prepared the hydroxy compound from sodium acetylide and ethylene oxide in liquid ammonia according to the procedure described by Schulte and Reiss[3] and further attempted to maximize the yield by varying the ratio of sodium: ethylene oxide: liquid ammonia used in the reaction. While the submitters obtained 3-butyn-1-ol in a yield of 60%, the checkers failed to obtain consistent results in repeated experiments and consequently could not define the optimum conditions for the reaction. Thus, the yield of 3-butyn-1-ol varied from 15 to 45% and 15 to 31% on the basis of sodium and ethylene oxide, respectively. Unknown and apparently subtle experimental factors affect the yield significantly.
5. When 3-butyn-1-ol was added to a solution of the anhydride, cooled to 0°, and the mixture was allowed to react at room temperature for 3 hours, the yield of the sulfonate dropped to 70–75%.
6. ^{1}H NMR of 3-butyn-1-ol trifluoromethanesulfonate (CCl_4) δ, (multiplicity, coupling constant *J* in Hz., number of protons): 2.05 (t, $J_{2,4}$ = 2.6, 1H), 2.76 (d of t, $J_{1,2}$ = 6.7, $J_{2,4}$ = 2.6, 2H), 4.57 (t, $J_{1,2}$ = 6.7, 2H).
7. The salt is available from Aldrich Chemical Company Inc. However, the checkers readily prepared it in the following way. To a stirred solution of 8.8 g. (0.22 mole) of sodium hydroxide in 400 ml. of 98% ethanol was added dropwise 25 g. (0.22 mole) of trifluoroacetic acid. After the addition was completed, the ethanol was removed under reduced pressure, and the residue was suspended in approximately 100 ml. of ether, filtered, and washed several times with ether. The yield was 25 g. (83.8%), and the salt was dried to a constant weight in a vacuum desiccator containing calcium sulfate (2 days).
8. Due to the high volatility of cyclobutanone, a substantial amount of the product is lost unless the mixture is sufficiently cooled during the process of neutralization.
9. The cooling to –40° was necessary to prevent the loss of highly volatile cyclobutanone.
10. The checkers redistilled this product through a 3-cm. column and determined its b.p. to be 96.5–97.5° (710 mm.); IR ($CHCl_3$), $cm.^{-1}$: 1780; ^{1}H NMR (CCl_4), δ (multiplicity, number of protons): 3.05 (m, 4H), 1.96 (m, 2H).

11. Subsequent to the publication of this procedure in the annual volume, the submitter has suggested the following changes, which have not been checked: After neutralization of the cyclobutanone with 1.83 moles of sodium hydroxide, the aqueous layer is made neutral or weakly alkaline with additional sodium hydroxide solution. Often the neutralization point can be observed as a weak color change (to a lighter color) of the dark brown reaction mixture. After separation of the ethereal layer and saturation of the aqueous layer with sodium chloride, the aqueous layer is extracted repeatedly (more than twice) with ether. The submitters obtained cyclobutanone in 66% yield.

3. Discussion

Cyclobutanone has been prepared by (1) reaction of diazomethane with ketene,[4] (2) treatment of methylenecyclobutane with performic acid, followed by cleavage of the resulting glycol with lead tetraacetate,[5] (3) ozonolysis of methylenecyclobutane,[6] (4) epoxidation of methylenecyclopropane followed by acid-catalyzed ring expansion,[7] (5) oxidative cleavage of cyclobutane trimethylene thioketal, which is prepared from 2-(ω-chloropropyl)-1,3-dithiane,[8] and (6) by hydrolytic conversion of 1-tosylcyclobutyl isocyanide, which is obtained by a one-step cyclodialkylation of tosylmethyl isocyanide with 1,3-dibromopropane.[9]

The present procedure[10] represents another synthesis of cyclobutanone through the unique acetylenic bond participation in solvolysis. Cyclobutane derivatives prepared in this way include 2-methyl-, 2-ethyl-, 2-isopropyl-, and 2-trifluoromethylcyclobutanone from the corresponding acetylenic compounds.[11] Condensed cyclobutanones are also easily accessible in good preparative yields by homopropargylic rearrangement: 7-methylbicyclo[3.2.0]heptan-6-one and 9-methylbicyclo[5.2.0]nonan-8-one are prepared by solvolyzing the corresponding *trans*-2-(1-propynyl)cycloalkyl-4-dimethylaminobenzenesulfonates in 67% sulfuric acid.[12]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 320
- Org. Syn. Coll. Vol. 6, 737
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

performic acid

cyclobutane trimethylene thioketal

2-methyl-, 2-ethyl-, 2-isopropyl-, and 2-trifluoromethylcyclobutanone

ethanol (64-17-5)

sulfuric acid (7664-93-9)

ammonia (7664-41-7)

ether, diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

1,3-dibromopropane (109-64-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

sodium (13966-32-0)

Ethylene oxide (75-21-8)

Ketene (463-51-4)

dichloromethane (75-09-2)

Diazomethane (334-88-3)

sodium acetylide

trifluoroacetic acid (76-05-1)

Cyclobutanone (1191-95-3)

3-butyn-1-ol (927-74-2)

trifluoromethanesulfonic acid (1493-13-6)

methylenecyclobutane (1120-56-5)

Methylenecyclopropane (6142-73-0)

3-Butyn-1-yl trifluoromethanesulfonate (32264-79-2)

tosylmethyl isocyanide (36635-61-7)

Trifluoromethanesulfonic anhydride (358-23-6)

sodium trifluoroacetate (2923-18-4)

2-(ω-chloropropyl)-1,3-dithiane

1-tosylcyclobutyl isocyanide

7-methylbicyclo[3.2.0]heptan-6-one

9-methylbicyclo[5.2.0]nonan-8-one

phosphorus pentoxide (1314-56-3)

lead tetraacetate

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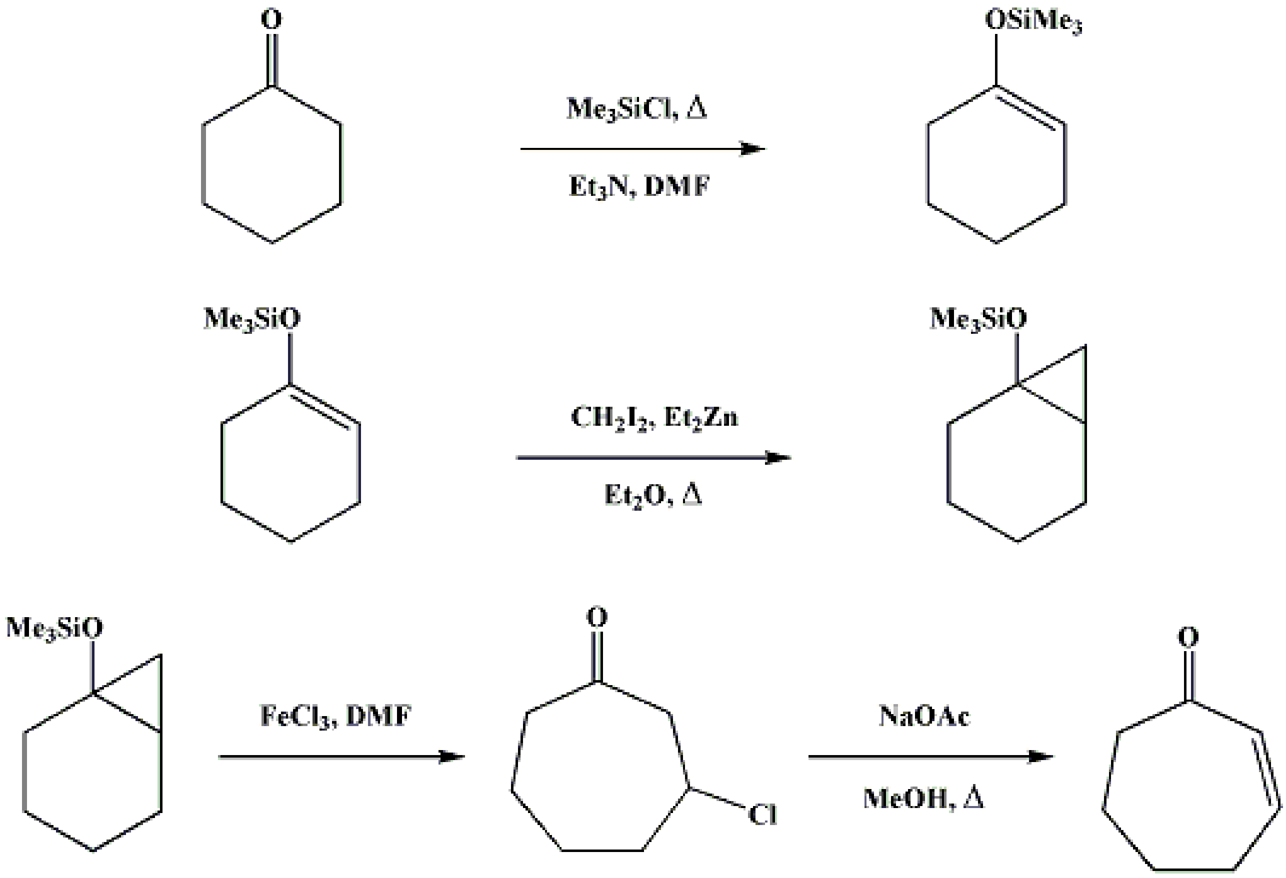
ONE-CARBON RING EXPANSION OF CYCLOALKANONES TO CONJUGATED CYCLOALKENONES: 2-CYCLOHEPTEN-1-ONE



Submitted by Yoshihiko Ito, Shotaro Fujii, Masashi Nakatuska, Fumio Kawamoto, and Takeo Saegusa[1].
Checked by Peter Senter, William F. Burgoyne, and Robert M. Coates.

1. Procedure

Caution! Diethylzinc, which is used in Part B of this procedure, is highly pyrophoric. Accordingly, this reagent must be kept under a nitrogen atmosphere; exposure to air must be avoided during transfers.

A. *1-Trimethylsilyloxycyclohexene*. A 500-ml., three-necked, round-bottomed flask fitted with a mechanical stirrer, a reflux condenser protected with a calcium chloride tube, and a rubber septum is charged with 100 ml. of *N,N*-dimethylformamide (Note 1) and 60.6 g. (0.600 mole) of triethylamine (Note 2). The solution is stirred while 32.6 g. (0.300 mole) of chlorotrimethylsilane (Note 3) and 24.5 g. (0.250 mole) of cyclohexanone are injected in succession through the septum into the flask. The resulting mixture is stirred and heated under reflux for 6 hours, cooled to room temperature, and diluted with 300 ml. of pentane. The triethylamine hydrochloride that precipitates is removed by filtering through a coarse, sintered-glass Büchner funnel, and the filter cake is washed with three 100-ml. portions of pentane. The filtrates are combined and washed with three 300-ml. portions of ice-cold sodium hydrogen carbonate solution. The organic layer is washed

rapidly with 100 ml. of ice-cold 3% hydrochloric acid and 100 ml. of ice-cold sodium hydrogen carbonate in succession. The pentane solution is washed with 50 ml. of sodium chloride solution, dried over anhydrous sodium sulfate, and evaporated. The residual liquid is distilled at reduced pressure through a 10-cm. Vigreux column, affording, after separation of a small forerun, 33–35.5 g. (78–84%) of 1-trimethylsilyloxycyclohexene, b.p. 74–75° (20 mm.) ((Note 4)).

B. *1-Trimethylsilyloxybicyclo*[4.1.0]*heptane*. A 250 ml., three-necked, round-bottomed flask is equipped with a magnetic stirring bar, a pressure-equalizing dropping funnel, a reflux condenser bearing a nitrogen inlet at its top, and a rubber septum. The apparatus is purged with nitrogen, flamed dry, and allowed to cool (Note 5). The flask is charged with 130 ml. of diethyl ether (Note 6), 17.0 g. (0.100 mole) of 1-trimethylsilyloxycyclohexene, and 18.5 g. (0.146 mole) of diethylzinc (Note 7), each being added through the septum with a syringe. The solution is stirred and maintained at room temperature with a water bath while 40.2 g. (0.150 mole) of diiodomethane (Note 8) is added slowly from the dropping funnel over a 1-hour period (Note 9). The reaction mixture is stirred and heated under reflux for 8 hours (Note 10). After the reaction is complete (Note 11), the contents of the flask are stirred and cooled in an ice-water bath as 5.4 ml. of concentrated aqueous ammonium chloride is added over *ca.* 30 minutes. A large amount of gas is evolved, and a white solid is formed during the hydrolysis. The salts are separated by filtering through a sintered-glass Büchner funnel and washed with 100 ml. of a 1:1 (v/v) ether–pentane solution. The combined filtrates are washed with four 50-ml. portions of ice-cold saturated aqueous ammonium chloride and two 100-ml. portions of ice-cold aqueous sodium chloride. The solution is filtered through a pad of anhydrous sodium sulfate and evaporated. The residual liquid is distilled through a 17.5-cm. Vigreux column under reduced pressure, affording a forerun of 2.1–3.5 g., b.p. 65–80° (12 mm.), and 14.2–15.2 g. (77–83%) of 1-trimethylsilyloxybicyclo[4.1.0]heptane, b.p. 80–82° (12 mm.) (Note 12).

C. *2-Cyclohepten-1-one*. A 250-ml., three-necked, round-bottomed flask equipped with a mechanical stirrer, a pressure-equalizing dropping funnel bearing a nitrogen inlet at its top, and a thermometer is charged with 17.9 g. (0.110 mole) of anhydrous iron(III) chloride (Note 13). The flask is immersed in an ice-water bath, stirring is begun, and 70 ml. of *N,N*-dimethylformamide (Note 1) is added slowly (Note 14). When all the iron(III) chloride has dissolved, a solution of 9.2 g. (0.050 mole) of 1-trimethylsilyloxybicyclo[4.1.0]heptane in 20 ml. of *N,N*-dimethylformamide is added dropwise through the dropping funnel over 1 hour while the internal temperature is maintained at 0–5°. After the addition is complete, the brown solution is stirred at room temperature for 2 more hours, then poured into *ca.* 200 ml. of ice-cold 1 *N* hydrochloric acid. The aqueous solution is extracted with three 50-ml. portions of chloroform. The combined chloroform extracts are washed successively with 50-ml. portions 1 *N* hydrochloric acid, saturated sodium hydrogen carbonate, and sodium chloride solution. The solution is dried by filtration through a pad of anhydrous sodium sulfate and evaporated. The remaining liquid (Note 15) is dissolved in 50 ml. of methanol saturated with sodium acetate and heated at reflux for 3 hours. The volume is reduced to *ca.* 25 ml. by evaporation under reduced pressure, 50 ml. of water is added, and the mixture is extracted with three 30-ml. portions of ether. The combined extracts are dried over anhydrous sodium sulfate, the ether is evaporated, and the residual liquid is distilled under reduced pressure through a 17.5-cm. Vigreux column, yielding after separation of a 0.4–1.0 g. forerun, 4.3–4.5 g. (78–82%) of 2-cyclohepten-1-one as a colorless liquid, b.p. 73–76° (18 mm.) (Note 16).

2. Notes

1. *N,N*-Dimethylformamide was purified by distillation from calcium hydride under a

nitrogen atmosphere and stored over Linde type 4A molecular sieves.

2. Triethylamine was distilled from lithium aluminum hydride.

3. Chlorotrimethylsilane is available from Aldrich Chemical Company, Inc. The reagent was distilled before use.

4. The product has the following spectral properties: IR (neat) cm.$^{-1}$: 1675 (C=C); ^{1}H NMR, δ (multiplicity, number of protons, assignment): 0.16 (s, 9H, Si(CH_3)$_3$), 1.3–2.1 (m, 8H, 4CH_2), 4.78 (m, 1H, vinyl *H*).

5. A slight positive pressure of nitrogen is maintained in the apparatus throughout this procedure.

6. Anhydrous diethyl ether from Mallinckrodt Chemical Works was distilled from sodium and benzophenone before use.

7. Diethylzinc in a cylinder pressurized with nitrogen was purchased from Alfa Division, Ventron Corporation, and distilled at atmospheric pressure under a nitrogen atmosphere before use, b.p. 118°. The distillate was collected in a two-necked receiver fitted with a rubber septum and kept under a nitrogen atmosphere. Aliquots of diethylzinc were withdrawn with a gas-tight syringe. The checkers destroyed excess or waste reagent by injecting it cautiously beneath the surface of ice-cold water through which argon was vigorously bubbled.

8. Diiodomethane from both Eastman Organic Chemicals and Aldrich Chemical Company, Inc., was used by the checkers after distillation under reduced pressure, b.p. 68–70° (12 mm.).

9. The solution becomes somewhat cloudy as the diiodomethane is added.

10. The checkers found considerable variation in the rate of the reaction in different runs, the time required for its completion ranging from 3 to 10 hours. It is therefore advisable to monitor the progress of the reaction. For this purpose small aliquots (*ca.* 0.05 ml.) were withdrawn from the flask with a syringe and hydrolyzed by injection into a vial containing ether and saturated ammonium chloride. The relative amounts of enol silane and cyclopropoxy silane were determined by GC on an 0.6 cm. × 3.7 m. column of 3% OV-17 coated on 100–120 mesh Chromosorb W. With a column temperature of 120° and a carrier gas flow rate of 20 ml. per minute, the retention times for the enol silane and the cyclopropoxy silane are *ca.* 1.9 and 2.3 minutes, respectively.

11. In one run that was particularly slow, an additional 9.9 g. of diiodomethane was added. The reaction then proceeded quickly to completion.

12. The spectral properties of the product are as follows: IR (neat) cm.$^{-1}$: 1250, 1209, 1010, 900, 865, 840; 220-MHz. ^{1}H NMR ($CDCl_3$), δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 0.13 [s, 9H, Si(CH_3)$_3$], 0.29 (t, J = 5, 1H, *endo* cyclopropyl *H* at C-7), 0.84 (d of d, J = 5 and J = 11, 1H, *exo* cyclopropyl *H* at C-7), 0.98–1.70 (m, 6H, cyclohexyl *H*), 1.82–2.18 (m, 3H, cyclohexyl *H*). A GC analysis as described in (Note 10) indicated the purity of the product to be *ca.* 95–98%, the remainder being 3–5% of unreacted enol silane.

13. Anhydrous iron(III) chloride was purchased by the submitters from Merck & Company, Inc. The checkers obtained the reagent from Aldrich Chemical Company, Inc. The reagent was dried at 60–70° under reduced pressure for several hours before use.

14. The dissolution of iron(III) chloride in *N*,*N*-dimethylformamide is exothermic.

15. A GC analysis on the liquid by the submitters using a Carbowax 20 M (polyethylene glycol) column at 170° showed a major peak assigned to 3-chlorocycloheptanone and minor peak for 2-cycloheptenone. The spectral properties of 3-chlorocycloheptanone are as follows: IR (neat) cm.$^{-1}$: 1705 (C=O); ^{1}H NMR (CCl_4), δ (multiplicity, number of protons, assignment): 1.4–2.3 [m, 6H, (CH_2)$_3$-CHCl], 2.3–2.6 (m, 4H, CH_2COCH_2), 4.1–4.4 (m, 1H, C*H*Cl); mass spectrum, *m/e* (intensity ratio): *M*+, 146 and 148 (3:1).

16. A GC analysis by the submitters as described in the preceding note indicated that the purity of the product was 98%. The purity of the product obtained by the checkers was estimated at 95% by a GC analysis at 140° as described in (Note 10). 2-Cyclohepten-1-one has the following spectral properties: IR (neat) cm.$^{-1}$: 1700 (C=O), 1660 (C=C), 1445, 1090, 888; ^{1}H NMR, δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 1.75 [m, 4H, $CH_2(CH_2)_2CH_2$], 2.45 [m, 4H, $CH_2(CH_2)_2CH_2$], 5.90 (d, *J* = 13, 1H, CH=C*H*CO), 6.52 (d of t, *J* = 5 and *J* = 13, 1H, C*H*=CHCO).

3. Discussion

This procedure illustrates a new three-step reaction sequence for the one-carbon ring expansion of cyclic ketones to the homologous α,β-unsaturated ketones.[2] The key step in the sequence is the iron (III) chloride-induced cleavage of the central bond of trimethylsilyloxycyclopropanes which are obtained by cyclopropanation of trimethylsilyl enol ethers. The procedure for the preparation of 1-trimethylsilyloxycyclohexene from cyclohexanone described in Part A is that of House, Czuba, Gall, and Olmstead.[3]

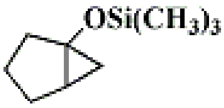
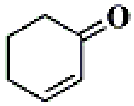
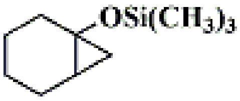
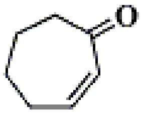
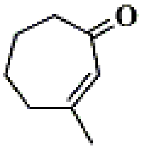
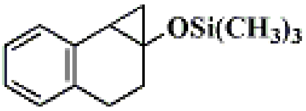
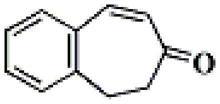
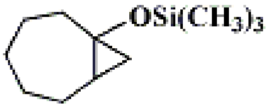
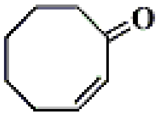
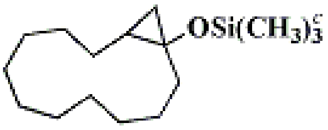
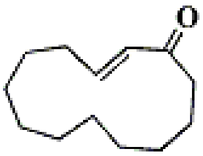
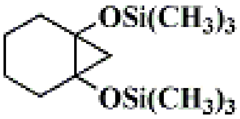
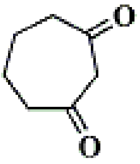
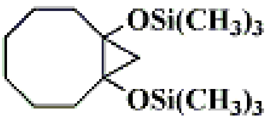
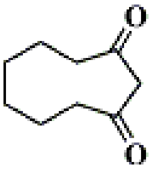
The cyclopropanation of 1-trimethylsilyloxycyclohexene in the present procedure is accomplished by reaction with diiodomethane and diethylzinc in ethyl ether.[4] This modification of the usual Simmons–Smith reaction[5,6] in which diiodomethane and activated zinc are used has the advantage of being homogeneous and is often more effective for the cyclopropanation of olefins such as enol ethers which polymerize readily. However, in the case of trimethylsilyl enol ethers, the heterogeneous procedures with either zinc–copper[7 8 9] or zinc–silver couple[10 11 12] are also successful. Attempts by the checkers to carry out Part B in benzene or toluene at reflux instead of ethyl ether afforded the trimethylsilyl ether of 2-methylenecyclohexanol, evidently owing to zinc iodide-catalyzed isomerization of the initially formed cyclopropyl ether.[13] The preparation of 1-trimethylsilyloxybicyclo[4.1.0]heptane by cyclopropanation with diethylzinc and chloroiodomethane in the presence of oxygen has been reported.[14]

The ring-opening reaction with iron(III) chloride in *N,N*-dimethylformamide is effective with a series of 1-trimethylsilyloxybicyclo[*n*.1.0]alkanes, as shown by the examples presented in Table I.[2] The corresponding 3-chlorocycloalkanones are usually isolable intermediates which are separately subjected to dehydrochlorination with sodium acetate in methanol, as in the preparation of 2-cyclohepten-1-one described here. However, the reaction of 1-trimethylsilyloxybicyclo[3.1.0]hexane with iron(III) chloride at 0–5° afforded 2-cyclohexen-1-one directly. The slower ring opening of 1-trimethylsilyloxybicyclo[10.1.0]tridecane was carried out at 80°, conditions which also effected spontaneous dehydrochlorination to *trans*-2-cyclotridecenone. The regiospecific ring enlargement of the unsymmetrical ketones, 2-methylcyclohexanone and β-tetralone, are of particular interest in view of the diversity of synthetic routes to trimethysilyl enol ethers.[15]

TABLE I

PREPARATION OF 2-CYCLOALKENONES AND CYCLOALKANE-1,3-DIONES BY IRON (III) CHLORIDE-INDUCED RING OPENING OF 1-TRIMETHYLSILYLOXY- AND 1,2-BIS (TRIMETHYLSILYOXY)BICYCLO[*n*.1.0]ALKANES

Silyloxybicyclo-[*n*.1.0]alkane	2-Cycloalkenone or Cycloalkane-1,3-dione	Yield (%)[a]

		98
		80[b]
		83
		83
		92
		81[c]
		68
		72

[a]The scale was 0.002–0.005 mole except as noted.

[b]This reaction was conducted on a 0.05-mole scale.

[c]This compound was a mixture of *cis* and *trans* isomers.

The present procedure for ring expansion has also been applied to 1,2-bis(trimethylsilyloxy)bicyclo [*n*.1.0]alkanes,[2,16] which are prepared by cyclopropanation of 1,2-bis(silyloxy)cycloalkenes.[17] The latter are readily available from acyloin condensations in the presence of chlorotrimethylsilane.[18] This reaction provides a new route to cyclic 1,3-diketones and macrocyclic compounds containing two 1,3-diketone units in the ring. It has been reported[19] that methylcyclopropanation of 1,2-bis-(trimethylsilyloxy)cyclohexene by 1,1-diiodoethane with zinc–copper couple or diethylzinc and the subsequent iron(III) chloride-induced ring expansion afforded 2-methylcycloheptane-1,3-dione in moderate yield.

The regiospecificity of the iron(III) chloride-induced ring cleavage contrasts with that observed in reactions of 1-silyloxybicyclo[*n*.1.0]alkanes with bromine[9] and potassium *tert*-butoxide.[11] Although the mechanism of the reaction is not known with certainty, it is reasonable to suppose that an alkoxy radical is involved, that this radical undergoes homolytic scission of the more highly substituted carbon–carbon bond of the cyclopropane ring, and that the resulting carbon radical abstracts a chlorine atom from iron(III) chloride.[20]

2-Cyclohepten-1-one has been prepared from cycloheptanone by dehydrohalogenation of the ethylene ketals of 2-chloro- and 2-bromocycloheptanone and subsequent hydrolysis.[21] [22] The α,β-dehydrogenation of cycloheptanone has also been effected *via* the α-phenylthio[23] and α-phenylseleno[24] ketones which were subjected to oxidation and thermal elimination. Another route to the title compound starts with cycloheptene, which is subjected to allylic bromination, hydrolysis, and chromic acid oxidation.[25]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 414
- Org. Syn. Coll. Vol. 9, 643

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silver couple

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

methanol (67-56-1)

ether, ethyl ether, diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

sodium acetate (127-09-3)

chloroform (67-66-3)

sodium hydrogen carbonate (144-55-8)

Cyclohexanone (108-94-1)

sodium chloride (7647-14-5)

bromine (7726-95-6)

sodium sulfate (7757-82-6)

oxygen (7782-44-7)

nitrogen (7727-37-9)

copper (7440-50-8)

toluene (108-88-3)

Benzophenone (119-61-9)

zinc (7440-66-6)

sodium (13966-32-0)

chromic acid (7738-94-5)

iron(III) chloride (7705-08-0)

Pentane (109-66-0)

diiodomethane (75-11-6)

diethylzinc (557-20-0)

lithium aluminum hydride (16853-85-3)

N,N-dimethylformamide (68-12-2)

2-methylcyclohexanone (583-60-8)

Cycloheptanone (502-42-1)

triethylamine (121-44-8)

Triethylamine hydrochloride (554-68-7)

calcium hydride (7789-78-8)

zinc iodide

β-Tetralone (530-93-8)

2-cyclohexen-1-one (930-68-7)

argon (7440-37-1)

CHLOROTRIMETHYLSILANE (75-77-4)

2-Cyclohepten-1-one, 2-cycloheptenone (1121-66-0)

1-trimethylsilyloxycyclohexene (6651-36-1)

1-Trimethylsilyloxybicyclo[4.1.0]heptane (38858-74-1)

3-chlorocycloheptanone

cyclopropyl ether

chloroiodomethane (593-71-5)

1-trimethylsilyloxybicyclo[3.1.0]hexane

1-trimethylsilyloxybicyclo[10.1.0]tridecane

1,2-bis-(trimethylsilyloxy)cyclohexene

1,1-diiodoethane (594-02-5)

2-methylcycloheptane-1,3-dione

2-bromocycloheptanone

cycloheptene

potassium tert-butoxide (865-47-4)

trans-2-cyclotridecenone

trimethylsilyl ether of 2-methylenecyclohexanol

2-chlorocycloheptanone

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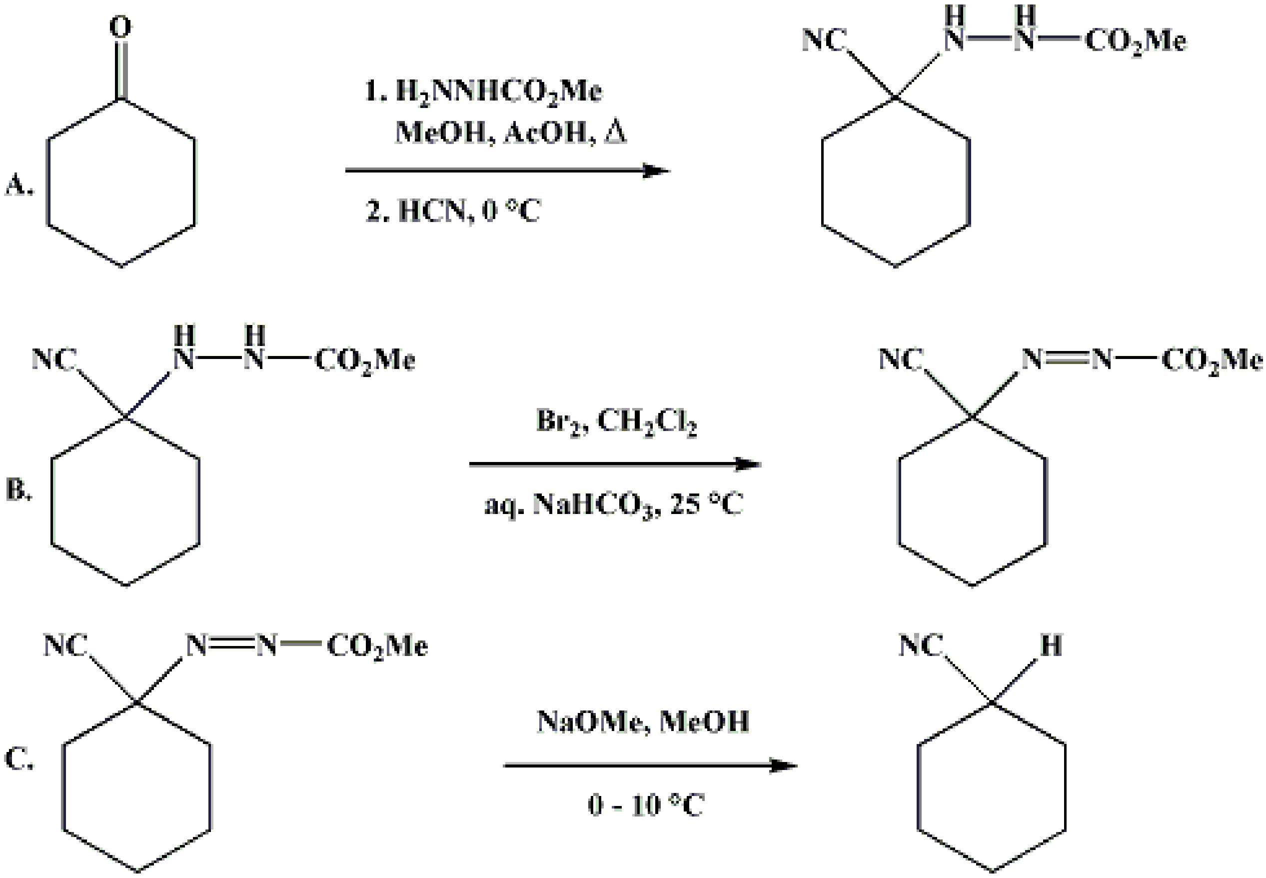
Organic Syntheses, CV 6, 334

NITRILES FROM KETONES: CYCLOHEXANECARBONITRILE



Submitted by P. A. Wender[1,2], M. A. Eissenstat[1], N. Sapuppo[1], and F. E. Ziegler[3].
Checked by D. F. Bushey and G. Büchi.

1. Procedure

Caution! Because of the toxicity of hydrogen cyanide, this procedure should be conducted in a well-ventilated hood, and rubber gloves should be worn. (See also (Note 3).)

A. *Methyl 2-(1-cyanocyclohexyl)hydrazine carboxylate* **(1)**. A 100-ml., three-necked flask equipped with a reflux condenser, thermometer, magnetic stirring bar, and gas-exhaust tube (Note 1) is charged with 9.0 g. (0.10 mole) of methyl carbazate (Note 2), 20 ml. of methanol, 2 drops of acetic acid, and 9.8 g. (0.10 mole) of cyclohexanone. The resulting mixture is refluxed for 30 minutes, then cooled to 0° and treated with 6 ml. (0.15 mole) of hydrogen cyanide (Note 3), added dropwise over a period of 3 minutes. After approximately 15 minutes the solution is allowed to warm to room temperature, during which time the hydrazine **1** crystallizes (Note 4) and (Note 5). After 2 hours the resulting mixture is vacuum filtered, and the crystalline residue is washed with 10 ml. of cold methanol (Note 6), yielding 17.7 g. of hydrazine **1**. Concentration of the filtrate provides

an additional 1.4 g. of product. The total yield of crude hydrazine **1**, m.p. 130–133°, (Note 7) is 97%. Recrystallization (methanol–pentane) provides an analytically pure sample, m. p. 135–136°.

B. *Methyl* 2-(1-*cyancyclohexyl)diaxenecarboxylate* **(2)**. A 5.5 *M* solution of bromine in dichloromethane is added dropwise to a vigorously stirred mixture of 19.1 g. (0.0970 mole) of hydrazine 1, 75 ml. of dichloromethane, 75 ml. of water, and 22 g. (0.26 mole) of sodium hydrogen carbonate in a 250-ml. flask, until a persistent, positive potassium iodide–starch paper test is obtained (Note 8). Excess bromine is discharged with aqueous sodium sulfite, the phases are separated, and the aqueous phase is extracted with two 50-ml. portions of dichloromethane. The combined organic extracts are washed with 30 ml. of water, dried over magnesium sulfate, filtered, concentrated using a rotary evaporator, and distilled, yielding 17.3 g. (93%) of the diazene **2** as a clear, bright yellow oil, b.p. 95–97° (0.2 mm.) (Note 7).

C. *Cyclohexanecarbonitrile* **(3)**. A 100-ml., three-necked, round-bottomed flask fitted with a thermometer, a magnetic stirring bar, and an addition funnel is charged with 2.7 g. (0.050 mole) of sodium methoxide and 25 ml. of methanol. The solution is cooled in ice and stirred while a solution of 17.3 g. (0.0887 mole) of diazene 2 in 10 ml. of methanol is added dropwise at a rate that maintains the solution temperature at 0–10° (Note 9). Stirring is continued for an additional 30 minutes at ambient temperature, and the mixture is poured into 70 ml. of water. The resulting solution is extracted with five 20-ml. portions of pentane, and the combined organic extracts are dried over magnesium sulfate, filtered, concentrated, and distilled to provide 8.6–9.4 g. (78–86%) of carbonitrile **3**, b.p. 117–119° (90 mm.) (Note 10).

2. Notes

1. The tube is connected to the top of the reflux condenser and attached to a length of tygon tubing. The end of the tubing is positioned in the exhaust vent of the hood to remove any hydrogen cyanide vapor.

2. Methyl carbazate was prepared by the method of Diels.[4] This reagent is available from Aldrich Chemical Company, Inc., under the name methyl hydrazinocarboxylate. All other chemicals used in this sequence were of the highest purity commercially available and were not further purified before use.
3. Hydrogen cyanide can be purchased from Fumico Inc., Amarillo, Texas. When large amounts of HCN are used, it is recommended that amyl nitrite pearls and an oxygen cylinder with mask be available. These in combination are effective antidotes for HCN poisoning. The checkers prepared HCN according to the method in *Org. Synth.*, **Coll. Vol. 1**, 314 (1941). The use of smaller quantities of HCN results in slower reaction and reduced yield.
4. Spontaneous crystallization usually occurs within 30 minutes; if not, crystallization is induced by scratching the bottom of the reaction flask.
5. The solid formed at this point usually interferes with stirring. The yield of product, however, is not affected by the nature of mixing beyond this point.
6. The methanol is used to transfer any residual material from the reaction flask as well as to wash the residue.

7. Further purification of this intermediate is unnecessary for the preparation of nitriles.
8. The endpoint of this oxidation is indicated by the appearance in the reaction mixture of a red-orange color caused by excess bromine.
9. Nitrogen is vigorously and instantaneously evolved as each drop is added.
10. Physical and analytical characterizations of cyclohexanecarbonitrile **(3)** agree with literature reports:[5] ^{1}H NMR ($CDCl_3$), δ (multiplicity, number of protons, assignment): 1.30–2.00 (m, 10H, 5CH_2), 2.40–2.90 (m, 1H, C*H*CN). The average overall yield of cyclohexanecarbonitrile **(3)** from cyclohexanone is 85% when the diazene **2** is distilled and 86–90% when crude diazene is used directly. The submitter reported 8.9 g. (92%) of carbonitrile **3**.

3. Discussion

The transformation of ketones to nitriles has been accomplished with varying success using several methods including cyanide displacement reactions of acetates[6] and halides[7] obtained from ketones; cyanohydrin formation, dehydration, and reduction of the unsaturated nitriles;[8] reaction of tosylhydrazones with potassium cyanide followed by pyrolysis of the cyanohydrazine;[9] and reaction of tosylmethylisocyanide with ketones.[10] Related transformations of ketones and ketone derivatives to nitrile derivatives have also been reported.[11]

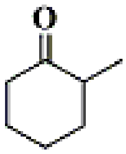
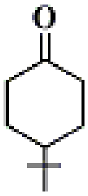
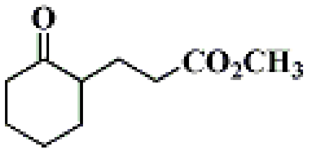
This procedure uses readily available reagents and provides a simple, efficient method for nitrile synthesis. The entire sequence of four steps can be performed in a single day. Although product formation in the second step is presumably thermodynamically controlled, the cyanohydrazine is favored in all cases studied except with aryl ketones. A water–methanol solution of ammonium chloride and potassium cyanide may also be employed for cyanohydrazine formation, but lower yields (*ca.* 60%) are obtained. The third step, a conveniently performed titration procedure with bromine as oxidant, can be effected with other oxidizing reagents such as 4-phenyl-4*H*-1,2,4-triazole-3,5-dione, *tert*-butyl hypochlorite, and Jones reagent.[12] The final diazene decomposition step is induced with bases and nucleophiles such as methoxide, ethoxide, hydroxide, and iodide. The diazine decomposition can be extended to the preparation of α-methylnitriles and α-carboalkoxynitriles.[13]

This procedures is general for the preparation of secondary nitriles (Table I), and can be used in the presence of other functional groups by the appropriate choice of oxidation and decomposition reagents.[14]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 281

TABLE I
KETONE TO NITRILE TRANSFORMATION

Ketone	Diazene Yield (%)[a]	Nitrile Yield (%)[b] (ratio of diastereomers)
	95	89 (50:50)
	94	97 (58:42)
	94	90 (50:50)

[a]Distilled yield based on starting ketone, obtained without purification of intermediate hydrazine.

[b]Yield based on purified diazene as determined by chromatographic analysis.

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3. Department of Chemistry, Yale University, New Haven, Connecticut 06520.
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

HCN

Methyl 2-(1-cyancyclohexyl)diaxenecarboxylate

Jones reagent

acetic acid (64-19-7)

methanol (67-56-1)

ammonium chloride (12125-02-9)

sodium sulfite (7757-83-7)

sodium hydrogen carbonate (144-55-8)

Cyclohexanone (108-94-1)

hydrogen cyanide (74-90-8)

bromine (7726-95-6)

nitrogen (7727-37-9)

potassium cyanide (151-50-8)

sodium methoxide (124-41-4)

Pentane (109-66-0)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

Cyclohexanecarbonitrile (766-05-2)

diazene (3618-05-1)

tosylmethylisocyanide (36635-61-7)

methyl carbazate, methyl hydrazinocarboxylate (6294-89-9)

tert-Butyl hypochlorite (507-40-4)

Methyl 2-(1-cyanocyclohexyl)hydrazine carboxylate (61827-29-0)

4-phenyl-4H-1,2,4-triazole-3,5-dione (4233-33-4)

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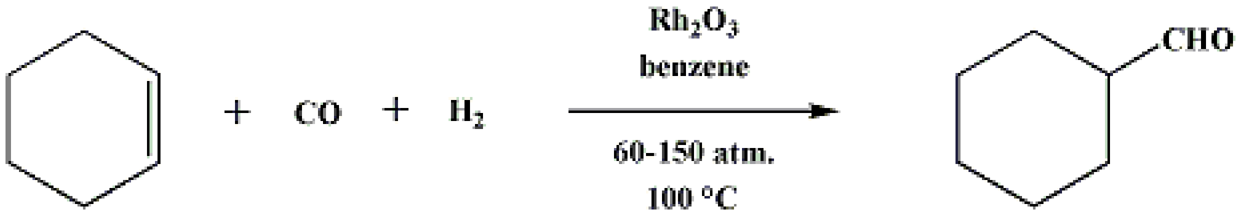
Organic Syntheses, CV 6, 338

ALDEHYDES FROM OLEFINS: CYCLOHEXANECARBOXALDEHYDE



Submitted by P. Pino[1] and C. Botteghi[2].
Checked by Mary M. Borecki, Joseph J. Mrowca, and Richard E. Benson.

1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

To a stainless-steel, 0.5-l. pressure vessel (Note 1) equipped with a 450-atm. manometer and a temperature recorder is added 0.2 g. (0.8 mmole) of rhodium(III) oxide (Note 2). The vessel is sealed and evacuated to 0.1 mm. pressure. A solution of 82 g. (1.0 mole) of cyclohexene (Note 3) in 140 ml. of anhydrous benzene is introduced by suction into the vessel. The vessel is placed in a heatable shaking device and pressured to 75 atm. with carbon monoxide; the total pressure is then increased to 150 atm. with hydrogen (Note 4). Shaking is begun and the vessel is heated to an internal temperature of 100° (Note 5). When the internal temperature reaches 100°, the pressure begins to fall. Whenever the pressure falls to 60 atm., rocking is stopped and the pressure is first increased to 105 atm. with carbon monoxide, then to 150 atm. with hydrogen. Rocking is started again, and the process is continued until no appreciable pressure decrease occurs. Approximately 2 hours is required, and the pressure decrease corresponds to the consumption of 2 moles of gas. The vessel is rapidly cooled to room temperature (Note 6) and the residual gas is carefully vented.

The vessel is opened, and the slightly yellow reaction mixture is transferred immediately to a 2-l., round-bottomed flask containing a freshly prepared solution of 200 g. of sodium hydrogen sulfite in 400 ml. of water. The flask is fitted with a stopper and is occasionally shaken at room temperature for a period of 3 hours (Note 7). The resulting precipitate is collected by suction filtration on a sintered-glass funnel and washed with 500 ml. of diethyl ether (Note 8). After drying in air, the bisulfite derivative is transferred to a 2-l. distillation flask containing 1 l. of 20% aqueous potassium carbonate. The resulting mixture is distilled, and the azeotropic mixture of water and aldehyde (b.p. 94–95°) is collected under nitrogen (Note 9).

The aldehyde is separated from the lower aqueous layer as a colorless liquid, dried over 10 g. of anhydrous sodium sulfate, filtered, and distilled under reduced pressure using a Claisen distillation apparatus, yielding 92–94 g. (82–84%) of cyclohexanecarboxaldehyde, b.p. 52–53° (18 mm.), n_D^{25} 1.4484 (Note 10), (Note 11). A purity of about 98% was established by GC analysis (Note 12); the product is suitable for synthetic use without further purification (Note 13).

2. Notes

1. The pressure vessel was tested to a pressure of 700 atm. at 300°.
2. The submitters used rhodium(III) oxide available from Fluka A G without further purification. The checkers obtained rhodium(III) oxide from Alfa Inorganics.
3. The cyclohexene was purified by distillation over sodium metal before use (n_D^{25} 1.4452). The submitters used the product available from Fluka A G, and the checkers used the product available from Aldrich Chemical Company, Inc.
4. The purity of the gases used was greater than 99%.
5. During the course of the reaction the temperature was maintained at 100° ± 2°.
6. This procedure avoids secondary reactions of the aldehydes, which lead to high-boiling products. It is particularly advisable when linear aliphatic aldehydes are synthesized using cobalt catalysts.[3]
7. The formation of the bisulfite derivative is an exothermic reaction; the flask is cooled with a bath of cold water for the first 10–15 minutes.
8. It is impossible to obtain a completely white precipitate by this procedure.
9. In order to avoid oxidation of the product the submitters recommend use of a nitrogen atmosphere for all manipulations involving cyclohexanecarboxaldehyde.
10. Literature[4] values for cyclohexanecarboxaldehyde: b.p. 78.5–80° (57 mm.), n_D^{25} 1.4485.
11. Cyclohexanecarboxaldehyde is stable at room temperature under nitrogen; the submitters noted no appreciable variation in the refractive index after 30 days.
12. The submitters state that GC analysis was made using a 2-m. column packed with polypropylene glycol (LB-550-X available from Perkin-Elmer) on Chromosorb. The retention time at 140° is 5.2 minutes at a flow rate of 30 ml./minute of nitrogen. The 2,4-dinitrophenylhydrazone derivative[4] melts at 173–174°, and the semicarbazone derivative[5] melts at 172–173°.
13. In addition to rhodium(III) oxide, cobalt(II) acetylacetonate or dicobalt octacarbonyl has been used by the submitters as catalyst precursors for the hydroformylation of cyclohexene. The results are given in Table I.

TABLE I
HYDROFORMYLATION OF CYCLOHEXENE WITH COBALT CATALYSTS[a]

Catalyst Precursor (mole/l.)	Solvent[b]	Reaction Temperature	Reaction Time (hours)	Yield[c] (%)
[Bis(acetylacetonate) cobalt(II)] (0.08)	Benzene	150°[d]	1.5	70
[Bis(acetylacetonate)[e] cobalt(II)] (0.08)	Heptane	110°	12	74
Dicobalt octacarbonyl[f] (0.006)	Benzene	120°	8	80

[a] 4.15 mole/l. of cyclohexene; $CO:H_2$ = 1:1; 150 atm. initial pressure.

[b] 140 ml.

[c] The aldehyde was isolated from the reaction mixture through its bisulfite derivative as described in the procedure.

[d] Induction time, 40–60 minutes.

[e] This catalyst precursor (5 g.) in 140 ml. of heptane was heated in the autoclave at 160° with a mixture of $CO:H_2$ (1:1) at 150 atm. for 2 hours. The vessel was cooled, the gas released, 1 mole of cyclohexene was charged, and the reaction was carried out according to the usual procedure.

[f] The submitters used product available from Fluka A G that was dried under reduced pressure after recrystallization from heptane at –70°.

3. Discussion

This preparation is an illustration of the hydroformylation of olefins (oxo synthesis). The reaction occurs in the presence of soluble catalytic complexes of Group VIII metals. Although the metal originally used by Roelen[6] and still largely used in industry for the production of aliphatic aldehydes and alcohols[7] is cobalt, the most active and selective catalysts are rhodium-containing compounds. The catalytic activity of the other Group VIII metals is, in general, much poorer. Although the hydroformylation of unsaturated substrates is a very general reaction,[7,8] some

important limitations associated with the olefin structure may lead to the formation of isomeric aldehydes. In addition, especially in the presence of cobalt catalysts, further reactions of synthesized aldehydes may occur under hydroformylation conditions.

With regard to the structure of the olefins, tetrasubstituted olefins do not undergo hydroformylation under typical reaction conditions, and olefinic substrates containing functional groups sometimes give poor yields and unexpected products.[7,8] If there is no plane of symmetry in the substrate across the double bond, at least two isomeric aldehydes are obtained.[9] Although methods for shifting the isomeric composition of the products have been proposed,[12,13,14] complete control of the isomeric composition has not been achieved despite the fact that the reaction mechanism is fairly well understood.[15] In addition, if the structure of the olefin is such that a double-bond shift is possible, isomers other than the two shown below can be formed.[10] Further reactions of the synthesized aldehydes may occur, especially when cobalt catalysts are used, leading to alcohols, aldol condensation products or acetal derivatives. Some of the secondary reactions can be avoided by carrying out the hydroformylation in the presence of orthoformic acid esters[16] or of other reagents protecting the aldehyde group.[17] However, care must be taken when ortho esters are used, since hydroformylation of ortho esters may occur and yield aldehydes or acetals.[18]

Although cobalt catalysts are the best known and the most commonly used, in recent years rhodium has been preferred for laboratory syntheses because of its higher activity and selectivity. As catalyst precursors Rh_2O_3,[11] $Rh_4(CO)_{12}$,[19] or $HRh(CO)(PPh_3)_3$[13] are commonly used. Rhodium complexes supported on polymers have also been used.[14] For typical organic syntheses the easily accessible Rh_2O_3 seems preferable, even if higher temperature and pressures are required to carry out the olefin hydroformylation. Using $HRh(CO)(PPh_3)_3$, olefin hydroformylation at room temperature and pressure is possible.[13] Carrying out the reaction in the presence of (–) DIOP [(4*R*,5*R*)-2,2-dimethyl-4,5-bis(5-dibenzophosphol-5-ylmethyl)-1,3-dioxolane], produced optically active aldehydes from monosubstituted ethylenes, as well as from 1,1- and 1,2-disubstituted ethylenes.[20]

The hydroformylation of cyclohexene has been extensively investigated.[13,14,16,21,22,23] The present procedure is an adaptation of the rhodium-catalyzed hydroformylation of 2-butene.[11]

Other methods for the preparation of cyclohexanecarboxaldehyde include the catalytic hydrogenation of 3-cyclohexene-1-carboxaldehyde, available from the Diels–Alder reaction of butadiene and acrolein,[24] the reduction of cyclohexanecarbonyl chloride by

lithium tri-*tert*-butoxyaluminum hydride,[25] the reduction of *N*,*N*-dimethylcyclohexanecarboxamide with lithium diethoxyaluminum hydride,[26] and the oxidation of the methane sulfonate of cyclohexylmethanol with dimethyl sulfoxide.[27] The hydrolysis, with simultaneous decarboxylation and rearrangement, of glycidic esters derived from cyclohexanone gives cyclohexanecarboxaldehyde.[4,28]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

dicobalt octacarbonyl

cobalt(II) acetylacetonate

Bis(acetylacetonate) cobalt(II)

Bis(acetylacetonate)[e] cobalt(II)

(–)DIOP [(4R,5R)-2,2-dimethyl-4,5-bis(5-dibenzophosphol-5-ylmethyl)-1,3-dioxolane]

methane sulfonate of cyclohexylmethanol

potassium carbonate (584-08-7)

Benzene (71-43-2)

diethyl ether (60-29-7)

hydrogen (1333-74-0)

carbon monoxide (630-08-0)

Acrolein (107-02-8)

Cyclohexanone (108-94-1)

Cyclohexene (110-83-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

sodium hydrogen sulfite (7631-90-5)

sodium (13966-32-0)

butadiene (106-99-0)

heptane (142-82-5)

cobalt (7440-48-4)

dimethyl sulfoxide (67-68-5)

N,N-Dimethylcyclohexanecarboxamide (17566-51-7)

Cyclohexanecarboxaldehyde (2043-61-0)

cyclohexanecarbonyl chloride (2719-27-9)

rhodium (7440-16-6)

rhodium(III) oxide (12036-35-0)

2-butene

3-cyclohexene-1-carboxaldehyde

lithium diethoxyaluminum hydride

lithium tri-tert-butoxyaluminum hydride

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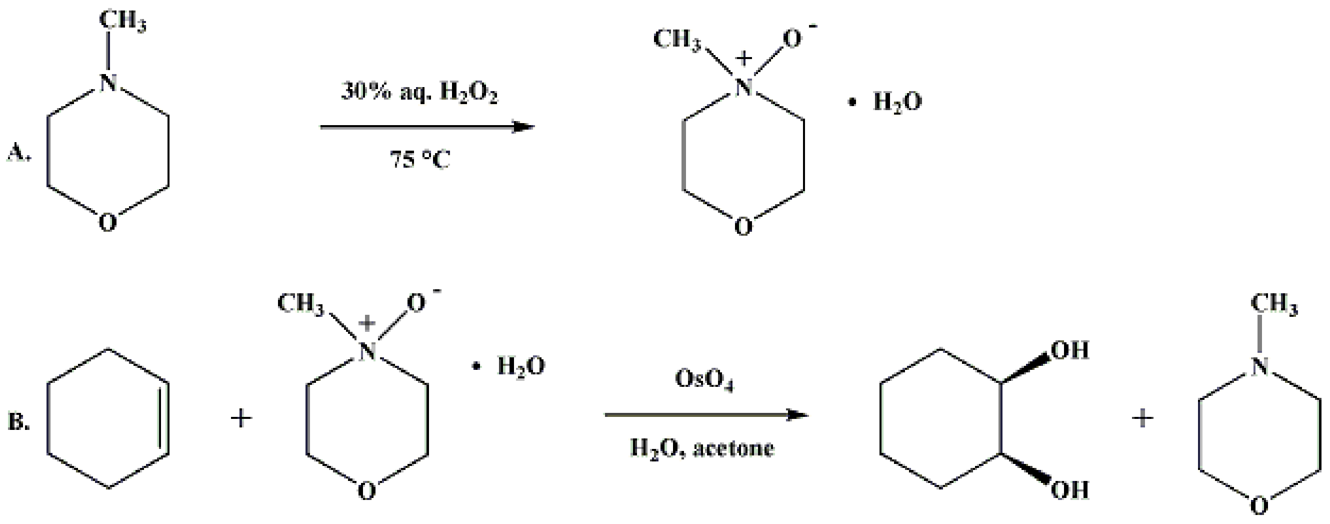
Organic Syntheses, CV 6, 342

CATALYTIC OSMIUM TETROXIDE OXIDATION OF OLEFINS: *cis*-1,2-CYCLOHEXANEDIOL



Submitted by V. VanRheenen, D. Y. Cha, and W. M. Hartley[1].
Checked by N. Meyer, W. Wykypiel, and D. Seebach.

1. Procedure

Caution! Care should be taken in handling osmium tetroxide. The vapor is toxic, causing damage to eyes, respiratory tract, and skin.

A. N-*Methylmorpholine* N-*oxide* (**1**) (Note 1). A 100-ml., three-necked, round-bottomed flask equipped with a reflux condenser, a magnetic stirring bar, and a dropping funnel is flushed with nitrogen or argon and charged with 32.3 g. (35.1 ml., 0.320 mole) of *N*-methylmorpholine (Note 2). The flask is immersed in an oil bath maintained at 75°, and 32.4 g. (29.1 ml., 0.286 mole) of 30% aqueous hydrogen peroxide is added dropwise over a period of 2.5 hours (Note 3). The mixture is stirred for 20 hours at 75°, at which time a negative peroxide test (potassium iodide paper) is obtained (Note 4). The reaction mixture is cooled to 50°, and a slurry of 50 ml. of methanol, 0.5 g. of charcoal, and 0.5 g. of Celite (Note 5) is added. After being stirred for 1 hour, the mixture is filtered and the filter cake washed with three 15-ml. portions of methanol. The filtrate and combined washings are concentrated with a rotary evaporator (water aspirator vacuum), with the bath temperature finally reaching 95°, where it is held for 10 minutes. The flask is fitted with a reflux condenser, and the residual viscous oil is dissolved in 25 ml. of acetone at 60°. On cooling to 40° (with seeding, if crystals of the *N*-oxide are available) the product spontaneously crystallizes. The slurry is stored at room temperature overnight, cooled in an ice bath, and filtered. The crystals are washed with three 15-ml. portions of 0° acetone and dried overnight at 40° (0.01 mm.) The yield of colorless crystalline monohydrate **1** is 32.4–34.3 g. (83.8–88.7%), m.p. 75–76° (Note 6) and (Note 7).

B. cis-1,2-*Cyclohexanediol* (**2**). A 250-ml., three-necked, round-bottomed flask, with a magnetic stirrer and a nitrogen inlet, is charged with 14.81 g. (0.1097 mole) of monohydrate 1, 40 ml. of water, and 20 ml. of acetone. To this solution is added *ca.* 70 mg. of osmium tetroxide (0.27 mmole) (Note 8) and 8.19 g. (10.1 ml., 0.100 mole) of cyclohexene (Note 9). This two-phase solution is stirred vigorously under nitrogen at room temperature. The reaction is slightly exothermic and is maintained at room temperature with a water bath. During the overnight stirring period, the reaction mixture becomes homogeneous and light brown in color. After 18 hours, TLC (Note 10) shows the reaction to be complete. Sodium hydrosulfite (0.5 g.) (Note 11) and 5 g. of Magnesol (Note 12) slurried in 20 ml. of water are added, the slurry is stirred for 10 minutes, and the mixture is filtered through a pad of 5 g. of Celite on a 150-ml. sintered-glass funnel. The Celite cake is washed with three 15-ml. portions of acetone. The filtrate, combined with acetone wash, is neutralized to pH 7 with 6.4 ml. of 12 *N* sulfuric acid. The acetone is evaporated under vacuum using a rotary evaporator. The pH of the resulting aqueous solution is adjusted to pH 2 with 2.3 ml. of 12 *N* sulfuric acid, and the *cis*-diol **2** is separated from *N*-methylmorpholine hydrosulfate by extraction with five 45-ml. portions of *n*-butanol (Note 13). The combined butanol extracts are extracted once with 25 ml. of 25% sodium

chloride solution, and the aqueous phase is backwashed with 50 ml. of butanol. The butanol extracts are evaporated under vacuum, giving 12.1 g. of white solid. The *cis*-diol **2** is separated from a small amount of insoluble material (*ca.* 0.7 g.) by boiling the solid with a 200-ml., an 80-ml., and a 20-ml. portion of diisopropyl ether (Note 14), decanting the solvent each time. The combined ether fractions are evaporated to *ca.* 50 ml. under vacuum, and crystalline white plates precipitate. The mixture is cooled to *ca.* –15°. The crystals are filtered, washed with two 10-ml. portions of cold diisopropyl ether, and dried, yielding 10.18–10.32 g. (89–90%) of the *cis*-diol **2** (m.p. 96–97°).

2. Notes

1. *N*-Methylmorpholine *N*-oxide (**1**) can also be purchased from Eastman Organic Chemicals or Fluka A G.
2. Commercial material was used without purification (the purity was checked by refractive index and ^{1}H NMR).
3. The slow addition (2.5 hours) is required to avoid overheating of the reaction mixture. The potential danger of using hydrogen peroxide at an elevated temperature is minimized by using a 10% excess of *N*-methylmorpholine and by choosing reaction conditions that ensure rapid consumption, avoiding accumulation of peroxide in the mixture. A 50% aqueous hydrogen peroxide solution can also be used. The content of the commercial hydrogen peroxide (*ca.* 30 or 50%) must be determined by iodometric titration.
4. Very sensitive ether peroxide test strips (Merckoquant, Art. No. 10011), available from E. Merck, Darmstadt, are used. If the test is still positive at this point, an additional 0.2 ml. of *N*-methylmorpholine is added. Stirring and heating at 75° are continued for another 5 hours. Remaining peroxide renders the work-up and drying of the product potentially hazardous. *N*-Methylmorpholine *N*-oxide (**1**) and hydrogen peroxide form a strong 1:1 complex. In the reaction with osmium tetroxide, this complex produces conditions similar to those of the Milas reaction,[2] and some ketol formation may result.
5. Darco G 60, Aktivkohle, Fluka A G No. 05100, and Celite 512 Hyflosuper, Firma Schneider, Winterthur, Switzerland, No. 5100025, were used.
6. The procedure is designed to maintain the proper amount of water in the crystallization mixture so that the monohydrate **1** is obtained. It has the highest melting point and is the least hydroscopic. Other hydrated forms, such as the dihydrate (m.p. 35–60°) and mixed hydrates, may be isolated. A Karl Fischer assay of the water content is not necessary if the obtained material melts within the range given.
7. A second crop of 1.7–4.3 g. (4.3–11.1%) of the product can be obtained by evaporating the mother liquid, heating the residue at 97° for 20 minutes under reduced pressure, dissolving it in 55 ml. of acetone at 60°, and continuing as described.
8. Commercial osmium tetroxide was used without purification. It is not easy to accurately weigh this material because it rapidly sublimes.
9. Commercial cyclohexene was used (the purity was checked by refractive index). Addition of cyclohexene caused a darkening of the reaction mixture. This is caused by a finite concentration of the osmate ester. The reaction becomes lighter in color when complete.
10. The reaction may be followed by TLC. The ratio of the R_f values for cyclohexene and *cis*-diol **2** is 2:1 (commercial silica gel plates, ethyl acetate). The plates are best visualized by first spraying with 1% aqueous potassium permanganate, then with methanolic sulfuric acid, followed by charring with heat. The checkers found that, if the procedure is followed exactly, monitoring the reaction by TLC is unnecessary.
11. Sodium hydrosulfite reduces the osmium tetroxide to insoluble lower-valent osmium species.
12. The submitter used Magnesol, industrial grade, available from Reagent Chemical Research, Inc., Pilot Engineering Division. The checkers used Florisil TLC, available from E. Merck, Darmstadt, No. 12519.
13. Since the *cis*-diol **2** is very water soluble, a polar solvent such as *n*-butanol is required to extract it. *n*-Butanol forms an efficient water azeotrope. More conventional solvents may be used for less polar products.
14. Diisopropyl ether readily forms explosive peroxides. It should be tested for peroxides, and contact with air should be minimized.

3. Discussion

cis-Dihydroxylation of olefins may be effected with potassium permanganate, osmium tetroxide, or silver iodoacetate according to Woodward's procedure.[3] Oxidation of cyclohexene to *cis*-diol **2** with potassium permanganate is reported to proceed in only 30–40% yields.[4,5] A modification of Woodward's procedure, in which iodine, potassium iodate, and potassium acetate in acetic acid were used, has given *cis*-diol **2** in 86% yield.[6] This procedure is particularly useful for placement of *cis*-diols on the more hindered side of more complex substrates.

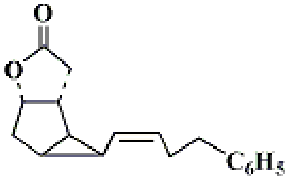
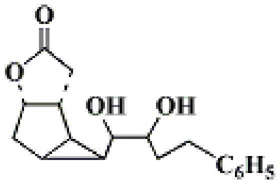
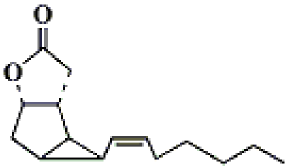
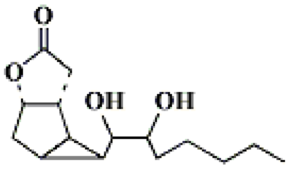
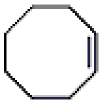
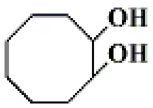
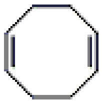
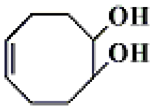
The reaction of an olefin with osmium tetroxide is the most reliable method for *cis*-dihydroxylation of a double bond, particularly for preparation of *cis*-diols on the least hindered side of the molecule. When used stoichiometrically, however, the high cost of osmium tetroxide can make a large-scale glycolization prohibitively expensive, and the work-up procedures can be cumbersome, particularly when pyridine is used. Also osmium tetroxide is volatile and toxic, resulting in handling problems. Catalytic osmylation using chlorate[7] or hydrogen peroxide (Milas reagent[2]) to regenerate osmium tetroxide avoids some of these problems, but overoxidation to an α-ketol commonly leads to losses in yield and separation problems. Preparation of *cis*-diol **2** with sodium chlorate and osmium tetroxide is reported to proceed in 46% yield,[4] and in 76% yield[8] when sodium chlorate, potassium osmate, and a detergent are used. A 62% yield of the *cis*-diol **2** from cyclohexene is reported in an interesting catalytic osmylation using *tert*-butyl hydroperoxide under alkaline conditions.[9] This method is particularly useful for oxidation of tri- and tetrasubstituted olefins.

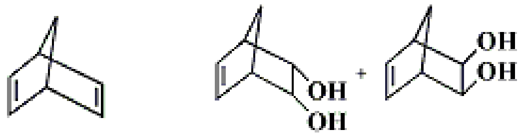
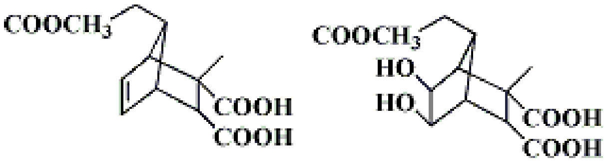
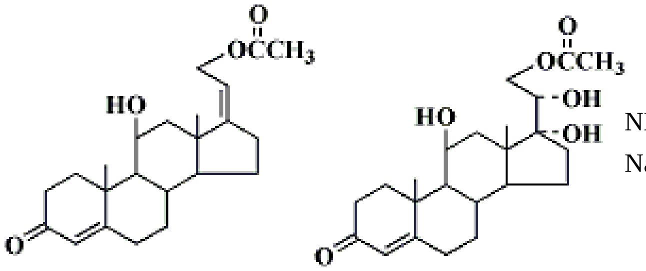
In this report we describe the conversion of cyclohexene to *cis*-diol **2**, in 90% yield, by catalytic osmylation using 1 mole equivalent of *N*-methylmorpholine *N*-oxide (**1**, NMO) to regenerate the osmium tetroxide catalyst. This procedure avoids the α-ketol by-products encountered with the currently available catalytic processes, and provides the high yields of the stoichiometric reaction without the expense and work-up problems.

The reaction is generally applicable to a variety of substrate types, as illustrated in Table I.[10] Compatible functionality includes hydroxyl, ester, lactone, acid, ketone, and electron-poor olefins such as those conjugated to α-ketones. Some selectivity between isolated double bonds is also found. The reaction generally gives nearly quantitative yields with simple olefins.

TABLE I

PREPARATION OF *cis*-DIOLS BY CATALYTIC OXIDATION OF OLEFINS WITH OSMIUM TETROXIDE

Starting Material	Product	Procedure	(Isolated yields, %)	Reference
		NMO[a]-OsO_4	(>95)	11
		NMO[a]-OsO_4	(>95)	10[b]
		NMO[a]-OsO_4 $NaClO_3$-OsO_4 $KMnO_4$ H_2O_2-OsO_4	(79) (30) (50) (11.4)	10[b] 12 13 12
		NMO[a]-OsO_4 OsO_4, 1 mole $KMnO_4$	(31) (14) (3)	10[b] 14 15

	NMO[a]-OsO_4	(25)	10[b]
	OsO_4, 1 mole	(21)	16
	$KMnO_4$	(28)	16
	NMO[a]-OsO_4	(55)	10[b]
	OsO_4, 1 mole	(53)	17
	$KClO_3$-OsO_4	(35)	17
	NMO[a]-OsO_4	(78)	18[c]
	$NaClO_3$-OsO_4	(79)	18[c]

[a]NMO = *N*-Methylmorpholine *N*-oxide.

[b]The reaction was carried out in aqueous acetone at room temperature using 0.2–1.0 mole % OsO_4 (see Experimental section).

[c]Solvent composition of 10:3:1 *tert*-butanol–tetrahydrofuran–water was preferred for this reaction.

The reaction is usually run in aqueous acetone in either one- or two-phase systems, but substrate solubility may require the use of other solvents. Aqueous *tert*-butanol, tetrahydrofuran, and the mixtures of these solvents have also been used successfully.

Other simple aliphatic amine oxides can be used as the oxidant in this reaction, but *N*-methylmorpholine *N*-oxide (**1**) is preferred because it generally gives a faster reaction rate and is easily prepared. The reaction can also be used to convert aliphatic amine oxides into amines.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 348

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

potassium osmate

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

ethyl acetate (141-78-6)

methanol (67-56-1)

potassium permanganate (7722-64-7)

Cyclohexene (110-83-8)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

sodium hydrosulfite (7775-14-6)

butanol, n-butanol (71-36-3)

iodine (7553-56-2)

acetone (67-64-1)

pyridine (110-86-1)

sodium chlorate (7775-09-9)

hydrogen peroxide (7722-84-1)

potassium acetate (127-08-2)

Tetrahydrofuran (109-99-9)

diisopropyl ether (108-20-3)

osmium tetroxide (20816-12-0)

tert-butanol (75-65-0)

argon (7440-37-1)

Magnesol

osmium

silver iodoacetate

potassium iodate (7758-05-6)

tert-butyl hydroperoxide (75-91-2)

N-methylmorpholine N-oxide (80913-66-2)

N-methylmorpholine (109-02-4)

cis-1,2-Cyclohexanediol (1792-81-0)

N-methylmorpholine hydrosulfate

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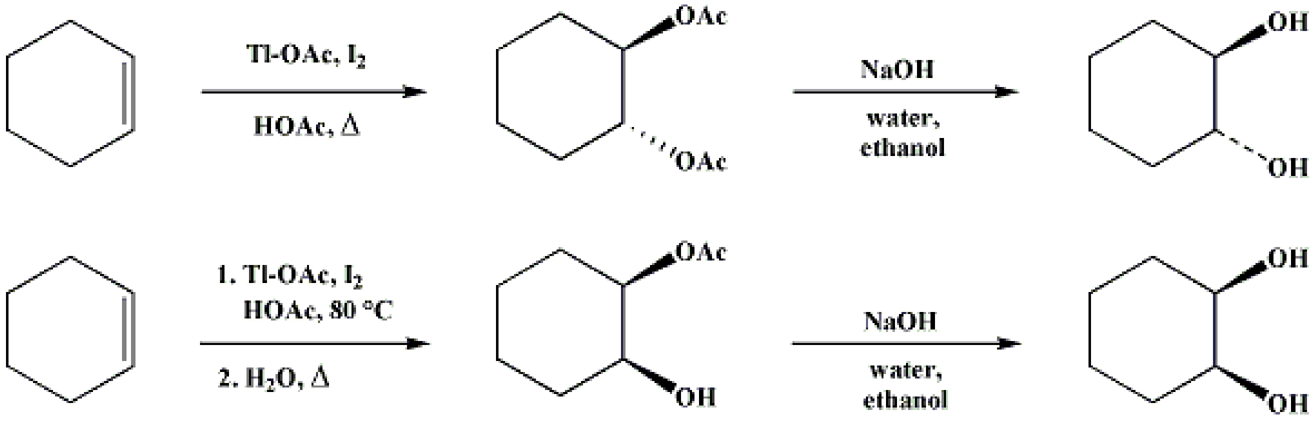
STEREOSELECTIVE HYDROXYLATION WITH THALLIUM(I) ACETATE AND IODINE: *trans*- AND *cis*-1,2-CYCLOHEXANEDIOLS



Submitted by R. C. Cambie and P. S. Rutledge[1].
Checked by D. Seebach, M. Liesner, and E.-M. Wilka.

1. Procedure

Caution! Thallium salts are very toxic. These procedures should be carried out in a well-ventilated hood, and rubber gloves should be worn. For disposal of thallium wastes, see Org. Synth., ***Coll. Vol. 6****, 791 (1988).*

A. trans-1,2-*Cyclohexanediol*. In a 100-ml., round-bottomed flask equipped with a reflux condenser protected with a drying tube are placed a magnetic stirring bar, 17.56 g. (0.05447 mole) of thallium(I) acetate (Note 1), and 40 ml. of dried acetic acid (Note 2). The mixture is stirred and heated at reflux for 1 hour. The mixture is cooled before 2.84 g. (3.50 ml., 0.0346 mole) of cyclohexene (Note 3) and 8.46 g. (0.0333 mole) of iodine (Note 4) are added. The resulting suspension is stirred and heated at reflux for 9 hours (Note 5), and then cooled to room temperature. The yellow thallium(I) iodide precipitate is filtered and washed thoroughly with diethyl ether. The filtrates are combined, the solvents are removed with a rotary evaporator (Note 6), and the residual liquid is dissolved in dry ether. The turbid solution is dried with anhydrous potassium carbonate, and the solvent is again removed by rotary evaporation (Note 6), affording 5.4–6.3 g. of *trans*-1,2-cyclohexanediol diacetate as a mobile, brown liquid (Note 7).

The diacetate is dissolved in 25 ml. of 95% ethanol, a solution of 2.9 g. (0.073 mole) of sodium hydroxide in 11 ml. of water is added, and the resulting mixture is heated at reflux for 3 hours. The solution is concentrated by rotary evaporation and the remaining syrup is extracted with six 50-ml. portions of chloroform. The combined extracts are dried over anhydrous magnesium sulfate and evaporated, providing 3.1–3.3 g. of a pale brown crystalline solid, m.p. 97–103°. Recrystallization from carbon tetrachloride gives 2.5–2.7 g. (65–70% based on iodine) of *trans*-1,2-cyclohexanediol, m.p. 103–104° (Note 8).

B. cis-1,2-*Cyclohexanediol*. A 500-ml., round-bottomed flask equipped with a reflux condenser and a magnetic stirring bar is charged with 17.56 g. (0.05447 mole) of thallium(I) acetate(Note 1), 160 ml. of glacial acetic acid, 3.0 g. (3.7 ml., 0.036 mole) of cyclohexene (Note 3), and 8.46 g. (0.0333 mole) of iodine (Note 4) in the order given. The suspension is stirred and warmed in a heating bath at 80° for 30 minutes. An 80-ml. portion of water is added, stirring is continued, and the mixture is heated at reflux for 9 hours. The product is isolated and hydrolyzed as described in Part A, affording 3.2–4.9 g. of *cis*-1,2-cyclohexanediol, m.p. 88–95° (Note 9). Recrystallization from carbon tetrachloride gives 2.7–2.9 g. (70–75% based on iodine) of *cis*-1,2-cyclohexanediol, m.p. 97–98° (Note 10).

2. Notes

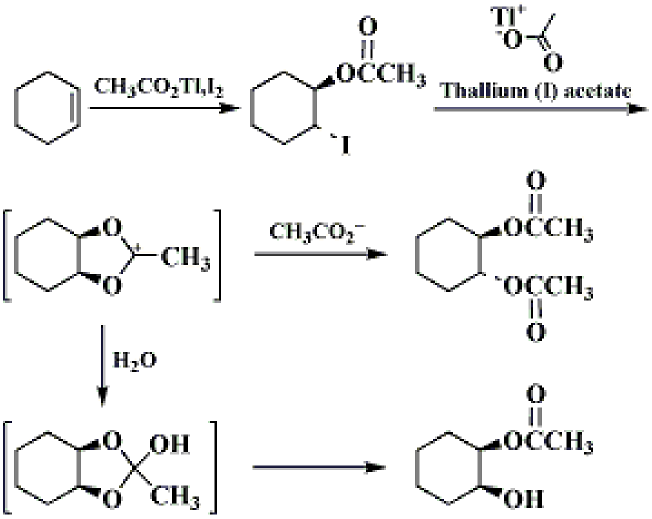
1. Thallium(I) acetate purchased from BDH Chemicals Ltd., Poole, England, or Fluka AG, Buchs, Switzerland, was used without further purification. This reagent is also available from Alfa Division, Ventron Corporation.
2. The submitters purchased glacial acetic acid from Showa Denko K. K., Tokyo, Japan, and acetic anhydride from Riedel de Haen AG, Seelze-Hannover, Germany. A solution prepared from 4 volumes of glacial acetic acid, 1 volume of acetic anhydride, and a catalytic amount of *p*-toluenesulfonic acid was heated under reflux for 24 hours and distilled. The distillate, which contained 5% water and 4% acetic anhydride according to ^{1}H NMR, analysis, was then used by the submitters. The water content was determined from the chemical shift of the hydroxyl proton.[2]
The checkers purchased analytical grade glacial acetic acid and anhydride from E. Merck, Darmstadt, Germany. A 4:1 (v/v) solution of glacial acetic acid and acetic anhydride containing 500 mg. of *p*-toluenesulfonic acid per liter was heated at reflux for 24 hours and then distilled. A forerun corresponding to 25% of the solution was discarded before a main fraction of acetic acid corresponding to 60% of the solution was collected. The main fraction, containing 17% acetic anhydride and 1% or less water as determined from its ^{1}H NMR spectrum, was used by the checkers.
3. Cyclohexene was purchased from BDH Chemicals Ltd., Poole, England, by the submitters and used without purification. This reagent was purchased by the checkers from Fluka AG, Buchs, Switzerland, and distilled before use.
4. Iodine purchased from Riedel de Haen AG, Seelze-Hannover, Germany, was sublimed before use by the submitters. The checkers used iodine from Siegfried AG, Zofingen, Switzerland, without purification.
5. After *ca.* 30 minutes the initially black-green solid becomes yellow.
6. The checkers recommend that excessive heating and evacuation be avoided during rotary evaporation to minimize the loss of product during this operation. They kept the heating bath temperature below 80° and used a water aspirator.
7. The diacetate was judged to be virtually pure by the submitters on the basis of GC analysis carried out at 150° using a glass column packed with 3% OV 17 (1:1 methyl–phenyl silicone) supported on 70–80 mesh Chromosorb W.
8. The submitters obtained 2.9 g. (75%) of product that melted at 103–105° (lit.,[3] m.p. 104°).
9. The unrecrystallized product obtained by the submitters melted at 91–95°. The purity of this material is estimated to be 96% on the basis of the melting point.[3]
10. The submitters obtained 3.0 g. (78%) of product which melted at 99–100°. The melting point of 97–98° shown above was obtained by the checkers using a Tottoli melting point apparatus (Büchi) equipped with a 50° range *Anschütz* thermometer. A melting point of 98° has been reported.[4]

3. Discussion

The present procedure offers a convenient alternative to the Prévost reaction[5 6] and the Woodward modification of the Prévost reaction[7] in which silver carboxylates are used instead of thallium(I) carboxylates. Thallium(I) salts have the advantages of being generally stable crystalline solids that can be readily prepared in high yield by neutralization of the appropriate carboxylic acid with thallium(I) ethoxide.[8] Silver salts, on the other hand, are frequently unstable and difficult to dry. Thallium and its compounds are, however, extremely toxic, and great care must be taken in the use and disposal of thallium salts.[9,10,11]

The mechanisms of these reactions are presumably analogous to those of the Prévost and Woodward–Prévost reactions.[5,6,7] In the first step of the reaction of iodine and thallium(I) acetate with cyclohexene, in both parts A and B of this procedure, produces *trans*-2-odocyclohexyl acetate. The second equivalent of thallium(I) acetate scavenges iodide ion during formation of the 1,3-dioxolan-2-ylium ion intermediate. Under the anhydrous conditions in Part A, the carbonium ion reacts with acetate ion at a ring carbon with inversion to give the diacetate. In part B the ion is captured by water, and the resulting ortho ester undergoes ring opening to the *cis*-diol monoacetate. No appreciable reaction occurs unless thallium(I) acetate, iodine, and cyclohexene are all present. Thus, in contrast to the Prévost and Woodward–Prévost procedures, acetyl hypoiodite

evidently cannot be prepared separately from thallium(I) acetate and iodine. The precise reasons for this difference are not clear.



trans-2-Iodocyclohexyl acetate can be isolated in essentially quantitative yield from the reaction of thallium(I) acetate, iodine, and cyclohexene in a 1:1:1 molar ratio in refluxing chloroform.[12] Similarly, iodo acetates from a representative series of alkenes, including cyclohexene, have been prepared in 80–98% yield[13] in glacial acetic acid which was not dried as described in this procedure. The corresponding iodo benzoates are obtained in comparable yields from reaction with thallium(I) benzoate and iodine in benzene. The deactivated olefin methyl cinnamate did not react under these conditions, and *o*-allylphenol underwent ring iodination to give 2-allyl-6-iodophenol.[14] The diterpenes, phyllocladene and isophyllocladene, upon reaction with thallium(I) benzoate and iodine,[15] afford the same mixture of allylic benzoates obtained from a Woodward–Prévost reaction. With the exception of 3-phenylpropene, the formation of iodo carboxylates from unsymmetrical alkenes occurs regioselectively in a Markovnikov sense.

Vicinal iodo carboxylates may also be prepared from the reaction of olefins either with iodine and potassium iodate in acetic acid,[16] or with *N*-iodosuccinimide and a carboxylic acid in chloroform.[17] A number of new procedures for effecting the hydroxylation or acyloxylation of olefins in a manner similar to the Prévost or Woodward–Prévost reactions include the following: iodo acetoxylation with iodine and potassium chlorate in acetic acid followed by acetolysis with potassium acetate;[18] reaction with *N*-bromoacetamide and silver acetate in acetic acid;[22] reaction with thallium(III) acetate in acetic acid;[19] and reaction with iodine tris (trifluoroacetate) in pentane.[20]

The preparation of *trans*-1,2-cyclohexanediol by oxidation of cyclohexene with performic acid and subsequent hydrolysis of the diol monoformate has been described,[21,10,11]

The mechanisms of these reactions are presumably analogous to those of the Prévost and Woodward–Prévost reactions.[5,6,7] In the first step of the reaction of iodine and thallium(I) acetate with cyclohexene, in both parts A and B of this procedure, produces *trans*-2-odocyclohexyl acetate. The second equivalent of thallium(I) acetate scavenges iodide ion during formation of the 1,3-dioxolan-2-ylium ion intermediate. Under the anhydrous conditions in Part A, the carbonium ion reacts with acetate ion at a ring carbon with inversion to give the diacetate. In part B the ion is captured by water, and the resulting ortho ester undergoes ring opening to the *cis*-diol monoacetate. No appreciable reaction occurs unless thallium(I) acetate, iodine, and cyclohexene are all present. Thus, in contrast to the Prévost and Woodward–Prévost procedures, acetyl hypoiodite evidently cannot be prepared separately from thallium(I) acetate and iodine. The precise reasons for this difference are not clear.

trans-2-Iodocyclohexyl acetate can be isolated in essentially quantitative yield from the reaction of thallium(I)

acetate, iodine, and cyclohexene in a 1:1:1 molar ratio in refluxing chloroform.[12] Similarly, iodo acetates from a representative series of alkenes, including cyclohexene, have been prepared in 80–98% yield[13] in glacial acetic acid which was not dried as described in this procedure. The corresponding iodo benzoates are obtained in comparable yields from reaction with thallium(I) benzoate and iodine in benzene. The deactivated olefin methyl cinnamate did not react under these conditions, and *o*-allylphenol underwent ring iodination to give 2-allyl-6-iodophenol.[14] The diterpenes, phyllocladene and isophyllocladene, upon reaction with thallium(I) benzoate and iodine,[15] afford the same mixture of allylic benzoates obtained from a Woodward–Prévost reaction. With the exception of 3-phenylpropene, the formation of iodo carboxylates from unsymmetrical alkenes occurs regioselectively in a Markovnikov sense.

Vicinal iodo carboxylates may also be prepared from the reaction of olefins either with iodine and potassium iodate in acetic acid,[16,17,18] A number of new procedures for effecting the hydroxylation or acyloxylation of olefins in a manner similar to the Prévost or Woodward–Prévost reactions include the following: iodo acetoxylation with iodine and potassium chlorate in acetic acid followed by acetolysis with potassium acetate;[18] reaction with *N*-bromoacetamide and silver acetate in acetic acid;[22] reaction with thallium(III) acetate in acetic acid;[19] and reaction with iodine tris(trifluoroacetate) in pentane.[20]

The preparation of *trans*-1,2-cyclohexanediol by oxidation of cyclohexene with performic acid and subsequent hydrolysis of the diol monoformate has been described,[21] and other methods for the preparation of both *cis*- and *trans*-1,2-cyclohexanediols have been cited. Subsequently the *trans* diol has been prepared by oxidation of cyclohexene with various peracids,[23] with hydrogen peroxide and selenium dioxide,[24] and with iodine and silver acetate by the Prévost reaction.[25] Alternative methods for preparing the *trans* isomer are hydroboration of various enol derivatives of cyclohexanone[26] and reduction of *trans*-2-cyclohexen-1-ol epoxide with lithium aluminum hydride.[27] *cis*-1,2-Cyclohexanediol has been prepared by *cis* hydroxylation of cyclohexene with various reagents or catalysts derived from osmium tetroxide,[28] by solvolysis of *trans*-2-halocyclohexanol esters in a manner similar to that of the Woodward–Prévost reaction,[18,22,20,25,29] by reduction of *cis*-2-cyclohexen-1-ol epoxide with lithium aluminum hydride,[27] and by oxymercuration of 2-cyclohexen-1-ol with mercury(II) trifluoroacetate in the presence of chloral and subsequent reduction.[30]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

methyl silicone

acetic acid and anhydride

performic acid

phyllocladene

isophyllocladene

phenyl silicone

ethanol (64-17-5)

potassium carbonate (584-08-7)

acetic acid (64-19-7)

Benzene (71-43-2)

ether, diethyl ether (60-29-7)

acetic anhydride (108-24-7)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

Cyclohexanone (108-94-1)

Cyclohexene (110-83-8)

carbon tetrachloride (56-23-5)

iodine (7553-56-2)

selenium dioxide (7446-08-4)

potassium chlorate (3811-04-9)

hydrogen peroxide (7722-84-1)

Pentane (109-66-0)

magnesium sulfate (7487-88-9)

chloral (75-87-6)

potassium acetate (127-08-2)

silver acetate (563-63-3)

lithium aluminum hydride (16853-85-3)

osmium tetroxide (20816-12-0)

N-Bromoacetamide (79-15-2)

3-phenylpropene (300-57-2)

2-cyclohexen-1-ol

N-Iodosuccinimide (516-12-1)

p-toluenesulfonic acid (104-15-4)

THALLIUM(I) ACETATE (563-68-8)

Thallium (7440-28-0)

thallium(I) iodide

thallium(I) ethoxide (20398-06-5)

acetyl hypoiodite

thallium(I) benzoate

methyl cinnamate (103-26-4)

2-allyl-6-iodophenol

potassium iodate (7758-05-6)

thallium(III) acetate (2570-63-0)

iodine tris(trifluoroacetate)

mercury(II) trifluoroacetate (13257-51-7)

trans-1,2-Cyclohexanediol (1460-57-7)

cis-1,2-Cyclohexanediol (1792-81-0)

trans-1,2-cyclohexanediol diacetate

trans-2-iodocyclohexyl acetate

o-allylphenol (1745-81-9)

trans-2-cyclohexen-1-ol epoxide

cis-2-cyclohexen-1-ol epoxide

trans-2-odocyclohexyl acetate

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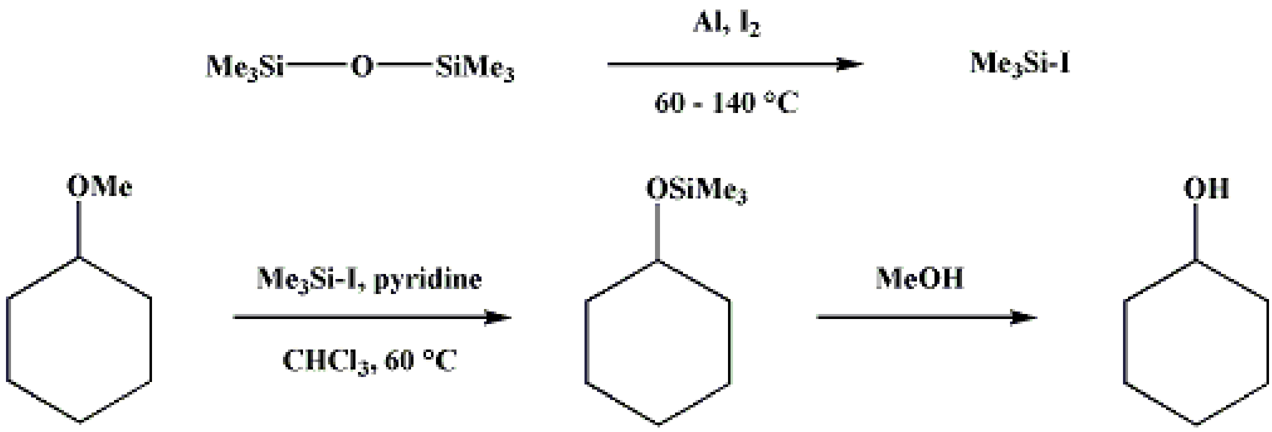
Organic Syntheses, CV 6, 353

CLEAVAGE OF METHYL ETHERS WITH IODOTRIMETHYLSILANE: CYCLOHEXANOL FROM CYCLOHEXYL METHYL ETHER



Submitted by Michael E. Jung[1] and Mark A. Lyster[12].
Checked by Joan Huguet, H. Shibuya, and S. Masamune.

1. Procedure

A. *Iodotrimethylsilane*. A 250-ml., two-necked, round-bottomed flask equipped with a magnetic stirring bar, an addition funnel for solids (Note 1), and a reflux condenser bearing a nitrogen inlet is charged with 5.6 g. (0.21 mole) of aluminum powder (Note 2) and 16.2 g. (0.100 mole) of hexamethyldisiloxane (Note 3) and purged with nitrogen. The mixture is stirred and heated with an oil bath at 60° as 50.8 g. (0.200 mole) of iodine is added slowly through the addition funnel over 55 minutes (Note 4). The bath temperature is raised to *ca.* 140°, and the mixture is heated under reflux for 1.5 hours. The reflux condenser is removed, and the flask is equipped for distillation at atmospheric pressure. The bath temperature is gradually raised from 140° to 210°, and the clear, colorless distillate is collected, yielding 32.6–35.3 g. (82–88%) of iodotrimethylsilane, b.p. 106–109° (Note 5) and (Note 6).

B. *Cyclohexanol*. A 25-ml., oven-dried, round-bottomed flask is charged with 1.722 g. (0.01524 mole) of cyclohexyl methyl ether (Note 7). The flask is purged with nitrogen and sealed with a rubber septum. With oven-dried syringes, 4 ml. of chloroform (Note 8), 0.5 g. (0.5 ml., 0.006 mole) of pyridine (Note 8) and (Note 9), and 4.8 g. (3.5 ml., 0.024 mole) of freshly prepared iodotrimethylsilane are injected into the flask in the order specified. When the iodotrimethylsilane is added, the solution becomes slightly yellow and a precipitate appears. The mixture is heated without stirring at 60° for 64 hours, after which the reaction is normally complete (Note 10). Anhydrous methanol (2 ml.) is added, the mixture is cooled to room temperature, and the volatile components (Note 11) are removed on a rotary evaporator. Approximately 10 ml. of anhydrous diethyl ether (Note 12) is added, and the resulting suspension is filtered, removing pyridinium hydroiodide. The flask and the filter cake are washed thoroughly with *ca.* 50 ml. of anhydrous ether. The ether is evaporated, and the residual oil is purified by chromatography on 70 g. of silica gel packed with anhydrous ether in a 3 × 50 cm. glass column. The column is eluted with anhydrous ether, and 5–7 ml.

fractions are collected and analyzed by TLC (Note 13). Fractions containing product are combined and evaporated, affording 1.26–1.35 g. (83–89%) of cyclohexanol (Note 14).

2. Notes

1. The submitters have used both an addition funnel with a worm gear delivery similar to those manufactured by Normag, and an Erlenmeyer flask attached to the neck of the reaction vessel with a piece of Gooch rubber tubing. Normag addition funnels are available from Lab Glass, Inc., P. O. Box 610, Vineland, New Jersey 08360.

2. The submitters purchased aluminum powder from MC and B Manufacturing Chemists. The metal used by the checkers was supplied by J. T. Baker Chemical Company.

3. Hexamethyldisiloxane is available from Aldrich Chemical Company, Inc. The reagent may also be prepared by the procedure described in the following paragraph. The submitters have used chlorotrimethylsilane purchased from Aldrich Chemical Company, Inc., and Silar Laboratories, Inc. (10 Alplaus Road, Scotia, New York 12302) either as supplied or after distillation from calcium hydride. No appreciable difference in yield was noted between preparations using undistilled and distilled reagent.

A 250-ml., three-necked, round-bottomed flask equipped with a magnetic stirring bar, a pressure-equalizing dropping funnel, and a reflux condenser bearing a nitrogen inlet is charged with a solution of 7 g. (0.4 mole) of water in 72.7 g. (76.0 ml., 0.601 mole) of *N,N*-dimethylaniline and flushed with nitrogen. Stirring is begun, and 62.49 g. (73.00 ml., 0.5754 mole) of chlorotrimethylsilane is added dropwise over 50 minutes. The mixture is heated under reflux in an oil bath at 125–130° for 1 hour. The reflux condenser is replaced by a distilling head, and the product is distilled at atmospheric pressure. The fraction boiling at 98–101° is collected, dried over anhydrous magnesium sulfate, and filtered, affording 43–44 g. (92–94%) of hexamethyldisiloxane as a clear colorless liquid.

4. In a similar procedure for the preparation of iodotrimethylsilane, aluminum, iodine, and hexamethyldisiloxane are combined, and the mixture is heated to reflux.[3] When this procedure was attempted by the submitters, violent exothermic reactions occurred at *ca.* 50–60°. The slow addition of iodine to the warm mixture described in the present procedure leads to a controlled, reproducible reaction.

5. The product is sometimes contaminated with a small amount of hexamethyldisiloxane. The amount of this contaminant is minimized by using longer reaction times and by careful handling to avoid contact with atmospheric moisture. The product may become discolored during storage, in which case it may be purified by distillation from copper powder. The ^{1}H NMR spectrum of iodotrimethylsilane ($CDCl_3$) exhibits a singlet at δ 0.71 in the presence of benzene as internal standard.

6. The submitters obtained 69.4 g. (87%) of product when the scale was doubled.

7. Cyclohexyl methyl ether was prepared by the method of Stoocknoff and Benoiton.[4]

A 250-ml., two-necked, round-bottomed flask is equipped with a magnetic stirring bar, a rubber septum, and a reflux condenser mounted with a nitrogen inlet. The flask is purged with nitrogen and charged with 8 g. (0.2 mole) of a 60% dispersion of sodium hydride in mineral oil. The sodium hydride is washed free of mineral oil with pentane and suspended in 75 ml. of tetrahydrofuran. After 10 g. (0.10 mole) of cyclohexanol is added by syringe, the mixture is heated under reflux for 22 hours. A 28.4-g. (12.5 ml.,

0.200 mole) portion of methyl iodide is injected into the flask, and the resulting mixture is heated under reflux for 18 hours. Water and chloroform are added to the cooled mixture. The aqueous layer is extracted with three 50-ml. portions of chloroform, the combined chloroform extracts are dried over anhydrous magnesium sulfate, and the solvents are evaporated. Distillation of the remaining liquid affords 7.1 g. (62%) of cyclohexyl methyl ether, b.p. 133–134°.

8. Chloroform and pyridine were dried over Linde type 4A molecular sieves.

9. Pyridine is added to neutralize small amounts of hydrogen iodide, often present in iodotrimethylsilane as a result of hydrolysis by contact with moisture. The amount of by-products, including cyclohexyl iodide, is reduced by the presence of pyridine. Hindered pyridine bases such as 2,6-di-*tert*-butyl-4-methylpyridine[5] have also been used for this purpose, by the submitters. The pyridine bases do not appear to react with iodotrimethylsilane.

10. The progress of the reaction may be conveniently monitored by ^{1}H NMR spectroscopy. After 64 hours the signal at δ 3.25 for the methoxyl group of cyclohexyl methyl ether had usually decreased to less than 1% of its original intensity, and peaks for cyclohexyl iodide could not be discerned. Although the submitters found that the reaction time was decreased by using larger amounts of iodotrimethylsilane, 5–10% of cyclohexyl iodide was also produced.

11. The volatile components are chloroform, methanol, methyl iodide, methyl trimethylsilyl ether, and hexamethyldisiloxane.

12. When the submitters used technical grade ether, the amount of iodine-containing by-products isolated from the chromatography was increased, and the yield of cyclohexanol was somewhat lower.

13. When an insufficient amount of iodotrimethylsilane was used by the submitters, cyclohexyl methyl ether remained at the end of the reaction and was eluted from the silica gel column before cyclohexanol. When present in the crude product, cyclohexyl iodide was also eluted from the column before cyclohexanol.

14. The identity and purity of the product were determined by GC, IR spectroscopy, and ^{1}H NMR spectroscopy by both the submitters and the checkers.

3. Discussion

This procedure describes a convenient method for the preparation of iodotrimethylsilane and illustrates the use of this reagent for ether cleavage, as in the regeneration of cyclohexanol from cyclohexyl methyl ether.[6] Iodotrimethylsilane was first prepared by Whitmore by the reaction of trimethylphenysilane with iodine.[7] The reagent has also been generated *in situ* by halide exchange between magnesium iodide and chlorotrimethylsilane.[8] The present procedure is essentially that of Voronkov and Khudobin,[3] modified by slowly adding iodine to a mixture of aluminum and hexamethyldisiloxane heated at 60° (see (Note 4)).

The use of methyl ethers as protecting groups for aliphatic alcohols has been hampered by the difficulty of liberating the alcohol from this inert derivative.[9,10] The cleavage of methyl ethers has been previously accomplished with boron reagents such as boron trichloride,[11,12,13,14,15]

boron trifluoride in acetic anhydride,[16,17] and diborane or sodium borohydride in the presence of iodine.[18,19] Two recent modifications of early methods for cleavage of aliphatic methyl ethers utilize hydrogen iodide generated *in situ*[10] and magnesium bromide in acetic anhydride.[20] Recently described methods for the hydrolysis of methyl ethers include the use of sodium cyanide in dimethyl sulfoxide,[21] anhydrous hydrogen bromide,[22] and thiotrimethylsilanes.[23]

The use of iodotrimethylsilane for this purpose provides an effective alternative to known methods. Thus, the reaction of primary and secondary methyl ethers with iodotrimethylsilane in chloroform or acetonitrile at 25–60° for 2–64 hours affords the corresponding trimethylsilyl ethers in high yield.[6] The alcohols may be liberated from the trimethylsiyl ethers by methanolysis. The mechanism of the ether cleavage is presumed to involve initial formation of a trimethylsilyl oxonium ion which is coverted to the silyl ether by nucleophilic attack of iodide at the methyl group. *tert*-Butyl, trityl, and benzyl ethers of primary and secondary alcohols are rapidly converted to trimethylsilyl ethers by the action of iodotrimethylsilane, probably *via* heterolysis of silyl oxonium ion intermediates. The cleavage of aryl methyl ethers to aryl trimethylsilyl ethers may also be effected more slowly by reaction with iodotrimethylsilane at 25–50° in chloroform or sulfolane for 12–125 hours,[6] with iodotrimethylsilane at 100–110° in the absence of solvent,[24,25] and with iodotrimethylsilane generated *in situ* from iodine and trimethylphenylsilane at 100°.[25,26]

Alkyl esters are efficiently dealkylated to trimethylsilyl esters with high concentrations of iodotrimethylsilane either in chloroform or sulfolane at 25–80°[27] or without solvent at 100–110°.[24,26] Hydrolysis of the trimethylsilyl esters serves to release the carboxylic acid. Amines may be recovered from *O*-methyl, *O*-ethyl, and *O*-benzyl carbamates after reaction with iodotrimethylsilane in chloroform or sulfolane at 50–60° and subsequent methanolysis.[28] The conversion of dimethyl, diethyl, and ethylene acetals and ketals to the parent aldehydes and ketones under aprotic conditions has been accomplished with this reagent.[29] The reactions of alcohols (or the corresponding trimethylsilyl ethers) and aldehydes with iodotrimethylsilane give alkyl iodides[30] and α-iodosilyl ethers,[31] respectively. Iodomethyl methyl ether is obtained from cleavage of dimethoxymethane with iodotrimethylsilane.[32] A review by Schmidt[33] covers the applications of iodotrimethylsilane listed above along with many more recently published examples.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

diborane

trimethylphenysilane

thiotrimethylsilanes

Benzene (71-43-2)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

acetic anhydride (108-24-7)

acetonitrile (75-05-8)

chloroform (67-66-3)

Cyclohexanol (108-93-0)

sodium cyanide (143-33-9)

hydrogen bromide (10035-10-6)

nitrogen (7727-37-9)

aluminum, aluminum powder (7429-90-5)

copper powder (7440-50-8)

iodine (7553-56-2)

pyridine (110-86-1)

hydrogen iodide (10034-85-2)

magnesium bromide (7789-48-2)

N,N-dimethylaniline (121-69-7)

Methyl iodide (74-88-4)

Pentane (109-66-0)

Dimethoxymethane (109-87-5)

magnesium sulfate (7487-88-9)

magnesium iodide

iodide (20461-54-5)

boron trifluoride (7637-07-2)

Tetrahydrofuran (109-99-9)

sodium hydride (7646-69-7)

methoxyl (2143-68-2)

boron trichloride (10294-34-5)

dimethyl sulfoxide (67-68-5)

calcium hydride (7789-78-8)

cyclohexyl iodide (626-62-0)

sodium borohydride (16940-66-2)

sulfolane (126-33-0)

CHLOROTRIMETHYLSILANE (75-77-4)

methyl trimethylsilyl ether (1825-61-2)

hexamethyldisiloxane (107-46-0)

Iodotrimethylsilane (16029-98-4)

CYCLOHEXYL METHYL ETHER (931-56-6)

pyridinium hydroiodide

silyl ether (13597-73-4)

trimethylphenylsilane (768-32-1)

Iodomethyl methyl ether (13057-19-7)

2,6-Di-tert-butyl-4-methylpyridine (38222-83-2)

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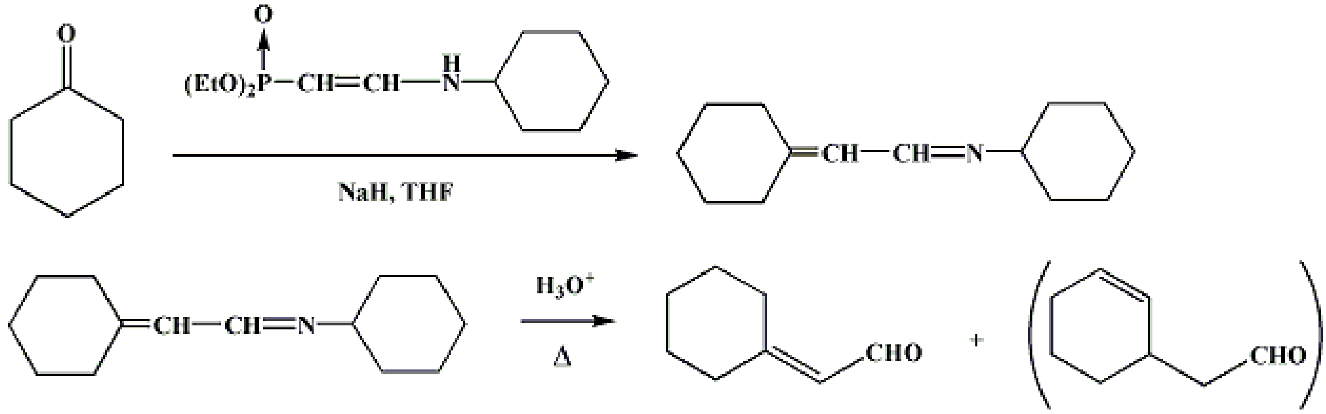
Organic Syntheses, CV 6, 358

PREPARATION OF α,β-UNSATURATED ALDEHYDES *via* THE WITTIG REACTION: CYCLOHEXYLIDENEACETALDEHYDE

[Acetaldehyde, cyclohexylidene-]



Submitted by Wataru Nagata[1], Toshio Wakabayashi[2], and Yoshio Hayase[1].
Checked by Kyo Abe and S. Masamune.

1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A 1-l., three-necked, round-bottomed flask, fitted with a magnetic stirrer, dropping funnel, and nitrogen inlet is charged with 5.45 g. (0.116 mole) of sodium hydride (51% oil dispersion) (Note 1) and 30 ml. of dry tetrahydrofuran (Note 2). The system is flushed with nitrogen and a solution of 30.2 g. (0.116 mole) of diethyl 2-(cyclohexylamino) vinylphosphonate [*Org. Synth.*, **Coll. Vol. 6**, 448 (1988)] in 90 ml. of dry tetrahydrofuran is added dropwise to the stirred mixture over a period of 15 minutes. During the addition the temperature is maintained at 0–5° with an ice bath. The mixture is stirred for an additional 15 minutes at 0–5° to ensure complete reaction. A solution of 10.3 g. (0.105 moles) of cyclohexanone (Note 3) in 70 ml. of dry tetrahydrofuran is added dropwise to the mixture over a period of 20 minutes, so that the temperature does not exceed 5°. The mixture is stirred for an additional 90 minutes at 20–25° in a water bath. During the stirring a gummy precipitate of sodium diethyl phosphate is observed. The mixture is poured into 500 ml. of cold water and extracted with three 300-ml. portions of diethyl ether. The combined ether extracts are washed twice with 200 ml. of saturated aqueous salt solution, dried over anhydrous sodium sulfate, and distilled under reduced pressure (35 mm.) at 25–30°. The residue is dissolved in 300 ml. of benzene and transferred to a 3-l., three-necked, round-bottomed flask equipped with a stirrer and a reflux condenser. To this solution is added a solution of 72 g. (0.57 mole) of oxalic acid dihydrate in 900 ml. of water (Note 4). The stirred mixture is refluxed for 2 hours under nitrogen, cooled, and transferred to a separatory funnel. The aqueous layer is extracted with two 300-ml. portions of ether. The combined organic extracts are washed with 200 ml. of water, then with 200 ml. of saturated aqueous salt solution, and dried over anhydrous sodium sulfate, and distilled under reduced pressure (35 mm.) at 25–30°. The residue is transferred to a 30-ml., round-bottomed flask and distilled under reduced pressure through a 5-cm. Vigreux column, yielding 10.8 g. (83%, (Note 5)) of cyclohexylideneacetaldehyde, b.p. 78–84° (12 mm.), containing *ca.* 15% of the isomeric cyclohexenylacetaldehyde (Note 6).

2. Notes

1. Sodium hydride (50–51% in mineral oil) was purchased from Metal Hydrides Inc. and used as 51%.
2. Reagent grade tetrahydrofuran was freshly distilled over sodium hydride before use. The checkers used lithium aluminum hydride to dry the solvent [see *Org. Synth.*, **Coll. Vol. 5**, 976 (1973) for warning note].
3. Reagent grade cyclohexanone was redistilled.
4. When a more concentrated solution (72 g. of oxalic acid in 450 ml. of water) was used, the product contained larger amounts of the β,γ-isomer, cyclohexenylacetaldehyde. To suppress this double bond isomerization, a 4–

7% aqueous oxalic acid solution was used.
5. The yields were 80–85% in several runs.
6. The submitters found that analysis of the final product by GC indicated a 15% contaminant of the by-product, cyclohexenylacetaldehyde. The analysis was conducted on a column packed with 5% XE-60 on Chromosorb W at 120°. The retention times for cyclohexenylacetaldehyde and cyclohexylideneacetaldehyde were 1.3 and 3.3 minutes, respectively. The checkers found that the product contained 10–15% of cyclohexenylacetaldehyde by GC analysis and 12–16% by NMR spectral analysis ($CDCl_3$), using the relative intensity of two signals (δ 9.53 and 9.97) due to the aldehydic protons of the two compounds. Reported physical constants are b.p. 58–62° (16 mm.) for cyclohexenylacetaldehyde and b.p. 80–85° (16 mm.) for cyclohexylideneacetaldehyde.[3]

3. Discussion

For the conversion of ketones into α,β-unsaturated aldehydes containing two additional carbon atoms, several multistep processes *via* ethynyl or vinyl carbinol intermediates have been reported.[3,4,5,6,7,8,9] Although the overall yields obtained by these routes for the conversion of cyclohexanone into cyclohexylideneacetaldehyde have never exceeded 50%, they were the only useful methods for this type of conversion until the Wittig[10,11] method appeared. This process consists of the normal aldol condensations of ketones with the lithium salt of ethylidenecyclohexylamine, followed by dehydration and hydrolysis.

The present procedure also illustrates an excellent, general method for the conversion of ketones and aldehydes[12] into the corresponding α,β-unsaturated aldehydes, using diethyl 2-(cyclohexylamino)vinylphosphonate.[13] The yield is usually high, and the reaction proceeds stereoselectively, affording only the *trans* isomer. In the reaction of 3-ketosteroids with this reagent, no β,γ-isomers were formed.[12] Recently Meyers and co-workers[14] reported a new method for the synthesis of α,β-unsaturated aldehydes.

A remarkable improvement of the present procedure, involving the *in situ* preparation of a solution of the lithium salt of diethyl 2-(*tert*-butylamino)vinylphosphonate[13] followed by addition of an aldehyde or a ketone, has recently been reported.[15]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Benzene (71-43-2)

ether, diethyl ether (60-29-7)

Cyclohexanone (108-94-1)

vinyl carbinol (107-18-6)

sodium sulfate (7757-82-6)

Oxalic acid (144-62-7)

nitrogen (7727-37-9)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

sodium hydride (7646-69-7)

sodium diethyl phosphate

Cyclohexylideneacetaldehyde, Acetaldehyde, cyclohexylidene- (1713-63-9)

oxalic acid dihydrate (6153-56-6)

cyclohexenylacetaldehyde

ethylidenecyclohexylamine (1193-93-7)

Diethyl 2-(cyclohexylamino)vinylphosphonate (20061-84-1)

lithium salt of diethyl 2-(tert-butylamino)vinylphosphonate

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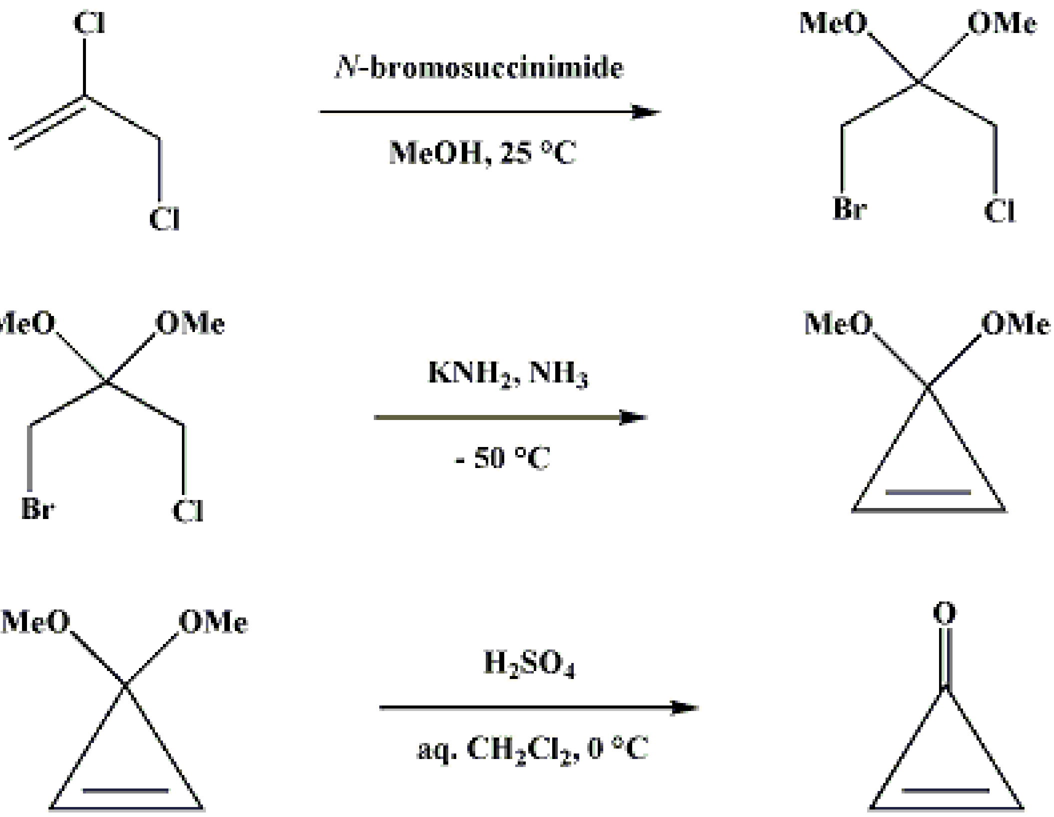
Organic Syntheses, CV 6, 361

CYCLOPROPENONE



Submitted by R. Breslow[1], J. Pecoraro, and T. Sugimoto.
Checked by R. Lüthi, H. Wüest, and G. Büchi.

1. Procedure

Caution! Because liquid ammonia is used in Part B, this part of the procedure should be conducted in a well-ventilated hood.

A. *1-Bromo-3-chloro-2,2-dimethoxypropane*. In a good hood, a 1-l., three-necked, round-bottomed flask equipped with magnetic stirrer and reflux condenser is charged with 300 ml. of anhydrous methanol, 111 g. (1.00 mole) of 2,3-dichloro-1-propene (Note 1), and a few drops of concentrated sulfuric acid. With stirring, 178 g. (1.00 mole) of *N*-bromosuccinimide is added in small portions through the condenser. After the final addition, the reaction mixture is stirred for another hour at room temperature before 5 g. of anhydrous sodium carbonate is added to neutralize the catalyst. The solution is stirred for an additional 15 minutes and poured into a large separatory funnel containing 300 ml. of water. The lower, organic layer is removed, and the aqueous layer is extracted with two 500-ml. portions of pentane. The combined organic extracts are washed twice with an equal volume of water, dried over anhydrous magnesium sulfate, filtered, and evaporated, giving a white semicrystalline mass, which is dissolved in refluxing pentane (250 ml.). The solution is cooled in an

acetone–dry-ice bath for 30 minutes, yielding 89–99 g. (41–45%) of the white crystalline ketal, m.p. 69.5–70.5° (Note 2).

B. *3,3-Dimethoxycyclopropene*. A 500-ml., three-necked, round-bottomed flask is equipped with a magnetic stirrer, a gas-inlet tube, a thermometer, and an acetone–dry-ice condenser topped with a drying tube containing sodium hydroxide pellets. An acetone–dry-ice bath is placed under the flask, and ammonia is condensed into the flask from a commercial cylinder. When 350–400 ml. of ammonia has condensed, the inlet tube is replaced by a stopper, and a small piece (0.5 g.) of potassium metal is added to the ammonia. The cooling bath is removed, and *ca.* 0.05 g. of anhydrous iron (III) chloride is added. When the ammonia reaches reflux temperature, the blue color of the dissolved potassium turns to gray, and the remainder of the potassium (11.7 g., 0.300-g.-atom total) is added in 0.5-g. pieces at such a rate that a gentle relux is maintained. The stopper is then replaced by an addition funnel containing a solution of 1-bromo-3-chloro-2,2-dimethoxypropane (21.7 g., 0.100 mole) in 50 ml. of anhydrous diethyl ether, which is added to the gray potassium amide–ammonia suspension over a period of 15 minutes, during which time the mixture is maintained at –50° to –60° with the cooling bath (Note 3). After 3 hours at this temperature, solid ammonium chloride (10.8 g., 0.20 mole) is added with stirring. Ammonia is allowed to evaporate by removing the cooling bath, and during the course of the evaporation it is replaced with 350 ml. of anhydrous ether. When the reaction temperature reaches *ca.* 0°, the resulting brown solution is filtered from inorganic salts and placed in a 500-ml., round-bottomed flask (Note 4). The ethereal solution is then subjected to a vacuum (50–80 mm.) applied through a carbon tetrachloride–dry-ice condenser (*ca.* –25°), while the flask is immersed in an ice bath. After 4–5 hours, when the quantity of residue seems to remain constant, the dry-ice condenser is replaced with a distilling head. The pressure is decreased to 1–2 mm., the receiver is maintained at –78° with a cooling bath, and distillation yields 4.0–6.5 g. (40–65%) of 3,3-dimethoxycyclopropene as a clear liquid (Note 5). This material has been purified further,[2] but it can be used directly in the next step. If it is stored, it should be kept below 0°.

C. *Cyclopropenone*. A stirred solution of 3.0 g. (0.030 mole) of 3,3-dimethoxycyclopropene in 30 ml. of dichloromethane, cooled to 0°, is treated dropwise with 5 ml. of cold water containing 3 drops of concentrated sulfuric acid. The reaction mixture is stirred at 0° for an additional 3 hours before 30 g. of anhydrous sodium sulfate is added in portions, with stirring, to the 0° solution. The drying agent is removed by filtration, and the solvent is evaporated at 50–80 mm. with a water bath maintained at 0–10°. The brown, viscous residue is then distilled at 1–2 mm, at a water bath temperature of 10°. The distillate, a mixture of methanol and dichloromethane, is collected in a receiver cooled to −78°. A new receiver is attached, and the bath temperature is gradually raised to 35° (Note 6), yielding 1.42–1.53 g. (88–94%) of cyclopropenone as a white solid, b.p. 26° (0.46 mm.), m.p. –29 to –28° (Note 7).

Cyclopropenone prepared in this way is quite pure and suitable for most chemical purposes. It can be repurified by crystallization from 3 volumes of ethyl ether at –60°

using a cooled filtering apparatus. The residual ethyl ether is then removed by evaporation at 1–2 mm. and 0°; very pure cyclopropenone is obtained in 60–70% recovery from the distilled material.

2. Notes

1. Commercial material was used without further purification. The reflux condenser is used to decrease evaporative losses of this material.
2. ^{1}H NMR (CCl_4), δ (multiplicity, number of protons): 3.27 (s, 6H), 3.48 (s, 2H), 3.63 (s, 2H); the IR and mass spectra are also as reported.[2]
3. Any crystals which may form at the tip of the addition funnel are scraped off and allowed to drop into the reaction flask.
4. The checkers found it inconvenient to complete Part B in one day and stored this ethereal solution overnight in the freezer compartment of a refrigerator.
5. The product usually contains small amounts of ether, as judged by its ^{1}H NMR spectrum. The yields given are based on pure cyclopropenone ketal. ^{1}H NMR ($CDCl_3$), δ (multiplicity, number of protons): 3.33 (s, 6H), 7.88 (s, 2H).
6. The bath temperature should be raised slowly to prevent decomposition of cyclopropenone.
7. IR ($CHCl_3$) $cm.^{-1}$: 1870, 1840, 1493; ^{1}H NMR ($CDCl_3$), δ: 9.11 (s).

3. Discussion

Cyclopropenone was first synthesized[3,4,5] by the hydrolysis of an equilibrating mixture of 3,3-dichlorocyclopropene and 1,3-dichlorocyclopropene (prepared by reduction of tetrachlorocyclopropene with tributyltin hydride), a procedure that has been adapted[5,4] for the preparation of labeled and deuterated cyclopropenones for use in physical studies. The current procedure is somewhat more convenient. It is closely based on the work of Baucom and Butler,[2] who have described this synthesis of dimethoxycyclopropene and shown that it can be hydrolyzed to cyclopropenone. The isolation of pure cyclopropenone by ketal hydrolysis parallels the method of Breslow and Oda,[5] which involves the hydrolysis of dichlorocyclopropenes.

Cyclopropenone is a molecule of considerable theoretical interest, since it combines remarkable stability with extreme strain. Various physical studies[6] suggest that much of its stability is derived from the special conjugative stabilization of the two-pi electron system, which is related to the cyclopropenyl cation. In addition, cyclopropenone has a number of interesting chemical properties[7,8] which suggest that it could be a useful synthetic intermediate. It has been used in the synthesis of cyclopropanone derivatives[7] and tropones,[7] the latter by rearrangement of products derived from Diels–Alder reactions. In addition, it undergoes a very interesting cyclization–rearrangement reaction with diazo compounds which leads to the overall insertion of a three-carbon unit between the diazo group and its original attachment

point.[7] Perhaps the most remarkable reaction of cyclopropenone so far reported is its conversion with Grignard reagents into 2-substituted resorcinols.[8] This reaction seems to be of some generality, and it represents a simple way to elaborate a resorcinol ring (all six carbons of the resorcinol system are derived from two molecules of cyclopropenone) onto a variety of alkyl groups. The ready availability of this compound should lead to other synthetic applications.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 173

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

ammonia (7664-41-7)

methanol (67-56-1)

ether, ethyl ether, diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

iron(III) chloride (7705-08-0)

potassium (7440-09-7)

2,3-dichloro-1-propene (78-88-6)

Pentane (109-66-0)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

N-bromosuccinimide (128-08-5)

potassium amide

cyclopropenone (2961-80-0)

1-Bromo-3-chloro-2,2-dimethoxypropane (22089-54-9)

3,3-Dimethoxycyclopropene (23529-83-1)

cyclopropenone ketal

3,3-dichlorocyclopropene

1,3-dichlorocyclopropene

tetrachlorocyclopropene

tributyltin hydride (688-73-3)

dimethoxycyclopropene

cyclopropenyl cation

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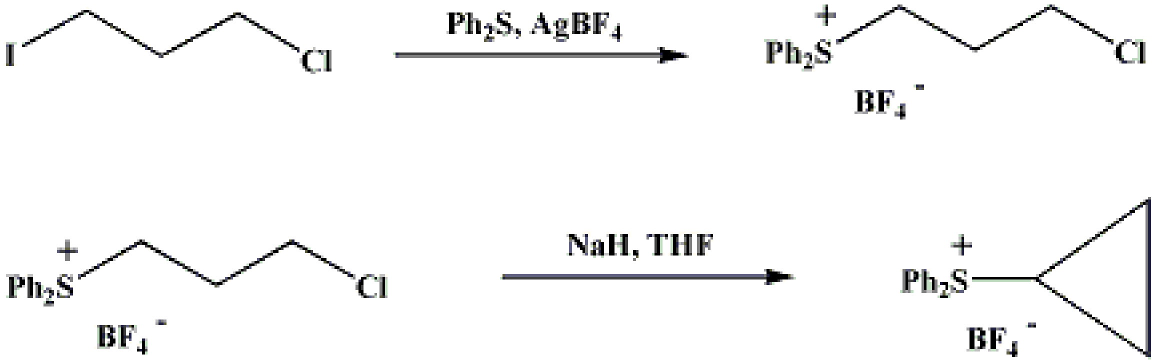
Organic Syntheses, CV 6, 364

CYCLOPROPYLDIPHENYLSULFONIUM TETRAFLUOROBORATE

[Sulfonium, cyclopropyldiphenyl tetrafluoroborate(1-)]



Submitted by Mitchell J. Bogdanowicz and Barry M. Trost[1].
Checked by Tsutomu Aoki and Wataru Nagata.

1. Procedure

A. *3-Chloropropyldiphenylsulfonium tetrafluoroborate*. A solution of 93.0 g. (0.500 mole) of diphenyl sulfide (Note 1) and (Note 2) and 347 g. (1.70 mole) of 1-chloro-3-iodopropane (Note 2), (Note 3), and (Note 4) in 200 ml. of nitromethane (Note 5) in a 1-l., one-necked flask equipped with a magnetic stirring bar and a nitrogen inlet tube is stirred at room temperature under nitrogen. The flask is shielded from light (Note 6), and 78 g. (0.40 mole) of silver tetrafluoroborate (Note 7) is added in one portion. Initially the temperature rises to 40°, then gradually falls to room temperature. No external cooling is necessary. After 16 hours 200 ml. of dichloromethane is added, the mixture is filtered through a sintered glass funnel fitted with a 35 g. pad of Florisil (Note 8), and the solid is washed with 100 ml. of dichloromethane. The dichloromethane portions are combined and evaporated at reduced pressure until a solid separates; 1 l. of diethyl ether is added to precipitate the product (Note 9). The off-white crystals are collected (Note 10), washed with ether, and dried under reduced pressure at 25°, yielding 122–140 g. (87–99%) of the sulfonium salt, m.p. 103–105° (Note 11).

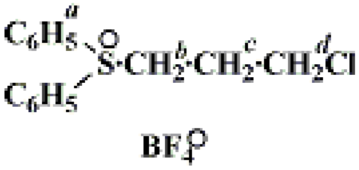
B. *Cyclopropyldiphenylsulfonium tetrafluoroborate*. A suspension of 118.7 g. (0.3386 mole) of 3-chloropropyldiphenylsulfonium tetrafluoroborate (Note 2) in 500 ml. of dry tetrahydrofuran (Note 12) is placed in a 2-l., one-necked flask equipped with a magnetic stirring bar and nitrogen inlet tube under nitrogen before 5-g. portions of 55% sodium hydride–mineral oil dispersion (15.2 g., 0.350 mole) are added in 30-minute intervals. The resulting mixture is stirred (Note 13) at room temperature for 24 hours. An aqueous solution of 25 ml. of 48% fluoroboric acid (Note 14), 15 g. of

sodium tetrafluoroborate (Note 7), (Note 15), and 400 ml. of water is added to the well-stirred reaction to destroy residual hydride and swamp out chloride ion (Note 16). After 5 minutes 300 ml. of dichloromethane is added, and the top organic layer is removed from the lower aqueous layer (Note 17). The dichloromethane solution is then extracted with 100 ml. of water. The combined water layers are extracted with an additional 100 ml. of dichloromethane. The organic phases are combined, dried over anhydrous sodium sulfate, and evaporated at reduced pressure until precipitation occurs. Addition of 1 l. of ether completes the precipitation of the salt. The crystals are collected, washed with ether, recrystallized from hot absolute ethanol (approximately 400 ml.) (Note 18), and dried under reduced pressure, yielding 79.5–88.0 g. (75–83%) of cyclopropyldiphenylsulfonium tetrafluoroborate, m.p. 137–139° (Note 19).

2. Notes

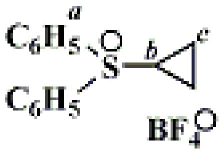
1. Available from Matheson, Coleman and Bell and utilized without further purification. The checkers used reagent grade diphenyl sulfide obtained from Tokyo Kasei Kogyo Co. Ltd., Japan.
2. The checkers carried out the experiment on a half scale and obtained the same results as described by the submitters.
3. Available from K & K Laboratories or may be prepared in 89% yield by the following procedure. To a solution of 393 g. (2.63 moles) of sodium iodide in 1 l. of reagent grade acetone is added 394 g. (2.50 moles) of 1-bromo-3-chloropropane (Aldrich Chemical Co.). After stirring 2 hours at room temperature, the mixture is filtered, the sodium bromide is washed with acetone, and the acetone is evaporated at reduced pressure. A dark iodine color is present along with some solid sodium salts. The oil is dissolved in ether, and the solution is washed with a 10% aqueous sodium thiosulfate. The ethereal layer is separated, dried over anhydrous sodium sulfate, and evaporated at reduced pressure, yielding 454 g. of an oil that can be used without further purification.
4. An excess of 1-chloro-3-iodopropane must be employed to compete effectively with the diphenyl sulfide for complexation with silver fluoroborate.
5. Available from Aldrich Chemical Co. and used without further purification. Dichloromethane may be substituted for the nitromethane. The checkers used reagent grade nitromethane available from Tokyo Kasei Kogyo Co. Ltd., Japan.
6. The flask is wrapped with aluminium foil to prevent decomposition of the silver salts.
7. Available from Ozark Mahoning Corp.
8. A pad of Florisil is employed to facilitate removal of the suspended silver salts.
9. An oil separated initially. Vigorous shaking of the mixture to extract the excess starting material out of the oily sulfonium salt layer induces crystallization.
10. The crystals obtained by the checkers were light brown at this stage, but could be purified by the following procedure.
11. The material is normally utilized directly without further purification. If the

solid is very gray, it may be recrystallized. For recrystallization the salt is dissolved in hot 95% ethanol (approximately 350 ml. per 100 g. of salt) containing decolorizing carbon and filtered rapidly. The clear supernatant liquid is allowed to cool in a freezer (–20°). In this way, white crystals, m.p. 106–107°, may be obtained with nearly quantitative recovery. The checkers obtained the purified material, m.p. 108–109°, with 95% recovery and used it for the next step. The purified material has the following spectral data; UV (95% C_2H_5OH) nm. max (ε): 236 shoulder (13,200), 262 (2200), 268 (2680), 275 (1010); IR (Nujol) cm.$^{-1}$: 3090 weak, 3060 weak (aromatic CH), 1580 weak (C=C); ^{1}H NMR ($CDCl_3$), first-order analysis: δ 2–2.5 (m, J_{bc} = 8 Hz., J_{cd} = 6.5 Hz., 2H, CH_2^c). 3.75 (t, 2H, CH_2^d), 4.3 (poorly resolved t, 2H, CH_2^b), 7.5–8.2 (m, 10H, $2C_6H_5^a$).



12. The tetrahydrofuran was dried by distilling from lithium aluminium hydride and then from sodium benzophenone ketyl (generated by adding small pieces of sodium metal and benzophenone) directly into the reaction flask. A blue-black color of the ketyl solution indicates dryness. The checkers purified terahydrofuran by distillation from sodium hydride dispersion under nitrogen, and used it immediately.
13. The checkers found that efficient stirring is essential for successful results.
14. Since 48% fluoroboric acid was not available in Japan, the checkers used 42% fluoroboric acid obtained from Wako Pure Chemicals Co. Ltd., and obtained the same result as described by the submitters.
15. The checkers prepared sodium tetrafluoroborate by neutralization of an ice-cold, aqueous, 42% solution of fluoroboric acid with an equivalent amount of sodium carbonate and addition of dry ethanol to the reaction mixture to effect complete crystallization of the product. The crystals were purified by washing with ethanol and obtained in 80% yield.
16. Normally no observable effect occurs upon this addition. Gas evolution with a slight exotherm indicates incomplete reaction.
17. The density of the dichloromethane and water layers are nearly equal. Thus, sometimes upon initial mixing, the dichloromethane starts out on the bottom, but the layers reverse on shaking. However, on occasion, the desired organic layer is found in fact to be the bottom one. It is therefore advisable to check the layers by addition of either water or dichloromethane. The checkers found that dichloromethane was on the bottom in the two experiments.
18. Ether may be added to the cold ethanol solution before filtration to insure complete precipitation.
19. The purified material has the following spectral data; UV (95% C_2H_5OH) nm. max (ε): 235 shoulder (12,200), 261 (1800), 267 (2200), 274 (1700); IR

(Nujol) cm^{-1}: 3100 weak, 3045 weak (aromatic CH), 1582 weak (C=C); ^{1}H NMR ($CDCl_3$), first-order analysis: δ 1.4–1.75 (m, 4H, $2CH_2^c$), 3.5–3.9 (m, 1H, CH^b), 7.5–8.1 (m, 10H, $2C_6H_5^a$).



3. Discussion

The utility of sulfur ylides in organic synthesis demands methods for the efficient preparation of the precursor sulfonium salts.[2] Among the salts, the diphenylsulfonium moiety provides the ability to generate the higher alkylides unambiguously but the low nucleophilicity of the sulfur of diphenyl sulfide dictated the need for exceptionally reactive alkylating agents. Oxonium salts,[3] dialkoxycarbonium salts,[4] and fluorosulfate esters[5] are capable of achieving such alkylations; however, the unavailability of such alkylating agents except for the very simple alkyl groups (*e.g.*, methyl and ethyl) does not allow generalization. On the other hand, alkyl halides complexed to silver salts form powerful alkylating agents and allow utilization of a wide range of alkyl halides susceptible to S_N2 displacement.[2,6] Although alkyl bromides may be employed, alkyl iodides are preferred. The latter are normally available in excellent yields from sulfonate esters, chlorides, or bromides by reaction with sodium iodide. Polyhalides may be employed without complications—reaction occurring preferably at a primary rather than secondary center. A nonsilver salt-based method for preparing 3-chloropropyldiphenylsulfonium tetrafluoroborate has also been reported recently.[7]

While sulfonium ylides do not normally undergo alkylations (except with reactive alkylating agents such as methyl iodide[8]), they do undergo intramolecular alkylation (cyclization) rather efficiently. The present procedure describes the synthesis of a particularly interesting reagent, cyclopropyldiphenylsulfonium tetrafluoroborate.[9] The ylide derived from this salt effects many different synthetic transformations which include facile syntheses of cyclobutanones,[9] γ-butyrolactones,[10] and specifically substituted cyclopentanones[11] from aldehydes and ketones and spiropentanes from α,β-unsaturated carbonyl partners.[9,12] Two reviews of the synthetic applications of the ylide have appeared.[13]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium benzophenone ketyl

terahydrofuran

ethanol (64-17-5)

ether, diethyl ether (60-29-7)

sodium carbonate (497-19-8)

sodium bromide (7647-15-6)

sodium sulfate (7757-82-6)

sodium thiosulfate (7772-98-7)

nitrogen (7727-37-9)

sulfur (7704-34-9)

acetone (67-64-1)

decolorizing carbon (7782-42-5)

Benzophenone (119-61-9)

sodium (13966-32-0)

1-bromo-3-chloropropane (109-70-6)

Methyl iodide (74-88-4)

sodium iodide (7681-82-5)

Nitromethane (75-52-5)

dichloromethane (75-09-2)

Diphenyl sulfide (139-66-2)

Tetrahydrofuran (109-99-9)

lithium aluminium hydride (16853-85-3)

sodium hydride (7646-69-7)

sodium tetrafluoroborate (13755-29-8)

sulfonium

fluoroboric acid (16872-11-0)

Cyclopropyldiphenylsulfonium tetrafluoroborate, Sulfonium, cyclopropyldiphenyl tetrafluoroborate(1-) (33462-81-6)

1-chloro-3-iodopropane (6940-76-7)

silver tetrafluoroborate, silver fluoroborate (14104-20-2)

3-Chloropropyldiphenylsulfonium tetrafluoroborate (33462-80-5)

diphenylsulfonium

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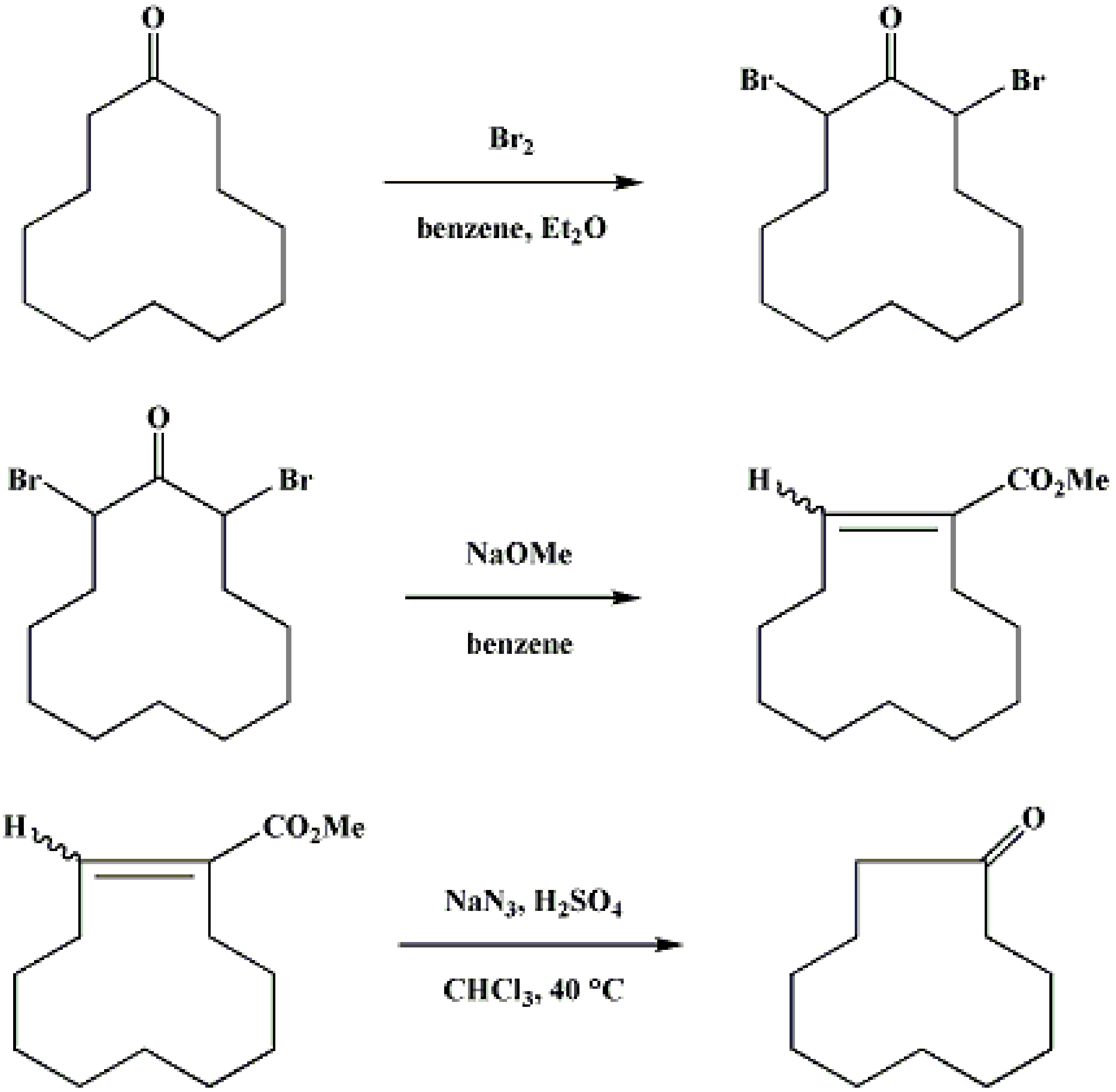
Organic Syntheses, CV 6, 368

RING CONTRACTION *via* A FAVORSKII-TYPE REARRANGEMENT: CYCLOUNDECANONE



Submitted by J. Wohllebe and E. W. Garbisch Jr[1].
Checked by J. M. Diakur and S. Masamune.

1. Procedure

Caution! Hydrazoic acid, which is used in Part C of this procedure, is very toxic. Consequently, the conversion of methyl 1-cycloundecenecarboxylate to cycloundecanone by the Schmidt degradation, including hydrolysis and subsequent steam distillation, should be conducted in a well-ventilated hood.

Pure hydrazoic acid in a condensed state has been reported in several instances to explode violently without apparent inducement, but explosions during Schmidt

reactions do not seem to have been observed. Nevertheless, it is recommended that this reaction be carried out behind a safety shield.

Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A. *2,12-Dibromocyclododecanone*. A 3-l., three-necked, round-bottomed flask is fitted with a magnetic stirrer (Note 1), a pressure-equalizing dropping funnel, a thermometer, and a gas-outlet tube. The outlet tube is connected by Tygon tubing to a calcium chloride drying tube, which is placed near an exhaust port of a hood. The flask is charged with 182 g. (1.00 mole) of cyclododecanone (Note 2), 1.4 l. of dry benzene (Note 3), and 150 ml. of anhydrous diethyl ether, and the funnel with 320 g. (2.00 moles) of bromine (Note 4). The reaction vessel is immersed in a water bath, stirring is initiated, and bromine is added at such a rate that the bromine in solution is consumed before the addition of each new drop; the addition requires 20–30 minutes. Ice is added to the water bath, as required, to hold the reaction temperature at 20–25°. The gas-outlet tube is then connected to a water aspirator, the dropping funnel is replaced with a stopper, and the water bath is filled with warm water. While stirring is continued, the pressure in the reaction flask is gradually decreased to evaporate the hydrobromic acid formed (together with most of the ether and some of the benzene) until the aspirator water is neutral to indicator paper (Note 5). Approximately 1 l. of solution remains in the flask, and this is used directly for the next step.

B. *Methyl 1-cycloundecenecarboxylate*. The benzene solution of 2,12-dibromocyclododecanone prepared in Part A is stirred and treated with 125 g. (2.31 moles) of powdered sodium methoxide (Note 6), which is added in portions over 30–40 minutes. Ice is added to the water bath, as required, to hold the reaction temperature at 25–30°. After being stirred at 25–30° for another 20 minutes, the reaction mixture is extracted successively with 500-ml. portions of water, 5% hydrochloric acid, and saturated aqueous sodium chloride. The aqueous phases are combined, extracted with 400 ml. of ether, and discarded. The combined organic phases are filtered through anhydrous sodium sulfate, the solvents are evaporated under reduced pressure, and the residual oil is distilled through a 7-cm., insulated Vigreux column (0.4 mm.). Collection of the fractions boiling below 104° provides 191–196 g. (91–93%) of methyl 1-cycloundecenecarboxylate (Note 7) as a pale yellow oil, most of which distils at 83–87° (0.4 mm.). This ester is sufficiently pure for use in the next step.

C. *Cycloundecanone*. In a well-ventilated hood a 3-l.; three-necked, round-bottomed flask is fitted with a magnetic stirrer (Note 1), a thermometer, a reflux condenser protected by a calcium chloride tube, and a rubber stopper. Concentrated sulfuric acid (600 ml.) is placed in the flask, stirred slowly, and cooled to 5° with an ice bath. Methyl 1-cycloundecenecarboxylate (191–196 g., 0.91–0.92 mole) is added through a long-stemmed funnel, the rate of stirring is increased until the mixture becomes a homogeneous solution, and 500 ml. of chloroform is added. The resulting mixture is

heated to 35° by immersion in a warm water bath. Vigorous stirring is continued while 78 g. (1.2 moles) of sodium azide (Note 8) is added in small portions over a 30–50-minute period, the reaction temperature being maintained at 40 ± 2° by adding ice to the water bath. *Caution! This operation should be performed behind a safety shield.* After an additional 10–15 minutes of stirring at 35–40°, the reaction mixture is cooled to 5°, poured onto 1 kg. of ice, and transferred together with 1.5–2 l. of water to a 5-l., three-necked flask set up for steam distillation. The chloroform is distilled off and saved, and the cycloundecanone is steam distilled with 3.5–4.0 kg. of steam. The steam distillate is extracted with the recovered chloroform, then with 500 ml. of ether. After the ethereal extract has been washed with concentrated aqueous sodium chloride, the organic phases are filtered through anhydrous sodium sulfate, combined, and concentrated under reduced pressure. Vacuum distillation of the residual oil affords 139–143 g. (83–85%) of cycloundecanone as a colorless or pale yellow oil, b.p. 84–85° (2 mm.), n_D^{25} 1.4794–1.4796 (Note 8).

2. Notes

1. A Thomas Magne-Matic Stirrer Model 15 (available from the Arthur H. Thomas Company, Philadelphia, Pennsylvania, was used in conjunction with a 5-cm., Teflon-coated, egg-shaped magnet.
2. Cyclododecanone was obtained from the Aldrich Chemical Company, Inc., and used without purification.
3. Solvent grade benzene was dried over sodium wire prior to use. If a voluminous sludge forms on drying, the solvent should be distilled from sodium.
4. Various brands and grades of bromine were used without noticeable difference (however, *cf.* reference [2]). Bromine was added until a light orange color persisted for more than 2 minutes, which occasionally required the addition of a few drops in excess of the theoretical amount.
5. At this stage, the addition of a small amount of anhydrous potassium hydrogen carbonate powder to the residual reaction mixture should not cause evolution of carbon dioxide gas.
6. The submitters used the reagent as supplied by Mallinckrodt Chemical Works. The checkers have occasionally found that commercially available sodium methoxide has deteriorated on storage over an extended period, unless the reagent has been properly protected from moisture. Therefore, it was prepared in the following manner. A 2-l., three-necked, round-bottomed flask was equipped with a magnetic stirrer and a reflux condenser and flushed with dry nitrogen through a gas bubbler attached to the top of the condenser. Into this flask was distilled approximately 600 ml. of absolute methanol (dried with magnesium methoxide), and then 69 g. of sodium was added in 1–3-g. portions. After all of the sodium had dissolved, the methanol was distilled, first at atmospheric and then at reduced pressure. The resulting mass of sodium methoxide was powdered under nitrogen and dried under vacuum at 150° for 8 hours. Titration of the reagent against 0.1311 *N* hydrochloric acid showed it to be 97.5% pure.

7. GC analysis of the product showed two major peaks (relative intensity, 5:1), and the mass spectrum of each peak revealed a molecular ion at *m/e* 210. The ^{1}H NMR spectrum of the mixture showed that the two products were geometrically isomeric esters.

8. Practical grade sodium azide was obtained from Eastman Organic Chemicals, and lumps were broken up with a spatula. Care was taken to avoid contact of sodium azide with the skin.

9. The cycloundecanone solidified on cooling and melted at 16.2–16.6°. GC analysis of the product showed a single peak [1.5 m. by 3.2 mm. column, 5% SE-30 on Chromosorb W, at 125° (submitters); 1.5 m. by 3.2 mm. column, UC-W98, 150°, retention time 10.25 minutes (checkers)]. ^{1}H NMR ($CDCl_3$), δ (multiplicity, number of protons): 1.3–2.1 (m, 16H), 2.4–2.7 (m, 4H); IR (neat) cm^{-1}: 1700, very strong.

3. Discussion

Cycloundecanone has been prepared in several ways: (a) pyrolysis of the thorium salt of dodecanedioic acid,[3] (b) reduction of 2-hydroxycycloundecanone,[4,5] (c) ring expansion of several lower homologs of cycloundecanone,[6] (d) Curtius degradation of 1-cycloundecenecarboxylic acid,[2] and (e) hydrolysis of 1-methoxycycloundecene.[7]

The present method, a modification of a procedure described previously by the submitters,[8] gives higher yields and is less expensive and more expeditious than the previously published methods. This route, involving a Favorskii-type rearrangement, has the potential of being widely applicable for the preparation of the lower homolog of a ketone having at least one hydrogen atom at each α-position. For example, cyclodecanone has been prepared in 77% yield from cycloundecanone by essentially the same procedure.[8]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

chloroform (67-66-3)

sodium chloride (7647-14-5)

HYDROBROMIC ACID (10035-10-6)

bromine (7726-95-6)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

sodium methoxide (124-41-4)

sodium (13966-32-0)

magnesium methoxide

sodium azide (26628-22-8)

Cyclodecanone (1502-06-3)

potassium hydrogen carbonate (298-14-6)

cyclododecanone (830-13-7)

Cycloundecanone (878-13-7)

Methyl 1-cycloundecenecarboxylate (3667-72-9)

2,12-Dibromocyclododecanone (24459-40-3)

2-hydroxycycloundecanone

1-cycloundecenecarboxylic acid

1-methoxycycloundecene

thorium salt of dodecanedioic acid

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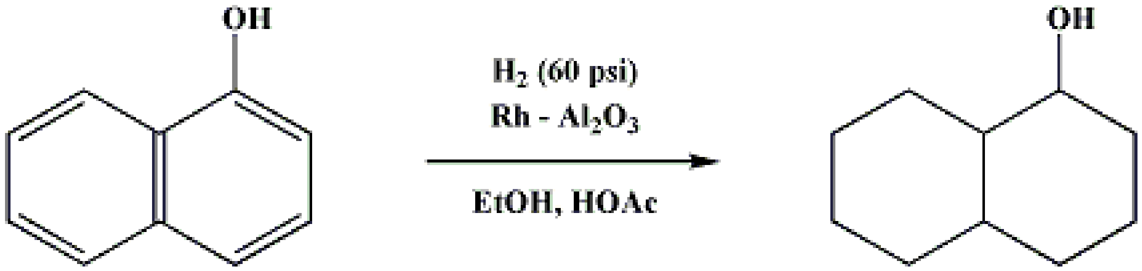
Organic Syntheses, *CV 6*, *371*

HYDROGENATION OF AROMATIC NUCLEI: 1-DECALOL



Submitted by A. I. Meyers[1], W. N. Beverung, and R. Gault[2].
Checked by P. Freidenreich and R. Breslow.

1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A 500 ml., Parr hydrogenation bottle is flushed with nitrogen, and 20.0 g. of 5% rhodium-on-alumina (Note 1) is weighed directly into the hydrogenation bottle. The catalyst is wet by cautiously adding 25 ml. of 95% ethanol, and a solution of 40.0 g. (0.278 mole) of 1-naphthol (Note 2) in 125 ml. of 95% ethanol is added to the bottle, along with 3 ml. of acetic acid. The mixture is shaken in a Parr apparatus (Note 3) at an initial pressure of 55–60 p.s.i. of hydrogen. The theoretical hydrogen absorption is reached in about 12 hours (Note 4). The catalyst is removed by suction filtration and washed twice with 50-ml. portions of ethanol (Note 5). The combined ethanol solutions are concentrated with a rotary evaporator, yielding a viscous residue (39–41 g.), which is dissolved in 150 ml. of benzene. The solution is washed with 75 ml. of 10% sodium hydroxide solution, then with 75 ml. of water, dried over magnesium sulfate for at least 3 hours, and concentrated with a rotary evaporator, giving 39–41 g. (94–97%) of a mixture[3] consisting of the geometrical isomers of 1-decalol. *cis,cis*-1-Decalol may be isolated as a crystalline solid from the mixture by the addition of 15–20 ml. of heptane, followed by cooling. The product is isolated by filtration and recrystallized from a minimum amount of *n*-heptane, yielding 13–14 g. (30–33%) of *cis,cis*-1-decalol, m.p.[4] 92–93°.

2. Notes

1. The catalyst is available from Engelhard Industries.
2. A purified grade of 1-naphthol should be used. Material available from

Eastman Organic Chemicals, Aldrich Chemical Company, Inc., and Matheson, Coleman and Bell is satisfactory. Experiments with technical grade 1-naphthol have indicated that this material requires purification by sublimation in order to give satisfactory results.

3. It has been found that the rhodium catalyst is not nearly as sensitive to poisoning as platinum or palladium catalyst. The metal inlet tube to the reaction bottle was merely rinsed with acetone, followed by ethanol, and the rubber stopper was soaked in 30–40% sodium hydroxide solution overnight.

4. A variety of experiments have shown that for bicyclic aromatic nuclei the weight ratio of reactant to catalyst should be 2:1, whereas for monocyclic aromatic nuclei, the reactant to catalyst ratio should be 3:1. For the latter systems, hydrogen absorption is usually complete within 6–8 hours (see Discussion section).

5. The catalyst may be reused after washing thoroughly with ethanol and drying at 125° for 12–15 hours. The activity, however, is somewhat decreased. *Care should be exercised to never leave the catalyst exposed to air in the presence of a flammable solvent.*

3. Discussion

1-Naphthol has been reduced to 1-decalol using platinum,[4] Raney nickel,[5] and Raney copper.[6] The reactions catalyzed by nickel and copper required elevated temperatures and pressure. The present procedure allows the preparation of substantial quantities of 1-decalol under much more convenient conditions and shorter reaction times. Previous methods[4,5,6] require costly catalysts or high-pressure equipment and frequently result in a high degree of hydrogenolysis. The submitters have found that the present method is applicable to a wide variety of aromatic nuclei, some of which are listed in Table I.

TABLE I
HYDROGENATION OF AROMATIC NUCLEI[a]

Compound	g. Catalyst/g. Reactant	Product	Yield, %
2-Naphthol	0.50	2-Decalol[b]	88
2-Methylbenzofuran	0.33	*cis*-2-Methylhexahydrobenzofuran[c]	94
2,2-Dimethyl-2,3-dihydrobenzofuran	0.33	*cis*-2,2-Dimethylhexahydrobenzofuran[c]	91
3-Hydroxybenzoic acid	0.33	3-Hydroxycyclohexanecarboxylic acid[b]	81
4-Methoxyphenol	0.33	4-Methoxycyclohexanol[b]	88
Hydroquinone	0.33	1,4-Cyclohexanediol[b]	90

Resorcinol	0.33	1,3-Cyclohexanediol[b]	85

[a] From ref. [3 7].

[b] Obtained as mixtures of geometric isomers.

[c] No detectable quantity of the *trans* isomer is obtained.

References and Notes

1. Department of Chemistry, Louisiana State University in New Orleans, New Orleans, Louisiana 70122. [Present address: Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523].
2. Present address: Wayne State University, Detroit, Michigan 48202.
3. A. I. Meyers, W. Beverung, and G. Garcia-Munoz, *J. Org. Chem.*, **29**, 3427 (1964). The discrepancy between the work reported earlier and the present work regarding isomer distribution may be due to variations in catalyst activity. The present reduction mixture consists of four decalol isomers of which the *cis-cis* product represents 50–55% as determined by gas chromatography analysis on a 250-cm. column containing 10% Carbowax 20M on Chromosorb P at 150–200°.
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

rhodium-on-alumina

Raney copper

ethanol (64-17-5)

acetic acid (64-19-7)

Benzene (71-43-2)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

hydroquinone (123-31-9)

nitrogen (7727-37-9)

1-Naphthol (90-15-3)

2-naphthol (135-19-3)

platinum (7440-06-4)

copper (7440-50-8)

nickel, Raney nickel (7440-02-0)

acetone (67-64-1)

palladium (7440-05-3)

resorcinol (108-46-3)

magnesium sulfate (7487-88-9)

heptane, n-heptane (142-82-5)

4-Methoxyphenol (150-76-5)

2-Decalol (825-51-4)

rhodium (7440-16-6)

1-Decalol (529-32-8)

2-Methylbenzofuran (4265-25-2)

2,2-Dimethyl-2,3-dihydrobenzofuran (6337-33-3)

3-Hydroxybenzoic acid (99-06-9)

3-Hydroxycyclohexanecarboxylic acid

4-Methoxycyclohexanol

1,4-Cyclohexanediol (556-48-9)

1,3-Cyclohexanediol (504-01-8)

cis,cis-1-decalol

cis-2-Methylhexahydrobenzofuran

cis-2,2-Dimethylhexahydrobenzofuran

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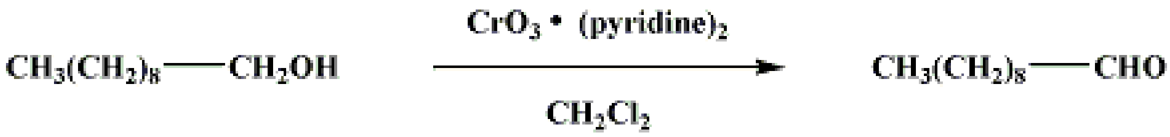
Organic Syntheses, CV 6, 373

OXIDATION WITH THE CHROMIUM TRIOXIDE-PYRIDINE COMPLEX PREPARED *in situ:* 1-DECANAL



Submitted by R. W. Ratcliffe[1]
Checked by Robert J. Newland and Carl R. Johnson.

1. Procedure

A 3-l., three-necked, round-bottomed flask equipped with a stirrer, a thermometer, and a drying tube is charged with 94.9 g. (1.20 moles) of pyridine (Note 1) and 1.5 l. of dichloromethane (Note 2). The solution is stirred with ice-bath cooling to an internal temperature of 5°, and 60.0 g. (0.600 mole) of chromium trioxide (Note 3) is added in one portion. The deep burgundy solution is stirred in the cold for an additional 5 minutes, then allowed to warm to 20° over a period of 60 minutes. A solution of 15.8 g. (0.100 mole) of 1-decanol (Note 4) in 100 ml. of dichloromethane is added rapidly, with immediate separation of a tarry, black deposit. The reaction mixture is stirred for 15 minutes and decanted from the tarry residue, which is washed with three 500-ml. portions of diethyl ether. The combined organic solution is washed successively with three 1-l. portions of ice-cold, aqueous 5% sodium hydroxide, 1 l. of ice-cold, 5% hydrochloric acid, 1 l. of aqueous 5% sodium hydrogen carbonate, and 1 l. of saturated brine. The solution is dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure. The resulting pale yellow liquid is distilled through a 15-cm., vacuum-jacketed Vigreux column (Note 5), yielding 9.8–10.2 g. (63–66%, (Note 6) of 1-decanal, b.p. 96–98° (13 mm.) (Note 7).

2. Notes

1. Anhydrous pyridine was obtained by distillation of reagent grade material from barium oxide and storage over 4A molecular sieves.
2. Dichloromethane was purified by shaking with concentrated sulfuric acid, washing with aqueous sodium hydrogen carbonate and water, drying over anhydrous calcium chloride, and distilling. The purified solvent was stored in the dark over 4A molecular sieves.
3. Chromium trioxide (obtained from J. T. Baker Chemical Company) was stored in a vacuum desiccator over phosphorus pentoxide prior to use. Six-mole equivalents of oxidant is required for rapid, complete conversion to aldehyde. With less than the 6:1 molar ratio, a second, extremely slow oxidation step

occurs (see reference [2]).
4. 1-Decanol was obtained from Aldrich Chemical Company, Inc.
5. Vigorous magnetic stirring of the pot material prevents excessive foaming during the distillation.
6. The submitters obtained 12.9–13.0 g. (83%). The checkers obtained a yield of 66% when all solvent and wash volumes used in the procedure were reduced by 50%.
7. The product was identified through comparison of its IR, ^{1}H NMR, and mass spectra and GC mobility with authentic 1-decanal, available from Aldrich Chemical Company, Inc.

3. Discussion

Dipyridine-chromium(VI) oxide[3] was introduced as an oxidant for the conversion of acid-sensitive alcohols to carbonyl compounds by Poos, Arth, Beyler, and Sarett.[4] The complex, dispersed in pyridine, smoothly converts secondary alcohols to ketones, but oxidations of primary alcohols to aldehydes are capricious.[5] In 1968, Collins, Hess, and Frank found that anhydrous dipyridine-chromium(VI) oxide is moderately soluble in chlorinated hydrocarbons and chose dichloromethane as the solvent.[6] With this modification, primary and secondary alcohols were oxidized to aldehydes and ketones in yields of 87–98%. Subsequently, Dauben, Lorber, and Fullerton showed that dichloromethane solutions of the complex are also useful for accomplishing allylic oxidations.[7]

The chief drawbacks to using the Collins reagent are the nuisance involved in preparing pure dipyridine-chromium(VI) oxide,[7] its hygroscopic nature,[6] and its propensity to inflame during preparation.[3,4,7] The present method avoids these difficulties by simply preparing dichloromethane solutions of the complex directly.[2] In addition, as noted previously,[6] the use of dichloromethane as solvent facilitates isolation of the products. Other modifications of the Collins procedure include the use of a celite-supported reagent which facilitates the isolation of sensitive products[8] and the finding that a 1:1 pyridine-chromium trioxide ratio gives oxidation results[9] comparable with those obtained using the customary 2:1 ratio in the *in situ* procedure.

Several other reagents finding utility for the oxidation of primary and secondary alcohols to the corresponding carbonyl compounds under mild and nonaqueous conditions have been developed in recent years. Of the chromium(VI)-based oxidants, pyridinium chlorochromate[10] in dichloromethane and pyridinium dichromate[11] in *N*,*N*-dimethylformamide or dichloromethane deserve special mention. Both reagents are easily prepared and stored, allow the efficient oxidation of a variety of alcohols using only a modest excess of oxidant, and may be amenable to large-scale operations.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 258

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

brine

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium hydrogen carbonate (144-55-8)

barium oxide

pyridine (110-86-1)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

chromium trioxide (1333-82-0)

dimethylformamide (68-12-2)

1-Decanal (112-31-2)

1-decanol (112-30-1)

pyridinium chlorochromate (26299-14-9)

pyridinium dichromate (20039-37-6)

Dipyridine-chromium(VI) oxide

phosphorus pentoxide (1314-56-3)

pyridine-chromium trioxide

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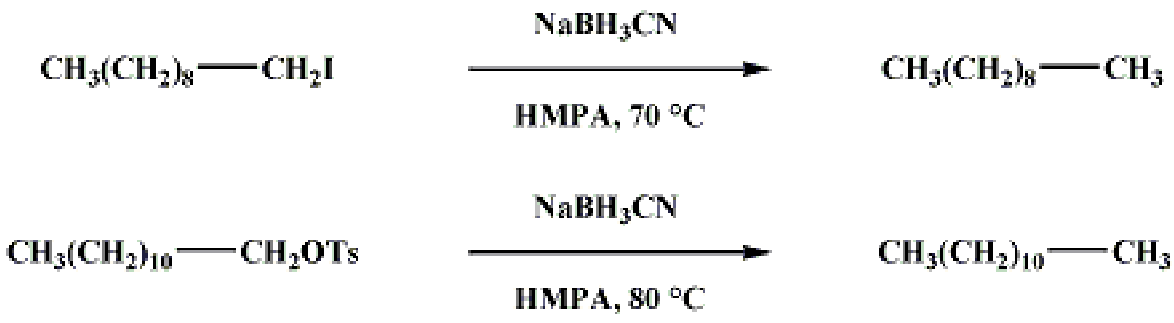
Organic Syntheses, CV 6, 376

REDUCTION OF ALKYL HALIDES AND TOSYLATES WITH SODIUM CYANOBOROHYDRIDE IN HEXAMETHYLPHOSPHORIC TRIAMIDE (HMPA): A. 1-IODODECANE TO *n*-DECANE B. 1-DODECYL TOSYLATE TO *n*-DODECANE



Submitted by Robert O. Hutchins[1], Cynthia A. Milewski, and Bruce E. Maryanoff.
Checked by Ronald I. Trust and Robert E. Ireland.

1. Procedure

Caution! Hexamethylphosphoric triamide (HMPA) vapors have been reported to cause cancer in rats.[2] All operations with hexamethylphosphoric triamide should be performed in a good hood, and care should be taken to keep the liquid off the skin.

A. n-*Decane*. A dry, 100-ml., three-necked flask equipped with a stirring bar, a thermometer, and a condenser protected with a drying tube is charged with 25 ml. of hexamethylphosphoric triamide (HMPA) (Note 1), 1-iododecane (2.7 g., 0.010 mole) (Note 2) and sodium cyanoborohydride (0.943 g., 0.0157 mole) (Note 3). The solution is stirred at 70° for 2 hours, diluted with 25 ml. of water, and extracted with three 30-ml. portions of diethyl ether. The combined extracts are washed twice with water and dried over anhydrous magnesium sulfate. The solvent is removed by distillation on a steam bath through a 12-in. vacuum-jacketed Vigreux column (Note 4). The residue is distilled at reduced pressure in a short-path apparatus *(Caution! foaming)*, yielding 1.25–1.29 g. (88–90%) (Note 5), (Note 6) of *n*-decane, b.p. 68–70° (14 mm.); n_D^{20} 1.4122, n_D^{26} 1.4085 (lit.,[3] n_D^{25} 1.4097 (Note 7).

B. n-*Dodecane*. A dry, 200-ml., three-necked flask equipped exactly as described in Section A is charged with 50 ml. of hexamethylphosphoric triamide (HMPA), 1-dodecyl tosylate (6.80 g., 0.0201 mole) (Note 8), and sodium cyanoborohydride (5.02

g., 0.0797 mole) (Note 3). The solution is stirred at 80° for 12 hours (Note 9), diluted with 50 ml. of water, and extracted with three 60-ml. portions of hexane. The hexane solution is washed twice with water, dried over anhydrous magnesium sulfate, and concentrated with a rotary evaporator. Distillation of the residue through a short-path apparatus (Note 5) *(Caution! foaming)* affords 2.49–2.64 g. (73–78%) of *n*-dodecane, b.p. 79–81°; (3.75 mm.) n_D^{24} 1.4217 (lit.,[4] n_D^{20} 1.4219) (Note 7).

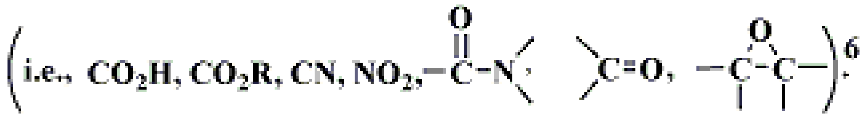
2. Notes

1. Commercial hexamethylphosphoric triamide was distilled from calcium hydride and stored over 13X molecular sieves (Linde).
2. Commercial 1-iododecane (Eastman Organic Chemicals) was filtered through activated charcoal and distilled before use.
3. Sodium cyanoborohydride was used as received from Aldrich Chemical Company, Inc., or Alfa Products, Thiokol/Ventron Division. No purification is necessary. Tan or brown material may be purified by the method of Purcell[5] or of Borch.[5]
4. If a hexane workup is used, and the solvent is removed with a rotary evaporator, considerable loss of product results from codistillation with the hexane. This should not present a significant problem when higher boiling materials are produced.
5. The condenser was cooled with an ethylene glycol–water mixture at –5°, and the receiver was cooled to –10° in an ice–salt bath.
6. Considerable mechanical loss was observed because of inability to distill the last portions of the product at 14 mm. To avoid this problem, the pressure was reduced near the end of the distillation to *ca.* 5 mm. This did not affect the purity of the product ((Note 7)).
7. Both products showed IR and ^{1}H NMR spectra identical to those of authentic samples, and no side products were detected by GC or ^{1}H NMR.
8. Dodecyl tosylate was prepared from 1-dodecanol by the procedure in *Org. Synth.*, **Coll. Vol. 3**, 366 (1955). Crystallization from a dried (magnesium sulfate) solution in light petroleum ether afforded white needles, m.p. 27.5–28.5°.
9. The large excess of sodium cyanoborohydride is recommended for the reduction of tosylates. Use of reduced molar excesses led to substantially lower yields. For example, a 3:1 cyanoborohydride to tosylate ratio afforded less than 60% yield of product at 80° for 5 hours, while a 1.5:1 excess gave only 52% yield at 70° for 8 hours.

3. Discussion

These preparations illustrate the use of sodium cyanoborohydride in hexamethylphosphoric triamide as an effective, selective, and convenient procedure for the reduction of alkyl halides and tosylates, and are essentially the same as

previously described.[6] The very mild reducing ability of sodium cyanoborohydride makes the method particularly valuable when other functional groups are present in the molecule. In addition, alkene side-products are seldom encountered, contrary to the situation with lithium aluminum hydride[7] or sodium borohydride in aqueous diglyme.[8] The combination of sodium borohydride in polar aprotic solvents is also effective for halide and tosylate removal,[9] although it is less selective.



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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

diethyl ether (60-29-7)

1-dodecanol (112-53-8)

ethylene glycol (107-21-1)

magnesium sulfate (7487-88-9)

lithium aluminum hydride (16853-85-3)

hexane (110-54-3)

calcium hydride (7789-78-8)

sodium borohydride (16940-66-2)

n-DECANE (124-18-5)

hexamethylphosphoric triamide (680-31-9)

tosylate (104-15-4)

sodium cyanoborohydride (25895-60-7)

cyanoborohydride

1-IODODECANE (2050-77-3)

1-DODECYL TOSYLATE, Dodecyl tosylate (10157-76-3)

n-DODECANE (112-40-3)

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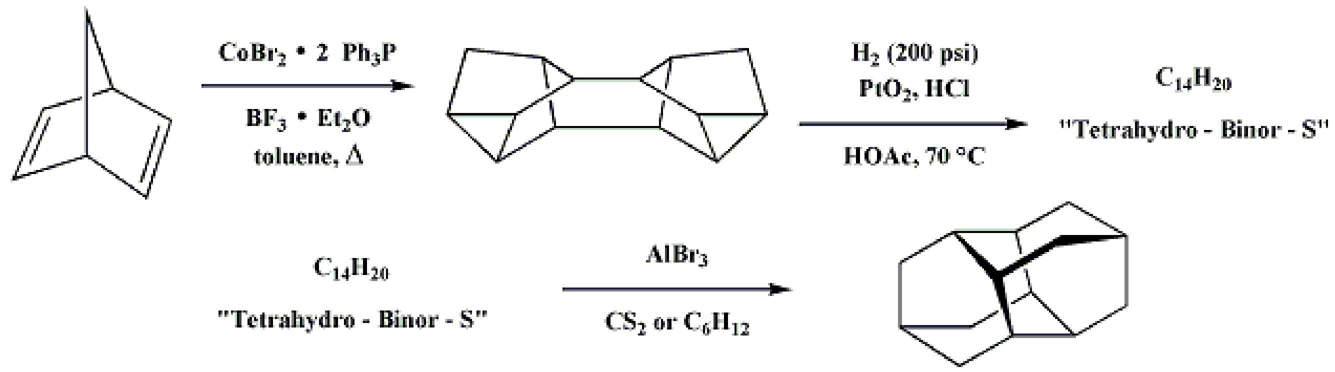
Organic Syntheses, CV 6, 378

DIAMANTANE: PENTACYCLO[7.3.1.1^{4,12}.0^{2,7}.0^{6,11}]TETRADECANE

[Butanetetraylnaphthalene, 3,5,1,7-[1,2,3,4]-decahydro-]



Submitted by Tamara M. Gund, Wilfried Thielecke, and Paul v. R. Schleyer[1].
Checked by H. Gurien, R. Regenye, and A. Brossi.

1. Procedure

A. *Binor-S*.[2] A 2-l., three-necked flask equipped with Teflon sleeves (Note 1), a thermometer, a condenser, a dropping funnel, and a mechanical stirrer is flushed with nitrogen and charged with 200 g. (2.18 moles) of freshly distilled norbornadiene (Note 2), 400 ml. of dry toluene, and 7.8 g. of cobalt bromide–triphenylphosphine catalyst (Note 3). While stirring at room temperature, 2.1 ml. of boron trifluoride diethyl etherate co-catalyst (Note 4) is added dropwise. The mixture is heated slowly to 105°, and the heating mantle is lowered. The ensuing exothermic reaction maintains the temperature at 105–110° for 15 minutes. When the temperature begins to fall, the mantle is raised, the mixture is brought to the reflux temperature, and stirring and refluxing are continued for 12 hours. The cooled mixture is diluted with 650 ml. of dichloromethane, transferred to a separatory funnel, and washed with three 650-ml. portions of water. The organic phase is dried over anhydrous magnesium sulfate, and the solvents are evaporated at reduced pressure. The residual crude material, 185–203 g., is distilled at 106–107° (1.5 mm.), giving 165–170 g. (82–85%) of Binor-S, which solidifies on cooling to a white solid, m.p. 59–63°.

B. *Tetrahydro-Binor-S*. Binor-S (135.0 g., 0.734 mole) is dissolved in 670 ml. of glacial acetic acid containing 5.7 ml. of concentrated hydrochloric acid. To this solution is added 1.0 g. of platinum oxide catalyst. The reaction mixture is hydrogenated at 200 p.s.i. hydrogen pressure and 70° for 3 hours, using a 1200-ml., glass-lined autoclave (Note 5). After cooling to room temperature, the catalyst is removed with suction filtration, and water (*ca.* 1.5 l.) is added to the filtrate until two layers form. The bottom layer, containing only tetrahydro-Binor-S, is removed, and the top layer, consisting of a mixture of acetic acid and water, is extracted with one 400 ml. and two 100-ml. portions of dichloromethane. The combined dichloromethane–tetrahydro-Binor-S layers are washed twice with 100 ml. of water, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residual tetrahydro-Binor-S is purified by distillation under reduced pressure, b.p. 105–110° (1.5 mm.), giving 125–130 g. (90–94%) of colorless liquid (Note 6).

C. *Diamantane*. A 500-ml., three-necked flask, equipped with a reflux condenser, a drying tube, a magnetic stirring bar, and a dropping funnel is charged with 28 g. (0.11 mole) of fresh aluminum bromide and 100 ml. of cyclohexane (Note 7). The apparatus is flushed with hydrogen bromide gas (Note 8). When the aluminum bromide has dissolved, 100 g. (0.532 mole) of hydrogenated Binor-S is added dropwise to the rapidly stirred solution, and the reaction mixture refluxes for a short time without external heat. The course of the reaction is monitored by GC until no starting material remains (Note 9). Occasionally, an additional 5 g. portion of aluminum bromide, and application of external heat are needed to complete the reaction. The total reaction time is about 2–3 hours (Note 10). The hot cyclohexane layer is carefully decanted, and the aluminum bromide layer is extracted with five 200-ml. portions of hot cyclohexane. Diethyl ether (400 ml.) is added to the cooled cyclohexane extracts (Note 11), and the combined solvent fractions are washed with two 100-ml. portions of water and dried over anhydrous magnesium sulfate. Evaporation of the solvent leaves a semi-solid residue, which is partially dissolved in about 100 ml. of pentane. The undissolved white solid, diamantane, is collected by suction filtration. Additional diamantane is obtained by concentrating the pentane solution to a small volume and collecting the solid that precipitates. The total amount of diamantane obtained, after drying, is

60–62 g. (60–62%), m.p. 240–241° (closed tube) (Note 12). This product is sufficiently pure for most purposes, but it may be purified further by recrystallization from pentane, giving white crystals, m.p. 244.0–245.4°.

2. Notes

1. Teflon sleeves were used to keep the joints from freezing.
2. Once distilled, norbornadiene may be stored below 0°. Samples as old as 2 weeks were used successfully.
3. This catalyst[3] is prepared in quantitative yield by refluxing by 200 ml. benzene solution containing 10 g. (0.046 mole) of anhydrous cobalt dibromide and 24.4 g. (0.0931 mole) of triphenylphosphine. A color change is observed, and the blue-green solid that precipitates on cooling to room temperature is filtered and dried. This catalyst, stored in a dry atmosphere, appears to be active indefinitely.
4. Boron trifluoride etherate may be used without prior distillation only if fresh material is available. Care must be taken with this reagent because of fuming. The dimerization does not proceed without this co-catalyst.
5. At 70° Binor-S remains in solution, and the uptake of hydrogen is rapid. The checkers have observed that occasionally hydrogen uptake is incomplete, and an additional 1 g. of catalyst must be added to complete the absorption of hydrogen. The submitters carried out the hydrogenation in a large-scale Parr apparatus under three atmospheres of pressure with similar results.
6. After a small solvent-containing forefraction, which is discarded, essentially all of the material should distill in the indicated range, but occasionally material boiling as high as 130° (1.5 mm.) is obtained. This is included in the product.
7. Either carbon disulfide or cyclohexane may be used with comparable yields. The advantage of carbon disulfide is the greater solubility of diamantane. When extracting with cyclohexane, a boiling solution must be used to increase solubility. However, cyclohexane is less poisonous, does not have a foul odor, and gives a whiter product. Therefore, the use of carbon disulfide was not examined by the checkers. Use of dichloromethane has been reported[2] to lead to an 82% yield.
8. Flushing the apparatus with hydrogen bromide may not be necessary, especially for small-scale runs.
9. A Carbowax 20M or 1500 GC column at a temperature of 180° may be used. Diamantane has a shorter retention time than tetrahydro-Binor-S. The checkers used a 10% OV101 GCQ column, 100/120, at 200°; retention times are Binor-S, 11.5 minutes; tetrahydro-Binor-S, 7.6 minutes; diamantane, 6.2 minutes.
10. About 30 minutes after the addition of tetrahydro-Binor-S is complete, the reaction mixture begins to cool and external heat must be supplied to continue the refluxing and complete the reaction. If GC monitoring reveals that the rearrangement is proceeding slowly, an additional 0.5 g. of aluminum bromide is added and refluxing is continued until all the starting material is converted to product.
11. Addition of ether prevents crystallization of the diamantane from cooled cyclohexane.
12. The material obtained is pure by GC and ^{1}H NMR. The ^{1}H NMR spectrum of diamantane shows only a singlet at δ 1.68 ($CDCl_3$).[4] The pentane mother liquors contain a by-product. A comparable yield can be obtained using aluminum chloride in boiling dichloromethane, and the crude mixture at the end of the reaction need not, in some instances, be worked up before subsequent functionalization reactions are carried out.[2,5]

3. Discussion

Like adamantane,[6] diamantane (also known as congressane[4]), the second member of the diamond family, may also be prepared by aluminum halide-catalyzed isomerization. A variety of starting materials have been shown to give diamantane,[2,4,7,8] but the very best results are obtained by the present procedure[2,8] starting with Binor-S.[2,3,9] Diamantane may be converted to a variety of functionalized derivatives.[2,5,10,11] 4-Methyldiamantane may also be prepared by rearrangement.[10] The mechanisms of these transformations have been analyzed.[12]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Diamantane

Binor-S

Tetrahydro-BINOR-S

DIAMANTANE: PENTACYCLO[7.3.1.1^{4,12}.0^{2,7}.0^{6,11}]TETRADECANE

congressane

4-Methyldiamantane

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

ether, diethyl ether (60-29-7)

hydrogen (1333-74-0)

hydrogen bromide (10035-10-6)

nitrogen (7727-37-9)

platinum oxide

cyclohexane (110-82-7)

aluminum chloride (3495-54-3)

toluene (108-88-3)

carbon disulfide (75-15-0)

Pentane (109-66-0)

aluminum bromide

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

boron trifluoride etherate, boron trifluoride diethyl etherate (109-63-7)

Adamantane (281-23-2)

norbornadiene

triphenylphosphine (603-35-0)

Butanetetraylnaphthalene, 3,5,1,7-[1,2,3,4]-decahydro-

cobalt dibromide, cobalt bromide (7789-43-7)

PENTACYCLO[7.3.1.1^{4,12}.0^{2,7}.0^{6,11}]TETRADECANE

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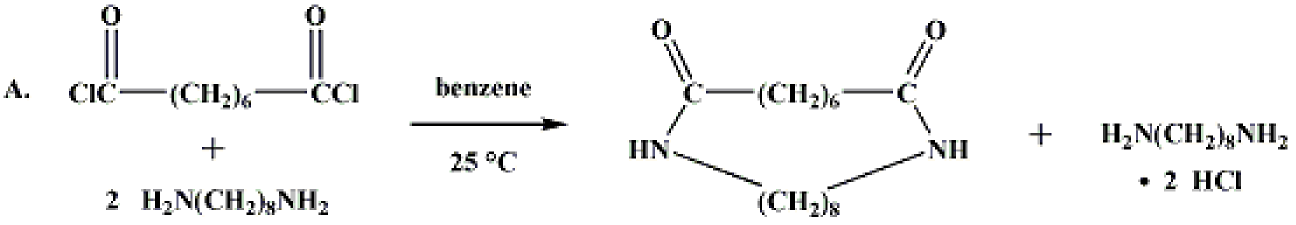
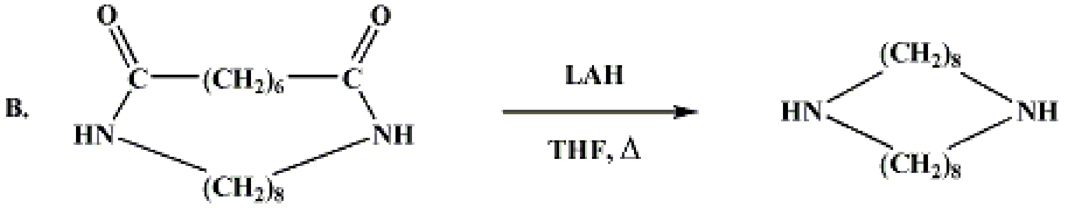
MACROCYCLIC DIIMINES: 1,10-DIAZACYCLOÖCTADECANE





Submitted by Chung Ho Park and Howard E. Simmons[1].
Checked by Stephen R. Wilson and Robert E. Ireland.

1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A. *1,10-Diazacycloöctadecane-2,9-dione*. A 12-l., 4-necked, round-bottomed flask with four indents is fitted with a mechanical stirrer, two dropping funnels (Note 1), and an inlet tube to maintain a static nitrogen atmosphere throughout the reaction. Four liters of benzene (Note 2) are placed in the flask and stirred vigorously. Two solutions, one of 33.8 g. (0.160 mole) of suberyl dichloride (Note 3) in 2.0 l. of benzene and the other of 48.2 g. (0.335 mole) of 1,8-diaminoöctane (Note 4) in 2.0 l. of benzene, are added simultaneously over a 6–7 hour period at room temperature. After the addition is complete, the resulting suspension is stirred slowly overnight. The addition funnels are removed from the flask and replaced by stoppers fitted with tubes of suitable dimensions to permit the reaction mixture to be siphoned from the reaction flask when a slight positive nitrogen pressure is present in the flask. The fine suspension in the reaction flask is agitated and siphoned into a large, fritted, filter funnel. The white solid is washed three times with benzene and dried in a vacuum oven. The resulting white solid is pulverized, placed in a continuous extractor (Note 5), and extracted for three days with 1 l. of boiling benzene in a 2-l., round-bottomed flask equipped with a magnetic stirring bar and heating mantle. After the extractor is allowed to cool to room temperature, filtration of the white solid suspension gives 23.1–23.6 g. (51–52%) of crude 1,10-diazacycloöctadecane-2,9-dione, m.p. 198–201°, which is used in the subsequent step without further purification (Note 6).

B. *1,10-Diazacycloöctadecane*. A 500-ml., round-bottomed flask equipped with a mechanical stirrer, condenser, and nitrogen bubbler is charged with 150 ml. of dry tetrahydrofuran (Note 7) and 3.8 g. (0.10 mole; 33% excess) of lithium aluminum hydride. While the suspension is stirred, 14.1 g. (0.0500 mole) of 1,10-diazacycloöctadecane-2,9-dione is added in small portions through a Gooch tube (Note 8). When the addition is complete and evolution of hydrogen subsides, the mixture is heated at reflux under a nitrogen atmosphere for 48 hours. The mixture is cooled to 5–10° with an ice bath and

decomposed by cautious, dropwise addition of 3.8 ml. of water, followed by 3.8 ml. of 15% sodium hydroxide, and finally by 11.8 ml. of water. The mixture is allowed to come to room temperature, stirred for an additional hour, and filtered through a fritted-glass funnel. The resulting cake is washed thoroughly with three 50-ml. portions of tetrahydrofuran, followed by three 50-ml. portions of diethyl ether. The combined filtrate is concentrated under reduced pressure. After purging with benzene to remove traces of water and storing under vacuum overnight, 12.7 g. of crude diimine remains as a colorless, waxy solid.

The crude product contains a small amount of unreduced dilactam, which can be detected in the IR spectrum. Treatment of the crude diimine again under the identical reduction conditions (Note 9) using the same amounts of the reagent and solvent gives 10.6 g. (83%) of product. Distillation under reduced pressure through a semimicro Vigreux column (10-cm.) yields 9.5 g. (75%) of pure 1,10-diazacycloöctadecane, b.p. 120–130° (0.05 mm.), m.p. 59–61° (Note 10).

2. Notes

1. Two graduated, 500-ml., pressure-equalizing dropping funnels with small diameter tips to allow solutions to be added in fine streams were used. They were equipped with screw-in type plungers with Teflon® fluorocarbon tips to allow fine adjustment of the flow rates. The checkers utilized standard, 500-ml. dropping funnels and two needle valve adapters, as shown in f. htmigure 1. It is important that the two solutions are added at the same slow rate. The submitters report that mixing of the two solutions in one portion halved the yield of the dilactam.

Figure 1.

Figure 1.

2. All of the benzene used was dried over sodium wire and distilled from sodium under a nitrogen atmosphere.
3. Suberyl dichloride purchased from Frinton Laboratories was used without further purification. The purity of the acid chloride was checked by GC after converting it to the diethyl ester.
4. 1,8-Diaminoöctane was purchased from Columbia Organic Chemicals Co., Inc. The purity was checked by GC and varied from batch to batch; only samples which were shown to be homogeneous were used. The diamine should be handled in an inert atmosphere, as it forms a carbonate rapidly.
5. A 2-l. extractor with a fritted disc with an 85 mm. diameter and coarse porosity was used (f. htmigure 2).

Figure 2.

Figure 2.

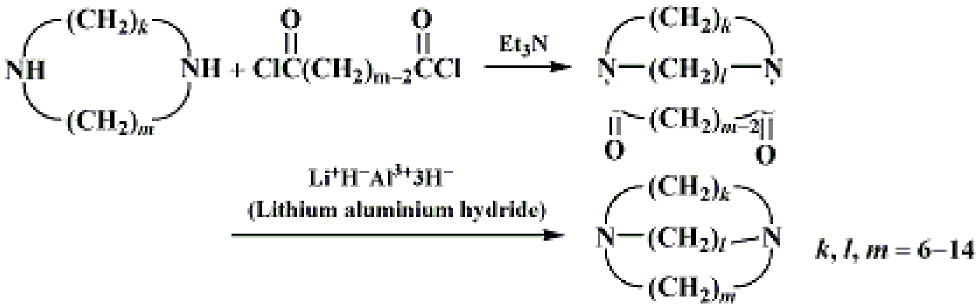
The desired product is only slightly soluble in benzene. Depending on the efficiency of extraction, this step may be extended to longer periods with beneficial results. A lower yield of the dilactam generally indicates incomplete extraction. An attempt to isolate the product by washing away the dihydrochloride from the solid mixture with water resulted in the formation of an emulsion.
6. A sample of the crude dilactam dissolved in an ethanol–water mixture gave no precipitate with silver nitrate, indicating that the product is not contaminated with octamethylenediamine dihydrochloride. If the purity is questionable, the crude product can be conveniently purified at this point by recrystallization from *N,N*-dimethylformamide or 50% ethanol in water, giving better than 90% recovery of pure product, m.p. 207–209°.
7. Commercially available tetrahydrofuran was distilled from $LiAlH_4$ prior to use.
8. The submitters suggest that on ten times this scale, the reaction flask be purged with a stream

of nitrogen during the addition of amide.
9. The repeated treatment with lithium aluminum hydride was necessary to obtain complete reduction, since use of the reducing agent in manyfold excess and longer reaction times failed to accomplish complete reduction in one step. If the product was purified by distillation without the second reduction, the yield of pure diimine was 9.1 g. (71%). The submitters report that on ten times the scale the yield with one reduction was 81 g. (64%).
10. The product obtained is analytically pure, and the submitters claim it is suitable for polymerization. It is also shown to be homogeneous by GC.

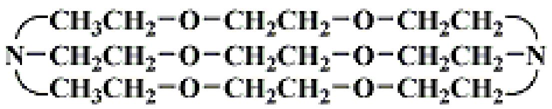
3. Discussion

1,10-Diazacycloöctadecane has also been prepared by another general method which involves reaction of 1,8-dibromoöctane and *N,N'*-ditosyl-1,8-octanediamine with potassium carbonate as base, followed by cleavage of the sulfonamide groups;[2] the yield, however, is not as good as that by the present method. The present procedure is essentially a scale-up of the general method used by Stetter and Marx[3] for preparing a series of macrocyclic diimines of 10- to 21-membered rings, with a 25–78% yield for the crucial cyclization step. The procedure is adaptable for even larger scale preparations, using 5 moles of the acid chloride and a 100-gallon reaction kettle.

The reaction is generally applicable, to further extension, for making macrobicyclic diamines[4] with bridgehead nitrogen atoms by using monocyclic diimines and an appropriate acid chloride. The main difference in the procedures is that triethylamine is used as the hydrogen chloride acceptor in the cyclization step instead of using an extra mole of diimine. Triethylamine hydrochloride does not interfere with purification in this case since the bicyclic diamides are fairly soluble in benzene but insoluble in water. The bicyclic diamides are isolated by first removing triethylamine hydrochloride from the reaction mixture by filtration and water washings, followed by evaporation of the solvent. If triethylamine is used as the base in the preparation of monocyclic dilactams, the products are invariably contaminated with triethylamine hydrochloride, and the yields of the pure products are lower.



The same sequence of reactions are used to prepare macrobicyclic diamines with polyether linkages.[5,6] The reduction of macrobicyclic diamides can be accomplished with diborane using the procedure described by Brown and Heim,[7] but the present procedure is less involved and gives good yields.



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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

potassium carbonate (584-08-7)

hydrogen chloride (7647-01-0)

Benzene (71-43-2)

diethyl ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

silver nitrate (7761-88-8)

nitrogen (7727-37-9)

sodium (13966-32-0)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

N,N-dimethylformamide (68-12-2)

suberyl dichloride (10027-07-3)

triethylamine (121-44-8)

Triethylamine hydrochloride (554-68-7)

fluorocarbon (593-53-3)

octamethylenediamine dihydrochloride

1,10-Diazacyclooctadecane (296-30-0)

1,10-Diazacyclooctadecane-2,9-dione (56369-11-0)

N,N'-ditosyl-1,8-octanediamine

1,8-diaminooctane

1,8-dibromooctane

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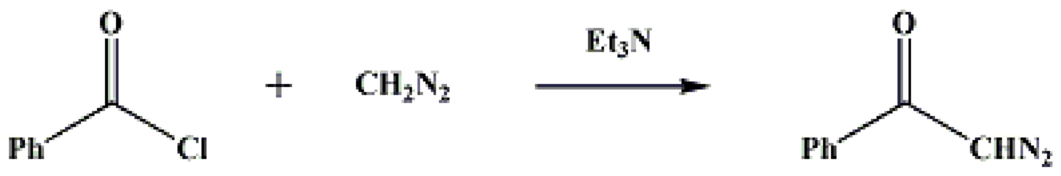
Organic Syntheses, CV 6, 386

DIAZOACETOPHENONE

[Ethanone, 2-diazo-1-phenyl-]



Submitted by John N. Bridson and John Hooz[1].
Checked by Dennis R. Murayama and Ronald Breslow.

1. Procedure

Caution! All operations should be conducted in an efficient fume hood. Diazomethane is hazardous; directions for safe handling are given in Org. Synth., ***Coll. Vol. 4****, 250 (1963);* ***Coll. Vol. 5****, 351 (1973). Diazoacetophenone is a skin irritant and direct contact should be avoided.*

A solution of 0.375 mole of diazomethane in 1 l. of diethyl ether (Note 1) is placed in a 2-l. flask fitted with a large magnetic stirring bar, a two-necked adapter, equipped with a drying tube (containing potassium hydroxide pellets), and a pressure-equalizing dropping funnel. Triethylamine (37.9 g., 52.1 ml., 0.375 mole) (Note 2) is added, and the flask contents are cooled to *ca.* –10° to –5°. A solution of 52.75 g. (43.56 ml., 0.3754 mole) of benzoyl chloride (Note 3) in 300 ml. of dry ether is added to the stirred mixture over a period of 0.5 hour (Note 4). An additional 50 ml. of ether is rinsed through the dropping funnel. Stirring is continued for one hour at approximately 0°, then overnight at room temperature.

The resulting triethylamine hydrochloride precipitate (41.4 g., 81%) is filtered and washed with 100 ml. of dry ether. The solvent is removed from the combined filtrate by rotary evaporation, and the semi-solid residue crystallizes to an orange-red solid after refrigeration for several hours at *ca.* 5°. Crystallization from a mixture of 150 ml. of pentane and 120 ml. of dry ether affords 38.8 g. of diazoacetophenone as yellow square plates, m.p. 44–48°. Concentration of the mother liquor and extraction of the residue with boiling pentane yields an additional 7.8 g. of pale yellow rods, m.p. 47.5–48.5°, bringing the total yield to 46.6 g. (85%) (Note 5) and (Note 6).

2. Notes

1. Diazomethane was prepared by the method in *Org. Synth:*, **Coll. Vol. 5**, 351 (1973), using 10% extra 2-(2-ethoxyethoxy)ethanol and an extra 100 ml. of water over that recommended, to prevent stirring difficulties in the later stages

of the distillation. The ethereal diazomethane solution was dried at 0° over potassium hydroxide pellets, and the concentration was determined by reaction of an aliquot with benzoic acid and analyzing the resulting methyl benzoate by GC.

2. Triethylamine, purchased from J. T. Baker Chemical Company, was refluxed over calcium hydride, then fractionally distilled through a 40-cm. Vigreux column, b.p. 81–82° (700 mm.); b.p. 89.5–90° (760 mm.).

3. Benzoyl chloride, obtained from British Drug House (Canada) Ltd., was purified, as described in *Org. Synth.*, **Coll. Vol. 3**, 112 (1955), by washing a benzene solution with 5% aqueous sodium hydrogen carbonate, drying over calcium chloride, and fractional distillation through a 40-cm. Vigreux column, b. p. 69–71° (12 mm.). The checkers used a fresh bottle, from Matheson, Coleman and Bell, without purification.

4. In the later stages of the addition a cake of crystals forms, preventing adequate stirring. This difficulty is overcome by temporarily interrupting the addition and swirling the flask manually—stirring then continues normally.

5. The submitters obtained a similar yield on twice the scale reported here.

6. Although crystallization from pentane gives better crystals, with an improved melting point range, recrystallization of the whole batch would require approximately 3 l. of solvent. Samples obtained from both ether-pentane and pentane evolve the theoretical amount of nitrogen on titration with 3 *N* hydrochloric acid.

3. Discussion

Apart from the reaction of diazomethane with benzoyl chloride,[2,3,4] diazoacetophenone has been prepared by the reaction of 2-aminoacetophenone hydrochloride with sodium nitrite,[5] from the mixed anhydride of benzoic acid and ethyl carbonate with diazomethane,[6] from benzoyl chloride and potassium methyldiazotate,[7] by treating the enamine formed from 2-formylacetophenone and *N*-methylaniline with *p*-toluenesulfonyl azide,[8] and from the reaction of the sodium enolate of 2-formylacetophenone with *p*-toluenesulfonyl azide.[9]

The reaction of an acid chloride with diazomethane illustrates a general method of preparing diazoketones. The acid chloride is slowly added to at least two equivalents of diazomethane; the hydrogen chloride liberated (Eq. 1) is then consumed according to Eq. 2. When the order of addition is reversed (*e.g.*, acid chloride is in excess) and only 1 mole of diazomethane is employed, the diazoketone reacts with hydrogen chloride, forming the α-chloroketone (Eq. 3).

$$RCOCl + CH_2N_2 \longrightarrow RCOCHN_2 + HCl$$

$$CH_2N_2 + HCl \longrightarrow CH_3Cl + N_2$$

$$RCOCHN_2 + HCl \longrightarrow RCOCH_2Cl + N_2$$

The method described here, discovered independently by Newman and Beal,[3] and Berenbom and Fones,[4] employs triethylamine (1 equivalent) to react with the hydrogen chloride; thus, only one equivalent of diazomethane is necessary. This modification was originally restricted to the use of either aromatic- or aliphatic acid chlorides lacking α-hydrogen atoms. Acid chlorides bearing α-hydrogens produce a mixture of products, presumably due to competing ketene formation and subsequent side reactions.

More recently it has been shown that, by operating at lower temperatures (–78°C), even simple aliphatic acid chlorides may also be successfully employed.[10] Some examples are the preparation of $C_6H_5CH_2CH_2COCHN_2$ (96%), *cyclo*-$C_6H_{11}COCHN_2$ (96%), $CH_3(CH_2)_7COCHN_2$ (96%), and $(CH_3)_2CHCOCHN_2$ (96%). However, this low temperature procedure is inapplicable to substrates with especially acidic α-hydrogens, such as phenylacetyl chloride, presumably due to competing ketene formation.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 919
- Org. Syn. Coll. Vol. 7, 438

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

potassium methyldiazotate

sodium enolate of 2-formylacetophenone

calcium chloride (10043-52-4)

hydrogen chloride, hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether, diethyl ether (60-29-7)

sodium hydrogen carbonate (144-55-8)

nitrogen (7727-37-9)

sodium nitrite (7632-00-0)

Benzoic acid (65-85-0)

benzoyl chloride (98-88-4)

potassium hydroxide (1310-58-3)

methyl benzoate (93-58-3)

Pentane (109-66-0)

Ketene (463-51-4)

phenylacetyl chloride (103-80-0)

Diazomethane (334-88-3)

ethyl carbonate

N-Methylaniline (100-61-8)

triethylamine (121-44-8)

Triethylamine hydrochloride (554-68-7)

calcium hydride (7789-78-8)

Diazoacetophenone, Ethanone, 2-diazo-1-phenyl- (3282-32-4)

2-(2-ethoxyethoxy)ethanol (111-90-0)

2-aminoacetophenone hydrochloride (5468-37-1)

2-formylacetophenone

p-toluenesulfonyl azide (941-55-9)

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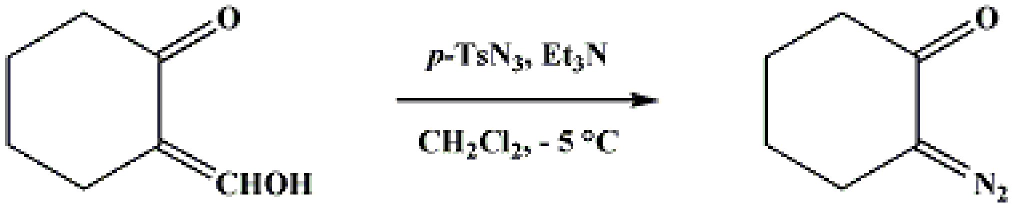
Organic Syntheses, *CV 6*, *389*

2-DIAZOCYCLOALKANONES: 2-DIAZOCYCLOHEXANONE

[Cyclohexanone, 2-diazo-]



Submitted by Manfred Regitz[1], Jörn Rüter, and Annemarie Liedhegener.
Checked by John D. Fenwick and Peter Yates.

1. Procedure

Caution! 2-Diazocyclohexanone may explode, especially on being heated. The workup and distillation should be carried out in a fume hood behind a safety shield.

A. 2-l., wide-necked Erlenmeyer flask is charged with 66.2 g. (0.525 mole) of 2-(hydroxymethylene)cyclohexanone (Note 1), 400 ml. of dichloromethane, and 106 g. (1.05 moles) of triethylamine (Note 2). The flask is cooled in an ice–salt bath at −12 to −15°, and 98.0 g. (0.500 mole) of *p*-toluenesulfonyl azide (Note 3) is added with vigorous mechanical stirring over a period of approximately 1 hour, at such a rate that the temperature of the reaction mixture does not rise above −5°. Stirring is continued for an additional 2 hours as the cooling bath melts. A solution of 30.8 g. (0.550 mole) of potassium hydroxide in 400 ml. of water is added, and the mixture is stirred for 15 minutes at room temperature. The resulting emulsion is placed in a 2-l. separatory funnel, the dichloromethane layer is separated after the emulsion has broken, and the aqueous, alcoholic layer is washed with two 100-ml. portions of dichloromethane. The combined dichloromethane solutions are washed with a solution of 2.8 g. of potassium hydroxide in 200 ml. of water, then with 200 ml. of water, and dried over anhydrous sodium sulfate (Note 4). The solvent is removed on a rotary evaporator at 35° (15 mm.) until the weight of the residue is constant, yielding 51.5–59.0 g. (83–95%) of yellow-orange 2-diazocyclohexanone (Note 5). Distillation with magnetic stirring (Note 6) of 20 g. of this crude product from a hot-water bath at 80° gave 17.0 g. of yellow-orange liquid, b.p. 46° (0.1 mm.) or 60° (0.4 mm.) (Note 7). The IR spectrum (liquid film) has a strong band at 2083 cm.$^{-1}$ attributable to the diazo function.

2. Notes

1. 2-(Hydroxymethylene)cyclohexanone was prepared from cyclohexanone

[*Org. Synth.*, **Coll. Vol. 4**, 536 (1963)] and was freshly distilled before use.
2. Freshly distilled; b.p. 88.5–90.5°.
3. *p*-Toluenesulfonyl azide was prepared from *p*-toluenesulfonyl chloride and sodium azide [*Org. Synth.*, **Coll. Vol. 5**, 179 (1973)]. The submitters found that when somewhat less than the stoichiometric quantity of *p*-toluenesulfonyl azide is used, 2-diazocyclohexanone is obtained free of azide; the excess 2-(hydroxymethylene)cyclohexanone is readily removed in the alkaline workup. The crude product obtained by the checkers, however, contained *p*-toluenesulfonyl azide (Note 5).
4. The basic, aqueous solution on acidification with 6 *N* hydrochloric acid gives *N*-formyl-*p*-toluenesulfonamide in almost quantitative yield. Crystallization from benzene gave crystals, m.p. 101–102° (lit.[2] 102–103°).
5. The submitters found that this product gave a single spot by TLC (Note 8), and that it can be used for most preparative purposes without distillation. The checkers found by ^{1}H NMR spectroscopy that the product contained *p*-toluenesulfonyl azide (*ca.* 5%) and triethylamine.
6. If the distillation is carried out with a capillary leak, decomposition of the diazo compound occurs. The checkers found that distillation on a larger scale led to extensive decomposition.
7. The distillation is not carried to completion because of the danger of explosion. It is carried out with the usual safety precautions (safety shield), although no explosion has yet occurred.
8. TLC was carried out on DC-Fertigplatte Merck Kieselgel F_{254} supplied by Firma Merck AG, 61 Darmstadt, Germany. For the solvent system dichloromethane/methanol (97/3) the product has an R_f value of 0.45.

3. Discussion

In addition to previously described syntheses[2,3] by diazo group transfer with deformylation,[4] 2-diazocyclohexanone has been prepared by two variants of this method. In one, the reaction of 2-(hydroxymethylene)cyclohexanone with *p*-toluenesulfonyl azide is carried out in ether/diethylamine, and an enamine is assumed to be formed as an intermediate;[5] in the other, the sodium salt of the hydroxymethylene compound was treated with the lithium salt of *p*-carboxybenzenesulfonyl azide in ether/tetrahydrofuran.[6] Its preparation from 1,2-cyclohexanedione mono-*p*-toluenesulfonylhydrazone was described earlier.[7]

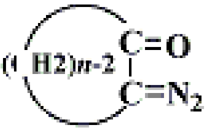
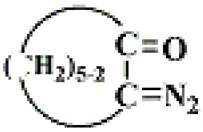
2-Diazocycloalkanones with five- to twelve-membered rings can be synthesized by the present procedure in good yields (Table I).[2] Diazo transfer with deformylation can also be used for the preparation of bicyclic α-diazo ketones.[8,9] A related procedure involving reaction of the sodium salt of an α-(hydroxymethylene) ketone with *p*-toluenesulfonyl azide in ethanol has been applied to the synthesis of diazoalkyl

ketones, α-diazo aldehydes, and α-diazo carboxylic esters.[10]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 197
- Org. Syn. Coll. Vol. 9, 400

TABLE I
PREPARATION OF 2-DIAZOCYCLOALKANONES

	Boiling Point or [Melting Point], °C.	Yield, %
5 	34–37 (0.8 mm.)	98
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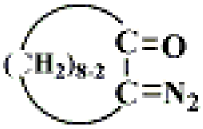
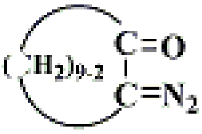
8 	[a]	87
9 	[a]	73

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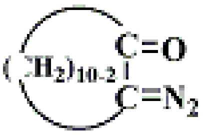	[54–55]	81
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	[b]	79
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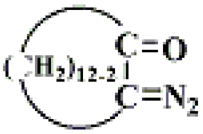	[42–43]	57

[a] Liquid, purified by crystallization from ether at −60°.

[b] Liquid, purified by crystallization from ethanol at −20°.

References and Notes

1. Institut für Organische Chemie der Universität des Saarlandes, 66 Saarbrucken 11, Germany. [Present address: Fachbereich Chemie, Universität Kaiserslautern, 675 Kaiserslautern, Germany.]
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium salt of the hydroxymethylene

2-Diazocycloalkanones

sodium salt of an α-(hydroxymethylene) ketone

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

methanol (67-56-1)

ether (60-29-7)

Cyclohexanone (108-94-1)

sodium sulfate (7757-82-6)

potassium hydroxide (1310-58-3)

diethylamine (109-89-7)

sodium azide (26628-22-8)

dichloromethane (75-09-2)

Tetrahydrofuran (109-99-9)

triethylamine (121-44-8)

2-(hydroxymethylene)cyclohexanone (823-45-0)

p-Toluenesulfonyl chloride (98-59-9)

2-Diazocyclohexanone, Cyclohexanone, 2-diazo- (3242-56-6)

p-toluenesulfonyl azide (941-55-9)

N-formyl-p-toluenesulfonamide

1,2-cyclohexanedione mono-p-toluenesulfonylhydrazone

lithium salt of p-carboxybenzenesulfonyl azide

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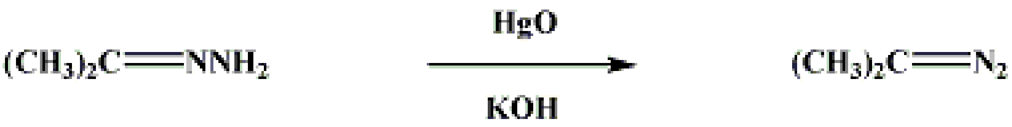
Organic Syntheses, CV 6, 392

2-DIAZOPROPANE

[Propane, 2-diazo-]



Submitted by S. D. Andrews[1], A. C. Day[1], P. Raymond[1], and M. C. Whiting[2].
Checked by G. Swift and W. D. Emmons.

1. Procedure

Caution! 2-Diazopropane is volatile and presumably toxic. All operations should be carried out in an efficient hood behind a protective screen.

A 250-ml., two-necked, round-bottomed flask, placed in a room temperature (*ca.* 20°) water bath, is equipped with a magnetic stirrer, a dropping funnel, and a distillation head carrying a thermometer, and connected *via* an acetone–dry-ice condenser to a receiver cooled to −78° in acetone and dry ice. In the distilling flask are placed 60 g. (0.27 mole) of yellow mercury(II) oxide (Note 1), 100 ml. of diethyl ether (Note 2), and 4.5 ml. of a 3 *M* solution of potassium hydroxide in ethanol (Note 3). The pressure throughout the system is reduced to 250 mm., and with vigorous stirring 15 g. (0.21 mole) of acetone hydrazone (Note 4) is added dropwise through the funnel (Note 5). With continued stirring, the pressure is reduced to 15 mm., and ether and 2-diazopropane co-distill and condense in the receiver (Note 6), yielding 70–90% (Note 7), (Note 8), and (Note 9) of product.

2. Notes

1. Laboratory Reagent yellow mercury(II) oxide purchased from British Drug House was used for most runs. The preparation was not apparently improved by the use of freshly precipitated mercury(II) oxide.
2. The quantity of ether can be varied over a wide range (the submitters have successfully used as little as 60 ml.), and is adjusted to yield the desired concentration of 2-diazopropane in the distillate.
3. A stock solution of potassium hydroxide in ethanol was prepared and stored under nitrogen. Old stocks are brown and contain a dark sediment, but are apparently just as effective as the freshly prepared reagent. Methanolic potassium hydroxide has also been used by the submitters; this remains clear and colorless for long periods but offers no other advantage over the ethanolic solution. In absence of the basic solution, the acetone hydrazone is not oxidized by mercury(II) oxide.

4. *Org. Synth.*, **Coll. Vol. 6**, 161 (1988). Yields are lower if the hydrazone is not freshly redistilled.
5. No special precautions are necessary to keep the reaction mixture cool, since boiling of the ether provides adequate cooling.
6. It is usually unnecessary to dry the distillate, because the water produced in the reaction is largely retained in the distilling flask. That which vaporizes is trapped as ice in the condenser.
7. The solution is *ca.* 2 *M*. Yields were determined by nitrogen evolution on adding acetic acid, or spectrometrically from the visible absorption band at 500 nm, which has ε 2 as calculated from the nitrogen evolution. Yields estimated by addition of a standard solution of benzoic acid and titration with alkali were consistently much lower. Both methods underestimate the yield, since decomposition with acid gives tetramethylethylene and some acetone azine in addition to the 2-propyl ester.[3] The nitrogen evolution method (and therefore the spectrometric method) probably underestimates the yield by *ca.* 10–20%. the titration method by more than 50%.
8. The entire preparation is very rapid (*ca.* 30 minutes) and is easily adaptable to the preparation of larger amounts of 2-diazopropane. Without difficulty, 2–3 *M* solutions can be obtained (see (Note 2)). The solutions are essentially mercury-free.
9. 2-Diazopropane is an unstable material. The decay is first-order with a half-life of 3 hours at 0°.

3. Discussion

This method[4] is an adaptation of that given by Staudinger and Gaule.[5] Highly unstable solutions have been obtained by Applequist and Babad[5] by use of silver oxide in place of mercury(II) oxide.

Contrary to previous reports,[5,6,7] 2-diazopropane, as indicated by the present procedure, is neither difficult to prepare nor unduly unstable. The method may be extended to other secondary aliphatic diazo compounds, which have given difficulty in the past.[8] The success of the method depends on the use of a basic catalyst for the oxidation. The desirability of a basic catalyst has been recognized previously[9,10] and is well illustrated by the contrast between the two preparations of diphenyldiazomethane[10,11] (contrast also refs. [9] and [12]). Miller has speculated on the role of the basic catalyst.[10]

2-Diazopropane is a potential source of *gem*-dimethyl groups. It undergoes 1,3-dipolar addition to acetylenes,[13,14] allenes,[15,16] and olefins,[17] and in all three classes the orientation of addition has been found to be sensitive to steric effects.[14,16,17] The adducts with acetylenes[14,18] and allenes[15,19] give cyclopropenes, and methylenecyclopropanes, respectively, upon photolysis. The adducts with certain

acetylenes bearing an α-leaving group, however, are converted photochemically into allenes and conjugated dienes by an ionic mechanism.[13]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

acetic acid (64-19-7)

ether, diethyl ether (60-29-7)

silver oxide (20667-12-3)

nitrogen (7727-37-9)

Benzoic acid (65-85-0)

mercury(II) oxide (21908-53-2)

acetone (67-64-1)

potassium hydroxide (1310-58-3)

tetramethylethylene (563-79-1)

Diphenyldiazomethane (883-40-9)

Acetone hydrazone (5281-20-9)

Acetone azine (627-70-3)

2-Diazopropane, Propane, 2-diazo- (2684-60-8)

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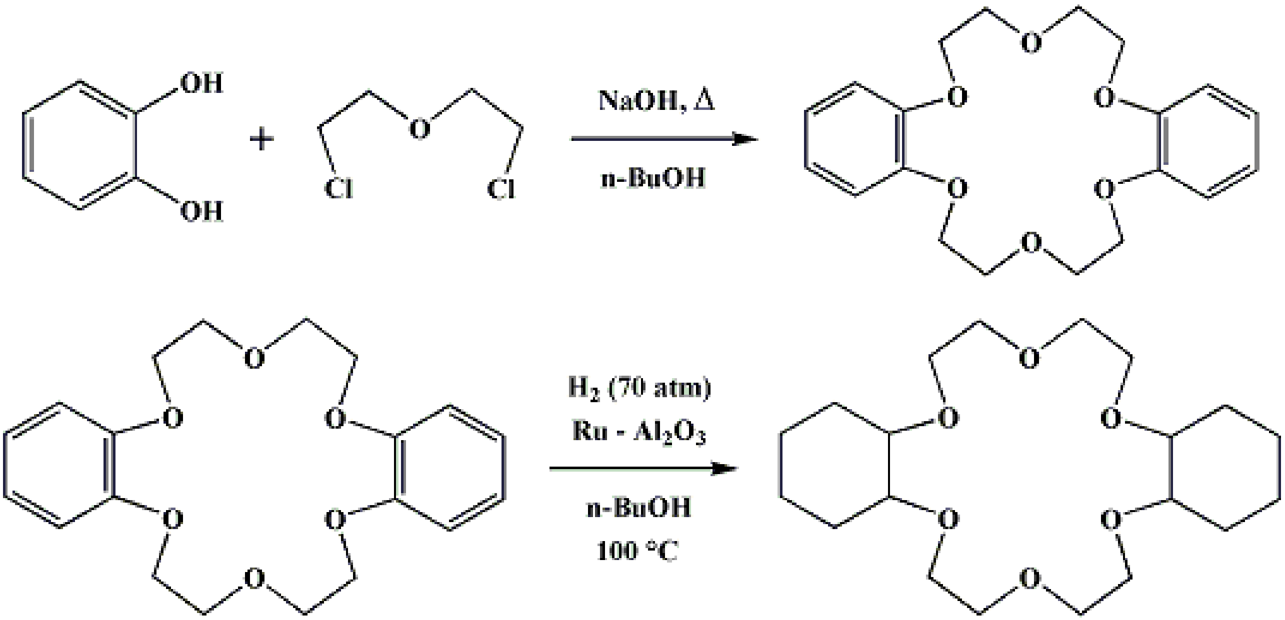
Organic Syntheses, CV 6, 395

MACROCYCLIC POLYETHERS: DIBENZO-18-CROWN-6 POLYETHER AND DICYCLOHEXYL-18-CROWN-6 POLYETHER

[Dibenzo [*b,k*] [1,4,7,10,13,16] hexaoxacycloöctadecin, 6,7,9,10,17,18,20,21-octahydro- and dibenzo [*b,k*] [1,4,7,10,13,16] hexaoxacycloöctadecin, eicosahydro-]



Submitted by Charles J. Pedersen[1]
Checked by Edith Feng and Herbert O. House.

1. Procedure

Caution! The subsequently described macrocyclic polyethers are toxic (Note 1) and should be handled with care.

Benzene has been identified as a carcinogen. OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A. *Dibenzo*-18-*crown*-6 *polyether*. A dry, 5-l., three-necked flask is fitted with a reflux condenser, a 500-ml., pressure-equalizing dropping funnel, a thermometer, and a mechanical stirrer. An inlet tube at the top of the reflux condenser is used to maintain a static nitrogen atmosphere in the reaction vessel throughout the reaction. The flask is charged with 330 g. (3.00 moles) of catechol (Note 2) and 2 l. of commercial *n*-butanol before stirring is started, and 122 g. (3.05 moles) of sodium hydroxide pellets are added. The mixture is heated rapidly to reflux (about 115°), and a solution of 222 g. (1.55 moles) of bis(2-chloroethyl) ether (Note 3) in 150 ml. of *n*-butanol is added, dropwise with continuous stirring and heating, over a 2-hour period. After the resulting mixture has been refluxed with stirring for an additional hour, it is cooled to 90° and an additional 122 g. (3.05 moles) of sodium hydroxide pellets are added. The mixture is refluxed, with stirring, for 30 minutes,

and a solution of 222 g. (1.55 moles) of bis(2-chloroethyl) ether (Note 3) in 150 ml. of *n*-butanol is added, dropwise with stirring and heating, over a period of 2 hours. The final reaction mixture is refluxed, with stirring, for 16 hours (Note 4), then acidified by the dropwise addition of 21 ml. of concentrated hydrochloric acid. The reflux condenser is replaced with a distillation head and approximately 700 ml. of *n*-butanol is distilled from the mixture. As the distillation is continued, water is added to the flask from the dropping funnel at a sufficient rate to maintain a constant volume in the reaction flask. This distillation is continued until the temperature of the distilling vapor exceeds 99° (Note 5), and the resulting slurry is cooled to 30–40°, diluted with 500 ml. of acetone, stirred to coagulate the precipitate, and filtered with suction. The residual crude product is stirred with 2 l. of water, filtered with suction, stirred with 1 l. of acetone, and again filtered with suction. The residual product is washed with an additional 500 ml. of acetone and dried with suction, yielding 221–260 g. (39–48%) of tan, fibrous crystals, m.p. 161–162°, which are sufficiently pure for use in the next step. Dibenzo-18-crown-6 polyether may be recrystallized from benzene, giving white, fibrous needles, m.p. 162.5–163.5° (Note 6).

B. *Dicyclohexyl*-18-*crown*-6 *polyether*. A 1-l., stainless-steel autoclave is charged with a mixture of 125 g. (0.347 mole) of dibenzo-18-crown-6 polyether, 500 ml. of redistilled *n*-butanol (Note 7), and 12.5 g. of 5% ruthenium-on-alumina catalyst (Note 8). After the autoclave has been closed, it is flushed with nitrogen and filled with hydrogen. The mixture is hydrogenated at 100° and a hydrogen pressure of about 70 atm. (1000 p.s.i.) until the theoretical amount of hydrogen (2.08 moles) has been absorbed. The autoclave is cooled to room temperature and vented, and the reaction mixture is filtered to remove the catalyst (Note 9). The filtrate is concentrated at 90–100° with a rotary evaporator (Note 10), and the residual crude product solidifies on standing (Note 11). To remove hydroxylic impurities, a solution of the crude product (about 130 g.) in 400 ml. of *n*-heptane is filtered through a 7-cm. by 20-cm. column of acid-washed alumina (80–100 mesh, activity I–II), and the column is eluted with additional *n*-heptane until the eluate exhibits hydroxyl absorption in the 3300–3400 cm^{-1} region of the IR. The solvent is removed from the combined eluates with a rotary evaporator, leaving 75–89 g. (58–69%) of mixture of diastereoisomeric dicyclohexyl-18-crown-6 polyethers as white prisms, melting within the range 38–54° (Note 12), which may be used to prepare complexes with various metal salts (Note 13) and (Note 14).

2. Notes

1. Dicyclohexyl-18-crown-6 polyether possesses unusual physiological properties which require care in its handling.[2] It is likely that other cyclic polyethers with similar complexing power are also toxic, and should be handled with equal care.
a. *Oral toxicity.* The approximate lethal dose of the dicyclohexyl-18-crown-6 polyether for ingestion by rats was 300 mg./kg. In a 10-day subacute oral test, the compound did not exhibit any cumulative oral toxicity when administered to male rats at a dose level of 60 mg./kg./day. It should be noted that dosage at the approximate lethal dose level caused death in 11 minutes, but that a dose of 200 mg./kg. was not lethal in 14 days.
b. *Eye irritation.* This dicyclohexyl polyether produced some generalized corneal injury, some iritic injury, and conjunctivitis when introduced as a 10% solution in propylene glycol. Although tests are not complete, there may be permanent injury to the eye even if the eye is washed after exposure.
c. *Skin absorption.* Dicyclohexyl-18-crown-6 polyether is very readily absorbed through the skin of test animals. It caused fatality when absorbed at the level of 130 mg./kg.
d. *Skin irritation.* Primary skin irritation tests run on this polyether indicate the material should be considered a very irritating substance.
2. Catechol of satisfactory purity may be purchased from Eastman Organic Chemicals or from Aldrich Chemical Company, Inc.

3. Bis(2-chloroethyl) ether may be obtained from Eastman Organic Chemicals. The checkers redistilled this material (b.p. 175–177°) before use.
4. A shorter period of refluxing may be sufficient.
5. The bulk of the material, a *n*-butanol–water azeotrope, distils at 92°.
6. The product has UV maxima (CH_3OH): 223 nm (ε 17,500) and 275 nm (ε 5500) with ^1H NMR peaks ($CDCl_3$), δ: 3.8–4.3 (m, 16H, 8C*H*$_2$O), 6.8–7.0 (m, 8H, aryl C*H*). The mass spectrum exhibits the following abundant peaks: *m/e* (rel. int.), 360 (M+, 29), 137 (29), 136 (74), 121 (100), 109 (23), 80 (31), 52 (21), 45 (27), and 43 (34).
7. It is advisable to use redistilled solvent to avoid the presence of catalyst poisons.
8. The 5% ruthenium-on-alumina catalyst is available from Engelhard Industries.
9. Since the catalyst, saturated with hydrogen, is pyrophoric, it should be kept wet with water after the filtration has been completed.
10. Since the product, a polyether, is apt to be oxidized by air, especially at elevated temperatures in the molten state, the product should be stored under a nitrogen atmosphere.
11. This residue is a mixture of stereoisomeric dicyclohexyl-18-crown-6 polyethers which may be contaminated with unchanged dibenzo-18-crown-6 polyether and alcohols, arising from hydrogenolysis of the polyether ring. The submitter reports that this residue is sufficiently pure for many purposes such as the preparation of complexes with potassium hydroxide which are soluble in aromatic hydrocarbons.
12. The submitter reports that the two major diastereoisomers present, designated isomer A, m.p. 61–62° and isomer B, as one of two crystalline forms, m.p. 69–70° or m.p. 83–84°, may be separated by chromatography on alumina.[3] An x-ray crystal structure determination for the complex of barium thiocyanate with isomer A of dicyclohexyl-18-crown-6 polyether has shown this polyether to have the *cis-syn-cis* stereochemistry.[4] An x-ray crystal structure determination for the complex of sodium bromide with isomer B has shown this isomer to have the *cis-anti-cis* stereochemistry.[5] The mixture of isomers A and B has negligible UV absorption (95% C_2H_5OH) and exhibits ^1H NMR (C_6D_6) multiplets at δ 0.9–2.2 (16H, aliphatic C*H*) and 3.3–4.0 (20H, OC*H*). The mass spectrum of the mixture exhibits the following relatively abundant peaks: *m/e* (rel. int.), 372 (M+, 2), 187 (35), 143 (100), 141 (47), 99 (92), 98 (46), 97 (41), 89 (66), 87 (41), 83 (45), 82 (55), 81 (99), 73 (77), 72 (46), 69 (58), 67 (42), 57 (50), 55 (58), 45 (77), 43 (61), and 41 (58). Although the IR (CCl_4) and ^1H NMR (C_6D_6, 100 mHz.) spectra of the pure isomers A and B differ slightly from one another, the checkers were unable to use these spectra to determine quantitatively the composition of mixtures of the two isomers. The most notable difference in these spectra is the shape of the ^1H NMR multiplet in the region 3.3–4.0 p.p.m.; this multiplet is considerably broader in isomer A than in isomer B allowing a qualitative estimate of the purity of each isomer.
13. The submitter prepared a toluene solution of the complex of potassium hydroxide with dicyclohexyl-18-crown-6 polyether by the following procedure. A mixture of 14.9 g. (0.0402 mole) of dicyclohexyl-18-crown-6 polyether (mixture of isomers) and 2.64 g. (0.0400 mole) of 85% potassium hydroxide was dissolved in 50 ml. of methanol with gentle warming on a steam bath. The solution was diluted with 100 ml. of toluene and then concentrated with a rotary evaporator to a volume of 50 ml. An additional 100 ml. of toluene was added, and the solution was again concentrated to a volume of 50 ml. This solution was diluted with toluene to a volume of 100 ml., 1 g. of decolorizing charcoal was added, and the mixture was allowed to stand overnight under a nitrogen atmosphere. After gravity filtration, a clear toluene solution of the complex was obtained. Titration with standard hydrochloric acid indicated the solution to be approximately 0.3 *M* in base. This solution, which must be protected from atmospheric moisture and carbon dioxide, has been used for the saponification of sterically hindered esters.[2]

14. The checkers prepared a crystalline complex of potassium acetate with isomer B of dicyclohexyl-18-crown-6 polyether by the following procedure. To a stirred solution of 15.0 g. (0.0404 mole) of dicyclohexyl-18-crown-6 polyether (mixture of isomers) in 50 ml. of methanol was added a solution of 5.88 g. (0.0600 mole) of anhydrous potassium acetate (dried at 100° under reduced pressure) in 35 ml. of methanol. The resulting solution was concentrated with a rotary evaporator, and the residual white solid was extracted with 35 ml. of boiling dichloromethane. The resulting mixture was filtered, and the filtrate was cooled in an acetone–dry-ice bath and slowly diluted with petroleum ether (b.p. 30–60°, approximately 200 ml. was required) to initiate crystallization. The resulting suspension of the crystalline complex was allowed to warm to room temperature and filtered with suction. Recrystallization of this complex from a dichloromethane–petroleum ether (b.p. 30–60°) mixture separated 4.21–4.35 g. (22–23%) of the complex of potassium acetate with isomer B of dicyclohexyl-18-crown-6 polyether as white needles, m.p. 165–250° (dec.). This complex has IR absorption (CH_2Cl_2) at 1570 and 1385 cm.$^{-1}$ (COO^-) with ^{1}H NMR absorption ($CDCl_3$), δ 1.0–2.1 (m, 16H, aliphatic C*H*), 1.95 (s, 3H, CH_3CO), 3.3–4.0 (m, 20H, OC*H*). A 4.21-g. sample of this complex was partitioned between 75 ml. of water and three 25-ml. portions of ether. The combined ether solutions were dried over anhydrous magnesium sulfate and concentrated under reduced pressure, yielding 1.82 g. of isomer B of dicyclohexyl-18-crown-6 polyether as white prisms, m.p. 68–69°.

3. Discussion

The preparation of dibenzo-18-crown-6 polyether directly from catechol and bis(2-chloroethyl) ether has been reported previously.[2] The present procedure is an improvement of this method. Although dibenzo-18-crown-6 polyether can be obtained in 80% yield from bis-[2-(*o*-hydroxyphenoxy)-ethyl] ether and bis(2-chloroethyl) ether, the former intermediate has to be synthesized by a method involving several steps. One of the hydroxyl groups of catechol must be protected against alkali with dihydropyran or chloromethylmethyl ether. The intermediate is treated with bis(2-chloroethyl) ether in the presence of alkali and, finally, converted into the desired intermediate by acid hydrolysis.[2] The yield of bis[2-(*o*-hydroxyphenoxy)-ethyl] ether was less than 40% so that the overall yield of dibenzo-18-crown-6 polyether never approached 39–48%, the yield of the present, direct method.

Dibenzo-24-crown-8 and dibenzo-30-crown-10 polyethers can be prepared by this method with the substitution of the appropriate ω,ω'-dichloropolyether for bis(2-chloroethyl) ether. However, dibenzo-12-crown-4 and macrocyclic polyethers containing two or more benzo groups and an uneven number of oxygen atoms have to be prepared by the alternative method mentioned above, using the intermediate catechol monoethers. Macrocyclic polyethers containing one benzo group can be synthesized by the direct reaction between one molecule of catechol and one molecule of ω, ω'-dichloropolyethers in the presence of alkali. Certain substituted crown compounds can be obtained by using catechol derivatives, such as 4-(*tert*-butyl)-catechol and 4-chlorocatechol, which do not give side reactions in the presence of alkali.

It is unusual to form a ring of eighteen atoms in a single operation by the reaction of catechol with bis(2-chloroethyl) ether. It seems possible that the ring-closure step is facilitated by the presence of sodium ion, which is solvated by the intermediate acyclic polyether. Some experiments appear to support this hypothesis. The yields of dibenzo-18-crown-6 polyether are higher when it is prepared with sodium or potassium hydroxide than when lithium or tetramethylammonium hydroxide is used; lithium and quaternary ammonium ions are not strongly complexed by the polyethers. Furthermore, the best ligands for alkali metal cations, polyethers containing rings of 15 to 24 atoms including 5 to

8 oxygen atoms, are formed in higher yields than smaller or larger rings, or rings of equal sizes with only 4 oxygen atoms.

The physical properties of many macrocyclic polyethers and their salt complexes have been already described.[2,6,7] Dibenzo-18-crown-6 polyether is useful for the preparation of sharp-melting salt complexes. Dicyclohexyl-18-crown-6 polyether has the convenient property of solubilizing sodium and potassium salts in aprotic solvents, as exemplified by the formation of a toluene solution of the potassium hydroxide complex (Note 13). Crystals of potassium permanganate, potassium *tert*-butoxide, and potassium palladium(II) tetrachloride ($PdCl_2$ + KCl) are dissolved in liquid aromatic hydrocarbons merely by adding dicyclohexyl-18-crown-6 polyether.[2] The solubilizing power of the saturated macrocyclic polyethers permits ionic reactions to occur in aprotic media. It is expected that this property will find practical use in catalysis, enhancement of chemical reactivity, separation and recovery of salts, electrochemistry, and analytical chemistry. There are some limitations. Although salts with high lattice energy, such as fluorides, nitrates, sulfates, and carbonates, form complexes with macrocyclic polyethers in alcoholic solvents as readily as more polarizable (softer) salts, their complexes cannot be isolated in the solid state because one or the other uncomplexed component precipitates on concentrating the solutions. For the same reason, these salts cannot be rendered soluble in aprotic solvents by the polyethers.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

sodium or potassium hydroxide

decolorizing charcoal

Dibenzo-18-crown-6 polyether

DICYCLOHEXYL-18-CROWN-6 POLYETHER

ruthenium-on-alumina

dicyclohexyl-18-crown-6 polyethers

polyether

dibenzo-30-crown-10 polyether

ω,ω'-dichloropolyether

ω,ω'-dichloropolyethers

lithium or tetramethylammonium hydroxide

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

methanol (67-56-1)

ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

potassium permanganate (7722-64-7)

sodium bromide (7647-15-6)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

n-butanol (71-36-3)

acetone (67-64-1)

potassium hydroxide (1310-58-3)

toluene (108-88-3)

Catechol (120-80-9)

dichloromethane (75-09-2)

propylene glycol (57-55-6)

magnesium sulfate (7487-88-9)

potassium acetate (127-08-2)

n-heptane (142-82-5)

dihydropyran

bis(2-chloroethyl) ether, chloromethylmethyl ether (111-44-4)

barium thiocyanate

Dibenzo-24-crown-8

dibenzo-12-crown-4

4-chlorocatechol (2138-22-9)

potassium palladium(II) tetrachloride

4-(tert-butyl)-catechol (98-29-3)

potassium tert-butoxide (865-47-4)

bis-[2-(o-hydroxyphenoxy)-ethyl] ether, bis[2-(o-hydroxyphenoxy)-ethyl] ether

Dibenzo [b,k] [1,4,7,10,13,16] hexaoxacyclooctadecin, 6,7,9,10,17,18,20,21-octahydro- (14187-32-7)

dibenzo [b,k] [1,4,7,10,13,16] hexaoxacyclooctadecin, eicosahydro- (16069-36-6)

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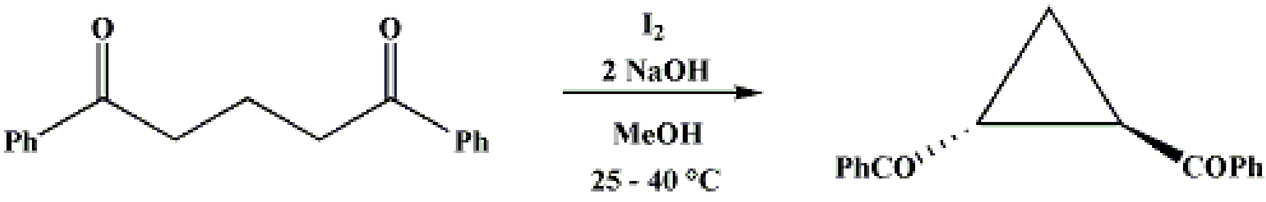
Organic Syntheses, *CV 6*, *401*

1,2-DIAROYLCYCLOPROPANES: *trans*-1,2-DIBENZOYLCYCLOPROPANE

[Methanone, 1,2-cyclopropanediylbis[phenyl]-, *trans*-]



Submitted by Ismael Colon, Gary W. Griffin, and E. J. O'Connell Jr[1].
Checked by Stephen P. Peters and Kenneth B. Wiberg.

1. Procedure

A 1-l., three-necked, round-bottomed flask equipped with a magnetic stirrer and a dropping funnel is charged with 35 g. (0.14 mole) of 1,3-dibenzoylpropane (Note 1) and a solution of 11.2 g. (0.280 mole) of sodium hydroxide in 400 ml. of methanol. The mixture is warmed to 45°, with stirring to dissolve the diketone. It is allowed to cool to 40°, and a solution of 35 g. (0.14 mole) of iodine in 200 ml. of methanol is slowly added to the stirred solution from the dropping funnel (Note 2). After the addition of iodine is completed, the resulting clear solution is stirred at room temperature for 1.5 hours. During this period, a white solid precipitates (Note 3). The mixture is filtered and the filtrate is placed in a round-bottomed flask. The white solid is washed with four, 100-ml. portions of water and dried at 1 mm. at 57° (1 mm.) for 15 hours, yielding 23–25 g. (66–72%) of *trans*-1,2-dibenzoylcyclopropane, m.p. 103–104° (Note 4). Additional material is obtained on evaporation of the filtrate using a rotary evaporator. The pale-red solid residue is treated with 25 ml. of aqueous 10% sodium bisulfite (Note 5), filtered, and dried as above giving 8–9 g. (23–26%) of the product, m.p. 95–98°. Recrystallization from methanol affords greater than 90% recovery of *trans*-1,2-dibenzoylcyclopropane, m.p. 102–103°. For the recrystallization of a 10-g. sample 200 ml. of methanol is used.

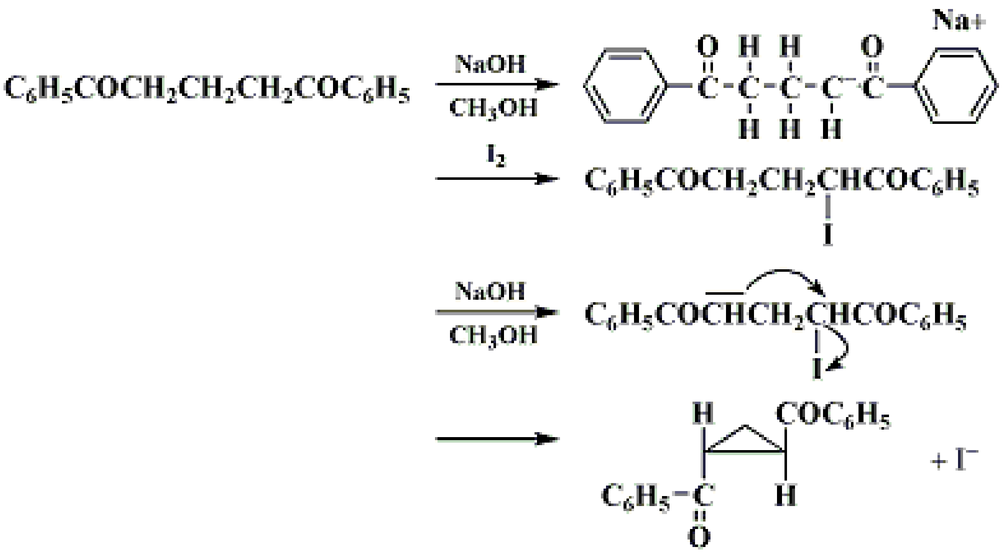
2. Notes

1. 1,3-Dibenzoylpropane was prepared by the method described for 1,4-dibenzoylbutane in *Org. Synth.*, **Coll. Vol. 2**, 169 (1943).
2. The iodine solution is added at a rate such that the color of the iodine is continually discharged by the rapidly stirred solution.
3. In some cases the precipitate may begin to form during the addition of the iodine solution. This has no effect on the yield.
4. Pertinent spectral data include a carbonyl stretching band in the IR at 1665 $cm.^{-1}$ and UV absorption maxima at 245 nm (ε 31,300), 278 nm (ε 2130), and 317 nm (ε 194). The ^{1}H NMR spectrum (CCl_4) has two triplets of equal intensity at δ 3.32 and 1.68 in addition to the aromatic proton bands at δ 7.3–8.2. The integrated peak areas

are in the ratio 1:1:5.
5. Sodium bisulfite solution is added to reduce unchanged iodine.

3. Discussion

1,3-Dibenzoylcyclopropane has been prepared by the method described here[2] and previously by Conant and Lutz.[3] Both procedures use 1,3-dibenzoylpropane as the reactant. The present procedure is accomplished in one step under very mild conditions and in nearly quantitative yield. The method of Conant and Lutz is a two-step process involving initial dibromination of the diketone followed by ring closure with zinc and sodium iodide, with an overall yield of *trans*-1,2-dibenzoylcyclopropane of approximately 15%. The submitters have extended the described method to the preparation of other *trans*-1,2-diaroylcyclopropanes, namely *trans*-1,2-bis(4-methoxybenzoyl)cyclopropane and *trans*-1,2-bis(2-methoxy-5-methylbenzoyl)cyclopropane. In theory the method is applicable to closure of all α,α'-disubstituted propanes having acidic hydrogens on both α-carbons. A probable mechanism for this transformation is as follows:



References and Notes

1. Department of Chemistry, Fairfield University, Fairfield, Connecticut 06430.
2. G. W. Griffin, E. J. O'Connell, and H. A. Hammond, *J. Am. Chem. Soc.*, **83**, 1003 (1963).
3. J. B. Conant and R. E. Lutz, *J. Am. Chem. Soc.*, **49**, 1083 (1927).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

methanol (67-56-1)

sodium hydroxide (1310-73-2)

sodium bisulfite (7631-90-5)

iodine (7553-56-2)

zinc (7440-66-6)

sodium iodide (7681-82-5)

1,4-Dibenzoylbutane (3375-38-0)

1,3-dibenzoylpropane (6263-83-8)

1,3-Dibenzoylcyclopropane

trans-1,2-Dibenzoylcyclopropane, Methanone, 1,2-cyclopropanediylbis[phenyl]-, trans- (38400-84-9)

trans-1,2-bis(4-methoxybenzoyl)cyclopropane

trans-1,2-bis(2-methoxy-5-methylbenzoyl)cyclopropane

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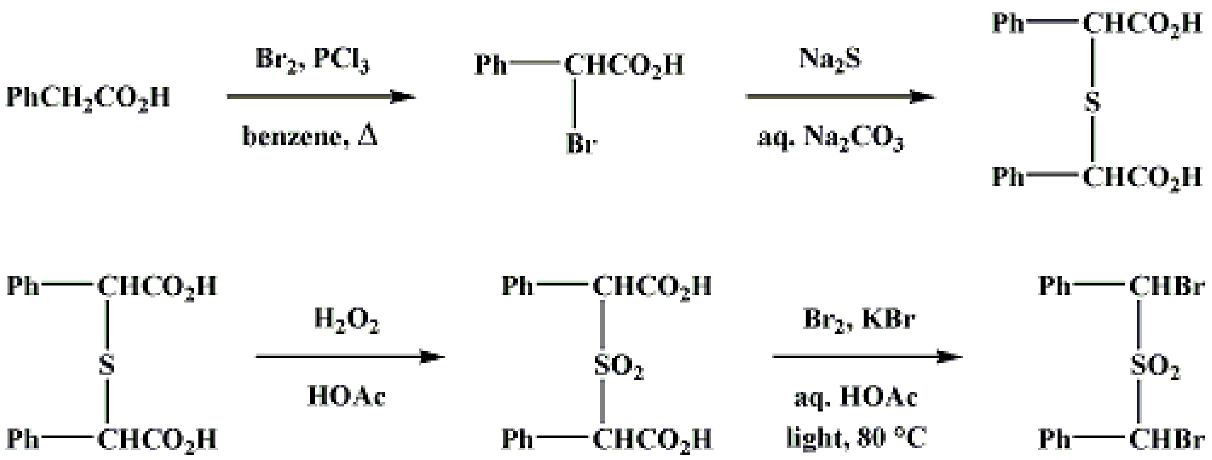
Organic Syntheses, CV 6, 403

α,α'-DIBROMODIBENZYL SULFONE

[Benzene, 1,1-[sulfonylbis(bromomethylene)]bis-]

[METHOD 1]



Submitted by Louis A. Carpino[1] and Louis V. McAdams III.
Checked by Timothy P. Higgs and Ronald Breslow.

1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A. *α-Bromophenylacetic acid.* A 3-l., round-bottomed flask fitted with a mechanical stirrer and an efficient reflux condenser (Note 1) is charged with 750 ml. of benzene, 230 g. (1.69 moles) of phenylacetic acid (Note 2), 15 g. (0.12 mole) of phosphorus trichloride and 288 g. (1.80 moles) of bromine (Note 3). The resulting solution is heated at gentle reflux for 2–3 days until the initial bromine color is discharged. The solution is allowed to cool to room temperature and after 1 hour is decanted from some polymeric material into a 2-l. distilling flask. Removal of the solvent by distillation at water bath temperatures with the aid of a water aspirator gives a black oil which is poured into 250–300 ml. of ligroin (b.p. 90–120°). The mixture is heated, dissolving the oil, and the solution is stored at –25° in a freezer for 12 hours. Filtration on a sintered-glass funnel followed by washing with 200 ml. of cold (10°) ligroin (b.p. 90–120°) gives 243 g. (67%) of α-bromophenylacetic acid as a white solid, m.p. 73–83°. Recrystallization from about 400 ml. of ligroin (b.p. 90–120°) with 15 g. of decolorizing carbon affords 217–233 g. (60–62%) of the purified acid, m.p. 80.5–84°.

B. *α,α'-Diphenylthiodiglycolic acid.* In a 4-l. Erlenmeyer flask a suspension of 223 g. (1.04 moles) of α-bromophenylacetic acid in 1.25 l. of water is brought into solution by addition of a solution of 157 g. (1.48 moles) of sodium carbonate in 700 ml. of water. A solution of 104 g. (0.8 mole) of sodium sulfide (60–62% pure fused flakes) (Note 4) in 700 ml. of water is added, and the resulting mixture is stirred mechanically at room temperature for 3 hours, heated to the boiling point, filtered while hot, cooled, and cautiously acidified (in a hood) with 3 *N* hydrochloric acid.

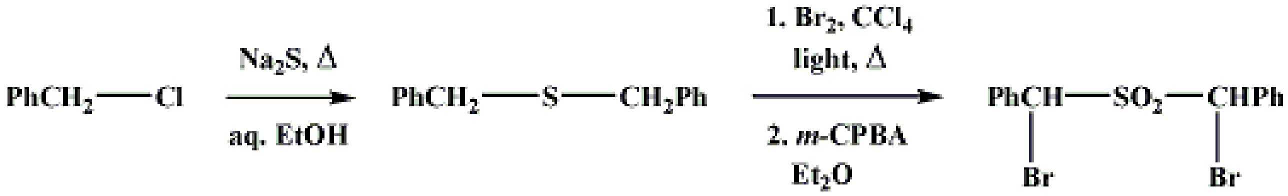
Filtration followed by washing with 200 ml. of water yields 135–140 g. (86–89%) of crude acid, m. p. 130–140°, which is sufficiently pure for use in the next step (Note 5).

C. *α,α'-Dibromodibenzyl sulfone*. To a solution of 24.9 g. (0.0824 mole) of crude α,α'-diphenylthiodiglycolic acid in 250 ml. of glacial acetic acid contained in a 500-ml., three-necked, round-bottomed flask fitted with a bulb condenser is added 37.4 g. (0.33 mole) of 30% hydrogen peroxide over a 30-minute period, with ice bath cooling and magnetic stirring. The mixture is allowed to come to room temperature (Note 6), and after 3 days 30 g. (0.19 mole) of bromine is added in one portion, followed by 30 g. of potassium bromide in 150 ml. of water. A sunlamp (Note 7), focused on the reaction mixture from a distance of 1 in., causes the solution to warm to 80° (Note 8). After heating at 80° for 30 minutes the mixture is cooled, and the solid is filtered and washed with water and ethanol, yielding 9–10 g. (27–30%) of crude α,α'-dibromodibenzyl sulfone, m.p. 135–150°. The mixture of diastereomers is pure enough to be used directly in the synthesis of 2,3-diphenylvinylene sulfone (Note 9).

2. Notes

1. An efficient bulb condenser (Allihn) was used to prevent loss of bromine.
2. The phenylacetic acid was used as supplied by the Eastman Kodak Co.
3. The bromine was washed just before use in a separatory funnel with 200 ml. of concentrated sulfuric acid.
4. The sodium sulfide was dissolved in the aqueous solution by warming, but the solution was cooled to room temperature before addition. The checkers used 192 g. (0.800 mole) of sodium sulfide nonahydrate.
5. After repeated crystallization from nitromethane the *meso* isomer, m.p. 177–180°, was obtained in a pure state in low yield.
6. After a few hours a precipitate appeared but it usually redissolved after 1.5 days. If the precipitate had not dissolved, it could be brought into solution by heating. The solution was then cooled before addition of bromine.
7. A General Electric 275-watt sunlamp was used.
8. The heat of the sunlamp maintained the temperature near 80°. For larger runs a heating mantle must be used to keep the temperature near 80°.
9. By recrystallization from ethanol it was possible to separate two isomeric dibromides, m. p. 155–157.5°, and 162–164°, in low yield.

[METHOD II]



1. Procedure

A. *Dibenzyl sulfide.* A solution of 25.8 g. (0.212 mole) of benzyl chloride in 75 ml. of 95% ethanol contained in a 250-ml., round-bottomed flask equipped with an efficient bulb condenser (Allihn) and a magnetic stirrer is brought to gentle reflux with a heating mantle. With stirring and heating, a solution of 36 g. (0.15 mole) of sodium sulfide nonahydrate in 50 ml. of water is added with a dropping funnel over a 4-hour period. The solution is heated at reflux for 3 days, after which the

ethanol is removed by distillation at atmospheric pressure. The hot aqueous solution is poured with stirring into a 250-ml. beaker half-filled with chipped ice. After the ice has melted, the resulting yellow solid is filtered on a Büchner funnel and washed with 50 ml. of water. After air-drying, the solid is distilled from an ordinary 50-ml. Claisen flask, yielding 17.6 g. (80%) of dibenzyl sulfide, b.p. 120° (0.15 mm.) (Note 1), which is pure enough to use directly in the next step. Recrystallization from 70% ethanol gives a pure sample, m.p. 46–48°.

B. *α,α'-Dibromodibenzyl sulfone*. To a gently refluxing solution of 11.35 g. (0.05304 mole) of dibenzyl sulfide in 150 ml. of carbon tetrachloride (Note 2) contained in a three-necked, round-bottomed flask is added, dropwise over a period of 1.5 hours, a solution of 17.6 g. (0.0978 mole) of bromine in 50 ml. of carbon tetrachloride, while a sunlamp (Note 3) is focused on the reaction mixture from a distance of 1 in. The solution is refluxed with a heating mantle for 3 hours, and the carbon tetrachloride removed at a water bath temperature of 50° with the aid of a water aspirator. To the residual dark oil is added 25 ml. of anhydrous diethyl ether (Note 4), and after cooling in an ice bath a solution of 32.5 (0.189 mole) of *m*-chloroperbenzoic acid (Note 5) in 150 ml. of anhydrous ether is added dropwise over a 30-minute period. The mixture is allowed to warm to room temperature and stirred for 2 days.

The solvent is evaporated with an air jet at room temperature, and to the residual solid is added saturated sodium hydrogen carbonate solution until effervescence ceases. Filtration of the remaining solid followed by washing with water and cold ethanol gives 6.5 g. (30%) of crude α,α'-dibromodibenzyl sulfone, m.p. 142–158°. This mixture of diastereomers is pure enough for use in conversion to 2,3-diphenylvinylene sulfone (Note 6).

2. Notes

1. The submitters report a similar percent yield on twenty times the scale.
2. Carbon tetrachloride was freshly distilled over phosphorus pentoxide.
3. A General Electric 275-watt sunlamp was used.
4. The ether was dried over sodium metal.
5. *m*-Chloroperbenzoic acid (assay: 85%) was used either as supplied by FMC Corporation or prepared as described in *Org. Synth.*, **Coll. Vol. 6**, 276 (1988).
6. Repeated fractional crystallization from ethanol gave, in low yield, pure samples of the same two diastereomeric dibromides, m.p. 155–157.5° and 162–164°, obtained previously through application of Method I.

3. Discussion

α-Bromophenylacetic acid has been prepared by the bromination of phenylacetic acid with elemental bromine at high temperature[2] or under UV irradiation,[3] or with *N*-bromosuccinimide,[4] and by treatment of mandelic acid with phosphorus and bromine[5] or fuming hydrobromic acid.[6] α,α'-Diphenylthiodiglycolic acid has been prepared by reaction of α-bromophenylacetic acid with sodium sulfide.[7] Dibenzyl sulfide has been obtained from the reaction of benzyl chloride with potassium sulfide[8] or benzylmercaptide.[9] α,α'-Dibromodibenzyl sulfone has been obtained by oxidation and subsequent brominative decarboxylation of α,α'-diphenylthiodiglycolic acid[10] or by bromination and subsequent oxidation of dibenzylsulfide.[10]

Both methods of preparation represent general techniques for the synthesis of α,α'-

dibromodibenzyl sulfones which are key intermediates in the synthesis of the vinylene sulfones.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 190
- Org. Syn. Coll. Vol. 6, 555

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ligroin

2,3-Diphenylvinylene sulfone

α,α'-Diphenylthiodiglycolic acid

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

ether, diethyl ether (60-29-7)

Mandelic acid (90-64-2)

sodium hydrogen carbonate (144-55-8)

HYDROBROMIC ACID (10035-10-6)

sodium carbonate (497-19-8)

bromine (7726-95-6)

PHOSPHORUS (7723-14-0)

carbon tetrachloride (56-23-5)

decolorizing carbon (7782-42-5)

sodium (13966-32-0)

benzyl chloride (100-44-7)

Phenylacetic acid (103-82-2)

phosphorus trichloride (7719-12-2)

potassium bromide (7758-02-3)

hydrogen peroxide (7722-84-1)

sodium sulfide (1313-82-2)

potassium sulfide (1312-73-8)

Nitromethane (75-52-5)

α-Bromophenylacetic acid (4870-65-9)

sodium sulfide nonahydrate (1313-84-4)

N-bromosuccinimide (128-08-5)

Dibenzyl sulfide, dibenzylsulfide (538-74-9)

Benzene, 1,1-[sulfonylbis(bromomethylene)]bis-, α,α'-Dibromodibenzyl sulfone (21966-50-7)

benzylmercaptide (538-74-9)

phosphorus pentoxide (1314-56-3)

m-Chloroperbenzoic acid (937-14-4)

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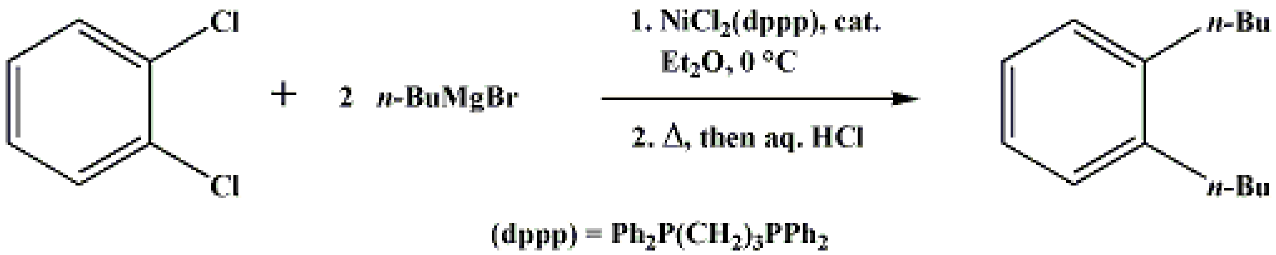
Organic Syntheses, CV 6, 407

PHOSPHINE–NICKEL COMPLEX CATALYZED CROSS-COUPLING OF GRIGNARD REAGENTS WITH ARYL AND ALKENYL HALIDES: 1,2-DIBUTYLBENZENE

[Benzene, 1,2-di-*n*-butyl-]



Submitted by Makoto Kumada, Kohei Tamao, and Koji Sumitani[1].
Checked by Teresa Y. L. Chan and S. Masamune.

1. Procedure

A 500-ml., three-necked flask equipped with a mechanical stirrer, a pressure-equalizing dropping funnel, and a reflux condenser attached to a nitrogen inlet is charged with 12.2 g. (0.502 g.-atom) of magnesium turnings. The magnesium is dried under a rapid stream of nitrogen with a heat gun. After the flask has cooled to room temperature, the rate of nitrogen flow is reduced, and 200 ml. of anhydrous diethyl ether (Note 1) and approximately 5 ml. of a solution of 68.5 g. (0.500 mole) of 1-bromobutane (Note 2) in 50 ml. of anhydrous ether are added. The mixture is stirred at room temperature, and within a few minutes an exothermic reaction begins. The flask is immersed in an ice bath, and the remaining ether solution is added dropwise over *ca.* 1 hour. After addition is complete, the mixture is refluxed with stirring for 30 minutes and then cooled to room temperature.

A 1-l., three-necked flask, equipped in the same manner, is charged with *ca.* 0.25 g. (*ca.* 0.5 mmole) of dichloro[1,3-bis(diphenylphosphino)propane]nickel(II) (Note 3), 29.5 g. (0.201 mole) of 1,2-dichlorobenzene (Note 4), and 150 ml. of anhydrous ether (Note 5). The Grignard reagent prepared above is transferred to the dropping funnel and added over 10 minutes, with stirring, to the mixture cooled in an ice bath. The nickel complex reacts immediately with the Grignard reagent, and the resulting clear-tan reaction mixture is allowed to warm to room temperature, with stirring. An exothermic reaction starts within 30 minutes, and the ether begins to reflux gently. After stirring for 2 hours at room temperature, most of the magnesium bromochloride salt has deposited (Note 6). The mixture is refluxed with stirring for 6 hours, cooled in an ice bath, and cautiously hydrolyzed with 2 *N* hydrochloric acid (*ca.* 250 ml.) (Note 7). The nearly colorless organic layer is separated and the aqueous layer extracted with two 70-ml. portions of ether. The combined organic layer and extracts are washed successively with water, aqueous saturated sodium hydrogen carbonate, and again

with water, dried over anhydrous calcium chloride, and filtered. After evaporation of the solvent the residue is distilled under reduced pressure through a 25-cm. column packed with glass helices, giving a forerun (*ca.* 4 g.) of 1-butyl-2-chlorobenzene, b.p. 52–54° (3.5 mm.), n_D^{20} 1.5110, followed by 30.0–31.5 g. (79–83%) of 1,2-dibutylbenzene, b.p. 76–81° (3.5 mm.), n_D^{20} 1.4920, as a colorless liquid (Note 8).

2. Notes

1. Ether was dried over sodium wire and freshly distilled before use.
2. Commercial 1-bromobutane was dried over anhydrous calcium chloride and distilled before use.
3. Dichloro[1,3-bis(diphenylphosphino)propane]nickel(II) can be easily prepared in an open reaction vessel.[2] To a hot solution of 9.5 g. (0.040 mole) of nickel(II) chloride hexahydrate in 175 ml. of a 5:2 (v/v) mixture of 2-propanol and methanol, is added, with stirring, a hot solution of 14.5 g. (0.0352 mole) of 1,3-bis(diphenylphosphino)propane in 200 ml. of 2-propanol. A reddish brown precipitate deposits immediately. The mixture is heated for 30 minutes and allowed to cool to room temperature. Filtration, washing with methanol, and drying under reduced pressure provide the red complex in almost quantitative yield. 1,3-Bis(diphenylphosphino)propane may be purchased from Strem Chemicals Inc., and nickel(II) chloride hexahydrate from Fisher Scientific Company.
4. Commercial G.R.-grade 1,2-dichlorobenzene can be used without further purification. At least a 20% excess of the Grignard reagent should be used to compensate for some loss through undesirable side reactions (see Discussion section).
5. The nickel complex is insoluble in the mixture.
6. If stirring becomes difficult, approximately 100 ml. of anhydrous ether may be added.
7. This hydrolysis is exothermic, and the acid should be added slowly, maintaining gentle refluxing of the ether.
8. GC analysis on a 3.5-m. column packed with Silicone DC 550 and operated at 200° showed that the product was at least 99.5% pure. The product has the following spectral properties: IR (neat): 750 cm^{-1} (1,2-disubstituted benzene); ^1H NMR (CCl_4), δ (multiplicity, number of protons, assignment): 0.7–1.7 (m, 14H, 2 $CH_2CH_2CH_3$), 2.60 (t, 4H, 2 benzylic CH_2), 7.0 (s, 4H, C_6H_4).

3. Discussion

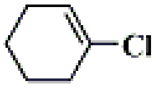
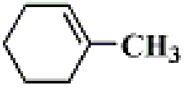
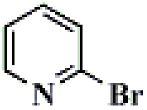
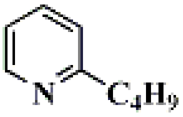
1,2-Dibutylbenzene has been prepared from cyclohexanone by tedious, multistep procedures.[3,4] The present one-step method is based on the selective cross-coupling of a Grignard reagent with an organic halide in the presence of a phosphine–nickel catalyst.[5]

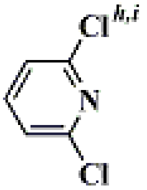
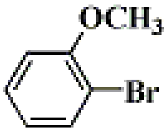
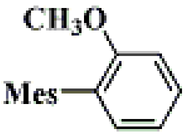
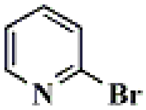
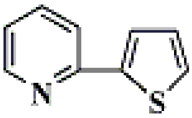
The phosphine–nickel complex catalyzes the cross-coupling of alkyl, alkenyl, aryl, and heteroaryl Grignard reagents with aryl, heteroaryl, and alkenyl halides. The method, thus, has wide application. Alkyl halides also exhibit considerable reactivity, but give a complex mixture of products. Some representative examples are listed in Table I. A labile diorganonickel complex involving the two organic groups originating from the Grignard reagent and from the organic halide, respectively, has been proposed as a reaction intermediate. The fact that simple alkyl Grignard reagents with hydrogen-bearing β-carbon

atoms react with equal efficiency is one of the most remarkable features of the present method, considering the great tendency with which transition metal alkyls undergo a β-elimination reaction, forming alkenes and metal hydrides.[6] Although the β-elimination may be responsible for the side products formed during the coupling, an appropriate choice of phosphine ligand for the nickel catalyst minimizes this side reaction. The catalytic activity of the phosphine–nickel complex depends not only on the nature of the phosphine ligand but also on the combination of the Grignard reagent and organic halide. Of several catalysts, including [$NiCl_2$(dppp)], [$NiCl_2$(dppe)], [$NiCl_2$(dmpe)], and [$NiCl_2\{P(C_6H_5)_3\}_2$], where dppe = $(C_6H_5)_2PCH_2CH_2P(C_6H_5)_2$ and dmpe = $(CH_3)_2PCH_2CH_2P(CH_3)_2$, the first has been found most effective in almost all cases, except for alkenyl Grignard reagents. The halide may be chloride, bromide, or iodide, although chlorides usually give the most satisfactory results. Even fluorides react with comparable facility in some cases.[7] Vinyl chloride is one of the most reactive halocompounds, and the coupling (Table I, entry 10) can be conveniently conducted in an open system, similar to that described here, by the gradual addition of the Grignard reagent at 0° to a mixture of vinyl chloride, [$NiCl_2$(dppp)], and ether, followed by stirring at room temperature for 2 hours.

TABLE I

CROSS-COUPLING OF GRIGNARD REAGENTS WITH VARIOUS ARYL AND ALKENYL HALIDES IN THE PRESENCE OF [$NiCl_2$(dppp)] AS A CATALYST[a]

Entry	RMgX	Halides	Product (% yield)[b]
1	CH_3MgBr		 (98)
2	$CH_3(CH_2)_3MgBr$	C_6H_5Cl	$C_6H_5C_4H_9$ (96)
3	$CH_3(CH_2)_3MgBr$		 (71)[c]
4	$(CH_3)_3SiCH_2MgCl$	1,3-$Cl_2C_6H_4$	1,3-$[(CH_3)_3SiCH_2]_2C_6H_4$ (83)[c]
5	$(CH_3)_2CHMgCl$	C_6H_5Cl	$(CH_3)_2CH$- and $CH_3(CH_2)_2C_6H_5$ (96:4) (89) (10:90) (84) [d]
6	$C_6H_5CH(CH_3)MgCl$	$CH_2{=}CHBr$[e,f]	(*S*)-(+)-$C_6H_5CH(CH_3)CH{=}CH_2$[g] (96)

7	$BrMg(CH_2)_{10}MgBr$		(33)
8	C_6H_5MgBr	(*Z*)-$C_6H_5CH{=}CHBr$	(*Z*)-$C_6H_5CH{=}CHC_6H_5$ (100)
9	C_6H_5MgBr	$ClCH{=}CHCl$[d,j]	(*Z*)-$C_6H_5CH{=}CHC_6H_5$[k] (95–100)
10	4-ClC_6H_4MgBr	$CH_2{=}CHCl$[l]	4-$ClC_6H_4CH{=}CH_2$ (79)[c]
11	2,4,6-$(CH_3)_3C_6H_2MgBr$		 (74)
12	$CH_2{=}C(CH_3)MgBr$	α-$C_{10}H_7Br$[d,h]	α-$C_{10}H_7C(CH_3){=}CH_2$ (78)
13			 (78)

[a]The reaction was carried out on a 0.01–0.02 mole scale in refluxing ethyl ether for 3–20 hours, unless otherwise noted.

[b]Determined by GC, unless otherwise noted.

[c]Isolated Yield.

[d]The catalyst is [$NiCl_2$(dmpe)], dmpe = $(CH_3)_2PCH_2CH_2P(CH_3)_2$.

[e]The catalyst is a mixture of $NiCl_2$ and (*S*)-Valphos. (*S*)-Valphos = (*S*)-(+)-(2-Dimethylamino-3-methylbutyl)diphenylphosphine (see ref. 8).

[f]At 0° for 2 days.

[g]Configuration of the predominant enantiomer; 13.0% enantiomeric excess.

[h]Solvent is tetrahydrofuran.

[i]At 40° for 9 hours.

[j]At room temperature for 2 hours.

[k](*Z*)-Stilbene is formed stereoselectively regardless of whether (*Z*)- or (*E*)-dichloroethene is used (see text).

[l]Carried out on a 0.2 mole scale at 0° to room temperature over 2 hours.

Several other features deserve comment. The coupling of secondary alkyl Grignard reagents is accompanied by alkyl group isomerization from secondary to primary, the extent of which is strongly dependent on the electronic nature of the phosphine ligand in the catalyst (entry 5).[7] Asymmetric cross-coupling can be achieved by using optically active phosphine–nickel complexes as catalysts (entry 6).[9,10,11,12,13,8,14] Cyclocoupling of di-Grignard reagents with dihalides offers a new, one-step route to cyclophanes (entry 7).[15] Though the cross-coupling of monohaloalkenes proceeds stereospecifically (entry 8),[16] that of 1,2-dihaloethylenes proceeds nonstereospecifically, yielding a (*Z*)-alkene, the stereoselectivity being dependent on the nature of the phosphine ligand in the catalyst (entry 9).[16] Sterically hindered aryl Grignard reagents also react with ease (entry 11).[14]

The couplings are usually exothermic, and care must be taken *not* to add the phosphine–nickel catalyst to a mixture of a Grignard reagent and an organic halide, particularly in a large-scale preparation. For example the addition of a small amount of [$NiCl_2$(dppp)] to a mixture of vinyl chloride and 4-chlorophenylmagnesium bromide in ether at 0° led, after a few minutes' induction period, to an uncontrollable, violent reaction.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 172
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

magnesium bromochloride

$(C_6H_5)_2PCH_2CH_2P(C_6H_5)_2$

$(CH_3)_2PCH_2CH_2P(CH_3)_2$

$[NiCl_2(dppp)]$

$[NiCl_2(dmpe)]$

(Z)- or (E)-dichloroethene

$NiCl_2(dppp)$

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

methanol (67-56-1)

ether, ethyl ether, diethyl ether (60-29-7)

sodium hydrogen carbonate (144-55-8)

magnesium (7439-95-4)

Cyclohexanone (108-94-1)

1-bromobutane (109-65-9)

nitrogen (7727-37-9)

nickel (7440-02-0)

sodium wire (13966-32-0)

2-propanol (67-63-0)

nickel(II) chloride hexahydrate (7791-20-0)

Tetrahydrofuran (109-99-9)

phosphine (7723-14-0)

vinyl chloride (9002-86-2)

1,2-Dibutylbenzene, Benzene, 1,2-di-n-butyl- (17171-73-2)

dichloro[1,3-bis(diphenylphosphino)propane]nickel(II) (15629-92-2)

1,2-dichlorobenzene (95-50-1)

1-butyl-2-chlorobenzene

1,3-bis(diphenylphosphino)propane (6737-42-4)

4-chlorophenylmagnesium bromide

(Z)-Stilbene (645-49-8)

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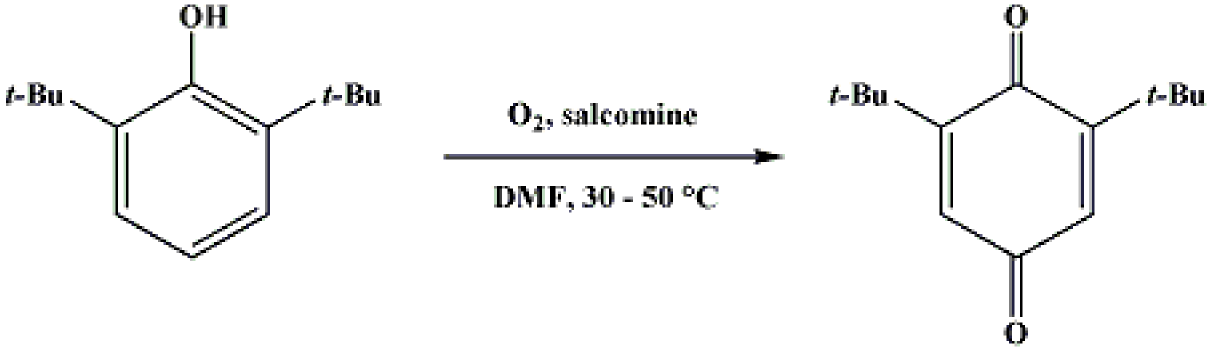
Organic Syntheses, CV 6, 412

OXIDATION WITH BIS(SALICYLIDENE) ETHYLENEDIIMINOCOBALT(II) (SALCOMINE): 2,6-DI-*tert*-BUTYL-*p*-BENZOQUINONE

[2,5-Cyclohexadiene-1,4-dione, 2,6-bis(1,1-dimethylethyl)-]



Submitted by C. R. H. I. De Jonge[1], H. J. Hageman, G. Hoentjen, and W. J. Mijs.
Checked by K. Balasubramanian, Robert K. Boeckman, and Carl R. Johnson.

1. Procedure

A 200-ml., three-necked flask equipped with a mechanical stirrer, a thermometer, and a gas-inlet tube is charged with 41.2 g. (0.200 mole) of 2,6-di-*tert*-butylphenol (Note 1) in 75 ml. of *N,N*-dimethylformamide (Note 2) and 2.5 g. (0.0075 mole) of salcomine (Note 3). With stirring, oxygen is introduced at such a rate that the temperature does not exceed 50°. This is continued for 4 hours, and at the end of the reaction the temperature drops to about 25°. The reaction mixture is then poured onto 500 g. of crushed ice and 15 ml. of 4 *N* hydrochloric acid. A yellow-brown precipitate is formed, collected by suction filtration, and washed on the filter with three 50-ml. portions of 1 *N* hydrochloric acid, with three 100-ml. portions of water, and twice with 25-ml. portions of cold ethanol. Drying under reduced pressure at 50° for 3 hours gives 43 g. of crude 2,6-di-*tert*-butyl *p*-benzoquinone as a dark-yellow crystalline solid. Recrystallization from ethanol gives 36.5 g. (83%) of pure 2,6-di-*tert*-butyl-*p*-benzoquinone, m.p. 65–66° (Note 4), (Note 5).

2. Notes

1. 2,6-Di-*tert*-butylphenol purchased from Aldrich Chemical Company, Inc., was used.
2. When chloroform or methanol is used as the solvent for the oxidation of phenols, other products, originating from coupling of aryloxy radicals, *e.g.*, polyphenylene ethers and/or diphenoquinones, are also formed.[2]

3. Bis(salicylidene)ethylenediiminocobalt(II) can be prepared according to the procedure described in *Inorg. Synth.*[3]
4. 2,6-Di-*tert*-butyl-*p*-benzoquinone should be stored in a brown bottle.
5. The product has the following spectral properties; IR ($CHCl_3$) $cm.^{-1}$: 1652, 1597; ^{1}H NMR ($CDCl_3$), δ 1.33, 6.56.

3. Discussion

Various 2,6-disubstituted *p*-benzoquinones have been prepared by oxidation of the corresponding 2,6-disubstituted phenols with potassium nitrosodisulfonate[4,5] or lead dioxide in formic acid.[6] Oxidative coupling of 2,6-disubstituted phenols to poly-2,6-disubstituted phenylene ethers followed by treatment of the polymers in acetic acid with lead dioxide is reported[7] to give low yields of the corresponding 2,6-disubstituted *p*-benzoquinones.

Salcomine is a useful catalyst for the selective oxygenation of 2,6-disubstituted phenols to the corresponding *p*-benzoquinones when *N,N*-dimethylformamide is used as the solvent; laborious procedures are avoided and high yields of pure *p*-benzoquinones are obtained. Following the procedure described above, the authors have prepared 2,6-diphenyl-*p*-benzoquinone (m.p. 134–135°, yield 86%) and 2,6-dimethoxy-*p*-benzoquinone (m.p. 252°, yield 91%) from the appropriate phenols.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

BIS(SALICYLIDENE)ETHYLENEDIIMINOCOBALT(II) (SALCOMINE)

salcomine

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

methanol (67-56-1)

chloroform (67-66-3)

oxygen (7782-44-7)

formic acid (64-18-6)

N,N-dimethylformamide (68-12-2)

Bis(salicylidene)ethylenediiminocobalt(II)

2,5-Cyclohexadiene-1,4-dione, 2,6-bis(1,1-dimethylethyl)-, 2,6-Di-tert-butyl-p-benzoquinone, 2,6-di-tert-butyl p-benzoquinone (719-22-2)

potassium nitrosodisulfonate

2,6-di-tert-butylphenol (128-39-2)

lead dioxide

2,6-diphenyl-p-benzoquinone

2,6-dimethoxy-p-benzoquinone

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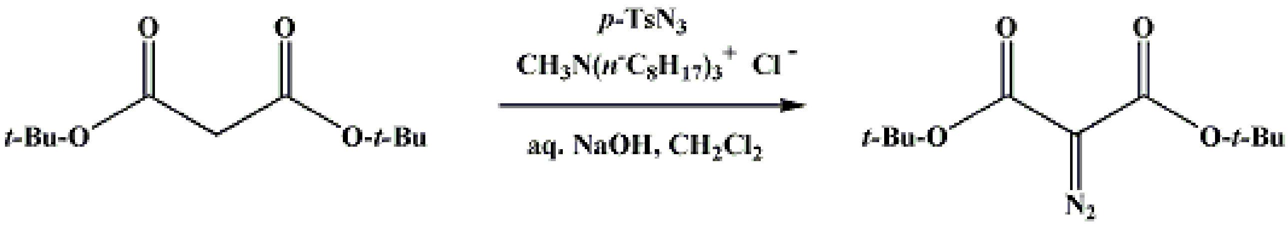
Organic Syntheses, CV 6, 414

DIAZO TRANSFER BY MEANS OF PHASE-TRANSFER CATALYSIS: DI-*tert*-BUTYL DIAZOMALONATE

[Propanedioic acid, diazo-, bis(1,1-dimethylethyl) ester]



Submitted by Henry J. Ledon[1]
Checked by Steven J. Hobbs and Robert M. Coates.

1. Procedure

Caution! Diazomalonic esters are toxic and potentially explosive. They must be handled with care. This preparation should be carried out in a well-ventilated hood, and the distillation of di-tert-butyl diazomalonate should be conducted behind a safety shield.

A 500-ml., three-necked, round-bottomed flask equipped with a reflux condenser, a dropping funnel, an argon inlet, and a Teflon-coated magnetic stirring bar is charged with 10.8 g. (0.0500 mole) of di-*tert*-butyl malonate (Note 1), 9.9 g. (0.0502 mole) of *p*-toluenesulfonyl azide (Note 2), 0.5 g. (0.001 mole) of methyltri-*n*-octylammonium chloride (Note 3), and 200 ml. of dichloromethane (Note 4). The solution is stirred vigorously as the flask is flushed with argon for 10 minutes, then 10 ml. (0.1 mole) of aqueous 10 *N* sodium hydroxide is added in one portion (Note 5). The mixture is stirred for 2 hours, during which time it changes from colorless to pale yellow. A 200-ml. portion of water is added; the organic layer is separated, washed with three 500-ml. portions of water (Note 6), and dried with anhydrous magnesium sulfate. After filtration of the drying agent, the solvent is removed on a rotary evaporator using a water bath kept at 30° (Note 7). The residual yellow-orange liquid is distilled at high vacuum (Note 8). The temperature of the heating bath is gradually raised to *ca.* 70° and kept at 70–75° during the distillation. After separation of a small forerun, 7.2–7.6 g. (59–63%) of di-*tert*-butyl diazomalonate is collected, b.p. 44–45° (0.02 mm.), n_D^{22} = 1.4568 (Note 9) and (Note 10).

2. Notes

1. Di-*tert*-butyl malonate is available commercially directly from Fluka AG, Buchs, Switzerland, or from its North American representative, Tridom Chemical Inc. Alternatively this compound may be prepared from malonic acid as described in *Org. Synth.*, **Coll. Vol. 4**, 261 (1963).

2. *p*-Toluenesulfonyl azide was prepared according to the procedure in *Org. Synth.*, **Coll. Vol. 5**, 179 (1973).

3. The submitter obtained methyltri-*n*-octylammonium chloride (Aliquat 336) from General Mills Company, Chemical Division, Kankakee, Illinois. The phase-transfer catalyst used by the checkers, which was supplied by Fluka AG through Tridom Chemical Inc., was a mixture in which the alkyl chains varied in length from *n*-octyl to *n*-decyl with the former

predominating.

4. Reagent grade dichloromethane was used without further purification.

5. The sodium hydroxide solution was deoxygenated by bubbling a stream of argon through it for 10 minutes.

6. The organic layer is washed with relatively large portions of water to avoid difficulty in separating the phases. The checkers found that vigorous shaking during the extractions gave intractable emulsions. The emulsions were avoided by gentle swirling of the dichloromethane–water mixtures.

7. To avoid foaming during the distillation, the checkers removed the last traces of solvent by evacuation at 0.1 mm. and room temperature for 12–24 hours.

8. The submitter recommends that the apparatus be purged with argon prior to the distillation.

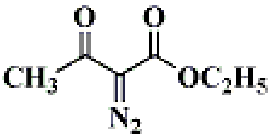
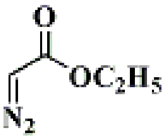
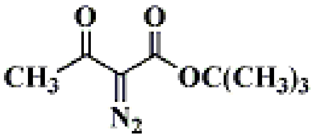
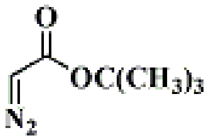
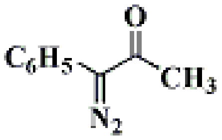
9. The checkers collected foreruns amounting to 0.3–0.7 g., b.p. 50–58° (0.003 mm.) and 40–45° (0.0006 mm.). The product was collected in two or three fractions, b.p. 53–57° (0.002–0.011 mm.), 54–58° (0.002–0.003 mm.), and 45–52° (0.0004–0.0006 mm.). Inspection and integration of the ^{1}H NMR spectra of the foreruns indicated that the fractions were mainly di-*tert*-butyl diazomalonate contaminated with 16–35% of di-*tert*-butyl malonate. The purest fractions usually crystallized on standing at room temperature to give a low-melting solid. A GC analysis on the product by the submitter, using an 0.3 × 80 cm. column packed with 10% silicone rubber (SE-30) supported on acid-washed, 60–80 mesh Chromasorb P at 80°, exhibited a single peak. The retention times of di-*tert*-butyl malonate, di-*tert*-butyl diazomalonate, and *p*-toluenesulfonyl azide were 2, 6, and 9 minutes, respectively. The purity of the product obtained by the checkers was estimated from ^{1}H NMR spectra to be *ca.* 94%, the remainder being di-*tert*-butyl malonate.

10. The spectral properties of the product are as follows: IR (liquid film) $cm.^{-1}$: 2137 ($C{=}N_2$), 1751 (C=O), 1730 (C=O), 1686; UV (C_2H_5OH) nm. max. (log ε): 255 (3.68); ^{1}H NMR ($CDCl_3$), δ (multiplicity, number of protons, assignment): 1.52 [s, 18H, $2C(CH_3)_3$]; ^{13}C NMR with proton decoupling ($CDCl_3$), δ (assignment): 28.5 (CH_3), 65.7 ($C{=}N_2$), 82.8 [$C(CH_3)_3$], 160.6 (C=O).

3. Discussion

The "diazo transfer reaction" between *p*-toluenesulfonyl azide and active methylene compounds is a useful synthetic method for the preparation of α-diazo carbonyl compounds.[2] However, the reaction of di-*tert*-butyl malonate and *p*-toluenesulfonyl azide to form di-*tert*-butyl diazomalonate proceeded to the extent of only 47% after 4 weeks with the usual procedure.[3] The present procedure, which utilizes a two-phase medium and methyltri-*n*-octylammonium chloride (Aliquat 336) as phase-transfer catalyst, effects this same diazo transfer in 2 hours and has the additional advantage of avoiding the use of anhydrous solvents.[4,5] This procedure has been employed for the preparation of diazoacetoacetates, diazoacetates, and diazomalonates (Table I).[5] Ethyl and *tert*-butyl acetoacetate are converted to the corresponding α-diazoacetoacetates with saturated sodium carbonate as the aqueous phase. When aqueous sodium hydroxide is used with the acetoacetates, the initially formed α-diazoacetoacetates undergo deacylation to the diazoacetates. Methyl esters are not suitable substrates, since they are too easily saponified under these conditions.

TABLE I
PREPARATION OF α-DIAZO CARBONYL COMPOUNDS VIA PHASE TRANSFER CATALYSIS[a]

Starting Material	Organic Phase	Aqueous Phase	Phase Transfer Catalyst[b]	Time and Temperature	Product	Yield (%)
Ethyl acetoacetate	pentane	saturated Na_2CO_3	A	15 hours, 25°		90
Ethyl acetoacetate	pentane	3 *N* NaOH	A	15 hours, 25°		53
tert-Butyl acetoacetate	pentane	saturated Na_2CO_3	A	15 hours, 25°		77
	dichloromethane	3 *N* NaOH	B	1 hour, 0°		92
tert-Butyl acetoacetate	pentane	3 *N* NaOH	A	15 hours, 25°		89
Phenyl acetone	benzene	10 *N* NaOH	A	15 hours, 0°		100

[a]These reactions were carried out with 0.005 mole of the carbonyl compound and 0.005 mole of *p*-toluenesulfonyl azide.

[b]A, tetrabutylammonium bromide; B, methyltri-*n*-octylammonium chloride (Aliquat 336).

Although the hazardous properties of di-*tert*-butyl diazomalonate are not known with certainty, it is reasonable to assume that they are similar to those of diazoacetic esters, which are considered to be moderate explosion hazards when heated.[6] Contact with rough or metallic surfaces should be avoided. The submitter has routinely distilled 10-g. quantities of di-*tert*-butyl diazomalonate under argon with no sign of decomposition.

Diazomalonic esters serve as intermediates for the synthesis of a wide variety of compounds including cyclopropanes,[7,8,9,10,11] cyclopropenes,[7,8,9,12] cycloheptatrienes,[13] sulfur ylides,[14,15] lactones,[16] and substituted malonates.[17]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 438
- Org. Syn. Coll. Vol. 9, 400

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Ethyl and tert-butyl acetoacetate

Benzene (71-43-2)

sodium hydroxide, NaOH (1310-73-2)

sodium carbonate, Na_2CO_3 (497-19-8)

Ethyl acetoacetate (141-97-9)

Pentane (109-66-0)

dichloromethane (75-09-2)

Malonic acid (141-82-2)

phenyl acetone (103-79-7)

magnesium sulfate (7487-88-9)

n-Decyl

argon (7440-37-1)

tetrabutylammonium bromide (1643-19-2)

Propanedioic acid, diazo-, bis(1,1-dimethylethyl) ester, Di-tert-butyl diazomalonate (35207-75-1)

Methyltri-n-octylammonium chloride (5137-55-3)

p-toluenesulfonyl azide (941-55-9)

n-Octyl

Di-tert-butyl malonate (541-16-2)

tert-Butyl acetoacetate (1694-31-1)

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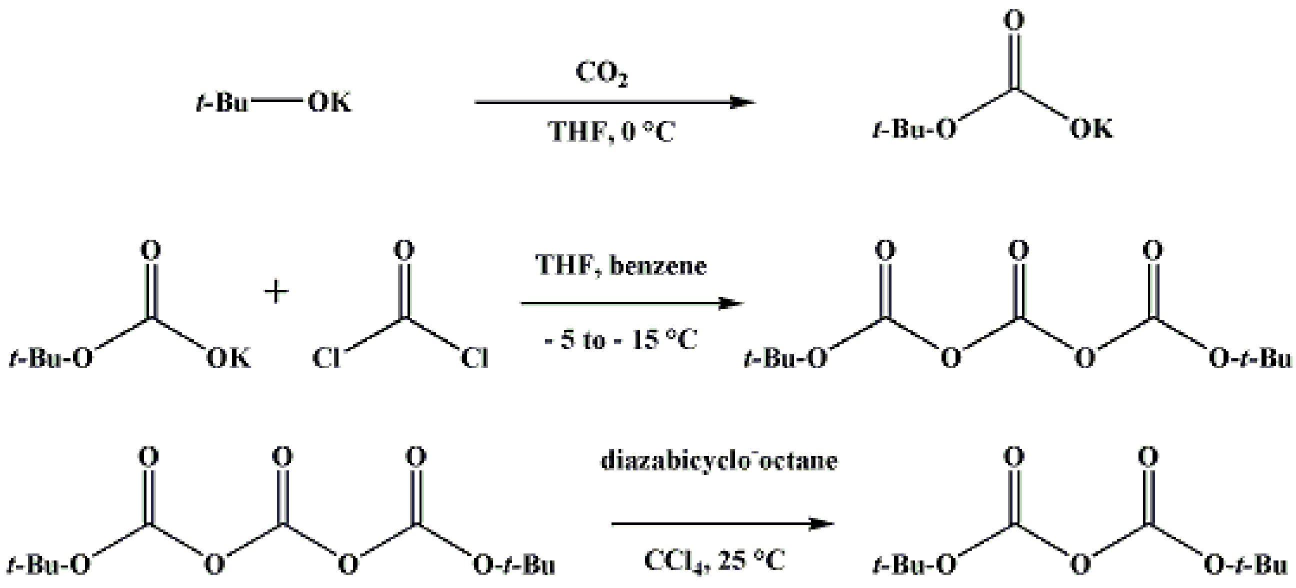
DI-*tert*-BUTYL DICARBONATE

[Dicarbonic acid, bis(1,1-dimethylethyl) ester]



Submitted by Barry M. Pope, Yutaka Yamamoto, and D. Stanley Tarbell[1].
Checked by John C. DuBose and Herbert O. House.

1. Procedure

Caution! Since the toxic gas phosgene is employed in this preparation, the reaction should be performed in an efficient hood. The glassware, which may be coated with a solution of phosgene, should be washed before it is removed from the hood.

Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A. *Di-*tert-*butyl tricarbonate.* A 1-l., three-necked flask, fitted with a mechanical stirrer, a 200-ml. pressure-equalizing dropping funnel, a calcium chloride-filled drying tube, and gas-inlet tube with a minimum internal diameter of 6 mm. (Note 1) extending nearly to the bottom of the flask, is dried either by heating with a free flame while passing anhydrous nitrogen through the apparatus, or by heating to 120° for several hours in an oven. Before use, the dropping funnel should be calibrated to indicate levels corresponding to 85 ml. and 105 ml. of liquid. While an atmosphere of anhydrous nitrogen (Note 2) is maintained inside the apparatus, it is allowed to cool before a mixture of 44.8 g. (0.400 mole) of alcohol-free potassium *tert*-butoxide (Note 3) and 550 ml. of anhydrous tetrahydrofuran (Note 4) is added to the reaction flask. The mixture is stirred under an atmosphere of anhydrous nitrogen for 5–10 minutes to obtain a solution. (Note 3), (Note 5). The reaction flask is immersed in an ice–salt bath maintained at –5° to –20°, and all subsequent steps, including solvent removal, are performed with this cooling bath in place. A stream of anhydrous carbon dioxide (Note 2) is passed through the cold reaction solution for 30 minutes with vigorous stirring, resulting in the formation of a thick, creamy slurry in the reaction flask. While the reaction mixture is being saturated with carbon dioxide, 85 ml. of anhydrous benzene is added to the dropping funnel. A stream of

phosgene is bubbled through the benzene until the total volume of the solution is 105 ml., corresponding to the addition of approximately 24 g. (0.24 mole) of phosgene (Note 6). When the addition of carbon dioxide is complete, the phosgene solution is added to the cold reaction slurry, dropwise and with vigorous stirring, over 1 hour, maintaining the temperature of the cooling bath at –5° to –15°. During this addition the reaction mixture becomes less viscous but remains a white slurry. When the addition of the phosgene solution is complete, the cold reaction mixture is stirred for an additional 45 minutes while a stream of anhydrous nitrogen is passed through the reaction solution to sweep out most of the excess phosgene. The fittings are removed from the reaction flask, two of the three necks are stoppered, and the volume of solvents in the reaction flask is reduced from about 650 ml. to 100 ml. with a rotary evaporator. During evaporation the flask should be continuously cooled in an ice–salt bath maintained at –5° to 0°. This evaporation should be performed with either a very efficient aspirator or with a mechanical vacuum pump fitted with an efficient cold trap. Since some phosgene is still present in the reaction mixture, the exhaust from the aspirator or the vacuum pump should be discharged in the hood and any material collected in a cold trap should be emptied in the hood. The residual slurry of finely divided potassium chloride is filtered with suction in a large-diameter, fritted-glass funnel, precooled with 50 ml. of ice-cold pentane. During filtration the filter funnel may be loosely covered with an inverted large-diameter funnel through which a stream of nitrogen is passed to protect the contents of the funnel from atmospheric moisture. The residue in the reaction flask is washed into the filter funnel with 350 ml. of ice-cold pentane and washed with two additional 100-ml. portions of ice-cold pentane, leaving white potassium chloride as a residue. The combined filtrate and pentane washings are concentrated to dryness at 0° with a rotary evaporator, under reduced pressure supplied by a vacuum pump equipped with an efficient cold trap, yielding 33.7–39.6 g. (64–75%, (Note 7)) of di-*tert*-butyl tricarbonate as a colorless solid. This crude product is recrystallized by dissolving it in 1250 ml. of pentane at room temperature, and cooling the solution to –15°. The pentane mother liquors are concentrated with a rotary evaporator, giving two additional crops of crystalline product. The total yield is 31.2–32.8 g. (59–62%) of the pure di-*tert*-butyl tricarbonate as colorless prisms, m.p. 62–63° (dec.) (Note 8).

B. *Di-tert-butyl dicarbonate.* A solution of 20.0 g. (0.0763 mole) of di-*tert*-butyl tricarbonate in 75 ml. of carbon tetrachloride is placed in a 600-ml. beaker fitted with a magnetic stirrer, and 0.10 g. (0.89 mmole) of freshly sublimed 1,4-diazabicyclo[2.2.2]octane (Dabco) is added (Note 9), resulting in the rapid evolution of carbon dioxide. The reaction mixture is stirred at 25° for 45 minutes, to complete the loss of carbon dioxide (Note 10), before 35 ml. of water, containing citric acid sufficient to make the aqueous layer slightly acidic, is added. The organic layer is separated, dried over anhydrous magnesium sulfate, and concentrated at 25° with a rotary evaporator. The residual liquid is distilled under reduced pressure, yielding 13.3–15.1 g. (80–91%) of di-*tert*-butyl dicarbonate as a colorless liquid, b.p. 55–56° (0.15 mm.) or 62–65° (0.4 mm.) n_D^{25} 1.4071–1.4072 (Note 11).

2. Notes

1. A gas-inlet tube of smaller diameter or a tube fitted with a fritted-glass outlet tends to become clogged during this preparation and is not recommended.
2. The submitters dried this gas by passing it successively through an empty trap, through a trap containing concentrated sulfuric acid, and through another empty trap. The checkers used this drying procedure for carbon dioxide but dried the nitrogen by passing it through a column of molecular sieves.
3. The submitters employed alcohol-free potassium *tert*-butoxide, purchased from K & K Laboratories, without further purification; the checkers employed comparable material taken from a freshly opened bottle purchased from MSA Research Corporation. The submitters report that among approximately ten different bottles of commercial potassium *tert*-butoxide used, only material from one bottle failed to form the tricarbonate. The defective material was

an extremely fine powder that failed to dissolve when stirred with tetrahydrofuran. Solubility in tetrahydrofuran appears to be a good criterion for the purity of alcohol-free potassium *tert*-butoxide. The checkers have observed that a 1:1 complex of potassium *tert*-butoxide and *tert*-butyl alcohol is much less soluble in ethereal solvents than is alcohol-free potassium *tert*-butoxide.

4. A reagent grade of tetrahydrofuran (b.p. 65–66°) was distilled from lithium aluminum hydride before use.

5. The submitters reported that their solution had a faint blue color at this point.

6. If desired, the dropping funnel may be removed from the reaction flask and replaced with a calcium chloride drying tube during the preparation of the phosgene solution. When preparation of the phosgene solution is complete, the drying tube should be removed and quickly replaced with the dropping funnel containing the phosgene solution.

7. Although the submitters report that this crude product is suitable for use in the next step of this preparation, the checkers found that once, when using the crude product, the subsequent reaction did not go to completion unless an extra quantity of the diamine base was added. This suggests that some potentially acidic impurity such as *tert*-butyl chloroformate may be present in the crude product and could interfere with the subsequent reaction. The checkers therefore recommend that the product be purified before use in the next step of this preparation.

8. Although this tricarbonate undergoes thermal decomposition when heated above its melting point (63°), forming *tert*-butyl alcohol, isobutylene, and carbon dioxide, the product appears to be stable to storage at temperatures of 25° or less. The product exhibits IR bands (CCl_4) attributable to C=O stretching at 1845, 1810, and 1780 cm.$^{-1}$; the ^{1}H NMR spectrum (CCl_4) exhibits a singlet at δ 1.55.

9. The submitters report that both 1,4-diazabicyclo[2.2.2]octane and triethylamine have been used to catalyze this decomposition. Triethylamine was less satisfactory as a catalyst because of its relatively rapid reaction with the solvent, carbon tetrachloride, to form triethylamine hydrochloride, and because of difficulty encountered in separating triethylamine from the dicarbonate product. The 1,4-diazabicyclo[2.2.2]octane was efficiently separated from the dicarbonate product by the procedure described in which the crude product was washed with very dilute acid.

10. The progress of this reaction may be monitored either by IR, observing the disappearance of the band at 1845 cm.$^{-1}$, or by ^{1}H NMR (CCl_4), following the replacement of the reactant peak (CCl_4) at δ 1.55 by the product peak at δ 1.50.

11. The submitters report that this product solidifies when cooled and melts at 21–22° and that the product is stable when stored in a refrigerator. The product exhibits IR absorption (CCl_4) attributable to C=O stretching at 1810 and 1765 cm.$^{-1}$ and a ^{1}H NMR (CCl_4) singlet at δ 1.50. The mass spectrum of the product exhibits the following relatively abundant fragment peaks: *m/e* (relative intensity), 60(10), 59(99), 57(34), 56(86), 55(47), 50(21), 44(100), 43(30), 41(91), 40(27), and 39(61).

3. Discussion

Di-*tert*-butyl tricarbonate, an example of hitherto unknown class of compounds, has been prepared only by the present procedure.[2,3,4] The corresponding sulfur compound, *tert*-$C_4H_9SCO_2CO_2COS$-*tert*-C_4H_9, also belongs to a new class of compounds and has been prepared by a similar procedure in comparable yields.[4,5] Both tricarbonates are smoothly converted by basic catalysts into the corresponding dicarbonates (sometimes called pyrocarbonates); kinetic studies and differences in thermal decomposition of both tricarbonates have been reported, as well as other reactions of these materials.[4,6] The amine-catalyzed decomposition of the tricarbonates to dicarbonates is believed to

involve initial nucleophilic attack by the amine at the center carbonyl group of the tricarbonate.[4,6] Di-*tert*-butyl dicarbonate had been obtained previously[7] in 5% yield; no study of its properties was reported.[7] The di-*tert*-butyl dicarbonate and its sulfur analog have been shown to react with amino acids and their derivatives to form the corresponding *N*-*tert*-butoxycarbonyl (*t*-BOC) and *N*-*tert*-butylthiocarbonyl derivatives,[3] which are valuable protecting groups for amino functions. The dicarbonates described in the present synthesis are very mild reagents for the preparation of *t*-BOC and *N*-*tert*-butylthiocarbonyl derivatives, and may have application in selective reactions with enzymes, nucleic acids and their component nucleotides and nucleosides. Diethyl dicarbonate has been extensively studied in reactions of this type.[8,9]

Other reagents which have been found useful for the synthesis of *t*-BOC derivatives include the hazardous *tert*-butoxycarbonyl azide[10] (see warning, p. 207), *tert*-butyl phenyl carbonate,[11] and 2-*tert*-butoxycarbonyloxyimino-2-phenylacetonitrile.[12]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 203
- Org. Syn. Coll. Vol. 6, 207
- Org. Syn. Coll. Vol. 7, 70
- Org. Syn. Coll. Vol. 9, 268

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Di-tert-butyl tricarbonate

alcohol-free potassium tert-butoxide

Diethyl dicarbonate

sulfuric acid (7664-93-9)

Benzene (71-43-2)

citric acid (77-92-9)

carbon tetrachloride (56-23-5)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

phosgene (75-44-5)

Pentane (109-66-0)

potassium chloride (7447-40-7)

magnesium sulfate (7487-88-9)

isobutylene (9003-27-4)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

triethylamine (121-44-8)

Triethylamine hydrochloride (554-68-7)

tert-butyl alcohol (75-65-0)

tert-butoxycarbonyl azide (1070-19-5)

2-tert-Butoxycarbonyloxyimino-2-phenylacetonitrile (58632-95-4)

tert-Butyl phenyl carbonate (6627-89-0)

1,4-diazabicyclo[2.2.2]octane (280-57-9)

Di-tert-butyl dicarbonate, Dicarbonic acid, bis(1,1-dimethylethyl) ester (24424-99-5)

potassium tert-butoxide (865-47-4)

tert-butyl chloroformate

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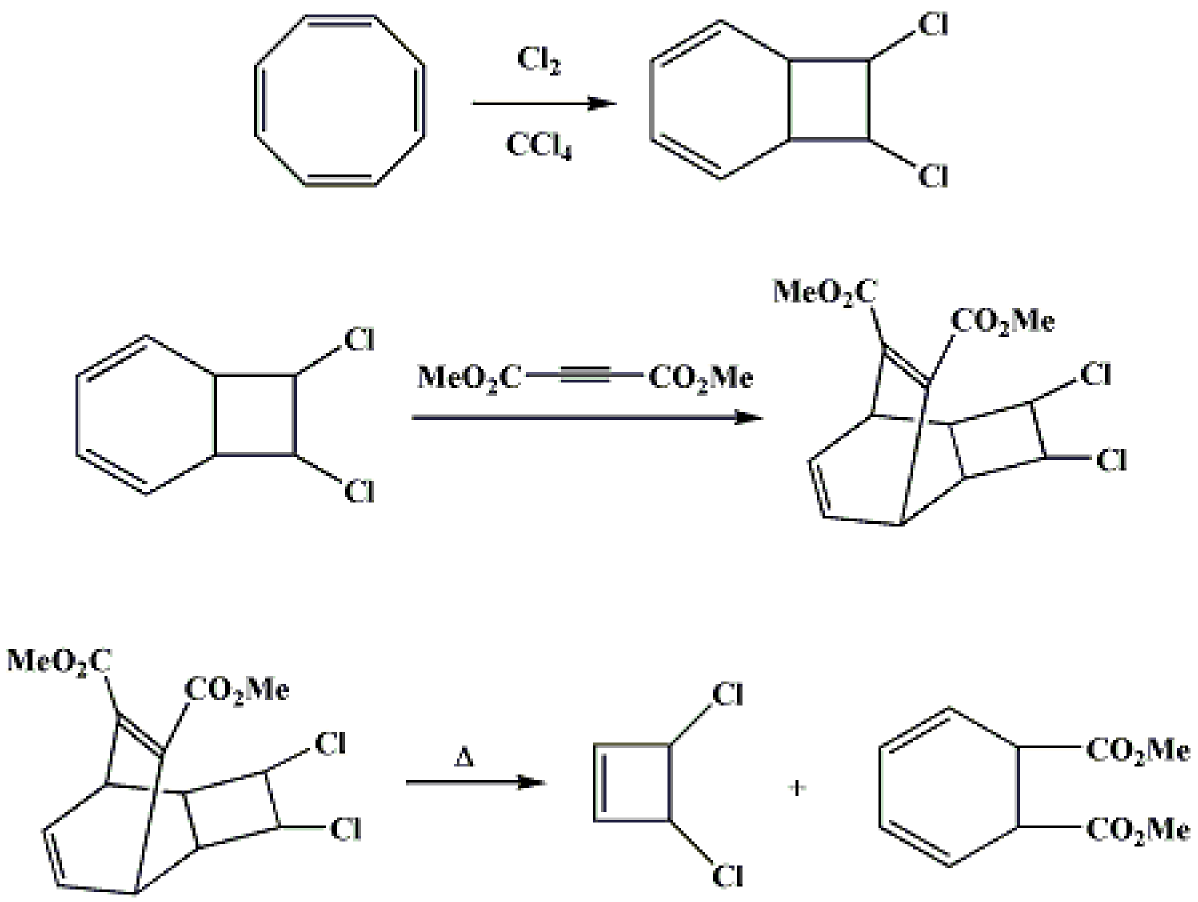
Organic Syntheses, *CV 6*, *422*

cis-3,4-DICHLOROCYCLOBUTENE

[Cyclobutene, 3,4-dichloro, *cis*-]



Submitted by R. Pettit[1] and J. Henery.
Checked by J. Napierski and R. Breslow.

1. Procedure

Dry chlorine gas is admitted into a solution of 104 g. (1.00 mole) of cycloöctatetraene in 150 ml. of dry carbon tetrachloride contained in a tared, 500-ml., three-necked flask equipped with a gas-inlet tube, a low-temperature thermometer, and a calcium chloride drying tube. The reaction mixture is maintained between –28° and –30° throughout the addition, which is terminated after 71 g. (1.0 mole) of chlorine has been added. After the addition, which takes approximately 1 hour, the reaction mixture is allowed to warm to 0° and 50 g. of powdered sodium carbonate is added, and the contents are shaken gently for several minutes. This treatment removes any hydrochloric acid which may have been produced during the reaction. The mixture is then filtered directly into a 1-l., round-bottomed flask containing 135 g. (0.951 mole) of dimethyl acetylenedicarboxylate. A condenser is fitted to the flask and the solution is heated at gentle reflux for 3 hours (Note 1). The solvent is removed under reduced pressure

(Note 2). The crude Diels-Alder adduct, which will slowly solidify on standing, is used directly in the next step.

The crude Diels-Alder adduct is transferred to a 500-ml., pressure-equalizing dropping funnel attached to a 1-l., three-necked, round-bottomed flask; the latter is immersed in an oil bath maintained at 200° and equipped with a distillation head, condenser, and receiving flask. The pressure inside the equipment is reduced to 20 mm. A magnetic stirrer in the pyrolysis flask is started, the Diels-Alder adduct (Note 3) is added slowly to the hot flask, and the pyrolysate collected in the receiving flask. The distillation temperature during the pyrolysis varies from 135° to 152°, depending on the rate of addition of the Diels-Alder adduct. After the addition is complete (about 1 hour), the pyrolysis is continued for a further 30 minutes or until very little material remains in the pyrolysis flask (Note 4). The crude pyrolysate is then redistilled at 12–15 mm., with all material boiling below 140° collected; this distillate consists mainly of a mixture of dichlorocyclobutene and 1,4-dichlorobutadiene, the residue being mainly dimethylphthalate.

A Final distillation at 55 mm. through a 36-in., platinum spinning band column yields 49–52 g. (40–43%) of pure *cis*-3,4-dichlorocyclobutene (b.p. 70–71°, 55 mm.); the forerun (b.p. 58–62°, 55 mm.) consists mainly of 1,4-dichlorobutadiene (Note 5).

2. Notes

1. The reaction is very exothermic and usually it is necessary to remove the external source of heat for a short period as soon as reflux has started.
2. Slight warming and pressures of about 1 mm. are required to remove the last of the solvent.
3. A sun lamp situated close to the funnel may be required to prevent solidification of the Diels-Alder adduct.
4. It is necessary to keep the internal pressure close to 20 mm. (place a manometer in the line). If lower pressures are used, the Diels-Alder adduct itself will distill over; if higher pressures are maintained, the rate of removal of the dichlorocyclobutene from the hot reaction flask is reduced and extensive thermal rearrangement to 1,4-dichlorobutadiene will occur.
5. A good fractionating column is required to separate the 1,4-dichlorobutadiene from the dichlorocyclobutene. At 55 mm. the dichlorobutadiene will distill at 58–62°; after this material has been removed, the temperature will rise fairly sharply to 70°, and at this point the reflux ratio may then be reduced from 10:1 to zero and the dichlorocyclobutene collected quickly. It usually is necessary to apply heat frequently with a sun lamp to prevent solidification of the dichlorobutadiene in the exit tube of the distillation apparatus, especially if the receiving flask is kept cold.

3. Discussion

This method of preparation, due to Nenitzescu, Avram, Marica, Dinulescu, Farcasiu,

Elian, and Mateescu,[2] is the only practical method available at this time for the preparation of 3,4-dichlorocyclobutene.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 310
- Org. Syn. Coll. Vol. 6, 1002

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

sodium carbonate (497-19-8)

carbon tetrachloride (56-23-5)

chlorine (7782-50-5)

Dimethyl acetylenedicarboxylate (762-42-5)

dichlorocyclobutene

3,4-dichlorocyclobutene

1,4-dichlorobutadiene

dimethylphthalate

dichlorobutadiene

cyclooctatetraene

cis-3,4-Dichlorocyclobutene, Cyclobutene, 3,4-dichloro, cis- (2957-95-1)

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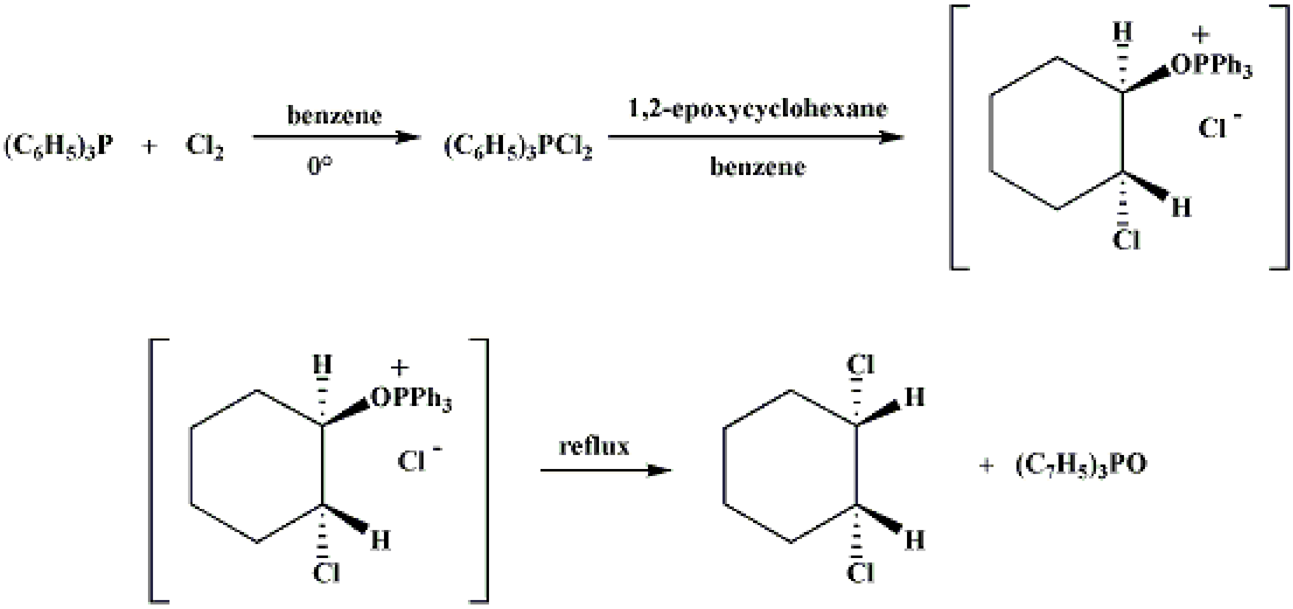
Organic Syntheses, CV 6, 424

cis-DICHLOROALKANES FROM EPOXIDES: *cis*-1,2-DICHLOROCYCLOHEXANE

[Cyclohexane, 1,2-dichloro-, *cis*-]



Submitted by James E. Oliver[1] and Philip E. Sonnet[2].
Checked by Jerrold M. Liesch and George Büchi.

1. Procedure

Caution! Benzene has been identified as a carcinogen. OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required. A hood should be employed for the chlorination.

A 1-l., three-necked flask is charged with 95 g. (0.36 mole) of triphenylphosphine (Note 1) and 500 ml. of anhydrous benzene, and fitted with a gas-inlet (Note 2), a mechanical stirrer, and a condenser with attached drying tube. The flask is cooled in an ice bath, stirring is begun, and chlorine is introduced through the gas-inlet. Dichlorotriphenylphosphorane separates as a white solid or as a milky oil; the flow of chlorine is discontinued when the mixture develops a strong lemon-yellow color (Note 3). The gas inlet is quickly replaced by an addition funnel, and a solution of 10 g. of triphenylphosphine in 60 ml. of benzene is added dropwise fairly rapidly (Note 4). A solution of 24.5 g. (0.250 mole) of 1,2-epoxycyclohexane (Note 5) in 50 ml. of benzene is then added dropwise over *ca.* 20 minutes. The ice bath is replaced by a heating mantle, and the mixture, which consists of two liquid phases, is stirred and refluxed for 4 hours. It is then cooled, and excess dichlorotriphenylphosphorane is destroyed by the slow addition of 10 ml. of methanol (Note 6). The mixture is concentrated on a rotary evaporator at *ca.* 100 mm., and the residue, which may be a white solid or a viscous oil, is triturated with 300 ml. of petroleum ether (30–60°). The solid triphenylphosphine oxide that separates is collected by suction filtration. The cake is thoroughly broken up with a spatula and washed with three 100-ml. portions of petroleum ether. The combined filtrates, from which a little more triphenylphosphine oxide precipitates, are refiltered, then washed with 250-ml. portions of aqueous 5% sodium bisulfite (Note 7) and with water. The organic phase is dried over magnesium sulfate, filtered, concentrated on a rotary evaporator at *ca.* 100 mm., and distilled through a 20-cm. Vigreux column. There is very little forerun before 27–

28 g. (71–73%) of *cis*-1,2-dichlorocyclohexane is collected at 105–110° (33 mm.), n_D^{25} 1.4977 (Note 8).

2. Notes

1. Triphenylphosphine was purchased from Aldrich Chemical Company, Inc. Use of a considerable excess of triphenylphosphine ensures complete reaction and obviates the need for rigorously dried glassware and reagents. Hydrochloric acid, generated by the reaction of dichlorotriphenylphosphorane and water, can react with the epoxide to produce a *trans*-chlorohydrin, which is, however, converted to a *cis*-dichloride by dichlorotriphenylphosphorane under the conditions of the reaction.
2. A glass tube of 7-mm. diameter is recommended. If chlorine is introduced through a fritted-glass tube, the dichlorotriphenylphosphorane collects on the frit as a sticky gum.
3. A sharp endpoint is not observed. A simple test for complete chlorination is as follows: the flow of chlorine and the stirrer are stopped, and the mixture is allowed to settle. Chlorine is then admitted without stirring. If unreacted triphenylphosphine is present, a visible clouding (formation of dichlorotriphenylphosphorane) will occur at the gas–liquid interface.
4. Although a slight excess of chlorine does not appear to be deleterious, a substantial excess is avoided by adding the last portion of triphenylphosphine at this point.
5. Commercial 1,2-epoxycyclohexane, supplied by Columbia Organic Chemicals Company, Inc., was used.
6. The reaction mixture may be allowed to stand overnight before addition of methanol.
7. The distilled *cis*-dichlorocyclohexane tends to become colored if the solution is not washed with a reducing agent.
8. The checkers, using a 10-cm. Vigreux column, found that it was necessary to take a wider boiling range fraction (105–115°, 33 mm.) to obtain similar yields. The product is virtually free of *trans*-1,2-dichlorocyclohexane (the isomeric 1,2-dichlorocyclohexanes are readily separated by GC on Carbowax 20M or on diethylene glycol succinate columns).

3. Discussion

This procedure is general for the conversion of epoxides to dichlorides with inversion of configuration at each of the two carbons and, in effect, provides a method for the *cis*-addition of chlorine to a double bond.[3] *cis*-1,2-Dichlorocyclohexane has also been prepared from 1,2-epoxycyclohexane and sulfuryl chloride,[4] but the stereospecificity of the reaction appears to be extremely sensitive to reaction conditions, and the yield is lower than that obtained by the method described here. Other methods give *cis*-1,2-dichlorocyclohexane contaminated with considerable amounts of the *trans*-isomer. This method has been used to convert *cis*- and *trans*-4,5-epoxyoctanes to *meso*- and *d,l*-4,5-dichloroöctanes, respectively, and *trans*-7,8-epoxyoctadecane to *threo*-7,8-dichloroöctadecane. These conversions were carried out on smaller amounts of material, and the products were purified by column chromatography on silica gel. Yields were 51–63%.

Halogenations with dihalotriphenylphosphoranes have been reviewed briefly by Fieser and Fieser.[5] Dibromotriphenylphosphorane appears to have been studied somewhat more than the dichloro compound, but both reagents effectively convert alcohols to alkyl halides, carboxylic acids and esters to acid halides, etc. The reaction of 1,2-epoxycyclohexane with dibromotriphenylphosphorane under conditions similar to those described here gives a mixture of *cis*- and *trans*-1,2-dibromocyclohexanes. A reagent prepared from triphenylphosphine and carbon tetrachloride has been used for similar transformations.[6]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

threo-7,8-dichlorooctadecane

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

methanol (67-56-1)

carbon tetrachloride (56-23-5)

sodium bisulfite (7631-90-5)

sulfuryl chloride (7791-25-5)

chlorine (7782-50-5)

1,2-epoxycyclohexane (286-20-4)

magnesium sulfate (7487-88-9)

triphenylphosphine (603-35-0)

triphenylphosphine oxide (791-28-6)

Dichlorotriphenylphosphorane (2526-64-9)

Dibromotriphenylphosphorane (1034-39-5)

cis-1,2-Dichlorocyclohexane, Cyclohexane, 1,2-dichloro-, cis- (10498-35-8)

cis-dichlorocyclohexane (2108-92-1)

trans-1,2-dichlorocyclohexane (822-86-6)

trans-7,8-epoxyoctadecane

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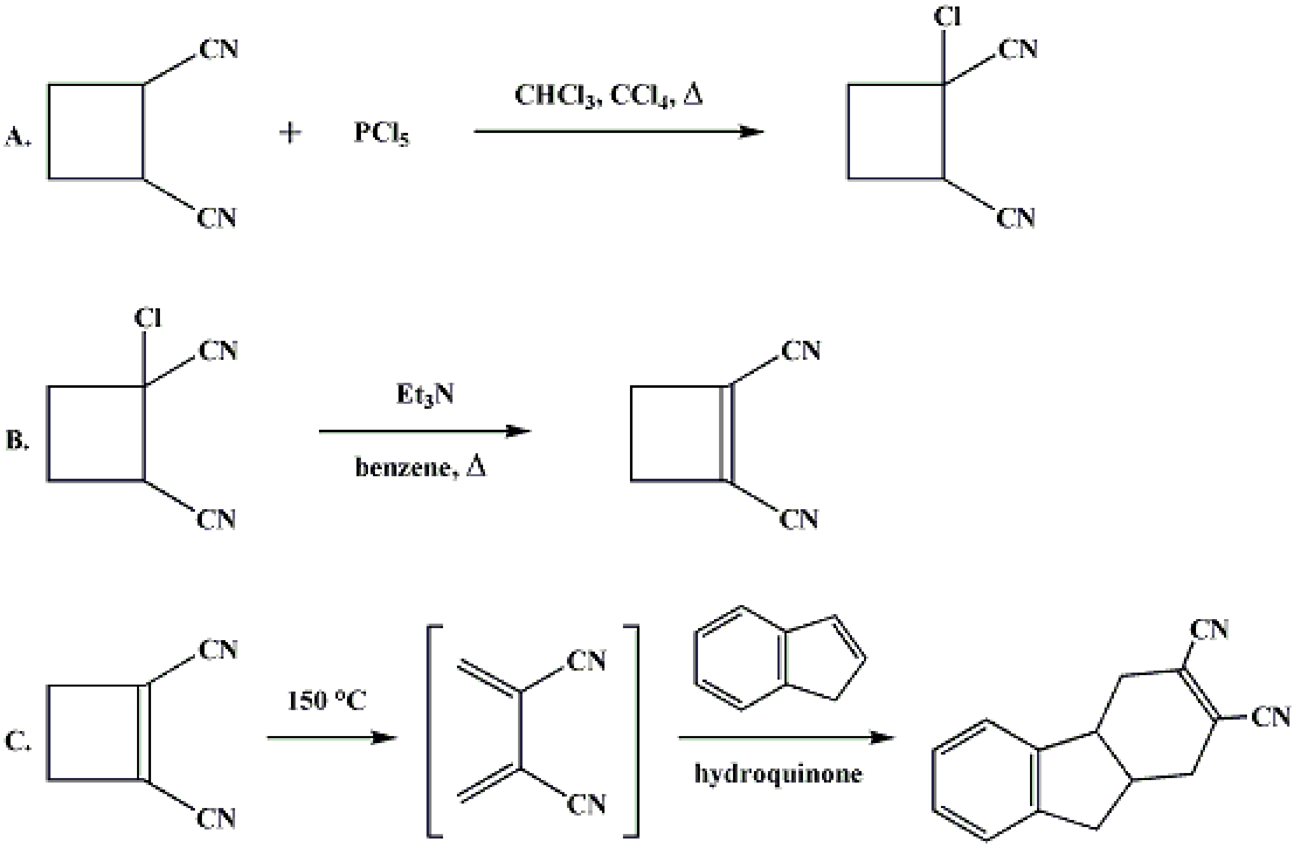
Organic Syntheses, CV 6, 427

2,3-DICYANOBUTADIENE AS A REACTIVE INTERMEDIATE BY *in situ* GENERATION FROM 1,2-DICYANOCYCLOBUTENE: 2,3-DICYANO-1,4,4*a*,9*a*-TETRAHYDROFLUORENE

[2,3-Fluorenedicarbonitrile, 1,4,4*a*,9*a*-tetrahydro-]



Submitted by D. Bellus[1], H. Sauter, and C. D. Weis.
Checked by A. J. Arduengo and William A. Sheppard.

1. Procedure

Caution! Benzene has been identified as a carcinogen. OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A. *1-Chloro-1,2-dicyanocyclobutane* (**1**). A 2-l., three-necked flask is equipped with a mechanical stirrer, a 500-ml. pressure-equalizing funnel, and an efficient reflux condenser provided with a gas-outlet tube connected by plastic tubing to a conical funnel inverted over a 5-l. beaker containing aqueous sodium hydroxide, for absorption of the evolved hydrogen chloride. The flask is charged with 562 g. (2.70 moles) of phosphorus pentachloride and 750 ml. of carbon tetrachloride. The rapidly stirred suspension is heated to reflux, and a solution of 159 g. (1.50 moles) of 1,2-dicyanocyclobutane (Note 1) in 120 ml. of chloroform is added dropwise over a period of 40 minutes (Note 2). After addition is complete, the solvents and the phosphorus trichloride formed during the reaction are removed by distillation at 100–150 mm. over a period of 40–60 minutes, with a bath temperature not exceeding 80° (Note 2). The residual liquid is cooled to room temperature and dissolved in 400 ml. of

diethyl ether (Note 3). The etheral solution is placed in a 500-ml.dropping funnel and added over a period of 3 hours to a stirred slurry of 1.7 kg. (12 moles) of sodium hydrogen carbonate, 800 g. of crushed ice, and 500 ml. of water. During the addition the temperature is maintained between −5° and 0° with an external ice–salt bath, and after the addition, stirring is continued for 1 hour at the same temperature. The precipitated salts are removed by suction filtration through a sintered-glass funnel of medium porosity and are thoroughly washed with 300 ml. of ether. The organic layer is separated, and the aqueous filtrate extracted with three 200-ml. portions of ether. The combined ether extracts are dried over anhydrous magnesium sulfate, filtered, and concentrated on a rotary evaporator, yielding 166–174 g. (79–83%) of a yellow oil consisting of an isomeric mixture of crude cyclobutane **1** (Note 4).

B. 1,2-*Dicyanocyclobutene* (**2**). A 2-l., three-necked, round-bottomed flask fitted with a 500-ml. pressure-equalizing dropping funnel, a mechanical stirrer, and a reflux condenser protected from moisture by a calcium chloride tube is charged with 131 g. (1.30 moles) of triethylamine (Note 5) and 400 ml. of benzene. The stirred solution is heated to gentle reflux, and a solution of 168.5 g. (1.199 moles) of crude cyclobutane 1 in 200 ml. of benzene is added dropwise over a period of 30 minutes. After addition is complete, the mixture is stirred under reflux for an additional 2 hours; the precipitated triethylamine hydrochloride is filtered from the cold solution and washed with 150 ml. of benzene. The combined filtrates are washed twice with 200-ml. portions of water and evaporated using a water aspirator at a bath temperature of 35°. The residue is distilled, yielding 105–110 g. (83–87%) of crude cyclobutene **2**, b.p. 55–60° (0.06 mm.) (Note 6).

C. 2,3-*Dicyano*-1,4,4a,9a-*tetrahydrofluorene* (**3**). A 100-ml., round-bottomed flask equipped with a reflux condenser under nitrogen pressure is charged with 10.4 g. (0.100 mole) of crude cyclobutene 2, 23.3 g. (0.201 mole) of indene (Note 7), and 0.3 g. of hydroquinone. The reaction mixture is stirred and heated at 150° for 4 hours under nitrogen. The reflux condenser is replaced by a still head, and 6.3 g. (0.053 mole) of indene is distilled from the flask at a bath temperature of about 95° (11 mm.) (Note 8). The dark-colored reaction mixture is transferred to a 500-ml., round-bottomed flask, diluted with 200 ml. of benzene followed by 1 g. of decolorizing carbon, and the resulting mixture is refluxed for 2 hours. After the mixture is cooled to room temperature, the carbon is removed by filtration, and the benzene is distilled. The residual oily residue solidifies on standing and is recrystallized from 45 ml. of ethanol, yielding 15.4–15.9 g. (70–72%) of crystalline fluorene **3**, m.p. 98.5–100° (Note 9).

2. Notes

1. 1,2-Dicyanocyclobutane (*cis*- and *trans*-isomer mixture) was purchased from Aldrich Chemical Company, Inc., and used without further purification.
2. The addition and distillation must be accomplished within the specified period of time; otherwise the amount of dichlorinated 1,2-dicyanocyclobutane increases considerably. The submitters found that an 80% molar excess of phosphorus pentachloride is optimum. A molar excess less than specified (under given experimental conditions) gives considerable unreacted starting material. Under forcing experimental conditions, such as longer reaction times and/or higher temperatures, the starting material can be completely consumed, even with less than 80% molar excess of phosphorus pentachloride, but a considerable amount of dichlorinated products is formed.
3. The checkers found that, because of the time required for completion of this step, a convenient modification is to cool the ether solution to −78° in dry ice and store overnight at −78°. A solid complex of phosphorus pentachloride and cyclobutane **1**, m.p. 88–91°, precipitates in the cold ether solution. This complex may not redissolve on warming to room temperature, but the suspension in ether can be used to proceed with the second half of Step A.
4. The checkers obtained the cyclobutane **1** as a colorless crystalline solid, m.p. 45–47° (a mixture of major and minor isomers), that is relatively free of 1,2-dichloro-1,2-dicyanocyclobutane. The product had the following spectral properties: ^{1}H NMR ($CDCl_3$) δ

(multiplicity): 2.35–3.15 (m), 3.40–4.20 (m); ^{13}C NMR ($CDCl_3$), δ: major isomer 21.58 (t), 38.41 (d), 37.24 (t), minor isomer 22.48 (t), 36.72 (d), 36.91 (t).

5. Reagent grade triethylamine was dried over sodium hydroxide and distilled before use (b.p. 88–89°).

6. The checkers obtained yields of 115 g. (92%) on a 1.2 mole scale and 94 g. (90%) on a 1.0 mole scale.

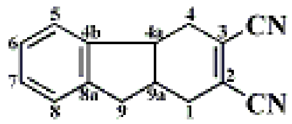
The product was analyzed by GC on a 1.23 m. × 0.65 cm. stainless-steel column of SE-52 on Varoport 30, which was heated to 150° and swept with helium at 60 ml. per minute. Retention times for the various components (minutes) are: cyclobutene **2**, (2.6); *trans*-1,2-dicyanocyclobutane(3.6); two isomeric 1,2-dichloro-1,2-dicyanocyclobutanes (5.1 and 5.9, respectively); *cis*-1,2-dicyanocyclobutane (9.8).

For most synthetic purposes, such as [4 + 2]- and [2 + 2]-cycloadditions,[2,3,4,5,6,7] ring-opening reactions,[2,8] and hydrolytic reactions,[2] this crude cyclobutene **2**, which contains approximately 1–3.5% of isomeric mixtures of 1,2-dichloro-1,2-dicyanocyclobutanes, can be used satisfactorily without further purification. Pure cyclobutene **2** can be prepared by treatment of the crude product with Raney cobalt, thereby removing residual quantities of isomeric 1,2-dichloro-1,2-dicyanocyclobutanes. In a typical experiment the crude product is placed in a 250-ml., round-bottomed flask and stirred with 10 g. of Raney cobalt for 4 hours at 70° under nitrogen. Distillation directly from the reaction vessel without filtering off the metal slurry yields 94–98 g. (60–63%) of cyclobutene **2** as a colorless liquid, n_D^{20} 1.4926, d_{22}^{4} 1.033. The Raney cobalt used by the submitters was obtained from Fluka A G, Buchs, Switzerland, as a suspension in water, and washed with tetrahydrofuran before use. Raney nickel and nickel tetracarbonyl, respectively, are also good dechlorinating reagents. The use of Raney cobalt, however, diminishes the danger of self-ignition during the preparation procedure. The spectral properties are as follows: IR (neat) cm^{-1}: 3002, 2957, 2230, 1612, 1422, 1251, 1169, 1003, and 623; UV (CH_3OH) nm. max. (log ε): 235 (4.06), 247 sh (3.90); ^{1}H NMR ($CDCl_3$), δ (multiplicity): 2.91 (s).

7. The indene used by the submitters was "practical grade," purchased from Fluka A G, Buchs, Switzerland. The indene used by the checkers was purchased from Aldrich Chemical Company, Inc. Both were distilled (b.p. 60–65°, 11 mm.) before use.

8. Recovered indene may be used for the next batch without further purification.

9. Fluorene **3** has the following spectral properties: IR (KBr) cm^{-1}: 2222, 1608, 1479, 1440, 773, and 742; UV (C_2H_5OH) nm. max. (log ε): 216 (4.10), 2.34 (3.99), 261 (3.16), 267 (3.11), and 274 (3.07); mass spectrum *m/e*: 220 (m^+) and 116 (base peak); ^{1}H NMR (100 MHz., $CDCl_3$): two complex multiplets for the aromatic and aliphatic protons (360 MHz., $CDCl_3$), δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 2.10 [d, *J* = 18; d, *J* = 7; and t, *J* = 3; one H of CH_2(1) or one H of CH_2(4)], 2.55–2.70 [m, one *H* of CH_2(1), one *H* of CH_2(4), one *H* of CH_2(9) and CH(9a)], 2.88 [d, *J* = 18; d, *J* = 7; d, *J* = 3; and d, *J* = 1.5; one *H* of CH_2(1) or one *H* of CH_2(4)], 3.11 [d, *J* = 15; d, *J* = 6, one *H* of CH_2(9)], 3.42 [d, *J* = 5; t, *J* = 7, C*H*(4a)], 7.20 (m, 4, aromatic *H*); ^{13}C NMR ($CDCl_3$), δ (assignment): 143.8 [*C*(8a)], 141.3 [*C*(4b)], 127.6, 127.2, and 125.6 [*C*(6), *C*(7), and *C*(8), not assigned individually], 126.6 and 125.9 [*C*(2) and *C*(3), not assigned], 123.2 [*C*(5)], 115.9 [two nitrile carbons], 40.2 [*C*(4a)], 38.4 [*C*(9)], 35.4 [*C*(9a)], 30.7 and 29.7 [*C*(1) and *C*(4), not assigned].



3. Discussion

Three syntheses of 1,2-dicyanocyclobutene (**2**) have been previously described. The first involves

dehydration of cyclobutene-1,2-dicarboxamide, with no specified yield.[9] The second procedure involves a concomitant chlorination and catalytic dehydrochlorination of 1,2-dicyanocyclobutane in the gas phase, yielding 1,2-dicyanocyclobutene (**2**) in a mixture of several other products.[10] The third method consists of dechlorination of 1,2-dichloro-1,2-dicyanocyclobutane using metals, such as zinc copper couple,[11] Raney nickel,[11] and, especially, Raney cobalt.[2] In comparison with the third synthesis, the overall yield of the present procedure is 5–10% higher. Furthermore, the reaction is performed in less time and utilizes considerably cheaper reagents.

Pure, crystalline 2,3-dicyanobutadiene has been prepared in high yield by gas-phase thermolysis of cyclobutene (**2**).[2,8] Analogously, thermolysis of derivatives of cyclobutene-1,2-dicarboxylic acid appears to represent a general procedure for the synthesis of derivatives of butadiene-2,3-dicarboxylic acid, of high purity.[2,12] These butadienes take part in [4 + 2]-cycloaddition reactions either as reactive dienes[2,13,14] or as reactive dienophiles.[2,14] In the pure state, however, they tend to polymerize, and even crystalline 2,3-dicyanobutadiene slowly polymerizes, yielding a highly cross-linked polymer without losing its original crystal form. A [2 + 4]-dimer of a 2,3-dicyanobutadiene is also formed by heating the dicyanocyclobutene in solution with a polymerization inhibitor.[2] Monomeric derivatives of butadiene-2,3-dicarboxylic acid cannot be prepared in solution because of rapid dimerization.[8,14]

The present procedure, *in situ* generation and trapping of 2,3-dicyanobutadiene in the presence of olefins, overcomes these problems and affords [4 + 2]-cycloadducts in good yields, particularly in the case of olefins possessing a strained double bond.[2] Substituted 1,2-dicyanocyclohexenes, prepared by the *in situ* [4 + 2]-cycloadditions, can be dehydrogenated to new aromatic *ortho*-dinitriles. For example, 2,3-dicyanofluorene is prepared in 56% yield by heating 2,3-dicyano-1,4,4*a*,9*a*-tetrahydrofluorene (3) at 200° in dimethylmaleate in the presence of 5% palladium on charcoal. Other aromatic *ortho*-dinitriles have also been prepared by this method.[2] Because 2,3-dicyanobutadiene is an electron-deficient diene, it does not react with electron-deficient olefins, such as maleic anhydride and fumaronitrile[2,8] using this procedure. However, by generating the dicyanobutadiene in refluxing chlorobenzene in the presence of maleic anhydride and 2,5-di-*tert*-butylbenzoquinone, as an inhibitor, the [2 + 4]-cyclic dicarbonitrile adduct, m.p. 201–202.5°, was formed in a yield of 38%.[15]

TABLE I

[4 + 2]-CYCLOADDITION REACTIONS OF 2,3-DICYANOBUTADIENE FORMED *in situ* FROM 1,2-DICYANOCYCLOBUTENE[2]

Olefin	Product	Yield (%)[a]	Temperature (°C)	Time (hours)
Norbornadiene	4,5-Dicyanotricyclo-[6.2.1.0^{2,7}]undeca-4,9-diene	79[b]	150	12
Acenaphthylene	8,9-Dicyano-6*b*,7,10,10*a*-tetrahydrofluoranthene	77	138	48
Cyclopentene	3,4-Dicyanobicyclo[4.3.0]non-3-ene	65	135	16
Ethylene	1,2-Dicyanocyclohexene	58	135	16
(*E*)-Stilbene	1,2-Dicyano-4,5-diphenylcyclohexene	32	138	24
Butyl vinyl ether	1,2-Dicyano-4-butoxycyclohexene	28	155	16

(*E*)-1,2-Dichloroethylene	1,2-Dicyano-4,5-*trans*-dichlorocyclohexene	8	135	16
2-Vinylpyridine	1,2-Dicyano-4-(2 -pyridyl) cyclohexene	5	138	48

[a] Yields of analytically pure products are given.

[b] A 70:24 mixture of *exo* and *endo* isomers. Some 2:1 cycloadduct was also isolated (2.4% yield).

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Raney cobalt

zinc copper couple

ethanol (64-17-5)

hydrogen chloride (7647-01-0)

Benzene (71-43-2)

ether, diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

phosphorus pentachloride (10026-13-8)

chloroform (67-66-3)

hydroquinone (123-31-9)

sodium hydrogen carbonate (144-55-8)

carbon tetrachloride (56-23-5)

nitrogen (7727-37-9)

Raney nickel (7440-02-0)

decolorizing carbon, carbon (7782-42-5)

chlorobenzene (108-90-7)

palladium (7440-05-3)

phosphorus trichloride (7719-12-2)

ethylene (9002-88-4)

magnesium sulfate (7487-88-9)

Cyclopentene (142-29-0)

indene (95-13-6)

Tetrahydrofuran (109-99-9)

maleic anhydride (108-31-6)

triethylamine (121-44-8)

Triethylamine hydrochloride (554-68-7)

Fumaronitrile (764-42-1)

helium (7440-59-7)

norbornadiene

cyclobutene (822-35-5)

2,3-DICYANOBUTADIENE

1,2-Dicyanocyclobutene, dicyanocyclobutene (3716-97-0)

1,2-dicyanocyclobutane

1,2-dichloro-1,2-dicyanocyclobutane

nickel tetracarbonyl

cyclobutene-1,2-dicarboxamide

cyclobutene-1,2-dicarboxylic acid

butadiene-2,3-dicarboxylic acid

2,3-dicyanofluorene

dimethylmaleate

dicyanobutadiene

4,5-Dicyanotricyclo-[6.2.1.0^{2,7}]undeca-4,9-diene

Acenaphthylene

3,4-Dicyanobicyclo[4.3.0]non-3-ene

1,2-Dicyanocyclohexene

1,2-Dicyano-4,5-diphenylcyclohexene

Butyl vinyl ether (111-34-2)

1,2-Dicyano-4-butoxycyclohexene

2-Vinylpyridine (100-69-6)

1,2-Dicyano-4-(2 -pyridyl)cyclohexene

(E)-stilbene (103-30-0)

2,5-di-tert-butylbenzoquinone

1-Chloro-1,2-dicyanocyclobutane (3716-98-1)

2,3-Dicyano-1,4,4a,9a-tetrahydrofluorene, 2,3-Fluorenedicarbonitrile, 1,4,4a,9a-tetrahydro- (52477-65-3)

cis-1,2-dicyanocyclobutane

(E)-1,2-Dichloroethylene (156-60-5)

1,2-Dicyano-4,5-trans-dichlorocyclohexene

trans-1,2-dicyanocyclobutane

8,9-Dicyano-6b,7,10,10a-tetrahydrofluoranthene

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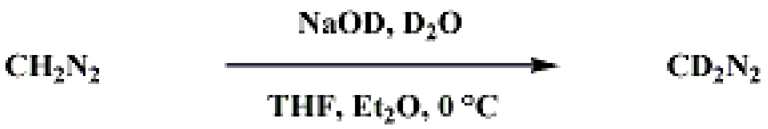
Organic Syntheses, CV 6, 432

DIDEUTERIODIAZOMETHANE

[Methane-d_2, diazo-]



Submitted by P. G. Gassman[1] and W. J. Greenlee.
Checked by David G. Melillo and Herbert O. House.

1. Procedure

Caution! Diazomethane is toxic and explosive. The operations described in this procedure must be carried out in a good hood with an adequate shield (Note 1).

A distilled, ethereal solution (300 ml.) containing approximately 0.06 mole of diazomethane (Note 1) is prepared from 22.5 g. of a 70% dispersion (15.8 g., 0.063 mole) of bis-(*N*-methyl-*N*-nitroso)terephthalamide (Note 2), 75 ml. of aqueous 30% sodium hydroxide, 55 ml. of diethylene glycol monoethyl ether, and 375 ml. of diethyl ether by the procedure described in *Org. Synth.*, **Coll. Vol. 5**, 351 (1973). The receiving flask containing the ethereal diazomethane is capped with a rubber stopper fitted with a drying tube containing potassium hydroxide pellets to protect the solution from atmospheric moisture. The concentration of diazomethane may be determined either by titration with ethereal benzoic acid (Note 3) or spectrophotometrically (Note 4).

A dry, 250-ml. Erlenmeyer flask equipped with a Teflon-coated magnetic stirring bar is charged with 11 ml. of a solution (Note 5) containing 0.01 mole of sodium deuteroxide in 10 ml. of deuterium oxide and 1 ml. of anhydrous tetrahydrofuran. After the solution has been cooled in an ice bath, 120 ml. of the ethereal solution containing 0.039 mole of diazomethane is added, the flask is stoppered loosely with a cork, and the reaction mixture is stirred vigorously at 0° for one hour. The lower deuterium oxide layer is removed with a pipette and a fresh 11-ml. portion of the sodium deuteroxide solution is added. This mixture is then stirred for one hour at 0°, and the process is repeated until a total of four exchanges have been performed. The ethereal diazomethane solution is then decanted into a clean, dry, 250-ml. Erlenmeyer flask and dried over 10 g. of anhydrous sodium carbonate. The resulting solution (approximately 110 ml.) contains (spectrophotometric analysis, (Note 4), or titration with benzoic acid, (Note 3)) 0.020–0.022 mole (51–56%) of dideuteriodiazomethane, which is 98–99% deuterated (Note 6).

2. Notes

1. Diazomethane is not only toxic, but also potentially explosive. Hence, one should wear heavy gloves and goggles and work behind a safety screen or a hood door with safety glass, as is recommended in the preparation of diazomethane described in *Org. Synth.*, **Coll. Vol. 4**, 250 (1963). As is also recommended, ground joints and sharp surfaces should be avoided; thus, all glass tubes should be carefully fire-polished, connections should be made with rubber stoppers, and separatory funnels should be avoided, as should etched or scratched flasks. Explosion of diazomethane has been observed at the moment crystals (sharp edges!) suddenly separated from a supersaturated solution. Stirring with a Teflon-coated magnetic stirrer is much preferred to swirling the reaction mixture by hand (there has been at least one case of a chemist whose hand was injured by an explosion during the preparation of diazomethane in a hand-swirled reaction vessel). It is imperative that diazomethane solutions not be exposed to direct sunlight or placed near a strong artificial light because light is thought to have been responsible for some of the explosions encountered with diazomethane. Particular caution should be exercised when an organic solvent boiling higher than ether is used. Because such a solvent has a vapor pressure lower than ether, the concentration of diazomethane in the vapor above the reaction mixture is greater and an explosion is more apt to occur. Since most diazomethane explosions occur during distillation, procedures that avoid distillation offer certain advantages. An ether solution of diazomethane satisfactory for many uses can be prepared as described in *Org. Synth.*, **Coll. Vol. 2**, 165 (1943), where nitrosomethylurea is added to a mixture of ether and 50% aqueous potassium hydroxide, and the ether solution of diazomethane is subsequently decanted from the aqueous layer and dried over potassium hydroxide pellets (not sharp-edged sticks!). However, the reported potent carcinogenicity[2] of nitrosomethylurea mitigates other advantages of this procedure. Two procedures involving distillation of diazomethane, those in *Org. Synth.*, **Coll. Vol. 4**, 250 (1963) and **Coll. Vol. 5**, 351 (1973), may be recommended. In neither case is there much diazomethane present in the distilling flask. The hazards associated with diazomethane are discussed by Gutsche.[3]

2. The submitters used an undistilled ethereal solution of diazomethane, prepared from nitrosomethylurea (Note 1).[4] For use in the hydrogen–deuterium exchange reaction described, ethereal diazomethane solutions prepared by any standard preparative procedures (Note 1) appear to be equally satisfactory: [*Org. Synth.*, **Coll. Vol. 4**, 250 (1963), **Coll. Vol. 2**, 165 (1943), and **Coll. Vol. 5**, 351 (1973)].

3. The concentration of diazomethane may be determined by reaction of an aliquot of the ethereal solution with a weighed excess of benzoic acid in cold (0°) ether solution, as described in *Org. Synth.*, **Coll. Vol. 2**, 165 (1943). The

unchanged benzoic acid is then determined by titration with standard aqueous 0.1 *M* potassium hydroxide.

4. *Caution! The following spectrophotometric analysis should be performed in a hood.* To determine the concentration of diazomethane obtained in this preparation, a 5-ml. aliquot of the distilled solution is diluted to 25 ml. with ether, and a portion of this solution is placed in a cylindrical Pyrex cell with an internal diameter of 1.0 cm. The optical density of the solution is determined at 410 nm with a suitable colorimeter such as a Bausch and Lomb Spectronic 20. From the molecular extinction coefficient, ε 7.2, at 410 nm for diazomethane in ether solution, the concentration of diazomethane can be calculated. In a typical preparation the optical density of the diluted solution at 410 nm was 0.46 corresponding to a diazomethane concentration of 0.064 *M*; thus, the concentration of the undiluted solution was 0.32 *M*, corresponding to a 77% yield of diazomethane.

5. It is convenient to prepare 110 ml. of this solution at a time. Since hydrogen is evolved, the solution should be prepared in a hood. A dry, 250-ml. three-necked flask is fitted with a magnetic stirrer, a rubber septum, a glass stopper, and a 125-ml. Erlenmeyer flask attached to the third neck of the reaction flask with a 10-cm. length of Gooch rubber tubing or nylon tubing. The apparatus is flushed with nitrogen from a hypodermic needle inserted through the rubber septum. Small, freshly cut chips of metallic sodium (2.3 g., 0.10 g.-atom) are placed in the Erlenmeyer flask and 100 ml. of deuterium oxide (99.7% pure grade obtained from Columbia Organic Chemicals Company, Inc.,) is placed in the reaction flask. With a hypodermic needle inserted through the rubber septum to permit the escape of hydrogen, the sodium chips are added, slowly and with stirring, to the reaction vessel. When reaction with the sodium is complete, the solution is diluted with 10 ml. of anhydrous tetrahydrofuran and stored under a nitrogen atmosphere.

6. The deuterium content can be determined by reaction of the deuterated diazomethane with benzoic acid- -*d* in anhydrous ether followed by analysis of methyl benzoate for deuterium content either by ^{1}H NMR spectroscopy or by mass spectroscopy. Benzoic acid- -*d* is prepared by heating a mixture of 48.6 g. (0.216 mole) of benzoic anhydride (obtained from Aldrich Chemical Company, Inc.), 0.10 g. (0.00090 mole) of anhydrous sodium carbonate, and 7.0 g. (0.35 mole) of deuterium oxide to 90° for 2 hours. The resulting mixture is distilled at atmospheric pressure in a short-path still fitted with a receiver protected from atmospheric moisture by a drying tube. After removal of a forerun, b.p. 100–101°, the benzoic acid-*O*-*d* is collected at 245–247°. During the distillation it is necessary to warm the distillation apparatus with a heat gun or an IR lamp to prevent solidification of the benzoic acid-*O*-*d* before it reaches the receiver. *Caution! The following reaction should be performed in a good hood (Note 1).* A cold (0°) solution of 1.43 g. (0.0116 mole) of benzoic acid-*O*-*d* in 10 ml. of anhydrous ether is placed in a dry, 100-ml., round-bottomed flask fitted with a rubber stopper and a Teflon-coated magnetic stirring bar. The flask is cooled in

an ice bath, and a sufficient amount of the ethereal dideuteriodiazomethane solution is added from a pipette, providing excess dideuteriodiazomethane in the reaction mixture. The reaction flask is stoppered loosely, and the resulting yellow solution is stirred at 0° for 10 minutes and concentrated by first warming the solution on a steam bath in the hood, then removing the last traces of solvent under reduced pressure. The residual liquid methyl benzoate (1.4–1.5 g., 90–95% yield) is analyzed for deuterium content. For a ^{1}H NMR analysis, the spectrum of the pure liquid is taken and the extent of deuteration is determined by integration of the areas under the multiplet in the region δ 7.1–8.3 (aromatic CH) and the peak at δ 3.82 (OCH_3). For mass spectroscopic analysis, the mass spectra of the deuterated sample and a sample of undeuterated methyl benzoate each are measured at an ionizing potential sufficiently low (approximately 12 eV.) to minimize the formation of an M-1 fragment at *m/e* 135 in the spectrum of the deuterated sample. The relative abundances of the *m/e* 136 and 137 peaks in the spectrum of the undeuterated sample are then used to correct the peaks at *m/e* 137, 138, and 139 in the deuterated sample for contributions from the ^{13}C isotope. From the relative abundances of the *m/e* 136 peak and the corrected *m/e* 137, 138, and 139 peaks in the spectrum of the undeuterated sample the relative proportions of d_0, d_1, d_2, and d_3 species in the deuterated methyl benzoate can be calculated. Both ^{1}H NMR and mass spectral analysis indicated the methyl benzoate to be 98% deuterated (6–7% d_2 species and 93–94% d_3 species). When the dideuteriodiazomethane solution was allowed to react with undeuterated benzoic acid, hydrogen–deuterium exchange occurred more rapidly than esterification. The methyl benzoate produced was 70% deuterated (^{1}H NMR analysis) and contained 4% d_0, 37% d_1, 30% d_2 and 29% d_3 species (mass spectral analysis).

3. Discussion

The exchange procedure described was developed for the preparation of dideuteriodiazomethane, for use in labeling studies. It is basically a modification of a procedure that has been used extensively;[5] however, the literature procedures give relatively little detail. This modified procedure permits the synthesis of fairly large amounts of high-purity dideuteriodiazomethane. Dideuteriodiazomethane has also been prepared from *N*-nitrosomethyl-d_3-urea and related trideuterated diazomethane precursors.[6] Deuterated chloroform and hydrazine hydrate have also been used to prepare dideuteriodiazomethane.[3,7]

The procedure described provides a general method for the hydrogen–deuterium exchange of simple diazoalkanes.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Methane-d_2, diazo-

N-nitrosomethyl-d_3-urea

ether, diethyl ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium carbonate (497-19-8)

nitrogen (7727-37-9)

Benzoic acid (65-85-0)

Benzoic anhydride (93-97-0)

potassium hydroxide, potassium hydroxide pellets (1310-58-3)

sodium (13966-32-0)

hydrazine hydrate (7803-57-8)

methyl benzoate (93-58-3)

Diazomethane (334-88-3)

Nitrosomethylurea

Tetrahydrofuran (109-99-9)

bis-(N-methyl-N-nitroso)terephthalamide

diethylene glycol monoethyl ether (111-90-0)

Dideuteriodiazomethane (14621-84-2)

sodium deuteroxide (14014-06-3)

deuterium oxide (7789-20-0)

deuterium (7782-39-0)

Benzoic acid- -d, benzoic acid-O-d (1005-01-2)

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Organic Syntheses, CV 6, 436

DIETHYLALUMINUM CYANIDE

[Aluminum, cyanodiethyl-]

$$Et_3Al + HCN \xrightarrow{\text{benzene}} Et_2AlCN + Et\text{-}H$$

Submitted by W. Nagata[1] and M. Yoshioka.
Checked by S. C. Welch, P. Bey, and Robert E. Ireland.

1. Procedure

Caution! This preparation should be conducted in a well-ventilated hood, and neat triethylaluminum must be handled with great care.

Benzene has been identified as a carcinogen. OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A tared, 500-ml., round-bottomed flask is fitted with a vacuum take-off, and the entire assembly is connected through an adaptor containing a stopcock to an inverted cylinder of triethylaluminum, as shown in f.htmigure 1. The assembly is connected to a nitrogen source (Note 1) through the vacuum take-off, and with the cylinder valve closed but the stopcock open, the system is alternately evacuated and filled with nitrogen four times. With the system filled with nitrogen the cylinder valve is opened and approximately 55 ml. (46 g; 0.40 mole) of triethylaluminum (Note 2) is allowed to flow into the reaction flask. The cylinder valve is then closed; the system is evacuated and filled three times with nitrogen, and the adaptor stopcock is then closed (Note 3). The reaction flask is then quickly removed, stoppered, and weighed to determine the exact amount of triethylaluminum collected. A magnetic stirring bar is added and the flask is fitted with a vacuum take-off and 250-ml., pressure-equalizing dropping funnel. The system is again placed under a nitrogen atmosphere, and the triethylaluminum is dissolved in 150 ml. of anhydrous benzene, added through the dropping funnel. The dropping funnel is charged with a solution of 11.9 g. (0.441 mole) of hydrogen cyanide (Note 4) in 100 ml. of anhydrous benzene, which is added dropwise to the solution of triethylaluminum, with stirring and cooling. Preferably, the addition is carried out at a constant rate such that the hydrogen cyanide solution is added in about 2 hours. The evolution of ethane becomes slow suddenly after one molar equivalent of hydrogen cyanide is added (Note 5). After the addition is complete, the reaction mixture is allowed to stir overnight (Note 6).

Figure 1. Apparatus for collection of triethylaluminum.

Figure 1. Apparatus for collection of triethylaluminum.

After this period, the dropping funnel and the vacuum take-off are replaced by the short-path distillation assembly shown in f.htmigure 2. The system is protected with a Drierite tube, and the benzene is distilled under reduced pressure (water aspirator). After the benzene is removed, the benzene-containing receiver is replaced with a clean, dry flask, and the system is connected to an efficient vacuum pump. The pressure in the system is reduced to 0.02 mm., and the flask is immersed deeply in an oil bath (f.htmigure 2) heated to about 200°. After about 1 ml. of forerun is collected, diethylaluminum cyanide distils at 162° (0.02 mm.) (Note 7) and is collected in a tared, 200-ml. receiver by heating the side arm and the adaptor with a stream of hot air or an IR lamp (Note 8). After all the distillate is collected in the receiver (Note 9), dry nitrogen is admitted to the evacuated apparatus, and the receiver is stoppered, giving 26.7–35.6 g. (60–80%) of diethylaluminum cyanide, usually as a pale, yellow syrup (Note 10) and (Note 11).

>Figure 2. Short-path distillation apparatus.

>Figure 2. Short-path distillation apparatus.

The stopper of the flask is quickly replaced with the nitrogen adaptor, and after placing the system under a nitrogen atmosphere, the diethylaluminum cyanide is treated with 130 ml. of dry benzene. The resulting mixture is allowed to stand with occasional swirling under nitrogen until the syrup goes into solution (Note 12). Sufficient dry benzene is then added to make the total volume of the solution 200 ml. After thorough mixing with a magnetic stirring bar, the resulting diethylaluminum cyanide solution (13.4–17.8%; 1.2–1.6 *M*) may be divided and stored in sealed ampoules (Note 13).

2. Notes

1. The nitrogen source described in *Org. Synth.*, **Coll. Vol. 4**, 133 (1963), Figure 5, was used.
2. The exact volume of the triethylaluminum added at this point is not critical, since the exact weight is determined later. The use of a 25% solution of triethylaluminum in benzene, available from the Stauffer Chemical Company, 299 Park Avenue, New York, eliminates the tedious preparation of the triethylaluminum solution described in this procedure.
3. These precautions will ensure the removal of any adhering triethylaluminum that will flame when the apparatus is disassembled.
4. A 10% molar excess of hydrogen cyanide was employed, and the quantity added at this point was determined by the amount of triethylaluminum collected.

Hydrogen cyanide can be prepared as described in *Tetrahedron Lett.*, 461 (1962).

5. The change in the rate of gas evolution is sometimes not clear, especially when the temperature of the hood is high. When the change is recognized distinctly, the addition of hydrogen cyanide solution may be stopped.

6. The reaction mixture containing about 13% (1.2 *M*) of diethylaluminum cyanide and a small amount of ethylaluminum dicyanide may be used for most hydrocyanation processes without further purification. Care must be taken to have no unchanged triethylaluminum, since the submitters have observed that hydrocyanation of Δ^8-11-keto steroids with diethylaluminum cyanide is greatly retarded by the presence of a small amount of unchanged triethylaluminum.[2,3]

7. The checkers collected diethylaluminum cyanide at 170–180° (0.35 mm.) and 167–175° (0.25 mm.).

8. Heating of the glassware above 150° with a hot air stream or IR lamp is needed to make the viscous product run into the receiver.

9. The pot residue contains ethylaluminum dicyanide as a nonvolatile mass, most of which may be removed with a spatula and decomposed with isopropyl alcohol and then water. The flask is then washed with running water and 20% hydrochloric acid to remove the mass completely.

10. The submitters have obtained an almost colorless syrup by reaction of purified triethylaluminum with hydrogen cyanide, followed by repeated distillation.

11. The yield depends on the efficiency of the collection of the viscous distillate in the receiver.

12. It takes considerable time (5–10 hours) to dissolve diethylaluminum cyanide. Magnetic stirring is not effective unless most of the material goes into solution.

13. Diethylaluminum cyanide dissolved in benzene, toluene, hexane, or isopropyl ether and stored in ampoules is stable for a long period. The cyanide is not stable in tetrahydrofuran. The anhydrous benzene used in the reaction may be replaced by diethyl or diisopropyl ether. A 1–2 *M* solution of diethylaluminum cyanide in benzene is commercially available from Alfa Products, Ventron Corporation, Danvers, Massachusetts.

3. Discussion

Formation of diethylaluminum cyanide from triethylaluminum and hydrogen cyanide was noted initially by the submitters[4] and later by Stearns,[5] but isolation and characterization of the product were first performed by the submitters.[3] An impractical process comprised of heating diethylaluminum chloride and sodium cyanide in benzene for 21 days has been reported.[6]

Diethylaluminum cyanide is a useful, potent reagent for hydrocyanation of various compounds. Features of this reagent as compared with the triethylaluminum–hydrogen

cyanide reagent may be obtained from the literature.[2,3,7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 307
- Org. Syn. Coll. Vol. 6, 520

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

diethyl or diisopropyl ether

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

sodium cyanide (143-33-9)

hydrogen cyanide (74-90-8)

nitrogen (7727-37-9)

toluene (108-88-3)

isopropyl alcohol (67-63-0)

ethane (74-84-0)

Tetrahydrofuran (109-99-9)

isopropyl ether (108-20-3)

hexane (110-54-3)

triethylaluminum (97-93-8)

Diethylaluminum cyanide (5804-85-3)

Aluminum, cyanodiethyl-

ethylaluminum dicyanide

diethylaluminum chloride

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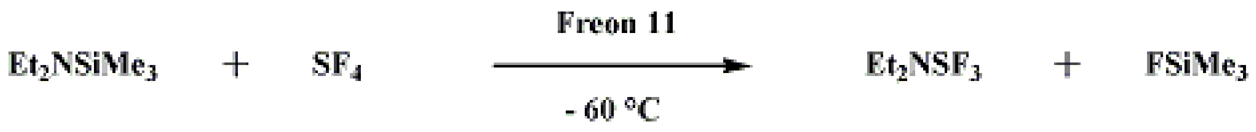
Organic Syntheses, CV 6, 440

DIETHYLAMINOSULFUR TRIFLUORIDE

[Sulfur, (diethylaminato)trifluoro-]



Submitted by W. J. Middleton[1] and E. M. Bingham[1].
Checked by Ronald F. Sieloff, Eugene R. Kennedy, and Carl R. Johnson.

1. Procedure

Caution! This procedure should be conducted in a good hood to avoid exposure to sulfur tetrafluoride. Protective gloves should be worn when handling diethylaminosulfur trifluoride since this material can cause severe HF burns.

A dry, 1-l., three-necked, round-bottomed flask is equipped with a thermometer (−100° to 50°), a magnetic stirrer, and two dry-ice condensers (one condenser is capped with a drying tube, the other with a gas-inlet tube). The apparatus is flushed with dry nitrogen, and 300 ml. of trichlorofluoromethane (Note 1) is added to the flask. As the nitrogen atmosphere is maintained, the trichlorofluoromethane is cooled to −70° with an acetone–dry ice bath, and 119 g. (1.10 moles) of sulfur tetrafluoride (Note 2) is added from a cylinder through the gas-inlet tube (Note 3), which is then replaced with a 250-ml., pressure-equalizing dropping funnel charged with a solution of 145 g. (1.00 mole) of *N*,*N*-diethylaminotrimethylsilane (Note 4) in 90 ml. of trichlorofluoromethane. This solution is added dropwise, with stirring, to the sulfur tetrafluoride solution at a rate slow enough to keep the temperature of the reaction mixture below −60° (about 40 minutes). The cooling bath is removed, and the reaction mixture is allowed to warm gradually to room temperature. The apparatus is prepared for distillation with a simple distillation head, and the solvent (b.p. 24°) and by-product fluorotrimethylsilane (b.p. 17°) are distilled into a well-cooled receiver by warming the reaction mixture gently to 45° with a heating mantle. The yellow to dark-brown residual liquid is transferred and distilled at reduced pressure through a spinning-band column, yielding 131 g. (81%) of diethylaminosulfur trifluoride as a light yellow liquid, b.p. 46–47° (10 mm.) (Note 5). This product can be stored for several months at room temperature in an inert plastic bottle (such as one made of polypropylene or Teflon FEP), or for short periods of time in a dry, glass bottle.

2. Notes

1. Trichlorofluoromethane (Freon 11) is available from E. I. duPont de Nemours and Company, Inc., or Matheson Gas Products.

2. Sulfur tetrafluoride is available from Air Products and Chemicals, Inc., or Matheson Gas Products.
3. If it is inconvenient to add sulfur tetrafluoride directly from a cylinder, it may first be condensed in a calibrated trap containing a boiling chip and cooled in an acetone–dry ice bath. When cooled to −78°, 119 g. of sulfur tetrafluoride has a volume of about 62 ml. The sulfur tetrafluoride can be added to the cooled flask by allowing it to distil slowly from the trap.
4. *N,N*-Diethylaminotrimethylsilane is available from PCR, Inc., or it can be prepared by the following procedure. A solution of 292 g. (413 ml.) of diethylamine in 1000 ml. of diethyl ether is cooled in an ice bath, and a solution of 216 g. (252 ml.) of chlorotrimethylsilane in 200 ml. of ether is added dropwise with mechanical stirring over a period of 1 hour. The precipitated solid is removed by filtration, thoroughly washed with ether, and the filtrate is fractionally distilled, yielding 175 g. (60%) of *N,N*-diethylaminotrimethylsilane as a colorless liquid, b.p. 124–125°.
5. The reaction of diethylaminosulfur trifluoride with water is highly exothermic; clean-up procedures should be carried out with caution.

3. Discussion

Diethylaminosulfur trifluoride is a useful and convenient reagent for replacing primary, secondary, and tertiary hydroxyl and aldehyde and ketone carbonyl oxygen[2,3] with fluorine, even in the presence of other halogens and other functional groups, such as carboxylic esters. In contrast to sulfur tetrafluoride, this reagent is a liquid easily measured and used in standard glass equipment at moderate temperatures and atmospheric pressure, and can be used on acid-sensitive compounds (such as pivaldehyde) to convert them into the fluorinated derivative. In contrast to other reagents such as SF_4, SeF_4 pyridine HF, HF.pyridine, and $(C_2H_5)_2NCF_2CFHCl$, this reagent can replace hydroxyl groups with fluorine in primary alcohols such as 2-methyl-1-propanol without causing extensive rearrangement or dehydration.

This preparation of diethylaminosulfur trifluoride is an adaptation of a procedure first described by von Halasz and Glemser.[4] The same procedure can also be used to prepare other dialkylaminosulfur trifluorides by the substitution of the diethylaminotrimethylsilane with other dialkylaminotrimethylsilanes.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 628
- Org. Syn. Coll. Vol. 6, 835

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Sulfur, (diethylaminato)trifluoro-

Freon 11

ether, diethyl ether (60-29-7)

nitrogen (7727-37-9)

diethylamine (109-89-7)

2-methyl-1-propanol (78-83-1)

trichlorofluoromethane (75-69-4)

sulfur tetrafluoride (7783-60-0)

CHLOROTRIMETHYLSILANE (75-77-4)

Diethylaminosulfur trifluoride (38078-09-0)

fluorotrimethylsilane (420-56-4)

diethylaminotrimethylsilane, N,N-diethylaminotrimethylsilane (996-50-9)

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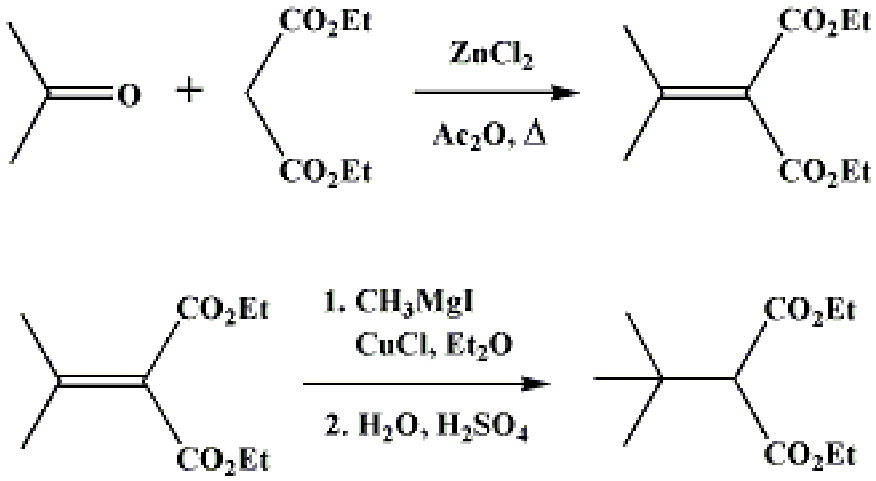
Organic Syntheses, CV 6, 442

DIETHYL *tert*-BUTYLMALONATE

[Propanedioic acid, (1,1-dimethylethyl)-, diethyl ester]



Submitted by E. L. Eliel[1,2], R. O. Hutchins[1,3], and Sr. M. Knoeber[1].
Checked by Walter J. Campbell and Herbert O. House.

1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

Methyl iodide, in high concentrations for short periods or in low concentrations for long periods, can cause serious toxic effects in the central nervous system. Accordingly, the American Conference of Governmental Industrial Hygienists[4] has set 5 p.p.m., a level which cannot be detected by smell, as the highest average concentration in air to which workers should be exposed for long periods. The preparation and use of methyl iodide should always be performed in a well-ventilated fume hood. Since the liquid can be absorbed through the skin, care should be taken to prevent contact.

A. *Diethyl isopropylidenemalonate*. A 2-l. flask equipped with a magnetic stirrer and a reflux condenser fitted with a calcium chloride drying tube is charged with 400 g. (2.50 moles) of diethyl malonate (Note 1), 216 g. (3.73 moles) of acetone (Note 2), 320 g. (3.14 moles) of acetic anhydride, and 50 g. (0.37 mole) of anhydrous zinc chloride (assay 98.9%, (Note 3)). The solution is heated at reflux, with stirring, for 20–24 hours, then cooled and diluted with 300–350 ml. of benzene. The resulting dark-colored solution is washed with four 500-ml. portions of water, and the combined aqueous layers are extracted with two 100-ml. portions of benzene. The combined

benzene solutions are concentrated with a rotary evaporator, and the residual liquid is fractionally distilled under reduced pressure through a 30-cm. Vigreux column or spinning band column. After separation of the unchanged diethyl malonate [119–135 g., b.p. 85–87° (9 mm.)] and intermediate fractions [b.p. 87–104° (9 mm.)], diethyl isopropylidenemalonate is collected as 231–246 g. (46–49%) of colorless liquid, b.p. 110–115° (9–10 mm.), n_D^{20} 1.4483–1.4490 (Note 4).

B. *Diethyl tert-butylmalonate*. A 1-l., three-necked flask fitted with a mechanical stirrer, a pressure-equalizing dropping funnel, a reflux condenser, and a nitrogen inlet tube is dried in an oven at 110–120°, then flushed with nitrogen and allowed to cool; an atmosphere of nitrogen is maintained in the reaction vessel throughout the subsequently described reactions. After 18.3 g. (0.753 g.-atom) of magnesium turnings have been placed in the flask, a solution of 113.5 g. (0.7993 mole) of methyl iodide (Note 5) in 200 ml. of anhydrous diethyl ether (Note 6) is added dropwise with stirring. The resulting solution of methylmagnesium iodide is cooled to 0–5° with an external ice–salt bath, and 1.0 g. (0.010 mole) of copper(I) chloride is introduced with stirring (Note 7). The temperature of the resulting mixture is kept at –5° to 0° while a solution of 100 g. (0.500 mole) of diethyl isopropylidenemalonate in 100 ml. of anhydrous ether (Note 6) is added, dropwise and with stirring over a period of 80–90 minutes. After the addition is complete, the cooling bath is removed; the reaction mixture is stirred for 30 minutes and poured onto a mixture of 500–1000 g. of ice and 400 ml. of 10% sulfuric acid. The ether layer is separated and the aqueous phase is extracted with three 200-ml. portions of ether. The combined ether solutions are washed with 100 ml. of saturated aqueous sodium thiosulfate (Note 8), dried over magnesium sulfate, and concentrated with a rotary evaporator. The residual liquid is distilled through a short Vigreux column, yielding 93.5–102 g. (87–94%) of diethyl *tert*-butylmalonate as a colorless liquid, b.p. 60–61° (0.7 mm.), n_D^{20} 1.4250 (Note 9).

2. Notes

1. A commercial grade of diethyl malonate was distilled before use, b.p. 90° (15 mm.).
2. The submitters used commercial acetone which was dried over potassium carbonate before use. The checkers dried acetone over Linde Molecular Sieves, No. 4A.
3. The checkers used a proportionate amount (52 g.) of anhydrous zinc chloride (assay, 95% minimum) purchased from the Mallinckrodt Chemical Works.
4. This procedure was described by Cope and Hancock.[5] The product has IR absorption (CCl_4) at 1730 (conjugated ester C=O) and 1650 cm.$^{-1}$ (conjugated C=C) with ^{1}H NMR peaks (CCl_4) at δ 1.12 (t, J = 7 Hz., 6H), 2.01 (s, 6H), 4.10 (q, J = 7 Hz., 4H), and a UV maximum (95% EtOH) at 218 nm (ε 10,200).
5. Reagent grade methyl iodide, obtained from J. T. Baker Chemical Company, Philadelphia, was used without further purification. The checkers used a pure

grade of methyl iodide purchased from Eastman Organic Chemicals without further purification.

6. Anhydrous ether, from freshly opened containers, obtained from the Mallinckrodt Chemical Works, was used without further purification. The checkers used Baker and Adamson anhydrous ether purchased from the Industrial Chemicals Division of Allied Chemical Company.

7. The checkers found that this preparation was equally successful when a solution of 0.50 mole of diethyl isopropylidenemalonate in 100 ml. of ether was added over 25 minutes to an ethereal solution of 0.55 mole of lithium dimethylcuprate. A solution of this reagent was prepared by adding 1.10 moles of methyllithium in ether solution (purchased from Foote Mineral Co., Exton, Pennsylvania) to a cold (–10°) suspension of 0.55 mole of copper(I) iodide in 200 ml. of anhydrous ether. The reaction mixture containing a suspension of yellow methylcopper was stirred at –5° for 5 minutes, then quenched with an aqueous mixture (pH 9) of ammonia and ammonium chloride. The product was isolated and distilled in the usual way, yielding 100 g. (93%) of the diethyl *tert*-butylmalonate, b.p. 57–61° (0.5–0.7 mm.), $n^{26.9}_{D}$ 1.4224.

8. The hydroiodic acid liberated during the hydrolysis step is frequently oxidized to iodine, which contaminates the final product. Washing the organic phase with aqueous sodium thiosulfate ensures the absence of this impurity in the final product.

9. The product has IR absorption (CCl_4) at 1750 cm.$^{-1}$ (ester C=O) with ^1H NMR peaks (CCl_4) at 1.08 (s, 9H), 1.22 (t, J = 7 Hz., 6H), 3.03 (s, 1H), and 4.05 (q, J = 7 Hz., 4H).

3. Discussion

Although diethyl *tert*-butylmalonate may be prepared in low yield by the alkylation of diethyl sodiomalonate with *tert*-butyl bromide[6] or *tert*-butyl chloride,[7] the alkylation of active methylene compounds such as malonic esters with *tert*-alkyl halides is normally a poor preparative procedure because of competing dehydrohalogenation of the alkyl halide.[8] A more satisfactory synthetic route to *tert*-alkyl derivatives of malonic esters and related compounds consists of the conjugate addition of alkyl- or arylmagnesium halides to alkylidenemalonates or alkylidenecyanoacetates.[8,9] Thus, diethyl *tert*-butylmalonate has been prepared in yields of 37–64% by the conjugate addition of methylmagnesium iodide to isopropylidenemalonate.[10,11]

The addition of copper salts was found to favor the conjugate addition of Grignard reagents to alkylidenemalonic esters,[12] and Munch-Peterson subsequently found that the addition of 1 mole % of copper(I) chloride was generally useful for promoting the addition of Grignard reagents to α,β-unsaturated esters.[13] The preformed copper(I) reagents such as the ether-soluble lithium dialkyl- or diarylcuprates are even more

effective reactants in conjugate additions to α,β-unsaturated carbonyl compounds.[14] The present preparation illustrates the use of copper(I) chloride to catalyze the addition of methylmagnesium iodide to an alkylidenemalonic ester. In this case high yields of the conjugate addition product are obtained either by this procedure or by the use of lithium dimethylcuprate (Note 7). In a related preparation[15] successive addition of three moles of methylmagnesium iodide in the presence of copper(I) bromide to $(CH_3S)_2C=C(CO_2C_2H_5)_2$ proceeds with elimination of thiomethylmagnesium halide in the first two stages.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 762
- Org. Syn. Coll. Vol. 7, 346

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

ammonia (7664-41-7)

Benzene (71-43-2)

ether, diethyl ether (60-29-7)

acetic anhydride (108-24-7)

ammonium chloride (12125-02-9)

magnesium turnings (7439-95-4)

tert-Butyl bromide (507-19-7)

sodium thiosulfate (7772-98-7)

nitrogen (7727-37-9)

iodine (7553-56-2)

acetone (67-64-1)

copper(I) bromide (7787-70-4)

zinc chloride (7646-85-7)

tert-Butyl chloride (507-20-0)

hydroiodic acid (10034-85-2)

copper(I) chloride (7758-89-6)

Methyl iodide (74-88-4)

methylmagnesium iodide (917-64-6)

diethyl malonate (105-53-3)

copper(I) iodide (7681-65-4)

magnesium sulfate (7487-88-9)

Methyllithium (917-54-4)

diethyl sodiomalonate

copper(I)

lithium dimethylcuprate

Propanedioic acid, (1,1-dimethylethyl)-, diethyl ester, Diethyl tert-butylmalonate (759-24-0)

Diethyl isopropylidenemalonate (6802-75-1)

methylcopper

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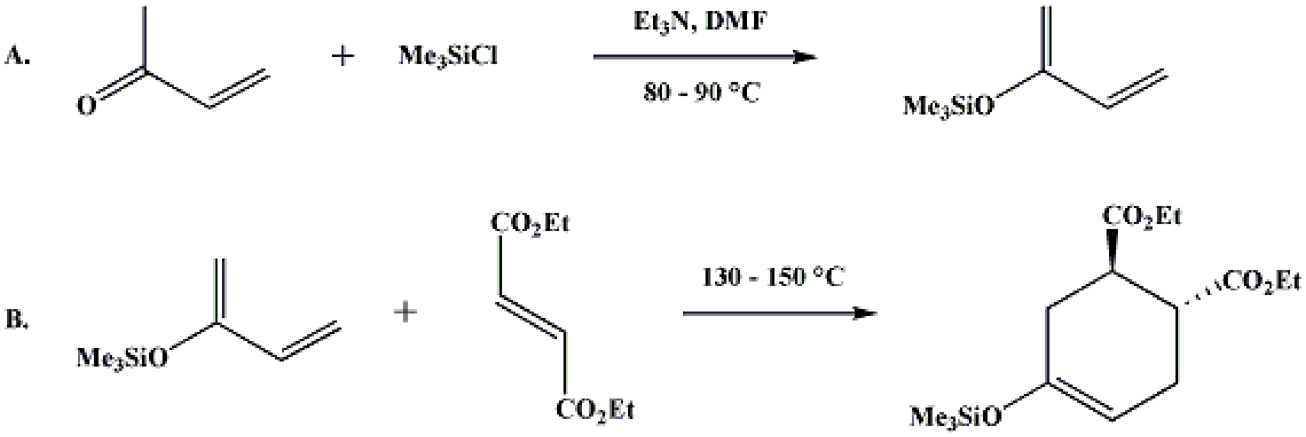
2-TRIMETHYLSILYLOXY-1,3-BUTADIENE AS A REACTIVE DIENE: DIETHYL *trans*-4-TRIMETHYLSILYLOXY-4-CYCLOHEXENE-1,2-DICARBOXYLATE

[4-Cyclohexene-1,2-dicarboxylic acid, 4-trimethylsilyloxy-, diethyl ester, *trans*-]



Submitted by Michael E. Jung and Charles A. McCombs[1].
Checked by Ping Sun Chu and George H. Büchi.

1. Procedure

Caution! Part A should be carried out in a hood, since the reagents are noxious.

A. 2-*Trimethylsilyloxy*-1,3-*butadiene* (**1**). An oven-dried, 500-ml., three-necked, round-bottomed flask is fitted with two oven-dried addition funnels, a glass stopper, and magnetic stirrer, and placed in a 80–90° oil bath. Under an inert atmosphere, methyl vinyl ketone (25.0 g., 0.357 mole) in 25 ml. of *N*,*N*-dimethylformamide and chlorotrimethylsilane (43.4 g., 0.400 mole) in 25 ml. of *N*,*N*-dimethylformamide are added over 30 minutes to a magnetically stirred solution of triethylamine (40.5 g., 0.400 mole) in 200 ml. of *N*,*N*-dimethylformamide (Note 1). The reaction gradually darkens from colorless to yellow or dark brown, and supports a white precipitate of triethylamine hydrochloride. The reaction is set up to run overnight, or *ca.* 14 hours.

The reaction is cooled to room temperature, filtered (Note 2), and transferred to a 2-l. separatory funnel containing 300 ml. of pentane. To this solution is added 1 l. of *cold* 5% sodium hydrogen carbonate solution to facilitate the separation of phases and remove the *N*,*N*-dimethylformamide. The pentane layer is separated, and the aqueous layer extracted twice with 300-ml. portions of pentane. The pentane extracts are combined, washed with 200 ml. of *cold* distilled water (Note 3), dried over powdered anhydrous sodium sulfate, and filtered into a 2-l., round-bottomed flask.

The pentane and other volatiles are removed by fractional distillation, using a 5-cm., steel wool-packed column and heating the pot in a 70° oil bath (Note 4). A water aspirator vacuum is applied, and 18.2–22.9 g. (36–45%) of the diene **1** is distilled as a colorless oil, b.p. 50–55° (50 mm.) (Note 5). On a smaller scale, yields of up to 50% have been obtained.

B. *Diethyl* trans-4-*trimethylsilyloxy*-4-*cyclohexene*-1,2-*dicarboxylate* (**2**). A 25-ml., round-bottomed flask equipped with a reflux condenser is charged with diene 1 (7.1 g., 0.050 mole) and diethyl fumarate (5.7 g., 0.033 mole) (Note 6). The mixture is stirred under a nitrogen atmosphere in an oil bath kept at 130–150°

for 24 hours (Note 7). Direct vacuum distillation using a short-path distillation apparatus affords a small amount of lower-boiling material, then 8.02 g. (77%) of cyclohexene **2**, b.p. 127–128° (0.5 mm.) (Note 8) and (Note 9).

2. Notes

1. The checkers obtained methyl vinyl ketone from Hoffmann-La Roche Company and chlorotrimethylsilane from Aldrich Chemical Company, Inc. Both were distilled from calcium hydride. Triethylamine, obtained from J. T. Baker Chemical Company, was distilled from calcium hydride, and *N*,*N*-dimethylformamide, from Fisher Scientific Company, was used from a freshly opened bottle.
2. Filtration was conveniently performed through a plug of glass wool directly into the separatory funnel.
3. The hydrogen carbonate extractions must be performed quickly, since the product slowly hydrolyzes in the presence of water. The best yields were obtained when the phases were shaken briskly for 10 seconds and separated as soon as foaming ceased. Foaming also occurred when the pentane extracts were washed with water, but did not prevent the separation of phases.
4. The checkers used a 18-cm. Vigreux column to remove low-boiling material, and then transferred the residue to a 250-ml., round-bottomed flask for fractional distillation under reduced pressure.
5. The distilled diene **1** has been obtained with 99% purity by the submitters. The product has the following spectral properties: ^{1}H NMR: (CCl_4 with benzene as internal standard). δ (multiplicity, number of protons): 0.4 (s, 9H), 4.4 (broad s, 2H), 5.1 (d of m, 1H), 5.5 (d of d, 1H), 6.3 (d of d, 1H). The impurities were triethylamine and hexamethyldisiloxane. When stored in a serum-capped flask, in a desiccator, and removed *via* syringe, the butadiene is stable for 2 months.
6. The checkers prepared diethyl fumarate by the sulfuric acid–catalyzed esterification of fumaric acid.[7] Diethyl fumarate obtained from Aldrich Chemical Company, Inc. contained dimethyl fumarate as a contaminant.
7. The submitters allowed the reaction to proceed for 24 hours after monitoring by GC (1.83 m. × 0.64 cm., 10% SE-30/60–80 mesh Chromosorb W, 150°) indicated that the disappearance of diethyl fumarate was not complete after 5.5 hours. The submitters made no attempt to optimize the reaction time. The checkers found the reaction to be complete after 7 hours at 135–145°.
8. The checkers distilled cyclohexene **2** after 7 hours reaction time using a Büchi Kügelrohr distillation oven to obtain 9.9–10.0 g. (95–96%) of cyclohexene **2**.
9. Cyclohexene **2** has the following spectral properties: **IR** (liquid film) cm^{-1}: 1730, 1670; **^{1}H NMR**: (CCl_4), δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 0.16 [s, 9H, $Si(CH_3)_3$], 1.17 (t, $J = 7$, 6H, $2OCH_2CH_3$), 2.00–3.16 (m, 6H, ring C*H*), 4.07 (q, $J = 7$, 4H, $2OCH_2CH_3$), 4.70 (broad s, 1H, olefinic C*H*).

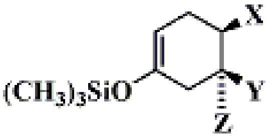
3. Discussion

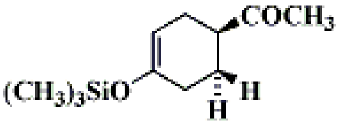
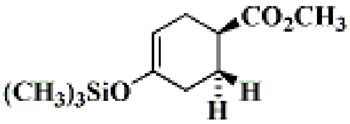
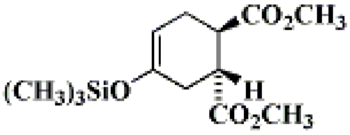
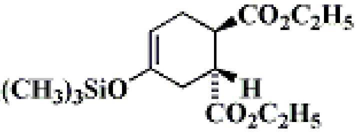
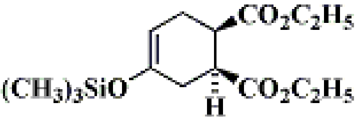
The first reference to 2-trimethylsilyloxy-1,3-butadiene (**1**) was a report[2] of its reaction with tetracyanoethylene by Cazeau and Frainnet without any mention of experimental details. Later, Conia[3] reported its synthesis in 50% yield with only a reference made to the usual House procedure[4] for silyl enol ethers. The diene **1** has also been prepared using lithium diisopropylamide as base and chlorotrimethylsilane in tetrahydrofuran–ether (1:1) in yields up to 65%, but on a smaller scale.[5]

Butadienes substituted with alkoxy groups in the 2-position, *e.g.*, 2-ethoxy-1,3-butadiene,[6 7] have been prepared from methyl vinyl ketone, but required several conversions and a tedious spinning-band distillation to purify the product. This slight modification of the House procedure has been used to conveniently prepare 2-trimethylsilyloxy-1,3-butadiene from the readily available methyl vinyl ketone. This one-step procedure has provided large amounts of a new and reactive diene for Diels–Alder reactions, as illustrated in Table I.

TABLE I

PREPARATION OF TRIMETHYLSILYLOXYCYCLOHEXENES



X	Y	Z	Yield(%)
$COCH_3$	H	H	 60
CO_2CH_3	H	H	 46
CO_2CH_3	H	CO_2CH_3	 71
$CO_2C_2H_5$	H	$CO_2C_2H_5$	 77
$CO_2C_2H_5$	$CO_2C_2H_5$	H	 39

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

ether (60-29-7)

sodium hydrogen carbonate (144-55-8)

Cyclohexene (110-83-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

Fumaric acid (110-17-8)

diethyl fumarate (623-91-6)

Pentane (109-66-0)

Tetrahydrofuran (109-99-9)

N,N-dimethylformamide (68-12-2)

methyl vinyl ketone (78-94-4)

triethylamine (121-44-8)

Tetracyanoethylene (670-54-2)

Triethylamine hydrochloride (554-68-7)

calcium hydride (7789-78-8)

Dimethyl fumarate (624-49-7)

lithium diisopropylamide (4111-54-0)

CHLOROTRIMETHYLSILANE (75-77-4)

hexamethyldisiloxane (107-46-0)

2-Trimethylsilyloxy-1,3-butadiene (38053-91-7)

2-ethoxy-1,3-butadiene

Diethyl trans-4-trimethylsilyloxy-4-cyclohexene-1,2-dicarboxylate, 4-Cyclohexene-1,2-dicarboxylic acid, 4-trimethylsilyloxy-, diethyl ester, trans- (61692-31-7)

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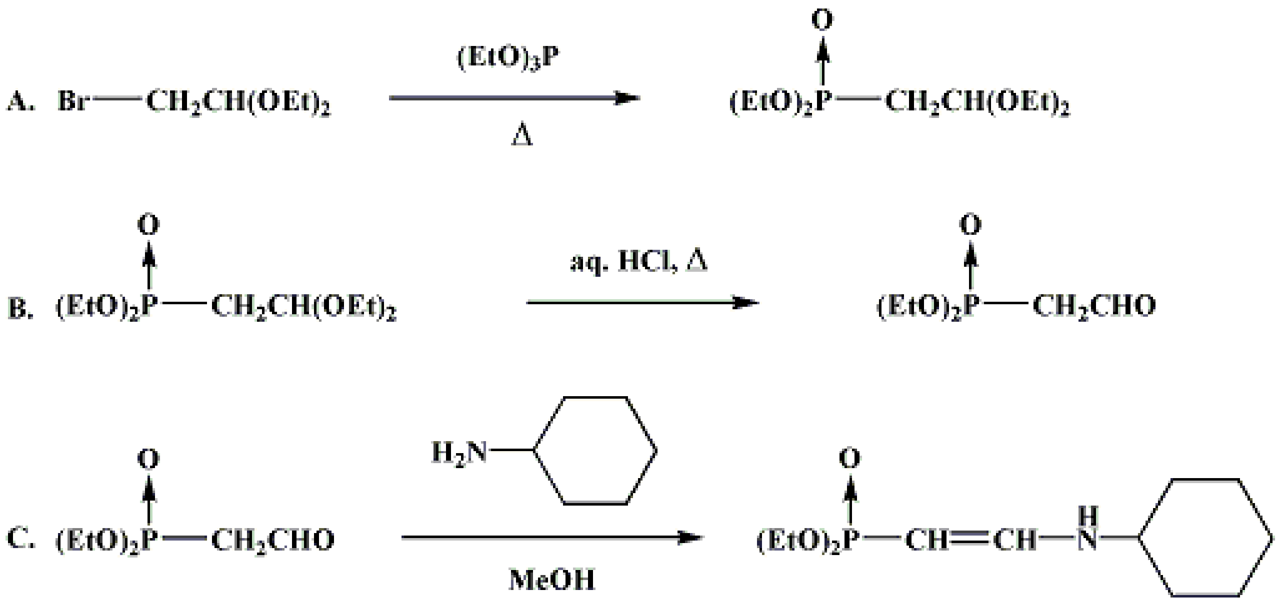
DIETHYL 2-(CYCLOHEXYLAMINO) VINYLPHOSPHONATE

[Phosphonic acid, [2-(cyclohexylamino)ethenyl]-, diethyl ester]



Submitted by Wataru Nagata[1], Toshio Wakabayashi[1], and Yoshio Hayase[2].
Checked by H. A. Davis, K. Abe, and S. Masamune.

1. Procedure

A. *Diethyl 2,2-diethoxyethylphosphonate* (Note 1). A 2-l., three-necked, round-bottomed flask fitted with a magnetic stirrer, dropping funnel, and nitrogen inlet is charged with 410 g. (2.08 moles) of bromoacetaldehyde diethyl acetal (Note 2), and a gentle stream of nitrogen is then passed continuously through the system. To the stirred solution is added dropwise 316 g. (1.90 moles) of triethyl phosphite (Note 3) over a period of 30 minutes, at 110–120°. The mixture is then stirred for 3 hours at 160°. The ethyl bromide evolved is trapped with a condenser and a receiver cooled in an ice bath. The low-boiling material (below 100°) is distilled under reduced pressure (22 mm.). The residual oil is fractionated under reduced pressure, and the fraction boiling at 101–103° (0.8 mm.) is collected, yielding 338 g. (70%) (Note 4).

B. *Diethyl formylmethylphosphonate* (Note 5). A mixture of 192 g. (0.755 mole) of diethyl 2,2-diethoxyethylphosphonate and 670 ml. of 2% hydrochloric acid is refluxed for 10 minutes under a nitrogen atmosphere. To the cooled (20–30°) mixture is added 240 g. of sodium chloride (Note 6). The resulting mixture is extracted with three, 500-ml. portions of dichloromethane. The combined organic extracts are washed successively with 40 ml. of 5% aqueous sodium hydrogen carbonate solution (Note 7) and 300 ml. of saturated aqueous salt solution, dried over anhydrous sodium sulfate, and distilled under reduced pressure (35 mm.) at water bath temperatures (60–70°). The resulting residue, weighing approximately 125 g., is fractionated under reduced pressure, and the fraction boiling at 100–103° (0.8 mm.) is collected, yielding 104 g. (76%) (Note 8) and (Note 9).

C. *Diethyl 2-(cyclohexylamino)vinylphosphonate*. A 1-l., two-necked, round-bottomed flask fitted with a magnetic stirrer, dropping funnel, and nitrogen inlet is charged with 90.0 g. (0.500 mole) of diethyl formylmethylphosphonate and 400 ml. of dry methanol. Under a nitrogen atmosphere, 49.6 g. (0.501 mole) of cyclohexylamine (Note 10) is added in portions to the stirred solution, over a period of 5 minutes. During the addition the temperature is maintained at 0–5° with an ice bath. The mixture is stirred for an additional 10 minutes at room temperature, and then the methanol is distilled from the mixture under reduced pressure (10–35 mm.) at water bath temperatures (25–30°). The residue is dissolved in 300 ml. of dry diethyl ether (Note 11), dried over anhydrous potassium carbonate (70 g.) (Note 12), and evaporated to dryness. The residual oil is fractionated under reduced pressure in the presence of 300 mg. of anhydrous potassium carbonate (Note 13), and the fraction boiling at 126–141° (0.08 mm.) is collected, giving 89 g. (68%) (Note 14). The fraction above is crystallized from dry pentane (Note 15), yielding 79 g. (60%) of diethyl 2-(cyclohexylamino)vinylphosphonate, m.p. 58–61° (Note 16).

2. Notes

1. This procedure is essentially the same as that described by Dawson and Burger.[3]
2. Bromoacetaldehyde diethyl acetal was distilled; b.p. 74–76° (25 mm.). Its preparation is described in *Org. Synth.*, **Coll. Vol. 3**, 123 (1955).
3. Triethyl phosphite was distilled; b.p. 43–44° (10 mm.). Its preparation is described in *Org. Synth.*, **Coll. Vol. 4**, 955 (1963).
4. The reported[3] boiling point is 128–130° (2 mm.). The checkers found the product to be pure by GC (UCW-98 at 150°). The ^{1}H NMR spectrum had the following characteristic peaks ($CDCl_3$): δ 1.22, 1.34 (2t, J = 7Hz., 12H, 4CH_3), 2.17 (d of d, J = 19 and 6Hz., 2H, CH_2CH), 3.6 [2q, J = 7Hz., 4H, CH(OCH_2CH_3)$_2$], 4.1 [2q, J = 7Hz., 4H, (CH_3CH_2O)$_2$PO], 4.90 [d of t, J = 6 and 6Hz., 1H, CH_2CH(OC_2H_5)$_2$].
5. This procedure is essentially the same as that described by Dawson and Burger.[3]
6. It is necessary to saturate the aqueous layer with sodium chloride in order to extract the product effectively.
7. The checkers found that it was necessary to neutralize any excess acid to prevent polymerization of the product during the distillation.
8. There is no report of the boiling point of the product in the literature.[3] The product has an IR absorption (CCl_4 solution) at 1732 cm.$^{-1}$ (aldehyde C=O).
9. The checkers found that the product contained a 5–6% contamination of starting material [GC (UCW-98, 120°) and ^{1}H NMR]. The ^{1}H NMR spectrum ($CDCl_3$): δ 1.35 (t, J = 7 Hz., 6H, 2CH_3), 3.11 [d of d, J = 22 and 3.5 Hz., 2h, P(O)CH_2CH], 4.2 [2q, J = 7 Hz., 4H, (CH_3CH_2O)$_2$PO], 9.70 (d of t, J = 3 and 1 Hz., 1H, CHO).
10. Reagent grade cyclohexylamine was redistilled before use.
11. Dry ether was used to minimize the water content of the solution.
12. To avoid acid-induced dimerization[4] of diethyl 2-(cyclohexylamino)vinylphosphonate, the solution was dried thoroughly, usually overnight, with anhydrous potassium carbonate.
13. The distillation was carried out in the presence of powdered anhydrous potassium carbonate to prevent dimerization[4] of diethyl 2-(cyclohexylamino)vinylphosphonate.

14. The yields were 65–75% in several runs. The distilled oil was sufficiently pure for further use.
15. Reagent grade pentane passed through Merck anhydrous neutral alumina was used. Crystallization was carried out at 0° using 50 ml. of dry pentane. Filtration of the crystals was carried out under dry nitrogen. The submitters succeeded in crystallizing diethyl 2-(cyclohexylamino)vinylphosphonate only after the publication of its preparation.[4] The crystalline product is stable for several months, if stored at 0° under anhydrous conditions.
16. The checkers were not able to obtain the product in crystalline form. The ^{1}H NMR spectrum ($CDCl_3$): δ 1,3 (t, *J* = 7 Hz., CH_3CH_2O), 1.0–2.1 (m, cyclohexyl *H*), 4.0 (quintet, *J* = 7 Hz., 2 CH_3CH_2O), 4.3–5.0 (broad, N*H*), 5.9–7.7 (m, -CH=CH-). The number of olefinic protons was estimated to be 1.7–1.8 by comparison of the area in the region δ 5.9–7.7 with the total area in the spectrum. Although this value is slightly low, it was found that the sample was sufficiently pure to carry out further transformations. The IR spectrum has the following absorptions (neat): 3300 (N-H str.), 1620, 1210, 1058, 1035, and 955 $cm.^{-1}$.

3. Discussion

Diethyl 2-(cyclohexylamino)vinylphosphonate has proved to be an excellent reagent for conversion of aldehydes and ketones into the corresponding α,β-unsaturated aldehydes.[4,5] Formylmethylenetriphenylphosphorane[6] and diethyl 2,2-(diethoxy)ethylphosphonate[7] have been prepared and used for the conversion of aldehydes, but not ketones and hindered aldehydes, into α,β-unsaturated aldehydes. When ethyl diethylphosphonoacetate[8] or diethyl cyanomethylphosphonate[9] is used to obtain an α,β unsaturated aldehyde, the conversion requires several stages.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 358

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alumina

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

sodium hydrogen carbonate (144-55-8)

sodium chloride (7647-14-5)

Ethyl bromide (74-96-4)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

Pentane (109-66-0)

dichloromethane (75-09-2)

cyclohexylamine (108-91-8)

Triethyl phosphite (122-52-1)

ethyl diethylphosphonoacetate (867-13-0)

Diethyl 2-(cyclohexylamino)vinylphosphonate, Phosphonic acid, [2-(cyclohexylamino) ethenyl]-, diethyl ester (20061-84-1)

bromoacetaldehyde diethyl acetal (2032-35-1)

Diethyl 2,2-diethoxyethylphosphonate, diethyl 2,2-(diethoxy)ethylphosphonate (7598-61-0)

Diethyl formylmethylphosphonate (1606-75-3)

Formylmethylenetriphenylphosphorane

diethyl cyanomethylphosphonate (2537-48-6)

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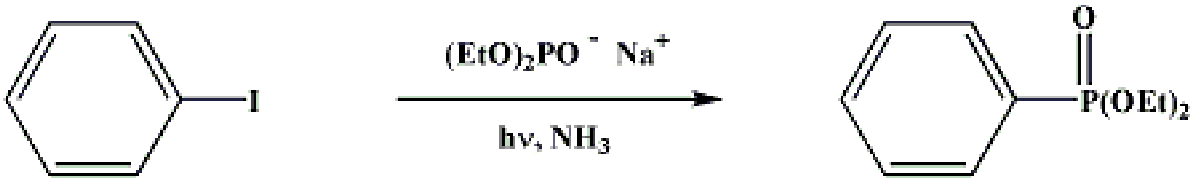
Organic Syntheses, CV 6, 451

RADICAL ANION ARYLATION: DIETHYL PHENYLPHOSPHONATE

[Phosphonic acid, phenyl-, diethyl ester]



Submitted by Joseph F. Bunnett[1] and Robert H. Weiss.
Checked by S. C. Busman and O. L. Chapman.

1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A 2-l., three-necked, round-bottomed flask is fitted with an ammonia condenser (Note 1) with an outlet protected with a soda–lime drying tube, a dropping funnel, a nitrogen inlet, and a magnetic stirrer. As a slow stream of nitrogen is passed through the system, the condenser is charged with dry ice and 2-propanol, the funnel is briefly removed, about a liter of liquid ammonia is added straight from a commercial cylinder (Note 2), and the funnel is replaced. Bright, freshly-pared sodium metal (11.8 g., 0.513 g.-atom) is added, turning the mixture blue. Diethyl phosphonate (70.4 g., 0.510 mole) (Note 3) is cautiously added dropwise to the sodium in ammonia in the manner of a titration; the endpoint is the change from blue to colorless (Note 4). Iodobenzene (52.4 g., 0.257 mole) (Note 5) is slowly added, giving the solution a slight yellowish tint (Note 6). The dropping funnel is replaced by a stopper, the frost is wiped off the outside of the flask with a towel dampened with acetone, and the whole system is mounted in a photochemical reactor of adequate design (Note 7). *Caution! The lamps must be shielded to prevent exposure of the eyes or skin to ultraviolet radiation.* The flask is irradiated for 1 hour (Note 8), but every 20 minutes the lamps are shut off briefly while the exterior of the flask is freed of frost by spraying it, still mounted in the reactor, with 2-propanol from a wash bottle.

After irradiation, the flask is removed from the reactor, and about 50 g. (0.62 mole) of solid ammonium nitrate is added with stirring to acidify the mixture. About 200 ml. of diethyl ether is added, nitrogen flow is stopped, the condenser is removed, and the open flask is placed on a cork ring in an operating hood and allowed to stand overnight while the ammonia evaporates. The next day 300 ml. of water (Note 9) and 300 ml. of

ether are added, the ether layer is separated, the water layer is extracted twice with ether, and the combined ether extracts are dried over anhydrous sodium sulfate. After evaporation of the ethyl ether, the residue is distilled under reduced pressure through a short Vigreux column. After a small forerun, 50.3–56.1 g. (90.4–92.5%) of diethyl phenylphosphonate (Note 10) is collected at 73–74° (0.020 mm.) (Note 11).

2. Notes

1. An ammonia condenser is an enlarged cold finger design. The interior of the "finger" is a reservoir for dry ice and 2-propanol.
2. When ammonia distilled from sodium metal is used, the yield is 3–5% greater, but use of ammonia straight from the tank is recommended because of the greater convenience.
3. Commercial diethyl phosphonate, formerly known as diethyl phosphite, was purchased from Aldrich Chemical Co., Inc. and used without further purification.
4. Some white foam forms as the diethyl phosphonate is added. Because water in the ammonia consumes some of the sodium, not quite all the diethyl phosphonate is required to reach the endpoint. Excess diethyl phosphonate is deleterious.
5. Commercial iodobenzene was dried over molecular sieves. Use of ratios of potassium diethyl phosphite to iodobenzene smaller than 2:1 gives lower yields. Bromobenzene is much less reactive than iodobenzene and gives poor yields by this procedure.
6. When distilled ammonia is used, this yellow coloration vanishes as the reaction occurs.
7. The submitters used a Rayonet Model RPR-100 Photochemical Reactor, manufactured by the Southern New England Ultraviolet Company, Hamden, Connecticut 06514, equipped with 16 Cat. No. RPR-3500A fluorescent lamps (*ca.* 24 W. each), rated to emit maximally at 350 nm. Equally good results were obtained with lamps rated to emit maximally at 300nm. For reactions on a 0.05-mole scale excellent yields were obtained, without using the commercial photochemical reactor, by irradiating for 1 hour with two circular kitchen-type fluorescent lamps mounted on either side of the flask so as to partially encircle it.
8. The yield was not significantly improved by irradiating for 2 hours.
9. Diethyl phenylphosphonate is appreciably soluble in water. Therefore, excessive amounts of water should be avoided.
10. Spectral characterization is as follows: IR (neat) cm^{-1}: 1440 (P-C aryl), 1250 (P=O), 1020 (POC_2H_5), and 3060 (H-C aryl); ^1H NMR ($CDCl_3$), δ (multiplicity, coupling constant *J* in Hz., assignment): 1.3 (t, $J = 7$, CH_3), 4.13 (quintet, $J = 7$, CH_2), 7.33–8.06 (m, C_6H_5).
11. The submitters obtained a yield of 46 g. (83%), b.p. 90–92° (0.1 mm.).

3. Discussion

The procedure reported here is based on a reaction discovered by Bunnett and Creary,[2]

and was first employed for preparative purposes by Bunnett and Traber.[3] It is attractive because of the high yield, the ease of work-up, and the cleanliness of the reaction. The reaction is believed to occur by the $S_{RN}1$ mechanism, which involves radical and radical anion intermediates.[2,4] The $S_{RN}1$ arylation of other nucleophiles, especially ketone enolate ions,[5] ester enolate ions,[6] picolyl anions,[7] and arenethiolate ions,[8] has potential application in synthesis.

This procedure has been utilized successfully with a variety of aryl iodides, but aryl bromides are much less reactive. *m*- and *p*-Diiodobenzene, *m*- and *p*-bromoiodobenzene, and *p*-chloroiodobenzene give the corresponding phenylenediphosphonate esters.[2,3] *o*-Haloiodobenzenes undergo a dark reaction leading to deiodination and other products, but the $S_{RN}1$ reaction affording phosphate esters may be made to predominate if irradiation is started quickly.[9]

The esters of arylphosphonic acids are cleaved to the acids by hydrochloric, hydrobromic, or hydroiodic acid.[10] Arylphosphonic dichlorides ($ArPOCl_2$) are easily converted to esters by reaction with the alcohol in pyridine solution.[11]

Other methods for synthesis of arylphosphonic acids or their derivatives fall into four main categories. First, many aromatic compounds react with phosphorus trichloride under aluminum trichloride catalysis, to form aryldichlorophosphines ($ArPCl_2$).[12,13] These add chlorine to form aryltetrachlorophosphoranes ($ArPCl_4$),[14,13] which may be hydrolyzed to arylphosphonic dichlorides or arylphosphonic acids. This sequence may be employed for preparations on a large scale, but is subject to the orienting effects of substituents when applied to substituted benzenes.

Second, arylphosphonic acids may be prepared by the copper-catalyzed reactions of arenediazonium tetrafluoroborates with phosphorus trichloride or tribromide. This method has found wide use.[15]

Third, arylphosphonic acid derivatives have been made by organometallic reactions, such as the reaction of phenylmagnesium bromide with diethyl chlorophosphate, or of phenyllithium with phosphorodipiperididic chloride.[16,13]

Fourth, the present procedure bears a resemblance to the photochemical reaction of aryl iodides with trialkyl phosphites, with which several dialkyl arylphosphonates have been prepared.[17] However, prolonged irradiation (>24 hours) in quartz vessels was employed.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Diethyl phosphonate

m- and p-Diiodobenzene

m- and p-bromoiodobenzene

hydrochloric, hydrobromic, or hydroiodic acid

phosphorus trichloride or tribromide

ammonia (7664-41-7)

Benzene (71-43-2)

ether, ethyl ether, diethyl ether (60-29-7)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

acetone (67-64-1)

aluminum trichloride (3495-54-3)

pyridine (110-86-1)

chlorine (7782-50-5)

sodium (13966-32-0)

2-propanol (67-63-0)

bromobenzene (108-86-1)

phosphorus trichloride (7719-12-2)

ammonium nitrate

Phenylmagnesium bromide (100-58-3)

Iodobenzene (591-50-4)

Phenyllithium (591-51-5)

diethyl phosphite (762-04-9)

diethyl chlorophosphate (814-49-3)

Diethyl phenylphosphonate, Phosphonic acid, phenyl-, diethyl ester (1754-49-0)

potassium diethyl phosphite

p-chloroiodobenzene (637-87-6)

phosphorodipiperididic chloride

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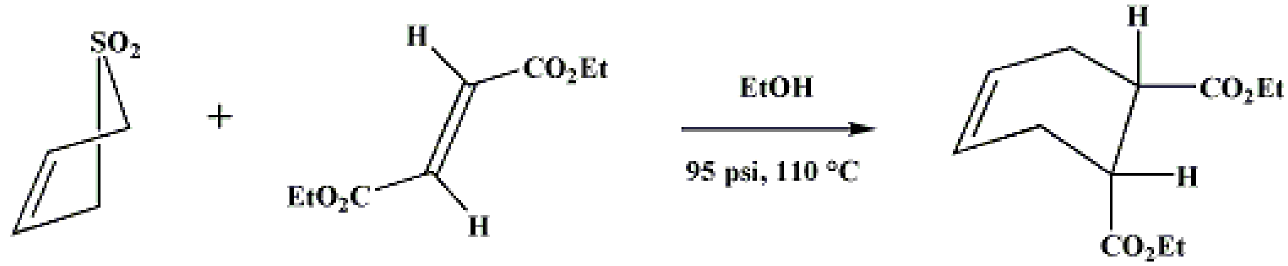
Organic Syntheses, *CV 6, 454*

DIETHYL *trans*-Δ4-TETRAHYDROPHTHALATE

[4-Cyclohexene-1,2-dicarboxylic acid, diethyl ester, *trans*-]



Submitted by Thomas E. Sample, Jr.[1] and Lewis F. Hatch[2].
Checked by Elaine Dotter Donald and Richard E. Benson.

1. Procedure

A 300-ml. pressure reaction vessel, capable of withstanding at least 250 p.s.i. at 125° (Note 1) is charged with 60.0 g. (0.508 mole) of 3-sulfolene (Note 2), 86.0 g. (82.0 ml., 0.500 mole) of diethyl fumarate (Note 3), and 1.0 g. of hydroquinone (Note 4). Commercial absolute ethanol (90 ml.) is added, and the mixture stirred until most of the solid is dissolved. The vessel is sealed, heated slowly to 105–110° (Note 5), and maintained at that temperature 8–10 hours (Note 6). The vessel is then allowed to cool to room temperature, opened (Note 7), and the yellowish, fluid reaction mixture is poured into a 1-l. Erlenmeyer flask.

The liquid is stirred vigorously (Note 8), and a solution of 60.0 g. (0.566 mole) of sodium carbonate in 350 ml. of water is added to the flask as rapidly as the concomitant evolution of carbon dioxide will permit. Stirring is continued for about 15 minutes after the addition is complete. The original reaction vessel is rinsed with 200 ml. of petroleum ether (b.p. 60–75°) (Note 9), the rinse is added to the Erlenmeyer flask containing the product, and the mixture is stirred for about 10 minutes at a rate sufficient to achieve homogenization. The resulting loose emulsion is quickly transferred to a 1-l. separatory funnel and allowed to separate; the lower (aqueous) phase is drawn off into the original Erlenmeyer flask and the upper (organic) layer containing the desired product is transferred to a 500-ml. flask. In exactly the same manner the aqueous phase is extracted by vigorous stirring with two 100-ml. portions of petroleum ether, the organic layers being added to the retention flask (Note 10). The combined organic layers are transferred from the flask to the same separatory funnel and shaken once with 100 ml. of cold, 5%, aqueous sodium carbonate and twice with 50-ml. portions of cold water. The organic layer is returned to the retention flask, dried over 10 g. of anhydrous magnesium sulfate, filtered by gravity, concentrated with a rotary evaporator (Note 11), and distilled under reduced pressure through a Vigreux column, yielding 75–82 g. (66–73%, based on diethyl fumarate) of the product, b.p. 129–132° (5 mm.), n_D^{25} 1.4565–1.4570, d_4^{25} 1.0584–1.0589 (Note 13).

2. Notes

1. The maximum static pressure developed at 110°, measured by the submitters, never exceeded 95 p.s.i.; however, for most of their runs they used stainless or carbon steel autoclaves with screw-on covers rated for service up to 500 p.s.i. at 250° (medium-

pressure catalytic hydrogenation bombs). Gaskets or inner-disk seals for the autoclave covers were cut from soft thin copper sheet stock instead of the more usual lead or lead-alloy material. Whereas use of lead-containing seals did not seem to affect the yields, when they were used the product invariably had the offensive odor of divalent organic sulfur which was still noticeable after final distillation; substitution of copper seals eliminated this problem completely. Close-fitting, removable glass liners for the autoclave were used by the submitters for convenience in weighing and mixing the charge, and for subsequent removal of the product mixture, but are not required. Several runs were made at 100–105° by the submitters, without difficulty, utilizing a hydrogenation bottle of heavy borosilicate glass tightly closed with a clamped-in Neoprene stopper and placed inside an iron sleeve for safety.

2. 3-Sulfolene (butadiene cyclic sulfone), m.p. 64–66°, from Shell Chemical Co., or from Aldrich Chemical Co., was found satisfactory for use as received. One lot purchased from another source required solution in hot methanol and treatment with activated carbon (250 ml. of methanol and 2 g. of Norit per 100 g. of material), filtration, and crystallization to free it of color, odor, and particulate matter.

3. Diethyl fumarate from Aldrich Chemical Co., n_D^{20} 1.4406, b.p. 97.5–97.7° (10 mm.), was employed without treatment.

4. Eastman Kodak Co. hydroquinone, m.p. 172–174°, was used. 4-*tert*-Butylcatechol, m.p. 38–42°, from the same supplier, proved to be an equally effective polymerization inhibitor.

5. The submitters used an ordinary hot-air oven with the usual simple bimetallic temperature regulator for the majority of their experiments. In several instances, however, a large oil bath regulated with a thermostat to within ±1.0° was employed, which, in providing more exact control of the total temperature environment of the reaction, gave a greater degree of reproducibility in product yield between successive runs at any set temperature; these precise runs were performed as a result of the checkers' observations emphasizing the important effect of reaction temperature on yields.

6. Longer heating periods (12–18 hours) were found by the submitters to elevate the yields only slightly. On the other hand, as the checkers noted, heating for the recommended 8–10 hours at temperatures above 110° will raise the yields quite significantly: the highest single product recovery obtained by the submitters was 86.8% using a strong steel autoclave (Note 1) immersed for 10 hours in a thermostat-equipped oil bath at 125°. However, the greater yield which may be realized through higher reaction temperatures should be carefully weighed against the ability of the reaction vessel to contain safely the greater pressures developed.

7. Little, if any, overpressure is released if the vessel is opened below 30°; this should be done in a hood because the contents will evolve sulfur dioxide until the sodium carbonate is added.

8. A magnetic stirrer is recommended for this operation.

9. Hexane and Skellysolve-B serve equally well; the product is miscible with aliphatic solvents, whereas 3-sulfolene is not.

10. No increase in product recovery was observed by the submitters when a 72-hours exhaustive extraction of the neutralized reaction mixture with hexane in a continuous apparatus was substituted for the procedure described.

11. The submitters observe that no more critical step in this procedure exists than the efficient removal of the rather large quantity of solvent from the product before distillation: entrainment losses during this operation usually were found chiefly responsible when the synthesis gave a low yield (recovery). The preferred apparatus for this step is a rotary evaporator equipped with a long, helical, water-cooled condenser; the distillation flask is attached to the evaporator and the product solution added portionwise as the concentration progresses; the temperature of the flask is held at 30–40° with a warm-water bath, or a heat

lamp, while the solvent is gently removed by a water aspirator (*ca.* 30-mm. minimum pressure). If a suitable rotary evaporator is unavailable, a 30–45 cm. Vigreux column may be used without excessive product loss, providing the flask is warmed in the same manner and a gentle boiling rate is maintained through control of the aspirator suction.

12. An elaborate apparatus for the diminished-pressure distillation is not required to obtain a product of excellent purity: sensitive GC analyses could detect no more than a doubtful trace of the *cis* isomer in the crude mixture, and other possible contaminants boil at least 45° (760 mm.) below the product. The submitters usually employed an 8 × 300 mm., vacuum-jacketed, silvered column with a helical, Nichrome-wire heat transfer insert. They consistently obtained a product which analyzed at least 99% pure using GC conditions which proved capable of cleanly separating the product from an authentic sample of its *cis*-isomer [*Org. Synth.*, **Coll. Vol. 4**, 304 (1963)], with the latter showing the longer retention time (terephthalic acid-terminated Carbowax 20M, 10% w/w on 60/80 mesh Chromosorb W, 6 mm. × 365 cm. aluminum column at 150°). The submitters note that distillation of the product at atmospheric pressure (b.p. 265–270°) is accompanied by very slight decomposition. (A b.p. of 150.5–151.5° at an unspecified pressure appears in the literature.[3])

13. The IR spectra of diethyl *trans*-Δ^4-tetrahydrophthalate and its *cis*-isomer [*Org. Synth.*, **Coll. Vol. 4**, 304 (1963)], (cm^{-1}, neat liquids purified by GC, 0.025-mm. cells) are similar in the fundamental region; however, the following particular absorptions in the "fingerprint" region afford reliable analytical criteria for distinguishing each from (or in the presence of) the other; *trans*-isomer, 971 (s), 755, 743 (m, s, doublet); *cis*-isomer, 945 (s), 893 (w), 727 (m). The 755, 743 doublet of the *trans*-isomer and the 727 single absorption of the *cis*-isomer appear to be characteristic, and related to out-of-plane deformations of the vinylic hydrogens; bands corresponding to the 971 and 755, 743 absorptions of the *trans*-isomer are present also in the spectrum of dimethyl *trans*-Δ^4-tetrahydrophthalate.[4]

3. Discussion

A report of Backer and Blaas[5] is responsible for evolution of the present procedure; these workers were first to conduct a Diels-Alder synthesis utilizing a 3-sulfolene in place of the free diene (by heating the cyclic adduct of sulfur dioxide and 2-methyl-3-thiomethyl-1,3-butadiene with maleic anhydride). The generality of the method as a variant of the conventional diene synthesis is limited largely by the availability of the appropriate 3-sulfolene; its greatest utility, perhaps, will be realized in those diene reactions normally requiring 1,3-butadiene, since 3-sulfolene itself is now the least expensive and most widely available diene cyclic sulfone.

The submitters, in addition to their successful work with 3-sulfolene itself, have generally obtained very satisfactory results performing diene syntheses based on the present procedure using several fumaric and maleic derivatives (notably fumaric acid and fumaronitrile, and diethyl maleate) in conjunction with 3-methyl-3-sulfolene (isoprene cyclic sulfone)[6] and 2,4-dimethyl-3-sulfolene (available from Aldrich Chemical Co.), as well as 3,4-dimethyl-3-sulfolene.[7]

In preparations wherein the dienophile could undergo side reaction with the solvent alcohol, either benzene or toluene usually proved to be a satisfactory reaction medium; lower-boiling solvents, such as ether, chloroform, or acetone, were avoided by the submitters because of the high reactive pressures developed. If the dienophile is highly reactive and not appreciably volatile below about 200°, the reaction may be successfully conducted without solvent by careful fusion of an intimate mixture of the reactants in an open vessel.[5,8] *Caution! Such fusions should*

be performed in a good fume hood because of the copious evolution of sulfur dioxide.

3-Sulfolene as an alternative reactant for 1,3-butadiene in diene syntheses has the following advantages: it presents no particular flammability hazard[9] and is practically nontoxic;[10] it is an odorless, crystalline, nonhygroscopic solid which may be stored without inhibitor at ordinary temperatures for years with no evidence of deterioration;[10] obviously, no low-temperature liquefication procedures are needed for its handling, as butadiene may require; medium-pressure reaction vessels can be safely employed since autogenous pressures are relatively low owing to the thermally controlled release of the 1,3-butadiene;[11] and, because the substantial excess of free diene often employed to force the usual reaction is not required, formation of troublesome polymeric by-products is greatly diminished.

For the preparation of diethyl *trans*-Δ^4-tetrahydrophthalate, the present synthesis is superior to the Diels-Alder reaction of butadiene with diethyl fumarate[3] for the reasons given above. In addition, a higher yield is obtained at a lower reaction temperature and shorter reaction time.

Whereas *cis*-Δ^4-tetrahydrophthalic anhydride and several of its derivatives are readily available in high purity from a number of suppliers (largely because of the great ease of addition of maleic anhydride to 1,3-butadiene),[12] the *trans* analogs are much more difficult and expensive to prepare and isolate in reasonable yields and purity; hence the latter are rarely procurable at present from the usual laboratory supply sources. Thus, the procedure described for the preparation of highly pure diethyl *trans*-Δ^4-tetrahydrophthalate not only illustrates a useful variation of the diene synthesis, but provides a convenient route to a large number of *trans*-1,2-disubstituted cyclohexyl derivatives that are currently difficult to secure and are of importance for a variety of studies concerned with structural problems.

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

Isoprene cyclic sulfone

cis-Δ^4-Tetrahydrophthalic anhydride

Diethyl trans-Δ^4-tetrahydrophthalate

butadiene cyclic sulfone

dimethyl trans-Δ^4-tetrahydrophthalate

ethanol (64-17-5)

Benzene (71-43-2)

methanol (67-56-1)

ether (60-29-7)

chloroform (67-66-3)

hydroquinone (123-31-9)

iron (7439-89-6)

sodium carbonate (497-19-8)

sulfur dioxide, sulfone (7446-09-5)

sulfur (7704-34-9)

carbon dioxide (124-38-9)

copper (7440-50-8)

acetone (67-64-1)

carbon, Norit (7782-42-5)

toluene (108-88-3)

Fumaric acid (110-17-8)

diethyl fumarate (623-91-6)

diethyl maleate (141-05-9)

magnesium sulfate (7487-88-9)

1,3-Butadiene, butadiene (106-99-0)

maleic anhydride (108-31-6)

3-methyl-3-sulfolene (1193-10-8)

hexane (110-54-3)

Fumaronitrile (764-42-1)

3-sulfolene

2-methyl-3-thiomethyl-1,3-butadiene

2,4-dimethyl-3-sulfolene

3,4-dimethyl-3-sulfolene

4-tert-butylcatechol (98-29-3)

4-Cyclohexene-1,2-dicarboxylic acid, diethyl ester, trans- (5048-50-0)

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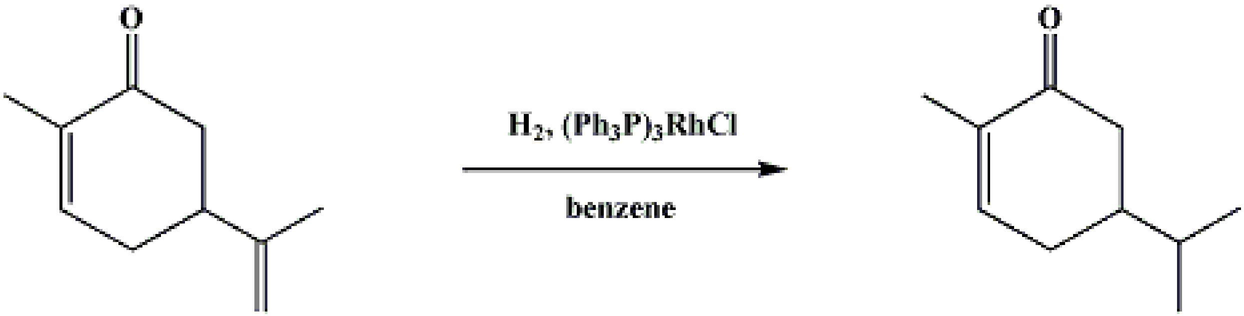
Organic Syntheses, CV 6, 459

HOMOGENEOUS CATALYTIC HYDROGENATION: DIHYDROCARVONE

[2-Cyclohexen-1-one, 2-methyl-5-(1-methylethyl)-]



Submitted by Robert E. Ireland[1] and P. Bey[2].
Checked by N. Haga and W. Nagata.

1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A 500-ml., two-necked, creased flask, containing a magnetic stirring bar and connected to an atmospheric pressure hydrogenation apparatus equipped with a graduated burette to measure the uptake of hydrogen, is charged with 0.9 g. (0.9×10^{-3} mole) of freshly prepared tris(triphenylphosphine)rhodium chloride (Note 1) and 160 ml. of benzene (Note 2). One neck is stoppered with a serum cap, and the mixture is stirred magnetically (Note 3) until the solution is homogeneous. The system is then evacuated and filled with hydrogen. Using a syringe, 10 g. (0.066 mole) of carvone (Note 4) is introduced into the hydrogenation flask. The syringe is rinsed with two, 10-ml. portions of benzene, and stirring is resumed. Hydrogen uptake starts immediately (Note 5) and stops 3.5 hours later when the theoretical amount of hydrogen has been absorbed. The solution is filtered through a dry column (4 cm. diameter) of 120 g. of Florisil (60–100 mesh). The column is washed with 300 ml. of diethyl ether, and the combined solvent fractions are concentrated under reduced pressure. Vacuum distillation of the yellow residue through an 11-cm. Vigreux column (Note 6) affords 9.1–9.5 g. (90–94%) of dihydrocarvone; b.p. 100–102° (14 mm.), n_D^{24} 1.479 (Note 7) and (Note 8).

2. Notes

1. The tris(triphenylphosphine)rhodium chloride catalyst was prepared

according to the procedure of G. Wilkinson and co-workers.[3]

2. The benzene was distilled from calcium hydride.

3. Efficient stirring is necessary to assure good surface contact during hydrogenation.

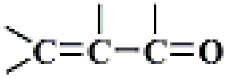
4. The carvone was distilled before use; b.p. 105–106° (14 mm.). The checkers used *l*-carvone obtained from Shiono Koryo K.K. (Japan).

5. With old catalyst, very erratic results with respect to the initiation time and the rate of hydrogen uptake have been observed.

6. When the hydrogenation is carried out on a smaller scale, purification can be affected by evaporative distillation in a bulb to bulb apparatus.

7. GC analysis shows contamination by less than 3% of carvone. The checkers used a 1 m. by 4 mm. glass column packed with 5% PEG 6000 on Chromosorb W (60/80 mesh). The retention times were 3.7 minutes and 2.75 minutes for carvone and dihydrocarvone, respectively, at 100° with a nitrogen flow rate of 90 ml. per minute.

8. The product shows the following spectral properties: IR (neat) 1678 cm.$^{-1}$



; UV (C_2H_5OH) λ_{max} 237 nm (ε = 9150); ^{1}H NMR ($CDCl_3$), δ 0.88 [d, J = 6 Hz., 6H, CH(CH_3)$_2$], 1.71 (d, J = 1.5 Hz., 3H, CH_3C=CH), 6.70 (m, 1H, C*H*=C).

3. Discussion

4

This procedure is an example of the use of a soluble transition metal complex for the catalytic transfer of hydrogen to an olefin. First developed by Wilkinson and co-workers,[3] subsequent extensive investigation in those laboratories and others[5] has shown that the hydrogenation is sensitive to steric congestion; only unhindered double bonds are reduced. As a result, the rhodium complex has been found useful for the selective saturation of unhindered double bonds in polyolefinic substances, such as carvone.[6] Unhindered double bonds may be reduced even in the presence of functions such as keto,[7,6] nitro,[6,8] and sulfide[6] groups. The mechanism[3] and stereochemistry[9] of the catalysis have been investigated, and *cis*-addition of hydrogen is the general rule. The catalyst is effective for deuterium addition to unhindered olefins[10] without the extensive hydrogen–deuterium exchange observed with palladium and platinum heterogeneous catalysis. The rhodium complex causes the decarbonylation of aldehydes and acid halides; the hydrogenation of such unsaturated systems is complicated by the loss of these functional groups.[3], Isomerization of nonreduced olefinic bonds is also an observed side reaction.[11]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Benzene (71-43-2)

diethyl ether (60-29-7)

hydrogen (1333-74-0)

nitrogen (7727-37-9)

platinum (7440-06-4)

palladium (7440-05-3)

calcium hydride (7789-78-8)

rhodium (7440-16-6)

deuterium (7782-39-0)

Dihydrocarvone

2-Cyclohexen-1-one, 2-methyl-5-(1-methylethyl)- (43205-82-9)

tris(triphenylphosphine)rhodium chloride

carvone, l-carvone

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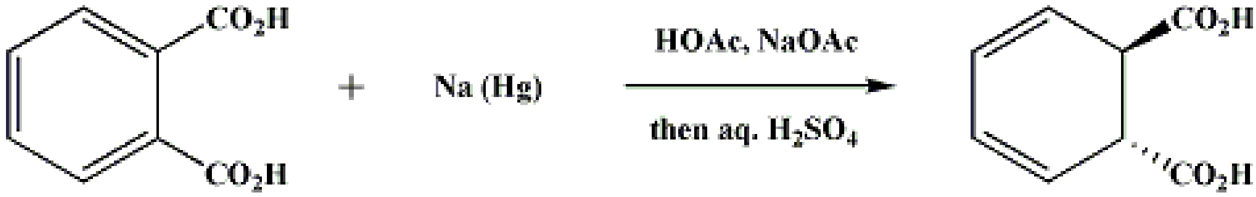
trans-1,2-DIHYDROPHTHALIC ACID

[3,5-Cyclohexadiene-1,2-dicarboxylic acid, *trans*-]



Submitted by Richard N. McDonald and Charles E. Reineke[1].
Checked by Herbert A. Kirst and E. J. Corey.

1. Procedure

A vigorously stirred, particle-free (Note 1) solution of 170 g. (1.02 moles) of phthalic acid and 281 g. of sodium acetate in 1.7 l. of water is cooled in an ice bath while a total of 3400 g. of 3% sodium amalgam (Note 2) is added in 50–100 g. portions (Note 3). With each portion of added amalgam there is also added 10–20 ml. (500 ml. total) of 50% acetic acid. The total addition time required is 4–5 hours. The solution is decanted from the mercury onto a Buchner funnel and filtered with suction through a layer of Celite 545. The cold filtrate is treated with 1.7 l. of cold 20% sulfuric acid; the acid begins to crystallize immediately. After standing for 4 hours at 20–22°, the acid is collected by suction filtration, washed well with ice-cold water, removing excess sulfuric acid, and dried in a vacuum desiccator over sulfuric acid, giving 124 g. (72%) of crystalline product, m.p. 210–213°. A purer product can be obtained by recrystallization. For minimum losses during recrystallization, the crude acid is divided into two portions, and each is added to 1.2–1.5 l. of rapidly stirred, boiling water to effect as rapid a solution as possible. When almost all of the solids have dissolved *ca.* 1 g. of activated charcoal (Norit) is added, the solution is filtered through a fluted filter, and the filtrate is cooled in ice to induce rapid crystallization (Note 4). The colorless crystals are collected by filtration and dried under reduced pressure, yielding 93–107 g. (54–62%) of the acid, m.p. 212–214°.

2. Notes

1. If any crystals of phthalic acid are present, crystallization will occur on cooling.
2. The 3% sodium amalgam was prepared by the procedure in *Org. Synth.*, **Coll. Vol. 2**, 609, (1943), (Note 3), with the following explanation. The mineral oil and sodium are placed in a 1-l. heavy-wall filter flask and heated on a hot plate until the sodium is molten. To this hot, strongly swirled mixture is added mercury from a 1-l. separatory funnel. The initial amounts of mercury (about the total) are added in a fine steady stream, gradually increasing the rate of flow as the initial crackling ceases. Fire flashes can be observed if the initial addition is too rapid.

Once the initial reaction subsides, the mercury should be added as rapidly as possible, and about the last third can be essentially poured in. The molten amalgam is *immediately* poured into a shallow, porcelainized, metal pan and stirred with a wide spatula so that large chunks are not allowed to form as the amalgam cools. Once cool, the amalgam pieces are washed repeatedly with petroleum ether, removing the mineral oil.
3. Another portion of amalgam and one of acid are added as soon as the gas evolution from the previous addition subsides.
4. The submitters report that treatment with decolorizing carbon may not be necessary. Although the crude product is invariably colorless, a yellow color develops during recrystallization. The checkers found that without decolorization a yellow product of somewhat lower m.p. was obtained.

3. Discussion

The present method, based on a recent publication,[2] is a modification of that previously reported.[3] *trans*-1,2-Dihydrophthalic acid has been converted to the *cis*-anhydride by heating in acetic anhydride,[2] which on photolysis (Hanovia, type L mercury lamp) yields the photo-anhydride, bicyclo[2.2.0]hex-5-ene-2,3-dicarboxylic anhydride.[2,4] The photoanhydride has been converted to bicyclo[2.2.0]hexa-2,5-diene,[4] bicyclo[2.2.0]hex-2-ene,[2] and *exo*-bicyclo[2.2.0]hexan-2-ol[2] as well as certain derivatives of the alcohol. The present procedure also gives a more complete preparation of 3% sodium amalgam.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

acetic anhydride (108-24-7)

sodium acetate (127-09-3)

mercury (7439-97-6)

decolorizing carbon (7782-42-5)

sodium (13966-32-0)

phthalic acid (88-99-3)

bicyclo[2.2.0]hex-5-ene-2,3-dicarboxylic anhydride

bicyclo[2.2.0]hexa-2,5-diene

bicyclo[2.2.0]hex-2-ene

trans-1,2-Dihydrophthalic acid, 3,5-Cyclohexadiene-1,2-dicarboxylic acid, trans- (5675-13-8)

exo-bicyclo[2.2.0]hexan-2-ol

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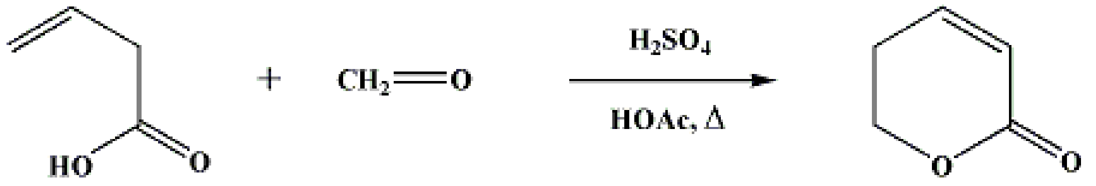
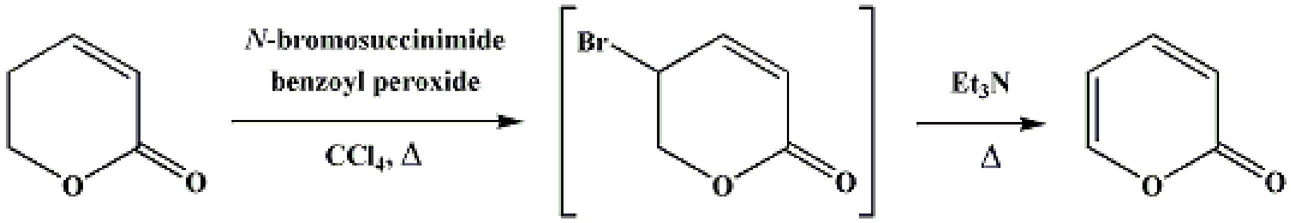
5,6-DIHYDRO-2*H*-PYRAN-2-ONE AND 2*H*-PYRAN-2-ONE





Submitted by M. Nakagawa[1], J. Saegusa[1], M. Tonozuka[1], M. Obi[1], M. Kiuchi[1], T. Hino[1], and Y. Ban[2].
Checked by A. Wick, D. Ehrlich, and A. Brossi.

1. Procedure

A. *5,6-Dihydro-2H-pyran-2-one.* In a 500-ml., one-necked, round-bottomed flask equipped with a reflux condenser are combined 43 g. (0.50 mole) of vinylacetic acid (Note 1), 30 g. (1 mole as CH_2O) of paraformaldehyde (Note 2), 3 ml. of concentrated sulfuric acid, and 125 ml. of glacial acetic acid. This mixture is refluxed gently for 3 hours, then cooled to room temperature and swirled while 16 g. of anhydrous sodium acetate is added. Acetic acid is removed at 50–55° on a rotary evaporator, 100 ml. of water is added, and the flask is fitted with a two-necked adapter, a thermometer, and a magnetic stirring bar. The flask is then immersed in an ice bath, and the solution is brought to pH 8 with aqueous 20% sodium hydroxide (Note 3), which is added dropwise and with stirring at a rate such that the temperature remains below 5°. The resulting solution is transferred to a 1-l. separatory funnel and extracted with four 300-ml. portions of dichloromethane (Note 4). After being washed with one 150-ml. portion of saturated aqueous sodium chloride (Note 5), the combined organic extracts are dried over anhydrous sodium sulfate and filtered. Removal of dichloromethane with a rotary evaporator leaves a mobile yellow oil, which is distilled under reduced pressure, yielding 12.3 g. (25.1%) of 5,6-dihydro-2*H*-pyran-2-one, b.p. 114–117° (18–19 mm.) (Note 6).

B. *2H-Pyran-2-one.* A mixture of 9.81 g. (0.100 mole) of 5,6-dihydro-2*H*-pyran-2-one, 200 mg. of benzoyl peroxide, 18.6 g. (0.105 mole) of *N*-bromosuccinimide (Note 7), and 800 ml. of carbon tetrachloride is prepared in a 2-l., three-necked, round-bottomed flask equipped with a reflux condenser and a mechanical stirrer. The resulting suspension is stirred and heated to reflux. After 1.5 hours at reflux, most of the solid is dissolved, and the solution gives a negative test with starch–iodide paper. The reaction mixture is then allowed to cool, during which time succinimide crystallizes out. The precipitate is removed by filtration, and the filtrate is concentrated under reduced pressure, leaving crude 5-bromo-5,6-dihydro-2*H*-pyran-2-one as an oil.

This residue is stirred at room temperature while 150 ml. of triethylamine (Note 8) is added. Triethylamine hydrobromide begins to precipitate soon after the addition is started, and the

resulting slurry is refluxed gently for 15 minutes. It is then cooled to room temperature, and the insoluble material is removed by filtration and washed with benzene. Concentration of the combined filtrates under reduced pressure leaves an oily residue, which is dissolved in 600 ml. of diethyl ether. The ethereal solution is transferred to a 1-l. separatory funnel, washed with two 20-ml. portions of saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, and filtered. Ether is removed with a rotary evaporator, and the resulting oil is distilled at reduced pressure. A forerun of 265 mg. is collected below 103° (22 mm.) before 6.7 g. (70%) of 2*H*-pyran-2-one distils as a colorless oil, b.p. 103–111° (19–22 mm.) (Note 9).

2. Notes

1. Vinylacetic acid is available from Tokyokasei Company, Ltd., Japan or from Fluka AG, Buchs, Switzerland. Commercial material, which shows about 3% of crotonic acid in its ^{1}H NMR spectrum, was distilled at 90–92° (40–43 mm.) prior to use.
2. The submitters obtained paraformaldehyde from Koso Chemical Company, Inc., Japan.
3. About 180 ml. is required.
4. In these extractions, the organic layer is the lower one. If the two phases do not separate readily, fine-grained precipitates are probably at fault. These may be removed by filtration through a Büchner funnel.
5. Excess washing should be avoided, since 5,6-dihydro-2*H*-pyran-2-one is fairly soluble in water.
6. A forerun of approximately 180 mg. is collected below 110° (18 mm.). The IR spectrum of this material is practically identical with that of the main distillate. Reported physical constants for 5,6-dihydro-2*H*-pyran-2-one are: b.p. 110° (15 mm.) and n_D^{25} 1.4730.[3]
7. The submitters obtained *N*-bromosuccinimide from Nakarai Chemicals Ltd., Japan, and crystallized it from water prior to use (m.p. 168–175°).
8. Triethylamine was purified by treatment with *p*-toluenesulfonyl chloride and distillation.
9. The IR spectrum of this material was essentially identical to that of the redistillate, b.p. 115–118° (37 mm.). Reported physical constants for 2*H*-pyran-2-one are: b.p. 206–209° (atmospheric pressure), n_D^{25} 1.5272,[4] and b.p. 110° (26 mm.), n_D^{25} 1.5270.[5]

3. Discussion

5,6-Dihydro-2*H*-pyran-2-one has been prepared by reductive cyclization of 5-hydroxy-2-pentynoic acid, which is obtained in two steps from acetylene and ethylene oxide;[3] and by the reaction of dihydropyran with singlet oxygen.[6,7] 2*H*-Pyran-2-one has been prepared by pyrolysis of heavy metal salts of coumalic acid,[8] by pyrolysis of α-pyrone-6-carboxylic acid over copper,[4] and by pyrolysis of coumalic acid over copper (66–70% yield).[5]

The present one-step procedure for preparation of 5,6-dihydro-2*H*-pyran-2-one is slightly modified from that described in the original paper.[9] It is simpler and easier than the three-step method[3] used in the past and represents the most convenient synthesis currently available. The present preparation of 2*H*-pyran-2-one has several advantages compared to the alternatives mentioned above: simplicity of apparatus and technique, mild reaction conditions, availability of reactants, and ease of product isolation.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 112

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

acetylene (74-86-2)

acetic acid (64-19-7)

Benzene (71-43-2)

ether, diethyl ether (60-29-7)

sodium acetate (127-09-3)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

oxygen (7782-44-7)

carbon tetrachloride (56-23-5)

copper (7440-50-8)

Ethylene oxide (75-21-8)

dichloromethane (75-09-2)

benzoyl peroxide (94-36-0)

Succinimide (123-56-8)

crotonic acid (3724-65-0)

N-bromosuccinimide (128-08-5)

dihydropyran

Vinylacetic acid (625-38-7)

Coumalic acid (500-05-0)

triethylamine (121-44-8)

triethylamine hydrobromide (636-70-4)

2H-Pyran-2-one (504-31-4)

α-pyrone-6-carboxylic acid

p-Toluenesulfonyl chloride (98-59-9)

5-hydroxy-2-pentynoic acid

5,6-Dihydro-2H-pyran-2-one (3393-45-1)

5-bromo-5,6-dihydro-2H-pyran-2-one

paraformaldehyde (30525-89-4)

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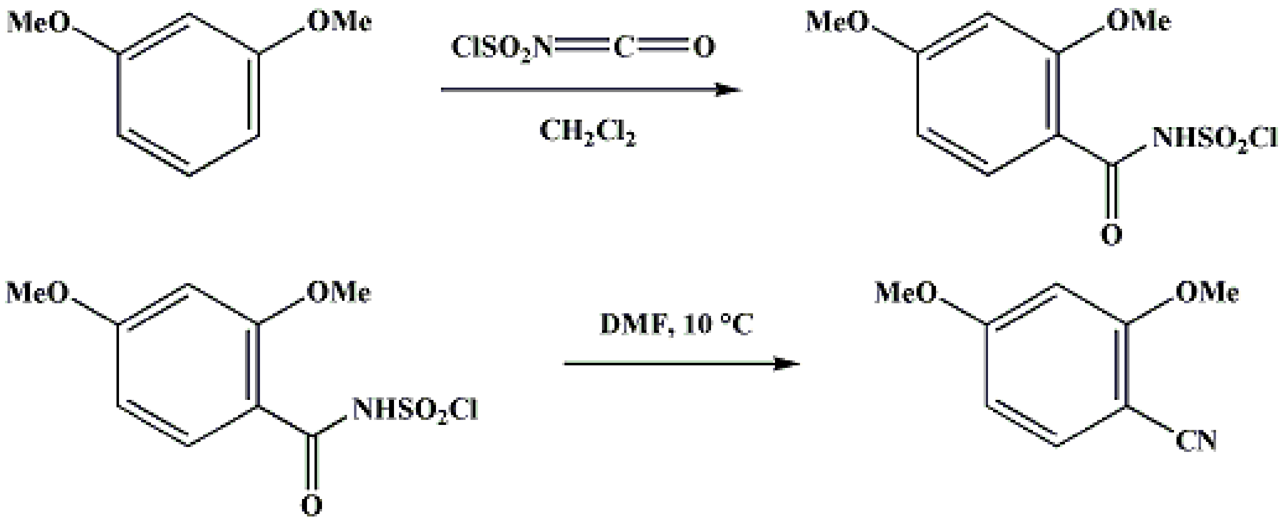
2,4-DIMETHOXYBENZONITRILE

[Benzonitrile, 2,4-dimethoxy-]



Submitted by G. Lohaus[1]
Checked by Jurgen K. Weise and Richard E. Benson.

1. Procedure

Caution! Chlorosulfonyl isocyanate is a highly corrosive, irritating compound. This reaction should be carried out in an efficient hood.

A 1-l., round-bottomed flask equipped with a stirrer, a thermometer, a dropping funnel, and a reflux condenser to which is attached a drying tube containing calcium chloride, is charged with 138 g. (131 ml., 1.00 mole) of resorcinol dimethyl ether and 200 ml. of dichloromethane. The solution is stirred, and a solution of 150 g. (1.06 moles) of chlorosulfonyl isocyanate (Note 1) in 100 ml. of dichloromethane is added with stirring at 15–20° over a 25-minute period. The amide *N*-sulfonyl chloride separates as a crystalline solid, and the mixture is stirred for an hour at room temperature. The resulting mixture is cooled to 10–12° (Note 2) and 154 g. (2.1 moles) of *N*,*N*-dimethylformamide (Note 3) is added over a period of 5 minutes. The cooling bath is removed and the temperature gradually rises to about 30°, then falls. After 1 hour the crystals dissolve and the reaction mixture is poured onto 200 g. of ice. After the ice has melted, dichloromethane (150 ml.) is added, the mixture is shaken, and the organic layer is separated. The aqueous layer is extracted with 100 ml. of dichloromethane, and the organic phases are combined and washed with 100 ml. of water. The dichloromethane is removed by distillation, giving a white solid that is triturated with 250 ml. of cold water, recovered by filtration, and dried, yielding 155–157 g. (95–96%) of 2,4-dimethoxybenzonitrile, m.p. 91°. GC using a Chromosorb W column with 10% butadiene sulfone as the stationary phase indicates that the product has a purity of 98%. The IR spectrum shows absorption at 2220 cm.$^{-1}$ attributable to the cyano group.

2. Notes

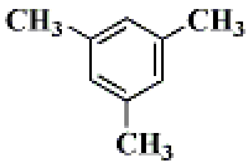
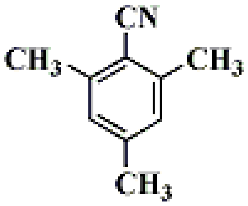
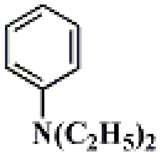
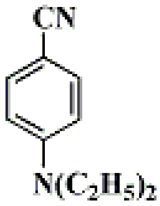
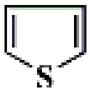
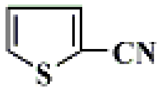
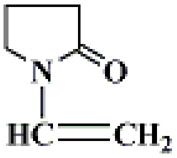
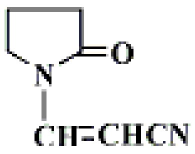
1. Chlorosulfonyl isocyanate may be prepared as described in *Org. Synth.*, **Coll. Vol. 5**, 226 (1973); it is available from Farbwerke Hoechst AG. The checkers found it necessary to distill the product before use.
2. A less pure product is obtained if the temperature is allowed to rise at this phase of the reaction.
3. Other amides also can be used, but *N,N*-dimethylformamide generally is preferred, especially because of its low molecular weight, high solvent power, and miscibility with water. In addition, it is readily available.

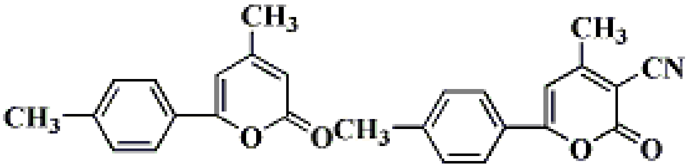
3. Discussion

This procedure[2] is an example of a broadly applicable, simple method for introducing the cyano substituent into compounds that readily undergo electrophilic substitution. The method is characterized by mild reaction conditions, a simple workup procedure, and, in most cases, good yields. Although the method has two steps, the reaction generally can be carried out without isolation of the intermediate chlorosulfonamide. An indication of its scope is given in Table I.[2] Additional examples of the substitution reaction of chlorosulfonyl isocyanate with aromatic and heterocyclic compounds and with olefins, yielding carboxylic acid amide *N*-sulfonyl chlorides are reported.[2,3,4,5,6]

TABLE I

Nitriles[2] Prepared from $ClSO_2NCO$

Reactant	Product	Yield, %
		67
		20
		66
		86



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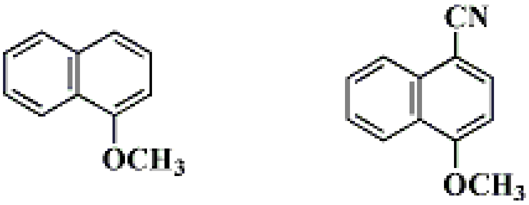

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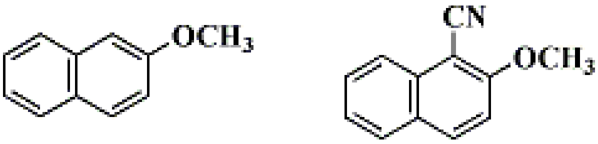

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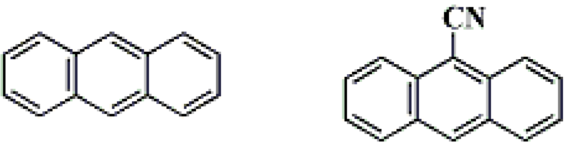

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Other procedures for the preparation of 2,4-dimethoxybenzonitrile include the reaction of 2,4-dimethoxybenzamide with thionyl chloride,[3] the action of acetic anhydride on 2,4-dimethoxybenzaldoxime,[7] the reaction of diazotized 2,4-dimethoxyaniline with potassium copper cyanide,[8] and the action of cyanogen bromide on resorcinol dimethyl ether in the presence of aluminum chloride.[9]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

butadiene sulfone

acetic anhydride (108-24-7)

thionyl chloride (7719-09-7)

aluminum chloride (3495-54-3)

dichloromethane (75-09-2)

Cyanogen bromide (506-68-3)

N,N-dimethylformamide (68-12-2)

CHLOROSULFONYL ISOCYANATE (1189-71-5)

2,4-DIMETHOXYBENZONITRILE, Benzonitrile, 2,4-dimethoxy- (4107-65-7)

resorcinol dimethyl ether (151-10-0)

2,4-dimethoxybenzamide

2,4-dimethoxybenzaldoxime

2,4-dimethoxyaniline (2735-04-8)

potassium copper cyanide

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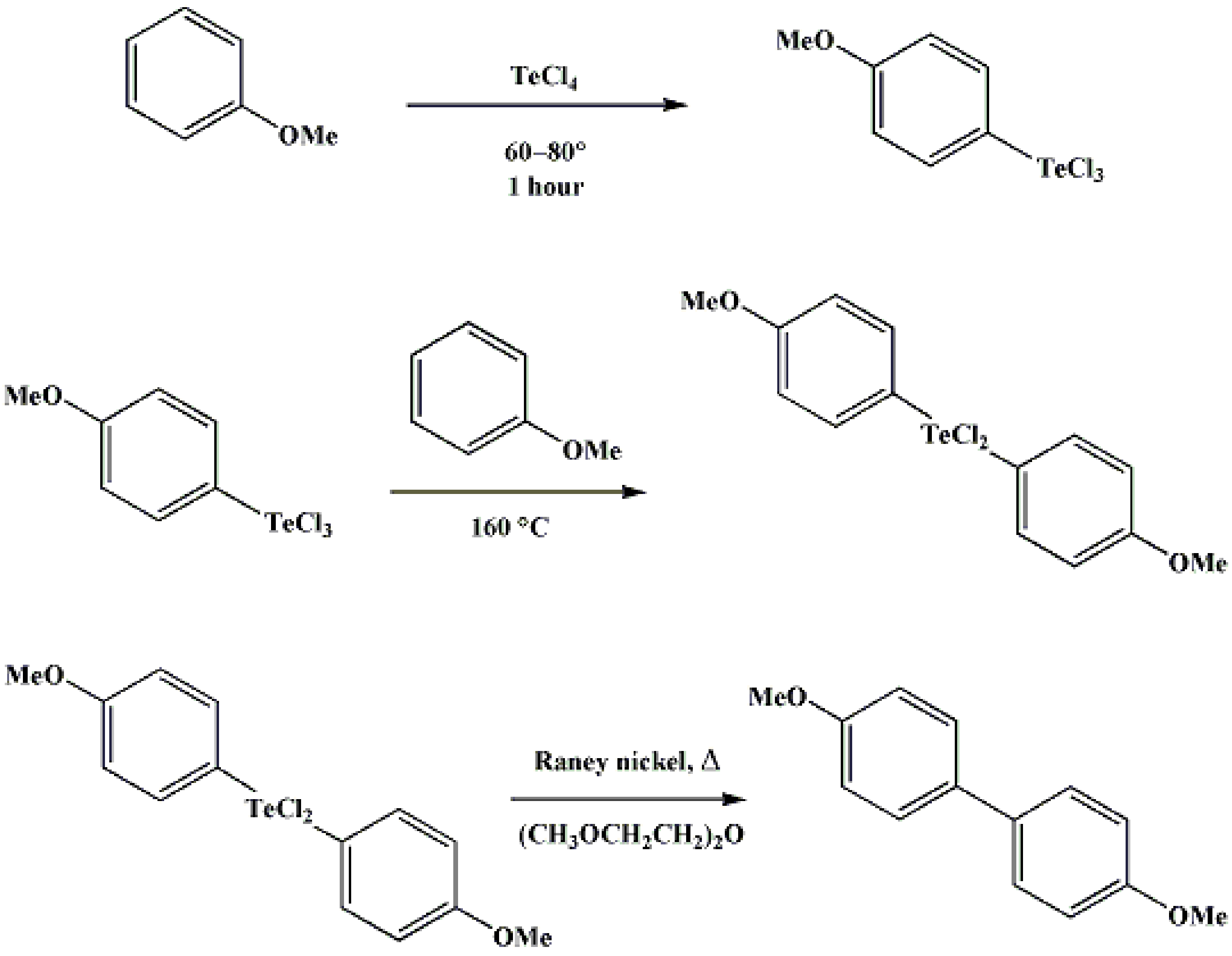
Organic Syntheses, CV 6, 468

BIARYLS FROM SIMPLE ARENES *via* ORGANOTELLURIUM INTERMEDIATES: 4,4'-DIMETHOXY-1,1'-BIPHENYL

[1,1'-Biphenyl, 4,4'-dimethoxy-]



Submitted by J. Bergman[1], R. Carlsson, and B. Sjöberg.
Checked by J. Diakur and S. Masamune.

1. Procedure

Caution! Because tellurium compounds have toxic effects similar to those of arsenic compounds,[2] care should be taken not to bring tellurium tetrachloride and its reaction products into contact with the skin. Avoid breathing fumes and dust of tellurium compounds. In addition, hydrogen chloride is evolved in Step A, and pyrophoric Raney nickel is used in Step B. Therefore all manipulations described in this procedure must be carried out in an efficient fume hood.

Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A. *Bis(4-methoxyphenyl)tellurium dichloride.* A dry, 500-ml., three-necked, round-bottomed flask

equipped with a thermometer and a reflux condenser fitted with a calcium chloride drying tube is charged with 27.0 g. (0. 100 mole) of tellurium tetrachloride (Note 1) and 64.8 g. (0.600 mole) of dry anisole (Note 2). The mixture is heated to 160° over a period of 30 minutes and maintained at this temperature for 6 hours. The reaction mixture is allowed to cool to room temperature, and the solvent is removed with the aid of a vacuum pump. The crude solid (Note 3) is dissolved in *ca.* 250 ml. of boiling acetonitrile and filtered while hot (Note 4). Upon cooling to −25°, crystals deposit (Note 5), which weigh 35.5–38.5 g. (84–90%), m.p. 182–183° (Note 6).

B. *4,4'-Dimethoxy-1,1'-biphenyl*. A 500-ml., three-necked, round-bottomed flask is equipped with a 500-ml. dropping funnel, a stopper, and a reflux condenser fitted with a two-way stopcock, one end of which is connected to an aspirator, and the other to a cylinder of dry, oxygen-free nitrogen. To this flask are added 60 g. of Raney nickel (Note 7) and 150 ml. of benzene. The system is flushed with nitrogen, and the solvent is evaporated under reduced pressure. The Raney nickel is then degassed behind an explosion shield (Note 8) in a hood by heating to 200° (2 mm.) for 2 hours.

The catalyst is allowed to cool under nitrogen, and 400 ml. of bis(2-methoxyethyl) ether is added from the dropping funnel. The stopper is then temporarily removed to add 20.6 g. (0.0497 mole) of bis(4-methoxyphenyl)tellurium dichloride. The mixture is refluxed for 8 hours and filtered while still hot. The filtrate is evaporated under reduced pressure (10–20 mm.), giving a residue which when recrystallized from ethanol yields 8.5–9.8 g. (78–90%) of the product, m.p. 175–176° (Note 9).

2. Notes

1. The submitters used tellurium tetrachloride available from E. Merck A G. The checkers purchased the reagent from Research Organic/Inorganic Chemical Corporation.
2. The checkers distilled anisole from calcium sulfate before use. This reagent functions not only as a reactant, but also as solvent. In some similar preparations the intermediate trichloride is rather insoluble, as in the case of bis(3-methyl-4-methoxyphenyl)tellurium dichloride. The addition of co-solvents such as bis(2-methoxyethyl) ether is beneficial.[3]
3. The crude product contains the 4,4'- and the 2,4'-isomers in the ratio 99.2/0.8. See (Note 5).
4. A small amount of tellurium (95 mg.) is formed during the preparation. The amount of tellurium increases slowly as the heating is prolonged. In a separate experiment pure bis(4-methoxyphenyl)tellurium dichloride was pyrolyzed at 250°. The main products were 1-chloro-4-methoxybenzene and tellurium.
5. Evaporation of the mother liquor gives a solid enriched in the 2,4'-isomer. Recrystallization of this solid from ethanol yields crystals containing 45% of the 2,4'-isomer.
6. The spectral details of the product are: ^{1}H NMR (DMSO-d_6), δ (multiplicity, number of protons, assignment): 3.80 (s, 6H, OCH_3), 7.05–8.0 (q, 8H, A_2B_2 aryl); mass spectrum *m/e* (relative intensity > 10% for peaks with *m/e* above 150): 379 (16), 377 (14), 344 (39), 342 (35), 340 (22), 272 (36), 270 (31), 237 (18), 235 (17), 233 (10), 215 (15), 214 (99), 200 (14), 199 (100), 172 (21). No peaks corresponding to the parent ion could be detected.
7. The catalyst was prepared from a nickel–aluminum (50:50) alloy using the procedure in *Org. Synth.*, **Coll. Vol. 3**, 181 (1955). The catalyst is used in large excess. Reduced amounts of catalyst resulted in decreased yields, and the product is contaminated with detectable (GC) amounts of bis(4-methoxyphenyl)telluride.
8. This operation has been performed several times without incident. However, it should be noted that the W6 and W7 forms of Raney nickel have been reported to explode [*Org. Synth.*, **Coll. Vol. 5**, 102 (1973)]. No explosions have been reported with the W2 form used in this preparation.
9. 4,4'-Dimethoxybiphenyl can also be prepared by simply refluxing bis(4-methoxyphenyl)

tellurium dichloride with degassed, commercial Raney nickel. The yields are, however, lower and less reproducible,[3] and the product may contain some bis(4-methoxyphenyl)telluride.

3. Discussion

Most synthetic methods for biaryl preparation, such as the Ullmann coupling and all variants of the Grignard coupling,[4,5,6] require halogen-substituted aromatic compounds as starting materials. Since these components are prepared by halogenation of the appropriate precursor, either directly or indirectly, it is evident that a direct coupling method offers obvious advantages. Such reactions may be effected electrochemically,[7] and by reagents such as palladium(II) acetate,[8,9] thallium(III) trifluoroacetone,[10] and vanadium tetrachloride.[11] The applicability of these reagents and the selectivity of the reactions are often restricted, when compared with the present procedure. For a recent review, see reference [12].

Tellurium tetrachloride reacts as an electrophilic reagent with aromatic compounds bearing activating substituents, such as RO-, R_2N-, and RS- groups, providing first aryltellurium trichlorides, then diaryltellurium dichlorides, as one raises the reaction temperature. The second step should, in order to prevent formation of elemental tellurium and chlorinated aromatics, be performed at as low a temperature as possible (Note 4). This is especially important when highly reactive substrates such as 1,3-dimethoxybenzene are used. The addition of a Lewis acid to the reaction mixture brings about an acceleration of the reaction with less reactive reactants such as benzene and chlorobenzene.[3] The rate of acceleration is dramatically enhanced when the ratio of $AlCl_3/TeCl_4$ is more than 1:1. Thus, refluxing a mixture of 1 equivalent of $TeCl_3$ and 3 equivalents of $AlCl_3$ in benzene provided diphenyltellurium dichloride in 58.5% yield.[13]

The coupling reaction proceeds better when a rigorously degassed Raney nickel catalyst is used, but a nickel catalyst prepared by a much simplified procedure (Note 9) is also effective. The coupling may also be promoted by other elements, including copper and palladium.

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Appendix

Compounds Referenced (Chemical Abstracts Registry Number)

oxygen-free nitrogen

thallium(III) trifluoroacetone

ethanol (64-17-5)

hydrogen chloride (7647-01-0)

Benzene (71-43-2)

acetonitrile (75-05-8)

nitrogen (7727-37-9)

Anisole (100-66-3)

copper (7440-50-8)

calcium sulfate (7778-18-9)

nickel, Raney nickel (7440-02-0)

chlorobenzene (108-90-7)

palladium (7440-05-3)

bis(2-methoxyethyl) ether (111-96-6)

1-chloro-4-methoxybenzene (623-12-1)

1,3-dimethoxybenzene (151-10-0)

tellurium

tellurium tetrachloride (10026-07-0)

Bis(4-methoxyphenyl)tellurium dichloride (4456-36-4)

bis(3-methyl-4-methoxyphenyl)tellurium dichloride

bis(4-methoxyphenyl)telluride

palladium(II) acetate (3375-31-3)

vanadium tetrachloride (7632-51-1)

diphenyltellurium dichloride

4,4'-dimethoxybiphenyl, 4,4'-Dimethoxy-1,1'-biphenyl, 1,1'-Biphenyl, 4,4'-dimethoxy- (2132-80-1)

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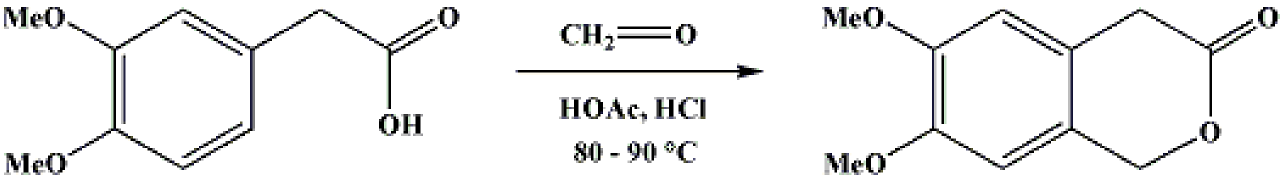
6,7-DIMETHOXY-3-ISOCHROMANONE

[3*H*-2-Benzopyran-3-one, 1,4-dihydro-6,7-dimethoxy-]



Submitted by J. Finkelstein[1] and A. Brossi[1,2].
Checked by Yoshinori Hamada and Wataru Nagata.

1. Procedure

A 500-ml., round-bottomed flask equipped with a mechanical stirrer, a dropping funnel, a thermometer, and a reflux condenser is charged with 49.0 g. (0.250 mole) of 3,4-dimethoxyphenylacetic acid (Note 1) and 125 ml. of acetic acid. The solution is stirred and heated at 80° on a steam bath, while 40 ml. of concentrated hydrochloric acid is added rapidly and followed immediately with 40 ml. of formalin (37% formaldehyde, by weight, in water) (Note 2) and (Note 3). The yellow solution is stirred and heated on a steam bath for 1 hour, during which time the reaction temperature reaches 90° (Note 4) and the solution assumes a dark-brown color. After cooling to room temperature the solution is poured, with stirring, into a mixture of 650 g. of chipped ice and 650 ml. of cold water. The mixture is transferred to a 2-l. separatory funnel, and the organic material is extracted with four 300-ml. portions of chloroform (Note 5). The combined chloroform extracts are washed with 250-ml. portions of aqueous 5% sodium hydrogen carbonate until neutral (Note 6), then with two, 250-ml. portions of water, and finally dried over anhydrous magnesium sulfate. The solvent is removed on a rotary evaporator with a water bath up to a temperature of 55° (Note 7), yielding 43.5–44.2 g. (83.7–85.1%) of crude 6,7-dimethoxy-3-isochromanone, m.p. 95–100°, as a yellow solid suitable for general synthetic purposes. A purer product is obtained by recrystallization from 55 ml. of ethanol (Note 8),(Note 9),(Note 10), giving 26–27.6 g. of white crystals which, after drying at 80°, melt at 106–108° (Note 11). Upon concentration of the mother liquor to a smaller volume, an additional 1.7–3.2 g. of the isochromanone, m.p. 103–105°, is obtained. The total yield is 29.2–29.3 g. (56.2–56.4%).

2. Notes

1. The 3,4-dimethoxyphenylacetic acid was purchased from Matheson, Coleman and Bell. The checkers prepared material of m.p. 97–98° according to the procedure described in *Org. Synth.*, **Coll. Vol. 2**, 333 (1961).
2. "Baker Analyzed" reagent grade formaldehyde solution obtained from J. T. Baker Chemical Company was used. The checkers used material purchased from Wako Pure Chemical Industries, Ltd., Japan.
3. About 30 seconds each is needed for the additions of concentrated hydrochloric acid and formalin.
4. The temperature of the reaction mixture falls to 68° on addition of the reagents but rises again within 10 minutes.
5. Fisher Scientific Company Certified A.C.S. chloroform was used. The checkers used

reagent grade chloroform purchased from Wako Pure Chemical Industries, Ltd., Japan.
6. The wash solution should be neutral to litmus. The checkers observed that the pH values of the first and the second wash solutions were 5–5.5 and 7.5, respectively.
7. The viscous, syrupy residue crystallizes on standing at room temperature or by addition of a small amount of methanol.
8. Anhydrous ethanol (Type 2B) was used.
9. Recrystallization can conveniently be performed with the initial syrupy residue.
10. The checkers found that a mixture of dichloromethane and ether was a more suitable solvent for crystallization of the product. The pure sample obtained from this solvent system melts at 108–109°.
11. The product has the following spectral properties; IR ($CHCl_3$) $cm.^{-1}$: 3040, 1750, 1616, 1520, 1253, and 1118; ^1H NMR ($CDCl_3$), δ (multiplicity, number of protons, assignment): 3.63 (s, 2H, CH_2CO_2), 3.88 (s, 6H, $2OCH_3$), 5.25 (s, 2H, CH_2OCO), 6.72 (s, 1H, aromatic *H*), 6.77 (s, 1H, aromatic *H*).

3. Discussion

The reaction is essentially that described by the submitters.[3] The procedure illustrates a convenient method for the synthesis of a type of lactone which could serve as an important intermediate in the synthesis of isoquinolones, tetrahydroisoquinolines, and isoquinoline alkaloids. Several analogous and closely related lactones have been reported.

The parent, unsubstituted isochromanone reacts with a variety of aromatic amines, giving *N*-substituted 1,4-dihydro-3(2*H*)-isoquinolones,[4] and with amines, giving amides.[5] 6,7-Methylenedioxy-3-isochromanone was used as an intermediate in the synthesis of protopine and its allied alkaloids,[6] and in the synthesis of the berberine ring system.[7] The 6-methoxy analog was prepared as a potential intermediate in a camptothecin synthesis[8] and 8-methoxy-4,5,6,7-tetramethyl-3-isochromanone was used as an intermediate in the synthesis of sclerin.[9]

The compound described herein was the basis of a facile synthesis of (±)-xylopinins,[10] and its reaction with hydrazine has been reported.[11] The compound was also used in the synthesis of pseudoberberine,[12] and when reacted with 1-methyltryptamine, 1-methyl-15,16,17,18,19,20-hexahydroyohimban was obtained.[13] When isochroman-3-ones are treated with tryptamine, the synthesis of the yohimban skeleton is achieved.[14] The preparation of α-methyldopa in a rigid framework is described.[15]

The procedure may have considerable scope, as shown by the synthesis of a heterocyclic lactone, an important intermediate in the synthesis of *d,l*-desoxycamptothecin, which on oxidation gave camptothecin.[16] A new synthesis of benzocyclobutenes by the thermal and electron impact-induced decomposition of 3-isochromanones was described.[17]

3-Isochromanone was allowed to react with phenol ethers in polyphosphoric acid, yielding dibenzo [*a,d*] tropylium salts, but in formic acid homoveratric acids were obtained.[18]

The nonaromatic lactones derived from *cis*-[19] and *trans*-2-hydroxymethylcyclohexaneacetic acid[20] are important intermediates in the synthesis of indole alkaloids.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

d,l-desoxycamptothecin

camptothecin

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

methanol (67-56-1)

ether (60-29-7)

formaldehyde, formalin (630-08-0)

chloroform (67-66-3)

sodium hydrogen carbonate (144-55-8)

formic acid (64-18-6)

hydrazine (302-01-2)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

3,4-dimethoxyphenylacetic acid (93-40-3)

6,7-Dimethoxy-3-isochromanone, 3H-2-Benzopyran-3-one, 1,4-dihydro-6,7-dimethoxy- (16135-41-4)

6,7-Methylenedioxy-3-isochromanone

8-methoxy-4,5,6,7-tetramethyl-3-isochromanone

1-methyltryptamine

1-methyl-15,16,17,18,19,20-hexahydroyohimban

tryptamine (61-54-1)

3-Isochromanone (4385-35-7)

trans-2-hydroxymethylcyclohexaneacetic acid

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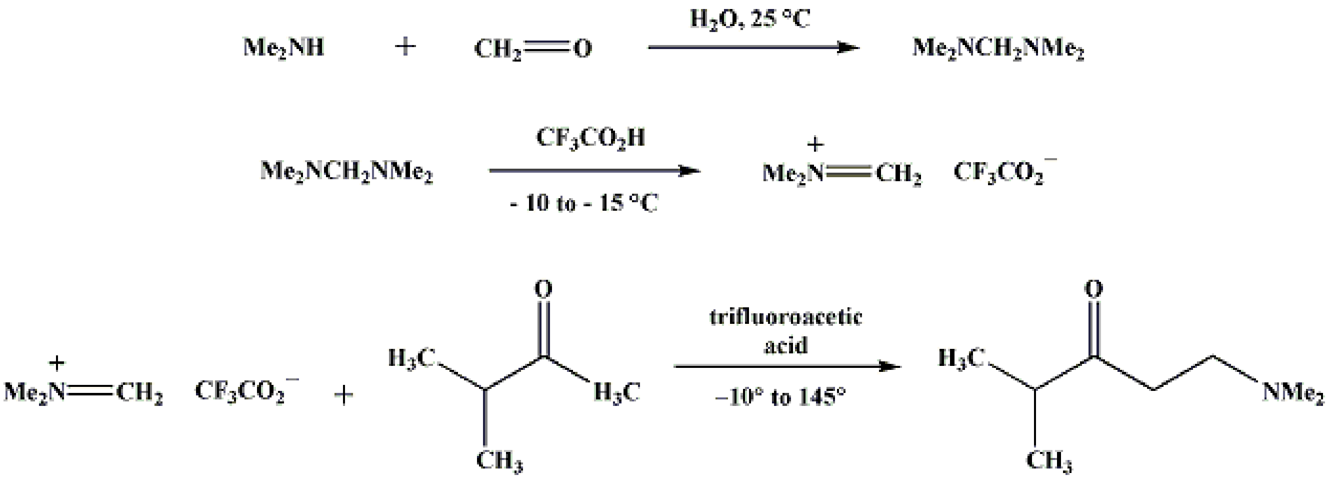
REGIOSELECTIVE MANNICH CONDENSATION WITH DIMETHYL (METHYLENE)AMMONIUM TRIFLUOROACETATE: 1-(DIMETHYLAMINO)-4-METHYL-3-PENTANONE

[3-Pentanone, 1-(dimethylamino)-4-methyl-]



Submitted by Michel Gaudry[1], Yves Jasor, and Trung Bui Khac.
Checked by Bernard L. Müller and George Büchi.

1. Procedure

Caution! Trifluoroacetic acid is highly toxic; consequently Part B of this procedure must be conducted in a well-ventilated hood.

A. *Bis(dimethylamino)methane.* A 500-ml., round-bottomed flask equipped with a magnetic stirring bar and a dropping funnel is charged with 100 g. (1.0 mole) of aqueous 30% formaldehyde (Note 1). The solution is stirred and cooled in an ice bath as 225 g. (2.0 moles) of a 40% solution of dimethylamine (Note 1) in water is added dropwise. The resulting aqueous solution is allowed to stand overnight at room temperature, after which it is saturated with solid potassium hydroxide. The two layers are separated, the upper layer is dried over potassium hydroxide pellets, and the drying agent is removed. Distillation at atmospheric pressure through a Vigreux column gives 85–88 g. (83–86%) of bis(dimethylamino)methane, b.p. 81.5–83°.

B. *1-(Dimethylamino)-4-methyl-3-pentanone.* A 100-ml., two-necked, round-bottomed flask equipped with a magnetic stirring bar and a pressure-equalizing dropping funnel bearing a calcium chloride drying tube is charged with 50 ml. of anhydrous trifluoroacetic acid (Note 2). The trifluoroacetic acid is stirred and cooled in an ice–salt bath at –10° to –15° while 10.2 g. (0.100 mole) of bis(dimethylamino)methane is added over a 50-minute period (Note 3). The temperature of the resulting solution of dimethyl(methylene)ammonium trifluoroacetate is kept below –10° as 8.6 g. (0.10 mole) of 3-methyl-2-butanone (Note 4) is gradually added. The cooling bath is removed and the solution is heated in an oil bath at 65° for 1.5 hours (Note 5). The temperature of the oil bath is then raised to 145° (Note 6). After 1.5 hours the solution is cooled and the trifluoroacetic acid is neutralized by adding the contents of the flask dropwise to an ice-cold solution of 100 g. of potassium carbonate in 100 ml. of water (Note 7). The crystals are collected by filtering through a sintered-glass Büchner funnel and washed with two 50-ml. portions of dichloromethane. The aqueous filtrate is extracted with four 50-ml. portions of dichloromethane. The dichloromethane extracts are combined, washed with 50 ml. of water, dried over anhydrous sodium sulfate, and concentrated with a rotary evaporator. The concentrate, which amounts to 12.7 g. (Note 8), is distilled under reduced pressure through an 18-cm. column packed with Raschig rings (Note 9), affording 7.0–8.2 g. (49–57%) of 1-(dimethylamino)-4-methyl-3-pentanone, b.p. 49° (3 mm.) (Note 10).

2. Notes

1. Formaldehyde and dimethylamine are available as aqueous 37% and 40% solutions, respectively, from

Aldrich Chemical Company, Inc.
2. The submitters purchased trifluoroacetic acid from Prolabo, Paris, France, or E. Merck, Darmstadt, Germany, and distilled it from phosphorus pentoxide. This reagent is also available from Aldrich Chemical Company, Inc., and J. T. Baker Chemical Company.
3. The reaction between bis(dimethylamino)methane and trifluoroacetic acid is very exothermic. If the temperature is carefully controlled, a colorless solution remains when the addition is complete.
4. 3-Methyl-2-butanone was purchased from Eastman Organic Chemicals and distilled before use.
5. The progress of the reaction can be monitored by taking ^{1}H NMR spectra at appropriate intervals. The following absorptions for dimethyl(methylene)ammonium trifluoroacetate in trifluoroacetic acid disappear as the reaction progresses: δ (multiplicity, number of protons, assignment): 3.89 (broad m, 6H, 2 NCH_3), 8.07 (broad m, 2H, N=CH_2).
6. At this temperature 4-(dimethylamino)-3,3-dimethyl-2-butanone, which is formed initially, isomerizes to 1-(dimethylamino)-4-methyl-3-pentanone.
7. Removing trifluoroacetic acid by evaporation is tedious. The neutralization procedure given here produces insoluble salts that are readily separated by filtration.
8. The ratio of the isomeric amino ketones in the crude product can be determined from the relative intensities of the signals for the $(CH_3)_2C$ grouping in a ^{1}H NMR spectrum taken in trifluoroacetic acid (see (Note 10)). In $CDCl_3$ these absorptions overlap.
9. To minimize losses of products during the distillation, the submitters used a circulating device to chill the condenser cooling water to 5–10°. In addition, the outlet to the vacuum line was located as far as possible from the drip tip, and the receivers were cooled in an ice bath.
10. The ^{1}H NMR spectrum of the product in trifluoroacetic acid shows that the isomeric purity is greater than 90%. The ^{1}H NMR spectra for the isomeric amino ketones in both trifluoroacetic acid and $CDCl_3$, δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 1-(dimethylamino)-4-methyl-3-pentanone (trifluoroacetic acid), 1.16 (d, *J* = 7, 6H, 2CCH_3), 2.98 (d, *J* = 5, 6H, 2NCH_3), 3.31 (m, 4H, CH_2CH_2); ($CDCl_3$), 1.10 (d, *J* = 7, 6H, 2CCH_3), 2.23 (s, 6H, 2NCH_3), 2.60 (s, 4H, CH_2CH_2); 4-(dimethylamino)-3,3-dimethyl-2-butanone (trifluoroacetic acid), 1.53 (s, 6H, 2CCH_3), 2.45 (s, 3H, COCH_3), 3.15 (d, *J* = 5, 6H, 2NCH_3), 3.40 (d, *J* = 5, 2H, CH_2N); ($CDCl_3$), 1.12 (s, 5H, 2CCH_3), 2.13 (s, 3H, COCH_3), 2.18 (s, 6H, 2NCH_3), 2.41 (s, 2H, CH_2N).

3. Discussion

The Mannich condensation has traditionally been carried out in the presence of water as a three-component condensation involving a carbonyl compound (or related carbon nucleophile), formaldehyde, and a primary or secondary amine.[2 3] The initial step is a condensation between the latter two reactants to form a mono- or dialkyl (methylene)ammonium ion which subsequently serves as the electrophilic partner in the reaction. With unsymmetrical ketones aminomethylation generally occurs at both positions, giving mixtures of isomeric β-amino ketones. The ratio of the isomers depends strongly on the structure of the ketone,[4] and the more highly branched β-amino ketone usually predominates.

In recent years a number of methods have been developed for the preparation of dialkyl(methylene)ammonium salts (Mannich reagents),[5,6,7,8,9] and their use in Mannich-type condensation reactions under anhydrous conditions has improved the scope and efficiency of this important synthetic process.[6,7,8,9,10,11,12,13] However, the orientation of the Mannich reaction may nevertheless be difficult to control. Apart from the work of the submitters, the preparation of isomerically pure Mannich bases has only been achieved by indirect methods in which specific enol derivatives are generated and allowed to react with dialkyl(methylene)ammonium salts.[10,12,14] The Mannich reaction of β-keto esters affords isomerically pure β-dimethylamino β'-keto esters which may in turn be converted to specific α-methylene ketones.[15] However, the β-amino ketones themselves are not as yet available by this method.

The submitters have found that the orientation of the reaction of Mannich reagents with unsymmetrical ketones in anhydrous solvents is highly dependent on the experimental conditions, the solvent, and the structures of the ketone and iminium ion reactants.[11] Under conditions of kinetic control, the reaction of methyl ketones with dimethyl (methylene)ammonium trifluoroacetate in trifluoroacetic acid leads to amino ketones in which the more highly substituted isomer predominates (≥85% when the α'-position is tertiary and 80% when the α'-position is secondary). In contrast, reaction with diisopropyl(methylene)ammonium perchlorate in acetonitrile gives almost exclusively the less highly substituted isomer (100% when the α'-position is tertiary and 90% when it is secondary). Although the latter method directly affords the less highly substituted Mannich bases in yields greater than 80%, it cannot be utilized

safely in large-scale preparative reactions owing to the hazardous nature of perchlorate salts.

The less highly substituted Mannich bases can also be prepared directly from ketones and dimethyl(methylene) ammonium trifluoroacetate by the procedure reported here, which takes advantage of the isomerization of Mannich bases in trifluoroacetic acid.[11] (In acetic acid the Mannich bases undergo elimination of dimethylamine to give α-methylene ketones.) This method is rapid and affords products, having an isomeric purity of at least 90%, without difficult separations. The 49–57% yield of 1-(dimethylamino)-4-methyl-3-pentanone obtained with this procedure compares favorably with the overall yields of amino ketones prepared by the indirect routes mentioned previously.

1-(Dimethylamino)-4-methyl-3-pentanone has been prepared by addition of isopropyl-magnesium bromide to methyl 3-(dimethylamino)propionate,[16] by reduction of 1-(dimethylamino)-4-methyl-1-penten-3-one with lithium aluminum hydride,[17] and by displacement of chloride from 1-chloro-4-methyl-3-pentanone with dimethylamine.[18] Although the preparation of 1-(dimethylamino)-4-methyl-3-pentanone by Mannich condensation of 3-methyl-2-butanone with dimethylamine hydrochloride and formaldehyde has been reported,[19] the product evidently is a mixture of the two isomeric β-dimethylamino ketones.[4,18]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

potassium carbonate (584-08-7)

acetic acid (64-19-7)

acetonitrile (75-05-8)

formaldehyde (630-08-0)

sodium sulfate (7757-82-6)

potassium hydroxide (1310-58-3)

dimethylamine hydrochloride (506-59-2)

dichloromethane (75-09-2)

dimethylamine (124-40-3)

3-methyl-2-butanone (563-80-4)

isopropyl-magnesium bromide (920-39-8)

lithium aluminum hydride (16853-85-3)

trifluoroacetic acid (76-05-1)

Bis(dimethylamino)methane (51-80-9)

DIMETHYL(METHYLENE)AMMONIUM TRIFLUOROACETATE

1-(DIMETHYLAMINO)-4-METHYL-3-PENTANONE, 3-Pentanone, 1-(dimethylamino)-4-methyl- (5782-64-9)

4-(dimethylamino)-3,3-dimethyl-2-butanone

diisopropyl(methylene)ammonium perchlorate

methyl 3-(dimethylamino)propionate (3853-06-3)

1-(dimethylamino)-4-methyl-1-penten-3-one

1-chloro-4-methyl-3-pentanone

phosphorus pentoxide (1314-56-3)

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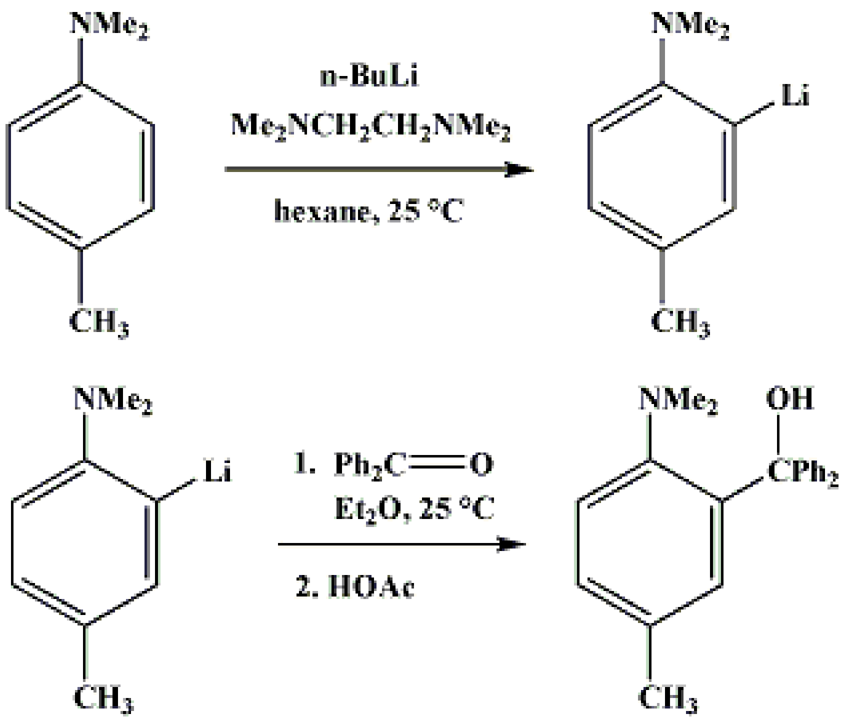
DIRECTED LITHIATION OF AROMATIC COMPOUNDS: (2-DIMETHYLAMINO-5-METHYLPHENYL)DIPHENYLCARBINOL

[Benzenemethanol, 2-(dimethylamino)-5-methyl-α,α-diphenyl-]



Submitted by J. V. Hay and T. M. Harris[1].
Checked by Robert A. Auerbach and Herbert O. House.

1. Procedure

A dry, 500-ml., two-necked flask containing 6.75 g. (0.0500 mole) of *N,N*-dimethyl-*p*-toluidine (Note 1) and 175 ml. of anhydrous hexane (Note 2) is fitted with a Teflon-coated magnetic stirring bar, a pressure-equalizing dropping funnel capped with a rubber septum, and a nitrogen inlet tube. The reaction vessel is flushed with nitrogen, and a static nitrogen atmosphere is maintained within the apparatus for the remainder of the reaction sequence. A solution of 8.8 g. (0.076 mole of *N,N,N',N'*-tetramethylethylenediamine (Note 3) in 40 ml. of anhydrous hexane is added to the dropping funnel, followed by a hexane solution containing 0.076 mole of *n*-butyllithium (Note 4). The resulting solution, which becomes warm as the organolithium-diamine complex forms, is allowed to stand for 15 minutes, then added to the reaction mixture, dropwise and with stirring over 15–20 minutes. The resulting bright yellow, turbid reaction mixture is stirred at room temperature for 4 hours longer before a solution of 13.8 g. (0.0758 mole) of benzophenone (Note 5) in 40 ml. of anhydrous diethyl ether is added to the reaction mixture, dropwise and with stirring

over 20 minutes. The resulting, deep-green solution is stirred for an additional 20 minutes, then poured into a vigorously stirred solution of 12 g. (0.20 mole) of acetic acid in 30 ml. of ether (Note 6). After the reaction solution has been successively extracted with 50 ml. of water and four 50-ml. portions of 5% hydrochloric acid, the aqueous extracts are combined (Note 7) and made basic with aqueous 10% sodium hydroxide. The alkaline mixture is heated to boiling and maintained at this temperature until the escaping vapor is no longer basic to moistened pHydrion paper (Note 8). The mixture is then cooled, and the white solid product which separates is collected on a Büchner funnel and washed with three 20-ml. portions of water. The crude product (m. p. 142–168°) is recrystallized from 250 ml. of 3 : 1 (v/v) hexane-ethyl acetate, giving 6.6–8.2 g. of the amino alcohol product as colorless prisms, m.p. 168–171°. Concentration of the mother liquors gives an additional 0.8–1.2 g. of product, m.p. 167–169°, for a total yield of 7.8–9.0 g. (49–57%). Although the product is sufficiently pure for most purposes, a second recrystallization from hexane-ethyl acetate raises the melting point to 169.5–172° (Note 9).

2. Notes

1. Commercial *N,N*-dimethyl-*p*-toluidine, obtained from Aldrich Chemical Company, Inc., was used without purification.
2. An A.C.S. grade of hexane, obtained from Fisher Scientific Company, was used without further purification.
3. *N,N,N',N'*-Tetramethylethylenediamine, purchased from Aldrich Chemical Company, Inc., was distilled from calcium hydride immediately before use; b.p. 120–122°.
4. Hexane solutions of *n*-butyllithium, purchased from either Alfa Inorganics, Inc., or Foote Mineral Company, were standardized by the titration procedure of Watson and Eastham.[2] A detailed procedure for this titration is provided in *Org. Synth.*, **Coll. Vol. 6**, 121 (1988).
5. Benzophenone, purchased from Fisher Scientific Company, was used without purification.
6. Reversal of this hydrolysis procedure, the addition of acetic acid to the reaction mixture, had an adverse effect on the yield of product.
7. Some of the aqueous extracts may contain small amounts of suspended particulate matter.
8. This simple steam distillation removes the unchanged *N,N*-dimethyl-*p*-toluidine present in the crude product.
9. The purified product has the following spectral properties: IR (CCl_4) 3050 $cm.^{-1}$ (associated OH); UV (95% C_2H_5OH) max (ε) 251 (905), 258 (823), 264 (720), and 275 nm (432); NMR ($CDCl_3$), δ 2.19 (s, 3H, C-CH_3), 2.38 [s, 6H, N(CH_3)$_2$] 6.55 (s, 1H, O*H*), and 7.00–7.50 (m, 13H, aromatic C*H*); *m/e* (rel. int.), 317(M^+, 100), 240(84), 225(28), 224(91), 222(43), 150(25), 134(41), 120(32), 105(41), 91(51), and 77(42).

3. Discussion

This procedure is an adaptation of one described by Hauser and co-workers.[3] The product has also been prepared from 2-bromo-*N*,*N*-dimethyl-*p*-toluidine by halogen-metal interchange with *n*-butyllithium followed by condensation with benzophenone,[3] a procedure less convenient than that presently described.

Tertiary amines such as *N*,*N*,*N'*,*N'*-tetramethylethylenediamine (TMEDA) and 1,4-diazabicyclo[2.2.2]octane (DABCO) strongly catalyze metallations by alkyllithium reagents. Uncatalyzed lithiation of toluene is very poor,[4] whereas a yield of 90% has been obtained when TMEDA is employed as a catalyst.[5]

It is noteworthy that metallation of *N*,*N*-dimethyl-*p*-toluidine takes place at a position *ortho* to the dimethylamino group rather than on or *ortho* to the aryl methyl group. Apparently, coordination of lithium by the amino group plays a dominant role in directing metallation even in the presence of TMEDA. Other cases have been reported in which the site of metallation is altered by addition of TMEDA.[6,7]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ethyl acetate (141-78-6)

ether, diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

nitrogen (7727-37-9)

toluene (108-88-3)

Benzophenone (119-61-9)

Benzenemethanol (100-51-6)

lithium (7439-93-2)

n-butyllithium (109-72-8)

hexane (110-54-3)

calcium hydride (7789-78-8)

1,4-diazabicyclo[2.2.2]octane (280-57-9)

(2-Dimethylamino-5-methylphenyl)diphenylcarbinol (23667-05-2)

tetramethylethylenediamine (20485-44-3)

N,N,N',N'-tetramethylethylenediamine (110-18-9)

N,N-dimethyl-p-toluidine (99-97-8)

2-bromo-N,N-dimethyl-p-toluidine

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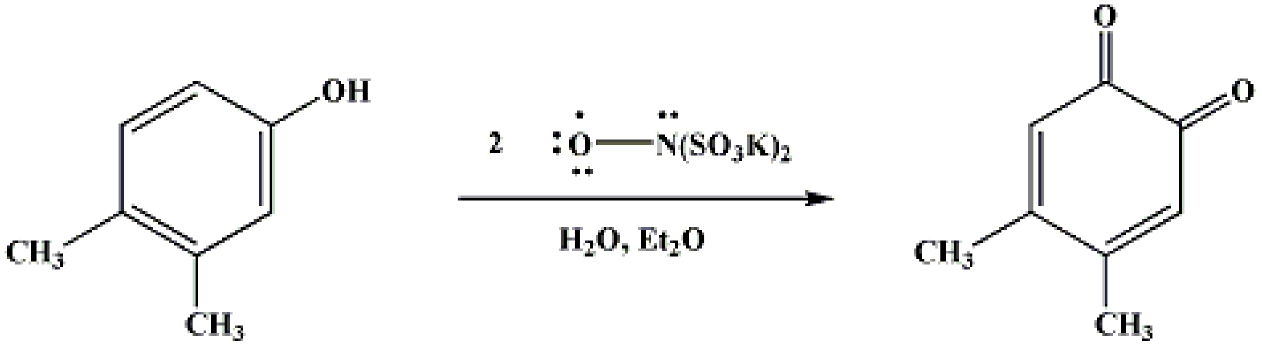
USE OF DIPOTASSIUM NITROSODISULFONATE (FREMY'S SALT): 4,5-DIMETHYL-*o*-BENZOQUINONE

[3,5-Cyclohexadiene-1,2-dione, 4,5-dimethyl-]



Submitted by H.-J. Teuber[1]
Checked by P. A. Wehrli, F. Pigott, and A. Brossi.

1. Procedure

A solution of 15 g. of sodium dihydrogen phosphate (Note 1) in 5 l. of distilled water is placed in a 6-l. separatory funnel. To this solution is added 90 g. (0.33 mole) of dipotassium nitrosodisulfonate (Fremy's salt) (Note 2). The mixture is shaken to dissolve the inorganic radical. A solution of 16 g. (0.13 mole) of 3,4-dimethylphenol (Note 3) in 350 ml. of diethyl ether is added quickly to the purple solution. As the mixture is shaken vigorously for 20 minutes (Note 4), the color of the solution changes to red-brown. The *o*-quinone thus formed is extracted in three portions with 1.2 l. of chloroform. The combined organic layers are dried over anhydrous sodium sulfate (Note 5), filtered, and evaporated under reduced pressure at 20–23° (Note 6). The residual, somewhat oily, red-brown crystals are slurried twice with 15 ml.-portions of ice-cold ether and collected on a filter. The dark-red crystals, after air drying, weigh 8.7–8.9 g. (49–50%), m.p. 105–107° (Note 7).

2. Notes

1. Monobasic sodium phosphate, $NaH_2PO_4 \cdot H_2O$, obtained from Merck & Co., Inc., was used. This buffer was found to be satisfactory for this reaction.
2. Fremy's salt may be purchased from Aldrich Chemical Company, Inc., or from Matheson, Coleman and Bell. The Fremy's salt used by the checker was prepared electrolytically.[2]
3. 3,4-Dimethylphenol was obtained from Eastman Organic Chemicals, m.p. 63–65°.
4. An efficient stirrer may be substituted for the shaking.
5. The drying was accomplished in about 5 minutes.

6. Higher temperatures may accelerate dimerization of the product.

7. The product is reported to melt at 102°.[3] This material has ^{1}H NMR peaks ($CDCl_3$) at δ 2.14 and 6.19 with relative intensities of 3 : 1. The IR spectrum ($CHCl_3$) shows the strongest absorption at 1670 cm^{-1} accompanied, among others, by four more bands at 1390, 1280, 1005, and 835 cm^{-1}. The product has UV maxima, nm (ε), ($CHCl_3$) at 260 (2600), 400 (1120), and 572 (288). It is reported that the material undergoes slow Diels-Alder dimerization.[4]

3. Discussion

o-Quinones exemplify a very important and reactive class of compounds for general organic synthesis. In the past they have been prepared from catechol derivatives by silver oxide dehydrogenation.[3] The unique oxidizing properties of Fremy's salt allow a number of readily available phenols to be converted to *o*-quinones in excellent yield.[4] The scope of this oxidation, the Teuber reaction, is the subject of numerous papers[5] which have been reviewed recently.[6]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

DIPOTASSIUM NITROSODISULFONATE (FREMY'S SALT)

Fremy's salt

ether, diethyl ether (60-29-7)

chloroform (67-66-3)

silver oxide (20667-12-3)

sodium sulfate (7757-82-6)

3,4-dimethylphenol (95-65-8)

sodium dihydrogen phosphate (7558-80-7)

DIPOTASSIUM NITROSODISULFONATE

3,5-Cyclohexadiene-1,2-dione, 4,5-dimethyl-, 4,5-Dimethyl-o-benzoquinone (4370-50-7)

sodium phosphate (7601-54-9)

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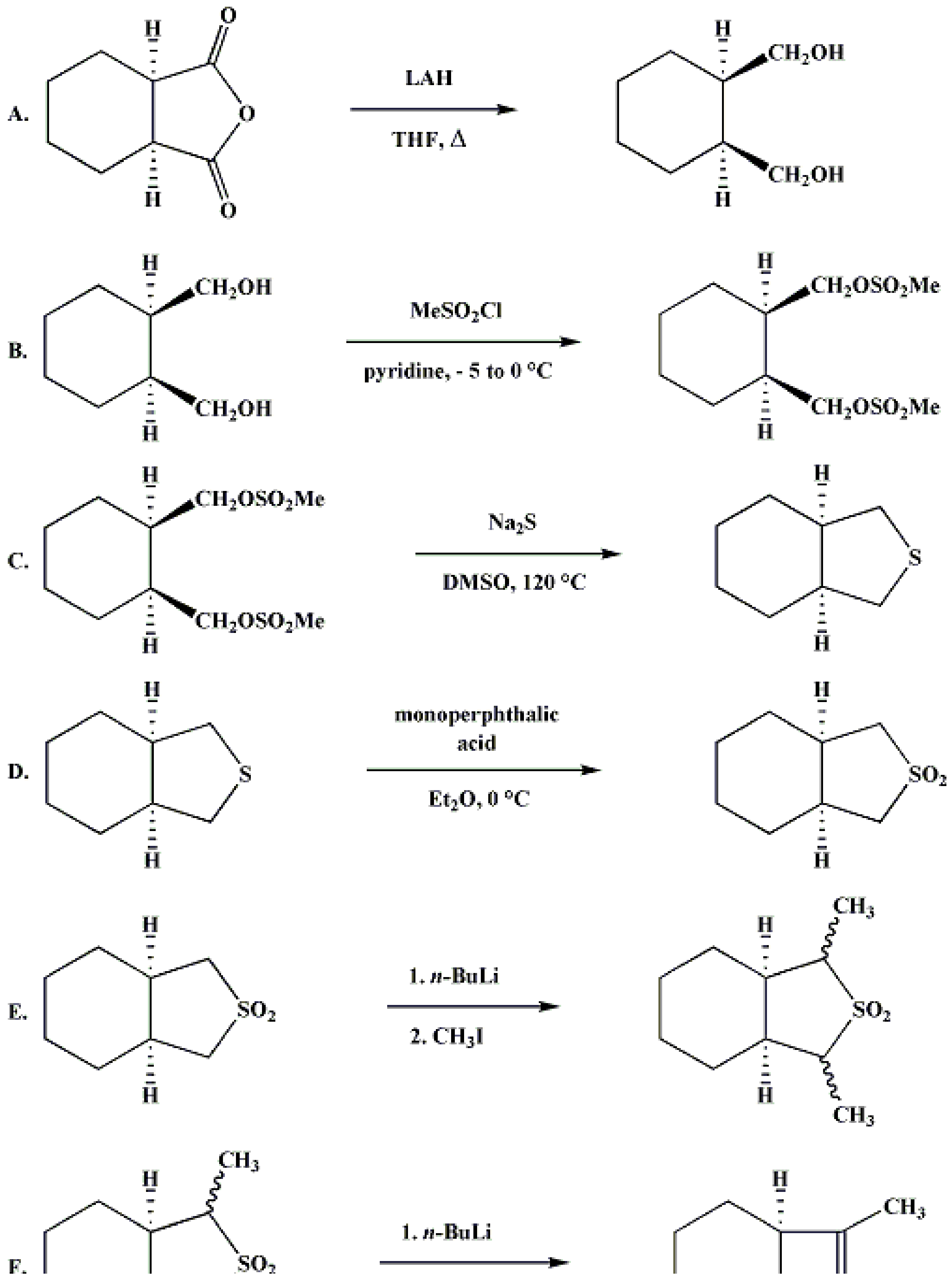
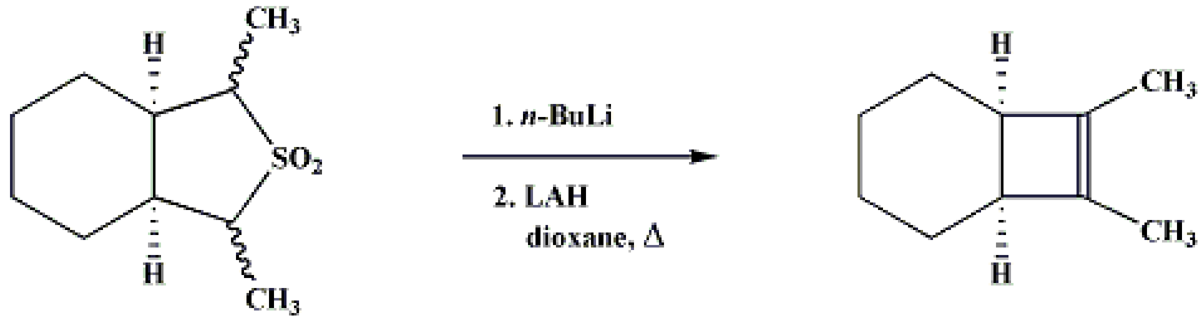
1,2-DIMETHYLCYCLOBUTENES BY REDUCTIVE RING-CONTRACTION OF SULFOLANES: *cis*-7,8-DIMETHYLBICYCLO[4.2.0]OCT-7-ENE

[Bicyclo[4.2.0]oct-7-ene, 7,8-dimethyl-, *cis*-]



F.



Submitted by James M. Photis and Leo A. Paquette[1].
Checked by C.-P. Mak and G. Büchi.

1. Procedure

Caution! Steps B and C should be performed in a hood because of the noxious odors produced.

Methyl iodide, in high concentrations for short periods or in low concentrations for long periods, can cause serious toxic effects in the central nervous system. Accordingly, the American Conference of Governmental Industrial Hygienists[2] has set 5 p.p.m., a level which cannot be detected by smell, as the highest average concentration in air to which workers should be exposed for long periods. The preparation and use of methyl iodide should always be performed in a well-ventilated fume hood. Since the liquid can be absorbed through the skin, care should be taken to prevent contact.

A. *cis-1,2-Cyclohexanedimethanol.* A 3-l., three-necked, round-bottomed flask fitted with a mechanical stirrer, addition funnel, and condenser is charged with 1.5 l. of anhydrous tetrahydrofuran (Note 1). With vigorous stirring, 14.8 g. (0.389 mole) of lithium aluminum hydride is added, followed by a solution of 50.0 g. (0.325 mole) of *cis*-1,2-cyclohexanedicarboxylic anhydride in 300 ml. of tetrahydrofuran introduced in a thin stream over 30 minutes. The resulting suspension is maintained at the reflux temperature for 3 hours with a heating mantle, after which heating is ceased and 100 ml. of a freshly prepared (Note 2), saturated aqueous sodium sulfate is cautiously added dropwise (Note 3). Highly granular insoluble salts, which change in appearance from gray to white, are removed by suction filtration through a Büchner funnel and washed thoroughly with diethyl ether. The combined filtrates are freed of solvent on a rotary evaporator, yielding 46.0–46.5 g. (98–100%) of the diol as a colorless, viscous oil which may slowly crystallize, m.p. 38–40° (Note 4). Pure *cis*-1,2-cyclohexanedimethanol is reported to have m.p. 42–43°.[3,4,5]

B. *cis-1,2-Cyclohexanedimethanol dimethanesulfonate.* A 5-l., three-necked, round-bottomed flask, immersed in an ice–salt bath and fitted with a mechanical stirrer and an addition funnel, is charged with a solution of 111 g. (0.969 mole) of methanesulfonyl chloride in 1.2. l of pyridine. While cooling and stirring, a solution of 46.4 g. (0.322 mole) of *cis*-1,2-cyclohexanedimethanol in 250 ml. of pyridine is added dropwise at a rate such that the temperature does not exceed 0° (Note 5). Upon completion of the addition, the mixture is stirred at –5° to 0° for an additional 2 hours. Two liters of cold, 10% hydrochloric acid is introduced at a rate which maintains the reaction mixture below 20° (Note 5). The solid which separates is isolated by suction filtration, washed sequentially with 1 l. of dilute hydrochloric acid and 2 l. of water, and air-dried, yielding 93–95 g. (96–98%) of the dimethanesulfonate,

m.p. 66–67.5°. Recrystallization from methanol gives needles melting at 75–76° (Note 6).

C. cis-8-*Thiabicyclo*[4.3.0]*nonane.* A 3-l., three-necked, round-bottomed flask fitted with a mechanical stirrer, capillary tube, heating mantle, and 90° adapter connected to a condenser and receiving flask is charged with 240 g. (1.00 mole) of recrystallized sodium sulfide nonahydrate (Note 7) and 2 l. of dimethyl sulfoxide. As the mixture is stirred, the internal pressure is reduced to 30 mm., and heat is applied until 300–350 ml. of distillate is collected (Note 8). After cooling to 40°, the capillary and take-off adapter are replaced with a thermometer and condenser, and 95 g. (0.32 mole) of *cis*-1,2-cyclohexanedimethanol dimethanesulfonate is introduced in one portion (Note 9). The mixture is then stirred at 120° for 18 hours, cooled, and transferred to a 5-l. separatory funnel containing 1500 g. of ice. After 1 l. of hexane is added and the two-phase mixture well shaken, the aqueous phase is reextracted with hexane (500 ml.). The combined organic layers are washed with four 1-l. portions of water, dried over anhydrous magnesium sulfate, and concentrated with a rotary evaporator. The sulfide is collected by bulb-to-bulb distillation at 0.05–0.1 mm. as a colorless liquid (30.8–31.6 g., 68.0–70.5%) (Note 10).

D. cis-8-*Thiabicyclo*[4.3.0]*nonane* 8,8-*dioxide* [*benzo*[c]*thiophene* 2,2-*dioxide*, cis-*octahydro*-]. A solution of the sulfide (43.0 g., 0.303 mole) in 1 l. of ether is cooled to 0°, stirred magnetically, and treated dropwise with 1.0 l. of 0.65 *N* ethereal monoperphthalic acid [*Org. Synth.*, **Coll. Vol. 3**, 619 (1955)]. The mixture is kept overnight at 0°, after which time the precipitated phthalic acid is separated by filtration and the filtrate is concentrated with a rotary evaporator. Bulb-to-bulb distillation of the residual oil at 0.05–0.1 mm. affords the sulfone as a colorless liquid (48.5–50 g., 92–95%) (Note 11). This product is crystallized from ether-hexane, yielding a colorless solid, m.p. 39–41° (Note 12).

E. 7,9-*Dimethyl*-cis-8-*thiabicyclo*[4.3.0]*nonane* 8,8-*dioxide.* A 2-l., one-necked, round-bottomed flask is charged with 800 ml. of anhydrous tetrahydrofuran and 49.0 g. (0.281 mole) of *cis*-8-thiabicyclo[4.3.0]nonane 8,8-dioxide. The solution is blanketed with nitrogen and the flask is fitted with a side-arm adapter having a nitrogen inlet and a rubber septum. The contents are cooled in a 2-propanol–dry ice bath and 225 ml. of 2.5 *M* *n*-butyllithium in hexane (0.562 mole) is introduced by syringe (Note 13), (Note 14). After 5–10 minutes, 142 g. (1.00 mole) of methyl iodide is added in similar fashion and the cooling bath is removed. Upon warming to room temperature, the reaction mixture is treated slowly with 1 l. of water followed by 1 l. of ether, and the organic layer is separated, washed once with 1 l. of water, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The resulting pale-yellow oil (49.5–51 g., 87–89.5%), which consists of a mixture of isomers, is not further purified.

F. cis-7,8-*Dimethylbicyclo*[4.2.0]*oct*-7-*ene.* A 1-l., one-necked, round-bottomed flask is charged with 50.5 g. (0.250 mole) of the sulfone from Part E and 200 ml. of dry dioxane (Note 15). The solution is blanketed with nitrogen, and the flask is fitted with a side-arm adapter having a nitrogen inlet and a rubber septum. With ice cooling and magnetic stirring, 150 ml. of 2.5 *M* *n*-butyllithium in hexane (0.375 mole) is added by syringe (Note 13), (Note 14). The resulting yellow-orange heterogeneous mixture is transferred under nitrogen to a 500-ml., pressure-equalizing dropping funnel and introduced over 25 minutes to a stirred refluxing mixture of lithium aluminum hydride (32.0 g., 0.843 mole) and 2 l. of dry dioxane (Note 16), (Note 17). Upon completion of the addition, the contents are heated at reflux temperature with

a mantle for 20 hours, whereupon 100 ml. of saturated aqueous sodium sulfate is added dropwise with cooling (Note 18). The precipitated solids are separated by filtration and washed repeatedly with hexane (Note 19). The combined filtrates are diluted with an additional liter of hexane and washed with four 1-l. portions of water. The organic phase is dried over anhydrous sodium sulfate and carefully concentrated with a rotary evaporator. The residual cyclobutene is purified by distillation, yielding 10.0–12.5 g. (29.5–37%) of colorless oil, b.p. 63–65° (33 mm.) (Note 20), (Note 21).

2. Notes

1. The tetrahydrofuran used in these preparations was distilled from lithium aluminum hydride.
2. A sodium sulfate solution which is not freshly prepared ultimately gives a precipitate of small particle size that is exceedingly difficult and tedious to separate by vacuum filtration.
3. Because the initial reaction is extremely vigorous and exothermic, the first few milliliters must be added very cautiously. In the more advanced stages of this addition the rate of flow may be judiciously increased.
4. Recrystallization of this material from benzene–light petroleum ether gives a pure product, m.p. 42–43°.
5. This reaction is significantly exothermic. Cooling with an acetone–dry ice bath can be employed if desired to expedite the addition of diol. In any event, a temperature in excess of 20° leads to unwanted, rapid hydrolysis and formation of water-soluble by-products.
6. This dimethanesulfonate is reported to have m.p. 75–76°.[4]
7. Sodium sulfide may be conveniently recrystallized from ethanol. Unrecrystallized material may be utilized. However, significantly lower yields will result if the ensuing minor modification is not followed.
8. If unpurified sodium sulfide is employed, a significant quantity of dark insoluble material is seen to adhere to the walls of the flask. Removal of these unwanted contaminants is readily effected by decantation of the hot solution into a second 3-l., three-necked flask before crystallization begins.
9. An exotherm is witnessed and the temperature rises to 70–80°. A color change from yellow to deep purple is also seen; the extent of coloration varies with the purity of the sodium sulfide nonahydrate.
10. The submitters report a yield of 42.0–43.5 g. (93.5–96.8%). The checkers could not reproduce these results in three attempts.

This sulfide has also been prepared from the corresponding dibromide.[6]
11. The checkers performed this step on a smaller scale (*ca.* 2/3) and noted (^{1}H NMR spectrum) occasional contamination (up to 10%) by phthalic anhydride. This impurity causes no subsequent difficulties. Washing of the crude reaction mixture with cold aqueous sodium hydrogen carbonate resulted in serious product loss because of its appreciable solubility in this medium and, therefore, should be avoided.
12. An earlier report of this sulfone cites a melting point of 39.5–41.0°.[6]
13. *n*-Butyllithium is available from Ventron Corp.
14. A 50-ml. syringe was employed and a series of transfers was, therefore, necessary.
15. The dioxane was dried before use by distillation from calcium hydride.
16. The apparatus consisted of a 5-l., three-necked, round-bottomed flask equipped with

a mechanical stirrer and reflux condenser capped with a nitrogen-inlet tube.

17. The addition rate is such that a gentle reflux is maintained without the need of external heating. Considerable evolution of gas is witnessed.

18. Hydrogen gas is vigorously evolved and the solids ultimately undergo a color change from gray to white.

19. *Caution! Because of the presence of malodorous by-products, it is recommended that the extraction and distillation be conducted in a well-ventilated hood.*

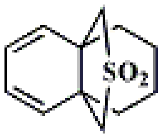
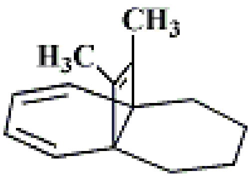
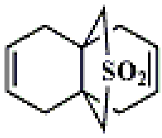
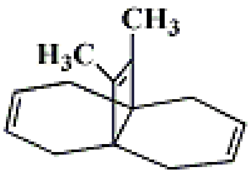
20. The ^{1}H NMR spectrum (CCl_4) consists of a broad methine signal centered at δ 2.55 and a methyl singlet at δ 1.53 superimposed upon a methylene absorption at δ 1.25–1.85. GC analysis indicated a purity of >98%.

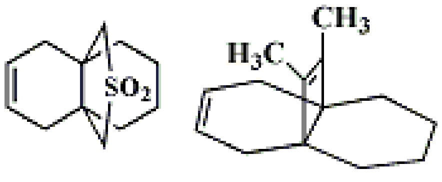
21. The checkers performed this step on one-half scale and obtained comparable results. However, when the product was distilled at higher pressures, b.p. 94–95° (*ca.* 70 mm.), consistently lower yields were obtained, in the range of 17–18%.

3. Discussion

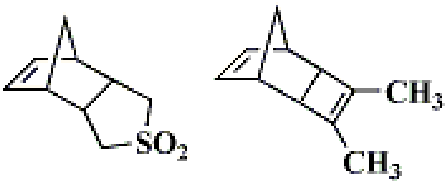
1-Substituted and 1,2-disubstituted cyclobutenes have previously been prepared by irradiation of 1,3-butadienes capable of photocyclization,[7,8,9] carbenic decomposition of acylcyclopropane tosylhydrazones,[10] photocycloaddition of α,β-unsaturated ketones to alkynes,[11] and reductive ring expansion of cyclopropane 3-carboxylates.[12] However, these and yet other less known methods[13,14,15,16] lack generality. The present procedure[17] is a versatile scheme which is widely applicable in scope.[18,19,20] Since a variety of five-membered ring sulfones are readily available from a number of different precursors, the method is fully applicable to a broad spectrum of structural types. Its application to the preparation of mutually stable cycloöctatetraene bond shift isomers is noteworthy.[20] The present procedure is illustrative of the general method. Other examples are given in Table I.

TABLE I
REDUCTIVE RING CONTRACTION OF α,α'-DISUBSTITUTED SULFOLANE ANIONS WITH LITHIUM ALUMINUM HYDRIDE

Sulfolane	Product	Overall yield, %
		54
		62



67



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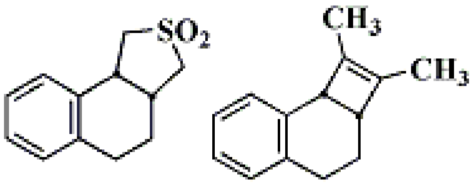
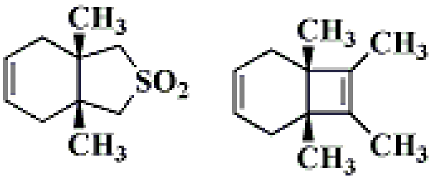


20



34

Such reductive ring contractions of sulfones are formally similar to two other methods capable of supplanting a sulfur atom by a carbon-carbon double bond: the Ramberg-Bäcklund[21] and Stevens rearrangements.[22] The distinguishing feature of this novel approach to cyclobutenes consists in the resulting higher level of alkyl substitution at the sp^2-hybridized centers.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Monoperphthalic acid

cis-8-Thiabicyclo[4.3.0]nonane 8,8-dioxide [benzo[c]thiophene 2,2-dioxide, cis-octahydro-]

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

hydrogen (1333-74-0)

sodium hydrogen carbonate (144-55-8)

sulfone (7446-09-5)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

phthalic anhydride (85-44-9)

pyridine (110-86-1)

Methyl iodide (74-88-4)

sodium sulfide (1313-82-2)

phthalic acid (88-99-3)

magnesium sulfate (7487-88-9)

dioxane (5703-46-8)

butyllithium, n-butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

sodium sulfide nonahydrate (1313-84-4)

hexane (110-54-3)

dimethyl sulfoxide (67-68-5)

calcium hydride (7789-78-8)

Methanesulfonyl chloride (124-63-0)

cyclooctatetraene

cis-1,2-cyclohexanedicarboxylic anhydride

Bicyclo[4.2.0]oct-7-ene, 7,8-dimethyl-, cis-, cis-7,8-Dimethylbicyclo[4.2.0]oct-7-ene (53225-88-0)

cis-1,2-Cyclohexanedimethanol (5059-76-7)

cis-1,2-Cyclohexanedimethanol dimethanesulfonate (66347-68-0)

cis-8-Thiabicyclo[4.3.0]nonane 8,8-dioxide (57479-57-9)

cis-8-Thiabicyclo[4.3.0]nonane (17739-77-4)

7,9-Dimethyl-cis-8-thiabicyclo[4.3.0]nonane 8,8-dioxide (60090-27-9)

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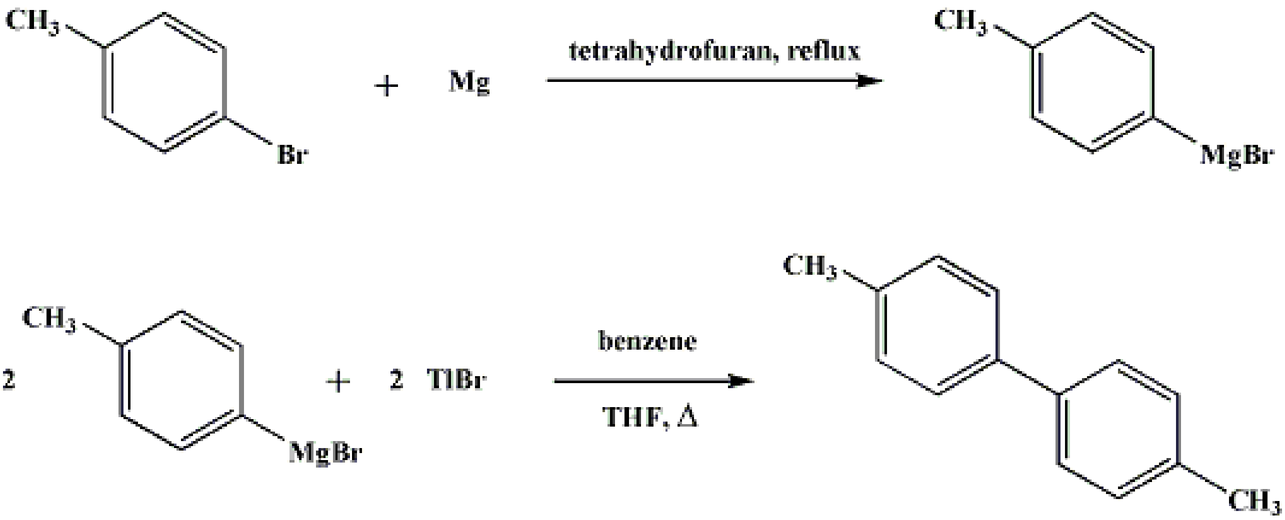
Organic Syntheses, CV 6, 488

4,4'-DIMETHYL-1,1'-BIPHENYL



Submitted by L. F. Elsom, Alexander McKillop[1], and Edward C. Taylor[2].
Checked by Ronald F. Sieloff and Carl R. Johnson.

1. Procedure

Caution! Thallium salts are very toxic. This preparation should be carried out in a well-ventilated hood. The operator should wear rubber gloves. For disposal of thallium wastes, see (Note 1) in Org. Synth., ***Coll. Vol. 6****, 791 (1988).*

Benzene has been identified as a carcinogen. OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A. *(4-methylphenyl)magnesium bromide.* A 500-ml., three-necked, round-bottomed flask equipped with a reflux condenser protected by a drying tube, a mercury-sealed mechanical stirrer, and a 250-ml., pressure-equalizing dropping funnel fitted with a gas-inlet tube is thoroughly purged with dry nitrogen (Note 1) and charged with 6.25 g. (0.256 g.-atom) of magnesium turnings and 50 ml. of anhydrous tetrahydrofuran (Note 2). The dropping funnel is charged with a solution of 42.7 g. (30.5 ml., 0.250 mole) of 4-bromotoluene (Note 3) in 100 ml. of anhydrous tetrahydrofuran. Approximately 10 ml. of the 4-bromotoluene solution is added to the flask, and the contents are stirred until the Grignard reaction commences (Note 4). When the initial vigorous reaction has subsided the remainder of the 4-bromotoluene solution is added at a rate such that the mixture refluxes gently. Generally the addition is complete at the end of 1 hour, and almost all of the magnesium has dissolved. The mixture is refluxed for a further hour and cooled. The yield of (4-methylphenyl)magnesium bromide is about 95% (Note 5).

B. *4,4'-Dimethyl-1,1'-biphenyl.* A 1-l., three-necked, round-bottomed flask equipped with a reflux condenser protected by a drying tube, a mercury-sealed mechanical stirrer, and a gas-inlet tube is charged with 101 g. (0.356 mole) of thallium(I) bromide and 400 ml. of anhydrous benzene. The slurry is stirred vigorously while a stream of dry nitrogen is passed through the apparatus. The reflux condenser is temporarily removed, and the solution of (4-methylphenyl)magnesium bromide

is added to the flask as rapidly as possible through a large filter funnel fitted with a *loose* plug of glass wool (Note 6). A black solid precipitates almost immediately from solution. The reflux condenser is replaced, and the contents of the flask are refluxed with stirring for 4 hours under a nitrogen atmosphere. The reaction mixture is then cooled, filtered, and the metallic thallium washed with 200 ml. of diethyl ether. The organic layer is washed once with 100 ml. of 0.1 *N* hydrochloric acid and once with 100 ml. of water, then dried over anhydrous sodium sulfate.

The organic solvent is removed by distillation under reduced pressure, giving 4,4'-dimethyl-1,1'-biphenyl contaminated with a small amount of bis(4-methylphenyl)thallium bromide. The crude product is dissolved in 30 ml. of benzene, and the solution is filtered through a short column of alumina (Note 7) using 250 ml. of benzene as eluent. Distillation of the benzene under reduced pressure leaves 19–21 g. (80–83%) of 4,4'-dimethyl-1,1'-biphenyl as a colorless solid, m.p. 118–120° (Note 8).

2. Notes

1. Nitrogen is dried by passage through two Drechsel bottles containing concentrated sulfuric acid and potassium hydroxide pellets, respectively.
2. Tetrahydrofuran was dried as described in *Org. Synth.*, **Coll. Vol. 4**, 259 (1963).
3. 4-Bromotoluene (purchased from Aldrich Chemical Company, Inc.) was distilled before use, b.p. 71–72° (15 mm.).
4. The Grignard reaction starts within a few minutes and should not require the use of a catalyst. If the reaction has not commenced within 5 minutes, the flask should be gently heated with a hot water bath until reaction starts.
5. The Grignard reagent may be standardized by the general procedure described for cyclohexylmagnesium chloride in *Org. Synth.*, **Coll. Vol. 1**, 187 (1932).
6. A loose plug of glass wool prevents any unreacted magnesium metal from being added to the reaction mixture. Care must be taken to ensure that the plug is loose enough to allow rapid addition of the Grignard reagent.
7. The dimensions of the alumina column are not critical. A column approximately 2.5 cm. × 12.5 cm. is recommended. The small amount of bis(4-methylphenyl)thallium bromide formed in the reaction remains on the top of the column.
8. The reaction may be conducted on two or three times the scale described with no decrease in yield.

3. Discussion

4,4'-Dimethyl-1,1'-biphenyl has been prepared by a wide variety of procedures, but few of these are of any practical synthetic utility. Classical radical biaryl syntheses such as the Gomberg reaction or the thermal decomposition of diaroyl peroxides give complex mixtures of products in which 4,4'-dimethyl-1,1'-biphenyl is a minor constituent. A radical process may also be involved in the formation of 4,4'-dimethyl-1,1'-biphenyl (13%) by treatment of 4-bromotoluene with hydrazine hydrate.[3] 4,4'-Dimethyl-1,1'-biphenyl has been obtained in moderate to good yield (68–89%) by treatment of either dichlorobis(4-methylphenyl)tellurium or 1,1'-tellurobis(4-methylbenzene) with degassed Raney nickel in 2-methoxyethyl ether.[4]

All of the useful procedures described for the preparation of 4,4'-dimethyl-1,1'-biphenyl involve coupling of either a 4-halotoluene by a metal or the corresponding Grignard reagents by a metal halide. 4-Halotoluenes can be coupled directly by treatment with lithium,[5] sodium,[6,7,8]

magnesium,[9] or copper[10],[11]; yields are, however, very low in the first three cases (5–15%) and only moderate (54–60%) when copper is employed, as in the Ullmann synthesis. Bis(1,5-cycloöctadiene) nickel(0) has also been used to couple 1-iodo-4-methylbenzene, giving the biaryl in 63% yield.[12]

The present method of preparation of 4,4'-dimethyl-1,1'-biphenyl is that described by McKillop, Elsom, and Taylor,[13] has the particular advantages of high yield and manipulative simplicity, and is, moreover, applicable to the synthesis of a variety of symmetrically substituted biaryls. 3,3'- and 4,4'-Disubstituted and 3,3',4,4'-tetrasubstituted 1,1'-biphenyls are readily prepared, but the reaction fails when applied to the synthesis of 2,2'-disubstituted-1,1'-biphenyls. The submitters have effected the following conversions with the present procedure (starting aromatic bromide, biphenyl product, % yield); bromobenzene, biphenyl, 85; 1-bromo-4-methoxybenzene, 4,4'-dimethoxy-1,1'-biphenyl, 99; 1-bromo-3-methylbenzene, 3,3'-dimethyl-1,1'-biphenyl, 85; 4-bromo-1,2-dimethylbenzene, 3,3',4,4'-tetramethyl-1,1'-biphenyl, 76; 1-bromo-4-chlorobenzene, 4,4'-dichloro-1,1'-biphenyl, 73; 1-bromo-4-fluorobenzene, 4,4'-difluoro-1,1'-biphenyl, 73.

Related procedures, in which treatment of (4-methylphenyl)magnesium halides with halides of copper(II),[14] silver(I),[15] cobalt(II),[16] or chromium(III)[17] also lead to the formation of 4,4'-dimethyl-1,1'-biphenyl, are either experimentally more difficult than, or do not give yields comparable to, the present method.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 468

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

diethyl ether (60-29-7)

magnesium (7439-95-4)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

copper (7440-50-8)

Raney nickel (7440-02-0)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

bromobenzene (108-86-1)

Biphenyl (92-52-4)

cyclohexylmagnesium chloride

hydrazine hydrate (7803-57-8)

lithium (7439-93-2)

Tetrahydrofuran (109-99-9)

2-methoxyethyl ether (111-96-6)

4,4'-Dimethyl-1,1'-biphenyl (613-33-2)

copper(II)

cobalt(II)

Thallium (7440-28-0)

4-bromotoluene (106-38-7)

(4-Methylphenyl)magnesium bromide (4294-57-9)

thallium(I) bromide

bis(4-methylphenyl)thallium bromide

dichlorobis(4-methylphenyl)tellurium

1-iodo-4-methylbenzene (624-31-7)

1-bromo-4-methoxybenzene (104-92-7)

1-bromo-3-methylbenzene (591-17-3)

4-bromo-1,2-dimethylbenzene (583-71-1)

1-bromo-4-chlorobenzene (106-39-8)

1-bromo-4-fluorobenzene (460-00-4)

silver(I)

chromium(III)

4,4'-Dimethoxy-1,1'-biphenyl (2132-80-1)

4,4'-difluoro-1,1'-biphenyl (398-23-2)

3,3'-dimethyl-1,1'-biphenyl (612-75-9)

1,1'-tellurobis(4-methylbenzene)

3,3',4,4'-tetramethyl-1,1'-biphenyl

4,4'-dichloro-1,1'-biphenyl

Bis(1,5-cyclooctadiene)nickel(0)

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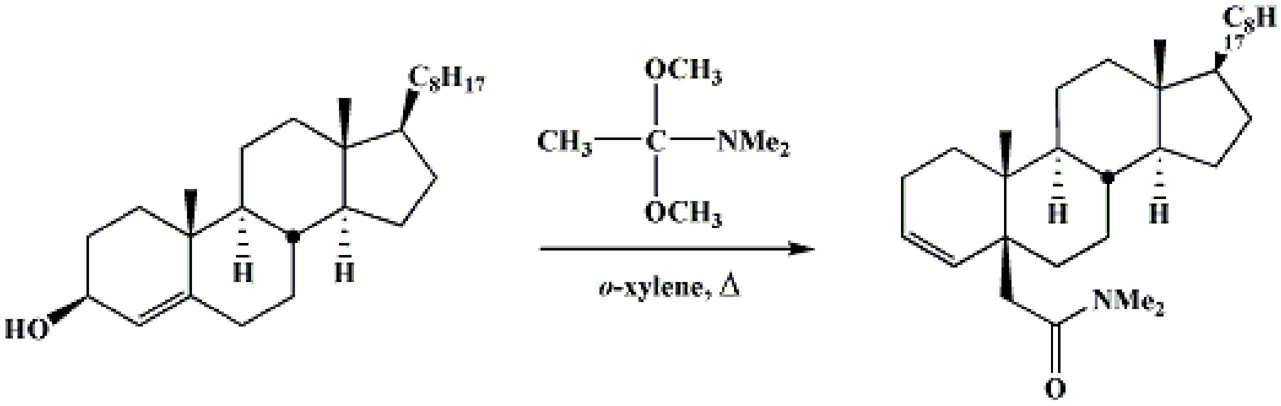
N,*N*-DIMETHYL-5β-CHOLEST-3-ENE-5-ACETAMIDE

[Cholest-3-ene-5-acetamide, *N*,*N*-dimethyl-, (5β)-]



Submitted by R. E. Ireland[1] and D. J. Dawson.
Checked by W. Pawlak and G. Büchi.

1. Procedure

A 50-ml., round-bottomed flask, equipped with a Teflon®-covered magnetic stirring bar and a reflux condenser connected to a gas-inlet tube, is charged with 970 mg. (2.51 mmoles) of cholest-4-en-3β-ol (Note 1) and 30 ml. of *o*-xylene (Note 2). The mixture is stirred to effect solution before 1.67 g. (0.0125 mole) of *N*,*N*-dimethylacetamide dimethyl acetal (Note 3) is added. The flask is flushed with argon, then heated (Note 4) at reflux under a positive pressure of argon with vigorous stirring for 65 hours. After cooling, the volatile materials are removed at reduced pressure (Note 5), and the yellow, oily residue (1.2 g.) is chromatographed on 60 g. of silica gel with diethyl ether (Note 6). Elution of the column with 200 ml. of ether gives a mixture of cholestadienes which is discarded; further elution with 500 ml. of ether affords 740 mg. of *N*,*N*-dimethyl-5β-cholest-3-ene-5-acetamide as a clear, colorless oil, which on trituration with acetone gives 740 mg. (65%) of the amide as white plates, m.p. 128–129.5°.

2. Notes

1. Cholest-4-en-3β-ol can be prepared by the procedure of Burgstahler and Nordin[2]. A melting point below 130° indicates that the material is contaminated with some of the 3α-hydroxy isomer. The material used above melted at 130.5–131° (from ethanol).
2. The Matheson, Coleman and Bell product was used without purification.
3. *N*,*N*-Dimethylacetamide dimethyl acetal was obtained from Fluka A. G. and used without purification.
4. A sand bath set into an electric heating mantle was found to be satisfactory for the long-term heating process.
5. The volatile materials were removed by rotary evaporation followed by vacuum (0.1 mm.) drying for 1 hour.
6. Merck silica gel (0.05–0.2 mm., 70–325 mesh ASTM) was used in a 2.5 × 25 cm. column. Mallinckrodt anhydrous ether was employed as the eluant.

3. Discussion

The amide–Claisen rearrangement procedure of Eschenmoser and co-workers[3] was modified for use with cholest-4-en-3β-ol.

References and Notes

1. Division of Chemistry and Chemical Engineering, Gates and Crellin Laboratories of Chemistry, California Institute of Technology, Pasadena, California 91109.
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

ether, diethyl ether (60-29-7)

acetone (67-64-1)

argon (7440-37-1)

cholest-4-en-3β-ol

o-Xylene (95-47-6)

N,N-Dimethyl-5β-cholest-3-ene-5-acetamide, Cholest-3-ene-5-acetamide, N,N-dimethyl-, (5β)- (56255-03-9)

N,N-dimethylacetamide dimethyl acetal (18871-66-4)

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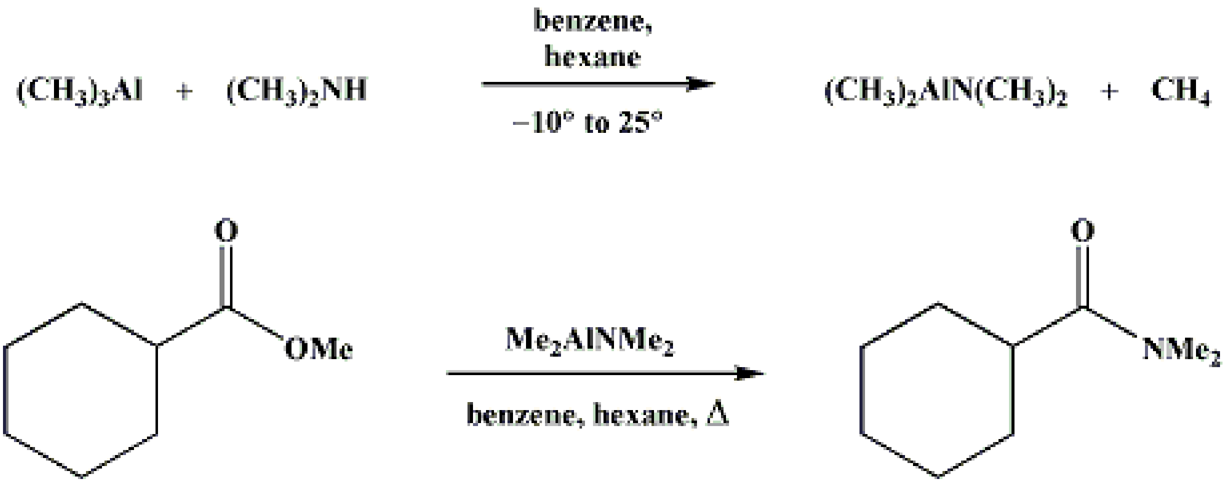
Organic Syntheses, CV 6, 492

CONVERSION OF ESTERS TO AMIDES WITH DIMETHYLALUMINUM AMIDES: *N,N*-DIMETHYLCYCLOHEXANECARBOXAMIDE



Submitted by Michael F. Lipton[1], Anwer Basha[1], and Steven M. Weinreb[1,2].
Checked by Charles W. Hutchins and Robert M. Coates.

1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A dry, 300-ml., two-necked, round-bottomed flask equipped with a reflux condenser fitted with a nitrogen inlet at its top, a rubber septum, and a magnetic stirring bar is charged with 100 ml. of benzene (Note 1) and flushed briefly with nitrogen, after which 22 ml. (0.057 mole) of a 25% solution of trimethylaluminum in hexane (Note 2) is injected through the septum into the flask. The solution is stirred and cooled in an ice–salt bath at –10° to –15°, and 2.47 g. (3.64 ml., 0.0549 mole) of dimethylamine (Note 3) is added slowly with a syringe. Twenty minutes after the addition is completed, the cooling bath is removed, and the contents of the flask are allowed to stir and warm slowly to room temperature over a 45-minute period. A solution of 7.10 g. (0.0500 mole) of methyl cyclohexanecarboxylate (Note 4) in 20 ml. of benzene (Note 1) is injected through the septum. The resulting solution is heated under reflux for 22 hours, cooled to room temperature, and hydrolyzed by slow, cautious addition of 82.5 ml. (0.055 mole) of 0.67 *M* hydrochloric acid (Note 5). The mixture is stirred for 30 minutes to ensure complete hydrolysis. The upper organic layer is separated, and the aqueous layer is extracted with three 25-ml. portions of ethyl acetate. The organic extracts are combined, washed with sodium chloride solution, dried with anhydrous magnesium sulfate, and evaporated under reduced pressure. Distillation of

the residual liquid under reduced pressure through a 10-cm. Vigreux column affords a 0.1–0.6 g. forerun of unreacted ester and 6.40–7.25 g. (83–93%) of *N,N*-dimethylcyclohexanecarboxamide, b.p. 100° (5.5 mm.), 57–60° (0.08 mm.) (Note 6).

2. Notes

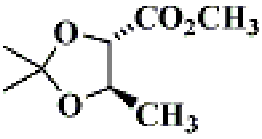
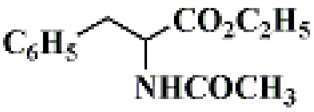
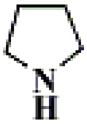
1. The benzene was dried by distillation from calcium hydride.
2. Trimethylaluminum in hexane solution was purchased from the Alfa Division, Ventron Corporation.
3. Dimethylamine was obtained in a cylinder from the Linde Division, Union Carbide Chemical Corporation, and condensed in a dry, two-necked flask fitted with a rubber septum and cooled to −78° under nitrogen.
4. Cyclohexanecarboxylic acid is available from Aldrich Chemical Company, Inc., and conveniently esterified by the procedure of Harrison, Haynes, Arthur, and Eisenbraun.[3] A dry, 500-ml., round-bottomed flask is charged with 225 ml. of anhydrous methanol, 1.0 ml. of concentrated sulfuric acid, and 41.0 g. (0.320 mole) of cyclohexanecarboxylic acid. The flask is fitted with a Soxhlet extractor containing 53 g. of Linde type 3A molecular sieves and a condenser bearing a calcium chloride drying tube at its top. The solution is heated at reflux for 19 hours and cooled to room temperature. The sulfuric acid is neutralized by adding 3.0 g. of sodium hydrogen carbonate, the salts are filtered, and the filtrate is evaporated under reduced pressure. The remaining liquid is distilled through a 15-cm. Vigreux column at reduced pressure, affording 35.7–36.8 g. (79–81%) of methyl cyclohexanecarboxylate, b.p. 73–76° (13 mm.).
5. To avoid excessive foaming at the beginning of the hydrolysis, the checkers recommend that the hydrochloric acid solution be added 1 or 2 drops at a time. The rate of addition may be increased once the initially vigorous foaming subsides.
6. The spectral properties of the product are as follows: IR (neat) cm.$^{-1}$: 1640 (C=O); ^{1}H NMR ($CDCl_3$), δ (multiplicity, number of protons, assignment): 1.05–1.95 (m, 10H, 5CH_2), 2.50 (m, 1H, C*H*), 2.94 (s, 3H, NCH_3), 3.06 (s, 3H, NCH_3). A boiling point of 107–108° (7 mm.) has been reported for *N,N*-dimethylcyclohexanecarboxamide.[4]

3. Discussion

This procedure,[5] based on the work of Ishii and co-workers,[6] affords a mild and general method for converting a wide variety of esters to primary, secondary, and tertiary amides (Table I). While the preparation of the tertiary amide, *N,N*-dimethylcyclohexanecarboxamide, described here is carried out in benzene, aluminum amides derived from ammonia and a variety of primary amines have been prepared by reaction with trimethylaluminum in dichloromethane and utilized for aminolysis in this solvent. Although 1 equivalent of dimethylaluminum amides, prepared from amines, was generally sufficient for high conversion within 5–48 hours, best results

were obtained when 2 equivalents of the aluminum reagent, prepared from ammonia, was used. Diethylaluminum amides can also effect aminolysis, but with considerably slower rates.

TABLE I
PREPARATION OF AMIDES FROM ESTERS BY AMINOLYSIS WITH DIMETHYLALUMINUM AMIDES[5]

Ester	Amine	Reaction Time (hours)[a]	Isolated Yield of Amide (%)
	NH_3	2[b]	70
	NH_3	16	69
	NH_3	12	86
		48	76
		45	74
		40	77
$CH_3CO_2(CH_2)_3CH_3$	$C_6H_5NH_2$	40	78
$C_6H_5CO_2C_2H_5$	$C_6H_5CH_2NH_2$	25	93
	$(CH_3)_3CNH_2$	45	79

[a] The solvent was dichloromethane except as noted.

[b] Benzene was used as solvent.

Although the preparation of carboxamides by direct aminolysis is a well-known and widely studied reaction,[7] the synthetic utility of this process is limited. The reactions generally require long heating periods at relatively high temperatures, and the reagents and catalysts used are usually strong bases.[8] The present procedure has the advantages of lower temperatures and moderate reaction times. The aluminum amides are conveniently prepared *in situ* and appear to be mild, nonbasic reagents, compatible with many functional groups.[5] The isolation is simple, since hydrolysis of the aluminum reagents and products affords only methane and acid-soluble aluminum salts. Another advantage is that amides of volatile amines may be prepared without the use of sealed tubes.

N,N-Dimethylcyclohexanecarboxamide has been prepared by acylation of dimethylamine with cyclohexanecarbonyl chloride[9] and by double alkylation of vinylidene-bis(dimethylamine) with 1,5-diiodopentane to the cyclic amidinium salt followed by hydrolysis.[4]

References and Notes

1. This work was carried out at the Department of Chemistry, Fordham University, Bronx, New York 10458.
2. Present address: Department of Chemistry, Pennsylvania State University, University Park, Pennsylvania 16802.
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

NH_3

$CH_3CO_2(CH_2)_3CH_3$

$C_6H_5NH_2$

$C_6H_5CO_2C_2H_5$

$C_6H_5CH_2NH_2$

$(CH_3)_3CNH_2$

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

Benzene (71-43-2)

ethyl acetate (141-78-6)

methanol (67-56-1)

sodium hydrogen carbonate (144-55-8)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

aluminum (7429-90-5)

dichloromethane (75-09-2)

Cyclohexanecarboxylic acid (98-89-5)

magnesium sulfate (7487-88-9)

dimethylamine (124-40-3)

hexane (110-54-3)

N,N-Dimethylcyclohexanecarboxamide (17566-51-7)

cyclohexanecarbonyl chloride (2719-27-9)

1,5-diiodopentane (628-77-3)

calcium hydride (7789-78-8)

trimethylaluminum (75-24-1)

methyl cyclohexanecarboxylate (4630-82-4)

vinylidene-bis(dimethylamine) (815-62-3)

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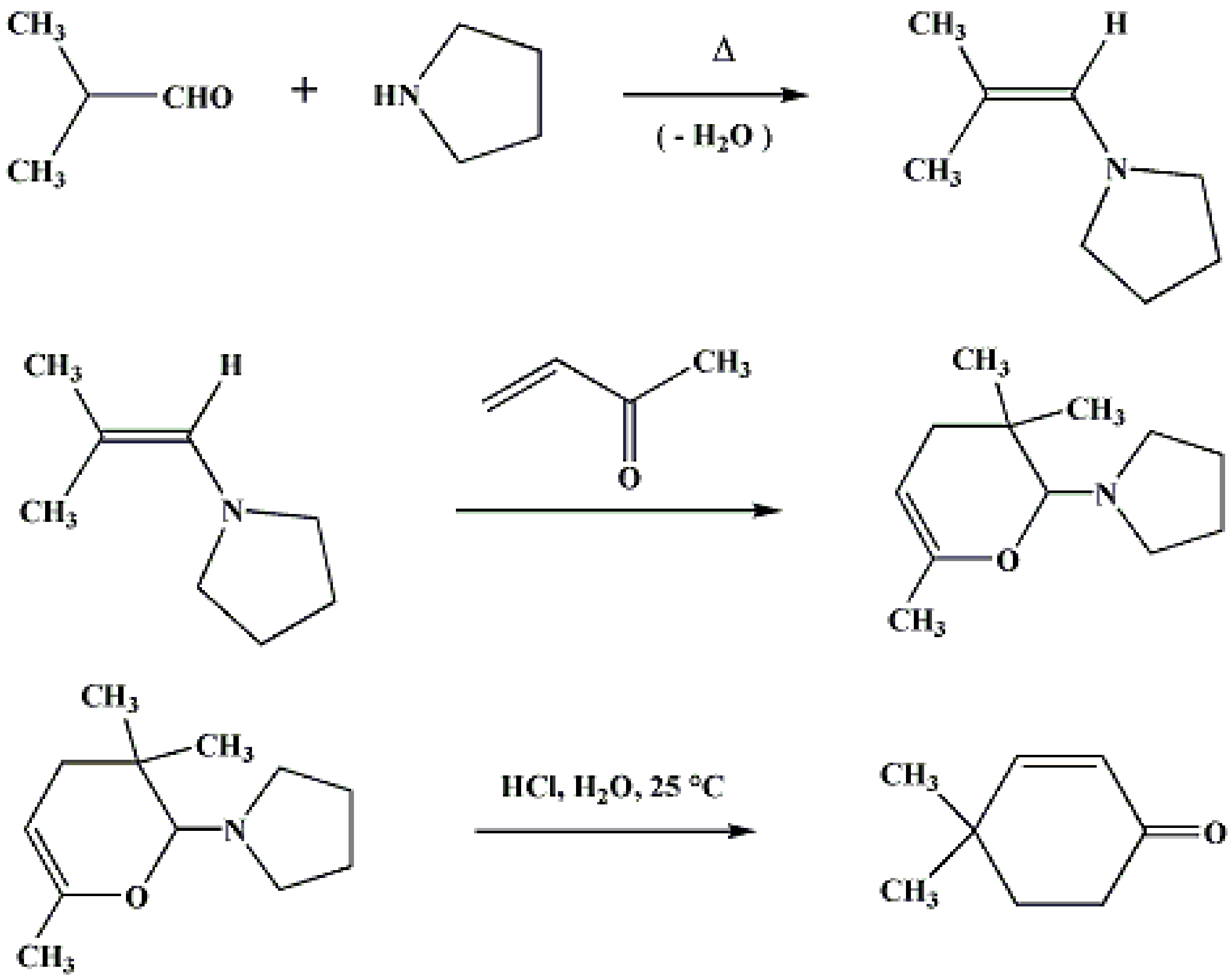
Organic Syntheses, CV 6, 496

4,4-DIMETHYL-2-CYCLOHEXEN-1-ONE

[2-Cyclohexen-1-one, 4,4-dimethyl-]



Submitted by Yihlin Chan and William W. Epstein[1].
Checked by Michael J. Umen and Herbert O. House.

1. Procedure

A. 1-(2-*Methylpropenyl)pyrrolidine.* A 200-ml., three-necked flask is equipped with a magnetic stirring bar, a heating mantle, a pressure-equalizing dropping funnel, a glass stopper, and a continuous water separator (a Dean-Stark trap, (Note 1)) fitted with a condenser and a nitrogen inlet tube. The reaction vessel is flushed with nitrogen, and 61.5 g. (0.853 mole) of isobutyraldehyde (Note 2) is added to the reaction flask. An additional amount of isobutyraldehyde (Note 2) is added to the continuous water separator, filling the water-collecting trap. A static nitrogen atmosphere is maintained in the reaction vessel throughout the reaction and distillation. To the reaction flask is added, dropwise and with stirring over 5 minutes, 60.6 g. (0.852 mole) of pyrrolidine (Note 3). After addition is complete, the dropping funnel is replaced with a glass

stopper and the reaction mixture is refluxed with stirring for 3.5 hours during which time about 15 ml. (0.83 mole) of water collects in the water separator (Note 4). The water separator and condenser are replaced with a distillation head, and the reaction mixture is distilled under reduced pressure, yielding 99.1–100.7 g. (94–95%) of the enamine as a colorless liquid, b.p. 92–106° (115–118 mm.), n_D^{25} 1.4708–1.4738 (Note 5).

B. *4,4-Dimethyl-2-cyclohexen-1-one.* A dry, 1-l., three-necked flask is equipped with a mechanical stirrer, a pressure-equalizing dropping funnel, a nitrogen inlet tube, and an ice-water cooling bath. The apparatus is flushed with nitrogen, and a static nitrogen atmosphere is maintained in the reaction vessel throughout the reaction. 1-(2-Methylpropenyl)pyrrolidine (62.6 g., 0.501 mole) is added to the reaction flask before 42.1 g. (0.601 mole) of methyl vinyl ketone (Note 6) is added, dropwise with stirring and cooling, over 5 minutes. After the resulting mixture has been stirred with cooling for 10 minutes, the ice bath is removed and stirring at room temperature is continued for 4 hours (Note 7). The reaction mixture is again cooled with an ice-water bath, and 250 ml. of 8 *M* hydrochloric acid is added, dropwise and with stirring (Note 8). After addition is complete, the mixture is stirred with cooling for 10 minutes, then stirred at room temperature for 14 hours (Note 9). The resulting brown reaction mixture is extracted with two 300-ml. portions of diethyl ether. The residual aqueous phase is neutralized by the cautious addition of 150–155 g. of solid sodium hydrogen carbonate and extracted with two 400-ml. portions of ether. The combined ethereal extracts (Note 10) are dried over anhydrous sodium sulfate and concentrated with a rotary evaporator. The residual liquid is distilled under reduced pressure, yielding 44.2–53.0 g. (71–85%) of 4,4-dimethyl-2-cyclohexen-1-one as a colorless liquid, b.p. 73–74° (14 mm.), n_D^{25} 1.4699–1.4726 (Note 11).

2. Notes

1. An illustration of a continuous water separator is provided in *Org. Synth.*, **Coll. Vol. 3**, 502 (1955).
2. The checkers employed isobutyraldehyde from Eastman Organic Chemicals. The aldehyde, b.p. 62–63°, was freshly distilled from a few milligrams of *p*-toluenesulfonic acid.
3. The pyrrolidine, obtained from Aldrich Chemical Company, Inc., was redistilled before use; b.p. 88–89°.
4. The water should not be drained from the water separator during the course of the reaction.
5. The enamine has IR absorption (pure liquid) at 1676 cm.$^{-1}$ (enamine C=C).
6. Methyl vinyl ketone (b.p. 35–36° at 140 mm.), obtained from Aldrich Chemical Company, Inc., was distilled immediately before use.
7. The use of solvents such as anhydrous ether or benzene is not only unnecessary but also undesirable, since yields are decreased by their presence. For best results the Diels-Alder adduct, which has been characterized by Opitz and Holtmann,[2] should not be isolated for the subsequent hydrolysis and

cyclization.

8. The hydrolysis product, 2,2-dimethyl-5-oxo-hexanal, can be isolated if desired by stirring the Diels-Alder adduct with either 50% acetic acid or 2 *M* hydrochloric acid followed by extraction with ether and distillation,[3] b.p. 92–94° (20 mm.).

9. Cyclization can also be accomplished by the use of an ion exchange resin.[4] On a 0.1-mole scale, 110 ml. of 1 *M* hydrochloric acid and 70 ml. of wet Amberlite 1R-120 resin (acidified with hydrochloric acid) are added to the Diels-Alder adduct, and the mixture is refluxed for 24 hours. The mixture is cooled and washed with four portions of ether. The ether extract is dried over anhydrous magnesium sulfate and distilled, separating 9.7–10.8 g. (78–87%) of 4,4-dimethyl-2-cyclohexen-1-one; b.p. 73–74° (14 mm.).

10. Washing the ethereal extract with either dilute acid, aqueous sodium hydrogen carbonate, or saturated brine only decreased the yield of product and is, therefore, omitted. An acid-catalyzed reaction of methyl vinyl ketone with isobutyraldehyde gives the product in 71% yield.[5]

11. The product exhibits a single peak (retention time 5.7 minutes) on a 4-m. GC column packed with silicone fluid QF_1 on Chromosorb P and heated to 191°. This material has the following spectral characteristics: IR (CCl_4) 1675 (conjugated C=O) and 1623 cm.$^{-1}$ (conjugated C=C); UV (95% C_2H_5OH) max 224 (10,600) and 321 nm (34); ^{1}H NMR (CCl_4), δ 1.17 (s, 6H, $2CH_3$), 1.7–2.6 (m, 4H, $2CH_2$), 5.71 (d, *J* = 10 Hz., 1H, vinyl C*H*), and 6.65 (d of t, *J* = 10 and 1.5 Hz., 1H, vinyl C*H*); *m/e* (rel. int.), 124(M^+, 49), 96(83), 82(100), 81(56), 68 (25), 67(42), 53(22), 43(21), 41(25), and 39(25).

3. Discussion

The procedure described is essentially that of Opitz and Holtmann.[2] The yield has been increased from 27% to 85% by making changes as indicated in (Note 7) and (Note 10). 4,4-Dimethyl-2-cyclohexen-1-one has also been prepared by Michael addition of methyl vinyl ketone to isobutyraldehyde followed by ring formation in basic media with yields of 25%,[6] 35%,[7] and 43%.[8] This procedure has general utility in preparing 4-substituted or 4,4-disubstituted cyclohexen-2-ones and, as such, constitutes a useful substitute for the Robinson annelation reactions.[9,10] Unlike the latter, the alkylation step in this procedure does not require strongly basic conditions. Consequently, side reactions such as aldol condensation of the carbonyl compounds and polymerization of methyl vinyl ketone are avoided. Moreover, since the location of the double bond in the enamines is controlled by the amines used,[11] it may be possible to direct the alkylation to either side of a given carbonyl group making this procedure potentially very versatile. Similar reactions using acrolein and enamines of cyclic ketones have been utilized for the synthesis of bicyclo[n.3.1] systems.[9,12]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

brine

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

ether, diethyl ether (60-29-7)

Acrolein (107-02-8)

sodium hydrogen carbonate (144-55-8)

Salt (7647-14-5)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

magnesium sulfate (7487-88-9)

isobutyraldehyde (78-84-2)

pyrrolidine (123-75-1)

methyl vinyl ketone (78-94-4)

p-toluenesulfonic acid (104-15-4)

4,4-Dimethyl-2-cyclohexen-1-one, 2-Cyclohexen-1-one, 4,4-dimethyl- (1073-13-8)

1-(2-Methylpropenyl)pyrrolidine (2403-57-8)

2,2-dimethyl-5-oxo-hexanal (13544-11-1)

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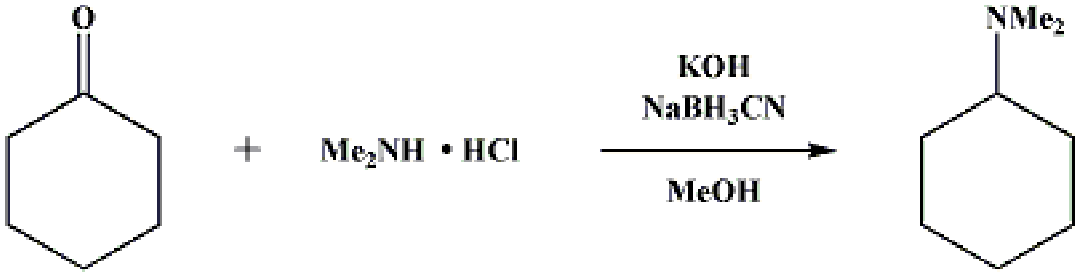
Organic Syntheses, CV 6, 499

REDUCTIVE AMINATION WITH SODIUM CYANOBOROHYDRIDE: *N,N*-DIMETHYLCYCLOHEXYLAMINE

[Cyclohexanamine, 4,4-dimethyl-]



Submitted by Richard F. Borch[1]
Checked by K. Abe and S. Masamune.

1. Procedure

A solution of 21.4 g. (0.262 mole) of dimethylamine hydrochloride in 150 ml. of methanol is prepared in a 500-ml., round-bottomed flask. Potassium hydroxide (4 g.) is added in one portion to the magnetically stirred solution (Note 1). When the pellets are completely dissolved, 19.6 g. (0.200 mole) of cyclohexanone is added in one portion. The resulting suspension is stirred at room temperature for 15 minutes before a solution of 4.75 g. (0.0754 mole) of sodium cyanoborohydride (Note 2) and (Note 3) in 50 ml. of methanol is added dropwise over 30 minutes to the stirred suspension. After the addition is complete, the suspension is stirred for 30 minutes. Potassium hydroxide (15 g.) is then added, and stirring is continued until the pellets are completely dissolved. The reaction mixture is filtered with suction, and the volume of the filtrate is reduced to approximately 50 ml. with a rotary evaporator while the bath temperature is kept below 45° (Note 4) and (Note 5). To this concentrate is added 10 ml. of water and 25 ml. of saturated aqueous sodium chloride, and the layers are separated. The aqueous layer is extracted with two 50-ml. portions of diethyl ether. The organic layer previously separated and the ethereal extracts are combined and extracted with three 20-ml. portions of 6 *M* hydrochloric acid (Note 6). The combined acid layers are saturated with sodium chloride and extracted with four 30-ml. portions of ether (Note 7). The aqueous solution is cooled to 0° in an ice bath and brought to pH > 12 by addition of potassium hydroxide pellets to the stirred solution (Note 8) and (Note 9). The layers are separated, and the aqueous layer is extracted with two 40-ml. portions of ether. The combined organic layers are washed with 10 ml. of saturated aqueous sodium chloride, dried over anhydrous potassium carbonate, and freed of ether with a rotary evaporator (Note 4). This crude product is fractionated through a

15-cm. Vigreux column (Note 10). After 1–3 g. of a forerun, b.p. 144–155° (Note 11) is separated, the fraction boiling at 156–159° is collected, yielding 13.3–13.7 g. (52–54%) of *N,N*-dimethylcyclohexylamine, n_D^{25} 1.4521 (Note 12).

2. Notes

1. Precipitation of potassium chloride begins immediately; the presence of this solid does not interfere with the reaction, and removal by filtration will result in loss of dimethylamine.
2. Sodium cyanoborohydride is available as a pale brown solid from Alfa Inorganics, Inc.
3. The commercially available material can be used without further purification. Use of material purified by the published procedure[2] gives a less colored crude product, but makes no improvement in yield or purity of the final product.
4. Since the product boils at 75° (15 mm.), care should be exercised to prevent loss of material in the evaporation process.
5. It is normal for additional potassium chloride to precipitate as the evaporation continues.
6. *Caution! This addition of hydrochloric acid into a separatory funnel occurs with considerable heat evolution, causing the ether to boil. The initial addition must be carried out with gentle swirling and cooling.*
7. GC analysis shows that the ethereal extract contains solely cyclohexanol (>98%).
8. The aqueous layer in this step is saturated with ether, and the addition of potassium hydroxide must be carried out gradually to prevent the contents of the flask from boiling over.
9. Copious amounts of potassium chloride precipitate during this addition. It is not necessary to remove the salt by filtration before the ether extraction.
10. A still pot with a volume of at least 100-ml. should be used for the distillation, since foaming occurs as the distillation proceeds.
11. On a 2-m. GC column packed with 10% Apiezon L and heated to 100°, the retention times for *N,N*-dimethylcyclohexylamine and cyclohexanol are 15 and 4 minutes, respectively. The composition of this forerun is 80–85% of the amine and 20–15% of the alcohol.
12. GC analysis of the product shows that the product is at least 99.2% pure and is contaminated only with trace amounts of cyclohexanol. The submitter reported a 62–69% yield (15.7–17.5 g.) using the indicated scale.

3. Discussion

N,N-Dimethylcyclohexylamine has been prepared by catalytic reductive alkylation[3,4] and by the Leuckart reaction.[5] The present method is experimentally simple, requires no special apparatus, and is generally applicable to the synthesis of a variety of primary, secondary, and tertiary amines, as illustrated in Table I.

TABLE I
REPRESENTATIVE REDUCTIVE AMINATIONS WITH $NaBH_3CN$[2]

Compound	Amine	Product	Yield, %
Cyclohexanone	NH_3	Cyclohexylamine	45
Cyclohexanone	CH_3NH_2	*N*-Methylcyclohexylamine	41
Cyclohexanone	CH_3NHCH_3	*N,N*-Dimethylcyclohexylamine	53
Acetophenone	NH_3	α-Phenylethylamine	77
Acetophenone	CH_3NH_2	*N*-Methylphenethylamine	78
Isobutyraldehyde	$PhNH_2$	*N*-Isobutylaniline	78
Glutaraldehyde	CH_3NH_2	*N*-Methylpiperidine	43

The submitter has found that use of sodium borohydride instead of sodium cyanoborohydride in the present procedure results in the almost exclusive formation of cyclohexanol with less than 3% of basic material.

References and Notes

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4. W. S. Emerson, *Org. React.*, **4**, 174 (1948).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

NH_3

CH_3NH_2

$PhNH_2$

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

Cyclohexanol (108-93-0)

Cyclohexanone (108-94-1)

sodium chloride (7647-14-5)

Acetophenone (98-86-2)

potassium hydroxide (1310-58-3)

dimethylamine hydrochloride (506-59-2)

potassium chloride (7447-40-7)

dimethylamine (124-40-3)

cyclohexylamine (108-91-8)

isobutyraldehyde (78-84-2)

α-Phenylethylamine (3886-69-9)

N-Methylphenethylamine (589-08-2)

glutaraldehyde (111-30-8)

N-Methylpiperidine (626-67-5)

sodium borohydride (16940-66-2)

sodium cyanoborohydride (25895-60-7)

Cyclohexanamine, 4,4-dimethyl-

N,N-Dimethylcyclohexylamine (98-94-2)

N-Methylcyclohexylamine (100-60-7)

N-Isobutylaniline

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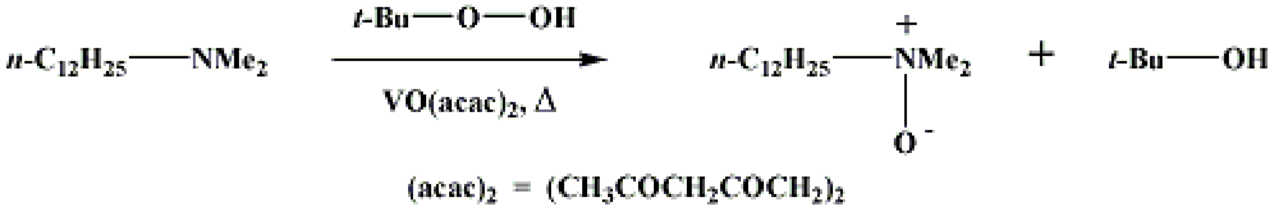
Organic Syntheses, CV 6, 501

N,*N*-DIMETHYLDODECYLAMINE OXIDE

[Dodecanamine, *N*,*N*-dimethyl-, *N*-oxide]



Submitted by M. N. Sheng and J. G. Zajacek[1].
Checked by William F. Fischer, Jr. and Herbert O. House.

1. Procedure

Caution! Methyl iodide, in high concentrations for short periods or in low concentrations for long periods, can cause serious toxic effects in the central nervous system. Accordingly, the American Conference of Governmental Industrial Hygienists[2] has set 5 p.p.m., a level which cannot be detected by smell, as the highest average concentration in air to which workers should be exposed for long periods. The preparation and use of methyl iodide should always be performed in a well-ventilated fume hood. Since the liquid can be absorbed through the skin, care should be taken to prevent contact.

A solution of 21.3 g. (0.100 mole) of freshly distilled *N*,*N*-dimethyldodecylamine (Note 1), 9.6 g. (0.10 mole) of 94% *tert*-butyl hydroperoxide (Note 2), and 0.050 g. of vanadium oxyacetylacetonate (Note 3) in 27 g. (34 ml.) of *tert*-butyl alcohol is placed in a 250-ml., round-bottomed flask fitted with a thermometer, a reflux condenser, and a heating mantle. The reaction mixture is heated to approximately 65–70°, at which point an exothermic reaction begins. The heating is discontinued until the vigorous exothermic reaction subsides (about 5 minutes); the reaction mixture is then heated at reflux (the reaction mixture boils at 90°) for 25 minutes. After the resulting mixture has been cooled to room temperature, *it is analyzed* (Note 4) *to establish the absence of tert-butyl hydroperoxide*, then concentrated with a rotary evaporator (30–35° bath with 30–40 mm. pressure). The crude solid residue is triturated with 50 ml. of cold (0–5°), anhydrous diethyl ether and filtered under conditions which prevent exposure of the residual amine oxide to atmospheric moisture (Note 5). The solid is washed with 50 ml. of cold (0–5°) anhydrous ether and dried under reduced pressure, leaving 12.9–15.5 g. of the crystalline amine oxide, m.p. 131–131.5°. Concentration of the mother liquors and trituration of the residual paste with 25 ml. of cold (0–5°) anhydrous ether separates another 4.9–3.4 g. of the amine oxide, m.p. 130–131°. The total yield of the crystalline amine oxide (Note 6) is 17.4–18.9 g. (76–83%).

2. Notes

1. *N*,*N*-Dimethyldodecylamine purchased from Eastman Organic Chemicals is approximately 90% pure. This material should be fractionally distilled with a

spinning band column to obtain the pure amine, b.p. 116–117° (4 mm.).
2. *tert*-Butyl hydroperoxide purchased from the Lucidol Division, Wallace and Tiernan, Inc., is approximately 92% pure. A portion of the major impurity, water, can be removed by drying the commercial material over anhydrous magnesium sulfate for 2 days, leaving material that is 94–97% pure.
3. Vanadium oxyacetylacetonate may be purchased from Alfa Inorganics, Inc., Beverly, Massachusetts.
4. Although consumption of the hydroperoxide is normally complete, the absence of this peroxide in the reaction mixture should be established by testing with moist starchiodide paper or by iodometric titration.[3] The amine oxide content may be determined by titration with standard hydrochloric acid after any amine present has reacted with methyl iodide for 1 hour at room temperature.[4] From this volumetric analysis the submitters determined the yield of amine oxide to be 86%. The checkers found that the reaction could be followed by measuring the ^{1}H NMR spectra in *tert*-butyl alcohol solution where the *N*-methyl signals of the amine (δ 2.03) and the amine oxide (δ 2.98) are readily observed.
5. The amine oxide is exceedingly hygroscopic and must be protected from atmospheric moisture during filtration. The submitters found it convenient to use a Büchner funnel covered with a large, inverted rubber stopper. After the mixture of amine oxide and ether is added to the funnel, the mouth of the funnel is covered with the inverted rubber stopper, and suction is applied. The flat surface of the inverted rubber stopper forms a seal against the mouth of the funnel, preventing the entrance of moist air while the last traces of ether are removed. The checkers employed a sintered-glass funnel fitted to maintain a nitrogen atmosphere above the crystalline product.
6. The hygroscopic amine oxide should be protected from moisture during storage. The checkers found that the initial product could be recrystallized from toluene under anhydrous conditions to yield the amine oxide as white needles, m.p. 130–131°.

3. Discussion

Aqueous or alcoholic solutions of amine oxides are normally obtained by oxidizing tertiary amines with either hydrogen peroxide or a peracid.[5] For example, *N,N*-dimethyldodecylamine oxide has been prepared by treating *N,N*-dimethyldodecylamine with aqueous hydrogen peroxide.[6] The procedure illustrated in this preparation permits the oxidation of tertiary amines with *tert*-butyl hydroperoxide in organic solvents under relatively anhydrous conditions.[7] In this procedure the reaction time is short, and the method is as convenient as that with aqueous hydrogen peroxide or a peracid as the oxidant. Furthermore, isolation of the anhydrous amine oxide is often relatively simple.

References and Notes

1. The Research and Development Department, ARCO Chemical Company, A Division of Atlantic Richfield Company, Glenolden, Pennsylvania. [Present address: The Research and Development Department, ARCO Chemical Company, A Division of Atlantic Richfield Company, Newtown Square, Pennsylvania 19073.]
2. American Conference of Governmental Industrial Hygienists (ACGIH), “Documentation of

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

peracid

vanadium oxyacetylacetonate

hydrochloric acid (7647-01-0)

ether, diethyl ether (60-29-7)

nitrogen (7727-37-9)

toluene (108-88-3)

hydrogen peroxide (7722-84-1)

Methyl iodide (74-88-4)

magnesium sulfate (7487-88-9)

tert-butyl alcohol (75-65-0)

tert-butyl hydroperoxide (75-91-2)

N,N-dimethyldodecylamine (112-18-5)

N,N-Dimethyldodecylamine oxide, Dodecanamine, N,N-dimethyl-, N-oxide (1643-20-5)

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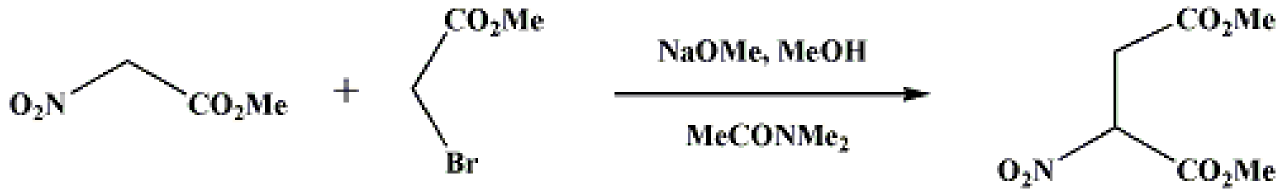
Organic Syntheses, CV 6, 503

DIMETHYL NITROSUCCINATE

[Butanedioic acid, 2-nitro-, dimethyl ester]



Submitted by S. Zen and E. Kaji[1].
Checked by M. Braun and G. Büchi.

1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A 1-l., three-necked, round-bottomed flask equipped with a calcium chloride drying tube, a mechanical stirrer, and a ground-glass stopper is charged with 28.2 g. (0.184 mole) of freshly distilled methyl bromoacetate, 500 ml. of anhydrous *N,N*-dimethylacetamide (Note 1), and 20.0 g. (0.168 mole) of methyl nitroacetate (Note 2). The solution is stirred vigorously while 146 ml. (0.168 mole) of 1.15 *N* sodium methoxide in methanol is added in one portion. The resulting light-yellow suspension is stirred for an additional 16 hours at room temperature during which time it changes into a clear yellow solution.

After dilution with 200 ml. of benzene, the solution is transferred to a 2-l. separatory funnel containing 800 ml. of ice water and shaken thoroughly. The aqueous layer is separated, acidified to pH 3–4 with 2–3 ml. of concentrated hydrochloric acid, and extracted with three 100-ml. portions of benzene. All the organic layers are combined and dried over anhydrous sodium sulfate. Filtration and concentration of the solution with a rotary evaporator, followed by exposure to high vacuum for 2–3 hours, affords 17.3–19.3 g. of the crude product (Note 3). Low-boiling impurities are removed by vacuum distillation (Note 4), the residual oil (14–15 g.) is transferred to a 50-ml. flask equipped with a short-path distillation apparatus, and vacuum distillation is continued. A forerun is taken until no rise in boiling point is observed before 7.2–8.5 g. (23–27%) of dimethyl nitrosuccinate is collected as a colorless oil, b.p. 85° (0.07 mm.), n_D^{20} 1.4441 (Note 5).

2. Notes

1. *N,N*-dimethylacetamide was treated with molecular sieves for 2 days, decanted, and distilled under reduced pressure, b.p. 85° (30 mm.), before use.
2. Methyl nitroacetate was prepared by the method in *Org. Synth.*, **Coll. Vol. 6**, 797 (1988). It should be distilled before use.
3. GC analysis of the crude mixture (SE-30 on Chromosorb W, 1 m., 150°) showed the

presence of some low-boiling materials (including unreacted methyl nitroacetate) and a significant amount of the doubly alkylated by-product, trimethyl 2-nitro-1,2,3-propanetricarboxylate.

4. The bath temperature should be maintained below 70–75°. Distillation was carried out using a Claisen head, and the receiving flasks were immersed in ice.

The checkers found it convenient to omit this distillation and the subsequent transfer. Instead the crude product was placed in a 25-ml. flask and carefully distilled (0.07 mm). The bath temperature was raised slowly, and a forerun was collected until the boiling point stabilized.

5. The distilled product was determined by the checkers to be 85–90% pure (GC analysis), the major impurity being the doubly alkylated by-product. Purity can be increased to 95% by redistillation. The checkers found that conducting the experiment on a scale resulted in increased yield (34%) and purity (90–93%) of once-distilled product.

For twice-distilled material: IR (liquid film) cm.$^{-1}$: 1745 strong, 1565 strong, 1430 medium strong; ^{1}H NMR ($CDCl_3$), δ (multiplicity, coupling constant *J* in Hz., number of protons): 3.14–3.45 (m, 2H), 3.76 (s, 3H), 3.86 (s, 3H), 5.6 (d of d, *J* = 6 and 8, 1H).

3. Discussion

Diethyl nitrosuccinate has been prepared by oxidation of diethyl nitrososuccinate,[2] and by the reaction of sodium nitrite with diethyl bromosuccinate, but in the latter case no experimental conditions were described.[3]

The present method is a simple, one-step procedure employing commercially available or readily accessible starting materials. Other α-nitro carboxylic esters may be prepared in this way;[4] for example, dimethyl 2-nitropentanedioate was prepared in 45–50% yield.

References and Notes

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3. R. Gelin and S. Gelin, *C.R. Hebd. Seances Acad. Sci.*, **256**, 3705 (1963).
4. S. Zen and E. Kaji, *Bull. Chem. Soc. Jpn.*, **43**, 2277 (1970); E. Kaji and S. Zen, *Bull. Chem. Soc. Jpn.*, **46**, 337 (1973).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

methanol (67-56-1)

sodium sulfate (7757-82-6)

sodium nitrite (7632-00-0)

sodium methoxide (124-41-4)

N,N-dimethylacetamide (127-19-5)

Dimethyl nitrosuccinate, Butanedioic acid, 2-nitro-, dimethyl ester (28081-31-4)

methyl bromoacetate (96-32-2)

Methyl nitroacetate (2483-57-0)

trimethyl 2-nitro-1,2,3-propanetricarboxylate

Diethyl nitrosuccinate

diethyl nitrososuccinate

diethyl bromosuccinate

dimethyl 2-nitropentanedioate

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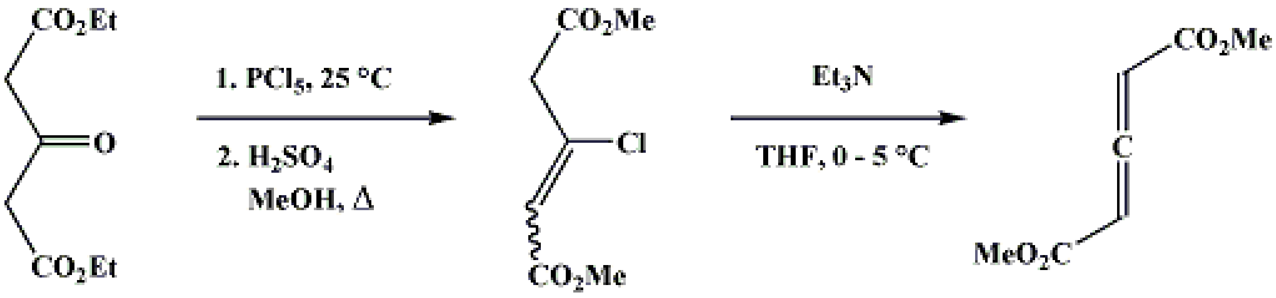
Organic Syntheses, CV 6, 505

DIMETHYL 2,3-PENTADIENEDIOATE

[2,3-Pentadienedioic acid, dimethyl ester]



Submitted by T. A. Bryson[1] and T. M. Dolak.
Checked by R. Shapiro and G. Hüchi.

1. Procedure

Caution! The reaction of phosphorus pentachloride with diethyl acetone-1,3-dicarboxylate should be carried out in a hood, since hydrogen chloride is evolved.

A. *Dimethyl 3-chloro-2-pentenedioate*. A dry, 500-ml., three-necked, round-bottomed flask fitted with a ground-glass stopper, a condenser provided with a gas bubbler, a gas-inlet adapter attached to a nitrogen (or argon) source, and a magnetic stirring bar, is charged with 60.0 g. (0.297 mole) of diethyl acetone-1,3-dicarboxylate (Note 1). A steady, gentle flow of nitrogen is started through the reaction vessel (Note 2), and 65.0 g. (0.313 mole) of phosphorus pentachloride (Note 3) is added in thirteen, approximately equal portions through the stoppered joint to the neat diester at 3-minute intervals with vigorous stirring (Note 4). After the addition is complete, the reaction mixture is warmed to 40° in a water bath for 30 minutes. The red solution is cooled in an ice bath and poured onto *ca.* 100 ml. of ice in a 500-ml. Erlenmeyer flask immersed in an ice bath. A 1 : 1 mixture of water and dichloromethane is used to rinse traces of the product from the reaction vessel into the Erlenmeyer flask, and the resulting mixture is stirred for 15 minutes (Note 5). After separating the two layers, the aqueous phase is extracted with three 100-ml. portions of dichloromethane, and the combined organic extracts are dried over anhydrous sodium sulfate. Filtration through glass wool and removal of solvents with a rotary evaporator affords *ca.* 60 g. of a red oil, which is placed in a 500-ml., round-bottomed flask containing 20 ml. of concentrated sulfuric acid in 300 ml. of anhydrous methanol (Note 6), and the solution is refluxed using a heating mantle for 18 hours. Excess methanol (200 ml.) is distilled, and the residual yellow solution is cooled to room temperature and poured into 100 ml. of water. Sodium chloride is added to saturation, and the solution is extracted with eight 100-ml. portions of diethyl ether. The combined extracts are washed successively with 150 ml. of aqueous saturated sodium hydrogen carbonate and 150 ml. of aqueous saturated sodium chloride, dried over anhydrous sodium sulfate, and filtered. Concentration of the extract with a rotary evaporator affords a yellow oil which is distilled, yielding 33.5–34.4 g. (59–60%) of dimethyl 3-chloro-2-pentenedioate[2] as a colorless liquid, b. p. 50–60° (0.02 mm.) (Note 7).

B. *Dimethyl 2,3-pentadienedioate*. A 500-ml., three-necked, round-bottomed flask, equipped with a gas-inlet adapter, a 50-ml. addition funnel, a ground-glass stopper, and a magnetic stirring bar, is charged with 27.0 g. (0.145 mole) of the diester from Part A and 100 ml. of anhydrous tetrahydrofuran (freshly distilled from sodium). The flask is flushed with nitrogen (or argon), and a positive pressure is maintained while the contents are cooled to 0° in an ice–salt bath and stirred with an efficient motor. Triethylamine (22 ml., 0.16 mole, freshly distilled from calcium hydride) is added through the addition funnel over a 10-minute period, the gas-inlet adapter is replaced with a calcium chloride tube, and the mixture is stirred at 0–5° for 18 hours (Note 8). The precipitate is removed by vacuum filtration and washed with three 100-ml. portions of anhydrous diethyl ether. The combined filtrate and washings are washed successively with three 75-ml. portions of 0.1 *N* hydrochloric acid and 100 ml. of aqueous saturated sodium chloride, dried over anhydrous sodium sulfate, filtered, and concentrated with a rotary evaporator. The residual oil is distilled (Note 9), yielding 13.3–13.9 g. (61–64%) of dimethyl 2,3-pentadienedioate[3] (Note 10), b.p. 58° (0.02 mm.).

2. Notes

1. Diethyl acetone-1,3-dicarboxylate was purchased from the Aldrich Chemical Company, Inc., and the checkers distilled this material under reduced pressure, b.p. 135–137° (12 mm.), discarding *ca.* 10% as a forerun.
2. A continuous flow of inert gas removes hydrogen chloride and phosphoryl chloride from the reaction flask.
3. Phosphorus pentachloride was purchased by the checkers from the J. T. Baker Chemical Company, and purchased from Eastman Organic Chemicals by the submitters.
4. Warming and foaming occur during the addition, and the temperature reaches *ca.* 40–45°.
5. The checkers found that unless the aqueous workup is cooled, the dichloromethane boils vigorously.
6. The checkers used commercial “anhydrous” methanol without further drying.
7. The checkers determined the product to be a mixture of isomers (approximately 6 : 1) by GC analysis (15% SE-30 on Chromosorb W, 0.3 × 244 cm., 175°) and by ^{1}H NMR. The mixture was characterized as follows: IR (liquid film) cm.$^{-1}$: 1745 strong (shoulder at 1720), 1640 medium strong, 1440 medium strong; ^{1}H NMR ($CDCl_3$), δ (multiplicity, number of protons): 3.75 (s, 6H), 4.12 (s, 2H), 6.21 (s, 1H), and 6.30 (s, 1H).
8. During this time a heavy precipitate of triethylamine hydrochloride forms; the mixture first becomes yellow and eventually brown in color.
9. The allene apparently polymerizes during distillation; it yellows in the receiving flask, and becomes orange and viscous even in the refrigerator overnight. The submitters obtained higher yields by distilling the product in batches.
10. The checkers characterized the product as follows: IR (liquid film) cm.$^{-1}$: 1970 strong, 1720 strong, 1440 strong; ^{1}H NMR ($CDCl_3$), δ (multiplicity, number of protons): 3.81 (s, 6H), 6.10 (s, 2H).

3. Discussion

Dimethyl 2,3-pentadienedioate has also been prepared from the enol phosphate of diethyl acetone-1,3-dicarboxylate.[4]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

enol phosphate of diethyl acetone-1,3-dicarboxylate

sulfuric acid (7664-93-9)

hydrogen chloride, hydrochloric acid (7647-01-0)

methanol (67-56-1)

diethyl ether (60-29-7)

phosphorus pentachloride (10026-13-8)

sodium hydrogen carbonate (144-55-8)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

sodium (13966-32-0)

diethyl acetone-1,3-dicarboxylate (105-50-0)

dichloromethane (75-09-2)

Tetrahydrofuran (109-99-9)

triethylamine (121-44-8)

Triethylamine hydrochloride (554-68-7)

calcium hydride (7789-78-8)

argon (7440-37-1)

Dimethyl 2,3-pentadienedioate, 2,3-Pentadienedioic acid, dimethyl ester (1712-36-3)

Dimethyl 3-chloro-2-pentenedioate (66016-88-4)

phosphoryl chloride (10025-87-3)

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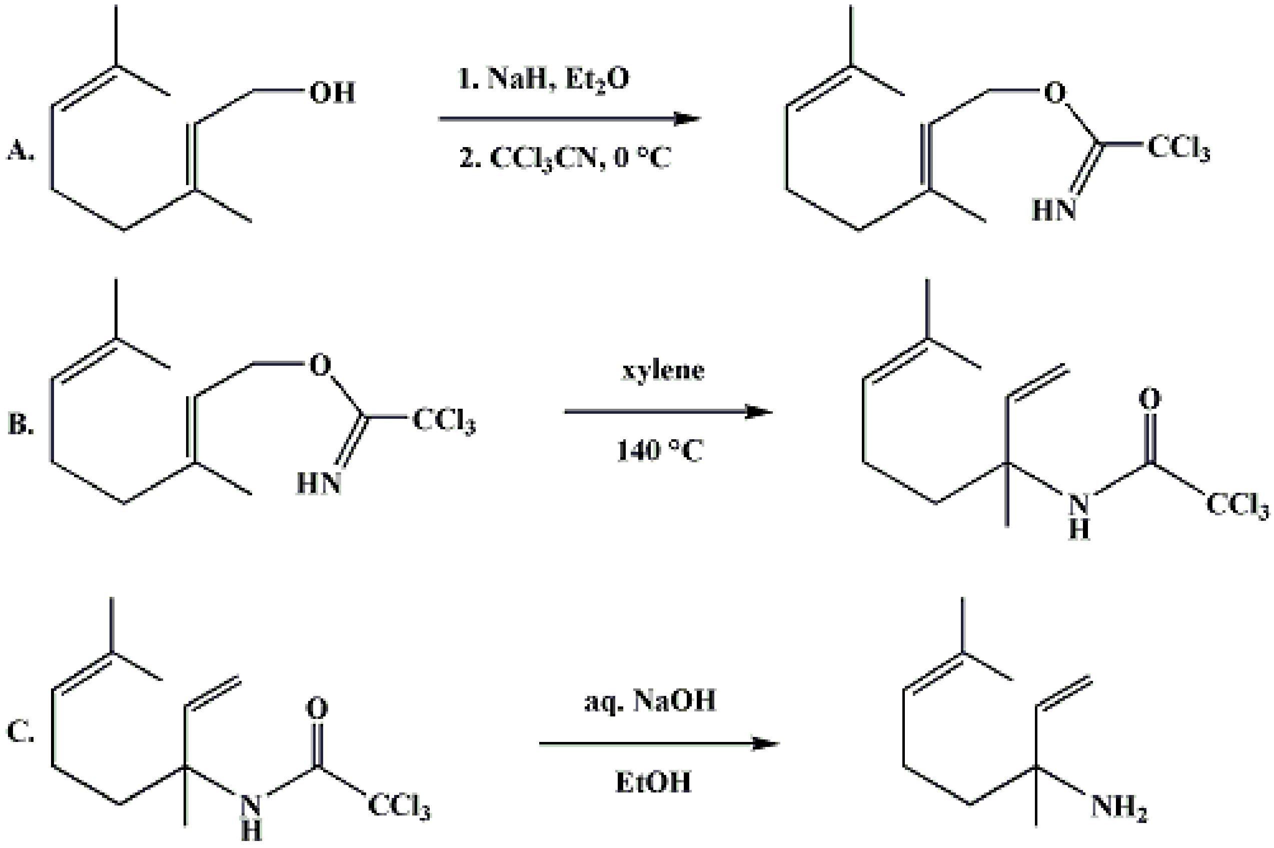
Organic Syntheses, CV 6, 507

ALLYLICALLY TRANSPOSED AMINES FROM ALLYLIC ALCOHOLS: 3,7-DIMETHYL-1,6-OCTADIEN-3-AMINE

[1,6-Octadien-3-amine, 3,7-dimethyl-]



Submitted by Lane A. Clizbe and Larry E. Overman[1].
Checked by A. Brossi, H. Mayer, and N. Kappeler.

1. Procedure

Caution! Part A should be carried out in a well-ventilated hood to avoid exposure to trichloroacetonitrile vapors.

A. *Geraniol trichloroacetimidate* (**1**). A dry, 250-ml., three-necked flask is equipped with a magnetic stirring bar, a pressure-equalizing dropping funnel, a thermometer, and a nitrogen inlet tube. The apparatus is flushed with nitrogen and charged with 410 mg. (0.0103 mole) of sodium hydride dispersed in mineral oil (Note 1) and 15 ml. of hexane. The suspension is stirred, and the hydride is allowed to settle. The hexane is removed with a long dropping pipette, 60 ml. of anhydrous diethyl ether is added, and a solution of 15.4 g. (0.0993 mole) of geraniol in 15 ml. of anhydrous ether is added over 5 minutes. After the evolution of hydrogen ceases (less than 5 minutes), the reaction mixture is stirred for an additional 15 minutes. The clear solution is then cooled to between –10 and 0° in an ice–salt bath.

Trichloroacetonitrile (10.0 ml., 14.4 g., 0.0996 mole) is added dropwise to the stirred solution, while the reaction temperature is maintained below 0° (Note 2). Addition is completed within 15 minutes, and the reaction mixture is allowed to warm to room temperature. The light amber mixture is poured into a 250-ml., round-bottomed flask, and the ether is removed with a rotary evaporator. Pentane [150 ml., containing 0.4 ml. (0.01 mole) of methanol] is added, the mixture is shaken vigorously for 1 minute, and a small amount of dark, insoluble material is removed by gravity filtration. The residue is washed two times with pentane (50 ml. total), and the combined filtrate is concentrated with a rotary evaporator, yielding 27–29 g. (90–97%) of nearly pure (Note 3) imidate **1.**

B. *3,7-Dimethyl-3-trichloroacetamido-1,6-octadiene* (**2**). A 500-ml., round-bottomed flask equipped with a condenser, a magnetic stirring bar, and a calcium chloride drying tube is charged with imidate **1** and 300 ml. of xylene. The solution is refluxed for 8 hours (Note 4). After cooling to room temperature the dark xylene solution is filtered through a short column (4.5 cm. in diameter) packed with silica gel (70 g.) and toluene. The column is eluted with an additional 250 ml. of toluene, and the combined light yellow eluant is concentrated with a rotary evaporator. Vacuum distillation through a 15-cm. Vigreux column yields 20–22 g. (67–74% for the two steps) of octadiene **2** as a colorless liquid, b.p. 94–97° (0.03 mm.) (Note 5).

C. *3,7-Dimethyl-1,6-octadien-3-amine* (**3**). A 500-ml., round-bottomed flask equipped with a magnetic stirring bar, a condenser, and a nitrogen inlet tube is charged with 9.0 g. (0.030 mole) of octadiene 2, 160 ml. of 95% ethanol, and 150 ml. of aqueous 6 *N* sodium hydroxide. The air is replaced with nitrogen (Note 6), and the solution is stirred at room temperature for 40 hours (Note 7). Ether (300 ml.) is added, the organic layer is separated, and the aqueous layer is washed twice with 50 ml. of ether. After drying over anhydrous potassium carbonate and filtration, the organic extracts are concentrated with a rotary evaporator, affording a white, semisolid residue, which is extracted four times with 50 ml. of boiling hexane. The extract is concentrated with a rotary evaporator, and the residual yellow liquid is distilled under reduced pressure using a short-path apparatus, yielding 2.99–3.45 g. (65–75%) of amine **3**, b.p. 58–61° (2.6 mm.) (Note 8) and (Note 9).

2. Notes

1. The reagents used in this procedure were obtained from the following sources: geraniol (99+%), Aldrich Chemical Company, Inc.; sodium hydride (58% dispersion in mineral oil), Alfa Products, Division of the Ventron Corporation; trichloroacetonitrile, Aldrich Chemical Company, Inc.; xylene (a mixture of isomers, b.p. 137–144°), Mallinckrodt Chemical Works; anhydrous ether, Mallinckrodt Chemical Works; Silica Gel (Grade 62), Grace Davidson Chemical. The reagents used by the checkers were obtained from the following sources: geraniol (98.7%), sodium hydride (58% dispersion in mineral oil), trichloroacetonitrile, and xylene (a mixture of isomers, b.p. 137–143°), Fluka A G, Chemische Fabrik, Buchs, Switzerland; Silica gel (70–230 mesh ASTM), E. Merck A G, Darmstadt, Germany.
2. For secondary or tertiary alcohols, the yields are improved by adding the alcohol–alkoxide solution dropwise to a solution of trichloroacetonitrile and ether at 0°.
3. The crude imidate **1** is sufficiently pure (checked by ^{1}H NMR) for most purposes and can be used in the next step without further purification. IR (neat) cm^{-1}: 3340

weak (N-H), 1660 strong (C=N); ^{1}H NMR (CCl_4), δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 1.58 (s, 3H, CH_3), 1.66 (s, 3H, CH_3), 1.73 (s, 3H, CH_3), 4.77 (d, *J* = 7, 2H, H_1), 5.1 (broad s, 1H, H_6), 5.5 (approx. t, *J* = 7, 1H, H_2), 8.3 (broad s, 1H, N*H*). The crude imidate **1** may be distilled rapidly through a short Vigreux column to give 24–28 g. (80–93%) of distilled product, b.p. 109–111° (0.1 mm.). However, the checkers found by ^{1}H NMR analysis that this product already contains substantial amounts of octadiene **2** formed by thermal rearrangement during distillation.

4. The reaction can be conveniently monitored in the IR by observing the decrease in the C=N stretching absorption at 1660 cm.$^{-1}$ or by TLC [silica, developed with hexane–ethyl acetate (9 : 1) or (4 : 1)].

5. The octadiene **2** appears pure by ^{1}H NMR and elemental analysis. A TLC [silica, developed with hexane–ethyl acetate (4 : 1), visualized with 5% ceric ammonium nitrate in 20% sulfuric acid and heating] shows a major spot at R_f = 0.4 and a very small impurity at 0.7. The trace impurity may be removed by crystallization from hexane at –78°. The checkers found that a GC (2% Silicone OV-17 on Gaschrom Q., 80–100 mesh, 200 × 0.22 cm., 120°) showed one major peak (97.0–97.2%) at a relative retention value of 1.00 (17.3 minutes, nitrogen, 30 ml. per minute), and a minor peak at 0.94 (<3%). The octadiene **2** has the following spectral properties: IR (neat) cm.$^{-1}$: 3423 and 3355 weak (N-H), 1722 strong (C=O), 1504 strong (CO-NH-, amide II band), 983 weak and 915 medium ($CH=CH_2$); ^{1}H NMR (CCl_4), δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 1.49 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 1.67 (s, 3H, CH_3), 4.9–5.3 (m, 3H, H_1 and H_6), 5.96 (approx. d of d, *J* = 9.5 and 18.5, 1H, H_2), 6.6 (broad s, 1H, N*H*); ^{13}C NMR (acetone-d_6), δ (assignment): 159.8 (*C*=O), 141.1 (C_2), 132.4 (C_7), 123.4 (C_6), 113.2 (C_1), 93.3 (*C*Cl_3), 58.7 (C_3), 38.8 (C_4), 25.7 (*C*H_3), 23.9 (*C*H_3), 22.5 (C_5), 17.5 (*C*H_3).

6. The apparatus described in *Org. Synth.*, **Coll. Vol. 4**, 132 (1963) was used to maintain a nitrogen atmosphere.

7. The reaction time may be cut to less than 1 hour by running the reaction at reflux, but the yield is 5–10% lower. The checkers found that under these conditions the weight yield of the distilled product was 67–70%. However, GC (3% Silicone GE-SE-30 on Gaschrom Q, 80–100 mesh, 200 × 0.22 cm., 60°) showed that the product contained substantial amounts (19–23%) of an unidentified by-product having a relative retention value of 1.22 (nitrogen, 30 ml. per minute) and a minor peak at 0.96 (<2%). The checkers also found that the reaction can be conveniently monitored by TLC [silica, hexane–ethyl acetate (4 : 1)].

8. The checkers found that the crude amine **3** (linalylamine) is more conveniently distilled at a pressure of 11–12 mm.

9. A GC (10% Carbowax 20 M–2% KOH on Chromosorb W, AW, 80–100 mesh, 180 × 0.3 cm., 90°) showed one major peak (99%) at a relative retention value of 1.00 (3.5 minutes, nitrogen, 50 ml. per minute), and a minor peak at 1.1 (<1%). Temperature programming to 200° detected the presence of several higher-boiling trace impurities (<1%). The checkers found that a GC (3% Silicone GE-SE-30 on Gaschrom Q, 80–100 mesh, 200 × 0.22 cm., 60°) showed one major peak (97.9–98.4%) at a relative retention value of 1.00 (11.8 minutes, nitrogen, 30 ml. per minute), and a minor peak at 0.96 (<2.1%). IR (neat) cm.$^{-1}$: 3345 and 3301 weak (N-H), 996 and 912 medium ($CH=CH_2$); ^{1}H NMR (CCl_4), δ (multiplicity, coupling constant *J* in Hz., number of

protons, assignment): 1.08 (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 1.63 (s, 3H, CH_3), 4.7–5.2 (m, 3H, H_1 and H_6), 5.84 (approx. d of d, J = 10.1 and 17.8, 1H, H_2).

3. Discussion

This procedure illustrates a general method for the preparation of rearranged allylic amines from allylic alcohols.[2,3] The method is experimentally simple and has been used to prepare a variety of allylic *n*-, *sec*-, and *tert*-carbonyl amines, as illustrated in Table I. The only limitation encountered so far is a competing ionic elimination reaction which becomes important for trichloroacetimidic esters of 3-substituted-2-cyclohexenols.[3,4] The rearrangement is formulated as a concerted [3,3]-sigmatropic rearrangement on the basis of its stereo- and regiospecificity[3,5] which are similar to those observed in related [3,3]-sigmatropic processes.[6] In certain cases the allylic imidate rearrangement may be accomplished at or below room temperature by the addition of catalytic amounts of mercury (II) salts.[2,3]

TABLE I
CONVERSION OF ALLYLIC ALCOHOLS INTO REARRANGED TRICHLOROACETAMIDES[3]

Alcohol	Trichloroacetamide Product	Overall Isolated Yield (%)
(*E*)-2-Hexen-1-ol	3-Trichloroacetamido-1-hexene	72
Cinnamyl alcohol	3-Phenyl-3-trichloroacetamido-1-propene	76
1-Hepten-3-ol	(*E*)-1-Trichloroacetamido-2-heptene	74
2-Cyclohexen-1-ol	3-Trichloroacetamido-1-cyclohexene	61
Linalool	3,7-Dimethyl-1-trichloroacetamido-2,6-octadiene[a]	83
3,5,5-Trimethyl-2-cyclohexen-1-ol	3,5,5-Trimethyl-3-trichloroacetamido-1-cyclohexene	10–43
3-(4,4-Ethylenedioxybutyl)-2-cyclohexen-1-ol	3-(4,4-Ethylenedioxybutyl)-3-trichloroacetamido-1-cyclohexene	20

a A mixture of *E* and *Z* isomers.

The experimental procedure for the addition of an alcohol to trichloroacetonitrile, a modification of the procedure of Cramer,[7] appears to be totally general. For hindered secondary or tertiary alcohols it is more convenient to form the catalytic alkoxide with

potassium hydride, and it is essential that the alcohol–alkoxide solution be added to (inverse addition) a solution of trichloroacetonitrile in ethyl ether at 0°.[3] The thermal rearrangement of allylic imidates was first reported by Mumm and Möller[8] in 1937, and has been noted in scattered reports since that time.[9] In these cases the imidates were not available by a general route (as is the case for trichloroacetimidates), and as a result this rearrangement had not become a generally useful synthetic method. Alternative methods for the allylic transposition of oxygen and nitrogen functions include the thermolysis of allylic sulfamate esters,[10] phenylurethanes,[11] oxime *O*-allyl ethers,[12] and *N*-chlorosulfonylurethanes,[13] as well as the S_N2' reaction of certain allylic alcohol esters with amines.[14] These procedures are much less attractive than the method reported here, usually affording mixtures of allylic isomers.[10,11,12,13,14] Other routes for the preparation of 3,7-dimethyl-1,6-octadien-3-amine have not, to our knowledge, been reported.

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

ethanol (64-17-5)

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether, ethyl ether, diethyl ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

oxygen (7782-44-7)

nitrogen (7727-37-9)

toluene (108-88-3)

xylene (106-42-3)

Pentane (109-66-0)

trichloroacetonitrile (545-06-2)

cinnamyl alcohol (104-54-1)

sodium hydride (7646-69-7)

hexane (110-54-3)

geraniol (106-24-1)

2-cyclohexen-1-ol

3,7-DIMETHYL-1,6-OCTADIEN-3-AMINE, 1,6-Octadien-3-amine, 3,7-dimethyl-, linalylamine (59875-02-4)

ceric ammonium nitrate

3-Trichloroacetamido-1-hexene

3-Phenyl-3-trichloroacetamido-1-propene

1-Hepten-3-ol (4938-52-7)

3-Trichloroacetamido-1-cyclohexene

Linalool (78-70-6)

3,5,5-Trimethyl-2-cyclohexen-1-ol

3,5,5-Trimethyl-3-trichloroacetamido-1-cyclohexene

3-(4,4-Ethylenedioxybutyl)-2-cyclohexen-1-ol

3-(4,4-Ethylenedioxybutyl)-3-trichloroacetamido-1-cyclohexene

potassium hydride (7693-26-7)

(E)-2-Hexen-1-ol (928-95-0)

Geraniol trichloroacetimidate (51479-75-5)

(E)-1-Trichloroacetamido-2-heptene

3,7-Dimethyl-3-trichloroacetamido-1,6-octadiene (51479-78-8)

3,7-Dimethyl-1-trichloroacetamido-2,6-octadiene

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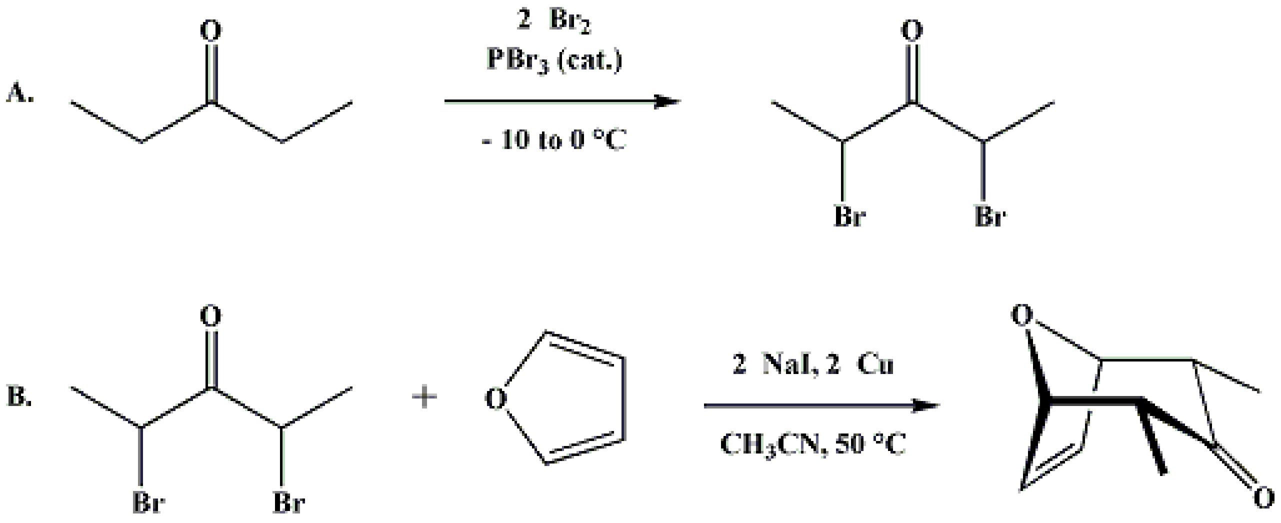
Organic Syntheses, CV 6, 512

BICYCLIC KETONES FOR THE SYNTHESIS OF TROPINOIDS: 2α,4α-DIMETHYL-8-OXABICYCLO[3.2.1] OCT-6-EN-3-ONE

[8-Oxabicyclo[3.2.1]oct-6-en-3-one, 2α,4α-dimethyl-]



Submitted by M. R. Ashcroft and H. M. R. Hoffmann[1].
Checked by D. M. Lokensgard and O. L. Chapman.

1. Procedure

Caution! This reaction should be carried out in an efficient hood. 2,4-Dibromo-3-pentanone is a potent lachrymator and a readily absorbed skin irritant. Contact with the skin produces a sensation of sunburn and should be treated immediately by washing with a soap solution, followed by washing with sodium hydrogen carbonate solution.

A. *2,4-Dibromo-3-pentanone* (**1**). A three-necked, 250-ml. flask is fitted with a stirrer, a dropping funnel, and a condenser protected by a calcium chloride drying tube. Bromine (160 g., 1.00 mole) is added rapidly to a stirred solution of 45 g. (0.52 mole) of 3-pentanone (Note 1) and 1 ml. of phosphorus tribromide maintained between −10° and 0° with an acetone–dry ice bath in an efficient hood. Toward the end of the reaction very large amounts of hydrogen bromide are evolved, and the rate of addition must be controlled to allow the hood to exhaust the gas. Alternatively, a gas trap may be used. Depending on the efficiency of the hood, the addition should take 20–40 minutes. The flask is then evacuated with a water pump, removing dissolved hydrogen bromide, and the reaction mixture is immediately fractionally distilled through a 40-cm. column packed with glass helices (or, more quickly, with a Dufton column)[2] under reduced pressure. The dibromoketone **1**, a mixture of *dl*- and *meso*-isomers,[3] distills at 67–82° (10 mm.), and 91 g. (72%) of product is collected as a colorless liquid (Note 2).

B. *2α,4α-Dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one* (**2**). A 1-l., three-necked, round-bottomed flask is fitted with a 100-ml. dropping funnel having a nitrogen inlet tube, a magnetic

stirrer, a thermometer, and an efficient double-surface condenser carrying a nitrogen outlet tube connected to a bubbler, and placed on a combined hotplate–magnetic stirring unit in a heat-resistant glass dish, acting as a water bath. Dry acetonitrile (200 ml.) (Note 3) is introduced into the flask, followed by 90 g. (0.60 mole) of dried powdered sodium iodide (Note 4), with vigorous stirring under a slow stream of nitrogen. When the stirring bar rotates steadily, 20 g. (0.31 g.-atom) of powdered copper bronze (Note 5) is added, followed by 28 g. (30 ml., 0.41 mole) of freshly-distilled furan (Note 6). The dropping funnel is then charged with a solution of 24.4 g. (0.100 mole) of dibromoketone 1 in 50 ml. of dry acetonitrile, which is rapidly added to the stirred reaction mixture (Note 7). On addition of dibromoketone **1**, the temperature rises to 45–50°, and a characteristic oatmeal-colored precipitate forms. After about 2 hours the temperature begins to drop, and the reaction is maintained at 50–60° with the water bath for a total reaction time of 4 hours (Note 8).

The flask is cooled to 0° with crushed ice (Note 9), and 150 ml. of dichloromethane is added with stirring. The reaction mixture is poured into a 2-l. beaker containing 500 ml. of water and 500 ml. of crushed ice; material remaining in the flask is rinsed into the beaker with 10 ml. of dichloromethane. The mixture is stirred thoroughly, further salts being precipitated, until the ice just melts, and filtered into a cooled filter flask under reduced pressure through a sintered or Büchner funnel and a kieselguhr filter-aid cake (Note 10). The beaker and filter cake are washed with 50 ml. of dichloromethane, and the clear combined filtrate is transferred to a 2-l. separatory funnel while still cold (Note 11).

The mixture is shaken vigorously, the lower layer is separated and stored in ice, and the aqueous layer is extracted with two, 50-ml. portions of dichloromethane. The combined, organic extracts are shaken with 100 ml. of ice-cold, concentrated aqueous ammonia (35% w/w) filtered through a filter-aid cake, and separated (Note 12). The extraction and filtration are repeated with fresh ammonia solution using the same filter (Note 13). The filter is washed with 50 ml. of dichloromethane, and the organic layer is separated and dried over anhydrous magnesium sulfate. The dried solution is filtered, the filter is washed with 50 ml. of dichloromethane, and the solvent is removed on a rotary evaporator at 30°. The flask containing the residual oil is cooled to 0° before exposure to air (Note 14).

The light-yellow oil is dissolved in 60 ml. of 30% anhydrous diethyl ether in pentane and treated with 2 g. of anhydrous sodium sulfate and 0.5 g. of decolorizing carbon. The mixture is swirled for a few minutes, allowed to settle, and filtered by gravity through three sheets of fine filter paper into a 100-ml., round-bottomed flask with a 14/20 joint. The filter is washed with 10 ml. of pentane, and the flask is sealed by wiring on a 14-mm. serum cap. The flask is placed on a cork ring, lowered into an insulated container (large Dewar bottle, styrofoam box, etc.) half filled with dry ice, and cooled slowly to −78°. When recrystallization is complete, a nitrogen supply is connected to the flask *via* a syringe needle; the supernatant liquid is then withdrawn by syringe and replaced with 50 ml. of pentane, previously cooled to −78°.

The flask is swirled, washing the crystals (Note 15), and the pentane is withdrawn. The flask is connected to a vacuum (water pump) *via* the nitrogen inlet and warmed to room temperature. The crude cycloadduct **2** (6.1–7.3 g., 40–48%) is isolated as colorless needles, m.p. 43.5–45°, from the first recrystallization (Note 16). Pure 2α,4α-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (**2**) can be obtained by recrystallization from pentane at −78° with minimal loss, m.p. 45–46° (Note 17).

2. Notes

1. 3-Pentanone is available from Aldrich Chemical Company, Inc.
2. A slight coloration has no effect on the yield of the subsequent reactions. The dibromoketone **1** should be stored cold in a well-stoppered bottle (dark) under nitrogen and is best handled cold to minimize spread of lachrymator vapors.
3. Commercial acetonitrile from Hopkins and Williams (GPR grade, given analysis 0.1% water, 0.02% acid) was used. Further purification of the solvent had no effect on the yield. The checkers used MCB reagent grade acetonitrile, refluxed over and distilled from calcium hydride.
4. The sodium iodide was dried at 150° for at least 3 hours, cooled in a desiccator, and finely powdered in a mortar. Although the use of less sodium iodide (*e.g.*, 33 g., 0.22 mole) gives similar yields, the separation of the aqueous phase on extraction with dichloromethane and the following work-up are easier under the given conditions.
5. The copper bronze was supplied by BDH Chemicals Ltd. (Poole, England) as an extremely fine powder. The use of more granular electrolytic copper had no effect on the yield, but made magnetic stirring more difficult.
6. Commercial furan was refluxed over and distilled from calcium hydride and anhydrous potassium carbonate prior to use. Furan, b.p. 31°, is more volatile than diethyl ether, and precautions must be taken to minimize losses through evaporation.
7. Addition of dibromoketone **1** has been carried out all at once, slowly over a period of half an hour, and over 1 hour with no apparent change in yield.
8. Although a filtered sample of the reaction mixture analyzed by ^{1}H NMR ($CDCl_3$) shows no more dihaloketone after a reaction time of 2 hours (excess of furan was discernible), the reaction mixture must be heated for an additional 2 hours to destroy traces of dihaloketone which make the subsequent work-up and analytical TLC of the product mixture difficult. When the reaction was carried out with less sodium iodide (33 g., 0.22 mole), the presence of diiodoketone in the final product was noted by formation of an iodine color and rapid decomposition of the cycloadduct to a black solid; also, the pentane washings developed an iodine color on exposure to light.
9. Since the dihaloketones may induce the decomposition of the product, it is essential that the solution be cooled in ice before allowing entry of air. Otherwise, the oily cycloadduct becomes brown, and polymeric material has to be removed, before crystallization, by passage down a 2 × 5 cm. column of silica gel (impregnated with 12% silver nitrate solution and redried).
10. Filtration through Hopkins and Williams kieselguhr filter-aid cake speedily removes even colloidal copper halides and breaks up any emulsion.
11. If the temperature is allowed to rise above 0°, the cycloadduct decomposes and the yellow copper compound present liberates blue-green copper(**II**) salts which make the work-up difficult.
12. The checkers, using 15 ml. of acetonitrile instead of 10 ml. of dichloromethane for rinsing the reaction vessel, found that no solid formed and filtration was not necessary. In this case three extractions with ammonia solution are required before addition of more ammonia fails to produce a blue color.
13. Using the same filter ensures that the ammonia solution is saturated with halide salts, which aid final separation.
14. The oil is essentially pure cycloadduct 2, but owing to traces of impurity, crystallization may be difficult at 0°. Analytical TLC on alumina, using low-polarity solvents such as pentane or carbon tetrachloride, was not successful in the presence of

traces of dihaloketone, although it gave high resolution with related compounds. When dehalogenation is complete, however, the resolution is restored (see also (Note 9)).

15. If product **2** appears to be colored at this point, the pentane solution can simply be warmed to dissolve the crystals and cooled to recrystallize.

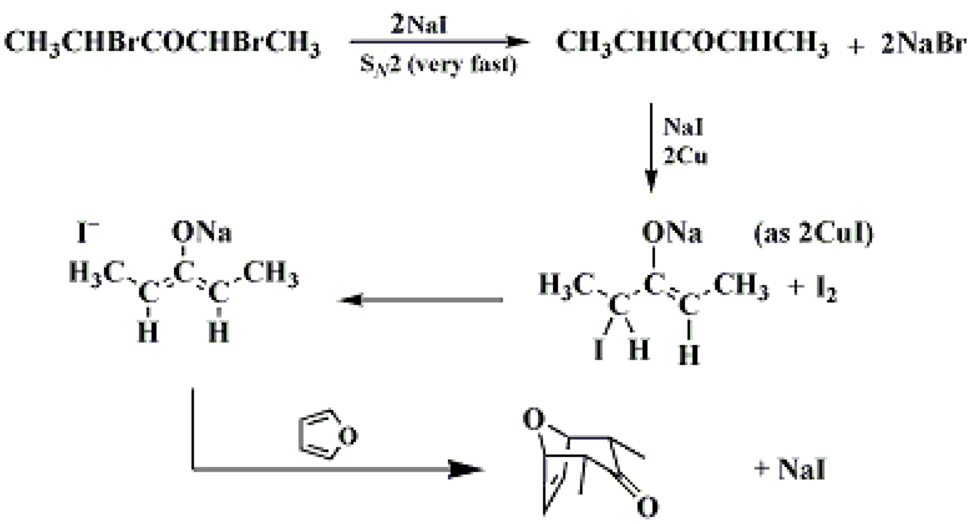
16. Approximately 0.4 g. of product **2** remaining in the supernatant solution can be recovered by repeated recrystallizations from the ether–pentane solution; however, the presence of 10 impurities (TLC) makes this rather impractical.

17. IR (CCl_4) $cm.^{-1}$: 1721 (very strong); ^1H NMR ($CDCl_3$), δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 0.98 (d, *J* = 7, 6H, 2CH_3), 2.8 (d of q, *J* = 5 and 7, 2H, C*H*COC*H*), 4.86 (d, *J* = 5, 2H, C*H*OC*H*), 6.35 (broad s, 2H, 2 olefinic *H*).[4]

3. Discussion

The reaction of 1,3-dibromo-1,3-diphenyl-2-propanone with sodium iodide in the presence of furan and cyclopentadiene, giving bridged seven-membered rings has been reported by Cookson,[5] who followed up earlier work by Fort.[6] Chidgey[7] [8] demonstrated that the reaction can be extended to simple dibromoketones such as **1** and improved by using metallic copper to remove molecular iodine liberated during the reaction. Mechanistically, the reaction seems to involve two very fast S_N2 displacements of bromide by iodide, as seen by the precipitation of sodium bromide. A subsequent slower nucleophilic attack of excess iodide ion on the positively polarized iodine of the diiodoketone is envisioned, yielding an allylic iodide which forms an allyl cation in a fairly facile S_N1 reaction. The allyl cation is trapped by furan, giving the oxygen-bridged seven-membered ring.[8] The secondary–tertiary dibromoketone, $CH_3CHBrCOCBr(CH_3)_2$, can also be used as an allyl cation precursor in this reaction, but the yields with the primary–tertiary dibromoketone, $CH_2BrCOCBr(CH_3)_2$, are less satisfactory. Zinc-induced cycloaddition works well,[9] in this instance, and also in the case of the ditertiary dibromoketone, $(CH_3)_2CBrCOCBr(CH_3)_2$, which fails to undergo the initial S_N2 displacement with sodium iodide. Hence, although the sodium iodide–copper procedure is probably less general than the zinc[4] and silver ion–promoted[10] cycloaddition, it is experimentally convenient and yields preferentially the thermodynamically more stable adduct *via* an allyl cation in a W-configuration and compact transition state.[8] The reaction involves inexpensive starting materials, proceeds under homogeneous conditions, and can be scaled-up readily.

The procedure described here has been used for the preparation of sensitive 6,7-dehydrotropinones in modest to good yields.[9] If in the present experiment furan is replaced by cyclopentadiene, an epimeric mixture of *cis*-diequatorial and *cis*-diaxial 2,4-dimethylbicyclo[3.2.1]oct-6-en-3-one is formed in almost 90% yield.[11] Instead of zinc or sodium iodide/copper, diiron nonacarbonyl may also be used as a reducing agent for dibromoketones.[12] Recently, 2α,4α-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (**2**) has been used as a precursor for the synthesis of (±)-nonactic acid, the building block of the macrotetrolide antibiotic nonactin.[13]



This preparation is referenced from:

- Org. Syn. 78, 212

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

copper bronze

Diiron nonacarbonyl

cis-diequatorial and cis-diaxial 2,4-dimethylbicyclo[3.2.1]oct-6-en-3-one

(±)-nonactic acid

potassium carbonate (584-08-7)

ammonia (7664-41-7)

ether, diethyl ether (60-29-7)

acetonitrile (75-05-8)

sodium hydrogen carbonate (144-55-8)

silver nitrate (7761-88-8)

hydrogen bromide (10035-10-6)

bromine (7726-95-6)

sodium bromide (7647-15-6)

sodium sulfate (7757-82-6)

phosphorus tribromide (7789-60-8)

carbon tetrachloride (56-23-5)

nitrogen (7727-37-9)

copper (7440-50-8)

iodine (7553-56-2)

decolorizing carbon (7782-42-5)

zinc (7440-66-6)

sodium iodide (7681-82-5)

Furan (110-00-9)

Pentane (109-66-0)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

3-pentanone (96-22-0)

CYCLOPENTADIENE (542-92-7)

calcium hydride (7789-78-8)

2α,4α-Dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one, 8-Oxabicyclo[3.2.1]oct-6-en-3-one, 2α,4α-dimethyl-

1,3-dibromo-1,3-diphenyl-2-propanone (958-79-2)

2,4-Dibromo-3-pentanone (815-60-1)

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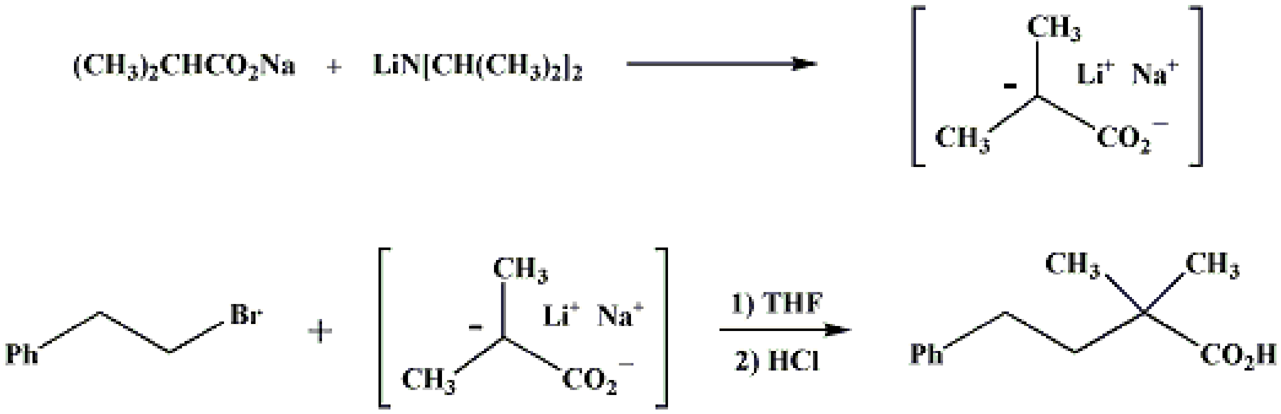
Organic Syntheses, *CV 6, 517*

2,2-DIMETHYL-4-PHENYLBUTYRIC ACID

[Benzenebutanoic acid, α,α-dimethyl-]



Submitted by P. L. Creger[1]
Checked by Paul Kalicky and Ronald Breslow.

1. Procedure

A 500-ml., three-necked flask is equipped with a mechanical stirrer and a two-necked adapter carrying a Friedrich condenser, and a thermometer which contacts the flask contents. The third neck of the flask carries a pressure-equalizing dropping funnel which is exchanged for a serum stopper as required. The condenser is attached to a suitable source of nitrogen. The reaction flask is placed in a heating mantle and charged with 7.75 g. (0.0767 mole) of diisopropylamine (Note 1), 3.68 g. (0.082 mole) of 54% sodium hydride in mineral oil (Note 2), and 75 ml. of tetrahydrofuran (Note 3). From the dropping funnel, 6.6 g. (0.075 mole) of isobutyric acid (Note 4) is added to the stirred mixture over 5 minutes. The internal temperature rises to 50–60° and hydrogen evolution is completed by heating the mixture to reflux for 15 minutes. After cooling to 0° with an externally applied ice–salt bath (Note 5), 52 ml. of a standard solution of *n*-butyllithium in heptane (1.45 mmole/ml.; 0.075 mole) (Note 6) is added through the stopper by injection (Note 7) at a temperature below 10°. The ice bath is retained for 15 minutes before the mixture is heated to 30–35° for 30 minutes to complete the metalation. The resulting turbid solution is cooled, and 13.9 g. (0.0751 mole) of (2-bromoethyl)benzene (Note 8) is added from the dropping funnel over 20 minutes at 0°. A colorless precipitate of sodium bromide begins to separate almost immediately. The ice bath is retained for 30 minutes, after which the mixture is heated to 30–35° for 1 hour.

At the conclusion of the reaction period, 100 ml. of water is added at a temperature below 15° (Note 9). The aqueous layer is separated and the reaction flask and organic layer are washed with a mixture of 50 ml. of water and 75 ml. of diethyl ether. The aqueous layers are combined, back-extracted with 50 ml. of ether, and acidified to Congo red with 6 *N* hydrochloric acid. The product is extracted with two 75-ml. portions of ether, washed with 50 ml. of saturated sodium chloride, and dried over anhydrous magnesium sulfate, and the solvent is evaporated. The remaining traces of solvent may be removed in a rotary evaporator, yielding 12–12.8 g. (83–90%) of crude 2,2-dimethyl-4-phenylbutyric acid, m.p. 89–94°, which is suitable for many purposes. Recrystallization from 75 ml. of hexane at room temperature followed by refrigeration

yields 8.4–9.7 g. (58–67%) of product as colorless needles, m.p. 98–99.5° (Note 10). Recrystallization of the filtrate residue from 20 ml. of hexane yields a small second crop, 1.2–1.6 g. (8–11%), m.p. 95–97°. The combined yield totals 10–11 g. (70–76%) (Note 11).

2. Notes

1. Diisopropylamine supplied by Matheson, Coleman and Bell was distilled from calcium hydride, b.p. 83–85°.
2. Sodium hydride supplied by Ventron Corp., is satisfactory. It is unnecessary to remove the mineral oil.
3. Tetrahydrofuran was obtained in drum quantities from E. I. duPont de Nemours Co., and transferred under nitrogen pressure to 1-gallon containers for stock. This material could be used without special treatment. The quality of the tetrahydrofuran should be determined [*Org. Synth.*, **Coll. Vol. 5**, 976 (1973)] if there is no assurance of the absence of gross contamination. A small excess of sodium hydride was used in the reaction to remove traces of moisture which may have been introduced during measurement.
4. Isobutyric acid supplied by Matheson, Coleman and Bell is satisfactory.
5. A brisk nitrogen flow is required to exclude air when cooling.
6. *n*-Butyllithium in 1-mole serum cap bottles from Foote Mineral Co., was used. The less volatile hexane or heptane solutions were preferred.
7. The *n*-butyllithium solution was forced into a 100-ml. syringe through a 1-in., 19 gauge hypodermic needle by slightly pressurizing (to 1 p.s.i.) the storage bottle with nitrogen. Nitrogen was admitted through a second, 2-in., 20 gauge needle inserted at an upward angle through the stopper into the void space of the inclined bottle. The pressure in the bottle should be released and the bottle should be returned to an upright position before the syringe is withdrawn. This operation should be conducted behind a safety shield.
8. (2-Bromoethyl)benzene was used as supplied by Matheson, Coleman and Bell.
9. At the beginning, water should be added cautiously since a small quantity of unreacted sodium hydride is present.
10. The literature[2,3,4,5,6,7] reports m.p. 97–98°.
11. NMR analysis of the filtrate residue indicates that it is *ca.* 90% product. The submitters carried out the procedure on four times this scale, with mechanical stirring.

3. Discussion

2,2-Dimethyl-4-phenylbutyric acid has been prepared by Clemmensen reduction[2,3,4,5,6] or by hydriodic acid-phosphorus reduction[7] of 3-benzoyl-2,2-dimethylpropionic acid, and by catalytic reduction[6] of 2,2-dimethyl-4-phenyl-3-butenoic acid.

The preparation of 2,2-dimethyl-4-phenylbutyric acid is a specific example of a generally applicable procedure for alkylating dialkylacetic acids. The present procedure represents an improvement on one described earlier[8] in that one equivalent of *n*-butyllithium is required. Sufficient experience has been accumulated by the submitter over several years to recommend the present method as a possible alternative to the multistep Haller-Bauer sequence.[9] The procedure offers the obvious advantages of being short, avoiding use of blocking groups for the carboxyl group which must be removed later, and affording ease of workup while still providing preparative yields of product. The scale of the reaction can be increased to 1–2 moles with only a

moderate increase in the size of the equipment.

The same procedure has been used to monoalkylate alkylacetic acids[10] and may be used to selectively monoalkylate methylated benzoic acids.[11] The metalated intermediates generated from alkylacetic acids are generally less soluble in the reaction medium specified, and heterogeneous mixtures result. The physical state of the reaction mixture has no apparent effect on the success of the subsequent alkylation[10] so long as metalation is complete. Homogeneous solutions may be obtained at the expense of operational convenience by suitable changes in the cation used,[11,12] or by use of hexamethylphosphoric triamide as co-solvent.[12,13] For warning concerning hexamethylphosphoric triamide, see *Science*, **190**, 422 (1975).

Metalated carboxylic acids have been employed as intermediates in a broad range of synthetic applications. The early literature has been summarized,[14] contrasting prior experience with the present method for generating carboxylic acid dianions. Likewise, more recent applications have been reviewed.[15,16]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

ether, diethyl ether (60-29-7)

hydrogen (1333-74-0)

sodium chloride (7647-14-5)

sodium bromide (7647-15-6)

nitrogen (7727-37-9)

magnesium sulfate (7487-88-9)

(2-bromoethyl)benzene (103-63-9)

n-butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

heptane (142-82-5)

sodium hydride (7646-69-7)

isobutyric acid (79-31-2)

hexane (110-54-3)

calcium hydride (7789-78-8)

hexamethylphosphoric triamide (680-31-9)

diisopropylamine (108-18-9)

2,2-Dimethyl-4-phenylbutyric acid, Benzenebutanoic acid, α,α-dimethyl- (4374-44-1)

hydriodic acid-phosphorus

3-benzoyl-2,2-dimethylpropionic acid

2,2-dimethyl-4-phenyl-3-butenoic acid

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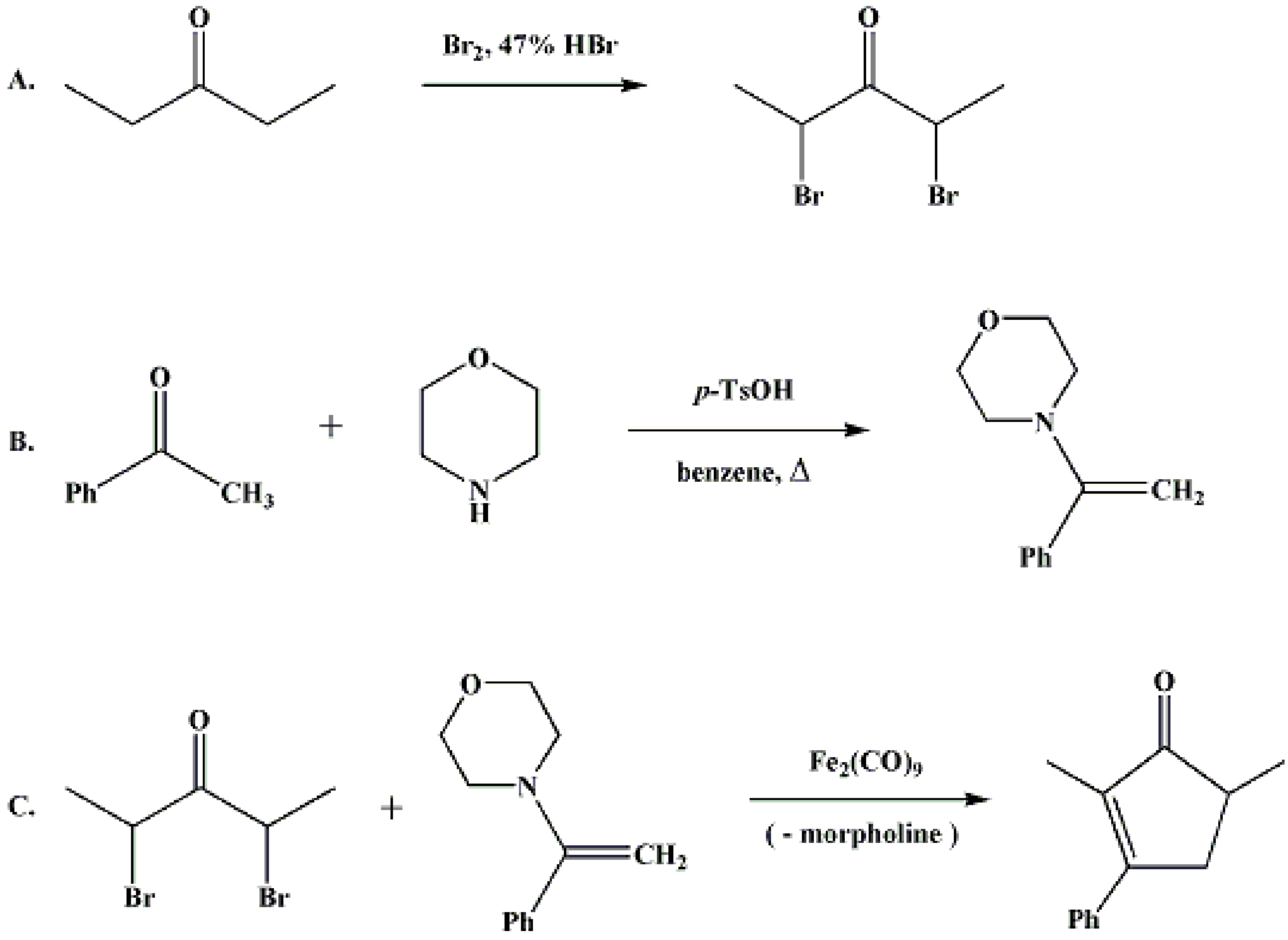
CYCLOPENTENONES FROM α,α'-DIBROMOKETONES AND ENAMINES: 2,5-DIMETHYL-3-PHENYL-2-CYCLOPENTEN-1-ONE

[2-Cyclopenten-1-one, 2,5-dimethyl-3-phenyl-]



Submitted by R. Noyori[1], K. Yokoyama, and Y. Hayakawa.
Checked by Michael J. Haire and William A. Sheppard.

1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required. The reaction in Part C should be carried out in a well-ventilated hood because iron carbonyls are highly toxic.

A. *2,4-Dibromo-3-pentanone* **(1)**. A 300-ml., three-necked, round-bottomed flask equipped with a magnetic stirrer, a thermometer, and a 125-ml., pressure-equalizing dropping funnel, connected to a trap for absorbing hydrogen bromide evolved during the reaction (Note 1), is charged with 43.0 g. (0.500 mole) of diethyl ketone and 100 ml. of 47% hydrobromic acid. The dropping funnel is charged with 160 g. (1.00 mole) of bromine, which is added with stirring over a 1-hour period, causing the temperature of the reaction mixture to increase to 50–60°. After addition is complete, stirring is continued for an additional 10 minutes, before 100 ml. of water is added to the reaction

mixture. The separated heavy organic layer is washed with 30 ml. of saturated aqueous sodium bisulfite. The brownish organic solution is dried over calcium chloride and distilled under reduced pressure through a 15-cm. vacuum-jacketed Vigreux column, yielding 85.2–92.5 g. (70–76%) of 2,4-dibromo-3-pentanone **(1)** (Note 2), b.p. 51–57° (3 mm.), as a slightly yellow liquid.

B. *α-Morpholinostyrene* **(2)**. A mixture of 75.0 g. (0.625 mole) of acetophenone, 81.0 g. (0.930 mole) of morpholine (Note 3), 200 mg. of *p*-toluenesulfonic acid, and 250 ml. of benzene is placed in a 500-ml., round-bottomed flask equipped with a water separator (Note 4), under a reflux condenser protected by a calcium chloride drying tube. Separation of water begins with reflux and is complete after 180 hours. After the mixture is cooled to room temperature, 200 mg. of sodium ethoxide is added to remove *p*-toluenesulfonic acid, and the mixture is concentrated with a vacuum rotary evaporator (50°, 80–100 mm.). The crude oily product is distilled under reduced pressure through a 15-cm. vacuum-jacketed Vigreux column. After 40–50 ml. of a mixture of morpholine and acetophenone is recovered as a forerun at 40–90° (20 mm.), 67.5–75.4 g. (57–64%) of α-morpholinostyrene is collected as a pale yellow liquid, b.p. 85–90° (0.03 mm.) (Note 5).

C. *2,5-Dimethyl-3-phenyl-2-cyclopenten-1-one* **(3)**. A 1-l., three-necked, round-bottomed flask equipped with a sealed mechanical stirrer, a rubber septum, and a bubbler filled with liquid paraffin is charged with 40.0 g. (0.110 mole) of diiron nonacarbonyl (Note 6) and 250 ml. of dry benzene (Note 7). The system is flushed with nitrogen, and 56.8 g. (0.300 mole) of α-morpholinostyrene (Note 8) and 24.4 g. (0.100 mole) of 2,4-dibromo-3-pentanone **(1)** are injected by syringe through the rubber septum. The flask is immersed in a 32° bath, and the reaction mixture is stirred under a nitrogen atmosphere (Note 9). After 20 hours 230 g. of silica gel (Note 10) and 100 ml. of benzene are added. The resulting slurry is stirred at 32° for an additional 2.5 hours (Note 11). The whole mixture is poured onto a silica gel pad (Note 10) and (Note 12) with the aid of 200 ml. of diethyl ether, and the pad is washed with 1 l. of ether (Note 13) and (Note 14). The combined organic solutions are concentrated on a vacuum rotary evaporator (Note 13), giving 35–45 g. of the desired cyclopentenone **3**, a brown oil contaminated by acetophenone formed by decomposition of the excess enamine. The oil is distilled under reduced pressure with a short-path distillation apparatus (Note 15). The forerun of 20–25 g., b.p. 35–50° (0.1 mm.), is recovered acetophenone. At 100–105° (0.02 mm.), 12.0–12.4 g. [64–67% yield (Note 14)] of cyclopentenone **3** is obtained as a pale yellow oil, which crystallizes on cooling with ice water. Recrystallization from hexane gives an analytical sample as colorless needles, m.p. 57–59° (Note 16).

2. Notes

1. See Figure 7 in *Org. Synth.*, **Coll. Vol. 1**, 95 (1941).
2. The submitter reported a yield of 116 g. (95%). Care should be taken to prevent the dibromoketone from coming into contact with the skin; allergic reactions have been observed in several cases. Also, the checkers found the crude product to have lachrymatory properties. Immediate use after distillation is recommended if high yield is to be obtained in the next step.
3. An excess of morpholine is required because a considerable amount is lost with the water that separates during the reaction.
4. See Figure 12 in *Org. Synth.*, **Coll. Vol. 3**, 381 (1955).
5. The distilled product is 97% pure and contaminated with 3% acetophenone (NMR analysis). Since the enamine is easily hydrolyzed and deteriorates on long standing, use of a freshly-distilled material is recommended. The checkers found that α-morpholinostyrene contaminated with 20% acetophenone could be used for the next step without any significant reduction in yield.
6. Diiron nonacarbonyl is available from Alpha Inorganics, Inc., or Strem Chemicals, Inc. The

submitters made the complex through photolysis of iron pentacarbonyl by the method of King.[2] Procedures for preparation are also given by Braye and Hübel,[3] who use the name diiron enneacarbonyl.

7. The submitters used benzene distilled from lithium aluminum hydride, but the checkers used ACS-grade benzene as well as benzene distilled from lithium aluminum hydride, with no significant change in yield.

8. The submitters obtained a markedly lower yield of product when an excess of the enamine was not used.

9. Evolution of carbon monoxide begins a few minutes after mixing the starting materials, continuing for *ca.* 3 hours. Cessation of gas evolution does not necessarily mean completion of the cyclocoupling reaction.

10. The submitters used Merck Kieselgel 60 (70–230 mesh ASTM).

11. This procedure is for elimination of morpholine from the labile primary product, 2,5-dimethyl-3-morpholino-3-phenylcyclopentanone.

12. The 150 g. of silica gel is packed in a 13 (diameter) × 12-cm. (length) glass filter.

13. The filter cake and the distillate must be treated with nitric acid to decompose the contaminates of iron carbonyl complexes. This treatment should be done very carefully in a well-ventilated hood, because carbon monoxide is evolved vigorously.

14. The submitters reported a yield of 14.8–15.6 g. (80–84%) based on the starting dibromide. The submitters report that the cyclopentenone product seems to absorb on silica gel, and 1 l. of ether is required to attain complete extraction. A smaller quantity of ether wash was used by the checkers. ^{1}H NMR analysis of the crude mixture before distillation indicated the formation of the cyclopentenone **3** in 83–87% yield.

15. See Figure 2 in *Org. Synth.*, **Coll. Vol. 6**, 436 (1988).

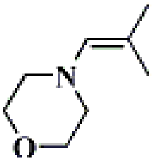
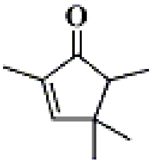
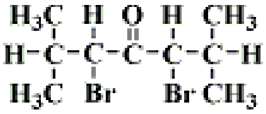
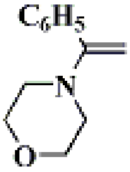
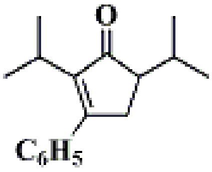
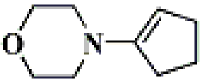
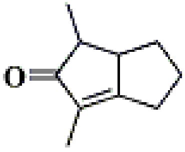
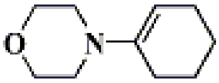
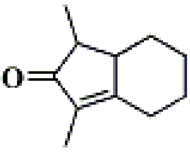
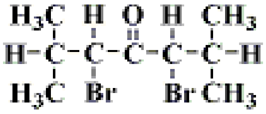
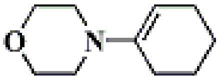
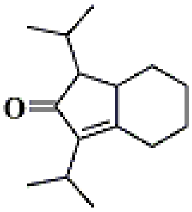
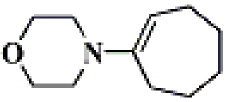
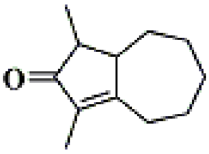
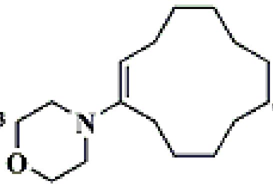
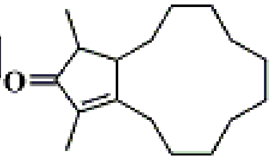
16. The spectral properties of pure product are as follows: IR (CCl_4) cm^{-1}: 1696 (conjugated C=O) and 1626 (conjugated C=C); UV (C_2H_5OH) nm. max. (ε): 220 (5220) and 279 (11,200); ^{1}H NMR (CCl_4), δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 1.22 (d, *J* = 7.0, 3H, $CHCH_3$), 1.91 (t, *J* = 2.0, 3H, vinyl CH_3), 2.1–2.7 (m, 2H, $CHCH_3$ and a methylene *H cis* to CH_3), 3.14 (d of d of q, *J* = 18, 7.5, and 2.0, 1H, methylene *H trans* to CH_3), and 7.38 (m, 5H, C_6H_5).

3. Discussion

The starting materials, 2,4-dibromo-3-pentanone[4] and α-morpholinostyrene,[5] have been prepared in satisfactory yields by modifying known procedures. The procedure for the 3 + 2 5 cyclocoupling reaction is essentially that described originally by the submitters.[6] The main advantages of this procedure are the directness, the availability of starting materials, and the wide generality for preparation of 2,5-dialkyl-2-cyclopenten-1-ones, as shown in Table I. Enamines derived from aldehydes, open-chain ketones, and cyclic ketones can be employed. The method has been extended to the synthesis of spiro[4.*n*]alkenones and certain azulene derivatives.[6] A reaction mechanism for the cyclocoupling reaction has been advanced.[7] The reactive oxyallyl intermediates generated from dibromoketones and iron carbonyls can be trapped efficiently by enamines,[6] aromatic olefins,[8] 1,3-dienes,[9,10] furans,[10,11] carboxamides,[12] and alkyl 1*H*-pyrrole-1-carboxylates.[13] Intramolecular trapping of the reactive species by olefin or furan has also been achieved.[14] At present, dibromides of methyl ketones cannot be used as starting materials except in intramolecular cyclocoupling reactions. However, polybromoketones, including α,α,α',α'-tetrabromoacetone, serve as a precursors of the reactive species in certain cases, and the coupling reactions have been applied to various naturally occurring products.[14,15,16,17,18,19]

TABLE I

Iron Carbonyl-Promoted Cyclopentenone Synthesis[a]

Dibromide	Enamine	Product[b]	Yield (%)[c]
			79
			72
			74
			100
			73
			100
			90

[a]Reference [6].

[b]A mixture of epimers, when possible, is obtained.

[c]Isolated yield based on starting dibromide.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

Diiron nonacarbonyl

α,α,α',α'-tetrabromoacetone

calcium chloride (10043-52-4)

Benzene (71-43-2)

ether, diethyl ether (60-29-7)

carbon monoxide (630-08-0)

nitric acid (7697-37-2)

HYDROBROMIC ACID, hydrogen bromide (10035-10-6)

bromine (7726-95-6)

nitrogen (7727-37-9)

sodium bisulfite (7631-90-5)

Acetophenone (98-86-2)

sodium ethoxide (141-52-6)

Furan (110-00-9)

diethyl ketone (96-22-0)

lithium aluminum hydride (16853-85-3)

morpholine (110-91-8)

hexane (110-54-3)

iron pentacarbonyl

p-toluenesulfonic acid (104-15-4)

2,5-Dimethyl-3-phenyl-2-cyclopenten-1-one, 2-Cyclopenten-1-one, 2,5-dimethyl-3-phenyl- (36461-43-5)

2,4-Dibromo-3-pentanone (815-60-1)

α-morpholinostyrene (7196-01-2)

2,5-dimethyl-3-morpholino-3-phenylcyclopentanone

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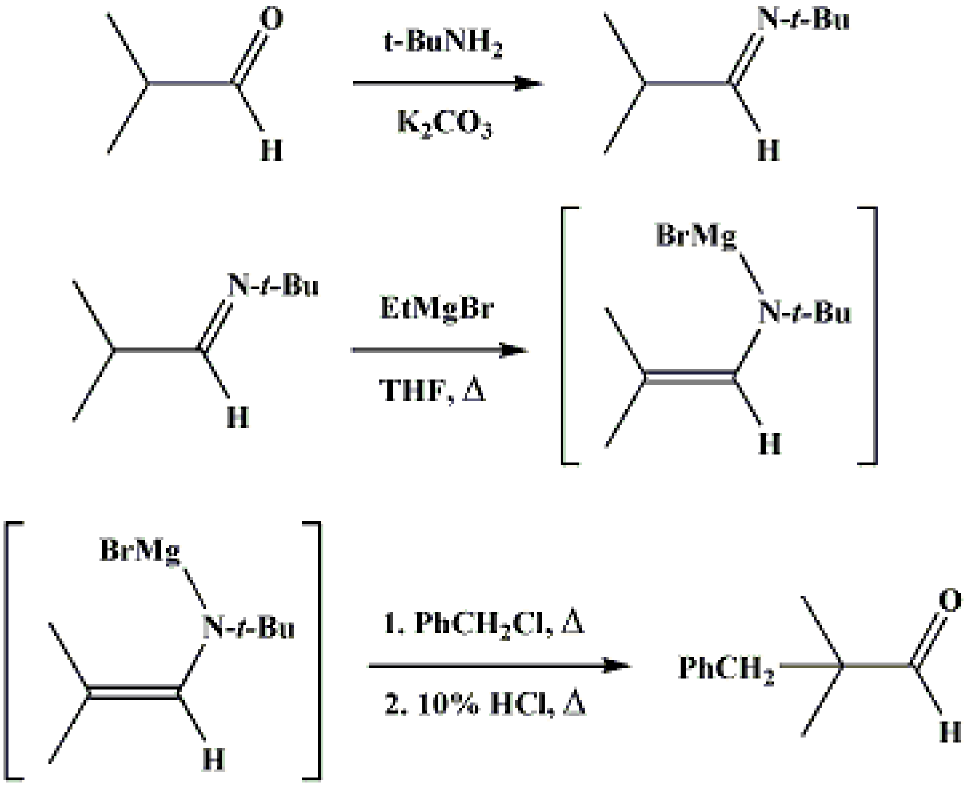
Organic Syntheses, CV 6, 526

ALKYLATIONS OF ALDEHYDES *via* REACTION OF THE MAGNESIOENAMINE SALT OF AN ALDEHYDE: 2,2-DIMETHYL-3-PHENYLPROPIONALDEHYDE

[Benzenepropanal, α,α-dimethyl-]



Submitted by G. Stork[1] and S. R. Dowd[2].
Checked by D. R. Williams and G. Büchi.

1. Procedure

A. N-(2-*Methylpropylidene*)-tert-*butylamine*. A 100-ml., three-necked, round-bottom flask equipped with a condenser, a nitrogen inlet tube, a 50-ml. dropping funnel, and a magnetic stirring bar is evacuated through a mercury bubbler, flamed dry, and flushed with nitrogen three times. The flask is charged with 36.0 g. (0.500 mole) of *tert*-butylamine (Note 1), and 36.5 g. (0.501 mole) of isobutyraldehyde (Note 1) is placed in the dropping funnel. Half of the isobutyraldehyde is added slowly through the dropping funnel before the remaining half-volume is added rapidly. The milky solution is allowed to stand at room temperature for 1 hour; the water layer is then pipeted out, and excess anhydrous potassium carbonate is added. Filtration and distillation of this reaction mixture gives 32.0 g. (50%) of *N*-(2-methylpropylidene)-*tert*-butylamine, b.p. 50° (75 mm.) (Note 2).

B. *2,2-Dimethyl-3-Phenylpropionaldehyde*. A 100-ml., three-necked, round-bottom flask equipped with an ether condenser, a nitrogen inlet tube, a 50-ml. Herschberg dropping funnel, and a magnetic stirring bar is evacuated through a mercury bubbler, flamed dry, and flushed with nitrogen three times. The system is left under a slight positive pressure of nitrogen, and all the reactants are added under a stream of nitrogen. A solution of 0.05 mole of ethylmagnesium bromide in 37 ml. of tetrahydrofuran (Note 3) is placed in the flask. A solution of 6.35 g. (0.0567 mole) of *N*-(2-methylpropylidene)-*tert*-butylamine (Note 4) in 5 ml. of tetrahydrofuran (Note 5) is then added from the dropping funnel. The resulting mixture is refluxed for 12–14 hours until 1 mole-equivalent of gas has evolved (Note 6). The reaction mixture is cooled to room temperature; 6.30 g. (0.0498 mole) of benzyl chloride (Note 1) is added from the dropping funnel; and the solution is refluxed for 20 hours, at which time the pH is 9–10 (pHydrion paper). To the cooled solution, which contains a large amount of solid, is added 20–30 ml. of 10% hydrochloric acid. The clear, yellow-brown solution is then refluxed for 2 hours, cooled, saturated with solid sodium chloride, and extracted five times with diethyl ether. The organic extracts are washed once with 25 ml. of 5% hydrochloric acid, then repeatedly with brine until the washings are neutral. The organic layer is dried over anhydrous magnesium sulfate and filtered, and the solvent is removed at atmospheric pressure through a 12-in. Vigreux column fitted with a partial take-off head. Distillation of the residue (Note 7) through a 20-in. vacuum-jacketed fractionating column affords 5.1–5.4 g. (63–66%) of 2,2-dimethyl-3-phenylpropionaldehyde, b.p. 70–73° (1.5 mm.) (Note 8).

2. Notes

1. These reagents were obtained from Eastman Organic Chemicals, but not distilled prior to use.
2. The checkers found that the yield could be improved (37–38 g., 58–60%) if the reaction mixture was allowed to remain over anhydrous potassium carbonate for 8–12 hours.
3. Ethylmagnesium bromide was prepared in dry tetrahydrofuran and stored no longer than 1 week in a 250-ml. tube fitted with a 3-way vacuum stopcock and a dropping buret. The solution is decanted into the buret, and the correct volume is transferred to the reaction flask with positive nitrogen pressure. The tetrahydrofuran was purified by distillation from lithium aluminum hydride. See *Org. Synth.*, **Coll. Vol. 5**, 976 (1973), for warning regarding the purification of tetrahydrofuran.
4. The aldimine is freshly distilled [b.p. 50° (75 mm.)] prior to use.
5. A vigorous reaction may result. At this stage of the reaction, control is maintained with an ice–water bath.
6. The volume of gas evolved is estimated with an inverted cylinder filled with water attached by rubber tubing to the outlet of the mercury bubbler.
7. GC analysis at 155° on a 5 ft. 5% SE-30 column shows only 2,2-dimethyl-3-phenylpropionaldehyde and solvent.

8. The IR spectrum ($CHCl_3$) showed absorption at 2705, 1725, and 1605 cm^{-1}. The 2,4-dinitrophenylhydrazone, recrystallized from ethanol–ethyl acetate as long, yellow-orange needles, melted at 150–152° (reported[3] 154–155°).

3. Discussion

This procedure illustrates the mono-alkylation of α-substituted aldehydes by the metalloenamine method.[4] The preparation of the aldimine has been adapted from the procedure of Tiollais[5] and is useful in the preparation of aldimines from low-boiling components. The readily prepared aldimine is treated with an alkyl Grignard reagent generating the magnesioenamine halide salt, which can be alkylated with a variety of alkylating agents at the α-position. The yields are high, monoalkylation is the exclusive reaction, and there is no rearrangement when using an allylic halide. The general method is applicable to the alkylation of ketones *via* the magnesium bromide salts of the corresponding ketimines (Table I).

TABLE I
REACTION OF VARIOUS ALDIMINE AND KETIMINE MAGNESIUM BROMIDE SALTS WITH ALKYLATING AGENTS IN TETRAHYDROFURAN

Imine	Halide	Yield, %				
N-(2-methylpropylidene)-*tert*-butylamine	*n*-butyl iodide	65				
N-(heptylidene)-*tert*-butylamine	*n*-butyl iodide	47				
N-(propylidene)-*tert*-butylamine	*n*-butyl bromide	60				
	n-butyl iodide	78	2-iodopropane	61	benzyl chloride	60
N-(cyclohexylidene) cyclohexylamine	*N*-(cyclopentylidene) cyclohexylamine	*n*-butyl iodide	72			
	N-(cycloheptylidene) cyclohexylamine	*n*-butyl iodide	75			

In a variation of this method, metalloenamines have been generated from the aldimine and lithium diisopropylamide in ether and alkylated in a limited number of cases.[6] A further variation, using lithium dialkylamides in hexamethylphosphoric triamide, has been shown by Cuvigny and Normant[7] to give good yields of alkylated aldehydes.

However, secondary alkyl halides fail to react, giving the dehydrohalogenation product instead. Another approach, that of Meyers and co-workers,[8] involves the alkylation of the lithio salt of 2-methyldihydro-1,3-oxazines, but suffers from the necessity of carrying out several low-temperature steps and a pH-controlled borohydride reduction.

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2. Present address: Department of Biological Sciences, Carnegie-Mellon University, Pittsburgh, Pennsylvania 15213.
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

2,4-dinitrophenylhydrazone

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

ether, diethyl ether (60-29-7)

sodium chloride (7647-14-5)

n-butyl bromide (109-65-9)

nitrogen (7727-37-9)

acetate

benzyl chloride (100-44-7)

ethylmagnesium bromide (925-90-6)

magnesium sulfate (7487-88-9)

2-iodopropane (75-30-9)

isobutyraldehyde (78-84-2)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

hexamethylphosphoric triamide (680-31-9)

lithium diisopropylamide (4111-54-0)

borohydride (16971-29-2)

2,2-Dimethyl-3-phenylpropionaldehyde, Benzenepropanal, α,α-dimethyl- (1009-62-7)

n-Butyl iodide (542-69-8)

tert-Butylamine (75-64-9)

N-(2-Methylpropylidene)-tert-butylamine (6852-60-4)

N-(heptylidene)-tert-butylamine

N-(propylidene)-tert-butylamine

N-(cyclohexylidene)cyclohexylamine

N-(cyclopentylidene)cyclohexylamine

N-(cycloheptylidene)cyclohexylamine

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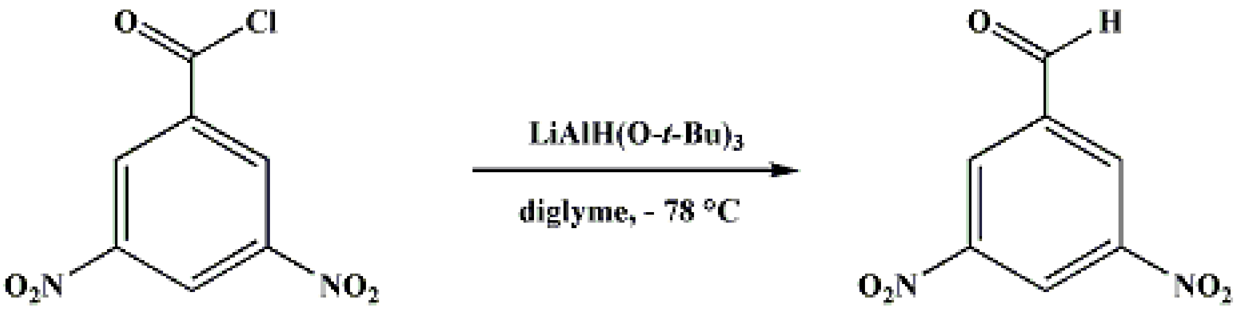
Organic Syntheses, *CV 6*, *529*

3,5-DINITROBENZALDEHYDE

[Benzaldehyde, 3,5-dinitro-]



Submitted by J. E. Siggins[1], A. A. Larsen[2], J. H. Ackerman[1], and C. D. Carabateas[1].
Checked by D. J. Bichan and Peter Yates.

1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A 3-l., three-necked, round-bottomed flask is equipped with an efficient stirrer, a pressure-equalizing dropping funnel with a nitrogen inlet, and a Y-tube fitted with a low temperature thermometer and a nitrogen outlet. The outlet is vented through a bubbler tube, maintaining a slight positive pressure. The flask and dropping funnel are flamed in a stream of dry nitrogen (Note 1). To the flask is added 115.0 g. (0.4989 mole) of 3,5-dinitrobenzoyl chloride (Note 2) followed by 500 ml. of dry diglyme (Note 3). The solution is stirred vigorously, and the flask is immersed in a cooling bath at −78° (Note 4). A diglyme solution of lithium aluminum tri-*tert*-butoxyhydride (Note 5) is prepared in the following manner. Dry diglyme (450 ml.) is added with vigorous stirring to an Erlenmeyer flask containing 140.0 g. (0.5512 mole) of lithium aluminum tri-*tert*-butoxyhydride. After standing overnight, the resulting suspension is filtered under a blanket of dry nitrogen through a thick layer of Celite packed tightly on a Büchner funnel (Note 6). The flask containing the filtrate is kept stoppered until the reducing agent is transferred to the dropping funnel. Dropwise addition of this solution is started when the contents of the reaction flask reach −72°. There is a color change and a temperature rise of a few degrees. The rate of addition is adjusted, maintaining the temperature of the mixture between −78° and −68° (Note 7). After addition is complete the mixture is stirred at −78° for 30 minutes longer.

The cold reaction mixture is poured slowly with stirring into a 3-l. beaker containing 150 ml. of concentrated hydrochloric acid, 300 ml. of saturated aqueous sodium

chloride, and 150 g. of ice. A white precipitate starts to separate (Note 8). An additional 150 ml. of saturated aqueous sodium chloride is added to the beaker and, after a minute, an upper layer begins to appear. The contents are transferred to a 2-l. separatory funnel and allowed to stand for 15 to 30 minutes while an upper brown layer separates. The upper layer is reserved while the lower layer is extracted with several portions of benzene, totalling 900 ml. The upper layer and the benzene extracts are combined and washed with seven 1-l. portions of water containing 10 ml. of concentrated hydrochloric acid. The benzene layer is washed successively with 100-ml. portions of aqueous 2% sodium hydrogen carbonate until the washings are basic, dried over 100 g. of anhydrous sodium sulfate, treated with 1 g. of charcoal, and filtered. The filtrate is concentrated at reduced pressure, yielding 59–62 g. (60–63%) of crude 3,5-dinitrobenzaldehyde, as a tan solid, m.p. 76–80°. Trituration in an ice bath with cold dry diethyl ether (*ca.* 0.3 ml./g.) gives a spongy solid, m.p. 85–87° (lit.[3] 85°), with losses of 5–10%, sufficiently pure for most uses. Further purification may be effected by recrystallization from toluene-hexane.

2. Notes

1. These operations are best done the day before the experiment is performed.
2. Since commercial 3,5-dinitrobenzoyl chloride is contaminated with 3,5-dinitrobenzoic acid, it was treated with thionyl chloride in boiling benzene under dry nitrogen. The product obtained after evaporation under vacuum melted at 68–70° and was stored over phosphorus pentoxide and potassium hydroxide in a vacuum desiccator.
3. "Diglyme" is the dimethyl ether of diethylene glycol. Commercial diglyme (Ansul Ether 141, Ansul Chemical Company, Marinette, Wisconsin) was used after drying over lithium aluminum hydride followed by distillation under reduced pressure; b.p. 59–61° (15 mm.).
4. An insulated bucket such as the "Nicer" available from B.F. Goodrich Company contains the mixture of dry ice and 2-propanol. Acetone foams excessively and has a high vapor pressure.
5. This hydride is obtained from Ventron, Inc., Beverly, Massachusetts.
6. Suspended particles will plug the dropping funnel in the subsequent operation. Two funnels may be used if the filtration is too slow.
7. At elevated temperatures reduction to the alcohol takes place. The addition time varies from 75 to 100 minutes.
8. The supernatant liquid is a brilliant yellow. A troublesome blue color may appear in an occasional run.

3. Discussion

3,5-Dinitrobenzaldehyde has been made previously by reducing 4-bromo-3,5-dinitrobenzaldehyde with copper(I) hydride.[3]

The method described is that of Brown.[4] Lithium aluminum tri-*tert*-butoxyhydride

reduction of acid chlorides to aldehydes is a synthetic method of wide utility, and the yields of 20 aromatic and 10 aliphatic aldehydes so prepared have been tabulated.[5] This reagent is also used widely to reduce steroid aldehydes and ketones to alcohols, frequently at 0°.[6] Having only one active hydrogen, it has been used for the partial reduction of diketones to hydroxy ketones.[7] With proper temperature control, it does not affect oxido,[8] ester,[6,9] acetal,[10] nitrile, or nitro groups, or lactone rings,[8] all of which react with lithium aluminum hydride. In contrast to some other complex hydrides, this reagent may reduce a ketone stereoselectively, resulting in a high relative yield of the more stable epimeric alcohol[11] and an improved absolute yield.[7,12]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

lithium aluminum tri-tert-butoxyhydride

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

diethyl ether (60-29-7)

hydrogen (1333-74-0)

thionyl chloride (7719-09-7)

sodium hydrogen carbonate (144-55-8)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

acetone (67-64-1)

potassium hydroxide (1310-58-3)

2-propanol (67-63-0)

lithium aluminum hydride (16853-85-3)

3,5-Dinitrobenzoic acid (99-34-3)

diglyme, dimethyl ether of diethylene glycol (111-96-6)

3,5-Dinitrobenzaldehyde, Benzaldehyde, 3,5-dinitro- (14193-18-1)

3,5-dinitrobenzoyl chloride (99-33-2)

toluene-hexane

4-bromo-3,5-dinitrobenzaldehyde

copper(I) hydride

phosphorus pentoxide (1314-56-3)

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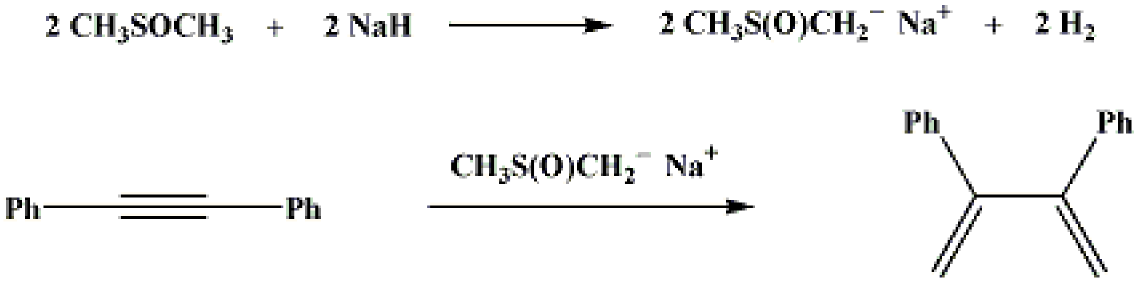
Organic Syntheses, CV 6, 531

2,3-DIPHENYL-1,3-BUTADIENE

[1,3-Butadiene, 2,3-diphenyl]



Submitted by Issei Iwai and Junya Ide[1].
Checked by James B. Sieja and Richard E. Benson.

1. Procedure

A 300-ml., three-necked, round-bottomed flask is fitted with a sealed mechanical stirrer, a thermometer, and a reflux condenser to which is attached a T-tube connected to a source of pure nitrogen. The remaining joint of the T-tube is connected to a bubbling device so that the rate of nitrogen flow can be observed throughout the course of the reaction. The flask is flushed with nitrogen and charged with 30 ml. of anhydrous dimethyl sulfoxide (Note 1) and 2.4 g. of about 50% sodium hydride in oil (*ca.* 0.05 mole) (Note 2). Stirring is begun and the contents of the flask are heated to 75° for 30 minutes (Note 3) under a slight pressure of nitrogen. The flask is cooled in a water bath to 30°, before a solution of 4.45 g. (0.0250 mole) of diphenylacetylene in 20 ml. of anhydrous dimethyl sulfoxide is added dropwise with stirring to the dark-gray solution. During the addition, the temperature of the reaction mixture gradually rises until it approaches 40°. After the addition is completed, the reaction mixture is heated to 65° and held at this temperature for 2.5 hours. The resulting red-brown reaction mixture is cooled to room temperature and poured into 500 ml. of an ice and water mixture with stirring. After the ice has melted, the mixture is extracted with five 150 ml. portions of diethyl ether. The ether extracts are combined, washed with three 100-ml. portions of water, then dried over sodium sulfate. The ether is removed by distillation at reduced pressure, and the product (about 6.0 g.) is chromatographed on 180 g. of alumina (Note 5). Elution with 1:7 (v/v) benzene:*n*-hexane gives ten 50-ml. fractions, of which the first two contain nearly all the mineral oil from the sodium hydride reagent. Fractions 3 through 8 are combined, and the ether is removed by distillation, yielding 1.2–1.4 g. (22–25%) of slightly impure 2,3-diphenyl-1,3-butadiene (Note 6). Recrystallization from methanol gives 0.55–0.70 g. (10.7–13.6%) of pure 2,3-diphenyl-1,3-butadiene, m.p. 47–48° (Note 7).

The ^1H NMR spectrum (60 MHz., CCl_4) shows a complex multiplet centered at δ 7.2

attributable to the aromatic protons, and two doublets centered at δ 5.4 and 5.2, respectively, attributable to the olefinic protons.

2. Notes

1. Commercially available dimethyl sulfoxide was freshly distilled in the presence of calcium hydride, b.p. 56–57° (5 mm.).
2. Sodium hydride in oil (about 50%), available from Metal Hydrides Inc., Beverly, Massachusetts, was used.
3. The formation of dimsyl(methylsulfinyl) anion is essentially complete at this time.
4. The preparation of diphenylacetylene is described in *Org. Synth.*, **Coll. Vol. 3**, 350 (1955) and **Coll. Vol. 4**, 377 (1963). The checkers purchased it from Eastman Organic Chemicals.
5. Aluminum Oxide Woelm neutral, activity grade 1, available from M. Woelm, Eschwege, Germany, was used. The column dimensions were 2.9 cm. × 29 cm., and the alumina was packed with *n*-hexane.
6. This grade of 2,3-diphenyl-1,3-butadiene is satisfactory for most purposes.
7. Crude 2,3-diphenyl-1,3-butadiene is unstable. The pure product should be stored in the dark in a refrigerator. The submitters have found it to be stable for at least one year under these conditions.

3. Discussion

This method provides a simple, one-step synthesis of 2,3-diphenyl-1,3-butadiene from the readily available diphenylacetylene and illustrates an unusual, relatively uninvestigated reaction. The scope of the reaction is unknown, but it appears that the procedure could be applied to disubstituted acetylenes having aryl substituents unaffected by the strong basic conditions of the reaction.

A conventional preparation of 2,3-diphenyl-1,3-butadiene involves dehydration of *meso*-2,3-diphenyl-2,3-butanediol by acidic reagents such as acetic anhydride,[2,3,4] acetyl bromide,[4] sulfanilic acid,[5] and potassium hydrogen sulfate.[6] Other procedures have been summarized[7] previously.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alumina

Benzene (71-43-2)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

acetic anhydride (108-24-7)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

potassium hydrogen sulfate (7646-93-7)

sulfanilic acid (121-57-3)

aluminum oxide (1344-28-1)

acetyl bromide (506-96-7)

sodium hydride (7646-69-7)

Diphenylacetylene (501-65-5)

n-hexane (110-54-3)

dimethyl sulfoxide (67-68-5)

calcium hydride (7789-78-8)

2,3-Diphenyl-1,3-butadiene, 1,3-Butadiene, 2,3-diphenyl (2548-47-2)

meso-2,3-diphenyl-2,3-butanediol

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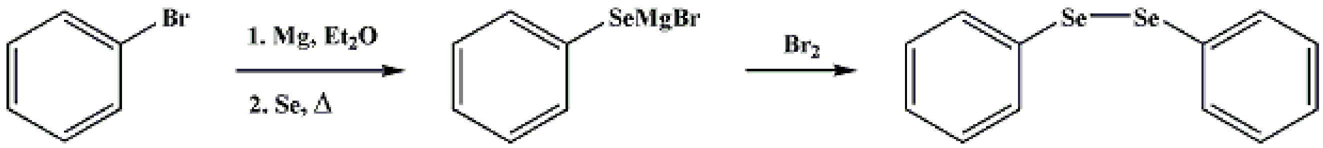
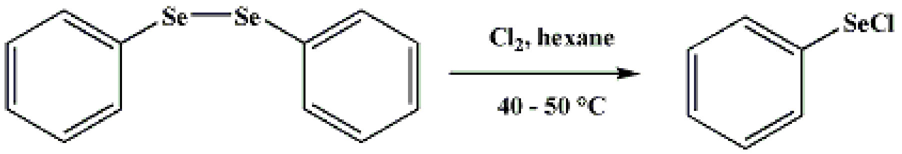
Organic Syntheses, CV 6, 533

REAGENTS FOR SYNTHESIS OF ORGANOSELENIUM COMPOUNDS: DIPHENYL DISELENIDE AND BENZENESELENENYL CHLORIDE





Submitted by Hans J. Reich[1], Martin L. Cohen, and Peter S. Clark.
Checked by Anna Vinogradoff, Albert W. M. Lee, and Robert V. Stevens.

1. Procedure

Caution! Most selenium compounds are toxic; care should be exercised to avoid contact with skin. All operations in this procedure should be conducted in a well-ventilated hood.

A. *Diphenyl diselenide*. A 2-l., three-necked, round-bottomed flask is equipped with a mechanical stirrer, a pressure-equalizing dropping funnel, and an efficient reflux condenser mounted with a combined inlet-outlet assembly connected to a nitrogen source and a bubbler. The apparatus is flamed dry while a slow stream of nitrogen is passed through the system. In the cooled flask a solution of phenylmagnesium bromide is prepared from 160 g. (1.02 mole) of bromobenzene, 24.0 g. (0.988 g.-atom) of magnesium, and 550 ml. of anhydrous diethyl ether. The dropping funnel is removed, and an Erlenmeyer flask containing 70 g. (0.89 g.-atom) of selenium (Note 1) is attached to the neck of the flask with a section of nylon tubing (Note 2). The selenium is added in portions at a rate sufficient to maintain a vigorous reflux (Note 3). The addition requires 15–30 minutes, after which the mixture is stirred and heated at reflux for another 30 minutes. The Erlenmeyer flask and nylon tubing are removed, and 3 g. (0.2 mole) of water is added to hydrolyze any excess Grignard reagent. The mixture is stirred and cooled in an ice bath while 74.3 g. (23.8 ml., 0.465 mole) of bromine is added dropwise at a rate such that the ether does not reflux (Note 4). Cooling and stirring are continued as a solution of 53.5 g. (1.00 mole) of ammonium chloride in 140 ml. of water is added slowly. The mixture is filtered by gravity into a 1-l., round-bottomed flask, and the granular precipitate is washed thoroughly with three 100-ml. portions of ether. The combined filtrates are evaporated, the remaining solid is dissolved insofar as possible in 500 ml. of hot hexane, and a small amount of insoluble material is separated by gravity filtration. The filtrate is allowed to crystallize at room temperature and then at 6°. The yellow microcrystalline solid is collected, washed with 30 ml. of pentane, and dried in the air, 89–97 g. (64–70%) of diphenyl diselenide, m.p. 60–62° (Note 5) and (Note 6).

B. *Benzeneselenenyl chloride*. A 1-l., three-necked, round-bottomed flask equipped with a magnetic stirring bar, a thermometer, a gas-inlet tube, and a reflux condenser is charged with 50 g. (0.16 mole) of diphenyl diselenide and 350 ml. of hexane (Note 7). The mixture is warmed to 40–50°, dissolving the solid. The resulting solution is stirred while chlorine gas is passed through the gas-inlet tube into the flask 1 cm. above the surface of the liquid, at a rate sufficient to maintain the temperature between 40° and 50°. Chlorination is continued until 11.3 g. (0.159 mole) of the gas is absorbed (Note 8). The solution is heated to reflux, filtered by gravity, and allowed to cool slowly at room temperature, then at 6° (Note 9). The mother liquor is decanted, the large, deep-orange crystals are washed with 25 ml. of pentane, and the residual solvent is evaporated by passing a slow stream of nitrogen over the crystals for 30 minutes, giving 51–54 g. (84–88%) of benzeneselenenyl chloride, m.p. 60–62° (Note 10).

2. Notes

1. The gray powdered form of selenium should be used. The submitters purchased this material from Research

Organic/Inorganic Chemical Corporation, 11686 Sheldon Street, Sun Valley, California 91352, and from Var-lac-oid Chemical Company, 666 South Front Street, Elizabeth, New Jersey 07202.

2. Alternatively the flask may be equipped with a Y-shaped adapter bearing a straight condenser on its vertical branch and fitted with a nitrogen inlet in its lower branch. A slow stream of nitrogen is passed through the nitrogen inlet while the portions of selenium are added through the top of the condenser. The top of the condenser is stoppered between additions.

3. Careful exclusion of oxygen during this operation is important.

4. The addition of bromine requires about 30 minutes, after which the maintenance of a nitrogen atmosphere is no longer necessary.

5. The submitters have carried out this procedure on a 3-mole scale and obtained similar yields. A melting point of 63.5° is reported[2] for diphenyl diselenide.

6. The appearance of a red coloration in the product indicates the presence of excess selenium. Free selenium begins to separate when the product is contaminated by more than *ca.* 1% of diphenyl triselenide. Even material that crystallizes as a brick-red solid may contain only 5% excess selenium. The procedure described here gives diphenyl diselenide containing less than 0.5% free selenium. More of this contaminant will be present, however, if the formation of the Grignard reagent is incomplete, or if oxygen is allowed to enter the flask during the addition of selenium.

7. Technical grade hexane is adequate.

8. The amount of chlorine absorbed can be measured by the increased weight of the flask. The progress of the reaction can also be monitored in the following manner. A white ring of phenylselenium trichloride forms on the wall of the flask just above the surface of the liquid during the chlorination. If diphenyl diselenide remains in the solution, the solid dissolves when the flask is tipped slightly to immerse the phenylselenium trichloride below the surface of the solution. The solid no longer dissolves after the reaction is complete. The remaining ring of phenylselenium trichloride can be removed by adding another small portion of diphenyl diselenide.

9. The solution should not be cooled below 0°, since impurities, including diphenyl selenide dichloride, may also crystallize.

10. The submitters obtained 54–57 g. (88–93%) of product, m.p. 62–64° (lit.,[3] m.p. 64–65°).

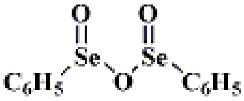
3. Discussion

Diphenyl diselenide has been prepared by disproportionation of phenyl selenocyanate in the presence of potassium hydroxide[4,5] or ammonia,[4] and by air oxidation of benzeneselenol.[6,7] The preparation of benzeneselenol is described in an earlier volume in this series.[8] In the present procedure phenylselenomagnesium bromide, formed from phenylmagnesium bromide and selenium,[8] is oxidized directly to diphenyl diselenide with bromine.[9] Thus, the liberation of the malodorous and toxic hydrogen selenide and benzeneselenol is avoided. Benzeneselenenyl chloride has been prepared by thermal elimination of ethyl chloride from ethyl phenyl selenide dichloride,[3,10] by thermal elimination of chlorine from phenylselenium trichloride,[11] and by chlorinolysis of diphenyl diselenide with either sulfuryl chloride[12,13] or chlorine.[9,13]

Diphenyl diselenide and benzeneselenenyl chloride have been utilized as intermediates for the preparation of several phenyl-substituted organoselenium reagents (Table I).[14] Benzeneselenenyl bromide is available by direct brominolysis of diphenyl diselenide.[9,15 16] The reaction of benzeneselenenyl halides with silver acetate and silver trifluoroacetate has been employed to generate benzeneselenenyl acetate[13] and trifluoroacetate[17] *in situ. N,N*-Dialkyl benzeneselenenamides have been isolated from the reaction of secondary amines with benzeneselenenyl chloride or bromide.[18] Oxidation of benzeneselenenyl chloride and diphenyl diselenide with ozone affords benzeneseleninyl chloride and benzeneseleninic anhydride, respectively.[9,19] The highly nucleophilic selenenylating reagent, selenophenoxide, is liberated in solution readily by reduction of diphenyl diselenide with sodium borohydride in ethanol[20] or with other reducing agents.[14] Solutions of selenophenol are conveniently prepared by reduction with hypophosphorous acid.[21]

TABLE I

ORGANOSELENIUM REAGENTS PREPARED FROM DIPHENYL DISELENIDE OR BENZENESELENENYL CHLORIDE

Organoselenium Reagent	M.p. or B.p. (·)	Reference(s)
C_6H_5SeBr	62	4,9,15,16
	a	13
	a	17
	39–40(0.1 mm.)	18
	75	9,19
	120–122	19
C_6H_5SeNa	*a*	14,20,21
C_6H_5SeH	*a*	21

[a] This reagent was generated in solution and used without isolation.

Diphenyl diselenide, benzeneselenenyl chloride, and organoselenium compounds derived from them have served as convenient reagents for introducing the phenylseleno group. The reaction of organolithium and Grignard reagents with diphenyl diselenide affords phenyl selenides.[22] The phenylseleno group has been introduced into the α-position of aldehydes, ketones, esters, nitriles, sulfones, and related compounds by reaction of enol derivatives, enolate anions, or carbanions with diphenyl diselenide or benzeneselenenyl chloride.[9,14,15] The addition of benzeneselenenyl halides,[13,23] acetate,[13] and trifluoroacetate[17] to olefins affords alkyl phenyl selenides substituted in the β-position with halo, acetoxy, and trifluoroacetoxy groups.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 23

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hypophosphorous acid

benzeneselenenyl chloride or bromide

C_6H_5SeNa

C_6H_5SeH

C_6H_5SeBr

ethanol (64-17-5)

ammonia (7664-41-7)

ether, diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

magnesium (7439-95-4)

bromine (7726-95-6)

oxygen (7782-44-7)

nitrogen (7727-37-9)

sulfuryl chloride (7791-25-5)

chlorine (7782-50-5)

potassium hydroxide (1310-58-3)

bromobenzene (108-86-1)

Phenylmagnesium bromide (100-58-3)

Pentane (109-66-0)

ozone (10028-15-6)

selenium

selenophenoxide

silver acetate (563-63-3)

hexane (110-54-3)

hydrogen selenide (7782-49-2)

Selenophenol

Benzeneselenol (645-96-5)

Diphenyl diselenide (1666-13-3)

ethyl chloride (75-00-3)

silver trifluoroacetate (2966-50-9)

sodium borohydride (16940-66-2)

Benzeneselenenyl chloride (5707-04-0)

benzeneselenenyl bromide (34837-55-3)

diphenyl triselenide

phenylselenium trichloride

diphenyl selenide dichloride (2217-81-4)

phenyl selenocyanate (2179-79-5)

phenylselenomagnesium bromide

ethyl phenyl selenide dichloride

benzeneselenenyl acetate

benzeneseleninyl chloride

benzeneseleninic anhydride (17697-12-0)

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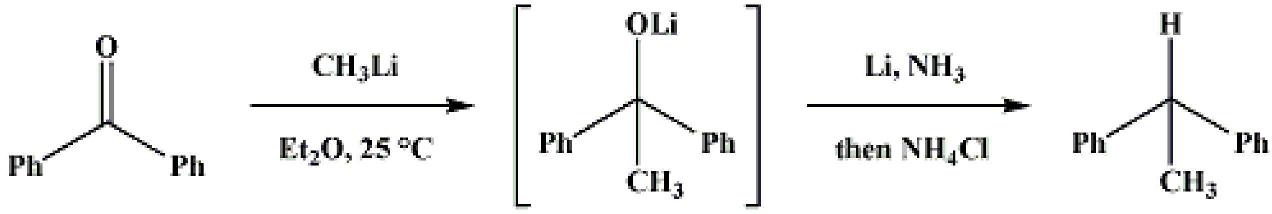
AROMATIC HYDROCARBONS FROM AROMATIC KETONES AND ALDEHYDES: 1,1-DIPHENYLETHANE

[Benzene, 1-phenylethyl-]



Submitted by Sharon D. Lipsky and Stan S. Hall[1].
Checked by Robert E. Ireland, Paula J. Clendening, Kathryn D. Crossland, and Alvin K. Willard.

1. Procedure

A 500-ml., three-necked, round-bottomed flask, equipped with a 5-cm., glass-coated, magnetic stirring bar, a Dewar condenser connected to a static argon line (Note 1), and a pressure-equalizing dropping funnel, is sealed with a rubber septum (Note 2). After flushing with argon, 30 ml. of anhydrous diethyl ether and 19.5 ml. of 1.89 *M* (0.0368 mole) methyllithium solution (Note 3) are injected through the septum into the flask (Note 4). A solution of 4.54 g. (0.0249 mole) of benzophenone (Note 5) in 35 ml. of anhydrous ether is placed in the dropping funnel and added to the reaction mixture over a 20-minute period. The mixture is allowed to stir for one half hour (Note 6). The septum is removed, and the side arm is quickly adapted with Tygon® tubing leading through a tower of solid potassium hydroxide to a tank of anhydrous ammonia. After approximately 75 ml. of ammonia is slowly distilled into the flask (Note 7), the tubing is removed, and 0.525 g. (0.0761 g.-atom, *ca.* 15 cm. added as 0.5 cm. pieces) of lithium wire (Note 8) is quickly added, and the flask is stoppered. After 15 minutes the dark blue color is discharged by the continuous addition of excess ammonium chloride (*ca.* 5 g. over a 15-minute period) (Note 9). The argon-inlet tube is disconnected, and the ammonia is allowed to evaporate. The residue is then partitioned between 100 ml. of aqueous saturated sodium chloride and 100 ml. of ether. The aqueous layer is separated and extracted with two 50-ml. portions of ether. The combined ether extracts are dried over anhydrous magnesium sulfate. Removal of the ether on a rotary evaporator yields 4.36–4.49 g. of crude product (Note 10). Filtration of the product through 60 g. of Woelm alumina (Grade III) with 150 ml. of petroleum ether affords 4.16–4.31 g. (92–95%) of 1,1-diphenylethane (Note 11), which on evaporative distillation in a Kügelrohr oven gives 4.12–4.21 g. (91–93%) of 1,1-diphenylethane, b.p. 100° (0.25 mm.), n_D^{28} 1.5691 (Note 12).

2. Notes

1. The entire reaction sequence is performed under an argon atmosphere. A T-tube

and an oil bubbler are utilized, and the system is operated at a moderate flow-rate throughout the synthesis.

2. All of the glassware is oven dried and cooled to room temperature in a large box desiccator, or the assembled glassware can be flamed dry under an argon atmosphere and allowed to cool.

3. Methyllithium in ether solution is available from Foote Mineral Company and the Aldrich Chemical Company.

4. If methyllithium of a different molarity is used, the total volume should be adjusted to 50 ml. by varying the amount of ether used.

5. Benzophenone is available from Matheson, Coleman and Bell.

6. Toward the end of this sequence 2-propanol and dry ice are added to the condenser in preparation for the reduction step.

7. To prevent splattering, the apparatus is tilted slightly to allow the condensing ammonia to run down the walls of the flask.

8. Evidently surface area is important, since when the 15 cm. of lithium wire was added as 1-cm. pieces, the reduction was incomplete. Lithium wire (0.32 cm., 0.02% sodium) available from Alpha Inorganics, Inc., was wiped free of oil and rinsed with petroleum ether immediately prior to use.

9. Ammonium chloride is most conveniently introduced by attaching a glass tube filled with the salt to a side arm with Tygon® tubing. When the ammonium chloride is to be added, the tube is raised and tapped gently to introduce the quenching agent smoothly. Often a very vigorous reaction occurs after a considerable (10-minute) induction period. Should this step start to become violent, the addition and the vigorous stirring should be momentarily stopped to avoid eruption.

10. GC on a 200 cm. by 0.6 cm. column packed with 10% Apiezon L on Chromosorb W (AW, DMCS) using a flame-detector instrument, at a 40 ml./minute helium carrier gas flow rate, gives a trace peak at 9.9 minutes (diphenylmethane), a major peak at 11.7 minutes (1,1-diphenylethane), and a trace peak at 15.4 minutes (1,1-diphenylethanol) when the oven is held at 190° for 10 minutes and then programmed at 10°/minute to 290°.

11. The sample is sufficiently pure at this point to use for most purposes. The chromatography step is an efficient means to remove any 1,1-diphenylethanol that was not reduced.

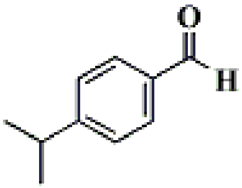
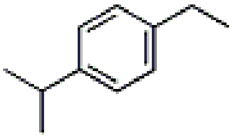
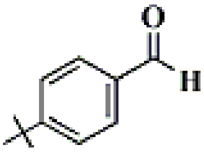
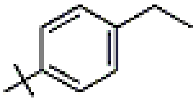
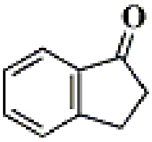
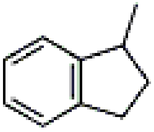
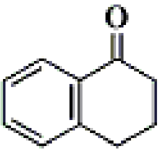
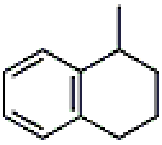
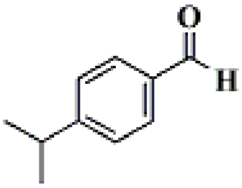
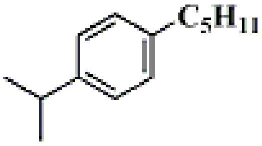
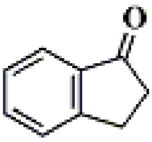
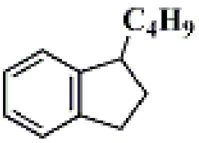
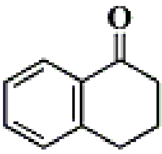
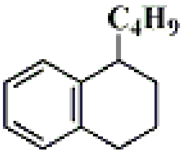
12. The spectral properties of the product are as follows; ^{1}H NMR (CCl_4), δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 1.54 (d, *J* = 7, 3H, CH_3), 4.03 (q, *J* = 7, 1H, C*H*), 7.12 (s, 10H, $2C_6H_5$); mass spectrum *m/e* (relative intensity): 182 (M, 32), 167 (100).

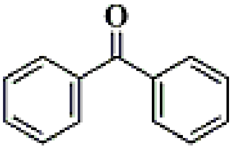
3. Discussion

This procedure illustrates a general method for preparing aromatic hydrocarbons by the tandem alkylation-reduction of aromatic ketones and aldehydes.[2] Additional examples are given in Table I. The advantages of the method are that the entire sequence is carried out in the same reaction vessel without isolation or purification of intermediates, the procedure consumes only a few hours, and in most cases the isolated yield of the aromatic hydrocarbon is excellent.

TABLE I

AROMATIC HYDROCARBONS FROM AROMATIC KETONES AND ALDEHYDES

Aromatic Carbonyl Compound	Organolithium Reagent	Product	Yield (%)
	CH_3Li		95
	CH_3Li		94
	CH_3Li		95
	CH_3Li		78
	C_4H_9Li		86[a,e]
	C_4H_9Li		89[a,e]
	C_4H_9Li		76[b,e]



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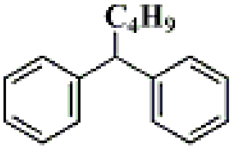
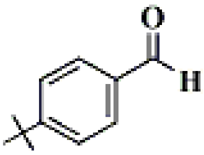


70[a,e]



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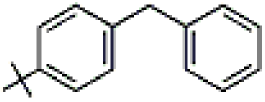
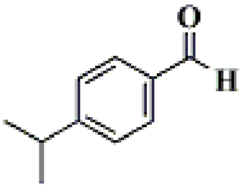


93[c,e]



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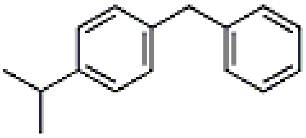
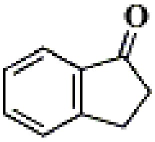
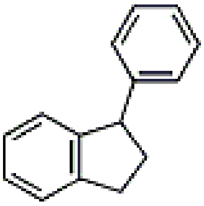


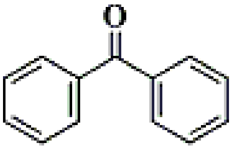
89[d,e]



C_6H_5Li



97[c,e]



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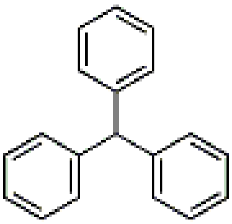

97[d,e]

[a]The organolithium reagent was generated *in situ* in ether from 1-bromobutane.

[b]Commercial butyllithium (Foote Mineral Company, *ca.* 15% in hexane) and six equivalents of lithium were used.

[c]The organolithium reagent was generated *in situ* in ether from bromobenzene.

[d]Commercial phenyllithium (the Aldrich Chemical Co., 2 *M* in cyclohexane-ether) and six equivalents of lithium were used.

[e]Reaction conducted on a 0.005 mole scale using as solvent 20 ml. of ether and 20 ml. of ammonia. Yield after column chromatography.

The method may be modified so that the organolithium reagent is generated *in situ* in ether from the corresponding bromide. Best results were obtained by having from the outset all of the lithium wire necessary to generate the organolithium reagent and reducing the intermediate benzyl alkoxide present.[3] Commercial organolithium reagents such as *n*-butyllithium in hexane or phenyllithium in cyclohexane–ether were satisfactory when twice as much lithium is used for the reduction step. In some cases, by running the alkylation step at −78° to minimize competing side reactions,[4] higher yields than those listed in Table I can be realized. In addition to the present method, other procedures have been reported for the synthesis of 1,1-diphenylethane.[5,6,7]

This alkylation-reduction sequence has now been extended to benzylidene carbonyls,[8] complex carbonyls,[9] and esters and lactones;[10] and has been used to synthesize α-cyclopropyl aromatic hydrocarbons,[11] β,γ-unsaturated aromatic hydrocarbons,[12] and 1,4-dienes from α,β,γ,δ-unsaturated ketones.[13]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alumina

petroleum ether

ammonia (7664-41-7)

ether, diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

sodium chloride (7647-14-5)

1-bromobutane (109-65-9)

cyclohexane (110-82-7)

potassium hydroxide (1310-58-3)

Benzophenone (119-61-9)

sodium (13966-32-0)

2-propanol (67-63-0)

Diphenylmethane (101-81-5)

bromobenzene (108-86-1)

Phenyllithium (591-51-5)

lithium (7439-93-2)

magnesium sulfate (7487-88-9)

butyllithium, n-butyllithium (109-72-8)

hexane (110-54-3)

Methyllithium (917-54-4)

helium (7440-59-7)

argon (7440-37-1)

1,1-Diphenylethane, Benzene, 1-phenylethyl- (612-00-0)

1,1-diphenylethanol (599-67-7)

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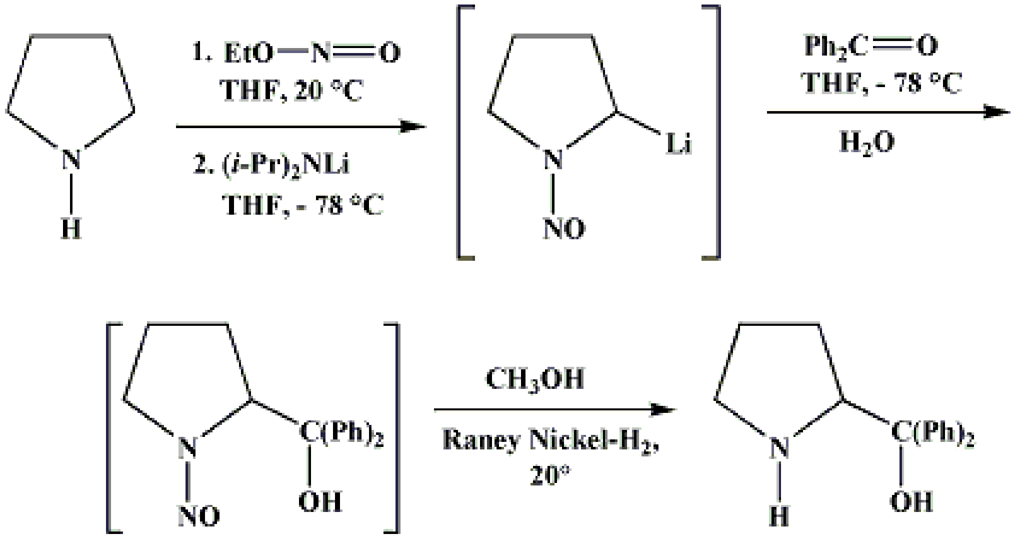
Organic Syntheses, *CV 6*, 542

NUCLEOPHILIC α-*sec*-AMINOALKYLATION: 2-(DIPHENYLHYDROXYMETHYL)PYRROLIDINE

[2-Pyrrolidinemethanol, α,α-diphenyl-, (±)-]



Submitted by D. Enders, R. Pieter, B. Renger, and D. Seebach[1].
Checked by C. Hutchins and M. F. Semmelhack.

1. Procedure

Caution! Since N-nitrosopyrrolidine is a potent carcinogen and is produced as an intermediate, this entire "one-pot" procedure should be performed in a well-ventilated hood. Wearing of disposable polyethylene gloves is recommended.

Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A dry, 250-ml., one-necked, round-bottomed flask equipped with a magnetic stirrer and a three-way stopcock is charged with 4 g. (0.05 mole) of ethyl nitrite (Note 1), 4 g. of dry tetrahydrofuran (Note 2), and 2.35 g. (0.0331 mole) of pyrrolidine (Note 3). The stopcock is closed (Note 4), and the mixture is stirred at room temperature for 2 days. Excess ethyl nitrite, tetrahydrofuran, and the ethanol formed are removed from the *N*-nitrosopyrrolidine (Note 5) by stirring at 25° under reduced pressure (10 mm., water aspirator, (Note 6) for 2 hours. The stopcock is fitted with a rubber septum, the air in the system is replaced with dry argon (Note 4) and (Note 7)), and 50 ml. of tetrahydrofuran is injected by syringe. A solution of lithium diisopropylamide is prepared in a separate, dry, 100-ml. flask by adding 21.1 ml. (0.0340 mole) of a 1.61 *M* solution of *n*-butyllithium in hexane (Note 8) to a solution of 3.44 g. (4.76 ml., 0.0341 mole) of diisopropylamine (Note 9) in 25 ml. of tetrahydrofuran at −78° (methanol–dry ice bath) with stirring under argon. The solution is warmed to 0° in 15 minutes, then added dropwise with a syringe within 4 minutes to the nitrosamine solution, stirred at −78°. Stirring of the yellow to orange solution is continued at this temperature for 25 minutes. A solution of 5.46 g. (0.0300 mole)

of benzophenone in 12 ml. of tetrahydrofuran is added dropwise by syringe (Note 10), and the mixture is stirred for 12 hours at −78°, then warmed to 0° within 2 hours. After addition of 0.6 ml. (0.03 mole) of water, the flask is transferred from the argon line to a rotary evaporator (within the hood). Solvents and diisopropylamine are removed under reduced pressure in a 40° bath (Note 11). The remaining solid is dissolved with slight warming in 120 ml. of dry methanol (Note 12), before 3.9 g. (66 equivalents) of Raney nickel (Note 13) is rinsed into the solution with 30 ml. of dry methanol. The reaction vessel is equipped again with the three-way stopcock, and the air in the flask is replaced with hydrogen (Note 7). The flask is filled five times with hydrogen from a balloon; during this operation vigorous stirring of the Raney nickel–methanol suspension is necessary. The flask is attached to a mercury bubbler to maintain a positive hydrogen pressure (200 mm.) supplied from a cylinder, as shown in f.htmigure 1. The reaction mixture is stirred for 3 hours at room temperature while a slow stream of hydrogen is passed through the system. The major part of the solution is decanted and filtered, and the remaining Raney-nickel suspension is extracted by refluxing three times for 10 minutes each with 20 ml. of methanol (Note 14). The combined methanol solutions are concentrated under reduced pressure. The residue is dissolved in 150 ml. of diethyl ether and 100 ml. of water, the layers are separated (Note 15), and the aqueous layer is extracted three times with 50-ml. portions of ether. The combined extracts are dried over sodium carbonate and concentrated in a rotary evaporator to a total volume of 150 ml. Dry hydrogen chloride gas is bubbled into the solution with stirring until the mixture is acidic, The almost colorless precipitate of the hydrochloride is filtered, washed two times with 30-ml. portions of dry ether, and dried in a desiccator under reduced pressure for 3 hours, giving 5.99–6.11 g. (58–60%, based on benzophenone) of the product, m.p. 244–249° (dec.). Recrystallization from methanol–acetone gives 5.06–5.20 g. (58–60%) of analytically pure product, m.p. 267–269° (dec.) (Note 16). The free base is obtained by treatment of the hydrochloride with 10% aqueous sodium hydroxide and extraction with ether, m.p. 82–83° (Note 17).

Figure 1.

Figure 1.

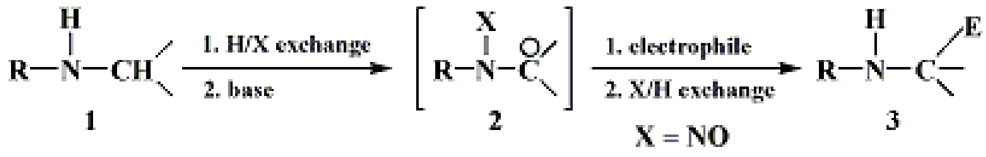
2. Notes

1. Ethyl nitrite was prepared as described in *Org. Synth.*, **Coll. Vol. 2**, 204 (1943), or purchased from Merck-Schuchardt and distilled before use, b.p. 17°. The volatile nitrite can be easily handled as a 50% tetrahydrofuran solution and stored in a refrigerator.
2. Technical grade tetrahydrofuran, available from BASF-A G or Fisher Scientific Company, was dried by distillation, first from potassium hydroxide then from lithium aluminum hydride and used for all operations in this procedure. For a warning note regarding the purification of tetrahydrofuran, see *Org. Synth.*, **Coll. Vol. 5**, 976 (1973).
3. Pyrrolidine, b.p. 87–88°, obtained from Aldrich Chemical Company, Inc., or BASF-A G was distilled from potassium hydroxide before use.
4. The three-way stopcock with standard-tapered joint must be securely fastened to the neck of the flask with wire, rubber bands, or springs [see f.htmigure 1 and *Org. Synth.*, **Coll. Vol. 6**, 316, 869 (1988).]
5. Nitrosamines are strong carcinogens[2,3]; *N*-nitrosopyrrolidine causes liver tumors in rats.[2,4] Although the one-pot procedure described here prevents contact with the nitrosamine, utmost care must be used to avoid contact with the reaction mixture during all manipulations.
6. At the beginning of the evacuation the pressure should be lowered slowly to prevent bumping.

7. This was done by alternately evacuating and filling with dry argon three times; during the reaction a pressure of about 50 mm. above atmospheric was maintained using a mercury bubbler.
8. Purchased from Metallgesellschaft, Frankfurt, or Alfa-Products, Division of the Ventron Corporation. The content of the solution was determined prior to use by acidimetric titration.
9. The diisopropylamine, b.p. 83–84°, available from Fluka A G, BASF-A G, or Aldrich Chemical Company, Inc., was purified by refluxing over potassium hydroxide and subsequent distillation. It was stored over calcium hydride.
10. Benzophenone, m.p. 47–49°, was purchased from Riedel-de-Haen-A G or from Fisher Scientific Company. The reaction mixture turns green and then blue during the addition, because of the formation of ketyl radicals.
11. The checkers found it more convenient to remove the volatile material at this stage by warming the stirred mixture at 40° and using a water aspirator vacuum (10 mm.). About 3 hours were required.
12. Methanol was dried by heating at reflux for 3 hours over magnesium, then distilling.
13. The Raney nickel reagent was prepared by addition of 9.5 g. of sodium hydroxide pellets over 8–10 minutes to a stirred suspension of 7.8 g of nickel–aluminum alloy (50% Ni, 50% Al powder, purchased from Merck-Schuchardt) in 120 ml. of distilled water, contained in a 250-ml. beaker. Fifteen minutes after the addition was completed, the beaker was immersed into a 70° water bath for 20 minutes. The water was decanted, and the catalyst was washed sequentially with two 20-ml. portions of distilled water and two 20-ml. portions of methanol.
14. *Caution! The dry Raney nickel catalyst is pyrophoric. The residues can be destroyed by allowing them to ignite and burn on filter paper in a safe place.*
15. Upon dissolving the residue in 200 ml. of ether and 100 ml. of water, the checkers obtained an emulsion that cleared slowly on standing for 2–3 hours.
16. The literature reports m.p. >240°,[5] >250°,[6] and 262–263°.[7] The yield given includes a small second crop obtained by recrystallization of the filtrate residue. The reported yield and m.p. data were obtained by the checkers. The submitters report 6.50–6.95 g. (75–80%, m.p. 260–265°) before recrystallization and 5.20–5.62 g. (60–65%, m.p. 267–269°) for analytically pure product.
17. The m.p. is reported to be 81–82°[6] and 83°.[5] The spectral properties are: IR spectrum (KI) cm^{-1}: strong absorptions at 3360, 3080, 3060, 3020, 2980–2800, 1595, 1490, 1450, 1400, 1190, 1100, 1060, 1030, 990, 900, 750, 700, 660, and 635; ^1H NMR ($CDCl_3$), δ (multiplicity, number of protons): 1.60 (m, 4H), 2.95 (m, 2H, with overlapping broad peak for O*H* and N*H*), 4.18 (m, 1H), 7.00–7.65 (m, 10H). The compound has psychostimulating activity.[7]

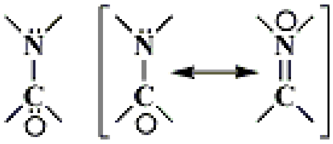
3. Discussion

The procedure described here is an example of the "nitrosamine method" for the electrophilic substitution of **1** to **3**, *via* the intermediate anion **2**, as outlined in detail in a recent review article.[8]



Currently, this is the only method that allows reversible enhancement of the acidity of α-nitrogen C-protons in a large variety of secondary amines, using nitroso-substituted nitrogen (X = NO, see examples in Table I). Nucleophile **2** is synthetically equivalent to α-aminocarbanion **4**, while the inherent reactivity of a carbon adjacent to an amino nitrogen is electrophilic (see the immonium ion

5).[8,9] Lithiated nitrosamines are also useful because their formation and reactions with electrophiles occur in high yield, as well as with a high degree of regio- and stereoselectivity (see Table I). For further information see the review article[8] and other recent publications.[10] This method has the disadvantage of carcinogenic nitrosamine intermediates, but this one-pot procedure reduces the danger of contact.



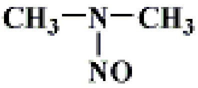
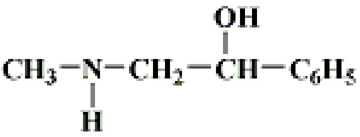
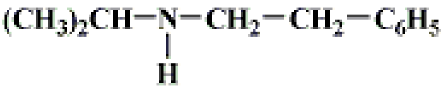
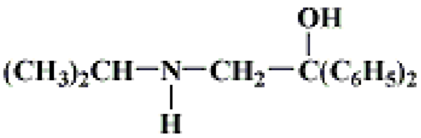
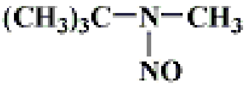
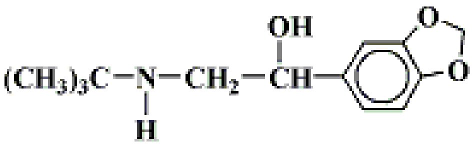
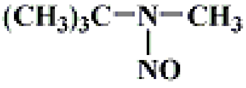
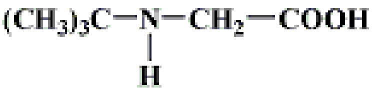
4 **5**

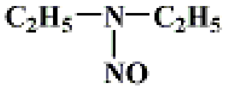
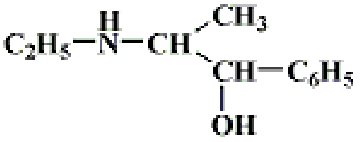
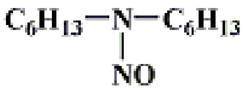
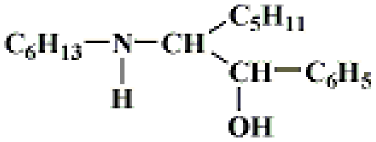
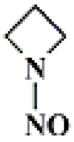
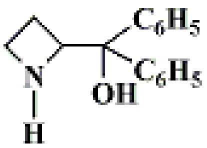
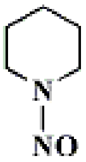
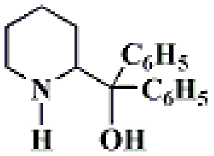
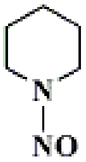
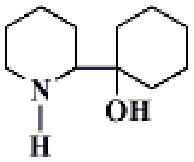
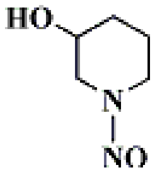
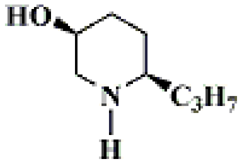
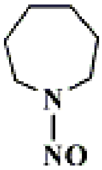
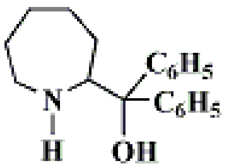
This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 447
- Org. Syn. Coll. Vol. 9, 676

TABLE I

α-SUBSTITUTED SECONDARY AMINES VIA ELECTROPHILIC SUBSTITUTION[8]

Starting Materials	Nitrosamine	Metallation Time (minutes)	Product[a]	Yield (%)
Benzaldehyde, dimethylamine		10		80
Benzylbromide, methylisopropylamine		10		80
Benzophenone, methylisopropylamine		10		75
Piperonal, methyl *tert*-butylamine		10		80
Carbon dioxide, methyl *tert*-butylamine		10		75[b]

Benzaldehyde, diethylamine		10		75[b]
Benzaldehyde, dihexylamine		10		80[b]
Benzophenone, azetidine		7		75[b]
Benzophenone, piperidine		180		50
Cyclohexanone, piperidine		180		55
Iodopropane, 3-hydroxypiperidine		240		40
Benzophenone, perhydroazepine		20		80[b]

[a] Isolated and characterized as hydrochlorides.

[b] Overall yield of stepwise procedure; the denitrosation was performed by bubbling gaseous hydrogen chloride into a benzene solution of the nitrosamine. This cleavage of nitrosamines is usually not as clean as the one with Raney nickel.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Raney-nickel

ethanol (64-17-5)

hydrogen chloride (7647-01-0)

Benzene (71-43-2)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

magnesium (7439-95-4)

Cyclohexanone (108-94-1)

sodium carbonate (497-19-8)

carbon dioxide (124-38-9)

benzaldehyde (100-52-7)

nickel, Raney nickel (7440-02-0)

acetone (67-64-1)

carbon (7782-42-5)

potassium hydroxide (1310-58-3)

Benzophenone (119-61-9)

piperidine (110-89-4)

ethyl nitrite (109-95-5)

diethylamine (109-89-7)

dimethylamine (124-40-3)

Benzylbromide (100-39-0)

n-butyllithium (109-72-8)

piperonal (120-57-0)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

pyrrolidine (123-75-1)

hexane (110-54-3)

nitrosamine (35576-91-1)

calcium hydride (7789-78-8)

argon (7440-37-1)

methylisopropylamine (4747-21-1)

Azetidine (503-29-7)

lithium diisopropylamide (4111-54-0)

diisopropylamine (108-18-9)

2-(Diphenylhydroxymethyl)pyrrolidine, 2-Pyrrolidinemethanol, α,α-diphenyl-, (±)- (112068-01-6)

N-nitrosopyrrolidine (930-55-2)

Iodopropane (107-08-4)

3-hydroxypiperidine (6859-99-0)

perhydroazepine (111-49-9)

methyl tert-butylamine (14610-37-8)

dihexylamine (143-16-8)

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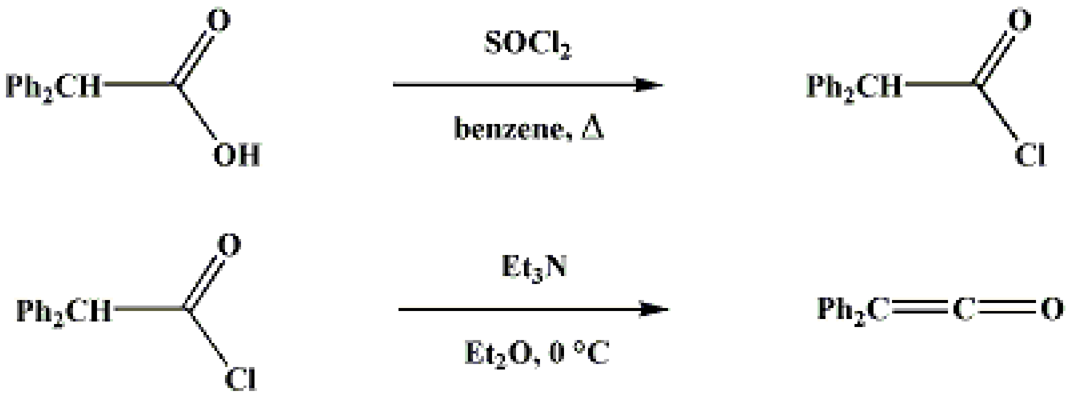
Organic Syntheses, CV 6, 549

DIPHENYLKETENE

[Ethenone, diphenyl-]



Submitted by Edward C. Taylor[1], Alexander McKillop[2], and George H. Hawks.
Checked by C. J. Michejda, D. D. von Riesen, R. W. Comnick, and Henry E. Baumgarten.

1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A. *Diphenylacetyl chloride.* A 500-ml., three-necked flask equipped with a dropping funnel and a reflux condenser carrying a calcium chloride drying tube is charged with 50.0 g. (0.236 mole) of diphenylacetic acid (Note 1) and 150 ml. of thiophene-free, anhydrous benzene. The mixture is heated under reflux, and 132 g. (80.1 ml., 1.11 mole) of thionyl chloride is added dropwise over 30 minutes. Refluxing is continued for 7 additional hours before the benzene and excess thionyl chloride are removed by distillation under reduced pressure. The pale yellow oil which remains contains a little thionyl chloride, best removed by adding 100 ml. of anhydrous benzene and again distilling under reduced pressure. The residue is dissolved in 150 ml. of refluxing, anhydrous hexane (Note 2). The hot solution is treated with charcoal and filtered, and the filtrate is chilled to 0° in a sealed flask. The product, which crystallizes as colorless plates (Note 3), is filtered, washed with a little cold hexane, dried at 25° under vacuum for 2 hours, and stored in a tightly stoppered bottle, giving 42–45 g. (77–84%) of product, m.p. 51–53°. Concentration of the hexane mother liquors to about 50 ml. followed by chilling to 0° and addition of a seed crystal gives an additional 2.5–4.0 g. (5–8%) of product of equal purity, for a total yield of 44.5–49 g. (82–94%) of diphenylacetyl chloride, m.p. 51–53° (Note 4).

B. *Diphenylketene.* A 500-ml., three-necked flask equipped with a magnetic stirring

bar, a gas-inlet tube, a calcium chloride drying tube, and a dropping funnel is charged with a solution of 23.0 g. (0.0997 mole) of diphenylacetyl chloride in 200 ml. of anhydrous diethyl ether. The flask is cooled in an ice bath, dry nitrogen is passed through the system, and 10.1 g. (0.100 mole) of triethylamine is added dropwise over 30 minutes to the stirred solution; triethylamine hydrochloride precipitates as a colorless solid, and the ether becomes bright yellow in color. When addition of the triethylamine is complete, the flask is tightly stoppered and stored overnight at 0°. The hydrochloride is collected on a 9-cm., sintered glass funnel and washed with anhydrous ether until the washings are colorless. The ether is removed under reduced pressure; the residual red oil is transferred to a 50-ml., distilling flask fitted with a 10-cm. Vigreux column and distilled (Note 5), giving 10.2–10.8 g. (53–57%) of diphenylketene as an orange oil, b.p. 118–120° (1 mm.) (Note 6). It can be stored at 0° in a tightly stoppered bottle for several weeks without decomposition.

2. Notes

1. Superior grade diphenylacetic acid, m.p. 147–148° (Matheson, Coleman and Bell) was used without further purification.
2. Commercial hexane, A. C. S. grade (Matheson, Coleman and Bell) was dried by distillation from potassium hydroxide.
3. Diphenylacetyl chloride crystallizes best when a seed crystal is added to the cold hexane solution. If, after several hours at 0°, crystallization has not commenced, scratching with a glass rod is sufficient to induce crystallization.
4. The checkers found it necessary to recrystallize the diphenylacetyl chloride twice to obtain the reported melting point.
5. Most of the diphenylketene distils cleanly at 118–119° (1 mm.) but strong heating is necessary for distillation of the final portion from the polymeric pot residue.
The checkers used a variety of different distillation setups. The best results were obtained when the oil being distilled filled the flask to about two-thirds its capacity, the Vigreux column was no longer than 10 cm. in length, the whole apparatus was kept as small as possible, and the distillation was conducted as rapidly as possible.
6. The submitters obtained yields of 73–84% on the scale described and yields of up to 70% on a scale twice that described. From IR analysis of the crude (undistilled) product the checkers concluded that this material represented a yield in excess of 80%. Thus, the critical step appears to be the distillation. The checkers have used the crude (undistilled) product for some applications, but this procedure has not been uniformly successful and is not recommended.

3. Discussion

Diphenylacetyl chloride has been obtained from the reaction of diphenylacetic acid with phosphorus pentachloride,[3] phosphorus oxychloride and phosphorus pentachloride,[4] or thionyl chloride.[5] It has also been prepared by treatment of

diphenylketene with hydrogen chloride.[6] The methods of preparation of diphenylketene have been reviewed earlier in this series.[7] To those cited should be added the debromination of α-bromodiphenylacetyl bromide with triphenylphosphine.[8] The procedure above is a modification of that described by Staudinger.[9]

The present preparation consists of two very simple steps, uses relatively inexpensive starting materials, and does not involve hazardous or toxic chemicals or special apparatus. An important advantage is that the diphenylketene, until it is finally distilled, is never exposed to temperatures greater than 30–35°; hence polymerization is minimized (cf. ref. [6]).

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrogen chloride (7647-01-0)

Benzene (71-43-2)

ether, diethyl ether (60-29-7)

phosphorus pentachloride (10026-13-8)

thionyl chloride (7719-09-7)

nitrogen (7727-37-9)

Phosphorus Oxychloride (21295-50-1)

potassium hydroxide (1310-58-3)

Diphenylacetic acid (117-34-0)

Diphenylacetyl chloride (1871-76-7)

Diphenylketene, Ethenone, diphenyl- (525-06-4)

hexane (110-54-3)

triethylamine (121-44-8)

Triethylamine hydrochloride (554-68-7)

triphenylphosphine (603-35-0)

α-bromodiphenylacetyl bromide (17397-37-4)

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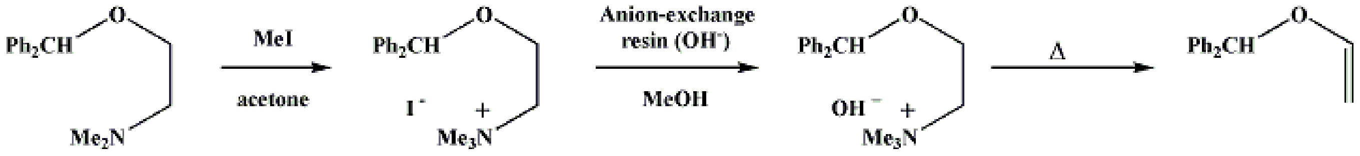
ALKENES *via* HOFMANN ELIMINATION: USE OF ION-EXCHANGE RESIN FOR PREPARATION OF QUATERNARY AMMONIUM HYDROXIDES: DIPHENYLMETHYL VINYL ETHER

[Benzene, 1,1'-[(ethenyloxy)methylene]bis-]



Submitted by Carl Kaiser and Joseph Weinstock[1].
Checked by P. Müller and G. Büchi.

1. Procedure

Caution! Methyl iodide, in high concentrations for short periods or in low concentrations for long periods, can cause serious toxic effects in the central nervous system. Accordingly, the American Conference of Governmental Industrial Hygienists[2] has set 5 p.p.m., a level which cannot be detected by smell, as the highest average concentration in air to which workers should be exposed for long periods. The preparation and use of methyl iodide should always be performed in a well-ventilated fume hood. Since the liquid can be absorbed through the skin, care should be taken to prevent contact.

A 250-ml., three-necked, round-bottomed flask equipped with a sealed mechanical stirrer, a dropping funnel, and a reflux condenser is charged with 13.3 g. (0.0522 mole) of 2-(diphenylmethoxy)-*N*,*N*-dimethylethylamine (Note 1) and 50 ml. of acetone. The solution is stirred, and 8.1 g. (0.057 mole) of methyl iodide in 15 ml. of acetone is added dropwise over 5 minutes (Note 2). After the addition is complete, the mixture is stirred for 30 minutes, then cooled to 0–10° with an ice bath. The crystalline product is filtered and washed with 15 ml. of acetone and 30 ml. of diethyl ether, yielding 20.0–20.2 g. (97–98%) of colorless, crystalline methiodide, m.p. 194–196°.

An excess (60 g., *ca.* 0.26 equivalent) of anion exchange resin (OH^- form, (Note 3)) in a 500-ml. Erlenmeyer flask is stirred with 200 ml. of methanol (Note 4) for 5 minutes. The methanolic slurry of resin is transferred to a 6.5 cm. × 25 cm. chromatography column, using 50–100 ml. of methanol to aid in the transfer. The resin column is washed with 750 ml. of methanol, added gradually so as to maintain about a 1–2.5 cm. solvent head above the upper resin level (Note 5). About two-thirds of the resin slurry is poured from the column (using about 100 ml. of methanol to aid the transfer) into a suspension of 19.9 g. (0.0499 mole) of the methiodide in 50 ml. of methanol (Note 6). The mixture is stirred and heated gently on a water bath, dissolving the crystalline methiodide. The resulting resin suspension is poured onto the column containing the remaining one-third of the resin. Additional methanol (*ca.* 50 ml.) is required to facilitate transferral. The column is eluted with about 500 ml. of methanol until the eluent no longer affords an alkaline reaction to pH paper (Note 7). The methanolic eluent is concentrated under reduced pressure (10–25 mm.), and the residual liquid (Note 8) is gradually heated to 100° under the water-aspirator vacuum. Following completion of thermal decomposition, as evidenced by the end of gas evolution (*ca.* 5–10 minutes), the residue is dissolved in 250 ml. of ether (Note 9). The ether solution is washed with 100 ml. of 0.2 *N* sulfuric acid and 100 ml. of water, dried over anhydrous magnesium sulfate, and filtered. The filtrate is concentrated, and distillation of the residue gives 8.5–9.0 g. (81–86%) of diphenylmethyl vinyl ether as a colorless liquid, b.p. 163–167° (18 mm.), n_D^{25} 1.5716 (Note 10) and (Note 11).

2. Notes

1. The submitters used 2-(diphenylmethoxy)-*N*,*N*-dimethylethylamine, b.p. 150–165° (2 mm.),[3] obtained from Searle Chemicals, Inc., or from the hydrochloride, m.p. 161–162°, which is available commercially from Gane's Chemical Works, Inc., New York, New York, under the generic name, diphenhydramine.
2. The reaction exotherm is just sufficient to cause moderate reflux.
3. A strongly basic, polystyrene, alkyl quaternary amine (hydroxide form) of medium porosity was employed. Research grade Rexyn 201 (OH) (purchased from Fisher Scientific Company) and Amberlite IRA-400 (purchased from Mallinckrodt Chemical Works) were found to be satisfactory. Chloride-form resins must be converted to the hydroxide form before use, as described below (Note 7).
4. It is necessary to wash the resin with methanol prior to packing of the column. If this is not done, swelling of the resin on treatment with the solvent may cause explosion of the column.
5. If the resin was not washed exhaustively with methanol, significant amounts of benzhydrol (α-phenylbenzenemethanol) and diphenylmethyl methyl ether were obtained in the final product.
6. Stirring of the methiodide with the anion exchange resin prior to introduction into the column is necessary, because of the insolubility of this quaternary salt in methanol. For methanol-soluble methiodides, a solution of the salt may be added directly to the methanol-washed resin column.
7. The recovered resin can be reconverted to the hydroxide form by eluting a column of the material with aqueous 10% sodium hydroxide until it is free of halide ion (silver nitrate–nitric acid test), then with water until the eluent is no longer alkaline to pH paper.

8. Heating should be carried out in a 1-l. (oversized) flask because decomposition is accompanied by considerable foaming.
9. A small amount of insoluble material, which is mainly unreacted 2-(diphenylmethoxy)-*N*,*N*-dimethylethylamine methiodide, can be removed at this point.
10. The product has the following spectral properties; IR (neat) cm.$^{-1}$: 1670, 1200, 770, 710; ^{1}H NMR ($CDCl_3$), δ (multiplicity, approx. coupling constant *J* in Hz., number of protons): 3.97 (d of d, J_{XY} = 2, J_{AX} = 7, 1H), 4.27 (d of d, J_{XY} = 2, J_{AY} = 14, 1H), 5.7 (S, 1H), 6.36 (q, J_{AX} = 7, J_{AY} = 14, 1H), 7.2 (S, 10H). The distilled product was about 98% pure by GC analysis on a 60 cm. × 0.6 cm. aluminum column packed with 10% SE-30 silicon rubber on Gas Chrom Z, 100–200 mesh, operated at 180°. The retention time was about 2.0 minutes. Minor amounts of benzhydrol and diphenylmethyl methyl ether (retention times 2.5 minutes and 1.8 minutes, respectively) accounted for the remainder of the distillate. The checkers found that GC analysis on a 1.8-m. column packed with 15% SE-30 on GAW, 60–80 mesh at 180°, at an injector temperature of 250° resulted in extensive decomposition. A satisfactory analysis, however, could be performed by lowering the injector temperature to 180°.
11. Reppe[4] reports b.p. 120° (15 mm.) for diphenylmethyl vinyl ether.

3. Discussion

Diphenylmethyl vinyl ether has also been prepared from benzhydrol and acetylene under high-pressure conditions.[4] In the described method, an adaptation of the procedure of Weinstock and Boekelheide,[5] improved yields of the alkene are obtained by using more convenient experimental conditions.

The described method for converting a quaternary halide to the corresponding hydroxide, utilizing an anion-exchange resin, has general application in the Hofmann elimination reaction.[6] It has been used extensively in the submitters' laboratories for the synthesis of a variety of alkenes[7] and for the preparation of a number of ethyl 1-benzylcyclopropanecarboxylates *via* abnormal Hofmann elimination of diethyl [2-(*N*,*N*-dimethylamino)ethyl]benzylmalonates.[8] It offers several notable advantages over more conventional methods for preparing quaternary hydroxides. Formation of quaternary hydroxides from iodides with bases (*e.g.*, silver oxide) that form insoluble iodides has disadvantages due to the expense of the reagent and, in some instances, the oxidizing power of silver salts in basic solution. Thallous ethoxide has been used to avoid the oxidation effect; however, it is expensive[9,10,11] and toxic. Quaternary methosulfates may be hydrolyzed to sulfates and converted to the hydroxide with barium hydroxide,[12] but this method has not found general application. The described procedure of exchange of hydroxide ion for halide is suitable for even very sensitive compounds and obviates most of the objectionable features of the precipitation methods.[5,6] In the event that methanol is undesirable, the conversion may be carried out in water.[5]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

acetylene (74-86-2)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

silver oxide (20667-12-3)

ethyl (2025-56-1)

acetone (67-64-1)

barium hydroxide (17194-00-2)

hydroxide, hydroxide ion (14280-30-9)

Methyl iodide (74-88-4)

silver (7440-22-4)

magnesium sulfate (7487-88-9)

benzhydrol, α-phenylbenzenemethanol (91-01-0)

silicon

Thallous ethoxide (20398-06-5)

Diphenylmethyl vinyl ether, Benzene, 1,1'-[(ethenyloxy)methylene]bis- (23084-88-0)

diphenhydramine, 2-(diphenylmethoxy)-N,N-dimethylethylamine (58-73-1)

diphenylmethyl methyl ether

2-(diphenylmethoxy)-N,N-dimethylethylamine methiodide

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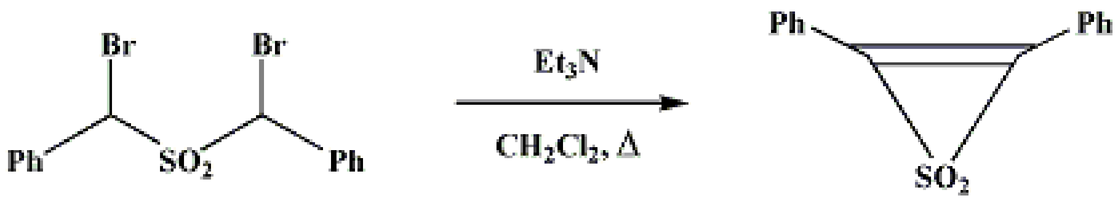
2,3-DIPHENYLVINYLENE SULFONE

[Thiirene, diphenyl-, 1,1-dioxide]



Submitted by Louis A. Carpino[1] and Louis V. McAdams III.
Checked by Timothy P. Higgs and Ronald Breslow.

1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

To a magnetically stirred solution of 6.36 g. (0.0157 mole) of crude α,α'-dibromodibenzyl sulfone (m.p. 135–150°; *Org. Synth.*, **Coll. Vol. 6**, 403 (1988)) in 40 ml. of dichloromethane contained in a 100-ml., round-bottomed flask fitted with a reflux condenser there is added in one portion 5.05 g. (0.0500 mole) of triethylamine. The solution is heated at reflux with stirring for 3 hours (Note 1), filtered, and the precipitate washed with 5 ml. of cold (0°) dichloromethane. The combined dichloromethane solution is washed with two 20-ml. portions of 3 *N* hydrochloric acid followed by one 10-ml. portion of water. Removal of the solvent by distillation from a water bath at 30° with the aid of a water aspirator gives 3.0 g. (80%) of the vinylene sulfone as a tan solid, m.p. 116–126° (dec.). The crude solid is washed with 5 ml. of cold (0°) ethanol and recrystallized from about 10 ml. of benzene, yielding 2.4–2.5 g. (63–67%) of the pure sulfone as tiny, snow-white needles, m.p. 123–126° (dec.) (Note 2).

2. Notes

1. After about 45 minutes triethylamine hydrobromide began to precipitate.
2. The submitters obtained a similar percent yield on ten times the scale.

3. Discussion

2,3-Diphenylvinylene sulfone has been prepared by dehydrohalogenation of either α, α'-dibromodibenzyl sulfone[2 3] or α,α'-dichlorodibenzyl sulfone,[4] as well as by oxidation of 2,3-diphenylvinylene sulfoxide.[5] The procedure described here illustrates

a general technique for the synthesis of diarylvinylene sulfones and has been extended to a number of substituted derivatives.[5,6] Aliphatic derivatives have been synthesized in other ways.[3,7,8] The vinylene sulfones are a group of compounds of considerable theoretical interest.[2,3,9,10,11,12,13]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

2,3-Diphenylvinylene sulfone

2,3-diphenylvinylene sulfoxide

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

sulfone (7446-09-5)

sulfur (7704-34-9)

dichloromethane (75-09-2)

triethylamine (121-44-8)

triethylamine hydrobromide (636-70-4)

α,α'-Dibromodibenzyl sulfone (21966-50-7)

Thiirene, diphenyl-, 1,1-dioxide (5162-99-2)

vinylene sulfone

α,α'-dichlorodibenzyl sulfone

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Organic Syntheses, CV 6, 556

1,3-DITHIANE

Submitted by E. J. Corey[1] and D. Seebach[2].
Checked by J. C. Reilly and W. D. Emmons.

1. Procedure

A 1-l., three-necked, round-bottomed flask with ground-glass fittings is charged with a mixture of 36 ml. of boron trifluoride diethyl etherate, 72 ml. of glacial acetic acid, and 120 ml. of chloroform (Note 1). The flask is equipped with a spiral reflux condenser, an efficient mechanical stirrer, and a dropping funnel (Note 2). The chloroform solution is heated and maintained at reflux with vigorous stirring, and a solution of 32 g. (30 ml., 0.30 mole) of 1,3-propanedithiol and 25 g. (29 ml., 0.33 mole) of methylal (dimethoxymethane) in 450 ml. of chloroform (Note 1) is added at a constant rate over 8 hours. The mixture is allowed to cool to room temperature, washed successively with four 80-ml. portions of water, twice with 120 ml. of 10% aqueous potassium hydroxide, and twice with 80-ml. portions of water. The chloroform solution obtained is dried over potassium carbonate and concentrated in a 500-ml., round-bottomed flask under reduced pressure with a rotating flask evaporator (Note 3). The residue, which crystallizes on cooling to room temperature, is dissolved in 60 ml. of methanol by heating to the boiling point. The hot solution is filtered rapidly through a prewarmed funnel, allowed to cool slowly to room temperature, then kept overnight at –20°. The colorless crystals are collected by filtration through a prechilled Büchner funnel, washed with cold methanol (–20°), and dried under reduced pressure (Note 3) and (Note 4), yielding 28–29 g. of product, m.p. 53–54°. Solvent is removed from the mother liquor, and the residue is recrystallized as described, giving an additional 1.5–2.0 g.; the total yield of recrystallized 1,3-dithiane is 29.5–31.0 g. (82–86% based on propane-1,3-dithiol). A purer sample (Note 5) can be prepared by subsequent sublimation of the recrystallized product at 0.1–0.5 mm. (45–48° bath temp.) (Note 6). The yield of pure product is 28–30 g. (78–84%), m.p. 53–54°. The residue from the sublimation is a brown syrup weighing less than 1 g.

2. Notes

1. The following components were used as supplied: boron trifluoride etherate, Eastman white label; chloroform and methylal, Fischer reagent; glacial acetic acid, du Pont reagent; 1,3-propanedithiol, Aldrich Chemical Co. The submitters have scaled up this preparation by a factor of 5 without difficulty.

2. Neither the boron trifluoride etherate nor the acetic acid should be added through the dropping funnel, since the presence of even small amounts of acid in the funnel would catalyze undesired condensation of the reagents to be added later. Furthermore the reagents added from the dropping funnel should fall directly into the boiling liquid.
3. Owing to the volatility of 1,3-dithiane, the pressure should be above 30 mm., and the operation should not be prolonged.
4. The crude product can also be distilled; b.p. 95° (20 mm).
5. This additional purification is recommended if the 1,3-dithiane is to be used in organometallic reactions.[3]
6. Using a sublimator large enough to contain all the recrystallized product obtained, the sublimation can be completed in *ca.* 2 hours at 0.1 mm.

3. Discussion

Although many workers have reported studies with 1,3-dithiane,[4,5,6,7,8] no satisfactory description of its preparation has been published. Generally, 1,3-propanedithiol and formaldehyde[4,6,8] have been used as components; in one instance, 1,3-dibromopropane was treated with sodium thiosulfate to form a precursor of the dithiol which was used as such with formalin.[5] The formation of linear condensation products is a serious side reaction under such conditions.

The procedure given here is a simple and efficient method for producing 1,3-dithiane, a valuable intermediate in the synthesis *via* lithio derivatives of a wide variety of compounds, including aldehydes, ketones, α-hydroxyketones, 1,2-diketones, and α-keto acid derivatives.[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 109
- Org. Syn. Coll. Vol. 6, 316
- Org. Syn. Coll. Vol. 7, 114

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

potassium carbonate (584-08-7)

acetic acid (64-19-7)

methanol (67-56-1)

formaldehyde, formalin (630-08-0)

chloroform (67-66-3)

1,3-dibromopropane (109-64-8)

sodium thiosulfate (7772-98-7)

potassium hydroxide (1310-58-3)

methylal, Dimethoxymethane (109-87-5)

boron trifluoride etherate, boron trifluoride diethyl etherate (109-63-7)

1,3-propanedithiol, propane-1,3-dithiol (109-80-8)

1,3-Dithiane (505-23-7)

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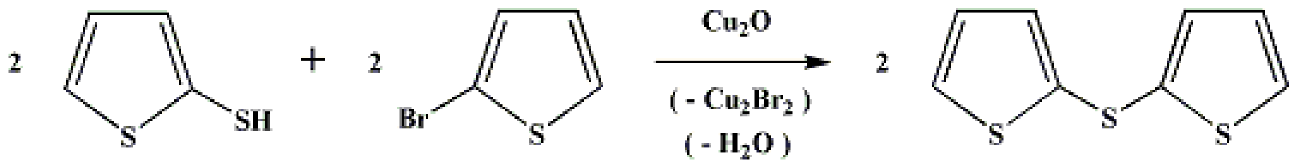
Organic Syntheses, CV 6, 558

2,2'-DITHIENYL SULFIDE

[Thiophene, 2,2'-thiobis-]



Submitted by E. Jones and I. M. Moodie[1].
Checked by Jerry G. Kohlhoff, Wayland E. Noland, and William E. Parham.

1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A three necked, 250-ml. flask fitted with a reflux condenser stirrer and a thermometer pocket with a nitrogen inlet is charged with 100 ml. of *N,N*-dimethylformamide, 5.6 g. (0.10 mole) of potassium hydroxide (Note 1), and 7.15 g. (0.0500 mole) of freshly precipitated copper(I) oxide[2] (Note 2). 2-Bromothiophene (16.4 g., 0.101 mole) (Note 3) is added, and the apparatus is flushed with nitrogen (Note 4). 2-Thiophenethiol[3] [11.6 g., 0.100 mole; *Org. Synth.*, **Coll. Vol. 6**, 979 (1988)] is then added slowly through the condenser; an exothermic reaction begins, and the temperature may rise to 50–60°. The flask is heated in an oil bath at 130–140° for 16 hours (Note 5). The mixture is cooled to room temperature before the contents of the flask are poured into 100 ml. of 6 *N* hydrochloric acid in ice. The mixture is stirred vigorously for 2 hours (Note 6); the oily black paste obtained is removed by filtration and thoroughly extracted in a Soxhlet extractor with benzene until a colorless extract is obtained. The filtrate is also extracted with two 100-ml. portions of benzene. These extracts are combined, washed with water until neutral, and dried over anhydrous sodium sulfate. Removal of the solvent gives a yellow-colored oil which, on vacuum distillation, yields 11.5–12.5 g. (58–63%) of 2,2'-dithienyl sulfide as a pale yellow oil, b.p. 75–78° (0.06 mm.) n_D^{25} 1.6643.

2. Notes

1. The presence of an equivalent of potassium or sodium hydroxide is necessary to promote the substitution reaction of the 2-bromothiophene with copper(I) oxide.
2. Freshly precipitated copper(I) oxide was dried at 110° before use. Commercial grades were found to give lower yields (*ca.* 35–40%) of the desired sulfide. The checkers dried copper(I) oxide in a vacuum oven at 100° for 6 hours.
3. 2-Bromothiophene was supplied by Columbia Organic Chemicals, Inc. 2-Chloro- or 2-iodothiophenes may be used; however, the former gives poorer yields of the sulfide.
4. Nitrogen is passed through the system to provide an inert atmosphere, preventing possible oxidation of the 2-thiophenethiol to the corresponding disulfide.
5. Reaction is sluggish at temperatures below 130°.
6. Vigorous stirring helps to break up the thick sludge formed on addition of the reaction mixture to the acid and also removes soluble inorganic salts.

3. Discussion

The submitters have also prepared 2,2'-dithienyl sulfide in 34% yield by condensation of 2-thiophenethiol with 2-bromothiophene in the presence of copper(I) oxide in a quinoline-pyridine mixture.[4] Challenger and Harrison[5] have obtained 2,2'-dithienyl sulfide in 50–55% yield by treatment of 2-thienylmagnesium bromide with excess sulfur. This sulfide may also be obtained in 20% yield by condensation of thiophene with sulfur monochloride, followed by pyrolysis of the resultant disulfide.[6]

This synthetic process offers a route to the preparation of the isomeric dithienyl sulfides[7] (2,3- and 3,3-) which cannot be prepared readily by any of the standard methods. Thus, condensation of 2-thiophenethiol with 3-bromothiophene or 3-thiophenethiol with 2-bromothiophene gives 2,3'-dithienyl sulfide in 63.0 and 73.5% yields, respectively. Similarly, 3,3'-dithienyl sulfide is obtained in 48% yield. The method has also been extended to the synthesis of the isomeric *bis*-(thienylthio) thiophenes in 40–50% yield.[4]

This method may also be used for the preparation in high yields of other aromatic sulfides.[8]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

2,2'-DITHIENYL SULFIDE

potassium or sodium hydroxide

2-Chloro- or 2-iodothiophenes

quinoline-pyridine

2,3'-dithienyl sulfide

3,3'-dithienyl sulfide

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

sulfur (7704-34-9)

copper(I) oxide

potassium hydroxide (1310-58-3)

sulfur monochloride

Thiophene (110-02-1)

N,N-dimethylformamide (68-12-2)

2-thiophenethiol (7774-74-5)

2-Bromothiophene (1003-09-4)

2-thienylmagnesium bromide

3-Bromothiophene (872-31-1)

3-thiophenethiol

Thiophene, 2,2'-thiobis- (3988-99-6)

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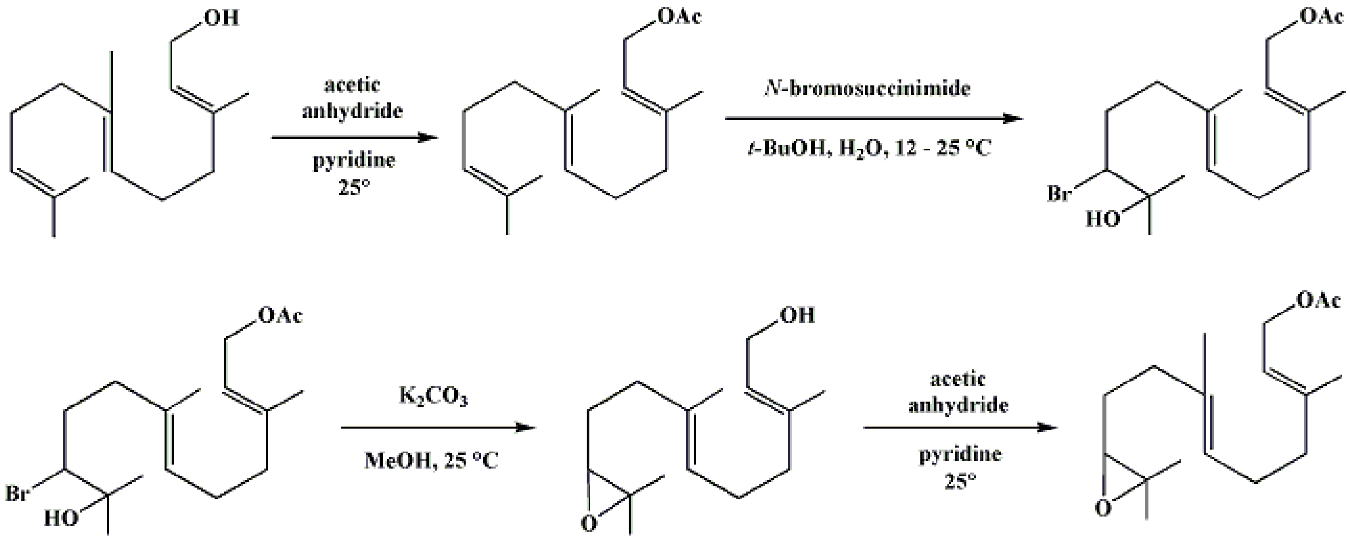
Organic Syntheses, CV 6, 560

SELECTIVE EPOXIDATION OF TERMINAL DOUBLE BONDS: 10,11-EPOXYFARNESYL ACETATE

[2,6-Nonadien-1-ol, 9-(3,3-dimethyloxiranyl)-3,7-dimethyl-, acetate, (*E*,*E*)-]



Submitted by R. P. Hanzlik[1]
Checked by A. Grieder and G. Büchi.

1. Procedure

A. ***Farnesyl acetate***. A solution of 25 g. (0.11 mole) of farnesol (Note 1) in 40 ml. of dry pyridine (Note 2) is prepared in a stoppered, 250-ml. Erlenmeyer flask, and 40 ml. of acetic anhydride is added in four portions over a 15-minute period. The mixture is stirred well, allowed to stand for 6 hours then poured onto 250 g. of ice. Water is added (400 ml.), and the mixture is extracted with five 100-ml. portions of petroleum ether (b.p. 60–68°). The organic extracts are combined and washed in succession with two 50-ml. portions each of water, 5% sulfuric acid, and saturated aqueous sodium hydrogen carbonate, dried over anhydrous magnesium sulfate (*ca.* 50 g.), and concentrated on a rotary evaporator, yielding 28–29 g. (94–98%) of farnesyl acetate as a colorless oil (Note 3).

B. *10-Bromo-11-hydroxy-10,11-dihydrofarnesyl acetate*. Farnesyl acetate (29 g., 0.11 mole) is dissolved in 1 l. of *tert*-butyl alcohol (Note 4) contained in a 3-l. Erlenmeyer flask. Water is added (500 ml.), and the solution is cooled to about 12° with an external ice water bath. Maintaining this temperature, rapid magnetic stirring is begun, and more water is added until a saturated solution is obtained. The second addition of water may be rapid initially, but the saturation point must be approached carefully, like the end point of a titration. A total of about 1200 ml. of water is required for the specified quantities of farnesyl acetate and *tert*-butyl alcohol. The solution must remain clear and homogeneous at about 12°, and if the saturation point is accidentally passed by adding too much water, *tert*-butyl alcohol should be added to remove the turbidity.

External cooling is discontinued, and 21.4 g. (0.120 mole) of *N*-bromosuccinimide (Note 5) is added. Stirring is continued until all of the solid is dissolved (*ca.* 1 hour). The resulting solution, which may be pale yellow, is concentrated with a rotary evaporator (bath temperature 40–45°) to a volume of about 300 ml. and extracted with five 120-ml. portions of diethyl ether. The combined ether extracts are dried over anhydrous magnesium sulfate (20–50 g.), and removal of solvent at reduced pressure provides an oil, which is purified by column chromatography on silica gel (Note 6). The pure bromohydrin acetate is obtained as a colorless oil in amounts of up to 26 g., a 65% yield based on farnesyl acetate (Note 7) and (Note 8).

C. *10,11-Epoxyfarnesyl acetate*. The bromohydrin acetate prepared in Part B is dissolved in 300 ml. of methanol, the solution is placed in a 500-ml. flask, and excess solid potassium carbonate (three times the molar amount of bromohydrin acetate) is added (Note 9). The mixture is stirred for 12 hours and then concentrated to *ca.* 100 ml. on a rotary evaporator (bath at 40–45°). Water is added (200 ml.), and the mixture is extracted with four 100-ml. portions of petroleum ether (b.p. 60–68°). The combined extracts are dried over anhydrous magnesium sulfate (*ca.* 40 g.) and evaporated, leaving 10,11-epoxyfarnesol as a colorless oil (Note 10).

This material is acetylated with 35 ml. of pyridine and 35 ml. of acetic anhydride for 6 hours at room temperature. The mixture is poured onto 250 g. of ice and extracted with five 75-ml. portions of ether. The combined ether extracts are washed successively with three 10-ml. portions each of saturated aqueous sodium hydrogen carbonate and water then dried over magnesium sulfate. It is important not to use strong acids such as hydrochloric or sulfuric to remove pyridine, as was done in Part A, since they can destroy the acid-sensitive product.

Concentration of the ethereal solution at reduced pressure gives the epoxyacetate as a colorless oil more viscous than water. The

overall yield based on farnesyl acetate is near 60% (Note 11). This material is reasonably pure if the preparation has been executed carefully, but it can be further purified by column chromatography (Note 12) or distillation (Note 13).

2. Notes

1. Farnesol was obtained from Fluka AG (Buchs, CH9470, Switzerland) as a mixture of 65% (*E*),(*E*)- and 35% (*Z*),(*E*)-isomers. It is also available from the Aldrich Chemical Company, Inc. This procedure works equally well with pure (*E*),(*E*)-farnesol, which may be obtained from the above mixture by careful distillation, at reduced pressure, through a Nester-Faust Teflon spinning-band column.
2. Pyridine was distilled from sodium hydroxide.
3. IR (neat) cm.$^{-1}$: 1740, 1240; ^{1}H NMR (CCl_4), δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 2.00 (s, 3H, O_2CCH_3), 4.46 (d, *J* = 7, 2H, CH_2O), 4.49–5.4 (m, 3H, olefinic *H*).
4. Tetrahydrofuran or glyme work equally well in place of *tert*-butyl alcohol as a co-solvent, but should be distilled under dry nitrogen from lithium aluminum hydride[2] or sodium and benzophenone [*Org. Synth.*, **Coll. Vol. 5**, 201 (1973)] prior to use, to destroy peroxides which may be present.
5. The *N*-bromosuccinimide should be nearly white and uncontaminated by free bromine. If necessary, it may be recrystallized from hot water and stored in a refrigerator.
6. The submitters mixed active anhydrous silica gel with water (12% w/w) and stored it in a sealed container for at least 24 hours prior to use. A ratio of 60–80 g. of silica gel per gram of crude product was used for column chromatographic separations, and a column was chosen that would give a 10:1 height:diameter ratio of adsorbent. Columns were wet-packed with distilled petroleum ether (b.p. 60–68°), and after the crude product had been applied a step-gradient was run through rapidly: 2% ether, 5% ether, and 10% ether (v/v) in petroleum ether. The column was then eluted with 20% v/v ether in petroleum ether until the bromohydrin acetate was obtained.
The checkers obtained roughly 30 g. of crude product in each run. Freshly opened Woelm silica gel (obtained from ICN Pharmaceuticals, 26201 Miles Ave., Cleveland, Ohio 44128) was deactivated as above, and 1800 g. was wet-packed with petroleum ether in a 65-mm.-internal-diameter column. In the first run the column was eluted as above, but a considerable amount of solvent was required to collect the product. Therefore, in the second run the crude product was applied to the column as a solution in petroleum ether, and 1-l. portions of 20% v/v ether:petroleum ether, 30% ether, 40% ether, 50% ether, 60% ether, and 70% ether were run through. None of these six fractions contained a significant weight of material. Elution with 2 l. of 80% v/v ether:petroleum ether provided the bromohydrin acetate.
Fractions may be monitored by TLC on silica gel, developing with 10% v/v ethyl acetate in hexane and visualizing with iodine vapor. The following R_f values were observed: farnesol, 0.07; farnesyl acetate, 0.35; bromohydrin acetate, 0.20.
7. In each of two runs, the checkers obtained 25 g. (63% yield).
8. IR (neat) cm.$^{-1}$: 3520, 3450, 1740, 1235; ^{1}H NMR (CCl_4), δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 1.32 [s, 6H, $OC(CH_3)_2$], 2.00 (s, 3H, O_2CCH_3), 3.7–4.0 (m, 1H, C*H*Br), 4.50 (d, *J* = 7, 2H, CH_2O), 4.9–5.5 (m, 2H olefinic H).
9. Using a smaller amount of K_2CO_3 made the reaction much slower and did not avoid or reduce the accompanying loss of the acetate group. Pyridine at room temperature is not sufficiently basic to form the epoxide. Other bases were not tested.
10. IR (neat) cm.$^{-1}$: 3450, 2940, 1450, 1375; ^{1}H NMR (CCl_4), δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment): δ 1.25 and 1.29 [2s, 6H, $OC(CH_3)_2$], 2.55 (t, *J* = 6, 1H, OC*H*), 3.97 (d, *J* = 7, 2H, OCH_2), 5.0–5.5 (m, 2H, olefinic C*H*).
11. In each of two runs, the checkers obtained 19 g. (61% yield). IR (neat) cm.$^{-1}$: 2950, 1740, 1380, 1235; ^{1}H NMR (CCl_4), δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 1.21 and 1.23 [2s, 6H, $OC(CH_3)_2$], 1.97 (s, 3H, O_2CCH_3), 2.50 (t, *J* = 6, 1H, OC*H*), 4.48 (d, *J* = 7, 2H, OCH_2), 5.0–5.5 (m, 2H, olefinic C*H*).
12. Deactivation of silica gel and preparation of the column is carried out as in (Note 6), except that the checkers consider 20 g. of silica gel per gram of crude product to be adequate in this case. Running through a gradient of petroleum ether containing increasing amounts of ether, the submitters found that the product was eluted with 15% (v/v) ether, but the checkers found that 25% (v/v) ether was required.
13. The submitters recommend distillation at 100° at less than 0.005 mm. The checkers distilled 1–2 g.-samples at 0.05 mm. (b.p. 113°) and at 0.15 mm. (b.p. 117°), and in both cases a clean product was obtained with high recovery.

3. Discussion

10,11-Epoxyfarnesol was first prepared by van Tamelen, Storni, Hessler, and Schwartz[3] using essentially this procedure, which is based on the findings of van Tamelen and Curphey[4] that *N*-bromosuccinimide in a polar solvent is a considerably more selective oxidant than others tried. This method has been applied to produce terminally epoxidized mono-, sesqui-, di-, and triterpene systems for biosynthetic studies and bioörganic synthesis.[5] It has also been applied successfully in a simple synthesis of tritium-labeled squalene and squalene-2,3-oxide[6] and in the synthesis of *Cecropia* juvenile hormone.[7]

The oxidation procedure described above is intended to illustrate the selectivity that may be achieved using this system for functionalizing only one of several superficially similar double bonds in a molecule. In the case of acyclic terpenes, the yield of the desired terminal monobromohydrin decreases from 75–80% with geraniol ($C_{10}H_{18}O$) to 30–35% with squalene ($C_{30}H_{50}$), due to

competing formation of polybromohydrins, allylic bromides, and bromocyclized material. The significant point, however, is that in all cases more than 95% of the monobromohydrin produced results from attack at the terminal double bond. A mechanistic investigation[8] showed that the *N*-bromosuccinimide was not merely providing a source of bromine or hypobromous acid, and that the reaction was promoted by acid and inhibited by base.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

petroleum ether

tritium-labeled squalene

squalene-2,3-oxide

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

acetic anhydride (108-24-7)

sodium hydroxide (1310-73-2)

sodium hydrogen carbonate (144-55-8)

bromine (7726-95-6)

nitrogen (7727-37-9)

iodine (7553-56-2)

pyridine (110-86-1)

Benzophenone (119-61-9)

sodium (13966-32-0)

hypobromous acid (13517-11-8)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

N-bromosuccinimide (128-08-5)

hexane (110-54-3)

geraniol (106-24-1)

tert-butyl alcohol (75-65-0)

farnesol

10,11-Epoxyfarnesyl acetate, 2,6-Nonadien-1-ol, 9-(3,3-dimethyloxiranyl)-3,7-dimethyl-, acetate, (E,E)- (50502-44-8)

Farnesyl acetate

10,11-epoxyfarnesol

squalene

10-Bromo-11-hydroxy-10,11-dihydrofarnesyl acetate (54795-59-4)

(E),(E)-farnesol

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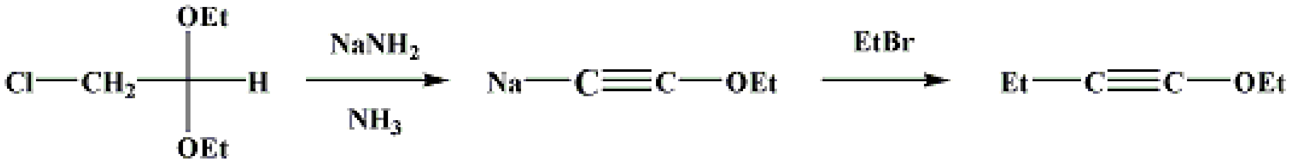
Organic Syntheses, *CV 6*, *564*

1-ETHOXY-1-BUTYNE

[1-Butyne, 1-ethoxy-]



Submitted by Melvin S. Newman[1] and W. M. Stalick[2].
Checked by P. J. Kocienski and G. Büchi.

1. Procedure

A 1-l., three-necked, round-bottomed flask equipped with an efficient dry-ice condenser (Note 1), a mechanical stirrer, and a gas-inlet tube is immersed in an acetone–dry ice bath, and 600 ml. of anhydrous ammonia is introduced. After replacing the inlet tube with a stopper, the cooling bath is lowered but kept beneath the flask. To the slowly stirred ammonia is added 0.5 g. of hydrated iron (III) nitrate. Air, dried by passing through calcium chloride, is bubbled through the solution for about 10 seconds (Note 2) after a small piece of freshly cut sodium is added (Note 3). Once hydrogen evolution has ceased, the blue color is discharged, leaving a finely divided, black precipitate. Small pieces of freshly cut sodium are then added over a 20 minute period until 36.0 g. (1.56 g.-atom) has been added. After the formation of sodium amide is complete (Note 4), the stopper is replaced with a pressure-equalizing dropping funnel containing 76.1 g. (0.499 mole) of chloroacetaldehyde diethyl acetal (Note 5), and the addition is made over a period of 20 minutes (Note 6). After 30–60 minutes the mixture becomes light gray, and 120 g. (1.10 mole) of freshly distilled ethyl bromide is added rapidly through the addition funnel (Note 7). The mixture is stirred vigorously for 2.5 hours, after which 30 ml. of cooled, saturated ammonium chloride solution is *cautiously* added through the addition funnel, followed by 120 ml. of pentane and an additional 370 ml. of the cooled, saturated ammonium chloride solution. The contents of the flask are transferred to a 2-l. separatory funnel (in the hood); the lower aqueous layer is removed and extracted with two 75-ml. portions of pentane (Note 8). The combined organic layers are filtered through glass wool to dissipate any emulsions, dried over magnesium sulfate, and filtered through a coarse-fritted funnel with gentle suction into a 500-ml., round-bottomed flask. A magnetic stirring bar is added, and the pentane is removed by distillation at atmospheric pressure through a 20 × 2 cm. column packed with glass beads (Note 9) and fitted with a well-cooled fractionating head. With an acetone–dry ice trap between the receiver and the vacuum source, the yellow residue is distilled under reduced pressure (Note 10), with rapid magnetic stirring, into dry-ice-cooled receivers, giving 1-ethoxy-1-butyne as a clear, colorless liquid at 43–45° (50 mm.). A lower-boiling fraction collection at 20–42° (50 mm.) is combined with any material removed from the dry-ice trap and redistilled, yielding additional product, for a total of 30.2–32.3 g. (62–66%) (Note 11).

2. Notes

1. A gas bubbling device is attached to the dry-ice condenser. A simple apparatus consists of two, 500-ml. filtering flasks equipped with one-hole neoprene stoppers and glass tubing extending to the bottom of the flasks. The two flasks are connected through the glass tubing by a short piece of Tygon tubing. About 150 ml. of mineral oil is then placed in the flask

distant from the condenser.
2. The checkers found that air was not necessary to initiate the formation of sodium amide. See Ref.[3]
3. The sodium is cut under dry pentane just before introducing each sample into the flask.
4. Complete conversion into sodium amide is indicated by cessation of gas evolution and disappearance of the blue color of the solution. This generally requires 20–30 minutes and results in a gray suspension of sodium amide in a dark-gray reaction medium.
5. Chloroacetaldehyde diethyl acetal was used as obtained from Aldrich Chemical Company, Inc.
6. During any of the additions in this preparation excessive foaming may occur. This may be effectively diminished by interrupting the addition of the reagent or by brief immersion of the reaction flask in the acetone–dry-ice bath. If foaming has reached the condenser, be certain that the condenser is not plugged before proceeding.
7. The addition of ethyl bromide is accompanied by vigorous reflux of the ammonia and should be carefully monitored.
8. Since 1-ethoxy-1-butyne is very volatile, extreme care should be taken during the work-up to minimize loss of product due to evaporation. Extractions should be accompanied by careful and frequent venting of the separatory funnel to prevent excessive pressure.
9. The checkers used a 20-cm. Widmer column for the distillation.
10. The pot temperature should be kept below 80°. Distillation must be conducted at temperatures below 90° to preclude dimerization.[4]
11. IR (CCl_4) $cm.^{-1}$, strong peaks: 1245, 1230, 1015, 855. ^1H NMR (CCl_4), δ (multiplicity, number of protons, assignment): 1.23 (overlapped t, 6H, $2CH_3$), 2.13 (q, 2H, $C{=}CCH_2$), 3.99 (q, 2H, OCH_2).

3. Discussion

The synthesis of 1-ethoxy-1-butyne has been reported previously, but the preparations have required multistep sequences. Two of the procedures use 1,2-dibromo-1-ethoxy butane which is dehydrohalogenated in two successive steps, first by an amine base and then by either powdered potassium hydroxide[5] or sodium amide;[6] no yields are given. The other procedure starts with 1,2-dibromoethyl ethyl ether which, upon treatment with *N,N*-diethylaniline, yields 2-bromovinyl ethyl ether. When 2-bromovinyl ethyl ether is allowed to react with lithium amide in ammonia, followed by alkylation with diethyl sulfate, 1-ethoxy-1-butyne is isolated in about 55% yield.[7]

Some studies seeking preferred conditions for this reaction have been reported.[8] Optimum yields of 1-ethoxy-1-propyne and 1-ethoxy-1-butyne are found when the product is worked up before allowing the ammonia solvent to evaporate, as the product evidently volatilizes with the ammonia. An experiment with 1-ethoxy-1-propyne showed a marked increase in yield when ammonia predried over calcium hydride was used instead of ammonia directly obtained from a cylinder. A twofold excess of ethyl bromide is required to obtain a good yield of 1-ethoxy-1-butyne, since elimination apparently competes with alkylation in this case.

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

calcium chloride (10043-52-4)

ammonia (7664-41-7)

ammonium chloride (12125-02-9)

hydrogen (1333-74-0)

Ethyl bromide (74-96-4)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

Pentane (109-66-0)

diethyl sulfate (64-67-5)

magnesium sulfate (7487-88-9)

N,N-diethylaniline (91-66-7)

sodium amide (7782-92-5)

iron(III) nitrate

1,2-dibromoethyl ethyl ether (2983-26-8)

lithium amide (7782-89-0)

chloroacetaldehyde diethyl acetal (621-62-5)

2-bromovinyl ethyl ether

calcium hydride (7789-78-8)

1-Ethoxy-1-butyne, 1-Butyne, 1-ethoxy- (14272-91-4)

1,2-dibromo-1-ethoxy butane

1-ethoxy-1-propyne

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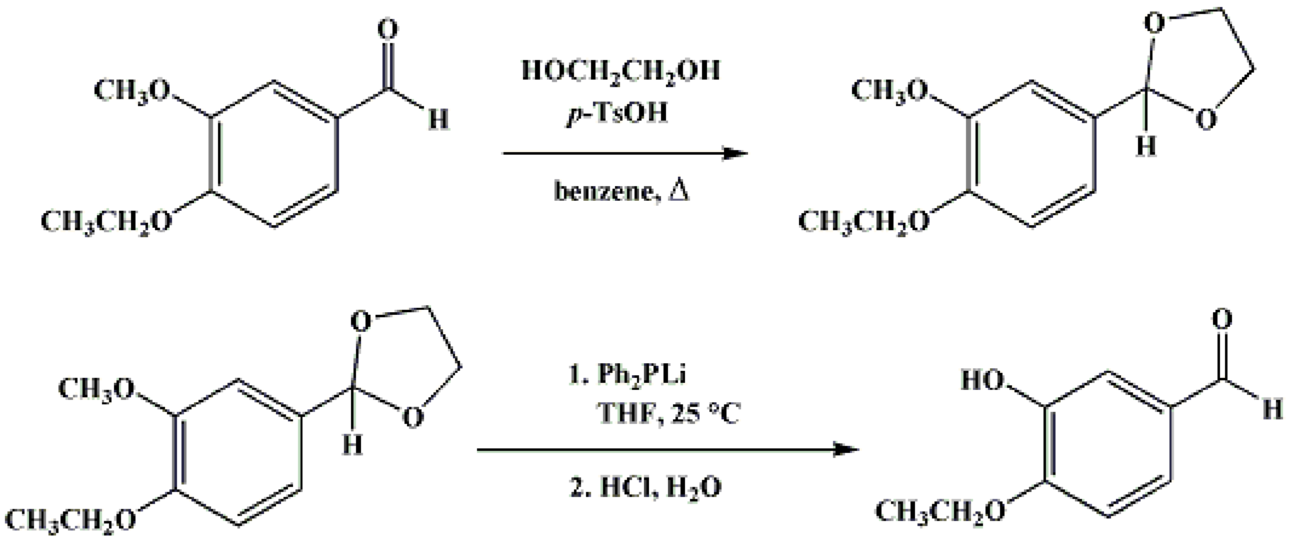
Organic Syntheses, CV 6, 567

DEMETHYLATION OF METHYL ARYL ETHERS: 4-ETHOXY-3-HYDROXYBENZALDEHYDE

[Benzaldehyde, 4-ethoxy-3-hydroxy-]



Submitted by Robert E. Ireland[1] and David M. Walba[2].
Checked by R. Andersen and G. Büchi.

1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A. *4-Ethoxy-3-methoxybenzaldehyde ethylene acetal.* A 500-ml., three-necked flask with vertical necks is fitted with a magnetic stirring bar and a 30-ml. water separator, to which is attached a condenser topped with an argon inlet. The flask is charged with 300 mg. (0.00158 mole) of *p*-toluenesulfonic acid monohydrate, 270 ml. of benzene (Note 1), 33 g. (30 ml., 0.53 mole) of ethylene glycol, and 5.0 g. (0.028 mole) of 4-ethoxy-3-methoxybenzaldehyde (Note 2), then placed under a positive pressure of argon, which is maintained throughout the reaction. Vigorous stirring is begun, and the solution is brought to reflux with an oil bath at 110°.

After 20 hours at reflux, the mixture is cooled to room temperature with a water bath and poured with vigorous stirring into 500 ml. of 10% aqueous potassium carbonate contained in a 1-l. separatory funnel. The benzene layer is washed successively with two 250-ml. portions of 10% aqueous potassium carbonate and 250 ml. of brine containing potassium carbonate (Note 3), dried over sodium sulfate for 10 minutes, and filtered. Removal of the solvent on a rotary evaporator with a 25–35° water bath provides a solid yellow residue, which is dried under vacuum.

To obtain a crystalline product, a solution of the residue in 30 ml. of benzene containing a few drops of triethylamine (Note 4) is placed in a 250-ml. Erlenmeyer flask, heated gently on a steam bath, and diluted with 150 ml. of hexane. Heating is continued for about 5 minutes (Note 5), after which the solution is allowed to cool to room temperature, seeded, and put in a freezer at –15° for

at least 5 hours. The resulting solid is collected by suction filtration, washed with cold hexane, and vacuum dried, giving 5.8 g. (94%) of light cream-colored crystals, m.p. 75–77°.

B. *4-Ethoxy-3-hydroxybenzaldehyde.* A 100-ml., three-necked flask containing a magnetic stirring bar and fitted with an argon inlet, a rubber septum, and a ground-glass stopper in the center neck is evacuated, flame-dried, and allowed to cool under a positive pressure of argon, which is maintained throughout the following sequence. Using a syringe, 30 ml. of dry tetrahydrofuran (Note 6) and 5.0 ml. (0.029 mole) of diphenylphosphine (Note 7) are added through the septum. The resulting solution is stirred and cooled with an ice bath, and 15 ml. (0.032 mole) of cold 2.1 *M* *n*-butyllithium–hexane solution (Note 8) is added by syringe over *ca.* 3 minutes. Stirring is continued as the red solution is allowed to warm to room temperature over about 30 minutes before 5.0 g. (0.022 mole) of 4-ethoxy-3-methoxybenzaldehyde ethylene acetal is added through the center neck. The flask is stoppered, and the mixture is stirred at room temperature for 2 hours.

The reaction mixture is then poured into a 500-ml. Erlenmeyer flask containing 200 ml. of vigorously stirred water, 10 ml. of 10% aqueous sodium hydroxide is added, and the mixture is transferred to a 500-ml. separatory funnel. The reaction vessel and Erlenmeyer flask are rinsed with water, and the rinsings are also poured into the funnel. Alkali-insoluble impurities are removed by washing the basic aqueous phase with four 100-ml. portions of diethyl ether, which are combined and backextracted with two 50-ml. portions of 10% aqueous sodium hydroxide. The combined aqueous layers are then put into a 1-l. Erlenmeyer flask, cooled in an ice bath, and acidified with concentrated hydrochloric acid to a Congo red end point. During acidification the clear yellow basic solution becomes cloudy white. This milky suspension is stirred without cooling for 3 minutes then extracted with 200 ml. of ether and two 100-ml. portions of ether. The combined ether layers are washed successively with 100 ml. of water and 100 ml. of saturated aqueous sodium chloride, dried over magnesium sulfate, and filtered. Removal of solvent with a rotary evaporator provides a residue that is vacuum dried, yielding 3.58–3.60 g. (97–98%) of a slightly yellow solid, m.p. 121.5–126°. One recrystallization from 20 ml. of benzene gives almost white crystals which are vacuum dried, affording 3.21–3.29 g. (87–88%) of 4-hydroxy-3-ethoxybenzaldehyde, m.p. 125.5–127° (Note 9) and (Note 10).

2. Notes

1. Reagent grade benzene was used without further purification.
2. Practical grade 4-ethoxy-3-methoxybenzaldehyde was obtained by the submitters from MC and B Manufacturing Chemists and by the checkers from Aldrich Chemical Company, Inc. This material was purified by distillation (b. p. 125–135°/0.1 mm.), followed by one recrystallization from cyclohexane (100 ml./10 g. crude solid). Colorless crystals, m.p. 60–62°, were obtained after filtration and vacuum drying. Purification of 20 g. of the commercial material gave about 15 g. of recrystallized product.
3. This solution is prepared by dilution of 25 ml. of 10% aqueous potassium carbonate to 250 ml. with saturated aqueous sodium chloride.
4. Triethylamine was distilled from calcium hydride prior to use and added to the benzene to protect the sensitive acetal from hydrolysis.
5. It is not necessary to boil the solution. This heating merely prevents crystals from coming out of solution too fast on addition of the hexane.
6. Tetrahydrofuran was purified and dried according to the procedure described in *Org. Synth.*, **Coll. Vol. 5**, 976 (1973).
7. Commercial diphenylphosphine obtained from Orgmet, Inc., may be used without further purification. Alternatively, the material may be prepared from triphenylphosphine as

follows. A 2-l., three-necked flask containing a magnetic stirring bar and fitted with an argon inlet is charged with 120 g. (0.458 mole) of triphenylphosphine and 1 l. of dry tetrahydrofuran ((Note 6)). To the stirred solution is added 18.42 g. (2.670 g.-atoms, 542 cm. of 0.32 cm.-diameter wire) of lithium wire, which has been washed with hexane and dried carefully with a paper towel. *(Caution! If the towel is rubbed against the lithium too fast, a fire will result.)* Lithium is added by cutting 3–5-mm. segments directly into the center neck of the flask with scissors. A slow argon flow is maintained throughout the addition, which requires about 20 minutes. The flask is stoppered, and the red solution is stirred for 2.5 hours under argon.

The solution is then filtered through a piece of glass wool (fitted loosely in a funnel) into a 2-l. beaker containing 600 g. of crushed ice. A glass rod is used to stir the mixture, and the reaction vessel and filter are rinsed with ether. The resulting two clear phases are transferred to a 2-l. separatory funnel and extracted with four 200-ml. portions of ether. The combined ether layers are washed with 250 ml. of 5% hydrochloric acid, 250 ml. of water, and two 250-ml. portions of saturated aqueous sodium chloride, then dried over magnesium sulfate for hour. Since diphenylphosphine is susceptible to air oxidation, especially in dilute ether solution, the extractions should be carried out as quickly as possible. After gravity filtration, the ether solution is concentrated on a rotary evaporator, and the residue is vacuum dried, yielding 83.7 g. (99%) of crude product. Pure material is then obtained by distillation. The submitters used a small (14/20 joints, 15 cm. long) Vigreux column and observed b.p. 90–103° (0.06 mm.). Using a 20-cm. Vigreux column, the checkers observed b.p. 95–115° (0.06 mm.). In either case, the yield of clear liquid was 62 g. (74%). If the product is stored under argon in a bottle sealed with a rubber serum cap, it is stable for months at room temperature. *Caution! Care should be taken not to get any diphenylphosphine on a paper towel, as it may ignite spontaneously.*

8. *n*-Butyllithium in hexane was obtained from Ventron Corporation and stored in a refrigerator under argon. The solution was titrated with 2-butanol in xylene, using 1,10-phenanthroline as indicator.

9. The literature m.p. for the colorless crystals is 127–128°.[3]

10. IR ($CHCl_3$) $cm.^{-1}$: 3550 (OH), 1680 (C=O), 1610, 1580, 1510, 1470; ^1H NMR ($CDCl_3$), δ (multiplicity, coupling constant *J* in Hz., number of protons): 1.47 (t, *J* = 7,

3. Discussion

4-Ethoxy-3-hydroxybenzaldehyde (isobourbonal) has been prepared in good yield

The present procedure illustrates the facile demethylation of methyl aryl ethers with lithium diphenylphosphide.[4] This reaction is specific for methyl ethers and may be carried out in the presence of ethyl ethers in high yield.[5] Use of excess reagent allows cleavage in the presence of enolizable ketones.[6] In the present case, the cleavage may be performed without protection of the aldehyde, but two equivalents of reagent are required, and the yield is reduced to *ca.* 60%.

The exact time and temperature required for complete reaction must be determined for each individual compound. It has been observed that nucleophilic demethylation of methyl *o*-alkoxyaryl ethers is accelerated relative to anisole,[7] and this reaction is no exception. Lithium diphenylphosphide cleavage of anisole is complete in about 4 hours in refluxing tetrahydrofuran, whereas the present reaction is complete within 2 hours at 25°.

References and Notes

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2. Present address: Department of Chemistry, University of Colorado, Campus Box 215, Boulder, Colorado 80309.
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6. Gloria Pfister, unpublished results, this laboratory.
7. G. I. Feutrill and R. N. Mirrington, *Aust. J. Chem.*, **25**, 1719, 1731 (1972).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

brine

4-Ethoxy-3-hydroxybenzaldehyde (isobourbonal)

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether, diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

Anisole (100-66-3)

cyclohexane (110-82-7)

ethylene glycol (107-21-1)

xylene (106-42-3)

lithium, Lithium wire (7439-93-2)

magnesium sulfate (7487-88-9)

n-butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

hexane (110-54-3)

triethylamine (121-44-8)

calcium hydride (7789-78-8)

triphenylphosphine (603-35-0)

argon (7440-37-1)

2-Butanol (78-92-2)

1,10-phenanthroline (66-71-7)

4-Ethoxy-3-hydroxybenzaldehyde, Benzaldehyde, 4-ethoxy-3-hydroxy- (2539-53-9)

4-ethoxy-3-methoxybenzaldehyde (120-25-2)

diphenylphosphine (829-85-6)

4-Ethoxy-3-methoxybenzaldehyde ethylene acetal (52987-93-6)

4-hydroxy-3-ethoxybenzaldehyde (121-32-4)

lithium diphenylphosphide

p-toluenesulfonic acid monohydrate (6192-52-5)

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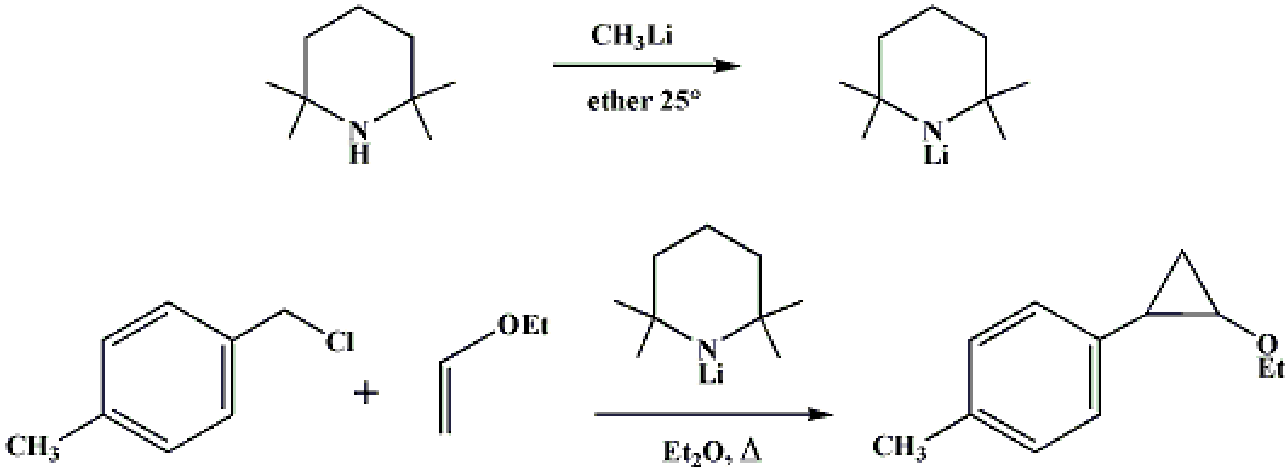
CARBENE GENERATION BY α-ELIMINATION WITH LITHIUM 2,2,6,6-TETRAMETHYLPIPERIDIDE: 1-ETHOXY-2-*p*-TOLYLCYCLOPROPANE

[Benzene, 1-(2-ethoxycyclopropyl)-4-methyl]



Submitted by Charles M. Dougherty[1] and Roy A. Olofson[2].
Checked by Mark W. Johnson and Robert M. Coates.

1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A 250-ml., three-necked, round-bottomed flask equipped with a 50-ml. pressure-equalizing dropping funnel capped by a rubber septum, an efficient reflux condenser connected to a nitrogen inlet, and a magnetic stirrer (Note 1) is charged with 7.02 g. (0.0500 mole) of α-chloro-*p*-xylene (Note 2) and 45.6 g. (0.633 mole) of ethyl vinyl ether (Note 3). A solution of 7.06 g. (0.0501 mole) of 2,2,6,6-tetramethylpiperidine (Note 4) in 15 ml. of dry diethyl ether is injected through the septum into the dropping funnel. Lithium 2,2,6,6-tetramethylpiperidide is generated *in situ* by injecting 46.5 ml. (0.0502 mole) of a 1.08 *M* solution of methyllithium in ether (Note 5) through the septum over a 5–10-minute period (Note 6) and (Note 7). After another 10 minutes, the contents are added dropwise to the vigorously stirred solution in the flask at a rate that maintains a gentle reflux. When the *ca.* 2-hour addition period is complete, the white slurry is stirred overnight at room temperature (Note 8). Water (10 ml.) is added dropwise to the stirred suspension, and the contents of the flask are poured into a separatory funnel containing 100 ml. of ether and 100 ml. of water. The aqueous layer is separated and extracted with two 100-ml. portions of ether. The combined ether solutions are washed successively with 10% aqueous citric acid (Note 9), 5% aqueous sodium hydrogen carbonate, and water, dried with anhydrous calcium chloride, filtered and evaporated with a rotary evaporator. The residual liquid is distilled at reduced pressure, affording 6.6–7.0 g. (75–80%) of 1-ethoxy-2-*p*-tolylcyclopropane, b.p. 116–118° (10 mm.), 95–96° (3.2 mm.) (Note 10).

2. Notes

1. The glassware is dried in an oven at approximately 125° and assembled while still warm. The nitrogen inlet, which consists of a T-tube assembly connected to an oil bubbler, is attached, and the apparatus is allowed to cool while being swept with a stream of dry nitrogen. The septum is placed on top of the dropping funnel, and the nitrogen flow adjusted to maintain a slight positive pressure of nitrogen within the apparatus during the reaction.

2. α-Chloro-*p*-xylene was obtained from Aldrich Chemical Company, Inc., and purified by distillation under reduced pressure.

3. Ethyl vinyl ether was supplied by Aldrich Chemical Company, Inc., and distilled from sodium. If simple alkenes are used in place of ethyl vinyl ether, the submitters find that the yields of cyclopropanes are improved by dilution of the olefin with one or two volumes of ethyl ether.

4. 2,2,6,6-Tetramethylpiperidine, furnished by Aldrich Chemical Company, Inc., Fluka A G, and ICN Life Sciences Group, is sometimes contaminated with traces of water, hydrazine, and/or 2,2,6,6-tetramethyl-4-piperidone. These impurities may be removed by drying with sodium hydroxide or potassium hydroxide pellets, filtering, and distilling at atmospheric pressure, b.p. 153–154°. The purified amine can be stored indefinitely under a nitrogen atmosphere.

5. Methyllithium in ethyl ether from Ventron Corporation was used. Directions for the preparation of ethereal methyllithium from methyl bromide are also available [see *Org. Synth.*, **Coll. Vol. 6**, 901 (1988).] The checkers standardized the solution immediately before use by diluting a 2.5-ml. aliquot with 10 ml. of benzene and titrating with a 1 *M* solution of 2-butanol in xylene according to the procedure of Watson and Eastham[3] [see *Org. Synth.*, **Coll. Vol. 6**, 121 (1988)], with 1,10-phenanthroline as indicator. The submitters report that the yield of arylcyclopropane is lower if a commercially available solution of *n*-butyllithium in hydrocarbon solvents is used.

6. The methane generated is vented by passage through the oil bubbler.

7. Since the reaction between methyllithium and 2,2,6,6-tetramethylpiperidine is relatively slow at lower temperatures, lithium 2,2,6,6-tetramethylpiperidide is best prepared at room temperature. The reagent may, however, be used over a wide range of temperatures.

8. Approximately the same yields are obtained if the product is isolated after 2–3 hours.

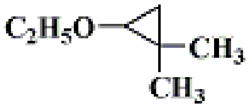
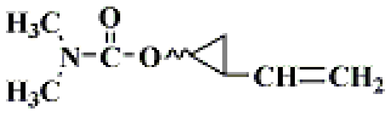
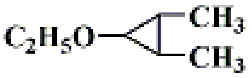
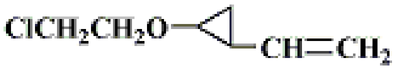
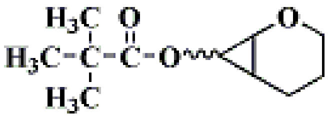
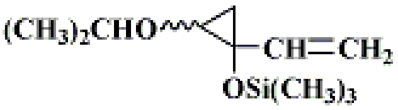
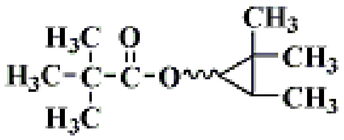
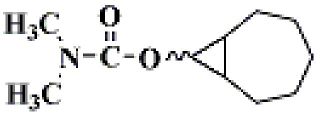
9. The use of aqueous citric acid avoids the formation of insoluble gelatinous precipitates, which result when hydrochloric acid is employed. Sulfuric acid is a suitable alternative to citric acid but must be used in substantial excess to prevent precipitation 2,2,6,6-Tetramethylpiperidine may be recovered from the citric acid extract by making the aqueous solution basic and extracting with ether.

10. The product, a mixture of *cis*- and *trans*-isomers in the ratio of about 2:1, has the following spectral properties: IR (liquid film) cm^{-1} (strong): 1510, 1440, 1370, 1340, 1120, 1080; ^{1}H NMR (CCl_4), δ (multiplicity, number of protons, assignment): 0.63–1.3 (m, 5H, cyclopropyl CH_2 and OCH_2CH_3), 1.4–2.0 (m, 1H, cyclopropyl C*H*), 2.23 (s, 1H, *trans*-aromatic CH_3), 2.28 (s, *ca.* 2H, *cis*-aromatic CH_3), 2.8–3.7 (m, 3H, $CHOCH_2CH_3$), 6.7–7.2 (m, 4H, C_6H_4). The following specific absorptions in the ^{1}H NMR spectrum may be used to estimate the ratio of the two isomers, δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment); *cis*-isomer: 0.92 (t, $J = 7$, 3H, OCH_2CH_3), 7.02 (center of *AA'BB'* m, 4H, C_6H_4); *trans*-isomer: 1.14 (t, $J = 7$, 3H, OCH_2CH_3), 6.88 (center of *AA'BB'* m, 4H, C_6H_4).

3. Discussion

This procedure describes the generation of the strong, nonnucleophilic amide base, lithium 2,2,6,6-tetramethylpiperidide, which is used in the regioselective abstraction of a proton from a very weak carbon acid containing other sites reactive toward nucleophilic attack.[4,5] In contrast, most other strong bases undergo preferential alkylation with benzyl halides. 1-Ethoxy-2-*p*-tolylcyclopropane is one of over a dozen aryl cyclopropanes, cyclopropenes, and cyclopropanone ketals that have been prepared by this method[5] (Table I). An analog, 1-methoxy-2-phenylcyclopropane, has been obtained in 8% yield from the reaction of methyllithium with dichloromethyl methyl ether in styrene.[6] The alkene is present in large excess, as is commonly the case for reactions involving short-lived carbene intermediates. In the present procedure ethyl vinyl ether serves as both solvent and reactant. For best results with alkenes lacking alkoxy substituents, approximately two volumes of ether or tetrahydrofuran should be used as diluent. Alkoxy,[7,8] acyloxy,[9] alkenyl,[5,10,11] trialkylsilyl,[10] and trialkylstannyl[10] carbenes have been generated and trapped *in situ* with alkenes and alkynes by this method, affording a variety of substituted cyclopropanes.

TABLE I
PREPARATION OF CYCLOPROPANES FROM ALKYL HALIDES, ALKENES, AND LITHIUM 2,2,6,6-TETRAMETHYLPIPERIDIDE

Product	Yield (%)	Product	Yield (%)
	66[7]		21[9]
	66[7]		64[8]
	74[8]		39[9]
	46[7]		62[8]
	35[9]		20 (24)[9]

Lithium 2,2,6,6-tetramethylpiperidide has also been used to advantage in a number of other types of reactions. This base reacts with aryl halides[5,10,12,13] (and, less cleanly, with aryl sulfonates[14]), giving benzynes, which have been trapped with thiolates,[5] acetylides,[5,14] enolates,[10,13,14] and

conjugated dienes.[10,12,14] Replacement of halogen by hydrogen, a major reaction observed between other dialkylamide bases and aryl halides, does not occur with lithium 2,2,6,6-tetramethylpiperidide.[5] While alkyl benzoates undergo selective deprotonation at the *ortho*-position upon treatment with this amide base,[15] methyl thiobenzoate and *N*,*N*-dimethylbenzamide are metallated at the methyl group, forming dipole-stabilized carbanions.[16] The organolithium intermediates produced condense with the remaining ester or amide, affording various aryl ketones. Lithiation of dibromomethane[17] and at the α-position of isocyanides[18] with lithium 2,2,6,6-tetramethylpiperidide produces an organolithium intermediate reactive toward carbonyl compounds. In the synthesis of enol carbonates from ketone enolates and chloroformates, this base is the only one to accomplish the reaction in high yield.[19] Lithium 2,2,6,6-tetramethylpiperidide has been shown to be the base of choice for irreversible ketone enolate formation[20] and has been used to discriminate sterically between two potential enolate sites to yield alkylation products with extremely high regioselectivity.[21] The enolate anions of esters[5,22] and dianions of β-keto esters[23] and propiolic acid[24] have been formed by reaction with lithium 2,2,6,6-tetramethylpiperidide. It is a superior base for metallation of selenides,[25] selenoacetals, and selenoketals.[26] Other reactions in which this hindered base has proved effective include the conversion of an epoxide to an enolate anion,[27] the generation of certain α-lithioörganoboranes,[28] the preparation of the highly strained tetracyclo(4.2.0.0^{2,4}.0^{3,5})oct-7-ene from the appropriate tosylhydrazone,[29] and the insertion of magnesium into bacteriopheophytin α.[30] In many of these reactions, other bases, including less hindered amide bases such as lithium diisopropylamide, gave either lower yields or different products entirely.

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Lithium 2,2,6,6-tetramethylpiperidide

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether, ethyl ether, diethyl ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

citric acid (77-92-9)

sodium hydrogen carbonate (144-55-8)

magnesium (7439-95-4)

nitrogen (7727-37-9)

methane (7782-42-5)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

methyl bromide (74-83-9)

xylene (106-42-3)

hydrazine (302-01-2)

dibromomethane (74-95-3)

styrene (100-42-5)

n-butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

Methyllithium (917-54-4)

ethyl vinyl ether (109-92-2)

Dichloromethyl methyl ether (4885-02-3)

2-Butanol (78-92-2)

lithium diisopropylamide (4111-54-0)

1,10-phenanthroline (66-71-7)

Benzene, 1-(2-ethoxycyclopropyl)-4-methyl, 1-Ethoxy-2-p-tolylcyclopropane

2,2,6,6-tetramethylpiperidine (768-66-1)

2,2,6,6-tetramethyl-4-piperidone (826-36-8)

1-methoxy-2-phenylcyclopropane

methyl thiobenzoate

propiolic acid (471-25-0)

tetracyclo(4.2.0.0^{2,4}.0^{3,5})oct-7-ene

α-chloro-p-xylene (104-82-5)

N,N-dimethylbenzamide (611-74-5)

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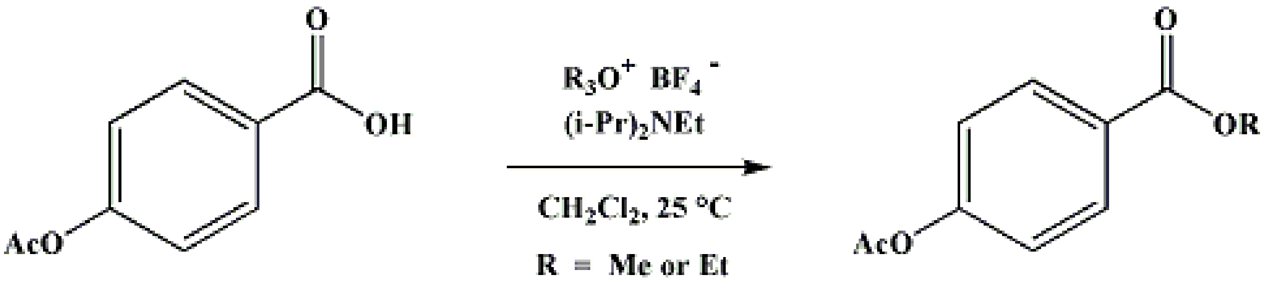
Organic Syntheses, CV 6, 576

ESTERIFICATION OF CARBOXYLIC ACIDS WITH TRIALKYLOXONIUM SALTS: ETHYL AND METHYL 4-ACETOXYBENZOATES

[Benzoic acid, 4-(acetyloxy)-, ethyl and methyl esters]



Submitted by Douglas J. Raber[1], Patrick Gariano, Jr., Albert O. Brod, Anne L. Gariano, and Wayne C. Guida.
Checked by H. Fliri and G. Büchi.

1. Procedure

A. *Ethyl 4-acetoxybenzoate.* A 100-ml., one-necked, round-bottomed flask is charged with 2.09 g. (0.0110 mole) of triethyloxonium tetrafluoroborate (Note 1) and (Note 2), 75 ml. of dichloromethane (Note 3), and 1.80 g. (0.0100 mole) of 4-acetoxybenzoic acid (Note 4). A magnetic stirring bar is added, and the solution is stirred while 1.4 g. (1.9 ml., 0.011 mole) of diisopropylethylamine (Note 5) is introduced with a syringe (Note 6). The flask is then stoppered and allowed to stand at room temperature for 16–24 hours.

Work-up is initiated by extracting the reaction mixture with three 50-ml. portions of 1 *N* hydrochloric acid, three 50-ml. portions of aqueous 1 *N* potassium hydrogen carbonate (Note 7) and (Note 8), and 50 ml. of saturated aqueous sodium chloride. The organic solution is dried over sodium sulfate (Note 9), filtered, and concentrated on a rotary evaporator. Purification of the residue by bulb-to-bulb distillation (Note 10) at about 140° (5 mm.) provides 1.77–1.98 g. (85–95%) of ethyl 4-acetoxybenzoate as a colorless, viscous liquid (Note 11).

B. *Methyl 4-acetoxybenzoate.* A 100-ml., one-necked, round-bottomed flask is charged with 1.63 g. (0.0110 mole) of trimethyloxonium tetrafluoborate (Note 2) and (Note 12), 75 ml. of dichloromethane (Note 3) and (Note 13), and 1.80 g. (0.0100 mole) of 4-acetoxybenzoic acid (Note 4). A magnetic stirring bar is added, and the suspension is stirred while 1.4 g. (1.9 ml., 0.011 mole) of diisopropylethylamine (Note 5) is introduced with a syringe (Note 6). The flask is then stoppered, and stirring is continued at room temperature for 16–24 hours, during which time the oxonium salt dissolves. Work-up exactly as that described in Part A is followed by bulb-to-bulb distillation (Note 10) at about 140° (5 mm.), yielding 1.65–1.84 g. (85–95%) of methyl 4-acetoxybenzoate, m.p.

78–80° (Note 14).

2. Notes

1. Triethyloxonium tetrafluoroborate was prepared according to *Org. Synth.*, **Coll. Vol. 5**, 1080 (1973). The submitters stored this material at −20° under ether in a tightly-stoppered jar and found that the use of a dry box or an inert atmosphere was not required in its handling. A sample of the oxonium salt–ether slurry was transferred to the tared reaction flask, ether was removed on a rotary evaporator, and the resulting solid was weighed and used without further purification. The checkers stored the dry oxonium salt under argon at −15°, maintained an argon atmosphere in all operations involving this reagent, and used dry solvent (Note 3). They obtained 98% yields in two runs of Part A and two runs of Part B.
2. A 10% molar excess of the oxonium salt with regard to the carboxylic acid gives slightly higher yields than does an equimolar quantity.
3. The submitters used reagent grade dichloromethane without purification. The checkers dried dichloromethane by distillation from phosphorus pentoxide.
4. This is prepared from 4-hydroxybenzoic acid and acetic anhydride following a procedure for 2-acetoxybenzoic acid.[2] The crude product is conveniently purified by stirring with chloroform (about 15 ml. per gram of acid) and removing any insoluble residue by filtration. Evaporation of the chloroform gives the desired material, m.p. 186–188° (lit.,[3] m.p. 189–190°).
5. This product was obtained from Aldrich Chemical Company, Inc. In many cases, the use of other amines may be satisfactory. Nevertheless, the use of a hindered base minimizes destruction of the oxonium salt by side reaction with the amine. Substitution of triethylamine for diisopropylamine in the procedure gave lower yields of the ester.
6. The use of a syringe affords a convenient method both for measuring the desired quantity of amine and adding it to the reaction mixture. In general, a mildly exothermic reaction takes place during addition of the amine. The submitters, working in an open vessel, suggest that if the reaction is scaled up or if the solution is more concentrated, care should be taken to add the amine gradually so that the reaction mixture does not boil over. For large-scale reactions they recommend the use of a dropping funnel. The checkers, working under argon and introducing the amine through a rubber septum, noted a considerable increase in pressure during the addition. Thus, with this experimental setup a suitable pressure vent is required.
7. Any unreacted carboxylic acid may be recovered by neutralization and extraction of the hydrogen carbonate solution.
8. In preparing ethers of phenols, aqueous 1 *N* sodium hydroxide should be substituted for the sodium hydrogen carbonate solution.
9. In many instances, the dichloromethane solution can be dried adequately by a simple filtration through coarse filter paper.
10. The “Kügelrohr” apparatus sold by Rinco Instrument Company, Inc., or any comparable bulb-to-bulb distillation apparatus is satisfactory. Fractional distillation is unnecessary.
11. The product crystallizes on standing overnight at −20° and melts at 30–32°. GC

analysis showed it to be at least 99% pure. Ethyl 4-acetoxybenzoate has been reported to melt at 34°.[4]

12. This compound was prepared according to *Org. Synth.*, **Coll. Vol. 6**, 1019 (1988). Both submitters and checkers stored and handled this material using the techniques outlined for triethyloxonium tetrafluoborate in (Note 1).

13. Trimethyloxonium tetrafluoroborate is only slightly soluble in dichloromethane. However, the use of a two-phase mixture presents no difficulties in either experimental procedure or yield.

14. GC analysis showed this material to be at least 99% pure. The melting point of methyl 4-acetoxybenzoate has been reported[5] as 81–81.6°. In both their runs, the checkers obtained a distilled product which melted from 60° to 74°, resolidified at 74°, and then remelted at 78–79°. A sample recrystallized from hexane showed the same behavior.

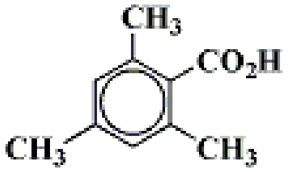
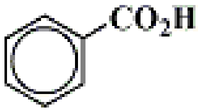
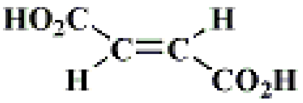
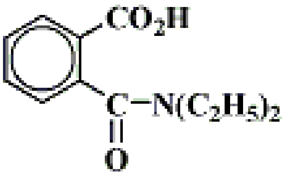
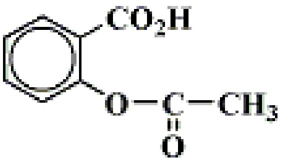
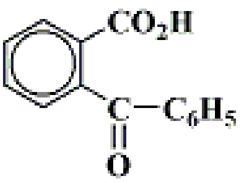
3. Discussion

This procedure provides a convenient method for the esterification of a wide variety of carboxylic acids.[6 7] The reaction proceeds smoothly with sterically hindered acids[6] and with those which contain various functional groups.[7] Esters are obtained in high purity using Kugelrohr distillation as the sole purification technique. In cases where traces of dichloromethane present no problems, the crude product is usually pure enough to be used directly in subsequent reactions. Methyl and ethyl ethers of phenols may also be prepared by this procedure (see (Note 8)).

Examples of polyfunctional carboxylic acids esterified by this method are shown in Table I. Yields are uniformly high, with the exception of those cases (maleic and fumaric acids) where some of the product appears to be lost during work-up as a result of water solubility. Even with carboxylic acids containing a second functional group (e.g., amide, nitrile) which can readily react with the oxonium salt, the more nucleophilic carboxylate anion is preferentially alkylated. The examples described in detail above illustrate the esterification of an acid containing a labile acetoxy group, which would not survive other procedures such as the traditional Fischer esterification.

TABLE I
ESTERIFICATION OF CARBOXYLIC ACIDS WITH TRIALKYLOXONIUM FLUOBORATES

	Triethyloxonium Fluoborate		Trimethyloxonium Fluoborate	
Acid	Yield (%)[a]	Purity (%)[b]	Yield (%)[a]	Purity (%)[b]

	90	>99	90	>99
	91	>99	92	>99
	77[c]	>99	80[c]	>99
	70[c]	>99	74[c]	>99
	91	>99	82	95
	88	>99	86	>99
	89	95	85	>99
	95	>99	95	>99

*a*Yield of distilled or crystallized ester.

*b*By GC.

*c*In the esterification of dibasic acids a corresponding increase in equivalents of oxonium salt is employed; the product is the diester.

The great utility of the trialkyloxonium salts is illustrated by the fact that high yields of esters are obtained using reagent which has been stored for up to 6 months under the submitters' conditions (Note 1) and (Note 12). Thus, either trimethyl- or triethyloxonium tetrafluoroborate can be prepared in quantity, stored, and used for esterification as required.

Other examples of esterification with triakyloxonium salts have been reported.[8,9] The present procedure offers the advantages that the reactive carboxylate ion is generated *in situ* and that a low-boiling, nonaqueous solvent is employed, simplifying the experimental procedure considerably. A related method which utilizes a hindered amine with dimethyl sulfate as the alkylating agent has been reported. The present procedure is carried out under somewhat milder conditions and avoids the use of highly toxic reagents.

The only other esterification method which rivals the present procedure in convenience, mildness of conditions, selectivity, and yield is the preparation of methyl esters with diazomethane.[10] Esterification with trialkyloxonium salts, however, allows preparation of both methyl and ethyl esters and avoids the toxicity and explosion hazard[11] of diazomethane.

Furthermore, recent studies indicate that esterifications involving triethyloxonium tetrafluoroborate are often very rapid. For example, subsequent to the checking of this procedure the submitters have found that the reaction time of Part A may be shortened from 16–24 hours to 0.5 hour with no decrease in yield. The longer reaction time is still recommended for esterifications involving the trimethyl salt, such as that of Part B, because of the heterogeneous nature of the reaction mixture in these cases.

12

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

amine

Benzoic acid, 4-(acetyloxy)-, ethyl and methyl esters

trimethyl- or triethyloxonium tetrafluoroborate

hydrochloric acid (7647-01-0)

ether (60-29-7)

acetic anhydride (108-24-7)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium hydrogen carbonate (144-55-8)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

dimethyl sulfate (77-78-1)

dichloromethane (75-09-2)

2-acetoxybenzoic acid (50-78-2)

Diazomethane (334-88-3)

4-hydroxybenzoic acid (99-96-7)

hexane (110-54-3)

triethylamine (121-44-8)

potassium hydrogen carbonate (298-14-6)

argon (7440-37-1)

Triethyloxonium fluoborate, triethyloxonium tetrafluoroborate (368-39-8)

trimethyloxonium fluoborate, Trimethyloxonium tetrafluoroborate (420-37-1)

diisopropylamine (108-18-9)

Ethyl 4-acetoxybenzoate (13031-45-3)

4-acetoxybenzoic acid (2345-34-8)

diisopropylethylamine (7087-68-5)

trimethyloxonium tetrafluoborate

Methyl 4-acetoxybenzoate (24262-66-6)

triethyloxonium tetrafluoborate

phosphorus pentoxide (1314-56-3)

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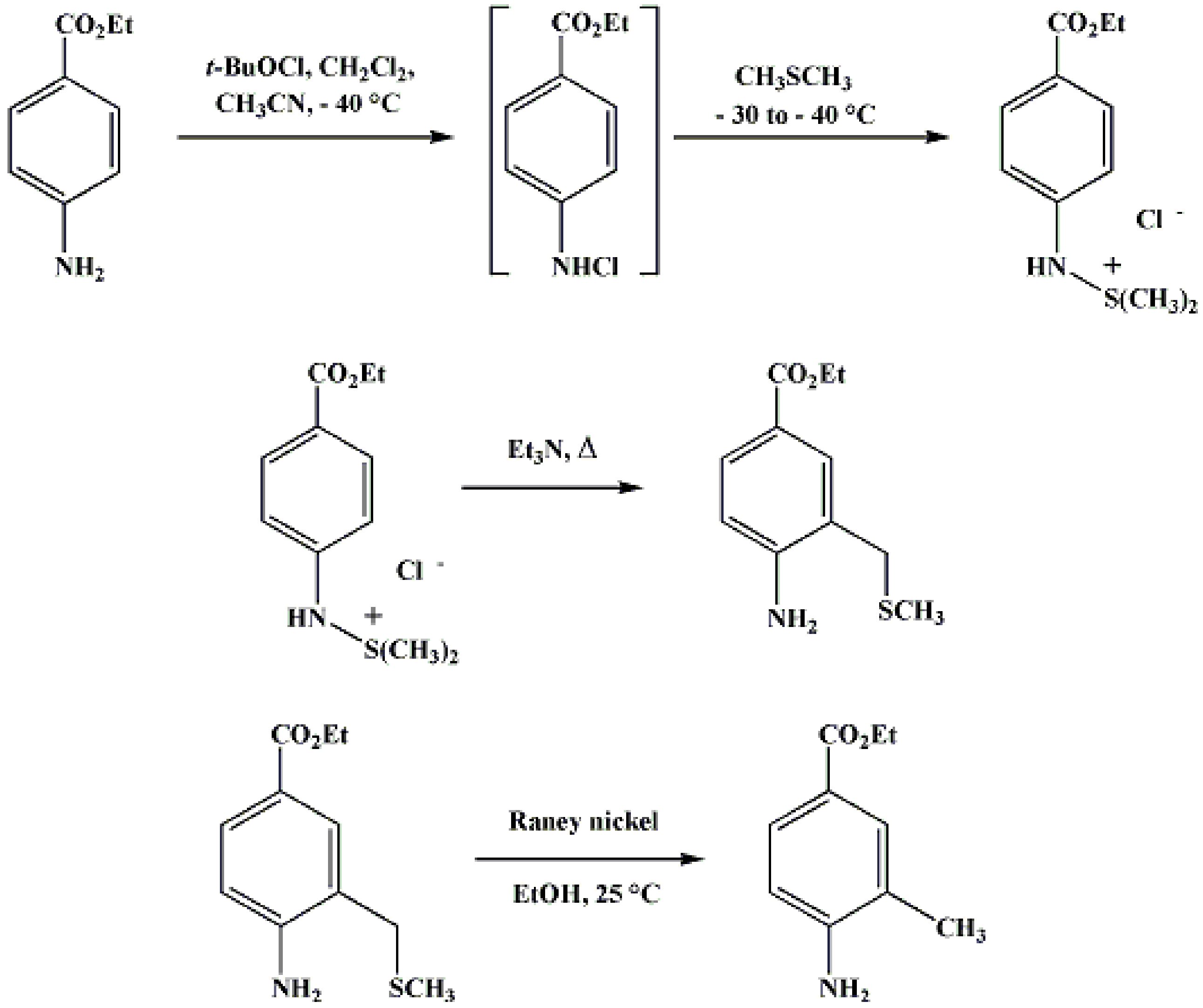
Organic Syntheses, CV 6, 581

ortho-ALKYLATION OF ANILINES: ETHYL 4-AMINO-3-METHYLBENZOATE

[Benzoic acid, 4-amino-3-methyl-, ethyl ester]



Submitted by P. G. Gassman[12] and G. Gruetzmacher.
Checked by M. Savitsky, R. R. Schmidt, III, and G. Büchi.

1. Procedure

Caution! Part A must be conducted in a hood due to the noxious odor of dimethyl sulfide. In Part B, the usual precautions associated with the pyrophoric reagent Raney nickel must be observed (see (Note 8)).

A. *Ethyl 4-amino-3-(methylthiomethyl)benzoate.* A 1-l., three-necked, round-bottomed flask is fitted with a mechanical stirrer, a condenser topped with a gas-inlet tube, a two-necked adapter holding a low-temperature thermometer, and a 100-ml., pressure-equalizing dropping funnel. The flask is charged with 16.50 g. (0.1000 mole) of ethyl 4-aminobenzoate (Benzocaine, (Note 1)), 300 ml. of acetonitrile, and 100 ml. of dichloromethane, flushed with nitrogen, and immersed in a 40%

aqueous methanol–dry-ice bath maintained between –40° and –50° (Note 2). When the reaction mixture has come to –40°, a solution of 10.85 g. (0.1000 mole) of *tert*-butyl hypochlorite [*Org. Synth.*, **Coll. Vol. 5**, 184 (1973)] in 25 ml. of dichloromethane is added dropwise over a 15-minute period. The addition funnel is rinsed with 25 ml. of dichloromethane, the reaction solution is stirred for another 5 minutes, and 23 g. (25 ml., 0.34 mole) of dimethyl sulfide (Note 3) is added at a rate that allows the vigorously stirred reaction mixture to be maintained below –30°.

Shortly after the addition is complete, a voluminous white precipitate appears, and the resulting slurry is stirred and maintained at –50° to –40° for 4 hours. Cooling and stirring are continued as 18 g. (25 ml., 0.18 mole) of triethylamine (Note 4) is added dropwise, during which time the reaction mixture first goes to a clear solution, then becomes cloudy. The resulting mixture is stirred at –50° to –40° for 1 hour.

The cooling bath is then replaced with a steam bath, and the reaction mixture is refluxed for 16 hours. It is then cooled, transferred to a one-necked, 1-l., round-bottomed flask, and concentrated to dryness on a rotary evaporator. The dark residue is dissolved in a mixture of 200 ml. of water, 200 ml. of dichloromethane, and 20 ml. of triethylamine, and the aqueous phase is separated and washed with two 200-ml. portions of dichloromethane. The organic phases are combined and washed with 300 ml. of saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and filtered. Removal of the solvent on a rotary evaporator gives a red oil, which solidifies on storage at 0–5° (Note 5). Recrystallization of this solid from 40 ml. of absolute ethanol gives 7.6–8.4 g. (34–37%) of ethyl 4-amino-3-(methylthiomethyl)benzoate, m.p. 83–85°. A second crop of 1.1–2.5 g. of crystalline material, m.p. 78–83°, may be obtained by concentration of the mother liquors (Note 6).

B. *Ethyl 4-Amino-3-methylbenzoate.* A 1-l., three-necked, round-bottomed flask equipped with a mechanical stirrer, a condenser, and a nitrogen-inlet tube is charged with 11.25 g. (0.05000 mole) of ethyl 4-amino-3-(methylthiomethyl)benzoate, 300 ml. of absolute ethanol, and 17 teaspoons (*ca.* 50 g.) of W-2 Raney nickel (Note 7). The reaction mixture is stirred at 25° for one hour before stirring is discontinued, and the ethanolic solution is decanted from the catalyst (Note 8). The catalyst is then washed with one 300-ml. portion of absolute ethanol and one 500-ml. portion of dichloromethane, the solvent being removed by decanting in each case. The organic solutions are combined and concentrated on a rotary evaporator, giving a solid which is dissolved in 200 ml. of dichloromethane, dried over anhydrous magnesium sulfate, filtered, and taken to dryness on a rotary evaporator, yielding 7.0–7.6 g. (77–84%) of ethyl 4-amino-3-methylbenzoate as a white solid, m.p. 75–78°.

2. Notes

1. Benzocaine was purchased from Mallinckrodt Chemical Works and recrystallized from absolute ethanol prior to use to give material of m.p. 91–92°.
2. Fairly precise temperature control is required, since the reaction mixture begins to solidify at about –50°.
3. Dimethyl sulfide was purchased from MC and B Manufacturing Chemists and used without further purification.
4. Triethylamine was purchased from the J. T. Baker Chemical Company and used without further purification.
5. Solidification is facilitated by dissolving the oil in a minimum amount of diethyl ether (*ca.* 100 ml.) and removing the ether on a rotary evaporator. Should the oil still refuse to solidify, this process is repeated several times with pentane.

6. The second crop of crystalline material is contaminated with a small amount of ethyl *p*-aminobenzoate and usually red-orange in color. It is of sufficient purity to be used in Part B.
7. W-2 Raney nickel was purchased from W. R. Grace & Company. Prior to use it was washed with distilled water until the washings were neutral, then washed three times with absolute ethanol and stored under ethanol until needed [*Org. Synth.*, **Coll. Vol. 3**, 181 (1955)].
8. Activated Raney nickel is pyrophoric and should never be allowed to become dry. Thus, decanting is preferred to filtration, and when decanting, a small amount of solvent must always be left behind to cover the catalyst powder. For safe (but environmentally unsound) disposal, the spent catalyst should be slurried in water and flushed down the drain under running water.

3. Discussion

This procedure illustrates a general method for the *ortho*-alkylation of anilines.[3] It can be utilized for both anilines and mono-*N*-substituted anilines, with a variety of functional groups on the aromatic ring. By substituting α-thioketones and α-thioesters for dialkyl sulfides, the method has been extended to produce indoles[4] and oxindoles,[5] respectively. An example of the indole synthesis appears elsewhere in this volume. Ethyl 4-amino-3-methylbenzoate has been reported previously.[6]

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2. Present address: Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455.
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

ether, diethyl ether (60-29-7)

acetonitrile (75-05-8)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

Raney nickel (7440-02-0)

Pentane (109-66-0)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

dimethyl sulfide (75-18-3)

Indole (120-72-9)

triethylamine (121-44-8)

Ethyl 4-amino-3-methylbenzoate, Benzoic acid, 4-amino-3-methyl-, ethyl ester (40800-65-5)

ethyl 4-aminobenzoate, Ethyl p-aminobenzoate (94-09-7)

Ethyl 4-amino-3-(methylthiomethyl)benzoate (50461-34-2)

tert-Butyl hypochlorite (507-40-4)

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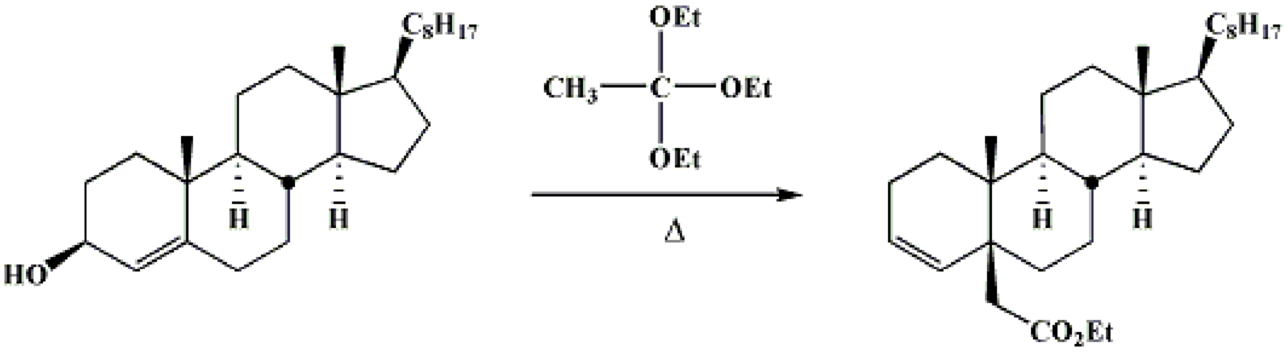
Organic Syntheses, CV 6, 584

ETHYL 5β-CHOLEST-3-ENE-5-ACETATE

[Cholest-3-ene-5-acetic acid, ethyl ester, (5β)-]



Submitted by R. E. Ireland[1] and D. J. Dawson.
Checked by W. Pawlak and G. Büchi.

1. Procedure

A 100-ml., Claisen distillation flask with two 14/20 standard taper joints and a thermometer-inlet is equipped with a gas-inlet adapter, a receiver, a thermometer, and a magnetic stirring bar. A 40-ml. calibration mark is made on the flask, and 970 mg. (2.50 mmoles) of cholest-4-en-3β-ol (Note 1) is introduced. Triethyl orthoacetate is then distilled under argon into the flask to the 40-ml. mark (Note 2). The mixture is stirred, effecting solution while the flask is purged with argon, then the top joint is sealed with a thermometer (f.htmigure 1). The stirred solution is heated under a positive pressure of argon so that the vapor reflux level is just below the side arm of the flask; the temperature on the lower thermometer is 142–147°; the upper thermometer temperature is kept between 25 and 70° (Note 3). After 8 days of reflux, during which time a small amount of the volatile material distills into the receiver, the reaction flask is cooled, and all the volatile materials are removed at reduced pressure (Note 4). The residue (1.3 g. of a pale yellow oil) is chromatographed on 120 g. of silica gel with 10% diethyl ether in petroleum ether as the eluant (Note 5). The side products eluted with the first 240 ml. of the solvent are discarded; further elution with 120 ml. of the solvent affords 690 mg. of ethyl 5β-cholest-3-ene-5-acetate as a clear, colorless oil. Trituration of this product with acetone produces 560–690 mg. (49–60%) of the ester as white plates, m.p. 89–92.5°.

Figure 1.

Figure 1.

2. Notes

1. Cholest-4-en-3β-ol can be prepared by the procedure of Burgstahler and Nordin.[2] A melting point below 130° indicates that the material is contaminated with some of the 3α-hydroxy isomer. The material used above melted at 130.5–131° (from ethanol).
2. The Matheson, Coleman and Bell product was used without purification. After a 10-ml. forerun, the triethyl orthoacetate was distilled (b.p. 142–147°) directly into the reaction flask.
3. A sand bath in an electric heating mantle was found to be satisfactory for the long-term

heating process.
4. The volatile materials were removed by rotary evaporation followed by vacuum (0.1 mm.) drying for 1 hour.
5. Merck silica gel (0.05–0.2 mm., 70–325 mesh ASTM) was used in a 3.5 × 26 cm. column. Mallinckrodt anhydrous ether and Baker petroleum ether (b.p. 30–60°) were employed as eluants.

3. Discussion

The ester–Claisen rearrangement procedure of Johnson and co-workers[3] was modified for use with cholest-4-en-3β-ol.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

ethanol (64-17-5)

ether, diethyl ether (60-29-7)

acetone (67-64-1)

triethyl orthoacetate (78-39-7)

argon (7440-37-1)

cholest-4-en-3β-ol

Ethyl 5β-cholest-3-ene-5-acetate, Cholest-3-ene-5-acetic acid, ethyl ester, (5β)- (56101-56-5)

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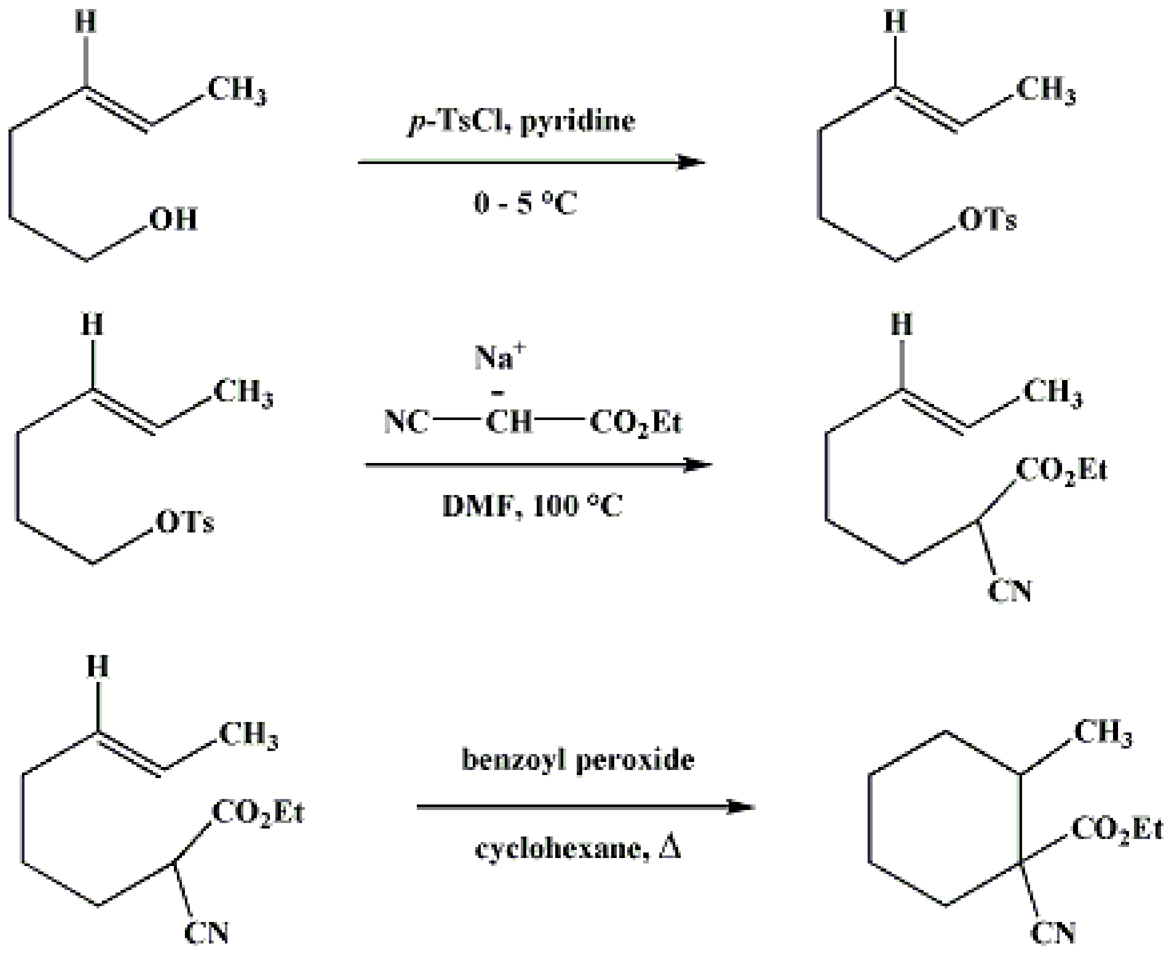
Organic Syntheses, CV 6, 586

FREE-RADICAL CYCLIZATION: ETHYL 1-CYANO-2-METHYLCYCLOHEXANECARBOXYLATE

[Cyclohexanecarboxylic acid, 1-cyano-2-methyl-, ethyl ester]



Submitted by Marc Julia and Michel Maumy[1].
Checked by Edward J. Zaiko and Herbert O. House.

1. Procedure

Caution! Since hydrogen is evolved in this procedure, it should be performed in an efficient hood.

A. *Ethyl (E)-2-cyano-6-octenoate.* A solution of 38.4 g. (0.384 mole) of (*E*)-4-hexen-1-ol (Note 1) in 160 ml. of anhydrous pyridine is placed in a 1-l. Erlenmeyer flask equipped with a magnetic stirring bar, and the solution is cooled in an ice bath. Over 1 hour, 91.5 g. (0.478 mole) of *p*-toluenesulfonyl chloride (Note 2) is added portionwise and with stirring to the reaction mixture while maintaining the temperature at 0–5°. The resulting slurry is allowed to stand overnight (Note 3) in a refrigerator, then poured into 500 g. of an ice-water mixture. The reaction mixture is extracted with four

150-ml. portions of diethyl ether, and the combined ethereal extracts are washed successively with four 150-ml. portions of 2 *N* sulfuric acid, 50 ml. of aqueous saturated sodium hydrogen carbonate, and two 50-ml. portions of water. The ethereal solution is dried over anhydrous sodium sulfate, and the solvent removed on a rotary evaporator at 25°, yielding 76–88 g. (78–91%) of crude (*E*)-4-hexen-1-yl *p*-toluenesulfonate as a pale yellow oil (Note 4).

A dry, 2-l., three-necked, round-bottomed flask is equipped with a sealed mechanical stirrer, a thermometer, and a pressure-equalizing dropping funnel fitted with a calcium chloride drying tube. Sodium hydride dispersion (Note 5), [19.2 g. of a 50% w/w suspension in mineral oil, 9.6 g. (0.40 mole) of sodium hydride] is placed in the flask, and 100 ml. of anhydrous pentane is added. After the dispersion has been stirred, the sodium hydride is allowed to settle, and the supernatant liquid is removed with a pipet or a siphon. This washing operation is repeated with two additional 100-ml. portions of pentane, and 400 ml. of anhydrous *N,N*-dimethylformamide (Note 6) is then added to the reaction flask. To the vigorously stirred suspension of sodium hydride in *N,N*-dimethylformamide is added, dropwise over 30 minutes, 68 g. (0.60 mole) of ethyl cyanoacetate (Note 7). The mixture is stirred until a clear solution is obtained before all of the previously prepared crude (*E*)-4-hexen-1-yl *p*-toluenesulfonate, dissolved in 100 ml. of anhydrous *N,N*-dimethylformamide (Note 6), is added in one portion. The resulting solution is slowly heated to 100°, with continuous stirring, over a period of 3 hours. During this time the reaction becomes dark red, and crystalline sodium *p*-toluenesulfonate separates. The mixture is allowed to stand overnight at room temperature, then transferred to a 2-l., one-necked, round-bottomed flask, and most of the solvent is removed on a rotary evaporator. The residual semisolid is mixed with 700 ml. of water and extracted with three 250-ml. portions of ether. The combined ethereal extracts are dried over anhydrous sodium sulfate and concentrated on a rotary evaporator. The residual liquid is fractionally distilled under reduced pressure through a 12-cm. Vigreux column. After removal of a low-boiling forerun, b.p. 54–57° (0.2 mm.), containing mainly ethyl cyanoacetate, 34.5–38.4 g. (46–51%) of colorless ethyl (*E*)-2-cyano-6-octenoate is collected, b.p. 84–86° (0.2 mm.), n_D^{25} 1.4458 (Note 8) and (Note 9).

B. *Ethyl 1-cyano-2-methylcyclohexanecarboxylate.* A 2-l., three-necked, round-bottomed flask is equipped with a heating mantle, a Teflon®-coated magnetic stirring bar, a 1-l. pressure-equalizing dropping funnel fitted with a Teflon® stopcock (Note 10), a stopper, and a reflux condenser fitted with a nitrogen-inlet tube. The apparatus is flushed with nitrogen, and 200 ml. of freshly distilled cyclohexane and 0.30 g. (0.0012 mole) of benzoyl peroxide are added to the flask. While a static nitrogen atmosphere is maintained in the flask (Note 11), a solution of 5.00 g. (0.0270 mole) of ethyl (*E*)-2-cyano-6-octenoate in 800 ml. of freshly distilled cyclohexane is added from the dropping funnel to the stirred, refluxing benzoyl peroxide solution over a period of 40 hours (Note 10). Three additional 0.30-g. (0.0012-mole) portions of benzoyl peroxide (total: 1.2 g., 0.0050 mole, (Note 11)), are added at 12-hour intervals during the

addition of the unsaturated ester. After the addition of the unsaturated ester and the benzoyl peroxide is complete, the reaction mixture is refluxed with stirring for an additional 20 hours (Note 12). The resulting colorless to pale-yellow solution is concentrated on a rotary evaporator to approximately 200 ml., diluted with 250 ml. of ether, and washed with 100 ml. of aqueous saturated iron(II) sulfate to destroy any unchanged benzoyl peroxide. The organic layer is then washed successively with two 200-ml. portions of aqueous saturated sodium hydrogen carbonate and two 200-ml. portions of water and dried over anhydrous calcium chloride. The solvent is removed on a rotary evaporator, and the residual liquid is fractionally distilled under reduced pressure through a 5-cm. Vigreux column. After separation of a 0.16–0.25-g. (3–5%) forerun, b.p. 63–64° (0.2 mm.), n_D^{25} 1.4550–1.4560, containing (Note 13) primarily the cyclized product, 3.68–3.82 g. (74–76%) of colorless ethyl 1-cyano-2-methylcyclohexanecarboxylate is collected, b.p. 64–75° (0.2 mm.), n_D^{25} 1.4532–1.4539 (Note 14) and (Note 15).

2. Notes

1. The preparation of this unsaturated alcohol is described in *Org. Synth.*, **Coll. Vol. 6**, 675 (1988).
2. The checkers employed a commercial sample of *p*-toluenesulfonyl chloride (obtained from Eastman Organic Chemicals) without further purification.
3. The checkers found that a longer period of standing before isolation lowered the yield of the sulfonate ester.
4. IR (CCl_4) cm.$^{-1}$: 1375, 1195, 1185, 975 [(*E*)CH=CH], 940.
5. The submitters employed a dispersion of sodium hydride in mineral oil obtained from Prolabo, Paris. The checkers employed 17 g. of mineral oil dispersion containing 57% sodium hydride obtained from Alfa Inorganics, Inc.
6. The submitters dried commercial *N,N*-dimethylformamide over anhydrous barium oxide for 5 days, then distilled the solvent at atmospheric pressure, b.p. 155°. The checkers allowed commercial *N,N*-dimethylformamide to stand over activated Linde 4A Molecular Sieves for several hours, then decanted the solvent and distilled it under reduced pressure, b.p. 43° (6 mm.).
7. The checkers employed commercial ethyl cyanoacetate (purchased from Eastman Organic Chemicals) without purification.
8. The checkers found this fractional distillation to be simplified if the initial crude product was first subjected to a rapid short-path distillation under reduced pressure to remove the bulk of the dialkylated material and other high molecular weight components.
9. The spectral properties of the product are as follows; IR (CCl_4) cm.$^{-1}$: 2250 (C N), 1745 (C=O), 970 [(*E*) CH=CH]; ^{1}H NMR (CCl_4), δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 1.0–2.4 (m, 9H, 3CH_2 and allylic CH_3), 1.31 (t, $J = 7$, 3H, OCH_2CH_3), 3.44 [t, $J = 6.5$, 1H, C*H* (CN)], 4.25 (q, $J = 7$, 2H, OCH_2CH_3), 5.1–5.8 (m, 2H, C*H*=C*H*). GC analysis of the checkers' product on a 5-m. column packed with ethylene glycol isophthalate

on Chromosorb P operated at 188° shows 2 products in the ratio of approximately 95:5, and retention times of 33.8 minutes and 37.0 minutes, respectively.

10. Because of difficulties in adjusting an ordinary glass stopcock to avoid leakage and to maintain a drop rate that would add the unsaturated cyanoester solution over a 40-hour period, the checkers recommend the use of a funnel equipped with a Teflon® stopcock.

11. The submitters report this reaction to be a radical chain process that requires less than 0.2 mole of benzoyl peroxide per mole of starting material. The checkers can offer additional evidence of the radical chain nature of the reaction from their finding that the cyclization reaction is almost completely inhibited if the refluxing solution is not protected from atmospheric oxygen.

12. The reaction solution can be analyzed to establish complete consumption of the starting unsaturated cyanoester by injecting an aliquot of the reaction solution onto a 5-m. GC column packed with ethylene glycol isophthalate suspended on Chromosorb P operated at 190°. Under these conditions the retention times of the starting unsaturated cyanoester and the cyclized cyanoester are 31.2 minutes and 28.0 minutes, respectively.

13. GC analysis (Note 12) of the forerun indicated the presence of ethyl 1-cyano-2-methylcyclohexanecarboxylate and minor amounts of five or more lower boiling impurities.

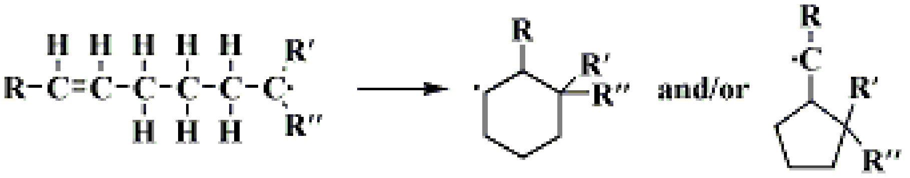
14. The product, which exhibits a single GC peak (Note 12), is presumably a mixture of stereoisomers. The spectral properties of the product are as follows; IR (CCl_4) cm.$^{-1}$: 2250 (C N), 1745 (C=O); ^{1}H NMR (CCl_4), δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 0.97 (d, *J* = 6.2, 3H, CH_3), 1.0–2.5 [m, 9H, $CH(CH_2)_4$], 1.32 (t, *J* = 7, 3H, OCH_2CH_3), 4.25 (q, *J* = 7, 2H, OCH_2CH_3). The methyl doublet at δ 0.97 is accompanied by a second weak doublet (*J* = 6.8 Hz.) at δ 1.02 that is presumably attributable to the second stereoisomer of ethyl 1-cyano-2-methylcyclohexanecarboxylate; mass spectrum *m/e* (relative intensity): 195 (M, 5), 141 (27), 136 (40), 126 (34), 123 (62), 122 (80), 108 (100), 98 (85), 95 (62), 94 (44), 82 (27), 81 (41), 70 (51), 67 (56), 55 (50), 53 (32), 42 (27), 41 (58), 39 (31).

15. The submitters report that this free radical cyclization was also effected by heating a solution of 5.00 g. (0.256 mole) of ethyl (*E*)-2-cyano-6-octenoate and 1.25 g. (0.00856 mole) of di-*tert*-butyl peroxide in 500 ml. of freshly distilled cyclohexane at 140° in an autoclave for 30 hours. The solution was concentrated and the residue was distilled to yield 3.4 g. (68%) of ethyl 1-cyano-2-methylcyclohexanecarboxylate.

3. Discussion

Ethyl 1-cyano-2-methylcyclohexanecarboxylate has been prepared by catalytically hydrogenating the Diels-Alder adduct of butadiene and ethyl 2-cyano-2-butenoate[2] and by the procedure described in this preparation.[3,4] This procedure illustrates a general method for the preparation of alicyclic compounds by the cyclization of δ-

ethylenic carbon radicals **1**.[5] Whereas the primary 5-hexen-1-yl radical **1** (R=R'=R"=H) cyclizes to form methylcyclopentane (*via* **3**),[6] the 1-cyano-1-carboethoxy disubstituted, radicals **1** (R'=CN, R"=$CO_2C_2H_5$) lead predominantly, and sometimes exclusively, to six-membered rings **2**. Monosubstituted radicals **1** (R"=H) often give mixtures of both isomers **2** and **3**.[4,5]



1 2 3

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

ether, diethyl ether (60-29-7)

hydrogen (1333-74-0)

sodium hydrogen carbonate (144-55-8)

sodium sulfate (7757-82-6)

oxygen (7782-44-7)

barium oxide

nitrogen (7727-37-9)

iron(II) sulfate (13463-43-9)

cyclohexane (110-82-7)

pyridine (110-86-1)

Ethyl cyanoacetate (105-56-6)

Pentane (109-66-0)

benzoyl peroxide (94-36-0)

butadiene (106-99-0)

N,N-dimethylformamide (68-12-2)

sodium hydride (7646-69-7)

methylcyclopentane (96-37-7)

p-Toluenesulfonyl chloride (98-59-9)

Ethyl 1-cyano-2-methylcyclohexanecarboxylate, Cyclohexanecarboxylic acid, 1-cyano-2-methyl-, ethyl ester (5231-79-8)

ethylene glycol isophthalate

ethyl 2-cyano-2-butenoate

sodium p-toluenesulfonate (657-84-1)

di-tert-butyl peroxide (110-05-4)

(E)-4-Hexen-1-ol (6126-50-7)

(E)-4-hexen-1-yl p-toluenesulfonate

Ethyl (E)-2-cyano-6-octenoate (25143-86-6)

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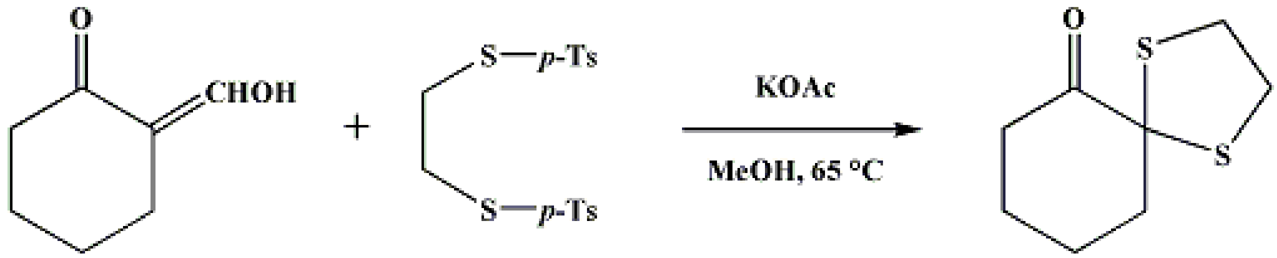
Organic Syntheses, CV 6, 590

2,2-(ETHYLENEDITHIO)CYCLOHEXANONE

[1,4-Dithiaspiro[4,5]decan-6-one]



Submitted by R. B. Woodward[1], I. J. Pachter[2], and M. L. Scheinbaum[3].
Checked by J. G. Green and S. Masamune.

1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A 300-ml., one-necked flask equipped with a reflux condenser, the top of which is attached to a nitrogen inlet tube, is charged with 3.85 g. (0.0338 mole) of 2-hydroxymethylenecyclohexanone (Note 1), 10 g. (0.025 mole) of ethylene dithiotosylate (Note 2), and 10 g. of potassium acetate in 150 ml. of methanol. The mixture is refluxed under nitrogen for 3 hours with stirring, the solvent is removed from the reaction mixture on a rotary evaporator, and the residue is extracted with three 50-ml. portions of diethyl ether. The combined ethereal extracts are washed with cold, aqueous 2 *N* sodium hydroxide (Note 3) until the aqueous layer is basic to litmus, then with 50 ml. of saturated aqueous sodium chloride. The ethereal layer is dried over anhydrous magnesium sulfate, filtered, and concentrated on a rotary evaporator. The oily residue is diluted with 1 ml. of benzene and 3 ml. of cyclohexane and transferred to a chromatographic column (14 × 2 cm.) prepared with 50 g. of alumina (Note 4) and a 3:1 mixture of cyclohexane and benzene. With this solvent system the desired product moves with the solvent front, and the first 100 ml. of eluent contains 85% of the total product. Further elution with approximately 100 ml. of the same solvent mixture removes the rest of the material before a second component begins to come off. Evaporation of the solvent from the combined 200 ml. of eluent leaves an oily residue which crystallizes on standing, yielding 2.76–3.04 g. (57–64%) of crude 2,2-(ethylenedithio)cyclohexanone. Recrystallization from approximately 50 ml. of pentane affords 2.1–2.6 g. (45–55%) of needles, m.p. 56–57° (Note 5).

2. Notes

1. 2-Hydroxymethylenecyclohexanone was prepared by both the submitters and checkers by a procedure similar to, but slightly modified from, that described in *Org. Synth.*, **Coll. Vol. 4**, 536 (1963). To a cooled (ice bath), stirred suspension of 10.2 g.

(0.189 mole) of commercial sodium methoxide in 75 ml. of anhydrous benzene under nitrogen was added dropwise, but rapidly (*ca.* 2 minutes), a mixture of 9.8 g. (0.10 mole) of distilled cyclohexanone and 14.8 g. (0.200 mole) of distilled ethyl formate. After addition, the reaction was allowed to warm to room temperature and left overnight. Ice water (100 ml.) was added to the resulting suspension. The aqueous layer was separated, and the benzene layer was washed three times with 50 ml. of cold, aqueous 0.1 *N* sodium hydroxide. The aqueous layers were combined, and the product was isolated according to the procedure referenced above. This modified version provided slightly higher yields of the product than that recorded in *Org. Synth.*, and the ease of handling sodium methoxide, compared with sodium metal, is advantageous.

2. Ethylene dithiotosylate, m.p. 73–73.5°, as described in *Org. Synth.*, **Coll. Vol. 6**, 1016 (1988), is employed.

3. Treatment with alkali removes the various acidic by-products and their salts (acetate, sulfinate, and formate) and also serves to hydrolyze and remove unreacted starting materials.

4. The checkers used "Aluminum Oxide" purchased from J. T. Baker Chemical Company.

5. The ^{1}H NMR spectrum of the product ($CDCl_3$): δ 1.83 (m, 4H), 2.42 (m, 2H), 2.73 (m, 2H), 3.30 (s, 4H).

3. Discussion

The procedure for the preparation of a dithiolane from a hydroxymethylene derivative of a ketone and ethylene dithiotosylate (ethane-1,2-dithiol di-*p*-toluenesulfonate) can be varied to produce dithianes, when the latter reagent is replaced with trimethylene dithiotosylate.[4,5] Dithiotosylates also react with enamine derivatives, producing dithiaspiro compounds.[5,6]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 1014
- Org. Syn. Coll. Vol. 6, 1016
- Org. Syn. Coll. Vol. 9, 180

References and Notes

1. 1965 Nobel Laureate in Chemistry; deceased July 8, 1979; formerly at the Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138.
2. Present address: Bristol Laboratories, Division of Bristol-Myers Company, Syracuse, New York 13201.
3. Present address: Sterling-Winthrop Research Institute, Rensselaer, New York 12144.
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Benzene (71-43-2)

methanol (67-56-1)

diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

Cyclohexanone (108-94-1)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

cyclohexane (110-82-7)

sodium methoxide (124-41-4)

sodium (13966-32-0)

ethyl formate (109-94-4)

Pentane (109-66-0)

magnesium sulfate (7487-88-9)

potassium acetate (127-08-2)

aluminum oxide (1344-28-1)

2-Hydroxymethylenecyclohexanone (823-45-0)

2,2-(Ethylenedithio)cyclohexanone, 1,4-Dithiaspiro[4,5]decan-6-one (27694-08-2)

ethylene dithiotosylate

trimethylene dithiotosylate (3866-79-3)

ethane-1,2-dithiol di-p-toluenesulfonate

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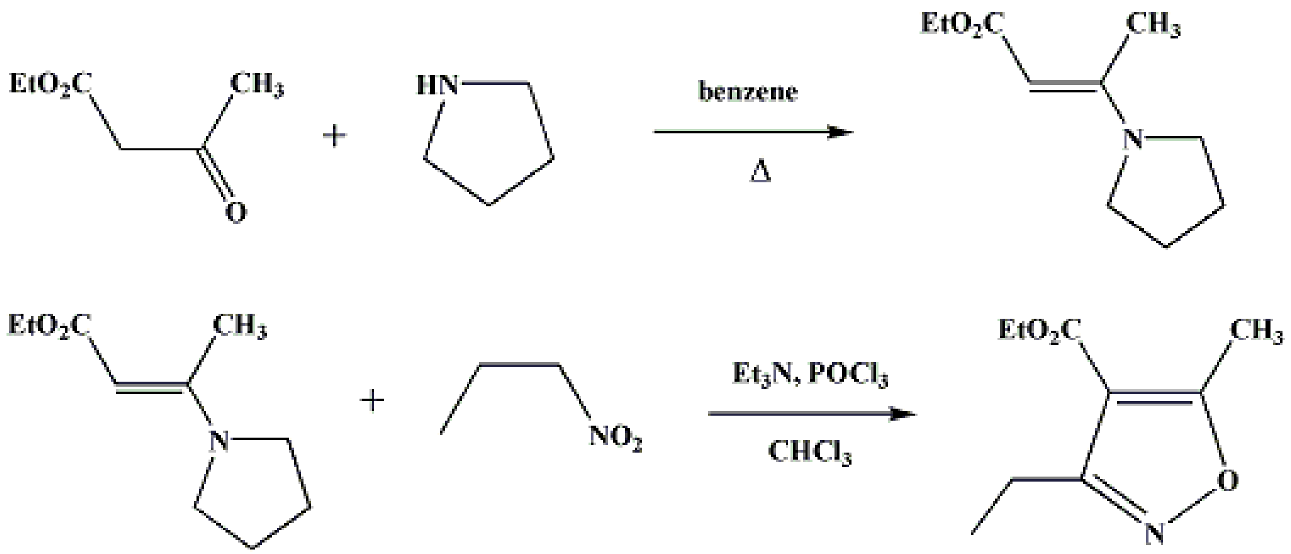
Organic Syntheses, CV 6, 592

A GENERAL SYNTHESIS OF 4-ISOXAZOLECARBOXYLIC ESTERS: ETHYL 3-ETHYL-5-METHYL-4-ISOXAZOLECARBOXYLATE

[4-Isoxazolecarboxylic acid, 3-ethyl-5-methyl-, ethyl ester]



Submitted by John E. McMurry[1]
Checked by U. P. Hochstrasser and G. Büchi.

1. Procedure

Caution! The following reactions should be performed in an efficient hood to protect the experimentalist from noxious vapors (pyrrolidine, phosphorus oxychloride, and triethylamine).

Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A. *Ethyl β-pyrrolidinocrotonate.* Ethyl acetoacetate (130 g., 1.00 mole) (Note 1) and pyrrolidine (71 g., 1.0 mole) are dissolved in 400 ml. of benzene and placed in a 1-l., one-necked flask fitted with a Dean-Stark water separator on top of which is a condenser fitted with a nitrogen inlet tube. The reaction mixture is placed under a nitrogen atmosphere (Note 2), then brought to and maintained at a vigorous reflux for 45 minutes, at which time the theoretical amount of water (18 ml.) has been collected. The benzene is removed with a rotary evaporator, yielding 180 g. (98%) of highly pure ethyl β-pyrrolidinocrotonate, which may be used without distillation (Note 3).

B. *Ethyl 3-ethyl-5-methyl-4-isoxazolecarboxylate.* Ethyl β-pyrrolidinocrotonate (183 g., 1.00 mole), 1-nitropropane (115 g., 116 ml., 1.29 mole), and triethylamine (400 ml.) are dissolved in 1 l. of chloroform and placed in a 5-l., three-necked flask fitted with a 500 ml., pressure-equalizing dropping funnel and a gas-inlet tube. The flask is cooled in an ice bath, and its contents are placed under a nitrogen atmosphere. While the contents of the flask are stirred magnetically, a solution of

170 g. (1.11 mole) of phosphorus oxychloride in 200 ml. of chloroform is added slowly from the dropping funnel. After 3 hours, addition is complete and the ice bath is removed. The reaction mixture is allowed to warm to room temperature and stirring is continued for an additional 15 hours.

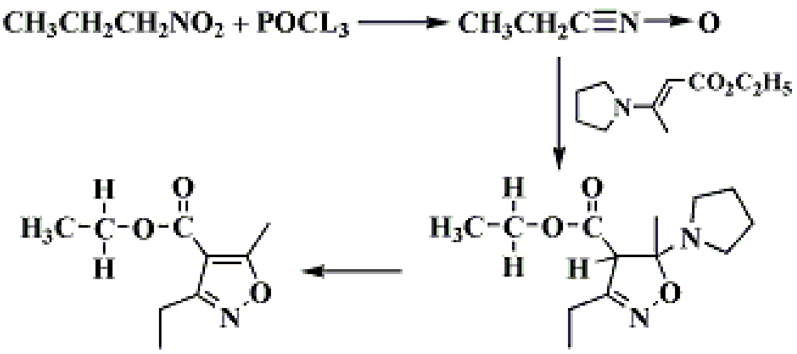
The reaction mixture is poured into a 4-l. separatory funnel and washed with 1 l. of cold water. The chloroform layer is washed with 6 *N* hydrochloric acid until the amine bases are removed and the wash remains acidic (Note 4) The chloroform extracts are washed successively with 5% aqueous sodium hydroxide (Note 5) and saturated brine, dried over anhydrous magnesium sulfate, and filtered. The solvent is removed with a rotary evaporator, and the product is distilled under vacuum, yielding 122–130 g. (68–71%) of ethyl 3-ethyl-5-methyl-4-isoxazolecarboxylate, b.p. 72° (0.5 mm.), n_D^{23} 1.4615 (Note 6).

2. Notes

1. The following reagents were used as supplied: pyrrolidine and triethylamine, Aldrich Chemical Company, Inc.; ethyl acetoacetate, Eastman Organic Chemicals (white label); nitropane, Matheson, Coleman and Bell (practical); phosphorus oxychloride, Matheson, Coleman and Bell (reagent).
2. Ethyl β-pyrrolidinocrotonate is typical of most enamines in that it discolors rapidly when exposed to air and therefore must be handled under an inert atmosphere.
3. Distillation is unnecessary and inadvisable, since discoloration usually occurs and there are product losses.
4. If this acid wash is not done thoroughly, the triethylamine hydrochloride remaining will sublime during distillation of the product and coat the still with a fluffy white powder. This impurity can be removed from the distillate, however, by a simple water wash.
5. This alkaline wash removes traces of ethyl acetoacetate which might form by hydrolysis of unreacted starting material during the preceding acid wash.
6. The product had the following spectral data: IR: 1725, 1605, 1300 cm.$^{-1}$; ^{1}H NMR (CCl_4); δ 1.3 (m, 6H, 2CH_3), 2.6 (s, 3H, C=CCH_3), 2.7 (q, 2H, CH_2CH$_3$), 4.2 (q, 2H, OCH_2CH$_3$).

3. Discussion

This procedure is illustrative of a general method for preparing a wide range of pure 3,5-disubstituted-4-isoxazolecarboxylic esters and (by hydrolysis) their acids,[2] free from positional isomers. A wide range of primary nitro compounds and enamino esters can be used,[2,3] and the esters thus obtained are useful as reagents in the isoxazole annelation reaction.[3,4] The only other general synthesis of these compounds involves chloromethylation and oxidation of a suitable 4-unsubstituted isoxazole,[5] but suffers from two difficulties: low yields and the unavailability of starting isoxazole. Most methods of isoxazole formation yield a mixture of positional isomers,[6] but the present method is quite selective. It has been shown that the reaction of a primary nitro compound with a dehydrating agent such as phosphorus oxychloride produces an intermediate nitrile oxide[7,8] which then undergoes a 1,3 dipolar cycloaddition to the enamine. This addition is remarkably selective with respect to orientation and no isomer formation is detected.[9] The intermediate isoxazoline then loses pyrrolidine enroute to the final product.



This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 781

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

brine

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

nitrogen (7727-37-9)

Phosphorus Oxychloride (21295-50-1)

Ethyl acetoacetate (141-97-9)

magnesium sulfate (7487-88-9)

pyrrolidine (123-75-1)

triethylamine (121-44-8)

Triethylamine hydrochloride (554-68-7)

1-nitropropane (108-03-2)

Ethyl 3-ethyl-5-methyl-4-isoxazolecarboxylate, 4-Isoxazolecarboxylic acid, 3-ethyl-5-methyl-, ethyl ester (53064-41-8)

Ethyl β-pyrrolidinocrotonate (54716-02-8)

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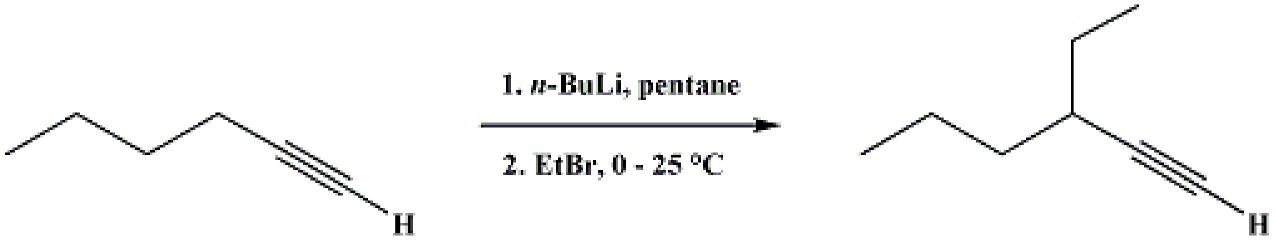
Organic Syntheses, CV 6, 595

3-ALKYL-1-ALKYNES SYNTHESIS: 3-ETHYL-1-HEXYNE

[1-Hexyne, 3-ethyl-]



Submitted by A. J. Quillinan and F. Scheinmann[1].
Checked by Y. Kita and G. Büchi.

1. Procedure

A dry, 2-l., three-necked, round-bottomed flask is fitted with a nitrogen inlet, a reflux condenser provided with a gas-outlet connected to a gas-bubbler, a rubber septum, and a magnetic stirrer. After being charged with 400 ml. of pure, dry pentane (Note 1) and 41 g. (0.50 mole) of 1-hexyne (Note 1), the flask is flushed with nitrogen and immersed in a cold bath (Note 2), and the contents are stirred. The nitrogen atmosphere is maintained, and a solution of *n*-butyllithium in hexane or pentane (500 ml. of a 2.5 *N* solution, or 1.25 mole) is transferred to the flask with a 100-ml. syringe or a cannula (Note 3). The mixture is allowed to warm to 10° and stirred for 30 minutes, until the initially formed precipitate has completely dissolved.

The clear yellow solution is recooled to 0° in an ice bath before a solution of 88 g. (0.80 mole) of freshly-distilled ethyl bromide (Note 4) in 100 ml. of pure pentane is added dropwise with stirring over a 30-minute period while the solution warms to room temperature. Formation of a precipitate begins after an hour and is virtually complete after 6 hours (Note 5). After the mixture has been stirred for 2 days, 400 ml. of 4 *N* hydrochloric acid is carefully added with cooling (ice bath) and stirring. The layers are separated, and the organic phase (Note 6) is washed with 15 ml. of water, dried over anhydrous potassium carbonate, and filtered. Low-boiling materials are removed by distillation through an efficient Vigreux column (Note 7). The residue is distilled using a spinning-band apparatus (Note 8), yielding 35.2–35.8 g. (64–65%) of 3-ethyl-1-hexyne as a colorless, pungent oil (Note 9), b.p. 113–114°, n_D^{20} 1.4101 (Note 10).

2. Notes

1. Solvents must be pure since higher-boiling impurities will accumulate in the reaction product, making the final distillation much more difficult and reducing the purity of the product. Commercial pentane was purified by redistillation through an efficient Vigreux column (Note 7) and collected at 33–34°. 1-Hexyne is available from Fluka A G, Tridom Chemical, Inc., and Koch-Light Laboratories, Ltd., or by synthesis from sodium acetylide and 1-bromobutane (L. Brandsma, "Preparative Acetylene Chemistry," Elsevier, Amsterdam, 1971, p. 45.).

2. The temperature is not critical; the submitters used a bath temperature of –35 to –20°, but claimed that an acetone–dry-ice bath is satisfactory or that an ice-water bath with slow addition of *n*-butyllithium can also be used.

3. All operations involving alkyllithium reagents should be carried out under an inert gas, since they tend to ignite spontaneously in air.

4. Commercial ethyl bromide was dried over anhydrous potassium carbonate, filtered, and redistilled prior to use.

5. The reaction may be conveniently terminated here, but reaction for two days gives a slightly higher yield at the expense of some hydrocarbon impurity formed from the slow reaction of excess alkyllithium with the alkyl bromide. If this impurity can contaminate the final product, the side reaction may be suppressed by conducting the reaction in the minimum amount of solvent necessary to dissolve the dilithium complex.

6. Dark coloration is usually a result of insufficient acidity; the aqueous phase at the separation stage should have a pH between 2 and 4.

7. A vacuum-jacketed Vigreux column of 1.5-cm. internal diameter and *ca.* 90-cm. length is satisfactory. With shorter or less efficient columns, redistillation of the distillate may be necessary to reduce losses in yield.

8. The submitters used a Büchi spinning-band distillation apparatus by Abegg (*ca.* 30 theoretical plates resolution), operated at a reflux ratio of 10–15:1 and having a capacity of 50–100 ml. The checkers found that this distillation required four days to obtain the pure product.

9. 3-Ethyl-1-hexyne is an irritant to the membranes of the nose and throat and should only be handled in a well-ventilated hood. Other 3-substituted 1-alkynes prepared in this series[2 3 4 5] have pleasant or neutral odors, but direct contact should be avoided, since toxicity data are not available.

10. The previously unknown 3-ethyl-1-hexyne was further characterized by the submitters as follows: IR cm.$^{-1}$: 3338, 2975, 2940, 2881, 2103, 1460, 1380, 1240; ^{13}C NMR ($CDCl_3$), δ 88.0, 69.23, 37.12, 33.29, 28.23, 20.69, 13.97, 11.71; ^{1}H NMR ($CDCl_3$), δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 0.99 (t, *J* = 6, 6H, 2CH_3), 1.2–1.7 (m, 6H, 3CH_2), 2.00 (d, *J* = 2, 1H, C≡C*H*), 2.3 (m, 1H, tertiary C*H*).

Hydrogenation at 20° over Adams catalyst, platinum oxide, at atmospheric pressure afforded the known 3-ethylhexane,[6] b.p. 118–119° (lit.,[2,3,4,5] b.p. 119°).

In an analogous synthesis,[2] 3-butyl-1-heptyne was also characterized by mercuric oxide–sulfuric acid hydration[7] to the known 3-butyl-2-heptanone,[8,9] which also formed the known semicarbazone.[9]

3. Discussion

This procedure has been shown[2,3,4,5] to be extremely general and applicable to the reaction of a wide variety of straight-chain 1-acetylenes, 4-substituted 1-acetylenes, and α,ω-diacetylenes with primary halides, sterically hindered primary halides, secondary halides, and α,ω-dihalides.

Most of the compounds formed are new and were formerly inaccessible,[10] available only by dehydrohalogenation of geminal or 1,2-dibromides which are often unavailable themselves.[10]

Alcoholic potassium hydroxide[11,12] or sodamide in liquid paraffin[10,13] under forceful conditions has been used for this elimination, but yields are generally not good.[10,11,12,13]

The procedure described here is characterized by good yields and mild conditions, and affords an easy route to a pure compound from readily available starting materials. Since tertiary aliphatic acetylenes do not form readily under these conditions, the excess of alkyllithium used is not particularly critical. The small amount of by-products that also forms is readily removed at the distillation stage.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

1-bromobutane (109-65-9)

Ethyl bromide (74-96-4)

nitrogen (7727-37-9)

platinum oxide

potassium hydroxide (1310-58-3)

Pentane (109-66-0)

sodamide (7782-92-5)

n-butyllithium (109-72-8)

sodium acetylide

hexane (110-54-3)

1-Hexyne (693-02-7)

3-Ethyl-1-hexyne, 1-Hexyne, 3-ethyl- (76347-58-5)

3-ethylhexane (619-99-8)

3-butyl-1-heptyne

3-butyl-2-heptanone

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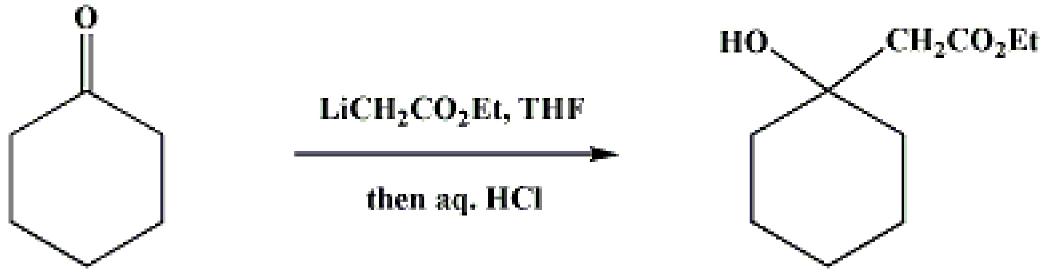
Organic Syntheses, CV 6, 598

β-HYDROXY ESTERS FROM ETHYL ACETATE AND ALDEHYDES OR KETONES: ETHYL 1-HYDROXYCYCLOHEXYLACETATE

[Cyclohexaneacetic acid, 1-hydroxy, ethyl ester]

$$HN[Si(CH_3)_3]_2 + n\text{-}C_4H_9Li \longrightarrow LiN[Si(CH_3)_3]_2 + n\text{-}C_4H_{10}$$

$$LiN[Si(CH_3)_3]_2 + CH_3CO_2C_2H_5 \longrightarrow LiCH_2CO_2C_2H_5 + HN[Si(CH_3)_3]_2$$



Submitted by Michael W. Rathke[1]
Checked by Y. Hoyano and S. Masamune.

1. Procedure

Caution! The first step of the reaction should be conducted in a well-ventilated hood since butane is liberated.

A. *Lithium bis(trimethylsilyl)amide* (Note 1). A dry, 500-ml., three-necked flask, fitted with a pressure-equalizing dropping funnel in the center neck and a stopcock in each side neck, is equipped for magnetic stirring and maintained under a static nitrogen pressure by attaching a nitrogen source to one stopcock and a mercury bubbler to the other. In the flask is placed 153 ml. of a hexane solution containing 0.250 mole of *n*-butyllithium (Note 2), and stirring is started. The flask is immersed in an ice-water bath, and 42.2 g. (0.263 mole) of hexamethyldisilazane (Note 3) is added dropwise over a period of 10 minutes. The ice-bath is removed, and the solution is stirred for 15 minutes longer. The hexane is removed under reduced pressure by replacing the mercury bubbler with heavy rubber tubing connected to a dry-ice condenser and an oil pump. During this step, the flask is immersed in a water bath at 40–50°, and stirring is continued as long as possible. After complete evaporation of the hexane, white crystals of lithium bis-(trimethylsilyl)amide appear. The flask is again subjected to a static pressure of nitrogen (Note 4), and 225 ml. of tetrahydrofuran (Note 5) is added to dissolve the crystals.

B. *Ethyl lithioacetate.* The reaction flask is immersed in an acetone–dry-ice bath, and the solution is stirred for 15 minutes to achieve thermal equilibration. After this time, 22.1 g. (0.250 mole) of ethyl acetate is added dropwise over a 10-minute period. Stirring is continued for an additional 15 minutes to complete formation of ethyl lithioacetate (Note 6).

C. *Ethyl 1-hydroxycyclohexylacetate.* A solution of 24.6 g. (0.250 mole) of cyclohexanone (Note 7) in 25 ml. of tetrahydrofuran is added dropwise to the reaction mixture over a 10-minute period. After an additional 5 minutes, the reaction mixture is hydrolyzed by adding 75 ml. of 20% hydrochloric acid in one portion (Note 8). The cooling bath is removed, and the stirred solution is allowed to reach room temperature.

The organic layer is separated, the aqueous layer is extracted with two 50-ml. portions of diethyl ether, and the combined extracts are dried over anhydrous sodium sulfate. The solvent is removed with a rotary evaporator (Note 9), and the almost-colorless residue is distilled under reduced pressure through a 10-cm. Vigreux column, yielding 37–42 g. (79–90%) of the β-hydroxy ester as a colorless liquid, b.p. 77–80° (1 mm.); n_D^{24} 1.4555–1.4557 (Note 10).

2. Notes

1. The preparation of lithium bis(trimethylsilyl)amide is adapted from an earlier procedure.[2] The original procedure specifies addition of *n*-butyllithium to hexamethyldisilazane in diethyl ether followed by a reflux period. It is generally more convenient to add the hexamethyldisilazane to the *n*-butyllithium; satisfactory results are obtained without using ether or refluxing.
2. A 1.63 *M* solution of *n*-butyllithium in hexane was purchased from Foote Mineral Company.
3. Hexamethyldisilazane was obtained from Pierce Chemical Company and used without further purification.
4. Lithium bis(trimethylsilyl)amide is hydrolyzed rapidly by moist air. It is therefore essential to break the vacuum by admitting nitrogen rather than air.
5. The submitters used reagent grade tetrahydrofuran (available from Fisher Scientific Company) from a freshly opened bottle. The checkers used tetrahydrofuran purified by distillation from lithium aluminum hydride. See *Org. Synth.*, **Coll. Vol. 5**, 976 (1973) for warning regarding purification of this solvent.
6. Solutions of ethyl lithioacetate prepared by this method are stable indefinitely at –78°, but decompose rapidly if allowed to reach room temperature.
7. White label cyclohexanone (Eastman Organic Chemicals) was used without further purification.
8. The yield of the β-hydroxy ester is somewhat lower if the reaction mixture is allowed to reach room temperature prior to hydrolysis.
9. Continuing the evaporation process for some time after removal of the solvent is helpful in removing any residual hexamethyldisilazane (b.p. 125°) together

with its hydrolysis product, hexamethyldisiloxane (b.p. 100°).

10. ^{1}H NMR ($CDCl_3$), δ 1.26 (t, *J* = 7 Hz., 3H, OCH_2CH_3), 1.52 (broad s, 10H, $5CH_2$), 2.45 (s, 2H, CH_2CO_2), 3.33 (s, 1H, OH), 4.19 (q, *J* = 7 Hz., 2H, OCH_2CH_3).

3. Discussion

Ethyl 1-hydroxycyclohexylacetate has been prepared by the Reformatsky reaction of cyclohexanone with zinc and ethyl bromoacetate (56–71%)[3] and by the condensation of ethyl acetate with cyclohexanone in liquid ammonia, using two equivalents of lithium amide (69%).[4]

This preparation illustrates a general method for the preparation of β-hydroxy esters from ethyl acetate and aldehydes or ketones.[5] The procedure is simpler and less time-consuming than other methods and the yields are usually higher. In addition, the β-hydroxy esters are obtained in a high state of purity.

The procedure is especially suited to small-scale preparations (25 mmoles or less) where the necessity of evaporating hexane from the lithium bis(trimethylsilyl)amide is much less of a handicap. In such cases, it is convenient to equip the reaction vessel with a septum-inlet and transfer all reagents with a syringe.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ethyl acetate (141-78-6)

diethyl ether (60-29-7)

Cyclohexanone (108-94-1)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

zinc (7440-66-6)

Ethyl bromoacetate (105-36-2)

butane (106-97-8)

n-butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

lithium amide (7782-89-0)

hexane (110-54-3)

lithium bis-(trimethylsilyl)amide, lithium bis(trimethylsilyl)amide (4039-32-1)

hexamethyldisiloxane (107-46-0)

Ethyl 1-hydroxycyclohexylacetate, Cyclohexaneacetic acid, 1-hydroxy, ethyl ester (1127-01-1)

hexamethyldisilazane

Ethyl lithioacetate

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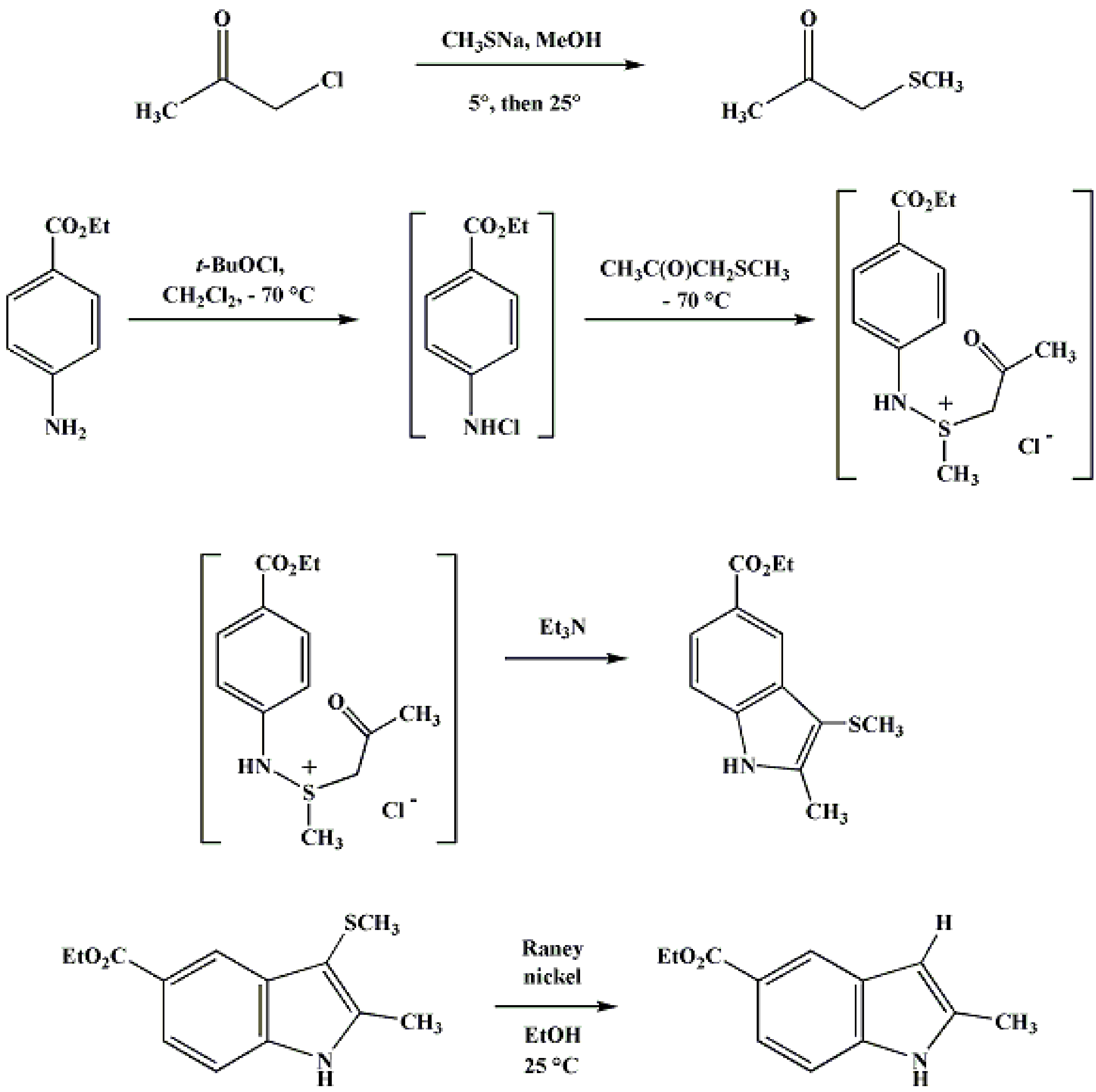
Organic Syntheses, CV 6, 601

INDOLES FROM ANILINES: ETHYL 2-METHYLINDOLE-5-CARBOXYLATE

[1*H*-Indole-5-carboxylic acid, 2-methyl, ethyl ester]



Submitted by P. G. Gassman[1] and T. J. van Bergen.
Checked by J. L. Belletire and G. Büchi.

1. Procedure

Caution! Part A must be conducted in an efficient hood to avoid exposure to methanethiol and chloroacetone, both of which are highly irritating. In Part C, the usual precautions associated with the pyrophoric reagent Raney nickel (Note 12) should be observed.

A. *Methylthio-2-propanone.*[2] A 2-l., three-necked, round-bottomed flask is equipped with a sealed

mechanical stirrer and a two-necked adapter holding a thermometer and a condenser topped with a silica gel drying tube. After 700 ml. of anhydrous methanol has been added, the third neck is stoppered, and the flask is immersed in an ice water bath. Stirring is begun, and 108 g. (2.00 moles) of sodium methoxide (Note 1) is added in small portions at a rate sufficiently gradual to prevent a large exotherm (Note 2). When all of the methoxide has dissolved and the temperature has returned to 5°, the stopper is replaced with a 200-ml., pressure-equalizing, jacketed addition funnel (Note 3). This funnel, charged previously with 130 ml. (2.20 moles) of methanethiol (Note 4), contains a 2-propanol-dry ice slurry in the cooling jacket, and is topped with a silica gel drying tube. Stirring and cooling are continued while the methanethiol is run into the flask over a 20-minute period, and for 15 minutes thereafter. The jacketed addition funnel is then replaced by a standard, 200-ml., pressure-equalizing addition funnel, which is used to add 185 g. (2.00 moles) of chloroacetone (Note 5) to the reaction mixture over 1 hour. When this addition is complete, the ice bath is removed, and the suspension is stirred overnight at room temperature. The insoluble material, largely inorganic salts, is removed by filtration through Celite, and the filter cake is washed with two 150-ml. portions of absolute methanol. After methanol has been removed from the combined filtrates by distillation, the residue is distilled through a 300-mm. Vigreux column, yielding 155–158 g. (74–76%) of methylthio-2-propanone, b.p. 153–154°, n_D^{23} 1.4728.

B. *Ethyl 2-methyl-3-methylthioindole-5-carboxylate*. A 1-l., three-necked, round-bottomed flask is equipped with a sealed mechanical stirrer, a 100-ml., pressure-equalizing addition funnel, and a two-necked adapter holding a low-temperature thermometer and a gas-inlet tube. The flask is charged with 16.5 g. (0.100 mole) of ethyl 4-aminobenzoate (Benzocaine) (Note 6) and 500 ml. of dichloromethane (Note 7), and a positive pressure of dry nitrogen is established while the solution is stirred and cooled to −70° with a 2-propanol–dry-ice bath. The resulting suspension is stirred vigorously, and a solution of 10.8 g. (0.0995 mole) of *tert*-butyl hypochlorite [*Org. Synth.*, **Coll. Vol. 5**, 184 (1973)] in 50 ml. of dichloromethane (Note 7) is added dropwise over a 10-minute period. The reaction mixture is stirred for 1 hour at −70°, followed by dropwise addition of a solution of 10.4 g. (0.100 mole) of methylthio-2-propanone in 50 ml. of dichloromethane (Note 7) over 10 minutes. A slight exotherm (*ca.* 5°) is noted during the addition, resulting in a clear yellow solution. After stirring for another hour at −70°, during which time a suspension of precipitated salts forms, a solution of 10.1 g. (0.100 mole) of triethylamine (Note 8) in 30 ml. of dichloromethane (Note 7) is added dropwise over 10 minutes. After an additional 15 minutes at −70°, the cooling bath is removed.

When the reaction mixture has warmed to room temperature, stirring is made more vigorous, and 100 ml. of water is added. The layers are separated, and the organic phase is dried over anhydrous magnesium sulfate and filtered. Removal of dichloromethane with a rotary evaporator leaves an oily residue, which is cooled in an ice bath, inducing crystallization. The resulting solid is stirred with 50 ml. of diethyl ether for 30 minutes at 0° (Note 9), collected by filtration, and washed with 25 ml. of ether at 0°. Concentration of the filtrate to 15 ml. and chilling at *ca.* 5° overnight yields a second crop of crystalline product, bringing the total crude yield to 14.7–18.0 g. (59–73%), m.p. 120.5–124° (Note 10). Recrystallization from absolute ethanol (5 ml. per 2 g.) yields 12.8–17.5 g. (51–70%) of ethyl 2-methyl-3-methylthioindole-5-carboxylate, m.p. 125.5–127°.

C. *Ethyl 2-methylindole-5-carboxylate*. A solution of 10.0 g. (0.0402 mole) of ethyl 2-methyl-3-methylthioindole-5-carboxylate in 300 ml. of absolute ethanol is placed in a 500-ml., three-necked, round-bottomed flask fitted with a mechanical stirrer. An excess (15 teaspoons), (Note 11) of freshly washed W-2 Raney nickel (Note 12) is added, and the mixture is stirred for one hour. Stirring is then stopped, the liquid phase is decanted, and the catalyst is washed twice by stirring for 15 minutes with 100-ml. portions of absolute ethanol and decanting the solvent. The combined ethanolic solutions are concentrated on a rotary evaporator. The residual solid is dissolved in 150 ml. of warm dichloromethane, dried over anhydrous magnesium sulfate, and filtered; the drying agent is washed with 40 ml. of dichloromethane. Concentration of the combined filtrates with a rotary evaporator gives 7.5–8.1 g. (93–99%) of ethyl 2-methylindole-5-carboxylate, m.p. 140.5–142.0° (Note 13).

2. Notes

1. Sodium methoxide was purchased from MC and B Manufacturing Chemists and used without

further purification. Accurate weighing is important, since the checkers noted that an excess of methoxide relative to chloroacetone, however slight, led to little or no product.

2. A convenient technique is to add the methoxide from an Erlenmeyer flask, connected to the previously stoppered neck of the reaction flask by a piece of flexible rubber tubing (Gooch tubing).

3. The addition funnel used in this preparation is depicted in f.htmigure 1.

Figure 1.

Figure 1.

4. Methanethiol was purchased from Matheson Gas Products. *Caution! This compound has a powerful, vile odor, even at extremely low concentrations.* The gas, which liquefies at 6°, may be condensed by calibrating the addition funnel at 130 ml. with a grease pencil, inserting a cold-finger condenser topped with a gas-inlet tube in the female joint, and protecting the male joint from moisture by a drying tube. A 2-propanol–dry-ice slurry is placed in the condenser and the cooling jacket, and methanethiol is introduced through the gas-inlet until the condensed liquid reaches the calibration mark.

5. Chloroacetone was purchased from Distillation Products (Eastman Organic Chemicals) and distilled prior to use. *Caution! This compound is an intensely powerful lachrymator.*

6. Ethyl *p*-aminobenzoate was purchased from the Aldrich Chemical Company, Inc., and used without further purification.

7. Commercial dichloromethane was distilled prior to use.

8. Triethylamine was purchased from the J. T. Baker Chemical Company and used without further purification.

9. If the ether is added prior to crystallization, a slightly reduced yield results.

10. Occasionally the product is contaminated with an impurity (1–2%), which appears as tiny red needles. This material has been tentatively identified as diethyl azobenzene-4,4'-dicarboxylate.

11. A level teaspoonful contains about 3 g. of nickel.

12. W-2 Raney nickel was purchased from W. R. Grace and Co. Prior to use it was washed with distilled water until neutral, then three times with absolute ethanol [*Org. Synth.*, **Coll. Vol. 3**, 181 (1955)]. This material may ignite spontaneously if allowed to become dry. Thus, in decanting, a small amount of solvent must be left behind to cover the catalyst. Although environmentally unsound, spent catalyst is discarded by slurrying in water and flushing the slurry down the drain with running water.

13. Little change in melting point results when the product is recrystallized from benzene.

3. Discussion

This procedure is an example of a new indole synthesis, which can be utilized to prepare 1-, 2-, 4-, 5-, 6-, or 7-substituted indoles.[3] Indoles substituted on the phenyl ring with nitro, ethoxycarbonyl, chloro, methyl, and acetoxy groups have been prepared; hydrogen, methyl, and phenyl groups have been placed in the 2-position; and the method has been used to prepare 1-methylindoles. A similar procedure substituting α-thioesters for α-thioketones yields oxindoles in good overall yields.[4] The major advantages of this sequence are the availab lity of starting materials and the high overall yields of indoles and oxindoles realized.[5]

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5. For a summary of other indole syntheses, see R. J. Sundberg, "The Chemistry of Indoles," Academic Press, New York, 1970.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

W-2 Raney nickel

ethanol (64-17-5)

Benzene (71-43-2)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

nitrogen (7727-37-9)

nickel, Raney nickel (7440-02-0)

sodium methoxide (124-41-4)

dichloromethane (75-09-2)

methoxide

chloroacetone (78-95-5)

magnesium sulfate (7487-88-9)

methanethiol (74-93-1)

Indole (120-72-9)

triethylamine (121-44-8)

ethyl 4-aminobenzoate, Ethyl p-aminobenzoate (94-09-7)

Ethyl 2-methylindole-5-carboxylate, 1H-Indole-5-carboxylic acid, 2-methyl, ethyl ester (53600-12-7)

methylthio-2-propanone (14109-72-9)

Ethyl 2-methyl-3-methylthioindole-5-carboxylate

tert-Butyl hypochlorite (507-40-4)

diethyl azobenzene-4,4'-dicarboxylate

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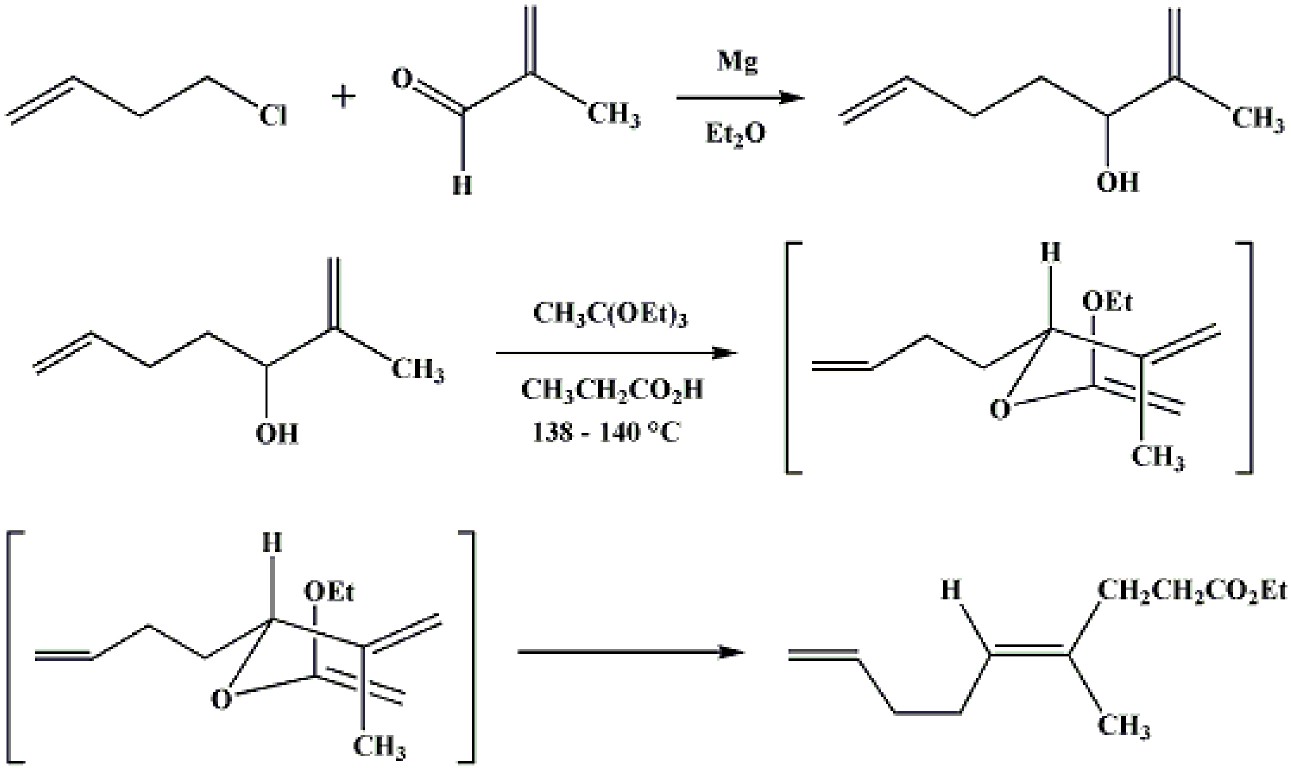
Organic Syntheses, *CV 6, 606*

STEREOSELECTIVE SYNTHESIS OF TRISUBSTITUTED OLEFINS: ETHYL 4-METHYL-(*E*)-4,8-NONADIENOATE

[4,8-Nonadienoic acid, 4-methyl, ethyl ester, *trans*-]



Submitted by Ronald I. Trust and Robert E. Ireland[1].
Checked by David G. Melillo and Herbert O. House.

1. Procedure

A. 2-*Methyl*-1,6-*heptadien*-3-*ol*. A dry, three-necked, 1-l., round-bottomed flask fitted with a mechanical stirrer, a reflux condenser with a nitrogen inlet tube, and a 125-ml., pressure-equalizing dropping funnel capped with a rubber septum is charged with 15.7 g. (0.646 g.-atom) of magnesium turnings. The flask is dried by heating with a flame while a stream of dry nitrogen is passed through the reaction vessel from the condenser and allowed to exit from a hypodermic needle inserted in the rubber septum. After drying, the hypodermic needle is removed and the flask is allowed to cool; a static nitrogen atmosphere is maintained in the reaction vessel for the remainder of the reaction. A small crystal of iodine and 450 ml. of anhydrous diethyl ether are added (Note 1). A solution of 49.4 g. (0.546 mole) of 4-chloro-1-butene (Note 2) in 50 ml. of anhydrous ether is then added from the dropping funnel, dropwise and with stirring. Sufficient external heat is applied to the reaction flask to keep the temperature of the reaction mixture at about 30°. After approximately 10–50% of the chloride solution has been added, a spontaneous reaction ensues as evidenced by the disappearance of the yellow iodine color, the appearance of a gray color in the reaction solution, and the commencement of gentle refluxing. The external heat is removed, and the remainder of the chloride solution is added at a rate that maintains gentle refluxing. After the addition is complete, the reaction mixture is refluxed for 30 minutes before a solution of 40.1 g. (0.572 mole) of methacrolein (Note 3) in 50 ml. of anhydrous ether is added, dropwise with stirring and refluxing, over 45 minutes. Since the reaction with methacrolein is exothermic, the application of external heat may not be necessary to

maintain refluxing during this addition. During the addition the reaction mixture usually becomes cloudy. When the addition is complete, the reaction mixture is refluxed with stirring for 1.5 hours before it is cooled in an ice water bath and 250 ml. of 5% hydrochloric acid is added slowly and with stirring (Note 4). The organic layer is separated and the aqueous layer is extracted with four 200-ml. portions of ether. The combined organic solutions are washed successively with 200 ml. of saturated aqueous sodium hydrogen carbonate and 200 ml. of saturated aqueous sodium chloride and dried over anhydrous sodium sulfate. The resulting ether solution is concentrated, and the residual liquid is distilled under reduced pressure, yielding 37.2–47.3 g. (54–69%) of 2-methyl-1,6-heptadien-3-ol as a colorless liquid, b.p. 85–88° (33 mm.), n_{D}^{25} 1.4531–1.4535 (Note 5).

B. *Ethyl 4-methyl-*(E)*-4,8-nonadienoate*. A 500-ml., one-necked, round-bottomed flask containing a magnetic stirring bar is fitted with a Claisen adapter, two thermometers, and a receiving flask as illustrated in f.htmigure 1. To the flask is added 186 g. (1.15 moles) of ethyl orthoacetate (Note 6), 25.2 g. (0.200 mole) of 2-methyl-1,6-heptadien-3-ol, and 0.70 g. (0.0094 mole) of propionic acid (Note 7). The mixture is heated with stirring to keep the temperature above the liquid at 138–142°. Heating is continued until ethanol no longer distils from the reaction flask (approximately one hour is required). The reaction mixture is allowed to cool to room temperature, and the excess ortho ester and propionic acid are removed by distillation under reduced pressure (approximately 50–60° at 20 mm.). The colorless to yellow residual liquid is then distilled under reduced pressure (0.25 mm., (Note 8)), giving 32.6–34.6 g. (83–88%) of ethyl 4-methyl-(*E*)-4,8-nonadienoate as a colorless liquid, b.p. 54–55° (0.25 mm.), n_{D}^{25} 1.4504 (Note 9).

Figure 1. Apparatus for the preparation of ethyl 4-methyl-(*E*)-4,8-nonadienoate.

Figure 1. Apparatus for the preparation of ethyl 4-methyl-(E)-4,8-nonadienoate.

2. Notes

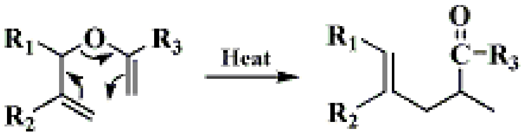
1. After drying, exposure of the reaction vessel and its contents to the atmosphere should be minimized. The iodine crystal should be added by lifting the dropping funnel, then replacing it quickly. The ether (anhydrous grade from Mallinckrodt Chemical Works) should be distilled from lithium aluminum hydride immediately before use and transferred to the reaction vessel with a stainless-steel cannula or a large hypodermic syringe inserted through the rubber septum.
2. 4-Chloro-1-butene is commercially available from Chemical Samples Company. The checkers employed this material without further purification. The submitters used material prepared from 3-buten-1-ol by a modified procedure of Roberts and Mazur.[2] Since material prepared according to the literature is invariably contaminated with thionyl chloride, which will interfere with formation of the Grignard reagent, the following modification is recommended. A two-necked, 200-ml., round-bottomed flask is equipped with a magnetic stirring bar, a 60-ml., pressure-equalizing dropping funnel, and a reflux condenser fitted with a calcium chloride drying tube. The flask is charged with 49.8 g. (0.691 mole) of 3-buten-1-ol and 1.57 ml. of anhydrous pyridine (distilled from calcium hydride). With stirring and external cooling (ice water bath), 82 g. (49 ml., 0.69 mole) of thionyl chloride (Matheson, Coleman and Bell commercial grade was used without further purification) is added dropwise over 3.5 hours. On completion of the addition, the mixture is heated under reflux for one hour. The external heating is then momentarily discontinued, and the condenser and dropping funnel are replaced by a stopper and short-path distilling head with receiver. Distillation of the mixture gives an opaque, colorless liquid (b.p. 68°). The crude product is washed with two 20-ml.

portions of saturated aqueous sodium hydrogen carbonate solution (frothing) and 20 ml. of saturated brine, then dried over magnesium sulfate and filtered. The filtrate is distilled, giving 43.4 g. (67–69%) of 4-chloro-1-butene as a colorless liquid, b.p. 68–70°.
3-Buten-1-ol, although commercially available from Aldrich Chemical Company, Inc., can be prepared economically and in large quantities by the addition of paraformaldehyde to allylmagnesium bromide [*Org. Synth.*, **Coll. Vol. 4**, 748 (1963)] in ether according to procedures outlined for a similar synthesis [*Org. Synth.*, **Coll. Vol. 1**, 188 (1944)]. In the present case, the submitters found it convenient to add the paraformaldehyde (Matheson, Coleman and Bell commercial grade was dried overnight under reduced pressure and in the presence of phosphorus pentoxide) directly to the allylmagnesium bromide solution. After a reaction period of 6 hours at reflux, the previously described [*Org. Synth.*, **Coll. Vol. 1**, 188 (1944)] isolation procedure gave 3-buten-1-ol in 56% yield.
3. Technical grade (90%) methacrolein (Aldrich Chemical Company, Inc.) was distilled (b.p. 67–69°) immediately before use.
4. Since the methacrolein is used in excess, frothing is no problem as there is no Grignard reagent remaining after the reaction is completed. Addition of 5% hydrochloric acid causes some coagulation of magnesium salts in the aqueous layer, which can be redissolved by addition of more 5% hydrochloric acid.
5. The product has the following spectral characteristics: IR (CCl_4), 3620 (free OH), 3480 (associated OH), 1645 (C=C), and 910 cm.$^{-1}$ ($CH=CH_2$); UV (95% C_2H_5OH) end absorption 210 mm (ε 208); ^1H NMR (CCl_4), δ 1.2–2.3 (m, 4H, $2CH_2$), 1.70 (s, 3H, CH_3), 2.93 (broad, 1H, O*H*), 4.00 (t, *J* = 6 Hz., 1H, OC*H*), 4.6–5.2 (m, 4H, vinyl C*H*), and 5.5–6.1 (m, 1H, vinyl C*H*); *m/e* (rel. int.), 111(28), 84(29), 83(21), 71(51), 71(100), 69(23), 67(28), 57(30), 55(51), 43(71), 41(49), and 39(37).
6. Ethyl orthacetate, available from Aldrich Chemical Company, Inc., was distilled before use. A large forerun was collected, consisting of hydrolysis products of the ortho ester. Material boiling at 135–142° is suitable for use in the reaction. It is convenient to transfer the material to the reaction flask with a stainless-steel cannula to avoid its exposure to atmospheric moisture. A fivefold excess of the ortho ester is needed, since the first step in the reaction is probably the reversible acid-catalyzed exchange of 2-methyl-1,6-heptadien-3-ol with ethanol.[3]
7. Practical grade propionic acid (Matheson, Coleman and Bell) was distilled before use (b.p. 141°).
8. On two occasions, the submitters noticed a sublimable solid crystallizing in the distilling head just before the product began to distill. The distilling head was rinsed with ether, dried, and replaced, and the distillation was continued. The checkers observed the same phenomenon.
9. The product has the following spectral properties: IR (CCl_4) 1735 (ester C=O), 1645 (C=C), and 920 cm.$^{-1}$ ($CH=CH_2$); UV (95% C_2H_5OH) end absorption 210 nm (ε 1960); ^1H NMR ($CDCl_3$), δ 1.24 (t, *J* = 7 Hz., 3H, OCH_2CH_3), 1.63 (broad, 3H, $C=CCH_3$), 1.9–2.2 (m, 4H, $2CH_2$), 2.37 (broad, 4H, $2CH_2$), 4.14 (q, *J* = 7 Hz., 2H, OCH_2CH_3), 4.8–5.4 (m, 3H, vinyl C*H*), 5.5–6.2 (m, 1H, vinyl C*H*); *m/e* (rel. int.), 196 (M^+, 4), 155(67), 151(30), 113(34), 109 (100), 108(33), 85(47), 81(80), 67(74), 55(41), 53(31), 43(32), and 41(30). In C_6D_6 the allylic CH_3 signal of the major component present, the *trans*-isomer, is found at δ 1.50 and is accompanied by a minor peak at δ 1.61 attributable[4] to 3–4% of the *cis*-olefin in the product.

3. Discussion

The use of the Claisen rearrangement and several other methods for the stereoselective synthesis of trisubstituted olefins has been reviewed.[4] In allyl vinyl ethers of type A, the stereochemistry of the rearrangement is determined largely by the steric requirements of R_1, which can be either axial or

equatorial in the transition state.[5] When R_3 = H, the *trans/cis* ratio is approximately equal to the equatorial/axial equilibrium ratio of R_1-cyclohexane at the reaction temperature. When R_3 is larger than hydrogen, the steric effect is even greater, due to a potential 1,3-interaction which would develop in the transition state if R_1 were axial. No significant effect of R_2 on the *trans/cis* ratio has been observed.



A B

The use of ethyl orthoacetate in the formation of vinyl ethers where $R_3 = OC_2H_5$ has been described.[3,6] The method described herein appears to be quite general, in that a variety of esters of type B ($R_3 = OC_2H_5$; $R_2 = CH_3$) may be prepared by merely varying the Grignard reagent used in preparing the starting allyl alcohol. The only limitation is the use of alcohols that are unsymmetrically bis-allylic, from which mixtures of structural isomers may be obtained.

Stereoselectivity in the synthesis of trisubstituted olefins is necessary for the study of biosynthetic routes to polyisoprenoids, the nonenzymatic cyclization of polyolefinic substrates, and the study of insect hormones.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 298

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

brine

Ethyl orthacetate

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ether, diethyl ether (60-29-7)

hydrogen (1333-74-0)

thionyl chloride (7719-09-7)

sodium hydrogen carbonate (144-55-8)

magnesium turnings (7439-95-4)

sodium chloride (7647-14-5)

propionic acid (79-09-4)

Allyl alcohol (107-18-6)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

iodine (7553-56-2)

pyridine (110-86-1)

magnesium sulfate (7487-88-9)

lithium aluminum hydride (16853-85-3)

Allylmagnesium bromide (1730-25-2)

methacrolein (78-85-3)

calcium hydride (7789-78-8)

3-buten-1-ol (627-27-0)

4-chloro-1-butene (927-73-1)

2-Methyl-1,6-heptadien-3-ol (53268-46-5)

ethyl orthoacetate

phosphorus pentoxide (1314-56-3)

Ethyl 4-methyl-(E)-4,8-nonadienoate, 4,8-Nonadienoic acid, 4-methyl, ethyl ester, trans- (53359-96-9)

paraformaldehyde (30525-89-4)

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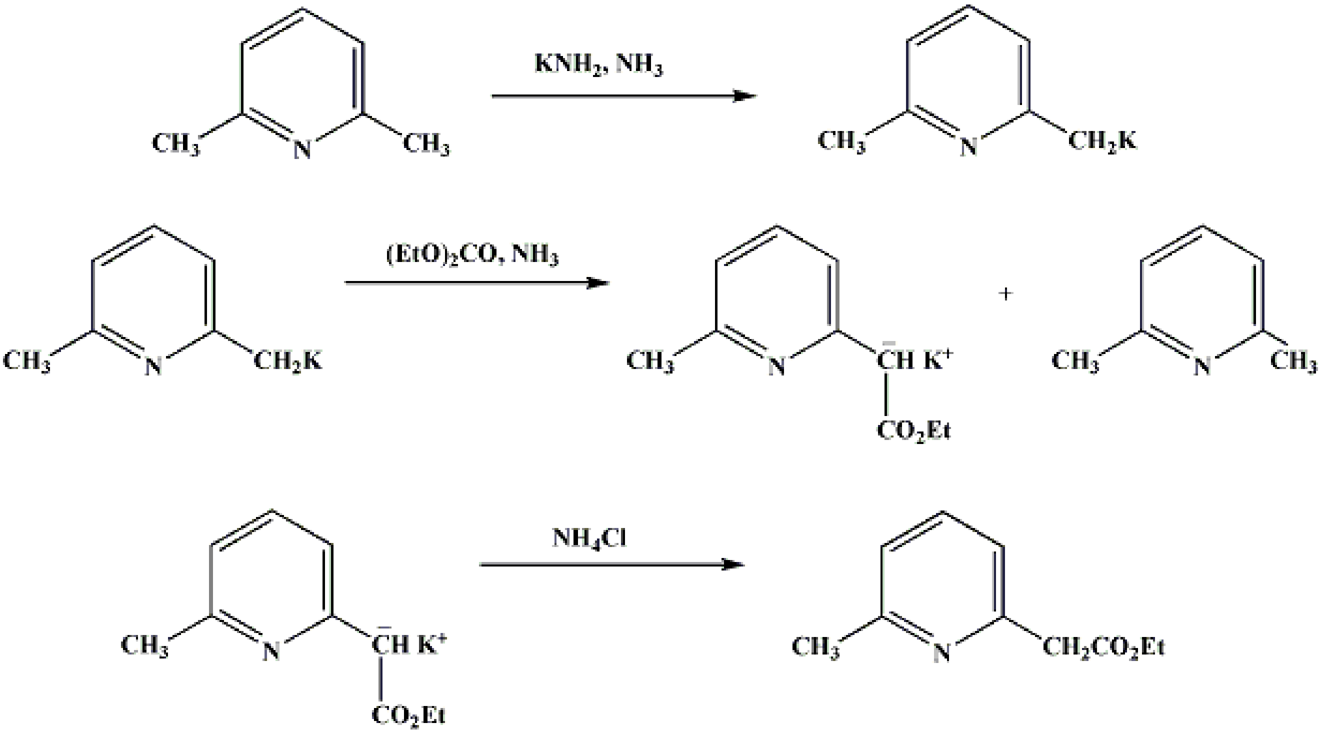
Organic Syntheses, CV 6, 611

METALATION OF 2-METHYLPYRIDINE DERIVATIVES: ETHYL 6-METHYLPYRIDINE-2-ACETATE

[Pyridineacetic acid, 6-methyl-, ethyl ester]



Submitted by William G. Kofron[1] and Leona M. Baclawski.
Checked by R. E. Ireland and R. A. Farr.

1. Procedure

Caution! This preparation should be carried out in a good hood to avoid exposure to ammonia.

A 1-l., three-necked flask is fitted with an acetone-dry ice condenser, a glass stirrer, and a glass stopper (Note 1). Potassium amide is prepared in 400 ml. of liquid ammonia with 8.0 g. (0.20 g.-atom) of potassium metal (Note 2). The glass stopper is replaced with an addition funnel containing 32.1 g. (0.300 mole) (Note 3) of 2,6-lutidine dissolved in *ca.* 20 ml. of anhydrous diethyl ether. The lutidine solution is added. to the amide solution, and the funnel is rinsed with a little ether, which is also added. The resulting orange potassiolutidine solution is stirred for 30 minutes, then cooled in an acetone–dry-ice bath (Note 3). As rapidly as possible, 11.8 g. (0.100 mole) of freshly distilled diethyl carbonate is added, the cooling bath is removed, and the solution changes to a green color. After 5 minutes the reaction mixture is neutralized by the addition of 10.7 g. (0.200 mole) of ammonium chloride. The green color is discharged; the final mixture is gray. The condenser is removed, and the ammonia is allowed to evaporate (Note 4). The residue is stirred with 500 ml. of ether, filtered, and extracted with an additional 100 ml. of ether. The combined ethereal extracts are concentrated with a rotary evaporator, and the residual oil is distilled using a modified Claisen flask. 2,6-Lutidine (22 g., 69%) is collected at 46–56° (10 mm.), and 10.7–13.4 g. (59–75%) of the ester is collected at 87° (0.7 mm.) as a bright yellow liquid, n_D^{25} 1.4995, d_4^{20} 1.0608 (Note 5).

2. Notes

1. A Teflon stirrer should not be used since Teflon is attacked by alkali metals, metal amides, and carbanions.
2. The preparation of potassium amide is described in *Org. Synth.*, **Coll. Vol. 5**, 187 (1973). *Caution! Potassium may form an explosive red or orange peroxide coating. Potassium is a silver-gray metal with a blue-violet cast, and any potassium showing an orange or red color, or with an appreciable oxide coating,*

should be considered extremely hazardous.[2]

3. The use of an extra mole of 2,6-lutidine and rapid addition of diethyl carbonate both decrease formation of urethane. The use of a dry-ice bath to cool the reaction mixture permits rapid addition of diethyl carbonate without excessive foaming. If urethane is formed from diethyl carbonate and ammonia, the yield of product is decreased and the distillation is difficult.

4. A steam bath or hot air gun may be used with care to speed up evaporation of the ammonia.

5. The ester has been reported[3] to boil at 132° (18 mm.). It was reported as a colorless oil, giving a hydrochloride melting at 112–115°. Ethyl pyridine-2-acetate was reported in *Org. Synth.*, **Coll. Vol. 3**, 413 (1955) as a light-yellow liquid, b.p. 135–137° (28 mm.). The ^{1}H NMR spectrum of the present product is in accord with the structure assigned, and the hydrochloride melts at 115°.

3. Discussion

Ethyl pyridine-2-acetate[4] and ethyl 6-methylpyridine-2-acetate have previously been prepared by carboxylation of the lithio derivatives of α-picoline and 2,6-lutidine, respectively. Use of diethyl carbonate to acylate the organometallic derivative avoids the intermediacy of the (unstable) carboxylic acid, and the yield is better. In the present procedure potassium amide is used as the metalating agent; the submitters report that the same esters may be formed by metalation with sodium amide (43% yield) or *n*-butyllithium (39% yield). The latter conditions also yield an appreciable amount of the acid (which decarboxylates).

5

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ammonia (7664-41-7)

ether, diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

potassium (7440-09-7)

2,6-Lutidine (108-48-5)

lutidine (583-61-9)

urethane (51-79-6)

sodium amide (7782-92-5)

n-butyllithium (109-72-8)

diethyl carbonate (105-58-8)

potassium amide

Ethyl pyridine-2-acetate (2739-98-2)

Ethyl 6-methylpyridine-2-acetate, Pyridineacetic acid, 6-methyl-, ethyl ester (5552-83-0)

potassiolutidine

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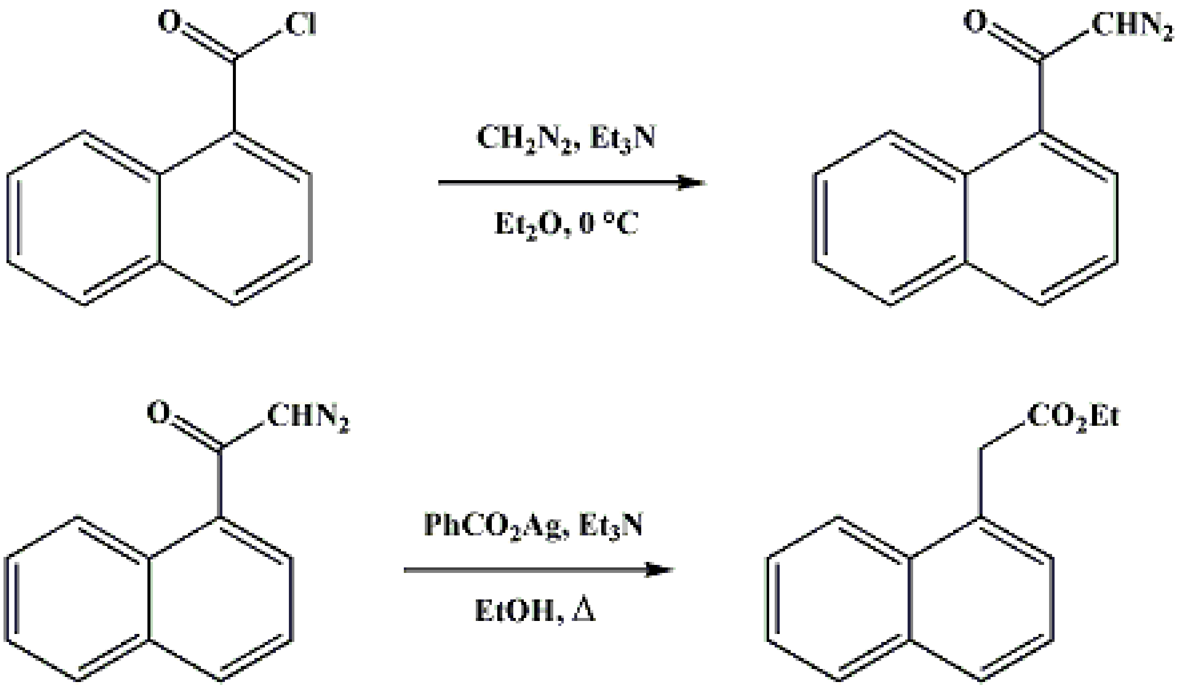
Organic Syntheses, CV 6, 613

ETHYL 1-NAPHTHYLACETATE

[1-Naphthaleneacetic acid, ethyl ester]



Submitted by Ving Lee and Melvin S. Newman[1].
Checked by Gordon F. Hambly and Peter Yates.

1. Procedure

*Caution! Diazomethane is hazardous. Follow the directions for its safe handling given in Org. Synth., **Coll. Vol. 4**, 250 (1963) and **Coll. Vol. 5**, 351 (1973). The intermediate, 1-(diazoacetyl) naphthalene, is a very strong skin irritant.*

A. *1-(Diazoacetyl)naphthalene*. A solution of 30.5 g. (0.160 mole) of 1-naphthoyl chloride (Note 1) and (Note 2) in 50 ml. of dry diethyl ether (Note 3) is added over 30 minutes to a magnetically stirred, ice-cooled solution of 6.72 g. (0.160 mole) of diazomethane [*Org. Synth.*, **Coll. Vol. 2**, 165 (1943); (Note 4)] and 16.1 g. (0.160 mole) of dry triethylamine (Note 5) in 900 ml. of dry ether. The mixture is stirred for 3 hours in the cold, and the triethylamine hydrochloride, removed by filtration, is washed twice with 30–50 ml. portions of dry ether (Note 6). The ether is removed from the combined filtrate and washings on a rotary evaporator. The yellow solid residue is dissolved in 75 ml. of dry ether, and the solution is cooled with an acetone–dry-ice mixture. The solid deposited is collected by filtration on a glass fritted-disk funnel, and the adhering ether is removed under reduced pressure as the temperature is allowed to reach room temperature, giving 26.6–28.8 g. (85–92%) of yellow 1-

(diazoacetyl)naphthalene, m.p. 52–53° (Note 7) and (Note 8).

B. *Ethyl 1-naphthylacetate*. A solution of 15.7 g. (0.0801 mole) of 1-(diazoacetyl) naphthalene in 50 ml. of absolute ethanol is placed in a 100-ml., two-necked flask equipped with a Teflon-coated magnetic stirring bar, a serum stopper cap, and a reflux condenser connected to a gas-collecting device. The solution is heated to reflux, and 1 ml. of a freshly prepared catalyst solution made by dissolving 1 g. of silver benzoate (Note 9) in 10 ml. of triethylamine is added by injection through the serum cap. Evolution of nitrogen occurs and the mixture turns black. Addition of a second milliliter of catalyst solution is made when the evolution of nitrogen almost stops. This procedure is continued until further additions cause no further evolution of nitrogen (Note 10). The reaction mixture is refluxed for 1 hour, cooled, and filtered. The solvents are removed from the filtrate on a rotary evaporator. The residue is taken up in 75 ml. of ether, and the solution is washed twice in turn with aqueous 10% sodium carbonate, water, and saturated brine. Each aqueous extract is extracted with ether, and the combined ethereal extracts and solution are dried by filtration through anhydrous magnesium sulfate. After removal of the ether, distillation affords 14.4–15.8 g. (84–92%) of colorless ethyl 1-naphthylacetate, b.p. 100–105° (0.1–0.2 mm.) (Note 11).

2. Notes

1. The submitters prepared pure 1-naphthoyl chloride, b.p. 95–96° (0.2 mm.), from pure 1-naphthoic acid in 95% yield by treatment with thionyl chloride or phosphorus pentachloride. The 1-naphthoic acid used was prepared by carbonation of 1-naphthylmagnesium bromide. As commercial 1-bromonaphthalene is impure, fractionation through a 17 × 600 mm. column is needed to obtain pure 1-bromonaphthalene, b.p. 105–108° (0.1–0.2 mm.), as indicated by GC.
2. The checkers prepared 1-naphthoyl chloride by treatment of 1-naphthoic acid, m.p. 157–161°, obtained from Aldrich Chemical Co., with phosphorus pentachloride.
3. All dry ether used was freshly distilled from ethylmagnesium bromide.
4. Solutions of diazomethane in ether were titrated with benzoic acid.
5. Triethylamine was dried by storage over anhydrous barium oxide.
6. About 90% of the theoretical yield of triethylamine hydrochloride is obtained.
7. This compound is a severe skin irritant; hence, great care should be exercised to avoid any contact. For best yields this crystallization is recommended, since the yield of ethyl 1-naphthylacetate is reduced by about 20% if the crude product is used in the rearrangement step. A sample of crystallized 1-(diazoacetyl) naphthalene, m.p. 52–53°, that had been stored in a screw-top bottle in a refrigerator for about 2 weeks afforded the same yield of ethyl 1-naphthylacetate as a freshly prepared sample.
8. The checkers obtained 26.1–26.5 g. (83–84.5%) of 1-(diazoacetyl) naphthalene, m.p. 47–49.5°, when 1-naphthoyl chloride prepared from

commercial 1-naphthoic acid was used (cf. (Note 1) and (Note 2)). Recrystallization from hexane gave 24.6 g. (78%) of 1-(diazoacetyl) naphthalene, m.p. 49.5–52°, that was used in Part B.

9. The silver benzoate was made by reaction of silver nitrate with sodium benzoate in water. The submitters dried the silver benzoate and recrystallized it from *N*-methylpyrrolidone or *N*,*N*-dimethylformamide. The checkers dried it in an oven at 130° for 1 hour immediately before use, but did not recrystallize it. Any precipitate present after dissolving the silver benzoate in triethylamine is removed by filtration or centrifugation.

10. Usually 3–4 additions are required. The total time of reaction should not be more than 45 minutes. The checkers added the catalyst solution in 0.5-ml. portions; nitrogen evolution was initially very vigorous, and only four such additions were required.

11. When propanol is used instead of ethanol, comparable results are obtained: propyl 1-naphthylacetate, b.p. 115–118° (0.1–0.2 mm.).

3. Discussion

Ethyl 1-naphthylacetate has been prepared by ethanolysis of 1-naphthylacetonitrile under acidic conditions[2] and by the Arndt-Eistert reaction of 1-(diazoacetyl) naphthalene with ethanol and silver oxide.[3]

The method described here represents a modified Arndt-Eistert reaction as developed by Newman and Beal,[4] gives results that are more reproducible than those of the original Arndt-Eistert reaction and, in general, allows the rearrangement to be carried out successfully on larger-scale runs. The use of triethylamine in the formation of diazo ketones makes possible the use of only one equivalent of diazomethane.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 426

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

brine

ethanol (64-17-5)

ether, diethyl ether (60-29-7)

phosphorus pentachloride (10026-13-8)

thionyl chloride (7719-09-7)

silver oxide (20667-12-3)

silver nitrate (7761-88-8)

sodium carbonate (497-19-8)

barium oxide

nitrogen (7727-37-9)

Benzoic acid (65-85-0)

sodium benzoate (532-32-1)

1-bromonaphthalene (90-11-9)

propanol (71-23-8)

ethylmagnesium bromide (925-90-6)

magnesium sulfate (7487-88-9)

Diazomethane (334-88-3)

1-Naphthoic acid (86-55-5)

1-naphthoyl chloride (879-18-5)

N,N-dimethylformamide (68-12-2)

hexane (110-54-3)

triethylamine (121-44-8)

Triethylamine hydrochloride (554-68-7)

N-methylpyrrolidone (872-50-4)

Ethyl 1-naphthylacetate (3121-70-8)

1-Naphthaleneacetic acid, ethyl ester (2122-70-5)

1-(diazoacetyl) naphthalene, 1-(Diazoacetyl)naphthalene (4372-76-3)

silver benzoate (532-31-0)

1-naphthylmagnesium bromide

propyl 1-naphthylacetate

1-naphthylacetonitrile (132-75-2)

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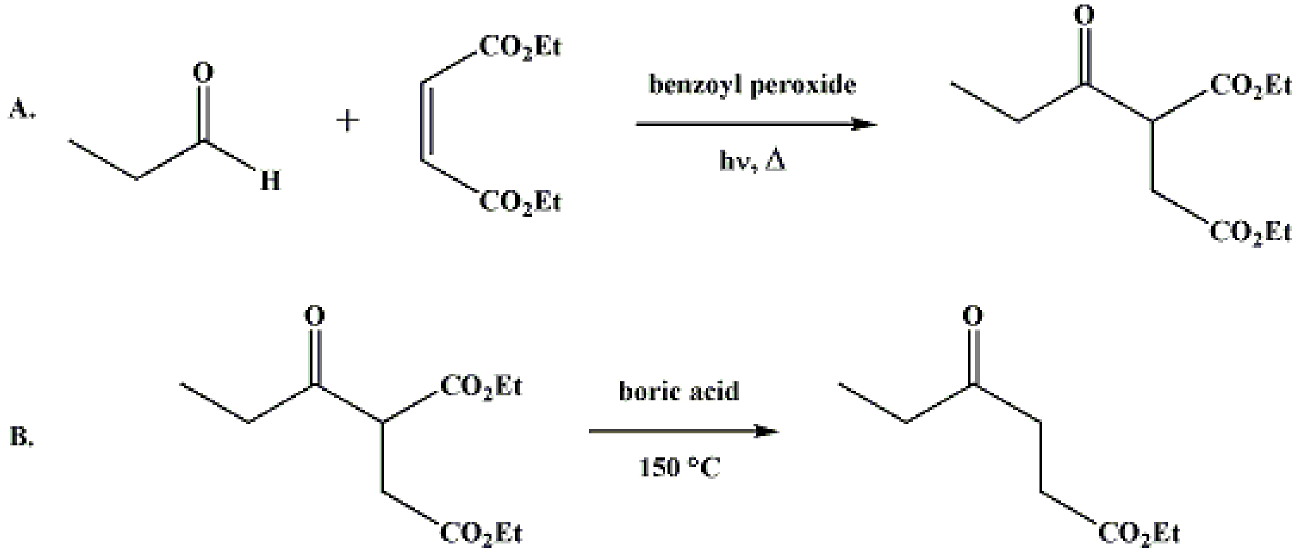
Organic Syntheses, CV 6, 615

γ-KETOESTERS FROM ALDEHYDES *VIA* DIETHYL ACYLSUCCINATES: ETHYL 4-OXOHEXANOATE

[Hexanoic acid, 4-oxo-, ethyl ester]



Submitted by Pius A. Wehrli[1] and Vera Chu.
Checked by William B. Farnham and William A. Sheppard.

1. Procedure

A. *Diethyl propionylsuccinate* **(1)**. A solution of 412 g. (2.40 mole) of diethyl maleate (Note 1), 278 g. (4.79 mole) of freshly distilled propionaldehyde (Note 2), and 1.2 g. (0.0048 mole) of benzoyl peroxide in a normal, 2-l. Pyrex flask is heated under reflux while undergoing irradiation with a UV lamp (Note 3). The initial reflux temperature is 60°. After 2 hours another 1.2 g. of benzoyl peroxide is added. Strong reflux and irradiation are maintained throughout the entire reaction period. After 18 hours of reflux, the internal pot temperature reaches 68°, at which point the last 1.2 g. of benzoyl peroxide is added. The reaction is continued for a total of 30 hours, at which time the pot temperature reaches 74.5°. The reflux condenser is then replaced with a distillation head, and the excess propionaldehyde (119 g.) is distilled under atmospheric pressure, b.p. 48–49°. Succinate **1** is distilled under reduced pressure. The main fraction, b.p. 145–151.5° (15–16 mm), provides 417–449 g. (75–81%) of product having sufficient purity for use in the next step (Note 4).

B. *Ethyl 4-oxohexanoate* **(2)**. A 1-l., three-necked, round-bottomed flask equipped with a mechanical stirrer, thermometer, and Claisen condenser connected to a gas-measuring device (Note 5) is charged with 276 g. (1.20 mole) of succinate **1** and 74.1 g. (1.20 mole) of boric acid (Note 6). The initially heterogeneous mixture is stirred and immersed in a 150° oil bath. Within 1 hour 36 g. of distillate (mainly ethanol) and approximately 2.3 l. of gas collect. As the temperature is raised to 170°, the rate of carbon dioxide evolution increases, a total of 24.9 l. of gas being collected after 1.5 hours. At this time gas evolution has almost ceased, and the reaction mixture has a clear, light-yellow appearance. The contents of the flask are cooled to room temperature, poured onto 1.5 l. of ice, and extracted with three 500-ml. portions of toluene. The combined organic layers are dried over anhydrous magnesium sulfate, and the solvent is removed under reduced pressure. The product is distilled through a 10-cm. Vigreux column, yielding 156–162 g. (82–85%) of ethyl 4-oxohexanoate, b.p. 109–

112° (18 mm.). GC analysis indicates the material to be 99.2% pure (Note 7).

2. Notes

1. Diethyl maleate, practical grade, available from Eastman Organic Chemicals, was used without further purification.
2. Propionaldehyde was obtained from Aldrich Chemical Company, Inc., and must be distilled before use.
3. The checkers used a 275-W. General Electric sunlamp. The submitters used a 140-W. Hanovia Ultraviolet Quartz lamp of a type no longer available.
4. The succinate **1** has the following ^1H NMR spectra ($CDCl_3$), δ (multiplicity, number of protons, assignment): 1.0–1.45 (m, 9H, $3CH_3$), 2.6–3.5 (m, 4H, $2CH_2$), 3.9–4.4 (m, 5H, $2OCH_2CH_3$ and C*H*).
5. As a gas-measuring device, the submitters used an inverted, calibrated, 10-l. bottle, filled with saturated sodium chloride, resting in an enamel bucket big enough to hold the volume to be displaced. The checkers used a gas meter. However, the rate of gas evolution can be estimated by using a simple gas bubbler.
6. Reagent grade boric acid, available from Aldrich Chemical Company, Inc., was used.
7. GC analysis was performed on a Hewlett-Packard Model 5720 with dual flame detector; column 1.85 m. × 0.313 cm. outer diameter, stainless steel; 10% UCW-98 on Diatoport 5, programmed at 30° per minute from 50–250°. The purity was calculated by an area comparison. Ester **2** has the following ^1H NMR spectrum ($CDCl_3$), δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 1.05 (t, $J = 7$, 3H, CH_3), 1.2 (t, $J = 7$, 3H, CH_3), 2.4–2.9 (m, 6H, $3CH_2$), 4.2 (q, $J = 7$, 2H, OCH_2CH_3).

3. Discussion

γ-Ketoesters, notably 5-substituted ethyl levulinates, have been prepared *via* radical addition of aldehydes to diethyl maleate to give acylated diethyl succinates.[2] These intermediates in turn had to be saponified,[2] decarboxylated,[2] and reesterified to give the corresponding 4-oxocarboxylates. A more direct method[3] utilizes the free radical addition of butyraldehyde to methyl acrylate, but the reported yield is low (11%).

The present method[4] is simple, versatile, and efficient in contrast to earlier methods, which were multistep or preparatively unsatisfactory. Various 5-substituted 4-oxocarboxylates can be prepared by this procedure.[4]

γ-Ketoesters, in general, and levulinic acid or esters, in particular, have extensive utility.[5] For example, they can serve as central intermediates for γ-butyrolactones,[6] 1,4-diols,[7] thiophenes,[8] pyrrolidones,[9] and 2-alkyl-1,3-cyclopentanediones.[10]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 774
- Org. Syn. Coll. Vol. 6, 799

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

sodium chloride (7647-14-5)

Propionaldehyde (123-38-6)

carbon dioxide (124-38-9)

toluene (108-88-3)

butyraldehyde (123-72-8)

diethyl maleate (141-05-9)

LEVULINIC ACID (123-76-2)

boric acid (10043-35-3)

benzoyl peroxide (94-36-0)

methyl acrylate (96-33-3)

magnesium sulfate (7487-88-9)

succinate

Ethyl 4-oxohexanoate, Hexanoic acid, 4-oxo-, ethyl ester (3249-33-0)

Diethyl propionylsuccinate (4117-76-4)

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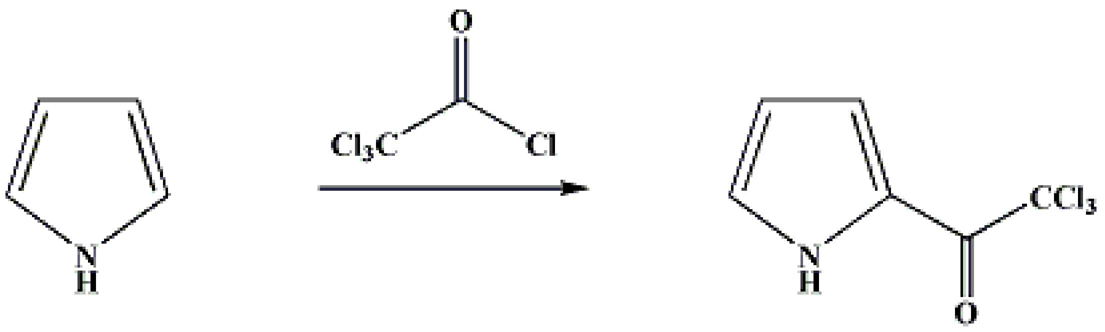
Organic Syntheses, CV 6, 618

ETHYL PYRROLE-2-CARBOXYLATE

[1*H*-Pyrrole-2-carboxylic acid, ethyl ester]



Submitted by Denis M. Bailey, Robert E. Johnson, and Noel F. Albertson[1].
Checked by A. Brossi and P. Wehrli.

1. Procedure

A. *2-Pyrrolyl trichloromethyl ketone*. A 3-l., three-necked, round-bottomed flask equipped with a sealed mechanical stirrer, a dropping funnel, and an efficient reflux condenser with a calcium chloride drying tube is charged with 225 g. (1.23 moles) of trichloroacetyl chloride and 200 ml. of anhydrous diethyl ether. The solution is stirred while 77 g. (1.2 moles) of freshly distilled pyrrole in 640 ml. of anhydrous ether is added over 3 hours (Note 1); the heat of reaction causes the mixture to reflux. Following the addition, the mixture is stirred for 1 hour before 100 g. (0.724 mole) of potassium carbonate in 300 ml. of water is slowly added through the dropping funnel (Note 2). The layers are separated, and the organic phase is dried with magnesium sulfate, treated with 6 g. of Norit, and filtered. The solvent is removed by distillation on a steam bath, and the residue is dissolved in 225 ml. of hexane. The dark solution is cooled on ice to induce crystallization. The tan solid is collected and washed with 100 ml. of cold hexane, giving 189–196 g. (77–80%) of the ketone, m.p. 73–75° (Note 3).

B. *Ethyl pyrrole-2-carboxylate*. A 1-l., three-necked, round-bottomed flask equipped with a sealed mechanical stirrer and powder funnel is charged with 1.0 g. (0. 44 g.-atom) of sodium and 300 ml. of anhydrous ethanol. When the sodium is dissolved, 75

g. (0.35 mole) of 2-pyrrolyl trichloromethyl ketone is added portionwise over a 10-minute period (Note 4). Once the addition is complete, the solution is stirred for 30 minutes, then concentrated to dryness using a rotary evaporator. The oily residue is partitioned between 200 ml. of ether and 25 ml. of 3 *N* hydrochloric acid. The ether layer is separated, and the aqueous layer is washed once with 100 ml. of ether. The combined ether solutions are washed once with 25 ml. of saturated sodium hydrogen carbonate solution, dried with magnesium sulfate, and concentrated by distillation. The residue is fractionated at reduced pressure, giving 44.0–44.5 g. (91–92%) of ethyl pyrrole-2-carboxylate as a pale yellow oil, b.p. 125–128° (25 mm.) (Note 5). The yield based on pyrrole is 70–74%. Upon standing at room temperature the product crystallizes, m.p. 40–42°.

2. Notes

1. If the addition time is shortened to 1 hour, the yield is decreased by about 5%.
2. Excessive frothing will occur if the potassium carbonate solution is added too fast.
3. A similar run on a scale 3.3 times as large with a 3-hour addition time gave the ketone in 74% yield.
4. The solution becomes warm during the addition, and the final color of the solution is reddish-brown.
5. A similar run on a scale three times as large gave the ester in 96% yield.

3. Discussion

Pyrrole-2-carboxylic acid esters have been prepared from ethyl chloroformate and pyrrolylmagnesium bromide[2] or pyrrolyllithium,[3] by hydrolysis and decarboxylation of dimethyl pyrrole-1,2-dicarboxylate followed by re-esterification of the 2-acid[4] and by oxidation of pyrrole-2-carboxaldehyde followed by esterification with diazomethane.[4]

Methods of acylating pyrrole similar to the present, using oxalyl chloride,[5] trifluoroacetic anhydride,[6] carbamic acid chloride,[7] and trichloroacetyl chloride,[8] have been reported. In the last preparation, it was necessary to separate the product from highly colored by-products with alumina chromatography. 2-Pyrrolyl trichloromethyl ketone has also been prepared by the reaction of pyrrolylmagnesium halide with trichloroacetyl chloride.[9]

The present procedure provides a facile and versatile synthesis, on large scale, of a variety of pyrrole-2-carboxylic acid derivatives without necessitating the use of moisture-sensitive organometallic reagents. The use of alcohols other than ethanol in the alcoholysis reaction provides virtually any desired ester. Ammonia or aliphatic amines readily give amides in high yields, and aqueous base can be used to give the free acid.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ether, diethyl ether (60-29-7)

sodium hydrogen carbonate (144-55-8)

sodium (13966-32-0)

ethyl chloroformate (541-41-3)

Pyrrole (109-97-7)

magnesium sulfate (7487-88-9)

Diazomethane (334-88-3)

carbamic acid chloride

oxalyl chloride (79-37-8)

hexane (110-54-3)

Pyrrole-2-carboxaldehyde (1003-29-8)

trifluoroacetic anhydride (407-25-0)

trichloroacetyl chloride (76-02-8)

Ethyl pyrrole-2-carboxylate, 1H-Pyrrole-2-carboxylic acid, ethyl ester (2199-43-1)

2-pyrrolyl trichloromethyl ketone (35302-72-8)

Pyrrole-2-carboxylic acid (634-97-9)

pyrrolylmagnesium bromide

pyrrolyllithium

dimethyl pyrrole-1,2-dicarboxylate

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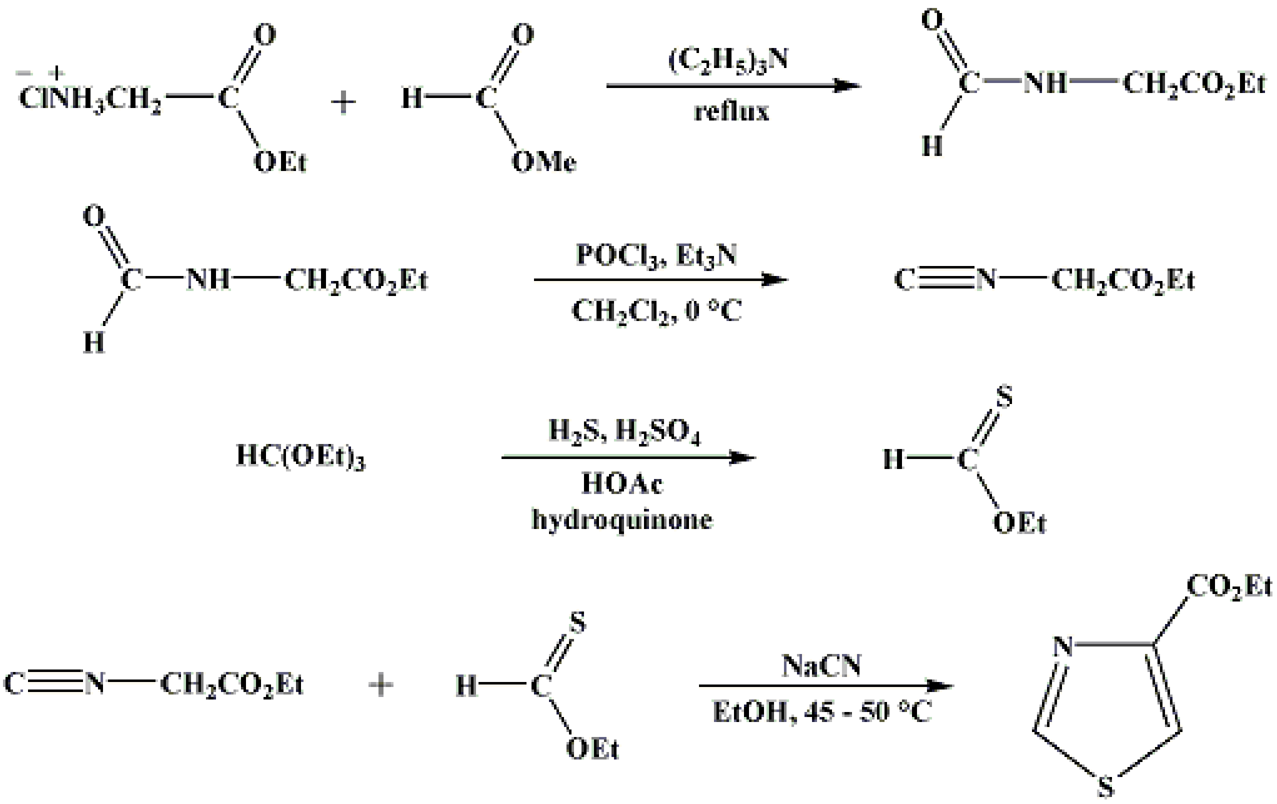
Organic Syntheses, *CV 6, 620*

THIAZOLES FROM ETHYL ISOCYANOACETATE AND THIONO ESTERS: ETHYL THIAZOLE-4-CARBOXYLATE

[4-Thiazolecarboxylic acid, ethyl ester]



Submitted by G. D. Hartman and L. M. Weinstock[1].
Checked by Louis E. Benjamin Sr, Norman W. Gilman, and Gabriel Saucy.

1. Procedure

A. N-*Formylglycine ethyl ester*. A 1-l., three-necked, round-bottomed flask fitted with a mechanical stirrer, a pressure-equalizing dropping funnel, and a reflux condenser bearing a calcium chloride drying tube is charged with 69.5 g. (0.495 mole) of glycine ethyl ester hydrochloride and 250 ml. of methyl formate (Note 1). The suspension is stirred and heated at reflux while 55.0 g. (0.544 mole) of triethylamine (Note 1) is added. The resulting mixture is stirred and heated under reflux for 20 hours, cooled to room temperature, and filtered through a Büchner funnel, removing triethylamine hydrochloride. The filtrate is concentrated on a rotary evaporator, and the remaining clear oil is distilled under reduced pressure, yielding 51.7–61.5 g. (79–94%) of *N*-formylglycine ethyl ester, b.p. 94–97° (0.05 mm., (Note 2)).

B. *Ethyl isocyanoacetate*. A 3-l., three-necked, round-bottomed flask equipped with a thermometer, a mechanical stirrer, and a pressure-equalizing dropping funnel bearing a nitrogen inlet is charged with 65.5 g. (0.500 mole) of *N*-formylglycine ethyl ester, 125.0 g. (1.234 moles) of triethylamine, and 500 ml. of dichloromethane, and the apparatus is flushed with nitrogen. The resulting solution is stirred and cooled to 0° to −2° in an ice–salt bath, and

76.5 g. (0.498 mole) of phosphorus oxychloride (Note 3) is added dropwise over 15–20 minutes while the temperature is kept at 0°. The mixture becomes reddish brown as it is stirred and cooled at 0° for an additional 1 hour. The ice–salt bath is removed and replaced by an ice-water bath. Stirring is continued as a solution of 100 g. of anhydrous sodium carbonate in 400 ml. of water is added dropwise at a rate such that the temperature of the mixture is maintained at 25–30° (Note 4). The two-phase mixture is stirred for another 30 minutes, after which water is added until the volume of the aqueous layer is brought to 1 l. The aqueous layer is separated and extracted with two 250-ml. portions of dichloromethane. The dichloromethane solutions are combined, washed with saturated sodium chloride solution, and dried over anhydrous potassium carbonate. Evaporation of the solvent under reduced pressure and distillation of the remaining brown oil afford 43–44 g. (76–78%) of ethyl isocyanoacetate, b.p. 89–91° (11 mm.) (Note 5).

C. O-*Ethyl thioformate*. *Caution! Hydrogen sulfide gas is highly toxic; this procedure should be conducted in a well-ventilated hood.* A 1-l., three-necked, round-bottomed flask is equipped with a mechanical stirrer, a gas-inlet tube with a fritted-glass tip extending near to the bottom of the flask, and a gas-outlet connected to a scrubber flask containing 0.5–1.0 l. of aqueous 20% sodium hydroxide (Note 6). The flask is charged with 333 g. (2.25 moles) of triethyl orthoformate (Note 7), 330 ml. of glacial acetic acid, 3.2 g. of hydroquinone, and 0.4 ml. of concentrated sulfuric acid. The resulting solution is stirred and cooled in an ice bath as hydrogen sulfide gas is passed through the gas-inlet tube into the solution (Note 8). After the solution becomes saturated with hydrogen sulfide, the contents of the flask are poured into a 4-l. beaker containing a mechanically stirred mixture of 2.3 l. of ice and 340 ml. of diethyl ether. The mixture is poured into a separatory funnel, and the layers are separated. The organic layer is washed successively with two 100-ml. portions of aqueous saturated sodium hydrogen carbonate solution, two 100-ml. portions of water, three 80-ml. portions of aqueous saturated sodium hydrogen carbonate, and two 80-ml. portions of aqueous saturated sodium chloride. The solution is dried over anhydrous sodium sulfate and distilled at atmospheric pressure through a 45-cm. Vigreux column, affording 60–76.7 g. (30–38%) of *O*-ethyl thioformate as a yellow liquid, b.p. 87–89° (Note 9) and (Note 10).

D. *Ethyl thiazole-4-carboxylate*. A 250-ml., three-necked, round-bottomed flask fitted with a thermometer, a mechanical stirrer, and a pressure-equalizing dropping funnel bearing a calcium chloride drying tube is charged with 0.25 g. (0.0051 mole) of sodium cyanide and 10 ml. of absolute ethanol. The suspension is stirred vigorously at room temperature as a solution of 4.52 g. (0.0439 mole) of ethyl isocyanoacetate and 3.60 g. (0.0400 mole) of *O*-ethyl thioformate in 15 ml. of absolute ethanol is added slowly. Because the reaction is exothermic the temperature of the mixture should be kept below 45° by adjusting the addition rate and, if necessary, cooling the flask in an ice bath (Note 11). When the addition is completed, the contents of the flask are stirred and heated at 50° for another 30 minutes. The solvent is removed by rotary evaporation, and the resulting dark oil is extracted with three 60-ml. portions of hot hexane (Note 12). The combined hexane extracts are concentrated with a rotary evaporator until the product begins to separate, and the concentrate is cooled in an ice bath, yielding 5.1–5.5 g. (81–87%) of ethyl thiazole-4-carboxylate as off-white needles, m.p. 52–53° (Note 13).

2. Notes

1. Glycine ethyl ester hydrochloride, methyl formate, and triethylamine were purchased from Aldrich Chemical Company, Inc., and were used without purification.
2. The submitters obtained 63 g. (96%), b.p. 104–106° (0.1 mm).
3. The submitters recommend that phosphorus oxychloride either be taken from a previously unopened bottle or distilled before use.
4. Foaming generally occurs during the addition.
5. Essentially no forerun need be taken prior to collection of the product. The last few milliliters of distillate were slightly yellow, and 2–3 g. of intractable material remained in the distillation flask. A boiling point of 76–78° (4 mm.) has been reported[2] for ethyl isocyanoacetate. The submitters have found the distilled product to be stable for up to 6 months when stored under nitrogen at –20°.
6. The checkers used a gas-inlet tube without a fritted-glass tip and aqueous 30% sodium hydroxide as scrubber solution.
7. Triethyl orthoformate is available from Aldrich Chemical Company, Inc.
8. Hydrogen sulfide is admitted into the flask slowly at first, with bubble formation kept to a minimum. Initially the gas dissolves readily. As the solution becomes saturated, more bubbling action is apparent in the flask and the scrubber.
9. The submitters reported a yield of 56.5 g. (28%), b.p. 90–92°. The product is often contaminated with *ca.* 5% of ethyl formate; however, this impurity does not interfere with Part D. The submitters state that the product is stable when stored under nitrogen at –20°.
10. The checkers found that glassware in which the product was stored acquired a disagreeable odor that was difficult to remove with aqueous sodium hydroxide.
11. Controlling the temperature in this manner prevents discoloration of the final product and improves its yield.
12. The product was obtained as tan needles when boiling hexane was used by the checkers. Off-white needles were isolated when the temperature of the hexane was 50–55°.
13. The submitters reported a yield of 5.8 g. (92%) of product as white needles, m.p. 53–54°. However, the checkers obtained colorless needles only after recrystallizing the product from hexane. The melting points of the discolored needles obtained initially by the checkers and the recrystallized material were identical (lit.,[3,4] m.p. 57° and 52–54°). The spectral properties of the product are as follows: IR ($CHCl_3$) $cm.^{-1}$: 3130, 3030, 1724 (C=O), 1500, 1270; ^1H NMR ($CDCl_3$), δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 1.39 (t, *J* = 7, 3H, OCH_2CH_3), 4.43 (q, *J* = 7, 2H, OCH_2CH_3), 8.33 (d, *J* = 2.5, 1H, *H* at C-5), 8.98 (d, *J* = 2.5, 1H, *H* at C-2).

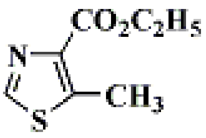
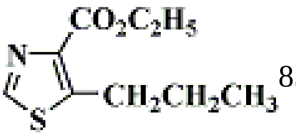
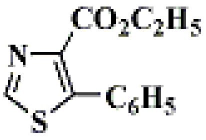
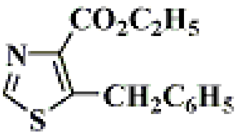
3. Discussion

Ethyl thiazole-4-carboxylate has been prepared by hydrogenolysis of ethyl 2-bromothiazole-4-carboxylate with Raney nickel in ethanol,[3] by desulfurization of ethyl 2-mercaptothiazole-4-carboxylate with hydrogen peroxide in concentrated hydrochloric acid,[4] and by condensation of ethyl bromopyruvate with thioformamide in ether.[5,6]

The present procedure is illustrative of a mild and general method for preparing thiazoles substituted at the 4-position with electron-withdrawing substitutents such as ethoxycarbonyl,[7]

cyano,[7] and *p*-toluenesulfonyl.[8] Thus, condensation of ethyl isocyanoacetate with various thiono esters affords the parent ethyl thiazole-4-carboxylate as well as a series of analogs bearing substituents in the 5-position (Table I).[7] A similar reaction of α-isocyanoacetonitrile with *O*-ethyl thioformate gave the cyano analog in 23% yield. However, the instability of the latter isocyanide hampers the utility of this reaction.

TABLE I
THIAZOLES FROM CONDENSATION OF ETHYL ISOCYANOACETATE AND α-ISOCYANOACETAMIDE WITH THIONO ESTERS

Thiazole	M.p. or B.p. (°)	Yield(%)
	89–90	82
	85–87 (0.15 mm.)	68
	183–185	22
	49–50	75
	55–56	23

The mechanism of the condensation in Part D probably involves thioformylation of the metallated isocyanoacetate followed by intramolecular 1,1-addition of the tautomeric enethiol to the isonitrile. This thiazole synthesis is analogous to the formation of oxazoles from acylation of metallated isonitriles with acid chlorides or anhydrides.[9,10] Interestingly, ethyl formate does not react with isocyanoacetate under the conditions of this procedure. Ethyl and methyl isocyanoacetate have been prepared in a similar manner by dehydration of the corresponding *N*-formylglycine esters with phosgene[2] and trichloromethyl chloroformate,[11] respectively. The phosphorus oxychloride method described here was provided to the

submitters by Professor U. Schöllkopf[12] and is based on the procedure of Böhme and Fuchs.[13] The preparation of *O*-ethyl thioformate was developed from a report by Ohno, Koizuma, and Tsuchihaski.[14]

4-Substituted thiazoles are important intermediates, as in the synthesis of thiabendazole [2-(4-thiazolyl)benzimidazole], a leading anthelminthic utilized for control of gastrointestinal nematodes in ruminants.[15] Other thiazoles have displayed significant pharmacologic activity as antiinflammatory[16] and antibacterial agents.[17] Recently, 4-substituted thiazoles were implicated as intermediates in the energy transfer mechanism of firefly bioluminescence.[18]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 242

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Glycine ethyl ester hydrochloride, methyl formate

Ethyl and methyl isocyanoacetate

ethanol (64-17-5)

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ether, diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

hydroquinone (123-31-9)

sodium hydrogen carbonate (144-55-8)

sodium cyanide (143-33-9)

sodium chloride (7647-14-5)

hydrogen sulfide (7783-06-4)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

isonitrile (57-12-5)

Raney nickel (7440-02-0)

Phosphorus Oxychloride (21295-50-1)

phosgene (75-44-5)

hydrogen peroxide (7722-84-1)

triethyl orthoformate (122-51-0)

ethyl formate (109-94-4)

methyl formate (107-31-3)

dichloromethane (75-09-2)

Glycine ethyl ester hydrochloride (623-33-6)

thiazole (288-47-1)

hexane (110-54-3)

triethylamine (121-44-8)

Triethylamine hydrochloride (554-68-7)

Trichloromethyl chloroformate (503-38-8)

Ethyl isocyanoacetate (2999-46-4)

Ethyl thiazole-4-carboxylate, 4-Thiazolecarboxylic acid, ethyl ester (14527-43-6)

ethyl 2-bromothiazole-4-carboxylate

ethyl 2-mercaptothiazole-4-carboxylate

ethyl bromopyruvate (70-23-5)

thioformamide (115-08-2)

α-isocyanoacetonitrile

isocyanoacetate

2-(4-thiazolyl)benzimidazole (148-79-8)

N-Formylglycine ethyl ester (3154-51-6)

O-ethyl thioformate (21071-39-6)

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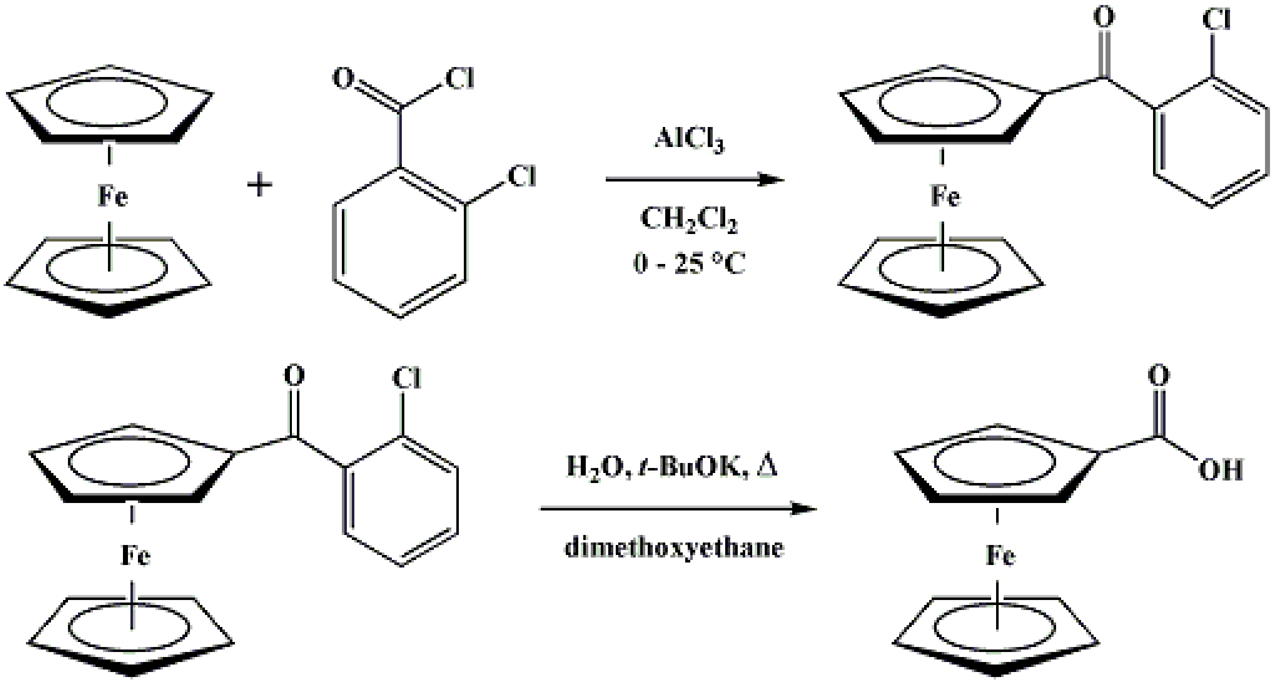
Organic Syntheses, CV 6, 625

CARBOXYLATION OF AROMATIC COMPOUNDS: FERROCENECARBOXYLIC ACID

[Ferrocene, carboxy-]



Submitted by Perry C. Reeves[1]
Checked by J. J. Mrowca, M. M. Borecki, and William A. Sheppard.

1. Procedure

A. (2-*Chlorobenzoyl*)*ferrocene*. A thoroughly dried, 1-l., three-necked, round-bottomed flask is equipped with a mechanical stirrer, a funnel for the addition of air-sensitive solids (Note 1), and a two-necked adapter holding a thermometer and a gas-inlet tube. Throughout the ensuing reaction the system is maintained under positive pressure of dry nitrogen. The flask is charged with 18.6 g. (0.100 mole) of ferrocene (Note 2), 17.5 g. (0.100 mole) of 2-chlorobenzoyl chloride (Note 3), and 200 ml. of dichloromethane, and the addition funnel contains 14.0 g. (0.105 mole) of anhydrous aluminum chloride. Stirring is begun, and the flask is immersed in an ice bath. When the solution has been chilled thoroughly, the aluminum chloride is added in small portions at such a rate that the reaction mixture remains below 5°. The appearance of a deep blue color indicates that the reaction is occurring. This addition requires about 20 minutes, and after its completion stirring is continued for 30 minutes with ice cooling and for 2 hours at room temperature.

The reaction mixture is cooled again in ice, 200 ml. of water is added cautiously, and the resulting two-phase mixture is stirred vigorously for 30 minutes. After transferring the mixture to a separatory funnel, the layers are separated, and the aqueous layer is extracted with two 50-ml. portions of dichloromethane. The combined dichloromethane solutions are washed once with 50 ml. of water, twice with 50-ml. portions of 10% aqueous sodium hydroxide, and dried over magnesium sulfate, filtered and evaporated to dryness at reduced pressure, yielding 30.4–

30.9 g. (94–96%) of (2-chlorobenzoyl)ferrocene as a viscous, red liquid, which gradually solidifies (Note 4).

B. *Ferrocenecarboxylic acid*. A dry, 500-ml., three-necked, round-bottomed flask equipped with a mechanical stirrer and a reflux condenser topped with a nitrogen-inlet tube is charged with 250 ml. of 1,2-dimethoxyethane (Note 5) and 46.0 g. (0.411 mole) of potassium *tert*-butoxide (Note 6). A nitrogen atmosphere is established in the system, and 2.2 ml. (0.12 mole) of water (Note 6) is added with stirring, producing a slurry, to which the crude (2-chlorobenzoyl)ferrocene is added. The red solution is stirred and refluxed under nitrogen. As the reaction proceeds the color fades to tan, and after 1 hour at reflux the reaction mixture is cooled and poured into 1 l. of water. The resulting solution is washed with three 150-ml. portions of diethyl ether, which are combined and back-extracted with two 50-ml. portions of 10% aqueous sodium hydroxide. The aqueous phases are then combined and acidified with concentrated hydrochloric acid. The precipitate is collected by filtration and air dried, yielding 17.0–19.2 g. (74–83% from ferrocene) of ferrocenecarboxylic acid as an air-stable yellow powder, m.p. 214–216° (dec., (Note 7)).

2. Notes

1. If such a funnel is not available, an Erlenmeyer flask connected to the reaction flask by a length of thin-walled rubber tubing (Gooch tubing) may be substituted. In this case, the reaction mixture must not be stirred so vigorously that liquid is splashed up into the neck of the flask, which would cause aluminum chloride to cake there and prevent it from falling into the flask.
2. Ferrocene was purchased from Strem Chemicals Incorporated, Danvers, Massachusetts.
3. 2-Chlorobenzoyl chloride was purchased from Aldrich Chemical Company, Inc., and used as received with a stated purity of 95%.
4. The crude material contains approximately 5% of unreacted ferrocene. Recrystallization from heptane affords pure (2-chlorobenzoyl)ferrocene as scarlet needles, m.p. 99–100°; however, the crude material may be used without purification for Part B.
5. 1,2-Dimethoxyethane was distilled from calcium hydride immediately prior to use.
6. Potassium *tert*-butoxide was purchased from Columbia Organic Chemicals Company, Columbia, South Carolina. The molar ratio of potassium *tert*-butoxide to water is critical, and the amounts specified represent optimum quantities for cleavage of 0. 10 mole of ketone.[2,3]
7. The decomposition point was obtained in a sealed capillary tube and not corrected. As the solid is heated, it first changes from yellow to brownish red and then decomposes to a dark red liquid. The decomposition temperature of this compound has been reported to be 208.5°,[4] 224–225°,[5] and 225–230°.[6]
The crude product is suitable for most purposes. It may be recrystallized from toluene (1 g. in 15–20 ml. of solvent, 80% recovery in the first crop), giving material melting at 220–222° (dec.).

3. Discussion

The carboxylic acids of organometallic systems, important synthetic intermediates, have been prepared by many different synthetic methods. Ferrocenecarboxylic acid has been studied the

most extensively,[7] and the best laboratory syntheses previously reported involve hydrolyses of cyanoferrocene[8] or *S*-methylferrocenethiocarbonate.[9]

The present synthesis[10] consists of two simple steps, uses readily available and inexpensive starting materials, and produces pure material in high overall yield. It is based on two observations: that nonenolizable ketones may be cleaved to carboxylic acids by potassium *tert*-butoxide–water,[2] and that aryl 2-chlorophenyl ketones may be cleaved with loss of the 2-chlorophenyl group, giving only one of the two possible acids.[11] Other compounds prepared by this route include carboxycyclopentadienyltricarbonylmanganese (79%)[10] and several substituted benzoic acids:[11] biphenyl-4-carboxylic acid (64%), 3,4-dimethylbenzoic acid (57%), 2,4,6-trimethylbenzoic acid (59%), 3,4-dimethoxybenzoic acid (73%), and 2,4-dimethoxybenzoic acid (60%). In cases where the cleavage reaction proceeds in low yield, substitution of 2,6-dichlorobenzoyl chloride for 2-chlorobenzoyl chloride may be helpful. With thiophene, for example, the yield of carboxylic acid was increased from 10% to 72% by this modification.[11]

References and Notes

1. Department of Chemistry, Southern Methodist University, Dallas, Texas 75275. [Present address: Abilene Christian University, Abilene, Texas 79601.] This work was supported by the Robert A. Welch Foundation.
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Ferrocene

(2-Chlorobenzoyl)ferrocene

Ferrocenecarboxylic acid

Ferrocene, carboxy-

S-methylferrocenethiocarbonate

hydrochloric acid (7647-01-0)

diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

nitrogen (7727-37-9)

aluminum chloride (3495-54-3)

toluene (108-88-3)

dichloromethane (75-09-2)

Thiophene (110-02-1)

magnesium sulfate (7487-88-9)

heptane (142-82-5)

2,4,6-trimethylbenzoic acid (480-63-7)

calcium hydride (7789-78-8)

1,2-dimethoxyethane (110-71-4)

2-chlorobenzoyl chloride (609-65-4)

carboxycyclopentadienyltricarbonylmanganese

biphenyl-4-carboxylic acid (92-92-2)

3,4-dimethylbenzoic acid (619-04-5)

3,4-dimethoxybenzoic acid (93-07-2)

2,4-dimethoxybenzoic acid (91-52-1)

2,6-dichlorobenzoyl chloride (4659-45-4)

potassium tert-butoxide (865-47-4)

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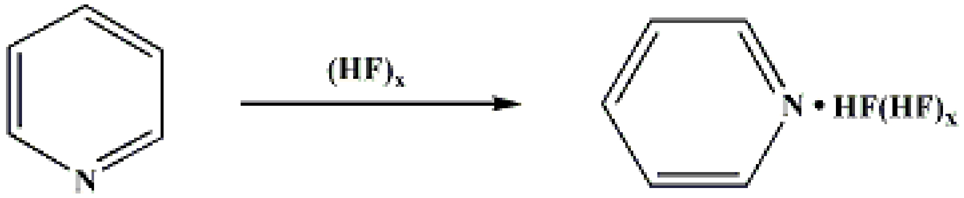
Organic Syntheses, CV 6, 628

FLUORINATIONS WITH PYRIDINIUM POLYHYDROGEN FLUORIDE REAGENT: 1-FLUOROADAMANTANE

[Tricyclo[3.3.1.1^{3,7}]decane, 1-fluoro-]

A.



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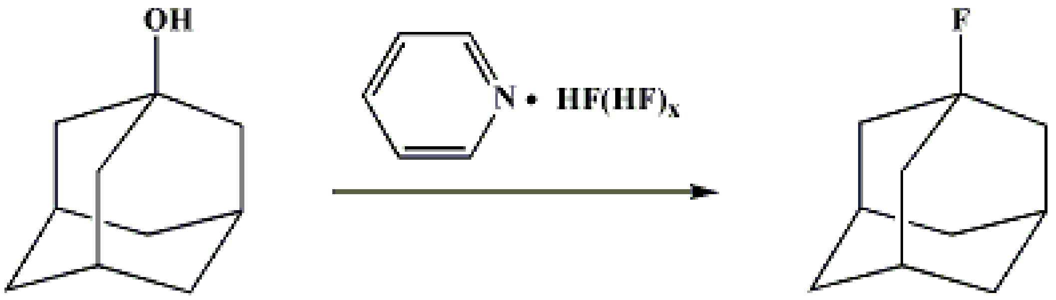

Submitted by George A. Olah[1] and Michael Watkins.
Checked by Paul G. Williard and G. Büchi.

1. Procedure

Caution! Proper precautions must be used when handling anhydrous hydrogen fluoride and pyridinium polyhydrogen fluoride. Hydrogen fluoride is extremely corrosive to human tissue, contact resulting in painful, slow-healing burns. Laboratory work with HF should be conducted only in an efficient hood, with the operator wearing a full-face shield and protective clothing (Note 1).

A. *Pyridinium polyhydrogen fluoride* (**1**). A tared, 250-ml., polyolefin bottle is equipped with a polyolefin gas-inlet and drying tube inserted through holes in the cap and sealed with Teflon tape. The bottle is charged with 37.5 g. (0.475 mole) of pyridine (Note 2) and cooled in an acetone–dry ice bath. After the pyridine has solidified, 87.5 g. (4.37 moles) of anhydrous hydrogen fluoride (Note 3) is condensed from a cylinder into the bottle through the inlet tube. The amount of hydrogen fluoride is determined by weighing the bottle. After the hydrogen fluoride has cooled, the bottle is cautiously swirled with cooling until the solid dissolves (Note 4). The solution can now be safely allowed to warm to room temperature.

B. *1-Fluoroadamantane* (**2**). A 250-ml., polyolefin bottle is equipped with a Teflon-coated magnetic stirring bar and a polyolefin drying tube inserted through a hole in the cap and sealed with Teflon tape. The bottle is charged with 5.0 g. (0.033 mole) of 1-adamantanol (Note 5) and 50 ml. of pyridinium polyhydrogen fluoride (**1**). The solution is allowed to stir for 3 hours at ambient temperature, after which 150 ml. of petroleum ether is added, and stirring is continued for another 15 minutes. The resulting two-phase solution is transferred to a 250-ml., polyolefin separatory funnel, and the bottom layer is discarded (Note 6). The organic layer is washed successively with 50 ml. of water, 50 ml. of a saturated sodium hydrogen carbonate solution and 50 ml. of water, then dried over magnesium sulfate. After the organic layer is filtered, the solvent is removed under reduced pressure (Note 7), yielding 4.5–4.6 g. (88–90%) of adamantane **2** as a white powder, m.p. 225–227° (sublimes in a sealed capillary) (Note 8), which can be purified by vacuum sublimation or by recrystallization from methanol-carbon tetrachloride.

2. Notes

1. The recommended first-aid for a hydrogen fluoride burn is to flood with water, pack with ice, and get medical attention as quickly as possible. Local medical personnel should be alerted and prepared when work with hydrogen fluoride is planned. Directions for proper medical treatment[2] are given in *Org. Synth.*, **Coll. Vol. 5**, 66 (1973).
2. The submitters used A.C.S. certified reagent grade pyridine from Fisher Scientific Company which was distilled from potassium hydroxide prior to use.
3. The submitters obtained anhydrous hydrogen fluoride from Harshaw Chemical Company, and the checkers purchased this reagent from Matheson Gas Products.
4. The dissolution is an extremely exothermic process that can be violent if the bath temperature is not carefully controlled at –78°. A preferred procedure developed by Dr. A. E. Feiring, Central Research and Development Department, Du Pont Experimental Station, involves keeping the pyridine as cold as possible without freezing (*ca.* –40°), then slowly condensing the hydrogen fluoride into the vessel so that the entire mixture remains liquid during the preparation. Stirring is also helpful.
5. This was obtained from Aldrich Chemical Company, Inc., and used without further purification.
6. The inorganic layer can be safely disposed by slow addition to large amounts of ice-cold water.
7. Since 1-fluoroadamantane sublimes easily, the water bath should be controlled at about 32°, and the vacuum evaporation of the solvent limited to as short a time as possible.
8. GC and IR analysis indicate no detectable amount of starting alcohol. ^{1}H NMR of adamantane **2** ($CDCl_3$) yields a series of multiplets centered at δ 1.62, 1.86, and 2.18.

3. Discussion

1-Fluoroadamantane can also be prepared by halogen exchange of the bromide with silver fluoride[3] or zinc fluoride.[4] The procedure described is more convenient and economical than the halogen exchanges, and has found successful application in the preparation of a wide variety of secondary and tertiary fluorides from the corresponding alcohols, with yields generally within the range of 70–90%[5] (Table I).

TABLE I
PREPARATION OF TERTIARY- AND SECONDARY-ALKYL FLUORIDES FROM ALCOHOLS WITH HYDROGEN FLUORIDE–PYRIDINE REAGENT

Alcohol	Temperature	Reaction Time (hours)	Alkyl Fluoride	b.p. (m.p.)	Yield (%)
Isopropyl	50	3.0	Isopropyl	–9 to –7	30
sec-Butyl	20	3.0	*sec*-Butyl	25–26	70
tert-Butyl	0	1.0	*tert*-Butyl	12	50
3-Ethyl-3-pentyl	0	0.5	3-Ethyl-3-fluoropentane	30–33 (60 mm.)	95
3-Methyl-3-heptyl	–70	0.5	3-Fluoro-3-methylheptane	35 (40 mm.)	85
3-Methyl-4-heptyl	0	2.0	4-Fluoro-3-methylheptane		35
Cyclohexyl	20	2.0	Cyclohexyl fluoride	100–102	99
2-Norbornyl	20	1.0	2-Fluoronorbornane	(56–59)	95
2-Adamantyl	20	0.5	2-Fluoroadamantane	(254–255)	98
α-Phenylethyl	20	0.5	1-Fluoro-1-phenylethane	46 (15 mm.)	65

The hydrogen fluoride–pyridine reagent is an effective complement to the dimethylaminosulfur trifluoride (DAST) reagent[6] in the preparation of alkyl fluorides from alcohols. DAST is also useful for the conversion of carbonyl groups to difluoromethylene functions. The hydrogen fluoride–pyridine reagent, however, can also be used for the hydrofluorination of alkenes,[7] alkynes,[7] cyclopropanes,[7] and diazo compounds,[8] the halofluorination of alkenes,[9] the preparation of fluoroformates from carbamates,[10] the preparation of α-fluorocarboxylic acids from α-amino acids,[11] and

as a deprotecting reagent in peptide chemistry.[12] Examples of the hydrofluorination of alkenes with hydrogen fluoride–pyridine are given in Table II.

TABLE II
HYDROFLUORINATION OF ALKENES WITH HYDROGEN FLUORIDE-PYRIDINE REAGENT

Alkene	Reaction Temperature	Product	b.p.(m. p.)	Yield (%)
Propene	20	Isopropyl fluoride	−11 to −9	35
Cyclopropane	20	*n*-Propyl fluoride	−3 to −1	75
2-Butene	0	*sec*-Butyl fluoride	24–25	40
2-Methylpropene	0	*tert*-Butyl fluoride	11–13	60
Cyclopentene	0	Cyclopentyl fluoride	51–52 (200 mm.)	65
Cyclohexene	0	Cyclohexyl fluoride	102–104	80
Cycloheptene	0	Cycloheptyl fluoride	70–71 (200 mm.)	90
Norbornene	0	2-Fluoronorbornane	(56–59)	65
1-Hexyne	0	2,2-Difluorohexane	85–87	70
3-Hexyne	0	3,3-Difluorohexane	84–86	75

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

PYRIDINIUM POLYHYDROGEN FLUORIDE

alcohol (64-17-5)

sodium hydrogen carbonate (144-55-8)

Propene (115-07-1)

Cyclohexene (110-83-8)

hydrogen fluoride (7664-39-3)

pyridine (110-86-1)

potassium hydroxide (1310-58-3)

cyclopropane (75-19-4)

magnesium sulfate (7487-88-9)

Cyclopentene (142-29-0)

Cyclohexyl (3170-58-9)

isopropyl (2025-55-0)

2-Methylpropene (9003-27-4)

1-Hexyne (693-02-7)

silver fluoride (7775-41-9)

α-Phenylethyl (2348-51-8)

Norbornene

Adamantane (281-23-2)

1-Adamantanol (768-95-6)

tert-BUTYL (1605-73-8)

difluoromethylene

Cyclohexyl fluoride (372-46-3)

cycloheptene

2-butene

1-Fluoroadamantane, Tricyclo[3.3.1.1^{3,7}]decane, 1-fluoro- (768-92-3)

methanol-carbon tetrachloride

zinc fluoride (7783-49-5)

dimethylaminosulfur trifluoride (3880-03-3)

3-Ethyl-3-pentyl

3-Ethyl-3-fluoropentane

3-Methyl-3-heptyl

3-Fluoro-3-methylheptane

3-Methyl-4-heptyl

4-Fluoro-3-methylheptane

2-Norbornyl (30967-37-4)

2-Fluoronorbornane

2-Adamantyl (21517-94-2)

2-Fluoroadamantane (16668-83-0)

1-Fluoro-1-phenylethane

Isopropyl fluoride (420-26-8)

Cyclopentyl fluoride (1481-36-3)

Cycloheptyl fluoride

2,2-Difluorohexane

3-Hexyne (928-49-4)

3,3-Difluorohexane

sec-butyl (2348-55-2)

n-Propyl fluoride (460-13-9)

sec-Butyl fluoride

tert-Butyl fluoride

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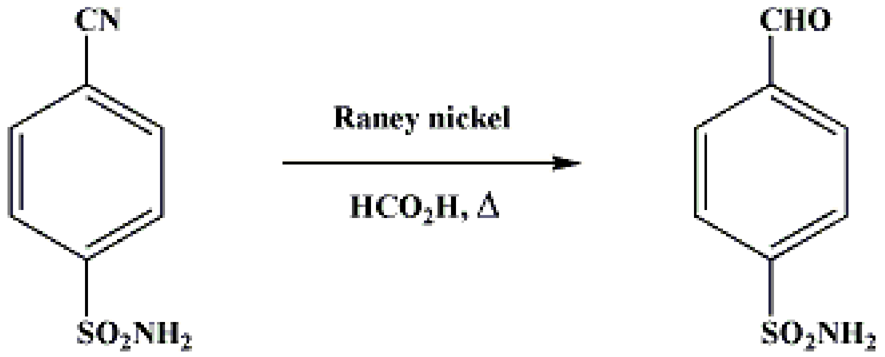
Organic Syntheses, CV 6, 631

ALDEHYDES FROM AROMATIC NITRILES: 4-FORMYLBENZENESULFONAMIDE

[Benzenesulfonamide, 4-formyl-]



Submitted by T. van Es and B. Staskun[1].
Checked by A. Brossi, L. A. Dolan, and A. Laurenzano.

1. Procedure

A 2-l., two-necked, round-bottomed flask fitted with a mechanical stirrer and a reflux condenser is charged with 40.0 g. (0.232 mole) of 4-cyanobenzenesulfonamide (Note 1), 600 ml. of 75% (v/v) formic acid, and 40 g. of Raney nickel alloy (Note 2). The stirred mixture is heated under reflux for 1 hour (Note 3). The mixture is filtered with suction through a Büchner funnel coated with a filter aid (Note 4), and the residue is washed with two 160-ml. portions of 95% ethanol. The combined filtrates are evaporated with a rotary evaporator (Note 5). The solid residue (Note 6) is dissolved in 400 ml. of boiling water and freed from a small amount of insoluble material by decantation through a plug of glass wool placed in a filter funnel. The filtrate is chilled in an ice bath, and the precipitate is collected by filtration with suction, washed with a small amount of cold water, and dried at 50° under vacuum, yielding about 32 g. of crude product, m.p. 112–114°.

The product is dissolved in 800 ml. of hot 95% ethanol, 15.5 g. of activated carbon (Note 7) is added, and the mixture is swirled periodically while it is allowed to cool for 1 hour. The activated carbon is removed by filtration with suction through a bed of filter aid (Note 4), the filter cake is washed with 50 ml. of 95% ethanol, and the combined filtrates are evaporated with a rotary evaporator. The residue is dissolved in 225 ml. of boiling water, and the hot solution is decanted through glass wool placed in a filter funnel. The filtrate is cooled to 0°, the product is collected by filtration with suction, washed with a small amount of cold water, and dried in a vacuum oven at 50°, yielding 25.6–28.0 g. (62.9–68.8%) of 4-formylbenzenesulfonamide, m.p. 117–118° (Note 8).

2. Notes

1. The checkers used 4-cyanobenzenesulfonamide purchased from Aldrich Chemical Company, Inc., m.p. 167–169°. The submitters prepared this material by diazotization of the corresponding amine,[2] followed by cyanation.[3] The product was crystallized from water, m.p. 152–154°.
2. The checkers used material purchased from Harshaw Chemical Company. The submitters used nickel–aluminum alloy (50% Ni, 50% Al) supplied by British Drug Houses Ltd.
3. The reaction proceeds with some frothing; this is more appreciable and vigorous in mixtures containing a higher proportion of water, as when the reduction is conducted in 50% formic acid.[4]
4. Hyflo Supercel, a filter aid purchased from Johns-Manville Corporation, was used by the checkers.
5. This procedure is to be avoided with steam-volatile aldehydes (e.g., 4-chlorobenzaldehyde), in which case the reduction product is isolated by solvent extraction.[4]
6. The product is contaminated with nickel salts; its IR spectrum showed little, if any, unchanged nitrile.
7. Norite A, purchased from Matheson, Coleman and Bell, was used.
8. The melting point of 4-formylbenzenesulfonamide has been reported as 118–120°,[4,5] 122°,[6] and 123–124°.[7]

3. Discussion

4-Formylbenzenesulfonamide has been prepared by chromic acid oxidation of *p*-toluenesulfonamide,[5] the Sommelet reaction on 4-chloromethylbenzenesulfonamide,[8] and by the Stephen reduction of 4-cyanobenzenesulfonamide.[5] The present method provides a general procedure for the synthesis of substituted aromatic aldehydes as illustrated in Table I.

TABLE I

ALDEHYDES FROM AROMATIC NITRILES[4]

Nitrile	Aldehyde	Yield, %[a]
C_6H_5CN	C_6H_5CHO	97
4-ClC_6H_4CN	4-ClC_6H_4CHO	100
4-$CH_3OC_6H_4CN$	4-$CH_3OC_6H_4CHO$	93
2-$C_{10}H_7CN$	2-$C_{10}H_7CHO$	95

[a] Determined as the 2,4-dinitrophenylhydrazone derivative.

Some studies seeking preferred conditions for this reaction have been made. Optimum

yields are obtained when the amount of water present is appreciable, and it was noted that the rate of hydrogen evolution increases with increasing water content. A 75% formic acid system appears to be generally preferred. Under the reaction conditions examined by the submitters, olefins, ketones, esters, amides, and acids are inert, but nitro compounds are reduced to the formamide derivative.

A related method for the synthesis of aldehydes from nitriles has also been studied.[9] This method, which has been found to be extremely effective for the reduction of hindered nitriles to aldehydes, uses moist, preformed Raney nickel catalyst in formic acid. Compounds synthesized by this method are illustrated in Table II.

TABLE II
ALDEHYDES FROM NITRILES WITH RANEY NICKEL CATALYST IN FORMIC ACID[9]

Nitrile	Aldehyde	Yield, %[a]
C_6H_5CN	C_6H_5CHO	72
2-$CH_3C_6H_4CN$	2-$CH_3C_6H_4CHO$	65–75
2-ClC_6H_4CN	2-ClC_6H_4CHO	70–83
2-$CH_3OC_6H_4CN$	2-$CH_3OC_6H_4CHO$	80
2,6-$(CH_3O)_2C_6H_3CN$	2,6-$(CH_3O)_2C_6H_3CHO$	60–65
$C_6H_5CH{=}CHCN$	$C_6H_5CH{=}CHCHO$	64

[a] Determined as the 2,4-dinitrophenylhydrazone derivative.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Raney nickel alloy

ethanol (64-17-5)

hydrogen (1333-74-0)

formic acid (64-18-6)

aluminum (7429-90-5)

nickel, Raney nickel (7440-02-0)

carbon, activated carbon (7782-42-5)

chromic acid (7738-94-5)

4-Formylbenzenesulfonamide, Benzenesulfonamide, 4-formyl- (3240-35-5)

4-cyanobenzenesulfonamide

4-chlorobenzaldehyde (104-88-1)

4-chloromethylbenzenesulfonamide

p-toluenesulfonamide (70-55-3)

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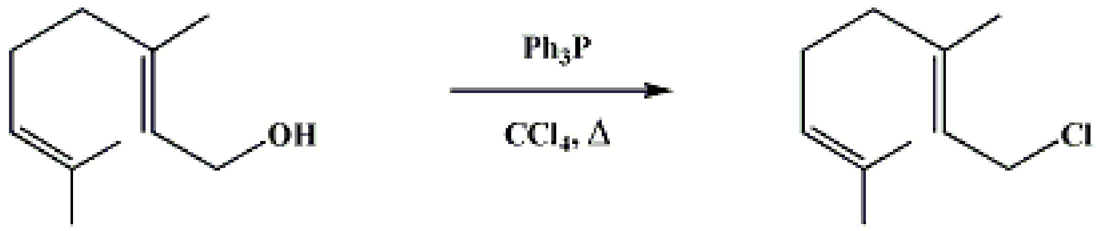
Organic Syntheses, *CV 6*, 634

GERANYL CHLORIDE

[2,6-Octadiene, 1-chloro-3,7-dimethyl-, *(E)*-]



Submitted by Jose G. Calzada and John Hooz[1].
Checked by K.-K. Chan, A. Specian, and A. Brossi.

1. Procedure

A dry, 300-ml., three-necked flask is equipped with a magnetic stirring bar and reflux condenser (to which is attached a Drierite-filled drying tube) and charged with 90 ml. of carbon tetrachloride (Note 1) and 15.42 g. of geraniol (0.1001 mole) (Note 2). To this solution is added 34.09 g. (0.1301 mole) of triphenylphosphine (Note 3), and the stirred reaction mixture is heated under reflux for 1 hour. This mixture is allowed to cool to room temperature; dry pentane is added (100 ml.), and stirring is continued for an additional 5 minutes.

The triphenylphosphine oxide precipitate is filtered and washed with 50 ml. of pentane. The solvent is removed from the combined filtrate with a rotary evaporator under water aspirator pressure at room temperature. Distillation of the residue through a 2-cm. Vigreux column attached to a short-path distillation apparatus (Note 4) provides 13.0–14.0 g. (75–81%) of geranyl chloride, b.p. 47–49° (0.4 mm.), n_D^{23} = 1.4794 (Note 5).

2. Notes

1. Carbon tetrachloride was dried over magnesium sulfate and distilled from phosphorus pentoxide through a 25-cm. Vigreux column. Lower yields were obtained when either the glassware or reagents were not dried.
2. Geraniol was purchased from Koch-Light Laboratories (>98% pure), dried over potassium carbonate and distilled through an 8-cm. Vigreux column, b.p. 108–109° (8 mm.). The checkers used geraniol purchased from Aldrich Chemical Co., Inc., and distilled it prior to use.
3. Triphenylphosphine, m.p. 80–81°, was obtained from Eastman Organic Chemicals and kept in a drying pistol held at approximately 65° (1 mm.) for 18 hours prior to use. When only 10–20% excess triphenylphosphine was employed the yield of geranyl chloride was approximately 75%, but the small amount of

unreacted geraniol which remained rendered product isolation more difficult.

4. A "Bantam-ware" distilling head and condenser assembly from Kontes Glass Co. (K-287100) was used. Foaming may occur due to incomplete removal of solvent. This can be avoided by cooling the distillation flask to approximately –50° and gradually lowering the pressure to 10 mm. The pot temperature is then allowed to increase gradually to room temperature, and the distillation then proceeds without difficulty.

5. The pure geranyl chloride has characteristic IR absorption (liquid film) at 845, 1255, and 1665 $cm.^{-1}$. The use of these absorptions to assay mixtures of geranyl and linalyl chloride has been discussed in detail.[2] The ^1H NMR spectrum (100 MHz., CCl_4) shows absorption at δ 1.61 and 1.67 [2s, 6H, C=C$(CH_3)_2$], 1.71 [d, J = 1.4 Hz., 3H, C=C(CH_3CH_2)], 2.05 (m, 4H, 2CH_2), 3.98 (d, J = 8 Hz., 2H, CH_2Cl), 5.02 [m, 1H, CH=C$(CH_3)_2$], and 5.39 (t of partially resolved m, 1H, C=C$H$$CH_2$Cl).

3. Discussion

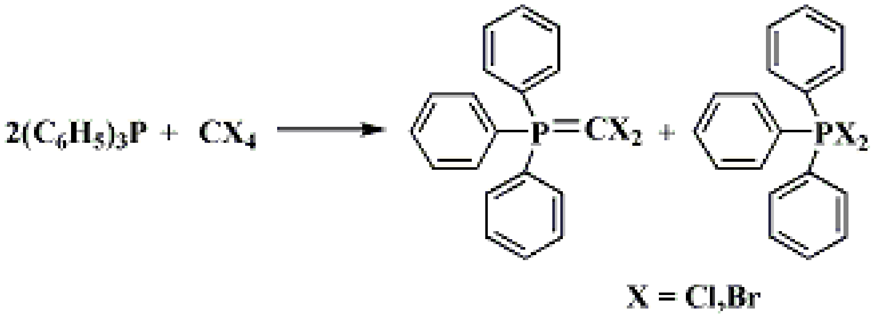
Geranyl chloride has been prepared by allylic rearrangement of linalool using hydrogen chloride in toluene solution at 100° or phosphorus trichloride in the presence of potassium carbonate at 0°.[3] The conversion of geraniol to geranyl chloride has been reported using hydrogen chloride in toluene,[3] phosphorus trichloride or phosphorus pentachloride in petroleum ether,[4] and thionyl chloride and pyridine.[5,6,7] These methods give mixtures[2,8] of geranyl and linalyl chloride, which are difficult to separate; tedious fractionation[6] is required to isolate the geranyl chloride. Procedures which give a pure product involve treatment of geraniol (a) in ether–hexamethylphosphoric triamide (HMPA) with methyllithium, followed by *p*-toluenesulfonyl chloride and lithium chloride in ether–HMPA;[9] (b) in 2,4,6-collidine with lithium chloride in *N*,*N*-dimethylformamide, followed by methanesulfonyl chloride;[10] and (c) in pentane with methanesulfonyl chloride at –5°, followed by the addition of pyridine.[8]

The present procedure is representative of a fairly general method of converting alcohols to chlorides using carbon tetrachloride and a tertiary phosphine. The reaction occurs under mild, essentially neutral conditions and, as illustrated by the present synthesis, may be employed to convert allylic alcohols to the corresponding halide without allylic rearrangement.

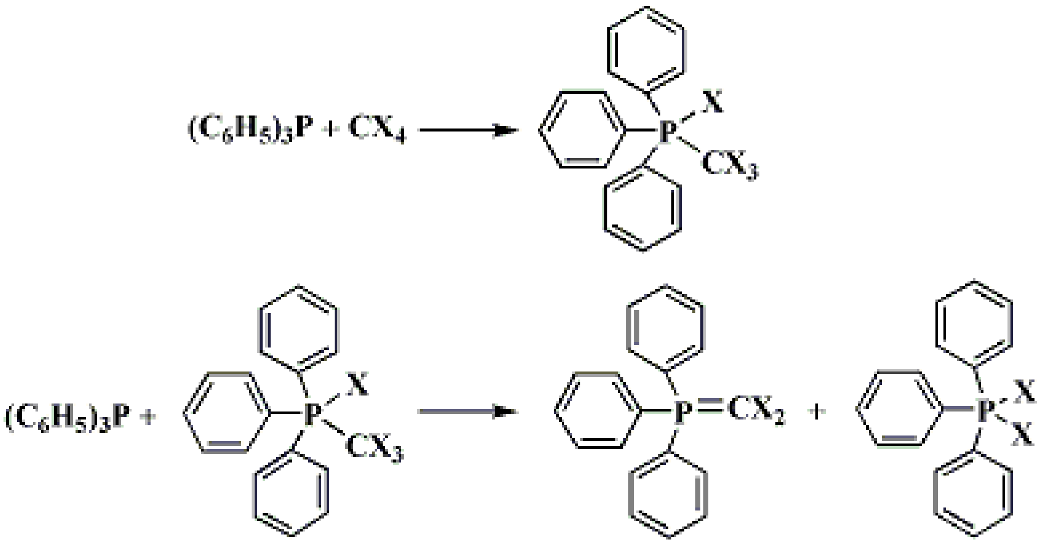
Carbon tetrachloride serves as both solvent and halogen source. Several trivalent phosphorus reagents may be employed, including triphenylphosphine,[11,12] tri-*n*-octylphosphine,[12] tri-*n*-butylphosphine,[13] and trisdimethylaminophosphine.[13] The latter "more nucleophilic" phosphines react more rapidly and under milder conditions than triphenylphosphine. When triphenylphosphine is employed, the by-product,

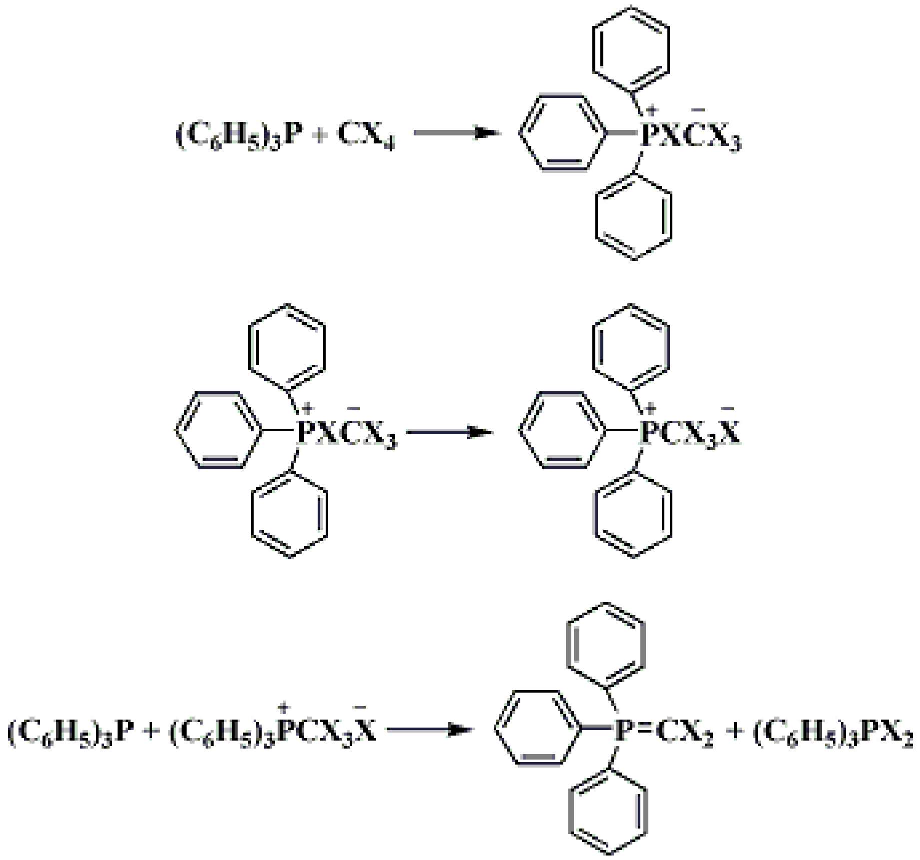
triphenylphosphine oxide, usually precipitates completely and is easily removed by filtration. After evaporation of the solvent, the product is isolated in high purity by distillation. On occasion, difficulties may be encountered in separating the alkyl halide from the accompanying oxide. The presence of residual soluble organophosphine oxide may pose a serious problem when attempting to isolate sensitive (*e.g.*, allylic or optically active) halides and can lead to loss of product, racemization, etc. This difficulty is usually resolved, as illustrated in the present synthesis, by adding a diluent such as pentane to ensure precipitation. Although precise conditions will undoubtedly depend on the specific substrate at hand, it is usually desirable to employ a modest excess of the organophosphine. This is especially helpful for the preparation of sensitive halides since, by ensuring complete consumption of alcohol, it simplifies the isolation procedure (Note 3) by avoiding the possible necessity of a careful fractionation step.

Triphenylphosphine reacts with carbon tetrachloride[14] or carbon tetrabromide[15] *in the absence of alcohols*, forming the corresponding triphenylphosphine dihalomethylene ylide and triphenylphosphine dihalide.



The mechanism has been viewed as involving either the formation of a pentacovalent phosphorus intermediate,[14,15] or alternatively, by initial nucleophilic attack on halogen, forming an intermediate phosphonium species.[16] These mixtures react with carbonyl compounds, providing a useful route to 1,1-dihaloalkenes.[14,15,17]





The success of the present method depends critically on the *initial* presence of an alcohol to trap the intermediate phosphonium species.[12] If the alcohol is added last, the R_3P-CX_4 reaction described above (an exothermic process for the more nucleophilic phosphines) may go to completion, in which case little or no alkyl halide is formed.[13] Since the reaction displays several characteristics of an S_N2 process, it is thought to proceed by the pathway illustrated:

$$R_3P + CX_4 \longrightarrow R_3\overset{+}{P}X\overset{-}{C}X_3$$

$$R_3PXCX_3 + R'OH \longrightarrow R_3\overset{+}{P}X\overset{-}{O}R' + HCX_3$$

$$R_3\overset{+}{P}X\overset{-}{O}R' \longrightarrow R_3\overset{+}{P}OR'\overset{-}{X}$$

$$R_3\overset{+}{P}OR'\overset{-}{X} \longrightarrow R'X + R_3PO$$

Yields of chlorides are good to excellent for primary and secondary alcohols, but a competing olefin-forming elimination process renders the method of limited value for preparing tertiary chlorides.[12] An adaptation of the procedure using carbon tetrabromide allows the synthesis of alkyl bromides. Some examples are the preparation of *n*-pentyl bromide (97%) and benzyl bromide (96%).[12] Farnesyl bromide has been prepared in 90% yield from farnesol.[22]

The advantages of the carbon tetrahalide–organophosphine–alcohol preparation of

halides are simplicity of experimental procedure, good yields, relatively mild, essentially neutral reaction conditions, and absence of allylic rearrangements. The reaction proceeds with inversion of configuration and is a useful simple device for converting optically active alcohols to chiral halides in high optical purity.[12,23]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 424
- Org. Syn. Coll. Vol. 7, 245
- Org. Syn. Coll. Vol. 8, 226
- Org. Syn. Coll. Vol. 8, 616

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

geranyl and linalyl chloride

organophosphine oxide

triphenylphosphine dihalomethylene ylide

triphenylphosphine dihalide

HMPA

potassium carbonate (584-08-7)

hydrogen chloride (7647-01-0)

ether (60-29-7)

phosphorus pentachloride (10026-13-8)

thionyl chloride (7719-09-7)

ALLYLIC ALCOHOLS (107-18-6)

carbon tetrachloride (56-23-5)

pyridine (110-86-1)

toluene (108-88-3)

phosphorus trichloride (7719-12-2)

Methyl iodide (74-88-4)

Pentane (109-66-0)

carbon tetrabromide (558-13-4)

magnesium sulfate (7487-88-9)

benzyl bromide (100-39-0)

N,N-dimethylformamide (68-12-2)

2,4,6-collidine (108-75-8)

phosphine (7723-14-0)

geraniol (106-24-1)

Methyllithium (917-54-4)

Lithium chloride (7447-41-8)

Methanesulfonyl chloride (124-63-0)

triphenylphosphine (603-35-0)

triphenylphosphine oxide (791-28-6)

trisdimethylaminophosphine (1608-26-0)

hexamethylphosphoric triamide (680-31-9)

tri-n-butylphosphine (998-40-3)

p-Toluenesulfonyl chloride (98-59-9)

farnesol

Linalool (78-70-6)

Geranyl chloride, 2,6-Octadiene, 1-chloro-3,7-dimethyl-, (E)- (5389-87-7)

Farnesyl bromide

n-pentyl bromide (110-53-2)

phosphorus pentoxide (1314-56-3)

tri-n-octylphosphine (4731-53-7)

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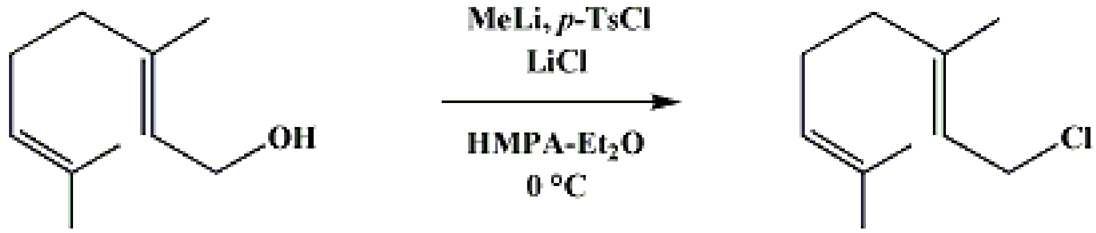
Organic Syntheses, CV 6, 638

ALLYLIC CHLORIDES FROM ALLYLIC ALCOHOLS: GERANYL CHLORIDE

[2,6-Octadiene, 1-chloro-3,7-dimethyl-, (*E*)-]



Submitted by Gilbert Stork[1], Paul A. Grieco[2], and Michael Gregson.
Checked by P. A. Aristoff and R. E. Ireland.

1. Procedure

Caution! Hexamethylphosphoric triamide (HMPA) vapors have been reported to cause cancer in rats.[3] All operations with hexamethylphosphoric triamide should be performed in a good hood, and care should be taken to keep the liquid off the skin.

A dry, 1-l., three-necked, round-bottomed flask is equipped with an overhead mechanical stirrer, a 125-ml. pressure equalizing dropping funnel fitted with a rubber septum, and a nitrogen inlet tube. The system is flushed with nitrogen, and 15.4 g. (0.100 mole) of geraniol (Note 1), 35 ml. of dry hexamethylphosphoric triamide (Note 2), 100 ml. of anhydrous diethyl ether (Note 3), and 50 mg. of triphenylmethane (Note 4) are placed in the flask. The stirred solution is cooled to 0° with an ice bath, and 63 ml. (0.1 mole) of 1.6 *M* methyllithium in ether (Note 5) is injected into the addition funnel. The methyllithium solution is added dropwise over a period of 30 minutes. After the addition is complete, the funnel is rinsed by injecting 5 ml. of dry ether.

A solution of 20.0 g. (0.105 mole) (Note 6) of *p*-toluenesulfonyl chloride in 100 ml. of anhydrous ether is injected into the addition funnel and added over a period of 30 minutes to the stirred, red, 0° reaction mixture. The red color immediately disappears upon addition. After addition is complete, 4.2 g. (0.0990 mole) of anhydrous lithium chloride (Note 7) is added. The reaction mixture is warmed to room temperature and stirred overnight (18–20 hours), during which time lithium *p*-toluenesulfonate precipitates.

After a total of 20–22 hours, 100 ml. of ether is added, followed by 100 ml. of water. The layers are separated, and the organic phase is washed four times with 100-ml. portions of water, and finally with 100 ml. of saturated sodium chloride. After drying the organic phase over anhydrous magnesium sulfate, the solvent is removed on a

rotary evaporator. The crude product is transferred to a 50-ml. flask and distilled through a 20-cm. Vigreux column, yielding 14.1–14.6 g. (82–85%) of geranyl chloride as a colorless liquid, b.p. 78–79° (3.0 mm.) (Note 8) and (Note 9).

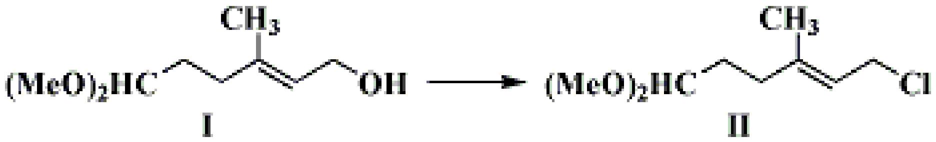
2. Notes

1. Geraniol (+99%) can be purchased from the Aldrich Chemical Company, Inc.
2. Hexamethylphosphoric triamide was purchased from the Fisher Scientific Company and the Aldrich Chemical Company, Inc., and distilled from calcium hydride prior to use.
3. Anhydrous ether, available from J. T. Baker Chemical Company, can be used without further drying.
4. Triphenylmethane is available from Eastman Organic Chemicals. Although not necessary, it was used as an indicator to check the molarity of the methyllithium used.
5. Methyllithium (prepared from methyl chloride), available from Foote Mineral Company, can be used without further purification. Attention should be drawn to the following: methyllithium purchased from Alfa Inorganics is prepared from methyl bromide and, thus, produces a mixture of geranyl bromide and chloride.
6. *p*-Toluenesulfonyl chloride available from either the Aldrich Chemical Company, Inc., or Matheson, Coleman and Bell, Inc., was used without further purification.
7. Available from Alfa Inorganics. If necessary, finely powdered lithium chloride can be dried by heating under vacuum (0.1 mm.) at 100° for several hours.
8. Our sample of geranyl chloride was identical (IR, ^{1}H NMR, and mass spectrum) to a sample prepared by an alternate route (Professor John Hooz, Department of Chemistry, University of Alberta).
9. The IR spectrum (neat) shows major absorptions at 2970, 2920, 2855, 1660, 1450, 1375, 1380, 1255, 835, and 660 cm.$^{-1}$ The ^{1}H NMR spectrum (CCl_4) has a four-line multiplet at δ 1.55–1.85, characteristic of the olefinic methyl protons, two peaks at δ 2.0–2.2, due to the four allylic methylene protons, a d at δ 4.02 (J = 7.0 Hz.), due to the allylic methylene protons adjacent to the chlorine, a very broad t at δ 5.09, and a broad t at δ 5.45. (J = 7.0 Hz.), both due to the vinyl protons.

3. Discussion

The reaction described here illustrates a general procedure for the preparation of allylic chlorides from allylic alcohols without rearrangement and under conditions allowing the retention of sensitive groups.[4] For example, the sensitive acetal alcohol I with geraniol geometry was similarly treated with ether-hexamethylphosphoric triamide, with methyllithium in ether, and then with *p*-toluenesulfonyl chloride and

lithium chloride. Workup afforded the corresponding chloride II in 80% yield with no detectable rearrangement. The method was equally successful with the *cis*-isomer of I.



In addition, 85–90% yields of neryl chloride can be obtained from nerol, the geometrical isomer of geraniol. A modification[5] of the above method has appeared which employs methanesulfonyl chloride and a mixture of lithium chloride, *N,N*-dimethylformamide, and 2,4,6-collidine at 0°; however, its applicability to compounds possessing sensitive groups was not demonstrated.

Initial attempts at preparing γ,γ-disubstituted allyl chlorides employing thionyl chloride in the presence of tri-*n*-butylamine[6] led to appreciable amounts of rearranged (tertiary) halides.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 634
- Org. Syn. Coll. Vol. 8, 190

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

geranyl bromide and chloride

ether, diethyl ether (60-29-7)

thionyl chloride (7719-09-7)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

methyl chloride (74-87-3)

methyl bromide (74-83-9)

Triphenylmethane (519-73-3)

magnesium sulfate (7487-88-9)

N,N-dimethylformamide (68-12-2)

2,4,6-collidine (108-75-8)

geraniol (106-24-1)

Methyllithium (917-54-4)

Lithium chloride (7447-41-8)

calcium hydride (7789-78-8)

Methanesulfonyl chloride (124-63-0)

tri-n-butylamine (102-82-9)

hexamethylphosphoric triamide (680-31-9)

p-Toluenesulfonyl chloride (98-59-9)

Geranyl chloride, 2,6-Octadiene, 1-chloro-3,7-dimethyl-, (E)- (5389-87-7)

acetal alcohol

neryl chloride

nerol

lithium p-toluenesulfonate

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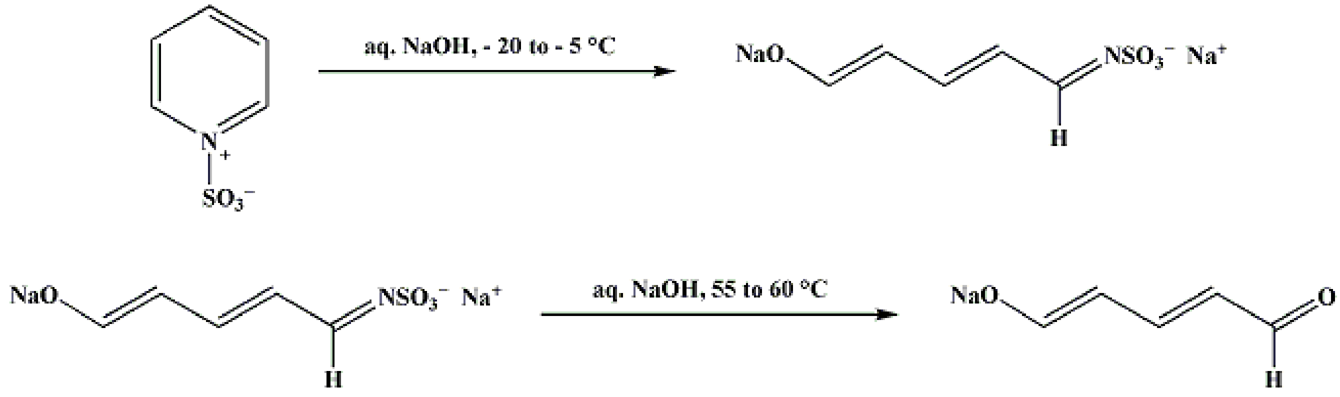
Organic Syntheses, CV 6, 640

GLUTACONALDEHYDE SODIUM SALT FROM HYDROLYSIS OF PYRIDINIUM-1-SULFONATE

[2-Pentenedial, ion (1−), sodium]



Submitted by Jan Becher[1]
Checked by J. P. O'Brien, S. Teitel, and G. Saucy.

1. Procedure

A 500-ml., three-necked, round-bottomed flask fitted with a mechanical stirrer and a thermometer is charged with 42 g. (1.1. moles) of sodium hydroxide dissolved in 168 ml. of water. The contents of the flask are cooled to −20° and stirred vigorously as 48 g. (0.30 mole) of pyridinium-1-sulfonate (Note 1), which has been previously chilled to −20°, is added in one portion. The mixture is stirred for 20 minutes while the temperature is kept below −5° (Note 2). The cooling bath is removed, and the stirred mixture is warmed gradually to 20° over 20 minutes. The temperature of the dark orange mixture is then raised to 55–60°, but after 1 hour lowered again to −5°. The brown crystals that separate are filtered by suction, pressed into a compact filter cake, and washed with three 100-ml. portions of acetone (Note 3), yielding 46–52 g. of crude product after drying on filter paper overnight or at 50° (1 mm.) for 1 hour (Note 4).

If further purification is desired, the crude product is added to 1 l. of methanol in a 2-l., three-necked, round-bottomed flask equipped with a reflux condenser and a mechanical stirrer. The mixture is stirred and heated under reflux for 30 minutes. A 10-g. portion of activated carbon is added, and after 5 minutes the hot mixture is filtered. The light yellow-red filtrate is concentrated to a volume of 50 ml. under reduced pressure and cooled to 0°. The resulting orange crystals are filtered, washed with two 25-ml. portions of acetone, and dried for 1 hour at 50° (1 mm.), affording 24–27 g. (50–58%) of glutaconaldehyde sodium salt dihydrate (Note 5) and (Note 6).

2. Notes

1. Pyridinium-1-sulfonate was prepared according to the procedure of Sisler and Audrieth.[2] The submitter reports that this procedure may be conveniently carried out at 5 times the specified scale. The reagent should be dry and used soon after its preparation. The checkers found that a technical grade of pyridinium-1-sulfonate (sulfur trioxide pyridine complex) purchased from Aldrich Chemical Company, Inc., gave substantially lower yields of product.
2. The initial exothermic reaction that occurs at this point produces the intermediate glutaconaldehyde iminesulfonate disodium salt shown in the scheme. It separates as a yellow, unstable precipitate that may be isolated by filtering, washing with ice-cold isopropyl alcohol, and drying. The yield of the disodium salt is 64 g. (96%).
3. The acetone washes serve to remove colored by-products.
4. The crude product is relatively stable and sufficiently pure for most purposes.
5. The submitter advises that the product be dried at room temperature for 17 hours prior to analysis. An analysis including a Karl Fischer titration for water content was reported by the checkers. Analysis calculated for $C_5H_5O_2Na\cdot(H_2O)_2$: C, 38.46; H, 5.82; H_2O, 23.08. Found: C, 38.67; H, 5.91; H_2O, 23.40. The m.p. of the product is higher than 350° and its spectral characteristics are as follows: IR (KBr) cm.$^{-1}$: 3320 (H_2O), 1723, 1715 (C=O), 1530 (C-O); ^1H NMR (DMSO-d_6), δ (multiplicity, coupling constant J in Hz., number of protons, assignment): 5.07 (d of d, J = 9 and 13, 2H, H_2 and H_4), 7.03 (t, J = 13, 1H, H_3), 8.58 (d, J = 9, 2H, H_1 and H_5); UV (aqueous 0.1 M sodium hydroxide) nm. max. (log ε): 363 (4.75).

6. The water of hydration that accompanies the glutaconaldehyde sodium salt described in this procedure may interfere with applications requiring anhydrous conditions. Consequently the submitter has provided the following alternative procedure for preparing the anhydrous potassium salt. Pyridinium-1-sulfonate (108 g., 0.679 mole) is added to a solution of 155 g. (3.88 moles) of potassium hydroxide in 378 ml. of water in a 1-l. flask; the solution is stirred and cooled to –20°. After 1 hour, the temperature is slowly raised to 20° over 4 hours. The mixture is heated at 30–40° for 30 minutes and cooled to 5°. The crude product that precipitates is filtered, washed with two 100-ml. portions of acetone, and dried in the air, giving 120 g. of yellow-brown crystals. This material is heated at reflux in 2.5 l. of methanol, 5 g. of activated carbon is added, the carbon is filtered, and the filtrate is concentrated under reduced pressure to a volume of 100 ml. The pale yellow crystals of glutaconaldehyde potassium salt are collected, washed with acetone, and dried, yielding 53–57 g. (57–62%). Analysis of the potassium salt indicates the empirical formula $C_5H_5O_2K$, and the salt melts above 350°. The ^{1}H NMR spectrum is identical to that of the sodium salt, and the UV spectrum in aqueous 0.1 *M* potassium hydroxide solution exhibits a maximum at 362 nm. (log ε, 4.84). The sodium and potassium salts of glutaconaldehyde are soluble only in polar solvents such as water, dimethyl sulfoxide, *N,N*-dimethylformamide, pyridine, and methanol. However, the stable tetrabutylammonium salt is soluble in relatively nonpolar solvents such as chloroform and ethyl acetate. It may be prepared from the potassium salt in the following manner. A 1-l. Erlenmeyer flask equipped with a magnetic stirring bar is charged with a solution of 13.6 g. (0.100 mole) of crude glutaconaldehyde potassium salt in 200 ml. of water and a solution of 33.9 g. (0.100 mole) of tetrabutylammonium hydrogen sulfate in 200 ml. of ice-cold water, the pH of which was adjusted to 10 by adding aqueous 2 *M* sodium hydroxide. The resulting mixture is stirred for 5 minutes in an ice bath and extracted with three 400-ml. portions of dichloromethane, previously dried by filtration through anhydrous potassium carbonate. The combined dichloromethane extracts are dried over 20 g. of anhydrous potassium carbonate and evaporated under reduced pressure. A 100-ml. portion of toluene is added, and the mixture is again evaporated under reduced pressure, removing residual water. The yield of dry, nearly colorless crystals of glutaconaldehyde tetrabutylammonium salt monohydrate is 23–25.1 g. (64–70%), m.p. 105–108°. Analysis corresponds to the empirical formula $C_{21}H_{41}NO_2 \cdot H_2O$, and the salt may be recrystallized from ethyl acetate.

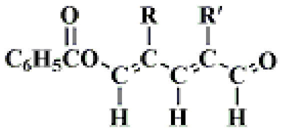
3. Discussion

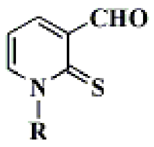
The sodium salt of glutaconaldehyde, first described by Baumgarten[3] in 1924, has been mentioned several times in the literature subsequently, but without full details of its preparation. The present procedure involves base-catalyzed hydrolysis of pyridinium-1-sulfonate at low temperature to glutaconaldehyde iminesulfonate dianion, followed by a second hydrolysis of the iminesulfonate at 55–60°, affording glutaconaldehyde sodium salt as a dihydrate.[4] The anhydrous potassium salt[5] and the monohydrated tetrabutylammonium salt may be prepared by similar procedures (see (Note 6)). In addition to being anhydrous, the potassium salt is more stable than the sodium salt; however, the sodium salt has the advantage of being more soluble in dimethyl sulfoxide and *N,N*-dimethylformamide. Analogous glutaconaldehyde iminesulfonate dianions with methyl and methoxy substituents at the 4-position are obtained by regiospecific ring opening of 3-methyl and 3-methoxy pyridinium-1-sulfonates.[6]

The reaction of glutaconaldehyde anion with benzoyl chloride and acetic anhydride gives the corresponding enol esters.[3,7] 4-Methyl- and 4-methoxyglutaconaldehyde enol benzoates are available by benzoylation of the corresponding iminesulfonate dianions and subsequent hydrolysis (Table I).[6] Halogenation of glutaconaldehyde anion or its enol benzoate gives a series of 2-halo and 2,4-dihalo derivatives (Table I).[6,8]

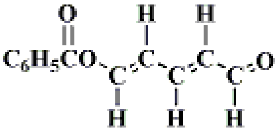
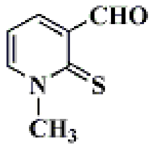
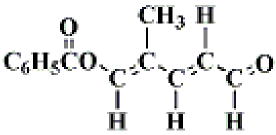
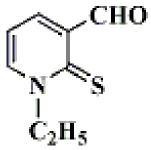
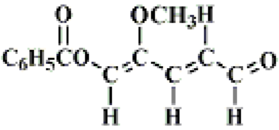
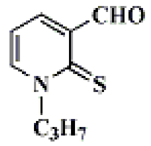
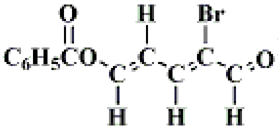
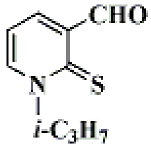
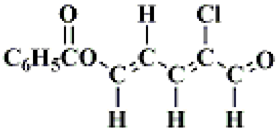
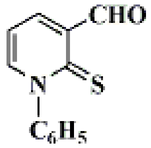
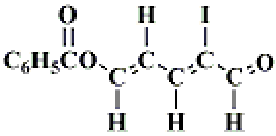
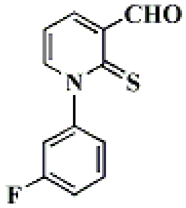
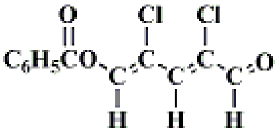
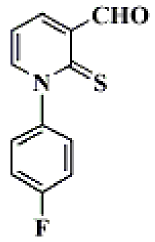
TABLE I

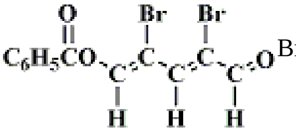
Glutaconaldehyde Enol Benzoates[6,7,8] and 1-Substituted 3-Formyl-2(1*H*)-Pyridinethiones[9] Prepared from Glutaconaldehyde Anion and Its Derivatives





R	R'	M.p. (°)	Yield (%)	R	M.p. (°)	Yield (%)[d]

H		H	119–121	87	CH_3		126–128	58
CH_3		H	138–139	61[a]	C_2H_5		109–110	61
CH_3O		H	123–124	27[a]	C_3H_7		88–90	65
H		Br	128–129	72[b]	*i*-C_3H_7		113–115	75
H		Cl	126–128	55[c]	C_6H_5		180–182	95
H		I	131–141	58[c]	3-FC_6H_4		171–173	97
Cl		Cl	114–116	66[c]	4-FC_6H_4		191–193	82

Br		
 Br	98–100	65[c]

[a]This ester was prepared by benzoylation of the corresponding glutaconaldehyde iminesulfonate dianion and subsequent hydrolysis.

[b]This ester was prepared by bromination of glutaconaldehyde enol benzoate.

[c]This ester was prepared by halogenation of glutaconaldehyde anion followed by benzoylation.

[d]The 3-formyl-2(1*H*)-pyridinethiones were prepared by reaction of glutaconaldehyde anion with the corresponding isothiocyanates (RN=C=S).

Glutaconaldehyde anion serves as an interesting intermediate for the synthesis of heterocyclic compounds. Pyrylium perchlorate has been prepared from glutaconaldehyde and 70% perchloric acid in ether at −55°.[10] The reactions of glutaconaldehyde anion with alkyl and aryl isothiocyanates and isoselenocyanates evidently occur initially at the 2-position of the former, leading to a variety of *N*-substituted 3-formyl-2(1*H*)pyridinethiones and the corresponding selenones (Table I).[9] A five-membered heterocycle, 2-isoxazolin-5-yl acetaldehyde oxime, is formed from reaction with hydroxylamine.[11] The chemistry of glutaconaldehyde is closely related to the chemistry of 5-amino-2,4-pentadienal, derivatives of which are interesting sources for a variety of polyenes. A review on glutaconaldehyde and 5-amino-2,4-pentadienal has recently been published.[12]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

H_2O

Glutaconaldehyde sodium salt

2-Pentenedial, ion (1−), sodium

glutaconaldehyde potassium salt

sodium and potassium salts of glutaconaldehyde

sodium salt of glutaconaldehyde

glutaconaldehyde sodium salt as a dihydrate

4-Methyl- and 4-methoxyglutaconaldehyde enol benzoates

3-formyl-2(1H)pyridinethiones

potassium carbonate (584-08-7)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether (60-29-7)

acetic anhydride (108-24-7)

sodium hydroxide (1310-73-2)

sulfur trioxide (7446-11-9)

chloroform (67-66-3)

acetone (67-64-1)

carbon, activated carbon (7782-42-5)

benzoyl chloride (98-88-4)

pyridine (110-86-1)

potassium hydroxide (1310-58-3)

toluene (108-88-3)

sodium (13966-32-0)

isopropyl alcohol (67-63-0)

hydroxylamine (7803-49-8)

dichloromethane (75-09-2)

N,N-dimethylformamide (68-12-2)

dimethyl sulfoxide (67-68-5)

perchloric acid (7601-90-3)

glutaconaldehyde

PYRIDINIUM-1-SULFONATE

glutaconaldehyde sodium salt dihydrate

glutaconaldehyde iminesulfonate disodium salt

tetrabutylammonium hydrogen sulfate (32503-27-8)

glutaconaldehyde tetrabutylammonium salt monohydrate

glutaconaldehyde iminesulfonate

glutaconaldehyde anion

Pyrylium perchlorate

glutaconaldehyde enol benzoate

2-isoxazolin-5-yl acetaldehyde oxime

5-amino-2,4-pentadienal

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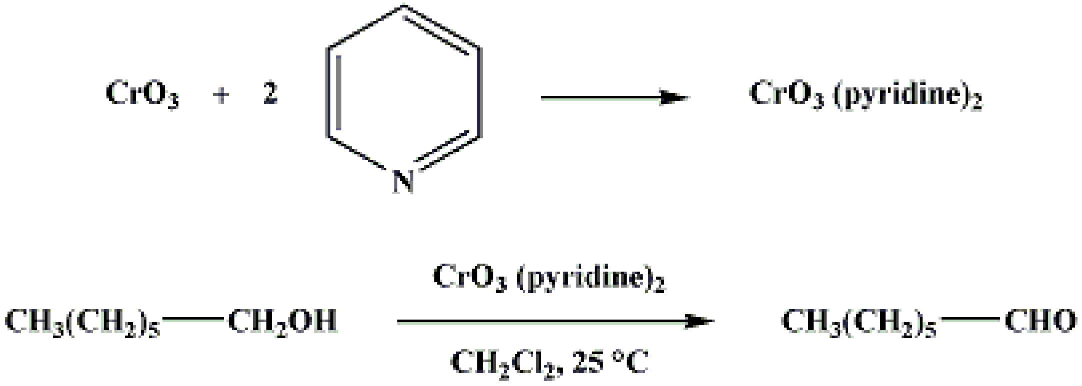
Organic Syntheses, CV 6, 644

ALDEHYDES FROM PRIMARY ALCOHOLS BY OXIDATION WITH CHROMIUM TRIOXIDE: HEPTANAL



Submitted by J. C. Collins[1] and W. W. Hess[2].
Checked by R. T. Uyeda and R. E. Benson.

1. Procedure

Caution! The reaction of chromium trioxide with pyridine is extremely exothermic; the preparation should be conducted in a hood, observing the precautions noted.

A. *Dipyridine chromium(VI) oxide* (Note 1). A dry, 1-l., three-necked flask fitted with a sealed mechanical stirrer, a thermometer, and a drying tube, is charged with 500 ml. of anhydrous pyridine (Note 2), which is stirred and cooled to approximately 15° (Note 3) with an ice bath. The drying tube is periodically removed and 68 g. (0.68 mole) of anhydrous chromium(VI) oxide (Note 4) is added in portions through the neck of the flask over a 30-minute period. The chromium trioxide should be added at such a rate that the temperature does not exceed 20° and in such a manner that the oxide mixes rapidly with the pyridine and does not adhere to the side of the flask (Note 5). As the chromium trioxide is added, an intensely yellow, flocculent precipitate separates from the pyridine and the viscosity of the mixture increases. When the addition is complete, the mixture is allowed to warm slowly to room temperature with stirring. Within one hour the viscosity of the mixture decreases and the initially yellow product changes to a deep red, macrocrystalline form that settles to the bottom of the flask when stirring is discontinued. The supernatant pyridine is decanted from the complex and the crystals are washed several times by decantation with 250-ml. portions of anhydrous petroleum ether. The product is collected by filtration on a sintered glass funnel and washed with anhydrous petroleum ether, avoiding contact with the atmosphere as much as possible. The complex is dried at 10 mm. until it is free-flowing, leaving 150–160 g. (85–91%) of dipyridine chromium(VI) oxide[3] as red crystals. The product is extremely hygroscopic; contact with moisture

converts it rapidly to the yellow dipyridinium dichromate.[4] It is stored at 0° in a brown bottle (Note 6).

B. *General oxidation procedure for alcohols*. A sufficient quantity of a 5% solution of dipyridine chromium(VI) oxide (Note 1) in anhydrous dichloromethane (Note 7) is prepared to provide a sixfold molar ratio of complex to alcohol, an excess usually required for complete oxidation to the aldehyde. The freshly prepared, pure complex dissolves completely in dichloromethane at 25° at 5% concentration, giving a deep red solution, but solutions usually contain small amounts of brown, insoluble material when prepared from crude complex (Note 8). The alcohol, either pure or as a solution in anhydrous dichloromethane, is added to the red solution in one portion with stirring at room temperature or lower. The oxidation of unhindered primary (and secondary) alcohols proceeds to completion within 5 to 15 minutes at 25° with deposition of brownish-black, polymeric, reduced chromium–pyridine products (Note 9). When deposition of reduced chromium compounds is complete (monitoring the reaction by GC or TLC is helpful), the supernatant liquid is decanted from the (usually tarry) precipitate, which is rinsed thoroughly with dichloromethane (Note 10).

The combined dichloromethane solutions may be washed with dilute hydrochloric acid, sodium hydrogen carbonate solution, and water, or filtered directly through a filter aid, or passed through a chromatographic column to remove traces of pyridine and chromium salts. The product is obtained by removal of dichloromethane; any pyridine that remains can often be removed under reduced pressure.

C. *Heptanal*. A dry, 1-l. three-necked round-bottomed flask is equipped with a mechanical stirrer, and 650 ml. of anhydrous dichloromethane (Note 7) is added. Stirring is begun and 77.5 g. (0.300 mole) of dipyridine chromium(VI) oxide (Note 1) is added at room temperature, followed by 5.8 g. (0.050 mole) of 1-heptanol (Note 11) in one portion. After stirring for 20 minutes, the supernatant solution is decanted from the insoluble brown gum, which is washed with three 100-ml. portions of ether. The ether and dichloromethane solutions are combined and washed successively with 300 ml. of aqueous 5% sodium hydroxide, 100 ml. of 5% hydrochloric acid (Note 12), two 100-ml. portions of saturated aqueous sodium hydrogen carbonate, and, finally, with 100 ml. of saturated aqueous sodium chloride. The organic layer is dried over anhydrous magnesium sulfate, and the solvent is removed by distillation. Distillation of the residual oil at reduced pressure through a small Claisen head separates 4.0–4.8 g. (70–84%) of heptanal, b.p. 80–84° (65 mm.), n_D^{25} 1.4094 (Note 13).

2. Notes

1. Dipyridine chromium(VI) oxide is available from Eastman Organic Chemicals. To be an effective reagent, it must be anhydrous. It should form a red solution on dissolution in anhydrous dichloromethane.
2. Commercial reagent grade pyridine was used. The checkers used material available from Allied Chemical Corporation, B and A grade.

3. To avoid the accumulation of excess, unchanged chromium trioxide and rapid temperature rise when it does react, *the initial temperature of the pyridine should never be below* 10°.
4. Reagent grade chromium(VI) oxide was dried over phosphorus pentoxide. The checkers used material available from Allied Chemical Corporation, B and A grade.
5. A glassine paper cone or glass funnel inserted in the drying tube neck of the flask during additions proved satisfactory, provided the cone or funnel was replaced frequently. The paper must be discarded carefully, since it may inflame. Adding the chromium trioxide from a flask through rubber tubing proved dangerous because it caused local excesses of the oxide below and in the neck of the flask. Pyridine added to chromium trioxide spontaneously ignites causing spot fires that extinguish themselves rapidly if the pyridine temperature is below 20° and stirring is efficient. Such fires should and can be avoided.
6. Since the complex itself loses pyridine under reduced pressure and darkens with surface decomposition, it should not be stored under vacuum or over acidic drying agents. Minimal exposure to the atmosphere is required to prevent hydration of the complex. The checkers found that a free-flowing product was obtained on drying for one hour.
7. Commercial dichloromethane was dried by distillation from phosphorus pentoxide. The dichloromethane may also be decanted from phosphorus pentoxide prior to use. Small amounts of suspended phosphorus pentoxide do not seem to interfere with the oxidation.
8. If the complex does not dissolve in dichloromethane, forming a red solution, either the complex has been hydrated in handling, or the dichloromethane is not anhydrous.
9. After the alcohol and complex are thoroughly mixed, the mixture may be stirred near its surface to avoid fouling of the stirrer by the thick, chromium-containing reduction product. Alternatively, the mixture may be swirled periodically to collect the reduction product on the side of the flask.
10. The reduced chromium precipitate is soluble in saturated sodium hydrogen carbonate, but no additional aldehyde was obtained on extracting this hydrogen carbonate solution with ether.
11. 1-Heptanol, obtained from Aldrich Chemical Company, Inc., was distilled before use, b.p. 176°.
12. A second washing with 100 ml. of 5% hydrochloric acid will reduce the amount of pyridine present in the final product without significantly decreasing the yield.
13. The product shows a strong band at 1720 cm.$^{-1}$ (C=O) in the IR. GC analysis indicated a purity of about 94–98%, with pyridine as the major impurity.

3. Discussion

Chromic acid, in a variety of acidic media, has been used extensively for the oxidation of primary alcohols to aldehydes but rarely has provided aldehydes in greater than

50% yield.[5] Chromium trioxide in pyridine was introduced as a unique, nonacidic reagent for alcohol oxidations and has been used extensively to prepare ketones,[6] but has been applied with only limited success to the preparation of aldehydes. While 2-methoxybenzaldehyde was obtained in 89% yield, 4-nitrobenzaldehyde and heptanal were obtained in 28% and 10% yields, respectively.[7]

Using the preformed dipyridine chromium(VI) oxide in dichloromethane, the rate of chromate ester formation and decay to the aldehyde[8] is enhanced at least twentyfold over the rate observed in pyridine solution.[4] Isolation of products is facile, and aldehydes appear to be relatively stable to excess reagent. The reagent has been used extensively to prepare acid-sensitive aldehydes, particularly intermediates in the total synthesis of prostaglandins[9] and steroids.[10] An 85% yield was reported for the conversion of 2-vinylcyclopropylcarbinol to the aldehyde.[11] Although excess reagent is required for the oxidations (usually sixfold), the reaction conditions are so mild and isolation of products so easy that the complex will undoubtedly find broad use as a specialty reagent. Isolation of the complex can be avoided by *in situ* preparation of the chromium oxide/pyridine complex.[12]

Other general syntheses of aldehydes from primary alcohols involve the use of dimethyl sulfoxide[13] with a dehydrating agent such as dicyclohexylcarbodiimide and phosphoric acid (or pyridinium trifluoroacetate),[14] diethylcarbodiimide,[15] or sulfur trioxide.[16] Alternatively, dimethyl sulfoxide has been used with derivatives of the alcohol such as the chloroformate,[17] the iodide,[18] and the tosylate.[19] Tertiary butyl chromate[20] and lead tetraacetate in pyridine[21] have been employed to oxidize aliphatic primary alcohols to aldehydes, while manganese dioxide[22] has been used to prepare aromatic and α,β-unsaturated aldehydes. More recently, pyridinium chlorochromate, pyridinium dichromate and chromium trioxide-3,5-dimethylpyrazole complex have been reported[23] to be effective reagents for the oxidation of primary alcohols to aldehydes in aprotic solvents.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 373
- Org. Syn. Coll. Vol. 8, 43

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

chromium trioxide-3,5-dimethylpyrazole

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sulfur trioxide (7446-11-9)

sodium hydrogen carbonate (144-55-8)

sodium chloride (7647-14-5)

pyridine (110-86-1)

phosphoric acid (7664-38-2)

chromic acid (7738-94-5)

manganese dioxide (1313-13-9)

1-heptanol (111-70-6)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

chromium trioxide, chromium(VI) oxide (1333-82-0)

chromium (7440-47-3)

chloroformate

4-nitrobenzaldehyde (555-16-8)

hydrogen carbonate (463-79-6)

chromium oxide (1308-38-9)

dimethyl sulfoxide (67-68-5)

Heptanal (111-71-7)

2-methoxybenzaldehyde (135-02-4)

dicyclohexylcarbodiimide (538-75-0)

pyridinium trifluoroacetate (464-05-1)

pyridinium chlorochromate (26299-14-9)

pyridinium dichromate, dipyridinium dichromate (20039-37-6)

dipyridine chromium(VI) oxide

2-vinylcyclopropylcarbinol

diethylcarbodiimide

Tertiary butyl chromate

phosphorus pentoxide (1314-56-3)

lead tetraacetate

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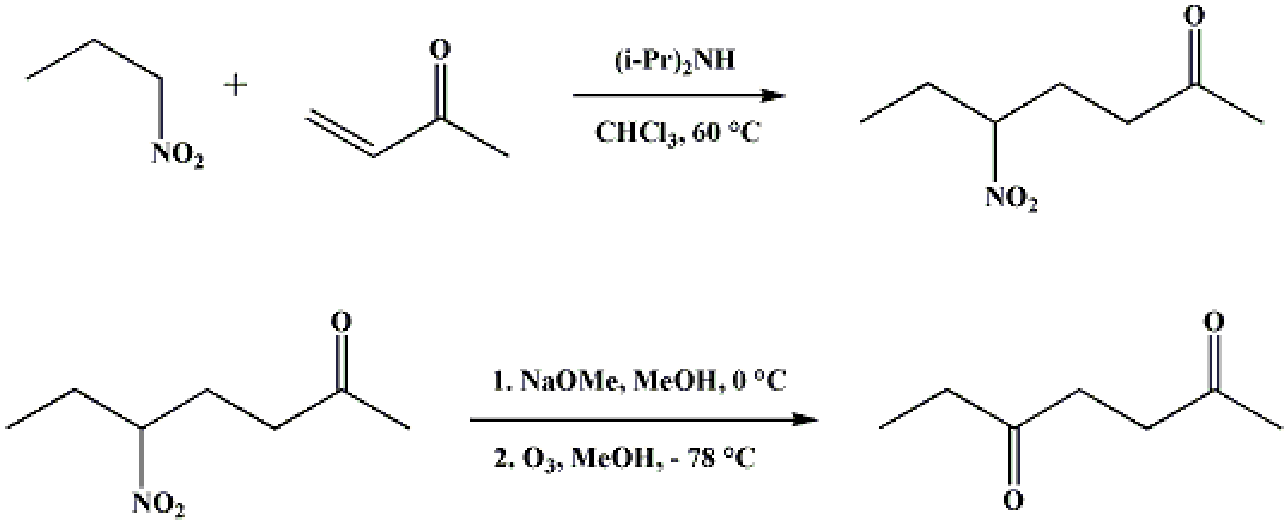
Organic Syntheses, *CV 6, 648*

CONVERSION OF NITRO TO CARBONYL BY OZONOLYSIS OF NITRONATES: 2,5-HEPTANEDIONE



Submitted by John E. McMurry[1] and Jack Melton.
Checked by Robert M. Coates and Robert W. Mason.

1. Procedure

A. 5-*Nitroheptan*-2-*one*. A 500-ml., three-necked flask equipped with a magnetic stirring bar, a 50-ml. addition funnel, and a condenser fitted with a nitrogen-inlet tube is flushed with nitrogen and charged with 36.0 g. (35.7 ml., 0.414 mole) of 1-nitropropane, 14.4 g. (20.0 ml., 0.142 mole) of diisopropylamine (Note 1), and 200 ml. of chloroform. The resulting solution is stirred and heated to 60°, and 28 g. (0.40 mole) of methyl vinyl ketone is added dropwise over a 2-hour period. The reaction mixture is then stirred for another 16 hours at 60°, allowed to cool to room temperature, and transferred to a 500-ml. separatory funnel, where it is washed with two 30-ml. portions of water and 30 ml. of 5% hydrochloric acid. After drying over anhydrous sodium sulfate, the chloroform solution is concentrated with a rotary evaporator. Distillation of the residue under reduced pressure gives 39.1 g. (61%) of 5-nitroheptan-2-one, b.p. 65–70° (0.2 mm.), n_D^{20} 1.4403 (Note 2).

B. 2,5-*Heptanedione*. Methanolic sodium methoxide is prepared by cautiously adding small pieces of freshly cut sodium (5.67 g., 0.247 g.-atom) to 200 ml. of cold methanol (Note 3) in a 500-ml., three-necked flask equipped with a mechanical stirrer, a 50-ml. addition funnel, and a condenser fitted with a nitrogen-inlet tube. The resulting solution is stirred and cooled in an ice bath while 38.6 g. (0.243 mole) of 5-nitroheptan-2-one is added over 15 minutes, after which stirring is continued for another 15 minutes at 0°. The ice bath is then replaced with an acetone–dry ice bath, the nitrogen-inlet tube and addition funnel are removed, and a fritted-glass dispersion tube is inserted into the solution. With continued cooling and vigorous stirring, an ozone–oxygen mixture is bubbled through the solution for 5 hours (Note 4) and (Note 5).

After ozone generation has been stopped, pure oxygen is passed through the reaction mixture, removing excess ozone. Dry ice cooling is continued while 21 g. (0.34 mole) of dimethyl sulfide is added in one portion (Note 6), and the mixture is then allowed to come to ambient temperature overnight (18 hours). Methanol is removed with a rotary evaporator, and the residual liquid is dissolved in 250 ml. of diethyl ether. This solution is percolated through a short mat of silica gel (50

g.), removing polar impurities, then concentrated with a rotary evaporator, leaving a residue which is stirred with 30 ml. of 5% hydrochloric acid for 45 minutes (Note 7). Chloroform (40 ml.) is added, the organic layer is separated, and the aqueous phase is further extracted with two 30-ml. portions of chloroform. The organic extracts are combined, washed with saturated aqueous sodium hydrogen carbonate, dried over anhydrous sodium sulfate, filtered, and concentrated with a rotary evaporator. Vacuum distillation of the residue with a Kugelrohr apparatus gives 22.7 g. (73%) of 2,5-heptanedione, b.p. 90° (20 mm.), n_D^{20} 1.4313 (Note 8).

2. Notes

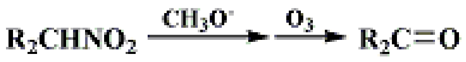
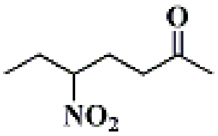
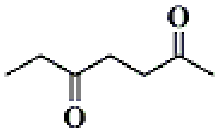
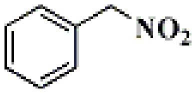
1. Nitropropane from MC and B Manufacturing Chemists and methyl vinyl ketone and diisopropylamine from Aldrich Chemical Company, Inc., were used as supplied.
2. IR (neat) cm.$^{-1}$: 1715, 1545; ^{1}H NMR (CCl_4), δ (multiplicity, coupling constant *J* in Hz., number of protons): 0.97 (t, *J* = 7, 3H), 2.13 (s, 3H), 4.38 (m, 1H).
3. By using 300 ml. of methanol at this point, the checkers were able to avoid crust formation on the gas-dispersion tube during ozonolysis (see (Note 5)).
4. Ozone was generated using a Welsbach ozonator, with a total gas flow of 1.0 l. per minute at 115 volts. This corresponds to an ozone flow of 0.104 mole per hour; thus, the time theoretically required to generate one equivalent of ozone in this reaction is 2.3 hours. The use of excess ozone is permissible only for secondary nitronates (see Discussion).
5. The precipitate that forms during ozonolysis sometimes impedes stirring, and in some cases it may be necessary to dilute the slurry with another 100 ml. of methanol after the first hour. Solid can also clog the gas-dispersion tube. The submitters scraped the fritted-glass tip occasionally to maintain a constant flow rate, whereas the checkers prepared a more dilute solution of nitronate anion (Note 3).
6. Dimethyl sulfide is added as a safety precaution, to reduce any highly oxidized and potentially dangerous by-products that might have formed during ozonolysis.
7. Acid treatment hydrolyzes dimethyl ketal by-products, which form to the extent of 5–10% during the reaction.
8. IR (neat) cm.$^{-1}$: 1710; ^{1}H NMR (CCl_4), δ (multiplicity, coupling constant *J* in Hz., number of protons): 1.01 (t, *J* = 7, 3H), 2.11 (s, 3H), 2.58 (s, 4H), 3.41 (q, *J* = 7, 2H). GC analysis by the checkers (6.3 mm. by 3 m. column of 20% SE-30 on Chromosorb W, 185°, 60 ml. of helium per minute) showed the presence of two minor impurities with retention times of 1.0 and 2.7 minutes. The major product, 2,5-heptanedione, had a retention time of 2.4 minutes.

3. Discussion

There are various methods available for transforming a nitro group into a carbonyl group, including the Nef reaction (strongly acidic),[2] permanganate oxidation of nitronate anions (basic, oxidative),[3] persulfate oxidation of nitronates (basic, oxidative),[4] treatment with a mixture of organic and inorganic nitrite (neutral, oxidative),[5] and treatment of either a free nitro compound or a nitronate anion with aqueous titanium(III) (neutral, reductive).[6] Each method is limited, however, by poor yield, inconvenience, or lack of generality.

With the proviso that the substrate not contain a reactive carbon-carbon double bond, the present ozonolysis procedure[7] appears to provide a convenient and efficient method for carrying out the desired transformation. As can be seen in Table I, both primary and secondary nitronates undergo the reaction. If a primary nitronate is to be used, however, one equivalent of ozone must be slowly metered in since use of an excess leads to overoxidation.

TABLE I

		Yield (%)
		73
		68
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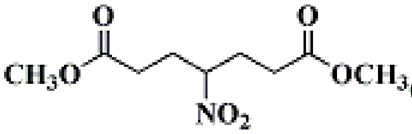	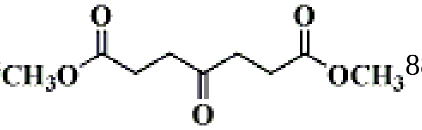	88

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

methanol (67-56-1)

diethyl ether (60-29-7)

chloroform (67-66-3)

sodium hydrogen carbonate (144-55-8)

sodium sulfate (7757-82-6)

oxygen (7782-44-7)

nitrogen (7727-37-9)

sodium methoxide (124-41-4)

sodium (13966-32-0)

ozone (10028-15-6)

dimethyl sulfide (75-18-3)

methyl vinyl ketone (78-94-4)

helium (7440-59-7)

1-nitropropane, Nitropropane (108-03-2)

diisopropylamine (108-18-9)

2,5-HEPTANEDIONE (1703-51-1)

5-nitroheptan-2-one (42397-25-1)

nitronate anion

titanium(III)

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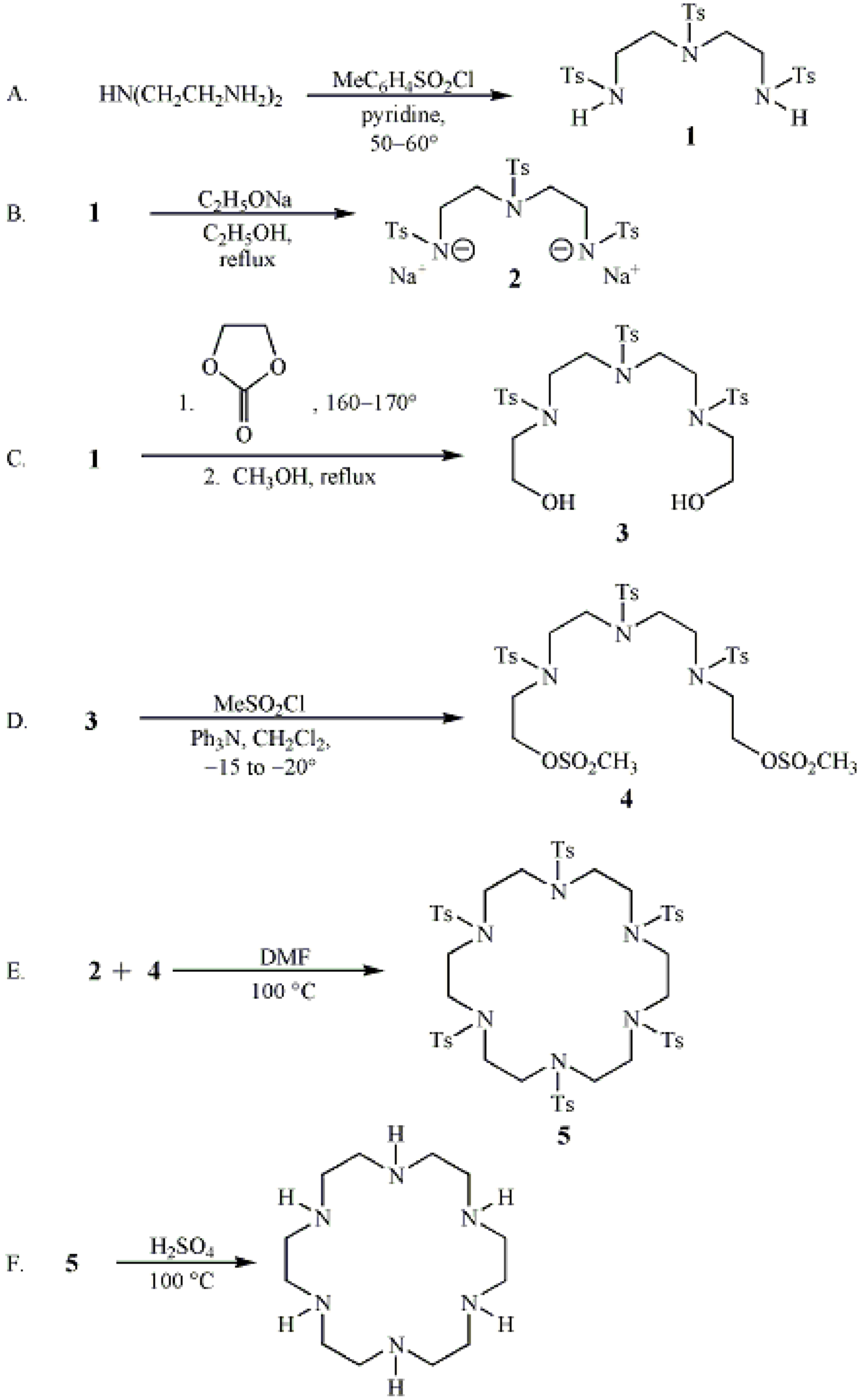
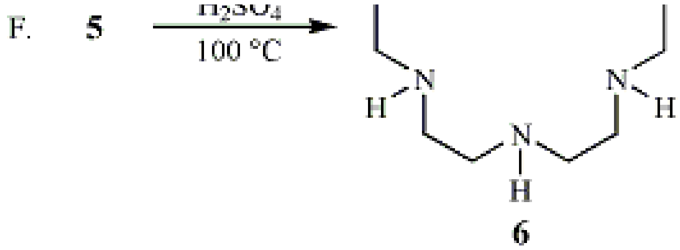
Organic Syntheses, CV 6, 652

MACROCYCLIC POLYAMINES: 1,4,7,10,13,16-HEXAÄZACYCLOÖCTADECANE





$Ts = p\text{-}CH_3C_6H_4SO_2\text{-}$

Submitted by T. J. Atkins[1], J. E. Richman, and W. F. Oettle.
Checked by K. Bernauer, F. Schneider, and A. Brossi.

1. Procedure

A. N,N',N"-*Tris*(p-*tolylsulfonyl*)*diethylenetriamine* **(1)**. A 5-l., three-necked, round-bottomed flask equipped with a mechanical stirrer, reflux condenser, thermometer, and addition funnel is charged with 1150 g. (6.037 moles) of *p*-toluenesulfonyl chloride (Note 1) and 3 l. of pyridine. The mixture is stirred and warmed to 50°, dissolving the solid; the flask is immersed in a 30° water bath; and a solution of 206 g. (2.00 moles) of diethylenetriamine (Note 1) in 300 ml. of pyridine is added through the addition funnel at a rate that maintains a reaction temperature of 50–60° (1 hour). The reaction mixture is kept at 50–60° for 30 minutes longer, cooled, and divided into two equal portions in 4-l. Erlenmeyer flasks. The pyridine solutions are mechanically stirred as 1000 ml. of water is slowly poured into each. After stirring overnight and cooling in an ice bath for 2 hours, the white solid is collected by filtration, thoroughly washed with ice-cold 95% ethanol, and dried in a vacuum oven at 100°, yielding 950–1015 g. (84–90%) of triamine **1**, m.p. 173–175°.

B. N,N',N"-*Tris*(p-*tolysulfonyl*)*diethylenetriamine*-N,N"-*disodium salt* **(2)**. A 3-l., three-necked, round-bottomed flask equipped with a mechanical stirrer, reflux condenser, and addition funnel is charged with 1 l. of absolute ethanol and 425 g. (0.752 mole) of triamine 1 under nitrogen. The stirred slurry is heated to reflux, the heat source is removed, and 1000 ml. of 1.5 *N* sodium ethoxide solution (Note 2) is added through the addition funnel as rapidly as possible. The solution is decanted from any undissolved residue into an Erlenmeyer flask. The disodium salt **2**, which crystallizes on standing overnight, is filtered under nitrogen, washed with absolute ethanol, and dried in a vacuum oven at 100°, yielding 400–440 g. (87–96%).

C. 3,6,9-*Tris*(p-*tolylsulfonyl*)-3,6,9-*triazaundecane*-1,11-*diol* **(3)**. A 2-l., three-necked, round-bottomed flask equipped with a mechanical stirrer, thermometer, reflux condenser, and heating mantle is charged with 226 g. (0.400 mole) of triamine 1, 77.5 g. (0.881 mole) of ethylene carbonate (Note 1), and 0.7 g. of powdered potassium hydroxide. The stirred mixture is heated at 160–170° for 4 hours (Note 3). The reaction mixture is then allowed to cool to 90°, and 500 ml. of methanol is added through the condenser as rapidly as possible. The solution is refluxed for 30 minutes, treated with 5 g. of activated carbon, and filtered through Celite. Water (120–140 ml.) is added dropwise to the stirred filtrate until the cloud point is reached. After crystallization is complete, diol **3** is collected and washed with 3 : 1 water–ethanol and dried in a vacuum oven at 50°, yielding 225–240 g. (86–92%) of colorless product, m.p. 108–112° (Note 4).

D. 3,6,9-*Tris*(p-*tolylsulfonyl*)-3,6,9-*triazaundecane*-1,11-*dimethanesulfonate* **(4)**. A 3-l.,

three-necked, round-bottomed flask equipped with a mechanical stirrer, addition funnel, nitrogen inlet, and low-temperature thermometer is charged with a dried solution of 200 g. (0.306 mole) of diol 3 and 100 ml. of triethylamine in 1500 ml. of dichloromethane (Note 5). The stirred solution is held at −15 to −20° in an acetone-dry ice bath as 74 g. (50 ml., 0.65 mole) of methanesulfonyl chloride (Note 1) is added over 10 minutes. The dry-ice bath is replaced with an ice bath, and the solution is stirred for 30 minutes, poured into a mixture of 1 l. of crushed ice and 500 ml. of 10% hydrochloric acid, and shaken. The layers are separated, and the organic layer is washed with two 500-ml. portions of water and 500 ml. of saturated salt solution, then dried over anhydrous magnesium sulfate. The solution is filtered and evaporated to dryness under reduced pressure giving a white solid, which is dissolved in 250 ml. of dichloromethane and crystallized by addition of 500 ml. of ethyl acetate and cooling in an ice bath, yielding 215–235 g. (87–95%) of methanesulfonate **4**, m. p. 146–148.

E. 1,4,7,10,13,16-*Hexakis*(p-*tolylsulfonyl*)-1,4,7,10,13,16-*hexaäzacycloöctadecane* **(5)**. A 5-l., three-necked, round-bottomed flask equipped with a mechanical stirrer, thermometer, and an addition funnel is charged with 151 g. (0.248 mole) of sodium salt 2 and 2000 ml. of *N*,*N*-dimethylformamide. The stirred solution is held at 100° as a solution of 200 g. (0.247 mole) of sulfonate 4 in 800 ml. of *N*,*N*-dimethylformamide is added dropwise over 3 hours. After 30 minutes the heat source is removed, and 500 ml. of water is added through the addition funnel. After cooling to room temperature and stirring overnight, the cyclic hexamine **5** is collected by filtration, washed with 95% ethanol, and dried in a vacuum oven at 100°, yielding 206–225 g. (70–77%), m.p. 260–290° (Note 6).

F. 1,4,7,10,13,16-*Hexaäzacycloöctadecane* **(6)**. A 3-l., three-necked, round-bottomed flask equipped with mechanical stirrer, nitrogen inlet, and addition funnel is charged with 200 g. (0.169 mole) of cyclic hexamine 5 and 500 ml. of concentrated (97%) sulfuric acid. The stirred mixture is held at 100° for 70 hours, then cooled in ice as 1300 ml. of anhydrous diethyl ether is slowly added. The precipitated polyhydrosulfate salt is filtered under nitrogen and washed with anhydrous ether (Note 7). The salt is then stirred in 200 ml. of water and cooled in ice as 71 ml. of aqueous 50% sodium hydroxide is added to neutralize the solution. Activated carbon (3 g.) is added, and the solution is heated to 80° and filtered through Celite. The filtrate is cooled in ice and reacidified to pH 1 by adding 42 ml. of concentrated sulfuric acid. The white, nonhygroscopic tris(sulfuric acid) salt of **6** that precipitates is collected and washed with 95% ethanol.

To the salt and 200 ml. of water in a 1-l., round-bottomed flask equipped with an efficient magnetic stirrer and cooled in ice is added 400 ml. of 50% sodium hydroxide solution. The resulting mixture is continuously extracted with tetrahydrofuran for 4 days (Note 8). The extract is concentrated to dryness at reduced pressure, and 1,4,7,10,13,16-hexaäzacycloöctadecane **(6)** is recrystallized from acetonitrile (30 ml. per g.), giving 19–22 g. (49–50%) of long, white needles, m.p. 147–150° (Note 9).

2. Notes

1. This reagent was purchased from Aldrich Chemical Company, Inc.
2. Sodium ethoxide was prepared under nitrogen just prior to use by dissolving 34.5

g. of sodium metal in 1000 ml. of absolute ethanol.

3. At 100–120° the solid begins to dissolve and carbon dioxide evolution commences.

4. Pure diol **3**, m.p. 110–112°, may be obtained by recrystallization from toluene (10 ml. per g.), but further purification is unnecessary for use in s.htmtep D.

5. This solution should be dried over 4-Å molecular sieves overnight.

6. The submitters obtained a yield of 190–210 g. (65–71%), m.p. 290–315° (dec.).

7. At this stage the grayish salt is quite hygroscopic and should be carefully kept from air to prevent difficulty in filtering.

8. A large excess of base is needed to reduce the water solubility of the amine. The precipitated solids contain product; any lumps should be broken up and the aqueous slurry efficiently stirred during the extraction.

9. The submitters found m.p. 154–156°.

3. Discussion

Macrocyclic polyamines and amine-ethers can be readily prepared without high-dilution techniques by this improved, general procedure.[2] Previous methods employed high-dilution techniques[3,4,5,6,7] or transition metal templates.[8] By adapting the present procedures, macrocycles of up to 24 members may be designed and directly synthesized in high yields from readily available starting materials.[2,9,10,11]

The critical cyclization step gives 50–85% yields when hydrocarbon segments between heteroatoms are short (see Table I) and when relatively equal segments of the target macrocycle are condensed. Methane- and di-*p*-toluenesulfonate esters[12,13] give markedly better yields than dihalides (see Table II). Cyclizations in *N*,*N*-dimethylformamide solvent are generally more convenient, although comparable yields are obtained in dimethyl sulfoxide and hexamethylphosphoric triamide [see *Science*, **190**, 422 (1975) for a toxicity warning concerning the latter compound]. Ether linkages or selectively substituted nitrogens may replace *N*-tosyl groups along the chain without seriously affecting cyclization yields. Other macrocyclic amines and amine-ethers[2,9,10,11,14] prepared by these methods are listed in Tables III and IV.

TABLE I

CONDENSATIONS OF TERMINAL ALKANE DITOSYLATES, TsO-$(CH_2)_n$-OTs

n	Yield (%)

2

71

3

84

4

81

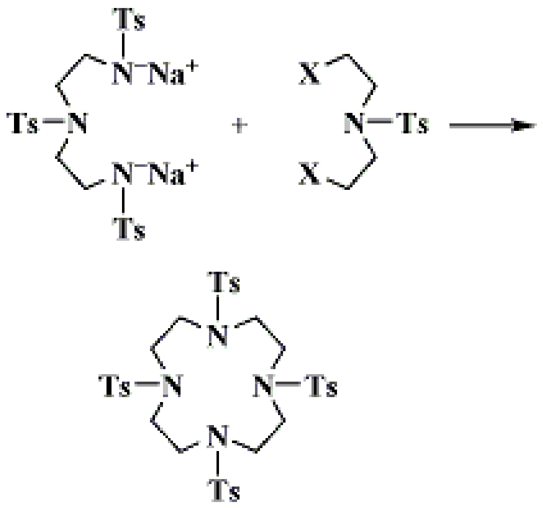
5

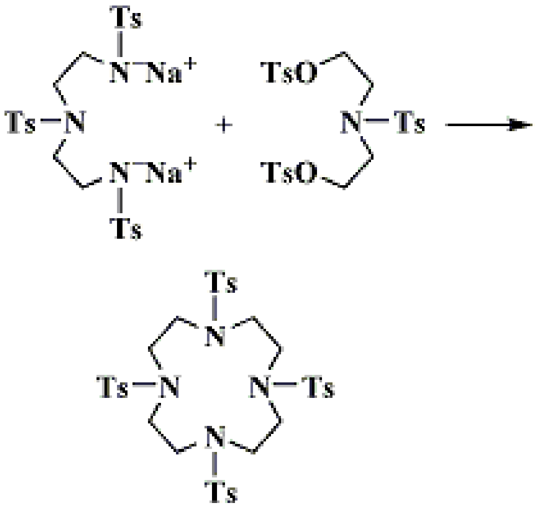
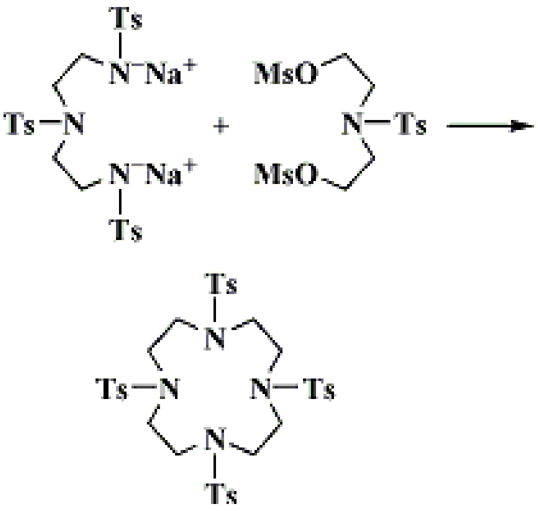
55

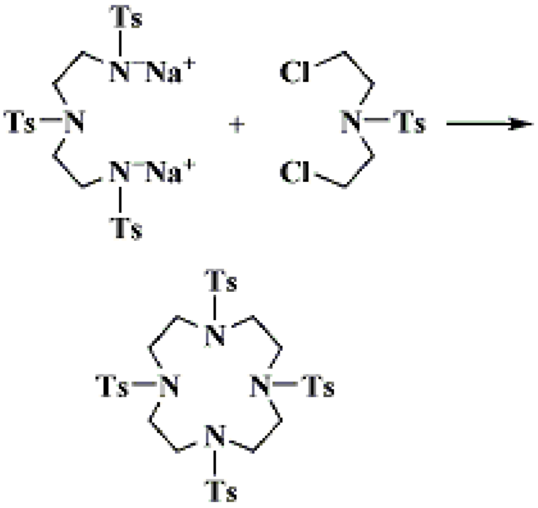
6

40–50

TABLE II
YIELDS OF CYCLIZATION FOR VARIOUS LEAVING GROUPS



X	Yield (%)
 -OTs	80
 -OMs	66



42

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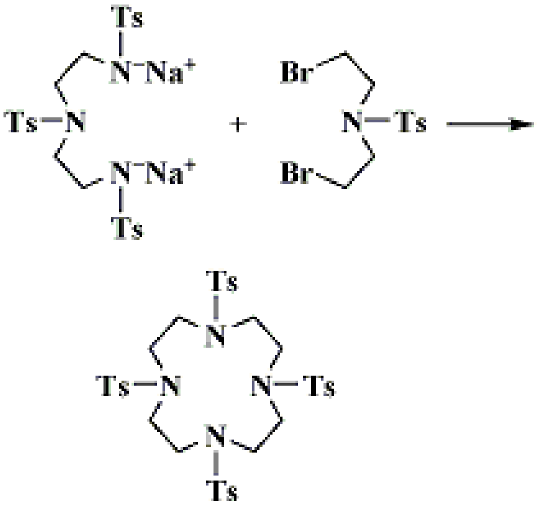
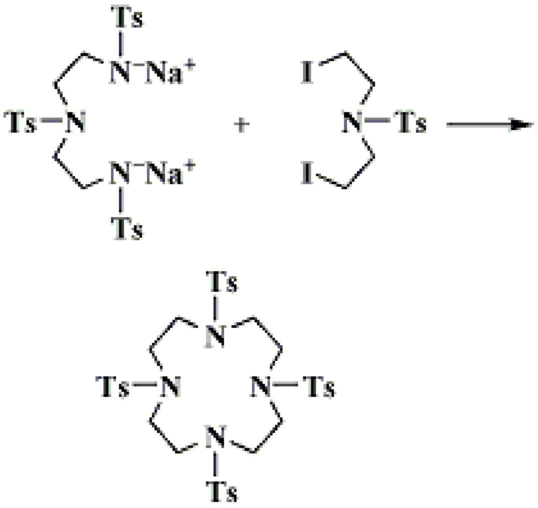


40

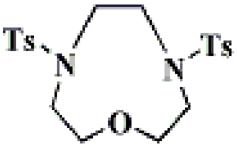
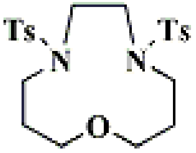
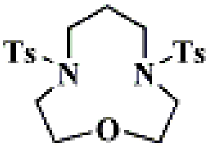
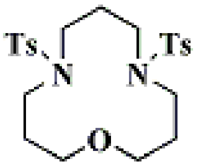
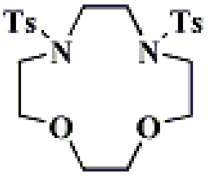
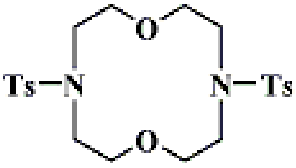
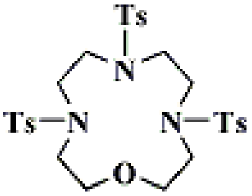
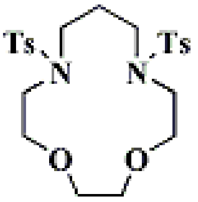
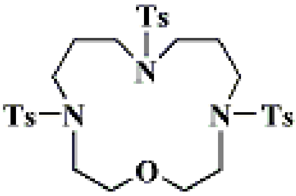
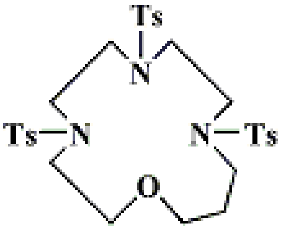
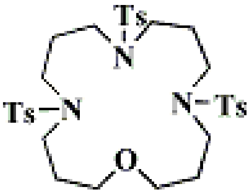
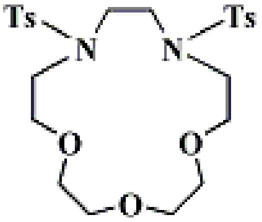
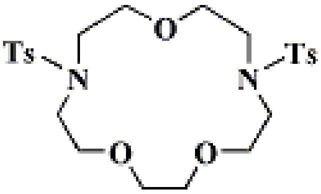
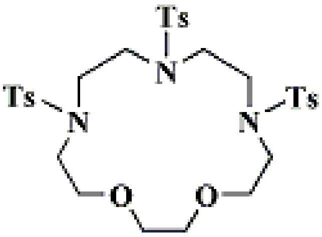
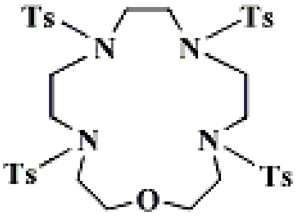
-Br

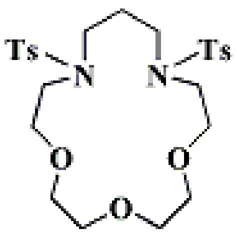
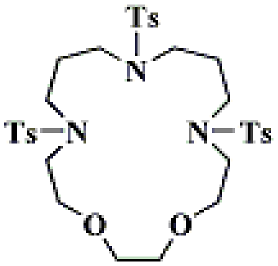
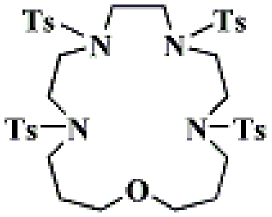
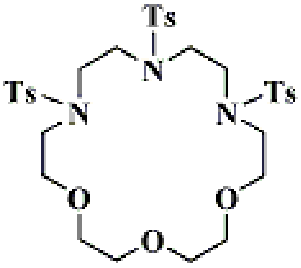
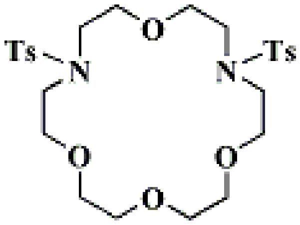
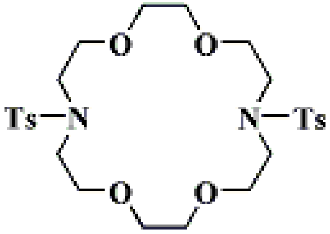


25

-I

TABLE III
YIELDS OF MACROCYCLIC AMINE–ETHERS

Amine-Ether	Yield (%)	Amine-Ether	Yield (%)	Amine-Ether	Yield (%)
	32[b] 79[c]		63[b]		66[b] 47[c]
	38[b]		52[b] 54[c]		80[a]
	90[a] 63[b]		28[b] 69[c]		58[c]
	29[b]		69[b]		23[b] 43[c]
	74[c]		71[b] 88[c]		52[b] 65[c]

	7[b]		85[b]		44[b]
	14[b]		69[c]		80[a]
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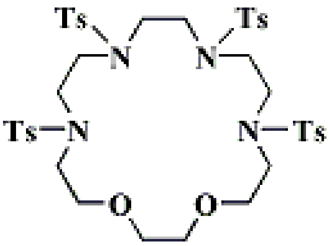
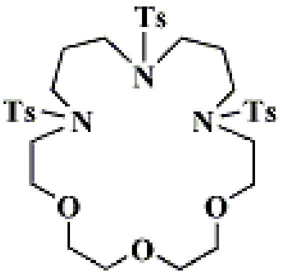
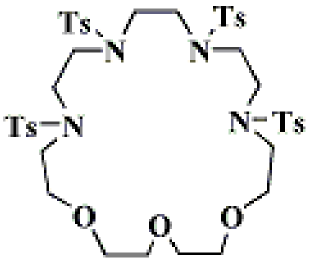
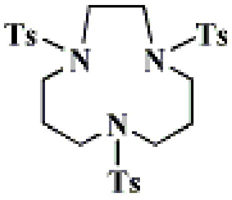
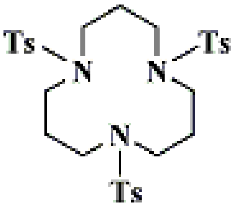
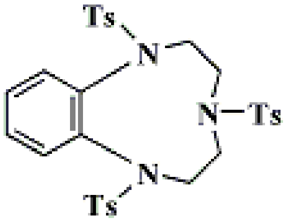
	25[b]		83[b]		35[b]
	72[a]				

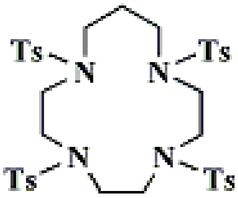
[a] Reference 2.

[b] Reference 9.

[c] T. J. Atkins, unpublished results.

TABLE IV
YIELDS OF MACROCYCLIC POLYAMINES

Polyamine	Yield (%)	Polyamine	Yield (%)	Polyamine	Yield (%)
	58		67		24



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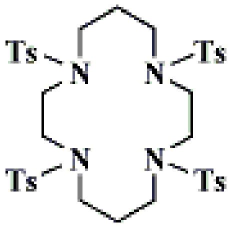

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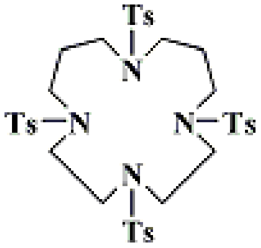

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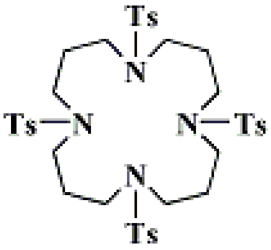

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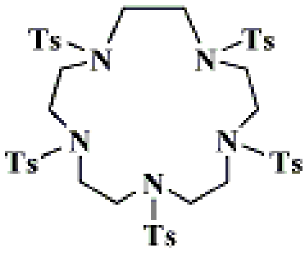

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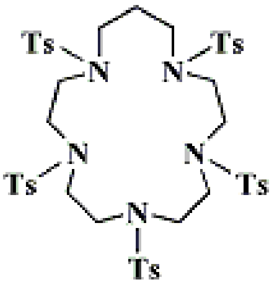

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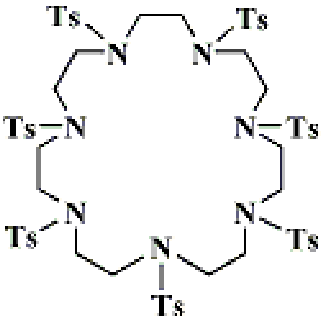

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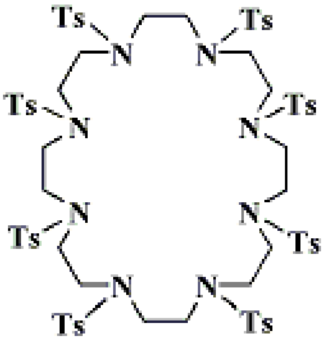

73

The hydroxyethylation of *sec*-sulfonamides has been adapted from Niederprüm, Voss, and Wechsberg.[15] Many new terminal diols for cyclization can be readily prepared by this method.

This preparation is referenced from:

- Org. Syn. 78, 73

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Chem., 1344 (1977).

12. The preparation of the dimesylate in the procedure is essentially that of R. K. Crossland and K. L. Servis, *J. Org. Chem.*, **35**, 3195 (1970).
13. Ditosylates can be prepared by the procedure described in C. S. Marvel and V. C. Sekera, *Org. Synth.*, **Coll. Vol. 3**, 366 (1955).
14. T. J. Atkins, J. E. Richman, and W. F. Oettle, unpublished results.
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

N,N',N"-Tris(p-tolylsulfonyl)diethylenetriamine

N,N',N"-Tris(p-tolysulfonyl)diethylenetriamine-N,N"-disodium salt

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

acetonitrile (75-05-8)

sodium hydroxide (1310-73-2)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

carbon (7782-42-5)

pyridine (110-86-1)

potassium hydroxide (1310-58-3)

toluene (108-88-3)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

N,N-dimethylformamide (68-12-2)

dimethyl sulfoxide (67-68-5)

triethylamine (121-44-8)

Methanesulfonyl chloride (124-63-0)

hexamethylphosphoric triamide (680-31-9)

ethylene carbonate (96-49-1)

p-Toluenesulfonyl chloride (98-59-9)

diethylenetriamine (111-40-0)

3,6,9-Tris(p-tolylsulfonyl)-3,6,9-triazaundecane-1,11-diol (74461-29-3)

3,6,9-Tris(p-tolylsulfonyl)-3,6,9-triazaundecane-1,11-dimethanesulfonate (74461-30-6)

1,4,7,10,13,16-Hexakis(p-tolylsulfonyl)-1,4,7,10,13,16-hexaazacyclooctadecane (52601-75-9)

1,4,7,10,13,16-Hexaazacyclooctadecane (296-35-5)

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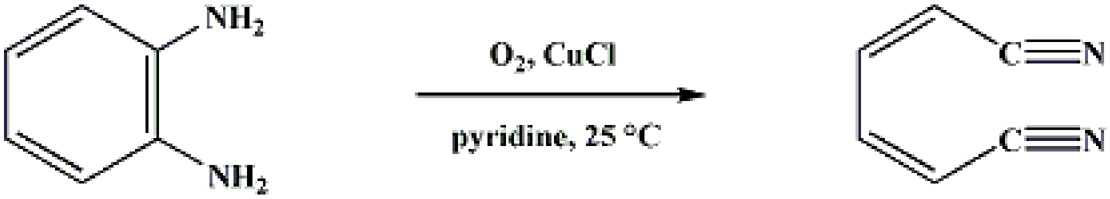
Organic Syntheses, CV 6, 662

CUPROUS ION-CATALYZED OXIDATIVE CLEAVAGE OF AROMATIC *o*-DIAMINES BY OXYGEN: (Z,Z)-2,4-HEXADIENEDINITRILE



Submitted by Jiro Tsuji[1] and Hiroshi Takayanagi.
Checked by Kyo Okada and Wataru Nagata.

1. Procedure

Caution! Benzene has been identified as a carcinogen. OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A 1-l. three-necked, round-bottomed flask equipped with a mechanical stirrer, a gas-inlet tube, and a dropping funnel is charged with 200 ml. of pyridine (Note 1) and 9.9 g. (0.10 mole) of copper(I) chloride (Note 2) which partially dissolves in pyridine, forming a yellow suspension (Note 3). Oxygen is bubbled into the suspension rapidly for 10 minutes; the suspension changes into a deep-green turbid solution (Note 4). A solution of 27 g. (0.25 mole) of 1,2-benzenediamine (Note 5) in 300 ml. of pyridine is added slowly from the dropping funnel during 2 hours, while vigorous stirring and bubbling of oxygen are continued (Note 6), (Note 7). The reaction mixture is transferred to a 1-l., round-bottomed flask, and pyridine is removed under reduced pressure (20 mm.) using a rotary evaporator until a deep-green solid residue is obtained, to which 400 ml. of 6 *N* hydrochloric acid and 400 ml. of dichloromethane are added. The mixture is shaken until the solid is dissolved, and the lower layer is separated (Note 8). The upper layer is extracted with three 100-ml. portions of dichloromethane. The combined dichloromethane solution is washed with 100 ml. of 5% aqueous sodium hydrogen carbonate, dried over anhydrous sodium sulfate, and evaporated. The brown residue is dissolved in 600 ml. of warm benzene, and the solution is filtered through filter paper. When the benzene is evaporated, 23–24 g. (88–93%) of crude product is obtained as a brownish solid, which is recrystallized twice from methanol (7 ml. for 1 g. of the crude material), yielding 19–20 g. (73–77%) of (Z,Z)-2,4-hexadienedinitrile as colorless needles, m.p. 128–129° (Note 9).

2. Notes

1. Commercial pyridine dried over potassium hydroxide pellets is satisfactory.
2. Reagent grade copper(I) chloride was obtained from Wako Pure Chemical Co., Osaka, Japan.
3. Powdered cuprous chloride should be added in small portions with efficient stirring in order to prevent coagulation.
4. When oxygen is bubbled too long, the solution becomes viscous and separation of solid mass occurs, but the mass dissolves with addition of 1,2-benzenediamine.
5. Reagent grade 1,2-benzenediamine was obtained from Wako Pure Chemical Co., Osaka, Japan.
6. The moment a drop of the diamine solution hits the reaction mixture, a spot becomes violet then turns to deep-green again. The addition should be slow, so that the violet color does not persist. The yeild of (*Z,Z*)-2,4-hexadienedinitrile decreases drastically if the addition is too fast.
7. The reaction is slightly exothermic, but no precaution is necessary for a small-scale experiment. It is advisable to cool the flask in a water bath when a large-scale synthesis is carried out.
8. As both layers are black and the interface is not easy to distinguish, careful separation is necessary. In addition, black amorphous material forms at the interface, making the separation difficult. It can be coagulated by standing or removed by filtration.
9. The IR spectrum ($CHCl_3$) shows bands at 2230 (medium strong), 1348, and 940 (medium) $cm.^{-1}$. The ^1H NMR spectrum ($CDCl_3$) shows absorption at δ 5.73 and 7.33 (AA'XX' pattern).

3. Discussion

A practical method of synthesizing (*Z,Z*)-2,4-hexadienedinitrile is the oxidative cleavage of 1,2-benzenediamine. Various oxidizing agents such as nickel peroxide,[2] lead tetraäcetate,[3] and silver oxide[4] are used in more than stoichiometric amounts, but the yields are below 50%. In comparison, the present method described by Takahashi, Kajimoto, and Tsuji[5] gives a very high yield and requires less than a stoichiometric quantity of copper(I) chloride. This procedure can also be applied satisfactorily to the preparation of mucononitrile derivatives from 1,2-benzenediamines substituted with an electron-donating group, but no reaction takes place with the derivatives substituted with an electron-withdrawing group.

References and Notes

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Takahashi, and J. Tsuji, *J. Org. Chem.*, **41**, 1389 (1976).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

methanol (67-56-1)

sodium hydrogen carbonate (144-55-8)

silver oxide (20667-12-3)

sodium sulfate (7757-82-6)

oxygen (7782-44-7)

pyridine (110-86-1)

potassium hydroxide (1310-58-3)

cuprous chloride, copper(I) chloride (7758-89-6)

dichloromethane (75-09-2)

1,2-benzenediamine (95-54-5)

nickel peroxide

(Z,Z)-2,4-Hexadienedinitrile (1557-59-1)

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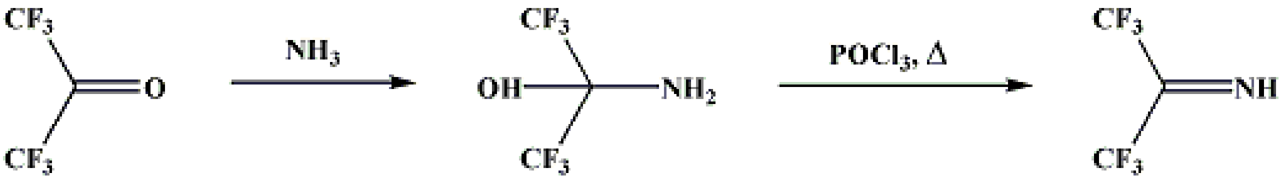
Organic Syntheses, CV 6, 664

HEXAFLUOROACETONE IMINE

[2-Propanimine, 1,1,1,3,3,3-hexafluoro-]



Submitted by W. J. Middleton[1] and H. D. Carlson.
Checked by L. Scerbo and W. D. Emmons.

1. Procedure

Caution! This procedure should be conducted in a good hood to avoid exposure to ammonia and hexafluoroacetone.

A 3-l., four-necked, round-bottomed flask is equipped with a thermometer (–50° to 150°), a dry ice-cooled reflux condenser (protected from the atmosphere through a T-tube that is also connected to a nitrogen source and a Nujol bubbler), and a gas-inlet tube above the liquid level. The flask and condenser are heated in an air oven at 125° for several hours and flamed under nitrogen with a Bunsen burner. Pyridine (1.2 l.), previously dried over potassium hydroxide pellets, is added to the flask. A nitrogen atmosphere is maintained in the system, the pyridine is cooled to –40°, and 462 g. (2.78 moles) of hexafluoroacetone (b.p. –28°) is added from a cylinder through the gas-inlet tube over 30 minutes (Note 1), (Note 2), and (Note 3). Liquid ammonia (58.3 ml., 47.6 g., 2.80 moles), previously distilled into a cold trap and measured at –78°, is distilled into the pyridine solution over a period of 1 hour ((Note 4)). During this addition the bath is held at –45° to –40°, keeping the solution at –25° to –30°.

As soon as the ammonia has been added, the gas-inlet tube is replaced with a 250-ml. pressure-equalized dropping funnel and the reaction mixture is heated with a heating mantle to 40° over 30 minutes or as quickly as possible (Note 5). The dry ice–cooled condenser is then replaced with a 24-in. water-cooled bulb condenser with Tygon tubing joining the top of the condenser to a 300-ml. cold trap protected from the atmosphere with a calcium chloride drying tube and cooled in a bath maintained at –30°. The condenser is cooled with 18–20° water. The heating mantle is turned off, and the dropping funnel is charged with 394 g. (235 ml., 2.57 moles) of phosphorus oxychloride, which is added dropwise at a rate to maintain a gentle reflux. The imine (b.p. 16°) collects in the cold trap. When addition is complete, the reaction mixture is heated to 100° over 20 minutes and maintained at this temperature for 30 minutes. The cold trap collects 320–360 g. of crude liquid product (Note 6), which is distilled through a Podbielniak still with a reflux head temperature of about 0° (Note 7), yielding 254–291 g. (55–65%) of the purified imine, b.p. 15.5–17° (Note 8). It can be stored indefinitely in a stainless-steel cylinder.

2. Notes

1. Hexafluoroacetone may be obtained from E. I. du Pont de Nemours and Company, Inc., or Allied Chemical Corporation.

2. If it is inconvenient to add the hexafluoroacetone directly from a cylinder, it may first be condensed in a calibrated trap containing a boiling chip and cooled in an acetone–dry ice bath. When cooled to −78°, 462 g. of liquid hexafluoroacetone has a volume of *ca.* 280 ml. The hexafluoroacetone can be added to the reaction mixture by allowing it to boil slowly from the trap.
3. The bath is maintained at −40°, and the pyridine solution is maintained below −20°. Acetone, to which pieces of dry ice are added periodically to adjust the temperature, is a convenient cooling bath.
4. The ammonia can be prevented from bumping with a magnetic stirrer in the trap. Heat for the distillation can be obtained from the air of the laboratory and by occasionally flushing the outside wall of the trap with room-temperature acetone.
5. Prolonged heating decreases the yield.
6. For storage until Podbielniak distillation can be carried out, the product can be drained into an evacuated, 500-ml. stainless-steel cylinder.
7. The checkers used a 60-cm., vacuum-jacketed column packed with glass helices, with satisfactory results.
8. This preparation has been run in the submitters' laboratory at four times this scale with yields as high as 67%.

3. Discussion

Hexafluoroacetone imine has been prepared by the reaction of hexafluoroacetone with triphenylphosphine imine,[2] by the pyrolysis of *N*-phenyl-2,2-diaminohexafluoropropane,[2,3] by the reaction of hexafluorothioacetone with hydrazoic acid,[4] and by the reaction of ammonia and phosphorus oxychloride with hexafluoroacetone.[4,5] The latter method, described here, is the most convenient, as it does not require preparation of several intermediates or use of pressure equipment. This method has also been used to prepare the imines of other fluoroketones, including those of chloropentafluoroacetone, dichlorotetrafluoroacetone, and perfluorodiethyl ketone.[5] Substitution of methylamine for ammonia in this procedure gives the *N*-methyl imine.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 161

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrazoic acid

ammonia (7664-41-7)

nitrogen (7727-37-9)

acetone (67-64-1)

Phosphorus Oxychloride (21295-50-1)

pyridine (110-86-1)

potassium hydroxide (1310-58-3)

methylamine (74-89-5)

Hexafluoroacetone imine, 2-Propanimine, 1,1,1,3,3,3-hexafluoro- (1645-75-6)

Hexafluoroacetone (684-16-2)

triphenylphosphine imine

hexafluorothioacetone

perfluorodiethyl ketone

chloropentafluoroacetone (79-53-8)

N-phenyl-2,2-diaminohexafluoropropane

N-methyl imine (2053-29-4)

dichlorotetrafluoroacetone

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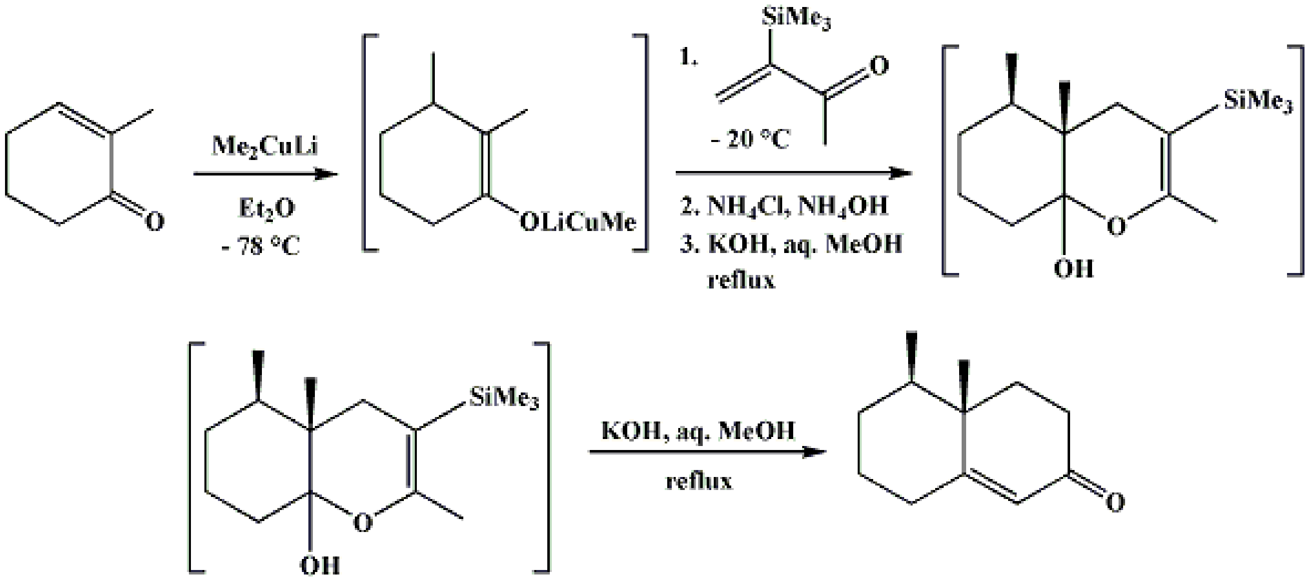
Organic Syntheses, CV 6, 666

3-TRIMETHYLSILYL-3-BUTEN-2-ONE AS MICHAEL ACCEPTOR FOR CONJUGATE ADDITION-ANNELATION: *cis*-4,4*a*,5,6,7,8-HEXAHYDRO-4*a*,5-DIMETHYL-2(3*H*)-NAPHTHALENONE

[2(3*H*)-Napthalenone, 4,4*a*,5,6,7,8-hexahydro-, 4*a*,5-dimethyl-, *cis*-, (±)-]



Submitted by Robert K. Boeckman, Jr.[1], David M. Blum, and Bruce Ganem[2].
Checked by Seiichi Inoue and Robert M. Coates.

1. Procedure

A 100-ml., three-necked flask fitted with an argon inlet, a rubber septum, a magnetic stirrer, and a 25-ml. pressure-equalizing dropping funnel (Note 1) is charged with 1.9 g. (0.010 mole) of copper(I) iodide (Note 2) and 40 ml. of anhydrous diethyl ether. The mixture is stirred and cooled in an ice bath while 10 ml. (0.02 mole) of a 2 *M* solution of methyllithium in ether (Note 3) is injected through the septum into the flask. The resulting straw-yellow solution of lithium dimethylcuprate is cooled to −78° in an acetone–dry ice bath, and a solution of 1.10 g. (0.0100 mole) of 2-methyl-2-cyclohexenone (Note 4) in 10 ml. of ether is injected into the flask, with stirring, over a 2–3 minute period. The cooling bath is allowed to warm slowly to about −20° over *ca.* 1 hour (Note 5) before a solution of 2.13 g. (0.0150 mole) of 3-trimethylsilyl-3-buten-2-one (Note 6) in 10 ml. of ether is added dropwise over 5 minutes. The stirred mixture is cooled between −20° and −30° for another hour by occasional addition of dry ice to the cooling bath. The contents of the flask are poured into 100 ml. of an ammonium chloride–ammonium hydroxide buffer solution (Note 7) that has been cooled to 0° (Note 8). The ether layer is extracted with two or three additional 100-ml. portions of buffer solution (Note 9), and the combined aqueous solutions are extracted with two 75-ml. portions of ether. The combined ether extracts are washed once with saturated sodium chloride, dried with anhydrous magnesium sulfate, and evaporated at reduced pressure.

The residual yellow liquid (2.7–3.4 g.) is dissolved in a mixture of 40 ml. of methanol and 5 ml. of 4% aqueous potassium hydroxide, then heated at reflux under an argon atmosphere for 4 hours. The methanol is evaporated from the cooled solution under reduced pressure, and the residue is dissolved in 50 ml. of ether. The ether solution is washed once with water, dried with anhydrous magnesium sulfate, and evaporated. Distillation of the residual liquid with a Kugelrohr apparatus (Note 10) at 0.5 mm. affords, after separation of a 0.1–0.2 g. forerun collected at an oven temperature of 50°, 0.76–1.02 g. (43–57%) of the octalone at an oven temperature of 85–90° (Note 11) and (Note 12).

2. Notes

1. The apparatus is flamed dry and maintained under an atmosphere of argon during the reactions.
2. The submitters purified copper(I) iodide by precipitation from a concentrated aqueous solution of potassium iodide as described by Kauffman and Teter,[3] and dried it at 100° over phosphorus pentoxide at high vacuum. Copper(I) iodide from Fisher Scientific Company was used by the checkers after drying at high vacuum.
3. A solution of methyllithium in ether may be purchased from Ventron Corporation. Directions for the preparation of ethereal methyllithium from methyl bromide are also available [*Org. Synth.*, **Coll. Vol. 6**, 901 (1988)]. The solution should be standardized before use by a titration procedure such as that of Watson and Eastham[4] [*Org. Synth.*, **Coll. Vol. 6**, 121 (1988)].
4. 2-Methyl-2-cyclohexenone is prepared by the method in *Org. Synth.*, **Coll. Vol. 4**, 162 (1963).
5. This warming operation was effected by the checkers by removing the original cooling bath and replacing it with another one that had been cooled to −30°. The bath temperature was then allowed to rise to −20° over *ca.* 1 hour.
6. 3-Trimethylsilyl-3-buten-2-one was prepared by the method in *Org. Synth.*, **Coll. Vol. 6**, 1033 (1988).
7. The buffer solution is prepared by adding enough concentrated ammonium hydroxide to 10% ammonium chloride to raise the pH to 8.
8. The checkers recommend that the mixture be stirred for 30 minutes at 0° to dissolve the pasty precipitate which forms and facilitate the following extractions.
9. The extractions with buffer solution should be continued until the characteristic blue color of copper (II) is no longer visible in the aqueous layer.
10. Kugelrohr distillation ovens produced by Büchi Glasapparatefabrik are available from Brinkmann Instruments, Inc.
11. The checkers collected the 0.1–0.2 g. forerun at an oven temperature of about 70–85° and the main fraction over a 5–10° range between about 105 and 120°. Combination of the main fraction from two runs gave 2.03 g., which, on redistillation with the Kugelrohr apparatus at 0.4 mm., provided a 0.2 g. forerun collected with an oven temperature of 45–53° and a main fraction totalling 1.5 g., collected at 88–93°.
12. The product has the following spectral properties: IR (thin film) cm^{-1}: 2960 (C-H), 1685 (C=O), 1620 (C=C); ^1H NMR (CCl_4), δ (multiplicity, number of protons, assignment): 0.92 (m, 3H, CH_3), 1.11 (s, 3H, CH_3), 5.64 (broad s, 1H, vinyl-*H*), minor absorption of an unidentified impurity at 5.75 (m, 0.1–0.2H, vinyl-*H*).
A GC analysis of the product by the submitters using a 1.8-m. column packed with 20% Carbowax 20 M suspended on Chromosorb P and operated at 150° with a flow rate of 30 ml. per minute showed a peak for the major component having a retention time of 16 minutes and two minor peaks having retention times of 4 and 7 minutes, with relative areas amounting to 6% and 2% of the major peak, respectively. The stereochemical purity of the product was shown to be >95% *cis* by the submitters by GC analysis using a 50-ft. capillary column coated with Carbowax 20 M and heated to 140°; these conditions give separate peaks for a 3 : 2 mixture of the *cis* and *trans* isomers of the two octalones.[5,6]

3. Discussion

4,4*a*,5,6,7,8-Hexahydro-4*a*,5-dimethyl-2(3*H*)-naphthalenone, an important intermediate in the total syntheses of the sesquiterpenes, aristolone,[5,6] and fukinone,[7] has been prepared in 15% yield as a 3 : 2 mixture of *cis* and *trans* isomers by the Robinson annelation reaction between 2,3-dimethylcyclohexanone and methyl vinyl ketone.[5,6] This *cis*-octalone has also been synthesized stereoselectively *via* the crystalline enol lactone, *cis*-3,4,4*a*,5,6,7-hexahydro-4*a*,5-dimethyl-2*H*-1-benzopyran-2-one.[6] In the procedure reported here the *cis*-octalone is prepared from 2-methyl-2-cyclohexen-1-one in a simple, three-step procedure consisting of conjugate addition with lithium dimethylcuprate, Michael addition of the resulting enolate anion to 3-trimethylsilyl-3-buten-2-one, and cyclization of the intermediate diketone.[8] Reasonable structures for the intermediates are proposed in the lead equation but have not been experimentally established. This procedure also illustrates the general utility of 1-trimethylsilylvinyl ketones in regio- and stereoselective enolate trapping

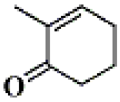
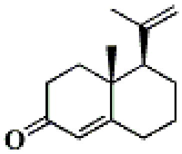
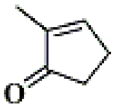
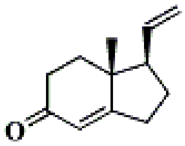
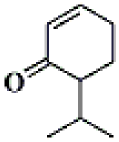
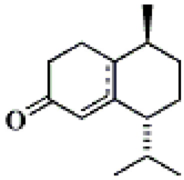
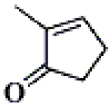
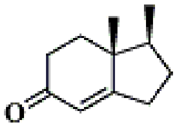
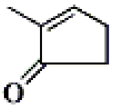
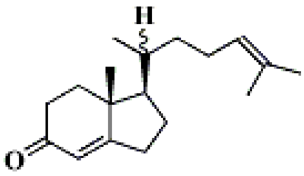
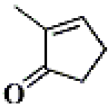
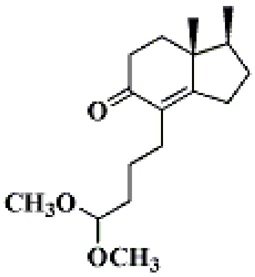
reactions[9] and the application of the method in the synthesis of polycyclic ketones (Table I).[8,9,10,11]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 1033

TABLE I

SYNTHESIS OF POLYCYCLIC KETONES[8,9,10,11]

Reactant	Product	Yield (%)
		57
		54
		53
		57
		67
		>60

References and Notes

1. Department of Chemistry, Wayne State University, Detroit, Michigan, 48202 [Present address: Department of

Chemistry, University of Rochester, Rochester, New York 14627].

2. Department of Chemistry, Cornell University, Ithaca, New York 14853.
3. G. B. Kauffman and L. A. Teter, *Inorg. Synth.*, **7**, 9 (1963).
4. S. C. Watson and J. F. Eastham, *J. Organomet. Chem.*, **9**, 165 (1967).
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7. E. Piers and R. D. Smillie, *J. Org. Chem.*, **35**, 3997 (1970).
8. R. K. Boeckman, Jr., *J. Am. Chem. Soc.*, **95**, 6867 (1973).
9. G. Stork and B. Ganem, *J. Am. Chem. Soc.*, **95**, 6152 (1973).
10. R. K. Boeckman, Jr., *J. Am. Chem. Soc.*, **96**, 6179 (1974).
11. G. Stork and J. Singh, *J. Am. Chem. Soc.*, **96**, 6181 (1974).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

sodium chloride (7647-14-5)

potassium iodide (7681-11-0)

potassium hydroxide (1310-58-3)

methyl bromide (74-83-9)

ammonium hydroxide (1336-21-6)

copper(I) iodide (7681-65-4)

magnesium sulfate (7487-88-9)

methyl vinyl ketone (78-94-4)

Methyllithium (917-54-4)

2-Methyl-2-cyclohexenone, 2-methyl-2-cyclohexen-1-one (1121-18-2)

argon (7440-37-1)

copper(II)

lithium dimethylcuprate

2,3-dimethylcyclohexanone

3-Trimethylsilyl-3-buten-2-one (43209-86-5)

phosphorus pentoxide (1314-56-3)

cis-4,4a,5,6,7,8-Hexahydro-4a,5-dimethyl-2(3H)-naphthalenone, 2(3H)-Napthalenone, 4,4a,5,6,7,8-hexahydro-, 4a,5-dimethyl-, cis-, (±)- (20536-80-5)

4,4a,5,6,7,8-Hexahydro-4a,5-dimethyl-2(3H)-naphthalenone

cis-3,4,4a,5,6,7-hexahydro-4a,5-dimethyl-2H-1-benzopyran-2-one

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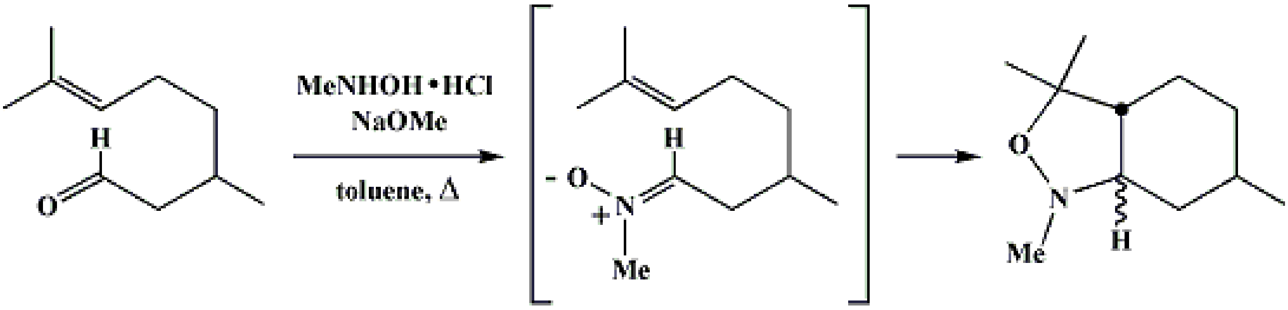
Organic Syntheses, CV 6, 670

NITRONES FOR INTRAMOLECULAR 1,3-DIPOLAR CYCLOADDITIONS: HEXAHYDRO-1,3,3,6-TETRAMETHYL-2,1-BENZISOXAZOLINE

[2,1-Benzisoxazole, 1,3,3*a*,4,5,6,7,7*a*-octahydro-1,3,3,6-tetramethyl-]



Submitted by Norman A. LeBel and Dorothy Hwang[1].
Checked by Christopher K. VanCantfort and Robert M. Coates.

1. Procedure

A 1-l., three-necked, round-bottomed flask is fitted with a mechanical stirrer, a reflux condenser attached to a Dean-Stark water separator, and a 250-ml. dropping funnel. The flask is charged with 25.0 g. (0.16 mole) of 3,7-dimethyl-6-octenal (Note 1) and 500 ml. of toluene. The solution is heated to reflux with stirring, and a solution of *N*-methylhydroxylamine, methanol, and toluene is added (see below).

To a cooled and magnetically stirred solution of 23.4 g. (0.280 mole) of *N*-methylhydroxylamine hydrochloride (Note 2) and (Note 3) in 40 ml. of methanol is added 15.3 g. (0.282 mole) of sodium methoxide. The cooling bath is removed, and the mixture is stirred at room temperature for 15 minutes. The mixture is filtered rapidly through a 35-mm., coarse, sintered-glass funnel, and the filter cake is washed with 10 ml. of methanol. The filtrates are combined, refiltered, and mixed with 150 ml. of toluene.

The two-phase mixture containing *N*-methylhydroxylamine is added dropwise to the refluxing toluene solution of the aldehyde over 3 hours. During this time the distillate is collected and discarded in 25-ml. portions until the last such portion collected and discarded is clear (Note 4). Reflux and stirring are continued for an additional 3 hours, and then the clear reaction mixture is allowed to cool. The product is extracted with three 80-ml. portions of 10% hydrochloric acid. The extracts are combined, and the pH of the solution is adjusted to >12 by the slow addition of 30% aqueous potassium hydroxide. The basic mixture is extracted with two 120-ml. portions of pentane (Note 5), and the combined extracts are washed once with 100 ml. of water and dried over anhydrous potassium carbonate. The pentane is removed on a rotary evaporator, and the residue is distilled through a short Vigreux column under reduced pressure, yielding 19.1–19.6 g. (64–67%) (Note 6) of hexahydro-1,3,3,6-tetramethyl-2,1-benzisoxazoline, b.p. 90–92° (9 mm.) (Note 7).

2. Notes

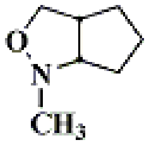
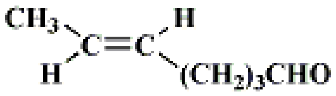
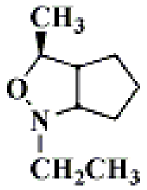
1. Matheson, Coleman and Bell technical grade 3,7-dimethyl-6-octenal (citronellal), b.p. 87–90° (10 mm.), is used after a simple distillation.

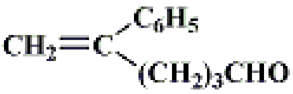
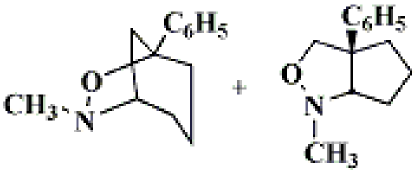
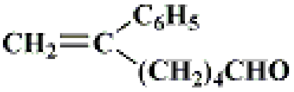
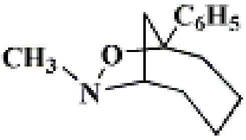
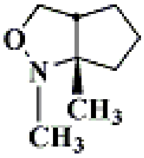
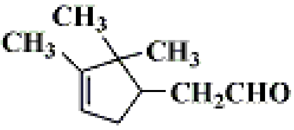
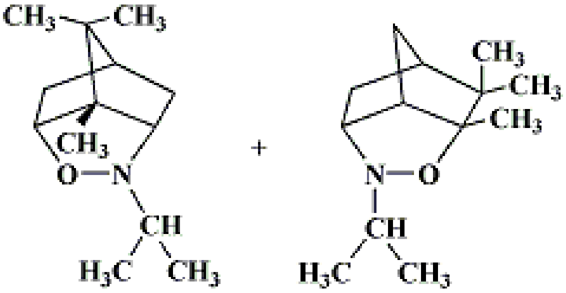
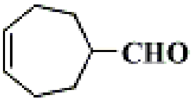
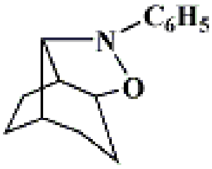
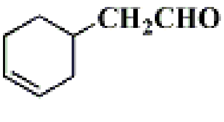
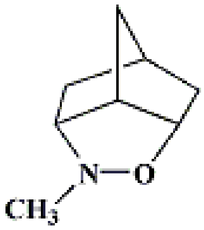
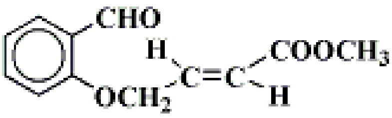
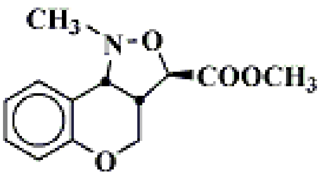
2. This quantity is a 0.72 molar excess. A molar excess of at least 0.5 is needed to maximize the yield.
3. *N*-Methylhydroxylamine hydrochloride, m.p. 83–84°, purchased from Aldrich Chemical Company, Inc., was used directly. Alternatively, the hydrochloride can be prepared by the reduction of nitromethane with zinc dust and ammonium chloride.[2]
4. Water and methanol are removed by this procedure, so that a higher reaction temperature can be achieved.
5. One to four additional extractions improve the yield slightly.
6. The yield is lowered by the presence of 3,7-dimethyl-7-octenal in the technical grade 3,7-dimethyl-6-octenal (citronellal) used.
7. A GC analysis carried out by the submitters using a 1.85 m. × 0.32 cm. stainless-steel column packed with 10% Polyglycol E-20M on Chromosorb W at 150° indicated that the product is a mixture of *trans*,*trans* and *cis*,*trans* stereoisomers in a ratio of 89 : 11. The spectral properties of the product are: IR (thin film) cm^{-1}: 1462, 1387, 1348, 1287, 1277, 1193, 1179, 1136, 1124, 935, 915, 877, 810; ^1H NMR ($CDCl_3$), δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 1.00 (d, *J* = 7, 3H, CH_3), 1.08 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 2.60 (s, 3H, NCH_3).

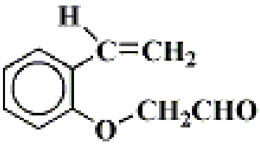
3. Discussion

This procedure is an adaptation[3] of the original method,[4] and avoids the isolation and purification of *N*-methylhydroxylamine. Nitrones undergo 1,3-dipolar cycloadditions with a wide variety of dipolarophiles (see recent review[5]). The intramolecular variation represents a useful synthetic approach, as carbocyclic or heterocyclic rings are generated together with the five-membered isoxazolidines.[6] The intermediate nitrone is usually not preformed (present example), although intermolecular cycloaddition is rarely a problem. *N*-alkyl-, *N*-alkenyl-, and *N*-arylhydroxylamines have been used with aldehydes and ketones to generate the nitrones *in situ*, and some typical examples are listed in Table I. Cyclic azomethine imine oxides are also important substrates for intramolecular cycloadditions.[6]

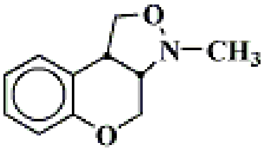
TABLE I
INTRAMOLECULAR1,3-DIPOLARCYCLOADDITIONS OFNITRONES TOALKENES

Carbonyl Compound	Hydroxylamine	Product	Yield (%)
$CH_2{=}CH(CH_2)_3CHO$	CH_3NHOH		41[4]
	C_2H_5NHOH		77[4]

	CH_3NHOH	 9 : 1 ratio	87[15]
	CH_3NHOH		78[15]
	CH_3NHOH		80[7]
	$(CH_3)_2CHNHOH$		70–80[8]
	C_6H_5NHOH		88[9]
	CH_3NHOH		55.4[10]
	CH_3NHOH		80[11]



CH_3NHOH



10[12]

Although isoxazolidines are less basic than the analogous amines, *N*-alkylisoxazolidines can form quaternary ammonium salts. Reductive cleavage of isoxazolidines and the methiodides can be effected with various reagents (zinc–acetic acid, hydrogen–palladium, lithium aluminum hydride), and the yields of 1,3-aminoalcohols are generally excellent.[4] Other reagents that result in modifications of the isoxazolidine ring include peroxyacids,[13] strong bases,[14] triplet photosensitizers,[14] and cyanogen bromide.[15]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Hexahydro-1,3,3,6-tetramethyl-2,1-benzisoxazoline

2,1-Benzisoxazole, 1,3,3a,4,5,6,7,7a-octahydro-1,3,3,6-tetramethyl-

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

methanol (67-56-1)

ammonium chloride (12125-02-9)

hydrogen (1333-74-0)

sodium methoxide (124-41-4)

potassium hydroxide (1310-58-3)

toluene (108-88-3)

zinc (7440-66-6)

palladium (7440-05-3)

Pentane (109-66-0)

hydroxylamine (7803-49-8)

Nitromethane (75-52-5)

Cyanogen bromide (506-68-3)

lithium aluminum hydride (16853-85-3)

3,7-dimethyl-6-octenal, citronellal (106-23-0)

3,7-dimethyl-7-octenal

N-methylhydroxylamine (593-77-1)

N-methylhydroxylamine hydrochloride (4229-44-1)

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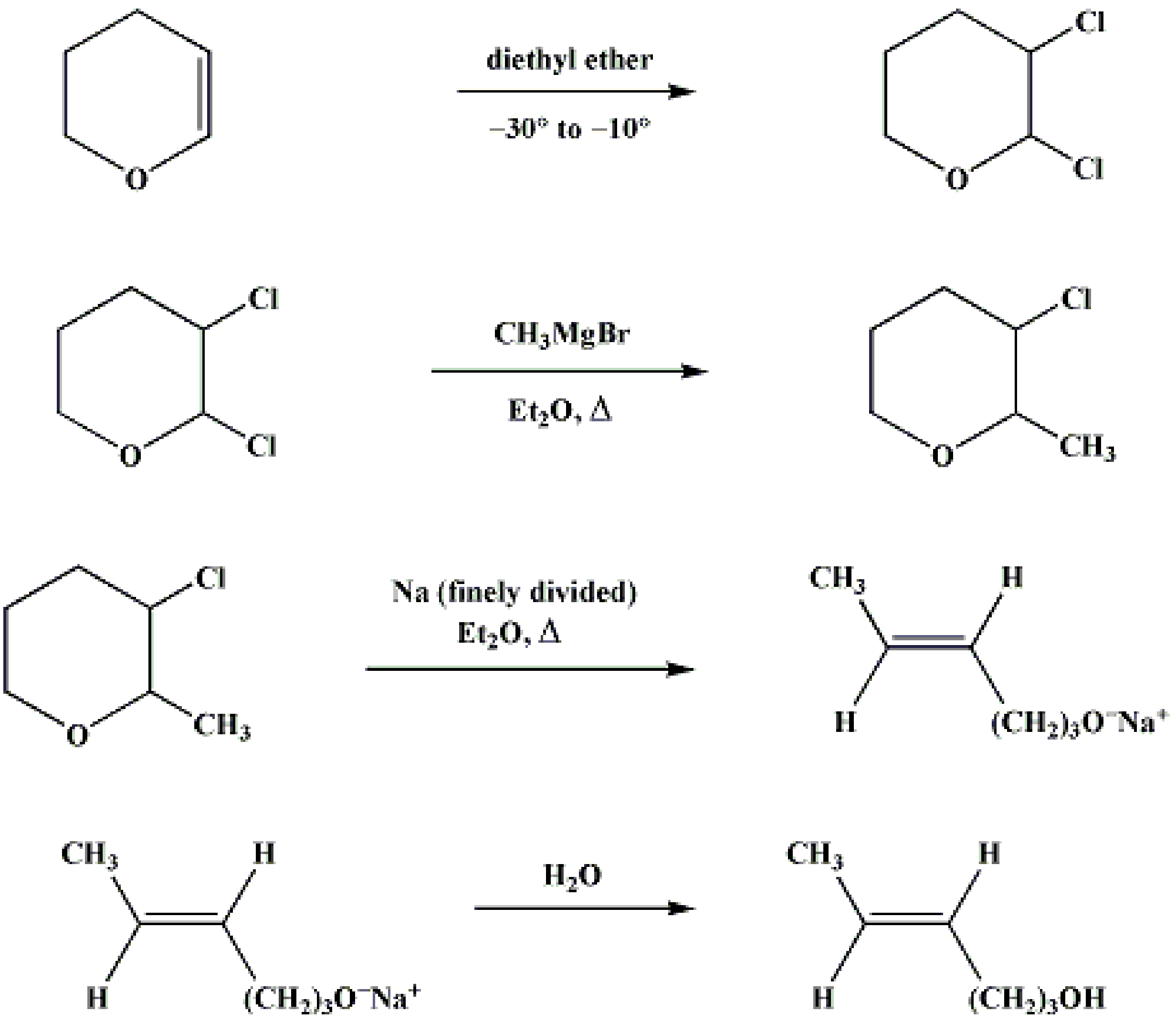
Organic Syntheses, *CV 6*, *675*

(*E*)-4-HEXEN-1-OL



Submitted by Raymond Paul, Olivier Riobé, and Michel Maumy[1].
Checked by Edward J. Zaiko and Herbert O. House.

1. Procedure

Caution! All operations described in this procedure should be performed in an efficient hood, because toxic chlorine and methyl bromide are used in Steps A and B, respectively, and hydrogen is evolved in Step C.

A. *2,3-Dichlorotetrahydropyran*. A 1-l., three-necked, round-bottomed flask fitted with a glass-inlet tube extending nearly to the bottom of the flask, a low-temperature thermometer, an exit tube attached to a calcium chloride drying tube, and a Teflon®-coated magnetic stirring bar is charged with a solution of 118 g. (1.40 moles) of dihydropyran (Note 1) in 400 ml. of anhydrous diethyl ether. While the solution is stirred continuously it is cooled to –30° with an acetone–dry ice bath. Anhydrous

chlorine (Note 2) is passed through the solution and introduced at such a rate that the temperature of the reaction solution does not rise above −10° (Note 3). Completion of the addition process (*ca.* 1 hour) is indicated by a rapid development of a yellow color (excess chlorine) in the reaction solution and a distinct decrease in the temperature of the reaction mixture. When the addition is complete, several drops of dihydropyran are added to discharge the yellow color, and the colorless solution is stored at −30° (Note 4) until it is used in the next step.

B. *3-Chloro-2-methyltetrahydropyran*. A dry, 4-l., three-necked, round-bottomed flask fitted with a powerful mechanical stirrer, a reflux condenser protected by a calcium chloride drying tube, and a gas-inlet tube extending nearly to the bottom of the flask is charged with 51 g. (2.11 g.-atoms) of magnesium turnings and 1.2 l. of anhydrous ether. Methyl bromide (200 g., 2.15 moles) is allowed to distill (Note 5) into the continuously stirred reaction mixture at such a rate as to maintain gentle refluxing. The formation of an ethereal solution of methylmagnesium bromide requires approximately 2 hours. The gas-inlet tube is then replaced with a dry, 1-l. dropping funnel, protected with a calcium chloride drying tube. The reaction mixture is cooled with stirring in an ice–salt bath. The cold, ethereal 2,3-dichlorotetrahydropyran solution is placed in the dropping funnel and added dropwise, with continuous stirring and cooling, to the solution of methylmagnesium bromide at such a rate that the reaction solution does not reflux too vigorously. When this addition is complete, the resulting slurry is refluxed with stirring for 3 hours, then cooled in an ice bath. To the resulting cold (0°), vigorously stirred suspension is slowly added 900 ml. of cold 15% hydrochloric acid. The organic layer is separated, and the aqueous phase is extracted with two 200-ml. portions of ether. The combined ethereal solution is dried over anhydrous potassium carbonate, then concentrated by distillation at atmospheric pressure. The residual liquid is distilled under reduced pressure through a 12-cm. Vigreux column, separating 122–136 g. (65–72%) of a mixture of *cis-* and *trans*-3-chloro-2-methyltetrahydropyran as a colorless liquid, boiling over the range 48–95° (17–18 mm.) (Note 6), sufficiently pure for use in the next step (Note 7).

C. (E)-4-*Hexen*-1-*ol.* A dry, 3-l., three-necked, round-bottomed flask fitted with a powerful mechanical stirrer, a 500-ml. dropping funnel, and a reflux condenser protected by a calcium chloride drying tube is charged with 53 g. (2.3 g.-atoms) of finely divided sodium (Note 8) and 1.2 l. of anhydrous ether. 3-Chloro-2-methyltetrahydropyran (136 g., 1.01 moles) is added dropwise to the rapidly stirred, ethereal suspension of sodium. When the reaction commences (Note 9), the reaction mixture turns blue. After the reaction has started, the remaining chloro-ether is added, dropwise and with stirring over approximately 90 minutes, at such a rate that a brisk reflux is maintained. The resulting mixture, which remains dark blue throughout the addition of the chloro-ether, is refluxed with stirring for an additional hour (Note 10), then cooled in an ice–salt bath. The cold reaction mixture is stirred vigorously as 30 ml. of absolute ethanol is added dropwise and with caution to the reaction mixture, after which, 700 ml. of water is added dropwise, with stirring and cooling. After the organic layer has been separated, the aqueous phase is extracted with two 200-ml.

portions of ether, and the combined ether extracts are dried over anhydrous potassium carbonate and concentrated by distillation at atmospheric pressure. The residual liquid is distilled under reduced pressure through a 12-cm. Vigreux column, separating 89–94 g. (88–93%) of (*E*)-4-hexen-1-ol as a colorless liquid, b.p. 70–74° (19 mm.), n_D^{25} 1.4389 (Note 11).

2. Notes

1. Dihydropyran (purchased from Eastman Organic Chemicals) was distilled before use; b.p. 84–86°.
2. The chlorine, obtained from a compressed gas cylinder, was passed through a wash bottle containing concentrated sulfuric acid before being passed into the reaction solution.
3. This addition of chlorine has been carried out at –5–0°, but the yield is slightly decreased and the time required for the addition is greatly extended.
4. 2,3-Dichlorotetrahydropyran may be stored for a few hours at 0°, but the yield in the subsequent step is decreased and partial decomposition may have occurred.
5. The checkers employed a sealed ampoule of methyl bromide (b.p. 5°, obtained from Eastman Organic Chemicals), which was cooled to 0° and opened. After a boiling chip had been added to the ampoule, it was connected to the gas-inlet tube of the reaction apparatus with rubber tubing and warmed in a water bath to distill the methyl bromide into the reaction vessel.
6. The submitters report that the boiling point of this mixture is 50–70° (18 mm.) or 60–80° (45 mm.), $n_D^{19.5}$ 1.4596. However, the checkers found that the product obtained from the initial distillation should be collected over a wider range [45–90° (17–18 mm.)], because the boiling point of the final portion of the product is raised by the higher molecular weight residue that remains in the stillpot. The isomers have been isolated by fractional distillation through a 90-cm. Crismer column.[2] The physical constants for the lower boiling *trans*-isomer: b.p. 56° (23 mm.), n_D^{21} 1.4543; for the higher-boiling *cis*-isomer: b.p. 72° (23 mm.), n_D^{21} 1.4646.
7. The checkers found that a fraction, b.p. 45–71° (18 mm.), had the following spectral properties; IR (CCl_4): no absorption in the 3300–1600 $cm.^{-1}$ region attributable to OH, C=O, or C=C vibrations; ^1H NMR ($CDCl_3$), δ (multiplicity, number of protons, assignment): 1.0–2.5 (m, 7H, CH_3 and $2CH_2$), 3.1–4.2 (m, 4H, $CHCl$ and CH_2OCH). TLC analysis of this fraction on silica gel plates using chloroform as eluent indicated the presence of a major component (the *cis*- and *trans*-isomers), R_f = 0.60, and a minor unidentified component, R_f = 0.14.
8. The finely divided sodium was prepared under boiling toluene or boiling xylene by agitation of the molten sodium with a Vibromixer. After the dispersion had cooled and the sodium had settled, the toluene or xylene was decanted, and the finely divided sodium was washed with two portions of anhydrous ether.

9. The reaction generally commences with the addition of approximately 5% of the chloro-ether; if not, the mixture should be heated to boiling to initiate the reaction. If a much larger proportion of the chloro-ether has been added before the reaction commences, initiation of the reaction may be too violent to control. The *cis*-isomer was found to be more reactive toward sodium than the *trans*-isomer.

10. The submitters reported that the blue color of the mixture fades during the reflux period, leaving a cream-white colored reaction mixture. In the checkers' runs (performed under a nitrogen atmosphere) the blue color was not discharged until ethanol was added to the reaction mixture.

11. The product exhibits the following spectral properties; IR (CCl_4) $cm.^{-1}$: 3620 (OH), 3330 broad (associated OH) 970 [(*E*) CH=CH]; ^{1}H NMR ($CDCl_3$) δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 1.3–2.4 (m, 4H, 2CH_2), 1.64 (d of d, *J* = 1 and *J* = 5, 3H, CH_3), 3.05 (broad, 1H, O*H*), 3.62 (t, *J* = 6.5, 2H, CH_2O), 5.1–5.9 (m, 2H, C*H*=C*H*); mass spectrum *m/e* (relative intensity): 100 (M, 3), 82 (38), 67 (100), 55 (47), 54 (22), 41 (95), 39 (36), and 31 (28). The submitters report that their product exhibited a single GC peak on several columns. GC analysis of the sample obtained by the checkers using a 6-m. column packed with 1,2,3-tris(β-cyanoethoxy)propane on Chromosorb P revealed one major peak having a retention time of 20.2 minutes and a second minor peak (6% of the total peak area) having a retention time of 22.6 minutes. The mass spectrum of this minor peak exhibited the following abundant peaks: *m/e* (relative intensity), 100 (M, 3) 82 (38), 67 (100), 55 (42), 54 (25), 41 (97), 40 (100), 39 (35), and 31 (30). Hence, this minor component appears to be an isomer of the major product, (*E*)-4-hexen-1-ol.

3. Discussion

This procedure illustrates a general method for the stereoselective synthesis of (*E*)-disubstituted alkenyl alcohols. The reductive elimination of cyclic β-halo-ethers with metals was first introduced by Paul,[3] and one example, the conversion of tetrahydrofurfuryl chloride to 4-penten-1-ol, is described in an earlier volume of this series.[4] In 1947 Paul and Riobé[5] prepared 4-nonen-1-ol by this method; subsequently, the general method has been used to obtain alkenyl alcohols with other substitution patterns.[2,6,7,8] (*E*)-4-Hexen-1-ol has been prepared by this method[9] and in lower yield by an analogous reaction with 3-bromo-2-methyltetrahydropyran.[10]

The coupling reaction of 2,3-dichlorotetrahydropyran and Grignard reagents, RMgBr, has been effected with a number of reagents including those where R = CH_3,[2] C_2H_5,[2] $CH_3CH_2CH_2$,[2] $CH_3(CH_2)_2CH_2$,[11] C_6H_5,[11] $CH_3(CH_2)_4CH_2$,[12] β-cyclohexenylethyl,[6] β-phenylethyl,[7,13,14] vinyl,[15] and ethynyl.[16]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 586

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ether, diethyl ether (60-29-7)

hydrogen (1333-74-0)

chloroform (67-66-3)

magnesium turnings (7439-95-4)

nitrogen (7727-37-9)

chlorine (7782-50-5)

toluene (108-88-3)

sodium (13966-32-0)

methyl bromide (74-83-9)

xylene (106-42-3)

methylmagnesium bromide (75-16-1)

dihydropyran

4-Penten-1-ol (821-09-0)

Tetrahydrofurfuryl chloride (3003-84-7)

vinyl (2669-89-8)

2,3-Dichlorotetrahydropyran (5631-95-8)

3-Chloro-2-methyltetrahydropyran (53107-05-4)

4-nonen-1-ol

3-bromo-2-methyltetrahydropyran (156051-16-0)

β-cyclohexenylethyl

β-phenylethyl

(E)-4-Hexen-1-ol (6126-50-7)

trans-3-chloro-2-methyltetrahydropyran

cis-3-chloro-2-methyltetrahydropyran (53107-04-3)

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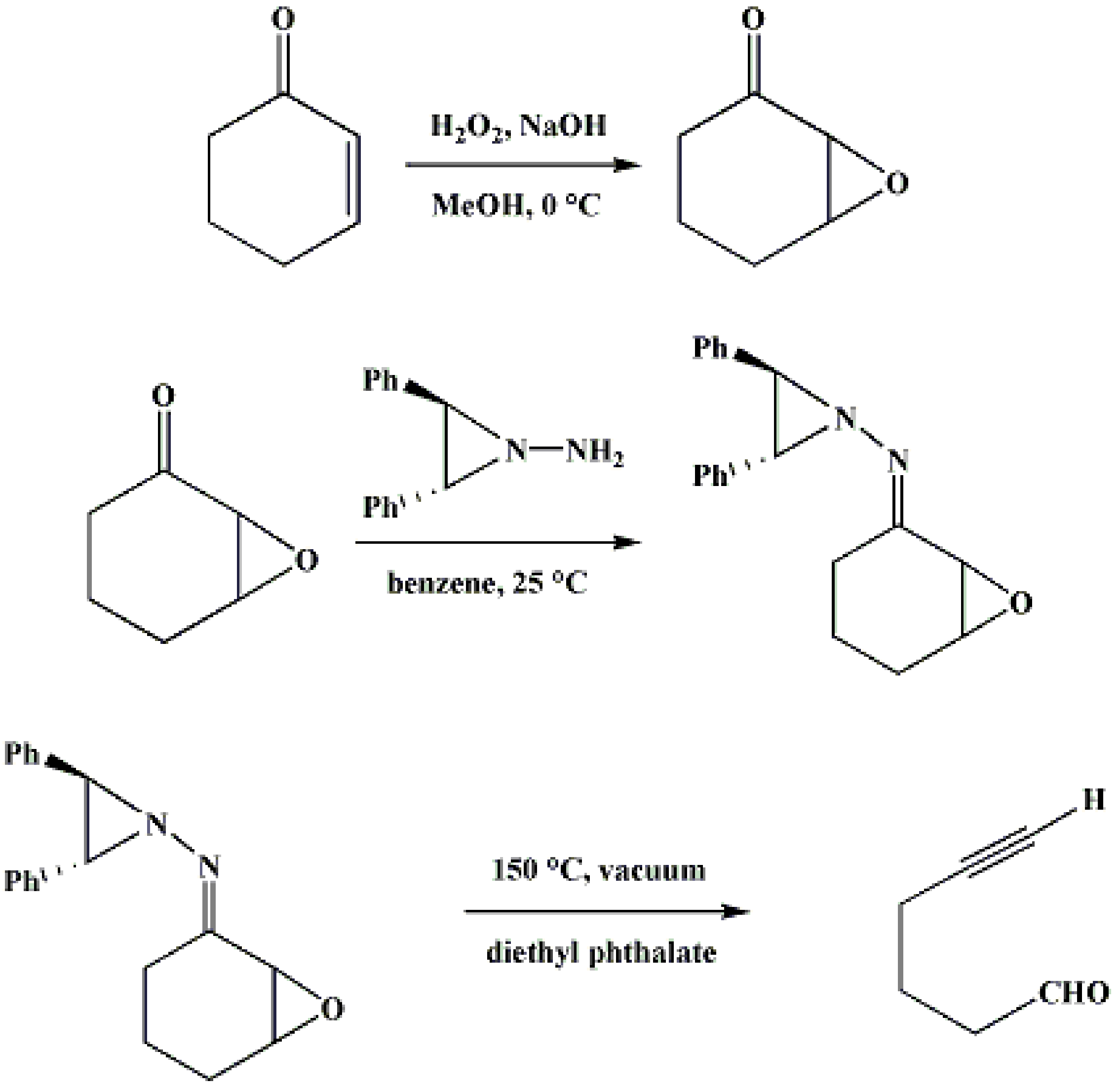
Organic Syntheses, CV 6, 679

FRAGMENTATION OF α,β-EPOXYKETONES TO ACETYLENIC ALDEHYDES AND KETONES: PREPARATION OF 2,3-EPOXYCYCLOHEXANONE AND ITS FRAGMENTATION TO 5-HEXYNAL

[5-Hexynal]



Submitted by Dorothee Felix, Claude Wintner, and A. Eschenmoser[1].
Checked by Robert E. Ireland and David M. Walba.

1. Procedure

A. *2,3-Epoxycyclohexanone*. A 300-ml., three-necked, round-bottomed flask equipped with a magnetic stirring bar and a thermometer is charged with a solution of 9.60 g. (0.100 mole) of 2-cyclohexen-1-one (Note 1) in 100 ml. of methanol. After the solution is cooled to 1–3° in an ice bath, 34 g. (30 ml., 0.30 mole) of 30% aqueous

hydrogen peroxide (Note 2) is added. The mixture is stirred vigorously and kept well cooled in the ice bath, and 0.15 ml. (0.75 mmole) of 20% aqueous sodium hydroxide is added in one portion. The temperature of the reaction mixture rises to approximately 30° within a few minutes then falls again to 3–5°. Fifteen minutes after addition of the sodium hydroxide solution, the cold reaction mixture is poured into a 1-l. separatory funnel containing 150 g. of ice and 200 ml. of saturated aqueous sodium chloride. The resulting suspension is extracted with 200 ml. of dichloromethane. After two further extractions of the aqueous layer with 150-ml. portions of dichloromethane, the combined organic extracts are dried over anhydrous magnesium sulfate, and the solvent is removed by distillation through a 30-cm. Vigreux column (Note 3). Distillation of the residue through a 15-cm. Vigreux column under reduced pressure affords a forerun fraction of approximately 0.7 g., b.p. 60–75° (11 mm.) (Note 4), then 8.4–8.6 g. (75–77% of pure 2,3-epoxycyclohexanone (Note 5) and (Note 6), b.p. 75–77° (11 mm.), n_D^{20} 1.4748, d_4^{20} 1.129.

B. 5-*Hexynal*. To a solution of 5.60 g. (0.0500 mole) of 2,3-epoxycyclohexanone in 120 ml. of benzene in a 500-ml., round-bottomed flask is added 10.82 g. (0.5152 mole) of *trans*-1-amino-2,3-diphenylaziridine [*Org. Synth.*, **Coll. Vol. 6**, 56 (1988)]. Initially, after brief swirling at room temperature, the reaction mixture is a colorless, homogeneous solution; however it rapidly turns yellow and cloudy due to separation of water. After 2 hours the benzene and water are removed as an azeotrope on a rotary evaporator with the bath maintained at approximately 30°. The resulting crude mixture of diastereomeric hydrazones weighs 15.4 g. (Note 7) and is subjected directly to fragmentation (Note 8).

The fragmentation is conveniently performed in a 100-ml., wide-necked (Note 9), round-bottomed flask with a side arm. The side arm is equipped with a capillary fitted with a balloon filled with argon or nitrogen. The capillary should be set so that it does not dip into the reaction mixture. The reaction flask is equipped with a magnetic stirring bar and fitted with a short assembly for distillation under reduced pressure. A dropping funnel extends through the stillhead to a level about that of the neck of the flask, and the receiver is cooled in an ice bath. A trap is positioned between the receiver and the vacuum source and cooled in a 2-propanol–dry ice mixture. The reaction flask is immersed in an oil bath at 150–155°, and the apparatus is evacuated to a pressure of 11 mm. The crude hydrazone mixture is dissolved in 20 ml. of diethyl phthalate (Note 10) and carefully added in small portions, from the funnel, into the heated flask, with the stirrer in operation. There is a rapid evolution of nitrogen, and 5-hexynal begins to distil. Addition of the entire hydrazone solution requires approximately 2 hours, after which the funnel is washed with 5 ml. of diethyl phthalate, and the temperature of the reaction flask is raised to 160–165°. The reaction is complete when there is no further evolution of nitrogen. The last traces of product can be driven into the receiver by warming the stillhead with a heat gun.

The contents of the receiver and trap are combined with the aid of a few drops of dichloromethane and distilled through a 15-cm. Vigreux column under reduced

pressure. After only a few drops of forerun, 2.87–3.17 g. (60–66%) of 5-hexynal, b.p. 61–62° (30 mm.), n_D^{20} 1.4447, d_4^{20} 0.875 (Note 11),(Note 12),(Note 13), is collected. GC analysis (Note 14) shows this material to contain 3–5% of unidentified impurities with longer retention times (Note 15).

2. Notes

1. 2-Cyclohexen-1-one is easily prepared by a two-step procedure from cyclohexane-1,3-dione as described in *Org. Synth.*, **Coll. Vol. 5**, 294, 539, (1973). It is available from Fluka AG CH-9470 Buchs.
2. A brand name of this reagent is Merck Perhydrol.
3. To avoid loss of the volatile epoxide, removal of the dichloromethane on a rotary evaporator is not recommended.
4. GC analysis at 120° on a 2.2-m. column packed with 10% diethylene glycol succinate showed the forerun fraction to contain approximately 50% product. The other fraction is pure 2,3-epoxycyclohexanone.
5. The IR [($CHCl_3$) 1710 cm.$^{-1}$ strong (C=O)] and UV [(C_2H_5OH) max. 298 nm. (ε 15)] spectra demonstrate the absence of the enone system. ^{1}H NMR spectrum, δ (multiplicity, coupling constant *J* in Hz., number of protons): 1.5–3.0 (m, 6H), 3.32 (d, *J* = 4, 1H), 3.60 (m, 1H).
6. A further 1.06 g. (9.4%) of product may be obtained by Kugelrohr distillation of the residue.
7. This crude product does not show carbonyl absorption at 1710 cm.$^{-1}$ in the IR spectrum due to unreacted 2,3-epoxycyclohexanone.
8. If the crude hydrazone mixture is not be used immediately, it must be stored in a refrigerator.
9. (*E*)-Stilbene sublimes during the pyrolysis and may block a narrow aperture.
10. "Pract"-grade diethyl phthalate (obtainable from Fluka AG) should be redistilled at 126–129° (1 mm.) before use. It is stable under the reaction conditions and does not co-distil with 5-hexynal.
11. 5-Hexynal is very susceptible to air oxidation.
12. The product has the following IR spectrum cm.$^{-1}$: 3310 (C≡CH), 2725 (CH=O), 2115 (C≡C), 1720 (C=O).
13. Use of a Kugelrohr (70–80°, 30 mm.) is also satisfactory.
14. GC analysis was performed on a 2.2-m. 10% diethylene glycol succinate column at 80°.
15. The checkers found that GC analysis of one sample using a 3055 cm. by 0.3 cm. column packed with 10% SF-96 on Chromosorb P operated at 70° with a 60 ml./minute helium carrier gas flow rate gave five minor impurity peaks, two at shorter retention times, and three at longer retention times. None of these impurities was present in greater than 1.1%; total impurities were 3%.

3. Discussion

2,3-Epoxycyclohexanone has been prepared in 30% yield[2] by epoxidation of 2-cyclohexen-1-one with alkaline hydrogen peroxide, using a procedure described for isophorone oxide (4,4,6-trimethyl-7-oxabicyclo[4.1.0]heptan-2-one).[3] A better yield (66%) was obtained using *tert*-butyl hydroperoxide and Triton B in benzene.[4] The procedure described here is simple and rapid.

The *N*-aminoaziridine version[5] of the α,β-epoxyketone alkynone fragmentation is a possible alternative in situations where the simple tosylhydrazone version[6,7] fails. The tosylhydrazone method often gives good yields at low reaction temperatures, but it tends to be unsuccessful with the epoxides of acyclic enones or those not fully substituted at the β-carbon atom. For example, it has been reported[7] that 2,3-epoxycyclohexanone does not produce 5-hexynal by the tosylhydrazone route. The *N*-aminoaziridine method can also be recommended for the preparation of acetylenic aldehydes as well as ketones.

Both *trans*-1-amino-2,3-diphenylaziridine and 1-amino-2-phenylaziridine give α,β-epoxyhydrazones that fragment in the desired manner between 100° and 200°, the choice of reagent being dictated by the ease of separation of the alkynone from the by-products, (*E*)-stilbene and styrene, respectively. The diphenylaziridine is especially useful when the alkynone is relatively volatile and easily separable by distillation from (*E*)-stilbene, as is the case in the present example. The phenylaziridine is less bulky and more stable to acid than the diphenyl derivative, and may be tried with sterically hindered epoxyketones. The fragmentation is often run in an inert, high-boiling solvent to reduce resinification, but in many cases it can be achieved by pyrolysis of the neat, crude hydrazone with concomitant distillation of the product.

The limitations of the reaction have not been systematically investigated, but the inherent lability of the aziridines can be expected to become troublesome in the case of epoxyketones which do not readily undergo hydrazone formation. The use of acid catalysis is curtailed by the instability of the aziridines, particularly the diphenylaziridine, in acidic media. Because of their solvolytic lability, the hydrazones are best formed in inert solvents: a procedure proved helpful in some cases is to mix the aziridine and the epoxyketone in anhydrous benzene, then to remove the benzene on a rotary evaporator at room temperature; water formed in the reaction is thus removed as the azeotrope. This process is repeated, if necessary, until no carbonyl band remains in the IR spectrum of the residue.

Additional examples and a mechanistic discussion are available.[5] Borrevang[8] has reported a closely related fragmentation involving diazirine derivatives of cyclic α,β-epoxyketones.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 56

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrazone

Triton B

Benzene (71-43-2)

methanol (67-56-1)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

2-propanol (67-63-0)

hydrogen peroxide (7722-84-1)

dichloromethane (75-09-2)

styrene (100-42-5)

magnesium sulfate (7487-88-9)

aziridine (9002-98-6)

cyclohexane-1,3-dione (504-02-9)

diethyl phthalate (84-66-2)

Isophorone oxide, 4,4,6-trimethyl-7-oxabicyclo[4.1.0]heptan-2-one (10276-21-8)

helium (7440-59-7)

2-cyclohexen-1-one (930-68-7)

diethylene glycol succinate

N-aminoaziridine

1-Amino-2-phenylaziridine (19615-20-4)

tert-butyl hydroperoxide (75-91-2)

2,3-Epoxycyclohexanone (6705-49-3)

5-Hexynal (29329-03-1)

diphenylaziridine

phenylaziridine (696-18-4)

(E)-stilbene (103-30-0)

trans-1-Amino-2,3-diphenylaziridine (28161-60-6)

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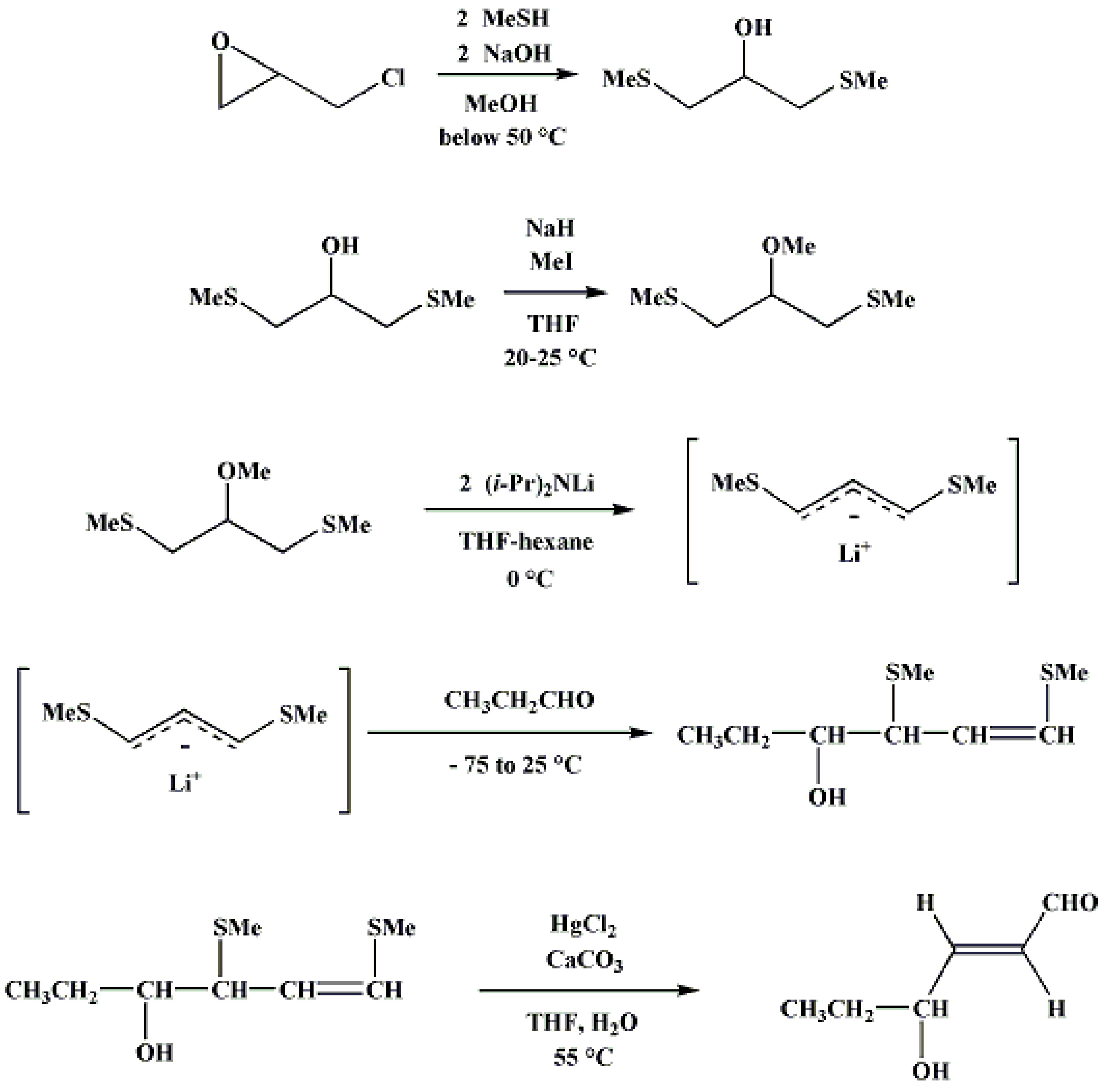
Organic Syntheses, CV 6, 683

γ-HYDROXY-α,β-UNSATURATED ALDEHYDES *VIA* 1,3-BIS (METHYLTHIO)ALLYLLITHIUM: *trans*-4-HYDROXY-2-HEXENAL

[2-Hexenal, 4-hydroxy-]



Submitted by Bruce W. Erickson[1]
Checked by Susumu Kamata and Wataru Nagata.

1. Procedure

Caution! This preparation requires the use of a good hood.

Methyl iodide, in high concentrations for short periods or in low concentrations for long periods, can cause serious toxic effects in the central nervous system. Accordingly, the American Conference of Governmental Industrial Hygienists[2] has set 5 p.p.m., a level which cannot be detected by smell, as the highest average concentration in air to which workers should be exposed for long periods. The preparation and use of methyl iodide should always be performed in a well-ventilated fume hood. Since the liquid can be absorbed through the skin, care should be taken to prevent contact.

A. *1,3-Bis(methylthio)-2-propanol*. A solution of 44 g. (1.1 moles) of sodium hydroxide in 300 ml. of methanol is placed in a 1-l., four-necked flask equipped with a dry ice reflux condenser, a mechanical stirrer, a thermometer, a gas-inlet, and an ice bath. While the solution is stirred and cooled, 50 g. (56 ml., 1.0 mole) of methanethiol (Note 1) is distilled from a lecture bottle into the solution at such a rate that the temperature is maintained below 20°. The gas-inlet is then replaced with a 60-ml., glass-stoppered, pressure-equalizing dropping funnel, and, while the reaction mixture is stirred and cooled, 44.4 g. (37.6 ml., 0.480 mole) of epichlorohydrin (Note 2) is added dropwise at such a rate that the temperature is maintained below 50° (Note 3).

The reaction mixture is stirred at 25° for 1 hour, diluted with 500 ml. of water, and extracted with two 200-ml. portions of diethyl ether. The combined extract is washed with five 100-ml. portions of water and 100 ml. of saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate (Note 4), filtered, and evaporated at 50° (30 mm.). The residual liquid is distilled under reduced pressure without a column (Note 5), and the fraction boiling at 110–111° (7 mm.) or 101–102° (4 mm.) affords 61.0–63.6 g. (84–87%) of 1,3-bis(methylthio)-2-propanol (Note 6), (Note 7).

B. *1,3-Bis(methylthio)-2-methoxypropane*. A dry, 1-l., three-necked flask equipped with a mechanical stirrer, a 60-ml. pressure-equalizing dropping funnel, and a thermometer is charged with 13.8 g. (0.339 mole) of sodium hydride dispersed in mineral oil (Note 8). The mineral oil is removed by washing the dispersion with five 100-ml. portions of hexane (Note 9), which is removed with a pipet after the sodium hydride has been allowed to settle (Note 10).

When most of the hexane has been removed, 500 ml. of dry tetrahydrofuran (Note 11) and (Note 12) is added. While the reaction mixture is stirred, 33.4 g. (0.220 mole) of 1,3-bis(methylthio)-2-propanol is added dropwise over 15 minutes. After the evolution of hydrogen ceases, the stirred mixture is cooled with a water bath. When the mixture reaches 20°, 34.2 g. (15.0 ml., 0.241 mole) of methyl iodide (Note 2) is added dropwise over 5 minutes. The dropping funnel is replaced with a glass stopper, and the reaction mixture is stirred at 20–25° for 24 hours.

The mixture is concentrated to about 200 ml. at 50° (30 mm.), diluted with 200 ml. of ether, and washed with 100 ml. of saturated aqueous sodium chloride, two 100-ml. portions of 0.5 *M* aqueous ammonium chloride, and 100 ml. of saturated aqueous sodium chloride. Each of the aqueous washes is extracted with the same 100-ml. portion of ether. The combined ethereal solution is dried over anhydrous magnesium sulfate (Note 4), filtered, and evaporated at 25° (10 mm). The residual material is distilled under reduced pressure without a column (Note 5), and the fraction boiling at 96–97° (9 mm.) or 89–90° (7 mm.) affords 31.4–35.7 g. (86–97%) of 1,3-bis(methylthio)-2-methoxypropane (Note 13), (Note 14).

C. *1,3-Bis(methylthio)-1-hexen-4-ol*. A dry, 500-ml., three-necked flask containing a Teflon®-coated magnetic stirring bar and equipped with a 100-ml., pressure-equalizing dropping funnel, a thermometer, and a side arm connected to a nitrogen bubbler system is charged with 11.65 g. (0.1153 mole) of diisopropylamine (Note 15) and 175 ml. of dry tetrahydrofuran (Note 11). The

flask is flushed with nitrogen, and a slight positive pressure is maintained with a slow stream of nitrogen during the following operation. The solution is magnetically stirred and cooled to about −75° with an acetone-dry ice bath. After 15 minutes, 77.0 ml. (0.112 mole) of 1.45 *M* solution of *n*-butyllithium butyllithium in hexane (Note 16) is added dropwise, using the pressure-equalizing dropping funnel. While the resulting solution of lithium diisopropylamide is stirred at −75°, 9.15 g. (0.0551 mole) of 1,3-bis(methylthio)-2-methoxypropane is added through a dropping funnel. The acetone–dry ice bath is replaced with an ice-water bath, and the solution is stirred at 0° for 2.5 hours. The solution slowly becomes deep purple in color as 1,3-bis(methylthio)allyllithium is generated (Note 17).

The solution is stirred and cooled to −75° with an acetone–dry ice bath, and 2.90 g. (0.0500 mole) of propionaldehyde (Note 18) is added through a dropping funnel. The solution is stirred at −75° for 5 minutes. The acetone–dry ice bath is replaced with a water bath, and the solution is stirred at 20° for 30 minutes. The solution is diluted with 250 ml. of ether and washed with two 100-ml. portions of 5 *M* aqueous ammonium chloride, two 100-ml. portions of water, and 100 ml. of saturated aqueous sodium chloride. Each of the aqueous washes is extracted with the same 250-ml. portion of ether. The combined ethereal solution is dried over anhydrous magnesium sulfate (Note 4), filtered, and evaporated at 40° (25 mm.). The residual liquid is distilled under reduced pressure through a 10 × 0.7 cm., unpacked, vacuum-jacketed column, and the material boiling at 93–98° (2 mm.) furnishes 7.90–7.99 g. (82–83%) of 1,3-bis(methylthio)-1-hexen-4-ol (Note 19), (Note 20).

D. trans-4-*Hydroxy*-2-*hexenal*. A 500-ml., one-necked flask containing a Teflon®-coated magnetic stirring bar is charged with 3.85 g. (0.0200 mole) of 1,3-bis(methylthio)-1-hexen-4-ol, 80 ml. of tetrahydrofuran (Note 11), and 6.00 g. (0.0600 mole) of powdered calcium carbonate. The mixture is stirred, and a solution of 16.4 g. (0.0603 mole) of mercury (II) chloride in 140 ml. of tetrahydrofuran and 40 ml. of water is added. The mixture is stirred and heated at 50–55° with a water bath for 15 hours. The reaction mixture is filtered (Note 21) with suction through a pad of diatomaceous earth in a sintered-glass funnel (Note 22). The filter cake is washed with a mixture of 200 ml. of pentane and 200 ml. of dichloromethane. The combined filtrate is washed with three 100-ml. portions of saturated aqueous sodium chloride. Each of the aqueous washes is extracted with a mixture of 100 ml. of pentane and 100 ml. of dichloromethane. The combined organic solution is dried over anhydrous magnesium sulfate (Note 4), filtered, and evaporated at 25° (25 mm.). When almost all the solvent is removed, the residue is slurried with a mixture of 4 ml. of chloroform and 1 ml. of ether as soon as possible. Purification of the product is effected by chromatography on a 3 × 20 cm. column of 50 g. of silicic acid (Note 23) by elution with 4:1 chloroform–ether. Each fraction (50 ml.) is monitored by TLC, and the fractions containing *trans*-4-hydroxy-2-hexenal uncontaminated with any by-product are collected. The solvent is evaporated at 25° (25 mm. and 1 mm.), yielding 1.37–1.41 g. (60–62%) of product, pure by GC (Note 24) and ^{1}H NMR spectroscopy (Note 25). Distillation without a column yields 1.32 g. (58%) of *trans*-4-hydroxy-2-hexenal, b.p. 48–51° (0.01–0.03 mm.), 2,4-dinitrophenylhydrazone, m.p. 198–199° (Note 26).

2. Notes

1. The submitter used methanethiol (b.p. 8°) obtained from Matheson Gas Products. The weight of the methanethiol distilled from the lecture bottle into the reaction flask was measured by difference. The pungent odor of this mercaptan is contained by slow distillation of the reagent into the flask and the use of a well-ventilated hood. The checkers used methanethiol (b.p. 8°, d_4^0 0.8948) obtained from Toyo Chemical Industries Co. (Japan) and

changed the above procedure as follows: methanethiol distilled from the lecture bottle was first trapped in an ice-cooled graduated flask equipped with a gas-inlet and a dry ice reflux condenser; 56 ml. of the liquid was then redistilled into the reaction mixture.

2. The submitter used reagent grade material obtained from Eastman Kodak Co., and the checkers used reagent grade material from Kanto Chemical Co., Inc. (Japan).

3. A large quantity of sodium chloride precipitates during addition of the epichlorohydrin.

4. The checkers used anhydrous sodium sulfate as a drying agent instead of anhydrous magnesium sulfate.

5. The checkers used a 15 × 1 cm., unpacked, vacuum-jacketed column for the distillation.

6. For GC analysis of the product, the submitter used a 3 ft. × 0.125 in. stainless-steel column of 5% LAC-446 (cross-linked diethylene glycol-adipic ester) on Diatoport S (60–80 mesh), swept with prepurified nitrogen at 30 ml. per minute. The retention time was 1.75 minutes at 140°. The checkers used a 1 m. × 4 mm. glass column of 5% OV-17 on Chromosorb W (60–80 mesh), swept with prepurified nitrogen at 90 ml. per minute. The retention time was 2.65 minutes at 150°.

7. The ^{1}H NMR spectrum (CCl_4) of the product [$(CH_3^a\ SCH_2^b\ )_2CH^cOH^d$] shows peaks at δ 2.12 (s, 6H, H^a), 2.63 (d, $J_{b,c}$ = 6 Hz., 4H, H^b), 3.86 (pentet, 1H, H^c), and 3.78 (s, 1H, H^d).

8. Sodium hydride was obtained as a 59% dispersion in mineral oil from Metal Hydrides, Inc.

9. The submitter used a reagent grade mixture of isomeric hexanes (b.p. 68–70°) obtained from Fisher Scientific Co., and the checkers used the same grade mixture of isomeric hexanes obtained from Wako Pure Chemical Industries Ltd. (Japan).

10. About 90% of the mineral oil was removed by this procedure. Because some sodium hydride is lost in the pipet, an excess is initially employed.

11. The submitter used tetrahydrofuran obtained from Fisher Chemical Co. and distilled from lithium aluminium hydride under nitrogen shortly before use; see *Org. Synth.*, **Coll. Vol. 5**, 926 (1973) for warning concerning the purification of tetrahydrofuran. The checkers used tetrahydrofuran obtained from Wako Pure Chemical Industries Ltd. (Japan) and distilled from sodium hydride under nitrogen shortly before use.

12. When dry ether was used in place of dry tetrahydrofuran, only about 15% of the alcohol was methylated in 36 hours.

13. Using the columns described in (Note 6), the retention times were 0.67 minute at 140° and 1.00 minute at 120° (submitter) and 2.30 minutes at 150° and 7.05 minutes at 120° (checkers), respectively.

14. The ^{1}H NMR spectrum (CCl_4) of the product [$(CH_3^a\ SCH_2^b\ )_2CH^cOCH_3^d$] exhibits absorption at δ 2.13 (s, 6H, H^a), 2.68 (d, $J_{b,c}$ = 5.4 Hz., 4H, H^b), 3.41 (s, 3H, H^d), and 3.50 (pentet, 1H, H^c).

15. The submitter used diisopropylamine from Aldrich Chemical Co., and the checkers used diisopropylamine from Wako Pure Chemical Industries Ltd. (Japan). It was distilled from calcium hydride before use.

16. The submitter used a 1.24 *M* solution of *n*-butyllithium in pentane obtained from Foot Mineral Co., and the checkers used a 1.45 *M* solution of *n*-butyllithium in hexane obtained from Wako Pure Chemical Industries Ltd. (Japan). The nominal titer of active alkyl on the bottle agreed well with the value found by titration[3] with 0.80 *M* (submitter) or 0.50 *M* (checkers) solution of 2-butanol in xylene using 1,10-phenanthroline as indicator.

17. Nearly quantitative generation of 1,3-bis(methylthio)allyllithium was proved, as this solution yielded 1,3-bis(methylthio)propene (88–89%) and 1,3-bis(methylthio)-1-butene (89%) by reaction with methanol and methyl iodide, respectively. The checkers found that

lithium diisopropylamide can be replaced by *n*-butyllithium without any trouble for the generation of 1,3-bis(methylthio)allyllithium, simplifying the procedure considerably at least in this particular case. Subsequent reaction with propionaldehyde gave 1,3-bis (methylthio)-1-hexen-4-ol in 85% yield, and no appreciable amount of by-product, such as the addition product of *n*-butyllithium with propionaldehyde or with the intermediate 1,3-bis (methylthio)propene, was formed.

18. The submitter used propionaldehyde from Aldrich Chemical Co., and the checkers used material obtained from Tokyo Chemical Industry Co. Ltd. (Japan). It was distilled from calcium hydride shortly before use.

19. For GC analysis of the products, the submitter used a 3 ft. × 0.125 in. stainless-steel column of 5% LAC-446 (cross-linked diethylene glycol-adipic ester) on Diatoport S (60–80 mesh), heated at 140° and swept with prepurified nitrogen at 30 ml. per minute. The four isomers were observed as three peaks at retention times of 3.08, 3.69, and 4.07 minutes. The checkers used a 1 m. × 4 mm. glass column of 10% DEGS on Gas Chrome Q (60–80 mesh), heated at 200° and swept with prepurified nitrogen at 75 ml. per minute. The four isomers were observed at retention times of 3.30, 3.85, 4.10, and 5.20 minutes.

20. The ^{1}H NMR spectrum (CCl_4) of the product [$CH^a(SCH_3^b)=CH^cCH^d(SCH_3^e)-CH^f(OH)CH_2^gCH_3^h$] exhibits absorption at δ 0.94 (t, $J_{g,h}$ = 7 Hz., 3H, H^h), 1.4 (m, 2H, H^g), 2.00, 2.03, and 2.05 (s, 3H, H^e), 2.22 and 2.26 (s, 3H, H^b), 2.6–3.8 (m, 2H, H^d and H^f), 5.0–5.8 (m, 1H, H^c), and 5.9–6.3 (m, 1H, H^a). The olefinic multiplets indicate[4] that two *trans* diastereomers and two *cis* diastereomers are present in the ratios 25:23:41:11, respectively.

21. At this stage, the submitter added 2 g. of sodium hydrogen carbonate to buffer the liquid phase near neutrality before filtration. The checkers found that this operation can be omitted without any trouble.

22. Diatomaceous earth is used to avoid clogging the sintered glass filter with the insoluble material in the reaction mixture.

23. To remove the remaining mercury(II) chloride and some by-products the submitter filtered a carbon tetrachloride solution of the product through a 1-cm. column of Merck silicic acid in an experiment of one-twentieth scale. For the larger-scale preparation the checkers found it necessary to carry out the chromatographic purification using silicic acid (M. Woelm Eshwege, Grade II) as described.

24. Using the same columns described in (Note 19), the product shows a retention time of 1.23 minutes at 140° (submitter) and 1.45 minutes at 200° (checkers).

25. The ^{1}H NMR spectrum (CCl_4) of the γ-hydroxy-α,β-unsaturated aldehyde [$O=CH^aCH^b=CH^cCH^d(OH)CH_2^eCH_3^f$] shows absorption at δ 0.96 (t, 3H, H^f), 1.2–1.9 (m, 2H, H^e), 2.22 (s, 1H, O*H*), 4.30 (m, 1H, H^d), 6.23 (d of d, 1H, H^b), 6.85 (d of d, 1H, H^c), and 9.49 (d, 1H, H^a), with coupling constants *J* in Hz.: $J_{a,b}$ = 7.6, $J_{b,c}$ = 15.5, $J_{b,d}$ = 1.0, $J_{c,d}$ = 4.3, and $J_{e,f}$ = 7.0. IR (CCl_4) cm^{-1}: 3615 medium, 3470 medium and broad (OH), 2805 weak, 2720 weak (CH of aldehyde), 1693 strong (C=O), 1640 weak (C=C).

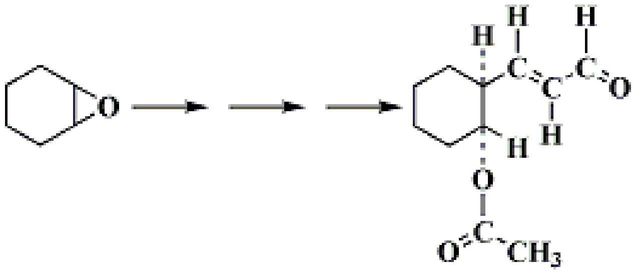
26. *trans*-4-Hydroxy-2-hexenal is unstable and decomposed on standing at room temperature, giving polymeric and dehydrated compounds. The checkers prepared the 2,4-dinitrophenylhydrazone, m.p. 198–199°,[5] for its identification in the usual way.

3. Discussion

1,3-Bis(methylthio)-2-methoxypropane is important as the precursor of 1,3-bis(methylthio) allyllithium,[6] a symmetrical nucleophile synthetically equivalent to the currently unknown (and probably intrinsically unstable) 3-lithio derivative of acrolein (Li-CH=CH-CH=O).

Reaction of 1,3-bis(methylthio)-2-methoxypropane with 2 moles of lithium diisopropylamide[6] (or *n*-butyllithium) effects (a) the elimination of methanol, forming 1,3-bis(methylthio)propene, and (b) the lithiation of this propene, generating 1,3-bis(methylthio)allyllithium in solution. Its conjugate acid, 1,3-bis(methylthio)propene, can be regenerated by protonation with methanol, and has also been prepared (a) in 31% yield by reaction of methylthioacetaldehyde with the lithio derivative of diethyl methylthiomethylphosphonate,[6] (b) in a low yield by acid-catalyzed pyrolysis of 1,1-bis(methylthio)-3-methoxypropane,[7] and (c) in low yield by acid-catalyzed coupling of vinyl chloride with chloromethyl methyl sulfide.[8]

A variety of α,β-unsaturated aldehydes are available by alkylation of 1,3-bis(methylthio)allyllithium and hydrolysis of the product. For example, *trans*-2-octenal is obtained in 75% yield overall on alkylation with 1-bromopentane and hydrolysis with mercuric chloride.[6]



Addition of 1,3-bis(methylthio)allyllithium to aldehydes, ketones, and epoxides followed by mercury(II) ion-promoted hydrolysis furnishes hydroxyalkyl derivatives of acrolein[6] that are otherwise available in lower yield by multistep procedures. For example, addition of 1,3-bis(methylthio)allyllithium to acetone proceeds in 97% yield, giving a tertiary alcohol that is hydrolyzed with mercury(II) chloride and calcium carbonate to *trans*-4-hydroxy-4-methyl-2-pentenal in 41% yield.[6] Addition to an epoxide and hydrolysis affords a δ-hydroxy-α,β-unsaturated aldehyde.[9] Similarly, addition of 1,3-bis(methylthio)allyllithium to an epoxide, acetylation of the hydroxyl group, and hydrolysis with mercury(II) chloride and calcium carbonate provides a δ-acetoxy-*trans*-α,β-unsaturated aldehyde,[6] as indicated in Table I. Cyclic *cis*-epoxides give aldehydes in which the acetoxy group is *trans* to the 3-oxopropenyl group.

TABLE I

CONVERSION OF EPOXIDES INTO δ-ACETOXY-*trans*-α,β-UNSATURATED ALDEHYDES

Epoxide	Coupling	Acetylation	Hydrolysis	Overall
	Yield, %			
Propylene oxide	97	100	81	78
Cyclopentene oxide	99	92	59	54
Cyclohexene oxide	96	100	85	82

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hexanes

2,4-dinitrophenylhydrazone

methanol (67-56-1)

ether, diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium hydrogen carbonate (144-55-8)

Epichlorohydrin (106-89-8)

Propene (115-07-1)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

carbon tetrachloride (56-23-5)

Propionaldehyde (123-38-6)

propylene oxide (75-56-9)

nitrogen (7727-37-9)

calcium carbonate (471-34-1)

acetone (67-64-1)

mercuric chloride, mercury(II) chloride, mercury (II) chloride (7487-94-7)

Cyclohexene oxide (286-20-4)

xylene (106-42-3)

Methyl iodide (74-88-4)

Pentane (109-66-0)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

methanethiol (74-93-1)

butyllithium, n-butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

lithium aluminium hydride (16853-85-3)

sodium hydride (7646-69-7)

hexane (110-54-3)

silicic acid (7699-41-4)

vinyl chloride (9002-86-2)

calcium hydride (7789-78-8)

2-Butanol (78-92-2)

lithium diisopropylamide (4111-54-0)

1,10-phenanthroline (66-71-7)

diisopropylamine (108-18-9)

1,3-BIS(METHYLTHIO)ALLYLLITHIUM

2-Hexenal, 4-hydroxy-

1,3-Bis(methylthio)-2-propanol (31805-83-1)

1,3-Bis(methylthio)-2-methoxypropane (31805-84-2)

1,3-Bis(methylthio)-1-hexen-4-ol (53107-07-6)

1,3-bis(methylthio)propene

1,3-bis(methylthio)-1-butene

methylthioacetaldehyde

1,1-bis(methylthio)-3-methoxypropane

chloromethyl methyl sulfide (2373-51-5)

1-bromopentane (110-53-2)

Cyclopentene oxide (285-67-6)

trans-4-Hydroxy-2-hexenal (17427-21-3)

trans-2-octenal

trans-4-hydroxy-4-methyl-2-pentenal

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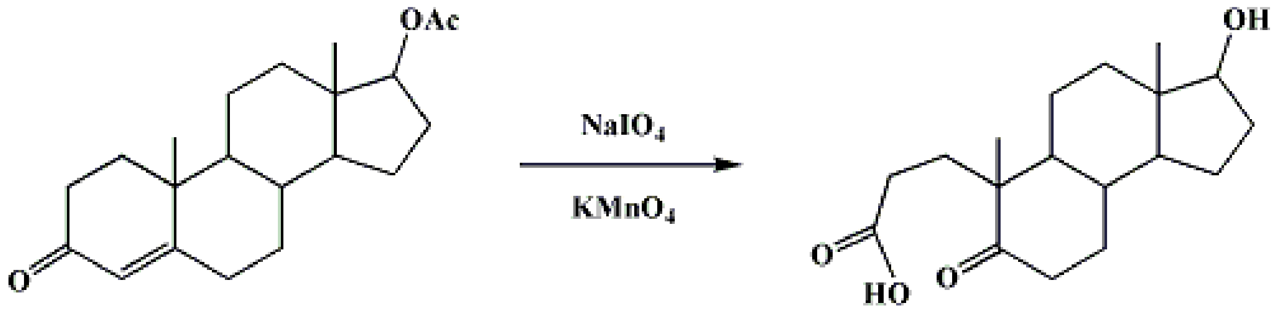
Organic Syntheses, *CV 6*, *690*

17β-HYDROXY-5-OXO-3,5-*seco*-4-NORANDROSTANE-3-CARBOXYLIC ACID

[1*H*-Benz[*e*]indene-6-propanoic acid, dodecahydro-3-hydroxy-3*a*,6-dimethyl-7-oxo-]



Submitted by L. Milewich[1] and L. R. Axelrod.
Checked by A. P. King and R. E. Benson.

1. Procedure

A 3-l., three-necked, round-bottomed flask fitted with an efficient mechanical stirrer, a 100-ml. dropping funnel, and a 500-ml. dropping funnel is charged with a solution of 10.0 g. (0.0303 mole) of testosterone acetate [17β-(acetyloxy)-androst-4-en-3-one] (Note 1) in 600 ml. of *tert*-butyl alcohol and a solution of 5.6 g. (0.041 mole) of anhydrous potassium carbonate in 150 ml. of water. To the flask are added 100 ml. of a solution prepared from 40.0 g. (0.187 mole) of sodium metaperiodate (Note 2) in 500 ml. of water, and 10 ml. of a solution prepared from 0.8 g. (0.005 mole) of potassium permanganate in 100 ml. of water. Stirring is begun, and the remaining portions of these solutions are transferred to the appropriate dropping funnels. The metaperiodate solution is added over a period of about 30 minutes, and the permanganate solution is added as needed to maintain a pink color (Note 3). Stirring is continued for an additional 1.5 hours (Note 4) before a solution of 20.0 g. of sodium bisulfite in 40 ml. of water is slowly added (Note 5). After stirring for 20 minutes the suspension is filtered through a 10-g. pad of Celite® filter aid (Note 6) on a coarse sintered-glass filter, and the residual cake is washed with two 50-ml. portions of *tert*-butyl alcohol. The filtrates are combined and concentrated by distillation (Note 7) to a volume of about 200 ml. After cooling, 25 ml. of 10% sulfuric acid is added. The resulting mixture is extracted with three 300-ml. portions of diethyl ether. The combined ethereal extracts are washed, first with two 50-ml. portions of water, twice with solutions prepared from 5.0 g. of sodium bisulfite in 20 ml. of water, and finally twice with 50 ml. of water. Crushed ice is added to the ethereal layer, and the mixture is extracted with three 70-ml. portions of 10% aqueous sodium hydroxide. The aqueous layers are combined and washed with 50 ml. of ether. The aqueous layer is transferred to a 2-l. separatory funnel, crushed ice is added, and 300 ml. of 10% sulfuric acid is introduced carefully. The separatory funnel is shaken gently, and the product separates as a gum or stringy mass (Note 8). The mixture is extracted with four 200-ml. portions of dichloromethane, and the extracts are combined and washed with

three 15-ml. portions of water. The organic layer is dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The resulting material is triturated with 50 ml. of acetone, and after a brief heating period crystals begin to separate. The mixture is cooled and filtered, yielding 6.0–6.5 g. (63–70%) of 17β-hydroxy-5-oxo-3,5-*seco*-4-norandrostane-3-carboxylic acid, m.p. 204–205° (Note 9). Additional product can be obtained from the filtrate by concentration and cooling.

2. Notes

1. Testosterone acetate was obtained from Steraloids, Inc.
2. Sodium metaperiodate was purchased from J. T. Baker Chemical Company.
3. During these additions the temperature of the reaction mixture rises to about 35°.
4. At this point the reaction mixture has a pH of about 5.2.
5. When the bisulfite solution is added, the solution acquires a deep brown color and iodine fumes develop.
6. The product was purchased from Johns-Manville Corporation.
7. Evaporation is carried out under reduced pressure with a bath temperature of 75°. A deep iodine-colored fraction distills first, followed by a colorless distillate.
8. The checkers found it convenient to separate the aqueous phase from the sticky amorphous mass and later dissolve the product in the dichloromethane solution that was used for the extractions.
9. The reported melting points are 206.5–207°,[2] 204–205.5°,[3] 200–202°,[4] 204–206°,[5] and 192°.[6] The product has the following spectral properties; IR (KBr) cm.$^{-1}$: 3390, 1717, 1700, and 1056; ^{1}H NMR ($CDCl_3$), δ: 0.82 (C_{18}-CH_3), 1.14 (C_{19}-CH_3), and additional broad absorptions; $[\alpha]^{28}_D$ +36°.

3. Discussion

17β-Hydroxy-5-oxo-3,5-*seco*-4-norandrostane-3-carboxylic acid has been prepared by ozonolysis of testosterone[2,3,4] or testosterone acetate, followed by alkaline hydrolysis,[5] and by the oxidation of testosterone acetate with ruthenium tetroxide.[6]

The present procedure corresponds to the method[7] described earlier for the synthesis of 5-oxo-3,5-*seco*-4-norcholestane-3-carboxylic acid and is useful for preparing large quantities of the title compound.

References and Notes

1. Southwest Foundation for Research and Education, Division of Biological Growth and Development, Department of Biochemistry, San Antonio, Texas 78284. [Present address: Department of Obstetrics and Gynecology, The University of Texas, Health Science Center at Dallas, Dallas, Texas 75235.]
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

ether, diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

potassium permanganate (7722-64-7)

sodium sulfate (7757-82-6)

sodium bisulfite (7631-90-5)

iodine (7553-56-2)

acetone (67-64-1)

dichloromethane (75-09-2)

tert-butyl alcohol (75-65-0)

ruthenium tetroxide (20427-56-9)

sodium metaperiodate (7790-28-5)

testosterone acetate, 17β-(acetyloxy)-androst-4-en-3-one

4-norandrostane-3-carboxylic acid

testosterone

17β-Hydroxy-5-oxo-3,5-seco-4-norandrostane-3-carboxylic acid

1H-Benz[e]indene-6-propanoic acid, dodecahydro-3-hydroxy-3a,6-dimethyl-7-oxo-

5-oxo-3,5-seco-4-norcholestane-3-carboxylic acid

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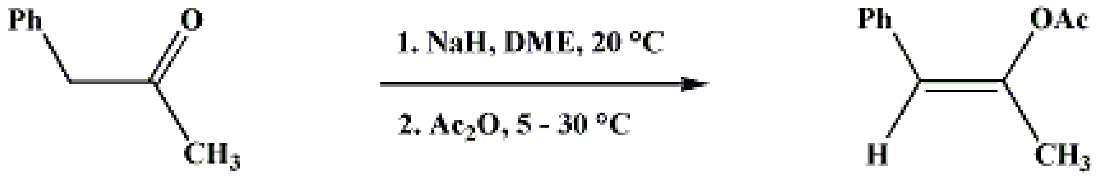
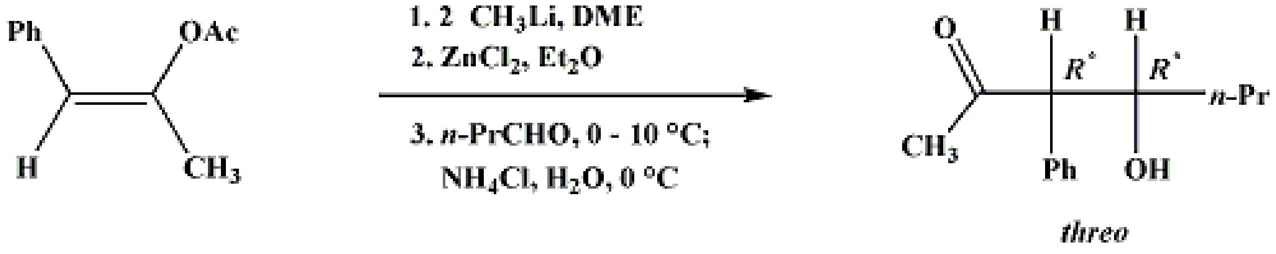
Organic Syntheses, CV 6, 692

DIRECTED ALDOL CONDENSATIONS: *threo*-4-HYDROXY-3-PHENYL-2-HEPTANONE

[2-Heptanone, 4-hydroxy-3-phenyl-, (*R*,*R*)-]





Submitted by Robert A. Auerbach, David S. Crumrine, David L. Ellison, and Herbert O. House[1].
Checked by Wataru Nagata and Norbuhiro Haga.

1. Procedure

Caution! Since hydrogen is liberated, this preparation should be performed in a hood.

A. 2-*Acetoxy*-trans-1-*phenylpropene*. A dry, 500-ml., three-necked flask is fitted with a mechanical stirrer, a pressure-equalizing dropping funnel, and a rubber septum, and the apparatus is arranged so that the flask may be cooled intermittently with an ice bath. After the reaction vessel has been flushed with nitrogen (admitted through a hypodermic needle in the rubber septum) a static nitrogen atmosphere is maintained in the reaction vessel for the remainder of the reaction. The flask is charged with 35 g. of a 57% dispersion of sodium hydride (20 g., 0.83 mole) in mineral oil (Note 1). The mineral oil is washed from the hydride with 200 ml. of anhydrous pentane. The supernatant pentane layer is removed with a stainless-steel cannula inserted through the rubber septum (Note 2). The residual sodium hydride is mixed with 250 ml. of anhydrous 1,2-dimethoxyethane (Note 3) before 65 g. (0.48 mole) of phenylacetone (Note 4) is added dropwise and with stirring over 50–60 minutes. During this addition an open hypodermic needle should be inserted in the rubber septum to permit the escape of hydrogen, and intermittent cooling with an ice bath may be necessary to keep the reaction solution from boiling. The resulting mixture is stirred for 3 hours while it is allowed to cool, then the mixture is allowed to stand for approximately 2 hours, permitting the excess sodium hydride to settle. The supernatant liquid is transferred under positive nitrogen pressure through a stainless-steel cannula (Note 2) into a 1-l., three-necked flask containing 108 g. (100 ml., 1.00 mole) of cold (0°), freshly distilled acetic

anhydride (b.p. 140°) and fitted with a mechanical stirrer, a thermometer, an ice bath, and a rubber septum into which are inserted a hypodermic needle to admit nitrogen and a cannula to transfer the enolate solution.

The enolate solution is added slowly with cooling and vigorous stirring so that the temperature of the reaction mixture remains below 30°. After all the supernatant enolate solution has been transferred, the residual slurry of sodium hydride is washed with an additional 50-ml. portion of anhydrous 1,2-dimethoxyethane (Note 3); these washings are also added to the acetic anhydride solution. The resulting viscous mixture is stirred at room temperature for an additional 30 minutes and poured cautiously into a mixture of 500 ml. of pentane, 500 ml. of water, and 130 g. (1.54 moles) of sodium hydrogen carbonate. When hydrolysis of the excess acetic anhydride and neutralization of the acetic acid are complete, the pentane layer is separated, and the aqueous phase is extracted with 100 ml. of pentane. The combined pentane solutions are dried over anhydrous magnesium sulfate and concentrated with a rotary evaporator. Distillation of the residual orange liquid through a 20–30-cm. Vigreux column (Note 5) provides 61.7–80.6 g. (73–95%) of 2-acetoxy-*trans*-1-phenylpropene, b.p. 82–89° (1 mm.), n_D^{25} 1.5320–1.5327 (Note 6).

B. threo-4-*Hydroxy*-3-*phenyl*-2-*heptanone*. A dry, 500-ml., three-necked flask is fitted with a Teflon®-coated magnetic stirring bar, a gas-inlet tube equipped with a stopcock, a low-temperature thermometer, and a rubber septum and mounted to permit the use of an external cooling bath. The apparatus is flushed with nitrogen, and a static nitrogen atmosphere is maintained in the reaction vessel throughout the reaction. After 10–20 mg. of 2,2'-bipyridyl has been added to the reaction flask as an indicator, an ethereal solution containing 0.412 mole of halide-free methyllithium (Note 7) is added to the reaction flask with a hypodermic syringe or stainless-steel cannula inserted through the rubber septum. The diethyl ether is removed under reduced pressure (Note 8) while the flask is warmed to 40° with a water bath, the reaction vessel is refilled with nitrogen, and 120 ml. of anhydrous 1,2-dimethoxyethane is added (Note 3). The resulting purple solution is cooled to –10 to –20° with a 2-propanol–dry ice bath before 35.2 g. (0.200 mole) (Note 9) of 2-acetoxy-*trans*-1-phenylpropene is added from a hypodermic syringe dropwise and with stirring over 15 minutes while the temperature of the reaction mixture is kept in the range –20 to +10°. The resulting red-brown solution is stirred for an additional 10 minutes at –10 to 0° before 285 ml. of an ethereal solution containing 0.202 mole of anhydrous zinc chloride (Note 10) is added to the cold (–10 to +10°) reaction mixture from a hypodermic syringe dropwise and with stirring over 10 minutes. The reddish-yellow cloudy reaction mixture (Note 11) is stirred at 0° for 10 minutes before 14.50 g. (0.2014 mole) of freshly distilled butyraldehyde (Note 12) is added rapidly (30 seconds) and with stirring to the cold (–5 to +10°) reaction mixture. After the mixture has been stirred at 0–5° for 4 minutes, it is poured with vigorous stirring into a cold (0–5°) mixture of 500 ml. of 4 *M* ammonium chloride and 200 ml. of ether. The ether layer is separated, and the aqueous phase is extracted with two 200-ml. portions of ether. The combined organic solutions are washed successively with two 100-ml. portions of 1 *M* ammonium chloride and with two 50-ml. portions of saturated aqueous sodium chloride, and the combined aqueous washings are extracted with an additional 100-ml. portion of ether. The combined ether solutions are dried over anhydrous magnesium sulfate and concentrated under reduced pressure (water aspirator) with a rotary evaporator,

removing the solvents and residual 1,2-dimethoxyethane. The residual liquid, which may crystallize on standing (Note 13), is triturated with 50 ml. of pentane, and the crystalline solid that separates is collected on a filter. The filtrate is concentrated under reduced pressure and again triturated with pentane, yielding an additional crop of the crude product. The combined crops of the crude *threo*-aldol product total 26.2–28.4 g. (64–69%), m.p. 57–62°. The crude product is recrystallized from 125–150 ml. of hexane. After the solution has been cooled to 0°, 21.3–24.1 g. of the *threo*-aldol product is collected as white needles, m.p. 71.5–72.5° (Note 14). The mother liquors are concentrated and cooled, separating additional fractions of the product (0.5–0.8 g.), m.p. 71–72°. The total yield of the *threo*-aldol product is 22.1–24.6 g. (53–60%).

2. Notes

1. The submitters used a 57% dispersion of sodium hydride in mineral oil obtained from Alfa Inorganics, Inc., and the checkers used a 50% dispersion of sodium hydride in mineral oil obtained from Metal Hydrides, Inc.
2. As a stainless-steel cannula was not available, the checkers made a minor modification in the operation without any trouble. They transferred the supernatant pentane and the solution of the sodium enolate using a Luer-lock hypodermic syringe with a stainless-steel needle preflushed with nitrogen, sweeping the apparatus with nitrogen during this operation.
3. The submitters distilled 1,2-dimethoxyethane (b.p. 83°) from lithium aluminum hydride immediately before use. The checkers distilled from sodium hydride immediately before use.
4. The submitters used a commercial sample of phenylacetone obtained from Aldrich Chemical Company, Inc.; the checkers used material of the same grade obtained from Maruwaka Chemical Industries Ltd. (Japan) without further purification.
5. The checkers used a 15 × 1 cm., unpacked, vacuum-jacketed column instead of Vigreux column for the distillation.
6. The results of GC analysis of the products made by the submitters are as follows: On a 3-m. GC column, packed with silicone fluid QF_1 supported on Chromosorb P, and heated to 190°, the product exhibits peaks at 5.8 minutes corresponding to 2–3% phenylacetone, at 7.5 minutes corresponding to 97–98% of the enol acetate (*cis* and *trans* isomers not resolved), and at 8.0 minutes corresponding to a trace (<1%) of 3-phenyl-2,4-pentanedione. On a second, 7-m. GC column, packed with silicone fluid DC-710 on Chromosorb P and heated to 190°, the product exhibits peaks at 21.0 minutes corresponding to phenylacetone, at 39.0 minutes corresponding to the *trans*-enol acetate (97–98% of the product), and at 42.2 minutes corresponding to the *cis*-enol acetate (2–3% of the product). The checkers used a 45 m. × 0.25 mm. stainless-steel column (Golay type) coated with Apiezon L, heated to 150° and swept with helium at 1.5 kg./cm.^{2} The product exhibits peaks at 5.5 minutes corresponding to phenylacetone (2–3% of product), at 14.2 minutes corresponding to the *trans*-enol acetate (91–92% of the product), and at 15.8 minutes corresponding to the *cis*-enol acetate (5–6% of the product). The product has IR absorption (CCl_4) at 1765 (enol ester C=O) and 1685 cm^{-1} (enol ester C=C) with UV maxima (95% C_2H_5OH) at 248.5 nm (ε 18,000) and 325 nm (ε 415) and ^1H NMR peaks (CCl_4) at δ 2.01 (partially resolved m, 6H, CH_3CO and vinyl CH_3), 5.82 (partially resolved m, 1H,

vinyl C*H*), and 7.0–7.4 (m, 5H, C_6H_5). The mass spectrum of the product has a parent ion at *m/e* 176 with abundant fragment peaks at *m/e* 134, 91, 45, 43, and 39.

7. The submitters used an ether solution of halide-free methyllithium, purchased from Foote Mineral Company, while the checkers prepared the compound from methyl chloride and lithium metal in ether according to the literature.[2] The solution was standardized before use by the titration procedure described in *Org. Synth.*, **Coll. Vol. 6**, 121 (1988). The checkers observed that use of a halide-containing ether solution of methyllithium resulted in a considerable decrease in yield of the product, principally due to difficulty in following the subsequent procedure described in the text.

8. A convenient apparatus for evacuating the reaction vessel and refilling it with nitrogen is described in *Org. Synth.*, **Coll. Vol. 6**, 121 (1988).

9. If the violet color of the reaction solution is completely discharged, indicating that all the methyllithium has been consumed, addition of the enol acetate should be stopped at that point. The actual concentration of enolate anion in the solution can be calculated from the amount of enol acetate added.

10. To prepare an ethereal solution of anhydrous zinc chloride (m.p. 283°), the submitters placed 50.0 g. (0.369 mole) of pulverized zinc chloride, obtained from either Mallinckrodt Chemical Works or Fisher Scientific Company, in a 1-l., round-bottomed flask, and the vessel was evacuated to about 1 mm. pressure. The flask was heated strongly with a burner with swirling until as much of the solid as practical had been melted. The evacuated flask was cooled and shaken *(Caution! Perform this operation behind a safety shield in a hood and with heavy gloves to protect the operator's hands in case the flask should implode)* to break up the large lumps of zinc chloride. This fusion under reduced pressure should be repeated three times. To the resulting anhydrous zinc chloride was added 500 ml. of anhydrous diethyl ether, freshly distilled from lithium aluminum hydride. The mixture was refluxed for 3 hours under a static nitrogen atmosphere and allowed to stand until the undissolved solid had settled. The resulting supernatant solution was transferred with a stainless-steel cannula under positive nitrogen pressure (Note 2) into a second dry flask or Schlenk tube capped with a rubber septum. Aliquots of this solution, diluted with aqueous ammonia, can be titrated with standard EDTA solution to a Erichrome Black T endpoint to determine the zinc content.[3] Alternatively, the chloride ion concentration of aliquots can be determined by a Volhard titration. Typical values found for these ether solutions are 0.73 *M* in zinc ion and 1.38 *M* in chloride ion, or 0.69–0.73 *M* in zinc chloride. If the final solution is significantly less concentrated than 0.7 *M* in zinc chloride, it is probable that the dehydration of the solid zinc chloride was not complete. In this event, the submitters recommend that a fresh solution of zinc chloride be prepared with more attention to the initial dehydration of the solid zinc chloride. The checkers used pulverized zinc chloride, obtained from Wako Pure Chemical Industries Ltd. (Japan).

11. The white precipitate that separates is a part of the lithium chloride formed in the reaction mixture. Separation of the material is not necessary.

12. The submitters used a commercial grade of butyraldehyde from Eastman Organic Chemicals; the checkers used butyraldehyde of the same grade from Wako Pure Chemical Industries Ltd. (Japan) and distilled it before use, b.p. 72–74°.

13. The ^1H NMR spectrum (C_6D_6) of the crude product exhibits benzylic CH

doublets at δ 3.42 (J = 5.3 Hz., attributable to 4–10% of the *erythro* aldol isomer) and 3.58 (J = 9.4 Hz., attributable to 90–96% of the *threo*-aldol isomer). This mixture may be separated by chromatography on acid-washed silicic acid, permitting the isolation of both the *threo* and the *erythro* diastereoisomers.[4]

14. The *threo*-hydroxy ketone exhibits IR absorption (CCl_4) at 3540 (associated OH) and 1705 cm.$^{-1}$ (C=O) with a series of weak (ε 300 or less) UV maxima (95% C_2H_5OH) in the region 240–270 nm as well as a maximum at 286 nm (ε 345). The ^1H NMR spectrum (CCl_4) of the product shows resonance at δ 0.6–1.9 [m, 7H, $(CH_2)_2CH_3$], 2.03 (s, 3H, CH_3CO), 3.35 (s, 1H, O*H*), 3.65 (d, J = 9.5 Hz., 1H, benzylic C*H*), 4.0–4.4 (m, 1H, C*H*O), and 7.1–7.5 (m, 5H, C_6H_5). The mass spectrum of the product exhibits the following relatively abundant peaks: *m/e* (relative intensity), 206 (M^+, 0.1), 188 (8), 146 (20), 135 (26), 134 (100), 117 (52), 92 (48), 91 (76), 65 (31), 44 (36), and 43 (60).

3. Discussion

The present procedures illustrate general methods for the use of preformed lithium enolates[5] as reactants in the aldol condensation[4] and for quenching alkali metal enolates in acetic anhydride, forming enol acetates with the same structure and stereochemistry as the starting metal enolate.[6] The aldol product, *threo*-4-hydroxy-3-phenyl-2-heptanone, has been prepared only by this procedure.

The methods previously used to obtain single aldol products (or their dehydrated derivatives) from reactants where several aldol products are possible[7] include the reaction of bromozinc enolates, from α-bromoketones, with aldehydes;[8] the reaction of bromomagnesium enolates, from either α-bromoketones, ketones and bromomagnesium amides or sterically hindered Grignard reagents, with aldehydes;[9,10] and the reaction of α-lithio derivatives of imines with aldehydes or ketones.[11] Like the present procedure, each of these methods relies upon trapping the intermediate β-keto alkoxide derivative as a metal chelate in an aprotic reaction solvent. The present procedure increases the versatility of the aldol condensation by utilizing the variety of specific lithium enolates that can be generated from unsymmetrical ketones.[5] In this procedure the lithium enolate is treated successively with anhydrous zinc chloride and an aldehyde, forming the zinc(II) chelate of a β-keto alkoxide. The optimum quantity of zinc chloride is that amount required to form zinc(II) salts of all strong bases in the reaction mixture. Thus, 1 mole of zinc chloride should be added for each mole of lithium enolate (and accompanying lithium *tert*-butoxide) formed from an enol acetate as in the present example. If the lithium enolate is formed from the ketone and lithium diisopropylamide or from a trimethylsilyl enol ether and methyllithium, then 0.5 mole of zinc chloride should be used for each mole of lithium enolate. The optimum reaction solvent is either ether or ether–1,2-dimethoxyethane mixtures, with a reaction temperature of –10 to +10° and a reaction time of 2–5 minutes. Longer reaction times and higher reaction temperatures may lead to a variety of by-products resulting from polycondensation and dehydration. The aldol products are efficiently isolated by *adding the reaction mixtures* to a cold (0–5°), aqueous solution of ammonium chloride followed by rapid separation of the aldol products. Since many of the aldol products are especially prone

to epimerization, dehydration, or reversal of the aldol condensation, they should not be exposed to strong acids or strong bases. Mixtures of stereoisomeric aldol products with similar physical properties can usually be separated by chromatography on acid-washed silicic acid.[4,12]

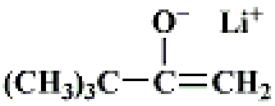
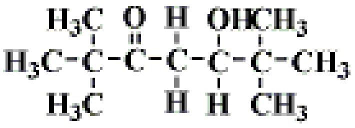
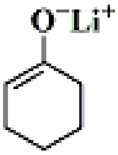
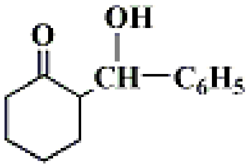
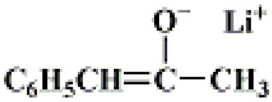
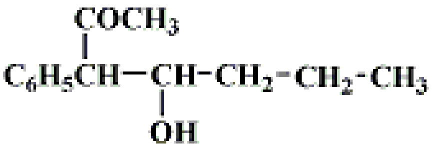
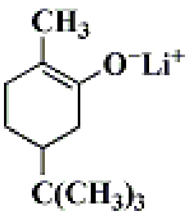
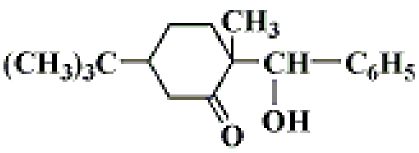
In several cases (including the present example) where diastereoisomeric aldol products are possible, there is a preference for the formation of the *threo*-diastereoisomer. This stereochemical preference presumably arises because the six-membered cyclic zinc chelate of the *threo*-isomer can exist in a chair conformation with both substituents in equatorial positions. Table I summarizes the results obtained from several aldol condensations performed by the present procedure.

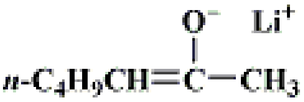
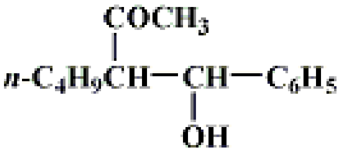
This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 277

TABLE I

[4]DIRECTED ALDOL CONDENSATIONS WITH PREFORMED LITHIUM ENOLATES IN THE PRESENCE OF ZINC CHLORIDE

Enolate	Aldol Product	Yield, %	Stereoisomer ratio, *threo*/*erythro*
		82	—
		76	4/1
		80	9/1
		84	2/1[a]

		80	1/1

[a] The aldol product contained 70% of isomers with an axial α-hydroxybenzyl substituent.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

threo-4-Hydroxy-3-phenyl-2-heptanone

ammonia (7664-41-7)

ether, diethyl ether (60-29-7)

acetic anhydride (108-24-7)

ammonium chloride (12125-02-9)

hydrogen (1333-74-0)

sodium hydrogen carbonate (144-55-8)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

methyl chloride (74-87-3)

zinc (7440-66-6)

butyraldehyde (123-72-8)

zinc chloride (7646-85-7)

Pentane (109-66-0)

phenylacetone (103-79-7)

lithium (7439-93-2)

magnesium sulfate (7487-88-9)

lithium aluminum hydride (16853-85-3)

sodium hydride (7646-69-7)

hexane (110-54-3)

Methyllithium (917-54-4)

silicic acid (7699-41-4)

Lithium chloride (7447-41-8)

hydride

1,2-dimethoxyethane (110-71-4)

helium (7440-59-7)

2,2'-bipyridyl (366-18-7)

lithium diisopropylamide (4111-54-0)

3-phenyl-2,4-pentanedione (5910-25-8)

EDTA (60-00-4)

lithium tert-butoxide (1907-33-1)

2-Acetoxy-trans-1-phenylpropene (19980-44-0)

2-Heptanone, 4-hydroxy-3-phenyl-, (R,R)- (42052-62-0)

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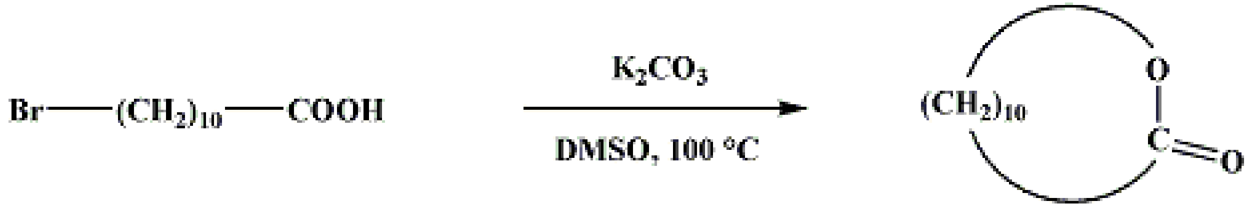
Organic Syntheses, CV 6, 698

MACROLIDES FROM CYCLIZATION OF ω-BROMOCARBOXYLIC ACIDS: 11-HYDROXYUNDECANOIC LACTONE

[Oxacyclododecan-2-one]



Submitted by C. Galli and L. Mandolini[1].
Checked by Kaoru Mori and Carl R. Johnson.

1. Procedure

A 1-l., three-necked, round-bottomed flask equipped with an internal thermometer, mechanical stirrer, dropping funnel, and calcium chloride drying tube is charged with 500 ml. of dimethyl sulfoxide and 15 g. (0.11 mole) of potassium carbonate (Note 1). The mixture is heated to 100°, and a solution of 10.0 g. (0.0377 mole) of 11-bromoundecanoic acid (Note 2) in 200 ml. of dimethyl sulfoxide is added dropwise with vigorous stirring over 1 hour. After cooling at room temperature, the mixture is decanted and filtered free of any suspended solid material (Note 3) through a Büchner funnel with occasional suction. The solid residue is rinsed with 50 ml. of dimethyl sulfoxide, and the washings are added to the original filtrate. The resulting clear solution is diluted with 250 ml. of water and extracted with three 250-ml. portions of petroleum ether. The combined organic layers are washed with 200 ml. of water, dried over anhydrous sodium sulfate, and concentrated, leaving *ca.* 7 g. of crude material. Simple distillation at reduced pressure from a small Claisen flask yields 5.5–5.8 g. (79–83%) of pure 11-hydroxyundecanoic lactone as a colorless, musk-smelling liquid, b.p. 124–126° (13 mm.), n_D^{19} 1.4721 (Note 4) and (Note 5). The residue is ground with 5 ml. of hexane and filtered, affording 0.4–0.7 g. (6–10%) of the 24-membered dilactone 1,13-dioxacyclotetracosane-2,14-dione as white crystals, m.p. 71.5–72° (from hexane) (Note 6).

2. Notes

1. Reagent grade dimethyl sulfoxide and anhydrous potassium carbonate were used.
2. 11-Bromoundecanoic acid, available from Aldrich Chemical Company, Inc., was used without further purification.

3. Filtration is optional; however, it does reduce the extent of emulsion formation during the subsequent extractions.
4. The submitters report that the pure lactone and dilactone can also be obtained by chromatography of the crude product on silica gel with chloroform as the eluant.
5. The product is pure by GC and TLC; IR (CCl_4) cm^{-1}: 1740; ^1H NMR (CCl_4), δ (multiplicity, number of protons, assignment): 1.2–1.8 (m, 16H), 2.30 (broad t, 2H, CH_2CO), 4.14 (broad t, 2H, CH_2O).
6. Stoll and Rouvè[2] report m.p. 71.5–72°.

3. Discussion

Available methods for the synthesis of macrolides include the cyclization of long-chain bifunctional precursors,[3] depolymerization processes,[4] ring-enlargement reactions,[5] and special methods such as the thermal decomposition of tricycloalkylidene peroxides.[6] The method reported here is essentially that of the submitters.[7] Its improvements result from a quantitative approach to the cyclization of a series of ω-bromo fatty acids under conditions well defined from the kinetic point of view. A unique feature of this procedure in comparison with other methods involving cyclization of α,ω-bifunctional precursors, which are generally run under Ziegler's high-dilution conditions, is that high rates of feed can be used, so that the special devices usually employed for the slow addition of the reagent into the reaction medium are not required. The synthesis is characterized by relatively mild reaction conditions and simple work-up. Moreover, it is suited for relatively large-scale preparations. Up to 50 g. of 11-bromoundecanoic acid can be cyclized in more than 70% yield in a single run, employing no more than 1 l. of solvent and an addition time of 3–4 hours.

The reaction illustrates a typical preparation of a macrolide. Lactones with more than 12 members can be obtained in even better yields. For example, 15-hydroxypentadecanoic lactone (m.p. 35–37°) and 17-hydroxyheptadecanoic lactone (m.p. 40–41°) were prepared by the submitters in about 95% yield, practically pure, with no trace of the corresponding dilactones.

Recent progress in chemistry and biochemistry of macrolides was recently reviewed.[8]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

potassium carbonate (584-08-7)

chloroform (67-66-3)

sodium sulfate (7757-82-6)

hexane (110-54-3)

dimethyl sulfoxide (67-68-5)

11-Hydroxyundecanoic lactone, Oxacyclododecan-2-one (39282-36-5)

1,13-dioxacyclotetracosane-2,14-dione

11-Bromoundecanoic acid (2834-05-1)

17-hydroxyheptadecanoic lactone

15-hydroxypentadecanoic lactone (106-02-5)

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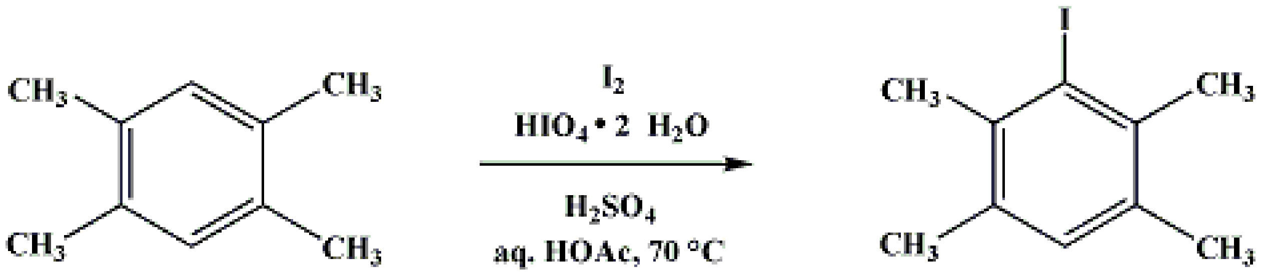
Organic Syntheses, CV 6, 700

DIRECT IODINATION OF POLYALKYLBENZENES: IODODURENE

[Benzene, 3-iodo-1,2,4,5-tetramethyl-]



Submitted by H. Suzuki[1]
Checked by Robert E. Ireland and Robert Czarny.

1. Procedure

A 200-ml., three-necked flask equipped with a reflux condenser, a thermometer, a glass stopper, and a magnetic stirring bar is charged with 13.4 g. (0.101 mole) of durene (Note 1), 4.56 g. (0.0215 mole) of periodic acid dihydrate, and 10.2 g. (0.0402 mole) of iodine. A solution of 3 ml. of concentrated sulfuric acid and 20 ml. of water in 100 ml. of glacial acetic acid is added to this mixture. The resulting purple solution is heated at 65–70° with stirring for approximately 1 hour until the color of iodine disappears. The reaction mixture is diluted with approximately 250 ml. of water, and the white-yellow solid that separates (Note 2) is collected on a Büchner funnel and washed three times with 100-ml. portions of water. The product is dissolved in a minimum amount of boiling acetone (about 125 ml. is required); the solution is cooled to room temperature and subsequently stored overnight in a refrigerator. The product is collected by rapid filtration through a Büchner funnel, yielding 20.8–22.6 g. (80–87%) of iododurene as colorless, fine needles, m.p. 78–80°.

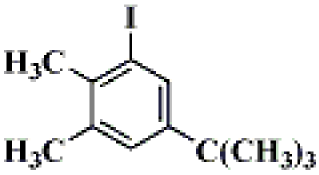
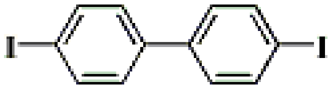
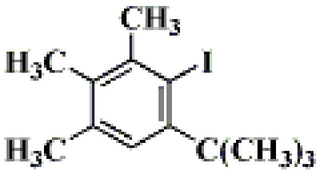
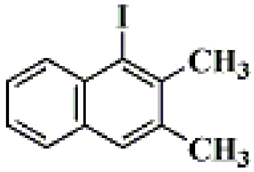
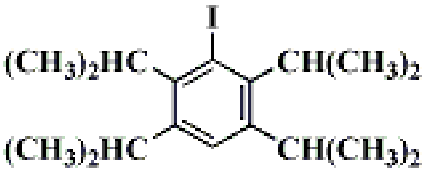
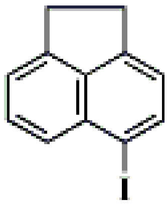
2. Notes

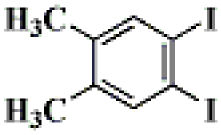
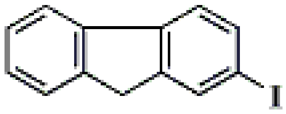
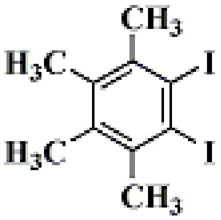
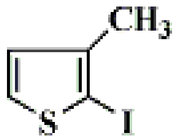
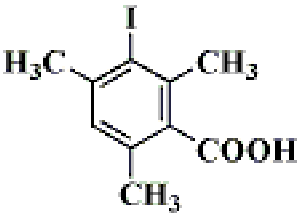
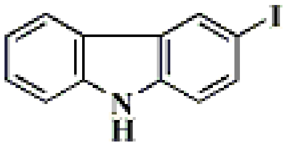
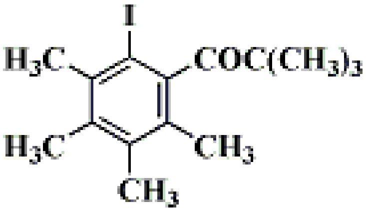
1. Durene (m.p. 79–80°), prepared according to the procedure in *Org. Synth.*, **Coll. Vol. 2**, 248 (1943), was used by the submitter. Commercially available durene, which melted at 79–80° after purification by the *Org. Synth.* procedure above, was used by the checkers.
2. Some crystals of iododurene that have formed during the heating period tend to take on a purple coloration because of occluded iodine. This impurity is readily removed by the recrystallization procedure.

3. Discussion

The present procedure is the most convenient method for the direct, high-yield preparation of mono-, di-, or triîodo derivatives from various polyalkylbenzenes and their derivatives. It is also applicable to some moderately activated heteroaromatic systems. However, the reaction fails with compounds bearing strongly deactivating substituent groups. Shorter reaction times and higher degree of product purity are assured by the use of periodic acid as an oxidizing agent. A feature of the reagent is that iodine is oxidized by periodic acid and periodic acid is reduced by iodine, both forming an active iodinating species which reacts with an aromatic compound, eventually leading to the formation of only the desired iodination product and water. A brief review of the iodine/periodic acid reagent has recently appeared.[2] The preparation of tetraiodo and more highly iodinated derivatives of alkylbenzenes by this procedure is difficult, and the Jacobsen reaction for the disproportionation of diîodo compounds by the action of sulfuric acid is preferred.[3] Polyiodo derivatives are useful for the characterization of polyalkylbenzenes and their derivatives, liquids available only in a small quantities, since the introduction of iodine atoms increases the molecular weight and converts a liquid hydrocarbon into a highly crystalline solid with a moderate melting range.[4] Table I illustrates the iodoarenes prepared from the corresponding arenes by conditions similar to that described herein.

TABLE I
IODOARENES PREPARED FROM THE CORRESPONDING ARENES

Iodoarenes	Ref.	Yield, %	Iodoarenes	Ref.	Yield, %
	5	81		6	94
	5	89		6	84
	5	85[a]		6	69

	5	85		6	86
	5	84		7	72
	8	86		6	85[b]
	9	85			

[a]Based on unrecovered hydrocarbon. The reaction proceeds quite slowly.

[b]A solution of periodic acid in acetic acid is added dropwise, with stirring, to a mixture of carbazole, iodine, and 80% (v/v) acetic acid. It is necessary to separate the product from colored substance by chromatography over alumina, using benzene as the eluant.

Iododurene has been prepared by treatment of durene with iodine and mercury(II) oxide,[10] sulfur iodide and nitric acid,[11] iodine and zinc chloride[12] or copper(II) chloride,[13] or iodoanisole and sulfuric acid.[14]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

Benzene (71-43-2)

nitric acid (7697-37-2)

mercury(II) oxide (21908-53-2)

iodine (7553-56-2)

acetone (67-64-1)

zinc chloride (7646-85-7)

copper(II) chloride (7758-89-6)

carbazole (86-74-8)

Durene (95-93-2)

periodic acid

Iododurene

Benzene, 3-iodo-1,2,4,5-tetramethyl- (2100-25-6)

periodic acid dihydrate

sulfur iodide

iodoanisole

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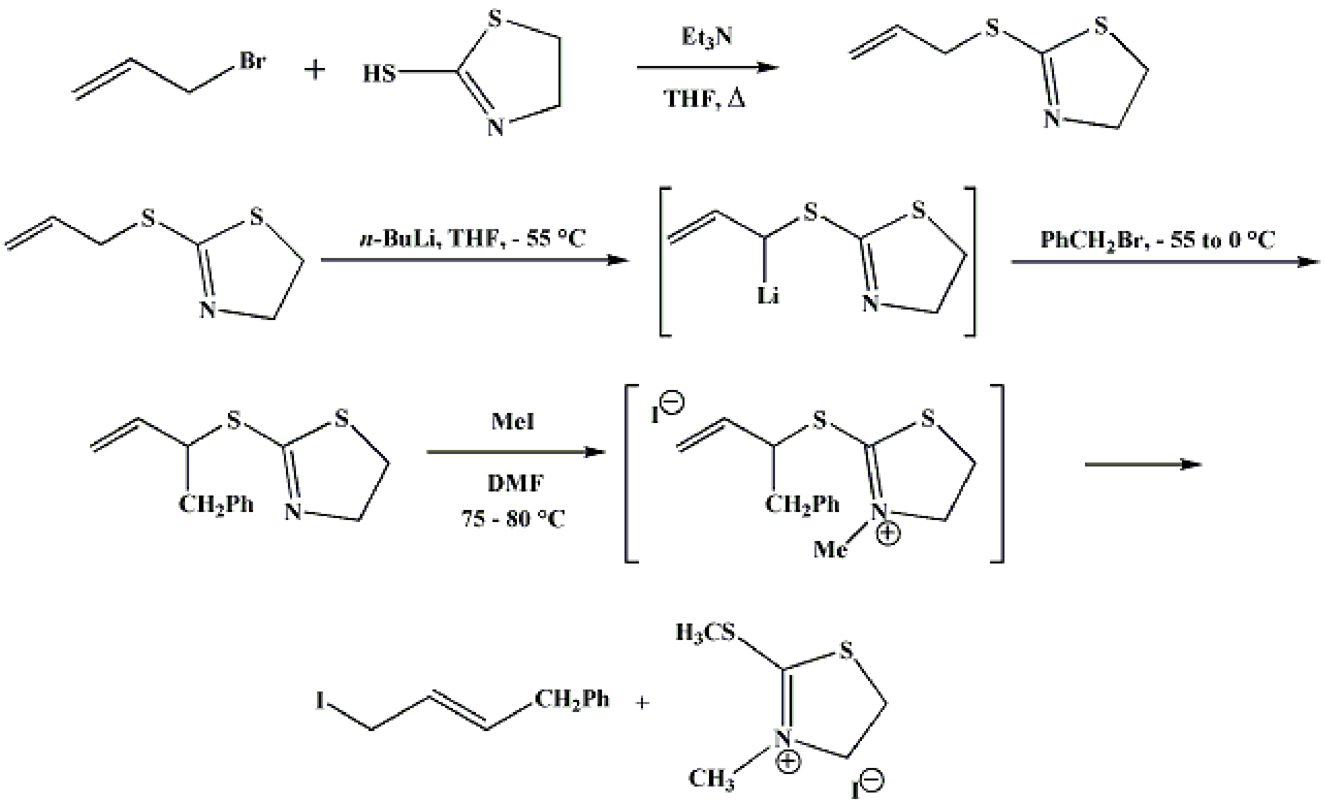
Organic Syntheses, CV 6, 704

trans-IODOPROPENYLATION OF ALKYL HALIDES: (*E*)-1-IODO-4-PHENYL-2-BUTENE

[2-Butene, 1-iodo-4-phenyl, (*E*)-]



Submitted by Koichi Hirai[1] and Yukichi Kishida.
Checked by S. F. Martin and G. Büchi.

1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

Hexamethylphosphoric triamide (HMPA) vapors have been reported to cause cancer in rats.[2] All operations with hexamethylphosphoric triamide should be performed in a good hood, and care should be taken to keep the liquid off the skin.

Methyl iodide, in high concentrations for short periods or in low concentrations for long periods, can cause serious toxic effects in the central nervous system. Accordingly, the American Conference of Governmental Industrial Hygienists[3] has set 5 p.p.m., a level which cannot be detected by smell, as the highest average concentration in air to which workers should be exposed for long periods. The preparation and use of methyl iodide should always be performed in a well-ventilated fume hood. Since the liquid can be absorbed through the skin, care should be taken to prevent contact.

A. *4,5-Dihydro-2-(2-propenylthio)thiazole*. A solution of 11.9 g. (0.100 mole) of 2-mercapto-2-thiazoline (Note 1) in 60 ml. of tetrahydrofuran is prepared in a 200-ml., one-necked, round-bottomed flask fitted with a 25-ml., pressure-equalizing dropping funnel. Allyl bromide (12.1 g., 8.74 ml., 0.100 mole) is added in one portion at room temperature, and 5 minutes later 10.1 g. (13.9 ml., 0.100 mole) of triethylamine is added dropwise over a 10-minute period. After the dropping funnel has been replaced with a condenser, the mixture is refluxed gently for 4 hours. The resulting slurry is cooled and filtered, removing triethylamine hydrobromide, which is washed with 20 ml. of fresh tetrahydrofuran, and the

combined organic solutions are concentrated with a rotary evaporator. The residue is dissolved in 100 ml. of diethyl ether, and this solution is washed with three 20-ml. portions of 5% aqueous potassium hydroxide and two 20-ml. portions of water. After drying over anhydrous magnesium sulfate, the ethereal solution is filtered and concentrated with a rotary evaporator. Vacuum distillation of the residue gives 10.9–11.1 g. (69–70%) of 4,5-dihydro-2-(2-propenylthio)thiazole, b. p. 51–54° (0.02 mm., bath temperature 75–80°, (Note 2)); n_D^{20} 1.5864 (Note 3).

B. *4,5-Dihydro-2-[(1-phenylmethyl-2-propenyl)thio]thiazole*. A dry, 100-ml., four-necked, round-bottomed flask is fitted with a thermometer, a rubber septum, a pressure-equalizing dropping funnel, and a mechanical stirrer (Note 4). A positive pressure of nitrogen, applied either through an adapter inserted in the top of the funnel or through a needle inserted in the septum, is maintained throughout the reaction. A solution of 2.0 g. (0.012 mole) of the thiazole prepared in part A in 24 ml. of dry tetrahydrofuran (Note 5) is placed in the flask, stirred vigorously, and cooled in an acetone–dry ice bath. When the internal temperature reaches –55°, 6.0 ml. (0.013 mole) of a 2.1 *M* solution of *n*-butyllithium in *n*-hexane (Note 6) is added by syringe at a rate such that the temperature remains below –55°; approximately 5 minutes is required. After stirring for an additional 20 minutes at –55° to –60°, a solution of 2.15 g. (0.0125 mole) of benzyl bromide (Note 7) in 2 ml. of dry tetrahydrofuran is added at a rate such that the temperature remains below –55°, which again requires approximately 5 minutes. The solution is stirred for another 50 minutes at –55° to –60°, allowed to warm to 0° over 30 minutes, and poured onto 70 ml. of ice water. The resulting mixture is extracted with three 25-ml. portions of ethyl acetate; the extracts are combined, washed with two 15-ml. portions of saturated aqueous sodium chloride, and dried over anhydrous magnesium sulfate.

Removal of solvent from the extracts leaves a residue that is purified by dry-column chromatography.[4] The residue is dissolved in 40 ml. of acetone in a 300-ml., round-bottomed flask, 30 g. of silica gel (Note 8) is added, and the acetone is removed with a rotary evaporator. The resulting solid mixture is placed on top of 360 g. of dry silica gel (Note 8) packed in flexible nylon tubing (Note 9), and the column is developed with 420 ml. of 10:1 (v/v) benzene–acetone. Approximately 150 ml. of solvent drips from the bottom of the column toward the end of development; this eluent is collected in 25-ml. fractions and checked for product by TLC (Note 10). The column itself is then cut into 2-cm. sections, the silica gel in each section is eluted with three 25-ml. portions of ethyl acetate, and the eluent from each section is analyzed by TLC (Note 10). Combination of all the product-containing fractions yields 1.2–1.5 g. (40–47%) of the benzylated compound as an oil, n_D^{20} 1.6083 (Note 11) and (Note 12).

C. *(E)-1-Iodo-4-phenyl-2-butene*. A 20-ml., round-bottomed flask is charged with 2.0 g. (0.008 mole) of the thiazole prepared in Part B, 5 ml. of methyl iodide, and 2 ml. of *N,N*-dimethylformamide. The resulting solution is heated at 75–80° for 2.5 hours under a nitrogen atmosphere (Note 13), cooled, and poured into 10 ml. of water. Extraction with three 12-ml. portions of ether separates the product from water-soluble by-products. The extracts are combined, washed with 8 ml. of 1% aqueous sodium thiosulfate and two 8-ml. portions of water, dried over anhydrous magnesium sulfate, and filtered. Removal of ether by distillation at 30° (100 mm.) leaves 1.5–1.7 g. (74–82%) of (*E*)-1-iodo-4-phenyl-2-butene (Note 14) and (Note 15).

2. Notes

1. This product was purchased from the Aldrich Chemical Company, Inc., and used without further purification.
2. Rapid distillation is required to avoid a [3,3]-sigmatropic rearrangement, which gives *N*-allylthiazolidine-2-thione.
3. IR (neat) cm.$^{-1}$: 1570, 995, 965, 920; ^{1}H NMR ($CDCl_3$), (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 3.39 (t, *J* = 7, 2H, ring CH_2), 3.75 (d, *J* = 6, 2H, allylic CH_2), 4.20 (t, *J* = 7, 2H, ring CH_2), 5.0–5.4 (m, 2H, $CH{=}CH_2$), 5.6–6.3 (m, 1H, $CH{=}CH_2$).
4. A three-necked flask may be used if magnetic stirring is substituted for mechanical stirring or if benzyl bromide is added with a syringe instead of a dropping funnel.
5. Tetrahydrofuran was distilled from lithium aluminum hydride immediately prior to use. See *Org. Synth.*, **Coll. Vol. 5**, 976 (1973) for precautions.
6. This product was purchased from Sankyo Kasei, Inc., Tokyo (submitters) and Ventron Corporation (checkers).
7. This product was purchased from the Aldrich Chemical Company, Inc., and distilled prior to use, b.p. 126–128° (80 mm.).
8. Woelm silica gel for dry-column chromatography, activity III/30 mm. (according to Brockmann and Schodder,[5]) was supplied by M. Woelm, Eschwege, Germany.
9. Woelm nylon column DCC-5 was used, giving a packed column 66–67 cm. high and 32 mm. in diameter.
10. Merck precoated silica gel F_{254} plates, layer thickness 0.25 mm., were used. Developed with 10:1 (v/v) benzene–acetone and visualized with UV light, the product appears at R_f 0.58–0.67. Normally the product is found

in the lower third of the column, and occasionally some is found in the last fractions of eluent collected during development. However, since the exact position of this material on the column depends critically on the way in which the column is packed, a thorough check of all fractions is advisable.

11. IR (neat) cm.$^{-1}$: 1570, 995, 965, 920, 740, 700; ^{1}H NMR ($CDCl_3$), δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 2.9–3.4 (m, 4H, ring CH_2 and $C_6H_5CH_2$), 4.14 (t, *J* = 8, 2H, ring CH_2), 4.3–4.7 (m, 1H, allylic C*H*), 4.9–5.3 (m, 2H, CH_2=CH), 5.5–6.2 (m, 1H, CH_2=C*H*), 7.23 (broad s, 5H, C_6H_5).

12. The submitters also tried to purify the crude product by distillation (130–145° at 0.005 mm.), but under these conditions decomposition occurred. It is possible to substitute thick-layer chromatography for the dry column. Using Merck silica gel F_{254} precoated plates, layer thickness 2 mm., and developing with 10:1 (v/v) benzene–acetone, the submitters report a 73% yield of pure product.

13. *N*-Methyl-2-methylthiothiazolium iodide (m.p. 132°) usually precipitates as the reaction proceeds.

14. (*E*)-1-Iodo-4-phenyl-2-butene is reported to decompose on attempted distillation at 4 mm.[6] The crude product, which is suitable for subsequent reactions (see (Note 15)), may be purified by thick-layer chromatography. Using the plates described in (Note 10) and developing with hexane, the product is found at R_f 0.5 as an oil, n_D^{20} 1.5940; IR (neat) cm.$^{-1}$: 1655 weak, 1600 medium, 1460 strong, 1150 strong, 960 strong (*trans*-CH=CH-), 740 strong, 690 strong; ^{1}H NMR ($CDCl_3$), δ (multiplicity, number of protons, assignment): 3.2–3.5 (m, 2H, $C_6H_5CH_2$), 3.7–4.0 (m, 2H, CH_2I), 5.6–5.9 (m, 2H, vinylic C*H*), 7.23 (broad s, 5H, C_6H_5).

15. This material may be converted directly to a phosphonium salt: 1.40 g. (0.00545 mole) of the crude iodide is dissolved in 20 ml. of benzene, and 1.42 g. (0.00542 mole) of triphenylphosphine is added. On standing, 2.5 g. (77%) of the triphenylphosphonium salt precipitates as a colorless 1:1 complex with benzene, m.p. 135–137°. Recrystallization from methanol–benzene raises the melting point to 140–142°. Analysis calculated for $C_{28}H_{29}PI \cdot C_6H_6$: C, 68.23; H, 5.39. Found: C, 68.15; H, 5.28.

3. Discussion

(*E*)-1-Iodo-4-phenyl-2-butene has been prepared previously by addition of phenyl and chloro units [generated by decomposition of phenyldiazonium chloride in the presence of a catalytic amount of copper(II) chloride] across the conjugated system of butadiene, followed by treatment with ethanolic potassium iodide.[6]

The present preparation illustrates a general and convenient method for the *trans*-iodopropenylation of an alkyl halide.[7] The iodopropenylated material is not usually stable but is a useful synthetic intermediate. For example, it forms a stable crystalline triphenylphosphonium salt for use in the Wittig reaction, and under Kornblum reaction conditions it gives an (*E*)-α,β-unsaturated aldehyde. In addition to the phosphonium salt described in (Note 15), the following have been prepared: (4-methoxyphenyl-2-butenyl)triphenylphosphonium iodide, m.p. 123–127°; (2-octenyl)triphenylphosphonium iodide, m.p. 98°; and (2-octadecenyl)triphenylphosphonium iodide, m.p. 50°.

The alkylation of 4,5-dihydro-2-(2-propenylthio)thiazole is noteworthy, since in general the coupling of an alkyllithium and an alkyl halide gives many by-products due to halogen–metal interconversion.[8] In the present case, alkylation α to sulfur occurred cleanly and may be attributed to a five-membered chelating effect.[9,10] In some cases, addition of 1/10–1/20 volume of hexamethylphosphoric triamide to the tetrahydrofuran solution facilitates the alkylation. Representative alkyl halides examined and the yields of products isolated are as follows: (a) amyl bromide, (63%); (b) decyl bromide, (70%); (c) anisyl chloride, (57%); (d) phenethyl bromide, (59%); and (e) cyclohexyl bromide, (52%).[7,9] The same type of alkylation occurred successfully with anions of the 4,5-dihydro derivatives of 2-(methylthio)thiazole, 2-[(3-phenyl-2-propenyl)thio]thiazole, and 2-(phenylmethylthio)thiazole, but attempts to alkylate 4,5-dihydro-2-(ethylthio)thiazole, 2-(methylthio)- or 2-(2-propenylthio)benzo[d]thiazole were unsuccessful.

The final step, C-S bond cleavage with allylic rearrangement, incorporates two useful features. First, it is stereospecific, producing only the (*E*)-iodopropenylated product. Second, the sulfur-containing moiety is converted to a water-soluble product; thus, the desired material may be isolated in reasonable purity by a simple water–ether partitioning of the crude reaction mixture. The present procedure represents an improvement over a previous iodomethylation sequence (lithiation of thioanisole, alkylation, and cleavage with methyl iodide and sodium iodide in *N*,*N*-dimethyl formamide at 75°), in which the product must be separated from thioanisole.[11]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

2-(methylthio)- or 2-(2-propenylthio)benzo[d]thiazole

Benzene (71-43-2)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

sodium chloride (7647-14-5)

Allyl bromide (106-95-6)

potassium iodide (7681-11-0)

sodium thiosulfate (7772-98-7)

nitrogen (7727-37-9)

phenyldiazonium chloride

sulfur (7704-34-9)

acetone (67-64-1)

potassium hydroxide (1310-58-3)

copper(II) chloride (7758-89-6)

Cyclohexyl bromide (108-85-0)

Methyl iodide (74-88-4)

sodium iodide (7681-82-5)

magnesium sulfate (7487-88-9)

phenethyl bromide (103-63-9)

butadiene (106-99-0)

benzyl bromide (100-39-0)

n-butyllithium (109-72-8)

2-mercapto-2-thiazoline

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

N,N-dimethylformamide, N,N-dimethyl formamide (68-12-2)

hexane, n-hexane (110-54-3)

triethylamine (121-44-8)

anisyl chloride (623-12-1)

triphenylphosphine (603-35-0)

triethylamine hydrobromide (636-70-4)

hexamethylphosphoric triamide (680-31-9)

thioanisole (100-68-5)

amyl bromide (110-53-2)

4,5-Dihydro-2-(2-propenylthio)thiazole (3571-74-2)

triphenylphosphonium

decyl bromide (112-29-8)

2-(methylthio)thiazole

2-[(3-phenyl-2-propenyl)thio]thiazole

2-(phenylmethylthio)thiazole

4,5-dihydro-2-(ethylthio)thiazole

(E)-1-Iodo-4-phenyl-2-butene, 2-Butene, 1-iodo-4-phenyl, (E)- (52534-83-5)

N-allylthiazolidine-2-thione

N-Methyl-2-methylthiothiazolium iodide

4,5-Dihydro-2-[(1-phenylmethyl-2-propenyl)thio]thiazole (52534-82-4)

(4-methoxyphenyl-2-butenyl)triphenylphosphonium iodide

(2-octenyl)triphenylphosphonium iodide

(2-octadecenyl)triphenylphosphonium iodide

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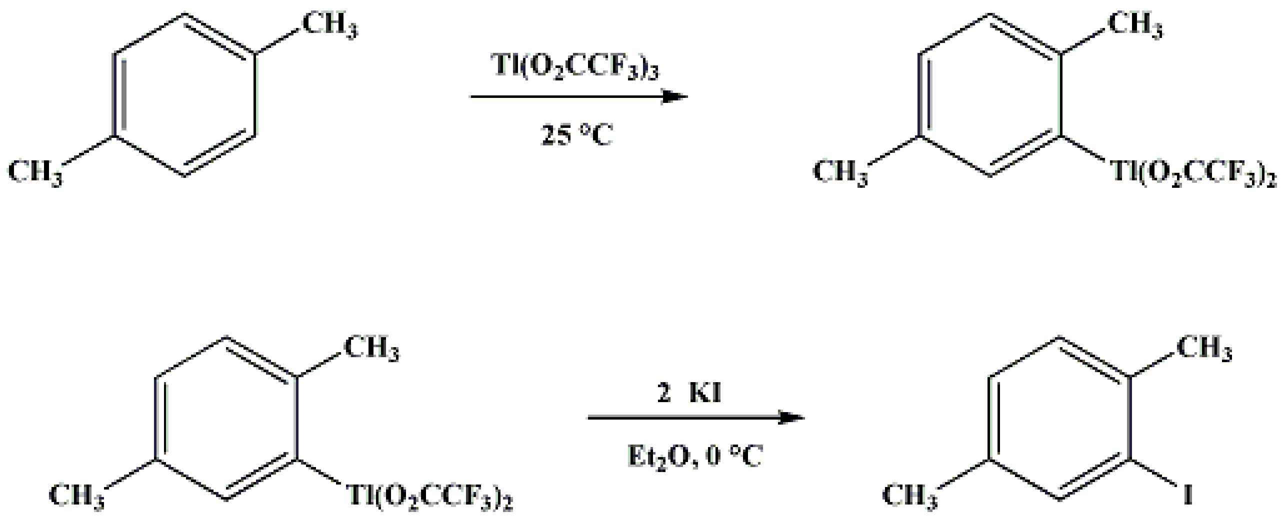
Organic Syntheses, CV 6, 709

2-IODO-*p*-XYLENE

[Benzene, 2-iodo-1,4-dimethyl]



Submitted by Edward C. Taylor[1], Frank Kienzle[1], and Alexander McKillop[2].
Checked by Gordon S. Bates and S. Masamune.

1. Procedure

Caution! Thallium salts are very toxic. This preparation should be carried out in a well-ventilated hood. The operator should wear rubber gloves. For disposal of thallium wastes, see (Note 1) in Org. Synth., ***Coll. Vol. 6****, 791 (1988).*

A 500-ml., round-bottomed flask equipped with a magnetic stirring bar and a glass stopper is charged with 110 ml. of trifluoroacetic acid (Note 1) and 54.34 g. (0.1008 mole) of solid thallium(III) trifluoroacetate (Note 2). A clear solution is obtained after 30 minutes of vigorous stirring. Upon addition of 10.6 g. (0.100 mole) of *p*-xylene (Note 3), the reaction mixture turns brown (Note 4). After vigorous stirring for 20 minutes, the trifluoroacetic acid is removed on a rotary evaporator with a bath temperature of 35°, and the residue is dissolved in 100 ml. of diethyl ether. The solvent is again evaporated, and the solid residue is dissolved in 100 ml. of ether. With ice cooling (Note 5), a solution of 33.2 g. (0.200 mole) of potassium iodide in 100 ml. of water is added in one portion. After the resulting dark suspension is stirred vigorously for 10 minutes, a solution of 3 g. of sodium bisulfite in 30 ml. of water is added (Note 6). Yellow thallium(I) iodide is removed by filtration after another 10 minutes of vigorous stirring and washed thoroughly with 150 ml. of ether. The aqueous layer is separated and extracted with two 60-ml. portions of ether. The combined ether extracts are washed once with 10% aqueous sodium hydroxide (Note 7) and twice with 20 ml. of water. After being dried over anhydrous magnesium sulfate for 1 hour, the ether is removed on a rotary evaporator. Distillation under reduced pressure yields 18.5–19.6 g. (80–84%) of pure 2-iodo-*p*-xylene, b.p. 110–113° (19 mm.) (Note 8),(Note 9),(Note 10).

2. Notes

1. This chemical is available from Aldrich Chemical Company, Inc., Halocarbon Products Corporation, Allied Chemical Corporation, or Eastman Organic Chemicals.
2. Both the submitters and the checkers used thallium(III) trifluoroacetate prepared from thallium(III) oxide and trifluoroacetic acid.[3] Although this material may be purchased from Aldrich Chemical Company, Inc., and Eastman Organic Chemicals, the submitters recommend that the reagent be prepared immediately prior to use.
3. This reagent is obtainable from major chemical suppliers.
4. The submitters report that *p*-xylylthallium bis(trifluoroacetate) precipitates after 5 minutes. The checkers did not obtain this precipitate until the bulk of the solvent had been evaporated.
5. The reaction of aqueous potassium iodide and *p*-xylylthallium bis(trifluoroacetate) is exothermic and the ether boils off unless the reaction mixture is cooled.
6. The sodium bisulfite is added to reduce any free iodine formed in this reaction. Due to the presence of trifluoroacetic acid in the reaction mixture, sulfur dioxide evolves upon addition of the bisulfite. If not added in small portions, this operation may cause overflow of the reaction mixture.
7. The sodium hydroxide solution should be added slowly, since the reaction with the acidic ether extract is exothermic and may cause the ether to boil. The ether extract should be washed with aqueous sodium hydroxide until the aqueous layer remains basic to litmus. This extraction is self-indicating; the ether turns from a bright yellow to a light brown and color appears in the aqueous phase.
8. There is usually a lower boiling fraction of 0.1–0.3 g. consisting mainly of unreacted *p*-xylene, along with 1.0–1.6 g. of a dark brown residue.
9. The purity of the product may be checked by GC. The submitters used a 10-m. column with 30% QF-1 on 45/60 Chrom W. The checkers used a 2-m. column of 10% UCW-98 on WAW DMCS operated at 150°.
10. The overall time needed for this preparation is less than 5 hours. The product decomposes slowly and should be refrigerated in the dark.

3. Discussion

This procedure for the synthesis of 2-iodo-*p*-xylene is slightly modified from that of Taylor and McKillop.[3] The reaction is generally applicable to a wide range of aromatic substrates,[3,4] and, with some modifications, to thiophenes. A critical feature of this synthesis is that the entering iodine substituent always replaces thallium at the same position on the aromatic ring. The great preference of the thallium electrophile for the *para*-position in activated aromatic substrates leads, therefore, to iodo-compounds of high isomeric purity. With substituents capable of chelating with the thallium(III) electrophile, thallation may occur by an intramolecular delivery route, resulting in exclusive *ortho*-substitution in optimum cases. Furthermore, aromatic electrophilic thallation is reversible, and under conditions of thermodynamic rather than kinetic control, *meta*-substitution often predominates. The preparation of aromatic iodo-compounds *via* arylthallium bis(trifluoroacetate) intermediates thus possesses the additional advantage of potential orientation control.[4]

2-Iodo-*p*-xylene has been prepared by the action of potassium iodide on diazotized *p*-xylidine (2,5-dimethylaniline) (21% yield),[5] from the reaction of *p*-xylene with molecular iodine in concentrated nitric acid (50% yield)[6] or in ethanol–sulfuric acid in the presence of hydrogen

peroxide (64% yield),[7] and with molecular iodine in glacial acetic acid–sulfuric acid in the presence of iodic acid as a catalyst (85% yield).[8]

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2. School of Chemical Sciences, University of East Anglia, Norwich, Norfolk NR4 7TJ, England.
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

ether, diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

nitric acid (7697-37-2)

sulfur dioxide (7446-09-5)

potassium iodide (7681-11-0)

sodium bisulfite (7631-90-5)

iodine (7553-56-2)

hydrogen peroxide (7722-84-1)

p-xylene (106-42-3)

iodic acid (7782-68-5)

bisulfite (7782-99-2)

magnesium sulfate (7487-88-9)

trifluoroacetic acid (76-05-1)

2,5-dimethylaniline, p-xylidine (95-78-3)

Thallium (7440-28-0)

thallium(I) iodide

thallium(III)

Benzene, 2-iodo-1,4-dimethyl, 2-Iodo-p-xylene (1122-42-5)

thallium(III) trifluoroacetate (23586-53-0)

thallium(III) oxide (1314-32-5)

p-xylylthallium bis(trifluoroacetate)

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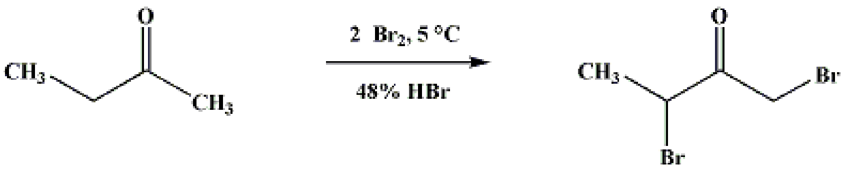
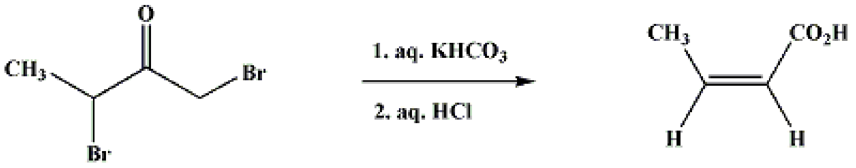
Organic Syntheses, CV 6, 711

cis-α,β-UNSATURATED ACIDS: ISOCROTONIC ACID

[2-Butenoic acid, (Z)-]





Submitted by C. Rappe[1]
Checked by A. F. Kluge and J. Meinwald.

1. Procedure

Caution! 1,3-Dibromo-2-butanone is a powerful lachrymator and a vesicant. This preparation should be carried out in a hood and contact of this compound with the skin should be avoided.

A. *1,3-Dibromo-2-butanone*. A mixture of 72.1 g. (90.0 ml., 1.00 mole) of 2-butanone and 100 ml. of precooled (5°) 48% hydrobromic acid is prepared in a 1-l., three-necked, round-bottomed flask equipped with a dropping funnel, a condenser (Note 1), and a Teflon stirrer. The flask is immersed in ice water, and when the temperature of the mixture reaches 5°, 319.6 g. (102.5 ml., 1.998 moles) of bromine is added dropwise at a rate such that the temperature does not rise above 10° and unreacted bromine does not accumulate (Note 2). After addition of the bromine is complete, 400 ml. of water is added, and the heavier organic layer is separated and immediately (Note 3) fractionated under reduced pressure (Note 4) through a 25-cm. Widmer column, giving 115–134 g. (50–58%) of pure 1,3-dibromo-2-butanone, b.p. 91–94° (13 mm.), n_D^{25} 1.5252 (Note 5) and (Note 6).

B. *Isocrotonic acid*. A solution of 100 g. (1.00 mole) of potassium hydrogen carbonate (Note 7) in 1 l. of water is placed in a 2-l., three-necked, round-bottomed flask equipped with a condenser, a dropping funnel, and a Teflon stirrer. 1,3-Dibromo-2-butanone (46.0 g., 0.200 mole) is added over a 5-minute period (Note 8). The mixture is stirred thoroughly, and after 2–3 hours (Note 9) when constant titration values against methyl orange are obtained, the solution is extracted with two 100-ml. portions of diethyl ether (Note 10) and acidified to pH 1–2 by dropwise addition of dilute hydrochloric acid (Note 11). The aqueous solution is re-extracted with six 100-ml. portions of ether, and the ether phase is dried overnight in a refrigerator over magnesium sulfate.

The ethereal solution is filtered with suction, and the ether is removed with a rotary evaporator connected to a 500-ml., acetone–dry ice trap. A water bath maintained at 5–10° is used to facilitate the removal of the ether (Note 12) and (Note 13).

The yield of crude isocrotonic acid is 11.8–13.2 g. (69–77%). It is sufficiently pure for most purposes although NMR analysis (Note 14) shows that the crude acid contains a small amount of the stable *trans*-isomer (Note 15). The crude product cannot be stored without isomerization. For purification, 13.0 g. of the product is dissolved in 25 ml. of petroleum ether (b.p. 40–65°) at 5°. When left at –15° for days, crystals separate and are filtered at 5°, yielding 9.3 g. of product, m.p. 12.5–14°, n_D^{25} 1.4453, which can be stored in the dark at 30° for 3 weeks or at 5° for years with no detectable isomerization (Note 16).

2. Notes

1. The hydrogen bromide evolved from the condenser should be absorbed in a gas trap.
2. Accumulation of bromine results in an uncontrolled reaction and a decrease in the yield. This step requires 6–8 hours.
3. The crude product soon begins to decompose if it is not distilled immediately.
4. Since corrosive vapor is evolved, a water pump should be used.
5. The distilled product might be highly colored (violet, green, and blue), but this has no effect on its further use.
6. The dihaloketone purified in this way is stable for years when stored at 5°.
7. The yield is slightly lower when other bases such as sodium hydrogen carbonate, sodium carbonate, or potassium carbonate are used.
8. The reaction is slightly exothermic.
9. Less time is required when stronger bases are used.
10. The nonacidic by-products are discarded.
11. Because of vigorous foaming, the addition must be made slowly and with care. The end-point can also be detected by a fading color of the reaction mixture. The checkers performed this acidification in the reaction flask with mechanical stirring which

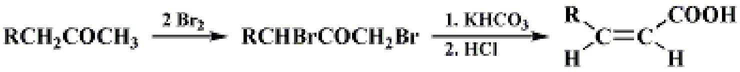
minimized the foaming.
12. The submitter used the following procedure for removal of ether. A 250-ml., two-necked, round-bottomed flask, fitted with a dropping funnel, is equipped for distillation under reduced pressure (water pump). The ethereal solution is added dropwise (Note 13) and, when all the solution is added and the pressure has dropped to 10 mm., the last traces of ether are removed with an oil pump (0.4 mm.) for a period of 30 minutes.
13. This is to avoid isomerization which is easily initiated at elevated temperature.
14. NMR spectroscopy is an excellent tool for distinguishing between the isomers.[2]
15. The checkers detected the presence of approximately 10% of the *trans*-acid by NMR analysis.
16. The crude acid could be distilled in 5–10 ml. portions at 1 mm. without isomerization (b.p. 36°), but these samples were found to be more sensitive to isomerization.

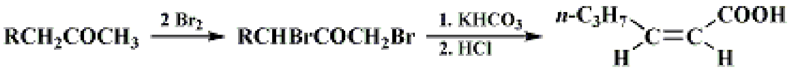
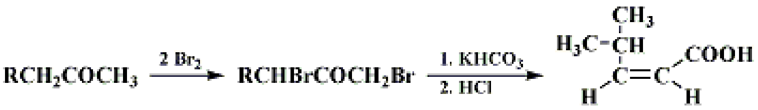
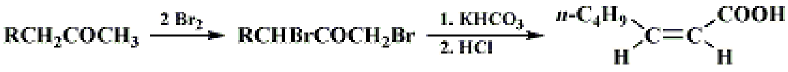
3. Discussion

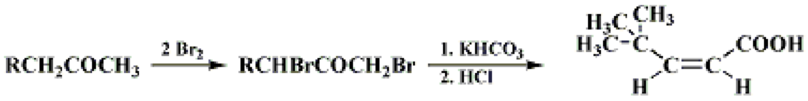
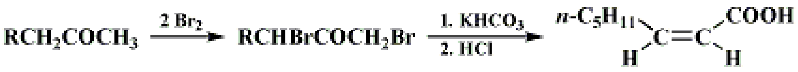
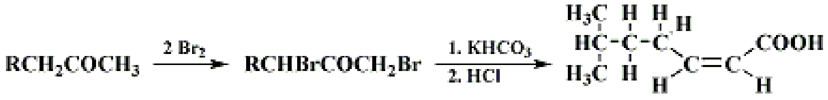
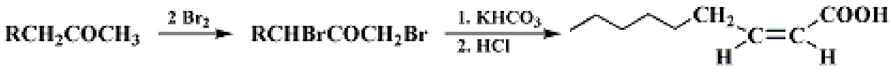
Isocrotonic acid can be prepared by the stereospecific *cis*-hydrogenation of tetrolic acid[3] or, mixed with the *trans*-isomer, by reduction of 3-chloro-*cis*-crotonic acid with sodium amalgam.[4] The *cis*-acid can also be prepared in small amounts by isomerization of the *trans*-acid.[5] The method described herein is much less laborious than the older procedures.[2]

The reaction is an example of a stereospecific Favorskii rearrangement,[6] and seems to have general applicability for the preparation of *cis*-α,β-unsaturated acids.[7] Only a limited number of the higher homologues have previously been prepared by the more laborious stereospecific *cis*-hydrogenation of the corresponding acetylenic acid,[1,8,9] and, moreover, in some cases, they seem to have been mixtures of the two geometric isomers. The rearrangements, starting with commercially available methyl ketones, yield the *cis*-isomer exclusively as determined by NMR spectroscopy.[7] The higher homologues can be purified by distillation with minimal losses. Purified in this manner, the samples can be stored at 5° for years without detectable isomerization. The yields and physical constants of the bromoketones and the *cis*-α,β-unsaturated acids are given in Table I.

TABLE I
PREPARATION OF BROMOKETONES AND *cis*-α,β-UNSATURATED ACIDS FROM METHYL KETONES



R	Bromoketone		*cis*-α,β-Unsaturated Acid				
	Yield, %	n_D^{25}	Yield, %	Time h	b.p., ° mm.	n_D^{25}	m.p., °
C_2H_5	57	1.5176	68	3	39–41 (0.4)	1.4473	–43
n-C_3H_7 	51	1.5080	61	24	71–73 (0.2)	1.4495	0–1
2-C_3H_7 	58	1.5099	85	24	59.5–60 (0.2)	1.4420	15.5–17.5
n-C_4H_9 	65	1.5043	64	20	69–70 (0.4)	1.4515	–19

	49	1.5071	75	48	60–61 (0.8)	1.4432	11–12
tert-C_4H_9							
n-C_5H_{11}							
	40	1.5001	50	48	75–76 (0.3)	1.4530	—
$(CH_3)_2CH(CH_2)_2$							
	35	1.4997	58	48	93–94 (0.2)	1.4518	—
n-C_6H_{13}							
	41	1.4983	28	96	91–92 (0.8)	1.4549	2–3

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 226

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

ether, diethyl ether (60-29-7)

sodium hydrogen carbonate (144-55-8)

HYDROBROMIC ACID, hydrogen bromide (10035-10-6)

sodium carbonate (497-19-8)

bromine (7726-95-6)

sodium (13966-32-0)

magnesium sulfate (7487-88-9)

butanone, 2-butanone (78-93-3)

bromoketone (593-95-3)

potassium hydrogen carbonate (298-14-6)

Tetrolic acid (590-93-2)

Isocrotonic acid, 2-Butenoic acid, (Z)- (503-64-0)

1,3-Dibromo-2-butanone (815-51-0)

3-chloro-cis-crotonic acid

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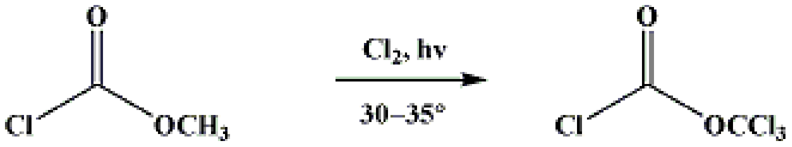
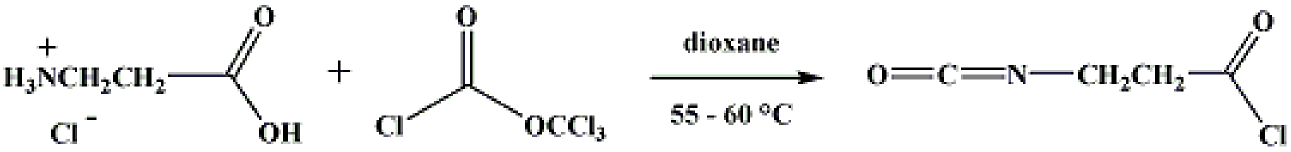
Organic Syntheses, CV 6, 715

TRICHLOROMETHYL CHLOROFORMATE AS A PHOSGENE EQUIVALENT: 3-ISOCYANATOPROPANOYL CHLORIDE

[Propanoyl chloride, 3-isocyanato-]





Submitted by Keisuke Kurita[1] and Yoshio Iwakura.
Checked by William F. Burgoyne, Christopher VanCantfort, and Robert M. Coates.

1. Procedure

Caution! Trichloromethyl chloroformate is toxic. These reactions should both be carried out in a well-ventilated hood (Note 1).

A. *Trichloromethyl chloroformate*. A 100-ml., three-necked, round-bottomed Pyrex flask is equipped with a thermometer, a reflux condenser protected at the top with a calcium chloride tube, and a gas-inlet tube with a coarse fritted-glass tip extending almost to the bottom of the flask. In the flask are placed 37.8 g. (0.400 mole) of freshly distilled methyl chloroformate (Note 2) and a Teflon-coated magnetic stirring bar. The flask is illuminated with a 100-W., high-pressure, mercury-vapor lamp (Note 3) placed beside it (Note 4) and (Note 5). The methyl chloroformate is stirred and irradiated as a slow stream of chlorine (Note 6) is passed into the flask through the gas-inlet tube (Note 7). When the temperature reaches 30° due to the exothermic reaction, the flask is immersed in a water bath (Note 8). The chlorine is then passed into the solution more rapidly so as to maintain the temperature at 30–35° (Note 9). After *ca.* 6.5–7 hours the colorless solution assumes the pale yellow-green color of chlorine, which indicates that the end point of the reaction has been reached (Note 10). Distillation under reduced pressure affords 65–72 g. (82–91%) of trichloromethyl chloroformate as a colorless liquid, b.p. 53–55° (53 mm.) (Note 11).

B. *3-Isocyanatopropanoyl chloride*. A 500-ml., two-necked flask is equipped with a thermometer and a reflux condenser protected at its top by a calcium chloride tube. A Teflon-coated magnetic stirring bar, 250 ml. of anhydrous dioxane (Note 12), 12.6 g. (0.100 mole) of finely pulverized 3-aminopropanoic acid hydrochloride (Note 13), and 23.8 g. (14.4 ml., 0.120 mole) of trichloromethyl chloroformate (Note 14) are placed in the flask in the order specified. The mixture is stirred and heated at 55–60°. After *ca.* 5 hours, the solid has completely dissolved, leaving a clear solution. The heating is discontinued after a total of 7 hours (Note 15), and the solvent is removed under reduced pressure. The residual oil is distilled rapidly under reduced pressure, yielding 11.2–12.4 g. (84–93%) of distillate at 75–85° (20 mm.) (Note 16). Redistillation affords 10.5–11.8 g. (79–88%) of 3-

isocyanatopropanoyl chloride as a colorless liquid, b.p. 92–94° (25 mm.) (Note 17).

2. Notes

1. Vapors of all of the polychlorinated methyl chloroformates are toxic.[2,3,4] Trichloromethyl chloroformate has a phosgene-like odor and is known to decompose to phosgene at elevated temperature[5] or on contact with iron(III) oxide or charcoal.[6]

2. Methyl chloroformate is available from Aldrich Chemical Company, Inc.

3. The checkers used a 200-W., high-pressure, mercury-vapor lamp and the corresponding transformer which are available from the Hanovia Lamp Division, Canrad-Hanovia, Inc., 100 Chestnut St., Newark 5, New Jersey 07105. The lamp was suspended vertically in a cylindrical, double-walled, Pyrex jacket cooled by flowing water. The inside diameter, outside diameter, and length of the cooling jacket were 3, 4, and 22 cm., respectively. The cooling jacket was clamped in place *ca.* 5 cm. from the reaction vessel to allow the cooling bath to be raised into position. The use of the 200-W. lamp did not alter the reaction time.

4. It is advisable to wrap the entire apparatus with aluminum foil to avoid exposure to UV light. The reaction solution can be observed through a small hole in the aluminum foil which is is shielded from the direct radiation of the lamp.

5. The irradiation should be started before the flow of chlorine gas is begun to avoid the risk of explosion.

6. The checkers used chlorine from a lecture bottle supplied by the Linde Division, Union Carbide Chemical Corp.

7. Chlorine should be introduced slowly at first to prevent an accumulation of unreacted chlorine in the solution and avoid the risk of a rapid, exothermic reaction. The accumulation of chlorine is indicated by the appearance of its characteristic yellow-green color.

8. The checkers used a 15 × 7.5 cm. Pyrex crystallizing dish as a transparent water bath.

9. Once the chlorine gas flow is properly adjusted, the solution remains colorless and the temperature stays in the 30–35° range without further adjustment until the end point is approached. However, the color and temperature should be observed frequently during the 6.5- to 7-hour reaction time.

Although this reaction can be carried out at higher temperatures, the yields are reduced, probably owing to loss of the volatile methyl chloroformate, b.p. 71°, and/or decomposition of the product. For example, the yields of trichloromethyl chloroformate are *ca.* 75% and 55% when the chlorination is carried out at 50–55° and 85–90°, respectively.

10. The checkers judged that the end point had been reached when the yellow-green color persisted for 2–3 minutes after the chlorine flow had been stopped. At the first appearance of the yellow-green color, the gas stream was shut off, and the color faded within *ca.* 15 sec. The chlorine flow was resumed at a slow rate until the end point was reached.

11. The product has the following spectral properties: IR (neat) $cm.^{-1}$: 1815 (C=O), 1054, 968, 912, 814, 764; ^{13}C NMR ($CDCl_3$), δ (assignment): 108.37 ($\mathit{C}Cl_3$), 143.93 (*C*=O). Trichloromethyl chloroformate is stable at room temperature, but decomposes to phosgene when heated above 300°[5] or on contact with iron(III) oxide or charcoal.[6] Decomposition to carbon tetrachloride and carbon dioxide occurs on exposure to alumina, aluminum chloride, or iron(III) chloride.[5,6,7,8]

12. The checkers dried and purified dioxane by distillation from the sodium–benzophenone ketyl.

13. 3-Aminopropanoic acid (β-alanine) is available from Aldrich Chemical Company, Inc., and from the Nutritional Biochemical Division, ICN Products. The hydrochloride salt is prepared in the following manner. A solution of 89 g. (1.0 mole) of 3-aminopropanoic acid in 200 ml. of water is acidified by addition of 100 ml. (1.20 mole) of concentrated hydrochloric

acid and concentrated to a white solid with a rotary evaporator. The solid is pulverized to a fine powder and dried at 60° under reduced pressure, yielding 113–125 g. (90–100%) of 3-aminopropanoic acid hydrochloride.

14. Although the reaction can be carried out with an equimolar amount of trichloromethyl chloroformate, a longer time (15–20 hours) is required to reach completion, and the yield is reduced somewhat. If a 1.5–2.0-fold excess of trichloromethyl chloroformate is used, the reaction time is decreased to *ca.* 5 hours and the yield is increased to 90–95%.

15. The checkers heated the suspension for a total of 10 hours, 7–8 hours having been required to dissolve the solid completely. The reaction time may depend on the particle size of the hydrochloride salt and the rate of stirring.

16. The submitters advise that the distillation be carried out rapidly to avoid the formation of a tarry residue.

17. The spectral properties of 3-isocyanatopropanoyl chloride are as follows: IR (liquid film) $cm.^{-1}$: 2278 (N=C=O), 1795 (O=C-Cl); ^{1}H NMR ($CDCl_3$), δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 3.17 (t, *J* = 6, 2H, CH_2CH_2N=C=O), 3.67 (t, *J* = 6, 2H, CH_2CH_2N=C=O); ^{13}C NMR ($CDCl_3$), δ (assignment): 38.3 (CH_2CH_2N=C=O), 47.6 (CH_2CH_2N=C=O), 123.0 (N=C=O), 171.6 (O=*C*-Cl). A small peak at δ 67.1 in the ^{13}C NMR spectrum of the product obtained by the checkers was attributed to a small amount of dioxane.

3. Discussion

The chlorination of methyl chloroformate in sunlight was first reported by Hentschel, but without a detailed description of either the procedure or the results.[5] The first step of the present procedure for the preparation of trichloromethyl chloroformate utilizes a UV light source and affords a simple, reproducible way to obtain this reagent. Although trichloromethyl chloroformate may also be synthesized by photochemical chlorination of methyl formate,[9,10,11] the volatility of methyl formate causes losses during the reaction and increases the hazard of forming an explosive mixture of its vapor and chlorine gas. The preparation of trichloromethyl chloroformate by chlorination of methyl chloroformate in the dark with diacetyl peroxide as initiator has been reported;[12] however, the procedure consists of several steps, and the overall yield is rather low.

Trichloromethyl chloroformate is synthetically useful as a substitute for phosgene, which, owing to its high volatility and toxicity, presents a severe hazard in the laboratory. Although trichloromethyl chloroformate is toxic, it is a dense and less volatile liquid (b.p. 128°, d^{15}_{15} 1.65), having a vapor pressure of only 10 mm. at 20°. Consequently it is more easily handled in a safe manner than phosgene.

Trichloromethyl chloroformate has proven effective in the preparation of *N*-carboxy-α-amino acid anhydrides from amino acids,[13] and various compounds having isocyanate, acid chloride, and chloroformate groups.[14,15] For example, trichloromethyl chloroformate may be used instead of phosgene in the preparation of 2-*tert*-butoxycarbonyloxyimino-2-phenylacetonitrile.[15] The use of this reagent is illustrated here by the synthesis of 3-isocyanatopropanoyl chloride from 3-aminopropanoic acid hydrochloride.

3-Isocyanatopropanoyl chloride has also been prepared by the reaction of 3-aminopropanoic acid hydrochloride with phosgene;[16] however, the yield is only 36%, and hydrogen chloride must be introduced to increase the yield to 92%. The present procedure effects this reaction without additional hydrogen chloride and avoids the hazards of handling phosgene. This procedure has been

successful in the synthesis of isocyanato acid chlorides and isocyanato chloroformates from amino acids and amino alcohols, respectively.[14] For example, 6-isocyanatohexanoyl chloride can be prepared in good yield with trichloromethyl chloroformate, although it is obtained in only trace amounts with phosgene unless additional hydrogen chloride is used. Isocyanato acid chlorides such as 3-isocyanatopropanoyl chloride, having two different, highly reactive electrophilic groups, are novel reagents for introducing amino acid residues into organic compounds[14] and polymers.[17]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 199
- Org. Syn. Coll. Vol. 9, 242

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alumina

benzophenone ketyl

hydrogen chloride, hydrochloric acid (7647-01-0)

carbon tetrachloride (56-23-5)

carbon dioxide (124-38-9)

aluminum chloride (3495-54-3)

chlorine (7782-50-5)

sodium (13966-32-0)

phosgene (75-44-5)

iron(III) chloride (7705-08-0)

methyl formate (107-31-3)

iron(III) oxide (1309-37-1)

β-Alanine, 3-aminopropanoic acid (107-95-9)

dioxane (5703-46-8)

methyl chloroformate, methyl chloroformates (79-22-1)

diacetyl peroxide (110-22-5)

Trichloromethyl chloroformate (503-38-8)

2-tert-Butoxycarbonyloxyimino-2-phenylacetonitrile (58632-95-4)

3-Isocyanatopropanoyl chloride, Propanoyl chloride, 3-isocyanato- (3729-19-9)

3-aminopropanoic acid hydrochloride

6-isocyanatohexanoyl chloride

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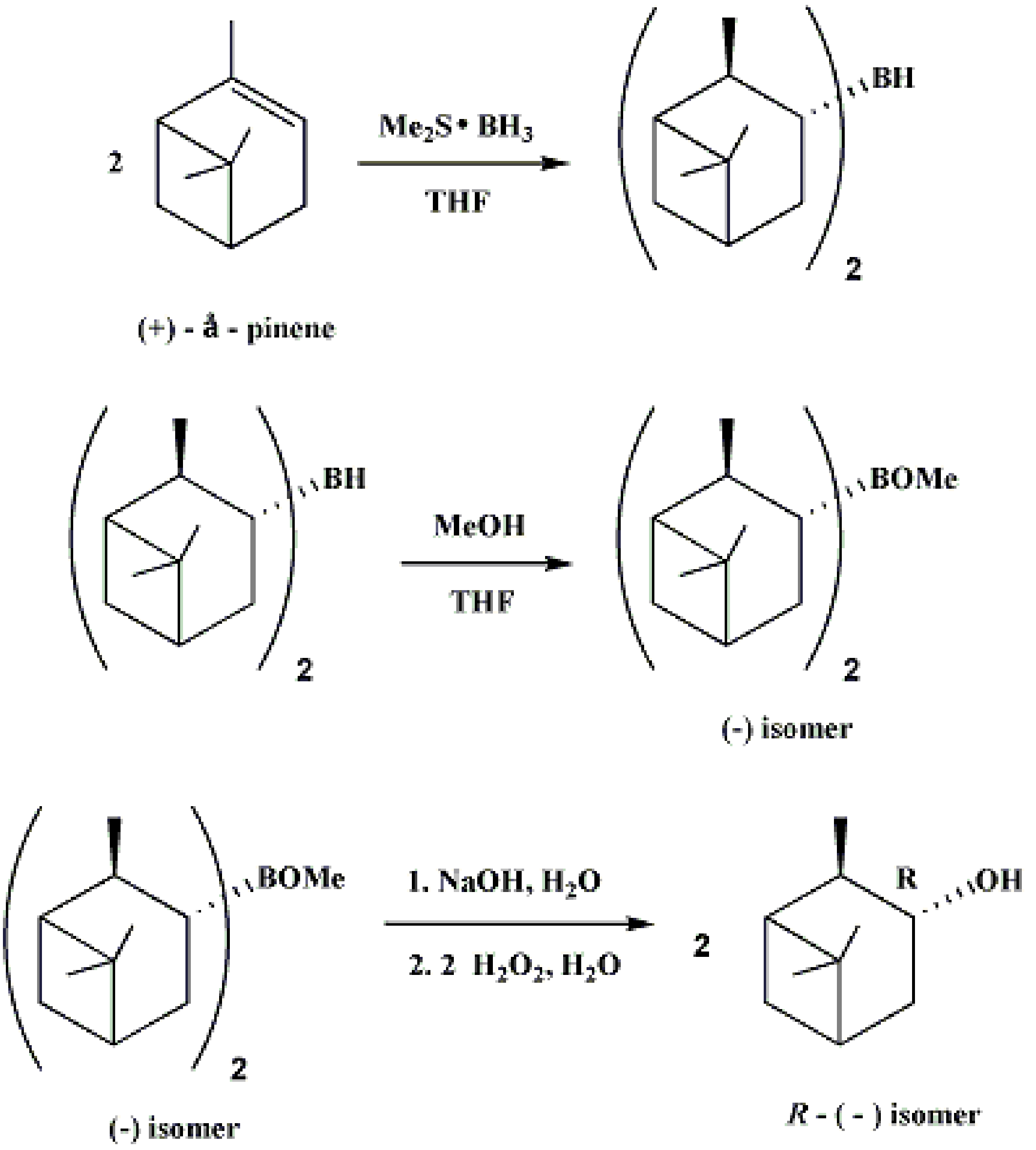
Organic Syntheses, CV 6, 719

(–)-ISOPINOCAMPHEOL

[Bicyclo[3.1.1]heptan-3-ol, 2,6,6-trimethyl-, [1*R*-(1α,2β,3α,5α)]-]



Submitted by C. F. Lane and J. J. Daniels[1].
Checked by D. M. Ryckman and R. V. Stevens.

1. Procedure

A 300-ml., three-necked flask (Note 1), equipped with a magnetic stirring bar, thermometer, pressure-equalizing dropping funnel fitted with septum inlet adapter (Note 2), and reflux condenser fitted with a hose adapter leading to a mineral oil bubbler (Note 3), is charged with 10.0 ml. (0.100 mole) of borane–methyl sulfide complex (Note 4) and 30 ml. of tetrahydrofuran (Note 5) and (Note 6). The flask is immersed in an ice-water bath as 27.2 g. (31.7 ml., 0.200 mole) of (+)-α-pinene (Note

7) is added dropwise at 0–3° to the well-stirred reaction mixture over a period of 15 minutes. The (–)-diisopinocampheylborane [(–)-di-3-pinanylborane] precipitates as a white solid as the reaction proceeds. Following addition, the reaction mixture is stirred for 3.5 hours at 0°. Under a slow stream of nitrogen, the outlet hose adapter on the reflux condenser is connected with rubber vacuum hose to a vacuum trap which is then cooled in an acetone–dry ice bath. The dimethyl sulfide and tetrahydrofuran are bulb-to-bulb vacuum-distilled (0.1 mm.) with the reaction flask in a room temperature water bath. When only a dry, white solid residue remains, the vacuum is released with nitrogen. The flask is again placed under a slight positive pressure of nitrogen. The solid is slurried in 36 ml. of tetrahydrofuran (Note 5) at room temperature. An additional 4.08 g. (4.76 ml., 0.030 mole) of (+)-α-pinene (Note 7) is added. The resulting slurry is stirred at room temperature for 5 minutes and then stored under nitrogen in a closed system in a cold room at 4° for 3 days (Note 8). The flask is then removed from the cold room and immersed in an ice-water bath. Under a slow stream of nitrogen, the outlet adapter on the reflux condenser is again connected to the mineral oil bubbler. The excess hydride is destroyed by the slow, dropwise addition of 8 ml. of methanol (Note 9), followed by the addition in one portion of 36.6 ml. of 3 *M* aqueous sodium hydroxide. The borinic acid intermediate is now oxidized by the dropwise addition of 24 ml. of 30% aqueous hydrogen peroxide (Note 10) to the well-stirred reaction mixture at 35° ± 3° (Note 11). After the hydrogen peroxide addition is complete, the ice-water bath is replaced with a warm-water bath and the reaction mixture is stirred for one hour at 50–55° (Note 12) and then cooled to room temperature. The aqueous layer is saturated with sodium chloride and 50 ml. of diethyl ether is added. The upper organic layer is removed, and the aqueous layer is extracted with two 100-ml. portions of ether. The organic layer and extracts are combined, dried over anhydrous potassium carbonate, filtered, and concentrated to an oil on a rotary evaporator at 60° (15 mm.) (Note 13). The crude product is fractionally distilled using a 30-cm. column packed with glass helices, giving 24.7 g. (80%) of (–)-isopinocampheol, b.p. 60–65° (0.1 mm.) (Note 14). The distillate crystallizes completely in the receiver, m.p. 49–55°, 97.5% purity by GC, $[\alpha]^{19}_{D}$ –34.3° (C, 20 in ethanol) (Note 15). Slurrying 4.7 g. in 2.3 ml. of pentane at room temperature, cooling to –78°, collecting on a filter, and air drying gives 3.8 g. of crystalline (–)-isopinocampheol, m.p. 52–55°, purity 99.2% by GC, $[\alpha]^{19}_{D}$ –34.9° (C, 20 in ethanol).

2. Notes

1. The apparatus is dried in an oven and assembled hot while being flushed with nitrogen. A slow stream of nitrogen is continued until the apparatus is cool. Alternatively, the apparatus can be assembled and then flame-dried while flushing with nitrogen.
2. A suitable septum inlet adapter is available from Aldrich Chemical Company (product number Z10, 130-3).
3. A suitable bubbler is available from Aldrich (product number Z10, 121-4) and used to maintain a slight positive pressure of nitrogen in the reaction vessel.

4. Borane–methyl sulfide complex was obtained from Aldrich and used as received.
5. An anhydrous grade of tetrahydrofuran was obtained from Aldrich and used as received.
6. Borane–methyl sulfide and anhydrous tetrahydrofuran are extremely moisture-sensitive. All transfers must be done under a nitrogen atmosphere, with syringe techniques being the most convenient.[2]
7. (+)-α-Pinene ($[\alpha]_D^{21}$ +47.1°) was obtained from Aldrich and was short-path vacuum-distilled under nitrogen from a small amount of lithium aluminum hydride.
8. The equilibrated (–)-diisopinocampheylborane obtained at this point can be utilized directly for asymmetric hydroboration.[3]
9. Since the pinene is hydroborated only to the dialkylborane stage (R_2BH), methanolysis liberates a large amount of hydrogen. The rate of evolution is controlled by the slow addition of methanol, and some foaming is observed. *The hydrogen must be vented to an efficient hood*. Water can be used to destroy the hydride, but methanol addition is easier to control and the final mixture is homogenous once methanolysis is complete.
10. Thirty percent aqueous hydrogen peroxide was obtained from Aldrich and used as received.
11. The oxidation is exothermic and can be quite vigorous. It should be controlled by the slow, dropwise addition of hydrogen peroxide. Cooling in an ice-water bath is necessary. However, a reaction temperature of around 35° must be maintained.
12. The additional one hour of heating is necessary to destroy excess hydrogen peroxide. Oxygen is evolved and some foaming occurs.
13. The oil solidifies upon cooling but can be easily remelted in a warm-water bath for transfer to a small distillation flask.
14. An air-cooled condenser is used for the distillation of isopinocampheol.
15. The enantiomeric excess of (–)-isopinocampheol was determined to be greater than 95% by 200 MHz ^1H NMR using the chiral shift reagent, tris[3-heptafluoropropylhydroxymethylene)-d-camphorato], europium(III). Addition of the lanthanide reagent (40 mg., 0.034 mmol.) to the chiral alcohol (30 mg., 0.21 mmol.) produced a shift of 7.5 p.p.m. in the peak centered around δ 4.05. Only one broad peak was observed.
Treatment of (±)-isopinocampheol in a similar manner gave two broad singlets of equal intensity centered around δ 10.75 (separated by 0.15 p.p.m.), attributable to the diastereomeric protons.

3. Discussion

Isopinocampheol has been prepared by hydroboration of α-pinene using *in situ* generated diborane with diglyme as the solvent.[4]

The present procedure employs a recently developed method which provides a product of greatly improved enantiomeric purity (>99%).[5] Also, this preparation utilizes commercially available borane–methyl sulfide and α-pinene of 92% enantiomeric purity. An equilibration is used to improve the optical purity of the intermediate dialkylborane.

Isopinocampheol is only of limited interest. More importantly this procedure provides optically pure (–)-diisopinocampheylborane, a very versatile reagent which has been used widely for the synthesis of many chiral products.[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 943
- Org. Syn. Coll. Vol. 7, 339
- Org. Syn. Coll. Vol. 9, 522

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

diborane

(–)-ISOPINOCAMPHEOL

(–)-diisopinocampheylborane

(–)-di-3-pinanylborane

tris[3-heptafluoropropylhydroxymethylene)-d-camphorato], europium(III)

ethanol (64-17-5)

potassium carbonate (584-08-7)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

oxygen (7782-44-7)

nitrogen (7727-37-9)

hydrogen peroxide (7722-84-1)

Pentane (109-66-0)

borane (7440-42-8)

methyl sulfide, dimethyl sulfide (75-18-3)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

diglyme (111-96-6)

Isopinocampheol (27779-29-9)

(+)-α-pinene, α-pinene

pinene (18172-67-3)

Bicyclo[3.1.1]heptan-3-ol, 2,6,6-trimethyl-, [1R-(1α,2β,3α,5α)]- (1196-00-5)

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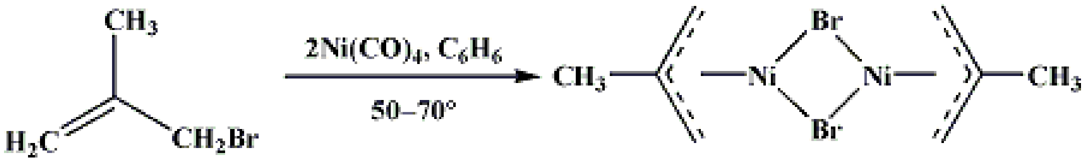
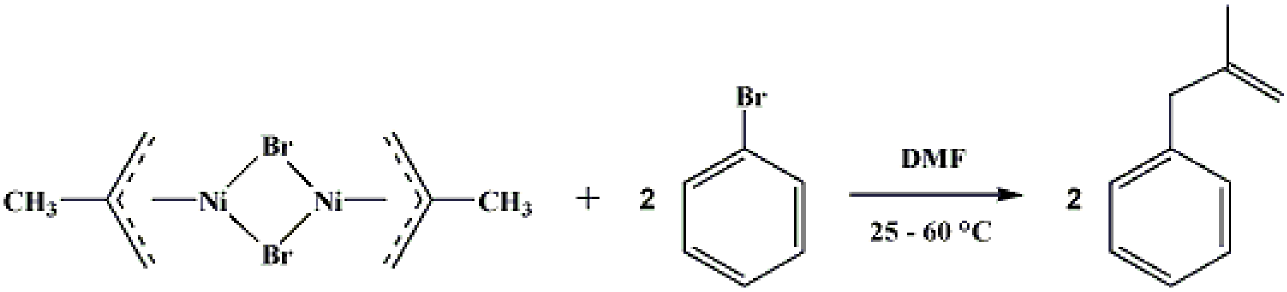
Organic Syntheses, CV 6, 722

REACTION OF ARYL HALIDES WITH π-ALLYLNICKEL HALIDES: METHALLYLBENZENE

[Benzene, (2-methyl-2-propenyl)-]





Submitted by Martin F. Semmelhack[1] and Paul M. Helquist[2].
Checked by Bradley E. Morris and Richard E. Benson.

1. Procedure

Caution! Nickel carbonyl is a flammable, volatile (b.p. 43°), highly toxic reagent. Safety glasses, gloves, and an apron should be worn when handling this reagent and the first step of this preparation should be conducted in an efficient hood (Note 1).

Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A 1-l., three-necked flask is equipped with a reflux condenser, a pressure-equalizing dropping funnel, a three-way stopcock, and a large magnetic stirring bar. The system is flushed with argon (Note 2), and 380 ml. of benzene (Note 3) is placed in the flask. From an inverted lecture cylinder 50.8 g. (38.5 ml., 0.298 mole) of nickel carbonyl (Note 4) is introduced into the addition funnel. The nickel carbonyl is added to the benzene while an atmosphere of argon is maintained, and the flask is immersed in an oil bath at 50°. With a syringe, 10.04 g. (0.07437 mole) of methallyl bromide (Note 5) is added over 10 minutes. After a short induction period, evolution of carbon monoxide becomes rapid and a deep red color appears. The exit gas is led from the top of the condenser through a gas bubbler tube to monitor the rate of gas evolution. As the gas evolution becomes vigorous, the bath temperature is raised to 70° and maintained at this temperature for 30 minutes after gas evolution ceases (the total time after addition of methallyl bromide is 1.5 hours). The resulting solution is allowed to cool to 25°, and the benzene and excess nickel carbonyl are removed under reduced pressure (water aspirator), applying an oil bath at 30° as needed to maintain a rapid rate of evaporation (Note 6). The residual, red, solid π-methallylnickel bromide (>85%) is used directly in the next step (Note 7).

A solution of 9.95 g. (0.0634 mole) of bromobenzene (Note 8) in 100 ml. of oxygen-free *N,N*-dimethylformamide is added, under an argon atmosphere at 25°, to a solution of the crude nickel complex (an 85% yield is assumed) in 65 ml. of oxygen-free *N,N*-dimethylformamide, over a 15-minute period. After the addition is complete, the reaction mixture is stirred at 25° for 12 hours, then warmed to 60° for one hour. Complete reaction of the nickel complex is indicated by a red to emerald green color change, characteristic of a solution of nickel dibromide in *N,N*-dimethylformamide. After being cooled to 25°, the solution is poured into a mixture of 250 ml. of water and 250 ml. of petroleum ether (b.p. 30–60°); 2 ml. of 12 *M* hydrochloric acid is added (Note 10), and the mixture is filtered through Celite filter aid, facilitating separation of the layers. The organic layer is separated, washed with two 100-ml. portions of water, dried over anhydrous magnesium sulfate, and concentrated with a rotary evaporator at water aspirator pressure, affording 8.0–9.6 g. of a clear, colorless liquid. Distillation through a short Vigreux column gives 5.58–6.02 g. (67–72% yield based on bromobenzene) of methallylbenzene as a colorless liquid, b.p. 67–68° (19 mm.), n_D^{25} 1.5064 (Note 11).

2. Notes

1. The treatment for nickel carbonyl poisoning involves intramuscular injection of BAL (2,3-dimercapto-1-propanol).[3]

2. Argon is preferred by the submitters for its high density which allows opening of the reaction vessel without significant displacement of the inert atmosphere by air. A nitrogen atmosphere was used by the checkers and was equally effective in preventing oxidation of the π-allylnickel complex.

3. Anhydrous, air-free benzene was prepared by distillation under argon, discarding a 20% forerun. The checkers used benzene from a freshly opened bottle (Fisher Scientific Company).

4. Nickel carbonyl, available from Matheson Gas Products, was used by the checkers.

5. Methallyl bromide is prepared from methallyl chloride (Eastman Organic Chemicals) with a halide exchange reaction. A solution of 148.3 g. (1.639 moles) of methallyl chloride and 213.8 g. (2.460 moles) of lithium bromide in 1 l. of dry acetone is refluxed for 5 hours. The mixture is filtered, and the filtrate is distilled through a 30-cm. Vigreux column, affording 69.2 g. (31.3%) of methallyl bromide, b.p. 88–93°, n_D^{25} 1.4672. The purity was 98 ± 2% by GC analysis on a 20% Carbowax column at 65°.

6. Nickel carbonyl is drawn into the aspirator flow during this operation. In many laboratories the hood plumbing is connected with the general plumbing line, and vapors of highly toxic nickel carbonyl may diffuse back to sinks at the laboratory bench. If such an arrangement is suspected, the solvent and excess nickel carbonyl can be collected by employing a cold trap (−78° or −196°) between the reaction mixture and the aspirator. Care should be used in the disposal of this mixture.

7. Pure π-methallylnickel bromide can be obtained by dissolving the residue in 150 ml. of oxygen-free anhydrous diethyl ether, filtering under argon, concentrating the filtrate until crystals begin to form, and cooling at −78° for 12 hours. The crystals are isolated by removing the liquid *via* suction through a syringe needle under a positive pressure of argon, yielding 12.1 g. (85%) of dark-red crystals. The ^1H NMR spectrum can be obtained only by rigorous exclusion of oxygen from the sample and filtration of the sample as the last stage of sample preparation. The ^1H NMR spectrum (C_6D_6) shows three singlets at δ 2.07 (3H), 2.82 (2H), and 2.83 (2H).

8. Bromobenzene was used as supplied by Aldrich Chemical Company, Inc. Purification by distillation under argon did not change the yield of methallylbenzene. The checkers used the product available from Eastman Organic Chemicals (white label).

9. *N,N*-Dimethylformamide was distilled from calcium hydride at 71° (32 mm.) and stored under argon. The checkers used a freshly opened bottle of the product (white label grade) available from Eastman Organic Chemicals.

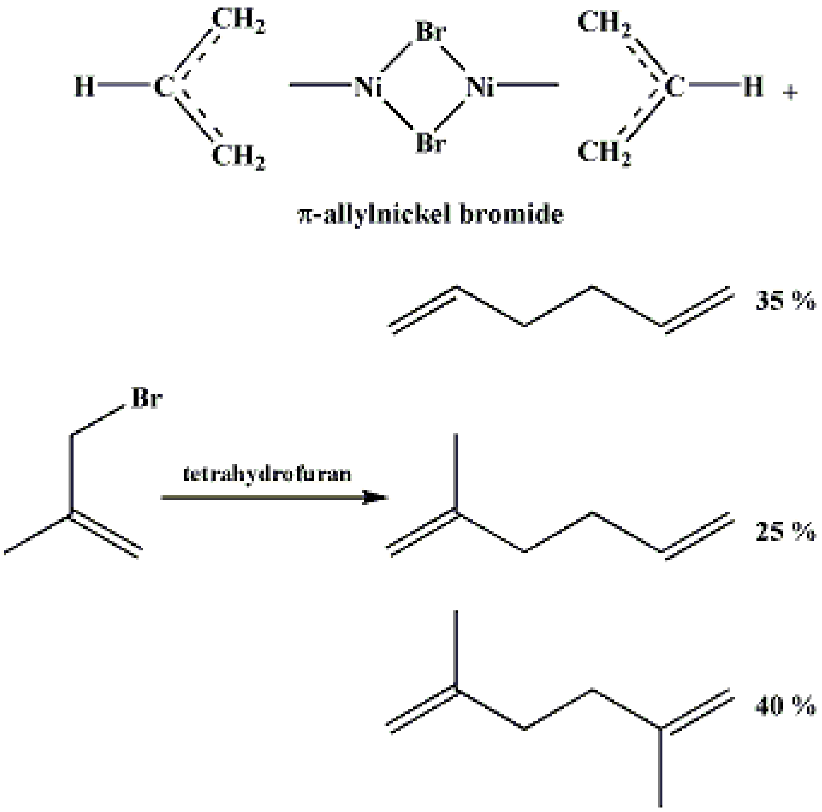
10. The hydrochloric acid solution is added to speed solution of the nickel salts, which would otherwise lead to emulsions during separation. If no emulsion is encountered after mixing the petroleum ether and water solutions, no hydrochloric acid need be added. Similarly, the filtration through Celite filter aid is intended to remove finely divided nickel metal and other insoluble particles which complicate the washing procedure. If no particles are present, the filtration step should be omitted.

11. The product consists of 99% methallylbenzene and 1% 2,5-dimethyl-1,5-hexadiene, by ^{1}H NMR analysis. The ^{1}H NMR spectrum of methallylbenzene (CCl_4) shows peaks at δ 1.63 (broad s, 3H, allylic CH_3), 3.25 (broad s, 2H, allylic CH_2), 4.75 (m, 2H, C=CH_2), and 7.15 (s, 5H, C_6H_5). The ^{1}H NMR spectrum of 2,5-dimethyl-1,5-hexadiene (CCl_4) shows peaks at δ 1.70 (broad s, 6H, 2CH_3), 2.12 (broad s, 4H, 2 allylic CH_2), and 4.75 (m, 4H, 2CH_2=C). A small forerun contained 0.30 g. (3% yield) of methallylbenzene and a larger quantity of 2,5-dimethyl-1,5-hexadiene. The distillation residue is composed of 0.24–0.34 g. (3–4% yield) of methallylbenzene and 0.38–0.52 g. (8–10% yield) of biphenyl. The distillation fractions may be analyzed by GC with a 180 cm. by 6.4 mm. column packed with 10% SE-30 on Chromosorb G. The retention times for methallylbenzene and 2,5-dimethyl-1,5-hexadiene are 4.0 minutes and 2.0 minutes, respectively, at 125°.

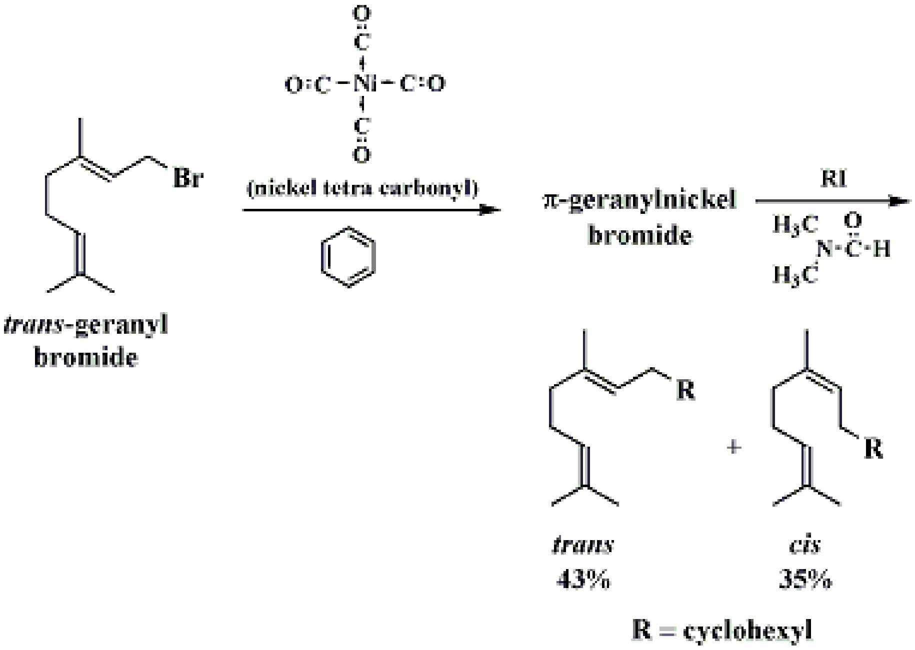
3. Discussion

The simple example outlined above, replacement of halogen by a methallyl group, could be carried out in an equally direct way using phenylmagnesium bromide and methallyl halide. However, the Grignard reaction is complicated by formation of the conjugated, isomeric β,β-dimethylstyrene,[4] or by a rearrangement to *trans*-2-butenylbenzene.[5] In no case has this approach afforded methallylbenzene in greater than 50% yield. Dehydration of (2-hydroxy-2-methylpropyl)benzene also produces a mixture of methallylbenzene (68%) and β,β-dimethylstyrene (32%).[6] Elimination of benzoic acid from the benzoate ester of (2-hydroxy-2-methylpropyl)benzene gives the same ratio of products, although the combined yield (86%) is lower.[7] The Wittig reaction of methylenetriphenylphosphorane with 1-phenyl-2-propanone produces methallylbenzene in only 2% yield.[8]

The preparation illustrates the procedure for formation of π-allylnickel halides and their reaction with aryl halides.[9] The complexes can be obtained from allylic chlorides, bromides, and iodides[10,11,12] even when the allylic halides bear alkyl, carboalkoxyl, or alkenyl side chains.[11] The coupling step is generally applicable to aryl, alkyl, and vinyl bromides or iodides;[9] organic chlorides are usually unreactive with π-allylnickel halides. Other polar aprotic solvents (hexamethylphosphoric triamide, dimethyl sulfoxide, *N*-methylpyrrolidone) have been used.[13] Protic solvents lead to the destruction of the π-allylnickel complex by slow protonation of the allyl ligand.[13] No reaction occurs between aryl, alkyl, or vinyl halides and π-allylnickel bromide in less polar solvents such as tetrahydrofuran, 1,2-dimethoxyethane, ether, or hydrocarbons. The π-allylnickel bromide complexes are very reactive with allyl halides, but halogen–metal exchange precedes coupling and a mixture of products is obtained as illustrated in the following example.[14]



The π-allylnickel complex from *trans*-geranyl bromide reacts with alkyl halides, giving a mixture of *cis* and *trans* products,[9] the double bond that participates in the π-allyl group is isomerized during the sequence of reactions:



Similarly, *trans*-4-iodocyclohexanol reacts with π-methallylnickel bromide, producing a mixture of epimeric 4-methallylcyclohexanols.[9] Note that the hydroxyl group has no significant effect on this reaction.

The advantages of π-allylnickel halides reside in their nonnucleophilic and nonbasic character which allow especially selective reactions with organic halides in the presence of a large number of other functional groups. Carbonyl and hydroxyl groups react much more slowly than organic halides (especially iodides) with π-allylnickel halides, while olefins, nitriles, alkyl chlorides, and

aromatic hydrocarbons are inert to these reagents.[9,13]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

π-methallylnickel bromide

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether, diethyl ether (60-29-7)

carbon monoxide (630-08-0)

oxygen (7782-44-7)

nitrogen (7727-37-9)

Benzoic acid (65-85-0)

nickel (7440-02-0)

acetone (67-64-1)

bromobenzene (108-86-1)

Biphenyl (92-52-4)

Phenylmagnesium bromide (100-58-3)

1-phenyl-2-propanone (103-79-7)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

nickel carbonyl

N,N-dimethylformamide (68-12-2)

dimethyl sulfoxide (67-68-5)

calcium hydride (7789-78-8)

1,2-dimethoxyethane (110-71-4)

nickel dibromide

methallyl chloride (563-47-3)

hexamethylphosphoric triamide (680-31-9)

argon (7440-37-1)

Methallylbenzene, Benzene, (2-methyl-2-propenyl)- (3290-53-7)

β,β-dimethylstyrene (768-49-0)

N-methylpyrrolidone (872-50-4)

trans-geranyl bromide (6138-90-5)

methallyl bromide (1458-98-6)

2,3-dimercapto-1-propanol (59-52-9)

lithium bromide (7550-35-8)

2,5-dimethyl-1,5-hexadiene (627-58-7)

(2-hydroxy-2-methylpropyl)benzene (100-86-7)

methylenetriphenylphosphorane (3487-44-3)

trans-2-butenylbenzene (1560-06-1)

trans-4-iodocyclohexanol

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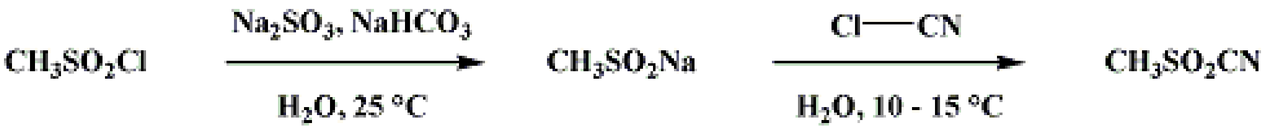
Organic Syntheses, CV 6, 727

SULFONYL CYANIDES: METHANESULFONYL CYANIDE



Submitted by M. S. A. Vrijland[1]
Checked by Y. Sugimura and G. Büchi.

1. Procedure

Caution! Since cyanogen chloride is highly toxic, the preparation and isolation of the sulfonyl cyanide should be conducted in a well-ventilated hood.

Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A 2-l., three-necked, round-bottomed flask equipped with a sealed mechanical stirrer, a pressure-equalizing dropping funnel capped with a gas-outlet, and a thermometer is charged with 126 g. (0.500 mole) of sodium sulfite heptahydrate, 84.0 g. (1.00 mole) of sodium hydrogen carbonate, and 1 l. of water (Note 1). Stirring is begun, and 57.3 g. (0.500 mole) of freshly distilled methanesulfonyl chloride (Note 2) is added dropwise over 30 minutes. The slightly exothermic reaction is accompanied by the evolution of carbon dioxide. After stirring for 2 hours, gas evolution ceases, and a clear, colorless solution of sodium methanesulfinate (Note 3) is obtained.

The dropping funnel is removed, the solution is cooled to 10° by the addition of ice, and 50 ml. (1.0 mole) of liquid cyanogen chloride (Note 4) is added in one portion with vigorous stirring. Addition of ice keeps the mixture at or below 15°. Within 1 minute the reaction mixture becomes turbid, and methanesulfonyl cyanide separates as a heavy, colorless oil. The mixture is stirred for an additional 15 minutes before 200 ml. of benzene is added (Note 5). After 3 minutes of stirring, the layers are separated in a 2-l. separatory funnel, and the aqueous layer is extracted with two 100-ml. portions of benzene. The combined extracts are washed with water and dried overnight over anhydrous calcium chloride. Filtration and removal of solvent with a rotary evaporator *in a hood* affords an almost pure product (Note 6) which is distilled, yielding 35.4–37.8 g. (67–72%) of methanesulfonyl cyanide, b.p. 68–69° (15 mm.), n_D^{20} 1.4301 (Note 7), which may be stored in a well-stoppered bottle, kept at or below 0°, for prolonged times without loss in purity (Note 8).

2. Notes

1. Excess sodium sulfite or sodium hydrogen carbonate should be avoided, since either would react with the sulfonyl cyanide once formed.
2. The procedure given is applicable to many other sulfonyl chlorides as well (see Table I). Solid sulfonyl chlorides are added as such. When heavy frothing occurs in the reduction (*e.g.*, with 4-nitrobenzenesulfonyl chloride), addition of 50 ml. of chloroform to the reaction mixture will eliminate the foam without reducing the final yield. When the sulfonyl chlorides were prepared according to Meerwein and co-workers,[2] it was found advantageous to use the crude, damp sulfonyl chlorides, since these are more easily reduced than the dried or recrystallized materials.

TABLE I

PREPARATION OF SULFONYL CYANIDES FROM SULFONYL CHLORIDES[a]

R =	RSO_2Cl from	m.p.	b.p.	Yield, %
Methyl	Commerce	—	68–69° (15 mm.)	72
Ethyl	$RSCN + Cl_2$[3]	—	80–80.5° (18 mm.)	84
Propyl	$R_2S_2 + Cl_2$[4]	—	81–81.5° (18 mm.)	76
Benzyl	$RSC(NH)NH_2 \cdot HCl$[5]	89.5–91°		91
Cyclohexyl	$RH + SO_2Cl_2$[6]		72–73° (0.4 mm.)	85
4-Methoxyphenyl	$RH + SO_2Cl_2$[7]	66–68°		88
p-Tolyl	Commerce	49.5–51°		89
Phenyl	Commerce	19–20°	118–119° (15 mm.)	92
4-Chlorophenyl	$RN_2^+ Cl^- + SO_2$[2]	57.5–59°		65[b]
4-Cyanophenyl	$RN_2^+ Cl^- + SO_2$[2]	123–125°		79[b]
4-Nitrophenyl	$RN_2^+ Cl^- + SO_2$[2]	122–123.5°		66[b]

[a]The preparations were performed on a 0.25 to 1-mole scale.

[b]Overall yield from the corresponding aniline as starting material.

3. When crude sulfonyl chlorides were used as starting materials, on completion of the reduction, and before the addition of cyanogen chloride, the reaction mixture was washed with a suitable solvent (benzene or dichloromethane, or, in some cases, chloroform) to remove organic impurities. In the case of higher-melting, crystalline sulfonyl chlorides, heating to 50° may be necessary to complete their reduction. The solution of the sulfinate salt may be kept overnight, if desired, with no decrease in the yield of sulfonyl cyanide.

4. Cyanogen chloride is commercially available in gas cylinders. It is liquefied by passing the gas through a condenser cooled with ice water. Where difficult to obtain, it may be prepared by passing chlorine gas through a stirred suspension of sodium tetrakis(cyano-C)zincate prepared *in situ* from sodium cyanide and zinc sulfate.[8]

5. If the benzenesulfinates were substituted with electron-withdrawing groups, *e.g.*, 4-nitro- and 4-cyanobenzenesulfinate, the yields were slightly improved when the reaction time with cyanogen chloride was lengthened to 1 hour.

The higher-melting sulfonyl cyanides which separate as solids should be dried when dissolved in a suitable solvent, *e.g.*, benzene. 4-Nitrobenzenesulfonyl cyanide is not readily extracted from the reaction mixture; it is collected on a Büchner funnel, pressed as dry as possible, dissolved in benzene, washed with water, and dried over anhydrous calcium chloride.

6. Solid sulfonyl cyanides show a melting point not more than 1–2° below that of recrystallized material. They may be used without further purification. Analytically pure samples are obtained by recrystallization from dry benzene, dry petroleum ether, or a mixture of the two.

7. The product was further characterized as follows: IR (liquid film) $cm.^{-1}$: 2195 strong, 1370 strong, 1170 strong; ^{1}H NMR resonance ($CDCl_3$), δ 3.43 (s).

8. Contrary to the findings of Cox and Ghosh,[9] methanesulfonyl cyanide may be distilled without decomposition. Samples of benzene-, 4-methoxybenzene-, and 4-chlorobenzenesulfonyl cyanides were kept for over a year without loss in purity.

3. Discussion

Whereas sulfonyl halides have been known for a long time and, especially the chlorides, have become of great synthetic value, sulfonyl cyanides were unknown until 1968. They were first prepared by van Leusen and co-workers from the reaction of sulfonylmethylenephosphoranes with nitrosyl chloride.[10] The same group also investigated part of their chemistry.[11,12,13,14,15] Since then, two more, completely different methods of synthesis have been published: one, involving the reactions of sulfinates with cyanogen chloride,[9] and another, the oxidation of thiocyanates.[16]

The procedure given above for the preparation of methanesulfonyl cyanide is essentially a combination of the sulfite reduction of a sulfonyl chloride, as originally described by Bere and Smiles,[17] and the sulfinate–cyanogen chloride reaction, first published by Cox and Ghosh.[9]

Some sulfinates are commercially available and may be used as starting materials for the preparation of sulfonyl cyanides. Yields, however, are not significantly better than when the much cheaper and more readily available sulfonyl chlorides are used as starting materials. Good to excellent results are obtained, even when starting from rather impure sulfonyl chlorides.[18] Illustrative examples are given in Table I.

Sulfonyl cyanides have an activated cyano group and show many interesting reactions. With a range of *N*-, *O*-, *S*-, and *C*-nucleophiles, of the cyano group to these nucleophiles is

observed.[11,19,20] Hydroxylamine, hydrazine, and phenylhydrazine (α-effect nucleophiles) add to the cyano group of sulfonyl cyanides, yielding products that could be converted into substituted 1,2,4-oxadiazoles[21] and 1,2,4-triazoles,[15,5] respectively. Dienes show Diels-Alder cycloadditions with sulfonyl cyanides.[12,13,14,19,22] 1,3-Dipolar cycloadditions to the cyano group give rise to substituted tetrazoles (from azides), to substituted 1,2,3-triazoles (from diazo compounds), or to substituted 1,2,4-oxadiazoles (from nitrile *N*-oxides).[12,19] Sulfonyl cyanides undergo free-radical additions to alkenes.[19,23] Chlorine and sulfenyl chlorides add to the cyano group of sulfonyl cyanides.[24,25,26]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

sodium tetrakis(cyano-C)zincate

4-nitro- and 4-cyanobenzenesulfinate

benzene-, 4-methoxybenzene-, and 4-chlorobenzenesulfonyl cyanides

mono-, di-, and trichloromethanesulfonyl chloride

ethylene- and 2,4-dinitrophenylsulfonyl chloride

calcium chloride (10043-52-4)

Benzene (71-43-2)

aniline (62-53-3)

sodium sulfite (7757-83-7)

chloroform (67-66-3)

sodium hydrogen carbonate (144-55-8)

sodium cyanide (143-33-9)

ethyl (2025-56-1)

propyl (2143-61-5)

Phenylhydrazine (100-63-0)

carbon dioxide (124-38-9)

chlorine (7782-50-5)

methyl (2229-07-4)

hydrazine (302-01-2)

hydroxylamine (7803-49-8)

dichloromethane (75-09-2)

zinc sulfate (7733-02-0)

nitrosyl chloride (2696-92-6)

benzyl (2154-56-5)

cyanogen chloride (506-77-4)

Cyclohexyl (3170-58-9)

p-tolyl

phenyl

Methanesulfonyl chloride (124-63-0)

sodium sulfite heptahydrate

Methanesulfonyl cyanide (24225-08-9)

sodium methanesulfinate

4-nitrobenzenesulfonyl chloride (98-74-8)

4-Methoxyphenyl

4-Chlorophenyl

4-Cyanophenyl

4-Nitrophenyl

4-Nitrobenzenesulfonyl cyanide

dimethylsulfamoyl chloride (13360-57-1)

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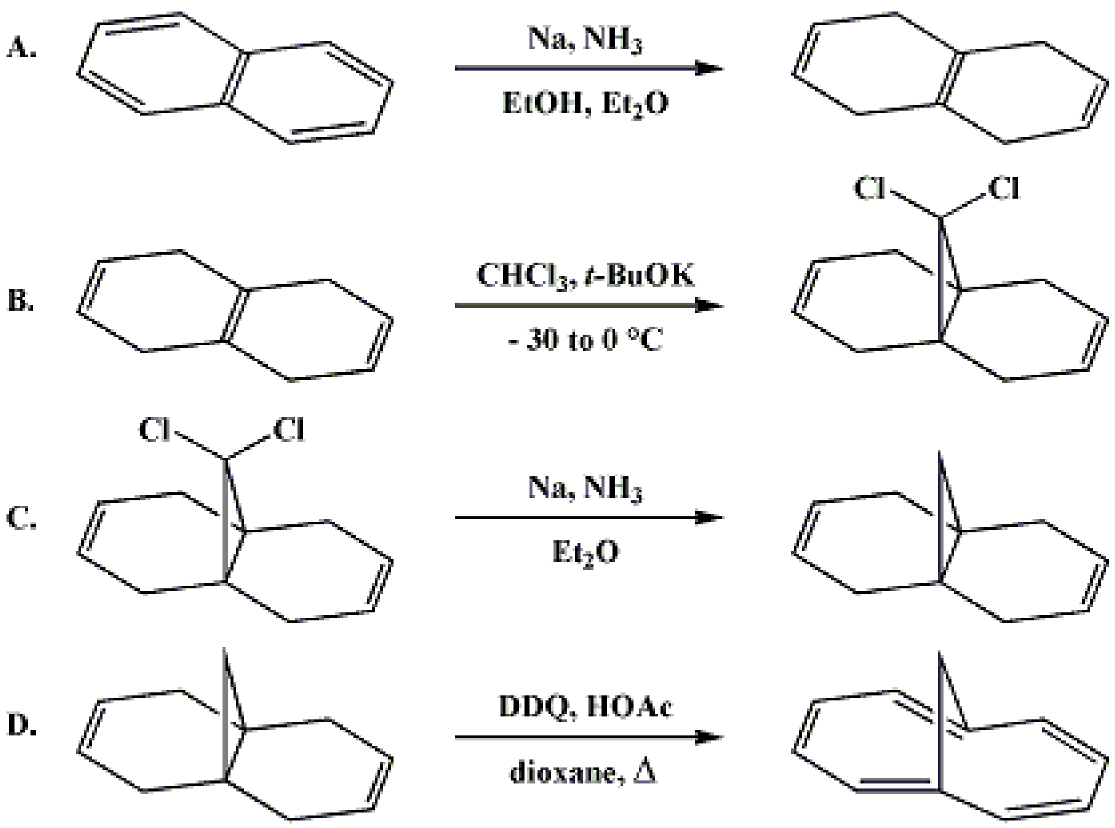
Organic Syntheses, CV 6, 731

1,6-METHANO[10]ANNULENE

[Bicyclo[4.4.1]undeca-1,3,5,7,9-pentaene]



Submitted by E. Vogel[1], W. Klug, and A. Breuer.
Checked by R. E. Ireland, R. A. Farr, H. A. Kirst, T. C. McKenzie, R. H. Mueller, R. R. Schmidt III, D. M. Walba, A. K. Willard, and S. R. Wilson.

1. Procedure

Caution! This reaction should be carried out in an efficient hood.

A. 1,4,5,8-*Tetrahydronaphthalene* (*isotetralin*). A 12-l. (Note 1),. three-necked, round-bottomed flask is immersed in an acetone–dry ice bath and fitted with a dry ice condenser (Note 2), a tube-sealed stirrer (Note 3), a drying tube (potassium hydroxide), and a gas delivery-tube running to the bottom of the flask. Ammonia (3 l.) is condensed (Note 4) into the flask. The gas delivery-tube is removed, and 192.3 g. (8.361 g.-atoms) of sodium is added in small portions (Note 5), with vigorous stirring, over a period of 1 hour. The flask is then fitted with a dropping funnel, through which a solution of 192.3 g. (1.502 mole) of naphthalene in a mixture of 750 ml. of diethyl ether and 600 ml. of ethanol is added dropwise to the blue solution over 3 hours. After the addition is complete, the reaction mixture is stirred at −78° (Note 6) for another 6 hours. The cooling bath is removed, and the ammonia is allowed to evaporate

overnight. The remaining white, solid residue is processed, with ice cooling and stirring under a nitrogen atmosphere, by slow addition of 120 ml. of methanol to destroy unreacted sodium, then 4–5 l. of ice water to dissolve the salts (Note 7). The reaction mixture is extracted with 1 l. of ether. Evaporation of the ether phase at room temperature under reduced pressure gives a coarse, white solid which is collected on a sintered-glass funnel and washed with water. Recrystallization from methanol (about 1.6 l.) using a heated funnel followed by drying of the crystals under reduced pressure (Note 8) gives 148–158 g. (75–80%) of isotetralin, m.p. 52–53° (purity □98%) (Note 9). Pure 1,4,5,8-tetrahydronaphthalene is reported to have m.p. 58°.[2]

B. 11,11-*Dichlorotricyclo*[4.4.1.$0^{1,6}$]*undeca*-3,8-*diene*. A 3-l., three-necked, round-bottomed flask fitted with a tube-sealed stirrer, a pressure-equalizing dropping funnel, and Claisen-adapter bearing an inlet tube for argon and a low temperature thermometer is charged with a solution of 132.2 g. (1.000 mole) of 1,4,5,8-tetrahydronaphthalene (isotetralin) in 1.3 l. of anhydrous ether (Note 10). To this solution is added 150 g. (1.33 mole) of potassium *tert*-butoxide (Note 11) under an argon atmosphere, and the resulting suspension is cooled to −30° with an acetone–dry ice bath and stirred efficiently. While these conditions are maintained, a solution of 119.5 g. (1.000 mole) of chloroform in 150 ml. of ether is added dropwise over 90 minutes (Note 12). The mixture is stirred for another 30 minutes at −30° before the temperature is allowed to rise above 0°. Following this, 300–350 ml. of ice water is added to dissolve the salts; the two layers formed are separated (Note 13). The organic layer is washed with two 300-ml. portions of water, while the aqueous layer is extracted with two 200-ml. portions of ether. The ether phases are combined, dried over magnesium sulfate, and filtered. The ether is removed with a rotary evaporator, and the residual liquid (or solid) is distilled under reduced pressure.

The distillation is expediently carried out using a 500-ml., round-bottomed flask, an electrically heated 1.5 × 30 cm. column packed with V4A wire spirals (4 mm.) (Note 14), a short, air-cooled condenser (Note 15), and an ice-cooled, three-necked, 250-ml. receiver flask. During the distillation, the liquid is stirred magnetically and heated with an oil bath. The first fraction, b.p. 55–58° (1 mm.), yields *ca.* 50 g. of isotetralin (Note 16), more of which is collected when the column is heated to about 100°. The temperature in the head of the column thereby rises to 90–95°, and it is necessary to change the receiver flask. The second fraction, collected at 95–102° (1 mm.), yields *ca.* 108 g. of 1:1-adducts, which consists of 92% of the desired tricyclo product and 8% of the side-addition product. The residue mainly contains the 2:1-adducts. The fraction containing the 1:1-adducts is recrystallized from methanol (about 500 ml.), giving 87–97 g. (40–45%, based on isotetralin) of 11,11-dichlorotricyclo[4.4.1.$0^{1,6}$]undeca-3,8-diene as long, colorless needles, m.p. 88–89° (Note 17).

C. *Tricyclo*[4.4.1.$0^{1,6}$]*undeca*-3,8-*diene*. Ammonia (800 ml.) is condensed into a 2-l., three-necked round-bottomed flask, immersed in an acetone–dry ice bath and fitted with a dry ice condenser, a tube-sealed stirrer, a drying tube, and a gas delivery tube running to the bottom of the flask. The gas delivery tube is removed, and with

vigorous stirring 56 g. (2.4 g.-atoms) of sodium is added in small portions with vigorous stirring over a period of 30 minutes (Note 18). The flask is then fitted with a dropping funnel, through which a solution of 81.4 g. (0.378 mole) of 11,11-dichlorotricyclo[4.4.1.0^{1,6}]-undeca-3,8-diene in 500 ml. of anhydrous ether is added over 1 hour, while cooling and stirring are maintained. After addition is complete, the acetone–dry ice bath is removed, and the ammonia is allowed to evaporate overnight. The flask is placed in the acetone–dry ice bath again, and a gentle stream of argon is passed continuously through the system. With stirring, a mixture of 90 ml. of methanol and 90 ml. of ether is added dropwise. The bath temperature is then allowed to rise to 0° and, with continued stirring, 500 ml. of ice water is added slowly. The reaction mixture is transferred to a 2–l. separatory funnel, and the two layers are separated. The organic layer is washed with 200 ml. of water, the aqueous layer is extracted with three 150-ml. portions of pentane (Note 19), and the combined ether–pentane phases are dried over magnesium sulfate. After filtration of the drying agent (Note 20) the solvent is removed by distillation through a 30-cm. Vigreux column. The remaining liquid is transferred to a 250-ml., round-bottomed flask and distilled under reduced pressure through a packed column (Note 21), yielding 46.9–49.7 g. (85–90%) of tricyclo[4.4.1.0^{1,6}]undeca-3,8-diene, collected as a colorless liquid at 80–81° (11 mm.), n_D^{20} 1.5180 (Note 22).

D. 1,6-*Methano*[10]*annulene*. A 2-l., three-necked, round-bottomed flask fitted with a tube-sealed stirrer, a reflux condenser protected with a calcium chloride drying tube, and an inlet tube for argon is charged with 900 ml. of anhydrous dioxane (Note 23). To this solvent is added, with stirring, 149 g. (0.656 mole) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (Note 24). When the DDQ has dissolved, 43.8 g. (0.300 mole) of tricyclo[4.4.1.0^{1,6}]undeca-3,8-diene and 10 ml. of glacial acetic acid are added. The system is then flushed with argon, and the stirred mixture is heated under reflux for 5 hours. The reaction starts within a few minutes, as evidenced by effervescing of the solution and massive precipitation of the hydroquinone. At the same time the originally red-brown color of the mixture turns almost black. Following the reflux period, the bulk of the dioxane (600–650 ml.) is removed by distillation through a 15-cm. Vigreux column while stirring is maintained. The resulting pasty mixture is cooled, and 150 ml. of *n*-hexane is added. The solid is suction filtered, washed with 500 ml. of warm *n*-hexane, and dried at 100°, giving *ca.* 144 g. (95%) of pure 2,3-dichloro-5,6-dicyanohydroquinone (Note 25). The filtrate and washings are combined and passed through a 5 × 30 cm. column of neutral alumina (Note 26), which is eluted with *n*-hexane (Note 27). The solvent is removed by distillation through a 30-cm. Vigreux column, and the residual liquid is distilled from a 250-ml., round-bottomed flask through a packed column (Note 28), yielding 36.2–37.0 g.. (85–87%) of faintly yellow 1,6-methano[10]annulene, b.p. 68–72° (1 mm.), which may crystallize in the receiver-flask, m.p. 27–28° (Note 29).

2. Notes

1. It is advisable to use a 10- or 12-l. flask for runs on this scale because the reaction mixture may effervesce if the naphthalene solution is added too quickly.
2. It is necessary to use a dry ice condenser to shorten the time required to condense the ammonia (4 hours compared with 6 hours without the condenser). The ammonia tank was warmed with an air gun during the distillation. The condenser was removed after the ammonia was collected.
3. It is necessary to use a strong stirring motor since the reaction mixture becomes, temporarily, rather viscous.
4. One should not pour the liquified ammonia directly out of the cylinder since particles of iron compounds might be carried along, catalyzing the formation of sodium amide. For the exclusion of moisture it is also necessary to use a drying tower (potassium hydroxide) between the cylinder and the flask.
5. The sodium should be cut into small particles to increase the speed of dissolution and diminish the danger of stirrer blockage.
6. During this period the reaction mixture might turn white. In this case, another portion of sodium must be added until the solution becomes blue again.
7. The white residue should be worked up as soon as possible. On standing the residue gradually turns brown-red due to the formation of decomposition products; isolation of isotetralin then becomes difficult, and the yield may drop sharply. The submitters evaporated any remaining ether from the reaction flask at reduced pressure and filtered the water slurry of isotetralin, obtaining the same yield after crystallization.
8. Isotetralin should not be kept under vacuum longer than necessary since the compound has a relatively high vapor pressure.
9. A second extraction of the aqueous phase with ether yields an additional 1.5 g. of material. A second crop, (29.4 g., m.p. 49–52°) of isotetralin can be obtained from the mother liquors of the recrystallization.
10. All solvents used should be anhydrous.
11. The yield of 11,11-dichlorotricyclo[4.4.1.0^{1,6}]undeca-3,8-diene strongly depends on the quality of the potassium *tert*-butoxide used. Commercially available, sublimed potassium *tert*-butoxide was employed. When freshly sublimed potassium *tert*-butoxide is utilized, yields of up to 45% of 11,11-dichlorotricyclo[4.4.1.0^{1,6}]undeca-3,8-diene can be obtained. Potassium *tert*-butoxide, prepared by the method of Doering,[3] gave yields comparable to those achieved with the commercial product.
12. The stated reaction temperature should be maintained carefully. Raising the temperature above −30° noticeably reduces the regio-selectivity of the addition of dichlorocarbene, whereas lowering the temperature causes the yield of 1:1-adducts to drop due to partial crystallization of isotetralin.
13. The formation of emulsions may render it difficult to discern the two rather dark layers. In this case it is helpful to acidify with dilute sulfuric acid.
14. The checkers used an electrically heated, 1.5 × 30 cm. Vigreux column and obtained the same results.
15. To prevent isotetralin and the 1:1-adducts from solidifying in the condenser external heating with an IR lamp was applied.

16. The recovered isotetralin can be reused.
17. The product is approximately 99% pure by GC (SE-30 on kieselguhr, 150°). After two or three recrystallizations from methanol, 11,11-dichlorotricyclo[4.4.1.0^{1,6}]undeca-3,8-diene shows m.p. 90–91°.
18. For the preparation of the solution of sodium in liquid ammonia, compare part A.
19. If emulsions occur, it is advisable to acidify with dilute sulfuric acid to attain separation of the two layers.
20. The drying agent should be washed well with pentane.
21. The column used for this distillation is described in part B.
22. Tricyclo[4.4.1.0^{1,6}]undeca-3,8-diene was shown to be approximately 99% pure by GC (SE-30 on kieselguhr, 150°).
23. The use of anhydrous solvents is necessary to avoid hydrolytic decomposition of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.
24. Commercially available 2,3-dichloro-5,6-dicyano-1,4-benzoquinone was employed. 1,6-Methano[10]annulene was obtained in equally good yields, when 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, prepared by the method of Walker and Waugh,[4] was utilized.
25. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone is readily regenerated in good yield from the hydroquinone by oxidation with nitric acid.[4]
26. Brockmann alumina, activity grade II–III, M. Woelm, 344 Eschwege, West Germany.
27. By contrast to the filtrate and washings, which are rather dark, the eluent is yellow due to the color of 1,6-methano[10]annulene.
28. The column used for this distillation is described in part B.
29. The purity of the 1,6-methano[10]annulene was shown by GC (SE-30 on kieselguhr, 150°) to be higher than 99%. Recrystallization of the hydrocarbon from methanol raises its melting point to 28–29°.

3. Discussion

The procedure described for the Birch reduction of naphthalene is a modification of the methods previously developed by Birch,[5] Hückel,[2] and Grob.[6] Apart from this reduction, no other practical approaches to isotetralin are known. The scale employed in the present procedure is not mandatory to achieve optimum yields. Equally good yields were realized when the runs were halved or enlarged up to fourfold. In the latter case, however, the apparatus reaches pilot plant dimensions.

Tricyclo[4.4.1.0^{1,6}]undeca-3,8-diene, the strategic intermediate in the synthesis of 1,6-methano[10]annulene from naphthalene, can alternatively be obtained in one step by the reaction of isotetralin with the Simmons–Smith reagent.[7] The two-step preparation of tricyclo[4.4.1.0^{1,6}]undeca-3,8-diene utilized here has the following merits: (1) dichlorocarbene adds to the central double bond of isotetralin with exceptionally high regioselectivity (as compared to that of methylene transfer reagents), giving 11,11-

dichlorotricyclo[4.4.1.0^{1,6}]undeca-3,8-diene as a readily isolable, crystalline compound; and (2) the transformation of the dichloro compound into tricyclo [4.4.1.0^{1,6}]undeca-3,8-diene with sodium in liquid ammonia[8] is a simple operation and affords the product in high yield and purity. The dichlorocarbene employed in the two-step cyclopropanation of isotetralin was generated by the original method of Doering and Hoffmann.[3] Other sources of dichlorocarbene, notably the methods of Parham and Schweizer[9] and of Makosza and Wawrzyniewicz,[10] have also been tried, but did not lead to improved yields of adduct.

The rapid conversion of tricylo[4.4.1.0^{1,6}]undeca-3,8-diene to 1,6-methano[10] annulene by the high potential quinone, DDQ, is yet another illustration of the usefulness of this agent as a means of dehydrogenation of hydroaromatic compounds.[11] If DDQ is not available, it is recommended that tricyclo[4.4.1.0^{1,6}] undeca-3,8-diene be aromatized by a bromination-dehydrobromination sequence similar to that described in the synthesis of 1,6-oxido[10]annulene;[12] both aromatization methods give essentially the same yield of 1,6-methano[10]annulene.

The synthesis of 1,6-methano[10]annulene outlined above is an improved version of the method first suggested by Vogel and Roth.[13] 1,6-Methano[10]annulene represents a Hückel-type aromatic ($4n + 2$) π-system and is similar to benzene or naphthalene in both its physical and chemical properties.[14] The aromatic nature of the hydrocarbon is born out most impressively by its ^{1}H NMR spectrum which exhibits an AA'BB'-system for the vinylic protons at relatively low field (δ 6.8–7.5) and a singlet for the bridge protons at relatively high field (δ 0.5). 1,6-Methano[10]annulene may serve as a starting material for the preparation of other molecules of current interest, such as the bicyclo[5.4.1]dodecapentaenylium ion[14] and benzocyclopropene.[15]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 862

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alumina

1,6-Oxido[10]annulene

1,4,5,8-Tetrahydronaphthalene (isotetralin)

isotetralin

tricylo[4.4.1.0^{1,6}]undeca-3,8-diene

ethanol (64-17-5)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

ammonia (7664-41-7)

Benzene (71-43-2)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

chloroform (67-66-3)

iron (7439-89-6)

nitric acid (7697-37-2)

nitrogen (7727-37-9)

sodium (13966-32-0)

Naphthalene (91-20-3)

Pentane (109-66-0)

magnesium sulfate (7487-88-9)

dioxane (5703-46-8)

sodium amide (7782-92-5)

n-hexane (110-54-3)

dichlorocarbene

argon (7440-37-1)

2,3-dichloro-5,6-dicyano-1,4-benzoquinone

2,3-dichloro-5,6-dicyanohydroquinone

Benzocyclopropene

1,6-Methano[10]annulene, Bicyclo[4.4.1]undeca-1,3,5,7,9-pentaene (2443-46-1)

1,4,5,8-Tetrahydronaphthalene (493-04-9)

11,11-Dichlorotricyclo[4.4.1.0^{1,6}]undeca-3,8-diene, 11,11-dichlorotricyclo[4.4.1.0^{1,6}]-undeca-3,8-diene (39623-22-8)

Tricyclo[4.4.1.0^{1,6}]undeca-3,8-diene (27714-83-6)

potassium tert-butoxide (865-47-4)

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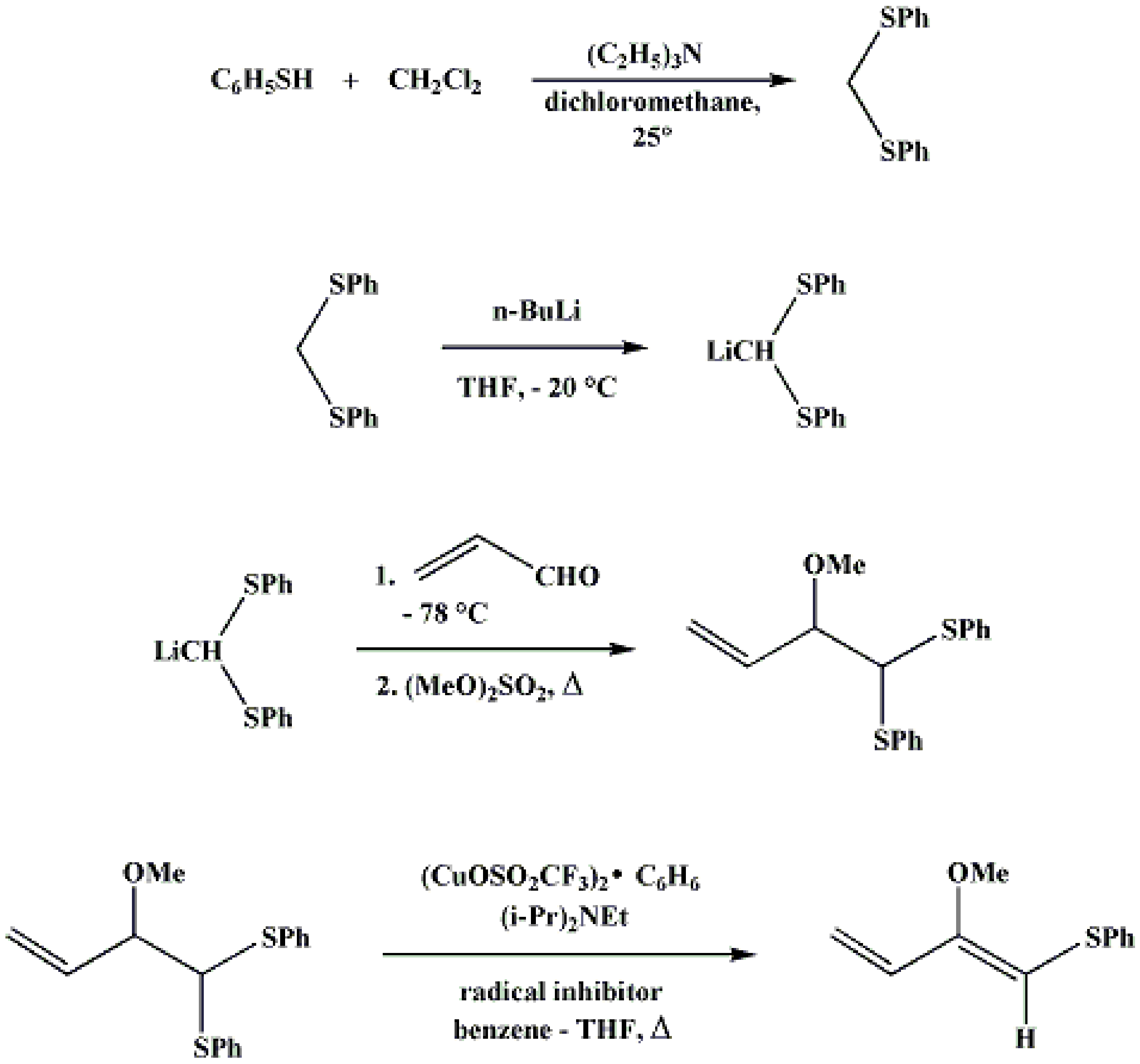
VINYL SULFIDES FROM THIOACETALS WITH COPPER(I) TRIFLUOROMETHANESULFONATE: (*Z*)-2-METHOXY-1-PHENYLTHIO-1,3-BUTADIENE

[Benzene, [(2-methoxy-1,3-butadienyl)thio]-, (*Z*)-]



Submitted by Theodore Cohen[1], Robert J. Ruffner, David W. Shull, Elaine R. Fogel, and J. R. Falck.
Checked by J. Bisaha and M. F. Semmelhack.

1. Procedure

Caution! Part A should be carried out in an efficient hood to minimize exposure to the foul-smelling thiophenol.

Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A. *Bis(phenylthio)methane*. A dry, 2-l., one-necked flask equipped with a magnetic stirring bar and a 250-ml., pressure-equalizing dropping funnel mounted with a combined inlet-outlet assembly for introducing argon (Note 1) is charged with 1.5 l. of distilled dichloromethane and 79.9 g. (110 ml., 0.791 mole) of triethylamine (Note 2), and purged with argon. The solution is stirred and cooled in an ice bath as 87 g. (81 ml., 0.79 mole) of thiophenol (Note 3) is added over 20–30 minutes. The mixture is allowed to warm to 20° and stirred at this temperature for another 3 hours. Triethylamine hydrochloride is removed by filtration through a fritted-glass Büchner funnel, and the filtrate is washed with two 200-ml. portions of 10% aqueous sodium hydroxide, two 200-ml. portions of 2 *N* hydrochloric acid, and one 300-ml. portion of water. The dichloromethane solution is dried over anhydrous magnesium sulfate and evaporated under reduced pressure. Recrystallization of the residue from petroleum ether gives 51.2–59.6 g. (56–65%) of bis(phenylthio)methane as white crystals, m.p. 35–37° (Note 4).

B. 4,4-*Bis(phenylthio)*-3-*methoxy*-1-*butene*. A 250-ml., two-necked, round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and a reflux condenser bearing an inlet-outlet assembly for argon (Note 1) is dried in an oven at 110° and cooled under a stream of argon passed through the septum with a syringe needle and vented through the argon bubbler. A solution of 5.00 g. (0.0215 mole) of bis(phenylthio)methane in 150 ml. of tetrahydrofuran (Note 5) is placed in the flask and cooled to –20° with a carbon tetrachloride–dry ice bath. A 15.8-ml. (0.0217 mole) aliquot from a 1.37 *M* solution of *n*-butyllithium in hexane (Note 6) is injected through the septum with a syringe. The resulting deep-yellow solution is stirred and cooled at –20° for 1 hour and then cooled to –78° with an acetone–dry ice bath. The color of the solution is discharged immediately when 1.4 g. (1.7 ml., 0.025 mole) of acrolein (Note 7) is added by syringe at –78°. Stirring and cooling are continued for 15 minutes, after which 2.90 g. (2.19 ml., 0.0230 mole) of dimethyl sulfate (Note 8) is added, and the cooling bath is removed. The solution is stirred at room temperature for 16 hours and heated at reflux for 2 hours. A 3-ml. portion of water is added to the cooled mixture, most of the tetrahydrofuran is removed by rotary evaporation, and the concentrate is partitioned between 30 ml. of water and 30 ml. of diethyl ether. The organic layer is washed three times with 10-ml. portions of concentrated ammonia and once with water. The ethereal solution is dried over anhydrous magnesium sulfate and evaporated under reduced pressure. Crystallization of the viscous yellow residue from 30 ml. of 95% ethanol at –20° gives 3.11–3.36 g. (48–52%) of 4,4-bis(phenylthio)-3-methoxy-1-butene as a light-yellow solid, m.p. 45–48°, which is of adequate purity for use in the next step (Note 9).

C. (Z)-2-*Methoxy*-1-*phenylthio*-1,3-*butadiene*. A 250-ml., two-necked, round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and a reflux condenser

bearing a combined inlet-outlet assembly for argon (Note 1) is flushed with argon and charged with 3.27 g. [0.00650 mole, 0.0126 g.-atom of copper(I)] of bis[copper(I) trifluoromethanesulfonate] benzene complex (Note 10), 0.036 g. (0.18 mmole) of 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide (Note 11), and 70 ml. of benzene (Note 12). With syringes 1.20 g. (0.00397 mole) of 4,4-bis(phenylthio)-3-methoxy-1-butene, 1.33 g. (1.80 ml., 0.0103 mole) of *N,N*-diisopropylethylamine (Note 13), and 14 ml. of tetrahydrofuran (Note 5) are injected through the septum into the flask. The suspension is stirred and heated under reflux for 4.75 hours (Note 14), after which the starting thioacetal has completely reacted, as judged by TLC (Note 15). Water (2 ml.) is added to the cooled mixture, the insoluble material is removed by filtration through Celite, and the flask is rinsed with several portions of ether. A 40-ml. portion of water is added to the filtrate, the layers are separated, and the aqueous layer is extracted with three 25-ml. portions of ether. The organic solutions are combined, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. Bulb-to-bulb distillation of the residual brown oil (0.782 g.) in a Kugelrohr apparatus (Note 16) with an oven temperature of 85–95° (0.005 mm.) provides 0.421–0.486 g. (55–64%) of (*Z*)-2-methoxy-1-phenylthio-1,3-butadiene as a light-yellow oil (Note 17) and (Note 18).

2. Notes

1. The inlet-outlet assembly is connected to both a source of argon and a bubbler which serves as exit for the inert gas. Argon is passed through the apparatus for 30 minutes, and the system is then kept under a slight positive pressure of inert gas by maintaining a slow flow of argon through the bubbler.
2. Triethylamine was purchased from Eastman Organic Chemicals and distilled from calcium hydride before use.
3. Thiophenol was purchased from Aldrich Chemical Company, Inc., and distilled, b.p. 75–77° (30 mm.), 168–169° (760 mm.).
4. The submitters obtained 59.6–64.1 g. (65–70%) of product, m.p. 36–37°, after recrystallization from ethanol. Reported melting points for bis(phenylthio) methane are 34–35°,[2] 38–40°,[3] and 39.5–40.5°.[4] The ^{1}H NMR spectrum (CCl_4) exhibits a two-proton singlet at δ 4.30 and a 10-proton multiplet at δ 7.10–7.56.
5. Tetrahydrofuran was distilled from lithium aluminum hydride by the submitters and collected in a flask containing molecular sieves. For a warning regarding this method of purifying tetrahydrofuran, see *Org. Synth.*, **Coll. Vol. 5**, 976 (1973).
6. *n*-Butyllithium in hexane was purchased from Alfa Division, Ventron Corporation.
7. Acrolein was purchased by the submitters from Cationics, Division of Columbia Organic Chemicals Company, Inc. (Columbia, South Carolina) and distilled immediately before use, b.p. 51–53°.
8. Dimethyl sulfate was used as supplied by Eastman Organic Chemicals. The submitters obtained lower yields when methyl iodide was substituted for dimethyl sulfate.

9. The yield and melting point data given are those of the checkers. The purity of the products was estimated to be at least 98% from analysis of its ^{1}H NMR spectrum. The submitters report that the crude product crystallized on standing in a freezer and that one recrystallization from absolute ethanol afforded 3.6–4.1 g. (55–63%) of product, m.p. 49.5–51°. The ^{1}H NMR spectrum (CCl_4) exhibits the following absorptions, δ (multiplictiy, coupling constant *J* in Hz., number of protons, assignment): 3.23 (s, 3H, OCH_3), 3.48–3.97 (m, 1H, $CHOCH_3$), 4.37 [d, J = 4.0, 1H, $CH(SC_6H_5)_2$], 5.03–5.43 (m, 2H, $CH{=}CH_2$), 5.67–6.13 (m, 1H, $CH{=}CH_2$), 6.90–7.57 (m, 10H, $2SC_6H_5$).

10. Bis[copper(I) trifluoromethanesulfonate] benzene complex was prepared by a modification of a procedure reported by Salomon and Kochi[5] as described in the following paragraph. The copper(I) oxide used was purchased from J. T. Baker Chemical Company, and trifluoromethanesulfonic anhydride was prepared by the procedure in *Org. Synth.*, **Coll. Vol. 6**, 324 (1988). The submitters have found once-distilled anhydride to be satisfactory provided that the weight of phosphorus pentoxide used was approximately equal to the weight of sulfonic acid, and the reaction mixture was stirred vigorously. When twice-distilled anhydride was used in the procedure below, reaction times as long as 13 hours were required before decolorization occurred. The submitters suggest that the enhanced rates observed with once-distilled anhydride may be attributed to the presence of the sulfonic acid. Although trifluoromethanesulfonic anhydride is available from Aldrich Chemical Company, Inc., the commercial reagent has not been used in this procedure.

A dry, 1-l., two-necked, round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and a reflux condenser bearing a combined inlet-outlet assembly for argon (Note 1) is purged with argon and charged with 18.0 g. (0.126 mole) of copper(I) oxide and 600 ml. of degassed benzene (Note 12). With a syringe, 42.7 g. (25.5 ml., 0.151 mole) of trifluoromethanesulfonic anhydride is injected through the septum into the flask. The suspension is stirred and heated under reflux until nearly all of the red copper(I) oxide has dissolved. Although 3–5 hours is normally sufficient, reaction times as long as 19 hours were required on some occasions (see preceding paragraph). The hot suspension is filtered through a Büchner funnel in an argon-filled glove bag kept dry with a dish of phosphorus pentoxide. The filtrate is allowed to cool in the glove bag for 1 hour, after which the crop of fine white crystals is collected on a fritted-glass Büchner funnel. The funnel is tightly covered with aluminum foil and then placed in a vacuum desiccator containing anhydrous calcium sulfate and phosphorus pentoxide. The desiccator is removed from the glove bag, evacuated overnight, refilled with argon, and returned to the glove bag. The dry bis[copper(I) trifluoromethanesulfonate] benzene complex, 37.6–49.5 g. (60–79%), is transferred to vials in the glove bag. The product maintains its activity indefinitely when protected from moisture and air.

The procedure described above provides a sufficient quantity of bis[copper(I) trifluoromethanesulfonate] benzene complex for several reactions at the scale used in Part C. If bis[copper(I) trifluoromethanesulfonate] benzene complex for a single reaction is desired, the same procedure can be followed at the appropriate

scale without the use of the glove bag. In this case, the decolorized solution is not filtered but instead cooled, and the product is crystallized in the reaction vessel. The supernatant benzene is decanted, and the crystals are washed in the flask with fresh benzene. The bis[copper(I) trifluoromethanesulfonate] benzene complex is then used without drying in the same flask.

11. 3-*tert*-Butyl-4-hydroxy-5-methylphenyl sulfide was purchased from Aldrich Chemical Company, Inc., and serves as a radical inhibitor, preventing the polymerization of the product. Lower yields of product were obtained when hydroquinone was used as the inhibitor.

12. Benzene was freshly distilled from calcium hydride and collected in a flask containing molecular sieves.

13. *N,N*-Diisopropylethylamine supplied by Aldrich Chemical Company, Inc., was distilled prior to use. The amine is added to prevent polymerization of the diene by acid generated during the reaction. If the product is not sensitive to acid, the amine may be omitted.

14. The temperature at which elimination of thiophenol occurs depends on the substituents on the sulfur-bearing carbon.[6] Thioketals react rapidly at 25°. In some cases the elimination of thiophenol from the less reactive thioacetals may also be performed at 25°. However, in the present case the combined inductive effects of the vinyl and methoxy groups evidently destabilize the incipient carbonium ion and necessitate a higher temperature for the reaction.

15. TLC was carried out on plates coated with silica gel, using 1:10 (v/v) ether–hexane as developing solvent.

16. Kugelrohr distillation ovens manufactured by Büchi Glasaparatefabrik are available from Brinkmann Instruments, Inc., Westbury, New York.

17. The yields and boiling point range given are those reported by the checkers. When the checkers used starting thioacetal that had been purified by both column chromatography and recrystallization (m.p. 50–52°), the yield was 0.486 g. (64%). Using recrystallized thioacetal, m.p. 49.5–51°, the submitters obtained 0.532–0.646 g. (70–85%) of product.

The ^{1}H NMR spectrum (CCl_4) of the diene exhibits the following absorptions, δ (multiplicity, number of protons, assignment): 3.70 (s, 3H, OCH_3), 4.87–5.52 (m, 2H, $CH=CH_2$), 5.64 (s, 1H, $CHSC_6H_5$), 5.83–6.31 (m, 1H, $CH=CH_2$), 6.98–7.37 (m, 5H, SC_6H_5). TLC on silica gel with 3:2 (v/v) benzene–hexane as developing solvent showed a single spot. The single sharp peak for the methoxy group in the ^{1}H NMR spectrum and the absence of a spot at a high R_f value from TLC established that the product was not contaminated by its *E*-isomer. A mixture of the two isomers in which the *E*-isomer predominates can be prepared by heating a solution of the product in dichloromethane at reflux for 4 hours. The stereochemistry of the original product is assigned as *Z* on the basis of its high reactivity in Diels-Alder reactions and on the exclusive formation of an adduct with *cis* stereochemistry from reaction with methyl vinyl ketone.[7] The *E*-isomer undergoes Diels-Alder reactions much more slowly.[8]

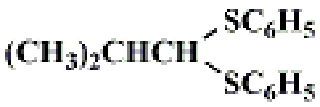
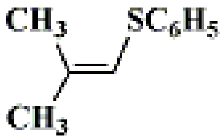
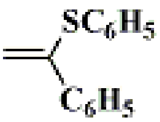
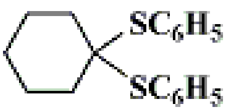
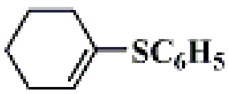
18. The product is stable for months when mixed with a small amount of the radical inhibitor, 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide, and stored in a

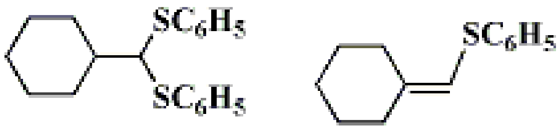
freezer. In the absence of the inhibitor, it isomerizes to a mixture of *E*- and *Z*-isomers over a period of some months.

3. Discussion

Part C of the present procedure illustrates a mild method for effecting the elimination of thiophenol from thioacetals and thioketals under essentially neutral conditions. The reaction of simple thioacetals and thioketals with bis[copper(I) trifluoromethanesulfonate] benzene complex in benzene-tetrahydrofuran at room temperature affords vinyl sulfides in high yield (Table I).[6,7] The reaction presumably occurs by coordination of the thiophilic copper(I) reagent with sulfur, heterolysis to a phenylthio-stabilized carbonium ion with formation of the insoluble copper(I) thiophenoxide, and finally proton loss, giving the vinyl sulfide. Since trifluoromethanesulfonic acid is generated in stoichiometric quantity during the reaction, the medium becomes highly acidic. If the reactant or product is unstable to acid, as is the case in the present procedure, the pH can be kept neutral by adding *N,N*-diisopropylethylamine.

TABLE I
VINYL SULFIDES FROM THIOACETALS AND THIOKETALS WITH COPPER(I) TRIFLUOROMETHANESULFONATE

Thioacetal or Thioketal	Vinyl Sulfide	Yield (%)
		91
		85
		85
		92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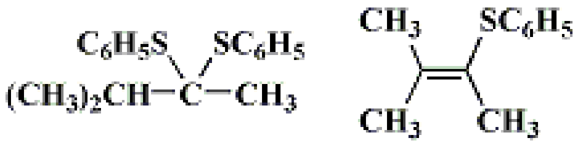
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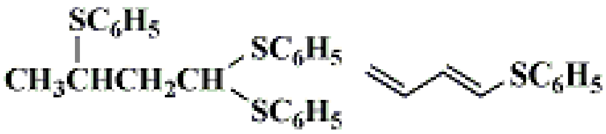
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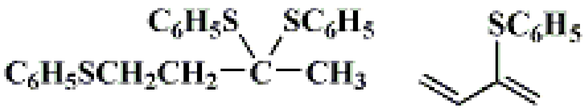
76

The reaction of crotonaldehyde and methyl vinyl ketone with thiophenol in the presence of anhydrous hydrogen chloride effects conjugate addition of thiophenol as well as acetal formation. The resulting β-phenylthio thioacetals are converted to 1-phenylthio- and 2-phenylthio-1,3-butadiene, respectively, upon reaction with 2 equivalents of copper(I) trifluoromethanesulfonate (Table I).[7] The copper(I)-induced heterolysis of carbon–sulfur bonds has also been used to effect pinacol-type rearrangements of bis(phenylthio)methyl carbinols.[9] Thus, the addition of bis(phenylthio)methyllithium to ketones and aldehydes followed by copper(I)-induced rearrangement results in a one-carbon ring expansion or chain-insertion transformation, giving α-phenylthio ketones. Monothioketals of 1,4-diketones are cyclized to 2,5-disubstituted furans by the action of copper(I) trifluoromethanesulfonate.[6,10]

The most common procedure previously employed to effect the elimination of thiols from thioacetals has been heating in the presence of a protic acid.[11,12] For example, propionaldehyde diethyl thioacetal is converted to 1-ethylthio-1-propene on heating at 175° in the presence of phosphoric acid.[11] The relatively high temperature and acidic conditions of such procedures are, however, distinct disadvantages of this method. Another approach consists of oxidation of a thioacetal to the mono *S*-oxide and thermal elimination of a sulfenic acid at 140–150°.[13]

Vinyl sulfides have found numerous synthetic applications. Vinyl sulfides unsubstituted in the 1-position are metallated readily, and the resulting 1-phenythio- or 1-alkylthiovinyllithium reagents have been utilized for nucleophilic acylation and other applications.[14,15] The phenylthio-substituted 1,3-butadienes serve as interesting

functionalized dienes in Diels-Alder reaction.[7,16,17] For example, (*Z*)-2-methoxy-1-phenylthio-1,3-butadiene and methyl vinyl ketone afford an adduct with the normally inaccessible "meta" relationship between the methoxy and acetyl substituents.[7] The isomeric 2-methoxy-3-phenylthio- and 1-methoxy-4-phenylthio-1,3-butadienes have been prepared recently by thermal ring opening of the appropriate cyclobutenes.[17]

When methacrolein is substituted for acrolein in the present procedure, (*Z*)-2-methoxy-3-methyl-1-phenylthio-1,3-butadiene is produced in good yield.[18] However, when a β-alkyl group is present on the enal, a rearranged product, a 4-alkyl-1-methoxy-2-phenylthio-1,3-butadiene, is produced as a pair of geometric isomers.[18]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

bis[copper(I) trifluoromethanesulfonate] benzene

benzene-tetrahydrofuran

2-methoxy-3-phenylthio- and 1-methoxy-4-phenylthio-1,3-butadienes

ethanol (64-17-5)

hydrogen chloride, hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

Benzene (71-43-2)

ether, diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

Acrolein (107-02-8)

hydroquinone (123-31-9)

sulfur (7704-34-9)

dimethyl sulfate (77-78-1)

copper(I) oxide

phosphoric acid (7664-38-2)

Methyl iodide (74-88-4)

dichloromethane (75-09-2)

Thiophenol (108-98-5)

magnesium sulfate (7487-88-9)

n-butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

hexane (110-54-3)

crotonaldehyde (123-73-9)

methyl vinyl ketone (78-94-4)

triethylamine (121-44-8)

Triethylamine hydrochloride (554-68-7)

methacrolein (78-85-3)

calcium hydride (7789-78-8)

argon (7440-37-1)

trifluoromethanesulfonic acid (1493-13-6)

copper(I) thiophenoxide (34012-88-9)

Trifluoromethanesulfonic anhydride (358-23-6)

N,N-diisopropylethylamine (7087-68-5)

COPPER(I) TRIFLUOROMETHANESULFONATE

Bis(phenylthio)methane (3561-67-9)

4,4-Bis(phenylthio)-3-methoxy-1-butene (60466-65-1)

vinyl sulfide (627-51-0)

bis(phenylthio)methyllithium

propionaldehyde diethyl thioacetal

1-ethylthio-1-propene

phosphorus pentoxide (1314-56-3)

(Z)-2-Methoxy-1-phenylthio-1,3-butadiene, Benzene, [(2-methoxy-1,3-butadienyl) thio]-, (Z)- (60466-66-2)

3-tert-butyl-4-hydroxy-5-methylphenyl sulfide (96-66-2)

(Z)-2-methoxy-3-methyl-1-phenylthio-1,3-butadiene

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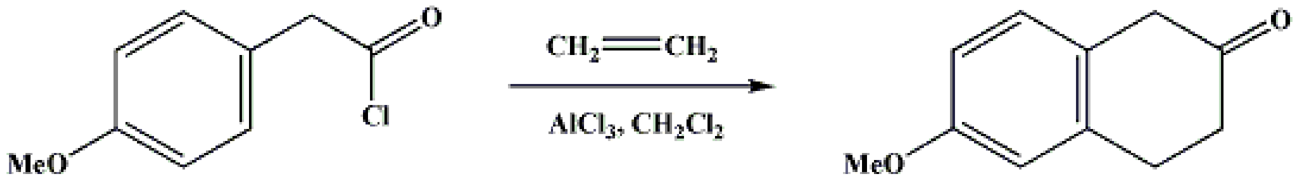
Organic Syntheses, CV 6, 744

6-METHOXY-β-TETRALONE

[2(1*H*)-Naphthalenone, 3,4-dihydro-6-methoxy-]



Submitted by James J. Sims[1], L. H. Selman, and M. Cadogan.
Checked by Robert E. Ireland and Ronald I. Trust.

1. Procedure

A 2-l., three-necked flask equipped with a mechanical stirrer, a reflux condenser fitted with a calcium chloride drying tube, and a pressure-equalizing dropping funnel is charged with 53.4 g. (0.400 mole) of anhydrous aluminum chloride (Note 1) and 800 ml. of dichloromethane (Note 2). The flask is placed in an acetone–dry ice bath, and the mixture is stirred for a few minutes before slowly adding a solution of 36.9 g. (0.200 mole) of (4-methoxyphenyl)acetyl chloride (Note 3) in 200 ml. of dichloromethane over 45 minutes. When the addition is complete, the funnel is replaced with a gas-inlet tube (Note 4), and ethylene is bubbled vigorously into the flask for about 10 minutes. The gas-inlet tube is replaced with a stopper, the cooling bath is removed, and the reaction mixture is allowed to warm to room temperature, then stirred for 3–3.5 hours (Note 5). The reaction mixture is cooled in an ice bath while 250 ml. of ice water is added *carefully* (Note 6). The mixture is stirred until all of the solid material is dissolved. The yellow organic layer is separated, washed two times with 150-ml. portions of 5% hydrochloric acid and two times with 150-ml. portions of saturated sodium hydrogen carbonate. The organic layer is dried over magnesium sulfate and filtered. The solvent is distilled with a rotary evaporator, keeping the bath temperature under 60°. Distillation (Note 7) of the yellow residue through a 15-cm. Vigreux column gives 21–24 g. (60–68%) of 6-methoxy-β-tetralone, b.p. 114–116° (0.2 mm.), which solidifies to a white solid on standing in the refrigerator, m.p. 33.5–35° (Note 8).

2. Notes

1. A 100% molar excess of aluminum chloride is necessary to obtain an acceptable yield in a short time. The reaction of phenylacetyl chloride with ethylene requires only 1 mole of aluminum chloride per mole of acid chloride.
2. Matheson, Coleman and Bell dichloromethane, b.p. 39.5–40.5°, was used without purification. The use of this solvent rather than carbon disulfide is the major improvement of this procedure over the published one.[2]
3. (4-Methoxyphenyl)acetyl chloride is prepared from (4-methoxyphenyl)acetic acid (Aldrich Chemical Company, Inc., m.p. 85–86.5°) by the procedure of Buckles and Cooper.[3] Thionyl chloride (50 ml.) is added to 100 g. (0.603 mole) of (4-methoxyphenyl)acetic acid in a 500-ml. round-bottomed flask containing a few boiling stones and a magnetic stirring bar, and fitted with a calcium chloride drying tube. The contents of the flask are stirred slowly for 24 hours at room temperature. Dry benzene (80 ml.) is added and removed by distillation on a rotary evaporator; the process is then repeated. The yellow-green liquid is transferred to a 200-ml. flask with a small volume of benzene and, after removal of the solvent under vacuum,

distillation of the liquid through a 15-cm. Vigreux column affords 102–108 g. (92–97%) of (4-methoxyphenyl)acetyl chloride, b.p. 80–88° (0.5 mm.).

4. A glass tube (6 mm. o.d.), flanged at one end and bent to direct gas bubbles in the direction of stirring is used. A fritted disk will become clogged during the addition and should not be used.

5. This reaction time was found to give the best yield of pure product. The progress of the reaction should be checked by either IR spectroscopy or GC. A small aliquot (1–2 ml.) is worked up in a test tube by quenching with water, separating the organic phase, and drying over magnesium sulfate. The IR spectrum will show a disappearance of the acid chloride carbonyl peak at 1786 $cm.^{-1}$ and appearance of the 6-methoxy-β-tetralone carbonyl peak at 1701 $cm.^{-1}$ GC was carried out in a 185 cm. × 3.2 mm. column packed with 5% by weight SE-30 on Diatoport S (60–80 mesh). The reaction may also be followed visually. The initial yellow suspension changes to green and finally to red-brown with a green cast. The reaction is essentially complete with the precipitation of dark green aluminum salts.

6. Much heat is generated on addition of water to the dark red-brown mixture. The addition should be dropwise until the heat is dissipated.

7. If the distillation is not carried out promptly, the crude product should be placed under nitrogen in a freezer. The tetralone seems to keep well under nitrogen at low temperature in glassware that has been rinsed with ammonium hydroxide and dried in an oven; the distillation flask and column were also routinely treated this way.

8. This material contains a small amount of impurity (2–5%). A higher grade material may be obtained by discarding a 1–2 g. forerun.

3. Discussion

This procedure, an improvement over the method of Burckhalter and Campbell,[2] represents the most convenient method of preparing 6-methoxy-β-tetralone, a valuable intermediate for the synthesis of natural products, and provides a general method for the synthesis of substituted β-tetralones.[2,4]

6-Methoxy-β-tetralone has been synthesized from 6-methoxy-3,4-dihydronaphthalenecarboxylic acid by the Curtius reaction.[5] Other preparations include the Birch reduction of 6-methoxy-2-naphthol,[6,7] oxidation of 6-methoxytetralin,[6,8] and synthesis from 6-methoxy-α-tetralone.[9] The other practical approaches depend upon tedious preparations of naphthalene derivatives.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

thionyl chloride (7719-09-7)

sodium hydrogen carbonate (144-55-8)

nitrogen (7727-37-9)

aluminum chloride (3495-54-3)

carbon disulfide (75-15-0)

ethylene (9002-88-4)

ammonium hydroxide (1336-21-6)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

phenylacetyl chloride (103-80-0)

6-methoxytetralin (1730-48-9)

6-Methoxy-2-naphthol (5111-66-0)

6-Methoxy-β-tetralone, 2(1H)-Naphthalenone, 3,4-dihydro-6-methoxy- (2472-22-2)

6-methoxy-α-tetralone (1078-19-9)

(4-methoxyphenyl)acetyl chloride (4693-91-8)

(4-methoxyphenyl)acetic acid (104-01-8)

6-methoxy-3,4-dihydronaphthalenecarboxylic acid

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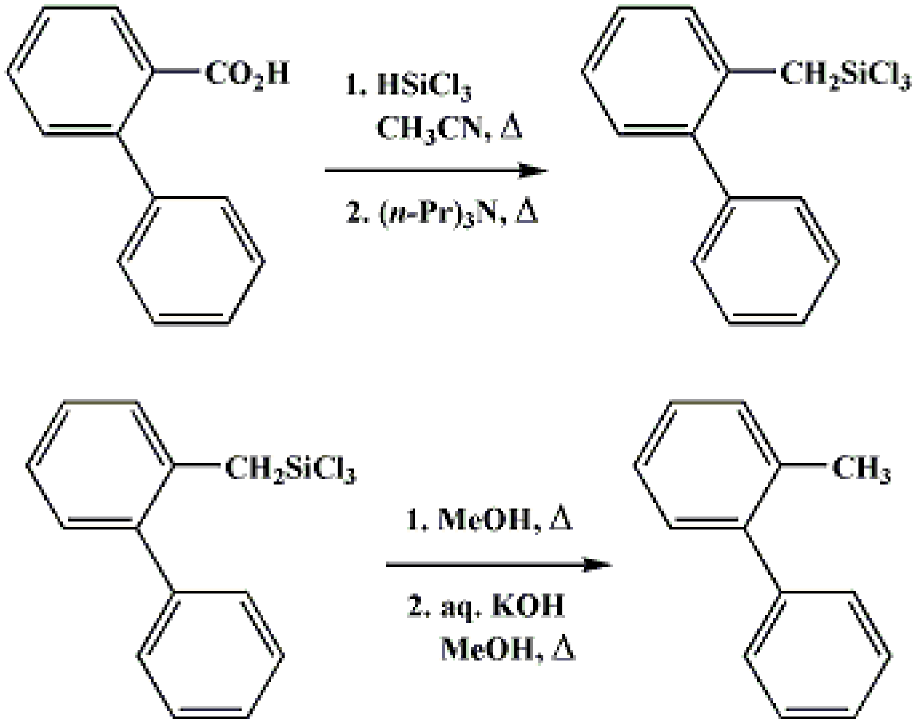
Organic Syntheses, CV 6, 747

METHYL GROUPS BY REDUCTION OF AROMATIC CARBOXYLIC ACIDS WITH TRICHLOROSILANE - TRI-*n*-PROPYLAMINE: 2-METHYLBIPHENYL

[1,1'-Biphenyl, 2-methyl]



Submitted by George S. Li, David F. Ehler, and R. A. Benkeser[1].
Checked by Kyo Okada and Wataru Nagata.

1. Procedure

Caution! This procedure should be conducted in a well-ventilated hood to avoid inhalation of trichlorosilane and hydrogen chloride.

A 300-ml., three-necked, round-bottomed flask is equipped with a magnetic stirrer, a thermometer, a glass stopper, and an efficient condenser attached to a nitrogen line with a gas bubbler (Note 1). The system is flushed with dry nitrogen, then charged with 19.8 g. (0.100 mole) of biphenyl-2-carboxylic acid (Note 2), 80 g. (60 ml., 0.59 mole) of trichlorosilane (Note 3) and (Note 4), and 80 ml. of acetonitrile (Note 5). A low nitrogen flow is maintained as the mixture is stirred and heated to reflux (40–45°) for 1 hour or until gas evolution ceases and the carboxylic acid has dissolved. The solution is then cooled in an acetone–dry ice bath to at least 0°, and the glass stopper is replaced with a 100-ml., pressure-equalizing dropping funnel charged with 37.8 g. (0.264 mole) of tri-*n*-propylamine (Note 6) and (Note 7), which is emptied rapidly into

the stirred solution. The cooling bath is removed, and the flask contents are allowed to stir until the reaction ceases to be exothermic. A heating mantle is then used to maintain reflux for 16 hours (Note 8), during which time the temperature rises to 70–75°.

As soon as reflux is terminated, the solution is poured rapidly into a 1-l. Erlenmeyer flask, allowed to cool, and diluted with enough anhydrous diethyl ether (Note 9) to make the total volume about 850 ml. (Note 10). After the flask has been sealed and refrigerated for one hour, the precipitate is removed by rapid filtration (water aspirator) through a 150-ml. Büchner funnel and washed with three 50-ml. portions of anhydrous ether. The clear yellow filtrate is concentrated as follows. A 300-ml., one-necked, round-bottomed flask is fitted with a magnetic stirring bar and a 100-mm. Vigreux column topped with a distillation head. The filtrate is placed in a 1-l., pressure-equalizing dropping funnel inserted into the top of the distillation head. Approximately 100 ml. is run down through the column into the flask, which is then heated. As ether is removed by distillation, the remainder of the filtrate is dripped into the flask at a constant rate, and in this way the solution is concentrated into a small flask in a continuous operation. Distillation is continued until most of the ether has been removed, and the resulting murky solution is heated at 40° (80 mm.), removing the remaining volatiles.

The Vigreux column, dropping funnel, and distilling head are then replaced by a 100-ml., pressure-equalizing dropping funnel charged with 100 ml. of methanol. With the top of the funnel left open to the atmosphere, the methanol is added slowly to the oily flask contents (Note 11). After vigorous boiling has ceased, the solution is heated under reflux for one hour, cooled in an ice bath, then treated slowly with a solution of 56 g. (1.0 mole) of potassium hydroxide in 25 ml. of water and 50 ml. of methanol.[2] The resulting mixture is heated under reflux for 19 hours (Note 8), dissolved in 600 ml. of water, and extracted three times with 100 ml. of ether. The extracts are combined, washed once with 50 ml. of 5 *N* hydrochloric acid, and dried over anhydrous magnesium sulfate. Ether is removed by distillation as described above, using a 300-ml., pressure-equalizing dropping funnel, a 50-ml., round-bottomed distilling flask, and a 100-mm. Vigreux column. Vacuum distillation of the remaining liquid gives 12.5–13.4 g. (74–80%) of 2-methylbiphenyl, b.p. 76–78° (0.5 mm.), n_D^{20} 1.5920 (Note 12) and (Note 13).

2. Notes

1. All glassware is thoroughly dried by flame or in an oven prior to use.
2. Biphenyl-2-carboxylic acid was purchased from Aldrich Chemical Company, Inc., and used without further purification.
3. The submitters used trichlorosilane supplied by Union Carbide Corporation. The checkers obtained trichlorosilane from Tokyo Chemical Industries Company, Ltd., Japan.
4. Good results may sometimes be achieved with a 4:1 or 5:1 mole ratio of trichlorosilane to carboxylic acid. Excess trichlorosilane is needed to

compensate for losses of this volatile reactant over extended reflux periods.

5. The submitters used reagent grade acetonitrile (Mallinckrodt Chemical Works) dried prior to use by storage over Matheson Linde type 4A molecular sieves. The checkers used reagent grade acetonitrile obtained from Ishizu Pharmaceutical Company, Japan, dried prior to use by storage over 4A molecular sieves obtained from Nakarai Chemicals, Ltd., Japan.

6. The submitters used tri-*n*-propylamine obtained from Aldrich Chemical Company, Inc., and the checkers used tri-*n*-propylamine obtained from Wako Pure Chemical Industries, Ltd., Japan. Both groups stored the reagent over Linde type 4A molecular sieves prior to use.

7. To ensure a homogeneous reducing medium, the tri-*n*-propylamine: trichlorosilane ratio should be about 1:2.

8. Overnight reflux was chosen partly for convenience. Similar results are possible with somewhat shorter reaction times.

9. The submitters employed anhydrous ether obtained from Mallinckrodt Chemical Works; the checkers used anhydrous ether obtained from Wako Pure Chemical Industries, Ltd., Japan and distilled it from sodium hydride under nitrogen shortly prior to use.

10. The volume of ether added should be sufficient to precipitate most of the tri-*n*-propylamine hydrochloride in solution. The checkers diluted to a total volume of about 1 l. to precipitate the salt more efficiently.

11. Vigorous evolution of hydrogen chloride is observed as the methanol is added.

12. The literature[3] value for a carefully purified sample of 2-methylbiphenyl is n_D^{20} 1.5914.

13. ^{1}H NMR ($CDCl_3$), δ (multiplicity, number of protons, assignment): 2.55 (s, 3H, CH_3), 7.27 (s, 4H, C_6H_4), 7.33 (s, 5H, C_6H_5). IR ($CHCl_3$) cm.$^{-1}$: 1600 medium, 1480 medium strong (aromatic), 1380 medium (CH_3). GC analysis of the product (1.5 m. by 0.5 cm. glass column, KF-54 on Chromosorb W, 60–80 mesh) showed a single peak with a retention time of 2.60 minutes at 170°.

3. Discussion

2-Methylbiphenyl has been prepared by diazotization of *o*-toluidine and coupling with benzene (8%);[4] by reaction of *o*-tolylmagnesium bromide with cyclohexanone, followed by dehydration of the resulting alcohol and dehydrogenation (30–50%);[5] and by coupling *o*-tolyllithium with chlorobenzene in the presence of piperidine (51%).[6] The present procedure gives 2-methylbiphenyl in much improved yield.

In a more general sense, this reduction method provides a convenient pathway for converting an aromatic carboxyl group to a methyl group (see Table I).[7] Previously, this transformation has been achieved by reduction of the acid to the alcohol with lithium aluminum hydride, conversion of the alcohol to the tosylate, and a second

reduction either with lithium aluminum hydride, or Raney nickel and hydrogen.[8] Alcohols of the benzylic type have also been reduced directly with hydrogen under pressure in the presence of various catalysts,[9] and benzoic acids have been reduced to toluenes with rhenium-type catalysts and hydrogen at high temperatures and pressures.[10]

TABLE I
REDUCTION OF AROMATIC ACIDS TO SUBSTITUTED BENZENES[7]

Starting Acid	Product (% Yield)
Benzoic	Toluene (78)
m-Toluic	*m*-Xylene (82)
p-Toluic	*p*-Xylene (74)
3,5-Dimethylbenzoic	Mesitylene (82)
4-Chlorobenzoic	*p*-Chlorotoluene (94)
4-Bromobenzoic	*p*-Bromotoluene (94)
Phthalic	*o*-Xylene (64)

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrogen chloride, hydrochloric acid (7647-01-0)

Benzene (71-43-2)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

hydrogen (1333-74-0)

acetonitrile (75-05-8)

Cyclohexanone (108-94-1)

nitrogen (7727-37-9)

nickel (7440-02-0)

chlorobenzene (108-90-7)

potassium hydroxide (1310-58-3)

toluene (108-88-3)

piperidine (110-89-4)

p-Chlorotoluene (106-43-4)

p-xylene (106-42-3)

Mesitylene (108-67-8)

magnesium sulfate (7487-88-9)

lithium aluminum hydride (16853-85-3)

sodium hydride (7646-69-7)

tri-n-propylamine (102-69-2)

biphenyl-2-carboxylic acid (947-84-2)

o-toluidine (95-53-4)

p-Bromotoluene (106-38-7)

TRICHLOROSILANE (10025-78-2)

2-Methylbiphenyl, 1,1'-Biphenyl, 2-methyl (643-58-3)

m-xylene (108-38-3)

o-Xylene (95-47-6)

o-tolylmagnesium bromide

o-Tolyllithium

tri-n-propylamine hydrochloride

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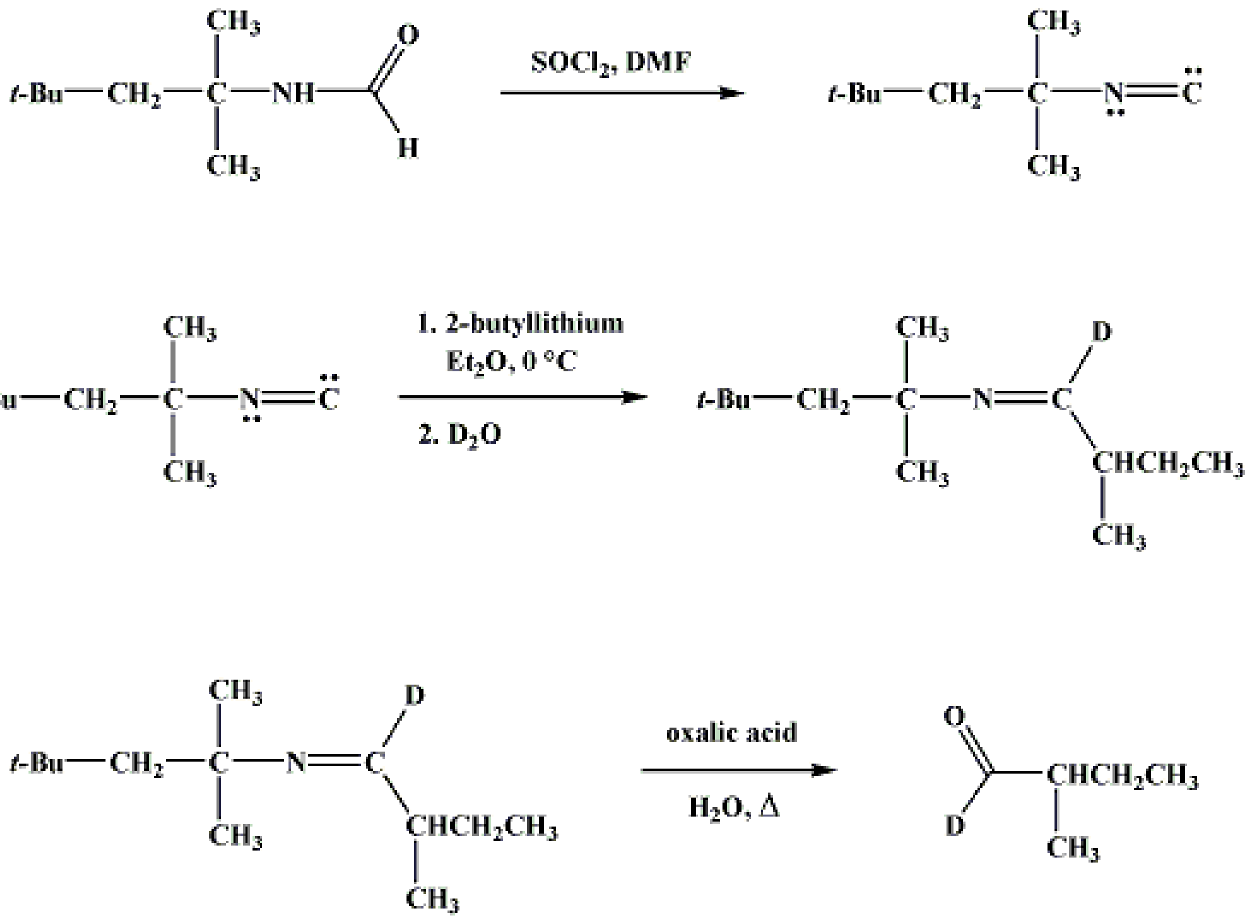
Organic Syntheses, CV 6, 751

1-*d*-ALDEHYDES FROM ORGANOMETALLIC REAGENTS: 2-METHYLBUTANAL-1-*d*

[Butanal-1-*d*, 2-methyl-]



Submitted by G. E. Niznik, W. H. Morrison, III, and H. M. Walborsky[1].
Checked by Frank E. Herkes and Richard E. Benson.

1. Procedure

A. 1,1,3,3-*Tetramethylbutyl isonitrile.* A 3-l., three-necked, round-bottomed flask fitted with a Hershberg stirrer, a 500-ml. pressure-equalizing addition funnel, and a nitrogen-inlet tube is flamed dry under a nitrogen atmosphere and allowed to cool. The nitrogen-inlet tube is replaced with a low-temperature thermometer, and the nitrogen line is attached to a Y-tube placed on the addition funnel. To the flask are added 118 g. (0.752 mole) of *N*-(1,1,3,3-tetramethylbutyl)formamide (Note 1) and 1500 ml. of *N,N*-dimethylformamide (Note 2). The addition funnel is charged with a premixed (Note 3) solution of 89 g. (55 ml., 0.75 mole) of thionyl chloride and 250 ml. of *N,N*-dimethylformamide. The flask is immersed in an acetone–dry ice bath, and moderately fast stirring is started. When the temperature of the flask reaches −50°, the solution in the funnel is added at a rate such that the temperature ranges between −55° and −50° (about 10 minutes are required for the addition). After the addition is complete, the bath is removed momentarily, allowing the reaction temperature to rise to −35°. The bath is then replaced, and 159 g. (1.50 mole) of dry sodium carbonate (Note 4) is added directly to the mixture (Note 5). After the addition the bath is removed,

and the flask contents are stirred for an additional 6 hours at room temperature (Note 6). The reaction mixture (Note 7) is poured into a 6-l. Erlenmeyer flask containing 3 l. of ice water (Note 8). The reaction flask is rinsed with 300 ml. of pentane and sufficient water to dissolve the inorganic material that may be present (Note 9). The washings are added to the Erlenmeyer flask. The mixture is stirred vigorously for 5 minutes, and the layers are separated. The upper layer is washed twice with 100-ml. portions of water and dried over anhydrous sodium sulfate. The solution is filtered, and the pentane is removed by distillation. The crude product is distilled through a 1.5 × 15 cm. Vigreux column; the fraction collected at 55.5–56.6° (11 cm.), yields 86–90 g. (82–87%) of 1,1,3,3-tetramethylbutyl isonitrile, n_D^{30} 1.4178, d^{25} 0.7944. The compound shows strong absorption in the IR (CCl_4) at 2130 cm.$^{-1}$ attributable to the isonitrile function. The ^{1}H NMR spectrum (neat, external tetramethylsilane reference) shows peaks at δ 1.08 (s, 9H, $C(CH_3)_3$), 1.43 (t, $J_{^{14}N\text{-}H}$ = 2 Hz., 6H, $C(CH_3)_2$), and 1.58 (t, $J_{^{14}N\text{-}H}$ = 2.3 Hz., 2H, CH_2).

B. N-(2-*Methylbutylidene*-1-*d*)-1,1,3,3-*tetramethylbutylamine* (Note 10). A 1-l., three-necked, round-bottomed flask fitted with a Teflon paddle stirrer, a 500-ml. pressure-equalizing addition funnel, and a nitrogen-inlet tube is flamed dry under a nitrogen atmosphere and allowed to cool. The nitrogen-inlet tube is replaced with a thermometer, and the nitrogen line is attached to a Y-tube placed on the addition funnel. A solution of 27.8 g. (35.1 ml., 0.200 mole) of 1,1,3,3-tetramethylbutyl isonitrile in 300 ml. of anhydrous diethyl ether is added to the flask. The flask is cooled to 0° with an ice–salt bath, and 0.2 mole of 2-butyllithium in hexane (Note 11) is transferred to the addition funnel with a syringe. The alkyllithium solution is added to the stirred (Note 12) solution at such a rate that the temperature never exceeds 5°. After the addition is complete, the mixture is stirred for 15 minutes as the temperature slowly drops to –5°, and 8 ml. (0.4 mole) of deuterium oxide (Note 13) is injected rapidly into the reaction mixture (Note 14). The ice bath is removed; the mixture is stirred for 30 minutes and filtered through a Büchner funnel into a 1-l., round-bottomed flask. The reaction flask is rinsed with pentane, and the rinse is added to the flask. After evaporation of the solvent, 33.7–34.9 g. (85–88%) of the aldimine is collected by distillation through a 1.5 × 15 cm. Vigreux column, b.p. 52.5–54° (1.5 mm.), $n_D^{24.5}$ 1.4321. The IR spectrum (neat) shows strong absorption at 1663 cm.$^{-1}$, attributable to the isonitrile function.

C. 2-*Methylbutanal*-1-*d*. A 1-l., three-necked, round-bottomed flask is equipped with a dropping funnel, a gas-inlet tube for steam, and a Dean-Stark trap attached to a condenser through which acetone cooled to –15° is circulated (Note 15). A solution of 50.4 g. (0.400 mole) of oxalic acid dihydrate in 200 ml. of water is added to the flask and heated at reflux. Steam is introduced into the flask, and when it begins to condense in the Dean-Stark trap, the aldimine from part B is added dropwise from the funnel. The aldehyde and water collect in the trap, and the water layer is periodically removed. After the distillation of the aldehyde is complete, the product is drained from the trap; the water layer is separated and discarded. The oil is washed with three 25-ml. portions of saturated sodium chloride and dried over anhydrous calcium sulfate. The crude aldehyde is decanted from the drying agent and distilled through a short Vigreux column, giving 13.0–13.3 g. (87–88%) of high-quality 2-methylbutanal-1-*d*, b.p. 92–93°, n_D^{30} 1.3896 (Note 16). The IR spectrum (neat) shows strong adsorption at 1721 cm.$^{-1}$ attributable to the carbonyl function.

2. Notes

1. *N*-(1,1,3,3-tetramethylbutyl)formamide is prepared in 86–90% yield by refluxing 194 g. (1.50 moles) of 1,1,3,3-tetramethylbutylamine with 138 g. (3.00 moles) of formic acid in 400 ml. of toluene. Azeotropic distillation using a Dean-Stark trap gradually removes all water and excess formic acid. The toluene is removed by distillation at atmospheric pressure, and

the product is distilled at reduced pressure, b.p. 76–77° (1 mm.), n_D^{25} 1.4521, yielding 203–214 g. (86–90%).
2. Industrial grade *N,N*-dimethylformamide is purified by distillation, first at atmospheric pressure to remove most of the water in the initial small fraction, and then by distillation at reduced pressure from barium oxide, b.p. 63° (30 mm.).
3. A temperature rise of about 30° is observed.
4. Commercial anhydrous sodium carbonate is dried in a vacuum oven at 130° for 1 hour.
5. The checkers used a solid addition funnel and added the sodium carbonate under nitrogen over a 10-minute period.
6. The mixture can be left stirring overnight since isonitrile is stable to the reaction conditions. Alternatively, a hot-water bath can be used, with very fast stirring, to heat the mixture quickly to 35°. The bath is then removed, and after 1 hour of additional stirring, the mixture is ready for the workup procedure.
7. *Isonitriles are presumed to be toxic*, and it is recommended that the workup procedure be performed in a hood. Unlike most isonitriles, however, 1,1,3,3-tetramethylbutyl isonitrile (TMBI) is not malodorous. It has a sweetish pine odor, which becomes unpleasant only after continued inhalation.
8. The addition of the reaction mixture to water is exothermic.
9. The inorganic salts are not always soluble in the amount of water specified.
10. This procedure uses the commercially available 2-butyllithium reagent. The submitters state that the corresponding Grignard reagent may also be used. A 300-ml., three-necked, round-bottomed flask is fitted with an addition funnel, a reflux condenser, a magnetic stirring bar, and a nitrogen-inlet tube. Magnesium turnings (3.65 g., 0.150 mole) and 80 ml. of anhydrous tetrahydrofuran (Note 17) are added to the flask, and a nitrogen atmosphere is maintained. 2-Bromobutane (20.6 g., 0.150 mole), 0.25 ml. of 1,2-dibromoethane, and 70 ml. of tetrahydrofuran are placed in the addition funnel. Stirring is begun, and the solution is added dropwise at a rate which sustains refluxing. After the addition is complete, the solution is stirred until room temperature is reached. The amount of Grignard reagent prepared is determined (Note 18). To this Grignard solution is added 14.2 g. (0.102 mole) of 1,1,3,3-tetramethylbutyl isonitrile (Note 19). After stirring for 4–6 hours (Note 20), the solution is cooled in an ice bath to 0°. To the rapidly stirred solution (Note 21) is injected 6.0 ml. (0.30 mole) of deuterium oxide (Note 13). The ice bath is removed, and the mixture is stirred for 10 minutes before 50 ml. of water is added (Note 22). The contents of the reaction flask are decanted into a 1-l. separatory funnel containing 200 ml. of ether. The aqueous layer is separated, and the ether layer is washed with 100 ml. of saturated sodium chloride. The magnesium salts remaining in the reaction vessel are washed twice with 100-ml. portions of ether. The ether extracts are washed with 100 ml. of saturated sodium chloride. The combined ether solutions are dried over anhydrous sodium sulfate and evaporated with a rotary evaporator, giving the crude aldimine. Distillation (see Part B) yields 13.7 g. (67%) of the pure aldimine. Hydrolysis and steam distillation (as described in Note 15) yield 5.85 g. (65%, overall) of the aldehyde (Note 23).
11. The commercially available organolithium reagent is titrated with benzoic acid, using triphenylmethane as an indicator according to the procedure of Eppley and Dixon.[2] The checkers used product available from Alfa Inorganics, Inc.
12. During the addition of the alkyllithium the mixture becomes gelatinous. As this happens, the stirring rate is increased to ensure thorough mixing.
13. Deuterium oxide having an isotopic purity of >99% was used. The product available from Columbia Organic Chemicals Company, Inc., was used by the checkers.
14. The stirring should be very rapid at this point or frothing will occur. The flask temperature will reach 30° during deuteriolysis. It is important that the temperature of the

ice–salt bath remains at −10° to −15°.
15. The submitters recommend the following procedure for steam distillation of low-boiling aldehydes. A 500-ml., three-necked flask is fitted with two addition funnels, one of which has a double-bore stopcock for external drainage. This addition funnel is fitted with a cold finger (–5°) and an inlet tube leading to a bubbler and a nitrogen source. The aldimine is placed in the other addition funnel. While the aldimine is added dropwise to the refluxing oxalic acid solution, the distillate passes up the equalizing pressure tube of the collecting funnel and is condensed by the cold finger. The water layer is periodically drained back into the flask. After distillation, the aldehyde is washed with saturated sodium chloride, then drained from the funnel through the external tube.
16. The submitters found that GC analysis of the undistilled aldehyde, conducted on a column packed with 16% LS-40 on Chromosorb P/AW at 100°, indicated a purity of 98.6%. ^{1}H NMR (CCl_4) analysis indicated an isotopic purity of 97.9% (trace of impurity at δ 9.60 due to C*H*O. If the crude aldimine is hydrolyzed, the aldehyde is obtained in 96% overall yield; however, the purity is only 94% by GC analysis. The checkers found no detectable impurity by GC in the distilled aldehyde, and the NMR spectrum indicated very high isotopic purity.
17. Alkyl magnesium halides form intermediates with tetramethylbutyl isonitrile which are not very soluble in ether. If it is necessary to prepare the Grignard reagent in ether, the ether should either be diluted with tetrahydrofuran or replaced by tetrahydrofuran. See the warning note in *Org. Synth.*, **Coll. Vol. 5**, 976 (1973), for purification of tetrahydrofuran.
18. The molarity is determined[3] by adding an excess of standardized acid and back-titrating with base. The moles of Grignard reagent present are determined based on a volume of 150 ml. When ether is used to prepare the Grignard reagent, an actual measurement of the volume is necessary. This can be done conveniently by transferring the solution back into the addition funnel with a large graduated syringe. The Grignard reagent content averages 0.102 mole.
19. The molar amount of 1,1,3,3-tetramethylbutyl isonitrile used is equivalent to the Grignard reagent content.
20. After 4 hours, periodic aliquots are taken and worked up. The disappearance of the isonitrile absorption at 2130 cm.$^{-1}$ and the appearance of the imine absorption at 1665 cm.$^{-1}$ are used for analysis. Usually within 6 hours the isonitrile peak vanishes or remains at a very low constant intensity indicative of completion of the reaction.
21. The sudden quenching with deuterium oxide minimizes the exchange between the 1-metalloaldimine and the active hydrogen at the C-2 position of the already-deuteriated aldimine. Performing the reaction in refluxing tetrahydrofuran produces an exchange (approximately 10%) with incorporation of deuterium in the C-2 position. If only the 1-H-aldehyde is desired, 50 ml. of water is added dropwise.
22. Saturated ammonium chloride solution slowly hydrolyzes the aldimine to the aldehyde, which, in this case, is undesirable.
23. NMR analysis shows that deuterium incorporation at the C-1 position is 95.3% and at C-2, 5%.

3. Discussion

This reaction illustrates a general procedure for the preparation of 1-*d*-aldehydes from aliphatic and alicyclic[4] Grignard[5] and lithium[6] reagents. The use of the lithium reagent is normally preferred because of higher yields and greater isotopic purity if the 1-*d*-aldehyde is desired. For the synthesis of aromatic aldehydes, the use of the lithium reagent is specifically preferred since aromatic Grignard reagents react poorly with 1,1,3,3-tetramethylbutyl isonitrile. The aldehydes prepared by

this method are illustrated in Table I.

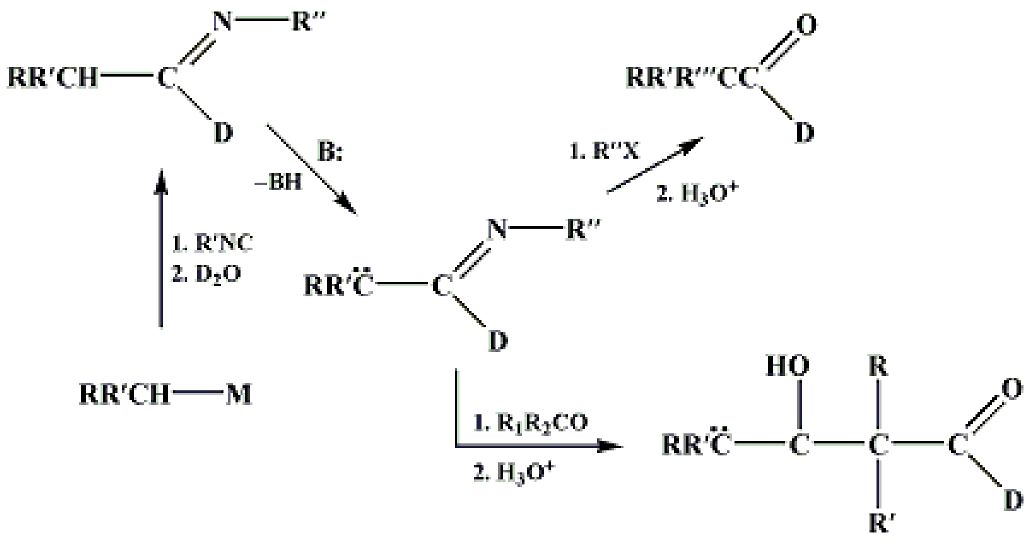


TABLE I

ALDEHYDES FROM1,1,3,3-TETRAMETHYLBUTYLISONITRILE ANDORGANOMETALLICREAGENTS

Organometallic Reagent	Aldehyde, % Yield
n-Butyllithium	93[a]
Phenyllithium	55[a]
2-Butylmagnesium bromide	67 (96[b,c])
tert-Butylmagnesium bromide	48[b]
n-Hexylmagnesium bromide	62[b]
2-Phenylethylmagnesium bromide	63 (80[b,c])
Cyclopentylmagnesium bromide	66 (89[b,c])

[a]Reference 6.

[b]Reference 5.

[c]Percent deuterium at C-1 as determined by NMR.

The intermediate aldimines can also be alkylated[7] or used as condensing agents[8] by removal of the α-hydrogen atom. The metalloaldimine is a useful intermediate for the preparation of α-keto acids, acyloins, β-hydroxy ketones, and silyl ketones.[5,6]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 232
- Org. Syn. Coll. Vol. 7, 27

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

1,1,3,3-tetramethylbutyl isonitrile (TMBI)

Benzyl and vinyllithium

ether, diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

hydrogen (1333-74-0)

thionyl chloride (7719-09-7)

magnesium turnings (7439-95-4)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

2-Bromobutane (78-76-2)

sodium sulfate (7757-82-6)

formic acid (64-18-6)

barium oxide

Oxalic acid (144-62-7)

nitrogen (7727-37-9)

Benzoic acid (65-85-0)

calcium sulfate (7778-18-9)

acetone (67-64-1)

toluene (108-88-3)

1,2-dibromoethane (106-93-4)

Pentane (109-66-0)

Triphenylmethane (519-73-3)

Phenyllithium (591-51-5)

lithium (7439-93-2)

n-butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

N,N-dimethylformamide (68-12-2)

hexane (110-54-3)

1,1,3,3-tetramethylbutylamine (107-45-9)

oxalic acid dihydrate (6153-56-6)

deuterium oxide (7789-20-0)

deuterium (7782-39-0)

1,1,3,3-tetramethylbutyl isonitrile (14542-93-9)

2-butyllithium (598-30-1)

tetramethylbutyl isonitrile

2-Butylmagnesium bromide

2-Phenylethylmagnesium bromide

Cyclopentylmagnesium bromide

2-METHYLBUTANAL-1-d, Butanal-1-d, 2-methyl- (25132-57-4)

N-(1,1,3,3-tetramethylbutyl)formamide (10151-02-7)

tert-Butylmagnesium bromide

n-Hexylmagnesium bromide (3761-92-0)

N-(2-Methylbutylidene-1-d)-1,1,3,3-tetramethylbutylamine (34668-70-7)

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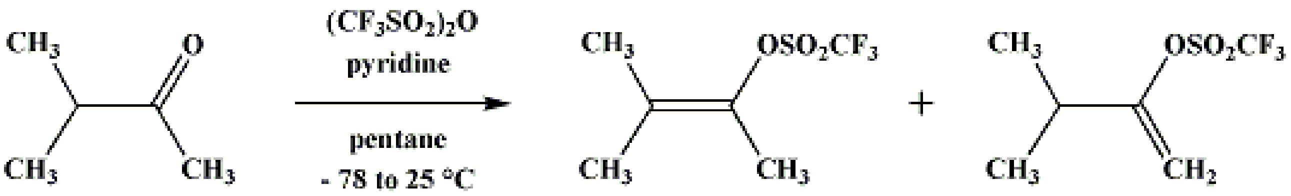
Organic Syntheses, CV 6, 757

PREPARATION OF VINYL TRIFLUOROMETHANESULFONATES: 3-METHYL-2-BUTEN-2-YL TRIFLATE

[Methanesulfonic acid, trifluoro-, 1,2-dimethyl-1-propenyl ester]

$$CF_3SO_3H \xrightarrow[-H_2O]{P_2O_5} (CF_3SO_2)_2O$$



1 2

Submitted by Peter J. Stang[1] and Thomas E. Dueber.
Checked by Wayne Jaeger and Herbert O. House.

1. Procedure

A. *Trifluoromethanesulfonic anhydride.* A dry, 100-ml., round-bottomed flask is charged with 36.3 g. (0.242 mole) of trifluoromethanesulfonic acid (Note 1) and 27.3 g. (0.192 mole) of phosphorus pentoxide (Note 2). The flask is stoppered and allowed to stand at room temperature for at least 3 hours. During this period the reaction mixture changes from a slurry to a solid mass. The flask is fitted with a short-path distilling head and heated first with a stream of hot air from a heat gun and then with the flame from a small burner. The flask is heated until no more trifluoromethanesulfonic anhydride distills, b.p. 82–115°, yielding 28.4–31.2 g. (83–91%) of the anhydride, a colorless liquid. Although this product is sufficiently pure for use in the next step, the remaining acid may be removed from the anhydride by the following procedure. A slurry of 3.2 g. of phosphorus pentoxide in 31.2 g. of the crude anhydride is stirred at room temperature in a stoppered flask for 18 hours. After the reaction flask has been fitted with a short-path distilling head, it is heated with an oil bath, yielding 0.7 g. of forerun, b.p. 74–81°, followed by 27.9 g. of the pure trifluoromethanesulfonic acid anhydride, b.p. 81–84° (Note 3).

B. 3-*Methyl*-2-*buten*-2-*yl triflate.* A solution of 2.58 g. (0.0300 mole) of 3-methyl-2-butanone (Note 4) and 2.78 g. (0.0352 mole) of anhydrous pyridine (Note 5) in 10 ml. of anhydrous *n*-pentane (Note 6) is placed in a dry, 50-ml. Erlenmeyer flask, and the flask is stoppered with a rubber septum. After the solution has been cooled in an acetone–dry ice cooling bath, 9.72 g. (5.80 ml., 0.0395 mole) of trifluoromethanesulfonic anhydride is added with a hypodermic syringe, dropwise and with swirling over 2–3 minutes. The resulting mixture, from which a white solid separates initially, is allowed to warm to room temperature over 22–24 hours. During this period the reaction mixture becomes red in color (Note 7), and a viscous, red semisolid separates. The supernatant pentane solution is decanted, and the residual viscous semisolid is washed with two 10-ml. portions of pentane. While the combined pentane solutions are stored over anhydrous potassium carbonate,

the remaining red semisolid is dissolved in 5 ml. of saturated aqueous sodium bicarbonate and extracted with three 5-ml. portions of pentane. The combined pentane solutions (including the solid potassium carbonate) are washed rapidly (Note 8) with 5 ml. of cold saturated aqueous sodium hydrogen carbonate and dried over anhydrous potassium carbonate. After the orange pentane solution has been concentrated to a volume of approximately 10 ml. with a rotary evaporator, it is transferred to a small distilling apparatus. The remaining pentane is removed by distillation at atmospheric pressure (Note 9). The residual liquid is fractionally distilled under reduced pressure, yielding 2.94–2.97 g. (45%) of a colorless, liquid fraction containing 3-methyl-2-buten-2-yl triflate and a lesser amount of 3-methyl-1-buten-2-yl triflate, b.p. 58–66° (22 mm.), n_D^{25} 1.3832–1.3898 (Note 10). Fractional distillation of this mixture with a 40-cm. spinning band column separated higher boiling fractions, b.p. 45–47° (12 mm.), that contained (Note 10) 98% of the 3-methyl-2-buten-2-yl triflate as a colorless liquid, n_D^{25} 1.3838 (Note 11).

2. Notes

1. Trifluoromethanesulfonic acid, purchased from Eastman Organic Chemicals, was used without purification. Trifluoromethanesulfonic acid in large quantities is available from 3M Company as Fluorocarbon Acid FC-24.
2. The phosphorus pentoxide should be protected from atmospheric moisture by weighing this reagent in a dry, stoppered flask. On a larger scale the yields are better and the reaction easier if the phosphorus pentoxide is premixed with an equal volume of Celite (filter aid).
3. This product exhibits one major GC peak (retention time 2.3 minutes, silicone fluid QF_1 on Chromosorb P) as well as one minor, unidentified, more rapidly eluted impurity. The product has strong IR absorption (CCl_4) at 1470, 1240, and 1130 cm.$^{-1}$.
4. 3-Methyl-2-butanone, purchased from Eastman Organic Chemicals, was used without purification. In general, commercially available ketones may be used without further purification.
5. A reagent grade of pyridine, purchased from Fisher Scientific Company, was dried over anhydrous potassium carbonate, distilled, and collected at 112–113°.
6. A commercial sample of *n*-pentane was distilled from calcium hydride to separate the pure solvent, b.p. 35–36°.
7. The intensity of color developed in the reaction mixture is an approximate indication of the extent of reaction. With reactive triflates a dark, almost tarry-looking mass develops in a few hours, while with the slower forming triflates several days at room temperature may be required for adequate color development. In no case was any product isolated when fairly dark color had not developed in the reaction mixture.
8. Only relatively stable vinyl triflates should be washed with water. More reactive triflates such as α-styryltriflate do not survive washing with water.
9. For the more volatile triflates, removal of the solvent should be accomplished by distillation to minimize loss of the volatile product. Also, care should be taken not to overheat the residual product since overheating can result in decomposition.
10. The fractions from this distillation may be analyzed by GC, employing a column packed with Carbowax 20 *M* suspended on Chromosorb P. The retention times for the various components (minutes) are: pentane (1.6), 3-methyl-2-butanone (4.2), 3-methyl-1-buten-2-yl triflate (6.7), and 3-methyl-2-buten-2-yl triflate (9.5).
11. The pure, more highly substituted olefin, n_D^{25} 1.3840, could also be separated by preparative GC, and the unchanged ketone could be separated from the two triflate isomers by chromatography on a silica gel column with pentane as the eluant. The pure product has IR absorption (CCl_4) at 1700 (enol C=C), 1210 and 1140 cm.$^{-1}$ (SO_2) with end absorption in the UV (heptane, ε 700 at 210 nm) and the following broad singlets in the ^{1}H NMR spectrum

(C_6H_6): δ 1.42 (3H, CH_3), 1.63 (3H, CH_3), and 1.82 (3H, CH_3). The mass spectrum of the product exhibits the following relatively abundant peaks, *m/e* (relative intensity): 218 (M^+, 58), 69 (75), 57 (92), 43 (100), 41 (44), and 39 (24).

3. Discussion

Vinyl trifluoromethanesulfonates (triflates) are a new class of compounds, unknown before 1969, that have been used most extensively in solvolytic studies to generate vinyl cations[2,3,4,5,6,7,8,9] and unsaturated carbenes.[10] Three methods have been used to prepare these sulfonic esters. The first, involving the preparation and decomposition of acyltriazines,[11] requires several steps to prepare the acyltriazines and is limited to the preparation of fully substituted vinyl triflates. The second method involves the electrophilic addition of trifluoromethanesulfonic acid to acetylenes[12,13,14] and, consequently, is not applicable to the preparation of trisubstituted vinyl triflates and certain cyclic vinyl triflates. However, this second procedure is relatively simple and often gives purer products in higher yield than the discussed reaction with ketones. Table I lists vinyl triflates prepared by this procedure.

TABLE I
VINYL TRIFLATES PREPARED BY THE REACTION OF ACETYLENES WITH TRIFLUOROMETHANESULFONIC ACID

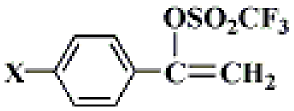
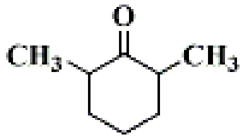
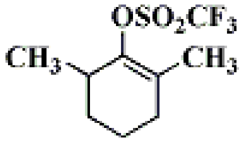
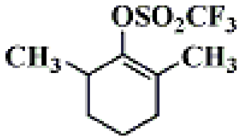
Substrate	Product	b.p.	Yield, %
CH_3C□CH	$CH_2{=}C(CH_3)OSO_2CF_3$	25–27° (12 mm.)	60–80
C_2H_5C□CC_2H_5	*cis* and *trans* $C_2H_5CH{=}C(C_2H_5)OSO_2CF_3$	68.5–69.5° (25 mm.)	40–60
$(CH_3)_3CC$□CH	$CH_2{=}C(OSO_2CF_3)C(CH_3)_3$	45–50° (15 mm.)	40–60
C_6H_5C□CH	$CH_2{=}C(C_6H_5)OSO_2CF_3$	44–45° (0.3 mm.)	20–60
$CH_3(CH_2)_3C$□CH	$CH_2{=}C(OSO_2CF_3)CH_2(CH_2)_2CH_3$	67–69° (15 mm.)	70
$(CH_3)_2CHC$□CH	$CH_2{=}C(OSO_2CF_3)CH(CH_3)_2$	37–40° (15 mm.)	62

The third procedure, illustrated by this preparation, involves the reaction of ketones with trifluoromethanesulfonic anhydride in a solvent such as pentane, dichloromethane, or carbon tetrachloride and in the presence of a base such as pyridine, lutidine, or anhydrous sodium carbonate[4,5,6,7,14,15] and, most recently, the sterically hindered, nonnucleophilic 2,6-di-*tert*-butyl-4-methylpyridine.[16] This procedure, which presumably involves either acid- or base-catalyzed enolization of the ketone followed by acylation of the enol with the acid anhydride, has also been used to prepare other vinyl sulfonate esters such as tosylates[8] or methanesulfonates.[9] Vinyl tosylates (but not vinyl triflates) may also be prepared from the ditosylate derivatives of 1,2-diols.[17]

Examples of the use of this procedure to prepare vinyl triflates from ketones are provided in Table II. Often mixtures of *cis* and *trans* isomers as well as the various double bond isomers of vinyl triflates are obtained by this procedure, and the amounts of these isomers produced may vary with the base and solvent used.[18] Also, small amounts of unchanged ketone may contaminate the initial crude product. Consequently, separation procedures such as preparative GC or efficient fractional distillation may be required to obtain a single vinyl triflate isomer.

TABLE II

VINYL TRIFLATES PREPARED FROM KETONES

Ketone	Reaction Conditions	Time, Days	Product	Yield, %
$XC_6H_4COCH_3$ (X = H, 4-Cl, 3-Cl, c-CF_3, 4-NO_2)	CH_2Cl_2, Na_2CO_3	3–21		15–45
	CH_2Cl_2, Na_2CO_3	14		28
	CCl_4, pyridine	5		54
$C_6H_5CH(CH_3)COCH_3$	CCl_4, pyridine	2–4	$C_6H_5C(CH_3)=C(CH_3)OSO_2CF_3$ (*cis*, 18%; *trans*, 51%) + $C_6H_5CH(CH_3)C(OSO_2CF_3)=CH_2$ (31%)	53
	CCl_4, P_2O_5	1	$C_6H_5C(CH_3)=C(CH_3)OSO_2CF_3$ (*trans*, 80%; *cis*, 20%)	32
	CH_2Cl_2, Na_2CO_3	10	$(CH_3)_2C=C(CH_3)OSO_2CF_3$ (**1**, 70%) + $(CH_3)_2CHC(OSO_2CF_3)=CH_2$ (**2**, 30%)	33
	CCl_4, pyridine	1	<.htmb>1 (90%) + **2** (10%)	58

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 97
- Org. Syn. Coll. Vol. 8, 126
- Org. Syn. Coll. Vol. 8, 306
- Org. Syn. Coll. Vol. 9, 553

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

P_2O_5

α-styryltriflate

potassium carbonate (584-08-7)

sodium bicarbonate, sodium hydrogen carbonate (144-55-8)

sodium carbonate, Na_2CO_3 (497-19-8)

carbon tetrachloride, CCl_4 (56-23-5)

pyridine (110-86-1)

Pentane, n-PENTANE (109-66-0)

dichloromethane, CH_2Cl_2 (75-09-2)

lutidine (583-61-9)

3-methyl-2-butanone (563-80-4)

calcium hydride (7789-78-8)

trifluoromethanesulfonic acid (1493-13-6)

Trifluoromethanesulfonic anhydride, trifluoromethanesulfonic acid anhydride (358-23-6)

3-Methyl-2-buten-2-yl triflate, Methanesulfonic acid, trifluoro-, 1,2-dimethyl-1-propenyl ester (28143-80-8)

3-methyl-1-buten-2-yl triflate

vinyl triflate

phosphorus pentoxide (1314-56-3)

2,6-Di-tert-butyl-4-methylpyridine (38222-83-2)

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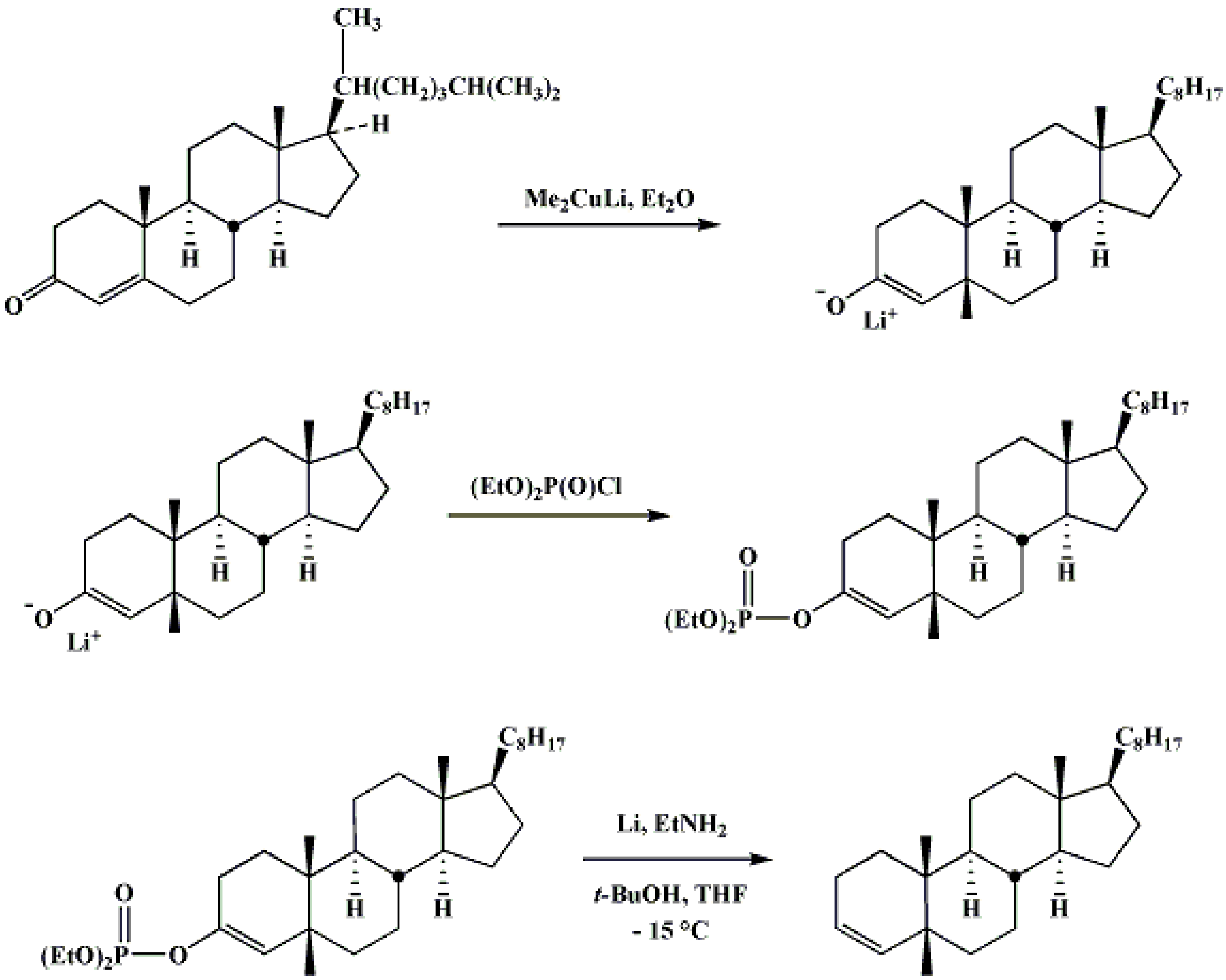
Organic Syntheses, CV 6, 762

PREPARATION AND REDUCTIVE CLEAVAGE OF ENOL PHOSPHATES: 5-METHYLCOPROST-3-ENE

[Cholest-3-ene, 5-methyl-, (5β)-]



Submitted by D. C. Muchmore[1]
Checked by David G. Melillo and Herbert O. House.

1. Procedure

A. *Diethyl 5-methylcoprost-3-en-3-yl phosphate.* A dry, 100-ml., three-necked flask equipped with a magnetic stirring bar, a pressure-equalizing dropping funnel, a nitrogen inlet tube, and a rubber septum is charged with 384 mg. (0.00201 mole) of copper(I) iodide (Note 1) and 20 ml. of anhydrous diethyl ether (Note 2). After the reaction vessel has been flushed with nitrogen, a static oxygen-free nitrogen atmosphere is maintained in the reaction vessel throughout the remainder of the reaction. The reaction mixture is cooled in an ice bath and an ether solution, containing 0.0040 mole of methyllithium (Note 3), is added with a hypodermic syringe, dropwise and with stirring. As the methyllithium is added, the initial yellow precipitate of polymeric methylcopper(I) redissolves, forming a colorless to pale-yellow solution of lithium dimethylcuprate (Note 4). To the resulting cold solution is added, dropwise and with stirring over 20 minutes, a solution of 576 mg. (0.00150 mole) of cholest-4-en-3-one (Note 5) in 20 ml. of ether (Note 2). During the addition of the enone, a yellow precipitate of polymeric methylcopper(I) separates from the reaction solution. After the addition is complete, the cooling bath is removed, and the reaction mixture is

stirred for 2 hours at room temperature. The dropping funnel is replaced with a second dry dropping funnel which contains a loose plug of glass wool above the stopcock. The reaction mixture is again cooled in an ice bath and a mixture of 4.0 ml. of triethylamine (Note 6) and 2.00 g. (0.0115 mole) of diethyl phosphorochloridate (Note 7) is added from the dropping funnel to the reaction mixture, rapidly and with stirring. After this addition, the cooling bath is removed, and stirring is continued for one hour. Saturated aqueous sodium hydrogen carbonate is added to hydrolyze any remaining organometallic reagents before the reaction mixture is transferred to a separatory funnel and washed successively with two 50-ml. portions of cold (0°) 1 *M* ammonium hydroxide and a 50-ml. portion of water. The aqueous washes are extracted in turn with a 30-ml. portion of ether. The combined ether solutions are dried over anhydrous sodium sulfate and concentrated with a rotary evaporator. A solution of the residual liquid in 3 ml. of ether is applied to a 2.5 cm. by 15 cm. chromatographic column packed with a slurry of 50 g. of silica gel (Note 8) in ether. The column is eluted with ether. After the first 70 ml. of eluent has been collected and discarded, the next 120 ml. of ether eluent is collected and concentrated with a rotary evaporator, yielding 420–480 mg. of crude phosphate ester (Note 9), a colorless liquid, sufficiently pure for use in the following procedure.

B. *5-Methylcoprost-3-ene.* A dry, 100-ml., three-necked flask equipped with a polyethylene-coated magnetic stirring bar, two gas-inlet tubes, and a pressure-equalizing dropping funnel is immersed in a 2-propanol–dry ice cooling bath maintained at −15° to −20°. The reaction vessel is flushed with either helium or argon, and a static atmosphere of one of these gases is maintained in the reaction vessel throughout the reaction. Ethylamine (Note 10) is distilled through a tower of sodium hydroxide pellets into the cold reaction flask until 50 ml. of the liquid amine has been collected. A 70-mg. (0.010 g.-atom) piece of lithium wire is cleaned by dipping it successively into methanol and pentane and added to the reaction flask. The resulting cold (−15°) mixture is stirred for 10 minutes to dissolve the lithium before a solution of the diethyl 5-methylcoprost-3-en-3-yl phosphate and 0.50 ml. (0.39 g., 0.0053 mole) of *tert*-butyl alcohol (Note 11) in 15 ml. of tetrahydrofuran (Note 2) is added, dropwise and with stirring over 15 minutes, to the cold, blue lithium–amine solution. The blue solution is stirred for an additional 15 minutes before 1 ml. of saturated ammonium chloride is added to consume excess lithium. The resulting colorless mixture is warmed, evaporating ethylamine, and the residue is diluted with 90 ml. of 10% aqueous sodium hydroxide and extracted with two 30-ml. portions of pentane. The combined organic solutions are washed with 50 ml. of aqueous sodium chloride, dried over anhydrous sodium sulfate, and concentrated with a rotary evaporator. The residual, viscous liquid is subjected to evaporative distillation, from a 25-ml. flask into a male 14–20 standard-taper glass joint as shown in f.htmigure 1. The air bath is heated to 150–180° while the pressure in the system is maintained at 0.05 mm. to 0.4 mm. Distillation of 5-methylcoprost-3-ene yields 260–295 mg. (45–51%) of colorless liquid, n_D^{25} 1.5115–1.5123 (Note 12).

Figure 1. Apparatus for evaporative distillation.

Figure 1. Apparatus for evaporative distillation.

2. Notes

1. A purified grade of copper(I) iodide, purchased from Fisher Scientific Company, was used without purification.
2. Reagent grade ether and tetrahydrofuran were distilled from lithium aluminum hydride immediately prior to use.
3. Ethereal solutions of methyllithium are available from either Foote Mineral Company or Alpha Inorganics, Inc. These solutions should be titrated immediately before use with 2-butanol and 2,2-bipyridyl as an indicator [*Org. Synth.*, **Coll. Vol. 5**, 211 (1973); *Org. Synth.*, **Coll. Vol. 6**, 121 (1988)].[2] In a typical run, 2.44 ml. of ethereal 1.64 *M* methyllithium was employed.
4. The appearance of a brown to black precipitate indicates either oxidative or thermal decomposition of the cuprate. If such decomposition has occurred, it is best to prepare the reagent again with greater care, avoiding molecular oxygen and/or excessive reaction temperatures.

5. A commercial sample of cholest-4-en-3-one from Eastman Organic Chemicals was used without further purification. The preparation of this ketone has also been described in *Org. Synth.*, **Coll. Vol. 4**, 192 (1963).
6. The glass wool filter collects any of the insoluble triethylammonium chloride which might be formed. A reagent grade of triethylamine (b.p. 88°) was distilled from calcium hydride prior to use. *N,N,N',N'*-Tetramethylethylenediamine has also been found to be a satisfactory Lewis base for less reactive enolates[3,4].
7. Commercial diethyl phosphorochloridate, b.p. 60–62° (1.5 mm.), purchased from Eastman Organic Chemicals, was distilled prior to use in this reaction.
8. A good grade of silica gel, such as that available from E. Merck and Company, Darmstadt, is appropriate for this chromatography.
9. The ^{1}H NMR spectrum ($CDCl_3$) of the crude product has absorption at δ 0.6–2.3 (m, *ca.* 52 H, aliphatic C*H*), 3.9–4.4 (m, 4H, 2CH_2O), and 5.1 (m, 1H, vinyl *H*).
10. Ethylamine (b.p. 17°) is available from Eastman Organic Chemicals.
11. A commercial grade of *tert*-butyl alcohol (b.p. 83°) should be distilled from calcium hydride before use.
12. The product exhibits end absorption in the UV (95% C_2H_5OH) with ε 330 at 210 nm and a series of ^{1}H NMR peaks ($CDCl_3$) at δ 0.67, 0.82, 0.85, 0.88, and 0.92 (18H, 6CH_3) with a multiplet at δ 1.0–2.2 and a partially resolved multiplet attributable to two vinyl protons. This latter absorption corresponds approximately to signals at δ 5.28 (d of t, *J* = 8 and 1 Hz., 1H) and 5.60 (d of t, *J* = 8 and 2.8 Hz., 1H). The mass spectrum of the product has the following abundant peaks: *m/e* (rel. int.), 384 (100, M^+), 369 (69), 355 (70), 229 (27), 122 (28), 109 (28), 107 (60), 95 (33), 93 (34), 81 (72), 55 (30), and 43 (31).
The submitters report that ozonolysis of the product at −10° in a mixture of ethyl acetate and acetic acid, followed by reaction with hydrogen peroxide, formed 3,4-*seco*-5-methylcoprostan-3,4-dioic acid as crystals from ethyl acetate, m.p. 168–172° with prior softening at 130°.

3. Discussion

The conjugate addition of lithium dimethylcuprate and other organocopper reagents to α,β-unsaturated ketones is a reaction which has had wide application and has been fairly well studied.[5 6 7] In order that the positional specificity which has been conferred upon the enolate anions generated by such additions might be maintained, these intermediates have been intercepted with acetic anhydride,[5] chlorotrimethylsilane,[8 9] diethyl phosphorochloridate,[4,10] tetramethyldiamidophosphorochloridate,[3,4] alkyl halides,[11 12] aldehydes,[13] ketones,[14] acid chlorides,[15] and Michael acceptors.[16]

The reductive fission of enol phosphates to olefins is a modification of the procedure used by Kenner and Williams[17] to deoxygenate phenols. The enol phosphates, which have been reduced by the action of lithium in ammonia or alkylamines and by the action of titanium metal,[18] have been prepared by treatment of α-bromoketones with triethyl phosphite,[4,19] by interception of enolates generated by the addition of lithium dimethylcuprate to α,β-unsaturated ketones,[4,10] by interception of enolates resulting from treatment of unsaturated ketones with lithium in ammonia,[10] and by phosphorylation of enolates of ketones.[20]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 346

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

acetic acid (64-19-7)

ammonia (7664-41-7)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

acetic anhydride (108-24-7)

ammonium chloride (12125-02-9)

sodium hydroxide (1310-73-2)

sodium hydrogen carbonate (144-55-8)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

oxygen (7782-44-7)

nitrogen (7727-37-9)

hydrogen peroxide (7722-84-1)

ammonium hydroxide (1336-21-6)

Pentane (109-66-0)

copper(I) iodide (7681-65-4)

lithium (7439-93-2)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

Methyllithium (917-54-4)

Cholest-4-en-3-one (601-57-0)

triethylamine (121-44-8)

tert-butyl alcohol (75-65-0)

Triethyl phosphite (122-52-1)

ethylamine (75-04-7)

calcium hydride (7789-78-8)

helium (7440-59-7)

argon (7440-37-1)

2-Butanol (78-92-2)

2,2-bipyridyl (366-18-7)

diethyl phosphorochloridate (814-49-3)

lithium dimethylcuprate

CHLOROTRIMETHYLSILANE (75-77-4)

methylcopper(I)

5-Methylcoprost-3-ene (23931-38-6)

Cholest-3-ene, 5-methyl-, (5β)-

Diethyl 5-methylcoprost-3-en-3-yl phosphate (23931-37-5)

triethylammonium chloride

tetramethyldiamidophosphorochloridate (1605-65-8)

titanium (7440-32-6)

N,N,N',N'-tetramethylethylenediamine (110-18-9)

3,4-seco-5-methylcoprostan-3,4-dioic acid

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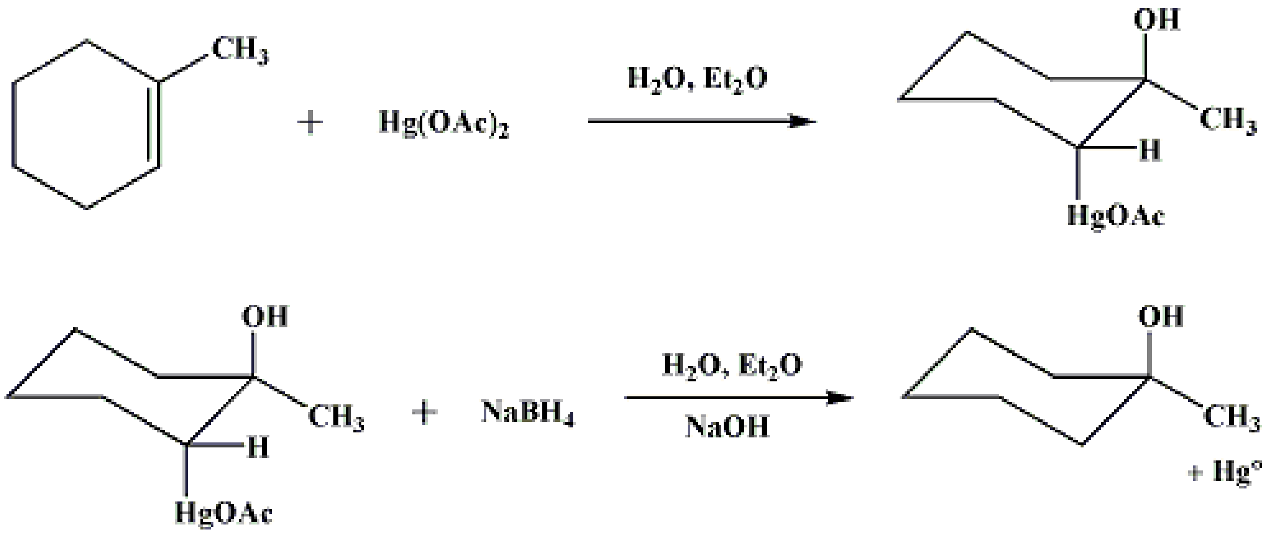
Organic Syntheses, CV 6, 766

OXYMERCURATION-REDUCTION: ALCOHOLS FROM OLEFINS: 1-METHYLCYCLOHEXANOL

[Cyclohexanol, 1-methyl-]



Submitted by J. M. Jerkunica and T. G. Traylor[1].
Checked by A. K. Willard and R. E. Ireland.

1. Procedure

A 3-l, three-necked flask fitted with a thermometer and a mechanical stirrer is charged with 95.7 g. (0.300 mole) of mercury(II) acetate (Note 1) and 300 ml. of water. After the acetate dissolves, 300 ml. of diethyl ether is added. While this suspension is stirred vigorously 28.8 g. (0.300 mole) of 1-methylcyclohexene (Note 2) and (Note 3) is added, and stirring is continued for 30 minutes at room temperature (Note 4). A solution of 150 ml. of 6 *N* sodium hydroxide is added followed by 300 ml. of 0.5 *M* sodium borohydride in 3 *N* sodium hydroxide. The borohydride solution is added at a rate such that the reaction mixture can be maintained at or below 25° with an ice bath.

The reaction mixture is stirred at room temperature for 2 hours, after which time the mercury is found as a shiny liquid. The supernatant liquid is separated from the mercury (Note 5), the ether layer is separated, and the aqueous solution is extracted with two 100-ml. portions of ether. The combined ether solutions are dried over magnesium sulfate and distilled, giving 24.1–25.8 g. (70.5–75.4%) of 1-methylcyclohexanol, b.p. 154.5–156°; n_D^{21} 1.4596 (Note 6).

2. Notes

1. The mercury(II) acetate was purchased from Mallinckrodt Chemical Works.
2. 1-Methylcyclohexene was purchased from K & K Laboratories and used without further purification.

3. Sometimes a yellow color [mercury(II) oxide] appears at this point and disappears as the reaction proceeds. If the yellow color does not disappear in about 10 minutes, 1.5 ml. of 70% perchloric acid per mole of mercury(II) acetate may be added to accelerate the reaction. Under these conditions even unreactive olefins are completely oxymercurated in about an hour.
4. The checkers found that extending the time of oxymercuration to 2 hours did not improve the yield.
5. The checkers found that the reaction mixture could be decanted from the mercury only if the mixture was allowed to stand for at least one hour after stirring was stopped. An alternate procedure, which proved quite satisfactory, was filtration of the entire reaction mixture through a Celite pad immediately after the stirring was stopped.
6. The distilled product slowly deposits mercury. In an effort to determine whether extent of this deposition is reduced by extending the time of reduction, the checkers found that stirring the crude alcohol with Celite for 15 hours, followed by filtration and distillation, did not diminish the amount of mercury deposited. However, in a typical run where the yield of distilled alcohol was 24.6 g. (72.0%), after standing for 24 hours, the distillate was decanted from the deposited mercury and redistilled to give 21.4 g. of 1-methylcyclohexanol, which did not deposit mercury upon standing for one week at room temperature. The yield of twice-distilled alcohol was 62.6%.

3. Discussion

This method of preparing alcohols is an adaptation of an oxymercuration procedure of Sand and Gensssler[2] and the reduction methods of Henbest and Nicholls.[3] Other methods for preparing 1-methylcyclohexanol are oxymercuration followed by reduction in tetrahydrofuran-water;[4 5 6] reaction of cyclohexanone with methylmagnesium halides;[7] and reduction of 1-methylcyclohexene epoxide or methylenecyclohexane epoxide with lithium aluminum hydride.[8]

Although the reaction proceeds faster in tetrahydrofuran–water[4,5,6] or in acetone–water, ether was used as solvent in this reaction for convenience of product separation and purification. However, the oxymercuration is acid catalyzed;[9] oxymercuration of unreactive olefins such as *cis*-cycloöctene can be accelerated by adding acid (Note 3). Rapid stirring also accelerates the reaction. An additional advantage of using ether is that less olefin is produced during the reduction using this solvent than when tetrahydrofuran is used. Elimination can be a serious side reaction during the reduction, amounting to 30% of total demercurated product when the oxymercurial from *cis*-cycloöctene is reduced in tetrahydrofuran–water. In ether–water, however, less than 10% olefin is produced.

As a general procedure, if the olefin is impure, the oxymercuration-reduction process may include an olefin purification step. Alternatively, this process may be used to purify the olefin for other purposes.[2,6] In such cases, acetone is substituted for ether, and after oxymercuration for the same length of time as suggested above, the solution is poured with stirring into two volumes of water containing one equivalent each of sodium hydrogen carbonate and sodium chloride. The mercury derivative is filtered, recrystallized from

ethanol–water, ether, dioxane, or ethyl acetate–heptane,[10] then either reduced, as described above (in 70–80% yield), producing pure alcohol, or deoxymercurated with cold 6 *N* hydrochloric acid,[2] ethereal lithium aluminum hydride[11] (added cautiously), or high concentrations of alkali halides,[6,11,12] producing the pure olefin.

Oxymercuration may also be used to prepare ethers, acetates, amines, or amides (Markownikoff adducts). Several excellent procedures for these syntheses have been published by Brown and co-workers.[5]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

ether, diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium hydrogen carbonate (144-55-8)

Cyclohexanone (108-94-1)

sodium chloride (7647-14-5)

mercury(II) acetate (1600-27-7)

mercury (7439-97-6)

mercury(II) oxide (21908-53-2)

acetone (67-64-1)

magnesium sulfate (7487-88-9)

dioxane (5703-46-8)

Tetrahydrofuran (109-99-9)

heptane (142-82-5)

lithium aluminum hydride (16853-85-3)

1-methylcyclohexene

perchloric acid (7601-90-3)

sodium borohydride (16940-66-2)

1-Methylcyclohexanol, Cyclohexanol, 1-methyl- (590-67-0)

methylenecyclohexane epoxide (185-70-6)

borohydride (16971-29-2)

1-methylcyclohexene epoxide

cis-cyclooctene (931-87-3)

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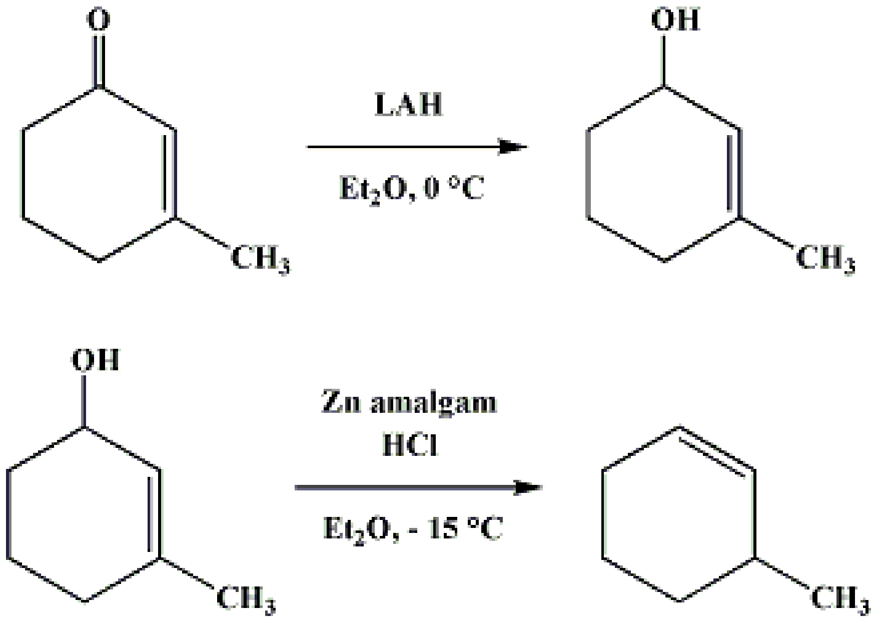
Organic Syntheses, *CV 6*, *769*

REDUCTIVE CLEAVAGE OF ALLYLIC ALCOHOLS, ETHERS, OR ACETATES TO OLEFINS: 3-METHYLCYCLOHEXENE

[Cyclohexene, 3-methyl-]



Submitted by I. Elphimoff-Felkin[1] and P. Sarda.
Checked by M. L. Lee and G. Büchi.

1. Procedure

A. *3-Methyl-2-cyclohexen-1-ol.* A solution of 33.6 g. (0.305 mole) of 3-methyl-2-cyclohexen-1-one (Note 1) in 600 ml. of anhydrous diethyl ether is placed in a 2-l., three-necked, round-bottomed flask fitted with a mechanical stirrer, a reflux condenser attached to a source of dry nitrogen, and a pressure-equalizing dropping funnel. The solution is stirred and cooled in an ice bath while 471 ml. (0.0825 mole) of a 0.175 *M* solution of lithium aluminum hydride in ether (Note 2) is added dropwise. When the addition is complete the reaction mixture is stirred at 0° for another 15 minutes. Cooling and gentle stirring are continued while moist ether is added through the dropping funnel until gas is no longer evolved. The resulting slurry is filtered, and the filtrate is washed with saturated aqueous sodium chloride and dried over magnesium sulfate. Removal of ether on a water bath and distillation of the residue under reduced pressure provide 33.7 g. (98%) of 3-methyl-2-cyclohexen-1-ol, b.p. 94–95° (31 mm.).

B. *Amalgamated zinc.* Zinc powder (206 g., 3.15 moles) is placed in a 1-l. beaker, covered with 250 ml. of 10% hydrochloric acid, and stirred for 2 minutes. The acid is then decanted and replaced by distilled water, the mixture is stirred, and the supernatant is decanted. Washing is continued in this way until the water is neutral to

litmus. A warm solution of 40 g. (0.15 mole) of mercury(II) chloride in 250 ml. of distilled water is then poured onto the zinc, and the mixture is stirred gently for 10 minutes. After filtration, the powder is washed with 250 ml. of distilled water, five 250-ml. portions of 95% ethanol, and five 250-ml. portions of anhydrous ether. Drying under vacuum gives 196 g. of zinc amalgam.

C. *3-Methylcyclohexene.* A 1-l., round-bottomed, three-necked flask equipped with a mechanical stirrer, a reflux condenser connected to a source of dry nitrogen, and a pressure-equalizing addition funnel is charged with 196 g. (3 moles) of dry amalgamated zinc powder (Note 3), 22.4 g. (0.200 mole) of 3-methyl-2-cyclohexen-1-ol, and 280 ml. of anhydrous ether. The flask is placed in an ethanol–water–dry ice bath maintained at −15° throughout the reaction. The reaction mixture is stirred gently for 5 minutes, then stirred vigorously while 153 ml. (0.40 mole) of 2.6 *M* hydrogen chloride in anhydrous ether (Note 4) is added dropwise over 1.5 hours. When the addition is complete, stirring is continued for an additional 15 minutes, after which the reaction medium is neutral to moist litmus (Note 5).

Decanting the reaction mixture separates residual zinc, which is washed thoroughly with two 200-ml. portions of ether. The ethereal solutions are combined, washed sequentially with two 50-ml. portions of water, 50 ml. of 10% aqueous sodium hydrogen carbonate, and two 50-ml. portions of saturated aqueous sodium chloride (Note 6), and dried over magnesium sulfate. After filtration, ether is removed by careful distillation through a Dufton column at atmospheric pressure (Note 7). When the residual solution is approximately 100 ml. in volume, it is transferred to a smaller apparatus and distilled slowly at atmospheric pressure. After a forerun of ether, 13.2–14.4 g. (68–75%) of 3-methylcyclohexene distils at 103–104° (Note 8).

2. Notes

1. The unsaturated ketone[2] can be purchased from Ega Chemie K.G. or from Frinton Laboratories, P.O. Box 301, South Vineland, New Jersey.
2. The concentration of this solution was established by decomposing the lithium aluminum hydride with excess iodine according to the following equation: $LiAlH_4 + 2I_2 \rightarrow 2H_2 + LiI + AlI_3$
The amount of unreacted iodine was determined by titration with sodium thiosulfate; the amount of iodine initially present was determined by a separate blank titration.[3]
Working solutions were prepared by dissolving 40 g. of iodine in 1 l. of anhydrous benzene and by dissolving 248 g. of sodium thiosulfate pentahydrate in 1 l. of water (*ca.* 1 *M*); an accurately prepared 0.100 *N* aqueous sodium thiosulfate solution is also required. For titration, a 25.0-ml. portion of the iodine solution was stirred vigorously in a 500-ml. Erlenmeyer flask, and 1.00 ml. of the lithium aluminum hydride solution was added rapidly, followed by 20

ml. of water, 2 drops of acetic acid, and 5.00 ml. of the 1 *M* sodium thiosulfate solution. With continued stirring, the solution was titrated to the colorless end point by adding V_a ml. of the 0.100 *N* sodium thiosulfate solution.
Separately, another 25.0-ml. portion of the iodine solution was stirred in a 500-ml. Erlenmeyer flask and treated with 5.00 ml. of the 1 *M* aqueous sodium thiosulfate, 20 ml. of water, and 2 drops of acetic acid. Titration was continued to the end point by adding, with continuous stirring, V_b ml. of 0.100 *N* aqueous sodium thiosulfate. The molarity of the lithium aluminum hydride solution was then calculated from the following equation: $M = 0.025(V_b - V_a)$

3. A large excess of zinc is used to make the reaction faster and to reduce the formation of polymeric by-products.

4. The solution of dry hydrogen chloride in ether was prepared as follows. Commercial hydrogen chloride gas was dried by passing it through an empty safety trap, a wash bottle of concentrated sulfuric acid, a calcium chloride tube, and another empty safety trap. Anhydrous ether was cooled in an ice bath, and the hydrogen chloride was bubbled through rapidly. Gas uptake was followed by weighing the ethereal solution occasionally, and the concentration of the final solution was determined by alcalimetric titration. The optimum concentration of hydrogen chloride is 2.5–3 *M*. Use of excess acid led to overreduction in the case of 2-phenyl-2-cyclohexen-1-ol, the desired 1-phenylcyclohexene being contaminated by phenylcyclohexane.

5. If the total reaction time is less than approximately 1.75 hours, starting material remains. Therefore, if the ethereal hydrogen chloride is added in less than 1.5 hours, the subsequent stirring must be lengthened accordingly.

6. If zinc chloride is not removed by washing, it causes polymerization of the olefin during distillation.

7. Slow distillation of the ether is essential in order to prevent the low-boiling olefin from codistilling with the solvent. For higher-boiling olefins the ether can be removed on a water bath prior to distillation of the olefin under reduced pressure.

8. GC analysis, using an HMDS-treated Chromosorb W column with 7% Craig polyester as the stationary phase, indicated the product to have a purity of 97%. The 3% impurity is most probably the isomeric 1-methylcyclohexene.

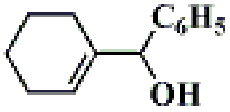
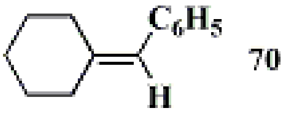
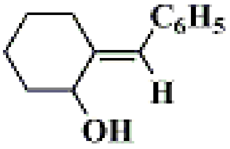
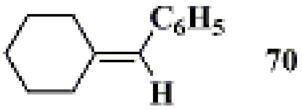
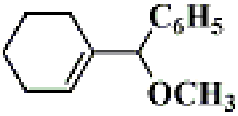
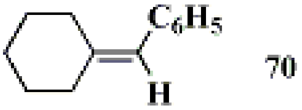
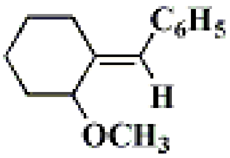
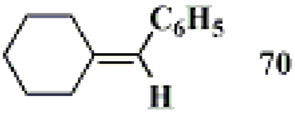
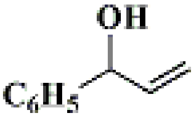
3. Discussion

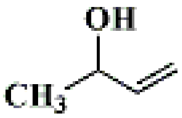
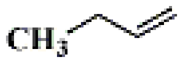
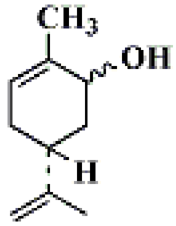
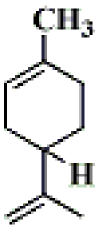
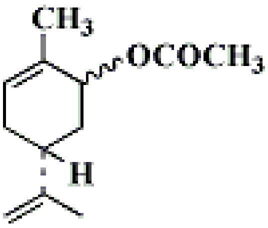
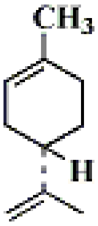
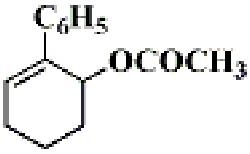
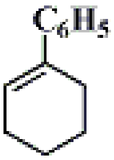
The model procedure described above is applicable to allylic alcohols, ethers, and acetates. The submitters' results for the conversion of several such compounds to the corresponding olefins, performed on a smaller scale, are summarized in Table I. Reductive cleavage of allylic alcohols, ethers, and acetates has often been reported in the literature. Typical reagents used are sodium in liquid ammonia,[4,5] zinc and acetic acid,[6] chloroaluminum hydride,[7] and propylmagnesium bromide in the presence of dichlorobis(triphenylphosphine)nickel.[8] In all of these procedures, however, when two or more isomeric olefins can be formed, the thermodynamically more stable olefin

generally predominates. The advantage of the present procedure[9] is that it leads, depending on the structure of the starting material, either exclusively or predominantly to the less stable isomer (see Table I). These results have been interpreted[9] by assuming that reduction takes place through an intermediate that behaves like an allylic metal halide. Studies of allylic metal halides such as crotyl zinc halides[10] and the crotyl Grignard reagent[11] suggest that such an intermediate would be protonated predominantly at the more substituted end of the allylic system. The method has been applied recently to the synthesis of some natural products.[12]

TABLE I

OLEFINS FROM ALLYLIC ALCOHOLS, ETHERS, AND ACETATES[9]

Starting Material	Total yield of Olefins (%)[a]	Major Olefin (relative %)[b]	
	85–90		70
	85–90		70
	85–90		70
	85–90		70
	70		80
	80		80

	not determined		80
 (*cis* + *trans*)[c]	70		(racemic)(racemic)
	70		(racemic)(racemic)
	80		

*a*Distilled product.

*b*Determined by GC.

*c*From lithium aluminum hydride reduction of (−) carvone.

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

amalgamated zinc

amalgamated zinc powder

ethanol (64-17-5)

hydrogen chloride, hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ammonia (7664-41-7)

Benzene (71-43-2)

ether, diethyl ether (60-29-7)

sodium hydrogen carbonate (144-55-8)

sodium chloride (7647-14-5)

sodium thiosulfate (7772-98-7)

nitrogen (7727-37-9)

iodine (7553-56-2)

zinc, zinc powder (7440-66-6)

sodium (13966-32-0)

zinc chloride (7646-85-7)

mercury(II) chloride (7487-94-7)

magnesium sulfate (7487-88-9)

phenylcyclohexane (827-52-1)

1-phenylcyclohexene (771-98-2)

lithium aluminum hydride (16853-85-3)

1-methylcyclohexene

3-methyl-2-cyclohexen-1-one

3-Methylcyclohexene, Cyclohexene, 3-methyl- (591-48-0)

sodium thiosulfate pentahydrate

3-Methyl-2-cyclohexen-1-ol (21378-21-2)

2-phenyl-2-cyclohexen-1-ol

chloroaluminum hydride

propylmagnesium bromide

dichlorobis(triphenylphosphine)nickel (14264-16-5)

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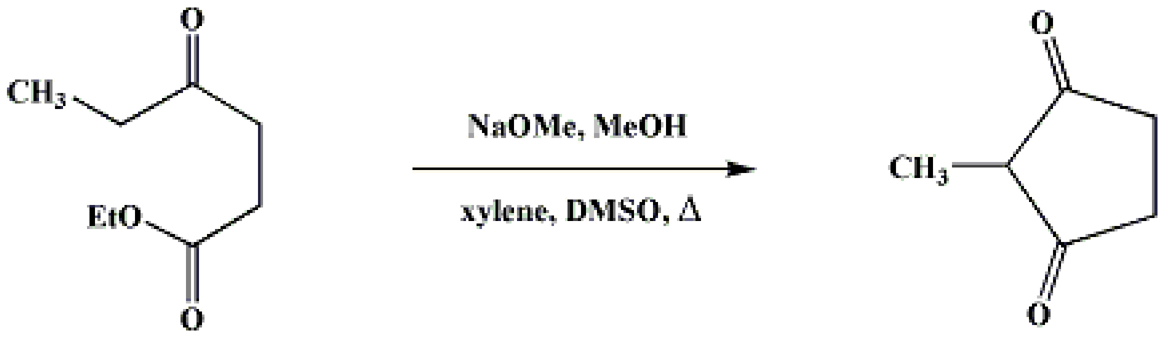
Organic Syntheses, CV 6, 774

γ-KETOESTERS TO PREPARE CYCLIC DIKETONES: 2-METHYL-1,3-CYCLOPENTANEDIONE

[1,3-Cyclopentanedione, 2-methyl-]



Submitted by U. Hengartner[1] and Vera Chu.
Checked by William B. Farnham and William A. Sheppard.

1. Procedure

A 3-l., three-necked, round-bottomed flask fitted with a dropping funnel (Note 1), a mechanical stirrer, and a distillation head with a thermometer and efficient Liebig condenser is charged with 1.4 l. of xylene (Note 2). The xylene is stirred and heated to boiling with a heating mantle, while 179 g. of a solution containing 43 g. (0.80 mole) of sodium methoxide in methyl alcohol (Note 3) is added over 20 minutes. During this period 450 ml. of solvent is distilled.

After addition is complete, 300 ml. of xylene is added and the distillation continued until the vapor temperature rises again to 138°. During that time an additional 250 ml. of distillate is collected, leaving a white suspension to which 18 ml. of dimethylsulfoxide is added. A solution of 100 g. (0.633 mole) of ethyl 4-oxohexanoate (Note 4) in 200 ml. of xylene is then added (Note 1) to the vigorously stirred sodium methoxide suspension over 25 minutes, while 900 ml. of distillate is collected continuously, maintaining the vapor temperature at 134–137°. The orange-colored mixture is stirred and heated for an additional 5 minutes, then cooled to room temperature. Addition of 165 ml. of water with vigorous stirring over a 5-minute period (Note 5) gives two clear phases, which are cooled in an ice bath and acidified by adding 82 ml. (0.98 mole) of 12 *N* hydrochloric acid with vigorous stirring. After the mixture is stirred at 0° for another 1.5 hours, the crystalline product is collected by suction filtration and carefully washed successively with 100-ml. and 50-ml. portions of ice-cooled diethyl ether (Note 6).

The crude product is dissolved in 1 l. of boiling water, and the solution is filtered

quickly through a preheated fritted-disk funnel (Note 7). The filtrate is concentrated on a hot plate at atmospheric pressure to a volume of 550–600 ml. and allowed to stand at 0° overnight. The crystals are collected by filtration and dried at 85°, yielding 50.0–50.6 g. (70–71%) of 2-methyl-1,3-cyclopentanedione, m.p.210–211° (Note 8).

2. Notes

1. A 500-ml. dropping funnel, provided with a calcium sulfate drying tube, was used.
2. Reagent grade xylene, b.p. 138–141°, from Fisher Scientific Company, was used.
3. The sodium methoxide solution was prepared as follows: 203 g. of methyl alcohol, available from Fisher Scientific Company, is placed in a 500-ml., two-necked flask under an inert atmosphere. The flask is equipped with a magnetic stirring bar and a reflux condenser provided with a calcium sulfate drying tube. Freshly cut, clean sodium (23 g., 1.0 mole) is added in small pieces at such a rate that reflux is maintained. The mixture is stirred until all the sodium has reacted.
4. Ethyl 4-oxohexanoate was prepared by the method in *Org. Synth.*, **Coll. Vol. 6**, 615 (1988).
5. The temperature of the mixture is kept at 25–35°.
6. The ether washings contain 11 g. of a brown viscous oil containing various condensation products.
7. A small amount of insoluble, tarry material is removed by this filtration. Preheating the funnel is necessary, since the product crystallizes easily on cooling. Dark-colored impurities in crude 2-methyl-1,3-cyclopentanedione can be removed by recrystallization from methanol.
8. 2-Methyl-1,3-cyclopentanedione, [*Org. Synth.*, **Coll. Vol. 5**, 747 (1973)] m.p. 210–212°, exists in the enol form in solution. It has the following spectral properties: UV (0.1 *N* HCl) nm. max. (ε): 252 (19,000); ^{1}H NMR (dimethyl sulfoxide-d_6) δ (multiplicity, number of protons, assignment): 1.51 (s, 3H, CH_3), 2.39 (s, 4H, $2CH_2$).

3. Discussion

2-Methyl-1,3-cyclopentanedione is a key intermediate in the total synthesis of steroids.[2] A number of methods have been described for its preparation, among them the condensation of succinic acid with propionyl chloride,[3] and that of succinic anhydride with 2-buten-2-ol acetate,[4] both in the presence of aluminum chloride. It has also been obtained from 3-methylcyclopentane-1,2,4-trione by catalytic hydrogenation[5] and Wolff–Kishner reduction.[6] The base-promoted cyclization of ethyl 4-oxohexanoate and diethyl propionylsuccinate with tertiary alkoxides was first reported by Bucourt.[7] The present cyclization process provides an experimentally

simple route to 2-methyl-1,3-cyclopentanedione. Using the same procedure, ethyl 4-oxohexanoate has been cyclized to give 2-ethyl-1,3-cyclopentanedione in 46% yield.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 615
- Org. Syn. Coll. Vol. 7, 363
- Org. Syn. Coll. Vol. 8, 578
- Org. Syn. Coll. Vol. 9, 570

References and Notes

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2. For leading references, see R. T. Blickenstaff, A. C. Ghosh, and G. C. Wolf, "Total Synthesis of Steroids," Academic Press, New York, 1974.
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

methyl alcohol, methanol (67-56-1)

ether, diethyl ether (60-29-7)

Succinic acid (110-15-6)

sodium methoxide (124-41-4)

aluminum chloride (3495-54-3)

sodium (13966-32-0)

xylene (106-42-3)

Succinic anhydride (108-30-5)

propionyl chloride (79-03-8)

dimethylsulfoxide (67-68-5)

1,3-Cyclopentanedione, 2-methyl-, 2-Methyl-1,3-cyclopentanedione (765-69-5)

3-methylcyclopentane-1,2,4-trione (4505-54-8)

Ethyl 4-oxohexanoate (3249-33-0)

2-buten-2-ol acetate

Diethyl propionylsuccinate (4117-76-4)

2-ethyl-1,3-cyclopentanedione (823-36-9)

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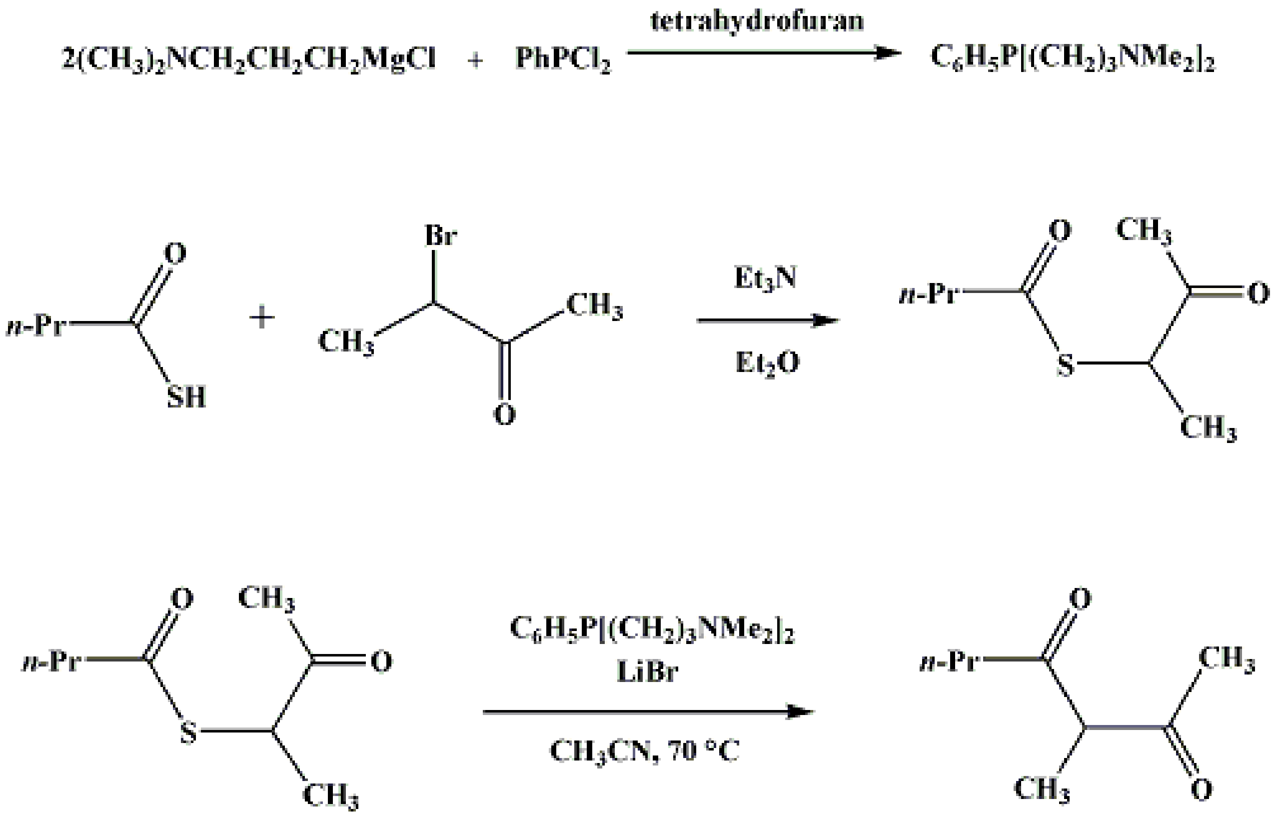
Organic Syntheses, *CV 6, 776*

SULFIDE CONTRACTION *via* ALKYLATIVE COUPLING: 3-METHYL-2,4-HEPTANEDIONE

[2,4-Heptanedione, 3-methyl-]



Submitted by P. Loeliger[1] and E. Flückiger[2].
Checked by K. Matsuo and G. Büchi.

1. Procedure

Caution! To avoid exposure to toxic dichlorophenylphosphine vapors, the Grignard reaction should be conducted in a hood.

Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A. *Bis(3-dimethylaminopropyl)phenylphosphine*. A 3-l. separatory funnel is charged with 395 g. (2.50 moles) of 3-chloro-*N*,*N*-dimethyl-1-propylamine hydrochloride (Note 1), and a cold solution of 179 g. of potassium hydroxide in 540 ml. of water is added. The mixture is extracted three times with 300-ml portions of 5:1 diethyl ether-dichloromethane. The organic extracts are washed with 300 ml. of aqueous 2 *N* potassium hydroxide, combined, and dried over anhydrous sodium sulfate. The solvent is removed by distillation through a 25-cm. Vigreux column at atmospheric pressure, and the residual liquid is distilled under

reduced pressure through a 13-cm. Vigreux column, giving 263–276 g. (87–91%) of 3-chloro-*N*,*N*-dimethyl-1-propylamine as a colorless liquid, b.p. 72–73° (100 mm.) (Note 2) and (Note 3), which is used immediately in the Grignard reaction (Note 4).

A 3-l., four-necked, round-bottomed flask equipped with a sealed mechanical stirrer, a pressure-equalizing dropping funnel, a thermometer, and a condenser fitted with a nitrogen-inlet tube is charged with 48.6 g. (2.00 g.-atoms) of magnesium turnings (Note 5). The flask is flushed with dry nitrogen and thoroughly dried with a heat gun, and 300 ml. of anhydrous tetrahydrofuran (Note 6) is added. The Grignard reaction is initiated by adding about 10% of a solution of 243.0 g. (1.98 moles) of 3-chloro-*N*,*N*-dimethyl-1-propylamine in 300 ml. of anhydrous tetrahydrofuran (Note 6), and 4 ml. of ethyl bromide while gently heating the flask with the drier (Note 7). The remainder of the 3-chloro-*N*,*N*-dimethyl-1-propylamine solution is added over a period of approximately 1 hour so as to maintain gentle reflux. The reaction mixture is heated at reflux for 3 hours, after which time most of the magnesium has reacted. The dark gray solution is cooled to 0° before a solution of 107.3 g. (81.29 ml., 0.5994 mole) of dichlorophenylphosphine (Note 8) in 200 ml. of anhydrous tetrahydrofuran (Note 6) is added dropwise, with efficient stirring, over a 1 hour period so that the temperature does not exceed 5° (Note 9). A greenish precipitate is formed locally where the phosphine is added. After the addition is complete, the reaction mixture is stirred and heated at reflux for 2 hours, during which time a heavy, greenish precipitate is formed. After cooling to room temperature, 600 ml. of ether (Note 10) is added, and the reaction mixture is left standing overnight, during which time the precipitate separates to the bottom of the flask. The solution is decanted into a 3-l. separatory funnel containing 300 ml. of 40% aqueous potassium hydroxide and 1 kg. of ice. The remainder of the reaction product is suction filtered with the aid of 1200 ml. of 5:1 ether–dichloromethane through a 3-cm. layer of Celite® (Note 11). The filtrate is added to the separatory funnel, and the organic layer is separated and washed twice with 600-ml. portions of saturated aqueous sodium chloride. The aqueous layer is extracted four times with 700-ml. portions of 5:1 ether–dichloromethane. The combined organic extracts are dried over anhydrous sodium sulfate, and the solvent is removed with a rotary evaporator. The crude yellow oil is distilled at high vacuum through a 14-cm. Vigreux column, yielding 109–116 g. (65–69%, based on phenylphosphonous dichloride) of bis(3-dimethylaminopropyl)phenylphosphine as a colorless liquid, b.p. 100–108° (0.005 mm.) (Note 12). Redistillation furnishes 94–97 g. (56–58%) of product, b.p. 102–105° (0.005 mm.) (Note 13), n_D^{24} 1.5265.

B. *S-(2-Oxobut-3-yl) Butanethioate*. A 750-ml., four-necked, round-bottomed flask equipped with a sealed mechanical stirrer, a pressure-equalizing dropping funnel, a thermometer, and a condenser fitted with a nitrogen-inlet tube is charged with 10.4 g. (0.100 mole) of thiobutyric acid (Note 14) in 300 ml. of anhydrous ether (Note 10). With stirring, 10.1 g. (0.100 mole) of triethylamine (Note 15) is added in one portion. Over a 15-minute period (Note 16), 15.1 g. (0.100 mole) of 3-bromo-2-butanone (Note 17) is added dropwise from the dropping funnel. The solution is heated at reflux with stirring for 1.5 hours and filtered through Celite®; the precipitate is washed with 60 ml. of ether. The ether solution is concentrated on a rotary evaporator. The residual orange-yellow oil is dissolved in 20 ml. of 5:1 benzene–ether and filtered through 70 g. of silica gel (Note 18), using 500 ml. of this solvent mixture as eluent. The solvent is removed on a rotary evaporator, yielding 17.0–17.4 g. (98–100%) of the thiol ester as a pale yellow oil which can be used without further

purification in the next step. (Note 19) and (Note 20).

C. 3-*Methyl*-2,4-*heptanedione*. A dry, 500-ml., three-necked, round-bottomed flask equipped with a magnetic stirring bar, a pressure-equalizing dropping funnel, a thermometer, and a condenser fitted with a nitrogen-inlet tube is charged with 17.8 g. (0.204 mole) of anhydrous lithium bromide (Note 21). Under a nitrogen atmosphere, 34.8 g. (0.218 mole) of *S*-(2-oxobut-3-yl)butanethioate dissolved in 120 ml. of anhydrous acetonitrile (Note 22) is added to the flask. With stirring, the mixture is heated with a drier until a homogeneous solution is obtained. From the dropping funnel, 67 g. (69 ml., 0.24 mole) of redistilled bis(3-dimethylaminopropyl)phenylphosphine is added in one portion to the warm (*ca.* 60°) solution. The temperature rises to about 70°, and after 1–2 minutes a thick, white precipitate appears. The reaction mixture is stirred at 70° for 15 hours (Note 23). After cooling to room temperature, the reaction mixture is transferred with 600 ml. of 5:1 ether–dichloromethane into a separatory funnel containing 900 ml. of cold 1 *N* hydrochloric acid. The organic layer is separated and washed three times with 500-ml. portions of saturated aqueous sodium chloride. The aqueous phase is washed twice with 600-ml. portions of 5:1 ether–dichloromethane. The combined organic layer is dried over anhydrous sodium sulfate, and the solvent removed on a rotary evaporator, the temperature of the bath not exceeding 30°. The crude yellow oil is distilled through a 10-cm. Vigreux column under reduced pressure, yielding 23.5–24.7 g. (83–87%) of 3-methyl-2,4-heptanedione as a colorless liquid, b.p. 74–76° (9 mm.), n_D^{23} 1.4455 (Note 24).

2. Notes

1. 3-Chloro-*N*,*N*-dimethyl-1-propylamine hydrochloride was purchased from Fluka AG CH-9470 Buchs or Aldrich Chemical Company, Inc.
2. The fractions may be analyzed by GC for absence of solvent; a 300 cm. by 0.3 cm. glass column packed with XE-60 (1.5% *w/w*) coated on Chromosorb G AW DCMS (80/100 mesh) was employed.
3. The spectral properties of the product are as follows; IR (neat) cm.$^{-1}$: 1470, 1465, 1265, 1040; ^{1}H NMR ($CDCl_3$), δ (multiplicity, coupling constant *J* in Hz., number of protons): 1.8–2.6 (m, 4H), 2.2 (s, 6H), 3.6 (t, *J* = 6, 2H).
4. It is advisable to distill the solvent one day, store the residue overnight under nitrogen at 0°, and distill the product the next morning, allowing ample time for the following Grignard reaction. On standing at room temperature a white solid precipitates.
5. Magnesium turnings were purchased from E. Merck & Company, Inc., Darmstadt, Germany or J. T. Baker Chemical Company.
6. Tetrahydrofuran (purchased from Fluka AG or J. T. Baker Chemical Company) was distilled from sodium hydride prior to use. For warnings regarding the purification of tetrahydrofuran, see *Org. Synth.*, **Coll. Vol. 5**, 976 (1973).
7. It is advisable to have available an ice bath for cooling, should the reaction become violent.
8. Dichlorophenylphosphine was purchased from Fluka AG or Aldrich Chemical Company, Inc.
9. The reaction is very exothermic and cooling with an ice–sodium chloride bath is necessary.
10. Anhydrous ether was purchased from Fluka AG or J. T. Baker Chemical Company.

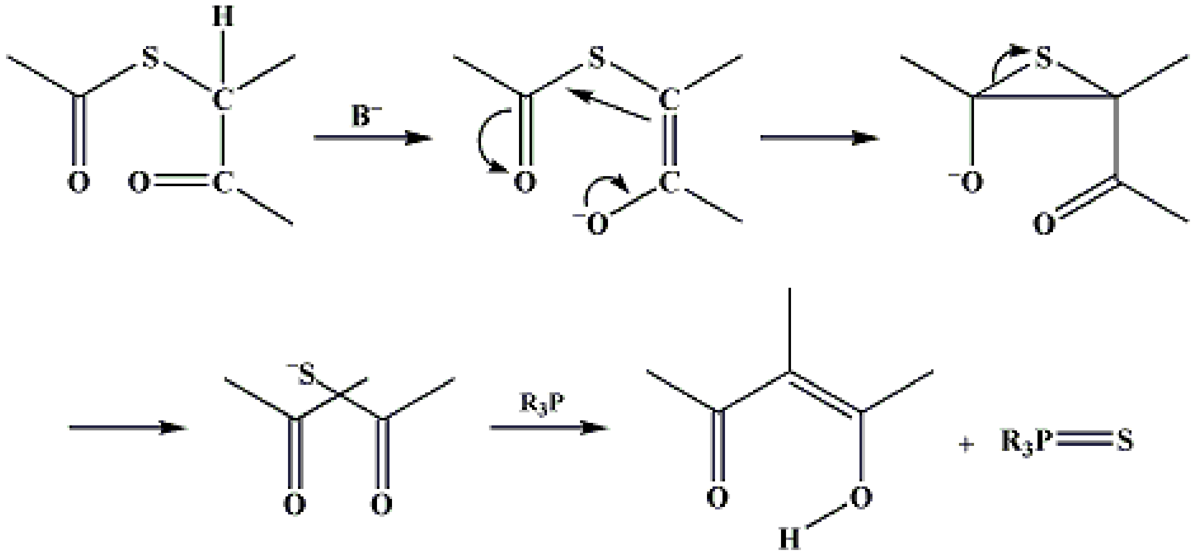
11. During this operation, the reaction vessel is washed with 5:1 ether–dichloromethane several times.
12. The colorless forerun weighs 12–20 g.; the dark brown residue weighs 13–22 g.
13. The reported b.p. is 102–105° (0.005 mm.); a full spectroscopic characterization is given in the original paper.[3]
14. The thiobutyric acid was prepared[4] as follows: A rapid stream of hydrogen sulfide is passed, with vigorous stirring at –30°, through 200 ml. of anhydrous pyridine, contained in a four-necked, round-bottomed flask equipped with a sealed mechanical stirrer, a gas-inlet tube, a pressure-equalizing dropping funnel, and a thermometer. Over approximately 1 hour, 50 g. of 1-butyryl chloride is added dropwise to this solution. Approximately 400 ml. of 5 *N* sulfuric acid is added slowly until the pH is 5. The organic acid, which separates as a yellow oil, is taken up in ether and dried over anhydrous sodium sulfate. After removal of the ether on a rotary evaporator, the product is distilled through a 14-cm. Vigreux column under a nitrogen atmosphere, yielding 23.1–32.1 g. (43–65%, not optimized by the submitters) of thiobutyric acid as a colorless liquid, b.p. 119–121°.
15. Triethylamine was purchased from Fluka AG or J. T. Baker Chemical Company.
16. A colorless precipitate of triethylamine hydrobromide is formed immediately. The temperature rises to about 35°.
17. 3-Bromo-2-butanone was purchased from Fisher Scientific Company. The submitters prepared it according to the literature[5] and checked its purity (>95%) by GC (Note 2).
18. Silica gel (70–230 mesh ASTM) purchased from E. Merck & Company, Inc., Darmstadt, Germany was used in a 2.5-cm. diameter column.
19. GC analysis (Note 2) indicated <2% impurities. IR (neat) cm.$^{-1}$: 1720, 1695.
20. The submitters obtained a similar yield on ten times the scale.
21. The absence of water in the lithium bromide is of great importance. Traces of water lower the yield of product by 10–20%. Lithium bromide dihydride (purchased from E. Merck & Company, Inc., Darmstadt or City Chemical Corporation) was dissolved three times in anhydrous 1:1 acetonitrile–benzene, and the solvents were removed each time with a rotary evaporator. The lithium bromide was dried under high vacuum at 100° for 1 hour, ground to a fine powder with a mortar and pestle while still warm, and again dried at 100°, as above, for 3 hours.
22. Acetonitrile was purchased from Fluka AG or J. T. Baker Chemical Company and distilled from potassium carbonate immediately prior to use.
23. The reaction is followed best by GC analysis (Note 2). Traces of water seem to slow down the rate of the reaction.
24. By GC analysis (Note 2) the product is >98% pure. In the literature,[3] a full spectroscopic characterization is given. IR (neat) cm.$^{-1}$: 1725, 1700, 1600, 1360.

3. Discussion

This procedure illustrates a broadly applicable method which is essentially that found in the literature[3] for the synthesis of enolizable β-dicarbonyl compounds.[3] Although there are various methods for the preparation of β-dicarbonyl systems,[6] sulfide contraction widens the

spectrum of available methods. The procedure can also be utilized in the sycnthesis of aza and diaza analogs of β-dicarbonyl systems. Eschenmoser[3] has utilized the method to produce vinylogous amides and amidines in connection with the total synthesis of corrins and vitamin B_{12}.[7,8]

S-Alkylation of a thiocarboxylic acid with an α-halogenated carbonyl compound gives a thiol ester in which the two carbons to be connected are linked *via* a sulfur bridge (see the scheme below). Enolization and formation of the episulfide creates the desired carbon–carbon bond. Removal of atomic sulfur by a thiophile, either a phosphine or a phosphite, liberates the β-dicarbonyl compound. The addition of base is necessary in most cases; however, in the vinylogous amidine systems[7,8] electrophilic catalysis was employed. Normally a teritary alkoxide is utilized in the contraction. The addition of anhydrous lithium bromide or lithium perchlorate allows the reaction to proceed with the use of a tertiary amine as the base. Presumably, the lithium salts complex with the carbonyl groups, enhancing the enolization and/or contraction step.



This procedure also incorporates the use of bis(3-dimethylaminopropyl)phenylphosphine as a combined amine–phosphine reagent. The merit of using this basic phosphine as opposed to a tertiary amine and a phosphine lies in the ease of workup. Excess phosphine and phosphine sulfide can be removed by extraction with dilute acid.

Since the new carbon–carbon bond is formed intramolecularly in the sulfide extrusion method, its main potential lies in cases where intermolecular condensations fail.[9,10]

References and Notes

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Eschenmoser, *Q. Rev. Chem. Soc.*, **24**, 366 (1970); A. Eschenmoser, *Spec. Lect.*, 23rd *Int. Congr.* IUPPC, Vol. II, Butterworth and Company, London, 1971, pp. 69–106.

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9. I. Felner and K. Schenker, *Helv. Chim. Acta*, **53**, 754 (1970).
10. A. Gossauer and W. Hirsch, *Tetrahedron Lett.*, 1451 (1973).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Celite

diethyl ether-dichloromethane

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether (60-29-7)

acetonitrile (75-05-8)

magnesium, magnesium turnings (7439-95-4)

sodium chloride (7647-14-5)

hydrogen sulfide (7783-06-4)

Ethyl bromide (74-96-4)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

pyridine (110-86-1)

potassium hydroxide (1310-58-3)

1-butyryl chloride (141-75-3)

dichloromethane (75-09-2)

Tetrahydrofuran (109-99-9)

sodium hydride (7646-69-7)

phosphine (7723-14-0)

triethylamine (121-44-8)

phenylphosphonous dichloride, dichlorophenylphosphine (644-97-3)

triethylamine hydrobromide (636-70-4)

lithium bromide (7550-35-8)

3-Methyl-2,4-heptanedione, 2,4-Heptanedione, 3-methyl- (13152-54-0)

Bis(3-dimethylaminopropyl)phenylphosphine (32357-32-7)

thiobutyric acid (3931-64-4)

3-bromo-2-butanone (814-75-5)

Lithium bromide dihydride

lithium perchlorate (7791-03-9)

3-chloro-N,N-dimethyl-1-propylamine hydrochloride (5407-04-5)

3-chloro-N,N-dimethyl-1-propylamine

S-(2-oxobut-3-yl)butanethioate, S-(2-Oxobut-3-yl) butanethioate (32425-98-2)

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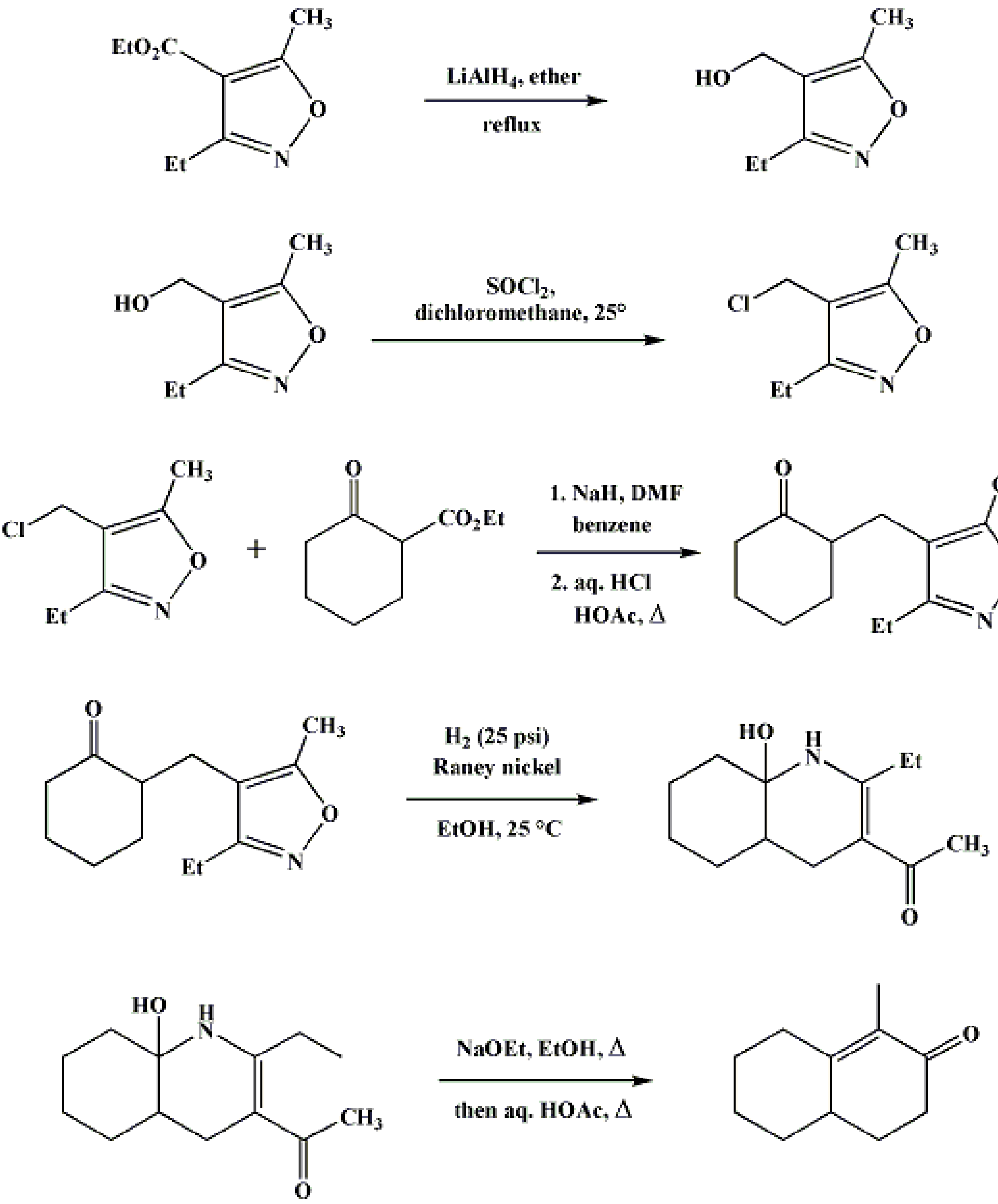
Organic Syntheses, CV 6, 781

ISOXAZOLE ANNELATION REACTION: 1-METHYL-4,4a,5,6,7,8-HEXAHYDRONAPHTHALEN-2(3*H*)-ONE

[2(3*H*)-Naphthalenone, 4,4a,5,6,7,8-hexahydro-1-methyl-]



Submitted by John E. McMurry[1]
Checked by U. P. Hochstrasser and G. Büchi.

1. Procedure

Caution! Lithium aluminum hydride can react with explosive violence on contact with water or when overheated, and great care must be taken in its handling.

Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A. *3-Ethyl-4-hydroxymethyl-5-methylisoxazole*. A slurry of lithium aluminum hydride (21.0 g., 0.553 mole) in anhydrous diethyl ether is prepared by cautiously adding the powdered reagent (Note 1) to 2.5 l. of freshly prepared anhydrous ether in a 5-l., three-necked flask fitted with a reflux condenser, a 500-ml. pressure-equalizing addition funnel, and a strong mechanical stirrer. The contents of the flask are then placed under a nitrogen atmosphere *via* a gas-inlet tube attached to the top of the condenser. Ethyl 3-ethyl-5-methyl-4-isoxazolecarboxylate (124 g., 0.678 mole) (Note 2), dissolved in 300 ml. of dry ether, is placed in the addition funnel and added dropwise over 4 hours to the lithium aluminum hydride slurry (Note 3). The reaction is refluxed gently for 4 hours, then placed in an ice bath. Quenching of excess reagent and hydrolysis of aluminate salts is effected by *cautious*, *slow* addition of 20 ml. of water, followed by 30 ml. of aqueous 10% sodium hydroxide and another 30 ml. of water (Note 4). The ether layer is filtered from granular aluminum salts, poured into a 2-l. separatory funnel, and washed with 250 ml. of saturated brine. The organic extract is dried over anhydrous magnesium sulfate and filtered, and the solvent is removed with a rotary evaporator. The residual oil is distilled, yielding 76–82 g. (80–86%) of 3-ethyl-4-hydroxymethyl-5-methylisoxazole, b.p. 99–101° (0.15 mm.); n_D^{23} 1.4835; IR: 3450, 1640 $cm.^{-1}$; ^1H NMR (CCl_4): δ 1.2 (t, 3H, CH_2CH_3), 2.2 (s, 3H, $C{=}CCH_3$), 2.6 (q, 2H, CH_2CH_3), 4.2 (s, 2H, CH_2O).

B. *4-Chloromethyl-3-ethyl-5-methylisoxazole*. *Caution! The following reaction should be carried out in a fume hood to avoid thionyl chloride vapors.*

3-Ethyl-4-hydroxymethyl-5-methylisoxazole (54 g., 0.38 mole) is dissolved in 70 ml. of dichloromethane and placed in a 500-ml., one-necked flask fitted with a 100-ml., pressure-equalizing addition funnel and a magnetic stirrer. The flask is placed in an ice bath, and its contents are stirred while a solution of 53 g. of thionyl chloride (32 ml., 0.45 mole) in 50 ml. of dichloromethane is added dropwise. Addition is complete in 1 hour, and the reaction is allowed to warm to room temperature and stirred for an additional hour. The solvent is removed with a rotary evaporator and the dark residual liquid is distilled, yielding 47–49 g. (78–81%) of 4-chloromethyl-3-ethyl-5-methylisoxazole, b.p. 77–78° (1.5 mm.); n_D^{23} 1.4845; IR: 1620, 680 $cm.^{-1}$; ^1H NMR (CCl_4): δ 1.3 (t, 3H, CH_2CH_3), 2.3 (s, 3H, $C{=}CCH_3$), 2.6 (q, 2H, CH_2CH_3), 4.3 (s, 2H, CH_2Cl).

C. *2-(3-Ethyl-5-methyl-4-isoxazolylmethyl)cyclohexanone*. Sodium hydride (10.0 g. of a 60% slurry in mineral oil, 0.25 mole) is degreased in a flame-dried, 1-l., three-necked flask fitted with a 250-ml., pressure-equalizing addition funnel and a condenser through which a stream of nitrogen is blown. The sodium hydride is washed by adding 20 ml. of dry benzene, stirring magnetically, allowing it to settle, and drawing off the supernatant benzene wash with a syringe. The washing process is repeated four more times before 100 ml. of dry benzene is added, followed with 100 ml. of dry *N,N*-dimethylformamide (Note 5). The contents of the flask are covered with a nitrogen atmosphere and a solution of ethyl 2-cyclohexanonecarboxylate (41.0 g., 0.241 mole) (Note 6) in 100 ml. of 1:1 benzene–dimethylformamide is added slowly over 45 minutes, with cooling, keeping the reaction mixture near room temperature (Note 7). A solution of 4-chloromethyl-3-ethyl-5-methylisoxazole (32 g., 0.20 mole) in 100 ml. of 1:1 benzene–dimethylformamide is then added

over 30 minutes, and the reaction is stirred for 2 days at room temperature. The reaction is diluted with 300 ml. of ether, poured into a 1-l. separatory funnel, washed three times with 100-ml. portions of water and once with brine, dried over anhydrous magnesium sulfate and filtered. The solvents are removed with a rotary evaporator, and the residual oil is dissolved in 150 ml. of glacial acetic acid and placed in a 500-ml., one-necked flask fitted with a magnetic stirrer and a reflux condenser. Hydrochloric acid (150 ml., 6 *N*) is added. The mixture is refluxed for 36 hours (Note 8), then concentrated with a rotary evaporator. The residue is taken up in 500 ml. of ether, poured into a 1-l. separatory funnel, and washed twice with 100-ml. portions of water, once with 5% aqueous sodium hydroxide, and once with brine. After drying over anhydrous magnesium sulfate and filtration, the organic extracts are concentrated with a rotary evaporator and distilled (Note 9), yielding 33–35 g. (75–80%) of 2-(3-ethyl-5-methyl-4-isoxazolylmethyl)cyclohexanone, b.p. 130° (0.001 mm.); n_D^{23} 1.4970; IR: 1710, 1630 cm.$^{-1}$; ^{1}H NMR (CCl_4): δ 1.2 (t, 3H, CH_2CH_3). 1.5–2.2 (m, 11H, $5CH_2$ and C*H*), 2.3 (s, 3H, C=CCH_3), 2.5 (q. 2H, C$H_2$$CH_3$).

D. 1-*Methyl*-4,4a,5,6,7,8-*hexahydronaphthalen*-2(3H)-*one*. *Caution! Sodium ethoxide formation should be carried out in a hood since a large volume of hydrogen gas is evolved.*

2-(3-Ethyl-5-methyl-4-isoxazolylmethyl)cyclohexanone (27.6 g., 0.125 mole) is dissolved in 250 ml. of ethanol in a Parr hydrogenation bottle, and 20 g. of freshly prepared W-4 Raney nickel catalyst (Note 10) is added. Hydrogenation is started at an initial hydrogen pressure of 25 p.s.i. Cleavage of the isoxazole ring is complete after 6 hours, after which time the reaction is stopped and the solution is filtered free of catalyst (Note 11). The catalyst is washed with ether and absolute ethanol, and the combined organic filtrates are concentrated with a rotary evaporator (Note 12).

The viscous, residual liquid is dissolved in 25 ml. of absolute ethanol and a stream of nitrogen is bubbled through the solution for 15 minutes, removing dissolved oxygen (Note 13). A solution of sodium ethoxide is then prepared by cautiously dissolving freshly cut sodium (11.5 g., 0.500 mole) in 150 ml. of absolute ethanol, under a nitrogen atmosphere, in a 500-ml., three-necked flask fitted with a reflux condenser topped with a gas-inlet, a magnetic stirrer, and a rubber serum cap on one of the sidearms. When ethoxide formation is complete, the deoxygenated solution of the hydrogenated isoxazole is injected into the stirred reaction mixture through the rubber serum cap with a syringe. The solution is refluxed until the UV spectrum of a small aliquot withdrawn with a syringe through the serum cap shows the absence of absorption at 345 nm. (Note 14). This requires about 30 hours.

A solution of 15 ml. of glacial acetic acid and 30 ml. of water is deoxygenated as described above and slowly injected with a syringe into the reaction. Refluxing is continued for 6 hours, the flask is cooled, and its contents are poured into a 1-l. separatory funnel along with 200 ml. of water. The solution is extracted four times with 100-ml. portions of ether, and the combined ether extracts are washed successively with 100 ml. of 6 *N* hydrochloric acid, 100 ml. of water, and 100 ml. of brine. The organic extracts are dried over anhydrous magnesium sulfate, filtered, concentrated with a rotary evaporator, and distilled, yielding 13.2–13.8 g. (65–67%) of 1-methyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one, b.p. 85–90° (0.5 mm.); n_D^{23} 1.5120; IR: 1670, 1605 cm.$^{-1}$; ^{1}H NMR (CCl_4): δ 1.0–2.5 (m, 13H, $6CH_2$ and C*H*), 1.7 (s, 3H, C=CCH_3).

2. Notes

1. The reagents used in this procedure were obtained from the following sources: lithium aluminum hydride, Alfa Inorganic, Inc.; thionyl chloride, Matheson, Coleman and Bell; sodium hydride, Metal Hydrides, Inc. The nitrogen was prepurified.
2. See *Org. Synth.*, **Coll. Vol. 6**, 592 (1988).

3. The addition must be done cautiously and the reaction watched constantly to see that efficient stirring is maintained. When the addition is approximately half-complete, doughy lumps, which tend to form on top of the solution, impede the stirring.

4. This quenching procedure is mentioned in the literature.[2]

5. *N,N*-Dimethylformamide was dried and purified by distillation from anhydrous copper sulfate.

6. Ethyl cyclohexanonecarboxylate was purchased from Aldrich Chemical Company, Inc., and contains approximately 40% methyl ester. The amount used takes this fact into account.

7. *N,N*-Dimethylformamide begins to decompose if the temperature rises too much.

8. The submitter stated that 24 hours of refluxing was sufficient for complete decarboxylation; however, the checkers found that after 24 hours at reflux, approximately 30% of the ester remained. Analysis was performed by GC (6-ft. column, 10% silicon rubber, 210°).

9. The distillation is most conveniently done in a short-path distillation apparatus with a mercury diffusion pump.

10. The W-4 Raney nickel is prepared according to the literature.[3]

11. *Caution! Since the catalyst is highly pyrophoric when dry, do not dry it completely.*

12. The hydrogenated isoxazole is quite sensitive to air and heat and should be used as soon as possible to prevent decomposition.

13. Oxygen must be rigorously avoided, particularly in smaller scale reactions, to prevent oxidation of the dihydropyridine intermediate to the corresponding pyridine.

14. The absorption maximum at 345 nm. corresponds to an acetyldihydropyridine intermediate (see Discussion) and disappears when the acetyl group is cleaved by ethoxide. Thus, the reaction can be readily followed spectroscopically.

3. Discussion

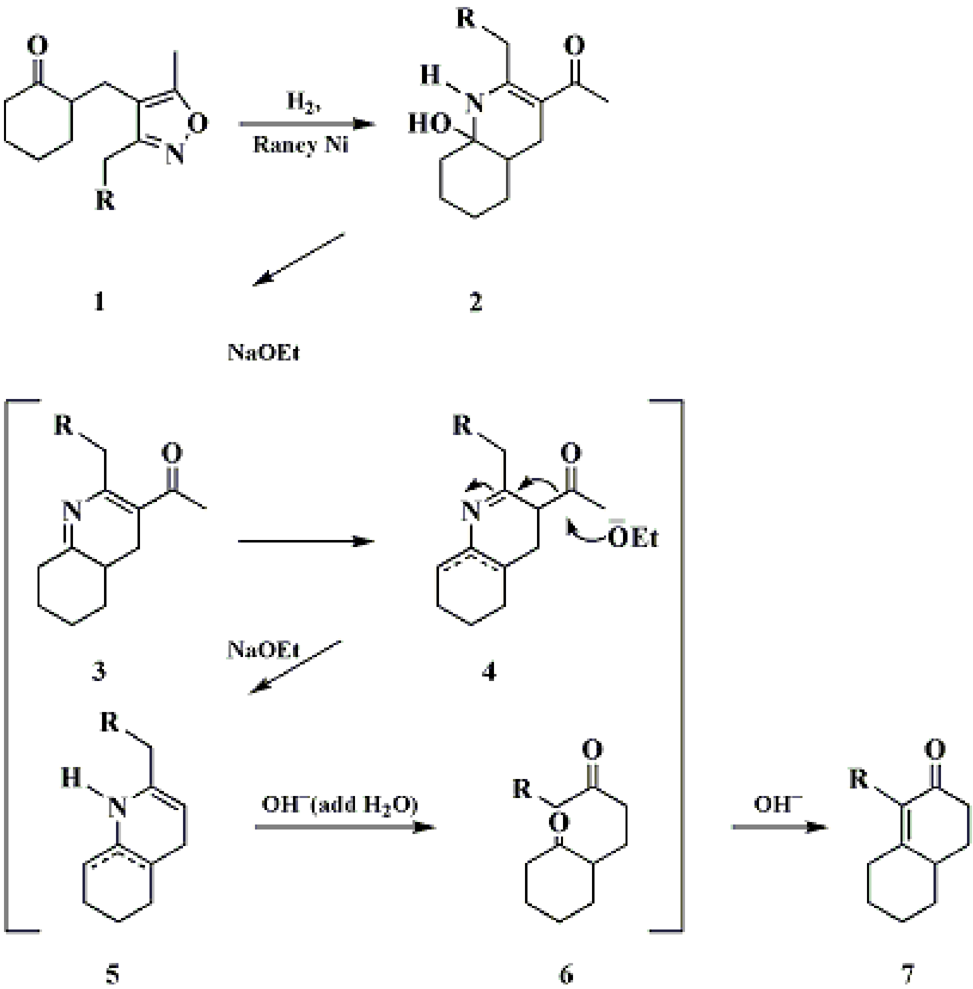
The isoxazole annelation reaction[4,5] is a general method for fusing a new cyclohexanone ring onto an existing system and complementary to the well-known Robinson annelation.[6] It has several major advantages:

1. The isoxazole ring serves as a "masked" or protected 3-oxobutyl side chain which can be positioned *alpha* to the existing ketone at an early stage in a complex synthesis. The isoxazole ring is stable to acids, bases, and hydride reducing agents[7] but can be cleanly and selectively cleaved by hydrogenolysis. Thus, at an appropriate time, the 3-oxobutyl side chain can be unmasked and annelation completed.

2. Although the present procedure attaches the isoxazole *via* alkylation of a β-keto ester, there are several different methods by which attachment could have been effected. Both alkylation of a cyclohexanone enamine[8] and direct alkylation of an enone anion followed by hydrogenation of the enone double bond have been used successfully.[4,5]

3. Since a wide range of 3-substituted-4-chloromethylisoxazoles can be easily prepared, the isoxazole annelation sequence allows one to construct a variety of substituted cyclohexenone systems.

The mechanism of the annelation sequence is of some interest and has been shown to proceed through the following path:[9]



The anhydrous, deoxygenated sodium ethoxide solution readily dehydrates carbinolamide **2** to the acyldihydropyridine **3**, but prevents hydrolysis or oxidation of **3**. Base-catalyzed double bond migrations can lead to **4**, the imine of a β-diketone, and the acetyl fragment can then be cleaved. Addition of water to the reaction causes hydrolysis of the cross-conjugated dienamine **5** to diketone **6**, which then cyclizes.

The present procedure is illustrative of the general method which finds its utility largely in the construction of more complex polycyclic systems. The specific compound synthesized herein can be made more conveniently by standard Robinson annelation techniques.[10]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

brine

W-4 Raney nickel

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

ether, diethyl ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

thionyl chloride (7719-09-7)

oxygen (7782-44-7)

nitrogen (7727-37-9)

copper sulfate (7758-98-7)

pyridine (110-86-1)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

ethoxide

ethyl 2-cyclohexanonecarboxylate, Ethyl cyclohexanonecarboxylate (1655-07-8)

lithium aluminum hydride (16853-85-3)

N,N-dimethylformamide, dimethylformamide (68-12-2)

sodium hydride (7646-69-7)

dihydropyridine

cyclohexenone (930-68-7)

isoxazole (288-14-2)

Ethyl 3-ethyl-5-methyl-4-isoxazolecarboxylate (53064-41-8)

3-Ethyl-4-hydroxymethyl-5-methylisoxazole (53064-42-9)

4-Chloromethyl-3-ethyl-5-methylisoxazole (40500-39-8)

2-(3-Ethyl-5-methyl-4-isoxazolylmethyl)cyclohexanone (53984-03-5)

acetyldihydropyridine

cyclohexanone enamine

carbinolamide (4312-87-2)

1-Methyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3H)-one, 2(3H)-Naphthalenone, 4,4a,5,6,7,8-hexahydro-1-methyl- (5164-37-4)

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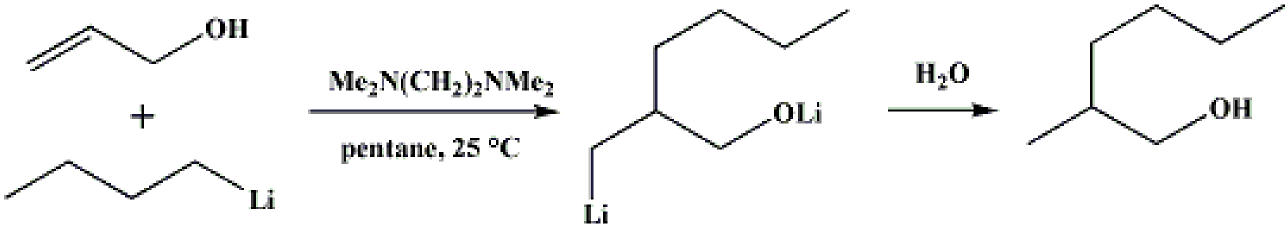
Organic Syntheses, CV 6, 786

ADDITION OF ORGANOLITHIUM REAGENTS TO ALLYL ALCOHOL: 2-METHYL-1-HEXANOL

[1-Hexanol, 2-methyl-]



Submitted by J. K. Crandall[1] and A. C. Rojas.
Checked by D. E. Berthet and G. Büchi.

1. Procedure

A 500-ml., three-necked, round-bottomed flask is fitted with a gas-inlet tube, a rubber septum, a reflux condenser connected to a mineral oil bubbler, and a sealed mechanical stirrer. The system is flamed with a Bunsen burner as it is flushed with dry nitrogen. The reaction vessel is cooled under nitrogen in an ice bath, and 7.25 g. (0.125 mole) of 2-propen-1-ol (Note 1), 70 ml. of pentane (Note 2), and 1.16 g. (0.0100 mole) of *N,N,N',N'*-tetramethyl-1,2-ethanediamine (Note 3) are added successively through the rubber septum with a syringe. While maintaining a positive nitrogen pressure, 180 ml. of 1.5 *M* (0.270 mole) *n*-butyllithium in pentane (Note 4) is added from a syringe over a 20-minute period (Note 5). The ice bath is removed, and the reaction mixture is stirred for an additional hour (Note 6). The ice bath is then restored, the gas-inlet tube replaced with a pressure-equalizing dropping funnel, and 70 ml. of water is added, cautiously at first, and then more rapidly after the exothermic reaction ceases. The resulting mixture is transferred to a separatory funnel, the aqueous layer is separated and discarded, and the pentane layer is washed with a 10-ml. portion of 3 *N* hydrochloric acid, then two 10-ml. portions of water. The organic layer is dried over anhydrous magnesium sulfate and filtered. The solvent is removed by distillation through a 20-cm. Vigreux column. Distillation of the residual oil through a short-path distillation apparatus yields 9.3–9.6 g. (64–66%) (Note 7) of 2-methyl-1-hexanol, b.p. 166–167° (Note 8) and (Note 9).

2. Notes

1. Commercial 2-propen-1-ol was purchased from Aldrich Chemical Company, Inc., and was distilled prior to use (b.p. 94.5–95°).
2. Technical grade pentane was distilled from concentrated sulfuric acid.
3. Commercial *N,N,N',N'*-tetramethyl-1,2-ethanediamine was obtained from Aldrich Chemical Company, Inc., and distilled prior to use (b.p. 119.5°).
4. Commercial solutions of *n*-butyllithium were obtained from Foote Mineral Company.
5. During the addition of *n*-butyllithium, a gel forms. If the solution is not well agitated during this period, the yield is somewhat lower.
6. Extending the reaction time did not increase the yield.
7. The checker's yield was 10.5–10.7 g. (72–74%) (see Note 5).
8. The purity of the product is greater than 99% as determined by GC analysis using a 6-m. column of 30% Carbowax 20M on 60–80 Chromosorb W. The major impurity (<1%) was shown to be 3-heptanol by comparison of GC retention times and mass spectral fragmentation

patterns with those of an authentic sample.

9. The spectral properties of the product are as follows; IR (neat) cm.$^{-1}$: 3268, 1377, 1037; ^{1}H NMR (CCl_4), δ (multiplicity, number of protons): 0.88 (m, 6H), 1.38 (m, 7H), 3.33 (unresolved d, 2H), 5.14 (broad s, 1H).

3. Discussion

This procedure illustrates a convenient method of converting allyl alcohol to 2-substituted-1-propanols by the addition of an organolithium reagent.[2] A variety of organolithiums have given moderate to high yields of the corresponding alcohols. The indicated organolithium species is a demonstrated intermediate which can, in principle, be employed in a host of further synthetic conversions.[2] Substituted allylic alcohols, however, do not undergo analogous conversions efficiently, except when the substituent is at the carbinol carbon.[2]

2-Methyl-1-hexanol has also been prepared by the reaction of 2-hexylmagnesium halides with formaldehyde,[3] the reduction of 2-methylhexanoic acid or its ester,[4,5] and by hydroformylation of 1-hexene[6,7,8] among others.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

formaldehyde (630-08-0)

Allyl alcohol, ALLYLIC ALCOHOLS, 2-propen-1-ol (107-18-6)

nitrogen (7727-37-9)

Pentane (109-66-0)

magnesium sulfate (7487-88-9)

n-butyllithium (109-72-8)

1-hexene (592-41-6)

2-Methyl-1-hexanol, 1-Hexanol, 2-methyl- (61949-26-6)

3-heptanol (589-82-2)

2-methylhexanoic acid (4536-23-6)

N,N,N',N'-tetramethyl-1,2-ethanediamine (110-18-9)

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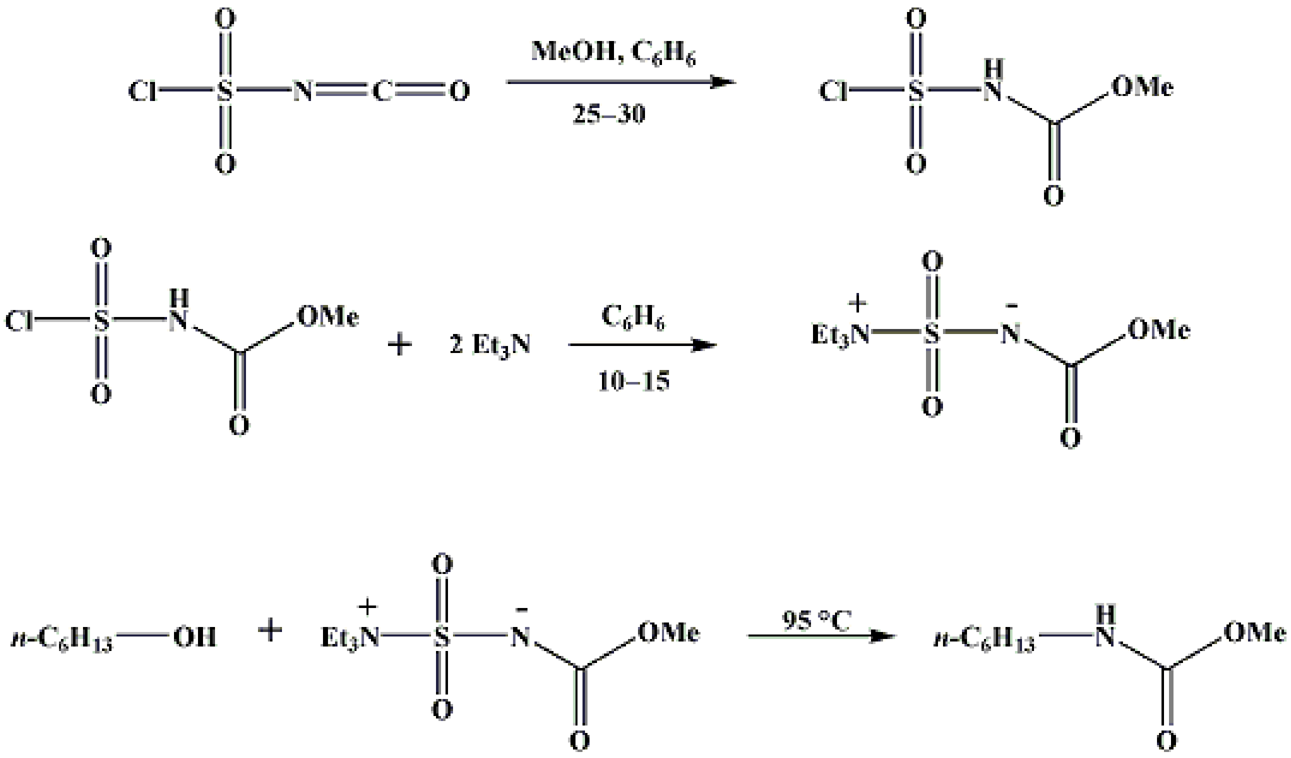
Organic Syntheses, CV 6, 788

CONVERSION OF PRIMARY ALCOHOLS TO URETHANES *via* THE INNER SALT OF METHYL (CARBOXYSULFAMOYL) TRIETHYLAMMONIUM HYDROXIDE: METHYL *n*-HEXYLCARBAMATE

[Carbamic acid, hexyl-, methyl ester]



Submitted by Edward M. Burgess[1], Harold R. Penton, Jr., E. Alan Taylor, and W. Michael Williams.
Checked by James E. Nottke and Richard E. Benson.

1. Procedure

Caution! Chlorosulfonyl isocyanate is highly corrosive. This preparation should be carried out in an efficient hood, and rubber gloves should be worn during the first step.

Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A. *Methyl (chlorosulfonyl)carbamate*. A dry, two-necked, 500-ml., round-bottomed flask fitted with a magnetic stirring bar, a 125-ml., pressure-equalizing dropping funnel, and a reflux condenser to which is attached a calcium chloride drying tube is charged with a solution of 70.8 g. (43.6 ml., 0.580 mole) of chlorosulfonyl isocyanate (Note 1) in 150 ml. of anhydrous benzene (Note 2). A solution of 16.0 g. (20.2 ml., 0.500 mole) of anhydrous methanol (Note 3) in 25 ml. of anhydrous benzene (Note 2) is placed in the dropping funnel. The flask is immersed in a water bath (Note 4),

stirring is begun, and the methanol–benzene solution is added dropwise over 0.5 hour. Cold water is added to the bath as required to maintain a temperature of 25–30°. The reaction mixture is stirred for an additional 0.5 hour before 125 ml. of olefin-free hexane (Note 5) is added from the addition funnel over a 5-minute period while cooling the flask to 0–5° with an ice bath. The moisture-sensitive product is removed by filtration, washed twice with 40 ml. of hexane, and dried under reduced pressure, giving 76–80 g. (88–92%) of methyl (chlorosulfonyl)carbamate as white crystals, m.p. 72–74° (Note 6). This material should be stored in a brown bottle protected from light (Note 7).

B. *Inner salt of methyl (carboxysulfamoyl)triethylammonium hydroxide*. A two-necked, 500-ml., round-bottomed flask is fitted with a magnetic stirring bar, a 500-ml., pressure-equalizing dropping funnel, and a condenser to which a calcium chloride drying tube is attached. A solution of 23.0 g. (31.8 ml., 0.225 mole) of anhydrous triethylamine (Note 8) in 50 ml. of anhydrous benzene (Note 2) is placed in the flask, stirring is begun, and a solution of 17.4 g. (0.100 mole) of methyl (chlorosulfonyl)carbamate in 225 ml. of dried benzene (Note 9) is added dropwise over 1 hour. During addition the flask is cooled with a water bath maintained at 10–15°. The resulting mixture is stirred at 25–30° for an additional 0.5 hour then filtered to remove triethylamine hydrochloride (13.8 g.). Evaporation of the filtrate under reduced pressure leaves 22–23 g. of light tan needles, m. p. 70–72° (dec.), which is dissolved in 160 ml. of anhydrous tetrahydrofuran (Note 10) at 30°. On cooling, 20.0–20.6 g. (84–86%) of the inner salt of methyl (carboxysulfamoyl)triethylammonium hydroxide precipitates as colorless needles, m.p. 70–72° (dec.) (Note 11).

C. *Methyl* n-*hexylcarbamate*. In a dry, 100-ml., round-bottomed flask fitted with a reflux condenser, to which a calcium chloride drying tube is attached, are placed a boiling chip, 14.8 g. (0.0622 mole) of the inner salt of methyl (carboxysulfamoyl)triethylammonium hydroxide, and 6.0 g. (0.058 mole) of freshly distilled 1-hexanol (Note 12). After a mildly exothermic reaction (occasionally there is a 5-minute induction period), the viscous, yellow reaction mixture is heated with an oil bath at 95° for 1 hour. The mixture is cooled to 30°, diluted with 50 ml. of water, and extracted with three 50-ml. portions of dichloromethane. The organic extracts are combined, washed successively with 100 ml. of 5% hydrochloric acid and 50 ml. of water, and dried over anhydrous magnesium sulfate. After filtration, dichloromethane is removed with a rotary evaporator. The residue is triturated with 50 ml. of anhydrous diethyl ether and filtered; the recovered solid is triturated with two further 50-ml. portions of ether. The three ethereal filtrates are combined and concentrated with a rotary evaporator, affording 8.0 g. of crude product. Fractionation of this oil through a short-path distillation apparatus gives 4.8–4.9 g. (51–52%) of methyl *n*-hexylcarbamate as a colorless oil, b.p. 59–60° (0.08 mm.); n_D^{20} 1.4361 (Note 13).

2. Notes

1. The preparation of chlorosulfonyl isocyanate is described in *Org. Synth.*, **Coll. Vol. 5**, 226 (1973). This compound is highly corrosive, reacts explosively with water, and may be contaminated with cyanogen chloride.
2. Throughout this preparation the submitters used reagent grade materials distilled prior to use. The checkers used ACS reagent grade benzene available from Fisher Scientific Company.
3. The checkers used ACS reagent grade methanol available from Fisher Scientific Company.
4. The water bath should not be positioned around the flask until after the solution of chlorosulfonyl isocyanate has been added.
5. The checkers used spectro-grade reagent available from Phillips Petroleum Company.
6. ^{1}H NMR (CD_3CN) δ: 3.64 (s).
7. The checkers observed a violent decomposition when product stored in a clear glass container was inadvertently exposed to sunlight.

8. Triethylamine was dried by distillation from phosphorus pentoxide at atmospheric pressure. The checkers used reagent grade material available from Eastman Organic Chemicals.
9. The compound dissolves readily in benzene on warming to 40°.
10. The checkers used ACS reagent grade material available from Fisher Scientific Company, taken from a freshly opened bottle.
11. IR ($CHCl_3$) $cm.^{-1}$: 1690 (C=O), 1345, 1110 (SO_2), 1260 (C-O); ^1H NMR ($CDCl_3$), δ (multiplicity, coupling constant *J* in Hz., number of protons): 1.15 (t, *J* = 7, 9H), 3.29 (q, *J* = 7, 6H), 3.66 (s, 3H).
12. The checkers used practical grade material (available from Eastman Organic Chemicals) distilled immediately prior to use.
13. IR (neat) $cm.^{-1}$: 3400, 2950, 1700, 1520, 1255, 1190, 774; ^1H NMR (neat), δ (multiplicity, number of protons): 0.8–1.5 (m, 13H), 3.6 (s, 3H), 6.14 (broad t, 1H).

3. Discussion

The above procedure describes the only known preparation of the inner salt of methyl (carboxysulfamoyl)triethylammonium hydroxide and illustrates the use of this reagent to convert a primary alcohol to the corresponding urethane.[2] Hydrolysis of the urethane would provide the primary amine. The method is limited to primary alcohols; secondary and tertiary alcohols are dehydrated to olefins under these conditions, often in synthetically useful yields.[2]

Other sequences that transform primary alcohols to primary amines include: (a) conversion of the alcohol to a cyanate, rearrangement to an isocyanate, and hydrolysis,[3] and (b) conversion of the alcohol to an *N*-alkylformamide *via* the Ritter reaction, followed by hydrolysis.[4]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

1-Hexanol (111-27-3)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

urethane (51-79-6)

cyanogen chloride (506-77-4)

Tetrahydrofuran (109-99-9)

hexane (110-54-3)

triethylamine (121-44-8)

Triethylamine hydrochloride (554-68-7)

CHLOROSULFONYL ISOCYANATE (1189-71-5)

METHYL (CARBOXYSULFAMOYL)TRIETHYLAMMONIUM HYDROXIDE (29684-56-8)

Carbamic acid, hexyl-, methyl ester (22139-32-8)

Methyl (chlorosulfonyl)carbamate (36914-92-8)

phosphorus pentoxide (1314-56-3)

METHYL n-HEXYLCARBAMATE

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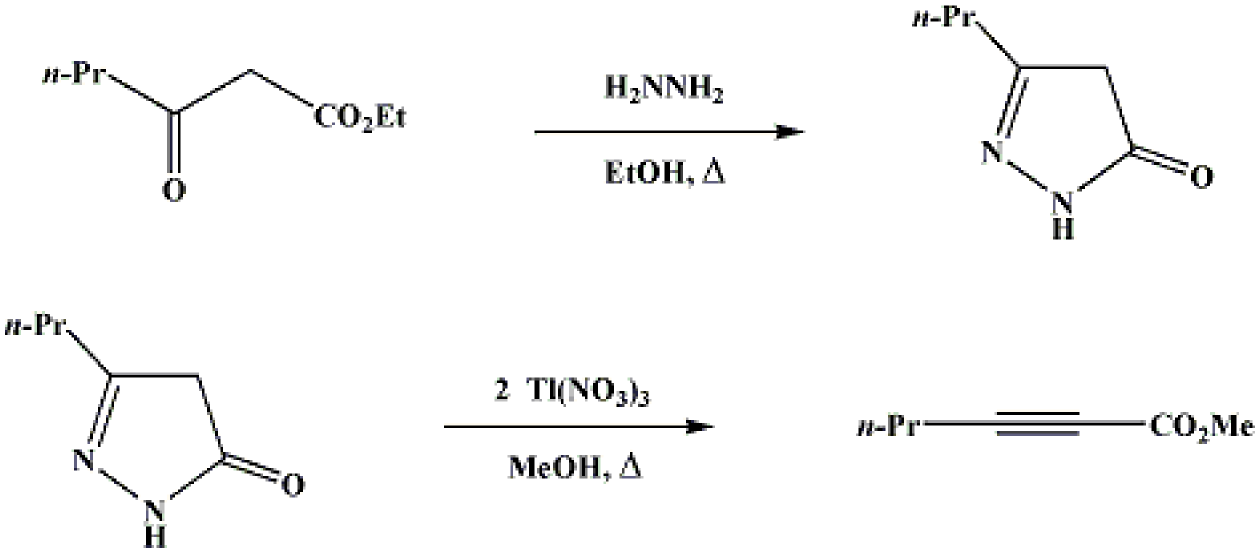
Organic Syntheses, CV 6, 791

METHYL 2-ALKYNOATES FROM 3-ALKYL-2-PYRAZOLIN-5-ONES: METHYL 2-HEXYNOATE

[2-Hexynoic acid, methyl ester]



Submitted by Edward C. Taylor[1], Roger L. Robey[1], David K. Johnson[1], and Alexander McKillop[2].
Checked by F. Kienzle and A. Brossi.

1. Procedure

Caution! Thallium compounds are highly toxic.[3] However, they may be safely handled if prudent laboratory procedures are practiced. Rubber gloves and laboratory coats should be worn and reactions should be carried out in an efficient hood. In addition, thallium wastes should be collected and disposed of separately (Note 1).

A. *3-(1-Propyl)-2-pyrazolin-5-one*. A 500-ml., round-bottomed flask equipped with a magnetic stirring bar and a reflux condenser is charged with 23.7 g. (0.150 mole) of ethyl 3-oxohexanoate (Note 2), 250 ml. of ethanol, and 9.8 g. (0.17 mole) of 85% aqueous hydrazine hydrate (Note 3). The mixture is stirred for 2 hours at 0° and 2 hours at reflux, then reduced in volume to 50–100 ml. on a rotary evaporator. The resulting suspension is cooled to 0–5° and suction filtered, giving 14–16 g. (77–83%) of 3-(1-propyl)-2-pyrazolin-5-one as colorless crystals, m.p. 204–206°, which are dried for 1–2 hours over anhydrous calcium chloride and used without further purification (Note 4).

B. *Methyl 2-hexynoate*. A 1-l., round-bottomed flask equipped with a magnetic stirring

bar and a reflux condenser is charged with 12.62 g. (0.1002 mole) of 3-(1-propyl)-2-pyrazolin-5-one and 500 ml. of methanol (Note 5). To this solution, 93.20 g. (0.2097 mole) of thallium(III) nitrate trihydrate (Note 6) is slowly added so as to avoid foaming. The reaction mixture is stirred for 20 minutes at room temperature and 20 minutes at reflux (Note 7) and (Note 8), then reduced to approximately half its volume by evaporation on a rotary evaporator. It is then cooled to 0–5° and filtered through fluted filter paper, removing precipitated thallium(I) nitrate. The filter cake is washed with 150 ml. of chloroform, and 250 ml. of water is added to the filtrate. The chloroform layer is separated, and two additional extractions with 100 ml. of chloroform are carried out. The combined chloroform layers are washed once with 100 ml. of 5% aqueous sodium hydrogen carbonate, twice with 100 ml. of water, and dried over anhydrous magnesium sulfate. The chloroform is removed on a rotary evaporator, and the residue is filtered through a 2 cm. by 12 cm. column of 100–200 mesh Florisil (Note 9) using approximately 250 ml. of chloroform as eluent. The chloroform is removed on a rotary evaporator, and the resulting pale yellow liquid is vacuum distilled through a 19-cm., unpacked column (Note 10), yielding 8.63–9.24 g. (68–73%) of methyl 2-hexynoate, b.p. 47–50° (5 mm.), as a colorless to slightly yellow liquid (Note 11).

2. Notes

1. The submitters recommend collection of solid wastes in an appropriate solid waste container, and liquid wastes (filtrates containing thallium residues, etc.) in suitably labeled bottles or cans. For the disposal of thallium wastes, a commercial organization specializing in the disposal of toxic materials was employed.
2. Ethyl 3-oxohexanoate is available under the name of ethyl butyrylacetate from Aldrich Chemical Company, Inc.
3. This product is available from Matheson, Coleman and Bell.
4. The pyrazolinone should be colorless. If it is not, it may be washed with a minimum of ice-cold ethanol. This procedure is convenient and yields material of adequate purity for the subsequent reaction. Additional pyrazolinone may be obtained by evaporating the filtrate and recrystallizing the residue from ethanol.
5. Commercially available anhydrous methanol was used without further treatment.
6. Thallium(III) nitrate trihydrate is best prepared fresh by dissolving, with stirring, 200 g. (0.439 mole) of thallium(III) oxide (available from American Smelting and Refining, Denver, Colorado) in 400 ml. of concentrated nitric acid. The submitters have found the proportion of 1 g. of thallium(III) oxide to 2 ml. of nitric acid to be best. Any suspended matter is removed by suction filtration through a medium fritted-glass funnel. The filtrate is cooled in an ice bath with mechanical stirring, yielding thallium(III) nitrate trihydrate as a fine white powder. The precipitate is separated by suction filtration through a medium fritted-glass funnel, pressed as dry as possible, and dried for approximately 6

hours in a vacuum desiccator over phosphorus pentoxide and potassium hydroxide. Longer drying times result in thallium(III) nitrate trihydrate of poorer quality. These crystals of thallium(III) nitrate trihydrate often occlude a considerable amount of nitric acid, with a consequent decrease in reactivity. To assure removal of occluded nitric acid, the submitters recommend grinding the initially dried material to a fine powder with a mortar and pestle and redrying in a vacuum desiccator, again over phosphorus pentoxide and potassium hydroxide, for an additional 6 hours. The resulting extremely reactive thallium(III) nitrate trihydrate should be stored in a desiccator, since it rapidly turns brown upon contact with moist air. Thallium residues may conveniently be removed with aqueous 1 *N* hydrochloric acid.

7. The reaction mixture first turns muddy brown, due to the hydrolysis of thallium(III) nitrate to thallium(III) hydroxide and thallium(III) oxide, and then yellow with the separation of colorless thallium(I) nitrate.

8. The reduction of thallium(III) to thallium(I) may be followed with potassium iodide–starch paper. A drop of solution is placed on the paper and allowed to dry. Thallium(III) gives a purple color when the paper is moistened with water, due to the oxidation of iodide to iodine by thallium(III). Thallium(I) gives a lemon-yellow color due to the formation of thallium(I) iodide.

9. This product is available from Floridin Company, Berkley Springs, West Virginia 25411. The checkers found that this filtration was not necessary.

10. Best results were obtained with an oil bath maintained at 80–85°. The bath temperature should never exceed 100°.

11. The spectral properties of the product are as follows; IR (film) $cm.^{-1}$: 2230 strong, 1718 strong, 1428 strong, 1261 strong, 1075 strong; ^{1}H NMR (neat), δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 1.01 (t, *J* = 7.2, 3H, CH_3), 1.63 (m, 2H, CH_2), 2.34 (t, *J* = 6.8, 2H, CH_2C C), 3.68 (s, 3H, OCH_3). GC analysis may be conveniently carried out using 10% Carbowax 20M on 60/80 Diatoport S.

3. Discussion

Methyl 2-hexynoate has been prepared by the esterification of 2-hexynoic acid, which was prepared by the carboxylation of sodium hexynylide.[4] α,β-Alkynoic acids have generally been obtained by either carboxylation of metal alkynylides or by elimination reactions.[5] In particular, they have been prepared by the elimination of enol brosylates and tosylates,[6] an intramolecular Wittig reaction involving triphenylphosphinecarbomethoxymethylene and carboxylic acid chlorides,[7] and the base-promoted elimination reaction of 3-substituted-4,4-dichloro-2-pyrazolin-5-ones.[8]

The present method[9] affords the methyl ester directly in high yields from 2-pyrazolin-5-ones, which are readily prepared in nearly quantitative yields from readily accessible β-keto-esters. In addition, the reaction is simple to carry out, conditions are mild, and

the product is easily isolated in a high state of purity. A limitation of the reaction is that only the methyl ester can be made, as other alcohols have been found to give poor yields and undesirable mixtures of products. Table I illustrates other examples of the reaction.[10]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 348
- Org. Syn. Coll. Vol. 6, 488
- Org. Syn. Coll. Vol. 6, 709
- Org. Syn. Coll. Vol. 7, 81

TABLE I[a]
METHYL2-ALKYNOATES FROM2-PYRAZOLIN-5-ONESSUBSTITUTED ATPOSITION3

Substituent	Yield of Ester (%)
CH_3-	53
CH_3CH_2-	70
$(CH_3)_2CHCH_2$-	79
$CH_3(CH_2)_3CH_2$-	79
$CH_3(CH_2)_4CH_2$-	78
C_6H_5-	67
4–ClC_6H_4-	43

[a] Yields are for 0.01 mole reactions.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

triphenylphosphinecarbomethoxymethylene

ethanol (64-17-5)

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

methanol (67-56-1)

chloroform (67-66-3)

sodium hydrogen carbonate (144-55-8)

nitric acid (7697-37-2)

potassium iodide (7681-11-0)

iodine (7553-56-2)

potassium hydroxide (1310-58-3)

hydrazine hydrate (7803-57-8)

magnesium sulfate (7487-88-9)

Thallium (7440-28-0)

thallium(I) iodide

thallium(I)

thallium(III)

thallium(III) oxide (1314-32-5)

Methyl 2-hexynoate, 2-Hexynoic acid, methyl ester (18937-79-6)

ethyl 3-oxohexanoate, ethyl butyrylacetate (3249-68-1)

3-(1-Propyl)-2-pyrazolin-5-one (29211-70-9)

thallium(III) nitrate trihydrate

thallium(I) nitrate (10102-45-1)

pyrazolinone

thallium(III) nitrate (13746-98-0)

thallium(III) hydroxide

2-hexynoic acid (764-33-0)

sodium hexynylide

phosphorus pentoxide (1314-56-3)

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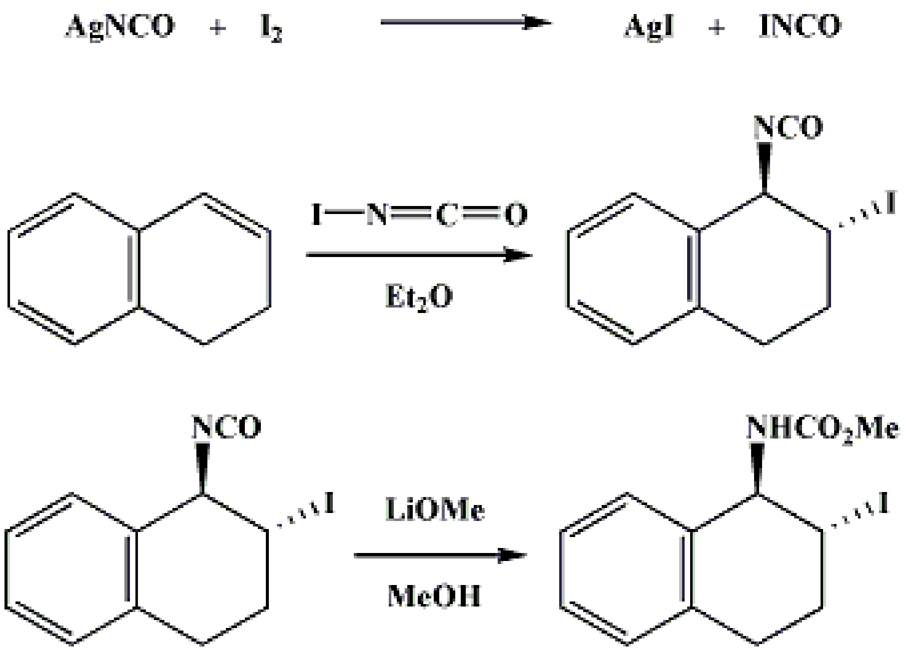
Organic Syntheses, CV 6, 795

METHYL (*trans*-2-IODO-1-TETRALIN)CARBAMATE

[Carbamic acid, (1,2,3,4-tetrahydro-2-iodo-1-naphthalenyl)-, methyl ester, *trans*-]



Submitted by C. H. Heathcock[1] and A. Hassner[2].
Checked by William G. Kenyon and Richard E. Benson.

1. Procedure

A 1-l., three-necked, round-bottomed flask fitted with a mechanical stirrer, a thermometer, and a calcium chloride drying tube is immersed in an ice-salt bath and charged with 38 g. (0.25 mole) of silver cyanate (Note 1), 34.7 g. of 75% 1,2-dihydronaphthalene (0.20 mole, (Note 2)), and 400 ml. of anhydrous diethyl ether. Stirring is begun, and when the temperature of the contents of the flask has reached 0°, 50.8 g. (0.200 mole) of iodine is added in one portion. The brown mixture is stirred vigorously for 2 hours at 0–5°, then for 6 hours at room temperature. The resulting mixture, which still retains the color of iodine, is filtered through a layer of filter aid. The filtrate is transferred to a 1-l. separatory funnel and washed with 75-ml. portions of 15% sodium bisulfite solution until the ether layer is nearly colorless. The resulting ether solution is concentrated to 200 ml. using a rotary evaporator at room temperature (20 mm.).

A solution of lithium methoxide, prepared from 0.015 g. of lithium in 200 ml. of methanol, is added to the ether solution, and the resulting mixture is allowed to stand at room temperature for 1 hour. The volume is reduced to 200 ml. by distillation using a rotary evaporator at room temperature (20 mm.) before the solution is added to 600

ml. of an ice-water mixture containing 3 g. of sodium bisulfite. The solid product that separates is collected by filtration, washed with water, and air-dried. The crude carbamate (57–64 g.) is dissolved in 180 ml. of hot methanol. The resulting mixture, which is slightly cloudy, is filtered rapidly through a coarse, fluted filter paper. The filtrate is warmed to redissolve the product, and 30 ml. of water is added slowly while the solution is heated. The flask is allowed to stand overnight, then cooled to 0°. The resulting solid crystalline is collected by filtration, washed with 10 ml. of ice-cold, 4:1 (v/v) methanol–water, and air-dried, yielding 39.6–41.0 g. (60–62%) of methyl (*trans*-2-iodo-1-tetralin)carbamate, m.p. 125.5–126.5°. The IR spectrum (KBr) shows strong absorption at 3220 and 1685 cm.$^{-1}$.

2. Notes

1. The purity of the silver cyanate used seems to be critical. Best results are obtained using product prepared in the following manner. A solution of 100 g. (0.588 mole) of silver nitrate in 3 l. of distilled water is added to a solution of 49.5 g. (0.611 mole) of potassium cyanate in 700 ml. of distilled water. The white precipitate is recovered by filtration and washed successively with distilled water, methanol, and ether. The product is protected from light and air-dried overnight on a filter funnel attached to an aspirator. The product is then dried over phosphorus pentoxide under vacuum for at least 24 hours.
2. The submitters used technical grade dihydronaphthalene of 83% purity (Columbia Organic Chemicals Company, Inc.) or of 75% purity (Aldrich Chemical Company, Inc.) as indicated by GC. The checkers used the Aldrich product.

3. Discussion

The addition of iodine isocyanate to olefins is a general reaction leading stereospecifically to *trans*-β-iodoisocyanates, convertible to *trans*-β-iodocarbamates or ureas.[3] The procedure described here is essentially that of Hassner and Heathcock.[4] The method is applicable to unsaturated alcohols, esters, ketones, and dienes, but not to conjugated unsaturated esters or ketones. The effect of solvent on the rate of reaction for the addition of iodine isocyanate to cyclohexene has been studied;[5] the rate of reaction in dichloromethane was found to be much greater than that in ether. Stereochemical and regiochemical effects as well as possible rearrangements during the addition have been evaluated.[6] β-Iodocarbamates serve as useful intermediates in the synthesis of aziridines,[4,7,8] azepines,[3] 1,2-diamines,[9] carbamates,[6] oxazolidones,[10] and amino alcohols.[10]

The conversion of methyl (*trans*-2-iodo-1-tetralin)carbamate to 1,2,3,4-tetrahydronaphthalene(1,2)imine is described in *Organic Syntheses.*[8]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 967

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

Cyclohexene (110-83-8)

silver nitrate (7761-88-8)

sodium bisulfite (7631-90-5)

iodine (7553-56-2)

dichloromethane (75-09-2)

potassium cyanate (590-28-3)

dihydronaphthalene, 1,2-dihydronaphthalene

lithium (7439-93-2)

silver cyanate (3315-16-0)

lithium methoxide (865-34-9)

iodine isocyanate (3607-48-5)

1,2,3,4-Tetrahydronaphthalene(1,2)imine (1196-87-8)

phosphorus pentoxide (1314-56-3)

Methyl (trans-2-iodo-1-tetralin)carbamate, Carbamic acid, (1,2,3,4-tetrahydro-2-iodo-

1-naphthalenyl)-, methyl ester, trans- (1210-13-5)

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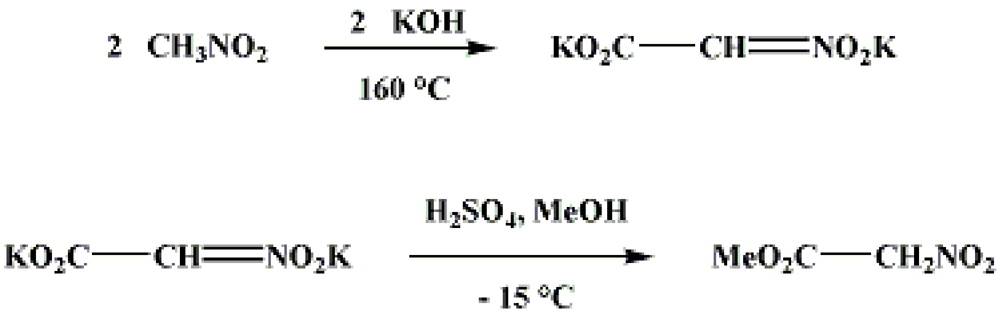
Organic Syntheses, CV 6, 797

METHYL NITROACETATE

[Acetic acid, nitro-, methyl ester]



Submitted by S. Zen, M. Koyama, and S. Koto[1].
Checked by M. Ando and G. Büchi.

1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A. *Dipotassium salt of nitroacetic acid*. A 3-l., three-necked, round-bottomed flask equipped with a sealed mechanical stirrer, a condenser fitted with a calcium chloride drying tube, and a pressure-equalizing dropping funnel is charged with a fresh solution of 224 g. of potassium hydroxide in 112 g. of water. From the dropping funnel is added, over 30 minutes (Note 1), 61 g. (1.0 mole) of nitromethane. The reaction mixture is heated to reflux for 1 hour in an oil bath maintained at approximately 160° (Note 2). After cooling to room temperature, the precipitated crystalline product is filtered, washed several times with methanol, and dried in a vacuum desiccator under reduced pressure, yielding 71.5–80.0 g. (79–88%) of the dipotassium salt of nitroacetic acid, m.p. 262° (dec.).

B. *Methyl nitroacetate*. A 2-l., three-necked, round-bottomed flask equipped with a sealed mechanical stirrer, a pressure-equalizing dropping funnel fitted with a calcium chloride drying tube, and a thermometer is charged with 70 g. (0.39 mole) of finely powdered dipotassium salt of nitroacetic acid (Note 4) and 465 ml. (11.6 moles) of methanol.

The reaction mixture is cooled to –15° ± 3° and 116 g. (1.16 moles) of concentrated sulfuric acid is added with vigorous stirring over approximately 1 hour at such a rate that the reaction temperature is maintained at –15°. The reaction mixture is allowed to warm to room temperature over a 4-hour period and stirred for another 4 hours at room temperature. The precipitate is removed by suction filtration, and the filtrate is

concentrated on a rotary evaporator at 30–40°. The residual oil is dissolved in benzene and washed with water. The organic layer is dried over anhydrous sodium sulfate, and the benzene is removed by distillation. Further distillation under reduced pressure yields 30–32 g. (66–70%) of methyl nitroacetate, b.p. 80–82° (8 mm.), 111–113° (25 mm.) (Note 5).

2. Notes

1. The reaction mixture heats to 60–80° during the addition of nitromethane. The mixture may require external heating to maintain this temperature. The initial, yellowish color begins to turn red-brown and gradually deepens as ammonia gas is liberated.
2. The reaction mixture should not be stirred mechanically during this period in order to avoid decomposition of the product.
3. This crude product is rather pure. It can and should be employed for the esterification step without further purification. Elemental analyses for $C_2HO_4NK_2$ were as follows; *calculated:* C, 13.26; H, 0.56; N, 7.73; K, 43.16%, *found:* C, 13.27; H, 0.57; N, 7.80; K, 42.68%. This is a hygroscopic crystalline powder and should be used immediately after drying. There is a report[2] regarding an explosion of the dry dipotassium salt prepared by another method. There is no evidence that this procedure produces the same unstable impurities.
4. This must be ground into a fine powder with a mortar and pestle immediately prior to use.
5. The spectral properties of the product are as follows; IR (neat) $cm.^{-1}$: 1776, 1760; ^1H NMR ($CDCl_3$), δ (multiplicity, number of protons, assignment): 3.83 (s, 3H, OCH_3), 5.20 (s, 2H, CH_2); n_D^{20} 1.4260.

3. Discussion

Methyl nitroacetate has been prepared from nitromethane *via* the dipotassium salt of nitroacetic acid by the classical Steinkopf method,[3] but in lower yield. The dipotassium salt was obtained in 45% yield. The method has been improved by Matthews and Kubler,[4] but the salt must be recrystallized prior to esterification.

This procedure[5] is an improvement in that the reaction time is reduced and the yield is improved by increasing the concentration of alkali.

The acid-catalyzed esterification has been accomplished with either hydrochloric acid[3] or sulfuric acid;[6] an improvement on the Steinkopf method has been reported,[7] but the procedure lacks the simplicity of the present method.

Application of sulfuric acid as the catalyst is considered more practical for esterification because of its higher boiling point, its incompatibility with benzene, and the stability of nitroacetic acid in the reaction mixture, which allows omission of the

final neutralization step.

The ethyl ester can also be prepared from ethyl acetoacetate (ethyl 3-oxobutanoate) by the method of Rodionov[8] as well as *via* Steinkopf's method.[3] Ethyl nitroacetate can be prepared in >70% yield[5] from the dipotassium salt, ethanol, and sulfuric acid, using anhydrous magnesium sulfate to avoid the Nef reaction.[9] The propyl and 2-propyl esters can also be obtained by this method.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 503

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

Benzene (71-43-2)

methanol (67-56-1)

sodium sulfate (7757-82-6)

potassium hydroxide (1310-58-3)

Ethyl acetoacetate, ethyl 3-oxobutanoate (141-97-9)

Nitromethane (75-52-5)

magnesium sulfate (7487-88-9)

ethyl nitroacetate (626-35-7)

Methyl nitroacetate, Acetic acid, nitro-, methyl ester (2483-57-0)

nitroacetic acid

Dipotassium salt of nitroacetic acid

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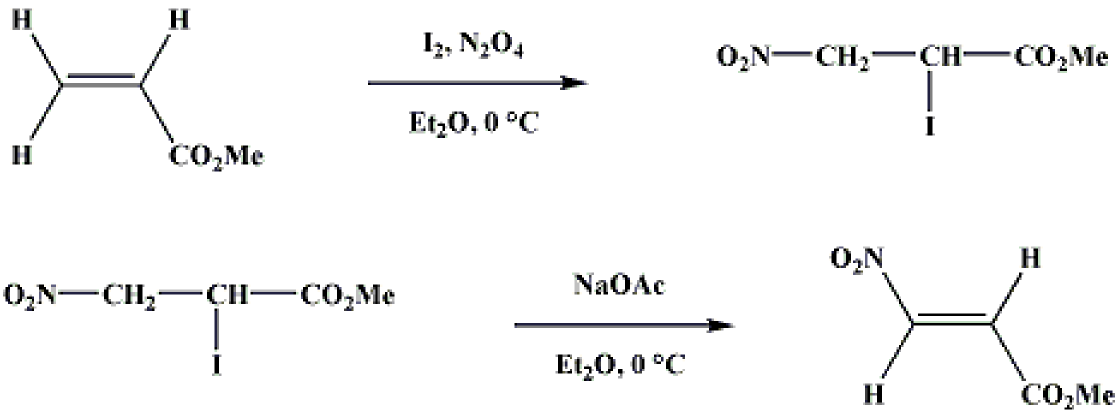
Organic Syntheses, CV 6, 799

METHYL (*E*)-3-NITROACRYLATE

[2-Propenoic acid, 3-nitro-, methyl ester (*E*)-]



Submitted by John E. McMurry[1], John H. Musser, Ian Fleming[2], J. Fortunak, and C. Nübling.
Checked by Wayland E. Noland and David D. McSherry.

1. Procedure

Caution! Part A should be carried out in an efficient fume hood to protect the operator from poisonous nitrogen dioxide vapors.

A. *Methyl 2-iodo-3-nitropropionate*. A dry, 5-l., three-necked, round-bottomed flask is fitted with a mineral oil-containing liquid-sealed mechanical stirrer, a gas-inlet tube connected to a drying tower containing 1:1 sodium hydroxide–Drierite, and an open neck that will later be connected to a rubber septum. The flask is flushed gently by passing dry nitrogen through the drying tower and gas-inlet tube as methyl acrylate (298.4 g., 331 ml., 3.47 moles) (Note 1) and anhydrous diethyl ether (2500 ml.) (Note 1) are added through the open neck. The flask is fitted with the rubber septum and then cooled to 0° by covering three-fourths of the flask with ice in a large ice bath made from a picnic cooler insulated on top with glass wool. The gas-inlet tube is removed just long enough to permit the addition of iodine (250 g., 0.98 mole) (Note 1). The mixture is stirred for about 15 minutes and then dinitrogen tetroxide (76.6 ml., 1.24 moles) (Note 1) and (Note 2) is introduced rapidly with a syringe (Note 3) through the rubber septum. The reaction solution is stirred at 0° for 30 hours. The solution is divided into three batches of about 1-l., which are cooled in a freezer to −4°. One batch at a time is removed and added to a 2-l. separatory funnel where it is washed with 80 ml. of aqueous 70% saturated sodium sulfite solution that had been precooled to −4° (Note 4). The ethereal solutions are washed alternately so that each batch is exposed to room temperature for the minimum time. The sodium sulfite washes are repeated two or three times on each batch until the color of the ethereal solution remains light yellow when kept at −4° (Note 5). The cooled ethereal solutions are then dried by washing each with precooled (to −4°) aqueous solutions containing 80 ml. of saturated sodium chloride and 15 ml. of saturated sodium sulfite. The ethereal solutions are then combined in a 4-l. Erlenmeyer flask and dried over anhydrous sodium sulfate at −4° overnight in a freezer. The dried solution is then filtered to remove the sodium sulfate, and concentrated by evaporating it in portions in a 1-l. round-bottomed flask on a rotating evaporator fitted with a cold-finger condenser containing a dry-ice bath (Note 6). The solution should be concentrated until it

contains approximately equal volumes of product and ether. The solution is then cooled to −78° for 30 minutes (Note 6) and (Note 7), causing the separation of 403.5–409 g. of ether–wet crystals. The crystals are filtered and stored in a freezer, and the filtrate is eluted through a chromatographic column containing 700 g. of silica gel (Baker Analyzed, 60–200 mesh, 7-cm. column diameter), using 30% diethyl ether/petroleum ether (b.p. 30–60°) as eluent. The solution containing the first band to be eluted, which is yellow, is evaporated on a rotating evaporator fitted with a cold finger condenser cooled with dry ice as described above. This gives a residue of 35–54.5 g. of yellowish crystals, which are a 7:3 mixture of methyl 2-iodo-3-nitropropionate and methyl (*E*)-3-nitroacrylate. The ether-wet product from the original filtration and the eluted product are combined in a 1-l. round-bottomed flask and dried at 0° under a vacuum (0.3–0.5 mm.) for 3–4 hours, giving 396–401 g. (78–79%), m.p. 32–35°, of methyl 2-iodo-3-nitropropionate containing a small amount of methyl (*E*)-3-nitroacrylate. This mixture may be used directly in the next step. The product can be recrystallized from 30% ether/petroleum ether (b.p. 30–60°) to obtain thermally unstable white plates, m.p. 33–35° (Note 8).

B. *Methyl* (E)-3-*nitroacrylate*. Anhydrous diethyl ether (2800 ml.) is placed in a dry 5-l. three-necked, round-bottomed flask fitted with a mineral-oil, liquid-sealed, mechanical stirrer and a drying tower. The contents are cooled to 0° by covering three-fourths of the flask with ice in a large ice bath made from a picnic cooler insulated on top with glass wool. Powdered anhydrous sodium acetate (95 g., 1.16 moles) (Note 9) is added to the flask, followed by methyl 2-iodo-3-nitropropionate (150 g., 0.579 mole). The flask that contained the ester is rinsed with cold anhydrous diethyl ether (200 ml.), which is then added to the 5-l. flask. The flask is stoppered and its contents are stirred vigorously at 0° for 40 hours (Note 10). The flask is then removed from the ice bath and may be kept, until needed, in a freezer for 5–7 days. The ethereal solution is then decanted and filtered to remove the sodium acetate. The residue in the flask is rinsed with three 150-ml. portions of ether; the rinse solutions are also filtered and added to the original ethereal solution. The ethereal solution is then divided into three batches (about 1-l. each), each of which is added successively to a 2-l. separatory funnel. Each batch is washed with three 80-ml. portions of aqueous 70% saturated sodium hydrogen carbonate solution, followed by one wash with 80 ml. of saturated brine. The ether solutions are then combined in a 4-l. Erlenmeyer flask and dried overnight over anhydrous sodium sulfate in a freezer at −4°. The solution is filtered to remove the drying agent and then evaporated in portions in a 1-l. round-bottomed flask on a rotating evaporator fitted with a cold-finger condenser cooled with dry ice as described in Part A. The yellow, solid residue is dissolved in a minimum of 50% diethyl ether/petroleum ether (b.p. 30–60°) and cooled to −20° for 30 minutes (Note 7). The yellow crystals are collected by filtration and washed with cold diethyl ether. The filtrate and ether wash are concentrated and cooled to −70° for 30 minutes, giving a small second crop of crystals. The combined yield of methyl (*E*)-3-nitroacrylate is 67–69 g. (88–91% from dried methyl 2-iodo-3-nitropropionate) as yellow plates, m.p. 33–35° (Note 11). *Caution! Methyl (E)-3-nitroacrylate is a potent lachrymator, like nitroolefins in general. Contact with the eyes, or accidental transfer from hands to eyes, should be avoided. If lachrymation occurs, the eyes should be washed thoroughly with water until the irritation stops.*

2. Notes

1. The submitters used the following reagents as supplied: iodine, ether, and sodium acetate from the Mallinckrodt Chemical Works; dinitrogen tetroxide from Matheson Gas Products, Inc.; and methyl acrylate from the Aldrich Chemical Company, Inc. The checkers obtained their reagents from the same sources, except that the iodine (resublimed) was obtained from Aldrich. The dinitrogen tetroxide was purchased in a lecture bottle.
2. Dinitrogen tetroxide is often contaminated with dinitrogen trioxide, giving the condensed

liquid a blue-green color. This can be oxidized by passing dry air through the condensed liquid at −10° for 1–2 hours until the characteristic amber-brown color of dinitrogen tetroxide persists.

3. Slower introduction of dinitrogen tetroxide by either dropwise addition of an ethereal solution or entrainment in a stream of nitrogen gas gives similar results. The direct injection method was found to be easiest. The syringe should be precooled in a dry-ice bath to avoid back pressure during the dinitrogen tetroxide additions.

4. The sodium sulfite solution is made by preparing a saturated solution at room temperature, cooling it to −4° and decanting it from the resulting precipitate, and diluting with cold water to 70% saturation.

5. If kept at higher temperatures, the solution will darken to red and eventually brown due to thermal decomposition with release of iodine.

6. Diethyl ether was used as the liquid phase of the slurry in the dry-ice baths.

7. The low crystallization temperatures require the use of a drying tower connected to the crystallization flask to prevent condensation of atmospheric moisture.

8. ^{1}H NMR (60 mHz, $CDCl_3$): δ 3.81 (s, 3H, OCH_3), 4.56–5.25 (m, 3H, CH_2CH).

9. The anhydrous sodium acetate (purchased from the Aldrich Chemical Company, Inc.) should be dried by heating at 135° overnight (12–16 hours), cooled in a vacuum desiccator, and then ground to a fine powder which is again dried in a vacuum desiccator for several hours.

10. The progress of the reaction can be monitored by ^{1}H NMR analysis of concentrated aliquots obtained by evaporation of the solvent and following the appearance of the vinyl signals of the product at δ 6.95 and 7.55 (Note 12) and the disappearance of the A_2B multiplet of the starting material at δ 4.56–5.25 (Note 8).

11. The progress of the reaction can be monitored by ^{1}H NMR analysis of concentrated aliquots obtained by evaporation of the solvent and following the appearance of the vinyl signals of the product at δ 6.95 and 7.55 (Note 12) and the disappearance of the A_2B multiplet of the starting material at δ 4.56–5.25 (Note 8).

12. ^{1}H NMR (60 MHz, $CDCl_3$): δ 3.8 (s, 3H, OCH_3), 6.95 (d, J = 14 hz, 1H, $=CHNO_2$-), 7.55 (d, J = 14 Hz, 1H, $=CHNO_2$): IR (CCl_4): cm.$^{-1}$ 3100 s, 3000 m, 2950 s, 2880 m (all CH), 1720 s (C=O), 1640 ms (C=C), 1530 s and 1350 s (NO_2).

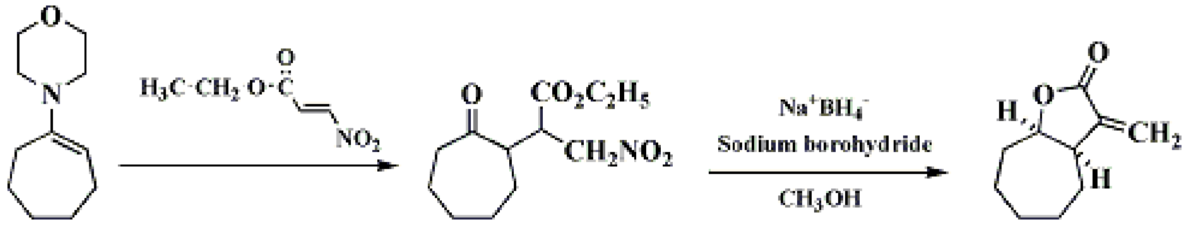
3. Discussion

This procedure for the synthesis of methyl (*E*)-3-nitroacrylate replaces the procedure for the corresponding ethyl ester given in Volume 56 of this series.[3] Both procedures were adapted from those for methyl (*E*)-3-nitroacrylate of Stevens and Emmons[4] for the addition and of Schechter, Conrad, Daulton, and Kaplan[5] for the elimination. Four major changes have been made in the procedures: (1) rapid introduction of dinitrogen tetroxide, (2) limited purification of the methyl 2-iodo-3-nitropropionate, (3) use of finely powdered anhydrous sodium acetate, and (4) carrying out the elimination at 0° for 40 hours followed by 5–7 days in a freezer. With these modifications, the preparation is reproducible and proceeds in 69–72% overall yield from iodine.

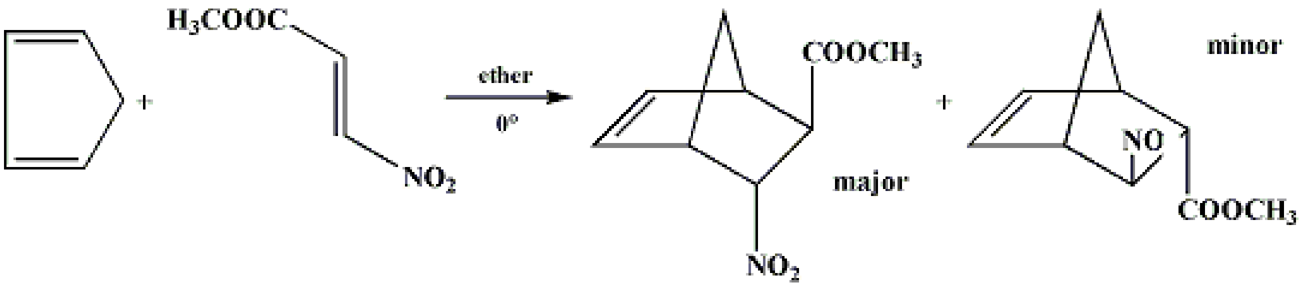
The compound has also been prepared by the reaction of methyl acrylate with dinitrogen tetroxide and oxygen in ether at 0°, followed by hydrolysis (of the 2-nitrito and 2-nitrato esters), neutralization, and distillation, in 13% overall conversion.[6] The methyl 2-hydroxy-3-nitropropionate obtained as a coproduct in 27% conversion was dehydrated by refluxing with acetyl chloride to give additional methyl (*E*)-3-nitroacrylate in 43% conversion.[6] The compound has also

been prepared by the reaction of methyl acrylate with nitrosyl chloride in ether in a sealed tube at room temperature to give methyl 2-chloro-3-nitropropionate in 32% yield, which was dehydrochlorinated with anhydrous sodium acetate in ether at –5° and +20° to methyl (*E*)-3-nitroacrylate in 37% yield.[7]

The homolog, ethyl (*E*)-3-nitroacrylate, has been shown to be an extremely reactive receptor in the Michael reaction. It has been used in the synthesis of the α-methylenebutyrolactone moiety[8] characteristic of many sesquiterpenes, as shown below.



Methyl (*E*)-3-nitroacrylate is a reactive dienophile in the Diels-Alder reaction. With cyclopentadiene it gives the corresponding adduct, methyl 6-nitro-2-norbornene-5-carboxylate, in 43% yield in refluxing benzene[9] or in quantitive yield in ether at 0°,[10] as shown below. The adduct was shown by NMR analysis to consist of an 86 : 14 mixture of *endo*- : *exo*-nitro stereoisomers, which could not be separated by crystallization.[10]



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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

dinitrogen tetroxide

brine

2-Propenoic acid, 3-nitro-, methyl ester (E)-

freezer

dinitrogen trioxide

Benzene (71-43-2)

ether, diethyl ether (60-29-7)

sodium acetate (127-09-3)

sodium sulfite (7757-83-7)

acetyl chloride (75-36-5)

sodium hydrogen carbonate (144-55-8)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

oxygen (7782-44-7)

nitrogen (7727-37-9)

iodine (7553-56-2)

nitrogen dioxide, exo-nitro (10102-44-0)

nitrosyl chloride (2696-92-6)

methyl acrylate (96-33-3)

vinyl (2669-89-8)

CYCLOPENTADIENE (542-92-7)

Methyl 2-iodo-3-nitropropionate

methyl 2-hydroxy-3-nitropropionate

methyl 2-chloro-3-nitropropionate

α-methylenebutyrolactone (547-65-9)

methyl 6-nitro-2-norbornene-5-carboxylate

METHYL (E)-3-NITROACRYLATE (52745-92-3)

ethyl (E)-3-nitroacrylate

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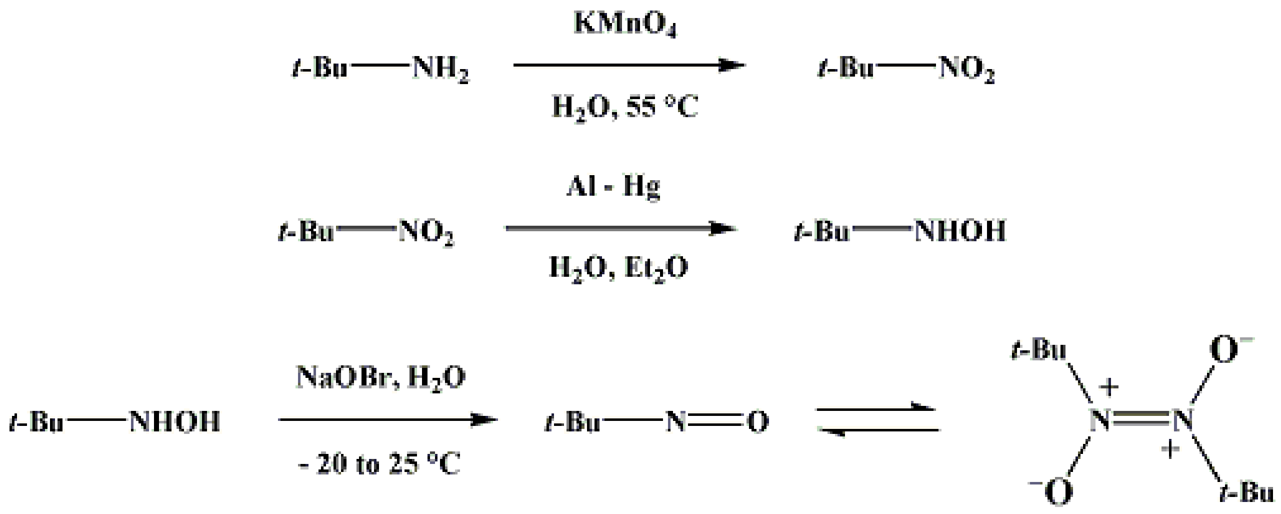
Organic Syntheses, CV 6, 803

2-METHYL-2-NITROSOPROPANE AND ITS DIMER

[Propane, 2-methyl 2-nitroso-]



Submitted by A. Calder, A. R. Forrester[1], and S. P. Hepburn.
Checked by David S. Crumrine and Herbert O. House.

1. Procedure

A. 2-*Methyl-2-nitropropane*. To a well-stirred suspension of 650 g. (4.11 moles) of potassium permanganate in 3 l. of water, contained in a 5-l., three-necked flask fitted with a reflux condenser, a mechanical stirrer, a thermometer, and a 250-ml. dropping funnel, is added, dropwise and with stirring over a 10- minute period, 100 g. (1.37 moles) of *tert*-butylamine (Note 1). When the addition is complete, the reaction mixture is heated to 55° over a period of approximately 2 hours, and maintained at 55° with continuous stirring for 3 hours. The dropping funnel and reflux condenser are replaced with a stopper and a still head fitted for steam distillation, and the product is steam distilled from the reaction mixture (Note 2). The liquid product is separated from the denser water layer, diluted with 250 ml. of diethyl ether, and washed successively with two 50-ml. portions of 2 *M* hydrochloric acid and 50 ml. of water. After the ethereal solution has been dried over anhydrous magnesium sulfate, the solution is fractionally distilled at atmospheric pressure, removing the ether. The residual crude product (Note 3) totals 106–128 g. and is sufficiently pure for use in the next step. In a typical run, distillation of 124 g. of the crude product affords 110 g. (78%) of the pure 2-methyl-2-nitropropane as a colorless liquid, b.p. 127–128°, n_D^{25} 1.3992, which slowly solidifies on standing to a waxy solid, m.p. 25–26° (Note 4).

B. N-tert-*Butylhydroxylamine*. *Caution! Since hydrogen may be liberated during the reduction with aluminum amalgam, the reaction should be conducted in a hood. Also, the aluminum amalgam may be pyrophoric. Consequently, it should be used immediately and not allowed to become dry.*

Aluminum foil (30 g. or 1.1 g.-atoms, thickness 0.002–0.003 cm.) is cut into strips 5 × 25

cm., and each strip is rolled into a cylinder about 1 cm. in diameter. Each of the aluminum foil cylinders is amalgamated by immersing it in a solution of 8.0 g. (0.030 mole) of mercury (II) chloride in 400 ml. of water for 15 seconds. Each amalgamated cylinder is then rinsed successively in ethanol and ether, and added to a mixture of 1.5 l. of ether and 15 ml. of water (Note 5) contained in a 3-l., three-necked flask fitted with a dropping funnel, a mechanical stirrer, and two efficient reflux condensers in series. The reaction mixture is stirred vigorously, and 60 g. (0.58 mole) of 2-methyl-2-nitropropane is added dropwise at a rate such that the ether refluxes briskly. The reaction usually exhibits a 5- to 7-minute induction period, after which a vigorous reaction occurs and cooling with an ice bath is necessary. After addition of the nitro compound is complete, the reaction mixture is stirred for an additional 30 minutes. The stirrer is then stopped and the gelatinous precipitate is allowed to settle. The colorless reaction solution is decanted through a glass wool plug into a 2-l. separatory funnel and washed with two 250-ml. portions of 2 *M* aqueous sodium hydroxide (Note 6). The precipitate in the reaction flask is washed with two 500-ml. portions of ether, and these washings are combined and washed with the aqueous sodium hydroxide solution (Note 6). The combined ethereal solutions are dried over anhydrous sodium sulfate and concentrated with a rotary evaporator. The residual crystalline solid is dried under reduced pressure (10–15 mm.) at room temperature, leaving 33.7–38.7 g. (65–75%) of the crude hydroxylamine product, m.p. 59–60°, which is sufficiently pure for use in the next step. The crude product may be recrystallized from pentane, yielding the pure *N*-*tert*-butylhydroxylamine as white plates, m.p. 64–65° (Note 7).

C. 2-*Methyl*-2-*nitrosopropane*. A solution of sodium hypobromite is prepared by adding, dropwise and with stirring over a 5-minute period, 57.5 g. (18.5 ml., 0.360 mole) of bromine to a solution of 36.0 g. (0.900 mole) of sodium hydroxide in 225 ml. of water. The resulting yellow solution, contained in a 1-l., three-necked flask fitted with a mechanical stirrer, a thermometer, and an acetone–dry ice cooling bath, is cooled to –20°. A suspension of 26.7 g. (0.300 mole) of *N*-*tert*-butylhydroxylamine in 50 ml. of water is added to the reaction flask, with continuous stirring, as rapidly as possible without allowing the temperature of the reaction mixture to exceed 0°. The reaction solution is again cooled to –20° before the cooling bath is removed and the mixture is stirred for 4 hours while the reaction mixture warms to room temperature. The solid product, the nitroso dimer which has separated, is collected on a sintered glass funnel, pulverized, and washed with 1 l. of water (Note 8). The residual solid is dried at room temperature under reduced pressure (10–15 mm.), leaving 19.6–22.2 g. (75–85%) of the 2-methyl-2-nitrosopropane dimer, m.p. 80–81° (Note 9). The product is sufficiently pure to be stored (Note 10) for use as a free radical trapping reagent.

2. Notes

1. *tert*-Butylamine, purchased from Aldrich Chemical Company, Inc., may be used without purification.
2. Approximately 1 l. of distillate needs to be collected to remove the product from the reaction mixture.
3. The principal contaminant is residual ether.
4. The purified product exhibits IR bands (CCl_4) at 1545 cm.$^{-1}$ (broad) and 1355 cm.$^{-1}$ (NO_2) with a UV maximum (95% C_2H_5OH) at 279 nm (ε 24) and a ^{1}H NMR (CCl_4) singlet at δ 1.58 [$(CH_3)_3C$]. The mass spectrum has the following abundant

fragment peaks: *m/e* (rel. int.), 57 (100), 41 (74), 39 (45), and 29 (57).
5. Since water is one of the reactants in this reduction, it is necessary that at least a stoichiometric quantity of water is present.
6. Since the hydroxylamine product is readily oxidized by air to the blue nitroso compound, these manipulations should be performed rapidly to minimize exposure of the product to atmospheric oxygen. Any nitroso compound formed at this stage will co-distil with the ether and is difficult to recover.
7. The product has IR absorption (CCl_4) at 3600 cm.$^{-1}$ and 3250 (broad) cm.$^{-1}$ (OH and NH) with ^{1}H NMR (CCl_4) singlets at δ 1.09 [9H, C(C*H*$_3$)] and 5.86 (2H, N*H* and O*H*). The mass spectrum has the following abundant peaks: *m/e* (rel. int.), 89 (M^+, 11), 74 (96), 58 (41), 57 (100), 56 (52), 42 (41), 41 (74), 39 (34), 29 (54), and 28 (39).
8. Thorough washing to remove the last traces of alkali is essential, or the nitroso dimer will decompose to volatile products on standing.
9. When the colorless nitroso dimer is dissolved in various solvents, it partially dissociates, forming a blue solution which contains an equilibrium mixture of monomer and dimer. In C_6D_6 and CCl_4, the ^{1}H NMR spectrum of the initial solutions of dimer changes rapidly and equilibrium is established within 20–30 minutes. From ^{1}H NMR measurements at about 40° the equilibrium mixtures in CCl_4 and C_6D_6 contain 80–81% of the monomer;[2] the ^{1}H NMR singlets attributable to *tert*-butyl groups are observed at δ 1.24 (monomer) and 1.57 (dimer) in CCl_4 and at δ 0.97 (monomer) and 1.49 (dimer) in C_6D_6. The IR spectrum of the equilibrated mixture (CCl_4) exhibits absorption at 1565 cm.$^{-1}$ attributable to the N=O group of the monomer; this peak is not observed in the IR spectrum (KBr) of the dimer. The mass spectrum of the product exhibits the following abundant fragment peaks: *m/e* (rel. int.), 72 (10), 57 (100), 56 (23), 55 (21), 42 (22), 41 (97), 39 (55), 30 (49), 29 (74), and 28 (53). A water solution of the dimer initially is colorless and exhibits a UV maximum at 287 nm (ε 8000). On standing, the solution slowly turns blue. A solution of the dimer in C_2H_5OH, after standing for 20–30 minutes, exhibits maxima at 292 nm (ε 682 dimer) and 686 nm (ε 14.5 monomer).
10. The submitters report that if the product is stored at 0° in the dark, it may be kept indefinitely.

3. Discussion

The oxidation of *tert*-butylamine to 2-methyl-2-nitropropane is an example of a procedure previously illustrated in *Org. Synth.*[3] *N*-*tert*-Butylhydroxylamine has previously been prepared by acid-catalyzed hydrolysis of 2-*tert*-butyl-3-phenyloxazirane[4] and by oxidation of *tert*-butylamine.[5] The procedure described here is based on a method mentioned briefly by Smith and co-workers.[6] 2-Methyl-2-nitrosopropane has been prepared directly by oxidation of *tert*-butylamine,[2,5] but is usually obtained by oxidation of the hydroxylamine.[7] 2-Methyl-2-nitrosopropane has also been prepared by electrolytic reduction[8] or by zinc dust reduction[9] of 2-methyl-2-nitropropane.

2-Methyl-2-nitrosopropane is an excellent scavenger of free radicals and is now widely used in "spin trapping" experiments[10,11] (although it has certain disadvantages).[12] In this

technique, a reactive radical is trapped by the nitroso compound and identified by analysis of the e.s.r. spectrum of the so-formed stable nitroxide radical. The perdeuterated derivative of 2-methyl-2-nitrosopropane has also been recommended for this purpose.[13] *tert*-Butylhydroxylamine, an intermediate in the present procedure, may also be used to synthesize *tert*-butylphenylnitrone which has been used as a "spin-trapping" reagent.[11] The reaction of 2-methyl-2-nitrosopropane with aryl Grignard reagents has been used to prepare *N*-aryl-*N*-*tert*-butylhydroxylamines.[14]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ether, diethyl ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

potassium permanganate (7722-64-7)

bromine (7726-95-6)

sodium sulfate (7757-82-6)

oxygen (7782-44-7)

aluminum (7429-90-5)

zinc (7440-66-6)

mercury(II) chloride (7487-94-7)

Pentane (109-66-0)

sodium hypobromite

magnesium sulfate (7487-88-9)

2-Methyl-2-nitropropane (594-70-7)

2-Methyl-2-nitrosopropane, Propane, 2-methyl 2-nitroso- (6841-96-9)

tert-Butylamine (75-64-9)

N-tert-Butylhydroxylamine, tert-Butylhydroxylamine (16649-50-6)

2-tert-Butyl-3-phenyloxazirane (7731-34-2)

tert-butylphenylnitrone

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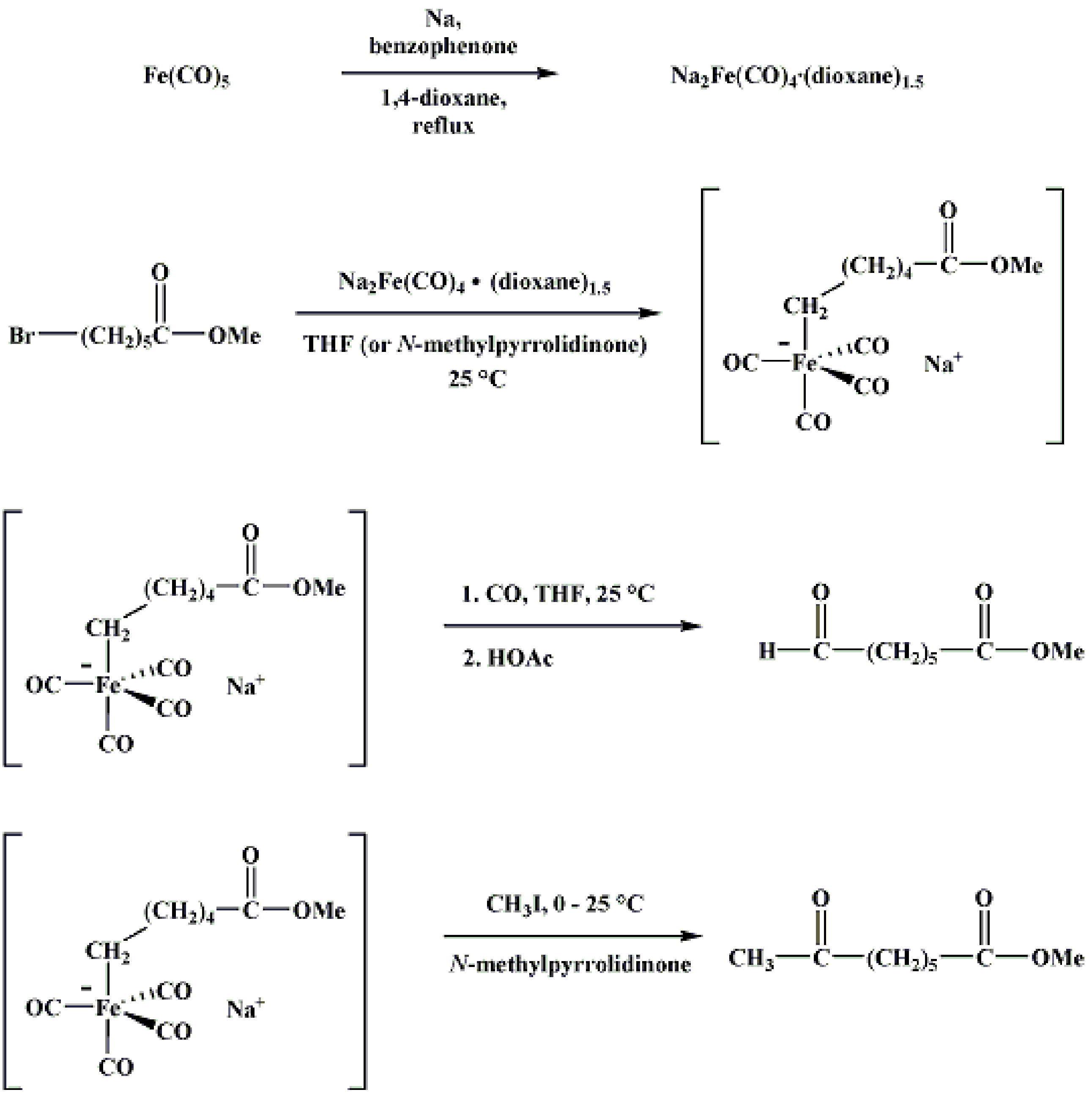
Organic Syntheses, CV 6, 807

NUCLEOPHILIC ACYLATION WITH DISODIUM TETRACARBONYLFERRATE: METHYL 7-OXOHEPTANOATE AND METHYL 7-OXOÖCTANOATE

[Octanoic acid, 7-oxo-, methyl ester]



Submitted by Richard G. Finke[1,2] and Thomas N. Sorrell[13].
Checked by Richard T. Taylor and Martin F. Semmelhack.

1. Procedure

Caution! Iron pentacarbonyl and carbon monoxide are highly toxic; consequently all parts of this procedure should be carried out in a well-ventilated hood. Iron pentacarbonyl is easily recognized by its musty odor. Since disodium tetracarbonylferrate is very pyrophoric, the reagent must be

kept under a dry inert atmosphere at all times.

Methyl iodide, in high concentrations for short periods and in low concentrations for long periods, can cause serious toxic effects in the central nervous system. Accordingly, the American Conference of Governmental Industrial Hygienists[4] has set 5 p.p.m., a level which cannot be detected by smell, as the highest average concentration in air to which workers should be exposed for long periods. The preparation and use of methyl iodide should always be performed in a well-ventilated fume hood. Since the liquid can be absorbed through the skin, care should be taken to prevent contact.

A. *Disodium tetracarbonylferrate sesquidioxanate* (Note 1). A dry, 2-l., three-necked, round-bottomed flask is equipped with a mechanical stirrer (Note 2), a three-way stopcock with one branch connected to a nitrogen source, and a Y-shaped adapter fitted with a reflux condenser vented through an oil bubbler and a pressure-equalizing dropping funnel capped by a rubber septum. The apparatus is flushed with nitrogen (Note 3) for 15 minutes and charged with 600 ml. of dry, deoxygenated dioxane (Note 4) and (Note 5), 10.6 g. (0.461 g.-atoms) of sodium, and 9.1 g. (0.050 mole) of benzophenone. The solution is stirred vigorously and heated under reflux with a heating mantle until the deep blue color of the benzophenone ketyl appears. With a gas-tight syringe, 45.3 g. (29.8 ml., 0.231 mole) of iron pentacarbonyl (Note 6) is injected into the dropping funnel. The blue solution is then titrated to a white or slightly yellow end point by adding iron pentacarbonyl to the refluxing solution over 2.5 hours (Note 7). The suspension is heated at reflux for another 45 minutes, then cooled to room temperature. Precipitation of the disodium tetracarbonylferrate sesquidioxanate as a white powder is completed by adding 600 ml. of dry, deoxygenated hexane (Note 5) and (Note 8). The Y-shaped adapter and the mechanical stirrer are removed under a rapid stream of nitrogen and quickly replaced with a tight-fitting rubber septum and a gas-dispersion tube with a fritted-glass tip (see f.htmigure 1). The solvent is forced up the gas-dispersion tube and out of the flask with nitrogen pressure (Note 9). The product is washed in the flask with two 400-ml. portions of hexane added *via* a cannula (Note 5), and the supernatant solvent is removed with nitrogen pressure in the same manner. The disodium tetracarbonylferrate sesquidioxanate is used directly in Parts B and C without drying or weighing (Note 10).

Figure 1.

Figure 1.

B. *Methyl 7-oxoheptanoate*. In the same three-necked, round-bottomed flask containing 72–78 g. (0.21–0.23 mole) of disodium tetracarbonylferrate sesquidioxanate, the gas-dispersion tube is replaced with a mechanical stirrer, and 1.5 l. of dry, deoxygenated tetrahydrofuran (Note 11) is added. The light tan suspension is stirred vigorously as 41.8 g. (0.200 mole) of methyl 6-bromohexanoate (Note 12) is added in one portion by syringe. The nitrogen is flushed from the flask with carbon monoxide (Note 13) and (Note 14) admitted through the other branch of the three-way stopcock, and the suspension is stirred under 10 p.s.i. of carbon monoxide for at least 14 hours, during which time the solid dissolves. A rapid flow of nitrogen is swept through the flask while the septum is removed and replaced quickly with a pressure-equalizing dropping funnel. The dropping funnel is flushed with nitrogen and charged with 50 ml. of glacial acetic acid, added dropwise to the orange solution (Note 15). Stirring is continued for 20 minutes, after which the deep red solution is concentrated to a volume of *ca.* 400 ml. with a rotary evaporator in the hood *(Caution! Some iron pentacarbonyl is present)* and poured into 2 l. of water. The mixture is extracted with four 400-ml. portions of diethyl ether, and the combined organic solutions are washed with 400 ml. of water. The

ethereal solution is mixed with 400 ml. of 2 *M* hydrochloric acid, and 68 g. of iron(III) chloride is added in small portions until carbon monoxide evolution subsides and the organic layer becomes green from triiron dodecacarbonyl. The organic layer is washed with successive 400-ml. portions of 2 *M* hydrochloric acid, water, saturated sodium hydrogen carbonate, and saturated sodium chloride. After being dried over anhydrous sodium sulfate, the ethereal solution is concentrated to a green oil with a rotary evaporator. Iron-containing by-products such as triiron dodecacarbonyl and iron pentacarbonyl are removed by rapid chromatography on a 7 × 40 cm. column prepared in hexane with 400 g. of silica gel (Note 16). The green triiron dodecacarbonyl is first eluted with *ca.* 3 l. of hexane before the product is eluted with 3 l. of 2:1 (v/v) ether–hexane. The ether–hexane eluate is dried over anhydrous magnesium sulfate and evaporated. Distillation of the residual oil through a 15-cm. Vigreux column at reduced pressure affords a small forerun of 1 ml. or less and 17.9–20.0 g. (57–63%) of methyl 7-oxoheptanoate, b.p. 65–80° (0.1 mm.), n_D^{20} 1.4388 (Note 17).

C. *Methyl 7-oxoöctanoate*. The 2-l., three-necked, round-bottomed flask containing 72–78 g. (0.21–0.23 mole) of disodium tetracarbonylferrate from Part A is flushed rapidly with nitrogen while the gas-dispersion tube is removed, a magnetic stirring bar is placed inside, and a pressure-equalizing dropping funnel is attached. The other branch of the three-way stopcock is connected to a bubbler, the dropping funnel is capped with a rubber septum, and 600 ml. of dry, deoxygenated *N*-methylpyrrolidinone (Note 5) and (Note 18) is added. The suspension is stirred and maintained under a static nitrogen atmosphere as 41.8 g. (0.200 mole) of methyl 6-bromohexanoate (Note 12) is injected into the dropping funnel with a gas-tight syringe and added dropwise into the flask. The resulting solution (Note 19) is stirred for 30 minutes at room temperature and cooled in an ice bath before 64 g. (28 ml., 0.45 mole) of methyl iodide is added over 20 minutes. The ice bath is removed, and stirring is continued for 20–40 hours (Note 14). The dark-red mixture is poured into 3 l. of saturated aqueous sodium chloride and extracted with three 400-ml. portions of ether and one 400-ml. portion of hexane. The combined organic solutions are washed with one 400-ml. portion of water and one 400-ml. portion of saturated sodium chloride. After 400 ml. of 2 *M* hydrochloric acid is added, the iron by-products are oxidized with iron(III) chloride exactly as described in Part B. The ethereal solution is evaporated under reduced pressure, the residual oil is applied to a column of silica gel packed in hexane, and the organic product is separated from the iron by-products by chromatography as described in Part B. The ether–hexane eluate is dried over anhydrous magnesium sulfate, the solvent is evaporated, and the remaining liquid is distilled at reduced pressure, giving 24.0–24.8 g. (70–72%) of methyl 7-oxoöctanoate, b.p. 112–127° (10 mm.), n_D^{20} 1.4360 (Note 20).

2. Notes

1. Approximately 4.5 hours are required to complete Part A.
2. A mechanical stirrer is necessary on any scale owing to the formation of a thick slurry toward the end of the reaction.
3. The submitters passed the nitrogen through *ca.* 100 g. of BASF catalyst R3-11 contained in a metal tube and heated at 160°, to remove oxygen, and through a column of Linde type 3A molecular sieves, to remove water. The catalyst (catalog number 18-3000-00) and pertinent literature were obtained from Chemical Dynamics Corporation, P.O. Box 395, South Plainfield, New Jersey 07080. The checkers used "prepurified" nitrogen and argon in separate runs without additional drying or oxygen scavenging.
4. Dioxane was heated at reflux with sodium overnight under nitrogen, benzophenone was added, and the solvent was distilled after appearance of the deep-blue color of the benzophenone ketyl.
5. The submitters recommend that the solvent be distilled under nitrogen into a two-necked receiving flask fitted with a three-way stopcock. The receiving flask is separated from the

distillation apparatus under a rapid nitrogen flow and fitted quickly with a rubber septum. The solvent is then transferred to the reaction vessel by needlestock techniques[5] as follows: A stainless-steel cannula with a 2-mm. inside diameter and both ends sharpened is inserted through the septum into the receiving flask above the surface of the liquid, and a stream of nitrogen is passed briefly through the stopcock and out the cannula, removing air. The other end of the cannula is then inserted through the septum on the reaction vessel, the end of the cannula in the receiver is pushed below the surface of the liquid, and the solvent is forced into the reaction vessel with nitrogen pressure.

6. Iron pentacarbonyl was purchased from PCR, Inc., Gainesville, Florida, and stored under nitrogen.

7. Approximately 95% of the iron pentacarbonyl is added within 2 hours, and the remaining 5% is then added dropwise over the next 30 minutes. The blue color should never be completely discharged prior to the end point, particularly toward the end of the reaction, since the remaining solution may be deactivated. Avoiding premature discharge of the blue color is especially important in small-scale preparations. At the end point 1 ml. or less of the iron pentacarbonyl remains in the dropping funnel. The checkers carried out the reaction on a smaller scale in two runs, adding 13.1 g. (8.62 ml., 0.0669 mole) of iron pentacarbonyl as a solution in 50 ml. of dry dioxane.

8. Reagent grade hexane was dried and deoxygenated by distillation from calcium hydride under nitrogen.

9. Alternatively, 300–400 ml. of the dioxane may be transferred by this method into another flask before the hexane is added. The recovered dioxane may then be used in another preparation without purification.

10. The yield is typically 72–78 g. (90–100%). An excess of the reagent is not detrimental to the procedures in Parts B and C. The submitters have doubled the scale of this procedure with no change in the yield. For smaller-scale reactions the submitters recommend that the reagent be purchased from Alfa Division, Ventron Corporation. The checkers used the commercially available reagent successfully in one run, the material having been transferred to the reaction vessel in a dry box.

11. Tetrahydrofuran was dried and deoxygenated by distillation from calcium hydride under nitrogen.

12. 6-Bromohexanoic acid was purchased from Aldrich Chemical Company, Inc., and esterified with sulfuric acid and methanol. Methyl 6-bromohexanoate was obtained as a colorless liquid, b.p. 92–94° (5 mm.), n_D^{20} 1.4510, judged to be greater than 99% pure according to GC analysis on dimethylsilicone (OV-101) as liquid phase.

13. A cylinder of carbon monoxide equipped with a suitable regulator calibrated in pounds per square inch (p.s.i.) is connected to the three-way stopcock. All joints and the septum must be secured with clamps or wire. A vertical tube containing mercury was connected to an exit tube from the reaction flask by the checkers. A pressure of carbon monoxide was maintained against a 500-mm. column of mercury.

14. Alkyl tetracarbonyl iron(0) reagents in solution decompose more rapidly with increasing concentration and temperature, especially above 0°. Carbon monoxide must be added without delay to convert this intermediate to the more stable acyl iron compound.

15. Subsequent operations may be conducted in air. However, the procedure should not be interrupted until the ethereal solution is drying over sodium sulfate.

16. Silica gel of mesh 60–200 was supplied by Davison Chemical Division, W. R. Grace and Company, Baltimore, Maryland, and dried at 70° before use. The flow rate of hexane during the chromatography was 4 l. per hour.

17. The checkers obtained 13.6 g. (43%) of product, b.p. 65–75° (0.1 mm.). The submitters determined the purity of the product to be greater than 90% by GC using 10% dimethylsilicone (OV-101) as liquid phase at 200°. The ^{1}H NMR spectrum ($CDCl_3$) shows

absorptions at δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 1.48 (m, 6H, 3CH_2), 2.32 (t, 2H, C$H_2CO_2CH_3$), 2.40 (t of d, *J* = 2 and 8, 2H, CH_2CH=O), 3.65 (s, 3H, CO_2CH_3), 9.62 (t, *J* = 2, 1H, C*H*=O).

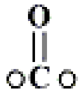
18. *N*-Methylpyrrolidinone was heated at reflux over calcium hydride under reduced pressure for at least 24 hours by the submitters, then distilled from the calcium hydride under reduced pressure. The checkers stirred the solvent in the presence of calcium hydride at 100° for 48 hours prior to distillation at 150 mm.

19. The homogeneous solution, if free of impurities, is bright yellow. Usually, however, the color is dark red or orange, evidently owing to the presence of trace amounts of impurities.

20. Starting with 13.1 g. (8.62 ml., 0.0669 mole) of iron pentacarbonyl, the checkers obtained 7.3–7.4 g. (71–75%) of product, b.p. 92–95° (2 mm.) A GC analysis by the submitters using dimethylsilicone (OV-101) as liquid phase at 200° showed the purity of the product to be greater than 95%. The spectral properties of the product are as follows: IR (thin film) cm.$^{-1}$: 1735 (ester C=O), 1715 (ketone C=O); ^{1}H NMR ($CDCl_3$), δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 1.46 (m, 6H, 3CH_2), 2.12 (s, 3H, CH_2COCH_3), 2.32 (t, *J* = 8, 2H, C$H_2CO_2CH_3$), 2.44 (t, *J* = 8, 2H, CH_2COCH_3), 3.67 (s, 3H, CO_2CH_3).

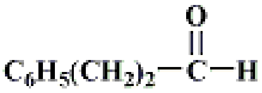
3. Discussion

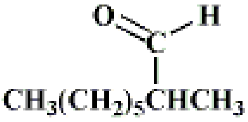
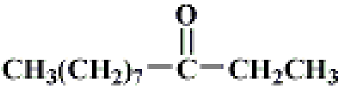
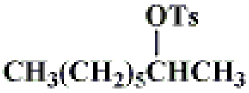
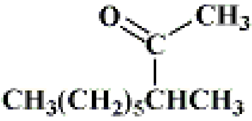
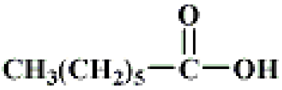
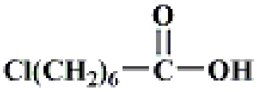
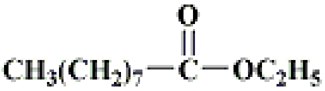
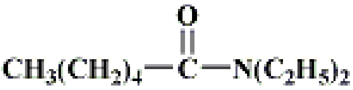
This procedure describes the preparation of disodium tetracarbonylferrate sesquidioxanate by reduction of iron pentacarbonyl with sodium and the use of the reagent for nucleophilic formylation and acylation of the primary bromide, methyl 6-bromohexanoate. Disodium tetracarbonylferrate serves as a synthetic equivalent of carbon monoxide dianion,



, in most preparations. Thus, the reagent reacts with alkyl halides and *p*-toluenesulfonates, forming anionic alkyltetracarbonyl iron(0) complexes which combine in a second step with various electrophiles, giving carbonyl compounds.[6] The reagent donates the new carbonyl carbon, which becomes bonded to both the alkyl group and the electrophile in the final product. If the electrophile is a proton from acetic acid or an alkyl group from a second alkyl halide, the overall transformations amount to nucleophilic formylation[6] and acylation,[7] respectively. The preparation of carboxylic acids, esters, and amides by formal nucleophilic carboxylation is accomplished by use of oxygen and water (or sodium hypochlorite and water), iodine and alcohols, and iodine and amines, respectively, as the electrophiles.[8] The general reactions are summarized by the following equations and several specific examples[7,8,9] are presented in Table I.

TABLE I
NUCLEOPHILIC ACYLATION AND CARBOXYLATION OF ALKYL HALIDES AND *p*-TOLUENESULFONATES WITH DISODIUM TETRACARBONYLFERRATE[7,8,9]

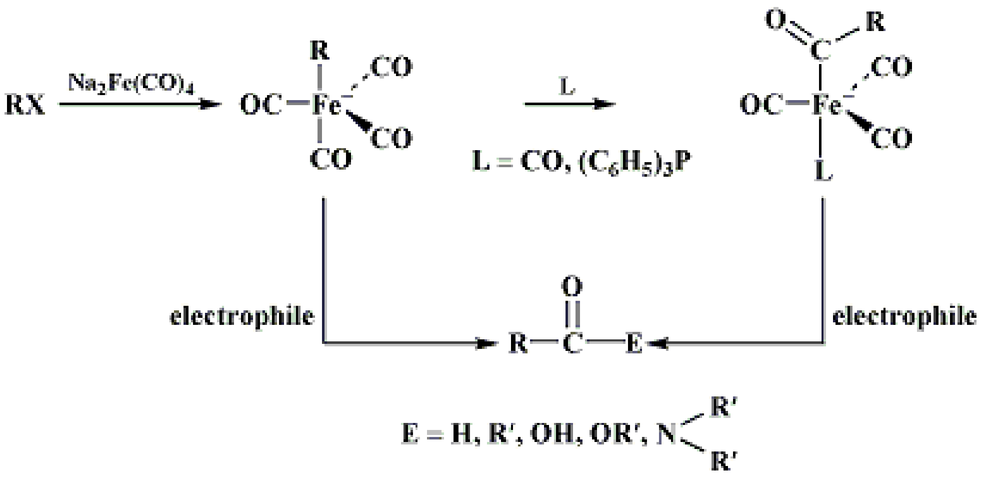
Alkyl Halide or *p*-Toluenesulfonate[a]	Electrophile	Product	Yield (%)
$C_6H_5(CH_2)_2Br$	CH_3CO_2H		86[b]

$(CH_3)_2C{=}CH(CH_2)_2Br$	CH_3CO_2H		81[b]
	CH_3CO_2H		50[b,c]
$CH_3(CH_2)_7Br$	CH_3CH_2I		80
	CH_3I		79
$CH_3(CH_2)_5Br$	O_2,H_2O		82
$Cl(CH_2)_6Br$	O_2, H_2O		84
$CH_3(CH_2)_7Br$	I_2, C_2H_5OH		84
$CH_3(CH_2)_4Br$	I_2, $(C_2H_5)_2NH$		80[b]

[a]The structural abbreviation Ts is used for *p*-toluenesulfonate.

[b]Yield determined by GC.

[c]Isomeric octenes identified as by-products.



The initial reaction between the alkyl halide (or *p*-toluenesulfonate) and disodium tetracarbonylferrate behaves as a typical S_N2-type substitution.[6,10] Thus, this step proceeds smoothly with primary and secondary reactants, but the tertiary analogs fail owing to elimination. Allylic substrates are also incompatible, since these undergo elimination, forming stable iron tricarbonyl-1,3-diene complexes. The initial substitution with secondary *p*-toluenesulfonates occurs more efficiently than with the corresponding halides, and the stereochemistry results from clean inversion. The solvents used are generally either tetrahydrofuran or *N*-methylpyrrolidinone, the reactions being as much as 10^4 times faster in the latter. The initially formed alkyl iron intermediate rearranges to an acyl iron complex either prior to or during the subsequent reaction with the electrophile.[6,7,8,9,11] The presence of carbon monoxide or triphenylphosphine enhances the rate of rearrangement to the more stable acyl iron intermediate. The reactions show high selectivity and are compatible with functional groups such as chloro, cyano, and esters. The reagent reacts with acid chlorides, forming the acyl iron complexes directly, which may then be hydrolyzed to aldehydes or utilized for nucleophilic acylation.

Methyl 7-oxoheptanoate has previously been synthesized from cycloheptanone in two steps with a 42% overall yield.[12] 7-Oxoöctanoic acid, the methyl ester of which is the product of Part C, has been prepared by base-induced ring cleavage of 2-acetylcyclohexanone.[13]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

H_2O

Disodium tetracarbonylferrate sesquidioxanate

DISODIUM TETRACARBONYLFERRATE

triiron dodecacarbonyl

dimethylsilicone

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

carbon monoxide (630-08-0)

sodium hydrogen carbonate (144-55-8)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

oxygen (7782-44-7)

nitrogen (7727-37-9)

6-Bromohexanoic acid (4224-70-8)

mercury (7439-97-6)

iodine (7553-56-2)

Benzophenone (119-61-9)

sodium (13966-32-0)

iron(III) chloride (7705-08-0)

Methyl iodide (74-88-4)

sodium hypochlorite (7681-52-9)

magnesium sulfate (7487-88-9)

dioxane (5703-46-8)

Tetrahydrofuran (109-99-9)

hexane (110-54-3)

Cycloheptanone (502-42-1)

calcium hydride (7789-78-8)

iron pentacarbonyl

triphenylphosphine (603-35-0)

argon (7440-37-1)

N-methylpyrrolidinone (872-50-4)

2-acetylcyclohexanone (874-23-7)

Methyl 7-oxoheptanoate (35376-00-2)

Octanoic acid, 7-oxo-, methyl ester, Methyl 7-oxooctanoate (16493-42-8)

methyl 6-bromohexanoate

p-toluenesulfonate

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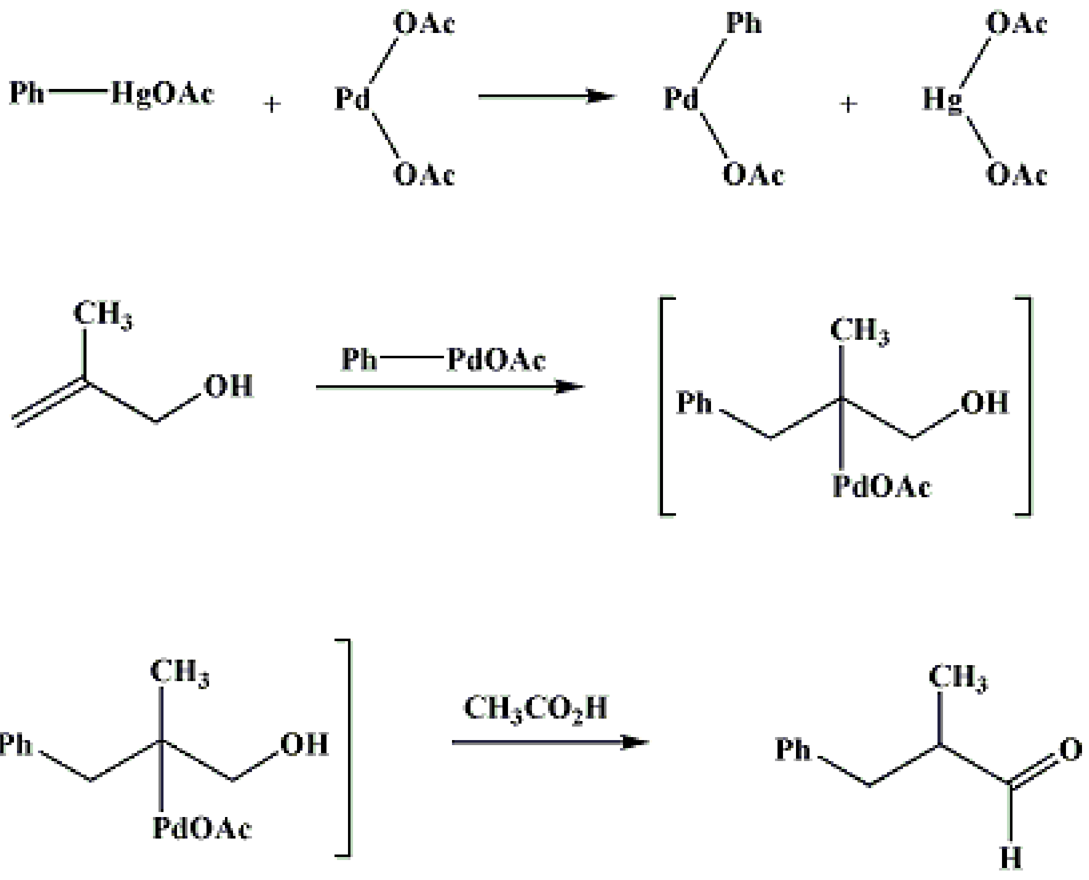
Organic Syntheses, CV 6, 815

ALDEHYDES FROM ALLYLIC ALCOHOLS AND PHENYLPALLADIUM ACETATE: 2-METHYL-3-PHENYLPROPIONALDEHYDE

[Benzenepropanal, α-methyl-]



Submitted by R. F. Heck[1]
Checked by Robert A. Clement and Richard E. Benson.

1. Procedure

A slurry comprised of 33.6 g. (0.0998 mole) of commercial phenylmercury(II) acetate, 200 ml. of acetonitrile, and 14.4 g. (16.8 ml., 0.200 mole) of methallyl alcohol (Note 1) is prepared in a 500-ml., three-necked flask fitted with a mechanical stirrer, a condenser, and a thermometer. The slurry is stirred and cooled in an ice bath, and 22.4 g. (0.0998 mole) of powdered palladium(II) acetate (Note 2) is added over 1 minute. Stirring is continued with cooling for 1 hour, then at room temperature for 3 more hours (Note 3). The temperature of the reaction mixture reaches a maximum of 27° after removal of the ice bath.

The black reaction mixture is diluted with about 100 ml. of diethyl ether and poured onto 200 g. of ether-wet alumina (Woelm, Activity Grade 1) in a 45 × 2.5 cm. glass

chromatographic column. The product is washed through the alumina with about 1 l. of ether. The brown eluate is concentrated by distilling the ether through a 45-cm. Vigreux column on a steam bath at atmospheric pressure. When the ether has been distilled, a slight vacuum is applied, removing most of the acetonitrile. After the volume reaches about 50 ml., the mixture is filtered into a 100-ml. distillation flask, removing some precipitated palladium metal. The flask is rinsed with 10-ml. of ether, and the rinse is combined with the product. The flask is equipped with a 10 cm. Vigreux column for distillation at reduced pressure. After removal of the solvent, 8.1–8.5 g. (55–58%) of 2-methyl-3-phenylpropionaldehyde is collected, b.p. 75–85° (3 mm.) (Note 4), n_D^{25} 1.5113 (Note 5).

2. Notes

1. Methallyl alcohol was obtained from Eastman Organic Chemicals.
2. Palladium(II) acetate was purchased from Engelhard Industries.
3. The yield improves slightly with stirring overnight; the checkers obtained the aldehyde in 69% yield in this manner.
4. The bulk of the product has b.p. 77–80° (3 mm.).
5. The product is 90–95% pure by GC and NMR analyses. The checkers estimated the purity to be at least 95% by these criteria. The ^{1}H NMR spectrum ($CDCl_3$) shows peaks at δ 0.95 (d, J = 6.5 Hz., 3H), 2.7 (complex m, 3H), 7.20 (s, 5H) and 9.65 (d, J = 1.5 Hz., 1H).

3. Discussion

The formation of 3-aryl-substituted aldehydes and 3-aryl-substituted ketones by the reaction of "arylpalladium salts" with allylic alcohols is general.[2] Illustrations of the preparation of two aldehydes and two ketones are given in Table I.

TABLE I

3-ARYLCARBONYL COMPOUNDS FROM ALLYLIC ALCOHOLS AND "PHENYLPALLADIUM ACETATE"[2]

Allylic Alcohol	Product	Yield, %	Boiling Point, °C.
CH_2=$CHCH_2OH$	$C_6H_5CH_2CH_2CHO$	35	220–225°[a]
trans-CH_3CH=$CHCH_2OH$	$C_6H_5CH(CH_3)CH_2CHO$	36	67–75° (1 mm.)
trans-CH_3CH=$CHCH(OH)CH_3$	$C_6H_5CH(CH_3)CH_2COCH_3$	51	70–75° (3 mm.)
$(CH_3)_2C$=$CHCH(OH)CH_3$	$C_6H_5C(CH_3)_2CH_2COCH_3$	29	83–87° (2 mm.)

[a] Purification by careful distillation is necessary in this example to remove cinnamaldehyde which is also formed in the reaction (b.p. 252°).

The presence of nitro, carboalkoxy, carboxyl, chloro, formyl, alkyl, and acyl groups does not interfere with the reaction. A single alkoxy group also does not interfere, but if two or more are present the yields are markedly decreased. The reaction is inhibited by the presence of unhindered, basic nitrogen substituents, by the phenolic group, and probably by the thiol group.

A variation of this procedure involves the use of a catalytic amount of palladium(II) chloride with copper(II) chloride as a reoxidant.[2] This method, however, generally gives lower yields and less pure products. Another related preparation uses palladium (II) acetate with two equivalents of triphenylphosphine, catalyzing the reaction of iodo-[3] or bromo-[4] benzene with methallyl alcohol in the presence of weak bases. Phenyldiazonium salts also may be used to react with methallyl alcohol and a palladium(0) catalyst to form the propionaldehyde.

Other preparations of 2-methyl-3-phenylpropionaldehyde include the pyrolysis of a mixture of the calcium salts of 2-methyl-3-phenylpropionic acid and formic acid,[5] the pyrolysis of the glycidic ester obtained from 2-phenyl-2-propanone and ethyl chloroacetate,[6] the hydroformylation of allylbenzene,[7] the benzylation of 2-ethylthiazoline followed by reduction with aluminum amalgam and cleavage with mercury(II) chloride,[8] and the reaction of phenylmagnesium bromide with 2-vinyl-5,6-dihydro-1,3-oxazine followed by methylation and hydrolysis.[9]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 361

10

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alumina

calcium salts of 2-methyl-3-phenylpropionic acid

ether, diethyl ether (60-29-7)

acetonitrile (75-05-8)

formic acid (64-18-6)

aluminum (7429-90-5)

palladium, palladium(0) (7440-05-3)

Ethyl chloroacetate (105-39-5)

mercury(II) chloride (7487-94-7)

copper(II) chloride (7758-89-6)

Phenylmagnesium bromide (100-58-3)

phenylmercury(II) acetate

cinnamaldehyde

palladium(II) chloride

methallyl alcohol (513-42-8)

allylbenzene (300-57-2)

triphenylphosphine (603-35-0)

palladium(II) acetate (3375-31-3)

PHENYLPALLADIUM ACETATE

2-Methyl-3-phenylpropionaldehyde, Benzenepropanal, α-methyl- (5445-77-2)

2-phenyl-2-propanone

2-ethylthiazoline

2-vinyl-5,6-dihydro-1,3-oxazine

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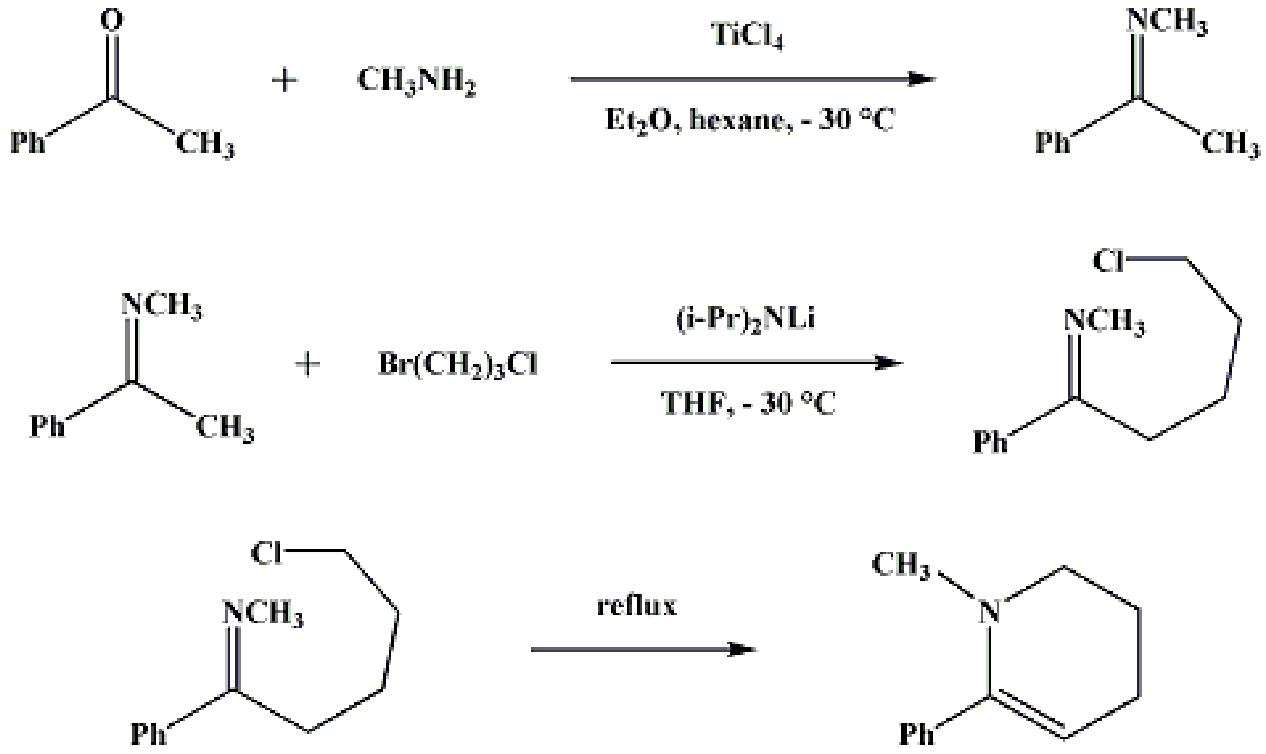
Organic Syntheses, CV 6, 818

ENDOCYCLIC ENAMINE SYNTHESIS: *N*-METHYL-2-PHENYL-Δ2-TETRAHYDROPYRIDINE

[Pyridine, 1,2,3,4-tetrahydro-1-methyl-5-phenyl-]



Submitted by D. A. Evans[1] and L. A. Domeier.
Checked by R. Decorzant and G. Büchi.

1. Procedure

2

A. N-(α-*Methylbenzylidene)methylamine*. Approximately 70 ml. of methylamine, passed through a potassium hydroxide trap, is condensed into a dry, premarked, nitrogen-purged, 1-l. flask (Note 1) equipped with a mechanical stirrer, an acetone–dry ice condenser with drying tube, and a 250-ml., pressure-equalizing addition funnel topped by a gas-inlet connection. The flask is cooled in a methanol–ice bath, and a solution of 48 g. (0.40 mole) of acetophenone (Note 2) in 200 ml. of dry diethyl ether (Note 3) is added through the addition funnel. The addition funnel is rinsed with 25 ml. of dry ether, purged with nitrogen, and charged with 220 ml. of 1 *M* titanium tetrachloride in hexane (Note 4), which is added to the cooled flask over a 1.5-hour period (Note 5). After stirring an additional 30 minutes in the methanol–ice bath and 30 minutes at room temperature, the mixture is filtered through a Büchner funnel into a 1-l., round-bottomed flask (Note 6), and the solid material is rinsed with an additional 100 ml. of ether. The solvents are removed on a rotary evaporator, and the yellow residue is transferred to a 100 ml. round-bottomed flask. Distillation through a short, vacuum-

jacketed, Vigreux column yields 37–47 g. (70–88%) of the colorless imine, b.p. 93–95° (11 mm.) (Note 7) and (Note 8).

B. N-*Methyl*-2-*phenyl*-Δ^2-*tetrahydropyridine*. A 500-ml., nitrogen-purged flask equipped with serum cap, reflux condenser with nitrogen inlet connection, thermometer, and stirring bar, is charged with 100 ml. of dry tetrahydrofuran (Note 9) and 21.0 ml. (0.155 mole) of diisopropylamine (Note 10). The solution is cooled to –30° with an acetone bath to which dry ice was added as needed, and 72.4 ml. (0.155 mole) of 2.14 *M* *n*-butyllithium in hexane (Note 11) is added while keeping the temperature below 0°. After cooling the mixture to –40°, 20.6 g. (0.155 mole) of the imine (from part A) is added *via* syringe over a period of about 2 minutes. The resulting yellow solution is maintained at –40° to –30° for 15 minutes then cooled to –60°. To the cold solution is added 25.2 g. (16.5 ml., 0.160 mole) of 1-bromo-3-chloropropane (Note 12) in one portion *via* syringe while the temperature is maintained below –40°. The reaction mixture is maintained between –60° and –50° for 5 minutes, the bath is removed, and the mixture is allowed to warm to room temperature. The reaction mixture is refluxed 3 hours to effect ring closure (Note 13). After the addition of 150 ml. of 10% aqueous potassium carbonate to the cooled solution, the reaction mixture is stirred several minutes and transferred to a nitrogen-purged separatory funnel. The reaction flask is rinsed with 100 ml. of 1 : 1 benzene–ether which is added to the separatory funnel, and the entire mixture is diluted with 150 ml. of water. After shaking, the aqueous layer is removed, the organic layer is washed with 100 ml. of brine, shaken with anhydrous granular sodium sulfate, and filtered into a 1-l., round-bottomed flask. The solvents are removed on a rotary evaporator, and the residue is transferred to a 100-ml., round-bottomed flask. Short-path distillation under high vacuum yields 18.8–21.7 g. (70–81%) of pale yellow enamine, b.p. 87–88° (4 mm.) (Note 14) and (Note 15).

2. Notes

1. All three necks of the flask should be vertical and not set at an angle, preventing the accumulation of large amounts of the methylamine complex of titanium tetrachloride on the sides of the reaction flask.
2. Acetophenone was purchased from Matheson, Coleman and Bell and used without further purification.
3. Anhydrous ether available from Mallinckrodt Chemical Co. can be used without further drying.
4. Titanium tetrachloride (purified grade) was purchased from J. T. Baker. A 1 *M* titanium tetrachloride solution was prepared by diluting 55 ml. of titanium tetrachloride (1.73 g./ml.) to a volume of 500 ml. with hexane which had been passed through 40–50 g. of basic alumina (Activity I).
5. The addition funnel should be thoroughly, but gently, flushed with nitrogen before being charged with the titanium tetrachloride solution. A slight flow of nitrogen should be maintained throughout the addition, preventing the diffusion of methylamine into the funnel where it will form a red insoluble titanium tetrachloride–amine complex.
6. If done quickly, the filtration need not be done under nitrogen, with no effect

on the yield in the case of this particular imine.

7. ^{1}H NMR (CCl_4): 2.1 (s, 3H, NC*H*$_3$), 3.2 (s, 3H, vinylic C*H*$_3$), 7.2 (m, 3H, aryl C*H*), 7.7 (m, 2H, aryl C*H*). IR (CCl_4) cm.$^{-1}$: 1645, 1450, 1370, 1290. Purity was confirmed by GC on a 4-ft., 10% Carbowax 20 *M* column at 165°.

8. The imine should be stored under nitrogen and exposed to the air as little as possible during handling.

9. Tetrahydrofuran was freshly distilled from lithium aluminum hydride. See *Org. Synth.*, **Coll. Vol. 5**, 976 (1973) for a note concerning the hazards involved in purifying tetrahydrofuran.

10. Diisopropylamine was purchased from Aldrich Chemical Co. and distilled from calcium hydride prior to use.

11. *n*-Butyllithium in hexane was purchased from Ventron Corp.

12. 1-Bromo-3-chloropropane was purchased from Matheson, Coleman and Bell and distilled from phosphorus pentoxide prior to use.

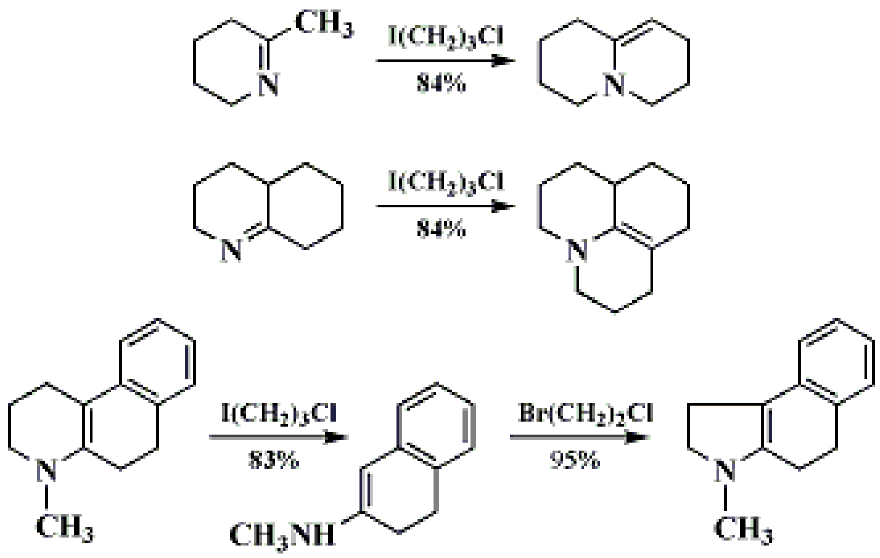
13. If the mixture is not refluxed, the intermediate imine may be isolated.

14. ^{1}H NMR (CCl_4): 1.5–2.1 (m, 4H, 2C*H*$_2$), 2.4 (s, 3H, NC*H*$_3$), 3.0 (m, 2H, NC*H*$_2$), 4.8 (t, *J* = 4 Hz., 1H, vinylic C*H*), 7.3 (m, 5H, C_6H_5). IR (CCl_4) cm^{-1}: 1640, 1605, 1500, 1460, 1375, 1360, 1130, 1040. Purity was confirmed by GC on a 4-ft., 10% Carbowax 20 M column at 165°.

15. The enamine should be refrigerated under nitrogen and used within a few days.

3. Discussion

N-Methyl-2-phenyl-Δ^2-tetrahydropyridine and similar compounds have previously been prepared by the hydrolysis and decarboxylation of α-benzoyl-*N*-methyl-2-piperidone[3] and by the addition of phenyl Grignard reagents to *N*-methyl-2-piperidone, followed by dehydration.[4] Both of these methods require that a heterocyclic ring already be present in the system. In contrast, this procedure offers a new, flexible route to the construction of five- or six-membered heterocyclic rings which may easily be incorporated into larger polycyclic products. Several examples[5] of this process demonstrate this utility:



A wide variety of more complex endocyclic enamines are thus made available as synthetic intermediates.

References and Notes

1. Department of Chemistry, University of California, Los Angeles, California 90024. [Present address: Division of Chemistry and Chemical Engineering, The Chemical Laboratories, California Institute of Technology, Pasadena, California 91125].
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alumina

brine

N-Methyl-2-phenyl-Δ^2-tetrahydropyridine

methylamine complex of titanium tetrachloride

potassium carbonate (584-08-7)

Benzene (71-43-2)

ether, diethyl ether (60-29-7)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

Acetophenone (98-86-2)

1-bromo-3-chloropropane (109-70-6)

methylamine (74-89-5)

n-butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

hexane (110-54-3)

titanium tetrachloride (7550-45-0)

calcium hydride (7789-78-8)

diisopropylamine (108-18-9)

titanium (7440-32-6)

Pyridine, 1,2,3,4-tetrahydro-1-methyl-5-phenyl-

phosphorus pentoxide (1314-56-3)

α-benzoyl-N-methyl-2-piperidone

N-methyl-2-piperidone (931-20-4)

N-(α-Methylbenzylidene)methylamine (6907-71-7)

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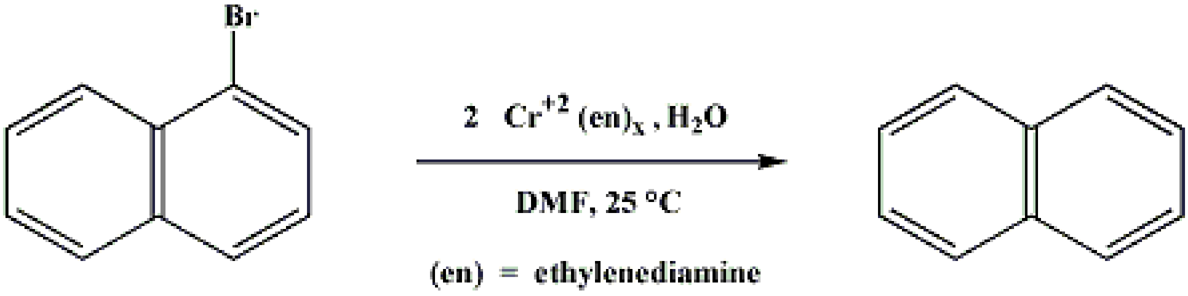
Organic Syntheses, CV 6, 821

HYDROGENOLYSIS OF CARBON-HALOGEN BONDS WITH CHROMIUM(II)-EN PERCHLORATE: NAPHTHALENE FROM 1-BROMONAPHTHALENE



Submitted by Ruth S. Wade and C. E. Castro[1].
Checked by Norton P. Peet and Herbert O. House.

1. Procedure

A 250-ml., three-necked flask equipped with a magnetic stirring bar, nitrogen inlet, and outlet stopcocks is charged with 60 ml. of *N*,*N*-dimethylformamide (Note 1) and 6.01 g. (0.100 mole) of ethylenediamine (Note 2). The outlet stopcock is connected to a trap containing mercury or Nujol, and the third neck of the flask is fitted with a rubber septum. While the solution in the flask is stirred, the system is flushed with nitrogen for 30 minutes; a static nitrogen atmosphere is maintained in the reaction vessel during the remainder of the reaction. An aqueous solution containing 0.03 mole of chromium(II) perchlorate (Note 3) is added to the reaction vessel with a hypodermic syringe, forming a purple solution of the chromium(II)-en complex. To this solution is added, with a hypodermic syringe, a solution of 1.66 g. (0.00802 mole) of 1-bromonaphthalene (Note 4) in 20 ml. of oxygen-free (Note 5) *N*,*N*-dimethylformamide (Note 1). The reaction solution is stirred for 70 minutes (Note 6), during which time the color changes from purple to deep red, and poured into a solution of 40 g. of ammonium sulfate in 400 ml. of 0.4 *M* hydrochloric acid. The resulting emulsion is extracted with five 60-ml. portions of diethyl ether. The combined ethereal extracts are washed with two 25-ml. portions of water, dried over potassium carbonate, and concentrated. The residue crystallizes, yielding 0.96–1.00 g. (93–98%) of naphthalene, m.p. 77–80°. Recrystallization from ethanol affords pure naphthalene as white plates, m.p. 80–81°.

2. Notes

1. Baker reagent grade *N*,*N*-dimethylformamide was used without purification.
2. The submitters employed, without purification, 98% ethylenediamine obtained from Mallinckrodt Chemical Works; the checkers employed material from Eastman Organic Chemicals, which was redistilled (b.p. 117–118°) before

use. The amount of ethylenediamine employed is sufficient to provide three equivalents of diamine for each mole of chromium(II) and to neutralize any acid remaining in the chromium(II) perchlorate solution.

3. The submitters employed a 1.64 *M* solution of chromium(II) perchlorate, prepared by stirring a mixture of 5.7 g. of pure chromium metal pellets (United Mineral and Chemical Corporation, 129 Hudson St., New York, 10013) with 60 ml. of 20% perchloric acid under a nitrogen atmosphere at 30° for 12 hours.[2,3] The rate of dissolution of the chromium metal is increased if the metal is washed successively with concentrated hydrochloric acid and water just before it is added to the perchloric acid. The checkers employed a 0.519 *M* solution of chromium(II) perchlorate, prepared in a comparable manner with chromium metal obtained from the Mining and Metals Division, Union Carbide Corporation. The deep-blue solution of chromium(II) perchlorate is transferred to a storage vessel with a siphon or a hypodermic syringe, and the solution is stored under a nitrogen atmosphere in a vessel fitted with a rubber septum. Provided this solution is protected from oxygen, it is stable for long periods of time; aliquots for standardization or reaction are conveniently removed with a hypodermic syringe. The solution is standardized by adding 5.00-ml. aliquots to excess 1 *M* iron(III) chloride followed by titration of the iron(II) ion produced with standard cerium(IV) sulfate solution, using phenanthroline as an indicator. [*Org. Synth.*, **Coll. Vol. 5**, 993 (1973)]. The submitters had recommended use of only slightly more [2.3 moles of chromium(II) complex per mole of halide] than the stoichiometric amount of chromium(II) complex in this reduction. However, because these concentrations of reagents lead to a very slow reaction rate in the last 5–10% of the reduction (Note 6), the checkers found it more convenient to employ excess reducing agent [3.8 moles of chromium(II) complex per mole of halide].

4. 1-Bromonaphthalene, m.p. 2–4°, obtained either from the Aldrich Chemical Company, Inc., or from Matheson, Coleman and Bell was used without further purification.

5. A slow stream of nitrogen was passed through the *N*,*N*-dimethylformamide for 30 minutes to remove any dissolved oxygen.

6. The progress of this reaction may be followed by quenching aliquots of the reaction solution in acidic aqueous ammonium sulfate followed by extraction with ether and analysis of the ethereal extract by GC. With a 1.2-m. GC column packed with silicone fluid, No. 710, on Chromosorb P and heated to 215°, the retention times of naphthalene and 1-bromonaphthalene were 1.9 minutes and 6.7 minutes, respectively. The submitters employed a 30-cm. GC column packed with Porpak P for this analysis. Since the presence of even 5–10% of unchanged 1-bromonaphthalene makes purification of the naphthalene difficult, it is important that the reduction be complete before the product is isolated. With reaction conditions described in this preparation [0.100 mole of ethylenediamine, 0.0080 mole of 1-bromonaphthalene, 60 ml. (0.031 mole) of 0.519 *M* chromium(II) perchlorate, and 80 ml. of *N*,*N*-dimethylformamide], the checkers found that reduction was usually complete in less than 15 minutes.

Under the conditions [0.032 mole of ethylenediamine, 0.0040 mole of 1-bromonaphthalene, 5.5 ml. (0.0090 mole) of 1.64 *M* chromium(II) perchlorate, and 40 ml. of *N*,*N*-dimethylformamide] originally suggested by the submitters, a reduction time of approximately 3 hours was required for complete reduction.

3. Discussion

1-Bromonaphthalene has been reduced to naphthalene in good yield by hydrogenation over Raney nickel in methanolic potassium hydroxide,[4] by triphenyltin hydride in benzene,[5] by magnesium in 2-propanol,[6] by sodium hydrazide and hydrazine in ether,[7] and by copper(I) acetate in pyridine.[8]

The present procedure illustrates the ease of reduction of aryl, vinyl, and primary alkyl halides to the corresponding hydrocarbons with the chromium(II)-en reagent.[9] This reagent will also convert epoxides and aliphatic halides, with good leaving groups in the β-position, to olefins.[9] Although the reduction of alkyl halides with this en complex is chemically similar to reductions with solutions of other chromium(II) salts in aqueous *N*,*N*-dimethylformamide,[10,11] the en complexes of the chromium(II) ion are more reactive than the aquated chromium(II) ion.[9] The checkers have found that the potential measured between platinum and calomel electrodes in a solution of chromium(II) perchlorate in aqueous *N*,*N*-dimethylformamide is increased by the addition of ethylenediamine until three equivalents of the diamine have been added. However, presumably at least one of the six coordination sites on the chromium(II) ion must be vacant at the time reduction of a halide occurs, permitting transfer of the halogen atom from the substrate to the chromium ion.[9]

Chromium(II) perchlorate is the salt of choice for preparing the en complex in *N*,*N*-dimethylformamide. At comparable concentrations chromium(II) sulfate[10] is insoluble, and chromium(II) chloride[2,11] is only partially soluble in the reaction solution.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

methanolic potassium hydroxide

CHROMIUM(II)-EN PERCHLORATE

chromium(II)-en complex

chromium(II) complex

ethanol (64-17-5)

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether, diethyl ether (60-29-7)

magnesium (7439-95-4)

oxygen (7782-44-7)

nitrogen (7727-37-9)

Raney nickel (7440-02-0)

pyridine (110-86-1)

2-propanol (67-63-0)

1-bromonaphthalene (90-11-9)

Naphthalene (91-20-3)

iron(III) chloride (7705-08-0)

ammonium sulfate (7783-20-2)

hydrazine (302-01-2)

chromium (7440-47-3)

N,N-dimethylformamide (68-12-2)

ethylenediamine (107-15-3)

chromium(II) chloride (10049-05-5)

perchloric acid (7601-90-3)

phenanthroline

cerium(IV) sulfate (13590-82-4)

CHROMIUM(II) SULFATE

chromium(II)

chromium(II) perchlorate

iron(II) ion

triphenyltin hydride (892-20-6)

sodium hydrazide

copper(I) acetate (598-54-9)

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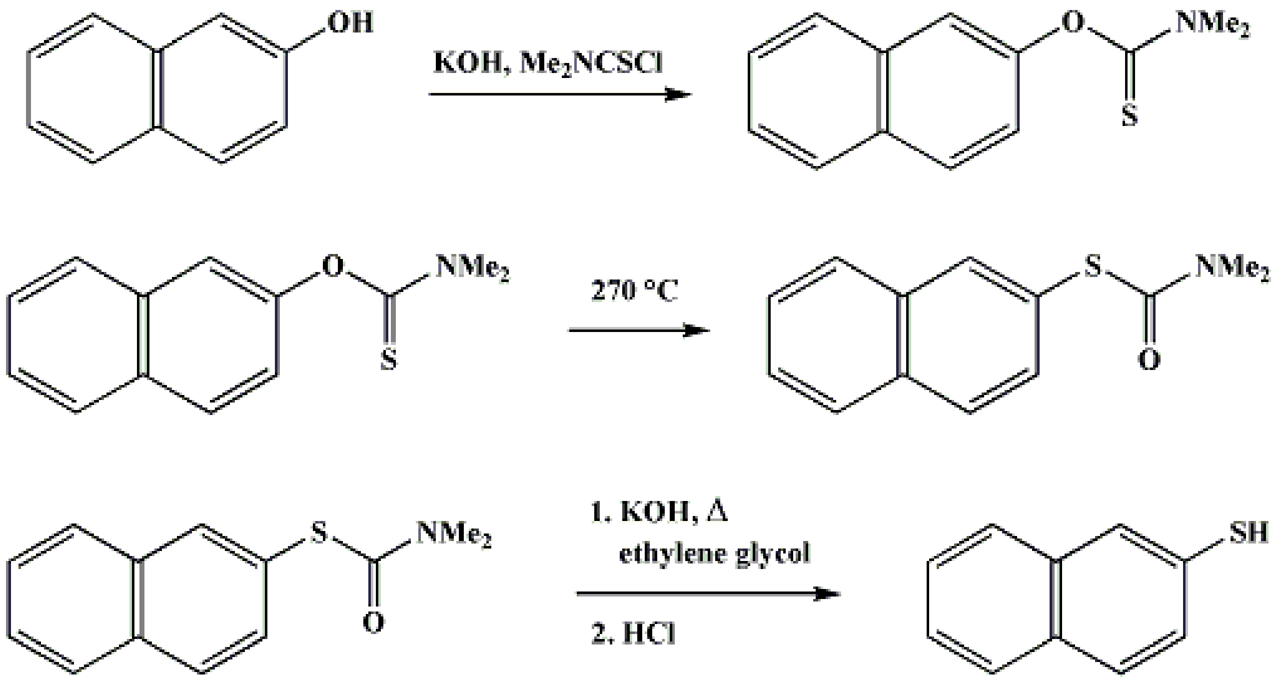
Organic Syntheses, CV 6, 824

THIOPHENOLS FROM PHENOLS: 2-NAPHTHALENETHIOL



Submitted by Melvin S. Newman[1] and Frederick W. Hetzel[2].
Checked by W. Schilling, R. Keese, and A. Eschenmoser.

1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A. *O-2-Naphthyl dimethylthiocarbamate*. A solution of 21.6 g. (0.150 mole) of 2-naphthol (Note 1) in 100 ml. of water containing 8.4 g. (0.15 mole) of potassium hydroxide is cooled below 10° in a 500-ml., three-necked flask equipped with a stirrer, a thermometer, and a 125-ml. addition funnel. A solution of 24.8 g. (0.201 mole) of *N,N*-dimethylthiocarbamyl chloride (Note 2) in 40 ml. of dry tetrahydrofuran (Note 3) is added over 20–30 minutes to the stirred solution at such a rate that the temperature never exceeds 12°. After the addition is complete, the cooling bath is removed and stirring is continued for 10 minutes. The reaction mixture is made alkaline with 50 ml. of 10% potassium hydroxide and shaken three times with 100-ml. portions of benzene. The organic layers are combined, washed with saturated sodium chloride, and dried by filtration through anhydrous magnesium sulfate. The solvent is removed by distillation, giving the crude product. Crystallization from 75 ml. of absolute methanol yields 23.5–25.2 g. (68–73%) of *O*-2-naphthyl dimethylthiocarbamate, as colorless crystals, m.p. 90–90.5°.

B. 2-*Naphthalenethiol*. A 250-ml. flask, fitted with a diffusion tube[3] and swept with nitrogen, is charged with 23.1 g. (0.100 mole) of *O*-2-naphthyl dimethylthiocarbamate (Note 4). The

flask is heated at 270–275° for 45 minutes in a salt bath (Note 5). After cooling, a solution of 8.4 g. (0.15 mole) of potassium hydroxide in 10 ml. of water and 75 ml. of ethylene glycol is added to the flask. The diffusion tube is replaced with a condenser, and the mixture is heated at reflux for 1 hour (Note 6). The cooled reaction mixture is poured onto 150 g. of ice. After the ice has melted, the mixture is shaken two times with 150-ml. portions of chloroform. The chloroform layers are discarded, and the aqueous layer is cautiously acidified with concentrated hydrochloric acid (Note 7) and shaken three times with 75-ml. portions of chloroform. The organic layers are combined and dried by filtration through anhydrous magnesium sulfate. The solvent is removed by distillation, yielding 13–15 g. of crude product. Distillation yields 10.3–12.8 g. (71–80%) of pure 2-naphthalenethiol, b.p. 92–94° (0.4 mm.), m.p. 80–81° (Note 8).

2. Notes

1. Practical 2-naphthol, obtained from Matheson, Coleman and Bell, was recrystallized twice from benzene, m.p. 123–124°.
2. *N,N*-Dimethylthiocarbamyl chloride can be prepared as described in *Org. Synth.*, **Coll. Vol. 4**, 310 (1963), or by rapidly adding 740 g. (10.5 moles) of chlorine dissolved in 3 l. of carbon tetrachloride to a stirred, refluxing suspension of 2400 g. (9.982 moles) of tetramethylthiram disulfide (Note 9) in 5 l. of carbon tetrachloride. After the addition is complete, approximately one-half of the solvent is removed by distillation. The reaction mixture is cooled, filtered, removing the precipitated sulfur, and further concentrated. The residue is distilled, yielding 1980 g. (80%) of *N,N*-dimethylthiocarbamyl chloride, b.p. 65–68° (0.2 mm.).
3. See *Org. Synth.*, **Coll. Vol. 5**, 976 (1973) for a warning note regarding the purification of tetrahydrofuran.
4. Crude *O*-2-naphthyl dimethylthiocarbamate should not be used in this step as the yield is markedly decreased.
5. The salt bath is described in *Org. Synth.*, **Coll. Vol. 4**, 498 (1963).
6. The hydrolysis should be performed in a hood because of the vigorous evolution of dimethylamine.
7. The dilute acid solution should be added slowly since foaming results from the evolution of carbon dioxide.
8. Purification can be accomplished by recrystallization from methanol, but the overall yield of pure material is 65–70%.
9. Tetramethylthiram disulfide was obtained from the Pennwalt Corporation.

3. Discussion

The procedure described is a good, general method[4] for obtaining a thiophenol from the respective phenol. It employs three steps: conversion of a phenol to the *O*-aryl dialkylthiocarbamate by treatment with *N,N*-dialkylthiocarbonyl chloride; pyrolysis of the *O*-aryl dialkylthiocarbamate to the *S*-aryl dialkylthiocarbamate; and hydrolysis of the latter to the aryl mercaptan.

Previous preparations of 2-naphthalenethiol have included reduction of 2 naphthylsulfonyl chloride with zinc and acid[5,6] or phosphorus and iodine.[7,8] Alternatively, 2-

naphthyldiazonium chloride has been converted to the thiol using potassium ethyl xanthate and sodium carbonate.[9]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

tetramethylthiram disulfide

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

methanol (67-56-1)

chloroform (67-66-3)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

PHOSPHORUS (7723-14-0)

carbon tetrachloride (56-23-5)

nitrogen (7727-37-9)

2-naphthol (135-19-3)

sulfur (7704-34-9)

carbon dioxide (124-38-9)

iodine (7553-56-2)

chlorine (7782-50-5)

potassium hydroxide (1310-58-3)

zinc (7440-66-6)

ethylene glycol (107-21-1)

potassium ethyl xanthate (140-89-6)

magnesium sulfate (7487-88-9)

dimethylamine (124-40-3)

2-naphthyldiazonium chloride

Tetrahydrofuran (109-99-9)

N,N-dimethylthiocarbamyl chloride (16420-13-6)

2-Naphthalenethiol (91-60-1)

O-2-naphthyl dimethylthiocarbamate (2951-24-8)

2 naphthylsulfonyl chloride (93-11-8)

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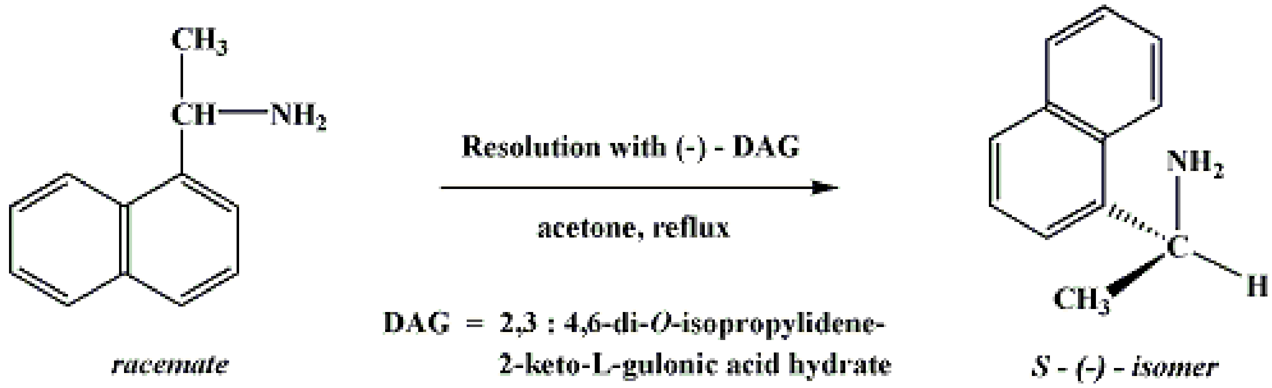
Organic Syntheses, *CV 6, 826*

(*S*)-(–)-α-(1-NAPHTHYL)ETHYLAMINE

[(*S*)-1-Naphthalenemethanamine, α-methyl-]



Submitted by E. Mohacsi and W. Leimgruber[1].
Checked by P. E. Georghiou, J. D. Lock, Jr., and S. Masamune.

1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A. (*S*)-(–)-α-(1-*Naphthyl)ethylamine*. A mixture of 58.44 g. (0.1849 mole) of (–)-2,3:4,6-di-*O*-isopropylidene-2-keto-L-gulonic acid hydrate [(–)-DAG] (Note 1) and 1.7 l. of acetone (Note 2) is placed in a 3-l. Erlenmeyer flask. A boiling chip is added, and the mixture is heated to a gentle boil. To the resulting hot solution is added cautiously but rapidly, over a 1-minute period, 34.24 g. (0.2002 mole) of racemic α-(1-naphthyl)ethylamine (Note 3) in 100 ml. of acetone. The mixture is allowed to stand at room temperature for approximately 4 hours. The (–)-amine (–)-DAG salt is filtered with suction, washed with 100 ml. of acetone, and dried in a vacuum oven at 60° to constant weight, yielding 73–76 g. of the crude (–)-amine (–)-DAG salt, m.p. 205–207° (dec.), (Note 4), $[\alpha]_D^{25}$ –14.2° (*c* 1.01%, methanol). The crude salt and 4.2 l. of ethanol (Note 5) are placed in a 5-l., round-bottomed flask fitted with a reflux condenser and a mechanical stirrer. The mixture is stirred and heated at reflux for about 4 hours, during which time a clear solution is obtained. The condenser is then placed in a descending position and approximately 1.4 l. of the ethanol is distilled at atmospheric pressure (Note 6), and stirring is continued (Note 7) at room temperature for about 16 hours. The purified salt is collected on a filter and dried to constant weight, yielding 36–37 g. of white needles, m.p. 216–218° (dec., (Note 4)), $[\alpha]_D^{25}$ –17.5° (*c* 1.02%, methanol). For recrystallization, the crude salt and 4.0 l. of ethanol are used. Removal of 3.0 l. of the solvent yields 33.5–33.9 g. (75–76%) of pure (–)-amine (–)-DAG salt as white needles, m.p. 219–221° (dec., (Note 4)), $[\alpha]_D^{25}$ –18.5° (*c* 0.90%, methanol).

To a slurry of 33.5–33.9 g. of the pure (−)-amine (−)-DAG salt in 130 ml. of water is added 56 ml. of 2 *N* aqueous sodium hydroxide, and the resulting oily suspension is extracted with four 80-ml. portions of diethyl ether. The combined ether extracts are washed with 50 ml. of water and dried over anhydrous magnesium sulfate. After filtration and removal of the ether on a rotary evaporator, the crude base is distilled under reduced pressure through a 20-cm. Vigreux column (Note 8), affording 10.9–11.7 g. (85–90% yield, based on the amount of the salt used) of the pure (−)-amine as a colorless liquid, b.p. 156–157° (11 mm.), n_D^{24} 1.6211–1.6212, d_4^{24} 1.056, $[\alpha]_D^{25}$ −80.1° (neat), $[\alpha]_D^{25}$ −60.4° (*c* 10.0%, methanol), $[\alpha]_D^{25}$ −59.3° (*c* 0.65%, methanol) (Note 9) and (Note 10).

B. *Recovery of* (−)-DAG. The basic aqueous solution (about 186 ml.), obtained after removal of the (−)-amine by ether extraction, is placed in a 600-ml. beaker and cooled to 0–5° with an ice bath. The solution is magnetically stirred and carefully acidified with 2 *N* hydrochloric acid at 0–5° to approximately pH 2 (Note 11). The precipitated (−)-DAG is filtered without delay (Note 12), washed with 20 ml. of ice water, and air dried to constant weight, yielding 20.0–20.9 g. (91–94%, yield based on the amount of the salt used) of (−)-DAG, m.p. 103° (dec.), $[\alpha]_D^{25}$ −21.6° (*c* 2.28%, methanol) (Note 13) and (Note 14).

2. Notes

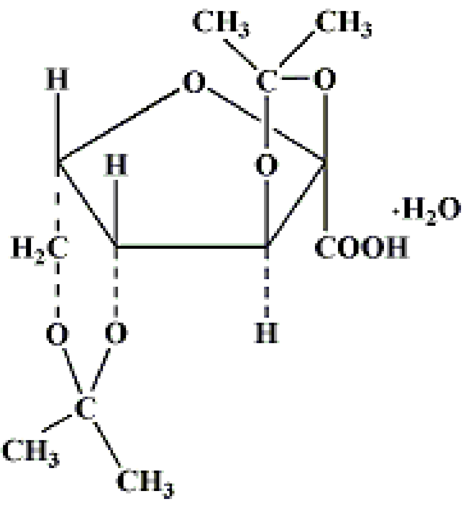
1. (−)-2,3:4,6-Di-*O*-isopropylidene-2-keto-L-gulonic acid hydrate [(−)-DAG] is available from the Commercial Development Dept., Hoffmann-La Roche Inc., Nutley, new Jersey 07110.
2. Mallinckrodt A.R. grade acetone was used. The checkers found that the use of 1.5 l. of acetone, as originally recommended by the submitters, resulted in an immediate precipitation of the (−)-DAG salt upon addition of the amine, inducing incomplete mixing of the two reagents.
3. Practical grade racemic α-(1-naphthyl)ethylamine (purchased from Norse Laboratories, Inc., Santa Barbara, California 93103) was distilled before use, b.p. 117–118° (2 mm.).
4. The melting point was measured in an evacuated, sealed capillary and found to deviate slightly from this value on occasion.
5. The checkers used ethanol containing a maximum of 0.1% (w/w) of water and a maximum of 0.001% (w/w) of benzene.
6. The salt begins to crystallize toward the end of this operation.
7. It is advisable to maintain stirring, avoiding the formation of lumps, thus assuring a uniform product.
8. The distillation apparatus was first flushed with nitrogen, as the amine formed a white crystalline solid on contact with atmospheric carbon dioxide.
9. Reported physical constants[2,3] of the amine are: b.p. 153° (11 mm.), d_4^{25} 1.055, $[\alpha]_D^{25}$ −80.8° (neat).
10. A 100 MHz. ^{1}H NMR spectrum ($CDCl_3$) of the amine in the presence of an equal amount of the chiral shift reagent, tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorato]europium(III)[4] (submitters), or in the presence of an equal amount of tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium(III) (checkers), revealed that the product contained no detectable enantiomeric isomer.

11. The pH was measured with a Beckman Zeromatic pH meter.
12. (−)-DAG is unstable in aqueous acid.
13. TLC of (−)-DAG on Silica Gel G using the solvent system, benzene:methanol:acetone:acetic acid (70:20:5:5), shows one spot, R_f □ 0.7.
14. The reported[5] m.p. is 98–99°.

3. Discussion

(*S*)-(−)-α-(1-Naphthyl)ethylamine has been prepared by resolution of the racemic amine with camphoric acid in unspecified yield.[2,3]

The procedure presented herein allows the preparation of the same optically active amine in approximately 70% yield by the use of a new resolving agent, (−)-2,3:4,6-di-*O*-isopropylidene-2-keto-L-gulonic acid hydrate, [(−)-DAG], whose utility for the resolution of a variety of amines has been thoroughly demonstrated.[6]



(-)-DAG

(−)-DAG is an ascorbic acid derivative with the following structure: It is an attractive resolving agent, because it is relatively inexpensive and commercially available on a ton scale for industrial applications. One of the remarkable properties of (−)-DAG, lacking in other acidic resolving agents, is its water-insolubility, which permits the recovery of the resolving agent in a simple and efficient manner.

Among the amines that have been resolved with (−)-DAG: α-phenylethylamine,[6] [(R-(R*, R*)]-2-amino-1-(4-nitrophenyl)-1,3-propanediol,[6] 1,2,3,4,5,6,7,8-octahydro-1-(4-methoxyphenylmethyl)isoquinoline,[6] 3-methoxymorphinan,[6] 1,2,3,4-tetrahydro-7-methoxy-4-phenylisoquinoline,[6] 3-hydroxy-*N*-methylmorphinan,[6] 1,2,3,4-tetrahydro-6,7-dimethoxy-1-[3,4-(methylenedioxy)phenyl]isoquinoline,[7] 1,2,3,4-tetrahydro-6,7-dimethoxy-1-(3,4,5-trimethoxyphenyl)isoquinoline,[7] 2-[4-(phenylmethoxy)phenyl]-2-(3,4-dimethoxyphenyl) ethanamine,[8] *N*-norlaudanosine,[9] and 1,2,3,4-tetrahydro-6,7-dimethoxy-1-[3-methoxy-4-(phenylmethoxy)phenyl]isoquinoline.[10]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

(−)-amine

(S)-(−)-α-(1-NAPHTHYL)ETHYLAMINE

(−)-2,3:4,6-di-O-isopropylidene-2-keto-L-gulonic acid hydrate

(−)-amine (−)-DAG

(−)-2,3:4,6-Di-O-isopropylidene-2-keto-L-gulonic acid hydrate [(−)-DAG]

tris[3-(trifluoromethylhydroxymethylene)-d-camphorato]europium(III)

tris[3-(heptafluoropropylhydroxymethylene)-d-camphorato]europium(III)

(−)-2,3:4,6-di-O-isopropylidene-2-keto-L-gulonic acid hydrate, [(−)-DAG]

N-norlaudanosine

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

acetone (67-64-1)

magnesium sulfate (7487-88-9)

α-Phenylethylamine (3886-69-9)

α-(1-naphthyl)ethylamine

camphoric acid

1,2,3,4,5,6,7,8-octahydro-1-(4-methoxyphenylmethyl)isoquinoline

1,2,3,4-tetrahydro-6,7-dimethoxy-1-[3,4-(methylenedioxy)phenyl]isoquinoline

1,2,3,4-tetrahydro-6,7-dimethoxy-1-(3,4,5-trimethoxyphenyl)isoquinoline

2-[4-(phenylmethoxy)phenyl]-2-(3,4-dimethoxyphenyl)ethanamine

1,2,3,4-tetrahydro-6,7-dimethoxy-1-[3-methoxy-4-(phenylmethoxy)phenyl]isoquinoline

(S)-1-Naphthalenemethanamine, α-methyl- (10420-89-0)

3-hydroxy-N-methylmorphinan (125-73-5)

3-methoxymorphinan

1,2,3,4-tetrahydro-7-methoxy-4-phenylisoquinoline

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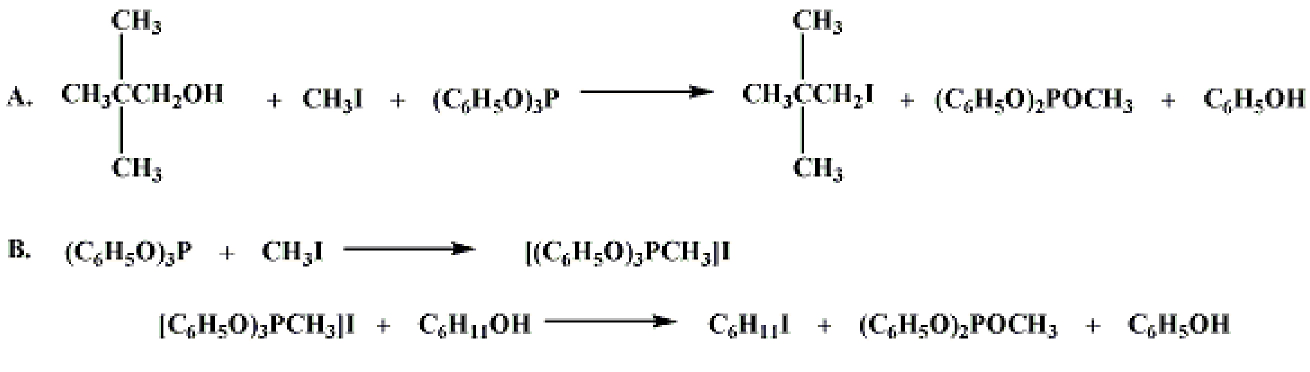
Organic Syntheses, CV 6, 830

ALKYL IODIDES: NEOPENTYL IODIDE AND IODOCYCLOHEXANE

[Propane, 1-iodo-2,2-dimethyl- and Cyclohexane, iodo-]



Submitted by H. N. Rydon[1]
Checked by W. Fuhrer, R. Keese, and A. Eschenmoser.

1. Procedure

Note. Two procedures are given. Procedure A is the simplest to perform, but B is preferred for sensitive alcohols and in cases where elimination to olefins is expected, for example, with all tertiary and many secondary alcohols. Procedure A is best for sterically hindered alcohols, for example, neopentyl alcohol.

Caution! Methyl iodide, in high concentrations for short periods or in low concentrations for long periods, can cause serious toxic effects in the central nervous system. Accordingly, the American Conference of Governmental Industrial Hygienists[2] has set five p.p.m., a level which cannot be detected by smell, as the highest average concentration in air to which workers should be exposed for long periods. The preparation and use of methyl iodide should always be performed in a well-ventilated fume hood. Since the liquid can be absorbed through the skin, care should be taken to prevent contact.

A. *Neopentyl iodide*. A 500-ml., two-necked, round-bottomed flask fitted with a reflux condenser equipped with a calcium chloride drying tube is charged with 136 g. (115 ml., 0.439 mole) of triphenyl phosphite, 35.2 g. (0.400 mole) of neopentyl alcohol, and 85 g. (37 ml., 0.60 mole) of methyl iodide (Note 1). A thermometer of sufficient length extends into the liquid contents of the flask. The mixture is heated under gentle reflux with an electric heating mantle until the temperature of the refluxing liquid rises from its initial value of 75–80° to about 130°, and the mixture darkens and begins to fume. The time required is about 24 hours. It is necessary to adjust the heat input from the mantle from time to time as the reaction proceeds and the reflux rate diminishes (Note 2).

The reaction mixture is distilled under reduced pressure through a 13-cm. Vigreux column. The fraction boiling below 65° (50 mm.) is collected and washed with 50 ml. of water, then with 50-ml. portions of cold 1 *N* sodium hydroxide until the washings no longer contain phenol (Note 3). The product is washed again with 50 ml. of water, dried over calcium chloride and redistilled, yielding 51–60 g. (64–75%) of neopentyl iodide, b.p. 54–55° (55 mm.), n_D^{21} 1.4882 (Note 4).

B. *Iodocyclohexane*. A 500-ml., two-necked, round-bottomed flask fitted with a reflux condenser equipped with a calcium chloride drying tube is charged with 124 g. (107 ml., 0.400 mole) of triphenyl phosphite and 85 g. (37 ml., 0.60 mole) of methyl iodide (Note 1). A thermometer of sufficient length extends into the liquid contents of the flask. The mixture is heated under gentle reflux with a heating mantle until the internal temperature has risen to about 120°. At this point the mixture is dark and viscous (Note 5). The flask is cooled, and 40 g. (0.40 mole) of cyclohexanol is added to the oily methyltriphenoxyphosphonium iodide. The mixture is shaken gently until homogeneous (Note 6) and allowed to stand overnight at room

temperature (Note 7). The mixture is distilled through a 13-cm. Vigreux column (Note 8), yielding 62.5–63 g. (74–75%) of iodocyclohexane, b.p. 66–68° (12 mm.), n_D^{22} 1.5475.

2. Notes

1. The use of 1.2 instead of 1.5 equivalents of methyl iodide proved beneficial in some runs carried out by the checkers; some difficulty was experienced in reaching the recommended final temperature.
2. To obtain the yields cited, it is essential that the reaction temperature reaches the indicated, final value, but heating should not be unnecessarily prolonged. The reaction is conveniently monitored by IR spectroscopy. As the reaction proceeds, a broad, strong band at 865 cm.$^{-1}$ with a shoulder at 880 cm.$^{-1}$ disappears, and another broad, strong band at 945 cm.$^{-1}$ and a sharp, medium band at 1310 cm.$^{-1}$ appear.
3. Testing with iron(III) chloride is recommended.
4. The product contains about 5% of *tert*-amyl iodide (^{1}H NMR); this is in agreement with the finding of Kornblum and Iffland,[3] who describe a simple way of removing this impurity.
5. As in procedure A, the heat input should be increased from time to time, and it is essential to attain the recommended final temperature; unnecessarily prolonged heating after this is reached should be avoided as the phosphonium iodide decomposes at high temperatures.
6. With some alcohols (*e.g.*, cyclohexanol) there is no appreciable rise in temperature, with others (*e.g.*, *tert*-amyl alcohol) it may be considerable, in which case the mixture should be cooled with water. In addition, there may be an induction period of up to 1 hour.
7. The reaction may be followed by IR spectroscopy: a strong, broad band at 1040 cm.$^{-1}$ disappears, and a similar band appears at 945 cm.$^{-1}$. The reaction appears to be complete after 6 hours.
8. It is not necessary to remove phenol from the reaction mixture if the alkyl iodide has a boiling point well below that of phenol. For isolation of higher boiling alkyl iodides phenol should be removed by dissolving the reaction mixture in ether (400 ml.) and washing as in procedure A.

3. Discussion

The methods described above are applicable to almost any alcohol. Procedure A is best for sterically hindered alcohols, while procedure B is especially useful for alcohols sensitive to rearrangement or alkene formation. The submitter's results for the conversion of a number of alcohols to the iodides on a preparative scale are summarized in Table I.

TABLE I
IODIDES FROM ALCOHOLS

Iodide	Procedure	Yield, %	Boiling Point, °C.
n-Butyl iodide	A	80	126–128° (760 mm.)
n-Hexyl iodide	A	75	64–66° (15 mm.)
2-Phenylethyl iodide	A	95	94–95° (1.5 mm.)
1,3-Diiodo-2,2-dimethylpropane[a]	A	75	70–71° (0.1 mm.)
tert-Amyl iodide	B	80	50–52° (50 mm.)
Ethyl 3-iodopropionate	B	90	65–66° (8 mm.)

[a]Reference 4.

Landauer and Rydon[4] describe the application of the method, on a smaller scale, to numerous other iodides; they also prepared alkyl bromides and alkyl chlorides by substituting benzyl bromide and benzyl chloride, respectively, for methyl iodide.

The preparation of alkyl iodides by the phosphorus and iodine method is described in an earlier volume of *Organic Syntheses.*[56]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 634

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

calcium chloride (10043-52-4)

ether (60-29-7)

sodium hydroxide (1310-73-2)

Cyclohexanol (108-93-0)

phenol (108-95-2)

benzyl chloride (100-44-7)

iron(III) chloride (7705-08-0)

Methyl iodide (74-88-4)

iodide (20461-54-5)

tert-amyl alcohol (75-85-4)

benzyl bromide (100-39-0)

2-Phenylethyl iodide (17376-04-4)

Iodocyclohexane, Cyclohexane, iodo- (626-62-0)

Ethyl 3-iodopropionate (6414-69-3)

Neopentyl alcohol (75-84-3)

Neopentyl iodide, Propane, 1-iodo-2,2-dimethyl- (15501-33-4)

triphenyl phosphite (101-02-0)

methyltriphenoxyphosphonium iodide (17579-99-6)

phosphonium iodide (12125-09-6)

n-Butyl iodide (542-69-8)

tert-amyl iodide (594-38-7)

n-Hexyl iodide (638-45-9)

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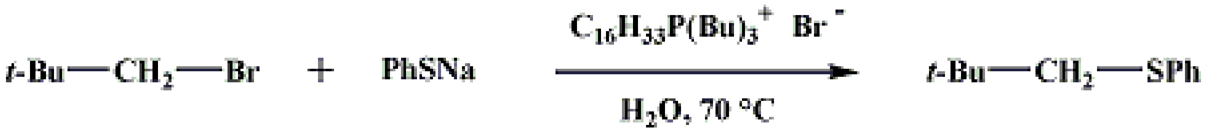
Organic Syntheses, CV 6, 833

SULFIDE SYNTHESIS IN PREPARATION OF DIALKYL AND ALKYL ARYL SULFIDES: NEOPENTYL PHENYL SULFIDE

[Benzene, [(2,2-dimethylpropyl)thio]-]



Submitted by D. Landini[1] and F. Rolla.
Checked by Ronald L. Sobczak and S. Masamune.

1. Procedure

A 100-ml., two-necked flask fitted with a reflux condenser, a gas-inlet, and a magnetic stirrer is charged with 15.1 g. (12.0 ml., 0.100 mole) of 1-bromo-2,2-dimethylpropane (Note 1), aqueous sodium benzenethiolate (0.1 mole) (Note 2), and 1.67 g. (0.00329 mole) of tributylhexadecylphosphonium bromide (Note 3) and (Note 4). This mixture is heated at 70° with vigorous stirring under nitrogen (Note 5) for 3.5 hours (Note 6). After the mixture has cooled to room temperature, the organic layer is separated, and the aqueous phase is extracted with two 20-ml. portions of diethyl ether. The combined organic phases are washed with 20 ml. of 10% aqueous sodium chloride and dried over calcium chloride. After removal of the solvent, the resulting, residual oil is distilled through a 10-cm. Vigreux column, giving 14.1–15.3 g. (78–85%) of colorless neopentyl phenyl sulfide (Note 7), b.p. 85–87° (5 mm.), 96–98° (8 mm.); n_D^{24} 1.5365 (Note 8).

2. Notes

1. 1-Bromo-2,2-dimethylpropane (neopentyl bromide) was obtained from Fluka A G or Tridom Chemical Inc.
2. Aqueous sodium benzenethiolate was prepared by adding 11.0 g. (10.2 ml., 0.100 mole) of commercial benzenethiol (listed as thiophenol by Aldrich Chemical Company, Inc., and Tridom Chemical Inc.) to an ice-cold solution of 4.0 g. of sodium hydroxide in 25 ml. of water.
3. The tributylhexadecylphosphonium bromide was prepared by heating 0.1 mole of 1-bromohexadecane and 0.1 mole of tributylphosphine at 60–70° for three days, according to Starks' procedure.[2] The product, while hot, was poured into 300 ml. of hexane and the mixture was stirred for 15 minutes. After cooling of the mixture to 0°, a solid product crystallized, was filtered on a Büchner funnel, and dried under reduced pressure, m.p. 54–56° (84%).

4. When the reaction was carried out using 0.033 mole equivalent of tricaprylylmethylammonium chloride (aliquat 336), obtained from General Mills Company, Chemical Division, Kankakee, Illinois, as catalyst, the reaction required about 10 hours for completion.
5. The nitrogen flow must be as slow as possible to avoid loss of 1-bromo-2,2-dimethylpropane.
6. The reaction time depends on the concentration of the catalyst; *e.g.*, with 0.1 and 0.01 mole equivalents of phosphonium salt, the reaction required 1 and 10 hours, respectively.
7. The catalyst could be recovered (80–90%) from the distillation residue, which also contained some neopentyl phenyl sulfide and diphenyl disulfide. These products were eliminated from the residue by column chromatography on silica (8 g. for 1 g. of phosphonium salt; eluent, ether). Extraction of the silica with two 25-ml. portions of boiling ethanol and evaporation of the solvent afforded the phosphonium salt, m.p. 48–51°. This material could be reused without further purification.
8. The product showed the following ^{1}H NMR spectrum ($CDCl_3$) δ (multiplicity, number of protons, assignment): 1.03 [s, 9H, $(CH_3)_3C$], 2.88 (s, 2H, CH_2), 7.02–7.52 (m, 5H, C_6H_5).

3. Discussion

This procedure[3] illustrates a simple and general method for the preparation of primary and secondary dialkyl and alkyl aryl thioethers *via* alkylation of sodium sulfide, sodium alkyl- or arylthiolates with alkyl chlorides or bromides. The method is an example of phase-transfer catalysis, characterized by mild reaction conditions, high yields, and simple work-up procedure.

Dineopentyl and neopentyl phenyl sulfides are obtained from 1-bromo-2,2-dimethylpropane. Some other examples are given in Table I.

TABLE I
PREPARATION OF DIALKYL AND ALKYL PHENYL SULFIDES

Alkyl Halide	Nucleophile	Catalyst (mole equivalent)	Temperature (°C)	Time (minutes)	Yield of Sulfide[a] (%)
1-Chloroöctane	Na_2S[b]	0.1	70	40	91
2-Chloroöctane	Na_2S[b]	0.1	70	300	90
1-Bromoöctane	Na_2S[b]	0.1	70	20	91
2-Bromoöctane	Na_2S[b]	0.1	70	80	91
Neopentylbromide	Na_2S[b]	0.1	70	500	81[c]

1-Chloroöctane	C_2H_5SNa[d]	0.033	40	40	90
2-Chloroöctane	C_2H_5SNa[d]	0.033	70	250	88
1-Bromoöctane	C_2H_5SNa[d]	0.033	40	15	91
2-Bromoöctane	C_2H_5SNa[d]	0.033	70	120	89
1-Chloroöctane	C_6H_5SNa[d]	0.033	40	30	92
2-Chloroöctane	C_6H_5SNa[d]	0.033	70	180	90
1-Bromoöctane	C_6H_5SNa[d]	0.033	40	10	91
2-Bromoöctane	C_6H_5SNa[d]	0.033	70	60	90

[a]Isolated products.

[b]Mole ratio of Na_2S to alkyl halide is 0.6.

[c]Reaction carried out under nitrogen.

[d]Mole ratio of sodium salt to alkyl halide is 1.

Neopentyl sulfides have been prepared by alkylation of sodium sulfide with neopentyl tosylate in high-boiling polar solvents,[4,5] or in low yields by reduction of alkyl 2,2-dimethylpropanethioate with lithium aluminum hydride in a large excess of boron trifluoride-diethyl etherate.[6]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica

ethanol (64-17-5)

calcium chloride (10043-52-4)

ether, diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

1-Bromooctane (111-83-1)

nitrogen (7727-37-9)

sodium (13966-32-0)

sodium sulfide (1313-82-2)

Thiophenol, Benzenethiol (108-98-5)

lithium aluminum hydride (16853-85-3)

hexane (110-54-3)

1-bromohexadecane (112-82-3)

boron trifluoride-diethyl etherate (109-63-7)

diphenyl disulfide (882-33-7)

tributylphosphine (998-40-3)

Neopentyl phenyl sulfide, Benzene, [(2,2-dimethylpropyl)thio]- (7210-80-2)

1-bromo-2,2-dimethylpropane, neopentyl bromide, Neopentylbromide (630-17-1)

sodium benzenethiolate

tributylhexadecylphosphonium bromide (14937-45-2)

tricaprylylmethylammonium chloride (5137-55-3)

neopentyl tosylate

1-Chlorooctane (111-85-3)

2-Chlorooctane

2-Bromooctane

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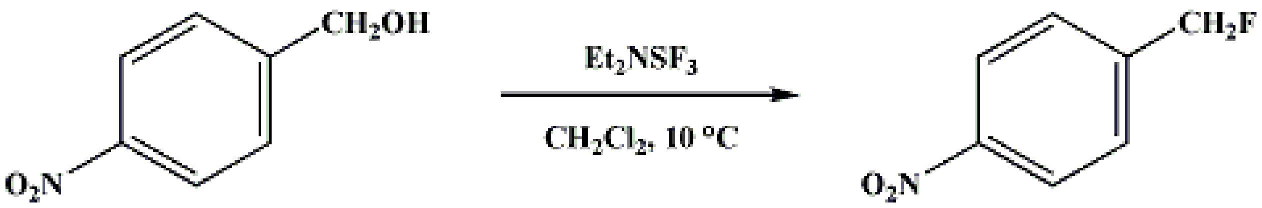
Organic Syntheses, CV 6, 835

4-NITROBENZYL FLUORIDE

[Benzene, 1-(fluoromethyl)-4-nitro-]



Submitted by W. J. Middleton[1] and E. M. Bingham.
Checked by Eugene R. Kennedy, Ronald F. Sieloff, and Carl R. Johnson.

1. Procedure

Caution! Protective gloves should be worn when handling diethylaminosulfur trifluoride because this material can cause severe HF burns.

A dry, 1-l., three-necked, round-bottomed flask is fitted with a 500-ml. dropping funnel, thermometer, a magnetic stirrer, and a reflux condenser protected from the atmosphere with a drying tube. The apparatus is flushed with dry nitrogen, and 150 ml. of dry dichloromethane and 21 ml. (0.16 mole) of diethylaminosulfur trifluoride [*Org. Synth.*, **Coll. Vol. 6**, 440 (1988)] are added to the flask. The contents of the flask are cooled to 10°, and a solution of 23.0 g. (0.150 mole) of 4-nitrobenzyl alcohol (Note 1) in 450 ml. of dichloromethane is added dropwise at a fast rate (45 minutes). The reaction mixture is allowed to come to room temperature and poured into a beaker containing 300 g. of ice, decomposing any unreacted diethylaminosulfur trifluoride. The organic layer is separated, and the water layer is extracted twice with 45-ml. portions of dichloromethane. The organic layer and extracts are combined, washed with 150 ml. of water, and dried over anhydrous magnesium sulfate. Evaporation to dryness under reduced pressure gives 20.9–22.1 g. (90–95%) of crude product. Recrystallization from 500 ml. of pentane yields 15.5 g. (67%) of 4-nitrobenzyl fluoride as colorless needle-shaped crystals, m.p. 36–37° (Note 2).

2. Notes

1. 4-Nitrobenzyl alcohol is available from Eastman Organic Chemicals or Aldrich Chemical Company, Inc.
2. An additional quantity of product of lesser purity can be obtained as a second crop by evaporation of the pentane.

3. Discussion

This procedure is an example of a broadly applicable, simple method for replacing the

hydroxyl group of functionally substituted and unsubstituted primary, secondary, and tertiary alcohols with fluorine. Diethylaminosulfur trifluoride,[2] the fluorinating reagent used in this procedure, is less likely to cause rearrangements or dehydration than other reagents sometimes used for this purpose (SF_4, HF, HF·pyridine, SeF_4·pyridine, and $(C_2H_5)_2NCF_2CHClF$).[3] Furthermore, diethylaminosulfur trifluoride is a liquid that can be measured easily and used in standard glass equipment at moderate temperatures and atmospheric pressure.

Some alcohols that have been converted into the corresponding fluorides by reactions with diethylaminosulfur trifluoride include 1-octanol, 2-methyl-2-butanol, 2-butanol, cycloöctanol, ethylene glycol, crotyl alcohol, 2-phenylethanol, 2-bromoethanol, ethyl lactate, and ethyl α-hydroxynaphthaleneacetate.[3]

4-Nitrobenzyl fluoride has also been prepared in 40–60% yield by the reaction of 4-nitrobenzyl bromide with mercuric fluoride[4] and in mixture with the *ortho* and *meta* isomers by the nitration of benzyl fluoride.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 440
- Org. Syn. Coll. Vol. 6, 628

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

nitrogen (7727-37-9)

2-BROMOETHANOL (540-51-2)

ethylene glycol (107-21-1)

Pentane (109-66-0)

dichloromethane (75-09-2)

2-phenylethanol (60-12-8)

ethyl lactate (687-47-8)

magnesium sulfate (7487-88-9)

1-Octanol (111-87-5)

2-Methyl-2-butanol (75-85-4)

Fluorine (7782-41-4)

mercuric fluoride (7783-39-3)

Crotyl alcohol

2-Butanol (78-92-2)

Diethylaminosulfur trifluoride (38078-09-0)

4-NITROBENZYL FLUORIDE, Benzene, 1-(fluoromethyl)-4-nitro- (500-11-8)

4-nitrobenzyl alcohol (619-73-8)

ethyl α-hydroxynaphthaleneacetate

4-nitrobenzyl bromide (100-11-8)

benzyl fluoride (350-50-5)

cyclooctanol

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Organic Syntheses, *CV 6, 837*

1-NITROCYCLOÖCTENE

[Cycloöctene, 1-nitro-]

Submitted by Wolfgang K. Seifert[1]
Checked by E. Lewars, P. H. McCabe, and Peter Yates.

1. Procedure

Caution! Dinitrogen tetroxide is very toxic (Note 1), and nitro nitrites are unstable. The reaction must be carried out in a well-ventilated hood with an adequate shield.

Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

Sodium-dried diethyl ether (150 ml.) is placed in a 1-l., four-necked flask equipped with a fritted gas-inlet extending to its bottom, a sealed mechanical stirrer (Note 2), a 100-ml., pressure-equalizing dropping funnel, a thermometer, and a dry ice condenser protected with a phosphorus pentoxide drying tube. Cycloöctene (44.4 g., 53.5 ml., 0.404 mole) (Note 3) is placed in the dropping funnel, and the system is swept with dry oxygen. Dinitrogen tetroxide (39.3 g., 27.1 ml. at –9°, 0.427 mole) (Note 4) is condensed (Note 5) in a graduated, calibrated trap that is protected with a phosphorus pentoxide drying tube and has been swept with dry oxygen.

The flask is cooled to –10°, and the dinitrogen tetroxide is distilled with a warm water bath from the trap into the ether, with slow stirring; the transfer is aided by a minimal flow of dry oxygen. The solution is allowed to warm to 0–5°, and the oxygen flow rate is increased to 10 ml. per minute (Note 6). The cycloöctene is dropped into the dinitrogen tetroxide solution, with vigorous stirring, over a 30-minute period. The reaction is exothermic, and the temperature is kept at 9–12° by cooling with a methanol–dry ice bath at –20°. The dropping funnel is rinsed with 25 ml. of ether, and the yellow solution (Note 7) is stirred for an additional 30 minutes at 10° with continued oxygen flow. Triethylamine (121 g., 1.20 moles) (Note 8) is added, with stirring, over a 12-minute period; the temperature of the reaction mixture is kept at 4–12° by maintaining the bath at –4° (Note 9). The mixture is kept at room temperature for an additional 30 minutes, diluted with 150 ml. of ether, and cooled to 0–5°. The excess triethylamine is neutralized with an ice-cold solution of 72 g. of acetic acid in 200 ml. of water, with stirring. The reaction mixture is transferred to a 2-l. separatory funnel and extracted with three 400-ml. portions of ether. The combined ethereal extracts are washed with two 200-ml. portions of water, three 150-ml. portions of saturated aqueous sodium hydrogen carbonate, and again with water (Note 10).

Most of the ether is removed at room temperature with a rotary evaporator. The water that separates is removed with the aid of a small separatory funnel, and the remaining ether, traces of water, and cycloöctane (Note 11) are distilled at room temperature (10 mm.) over 3 hours, yielding 59–61 g. of crude 1-nitrocycloöctene as a yellow oil (Note 12) and (Note 13). Chromatography on silica gel (Note 14) with successive elution with *n*-hexane and benzene gives 39–40 g. (63–64%) of 1-nitrocycloöctene (Note 15). Distillation (Note 16) gave an analytically pure sample, b.p. 60° (0.2 mm.), n_D^{20} 1.5116 (Note 17).

2. Notes

1. Concentrations of dinitrogen tetroxide of 100–150 p.p.m. are dangerous for exposures of 30–60 minutes, and concentrations of 200–700 p.p.m. may be fatal after even very short exposures.
2. The checkers found that magnetic stirring could be used in place of mechanical stirring.
3. Cycloöctene (95% pure) from Columbia Carbon Co., a division of Cities Service, was used without further purification.
4. A slight excess of dinitrogen tetroxide over olefin is necessary for maximum yields.
5. For good yields all reagents must be absolutely dry. For condensation of dry dinitrogen tetroxide free of dinitrogen trioxide, streams of dry oxygen (run through a flow meter, a calcium chloride tube, and concentrated sulfuric acid) and dinitrogen tetroxide (99.5% pure from the Matheson Company), are combined and run slowly through a phosphorus pentoxide tube before condensation. The freezing point of dinitrogen tetroxide is −9.3°, and a convenient cooling bath for condensation is methanol–dry ice at −8° to −10°.
6. The use of oxygen in this reaction prevents formation of undesirable by-products, *e.g.*, nitro nitroso compounds.[2] For the preparation of 1-nitro-1-octadecene the optimum mole ratio of olefin to oxygen was found[3] to be 1/50 to 1/150, compared with 1/30 in this procedure.
7. Nitro nitrites are unstable, and it is safe practice to keep them in solution until they are converted to nitro alcohols[2] or nitro olefins.[3]
8. Commercial triethylamine (Eastman Kodak Co.) was used without further purification. Stoichiometric amounts of triethylamine based on olefin produced poor yields of nitro olefins, owing to the slow rate of elimination of the nitro nitrite compounds.[3] A twofold molar ratio of triethylamine to olefin was sufficient to produce 1-nitro-1-octadecene from 1-nitro-2-octadecyl nitrite in 92% yield.[3] The same excess applied to the crude reaction product from cycloöctene and dinitrogen tetroxide resulted in only an 80% yield of 1-nitrocycloöctene.
9. At the end of the exothermic elimination reaction the color turns brown with simultaneous precipitation of the triethylammonium salts.
10. The checkers washed the ethereal extracts with saturated brine and dried

them over anhydrous magnesium sulfate before removal of ether.
11. Cycloöctane is the major impurity in the starting material.
12. The submitter estimated the crude product to be 95% pure by IR spectroscopy: $\varepsilon_{6.59\bullet}/\varepsilon_{3.40\bullet}$ = 3.00 (CCl_4: matched 0.1-mm. cells; analytical absorbances, 0.2–0.7).
13. For further reactions involving reduction,[4] the crude product can be used.
14. The silica gel column was 14 × 2.5 in. I.D.; a shorter column may suffice.
15. The checkers found for this product: n_D^{26} 1.5106; ^1H NMR ($CDCl_3$), δ 1.6 (m, 8 H), 2.3 (m, 2 H), 2.7 (m, 2 H), and 7.24 (t, *J* 9 Hz., 1 H).
16. It is safe practice to remove the peroxide that may be formed in this free radical reaction by chromatography before distillation. The submitter distilled an aliquot (12.7 g.) of the hexane eluate, giving 9.9 g. of product, $\varepsilon_{6.59\bullet}/\varepsilon_{3.40\bullet}$ = 3.12 (Calcd. for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 61.84; H, 8.27; N, 8.80).
17. Slow decomposition with simultaneous precipitation of a solid occurred on standing for several weeks at 23°. Immediate analysis and use of the product are advised.

3. Discussion

The major advantage of the present method, the only method reported[3] for the preparation of 1-nitrocycloöctene, is the convenience of converting an olefin to a 1-nitro olefin in good yield without isolation of any intermediate. The submitter has also used this method[3] successfully for the preparation of 1-nitro-1-octadecene from 1-octadecene.

In the past the products from the addition of dinitrogen tetroxide to olefins have been hydrolyzed and converted to 1-nitro olefins by various methods, *e.g.*, acetylation of the isolated nitro alcohol and elimination of acetic acid with potassium carbonate,[5,6] dehydration of the nitro alcohol with phthalic anhydride[7] or potassium hydrogen sulfate,[8] and base-catalyzed elimination of nitrous and nitric acid from dinitro compounds and nitro nitrates, respectively.[2] Besides representing longer syntheses, these routes require separation of the nitro alcohol from the dinitro compound and, since these substances occur in approximately equal amounts, 50% of the yield is lost in the first step. Furthermore, in the case of the higher 1-olefins, this separation is difficult[9,10] and tedious.[3] 1-Nitro 1-olefins have been employed in the preparation of saturated nitro compounds and oximes.[4]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

dinitrogen tetroxide

dinitrogen trioxide

nitrous and nitric acid

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

Benzene (71-43-2)

ether, diethyl ether (60-29-7)

sodium hydrogen carbonate (144-55-8)

oxygen (7782-44-7)

phthalic anhydride (85-44-9)

potassium hydrogen sulfate (7646-93-7)

magnesium sulfate (7487-88-9)

hexane, n-hexane (110-54-3)

triethylamine (121-44-8)

cyclooctene

cyclooctane (292-64-8)

1-nitro-1-octadecene

1-nitro-2-octadecyl nitrite

1-octadecene (112-88-9)

1-NITROCYCLOOCTENE, Cyclooctene, 1-nitro- (1782-03-2)

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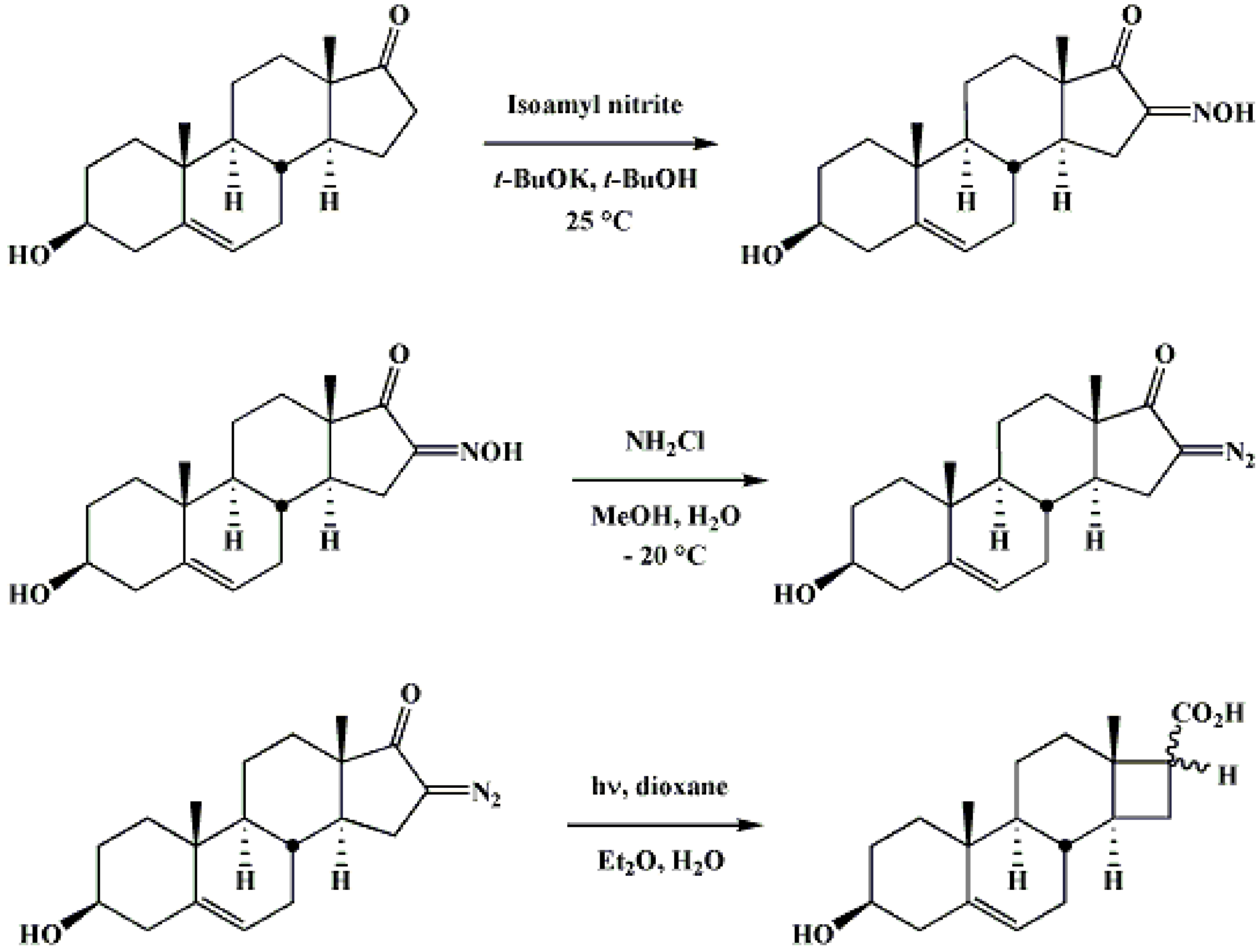
Organic Syntheses, CV 6, 840

FORMATION AND PHOTOCHEMICAL WOLFF REARRANGEMENT OF CYCLIC α-DIAZO KETONES: D-NORANDROST-5-EN-3β-OL-16-CARBOXYLIC ACIDS

[D-Norandrost-5-ene-16-carboxylic acids, 3β-hydroxy-, (3β,16α) and (3β,16β)-]



Submitted by Thomas N. Wheeler and J. Meinwald[1].
Checked by R. A. Blattel, D. G. B. Boocock, and Peter Yates.

1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A. *16-Oximinoandrost-5-en-3β-ol-17-one*. A 2-l., three-necked, round-bottomed flask fitted with a reflux condenser, a mechanical stirrer, and a pressure-equalizing dropping funnel is charged with 750 ml. of anhydrous *tert*-butyl alcohol (Note 1). As the *tert*-butyl alcohol is slowly stirred, a stream of dry nitrogen is passed through the flask and 12.2 g. (0.312 g.-atom) of potassium metal is added cautiously. The flask is surrounded by a water bath maintained at 70° to assist in dissolving the potassium metal. After 1.5 hours the stirred mixture is homogeneous, the water bath is removed, and the reaction mixture is allowed to cool to room temperature. To the potassium *tert*-butoxide solution

is slowly added 45.0 g. (0.156 mole) of dehydroisoandrosterone (Note 2), and stirring is continued for one hour until the gold-colored mixture is again homogeneous. To the reaction mixture is now added, dropwise, 36.5 g. (42.0 ml., 0.312 mole) of isoamyl nitrite (Note 3), and stirring is continued overnight at room temperature.

The deep-orange reaction mixture is diluted with an equal volume of water, poured into a 2-l. separatory funnel, and acidified with 3 *M* hydrochloric acid. The addition of 400 ml. of diethyl ether assists in effecting the separation of the clear, yellow, aqueous, lower layer from the fluffy-white ethereal suspension that forms the upper layer. This suspension is filtered through a 250-ml. coarse sintered glass funnel, and the precipitate of oximino ketone is washed with ether several times. After drying overnight in a vacuum desiccator at –5°, 48.0–48.5 g. (79% (Note 5) and (Note 6)) of a white product, m.p. 245–247° (dec.), is obtained; its ^{1}H NMR spectrum (pyridine) shows it to be a 1:1 solvate of the oximino ketone with *tert*-butyl alcohol (Note 4). This product is used without further purification in the synthesis of the α-diazo ketone (Note 7).

B. *16-Diazoandrost-5-en-3β-ol-17-one*. A 1-l., three-necked, round-bottomed flask is fitted with a mechanical stirrer, a 50-ml., pressure-equalizing dropping funnel, and a thermometer. As stirring is initiated, 375 ml. of methanol and 72 ml. of 5.0 *M* aqueous sodium hydroxide (0.36 mole) is added to the flask, followed by 18.0 g. (0.0460 mole) of the 1:1 solvate of 16-oximinoandrost-5-en-3β-ol-17-one with *tert*-butyl alcohol. The oximino ketone readily dissolves, giving a yellow solution. To the reaction mixture is added 28.3 ml. of concentrated aqueous ammonia (0.425 mole), and the flask is surrounded by an ice bath, maintaining the reaction temperature at 20°. Through the dropping funnel 133 ml. of 3.0 *M* aqueous sodium hypochlorite (0.40 mole) is added dropwise. The sodium hypochlorite solution should be kept near 0°; 25-ml. portions should be added to the addition funnel and the remaining solution should be kept in an ice bath (Note 8). It is important that the rate of addition of the sodium hypochlorite, and the position of the ice bath be adjusted so as to maintain the temperature of the reaction mixture at 20° ± 1° (Note 9). As soon as all of the sodium hypochlorite has been added, the ice bath is removed, and the reaction mixture is allowed to warm to room temperature and stirred for 6 hours.

The reaction mixture is diluted with an equal volume of water and extracted with 400-ml. and 200-ml. portions of dichloromethane. The combined dichloromethane extracts are washed with three 250-ml. portions of 20% aqueous sodium chloride, dried over anhydrous magnesium sulfate, and concentrated, leaving a yellow solid. Recrystallization from acetone gives 8.0–9.3 g. (55–64%) of crystalline α-diazo ketone, m.p. 200–202° (dec.) (Note 10).

C. D-*Norandrost*-5-*en*-3β-*ol*-16α- *and* 16β-*carboxylic acids*. In a solution of 500 ml. of 1,4-dioxane, 1250 ml. of ether, and 250 ml. of water contained in a 3-l. three-necked, round-bottomed flask is dissolved 7.50 g. (0.0239 mole) of 16-diazoandrost-5-en-3β-ol-17-one. The flask is fitted with a reflux condenser, a quartz immersion well, and a nitrogen inlet. After the reaction vessel has been flushed with nitrogen, the diazo ketone solution is irradiated for 48 hours with a 450-watt Hanovia lamp with a Corex filter (Note 11). The photolysis mixture is decanted in portions into a 2-l. separatory funnel, washed three times with 500-ml. portions of water, removing the dioxane, and dried over magnesium sulfate. The ether is evaporated, leaving a pale-yellow residue. The residue is digested with 125 ml. of boiling dichloromethane under reflux for 30 minutes. The dichloromethane solution is allowed to cool to room temperature and filtered, separating about 1.4 g. of the crude α-isomer as a white powder. This solid is recrystallized by dissolving it in a large volume of methanol (125 ml.) and concentrating the solution to a small volume (25 ml.), yielding 1.2 g. (17%) of D-norandrost-5-en-3β-ol-16α-carboxylic acid as a white solid, m.p. 271–274° (Note 12). The β-isomer is most readily obtained by concentrating the dichloromethane mother liquor and dissolving the

residue in a mixture of 75 ml. of methanol and 25 ml. of ether. This solution is treated with an excess of diazomethane in ether at room temperature. After one hour at room temperature, the excess diazomethane is removed with a stream of nitrogen, the solvent is evaporated, and the solid residue is chromatographed on 175 g. of Woelm neutral alumina Activity Grade II. Elution with a 3:1 (v/v) benzene–ether mixture gives 3.9 g. of a white solid, which is recrystallized from ether-heptane, giving 3.0–3.1 g. (39–41%) of white, crystalline methyl D-norandrost-5-en-3β-ol-16β-carboxylate, m. p. 161–163° (Note 13) and (Note 14).

2. Notes

1. Anhydrous *tert*-butyl alcohol may be conveniently prepared by distilling it from calcium hydride into a receiver containing Type 4A molecular sieves.
2. Dehydroisoandrosterone is available from Searle Chemicals, Inc.
3. Isoamyl nitrite of sufficient purity may be prepared by the method in *Org. Synth.*, **Coll. Vol. 2**, 108 (1943). The isoamyl nitrite is stored over anhydrous magnesium sulfate until used.
4. The ^{1}H NMR spectrum (pyridine) included signals at δ 0.97 (s, 3H), 1.03 (s, 3H), 1.42 (s, 9H) and 5.37 (m, 1H).
5. The submitters, working on twice the scale described, obtained 90.0 g. (74%) of the solvate, m.p. 245–247°.
6. This oximino ketone has been previously prepared by a somewhat different procedure[2] and recrystallized from 2-propanol, m.p. 247–248°.
7. Other oximino ketones may be too soluble in ether to permit utilization of this isolation procedure. In this case, the submitters, working on twice the scale described, utilized the following procedure. After acidification of the reaction mixture, the oximino ketone is extracted into 1000 ml. of ether, and the ethereal extract is washed with four 100-ml. portions of saturated aqueous sodium hydrogen carbonate and exhaustively extracted with 0.5 *M* aqueous potassium hydroxide in 250-ml. portions until acidification of the basic extract gives no oximino ketone. A stream of nitrogen is bubbled through the combined basic extracts, removing any dissolved ether before the solution is cooled in an ice bath and acidified with 3 *M* hydrochloric acid. The precipitate is collected by suction filtration and dried in a vacuum desiccator.
8. A procedure for preparing concentrated sodium hypochlorite solution is given by Coleman and Johnson.[3] Common bleach solution, such as Clorox, may also be used, although the volume of the solution is considerably increased.
9. If the temperature of the reaction mixture is maintained below 20°, an appreciable amount of colorless α-dichloro ketone is obtained.[4] If the temperature rises above 20°, the chloramine decomposes before it has time to react with the oximino ketone. The generation of chloramine *in situ* is quite exothermic, and care must be taken to maintain the temperature at 20°.
10. The submitters, working on twice the scale described, obtained 21.6 g. (74%) of product, m.p. 201–202° (dec.).
11. A Pyrex filter has been used; however, the photolysis appears to proceed more cleanly through Corex. The photolysis is considered complete when the IR spectrum of a sample shows no diazo absorption at 2065 cm^{-1}.
12. Utilizing a somewhat different procedure, Mateos and Pozas have also obtained the α-carboxylic acid, m.p. 272–275°.[5]
13. The reported melting point of the β-methyl ester is 163–164°.[5]
14. The submitters, working on twice the scale described, obtained 2.8 g. (19%) of the α-acid, m.p. 272–275°, and 9.2 g. (61%) of the methyl ester of the β-acid, m.p. 161–163°.

3. Discussion

The earliest methods for preparing cyclic α-diazo ketones involved the oxidation of the monohydrazones prepared from α-diketones, generally using mercury(II) oxide.[6,7] Recent modifications of this procedure include the use of calcium hypochlorite in aqueous sodium hydroxide or "activated" manganese dioxide as oxidants.[8] The latter reagent, especially, seems preferable to mercury(II) oxide. The base-catalyzed decomposition of the monotosylhydrazones of α-diketones has been used to prepare α-diazo ketones. Such reactions have been performed in aqueous sodium hydroxide,[9,10] with basic aluminum oxide in dichloromethane,[11] and with a variety of other bases. A promising and novel approach to cyclic α-diazo ketones involves the reaction of α-hydroxymethylene ketones with diethylamine and tosyl azide, giving high yields of the α-diazo ketone.[12]

The present procedure for the synthesis of an α-diazo ketone is a modification of the Forster reaction,[13] which has been recently exploited by numerous workers.[10,14,15,16,17,18] The synthesis is convenient, generally applicable to cyclic ketones, and offers moderate yields (60–70%) of pure α-diazo ketones.

The photochemical Wolff rearrangement represents a generally useful ring contraction technique.[19,20]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alumina

D-Norandrost-5-ene-16-carboxylic acids, 3β-hydroxy-, (3β,16α) and (3β,16β)-

dehydroisoandrosterone

D-norandrost-5-en-3β-ol-16α-carboxylic acid

methyl D-norandrost-5-en-3β-ol-16β-carboxylate

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

Benzene (71-43-2)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium hydrogen carbonate (144-55-8)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

mercury(II) oxide (21908-53-2)

acetone (67-64-1)

pyridine (110-86-1)

potassium hydroxide (1310-58-3)

2-propanol (67-63-0)

manganese dioxide (1313-13-9)

potassium (7440-09-7)

diethylamine (109-89-7)

sodium hypochlorite (7681-52-9)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

dioxane (5703-46-8)

Isoamyl nitrite (110-46-3)

Diazomethane (334-88-3)

aluminum oxide (1344-28-1)

calcium hypochlorite (7778-54-3)

heptane (142-82-5)

chloramine (10599-90-3)

tert-butyl alcohol (75-65-0)

calcium hydride (7789-78-8)

1,4-dioxane (123-91-1)

16-oximinoandrost-5-en-3β-ol-17-one (21242-37-5)

16-Diazoandrost-5-en-3β-ol-17-one (26003-42-9)

tosyl azide (941-55-9)

potassium tert-butoxide (865-47-4)

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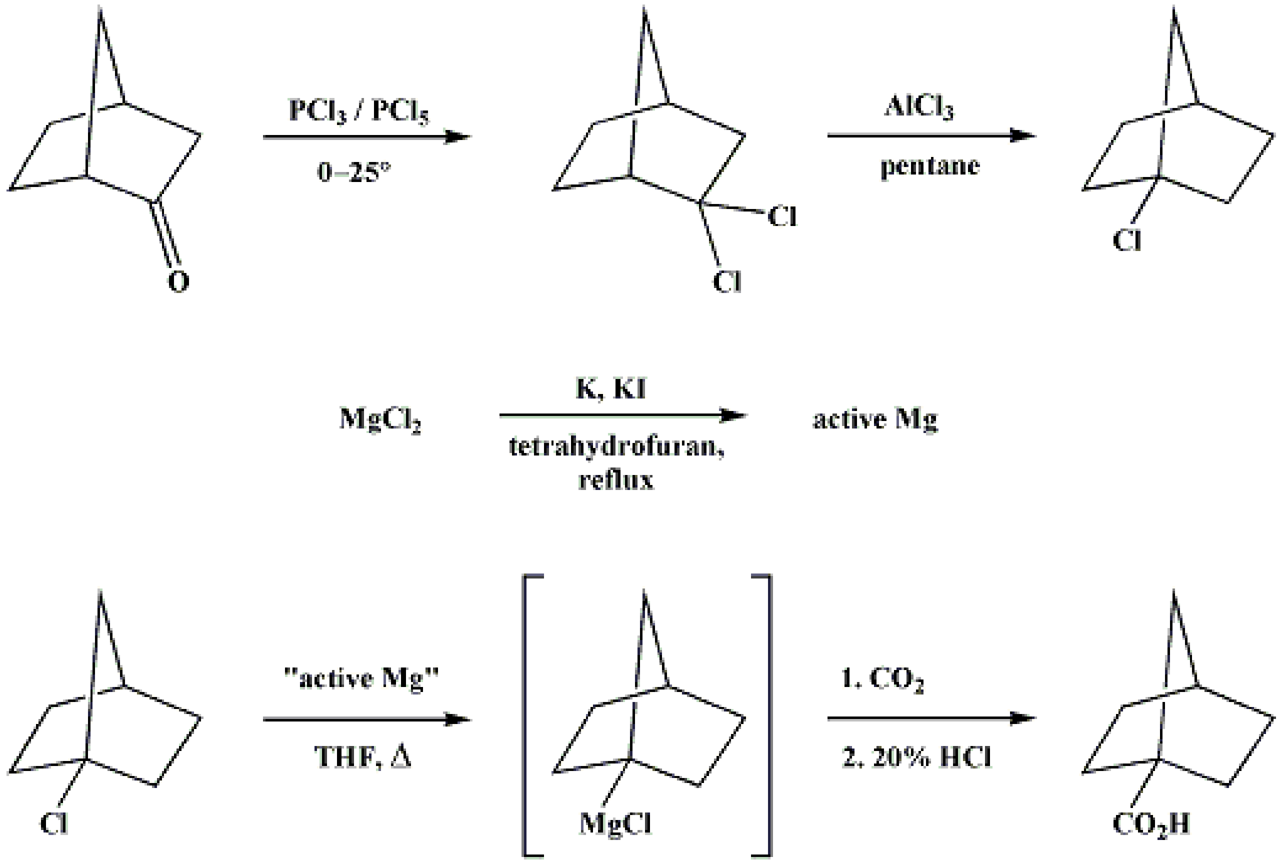
Organic Syntheses, *CV 6, 845*

HIGHLY REACTIVE MAGNESIUM FOR THE PREPARATION OF GRIGNARD REAGENTS: 1-NORBORNANECARBOXYLIC ACID

[Bicyclo[2.2.1]heptane-1-carboxylic acid]



Submitted by Reuben D. Rieke[1], Stephen E. Bales, Phillip M. Hudnall, Timothy P. Burns, and Graham S. Poindexter.
Checked by Dennis P. Stack and Robert M. Coates.

1. Procedure

Caution! Potassium is highly reactive. Although it may be handled safely in air if it is covered with a hydrocarbon solvent such as heptane or mineral oil, it will spark and ignite flammable organic vapors on contact with water. The magnesium formed in this reaction is highly reactive and pyrophoric (Note 1). Accordingly, Parts C and D of this procedure should be carried out behind a safety shield.

A. *2,2-Dichloronorbornane.* A 1-l., round-bottomed flask equipped with a mechanical stirrer and a calcium sulfate drying tube is charged with 91.3 g. (0.665 mole) of phosphorus trichloride and 90.0 g. (0.817 mole) of norcamphor (Note 2). The solution is stirred and cooled to 0° in an ice–salt bath, then 193 g. (0.927 mole) of phosphorus pentachloride is added in portions over a 1-hour period. The mixture is allowed to warm to room temperature and stand overnight. The

contents of the flask are poured carefully onto 1000 g. of crushed ice. The mixture is thoroughly dispersed and extracted with four 500-ml. portions of pentane. The combined pentane layers are washed with two 600-ml. portions of water, and the aqueous layers are extracted with one 500-ml. portion of pentane. The pentane extracts are combined, dried over anhydrous sodium sulfate, and evaporated under reduced pressure. Distillation of the residual brown liquid affords 111–114 g. (82–85%) of 2,2-dichloronorbornane as a clear liquid, b.p. 70–74° (14 mm.), which solidifies on standing (Note 3).

B. *1-Chloronorbornane.* A 5-l., three-necked, round-bottomed flask equipped with a mechanical stirrer, a condenser fitted with a drying tube, and a stopper is charged with 230 g. (1.39 moles) of 2,2-dichloronorbornane and 3 l. of pentane (Note 4). The solution is stirred as 87.0 g. (0.652 mole) of aluminum chloride is added over 4.5 hours. The mixture is stirred for 40 hours, during which time hydrogen chloride gas evolves and a brown sludge accumulates on the walls of the flask. The supernatant pentane solution is decanted, and the brown sludge remaining in the flask is thoroughly extracted with four 200-ml. portions of pentane. The combined pentane extracts are washed with three 600-ml. portions of water and one 600-ml. portion of saturated sodium chloride. The combined aqueous washes are extracted with two additional 500-ml. portions of pentane, which are combined with the preceding pentane solution and dried over anhydrous sodium sulfate. The pentane solution is concentrated by distillation through a 3 × 30 cm. Vigreux column, and the residual liquid is distilled, affording 110–114 g. (60–63%) of 1-chloronorbornane as a colorless liquid, b.p. 70–74° (55 mm.), which solidifies on standing at room temperature (Note 5).

C. *Active magnesium.* A 200-ml., three-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar, stopper, rubber septum, and condenser connected to an argon inlet (Note 6) is charged with 1.5 g. (0.038 g.-atom) of freshly cut potassium (Note 7), (Note 8), and (Note 19), 2.01 g. (0.0211 mole) of anhydrous magnesium chloride (Note 9), 3.55 g. (0.0214 mole) of anhydrous potassium iodide (Note 10), and 50 ml. of tetrahydrofuran (Note 11). The mixture is stirred vigorously (Note 12) and heated to reflux with an electric heating mantle (Note 13). A black precipitate starts to form within a few minutes. After 3 hours at reflux temperature, the reduction should be complete (Note 14), producing active magnesium as a black powder that settles very slowly when the stirring is stopped (Note 15).

D. *1-Norbornanecarboxylic acid.* The mixture of active magnesium metal and potassium salts is allowed to cool to room temperature, after which 1.25 g. (0.00958 mole) of 1-chloronorbornane is injected with a syringe through the septum into the flask (Note 16). The reaction mixture is heated under reflux for 6 hours and cooled to room temperature. A large excess of freshly sublimed dry ice chunks is added quickly to the Grignard reagent through the extra neck of the flask. The mixture is stirred vigorously, warmed to room temperature, acidified with 50-ml. of 20% hydrochloric acid, and extracted with three 100-ml. portions of diethyl ether. The combined ether layers are extracted with 100 ml. of 10% aqueous sodium hydroxide. The alkaline solution is acidified with concentrated hydrochloric acid, and the acidic solution is extracted with two 100-ml. portions of ether. The ether extracts are combined, washed with two 50-ml. portions of water, dried over anhydrous sodium sulfate, and evaporated, giving 0.80–0.94 g. (60–70%) of 1-norbornanecarboxylic acid as a slightly yellow crystalline solid, m.p. 106–109° (Note 17) and (Note 18).

2. Notes

1. Although the submitters have never had a fire or explosion caused by active magnesium or other activated metals, they suggest extreme caution in working with these reactive materials, especially while the worker familiarizes him- or herself with the characteristics of each step in the procedure. If the active magnesium is wet with solvent when removed from the reaction vessel, it does not ignite spontaneously. If, however, the magnesium is allowed to dry first, it begins to glow when exposed to air. The submitters advise that the magnesium powder be kept under an argon atmosphere at all times.

2. The submitters purchased norcamphor from Aldrich Chemical Company, Inc. The checkers prepared this compound according to *Org. Synth.*, **Coll. Vol. 5**, 852 (1973).

3. The spectral characteristics of 2,2-dichloronorbornane are as follows: IR (CCl_4) $cm.^{-1}$: 1449, 1307, 1072, 966, 933, 713; ^1H NMR (CCl_4), δ (number of protons): 1.1–2.8 (10H).

4. Pentane was dried by distillation from aluminum chloride.

5. 1-Chloronorbornane has the following spectral properties: IR (CCl_4) $cm.^{-1}$: 1451, 1310, 1298, 1037, 992, 947, 905, 838; ^1H NMR (CCl_4), δ (multiplicity, number of protons, assignment): 1.2–1.9 (broad m, 10H, 5CH_2) and 2.2 (broad s, 1H, CH); ^{13}C NMR ($CDCl_3$): δ (off-resonance multiplicity, assignment): 31.0 (m, C-2 and C-6 or C-3 and C-5), 34.8 (d, C-4), 38.4 (m, C-2 and C-6 or C-3 and C-5), 46.8 (t, C-7), 70.0 (s, C-1).

6. The apparatus is dried in an oven and maintained under an argon atmosphere during the reaction. The submitters recommend against the use of nitrogen, since there are indications that nitrogen reacts with active magnesium. Argon, used as supplied by Matheson Gas Products or the Linde Division of Union Carbide Corporation, was delivered to the gas-inlet through a combination of glass and Tygon tubing. A minimum of Tygon tubing is advised to avoid the diffusion of air into the argon stream.

7. Purified grade potassium from J. T. Baker Chemical Company has been found by the submitters to give the most consistent results. The checkers used potassium metal from Allied Chemical Corporation. Very impure potassium or sodium generally gives magnesium powder with much reduced reactivity. Sodium may be used in place of potassium provided that the boiling point of the solvent chosen (Note 11) is higher than the melting point of the metal.

8. The potassium is usually cut into two or three pieces under hexane or heptane and placed wet in a tared flask that has been purged with argon. The flask is evacuated, removing the hydrocarbon, filled again with argon, and weighed to determine the exact amount of potassium. The amount of potassium used by the checkers varied from 1.4 to 1.6 g., the weights of the other reagents being adjusted proportionately. With this procedure the pieces of potassium are shiny and relatively free from oxide coating. Alternatively, the potassium cuttings may be wiped free of solvent, quickly weighed in air, and placed in the flask. The submitters recommend that the first procedure be used.

9. Anhydrous magnesium chloride from Alfa Division, Ventron Corporation, was used as supplied by both the submitters and checkers. The submitters have subsequently had success with anhydrous magnesium chloride and bromide purchased from Cerac, Inc., P. O. Box 1178, Milwaukee, Wisconsin 53201. The checkers were unsuccessful in several attempts to prepare suitably active magnesium from analytical grade anhydrous magnesium chloride, purchased from Research Organic/Inorganic Chemical Corporation. The submitters stress that the reagent must be anhydrous. It may be stored in a desiccator containing anhydrous calcium sulfate and, if required, dried overnight in an oven at 120°. Anhydrous magnesium chloride cannot, however, be prepared by heating the hexahydrate under vacuum, since hydrogen chloride is released before dehydration is complete. The

submitters have prepared active magnesium from anhydrous magnesium bromide and iodide; however, highly insoluble magnesium salts such as the fluoride or sulfate are not reduced. A small excess of magnesium chloride is used in this procedure to ensure that the potassium is completely consumed. The submitters have also provided the following unchecked procedure, which is suitable for preparing both anhydrous magnesium chloride and bromide. The magnesium turnings and 1,2-dibromoethane used were purchased from J. T. Baker Chemical Company and Aldrich Chemical Company, Inc., respectively. A 200-ml., three-necked, round-bottomed flask equipped with a magnetic stirring bar, two stoppers, and a condenser connected to an argon inlet (Note 6) is charged with 0.35 g. (0.014 g.-atom) of magnesium turnings, 50 ml. of tetrahydrofuran (Note 11), and 3.0 g. (0.016 mole) of 1,2-dibromoethane. The suspension is warmed gently, initiating the reaction. After the initially exothermic reaction subsides, the mixture is heated at reflux for 50 minutes. The solvent is evaporated under a reduced pressure of argon or nitrogen, leaving a white solid. The flask is then evacuated and heated in an oil bath at 150° for 1 hour. The dry magnesium bromide is ready for preparing active magnesium in the same flask.

10. Potassium iodide (>99% purity) from Allied Chemical Corporation or Mallinckrodt Chemical Works is finely ground with a mortar and pestle, dried overnight in an oven at 120°, and stored in a desiccator. The molar ratio of potassium iodide to magnesium chloride is not highly critical and may vary from 0.05 to 2.0. However, the optimum ratio is 1:1, as specified in the procedure. If the potassium iodide is omitted, the black magnesium powder produced reacts with bromobenzene at −78°. However, since the magnesium prepared in this way does not react with fluorobenzene in refluxing tetrahydrofuran, it is evidently less reactive than that produced in the presence of potassium iodide.

11. The submitters purified the tetrahydrofuran prior to use by distillation from lithium aluminum hydride. For a warning concerning potential hazards of this procedure, see *Org. Synth.*, **Coll. Vol. 5**, 976 (1973). The checkers distilled the solvent from the sodium ketyl of benzophenone. The submitters have found that diglyme and 1,2-dimethoxyethane are also effective solvents. The reactivity of the magnesium obtained with 1,2-dimethoxyethane as solvent is slightly reduced. Hydrocarbons, amines, and dioxane proved to be ineffective solvents, owing to the insolubility of the magnesium salts and consequent incomplete reduction.

12. Efficient stirring is essential for the generation of highly reactive magnesium. If the stirring is not effective, the reduction may not be complete after the 3-hour reaction time. The remaining unreacted potassium is a fire hazard during the isolation of the product. If the scale of the reaction is increased, measures should be taken to ensure that effective stirring can be maintained throughout the reaction period. The submitters recommend that, as a precaution, the scale be increased gradually.

13. The mildly exothermic reduction may result in excessive foaming which carries potassium particles up into the condenser. This problem is avoided by using a relatively large flask (in this case, 200 ml. instead of 100 ml.) and by carefully controlling the temperature at the beginning of the reduction.

14. The reduction appears to be essentially complete in 30–45 minutes. However, a reaction time of 3 hours is recommended to ensure complete consumption of the potassium (Note 12).

15. Although the submitters have found that the active magnesium may be stored under argon for several days, they advise that the preparation be used within a few hours to obtain the maximum reactivity. Most of the reactions carried out by the submitters with

the active magnesium were performed in the same flask and solvent used for the reduction. Attempts to evaporate the tetrahydrofuran and replace it with different solvents resulted in magnesium suspensions of reduced reactivity. The active magnesium may be conveniently transferred to another reaction vessel, if desired, as a slurry under an atmosphere of argon.

16. The solid chloride was melted by warming on a steam bath and drawn into a syringe that had been warmed briefly in an oven.

17. The submitters reported a melting point of 114–116°. The checkers obtained analytically pure material with a recovery of 80% after decolorization with activated carbon and recrystallization from 2–3 ml. of hexane at 0°. The product was also purified with comparable efficiency by sublimation at 85–90° (10 mm.). A small amount of a yellow, volatile impurity was removed from the cold finger before the product began to sublime. The melting point of the product after purification by the checkers was 110–112°. (lit.,[2] m.p. 114–116°).

18. The spectral properties of the product are as follows: IR (KBr) cm.$^{-1}$: 2960 (OH), 1693 (C=O), 1422, 1312, 1262, 952, 734; ^{1}H NMR (CCl_4), δ (multiplicity, number of protons, assignment): 1.1–1.9 (m, 10H, 5 CH_2), 2.2 (broad s, 1H, C*H*), 12.5 (s, CO_2*H*); ^{13}C NMR ($CDCl_3$), δ (off-resonance multiplicity, assignment): 30.0 and 33.0 (m, C-2, C-3, C-5, C-6), 37.8 (d, C-4), 42.4 (t, C-7), 52.2 (s, C-1), 183.8 (s, carboxyl C).

19. The submitters have recently developed the following unchecked procedure, which is suitable for preparing highly reactive magnesium powder, using lithium as a reducing agent.[3] This procedure avoids potassium and produces a magnesium powder equal in reactivity to that obtained using potassium as the reducing agent. A 50-ml., two-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar, rubber septum, and condenser connected to an argon inlet (Note 6) is charged with 0.224 g. (0.0325 g.-atom) of freshly cut lithium (Note 20), 1.57 g. (0.0165 mole) of anhydrous magnesium chloride (Note 9), 0.436 g. (0.00341 mole) of naphthalene and 10 ml. of tetrahydrofuran (Note 11). The mixture is stirred vigorously at room temperature for 24 hours (Note 21). After complete reduction, the highly reactive magnesium appears as a dark gray to black powder which slowly settles after stirring is stopped. In some cases, the tetrahydrofuran has a slight olive green color due to a small amount of lithium naphthalide. This can be ignored when the highly reactive magnesium is reacted. If desired this can be removed by withdrawing the tetrahydrofuran with a syringe and adding fresh, dry tetrahydrofuran or other solvent.

20. Lithium (99.9%, rod, 1.27 cm. dia.) from Alfa has been used extensively in our studies. The lithium is cut under oil, rinsed in hexane, and transferred to a tared 24/40 adapter with a stopcock and rubber septum which has been filled with argon. The adapter is evacuated, removing the hexane, filled with argon and weighed. The lithium is then transferred to the reaction vessel under an argon stream.

21. It is important that the reaction be stirred vigorously and that the lithium make frequent contact with the stirring bar, as the lithium has a tendency to become coated with magnesium and stop the reduction from continuing. If reduction does stop, it can be initiated again by gently rubbing the piece of lithium against the wall of the flask with a metal spatula, the rubber septum can be temporarily removed under a stream of argon to carry out this procedure.

3. Discussion

The procedures for the preparation of 2,2-dichloronorbornane and 1-chloronorbornane are based on those of Bixler and Nieman.[2] The active magnesium generated in Part C of this procedure[4,5,6] is useful for the formation of Grignard reagents from alkyl and aryl halides that do not react, or react only slowly, with magnesium turnings or magnesium activated by previously known methods. Prior to the development of this procedure, four basic modifications of the usual methods for preparing Grignard reagents were utilized for relatively unreactive halides: the use of (1) higher reaction temperatures by variation of the solvent, (2) more strongly coordinating solvents such as tetrahydrofuran,[7,8,9] (3) various procedures to activate the surface of the magnesium,[10,11,12,13,14] and (4) magnesium slurries prepared by co-condensation of magnesium vapor and solvent.[15]

Activation of magnesium in the third method has been effected by reduction of the size of the metal particles[13] and chemical reactions. The Gilman procedure,[10] which consists of adding iodine to activate the magnesium surface, is representative of the latter technique. Ethyl bromide and 1,2-dibromoethane have been employed in catalytic amounts to activate the metal surface, and in stoichiometric proportions for entrainment.[11] Certain transition metal halides have also proved to be effective catalysts.[12] The magnesium preparations obtained by the co-condensation method are quite active, though considerably less active than those generated by the reduction process.[16] An alternative procedure has recently been published for the reduction of magnesium halides to activated magnesium with sodium naphthalene radical anion.[17]

Some results from an investigation into the reactions of activated magnesium with various halides and dihalides, some of which react with difficulty under the conditions of normal Grignard preparations, are given in Table I.[6] A number of important features can be noted from the table, including the facile formation of di-Grignard reagents and allyl-and vinylmagnesium halides. Alkyl and aryl fluorides are easily converted to the corresponding magnesium fluorides. The formation of Grignard reagents may be effected at temperatures of –78° or below with active magnesium, thus allowing Grignard reactions to be carried out with unstable compounds.

TABLE I
REACTION OF VARIOUS HALIDES WITH ACTIVATED MAGNESIUM

Halide	Magnesium/Halide[a] Ratio	Temperature (°)	Time (minutes)	Yield of Product (%) Mono-Grignard[b]	Di-Grignard[b]	Carboxylic Acid[c]
1,4-Dibromobenzene	4	25	15		100	
1,4-Bromochlorobenzene	4	25	15	100	10	
	4	25	120	100	100	
1,4-Dichlorobenzene	2	25	180	90	0	80
	4	25	120	100	30	
Fluorobenzene	4	66	60			69
tert-Butyl chloride	2	25	10	100		52
1-Chloronorbornane	1.7	66	360	74		63

Methallyl chloride	2	25	60		82
2-Bromopropene	2	25	5	100	71

[a]With the aryl halides and 1-chloronorbornane the activated magnesium was formed in the presence of potassium iodide.

[b]Yield of hydrocarbon determined by GC after hydrolysis.

[c]Isolated yield based on halide after carbonation.

The Grignard reagents prepared from activated magnesium appear to react normally with electrophiles. Thus, reactions with proton donors, ketones, and carbon dioxide afford hydrocarbons, alcohols, and carboxylic acids, respectively. The reductive coupling of ketones to pinacols had also been accomplished with activated magnesium.[16]

1-Norbornanecarboxylic acid has been prepared by concurrent rearrangement and hydrogenolysis of *endo*-2-bromo-2-norbornanecarboxylic acid,[18] by sequential reduction and hydrolysis of *exo*-2-bromo-1-norbornanecarboxamide,[19] by ozonolysis of 1-(4-methoxyphenyl) norbornane,[20] and by carbonation of 1-norbornyllithium.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 580

References and Notes

1. Department of Chemistry, University of Nebraska—Lincoln, Lincoln, Nebraska 68588. This work was supported in part by grants from the Research Corporation, National Science Foundation, North Carolina Board of Science and Technology, the Alfred P. Sloan Foundation, the Army Research Office, and the Division of Sciences, Department of Energy (Contract No. DE-AC02-80ER-1063).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium ketyl of benzophenone

magnesium bromide and iodide

hydrogen chloride, hydrochloric acid (7647-01-0)

ether, diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

phosphorus pentachloride (10026-13-8)

magnesium, magnesium turnings, magnesium powder (7439-95-4)

sodium chloride (7647-14-5)

bromide (24959-67-9)

Ethyl bromide (74-96-4)

sodium sulfate (7757-82-6)

potassium iodide (7681-11-0)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

calcium sulfate (7778-18-9)

iodine (7553-56-2)

carbon (7782-42-5)

aluminum chloride (3495-54-3)

sodium (13966-32-0)

bromobenzene (108-86-1)

phosphorus trichloride (7719-12-2)

1,2-dibromoethane (106-93-4)

Naphthalene (91-20-3)

tert-Butyl chloride (507-20-0)

potassium (7440-09-7)

magnesium bromide (7789-48-2)

Pentane (109-66-0)

lithium (7439-93-2)

dioxane (5703-46-8)

Fluorobenzene (462-06-6)

magnesium chloride

Tetrahydrofuran (109-99-9)

heptane (142-82-5)

lithium aluminum hydride (16853-85-3)

hexane (110-54-3)

1,2-dimethoxyethane (110-71-4)

diglyme (111-96-6)

methallyl chloride (563-47-3)

1-Chloronorbornane (765-67-3)

argon (7440-37-1)

Norcamphor (497-38-1)

1,4-Bromochlorobenzene (106-39-8)

1-Norbornanecarboxylic acid, Bicyclo[2.2.1]heptane-1-carboxylic acid (18720-30-4)

2,2-Dichloronorbornane (19916-65-5)

lithium naphthalide

1,4-Dibromobenzene (106-37-6)

1,4-Dichlorobenzene (106-46-7)

2-Bromopropene (557-93-7)

1-(4-methoxyphenyl)norbornane

1-norbornyllithium

endo-2-bromo-2-norbornanecarboxylic acid

exo-2-bromo-1-norbornanecarboxamide

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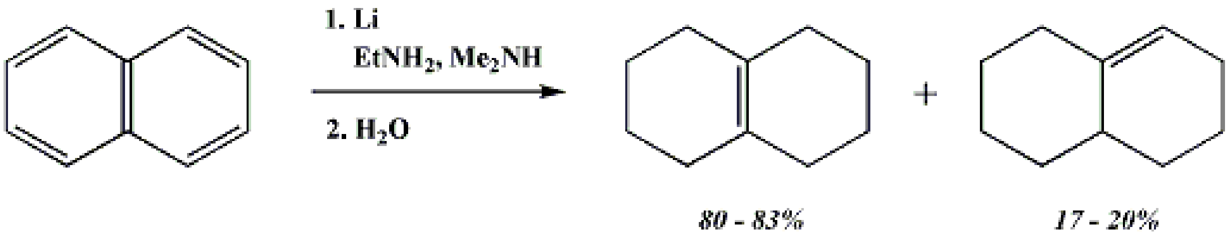
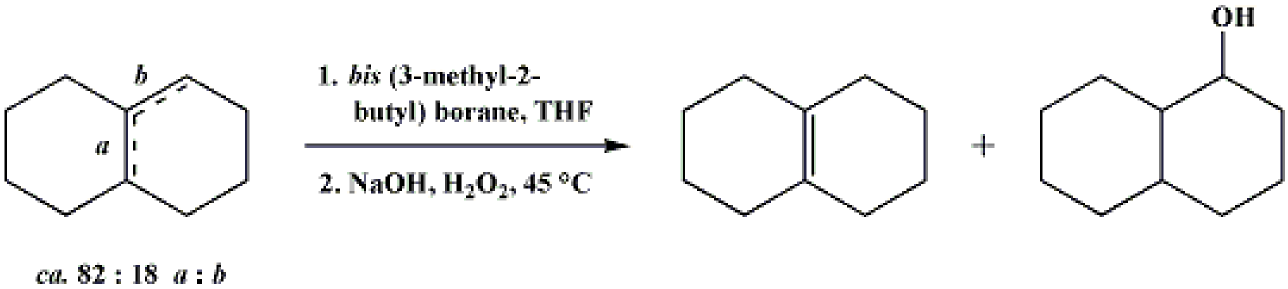
Organic Syntheses, CV 6, 852

Δ^{9,10}-OCTALIN

[Naphthalene, 1,2,3,4,5,6,7,8-octahydro-]





Submitted by Edwin M. Kaiser[1] and Robert A. Benkeser[2].
Checked by Frederick J. Sauter and Herbert O. House.

1. Procedure

Caution! This preparation should be performed in a hood to avoid exposure to amine vapors.

A. Δ^{9,10}-*and* Δ^{1,9}-*Octalin.* Naphthalene (25.6 g. or 0.200 mole, (Note 1)) is dissolved in a mixture of 250 ml. of anhydrous ethylamine and 250 ml. of anhydrous dimethylamine (Note 2) in a 1-l., three-necked flask fitted with a mechanical stirrer (Note 3) and a dry ice condenser and cooled in an ice bath. To this solution is added rapidly (Note 4), piecewise with stirring, 11.55 g. (1.674 g.-atoms) of lithium metal wire cut into 0.5-cm. lengths (Note 5). After the addition is complete, the cooling bath is removed and the blue solution is stirred for 14 hours, additional dry ice being added to the condenser as required. The dry ice condenser is replaced with a water condenser and the mixture is allowed to stand overnight, during which time the volatile amine solvents evaporate (Note 6). The top of the condenser is protected with an anhydrous calcium sulfate drying tube, maintaining anhydrous conditions in the reaction vessel during the evaporation of solvent (Note 7). The reaction flask is placed in an ice bath and the grayish-white residue is hydrolyzed by the *cautious*, dropwise addition of 500 ml. of water, with occasional stirring. After the resulting suspension has been filtered with suction, the residual solid is washed with four 25-ml. portions of diethyl ether. The ether layer is separated, and the aqueous phase of the filtrate is extracted with four additional 25-ml. portions of ether. The combined ethereal solutions are dried over calcium sulfate and concentrated with a rotary evaporator. The residual liquid is distilled under reduced pressure, separating 19–20 g. (70–74%) of the product, b.p. 72–77° (14 mm.), n_D^{23} 1.4978. Analysis of the product by GC (Note 8) shows the presence of 80–83% of Δ^{9,10}-octalin and 17–20% of Δ^{1,9}-octalin. This mixture should be either stored under a nitrogen atmosphere or immediately subjected to the described purification procedure (Note 9).

B. *Purification of* Δ^{9,10}-*octalin*. A 1-l., three-necked flask is equipped with a magnetic stirrer, a

pressure-equalizing dropping funnel, and a reflux condenser fitted with a nitrogen inlet tube, to maintain a nitrogen atmosphere in the reaction vessel throughout the portions of this preparation where anhydrous conditions are employed. A solution of 2.35 g. (0.0618 mole) of sodium borohydride and 11.55 g. (0.1650 mole) of 2-methyl-2-butene (Note 10) in 100 ml. of anhydrous tetrahydrofuran is added to the reaction flask. A solution of 11.75 g. (0.08275 mole) of boron trifluoride diethyl etherate in 22 ml. of anhydrous tetrahydrofuran is then added, dropwise and with stirring, over a 45-minute period. Although the initial rate of addition must be slow to control the exothermic reaction, the rate can be increased during the latter part of the reaction. To the resulting tetrahydrofuran solution of bis(3-methyl-2-butyl)borane is added, dropwise and with stirring over 10 minutes, the mixture of $\Delta^{9,10}$- and $\Delta^{1,9}$-octalins (19–20 g. containing *ca.* 0.03 mole of $\Delta^{1,9}$-octalin) obtained in Part A. The reaction mixture is stirred at room temperature for 3.5 hours and treated with 50 ml. of water. After 35 ml. of 3 *M* aqueous sodium hydroxide has been added, dropwise and with stirring over 10 minutes, 35 ml. of 30% aqueous hydrogen peroxide is added dropwise over a 45-minute period, with continuous stirring. The resulting mixture is heated to 45° (Note 11) with stirring for 5 hours, then allowed to cool to room temperature. The organic layer is separated, washed with four 30-ml. portions of water, and dried over calcium sulfate. After the organic solution has been tested with moist starch-iodide paper to ensure the absence of peroxides, the volatile solvents are removed with a rotary evaporator, and the residual liquid is distilled under reduced pressure in an apparatus fitted with a capillary tube to admit nitrogen as an ebullator (Note 12). After 1–2 g. of forerun has been separated, 9–13 g. (33–48% based on the starting naphthalene) of $\Delta^{9,10}$-octalin is collected at 75–77° (14 mm.), n_D^{20} 1.4990. The product is at least 99% $\Delta^{9,10}$-octalin, by GC analysis (Note 8), and is stored under a nitrogen atmosphere (Note 9).

2. Notes

1. Naphthalene purchased from Eastman Organic Chemicals was used without purification.
2. Ethylamine (b.p. 16.6°) and dimethylamine (b.p. 7.4°) may be distilled into the reaction flask from cylinders. The checkers employed amines, sealed in ampules, purchased from Eastman Organic Chemicals. After the ampules had been cooled to 0° in an ice bath, they were opened and the contents were added to flasks cooled in ice baths. Small portions (0.5–1.0 g.) of sodium metal were added to each of the cold amines. The cooling baths were then removed, and the amines were allowed to distill from the sodium into the reaction flask.
3. Stirrers with Teflon paddles should not be used. Although the reaction proceeds satisfactorily, the Teflon parts are blackened (and presumably partially degraded) by the reaction solution.
4. The reaction is very exothermic during the initial addition of lithium metal. The use of an external ice bath reduces the number of times additional dry ice must be added to the acetone–dry ice condenser.
5. The lithium wire is coated with a hydrocarbon grease. As 0.5-cm. pieces are cut with scissors, they should be dropped into a beaker of anhydrous hexane to dissolve the grease. The pieces of bare lithium wire are then removed with forceps, drained briefly by touching them to a dry towel, and weighed in a second beaker of anhydrous hexane. The pieces of metal are then removed from the second beaker with forceps and added to the reaction mixture.
6. If evaporation of the solvent is not complete, the remainder can be removed by immersing the reaction flask in a bath of warm water.
7. If anhydrous conditions are not maintained, the product becomes contaminated with a tarry material.
8. A GC column packed with Apiezon L suspended on Chromosorb P was employed for this analysis. In a typical analysis at 140° the retention times were: $\Delta^{1,9}$-octalin, 46.2 minutes; $\Delta^{9,10}$-octalin, 49.2 minutes. The ^{1}H NMR spectrum (CCl_4 at 60 mHz.) of this mixture exhibits a multiplet at δ 0.8–2.6 (aliphatic C*H*) with a weak, partially resolved multiplet at δ 5.25 (vinyl

C*H* of $\Delta^{1,9}$-octalin).
9. The octalins usually react rapidly with oxygen, forming unidentified, oxygenated products. The checkers found that, if the crude product is not protected from air oxidation, the yield of $\Delta^{9,10}$-octalin isolated from the purification procedure is lowered substantially.
10. 2-Methyl-2-butene, purchased either from Phillips Petroleum Company or Aldrich Chemical Co., was used without purification.
11. The checkers found a large oil bath to be a convenient method for heating the reaction mixture to 45°.
12. The mixture tends to foam badly during this distillation.

3. Discussion

Among the preparative routes to the octalin mixtures, the acid-catalyzed dehydration of 2-decalol[3] and the metal-amine reduction of naphthalene[4] appear most satisfactory. Apart from the purification method described in this preparation, pure $\Delta^{9,10}$-octalin has also been obtained by reaction of the octalin mixture with nitrosyl chloride. After separation of the adducts by fractional crystallization, the pure $\Delta^{9,10}$-octalin has been regenerated from its nitrosyl chloride adduct.[3,5]

Lithium dissolved in amines of low molecular weight constitutes a useful and convenient reagent for reducing aromatic hydrocarbons to monoölefins.[6] Although mixtures of isomeric olefins are usually obtained with primary amine solvents, the use of secondary amines as co-solvents dramatically increases the selectivity of these reductions so that the more thermodynamically stable olefin usually becomes the predominant product. Thus, in the reduction of naphthalene, the yield of $\Delta^{9,10}$-octalin increases from 52% in pure ethylamine to 80–82% in an ethylamine–dimethylamine mixture. As another example, the reduction of *tert*-butylbenzene with lithium in pure ethylenediamine yields a product mixture 70% in 1-*tert*-butylcyclohexene.[7] When a mixture of ethylenediamine and morpholine is used as the reaction solvent, the product mixture is 84% 1-*tert*-butylcyclohexene.[8]

Aromatic hydrocarbons may also be reduced to monoölefins by calcium in low molecular weight amines.[9] For example, this metal in methylamine–ethylenediamine converts naphthalene to $\Delta^{9,10}$- and $\Delta^{1,9}$-octalin in yields identical to those obtained from the lithium–amine system used in this preparation. Calcium may even be employed to effect such reductions in ether provided small amounts of hexamethylphosphoric triamide (HMPA) are present; for a warning concerning the use of HMPA, see J. A. Zapp, Jr., *Science*, **190**, 422 (1975).

The separation procedure[4] described in this preparation illustrates the *in situ* generation of a tetrahydrofuran solution of bis(3-methyl-2-butyl)borane and use of this sterically hindered borane to react with a trisubstituted olefin ($\Delta^{1,9}$-octalin) in preference to a more hindered tetrasubstituted olefin ($\Delta^{9,10}$-octalin).[10] The alkylborane adduct produced from $\Delta^{1,9}$-octalin is oxidized with alkaline hydrogen peroxide to 1-decalol, which is easily separated from the olefinic product.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

$\Delta^{9,10}$-Octalin

$\Delta^{9,10}$-and $\Delta^{1,9}$-Octalin

$\Delta^{9,10}$- and $\Delta^{1,9}$-octalin

($\Delta^{1,9}$-octalin)

($\Delta^{9,10}$-octalin)

$\Delta^{1,9}$-octalin

ether, diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

oxygen (7782-44-7)

nitrogen (7727-37-9)

calcium sulfate (7778-18-9)

calcium (7440-70-2)

sodium (13966-32-0)

Naphthalene (91-20-3)

hydrogen peroxide (7722-84-1)

methylamine (74-89-5)

nitrosyl chloride (2696-92-6)

lithium, Lithium wire, lithium metal wire (7439-93-2)

dimethylamine (124-40-3)

2-methyl-2-butene (513-35-9)

Tetrahydrofuran (109-99-9)

ethylenediamine (107-15-3)

morpholine (110-91-8)

hexane (110-54-3)

boron trifluoride diethyl etherate (109-63-7)

ethylamine (75-04-7)

sodium borohydride (16940-66-2)

hexamethylphosphoric triamide (680-31-9)

2-Decalol (825-51-4)

1-Decalol (529-32-8)

Naphthalene, 1,2,3,4,5,6,7,8-octahydro- (493-03-8)

Bis(3-methyl-2-butyl)borane (1069-54-1)

tert-butylbenzene (98-06-6)

1-tert-butylcyclohexene

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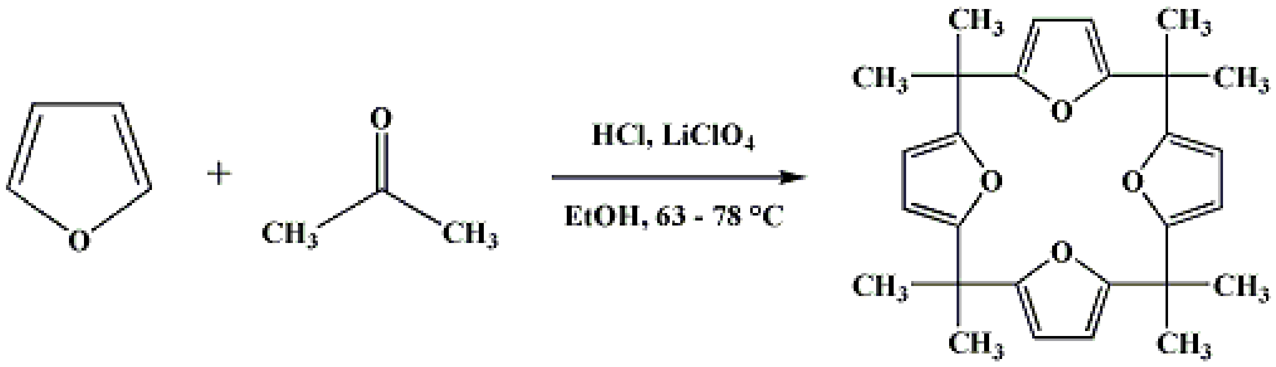
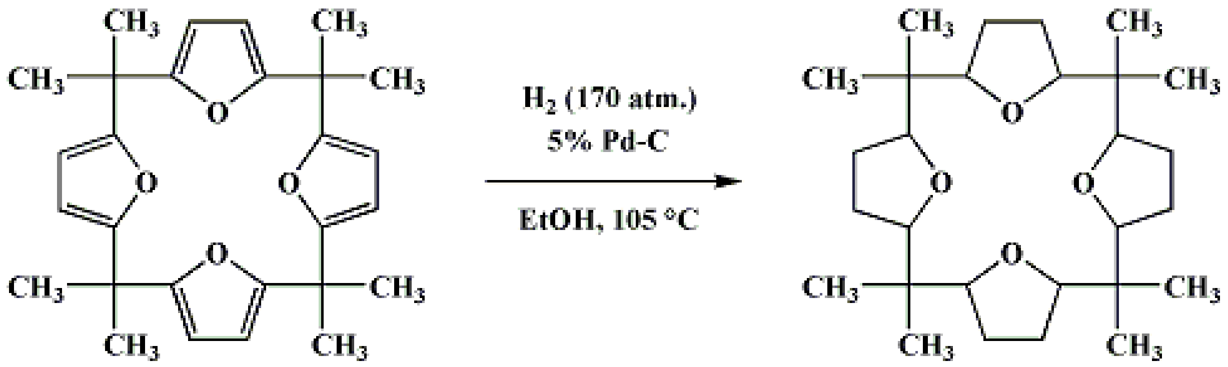
Organic Syntheses, CV 6, 856

2,2,7,7,12,12,17,17-OCTAMETHYL-21,22,23,24-TETRAOXAPERHYDROQUATERENE

[21,22,23,24-Tetraoxapentacyclo-[16.2.1.1^{3,6}.1^{8,11}.1^{13,16}]tetracosane, 2,2,7,7,12,12,17,17-octamethyl-]





Submitted by Maurice Chastrette[1], Francine Chastrette, and Jean Sabadie.
Checked by William V. Phillips, Herbert O. House, James C. Kauer, and William A. Sheppard.

1. Procedure

A. 2,2,7,7,12,12,17,17-*Octamethyl*-21,22,23,24-*tetraoxaquaterene.* A 1-liter, three-necked flask fitted with a mechanical stirrer, a dropping funnel, and a condenser is charged with 27.2 g. (0.400 mole) of freshly distilled furan (Note 1), 24 ml. of absolute ethanol, 57.3 g. (0.200 mole) of the lithium perchlorate–1,2-dimethoxyethane complex (Note 2), and 16 ml. of reagent grade concentrated hydrochloric acid. The resulting pale-yellow to pale-tan solution is stirred continuously and heated to 63° with an oil bath before 58.1 g. (0.80 mole) of acetone (Note 3) is added dropwise over 1 hour. During this addition the heat of reaction causes the solution to reflux, and some white solid begins to separate. After the addition is complete, stirring and heating are continued until refluxing ceases (about 30 minutes). The temperature of the bath is then raised to 78°, and the mixture is refluxed with stirring for an additional 30 minutes. The reaction mixture, a dark red-brown solution containing a pasty white precipitate, is cooled to room temperature with continuous stirring, and 25 ml. of water and 300 ml. of diethyl ether are added. The resulting mixture is stirred at room temperature for 1 hour, converting the precipitate into a finely divided white solid, and the mixture is filtered with

suction, employing a medium-porosity, sintered-glass funnel. The residual crude product is washed thoroughly (Note 4) with portions of ether (total volume 100 ml.) followed by portions of 95% ethanol (total volume 50 ml.) and allowed to air-dry. The crude product (14.2–14.8 g.), m.p. 231–240°, is recrystallized from 140–150 ml. of reagent grade chloroform, yielding 7.3–7.4 g. of product as white needles, m.p. 241.5–243°. The mother liquors are concentrated to one-third their initial volume, separating 2.9–3.1 g. of a second crop of crystalline product, m.p. 240–242°, for a total yield of the tetraoxaquaterene of 10.2–10.5 g. (24–25%) (Note 5).

B. 2,2,7,7,12,12,17,17-*Octamethyl*-21,22,23,24-*tetraoxaperhydroquaterene.* A 400-ml., stainless-steel, shaking autoclave is charged with 4.0 g. (0.0092 mole) of the tetraoxaquaterene from Part A, 200 ml. of ethanol, and 400 mg. of 5% palladium on charcoal (Note 6). The autoclave is filled with hydrogen at an initial pressure of 170 atm. and heated with shaking for 4 hours at 105°. The catalyst and a white solid are removed by filtration (Note 7), the solid is dissolved in 100 ml. of warm chloroform, the solution is filtered, the chloroform is evaporated, and the white solid obtained is dried under reduced pressure at 60° (Note 8), leaving the tetraoxaperhydroquaterene as a white solid, m.p. 204–209° (Note 9), in a yield of 2.85–2.97 g. (69–72%).

2. Notes

1. Furan, purchased from Aldrich Chemical Company, Inc., was distilled before use; b. p. 31–32°.
2. Anhydrous lithium perchlorate (60 g.), obtained from Ventron Corporation, was placed in a 500-ml. flask under dry nitrogen, and 85 ml. of anhydrous 1,2-dimethoxyethane was added. The resulting warm mixture was swirled and heated on the steam bath under dry nitrogen until all of the solid dissolved. The resulting solution was cooled and gradually crystallized to a solid mass. Additional 1,2-dimethoxyethane (155 ml.) was added, the mixture was stirred, and supernatant liquid was removed with a sintered-glass filter stick. The resulting solid was vacuum dried briefly in a vacuum dessicator (0.3 mm.) for 20 minutes then sealed under vacuum overnight. The resulting, solvated lithium perchlorate, $LiClO_4(C_4H_{10}O_2)_2$, 108 g, may be stored in a brown bottle under dry nitrogen until needed. When lithium perchlorate was initially dissolved in the entire 240 ml. of 1,2-dimethoxyethane and processed as above, the yield was considerably lower. The submitters report that if less lithium perchlorate is used in the preparation of the octamethyltetraoxaquaterene the yield of the product is lowered.
3. Reagent grade acetone was used. The submitters state that an excess of acetone is necessary. When a 1:1 mole ratio of acetone to furan was used, they obtained a 21% yield of crude product; when a 1:2 ratio of acetone to furan was employed, the yield of product was less then 5%.
4. The submitters report that if this material is not washed thoroughly to remove the soluble, low molecular weight, linear polymers present the crude product will melt and/or darken at much lower temperatures than 231–240°.
5. The product has the following spectral properties; ^1H NMR ($CDCl_3$), δ (multiplicity, number of protons, assignment): 1.48 (s, 24H, 8CH_3), 5.90 (s, 8H, 8CH); mass spectrum *m/e* (relative intensity): 432 (M^+, 40) 418 (34), 417 (100), 201 (28), 186 (31), 149 (55), 85 (46), 83 (67), 75 (21), 60 (21), 47 (20), 45 (24), 43 (53), and 41 (26).
6. Catalyst obtained from Engelhard Industries was used. The submitters used 200 mg.

of Fluka 10% palladium on charcoal catalyst with 5 g. of starting material in 250 ml. of ethanol and obtained a total yield of 2.3 g. (46%), m.p. 208–211°.

7. The ethanolic filtrate can be concentrated to 10–15 ml. under reduced pressure to obtain 0.3 g. (7%) of crude product, m.p. 187–202°. Unchanged starting material, if present, is concentrated in this second fraction and may be detected by the furan resonance at δ 5.85 in the ^{1}H NMR spectrum or by a sharp IR absorption at 772 $cm.^{-1}$, not present in the product. Elemental analyses of these second crops suggested that other impurities were also present.

8. The solid tenaciously holds a small amount of chloroform which can be detected by ^{1}H NMR (δ 7.25). Vacuum drying overnight at 60° removes this impurity.

9. In one isolated case the checkers found that no hydrogen uptake occurred, and unreacted starting material was recovered. This erratic result may have resulted from accidental poisoning of the catalyst by contaminants present in the autoclave or associated valves and lines. If multiple runs are carried out, the products of each should be checked by IR or ^{1}H NMR spectroscopy before being combined. The ^{1}H NMR spectrum ($CDCl_3$) shows singlets at δ 0.74, 0.82, 0.93, and 1.04 (24H, 8CH_3) and multiplets at 1.2–1.9 (16H, 8CH_2), 1.9–2.8 (4H, 2CH_2), and 3.0–4.2 (8H, 4CH_2); IR (Nujol) $cm.^{-1}$ strong absorptions: 1078, 1039, medium: 999, 991, 552, 528, 520, and weaker: 1285, 1248, 1204, 977, 884, 840, 719, 659, 598, 560. The checkers concluded from examination of the spectra that a variable mixture of isomers is obtained from the hydrogenation.

3. Discussion

The unsaturated tetraoxaquaterene (accompanied by linear condensation products) was first synthesized in 18.5% yield by the acid-catalyzed condensation of furan with acetone in the absence of added lithium salts.[2] Other ketones also condensed with furan, giving analogous products in 6–12% yield.[2,3,4] A corresponding macrocycle was also prepared in 9% yield from pyrrole and cyclohexanone.[4] The macrocyclic ether products have also been obtained by condensation of short, linear condensation products of 2, 3, or 4 furan rings with a carbonyl compound.[5]

The method described here gives higher yields of the macrocyclic tetraethers and allows the product from furan and cyclohexanone to be formed directly in 5–10% yield, whereas this product was previously obtained only by an indirect route. Lithium perchlorate undoubtedly accelerates the reaction; after short reaction times, the product was isolated in 20% yield when the salt was present and in only 5% yield when the salt was absent. The lithium cation presumably acts as a template which coordinates with the oxygen atoms of the furan units, favoring cyclization instead of linear polymerization.[6] The hydrogenated macrocycle has been shown to form complexes with lithium salts.[6,7]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

2,2,7,7,12,12,17,17-Octamethyl-21,22,23,24-tetraoxaperhydroquaterene

2,2,7,7,12,12,17,17-Octamethyl-21,22,23,24-tetraoxaquaterene

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ether, diethyl ether (60-29-7)

hydrogen (1333-74-0)

chloroform (67-66-3)

Cyclohexanone (108-94-1)

oxygen (7782-44-7)

nitrogen (7727-37-9)

acetone (67-64-1)

palladium (7440-05-3)

Furan (110-00-9)

Pyrrole (109-97-7)

1,2-dimethoxyethane (110-71-4)

lithium perchlorate (7791-03-9)

21,22,23,24-Tetraoxapentacyclo-[16.2.1.1^{3,6}.1^{8,11}.1^{13,16}]tetracosane, 2,2,7,7,12,12,17,17-octamethyl-

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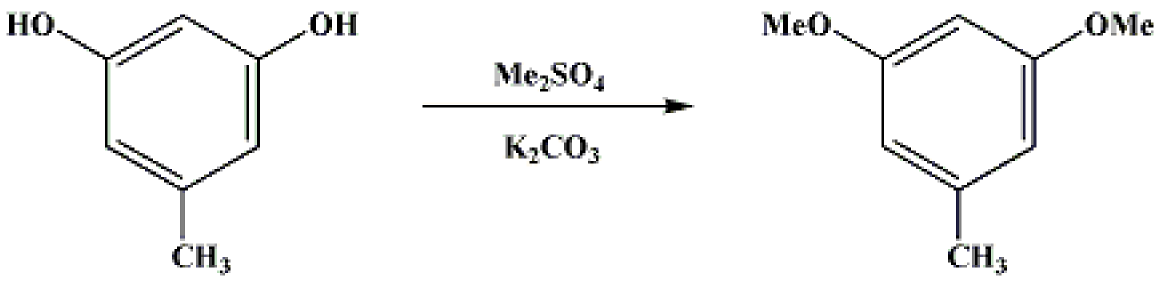
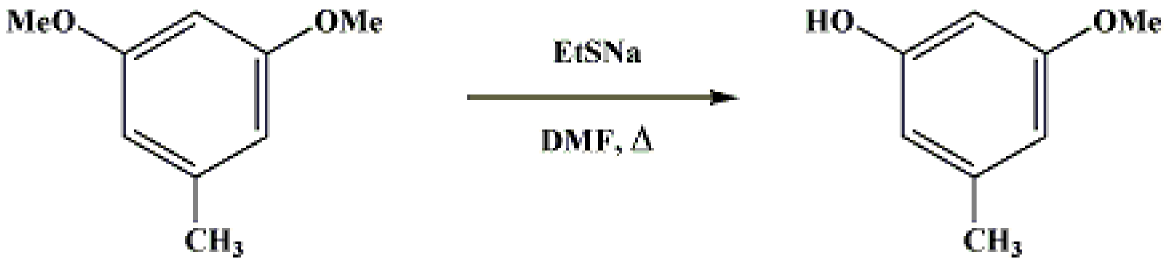
ORCINOL MONOMETHYL ETHER

[Phenol, 3-methoxy-5-methyl-]





Submitted by R. N. Mirrington and G. I. Feutrill[1].
Checked by H. Gurien, G. Kaplan, and A. Brossi.

1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A. *Orcinol dimethyl ether.* A 1-l., three-necked flask fitted with a mechanical stirrer, a condenser, and a 100-ml. dropping funnel is charged with 124 g. (0.984 mole) of anhydrous potassium carbonate, 410 ml. of acetone (Note 1), and 42.6 g. (0.344 mole) of orcinol monohydrate (Note 2). The stirrer is started, and 94.5 g. (70.9 ml., 0.750 mole) of dimethyl sulfate is added from the dropping funnel to the pink mixture over a period of 2 minutes. The mixture warms appreciably and begins to reflux after an additional 5 minutes. When the spontaneous boiling has subsided (15–20 minutes after addition of the dimethyl sulfate), the stirred mixture is heated gently under reflux for 4 hours longer. The condenser is then arranged for distillation and 200 ml. of acetone is distilled. A 50-ml. portion of concentrated aqueous ammonia is added to the reaction mixture; stirring and heating are continued for 10 minutes. The mixture is diluted with water to a total volume of approximately 750 ml., the layers are separated, and the organic layer is combined with two 150-ml. ethereal extracts of the aqueous layer. The organic phase is washed with 50 ml. of water, twice with 50-ml. portions of 3 *N*

sodium hydroxide solution (Note 3), once with 50 ml. of saturated aqueous sodium chloride, and dried over magnesium sulfate. After evaporation of the ether at atmospheric pressure, the residual liquid is distilled under reduced pressure, yielding 42.9–43.7 g. (94–96%) of orcinol dimethyl ether, b.p. 133–135° (40 mm.) (Note 4) and (Note 5).

Caution! Because hydrogen is evolved and large volumes of foul-smelling ethyl methyl sulfide are liberated, this step should be conducted in a well-ventilated hood.

B. *Orcinol monomethyl ether.* A 1-l., three-necked flask equipped with a magnetic stirrer, a condenser, a dropping funnel, and a nitrogen inlet is charged with 250 ml. of dry *N*,*N*-dimethylformamide (Note 6) and 22 g. (0.55 mole) of sodium hydride (60% oil dispersion). The suspension is stirred under an atmosphere of dry nitrogen and cooled with an ice bath while a solution of 31 g. (37 ml., 0.50 mole) of ethanethiol (Note 7) in 150 ml. of dry *N*,*N*-dimethylformamide (Note 6) is added slowly from the dropping funnel over a period of 20 minutes. The ice bath is removed and stirring is continued for an additional 10 minutes. A solution of 38.0 g. (36.5 ml., 0.250 mole) of orcinol dimethyl ether in 100 ml. of dry *N*,*N*-dimethylformamide (Note 6) is added in one lot, and the mixture is refluxed under an atmosphere of dry nitrogen for 3 hours (Note 8) and (Note 9). The mixture is cooled, poured into 1.8 l. of cold water, and extracted with two 250-ml. portions of petroleum ether (b.p. 50–70°), which are discarded. The aqueous layer is acidified with 330 ml. of ice-cold 4 *N* hydrochloric acid and extracted with three 250-ml. portions of ether. The combined ethereal extracts are washed with 100 ml. of saturated aqueous sodium chloride and dried over magnesium sulfate. After the ether is distilled at atmospheric pressure, the residual liquid is distilled under reduced pressure, yielding 28–30.5 g. (81–88%) of orcinol monomethyl ether, b.p. 89–90° (0.2 mm.) or 156–158° (25 mm.) (Note 10) and (Note 11)

2. Notes

1. Technical acetone containing about 1% water is quite satisfactory.
2. British Drug Houses Ltd. reagent grade orcinol monohydrate was used without further purification.
3. If the first washing is colorless, as is usually the case, the second washing is unnecessary. Washing with sodium hydroxide solution should be continued until the washings are colorless.
4. A similar run using 100 g. of orcinol monohydrate afforded 102 g. (95%) of orcinol dimethyl ether, b.p. 67.5–68.5° (0.2 mm.).
5. GC analysis of the product on two columns (silicone gum rubber SE-30 and OV-1) indicated the presence of traces of two other compounds with retention times longer than that of orcinol dimethyl ether. These impurities, which were most likely *C*-methylated materials,[2] totaled less than 0.5% of the product.
6. *N*,*N*-Dimethylformamide, b.p. 58° (25 mm.), was distilled from calcium

hydride under a reduced pressure of nitrogen immediately before use.
7. British Drug Houses Ltd. reagent grade ethanethiol was distilled from calcium hydride before use (b.p. 36°).
8. The mixture may become gelatinous during this time, but stirring is not necessary.
9. A polythene tube leading from the top of the condenser to the back of the hood is advisable, preventing any diffusion of the by-product, ethyl methyl sulfide, into the laboratory. Alternatively, this by-product may be collected, if desired, by passing the vapors through a cold trap (dry ice in acetone).
10. This distillate, which is sufficiently pure for most reactions, solidifies after standing for 4–6 hours. A sample crystallizes from benzene-petroleum ether as off-white prisms, m.p. 61–62°, and is relatively free of sulfurous odor.
11. ^{1}H NMR (CCl_4): δ 2.19 (s, 3H, CH_3), 3.63 (s, 3H, OCH_3), 6.17 (m, 3H, C_6H_3), 6.38 (broad s, 1H, O*H*).

3. Discussion

Previous preparations of orcinol monomethyl ether have been effected by partial methylation of oricinol with methyl iodide and potassium hydroxide[3] or sodium ethoxide,[4] or with dimethyl sulfate and sodium hydroxide.[5] These procedures required tedious purification steps and the pure monomethyl ether was obtained in 37% yield at best.[5]

This procedure is characterized by the easy isolation of a high-purity product in excellent yield. The reaction illustrates a general method[6] for the conversion of aryl methyl ethers to the corresponding phenols, and has proved to be of special advantage with acid-sensitive substrates.[6,7]

A unique feature of this procedure is the selective monodemethylation of the dimethyl ether. The scope of this reaction is illustrated[6] in part by the preparation in high yield of 4-methoxyphenol, guaiacol, and phloroglucinol dimethyl ether from the respective fully *O*-methylated compounds. An exception is pyrogallol trimethyl ether which affords pyrogallol 1-monomethyl ether in high yield.[6]

References and Notes

1. Department of Organic Chemistry, University of Western Australia, Nedlands, W.A., 6009. [Present address: Department of Organic Chemistry, University of Melbourne, Parkville, Victoria 3052, Australia]
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

benzene-petroleum ether

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

Benzene (71-43-2)

ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

dimethyl sulfate (77-78-1)

dimethyl ether (115-10-6)

acetone (67-64-1)

potassium hydroxide (1310-58-3)

sodium ethoxide (141-52-6)

Guaiacol (90-05-1)

Methyl iodide (74-88-4)

magnesium sulfate (7487-88-9)

N,N-dimethylformamide (68-12-2)

sodium hydride (7646-69-7)

ethanethiol (75-08-1)

Pyrogallol 1-monomethyl ether (934-00-9)

calcium hydride (7789-78-8)

4-Methoxyphenol (150-76-5)

Orcinol monomethyl ether, Phenol, 3-methoxy-5-methyl- (3209-13-0)

orcinol monohydrate (6153-39-5)

Orcinol dimethyl ether (4179-19-5)

ethyl methyl sulfide (624-89-5)

phloroglucinol dimethyl ether (500-99-2)

pyrogallol trimethyl ether (634-36-6)

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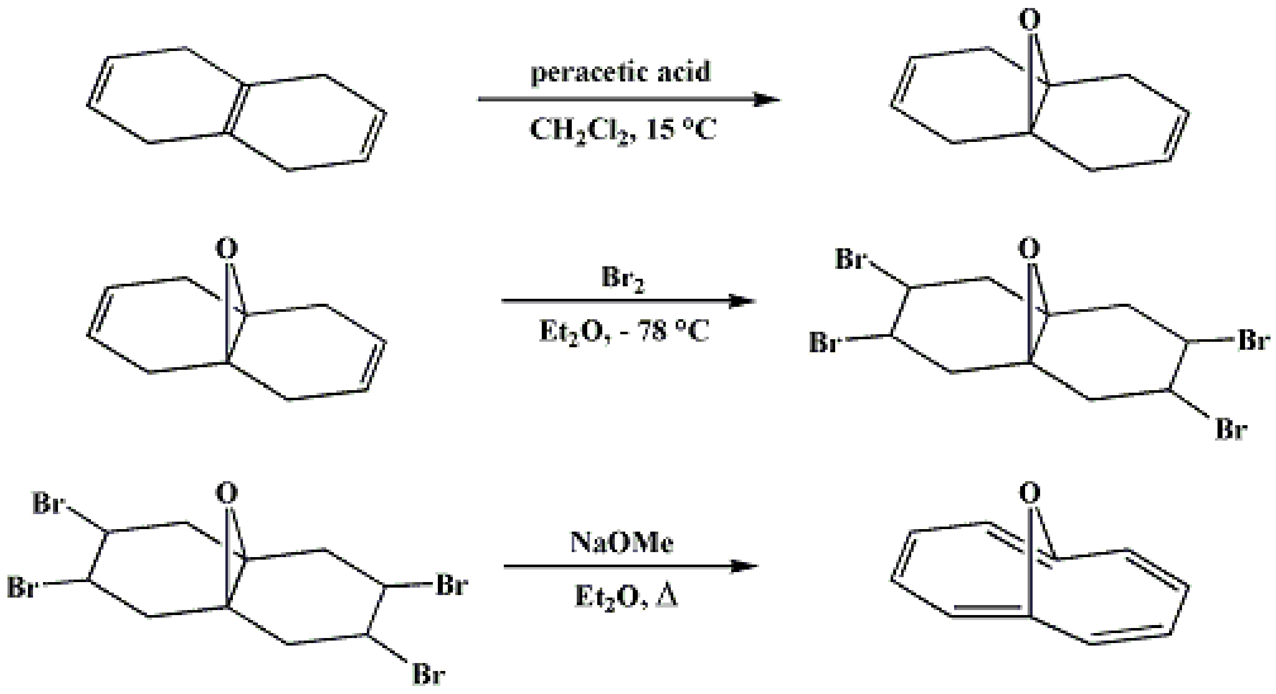
1,6-OXIDO[10]ANNULENE

[11-Oxabicyclo[4.4.1]undeca-1,3,5,7,9-pentaene]



Submitted by E. Vogel, W. Klug[1], and A. Breuer.
Checked by D. Knopp, U. Schwieter, and A. Brossi.

1. Procedure

A. 11-*Oxatricyclo*[4.4.1.0^{1,6}]*undeca*-3,8-*diene.* A 1-l., three-necked, round-bottomed flask equipped with a sealed mechanical stirrer, a pressure-equalizing dropping funnel, and a thermometer is charged with 66.1 g. (0.501 mole) of 1,4,5,8-tetrahydronaphthalene [*Org. Synth.*, **Coll. Vol. 6**, 731 (1988)] and 200 ml. of anhydrous dichloromethane. To the resulting solution is added 75 g. of anhydrous sodium acetate. After the suspension is cooled with an ice bath, 104.5 g. (0.55 mole) of commercial 40% peracetic acid (Note 1) and (Note 2) is added dropwise over a period of 20–30 minutes, while maintaining the temperature at approximately 15° (Note 3) and stirring vigorously. To the reaction mixture is added, without delay, 500 ml. of water, to dissolve the sodium acetate and extract the bulk of the acetic acid. The organic layer is washed successively with two 100-ml. portions of 5% aqueous sodium hydroxide and two 100-ml. portions of water and dried over anhydrous potassium carbonate. The solvent is removed on a rotary evaporator, leaving a solid residue. Two recrystallizations from approximately 50 ml. of petroleum ether (b.p. 40–60°), cooling the solution to –40°, yields 58.5–62.0 g. (79–84%) of 11-oxatricyclo[4.4.1.0^{1,6}]undeca-3,8-diene as white needles, m.p. 58–61° (Note 4).

B. 3,4,8,9-*Tetrabromo*-11-*oxatricyclo*[4.4.1.0^{1,6}]*undecane.* A 1-l., three-necked, round-bottomed flask fitted with a sealed mechanical stirrer, a pressure-equalizing dropping funnel, and a calcium chloride drying tube is charged with 59.2 g. (0.400 mole) of 11-oxatricyclo

[4.4.1.0^{1,6}]undeca-3,8-diene and 500 ml. of anhydrous diethyl ether (Note 5). The resulting solution is cooled in an acetone–dry ice bath, and 120 g. (0.75 mole) of bromine (Note 6) is added with stirring over a period of 1.5 hours (Note 7). After the addition is complete, the ether is removed on a rotary evaporator. The solid residue is dissolved in 800 ml. of hot chloroform. To this solution is added, with gentle stirring, 150 ml. of hot petroleum ether (b. p. 60–90°). The resulting, clear mixture, from which the product begins to crystallize, is allowed to cool to room temperature and then stand in a refrigerator at –40° overnight, completing the crystallization. The yield of white crystalline tetrabromide obtained is 115–125 g. (61–67%), m.p. 151–153° (Note 8). An additional 18–25 g. of product, m.p. 149–152°, is recovered from the mother liquor by concentration to about one quarter of the volume, giving a total yield of 136–144 g. (73–77%) of material sufficiently pure to be used in the following step.

C. 1,6-*Oxido*[10]*annulene.* A 2-l., three-necked, round-bottomed flask equipped with a sealed mechanical stirrer and a reflux condenser protected by a calcium chloride drying tube is charged with 81 g. (1.5 moles) of sodium methoxide (Note 9) and 600 ml. of anhydrous ether. To this slurry is added, with stirring, 117 g. (0.250 mole) of finely powdered 3,4,8,9-tetrabromo-11-oxatricyclo[4.4.1.0^{1,6}]undecane. The reaction mixture is refluxed with stirring for 10 hours and allowed to stand overnight. Following this, 500 ml. of water is added slowly, dissolving the solids. The ether layer is separated, and the aqueous layer is extracted with two 100-ml. portions of ether. The combined ethereal solution is washed with 250 ml. of water and dried over anhydrous potassium carbonate. Removal of the ether on a rotary evaporator affords a brown oil, which when distilled gives 34.4–35.1 g. of yellow 1,6-oxido [10]annulene, b.p. 77° (0.02 mm.) (Note 10). This material readily solidifies at room temperature, and two recrystallizations at –40° from 225 ml. of (5:1) pentane–ether yields 18.3–18.5 g. (51%) of 1,6-oxido[10]annulene as pale yellow needles, m.p. 51–52° (Note 11) and (Note 12).

2. Notes

1. Satisfactory 40% peracetic acid is obtainable from Buffalo Electrochemical Corporation, Food Machinery and Chemical Corporation, Buffalo, New York. The specifications given by the manufacturer for its composition are: peracetic acid, 40%; hydrogen peroxide, 5%; acetic acid, 39%; sulfuric acid, 1%; water, 15%. Its density is 1.15 g./ml. The peracetic acid concentration should be determined by titration. A method for the analysis of peracid solutions is based on the use of ceric sulfate as a titrant for the hydrogen peroxide present, followed by an iodometric determination of the peracid present.[2] The checkers found that peracetic acid of a lower concentration (27.5%) may also be used without a decrease in yield. The product was found to be sufficiently pure, after only one recrystallization from 60 ml. of petroleum ether (b.p. 40–60°) and cooling overnight to –18°, to be used in the next step.

2. Alternatively *m*-chloroperbenzoic acid may be used.[3]

3. The yields of the desired product decrease substantially if the temperature exceeds 20°.

4. The reported m.p. is 64°.[4] GC analysis using a 1-m. column containing 20% Reoplex 400 on Diatoport S 6080, operated at 160°, indicates the purity of the product

to be 98%.

5. The rate of bromination of 11-oxatricyclo[4.4.1.0^{1,6}]undeca-3,8-diene is markedly higher in ether than in dichloromethane or chloroform. The former solvent thus permits the reaction to be carried out at relatively low temperatures.

6. Bromine was freshly distilled from phosphorus pentoxide.

7. The addition of bromine should not be started before the solution has cooled to approximately –70°.

8. The tetrabromide apparently consists of a mixture of stereoisomers. After several recrystallizations from chloroform–petroleum ether (60–90°) the major isomer, m.p. 160–162°, is obtained.

9. As reported by Shani and Sondheimer,[3,5] the dehydrohalogenation of the tetrabromide with potassium hydroxide in ethanol at 50–55° affords a mixture, readily separated by chromatography on alumina, of 1,6-oxido[10]annulene and the isomeric 1-benzoxepin. The latter compound is also formed during chromatography of 1,6-oxido[10]annulene on silica gel.[6]

10. To avoid acid-catalyzed rearrangements of 1,6-oxido[10]annulene it is recommended that the distillation flask be treated with a base before use.

11. The reported m.p. is 52–53°.[6] The purity of the product is greater than 99% as established by TLC, using plates prepared with Silica Gel Si F, obtained from Riedel-De Haen AG, 3016 Seelze, West Germany. If 1,6-oxido[10]annulene is to be used for spectroscopic investigations, care should be taken that its potential contaminants, such as naphthalene, 1-bromonaphthalene, α-naphthol, and 1-benzoxepin, are absent, as checked by TLC. The checkers could not obtain the reported yield of 24.5–25.6 g. (68–71%). Likewise, in experiments where the ether was replaced with tetrahydrofuran or dioxane, the yield given by the submitters could not be obtained.

12. The spectral properties of the product are as follows; ^{1}H NMR ($CDCl_3$), δ (multiplicity, assignment): 7.25–7.75 (m, AA'BB', aromatic *H*); UV (95% C_2H_5OH) nm. max. (ε): 255 (74,000), 299 (6900), 393 (240) complex band; mass spectrum (250°, 70 eV) *m/e* (relative intensity > 10%): 144 (M, 43), 116 (40), 115 (100), 89 (15), 63 (15), 51 (10), 39 (11).

3. Discussion

The preparation of 1,6-Oxido[10]Annulene, described simultaneously by Sondheimer and Shani[3,5] and by Vogel, Biskup, Pretzer, and Böll,[6] is illustrative of the rather general synthesis of aromatic 1,6-bridged [10]annulenes from 1,4,5,8-tetrahydronaphthalene. In addition to the present compound, the following bridged [10]annulenes have thus far been obtained by this approach: 1,6-methano[10]annulene,[7,8,9] the 11,11-dihalo-1,6-methano[10]annulenes,[9,10] and 1,6-imino[10]annulene.[11]

The epoxidation of 1,4,5,8-tetrahydronaphthalene exemplifies the well-known selectivity of peracids in their reaction with alkenes possessing double bonds that differ in the degree of alkyl substitution.[12] Regarding the method of aromatization employed in the conversion of 11-oxatricyclo[4.4.1.0^{1,6}]undeca-3,8-diene to 1,6-oxido[10]annulene, the two-step bromination–dehydrobromination sequence is given preference to the one-step DDQ-dehydrogenation, which was advantageously applied in the synthesis of 1,6-methano[10]

annulene,[7,9] since it affords the product in higher yield and purity.

1,6-Oxido[10]annulene closely resembles 1,6-methano[10]annulene in many of its spectral properties, particularly in its ^{1}H NMR, UV, IR, and ESR spectra,[13] but is chemically less versatile than the hydrocarbon analog due to its relatively high sensitivity toward proton and Lewis acids.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 731

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

1,6-Oxido[10]annulene

ethanol (64-17-5)

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

ether, diethyl ether (60-29-7)

sodium acetate (127-09-3)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

bromine (7726-95-6)

α-naphthol (90-15-3)

sodium methoxide (124-41-4)

potassium hydroxide (1310-58-3)

1-bromonaphthalene (90-11-9)

Naphthalene (91-20-3)

hydrogen peroxide (7722-84-1)

Pentane (109-66-0)

dichloromethane (75-09-2)

dioxane (5703-46-8)

Tetrahydrofuran (109-99-9)

peracetic acid (79-21-0)

ceric sulfate (13590-82-4)

1,6-Methano[10]annulene (2443-46-1)

1,4,5,8-Tetrahydronaphthalene (493-04-9)

11-Oxabicyclo[4.4.1]undeca-1,3,5,7,9-pentaene (4759-11-9)

11-Oxatricyclo[4.4.1.$0^{1,6}$]undeca-3,8-diene (16573-72-1)

3,4,8,9-Tetrabromo-11-oxatricyclo[4.4.1.$0^{1,6}$]undecane (16573-82-3)

1-benzoxepin

phosphorus pentoxide (1314-56-3)

m-Chloroperbenzoic acid (937-14-4)

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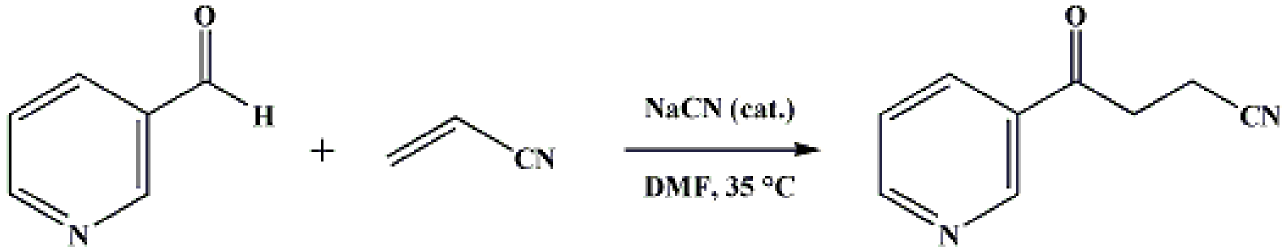
Organic Syntheses, CV 6, 866

CYANIDE-CATALYZED CONJUGATE ADDITION OF ARYL ALDEHYDES: 4-OXO-4-(3-PYRIDYL)BUTYRONITRILE

[3-Pyridinebutanenitrile, γ-oxo]



Submitted by H. Stetter[1], H. Kuhlmann, and G. Lorenz.
Checked by Benjamin G. Padilla and George Büchi.

1. Procedure

Caution! Sodium cyanide is highly toxic. Care should be taken to avoid direct contact of the chemical or its solutions with the skin, and impervious gloves should be worn to handle the reagent.

A 1-l., three-necked, round-bottomed flask equipped with a mechanical stirrer, a reflux condenser fitted with a potassium hydroxide drying tube, and a pressure-equalizing dropping funnel mounted with a nitrogen-inlet tube is charged with 4.9 g. (0.18 mole) of finely ground sodium cyanide (Note 1) and 500 ml. of dry *N,N*-dimethylformamide (Note 2). The flask is immersed in a water bath kept at 35°, stirring is begun, and the apparatus is purged thoroughly with dry nitrogen (Note 3). After 15 minutes 107.1 g. (1.001 mole) of 3-pyridinecarboxaldehyde (Note 4) is added dropwise over a period of 30 minutes. The dark brown solution is stirred for another 30 minutes (Note 5), after which 39.8 g. (0.751 mole) of freshly distilled acrylonitrile is added over 1 hour. The solution, now red-orange in color and quite viscous (Note 6), is stirred for 3 hours, 6.6 g. (0.11 mole) of acetic acid is added, and stirring is continued for 5 additional minutes. The solvent is removed with a rotary evaporator, the residue is dissolved in 500 ml. of water, and the solution is extracted continuously (Note 7) with 500 ml. of chloroform for 12 hours (Note 8). The solvent is evaporated under reduced pressure, and the residual liquid is distilled under reduced pressure through a short-path distillation apparatus. An initial fraction, consisting mainly of 3-pyridinecarboxaldehyde, collects in the cold trap. The product, b.p. 150–152° (0.1 mm.), solidifies in the condenser and is freed by heating the water in the cooling jacket to nearly 100°, yielding 94–101 g. (78–84%) of the light yellow, solid distillate. Recrystallization from 400 ml. of 2-propanol gives 77–82 g. (64–68% based on acrylonitrile) of 4-oxo-4-(3-pyridyl)butyronitrile as yellow-tinged, white crystals, m.p. 70–72° (Note 9).

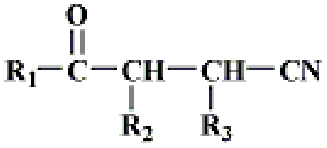
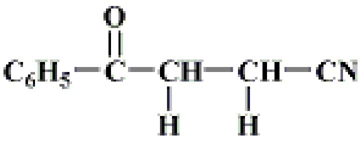
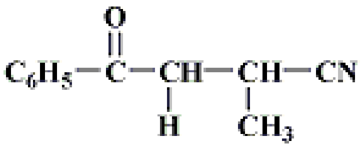
2. Notes

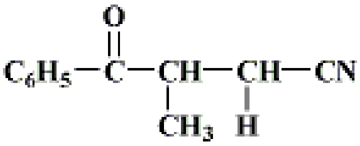
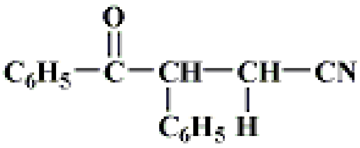
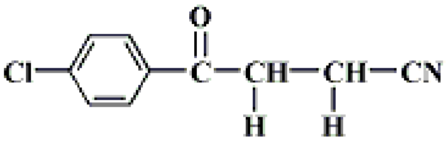
1. Analytical grade (*pro analysi*) sodium cyanide, purchased by the submitters from Merck, Darmstadt, Germany, was dried for 24 hours in a vacuum desiccator containing potassium hydroxide pellets. The checkers obtained sodium cyanide from Fisher Scientific Company and dried the reagent in the same manner.

2. The submitters purified technical grade *N,N*-dimethylformamide by distillation from powdered calcium hydride. The checkers used *N,N*-dimethylformamide that had been dried over Linde type 4A molecular sieves. A small amount of dimethylamine in the solvent does not interfere with the reaction.
3. The drying tube was connected to a Nujol bubbler. A nitrogen atmosphere was maintained during the reaction by passing nitrogen through the apparatus at a rate of *ca.* one bubble per second.
4. 3-Pyridinecarboxyaldehyde (nicotinaldehyde) was supplied by Aldrich-Europe, Beerse, Belgium. The checkers purified this reagent by fractional distillation, b.p. 95–97° (15 mm.). The submitters stress that 3-pyridinecarboxaldehyde should be completely free from contamination by the acid. They stirred 150 g. of the aldehyde with 100 g. of potassium carbonate and 300 ml. of ethanol for 12 hours, filtered the suspended solid, and fractionally distilled the filtrate through a 30-cm. Vigreux column, using a water aspirator. However, the checkers found that the recovery of aldehyde from this procedure was very low, and recommend vacuum distillation instead. 3-Pyridinecarboxaldehyde is a powerful skin irritant and should be handled with protective gloves.
5. The solution, in which some sodium cyanide remains suspended, becomes quite thick at this stage owing to formation of the benzoin-type dimer of 3-pyridinecarboxaldehyde. An adequate amount of *N,N*-dimethylformamide should be used as solvent to ensure that the dimer does not crystallize.
6. Although the solution becomes very viscous at this point, stirring is still possible and should be continued.
7. Continuous extraction is only necessary if the product is appreciably soluble in water. Products such as those shown in Table I may be isolated by extraction in a separatory funnel.

TABLE I

γ-KETONITRILES PREPARED BY CYANIDE-CATALYZED CONJUGATE ADDITION OF ARYL ALDEHYDES TO α,β-UNSATURATED NITRILES

	Distilled Yield(%)[a]	Recrystallized Yield(%)[b]	B.p.(°) (pressure, mm.)	M. p. (°)
$R_1 = C_6H_5$, $R_2 = R_3 = H$				
	71	50[c]	131–134 (0.2)	72–73
$R_1 = C_6H_5$, $R_2 = H$, $R_3 = CH_3$				
	73–76	34–37[d]	113–115 (0.1)	42–43

$R_1 = C_6H_5$, $R_2 = CH_3$, $R_3 = H$				
	62–64	45–47[d]	111–113 (0.15)	58–59
$R_1 = R_2 = C_6H_5$, $R_3 = H$				
	83	56[e]	157–159 (0.05)	83–84
$R_1 = 4\text{-}ClC_6H_4$, $R_2 = R_3 = H$				
	88–89	71–72[c]	152–154 (0.1)	70–71

[a]The distilled products were almost pure.

[b]The recrystallized products were pure, but considerable losses were entailed.

[c]Recrystallized from aqueous ethanol (decolorized with activated carbon).

[d]Recrystallized from ethyl acetate–petroleum ether at −30°.

[e]Recrystallized from 2-propanol.

8. The submitters state that the solution need not be dried, since water is removed by azeotropic distillation as the chloroform is evaporated. However, the checkers dried the chloroform solution with anhydrous magnesium sulfate prior to evaporation.
9. The checkers dried the product in a vacuum desiccator for 24 hours to remove all the 2-propanol and obtained 77–79 g. (64–66%), m.p. 70–72°. The yield reported by the submitters was 82–89 g. (68–74%), m.p. 73–74° (lit.,[2] m.p. 66–67°). The product's ^1H NMR spectrum (90MHz., $CDCl_3$), δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 2.84 (t, J = 6.6, 2H, CH_2CH_2CN), 3.40 (t, J = 6.6, 2H, CH_2CH_2CN), 7.49 (d of d, J = 4.4 and 7.3, 1H, H_5), 8.24 (d of t, J = 2.0 and 7.3, 1H, H_4), 8.82 (d of d, J = 2.0 and 4.5, 1H, H_6), 9.16 (d, J = 2.0, 1H,H_2); mass spectrum *m/e* (relative intensity): 160 (M^+, 8), 106 (74), 78 (100), 51 (100).

3. Discussion

4-Oxo-4-(3-pyridyl)butyronitrile has been prepared in three steps by Leete, Chedekel, and Bodem,[2] and in one step by Stetter and Schreckenberg[3] using a method closely related to the present procedure. This compound serves as precursor in syntheses of myosmine[2] and various nicotine analogs. Other general methods for the preparation of γ-ketonitriles include the addition of hydrogen cyanide to α,β-unsaturated ketones,[4] the reaction of potassium cyanide with the hydrochlorides of Mannich bases from ketones,[5] and a variety of new methods for nucleophilic acylation.[6]

The addition of 3-pyridinecarboxyaldehyde to acrylonitrile is only one example of a wide range of reactions involving the conjugate addition of aldehydes to electron-deficient olefins. The reaction is not limited to α,β-unsaturated nitriles;[3,7] For example, γ-diketones[7,8] and γ-keto esters[7,9] may be similarly prepared by addition of aldehydes to α,β-unsaturated ketones and esters. Important advantages of this method are the simplicity of the procedure, the catalytic nature of the reaction, and low-cost reagents.

The γ-ketonitriles shown in Table I were prepared by the cyanide-catalyzed procedure described here. While this procedure is generally applicable to the synthesis of γ-diketones, γ-keto esters, and other γ-ketonitriles, the addition of 2-furancarboxaldehyde is more difficult, and a somewhat modified procedure should be employed.[10] Although the cyanide-catalyzed reaction is generally limited to aromatic and heterocyclic aldehydes, the addition of aliphatic aldehydes to various Michael acceptors may be accomplished in the presence of thioazolium ions,[7,11] which are also effective catalysts for the additions.[7,12]

The mechanism of the cyanide- and thioazolium ion-catalyzed conjugate addition reactions[7] is considered to be analogous to the Lapworth mechanism for the cyanide-catalyzed benzoin condensation. Thus, the cyano-stabilized carbanion, resulting from deprotonation of the cyanohydrin of the aldehyde, is presumed to be the actual Michael donor. After conjugate addition to the activated olefin, cyanide is eliminated, forming the product and regenerating the catalyst.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

ethanol (64-17-5)

potassium carbonate (584-08-7)

acetic acid (64-19-7)

ethyl acetate (141-78-6)

chloroform (67-66-3)

sodium cyanide (143-33-9)

hydrogen cyanide (74-90-8)

nitrogen (7727-37-9)

potassium cyanide (151-50-8)

potassium hydroxide (1310-58-3)

2-propanol (67-63-0)

2-furancarboxaldehyde (98-01-1)

magnesium sulfate (7487-88-9)

dimethylamine (124-40-3)

acrylonitrile (107-13-1)

N,N-dimethylformamide (68-12-2)

calcium hydride (7789-78-8)

4-Oxo-4-(3-pyridyl)butyronitrile, 3-Pyridinebutanenitrile, γ-oxo (36740-10-0)

3-pyridinecarboxaldehyde, 3-Pyridinecarboxyaldehyde, nicotinaldehyde (500-22-1)

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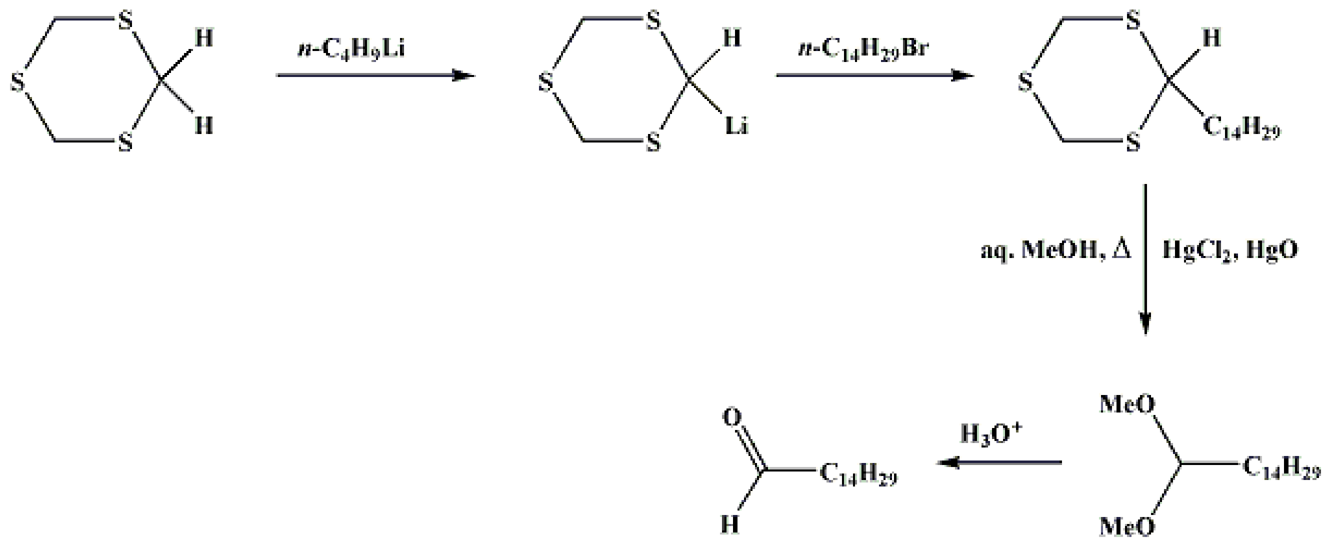
Organic Syntheses, CV 6, 869

ALDEHYDES FROM *sym*-TRITHIANE: *n*-PENTADECANAL

[Pentadecanal]



Submitted by D. Seebach[1] and A. K. Beck.
Checked by A. Brossi, N. W. Gilman, and G. Walsh.

1. Procedure

A. 2-*Tetradecyl*-sym-*trithiane*. A 1-l., round-bottomed, side-armed flask containing a magnetic stirring bar is charged with 25.0 g. (0.180 mole) of finely ground, pure, *sym*-trithiane (Note 1). The flask is equipped with a three-way stopcock and a rubber septum on the side arm. The air in the flask is replaced with dry nitrogen (Note 2). Tetrahydrofuran (Note 3) (350 ml.) is added by syringe, and the resulting slurry is stirred vigorously in a cooling bath at −30° (Note 4). After the addition of 0.190 mole of *n*-butyllithium (1.5–2.5 molar in *n*-hexane) (Note 5), the mixture is stirred for 1.5–2.5 hours, keeping the bath temperature between −25° and −15°. After this period of time the trithiane is dissolved (Note 6), and dry ice is added (no excess!) to the bath until the temperature is about −70°. To this cooled solution is rapidly added 50.0 g. (49.5 ml., 0.180 mole) of 1-bromotetradecane (myristyl bromide) (Note 7) by syringe, and the resulting mixture is stirred overnight, during which time the bath temperature rises to 0–25° and a heavy, colorless precipitate separates. Stirring is continued for 1 hour at room temperature before the mixture is poured into a 2-l. separatory funnel containing 800 ml. of water and 500 ml. of carbon tetrachloride. After shaking, the layers are separated and the aqueous layer is shaken with two additional 500-ml. portions of carbon tetrachloride. Some undissolved trithiane is filtered from the combined organic layers, which are washed with water and dried over anhydrous potassium carbonate. The solvent is removed by evaporation, yielding 54–59 g. of crude, solid 2-tetradecyl-*sym*-trithiane, after drying under reduced pressure (Note 8).

B. *Pentadecanal dimethyl acetal*. The crude material obtained from Part A is placed in a 2-l., three-necked flask fitted with an overhead stirrer, a reflux condenser with drying tube, and a stopper. Methanol (1 l., reagent grade) is added, the stirrer is started, and 40 g. (0.18 mole) of mercury(II) oxide and 100 g. (0.368 mole) of mercury(II) chloride are introduced. The mixture is heated under reflux for 4.5 hours and filtered through a Büchner funnel after cooling. The residue is washed with 300 ml. of pentane (Note 9), and the combined organic solutions are poured into 1 l. of water. The layers are separated, and the lower aqueous layer is shaken with two 500-ml. portions of pentane. The combined organic layers are quickly washed with 10% ammonium acetate solution (Note 10) and water and dried over sodium sulfate. The pentane is evaporated under reduced pressure, giving 30.0–32.5 g. of the crude acetal as a mobile, slightly yellow oil.

C. n-*Pentadecanal*. The crude acetal from Part B is dissolved in 600 ml. of tetrahydrofuran, and 150 ml. of water containing 2 g. of *p*-toluenesulfonic acid monohydrate is added. The resulting pale mixture is heated at reflux for

1 hour and cooled. The hydrolysate is poured into 600 ml. of water and extracted with three 300-ml. portions of pentane (Note 9). The colorless pentane extracts are combined, washed three times with saturated sodium hydrogen carbonate solution and once with water, and dried over sodium sulfate. Evaporation of the solvent furnishes an oil which upon distillation under reduced pressure (Note 11) yields 18.7–22.5 g. of *n*-pentadecanal, b. p. 103–106° (0.2 mm.). The overall yield from 1-bromotetradecane is 47–55%. The product solidifies eventually and should be kept under an inert atmosphere in the refrigerator.

2. Notes

1. It is essential that the *sym*-trithiane be of good purity. Commercial *sym*-trithiane can be purified by extraction from a thimble in a hot extractor using 300 ml. of toluene for 30 g. of trithiane. After cooling the extract to 0°, *sym*-trithiane is recovered by filtration and recrystallized from toluene. In one run the checkers used *sym*-trithiane as obtained from Eastman Organic Chemicals and observed a 10% decrease in yield of *n*-pentadecanal.
2. This is done by evaporating and filling with dry nitrogen three times; during the reaction a pressure of about 50 mm. is maintained against the atmosphere using a mercury bubbler.
3. Tetrahydrofuran is distilled from a blue solution of benzophenone ketyl, obtained by refluxing tetrahydrofuran in the presence of sodium wire, some potassium, and benzophenone. See *Org. Synth.*, **Coll. Vol. 5**, 976 (1973) for a warning note regarding the purification of tetrahydrofuran.
4. A 2-l. Dewar cylinder was used.
5. The checkers used 120 ml. of 1.6 *M* *n*-butyllithium in hexane, obtained from Foote Mineral Company.
6. If the trithiane, apart from a few crystals, does not dissolve entirely, the workup procedure is complicated. The crude tetradecyltrithiane must then be purified (by dissolving in 500 ml. of carbon tetrachloride at 30°, filtering, and precipitating with 1.5 l. of methanol) before conversion to the acetal.
7. A commercial product (Aldrich Chemical Company, Inc., or Matheson, Coleman and Bell) proved satisfactory without further purification. The purity should be checked by refractive index and/or GC.
8. The crude tetradecyltrithiane contains 4–6% of *sym*-trithiane, m.p. 69–71°; recrystallization (Note 6) gives pure product, m.p. 76.3–76.6°.
9. Low-boiling ligroin can be used as well.
10. A white precipitate is formed during the first and second washing.
11. A short-path distillation apparatus with a cold finger, but no condenser, should be used since the product may crystallize. The distillation is carried out under nitrogen or argon (balloon at capillary).

3. Discussion

The procedure described here provides a convenient route to aldehydes, with trithiane serving as an inexpensive, "masked" carbonyl group.[2,3,4] The reaction is limited, however, to the use of primary alkyl halides, aldehydes, and ketones for elaboration of the carbon chain through attack on the metallated trithiane. Examples of aldehydes synthesized by this method are given in Table I.

TABLE I
ALDEHYDES FROM 2-LITHIO-1,3,5-TRITHIANE AND ALKYL HALIDES

			Aldehyde	
Halide	2-Alkyl-1,3,5-Trithiane %[a,b,c]	Aldehyde Dimethyl Acetal Yield, Yield, %[a,b]	Product	Yield, %[a,e,f]
1-Bromopentane	96	66[d]	Hexanal	43
(S)-(+)-1-Iodo-2-methylbutane	98	67[d,g]	(S)-(–)-3-Methylpentanal	41
1-Bromoheptane	100	60[d]	Octanal	45
1-Bromodecane	100	99[c]	Undecanal	65
1-Bromohexadecane	100	60[c]	Heptadecanal	32
Benzyl Bromide	100	32[d]	Phenylacetaldehyde	20

[a] Based on halide.

[b] Reaction conducted on 100 mmoles scale.

[c] Crude product.

[d] Distilled product.

[e] Reaction conducted on 5–10 mmoles scale.

[f] Yield of distilled or recrystallized product.

[g] (+)-Iodide with optical purity of 89% gave acetal with α_D + 7.6° (neat, *l* = 100 mm.).

The *S*-acetal is converted to the *O*-acetal in anhydrous methanol because hydrolysis of monosubstituted trithianes in aqueous methanol furnishes a mixture of the free aldehyde and its *O*-acetal derivative. It is advantageous to store aldehydes as the *O*-acetal derivatives since free aldehydes are susceptible to polymerization and oxidation.

This method has several common features with the dithiane method[5] that is useful for the synthesis of aldehydes and ketones.[4] This latter method is illustrated by the synthesis of cyclobutanone [*Org. Synth.*, **Coll. Vol. 6**, 316 (1988)].

n-Pentadecanal has also been prepared by pyrolysis of α-hydroxy-[6] and α-methoxypalmitic acid,[7] from α-bromopalmitic acid chloride and sodium azide,[8] and from α-hydroxypalmitic acid and lead tetraäcetate.[9]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 542
- Org. Syn. Coll. Vol. 7, 290
- Org. Syn. Coll. Vol. 7, 447
- Org. Syn. Coll. Vol. 8, 444

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ligroin

benzophenone ketyl

(S)-(−)-3-Methylpentanal

potassium carbonate (584-08-7)

methanol (67-56-1)

ammonium acetate (631-61-8)

sodium hydrogen carbonate (144-55-8)

sodium sulfate (7757-82-6)

carbon tetrachloride (56-23-5)

nitrogen (7727-37-9)

mercury(II) oxide (21908-53-2)

toluene (108-88-3)

Benzophenone (119-61-9)

mercury(II) chloride (7487-94-7)

potassium (7440-09-7)

Pentane (109-66-0)

sodium azide (26628-22-8)

1-bromoheptane (629-04-9)

benzyl bromide (100-39-0)

phenylacetaldehyde (122-78-1)

butyllithium, n-butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

hexane, n-hexane (110-54-3)

1-bromohexadecane (112-82-3)

Cyclobutanone (1191-95-3)

argon (7440-37-1)

OCTANAL (124-13-0)

1-bromopentane (110-53-2)

1-Bromodecane (112-29-8)

Pentadecanal, n-PENTADECANAL (2765-11-9)

trithiane (3325-33-5)

1-bromotetradecane, myristyl bromide (112-71-0)

Hexanal (66-25-1)

(S)-(+)-1-Iodo-2-methylbutane (29394-58-9)

Undecanal (112-44-7)

Heptadecanal

tetradecyltrithiane

α-methoxypalmitic acid

α-bromopalmitic acid chloride

α-hydroxypalmitic acid (764-67-0)

p-toluenesulfonic acid monohydrate (6192-52-5)

sym-Trithiane (291-21-4)

2-Tetradecyl-sym-trithiane (24644-07-3)

Pentadecanal dimethyl acetal (52517-73-4)

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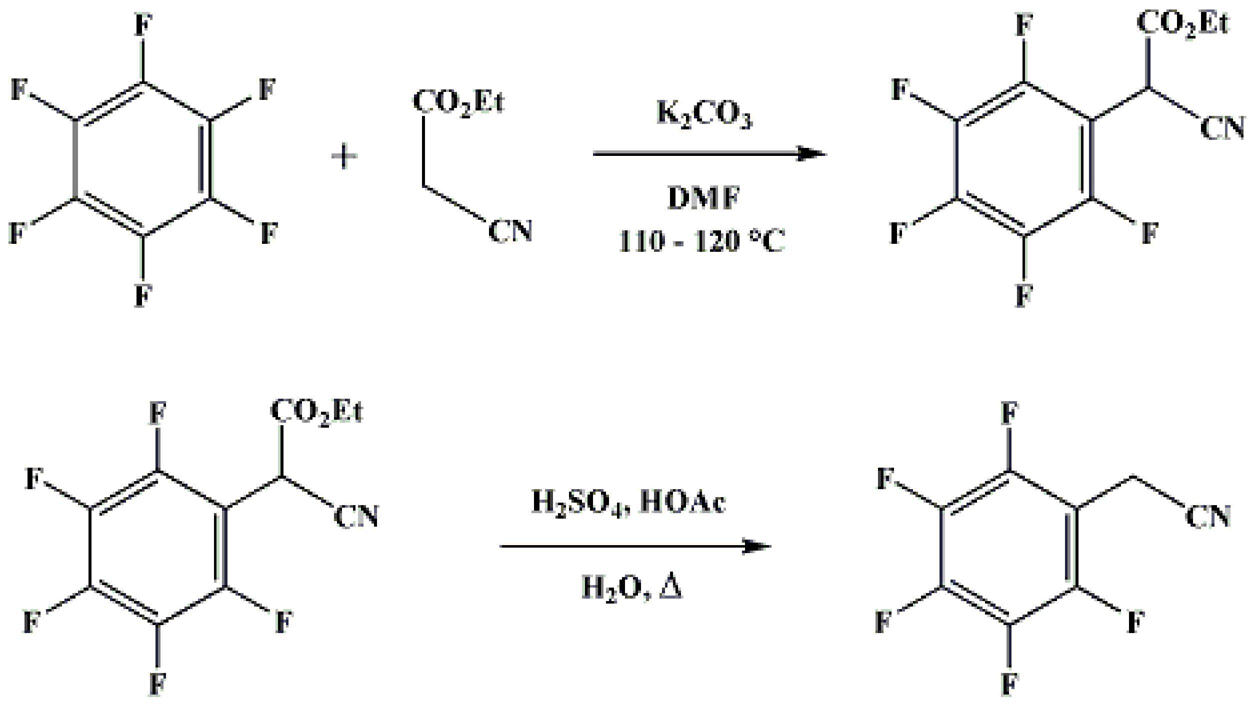
Organic Syntheses, CV 6, 873

(PENTAFLUOROPHENYL)ACETONITRILE

[Benzeneacetonitrile, 2,3,4,5,6-pentafluoro-]



Submitted by Robert Filler[1] and Sarah M. Woods[2].
Checked by Andrew E. Feiring and William A. Sheppard.

1. Procedure

A. *Ethyl cyano(pentafluorophenyl)acetate*. A 2-l., four-necked flask equipped with mechanical stirrer, addition funnel, thermometer, and condenser is charged with 650 ml. of *N*,*N*-dimethylformamide (Note 1) and 140 g. (1.01 mole) of anhydrous potassium carbonate. The rapidly stirred mixture is heated to 152–154° and 113 g. (1.00 mole) of ethyl cyanoacetate is added dropwise over 10–15 minutes without further heating. The temperature of the mixture is allowed to drop to 110–120° and maintained within this range while 186 g. (1.00 mole) of hexafluorobenzene (Note 2) is added dropwise over 1 hour. The dark mixture is stirred for 3 hours after the addition is complete, poured into 3 l. of ice water contained in a 5-l. Erlenmeyer flask, and acidified *(Caution! Foaming)* with 20% sulfuric acid. After being cooled overnight in the refrigerator, the top, aqueous layer is decanted from a lower viscous organic layer. The organic layer is dissolved in 600 ml. of diethyl ether, washed with water, and aqueous 10% sodium hydrogen carbonate, and dried over anhydrous magnesium sulfate. The ether is removed on a rotary evaporator, affording 217 g. (78%) of dark oil which crystallizes on standing (Note 3). An analytical sample is prepared by dissolving 2 g. of the crude material in 5 ml. of boiling 95% ethanol. Hexane is added until mixture becomes turbid. Crystallization occurs when the

mixture is cooled with vigorous stirring in an acetone–dry ice bath. The solid is quickly collected on a Büchner funnel and transferred to a sublimator. Sublimation at 30° (0.5–1.0 mm.) affords white crystals, m.p. 38–38.5°, of analytically pure ethyl cyano(pentafluorophenyl)acetate (Note 4).

B. *(Pentafluorophenyl)acetonitrile*. A 1-l., one-necked flask equipped with magnetic stirrer and a reflux condenser is charged with 139.5 g. (0.500 mole) of crude ethyl cyano(pentafluorophenyl)acetate, 350 ml. of aqueous 50% acetic acid, and 12.5 ml. of concentrated sulfuric acid. The mixture is heated at reflux for 15 hours. After cooling to room temperature, the mixture is diluted with an equal volume of water and cooled in an ice bath for 1 hour. The top layer is decanted from a dark organic layer which settles to the bottom of the flask. The organic phase is dissolved in 200 ml. of ether and washed with water and aqueous 10% sodium hydrogen carbonate. After being dried over anhydrous magnesium sulfate, the ether is removed on a rotary evaporator. The residue is distilled through a 25-cm. jacketed Vigreux column, affording 74–78 g. (71–75%) of (pentafluorophenyl)acetonitrile as a colorless liquid, b.p. 105° (8 mm.), n_D^{25} 1.4370 (Note 5).

2. Notes

1. Technical grade *N,N*-dimethylformamide was stirred over anhydrous cupric sulfate, filtered, and distilled under reduced pressure. The submitters used reagent grade *N,N*-dimethylformamide without purification.
2. Hexafluorobenzene was purchased from PCR, Inc., Gainesville, Florida, and distilled (b.p. 80–81°) before use.
3. In one run the checkers obtained only 135 g. of crude product by this procedure. The aqueous solution which was decanted from the crude product was divided into three portions and each portion was extracted with one 250-ml. portion of ether. The combined ether extracts were washed with water and aqueous 10% sodium hydrogen carbonate, dried over anhydrous magnesium sulfate, and concentrated on the rotary evaporator, affording an additional 83 g. of crude product, for a total of 218 g.
4. ^{1}H NMR (CCl_4), δ (multiplicity, number of protons): 1.38 (t, 3H) 4.35 (q, 2H), 5.05 (s, 1H); IR ($CHCl_3$) cm.$^{-1}$: 3003, 2933, 2257, 1760, 1661, 1527, 1513; ^{19}F NMR (CCl_4, $CFCl_3$ internal standard): δ 141.2 (sym. m, 2 *ortho* F), 151.8 (t of t, $J_{1,2}$ = 20.3 Hz., $J_{1,3}$ = 2.5 Hz., *para* F), 161.1 (m, 2 *meta* F). The pKa in dimethyl sulfoxide is 5.06 ± 0.02.[3]
5. ^{1}H NMR (CCl_4), δ: 3.75 (s, with fine structure); IR (neat) cm.$^{-1}$: 2985, 2273, 1667, 1527, 1515; ^{19}F NMR (CCl_4, $CFCl_3$ internal standard), δ 142.4 (sym. m, 2 *ortho* F), 153.8 (t, with fine structure, J = 20 Hz., *para* F), 161.7 (m, 2 *meta* F). The pKa in dimethyl sulfoxide is 15.8 ± 0.3.[3]

3. Discussion

The formation of ethyl cyano(pentafluorophenyl)acetate illustrates the *intermolecular* nucleophilic displacement of fluoride ion from an aromatic ring by a stabilized carbanion. The reaction proceeds readily as a result of the activation imparted by the electron-withdrawing fluorine atoms.[4] The selective hydrolysis of a cyano ester to a nitrile has been described.[5] (Pentafluorophenyl)acetonitrile[6] has also been prepared by cyanide displacement on (pentafluorophenyl)methyl halides. However, this direct displacement is always accompanied by an undesirable side reaction, yielding 15–20% of 2,3-bis(pentafluorophenyl)propionitrile. The reaction of one equivalent of hexafluorobenzene with one equivalent of lithioacetonitrile (prepared from acetonitrile and *n*-butyllithium) provides a low yield (7–10%) of (pentafluorophenyl)acetonitrile and about a 22% yield of bis(pentafluorophenyl)acetonitrile (m.p. 65°; the pKa in dimethyl sulfoxide is 7.95 ± 0.04[3]). The yield of the latter compound can be increased by use of excess lithioacetonitrile.[7]

(Pentafluorophenyl)acetonitrile is a useful intermediate to 4,5,6,7-tetrafluoroindole.[8] The nitrile is readily converted to 2-(pentafluorophenyl)ethylamine hydrochloride in 80% yield by catalytic hydrogenation in dilute hydrochloric acid. Although the salt is stable, the amine undergoes a facile intermolecular nucleophilic aromatic substitution reaction, even at room temperature. However, freshly distilled 2-(pentafluorophenyl)ethylamine is converted by heating in the presence of anhydrous potassium fluoride in *N,N*-dimethylformamide to 4,5,6,7-tetrafluoroindoline (62% yield) by intramolecular nucleophilic displacement of fluoride ion.[9] The indoline is aromatized by treatment with activated manganese dioxide,[10] giving 4,5,6,7-tetrafluoroindole (82% yield). The anion of (pentafluorophenyl)acetonitrile is converted to bis(pentafluorophenyl)acetonitrile on treatment with hexafluorobenzene (*vide supra*).[11]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ether, diethyl ether (60-29-7)

acetonitrile (75-05-8)

sodium hydrogen carbonate (144-55-8)

cupric sulfate (7758-98-7)

manganese dioxide (1313-13-9)

Ethyl cyanoacetate (105-56-6)

magnesium sulfate (7487-88-9)

n-butyllithium (109-72-8)

potassium fluoride (7789-23-3)

N,N-dimethylformamide (68-12-2)

hexane (110-54-3)

dimethyl sulfoxide (67-68-5)

Fluorine (7782-41-4)

(Pentafluorophenyl)acetonitrile, Benzeneacetonitrile, 2,3,4,5,6-pentafluoro- (653-30-5)

hexafluorobenzene (392-56-3)

Ethyl cyano(pentafluorophenyl)acetate (2340-87-6)

octafluorotoluene (434-64-0)

2,3-bis(pentafluorophenyl)propionitrile

lithioacetonitrile

bis(pentafluorophenyl)acetonitrile

4,5,6,7-tetrafluoroindole (16264-67-8)

2-(pentafluorophenyl)ethylamine hydrochloride

2-(pentafluorophenyl)ethylamine

4,5,6,7-tetrafluoroindoline

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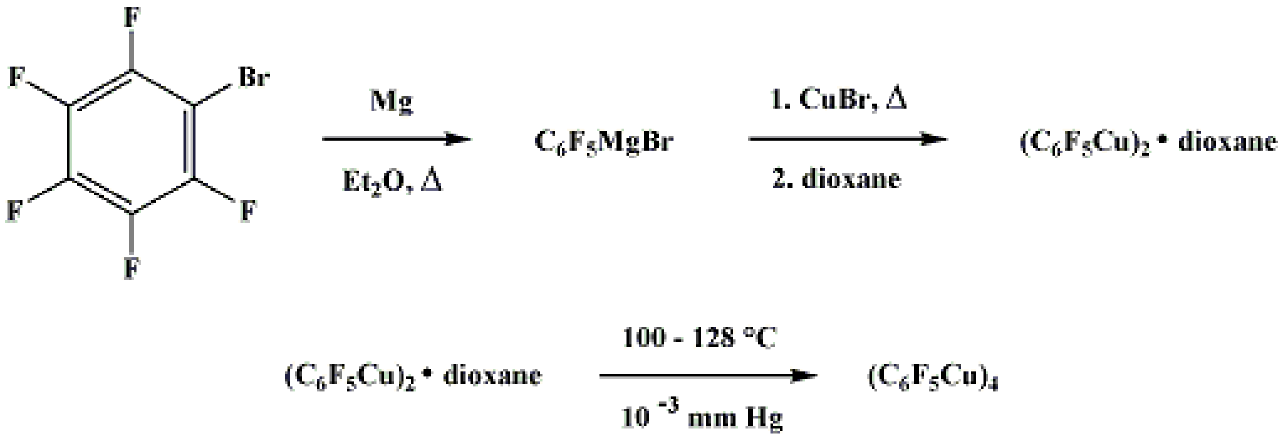
Organic Syntheses, CV 6, 875

PENTAFLUOROPHENYLCOPPER TETRAMER, A REAGENT FOR SYNTHESIS OF FLUORINATED AROMATIC COMPOUNDS

[Copper, tetrakis(pentafluorophenyl)tetra]



Submitted by Allan Cairncross[1], William A. Sheppard[2], and Edward Wonchoba.
Checked by William J. Guilford, Cynthia B. House, and Robert M. Coates.

1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A 1-l., four-necked, round-bottomed flask fitted with a condenser bearing a nitrogen inlet, a pressure-equalizing dropping funnel, a thermometer, and a mechanical stirrer is charged with 5.40 g. (0.222 g.-atom) of magnesium turnings (Note 1). The flask is flame dried while being flushed with nitrogen and kept dry and oxygen-free with a static nitrogen atmosphere throughout the preparation (Note 2). After 150 ml. of diethyl ether (Note 3) is introduced into the flask with a syringe, 54.9 g. (28.2 ml., 0.222 mole) of bromopentafluorobenzene (Note 4) is added dropwise over *ca.* 45 minutes at a rate that maintains a gentle reflux. The reflux is maintained for another 15 minutes by heating at 35° (Note 1). The resulting black solution is cooled to room temperature, and 63.1 g. (0.440 mole) of powdered, anhydrous copper(I) bromide (Note 5) is added in three 21-g. portions at 1-minute intervals. An exothermic reaction occurs after each addition (Note 6).

The brown mixture is stirred for 30 minutes, 100 ml. of ether is added, and the mixture heated at reflux for another 30 minutes. The brown suspension is diluted with 400 ml. of ether, after which 100 ml. of 1,4-dioxane (Note 7) is added carefully over 15 minutes, moderating the mildly exothermic reaction. The light-gray suspension is stirred for 30 minutes.

The dropping funnel is replaced with a three-way stopcock with an attached nitrogen source and a bubbler open to the system (see f.htmigure 1). The thermometer and mechanical stirrer are

replaced with ground-glass plugs (Note 8), and the condenser is replaced with a 1-l., 90-mm., medium-porosity fritted-disk nitrogen pressure funnel attached to a 1-l., round-bottomed, two-necked flask fitted with a three-way stopcock on the side arm (f.htmigure 1). All joints are either clamped or taped together, and the apparatus is carefully inverted, pouring the slurry into the funnel. The mixture is filtered with nitrogen pressure into the 1-l. receiving flask (Note 9), which is maintained under a nitrogen atmosphere. The solid filter cake is rinsed with three 50-ml. portions of 4:1 (v/v) ether–dioxane injected with a long needle syringe through the three-way stopcock. The four-necked flask is rinsed by manipulation of the needle, and the apparatus and the solids are dispersed in each rinse. The pale-yellow filtrate is evaporated to dryness under reduced pressure with a warm water bath at 40°, and the powdery white solid is dried at 10-mm. pressure for 4 hours at 25°, yielding 38.3–48.8 g. (63–80%) of bis (pentafluorophenylcopper)dioxane complex (Note 10). The color of this dioxane complex varies from tan to white. The complex is transferred to a 200-ml., round-bottomed flask under a nitrogen atmosphere. The flask is evacuated to a pressure of 0.001 mm., immersed in an oil bath, and slowly heated to 100° over 1 hour (Note 11). The temperature is slowly and constantly increased to 128° during a second hour and maintained at 128° for 4 hours (Note 12). Pure pentafluorophenylcopper tetramer is obtained as a gray to tan powder weighing 29.8–34.7 g. (58–68%) (Note 13).

Figure 1.

Figure 1.

2. Notes

1. Magnesium metal turnings, from Fisher Scientific Company or Mallinckrodt Chemical Works, were used. Excess magnesium or incomplete formation of the Grignard must be avoided, since any free magnesium reacts when the copper salts are added, producing a dark product in lower yield and of questionable purity.
2. All glassware must be flame dried, and an absolute nitrogen atmosphere must be maintained during each step, since pentafluorophenylcopper hydrolyzes easily and undergoes oxidative coupling in air. The checkers used dry grade nitrogen from a cylinder, supplied by the Linde Division, Union Carbide Corporation.
3. Anhydrous ether, purchased from Fisher Scientific Company or Mallinckrodt Chemical Works, was dried over Linde type 3A molecular sieves. The checkers degassed the solvent immediately before use by evacuating and filling the container with nitrogen three times.
4. Bromopentafluorobenzene, obtained from either PCR, Inc., or Columbia Organic Chemicals Company, Inc., was used without purification.
5. Anhydrous copper(I) bromide, from Fisher Scientific Company, was powdered and used without drying by the submitters. The checkers dried the copper(I) bromide at 140° for 2 hours under reduced pressure before use.
6. The copper(I) bromide can also be added gradually from a solid addition apparatus such as a 50-ml. Erlenmeyer flask connected to a ground-glass adapter with a short piece of gooch tubing.
7. Spectral grade 1,4-dioxane, from MC and B Manufacturing Chemists or Mallinckrodt Chemical Works, was dried over Linde type 4A molecular sieves. The checkers degassed the solvent prior to use as described in (Note 3).
8. The checkers used rubber septa, secured with wire bands.

9. The filtering operation can also be conveniently done in a high-quality nitrogen atmosphere dry box by vacuum filtration through a 90-mm., 60-ml., medium-porosity, fritted-disk Büchner funnel.
10. Pentafluorophenylcopper is first isolated as a 1:1 complex with dioxane and is usually white. Half of the complexed dioxane is very labile and is usually lost during vacuum drying, giving the 2:1 complex. Excessive heating can cause loss of additional dioxane (lower apparent yield) and eventual decomposition of the product.
If the product is isolated in a nitrogen dry box, the filtrate is evaporated without heat until a small amount of solvent remains. The precipitate is collected cold and rinsed with cold ether. The nearly white 1:1 pentafluorophenylcopper·dioxane complex is obtained with no significant loss of yield.
11. The rate of heating is critical. The temperature must be increased very gradually to remove the dioxane without causing decomposition of the product. A vacuum of 0.1 to 1.0 mm is sufficient to remove the last of the dioxane although 0.001 mm was usually used by the submitters. Occasionally, cold traps become plugged with frozen dioxane (m. p. 12°), resulting in loss of vacuum, overheating, and decomposition of the pentafluorophenyl dioxane complexes.
12. If the product is heated to 130° or higher, decomposition of product occurs with the formation of a copper mirror.
13. The spectral properties of pentafluorophenylcopper tetramer are as follows: IR (Nujol) $cm.^{-1}$: 1630 medium; 1391 medium; 1353 medium; 1275 medium; 1090, 1081, and 1071 strong triplet; 978 strong; 785 medium; ^{19}F NMR (tetrahydrofuran with $CFCl_3$ as internal reference): δ (multiplicity, coupling constant *J* in Hz., number of fluorines, assignment): 107.2 (20-line m, 2F, *ortho* F), 153.4 (t of t, *J* = 1.3 and 20, 1F, *para* F), 162.3 (17-line m, 2F, *meta* F). Absorptions at 820–900, 1100–1125, and 1290 $cm.^{-1}$ in the IR spectrum and at δ 3.05 in the ^{1}H NMR spectrum indicate that dioxane is still present.
The pentafluorophenylcopper tetramer is usually analytically pure as isolated and melts at 200° with decomposition. If any significant decomposition occurs during the final drying, the product can be purified by dissolution in ether, filtration to remove copper metal, and precipitation by addition of hexane. It can also be recrystallized from benzene. When kept in a sealed container under nitrogen at room temperature, pentafluorophenyl copper tetramer appears to be stable for reasonable periods. It can be stored indefinitely at –78° under an atmosphere of carbon dioxide.

3. Discussion

Pentafluorophenylcopper is representative of a series of fluorinated organocopper compounds that are highly soluble in organic solvents, more thermally stable than their hydrocarbon analogs, and useful as synthetic intermediates.[3,4,5,6] Pentafluorophenylcopper has been used to introduce the pentafluorophenyl group[7,8,9] and as a reagent for an improved, Ullman diphenyl ether synthesis.[10] It is also an effective catalyst for decarboxylation of aromatic acids,[11,12] rearrangement of bicyclic hydrocarbons,[13] and decomposition of alkyldiazo compounds.[3,4,5] It also is an excellent reagent for the preparation of anhydrous copper salts of carboxylic acids[11] and can be used for coating substrates with copper by thermal decomposition.[14]

Pentafluorophenylcopper exists as a tetramer.[15] It forms complexes with a variety of reagents

and solvents as well as "ate" complexes; a representative list is given in Table I. For many syntheses the crude reaction mixtures of copper(I) halide with either pentafluorophenylmagnesium bromide, or pentafluorophenyllithium,[8,9] or the pentafluorophenylcopper·dioxane complex[7] react as well as the solvent-free tetramer.

TABLE I

COMPLEXES OF PENTAFLUOROPHENYLCOPPER[3,4,5]

Complex	Properties
C_6F_5Cu·benzonitrile	m.p. 101°
C_6F_5Cu·tributylamine	liquid at room temperature
$(C_6F_5Cu)_2$·dioxane	m.p. 200–220° (dec.)
C_6F_5Cu·quinoline	m.p. 170–176°
$(C_6F_5Cu)_2$·1,5-cycloöctadiene	dec. 160°
C_6F_5Cu·dimethylacetylene	dec. 145°
$(C_6F_5Cu)_2$·butadiene	dec. 215°
C_6F_5Cu·tetraethylammonium cyanide	dec. 160°

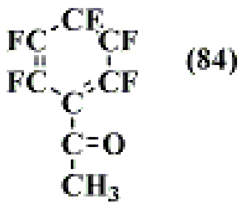
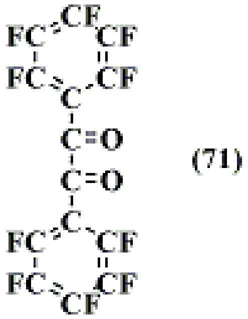
[a] A, $(C_6F_5Cu)_4$; B, $(C_6F_5Cu)_2$.dioxane; C, reagent prepared *in situ* from C_6F_5MgX and CuX; D, reagent prepared *in situ* from C_6F_5Li and CuX.

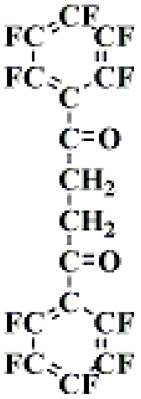
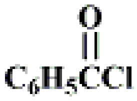
A selection of synthetic uses of pentafluorophenylcopper is given in Table II. Two unchecked experimental procedures illustrating the use of pentafluorophenylcopper tetramer and the dioxane complex to introduce the pentafluorophenyl group are given below. In coupling reactions hexane is usually the preferred solvent, particularily with alkyl halides that can readily form carbonium ion intermediates. Aromatic solvents are often alkylated during coupling, giving undesired by-products.

TABLE II

SUMMARY OF REACTIONS OF PENTAFLUOROPHENYLCOPPER

Reactant	Form of C_6F_5Cu[a]	Conditions	Product (% yield)	Reference
H_2O	B	ether, 25°, 1 hour	C_6F_5H (87)	5
None	B	200°	C_6F_5-C_6F_5 (60)	5
Br_2	B	hexane, 0°	C_6F_5Br(4) + C_6F_5-C_6F_5 (47)	3
$CuBr_2$	B	hexane, reflux	C_6F_5-C_6F_5 (68)	3
CO_2	A or B	neat or aprotic solvent, –78° to 25°	no reaction	3
CH_3I	A	hexane, 25°, 5 days	CH_3-C_6F_5 (39)	3

$C_6H_5CH_2Br$	B	ether, 25°, 4 hours	$C_6H_5CH_2C_6F_5$ (40)	3
1-Bromobicyclo-[2.2.2] octane	A	hexane, reflux, 20 hours	1-pentafluorophenylbicyclo [2.2.2]octane (83)	3, 4
$C_2H_5O_2CCHN_2$	A	tetrahydrofuran, 0°; hydrolysis	$(C_2H_5O_2)CCH_2C_6F_5$ (43)	3
C_6H_5I	A	benzene, reflux, 2 hours	C_6F_5-C_6H_5 (87)	3
3-FC_6H_4I	B	benzene, reflux, 2 hours	3-FC_6H_4-C_6F_5 (73)	7
		meta: benzene, reflux, 2 hours	$O_2NC_6H_4C_6F_5$ *meta* (85)	7
$O_2NC_6H_4I$	B	*para:* benzene, reflux, 2 hours	*para* (85)	7
		ortho: ether, reflux (exothermic)	*ortho* (73)	5
4-$(CH_3)_2NC_6H_4I$	B	benzene, reflux, 2 hours	4-$(CH_3)_2NC_6H_4C_6F_5$ (26)	7
4-$C_2H_5O_2CC_6H_4I$	B	benzene, reflux, 2 hours	4-$C_2H_5O_2CC_6H_4C_6F_5$ (97)	7
CF_2=CFI	C	tetrahydrofuran, 25–55°, 5 hours	C_6F_5CF=CF_2 (55)	16
CBr_2=$CHBr$	C	tetrahydrofuran, –5°, 3 hours	C_6F_5C CC_6F_5 (43)	17
	D	tetrahydrofuran–hexane, 0°, several hours	 (84)	9
	D	tetrahydrofuran, 0° (exothermic)	 (71)	18

	C	tetrahydrofuran, −5°, 3 hours	 (71)	17
C_6H_5I	C	tetrahydrofuran, 66°, 10 hours	C_6H_5-C_6F_5 (74)	16
	C	tetrahydrofuran, −5°, 3 hours	(77)	17
$(C_2H_5)_3SiC$□CBr	C	tetrahydrofuran, 25°, 1 hour; reflux, 10 hours	$(C_2H_5)_3SiC$□CC_6F_5 (85)	19

A. *(Pentafluorophenyl)benzene*. A 100-ml., round-bottomed flask equipped with a magnetic stirring bar and a reflux condenser bearing a nitrogen inlet is flushed with nitrogen and charged with a solution of 2.40 g. (0.00259 mole) of pentafluorophenylcopper tetramer in 25 ml. of benzene; 2.12 g. (0.0104 mole) of iodobenzene is then added. A static nitrogen atmosphere is maintained in the flask as the solution is heated to reflux. Copper(I) iodide starts to precipitate almost immediately. After 2 hours at reflux, the mixture is cooled and filtered, separating 1.67 g. of copper(I) iodide. The filtrate is evaporated, and the remaining pale-brown residue is sublimed at 100° (0.1 mm.), affording 2.01 g. (79%) of (pentafluorophenyl)benzene as a colorless solid, m.p. 110.0–112.4°. The presence of about 3% of decafluorobiphenyl in the product is revealed by GC analysis. (Pentafluorophenyl)benzene may be further purified by column chromatography on acid-washed alumina (Woelm, activity grade I) with hexane as an eluent, the decafluorobiphenyl impurity being eluted first. The purified product melts at 111.3–112.0°.

B. 1-*(Pentafluorophenyl)adamantane*. A 500 ml., three-necked flask equipped with a thermometer, a magnetic stirring bar, and a reflux condenser bearing a nitrogen inlet is maintained under nitrogen, and charged with 32.5 g. (0.00590 mole) of bis (pentafluorophenylcopper)·dioxane complex, 24.9 g. (0.116 mole) of 1-bromoadamantane, and 175 ml. of spectral grade hexane. The mixture is stirred and slowly warmed until the onset of an exothermic reaction which causes the mixture to reflux for approximately 15 minutes. After the exothermic reaction subsides, the mixture is heated at reflux overnight, stirred briefly with 3 ml. of water, and filtered, separating 17.0 g. of copper(I) bromide. The filtrate is concentrated, and the residue is recrystallized from ethanol, affording 32.6 g. (93%) of colorless crystals of 1-pentafluorophenyladamantane. After sublimation at 100° (0.1 mm.) the product melts at 109.9–

111.0°.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

H_2O

Pentafluorophenylcopper tetramer

Copper, tetrakis(pentafluorophenyl)tetra

bis(pentafluorophenylcopper)dioxane complex

pentafluorophenylcopper·dioxane complex

pentafluorophenyl copper tetramer

C_6F_5Cu·benzonitrile

C_6F_5Cu·tributylamine

C_6F_5Cu·quinoline

C_6F_5Cu·dimethylacetylene

$(C_6F_5Cu)_2$·butadiene

C_6F_5Cu·tetraethylammonium cyanide

bis(pentafluorophenylcopper)·dioxane complex

$(C_6F_5Cu)_2$·1,5-cyclooctadiene

ethanol (64-17-5)

Benzene (71-43-2)

ether, diethyl ether (60-29-7)

magnesium, magnesium turnings, Magnesium metal turnings (7439-95-4)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

copper (7440-50-8)

copper(I) bromide (7787-70-4)

Iodobenzene (591-50-4)

copper(I) iodide (7681-65-4)

dioxane (5703-46-8)

Tetrahydrofuran (109-99-9)

hexane (110-54-3)

1-bromoadamantane (768-90-1)

1,4-dioxane (123-91-1)

PENTAFLUOROPHENYLCOPPER

bromopentafluorobenzene (344-04-7)

pentafluorophenylmagnesium bromide

pentafluorophenyllithium

(pentafluorophenyl)benzene (784-14-5)

decafluorobiphenyl (434-90-2)

1-Bromobicyclo-[2.2.2]octane (7697-09-8)

1-pentafluorophenylbicyclo[2.2.2]octane

1-pentafluorophenyladamantane, 1-(Pentafluorophenyl)adamantane

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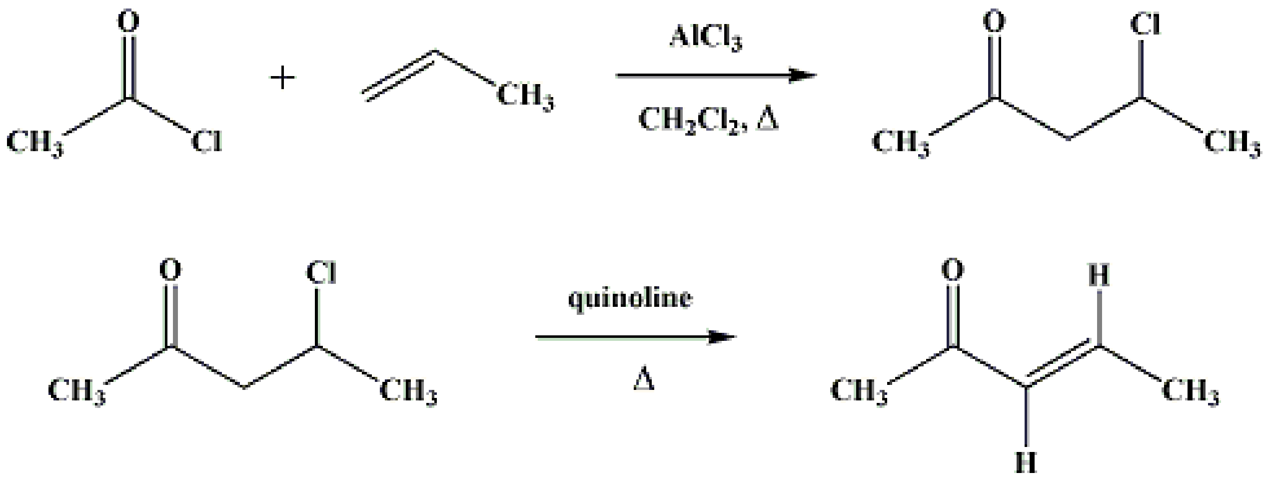
Organic Syntheses, CV 6, 883

trans-3-PENTEN-2-ONE

[3-Penten-2-one, *trans*-]



Submitted by H. C. Odom and A. R. Pinder[1].
Checked by Walter J. Campbell and Herbert O. House.

1. Procedure

Caution! Since both hydrogen chloride and propene may escape from the reaction vessel during this preparation, the reaction should be performed in a hood.

A 2-l., three-necked flask is equipped with an efficient mechanical stirrer, a gas-inlet tube extending almost to the bottom of the flask, and an efficient reflux condenser fitted with a calcium chloride drying tube. After the apparatus has been dried in an oven, 800 ml. of dichloromethane (Note 1) and 157 g. (142 ml., 2.00 moles) of acetyl chloride (Note 2) are added to the flask. This solution is stirred while 320 g. (2.40 moles) of powdered, anhydrous aluminum chloride (Note 3) is added in portions over a 15-minute period. As soon as this addition is complete, a stream of propene gas (Note 4) is passed through the continuously stirred reaction solution at a rate sufficient to maintain a gentle reflux. The gas flow is continued until no more heat is evolved and refluxing ceases (10–30 hours, (Note 4), at which time the flask is nearly full and the contents separate into two layers after stirring is stopped. The contents of the flask are poured cautiously onto about 1.5 kg. of ice (Note 5), and the upper organic layer is separated. The aqueous phase is shaken with three 100-ml. portions of dichloromethane (Note 6), and the combined organic solutions are washed with 50 ml. of water and dried over anhydrous magnesium sulfate.

The resulting dark brown solution is placed in a 2-l., round-bottomed flask equipped with a thermometer, a magnetic stirring bar, a heating mantle, and an assembly consisting of a distilling head, a condenser, and a receiver which permits distillation under reduced pressure. The bulk of the dichloromethane and volatile hydrocarbons are distilled from the mixture at water-aspirator pressure while sufficient heat is supplied with the heating mantle, maintaining the temperature of the mixture at about 0° (Note 7). When the bulk of

the solvent has been removed, a 1-l., round-bottomed flask, cooled in a 2-propanol–dry ice bath, is attached to the apparatus as a receiver, and the pressure is reduced to 1 mm. or less with a vacuum pump. With the heating mantle, the temperature of the viscous liquid in the distillation flask is raised slowly from about 0° to 45° over a period of 90 minutes, distilling the volatile products (dichloromethane, low molecular-weight hydrocarbons, 4-chloropentan-2-one, and 3-penten-2-one) (Note 7). The resulting distillate (400–500 g. of pale green liquid) is mixed with 256 g. (1.98 moles) of quinoline (Note 8) and heated to boiling. To remove the remaining dichloromethane and other low-boiling materials (Note 9), liquid is allowed to distil from the mixture until the temperature of the distilling liquid reaches 110–120°. The remaining solution is refluxed for 30 minutes, then cooled and diluted with the previously removed distillate and 200 ml. of pentane. The resulting solution is washed with successive 250-ml. portions of 10% hydrochloric acid until the aqueous washings are acidic. The aqueous washings are combined, acidified, and shaken with three 100-ml. portions of pentane. The combined organic solutions are washed with 50 ml. of saturated aqueous sodium hydrogen carbonate and dried over anhydrous magnesium sulfate. The resulting organic solution is fractionally distilled through a 30-cm. Vigreux column, and 42–63 g. (25–37%) of crude product is collected in the fraction boiling at 119–124°. This contains 3-penten-2-one of 86–92% purity (Note 10). If greater purity is desired, the crude product may be distilled through a 60-cm., spinning band column. Since this distillation may be accompanied by partial isomerization of the α,β-unsaturated ketone to the lower boiling β,γ-isomer (Note 10), the product from the fractional distillation should be subjected to an acid-catalyzed equilibration. In a typical purification 79.4 g. of a mixture of penten-2-one isomers, b.p. 117–119°, from a fractional distillation, is mixed with 400 mg. of *p*-toluenesulfonic acid and refluxed for 30 minutes. The resulting mixture is diluted with 100 ml. of diethyl ether and washed with 50 ml. of saturated aqueous sodium hydrogen carbonate and dried over anhydrous magnesium sulfate. The resulting ether solution is fractionally distilled through a 16-cm. Vigreux column, giving 60.4 g. of *trans*-3-penten-2-one of 97% purity, b.p. 121.5–124°, n_D^{25} 1.4329 (Note 11).

2. Notes

1. Dichloromethane was dried over calcium chloride before use.
2. The submitters used a practical grade of acetyl chloride obtained from Eastman Organic Chemicals. The checkers used reagent grade acetyl chloride obtained from the Industrial Chemicals Division, Allied Chemical Corporation.
3. The reagent grade of powdered, anhydrous aluminum chloride employed was obtained from the Specialty Chemicals Division, Allied Chemical Corporation.
4. A chemically pure grade of propene, obtained from Matheson Gas Products, was employed. A large excess of propene is used since much of the olefin is converted to polymeric products. The submitters report obtaining markedly lower yields of product when an excess of propene was not used.
5. At this point there should be only a relatively mild exothermic reaction as the anhydrous aluminum salts are hydrolyzed and solvated.
6. In these extractions the organic layer is the lower one.
7. The submitters had originally distilled the volatile products from this mixture,

containing mainly polymeric material, by a more conventional procedure. However, the checkers found the problem of foaming during distillation so severe that the alternative, low-temperature distillation procedure was adopted.

8. The practical grade of quinoline employed was obtained from Aldrich Chemical Company, Inc.

9. The reaction solution must reach a temperature of approximately 90° for rapid dehydrochlorination to occur. If low-boiling impurities prevent the reaction mixture from reaching this temperature, the final product may be contaminated with the intermediate β-chloroketone. On a GC column packed with Carbowax 20M suspended on Chromosorb P, the retention times for the α,β-unsaturated ketone and the intermediate β-chloroketone are 4.9 minutes and 12.0 minutes, respectively. A sample of 4-chloro-2-pentanone, collected from this GC column, has IR absorption ($CHCl_3$) at 1720 $cm.^{-1}$ (C=O) with ^1H NMR absorption ($CDCl_3$) at δ 1.55 (d, *J* = 7 Hz., 3H, CH_3), 2.20 (s, 3H, CH_3CO), 2.5–3.3 (m, 2H, CH_2), and 4.45 (sextuplet, *J* = 7 Hz., 1H, C*H*Cl).

10. The product was analyzed with a 2-m. GC column packed with Carbowax 20M suspended on Chromosorb P. In chromatograms obtained from this column at 100°, the retention times of 4-penten-2-one and 3-penten-2-one are 2.6 and 3.9 minutes, respectively. The crude product contains several additional low-boiling components with GC retention times in the range 1.6–2.8 minutes. Any 4-penten-2-one present as an impurity exhibits IR absorption (CCl_4) at 1720 $cm.^{-1}$ (nonconjugated C=O).

11. The pure *trans*-3-penten-2-one has IR absorption (CCl_4) at 1680 and 1705 $cm.^{-1}$ (cisoid and transoid conformers[2] of the conjugated C=O), 1635 $cm.^{-1}$ (conjugated C=C), and 970 $cm.^{-1}$ (*trans*-CH=CH) with a UV maximum (95% C_2H_5OH) at 220 nm (ε 11,000) and ^1H NMR absorption ($CDCl_3$) at δ 1.88 (d of d, *J* = 1.5 and 7 Hz., 3H, CH_3), 2.22 (s, 3H, CH_3CO), 6.10 (d of partially resolved m, *J* = 16 Hz., 1H, α-vinyl C*H*), and 6.85 (d of q, *J* = 7 and 16 Hz., 1H, β-vinyl C*H*). The mass spectrum of the product has the following relatively abundant peaks: *m/e* (relative intensity), 84(M^+, 36), 69(100), 43(57), 41(78), and 39(33).

3. Discussion

trans-3-Penten-2-one has been prepared by the dehydration of 4-hydroxy-2-pentanone with heat,[3] acetic anhydride,[3] sulfuric acid,[4] or iodine.[5] It has also been obtained by fractional distillation of a commercial product from the aldol condensation of acetaldehyde and acetone.[6] Preparations are described involving reactions of acetyl bromide with propene, in the presence of anhydrous aluminum bromide,[7] and of acetic anhydride or acetyl chloride with propene, in the presence of anhydrous aluminum chloride.[8] Other preparative methods include the oxidation of *trans*-3-penten-2-ol with chromic acid[6] and the Wittig reaction between acetylmethylenetriphenylphosphorane and acetaldehyde.[9]

The present procedure, an adaption of one described previously,[8] illustrates the acylation of an olefin in the presence of a Lewis-acid catalyst. Although this method may lead to

complex mixtures of acylated products when higher molecular-weight olefins are acylated in the presence of excess aluminum chloride, the application of this procedure to propene gives a single, monomeric, acetylated product, accompanied by a complex mixture of low molecular-weight hydrocarbons and unidentified, higher molecular-weight materials. The relatively low boiling point of the monoacetylated product permits its ready separation from most of the components of this mixture, after which it is dehydrochlorinated to the desired product. The product of this reaction is of sufficient purity to serve as a synthetic intermediate in annelation reactions with cycloalkanones.[10]

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10. See, for example, J. A. Marshall, H. Faubl, and T. M. Warne, Jr., *Chem. Commun.*, 753 (1967); R. M. Coates and J. E. Shaw, *Chem. Commun.*, 47 (1968); H. C. Odom and A. R. Pinder, *J. Chem. Soc. Chem. Commun.*, 26 (1969); J. A. Marshall and R. A. Ruden, *Tetrahedron Lett.*, 1239 (1970).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

calcium chloride (10043-52-4)

acetaldehyde (75-07-0)

sulfuric acid (7664-93-9)

hydrogen chloride, hydrochloric acid (7647-01-0)

ether, diethyl ether (60-29-7)

acetic anhydride (108-24-7)

acetyl chloride (75-36-5)

sodium hydrogen carbonate (144-55-8)

Propene (115-07-1)

iodine (7553-56-2)

acetone (67-64-1)

aluminum chloride (3495-54-3)

chromic acid (7738-94-5)

Quinoline (91-22-5)

Pentane (109-66-0)

aluminum bromide

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

acetyl bromide (506-96-7)

4-hydroxy-2-pentanone

3-penten-2-one (625-33-2)

p-toluenesulfonic acid (104-15-4)

4-chloropentan-2-one, 4-chloro-2-pentanone

4-penten-2-one

acetylmethylenetriphenylphosphorane

trans-3-Penten-2-one, 3-Penten-2-one, trans- (3102-33-8)

trans-3-penten-2-ol

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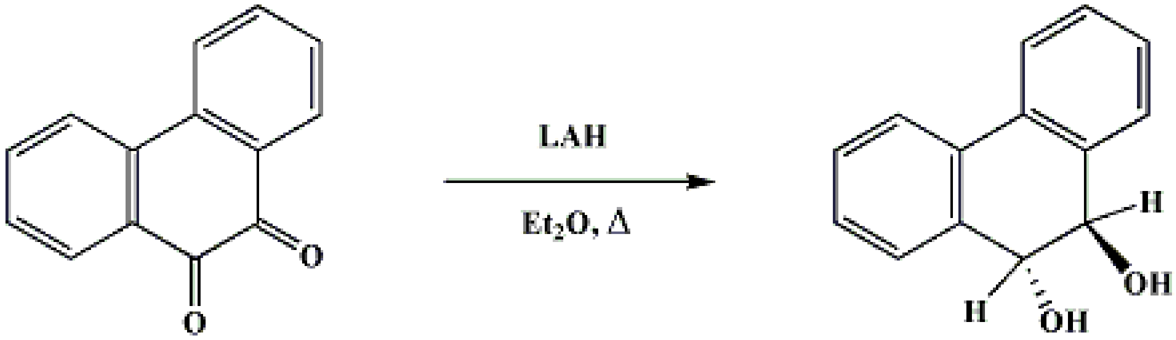
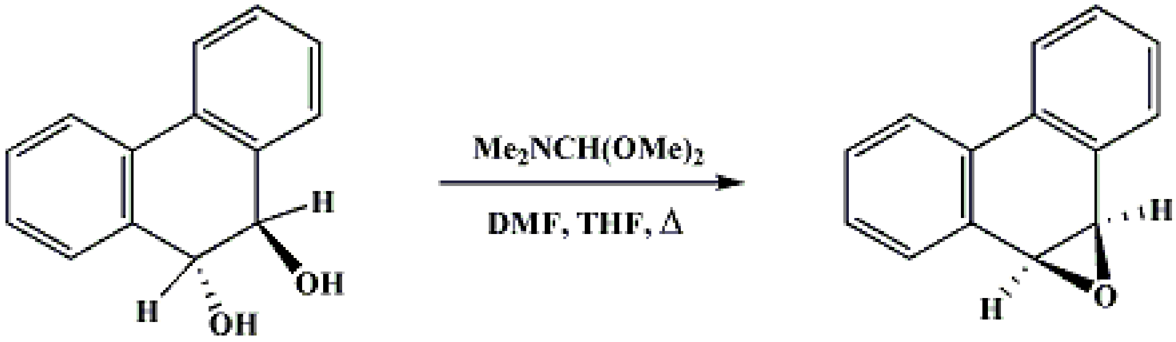
Organic Syntheses, CV 6, 887

ARENE OXIDE SYNTHESIS: PHENANTHRENE-9,10-OXIDE

[Phenanthro[9,10-*b*]oxirene, 1*a*,9*b*-dihydro-]





Submitted by Cecilia Cortez and Ronald G. Harvey[1].
Checked by James Jackson and Orville L. Chapman.

1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A. *trans-9,10-Dihydro-9,10-phenanthrenediol* (**1**). Phenanthrenequinone (6 g., 0.03 mole) (Note 1) is placed in a fritted-glass (coarse porosity) extraction thimble of a Soxhlet apparatus over a 1-l. flask containing a suspension of 3 g. of lithium aluminum hydride in 500 ml. of anhydrous diethyl ether (Note 2). Extraction of the quinone over a period of 16 hours affords a green solution (Note 3). The reaction is quenched by the cautious addition of water (Note 4) and neutralized with glacial acetic acid. The ether layer is separated, and the aqueous layer is extracted with two 200-ml. portions of ether. The combined ether extracts are washed consecutively with aqueous sodium hydrogen carbonate and water, then dried over magnesium sulfate. Evaporation of the solvent under reduced pressure gives the crude product (Note 5), which is

recrystallized from benzene, giving 3.8–4.1 g. (62–68%) of pure diol **1** as fluffy, white needles, m.p. 185–190°, (Note 6).

B. *Phenanthrene*-9,10-*oxide* (**2**). A solution of 10.6 g. (0.0500 mole) of **1** and 13 g. of *N,N*-dimethylformamide dimethyl acetal (Note 7) in 40 ml. of *N,N*-dimethylformamide (Note 8) and 100 ml. of dry tetrahydrofuran (Note 9) is heated at reflux for 16 hours. The solution is then allowed to cool to room temperature, and 200 ml. of water and 100 ml. of ether are added. The organic layer is separated, the aqueous layer is washed with two 200-ml. portions of ether, and the combined ether phases are dried over magnesium sulfate. Evaporation of the solvent under reduced pressure gives 9.6 g. of a yellow solid. Trituration with 25 ml. of hexane removes colored impurities, and recrystallization from benzene–cyclohexane (Note 10) gives 5.6–6.2 g. (58–64%) of oxide 2 as off-white plates, m.p. 125° (dec.) (Note 11). A second crop of 1.0 g can be obtained, for an overall yield of 68–74% (Note 12).

2. Notes

1. Phenanthrenequinone, free of anthraquinone, is available from Aldrich Chemical Company, Inc., or from J. T. Baker Chemical Company and should be recrystallized from benzene before use.
2. Use of more efficient solvents (tetrahydrofuran, isopropyl ether, dimethoxyethane) or more soluble metal hydride reagents (sodium borohydride, lithium tributoxy aluminum hydride, sodium bis(2-methoxyethyl) aluminum hydride) favors the alternative reduction pathway to the hydroquinone.
3. The checkers noted that use of a paper thimble resulted in increased time for extraction. The submitters recommend use of a glass thimble, since prolonged heating can lead to lower yields. It is easier to determine when extraction is complete with a transparent thimble. Other quinones may require longer extraction periods.
4. Care must be taken to add water cautiously and slowly, since the reaction between water and lithium aluminum hydride is vigorous. The reaction is quenched when the solution stops refluxing.
5. The crude product may darken on drying because of the presence of minor amounts of the air-sensitive hydroquinone by-product.
6. Large-scale reactions usually result in lower yields. The checkers obtained product, m.p. 189–191°, in runs with slightly lower yields.
7. *N,N*-Dimethylformamide dimethyl acetal, obtained from Aldrich Chemical Company, Inc., was redistilled before use.
8. *N,N*-Dimethylformamide was distilled under reduced pressure and stored over molecular sieves, type 4Å.
9. Tetrahydrofuran was distilled from lithium aluminum hydride. For a warning concerning potential hazards of this procedure, see *Org. Synth.*, **Coll. Vol. 5**, 976 (1973).
10. Excessive heating during recrystallization should be avoided because it can lead to thermal decomposition of the product.

11. Because of the relative facility of thermal rearrangement to phenols, melting points of arene oxides are not an entirely reliable index of purity. The checkers found variation from 119 to 135° (dec.). Purification by chromatography on activity IV alumina is also possible, but residence time on the column should be held to a minimum.
12. The ^{1}H NMR spectrum ($CDCl_3$) of pure **2** showed a characteristic oxiranyl singlet peak at δ 4.67 (s, 2H) and an aromatic signal at 7.2–7.8 (m, 8H).

3. Discussion

The method employed here is essentially that reported earlier,[2] modified by subsequent experience.[3] In the second step, *N,N*-dimethylformamide dimethyl acetal acts as a dehydrating agent, giving the epoxide, and is converted to *N,N*-dimethylformamide and methanol. Phenanthrene-9,10-oxide has also been prepared by cyclization of 2,2'-biphenyldicarboxaldehyde with hexamethylphosphorus triamide[4] and by dehydrohalogenation of 10-chloro-9,10-dihydro-9-phenanthrenyl acetate, obtained through reaction of the corresponding 2-alkoxy-1,3-dioxolane with trimethylsilyl chloride.[5] The present procedure is simpler, requiring fewer steps from readily available starting materials; both alternative procedures start with phenanthrene. The product is relatively easy to purify, since the only by-products are *N,N*-dimethylformamide and methanol (an important consideration with molecules sensitive to decomposition), and appears to be more stable on storage than the compound obtained *via* the dialdehyde route.

The cyclization method utilized in this synthesis appears quite general in its applicability, having been applied successfully in our laboratory[3] to the preparation of the K-region arene oxides[6] of benz[*a*]anthracene, chrysene, dibenz[*a,h*]anthracene, benzo[*c*]phenanthrene, pyrene, 1-methylphenanthrene, benzo[*a*]pyrene, and 7,12-dimethylbenz[*a*]anthracene, among others. The latter two are potent carcinogens; the K-region oxides of these have been shown to be formed metabolically and exhibit significant biological activity.[7]

The K-region quinones required as starting materials in this synthesis are in certain cases (*e.g.*, phenanthrene, chrysene, benzo[*c*]phenanthrene) available from direct oxidation of the parent hydrocarbons with chromic acid. When oxidation occurs preferentially elsewhere in the molecule, the K-region dihydroaromatic derivatives can often be converted to the corresponding quinone through oxidation with dichromate in acetic acid–acetic anhydride;[8] yields, however, are only in the 20–30% range. Alternatively, the K-region quinones may be obtained from the hydrocarbons through oxidation with osmium tetroxide to the corresponding *cis*-diols, followed by a second oxidation with pyridine–sulfur trioxide and dimethyl sulfoxide,[2,3] generally the most useful procedure. A significant advantage is that all possible K-region oxidized derivatives (*cis*-diols, quinones, *trans*-diols, phenols,[3] and hydroquinones[9]) with intact

ring systems can be obtained directly or by appropriate modification of the general sequence. The disadvantages of this method, and of any alternative procedure[4,5] involving the *cis*-diol, is the hazardous and expensive osmium tetroxide employed.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alumina

acetic acid (64-19-7)

Benzene (71-43-2)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

acetic anhydride (108-24-7)

sulfur trioxide (7446-11-9)

hydroquinone (123-31-9)

sodium hydrogen carbonate (144-55-8)

Anthraquinone (84-65-1)

cyclohexane (110-82-7)

pyridine (110-86-1)

chromic acid (7738-94-5)

phenanthrenequinone (84-11-7)

magnesium sulfate (7487-88-9)

phenanthrene (85-01-8)

Tetrahydrofuran (109-99-9)

isopropyl ether (108-20-3)

lithium aluminum hydride (16853-85-3)

Benz[a]anthracene (56-55-3)

pyrene (129-00-0)

N,N-dimethylformamide (68-12-2)

osmium tetroxide (20816-12-0)

hexane (110-54-3)

dimethyl sulfoxide (67-68-5)

dimethoxyethane (534-15-6)

sodium borohydride (16940-66-2)

hexamethylphosphorus triamide (680-31-9)

chrysene (218-01-9)

trimethylsilyl chloride (75-77-4)

Phenanthrene-9,10-oxide

sodium bis(2-methoxyethyl) aluminum hydride

10-chloro-9,10-dihydro-9-phenanthrenyl acetate

N,N-dimethylformamide dimethyl acetal (4637-24-5)

2,2'-biphenyldicarboxaldehyde (1210-05-5)

benzo[c]phenanthrene (195-19-7)

trans-9,10-Dihydro-9,10-phenanthrenediol (25061-61-4)

Phenanthro[9,10-b]oxirene, 1a,9b-dihydro- (585-08-0)

lithium tributoxy aluminum hydride

dibenz[a,h]anthracene (53-70-3)

1-methylphenanthrene (832-69-9)

benzo[a]pyrene (50-32-8)

7,12-dimethylbenz[a]anthracene (57-97-6)

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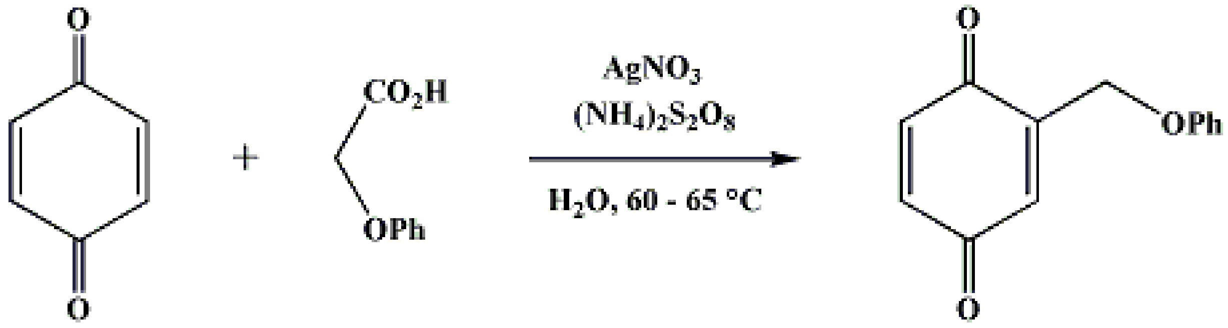
FREE-RADICAL ALKYLATION OF QUINONES: 2-PHENOXYMETHYL-1,4-BENZOQUINONE

[2,5-Cyclohexadiene-1,4-dione, 2-(phenoxymethyl)-]



Submitted by Niels Jacobsen[1]
Checked by R. J. DeFranco and R. E. Benson.

1. Procedure

A 250-ml., three-necked flask fitted with a mechanical stirrer, a thermometer, and a 25-ml., graduated, pressure-equalizing dropping funnel is charged with 7.60 g. (0.0500 mole) of phenoxyacetic acid (Note 1), 5.40 g. (0.0500 mole) of 1,4-benzoquinone (Note 2), 1 g. (0.006 mole) of silver nitrate (Note 3), and 125 ml. of water (Note 4). The mixture is stirred and heated to 60–65° with a heating mantle until dissolution is complete. The resulting solution is stirred vigorously while a solution of 13.7 g. (0.0601 mole) of ammonium peroxydisulfate (Note 5) in 25 ml. of water is added at a rate of 0.5 ml. per minute for the first 40 minutes, then at a rate of 0.25 ml. per minute for the last 20 minutes. Throughout the addition, the reaction mixture is maintained at 60–65° (Note 6) and (Note 7).

After the addition is complete the mixture is stirred for 5 minutes at 65° then cooled to 5–10° in an ice bath. The precipitated solid is collected by suction filtration (Note 8), washed with 50 ml. of cold water, and pressed, removing most of the liquid. Inorganic contaminants, usually present in small amounts, are removed by dissolving the solid in 350 ml. of boiling acetone and filtering the hot solution through fluted filter paper. Concentration of the filtrate on a rotary evaporator gives a dark red crude product (10.5–11.4 g.), which is dissolved in 220–240 ml. of boiling 95% ethanol. On cooling the solution to 5°, the alkylated quinone crystallizes in brownish-yellow needles, which are collected by filtration and air-dried, yielding 6.7–8.0 g., m.p. 135–137°. Recrystallization from 30 ml. of ethanol per gram of product gives 6.6–7.4 g. (61–69%) of 2-phenoxymethyl-1,4-benzoquinone, m.p. 137–138° (Note 9).

2. Notes

1. The submitter used Fluka *puriss* grade phenoxyacetic acid. The checkers used material available from Eastman Organic Chemicals.
2. The submitter used Fluka *purum* grade benzoquinone, recrystallized once from petroleum ether (b.p. 60°), m.p. 111–113°. The checkers used Fisher purified grade material without recrystallization.
3. The submitter used reagent grade silver nitrate available from Merck & Company, Inc.
4. In the case of a water-insoluble quinone or carboxylic acid, acetonitrile can be used as a co-solvent.[2]
5. Fluka *purum* grade ammonium peroxydisulfate was used by the submitter. The checkers used ACS reagent grade material available from Fisher Scientific Company.
6. The reaction is slightly exothermic, but it is necessary to heat the mixture occasionally in order to maintain it at 60–65°.
7. The checkers found that increasing the addition rate of persulfate solution to 1.5 ml. per minute, while giving a somewhat lower initial yield (62% after one recrystallization), resulted in a product of sufficient purity (m.p. 137–138°) as to require no further recrystallization.
8. This work-up procedure applies only when the crude product can be crystallized from the reaction mixture. If the product is partly soluble in the reaction medium or if it separates as a gum, an extraction procedure is employed.
9. IR ($CHCl_3$) $cm.^{-1}$: 1660 strong, 1600 medium, 1590 medium; UV (95% C_2H_5OH) nm. max (ε): 220 (12,700), 248 (18,600), 269 shoulder, 276 shoulder; ^1H NMR ($CDCl_3$), δ (multiplicity, coupling constant *J* in Hz., number of protons): 4.9 (d, *J* = 2, 2H, CH_2O), 6.7–7.5 (m, 8H).

3. Discussion

The procedure described above has been used to prepare various, alkylated 1,4-benzoquinones and 1,4-napthoquinones,[2,3] including some naturally occurring quinones.[4] A few examples are listed in Table I, showing the scope of the method.

TABLE I
SUBSTITUTED QUINONES DERIVED BY ALKYLATION

Parent Quinone	Acid	Derived Substituted Quinone	Yield (%)[a]	Reference
1,4-Benzoquinone	Pivalic	2-*tert*-Butyl	67[b]	2
1,4-Benzoquinone	Phenylacetic	2-Benzyl	87	2
1,4-Benzoquinone	α-Chloropropionic	2-(α-Chloroethyl)	45[b]	2

1,4-Naphthoquinone	Methoxyacetic	2-Methoxymethyl	50	2
1,4-Naphthoquinone	Adipic	2-(ω-Carboxybutyl)	51	2
2-Methyl-1,4-naphthoquinone	Cyclopropanecarboxylic	2-Cyclopropyl-3-methyl	37	3
2-Acetoxy-1,4-naphthoquinone	4-Methyl-3-pentenoic	2-Acetoxy-3-(γ,γ-dimethylallyl)	73	4

[a]Yields are based on the parent quinone.

[b]Modified procedure (see Discussion).

The reaction is a free-radical alkylation in which radicals are derived from a carboxylic acid by decarboxylation with silver peroxydisulfate. It has the advantage that the reaction medium can be adjusted so that the monoalkylated product precipitates as it is formed, thereby suppressing di- or polyalkylation.[5]

The reaction fails if the decarboxylation produces a radical that is easily oxidized, such as an α-hydroxyalkyl radical.[2] In intermediate cases, such as *tert*-alkyl or α-alkoxyalkyl radicals,[2] the yield based on the parent quinone is usually improved by using an excess of the peroxydisulfate and carboxylic acid to compensate for the loss of radicals due to oxidation (footnote *b*, Table I).

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 741

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

ethanol (64-17-5)

acetonitrile (75-05-8)

silver nitrate (7761-88-8)

acetone (67-64-1)

Quinone, 1,4-benzoquinone, benzoquinone (106-51-4)

1,4-Naphthoquinone (130-15-4)

ammonium peroxydisulfate (7727-54-0)

2-methyl-1,4-naphthoquinone

2-Phenoxymethyl-1,4-benzoquinone, 2,5-Cyclohexadiene-1,4-dione, 2-(phenoxymethyl)- (7714-50-3)

phenoxyacetic acid (122-59-8)

silver peroxydisulfate

2-Acetoxy-1,4-naphthoquinone

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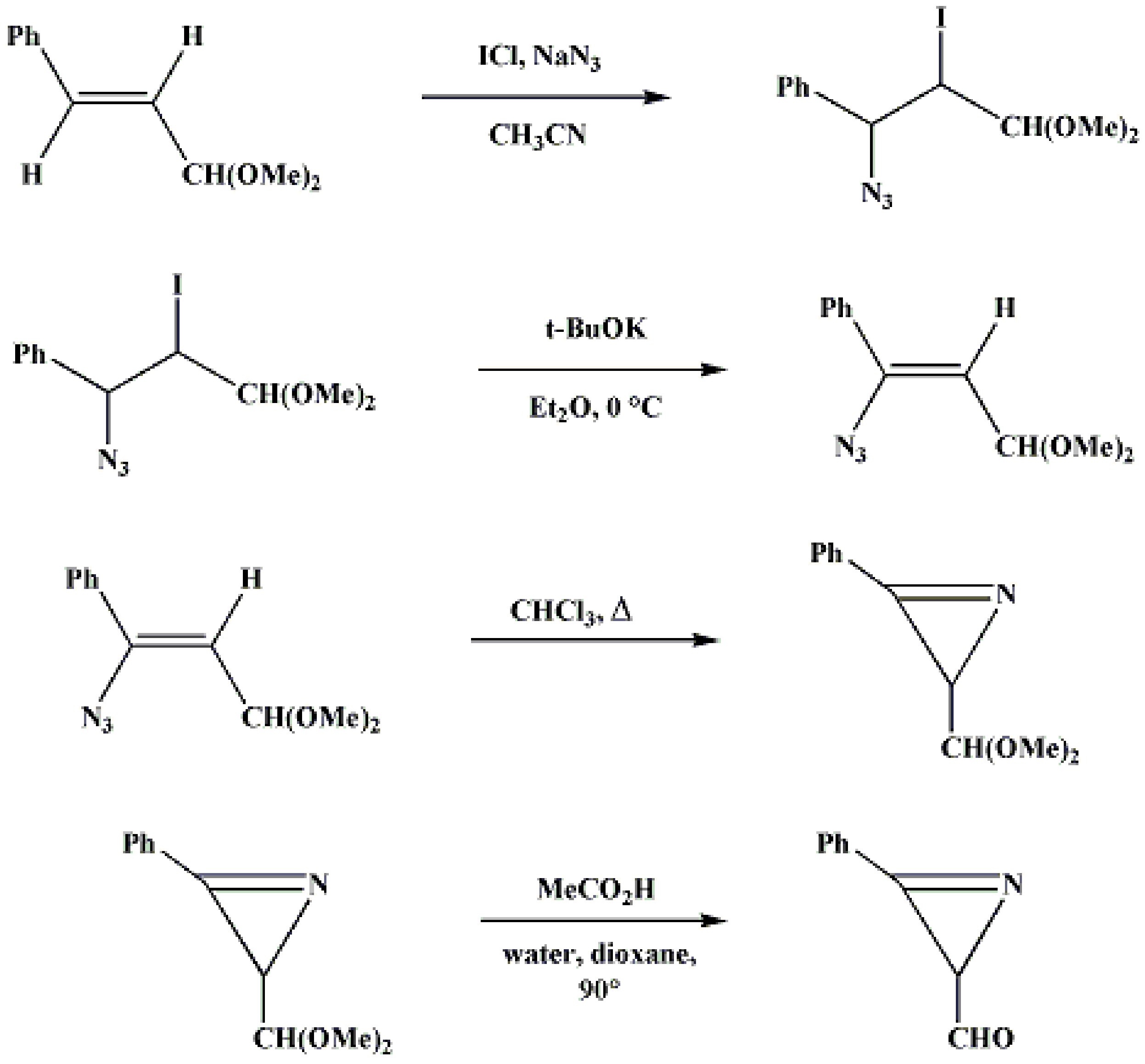
Organic Syntheses, CV 6, 893

3-PHENYL-2*H*-AZIRINE-2-CARBOXALDEHYDE

[2*H*-Azirine-2-carboxaldehyde, 3-phenyl-]



Submitted by Albert Padwa[1], Thomas Blacklock, and Alan Tremper.
Checked by W. F. Oettle, E. R. Holler, and William A. Sheppard.

1. Procedure

Caution! Although the organic azide intermediates used in this procedure have not shown any explosive hazard under the experimental conditions, they should always be handled with adequate shielding and normal protective equipment such as face shield and leather gloves.

A. *(1-Azido-2-iodo-3,3-dimethoxypropyl)benzene*. A dry, 1-l., three-necked, round-

bottomed flask fitted with an efficient magnetic stirrer and two 250-ml. pressure-equalizing dropping funnels charged with 75 g. (1.l moles) of sodium azide and 450 ml. of dry acetonitrile (Note 1). The mixture is stirred and cooled in an ice–salt bath (−5° to 0°), and 83 g. (0.51 mole) of iodine monochloride (Note 2) is added dropwise from one of the addition funnels over 10–20 minutes. The solution is stirred for an additional 5–10 minutes before 81 g. (0.45 mole) of cinnamaldehyde dimethyl acetal (Note 3) is added from the other dropping funnel over a 15–20 minute period, while the cooling bath temperature is maintained at 0–5°. The resulting red-brown mixture is stirred for 12 hours at room temperature, poured into 500 ml. of water, and extracted with three 500-ml. portions of diethyl ether. The combined organic extracts are washed successively with 700 ml. of 5% aqueous sodium thiosulfate (Note 4) and 1 l. of water. The ether solution in dried over magnesium sulfate. The solvent is removed with a rotary evaporator, giving the azide product as a orange oil (Note 5), 150–156 g. (97–98%), of sufficient purity to be used for the next step.

B. *(1-Azido-3,3-dimethoxy-1-propenyl)benzene*. A 2-l., one-necked, round-bottomed flask equipped with a magnetic stirrer and powder funnel is charged with 156 g. (0.450 mole) of the iodoazide from Part A and 1500 ml. of anhydrous ether. The solution is stirred and cooled in an ice-salt bath (−5° to 0°), and 62 g. (0.55 mole) of potassium *tert*-butoxide (Note 6) is added. The powder funnel is replaced with a calcium chloride drying tube and the mixture is stirred for 4–5 hours at 0° , at which time 350 ml. of water is added while the mixture is still cold. The ethereal layer is separated, washed with three 350-ml. portions of water, and dried over magnesium sulfate. The solvent is removed with a rotary evaporator without heating, leaving 67–75 g. (68–76%) of (1-azido-3,3-dimethoxy-1-propenyl)-benzene as a dark oily liquid (Note 7), which can be used without further purification for Part C (Note 8).

C. *2-(Dimethoxymethyl)-3-phenyl-2H-azirine*. The crude product (71–75 g., 0.32–0.34 mole) obtained from p.htmart B is heated at reflux in 1 l. of chloroform in a 2-l., round-bottomed flask for 12 hours (Note 9). The solvent is removed with a rotary evaporator and the crude residue is distilled, giving 48–61 g. (78–93%) of 2-(dimethoxymethyl)-3-phenyl-2*H*-azirine, b.p. 103–105° (0.27 mm.) as a colorless oil (Note 10).

D. *3-Phenyl-2H-azirine-2-carboxaldehyde*. The product from Part C (59.0 g., 0.31 mole) is placed in a 3-l., three-necked, round-bottomed flask fitted with a mechanical stirrer, a reflux condenser, and a thermometer of sufficient length to extend into the liquid contents of the flask. After addition of 600 ml. of 1,4-dioxane (Note 11) and 800 ml. of 20% acetic acid, the mixture is stirred and heated sufficiently to bring the temperature of the reaction mixture up to 90° over a period of one hour (Note 12). The temperature of the reaction mixture is held at 90° for an additional 5 minutes, then the flask is rapidly cooled in an ice-salt bath (−5° to 0°). The product is extracted with four 1-l. portions of ether, and the combined organic extracts are washed successively with 1 l. of 5% aqueous sodium hydrogen carbonate and 1-l. of saturated aqueous sodium chloride. After the ether layer has been dried over anhydrous magnesium sulfate, the solvent is removed with a rotary evaporator, and a mixture of 5 ml. of ether

and 10 ml. of pentane is added. The residual oil is allowed to stand in a refrigerator (0–3°) for 12 hours, completing the crystallization of the crude product. The crystalline solid is collected on a cold filter and sublimed at 35° (0.01 mm.), giving 13.3 g. (30%) (Note 13) of 3-phenyl-2*H*-azirine-2-carboxaldehyde, m.p. 49–51° (Note 14).

2. Notes

1. Reagent grade acetonitrile (J. T. Baker Chemical Company) was used without further purification.
2. Iodine monochloride, purchased from J. T. Baker Chemical Company, was used without further purification.
3. Cinnamaldehyde dimethyl acetal was prepared by the method used to prepare the corresponding diethyl acetal.[2] A mixture of 66.0 g. (0.50 mole) of *trans*-cinnamaldehyde (Aldrich Chemical Company, Inc.), 100 g. (1.06 mole) of trimethyl orthoformate (Eastman Organic Chemicals), 450 ml. of anhydrous methanol (J. T. Baker Chemical Company), and 0.5 g. of *p*-toluenesulfonic acid monohydrate (Fisher Scientific Company) is stirred at room temperature for 24 hours. At the end of this time, the alcohol is removed with a rotary evaporator, and the residue is distilled, giving 81–83 g. (91–93%) of cinnamaldehyde dimethyl acetal, b.p. 93–96° (0.2 mm.).
4. The orange color of the ethereal solution is completely discharged after washing with 5% aqueous sodium thiosulfate.
5. The product has the following spectral properties: IR (neat) cm.$^{-1}$: 2120 (strong N_3 absorption); ^{1}H NMR ($CDCl_3$), δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 3.38 (s, 3H, OCH_3), 3.46 (s, 3H, OCH_3), 3.93 (d, $J = 4$, 1H, 1- or 3-C*H*), 4.38 (d of d, $J = 9$ and 4, 1H, C*H*I) 4.78 (d, $J = 9$, 1H, 1- or 3-C*H*), 7.33 (s, 5H, C_6H_5).
6. Potassium *tert*-butoxide, purchased from Columbia Organic Chemicals Company, Inc., was sublimed at 150° (0.02 mm.) before use and was added in one portion.
7. The submitters reported a yield of 94–96 g. (97–98%). The spectral properties of the product are: IR (neat) cm.$^{-1}$: 2151 and 1642; ^{1}H NMR ($CDCl_3$), δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 3.26 (s, 6H, 2 OCH_3), 4.78 [d, $J = 8$, 1H, $CH(OCH_3)_2$], 5.60 (d, $J = 8$, 1H, C*H*), 7.45 (s, 5H, C_6H_5).
8. The intermediate vinyl azide should either be used immediately or stored cold in a vented container, since it slowly evolves nitrogen on standing at room temperature.
9. The reaction can be conveniently monitored by IR spectroscopy by observing the intensity of the band at 2150 cm.$^{-1}$ (N_3).
10. The spectral properties are: IR (neat) cm.$^{-1}$: 1754 (azirine); ^{1}H NMR ($CDCl_3$), δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 2.38 (d, $J = 3$, 1H, C*H*), 3.35 (s, 3H, OCH_3), 3.47 (s, 3H, OCH_3),

4.39 [d, J = 3, 1H, C$H(OCH_3)_2$], 7.3–8.0 (m, 5H, C_6H_5).

11. 1,4-Dioxane available from Fisher Scientific Company was used without further purification.

12. The mixture is brought to 90° by heating at a rate of 1° per minute. The mixture *must not be overheated*, or else the final product will be very difficult to crystallize.

13. Starting with 45.3 g. (0.237 mole) of the dimethyl acetal from p.htmart C, the checkers obtained 10.2 g. (30%) of the product.

14. The submitters reported a yield of 35–38 g. (55–60%) based on 78–84 g. of starting material and using appropriate proportions of reagents. Their product had m.p. 45–47°. The spectral properties of the azirine product are: IR (KBr) cm.$^{-1}$ 1786 and 1709; ^{1}H NMR ($CDCl_3$), δ (multiplicity, coupling constant J in Hz., number of protons, assignment): 2.89 (d, J = 7, 1H, CH), 7.5–8.0 (m, 5H, C_6H_5), 9.04 (d, J = 7, 1H, CHO).

3. Discussion

The formation of substituted azirines by the thermal decomposition of vinyl azides is a general reaction.[3] Iodine azide offers an excellent route to vinyl azides;[4,5] it adds to many olefinic compounds, giving α iodoazides which can easily eliminate hydrogen iodide upon treatment with base. The direction of iodine azide addition is consistent with electrophilic attack of I, giving a cyclic iodonium ion which is opened by azide ion. The presence of the dimethyl acetal moiety in the system above does not not interfere with the iodine azide reaction. This procedure does not work with *trans*-cinnamaldehyde, owing to a competing aldol condensation in the elimination step.

The aldehyde functionality present in 3-phenyl-2*H*-azirine-2-carboxaldehyde reacts selectively with amines, and Grignard and Wittig reagents, yielding a variety of substituted azirines,[6] which have been used, in turn, to prepare a wide assortment of heterocyclic rings such as oxazoles, imidazoles, pyrazoles, pyrroles, and benzazepins.[6,7]

In addition to the present method, 2*H*-azirines can be prepared by a modified Neber reaction,[8,9,10] or by heating 4,5-dihydro-1,2,5-oxazaphospholes.[11,12,13,14]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

acetic acid (64-19-7)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

acetonitrile (75-05-8)

chloroform (67-66-3)

sodium hydrogen carbonate (144-55-8)

sodium chloride (7647-14-5)

sodium thiosulfate (7772-98-7)

nitrogen (7727-37-9)

hydrogen iodide (10034-85-2)

Pentane (109-66-0)

sodium azide (26628-22-8)

magnesium sulfate (7487-88-9)

iodine monochloride (7790-99-0)

1,4-dioxane (123-91-1)

cinnamaldehyde dimethyl acetal

Iodine azide

(1-azido-3,3-dimethoxy-1-propenyl)-benzene, (1-Azido-3,3-dimethoxy-1-propenyl) benzene (56900-67-5)

trimethyl orthoformate (149-73-5)

p-toluenesulfonic acid monohydrate (6192-52-5)

potassium tert-butoxide (865-47-4)

trans-cinnamaldehyde (104-55-2)

3-Phenyl-2H-azirine-2-carboxaldehyde, 2H-Azirine-2-carboxaldehyde, 3-phenyl- (42970-55-8)

2-(Dimethoxymethyl)-3-phenyl-2H-azirine (56900-68-6)

(1-Azido-2-iodo-3,3-dimethoxypropyl)benzene (56900-66-4)

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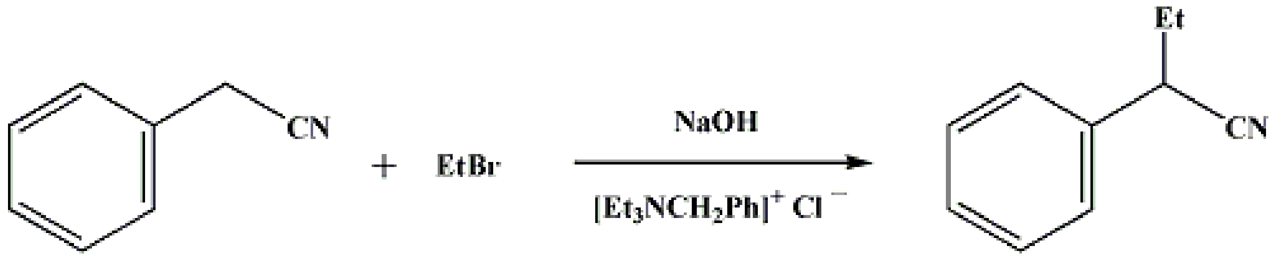
Organic Syntheses, CV 6, 897

PHASE-TRANSFER ALKYLATION OF NITRILES: 2-PHENYLBUTYRONITRILE

[Benzeneacetonitrile, α-ethyl-]



Submitted by M. Makosza[1] and A. Jonczyk.
Checked by Harold W. Wagner and Richard E. Benson.

1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A 3-l., four-necked, round-bottomed flask equipped with a mechanical stirrer, a dropping funnel, a thermometer, and an efficient reflux condenser is charged with 540 ml. of 50% aqueous sodium hydroxide, 257 g. (253 ml., 2.20 moles) of phenylacetonitrile (Note 1), and 5.0 g. (0.022 mole) of benzyltriethylammonium chloride (Note 2). Stirring is begun, and 218 g. (150 ml., 2.00 moles) of ethyl bromide (Note 3) is added dropwise over a period of approximately 100 minutes at 28–35°. If necessary, the flask may be cooled with a cold-water bath to keep the temperature of the mixture at 28–35°. After the addition of ethyl bromide is complete, stirring is continued for 2 hours, then the temperature is increased to 40° for an additional 30 minutes. The reaction mixture is cooled to 25°, 21.2 g. (20.3 ml., 0.200 mole) of benzaldehyde (Note 4) is added, and stirring is continued for 1 hour. The flask is immersed in a cold-water bath, and 750 ml. of water and 100 ml. of benzene are added. The layers are separated, and the aqueous phase is extracted with 200 ml. of benzene. The organic layers are combined and washed successively with 200 ml. of water, 200 ml. of dilute hydrochloric acid (Note 5), and 200 ml. of water. The organic layer is dried over anhydrous magnesium sulfate, and the solvent is removed by distillation under reduced pressure. The product is distilled through a Vigreux column, giving 225–242 g. (78–84%) of 2-phenylbutyronitrile, b.p. 102–104° (7 mm.), n_D^{25} 1.5065–1.5066 (Note 6),(Note 7),(Note 8).

2. Notes

1. The checkers used phenylacetonitrile obtained from Aldrich Chemical Company, Inc., and distilled it before use. It may also be purified according to the directions

given in *Org. Synth.*, **Coll. Vol. 1**, 108 (1948).
2. Benzyltriethylammonium chloride is available from Fisher Scientific Company. The preparation of this reagent is described in *Org. Synth.*, **Coll. Vol. 6**, 232 (1988).
3. Ethyl bromide (available from Fisher Scientific Company) was distilled before use.
4. Benzaldehyde (available from Fisher Scientific Company) was distilled before use. It is added at this point to convert any unreacted phenylacetonitrile to the high-boiling α-phenylcinnamonitrile (Note 7).
5. The acid solution was prepared by adding 1 volume of acid to 5 volumes of water.
6. The checkers obtained a forerun of 7–12 g. of product having n_D^{25} 1.5065–1.5066.
7. The α-phenylcinnamonitrile (Note 4) present in the distillation flask can be recovered. The residue is broken up with 75 ml. of methanol, the mixture stirred and cooled, and the product recovered by filtration. Recrystallization from methanol gives 17–20 g. of crystalline material, m.p. 86–88°. The ^1H NMR spectrum ($CDCl_3$) shows complex multiplets at δ 7.20–8.00.
8. GC analysis on a column packed with silicone gum nitrile on acid-washed Gas Chrome Red, 80–100 mesh and heated at 150°, shows that the product is about 97% pure. The material has the following spectral properties; IR (neat) $cm.^{-1}$: 2250 (C N), 1610, 1590 shoulder and 1500 (aromatic C C), 1385 ($C\text{-}CH_3$), and 760 and 697 (monosubstituted aromatic); ^1H NMR (CCl_4), δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 0.99 (t, $J = 7$, 3H, CH_3), 1.82 (m, 2H, CH_2), 3.70 (t, $J = 7$, 1H, C*H*), 7.32 (s, 5H, C_6H_5).

3. Discussion

This reaction is illustrative of a general procedure for the tetraalkylammonium salt-catalyzed alkylation of active methylene functions in the presence of concentrated aqueous alkali. This catalytic method has been used to alkylate arylacetonitriles with monohaloalkanes,[2] dihaloalkanes,[3] α-chloroethers,[4] chloronitriles,[5] haloacetic acid esters,[6] and halonitro aromatic compounds.[7] It has also been used to alkylate ketones,[8] 1*H*-indene,[9] 9*H*-fluorene,[10] and the Reissert compound.[11] The reaction is inhibited by alcohols and iodide ion.[2]

Methods for the alkylation of nitriles have been reviewed.[12] These procedures, as well as those applied to other active methylenes, generally involve the use of dangerous and expensive condensing agents (sodium amide, metal hydrides, triphenylmethide, potassium *tert*-butoxide, etc.) and strictly anhydrous organic solvents (ether, benzene, *N*,*N*-dimethylformamide, dimethyl sulfoxide, etc.) or liquid ammonia. The catalytic method is much simpler and generally gives good yields of purer products. Because of its high selectivity[13] it is particularly adapted to the synthesis of pure monoalkyl derivatives of phenylacetonitrile which have also been obtained by alkylation of ethyl cyanophenylacetate[14] or cyanophenylacetic acid,[15] followed by elimination of the ethoxycarbonyl or carboxyl groups.

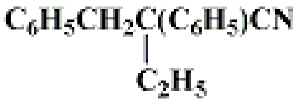
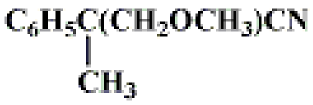
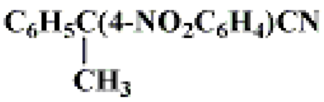
The catalytic conditions (aqueous concentrated sodium hydroxide and tetraälkylammonium catalyst) are very useful in generating dihalocarbenes from the corresponding haloforms. Dichlorocarbene thus generated reacts with alkenes, giving high yields of

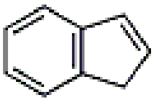
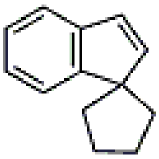
dichlorocyclopropane derivatives,[16] even in cases where other methods have failed,[17] and with some hydrocarbons, yielding dichloromethyl derivatives.[18] Similar conditions are suited for the formation and reactions of dibromocarbene,[19] bromofluoro- and chlorofluorocarbene,[20] and chlorothiophenoxy carbene,[21] as well as the Michael addition of trichloromethyl carbanion to unsaturated nitriles, esters, and sulfones.[22]

This method exemplifies a broad class of processes that proceed *via* transfer of reacting species between two liquid phases. Such processes may require a catalyst that can combine with species present in one phase and effect their transfer in this form to the second phase where the main reaction occurs. Starks[23] has termed such a process "phase-transfer catalysis" and has demonstrated its utility in reactions involving inorganic anions. For example, he has shown that the rates of some displacement, oxidation, and hydrolysis reactions conducted in two-phase systems are dramatically enhanced by the presence of ammonium and phosphonium salts. However, in reactions involving weakly active methylenes, the catalyst seems to be more than a simple transfer agent; it is necessary for carbanion formation.

The versatility of this method for the alkylation of compounds containing active methylene groups is illustrated by Table I. Review articles have recently appeared,[24] and the application to the Hofmann carbylamine reaction is described in *Org. Synth.*, **Coll. Vol. 6**, 232 (1988).

TABLE I
ALKYLATIONS IN AQUEOUS MEDIUM

Compound	Alkylation Agent	Product	(%) Yield	Reference
$C_6H_5CH_2CN$	$(C_6H_5)_2CHCl$	$(C_6H_5)_2CHCH(C_6H_5)CN$	94	2
$C_6H_5CH_2CN$	$Br(CH_2)_4Br$		88	3
$C_6H_5CH(C_2H_5)CN$	$C_6H_5CH_2Cl$		94	2
$(C_6H_5)_2CHCN$	$BrCH_2CH_2Br$	$(C_6H_5)_2C(CH_2CH_2Br)CN$	91	3
$C_6H_5CH(CH_3)CN$	$ClCH_2OCH_3$		68	4
$C_6H_5CH(CH_3)CN$	$4\text{-}ClC_6H_4NO_2$		82	11

$C_6H_5CH(C_2H_5)CN$	$ClCH_2COOC_4H_9$-*tert*		77	6
$C_6H_5CH_2COCH_3$	$BrCH_2CH_2Br$		54	8
	$Br(CH_2)_4Br$		64	9

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 232
- Org. Syn. Coll. Vol. 6, 940
- Org. Syn. Coll. Vol. 6, 954

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

triphenylmethide

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

Benzene (71-43-2)

methanol (67-56-1)

ether (60-29-7)

sodium hydroxide (1310-73-2)

Ethyl bromide (74-96-4)

benzaldehyde (100-52-7)

phenylacetonitrile (140-29-4)

magnesium sulfate (7487-88-9)

1H-Indene (95-13-6)

9H-fluorene (86-73-7)

sodium amide (7782-92-5)

N,N-dimethylformamide (68-12-2)

α-Phenylcinnamonitrile (2510-95-4)

dimethyl sulfoxide (67-68-5)

ethyl cyanophenylacetate (4553-07-5)

dichlorocarbene

benzyltriethylammonium chloride (56-37-1)

2-Phenylbutyronitrile, Benzeneacetonitrile, α-ethyl- (769-68-6)

cyanophenylacetic acid

dibromocarbene (4371-77-1)

chlorofluorocarbene

chlorothiophenoxy carbene

potassium tert-butoxide (865-47-4)

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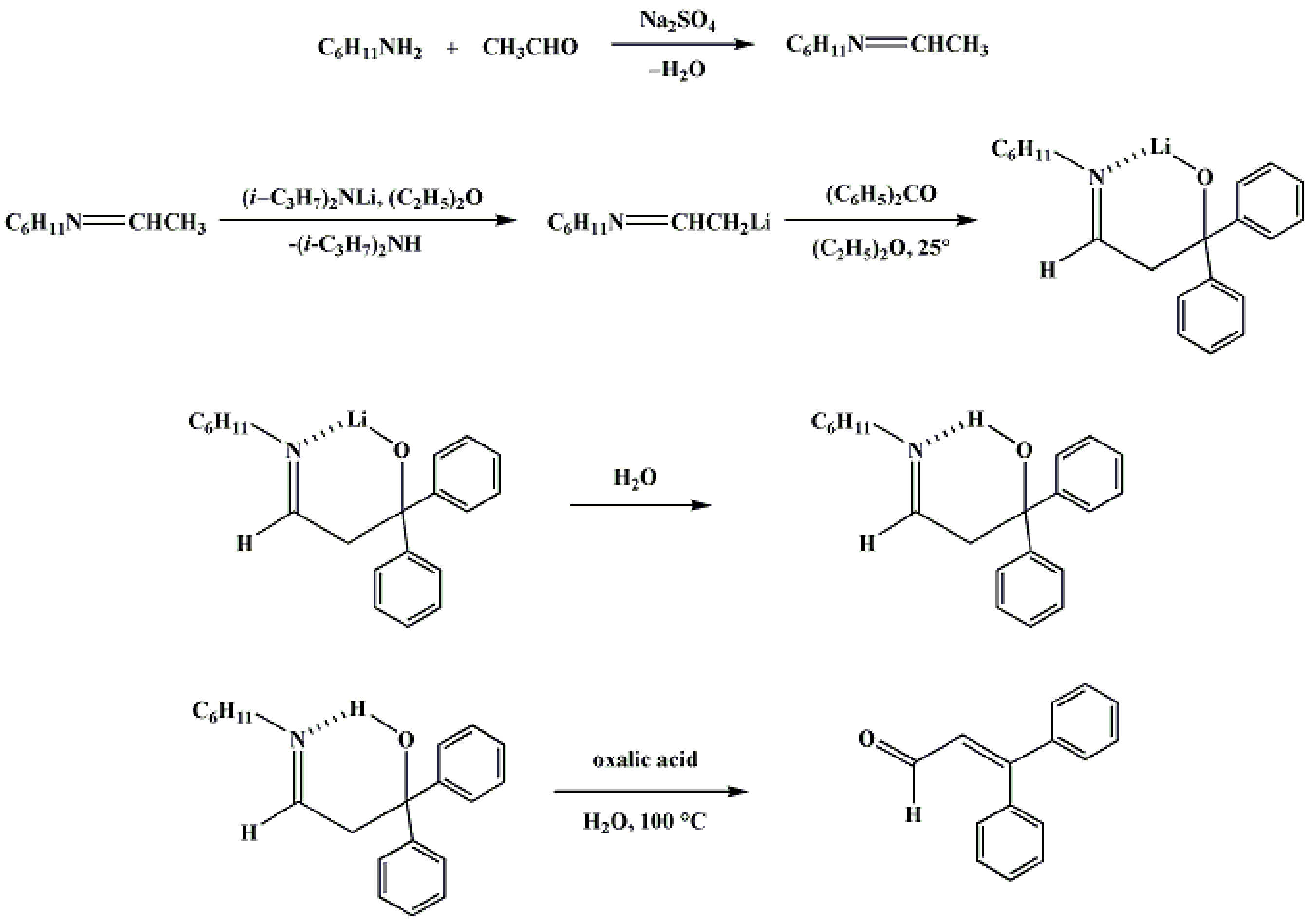
Organic Syntheses, *CV 6*, *901*

DIRECTED ALDOL CONDENSATIONS: β-PHENYLCINNAMALDEHYDE

[2-Propenal, 3,3-diphenyl-]



Submitted by G. Wittig[1] and A. Hesse.
Checked by Allan Y. Teranishi and Herbert O. House.

1. Procedure

A. N-*Ethylidenecyclohexylamine*. A dry, 500-ml., round-bottomed flask fitted with a magnetic stirrer is flushed with nitrogen and stoppered with a rubber septum. With a hypodermic syringe 99.2 g. (1.00 mole) of freshly distilled cyclohexylamine (b.p. 133–134°) is added to the flask. After the amine has been cooled to approximately –20° (Note 1) with an acetone–dry ice bath, 44.1 g. (1.00 mole) of freshly distilled acetaldehyde (b.p. 21°) is added from a hypodermic syringe dropwise and with stirring over a 15-minute period. During the initial phase of this addition a white solid separates but redissolves as the addition is continued. The resulting cold solution is stirred at –20° for approximately 45 minutes, at which time a large amount of white solid separates and further stirring is impractical. The resulting mixture is allowed to stand at –20° for 15 minutes before 15 g. of anhydrous sodium sulfate is added and the mixture is allowed to melt and warm to room temperature. The resulting mixture is gravity filtered, and the residue is washed with approximately 15 ml. of diethyl ether. The combined filtrates are dried over 5 g. of anhydrous magnesium sulfate and filtered. The filtrate is distilled under reduced pressure, separating 95–99 g. (76–79%) of *N*-ethylidenecyclohexylamine as a colorless liquid, b.p. 47–48° (12 mm.) or 54–55° (16 mm.), n_D^{20} 1.4579; n_D^{25} 1.4560. This product should either be used immediately in the next step or stored in a refrigerator (5–10°) under a nitrogen atmosphere.

B. N-(3-*Hydroxy*-3,3-*diphenylpropylidene)cyclohexylamine*. A dry, 250-ml., round-bottomed flask or dry 250-ml. Schlenk tube fitted with a magnetic stirrer is flushed with oxygen-free nitrogen (Note 2), stoppered with a rubber septum, and cooled in an ice bath. A slight positive pressure of oxygen-free nitrogen (Note 2) is maintained in the vessel throughout the reaction with a nitrogen line connected both to a pressure relief valve and a hypodermic needle which is inserted through the rubber septum. With a hypodermic syringe a solution of 2.53 g. (3.60 ml. or 0.0250 mole) of pure diisopropylamine (Note 3) in 25 ml. of absolute ether (Note 4) is added to the cold reaction vessel. An ethereal solution containing 0.025 mole of methyllithium (Note 5) is added from a hypodermic syringe dropwise and with stirring. During this addition a vigorous evolution of methane is observed. After the solution of lithium diisopropylamide has been stirred at 0° for 5–10 minutes a negative Gilman color test[2]

for methyllithium is obtained. A solution of 3.13 g. (0.0250 mole) of *N*-ethylidenecyclohexylamine in 20 ml. of absolute ether (Note 4) is added from a hypodermic syringe, dropwise and with stirring, to the cold (0°) solution of lithium diisopropylamide, and the resulting solution is stirred for 10 minutes (Note 6). This solution is then cooled to −70° with a methanol–dry ice bath, and a solution of 4.55 g. (0.0250 mole) of benzophenone in 25 ml. of absolute ether is added to the cold (–70°) reaction vessel with a hypodermic syringe. The resulting solution is allowed to warm to room temperature and stand for 24 hours, during which time a white solid separates. The reaction mixture is cooled to 0° in an ice bath, treated with approximately 50 ml. of water, and stirred at 0° for 30 minutes. The cold mixture is filtered with suction, removing the white crystalline product, and the organic phase from the filtrate is separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The combined residues from the filtration and concentration of the organic phase of the filtrate are recrystallized from hexane, separating 6.80–7.06 g. (89–92%) of *N*-(3-hydroxy-3,3-diphenylpropylidene)cyclohexylamine as white needles, m.p. 127–128° (Note 7).

C. β-*Phenylcinnamaldehyde*. A mixture of 1.54 g. (0.00520 mole) of *N*-(3-hydroxy-3,3-diphenylpropylidene)cyclohexylamine and 10 g. (0.11 mole) of oxalic acid is subjected to steam distillation, which is continued until a clear distillate is obtained; this requires about 2 hours. The steam distillate is extracted with two 25-ml. portions of ether, and the combined ethereal extracts are dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residual crude product (approximately 1.0 g., m.p. 42–44°) is recrystallized from pentane, yielding 0.80–0.88 g. (78–85%) of β-phenylcinnamaldehyde as pale yellow needles, m.p. 46–47° (Note 8).

2. Notes

1. The amine (m.p. –21°) should be cooled with stirring until it just begins to freeze. At this point the temperature of the external cooling bath should be maintained at –20° by the periodic addition of pieces of dry ice.

2. One suitable arrangement for the purification of nitrogen is described by H. Metzger and E. Müller.[3] The checkers used a prepurified grade of nitrogen without further purification.

3. Diisopropylamine (b.p. 83–84°, available from Fluka AG or from Eastman Organic Chemicals) was purified by refluxing it over either sodium wire or sodium hydride for approximately 30 minutes, then distilling the amine into a dry receiver under a nitrogen atmosphere. Because of the relatively low boiling point of the amine, a dispersion of sodium hydride in mineral oil, available from Metal Hydrides, Inc., Beverly, Massachusetts, can be used directly in this purification without prior removal of the mineral oil.

4. The submitters purified the ether by refluxing it over sodium wire until the blue color of benzophenone ketyl persisted when benzophenone was added, and distilling the ether into a dry receiver under a nitrogen atmosphere. The checkers further purified an absolute grade of ether obtained from Mallinckrodt Chemical Works by distilling it from lithium aluminum hydride under a nitrogen atmosphere.

5. An ethereal solution of methyllithium may be prepared in the following manner. A dry, 1-l., three-necked flask is fitted with a magnetic stirrer, a gas-inlet tube, and a dry ice reflux condenser. In the flask are placed 800 ml. of absolute ether (Note 4) and 16 g. (2.3 g.-atoms) of pieces of lithium wire. Over a period of 4–5 hours, 100 g. (1.05 moles) of methyl bromide is distilled into the reaction flask with continuous stirring. The resulting mixture is stirred for an additional hour and allowed to stand overnight under a nitrogen atmosphere, permitting the insoluble particles to settle. The supernatant liquid is transferred under a nitrogen atmosphere to a dry storage buret or some other dry vessel capped with a rubber septum. Alternatively, an ethereal solution of methyllithium may be purchased from Foote Mineral Co., Exton, Pennsylvania.

Aliquots of the methyllithium solution should be removed from the storage buret or storage vessel for standardization. The checkers employed the titration procedure of Watson and Eastham [*Org. Synth.*, **Coll. Vol. 5**, 211 (1973)][4] with either 2,2'-dipyridyl or *o*-phenanthroline as an indicator for standardizing the methyllithium solution.

6. When an aliquot of this solution is subjected to a Gilman color test,[2] a wine-red color is obtained.

7. The product has IR absorption ($CHCl_3$) at 3250 (broad, associated OH) and 1665 cm.$^{-1}$ (C=N) with ^1H NMR peaks ($CDCl_3$) at δ 1.0–3.0 (m, 11H, C_6H_{11}), 3.12 (d, J = 4 Hz., 2H, CH_2), 7.0–7.7 (m, 10H, $2C_6H_5$), and 7.78 (t, J = 4 Hz., 1H, C*H*=N).

8. The product has IR absorption (CCl_4) at 2720, 2745, and 2840 cm.$^{-1}$ (aldehyde CH) and at 1675 cm^{-1} (conjugated C=O) with UV maxima (95% C_2H_5OH) at 224 nm (ε 13,500) and 300 nm (ε 16,500) and ^1H NMR peaks (CCl_4) at δ 6.22 (d, J = 8 Hz., 1H, C*H*), 7.1–7.5 (m, 10H, $2C_6H_5$), and 9.40 (d, J = 8 Hz., 1H, C*H*O).

3. Discussion

Until recently it has not been possible to control the aldol condensation;[5] the enolate anion derived from an aldehyde could not be condensed with a carbonyl group of a ketone, because of the rapidity of the self-condensation of the aldehyde. This problem can be circumvented if the aldehyde is first converted to the corresponding azomethine derivative. The anion derived from this "protected" aldehyde can be added to another carbonyl group, giving an easily crystallized β-hydroxy imine adduct. Subsequent dehydration and concurrent removal of the imino protecting group yields an α,β-unsaturated aldehyde. The overall procedure,

utilizing an organometallic intermediate, constitutes a new method for effecting an aldol condensation. With reaction conditions illustrated in this preparation other carbonyl compounds with acidic α-hydrogens, such acetone or β-ionone, can also be used, because the deprotonation of the carbonyl compound by the metalated Schiff base is largely suppressed. This directed aldol condensation is useful for the preparation of naturally occurring α,β-unsaturated carbonyl compounds or intermediates useful in the syntheses of these substances.[6] The method can also be applied to the synthesis of α,β-unsaturated ketones if a ketimine is used as the azomethine component in the condensation.[6] Although the condensation is also successful with acetaldimine derivatives which contain one α-alkyl substituent, only very poor yields of condensation products are obtained when two α-alkyl substituents are present.[6] This limitation is possibly the result rate of a retarded rate of proton abstraction from the imine, due to the steric hindrance offered by the α-alkyl substituents.[7]

Although the reaction of aldehydes with β-carbonylmethylene phosphoranes constitutes a good synthetic route to α,β-unsaturated carbonyl compounds,[8,9,10,11] this procedure is normally not applicable to ketones. This limitation has recently been overcome by the reaction of ketones with the cyclohexylimine derivative of β-carbonylmethylenephosphonates.[12]

With the aid of the directed aldol condensation procedure, *N*-(3-hydroxy-3,3-diphenylpropylidene)cyclohexylamine has been prepared for the first time. Previous methods employed for the synthesis of β-phenylcinnamaldehyde include the application of the Sommelet reaction to 3,3-diphenylallyl bromide with isolation of the aldehyde as its semicarbazone,[13] the reaction of β,β-diphenylvinylmagnesium bromide with *N*-methylformanilide followed by hydrolysis,[14] and the reaction of this same Grignard reagent with ethyl orthoformate followed by hydrolysis of the resulting acetal.[15] This unsaturated aldehyde has also been prepared by the formylation of 1,1-diphenylethylene with *N*-methylformanilide and phosphorus oxychloride,[16] by the oxidation of β-phenylcinnamyl alcohol with manganese dioxide,[17] and by the rearrangement of 1,1-diphenyl-2-propyn-1-ol in an ethylene glycol solution containing boron trifluoride and mercury(II) oxide, followed by hydrolysis of the intermediate acetal.[18]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 121
- Org. Syn. Coll. Vol. 6, 571
- Org. Syn. Coll. Vol. 6, 666
- Org. Syn. Coll. Vol. 6, 692
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

benzophenone ketyl

rubber septum

o-phenanthroline

acetaldehyde (75-07-0)

ether, diethyl ether (60-29-7)

sodium sulfate (7757-82-6)

Oxalic acid (144-62-7)

nitrogen (7727-37-9)

mercury(II) oxide (21908-53-2)

Phosphorus Oxychloride (21295-50-1)

Benzophenone (119-61-9)

sodium (13966-32-0)

ethylene glycol (107-21-1)

methyl bromide (74-83-9)

manganese dioxide (1313-13-9)

1,1-Diphenylethylene (530-48-3)

Pentane (109-66-0)

lithium (7439-93-2)

magnesium sulfate (7487-88-9)

boron trifluoride (7637-07-2)

cyclohexylamine (108-91-8)

lithium aluminum hydride (16853-85-3)

N-methylformanilide (93-61-8)

sodium hydride (7646-69-7)

hexane (110-54-3)

Methyllithium (917-54-4)

2,2'-dipyridyl (366-18-7)

lithium diisopropylamide (4111-54-0)

diisopropylamine (108-18-9)

N-Ethylidenecyclohexylamine (1193-93-7)

β-Phenylcinnamaldehyde, 2-Propenal, 3,3-diphenyl- (1210-39-5)

3,3-diphenylallyl bromide

β,β-diphenylvinylmagnesium bromide

β-phenylcinnamyl alcohol

1,1-diphenyl-2-propyn-1-ol (3923-52-2)

N-(3-Hydroxy-3,3-diphenylpropylidene)cyclohexylamine (1235-46-7)

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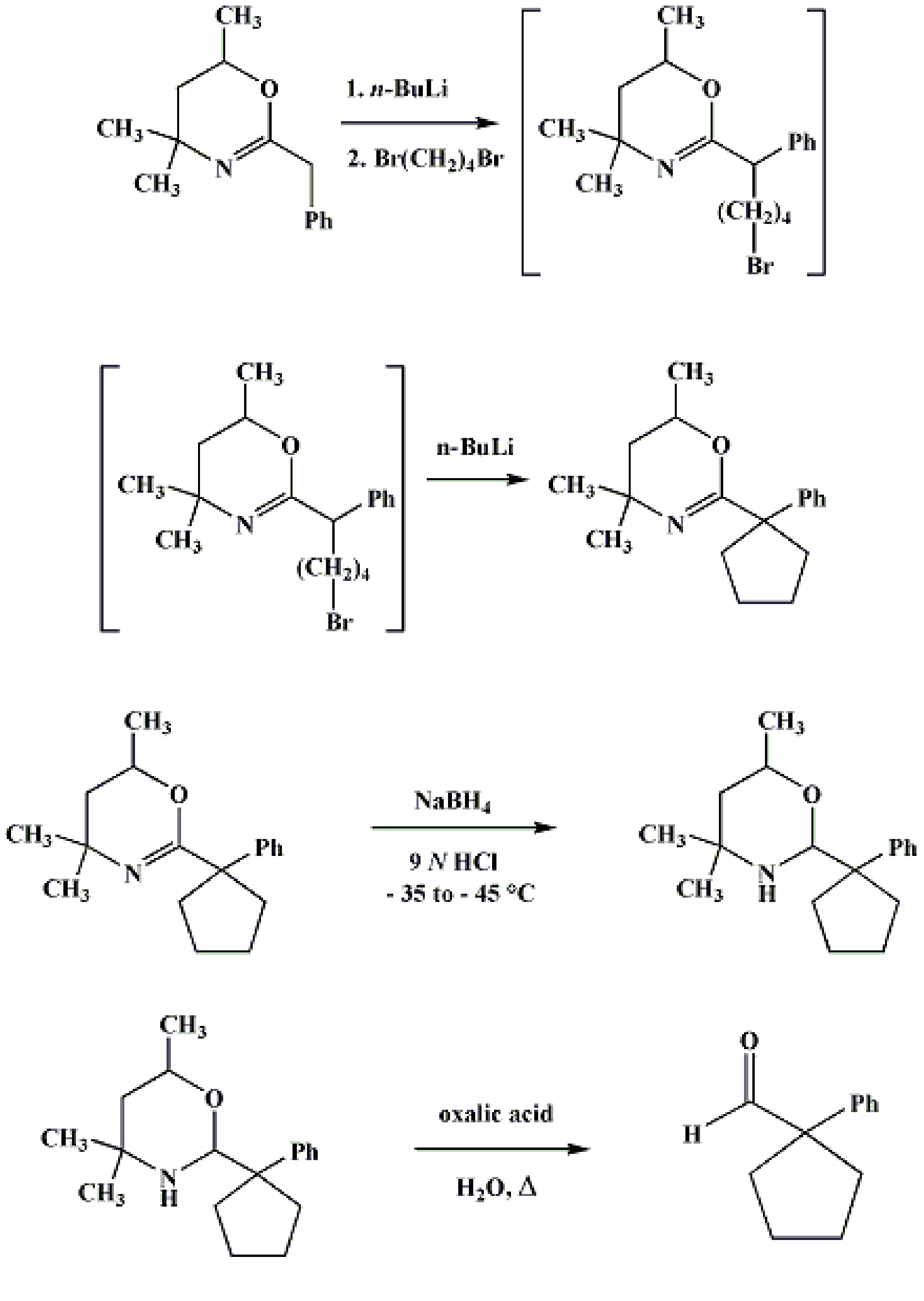
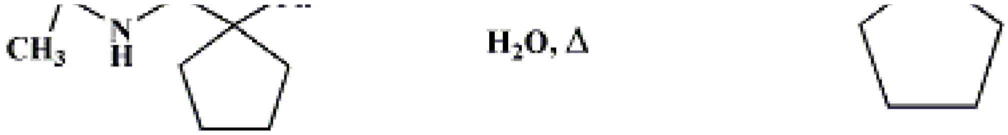
Organic Syntheses, *CV 6, 905*

ALDEHYDES FROM 2-BENZYL-4,4,6-TRIMETHYL-5,6-DIHYDRO-1,3(4*H*)-OXAZINE: 1-PHENYLCYCLOPENTANECARBOXALDEHYDE

[Cyclopentanecarboxaldehyde, 1-phenyl-]





Submitted by Ieva R. Politzer and A. I. Meyers[1].
Checked by Dennis R. Rayner and Richard E. Benson.

1. Procedure

A. 2-(1-*Phenylcyclopentyl*)-4,4,6-*trimethyl*-5,6-*dihydro*-1,3(4H)-*oxazine*. A 1-l., three-necked flask is equipped with a magnetic stirring bar, a 125-ml. pressure-equalizing funnel fitted with a rubber septum, and a nitrogen inlet tube. The system is flushed with nitrogen, and 500 ml. of dry tetrahydrofuran (Note 1) and 21.7 g. (0.100 mole) of 2-benzyl-4,4,6-trimethyl-5,6-dihydro-1,3(4*H*)-oxazine (Note 2) are added to the flask. The stirred solution is cooled to −78° with an acetone–dry ice bath, and 49 ml. (0.11 mole) of a 2.25 *M* solution of *n*-butyllithium in *n*-hexane (Note 3) is injected into the addition funnel. The *n*-butyllithium solution is added over a period of 15 minutes, and the funnel is rinsed by injecting 5 ml. of dry tetrahydrofuran. The yellow to orange solution is allowed to stir at −78° for 30 minutes (Note 4).

1,4-Dibromobutane (23.8 g., 0.110 mole) (Note 5) is injected into the addition funnel and added to the solution with stirring over a period of about 15 minutes. The funnel is rinsed by injection of 5 ml. of dry tetrahydrofuran, and the reaction is stirred at −78° for 45 minutes. *n*-Butyllithium (55 ml., 0.12 mole) in *n*-hexane is injected into the addition funnel and added to the solution over a period of 15 minutes. The reaction is stirred at −78° for 1 hour and stored at −20° overnight (Note 6). The mixture is poured into about 300 ml. of ice water and acidified to pH 2–3 with 9 *N* hydrochloric acid. The acidic solution is shaken with three 200-ml. portions of diethyl ether, and the ether extracts are discarded. The aqueous layer is made basic by careful addition of 40% sodium hydroxide (Note 7). The resulting mixture is shaken with four 200-ml. portions of ether, and the ether extracts are dried over anhydrous potassium carbonate. The ether is removed with a rotary evaporator, giving 24.4–25.8 g. (90–95%) of crude 2-(1-phenylcyclopentyl)-4,4,6-trimethyl-5,6-dihydro-1,3(4*H*)-oxazine, which is sufficiently pure for use in the following step.

B. 2-(1-*Phenylcyclopentyl*)-4,4,6-*trimethyltetrahydro*-1,3-*oxazine*. A 600-ml. beaker containing a magnetic stirring bar is charged with 200 ml. of tetrahydrofuran, 200 ml. of 95% ethanol, and 25.0 g. (0.0922 mole) of the oxazine obtained in Part A. The mixture is stirred and cooled to −35 to −40° with an acetone bath to which dry ice is added as needed. A 9 *N* hydrochloric acid solution is added dropwise to the stirred solution until an approximate pH of 7 is obtained as determined by pH paper. A solution of sodium borohydride is prepared by dissolving 5.0 g. (0.13 mole) in a minimum amount of water (5–8 ml.) to which 1 drop of 40% sodium hydroxide is added (Note 8). The sodium borohydride solution and 9 *N* hydrochloric acid solution are alternately added dropwise to the stirred solution so that a pH 6–8 is maintained (Note 9). During the addition care is taken to maintain a temperature between −35 and −45°. After addition of the borohydride solution is complete, the reaction mixture is

stirred at –35° for 1 hour. A pH of 7 is maintained by occasional addition of 9 *N* hydrochloric acid (Note 10). The reaction mixture is then stored at –20° overnight.

The reaction mixture is poured into 300 ml. of water, and the resulting mixture is made basic with 40% sodium hydroxide. The mixture is shaken three times with 200-ml. portions of ether, and the combined ether extracts are washed with 10 ml. of saturated sodium chloride. After drying over potassium carbonate, the ether is removed with a rotary evaporator, giving 22.9–25.0 g. (91–99%) of product, which is used without purification in the next step (Note 11).

C. *1-Phenylcyclopentanecarboxyaldehyde*. The crude tetrahydroöxazine (25.0 g., 0.0916 mole) from Part B is heated at reflux with 300 ml. of water containing 37.8 g. (0.300 mole) of oxalic acid dihydrate for 3 hours. The solution is cooled, and the aldehyde is extracted with four 150-ml. portions of petroleum ether (b.p. 40–60°). The organic extracts are combined, washed with 10 ml. of saturated sodium hydrogen carbonate, and dried with anhydrous powdered magnesium sulfate. The petroleum ether is removed with a rotary evaporator, and the product is distilled through a Vigreux column, giving 7.8–8.7 g. (50–55%) of 1-phenylcyclopentanecarboxaldehyde, b.p. 70–73° (0.1 mm.) $n_D^{26.5}$ 1.5350, IR spectrum (neat) 1720 cm.$^{-1}$ (C=O) (Note 12).

2. Notes

1. Tetrahydrofuran is dried by distillation from lithium aluminum hydride. [See *Org. Synth.*, **Coll. Vol. 5**, 976 (1973) for warning regarding the purification of tetrahydrofuran.]
2. 2-Benzyl-4,4,6-trimethyl-5,6-dihydro-1,3(4*H*)-oxazine is available from Columbia Organic Chemicals Company, Inc. The product was distilled, b.p. 80–82° (0.25 mm.). It may be prepared according to a modification of the method of Ritter and Tillmanns.[2] A 2-l. flask equipped with a thermometer, a stirrer, and a 250-ml. addition funnel is charged with 200 ml. of concentrated sulfuric acid (95–98%). Stirring is begun, the acid is cooled to 0–5° with an ice bath, and 128.7 g. (1.100 moles) of phenylacetonitrile is added from the funnel at such a rate that the temperature is maintained at 0–5°. After the addition is complete, 118 g. (1.00 mole) of 2-methyl-2,4-pentanediol is added at a rate to maintain a reaction temperature of 0–5°. The mixture is stirred for an additional hour and poured onto 700 g. of crushed ice. The aqueous solution is washed with two 75-ml. portions of chloroform, and the extracts discarded. The aqueous solution is made alkaline with 40% sodium hydroxide, with ice being added periodically during the neutralization to keep the solution temperature below 35°. The yellow oil is separated, and the aqueous solution is washed three times with 75-ml. portions of ether. The oil and ether extracts are combined, and the solution is dried over anhydrous potassium carbonate. The ether is removed with a rotary evaporator, and the product is distilled through a 25-cm. Vigreux column, yielding 107–115 g. (49–53%) of 2-benzyl-4,4,6-trimethyl-5,6-dihydro-1,3(4*H*)-oxazine as a straw-yellow liquid, b.p. 78–80° (0.25 mm.); n_D^{27} 1.5085; IR

spectrum (neat) 1660 and 1600 cm.$^{-1}$, ^{1}H NMR ($CDCl_3$) δ 1.08 (s, 6H), 3.32 (s, 2H), 4.04 (m, 1H) and 7.08 (m, 5H).

3. *n*-Butyllithium in *n*-hexane is available from Lithium Corporation of America, Inc.

4. If less solvent is used, the anion may appear as a yellow precipitate, but it is also usable in this form.

5. 1,4-Dibromobutane was distilled, b.p. 40–45° (0.5 mm.).

6. Alternatively, the reaction mixture may be allowed to reach room temperature over a period of 2–3 hours.

7. Ice may be added to keep the mixture cool during the neutralization.

8. The aqueous borohydride suspension is warmed, and the borohydride lumps crushed to achieve a homogeneous solution. The product available from Alfa Inorganics, Inc., was used by the checkers.

9. It is convenient to introduce the acid and hydride solutions from two burets or dropping funnels placed above the beaker. A total volume of about 15 ml. of 9 *N* hydrochloric acid is required.

10. The reaction can be conveniently monitored by IR spectroscopy, observing the intensity of the band at 1650 cm.$^{-1}$ (C=N). The submitters observed almost complete disappearance of this band, whereas the checkers found it still present in medium intensity in their product. In those instances where the α-carbon bears three alkyl substituents, steric effects retard the rate of addition, and in some cases (i.e., α,α,α-triethyl or larger groups) the C=N bond is resistant to reduction.

11. The intensity of the IR band at 1650 cm.$^{-1}$ should be weak.

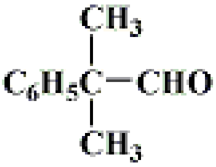
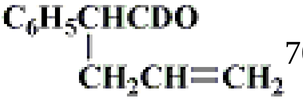
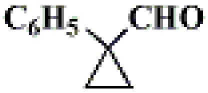
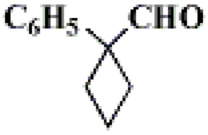
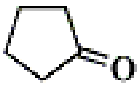
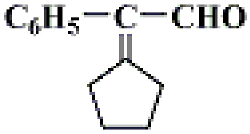
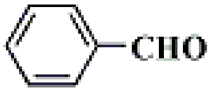
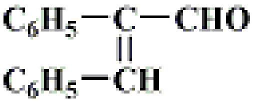
12. The ^{1}H NMR spectrum (CCl_4) shows peaks at δ 1.5–2.7 (m, 8H, 4CH_2), 7.2 (s, 5H, C_6H_5), and 9.3 (s, 1H, C*H*O). GC on a 240 cm. × 6 mm. column packed with 10% SE-30 on Chromosorb P at 120° gives a single peak with a retention time of 1.3 minutes.

3. Discussion

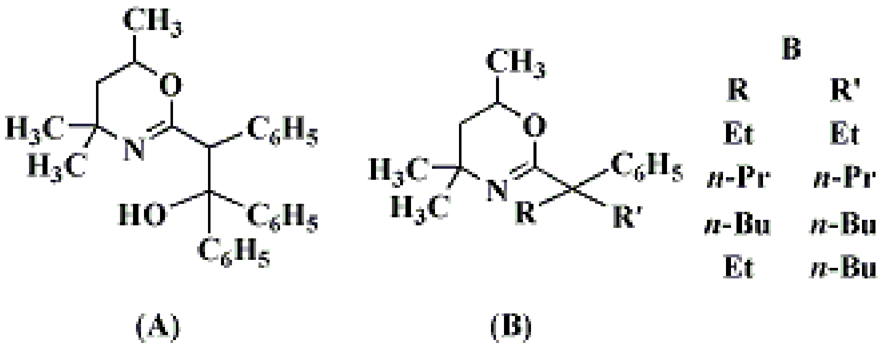
This procedure illustrates a general method for preparing α-phenyl aldehydes.[3] Additional examples are given in Table I.

TABLE I
ALDEHYDES FROM2-BENZYL-4,4,6-TRIMETHYL-5,6-DIHYDRO-1,3(4*H*)-OXAZINE[4,5,6,7]

Alkylating Agent
Aldehyde
Yield, %

CH_3I		65
CH_3I (2,0 equiv.)		48
$CH_3CH_2CH_2Br$		64
$CH_2{=}CHCH_2Br$		70[a]
$BrCH_2CH_2Br$		57
$Br(CH_2)_3Br$		49
		54
		63

[a] Reduction was performed with $NaBD_4$.



A limitation to this reaction sequence is that the reduction of the dihydroöxazine fails if bulky substituents are present. Thus, the alkylated oxazines A and B were not reduced under the reaction conditions specified in this procedure.

This technique may also be modified to prepare acetaldehyde derivatives, using 2,4,4,6-tetramethyl-5,6-dihydro-1,3(4*H*)-oxazine[3,4,5,6,7] and 2-carboethoxy acetaldehydes, using 2-(carboethoxymethyl)-4,4,6-trimethyl-5,6-dihydro-1,3(4*H*)-oxazine.[3] Functionalized aldehydes and dialdehydes may also be obtained by suitable modification.[8] Generally, the intermediates can be used without purification, and the overall yields of the aldehydes range from 50 to 70%.

In addition to the present method, 1-phenylcyclopentanecarboxaldehyde has been prepared by the reduction of *N*-acylaziridines obtained from 1-phenylcyclopentanecarboxylic acid.[9]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 17

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

ethanol (64-17-5)

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ether, diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium hydrogen carbonate (144-55-8)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

phenylacetonitrile (140-29-4)

magnesium sulfate (7487-88-9)

n-butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

n-hexane (110-54-3)

sodium borohydride (16940-66-2)

1,4-dibromobutane (110-52-1)

oxalic acid dihydrate (6153-56-6)

1-Phenylcyclopentanecarboxaldehyde, Cyclopentanecarboxaldehyde, 1-phenyl-, 1-Phenylcyclopentanecarboxyaldehyde (21573-69-3)

2-methyl-2,4-pentanediol (107-41-5)

1-phenylcyclopentanecarboxylic acid (77-55-4)

2-BENZYL-4,4,6-TRIMETHYL-5,6-DIHYDRO-1,3(4H)-OXAZINE (26939-22-0)

2-(1-Phenylcyclopentyl)-4,4,6-trimethyl-5,6-dihydro-1,3(4H)-oxazine

2,4,4,6-tetramethyl-5,6-dihydro-1,3(4H)-oxazine

2-(carboethoxymethyl)-4,4,6-trimethyl-5,6-dihydro-1,3(4H)-oxazine

2-(1-Phenylcyclopentyl)-4,4,6-trimethyltetrahydro-1,3-oxazine

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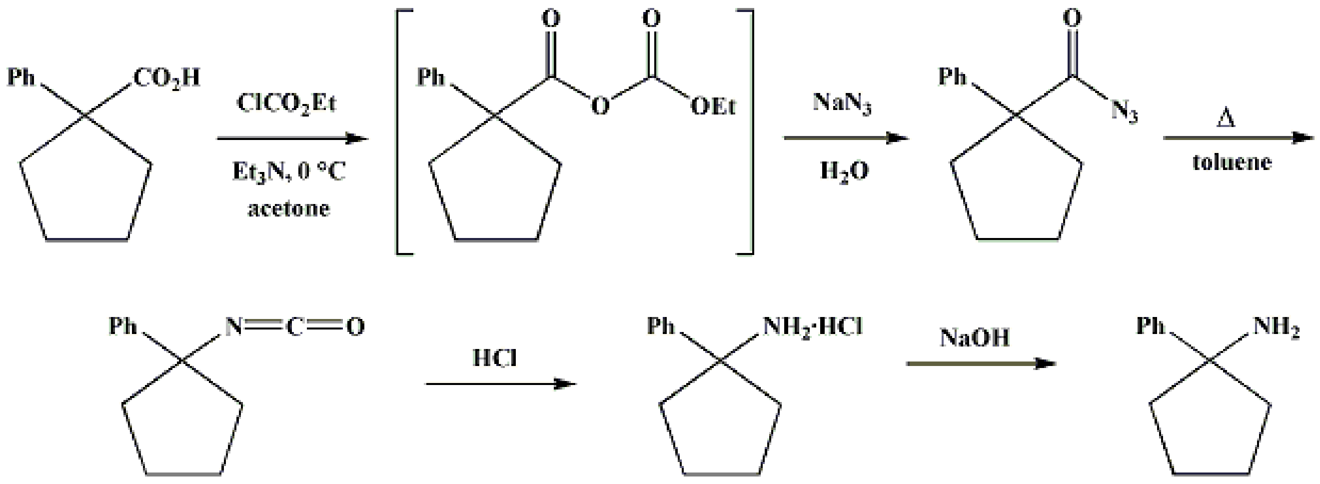
Organic Syntheses, CV 6, 910

AMINES FROM MIXED CARBOXYLIC-CARBONIC ANHYDRIDES: 1-PHENYLCYCLOPENTYLAMINE

[Cyclopentanamine, 1-phenyl-]



Submitted by Carl Kaiser and Joseph Weinstock[1].
Checked by A. Brossi, R. A. Micheli, and L. Portland.

1. Procedure

A 1-l., three-necked, round-bottomed flask equipped with an air stirrer, dropping funnel, and low-temperature thermometer is charged with 38.0 g. (0.200 mole) (Note 1) of 1-phenylcyclopentanecarboxylic acid and 150 ml. of acetone. The mixture is stirred, and 22.3 g. (30.6 ml., 0.221 mole) of triethylamine is added over 5 minutes (a 2° rise in temperature is observed). The solution is chilled to −5 to 0° in an ice-salt bath, and 24.0 g. (21.1 ml., 0.221 mole) of ethyl chlorocarbonate (Note 2) in 50 ml. of acetone is added slowly (25 minutes), maintaining the temperature between −5 to 0°. After the addition is complete, the cold mixture is stirred for an additional 15 minutes. A solution of 26.0 g. (0.400 mole) of sodium azide in 75 ml. of water is added over a 25-minute period while the temperature is kept at −5 to 0°. The mixture is stirred for 30 minutes longer at this temperature, poured into 750 ml. of ice water, and shaken with four 250-ml. portions of toluene (Note 3). The combined toluene extracts are dried over anhydrous magnesium sulfate and transferred to a 2-l., three-necked, round-bottomed flask equipped with a two-necked, Claisen-type adapter, stirrer, and reflux condenser. The stirred solution is heated cautiously (Note 4) under reflux for 1 hour on a steam bath (nitrogen evolution is observed initially). The toluene is then removed at 50° with a rotary evaporator (aspirator pressure). The flask containing the residual, oily isocyanate is again fitted with the Claisen-type adapter, stirrer, and reflux condenser. The oil is stirred, cooled in an ice bath, and 300 ml. of 8 *N* hydrochloric acid (Note 5) is added. The cooling bath is removed, the stirred mixture is gradually heated on a steam bath (Note 6) until carbon dioxide evolution has subsided (30 minutes), and the solution is heated under reflux for 10 minutes. The flask is evacuated with a water aspirator and warmed in a bath at 50° for about 10 minutes. About 10–20 ml. of distillate is collected before a crystalline product separates (Note 7). Ice water (200 ml.) is added to the flask with cooling in an ice bath, and 1 l. of 2.5 *N* sodium hydroxide is added slowly to pH 12. The mixture is shaken with three 200-ml. portions of diethyl ether, the combined extracts are dried over anhydrous magnesium sulfate, and the ether is removed by distillation at 50° with a water aspirator, yielding 29.7 g. of an oil. Distillation of the crude product gives 24.5–26.1 g. (76–81%) of 1-phenylcyclopentylamine, b.p. 112–114° (9 mm.), $n_D^{20.5}$ 1.5439 (Note 8).

2. Notes

1. 1-Phenylcyclopentanecarboxylic acid,[2,3] m.p. 157–159°, was obtained from Aldrich Chemical Company, Inc.
2. A commercial grade of ethyl chlorocarbonate, stabilized with calcium carbonate, was employed without purification.
3. Approximately 3.6–3.9 g. of 1-phenylcyclopentanecarboxylic acid (m.p. 158–159.5°) can be recovered by

acidification of the aqueous solution which remains after washing with toluene.

4. Rearrangement of the azide must be carried out carefully as the reaction is exothermic, and a large volume of nitrogen is evolved. The submitters have encountered no difficulties if the described dilution (0.2 mole of azide in 1 l. of toluene) is employed. The steam bath should be replaced by a cooling bath if the solution refluxes vigorously.

5. Approximately 8 *N* hydrochloric acid was prepared by addition of 100 ml. of water to 200 ml. of 37.5% hydrochloric acid.

6. Heating should be gradual and in a large reaction vessel as hydrolysis of isocyanate is accompanied by evolution of carbon dioxide and considerable foaming may occur. If excessive foaming occurs, the steam bath should be removed.

7. The checkers carried the synthesis through to this point without interruption. Since this required about 8 hours on the scale described, the equipment and chemicals were made ready the preceding day.

8. ^{1}H NMR spectrum ($CDCl_3$) δ 1.30 (s, 2H, NH_2), 1.83 (broad s, 8H, 4CH_2), and 7.33 (m, 5H, C_6H_5). The distilled product was of high purity, as determined by GC analysis. A 122 cm. × 6.4 mm. O.D. stainless-steel column containing 3% SE-30 on Diatoport S (80–100 mesh) and programmed from 100–200° at 10°/minute was used. The retention time is about 5 minutes.

3. Discussion

1-Phenylcyclopentylamine has also been prepared from 1-phenylcyclopentanecarboxylic acid by the Hofmann degradation of the intermediate amide[4,5] and from the intermediate carboxylic acid chloride by the Curtius reaction.[6] In the method described, using the mixed carboxylic-carbonic anhydride,[7] improved yields of the amine are obtained.

The usual procedure of preparing acid azides, which involves treating an acid chloride with sodium azide,[8,9] suffers from the disadvantage that it is often difficult to obtain pure acid chlorides in good yields from acids which either decompose or undergo isomerization in the presence of mineral acids.[7] Synthesis of the azide by way of the ester and hydrazide[10] has been used to circumvent this difficulty, but is much less convenient. The present procedure permits ready formation of acid azides in excellent yields from mixed carboxylic–carbonic anhydrides and sodium azide under very mild conditions.

A possible limitation to this procedure, however, is that it is dependent upon the relative reactivity of the two carbonyl groups of the mixed carboxylic–carbonic anhydride toward the azide anion. Although either carbonyl group may be attacked by the azide ion, an attack on the more electrophilic carbonyl group is usually strongly favored and high yields of the acid azides generally result. Steric considerations may be important, but preference for azide attack on even a somewhat hindered carboxylic carbonyl is illustrated by the present example in which this group is proximal to phenyl and cyclopentyl groups.

This modification of the Curtius reaction has been used extensively in many laboratories and has been found to be generally applicable. Some examples from the literature include the stereoselective synthesis of a wide variety of cyclopropylamine derivatives from the corresponding acids,[11,12,13] the stereoselective preparation of some substituted norbornylamines from easily isomerized acids,[14] the preparation of some 1-aminocyclobutanecarboxylic acids from the corresponding acid esters,[15] the preparation of a substituted cyclobutanone from the corresponding cyclobutane-1,1-dicarboxylic acid *via* the 1,1-diamine,[16] and the preparation of a variety of heterocyclic amines from the corresponding acids.[17,18,19]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 433

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

ether, diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

calcium carbonate (471-34-1)

acetone (67-64-1)

toluene (108-88-3)

sodium azide (26628-22-8)

ethyl chlorocarbonate (541-41-3)

magnesium sulfate (7487-88-9)

triethylamine (121-44-8)

1-phenylcyclopentanecarboxylic acid (77-55-4)

1-Phenylcyclopentylamine, Cyclopentanamine, 1-phenyl- (17380-74-4)

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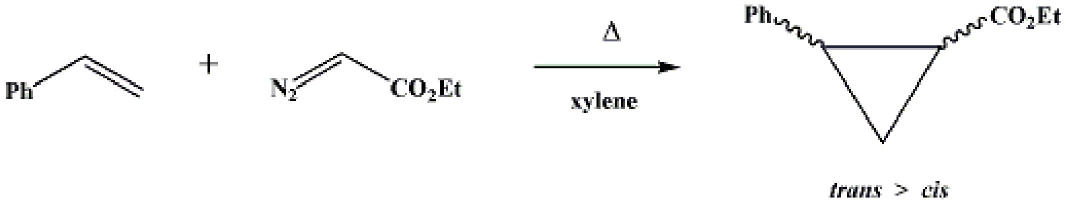
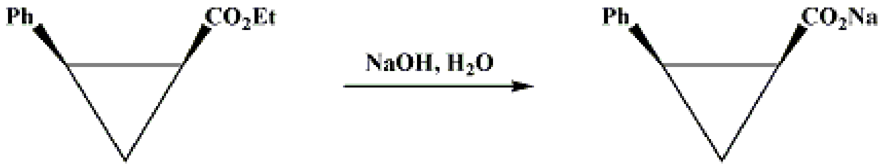
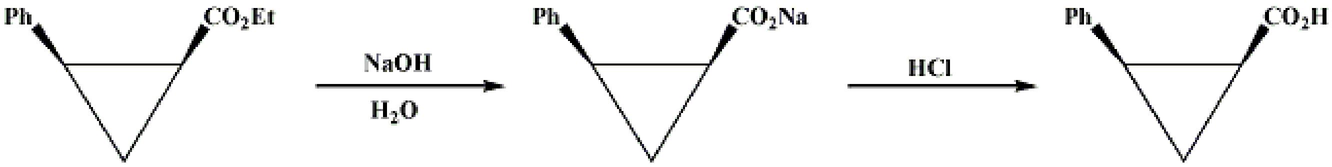
Organic Syntheses, CV 6, 913

cis-2-PHENYLCYCLOPROPANECARBOXYLIC ACID

[Cyclopropanecarboxylic acid, 2-phenyl-, *cis*-]







Submitted by Carl Kaiser, Joseph Weinstock[1], and M. P. Olmstead.
Checked by William E. Parham, Wayland E. Noland, Paul Cahill, and Thomas S. Straub.

1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A. *Ethyl* cis- *and* trans-*2-phenylcyclopropanecarboxylate*. Xylene (500 ml., (Note 1)) is heated to reflux in a 2-l. flask equipped with a mechanical stirrer, dropping funnel, and reflux condenser. A solution of 179 g. (1.57 moles) of ethyl diazoacetate [*Org. Synth.*, **Coll. Vol. 4**, 424 (1963)] (Note 2) and 163 g. (1.57 moles) of styrene (Note 3) is placed in the dropping funnel and added dropwise to the refluxing, stirred xylene over a period of 90 minutes. After addition is complete, the solution is stirred and heated at the reflux temperature for an additional 90 minutes (Note 4). Xylene is removed under reduced pressure, and the residual red oil is distilled through a short Vigreux column. The fraction boiling at 85–93° (0.5 mm.) is collected, yielding 155 g. (52%) of colorless product, n_D^{26} 1.5150, n_D^{20} 1.5166 (Note 5) and (Note 6).

B. cis-2-*Phenylcyclopropanecarboxylic acid*. A 1-l., three-necked flask equipped with a dropping funnel, stirrer, and a short Vigreux column (Note 7), to which is attached a partial take-off distilling head with reflux condenser, is charged with 155 g. (0.816 mole) of ethyl *cis*- and *trans*-2-phenylcyclopropanecarboxylate, 200 ml. of ethanol, 65 ml. of water, and 24.5 g. (0.612 mole) of sodium hydroxide pellets (Note 8). The mixture is heated at the reflux temperature for 5 hours during which time 200 ml. of ethanol is slowly distilled and replaced by an equal volume of water added through the dropping funnel. Heating is discontinued, 250 ml. of water and 150 ml. of benzene are added, and the mixture is stirred for 2–3 minutes. The layers are separated, and the aqueous layer is washed with two 50-ml. portions of benzene (Note 9).

The benzene extracts are placed in the apparatus used above, and 130 ml. of water and 13 g. (0.32 mole) of sodium hydroxide pellets are added. Benzene (200 ml.) is distilled and then the 200 ml. of ethanol obtained in the initial hydrolysis is added. The reflux-distillation process is continued for 5 hours, during which time 250 ml. of distillate is obtained. The mixture is cooled, and 65 ml. of benzene and 30 ml. of concentrated hydrochloric acid are added. The

layers are separated, and the aqueous solution is washed twice with 35-ml. portions of benzene. The combined benzene extracts are concentrated and dried by distillation of 90 ml. of benzene. The hot concentrate is decanted from a trace of salt, 70 ml. of petroleum ether is added, and the resulting solution is stored overnight at 0°. Filtration of the solid from the cold petroleum ether solution and washing with a small volume of cold 50:50 benzene–petroleum ether yields 19.5–23.8 g. (14.6-20.7% based on the mixed ester used, or 38–46.4% based on the *cis* ester, (Note 10)) of *cis*-2-phenylcyclopropanecarboxylic acid, m.p. 106–109° (Note 11). An additional 2–3 g. of the *cis* acid may be obtained by concentrating the mother liquors to low volume, adding petroleum ether, and chilling the resulting solution for several days.

2. Notes

1. The checkers used xylene distilled from sodium.
2. Ethyl diazoacetate is available from Aldrich Chemical Co. *Diazoacetic esters are potentially explosive and, therefore, must be handled with caution.* [See *Org. Synth.*, **Coll. Vol. 4**, 424 (1963).]
3. Redistilled styrene, b.p. 52–3° (28 mm.) was used by the submitters. The checkers used reagent grade styrene obtained from Eastman Organic Chemicals without further purification.
4. Refluxing was discontinued after nitrogen evolution ceased.
5. GC of several samples of the mixed ester revealed a composition of 55–65% *trans*-, 30–40% *cis*-ester, and 5% impurities.
6. The checker obtained 204 g. of product (68% yield), n_D^{26} 1.5160, with the approximate composition 39% *cis*–60% *trans*-ester.
7. The checkers used a 50-cm. Vigreux column.
8. The amount of base used is 0.75 mole per mole of mixed esters. This is slightly more than necessary to saponify all the *trans*-ester, present. Since the *trans*-ester is saponified more rapidly than the *cis*-ester, this affords an effective separation of the isomer. This procedure is a modification of that of Walborsky and Plonsker.[2]
9. *trans*-2-Phenylcyclopropanecarboxylic acid may be obtained from the aqueous solution in the following way. The aqueous solution is treated with 65 ml. of concentrated hydrochloric acid, and the mixture is extracted with one 130-ml. portion of benzene and two 20-ml. portions of benzene. The carefully separated benzene layers are combined and dried by distilling 100 ml. of benzene. The resulting solution is decanted from the small amount of salt present and diluted with 200 ml. of petroleum ether. The resulting solution is cooled at 0° overnight, and the precipitate is collected and washed with a small amount of a cold, 50:50 mixture of petroleum ether–benzene, yielding 63–65 g. (80% based on *trans*-ester originally present) of needles, m.p. 87–93°. Recrystallization of this product several times from carbon tetrachloride–petroleum ether gives the pure *trans*-acid, m.p. 93°.
10. The submitters obtained 25–28 g. of *cis*-acid (19–21% based on the mixed ester used).
11. Burger and Yost[3] reported m.p. 106–107° for pure *cis*-2-phenylcyclopropanecarboxylic acid and m.p. 93° for pure *trans*-2-phenylcyclopropanecarboxylic acid.

3. Discussion

The method described is a modification of that described by Walborsky and Plonsker.[2] It is based on the more rapid hydrolysis, due to less steric hindrance, of the *trans*- over the *cis*-ester. The *cis*-acid has also been obtained by fractional crystallization of the mixed acids.[3]

The present method offers a convenient preparation of *cis*-2-phenylcyclopropanecarboxylic acid that is amenable to large-scale work. The process above has been carried out by the submitters on a twentyfold scale with essentially the same results. The method also provides an example of the separation of two isomers based on differences in reaction rate.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

sodium hydroxide (1310-73-2)

carbon tetrachloride (56-23-5)

nitrogen (7727-37-9)

sodium (13966-32-0)

xylene (106-42-3)

styrene (100-42-5)

ethyl diazoacetate (623-73-4)

cis-2-Phenylcyclopropanecarboxylic acid, Cyclopropanecarboxylic acid, 2-phenyl-, cis- (939-89-9)

trans-2-Phenylcyclopropanecarboxylic acid (939-90-2)

Ethyl cis- and trans-2-phenylcyclopropanecarboxylate (946-39-4)

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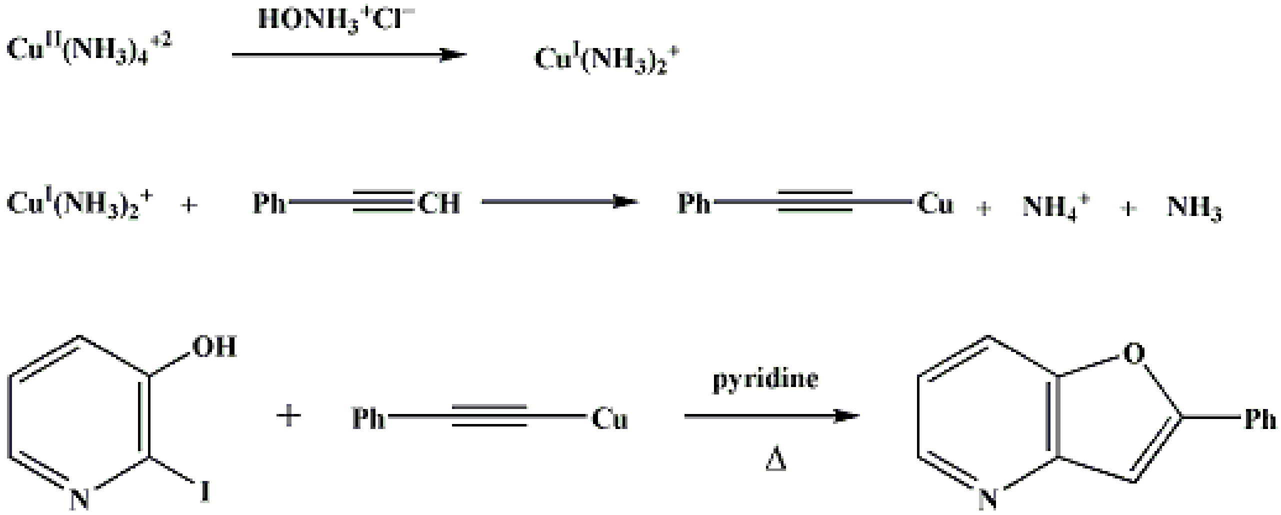
Organic Syntheses, CV 6, 916

SUBSTITUTION OF ARYL HALIDES WITH COPPER(I) ACETYLIDES: 2-PHENYLFURO[3,2-*b*]PYRIDINE

[Furo[3,2-*b*]pyridine, 2-phenyl-]



Submitted by D. C. Owsley and C. E. Castro[1].
Checked by Michael J. Umen and Herbert O. House.

1. Procedure

A. *Copper(I) phenylacetylide*. A 2-l. Erlenmeyer flask fitted with a large magnetic stirring bar (Note 1) and an ice-water cooling bath is charged with a solution of 25.0 g. (0.100 mole) of copper(II) sulfate pentahydrate (Note 2) in 100 ml. of concentrated aqueous ammonia. The solution is stirred with cooling for 5 minutes while a stream of nitrogen is passed over the solution (Note 3). Water (400 ml.) is added, and stirring and cooling under a nitrogen atmosphere (Note 3) are continued for 5 minutes. Solid hydroxylamine hydrochloride (13.9 g., 0.200 mole, (Note 4)) is added to the reaction solution, with continuous stirring and cooling under nitrogen, over 10 minutes (Note 5). A solution of 10.25 g. (0.1005 mole) of phenylacetylene (Note 6) in 500 ml. of 95% ethanol is then added rapidly to the pale blue solution. The reaction flask is swirled by hand, copper(I) phenylacetylide separates as a copious yellow precipitate, and an additional 500 ml. of water is added. After the mixture has been allowed to stand for 5 minutes, the precipitate is collected on a sintered glass filter (Note 7) and washed successively with five 100-ml. portions of water, five 100-ml. portions of absolute ethanol, and five 100-ml. portions of anhydrous diethyl ether. The copper(I) acetylide is dried in a 250-ml., round-bottom flask heated to 65° for 4 hours under reduced pressure on a rotary evaporator, yielding 14.8–16.4 g. (90–99%) of a bright yellow solid. The dry acetylide may be stored under nitrogen in a brown bottle (Note 8).

B. 2-*Phenylfuro*[3,2-b]*pyridine*. A 300-ml., three-necked flask fitted with a nitrogen inlet stopcock, a magnetic stirring bar, and a condenser attached to a nitrogen outlet stopcock and a mercury trap is charged with 2.47 g. (0.0150 mole) of copper(I) phenylacetylide. The system is purged with nitrogen for 20 minutes before 80 ml. of pyridine (Note 9) is added. The resulting mixture is stirred for 20 minutes under a nitrogen atmosphere (Note 10), and 3.30 g. (0.0149

mole) of 3-hydroxy-2-iodopyridine (Note 11) is added. The mixture, which changes in color from yellow to dark green as the acetylide dissolves (Note 12), is warmed in an oil bath at 110–120° for 9 hours with continuous stirring under a nitrogen atmosphere (Note 10). The reaction solution is transferred to a 500-ml., round-bottom flask and concentrated to a volume of 20 ml. at 60–70° (20–80 mm.) with a rotary evaporator. The pyridine solution is treated with 100 ml. of concentrated aqueous ammonia, and the resulting deep-blue mixture is stirred for 10 minutes and extracted with five 100-ml. portions of ether. The combined ethereal extracts are washed with three 250-ml. portions of water, dried over anhydrous magnesium sulfate, and concentrated with a rotary evaporator. The crude product, 2.6–2.76 g. of orange semisolid, is dissolved in 100 ml. of boiling cyclohexane. The solution is filtered, concentrated to a volume of about 30 ml., and cooled in an ice bath. The partially purified product crystallizes as 2.3–2.7 g. of orange solid, m.p. 83–89°. Further purification is effected by sublimation at 110–120° (0.01–0.2 mm.), yielding 2.2–2.4 g. (75–82%) of a yellow solid, m.p. 90–91° (Note 13).

2. Notes

1. An 8-cm., Teflon-coated stirring bar is convenient.
2. A reagent grade copper(II) sulfate pentahydrate, purchased from either Mallinckrodt Chemical Works or J. T. Baker Chemical Company, may be employed.
3. A nitrogen atmosphere is maintained above the reaction solution throughout the preparation of the copper(I) acetylide.
4. Material of satisfactory purity was obtained either from J. T. Baker Chemical Company or from Matheson, Coleman and Bell.
5. Too rapid an addition of the hydroxylamine salt results in precipitation of a dark solid that dissolves slowly. If solids do separate, they should be pulverized to hasten solution.
6. Phenylacetylene, purchased either from K & K Laboratories or from Aldrich Chemical Company, Inc., was used without purification.
7. A 600-ml., coarse porosity, sintered glass filter is recommended to shorten the filtration time. The filtration may also be hastened by periodically scraping the bottom of the funnel with a spatula.
8. The submitters report that the acetylide is stable for years under these conditions.
9. A reagent grade of pyridine, purchased from either J. T. Baker Chemical Company or Fisher Scientific Company, was employed.
10. Oxygen will convert the acetylide to 1,4-diphenylbutadiyne.[2]
11. This material, obtained from Aldrich Chemical Company, Inc., was used without purification.
12. Although the reaction mixture becomes homogeneous in this example, the submitters report that only partial solution occurs in other successful substitution reactions. The solubilities of the acetylides and the heterogeneous character of the cyclization have been described.[3]
13. The product exhibits UV maxima (95% C_2H_5OH solution) at 312 nm (ε 32,900) and 326 nm (ε 27,100) with ^1H NMR peaks (acetone-d_6) at δ 7.1–8.1 (m, 8H) and 8.49 (d of d, J = 1.4 and 4.7 Hz., 1H). The mass spectrum has the following relatively abundant peaks: *m/e* (rel. int.), 196 (25), 195 (100, M^+), 166 (13), 139 (8), 102 (5), and 39 (6).

3. Discussion

Copper(I) acetylides can be prepared from ammoniacal copper(I) iodide and acetylenes.[4,5] The generation of fresh solutions of the copper(I) salts results in a higher purity acetylide.

The substitution of aryl halides by copper(I) acetylides provides a convenient, high-yield route to aromatic acetylenes.[2,5,6,7,8,9] Aliphatic acetylenes can also be obtained under forcing conditions.[10] The procedure is also useful for the preparation of conjugated acetylenic ketones and alkynyl sulfides.[3] Moreover, the reaction provides the basis for the facile synthesis of an exceedingly broad scope of heterocycles. Thus, a halide bearing an adjacent nucleophilic substituent can be cyclized by the copper(I) salt. The example described is illustrative of the preparation of indoles,[2] benzo[*b*]thiophenes,[11] phthalides,[2] benzofurans,[2] 3(*H*)-isobenzofurans,[3] furans,[10] 1(*H*)-2-benzopyrans,[3] 1(*H*)-thieno[3,4-*b*]-2-pyranones,[12] furo[3,2-*b*]pyridines,[12] furo [3,2-*c*]pyridines,[12] pyrrolo[3,2-*b*]pyridines,[3] and 4,5-dihydro-4-keto[3] benzoxepins. The furo [3,2-*b*]pyridine system has only been prepared by this route.[12]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

ammonia (7664-41-7)

ether, diethyl ether (60-29-7)

oxygen (7782-44-7)

nitrogen (7727-37-9)

cyclohexane (110-82-7)

pyridine (110-86-1)

Hydroxylamine hydrochloride (5470-11-1)

Phenylacetylene (536-74-3)

copper(I) iodide (7681-65-4)

magnesium sulfate (7487-88-9)

copper(II) sulfate pentahydrate (7758-99-8)

1,4-diphenylbutadiyne (886-66-8)

copper(I) phenylacetylide (13146-23-1)

copper(I) acetylide

3-hydroxy-2-iodopyridine (40263-57-8)

2-Phenylfuro[3,2-b]pyridine, Furo[3,2-b]pyridine, 2-phenyl- (18068-82-1)

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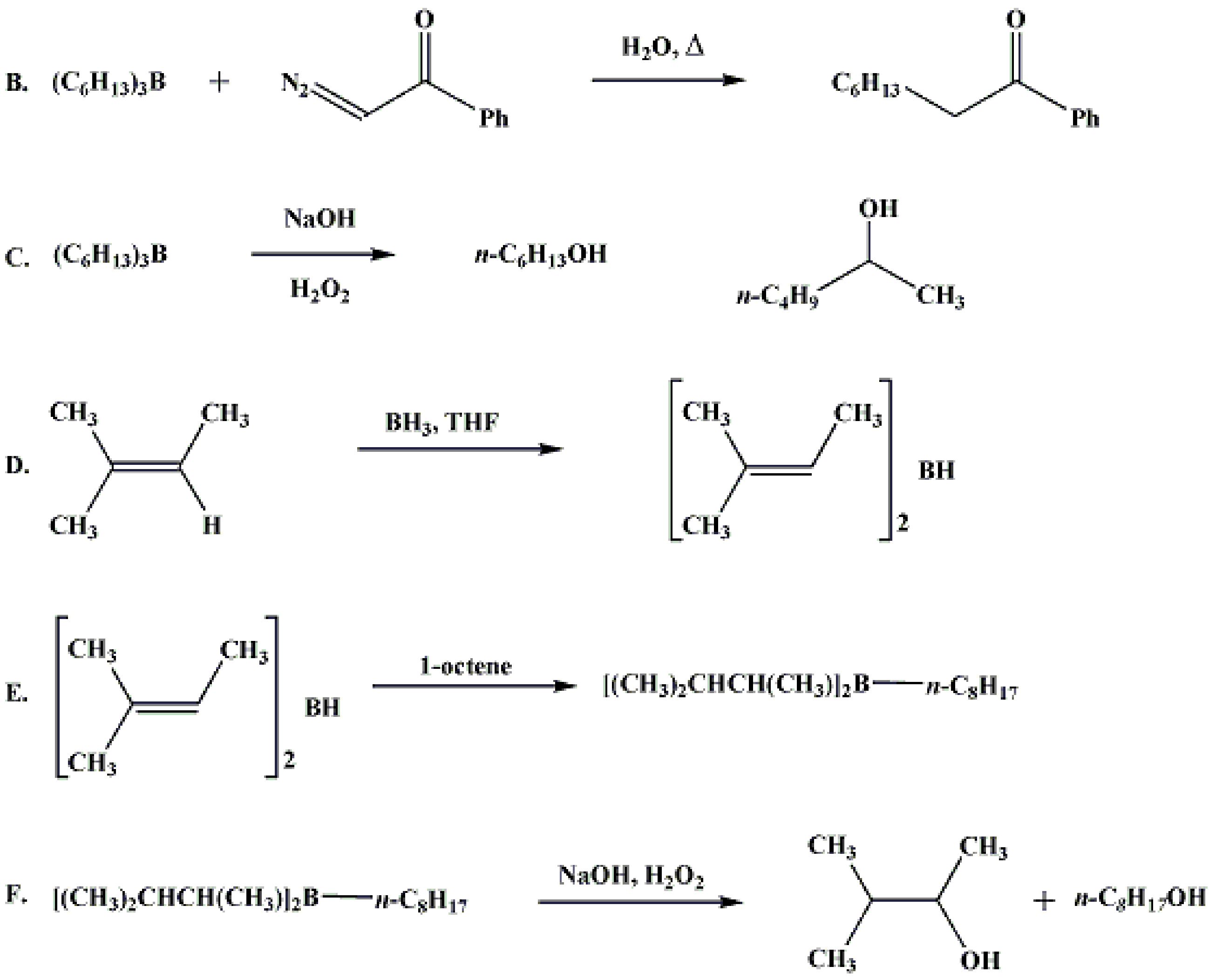
Organic Syntheses, CV 6, 919

KETONES AND ALCOHOLS FROM ORGANOBORANES: PHENYL HEPTYL KETONE, 1-HEXANOL, AND 1-OCTANOL

[1-Octanone, 1-phenyl-]



Submitted by Hiromichi Kono and John Hooz[1].
Checked by Dennis R. Murayama, Jack Emert, J. M. Pecoraro, and Ronald Breslow.

1. Procedure

A. *Trihexylborane*. A dry, 1-l., three-necked flask is equipped with a magnetic stirring bar, a reflux condenser fitted with a drying tube, a pressure-equalizing dropping funnel to which is attached a rubber septum cap, and a three-way, parallel sidearm connecting tube fitted with a thermometer and an inlet tube (containing a stopcock), permitting introduction of a dry nitrogen atmosphere. The apparatus is flushed with nitrogen and charged with 27.8 g. (0.331 mole) of 1-hexene (Note 1) and 150 ml. of anhydrous tetrahydrofuran (Note 2) with a hypodermic syringe, and 103 ml. (0.110 mole) of a 1.07 *M* solution of borane in tetrahydrofuran (Note 3) is added dropwise over a 20-minute period to the stirred solution, while the reaction temperature is maintained below *ca.* 20° with an ice bath. After the

addition, the reaction mixture is stirred for an additional one hour at room temperature. The resulting solution of trihexylborane (Note 4) is ready for use in the next step.

B. *Phenyl heptyl ketone*. To the solution prepared in Section A. is added 18 ml. (1.0 mole) of water. The nitrogen flow is ceased, and the drying tube is quickly replaced with a stopcock attached with Tygon tubing, to a gas-measuring tube. A solution of 14.6 g. (0.100 mole) of diazoacetophenone (Note 5) in 125 ml. of tetrahydrofuran is added to the stirred solution over a period of one hour. After the addition is complete, the mixture is stirred vigorously for one hour at room temperature, then heated to reflux for one hour. The resulting mixture is cooled to approximately 25° with an ice bath (Note 6), (Note 7), and (Note 8). A solution of 73 ml. (0.2 mole) of 3 *N* sodium acetate solution is added, followed by the dropwise addition of 23 ml. (0.22 mole) of 30% hydrogen peroxide, maintaining the reaction temperature below *ca.* 20° (ice-cooling). The cooling bath is then removed, and the mixture is stirred at room temperature for one hour.

The resulting mixture is saturated with sodium chloride. The organic phase is separated, washed with three 50-ml. portions of saturated brine solution, dried over sodium sulfate, and concentrated on a rotary evaporator. Distillation of the residue through a 7-cm. Vigreux column separates 15.34–15.99 g. (75–80%) of phenyl heptyl ketone, b.p. 118–120° (0.60 mm.) n_D^{26} 1.5034 (Note 9).

C. 1-*Hexanol*. To a solution of trihexylborane in a 500-ml. three-necked flask [prepared from 25.3 g. (0.301 mole) of 1-hexane in 150 ml. of tetrahydrofuran and 84 ml. of a 1.20 *M* solution of borane in tetrahydrofuran, as described in Section A] is added 34 ml. (0.1 mole) of a 3 *N* solution of sodium hydroxide. This is followed by the dropwise addition of 36 ml. (0.35 mole) of 30% hydrogen peroxide at a rate such that the reaction temperature is maintained at approximately 35° (water bath). After being stirred at room temperature for one hour, the mixture is poured into 100 ml. of water. The organic phase is separated, and the aqueous phase is extracted with 50 ml. of diethyl ether. The combined organic extracts are washed with three 50-ml. portions of saturated brine solution and dried over Drierite. After the bulk of the solvent is removed by distillation, the residue is fractionated with a 24-in., Teflon spinning band column (Note 10), yielding 7.7–8.2 g. (25.1–26.7%) of 1-hexanol of 95% purity, b.p. 145–153° and 10.1–15.4 g. (33.3–50.3%) of pure 1-hexanol, b.p. 153–155° (Note 11). The total yield of material with >95% purity is 58.4–77%.

D. *Bis*(3-*methyl*-2-*butyl*)*borane (disiamylborane)*.[2] A dry, 500-ml., three-necked flask is equipped as described in Section A. The apparatus is flushed with nitrogen, and the flask is charged with 92 ml. (0.11 mole) of a 1.2 *M* solution of borane in tetrahydrofuran. The flask is cooled with an ice bath before a solution of 15.4 g. (0.220 mole) of 2-methyl-2-butene (Note 12) in 40 ml. of anhydrous tetrahydrofuran is added to the stirred solution over a 30-minute period. After the addition is complete, the reaction mixture is kept below *ca.* 10° for 2 hours. The resulting solution is used directly in the next step.

E. *Addition of disiamylborane to* 1-*octene*. To the solution prepared in Section D is added a solution of 11.2 g. (0.100 mole) of 1-octene (Note 13) in 20 ml. of anhydrous tetrahydrofuran over a 30-minute period, while the reaction temperature is maintained below *ca.* 20°. The ice bath is removed and stirring is continued for one hour at room temperature.

F. 1-*Octanol*. The stirred solution prepared in Section E is cooled below *ca.* 10° with an ice bath, and a solution of 34 ml. (0.1 mole) of 3 *N* sodium hydroxide is introduced. This is followed by the dropwise addition of 36 ml. (0.35 mole) of 30% hydrogen peroxide, added at a rate such that the reaction temperature is maintained between 30–35°. After the addition is complete, the mixture is stirred at room temperature for 1.5 hours. The reaction mixture is then extracted with 100 ml. of ether. The ether extract is washed with four 100-ml. portions of water and dried over Drierite. After removal of solvent on a rotary evaporator, the residue is distilled through a 3-cm. Vigreux column, giving, as a forerun, 9.6–10.5 g. of 3-methyl-2-butanol, b.p. 110–115°, followed by 8.5–9.1 g. (65–70%) of 1-octanol, b.p.

182–186° (Note 14).

2. Notes

1. 1-Hexene (99%), purchased from Aldrich Chemical Company, Inc., was stored over molecular sieves and distilled prior to use.
2. Commercial tetrahydrofuran, purchased from British Drug House (Canada) Ltd. or Fisher Scientific Company, was refluxed over sodium metal, distilled from sodium metal, then redistilled from lithium aluminum hydride under a nitrogen atmosphere. [See *Org. Synth.*, **Coll. Vol. 5**, 976 (1973) for warning regarding the purification of tetrahydrofuran.]
3. A commercial one molar solution of borane in tetrahydrofuran, obtained from Alfa Inorganics, Inc., was standardized by measuring the amount of hydrogen evolved on titration with 40% aqueous ethylene glycol.
4. The trihexylborane solution contains approximately 94% primary and 6% secondary boron-bound alkyl groups.[3,4]
5. Diazoacetophenone was prepared as described in *Org. Synth.*, **Coll. Vol. 6**, 386 (1988).
6. Approximately 95% of the theoretical amount of nitrogen is evolved.
7. GC indicates a 92% yield of product. Using a 10 ft. by 0.25 in. column packed with 20% NPGSE (Neopentyl Glycol Sebacate Ester) suspended on Chromosorb W heated to 235° and a helium flow rate of 60 ml. per minute, the submitters found a retention time of 21 minutes for phenyl heptyl ketone.
8. Distillation of the product from the crude reaction mixture at this stage gives somewhat lower yields. Therefore, residual organoboranes are oxidized prior to isolation of product.
9. 1-Hexanol, 18.5–20.3 g. (78–86%), boiling at approximately 35° (0.75 mm.), is obtained as a forerun. The checkers found that two distillations were required to give a product of >95% purity.
10. A forerun of approximately 1.0 g., b.p. 135–145°, comprised largely of 2-hexanol (75%), is discarded. The submitters used a stainless-steel spinning band column with equivalent results.
11. The product may be analyzed by use of a GC column packed with 20% SF-96 suspended on Chromosorb WAW, 5 ft. by 0.25 in., operated at 105°. Using a helium flow rate of 60 ml. per minute, the submitters found a retention time of 4 minutes.
12. Commercial 2-methyl-2-butene (99%), purchased from Chemical Samples Company, 4692 Kenny Road, Columbus, Ohio 43220, was used as received.
13. 1-Octene (97%), b.p. 122–123°, purchased from the Aldrich Chemical Company, Inc., was stored over molecular sieves and distilled prior to use.
14. The product may be analyzed by using a GC column packed with 20% SF-96 suspended on Chromosorb WAW, 5 ft. by 0.25 in., operated at 140°. Using a helium flow rate of 60 ml. per minute the submitters found a retention time of 3.5 minutes.

3. Discussion

Phenyl heptyl ketone has been prepared by the Friedel-Crafts acylation of benzene with octanoyl chloride.[5] It is also a product of the thermal decomposition of the mixed iron(II) salts of benzoic and octanoic acids.[6]

The present preparation of phenyl heptyl ketone illustrates the formation of a homologated ketone from the reaction of a trialkylborane with an α-diazoketone. It is representative of a fairly general reaction between an organoborane and a stabilized diazo compound, as illustrated in the accompanying equation, yielding the corresponding ketone,[7] diketone,[8] nitrile,[9] ester,[9] or aldehyde.[10]

$$R_3B + N_2CHA \xrightarrow[H_2O]{-N_2} RCH_2A$$

$$A = COCH_3,\ COC_6H_5,\ CO(CH_2)n\ COCHN_2,\ CN,\ CO_2C_2H_5,\ CHO$$

The extent of reaction is conveniently monitored by measuring the quantity of nitrogen evolved. Organoboranes derived from terminal olefins react readily (>90% gas evolution) at room temperature or below, whereas more highly hindered organoboranes react more sluggishly (*ca.* 3–6 hours of reflux) to complete the liberation of nitrogen.

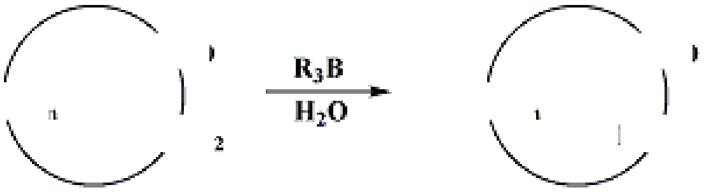
The enol borinate intermediates are rapidly hydrolyzed to product in the presence of water.[10,11] Since neither the organoborane nor diazo compound reacts with water appreciably under the experimental conditions, hydrolysis is conveniently accomplished *in situ* by adding water to the organoborane solution prior to the addition of diazo substrate. Although the product may be isolated from the crude mixture by extraction and distillation, an oxidation step (to convert residual organic boron-containing material to boric acid) is employed, since it gives somewhat higher isolated yields.

An adaptation of the procedure, employing deuterium oxide as the hydrolytic medium, permits the synthesis of α-deuterio ketones and esters in high isotopic purity. α,α-Dideuterio ketones and esters are also produced in high purity using the appropriate α-deuteriodiazocarbonyl precursor.[12]

$$R_3B + N_2CHA \xrightarrow{D_2O} R{-}CH(D){-}A$$

$$A = COCH_3,\ COC_6H_5,\ CO_2C_2H_5$$

A useful extension of the facile, *in situ* hydrolysis is the alkylation of cyclic α-diazo ketones[13] (n = 3,4,5,6). This adaptation obviates the necessity of the several separate (yield-lowering) steps required for the removal of activating or blocking groups by other alkylation methods.[14]



The principal disadvantage of this procedure is that only one alkyl group of the trialkylborane is constructively utilized. The reaction is also sensitive to steric factors. Although yields are excellent for terminal olefins, the reaction becomes more sluggish and yields of ketone decrease progressively as steric effects in the trialkylborane are increased. The method is of limited utility for rare olefins. However, the overall simplicity, mild reaction conditions, and absence of any isomeric contaminants recommend the method for reactions involving rarer diazocarbonyl substrates.

Apart from the oxidation of trihexylborane,[15] 1-hexanol has been prepared by a previous *Organic Syntheses*[16] procedure involving the reaction of ethylene oxide with *n*-butylmagnesium bromide; alternate methods of synthesis are reviewed therein.

The present preparation illustrates the hydroboration[17] of a terminal olefin and the oxidation of the resultant trialkylborane.

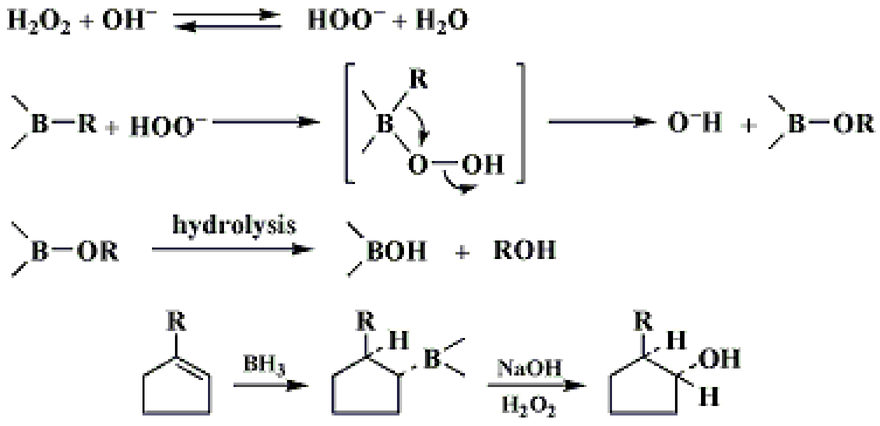
The hydroboration of an olefin involves a *cis* addition of a boron–hydrogen bond to an alkene linkage, and for unsymmetric olefins occurs in an anti-Markownikoff fashion. 1-Alkenes and simple 1,2-disubstituted olefins undergo rapid conversion to the corresponding trialkylborane, whereas addition of diborane to tri- and tetrasubstituted olefins may be conveniently terminated at the respective di- and monoalkylborane stage. 1-Alkenes yield trialkylboranes in which there is a preponderant

(approximately 94%) addition of the boron atom to the terminal carbon.[3,4]

The oxidation of a trialkylborane may be effected by perbenzoic acid or by aqueous hydrogen peroxide in the presence of alkali.[19] A detailed systematic study of the reaction parameters (oxidation temperature, base concentration, hydrogen peroxide concentration) of the latter method has led to the development[3] of a standard and common procedure for oxidising organoboranes, and is illustrated in the present procedure.

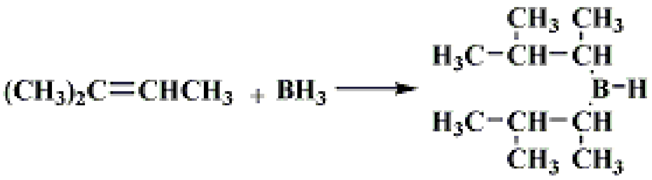
The oxidation step occurs with retention of configuration of the carbon atom undergoing migration. The mechanism is believed to proceed as illustrated in the following equation.[3] As a result, the sequence involving the hydroboration of an olefin followed by treatment with sodium hydroxide–hydrogen peroxide constitutes a useful device for effecting the overall anti-Markownikoff *cis* hydration of an olefin.

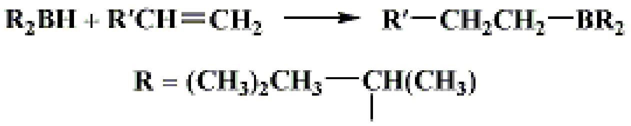
The principal disadvantage of this procedure resides in its application to terminal olefins. Since the hydroboration step produces *ca.* 94% primary boron-bound alkyl groups, the maximum purity of primary carbinol is obviously limited to *ca.* 94%. Isolation of primary alcohol free of the contaminant secondary alcohol requires a tedious, yield-lowering fractionation procedure. This difficulty may be circumvented by employing a more selective hydroborating reagent, disiamylborane, as illustrated in the synthesis of 1-octanol.



1-Octanol has previously been prepared from ethyl caprylate by catalytic hydrogenolysis,[20] and by the Bouveault-Blanc method using sodium and alcohol in toluene.[21] Other preparative methods include the reaction between *n*-hexylmagnesium bromide and ethylene oxide,[22] and the oxidation of trioctylborane.[23]

The hydroboration of a trisubstituted olefin, exemplified by the reaction of 2-methyl-2-butene with diborane, is conveniently stopped at the dialkylborane stage, producing disiamylborane. As a result of its rather large steric requirements this reagent selectively hydroborates terminal olefins, placing *ca.* 99% of the boron atom on the terminal carbon. Consequently, oxidation produces essentially homogeneous 1-alkanol. This procedure is the method of choice for converting terminal olefins to primary alcohols without the accompanying formation of isomers.





The advantages of a hydroboration-oxidation synthesis of alcohols are simplicity of procedure, relatively mild reaction conditions, high overall yields, absence of skeletal rearrangements, and production of a carbinol in which there is an overall *cis* addition of water to a double bond in an anti-Markownikoff sense.

References and Notes

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2. This trivial term, which now finds common usage, was coined as a contraction of the only *sec*-isoamyl structure possible, $(CH_3)_2CHCH(CH_3)$.[3]
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17. Although the term hydroboration is most commonly employed[3,4,14] to denote the addition of a boron–hydrogen linkage to carbon–carbon multiple bonds, it has also been used "for the two-step oxidative process to distinguish it from the process of reduction involving H-B addition and protonolysis."[18]
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Drierite

brine

diborane

disiamylborane

1-hexane

Bis(3-methyl-2-butyl)borane (disiamylborane)

Benzene (71-43-2)

ether, diethyl ether (60-29-7)

sodium acetate (127-09-3)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

toluene (108-88-3)

sodium (13966-32-0)

Ethylene oxide (75-21-8)

ethylene glycol (107-21-1)

hydrogen peroxide (7722-84-1)

1-Hexanol (111-27-3)

n-butylmagnesium bromide (693-03-8)

boric acid (10043-35-3)

borane (7440-42-8)

1-Octanol (111-87-5)

3-methyl-2-butanol (598-75-4)

2-methyl-2-butene (513-35-9)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

ethyl caprylate (106-32-1)

1-hexene (592-41-6)

Diazoacetophenone (3282-32-4)

helium (7440-59-7)

Perbenzoic acid (93-59-4)

1-octene (111-66-0)

deuterium oxide (7789-20-0)

Phenyl heptyl ketone, 1-Octanone, 1-phenyl- (1674-37-9)

Trihexylborane

2-hexanol (626-93-7)

octanoyl chloride (111-64-8)

trioctylborane

n-Hexylmagnesium bromide (3761-92-0)

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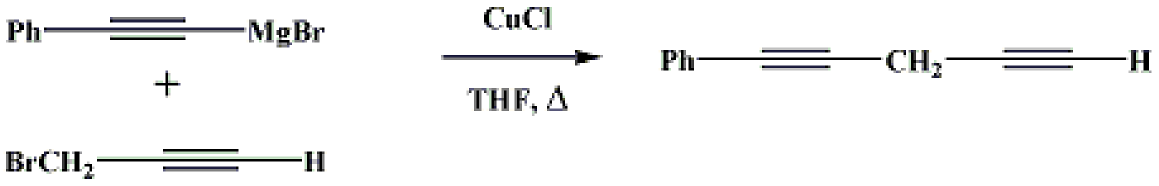
Organic Syntheses, CV 6, 925

1-PHENYL-1,4-PENTADIYNE AND 1-PHENYL-1,3-PENTADIYNE

[Benzene, 1,4-pentadiynyl- and Benzene, 1,3-pentadiynyl-]



Submitted by H. Taniguchi, I. M. Mathai, and Sidney I. Miller[1].
Checked by Marion F. Habibi and Richard E. Benson.

1. Procedure

A. *Phenylethynylmagnesium bromide*. A 1-l., four-necked flask fitted with a sealed mechanical stirrer, a reflux condenser carrying calcium chloride and soda lime tubes, a nitrogen gas inlet, and a dropping funnel is charged with 19 g. (0.81 g.-atom) of magnesium. The flask is flushed with prepurified nitrogen, the stirrer is started, and 109 g. of ethyl bromide (1.00 mole) in 350 ml. of anhydrous tetrahydrofuran (Note 1) is added. After the magnesium has dissolved (Note 2), 102 g. (1.00 mole) of phenylacetylene (Note 3) in 150 ml. of tetrahydrofuran is added over a period of *ca.* 30 minutes at a rate that maintains a gentle reflux (Note 4). The reaction mixture is then heated at reflux for *ca.* 1.5 hours (Note 5).

B. 1-*Phenyl*-1,4-*pentadiyne*. Anhydrous copper(I) chloride (2 g.) is added to the flask, and heating under reflux is continued for 20 minutes. At this point 96 g. (0.81 mole) of propargyl bromide in 120 ml. of tetrahydrofuran (Note 1) and (Note 6) is added over 30–40 minutes at a rate that maintains a gentle reflux. The mixture, containing a yellow solid, is heated another 30–40 minutes, allowed to cool to ambient temperature, and poured slowly into 2 l. of ice-water slush containing 50 ml. of concentrated sulfuric acid. The whole mixture, which should be acidic at this point, is stirred thoroughly and extracted five times with 200-ml. portions of diethyl ether (Note 7). The ether extracts are combined and washed with 100-ml. portions of water until the water layer is no longer acidic to litmus paper (3–4 washings are usually required). The ether layer is dried over magnesium sulfate overnight, separated from the desiccant, and concentrated by distillation.

The product is distilled under nitrogen using a 25-cm. Vigreux column (Note 8) and (Note 9). After removal of unreacted propargyl bromide and phenylacetylene, 51–64 g. (45–57%) of 1-phenyl-1,4-pentadiyne is collected as the main fraction, b.p. 64–66° (0.45 mm.), n_D^{25} 1.5713 (Note 9) and (Note 10). The colorless product is best stored under nitrogen at *ca.* −78°. The ^{1}H NMR spectrum (60 mHz., neat, external tetramethylsilane reference) shows peaks at δ

1.76 (t, 1H), 2.92 (d, 2H), and 6.87 (m, 5H) (Note 11).

C. *1-Phenyl-1,3-pentadiyne*. A flask containing a magnetic stirrer and a solution of 2 g. of sodium hydroxide in 50 ml. of ethanol is flushed with nitrogen, and 10 g. (0.071 mole) of 1-phenyl-1,4-pentadiyne is added. The flask is stoppered, and the contents are stirred for *ca.* 2 hours. The brown solution is then poured into 200 ml. of water, and the mixture extracted four times with 50-ml. portions of ether. The extracts are combined and washed with two 50-ml. portions of water. The ether layer is dried over magnesium sulfate, filtered, and concentrated by distillation. The product is distilled as described in Part B, yielding 5.4–7.5 g. (54–75%) of 1-phenyl-1,3-pentadiyne as a colorless oil, b.p. 62° (0.15 mm.), n_D^{25} 1.6324. The ^{1}H NMR spectrum (60 mHz., neat, external tetramethylsilane reference) shows peaks at δ 1.47 (s, 3H) and 6.87 (m, 5H) (Note 11).

2. Notes

1. Reagent grade tetrahydrofuran available from Fisher Scientific Company was used by the checkers. For warning regarding the purification of tetrahydrofuran see *Org. Synth.*, **Coll. Vol. 5**, 976 (1973).
2. The flask may be warmed to hasten the dissolution of magnesium.
3. Phenylacetylene was distilled under nitrogen, b.p. 91–92° (17.5 mm.).
4. An ice-water bath should be kept at hand to cool the flask should the refluxing become too vigorous.
5. If the reaction is slow, the solution is kept at reflux overnight under an atmosphere of nitrogen. More tetrahydrofuran (50 ml.) may be added if stirring becomes difficult. It is desirable that procedure B follow A as soon as possible.
6. Propargyl bromide was redistilled, b.p. 82–83°.
7. The diyne discolors at room temperature and on exposure to air. Therefore, it is desirable to proceed without delay in the workup steps.
8. The checkers found it advantageous to do a crude preliminary distillation using a vapor-bath still. The resulting distillate can be redistilled using a spinning band column. This procedure appeared to avoid an exothermic reaction that occurred when the bath temperature rose above 110° (Note 9).
9. After the 1,4-diyne has distilled, overheating the pot contents is to be avoided since an exothermic reaction can occur.
10. The checkers observed yields of 44–50%, conducting the reaction on a scale one-half that described here.
11. Where they differ from those reported previously,[2] the values of the physical properties are those obtained by the checkers.

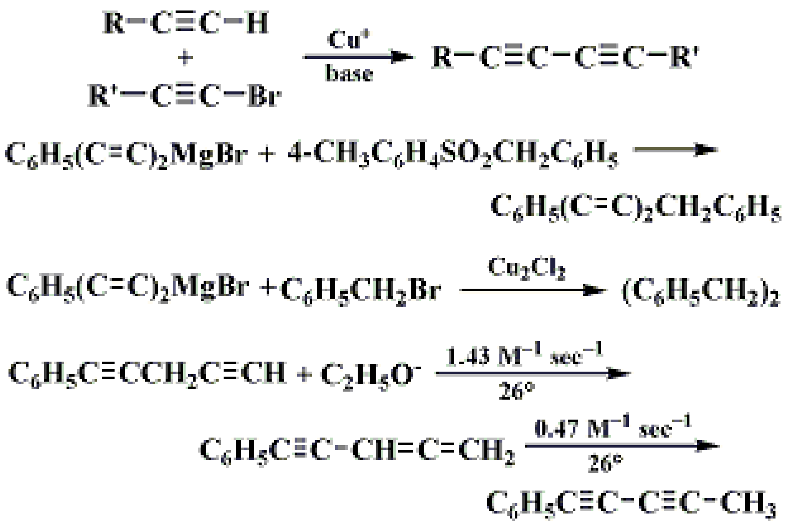
3. Discussion

The synthetic route described here has been used for various "skipped" diynes and related 1,3-diynes, among which are precursors or analogs of naturally occurring polyynes.[2] The copper (I) chloride-promoted coupling reaction in tetrahydrofuran provides the best and often the sole route to 1,4-diynes.[2] From these it is simple to proceed to the 1,3-diyne and, possibly, the isomeric allene.[2,3] Because all of these compounds appear to be sensitive to heat and oxygen the relatively mild reaction conditions are noteworthy.

1-Phenyl-1,4-pentadiyne has been prepared by coupling in tetrahydrofuran without a copper chloride catalyst in 22% yield,[4] and in ether with a copper chloride catalyst in 28% yield.[5] In general, the coupling of propargyl halides with various metallic acetylides, *e.g.*, sodium, silver, gives 1,4-pentadiynes in low yields at best.[2] For example, 1,4-pentadiyne was prepared from propargyl bromide and acetylenemagnesium bromide in tetrahydrofuran in 20% yield.[6] Strongly basic reactants such as alkali acetylides or basic conditions for workup and purification, *e.g.*, column chromatography over alumina, promote the isomerization of the 1,4-diyne.[2,3] The evolution of the present method, which emphasizes the use of tetrahydrofuran as solvent, a copper(I) salt, a short coupling time, and neutral reaction and workup conditions, has been described in detail.[2]

1-Phenyl-1,3-pentadiyne has been prepared by the dehydrobromination of the corresponding butadiene tetrabromide.[7] Other unsymmetrical 1,3-diynes have been prepared, as described in scheme 1.[8] It is, of course, typical of crossed-coupling reactions that some should proceed as desired in (2),[2] and that others should go astray, as in (3).[2] The conversion of 1,4- to 1,3-diynes by strong base in ethanol or methanol at reflux has been described.[4,5] As judged by the isomerization rates in sodium ethoxide–ethanol, heating appears to be unnecessary. Typical rate constants are given in (4).[3]

The present route to conjugated diynes is the method of choice *if* the corresponding skipped diyne or allene is available.[2,3] With naturally occurring polyynes this is often the case. Depending on the 1,4-diyne, the base-catalyzed isomerization may be successfully stopped (by acidification), yielding the intermediate allenylacetylene. Since the isolation of the allene may or may not be desired, it seems prudent to monitor the progress of isomerization of new 1,4-diynes, *e.g.*, by ^{1}H NMR, and establish the approximate lifetimes of transient species. In this way allenes as well as conjugated diynes may be obtained.[3]



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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

sulfuric acid (7664-93-9)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

magnesium (7439-95-4)

Ethyl bromide (74-96-4)

oxygen (7782-44-7)

nitrogen (7727-37-9)

sodium ethoxide (141-52-6)

copper(I) chloride (7758-89-6)

copper chloride (7758-89-6)

Phenylacetylene (536-74-3)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

phenylethynylmagnesium bromide

propargyl bromide (106-96-7)

1-Phenyl-1,4-pentadiyne, Benzene, 1,4-pentadiynyl- (6088-96-6)

1-Phenyl-1,3-pentadiyne, Benzene, 1,3-pentadiynyl- (4009-22-7)

acetylenemagnesium bromide

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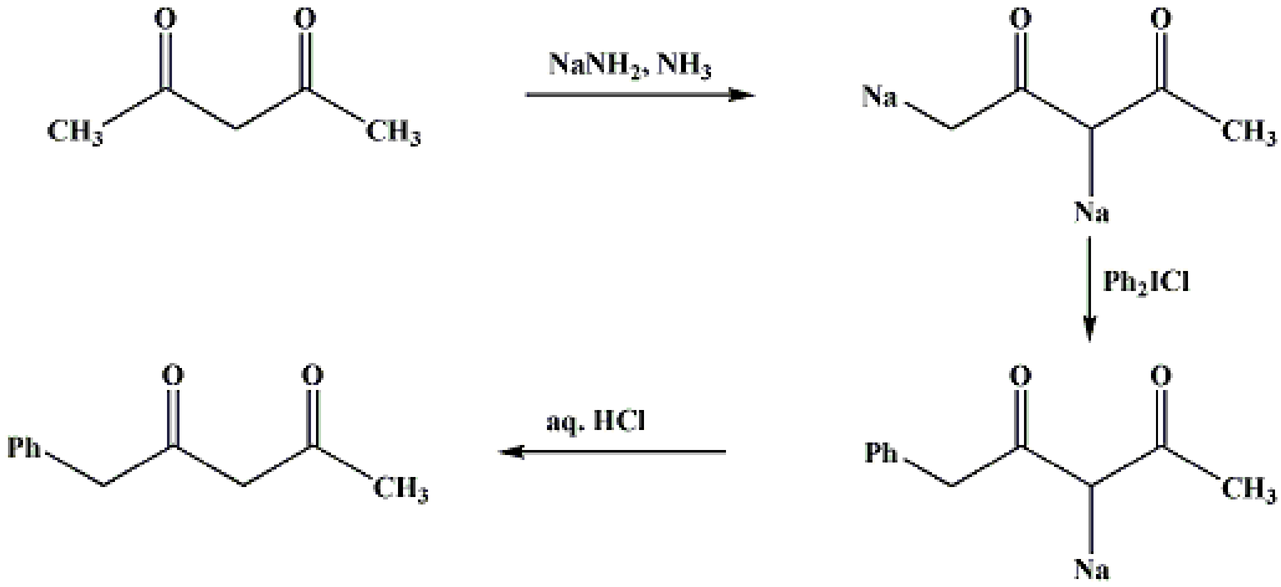
Organic Syntheses, CV 6, 928

PHENYLATION WITH DIPHENYLIODONIUM CHLORIDE: 1-PHENYL-2,4-PENTANEDIONE

[2,4-Pentanedione, 1-phenyl-]



Submitted by K. Gerald Hampton[1], Thomas M. Harris[2], and Charles R. Hauser[3].
Checked by William N. Washburn and Ronald Breslow.

1. Procedure

Caution! This preparation should be carried out in an efficient hood to avoid exposure to ammonia.

A 1-l., three-necked flask is equipped with an air condenser (Note 1), a ball-sealed mechanical stirrer, and a glass stopper. The stopper is removed, and 800 ml. of anhydrous liquid ammonia is introduced from a cylinder through an inlet tube. The tube is removed and replaced by the stopper. A small piece of sodium is added to the stirred ammonia. After the appearance of a blue color a few crystals of iron(III) nitrate hydrate (about 0.25 g.) are added, followed by small pieces of freshly cut sodium until 18.4 g. (0.800 g.-atom) has been added. After the formation of sodium amide is complete (Note 2), the glass stopper is replaced with a pressure-equalizing dropping funnel containing 40.0 g. (0.400 mole) of 2,4-pentanedione (Note 3) in 30 ml. of anhydrous diethyl ether. The top of the addition funnel is fitted with a nitrogen inlet tube. The reaction flask is immersed at least 3 inches into an acetone–dry ice bath (Note 4), and the slow introduction of dry nitrogen through the inlet tube is begun simultaneously. After the reaction mixture is cooled thoroughly (about 20 minutes), the 2,4-pentanedione solution is added in small portions (Note 4) over 10 minutes. The cooling bath is removed, and the nitrogen flow is stopped. After 30 minutes the addition funnel is removed, and 63.3 g. (0.200 mole) of diphenyliodonium chloride (Note 5) is added through Gooch tubing from an Erlenmeyer flask over 15–25 minutes (Note 6). The reaction mixture is stirred for 6 hours, during which time the ammonia gradually evaporates. The Gooch tubing is replaced with an

addition funnel, and 400 ml. of anhydrous ether is added. The remaining ammonia is removed by cautious heating on a warm-water bath. After the ether has distilled gently for 15 minutes, the flask is cooled in an ice-water bath, and 200 g. of crushed ice is added. A mixture of 60 ml. of concentrated hydrochloric acid and 10 g. of crushed ice is then added. The reaction mixture is stirred until the solid material has dissolved (Note 7) and transferred to a separatory funnel, the flask being washed with a little ether and dilute hydrochloric acid. The ethereal layer is separated, and the aqueous layer (Note 8) and (Note 9) is shaken three times with 50-ml. portions of ether. The combined ethereal extracts are dried over anhydrous magnesium sulfate. After filtration and removal of the solvent, the residual oil is purified by vacuum distillation, giving 21.0–22.5 g. (60–64%) (Note 10) of 1-phenyl-2,4-pentanedione, b.p. 133–136° (10 mm.), as a colorless to light yellow liquid (Note 11).

2. Notes

1. The flask is insulated with cloth towels to reduce the rate of ammonia evaporation. In addition the towels exclude light, thus reducing the photolytic production of iodine from diphenyliodonium chloride and the reaction products.
2. Conversion to sodium amide is indicated by the disappearance of the blue color. This generally requires about 20 minutes.
3. 2,4-Pentanedione, obtained from Aldrich Chemical Company, Inc., was dried over potassium carbonate and distilled before use, the fraction b.p. 133–135° being used.
4. The addition of 2,4-pentanedione to liquid ammonia is highly exothermic. Also, ammonia vapor reacts with the β-diketone, producing an insoluble ammonium salt which tends to clog the tip of the addition funnel. Cooling the reaction mixture in an acetone–dry ice bath reduces the vigor of the reaction and minimizes the clogging of the addition funnel. The 2,4-pentanedione should be added in spurts which fall on the surface of the reaction mixture rather than on the wall of the flask.
5. Diphenyliodonium chloride prepared by the method of Beringer and co-workers was used,[4] but it can also be prepared by the method described in *Org. Synth.*, **Coll. Vol. 3**, 355 (1955), or may be purchased from Aldrich Chemical Company, Inc.
6. If the addition is too fast, the reaction mixture will foam out of the flask.
7. A little diphenyliodonium salt may remain which will not dissolve. It will settle between the layers.
8. The aqueous layer should be acidic to litmus paper. If it is basic, more hydrochloric acid should be added until an acidic test is obtained.
9. The ethereal solution is usually dark, but should not have a purple color. A purple color indicates the presence of iodine. Iodine can arise by a light-catalyzed reaction in the latter stages of the reaction and during isolation of the product. For this reason the reaction should be shielded from strong light. In addition it is advisable for the ether employed in the reaction mixture to be peroxide-free. If iodine is present in the reaction product, it must be removed by extraction with aqueous sodium thiosulfate solution, since an adequate separation is not obtained by distillation.
10. The submitters have obtained the product in yields as high as 92% by a similar procedure and 85–91% by this procedure on this scale. The yield is calculated with the assumption that only one of the phenyl groups of diphenyliodonium ion is available for phenylation. This is not rigorously true; however, the magnitude of error is not great.[5]
11. A forerun of 2,4-pentanedione and iodobenzene, b.p. 32–92° (35 mm.), is obtained before the pressure is reduced to 10 mm. The purity of the product may be demonstrated

by GC at 130° using a 180-cm. column packed with silicone gum rubber (Hewlett-Packard Co.). The chromatogram obtained showed only traces of iodobenzene and 3-phenyl-2,4-pentanedione.

3. Discussion

The method described is that of Hampton, Harris, and Hauser[5] and is an improvement over the benzyne method, which gives poor yields.[5,6] This β-diketone has been prepared by Claisen condensation of ethyl phenylacetate with acetone,[7] but the yield is poorer and the product has been shown by GC to be impure.[5] The β-diketone has also been prepared by hydrolysis of 4-methoxy-5-phenyl-3-penten-2-one[8] and by hydrolysis and decarboxylation of ethyl 1-acetyl-2-oxo-3-phenylbutyrate[9] but these compounds are more difficult to obtain than the starting materials used in the present synthesis.

This procedure represents a novel, convenient, and fairly general method of preparing γ-aryl-β-diketones. By this method the submitters have phenylated the dianion of 1-phenyl-1,3-butanedione (61%), 2,4-heptanedione (98%), 2,4-nonanedione (78%), 2,4-tridecanedione (53%), and 3,5-heptanedione (50%).[5] Substituted diaryliodonium salts have also been used to produce 1-(4-chlorophenyl)-2,4-pentanedione (44%), 4-(4-methylphenyl)-1-phenyl-1,3-butanedione (44%), and 1-(4-methylphenyl)-2,4-nonanedione (21%).[5] Under these conditions no more than a trace, if any, of arylation at the α-position of the β-diketones was observed by GC analysis.

Although the phenylation of monoanions of β-diketones does not proceed at a significant rate under the present conditions, phenylation of monoanions using diphenyliodonium salts under somewhat more vigorous conditions has been observed. The monoanions of 5,5-dimethyl-1,3-cyclohexanedione,[10,11] dibenzoylmethane,[10] tribenzoylmethane,[10] 1,3-indandione,[12] 2-mesityl-1,3-indandione,[13] and 2-phenyl-1,3-indandione[12] have been phenylated to give the mono- or diphenylated products. Keto esters such as ethyl 1,3-indandione-2-carboxylate,[12] ethyl cyclohexanone-2-carboxylate,[14] and other esters such as ethyl phenylacetate,[14] ethyl diphenylacetate,[14] diethyl acetamidomalonate,[14] diethyl ethylmalonate,[14] diethyl phenylmalonate,[14] and diethyl malonate[15] have been arylated in fair to good yields. Kornblum and Taylor have also found that nitroalkanes can be phenylated in 54–69% yield. These include 1-nitropropane, 2-nitropropane, 2-nitrobutane, 2-nitroöctane, nitrocyclohexane, and ethyl 1-nitrocaproate.[16]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

benzyne (71-43-2)

ether, diethyl ether (60-29-7)

sodium thiosulfate (7772-98-7)

nitrogen (7727-37-9)

iodine (7553-56-2)

acetone (67-64-1)

sodium (13966-32-0)

Dibenzoylmethane (120-46-7)

diethyl malonate (105-53-3)

Ethyl phenylacetate (101-97-3)

Iodobenzene (591-50-4)

magnesium sulfate (7487-88-9)

5,5-Dimethyl-1,3-cyclohexanedione (126-81-8)

diethyl phenylmalonate (83-13-6)

sodium amide (7782-92-5)

ethyl cyclohexanone-2-carboxylate (1655-07-8)

2,4-pentanedione (123-54-6)

1-phenyl-1,3-butanedione (93-91-4)

diethyl ethylmalonate (133-13-1)

2-nitropropane (79-46-9)

iron(III) nitrate hydrate

Diethyl acetamidomalonate (1068-90-2)

1-nitropropane (108-03-2)

2,4-Nonanedione (6175-23-1)

2,4-tridecanedione

diphenyliodonium chloride (1483-72-3)

3-phenyl-2,4-pentanedione (5910-25-8)

1-Phenyl-2,4-pentanedione, 2,4-Pentanedione, 1-phenyl- (3318-61-4)

4-methoxy-5-phenyl-3-penten-2-one

ethyl 1-acetyl-2-oxo-3-phenylbutyrate

2,4-heptanedione (7307-02-0)

3,5-heptanedione (7424-54-6)

1-(4-chlorophenyl)-2,4-pentanedione

4-(4-methylphenyl)-1-phenyl-1,3-butanedione

1-(4-methylphenyl)-2,4-nonanedione

tribenzoylmethane (641-44-1)

1,3-indandione (606-23-5)

2-mesityl-1,3-indandione

2-phenyl-1,3-indandione (83-12-5)

ethyl 1,3-indandione-2-carboxylate

ethyl diphenylacetate

2-nitrobutane (600-24-8)

nitrocyclohexane (1122-60-7)

ethyl 1-nitrocaproate

2-nitrooctane

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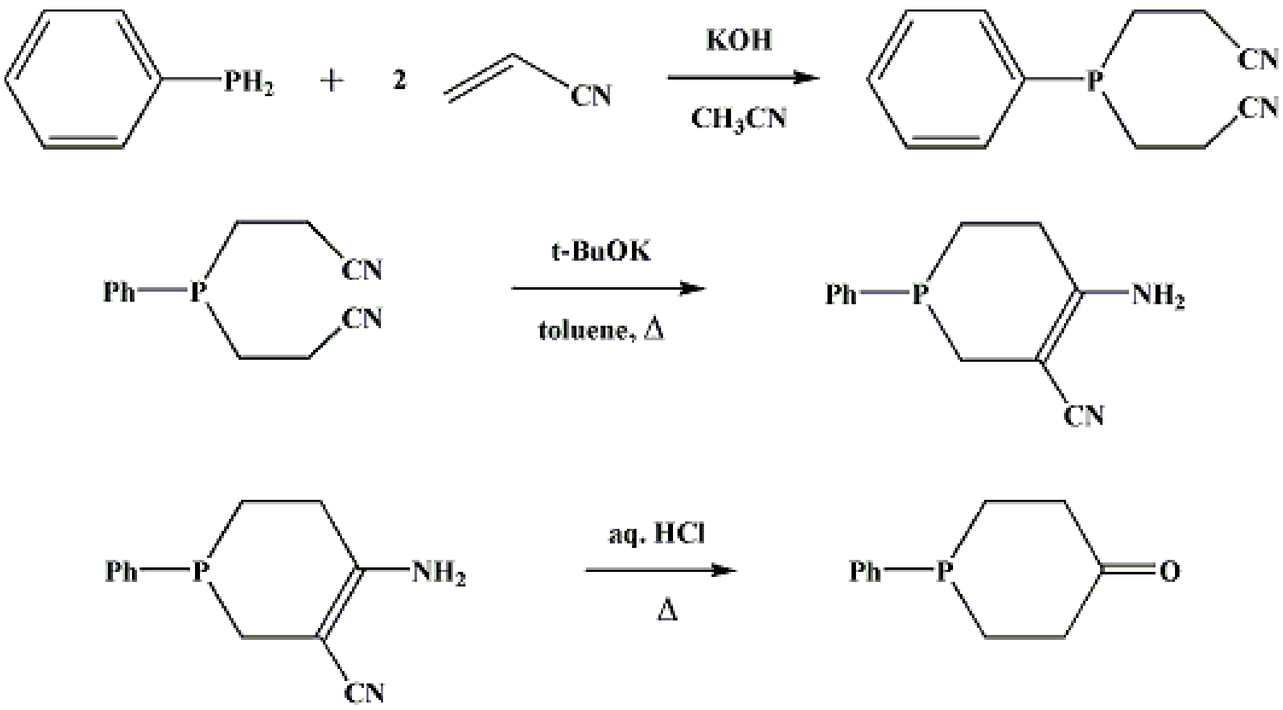
Organic Syntheses, *CV 6, 932*

1-PHENYL-4-PHOSPHORINANONE

[4-Phosphorinanone, 1-phenyl-]



Submitted by Theodore E. Snider, Don L. Morris, K. C. Srivastava, and K. D. Berlin[1].
Checked by John R. Berry and Richard E. Benson.

1. Procedure

A. *Bis(2-cyanoethyl)phenylphosphine.* A 250-ml., three-necked flask is equipped with a magnetic stirrer, a thermometer, a pressure-equalizing dropping funnel, and a reflux condenser, with the entire system flushed with nitrogen. To the flask is added under an atmosphere of nitrogen 50.0 g. (0.454 mole) of phenylphosphine (Note 1), 50 ml. of acetonitrile, and 10 ml. of 10 *N* potassium hydroxide (Note 2). An ice-water bath is prepared for immediate cooling of the reaction flask. To the reaction mixture is added dropwise 50.0 g. (0.943 mole) of acrylonitrile (Note 3) with stirring and cooling over a period of 45–60 minutes. The rate of addition is controlled so that the temperature of the solution never exceeds 35° (Note 4). After the addition is complete, the solution is stirred at room temperature for an additional 2.5 hours. The reaction mixture is diluted with 100 ml. of ethanol and chilled to 0°. The product starts to crystallize, and the mixture is allowed to stand until crystallization is complete. The heavy slurry is filtered, and the crystalline product is washed with 200 ml. of cold ethanol and dried at 60° (2 mm.), yielding 74–84 g. (76–86%) of bis(2-cyanoethyl)phenylphosphine, m.p. 71–74° (Note 5). An additional 5–9 g. of product may be recovered from the combined washings and filtrate by concentration of the solution with subsequent chilling, bringing the total yield to 79–91 g. (80–93%).

B. 4-*Amino*-1,2,5,6-*tetrahydro*-1-*phenylphosphorin*-3-*carbonitrile.* A nitrogen-flushed, 1-l., three-necked flask equipped with a mechanical stirrer, a pressure-equalizing addition funnel, and a reflux condenser is charged with 25 g. (0.22 mole) of potassium *tert*-butoxide (Note 6) and 200 ml. of toluene (Note 7). The mixture is heated to reflux, and a solution of 43.2 g. (0.200 mole) of bis(2-cyanoethyl)phenylphosphine in 400 ml. of toluene is added dropwise with stirring over a period of

40–50 minutes (Note 8). After the addition is complete, the mixture is stirred and heated at reflux for an additional 3 hours. The mixture is cooled to room temperature, 250 ml. of water is added, and the resulting mixture is stirred for 30 minutes while the product is washed with two 50-ml. portions of cold ethanol and dried at 78° (1 mm.), yielding 36–38 g. (84–88%) of 4-amino-1,2,5,6-tetrahydro-1-phenylphosphorin-3-carbonitrile, m.p. 134.5–137° (Note 9). A small amount of product can be recovered from the filtrate (Note 10).

C. 1-*Phenyl*-4-*phosphorinanone.* A solution of 35 g. (0.16 mole) of 4-amino-1,2,5,6-tetrahydro-1-phenylphosphorin-3-carbonitrile in 400 ml. of 6 *N* hydrochloric acid is heated at a vigorous reflux under nitrogen for 30 hours in a 1-l., three-necked flask equipped with a mechanical stirrer and a reflux condenser (Note 11). The mixture is then cooled with an ice bath, and 300 ml. of cold 10 *N* potassium hydroxide is added with stirring over a period of 10 minutes (Note 12). The resulting solution is stirred an additional 10 minutes (Note 13) and extracted with 300 ml. of diethyl ether. The ether layer is separated and washed two times with 100-ml. portions of water, then dried. The solvent is removed by distillation using a rotary evaporator, and the resulting oil crystallizes on standing, giving 23–26 g. of crude product, m.p. 38–43°. Distillation through a short-path column yields 21.5–21.7 g. (68–69%) of pure 1-phenyl-4-phosphorinanone, m.p. 43.5–44°, b.p. 120–122° (0.02 mm.) (Note 14).

2. Notes

1. Phenylphosphine is available from Pressure Chemical Company and Strem Chemicals Inc., and best stored in a dry box under nitrogen. The compound is extremely air sensitive and malodorous. The container should be handled in the hood while wearing rubber gloves. Satisfactory preparations of phenylphosphine have been described.[2]
2. Potassium hydroxide solution is prepared by adding 5.6 g. of potassium hydroxide to sufficient water, giving a final volume of 10 ml.
3. Practical grade acetonitrile, available from Eastman Organic Chemicals, is satisfactory.
4. The optimum reaction temperature is approximately 30°. A yellow product results at higher reaction temperatures, while lower reaction temperatures lead to an uncontrollable reaction resulting from the base-initiated polymerization of acrylonitrile.
5. This product is of satisfactory purity for the next step. If a purer product is desired, bis(2-cyanoethyl)phenylphosphine may be recrystallized from hot ethanol or distilled, b.p. 215–223° (0.2 mm.).[3] The IR adsorption maxima (KBr), $cm.^{-1}$, occur at 3086, 2242, 1481, 1429, 1333, 750, 716, and 694. ^1H NMR spectrum ($CDCl_3$) shows complex multiplets centered at δ 7.2 (8H) and 7.6 (5H). The ^{31}P NMR spectrum (40.5 MHz, C_2H_5OH) has a signal at −21.4 p.p.m. relative to 85% phosphoric acid.
6. Potassium *tert*-butoxide is available from MSA Research Corp.
7. Reagent grade toluene was dried by standing over sodium ribbon.
8. The reaction mixture becomes quite viscous when the addition is about two-thirds complete.
9. The product, as isolated, is pure enough for conversion to 1-phenyl-4-phosphorinanone. If a higher degree of purity is desired, the product may be recrystallized from ethanol–water or chromatographed on alumina. IR absorption maxima (KBr), cm^{-1} occur at 3401, 3344, 3236, 2874, 2169, 1642, 1603, 1399, 1323, 1188, 830, 781, 737, and 690. The ^1H NMR spectrum ($CDCl_3$, containing a small amount of dimethylsulfoxide-d_6) shows peaks at δ 1.8–3.0 (m, 2H), 5.15 (broad s, 2H), and 7.4–7.8 (m, 5H).
10. A small amount of product can be recovered from the filtrate by extracting the water layer with chloroform.

11. A white precipitate forms in the reaction medium after approximately 6 hours of reaction time. This precipitate may be the hydrochloride salt of 1-phenyl-4-phosphorinanone, m.p. >200°.
12. Rapid addition of base seems to result in higher yields than a more cautious addition, even though the temperature of the solution increases to about 40°. The solution must be strongly basic for efficient extraction.
13. Impure 1-phenyl-4-phosphorinanone may crystallize at this point. If crystallization occurs, the solid is recovered by filtration and washed thoroughly with two 20-ml. portions of water. The material is dried in a desiccator over phosphorus pentoxide, giving a product of m.p. 42.5–44°. To obtain a product satisfactory for distillation, the checkers found it necessary to dissolve the material in ether and wash it with water before distillation.
14. GC analysis of the product on a column containing 10% SE-30 on acid-washed Chromosorb U indicated one component, injected as a 20% solution in ethanol at 230° and helium flow of 15 ml. per minute with a retention time of 760 seconds. The ^{1}H NMR spectrum ($CDCl_3$) shows multiplets centered at δ 2.4 (8H) and 7.4 (5H). IR absorption maxima (KBr), cm^{-1}, occur at 3077 (=CH), 2976 and 2924 (CH), 1704 (C=O), 1595 and 1486 (aromatic C=C), 1433 (P-phenyl), 754 and 701 (monosubstituted phenyl). The ^{31}P NMR spectrum (40.5 MHz., $CHCl_3$) shows a signal at −39.3 p.p.m. relative to 85% phosphoric acid.

3. Discussion

This reaction sequence illustrates a broadly applicable synthetic route to a functionalized phosphorus heterocycle and has been utilized for the synthesis of 1-phenyl-,[4,5] 1-ethyl-,[4] and 1-methyl-4-phosphorinanone.[6]

The cyanoethylation of phenylphosphine has been carried out in the presence of a basic catalyst,[3] and at high temperature.[7,8] (2-Cyanoethyl)phenylphosphine has been reported as a contaminant but this difficulty has not been observed in the procedure reported herein.

The intermediates, bis(2-cyanoethyl)phenylphosphine and 4-amino-1,2,5,6-tetrahydro-1-phenylphosphorin-3-carbonitrile, are easily isolated and characterized, and show little or no oxidation when exposed to the air. 1-Phenyl-4-phosphorinanone is a highly-crystalline material, more sensitive to air oxidation than its two precursors. However, 1-phenyl-4-phosphorinanone may be stored in a well-capped bottle for several months without appreciable oxidation. It is best stored in a dark bottle in a dry box under nitrogen.

An extension of this type of synthetic sequence is illustrated by the cyclization of 2-cyanoethyl(2-cyanophenyl)phenylphosphine to the corresponding 2-enaminenitrile followed by hydrolysis with acid, yielding 2,3-dihydro-1-phenyl-4(1*H*)phosphinolinone.[9] The only other reported synthesis of this class of compounds involves the addition of phenylphosphine to substituted divinyl ketones.[10,11]

Phosphorinanones have been utilized as substrates for the preparation of alkenes,[12] amines,[13] indoles,[5,14] and in the synthesis of a series of secondary and tertiary alcohols *via* reduction,[10] and by reaction with Grignard[6,12] and Reformatsky[12,15] reagents. Phosphorinanones have also been used as precursors to a series of 1,4-disubstituted phosphorins.[16] The use of 4-amino-1,2,5,6-tetrahydro-1-phenylphosphorin-3-carbonitrile for the direct formation of phosphorino[4,3-*d*]

pyrimidines has been reported.[17] The ^{13}C NMR spectra of 1-phenylphosphorinanone has been reported.[18]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 362

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ether, diethyl ether (60-29-7)

acetonitrile (75-05-8)

chloroform (67-66-3)

PHOSPHORUS (7723-14-0)

nitrogen (7727-37-9)

potassium hydroxide (1310-58-3)

toluene (108-88-3)

sodium (13966-32-0)

acrylonitrile (107-13-1)

helium (7440-59-7)

phenylphosphine (638-21-1)

1-Phenyl-4-phosphorinanone, 4-Phosphorinanone, 1-phenyl- (23855-87-0)

bis(2-cyanoethyl)phenylphosphine (15909-92-9)

4-Amino-1,2,5,6-tetrahydro-1-phenylphosphorin-3-carbonitrile (84819-76-1)

1-methyl-4-phosphorinanone

(2-Cyanoethyl)phenylphosphine

2-cyanoethyl(2-cyanophenyl)phenylphosphine

phosphorus pentoxide (1314-56-3)

potassium tert-butoxide (865-47-4)

2,3-dihydro-1-phenyl-4(1H)phosphinolinone

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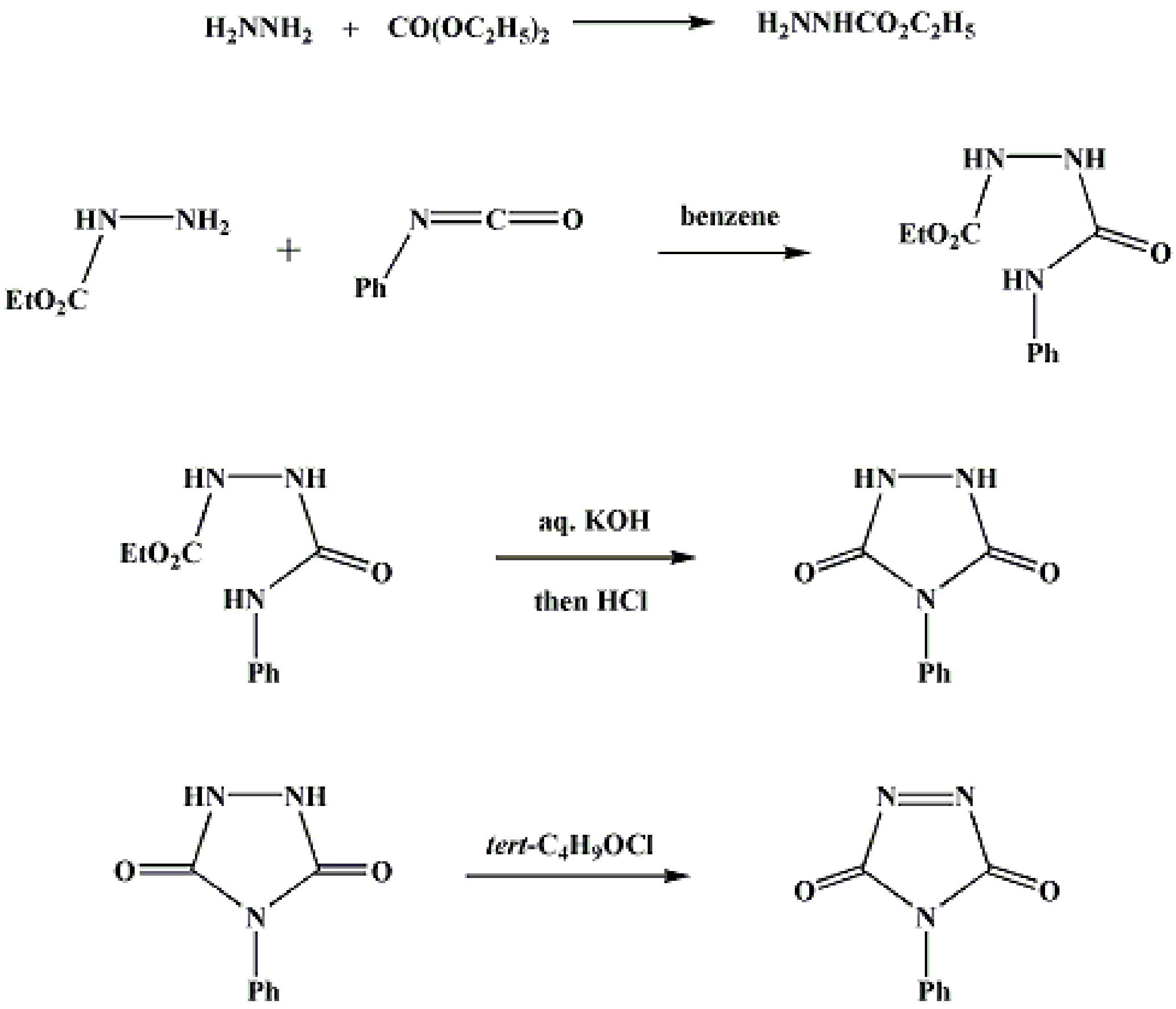
Organic Syntheses, CV 6, 936

4-PHENYL-1,2,4-TRIAZOLINE-3,5-DIONE

[3*H*-1,2,4-Triazole-3,5(4*H*)-dione, 4-phenyl-]



Submitted by R. C. Cookson[1], S. S. Gupte, I. D. R. Stevens, and C. T. Watts.
Checked by Y. Chao and R. Breslow.

1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A. *Ethyl hydrazinecarboxylate.* To 100 g. (96.9 ml., 2.00 moles) of 100% hydrazine hydrate, contained in a 1-l., round-bottomed flask, is added 236 g. (243 ml., 2.00 moles) of diethyl carbonate (Note 1). The flask is fitted with a calcium chloride-containing drying tube and shaken vigorously, mixing the two liquids. After about 5 minutes, the milky emulsion becomes warm, and shaking is continued until a clear solution is obtained

(approximately 20 minutes). The flask is equipped with a reflux condenser fitted with a calcium chloride-containing drying tube and heated on a steam bath for 3.5 hours. The reaction mixture is transferred to a 500-ml., round-bottomed flask and is distilled through a 15-cm. Vigreux column under reduced pressure, yielding 161–176 g. (77–85%) of a colorless liquid collected at 102–103° (18 mm.) or 117–118° (40 mm.) (Note 2), n_D^{22} 1.4495; IR cm^{-1} 1640, 1725, 3350. The product, which may crystallize on standing, m.p. 45–47°, need not be purified for the next step.

B. *4-Phenyl-1-carbethoxysemicarbazide.* A 1-l., three-necked, round-bottomed flask equipped with a liquid-sealed mechanical stirrer (Note 3), a constant-pressure dropping funnel, and a reflux condenser fitted with a drying tube containing silica gel is charged with a solution of 52 g. (0.50 mole) of ethyl hydrazinecarboxylate in 550 ml. of dry benzene (Note 4). After the solution is cooled with an ice bath, stirring is begun and 59.7 g. (54.5 ml., 0.501 mole) of phenyl isocyanate is added dropwise to the solution over a 45-minute period. After about one-half of the isocyanate has been added, a white precipitate of the product appears, and the reaction mixture becomes progressively thicker. After addition is complete the ice bath is removed; the mixture is stirred at room temperature for 2 hours, then heated under reflux for 2 hours. The suspension is allowed to cool to room temperature, and 4-phenyl-1-carbethoxysemicarbazide is isolated by suction filtration, washed with 500 ml. of benzene, and dried in a vacuum desiccator, yielding 108 g. (97%) of 4-phenyl-1-carbethoxysemicarbazide, m.p. 151–152°. The product is not further purified for use in the next step, but may be recrystallized from ethyl acetate to yield white crystals, m.p. 154–155°; IR cm.$^{-1}$ 1645, 1687, 1797, and 3300 (Note 6).

C. *4-Phenylurazole.* A 250-ml. Erlenmeyer flask is charged with 100 ml. of aqueous 4 *M* potassium hydroxide and 44.6 g. (0.200 mole) of 4-phenyl-1-carbethoxysemicarbazide. The suspension is warmed on a steam bath, the flask being swirled occasionally to wash the solid off the sides. After 1.5 hours most of the solid has dissolved, and the hot solution is filtered. After cooling to room temperature, the solution is acidified with concentrated hydrochloric acid (about 33 ml. is required). The mixture is again cooled to room temperature and the precipitated 4-phenylurazole is isolated by suction filtration. The mother liquor is evaporated to dryness on a rotary evaporator, and the residue is extracted twice with 100-ml. portions of boiling absolute ethanol (Note 7). The ethanol solutions are combined, filtered, and evaporated to dryness on a rotary evaporator, and the additional 4-phenylurazole recovered is combined with that obtained above. The product is crystallized from 95% ethanol (about 80 ml.), yielding 30.0–33.5 g. (85–95%) of 4-phenylurazole, m.p. 209–210°; IR cm.$^{-1}$ 1685 and 3120 (Note 8),(Note 9), and (Note 10).

D. *4-Phenyl-1,2,4-triazoline-3,5-dione.* A 100-ml., three-necked, round-bottomed flask equipped with a dropping funnel, a gas-inlet tube, a calcium chloride-containing drying tube, and a magnetic stirrer is flushed with oxygen-free nitrogen (Note 11) and charged with 12 ml. of ethyl acetate (Note 12) and 4.4 g. (0.025 mole) of 4-phenylurazole (Note 13). The stirrer is started, and 2.5 g. (2.8 ml., 0.023 mole) of *tert*-butyl hypochlorite (Note 14) and (Note 15) is added to the flask over a period of approximately 20 minutes, the reaction mixture being maintained close to room temperature with a cold-water bath (Note 16) and (Note 17). After the addition is complete, the resulting suspension is stirred for 40

minutes at room temperature. The reaction mixture is transferred to a 100-ml., round-bottomed flask, and the solvent is removed on a rotary evaporator, keeping the temperature below 40°. The last traces of solvent are removed with a high-vacuum pump (about 0.1 mm.). The product is sublimed (Note 18) onto an ice-cooled cold finger under vacuum (100° at 0.1 mm.), yielding 2.7–2.8 g. (62–64%) of the triazoline as carmine-red crystals which decompose (165–175°) before melting; IR cm.$^{-1}$ 1760 and 1780; UV (dioxane) nm (ε) 247 (2300), 310 (1020), and 532 (171) (Note 19) and (Note 20).

2. Notes

1. Both the hydrazine hydrate and diethyl carbonate were British Drug Houses Ltd. or Matheson Laboratory reagent grade and used without further purification.
2. A forerun of approximately 100 ml., boiling below 80° (18 mm.), containing ethanol, water, and unreacted starting materials, is also collected.
3. An efficient stirrer should be employed, since the reaction mixture becomes quite viscous. If efficient mixing is not maintained a violent reaction can occur. This is especially important when using aliphatic isocyanates.
4. British Drug Houses Ltd. or Amend Drug & Chemical Co., Inc., reagent grade benzene, dried over sodium wire, is adequate.
5. British Drug Houses Ltd. or Matheson Laboratory reagent grade phenyl isocyanate was used without further purification. When using other isocyanates, care should be taken to ensure their purity as the yield is greatly dependent upon this, commercially available 4-nitrophenyl isocyanate being a case in point.
6. The submitters report a similar yield on a scale three times that illustrated here. This method has been employed for the preparation of the 4-methyl- (100%, m.p. 143° from ethyl acetate), 4-*tert*-butyl- (100%, m.p. 147° from ethyl acetate), and 4-(4-nitrophenyl)-1-carbethoxysemicarbazide (90%, m.p. 219° from methanol). Because of the impure nature of commercial 4-nitrophenyl isocyanate, the product from that reaction may be contaminated with 4-nitrophenylurea. It can be used in the impure form for preparing the corresponding urazole, as the contaminant is alkali insoluble.
7. The extraction procedure increases the yield of 4-phenylurazole by about 6%. This step is unnecessary when preparing 4-(4-nitrophenyl)urazole, as it is insoluble in water.
8. This method has been used to prepare 4-methyl- (90%, m.p. 240° from methanol) and 4-(4-nitrophenyl)urazole (80%, m.p. 264° from ethanol).
9. 4-*tert*-Butyl-1-carbethoxysemicarbazide can be cyclized by refluxing with 4% sodium ethoxide in ethanol for 4 hours, followed by acidification with an ethanolic solution of hydrogen chloride. Filtration, evaporation of the filtrate, and crystallization from ethyl acetate yields 4-*tert*-butylurazole (89%, m.p. 168°).
10. 4-Benzalaminourazole (m.p. 255°) can be prepared from 4-aminourazole[2] by condensation with benzaldehyde.
11. A gentle stream of nitrogen is maintained through the apparatus during the entire reaction. Hydrogen chloride is evolved and adequate precautions should be taken to prevent exposure to the gas.

12. Ethyl acetate was purified by Fieser's method.[3]
13. The 4-phenylurazole should be ground with a pestle and mortar before use.
14. *tert*-Butyl hypochlorite was prepared by the method described in *Org. Synth.*, **Coll. Vol. 4**, 125 (1963).
15. An excess of *tert*-butyl hypochlorite should not be used, as it cannot be removed and interferes with the sublimation of the product.
16. When preparing the 4-(4-nitrophenyl)- and 4-benzalamino- analogs, the reaction mixture should be maintained at 0–5°.
17. As soon as the first drop of hypochlorite is added, the reaction mixture becomes red in color, with the color deepening as the addition proceeds.
18. The impure material has a limited stability and should be sublimed as quickly as possible. The scale of the reaction should not be greatly increased unless an efficient large subliming apparatus is available. The submitters report similar yields on experiments four times this scale.
19. The product has a shelf life of several months if stored in the dark in a refrigerator.
20. This method has been used to prepare 4-methyl- [sublimed at 50° (0.1 mm.), 85%, m.p. 104°], 4-*tert*-butyl- [50° (0.1 mm.). 80%, m.p. 119°], 4-(4-nitrophenyl)- [100° (0.1 mm.), 25%, m.p. 130°], and 4-benzalamino-1,2,4-triazoline-3,5-dione [100° (0.1 mm.), 75%].

3. Discussion

Ethyl hydrazinecarboxylate has been prepared from hydrazine hydrate and ethyl *N*-tricarboxylate in good yield.[4] The method described here is comparable in efficiency, but has the added advantage that both starting materials are commercially available.

Methods for preparing 4-phenyl-1-carbethoxysemicarbazide and 4-phenylurazole have been described in principle by Zinner and Deucker.[5] 4-Phenylurazole has also been prepared from biurea and aniline hydrochloride;[6,7] however, the method is unreliable, with yields varying from 0 to 20%. 4-Substituted urazoles have also been made by heating the corresponding *N*,*N'*-disubstituted diamides of hydrazodicarboxylic acid,[8] but the results are difficult to reproduce.

4-Phenyl-1,2,4-triazoline-3,5-dione has been prepared by oxidizing 4-phenylurazole with lead dioxide,[6] and with ammoniacal silver nitrate followed by treatment with an ethereal solution of iodine.[7] The yields are low for both methods. 4-Substituted triazolinediones can also be made by oxidation of the corresponding urazole with fuming nitric acid[8] or dinitrogen tetroxide.[9] Oxidation with *tert*-butyl hypochlorite in acetone has also been described;[10,11] however, it yields an unstable product, even after sublimation. Dioxane[11] and ethyl acetate are preferred as solvents for the reaction, since the product is obtained in a stable form. The latter solvent is superior since 4-phenylurazole has a greater solubility in it.

In common with other azodicarboxylic acid derivatives, 4-phenyl-1,2,4-triazoline-3,5-

dione has many uses. It undergoes Diels-Alder reactions with most dienes[10,11,12,13] and is, in fact, the most reactive dienophile so far reported.[14,15] As with the formation of all Diels-Alder adducts the reaction is reversible, and in the case of the adduct with 3β-acetoxy-17-cyano-5,14,16-androstatriene, the reverse reaction can be made to proceed under especially mild conditions.[13] An instance has also been reported of the dione photochemically catalyzing other retro Diels-Alder reactions.[16] Along with the proved use of azodicarboxylic ester,[17,18] the dione should be potentially important in the preparation of strained ring compounds.

4-Phenyl-1,2,4-triazoline-3,5-dione also undergoes "addition-abstraction" reactions (*e.g.*, with acetone[16]). As would be expected for such a species, it will oxidize alcohols to the corresponding aldehydes or ketones.[19] This oxidation is especially mild (room temperature in benzene, chlorobenzene or ethyl acetate) and is, as such, a valuable method of oxidizing or preparing compounds sensitive to acid, base, or heat.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

dinitrogen tetroxide

Ethyl N-tricarboxylate

oxygen-free nitrogen

ethanol (64-17-5)

hydrogen chloride, hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ethyl acetate (141-78-6)

methanol (67-56-1)

nitric acid (7697-37-2)

silver nitrate (7761-88-8)

nitrogen (7727-37-9)

aniline hydrochloride (142-04-1)

benzaldehyde (100-52-7)

iodine (7553-56-2)

acetone (67-64-1)

chlorobenzene (108-90-7)

potassium hydroxide (1310-58-3)

sodium wire (13966-32-0)

sodium ethoxide (141-52-6)

hydrazine hydrate (7803-57-8)

phenyl isocyanate (103-71-9)

dioxane (5703-46-8)

diethyl carbonate (105-58-8)

Ethyl hydrazinecarboxylate (4114-31-2)

urazole (3232-84-6)

4-Phenyl-1,2,4-triazoline-3,5-dione, 4-Phenylurazole (15988-11-1)

4-Phenyl-1-carbethoxysemicarbazide

4-nitrophenyl isocyanate (100-28-7)

4-(4-nitrophenyl)-1-carbethoxysemicarbazide

4-nitrophenylurea

4-(4-nitrophenyl)urazole, 4-(4-Nitrophenyl)-1,2,4-triazoline-3,5-dione

4-Benzalaminourazole, 4-benzalamino-1,2,4-triazoline-3,5-dione

4-aminourazole

biurea (110-21-4)

3β-acetoxy-17-cyano-5,14,16-androstatriene

lead dioxide

tert-Butyl hypochlorite (507-40-4)

4-tert-Butyl-1-carbethoxysemicarbazide

4-tert-butylurazole

3H-1,2,4-Triazole-3,5(4H)-dione, 4-phenyl- (4233-33-4)

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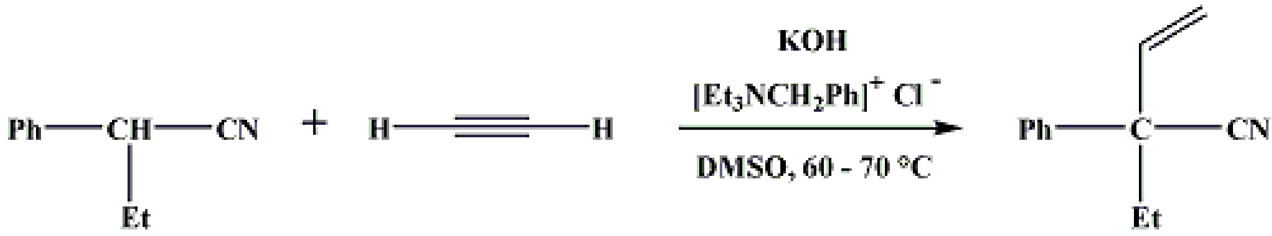
Organic Syntheses, CV 6, 940

2-PHENYL-2-VINYLBUTYRONITRILE

[Benzeneacetonitrile, α-ethenyl-α-ethyl-]



Submitted by M. Makosza[1], J. Czyzewski, and M. Jawdosiuk.
Checked by John C. Sauer and Richard E. Benson.

1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A 1-l., four-necked, round-bottomed flask equipped with a sealed mechanical stirrer, a thermometer, and a gas-inlet tube is charged with 145 g. (1.00 mole) of 2-phenylbutyronitrile (Note 1), 2.3 g. (0.010 mole) of benzyltriethylammonium chloride (Note 2), and 50 ml. of dimethyl sulfoxide (Note 3). The gas-inlet tube is adjusted to extend below the surface of the liquid, and a gas-exit tube is attached to the flask. A slow stream of acetylene (Note 4) is passed through the gas-inlet tube into the flask, removing the air. After 5 minutes, 56 g. of finely powdered potassium hydroxide is added and stirring is begun. Acetylene is introduced at the rate of 15–20 l./hour. An exothermic reaction occurs; the temperature rises to 70–80° and is held in this range with a cold water bath (Note 5). After 40–60 minutes, a warm bath is required to maintain the temperature of the reaction mixture at 60–70°, and stirring is continued for an additional 20–30 minutes (Note 6). The mixture is cooled to room temperature, the inlet tube is replaced with a pressure-equalizing dropping funnel, and 500 ml. of water is added slowly (Note 7). The resulting dark-brown mixture is transferred to a separatory funnel and washed twice with 200-ml. portions of benzene. The benzene layers are combined and washed successively with 200 ml. of water, 100 ml. of 10% hydrochloric acid, and 200 ml. of water. The organic layer is dried over anhydrous magnesium sulfate, and the benzene is removed by distillation at reduced pressure. The residual oil is distilled through a short Vigreux column, giving 125–135 g. of crude product, b.p. 115–125° (13 mm.). Redistillation of this product through a Vigreux column gives 101–107 g. (59–63%) of colorless 2-phenyl-2-vinylbutyronitrile, b.p. 110° (8 mm.), n_D^{25} 1.5157 (Note 8).

2. Notes

1. The preparation of 2-phenylbutyronitrile is described in *Org. Synth.*, **Coll. Vol. 6**,

897 (1988).

2. The checkers used the product available from Aldrich Chemical Company, Inc. The preparation of this reagent is described in *Org. Synth.*, **Coll. Vol. 6**, 232 (1988).

3. The checkers used the product available from Fisher Scientific Company.

4. The checkers used acetylene available from Matheson Gas Products. The gas was purified by passing it through concentrated sulfuric acid, through a tower filled with potassium hydroxide pellets, then into a 1-l. safety flask which was connected to the gas-inlet tube with rubber tubing. The checkers used a rotameter, calibrated with air, to determine the flow rate of acetylene.

5. The checkers attempted to keep the temperature at 65–70°.

6. The reaction may be monitored by GC. The submitters used a 2-m. column containing silicone oil on diatomite support (190°).

7. The water should be added slowly, since the mixture is saturated with acetylene and the gas may be evolved vigorously.

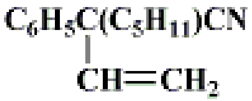
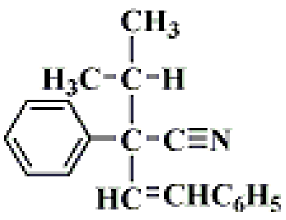
8. The checkers found the product to be at least 95% pure on a GC column containing 10% silicone 200 on nonacid washed Chromosorb W operated at 125°. The spectral properties of the product are as follows; IR (neat) $cm.^{-1}$: 1639, 1000, 930 ($CH{=}CH_2$); ^1H NMR (neat), δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 0.92 (t, $J = 7$, 3H, CH_3), 1.87 (q, $J = 7$, 2H, CH_2), 5.00–6.20 (m, 3H, $CH{=}CH_2$), 7.17–7.57 (m, 5H, C_6H_5).

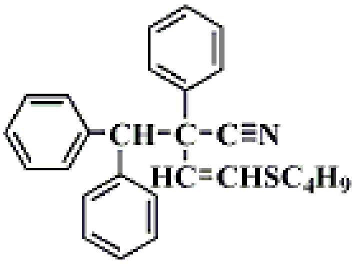
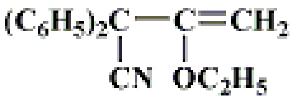
3. Discussion

This procedure, which involves the addition of an anion derived from a nitrile to an unactivated acetylenic bond under rather mild conditions, is a convenient, general method for the synthesis of α-vinylnitriles (see Table I). The reaction proceeds smoothly in either dimethyl sulfoxide or hexamethylphosphoric triamide [*see* J. A. Zapp, Jr., *Science*, **190**, 422 (1975) *for a toxicity warning concerning this compound*] with a tetraalkylammonium salt as catalyst. The products thus prepared are obtained in yields higher[2] than those obtained under conventional conditions, which generally require higher temperatures and elevated pressures.[3,4]

TABLE I

α-VINYLNITRILES DERIVED FROM ACETYLENES

Nitrile	Acetylene	Product	b.p.	Yield (%)
$C_6H_5CH(C_5H_{11})CN$	HC□CH		139° (8 mm.)	88
$C_6H_5CH(2\text{-}C_3H_7)CN$	HC□CC_6H_5		145° (0.8 mm.)	83

$(C_6H_5)_2CHCH(C_6H_5)CN$	$HC\equiv CSC_4H_9$		113°[c]	96
$(C_6H_5)_2CHCN$	$HC\equiv COC_2H_5$		146° (0.6 mm.)	77

[a]Product is a 2:1 mixture of (*Z*) and (*E*) isomers; (*Z*) isomer, m.p. 62°.

[b]Only the (*Z*) isomer is obtained.

[c]Melting point.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

$HC\equiv CH$

sulfuric acid (7664-93-9)

acetylene (74-86-2)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

potassium hydroxide (1310-58-3)

magnesium sulfate (7487-88-9)

dimethyl sulfoxide (67-68-5)

hexamethylphosphoric triamide (680-31-9)

benzyltriethylammonium chloride (56-37-1)

2-Phenylbutyronitrile (769-68-6)

2-Phenyl-2-vinylbutyronitrile, Benzeneacetonitrile, α-ethenyl-α-ethyl- (13312-96-4)

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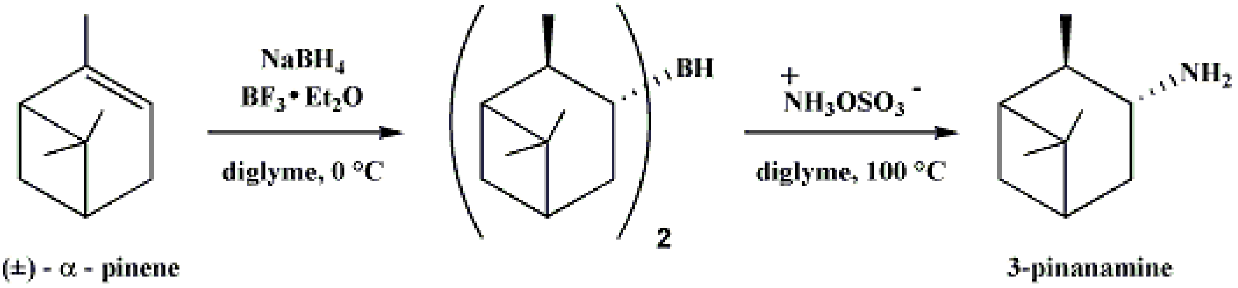
Organic Syntheses, CV 6, 943

BORANES IN FUNCTIONALIZATION OF OLEFINS TO AMINES: 3-PINANAMINE

[Bicyclo[3.1.1]heptan-3-amine, 2,6,6-trimethyl-]

A. $(NH_2OH)_2 \cdot H_2SO_4 + 2ClSO_3H \longrightarrow \overset{+}{N}H_3OSO_3^- + 2HCl + H_2SO_4$

B.



Submitted by Michael W. Rathke[1] and Alan A. Millard.
Checked by Arnold Brossi and Jun-ichi Minamikawa.

1. Procedure

A. *Hydroxylamine-O-sulfonic acid* (**1**). A 500-ml., three-necked, round-bottomed flask is fitted with a mechanical stirrer, dropping funnel, and calcium chloride drying tube. Finely powdered hydroxylamine sulfate (26.0 g., 0.158 mole) (Note 1) is placed in the flask, and 60 ml. (107 g., 0.92 mole) of chlorosulfonic acid (Note 1) is added dropwise over 20 minutes with vigorous stirring (Note 2). After the addition is complete, the flask, with stirring, is placed in a 100° oil bath for 5 minutes. The pasty mixture is cooled to room temperature, and the flask is placed in an ice bath. To the stirred mixture 200 ml. of diethyl ether is slowly added over 20–30 minutes (Note 3). During the ether addition, the pasty contents change to a colorless powder which is collected by suction on a Büchner funnel. The powder is washed with 300 ml. of tetrahydrofuran, then with 200 ml. of ether. The product **1**, after drying, weighs 34–35 g. (95–97%). Iodometric titration shows the product is 96–99% pure (Note 4) and adequate for the following reaction.

B. 3-*Pinanamine* (**3**). A 1000-ml., three-necked, round-bottomed flask is fitted with a gas-inlet tube, a reflux condenser connected to a mineral oil bubbler, and a sealed mechanical stirrer. The system is flamed with a Bunsen burner while being flushed with dry nitrogen. The reaction vessel is then cooled under a nitrogen stream in an ice bath while a slight positive pressure of nitrogen is maintained. A solution of 3.12 g. (0.0824 mole) of sodium borohydride (Note 5) in 100 ml. of diglyme (Note 6) is added to the flask, followed by 27.25 g. (0.2004 mole) of (±)-α-pinene (Note 7). Hydroboration is achieved by dropwise addition of 15.6 g. (0.110 mole) of boron trifluoride diethyl etherate (Note 8) over a 15-minute period. Di-3-pinanylborane (**2**) precipitates as a white solid. The ice bath is removed, and the reaction mixture is stirred at room temperature for 1 hour. Hydroxylamine-*O*-sulfonic acid (**1**) (24.9 g., 0.220 mole) in 100 ml. of diglyme is added dropwise to the mixture over a 5-minute period (Note 9). The mixture is then heated in a 100° oil bath for 3 hours. The mixture is cooled to room temperature, and 80 ml. of concentrated hydrochloric acid is added over a 5-minute period. The mixture is poured into 800 ml. of water and extracted with two 100-ml. portions of ether. The ether layers are discarded, and the aqueous layer is made alkaline with sodium hydroxide pellets (60–65 g. is needed). The aqueous layer is extracted with two 100-ml. portions of ether, the combined ether extracts are dried over anhydrous sodium sulfate, and the drying agent is removed by filtration. The filtrate is transferred to a

500-ml. ice-cooled flask fitted with a magnetic stirring bar. A solution of 85–88% phosphoric acid (12 g., 0.10 mole) in 100 ml. of ethanol is added to the flask over 10 minutes with stirring. The precipitated colorless crystals are collected with suction on a Büchner funnel, and the salt is suspended in 300 ml. of hot water contained in a 1-l. flask. The mixture is heated and magnetically stirred in a 120–130° oil bath until all the salt has dissolved (*ca.* 20–30 minutes) then quickly filtered with suction. Pure phosphate salt immediately precipitates as colorless plates, which are collected on a Büchner funnel and dried in a desiccator. The yield is 16.6 g. (33.1%). A second crop of 4.4 g. can be obtained by concentrating the mother liquor to about half its original volume. The total yield of pure phosphate salt is 21.0 g. (41.8%), m.p. 275–280° (dec.) (Note 10). The salt is easily converted to free amine **3** by the following procedure: 10 g. (0.040 mole) of the salt is dissolved in 40 ml. of aqueous 3 *M* sodium hydroxide and extracted with two 50-ml. portions of ether. The combined extracts are dried over anhydrous sodium sulfate, the drying agent is removed by filtration, and the solvent is removed under reduced pressure with a rotary evaporator. The residual oil is distilled, giving 5.9 g. (93% from phosphate salt) of amine **3** as a colorless liquid, b.p. 83° (13 mm.) (Note 11).

2. Notes

1. Commercial hydroxylamine sulfate and chlorosulfonic acid, obtained from Eastman Kodak Company, were used directly. The checkers found that commercially available hydroxylamine-*O*-sulfonic acid is sometimes of low purity; therefore, the use of freshly prepared reagent is recommended.
2. Hydrogen chloride gas is evolved during the addition. The reaction should be carried out in a hood, and an aqueous base scrubber is recommended.
3. Rapid addition of the ether must be avoided because of its high reactivity with chlorosulfonic acid.
4. Iodometric titration was carried out as follows: About 100 mg. of hydroxylamine-*O*-sulfonic acid was exactly weighed and dissolved in 20 ml. of distilled water. Sulfuric acid (10 ml. of 10% solution) and 1 ml. of saturated potassium iodide solution were then added. After the solution was allowed to stand for 1 hour, liberated iodine was titrated with 0.1 *N* sodium thiosulfate solution until the iodine color disappeared. The following stoichiometric relation was used: 0.1 *N* $Na_2S_2O_3$ (1 ml.) = 5.66 mg.

$$H_3\overset{+}{N}OSO_3^-$$

. Hydroxylamine-*O*-sulfonic acid should be stored in tightly sealed bottles in a refrigerator.
5. Commercial sodium borohydride was obtained from Ventron Corporation and used directly.
6. Commercial diglyme (dimethyl ether of diethylene glycol) was obtained from Ansul Chemical Company, Marinette, Wisconsin, and purified by distillation from lithium aluminum hydride at 62–63° (15 mm.) [*Org. Synth.*, **Coll. Vol. 6**, 719 (1988)].
7. (±)-α-Pinene, b.p. 54° (22 mm.), was obtained from Aldrich Chemical Company, Inc., and distilled before use.
8. Commercial boron trifluoride etherate, b.p. 46° (10 mm.), available from Matheson, Coleman and Bell, was distilled from calcium hydride before use.
9. *Caution! Since (±)-α-pinene is hydroborated to the dialkylborane state (R_2BH), a large amount of hydrogen is evolved on addition of hydroxylamine-O-sulfonic acid. Consequently, the addition should be carried out dropwise and adequate ventilation should be provided.*
10. The phosphate salt has the empirical formula $C_{10}H_{19}N \cdot H_3PO_4$.
11. The product showed one peak on GC (3% SE-30, 70°C).

3. Discussion

Hydroxylamine-*O*-sulfonic acid can also be prepared from hydroxylamine sulfate and 30% fuming

sulfuric acid (oleum).[2] The present procedure is essentially that of F. Sommer *et al.*[3]

The hydroboration–amination sequence in diglyme is a general procedure for the conversion of olefins to primary amines without rearrangement and with predictable stereochemistry.[4] An alternative procedure, using tetrahydrofuran as solvent and either hydroxylamine-*O*-sulfonic acid or chloramine, can be applied to terminal olefins and relatively unhindered internal and alicyclic olefins.[5] *O*-Mesitylenesulfonylhydroxylamine also gave desired amines in comparable yield.[6] Alternative procedures for the hydroboration of olefins use commercially available solutions of diborane in tetrahydrofuran[7] or dimethylsulfide.[8]

Olefins may be converted to primary amines by the Ritter reaction[9] or by reaction with mercury(II) nitrate in acetonitrile.[10] In both cases regiospecificity for the formal addition of ammonia across the double bond is opposite to that observed in the hydroboration–amination sequence.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 254

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrogen chloride, hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ether, diethyl ether (60-29-7)

hydrogen (1333-74-0)

acetonitrile (75-05-8)

sodium hydroxide (1310-73-2)

chlorosulfonic acid (7790-94-5)

sodium sulfate (7757-82-6)

potassium iodide (7681-11-0)

sodium thiosulfate (7772-98-7)

nitrogen (7727-37-9)

iodine (7553-56-2)

phosphoric acid (7664-38-2)

hydroxylamine sulfate (10046-00-1)

mercury(II) nitrate

dimethylsulfide (75-18-3)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

chloramine (10599-90-3)

boron trifluoride etherate, boron trifluoride diethyl etherate (109-63-7)

calcium hydride (7789-78-8)

diglyme, dimethyl ether of diethylene glycol (111-96-6)

sodium borohydride (16940-66-2)

Hydroxylamine-O-sulfonic acid (2950-43-8)

(±)-α-pinene

Di-3-pinanylborane (21947-87-5)

3-Pinanamine, Bicyclo[3.1.1]heptan-3-amine, 2,6,6-trimethyl- (17371-27-6)

O-Mesitylenesulfonylhydroxylamine

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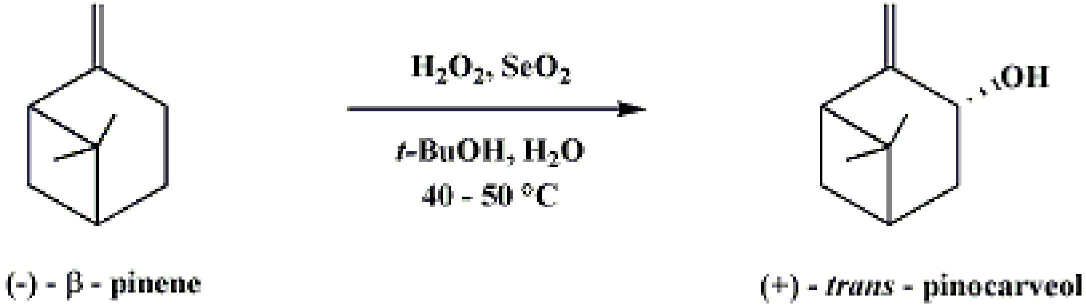
Organic Syntheses, CV 6, 946

ALLYLIC OXIDATION WITH HYDROGEN PEROXIDE–SELENIUM DIOXIDE: *trans*-PINOCARVEOL

[Bicyclo[3.1.1]heptan-3-ol, 6,6-dimethyl-2-methylene-, (1α,3α,5α)-]



Submitted by J. M. Coxon, E. Dansted, and M. P. Hartshorn[1].
Checked by D. W. Brooks and S. Masamune.

1. Procedure

Caution! Selenium compounds are exceedingly toxic (Note 1). Hydrogen peroxide attacks the skin and may decompose violently (Note 2). The reaction should be carried out behind a safety screen and in an efficient fume hood, and the operator should wear safety glasses and rubber gloves.

Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A 500-ml., three-necked, round-bottomed flask is fitted with a mechanical stirrer, a thermometer, a dropping funnel, and a reflux condenser. A solution of 0.74 g. (0.0067 mole) of selenium dioxide in 150 ml. of *tert*-butyl alcohol is introduced into the flask, followed by 68 g. (0.50 mole) of β-pinene (Note 3). The resulting mixture is warmed to 40° with a hot water bath before 35 ml. (0.62 mole) of 50% aqueous hydrogen peroxide (Note 2) is added dropwise over 90 minutes, during which time the mixture is maintained at 40–50° by occasional immersion in a cold water bath. After stirring for an additional 2 hours, the reaction mixture is diluted with 50 ml. of benzene, washed with three 50-ml. portions of saturated aqueous ammonium sulfate, and dried over sodium sulfate. A small amount of hydroquinone is added (Note 4), and the solvents are removed on a rotary evaporator. *trans*-Pinocarveol is isolated by simple distillation under reduced pressure, yielding 37–42 g. (49–55%), b.p. 60–70° (1 mm.), n_D^{22} 1.4972, $[\alpha]_D^{20}$ + 53.5 to + 60.0° (*c* 2.5, methanol) (Note 5).

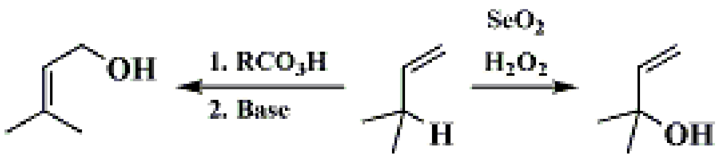
2. Notes

1. The physiological properties of selenium compounds are similar to those of arsenic compounds. Any selenium dioxide solid or solution spilled on the skin should be removed immediately by washing under running water.
2. Aqueous 50% hydrogen peroxide causes immediate blistering if allowed to come into contact with the skin. The presence of metal salts may cause decomposition of the hydrogen peroxide.
3. The checkers purchased β-pinene, $[\alpha]_D^{20}$ – 16.6° (*c* 1.9, methanol), from Aldrich Chemical Company, Inc.
4. Hydroquinone stabilizes the product during distillation by reducing traces of peroxide present in the reaction product.
5. GC analysis (capillary column coated with polypropylene glycol, 60.9 m., 100°) indicated that the product was *ca.* 95% pure (submitters). The checkers found the once-distilled material to be analytically pure. Analysis calculated for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.71; H, 10.55. IR (CCl_4) cm.$^{-1}$: 3600 medium, 3460 broad, medium, 1645 medium; ^{1}H NMR (CCl_4), δ (multiplicity, coupling constant *J* in Hz., number of protons): 0.63 (s, 3H), 1.26 (s, 3H), 1.6–2.5 (m, 6H), 2.88 (s, 1H, O*H*), 4.33 (approx. d, *J* = 7, 1H), 4.74 (approx. s, 1H), 4.96 (approx. s, 1H).

3. Discussion

trans-Pinocarveol is an important intermediate in the preparation of substituted pinane systems. It has been prepared by oxidation of β-pinene with lead tetraäcetate and hydrolysis of the corresponding ester (32%);[2] by photosensitized oxidation of α-pinene, followed by reduction of the corresponding hydroperoxide (35%);[3] by oxidation of β-pinene with molar quantities of selenium dioxide (53–64%);[4] and by epoxidation of α-pinene followed by isomerization with a variety of bases, of which lithium diethylamide (74–80% yield over the two steps) is best.[5]

The present procedure is a convenient, one-step method of preparing optically active *trans*-pinocarveol. Although lower in yield than the lithium diethylamide procedure, it is more readily adaptable to large-scale work. Moreover, the two methods are complimentary in the conditions required (neutral *vs.* basic) and in the overall transformation accomplished:



Since only catalytic quantities of selenium dioxide are required, the danger of handling large quantities of this material (Note 1) is avoided. Furthermore, the problems

associated with the formation of selenium and organoselenides, which commonly arise in oxidations using molar quantities of selenium dioxide, are not encountered.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

trans-Pinocarveol

Benzene (71-43-2)

methanol (67-56-1)

hydroquinone (123-31-9)

sodium sulfate (7757-82-6)

selenium dioxide (7446-08-4)

hydrogen peroxide (7722-84-1)

ammonium sulfate (7783-20-2)

selenium

tert-butyl alcohol (75-65-0)

lithium diethylamide

α-pinene

β-pinene (18172-67-3)

Bicyclo[3.1.1]heptan-3-ol, 6,6-dimethyl-2-methylene-, (1α,3α,5α)-

lead tetraacetate

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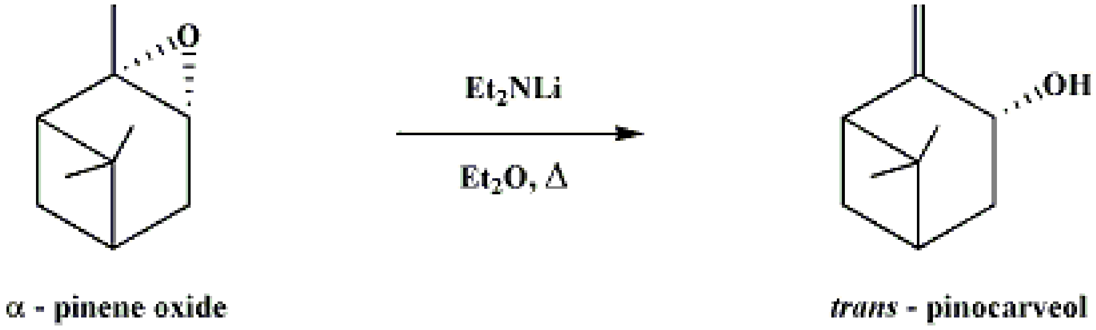
Organic Syntheses, CV 6, 948

BASE-INDUCED REARRANGEMENT OF EPOXIDES TO ALLYLIC ALCOHOLS: *trans*-PINOCARVEOL

[Bicyclo[3.3.1]heptan-3-ol, 6,6-dimethyl-2-methylene-, (1α,3α,5α-]



Submitted by J. K. Crandall[1] and L. C. Crawley.
Checked by Shoichiro Uyeo and Wataru Nagata.

1. Procedure

A dry, 300-ml., three-necked, round-bottomed flask is fitted with an effective reflux condenser, a 50-ml. pressure-equalizing dropping funnel, a rubber septum, a magnetic stirring bar, and a nitrogen inlet tube on the top of the condenser to maintain a static nitrogen atmosphere in the reaction vessel throughout the reaction. The flask is flushed with dry nitrogen, then charged with 2.40 g. (0.0329 mole) of diethylamine (Note 1) and 100 ml. of anhydrous diethyl ether (Note 2). The flask is immersed in an ice bath, the stirrer is started, and 25 ml. (0.035 mole) of 1.4 *M* *n*-butyllithium in hexane (Note 3) and (Note 4) is added carefully through the rubber septum with a syringe. After stirring for 10 minutes, the ice bath is removed and 5.00 g (0.0329 mole) of α-pinene oxide (Note 5) in 20 ml. of anhydrous ether is added dropwise over a 10-minute period. The resulting mixture is heated to reflux with stirring for 6 hours (Note 11). After the clear homogeneous mixture is cooled in an ice bath, it is stirred vigorously while 100 ml. of water is added. The ether phase is separated and washed successively with 100 ml. portions of 1 *N* hydrochloric acid, water, saturated aqueous sodium hydrogen carbonate, and water. The aqueous phase and each washing are extracted twice with 50 ml. portions of ether, and the ethereal extracts are combined and dried over anhydrous magnesium sulfate. Evaporation of the solvent on a rotary evaporator yields a light-yellow, oily residue which is distilled through a short-path distillation head, giving 4.50–4.75 g. (90–95%) of *trans*-pinocarveol as a colorless oil, b.p. 92–93° (8 mm.) n_D^{25} 1.4955 (Note 12) and (Note 13).

2. Notes

1. Commercial diethylamine, b.p. 55–58°, purchased from Fisher Scientific

Company, was distilled from calcium hydride before use. The checkers used material purchased from Kanto Chemical Company, Inc. (Japan) and distilled it from sodium hydride.

2. The checkers used anhydrous ether, distilled from sodium hydride before use.

3. The *n*-butyllithium in hexane solution was purchased from Foote Mineral Company. The checkers obtained their material from Wako Pure Chemical Industries Ltd. (Japan) and titrated it with 0.80 *M* 2-butanol in xylene using 1,10-phenanthroline as indicator.[2] Care should be exercised in handling *n*-butyllithium solutions.

4. The submitters used about three molar equivalents of lithium diethylamide in about twice as much solvent. The checkers found that an amount of base slightly in excess of one molar equivalent was sufficient to convert the epoxide to exocyclic methylene alcohol of superior purity.

5. The submitters purchased α-pinene oxide from F.M.C. Corporation. However, since the compound is no longer available, the checkers prepared it from α-pinene as follows. A three-necked, round-bottomed flask fitted with a 50-ml. dropping funnel, a thermometer, and a magnetic stirring bar is charged with 22.0 g. (0.102 mole) of *m*-chloroperbenzoic acid (Note 6), 11.0 g. (0.131 mole) of sodium hydrogen carbonate, and 250 ml. of dichloromethane. The suspension is stirred with a powerful stirrer while being cooled with an ice–salt bath. To this mixture is added dropwise a solution of 13.6 g. (0.986 mole) of α-pinene (Note 7) in 20 ml. of dichloromethane at a rate such that the inner temperature is kept between 5–10° (Note 8). During the addition, sodium *m*-chlorobenzoate begins to crystallize indicating that the reaction is proceeding. After completion of the addition, stirring is continued for 1 hour longer at the same temperature (Note 9). A solution of 5 g. of sodium sulfite in 50 ml. of water is added, and the mixture is stirred vigrously at room temperature for 30 minutes. Water (50 ml.) is added, and the dichloromethane phase is separated and washed with 100 ml. of 5% aqueous sodium carbonate. The two aqueous washings are extracted with 50 ml. of dichloromethane, and the organic solutions are combined and dried over anhydrous magnesium sulfate. Evaporation of the solvent on a rotary evaporator gives an oily residue that is distilled through a vacuum-jacketed column, yielding 12.5–12.8 g. (82–85%) of α-pinene oxide as a colorless oil, b. p. 89–90° (28 mm.) (Note 10).

6. *m*-Chloroperbenzoic acid was obtained from F.M.C. Corporation. It was shown to be 80% pure by titration.

7. Technical grade α-pinene, purchased from Wako Pure Chemical Industries Ltd. (Japan), was used without purification.

8. A more efficient cooling system, such as an acetone–dry ice bath, is necessary to shorten the addition time in large-scale preparations.

9. Completion of the reaction may be checked by GC.

10. GC of this product using a 1-m. column containing 5% KF-54 on Chromosorb W at 100° gave a single peak. The material gave the following ^{1}H NMR spectrum ($CDCl_3$): δ 0.95, 1.30, and 1.33 (3 s, 9H, 3CH_3), 1.53–2.20 (m,

6H, 2CH_2 and 2C*H*), 3.03 (m, 1H, C*H*OC). The boiling point is reported to be 70–71° (12 mm.).[3]

11. Completion of the reaction may be checked by GC analysis. Refluxing for prolonged periods can give saturated ketone as an impurity if excess base is used.

12. The reported[4] value is n_D^{20} 1.4993.

13. The spectral properties are: IR (neat) cm.$^{-1}$ 3360 ms (OH), 1644 vw (C=C), 893 ms (C=CH_2); ^{1}H NMR ($CDCl_3$): δ 0.65 and 1.28 (2 s, 6H, 2CH_3), 1.63–2.55 (m, 6H, 2CH_2 and 2C*H*), 4.42 (d, *J* = 7 Hz., 1H, C*H*OH), 4.82 and 5.00 (2 m, 2H, C=CH_2). Purity of the product is greater than 98% as determined by GC using a Carbowax 20 M on 60–80 Chromosorb W column or a 1-m. column containing 5% KF-54 on Chromosorb W at 100°.

3. Discussion

Pinocarveol has been prepared by the autoxidation of α-pinene,[5] by the oxidation of β-pinene with lead teträcetate,[6] and by isomerization of α-pinene oxide with diisobutylaluminum,[7] lithium aluminum hydride,[8] activated alumina,[9] potassium *tert*-butoxide in dimethyl sulfoxide,[10] and lithium diethylamide.[11] The present method is preferred for the preparation of pinocarveol, since the others give mixtures of products. It also illustrates a general method for converting 1-methylcycloalkene oxides into the corresponding exocyclic methylene alcohols.[11] The reaction is easy to perform, and the yields are generally high.

In general, the strong base isomerization of epoxides to allylic alcohols constitutes a useful synthetic reaction. Since the rearrangement is a highly specific process, it should be of value in organic synthesis. For example, there is a very high propensity for Hofmanntype eliminations to yield the least substituted double bond from unsymmetrically substituted epoxides.[12] There is also a large conformational effect arising from the operation of a *syn*-elimination mechanism which leads to specificity in eliminations of cyclic epoxides.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 946

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alumina

trans-Pinocarveol

Bicyclo[3.3.1]heptan-3-ol, 6,6-dimethyl-2-methylene-, (1α,3α,5α-

Pinocarveol

hydrochloric acid (7647-01-0)

ether, diethyl ether (60-29-7)

sodium sulfite (7757-83-7)

sodium hydrogen carbonate (144-55-8)

sodium carbonate (497-19-8)

nitrogen (7727-37-9)

xylene (106-42-3)

diethylamine (109-89-7)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

butyllithium, n-butyllithium (109-72-8)

lithium aluminum hydride (16853-85-3)

sodium hydride (7646-69-7)

hexane (110-54-3)

dimethyl sulfoxide (67-68-5)

lithium diethylamide

calcium hydride (7789-78-8)

2-Butanol (78-92-2)

1,10-phenanthroline (66-71-7)

methylene alcohol (463-57-0)

α-pinene

β-pinene (18172-67-3)

α-pinene oxide (72936-74-4)

diisobutylaluminum (1191-15-7)

m-Chloroperbenzoic acid (937-14-4)

potassium tert-butoxide (865-47-4)

sodium m-chlorobenzoate

lead tetracetate

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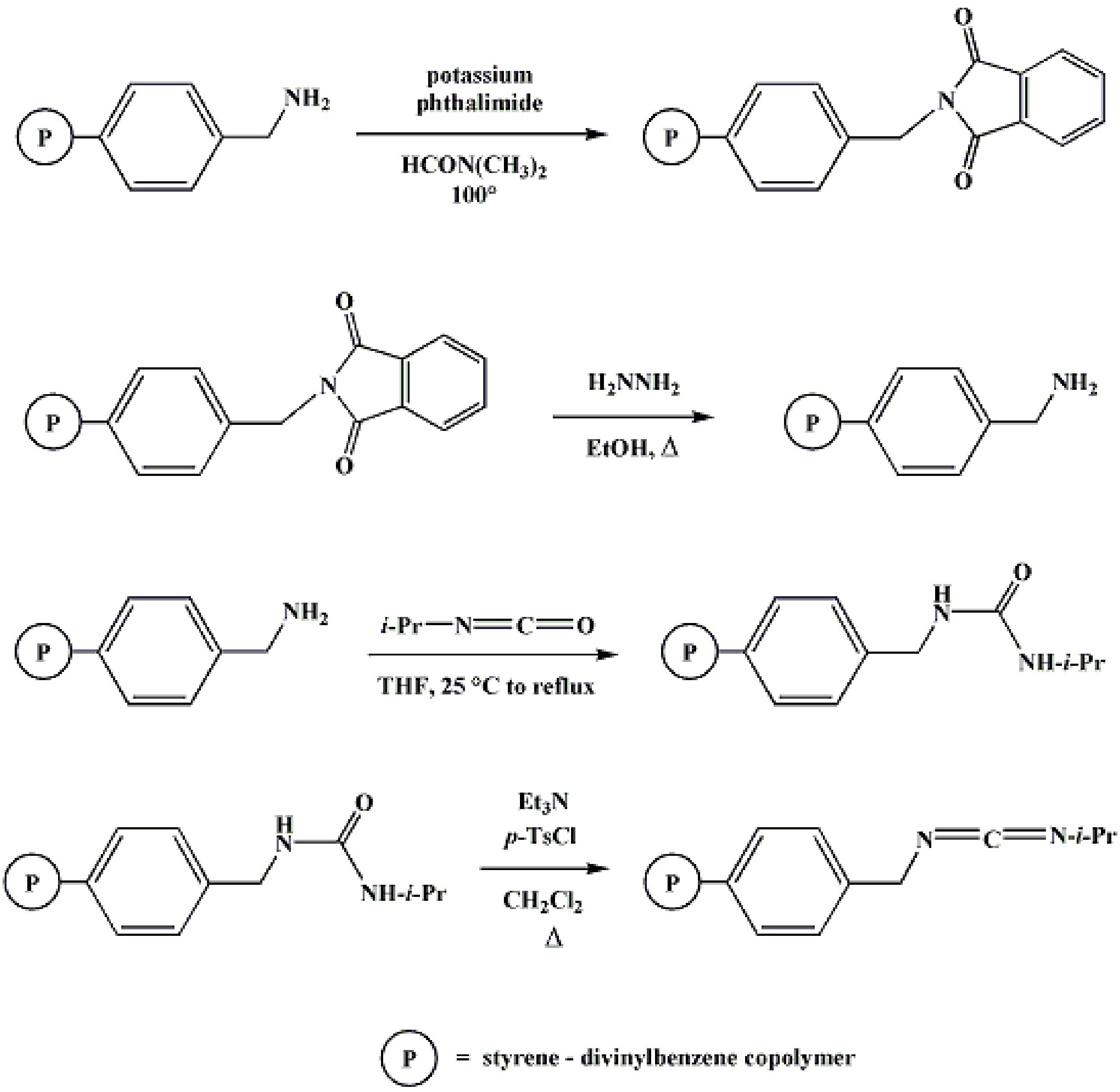
Organic Syntheses, CV 6, 951

POLYMERIC CARBODIIMIDE. PREPARATION

[Benzene, diethenyl-, polymer with ethenylbenzene, [[[[(1-methylethyl)imino] methylene]amino]methyl]deriv.]]



Submitted by Ned M. Weinshenker[1], Chah M. Shen, and Jack Y. Wong.
Checked by A. Fukuzawa and S. Masamune.

1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A. *Polymeric benzylamine*. A 300-ml., one-necked, round-bottomed flask equipped with a reflux condenser and a magnetic stirrer is charged with 125 ml. of *N*,*N*-dimethylformamide (Note 1) and

10.0 g. of chloromethylated polystyrene beads (0.0106 mole of active chloride) (Note 2) and (Note 3). A gas-inlet is attached to the top of the condenser, and the system is maintained under a slight positive pressure of nitrogen. The temperature is then raised to 100° with an oil bath, and 2.95 g. (0.0159 mole) of potassium phthalimide (Note 4) and (Note 5) is added while the mixture is stirred. After stirring at 100° overnight, the mixture is cooled and filtered. The polymer beads are washed with 200 ml. each of distilled water and methanol and dried under reduced pressure, giving 11.70 g. of phthalimido polymer.

The beads prepared above (11.58 g.) are suspended in 175 ml. of boiling absolute ethanol, and 0.94 g. (0.016 mole) of 85% aqueous hydrazine monohydrate is added with stirring. The resulting mixture is refluxed for 10 hours, after which the polymer is collected by filtration and washed with 150-ml. portions of ethanol, aqueous 0.2 *N* sodium hydroxide, distilled water, and anhydrous methanol. After vacuum drying at 60° for four hours, the yield of polymeric benzylamine is 10.38 g.

B. *Polymeric urea*. A 10.0-g. portion of the benzylamine polymer beads prepared in Part A and 125 ml. of tetrahydrofuran (Note 6) are combined in a 300-ml., three-necked, round-bottomed flask equipped with a magnetic stirrer, a dropping funnel, and a condenser fitted with a gas-inlet tube. A nitrogen atmosphere is established in the system, and the slurry is stirred while 1.35 g. (0.0159 mole) of 2-isocyanatopropane is added. An exothermic reaction ensues and subsides after about 20 minutes. The mixture is then stirred at room temperature for 22 hours, and at reflux for an additional 4 hours. The beads are collected by filtration, washed with 150-ml. portions of tetrahydrofuran (Note 6) and methanol, and dried under reduced pressure over calcium chloride, yielding 9.09 g. of the 2-propyl urea polymer.

C. *Polymeric carbodiimide*. The polymeric urea prepared above (9.09 g.) is combined with 100 ml. of dichloromethane in a 300-ml., three-necked, round-bottomed flask equipped with a magnetic stirrer, a condenser fitted with a gas-inlet tube, and a stopper. Under a blanket of nitrogen, 5.76 g. (0.0570 mole) of triethylamine and 2.75 g. (0.0145 mole) of *p*-toluenesulfonyl chloride (Note 7) are added to the stirred reaction mixture. The resulting slurry is refluxed with stirring for 50 hours, cooled to room temperature, and filtered. The polymer beads are washed successively with 100-ml. portions of dichloromethane, ice water, 3:1 dioxane–water, dioxane, and anhydrous diethyl ether. Vacuum drying yields 8.61 g. of polymeric carbodiimide, containing 0.98–1.01 millimoles of carbodiimide per gram (Note 8).

2. Notes

1. *N,N*-Dimethylformamide was dried overnight over Linde type 4A molecular sieves.
2. The checkers used beads of chloromethylated polymer available from Bio. Rad. Laboratories, Richmond, California (Bio Beads S·X2). Chlorine analysis (Note 3) showed that the resin contained 1.06 milliequivalents of chlorine per gram, as specified by the manufacturer.
The submitters prepared the polymer as follows. *Caution! Chloromethyl methyl ether is a carcinogen and is listed as such on the OSHA list. Therefore, preparation of the chloromethylated resin must be performed in a fume hood, the operator must wear gloves, and the reagent must be disposed of in an appropriate manner.* A slurry of 200 g. (1.93 moles) of polystyrene crosslinked with 2% divinylbenzene (Amberlite XE-305, obtained from the Rohm and Haas Company, Philadelphia) and 2.5 l. of chloroform was prepared in a 3-l., three-necked, round-bottomed flask equipped with a dropping funnel, a condenser, and a mechanical stirrer. After stirring for 0.5 hour at room temperature, the mixture was cooled in an ice-water bath, and a mixture of chloromethyl methyl ether (430 ml., 5.69 moles) and anhydrous tin(IV) chloride (45 ml., 0.39 mole) was added dropwise with continuous stirring. After the addition was completed, the ice bath was removed, and the mixture was stirred for an additional 4 hours at room temperature. The beads were collected by filtration and washed successively with 2 l. of

3 : 1 dioxane–water, 2 l. of 3 : 1 dioxane–3 *N* hydrochloric acid, 1 l. of dioxane, 1 l. of water, and 1 l. of methanol. It is desirable to allow each of the solvents used in the washing procedure to be in contact with the beads for 5–10 minutes before filtration to ensure complete penetration. Drying over calcium chloride under reduced pressure yields 252 g. of the chloromethylated polymer. The chlorine content was 15.50%, equivalent to 4.29 milliequivalents of chlorine per gram of polymer (Note 3).

3. The chlorine content can be determined by either chlorine elemental analysis or a potentiometric titration using a chloride-ion electrode. For titration, about 0.2 g. of polymer is heated in 3 ml. of pyridine at 100° for 2 hours. This suspension is then transferred to a 50-ml. beaker containing 30 ml. of 50% acetic acid and 5 ml. of concentrated nitric acid, and the resulting mixture is titrated against aqueous 0.1 *N* silver nitrate.

4. All chemicals used were reagent grade unless otherwise specified. A 50% molar excess of reagents was employed throughout the synthesis in order to drive the reactions to completion.

5. Potassium phthalimide was washed with acetone prior to use according to the procedure in *Org. Synth.*, **Coll. Vol. 4**, 810 (1963).

6. Tetrahydrofuran was dried and distilled from lithium aluminum hydride prior to use. For a warning concerning potential hazards of this procedure, see *Org. Synth.*, **Coll. Vol. 5**, 976 (1973).

7. *p*-Toluenesulfonyl chloride was recrystallized from hexane prior to use.

8. The *maximum* content of active carbodiimide groups can be determined by a nitrogen elemental analysis. The submitters determined the *minimum* carbodiimide content by treating the reagent with excess acetic acid: *ca.* 1 g. of accurately weighed polymeric carbodiimide was suspended in a mixture of 7 ml. of benzene, 3 ml. of ether, and 1.2 g. of acetic acid. After 20 hours of stirring, the conversion to acetic anhydride was determined by GC using a Carbowax 20M column operated at 160°. Triglyme was used as an internal standard. The final, deactivated polymer still showed a very strong absorption at 2140 cm.$^{-1}$ (KBr) in its IR spectrum. The checkers modified the above procedure slightly by using glutaric acid instead of acetic acid.

3. Discussion

The general procedure described here was originally published by the submitters,[2] who have used this insoluble reagent to prepare aldehydes and ketones under Moffat oxidation conditions.[3] A polymeric reagent offers two advantages: (a) when an oxidation is complete, the urea by-product is cleanly separated from the products by a simple filtration; and (b) the deactivated urea form of the polymer can be recycled efficiently to the carbodiimide form, as outlined in Part C of the present procedure. The use of polyhexamethylenecarbodiimide in peptide syntheses has been mentioned previously.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 218

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Polymeric urea

Polymeric benzylamine

Polymeric carbodiimide

Benzene, diethenyl-, polymer with ethenylbenzene

[[[[(1-methylethyl)imino]methylene]amino]methyl]deriv.]

chloromethylated polystyrene beads

phthalimido polymer

2-propyl urea polymer

chloromethylated polymer

polyhexamethylenecarbodiimide

ethanol (64-17-5)

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

acetic anhydride (108-24-7)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

nitric acid (7697-37-2)

silver nitrate (7761-88-8)

nitrogen (7727-37-9)

acetone (67-64-1)

pyridine (110-86-1)

chlorine (7782-50-5)

Potassium Phthalimide (1074-82-4)

urea (57-13-6)

hydrazine monohydrate (7803-57-8)

Glutaric acid (110-94-1)

dichloromethane (75-09-2)

chloromethyl methyl ether (107-30-2)

chloride

tin(IV) chloride (7646-78-8)

dioxane (5703-46-8)

benzylamine (100-46-9)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

N,N-dimethylformamide (68-12-2)

hexane (110-54-3)

triethylamine (121-44-8)

carbodiimide

p-Toluenesulfonyl chloride (98-59-9)

divinylbenzene

2-isocyanatopropane (1795-48-8)

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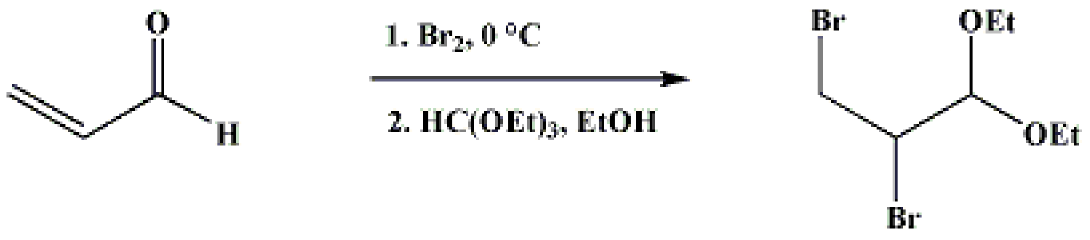
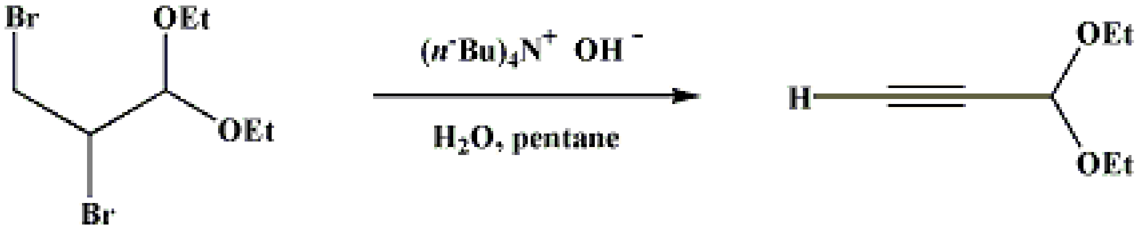
Organic Syntheses, *CV 6*, 954

ALKYNES *via* PHASE TRANSFER–CATALYZED DEHYDROHALOGENATION: PROPIOLALDEHYDE DIETHYL ACETAL

[1-Propyne, 3,3-diethoxy-]





Submitted by A. Le Coq[1] and A. Gorgues.
Checked by G. Saucy and P. S. Manchand.

1. Procedure

A. *2,3-Dibromopropionaldehyde diethyl acetal*. A 500-ml., three-necked, round-bottomed flask is equipped with a mechanical stirrer, a pressure-equalizing dropping funnel fitted with a calcium chloride drying tube, and a thermometer. The flask and dropping funnel are charged with 28.0 g. (0.500 mole) of freshly distilled acrolein and 80.0 g. (0.500 mole) of bromine, respectively. The acrolein is stirred rapidly and cooled to 0° in an ice–salt bath, then bromine is added at a rate such that the temperature is kept at 0–5°, until a permanent red color indicates a slight excess of bromine in the flask. A total of 78–79 g. of bromine is added over a 1-hour period. The crude 2,3-dibromopropionaldehyde is stirred while a solution of 80 g. (0.54 mole) of freshly distilled triethyl orthoformate in 65 ml. of absolute ethanol (Note 1) is added over 15 minutes. The solution warms to 45° and is stirred for 3 hours, after which ethyl formate, ethanol, and triethyl orthoformate are removed on a rotary evaporator. Distillation of the residual liquid through a 15-cm. Vigreux column affords 107–112 g. (74–77%) of 2,3-dibromopropionaldehyde diethyl acetal, b.p. 113–115° (11 mm.), as a pale-yellow liquid (Note 2).

B. *Propiolaldehyde diethyl acetal*. A 500-ml., three-necked, round-bottomed flask equipped with a mechanical stirrer (Note 3), a double-walled condenser, and a pressure-equalizing dropping funnel is charged with 100 g. (0.295 mole) (Note 4) of

tetrabutylammonium hydrogen sulfate (Note 5) and 20 ml. of water. The mixture is stirred, forming a thick paste to which a solution of 29 g. (0.10 mole) of 2,3-dibromopropionaldehyde diethyl acetal in 75 ml. of pentane is added. The resulting mixture is stirred rapidly and cooled to 10–15° as a cold (10–15°) solution of 60 g. (1.5 moles) of sodium hydroxide in 60 ml. of water is added over 10 minutes. About 5 minutes later the pentane begins to boil and continues to reflux for another 10–20 minutes. The mixture is stirred for 2 hours at room temperature, cooled to 5°, and made slightly acidic (Note 6) by adding *ca.* 120 ml. of cold (*ca.* 5°) 25% sulfuric acid. Stirring is stopped, the layers are allowed to separate for 30 minutes, and the upper organic layer is carefully decanted (Note 7). The lower, aqueous layer is filtered, removing sodium sulfate, extracted with three 50-ml. portions of pentane, and, if desired, processed to recover the tetrabutylammonium salt (Note 8). The pentane solutions are combined, dried over anhydrous sodium sulfate, and evaporated. The colorless concentrate is distilled, giving 7.8–8.6 g. (61–67%) of propiolaldehyde diethyl acetal as a colorless liquid, b.p. 138–139° (760 mm.), 95–96° (170 mm.) (Note 9).

2. Notes

1. Absolute ethanol from a commercial supplier was used without further treatment.
2. The submitters report a yield of 113–122 g. (78–84%), b.p. 113–115° (11 mm.) (lit.,[2] b.p. 108–110°, 10 mm.). The product obtained by the checkers was analyzed. Analysis calculated for $C_7H_{14}Br_2O_2$: C, 28.99; H, 4.87; Br, 55.11. Found: C, 28.81; H, 4.88; Br, 55.37. The ^1H NMR spectrum ($CDCl_3$), δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 1.27 (t, *J* = 7, 6H, 2 OCH_2CH_3), 3.6–3.9 (m, 6H, 2 OCH_2CH_3 and CH_2Br), 4.22 (apparent d of t, *J* = 4 and 7, 1H, C*H*Br), 4.72 (d, *J* = 4, 1H, C*H*).
3. The submitters used a 1-l. Erlenmeyer flask and a magnetic stirrer. The Erlenmeyer flask was recommended to minimize splattering of the pasty mixture into the condenser. The checkers preferred a 500-ml., round-bottomed flask equipped as described above.
4. The submitters found that the yield of product was reduced to *ca.* 50% when only 1 equivalent (0.2 mole) of tetrabutylammonium hydrogen sulfate was used.
5. The submitters purchased tetrabutylammonium hydrogen sulfate (97% pure) from Fluka AG, Buchs, Switzerland; it was obtained by the checkers from Aldrich Chemical Company, Inc.
6. Care must be exercised during acidification, since excess sulfuric acid lowers the yield, presumably through hydrolysis of the acetal.
7. The checkers often obtained a thick emulsion which separated into three layers after standing for *ca.* 2 hours. When this occurred, the mixture was poured into 500 ml. of water, and the product was extracted with three 150-ml. portions of pentane.
8. The following unchecked procedure has been provided by the submitters for the purpose of recovering the tetrabutylammonium salt. The aqueous layer,

which contains 12 g. of sodium bromide, is extracted with two 100-ml. portions of dichloromethane. The solution is dried and evaporated, giving 91–93 g. (96–98%) of crude tetrabutylammonium bromide which can be recrystallized from ethyl acetate or employed directly for regenerating the hydrogen sulfate salt. The submitters recommend that the bromide be accumulated from several runs and then converted to the hydrogen sulfate by the procedure of Brandström.[3] A two-necked, round-bottomed flask fitted with a short distillation column and a dropping funnel is charged with 196 g. (0.609 mole) of recovered tetrabutylammonium bromide and 300 ml. of chlorobenzene. The contents of the flask are heated, and 92 g. (0.73 mole) of dimethyl sulfate is then added dropwise to the hot solution. The methyl bromide formed distills from the flask and is collected in a trap cooled with acetone–dry ice. As the rate of production of methyl bromide decreases, the heating is increased until the temperature at the top of the distillation column starts to rise rapidly. A solution of 1.5 ml. of concentrated sulfuric acid in 600 ml. of water is then cautiously added. The mixture is heated at reflux for 48 hours and evaporated to dryness under reduced pressure. After the residue has been dissolved in 500 ml. of dichloromethane, the resulting solution is washed with two 50-ml. portions of water and dried with anhydrous sodium sulfate. Evaporation of the solvent provides 202.5 g. of almost pure tetrabutylammonium hydrogen sulfate which can be recrystallized from isobutyl methyl ketone.

9. The submitters report a yield of 8.6–9.5 g. (67–74%), b.p. 95–96° (170 mm.) (lit.,[2] b.p. 138–139.5°, 760 mm.). The submitters recommend that the product be distilled under reduced pressure. The spectral characteristics of the product are as follows: IR (liquid film) cm^{-1}: 3260 ($\equiv$CH), 2125 (C$\equiv$C); ^{1}H NMR ($CDCl_3$), δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 1.24 (t, $J = 7$, 6H, $2CH_3$), 2.58 (d, $J = 2$, 1H, $\equiv CH$), 3.71 (apparent q of d, $J = 7$ and 2, 4H, $2CH_AH_BCH_3$), 5.21 (d, $J = 2$, 1H, $CH(OC_2H_5)_2$).

3. Discussion

The preparation of 2,3-dibromopropionaldehyde diethyl acetal described here is based on the procedure of Grard.[2,4] The dehydrobromination of the dibromide to propiolaldehyde diethyl acetal has previously been carried out with potassium hydroxide in ethanol.[2,4] and with sodium amide in liquid ammonia.[5] In the present procedure the elimination is effected with aqueous sodium hydroxide in the presence of the phase-transfer agent, tetrabutylammonium hydrogen sulfate.[6,7] The principal advantage of the phase-transfer procedure is its operational simplicity. The method has been used to prepare diphenylacetylene (75%), phenylacetylene (87%), *p*-tolylacetylene (77%), and 3-chloropropiolaldehyde diethyl acetal (70%).[8] The halide reactants were the corresponding 1,2-dibromides in the first two examples and vinyl

chlorides in the second two cases. The yields obtained with this method are better than those from traditional procedures, and the conditions are generally milder. In addition, the extent of substitution and dehalogenation, side reactions that frequently complicate the synthesis of acetylenes by elimination with alkoxide or amide bases, is diminished.[9] The ability to recover efficiently the tetrabutylammonium salt enhances the practicality of this procedure.[3]

Propiolaldehyde diethyl acetal has found numerous synthetic applications in the literature. The compound has been utilized in the synthesis of unsaturated and polyunsaturated acetals and aldehydes by alkylation of metallated derivatives,[5,10,11,12,13] by Cadiot-Chodkiewicz coupling with halo acetylenes,[13,14] and by reaction with organocuprates.[15] Syntheses of heterocyclic compounds including pyrazoles,[16] isoxazoles,[16] triazoles,[2] and pyrimidines[17,18] have employed this three-carbon building block. Propiolaldehyde diethyl acetal has also been utilized in the synthesis of naturally occurring polyacetylenes[19,20,21,22,23] and steroids.[24]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

1,2-dibromides

ACETAL (105-57-7)

ethanol (64-17-5)

sulfuric acid, hydrogen sulfate (7664-93-9)

ammonia (7664-41-7)

ethyl acetate (141-78-6)

sodium hydroxide (1310-73-2)

Acrolein (107-02-8)

bromide (24959-67-9)

bromine (7726-95-6)

sodium bromide (7647-15-6)

sodium sulfate (7757-82-6)

dimethyl sulfate (77-78-1)

chlorobenzene (108-90-7)

potassium hydroxide (1310-58-3)

methyl bromide (74-83-9)

triethyl orthoformate (122-51-0)

ethyl formate (109-94-4)

Pentane (109-66-0)

isobutyl methyl ketone (108-10-1)

dichloromethane (75-09-2)

Phenylacetylene (536-74-3)

sodium amide (7782-92-5)

Diphenylacetylene (501-65-5)

tetrabutylammonium bromide (1643-19-2)

tetrabutylammonium

tetrabutylammonium hydrogen sulfate (32503-27-8)

Propiolaldehyde diethyl acetal, 1-Propyne, 3,3-diethoxy- (10160-87-9)

2,3-dibromopropionaldehyde (5221-17-0)

2,3-Dibromopropionaldehyde diethyl acetal (10160-86-8)

3-chloropropiolaldehyde diethyl acetal

p-tolylacetylene (766-97-2)

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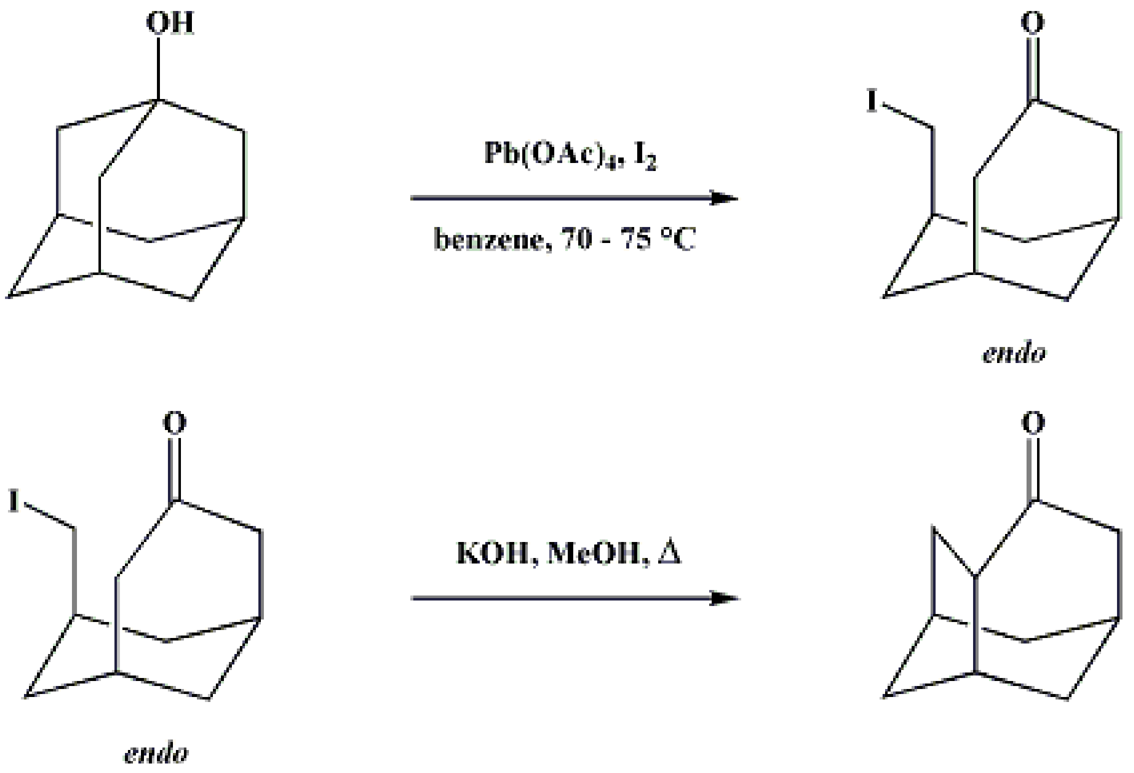
Organic Syntheses, CV 6, 958

REARRANGEMENT OF BRIDGEHEAD ALCOHOLS TO POLYCYCLIC KETONES BY FRAGMENTATION-CYCLIZATION: 4-PROTOADAMANTANONE (TRICYCLO-[4.3.1.0^{3,8}]DECAN-4-ONE)

[2,5-Methano-1*H*-inden-7(4*H*)-one, hexahydro]



Submitted by Zdenko Majerski[1] and Zdenko Hamersak[1].
Checked by Thomas P. Demuth and Andrew S. Kende.

1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedure involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A. *endo-7-Iodomethylbicyclo[3.3.1]nonan-3-one*. A 2-l., three-necked, round-bottomed flask equipped with an efficient mechanical stirrer and a reflux condenser is charged with 600 ml. of dry benzene (Note 1). The flask is immersed in a water bath, stirring is initiated, and 58.3 g. (0.132 mole) of lead tetraäcetate (Note 2), 37.4 g. (0.147 mole) of iodine, and 10.0 g. (0.0654 mole) of 1-adamantanol (Note 3) are added (Note 4). The bath temperature is gradually raised to 80° over a 20-minute period, then allowed to cool to 70–75°. Stirring is continued for 2 hours at 70–75° (Note 5) and for

an additional hour with the mixture is cooled to room temperature. The inorganic salts are filtered and carefully washed with five 50-ml. portions of diethyl ether. The benzene filtrate and ether washings are combined in a 2-l. separatory funnel and shaken with 500 ml. of saturated aqueous sodium bisulfite (Note 6) until the dark red color disappears. The layers are *not* separated. If the color reappears within 10–15 minutes, the mixture is shaken again until colorless. This procedure is repeated as many times as necessary. The layers are then separated, and the organic layer is washed with 500 ml. of water and 250 ml. of saturated aqueous sodium hydrogen carbonate. The benzene–ether solution is dried over anhydrous magnesium sulfate for 1 hour and concentrated in a 500-ml., round-bottomed flask with a rotary evaporator (Note 7). The resulting crude, oily iodo ketone weighs 14–16 g. (Note 8) and is used immediately in Part B.

B. 4-*Protoadamantanone*. The flask containing the crude iodo ketone is equipped with a magnetic stirring bar and a reflux condenser. A solution of 7 g. (0.1 mole) of potassium hydroxide in 150 ml. of methanol is added, and the mixture is stirred and heated at reflux for 3 hours. The contents of the flask are allowed to cool to room temperature and poured into 300 ml. of ice water. The resulting mixture is extracted with five 100-ml. portions of ether. The combined extracts are dried over anhydrous magnesium sulfate and evaporated under reduced pressure, leaving 8.6–9.1 g. of a yellow solid (Note 9). A solution of this crude product in 3 ml. of chloroform is allowed to percolate onto a chromatography column packed with 200 g. of activity III, neutral alumina in pentane (Note 10). The column is eluted first with 100 ml. of pentane, then with 500 ml. of 3:7 (v/v) ether–pentane, as 25-ml. fractions are collected and analyzed by GC (Note 11). Those fractions containing product whose purity is judged to be 98% or greater are combined and evaporated, affording 7.0–8.1 g. (71–82% based on 1-adamantanol) of 4-protoadamantanone as a colorless or pale-yellow solid, m.p. 202–204° (Note 12).

2. Notes

1. Solvent grade benzene was dried over sodium wire prior to use. If the benzene is wet, a considerable amount of starting 1-adamantanol remains unreacted owing to hydrolysis of lead tetraäcetate.
2. Lead tetraäcetate, both purchased from Fluka AG, Buchs, Switzerland, and prepared according to a literature procedure,[2] was used by the submitters without any noticeable difference. Lead tetraäcetate was dried prior to use for at least 12 hours over potassium hydroxide and phosphorus pentoxide in an evacuated desiccator (12 mm.), protected from direct light. If well protected from moisture, lead tetraäcetate can be kept for weeks. However, after exposure to moisture in the air it usually turns brown due to hydrolysis to lead hydroxide. The reactivity of such lead tetraäcetate is diminished somewhat, but it can still be used. If it has turned black, the reagent should be recrystallized from glacial acetic acid and dried prior to use, as described above.

3. 1-Adamantanol is available from the following three suppliers: Aldrich Chemical Company, Inc.; Fluka AG, Buchs, Switzerland; E. Merck, Darmstadt, Germany. It may also be prepared from adamantane by bromination to 1-bromoadamantane and hydrolysis.[3] Adamantane is sold by the same three suppliers.
4. The resulting solution is dark red in color.
5. The temperature of the bath should be *carefully* maintained in this range. At temperatures below 70° the reaction is much slower and increased amounts of unreacted 1-adamantanol will contaminate the product. At temperatures above 75° the amount of tar in the product is increased.
6. Other reducing agents such as sodium thiosulfate or sodium metabisulfite may be used as well.
7. Most of the solvent was evaporated with a bath temperature of 40–50°. The last 40–50 ml. was removed without heating. *endo*-7-Iodomethylbicyclo[3.3.1]nonan-3-one should be handled as quickly as possible, since this iodo ketone is thermally unstable. In the absence of solvent, decomposition may be rapid even at room temperature.
8. The crude iodo ketone usually contains up to 10% benzene, which does not interfere with the cyclization step (Part B). Complete removal of the benzene takes time, during which a considerable proportion of the iodo ketone may decompose.
9. A GC analysis on the crude product was carried out by the submitters using a 1.5 m. × 3.2 mm. column packed with 10% diethylene glycol succinate supported on 60/80 mesh Chromosorb W and heated at 140°. The chromatogram showed peaks for product, 1–3% unreacted 1-adamantanol, and a total of 1–2% of several other minor by-products.
10. Activity III alumina is prepared by adding 6% (w/w) of water to neutral alumina of activity grade I. The submitters used a 50 × 3 cm. glass column for the chromatography.
11. The conditions for GC are given in Note 9. The product was found mainly in fractions 2–20 by the submitters. The first 25-ml. fraction contained considerable amounts of by-products, while fractions 21 and higher contained 1-adamantanol. The checkers collected 10-ml. fractions with an automatic fraction collector.
12. Recrystallization from aqueous methanol raised the melting point to 207–210° (lit.,[4] m.p. 210–212°). The product obtained by the checkers was analytically pure. Analysis calculated for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 80.19; H, 9.31. The spectral characteristics of 4-protoadamantanone are as follows: IR (KBr) $cm.^{-1}$: 2920, 2860, 1710 (C=O), 1322, 1235; ^{1}H NMR ($CDCl_3$), δ (multiplicity, number of protons): 1.0–2.0 (m, *ca.* 7H), 2.0–3.0 (m, *ca.* 7H); ^{13}C NMR ($CDCl_3$) δ (assignment): 216.2 (*C*=O), 51.1 (*C*H), 45.0 (CH_2), 41.4 (CH_2), 38.2 (CH_2), 37.3 (CH_2 and *C*H), 37.2 (*C*H), 34.9 (CH_2), 29.6 (*C*H); mass spectrum *m/e* (relative intensity): 150 (M^+, 100), 95 (63), 93 (23), 81 (24), 80 (40), 79 (46), 67 (30), 66 (40).

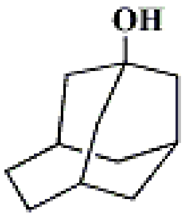
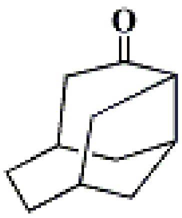
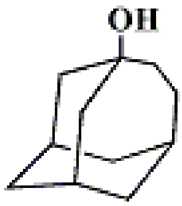
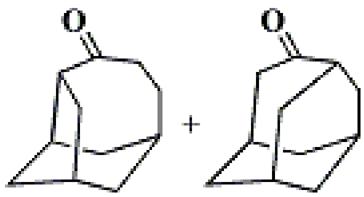
3. Discussion

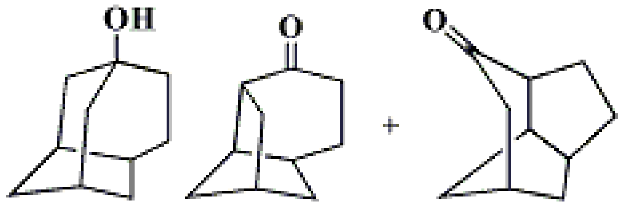
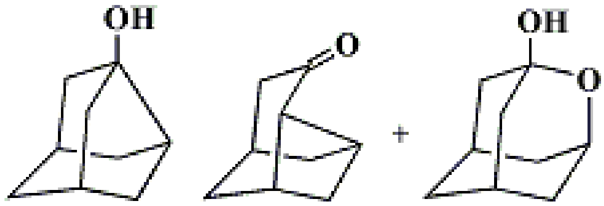
4-Protoadamantanone is a versatile intermediate for the synthesis of not only protoadamantane derivatives,[5,6,7] but also 1,2- and 2,4-disubstituted adamantanes,[8,9,10] 2-substituted noradamantanes,[11] and 4(5)-substituted 4-homoprotoadamantanes.[12]

4-Protoadamantanone has been prepared by the nitrous acid deamination of 2-amino-1-adamantanol (77%),[5] by aprotic diazotization of *endo*-7-aminomethylbicyclo[3.3.1]nonan-3-one in benzene with an equivalent amount of acetic acid (67%),[13] and by thermolysis of 1-adamantyl hypohalites followed by base-promoted cyclization of the resulting halo ketones (32–37%),[4,14,15] In spite of low and erratic yields, the last reaction sequence has provided the most convenient route to the protoadamantanes, since the other two approaches require lengthy syntheses of the starting materials.

The procedure described here is a modification of one involving the thermal fragmentation of 1-adamantyl hypoiodite and cyclization of the resulting iodo ketone.[4,14,16] With this procedure, 4-protoadamantanone is obtained from 1-adamantanol with consistent yields in the range of 71 to 82% and a purity greater than 98%. This method is also applicable to the preparation of other polycyclic ketones from the related bridgehead alcohols with α-bridges of zero, one, or two carbon atoms (see Table I).

TABLE I
Rearranged Polycyclic Ketones Prepared by Fragmentation and Recyclization of Bridgehead Alcohols

Alcohol	Product(s)	Ratio	Yield (%)	Reference
		—	74	16
		2:3	78	17

	1:1	69	18
	2:1[a]	30	18

[a] The base-catalyzed cyclization was carried out in aqueous 70% dioxane at reflux.

With unsymmetrical bridgehead alcohols the structure of the product depends on the regioselectivity of both the fragmentation and intramolecular alkylation reactions. The position of the bond cleavage in the fragmentation step appears to be controlled by the relative thermodynamic stability of the keto free radical intermediates which subsequently react with iodine to produce the iodo ketones. In most cases this can be approximated simply by combination of the relative strain energies of the corresponding hydrocarbons and the relative stabilities of the free radical centers. The course of the cyclization is controlled by the balance of at least three factors: preferential enolization toward one α-methylene group, the size of the smallest ring to be formed, and the relative degree of distortion of the preferred collinear arrangement of the two enolate α-carbon atoms and the carbon-leaving group bond.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium metabisulfite

4-Protoadamantanone

4-PROTOADAMANTANONE (TRICYCLO-[4.3.1.0^{3,8}]DECAN-4-ONE

2-l. separatory funnel

acetic acid (64-19-7)

Benzene (71-43-2)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

chloroform (67-66-3)

sodium hydrogen carbonate (144-55-8)

lead hydroxide

sodium thiosulfate (7772-98-7)

nitrous acid (7782-77-6)

sodium bisulfite (7631-90-5)

iodine (7553-56-2)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

Pentane (109-66-0)

magnesium sulfate (7487-88-9)

dioxane (5703-46-8)

Adamantane (281-23-2)

1-Adamantanol (768-95-6)

1-bromoadamantane (768-90-1)

iodo ketone

2,5-Methano-1H-inden-7(4H)-one, hexahydro (27567-85-7)

2-amino-1-adamantanol

1-adamantyl (19740-18-2)

1-adamantyl hypoiodite

phosphorus pentoxide (1314-56-3)

endo-7-Iodomethylbicyclo[3.3.1]nonan-3-one (29817-49-0)

endo-7-aminomethylbicyclo[3.3.1]nonan-3-one

lead tetraacetate

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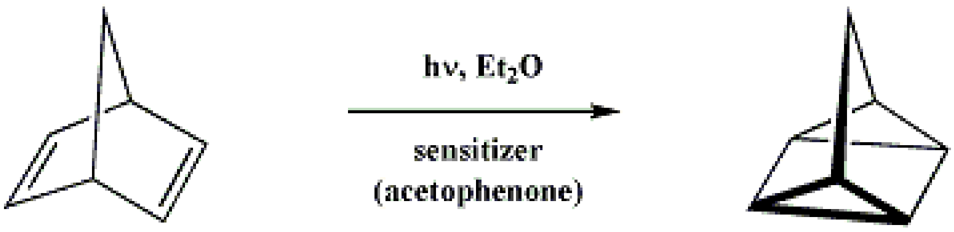
Organic Syntheses, CV 6, 962

QUADRICYCLANE

[Tetracyclo[3.2.0.0^{2,7}.0^{4,6}]heptane]



Submitted by Claibourne D. Smith[1]
Checked by A. J. Taggi and J. Meinwald.

1. Procedure

A Hanovia, 550-watt, immersion photochemical reactor (Note 1) equipped with a magnetic stirrer and water condenser (Note 2) is charged with 1 l. of diethyl ether, 180 g. (1.96 moles) of bicyclo[2.2.1]hepta-2,5-diene (2,5-norbornadiene, (Note 3), and 8 g. of acetophenone. The system is flushed briefly with a stream of nitrogen, then irradiated for about 36–48 hours (Note 4). After irradiation, the ether is removed by distillation through a 20-cm. Vigreux column (Note 5). The residue, a clear liquid weighing about 185 g., is distilled through a spinning-band column under reduced pressure (Note 6), yielding 126–145 g. (70–80%) of quadricyclane as a colorless liquid, b.p. 70° (200 mm.) (Note 7).

2. Notes

1. The reactor, manufactured by the Hanovia Division of Engelhard Industries, consists of a water-jacketed Pyrex well through which a stream of water is continuously passed. The well is placed in an appropriately shaped flask containing the solution to be irradiated [*Org. Synth.*, **Coll. Vol. 5**, 528 (1973)]. The essentially cylindrical flask is equipped with a sidearm near the top which is connected to a water-cooled condenser. There should be sufficient clearance between the bottom of the well and the flask for a magnetic stirring bar. The flask is so designed that the liquid level is above the top of the lamp.
2. A source of nitrogen is attached to the top of the condenser, protecting the system from oxygen. The condenser serves as a safeguard in case the temperature of the system exceeds the boiling point of the solvent.
3. Bicyclo[2.2.1]hepta-2,5-diene was obtained from Shell Chemical Company and can be used as supplied. However, if the diene is distilled it should be used at once. The uninhibited diene may form a white, insoluble polymer or peroxide if allowed to stand in the presence of air and light. The use of undistilled diene results in a slightly lower yield of quadricyclane. The checkers used bicyclo

[2.2.1]hepta-2,5-diene supplied by the Aldrich Chemical Company, Inc., which was distilled prior to use, giving a pure sample, b.p. 89–90.5°, $n_D^{26.5}$ 1.4680.
4. Other sensitizers (acetone, benzophenone) can be used, but with slightly reduced yields. The reaction may be monitored by removing aliquots and analyzing by GC or ^{1}H NMR. For GC analysis a 2-m. column containing 20% by weight of 1,2,3-tris(2-cyanoethoxy)propane suspended on Gas Chrome R (60–80 mesh) is used at a temperature of 75° with a flow rate of 85 ml./minute of helium. The retention time for quadricyclane is 5.2 minutes. For ^{1}H NMR analysis the disappearance of the absorption of the olefinic protons at δ 6.75 is monitored.
Lower wattage lamps can be used, although the irradiation time would be somewhat longer. The checkers found this reaction to be almost complete in about half this time; lamp age and other factors will cause appreciable variation in the irradiation time required.
5. Rapid distillation of the solvent may slightly reduce the yield of product.
6. The only volatile impurity at this point is bicyclo[2.2.1]hepta-2,5-diene. If the irradiation has been carried out for a sufficient period of time, the amount of diene present is less than 2%. Distillation through an efficient column will remove most of the diene, b.p. 91° (760 mm.) or 51° (200 mm.) Traces of acid[2] or noble metal ions and complexes[3] may cause quadricyclane to isomerize to the diene. The checkers used a 60-cm., Teflon-coated, spinning-band column available from Nester-Faust Corporation. The submitter used a similar 43-cm. column.
7. The checkers found n_D^{26} 1.4830 (lit.,[4] 1.4830) for the distillate. The ^{1}H NMR spectrum[2] shows peaks at δ 1.41 (6H) and δ 2.00 (2H). No olefinic absorption was detectable. The IR spectrum (CCl_4) shows three unusually well-resolved bands in the C-H stretching region at 3069, 2929, and 2852 $cm.^{-1}$.

3. Discussion

Quadricyclane may be prepared by direct irradiation of bicyclo[2.2.1]hepta-2,5-diene[2] and 2,3-diazatetracyclo[4.3.0.0^{4,8}.0^{7,9}]non-2-ene,[4] or by photosensitized isomerization of bicyclo[2.2.1]hepta-2,5-diene.[5,6] Several substituted quadricyclanes have been prepared by direct irradiation[7,8,9,10] and by photosensitization.[11,12,13] The procedure described above can be used to isomerize substituted bicycloheptadienes to the corresponding quadricyclanes when traces of sensitizers can be conveniently removed or their presence does not interfere with further use of the quadricyclane.

Quadricyclane is a highly strained and reactive compound. It reacts readily with acetic acid, giving a mixture of nortricyclyl acetate and *exo*-norbornyl acetate and with bromine, yielding a mixture of 2,6-dibromonortricyclene and *exo*-5-*anti*-7-dibromonobornene.[2] Quadricyclane undergoes cycloaddition reactions with a variety of dienophiles, giving 1:1 adducts.[14]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Nortricyclyl acetate

Quadricyclane

20-cm. Vigreux column

quadricyclanes

2,6-dibromonortricyclene

exo-5-anti-7-dibromonobornene

acetic acid (64-19-7)

ether, diethyl ether (60-29-7)

bromine (7726-95-6)

oxygen (7782-44-7)

nitrogen (7727-37-9)

acetone (67-64-1)

Acetophenone (98-86-2)

Benzophenone (119-61-9)

peroxide (7722-84-1)

helium (7440-59-7)

bicyclo[2.2.1]hepta-2,5-diene, 2,5-norbornadiene

1,2,3-tris(2-cyanoethoxy)propane (2465-93-2)

Tetracyclo[3.2.0.0^{2,7}.0^{4,6}]heptane (278-06-8)

2,3-diazatetracyclo[4.3.0.0^{4,8}.0^{7,9}]non-2-ene

exo-norbornyl acetate

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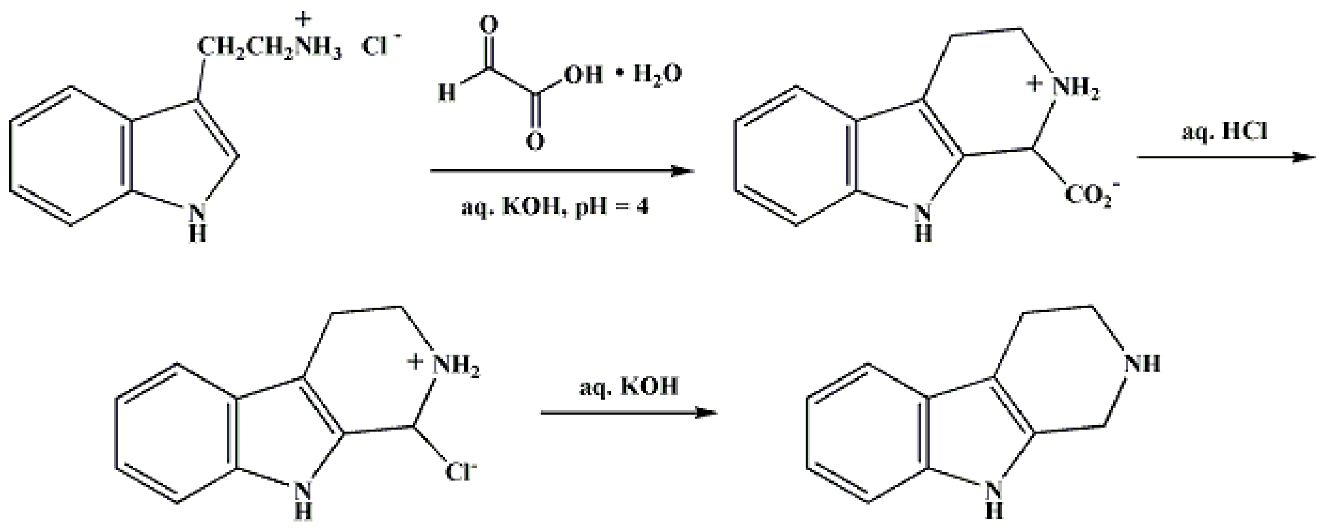
1,2,3,4-TETRAHYDRO-β-CARBOLINE

[1*H*-Pyrido[3,4-*b*]indole, 2,3,4,9-tetrahydro-]



Submitted by Beng T. Ho and K. E. Walker[1].
Checked by S. Teitel, J. O'Brien, and A. Brossi.

1. Procedure

In a 1-l. Erlenmeyer flask, 25 g. (0.13 mole) of tryptamine hydrochloride (Note 1) is dissolved in 400 ml. of water by stirring and warming on a steam bath to approximately 45°. After cooling to room temperature, a solution of 13.2 g. (0.143 mole) of glyoxylic acid monohydrate (Note 2) in 30 ml. of water is added followed by the slow addition (about 3 minutes) of a cooled solution of 7.05 g. (0.126 mole) of potassium hydroxide in 35 ml. of water (Note 3). Precipitation of tetrahydro-β-carboline-1-carboxylic acid takes place during the addition of the potassium hydroxide solution or soon thereafter. After stirring at ambient temperature for 1 hour, the solid is collected on a filter and washed thoroughly with 100 ml. of water. The damp filter cake is transferred to a 1-l. beaker and suspended in 240 ml. of water; 34 ml. of concentrated hydrochloric acid is slowly added (Note 4) with stirring. The mixture is boiled on a hot plate for 30 minutes before an additional 35 ml. of concentrated hydrochloric acid is added. Heating is continued for another 15 minutes, and the resulting solution is allowed to cool to room temperature. The precipitated hydrochloride salt is collected on a filter and washed with 30 ml. of water. The product is dissolved in 400 ml. of water by stirring and warming on a steam bath to approximately 55°, and the solution is adjusted to pH 12 with 20% aqueous potassium hydroxide (approximately 50 ml. is required). After cooling to room temperature, the product is collected by suction filtration, washed with 400 ml. of water, and dried in a vacuum desiccator over phosphorus pentoxide, yielding 17.0–17.6 g. (78–80%) of 1,2,3,4-tetrahydro-β-carboline, m.p. 204–205° (Note 5); ^{1}H NMR spectrum (dimethyl sulfoxide-d_6): δ 2.70 (t, 2H, CH_2CH_2N), 2.72 (s, 1H, N*H*), 3.00 (t, 2H, CH_2CH_2N), 3.85 (s, 2H, CCH_2N), 6.80–7.50 (m, 4H, C_6H_4), and 10.53 (s, 1H, N*H*).

2. Notes

1. The checkers used tryptamine hydrochloride (m.p. 253–255°) purchased from Regis Chemical Company.
2. Glyoxylic acid monohydrate is available from Pierce Chemical Company.
3. The resulting solution should have a pH between 3.5 and 4.0; if not, it should be adjusted with either potassium hydroxide or hydrochloric acid solution.
4. If all the hydrochloric acid is added at once, foaming makes the reaction unmanageable.
5. The melting point agrees with that of the literature[2] and is unchanged on recrystallization of the product from ethanol.

3. Discussion

1,2,3,4-Tetrahydro-β-carboline has been prepared by the condensation of tryptamine with formaldehyde in the presence of sulfuric acid[3] and has also been obtained as a by-product in the acid-catalyzed esterification of 1,2,3,4-tetrahydro-β-carboline-1-carboxylic acid.[2]

The described two-step procedure is uncomplicated and can be carried out in 1 day, giving in good yield a product that does not require further purification. This procedure has been used for the preparation of 3-methyl-, 9-methyl-, and 6-methoxy-1,2,3,4-tetrahydro-β-carboline[4] and has been modified for 9-phenyl-1,2,3,4-tetrahydro-β-carboline.[5] The method is generally applicable to the preparation of other 1-unsubstituted tetrahydro-β-carbolines providing the 1-carboxylic acid precursor is soluble in the hot acid used to effect decarboxylation.

Reviews of the chemistry of the carbolines have been published.[6,7]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

3-methyl-, 9-methyl-, and 6-methoxy-1,2,3,4-tetrahydro-β-carboline

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid, hydrochloride (7647-01-0)

formaldehyde (630-08-0)

potassium hydroxide (1310-58-3)

tryptamine (61-54-1)

1,2,3,4-Tetrahydro-β-carboline, tetrahydro-β-carbolines, 1H-Pyrido[3,4-b]indole, 2,3,4,9-tetrahydro- (16502-01-5)

tryptamine hydrochloride (343-94-2)

glyoxylic acid monohydrate (6000-59-5)

1,2,3,4-tetrahydro-β-carboline-1-carboxylic acid, tetrahydro-β-carboline-1-carboxylic acid

9-phenyl-1,2,3,4-tetrahydro-β-carboline

phosphorus pentoxide (1314-56-3)

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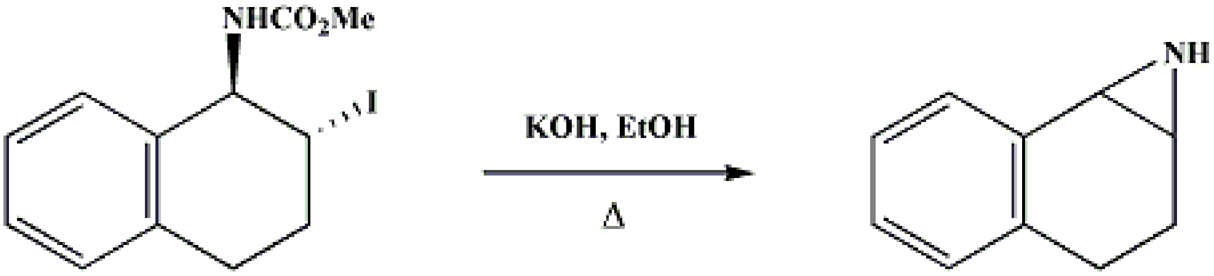
AZIRIDINES FROM β-IODOCARBAMATES: 1,2,3,4-TETRAHYDRONAPHTHALENE(1,2)IMINE

[1*H*-Naphth[1,2-*b*]azirine, 1a,2,3,7b-tetrahydro-]



Submitted by C. H. Heathcock[1] and A. Hassner[2].
Checked by William G. Kenyon and Richard E. Benson.

1. Procedure

A 500-ml., round-bottomed flask equipped with a reflux condenser is charged with a solution of 25 g. of potassium hydroxide in 250 ml. of 95% ethanol, to which is added 16.6 g. (0.0498 mole) of methyl (*trans*-2-iodo-1-tetralin)carbamate (Note 1). The resulting mixture is heated under reflux on a stream bath for 2 hours, cooled, and added to 500 ml. of water. The clear, yellow solution is shaken three times with 100-ml. portions of diethyl ether. The ether layers are combined, washed three times with 125-ml. portions of water and once with 125 ml. of a saturated sodium chloride, dried over 5 g. of anhydrous potassium carbonate, and filtered. The ether is removed by distillation on a steam bath, giving the crude imine as a yellow-brown oil (Note 2). The oil is transferred to a small flask, the container is rinsed with ether, and the rinse is added to the distillation flask. The product is collected by distillation through a small Vigreux column with warm water circulating through the condenser to prevent crystallization of the product. The fraction boiling at 80–82° (0.15–0.25 mm.) is collected as a solid that forms in the receiver, yielding 4.9–5.1 g. (68–70%) of the imine, m.p. 54–56° (Note 2); the IR spectrum has a band at 3205 cm.$^{-1}$ (NH) (Note 3).

2. Notes

1. The methylcarbamate may be prepared by the procedure in *Org. Synth.*, **Coll. Vol. 6**, 795 (1988).
2. The submitters state that product, m.p. 49–51°, can be obtained by direct crystallization of the oil. The oil from a run conducted on a scale twice that described above is cooled to −15° and 30 ml. of pentane is added. Upon scratching the flask, the product crystallizes, is collected by filtration, and washed with a little cold pentane, yielding 9–10 g. (62–69%), m.p. 49–51°.

3. The ^{1}H NMR spectrum (CCl_4) shows a broad singlet centered at δ 0.7 (1H) and complex multiplets at 1.1–3.05 (6H) and 6.76–7.30 (4H).

3. Discussion

The procedure reported here, that of Hassner and Heathcock,[3] is more convenient than the Wenker synthesis of aziridines[4] and appears to be more general.[5] It represents a simple route from olefins to aziridines (*via* β-iodocarbamates).[3,5,6] Aziridines are also useful as intermediates in the synthesis of amino alcohols and heterocyclic systems.[5,7,8,9]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 795

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

β-IODOCARBAMATES

ethanol (64-17-5)

potassium carbonate (584-08-7)

ether, diethyl ether (60-29-7)

sodium chloride (7647-14-5)

potassium hydroxide (1310-58-3)

Pentane (109-66-0)

1,2,3,4-Tetrahydronaphthalene(1,2)imine, 1H-Naphth[1,2-b]azirine, 1a,2,3,7b-tetrahydro- (1196-87-8)

methylcarbamate

Methyl (trans-2-iodo-1-tetralin)carbamate (1210-13-5)

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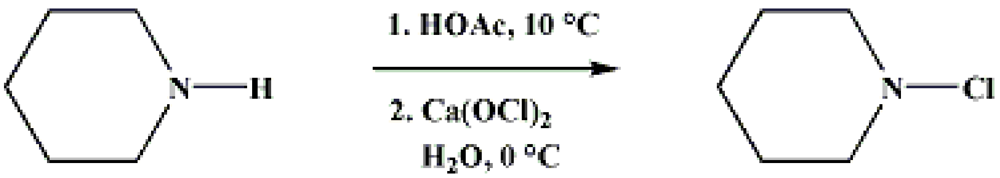
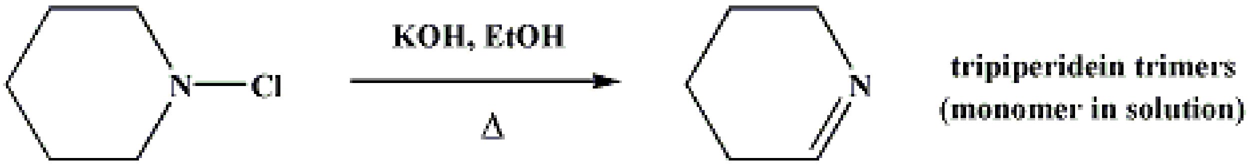
Organic Syntheses, CV 6, 968

2,3,4,5-TETRAHYDROPYRIDINE TRIMER

[Pyridine, 2,3,4,5-tetrahydro-, trimer]





Submitted by George P. Claxton, Lloyd Allen, and J. Martin Grisar[1].
Checked by Henry F. Russell, Richard J. Sundberg, and Carl R. Johnson.

1. Procedure

A. N-*Chloropiperidine*. A 500-ml., three-necked flask fitted with a mechanical stirrer, a dropping funnel, and a thermometer is charged with 170 g. (2.00 moles) of piperidine (Note 1). The flask is cooled in an acetone–ice bath, the piperidine is stirred, and 120 g. (2.00 moles) of glacial acetic acid is added dropwise at such a rate that the temperature does not exceed 10° (Note 2).

A 3-l., three-necked flask fitted with a mechanical stirrer, a dropping funnel, and a thermometer is charged with an aqueous solution of 2.2 moles of calcium hypochlorite (Note 3), and the piperidine acetate prepared above is placed in the dropping funnel. The hypochlorite solution is stirred and cooled to 0° to –5° with a methanol–ice bath, and the piperidine acetate is added dropwise over a period of 1.25 hours while the temperature is maintained below 0°. After an additional 15 minutes of stirring, equal portions of the mixture are placed in two 2-l. separatory funnels and extracted three times with a total of about 1300 ml. of diethyl ether. The ether extract is placed in a 2-l. flask dried overnight over anhydrous sodium sulfate in a cold room at 4° and filtered. The bulk of the ether is removed with a water bath maintained below 60° (Note 4).

B. 2,3,4,5-*Tetrahydropyridine trimer*. A 3-l., three-necked, round-bottomed flask equipped with a sealed mechanical stirrer, a dropping funnel, and a reflux condenser fitted with a calcium chloride drying tube is charged with 264 g. (4.71 moles) of potassium hydroxide and 1250 ml. of absolute ethanol. This mixture is stirred with a Teflon paddle (Note 5) and heated to reflux, effecting solution. The *N*-chloropiperidine

solution prepared in Part A is filtered through glass wool directly into the dropping funnel and added dropwise to the well-stirred, boiling reaction mixture over a period of *ca.* 2.5 hours (Note 6). The resulting mixture is stirred for an additional 2 hours without heating and allowed to stand at least 24 hours at room temperature, during which time tetrahydropyridine trimerizes. Precipitated potassium chloride is removed by filtration, washed with two 150-ml. portions of absolute ethanol, and set aside for later use. The washes are combined with the filtrate, ethanol is distilled off an a steam bath under reduced pressure, and the distillate saved for further processing (Note 7). The residue remaining after distillation and the recovered potassium chloride are then combined in 750 ml. of water, and the resulting solution is extracted four times with a total of 500 ml. of ether. After standing over anhydrous magnesium sulfate for 4 hours, the extract is filtered and concentrated on a rotary evaporator with gentle warming. The resulting oily residue is dissolved in 75 ml. of acetone, and the solution is cooled to −20° overnight. If no seed crystals are available, the walls of the flask are scratched with a glass rod, inducing crystallization. The precipitate is collected by vacuum filtration and washed twice with 20-ml. portions of cold (−20°) acetone, giving 64–80 g. (39–48%) of tetrahydropyridine trimer, m.p. 58–61° (Note 8).

2. Notes

1. Freshly distilled piperidine was used.

2. Ice was added to the mixture as required to dissolve any precipitated material and keep the viscous solution clear.

3. MC and B Manufacturing Chemists HTH grade 70% calcium hypochlorite was used. The solution required for the procedure was prepared by placing 680 g. of 70% calcium hypochlorite and 3 l. of water in a 5-l. flask and stirring overnight. The mixture was allowed to settle for several hours, and the supernatant was vacuum-filtered through Celite and glass wool, giving enough hypochlorite solution for a single run. By centrifugation of the suspension remaining after decanting, enough hypochlorite solution for another run could be obtained. The molarity of the solution was determined by iodometric titration: 1 g. of potassium iodide was dissolved in 25 ml. of water, and 15 ml. of 10% sulfuric acid and 1 ml. of the hypochlorite solution were added. The red solution was titrated with 0.10 *N* sodium thiosulfate. When the color changed to faint yellow, 1 ml. of starch solution was added, and the titration was continued to the colorless end point. The concentration was then determined according to the following formula: [(ml. $Na_2S_2O_3$ reagent)(normality $Na_2S_2O_3$)] = molarity of $Ca(OCl)_2$

4. *Caution! To avoid a rapid, spontaneous decomposition that results in complete loss of N-chloropiperidine, the ether should not all be boiled off, nor should the temperature exceed 60°. The crude product should be used immediately in Part B.*

5. Use of a wire stirrer caused darkening of the ethanolic potassium hydroxide solution.

6. Isotripiperidein (m.p. 97–98°) is obtained if insufficient potassium hydroxide

is used or if stirring is not sufficiently vigorous[2] (see Discussion).

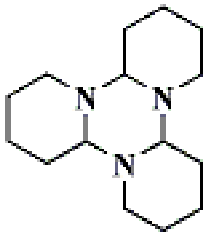
7. It is recommended that this solvent be reused in later runs.[2,3] The submitters found that substantial amounts of product can be recovered from this distillate after a few days of standing. Thus, it appears that some tetrahydropyridine distils as monomer with the ethanol and trimerizes in the distillate. The checkers found that when the reaction was worked up after 24 hours of standing, the majority of the product was in the ethanol distillate. Therefore, they allowed the distillate to stand for several days, concentrated it by rotary evaporation, and crystallized the residue from acetone. The resulting tetrahydropyridine trimer was combined with the otherwise obtained.

8. Two trimers are known: α- (m.p. 60–62°) and β- (m.p. 70–73°) tripiperidein.[2] The β-form, usually obtained as a crude, white solid (m.p. 40–68°), may be converted to the more stable α-isomer by recrystallizing from acetone containing 2% water.[2] α-Tripiperidein is best stored in a close container over potassium hydroxide and may be kept for over a year in this manner.

3. Discussion

There is one standard procedure for preparing 2,3,4,5-tetrahydropyridine.[2,3] No acceptable alternative method is available except that *N*-chlorosuccinimide may be substituted for calcium hypochlorite.[4] Similar reaction sequences have been used to prepare substituted 2,3,4,5-tetrahydropyridines,[4,5] pyrroline,[6] and substituted pyrrolines.[7]

2,3,4,5-Tetrahydropyridine is useful for condensation with pyrroles and indoles,[8,9,10] β-ketoacids,[11,12,13,14] β-ketoesters,[15] and for a novel and very general reaction with magnesium chelates formed by reaction of methyl ketones with magnesium methyl carbonate.[16,17] The highly reactive monomer trimerizes on standing to tripiperidein, which exists in two interconvertible crystalline forms designated as α and β:



In the absence of base, the trimer can rearrange to iso-tripiperidein, a product of self-condensation.[11,18] In the presence of base, however, α-tripiperidein is stable for over a year. In solution, tripiperidein readily detrimerizes to the monomer, which is in equilibrium with δ-aminovaleraldehyde (5-aminopentanal).[9]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 26

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanolic potassium hydroxide

2,3,4,5-Tetrahydropyridine trimer

Pyridine, 2,3,4,5-tetrahydro-, trimer

tetrahydropyridine trimer

Isotripiperidein

tripiperidein

α-Tripiperidein

2,3,4,5-tetrahydropyridines

iso-tripiperidein

ethanol (64-17-5)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

ether, diethyl ether (60-29-7)

sodium sulfate (7757-82-6)

potassium iodide (7681-11-0)

sodium thiosulfate (7772-98-7)

acetone (67-64-1)

potassium hydroxide (1310-58-3)

piperidine (110-89-4)

potassium chloride (7447-40-7)

hypochlorite (14380-61-1)

magnesium sulfate (7487-88-9)

calcium hypochlorite (7778-54-3)

piperidine acetate

N-chlorosuccinimide (128-09-6)

magnesium methyl carbonate

PYRROLINE

TETRAHYDROPYRIDINE, 2,3,4,5-TETRAHYDROPYRIDINE

N-Chloropiperidine (2156-71-0)

δ-aminovaleraldehyde, 5-aminopentanal

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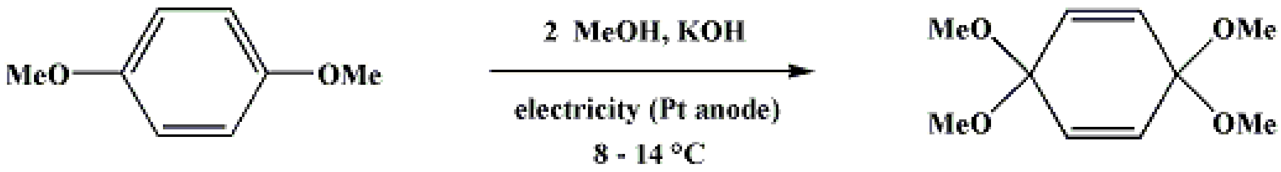
Organic Syntheses, CV 6, 971

3,3,6,6-TETRAMETHOXY-1,4-CYCLOHEXADIENE

[1,4-Cyclohexadiene, 3,3,6,6-tetramethoxy-]



Submitted by Paul Margaretha[1] and Paul Tissot[2].
Checked by Ronald F. Sieloff and Carl R. Johnson.

1. Procedure

A 600-ml., tall-form beaker is equipped with a thermometer, a magnetic stirring bar, and two electrodes, a 45-mesh, cylindrical platinum anode (Note 1) surrounded by a cylindrical nickel cathode (Note 2). The electrodes are held in place (distance between anode and cathode: 0.75 cm.) and suspended in the beaker with a clamp formed from Delrin rods (Note 3). The electrodes are connected to an adjustable DC power supply (Note 4), (Note 5).

A solution of 27.6. g. (0.200 mole) of 1,4-dimethoxybenzene (Note 6), 4.0 g. of potassium hydroxide, and 400 ml. of methanol is placed in the apparatus. The beaker and contents are cooled with a 0° bath. The magnetically stirred solution is electrolyzed for 6 hours at a current intensity maintained at 2.0 amp. (Note 5), (Note 7). The temperature of the solution varies between 8° and 14°. During this time small amounts of methanol are added from time to time to compensate for evaporation.

After electrolysis the solution is reduced to a volume of 100 ml. with a rotary evaporator and extracted 10 times with 100-ml. portions of hexane. The hexane fractions are dried over anhydrous magnesium sulfate and the hexane evaporated with a rotary evaporator, yielding white crystals. Recrystallization from 75 ml. of pentane (Note 8) affords 27.8–28.2 g. (70–71%) of pure 3,3,6,6-tetramethoxy-1,4-cyclohexadiene, m.p. 40–43° (Note 9).

2. Notes

1. The platinum anode used was Model 611 obtained from Engelhard Industries. This electrode has a height of 5.6 cm. and a diameter of 5.1 cm. The total surface area claimed by the supplier is 200 $cm.^2$
2. The nickel cathode, fashioned from 22 gauge nickel sheet obtained from Huntington Alloys, Inc., Huntington, W. Va. 25720, had a height of 5.6 cm. and a diameter of 6.6 cm. When the sheet was rolled into a cylinder a small gap was left at the seam.
3. The clamp consisted of a 30 cm. vertical Delrin rod (0.5 cm. in diameter) threaded through the center of two 7-cm. horizontal Delrin rods (1.25 cm. in diameter). The horizontal rods were notched to hold the electrodes between them.
4. The power source used by the checkers was a 30-volt, 3-amp. adjustable DC supply.
5. The submitters used a cathode of nickel foil (140 × 71 × 0.5 mm.) rolled into a cylinder 3.5 cm. in diameter surrounded by three curved platinum anodes each having the dimensions 70 × 30 × 1 mm. (total surface area 130 $cm.^2$) with a distance of 0.5–1 cm.

between the cathode and the anodes. The submitters electrolyzed for 6 hours at a current maintained at 3.25 amp. This corresponds to a total of 19.5 amp.-hours and an anodic current density of 0.025 amp./$cm.^2$ Under these conditions the submitters report yields of 81–84%.

6. 1,4-Dimethoxybenzene was obtained from Aldrich Chemical Company Inc.

7. This corresponds to 12 amp.-hours (theoretical value is 10.6 amp.-hours). Longer electrolysis times did not significantly increase the yield of product.

8. Cooling is necessary to complete crystallization.

9. ^{1}H NMR ($CDCl_3$) δ (multiplicity, number of protons, assignment): 3.30 (s. 12H $4OCH_3$), 6.10 (s, 4H, 4C*H*).

3. Discussion

The procedure described is essentially that of Belleau and Weinberg[3] and represents the only known way of obtaining the title compound. One other quinone ketal, 1,4,9,12-tetraoxadispiro[4.2.4.2]tetradeca-6,13-diene, has been synthesized by a conventional method (reaction of 1,4-cyclohexanedione with ethylene glycol followed by bromination and dehydrobromination[4]) as well as by an electrochemical method [anodic oxidation of 2,2-(1,4-phenylenedioxy)diethanol[5]]. Quinone ketals have been used as intermediates in the synthesis of 4,4-dimethoxy-2,5-cyclohexadienone, *syn*-bishomoquinone,[4,6] and compounds related to natural products.[7]

Aromatic diethyl ethers and furans undergo alkoxylation by addition upon electrolysis in alcohol containing a suitable electrolyte.[8,9,10,11,12] Other compounds such as aromatic hydrocarbons, alkenes, *N*-alkyl amides, and ethers lead to alkoxylated products by substitution. Two mechanisms for these electrochemical alkoxylations are currently discussed. The first one consists of direct oxidation of the substrate, giving the radical cation which reacts with the alcohol, followed by reoxidation of the intermediate radical, and either alcoholysis or elimination of a proton to the final product. In the second mechanism the primary step is the oxidation of the alcoholate, giving an alkoxyl radical which reacts with the substrate, the consequent steps then being the same as above. The formation of quinone ketals in particular seems to proceed *via* the second mechanism.[5]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

syn-bishomoquinone

methanol (67-56-1)

nickel (7440-02-0)

potassium hydroxide (1310-58-3)

ethylene glycol (107-21-1)

Pentane (109-66-0)

magnesium sulfate (7487-88-9)

hexane (110-54-3)

1,4-dimethoxybenzene (150-78-7)

1,4-Cyclohexanedione (637-88-7)

3,3,6,6-Tetramethoxy-1,4-cyclohexadiene, 1,4-Cyclohexadiene, 3,3,6,6-tetramethoxy- (15791-03-4)

quinone ketal

1,4,9,12-tetraoxadispiro[4.2.4.2]tetradeca-6,13-diene

2,2-(1,4-phenylenedioxy)diethanol (104-38-1)

4,4-dimethoxy-2,5-cyclohexadienone

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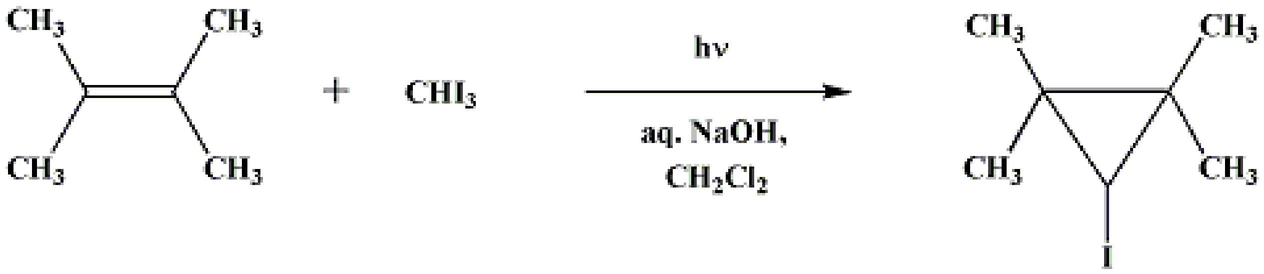
Organic Syntheses, CV 6, 974

2,2,3,3-TETRAMETHYLIODOCYCLOPROPANE

[Cyclopropane, 3-iodo-1,1,2,2-tetramethyl]



$$I_2 + 2\ NaOH \longrightarrow NaI + NaOI + H_2O$$

Submitted by T. A. Marolewski and N. C. Yang[1].
Checked by T. Nakahira and K. B. Wiberg.

1. Procedure

Caution! The intense emission from the light source should be shielded from visibility in order not to damage the eyesight of the experimentalist.

Each of three 250-ml., round-bottomed Pyrex flasks is charged with 8.4 g. (0.10 mole) of 2,3-dimethyl-2-butene (Note 1), 175 ml. of dichloromethane, and 50 ml. of an aqueous 5 *M* sodium hydroxide solution. The flasks are kept rather full, making more efficient use of the incident light. A Teflon-covered magnetic stirring bar 2.5 cm. in length is added to each flask. Three 170 cm. by 90 cm. Pyrex crystallization dishes are partially filled with an ice–water mixture (Note 2), each dish is placed above a Mag-Mix magnetic stirrer, and each flask is immersed in the ice–water bath and held in place with a clamp. The three assemblies are arranged symmetrically around a Hanovia quartz immersion well (Note 3) cooled with running tap water, containing a Hanovia 450-watt, medium pressure, mercury lamp. The edge of each flask is placed approximately 1 cm. from the wall of the well. After 2.0 g. of iodoform is added to each flask, the mixtures are irradiated with stirring until the yellow color of the iodoform disappears. This process is continued until 39.4 g. (0.100 mole) of iodoform, equally distributed between the flasks, has been consumed (Note 4). After the reaction is complete, the reaction mixtures are combined and the organic layer is separated, washed once with water, and dried over anhydrous sodium sulfate. The solvent is removed with a rotary evaporator and a water pump. The residue is transferred to a 50-ml. flask, and 1.0 g. of sodium methoxide is added (Note 5). The mixture is distilled under reduced pressure in an apparatus with a 5-cm. Vigreux sidearm. The receiver is cooled in an ice–water bath and the first fraction, which boils at 45–48° (5 mm.), n_D^{25} 1.5087, is collected, yielding 14.0–15.0 g. (63–67%) of a clear distillate which should be stored in a refrigerator (Note

6) and (Note 7).

2. Notes

1. 2,3-Dimethyl-2-butene (99%) was purchased from the Chemical Samples Co.
2. At the beginning of irradiation, the mixture is mostly ice and contains just enough water to make efficient contact with the flask. The ratio of ice to water will vary during the course of irradiation, and ice is added to replace excess water from time to time.
3. Vycor or Pyrex wells are also satisfactory since the irradiation is carried out in Pyrex flasks.
4. The total period of irradiation was about 8 hours; however, this may vary with the equipment used.
5. The presence of sodium methoxide prevents decomposition of the product during the distillation.
6. The checkers also carried out the reaction using equimolar quantities of 2,3-dimethyl-2-butene and iodoform (0.1 mole each) and obtained 12.6–13.0 g. (56–58%) of the product. The submitters made the same observation. They found that the yield increased slightly as the mole ratio of olefin to iodoform was increased from 1:1 to 3:1. Use of a larger excess of olefin resulted in no further increase in yield.
7. 1-Iodo-*cis,trans*-2,3-dimethylcyclopropane, b.p. 25–27° (8–10 mm.), n_D^{25} 1.5105, may be prepared in 56% yield from *trans*-2-butene (Matheson Gas Products) with this procedure. Both the 2,2,3,3-tetramethyliodocyclopropane and the 1-iodo-*cis,trans*-2,3-dimethylcyclopropane prepared by this procedure give only one peak on GC. The retention times are 272 and 114 seconds, respectively, on a 60-cm. 20% SE-30 on Chromosorb W column at a temperature of 81° and a helium flow rate of 41 ml. per minute.

3. Discussion

Bromo- and iodocyclopropanes cannot be prepared by the direct halogenation of cyclopropanes. Substituted chloro- and bromocyclopropanes have been synthesized by the photochemical decomposition of α-halodiazomethanes in the presence of olefins;[2] iodocyclopropanes have been prepared by the reaction of an olefin with iodoform and potassium *tert*-butoxide, followed by the reduction of the diiodocyclopropane formed with tri-*n*-butyltin hydride.[3] The method described employs a readily available light source and common laboratory equipment, and is relatively safe to carry out. The method can be modified for the preparation of cyclopropanes and halocyclopropanes as well, by using diiodomethane and halodiiodomethanes instead of iodoform.[4,5] If the olefin used gives two isomeric halocyclopropanes, the isomers are usually separable by chromatography.[4]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Bromo- and iodocyclopropanes

sodium hydroxide (1310-73-2)

sodium sulfate (7757-82-6)

sodium methoxide (124-41-4)

diiodomethane (75-11-6)

iodoform (75-47-8)

dichloromethane (75-09-2)

2,3-dimethyl-2-butene (563-79-1)

helium (7440-59-7)

tri-n-butyltin hydride (688-73-3)

2,2,3,3-Tetramethyliodocyclopropane, Cyclopropane, 3-iodo-1,1,2,2-tetramethyl (39653-50-4)

diiodocyclopropane

potassium tert-butoxide (865-47-4)

trans-2-Butene (624-64-6)

1-Iodo-cis,trans-2,3-dimethylcyclopropane

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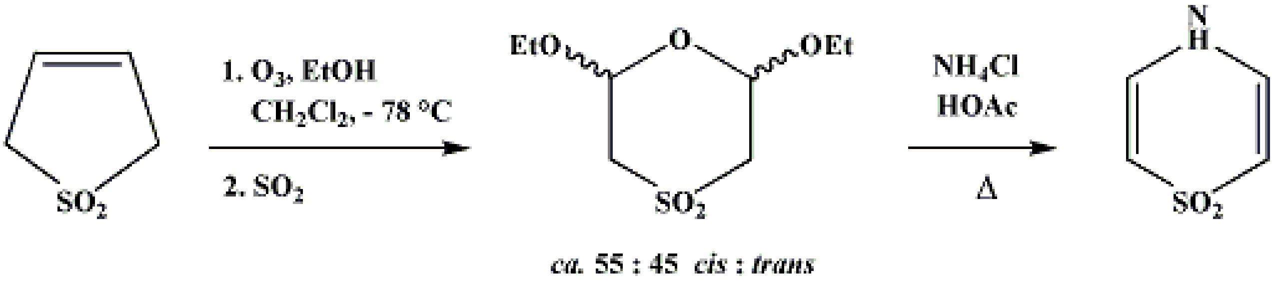
Organic Syntheses, CV 6, 976

4*H*-1,4-THIAZINE 1,1-DIOXIDE



Submitted by Wayland E. Noland[1] and Robert D. DeMaster[2].
Checked by H. Gurien, G. Kaplan, and A. Brossi.

1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A. cis *and* trans-2,6-*Diethoxy*-1,4-*oxathiane* 4,4-*dioxide*. Ozone (Note 1) is passed into a solution of 2,5-dihydrothiophene 1,1-dioxide (30.0 g., 0.254 mole) (Note 2) in 50 ml. of absolute ethanol (Note 3) and 250 ml. of dichloromethane contained in a 1-l., three-necked, round-bottomed flask fitted with a straight glass-inlet tube, a calcium chloride drying tube, and a glass stopper. The solution is cooled in a methanol–dry ice bath and magnetically stirred while the ozone is added. When the solution becomes blue (Note 4), the addition of ozone is stopped and liquid sulfur dioxide (35 ml., 0.78 mole) (Note 5) is added in portions over a period of 10–15 seconds. After 2 minutes, the cold bath is removed and the reaction solution is allowed to warm to room temperature over a period of 8–16 hours. The resulting dark-brown solution is poured into a 4-l. beaker containing a rapidly stirred mixture of aqueous sodium carbonate (120 g. in 1 l. of cold water) and 200 g. of ice. The reaction flask is rinsed with 50 ml. of water, which is added to the basic mixture. After being stirred for 5 minutes, the basic mixture is poured into a 2-l. separatory funnel and the lower dichloromethane layer is separated and saved. The beaker is rinsed with 200 ml. of dichloromethane and 100 ml. of water, which are then added to the separatory funnel. The contents of the separatory funnel are shaken, and the lower, dichloromethane layer is separated and saved. The aqueous layer is extracted with two more 150-ml. portions of dichloromethane. All of the dichloromethane layers and extracts are combined, and washed with 300 ml. of water and 300 ml. of saturated aqueous sodium chloride. The solution is dried over 3–6 g. of anhydrous magnesium sulfate, filtered, and evaporated with a rotary evaporator at 50–60° in a water bath under aspirator pressure. The residual, cream-colored solid (50–52 g., 88–91%), m.p. 76–118°, is dissolved with magnetic stirring in 850–950 ml. of boiling heptane (Note 6) containing 1–2 g. of activated carbon and filtered hot.

The filtrate is cooled to 0° in a refrigerator overnight. The resulting precipitate is filtered, giving *cis*- and *trans*-2,6-diethoxy-1,4-oxathiane 4,4-dioxide as a white solid (42–46 g., 74–81%), m.p. 83–117° (Note 7).

B. *4H*-1,4-*Thiazine* 1,1-*dioxide*. *Caution! This step should be carried out in a hood to avoid exposure to hydrogen chloride gas.* A mixture of *cis*- and *trans*-2,6-diethoxy-1,4-oxathiane 4,4-dioxide (15.0 g., 0.0669 mole), 3.8 g. (0.071 mole) of ammonium chloride (Note 8), and 300 ml. of glacial acetic acid is placed in a 500-ml., one-necked, round-bottomed flask fitted with a reflux condenser and a magnetic stirring bar. The mixture is placed in an oil bath preheated to 125–130° and refluxed, with magnetic stirring, for 25–35 minutes, during which the ammonium chloride dissolves, hydrogen chloride is evolved, and the solution becomes brownish yellow in color (Note 9). The acetic acid is evaporated with a rotary evaporator at 70–80° in a water bath under aspirator pressure. The residual yellow solid is magnetically stirred with a solution of 75 ml. of diethyl ether containing 10 ml. of 2-propanol for 10 minutes (Note 10). The resulting suspension is filtered, then sucked dry on a Büchner funnel. The yellow solid (8.7–9.2 g.), m.p. 208–212°, is boiled with 225–250 ml. of 2-propanol and filtered hot, removing the residual, greenish-black, insoluble material (0.5–1 g.). The filtrate is cooled to −10° to −5° in a freezer overnight, causing separation of 4.6–5.3 g. (52–60%) of *4H*-1,4-thiazine 1,1-dioxide as small yellow needles, m.p. 237–240° (Note 11), which are filtered. Concentration of the filtrate to 50 ml., followed by filtration and cooling, causes separation of an additional 1.5–2.0 g. (17–23%) of crude yellow solid, m.p. 234–240°.

2. Notes

1. A Welsbach Corporation Ozonator, style T-23, was used, with the voltage set at 120 volts and the oxygen pressure at 8 p.s.i. to give a 4–5% ozone concentration. The checkers used a Welsbach Corporation Ozonator, style T-408, to give a 1–2% ozone concentration. The input oxygen was dried by being passed through a tower of color-indicating Hammond Drierite.
2. 2,5-Dihydrothiophene 1,1-dioxide (butadiene sulfone, or 3-sulfolene) was purchased from the Aldrich Chemical Company, Inc.
3. Use of larger amounts of absolute ethanol causes formation of more of the acyclic 3-thiapentane-1,5-dial bis(diethyl acetal) 3,3-dioxide, with a corresponding reduction in yield of the cyclic product.
4. Appearance of the blue color of ozone signals complete cleavage of the double bond. Further addition of ozone could cause undesirable oxidation.
5. Sulfur dioxide was purchased in lecture-size bottles from the City Chemical Corporation. The gas was condensed into a precalibrated, 50-ml. Erlenmeyer flask cooled in the methanol–dry ice bath used for cooling the ozonolysis reaction.
6. Eastman Organic Chemicals Technical Grade "Heptanes," b.p. 96–100°, containing 70% heptanes and the rest octanes, was used.
7. In one instance the submitters obtained an 85% yield when the reaction mixture was stirred with sulfur dioxide for 18 hours, followed by crystallization of the resulting crude material (32 g. per l.) without the use of charcoal.
The product is obtained as an approximately 55:45 mixture of *cis*- and *trans*-isomers, as indicated by ^{1}H NMR absorption ($CDCl_3$) at δ 1.27 (t, J = 7 Hz., 5.9H, 2 OCH_2CH_3), 2.77–3.47 (m, 4.0H, $CH_2SO_2CH_2$), 3.47–4.27 (m, 4.1H, 2 OCH_2CH_3), 4.95 (d of d, $J_{a,a}$ = 8 Hz., $J_{a,e}$ = 2 Hz., 1.1H, C*H* proton of the *cis*-isomer), and 5.33 (t, J = 4 Hz., 0.9H, C*H* proton of the *trans*-isomer). The IR spectrum (Nujol) has strong bands at 1312, 1118, 1029, and 972 cm.$^{-1}$, which are attributed to the SO_2 and CO groups. The *cis*-isomer, m. p. 103–105°, can be separated from the mixture by three or four fractional crystallizations from methanol, while the *trans*-isomer, m.p. 136–137°, can be separated from the

mixture (or from the residue obtained by evaporation of the methanol mother liquors from which the *cis*-isomer was crystallized) by two or three fractional crystallizations from benzene-petroleum ether (b.p. 60–68°).

8. "Baker Analyzed" Reagent Grade ammonium chloride was purchased from the J. T. Baker Chemical Company.

9. Refluxing for longer times causes formation of increased amounts of a dark, greenish-brown by-product, which complicates purification by crystallization. If the acetic acid becomes black-brown, the residue (which is sometimes tarry) obtained on evaporation can be purified by rapid chromatography through a 3.8-cm.-deep column of activated alumina, using acetone as a transfer agent and eluent.

10. The purpose of the wash with ether and 2-propanol is to remove the remaining acetic acid and any residual hydrogen chloride, which may cause decomposition during the subsequent crystallization.

11. The analytical sample melted at 240–241.5°. The IR spectrum (Nujol) has a strong NH band at 3360, a strong band in the double bond region at 1645 and another at 1511, and a group of bands at 1265 and 1255 (medium strong) and 1238, 1226, 1102, and 1093 (all strong), some of which are attributable to the sulfonyl group, and a strong band at 692 cm.$^{-1}$. The ^{1}H NMR spectrum (dimethyl sulfoxide-d_6) has an AA'BB' pattern with major peaks at δ 7.12 and 6.99 (2.0H) and 6.02 and 5.88 (2.0H), attributed to the 4 C*H* protons. The UV spectrum has maxima (95% C_2H_5OH) nm at (log ε) 226 (3.75), 230, inflection (3.72), 237, inflection (3.47), 277 (3.52), and 287 (3.55).

3. Discussion

This procedure represents the first reported synthesis of *cis*- and *trans*-2,6-diethoxy-1,4-oxathiane 4,4-dioxide[3] and of its further reaction product, 4*H*-1,4-thiazine 1,1-dioxide.[3] A derivative of the latter, 3,5-diphenyl-4*H*-1,4-thiazine 1,1-dioxide, has been prepared previously by reaction of phenacyl sulfone with ammonia.[4,5] Primary amines, in addition to ammonia, can be converted to the corresponding 4-substituted 4*H*-1,4-thiazine 1,1-dioxides by condensation with 2,6-diethoxy-1,4-oxathiane 4,4-dioxide, using the procedure described above. For example, 4-aminobenzoic acid hydrochloride gave 4-(4-carboxyphenyl)-4*H*-1,4-thiazine 1,1-dioxide in 83% yield.[3] The submitters have also observed,[3] as have others,[4] that the 4*H*-1,4-thiazine 1,1-dioxide system may be *N*-alkylated with an alkyl halide using potassium carbonate in anhydrous acetone.

The ozonolysis reaction, followed by reductive workup with sulfur dioxide, as described in Part A of the present procedure, illustrates a general method which has been developed for the preparation of acetals.[3] Application of the procedure is illustrated by conversion of the following olefins in alcoholic solution to the corresponding acetals:[3] (1) 1-chloro-4-(2-nitrophenyl)-2-butene to 2-nitrophenylacetaldehyde dimethyl acetal in 84% yield; (2) 1,4-dibromo-2-butene to bromoacetaldehyde dimethyl acetal in 67% yield; (3) 3-butenoic acid to malonaldehydic acid diethyl acetal ethyl ester in 61% yield; (4) cyclopentadiene to malonaldehyde bis(diethyl acetal) in 48% yield; and (5) 1,4-dinitro-2-butene (produced *in situ* from 1,3-butadiene and dinitrogen tetroxide) to nitroacetaldehyde diethyl acetal in 21% yield.

References and Notes

1. School of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455.
2. Safety and Security Systems Laboratory, 3M Company, St. Paul, Minnesota 55101.

3. Robert D. DeMaster, Ph.D. Dissertation, University of Minnesota, Minneapolis, Minnesota, June 1970 [*Diss. Abstr. Int. B*, **31**, 5871 (1971)].
4. C. R. Johnson and I. Sataty, *J. Med. Chem.*, **10**, 501 (1967).
5. I. Sataty, *J. Org. Chem.*, **34**, 250 (1969).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

benzene-petroleum ether

dinitrogen tetroxide

butadiene sulfone

ethanol (64-17-5)

potassium carbonate (584-08-7)

hydrogen chloride (7647-01-0)

acetic acid (64-19-7)

ammonia (7664-41-7)

Benzene (71-43-2)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

sulfur dioxide (7446-09-5)

oxygen (7782-44-7)

acetone (67-64-1)

carbon (7782-42-5)

2-propanol (67-63-0)

dichloromethane (75-09-2)

ozone (10028-15-6)

magnesium sulfate (7487-88-9)

1,3-Butadiene (106-99-0)

heptane (142-82-5)

3-Butenoic acid (625-38-7)

CYCLOPENTADIENE (542-92-7)

malonaldehyde bis(diethyl acetal) (122-31-6)

3-sulfolene, 2,5-dihydrothiophene 1,1-dioxide

3-thiapentane-1,5-dial bis(diethyl acetal) 3,3-dioxide

phenacyl sulfone

2,6-diethoxy-1,4-oxathiane 4,4-dioxide, cis and trans-2,6-Diethoxy-1,4-oxathiane 4,4-dioxide, cis- and trans-2,6-diethoxy-1,4-oxathiane 4,4-dioxide (40263-59-0)

4-aminobenzoic acid hydrochloride

1-chloro-4-(2-nitrophenyl)-2-butene

2-nitrophenylacetaldehyde dimethyl acetal

1,4-dibromo-2-butene

bromoacetaldehyde dimethyl acetal (7252-83-7)

malonaldehydic acid diethyl acetal ethyl ester

Nitroacetaldehyde diethyl acetal (34560-16-2)

4H-1,4-Thiazine 1,1-dioxide (40263-61-4)

3,5-diphenyl-4H-1,4-thiazine 1,1-dioxide

4H-1,4-thiazine

4-(4-carboxyphenyl)-4H-1,4-thiazine 1,1-dioxide

1,4-dinitro-2-butene

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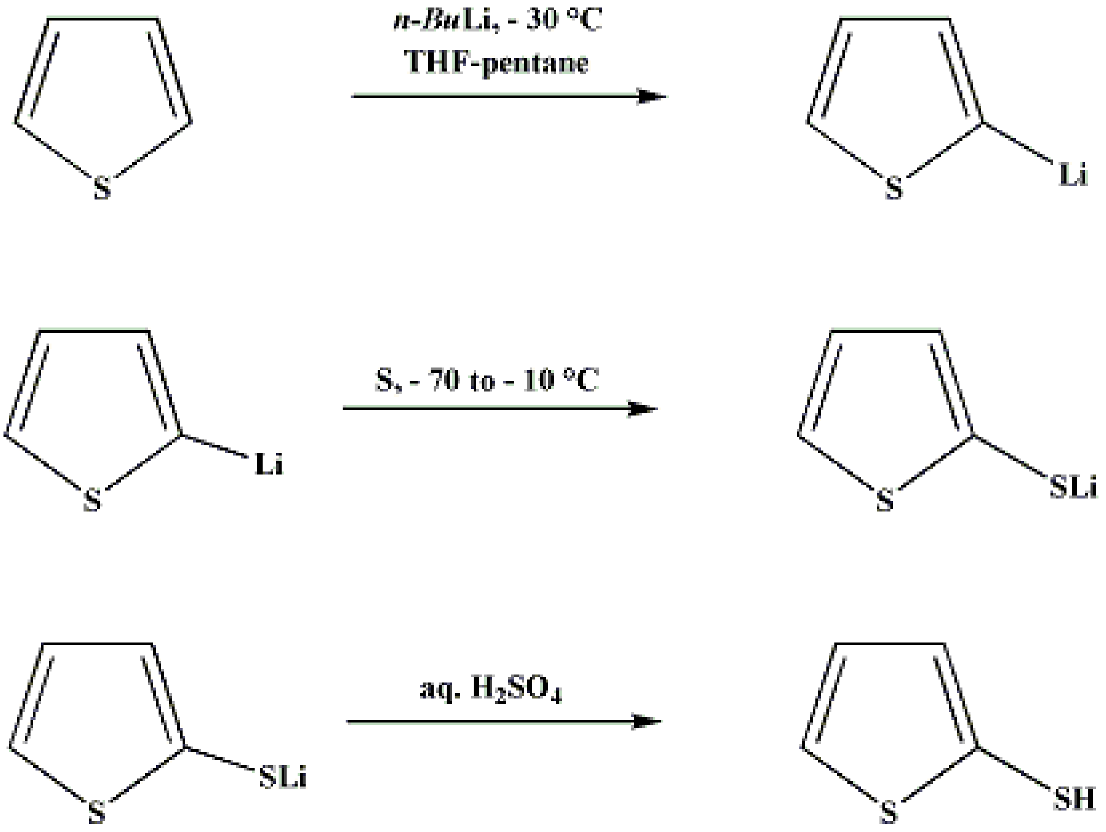
2-THIOPHENETHIOL



Submitted by E. Jones[1] and I. M. Moodie.
Checked by E. J. Corey and Joel I. Shulman.

1. Procedure

A 3-l. three-necked flask fitted with a mechanical stirrer, a 600-ml. dropping funnel, and filled with dry nitrogen is charged with 500 ml. of tetrahydrofuran (distilled from lithium aluminum hydride; see *Org. Synth.*, **Coll. Vol. 5**, 976 (1973) for warning concerning the purification of tetrahydrofuran) and 56 g. (53 ml., 0.67 mole) of thiophene. This mixture is stirred under nitrogen and cooled to −40° with an acetone–dry ice bath while 490 ml. (0.662 mole) of 1.35 *M n*-butyllithium in pentane (Note 1) and (Note 2) is added over a 5-minute period *via* the dropping funnel. The temperature of the mixture is held between −30° and −20° for 1 hour, then lowered to −70° by the addition of dry ice to the bath. Powdered sulfur crystals (20.4 g., 0.638 g.-atom) are added in one aliquot to the stirred mixture. After 30 minutes the temperature is allowed to rise to −10°, whereupon the yellow solution is carefully poured into 1 l. of rapidly stirred ice water, dissolving the lithium thiolate and destroying any unreacted 2-thienyllithium. The pentane layer is extracted with three 100-ml. portions of water. These aqueous extracts are combined with the aqueous layer, and the whole is chilled and carefully acidified with 4 *N* sulfuric acid (Note 3). This aqueous phase is immediately extracted with three 200-ml. portions of diethyl ether (Note 4). The

combined ether extracts are washed twice with 100-ml. portions of water to remove acid and remaining tetrahydrofuran and dried over anhydrous sodium sulfate. After removal of ether, the residual, golden-brown oil is purified by distillation at reduced pressure. The portion boiling at 53–56° (5 mm.) is collected, yielding 49.5–53.5 g. (65–70%) of 2-thiophenethiol as a yellow oil, n_D^{25} 1.6110.

2. Notes

1. The checkers obtained *n*-butyllithium from the Foote Mineral Co., Exton, Pennsylvania. The concentration of *n*-butyllithium was determined by the method of Gilman and Haubein.[2] This reagent is conveniently transferred to a precalibrated addition funnel under nitrogen pressure, through a short length of inert (*e.g.*, Teflon) tubing.
2. The submitters employed *n*-butyllithium prepared by the method of Jones and Gilman.[3] The *n*-butyllithium solution so prepared was filtered to remove finely divided lithium, using an apparatus previously described.[4]
3. The general procedure is similar to that described by Gronowitz[5] in the preparation of 3-thiophenethiol, the principal differences being the use of tetrahydrofuran–pentane solvent and the omission of a 10% potassium hydroxide extraction before acidification with sulfuric acid. This omission leads to higher yields of thiol.
4. Undue delay in the ether extraction of the thiol has been found to result in reduced yields.

3. Discussion

Houff and Schuetz[6] have prepared 2-thiophenethiol by two different routes. One involves the sulfurization of 2-thienylmagnesium bromide followed by acidification, giving the thiol; the other method is an *in situ* reduction of 2-thienylsulfonyl chloride with zinc dust and sulfuric acid. Gronowitz[5] has prepared the isomeric 3-thiophenethiol by sulfurization of 3-thienyllithium, which was obtained by metalation of 3-bromothiophene with *n*-butyllithium.

This method is based on the known reactivity of the 2-position of thiophene; the desired 2-thiophenethiol may be prepared in good yield by direct substitution of thiophene. 2-Chloro-5-thiophenethiol may also be prepared by this method in 59% yield from 2-chlorothiophene.[7]

Direct substitution in the 3-position of the thiophene ring is difficult and can be achieved only by activation of this reaction site. Thus, the isomeric 3-thiophenethiol may be prepared by this general method starting with a 3-halogenothiophene. For example, 3-thiophenethiol may be obtained from 3-bromothiophene in 63% yield.[5]

The procedure outlined above also offers a general method for the synthesis of alkyl and aryl thiols starting from the appropriate halides. Thus, thiophenol may be obtained in 62% yield by lithiation and sulfurization of bromobenzene.[8]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 109
- Org. Syn. Coll. Vol. 6, 558

References and Notes

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2. H. Gilman and A. H. Haubein, *J. Am. Chem. Soc.*, **66**, 1515 (1944).
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4. H. Gilman, W. Langham, and F. W. Moore, *J. Am. Chem. Soc.*, **62**, 2327 (1940).
5. S. Gronowitz and R. Hakansson, *Ark. Kemi*, **16**, 309 (1960).
6. W. H. Houff and R. D. Schuetz, *J. Am. Chem. Soc.*, **75**, 6316 (1953).
7. E. Jones and I. M. Moodie, *Tetrahedron*, **21**, 2413 (1965).
8. H. Gilman and L. Fullhart, *J. Am. Chem. Soc.*, **71**, 1478 (1949).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

ether, diethyl ether (60-29-7)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

sulfur (7704-34-9)

potassium hydroxide (1310-58-3)

zinc (7440-66-6)

bromobenzene (108-86-1)

Pentane (109-66-0)

Thiophenol (108-98-5)

Thiophene (110-02-1)

lithium (7439-93-2)

butyllithium, n-butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

2-thiophenethiol (7774-74-5)

2-thienylmagnesium bromide

3-Bromothiophene (872-31-1)

3-thiophenethiol

2-thienyllithium

2-thienylsulfonyl chloride (16629-19-9)

3-thienyllithium

2-Chloro-5-thiophenethiol

2-chlorothiophene (96-43-5)

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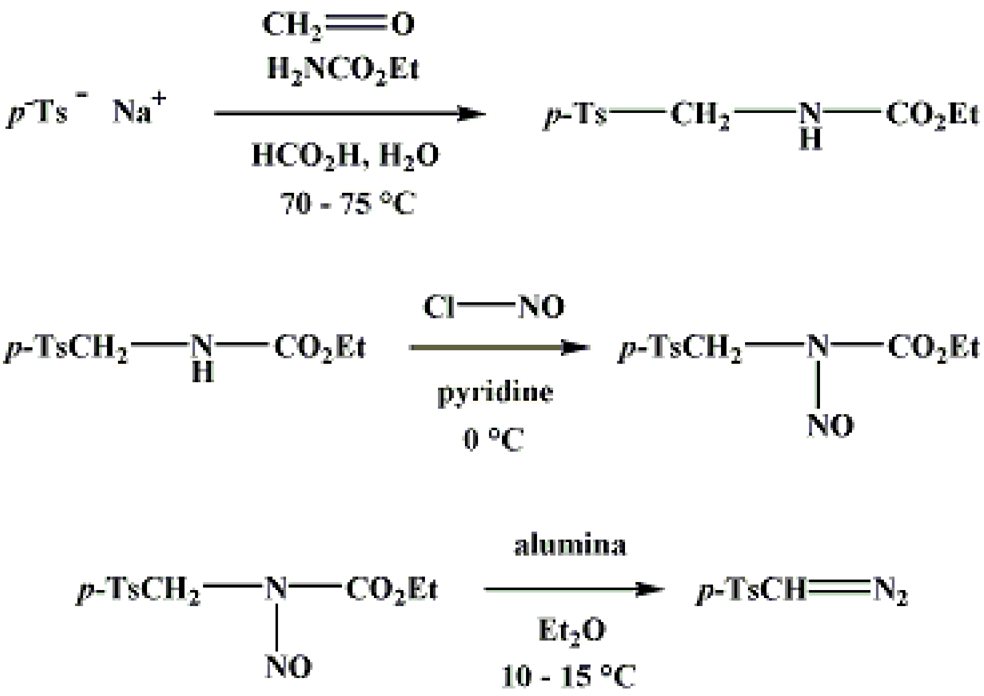
Organic Syntheses, CV 6, 981

p-TOLYLSULFONYLDIAZOMETHANE

[Benzene, 1-[(diazomethyl)sulfonyl]-4-methyl-]



Submitted by A. M. van Leusen[1] and J. Strating.
Checked by Bruce A. Carlson and William A. Sheppard.

1. Procedure

Caution! Part B must be conducted in a efficient hood to avoid exposure to toxic nitrosyl chloride.

A. *Ethyl* N-(p-*tolylsulfonylmethyl)carbamate*. A solution of 178 g. (1.00 mole) of sodium *p*-toluenesulfinate (Note 1) in 1 l. of water is placed in a 3-l., three-necked flask equipped with a condenser, an efficient mechanical stirrer, and a thermometer. After addition of 100 ml. (108 g.) of an aqueous 34–37% solution of formaldehyde (*ca.* 1.2–1.4 moles) (Note 2), 107 g. (1.20 moles) of ethyl carbamate (Note 3), and 250 ml. of formic acid (Note 4), the stirred solution is heated to 70°. Soon after this temperature is reached, the reaction mixture becomes turbid due to separation of the product as oily droplets, which are kept dispersed with vigorous stirring. After heating for 2 hours at 70–75°, the heating mantle is replaced with an ice bath, while stirring is continued. At about 60° the product begins to solidify. Under continued stirring the mixture is cooled further and kept in the ice bath for 2 hours after a temperature of 5° is reached (Note 5). The precipitate is collected by suction filtration and washed three times by stirring efficiently with 400-ml. portions of cold water. After drying at 70° to constant weight, 214–232 g. (83–90%) (see (Note 1)) of white, microcrystalline ethyl

N-(*p*-toluenesulfonylmethyl)carbamate, m.p. 108–110°, is obtained; it is sufficiently pure for use in the next step of the reaction. Recrystallization from 95% ethanol provides colorless flasks, m.p. 109–111°

B. *Ethyl* N-*nitroso*-N-(p-*tolylsulfonylmethyl*)*carbamate*. A solution of 154 g. (0.599 mole) of the ethyl *N*-(*p*-tolylsulfonylemthyl)carbamate in 600 ml. of pyridine (Note 6) is placed in a 1-l., four-necked flask equipped with a thermometer, a mechanical stirrer, a gas-inlet tube leading into the solution, and a gas outlet leading to the exhaust. The weight of the flask together with its contents is determined, preferably on a balance placed in the same hood. The solution is cooled to 0° in an ice–salt mixture. Gaseous nitrosyl chloride (Note 7) is introduced, *via* a mineral oil bubbler and a trap, into the stirred solution at such a rate that the temperature is kept between 0° and 5°. After 52–65 g. (0.79–0.99 mole) of nitrosyl chloride has been taken up (Note 8), the reaction is completed by stirring for 30 minutes at about 0°, at which point the reaction mixture is poured in a thin stream into a hand-stirred mixture of 4 l. of ice and water, giving a pale-yellow oil that readily solidifies (Note 9). The solid is collected by suction filtration after standing for 1 hour at 0°. Any lumps present are pulverized, and the solid is washed thoroughly in a beaker with four 500-ml. portions of cold water, removing pyridine. The moist product is dissolved in sufficient dichloromethane (*ca.* 1.5 l.) and the water layer is removed. The dichloromethane solution is dried over anhydrous magnesium sulfate and concentrated to dryness under reduced pressure, giving 157–171 g. (92–100%) of crude ethyl *N*-nitroso-*N*-(*p*-tolylsulfonylmethyl) carbamate, m.p. 86–89° (slight dec.). The crude nitroso compound can be used without purification in the next step of the reaction, provided that it is free of starting material (Note 10).

If the nitrosocarbamate is to be stored (preferably at –20°) for periods longer than a month, it should be recrystallized once from 1:2 dichloromethane-diethyl ether (Note 11), m.p. 87–89°. In this purified form it can be stored for several months at –20° without noticeable decomposition.

C. p-*Tolylsulfonyldiazomethane*. *Warning! α-Diazosulfones slowly decompose under the influence of light. Exposure to light should therefore be kept at a minimum in all stages of the reaction.* A 3-l., three-necked, round-bottomed flask equipped with a condenser, an efficient mechanical stirrer, and a stopper, is charged with 570 g. of alumina (Note 12). The flask is wrapped with aluminum foil or covered with dark cloth or black paper. With stirring, 1.5 l. of ether (Note 13) is added. The mixture is cooled to 10–15° with a water–ice bath, and a solution of 57.3 g. (0.200 mole) of ethyl *N*-nitroso-*N*-(*p*-tolylsulfonylmethyl)carbamate in 150 ml. of dichloromethane (Note 14) is added in one portion. Stirring is continued for 2 hours at 10–15° (Note 15); during this time the ether solution soon develops the bright-yellow color of *p*-tolylsulfonyldiazomethane. The ether solution is decanted from the alumina. The alumina is extracted thoroughly by stirring for periods of 5 minutes with two portions of 500 ml. and three portions of 250 ml. of ether. The combined ether solutions are filtered through coarse filter paper and concentration is a vacuum rotary flash

evaporator. The temperature of the water bath must not exceed 25°. When the volume is reduced to about 200 ml., the water bath is removed entirely and concentration is continued until the cold residue crystallizes spontaneously (Note 16). The crystal mass is stirred for about 2 minutes in 50 ml. of ice-cold petroleum ether (40–60°). The crystals are collected on a sintered-glass filter and washed on the filter with two 25-ml. portions of cold petroleum ether. Drying overnight at 0° in a vacuum desiccator over anhydrous calcium chloride, yields 26–30 g. (66–76%) of yellow *p*-tolylsulfonyldiazomethane, m.p. 35–38° (slight dec.) (Note 17). Recrystallization from anhydrous ether-pentane (Note 18) will raise the melting point to 36–38° (slight dec.) at the expense of 5–10% of material. *p*-Tolylsulfonyldiazomethane should be stored at or below 0° in the absence of light in an *unsealed* container (Note 19).

2. Notes

1. Commercially available anhydrous sodium *p*-toluenesulfinate, purum, *ca.* 97% (Fluka A G, Busch S. G., Switzerland) was used. Sodium *p*-toluenesulfinate dihydrate can be used equally well. The checkers used anhydrous sodium *p*-toluenesulfinate from Aldrich Chemical Company, Inc., which was determined by titration to be 87% pure and gave lower yields. The yield stated was obtained by using stoichiometric amounts based on calculated purity. Sodium *p*-toluenesulfinate from other suppliers was found less pure and gave considerably lower yields.
Alternatively, sulfinates can be synthesized conveniently by the method of Truce and Roberts,[2] or by that of Oxley and colleagues.[3]
2. Commercial aqueous formaldehyde solution, containing about 8% of methanol, was used.
3. Ethyl carbamate (J. T. Baker Chemical Company), with a reporter melting point of 48–50° (46–49° was found), was used without purification. The solid was added to the reaction mixture.
4. Formic acid (97%) from J. T. Baker Chemical Company was used.
5. By cooling and stirring as described, the product is obtained in a finely divided form, which can be removed from the flask easily and washed efficiently.
6. Commercial pyridine (J. T. Baker Chemical Company) was used without purification.
7. Nitrosyl chloride (Matheson Gas Products) with a purity specified as >97% was used. Occasionally, the needle valve of the nitrosyl chloride tank clogs. After closing the tank, the valve is disconnected and flushed with acetone until the acetone remains colorless. The needle valve is reconnected after being dried with compressed air.
Nitrosyl chloride also can be prepared conveniently from hydrochloric acid and sodium nitrite.[4] Alternatively, the nitrosation can be carried out conveniently with nitrosonium tetrafluoroborate (Aldrich Chemical Company, Inc.). Ethyl *N*-nitroso-*N*-(*p*-tolylsulfonylmethyl)carbamate (99%) was obtained when 0.06

mole of nitrosonium tetrafluoroborate, a hygroscopic solid, was added over 45 minutes, from an Erlenmeyer flask connected to the reaction flask with a piece of Tygon® tubing, to a –10 to 0° solution of ethyl *N*-(*p*-tolylsulfonylmethyl) carbamate (0.05 mole) in 50 ml. of pyridine.

8. The color of the pyridine solution changes rapidly from blue and green to yellow. After roughly I equivalent (0.6 mole) of nitrosyl chloride has been taken up (*ca.* 1 hour), the color of the solution changes to dark red-brown. During the reaction a precipitate of pyridinium chloride is formed; however, it will disappear during the workup with water as described. A large excess of nitrosyl chloride (up to 3 equivalents) has been used occasionally without any disadvantages.

9. Preferably, a few drops of the pyridine solution are rubbed first with a little water, providing seed crystals so that the product will solidify immediately, giving a finely divided material which can be washed more easily.

10. The presence of ethyl *N*-(*p*-tolylsulfonylemthyl)carbamate in the reaction product is most readily detected by the N-H IR absorption band at 3370 cm.$^{-1}$. If the nitrosation is incomplete, the reaction with nitrosyl chloride should be repeated on the mixture of compounds, rather than to try to purify the product by recrystallization.

11. Ether (*ca.* 1.4 l.) is added to a warm, filtered solution of 100 g. of the crude nitroso compound in *ca.* 0.7 l. of dichloromethane until the solution becomes slightly turbid. The nitrosocarbamate is collected after cooling overnight at –20° and dried under reduced pressure at 0°, providing 88–93 g. of yellow crystals with a pink luster, m.p. 87–89.

12. Alumina Number 1076, "aktiv basisch," for chromatography (E. Merck, Darmstadt) was usually employed. Occasionally, when alumina Number 1077, "aktiv neutral," from the same company, was used, a longer reaction time was required (compare (Note 15)).

13. Commercial ether was stored over potassium hydroxide pellets and used without distillation. Because some heat is evolved when the ether is added to the alumina, the flask is equipped with a condenser.

14. Commercial dichloromethane was used without purification.

15. The time necessary for completion of the reaction may vary from 0.5 to 4 hours, depending on the actual activity of the alumina. The progress of conversion should be monitored by IR analysis of a concentrated sample of the solution. Stirring should be continued for 15 minutes after the nitroso band at 1540 cm.$^{-1}$ has disappeared. A strong diazo band at about 2100 cm.$^{-1}$ will then be present. The carbonyl band a 1750 cm.$^{-1}$, initially due to nitrosocarbamate, will usually not disappear completely during the reaction, because some diethyl carbonate is formed in addition to carbon dioxide and ethanol. Diethyl carbonate is removed during the workup procedure.

During the reaction the alumina usually attains a pink color, due to some decomposition of *p*-tolylsulfonyldiazomethane. However, the colored decomposition products adhere strongly to the alumina and will not, therefore, contaminate the final product. If the alumina becomes reddish rather than pink,

the type of the alumina in use may be too basic, causing more extensive decomposition of the *p*-tolylsulfonyldiazomethane; the reaction time should then be reduced as much as possible to prevent a considerable decrease in yield.
16. If crystallization does not occur, it can be induced readily by scratching.
17. Spectral data of *p*-tolylsulfonyldiazomethane; IR (Nujol) cm.$^{-1}$: 2125 (C=N=N), 1330 (SO_2), 1150 (SO_2); ^1H NMR ($CDCl_3$), δ (multiplicity, number of protons, assignment): 2.46 (s, 3H, CH_3), 5.36 (s, 1H, C*H*), 7.30, 7.43, 7.73, 7.87 (AB q, 4H, C_6H_4); visible (40% dioxane-water) nm. max. (log ε): 394 (1.8).
18. *p*-Tolylsulfonyldiazomethane tends to separate as an oil when pentane is in excess of an ether to pentane ratio of 2:1. The *p*-tolylsulfonyldiazomethane is dissolved at room temperature in anhydrous ether (about 20 ml. per 10 g. of *p*-tolylsulfonyldiazomethane), and pentane (about 7 ml. per 10 g.) is added, followed by seeding. The solution is cooled first at 0°, then at −20°, before the crystals are collected.
19. *p*-Tolylsulfonyldiazomethane is insensitive to impact detonation; however, it decomposes on warming, evolving significant quantities of nitrogen at temperature as low as 32°. It should never be stored for any length of time in a sealed container and should be stored at or below 0° if not used immediately.

3. Discussion

p-Tolylsulfonyldiazomethane represents a class of compounds called α-diazosulfones, which was discovered in 1961 by the submitters. Besides being useful synthetic intermediates, α-diazosulfones are the only known source of α-sulfonylcarbenes.[5]

Several new trisubstituted methane derivatives have been prepared by replacing the diazo group of α-diazosulfones.[5] For example, *p*-tolylsulfonyldiazomethane (RSO_2CHN_2, R = *p*-tolyl throughout) reacts with *p*-toluenesulfenyl chloride,[6] giving chloro-*p*-tolylsulfonyl-*p*-tolylthiomethane [$RSO_2CH(Cl)SR$] in 83% yield;[7] with nitrosyl chloride yielding the previously unknown *N*-hydroxy-1-(*p*-tolysulfonyl) methanimidoyl chloride [$RSO_2C(Cl)=NOH$] in 28% yield,[8] with 70% perchloric acid in dichloromethane, giving the isolable covalent perchlorate ($RSO_2CH_2OClO_3$) in 49% yield;[9,5] and with *tert*-butyl hypochlorite in *tert*-butyl alcohol, giving 1-(1-*tert*-butoxy-1-chloromethysulfonyl)-4-methylbenzene [$RSO_2CH(Cl)OC(CH_3)_3$] in 62% yield or 1-(1-chloro-1-ethoxymethylsulfonyl)-4-methylbenzene [$RSO_2CH(Cl)OC_2H_5$] in 84% yield when carried out in ethanol.[10]

The photolysis of α-diazosulfones dissolved in alkenes provides sulfonyl-substituted cyclopropanes in high yields.[5] This is exemplified by the preparation of 1-(4-methoxyphenylsulfonyl)-2,2,3,3-tetramethylcyclopropane in 75% yield from 4-methoxybenzenesulfonyldiazomethane and 2,3-dimethyl-2-butene. A similar addition to *trans*-2-butene gives (*d,l*)-1-(4-methoxyphenylsulfonyl)-*trans*-2,3-

dimethylcyclopropane in 79% yield, resulting from a stereospecific *cis*- addition, indicating a singlet sulfonylcarbene intermediate.[11]

Originally, *p*-tolylsulfonyldiazomethane was prepared by passing an ethereal solution of its precursor, ethyl *N*-nitroso-*N*-(*p*-tolylsulfonylmethyl)carbamate, slowly through a column of alumina.[12] This procedure, which results in yields about 10% higher, is convenient only for small-scale preparations, up to a maximum of 5 g. of *p*-tolylsulfonyldiazomethane. The present modification is that of Middelbos.[13]

The conversion of nitrosocarbamates into α-diazosulfones is also effected with certain bases, notably with aqueous potassium hydroxide.[12] Potassium hydroxide, however, causes rapid decomposition of *p*-tolylsulfonyldiazomethane. Alumina is thought to act as a solid base and does not cause significant decomposition.

Other syntheses of *p*-tolylsulfonyldiazomethane have been worked out. Reaction of 4-carboxybenzenesulfonyl azide and ammonia with *p*-tolylsulfonylacetaldehyde hemihydrate or *p*-tolylsulfonylacetaldehyde enol acetate gives *p*-tolylsulfonyldiazomethane in yields of 73 and 58%, respectively.[14] Furthermore, *p*-tolylsulfonyldiazomethane is obtained in 60% yield by reaction of *p*-tolylsulfonylmethylenetriphenylphosphorane and either *p*-tolylsulfonyl azide or 4-carboxybenzenesulfonyl azide.[14] A method similar to the first of these syntheses has been used for preparation of (alkyl- or arylsulfonyl)phenyldiazomethanes; however, the present procedure has the advantages of being simple and easily scaled-up, and uses readily available, inexpensive starting materials.

An alternative to the synthesis of arylsulfonylmethylcarbamates by the Mannich condensation as described here,[15] is the Curtius rearrangement of the hydrazides of arylsulfonylacetic acids.[16]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 987

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alumina

petroleum ether

N-(p-tolylsulfonylemthyl)carbamate

J. T. Baker Chemical Company

ethyl N-(p-tolylsulfonylemthyl)carbamate

N-hydroxy-1-(p-tolysulfonyl)methanimidoyl chloride

1-(1-tert-butoxy-1-chloromethysulfonyl)-4-methylbenzene

p-tolylsulfonylacetaldehyde hemihydrate

ethanol (64-17-5)

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

formaldehyde (630-08-0)

ethyl (2025-56-1)

formic acid (64-18-6)

nitrogen (7727-37-9)

sodium nitrite (7632-00-0)

sulfur (7704-34-9)

aluminum (7429-90-5)

carbon dioxide (124-38-9)

acetone (67-64-1)

pyridine (110-86-1)

potassium hydroxide (1310-58-3)

Pentane (109-66-0)

dichloromethane (75-09-2)

nitrosyl chloride (2696-92-6)

2,3-dimethyl-2-butene (563-79-1)

magnesium sulfate (7487-88-9)

dioxane (5703-46-8)

ethyl carbamate (51-79-6)

diethyl carbonate (105-58-8)

tert-butyl alcohol (75-65-0)

perchloric acid (7601-90-3)

p-tolylsulfonyl azide (941-55-9)

Benzene, 1-[(diazomethyl)sulfonyl]-4-methyl-, p-Tolylsulfonyldiazomethane (1538-98-3)

nitrosonium tetrafluoroborate (14635-75-7)

pyridinium chloride (628-13-7)

1-(1-chloro-1-ethoxymethylsulfonyl)-4-methylbenzene

1-(4-methoxyphenylsulfonyl)-2,2,3,3-tetramethylcyclopropane

4-methoxybenzenesulfonyldiazomethane

4-carboxybenzenesulfonyl azide (17202-49-2)

Sodium p-toluenesulfinate

tert-Butyl hypochlorite (507-40-4)

p-Toluenesulfenyl chloride (933-00-6)

sodium p-toluenesulfinate dihydrate (7257-26-3)

trans-2-Butene (624-64-6)

ethyl N-(p-toluenesulfonylmethyl)carbamate, ethyl N-(p-tolylsulfonylmethyl)carbamate (2850-26-2)

Ethyl N-nitroso-N-(p-tolylsulfonylmethyl)carbamate (2951-53-3)

chloro-p-tolylsulfonyl-p-tolylthiomethane

(d,l)-1-(4-methoxyphenylsulfonyl)-trans-2,3-dimethylcyclopropane

p-tolylsulfonylacetaldehyde enol acetate

p-tolylsulfonylmethylenetriphenylphosphorane

N-nitroso-N-(p-tolylsulfonylmethyl)carbamate

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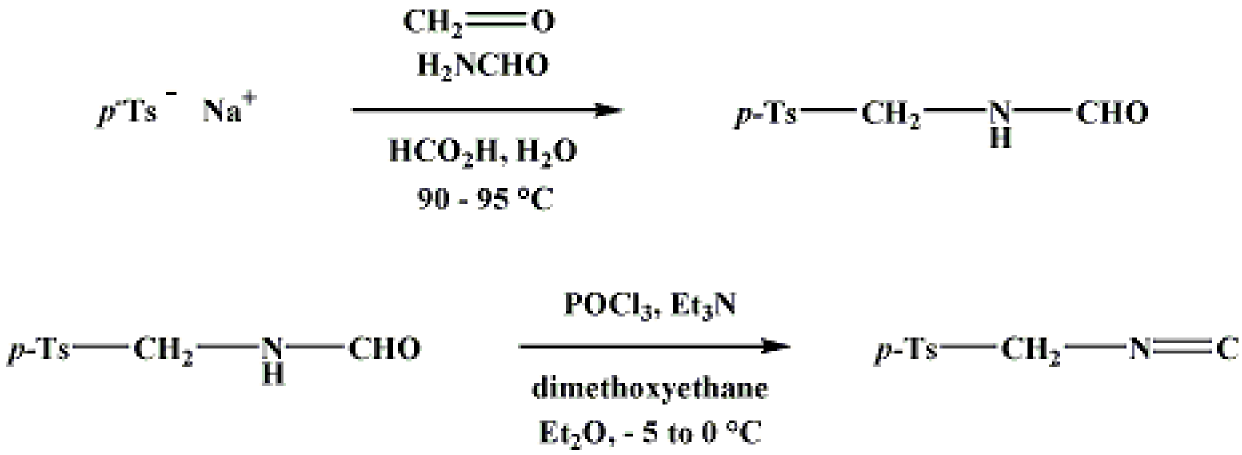
Organic Syntheses, CV 6, 987

p-TOLYLSULFONYLMETHYL ISOCYANIDE

[Benzene, 1-((isocyanomethyl)sulfonyl)-4-methyl-]



Submitted by B. E. Hoogenboom, O. H. Oldenziel, and A. M. van Leusen[1].
Checked by Teresa Y. L. Chan and S. Masamune.

1. Procedure

Caution! The reaction should be conducted in a well-ventilated fume hood.

Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A. *N-(p-Tolylsulfonylmethyl)formamide.*[2] A 3-l., three-necked, round-bottomed flask equipped with a mechanical stirrer, a condenser, and a thermometer is charged with 267 g. (1.50 moles) of sodium *p*-toluenesulfinate (Note 1). After addition of 750 ml. of water, 350 ml. (378 g.) of an aqueous 34–37% solution of formaldehyde (*ca.* 4.4 moles) (Note 2), 680 g. (600 ml., 15.5 moles) of formamide (Note 3), and 244 g. (200 ml., 5.30 moles) of formic acid (Note 4), the stirred reaction mixture is heated at 90°. The sodium *p*-toluenesulfinate dissolves during heating, and the clear solution is kept at 90–95° for 2 hours (Note 5). The reaction mixture is cooled to room temperature in an ice–salt bath with continued stirring, then further cooled overnight in a freezer at –20°. The white solid (Note 6) is collected by suction filtration and washed thoroughly in a beaker by stirring with three 250-ml. portions of ice water. The product is dried under reduced pressure over phosphorus pentoxide at 70° (Note 7), yielding 134–150 g. (42–47%) of crude *N*-(*p*-tolylsulfonylmethyl)formamide, m.p. 106–110° (Note 8), which is sufficiently pure for use in the next step.

B. *p-Tolylsulfonylmethyl isocyanide.* A 3-l., four-necked, round-bottomed flask

equipped with a mechanical stirrer, a thermometer, a 250-ml. dropping funnel, and a drying tube is charged with 107 g. (0.502 mole) of crude *N*-(*p*-tolylsulfonylmethyl) formamide, 250 ml. of 1,2-dimethoxyethane, 100 ml. of anhydrous diethyl ether, and 255 g. (350 ml., 2.52 moles) of triethylamine (Note 9). The stirred suspension is cooled in an ice–salt bath to −5°. A solution of 84 g. (50 ml., 0.55 mole) of phosphorus oxychloride (Note 10) in 60 ml. of 1,2-dimethoxyethane is added from the dropping funnel at such a rate that the temperature is kept between −5° and 0° (Note 11). During the reaction, the *N*-(*p*-tolylsulfonylmethyl)formamide gradually dissolves and triethylamine salts precipitate. Near the completion of the reaction the white suspension slowly turns brown (Note 12). After stirring for another 30 minutes at 0°, 1.5 l. of ice water is added with continued stirring. The solid material dissolves, giving a clear, dark-brown solution before the product begins to separate as a fine, brown, crystalline solid. After stirring for an additional 30 minutes at 0°, the precipitate is collected by suction filtration and washed with 250 ml. of cold water. The wet product is dissolved in 400 ml. of warm benzene (40–60°), the aqueous layer is removed with a separatory funnel, and the dark-brown benzene solution is dried over anhydrous magnesium sulfate. After removal of the magnesium sulfate, 2 g. of activated carbon (Note 13) is added, and the mixture is heated at about 60° for 5 minutes and filtered (Note 14). One liter of petroleum ether (b.p. 40–60°) is added to the filtrate with thorough swirling. After 30 minutes the precipitate is collected by suction filtration and dried in a vacuum desiccator, yielding 74–82 g. (76–84%) of crude *p*-tolylsulfonylmethyl isocyanide as a light-brown, odorless solid, m.p. 111–114° (dec.) (Note 15), which can be used for synthetic purposes without further purification.

Completely white material is obtained by rapid chromatography through alumina (Note 16). An analytically pure product, m.p. 116–117° (dec.), is obtained after one recrystallization from methanol.

2. Notes

1. The submitters used anhydrous sodium *p*-toluenesulfinate ("purum" quality, *ca.* 97% from Fluka A G), and the checkers purchased the reagent from Aldrich Chemical Company, Inc. Compare also Note 1 in the preparation of *p*-tolylsulfonyldiazomethane [*Org. Synth.*, **Coll. Vol. 6**, 981 (1988)].
2. Commercial aqueous formaldehyde solution containing 8% methanol was used. Formaldehyde is needed in excess; otherwise the yield is considerably diminished.
3. Commercial formamide (E. Merck, Darmstadt) was used. The use of a large excess of formamide with respect to the sulfinate is required to obtain the yield specified.[2]
4. Commercial 97% formic acid (J. T. Baker Chemical Company) was used.
5. Prolonged heating lowers the yield considerably.
6. When no solid is formed overnight, crystallization may be induced by scratching. In this case the solution should be kept for another 4 hours at −20°

before the product is collected.

7. The drying process can be speeded up by dissolving the wet product in dichloromethane, removing the water layer in a separatory funnel, drying the dichloromethane solution over anhydrous magnesium sulfate, and removing the solvent on a rotary evaporator.

8. Recrystallization from 95% ethanol or benzene raised the m.p. to 108–110°.

9. 1,2-Dimethoxyethane and triethylamine, both in "zur Synthese" quality, were purchased from E. Merck, Darmstadt. Ether was distilled from phosphorus pentoxide and stored over sodium wire.

10. Commercial phosphorus oxychloride ("tout pur" from UCB, Belgium) was used without purification.

11. The addition requires about 1 hour. At the beginning of the reaction much heat is evolved, and, therefore, the phosphorus oxychloride solution should initially be added very slowly.

12. The development of a brown color indicates that sufficient phosphorus oxychloride has been added. If the mixture remains colorless, the final product is likely to be contaminated with unreacted *N*-(*p*-tolylsulfonylmethyl) formamide. It is therefore advantageous to add more phosphorus oxychloride and continue stirring until the brown color is obtained.

13. Activated carbon was purchased from J. T. Baker Chemical Company.

14. The color of the solution is lightened only slightly by treatment with activated carbon, but eventually a purer product is obtained.

15. The product has the following spectral properties; IR (Nujol) cm.$^{-1}$: 2150 (N=C), 1320 and 1155 (SO_2); ^{1}H NMR ($CDCl_3$), δ (multiplicity, number of protons, assignment): 2.5 (s, 3H, CH_3), 4.6 (s, 2H CH_2), 7.7 (q, 4H, C_6H_4).

16. A solution of 50 g. of *p*-tolylsulfonylmethyl isocyanide in 150 ml. of dichloromethane is placed on a 40 × 3 cm. column containing about 100 g. of neutral alumina slurried in dichloromethane. A nearly colorless solution (*ca.* 700 ml.) is collected over about 1 hour. This solution is evaporated to dryness on a rotary evaporator, providing 42–47 g. of white *p*-tolylsulfonylmethyl isocyanide, m.p. 113–114° (dec.).

3. Discussion

p-Tolylsulfonylmethyl isocyanide was originally obtained by irradiation of *p*-tolylsulfonyldiazomethane[3] in liquid hydrogen cyanide.[4] This isocyanide represents a group of sulfonylmethyl isocyanides, most of which have been prepared, as in the present procedure, by dehydration of the corresponding formamides.[4,5] *p*-Tolylsulfonylmethyl isocyanide has also been prepared by reaction of *p*-tolylsulfonyl fluoride with isocyanomethyllithium.[4,6] The advantages of the present dehydration method are twofold: (1) it is a simple procedure using readily available and inexpensive starting materials and (2) the use of the foul-smelling methyl isocyanide is avoided.

p-Tolylsulfonylmethyl isocyanide is a useful and versatile reagent.[7] It has been used for the synthesis of several azole ring systems by base-induced addition of its C-N=C moiety to various C=O, C=N, C=S, C=C, and N=N containing substrates. Thus, oxazoles,[7,8,9,10] imidazoles,[7,8,11,12] thiazoles,[7,13] pyrroles,[7,8] and 1,2,4-triazoles,[7] have been prepared, respectively. Furthermore, *p*-tolylsulfonylmethyl isocyanide has found use in a one-step conversion of ketones and aldehydes to cyanides containing one more carbon atom.[7,14]

Another application is based on the umpolung principle. In this sense *p*-tolylsulfonylmethyl isocyanide is a formaldehyde anion or dianion equivalent,[7,10] which has been used in the synthesis of symmetrical and unsymmetrical ketones,[7,15,16] α-diketones,[7,17] α-hydroxy aldehydes,[7] and α-hydroxy ketones.[7] Under reducing reaction conditions amino, methylamino or β-hydroxy methylamino compounds have been prepared from the same intermediates.[7]

Finally, *p*-tolylsulfonylmethyl isocyanide can be transformed into 1-isocyano-1-tosylalkenes,[7] which are useful synthons in their own right, as appears from their use in the synthesis of imidazoles[12] and pyrroles.[7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 41

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

ethanol (64-17-5)

Benzene (71-43-2)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

formamide (75-12-7)

formaldehyde (630-08-0)

hydrogen cyanide (74-90-8)

formic acid (64-18-6)

sulfur (7704-34-9)

carbon (7782-42-5)

Phosphorus Oxychloride (21295-50-1)

sodium wire (13966-32-0)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

triethylamine (121-44-8)

1,2-dimethoxyethane (110-71-4)

Methyl isocyanide (593-75-9)

Benzene, 1-((isocyanomethyl)sulfonyl)-4-methyl-, p-Tolylsulfonylmethyl isocyanide (36635-61-7)

p-Tolylsulfonyldiazomethane (1538-98-3)

isocyanomethyllithium

phosphorus pentoxide (1314-56-3)

Sodium p-toluenesulfinate

N-(p-tolylsulfonylmethyl)formamide (36635-56-0)

p-tolylsulfonyl fluoride (455-16-3)

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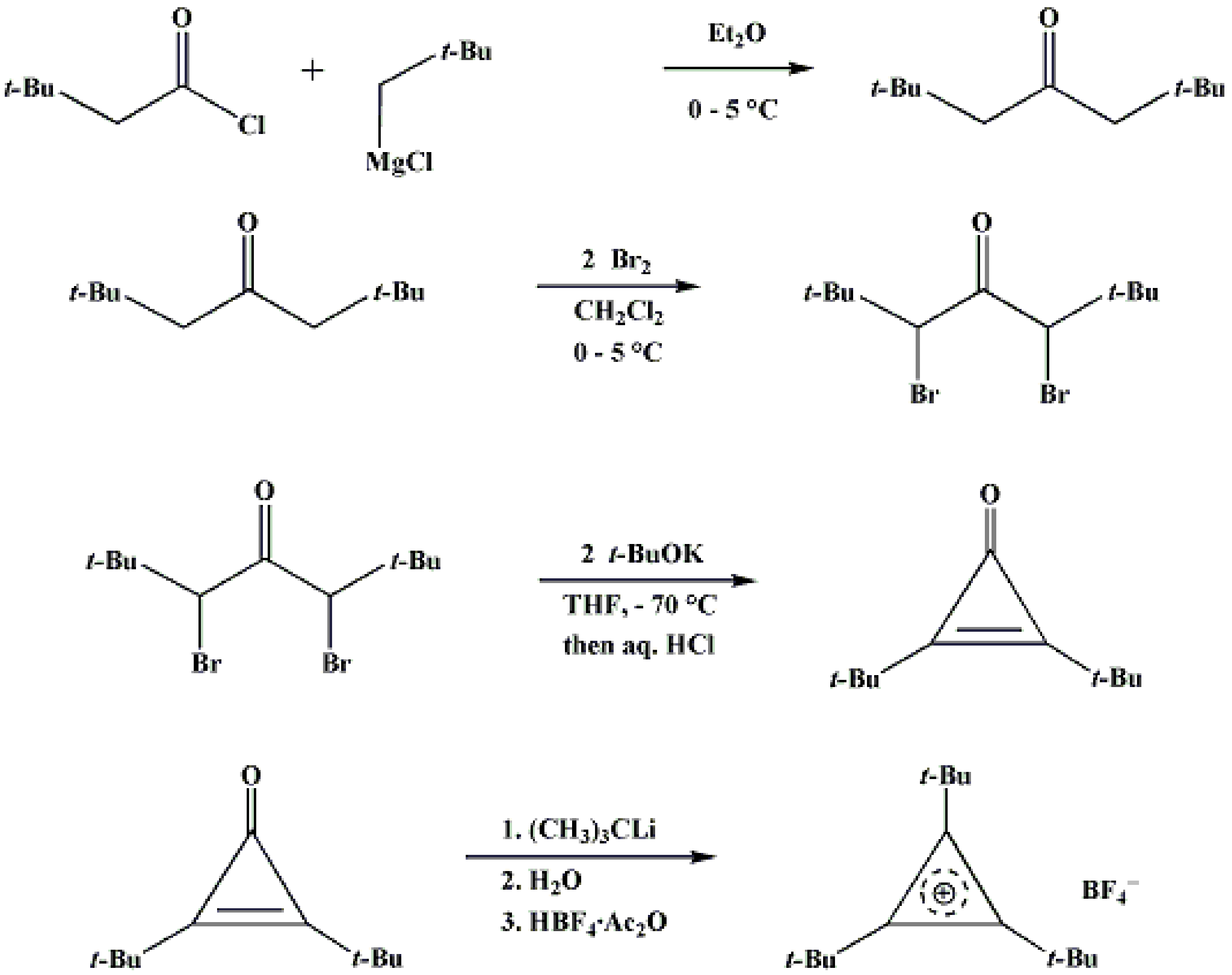
Organic Syntheses, CV 6, 991

TRI-*tert*-BUTYLCYCLOPROPENYL TETRAFLUOROBORATE

[Cyclopropenylium, 1,2,3-tris(1,1-dimethylethyl)-, tetrafluoroborate(1-)]



Submitted by J. Ciabattoni[1], E. C. Nathan, A. E. Feiring, and P. J. Kocienski.
Checked by L. M. Leichter and S. Masamune.

1. Procedure

A. *Dineopentyl ketone*. A dry, 2-l., three-necked flask is fitted with a reflux condenser, a precision, pressure-equalizing addition funnel, and a mechanical stirrer. A gas-inlet tube at the top of the condenser is used to maintain a static nitrogen atmosphere in the reaction vessel throughout the reaction. The flask is charged with 900 ml. of anhydrous diethyl ether, 45 g. (1.85 g.-atoms) of magnesium turnings, and 74.6 g. (0.700 mole) of 1-chloro-2,2-dimethylpropane (Note 1). The vigorously stirred mixture is heated to gentle reflux before 156 g. (0.839 mole) of 1,2 dibromoethane in 150 ml. of dry ether is added over a 12-hour period (Note 2). After addition is complete, the reaction mixture is refluxed for an additional 2 hours. The mixture is then cooled to 0–5° in an ice bath, and 71.7 g. (0.533 mole) of *tert*-butylacetyl chloride (Note 3) in 150 ml. of dry ether is added dropwise to the rapidly stirred Grignard reagent over a period of 1.5 hours (Note 4). The mixture is then stirred at 0–5° for an additional 1.5 hours and poured with stirring onto a mixture of 800 g. of cracked ice and 150 ml. of concentrated hydrochloric acid. The ether layer is

separated and washed consecutively with 100 ml. each of water, 5% aqueous sodium carbonate solution, and finally saturated aqueous sodium chloride. After drying over anhydrous magnesium sulfate, filtration, and removal of solvent with a rotary evaporator, the yellow residual oil is distilled under reduced pressure, yielding 81.2 g. (90%) of dineopentyl ketone as a colorless oil, b. p. 86–90° (22 mm.) (Note 5) and (Note 6).

B. *α,α'-Dibromodineopentyl ketone*. *Caution! The dibromoketone, a highly volatile compound with lachrymatory properties, is a skin irritant which may induce allergic effects. Therefore, steps B and C should be performed in a well-ventilated hood. Rubber gloves should be worn.* A 1-l., three-necked flask fitted with a thermometer, an addition funnel, a magnetic stirring bar, and a gas-exit tube, which is connected with Tygon tubing to a funnel inverted over a beaker of water for trapping hydrogen bromide, is charged with 82 g. (0.48 mole) of dineopentyl ketone in 500 ml. of dichloromethane, and the solution is cooled to 0–5° in an ice bath. Over a period of 5 hours, 160 g. (1.00 mole) of bromine is added dropwise (Note 7), and the mixture is stirred an additional hour at 0–5°. The reaction mixture is carefully transferred to a 1-l. separatory funnel, and the excess bromine is destroyed by extraction with 100 ml. of saturated aqueous sodium sulfite (Note 8). After washing with 100 ml. of 5% aqueous sodium hydrogen carbonate solution and 100 ml. of aqueous saturated sodium chloride, the organic layer is dried over magnesium sulfate, filtered, and evaporated with a rotary evaporator. The yellow, crystalline residue is dissolved in 350 ml. of hot hexane and cooled in ice, giving the dibromoketone as white needles, which are collected by suction filtration, washed with 100 ml. of cold hexane (Note 9), and air dried in a well-ventilated hood, yielding 83 g. of product. Concentration of the mother liquors provides two additional crops of crystals (40 g. and 12 g.) for a total yield of 135 g. (85%) of dibromoketone, m.p. 69–72° (Note 10).

C. *Di-tert-butylcyclopropenone*. *Caution! The same precautions described in Part B should be exercised in this step.* A dry, 1-l., three-necked flask fitted with an efficient mechanical stirrer, a low temperature thermometer, and a solid addition assembly (Note 11) is charged with 97 g. (0.30 mole) of the dibromoketone and 700 ml. of anhydrous tetrahydrofuran (Note 12). After the reaction vessel has been flushed with nitrogen, a static nitrogen atmosphere is maintained in the reaction vessel throughout the remainder of the reaction. The vigorously stirred solution is cooled to −70° in an acetone–dry ice bath before 80 g. (0.71 mole) of powdered potassium *tert*-butoxide (Note 13) is added over a 2-hour period. The addition is completed, the mixture is stirred an additional hour at −70°, and 50 ml. of 10% hydrochloric acid is added dropwise. The cooling bath is then removed, and the mixture is allowed to warm to room temperature. The precipitated salts are filtered and washed with 100 ml. of tetrahydrofuran, and the filtrate and washing are combined. Most of the tetrahydrofuran is removed under reduced pressure, the nearly colorless residue is dissolved in 450 ml. of hexane (Note 14), and this solution is extracted twice with 100 ml. of water and once with 100 ml. of saturated aqueous sodium chloride. The organic layer is dried over magnesium sulfate, filtered, and concentrated with a rotary evaporator, leaving a pale-yellow oil which crystallizes upon standing. Sublimation of the crude product at 55° (1 mm.) provides 39–41 g. (79–83%) of the cyclopropenone, m.p. 61–63° (Note 15) and (Note 16).

D. *Tri-tert-butylcyclopropenyl tetrafluoroborate*. A dry, 500-ml., three-necked flask equipped with a magnetic stirring bar, a pressure-equalizing addition funnel, and a nitrogen inlet system is charged with 56 ml. of a 2.34 *M* commercial solution of *tert*-butyllithium (0.126 mole) in pentane (Note 17) and cooled in an ice bath to 0°. A solution of 20.0 g. (0.120 mole) of di-*tert*-butylcyclopropenone in 200 ml. of pentane is added over 30 minutes, and then the ice bath is removed. The reaction mixture is stirred an additional 30 minutes, and the nearly colorless mixture is poured, with vigorous stirring, into 150 ml. of water. The pentane layer is separated, washed

with two 75-ml. portions of water, dried over magnesium sulfate, filtered, and concentrated using a rotary evaporator, leaving a pale-yellow oil which is transferred to a 1-l. Erlenmeyer flask and diluted with 600 ml. of ether. After cooling the ether solution to 0° with an ice bath, a freshly prepared 10% solution of fluoroboric acid in acetic anhydride (Note 18) is added with rapid magnetic stirring. After the resulting suspension is stirred for 20 minutes the white precipitate is collected on a sintered glass funnel (medium porosity) under vacuum and washed thoroughly with 75-ml. portions of ether. The product is dissolved in a minimal amount of boiling acetone (*ca.* 300 ml.), cooled in a freezer (*ca.* –25°), filtered, and washed with ether, yielding 15.3 g. of tri-*tert*-butylcyclopropenyl tetrafluoroborate as white needles. Concentration of the mother liquors gives two additional crops (6.6 and 2.1 g.) of pure product, for a total yield of 24–28 g. (68–79%). When heated on a hot stage, the material darkens with decomposition above 300° (Note 19).

2. Notes

1. Reagent grade anhydrous ether is employed in all operations without prior purification. The magnesium turnings were available from the J. T. Baker Chemical Company, and the 1-chloro-2,2-dimethylpropane (b.p. 84–85°), obtained from Matheson, Coleman and Bell, should be distilled before use.
2. The 1,2-dibromoethane (Eastman Organic Chemicals) was used without prior purification.
3. The *tert*-butylacetyl chloride (b.p. 126–129°) was purchased from Aldrich Chemical Company, Inc., and used without prior purification.
4. Inverse addition of the Grignard reagent to an ethereal solution of the *tert*-butylacetyl chloride does not improve the yield.
5. Fractional distillation is not necessary since the only volatile components are ether and dineopentyl ketone. A dark, high-boiling residue remains in the pot.
6. The ^1H NMR spectrum ($CDCl_3$) shows two singlets at δ 1.03 (18H) and 2.29 (4H). The IR spectrum (CCl_4) exhibits bands at 2950 (s), 2900 (s), 2865 (s), 1715 (s), 1480 (s), 1470 (s), 1370 (s), and 1355 cm^{-1} (s).
7. Irradiation with a sun lamp or addition of one drop of concentrated hydrochloric acid may be necessary to initiate the bromination.
8. *Caution! The extraction with sodium sulfite should be performed with caution since a considerable amount of heat is evolved.*
9. The dibromoketone is quite soluble in hexane; therefore, filtration should be conducted as rapidly as possible. The hexane should be precooled to at least 0°.
10. Very pure dibromoketone (m.p. 70–71°) may be obtained by sublimation at 25° (1 mm.); however, the product obtained by recrystallization is sufficiently pure for the next step. The ^1H NMR spectrum ($CDCl_3$) shows singlets at δ 1.18 (18H) and 4.42 (2H). The IR spectrum (CCl_4) shows peaks at 2960 (s), 2935 (m), 2910 (m), 2870 (m), 1740 (s), 1720 (m), 1715 (m), 1485 (s), 1475 (s), 1400 (m), 1375 (s), and 1340 $cm.^{-1}$ (s).
11. A convenient apparatus for the addition of pottassium *tert*-butoxide consists of a 250-ml. filter flask connected to the reaction vessel with Gooch tubing. The sidearm of the filter flask serves as a nitrogen inlet.
12. The tetrahydrofuran should be freshly distilled from lithium aluminium hydride. See *Org. Synth.*, **Coll. Vol. 5**, 926 (1973) for a warning concerning the purification of tetrahydrofuran.
13. Alcohol-free potassium *tert*-butoxide, obtained from the MSA Research Corporation, Callery, Pennsylvania, should be weighed and transferred under anhydrous conditions.
14. Hexane is most effective in permitting extraction of residual tetrahydrofuran into water. Failure to remove the tetrahydrofuran can delay the crystallization of the cyclopropenone.

15. The checkers noted the presence of an oil which also distilled onto the cold-finger during the sublimation. The easiest way to remove this oil is to press the sublimed cyclopropenone between two sheets of filter paper. The melting point is recorded after having removed the oil in this manner. This oil poses no hindrance in the next step. Alternatively, the submitters report that the pure cyclopropenone can be obtained more rapidly, but in slightly reduced yield, by recrystallization of the crude product from pentane at low temperature (*ca.* −70°).

16. The ^1H NMR spectrum ($CDCl_3$) shows a singlet at δ 1.34. The IR spectrum (CCl_4) shows bands at 2980 (s), 2945 (m), 2920 (m), 2880 (m), 1875 (m), 1855 (s), 1820 (s), 1640 (s), 1485 (m), 1465 (m), and 1375 $cm.^{-1}$ (m). The UV spectrum exhibits a maximum at 260 nm (log ε 1.66) in 95% C_2H_5OH and at 285 nm (log ε 1.79) in cyclohexane. The mass spectrum shows peaks at *m/e* 166, 138, 123, 95, 81, and 67.

17. The *tert*-butyllithium was obtained from Alfa Inorganics, Inc.

18. *Caution! The reaction of fluoroboric acid with acetic anhydride is exothermic and should be conducted with caution.* Under an atmosphere of nitrogen, 102 g. (1.00 mole) of acetic anhydride (J. T. Baker Chemical Company) is cooled to −40° in an acetone–dry ice bath. With magnetic stirring, 20.4 g. (0.116 mole) of 50% fluoroboric acid (J. T. Baker Chemical Company) is added over 10 minutes. After carefully warming to 0°, the freshly prepared solution is used immediately.

19. The ^1H NMR spectrum ($CDCl_3$) shows a singlet at δ 1.58. The IR spectrum (KBr) exhibits bands at 2980 (s), 1485 (s), 1465 (m), 1425 (m), 1370 (s), 1225 (s), 1197 (m), 1070 (s), 940 (m), 860 (m), and 525 $cm.^{-1}$ (m).

3. Discussion

The preparation of tri-*tert*-butylcyclopropenyl tetrafluoroborate involves a modification of the method originally employed in the synthesis of triphenylcyclopropenyl perchlorate[2] from diphenylcyclopropenone.[2,3] The overall yields of tri-*tert*-butylcyclopropenyl tetrafluoroborate and di-*tert*-butylcyclopropenone are 40% and 52%, respectively. Other substituted di-*tert*-butylcyclopropenyl cations have also been prepared by the above procedure.[4] It should be pointed out, however, that the synthesis of cyclopropenyl cations using the reaction of cyclopropenones with organometallic reagents is not general.[2,4] Possible competing side reactions include conjugate addition[5] and proton abstraction (if the cyclopropenone contains an acidic hydrogen).

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

α,α'-Dibromodineopentyl ketone

pottassium tert-butoxide

hydrochloric acid (7647-01-0)

ether, diethyl ether (60-29-7)

acetic anhydride (108-24-7)

hydrogen (1333-74-0)

sodium sulfite (7757-83-7)

sodium hydrogen carbonate (144-55-8)

magnesium turnings (7439-95-4)

sodium chloride (7647-14-5)

hydrogen bromide (10035-10-6)

sodium carbonate (497-19-8)

bromine (7726-95-6)

nitrogen (7727-37-9)

acetone (67-64-1)

1,2-dibromoethane, 1,2 dibromoethane (106-93-4)

Pentane (109-66-0)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

lithium aluminium hydride (16853-85-3)

hexane (110-54-3)

Diphenylcyclopropenone (886-38-4)

fluoroboric acid (16872-11-0)

Cyclopropenylium, 1,2,3-tris(1,1-dimethylethyl)-, tetrafluoroborate(1-), Tri-tert-butylcyclopropenyl tetrafluoroborate (60391-90-4)

1-chloro-2,2-dimethylpropane (753-89-9)

Dineopentyl ketone (4436-99-1)

triphenylcyclopropenyl perchlorate

tert-Butyllithium (594-19-4)

potassium tert-butoxide (865-47-4)

tert-butylacetyl chloride (7065-46-5)

Di-tert-butylcyclopropenone (19985-79-6)

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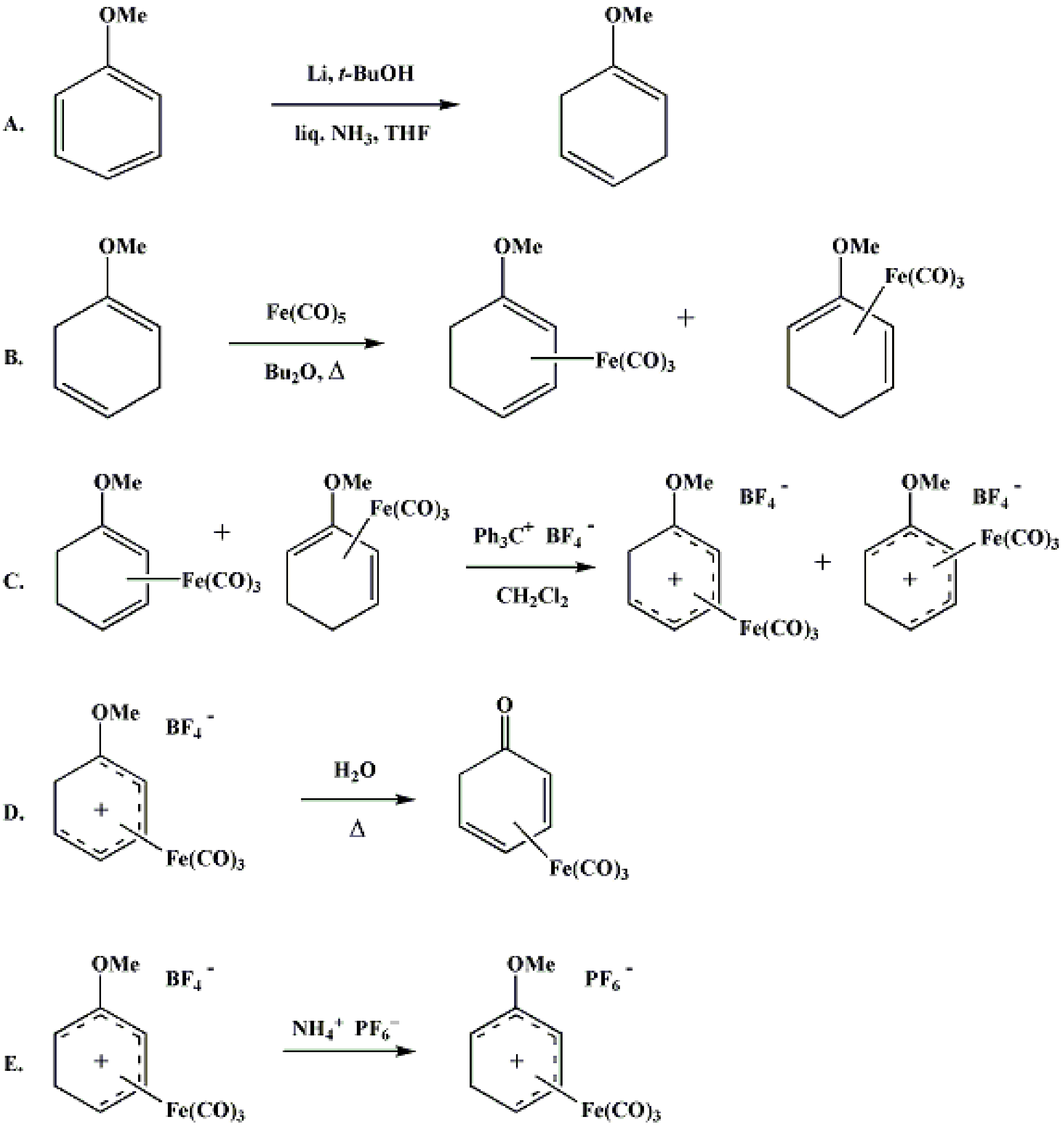
TRICARBONYL[(2,3,4,5-η)-2,4-CYCLOHEXADIEN-1-ONE]IRON AND TRICARBONYL[(1,2,3,4,5-η)-2-METHOXY-2,4-CYCLOHEXADIEN-1-YL]IRON(1+) HEXAFLUOROPHOSPHATE(1–) FROM ANISOLE

[Iron, tricarbonyl[(2,3,4,5-η)-2,4-cyclohexadien-1-one] and Iron(1+), tricarbonyl[(1,2,3,4,5-η)-2-methoxy-2,4-cyclohexadien-1-yl] hexafluorophosphate (1–)]



Submitted by A. J. Birch[1] and K. B. Chamberlain.
Checked by Susumu Kamata, Tsutomu Aoki, and Wataru Nagata.

1. Procedure

Caution! Parts A and B must be conducted in an efficient hood to prevent exposure to ammonia, iron pentacarbonyl, and carbon monoxide.

A. *1-Methoxy-1,4-cyclohexadiene.* A 3-l., three-necked, round-bottomed flask equipped with an inlet tube, mechanical stirrer, and an acetone–dry ice condenser fitted with a drying tube is charged with 150 ml. of tetrahydrofuran, 250 ml. of *tert*-butyl alcohol, and 50 g. (0.46 mole) of anisole (Note 1). About 1.5 l. of dried liquid ammonia (Note 2) is distilled into the reaction vessel from a steam bath. Lithium (11.5 g., 1.66 g.-atoms) (Note 3), (Note 4) is added cautiously with stirring and, when the addition is complete, the stirring is continued for 1 hour with refluxing. The blue color is discharged by cautiously adding methanol dropwise (about 100 ml. is required); 750 ml. of water is then added carefully. The excess ammonia is allowed to evaporate overnight, more water is added, dissolving the lithium salts, and the mixture is extracted three times with 100-ml. portions of petroleum ether (b.p. 30–40°) (Note 5). The combined extracts are washed four times with 75-ml. portions of water, removing *tert*-butyl alcohol and methanol, and dried over anhydrous magnesium sulfate, and the solvent is removed through a 30-cm. Vigreux column (Note 6) under reduced pressure (20 mm.). Distillation of the residue yields 1-methoxy-1,4-cyclohexadiene (38–40 g., about 75%) (Note 7), (Note 8), b.p. 40° (20 mm.).

B. *Tricarbonyl*[(1,2,3,4-η)-1- *and* 2-*methoxy*-1,3-*cyclohexadiene]iron.* A 500-ml., three-necked, round-bottomed flask equipped with a nitrogen-inlet tube, a condenser provided with a gas bubbler, and a stopper is flushed with nitrogen and charged with 39 g. (0.35 mole) of 1-methoxy-1,4-cyclohexadiene, 320 ml. of dibutyl ether (Note 9), and 95 g. (65 ml., 0.49 mole) of filtered iron pentacarbonyl (Note 10),(Note 11), (Note 12). Using a heating mantle, the mixture is refluxed for 18 hours (Note 13) under a slow nitrogen stream. After cooling, the reaction mixture is filtered by suction through Celite, removing iron particles (Note 14), the Celite is washed twice with 15-ml. portions of dibutyl ether, and the washings and filtrate are combined. The crude product (Note 15) is obtained by evaporating excess iron pentacarbonyl, unreacted diene, and the dibutyl ether using a rotary evaporator (in a fume hood), with a hot-water bath and ice cooling of the receiver. The distillate is again refluxed for 18 hours under nitrogen as before and worked up in the same manner. This procedure is then repeated again. Distillation of the combined residues using a nitrogen leak (Note 16) yields 54 g. of the product as a yellow oil, b.p. 66–68° (0.1 mm.) (Note 17). The distillation residue, after elution through a short acidic alumina column with light petroleum ether and solvent evaporation, yields an additional 5 g. of product, giving a total yield of 59–68 g. (67–78%) (Note 18), (Note 19).

C. *Tricarbonyl*[(1,2,3,4,5-η)-1- *and* 2-*methoxy*-2,4-*cyclohexadien*-1-*yl*]*iron*(1+) *tetrafluoroborate*(1–). Triphenylmethyl tetrafluoroborate (34 g., 0.10 mole) (Note 20) is dissolved in a minimum volume of dichloromethane, and 18 g. (0.072 mole) of tricarbonyl (1- and 2-methoxy-1,3-cyclohexadiene)iron dissolved in a like volume of dichloromethane is added. The resulting dark solution is left for 20–30 minutes and added with stirring to three times its volume of diethyl ether (Note 21). The precipitate is collected and washed with ether, yielding 21–22 g. (87–91%) of product as a yellow solid (Note 19).

D. *Tricarbonyl*[(2,3,4,5-η)-2,4-*cyclohexadian*-1-*one*]*iron.* The tetrafluoroborate mixture from Part C (21 g., 0.062 mole) is heated on a steam bath for 1 hour in 450 ml. of water, during which time orange crystals separate. After cooling, the mixture is extracted three times with 100-ml. portions of ether, into which most of the solid dissolves. (The aqueous layer is used in Part E.) The extracts are dried over anhydrous magnesium sulfate, and the ether is evaporated, yielding 7–7.5 g. (47–51%) of the yellow crystalline dienone complex (Note 22).

E. *Tricarbonyl*[(1,2,3,4,5-η)-2-*methoxy*-2,4-*cyclohexadien*-1-*yl*]*iron*(1+) *hexafluorophosphate*(1–). To the aqueous layer from Part D is added with swirling 7.1 g. (0.044 mole) of ammonium hexafluorophosphate (Note 23) in 30 ml. water. After 30 minutes, the light-yellow product is filtered, washed with water, and air dried, yielding 9–10 g. (35–44%) (Note 19), (Note 24).

2. Notes

1. Anisole (500 g.) was purified[2] by washing twice with 50 ml. of 2 *N* sodium hydroxide, twice with 50 ml. of water, drying over anhydrous magnesium sulfate, and distillation, b.p. 43–46° (20 mm.). The checkers used anisole obtained from Kanto Chemical Co., Ltd., Japan.

2. Liquid ammonia, from a cylinder, is purified by addition of 2–3 g. of sodium cut into small pieces and distillation into the reaction vessel.

3. The submitters used lithium wire (Merck & Company, Inc.) (12 in. = 1 g.) cut into small pieces. The checkers used a block of lithium cut into small pieces.

4. The lithium pieces must be small and added to the ammonia solution cautiously. If too much is added at one time, the reaction becomes violent and froths.

5. Frequently not all of the ammonia evaporates; the first extraction should be by swirling in a separatory funnel without a stopper, and subsequent extractions should be done with frequent pressure release.

6. The solvent must be carefully removed; use of a rotary evaporator results in considerable loss of the product.

7. The IR spectrum of the 1-methoxy-1,4-cyclohexadiene shows the absence of strong aromatic absorption at 1600 $cm.^{-1}$; the UV spectrum shows absence of absorption at 270 nm., indicating absence of the conjugated isomer.

8. ^1H NMR spectrum, δ (number of protons): δ 2.5–2.9 (4H), 3.48 (3H), 3.50 (1H), 5.60 (2H).

9. Dibutyl ether must be dry and peroxide-free. This can be achieved by filtering it through a large column of basic alumina, or by leaving overnight over sodium wire and distillation. If these precautions are not observed, low yields result. The checkers purified dibutyl ether by distillation from a sodium hydride dispersion.

10. During the reaction the hood must be operating at all times, as carbon monoxide is evolved.

11. Iron pentacarbonyl is toxic and volatile; consequently, it should only be handled in a good hood, while wearing gloves.

12. The submitters used iron pentacarbonyl "pract." grade obtained from Fluka A G. The checkers used iron pentracarbonyl obtained from Merck, Germany.

13. When the reaction was followed by ^1H NMR spectroscopy, it was found that the yield reached a maximum after 18 hours; longer refluxing resulted in decomposition and lower yields. At that point as well, the maximum proportion of the 1-methoxy isomer was produced; this isomer is converted into the dienone complex.

14. Care should be exercised in filtering the reaction mixture. The solid collected is largely finely divided iron and pyrophoric; it should not be allowed to dry.

15. The crude product is unstable and should be stored under nitrogen with refrigeration.

16. Alternatively, rapid magnetic stirring will prevent bumping and allow distillation without a gas bleed.

17. For smaller batches, purification by elution of the product through a short column of acidic alumina with light petroleum ether and evaporation of the solvent is satisfactory.

18. In one of the checker's experiments almost all the material could be distilled, giving 68.14 g. (77.9%) of the product, b.p. 66–67° (0.3–0.4 mm.).

19. For ^1H NMR and IR spectra, see Birch and co-workers.[3]

20. Triphenylmethyl fluoroborate is prepared by dissolving 27 g. (0.10 mole) of triphenylmethanol ("purum," Fluka A G) in 260 ml. of propionic anhydride by warming on a steam bath. With an acetone–dry ice bath the solution is cooled to 10° and maintained between 10° and 20° while 31 ml. of 43% (w/w) fluoroboric acid is added portionwise with swirling. The yellow solid is collected, washed well with dry ether, and dried in a desiccator under vacuum, yielding 34 g. (90–99%). The product is very hygroscopic, taking up water with hydrolysis. It is desirable to prepare this reagent immediately before use.

21. The ether should be reagent grade but not sodium-dried. The traces of water present destroy excess reagent, leading to a cleaner product.

22. The product at this stage is sufficiently pure for most purposes. It can be recrystallized in small

batches from water,[3] m.p. 104–104.5°; it can be chromatographed on silica or acidic alumina or sublimed at 80–90° (0.2 mm.). The checkers obtained the purified material (m.p. 104–105°) by recrystallization from dichloromethane-ether. The purified material has the following IR spectrum ($CHCl_3$) cm.$^{-1}$: 2070 strong, 2000 strong, 1665 strong; ^{1}H NMR spectra ($CDCl_3$), δ (multiplicity, number of protons): 2.28–2.45 (m, 2H), 3.1–3.46 (m, 2H), 5.6–6.1 (m, 2H).
23. Obtained from Ozark-Mahoning Chemical Co.
24. The complex can be stored for long periods under nitrogen in a refrigerator with only slight darkening. The purified material has the following IR spectrum (Nujol) cm^{-1}: 2110 strong, 2060 strong, 1515 weak, 1494 weak, 1253 medium strong.

3. Discussion

Anisole is reduced using the solvent of Dryden and collegues.[4] Iron pentacarbonyl and 1-methoxy-1,4-cyclohexadiene react as shown by Birch and co-workers,[3] although dibutyl ether has been found to be a superior solvent.[5] The tricarbonyl(methoxy-1,3-cyclohexadiene)iron isomers undergo hydride abstraction[3,6] with triphenylmethyl tetrafluoroborate, forming the dienyl salt mixture, of which the 1-methoxy isomer is hydrolyzed by water to the cyclohexadienone complex. The 2-methoxy isomer can be recovered by precipitation as the hexafluorophosphate salt. By this method the 3-methyl-substituted dienone complex has also been prepared[3] from 1-methoxy-3-methylbenzene. The use of the conjugated 1-methoxy-1,3-cyclohexadiene in Part B led to no increase in yield or rate and resulted chiefly in another product of higher molecular weight. An alternative route to the dienone is the reaction of tricarbonyl(1,4-dimethoxycyclohexadiene)iron with sulfuric acid.[7]

The dienone complex is an effective phenylating agent for aromatic amines; *e.g.*, aniline and tricarbonylcyclohexadienoneiron react in glacial acetic acid at 75° overnight, giving diphenylamine in 95% yield.[8] Under appropriate experimental conditions cyclohexadienone complexes react with lithium alkyls and, upon removal of iron tricarbonyl, the alkylbenzene is formed.[9] The 2-methoxy cation has now been resolved, *via* the menthoxy derivative.[10] This cation is equivalent to sterically directed 2-cyclohexen-1-one 4-cation.[9]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 1001

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Appendix

Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

Tricarbonyl[(2,3,4,5-η)-2,4-cyclohexadien-1-one]iron

TRICARBONYL[(1,2,3,4,5-η)-2-METHOXY-2,4-CYCLOHEXADIEN-1-YL]IRON(1+) HEXAFLUOROPHOSPHATE(1−)

Iron, tricarbonyl[(2,3,4,5-η)-2,4-cyclohexadien-1-one]

Iron(1+), tricarbonyl[(1,2,3,4,5-η)-2-methoxy-2,4-cyclohexadien-1-yl] hexafluorophosphate (1−)

Tricarbonyl[(1,2,3,4-η)-1- and 2-methoxy-1,3-cyclohexadiene]iron

Tricarbonyl[(1,2,3,4,5-η)-1- and 2-methoxy-2,4-cyclohexadien-1-yl]iron(1+) tetrafluoroborate(1−)

tricarbonyl (1- and 2-methoxy-1,3-cyclohexadiene)iron

Tricarbonyl[(2,3,4,5-η)-2,4-cyclohexadian-1-one]iron

iron pentracarbonyl

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

ammonia (7664-41-7)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

aniline (62-53-3)

sodium hydroxide (1310-73-2)

carbon monoxide (630-08-0)

iron (7439-89-6)

nitrogen (7727-37-9)

Anisole (100-66-3)

sodium (13966-32-0)

dibutyl ether (142-96-1)

dichloromethane (75-09-2)

diphenylamine (122-39-4)

triphenylmethanol (76-84-6)

lithium (7439-93-2)

magnesium sulfate (7487-88-9)

propionic anhydride (123-62-6)

Tetrahydrofuran (109-99-9)

sodium hydride (7646-69-7)

tert-butyl alcohol (75-65-0)

iron pentacarbonyl

fluoroboric acid (16872-11-0)

Triphenylmethyl tetrafluoroborate, Triphenylmethyl fluoroborate

1-Methoxy-1,4-cyclohexadiene (2886-59-1)

ammonium hexafluorophosphate

1-methoxy-3-methylbenzene (100-84-5)

1-methoxy-1,3-cyclohexadiene

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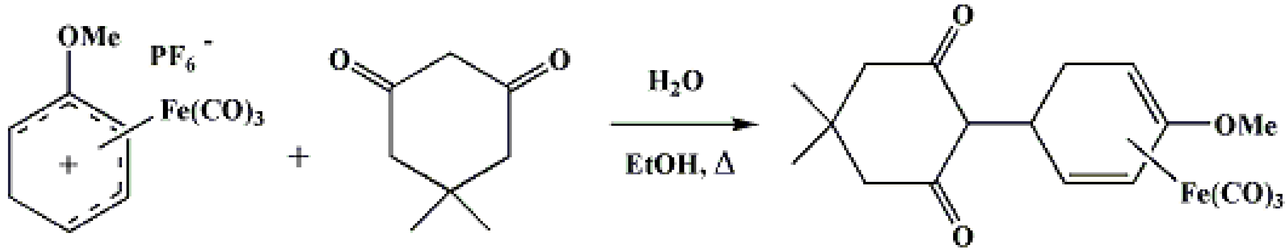
Organic Syntheses, CV 6, 1001

ALKYLATION OF DIMEDONE WITH A TRICARBONYL (DIENE)IRON COMPLEX: TRICARBONYL[2-[(2,3,4,5-η)-4-METHOXY-2,4-CYCLOHEXADIEN-1-YL]-5,5-DIMETHYL-1,3-CYCLOHEXANEDIONE]IRON

[Iron, tricarbonyl[2-[(2,3,4,5-η)-4-methoxy-2,4-cyclohexadien-1-yl]-5,5-dimethyl-1,3-cyclohexanedione]-]



Submitted by A. J. Birch and K. B. Chamberlain[1].
Checked by T. Aoki, S. Kamata, and W. Nagata.

1. Procedure

A 500-ml., round-bottomed flask equipped with a condenser is charged with 5 g. (0.013 mole) of tricarbonyl[(1,2,3,4,5-η)-2,4-cyclohexadien-1-yl]iron(1+) hexafluorophosphate(1−) (Note 1), 150 ml. of water, and 50 ml. of ethanol and heated on the steam bath with occasional swirling until the salt is dissolved. Dimedone (1,3-Cyclohexanedione, 5,5-dimethyl-) (2.5 g., 0.018 mole) is dissolved in 50 ml. of ethanol by warming. The two solutions are mixed and refluxed for 15 minutes. After cooling to about 25°, the mixture is poured into 500 ml. of water with stirring, and the precipitate is collected, washed with water, and air-dried, yielding 4.4 g. of crude product. The product is recrystallized by first dissolving in a minimum volume of boiling ethanol and adding water until the first sign of turbidity. On standing under refrigeration overnight, crystallization occurs. After collection by filtration, the product is washed with water and air-dried, yielding 3.7 g. of small, white to buff-colored crystals (Note 2), which darken above 140° but do not melt. On addition of water to the filtrate a crop of 0.6 g. is obtained, giving a total yield of 4.3 g. (87%).

2. Notes

1. The preparation of this salt is described in *Org. Synth.*, **Coll. Vol. 6**, 996 (1988).
2. ^{1}H NMR (100 MHz, acetone-d_6), δ (multiplicity, number of protons): δ 1.02 (s, 6H), 1.88 (q, 1H), 2.23 (s), 2.52 (quintet), 2.48–3.52 (m)—the preceding four signals account for 10 protons—3.66 (s, 3H), 5.24 (q, 1H); IR (Nujol) cm.$^{-1}$: 2040, 1980, 1950, 1560; mass spectrum *m/e*: 388 (M+).

3. Discussion

Hexafluorophosphate and tetrafluoroborate dienyl salts react with many nucleophiles.[2] The tetrafluoroborate salts are preferred, being more soluble in organic solvents than the hexafluorophosphates.

In all cases so far investigated, including a useful direct reaction with ketones,[3] the methoxydienyl salt is substituted at the 5-position and not at the alternative 1-position. The iron tricarbonyl group can conveniently be removed from many of these adducts by the action of iron(III) chloride in ethanol.[3]

References and Notes

1. Research School of Chemistry, Australian National University, P.O. Box 4, Canberra, A.C.T. 2600, Australia.
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

TRICARBONYL[2-[(2,3,4,5-η)-4-METHOXY-2,4-CYCLOHEXADIEN-1-YL]-5,5-DIMETHYL-1,3-CYCLOHEXANEDIONE]IRON

Iron, tricarbonyl[2-[(2,3,4,5-η)-4-methoxy-2,4-cyclohexadien-1-yl]-5,5-dimethyl-1,3-cyclohexanedione]-

tricarbonyl[(1,2,3,4,5-η)-2,4-cyclohexadien-1-yl]iron(1+) hexafluorophosphate(1−)

ethanol (64-17-5)

iron(III) chloride (7705-08-0)

tetrafluoroborate (14874-70-5)

1,3-Cyclohexanedione, 5,5-dimethyl-, dimedone (126-81-8)

hexafluorophosphate

TRICARBONYL(DIENE)IRON

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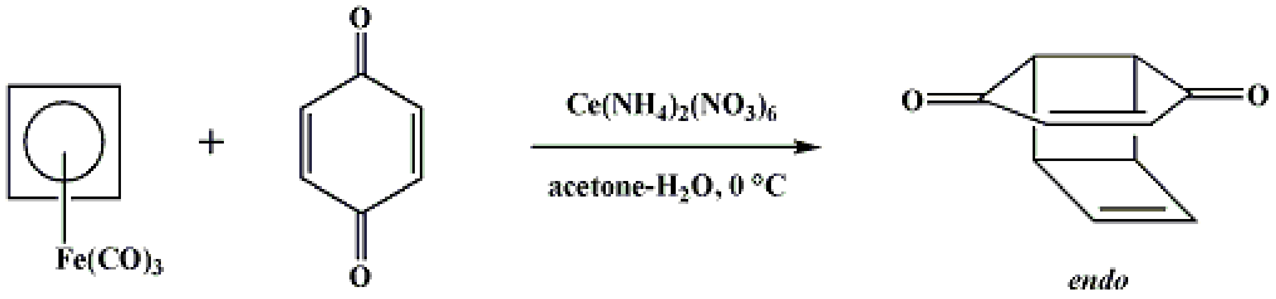
Organic Syntheses, *CV 6, 1002*

CYCLOBUTADIENE IN SYNTHESIS: *endo*-TRICYCLO [4.4.0.0^{2,5}]DECA-3,8-DIENE-7,10-DIONE



Submitted by L. Brener, J. S. McKennis, and R. Pettit[1,2].
Checked by R. E. Ireland and G. Brown.

1. Procedure

Caution! Because of the evolution of carbon monoxide, this procedure should be carried out in a well-ventilated hood.

A 500-ml., three-necked, round-bottomed flask fitted with a sealed mechanical stirrer and an outlet leading to a gas bubbler, is charged with a solution containing 4.0 g. (0.021 mole) of cyclobutadieneiron tricarbonyl[2] and 2.0 g. (0.018 mole) of freshly sublimed *p*-benzoquinone (Note 1) in 72 ml. of acetone and 8 ml. of water. To the vigorously stirred, ice-cold solution, approximately 40–42 g. of ceric ammonium nitrate (Note 2) is added portionwise over a period of 10–12 minutes (Note 3), until the carbon monoxide evolution has ceased. The reaction mixture is then poured into 600 ml. of cold brine, and the resulting mixture is extracted with five 150-ml. portions of diethyl ether. The combined extracts are washed with four 250-ml. portions of water and dried over anhydrous magnesium sulfate.

Removal of the solvent under reduced pressure affords 1.9–2.1 g. of the crude yellow adduct (Note 4). This crude material is dissolved in 8 ml. of hot dibutyl ether (70–80°) and rapidly percolated through approximately 2.0 g. of Florisil (Note 5). Cooling and filtering the eluent affords 1.2–1.3 g. (40–44%) of yellow crystals, m.p. 77–80°. An additional recrystallization from dibutyl ether or ethyl acetate–hexane yields pale yellow crystals, m.p. 78.5–80° (Note 6).

2. Notes

1. In most syntheses using cyclobutadiene, it is advantageous to use an excess of the trapping agent, but here excess *p*-benzoquinone hampers isolation of the pure adduct.
2. Other oxidizing agents may be used to degrade cyclobutadieneiron tricarbonyl; in those cases in which the reactants or products are sensitive to the acidic ceric ammonium nitrate solutions, lead tetraäcetate in pyridine can be used.
3. Slower addition results in a diminished yield.
4. The ^{1}H NMR spectrum (C_6H_6-d_6) indicated the presence of less than 5% *p*-benzoquinone. This material darkens upon standing, even in a refrigerator;

recrystallization should be performed as soon as possible.
5. It is imperative to use a hot narrow column to prevent crystallization and to avoid passage of dark material through the column. The column was made in a Liebig condenser (6 mm. dia.). The Florisil filled 14 cm. of the condenser. A temperature of 70–80° is sufficient to melt even pure product but avoid passage of dark material.
6. The pure adduct had the following ^{1}H NMR spectrum ($CDCl_3$), δ (multiplicity, number of protons, assignment): 3.5 (broad m, 4H, cyclobutane protons), 6.20 (m, 2H, cyclobutene vinyl protons), and 6.75 (s, 2H, cyclohexene vinyl protons).

3. Discussion

This procedure is illustrative of the synthetic use of cyclobutadieneiron tricarbonyl[3] as a source of highly reactive cyclobutadiene. Cyclobutadiene has been employed, for example, in the synthesis of cubane, Dewar benzenes, and a variety of other systems.[3,4]

The synthesis of *endo*-tricyclo[4.4.0.0^{2,5}]deca-3-8-dien-7,10-dione and verification of its *endo*-configuration has been reported earlier.[3] This adduct is a useful starting material for the syntheses of tetracyclo[5.3.0.0^{2,6}.0^{3,10}]deca-4-8-diene,[5] tricyclo[4.4.0.0^{2,5}]deca-3,7,9-triene,[6] *cis, syn, cis*-tricyclo[5.3.0.0^{2,6}]deca-4-8-dien-3,10-dione,[7] and 4-oxahexa-cyclo [5.4.0.0^{2,6}.0^{3,10}.0^{5,9}.0^{8,11}]undecane.[8]

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1. Deceased December 10, 1981; work done at Department of Chemistry, University of Texas, Austin, Texas 78712.
2. J. Henery and R. Pettit, *Org. Synth.*, **Coll. Vol. 6**, 422 (1988); R. Pettit and J. Henery, *Org. Synth.*, **Coll. Vol. 6**, 310 (1988); R. H. Grubbs, *J. Am. Chem. Soc.*, **92**, 6693 (1970).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

brine

Cyclobutadieneiron tricarbonyl

ethyl acetate (141-78-6)

diethyl ether (60-29-7)

carbon monoxide (630-08-0)

acetone (67-64-1)

pyridine (110-86-1)

dibutyl ether (142-96-1)

p-benzoquinone (106-51-4)

magnesium sulfate (7487-88-9)

hexane (110-54-3)

CYCLOBUTADIENEIRON

TRICARBONYL

Dewar benzenes

ceric ammonium nitrate

CYCLOBUTADIENE

tetracyclo[5.3.0.0^{2,6}.0^{3,10}]deca-4-8-diene

tricyclo[4.4.0.0^{2,5}]deca-3,7,9-triene

4-oxahexa-cyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}.0^{8,11}]undecane

endo-Tricyclo[4.4.0.0^{2,5}]deca-3,8-diene-7,10-dione, endo-tricyclo[4.4.0.0^{2,5}]deca-3-8-dien-7,10-dione (34231-42-0)

cis, syn, cis-tricyclo[5.3.0.0^{2,6}]deca-4-8-dien-3,10-dione

lead tetraacetate

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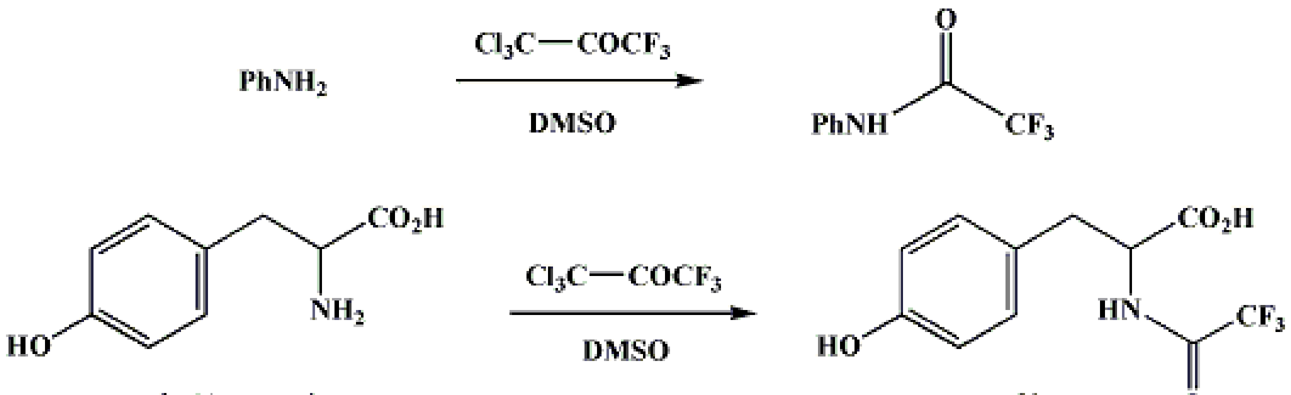
Organic Syntheses, CV 6, 1004

TRIFLUOROACETYLATION OF AMINES AND AMINO ACIDS UNDER NEUTRAL, MILD CONDITIONS: *N*-TRIFLUOROACETANILIDE AND *N*-TRIFLUOROACETYL-L-TYROSINE

[Acetamide, 2,2,2-trifluoro-*N*-phenyl- and L-Tyrosine, *N*-(trifluoroacetyl)-]



l - (-) - tyrosine   *l* isomer

Submitted by C. A. Panetta[1]
Checked by R. M. Freidinger and G. Büchi.

1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A. N-*Trifluoroacetanilide*. A two-necked, round-bottomed flask fitted with a thermometer, a Drierite tube, and a magnetic stirring bar is charged with 4.66 g. (4.56 ml., 0.0501 mole) of aniline (Note 1) and 15 ml. of dimethyl sulfoxide (Note 2). The resulting solution is stirred and cooled in an ice water bath, and when the internal temperature has dropped to 10–15°, 21.5 g. (0.0998 mole) of 1,1,1-trichloro-3,3,3-trifluoroacetone (Note 3) is added in portions through the condenser. A mild exotherm results, and the addition is extended over *ca.* 5 minutes, maintaining a reaction temperature below 40°. When the addition is complete, the ice bath is removed, and the amber solution is stirred at room temperature for 22 hours. The reaction mixture is poured into 750 ml. of water. A crystalline solid separates, and the resulting slurry is stirred for 1 hour before filtration. After being washed with water, the crystals are dried in a vacuum oven at 50° for 40 minutes, giving 6.49–6.53 g. (69%) of *N*-trifluoroacetanilide, m.p. 86.0–86.5° (cor.) (Note 4),(Note 5), (Note 6).

B. N-*Trifluoroacetyl*-L-*tyrosine*. A two-necked, round-bottomed flask fitted with a thermometer, a condenser protected with a Drierite tube, and a magnetic stirrer is charged with 18.12 g. (0.1001 mole) of L-(−)-tyrosine (Note 7) and 130 ml. of dimethyl sulfoxide (Note 2). The suspension is stirred and cooled in an ice water bath. When the internal temperature reaches 10–15°, 64.62 g. (0.2999 mole) of 1,1,1-trichloro-3,3,3-trifluoroacetone (Note 3) is added through the condenser at a rate such that the temperature of the reaction temperature does not exceed 35°. The cooling bath

is removed, and the reaction mixture is stirred at room temperature for 22 hours, during which time the suspension becomes a solution. This solution is poured into 660 ml. of ice water, and the resulting mixture is extracted with two portions (660 ml. and 400 ml.) of 1-butanol. The organic extracts are concentrated, first on the rotary evaporator and then at 40° (0.1 mm.), giving a red-orange semisolid, which is dissolved in a minimum amount of acetone and placed on a column of silica gel (Note 8). Elution with benzene–acetone mixtures (Note 9) provides 20.0–22.2 g. (72–80%) of *N*-trifluoroacetyl-L-tyrosine as a colorless to light yellow solid. Recrystallization from either benzene–acetone or water gives white needles, m.p. 192.5–193.5° (cor.) (Note 6) and (Note 10).

2. Notes

1. Commercial aniline from Fisher Scientific Company (purified grade) was used as supplied.
2. Dimethyl sulfoxide from the J. T. Baker Chemical Company (reagent grade) was used as supplied.
3. 1,1,1-Trichloro-3,3,3-trifluoroacetone is available from PCR, Inc., P.O. Box 14318, Gainesville, Florida. It may also be prepared easily by the following procedure. Fresh, anhydrous aluminum chloride (18.5 g., 0.139 mole) and 35.0 g. (0.192 mole) of chloropentafluoroacetone (b.p. 7.8°; available from PCR, Inc., or Allied Chemical Corp.) are combined in a flask fitted with a dry ice condenser and a magnetic stirring bar. The refluxing mixture is stirred for 4–6 hours and allowed to warm gradually to room temperature. The contents of the flask are extracted three times with anhydrous ether, and the combined extracts are distilled at atmospheric pressure. After the ether has been removed, continued distillation gives 22.8–28.5 g. (55–69%) of 1,1,1-trichloro-3,3,3-trifluoroacetone, b.p. 83.5–84.5°; IR (film) 1790 cm.$^{-1}$. This compound is stored at room temperature in a tightly stoppered bottle. In the absence of reliable toxicity data, it should be handled with normal precautions.
4. IR (CH_2Cl_2) cm.$^{-1}$: 3401 and 3049 (NH, CH), 1740 (C=O), 1235 (C-F), (lit.,[2] m.p. 87.6°).
5. The checkers suspected that some product was lost during the drying process. Therefore, they purified the crude product by sublimation at 55° (0.15 mm.), which gave 3.76–3.84 g. (80–81%) of *N*-trifluoroacetanilide in half-scale runs (Note 6).
6. The checkers ran Parts A and B at half the submitter's scale, and the yields were comparable or higher in all cases.
7. Reagent-grade L-(–)-tyrosine was obtained from Fisher Scientific Company.
8. Silica gel 60 (70–230 mesh) was purchased from E. Merck, Darmstadt, Germany.
9. The checkers, working at one half the submitter's scale, obtained 17.5 g. of crude product and used 175 g. of silica gel in their column. They eluted as follows:

Fraction	Eluent (Benzene: Acetone Ratio, ml.)	Eluate
1	9:1, 425	1.2 g., yellow oil
2	17:3, 100	1.7 g., pale yellow solid, m.p. 85–92°
3	3:1, 850	9.4 g., colorless solid, m.p. 194–196°
4	3:2, 600	0.4 g., colorless solid, m.p. 209–212°

Fraction 2 was recrystallized from benzene–acetone to give 1.2 g. of colorless solid, m.p.

194–196° (uncor.), which was combined with fraction 3 to give 10.6 g. (76%) of product.
10. IR (Nujol) cm.$^{-1}$: 1695 (C=O), 1180 (C-F), (lit.,[3] m.p. 192.5–193.5°).

3. Discussion

The original procedure for the trifluoroacetylation of amino acids used trifluoroacetic anhydride,[4] which, although inexpensive and readily available, has certain disadvantages: it is a highly reactive compound and has caused undesired reactions such as the cleavage of amide or peptide bonds;[5] unsymmetrical anhydrides are formed between the newly formed *N*-trifluoroacetylamino acids and the by-product trifluoroacetic acid; and excess trifluoroacetic anhydride has caused racemization of asymmetric centers.

Thus, other trifluoroacetylation reagents have been investigated. *S*-Ethyl trifluorothioacetate[6] has none of the above disadvantages. It does require, however, weakly basic conditions (pH 8–9) and an aqueous medium. Phenyl trifluoroacetate[7] effects trifluoroacetylation of amino acids under essentially neutral conditions. Its main disadvantages are high cost and the elevated temperatures (120–150°) required.

1,1,1-Trichloro-3,3,3-trifluoroacetone is a relatively unreactive compound that is volatile and easily handled. It may be obtained either commercially or by a simple laboratory preparation (Note 3), and it trifluoroacetylates amino groups in amino acids and other compounds under neutral and extremely mild conditions.[8] Table I lists some compounds that have been prepared with this reagent.

TABLE I
TRIFLUOROACETYLAMINO COMPOUNDS PREPARED WITH CF_3COCCl_3[a]

Product	Yield (%)
TFA-Aniline	69
TFA-L-Valine	94
TFA-DL-Phenylalanine	52
TFA-L-Phenylalanine	57
TFA-L-Leucine	100
TFA-L-Tyrosine	80
TFA-L-Proline	100
TFA-DL-Alanine	20
TFA-Glycylglycine	43
TFA-L-Prolyglycine, ethyl ester	23
TFA-L-Asparagine	26
TFA-Dehydroabietylamine	11

[a] Except for the first entry, all the compounds listed were prepared by the procedure of Part B.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

L-(−)-tyrosine

N-trifluoroacetylamino acids

TFA-L-Prolyglycine, ethyl

TFA-Dehydroabietylamine

Benzene (71-43-2)

ether (60-29-7)

aniline (62-53-3)

1-butanol (71-36-3)

acetone (67-64-1)

aluminum chloride (3495-54-3)

dimethyl sulfoxide (67-68-5)

trifluoroacetic acid (76-05-1)

trifluoroacetic anhydride (407-25-0)

1,1,1-trichloro-3,3,3-trifluoroacetone (758-42-9)

chloropentafluoroacetone (79-53-8)

TFA-Aniline, Acetamide, 2,2,2-trifluoro-N-phenyl- (404-24-0)

TFA-Glycylglycine (400-58-8)

Phenyl trifluoroacetate (500-73-2)

N-Trifluoroacetanilide

N-Trifluoroacetyl-L-tyrosine, L-Tyrosine, N-(trifluoroacetyl)-, TFA-L-Tyrosine (350-10-7)

S-Ethyl trifluorothioacetate (383-64-2)

TFA-L-Valine

TFA-DL-Phenylalanine

TFA-L-Phenylalanine

TFA-L-Leucine

TFA-L-Proline

TFA-DL-Alanine

TFA-L-Asparagine

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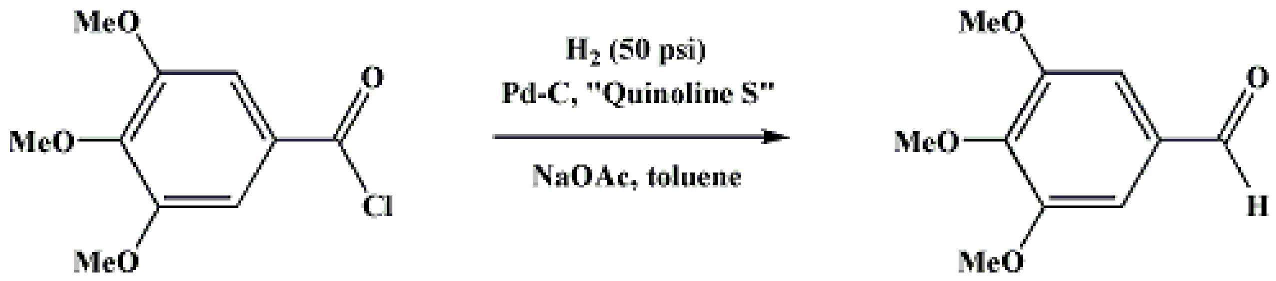
Organic Syntheses, *CV 6, 1007*

ALDEHYDES FROM ACID CHLORIDES BY MODIFIED ROSENMUND REDUCTION: 3,4,5-TRIMETHOXYBENZALDEHYDE

[Benzaldehyde, 3,4,5-trimethoxy-]



Submitted by A. I. Rachlin, H. Gurien, and D. P. Wagner[1].
Checked by James H. Sherman and Richard E. Benson.

1. Procedure

A pressure vessel (Note 1) is charged in order with 600 ml. of dry toluene (Note 2), 25 g. (0.30 mole) of anhydrous sodium acetate (Note 3), 3 g. of dry, 10% palladium-on-carbon catalyst (Note 4), 23 g. (0.10 mole) of 3,4,5-trimethoxybenzoyl chloride (Note 5), and 1 ml. of Quinoline S (Note 6). The pressure vessel is flushed with nitrogen, sealed, evacuated briefly, and pressured to 50 p.s.i. with hydrogen. The mixture is shaken with 50 p.s.i. of hydrogen for 1 hour at room temperature (Note 7), then heated at 35–40° for 2 hours. Agitation is continued overnight while the reaction mixture cools to room temperature. The pressure on the vessel is released, the vessel is opened, and the mixture is filtered through 10 g. of Celite filter aid, and the insoluble material is washed with 25 ml. of toluene. The combined filtrates are washed successively with 25 ml. of 5% sodium carbonate solution and 25 ml. of water. The toluene solution is dried over 5 g. of anhydrous sodium sulfate and filtered. The filtrate is concentrated by distillation at reduced pressure using a water aspirator. The residue (Note 8) is distilled through a 10-cm. Vigreux column with warm water circulating through the condenser, to prevent crystallization of the distillate, yielding 12.5–16.2 g. (64–83%) of 3,4,5-trimethoxybenzaldehyde, b.p. 158–161° (7–8 mm.), m.p. 74–75° (Note 9) and (Note 10).

2. Notes

1. Both glass-lined and stainless-steel autoclaves have been used successfully. The checkers used a 1.2-l., Hastelloy autoclave.
2. Reagent grade toluene was heated at reflux to remove a small forerun, then allowed to cool.
3. Anhydrous sodium acetate was dried in a vacuum oven at 115° for 48 hours. The use of less than 3 moles of sodium acetate per mole of acid chloride results in a lower yield of product.

4. A catalyst available from Engelhard Industries was used after being dried in a vacuum oven at 115° for 48 hours. *Caution! Palladium-on-carbon is pyrophoric, and vacuum drying increases this hazard. Catalysts kept in the oven for longer periods of time were extremely pyrophoric.*
5. The acid chloride or the acid may be purchased from Aldrich Chemical Company, Inc. The acid chloride must be pure (99% minimum by GC analysis) whether purchased or prepared. Purification was effected by recrystallization from Skellysolve B.
6. Quinoline S was prepared according to the procedure in *Org. Synth.*, **Coll. Vol. 3**, 629 (1955).
7. Repressuring with hydrogen is required during this period. The amount of repressuring required is dependent upon the free space of the pressure vessel. The submitters report lower yields if the pressure falls below 30 p.s.i. No further repressuring is made at the end of 1 hour.
8. The crude aldehyde (prior to distillation) is sufficiently pure for most purposes. Isolation of the aldehyde may also be achieved *via* the bisulfite-addition compound.[2]
9. The product shows a strong IR band (KBr) at 1690 $cm.^{-1}$ (C=O). The ^1H NMR spectrum (CCl_4) has peaks at δ 3.84 (s, 3H), 3.87 (s, 6H), 7.03 (s, 2H), and 9.76 (s, 1H).
10. The submitters state that the aldehyde is obtained in 78–84% yield when the reaction is conducted on a scale 5 times that described. The amount of catalyst and Quinoline S need not be increased proportionately. The pressure vessel is charged with 3 l. of dry toluene, 123 g. of anhydrous sodium acetate, 10 g. of dry, 10% palladium-on-carbon catalyst, 115 g. of 3,4,5-trimethoxybenzoyl chloride, and 4 ml. of Quinoline S.

3. Discussion

3,4,5-Trimethoxybenzaldehyde has been prepared by the classical Rosenmund[3,4,5] reduction, by methylation of 5-hydroxyvanillin,[6] and by oxidation of 3,4,5-trimethoxybenzyl alcohol.[7]

The normal Rosenmund reduction has often been used for small-scale reactions, but for large preparations it has the following disadvantages: long reaction cycles at elevated temperatures, inefficient use of hydrogen, the hazard of passing hydrogen through and away from a hot reaction, the use of relatively high catalyst to substrate ratios, and the necessity of monitoring evolved hydrogen chloride as a means of following the reaction. These shortcomings have been eliminated by carrying out the reaction in a closed system at low pressure in the presence of a hydrogen chloride acceptor.

The reaction has been carried out on large- and small-scale batches (Note 10). This modification[8] has been applied by the submitters to the preparation of other aldehydes,[9] such as 3,4-dimethylbenzaldehyde[10] (90% yield), 3-benzyloxy-4,5-dimethoxybenzaldehyde[11] (88% yield, with retention of the benzyl group), and 3-methoxy-4-nitrobenzaldehyde[12] (62% yield, with retention of the nitro group).

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 268
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Quinoline S

palladium-on-carbon

hydrogen chloride (7647-01-0)

sodium acetate (127-09-3)

hydrogen (1333-74-0)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

toluene (108-88-3)

3,4,5-Trimethoxybenzaldehyde, Benzaldehyde, 3,4,5-trimethoxy- (86-81-7)

3,4,5-trimethoxybenzoyl chloride (4521-61-3)

5-hydroxyvanillin (3934-87-0)

3,4,5-trimethoxybenzyl alcohol (3840-31-1)

3,4-dimethylbenzaldehyde (5973-71-7)

3-benzyloxy-4,5-dimethoxybenzaldehyde

3-methoxy-4-nitrobenzaldehyde

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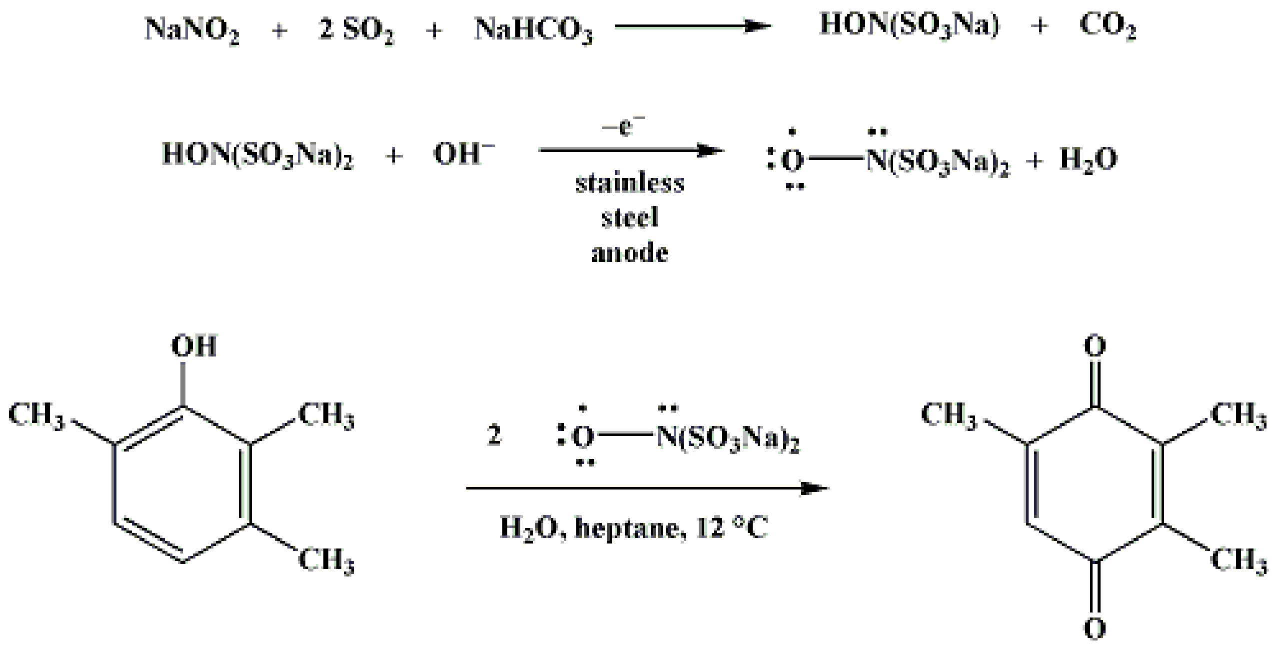
Organic Syntheses, CV 6, 1010

OXIDATION WITH THE NITROSODISULFONATE RADICAL. I. PREPARATION AND USE OF DISODIUM NITROSODISULFONATE: TRIMETHYL-*p*-BENZOQUINONE

[Nitrosodisulfonic acid, disodium salt and 2,5-Cyclohexadiene-1,4-dione, 2,3,5-trimethyl-]



Submitted by Pius A. Wehrli and Foster Pigott[1].
Checked by Don Koepsell and Herbert O. House.

1. Procedure

A. *Disodium nitrosodisulfonate*. A 1-l., resin kettle equipped with a mechanical stirrer, a thermometer, a gas-inlet tube suspended about 0.5 cm. above the bottom of the vessel, and an ice-cooling bath is charged with 15.0 g. (0.217 mole) of sodium nitrite (Note 1), 16.8 g. (0.200 mole) of sodium hydrogen carbonate (Note 1), and 400 g. of ice. Sulfur dioxide (25.6 g., 0.400 mole, (Note 2)) is passed into the cold, initially heterogeneous mixture with stirring over a period of 40 minutes. Near the end of the sulfur dioxide addition, the light brown color of the reaction mixture fades almost completely. The resulting colorless to pale-yellow solution of disodium hydroxylaminedisulfonate (Note 3), which has an approximate pH of 4, is stirred for 10 minutes before 59.5 g. (0.480 mole) of sodium carbonate monohydrate (Note 1) is added, giving a solution of pH 11. The gas-inlet tube is removed from the reaction vessel and replaced with a rectangular anode constructed from a 3.5 cm. by 4.7 cm. piece of stainless-steel mesh (about 16 mesh/cm.^{2}) with a stainless-steel wire as an electrical lead. The cathode is a cylindrical coil formed from a 1.5-mm. by 40-cm. piece of stainless-steel wire suspended in a 5-cm. by 10-cm. porous porcelain thimble filled with

aqueous 10% sodium carbonate. The porcelain thimble containing the cathode is suspended in the reaction vessel so that the liquid levels in the anode and cathode compartments are the same. The cathode-anode resistance of the electrolysis cell should be in the range of 5–10 ohms. While the reaction solution is continuously stirred and maintained at a temperature of 12° with an ice bath, the electrolysis is started by applying a sufficient potential (approximately 10 volts, (Note 4)) to the anode and cathode leads, giving a cell current of 2.0 amp. As the electrolysis proceeds, the potential applied to the cell is adjusted to maintain a cell current of 2.0 amp. The formation of the nitrosodisulfonate radical is evidenced by the appearance of a deep purple color (Note 5). The electrolysis is continued with stirring and cooling until quantitative measurement of the optical density of the reaction solution (Note 5), indicates the concentration of disodium nitrosodisulfonate to be 0.42–0.47 *M* (84–94% yield). The typical reaction time is 4 hours; the amount of electricity passed through the cell totals approximately 28,800 coulombs or 8 amp-hours (theoretically, 19,300 coulombs or 5.4 amp-hours). This solution of the nitrosodisulfonate radical is removed from the anode compartment of the electrolysis cell and used directly in the next step (Note 6).

B. *Trimethyl-p-benzoquinone*. The aqueous solution containing approximately 0.17 mole of disodium nitrosodisulfonate is placed in a 1-l., round-bottomed flask fitted with a mechanical stirrer, a thermometer, and an ice bath. A solution of 10.0 g. (0.0734 mole) of 2,3,6-trimethylphenol (Note 7) in 100 ml. of heptane is added to the reaction flask, and the resulting mixture is stirred vigorously for 4 hours with continuous cooling, maintaining the reaction temperature below 12°. The yellow heptane layer is separated, and the brown aqueous phase is extracted with two 100-ml. portions of heptane. The combined heptane solutions are quickly (Note 8) washed with three 50-ml. portions of cold (0–5°), 4 *M* aqueous sodium hydroxide, followed by two 100-ml. portions of saturated aqueous sodium chloride. The organic solution is dried over anhydrous magnesium sulfate and concentrated at 40° with a rotary evaporator, yielding 10.0–10.9 g. (91–99%) of crude trimethyl-*p*-benzoquinone as a yellow liquid, which crystallizes when cooled below room temperature. Further purification may be accomplished by distillation under reduced pressure, yielding 8.5–8.7 g. (77–79%) of the quinone, b.p. 53° (0.4 mm.), which crystallizes on standing as yellow needles, m.p. 28–29.5° (Note 9).

2. Notes

1. Reagent grades of these inorganic reagents were employed.
2. Sulfur dioxide was purchased from Matheson Gas Products. It is convenient to use sulfur dioxide contained in a lecture bottle so that the small cylinder can be mounted on a balance allowing continuous measurement of the weight of sulfur dioxide added.
3. The following alternative procedure may be used to prepare a solution of disodium hydroxylaminedisulfonate. Sodium nitrite (15 g., 0.22 mole) and 41.6 g. (0.400 mole) of sodium bisulfite are added to 250 g. of ice. With stirring, 22.5 ml. (0.393 mole) of acetic acid is added in one portion, and the mixture is stirred for 90 minutes in an ice bath. At the end of the stirring period the reaction solution is pH 5 and a potassium iodide-starch test is negative. A solution of 50 g. (0.47 mole) of sodium carbonate in water (total volume 250 ml.) is added. This buffered solution of disodium hydroxylaminedisulfonate may be used for electrolytic oxidation.

4. Since accurate control of the anode potential is not required in this oxidation, a variety of direct current sources may be employed, provided they are able to supply continuously a current of about 2 amp. at a potential of about 12 volts. One of the simplest direct current sources is an unfiltered rectifier of the type used to charge automobile batteries.
5. In 1 *M* aqueous potassium hydroxide solution, the nitrosodisulfonate radical has a maximum in the visible at 544 nm (ε 14.5).
6. The submitters report that approximately half of the nitrosodisulfonate radical had decomposed after the solution was stored at 0° for 2 weeks. They report the following procedure for the isolation of Fremy's salt (dipotassium nitrosodisulfonate).

Caution! Fremy's salt may decompose spontaneously in the solid state.[2]
To the cold (12°), purple solution of disodium nitrosodisulfonate was added, dropwise and with stirring, a solution of 37.3 g. (0.501 mole) of potassium chloride in 100 ml. of water. The resulting mixture, from which the orange-yellow dipotassium nitrosodisulfonate crystals precipitated, was allowed to stand overnight in the refrigerator, and the crystals were filtered with suction and washed with 100 ml. of 1 *M* aqueous potassium-hydroxide. The damp crystals weighed 55 g. A 1-g. aliquot of the wet material was dried at room temperature in a desiccator over Drierite, leaving 0.76 g. of orange crystals (72% yield based on sodium nitrite). On two occasions small samples of dried material decomposed spontaneously. *It is again stressed that if the electrolyzed solution is not used directly, any isolated Fremy's salt should be stored as a slurry in* 0.5 M *potassium carbonate at 0°.*
7. Crude 2,3,6-trimethylphenol, purchased from Aldrich Chemical Company, Inc., was purified by recrystallization from either hexane or chlorobenzene, m.p. 62–63°.
8. This extraction with aqueous sodium hydroxide removes phenolic by-products and starting material and must be performed quickly because *p*-quinones are unstable with strong bases.
9. The product has IR absorption ($CHCl_3$) at 1645 (conjugated C=O) and 1619 cm^{-1} (C=C) with UV maxima (95% C_2H_5OH) nm (ε) at 256 (16,700), 341 (3880), and 430 (shoulder, 30). The material has ^1H NMR peaks ($CDCl_3$) at 1.9–2.2 (partially resolved m, 9H, 3CH_3) and 6.5–6.7 (m, 1H, C*H*), with the following abundant peaks in its mass spectrum: *m/e* (rel. int.), 150 (100, M^+), 122 (24), 121 (14), 107 (30), 79 (18), 68 (20), 54 (14), 40 (18), and 39 (16).

3. Discussion

The nitrosodisulfonate salts, particularly the dipotassium salt (Fremy's salt), are useful reagents for the selective oxidation of phenols and aromatic amines to quinones (the Teuber reaction).[3,4] Dipotassium nitrosodisulfonate, commercially available, has been prepared by the oxidation of a hydroxylaminedisulfonate salt with potassium permanganate,[3,5,4] with lead dioxide,[6] or by electrolysis.[2,7] The present procedure illustrates the electrolytic oxidation, forming an alkaline, aqueous solution of the relatively soluble disodium nitrosodisulfonate and avoids a preliminary filtration, which is required to remove manganese dioxide formed when potassium permanganate is used as the oxidant.[3,5,4]

Solutions of nitrosodisulfonate salts are most stable in weakly alkaline solutions (pH 10)

and decompose rapidly when the solution is acidic or strongly alkaline.[3] Dipotassium nitrosodisulfonate has been reported to decompose spontaneously,[2,3] suggesting that procedures involving the use of substantial quantities of the dry solid salt may be hazardous. In the present procedure, separation and use of the solid salt is avoided since the disodium nitrosodisulfonate is formed and used in aqueous solution. In this procedure, two moles of the preformed nitrosodisulfonate salt are consumed in the oxidation of one mole of the phenol to the benzoquinone derivative.[3] The submitters report that only one molar equivalent of the nitrosodisulfonate salt is required if the electrochemical oxidation is carried out in a heptane solution of the phenol.

Trimethyl-*p*-benzoquinone has been prepared by the oxidation of 2,3,5-trimethyl-1,4-benzenediamine with iron(III) chloride[8] and by the oxidation of 2,3,5-trimethylphenol with dipotassium nitrosodisulfonate.[9]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Drierite

potassium carbonate (584-08-7)

acetic acid (64-19-7)

sodium hydroxide (1310-73-2)

sodium hydrogen carbonate (144-55-8)

potassium permanganate (7722-64-7)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

sulfur dioxide (7446-09-5)

sodium nitrite (7632-00-0)

sodium bisulfite (7631-90-5)

chlorobenzene (108-90-7)

potassium hydroxide, potassium-hydroxide (1310-58-3)

manganese dioxide (1313-13-9)

iron(III) chloride (7705-08-0)

disodium hydroxylaminedisulfonate

potassium chloride (7447-40-7)

magnesium sulfate (7487-88-9)

heptane (142-82-5)

hexane (110-54-3)

sodium carbonate monohydrate (5968-11-6)

2,3,6-trimethylphenol (2416-94-6)

DIPOTASSIUM NITROSODISULFONATE

Disodium nitrosodisulfonate, Nitrosodisulfonic acid, disodium salt

2,5-Cyclohexadiene-1,4-dione, 2,3,5-trimethyl-, Trimethyl-p-benzoquinone (935-92-2)

2,3,5-trimethyl-1,4-benzenediamine

2,3,5-trimethylphenol (697-82-5)

lead dioxide

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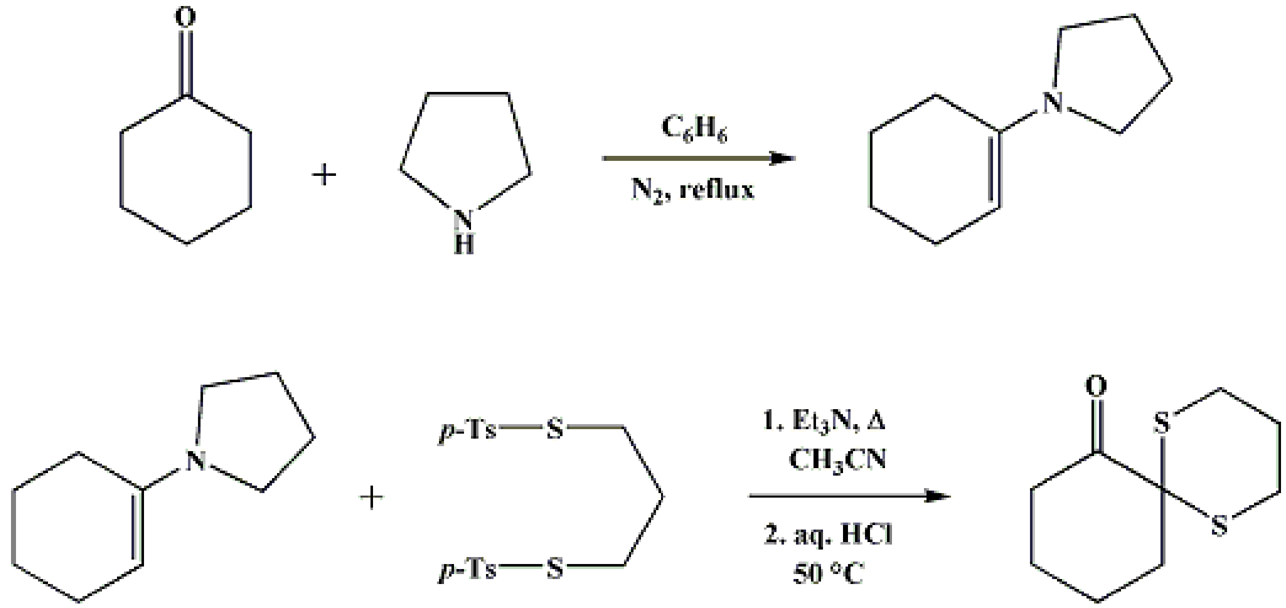
Organic Syntheses, CV 6, 1014

2,2-(TRIMETHYLENEDITHIO)CYCLOHEXANONE

[1,5-Dithiaspiro[5.5]undecan-7-one]



Submitted by R. B. Woodward[1], I. J. Pachter[2], and M. L. Scheinbaum[3].
Checked by G. S. Bates and S. Masamune.

1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A. *1-Pyrrolidinocyclohexene*.[4] A solution of 29.4 g. (0.300 mole) of cyclohexanone and 28.4 g. (0.394 mole) of pyrrolidine in 150 ml. of benzene is placed in a 500-ml., one-necked flask attached to a Dean-Stark trap. The solution is refluxed under a nitrogen atmosphere until the separation of water ceases (Note 1). The excess pyrrolidine and benzene are removed from the reaction mixture on a rotary evaporator. The resulting residue is stored under refrigeration and distilled just before use in the next step, yielding 44.6 g. (98%) of 1-pyrrolidinocyclohexene, b.p. 76–77° (0.5 mm.), 105–106° (13 mm.).

B. *2,2-(Trimethylenedithio)cyclohexanone*. A solution of 3.02 g. (0.0200 mole) of freshly distilled 1-pyrrolidinocyclohexene, 8.32 g. (0.0200 mole) of trimethylene dithiotosylate[4] (Note 2), and 5 ml. of triethylamine (Note 3) in 40 ml. of anhydrous acetonitrile (Note 4), is refluxed for 12 hours in a 100-ml., round-bottom flask under a nitrogen atmosphere. The solvent is removed with a rotary evaporator, and the residue is treated with 100 ml. of 0.1 *N* hydrochloric acid for 30 minutes at 50° (Note 5). The mixture is cooled to ambient temperature and extracted with three 50-ml. portions of diethyl ether. The combined ether extracts are washed with 10% aqueous potassium hydrogen carbonate solution (Note 6), until the aqueous layer remains basic to litmus, and with saturated sodium chloride solution. The ethereal solution is dried over

anhydrous sodium sulfate, filtered, and concentrated on a rotary evaporator. The resulting oily residue is diluted with 1 ml. of benzene then with 3 ml. of cyclohexane. The solution is poured into a chromatographic column (13 × 2.5 cm.), prepared with 50 g. of alumina (Note 7) and 3:1 cyclohexane–benzene. With this solvent system, the desired product moves with the solvent front; the first 250 ml. of eluent contains 95% of the total product. Elution with an additional 175 ml. of solvent removes the remainder. The combined fractions are evaporated, and the pale-yellow, oily residue crystallizes readily on standing. Recrystallization of this material from pentane gives 1.82 g. (45% yield) of white, crystalline 2,2-(trimethylenedithio)cyclohexanone, m. p. 52–55° (Note 8).

2. Notes

1. The time required for this operation generally is 3.5–5 hours.
2. Trimethylene dithiotosylate, m.p. 66–67°,[4] as described in *Org. Synth.*, **Coll. Vol. 6**, 1016 (1988) was employed.
3. Eastman white label triethylamine was distilled from sodium hydroxide.
4. Fisher Reagent acetonitrile was distilled from phosphorus pentoxide.
5. Treatment with the dilute acid effects aqueous extraction of pyrrolidine and hydrolysis of unreacted dithiotosylate and enamine starting materials.
6. Hydrogen carbonate washing ensures removal of the sulfonic and sulfinic acids.
7. The checkers used "Aluminum Oxide" purchased from J. T. Baker Chemical Company.
8. The ^1H NMR spectrum of the product ($CDCl_3$) exhibits multiplets in the region δ 1.65–2.45. The IR spectrum ($CHCl_3$) shows peaks at 2980 (m), 2940 (s), 2870 (m), 1690 (s), 1445 (m), 1420 (m), 1120 (m), 1110 (m), and 910 (s) cm^{-1}.

3. Discussion

The preparation of dithianes from enamines by reaction with trimethylene dithiotosylate has been applied with enamines derived from cholestan-3-one, acetoacetic ester, and phenylacetone.[5] Reactions of trimethylene dithiotosylate with hydroxymethylene derivatives of ketones also give rise to dithianes; thus, the hydroxymethylene derivative of cholest-4-en-3-one can be converted to 2,2-(trimethylenedithio)cholest-4-en-3-one.[6] 1,3-Dithiolanes are obtained in a similar manner by reaction of ethylene dithiotosylate[7] with the appropriately activated substrate.[5,8]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 590

References and Notes

1. 1965 Novel Laureate in Chemistry; deceased July 8, 1979; formerly at the Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138.
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3. Present address: Sterling-Winthrop Research Institute, Rensselaer, New York 12144.
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

acetoacetic ester

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether, diethyl ether (60-29-7)

acetonitrile (75-05-8)

sodium hydroxide (1310-73-2)

Cyclohexanone (108-94-1)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

cyclohexane (110-82-7)

Pentane (109-66-0)

phenylacetone (103-79-7)

cholestan-3-one (566-88-1)

aluminum oxide (1344-28-1)

pyrrolidine (123-75-1)

triethylamine (121-44-8)

potassium hydrogen carbonate (298-14-6)

ethylene dithiotosylate

trimethylene dithiotosylate (3866-79-3)

2,2-(Trimethylenedithio)cyclohexanone, 1,5-Dithiaspiro[5.5]undecan-7-one (51310-03-3)

Laureate

1-Pyrrolidinocyclohexene (1125-99-1)

2,2-(trimethylenedithio)cholest-4-en-3-one

phosphorus pentoxide (1314-56-3)

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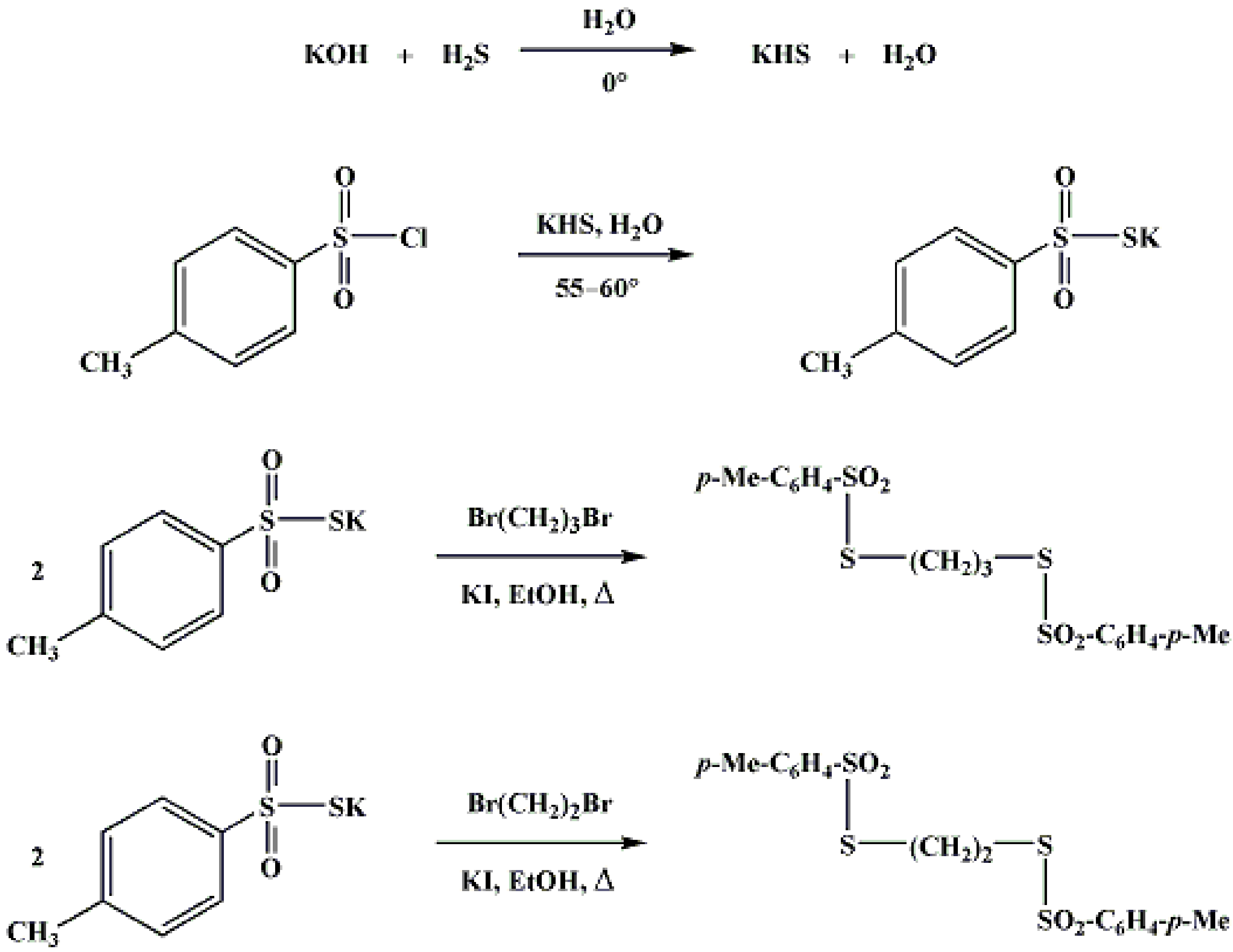
Organic Syntheses, CV 6, 1016

TRIMETHYLENE DITHIOTOSYLATE AND ETHYLENE DITHIOTOSYLATE

[Benzenesulfonothioic acid, 4-methyl-, *S,S'*-1,3-propanediyl and *S,S'*-1,2-ethanediyl esters]



Submitted by R. B. Woodward[1], I. J. Pachter[2], and Monte L. Scheinbaum[3].
Checked by P. A. Rossy and S. Masamune.

1. Procedure

Caution! This procedure should be carried out in a hood to avoid inhalation of hydrogen sulfide.

A. *Potassium thiotosylate*. A solution of 64.9 g. (1.00 mole) of 86.5% potassium hydroxide (Note 1) in 28 ml. of water is cooled in an ice bath, saturated with hydrogen sulfide, and flushed with nitrogen to ensure complete removal of excess hydrogen sulfide (Note 2) and (Note 3). The freshly prepared potassium hydrosulfide solution is diluted with 117 ml. of water and stirred under nitrogen at 55–60° before 95.3 g. (0.500 mole) of finely ground *p*-toluenesulfonyl chloride (Note 3) is introduced in small portions at a uniform rate so that the reaction temperature is maintained at 55–60° (Note 2). A mildly exothermic reaction ensues, and the solution becomes

intensely yellow. After about 90 g. of the tosyl chloride has been introduced, the yellow color disappears, and the dissolution of the chloride ceases. The reaction mixture is rapidly filtered with suction through a warmed funnel, and the filtrate is cooled several hours at 0–5°. The crystals of potassium thiotosylate are filtered, dissolved in 200 ml. of hot 80% ethanol, filtered hot to remove traces of sulfur, and cooled several hours at 0–5°. The recrystallized salt is filtered and air-dried, providing 48–55 g. (42–49%) of white crystals.

B. *Trimethylene dithiotosylate*. To 150 ml. of 95% ethanol containing 10–20 mg. of potassium iodide is added 40 g. (0.18 mole) of potassium thiotosylate and 20 g. (0.10 mole) of 1,3-dibromopropane (trimethylene dibromide) (Note 4). The mixture is refluxed with stirring for 8 hours in the dark and under nitrogen. The reaction mixture is cooled to ambient temperature, diluted with an equal volume of cold water, and agitated. After decantation of the supernatant liquid, the residual honeylike layer of product is washed with three 200-ml. portions of cold water, once with 100 ml. of cold 95% ethanol, and once with 100 ml. of cold absolute ethanol. The crude product (Note 5) is dissolved in 10 ml. of acetone, diluted with 80 ml. of hot absolute ethanol, and stirred under nitrogen at 0°. The oil which separates is redissolved by the addition of a minimum amount (*ca.* 5 ml.) of acetone. Seed crystals are introduced (Note 6), and the mixture is stirred for 1 hour at 0° under nitrogen and stored at –30° for several hours. The microcrystalline product is collected by filtration and weighs 20.2 g., m.p. 63.5–65.0°. Three recrystallizations from nine parts (180 ml.) of ethanol give 17.2 g. (41%) of white needles, m.p. 66–67° (Note 7). During the recrystallizations some of the material oils out when the solution is cooled to room temperature. The supernatant liquid is decanted, seeded, and stored at –30° for several hours. The oil is not further purified. The recrystallized material is chemically pure for further use [*Org. Synth.*, **Coll. Vol. 6**, 590 (1988)].

C. *Ethylene dithiotosylate*. To 200 ml. of ethanol containing 10–20 mg. of potassium iodide is added 45.3 g. (0.200 mole) of potassium thiotosylate and 18.8 g. (0.100 mole) of 1,2-dibromopropane. The mixture is refluxed with stirring for 8 hours in the dark and under a nitrogen atmosphere. The solvent is removed, and the resulting white solid is washed with a mixture of 80 ml. of ethanol and 150 ml. of water. After decantation, the solid is washed three times with 50-ml. portions of water and recrystallized from approximately 150 ml. of ethanol, yielding 28.7 g. of crude product, m.p. 72–75°. Three recrystallizations from a mixture of ethyl acetate and ethanol afford 24 g. (60%) of white crystals, m.p. 75–76° (Note 8).

2. Notes

1. Potassium hydroxide pellets of reagent grade commonly available, such as that from Fisher Scientific Company, contain 10–15% water. The checkers used the amount calculated on the basis of 86.5%, as specified.
2. Hydrogen sulfide is undesirable because its presence can lead to the formation of potassium *p*-toluenesulfinate. The latter can be formed by the desulfurization of thiotosylate by hydrogen sulfide generated in the reaction of potassium hydrosulfide with the tosyl chloride. Attention should be directed toward control of the reaction temperature so that hydrogen sulfide is rapidly removed, thereby ensuing survival of the S-S bond of the thiotosylate. *p*-Toluenesulfinate ion can displace bromide to form stable sulfones which are less soluble in common solvents, such as benzene, than trimethylene dithiotosylate. Therefore, purification of the dithiotosylate contaminated with the sulfones is difficult to achieve by fractional recrystallization.
3. The *p*-toluenesulfonyl chloride should be free of *p*-toluenesulfonic acid, otherwise

potassium *p*-toluenesulfonate will be formed and result in the formation of tosylates, rather than thiotosylates. The reagent used by the checkers was obtained from British Drug Houses Ltd. and was purified by washing benzene solution of the tosyl chloride with 5% aqueous sodium hydroxide, drying with magnesium sulfate, and distilling under reduced pressure, b.p. 146° (15 mm.).[4]

4. Trimethylene dibromide, available from Eastman Organic Chemicals, was distilled prior to use (b.p. 167–168°).

5. The checkers found that the crude oily product crystallizes after storage for a few days under nitrogen at −30°. Some of this solid was saved and used as seed crystals.

6. The submitters reported that seed crystals were obtained by column chromatography, using 40 parts by weight of Woelm neutral alumina (activity grade one) and benzene elution. The center cuts of m.p. 65° or higher were combined and recrystallized from nine parts of ethanol to give white needles, m.p. 67°. Two recrystallizations of chromatographed gave trimethylene dithiotosylate, m.p. 67.5°.

7. The purified trimethylene dithiotosylate exhibits IR bands ($CHCl_3$) at 3030 (w), 2930 (w), 1590 (w), 1490 (w), 1440 (w), 1410 (w), 1325 (s), 1300 (m), 1180 (w), 1140 (s), 1075 (s), 1015 (w), and 810 (m) cm^{-1}. The ^1H NMR spectrum ($CDCl_3$ included signals at δ 1.98 (quinlet, *J* = 7 Hz., 2H, $CH_2CH_2CH_2$), 2.43 (s, 6H, 2 CH_3), 2.97 (t, *J* = 7 Hz., 4H, $CH_2CH_2CH_2$), 7.30 (d, *J* = 9 Hz., 4H), and 7.75 (d, *J* = 9 Hz., 4H). Analysis calculated for $C_{17}H_{20}O_4S_4$: C, 49.01; H, 4.84; S, 30.79. Found: C, 49.13; H, 4.81; S, 30.51 (submitters). Found: C, 48.71; H, H, 4.64; S, 30.45 (checkers). The checkers found that the product exhibited a single peak on a 3 ft. × 1/8 in. Waters Associates Analytical Liquid Chromatographic column, packed with Durapak-Carbowax 400/Poracil C. Chloroform was used as the eluting solvent.

8. The ^1H NMR spectrum ($CDCl_3$) has absorptions at δ 2.47 (s, 6H, $2CH_3$), 3.31 (s, 4H, $2CH_2$), 7.48 (complex in, *J* = 9 Hz., 4H) and 7.97 (d, *J* = 9 Hz., 4H). Analysis calculated for $C_{16}H_{18}S_4O_4$: C, 47.73; H, 4.51; S, 31.86. Found: C, 47.89; H, 4.44; S, 32.22.

3. Discussion

Although it has been long known that trimethylene dithiotosylate can be prepared by the reaction of thiotosylate ion with trimethylene dibromide,[5,6] various difficulties are associated with the preparation. These problems are to a considerable extent related to the mode of preparation and the resultant purity of potassium thiotosylate. The thiotosylate salt must be free of tosylate and *p*-toluenesulfinate impurities, otherwise side products such as tosylates or sulfones will form. One such by-product, tosyltrimethylene thiotosylate, $CH_3C_6H_4SO_2(CH_2)_3SSO_2C_6H_4CH_3$, m.p. 92°, was isolated from contaminated samples of trimethylene dithiotosylate. It is products such as these, that make crystallization of the dithiotosylate difficult. The procedure described herein serves as a reliable technique for minimizing these experimental difficulties. More recently, it has been shown[7] that trimethylene dithiotosylate can be prepared easily by the reaction of tosyl chloride and 1,3-propanedithiol in pyridine. This procedure, however, is unchecked.

Trimethylene dithiotosylate can react with activated methylene groups, enamines, or hydroxyethylene derivatives of carbonyl compounds to form dithiane derivatives. In this context, trimethylene dithiotosylate has been employed in the preparation[8] and modification[9,10] of several steroids. It has also been used in the synthesis of alkaloids,[11,12,13] 10-membered ring lactones,[14] and vernolepin analogues.[15] Ethylene dithiotosylate undergoes similar reactions, forming

dithiolanes.[3,16]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 590
- Org. Syn. Coll. Vol. 6, 1014

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Benzenesulfonothioic acid, 4-methyl-, S,S'-1,3-propanediyl

S,S'-1,2-ethanediyl esters

ethanol (64-17-5)

Benzene (71-43-2)

ethyl acetate (141-78-6)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

hydrogen sulfide (7783-06-4)

1,2-dibromopropane (78-75-1)

trimethylene dibromide, 1,3-dibromopropane (109-64-8)

potassium iodide (7681-11-0)

nitrogen (7727-37-9)

sulfur (7704-34-9)

acetone (67-64-1)

pyridine (110-86-1)

potassium hydroxide (1310-58-3)

potassium hydrosulfide (1310-61-8)

magnesium sulfate (7487-88-9)

p-toluenesulfonic acid (104-15-4)

1,3-propanedithiol (109-80-8)

tosyl chloride, p-Toluenesulfonyl chloride (98-59-9)

ethylene dithiotosylate

trimethylene dithiotosylate (3866-79-3)

potassium thiotosylate

tosyltrimethylene thiotosylate

potassium p-toluenesulfonate

potassium p-toluenesulfinate

p-toluenesulfinate

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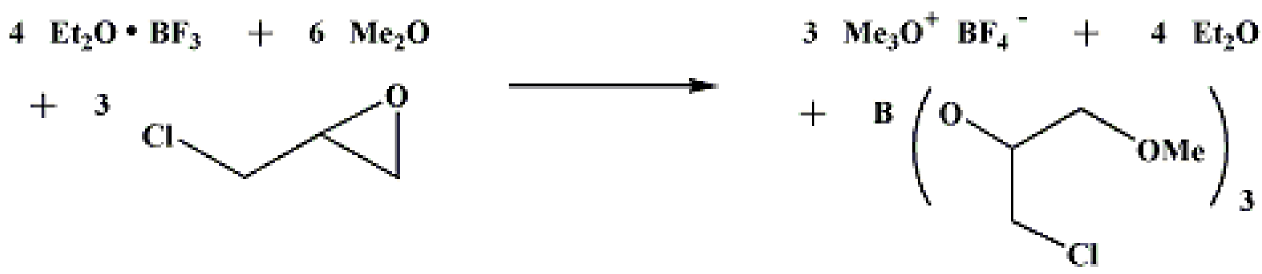
Organic Syntheses, CV 6, 1019

TRIMETHYLOXONIUM TETRAFLUOROBORATE

[Oxonium, trimethyl- tetrafluoroborate(1-)]



Submitted by T. J. Curphey[1]
Checked by A. Eschenmoser, R. Keese, and A. Daniel.

1. Procedure

A 500-ml., three-necked flask fitted with a mechanical stirrer, a Dewar condenser (Note 1) connected by a T-tube to a mineral oil bubbler and a source of dry nitrogen, and a gas-inlet tube connected to a source of dry dimethyl ether (Note 2) is charged with 80 ml. of dichloromethane and 38.4 g. (33.3 ml., 0.271 mole) of boron trifluoride diethyl etherate (Note 3). After establishing a nitrogen atmosphere in the flask, the condenser is filled with an acetone–dry ice mixture. With gentle stirring, dimethyl ether is passed into the solution until approximately 75 ml. has collected (Note 4). The gas-inlet tube is replaced with a pressure-equalizing dropping funnel containing 28.4 g. (24.1 ml., 0.307 mole) of epichlorohydrin, which is added dropwise with vigorous stirring over a 15-minute period. The mixture is stirred overnight under an atmosphere of nitrogen (Note 5). The stirrer is replaced by a filter stick, and the supernatant liquid is drawn off from the crystalline trimethyloxonium tetrafluoroborate, while keeping the mixture under nitrogen. The oxonium salt is washed with two 100-ml. portions of anhydrous dichloromethane and two 100-ml. portions of sodium-dried diethyl ether (Note 6), and dried by passing a stream of nitrogen over the salt until the odor of ether is no longer detected, yielding 28–29 g. (92.5–96.5%) of a white crystalline solid, m.p. (sealed tube) 179.6–180.0° (dec.), (Note 7) and (Note 8).

2. Notes

1. A Kontes K-45750 condenser was used.
2. Dimethyl ether and nitrogen were dried by passage through columns of Drierite. Boron trifluoride etherate (Eastman Practical Grade) was redistilled. Epichlorohydrin (Eastman Organic Chemicals) and dichloromethane (Fisher Scientific Company) were used as received.
3. According to ^{1}H NMR analysis the use of boron trifluoride etherate does not

cause any detectable introduction of ethyl groups into the product.

4. This may conveniently be done by placing, prior to conducting the reaction, a mark on the reaction flask at a level of 190 ml., and collecting dimethyl ether up to the mark. The exact amount of dimethyl ether used is not critical.

5. After 2–3 hours of stirring the reaction appears to be over, and the dry ice in the condenser need no longer be renewed. The reaction mixture may be worked up at this point without appreciable reduction in the product yield or purity.

6. According to analysis by ^{1}H NMR the use of diethyl ether at this point does not cause any detectable exchange of methyl by ethyl groups in the oxonium salt. A user[2] has reported obtaining the best samples of oxonium salt by using boron fluoride dimethyl etherate instead of the diethyl etherate and omitting the diethyl ether washing of the product. Oxonium salt prepared in this way was used to prepare methyl esters (from the corresponding amides) with no detectable (by GC analysis) ethyl esters.

7. The melting point of trimethyloxonium tetrafluoroborate apparently depends upon the procedure by which it is prepared and the method of melting-point determination. It has, for example, been reported to melt at 124.5°,[3] 141–143° [*Org. Synth.*, **Coll. Vol. 5**, 1096 (1973)], and 175°.[4]] The ^{1}H NMR spectrum, determined (liquid SO_2, purissimum Fluka AG) in a sealed tube at room temperature shows a single methyl resonance at δ 4.54; a trace of impurity is discernible as a singlet at δ 3.39.

8. When prepared as described, the oxonium salt is stable and nonhygroscopic, and may readily be handled in the air for short periods of time. A sample kept in a desiccator over Drierite for 1 month at −20° showed no change in melting point, and batches stored in this manner for over a year have been successfully used for alkylations.

3. Discussion

Trialkyloxonium salts were first discovered by Meerwein,[3] who also investigated much of their chemistry. A discussion of the literature prior to 1963 has been published.[5] Simple trialkyloxonium cations which have been prepared, other than trimethyl, include triethyl,[6] tri-*n*-propyl,[7] and tri-*n*-butyl,[8] with tetrafluoroborate or hexachloroantimonate anions, in most cases. Methods used to prepare trimethyloxonium tetrafluoroborate, which are typical of the class as a whole, include the reaction of boron trifluoride with epichlorohydrin in the presence of dimethyl ether,[3,4,9] the reaction of dimethyloxonium tetrafluoroborate with diazomethane or diazoacetic ester,[10] and the alkylation of dimethyl ether by triethyloxonium tetrafluoroborate[11] or dimethoxycarbonium tetrafluoroborate.[12] Several of these reactions involve the initial formation of a mixed oxonium ion $[R_1R_2OCH_3]^+$, which then methylates dimethyl ether, providing R_1R_2O and the trimethyloxonium ion. Of the available procedures, the one described here is probably the most convenient, involving as it does a single-step preparation from inexpensive, commercially available, and

nonhazardous reagents. Under the proper conditions (Note 8), the resulting product has storage properties comparable to those of the less-accessible trimethyloxonium 2,4,6-trinitrobenzenesulfonate.[13]

The trialkyloxonium salts are powerful alkylating agents. Trimethyl- and triethyloxonium tetrafluoroborates, in particular, have been widely employed for methylation and ethylation of sensitive or weakly nucleophilic functional groups. Alkylations of over 50 such functional groups have been reported in the literature. Examples include amides,[4,7,14,15,16] lactams,[16,17,18,19] sulfides,[3,20] nitro compounds,[9] enols and enolates,[3,21] ethers,[7,11,22] phenols,[3] sulfoxides,[3,7] amine oxides,[3,7,23] carboxylic acids,[3] lactones,[3,4] ketones,[3,16] metal carbonyls,[12,24] thiophenes,[25] and phosphonitriles.[26]. Oxonium salts have also been advantageously employed as quarternizing agents for a variety of heterocyclic amines.[27,28,29,30,31,32,33,34] In this way the first diquarternary salts of several heterocyclic diazines have been prepared,[30,31] as have reagents for peptide synthesis,[33,34] for the synthesis of polycyclic ketones,[32] and for cyanine dyes.[28]

One of the major advantages of oxonium salts is that alkylations can be effected under reaction conditions that are generally much milder than those necessary with the more conventional alkyl halides or sulfonates. Triethyloxonium tetrafluoroborate, for example, has usually been employed at room temperature in dichloromethane or dichloroethane solution. Occasionally chloroform[17,23] or no solvent at all[4,21] is used. Difficult alkylations can be effected in refluxing dichloroethane.[30,31] The less soluble trimethyloxonium tetrafluoroborate has been used as a suspension in dichloromethane or dichloroethane, or as a solution in nitromethane or liquid sulfur dioxide. Reports of alkylations in water[24] and trifluoroacetic acid[22] have also appeared. Direct fusion with trimethyloxonium tetrafluoroborate has succeeded in cases where other conditions have failed.[26,31]

Alkylations by oxonium salts have added several new weapons to the synthetic chemist's armamentarium. For example, the *O*-alkylated products from amides $[R_1C(OR)=NR_2R_3]^+$ ($R=CH_3$ or C_2H_5) may be hydrolyzed under mild conditions to amines and esters,[15,35] reduced to the amines $R_1CH_2NR_2R_3$ by sodium borohydride,[14] converted to amide acetals $R_1C(OR)_2NR_2R_3$ by alkoxides,[4,16] and (for R_3=H) deprotonated to the imino esters $R_1C(OR)=NR_2$.[17,18,19] Amide acetals and imino esters are themselves in turn useful synthetic intermediates. Indeed, oxonium salts transform the rather intractable amide group into a highly reactive and versatile functionality, a fact elegantly exploited in recent work on the synthesis of corrins.[35]

Other reagents which approach or exceed the oxonium salts in alkylating ability include dialkoxycarbonium ions,[36] alkyl trifluoromethanesulfonates,[37] alkyl fluorosulfonates,[38] dialkylhalonium ions,[39] and alkyl halides in the presence of silver

salts.[25,37,40] In terms of availability, stability, and freedom from hazards,[25] oxonium salts often appear to be the reagents of choice. When either methylation or ethylation is acceptable, methylation may be preferable. Triethyloxonium tetrafluoroborate must be stored under ether and handled in a dry box,[6] whereas the trimethyl salt can be stored solvent-free in the freezing compartment of a refrigerator and dispensed in the open atmosphere. Moreover, while information on the relative alkylating ability of the oxonium salts is not extensive, a few cases have been reported in which trimethyloxonium tetrafluoroborate effected alkylations which the triethyl analog did not.[20,31] The trimethyloxonium salt, therefore, appears to be the more potent alkylating agent.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 1080
- Org. Syn. Coll. Vol. 5, 1096
- Org. Syn. Coll. Vol. 5, 1099
- Org. Syn. Coll. Vol. 6, 576

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Drierite

boron fluoride dimethyl etherate

liquid SO_2

dimethoxycarbonium tetrafluoroborate

ether, diethyl ether (60-29-7)

chloroform (67-66-3)

Epichlorohydrin (106-89-8)

sulfur dioxide (7446-09-5)

nitrogen (7727-37-9)

dimethyl ether (115-10-6)

Nitromethane (75-52-5)

dichloromethane (75-09-2)

Diazomethane (334-88-3)

boron trifluoride (7637-07-2)

boron trifluoride etherate, boron trifluoride diethyl etherate (109-63-7)

dichloroethane (75-34-3)

trifluoroacetic acid (76-05-1)

sodium borohydride (16940-66-2)

triethyloxonium tetrafluoroborate (368-39-8)

Trimethyloxonium tetrafluoroborate, Oxonium, trimethyl- tetrafluoroborate(1-) (420-37-1)

Trimethyloxonium 2,4,6-trinitrobenzenesulfonate (13700-00-0)

dimethyloxonium tetrafluoroborate

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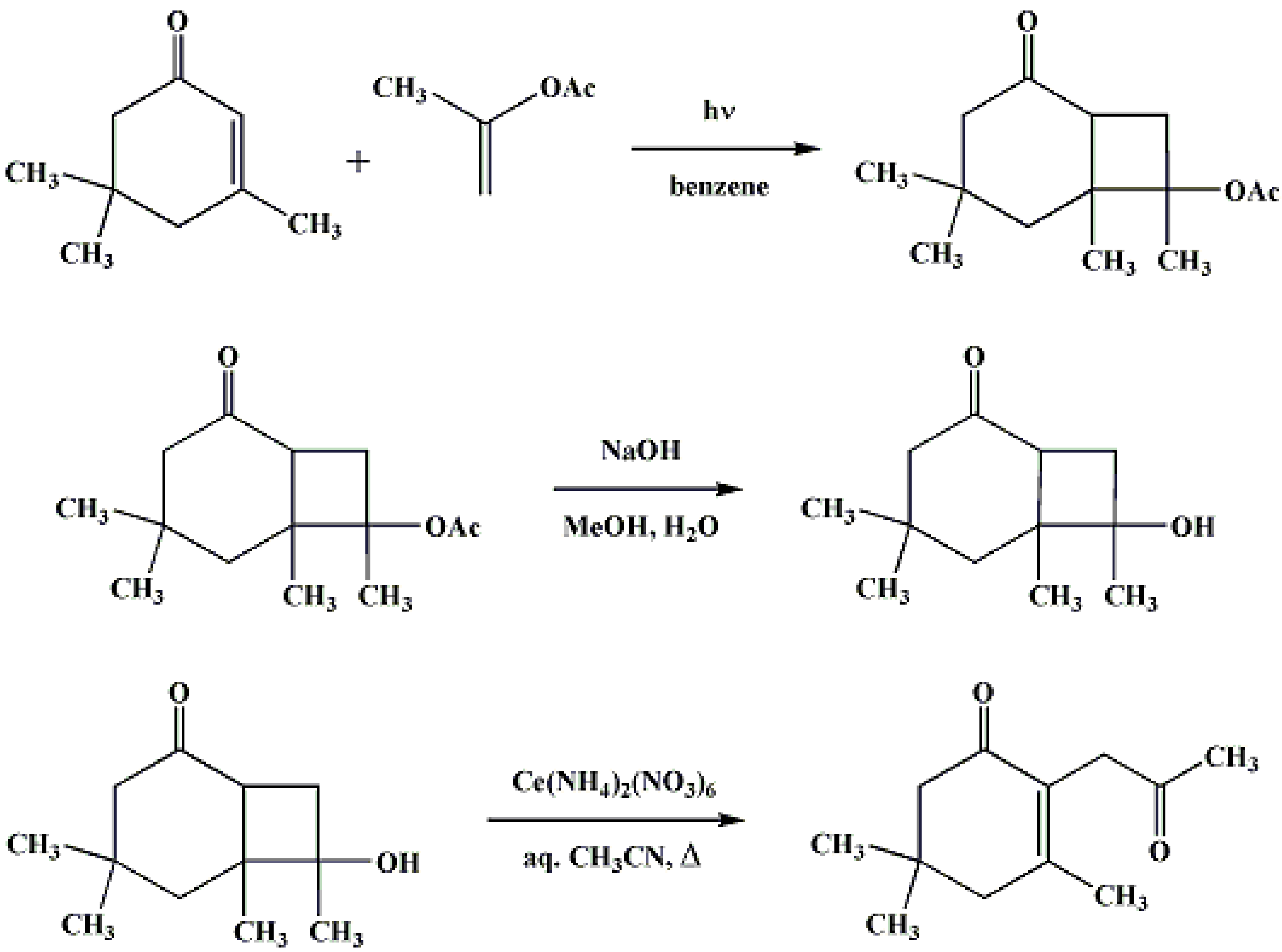
Organic Syntheses, CV 6, 1024

3,5,5-TRIMETHYL-2-(2-OXOPROPYL)-2-CYCLOHEXEN-1-ONE

[2-Cyclohexen-1-one, 3,5,5-trimethyl-2-(2-oxopropyl)-]



Submitted by Z. Valenta[1] and H. J. Liu[2].
Checked by T. H. O'Neill, W. Thompson, D. H. Hawke, and R. E. Ireland.

1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A. *7-Acetoxy-4,4,6,7-tetramethylbicyclo[4.2.0]octan-2-one*. The apparatus used for the photocycloaddition reaction is shown in f.htmigure 1. In the reaction vessel is placed a solution of 34.5 g. (0.250 mole) of 3,5,5-trimethyl-2-cyclohexen-1-one (isophorone) (Note 1) and 500 g. (5.00 moles) (Note 2) of 1-propen-2-yl acetate (Note 3) in 625 ml. of benzene. A constant and moderate flow of argon (Note 4) is maintained, agitating the solution throughout the reaction period. The trap is filled with 2-propanol and dry ice (Note 5). The solution is irradiated with a 450-watt, Hanovia high-pressure, quartz, mercury vapor lamp, using a Pyrex filter, for 96 hours (Note 6). Concentration of the resulting solution under reduced pressure (water aspirator) gives 65–80 g. of

crude 7-acetoxy-4,4,6,7-tetramethylbicyclo[4.2.0]octan-2-one (Note 7).

Figure 1. *A*, Dewar flask; *B*, sintered-glass filter; *C*, metal cooling coil; *D*, water inlet; *E*, water outlet; *F*, reaction vessel; *G*, quartz immersion well; *H*, Pyrex filter; *I*, lamp; *J*, nitrogen gas inlet; *K*, ground glass joint; *L*, condenser; *M*, calcium chloride drying tube.

Figure 1. A, Dewar flask; B, sintered-glass filter; C, metal cooling coil; D, water inlet; E, water outlet; F, reaction vessel; G, quartz immersion well; H, Pyrex filter; I, lamp; J, nitrogen gas inlet; K, ground glass joint; L, condenser; M, calcium chloride drying tube.

B. *7-Hydroxy-4,4,6,7-tetramethylbicyclo[4.2.0]octan-2-one*. The preceding crude photo-adduct is dissolved in 250 ml. of methanol and transferred to a 1-l., three-necked, round-bottomed flask fitted with overhead stirrer with Teflon blade, addition funnel, and argon inlet. The solution is cooled with an ice bath, and 500 ml. of 4 *M* aqueous sodium hydroxide is added, with stirring, over a period of 20 minutes. Upon completion of the addition, the ice bath is removed, and stirring is continued for 16 hours. The brown solution is extracted with four 500-ml. portions of chloroform. The organic extract is washed with saturated sodium chloride solution, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. Distillation of the residue through a 6-cm. Vigreux column affords, after a small forerun, 23.0–27.9 g. (47–57%) of 7-hydroxy-4,4,6,7-tetramethylbicyclo[4.2.0]octan-2-one (Note 8), collected at 92–101° (0.2 mm.).

C. *3,5,5-Trimethyl-2-(2-oxopropyl)-2-cyclohexen-1-one*. A 2-l., three-necked, round-bottomed flask, fitted with an overhead stirrer with Teflon blade, a Fries condenser, and a stopper, is charged with a solution of 9.8 g. (0.050 mole) of 7-hydroxy-4,4,6,7-tetramethylbicyclo[4.2.0]octan-2-one in 600 ml. of 50% (by volume) aqueous acetonitrile, and 82 g. (0.15 mole) (Note 9) of ceric ammonium nitrate (Note 10) is added in one portion with stirring. Immediately after completion of the addition, the flask is immersed in an oil bath preheated to 170°. Refluxing occurs in about 10 minutes and is continued for 5 minutes. During this period the color of the solution changes from light brown to pale yellow. At the end of this time the reaction mixture is immediately poured onto crushed ice and extracted with four 600-ml. portions of chloroform. The combined extracts are washed with saturated sodium hydrogen carbonate and saturated sodium chloride, dried over magnesium sulfate, and filtered. The solvent is removed under reduced pressure, and the residue distilled, using a short-path distillation apparatus. All material boiling at 70–100° (0.25 mm.) is collected. Fractionation of the yellow oil through a 6-cm. Vigreux column gives 4.68–4.71 g. (48–50%) of 3,5,5-trimethyl-2-(2-oxopropyl)-2-cyclohexene-1-one, b.p. 81–85° (0.4 mm.) (Note 11).

2. Notes

1. Isophorone obtained from M C and B Manufacturing Chemists was freshly distilled, b.p. 73° (4.5 mm.).
2. To minimize the formation of cyclohexenone dimer and achieve a cleaner photo-adduct, it is essential to use a large excess of olefin.[3]

3. 1-Propen-2-yl acetate was supplied by Aldrich Chemical Company, Inc.
4. Submitters used nitrogen purified by passing it through a set of gas wash bottles containing Fieser's solution,[4] concentrated sulfuric acid, sodium hydroxide, and calcium chloride.
5. The submitters filled the Dewar flask with ice and water. After 2 hours the ice had melted and water was left in the flask for cooling.
6. The progress of the reaction was monitored by injecting, after each 24-hour period, an aliquot into a GC and checking the peak corresponding to isophorone. Alternatively, TLC (E. Merck 0.25-mm. silica gel plates developed with ethyl acetate) can be used.
7. This crude product is contaminated mainly by polymeric compounds. An attempted distillation of this material was unsuccessful; partial decomposition occurred at 110–125° (0.3 mm.). If it is desirable, purification can be achieved by extensive silica gel column chromatography with 5% ether in benzene.
8. The product is a mixture of at least two diasteriomers as indicated by its ^{1}H NMR spectrum (CCl_4), showing eight singlets at δ 0.9–1.22, for a total of twelve methyl protons. Its IR spectrum (neat) exhibits absorption bands at 3440 and 1695 cm.$^{-1}$ A molecular ion peak at 196.1447 (calcd. for $C_{12}H_{20}O_2$:196.1463) is displayed in its mass spectrum.
9. Use of less of the reagent resulted in partial recovery of the starting material.
10. Ceric ammonium nitrate was supplied by Fisher Scientific Company.
11. IR (neat) cm.$^{-1}$: 1720, 1670, 1645; ^{1}H NMR ($CDCl_3$), δ: 1.03, 1.87, 2.13, 2.20, 2.25, 3.43 (all singlets); mass spectrum *m/e* 194.1299 (M^+).

3. Discussion

Recently, the application of photocycloaddition reactions to organic synthesis has been gaining importance.[5,6] The procedure described is illustrative of a general method,[3] based on a photocycloaddition reaction, for the introduction of an activated alkyl group specifically to the α-carbon atom of an α,β-unsaturated cyclohexenone. Especially significant is the fact that the method is also applicable to α,β-unsaturated cyclohexenones which do not possess enolizable γ-hydrogen atoms and to which normal alkylation reactions[7] cannot be applied. A closely related procedure involving the photocycloaddition of vinyl acetate to 2-cyclohexenones (in which enolization toward the 6-position is forbidden) followed by bromination and fragmentation of the adduct has been reported.[3,8] It has also been observed[9] that photoadducts of cycloalkenones and vinylene carbonate undergo fragmentation upon alkali treatment, giving 2-(2-oxoethyl)-2-cycloalken-1-ones.

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

cyclohexenone dimer

calcium chloride (10043-52-4)

Benzene (71-43-2)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether (60-29-7)

acetonitrile (75-05-8)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium hydrogen carbonate (144-55-8)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

2-propanol (67-63-0)

magnesium sulfate (7487-88-9)

1-propen-2-yl acetate (108-22-5)

vinyl acetate (108-05-4)

isophorone, 3,5,5-trimethyl-2-cyclohexen-1-one

argon (7440-37-1)

ceric ammonium nitrate

3,5,5-Trimethyl-2-(2-oxopropyl)-2-cyclohexen-1-one, 2-Cyclohexen-1-one, 3,5,5-trimethyl-2-(2-oxopropyl)-, 3,5,5-trimethyl-2-(2-oxopropyl)-2-cyclohexene-1-one (61879-73-0)

7-Acetoxy-4,4,6,7-tetramethylbicyclo[4.2.0]octan-2-one (66016-89-5)

7-Hydroxy-4,4,6,7-tetramethylbicyclo[4.2.0]octan-2-one (61879-76-3)

sulfuric acid, sodium hydroxide

vinylene carbonate

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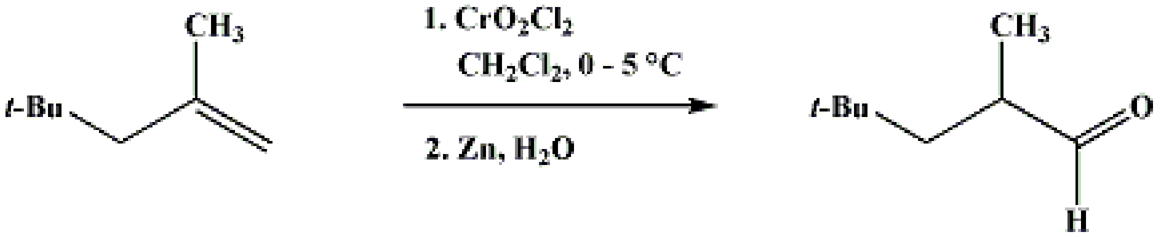
Organic Syntheses, CV 6, 1028

ALDEHYDES BY OXIDATION OF TERMINAL OLEFINS WITH CHROMYL CHLORIDE: 2,4,4-TRIMETHYLPENTANAL

[Pentanal, 2,4,4-trimethyl-]



Submitted by Fillmore Freeman[1], Richard H. DuBois, and Thomas G. McLaughlin.
Checked by Graham Hagens and Peter Yates.

1. Procedure

A 5-l., three-necked flask fitted with a mechanical stirrer, a thermometer, and a dropping funnel equipped with a calcium chloride drying tube is charged with 112.2 g. (1.002 mole) of freshly distilled 2,4,4-trimethyl-1-pentene (Note 1) and 1 l. of dichloromethane (Note 2). The flask is immersed in an ice–salt bath, and the stirred solution is cooled to 0–5°. A solution of 158 g. (1.02 moles) (Note 3) of freshly distilled chromyl chloride (Note 4) in 200 ml. of dichloromethane (Note 5) is added dropwise with stirring from the dropping funnel while the temperature is maintained at 0–5° (Note 6). The reaction mixture is stirred for 15 minutes, and 184 g. of 90–95% technical grade zinc dust (Note 7) is added. The mixture is stirred for 5 minutes, 1 l. of ice water and 400 g. of ice are added as rapidly as possible (Note 8), and the mixture is stirred for an additional 15 minutes. The ice–salt bath is replaced with a heating mantle, and the flask is fitted for steam distillation. After distillation of the dichloromethane the residue is steam distilled (Note 9). The distillate is transferred to a separatory funnel, the organic layer is separated, and the aqueous layer is washed with three 50-ml. portions of dichloromethane. The combined organic phases are distilled (Note 10) through a 56-cm., vacuum-jacketed, Vigreux column, removing the solvent. The product is transferred to a 250-ml. round-bottomed flask and distilled. After removal of a small amount of dichloromethane the fraction boiling at 45–52° (15 mm.) is collected, giving 90–100 g. (70–78%) (Note 11) of 2,4,4-trimethylpentanal.

2. Notes

1. The alkene is available from Aldrich Chemical Company, Inc., or Phillips Petroleum Company, and can be used without distillation.

2. The material available from Matheson, Coleman and Bell or Eastman Organic Chemicals is satisfactory except as explained in (Note 5).
3. Since chromyl chloride is easily hydrolyzed, a slight excess is used.
4. The fraction, b.p. 115.5–116.5°, is used. Chromyl chloride is available from Alfa Inorganics, Inc.
5. Chromyl chloride tends to react slowly with the commercially available dichloromethane. This can be avoided with a slight increase in yield if the dichloromethane used to dissolve the chromyl chloride is distilled through a 15–20 cm. Vigreux column immediately before use.
6. The time required for the addition is about 60 minutes.
7. This approximate fivefold excess is necessary to reduce the higher valence chromium salts, thereby eliminating overoxidation and double bond cleavage. The zinc dust used was obtained from Allied Chemical Corporation.
8. The temperature usually increases to 8–10°.
9. Steam distillation is discontinued when the distillate gives a negative test with 2,4-dinitrophenylhydrazine.
10. It is not necessary to dry the organic phase.
11. The checkers, working at two-thirds scale, obtained the product in 70–71% yield.

3. Discussion

2,4,4-Trimethylpentanal has been prepared by the catalytic isomerization of 1,2-epoxy-2,4,4-trimethylpentane in both the liquid and gas phases (77–92%),[2] and by the oxidation of 2,4,4-trimethyl-1-pentene with chromium trioxide in acetic anhydride.[3] Although the catalytic isomerization of the epoxide[2] gives 2,4,4-trimethylpentanal in good yield, this requires epoxidation of the alkene as the first step. The chromyl acetate and chromic acid oxidative methods give unsatisfactory yields.[3] In the preparation described here, 2,4,4-trimethylpentanal is obtained from the alkene in good yield, in one step. Also, this preparation illustrates a general and convenient procedure for the direct oxidation of 2,2-disubstituted-1-alkenes (Table I) to unstable and reactive aldehydes.[4] The reaction is very fast and the aldehyde is the major product.

TABLE I
ALDEHYDES BY OXIDATION OF TERMINAL OLEFINS WITH CHROMYL CHLORIDE

Alkene	Aldehyde	Yield, %
4,4-Dimethyl-2-neopentyl-1-pentene	4,4-Dimethyl-2-neopentylpentanal	80.8[a]
2-Phenylpropene	2-Phenylpropanal	60.0[b]
1,1-Diphenylethylene	Diphenylacetaldehyde	62.7[b]

*a*Reference [4].

*b*Reference [5].

4,4-Dimethyl-2-neopentylpentanal,[6] 2-phenylpropanal,[7] and Diphenylacetaldehyde[8] are generally prepared by isomerization of the corresponding epoxide and/or by multistep syntheses.

In contrast to the relative simplicity of the chromyl chloride oxidation of 2,2-disubstituted-1-alkenes to aldehydes, the chromyl acetate and chromic acid oxidations generally lead to epoxides, acids, and carbon–carbon double bond cleavage. For example, chromyl acetate oxidizes 4,4-dimethyl-2-neopentyl-1-pentene primarily to 1,2-epoxy-4,4-dimethyl-2-neopentylpentane in low yield,[9] and chromic acid oxidizes the alkene principally to 4,4-dimethyl-2-neopentylpentanoic acid.[6,10]

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1. Department of Chemistry, California State College, Long Beach, California 90801. This investigation was supported by the Long Beach California State College Foundation, the Research Corporation, and the Petroleum Research Fund administered by the American Chemical Society. [Present address: Department of Chemistry, University of California, Irvine, California 92717].
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

acetic anhydride (108-24-7)

zinc (7440-66-6)

chromic acid (7738-94-5)

1,1-Diphenylethylene (530-48-3)

dichloromethane (75-09-2)

chromyl chloride

chromium trioxide (1333-82-0)

2,4-Dinitrophenylhydrazine (119-26-6)

2-phenylpropanal (93-53-8)

Diphenylacetaldehyde (947-91-1)

2-Phenylpropene (98-83-9)

2,4,4-Trimethylpentanal, Pentanal, 2,4,4-trimethyl- (17414-46-9)

2,4,4-trimethyl-1-pentene (107-39-1)

1,2-epoxy-2,4,4-trimethylpentane

chromyl acetate

4,4-Dimethyl-2-neopentylpentanal

4,4-Dimethyl-2-neopentyl-1-pentene (141-70-8)

1,2-epoxy-4,4-dimethyl-2-neopentylpentane

4,4-dimethyl-2-neopentylpentanoic acid

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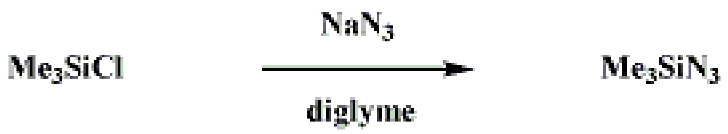
Organic Syntheses, CV 6, 1030

TRIMETHYLSILYL AZIDE

[Silane, azidotrimethyl-]



Submitted by L. Birkofer[1] and P. Wegner.
Checked by R. F. Merritt and W. D. Emmons.

1. Procedure

Caution! This reaction should be conducted behind a safety screen in a hood. If the system is not completely dry, the presence of toxic hydrazoic acid is probable.

A 1-l., three-necked flask fitted with a stirrer, reflux condenser equipped with a drying tube, and addition funnel provided with a pressure-equalizer arm is dried in a 100° oven and assembled while warm. The warm apparatus is immediately purged with dry nitrogen, introducing the nitrogen at the top of the addition funnel. The flask is charged with 81 g. (1.2 moles) of sodium azide (Note 1) and 500 ml. of freshly distilled diethylene glycol dimethyl ether (Note 2). A simple distillation apparatus is then dried in the oven and assembled while warm under a slow nitrogen purge. The distillation flask is charged with 112 g. of chlorotrimethylsilane (Note 3), and after a forerun of approximately 2 g. the remaining material is distilled (b.p. 57–58°) directly into the addition funnel of the reaction flask. During this distillation it is convenient to disconnect the nitrogen stream from the top of the addition funnel and introduce it into the distillation flask. After the distillation is complete, the distillation apparatus is disconnected and the nitrogen stream is again introduced at the top of the addition funnel. The chlorotrimethylsilane (108.6 g., 1.000 mole) (Note 4) is then added rapidly to the sodium azide slurry, and this mixture is stirred at 70° for 60 hours. During this period the nitrogen flow is terminated (Note 5).

After the heating period is complete, the nitrogen stream is again initiated, and the mixture is cooled to 30°. The addition funnel and reflux condenser are replaced with two gas-inlet tubes with stopcocks. One inlet tube is connected to the nitrogen source and the other to a standard vacuum trap, of at least 150 ml. capacity. A vacuum (15–20 mm.) is applied to the trap after the latter is cooled to –78°, and the product is then distilled at 30° (15 mm.) into the trap. Slight heating is necessary to maintain 30°, and rapid stirring should be continued throughout. Removal of volatile product is complete within 5 hours under these conditions. The entire system is then slowly pressurized to atmospheric pressure with nitrogen, and the product is redistilled through a 5-cm. Vigreux column. From 121 g. of crude flash distillate are obtained 4.0 g. of forerun

and 98 g. (85%) of pure trimethylsilyl azide, b.p. 95–99°. During the distillation the pot temperature is maintained at 135–140° with a thermostated oil bath. The pot residue contains 19 g. of diethylene glycol dimethyl ether with traces of trimethylsilyl azide. The purity of the product cut as established by ^{1}H NMR (CCl_4) is 98%. A single peak at 13 cps. downfield from tetramethylsilane is observed, the only impurity being siloxane hydrolysis products. Chlorotrimethylsilane is conspicuous by its absence.

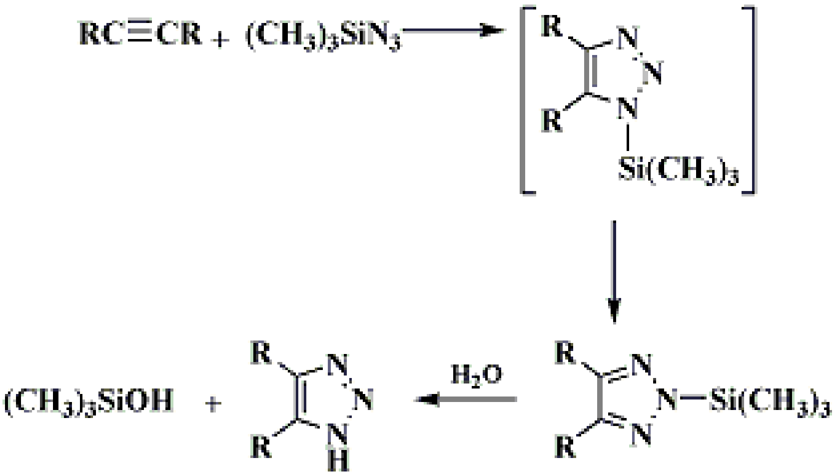
2. Notes

1. Sodium azide was obtained from Alpha Inorganics, Inc., Beverly, Massachusetts, and the freshly opened material was used without further purification or drying.
2. Diethylene glycol dimethyl ether from Aldrich Chemical Co. was distilled under a nitrogen atmosphere, and the fraction boiling at 161–162° was used.
3. The chlorotrimethylsilane was obtained from Pennisula Chem-research Corp., Gainesville, Florida.
4. It is undesirable to reweigh the chlorotrimethylsilane in the addition funnel because moisture contamination is possible. An excess of sodium azide is used in this preparation, and the exact amount of the silane used is not critical.
5. If the nitrogen flow is maintained during the heating period, the volatile materials will be swept out and the yield will be reduced.

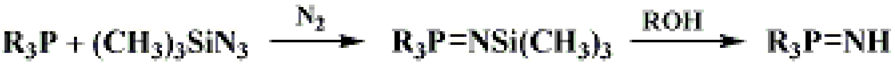
3. Discussion

Trimethylsilyl azide has been prepared by the thermolysis of 1-trimethylsilyl-5-trimethylsilylaminotetrazole, by reaction of hydrazoic acid with hexamethyl-disilazane, and by reaction of chlorotrimethylsilane with sodium azide.[2] With a suitable solvent and anhydrous conditions the last procedure is the method of choice and has been extended to other trialkyl and triarylsilyl azides.[3]

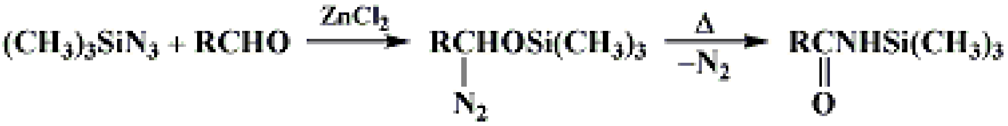
Unlike hydrazoic acid, trimethylsilyl azide is thermally quite stable. Even at 200° it decomposes slowly and without explosive violence. Accordingly, it is a very convenient and safe substitute for hydrazoic acid in many reactions. A notable example is the cycloaddition of hydrazoic acid to acetylenes, a general route to substituted triazoles.[4] The reaction of trimethylsilyl azide with acetylenes is also a general reaction, from which 2-trimethylsilyl-1,2,3-triazoles may be obtained in good yield.[5] These adducts are hydrolyzed under mild conditions to the parent alkyl 1,2,3-triazoles.[5]



Another interesting application of trimethylsilyl azide is as a convenient preparation of trialkyl- or triarylphosphinimines, first prepared by Appel and Hauss using chloramine.[6]



This synthesis is quite simple and its success lies in the facile cleavage of the Si-N bond.[7,8] Trimethylsilyl azide also reacts with aldehydes, giving the stable adducts, 1-trimethylsiloxyalkyl azides, which on thermolysis yield *N*-trimethylsilyl amides.[9]



This preparation is referenced from:

- Org. Syn. 79, 165

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrazoic acid

nitrogen (7727-37-9)

sodium azide (26628-22-8)

chloramine (10599-90-3)

diethylene glycol dimethyl ether (111-96-6)

tetramethylsilane (75-76-3)

CHLOROTRIMETHYLSILANE (75-77-4)

siloxane (13597-73-4)

hexamethyl-disilazane

TRIMETHYLSILYL AZIDE, Silane, azidotrimethyl- (4648-54-8)

1-trimethylsilyl-5-trimethylsilylaminotetrazole

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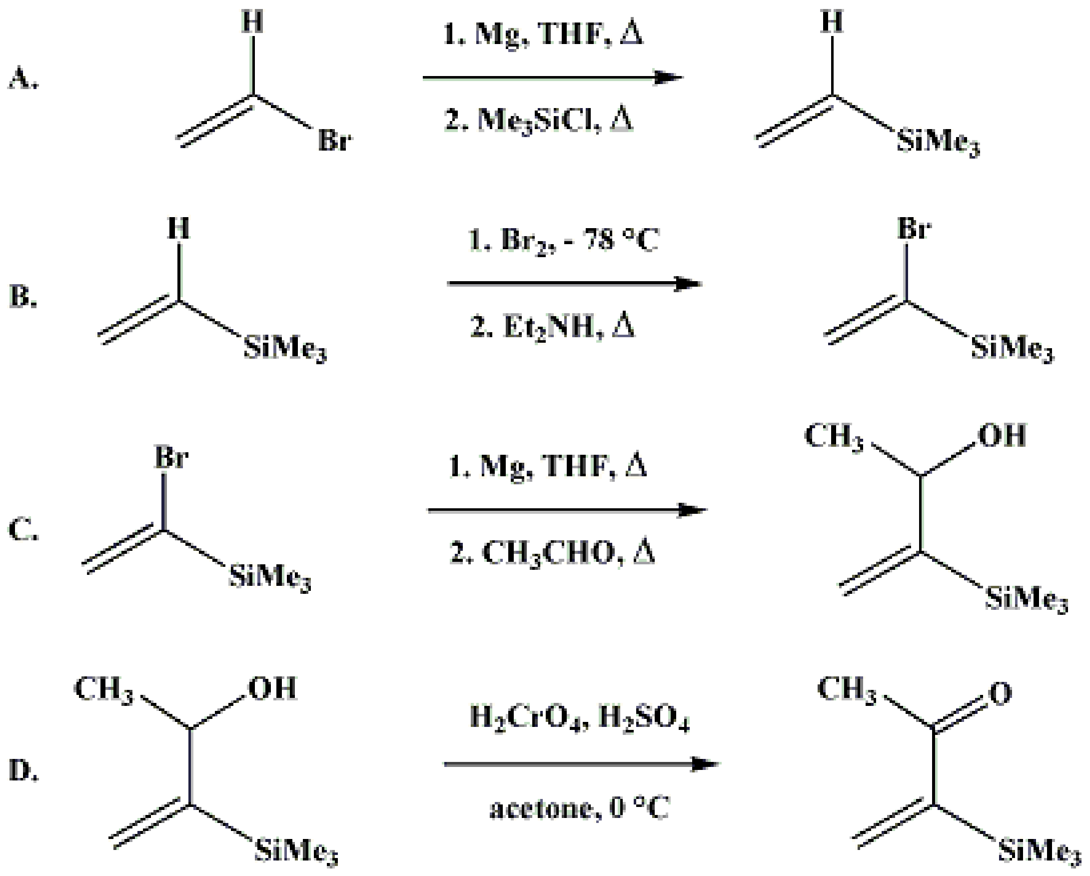
Organic Syntheses, CV 6, 1033

3-TRIMETHYLSILYL-3-BUTEN-2-ONE: A MICHAEL ACCEPTOR

[3-Buten-2-one, 3-(trimethylsilyl)-]



Submitted by Robert K. Boeckman, Jr.[12], David M. Blum[1], Bruce Ganem[3], and Neil Halvey[3].
Checked by William R. Baker and Robert M. Coates.

1. Procedure

A. *Vinyltrimethylsilane* (**1**). A 2-l., three-necked, round-bottomed flask fitted with a mechanical stirrer, a reflux condenser, and a 500-ml., pressure-equalizing dropping funnel (Note 1) is charged with 26.4 g. (1.09 g.-atom) of magnesium turnings and 800 ml. of dry tetrahydrofuran (Note 2). A solution of 107 g. (70.5 ml., 1.00 mole) of vinyl bromide (Note 3) in 200 ml. of tetrahydrofuran is placed in the addition funnel and slowly added dropwise to the reaction vessel. After the reaction has begun (Note 4), the addition rate is regulated, maintaining a gentle reflux during the remainder of the addition period. The mixture is heated at reflux for an additional hour, and a solution of 108 g. (0.995 mole) of chlorotrimethylsilane (Note 5) in 100 ml. of tetrahydrofuran is added dropwise while the reaction is maintained at reflux with continued heating and stirring (Note 6). The suspension is stirred for another 2 hours under reflux, then

cooled to room temperature and stirred overnight.

The condenser and dropping funnel are removed, and the flask is equipped for distillation with a 30.5-cm. Vigreux column. The distillate (b.p. 60–65°) is collected, transferred to a separatory funnel, and washed with 10–20 100-ml. portions of water (Note 7), yielding 67–78 g. (67–78%) of silane **1** as a colorless liquid containing small amounts of tetrahydrofuran (Note 8).

B. (1-Bromoethynl)trimethylsilane **(2).** A 1-l., three-necked, round-bottomed flask equipped with a mechanical stirrer and a 250-ml. dropping funnel is charged with 89.8 g. (approximately 0.90 mole, (Note 8)) of silane **1.** The contents of the flask are stirred and cooled to −78°, and 168 g. (1.06 mole) of bromine is added dropwise over *ca.* 1 hour. The cooling bath is removed, and the red viscous mixture is warmed to room temperature. The flask is fitted with an efficient, water-cooled condenser, and 425 g. (600 ml., 5.82 moles) of diethylamine (Note 9) is cautiously (Note 10) added with continued stirring. After the addition is complete, the reaction mixture is heated at reflux for 12 hours, during which time a precipitate of diethylamine hydrochloride forms. The salts are separated from the cooled suspension by filtration and washed with several 300-ml. portions of diethyl ether. The ether filtrate is carefully washed, first with 100-ml. portions of 10% hydrochloric acid until the aqueous layer remains acidic (pH *ca.* 2), then with 100 ml. of water and 200 ml. of saturated aqueous sodium chloride. The ether solution is dried with anhydrous magnesium sulfate, concentrated with a rotary evaporator, and distilled under reduced pressure through a 20.3-cm. Vigreux column, affording 104–110 g. (65–68%) of silane **2**, b.p. 72–75° (120 mm.) (Note 11).

C. *3-Trimethylsilyl-3-buten-2-ol* **(3).** A 500-ml., three-necked, round-bottomed flask equipped with two 30.5-cm. Liebig condensers connected in series, a pressure-equalizing dropping funnel, and a magnetic stirrer is charged with 9.2 g. (0.38 g.-atom) of magnesium turnings and 100 ml. of tetrahydrofuran (Note 1) and (Note 2). About 2 g. of 1,2-dibromoethane is added, initiating the formation of the Grignard reagent. When the supernatant solution becomes warm and begins to reflux from reduction of 1,2-dibromoethane, a solution of 50 g. (0.28 mole) of silane **2** in 75 ml. of tetrahydrofuran is added dropwise to the stirred mixture at a rate that maintains gentle reflux. After the addition is complete, the reaction mixture is kept at reflux for an additional hour before freshly distilled acetaldehyde (25.0 g., 0.568 mole) is introduced. The temperature is maintained at reflux, and stirring is continued throughout the addition and for an additional hour. The flask is then fitted with a distillation head and heated until *ca.* 100 ml. of distillate has been collected. The reaction mixture is cooled (ice-water bath) and stirred, diluted with 100 ml. of ether, and hydrolyzed by addition of enough saturated ammonium chloride (approximately 50 ml.) to dissolve the thick, sticky precipitate. The salts are filtered and washed with ether, and the aqueous layer of the filtrate is extracted with three 150-ml. portions of ether. The combined ether layers are washed with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and concentrated by distillation at

atmospheric pressure (Note 12), giving 48–55 g. of crude butenol **3** as a liquid that is used in the next step without further purification.

D. *3-Trimethylsilyl-3-buten-2-one* **(4).** A solution of 55 g. of crude butenol **3** in 100 ml. of acetone is placed in a 500-ml., three-necked, round-bottomed flask equipped with a mechanical stirrer and a 250-ml. dropping funnel. The reaction vessel is immersed in an ice-water bath, and 95 ml. of an aqueous solution containing chromium trioxide and sulfuric acid (Note 13) is added to the stirred acetone solution. After completion of the addition, 2-propanol is added to the reaction mixture until a green endpoint is reached, indicating consumption of excess oxidant. The contents are poured into 450 ml. of ether, 300 ml. of water are added, and the aqueous layer is saturated with sodium chloride. The layers are separated, and the aqueous solution is extracted with five 150-ml. portions of ether. The combined ether solutions are washed with two 150-ml. portions of saturated aqueous sodium chloride, dried with anhydrous magnesium sulfate, and concentrated by distillation at atmospheric pressure through a 30.5-cm. Vigreux column. Continued distillation under reduced pressure gives, after separation of a low boiling forerun, 14.7–15 g. (37–38%) of butenone **4** as a pale yellow liquid, b.p. 98–103° (100 mm.) (Note 14) and (Note 15).

2. Notes

1. The apparatus is flamed dry under an argon atmosphere and maintained under argon during the reaction.
2. The submitters purified the tetrahydrofuran by distillation from lithium aluminum hydride. The checkers used tetrahydrofuran that had been distilled from the sodium ketyl of benzophenone. *(Caution! See Org. Synth.,* ***Coll. Vol. 5****, 976 (1973), for a warning regarding the purification of tetrahydrofuran.)*
3. Gaseous vinyl bromide is condensed in a 500-ml. flask cooled in an acetone–dry ice bath and diluted with 200 ml. of tetrahydrofuran. The submitters used vinyl bromide supplied by J. T. Baker Chemical Company; the checkers purchased this reagent from Linde Specialty Gases. Vinyl bromide is also available from Aldrich Chemical Company, Inc.
4. Approximately 70 ml. is added over a 20-minute period before formation of the Grignard reagent begins. The total addition time is *ca.* 1 hour.
5. The submitters used practical grade chlorotrimethylsilane purchased from PCR, Inc., which was distilled before use. Chlorotrimethylsilane from Aldrich Chemical Company, Inc., was employed by the checkers, both with and without prior distillation. Approximately the same yield was obtained in either case.
6. A white precipitate, presumed to be magnesium salts, is deposited as the solution of chlorotrimethylsilane is added.
7. The layers must be allowed to separate completely to avoid sizable mechanical losses. The submitters used 10 water extractions, whereas the checkers continued the extractions until the organic layer reached an approximately constant weight.
8. The ^{1}H NMR spectrum of the product obtained by the checkers revealed the

presence of 6 ± 2% of tetrahydrofuran.

9. Diethylamine is available from Aldrich Chemical Company, Inc.

10. The reaction of the excess bromine with diethylamine is exothermic; consequently it may be necessary to moderate the reaction by cooling with an ice-water bath during the early stages of the addition.

11. ^{1}H NMR spectrum ($CDCl_3$), δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 0.16 [s, 9H, Si(CH_3)$_3$], 6.12 (d, *J* = 2, 1H, C*H*), 6.21 (d, *J* = 2, 1H, C*H*).

12. The checkers terminated the distillation when the head temperature reached 44°.

13. The oxidizing reagent is prepared as described in *Org. Synth.*, **Coll. Vol. 5**, 866 (1973).

14. GC analysis of the product by the submitters on a 1.85-m. 3% silicone gum rubber (SE-30) column at 25° gave a single peak. Butenone **4** has the following ^{1}H NMR spectrum (CCl_4), δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 0.14 [s, 9H, Si(CH_3)$_3$], 2.23 (s, 3H, CH_3), 6.18 (d, *J* = 2, 1H, C*H*), 6.53 (d, *J* = 2, 1H, C*H*).

15. This material showed no tendency to deteriorate when stored under an argon atmosphere at –20°.

3. Discussion

Butenone **4** has been obtained by Brook and Duff[4] from the reaction of 1-trimethylsilylvinylmagnesium bromide and acetic anhydride at –120°. However, the product was a mixture of butenone **4** and a dimeric substance which apparently resulted from subsequent conjugate addition of the Grignard reagent to the ketone. The procedures in the present reaction sequence for the preparation of silane **1**, silane **2**, and 1-trimethylsilylvinylmagnesium bromide are based on those reported by Ottolenghi, Fridkin, and Zilkha.[5] Similarly, other 1-trimethylsilylvinyl ketones may be prepared by reaction of the appropriate aldehyde with 1-trimethylsilylvinylmagnesium bromide and subsequent oxidation with chromic acid. The 1-trimethylsilylvinyl ketones are remarkably stable and useful in a variety of conjugate addition reactions.[6]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 666

References and Notes

1. Department of Chemistry, Wayne State University, Detroit, Michigan 48202.
2. Present address: Department of Chemistry, University of Rochester, Rochester, New York 14627.
3. Department of Chemistry, Cornell University, Ithaca, New York 14853.
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium ketyl of benzophenone

(1-Bromoethynl)trimethylsilane

acetaldehyde (75-07-0)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ether, diethyl ether (60-29-7)

acetic anhydride (108-24-7)

ammonium chloride (12125-02-9)

magnesium turnings (7439-95-4)

sodium chloride (7647-14-5)

bromine (7726-95-6)

acetone (67-64-1)

2-propanol (67-63-0)

chromic acid (7738-94-5)

1,2-dibromoethane (106-93-4)

diethylamine (109-89-7)

magnesium sulfate (7487-88-9)

chromium trioxide (1333-82-0)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

diethylamine hydrochloride (660-68-4)

butenone (78-94-4)

vinyl bromide (593-60-2)

silane

argon (7440-37-1)

CHLOROTRIMETHYLSILANE (75-77-4)

3-Trimethylsilyl-3-buten-2-one, 3-Buten-2-one, 3-(trimethylsilyl)- (43209-86-5)

butenol

1-trimethylsilylvinylmagnesium bromide

Vinyltrimethylsilane (754-05-2)

3-Trimethylsilyl-3-buten-2-ol (66374-47-8)

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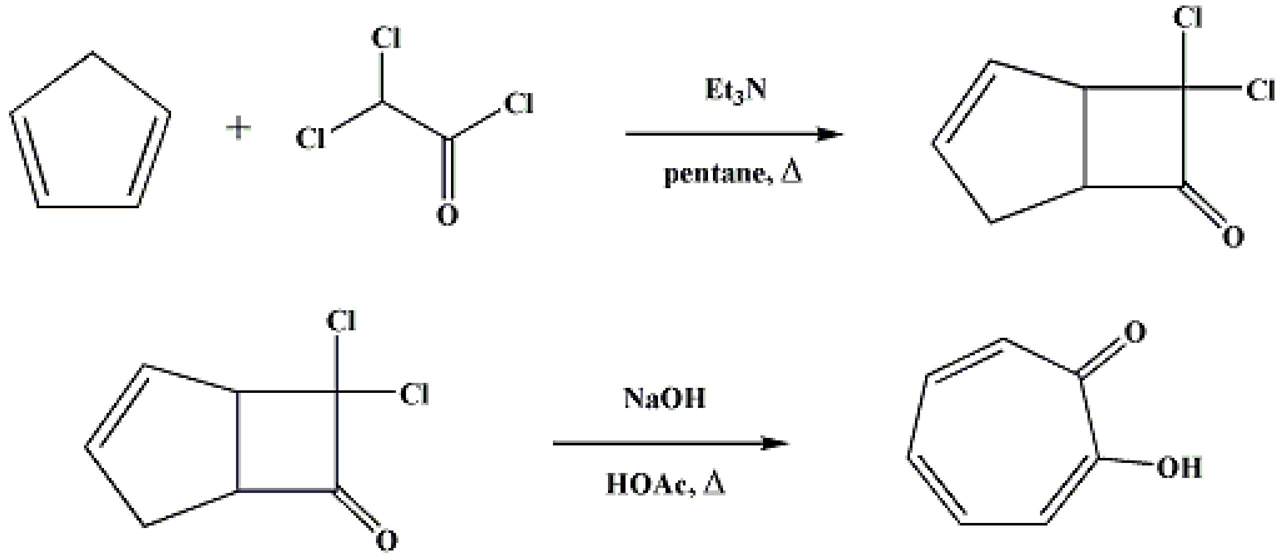
Organic Syntheses, CV 6, 1037

TROPOLONE

[2,4,6-Cycloheptatrien-1-one, 2-hydroxy-]



Submitted by Richard A. Minns[1]
Checked by Arthur J. Elliott and William A. Sheppard.

1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A. *7,7-Dichlorobicyclo*[3.2.0]*hept-2-en-6-one*. A 2-l., three-necked, round-bottomed flask fitted with an addition funnel, a reflux condenser, and a mechanical stirrer is charged with 100 g. (0.678 mole) of dichloroacetyl chloride (Note 1), 170 ml. (2 moles) of cyclopentadiene (Note 2), and 700 ml. of pentane (Note 3). The solution is heated to reflux under nitrogen and rapidly stirred while a solution of 70.8 g. (0.701 mole) of triethylamine (Note 4) in 300 ml. of pentane is added over a period of 4 hours (Note 5). After the cream-colored mixture has been refluxed for an additional 2 hours, 250 ml. of distilled water is added, dissolving the triethylamine hydrochloride; the layers are separated in a 2-l. separatory funnel. After extraction of the aqueous layer with two 100-ml. portions of pentane, the combined organic layers are filtered and dried by passage through absorbent cotton. Pentane and excess cyclopentadiene are then removed by rapid distillation. The resulting viscous, orange liquid is fractionally distilled under reduced pressure through a 30-cm. Vigreux column. Heat is supplied from an oil bath held at 105°. During collection of the first fraction, which consists mainly of dicyclopentadiene (Note 6), b.p. 61–62° (9 mm.), the cold finger and take-off tube must be warmed periodically with a heat gun to prevent plugging. The 7,7-dichlorobicyclo[3.2.0]hept-2-en-6-one, 101–102 g. (84–85%), is collected as a colorless liquid, b.p. 66–68° (2 mm.), n_D^{25} 1.5129, having a purity >99% as determined by GC analysis (Note 6) and (Note 7).

B. *Tropolone*. A 1-l., three-necked, round-bottomed flask equipped with a mechanical stirrer, addition funnel, and a reflux condenser is charged with 500 ml. of glacial acetic acid and then, *cautiously*, 100 g. of sodium hydroxide pellets. After the pellets have dissolved, 100 g. (0.565 mole) of 7,7-dichlorobicyclo[3.2.0]hept-2-en-6-one is added and the solution is maintained at reflux under nitrogen for 8 hours. Concentrated hydrochloric acid is added until the mixture is about pH 1; approximately 125 ml. of acid is required. After the addition of 1 l. of benzene, the mixture is filtered and the solid sodium chloride is washed with three 100-ml. portions of benzene. The two phases of the filtrate are separated, and the aqueous phase is transferred to a magnetically stirred, 1-l., continuous extractor (Note 8). The combined benzene phase is transferred to a 2-l. pot connected to the extractor, and the aqueous phase is extracted for 13 hours. Following distillation of the benzene, the remaining orange liquid is distilled under reduced pressure through a 30-cm. Vigreux column, removing acetic acid. When tropolone begins to distill into the column, the condenser is replaced with a two-necked flask immersed in ice water. With vacuum applied through one neck of this receiver, tropolone distills at 60° (0.1 mm.) and is collected as a crude yellow solid, 66.4 g. (96%). A solution of the impure product in 150 ml. of dichloromethane is diluted with 600 ml. of pentane, 4 g. of activated carbon is added, and the mixture is heated to boiling. After removal of the carbon by filtration, the solution is maintained at –20° until crystallization is complete. Tropolone, 53 g. (77%) (Note 9), is collected as white needles, m.p. 50–51°, by filtration. Evaporation of the filtrate to dryness, dissolution of the residue in 800 ml. of pentane, treatment with activated carbon, and cooling to –20° yields an additional 8 g. (12%) of tropolone as pale-yellow crystals, m.p. 49.5–51°.

2. Notes

1. Freshly opened bottles of dichloroacetyl chloride from Aldrich Chemical Company, Inc., were used. The acid chloride can also be prepared by the dropwise addition of 1 volume of dichloroacetic acid to 2.5 volumes of phthaloyl chloride heated to 140°. After the addition is complete, the solution is vigorously heated and dichloroacetyl chloride, b.p. 106–108°, is distilled through a 30-cm. column packed with glass beads; the yield is 85%.
2. Cyclopentadiene was prepared by cracking dicyclopentadiene [*Org. Synth.*, **Coll. Vol. 4**, 475 (1963)] of 95% purity purchased from Aldrich Chemical Company, Inc.
3. Technical grade pentane from Fisher Scientific Company was used.
4. Triethylamine from Eastman Organic Chemicals was used without further purification.
5. Faster addition results in some polymerization of the dichloroketene and darkens the precipitate.
6. Fractions were analyzed by GC (column: 0.3 × 120 cm., 20% SE-52 on Chromosorb P 60/80, 130°, helium flow rate of 60 ml./min.). Retention times of 1.9 minutes for dicyclopentadiene and 4.6 minutes for the 7,7-dichlorobicyclo[3.2.0]hept-2-en-6-one were found.
7. 7,7-Dichlorobicyclo[3.2.0]hept-2-en-6-one has the following spectral characteristics: IR (neat) cm.$^{-1}$: 1806 (C=O), 1608 (C=C); ^{1}H NMR (CCl_4), δ (multiplicity, number of protons, assignment): 2.70 (m, 2H, CH_2), 4.10 (m, 2H, 2C*H*), 5.90 (m, 2H, C*H*=C*H*).
8. A continuous extractor has been described in *Org. Synth.*, **Coll. Vol. 5**, 630 Note 10 (1973).
9. Tropolone has the following spectral characteristics: IR (KBr pellet) cm.$^{-1}$: 3210

(O*H*), 1613 (C=O), 1548 (C=C); ^{1}H NMR ($CDCl_3$), δ (multiplicity, number of protons, assignment): 7.33 (m, 5H, 5C*H*), 8.76 (s, 1H, O*H*).

3. Discussion

Tropolone has been made from 1,2-cycloheptanedione by bromination and reduction,[2] and by reaction with *N*-bromosuccinimide;[3] from cycloheptanone by bromination, hydrolysis, and reduction;[4] from diethyl pimelate by acyloin condensation and bromination;[5] from cycloheptatriene by permanganate oxidation;[6] from 3,5-dihydroxybenzoic acid by a multistep synthesis;[7] from 2,3-dimethoxybenzoic acid by a multistep synthesis;[8] from tropone by chlorination and hydrolysis,[9] by amination with hydrazine and hydrolysis,[10] or by photoöxidation followed by reduction with thiourea;[11] from cyclopentadiene and tetrafluoroethylene;[12] and from cyclopentadiene and dichloroketene.[13,14]

The present procedure, based on the last method, is relatively simple and uses inexpensive starting materials. Step A exemplifies the 2 + 2 cycloaddition of dichloroketene to an olefin,[15,16,17] and the specific cycloadduct obtained has proved to be a useful intermediate in other syntheses.[18,19,20] Step B has been the subject of several mechanistic studies,[21,22,23,24] and its yield has been greatly improved by the isolation technique described above. This synthesis has also been extended to the preparation of various tropolone derivatives.[14,21,22,25,26,27,28]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

acyloin

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

carbon (7782-42-5)

phthaloyl chloride (88-95-9)

Pentane (109-66-0)

dichloromethane (75-09-2)

dichloroacetic acid (79-43-6)

thiourea (62-56-6)

dichloroacetyl chloride (79-36-7)

N-bromosuccinimide (128-08-5)

3,5-Dihydroxybenzoic acid (99-10-5)

Cycloheptanone (502-42-1)

triethylamine (121-44-8)

CYCLOPENTADIENE (542-92-7)

dicyclopentadiene

Triethylamine hydrochloride (554-68-7)

cycloheptatriene (544-25-2)

tetrafluoroethylene (9002-84-0)

Tropolone, 2,4,6-Cycloheptatrien-1-one, 2-hydroxy- (533-75-5)

7,7-Dichlorobicyclo[3.2.0]hept-2-en-6-one (5307-99-3)

dichloroketene (4591-28-0)

1,2-cycloheptanedione

diethyl pimelate (2050-20-6)

2,3-dimethoxybenzoic acid (1521-38-6)

Tropone (492-37-5)

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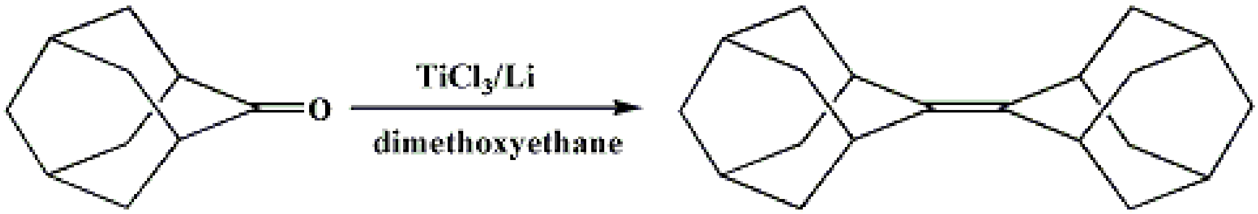
Organic Syntheses, CV 7, 1

REDUCTIVE COUPLING OF CARBONYLS TO ALKENES: ADAMANTYLIDENEADAMANTANE

[Tricyclo[3.3.1.1^{3,7}]decane, tricyclo[3.3.1.1^{3,7}]decylidene-]



Submitted by Michael P. Fleming and John E. McMurry[1].
Checked by Steven R. Villaseñor and Carl R. Johnson.

1. Procedure

A 2-L, three-necked flask is thoroughly flamed while being flushed with argon and is then fitted with three rubber septa. Anhydrous titanium trichloride (63.16 g, 0.409 mol) (Note 1) and (Note 2) is added to the weighed flask in an argon-filled glove bag. The flask is reweighed, and one of the rubber septa is replaced with a dry (12 hr at 120°C) reflux condenser through which a stream of argon is flowing (Note 3). The flask is fitted with a mechanical stirrer equipped with a glass shaft and Teflon paddle (Note 4). Into the flask is syringed 600 mL of 1,2-dimethoxyethane (Note 5), and the remaining rubber septum is exchanged for a glass stopper. Lithium (8.52 g, 1.23 mol) (Note 6) is etched to brilliance in methanol, quickly washed in petroleum ether (Note 7), and cut into small pieces directly into the stirred suspension. The mixture is heated at reflux for 1 hr by an oil bath that is then removed (Note 8). Immediately after the solvent has ceased to reflux, 2-adamantanone (15.36 g, 0.102 mol) (Note 1) is added in one portion, and the mixture is heated at reflux for 18 hr.

Stirring is maintained as the mixture is allowed to cool to room temperature, and 600 mL of petroleum ether (Note 7) is added in 100-mL portions at 5-min intervals (Note 9). The stirrer is disconnected from its motor, and the solution is poured into a sintered-glass funnel containing 50 g of Florisil (approximately 7 cm in depth) (Note 1). The black material remaining in the reaction vessel is washed with eight 50-mL portions of petroleum ether, which are poured into the same pad of Florisil (Note 10) and (Note 11). The filter pad is then washed with 400 mL of petroleum ether. Removal of the solvent from the combined filtrates by means of a rotary evaporator followed by high vacuum (0.05 mm) gives 12–13 g of a white crystalline solid. This crude product is dissolved in 3.5 L of hot methanol (Note 1), and the volume is reduced to 2 L by boiling. The solution is allowed to slowly cool to room temperature. The colorless needles are vacuum filtered through sintered glass (medium frit) and washed with 50 mL of ice-cold methanol. The crystals are dried under vacuum (0.05 mm Hg) to give 10.3–10.4 g (75–76%) of adamantylideneadamantane, mp 184–186°C; ^{1}H NMR ($CDCl_3$) δ: 1.5–2.1 (br m, 24 H)

2.7–3.1 (br m, 4 H). Concentration of the mother liquor to 350 mL and crystallization as described above yields an additional 1.2–1.5 g (9-11%) of product, mp 182–184°C (Note 12).

2. Notes

1. The following reagents were used as supplied: titanium trichloride from Alfa Products, Morton Thiokol, Inc.; 2-adamantanone from Aldrich Chemical Company, Inc.; methanol from MCB, Inc.; and acetone from Mallinckrodt, Inc.
2. Because of its sensitivity toward oxygen and water, anhydrous titanium trichloride should always be handled under an inert atmosphere. The submitters report that titanium trichloride in bottles that have been opened and resealed undergoes a slow deterioration that causes erratic results in the coupling reaction. This decomposition is frequently detectable by the evolution of white fumes from the titanium trichloride during transfer. If a number of small-scale reactions are to be performed, the use of a Schlenk tube is advisable to extend the useful life of the titanium trichloride.
3. Substitution of nitrogen for argon does not significantly decrease the yield.
4. The coupling reaction may be adversely affected if metallic stirrers are employed. The bore of the stirrer should be water-cooled. Lubricants such as mineral oil are to be avoided since they complicate product isolation.
5. The 1,2-dimethoxyethane was obtained from Aldrich Chemical Company, Inc., and was allowed to stand over molecular sieves (type 4A in 1/16-in. pellet form from Union Carbide Corporation) for several days. Final purification was accomplished by heating at reflux over potassium in a nitrogen atmosphere for at least 10 hr, followed by distillation from potassium. The solvent was used on the same day that it was distilled to minimize the formation of peroxides.
6. Lithium wire (3.2-mm diam, 0.02% sodium) was obtained from Alfa Products, Morton Thiokol, Inc., and was washed in petroleum ether before weighing.
7. Petroleum ether (bp 35–65°C) was obtained from Fisher Scientific Company and was distilled from potassium permanganate.
8. The color of the reaction mixture at this point varies from gray-green to gray-black. The success of the reaction seems to be independent of the color.
9. Addition of petroleum ether causes a viscous black precipitate to cling to the walls of the flask, leaving a milky-white solution that can be conveniently poured into the filter.
10. The black residue, which consists of inorganic salts, titanium, and unreacted lithium, is retained in the reaction vessel, where it is washed with petroleum ether while the mass is manually stirred with the paddle. No problem has been encountered in exposing the black material to the air during the washing procedure.
11. The black residue is destroyed in the following manner. The stirrer motor is reattached, and the flask is flushed with argon. The flask is cooled in an ice–water bath before adding 300 mL of petroleum ether and 300 mL of acetone. As the mixture is vigorously stirred, ca. 10 mL of methanol is added from a dropping funnel. After reaction has begun (an induction period of up to 0.5 hr may occur before gas evolution becomes noticeable), an additional 590 mL of methanol is added dropwise over a 6–10-hr period. Stirring is continued at 0°C until pieces of

lithium can no longer be seen (approximately 1 hr after the addition of the methanol has been completed).
12. The second crop is slightly impure, as shown by its NMR spectrum.

3. Discussion

Adamantylideneadamantane has been prepared by (1) photolysis of 2-adamantylketene dimer,[2] (2) reduction of 4*e*-chloroadamantylideneadamantane with sodium in liquid ammonia,[3] (3) rearrangement of spiro[adamantane-2,4'-homoadamantan-5'-ol] with Lewis acids,[4], [5] (4) reduction of 2,2-dibromoadamantane with magnesium[6] or zinc-copper couple,[7] and (5) treatment of the azine of 2-adamantanone with hydrogen sulfide, followed by oxidation with lead tetraacetate and heating with triphenylphosphine.[8]

The present method is a modification of a previous procedure by the submitters.[9] Handling of lithium in the air is less hazardous and more convenient than that of potassium, which was originally used. Higher yields were obtained when the higher-boiling solvent 1,2-dimethoxyethane was employed rather than tetrahydrofuran. Although the titanium trichloride-lithium system results in slightly lower yields for aliphatic ketones than the corresponding potassium method, the former is considerably more convenient for large-scale reactions. The lithium procedure is applicable to both aromatic and aliphatic aldehydes and ketones (Table I). Reductive coupling of unsymmetrical carbonyl compounds usually results in a mixture of geometric isomers.

Details of the titanium-induced dicarbonyl coupling reaction can be found in a full paper[10] and in a review article.[11]

TABLE I
REACTION OF KETONES AND ALDEHYDES WITH TITANIUM TRICHLORIDE-LITHIUM IN 1,2-DIMETHOXYETHANE

Carbonyl Compound	Yield of Alkene Product (%)
Acetophenone	94
Benzaldehyde	97
Benzophenone	96
Cholestanone	84
Cyclododecanone	90
Cycloheptanone	85
Cyclohexanone	81
Decanal	59
Hexanal	58 (28 : 72, *cis* : *trans*)

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

2-adamantylketene dimer

spiro[adamantane-2,4'-homoadamantan-5'-ol]

azine of 2-adamantanone

titanium trichloride-lithium

ammonia (7664-41-7)

methanol (67-56-1)

magnesium (7439-95-4)

Cyclohexanone (108-94-1)

potassium permanganate (7722-64-7)

hydrogen sulfide (7783-06-4)

oxygen (7782-44-7)

nitrogen (7727-37-9)

benzaldehyde (100-52-7)

acetone (67-64-1)

Acetophenone (98-86-2)

Benzophenone (119-61-9)

sodium (13966-32-0)

potassium (7440-09-7)

lithium, Lithium wire (7439-93-2)

Cholestanone (566-88-1)

zinc-copper

Tetrahydrofuran (109-99-9)

Cycloheptanone (502-42-1)

1,2-dimethoxyethane (110-71-4)

triphenylphosphine (603-35-0)

cyclododecanone (830-13-7)

argon (7440-37-1)

2-adamantanone (700-58-3)

Decanal (112-31-2)

titanium (7440-32-6)

Hexanal (66-25-1)

Adamantylideneadamantane, Tricyclo[3.3.1.1^{3,7}]decane, tricyclo[3.3.1.1^{3,7}]decylidene- (30541-56-1)

titanium trichloride (7705-07-9)

2,2-dibromoadamantane

4e-chloroadamantylideneadamantane

lead tetraacetate

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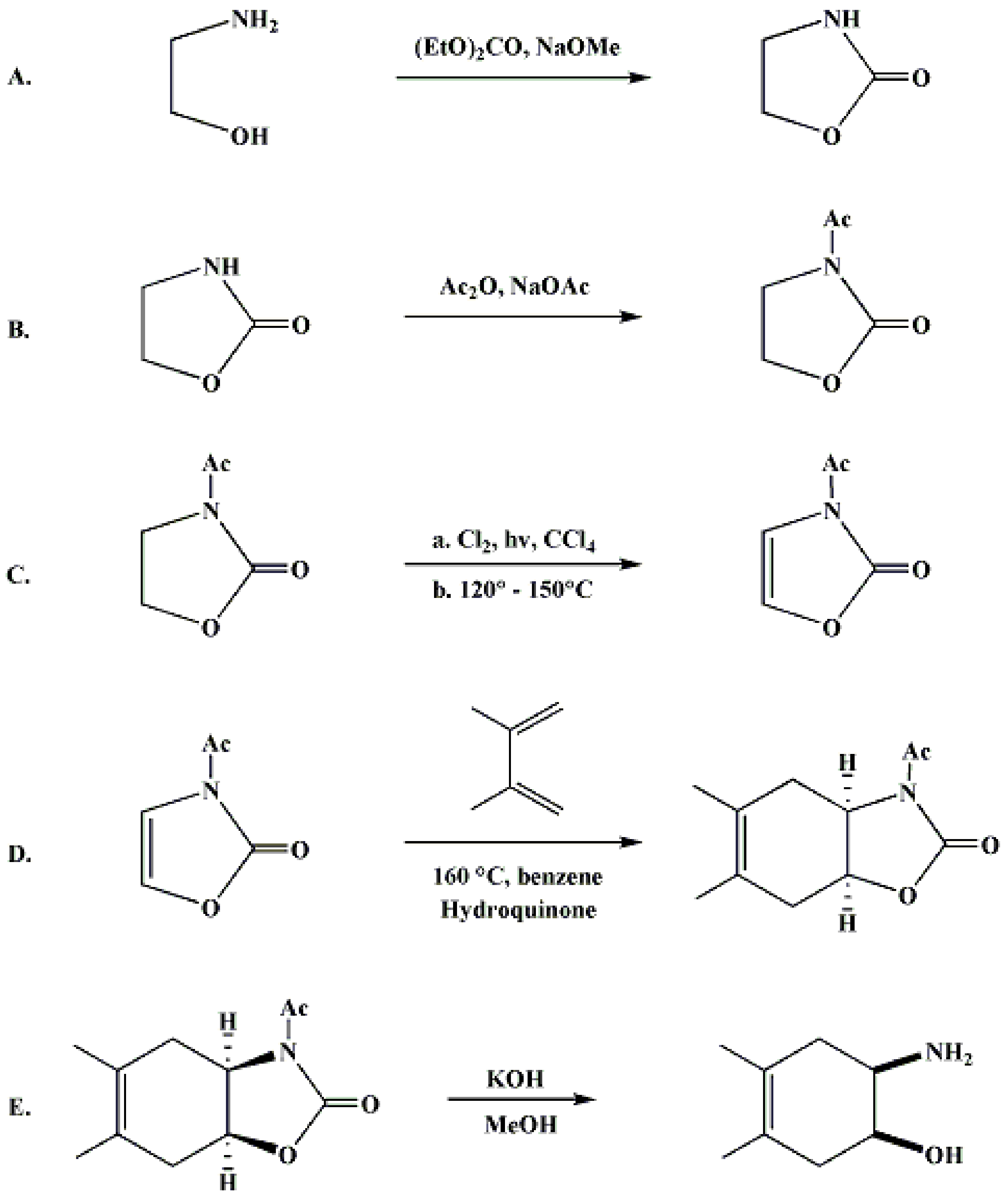
Organic Syntheses, CV 7, 4

SYNTHESIS AND DIELS–ALDER REACTIONS OF 3-ACETYL-2(3*H*)-OXAZOLONE: 6-AMINO-3,4-DIMETHYL-*cis*-3-CYCLOHEXEN-1-OL

[2(3*H*)-Oxazolone, 3-acetyl- and 3-cyclohexen-1-ol, 6-amino-3,4-dimethyl-, *cis*-]



Submitted by Karl-Heinz Scholz, Hans-Georg Heine, and Willy Hartmann[1].
Checked by Ashok B. Shenvi, Bruce M. Monroe, Richard E. Benson, and Bruce E. Smart.

1. Procedure

A. *2-Oxazolidinone*. A 2-L, three-necked flask equipped with a thermometer, magnetic stirring bar, and a Vigreux column fitted with a distillation head is charged with 305 g (5.0 mol) of freshly distilled 2-aminoethanol, 730 g (6.2 mol) of diethyl carbonate, and 2.5 g (0.05 mol) of sodium methoxide (Note 1). The mixture is stirred and the flask is heated in an oil bath maintained at 125–130°C. Ethanol begins to distill off when the internal temperature reaches 95–100°C. After heating for about 8 hr, the internal temperature reaches 125°C and ethanol ceases to distill (Note 2). The reaction mixture is allowed to cool to 60–70°C and is poured into 1 L of cold chloroform (Note 3). The resulting solution is chilled thoroughly in an ice–water bath and the precipitated product is recovered by filtration. The filtrate is concentrated to 250 mL and chilled to give a second crop. The combined crops are dried in a vacuum oven at 50°C to give 320–339 g (74–78%) of white crystals, mp 86–88°C [lit.[2] mp 87–89°C] (Note 4).

B. *3-Acetyl-2-oxazolidinone*. A 3-L, one-necked flask equipped with a reflux condenser and a magnetic stirring bar is charged with 326 g (3.75 mol) of 2-oxazolidinone, 94 g (1.15 mol) of anhydrous sodium acetate, and 1.6 L of acetic anhydride. The stirred solution is refluxed for 3 hr and the acetic anhydride is then removed by distillation at 15–20 mm. The residue is extracted with three 875–mL portions of boiling toluene (Note 5), and the hot toluene extractions are filtered, combined, and concentrated to a total volume of 675 mL. Diethyl ether (675 mL) is added with stirring to the toluene solution and the mixture is chilled in an ice–water bath. The precipitate is removed by filtration and washed with 250 mL of diethyl ether to give 328–403 g (68–83%) of colorless to very light tan crystals, mp 65–67°C [lit.[2] mp 69–70°C] (Note 6). A second crop of 63–24 g (13–5%), mp 65–68°C, is obtained by concentrating the filtrate to 275 mL and chilling it in an ice–water bath.

C. *3-Acetyl 4- and 5-chloro-2-oxazolidinone*. A 3-L, four-necked flask is equipped with a reflux condenser topped with a gas discharge tube, thermometer, fritted-glass inlet tube extending to the bottom of the flask, and a glass sleeve for accepting an ultraviolet (UV) lamp (Note 7). The reaction vessel is charged with 258 g (2.0 mol) of 3-acetyl-2-oxazolidinone, 2 L of carbon tetrachloride, and several boiling chips. The mixture is heated to gentle reflux, the light source is turned on, and 155 g (2.18 mol) of chlorine gas (Note 8) is introduced at such a rate that no chlorine escapes from the condenser (Note 9). After the addition is complete, heating is discontinued and nitrogen is bubbled through the reaction mixture to remove the dissolved hydrogen chloride. The solvent is then removed on a rotary evaporator to give a yellow oil, which consists of a mixture of 3-acetyl 4- and 5-chloro-2-oxazolidinones[3] and is used in Step D without further purification.

D. *3-Acetyl-2(3H)-oxazolone.* The crude mixture of 3-acetyl 4- and 5-chloro-2-oxazolidinone from Step C is placed in a 2-L, three-necked flask equipped with a thermometer, sealed mechanical stirrer, and gas discharge tube. The material is heated to 120°C with stirring, and the temperature is then slowly increased to 150°C and held there until the evolution of gas ceases (Note 10). The cooled, black reaction mixture is distilled at 20 mm. The fractions boiling up to 150°C are collected and redistilled through a 50-cm × 3-cm Vigreux column fitted with a variable take-off head. There is obtained 140–172 g (55–68%) of product, bp 108–112°C (24 mm), which solidifies, mp 35–37°C (Note 11).

E. *4-Acetyl-7,8-dimethyl-2-oxa-4-azabicyclo[4.3.0]non-7-en-3-one.* A solution of 63.5 g (0.5 mol) of 3-acetyl-2(3H)-oxazolone, 27.5 g (0.33 mol) of 2,3-dimethylbutadiene (Note 12), and 2.0 g of hydroquinone in 125 mL of benzene is heated at 160°C under nitrogen in a 360-ml Hastelloy C shaker tube (Note 13). After 12 hr, the pressure vessel is cooled to room temperature, recharged with 27.5 g of 2,3-dimethylbutadiene, and heated another 12 hr at 160°C. The vessel is again cooled, recharged with 27.5 g of 2,3-dimethylbutadiene, and heated at 160°C for a final 12 hr. The resulting mixture is distilled to give 36.4–40.3 g (35–39%) of crude product, bp 115–130°C (0.5 mm), which solidifies (Note 14) and (Note 15). This material can be recrystallized by adding 36.4 g of melted product to 50 mL of boiling hexane, followed by cooling to give 27.6 g (26%) of crystals, mp 72–78°C (Note 16).

F. *6-Amino-3,4-dimethyl-cis-3-cyclohexen-1-ol.* A solution of 26.1 g (0.125 mol) of 4-acetyl-7,8-dimethyl-2-oxa-4-azabicyclo[4.3.0]non-7-en-3-one and 42.0 g (0.75 mol) of potassium hydroxide in 200 mL of methanol and 100 mL of water is refluxed for 36 hr. The resulting mixture is exhaustively extracted with diethyl ether using a liquid–liquid continuous extraction apparatus. The ethereal extract is concentrated on a rotary evaporator and the residue is taken up in 150 mL of methylene chloride. The resulting solution is dried over anhydrous sodium sulfate, the drying agent is removed by filtration, and the filtrate is concentrated to dryness. The solid residue (16.5 g) is recrystallized from 100 mL of diethyl ether to give 11.2 g (64%) of colorless crystals, mp 63–65.5°C. A second crop of 2.3 g (13%) is obtained by concentrating the mother liquor to 50 mL and chilling in an ice–water bath (Note 17).

2. Notes

1. The checkers obtained 2-aminoethanol, diethyl carbonate, and anhydrous sodium methoxide from the Aldrich Chemical Company.
2. About 625 mL (theoretical: 583 mL) of ethanol is collected. If the reaction is stopped before this volume is collected, the yield is reduced.
3. If the reaction mixture cools below 60°C, the product solidifies in the flask.
4. The product shows the following ^{1}H NMR spectrum (d_6-DMSO) δ: 3.3–3.8 (m, 2 H), 4.2–4.6 (m, 2 H), 6.5–7.5 (br s, 1 H) and is analytically pure. Anal. calcd. for $C_3H_5NO_2$: C, 41.38; H, 5.79; N, 16.09. Found: C, 41.61; H, 5.70; N, 16.06. The submitters report that they obtained pure material, mp 89–90°C, after three recrystallizations from chloroform.

5. This is conveniently done by adding the toluene to the residue in the flask, heating to reflux in an oil bath, and then filtering the hot mixture.
6. This material shows the following ^1H NMR spectrum ($CDCl_3$) δ: 2.49 (s, 3 H), 3.8–4.7 (complex m, 4 H) and has acceptable analysis. Anal. calcd. for $C_5H_7NO_3$: C, 46.51; H, 5.46; N, 10.85. Found: C, 46.49; H, 5.40; N, 10.99. The submitters report that they obtained colorless, analytically pure material, mp 69–70°C, after three recrystallizations from benzene.
7. The submitters used a Philips HPK 125-W high-pressure mercury vapor lamp. The sleeve is 2-mm Pyrex glass with an NS45 ground joint. The lamp does not require cooling. The checkers obtained equally good results by shining a Westinghouse 250-W sun lamp on the reaction flask from a distance of 25 cm.
8. The chlorine gas is passed successively through three wash bottles. The center bottle is filled with concentrated sulfuric acid and the other two are left empty to serve as safety traps.
9. The photochlorination takes 4–6 hr. The hydrogen chloride evolved is absorbed in water.
10. Dehydrochlorination begins at about 120°C. The temperature is raised about 10°C/hr to 150°C to avoid vigorous gas evolution. The elimination of hydrogen chloride is complete after 5–6 hr.
11. The submitters report yields of 150–200 g, and that analytically pure material boils at 110°C (24 mm) and melts at 35–37°C after recrystallization from diethyl ether. The material obtained by the checkers showed a satisfactory analysis without further purification. Anal. calcd. for $C_5H_5NO_3$: C, 47.25; H, 3.97; N, 11.02. Found: C, 46.81; H, 4.00; N, 11.21. The material shows the following ^1H NMR spectrum ($CDCl_3$) δ: 2.63 (s, 3 H), 6.90 (d, 1 H, J = 2.5), 7.30 (d, 1 H, J = 2.5); IR (CCl_4) cm^{-1}: 1880, 1735 (C=O).
12. The sample of 2,3-dimethylbutadiene was obtained from the Aldrich Chemical Company.
13. The submitters employed a nickel autoclave and noted that product from Step D may contain a small amount of hydrogen chloride or chlorinated material that can adversely affect a stainless-steel pressure vessel. Hastelloy C is a high-nickel alloy.
14. The submitters obtained 48.0 g of product and 33.5 g of recovered starting material, bp 110°C (24 mm). The checkers found that the forerun collected at 108–112°C (24 mm) contained starting material, but it was highly contaminated with unidentified by-products.
15. The checkers obtained erratic results in this step, possibly because of surface effects or trace impurities in the pressure vessel. In two other runs, only 16.8–18.8 g of crude product were obtained. In one case, high-boiling oligomers were formed, but none of the desired product was produced. Impurities in the diene or dienophile did not appear to be the problem since runs that employed recrystallized 3-acetyl-2(3*H*)-oxazolone and redistilled 2,3-dimethylbutadiene also gave variable results.
16. The submitters report pure product with bp 135–137°C (1.2 mm) and mp 78–80°C after recrystallization from chloroform. The checkers found that recrystallization from chloroform gave very poor recovery of product with mp 75–

78°C. Material with mp 72–78°C is pure by NMR, mass spectroscopy, and combustion analysis; ^{1}H NMR ($CDCl_3$) δ: 1.70 (s, 6 H), 2.33 (m, 4 H), 2.45 (s, 3 H), 4.40 (d of t, 1 H, J = 9.0, 4.5), 4.83 (d of t, 1 H, J = 9.0, 4.5); infrared (IR) (KBr) cm^{-1}: 1780, 1690. Mass spectrum *m/e* calculated: 209.1051. Found: 209.1030. Anal. calcd. for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.19; H, 7.10; N, 6.67.

17. The product shows the following ^{1}H NMR spectrum ($CDCl_3$) δ: 1.60 (s, 6 H), 2.13 (br m, 4 H), 2.30 (s, 3 H), 3.00 (m, 1 H), 3.80 (m, 1 H) and is analytically pure. Anal. calcd. for $C_8H_{15}ON$: C, 66.35; H, 10.71; N, 9.92. Found: C, 66.17, H, 10.48; N, 10.26.

3. Discussion

The dienophile, 3-acetyl-2(3*H*)-oxazolone,[4] is an attractive intermediate for the synthesis of vicinal aminoalcohols with cis configurations. It reacts with 1,3-dienes, even under quite mild conditions, to form (4 + 2) cycloadducts.[5], [6] Its high reactivity with deactivated 1,3-dienes is noteworthy. This property is present also in 2(3*H*)-oxazolone,[4] which can be obtained easily through solvolysis of 3-acetyl-2(3*H*)-oxazolone in methanol. 3-Acetyl-2(3*H*)-oxazolone, on UV irradiation in the presence of a sensitizer, combines easily with olefins to form (2 + 2) cycloadducts,[7] the hydrolysis of which leads to the class of *cis*-2-aminocyclobutanols.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

3-acetyl 4- and 5-chloro-2-oxazolidinones

3-acetyl 4- and 5-chloro-2-oxazolidinone

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrogen chloride (7647-01-0)

Benzene (71-43-2)

methanol (67-56-1)

diethyl ether (60-29-7)

acetic anhydride (108-24-7)

sodium acetate (127-09-3)

chloroform (67-66-3)

hydroquinone (123-31-9)

sodium sulfate (7757-82-6)

carbon tetrachloride (56-23-5)

nitrogen (7727-37-9)

mercury (7439-97-6)

sodium methoxide (124-41-4)

chlorine (7782-50-5)

potassium hydroxide (1310-58-3)

toluene (108-88-3)

methylene chloride (75-09-2)

2-aminoethanol (141-43-5)

diethyl carbonate (105-58-8)

2,3-Dimethylbutadiene (513-81-5)

hexane (110-54-3)

2-Oxazolidinone (497-25-6)

5-chloro-2-oxazolidinone

3-Acetyl-2-oxazolidinone (1432-43-5)

3-Acetyl-2(3H)-oxazolone, 2(3H)-Oxazolone, 3-acetyl- (60759-49-1)

4-Acetyl-7,8-dimethyl-2-oxa-4-azabicyclo[4.3.0]non-7-en-3-one (65948-43-8)

6-Amino-3,4-dimethyl-cis-3-cyclohexen-1-ol, 3-cyclohexen-1-ol, 6-amino-3,4-dimethyl-, cis- (65948-45-0)

2(3H)-oxazolone

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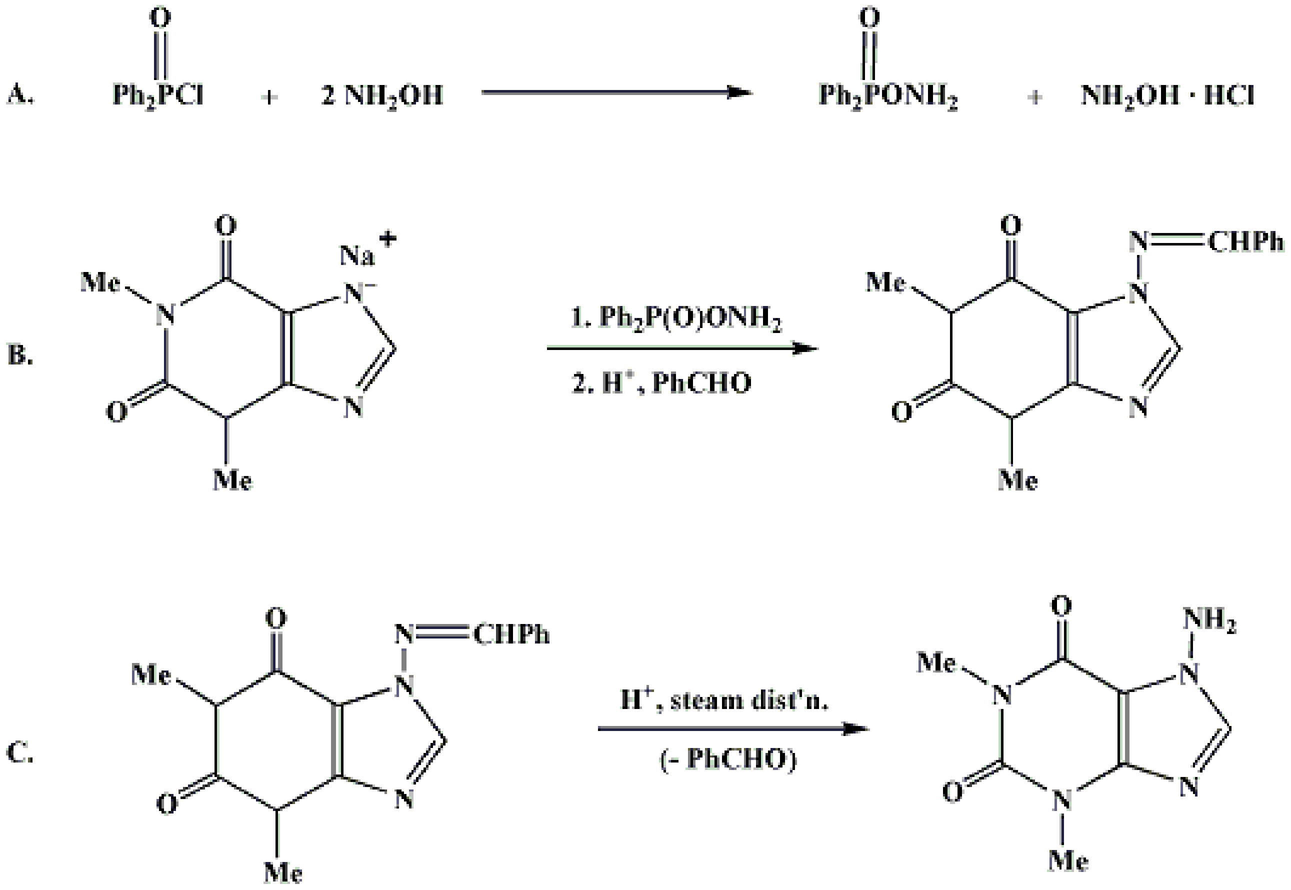
ELECTROPHILIC *N*-AMINATION OF IMIDE SODIUM SALTS WITH *O*-DIPHENYLPHOSPHINYLHYDROXYLAMINE (DPH): 7-AMINOTHEOPHYLLINE

[1*H*-Purine-2,6-dione, 7-amino-3,7-dihydro-1,3-dimethyl-]



Submitted by W. Klötzer, J. Stadlwieser, and J. Raneburger[1].
Checked by Michael J. Luzzio and Andrew S. Kende.

1. Procedure

A. *O-Diphenylphosphinylhydroxylamine*.[2] A 500-mL, round-bottomed flask, equipped with a reflux condenser, drying tube, an efficient mechanical stirrer, a dropping funnel, and a nitrogen-inlet tube, is charged with 300 mL of anhydrous methylene chloride, 16.5 g (0.5 mol) of hydroxylamine base (Note 1), and 1.0 g of dry sodium bicarbonate. While the suspension is stirred vigorously at −30°C (bath temperature), a solution of 52.06 g (0.22 mol) of diphenylphosphinyl chloride (Note 2) in 70 mL of anhydrous methylene chloride is added under a nitrogen atmosphere at a constant rate within 30 min. The resulting thick suspension is stirred at −30°C for 2 hr and for an additional 2 hr after the cooling bath is removed. The reaction mixture is filtered through a sintered-glass funnel (porosity 3) and the residue is washed with two 80-mL portions of methylene chloride. The methylene chloride is removed from the colorless solid by a stream of air for 2 hr. The dry solid, still on the funnel, is then mixed thoroughly with 200 mL of deionized water. The

water is removed by suction. The same operation is performed sequentially with 150 mL of 5% aqueous sodium bicarbonate solution and then with two 150-mL portions of water. This solid, which retains water tenaciously, is dried by suction and by pressing down on the funnel for several hours, followed by drying in a phosphorus pentoxide-charged vacuum desiccator until its weight is constant (24 hr) to give 36 g (70%) of impure *O*-diphenylphosphinylhydroxylamine, mp 120–135°C, with decomposition.

A 500-mL, two-necked flask, equipped with a reflux condenser and a drying tube, is charged with 240 mL of anhydrous ethanol. The solvent is preheated to 70°C and a 12-g portion of this finely powdered dry product is added all at once. The resulting suspension is refluxed for 2–3 min when almost all of the solid has dissolved. The hot solution is filtered as quickly as possible through a sintered-glass funnel (porosity 3) and the filtrate is chilled to 0°C for 30 min. Isolation of the crystalline deposit and washing with 20 mL of ether provides 7.8 g of pure product. Recrystallization of three 12-g portions furnishes 23.4 g (44%) of *O*-diphenylphosphinylhydroxylamine, mp >140°C, with decomposition (Note 3).

B. *7-Benzylideneaminotheophylline*. A 2000-mL, round-bottomed flask, equipped with an efficient mechanical stirrer, thermometer, and drying tube, is charged with 600 mL of anhydrous *N*-methylpyrrolidone (Note 4) and 20.2 g (0.1 mol) of anhydrous theophylline sodium salt (Note 5). The flask is cooled with an ice–salt bath to 0°C (internal temperature). Then 23.4 g (0.1 mol) of *O*-diphenylphosphinylhydroxylamine is added in three equal portions while the suspension is stirred vigorously. After the ice–salt bath is removed, the resulting viscous suspension is stirred for 6 hr at 20°C.

After the solution is diluted with 1200 mL of water, the pH is adjusted to 1–2 with concentrated hydrochloric acid and the mixture stirred at 5°C for 1 hr. The precipitated diphenylphosphinic acid is isolated by filtration and washed with 50 mL of water (Note 6). The filtrate is placed in a 2000-mL, round-bottomed flask, equipped with a reflux condenser and an efficient mechanical stirrer. A solution of 20 mL of benzaldehyde in 50 mL of ether is added and the mixture is stirred vigorously for 20 min. The precipitate that forms is isolated by filtration and washed sequentially with 50 mL of water and 50 mL of ether to yield 19.6 g (69%) of 7-benzylideneaminotheophylline, mp 207–209°C.[3] An analytical sample may be prepared by recrystallization from ethanol (mp 209°C).

C. *7-Aminotheophylline*. The reaction flask of a steam distillation apparatus is charged with 19.6 g (0.069 mol) of 7-benzylideneaminotheophylline and 100 mL (0.1 mol) of 1 *N* hydrochloric acid. The suspension is steam-distilled until no more benzaldehyde is detected in the distillate (Note 7). The resulting clear solution in the reaction flask is concentrated by rotary evaporation to a volume of 30 mL, adjusted to pH 10 with concentrated ammonium hydroxide, transferred to a separatory funnel, and extracted with five 60-mL portions of chloroform. The combined chloroform extracts are dried with anhydrous sodium sulfate, filtered, and concentrated to dryness by rotary evaporation. The residue is recrystallized from 75 mL of water to afford 11.3 g (84%) of 7-aminotheophylline, mp 222°C.[3]

2. Notes

1. Hydroxylamine base has been prepared by the method of Lecher and Hofmann.[4] The free base can be stored in a tightly stoppered flask at –20°C for several days. The checkers found it expedient to prepare free hydroxylamine by a modification of the Lecher–Hofmann procedure in which a Schlenk tube under dry N_2 was used to filter the NaCl precipitate and

the NH_2OH base was crystallized from the filtrate at −30°C, then isolated by inverting the Schlenk apparatus and filtering the product (74% yield from the hydrochloride).
2. Diphenylphosphinyl chloride can be purchased from Aldrich Chemical Company, Inc. or from EGA-Chemie, D-7924 Steinheim, West Germany (an Aldrich Chemical Company). Diphenylphosphinyl chloride can also be prepared by oxygen-mediated oxidation of diphenylchlorophosphine[5] (purchased from Fluka AG, CH-9470 Buchs, Switzerland).
3. The recrystallization should be performed as quickly as possible in portions below 15 g. Prolonged heating in ethanolic solution causes substantial losses. The pure, dry compound can be stored in a tightly stoppered flask at 0°C for at least 6 months without loss of aminating capacity. The submitters report that the pure compound showed no signs of spontaneous decomposition during 4 years of use, except when heated to >140°C, where the compound decomposes with effervescence.
4. *N*-Methylpyrrolidone (purum grade) was purchased from Fluka AG, CH-9470 Buchs, Switzerland, dried over calcium hydride, and vacuum-distilled [bp 78–79°C (12 mm)].
5. The sodium salt of theophylline was obtained as follows: to a solution of 36.34 g (0.2 mol) of theophylline in 120 mL of 50% aqueous ethanol at 80°C was added 50 mL (0.2 mol) of aqueous 4 *N* sodium hydroxide. Chilling to 0°C, filtration of the precipitate, washing with 50 mL of 96% ethanol, then with 100 mL of ether, and drying in a vacuum desiccator over phosphorus pentoxide provides 28.0 g of the anhydrous salt.
6. The recovered and dried diphenylphosphinic acid, 19.6 g (90%), is ready to be recycled to diphenylphosphinyl chloride.[6, 7]
7. Traces of benzaldehyde can be detected with Brady's reagent (2,4-dinitrophenylhydrazine sulfate solution) or by its characteristic smell.

3. Discussion

Electrophilic *N*-aminations of imide salts have been performed with hydroxylamine-*O*-sulfonic acid (HOSA),[8,9,10] *O*-(2,4-dinitrophenyl) hydroxylamine,[11, 12] and *O*-mesitylenesulfonylhydroxylamine (MSH).[11] The use of HOSA is mainly restricted to aqueous reaction media.[8, 9] *O*-(2,4-Dinitrophenyl) hydroxylamine, MSH, and *O*-diphenylphosphinylhydroxylamine (DPH) can be applied in anhydrous or even nonpolar solvents. *O*-(2,4-Dinitrophenyl) hydroxylamine and MSH require *N*-protected hydroxylamine for their preparation.[11, 12] MSH has been found to be explosive.[13, 14] DPH has the advantage of being prepared directly from unprotected hydroxylamine and seems to have no tendency toward spontaneous decomposition. The possibility of recycling diphenylphosphinic acid may be regarded as a further advantage. The advantage of using unprotected hydroxylamine to prepare DPH is partially negated by the required somewhat delicate preparation and handling of the free hydroxylamine base. The large amount of solvent that is sometimes required because of the low solubility of DPH and the resulting diphenylphosphinic acid salt may be regarded as a disadvantage, too.

O-Diphenylphosphinylhydroxylamine has also been used to aminate carbanions,[15, 16] tertiary phosphines, and thio ethers.[2]

TABLE I

***N*-AMINOCOMPOUNDS FROM IMIDE SODIUM SALTS AND DPH**[a]

Educt Alkali Salt	Solvent[b]	Product	Yield (%)	Ref.
Imidazole	DMF	1-Aminoimidazole	28	3
2-Nitroimidazole	NMP	1-Amino-2-nitroimi-dazole	40	3
2-Methyl-4(5)-nitroimidazole	NMP	1-Amino-2-methyl-4-nitroimidazole	30	3
Theobromine	DMF	1-Aminotheobromine	71	3
Theophylline	NMP	7-Aminotheophylline	60	3
Phthalimide	DMF	*N*-Aminophthalimide	90	3

[a]DPH = *O*-diphenylphosphinylhydroxylamine.

[b]DMF = anhydrous dimethylformamide; NMP = anhydrous N-methylpyrrolidone.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

O-DIPHENYLPHOSPHINYLHYDROXYLAMINE (DPH)

1-Amino-2-nitroimi-dazole

2-Methyl-4(5)-nitroimidazole

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

benzaldehyde (100-52-7)

Phthalimide (85-41-6)

ammonium hydroxide (1336-21-6)

hydroxylamine (7803-49-8)

methylene chloride (75-09-2)

dimethylformamide (68-12-2)

Imidazole (288-32-4)

calcium hydride (7789-78-8)

Hydroxylamine-O-sulfonic acid (2950-43-8)

diphenylchlorophosphine (1079-66-9)

N-methylpyrrolidone (872-50-4)

7-Aminotheophylline, 1H-Purine-2,6-dione, 7-amino-3,7-dihydro-1,3-dimethyl- (81281-58-5)

diphenylphosphinyl chloride (1499-21-4)

theophylline sodium salt, sodium salt of theophylline

diphenylphosphinic acid (1707-03-5)

7-Benzylideneaminotheophylline (81281-59-6)

theophylline (58-55-9)

2,4-dinitrophenylhydrazine sulfate

1-Aminoimidazole

2-Nitroimidazole (527-73-1)

1-Amino-2-methyl-4-nitroimidazole

Theobromine (83-67-0)

1-Aminotheobromine

phosphorus pentoxide (1314-56-3)

N-aminophthalimide (1875-48-5)

O-Mesitylenesulfonylhydroxylamine

O-Diphenylphosphinylhydroxylamine (72804-96-7)

O-(2,4-dinitrophenyl) hydroxylamine

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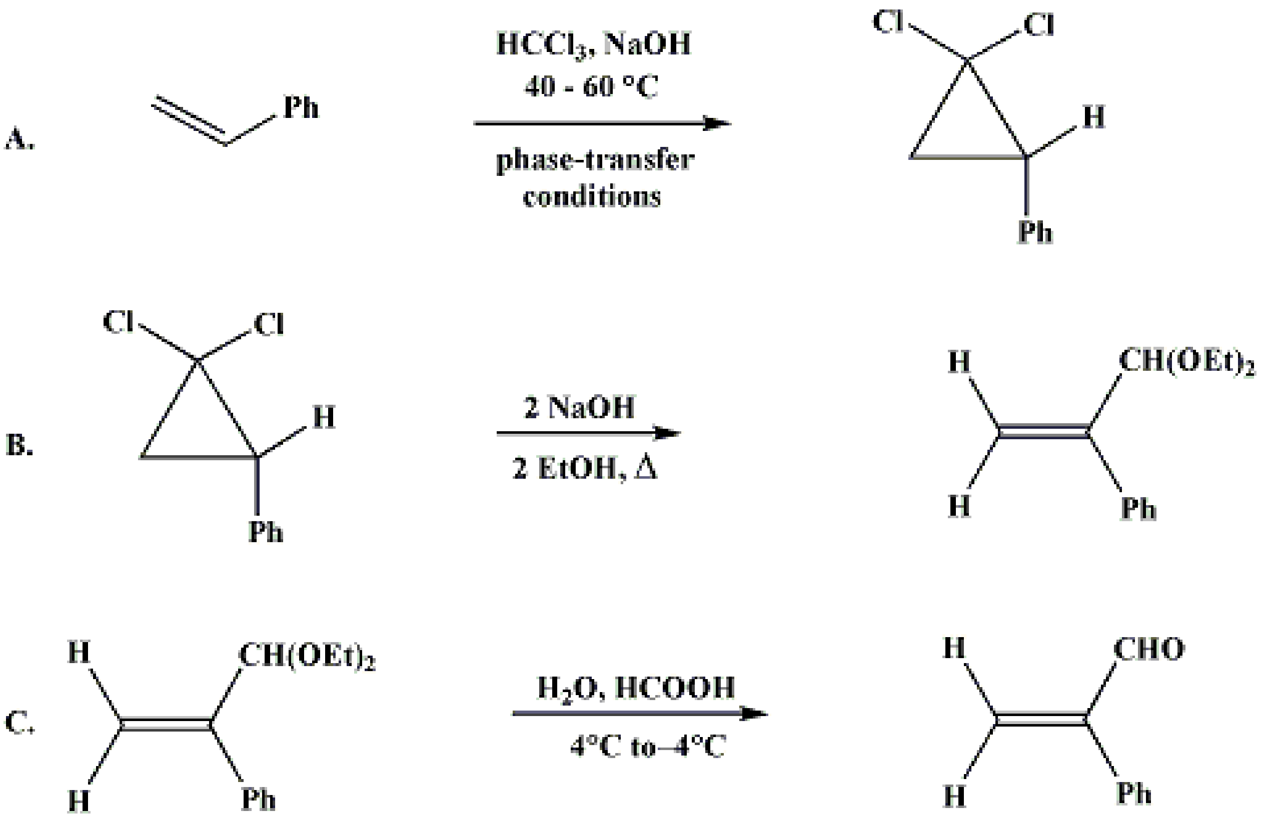
Organic Syntheses, CV 7, 12

ATROPALDEHYDE

[Benzeneacetaldehyde, α-methylene]



Submitted by Ingolf Crossland[1]
Checked by Thomas J. Blacklock and Andrew S. Kende.

1. Procedure

A. *1,1-Dichloro-2-phenylcyclopropane.* In a 1-L, three-necked, round-bottomed "Morton" flask (Note 1) equipped with a mechanical stirrer, a thermometer, and a reflux condenser are placed 57 mL (0.50 mol) of styrene, 50 mL of chloroform, 2 g of triethylbenzylammonium chloride, 25 mL of methylene chloride, and a solution of 77 g of sodium hydroxide in 77 mL of water (Note 2). The mixture is stirred vigorously.

The temperature is allowed to rise to 40°C and then kept between 40 and 45°C by cooling with water (Note 3). After about an hour evolution of heat subsides, and the dark reaction mixture is heated to 55–60°C for an additional hour. The products are transferred to a 1-L separatory funnel with 250 mL of water and shaken. The organic layer is separated and the aqueous phase extracted with 25 mL of petroleum ether (Note 4). The organic fractions are combined, dried over anhydrous magnesium sulfate, filtered, concentrated in vacuo, and distilled through a 20-cm Vigreux column. A forerun at about 50°C (16 mm) consists mainly of styrene. Distillation of the remainder affords 80–82 g (86–88%) of dichlorophenylcyclopropane, bp 118–120°C (16 mm)

(Note 5).

B. *Atropaldehyde diethyl acetal*. A mixture of 18.7 g (0.100 mol) of 1,1-dichloro-2-phenylcyclopropane, 16 g (0.40 mol) of sodium hydroxide, and 160 mL of ethanol is placed in a 250-mL flask fitted with a reflux condenser. The mixture is heated under reflux for 24 hr. Some bumping may occur. Water (200 mL) is added, and the mixture is extracted with three 30-mL portions of petroleum ether. The extracts are combined, dried as above with magnesium sulfate, concentrated in vacuo, and distilled through a 20-cm Vigreux column. The acetal begins to distill at about 70°C (0.5 mm), and the product (14–15 g) is collected until the temperature reaches about 100°C. Gas chromatographic analysis of the product shows it to be about 85% pure (yield 58–62%) (Note 6).

C. *Atropaldehyde*. The acetal (15 g), placed in a 100-mL flask fitted with a magnetic stirrer and a thermometer, is cooled to about 4°C in an ice bath. A mixture of 15 mL of formic acid and 4 mL of water is similarly cooled and added in one lot with stirring to the acetal. The temperature drops to about −4°C. The homogenous mixture is stirred for 60 sec and then quenched by adding 15 mL of petroleum ether and 25 mL of water. The mixture is transferred to a separatory funnel and thoroughly shaken. The aqueous phase is extracted with two additional 15-mL portions of petroleum ether, and the combined extracts are dried as above with magnesium sulfate and concentrated in vacuo (Note 7). A mixture of 10 mL each of petroleum ether and diethyl ether is added to the crude aldehyde, and the solution is cooled to about −50°C. After 15 min the colorless crystals are filtered and washed with a few milliliters of the solvent cooled to 0°C. The yield of vacuum-dried product (Note 7) is 5.8–6.8 g (71–83%). Recrystallization from a mixture of 10 mL each of diethyl ether and petroleum ether as above gives 5–6 g, mp 38–40°C (Note 8) and (Note 9).

2. Notes

1. The checkers used a 1-L, three-necked "Morton" flask[2] containing deep vertical creases for more efficient mixing and temperature control. The sodium hydroxide solution was added to the stirred reaction mixture through the reflux condenser in one portion.
2. The submitters used Merck styrene 99%, stabilized with 4-tert-butylpyrocatechol. Triethylbenzylammonium chloride was prepared by refluxing equimolar amounts of triethylamine and benzyl chloride in ethanol for 2 hr and removing the solvent in vacuo. The salt is commercially available. The other reagents were technical grade.
3. The reaction is exothermic, and it may be a problem to keep the temperature low enough during the first 5 min. A bath with cold water must be kept ready below the flask. The methylene chloride may be added to moderate the reaction.
4. The organic layer is heavier than the aqueous phase. It may be necessary to allow the mixture to stand for an hour before the phases separate.
5. The product shows ^{1}H NMR (60 MHz, CCl_4) δ: 1.87 (q, 2), 2.83 (triplet, 1), 7.20 (singlet, 5). The reported bp is 118–119°C (16 mm) or 114°C (13 mm).[3,4]

Gas chromatographic analysis indicates the product to be 99% pure, n_D^{23} 1.551.

6. The product shows ^1H NMR (90 MHz, $CDCl_3$) δ: 1.18 (triplet J = 7 Hz, 6), 3.58 (multiplet, 4), 5.22 (singlet, 1), 5.54 (singlet, 2), 7.18–7.58 (multiplets, 5). Minor resonance signals near the foot of the triplet revealed the presence of 1-phenyl-2,2-diethoxycyclopropane as the major by-product. Gas chromatographic analyses on a 44-m SCOT column, 150–200°C, indicated that the crude product contained the ketal (10%), the starting material (2%), and an unidentified compound (2%). The submitters have not observed polymerization or other deterioration of the crude acetal when it was stored without special precautions in the laboratory for 2 months at ca. 20°C.

7. The aldehyde must be kept cold; see (Note 8). If the solution is cooled much below room temperature, crystallization of the aldehyde may take place and render some of the manipulations difficult. The crystals may be dissolved in diethyl ether.

8. The product shows ^1H NMR (90 MHz, $CDCl_3$) δ: 6.11 (singlet, 1), 6.56 (singlet, 1), 7.36 (multiplet, 5), 9.72 (singlet, 1). Mass spectrum (70 eV, *m/e*, relative intensity): 132 (M^+, 51%), 104 (69%), 86 (100%), 78 (13%), 77 (35%). The crystalline aldehyde is unstable at room temperature. When kept for 24 hr in a vacuum-sealed ampoule at 20°C, the crystals slowly deliquesce. The aldehyde may, however, be kept at –6°C for 10 days without any observable deterioration.

9. Procedures B and C work well on a larger scale. Thus atropaldehyde was obtained in 20–26-g quantities from 0.5 mol of styrene (30–39%).

3. Discussion

The method presented here is a simple procedure for the preparation of pure atropaldehyde via its stable acetal, starting from inexpensive chemicals.

The described synthesis of 1,1-dichloro-2-phenylcyclopropane is a slightly modified version of published procedures.[3,4]

Syntheses of acetals of atropaldehyde have been reported previously, but all required either multistep sequences or difficultly accessible starting materials.[5,6] Thus the ethylene glycol acetal has been prepared from 2-phenylpropanal in a three-step procedure.[5] Ring openings of dihalocyclopropanes to give acetals are well known.[7,8,9,10] The reaction of 1,1-dichloro-2-phenylcyclopropane with methanolic sodium methoxide has been shown to give 1-phenyl-2,2-dimethoxycyclopropane.[11]

The only described preparatively useful route to atropaldehyde is the hydrolysis of the ethylene glycol acetal mentioned above.[5] The present method is fast and affords labile aldehyde that is pure enough to allow crystallization. A cyclopropene is suggested to be an intermediate in the ring-opening reaction.[12] Nitro-substituted atropaldehydes have been prepared *via* a Mannich reaction.[13]

Formally the reactions amount to an α-formylation of styrene. The homologous aldehyde may be prepared from propenylbenzene.[10]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 10
- Org. Syn. Coll. Vol. 6, 187

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

ethylene glycol acetal

Nitro-substituted atropaldehydes

ethanol (64-17-5)

diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

formic acid (64-18-6)

sodium methoxide (124-41-4)

benzyl chloride (100-44-7)

methylene chloride (75-09-2)

styrene (100-42-5)

propenylbenzene

magnesium sulfate (7487-88-9)

2-phenylpropanal (93-53-8)

triethylamine (121-44-8)

Cyclopropene (2781-85-3)

triethylbenzylammonium chloride (56-37-1)

Atropaldehyde, Benzeneacetaldehyde, α-methylene (4432-63-7)

dichlorophenylcyclopropane

1,1-Dichloro-2-phenylcyclopropane (2415-80-7)

4-tert-butylpyrocatechol (98-29-3)

1-phenyl-2,2-diethoxycyclopropane

1-phenyl-2,2-dimethoxycyclopropane

Atropaldehyde diethyl acetal (80234-04-4)

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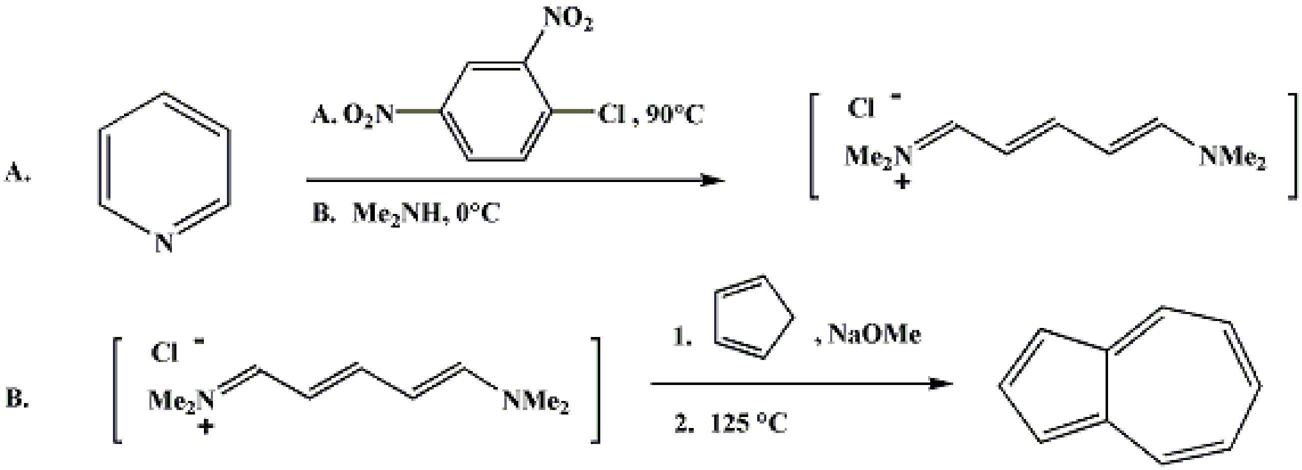
Organic Syntheses, CV 7, 15

AZULENE



Submitted by Klaus Hafner and Klaus-Peter Meinhardt[1].
Checked by Stephen G. Senderoff and Andrew S. Kende.

1. Procedure

A 4-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, 500-mL pressure-equalizing dropping funnel, thermometer, and reflux condenser provided with a calcium chloride drying tube is charged with 202.6 g (1.0 mol) of 1-chloro-2,4-dinitrobenzene (Note 1) and 1.2 L of dry pyridine (Note 2). The mixture is heated while it is stirred in a water bath to 80–90°C for 4 hr, during which time a thick yellow precipitate of *N*-(2,4-dinitrophenyl)pyridinium chloride is formed (Note 3). After cooling to 0°C a solution of 100.0 g (2.22 mol) of dimethylamine in 300 mL of dry pyridine was prechilled to 0°C and added dropwise over a period of about 30 min with stirring. The resulting brownish-red liquid reaction mixture is allowed to warm to room temperature and stirring is continued for 12 hr. The drying tube is replaced by a gas inlet and the system is flushed with dry nitrogen in a hood. Under nitrogen, 70.0 g (1.06 mol) of ice-cold, freshly distilled cyclopentadiene (Note 4) is added, and subsequently 400 mL of 2.5 *M* sodium methoxide solution (Note 5) is slowly added dropwise to the stirred reaction mixture. During addition of the sodium methoxide, the temperature rises to 35–40°C. After the addition is completed, stirring is continued for another 4 hr. The reaction vessel is immersed in an oil bath, the dropping funnel removed, and the flask is fitted with a distillation head. The stirred mixture is cautiously heated under nitrogen (Note 6), and a mixture of pyridine and methanol is distilled off until the temperature of the reaction mixture has increased to 105–110°C (Note 7). After the distillation head is removed and 1 L of dry pyridine added, the black mixture is heated with stirring under a nitrogen atmosphere for 4 days with a bath temperature of 125°C. It is then cooled to 60°C, the reflux condenser is replaced by a distillation head, and pyridine is removed under reduced pressure (Note 8). The gummy black solid residue is removed by a spatula and rinsed with hexanes. It is extracted in a Soxhlet apparatus with 1.5 L of hexanes in several batches. To remove the remaining pyridine, the combined blue hexane rinse and the extraction solutions are carefully washed with two 150-L portions of 10% aqueous hydrochloric acid, then water (Note 9). The organic layer is dried with anhydrous sodium sulfate, the drying agent is removed by filtration, and the solvent is distilled through a 50-cm vacuum-jacketed Vigreux column. The crude azulene is purified by chromatography on activity II alumina (Note 10) with hexane and yields azulene as blue plates, mp 96–97°C, yield 65–75 g (51–59%) (Note 11).

2. Notes

1. Commercial 1-chloro-2,4-dinitrobenzene was obtained from Aldrich Chemical Company, Inc. (Milwaukee) or from Bayer, AG (Leverkusen, FRG) and used directly.

2. Commercial pyridine was dried over potassium hydroxide or calcium hydride and distilled prior to use. The checkers used reagent-grade pyridine (Mallinckrodt AR), which was distilled from KOH and stored over Linde 4A molecular sieves.
3. The reaction mixture should be evenly warmed to 80–90°C within 30 min with efficient mechanical stirring to prevent caking or "hot spots."
4. Dicyclopentadiene, obtained from the Aldrich Chemical Company, Inc. (or E. Merck, Darmstadt, FRG), was cracked just prior to use according to the procedure of Fieser and Williamson,[2] to give the monomer, bp 40–42°C.
5. Sodium methoxide was prepared just prior to use from 23.0 g (1.0 g-atom) of sodium metal and 400 mL of anhydrous methanol (distilled from magnesium turnings), then cooled to room temperature.
6. *Caution!* Dimethylamine is evolved.
7. Approximately 600 mL of distillate will be collected.
8. The blue pyridine distillate is redistilled through a 50-cm vacuum-jacketed Vigreux column (to avoid loss of azulene) until approximately 1.7 L is collected; the residual azulene is combined with the main residues for extraction.
9. A total volume of 2 L of hexane washes results, accompanied by the gradual precipitation of a yellow solid from the hexane washes. The acid-wash procedure frequently leads to emulsions and gummy yellow solid in both phases; back-extraction of the "aqueous" layer with hexane may be necessary.
10. Alumina was purchased from Macherey, Nagel and Co., Düren [Federal Republic of Germany (FRG)]. The checkers employed 650 g of neutral alumina (Fisher, adsorption grade, 80–200 mesh) packed in a 40-cm-high column. Yellow impurities remained on the column, while the blue azulene came off with the hexane solvent front.
11. Further purification of azulene may be achieved by sublimation at reduced pressure, mp 99°C.[3 4] The checkers found that mechanical losses, particularly as mentioned in (Note 9), lead to reduction in yield with reduction in scale (0.1 mol, 39% yield; 0.5 mol, 43% yield; 0.8 mol, 79% yield).

3. Discussion

Azulene has been synthesized by a variety of methods: by dehydrogenation of hydroazulenes,[3 4] by annelation of a seven-membered ring on a five-membered ring either by ring-closure of vinylogous aminopentafulvenes,[5 6,7] or by cycloadditions of aminopentafulvenes with activated 1,3-dienes or alkynes,[8 9 10 11] and by annelation of a five-membered ring on a seven-membered ring starting from troponoids or heptafulvenes.[12 13 14 15,4] Of these, the Ziegler–Hafner synthesis of azulene[5 6] by thermal cyclization of the 6-(4-methylanilino-1,3-butadienyl) pentafulvene proved to be the most versatile. Azulene is also simply prepared from 6-dimethylaminopentafulvene and thiophene 1,1-dioxide or from 6-acyloxypentafulvenes and 1-diethylaminobutadiene, but with lower yields.[9,11],e

The present procedure, based on the Ziegler–Hafner synthesis, is simple and avoids the use of benzidine for the ring closure of the pentafulvene and isolation of the 5-dimethylamino-2,4-pentadienylidenedimethyliminium perchlorate.[16 17] Other amines were also checked; with *N*-methylaniline, ring closure of the resulting pentafulvene in pyridine failed; and with diethylamine, a delay in boiling can take place during the reaction.

Substituted azulenes can be prepared in the same manner by the use of substituted cyclopentadienes or substituted pentamethinium salts.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alumina

5-dimethylamino-2,4-pentadienylidenedimethyliminium perchlorate

hexanes

hydroazulenes

6-(4-methylanilino-1,3-butadienyl) pentafulvene

6-dimethylaminopentafulvene

6-acyloxypentafulvenes

hydrochloric acid (7647-01-0)

methanol (67-56-1)

magnesium turnings (7439-95-4)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

sodium methoxide (124-41-4)

pyridine (110-86-1)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

diethylamine (109-89-7)

benzidine (92-87-5)

dimethylamine (124-40-3)

1-chloro-2,4-dinitrobenzene (97-00-7)

N-Methylaniline (100-61-8)

hexane (110-54-3)

Azulene (275-51-4)

CYCLOPENTADIENE (542-92-7)

dicyclopentadiene

calcium hydride (7789-78-8)

thiophene 1,1-dioxide

1-diethylaminobutadiene

N-(2,4-Dinitrophenyl)pyridinium chloride

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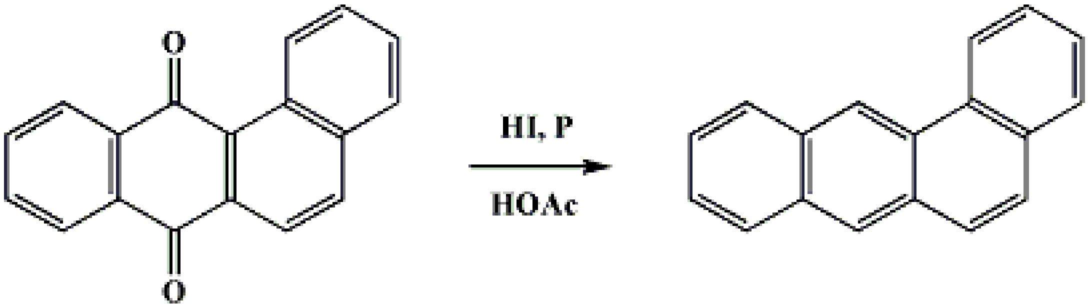
Organic Syntheses, CV 7, 18

REDUCTION OF QUINONES WITH HYDRIODIC ACID: BENZ[*a*]ANTHRACENE



Submitted by Maria Konieczny and Ronald G. Harvey[1].
Checked by Gregory A. Reed and Carl R. Johnson.

1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required. Benz[a]anthracene is also a known carcinogen.

A 500-mL, one-necked, round-bottomed flask is equipped with a magnetic stirring bar and an efficient condenser, and charged with 10.3 g (0.04 mol) of benz[*a*]anthracene-7,12-dione (Note 1), 5 g (0.16 mol) of red phosphorus (Note 2), and 100 mL of glacial acetic acid. The stirred suspension is heated to reflux, and 60 mL of 56% hydriodic acid (ca. 0.44 mol) (Note 3) is introduced through the condenser. The suspension is heated at reflux for 24 hr. The hot reaction mixture is poured into 500 mL of distilled water containing 30 g of sodium bisulfite. The suspension is stirred for 16 hr and filtered. The dry filter cake is transferred to a beaker and treated with sufficient hot dichloromethane (120 mL) to dissolve all of the benz[*a*]anthracene, and the mixture is filtered once again to remove the residual phosphorus. The volume of the filtrate is reduced to 40 mL. The solution is adsorbed on basic alumina, activity I (Note 4). A 2-cm × 40-cm chromatography column is slurry-packed with ca. 10 g of basic alumina and the benz[*a*]anthracene adsorbed on alumina is added to the top of the column. Elution with 5% benzene in hexane (occasional rinsing of the column tip with benzene to remove crystallized product may be necessary) and evaporation of the solvent in a rotary evaporator affords 7.7–7.9 g (84–87%) of pure, white benz[*a*]anthracene, mp 159.5–160°C (Note 5).

2. Notes

1. Benz[*a*]anthracene-7,12-dione, 12-dione, available from Eastman Organic

Chemicals, was used without further purification.
2. Phosphorus, which serves to scavenge the I_2 produced, can be omitted. However, the product tends to retain traces of a yellow impurity that is difficult to remove.
3. The hydriodic acid employed was a 56% aqueous solution preserved with 0.8% hypophosphorous acid obtained from Fisher Scientific Co. Once a bottle is opened, the contents tend to deteriorate, becoming dark-colored in less than 2 days. However, shelf life can be extended indefinitely if the container is purged with dry nitrogen before resealing.
4. Alumina sufficient to adsorb the complete solution is added, then the solvent is removed under vacuum. While benz[*a*]anthracene, mp 157–158°C, sufficiently pure for most purposes, can be obtained by crystallization of the crude product from ethanol-water, "filtration" through alumina removes residual, colored impurities, affording a pure, white product.
5. Pure benz[*a*]anthracene has been reported to melt at 158–159°,[2] 160°,[3] and 167°C.[4] The submitters report a melting point of 164–164.5°C. The submitters conducted this preparation on a scale five times larger and reported yields of up to 95%.

3. Discussion

The synthetic procedure described is based on that reported earlier for the synthesis on a smaller scale of anthracene, benz[*a*]anthracene, chrysene, dibenz[*a, c*]anthracene, and phenanthrene[5] in excellent yields from the corresponding quinones.[6] Although reduction of quinones with HI and phosphorus was described in the older literature, relatively drastic conditions were employed and mixtures of polyhydrogenated derivatives were the principal products.[7] The relatively milder experimental procedure employed herein appears generally applicable to the reduction of both *ortho*- and *para*-quinones directly to the fully aromatic polycyclic arenes. The method is apparently inapplicable to quinones having an olefinic bond, such as *o*-naphthoquinone, since an analogous reaction of the latter provides a product of undetermined structure (unpublished result). As shown previously,[6] phenols and hydroquinones, implicated as intermediates in the reduction of quinones by HI, can also be smoothly deoxygenated to fully aromatic polycyclic arenes under conditions similar to those described herein.

Although previous experience indicates that phosphorus is not essential for these reductions,[6,8] purification of the product is more difficult with its omission. With hydrocarbons sensitive to further reduction, phosphorus can have a deleterious effect through promotion of hydrogenation of the desired product. Whether or not phosphorus should be employed in an individual case will be dictated by experience with the particular compound and by the degree of purity required.

While the reduction of polycyclic quinones to phenols, hydroquinones, dihydrodiols, dihydro arenes, and arenes by a variety of reagents has been described, no entirely satisfactory general method is currently available for reduction directly to the fully

aromatic arenes. Reagents previously employed for this purpose include $LiAlH_4$,[9,10] $NaBH_4$,[11 12 13] $NaBH_4$-BF_3,[11,14] diborane,[14] aluminum and cyclohexanol,[15] zinc dust distillation,[16] and diphenylsilane.[17] These methods commonly furnish lower yields and are less general than the present procedure.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

red phosphorus

alumina

Benz[a]anthracene-7,12-dione, 12-dione

hypophosphorous acid

quinones

o-naphthoquinone

$NaBH_4$-BF_3

acetic acid (64-19-7)

Benzene (71-43-2)

Cyclohexanol (108-93-0)

PHOSPHORUS (7723-14-0)

nitrogen (7727-37-9)

aluminum (7429-90-5)

sodium bisulfite (7631-90-5)

zinc (7440-66-6)

hydriodic acid (10034-85-2)

anthracene (120-12-7)

dichloromethane (75-09-2)

phenanthrene (85-01-8)

$LiAlH_4$ (16853-85-3)

Benz[a]anthracene (56-55-3)

hexane (110-54-3)

$NaBH_4$ (16940-66-2)

chrysene (218-01-9)

diphenylsilane (775-12-2)

benz[a]anthracene-7,12-dione (2498-66-0)

dibenz[a, c]anthracene (215-58-7)

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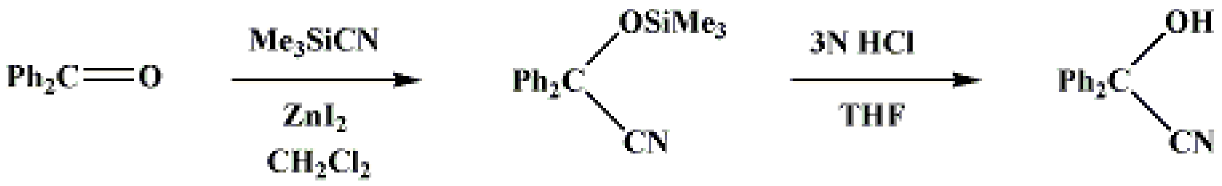
Organic Syntheses, CV 7, 20

CONVERSION OF KETONES TO CYANOHYDRINS: BENZOPHENONE CYANOHYDRIN

[Benzeneacetonitrile, α-hydroxy-αphenyl]



Submitted by Paul G. Gassman and John J. Talley[1].
Checked by Tod Holler and George Büchi.

1. Procedure

A. *O-(Trimethylsilyl)benzophenone cyanohydrin*. A 250-mL, one-necked flask equipped with a reflux condenser, magnetic stirring bar, and drying tube is charged with 22.0 g (0.12 mol) of benzophenone (Note 1), 13.9 g (0.14 mol) of trimethylsilyl cyanide (Note 2), 600 mg (1.9 mmol) of anhydrous zinc iodide (Note 3), and 50 mL of dry methylene chloride (Note 4). The solution is heated at 65°C in an oil bath for 2 hr (Note 5) and (Note 6). The solvent is removed on a rotary evaporator to yield 36.4–37.9 g of crude product (Note 7), which is used in the next step without purification (Note 8).

B. *Benzophenone cyanohydrin*. To the 250-mL flask, which contains the crude O-(trimethylsilyl) benzophenone cyanohydrin, is added 50 mL of tetrahydrofuran (Note 9) and 30 mL of 3 *N* hydrochloric acid. The mixture is heated at 65°C (oil bath temperature) for 1 hr. The solution is poured into a separatory funnel and 30 mL of water is added. The aqueous phase is separated and back-extracted with three 100-mL portions of diethyl ether. The ethereal extracts are combined with the tetrahydrofuran solution and dried over anhydrous magnesium sulfate, filtered, and solvent is removed by evaporation on a rotary evaporator to give a yellow solid. The material is recrystallized from 300 mL of toluene and dried at a pressure of 0.05 mm overnight to give 17.7–18.8 g of white crystals. Concentration of the mother liquors to 100 mL produced a second crop of 1.1–3.8 g for a combined yield of 17.9–21.5 g (79–86%), mp 127–130°C (Note 10).

2. Notes

1. Benzophenone was purchased from Distillation Products (Eastman Organic Chemicals) and used without purification.
2. Trimethylsilyl cyanide was prepared shortly before use according to the procedure of Livinghouse, T. *Org. Synth. Coll. Vol. VII* **1990**, 517.

3. Anhydrous zinc iodide was purchased from Alfa Products, Ventron Corporation, and used without further purification.
4. The use of this solvent is optional. The reaction can be carried out in the absence of solvent without significant change in yield. For certain unhindered ketones the solvent is helpful in dissipating the heat generated in the reaction.
5. For certain unhindered ketones external cooling may be necessary instead of heating due to the exothermicity of the reaction.
6. The checkers followed the reaction by IR spectroscopy and found that the benzophenone carbonyl peak (1640 cm^{-1}) disappeared after 2 hr.
7. If purification is desired, it may be achieved by vacuum distillation of this crude product, bp 104°C (0.5 mm).
8. On prolonged standing the crude product appears to undergo some decomposition. Thus it should be used directly in the next step for maximum yield.
9. For many analogs the use of solvent and/or heating is not necessary. However, both solvent and heating are necessary for hindered cyanohydrins, such as the one described in this procedure.
10. The submitters report a melting point of 131–132.5°C. The melting point has been previously reported to be 127–130°C.[2]

3. Discussion

Traditionally cyanohydrins have been prepared by processes that require the establishment of an equilibrium between a ketone and its corresponding cyanohydrin. For many ketones, especially those that are sterically hindered, the position of the equilibrium is unsatisfactory for the effective synthesis of the cyanohydrin. We describe herein a general method for the synthesis of cyanohydrins that does not depend on an equilibrium process. As a result this synthetic procedure can be used to convert a wide variety of dialkyl, diaryl, and arylalkyl ketones into their corresponding cyanohydrins. In addition to the described conversion of benzophenone into its cyanohydrin, acetophenone, fluorenone, *tert*-butyl phenyl ketone, and a wide variety of aliphatic ketones have been converted into cyanohydrins by this general procedure (Table I).[3]

O-(Trimethylsilyl) benzophenone cyanohydrin has been prepared previously by the addition of trimethylsilyl cyanide to benzophenone using an aluminum chloride catalyst.[4] The preparation of cyanohydrin silyl ethers described in the synthesis is based on the general procedure of Evans, Carroll, and Truesdale.[5] Trimethylsilyl cyanide has been prepared also by Zubrick, Dunbar, and Durst.[6] The overall procedure is that of Gassman and Talley.[3]

Benzophenone cyanohydrin has been synthesized previously by the nitrogen dioxide oxidation of 1,2-dicyanotetraphenylethane.[2]

TABLE I

PREPARATION OF CYANOHYDRINS

Yield	Product (%)	mp [bp] (°C)
Cyclohexanone cyanohydrin	90	27–28 [63° (10^{-6} mm)]
Cyclooctanone cyanohydrin	93	115–116
Fluorenone cyanohydrin	98	118.5–120
tert-Butyl phenyl ketone cyanohydrin	99	82–83
p-Chloroacetophenone cyanohydrin	94	91.5–92.5
p-Nitroacetophenone cyanohydrin	89	112–113
p-Acetylbenzonitrile cyanohydrin	95	77.5–78.5
p-Methoxyacetophenone cyanohydrin	96	78–80
p-Methylacetophenone cyanohydrin	97	79.5–80

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

BENZOPHENONE CYCANOHYDRIN

hydrochloric acid (7647-01-0)

diethyl ether (60-29-7)

Acetophenone (98-86-2)

aluminum chloride (3495-54-3)

toluene (108-88-3)

Benzophenone (119-61-9)

nitrogen dioxide (10102-44-0)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

fluorenone (486-25-9)

cyclohexanone cyanohydrin (931-97-5)

zinc iodide

Trimethylsilyl cyanide (7677-24-9)

tert-Butyl phenyl ketone (938-16-9)

Benzeneacetonitrile, α-hydroxy-αphenyl, Benzophenone cyanohydrin (4746-48-9)

1,2-dicyanotetraphenylethane

Cyclooctanone cyanohydrin

Fluorenone cyanohydrin

O-(trimethylsilyl) benzophenone cyanohydrin, O-(Trimethylsilyl)benzophenone cyanohydrin (40326-25-8)

tert-Butyl phenyl ketone cyanohydrin

p-Chloroacetophenone cyanohydrin

p-Nitroacetophenone cyanohydrin

p-Acetylbenzonitrile cyanohydrin

p-Methoxyacetophenone cyanohydrin

p-Methylacetophenone cyanohydrin

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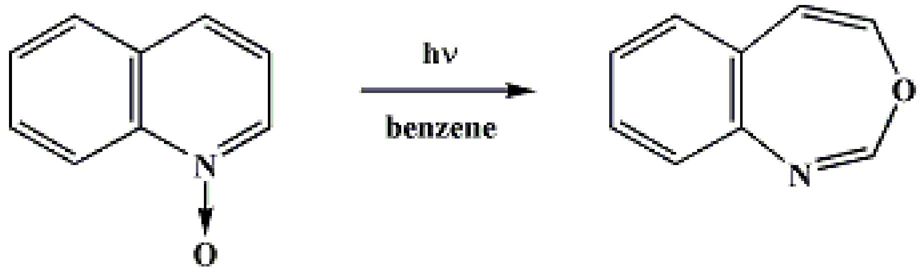
Organic Syntheses, CV 7, 23

1,3-OXAZEPINES VIA PHOTOISOMERIZATION OF HETEROAROMATIC *N*-OXIDES: 3,1-BENZOXAZEPINE



Submitted by Angelo Albini, Gian Franco Bettinetti, and Giovanna Minoli[1].
Checked by Patrick MacManus and Robert M. Coates.

1. Procedure

Caution! 3,1-Benzoxazepine is a strong lacrimator and a moderate skin irritant. The preparation should be carried out in a well-ventilated hood. The apparatus should be shielded to avoid exposure to ultraviolet light.

Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

Irradiation is carried out in a round-bottomed, cylindrical, Pyrex vessel (Note 1) equipped with a Pyrex immersion well (Note 2), nitrogen inlet, distillation sidearm, a small sidearm fitted with a rubber septum for removing aliquots, and a magnetic stirring bar. The flask is charged with 12 g (0.066 mol) (Note 3) of quinoline *N*-oxide dihydrate (Note 4) and 1.3 L of dry benzene (Note 5). The mixture is stirred and heated to boiling with a heating mantle as a slow stream of nitrogen (Note 6) is bubbled into the vessel. Benzene is distilled through the sidearm until the distillate is perfectly clear (Note 7). The lamp (Note 8) is placed in the immersion well, water is circulated through the cooling jacket, and the nitrogen flow is adjusted as necessary to maintain an outward flow of gas while the light yellow solution cools to room temperature (Note 9). The solution is stirred vigorously (Note 10) and irradiated for 2.5–3 hr, at which time the *N*-oxide is largely consumed (Note 11). The orange solution is transferred to a 1-L, round-bottomed flask, and the benzene is removed by rotary evaporation at room temperature. The red-orange oily residue, which contains some solid, is extracted with three 40-mL portions of dry cyclohexane, the combined cyclohexane extracts are evaporated under reduced pressure at room temperature, and the extraction operation is repeated on the oil thus obtained (Note 12). Evaporation of the combined cyclohexane extracts affords 6.1–6.3 g (63–65%) of crude 3,1-

benzoxazepine (Note 13). Bulb-to-bulb distillation in a Kugelrohr apparatus at 0.2 mm with an oven temperature of 80°C affords 4.7–4.8 g (49–50%) of 3,1-benzoxazepine as a pale yellow oil, n_D^{24} 1.6074 (Note 14) and (Note 15).

2. Notes

1. The apparatus used by the checkers for irradiations at a 9-g scale was 33 cm high and 9 cm in diameter and had a 60/50 T joint at the top for the immersion well. The joints for the distillation and sampling sidearms were 24/40 and 14/20, respectively. The gas inlet was located about 6 cm from the bottom of the vessel to accommodate the use of a heating mantle. A disk of coarse, sintered glass was sealed into the gas inlet near its point of attachment. The capacity of the vessel with the immersion well in place was ca. 900 mL. The submitters used a similar but flat-bottomed apparatus of 1.2-L capacity. The flat-bottomed vessel facilitates vigorous stirring, but it does not fit as well into the heating mantle and may therefore be somewhat hazardous to use.
2. The checkers used a Vycor immersion well and a Pyrex filter sleeve. The immersion well, 450-W mercury lamp, and the requisite transformer are available from Hanovia Lamp Division, Canrad-Hanovia Inc., 100 Chestnut Street, Newark, NJ 07105.
3. The checkers carried out the irradiation on a 9-g scale in 750 mL of benzene after azeotropic distillation.
4. Quinoline *N*-oxide dihydrate is supplied by Aldrich Chemical Company, Inc. and EGA Chemie KG, Steinheim/Albuch, Germany. The submitters prepared the compound by the procedure of Hayashi[2] with minor modifications. The water of hydration may be removed under reduced pressure in a drying pistol. However, since the anhydrous *N*-oxide is very hygroscopic, the submitters have found that it is more expedient to use the dihydrate and remove the water by azeotropic distillation in the irradiation vessel.
5. The checkers dried the benzene by distillation from calcium hydride immediately before use. The submitters report that toluene may be used instead of benzene; however, since the product is not very thermally stable, they advise that the toluene should be evaporated without heating above 35–40°C during the isolation.
6. Other dry gases may be used. The submitters report that the reaction is not quenched by oxygen.
7. A total of ca. 150–300 mL was collected. The distillation time may be reduced by insulating the vessel and sidearm with glass wool.
8. The submitters used a Helios Italquartz 500-W lamp which has emission characteristics similar to those of the Hanovia 450-W medium pressure mercury lamp used by the checkers.
9. The checkers noticed that a thin film of oil that was evidently quinoline *N*-oxide deposited on the surface of the immersion well and irradiation vessel during cooling.
10. Vigorous stirring is essential for optimum yields. The checkers obtained lower isolated yields (ca. 32–33%) in two runs in which a relatively slow

stirring rate was employed. The low yields were probably caused in part by deposition of oil on the surface of the immersion well and the resulting interference with the transmission of UV light into the solution.

11. The submitters emphasize the importance of terminating the irradiation before all of the *N*-oxide is consumed. Overirradiation gives rise to a more complicated mixture of products from which the product can no longer be isolated by the simple extraction procedure described.

The progress of the irradiation was determined by the checkers by proton NMR analysis. At appropriate intervals 5-mL aliquots were removed, the solvent was evaporated, and hexamethylbenzene was added as an internal standard. The ratio of *N*-oxide, benzoxazepine, and hexamethylbenzene was determined from integration of the resonances at δ 2.26 (s, 18H), 5.55 (d, 1H, *J* = 6), and 8.46 (d, 1H, *J* = 6), respectively, in chloroform-*d*. After 2.5–3 hr of irradiation the amount of benzoxazepine present was ca. 60–68% of theoretical and ca. 10% of starting *N*-oxide remained.

The submitters followed the course of the irradiation by TLC analysis on silica gel with 5% (v/v) methanol in chloroform as developing solvent. Since some by-products have R_1 values coincident with the *N*-oxide, this spot will not completely disappear and caution must be exercised to avoid overirradiation.

12. This extraction procedure separates most of the carbostyril, that is, 2(1*H*)-quinolinone, which is formed to the extent of ca. 20% in the irradiation. The submitters have isolated the carbostyril by-product by crystallization of the extraction residue from 95% ethanol in runs carried out to high conversion. Alternatively, the carbostyril may be isolated by chromatography of the crude product on silica gel with 5% methanol-chloroform as eluant. However, the benzoxazepine cannot be obtained by this method since it undergoes hydrolysis during the chromatography.

13. The purity of the crude product is about 90% according to NMR analysis, the remaining material being mostly unchanged *N*-oxide.

14. The spectral properties of the product are as follows: IR (liquid film) cm^{-1}: 1665 (C=N), 1630 (C=C), 1480 (sharp), 1440 (sharp), 1035 (strong), 765 (strong); ^{1}H NMR ($CDCl_3$) δ: 5.55 (d, 1 H, *J* = 6, C*H*=CH-O), 5.84 (d, 1 H, *J* = 6, CH=C*H*-O), 6.44 (s, 1 H, O-CH=N), 6.96 (m, 4 H, aromatic protons).

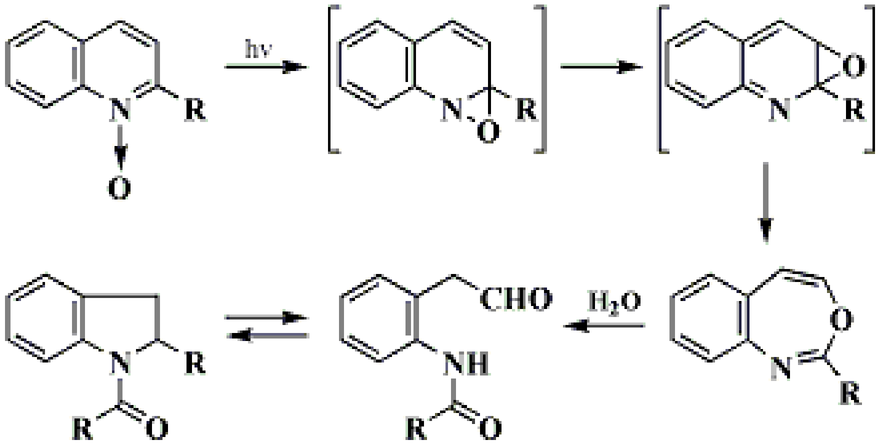
15. Samples of the product stored in tightly stoppered flasks in a freezer at –20° C for several weeks showed no sign of decomposition.

3. Discussion

The preparation of 3,1-benzoxazepines by photochemical isomerization of quinoline *N*-oxides constitutes a rather general entry into this class of seven-membered heterocycles. Since the structure of the photoisomer of 2-phenylquinoline *N*-oxide was first recognized as 2-phenyl-3,1-benzoxazepine by Buchardt et al.,[3] the scope of this method for oxidative ring expansion of six-membered heterocyclic *N*-oxides to 1,3-oxazepines has been extensively explored.[4 5] For example, irradiation of 2-cyano-, 2-phenyl-, and 2-methoxyquinoline *N*-oxides affords the corresponding 2-substituted 3,1-

benzoxazepines in 70–90% yield.[6 7 8 9] However, isolation of the moisture-sensitive parent compound was only recently accomplished in the submitters' laboratories.[10]

Related 1,3-oxazepines have been obtained from irradiation of many other heterocyclic *N*-oxides including pyridine *N*-oxides, isoquinoline *N*-oxides, quinoxaline *N*-oxides, quinazoline *N*-oxides, phenanthridine *N*-oxides, benzophenazine *N*-oxides, and acridine *N*-oxides.[4 5] However, the reported yields are variable and have generally been higher for phenyl and other aryl-substituted derivatives. This procedure is also satisfactory for 1,3-benzoxazepine (from isoquinoline *N*-oxide) and, in general, for oxazepines not substituent-stabilized.



A mechanism involving initial cyclization to an oxaziridine, [1,5] sigmatropic rearrangement to an imino epoxide, and electrocyclic ring opening was originally proposed for the photochemical isomerization.[4 5] However, since later attempts to detect intermediates by flash photolysis were unsuccessful,[11 12] ground-state oxaziridines, if formed at all, must have exceedingly short lifetimes. The benzoxazepines undergo facile hydrolysis to *o*-(*N*-acylamino)phenylacetaldehydes, which frequently exist as the cyclic carbinol amide tautomers. If water is present during the irradiation from use of the *N*-oxide hydrate or moist solvent, the hydrolysis products may be isolated instead of the benzoxazepine. Dehydration of the carbinol amide to *N*-acyl indoles may also occur during irradiation and/or purification of the products. The formation of carbostyrils is sometimes an important competing reaction in the irradiation of quinoline *N*-oxides, and this by-product is, in fact, formed to the extent of ca. 20% in the present procedure. The use of polar protic solvents such as water or alcohols favors carbostyril formation in contrast to aprotic solvents such as benzene or acetone in which the pathway leading to benzoxazepines usually predominates.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

1,3-OXAZEPINES

3,1-benzoxazepines

quinoline N-oxides

pyridine N-oxides

isoquinoline N-oxides

quinoxaline N-oxides

quinazoline N-oxides

phenanthridine N-oxides

benzophenazine N-oxides

acridine N-oxides

carbostyrils

benzoxazepines

ethanol (64-17-5)

Benzene (71-43-2)

methanol (67-56-1)

chloroform (67-66-3)

oxygen (7782-44-7)

nitrogen (7727-37-9)

mercury (7439-97-6)

cyclohexane (110-82-7)

acetone (67-64-1)

toluene (108-88-3)

Hexamethylbenzene (87-85-4)

carbostyril (59-31-4)

calcium hydride (7789-78-8)

quinoline N-oxide (1613-37-2)

isoquinoline N-oxide (1532-72-5)

chloroform-d (865-49-6)

3,1-Benzoxazepine (15123-59-8)

benzoxazepine

2-phenyl-3,1-benzoxazepine

1,3-benzoxazepine

quinoline N-oxide dihydrate

2(1H)-quinolinone

2-phenylquinoline N-oxide

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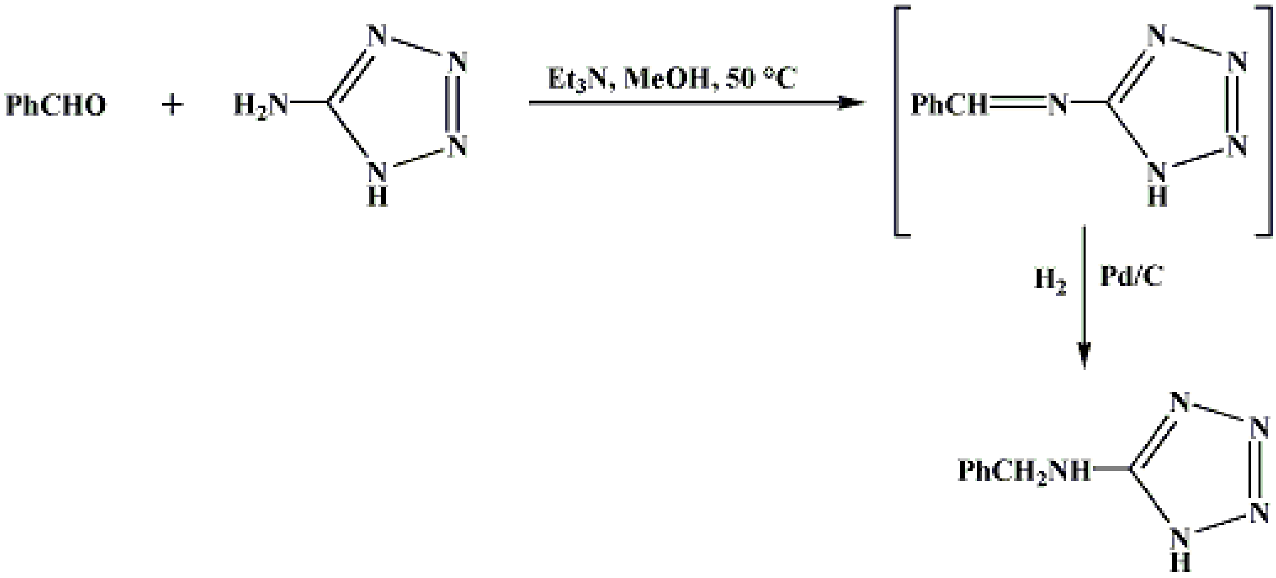
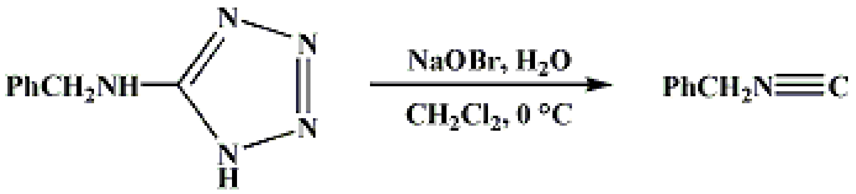
Organic Syntheses, CV 7, 27

OXIDATION OF 5-AMINOTETRAZOLES: BENZYL ISOCYANIDE

[Benzene, isocyanomethyl]





Submitted by Gerhard Höfle and Bernd Lange[1].
Checked by Orville L. Chapman and Thomas C. Hess.

1. Procedure

Caution! This preparation should be conducted in an efficient hood because of the obnoxious odor of the isocyanide.

A. *5-Benzylaminotetrazole*. Freshly distilled benzaldehyde (21.2 g, 0.2 mol) is added in one portion to a warm (50°C) solution of 5-aminotetrazole (17.2 g, 0.2 mol) (Note 1) and triethylamine (20.2 g, 0.2 mol) in 100 mL of absolute methanol. After 15 min the reaction mixture is cooled to room temperature, transferred to an autoclave, and hydrogenated with agitation at room temperature over Pd (10%) on carbon (1 g) for 18 hr at 500 psi (pounds per square inch) of hydrogen. The catalyst is removed by filtration and all volatile material is removed at 60°C under aspirator pressure. The gummy tan solid is triturated with 250 mL of hot water. Aqueous 20% HCl is added until pH 3 is reached. The mixture is cooled to room temperature and the solid collected, washed with water, and dried over-night at room temperature under reduced pressure (100 •); yield: 27.5 g (80%), mp 183.5–185°C (lit.[2] mp 183° C).

B. *Benzyl isocyanide*. In a 500-mL, round-bottomed flask equipped with a magnetic stirring bar and a pressure-equalizing funnel are placed 5-benzylaminotetrazole (10.5 g, 60 mmol), 100 mL of 10% sodium hydroxide solution, and 70 mL of dichloromethane. The mixture is cooled to 0° C and a solution of NaOBr in water (165 mL, 65 mmol) (Note 2) is added with vigorous stirring over a 15-min period (Note 3). The dichloromethane layer is separated and the aqueous phase extracted with five 50-mL portions of dichloromethane. The combined dichloromethane extracts are dried over anhydrous $MgSO_4$, the drying agent is removed by filtration, and the dichloromethane is removed by simple distillation. The pressure is then reduced to 20 mm with an aspirator and benzyl isocyanide is distilled at 98–100°C; yield: 5.91 g (84%) (Note 4) and (Note 5).

2. Notes

1. 5-Aminotetrazole monohydrate is available from Aldrich Chemical Company, Inc.; it was dehydrated by heating over P_2O_5 at 100°C under reduced pressure (100 •) for 4 hr.

2. The NaOBr solution was prepared according to a procedure described in *Organic Syntheses*.[3] Bromine [12.6 g (4 mL, 79 mmol)] was added dropwise with vigorous stirring to 150 mL of a 10% NaOH solution at –10°C. Enough 10% NaOH solution was added to the yellow solution to give 200 mL of reagent.

3. During addition of the NaOBr solution the mixture warms to 20°C. The reaction is virtually instantaneous and can be monitored by the liberated nitrogen.

4. The product was pure by IR and NMR spectroscopy. The IR spectrum showed a very strong band at 2150 cm^{-1}, the NMR spectrum a distorted triplet at δ 4.5 (2 H) and a broad singlet at δ 7.3 (5 H).

5. Glassware can be freed from the odor of isocyanide by rinsing with a 1 : 10 mixture of concentrated hydrochloric acid and methanol.

3. Discussion

By this method high yields of isocyanides are obtained by an oxidation process. Since this oxidation can also be performed anodically or with bromine or lead tetraacetate and triethylamine in the absence of water (see Table I),[4] it represents a valuable alternative to other procedures: dehydration reactions,[5,6,7] the alkylation of silver cyanide[8,9] or the carbylamine (isocyanide) reaction.[10] The starting materials, 5-aminotetrazoles, can be readily obtained by reductive alkylation of 5-aminotetrazole[2] or from monosubstituted thioureas and sodium azide.[11] A limitation of the reaction is that the substituent R must be stable toward oxidation. From a mechanistic point of view the oxidation of 5-aminotetrazoles is a two step process with a pentaazafulvene as an unstable, undetectable intermediate.

TABLE I
PREPARATION OF ISOCYANIDES (R-N=C) BY OXIDATION OF 5-AMINOTETRAZOLES

	Yield (%)

R	NaOBr[a]	$Pb(OAc)_4/NEt_3$[b]	Br_2/Net_3[b]	Anodic Oxidation[a]
C_6H_5	92	70	43	39
C_4H_9	75			
$C_6H_5CH_2$	84			48

[a] In 2*N* sodium hydroxide solution.

[b] In dichloromethane.

Benzyl isocyanide is a useful precursor of compounds containing the α-benzylamino moiety. Substituted styrenes, vinyl isocyanides, 2-oxazolines, 1-pyrrolines, imidazoles, and α-amino acids and ketones can be obtained by metalation of isocyanides with butyllithium[12] or copper salts,[13] and subsequent reaction with various electrophiles.[12]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Pd

hydrochloric acid, HCl (7647-01-0)

methanol (67-56-1)

hydrogen (1333-74-0)

sodium hydroxide, NaOH (1310-73-2)

bromine (7726-95-6)

nitrogen (7727-37-9)

benzaldehyde (100-52-7)

carbon (7782-42-5)

Benzyl isocyanide, Benzene, isocyanomethyl (10340-91-7)

sodium azide (26628-22-8)

dichloromethane (75-09-2)

NaOBr

magnesium sulfate (7487-88-9)

butyllithium (109-72-8)

silver cyanide (506-64-9)

triethylamine (121-44-8)

5-aminotetrazole (4418-61-5)

5-Benzylaminotetrazole (14832-58-7)

5-Aminotetrazole monohydrate

pentaazafulvene

phosphorus pentoxide (1314-56-3)

lead tetraacetate

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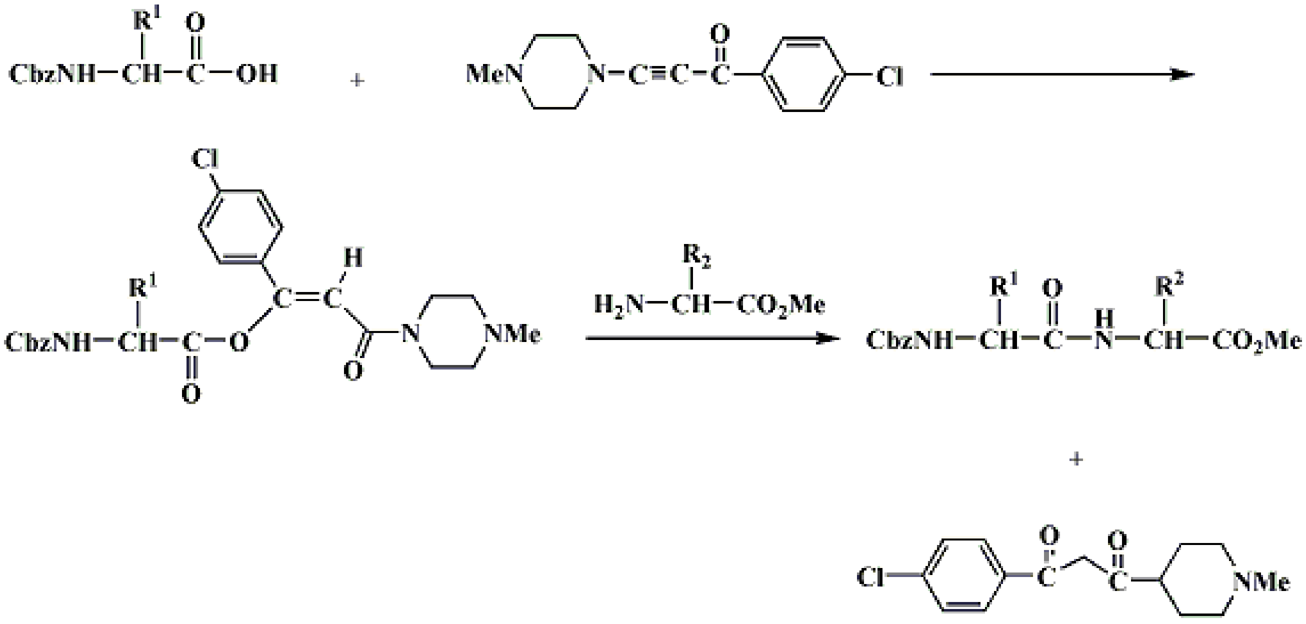
Organic Syntheses, CV 7, 30

PEPTIDE SYNTHESIS USING 1-(4-CHLOROPHENYL)-3-(4'-METHYL-1'-PIPERAZINYL)-2-PROPYN-1-ONE AS REAGENT: BENZYLOXYCARBONYL-L-ALANYL-L-CYSTEINE METHYL ESTER AND BENZYLOXYCARBONYL-L-ASPARTYL-(*tert*-BUTYL ESTER)-L-PHENYLALANYL-L-VALINE METHYL ESTER



Submitted by H. P. Fahrni, U. Lienhard, and M. Neuenschwander[1].
Checked by David R. Bolin and Gabriel Saucy.

1. Procedure

A. *Benzyloxycarbonyl-L-alanyl-L-cysteine methyl ester*. A round-bottomed, three-necked, 100-mL flask is equipped with a magnetic stirring bar, 10-mL dropping funnel, thermometer, and nitrogen bubbler (Note 1). The apparatus is flushed with dry nitrogen and then charged with 446.5 mg (0.002 mol) of benzyloxycarbonyl-L-alanine in 10 mL of dry dichloromethane. The mixture is stirred until solution is complete and then cooled to 0°C. Within 20 min a solution of 525.5 mg (0.002 mol) of 1-(4-chlorophenyl)-3-(4'-methyl-1'-piperazinyl)-2-propyn-1-one (Note 2) in 5 mL of dry dichloromethane is added. Stirring is continued for 1 hr at 0°C and for an additional hour at room temperature (t_1). The mixture is cooled again to 0°C and a suspension of 343.3 mg (0.002 mol) of L-cysteine methyl ester hydrochloride is quickly added, followed by a solution of 202.3 mg (0.002 mol) of *N*-methylmorpholine in 5 mL of dry dichloromethane. While the nitrogen atmosphere is maintained, the mixture is allowed to warm up and is stirred for 12 hr (t_2) at room temperature. The solvent is removed by rotary evaporation, and the residue is shaken intensively with 30 mL of ethyl acetate and 10 mL of water. The organic layer is extracted two times with 10-mL portions of aqueous 10% citric acid and once with 5 mL of 1 *N* sodium hydrogen carbonate. The organic phase is dried over sodium sulfate. The solvent is removed by rotary evaporation to leave 647 mg (95%) of the crude pale-yellow dipeptide. Recrystallization from ethyl acetate provides 551 mg (81%) of colorless crystals of benzyloxycarbonyl-L-alanyl-L-cysteine methyl ester, mp 115–117°C; $[\alpha]_D^{20}$ – 26.4° (CH_3OH, *c* 1.29) (Note 3).

B. *Benzyloxycarbonyl-L-aspartyl-(tert-butyl ester)-L-phenylalanyl-L-valine methyl ester*. A round-bottomed, three-necked, 100-mL flask is equipped with a 10-mL dropping funnel, thermometer, magnetic stirring bar, and a nitrogen bubbler. The flask is flushed with dry nitrogen and then charged with a solution

of 941.1 mg (0.002 mol) of benzyloxycarbonyl-L-aspartyl-(*tert*-butyl ester)-L-phenylalanine (Note 4) in 10 mL of dry dichloromethane. The flask is maintained under a dry nitrogen atmosphere and cooled to 0°C with an ice–salt bath. The mixture is stirred and a solution of 525.5 mg (0.002 mol) of 1-(4-chlorophenyl)-3-(4'-methyl-1'-piperazinyl)-2-propyn-1-one (Note 2) in 5 mL of dry dichloromethane is added during a period of 20 min. Stirring is continued for 1 hr at 0°C and for 5 hr at room temperature (t_1). The mixture is again cooled to 0°C and a suspension of 335.3 mg (0.002 mol) of L-valine methyl ester hydrochloride and 202.3 mg (0.002 mol) of *N*-methylmorpholine in 5 mL of dichloromethane is added. After 30 min the reaction mixture is allowed to warm up and is stirred overnight (18 hr; t_2) at room temperature. The solvent is removed by rotary evaporation and the residue is shaken intensively with 40 mL of ethyl acetate and 10 mL of water. The organic layer is extracted twice with 10-mL portions of aqueous 10% citric acid and once with 5 mL of 1 *N* sodium hydrogen carbonate.

The organic phase is dried over sodium sulfate, and solvent is removed by rotary evaporation to leave 1132 mg (97%) of the crude pale-yellow tripeptide. For further purification the crude product is dissolved in ethyl acetate, treated with some activated carbon, and filtered through Celite. Removal of the solvent and crystallization from ethyl acetate/ether/petroleum ether (ca. 2 : 1 : 1) yields 993 mg (85%) of colorless crystals of benzyloxycarbonyl-L-aspartyl-(*tert*-butyl ester)-L-phenylalanyl-L-valine methyl ester; mp 119–120°C (Note 5).

2. Notes

1. Cysteine derivatives are oxidized to cystine by oxygen. The nitrogen atmosphere for preparation of Cbz-alanylcysteine methyl ester is therefore indispensable and is recommended for other cases as well.
2. This reagent is available from Fluka Chemical Corp.
3. The literature[2] value is $[\alpha]_D^{20}$ − 26.5° (CH_3OH, *c* 1.27). The reported[2] mp is 116.5–118°C.
4. Benzyloxycarbonyl-L-aspartyl-(*tert*-butyl ester)-L-phenylalanine dicyclohexylamine salt was conveniently prepared by standard procedures.[3] The salt was dissolved in ethyl acetate and extracted three times with aqueous 10% citric acid, and once with water. The organic phase was dried and solvent was removed to leave the dipeptide as an oil.
5. The product has the following physical properties: Specific rotation: $[\alpha]_D^{20}$ − 36.5° (C_2H_5OH, *c* 2); IR (KBr), cm^{-1}: 3285, 1732, 1691, 1640, 1531, 1367, 1229, 1158, 1050, 746, 701; ^1H NMR (100 MHz, $CDCl_3$) δ: 0.81 (d, 3 H, *J* = 7) 0.84 (d, 3 H, *J* = 7), 1.41 (s, 9 H), 1.8–2.3 (m, 2 H), 2.62 (d of d, 1 H, *J* = 17, *J'* = 6), 2.86 (d of d, 1 H, *J* = 17, *J'* = 5), 3.08 (d, 1 H, *J* = 8), 3.71 (s, 3 H), 4.3–4.8 (m, in total 3 H), 5.11 (s, 2 H), 5.78 (d, 1 H, *J* = 8), 6.28 (d, 1 H, *J* = 8), 7.02 (d, 1 H, *J* = 8), 7.21 (s, 5 H), 7.57 (s, 5 H).

3. Discussion

This procedure illustrates the use of 1-(4-chlorophenyl)-3-(4'-methyl-1'-piperazinyl)-2-propyn-1-one[4 5] as a reagent for peptide synthesis.[6] The same method also gives amides in excellent yields.[7]

The preparation of Cbz-L-alanylcysteine methyl ester shows the advantage of using, as the amine component, an amino acid with an unprotected sulfhydryl moiety. No problems were encountered with the use of amino acid derivatives with unprotected hydroxyl or sulfhydryl groups as either the amine[6] or carboxyl component.[8] This procedure is based on the pronounced selective reactivity of the enol ester, which is generated by the addition of carboxylic acids to "push–pull acetylenes." Generally, the yields of peptides are good and a broad variety of solvents (e.g., dichloromethane, tetrahydrofuran, acetonitrile, dimethylformamide) may be used, depending on the solubility of the coupling components. It is also possible to change the solvent after the activation step or to isolate the activated components. Normally, however, this is neither necessary nor recommended. Purification of the reaction mixture is simple, since the piperazine by-product is conveniently extracted with an acidic water phase.

The following peptides and further examples have been prepared[6] by the following procedure.

Peptide	t_1^a	t_2^b	Yield (%)[c]
Cbz-L-Ala-Gly-OMe	2[d]	12	91
Cbz-L-Ala-L-Val-OMe	2[d]	24	84
Cbz-L-Ala-L-Phe-OMe	2[d]	18	88
Cbz-Gly-L-Phe-Gly-OEt	2	12	90
Cbz-L-Asp(O-*t*-Bu)-L-Phe-L-Val-OMe	6	18	85
Cbz-L-Ile-L-Ile-OBzl	18	24	75
Cbz-L-Ala-L-Ser-OMe	2[d]	72	90
Cbz-L-Ala-L-Tyr-OMe	2[d]	72	91
Cbz-L-Ala-L-Cys-OMe	2[d]	12	81
Cbz-L-Ala-L-Met-OMe	2[d]	15	85
Cbz-L-Ser-Gly-OEt	2	24	81

[a] t_1: time for activation of the carboxylic component (see procedures).

[b] t_2: time for coupling (see procedures).

[c] Yield of pure recrystallized product.

[d] Stirring 1 hr at 0°C, then 1 hr at 20°C.

During our experiments no side reactions were detected. This is in contrast to peptide synthesis with isoxazolium salts,[9] [10] where some side reactions, one leading to a diacyl amino compound, were observed.[11] In most cases, these side reactions are due to a secondary amino group in the reagent which is impossible in the case of push–pull acetylenes.

Compared with ynamines, which have also been applied to peptide synthesis,[12] push–pull acetylenes are much more selective. They do not show the side reactions observed with ynamines,[13] and the yields are not markedly influenced by the sequence of addition of compounds in the activation step or by excess of acetylene reagent.

A crucial point in peptide synthesis is racemization of the activated amino acid. Three different tests were made to evaluate the degree of racemization. Using the Anderson test peptide[14] Cbz-Gly-Phe-Gly-OEt, no racemization could be detected when the peptide was prepared in dichloromethane, acetonitrile, or tetrahydrofuran. This means racemization is below the detection limit of 1%. Benzylleucylglycine ethyl ester is used in the very sensitive Young test.[15] In this test, designed to exaggerate racemization, we found 5% of racemate, when the solvent was dichloromethane. In the more polar solvent, dimethylformamide, this value rose to 12%. Therefore, racemization is in the same range as that observed for the racemization-resistant azide procedure. The coupling of Cbz-L-aspartyl(O-*t*-Bu)-L-phenylalanine with valine methyl ester is reported to be very sensitive to racemization.[16] The tripeptide was prepared as described above, and the crude product was hydrolyzed. Gas-layer chromatography (GLC) showed the presence of 2-3% D-phenylalanine. Again, in contrast to the ynamine procedure,[17] racemization seems to be no problem when push–pull acetylenes are used.

So far, the only observable disadvantage of the reagent is the somewhat long reaction time for the coupling

of the activated amino acids (or peptides) with the amine component. The increase in reaction time t_2 could be a limiting factor, if longer peptide fragments are to be linked.

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

Benzyloxycarbonyl-L-aspartyl-(tert-butyl ester)-L-phenylalanyl-L-valine methyl ester

benzyloxycarbonyl-L-aspartyl-(tert-butyl ester)-L-phenylalanine

Benzyloxycarbonyl-L-aspartyl-(tert-butyl ester)-L-phenylalanine dicyclohexylamine salt

Cbz-L-Ala-Gly-OMe

Cbz-L-Ala-L-Val-OMe

Cbz-L-Ala-L-Phe-OMe

Cbz-Gly-L-Phe-Gly-OEt

Cbz-L-Asp(O-t-Bu)-L-Phe-L-Val-OMe

Cbz-L-Ile-L-Ile-OBzl

Cbz-L-Ala-L-Ser-OMe

Cbz-L-Ala-L-Tyr-OMe

Cbz-L-Ala-L-Cys-OMe

Cbz-L-Ala-L-Met-OMe

Cbz-L-Ser-Gly-OEt

Cbz-Gly-Phe-Gly-OEt

Cbz-L-aspartyl(O-t-Bu)-L-phenylalanine

acetylene (74-86-2)

ethyl acetate (141-78-6)

ether (60-29-7)

acetonitrile (75-05-8)

citric acid (77-92-9)

sodium hydrogen carbonate (144-55-8)

L-alanine (56-41-7)

sodium sulfate (7757-82-6)

oxygen (7782-44-7)

nitrogen (7727-37-9)

carbon (7782-42-5)

cystine (56-89-3)

dichloromethane (75-09-2)

Tetrahydrofuran (109-99-9)

dimethylformamide (68-12-2)

benzyloxycarbonyl

piperazine (110-85-0)

VALINE METHYL ESTER

cysteine methyl ester hydrochloride (18598-63-5)

L-valine methyl ester hydrochloride (5619-05-6)

Cbz-alanylcysteine methyl ester, Cbz-L-alanylcysteine methyl ester, Benzyloxycarbonyl-L-alanyl-L-cysteine methyl ester

Benzylleucylglycine ethyl ester

N-methylmorpholine (109-02-4)

1-(4-CHLOROPHENYL)-3-(4'-METHYL-1'-PIPERAZINYL)-2-PROPYN-1-ONE

D-phenylalanine

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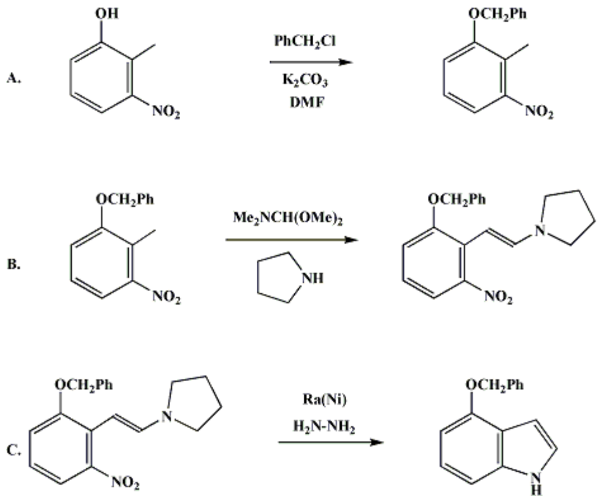
Organic Syntheses, CV 7, 34

INDOLES FROM 2-METHYLNITROBENZENES BY CONDENSATION WITH FORMAMIDE ACETALS FOLLOWED BY REDUCTION: 4-BENZYLOXYINDOLE

[1*H*-Indole, 4-(phenylmethoxy)-]



Submitted by Andrew D. Batcho[1] and Willy Leimgruber[2].
Checked by David J. Wustrow and Andrew S. Kende.

1. Procedure

A. *6-Benzyloxy-2-nitrotoluene*. A stirred mixture of 124.7 g (0.81 mol) of 2-methyl-3-nitrophenol (Note 1), 113.2 g (0.90 mol) of benzyl chloride, 112.2 g (0.81 mol) of anhydrous potassium carbonate, and 800 mL of dimethylformamide (DMF) is heated at 90°C for 3 hr. Most of the DMF is removed on a rotary evaporator (20 mm) and the oily residue is poured into 400 mL of 1 *N* sodium hydroxide and extracted with ether (3 × 800 mL). The combined extracts are dried (Na_2SO_4), filtered, and evaporated to give 203.5 g of yellowish solid. Recrystallization from 1 L of methanol cooled to 0°C affords 177.6 (90%) of 6-benzyloxy-2-nitrotoluene as pale-yellow crystals, mp 61–63°C[3] (Note 2).

B. *(E)-6-Benzyloxy-2-nitro-β-pyrrolidinostyrene*. To a solution of 175.4 g (0.72 mol) of 6-benzyloxy-2-nitrotoluene in 400 mL of DMF are added 102.5 g (0.84 mol) of *N,N*-dimethylformamide dimethyl acetal (Note 3) and 59.8 g (0.84 mol) of pyrrolidine. The solution is heated at reflux (110°C) for 3 hr (Note 4) under nitrogen and allowed to cool to room temperature. The volatile components are removed on a rotary evaporator, and the red residue (Note 5) is dissolved in 200 mL of methylene chloride and 1.60 L of methanol. The solution is concentrated to a volume of about 1.40 L on the steam bath and then is cooled to 5°C. Filtration and washing of the filtercake with 200 mL of cold methanol affords 209.8 g of red crystals, mp 87–89°C (Note 6). The mother liquors are evaporated, and the residue is recrystallized from 50 mL of methanol (5°C) to give an additional 12.30 g of red solid, mp 81–83°C (Note 7). Thus the total yield is 222.1 g (95%) of a 15 : 1 mixture of (*E*)-6-benzyloxy-2-nitro-β-pyrrolidinostyrene (Note 8) and (*E*)-6-benzyloxy-β-dimethylamino-2-nitrostyrene.

C. *4-Benzyloxyindole*. To a stirred solution of 162.2 g (0.50 mol) of (*E*)-6-benzyloxy-2-nitro-β-pyrrolidinostyrene (Note 9) in 1 L of THF and 1 L of methanol at 30°C under nitrogen is added 10 mL of Raney nickel (Note 10) followed by 44 mL (0.75 mol) of 85% hydrazine hydrate. Vigorous gas evolution is observed. The red color turns to dark brown within 10 min, and the reaction temperature rises to 46°C. An additional 44 mL of 85% hydrazine hydrate is added after 30 min and again 1 hr later. The temperature is maintained between 45 and 50°C with a water bath during the reaction and for 2 hr after the last addition. The mixture is cooled to room temperature and the catalyst is removed by filtration through a bed of Celite (Note 11) and is washed several times with methylene chloride. The filtrate is evaporated and the residue dried by evaporating with 500 mL of toluene. The reddish residue (118.5 g), dissolved in ca. 1 L of toluene-cyclohexane (1 : 1), is applied to a column of 500 g of silica gel (70–230-mesh, Merck) prepared in the same solvent. Elution with 6.0 L of toluene–cyclohexane (1 : 1) followed by 3 L of toluene–cyclohexane (1 : 2) affords 108.3 g of white solid, which is crystallized from 150 mL of toluene and 480 mL of cyclohexane (Note 12). A total of 107.3 g (96% yield) of 4-benzyloxyindole (Note 13) is obtained in three crops as white prisms, mp 60–62°C (Note 14).

2. Notes

1. 2-Methyl-3-nitrophenol was obtained from Aldrich Chemical Company, Inc.
2. The ^1H NMR spectrum is as follows δ: 2.42 (s, 3 H), 5.10 (s, 2 H), 7.13 (m, 3 H), 7.35 (m, 5 H).
3. *N,N*-Dimethylformamide dimethyl acetal was prepared according to a procedure of Bredereck.[4] *N,N*-Dimethylformamide diethyl acetal can also be used. Both the dimethyl and the diethyl acetal are commercially available from Aldrich Chemical Company, Inc.
4. The reaction was followed by TLC on silica gel plates developed with ether–petroleum ether (1 : 1).
5. Since it contained *non*volatile *N*-formylpyrrolidine, direct reduction of the crude material was not attempted.
6. This crop contained 5% 6-benzyloxy-β-dimethylamino-2-nitrostyrene (by NMR). Pure 6-benzyloxy-2-nitro-β-pyrrolidinostyrene melts at 91.5–92.5°C.
7. This crop contained 15% 6-benzyloxy-β-dimethylamino-2-nitrostyrene (by NMR).
8. The ^1H NMR spectrum is as follows: δ: 1.8 (m, 4 H), 3.08 (m, 4 H), 5.03 (5, 2 H), 5.20 (d, 1 H, J = 12.2), 6.91 (dd, 2 H, J = 9), 7.25 (m, 6 H), 7.75 (d, 1 H, J = 12.2).
9. This compound may contain varying amounts of 6-benzyloxy-β-dimethylamino-2-nitrostyrene.
10. Raney nickel is commercially available as type #28 from the Davison Chemical Division of W. R. Grace and Co.
11. The catalyst is pyrophoric and should not be sucked dry.
12. The material tenaciously holds hydrocarbons, such as pentane, hexane, and petroleum ether, which cannot be removed even under high vacuum. The solvated crystals show hydrocarbon protons in NMR and exhibit a broad melting point. However, we found that cyclohexane is not retained in the crystals.
13. The ^1H NMR spectrum is as follows: δ: 6.65 (m, 2 H), 6.95 (m, 3 H), 7.9 (br s, 1 H), 7.32 (m, 5 H).
14. We could not reproduce the reported[5] melting point of 72–74°C (toluene). The material has the proper microanalysis and is pure by NMR and thin-layer chromatography (TLC).

3. Discussion

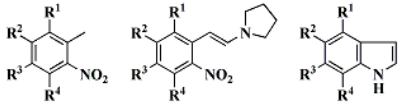
Through the years, widespread interest in the synthesis of natural products and their analogs bearing the oxygenated indole nucleus has led to the development of several routes to protected hydroxylated indoles. However, 4-benzyloxyindole was first prepared relatively recently in modest overall yield by the Reissert method, which involves condensation of 6-benzyloxy-2-nitrotoluene with ethyl oxalate, reductive cyclization to the indole-2-carboxylate, hydrolysis to the acid, and decarboxylation.[5]

Although a variety of synthetic methods have been used to prepare indoles,[6,7] many of these lack generality and are somewhat restrictive since they employ conditions, such as acid or strongly basic cyclizations or thermal decarboxylations, which are too harsh for labile substituents. This efficient, two-step procedure[8,9] illustrates a general, simple, and convenient process for preparing a variety of indoles substituted in the carbocyclic ring, as can be seen in Table I. Since many of these examples served to determine the scope of this method, the yields in most cases have not been optimized. In many cases, the starting materials are readily available or can be easily prepared.

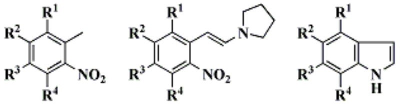
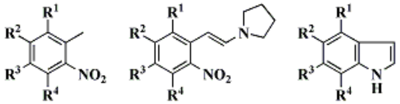
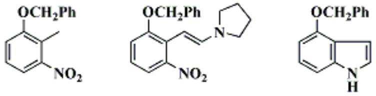
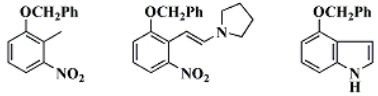
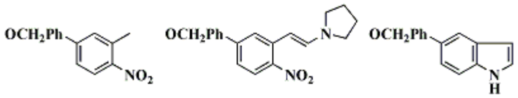
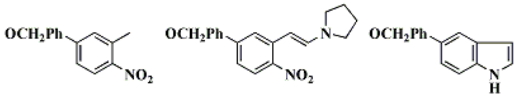
As can be seen in Table I, variation of the substituent has a profound effect on the rate of reaction of the *o*-nitrotoluene derivative with dimethylformamide acetals but has little effect on the yields, which are often almost quantitative. As can be predicted, electron-withdrawing groups accelerate the reaction. To shorten the somewhat lengthy reaction times that are often necessary when electron-donating substituents are present, more reactive aminomethylenating reagents such as pyrrolidine (or piperidine) acetals,[8] aminals,[10] or trisaminomethanes[11] can be employed. Alternatively, as described above, simply adding pyrrolidine to the reaction mixture also generates in situ a very effective aminomethylenating reagent.[12,13] Thus, for example, in the case of 6-benzyloxy-2-nitrotoluene, the reaction with *N*,*N*-dimethylformamide dimethyl acetal requires 51 hr versus 3 hr when pyrrolidine is added. Pyrrolidine undergoes exchange reactions with *N*,*N*-dimethylformamide acetals to produce an equilibrium mixture of formylpyrrolidine acetal and the mixed pyrrolidine dimethylamine aminal (alkoxydimethylaminopyrrolidinomethane) as well as other trisaminomethane species.[14] (In cases where pyrrolidine reacts with the aromatic substrate, addition of the substrate can be delayed until pyrrolidine exchange is complete.) This mixture of reagents gives rise to condensation products—pyrrolidine enamines—that contain 5–10% of the corresponding *N*,*N*-dimethylenamines.

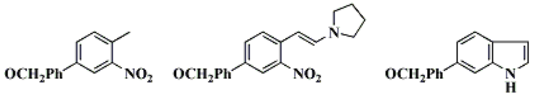
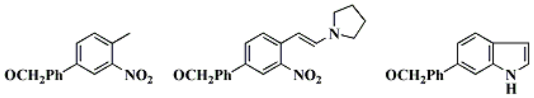
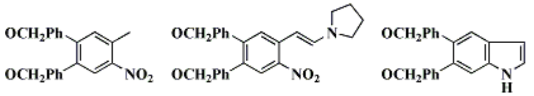
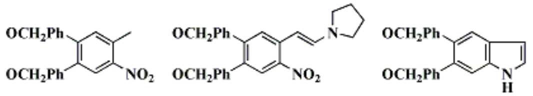
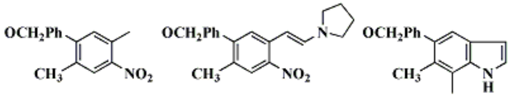
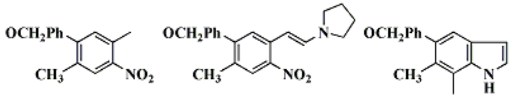
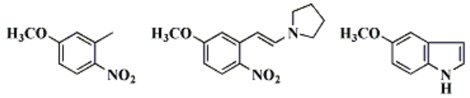
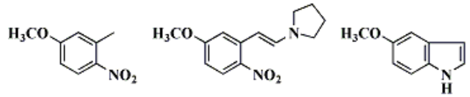
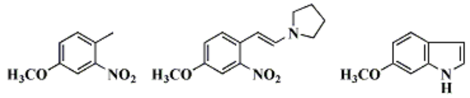
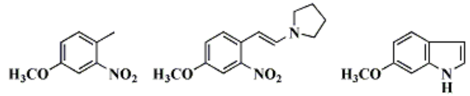
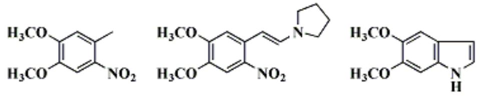
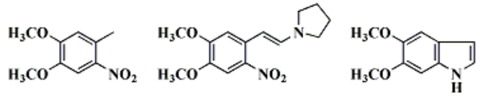
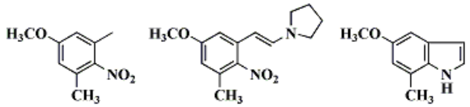
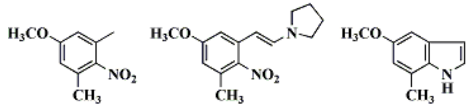
TABLE I

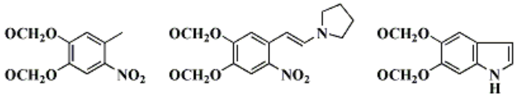
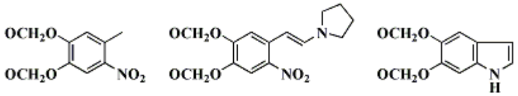
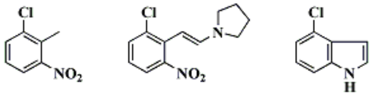
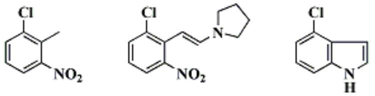
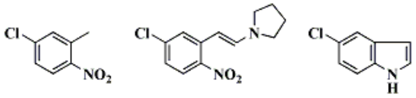
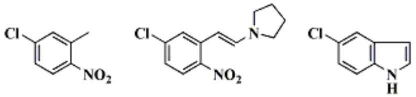
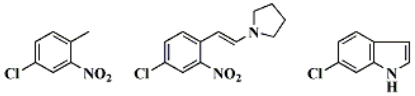
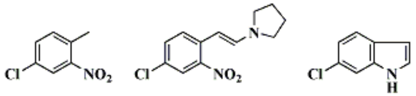
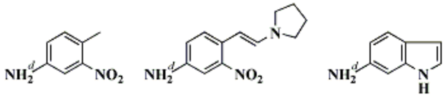
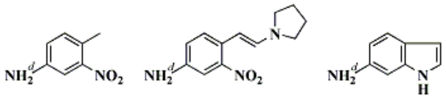
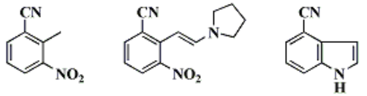
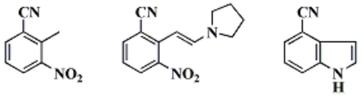
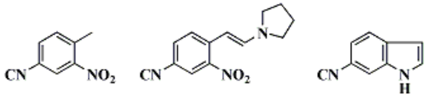
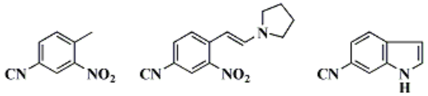
INDOLES FROM 2-METHYLNITROBENZENES BY CONDENSATION WITH *N*,*N*-DIMETHYLFORMAMIDE ACETALS AND REDUCTION

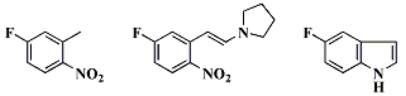
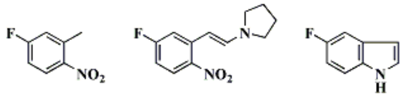
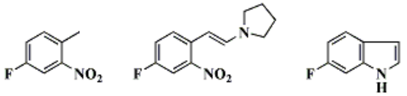
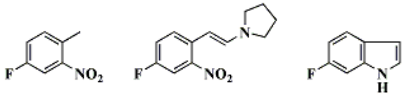
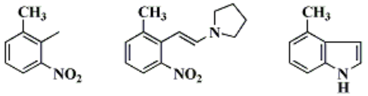
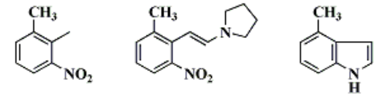
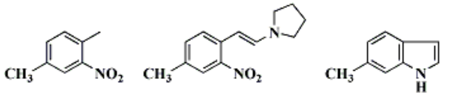
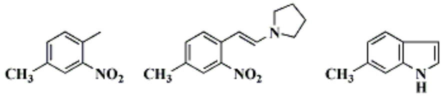
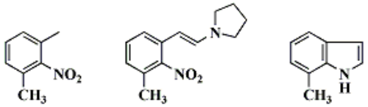
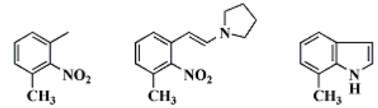
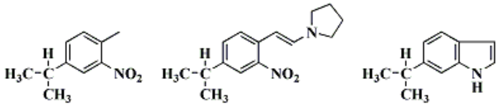
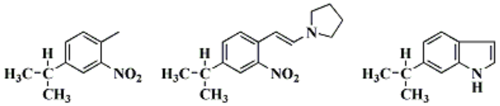
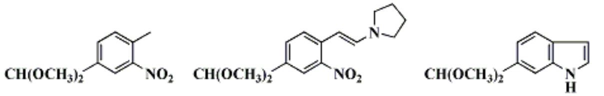
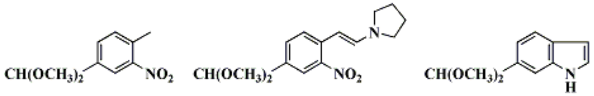


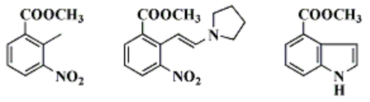
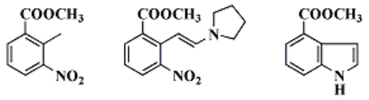
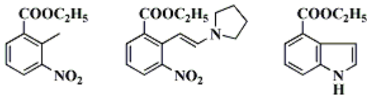
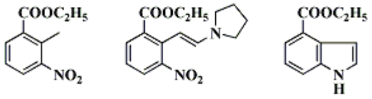
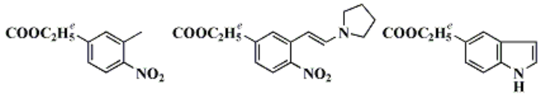
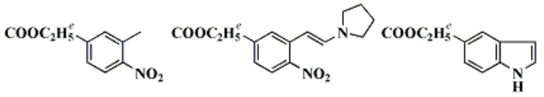
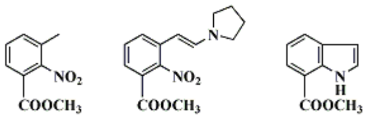
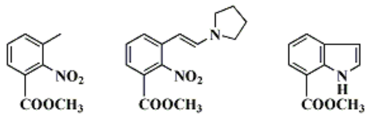
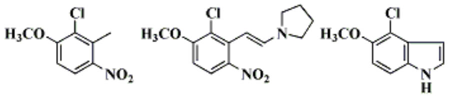
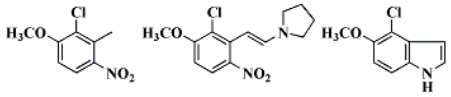
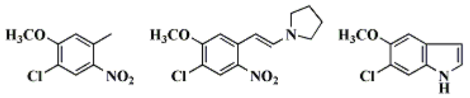
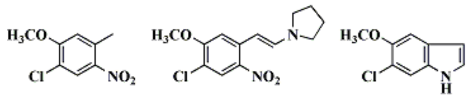
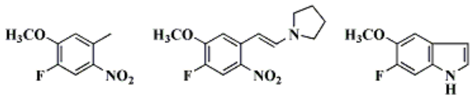
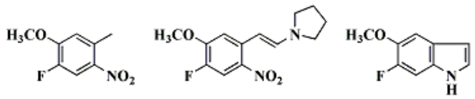
1 2 3

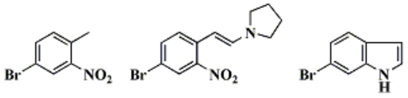
Substituents									
R1	R2	R3	R4	Intermediates **2** (mp or bp/mm)	Reaction Time	Purified Yield (%) (Procedure) [a]	Indoles **3** (mp or bp/mm)	Yield (%) (Procedure) [b]	Refs.
—	—	—	—	 1 2 3 125°/0.03	22 hr	97(M,E)	 1 2 3 52.5–53.5°	80(A)	8, 9
OCH_2Ph	—	—	—	 1 2 3 67–68°	51 hr	90(M)	 1 2 3 60–62°	70(B)	12
—	OCH_2Ph	—	—	 1 2 3 98–99°	29 hr	78(E)	 1 2 3 103–105°	45(B)[64][c]	8, 9, 12

—	—	OCH_2Ph	—	 1 2 3 108.5–110°	41 hr	97(M)	 1 2 3 118–120°	75(B)[i]	12
—	OCH_2Ph	OCH_2Ph	—	 1 2 3 99.5–101°	48 hr	86(M)	 1 2 3 112–113°	54(B)[j]	8, 9
—	OCH_2Ph	CH_3	—	 1 2 3 113–134°	31 hr	87(M)	 1 2 3 82–83°	84(B)	12
—	OCH_3	—	—	 1 2 3 68.5–70°	16 hr	92(M)	 1 2 3 56.5–57.5°	83(A)	8, 9
—	—	OCH_3	—	 1 2 3 152°/0.06	70 hr	64(E)	 1 2 3 88–90°	63(A)[62][c]	8, 9, 12
—	OCH_3	OCH_3	—	 1 2 3 125–126°	48 hr	68(M)	 1 2 3 154–155°	28(A)	8, 9
—	OCH_3	—	CH_3	 1 2 3 100–101°	8 hr	54(M)	 1 2 3 100–110°/0.15	66(A)	15

—	OCH_2O		—	 1 2 3 114–116°	18 hr	72(E)	 1 2 3 110–111°	50(A)[52][c]	8, 9, 12
Cl	—	—	—	 1 2 3 111°/0.03	6 hr	89(E)	 1 2 3 90°/0.04	63(B)	8, 9
—	Cl	—	—	 1 2 3 81.5–82.5°	7 hr	88(E)	 1 2 3 71–72°	78(B)	8, 9
—	—	Cl	—	 1 2 3 44–46°	24 hr	57(M)	 1 2 3 86.5–88°	52(B)[75][c]	8, 9, 12
—	—	NH_2[d]	—	 1 2 3 173–174°	2 hr	82(E)[f]	 1 2 3 77.5–78.5°	43(A)	8, 9, 12
CN	—	—	—	 1 2 3 66–68°	3 hr	93(M)	 1 2 3 116–117°	67(C)	22
—	—	CN	—	 1 2 3 134–137.5°	2.5 hr	86(E)	 1 2 3 128–129°	65(A)	8, 9

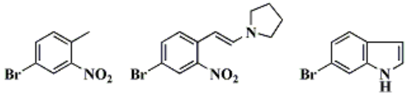
—	F	—	—	 1 2 3 57.5–59°	3.5 hr	92(E)	 1 2 3 46.5–47°	51(B)	8, 9
—	—	F	—	 1 2 3 46–47°	22 hr	63(M)	 1 2 3 74–75°	80(B)[80][c]	8, 12
CH_3	—	—	—	 1 2 3 108°/0.05	24 hr	70(E)	 1 2 3 82°/0.4	57(A)	8, 9
—	—	CH_3	—	 1 2 3 41.5–43.5°	37 hr	83(M)	 1 2 3 29–30.5°	83(A)	16
—	—	—	CH_3	 1 2 3 76–76.5	46 hr	40(E)	 1 2 3 83–84°	48(A)	8, 9
—	—	CH $(CH_3)_2$	—	 1 2 3 138–140°/0.06	42 hr	84(E)	 1 2 3 40–41°	51(A)	8, 9
—	—	CH $(OCH_3)_2$	—	 1 2 3 67–68°	8 hr	55(E)	 1 2 3 62–63.5°	31(A)	8, 9

$COOCH_3$	—	—	—	 1 2 3 120–130°/0.2	6 hr	86(M)	 1 2 3 63°	82(A)[63][c]	22, 17
$COOC_2H_5$	—	—	—	 1 2 3 (Oil)	5 days	93(E)	 1 2 3 67–69°	38(D)	22
—	$COOC_2H_5$[e]	—	—	 1 2 3 55–56.5°	4.5 hr	70(E)	 1 2 3 95–96°	39(A)	8, 9
—	—	—	$COOCH_3$	 1 2 3 132–134°	9 hr	88(M)	 1 2 3 46–48°	72(A)[g]	12
Cl	OCH_3	—	—	 1 2 3 —	Overnight	—(M)	 1 2 3 109–111°	(B)[59][c]	18
—	OCH_3	Cl	—	 1 2 3 140–141°	Overnight	78(M)	 1 2 3 126–128°	46(B)[45][c]	18
—	OCH_3	F	—	 1 2 3 116–117°	Overnight	64(M)	 1 2 3 73–74°	54(B)	18

— — Br 

1 2 3

—

— 31 hr —(M)  37(B)[h] 19

1 2 3

93°

[a](M) = N,N-Dimethylformamide dimethyl acetal; (E) = N,N-dimethylformamide diethyl acetal.

[b]A = Catalytic hydrogenation in benzene using palladium on charcoal; B = catalytic hydrogenation in benzene using Raney nickel; C = iron in acetic acid; D = stannous chloride.

[c]Yield in brackets represents overall yield without purification of intermediate 2.

[d]$R^3 = NO_2$ in compounds 1 and 2.

[e]R^2 = COOH in compound 1.

[f]No solvent was used.

[g]Methanol was the solvent.

[h]Ethanol was the solvent.

[i](M) + pyrrolidine gave a mixture (10 : 1) of pyrrolidine enamine, mp 108–110° (MeOH), and *N,N*-dimethylenamine (5 hr reflux, 97% yield), which, on reduction (Raney nickel–hydrazine), gave the indole (93% yield).

[j](M) + pyrrolidine gave a mixture (9 : 1) of pyrrolidine enamine and *N,N*-dimethylenamine (5 hr reflux, 95% yield), which, on reduction (Raney nickel–hydrazine), gave the indole (89% yield).

The enamine intermediates are usually crystalline, red compounds that can be stored at room temperature for reasonable periods. In cases where the enamines are noncrystalline, it is recommended that the crude product be used directly in the next step, since purification is, in such cases, not practical. Although the more volatile derivatives can be distilled under high vacuum, this entails some risk because of their thermal instability. Moreover, the enamines are not stable to silica gel (TLC or column) chromatography.

Conversion of the intermediate nitroenamine into the indole requires selective reduction of the nitro group. Catalytic hydrogenation results in spontaneous formation of the indole and is generally the mildest and most convenient method of reduction. Although selectivity does vary with the substituent on the aromatic ring, it is generally highly in favor of the nitro group. However, scale-up requires access to large autoclaves or special equipment. To avoid hydrogenolysis of benzyl or chloro functions, Raney nickel is the catalyst of choice. Excellent yields have been obtained using hydrazine and the appropriate catalyst[20] as, in essence, a hydrogenation process which does not require an autoclave or special equipment and can be easily carried out in the laboratory.

Alternative methods of reduction have also been used: sodium dithionite,[21] iron in acetic acid,[22] stannous chloride,[22] and titanium trichloride.[23]

This method has been applied to the preparation of polycyclic indoles[12,24] and azaindoles[24,25,26] as well.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

2-METHYLNITROBENZENES

toluene-cyclohexane

dimethylformamide acetals

pyrrolidine enamines

N,N-dimethylenamines

N,N-dimethylenamine

ethanol (64-17-5)

potassium carbonate (584-08-7)

acetic acid (64-19-7)

Benzene (71-43-2)

methanol (67-56-1)

ether (60-29-7)

sodium hydroxide (1310-73-2)

iron (7439-89-6)

Na_2SO_4 (7757-82-6)

nitrogen (7727-37-9)

sodium dithionite (7775-14-6)

stannous chloride

cyclohexane (110-82-7)

Raney nickel (7440-02-0)

toluene (108-88-3)

palladium (7440-05-3)

benzyl chloride (100-44-7)

hydrazine hydrate (7803-57-8)

Ethyl oxalate

Pentane (109-66-0)

hydrazine (302-01-2)

methylene chloride (75-09-2)

dimethylenamine (9002-98-6)

dimethylamine (124-40-3)

THF (109-99-9)

N,N-dimethylformamide, dimethylformamide, DMF (68-12-2)

pyrrolidine (123-75-1)

hexane (110-54-3)

pyrrolidine enamine

N,N-Dimethylformamide diethyl acetal (1188-33-6)

titanium trichloride (7705-07-9)

4-Benzyloxyindole, 1H-Indole, 4-(phenylmethoxy)- (20289-26-3)

2-methyl-3-nitrophenol (5460-31-1)

6-Benzyloxy-2-nitrotoluene (20876-37-3)

6-benzyloxy-β-dimethylamino-2-nitrostyrene

6-benzyloxy-2-nitro-β-pyrrolidinostyrene

indole-2-carboxylate

formylpyrrolidine acetal

trisaminomethane

N,N-dimethylformamide dimethyl acetal (4637-24-5)

(E)-6-Benzyloxy-2-nitro-β-pyrrolidinostyrene (99474-12-1)

(E)-6-benzyloxy-β-dimethylamino-2-nitrostyrene

N-formylpyrrolidine (3760-54-1)

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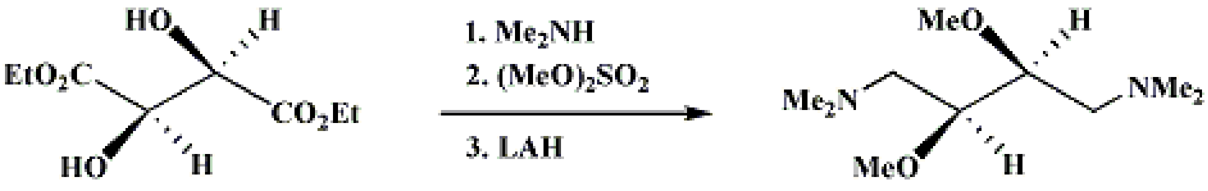
CHIRAL MEDIA FOR ASYMMETRIC SOLVENT INDUCTIONS. (*S,S*)-(+)-1,4-BIS(DIMETHYLAMINO)-2,3-DIMETHOXYBUTANE FROM (*R,R*)-(+)-DIETHYL TARTRATE

[1,4-Butanediamine, 2,3-dimethoxy-*N,N,N',N'*-tetramethyl-[*S,S*]-]



(+) - (*R, R*) (+) - (*S, S*) "DDB"

Submitted by Dieter Seebach, Hans-Otto Kalinowski, Werner Langer, Gerhard Crass, and Eva-Maria Wilka[1].
Checked by M. F. Semmelhack and Diane Facciolo.

1. Procedure

Caution! Because of the high toxicity and carcinogenicity of dimethyl sulfate (Step B), this step should be carried out in a well-ventilated hood.

A. *(R,R)-(+)-N,N,N',N'-Tetramethyltartaric acid diamide*. Into a mixture of 618 g (3 mol) of diethyl tartrate (Note 1) and 600 mL of freshly distilled methanol in a 2-L Erlenmeyer flask is poured at least 450 mL (7 mol) of liquid, anhydrous, cold (–78°C) dimethylamine (Note 2). The mixture is swirled briefly and then allowed to stand in a hood for 3 days with a drying tube in place. After seeding (Note 3) and cooling in a refrigerator overnight, the massive crystals are collected by suction filtration. The filtrate is concentrated, seeded, and cooled to yield a second crop. The combined crystals are washed with cold methanol (–30°C) and dried under reduced pressure at 70–100°C (oil bath). The diamide thus obtained is sufficiently pure to be used in the following step. The yield is 570–580 g (93–95%). Recrystallization from methanol–ethyl acetate furnishes an analytically pure sample, mp 189–190°C, $[\alpha]_D$ +43° (ethanol, *c* 3.0).

B. *(R,R)-(+)-2,3-Dimethoxy-N,N,N',N'-tetramethylsuccinic acid diamide*. Into a 4-L, three-necked, round-bottomed flask, fitted with a mechanical stirrer, reflux condenser, and stopper, are introduced 240 mL of 50% aqueous sodium hydroxide (3 mol), 1.5 L of methylene chloride, 0.2 g of benzyltriethylammonium chloride (TEBA), and then 260 g (2.06 mol) of dimethyl sulfate (Note 4). The mixture is stirred vigorously (Note 5), and a total of 204 g (1 mol) of the powdered tartaric acid diamide is added in portions at such a rate as to maintain refluxing (Note 6). Stirring is continued for 24 hr without heating, whereupon 1 L of water is added. Separation of the organic phase, extraction of the aqueous layer with three 300-mL portions of methylene chloride, drying of the combined

organic solutions over sodium sulfate, and removal of the solvent in a rotary evaporator (bath temperature below 80°C, water aspirator vacuum) furnishes a slightly yellow oil that crystallizes at 25°C and is sufficiently pure for use in the following reduction step. Recrystallization from cyclohexane/benzene yields 220 g (95%, (Note 7)) of colorless prisms, mp 63.2–63.5°C, $[\alpha]_D$ + 116° (benzene, *c* 3).

C. *(S,S)-(+)-1,4-Bis (dimethylamino)-2,3-dimethoxybutane (DDB)*. A 4-L, three-necked, round-bottomed flask is fitted with a heating jacket, mechanical stirrer, reflux condenser with drying tube, and a stoppered, pressure-equalizing dropping funnel, flushed with nitrogen or argon, and charged with 2.2 L of dry tetrahydrofuran (THF, (Note 8)) and 60 g (1.6 mol) of lithium aluminum hydride ($LiAlH_4$, (Note 9)). A mixture of 250 mL of THF and 232 g (1.0 mol) of the diamide is added, with stirring, at a rate sufficient to reach and maintain refluxing. After the addition is completed, the reaction mixture is kept boiling for 2 hr. The flask is immersed in an ice bath, and 60 mL of water, 180 mL of 10% aqueous potassium hydroxide, and again 60 mL of water are added cautiously with very vigorous stirring. The hydrogen gas that is generated is led well above the stirring motor into the hood exhaust. Temporarily, the slurry becomes viscous and difficult to stir; during this period addition has to be made extremely carefully. The pale yellow, completely hydrolyzed slurry is filtered by suction, the filter cake extracted twice by refluxing with THF in a round-bottomed flask, and the combined solutions are concentrated in a rotary evaporator. The residual liquid is distilled through a 20-cm Vigreux column; bp 62–64°C (3 mm), yield 180 g (88%). For use in organometallic reactions, DDB is freshly distilled from $LiAlH_4$, $[\alpha]_D$ + 14.7° (neat), d_4^{20} 0.896 (Note 10).

2. Notes

1. Commercial (*R*,*R*)-(+)-diethyl tartrate can be used. The submitters prepared it from (*R*,*R*)-(+)-tartaric acid (Firma Benckiser, D-Ludwigshafen, or Firma Boehringer, D-Ingelheim), $[\alpha]_D$ +12.7° (water, *c* 17): a 4-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, water separator for organic solvents heavier than water, and a stopper is charged with 1.5 kg (10 mol) of tartaric acid, 1.5 L (26 mol) of 96% ethanol, 1 L of chloroform, and 30 g of freshly activated (1 *N* HCl), highly acidic ion-exchange resin (Lewatit 3333). The stirred mixture is heated at reflux until no more water separates (up to 60 hr). Filtration, evaporation, and vacuum distillation (oil bath temperature must not exceed 145°C, no column, fast distillation) yield 1.85 kg (90%) of the ester, $[\alpha]_D$ +8.16° (neat).

2. Dimethylamine (bp 6°C) is condensed into a 1-L flask cooled to −78°C and fitted with an inlet tube and an opening protected from atmospheric moisture with a silica gel drying tube. It is either taken from a cylinder or freed from 1.5 L of a stirred 40% aqueous solution by heating at 60–80°C with 50 g of potassium hydroxide and leading the amine vapors first through a reflux condenser, then through a 50-cm (2 cm i.d.) drying tube filled with potassium hydroxide pellets, and finally into the receiver flask cooled to −78°C.

3. Sometimes spontaneous crystallization occurs; if it does not, a small amount of the solution is withdrawn and evaporated on a watch glass, and the crystals that are obtained by scratching with a glass rod are used for seeding.

4. Dimethyl sulfate was purchased from Riedel de Haen, D-Seelze-Hannover, and

used without purification.
5. Since the reaction mixture becomes very gelatinous on addition of the tartaric acid amide, a powerful motor and a large stirring blade are necessary.
6. Since dimethyl sulfate decomposes rapidly in concentrated alkaline medium, addition of the powdered tartaric acid amide must begin *immediately* after the dimethyl sulfate is introduced. The amide should be added *as fast as possible* (ca. 20–30 min) within the limits of the capacity of the reflux condenser and the mechanical stirrer. The amount of dimethyl sulfate can be increased up to 2.5 equivalents and fresh benzyltriethylammonium chloride can be added toward the end of the addition. With less rapid addition and stirring, the yield drops to 45–55%.
7. The yield obtained by the checkers was 78%.
8. Tetrahydrofuran (THF) was obtained from BASF AG, D-Ludwigshafen, and was distilled twice from potassium hydroxide pellets.
9. Lithium aluminum hydride ($LiAlH_4$) was used as a white powder purchased from the Metallgesellschaft AG, D-Frankfurt.
10. The specific rotation is highly sensitive to the water content of the DDB; only material distilled from $LiAlH_4$ shows this value.

3. Discussion

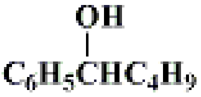
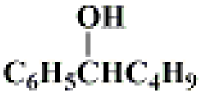
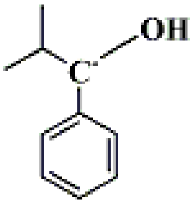
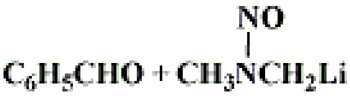
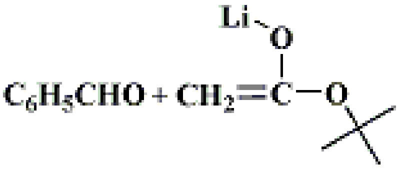
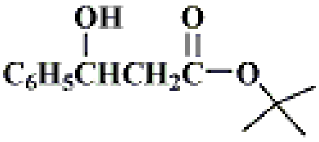
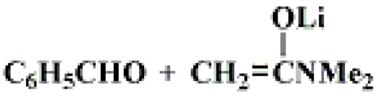
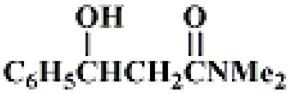
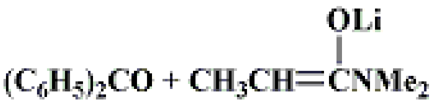
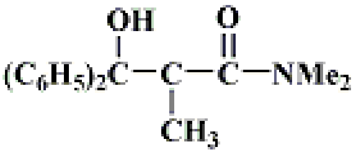
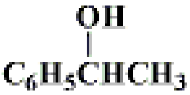
The three compounds whose syntheses are described in the present procedure have been reported previously by the submitters.[2,3]

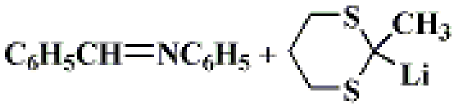
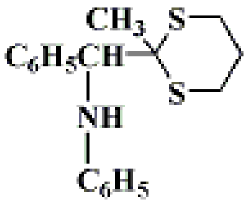
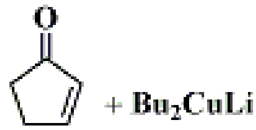
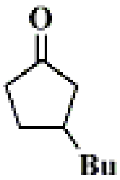
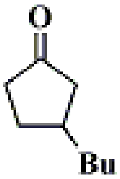
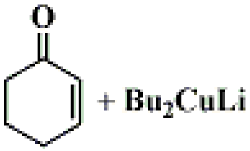
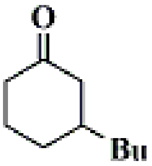
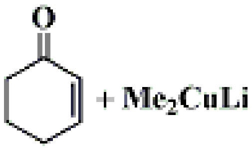
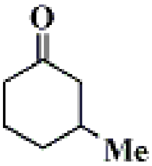
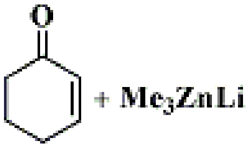
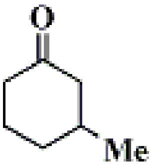
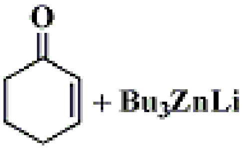
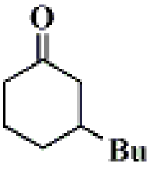
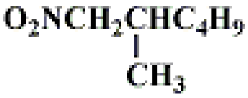
The amino ether DDB has been used extensively as a chiral solvent for asymmetric syntheses.[2,3,4,5,6,7,8] It is readily available on a large scale in both enantiomeric forms: starting from the unnatural (*S,S*)-(–)-tartaric acid,[9] (–)-DDB is equally accessible[3] following the procedures described herein.

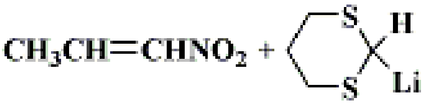
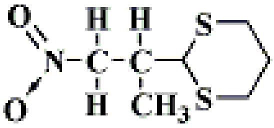
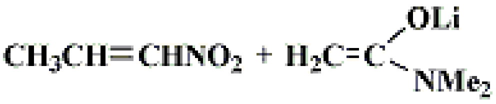
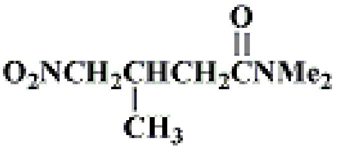
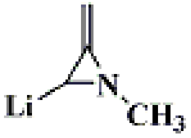
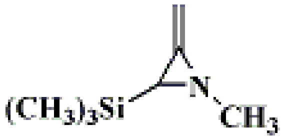
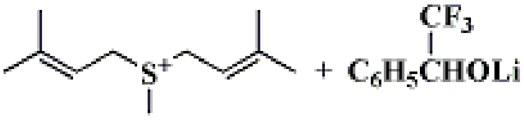
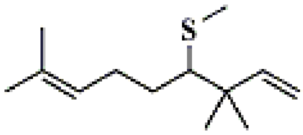
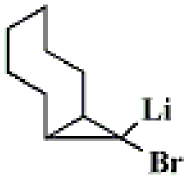
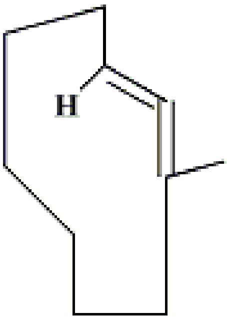
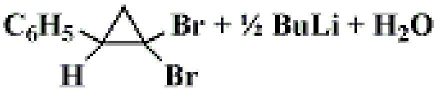
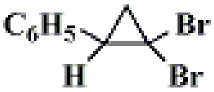
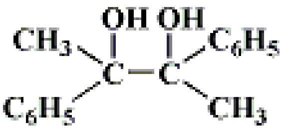
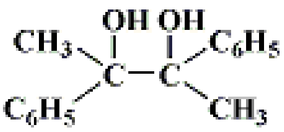
As demonstrated by the examples listed in Table I, DDB induces chirality in enantioface, enantiotope, and enantiomer differentiating[10] reactions in which it acts as a metal (Li, Mg, Cu, Zn) complexing ligand, as a hydrogen-bond mediating component, and as a base catalyst. It can be used at temperatures as low as −150°C if mixed with appropriate cosolvents.[3] It is readily recovered and separated from products by acid extraction during workup. The enantiomeric excess (e.e.) obtained in this asymmetric induction is generally in the range of 10–20%; in optimized and/or fortuitous cases, optical yields of up to 50% have been obtained. The chemical yields are as high as in conventional achiral solvent systems. An application of DDB is described on p. 000 of this volume.

TABLE 1
ASYMMETRIC SYNTHESES WITH (+)-DDB AS A CHIRAL AUXILIARY AGENT[2,3,4,5,6,7,8]

Reagents	Conditions (DDB : Reagent, Temp. °C, Solvent)	Product	$[\alpha]_D$ (Solvent, *c*) (%, e.e)

$C_6H_5CHO + Bu_2Mg$	2 : 1, –78, ether		–2.5° (C_6H_6, 7.0) (8)
C_6H_5CHO + BuLi	10 : 1, –150, pentane		+7° (neat) (40)
C_6H_5CHO + *i*-PrLi	4 : 1, –120, pentane		+6.1° (ether, 7.5) (14)
$C_6H_5CHO + (C_6H_5S)_3CLi$	10 : 1, –78, pentane		+23° (C_6H_6, 1.03) (12)
	10 : 1, –78, pentane		+6.5 (CH_2Cl_2, 3.0) (14.8)
	10 : 1, –78, pentane		+5.1° (C_6H_6, 11.1)
	10 : 1, –78, pentane		+9.1° (C_6H_6, 12.4) (14)
	10 : 1, –78, pentane		+8.5° (C_6H_6, 11.3) (22)
$C_6H_5COCH_3 + LiAlH_4$	–78, pentane		+4.7° (neat) (11)

	3 : 1, –30, hexane		+15.5° (CH_2Cl_2, 18.7)
	10 : 1, –78, ether		–10° (C_6H_6, 5.9)
	10 : 1, –78, ether		+6.9° (C_6H_6, 6.8)
	10 : 1, –78, ether		–0.9° (C_6H_6, 11.5)
	10 : 1, –78, ether		–1.7° (neat) (13.6)
	10:1, –78, ether		–0.74° (C_6H_6, 6)
	10:1, –78, ether		–1.0° (C_6H_6, 4.3)
$CH_3CH{=}CHNO_2$ + BuLi	10:1, –78, pentane		+ 0.9° (C_6H_6, 10.4) (28)

	10:1, –78, pentane		–4.3° (C_6H_6, 7.5) (45)
	10:1, –78, pentane		+0.7° (C_6H_6, 5.4) (10)
$(CH_3)_3SiCl$ + 	9:1, –125, pentane		–27.5° (C_6D_6, 4.9) (12.4)
	–20, THF		+2.9 ± 0.3° [365 nm] ($CHCl_3$, 0.62) (12)
	10:1, –78, pentane		+8.2° (neat) (5)
	10:1, –100, pentane		+1.9° (neat)
$C_6H_5COCH_3$ + *hv*	7.5:1, –72, pentane		+8.0° (C_2H_5OH, 5.0) (23.5)
$C_6H_5COCH_3$ + cathodic, electrochemical reduction	24, methanol		+2.2° (C_2H_5OH, 5.0) (6.4)

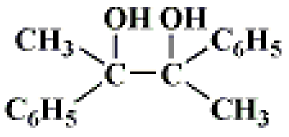
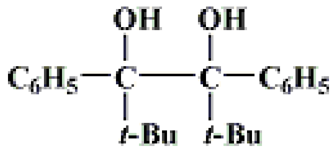
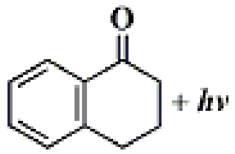
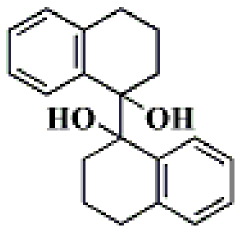
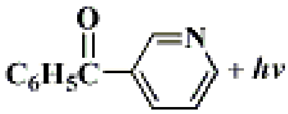
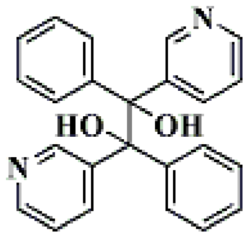
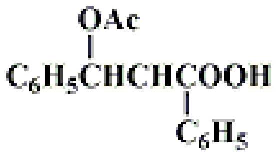
$C_6H_5COCH_3$ + Li/naphthalene	6:1, 25,		2.5° (C_2H_5OH, 5.0) (7.3)
C_6H_5CO-*t*-Bu + *hv*	–30, neat DDB		–1.2°[$(C_2H_5)_2O$, 5.0]
	–35, pentane		+22.3° ($CHCl_3$, 5.0)
	–15, neat DDB		–20.0° (CH_3SOCH_3, 2.0)
C_6H_5CHO + $C_6H_5CH_2COOH$ + AcOAc	6:1, –25		diastereomer a +5.0°, diastereomer b +26.0° (C_2H_5OH, 3)

TABLE II

COMPARISON OF TMB[a] WITH DDB[b] USED AS COSOLVENTS IN THE ADDITION OF BUTYLLITHIUM TO VARIOUS ALDEHYDES AT –78°C IN PENTANE[3]

RCHO + C_4H_9Li $RCH(OH)C_4H_9$

R	e.e. (%) With TMB[a]	With DDB[b]	Sense of Rotation, Absolute Configuration
CH_3	1.2	7.5	(+)-*S*
C_2H_5	8.8	11.5	(+)-*S*
i-C_3H_7	18.0	19.0	(+)-*R*

t-C_4H_9	22.8	13.5	(+)-*R*
$(C_2H_5)_2CH$	20.0	19.0	(+)
c-C_6H_{11}	25.0	22.5	(+)-*R*
C_6H_5	30.0	19.0	(+)-*R*
4-CH_3-C_6H_4	32.5	11.5	(+)
2-CH_3-C_6H_4	45.3	10.5	(+)
2,4,6-$(CH_3)_3$-C_6H_2	23.0	2.3	(+)

[a]TMB = (*S,S*)-(−)-1,2,3,4-tetramethoxybutane.

[b]DDB = (*S,S*)-(+)-1,4-bis (dimethylamino)-2,3-dimethoxybutane.

Another chiral cosolvent, which is less readily separated from low-boiling and/or water-soluble products and is somewhat less stable toward organolithium reagents, is (*S,S*)-(−)-1,2,3,4-tetramethoxybutane (TMB).[3] As is shown in Table II, it is a cosolvent that is superior to DDB in differentiating between the enantiotopic faces of aldehydes with organolithium reagents.[3] Finally, the octamethyl-1,4-diamino-2,3-bis (2-aminoethoxy) butane (DEB)[5] can be used in a 2 : 1 ratio with alkyllithium reagents to produce carbinols in even higher enantiomeric yields.

DDB, TMB, and DEB are far superior to other neutral chiral auxiliary agents used in the same reactions.[3,10,11,12,13]

This preparation is referenced from:

- Org. Syn. 76, 86
- Org. Syn. 77, 176

References and Notes

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9. Natural (*R*,*R*)-(+)-tartaric acid costs DM 142/3 kg (Aldrich Chemical Company, Inc.); the unnatural (*S*,*S*)-enantiomer can be purchased from Chemische Fabrik Uetikon, CH-Uetikon, at SFr. 350/kg, 195/kg (as a 100-kg batch), or 70/kg (> 1000-kg batch).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

(S,S)-(+)-1,4-Bis (dimethylamino)-2,3-dimethoxybutane (DDB)

Lithium aluminum hydride ($LiAlH_4$)

(S,S)-(–)-tartaric acid

C_6H_5CHO

Bu_2Mg

i-PrLi

$(C_6H_5S)_3CLi$

$C_6H_5COCH_3$

$CH_3CH=CHNO_2$

C_6H_5CO-t-Bu

$C_6H_5CH_2COOH$

AcOAc

(S,S)-(–)-1,2,3,4-tetramethoxybutane

(S,S)-(–)-1,2,3,4-tetramethoxybutane (TMB)

octamethyl-1,4-diamino-2,3-bis (2-aminoethoxy)butane (DEB)

Li

ethanol (64-17-5)

HCl (7647-01-0)

Benzene (71-43-2)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

dimethyl sulfate (77-78-1)

cyclohexane (110-82-7)

potassium hydroxide (1310-58-3)

Naphthalene (91-20-3)

tartaric acid (87-69-4)

Pentane (109-66-0)

methylene chloride (75-09-2)

dimethylamine (124-40-3)

BuLi (109-72-8)

Tetrahydrofuran, THF (109-99-9)

lithium aluminum hydride, $LiAlH_4$ (16853-85-3)

hexane (110-54-3)

argon (7440-37-1)

benzyltriethylammonium chloride (56-37-1)

diethyl tartrate

(R,R)-(+)-tartaric acid (87-69-4)

(R,R)-(+)-N,N,N',N'-Tetramethyltartaric acid diamide (26549-65-5)

(S,S)-(+)-1,4-BIS(DIMETHYLAMINO)-2,3-DIMETHOXYBUTANE, 1,4-Butanediamine, 2,3-dimethoxy-N,N,N',N'-tetramethyl-[S,S]-, (S,S)-(+)-1,4-bis(dimethylamino)-2,3-dimethoxybutane (26549-21-3)

(R,R)-(+)-DIETHYL TARTRATE (87-91-2)

(R,R)-(+)-2,3-Dimethoxy-N,N,N',N'-tetramethylsuccinic acid diamide (26549-29-1)

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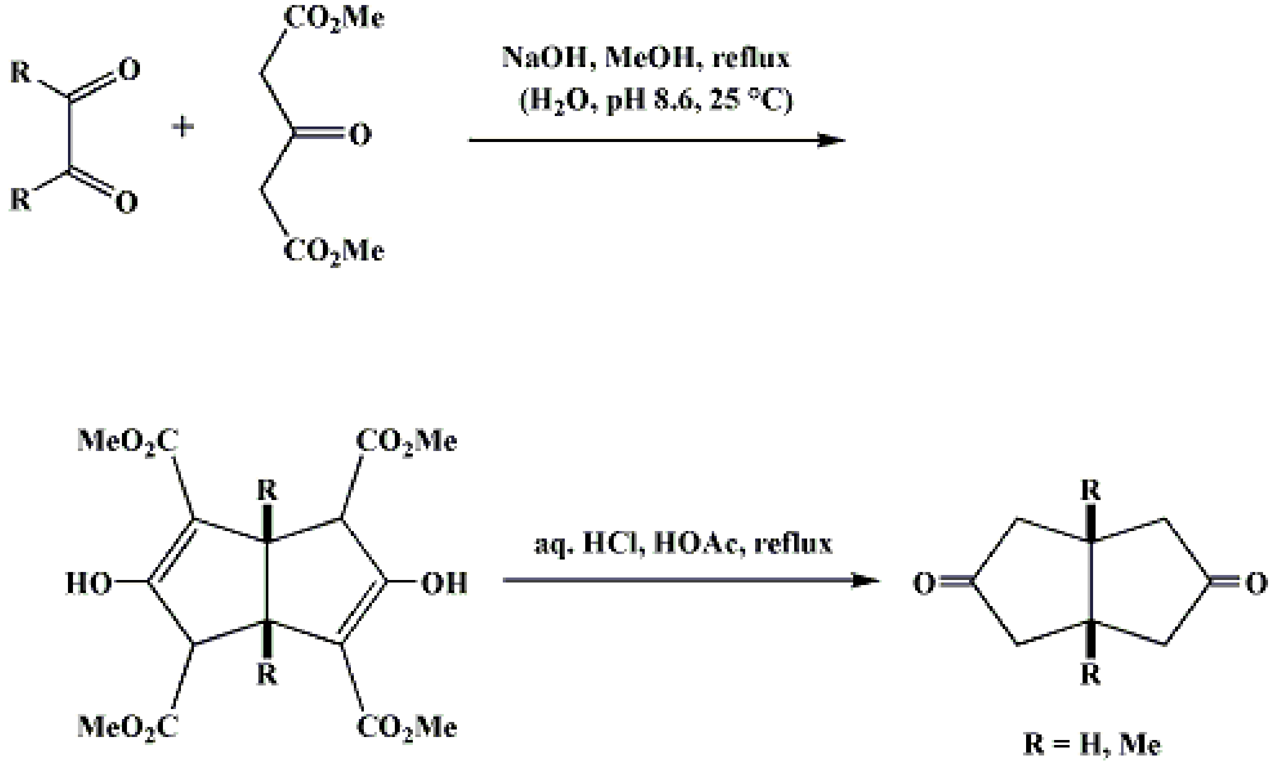
CONDENSATION OF DIMETHYL 1,3-ACETONEDICARBOXYLATE WITH 1,2-DICARBONYL COMPOUNDS: *cis*-BICYCLO[3.3.0]OCTANE-3,7-DIONES

[2,5(1*H*,3*H*)-Pentalenedione, tetrahydro-, *cis*-, and 2,5(1*H*,3*H*)-pentalenedione, tetrahydro-, 3a,6a-dimethyl-, *cis*]



Submitted by Steven H. Bertz[1], James M. Cook[2], Ali Gawish[2], and Ulrich Weiss[3].
Checked by Todd K. Jones, Scott E. Denmark, S. V. Govindan, and Robert M. Coates.

1. Procedure

I. Specific Procedure for Glyoxal

A. *Tetramethyl 3,7-dihydroxybicyclo[3.3.0]octa-2,6-diene-2,4,6,8-tetracarboxylate*. A 3-L, three-necked, round-bottomed flask is equipped with a thermometer, mechanical stirrer, pressure-equalizing dropping funnel, reflux condenser (Note 1), and a heating mantle. A solution of 64 g (1.60 mol) of sodium hydroxide (Note 2) in 1.15 L of methanol is prepared in the flask, cooled in an ice bath, and stirred as 273 g (1.57 mol) of dimethyl 1,3-acetonedicarboxylate (Note 3) is added dropwise. The resulting slurry is stirred and heated to reflux, at which point the white salt dissolves. The heating mantle is removed, and the solution is stirred rapidly while 128.5 g of aqueous 40% glyoxal (51.4 g, 0.886 mol) (Note 3) and (Note 4) is added at a rate sufficient to maintain the internal temperature at 65°C (Note 5). After the addition is completed (40–60 min, (Note 6)), the mixture is allowed to

cool to room temperature and stirred overnight (Note 7). The precipitate is collected by suction filtration, washed with 500 mL of methanol (Note 8), and dried under reduced pressure. The yield of the white to light yellow disodium salt is 197–215 g (58–63%) (Note 9).

A 6-L Erlenmeyer flask equipped with a large magnetic stirring bar (Note 10) is charged with 1 L of chloroform and a solution of the disodium salt (0.46–0.50 mol) in 800 mL of water. The two-phase mixture is stirred rapidly as 2.00 equiv (920–1000 mL, 0.92–1.00 mol) of cold 1 *M* hydrochloric acid is added. The layers are separated and the aqueous phase is extracted with three 500-mL portions of chloroform. The combined organic layers are washed once with saturated sodium chloride, dried over anhydrous sodium sulfate, and concentrated under reduced pressure by rotary evaporation, keeping the water bath temperature at or below 40°C. Crystallization of the remaining waxy solid from 2 : 1 hexane–ethyl acetate affords 158–171 g (54–59% based on dimethyl 1,3-acetonedicarboxylate) of the tetraester, mp 97–100°C (Note 11).

B. *cis-Bicyclo[3.3.0]octane-3,7-dione*. A 3-L, three-necked, round-bottomed flask equipped with a heating mantle, two reflux condensers, and a magnetic stirrer (Note 12) is charged with 135 g (0.364 mol) of the tetraester, 66 mL of glacial acetic acid, and 600 mL of 1 *M* hydrochloric acid (Note 13). The mixture is stirred vigorously and heated at reflux for 2.5 hr (Note 14). The solution is cooled in an ice bath and the product is extracted with five 250-mL portions of chloroform. The chloroform extracts are combined, and the solution is concentrated by rotary evaporation (bath temperature at or below 40°C) until most of the acetic acid is removed. The residue is dissolved in 300 mL of fresh chloroform. The solution is washed with 60-mL portions of saturated sodium bicarbonate until the aqueous layer remains basic to litmus paper, dried with anhydrous sodium sulfate, and evaporated cautiously under reduced pressure. The yield is 44–45.5 g (88–90%) of white to light yellow solid, mp 84–85°C (Note 15). The product is sufficiently pure for most purposes; it may be purified by recrystallization from methanol or ethanol and/or by sublimation at 70°C (0.1 mm).

II. General Procedure Using Aqueous Buffer

A. *Tetramethyl 3,7-dihydroxy-1,5-dimethylbicyclo[3.3.0]octa-2,6-diene-2,4,6,8-tetracarboxylate*. A freshly prepared solution (pH 8.3) of 5.6 g of sodium bicarbonate in 400 mL of water, 70 g (0.40 mol) of dimethyl 1,3-acetonedicarboxylate, and a magnetic stirring bar are placed in a 1-L Erlenmeyer flask. The resulting solution is stirred rapidly as 17.2 g (0.20 mol) of biacetyl (Note 3) is added in one portion. Stirring is continued for 24 hr, during which time white crystals separate. The solid is collected by suction filtration and dried under reduced pressure to afford 60–62 g, mp 155–158°C. The filtrate is cooled in an ice bath, acidified to pH 5 (pHydrion paper) with dilute hydrochloric acid, and extracted with three 100-mL portions of chloroform. The chloroform extracts are combined, washed with saturated sodium chloride, and dried with anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure gives another 2–4 g of crude product (Note 16). Recrystallization from hot methanol gives 58–60 g (73–75%) of the tetraester, mp 155–157°C, in two crops (Note 17).

B. *cis-1,5-Dimethylbicyclo[3.3.0]octane-3,7-dione*. A 1-L, one-necked, round-bottomed flask is equipped with a heating mantle, reflux condenser, and a magnetic stirring bar. The flask is charged with 200 mL of 1 *M* hydrochloric acid, 40 mL of glacial acetic acid, and 24 g (0.060 mol) of the tetraester from Section IIA. The mixture is stirred vigorously and heated at reflux for 3–6 hr (Note 18). The solution is cooled in an ice bath and the product is isolated as described in Section IB above. The yield of c white to light yellow solid, mp 219–221°C, is 9.5–9.8 g (95–98%). Recrystallization from a minimum amount of hot ethanol affords 7.5–7.7 g (75–77%) of the diketone, mp 222–225°C, in one crop (Note 19).

2. Notes

1. The dropping funnel and the reflux condenser were connected to the same neck using a Claisen adapter.
2. The submitters recommend that a high-purity grade of sodium hydroxide be used. Otherwise insoluble impurities are formed that must be removed by filtration through a sintered-glass Buchner funnel.
3. Dimethyl 1,3-acetonedicarboxylate, aqueous 40% glyoxal, and biacetyl were purchased from Aldrich Chemical Company, Inc. The submitters advise against using glyoxal solution that contains a significant amount of white solid.
4. The submitters report that the yield is decreased by 5% if exactly 0.5 equiv of glyoxal is used. The yield is improved to 75–76% in runs carried out on smaller scale (ca. 0.1 mol of glyoxal).
5. Heating should be resumed if necessary to maintain a temperature of 65°C. The submitters report that lower yields are obtained at lower temperatures (e.g., 37% at 25°C).
6. The submitters caution that the addition time is critical. In one run by the checkers with a 30-min addition time, the yield of the disodium salt was reduced to 49%.
7. Similar yields were obtained by the submitters when the reaction mixture was allowed to cool at room temperature for 2 hr and in an ice bath for another 2 hr.
8. The solid is washed first by allowing methanol to percolate through the filter cake with gentle suction until the brown color is removed. The product is suspended in methanol, filtered, and washed again by the percolation procedure.
9. The submitters obtained 411–430 g (61–64%) from reactions conducted on twice the scale described using a 2-hr addition time. Elemental analyses by the submitters and checkers indicate a variable degree of hydration (*n* = 1–2) for the product. The yield and molar quantities of the disodium salt are calculated assuming a monohydrate, $C_{16}H_{16}O_{10}Na_2 \cdot H_2O$. For further characterization of this salt, see [4 5].
10. The checkers used a mechanical stirrer to achieve more efficient mixing of the layers.
11. The submitters obtained 176–182 g (62–64%) of product, mp 103–105°C, after trituration with a minimum amount of cold methanol. Crystallization was facilitated by scraping the sticky solid with a silver spatula. The reported melting point is 104–107°C.[6 7] The crude product obtained initially by the checkers was a low-melting solid, mp 70–75°C, that was conveniently transferred and purified by recrystallization from about 1 L of hot 2 : 1 hexane–ethyl acetate. Elemental analyses of the product by the submitters were within ±0.4% of the theoretical value. The spectral properties of the product are as follows: IR ($CHCl_3$) cm^{-1}: 3025, 2960,

1740, 1673, 1632, 1450, 1438, 1330, 1250, 1200, 1155, 1058; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 3.64 (apparent t, 2 H, J_{app} = 2.4, two CH), 3.78 (s, 6 H, two OCH_3), 3.81 (s, 6 H, two OCH_3), 3.87 (apparent t, 2 H, J_{app} = 2.4, two CH), 10.35 (broad s, 2 H, two enolic OH).

12. The volume of the flask should be at least three times larger than the volume of the solution to avoid losses from excessive foaming caused by rapid evolution of carbon dioxide. The checkers used a mechanical stirrer to facilitate stirring of the initially heterogeneous mixture. Two reflux condensers are recommended for efficient venting of the gas evolved.

13. The submitters point out that the disodium salt may be used directly provided that two additional equivalents of 1 *M* hydrochloric acid are employed. Acetic acid may be omitted to simplify the isolation procedure. In this case the reaction mixture remains heterogeneous throughout.

14. Progress of the reaction can be followed by observing the gas evolved through a bubbler connected to the top of the reflux condensers.

15. The product gave satisfactory elemental analyses. Calcd. for $C_8H_{10}O_2$: C, 69.54; H, 7.30. Found: C, 69.42; H, 7.36. The literature melting point is 84–86°C.[6,7] The spectral properties of the product are as follows: IR ($CHCl_3$) cm^{-1}: 1738 (C=0), 1405, 1222, 1208, 1175, 792; ^{1}H NMR ($CDCl_3$, 220 MHz) δ: 2.16 (dd, 4 H, *J* = 4.2, 19.3, H_A of CH_AH_B), 2.59 (dd, 4 H, *J* = 8.5, 19.3, H_B of CH_AH_B), 3.04 (m, 2 H, CH); ^{13}C NMR ($CDCl_3$) δ: 35.5 (d, CH), 42.6 (t, CH_2), 217.2 (s, C=O); mass spectrum (70 eV) *m/e* (relative intensity): 138 (M^+, 41), 69 (36), 68 (58), 41 (100), 39 (53).

16. The checkers obtained ca. 19 g of a viscous red oil that on dissolution in ca. 150 mL of methanol deposited 4 g of crude crystalline product.

17. The product gave a satisfactory elemental analysis. Calcd. for $C_{18}H_{22}O_{10}$: C, 54.28; H, 5.53. Found: C, 54.00; H, 5.57. The melting point reported initially (167–169°C after sublimation)[8] is apparently incorrect. The spectral properties of the product are as follows: IR (KBr) cm^{-1}: 3539, 1742, 1664, 1425, 1340, 1260, 1235, 1070, 1020; ^{1}H NMR ($CDCl_3$) δ: 1.29 (s, 6 H, two CH_3), 3.75 (s, 6 H, two CO_2CH_3), 3.87 (s, 6 H, two CO_2CH_3), 3.94 (s, 2 H, two CH), 10.62 (br s, 2 H, two OH).

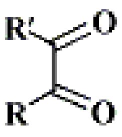
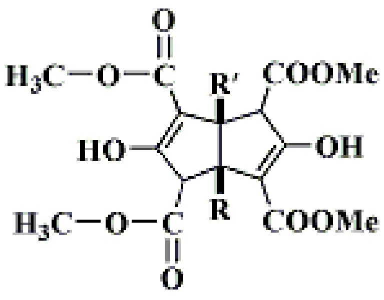
18. The checkers recovered a 1 : 1 mixture of tetraester and diketone from two runs conducted for 2.5 hr. When the reflux time was extended to 6 hr, complete conversion to product was attained. The reaction progress was monitored by gas evolution (Note 14). Some variability of reaction times is probably attributable to differences in stirring efficiency, temperature gradients, and/or particle size of the crystalline starting material.

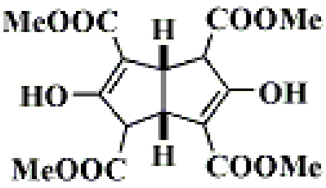
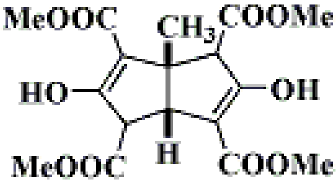
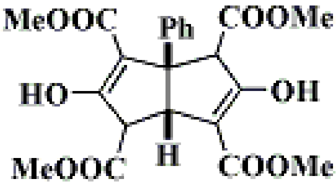
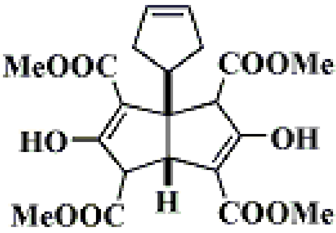
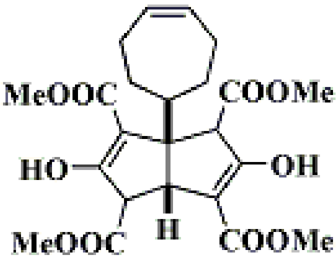
19. The recrystallized product was analyzed by the checkers. Calcd. for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.45; H, 8.54. The spectral properties of the product are as follows: IR (KBr) cm^{-1}: 1736, 1390, 1245, 1210, 1180, 1145, 1070; ^{1}H NMR ($CDCl_3$, 360 MHz) δ: 1.22 (s, 6 H, two CH_3), 2.36 and 2.39 (AB q, 8 H, *J* = 18.5, four CH_2).

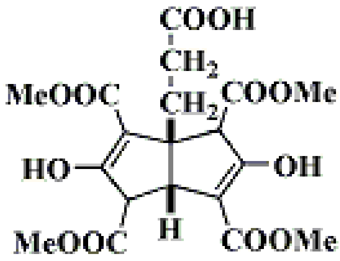
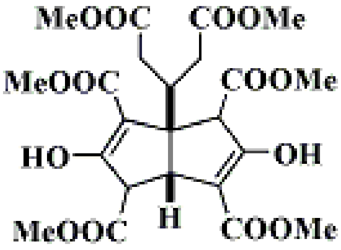
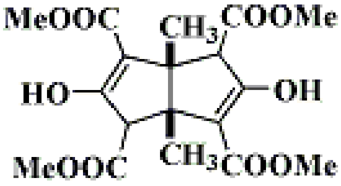
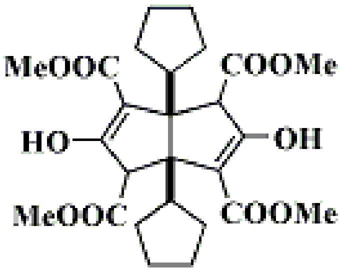
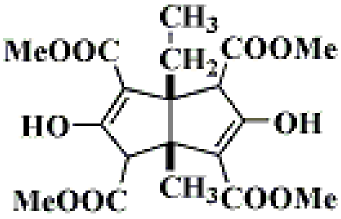
3. Discussion

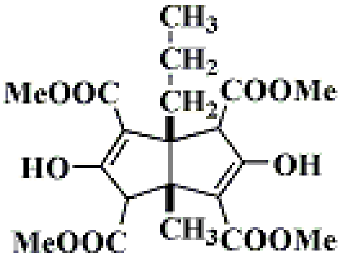
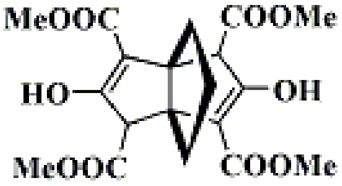
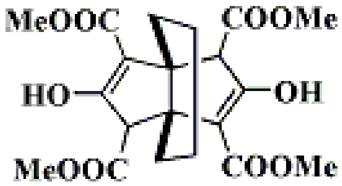
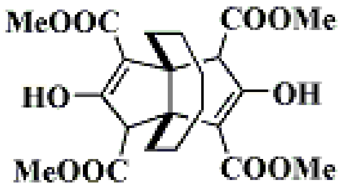
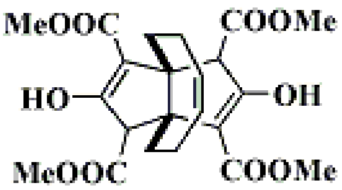
Bicyclo[3.3.0]octane-3,7-dione has been prepared in five steps from dimethyl malonate and chloral in about 20% overall yield.[6,7] The direct formation of bicyclo[3.3.0]octane-3,7-diones by the 2 : 1 condensation of acetone-1,3-dicarboxylate and 1,2-dicarbonyl compounds was discovered by Weiss and Edwards[8] and is commonly called the Weiss Reaction.[3] The variation described in Section I has been optimized for large-scale preparation of the parent diketone.[4 5] It is a good example of what Turner[9] has called a "point reaction," as it is very sensitive to experimental details such as temperature and stirring rate. The aqueous buffer procedure given in Part II is a "plateau reaction"[9] and affords a general method for preparing a variety of angularly-substituted bicyclo[3.3.0]octane-3,7-diones (Table I).[10,11,12,13,14,15,16,17] The parent diketone can also be prepared by the aqueous buffer procedure (Part II), but chromatography is required to purify the product.[15] The mechanism of this novel annulation reaction involves a complex sequence of aldol condensations, dehydrations, and Michael additions,[11,18 19 20,21] the order of which may be pH-dependent.[21] The isolation of γ-hydroxycyclopentenones in certain cases[11,18,19,20] implicates these reactive Michael acceptors as intermediates. A number of other interesting products have been isolated from reaction of glyoxal with acetonedicarboxylate.[21,22 23 24] The various bicyclic diketones prepared by this method have served as starting materials for syntheses of polycyclic compounds[25 26 27 28 29 30 31 32 33 34 35 36 37] and natural products.[38 39 40 41 42 43 44 45] The reaction of dimethyl 1,3-acetonedicarboxylate with cyclic 1,2-diketones is a particularly effective method of propellane synthesis;[8,12,46 47 48] for instance, Ginsburg has used it to prepare a propellanex with a 40-membered ring.[48] Routes have been developed to triquinacene[49] and its derivatives[50 51 52] which employ as the key step the chemistry discussed in this procedure. This general synthesis of bicyclo[3.3.0]octane derivatives has also been extended to selected examples of bicyclo[3.3.1]nonane and bicyclo[3.3.2]decane systems by substituting malondialdehyde[53] and *o*-phthalaldehyde,[54] respectively, for glyoxal. Reviews of recent progress by the Cook group are available.[55 56]

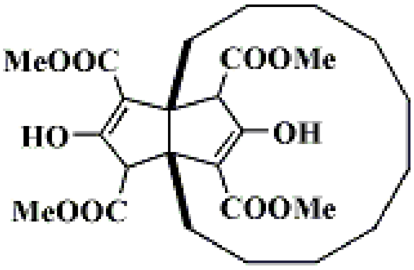
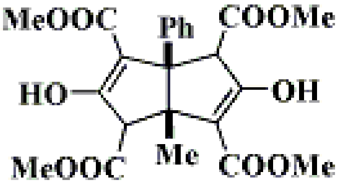
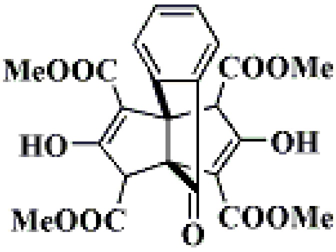
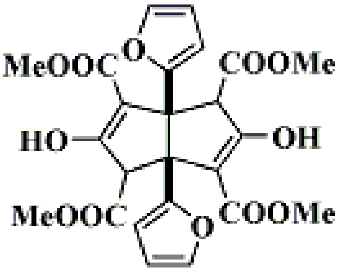
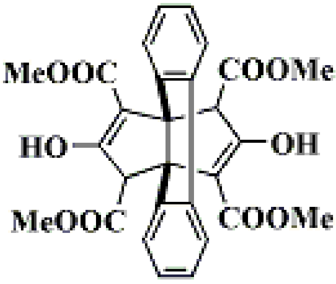
TABLE I
2 : 1 CONDENSATION OF DIMETHYL 1,3-ACETONEDICARBOXYLATE WITH VARIOUS 1,2-DICARBONYL COMPOUNDS

		Yield (%)	Ref.

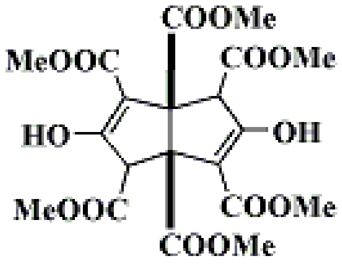
	R = R' = H		
Glyoxal		70	[4,5], [15]
	R = H, R' = CH_3		
Pyruvaldehyde		52	[8]
	R = H, R' = Ph		
Phenylglyoxal		66	[11]
	R = H, R' = C_5H_7		
3-Cyclopentenylglyoxal		90	[17]
	R = H, R' = C_7H_{11}		
4-Cycloheptenylglyoxal		70	[17]

	R = H, R' = $CH_2CH_2CO_2H$		
4,5-Dioxopentanoic Acid		80	10
	R = H, R' = $CH(CH_2CO_2CH_3)_2$		
Dimethyl 3-(dioxo ethyl) glutarate		51	18
	R = R' = CH_3		
Biacetyl		84	8
	R = R' = C_5H_9		
Bis(cyclopentyl) 1,2-ethanedione		12	17, 18
	R = CH_3, R' = CH_2CH_3		
2,3-Pentanedione		70	17

	$R = CH_3$, $R' = CH_2CH_2CH_3$		
2,3-Hexanedione		64	17
	$R = R' = (CH_2)_3$		
Cyclopentane-1,2-dione		45	8, 16
	$R = R' = (CH_2)_4$		
Cyclohexane-1,2-dione		81	12
	$R = R' = (CH_2)_6$		
Cyclooctane-1,2-dione		80	13
	$R = R' = (CH_2)_2CH{=}CH(CH_2)_2$		
Cyclooct-5-ene-1,2-dione		87	14

	R = R' = $(CH_2)_{10}$		
Cyclododecane-1,2-dione		94	13
	R = CH_3, R' = Ph		
1-Phenyl-1,2-propanedione		68	17
	R = R' = C_7H_4O		
Ninhydrin		60	11
	R = R' = C_4H_3O		
Furil		60	20
	R – R' = 2,2'-biphenyl		
Phenanthrenequinone		54	17, 20

$R = R' = CO_2CH_3$

Dimethyl 2,3-dioxosuccinate		14	31

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

cis-BICYCLO[3.3.0]OCTANE-3,7-DIONES

2,5(1H,3H)-Pentalenedione, tetrahydro-, cis-, and 2,5(1H,3H)-pentalenedione, tetrahydro-, 3a,6a-dimethyl-, cis

$C_{16}H_{16}O_{10}Na_2 \cdot H_2O$

propellane

triquinacene

o-phthalaldehyde

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ethyl acetate (141-78-6)

methanol (67-56-1)

glyoxal (107-22-2)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

carbon dioxide (124-38-9)

Phenylglyoxal (1074-12-0)

phenanthrenequinone (84-11-7)

chloral (75-87-6)

biacetyl (431-03-8)

2,3-Pentanedione (600-14-6)

1-phenyl-1,2-propanedione (579-07-7)

hexane (110-54-3)

Cyclohexane-1,2-dione (765-87-7)

Pyruvaldehyde (78-98-8)

bicyclo[3.3.1]nonane (280-65-9)

ninhydrin (938-24-9)

DIMETHYL 1,3-ACETONEDICARBOXYLATE (1830-54-2)

Bicyclo[3.3.0]octane-3,7-dione

dimethyl malonate (108-59-8)

acetone-1,3-dicarboxylate

3-Cyclopentenylglyoxal

4-Cycloheptenylglyoxal

4,5-Dioxopentanoic Acid

Dimethyl 3-(dioxo ethyl)glutarate

Bis(cyclopentyl) 1,2-ethanedione

2,3-Hexanedione (3848-24-6)

Cyclopentane-1,2-dione

Cyclooctane-1,2-dione

Cyclooct-5-ene-1,2-dione

Cyclododecane-1,2-dione

Dimethyl 2,3-dioxosuccinate

bicyclo[3.3.2]decane (283-50-1)

malondialdehyde (542-78-9)

cis-1,5-Dimethylbicyclo[3.3.0]octane-3,7-dione (21170-10-5)

cis-Bicyclo[3.3.0]octane-3,7-dione (51716-63-3)

Tetramethyl 3,7-dihydroxybicyclo[3.3.0]octa-2,6-diene-2,4,6,8-tetracarboxylate (82416-04-4)

Tetramethyl 3,7-dihydroxy-1,5-dimethylbicyclo[3.3.0]octa-2,6-diene-2,4,6,8-tetracarboxylate (79150-94-0)

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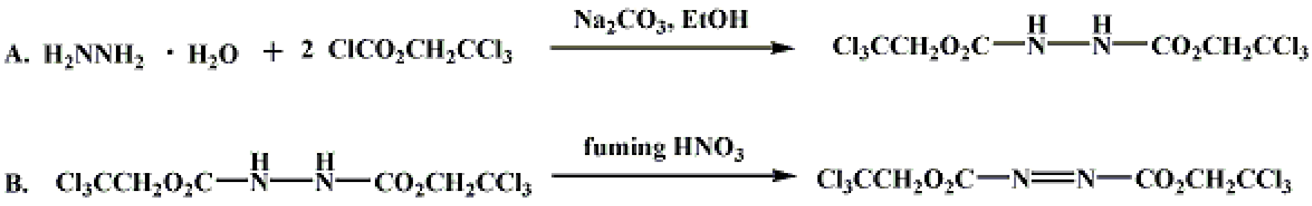
Organic Syntheses, CV 7, 56

BIS(2,2,2-TRICHLOROETHYL) AZODICARBOXYLATE

[Diazenedicarboxylic acid, bis(2,2,2-trichloroethyl) ester]



Submitted by R. Daniel Little and Manuel G. Venegas[1, 2].
Checked by Sandy Banks and Orville L. Chapman.

1. Procedure

A. *Bis (2,2,2-trichloroethyl)hydrazodicarboxylate*. In a 500-mL, three-necked flask equipped with mechanical stirrer, thermometer, and 250-mL and 125-mL dropping funnels (Note 1) is placed a solution of 13.34 g (0.23 mol) of 64% hydrazine hydrate (Note 2) in 60 mL of 95% ethanol. The reaction flask is cooled in an ice bath and 96 g (0.46 mol) of 2,2,2-trichloroethyl chloroformate (Note 3) is added dropwise so that the temperature is kept below 20°C. During the addition of 1 equiv of the chloroformate, a white precipitate is formed. After exactly one-half of the chloroformate has been added, a solution of 25 g (0.24 mol) of sodium carbonate in 100 mL of water is added dropwise along with the remaining chloroformate. The rate of addition of these two reagents is such that the flow of the chloroformate is faster than that of the sodium carbonate so that there is always an excess of chloroformate present; the temperature is kept below 20°C during the addition. As the second equivalent of chloroformate is added the white precipitate dissolves.

After the addition of the reactants is complete, the reaction is allowed to stir for an additional 30 min while the solution warms to room temperature. The reaction mixture is then transferred to a separatory funnel. The viscous organic bottom layer is separated from the aqueous layer and is dissolved in 200 mL of ether. The reaction vessel is washed with 100 mL of ether, and this ether portion is used to extract further the aqueous layer. The ether layers are combined, dried over magnesium sulfate, and filtered, and the solvent is removed under reduced pressure. The viscous oil is allowed to crystallize in an ice bath (0°C). The crystals are collected on a Büchner funnel, washed with 500 mL of water, and dried in a vacuum desiccator at 0.5 mm for 48 hr. 80.8 g (93%) of white crystalline bis(2,2,2-trichloroethyl) hydrazodicarboxylate (mp 85–89°C) is obtained. This material is sufficiently pure for the next preparation. However, further purification can be achieved using an Abderhalden drying apparatus (refluxing 95% EtOH for 12 hr at 0.05 mm; $MgSO_4$ desiccant). Material purified in this way melted at 96.5–97.5°C (Note 4) and (Note 5).

B. *Bis (2,2,2-trichloroethyl) azodicarboxylate*. *Caution! Large amounts of nitrogen oxides are evolved during the oxidation with fuming nitric acid. Therefore, operations should be conducted in an efficient fume hood.*

In a 500-mL, three-necked flask equipped with mechanical stirrer, thermometer, pressure-equalizing dropping funnel, and gas outlet tube is added 78.55 g (0.21 mol) of bis(2,2,2-trichloroethyl) hydrazodicarboxylate dissolved in 180 mL of chloroform (Note 6). The solution is cooled to 0°C and 53.2 mL (1.26 mol) of fuming nitric acid (Note 7) and (Note 8) is added so that the temperature of the solution does not rise above 5°C. The reaction mixture is then allowed to warm slowly to room temperature over 4 hr (Note 9). After an additional 2 hr at room temperature, the material is transferred to and shaken in a 1-L separatory funnel half-filled with ice chips. The two layers are allowed to separate and the bottom organic layer is removed. The aqueous layer is extracted with 250 mL of chloroform. The organic layers are combined and washed with 300 mL of water, 300 mL of aqueous 5% sodium bicarbonate, and again with 300 mL of water. The organic layer is dried with magnesium sulfate, filtered, and the solvent is removed under reduced pressure. The yellow crystals that form are collected on a Büchner funnel and washed with more pentane. The pentane filtrate is concentrated under reduced pressure to afford more crystalline material which is again collected on a Büchner funnel and washed

with more pentane. The cycle is repeated until no more crystals appear after removal of pentane. The yellow crystals so obtained are air dried for 1 hr to afford 59.2 g (75.8%) of bis(2,2,2-trichloroethyl) azodicarboxylate which melts at 108–110°C. Further drying using an Abderhalden drying apparatus (refluxing 95% EtOH for 12 hr at 0.5 mm; $MgSO_4$ desiccant) affords a compound that melts at 109–110.5°C (Note 10),(Note 11),(Note 12).

2. Notes

1. The thermometer is fitted into one of the necks of the flask so that when it is immersed in the solution, the range between 10 and 20°C is easily visible. A two-necked adapter is used for the dropping funnels.
2. Hydrazine hydrate, 64%, practical grade, was obtained from MCB, Inc.
3. 2,2,2-Trichloroethyl chloroformate (96%) is commercially available from Aldrich Chemical Company, Inc., and is used without further purification.
4. The average yield obtained for five runs performed by three different people was 83%.
5. The spectral properties of bis (2,2,2-trichloroethyl) hydrazodicarboxylate are as follows: ^{1}H NMR ($CDCl_3$) δ: 4.80 (s, 4 H, CH_2CCl_3), 7.0–7.6 (s, br, 2 H, -N*H*, the position is concentration-dependent).
6. The solution can be warmed gently without harm to facilitate solution of the hydrazo compound.
7. Mallinckrodt fuming nitric acid (90–95%, *d* 1.5) was used.
8. The reaction seems to be surprisingly dependent on the amount of nitric acid used. A run with 78.6 g of hydrazo compound and a sixfold excess of nitric acid was quenched after 22 hr and afforded 100% conversion to the desired azo compound (NMR analysis). Another run with 80.0 g of hydrazo compound and a fivefold excess of nitric acid gave only 92% conversion after 25 hr. In another run with 2.0 g of hydrazo compound and a sixfold excess of nitric acid the reaction was complete after 4 hr. In addition, the oxidation was found to be temperature dependent. For example, in a run in which the temperature was maintained between 0 and 5°C for 3 hr and the solution was not allowed to warm to room temperature, only 18% yield was obtained (NMR analysis).
9. The evolution of large amounts of nitrogen oxides was noticed after approximately 1.5 hr (the temperature had reached 13°C).
10. Yields ranged from 76 to 94% (six runs performed by three different people).
11. The NMR spectrum ($CDCl_3$) for bis(2,2,2-trichloroethyl) azodicarboxylate shows only a singlet at δ 5.05.
12. The title compound is now commercially available from Aldrich Chemical Co., Inc.

3. Discussion

Bis (2,2,2-trichloroethyl) azodicarboxylate has been prepared by oxidation of bis(2,2,2-trichloroethyl) hydrazodicarboxylate with dinitrogen tetroxide.[3]

Bis(2,2,2-trichloroethyl) azodicarboxylate is a yellow crystalline material that is stable indefinitely in a vacuum desiccator stored in the dark. This compound offers a number of important advantages over diethyl and dimethyl azodicarboxylate for the synthesis of azo compounds. Probably the most important advantage is that in contrast to the ethyl and methyl esters, the trichloroethyl ester grouping can be removed under neutral conditions—a requirement when the product of the transformation is acid- or base-labile.[4 5 6 7 8 9] Furthermore, in contrast to dimethyl azodicarboxylate and diethyl azodicarboxylate, which have been known to explode when heated and require distillation for purification, (2,2,2-trichloroethyl) azodicarboxylate is isolated as a crystalline solid requiring no heating whatsoever. Another advantage is that Diels–Alder cycloadducts with bis(2,2,2-trichloroethyl) azodicarboxylate are often crystalline solids that can be purified by recrystallization. This is in marked contrast to the viscous oils that are often obtained when the commercially available diethyl azodicarboxylate is used. Finally, we have found that Diels–Alder cycloadditions using bis(2,2,2-trichloroethyl) azodicarboxylate often proceed faster and at a temperature lower than that required for the dimethyl and diethyl analogues (e.g., reaction with 6,6-dimethylfulvene and 6-acetoxyfulvene).

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 264

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

nitrogen oxides

dinitrogen tetroxide

diethyl and dimethyl azodicarboxylate

ethanol, EtOH (64-17-5)

ether (60-29-7)

chloroform (67-66-3)

sodium bicarbonate (144-55-8)

nitric acid (7697-37-2)

sodium carbonate (497-19-8)

hydrazine hydrate (7803-57-8)

Pentane (109-66-0)

magnesium sulfate (7487-88-9)

diethyl azodicarboxylate (1972-28-7)

Bis(2,2,2-trichloroethyl) azodicarboxylate, Diazenedicarboxylic acid, bis(2,2,2-trichloroethyl) ester, Bis (2,2,2-trichloroethyl) azodicarboxylate (38857-88-4)

2,2,2-trichloroethyl chloroformate (17341-93-4)

Bis(2,2,2-trichloroethyl) hydrazodicarboxylate, bis (2,2,2-trichloroethyl) hydrazodicarboxylate (38858-02-5)

dimethyl azodicarboxylate (2446-84-6)

(2,2,2-trichloroethyl) azodicarboxylate

6,6-dimethylfulvene

6-acetoxyfulvene

Bis (2,2,2-trichloroethyl)hydrazodicarboxylate

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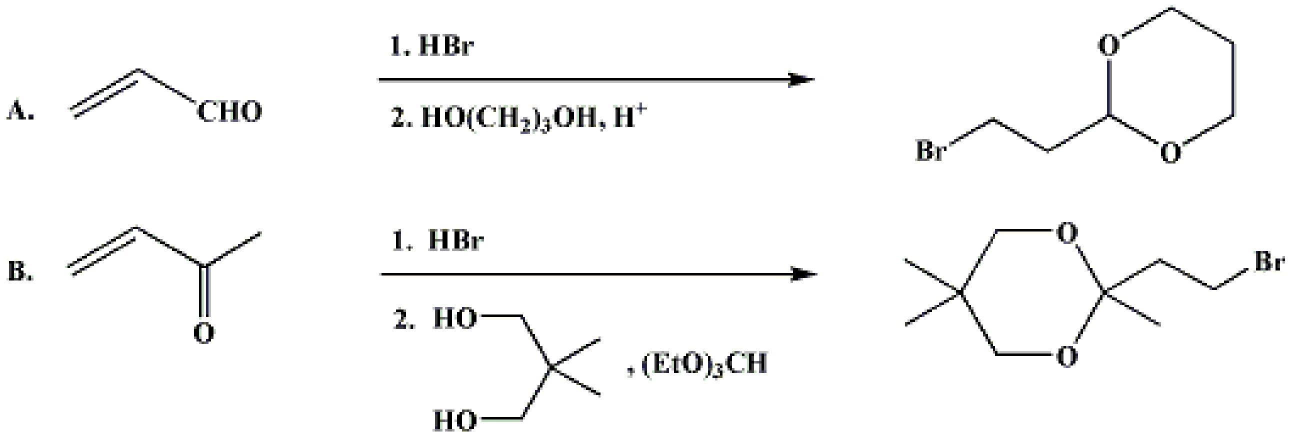
β-HALOACETALS AND KETALS: 2-(2-BROMOETHYL)-1,3-DIOXANE AND 2,5,5-TRIMETHYL-2-(2-BROMOETHYL)-1,3-DIOXANE



Submitted by J. C. Stowell, D. R. Keith, and B. T. King[1].
Checked by Yumi Nakagawa and Robert V. Stevens.

1. Procedure

A. *2-(2-Bromoethyl)-1,3-dioxane* (**1**). A 2-L, three-necked flask is equipped with a mechanical stirrer, thermometer, and gas inlet tube. In the flask are placed 750 mL of dichloromethane, 112 g (2.00 mol) of acrolein (Note 1), and 0.10 g of dicinnamalacetone indicator (Note 2) under nitrogen. The yellow solution is cooled to 0–5°C with an ice bath. Gaseous hydrogen bromide (Note 3) is bubbled into the solution with stirring until the indicator becomes deep red (Note 4). The ice bath is removed and 1.0 g of *p*-toluenesulfonic acid monohydrate and 152.2 g (2.00 mol, 144 mL) of 1,3-propanediol (Note 1) are added. The yellow solution is stirred at room temperature for 8 hr and then concentrated with a rotary evaporator. The residual oil is washed with two 250-mL portions of saturated aqueous sodium bicarbonate and dried over anhydrous potassium carbonate. Vacuum distillation through a 30-cm Vigreux column yields 252 g (65%) of **1** as a colorless liquid, bp 72–75°C (2.0 mm), n_D^2 1.4809 (Note 5).

B. *2,5,5-Trimethyl-2-(2-bromoethyl)-1,3-dioxane* (**2**). A 1-L, three-necked flask is equipped with a magnetic stirrer and a gas inlet tube. In the flask are placed 700 mL of dichloromethane, 140 g (2.00 mol) of methyl vinyl ketone (Note 6), and 0.010 g of dicinnamalacetone indicator (Note 2). Anhydrous hydrogen bromide (Note 3) is bubbled into the solution with stirring until the indicator changes to deep red (Note 7). The gas inlet tube is removed and 208 g (2.00 mol) of neopentanediol, 296 g (2.00 mol) of triethyl orthoformate, and 0.67 g of *p*-toluenesulfonic acid monohydrate are added to the solution. The flask is stoppered and stirred at room temperature for 1–2 hr and then concentrated by rotary evaporation (Note 8). The concentrated solution is washed twice with saturated sodium bicarbonate solution. *(Caution! There is some foaming.)* The bicarbonate washes are extracted three times with dichloromethane and the combined organic portions dried over anhydrous K_2CO_3. Rotary evaporation followed by vacuum distillation of the residue through a 30-cm Vigreux column yields 256 g (54%) of **2** as a clear, colorless oil, bp 65°C (0.3 mm), n_D^3 1.4687 (Note 9).

2. Notes

1. The acrolein, 1,3-propanediol, and cinnamaldehyde were purchased from Aldrich Chemical Company, Inc.

2. The indicator was prepared by the method of Diehl and Einhorn.[4] A solution of 5 g of sodium hydroxide in 50 mL of water and 40 mL of ethanol is prepared in a 250-mL Erlenmeyer flask. To this is added a solution of 1.84 mL (0.025 mol, 1.45 g) of acetone in 6.3 mL (0.050 mol, 6.6 g) of freshly distilled cinnamaldehyde (Note 1). This mixture is stirred thoroughly at room temperature for 30 min. The resulting voluminous yellow precipitate is filtered with suction, washed with 100 mL of water, and dried, affording 6.5 g of 1,9-diphenylnona-1,3,6,8-tetraen-5-one. Recrystallization from 200 mL of hot 95% ethanol gives 3.5 g of yellow crystals, mp 142–143°C (lit.[4] mp 142°C). This indicator is also available from Aldrich Chemical Co.

3. The anhydrous hydrogen bromide was purchased in a lecture bottle from Matheson. A trap is used between the lecture bottle and the gas inlet tube.

4. When the red color persists 5 min after the hydrogen bromide has been turned off, the addition is finished. At this point the proton magnetic resonance spectrum shows only dichloromethane and 3-bromopropanal (60 MHz, CH_2Cl_2) δ: 3.04 (t, 2 H), 3.59 (t, 2 H), 10.67 (s, 1 H).

5. Product **1** has the following spectral characteristics: IR (neat) cm^{-1}: 2980, 2870, 1250, 1150, 1140, 1015; ^{1}H NMR (90 MHz, $CDCl_3$) δ: 1.38 (d of m, 1 H, one 5-position on dioxane ring), 1.8–2.4 (m, the other 5-position on the dioxane ring), 2.14 (d of t, 2 H, CH_2-C-Br), 3.45 (t, 2 H, CH_2Br), 3.80 (d of t, 2 H, 4, and 6-positions on ring), 4.15 (d of double d, 2 H, 4, and 6-positions on ring), 4.71 (t, 1 H, 2-position on ring; ^{13}C magnetic resonance (22.5 MHz, $CDCl_3$) δ: 100.06, 66.86, 38.08, 27.79, 25.79.

6. The neopentanediol and triethyl orthoformate were purchased from Aldrich Chemical Co., Inc. and used as received. Failure to distill the methyl vinyl ketone, also obtained from Aldrich Chemical Co. Inc., to a clear, colorless liquid before use resulted in difficulty in determining the endpoint of the reaction with HBr. Therefore, the methyl vinyl ketone was distilled prior to use at reduced pressure.

7. When the red color persists 5 min after the hydrogen bromide has been turned off, the addition is finished. At this point the proton magnetic resonance spectrum shows only dichloromethane and 4-bromo-2-butanone (60 MHz, CH_2Cl_2) δ: 2.15 (s, 3 H, CH_3CO), 3.02 (t, 2 H, CH_2CO), 3.52 (t, 2 H, CH_2Br); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ: 25.75, 30.11, 45.91, 205.12. Little or no exotherm is noticed during the hydrogen bromide addition.

8. The reaction can be conveniently monitored by TLC using silica plates and eluting with 1 : 4 ethyl acetate–heptane.

9. Product 2 has the following characteristics: IR (neat liquid) cm^{-1}: 2970, 2880, 1260, 1220, 1125, 1085; ^{1}H NMR (60 MHz, $CDCl_3$) δ: 0.81 (s, 3 H, 5-methyl), 1.01 (s, 3 H, 5-methyl), 1.34 (s, 3 H, 2-methyl), 2.05–2.45 (m, 2 H, CH_2-C-Br), 3.2–3.8 (m, 6 H, CH_2O and CH_2Br); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ: 19.64, 22.24, 22.76, 26.99, 29.72, 43.25, 70.23, 98.26.

3. Discussion

Cyclic β-haloacetals and ketals have been prepared by variations of two basic methods. The most frequently used method involves the combination of an α,β-unsaturated carbonyl compound

(acrolein, methyl vinyl ketone, crotonaldehyde, etc.) a diol, and the anhydrous hydrogen halide. All possible sequences of combining these three have been used. In most cases the anhydrous acid was dissolved in the diol and then the carbonyl compound was added slowly.[5,6] Alternatively, the acetals of the α,β-unsaturated carbonyl compounds were prepared and isolated and then the hydrogen halide was added.[7] Finally the hydrogen halide may be added to the α,β-unsaturation followed by acetal formation,[8] and this is the basis of the present procedures.

The second general method is the aluminum halide-catalyzed reaction of acid halides with ethylene to give β-halo ketones, which are subsequently converted to ketals.[9,10]

The preparations are much simplified if a stoichiometric amount of hydrogen halide is added using an indicator to determine the endpoint. We have found that 1,9-diphenylnona-1,3,6,8-tetraen-5-one (dicinnamalacetone)[11] is of appropriate basicity to detect excess anhydrous hydrogen halides in organic solvents including chloroform, dichloromethane, benzene, toluene, acetic acid, and acetone (but not in alcohols). The reaction between the hydrogen halide and the α,β-unsaturated carbonyl compound is fast enough at 0–25°C that the endpoint is readily detected, and the yield-lowering use of excess hydrogen halide or long contact times[12] are avoidable. The intermediate β-halo aldehydes are unstable toward trimerization[13] if they are not diluted by a solvent and therefore should not be isolated but used directly in the next step. β-Bromo ketones darken on isolation and brief storage, so they, too, should be protected directly.

The conversion of the intermediate bromo aldehyde to the dioxane proceeds readily because of a favorable equilibrium position. However, the equilibrium for the reaction of the bromo ketone with the diol is unfavorable and requires removal of the by-product, water. This is done under mild conditions using ethyl orthoformate.[14]

We have chosen to use 1,3-diols because the Grignard reagents derived from the 1,3-dioxanes are thermally stable.[15] This contrasts with the use of ethylene glycol where the resulting β-haloalkyl dioxolanes give Grignard reagents that decompose at 25–35°C.[16,17,18] Acyclic acetals give insufficient protection to allow preparation of Grignard reagents.[18]The protection of the ketone with 1,3-propanediol is not readily driven to completion, but with neopentanediol the equilibrium lies further toward ketal formation,[2] giving a better yield of more stable ketal.

β-Haloacetals and ketals have recently seen wide use as alkylating agents[9,19,3,20,21] and in the preparation of Grignard reagents. The Grignard reagents have been alkylated,[22] acylated,[15,23] added to carbonyl groups,[24,17,25,26,27,28,29,30] and used in Michael additions.[31,32,33] One example also gives a useful Wittig reagent.[8] Subsequent reactions of these products generally require removal of the acetal and ketal groups to regenerate the carbonyl function. This is readily done with aqueous acid in most cases, but not when aldehydes were protected with 1,3-diols because of the high equilibrium stability of the corresponding dioxanes. This problem is readily overcome by first converting to the dimethyl acetal in methanol and then using aqueous acid hydrolysis, or by using other specialized methods.[8,1534,35]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

potassium carbonate (584-08-7)

acetic acid (64-19-7)

Benzene (71-43-2)

ethyl acetate (141-78-6)

methanol (67-56-1)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

Acrolein (107-02-8)

sodium bicarbonate (144-55-8)

hydrogen bromide, HBr (10035-10-6)

1,3-propanediol (504-63-2)

nitrogen (7727-37-9)

acetone (67-64-1)

toluene (108-88-3)

ethylene glycol (107-21-1)

ethylene (9002-88-4)

Ethyl orthoformate

triethyl orthoformate (122-51-0)

cinnamaldehyde

dichloromethane (75-09-2)

heptane (142-82-5)

crotonaldehyde (123-73-9)

methyl vinyl ketone (78-94-4)

2-(2-Bromoethyl)-1,3-dioxane (33884-43-4)

2,5,5-Trimethyl-2-(2-bromoethyl)-1,3-dioxane (87842-52-2)

dicinnamalacetone, 1,9-diphenylnona-1,3,6,8-tetraen-5-one (622-21-9)

neopentanediol

3-bromopropanal

4-bromo-2-butanone

p-toluenesulfonic acid monohydrate (6192-52-5)

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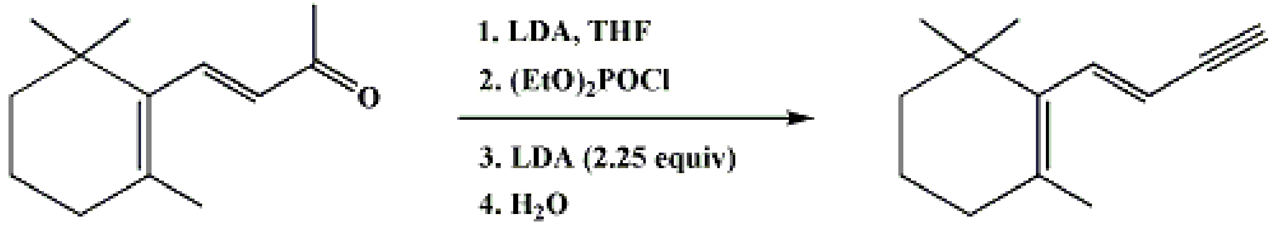
CONVERSION OF METHYL KETONES INTO TERMINAL ALKYNES: (*E*)-BUTEN-3-YNYL-2,6,6-TRIMETHYL-1-CYCLOHEXENE

[Cyclohexene, 2-(1-buten-3-ynyl)-1,3,3-trimethyl-, (*E*)-]



Submitted by Ei-ichi Negishi, Anthony O. King, and James M. Tour[1].
Checked by Weyton W. Tam and Robert V. Stevens.

1. Procedure

An oven-dried, 500-mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar, a rubber septum inlet, and an outlet connected to a mercury bubbler is flushed with nitrogen and charged with 100 mL of tetrahydrofuran (THF) (Note 1). To this are added sequentially at 0°C, diisopropylamine (Note 2) (10.6 g, 14,7 mL, 105 mmol) and butyllithium in hexane (Note 3) (2.22 *M*, 47.3 mL, 105 mmol). The reaction mixture is stirred for 30 min and cooled to −78°C. β-Ionone (Note 4) (19.2 g, 20.3 mL, 100 mmol) is slowly added. After stirring the mixture for 1 hr at −78°C, diethyl chlorophosphate (Note 5) (18.1 g, 15.2 mL, 105 mmol) is added, and the reaction mixture is allowed to warm to room temperature over 2–3 hr (reaction mixture A) (Note 6).

Lithium diisopropylamide is prepared in a separate 1-L flask from diisopropylamine (22.8 g, 31.6 mL, 225 mmol), butyllithium in hexane (2.22 *M*, 101 mL, 225 mmol), and THF (200 mL), as described above. To this is added over approximately 45 min at −78°C reaction mixture A prepared above via a 16-G double-ended needle under a slight pressure of nitrogen. The resulting mixture is allowed to warm to room temperature over 2–3 hr and is quenched with water (200 mL) at 0°C. The organic layer is separated, and the aqueous layer is extracted with pentane (3 × 50 mL). The combined organic layer is treated with ice-cold hydrochloric acid (1 *N*, 200 mL), water (2 × 100 mL), and saturated aqueous sodium bicarbonate (100 mL) to pH ≥8 (Note 7). After drying over magnesium sulfate, the volatile compounds are evaporated using a rotary evaporator at ca. 20 mm. The residue is distilled at 0.7 mm to provide (E)-buten-3-ynyl-2,6,6-trimethyl-1-cyclohexene (Note 8) in one fraction boiling at 69–73°C (0.7 mm) (Note 9). The yield by isolation has ranged from 12.5 g (72%) to 14.8 g (85%) (Note 10). The purity of the product by GLC is 98%.

2. Notes

1. Tetrahydrofuran available from Aldrich Chemical Company, Inc. was purified by

distillation from sodium and benzophenone.

2. The submitters used diisopropylamine (99%) available from Aldrich Chemical Company, Inc. without further purification.

3. The submitters used butyllithium in hexane available from Alfa Products, Morton Thiokol, Inc.

4. The submitters used 98% pure β-ionone available from Aldrich Chemical Company, Inc. without further purification.

5. The submitters used diethyl chlorophosphate available from Aldrich Chemical Company, Inc.

6. Reduced yields of product were obtained by the checkers when reaction time at room temperature was reduced from 2–3 hr to 1 hr.

7. After extraction with hydrochloric acid, the pentane layer, on addition of 100 mL of water, formed a poorly separating emulsion. Checkers found that, by addition of 100 mL of saturated aqueous sodium bicarbonate to this pentane–water emulsion, two easily separable layers can be formed.

8. The distilled product was found to be slightly yellow, and deepened to orange at room temperature. Storage at –5°C maintained the initial coloration for several weeks.

9. The product displays the following data: n_D^{24} 1.5130; IR (neat) cm^{-1}: 3300 (s), 2920 (s), 2080 (m), 1770 (w), 1630 (w), 1600 (w), 1455 (s), 1380 (m), 1355 (m), 1200 (m), 1030 (m), 960 (s); ^1H NMR ($CDCl_3$, TMS) δ: 1.01 (s, 6 H), 1.2–1.8 (m with a singlet at 1.71, 7 H), 1.85–2.15 (m, 2 H), 2.90 (d, 1 H, *J* = 2), 5.42 (dd, l H, *J* = 17 and 2), 6.67 (d, l H. *J* = 17); ^{13}C NMR ($CDCl_3$, TMS) δ: 19.17, 21.48, 28.75, 33.07, 33.98, 39.59, 77.29, 83.10, 111.36, 131.38, 136.90, 142.33.

10. The GLC trace (SE-30) of the reaction mixture shows essentially one peak (≥98) in the product region. In separate 5–20-mmol scale experiments, the GLC yields observed by using a paraffin internal standard were 90–95%.

3. Discussion

This procedure is based on a study of conversion of methyl ketones into terminal alkynes.[2] The scope of the procedure may be indicated by the results summarized in Table I.

TABLE I
CONVERSION OF METHYL KETONES INTO TERMINAL ACETYLENES VIA ENOL PHOSPHATES

		Yield of Acetylene (%)	
Ketone	Base[a]	GLC	Isolated
β-Ionone	LDA	95	85
Dihydro-β-ionone	LDA	90	85
Acetophenone	LDA	85	80
Pinacolone	LDA	90	78
Cyclohexyl methyl ketone	LDA	85	80
2-Octanone	LDA	23	—

2-Octanone	LTMP	75	—
6-Methyl-5-hepten-2-one	LDA	25	—
6-Methyl-5-hepten-2-one	LTMP	75	61

[a]LDA = lithium diisopropylamide; LTMP = lithium 2,2,6,6-tetramethylpiperidide.

As can be seen in Table I, lithium diisopropylamide (LDA) is a satisfactory base in cases where the carbon group (R) of a methyl ketone ($RCOCH_3$) either is bulky or does not contain an α-methylene or α-methine group. In the other cases, LDA is relatively ineffective. In such cases, however, the use of lithium 2,2,6,6-tetramethylpiperidide (LTMP) in place of LDA gives satisfactory results. The LTMP procedure appears to be the only documented method that is satisfactory for the conversion of the above-mentioned type.

The submitters have attempted the conversion of β-ionone into the desired dienyne by various known methods. In general, those involving acidic reagents or reaction conditions yielded the desired product in low yields (<50%) along with by-products, such as isomeric allenes, that appear near the product on GLC traces (SE-30). Such procedures include (a) PCl_5 in benzene, then $NaNH_2$ in NH_3;[3] (b) PCl_5 and 2,6-lutidine, then $NaNH_2$ in NH_3;[4] (c) $POCl_3$ in DMF, then NaOH;[5] and (d) $(CF_3SO_2)_2O$, CCl_4, pyridine, then heat.[6] Also unsatisfactory in the hands of submitters was a method involving the use of hydrazine in triethylamine, then iodine and triethylamine in THF, then methanolic potassium hydroxide.[7] A procedure involving the use of sodium ethoxide, then diethyl chlorophosphate, and finally $NaNH_2$ in NH_3,[8] on the other hand, converted β-ionone into the desired dienyne in ≤73% GLC yield. The procedure reported here may be viewed as a modification of the method described above.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 411

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

METHYL KETONES

Lithium 2,2,6,6-tetramethylpiperidide

PCl_5

NH_3

$POCl_3$

$(CF_3SO_2)_2O$

methanolic potassium hydroxide

acetylene (74-86-2)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

NaOH (1310-73-2)

sodium bicarbonate (144-55-8)

CCl_4 (56-23-5)

nitrogen (7727-37-9)

iodine (7553-56-2)

Acetophenone (98-86-2)

Pinacolone (75-97-8)

pyridine (110-86-1)

Benzophenone (119-61-9)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

Pentane (109-66-0)

hydrazine (302-01-2)

2-Octanone (111-13-7)

magnesium sulfate (7487-88-9)

2,6-Lutidine (108-48-5)

$NaNH_2$ (7782-92-5)

butyllithium (109-72-8)

Tetrahydrofuran, THF (109-99-9)

DMF (68-12-2)

hexane (110-54-3)

triethylamine (121-44-8)

Cyclohexyl methyl ketone (823-76-7)

diethyl chlorophosphate (814-49-3)

lithium diisopropylamide (4111-54-0)

diisopropylamine (108-18-9)

β-Ionone, Dihydro-β-ionone

(E)-Buten-3-ynyl-2,6,6-trimethyl-1-cyclohexene, Cyclohexene, 2-(1-buten-3-ynyl)-1,3,3-trimethyl-, (E)- (73395-75-2)

6-Methyl-5-hepten-2-one (110-93-0)

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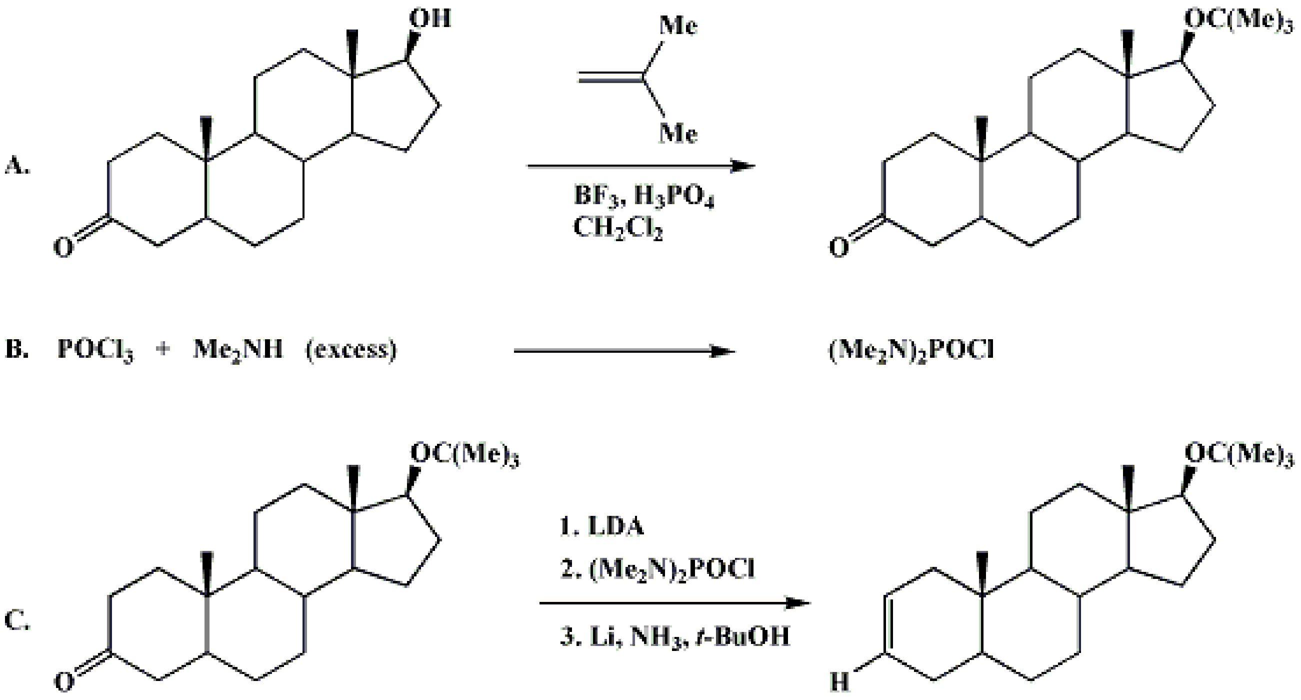
REDUCTIVE CLEAVAGE OF VINYL PHOSPHORODIAMIDATES: 17β-*tert*-BUTOXY-Gα-ANDROST-2-ENE



Submitted by Robert E. Ireland[1], Thomas H. O'Neil, and Glen L. Tolman.
Checked by James W. Herndon, M. F. Semmelhack, and Dieter Seebach.

1. Procedure

A. *Protection of the 17-hydroxyl group*. A solution of androstanolone ((Note 1), 4.10 g, 14 mmol) in 60 mL of dichloromethane in a 250-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar and a rubber septum bearing two syringe needles (argon inlet and exit) is cooled to −20°C (refrigerated bath). Argon is allowed to pass over the surface of the mixture for 15 min and then boron trifluoride etherate ((Note 2), 0.125 mL, 0.90 mmol) is added rapidly, via syringe, followed by anhydrous phosphoric acid ((Note 3), 0.053 mL, 1.0 mmol). Isobutene (Note 4) is added as a gas through a large-bore syringe needle until approximately 100 mL has condensed. The steroid precipitates during addition of the isobutene and redissolves as the reaction proceeds. The drying tube is replaced with a stopper, the tightly sealed flask is allowed to warm to 25°C, and the mixture is stirred at this temperature for 4 hr (Note 5). The flask is cooled to 0°C, opened, and warmed to 25°C to allow excess isobutene to evaporate. The residue is poured into 2 *N* aqueous ammonium hydroxide (100 mL) and ethyl acetate (75 mL) is added. After the layers are vigorously shaken, the aqueous solution is washed with a second portion of ethyl acetate. The combined organic extracts are washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation. The residue is recrystallized from hexane to give colorless crystals, mp 146–148°C, 4.10 g (86%, (Note 6)).

B. *Preparation and reductive cleavage of the vinyl phosphorodiamidate*. A dry, 250-mL flask equipped with magnetic stirrer, syringe port (Note 7), and argon outlet is flushed three times with argon. To the flask are added 40 mL of dry tetrahydrofuran (THF) and 1.17 mL (8.4 mmol) of dry diisopropylamine (Note 8). The flask is cooled in an acetone–dry-ice bath while 7.4 mmol of butyllithium in hexane (Note

9) is added dropwise with stirring. After the addition is complete, the solution is allowed to warm for 15 min. The flask is then cooled in an ice–water bath. To this solution is added 1.61 g (4.6 mmol) of 17β-*tert*-butoxy-5α-androstan-3-one in 30 mL of 2:1 THF/DMPU (Note 8) solution. The reaction mixture is stirred with ice cooling for 15 min. *N,N,N',N'*-Tetramethyldiamidophosphorochloridate, 5.83 mL (0.038 mol) (Note 10), is added dropwise with stirring. After 15 min, the bath is removed; the flask is allowed to warm to 25°C and is stirred for an additional 2 hr. The excess reagent is hydrolyzed by slow addition of 30 mL of saturated aqueous sodium bicarbonate solution and stirring for 30 min. After three extractions with 100-mL portions of diethyl ether, the combined organic layers are washed twice with 100 mL of water and 100 mL of saturated sodium chloride solution. The solution is dried over anhydrous magnesium sulfate and the ether is removed under reduced pressure on a rotary evaporator to afford 2.9–3.0 g of a crude yellow solid (Note 11). The crude phosphorodiamidate is dissolved in 40 mL of dry THF and added to a dry, three-necked, 250-mL flask equipped with overhead stirrer, cold finger condenser (acetone–dry ice), argon bubbler, and acetone–dry-ice bath. Dry ammonia is distilled into the flask until the phosphorodiamidate begins to precipitate. The bath is removed and the solution is allowed to warm to reflux. Dry *tert*-butyl alcohol (1.75 mL, (Note 12)) is added in one portion. To the clear solution is added 1.5 cm of 1/8-in., cleaned lithium wire in 0.3-cm portions. The blue color is maintained (by the addition of lithium wire if necessary) with stirring for 4 hr and then allowing the stirred solution to warm to room temperature overnight. Sodium benzoate is added in 25-mg portions until the blue color is discharged. Ammonium chloride (0.50 g) is added in one portion, the condenser removed, and the ammonia allowed to evaporate. The residue is taken up in 100 mL of diethyl ether and 100 mL of water. The layers are separated and the aqueous phase is extracted with 100 mL of diethyl ether. The combined organic layers are washed with 100 mL of saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, and filtered. The ether is removed under reduced pressure on a rotary evaporator. The crude olefin is filtered through 15 g of silica gel (Note 13) using benzene–ethyl acetate (2:1) as eluant, to give an off-white solid that is recrystallized from a minimum amount of absolute ethanol to give, after drying, 1.0 g (67%) (Note 14) of 17β-*tert*-butoxy-5α-androst-2-ene, mp 114–117°C (Note 15).

2. Notes

1. Androstanolone was obtained from Aldrich Chemical Company, Inc., and used without purification. The recheckers used material from Fluka Chemical Corp.
2. Boron trifluoride etherate was distilled before use.
3. Anhydrous phosphoric acid was prepared by slow addition of 5 g of 15% phosphoric acid to 2 g of phosphorus pentoxide.[2]
4. Isobutene, reagent grade, was obtained from Phillips Company.
5. The flask was stoppered with a greased 24/40 ground-glass stopper held in place by rubber bands stretched over appropriately placed wire hooks. The pressure at 25°C was slightly more than 1 atm.
6. The spectral properties are as follows: ^{1}H NMR ($CDCl_3$) δ: 0.74 (s, 3 H), 1.02 (s, 3 H), 1.13 (s, 9 H), 3.36 (m, 1 H); IR ($CHCl_3$) cm^{-1}: 1715 (C=0), 1255, 1205.
7. All solutions were added via glass syringes under rigorously anhydrous conditions.
8. Diisopropylamine and tetrahydro-1,3-dimethyl-2-(1H)-pyrimidinone (dimethyl propylene urea, DMPU) (Fluka Chemical Corp.) were distilled from calcium hydride. The original procedure used a THF–hexamethylphosphoric amide (HMPA) mixture. Because of the suspected carcinogenicity of HMPA, *Organic Syntheses* is recommending its replacement with DMPU whenever possible.
9. Butyllithium in hexane was obtained from Alfa Products. Morton Thiokol, Inc. or Foote Mineral Company. The checkers titrated the solution before[3] use.
10. *N,N,N',N'*-Tetramethyldiamidophosphorochloridate was obtained by the recheckers from Fluka Chemical Corp. If desired, it may be prepared as follows. In a dry, 2-L, three-necked flask

equipped with overhead stirrer, thermometer, argon outlet, and pressure-equalizing addition funnel is placed 400 mL of diethyl ether (Note 7). The flask is cooled in an isopropyl alcohol–dry-ice bath while 100 g (2.2 mol) of anhydrous dimethylamine is added in one portion. A solution of 85 g (0.56 mol) of phosphoryl chloride in 200 mL of diethyl ether is added at a rate to maintain the temperature at –35 ± 5°C. The addition time is approximately 1.5 hr. After the addition is complete, the bath is removed, and stirring is continued for 4 hr. The thick white slurry is filtered through a coarse frit and the filter cake is washed with 4000 mL of diethyl ether. The combined filtrates are concentrated under aspirator pressure on a rotary evaporator. Fractional distillation of the concentrate through a 10-cm Vigreux column gives 71–80 g (74–84%) of the *N,N,N',N'*-tetramethyldiamidophosphorochloridate, bp 58.5–59°C (0.6 mm) *d* 1.126; IR (neat) cm^{-1}: 1470, 1450, 1290, 1230, 980; ^1H NMR (neat) δ: 2.69 (d $J_{P\text{-}H}$ = 13).

11. Spectral data are as follows: IR (CCl_4) cm^{-1}: 1660, 1350, 1215; ^1H NMR ($CDCl_3$) δ: 0.69 (s, 3 H, CH_3), 0.78 (s, 3 H, CH_3), 1.11 (s, 9 H, CH_3), 2.60 (d, 3 H, $J_{P\text{-}H}$ = 10, *N*-CH_3), 3.28 (m, 1 H, OC*H*), 5.12 (m, 1 H, C=C*H*).
12. *tert*-Butyl alcohol was dried by distillation from calcium hydride.
13. Silica gel 60 (particle size 0.063–0.200 •m) is available from E. Merck, A. G.
14. In the original procedure employing HMPA, the yield was 1.1–1.2 g (71–78%).
15. Spectral data are as follows: ^1H NMR ($CDCl_3$) δ: 0.63 (s, 3 H, CH_3), 0.67 (s, 3 H, CH_3), 1.02 (s, 9 H, CH_3), 3.28 (m, 1 H, OC*H*), 5.43 (m, 2 H, vinyl H); IR ($CHCl_3$): The product was characterized by cleavage of the *tert*-butyl ether (CF_3CO_2H, CH_2Cl_2, 0°C) to give 17β-hydroxy-5α-androst-2-ene, mp 161–162°C, lit.[4] mp 163–165°C.

3. Discussion

The reduction of a carbonyl group to an olefin has been accomplished by the Shapiro modification[5] of the Bamford–Stevens reaction and by the hydride reduction of the corresponding enol ether,[6] enol acetate,[7] or enamine.[8] The nickel reduction of the thioketal has also been used successfully.[9]

The lithium/amine reduction of *N,N,N',N'*-tetramethylphosphorodiamidates is a general method for the cleavage of the C-O bond.[10] In addition to the reductive deoxygenation of carbonyl compounds to generate olefins, the phosphorodiamidates of alcohols are reduced in high yield to give alkanes. Alcohols in which the hydroxyl group is greatly hindered could be unreactive toward *N,N,N',N'*-tetramethyldiaminophosphorochloridate. In such cases, treatment of the alcohols with butyllithium and *N,N*-dimethylphosphoramidic dichloride in 1,2-dimethoxyethane and *N,N,N',N'*-tetramethylethylenediamine followed by addition of dimethylamine gave rise to *N,N,N',N'*-tetramethylphosphorodiamidates in good yields.[11] Combined in a two-step process (e.g., RCOR' RCHOHR' RCH_2R'), the method allows the reductive removal of a carbonyl functionality. This two-step process compares favorably with the analogous Wolff–Kishner reduction. Additionally, reduction of the enol phosphorodiamidate by dialkyl cuprate reagents generates a substituted olefin.[12]

The phosphorodiamidate group can also serve as a protecting group for the hydroxyl function, since it is stable to CH_3Li, $LiAlH_4$, KOH, and 0.2 *N* aqueous HCl, but is quantitatively cleaved by butyllithium–TMEDA (tetramethylethylenediamine).[10]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 126

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

VINYL PHOSPHORODIAMIDATES

17β-tert-BUTOXY-Gα-ANDROST-2-ENE

ethanol (64-17-5)

ammonia (7664-41-7)

Benzene (71-43-2)

ethyl acetate (141-78-6)

ether, diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

nickel (7440-02-0)

phosphoric acid (7664-38-2)

sodium benzoate (532-32-1)

ammonium hydroxide (1336-21-6)

dichloromethane (75-09-2)

Lithium wire (7439-93-2)

magnesium sulfate (7487-88-9)

dimethylamine (124-40-3)

isobutene (9003-27-4)

butyllithium (109-72-8)

Tetrahydrofuran, THF (109-99-9)

hexane (110-54-3)

tert-butyl alcohol (75-65-0)

boron trifluoride etherate (109-63-7)

calcium hydride (7789-78-8)

1,2-dimethoxyethane (110-71-4)

argon (7440-37-1)

diisopropylamine (108-18-9)

tetramethylethylenediamine (20485-44-3)

phosphoryl chloride (10025-87-3)

N,N,N',N'-Tetramethyldiamidophosphorochloridate (1605-65-8)

androstanolone (521-18-6)

vinyl phosphorodiamidate

phosphorodiamidate

tetrahydro-1,3-dimethyl-2-(1H)-pyrimidinone (7226-23-5)

dimethyl propylene urea (7226-23-5)

17β-hydroxy-5α-androst-2-ene

N,N,N',N'-tetramethyldiaminophosphorochloridate

phosphorus pentoxide (1314-56-3)

N,N,N',N'-tetramethylethylenediamine (110-18-9)

17β-tert-Butoxy-5α-androstan-3-one (87004-41-9)

17β-tert-Butoxy-5α-androst-2-ene (87004-43-1)

N,N-dimethylphosphoramidic dichloride (677-43-0)

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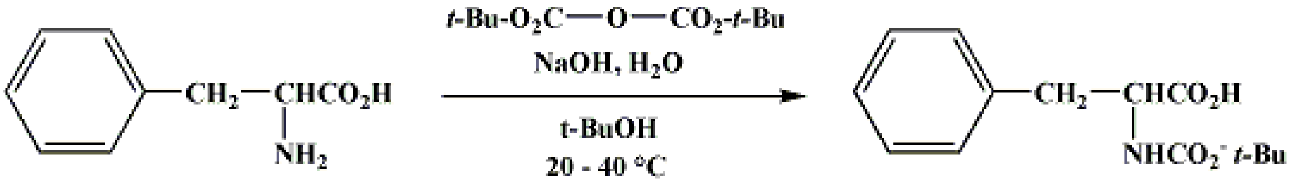
Organic Syntheses, CV 7, 70

tert-BUTOXYCARBONYLATION OF AMINO ACIDS AND THEIR DERIVATIVES: *N-tert*-BUTOXYCARBONYL-l-PHENYLALANINE

[L-Phenylalanine, *N*-[(1,1-dimethylethoxy)carbonyl]-]



Submitted by Oskar Keller, Walter E. Keller, Gert van Look, and Gernot Wersin[1].
Checked by Thomas von Geldern, Mark A. Sanner, and Clayton H. Heathcock.

1. Procedure

A 4-L, four-necked, round-bottomed flask, equipped with an efficient stirrer, a dropping funnel, reflux condenser, and thermometer is charged with a solution of 44 g (1.1 mol) of sodium hydroxide in 1.1 L of water. Stirring is initiated and 165.2 g (1 mol) of L-phenylalanine (Note 1) is added at ambient temperature, and then diluted with 750 mL of *tert*-butyl alcohol (Note 2). To the well-stirred, clear solution (Note 3) is added dropwise within 1 hr, 223 g (1 mol) of di-*tert*-butyl dicarbonate (Note 4). A white precipitate appears during addition of the di-*tert*-butyl dicarbonate. After a short induction period, the temperature rises to about 30–35°C. The reaction is brought to completion by further stirring overnight at room temperature. At this time, the clear solution will have reached a pH of 7.5–8.5. The reaction mixture is extracted two times with 250 mL of pentane, and the organic phase is extracted three times with 100 mL of saturated aqueous sodium bicarbonate solution. The combined aqueous layers are acidified to pH 1–1.5 by careful addition of a solution of 224 g (1.65 mol) of potassium hydrogen sulfate in 1.5 L of water (Note 5). The acidification is accompanied by copious evolution of carbon dioxide. The turbid reaction mixture is then extracted with four 400-mL portions of ethyl ether (Note 6). The combined organic layers are washed two times with 200 mL of water, dried over anhydrous sodium sulfate or magnesium sulfate, and filtered. The solvent is removed under reduced pressure using a rotary evaporator at a bath temperature not exceeding 30°C (Note 7). The yellowish oil that remains is treated with 150 mL of hexane and allowed to stand overnight (Note 8). Within 1 day the following portions of hexane are added with stirring to the partially crystallized product: 2 × 50 mL, 4 × 100 mL, and 1 × 200 mL. The solution is placed in a refrigerator overnight; the white precipitate is collected on a Büchner funnel and washed with cold pentane. The solid is dried under reduced pressure at ambient temperature to constant weight to give a first crop. The mother liquor is evaporated to dryness leaving a yellowish oil, which is treated in the same manner as described above, giving a second crop (Note 9). The total yield of pure white *N-tert*-butoxycarbonyl-L-phenylalanine is 207–230 g (78–87%), mp 86–88°C, $[\alpha]_D^{20}$ + 25.5° (ethanol, *c* 1.0) (Note 10).

2. Notes

1. L-Phenylalanine puriss. from Fluka AG or Tridom Chemical Inc. was used.
2. All the solvents and reagents used were of pure grade and obtained from Fluka AG.
3. At this stage, the reaction mixture has a pH of 12–12.5.

4. Di-*tert*-butyl dicarbonate can be prepared according to Pope, B. M.; Yamamoto, Y.; Tarbell, D. S. *Org. Synth., Coll. Vol. VI* **1988**, 418 or purchased from Fluka AG. Di-*tert*-butyl dicarbonate melts at 22–24°C; this compound can be liquified by immersing the reagent bottle in a water bath with a maximum temperature of 35°C. Commercial material is 97–98% pure; a total of 223 g must be employed.
5. It is recommended that acidification be carried out at a temperature of 0–5°C.
6. Ethyl or isopropyl acetate may also be used as extraction solvents for less lipophilic *N-tert*-butoxycarbonyl amino acids.
7. Evaporation should be performed first at 10–20 mm, then at a pressure less than 1 mm in order to remove the *tert*-butyl alcohol completely. Remaining small quantities of *tert*-butyl alcohol lead to difficulty in crystallization.
8. Seeding or scratching with a glass rod helps to induce crystallization.
9. Normally it is not worthwhile to isolate a third crop, which is of lower purity.
10. *N-tert*-Butoxycarbonyl-L-phenylalanine prepared by this method is obtained in a very pure state. Thin-layer chromatography shows a single spot and a content of less than 0.05% free amino acid. Acylation of lipophilic amino acids with excess di-*tert*-butyl dicarbonate may result to some extent in formation of the corresponding *N-tert*-butoxycarbonyl dipeptide.

3. Discussion

In recent years the *tert*-butoxycarbonyl (Boc) group has achieved a leading role as a protective group for the amino moiety of amino acids in peptide synthesis.[2] At one time the most widely used *tert*-butoxycarbonylating agent was the hazardous[3 4 5 6] and toxic *tert*-butyl azidoformate.[7 8] Di-*tert*-butyl dicarbonate[9 10 11] is a highly reactive and safe reagent of the "ready-to-use" type that reacts under mild conditions with amino acids,[9],[12 13 14 15 16 17 18 19 20] peptides,[21 22 23] hydrazine and its derivatives,[24 25] amines,[26 27 28 29 30 31 32] and CH-acidic compounds[33] in aqueous organic solvent mixtures to form pure derivatives in very good yields. Acylation with di-*tert*-butyl dicarbonate proceeds normally without strict pH control. The procedure given here demonstrates a suitable large-scale and safe preparation of an *N-tert*-butoxycarbonylamino acid with extremely simple experimental operations. Table I shows some other Boc-amino acids and derivatives prepared by this method. *N-tert*-Butoxycarbonyl-L-phenylalanine has also been prepared by acylation of L-phenylalanine with other *tert*-butoxycarbonylating agents: *tert*-butyl 4-nitrophenyl carbonate,[34] *tert*-butyl azidoformate,[35 36 37] *tert*-butyl 2,4,5-trichlorophenyl carbonate,[38] *tert*-butyl pentachlorophenyl carbonate,[39] *tert*-butyl 8-quinolyl carbonate,[40] *tert*-butyl chloroformate,[41 42] *tert*-butyl fluoroformate,[43] *tert*-butyl phenyl carbonate,[44] *N-tert*-butoxycarbonyl-1*H*-1,2,4-triazole,[45] *tert*-butyl 4,6-dimethylpyrimidyl-2-thiol carbonate,[46] *N-tert*-butoxycarbonyloxyimino-2-phenylacetonitrile,[47] *tert*-butyl α-methoxyvinyl carbonate,[48] *tert*-butyl aminocarbonate (*tert*-butoxycarbonyloxyamine).[49] Recently, a simple method for the 4-dimethylaminopyridine-catalyzed *tert*-butoxycarbonylation of various types of amides has been reported.[50]

TABLE I
BOC-AMINOACIDSPREPARED BYACYLATION WITHDI-*tert*-BUTYL DICARBONATE

Boc-Amino Acids[a]	Solvent[b]	Base	Time (hr)[c]	Yield, (%)	mp, (°C)	$[\alpha]^{20}_{D}$	Remarks
Boc-Ala-OH	A	NaOH	16	92–94	82–83	−25.5 (acetic acid, *c* 2.0)	pH 8.0[e]

Boc-β-Ala-OH	A	NaOH	16	85–86	76–77		
Boc-Arg-OH	B	—	15	88	159–160 (dec)	−6.8 (acetic acid, *c* 1.0)	Extraction with *n*-butyl alcohol
Boc-Arg (NO_2)-OH[d]	B	NaOH	15	82	107	−22.0 (pyridine, *c* 2.0)	pH 8.5[e]
Boc-Asn-OH	C	NaOH	18	80–81	176 (dec)	−7.2 (dimethylformamide, *c* 2.0)	5 hr, 45–50° C
Boc-Asp (OBzl)-OH	A	NaOH	16	81–89	101–102	−19.7 (dimethylformamide, *c* 2.0)	pH 8.0[e]
Boc-Cys (Bzl)-OH	B	NaOH	15	65	86–87	−43.4 (acetic acid, *c* 1.0)	
$(Boc\text{-}Cys\text{-}OH)_2$	D	NaOH	16	85	143–145 (dec)	−115.6 (acetic acid, *c* 2.0)	
Boc-Gln-OH	E	NaOH	18	76	125 (dec)	−3.4 (ethanol, *c* 2.0)	pH 8.0[e]
Boc-Glu (OBzl)-OH[f]	B	NaOH	15	86	142–143	+13.2(methanol, *c* 1.0)	pH 8.5–9[e]
Boc-Gly-OH	A	NaOH	16	96	87–88		
Boc-His (Boc)-OH	A	$KHCO_3$	18	75	170 (dec)	+19.5 (chloroform, *c* 2.0)	
Boc-Ile-OH	A	NaOH	16	78	69–71	+2.8 (acetic acid, *c* 2.0)	
Boc-Leu-OH[g]	A	NaOH	18	96	85–87	−24.7 (acetic acid, *c* 2.0)	
Boc-Lys (Boc)-OH[f]	A	NaOH	16	82	138–139	+6.1 (dimethylformamide, *c* 1.5)	
Boc-Lys (CBZ)-OH	A	NaOH	18	96	Oil		
Boc-Met-OH	A	NaOH	18	60[h]	50–51	−22.8 (methanol, *c* 1.3)	
Boc-Met-OH[f]	A	NaOH	18	85	139–140	+18.2 (ethanol, *c* 2.0)	
Boc-Pro-OH	A	NaOH	12	95	134–135	−60.6 (acetic acid, *c* 2.0)	
Boc-Ser-OH	A	NaOH	16	66–82	86–88	−3.6 (acetic acid, *c* 2.0)	pH 8.5–9[e]
Boc-Ser (Bzl)-OH	B	NaOH	16	90	62–63	+19.2 (80% ethanol, *c* 2.0)	pH 8.5–9[e]
Boc-Thr-OH	A	NaOH	16	85	71–73	−8.2 (acetic acid, *c* 1.0)	

Boc-Trp-OH[i]	A	NaOH	16	96	137–138 (dec)	−18.2 (dimethylformamide, *c* 1.0)	
Boc-Trp-(FOR)-OH[f]	F	Et_3N	48	61	158–159[k]	+36.0 (ethanol, *c* 2.0)	
Boc-Tyr-OH	A	NaOH[l]	24	75	137[m]	+2.6 (acetic acid, *c* 1.0)	
Boc-Tyr-OH[f]	A	NaOH[l]	24	84	216	+2.6 (acetic acid, *c* 1.0)	
Boc-Tyr (Bzl)-OH	B	NaOH	18	70	110–111	+27.6 (ethanol, *c* 1.0)	pH 10.4[e]
Boc-Tyr (2,6-Cl_2-Bzl)-OH	A	NaOH	24	48	104 (dec)	+20.6 (ethanol, *c* 2.0)	
Boc-Val-OH	A	NaOH	16	85	76–78	−7.5 (acetic acid, *c* 1.0)	

[a]The amino acids used, with the exception of β-alanine and glycine, were of L-configuration The abbreviations used for amino acids and their protecting substituents concur with E. Wünsch.[2]

[b]Solvent systems: A: *tert*-butyl alcohol–water; B: dioxane–water; C: dimethylformamide–water; D: methanol–water; E: acetonitrile–water; F: dimethylformamide.

[c]The reaction was generally carried out at room temperature after the exothermic starting period had subsided. Progress of the reaction was monitored by TLC. Reaction times are not optimized.

[d]Crystallizes with 15% solvent (ethyl acetate).

[e]pH control is necessary.

[f]Dicyclohexylamine salt.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Ethyl or isopropyl acetate

Boc-Ala-OH

Boc-β-Ala-OH

Boc-Arg-OH

Boc-Arg(NO_2)-OH

Boc-Asn-OH

Boc-Asp(OBzl)-OH

Boc-Cys(Bzl)-OH

$(Boc\text{-}Cys\text{-}OH)_2$

Boc-Gln-OH

Boc-Glu(OBzl)-OH

Boc-Gly-OH

Boc-His(Boc)-OH

Boc-Ile-OH

Boc-Leu-OH

Boc-Lys(Boc)-OH

Boc-Lys(CBZ)-OH

Boc-Met-OH

Boc-Pro-OH

Boc-Ser-OH

Boc-Ser(Bzl)-OH

Boc-Thr-OH

Boc-Trp-OH

Boc-Trp-(FOR)-OH

Boc-Tyr-OH

Boc-Tyr(Bzl)-OH

Boc-Tyr(2,6-Cl_2-Bzl)-OH

Boc-Val-OH

ethanol (64-17-5)

acetic acid (64-19-7)

ethyl acetate (141-78-6)

methanol (67-56-1)

ethyl ether (60-29-7)

acetonitrile (75-05-8)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

carbon dioxide (124-38-9)

potassium hydrogen sulfate (7646-93-7)

n-butyl alcohol (71-36-3)

pyridine (110-86-1)

Glycine (513-29-1)

Pentane (109-66-0)

β-Alanine (107-95-9)

magnesium sulfate (7487-88-9)

dioxane (5703-46-8)

L-phenylalanine (63-91-2)

dimethylformamide (68-12-2)

hexane (110-54-3)

tert-butyl alcohol (75-65-0)

Boc-amino

tert-Butyl azidoformate (1070-19-5)

N-tert-butoxycarbonyloxyimino-2-phenylacetonitrile (58632-95-4)

tert-Butyl phenyl carbonate (6627-89-0)

Di-tert-butyl dicarbonate (24424-99-5)

tert-butyl chloroformate

tert-butyl 2,4,5-trichlorophenyl carbonate (16965-08-5)

tert-butyl fluoroformate

tert-butyl α-methoxyvinyl carbonate

N-tert-Butoxycarbonyl-L-phenylalanine, L-Phenylalanine, N-[(1,1-dimethylethoxy)carbonyl]- (13734-34-4)

tert-butyl 4-nitrophenyl carbonate (13303-10-1)

tert-butyl pentachlorophenyl carbonate (18942-25-1)

tert-butyl 8-quinolyl carbonate

N-tert-butoxycarbonyl-1H-1,2,4-triazole (41864-24-8)

tert-butyl 4,6-dimethylpyrimidyl-2-thiol carbonate

tert-butyl aminocarbonate, tert-butoxycarbonyloxyamine

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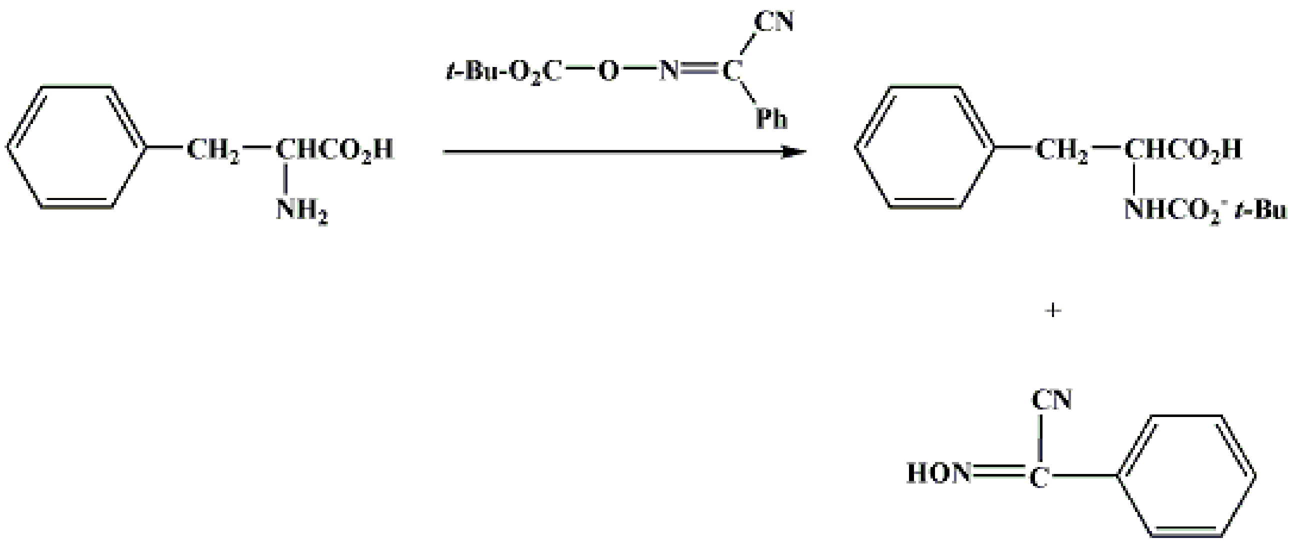
N-*tert*-BUTOXYCARBONYL-l-PHENYLALANINE

[L-Phenylalanine, *N*[(1,1-dimethylethoxy)carbonyl)]-]



Submitted by William J. Paleveda, Frederick W. Holly, and Daniel F. Veber[1].
Checked by Mark A. Sanner, Thomas von Geldern, and Clayton H. Heathcock.

1. Procedure

To a stirred mixture of 16.51 g (0.1 mol) of L-phenylalanine in 60 mL of water and 60 mL of peroxide-free dioxane (Note 1) is added 21 mL of triethylamine. To the resulting solution is added 27.1 g (0.11 mol) of 2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile (Note 2). Solution is obtained during the first hour of stirring. After 3 hr (Note 3) the solution is diluted with 150 mL of water. The resulting turbid solution is extracted with at least four 200-mL portions of ethyl ether (Note 4). The aqueous layer is then acidified to pH 2.5 with cold 2.5 *N* hydrochloric acid to yield an oily layer. The mixture is extracted with three 100-mL portions of methylene chloride. The combined organic extracts are dried with anhydrous sodium sulfate. After filtration of the sodium sulfate, the filtrate is evaporated under reduced pressure at a bath temperature of 30°C. Hexane is added to the thick oil to turbidity. Crystallization occurs after cooling and stirring the mixture for a short time. More hexane is added in portions until no further crystallization occurs. A total of 200 mL of hexane is required. The mixture is allowed to stand for 1 hr. The white crystalline solid is collected by filtration, washed with three 100-mL portions of hexane, and dried under reduced pressure to yield 21.4–22.0 g (80–83%) of *tert*-butoxycarbonyl-L-phenylalanine, mp 86–88°C, $[\alpha]_D^{20}$ −3.6° (HOAc, *c* 1), $[\alpha]_{546}^{20}$ 29.9° [EtOH, *c* 1) (Note 5).

2. Notes

1. Peroxides are removed from dioxane by its passage through a column of neutral alumina.[2]
2. 2-(*tert*-Butoxycarbonyloxyimino)-2-phenylacetonitrile is obtained from Aldrich Chemical Company, Inc., under the trademark "BOC-ON."
3. The reaction is allowed to continue until TLC (Whatman K1F, ethyl acetate–pyridine–acetic acid–water, 10:5:1:3) shows that the unprotected amino acid (R_f 0.4) is no longer present, as evidenced by negative ninhydrin spray.

4. It is imperative that all the by-product is removed at this point; otherwise it will contaminate the product, making crystallization difficult. Each ether extract is spotted on a Whatman K1F plate and the plate viewed under UV light to ascertain that all of the by-product has been extracted. The checkers found that six or seven ether extractions were required to remove the by-product completely.

5. The literature gives melting points ranging from 79–80°C to 84–86°C; the optical rotation is reported as $[\alpha]_D^{25}$ −0.8° (HOAc, *c* 4.957), $[\alpha]_D^{20}$ −4.8° (HOAc, *c* 1), $[\alpha]_{546}^{20}$ 30° (EtOH, *c* 1). The spectral properties of *tert*-butoxycarbonyl-L-phenylalanine are as follows: ^{1}H NMR (CD_3OD) δ: 1.36 (s, 9 H, *t*-butyl), 2.87 (dd, 1 H, J = 14.9, H_β), 3.16 (dd, 1 H, J = 14.6, H_β), 4.36 (dd, 1 H, J = 9.6, H_α), 7.26 (s, 5 H, phenyl). In $CDCl_3$ solution, both carbamate rotamers may be seen in the ^{1}H NMR spectrum.

3. Discussion

Various reagents have been used for the introduction of the *tert*-butoxycarbonyl group, including *tert*-butyl *p*-nitrophenyl carbonate,[3] *tert*-butyl azidoformate[4] (no longer commercially available because of its toxic and potentially explosive nature), *tert*-butyl 2,4,5-trichlorophenyl carbonate,[5] di-*tert*-butyl dicarbonate,[6] and the reagent described herein, 2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile.[7] Using the same reagent, the crystalline BOC derivatives of the following amino acids have been prepared in these laboratories in the indicated yields: 7-aminoheptanoic acid (88%), DL-tyrosine (96%), 6-fluoro-DL-tryptophan (87%), 5-methyl-DL-tryptophan (95%), 5-bromo-DL-tryptophan (94%), 5-methoxy-DL-tryptophan (67%), 1-methyl-DL-tryptophan (82%), and 5-fluoro-DL-tryptophan (62%).

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alumina

L-Phenylalanine, N[(1,1-dimethylethoxy)carbonyl)]-

hydrochloric acid (7647-01-0)

ether, ethyl ether (60-29-7)

sodium sulfate (7757-82-6)

methylene chloride (75-09-2)

dioxane (5703-46-8)

L-phenylalanine (63-91-2)

hexane (110-54-3)

triethylamine (121-44-8)

tert-Butyl azidoformate (1070-19-5)

2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile (58632-95-4)

ninhydrin (938-24-9)

7-aminoheptanoic acid (929-17-9)

Di-tert-butyl dicarbonate (24424-99-5)

tert-butyl 2,4,5-trichlorophenyl carbonate (16965-08-5)

N-tert-Butoxycarbonyl-L-phenylalanine, tert-butoxycarbonyl-L-phenylalanine (13734-34-4)

tert-butyl p-nitrophenyl carbonate (13303-10-1)

DL-tyrosine

6-fluoro-DL-tryptophan (7730-20-3)

5-methyl-DL-tryptophan (951-55-3)

5-bromo-DL-tryptophan (6548-09-0)

5-methoxy-DL-tryptophan (28052-84-8)

1-methyl-DL-tryptophan (26988-72-7)

5-fluoro-DL-tryptophan (154-08-5)

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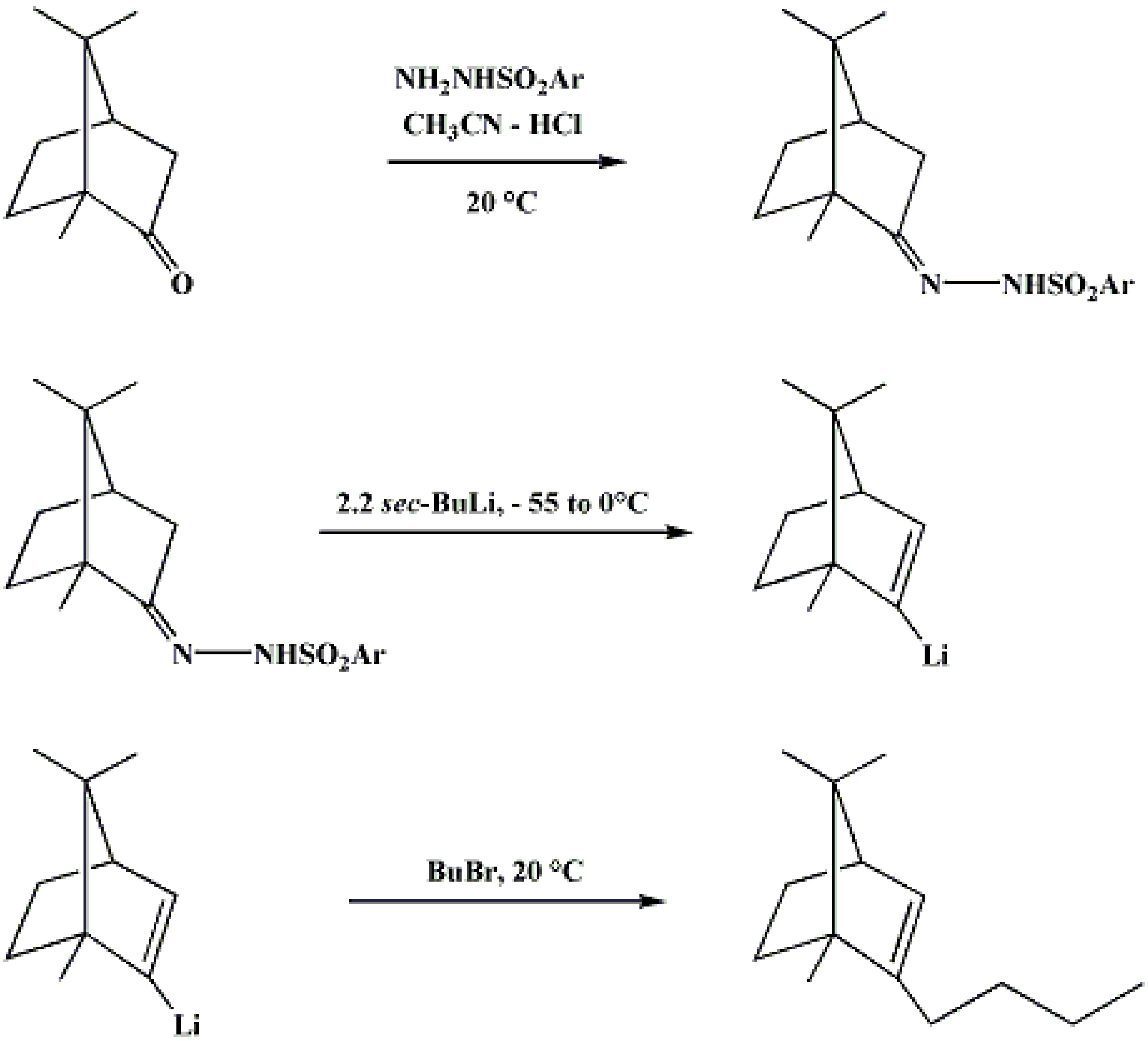
GENERATION AND REACTIONS OF ALKENYLLITHIUM REAGENTS: 2-BUTYLBORNENE



Submitted by A. Richard Chamberlin, Ellen L. Liotta, and F. Thomas Bond[1].
Checked by Hiroko Masamune and Robert V. Stevens.

1. Procedure

A. *d-Camphor* 2,4,6-*triisopropylbenzenesulfonylhydrazone*. In a 500-mL Erlen-meyer flask equipped with a magnetic stirring bar is placed 66.0 g (0.22 mol) of 2,4,6-triisopropylbenzenesulfonylhydrazide (Note 1), 30.4 g (0.20 mol) of *d*-camphor (Note 2), 100 mL of freshly distilled acetonitrile, and 20.0 mL (0.24 mol) of concentrated hydrochloric acid. The resulting solution is stirred overnight while a granular solid precipitates. The white crystals are cooled at −10°C for 4 hr and collected by suction filtration, dissolved in 175 mL of dichloromethane, filtered to remove a small amount of insoluble material, and concentrated under reduced pressure on a rotary evaporator

to give 60.8–63.4 g (70–73%) of a white solid, mp 196–199°C (dec) (Note 3).

B. *2-Butylbornene*. A 1-L, three-necked flask is equipped with a 250-mL addition funnel (sealed with a rubber septum), a mechanical stirrer, and a rubber septum. The system is vented (via a hypodermic needle inserted through the addition funnel septum) through a mineral oil bubbler, and the apparatus is flame-dried while it is flushed with prepurified nitrogen introduced through the septum of the flask. The flask is charged with 40.0 g (0.092 mol) of *d*-camphor 2,4,6-triisopropylbenzenesulfonylhydrazone, resealed, and again flushed with nitrogen. Hexane, 200 mL, (Note 4), and 200 mL of tetramethylethylenediamine (Note 5) are added, and the stirred solution, under an atmosphere of nitrogen, is cooled to approximately –55°C with an ethanol–water(2:1)/dry ice bath. Using a Luer-Lok syringe, 158 mL (0.20 mol) of 1.29 *M sec*-butyllithium (Note 6) is transferred to the addition funnel. The solution is stirred rapidly and the *sec*-butyllithium added over a period of 15–20 min. The resulting orange solution is stirred for 2 hr, and the cold bath removed. After 20 min the flask is immersed in an ice bath until nitrogen evolution ceases (approximately 10 min).

To this stirred solution of 2-lithiobornene is added, via syringe, 15.2 g (0.11 mol) of butyl bromide (Note 7) over a 1-min period. The ice bath is then removed, and the reaction mixture is stirred at room temperature overnight. The mixture is poured into 500 mL of water. The layers are separated and the aqueous layer extracted with two 100-mL portions of ether. The combined organic extracts are washed with five 200-mL portions of water, one 50-mL portion of 1 *N* hydrochloric acid, and two 200-mL portions of water. The solution is dried over anhydrous magnesium sulfate, filtered, and concentrated on a rotary evaporator at aspirator pressure and room temperature. Distillation of the residual yellow liquid through a 20-cm Vigreux column affords 8.9–9.4 g (50–53%) of product as a colorless liquid, bp 57–59°C (0.5 mm), n_D^{25} 1.4664, $[\alpha]_D^{25}$ – 10.7° (*c* MeOH, 0.0747) (Note 8).

2. Notes

1. The submitters used material prepared following a literature procedure.[2]
2. *d*-Camphor was purchased from Eastman Kodak Co., $[\alpha]_D^{25}$ + 39.5°.
3. The ^{1}H NMR spectrum is as follows: δ: 0.61 (s, 3 H), 0.86 (s, 6 H), 1.26 (overlapping doublets, *J* = 6.7, 18 H), 1.4–2.2 (m, 7 H), 2.90 (septuplet, *J* = 7, 1 H), 4.20 (septuplet, *J* = 7, 2 H), 7.15 (s, 2 H).
4. MCB, Inc. reagent-grade hexane was distilled from lithium aluminum hydride.
5. This compound was purchased from Aldrich Chemical Company, Inc., and distilled from lithium aluminum hydride.
6. The *sec*-butyllithium was purchased from Alfa Products, Morton Thiokol, Inc. and standardized by double titration or diphenylacetic acid titration. Other alkyllithium bases such as butyllithium and methyllithium cannot be substituted for the stronger *sec*-butyllithium since larger amounts of bornylene are formed because of incomplete dianion formation. Careful attention must be paid to

stoichiometry in this reaction; failure to do so also results in increasing the amount of bornylene formed.

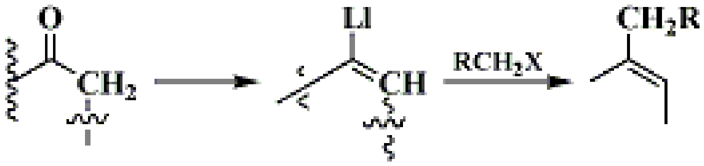
Even under ideal conditions the NMR of crude product shows 20–30% bornylene, which, however, is easily separated from the desired product during distillation as a "forerun" which sublimes into the vacuum pump trap.

7. Analytical reagent material was purchased from Mallinckrodt, Inc., and distilled from calcium hydride.

8. The ^{1}H NMR spectrum ($CDCl_3$) is as follows: δ 0.74 (s, 3 H), 0.76 (s, 3 H), 0.94 (s, 3 H), 0.7–1.0 (broad m, 7 H), 1.4 (m, 4 H), 1.9 (m, 2 H), 2.19 ("t", *J* = 4, 1 H), 5.51 (m, 1 H).

3. Discussion

The sequence described here illustrates a general procedure for converting ketones into alkylated olefins:



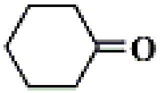
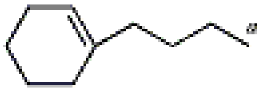
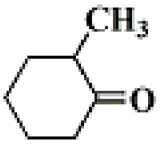
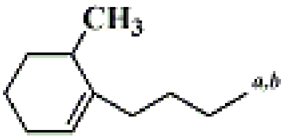
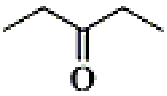
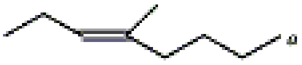
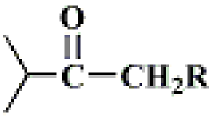
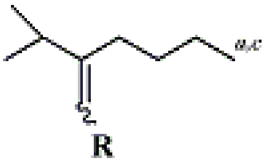
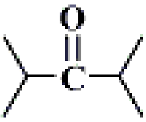
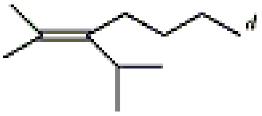
It is a modification of the Shapiro olefin synthesis[3] that allows the alkenyl anion intermediate to be trapped with primary halides and other electrophiles. Use of triisopropylbenzenesulfonylhydrazones as the vinyllithium precursor[4] is an improvement over previously[4] used toluenesulfonylhydrazones,[5,6] which can be employed in the sequence provided excess *sec*-butyllithium (typically 4.5 equiv) and alkyl halide (3.0 equiv) are used. Methyl ketones (e.g., acetone, acetophenone, 2-octanone) can also be used and can be converted into their dianions using 2.2 equiv of the weaker base, butyllithium. The conditions described above, with the slight modifications noted, have been used for a variety of ketones as shown in Table I.

The submitters have found that the hexane–tetramethylethylenediamine solvent system described above, which is required for toluenesulfonylhydrazones, may be replaced with tetrahydrofuran when triisopropylbenzenesulfonylhydrazones are used, provided that the electrophilic reagent is added to the alkenyllithium species as soon as it is formed (as indicated by cessation of nitrogen evolution).

Primary alkyl bromides react well in this sequence except for particularly reactive compounds (e.g., methyl bromide, allyl bromide) that give the vinyl halide by metal-halogen exchange. Secondary halides, as expected, suffer from elimination as a side reaction. Other electrophiles have been used successfully including D_2O, aldehydes and ketones, dimethylformamide,[4,7] chlorotrimethylsilane,[4,8] 1,2-dibromoethane,[4] and carbon dioxide. Such sequences allow for relatively straightforward preparation of deuterated olefins, allylic alcohols, α,β-unsaturated aldehydes, alkenylsilanes, alkenyl bromides, and α,β-unsaturated acids. The major advantages of this route to

alkenyllithium reagents[9] lie in the availability of the ketone precursors and the regiospecificity of the Shapiro reaction.[3,10] There are numerous alternative routes to trisubstituted olefins.[11]

TABLE I
KETONE TO BUTYLALKENE CONVERSIONS

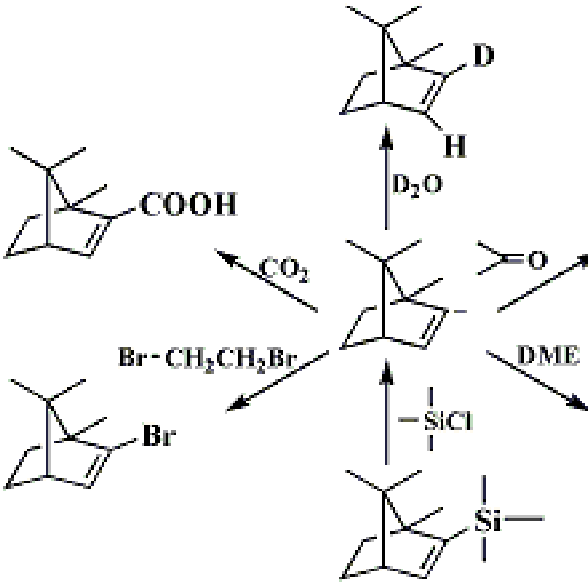
Ketone	Product
	 [a]
	 [a,b]
	 [a]
	 [a,c]
	 [d]

[a] *sec*-Butyllithium is added at –8°C.

[b] Approximately 2% of the isomeric 1-butyl-2-methylcyclohexene is formed.

[c] A mixture of (*Z*) and (*E*) isomers is formed.

[d] Tertiary hydrogen removal is slower. *sec*-Butyllithium (3.0 equiv) is added at −78°C; the solution is immediately warmed to room temperature and stirred for 1–2 hr before butyl bromide (2.0 equiv) is added.



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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

M sec-butyllithium

hydrochloric acid (7647-01-0)

ether (60-29-7)

hydrogen (1333-74-0)

acetonitrile (75-05-8)

Allyl bromide (106-95-6)

Butyl bromide (109-65-9)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

acetone (67-64-1)

Acetophenone (98-86-2)

1,2-dibromoethane (106-93-4)

methyl bromide (74-83-9)

Diphenylacetic acid (117-34-0)

dichloromethane (75-09-2)

2-Octanone (111-13-7)

magnesium sulfate (7487-88-9)

d-camphor (21368-68-3)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

dimethylformamide (68-12-2)

hexane (110-54-3)

Methyllithium (917-54-4)

calcium hydride (7789-78-8)

vinyllithium (917-57-7)

CHLOROTRIMETHYLSILANE (75-77-4)

tetramethylethylenediamine (20485-44-3)

sec-butyllithium (598-30-1)

2-Butylbornene (87068-33-5)

2,4,6-triisopropylbenzenesulfonylhydrazide (39085-59-1)

2-Lithiobornene

bornylene

1-butyl-2-methylcyclohexene

D-Camphor 2,4,6-triisopropylbenzenesulfonylhydrazone

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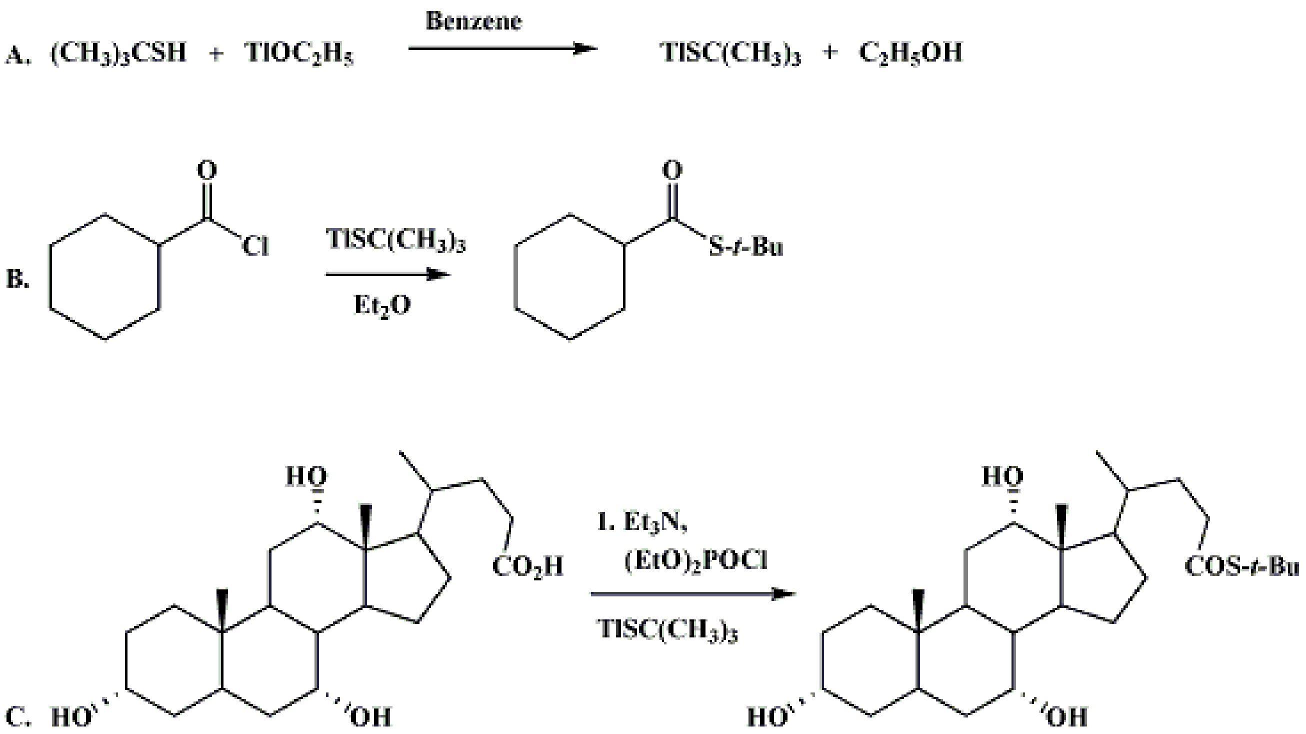
Organic Syntheses, CV 7, 81

PREPARATION OF THIOL ESTERS: S-*tert*-BUTYL CYCLOHEXANECARBOTHIOATE AND *S*-*tert*-BUTYL 3α,7α,12α-TRIHYDROXY-5β-CHOLANE-24-THIOATE

[Cyclohexanecarbothioic acid, *S*-(1,1-dimethylethyl)ester and cholane-24-thioic acid, 3,7,12-trihydroxy-S-(1,1-dimethylethyl)ester, (3α,5β,7α,12α)]



Submitted by Gary O. Spessard[1], Wan Kit Chan[2], and S. Masamune[2].
Checked by Trina Kittredge and Robert V. Stevens.

1. Procedure

Caution! Thallium compounds are very toxic. However, they may be safely handled if prudent laboratory practices are followed. Rubber gloves and laboratory coats should be worn, and reactions should be carried out in an efficient hood. Thallium wastes should be collected and disposed of separately.[3]

A. *Thallium(I) 2-methylpropane-2-thiolate*. A 500-mL, round-bottomed flask equipped with a magnetic stirring bar and a pressure-equalizing dropping funnel to which a nitrogen inlet adapter is attached is charged with 47.2 g (0.189 mol) of thallium(I) ethoxide (Note 1) and 200 mL of anhydrous benzene (Note 2). Over a period of 15 min 19.2 g (24 mL, 0.213 mol) of 2-methylpropane-2-thiol (Note 1) is added. The reaction mixture is stirred under a nitrogen atmosphere for 1 hr and the resulting precipitate is collected by filtration. After washing with three 100-mL portions of anhydrous pentane (Note 3), 48.5–51.2 g (90–95%) of the product is obtained as bright yellow crystals, mp 165–170°C dec (Note 4). This material is sufficiently pure for use in the following steps.

B. *S-tert-Butyl cyclohexanecarbothioate*. A solution of 4.38 g (0.030 mol) of cyclohexanecarboxylic acid chloride (Note 5) in 150 mL of ether (Note 6) is placed in a dry, 500-mL, round-bottomed flask equipped with a magnetic stirring bar and a gas inlet. The system is flushed with nitrogen and the solution is cooled in an ice bath. Stirring is initiated and 8.82 g (0.031 mol) of the thallium(I) 2-methylpropane-2-thiolate prepared in Step A is added. After the resulting milky suspension is stirred for 2 hr at room temperature,

the fine precipitate is removed by filtration through Celite (Note 7) and washed thoroughly with four 50-mL portions of ether. The combined filtrate and washings are concentrated on a rotary evaporator to give a pale-yellow oil, which is distilled under reduced pressure through a 5-cm Vigreux column. After separation of a forerun, 5.36–5.44 g (90–91%) of the colorless thiol ester is collected, bp 100°C (7 mm) (Note 8).

C. *S-tert-Butyl ester from cholic acid*. A dry, 250-mL, one-necked, round-bottomed flask is equipped with a magnetic stirring bar and a nitrogen inlet adapter; the system is purged with, and maintained under, dry nitrogen. After 4.90 g (0.0120 mol) of cholic acid (Note 9), 1.33 g (0.0131 mol) of triethylamine (Note 10), and 60 mL of dry tetrahydrofuran (THF, (Note 11)) are placed in the flask, a stoppered, pressure-equalizing dropping funnel charged with a solution of 2.18 g (0.0127 mol) of diethyl phosphorochloridate (Note 9) in 30 mL of dry THF is attached to the top of the nitrogen inlet adapter (see f.htmigure 1). The solution is added to the stirred reaction mixture over a period of 5 min and stirring is continued for 3.5 hr at room temperature. The dropping funnel is removed, and the reaction mixture is taken up into a dry, 100-mL syringe and transferred to a dry filtering apparatus. This apparatus is shown in f.htmigure 2. The glass-fritted filter funnel of medium porosity with a built-in vacuum adapter is connected to the middle neck of a 500-mL, three-necked, round-bottomed flask. A calcium chloride drying tube is connected to the vacuum adapter and a nitrogen inlet adapter is attached to the top of the filter funnel. The precipitated triethylamine hydrochloride is now removed from the reaction mixture by stoppering the nitrogen inlet adapter and using the positive nitrogen pressure to force the solution through the glass frit. Dry tetrahydrofuran, 40 mL, is used to rinse the original reaction flask. The stopper of the nitrogen inlet adapter (.htmFigure 2) is removed, and this washing is transferred via the same syringe to the filtering apparatus and forced through the filter in the same manner described above. One of the stoppers of the three-necked flask is replaced by a nitrogen inlet adapter and the filter funnel is replaced by a mechanical stirrer. As the filtrate is stirred at room temperature, the remaining stopper is removed and 3.90 g (0.0133 mol) of thallium(I) 2-methylpropane-2-thiolate is added. After the addition is complete, the neck is restoppered, and the resulting mixture is vigorously stirred under nitrogen at room temperature overnight. The precipitate is removed by suction filtration through Celite filter aid (Note 7) and washed with three 30-mL portions of THF. The filtrate and washings are combined and concentrated under reduced pressure, and the resulting residue is dissolved in 160 mL of ethyl acetate. This solution is washed with two 100-mL portions of aqueous 5% $NaHCO_3$, then with 50 mL of aqueous saturated NaCl, and finally is dried over anhydrous Na_2SO_4. The solvent is removed by rotary evaporator to afford a white, gummy paste which crystallizes upon trituration with 20 mL of acetonitrile. The crystals are collected by suction filtration to afford 4.2 g of crude product. Recrystallization from 90 mL of hot acetonitrile provides 3.5 g of the thiol ester as small white needles, mp 166–167°C (Note 12). A second crop of 0.5 g, mp 165–166°C, can be obtained upon concentration of the mother liquor to approximately 30 mL, for a combined yield of 70%.

Figure 1

Figure 1

Figure 2

Figure 2

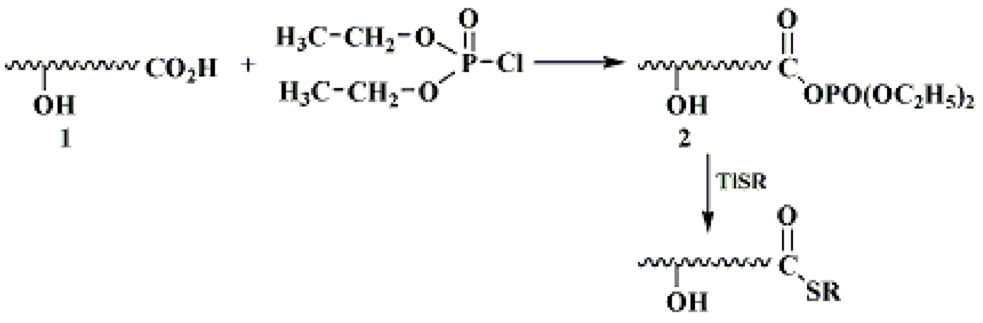
2. Notes

1. Thallium(I) ethoxide and 2-methylpropane-2-thiol were purchased from Aldrich Chemical Company, Inc.
2. Benzene, reagent grade, was purified and dried by first removing the benzene–water azeotrope by simple distillation and then collecting the remaining liquid under an atmosphere of nitrogen.
3. Dry pentane was obtained by allowing practical grade pentane to be shaken with and then distilled from concentrated sulfuric acid.

4. The product should be stored in a dark bottle under an atmosphere of argon to prevent discoloration and possible decomposition.
5. Cyclohexanecarboxylic acid chloride may be prepared in the following way: a pressure-equalizing addition funnel fitted with a nitrogen inlet tube is attached to a 500-mL, round-bottomed flask equipped with a magnetic stirring bar and also charged with 12.8 g (0.100 mol) of cyclohexanecarboxylic acid (purchased from Aldrich Chemical Company, Inc.) and 250 mL of anhydrous ether. (Anhydrous benzene may also be used.) The ethereal solution is cooled to ice-bath temperature and 25.4 g (0.200 mol) of oxalyl chloride (purchased from Aldrich Chemical Company, Inc.) is added over a period of 20 min. Under nitrogen, the resulting solution is stirred for 26 hr before it is concentrated on a rotary evaporator to afford a pale-yellow oil. Distillation of the oil yields 13.5 g (92%) of cyclohexanecarboxylic acid chloride as a clear, colorless liquid, bp 75°C (30 mm); IR (liquid film) cm^{-1}: 1800 (strong).
6. Anhydrous ether was obtained from Mallinckrodt Inc. and used without further purification.
7. Celite (C-211), purchased from Fisher Scientific Company, was washed thoroughly with ether.
8. The spectral characteristies of the product are as follows: IR (liquid film) cm^{-1}: 1675 (strong); ^{1}H NMR (neat) δ: 1.42 [s, 9 H, $C(CH_3)_3$], 1.0–2.0 (m, 10 H, all CH_2 in cyclohexane portion), 2.3 (m, 1 H, C*H*).
9. Cholic acid and diethyl phosphorochloridate were obtained from Aldrich Chemical Company, Inc.
10. Triethylamine was purchased from Eastman Organic Chemicals.
11. Tetrahydrofuran, reagent grade, was refluxed over and distilled from lithium aluminum hydride immediately prior to use (see *Org. Synth., Coll. Vol. V* **1973**, 976 for warning).
12. The spectral properties of the product are as follows: IR ($CHCl_3$) cm^{-1}: 3600 (sharp, weak), 3430 (broad, medium), 1675 (strong), no absorption at 1700.

3. Discussion

Methods available before 1971 for the preparation of thiol esters are briefly summarized in a review article.[4] Since then, several newer techniques have been developed to meet a certain set of criteria required for recent synthetic operations. This development may be summarized as follows. Whenever an acid chloride is available, the reaction of the Tl(I) salt of a thiolate of virtually any kind, including alkane-, benzene-, 2-benzothiazoline-, and 2-pyridinethiol, proceeds efficiently and near-quantitatively. However, if selective thiol ester formation in the presence of hydroxy or other functional groups in the same molecule is required, three main procedures are available. First, reaction of an acid (**1**), with a dialkyl or diphenyl phosphorochloridate affords the anhydride (**2**) (with the hydroxy groups intact) which is subsequently converted to the thiol ester.[5] This method can be applied to any type of thiol and a variety of hydroxy acids (except for β-hydroxy acids[6 7]). A mixed anhydride method using ethyl chloroformate and pyridine also effects selective thiol ester formation in many cases.[8] Second, the imidazolide of an acid that is prepared from **1** and *N,N*-carbonyldiimidazole reacts efficiently with relatively acidic thiols such as benzenethiol to yield the thiol ester.[6,7,11] Third, use of a disulfide and triphenylphosphine effects the selective formation of thiol esters, but this technique is applicable only to relatively reactive disulfides such as those derived from 2-benzothiazole-, 2-pyridinethiol,[9,10,12] and 4-*tert*-butyl-*N*-isopropylimidazole-2-thiol.[13]



Other methods that can be used to prepare thiol esters from carboxylic acids include the use of aryl thiocyanates,[14] thiopyridyl chloroformate,[15] 2-fluoro-*N*-methylpyridinium tosylate,[16] 1-hydroxybenzotriazole,[17] and boron thiolate.[18] Direct conversion of *O*-esters to *S*-esters can also be effected via aluminum and boron reagents.[19 20 21] However, the applicability of these[14,15,16,17,18,19,20,21] and other methods,[22 23 24 25] including the carboxyl group activation by means of 4-dimethylaminopyridine (DMAP) and dicyclohexylcarbodiimide (DCC),[25] to the selective thiol ester formation discussed above has not been clearly defined.

Thiol esters have recently been utilized, with and without activation, for the preparation of *O*-esters for lactones, in particular, in macrolide syntheses. The accompanying procedure illustrates this conversion.[26]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 87

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

2-benzothiazole-

boron thiolate

Celite (C-211)

sulfuric acid (7664-93-9)

Benzene (71-43-2)

ethyl acetate (141-78-6)

ether (60-29-7)

acetonitrile (75-05-8)

$NaHCO_3$ (144-55-8)

NaCl (7647-14-5)

Na_2SO_4 (7757-82-6)

nitrogen (7727-37-9)

aluminum (7429-90-5)

pyridine (110-86-1)

Pentane (109-66-0)

Cyclohexanecarboxylic acid (98-89-5)

ethyl chloroformate (541-41-3)

Benzenethiol (108-98-5)

boron (7440-42-8)

Tetrahydrofuran, THF (109-99-9)

oxalyl chloride (79-37-8)

lithium aluminum hydride (16853-85-3)

triethylamine (121-44-8)

Triethylamine hydrochloride (554-68-7)

cyclohexanecarboxylic acid chloride (2719-27-9)

triphenylphosphine (603-35-0)

dicyclohexylcarbodiimide (538-75-0)

argon (7440-37-1)

diethyl phosphorochloridate (814-49-3)

Thallium (7440-28-0)

thallium(I)

thallium(I) ethoxide (20398-06-5)

cholane-24-thioic acid, 3,7,12-trihydroxy-S-(1,1-dimethylethyl)ester, (3α,5β,7α,12α), S-tert-BUTYL 3α,7α,12α-TRIHYDROXY-5β-CHOLANE-24-THIOATE (58587-05-6)

2-methylpropane-2-thiolate

2-methylpropane-2-thiol (75-66-1)

cholic acid

2-pyridinethiol (73018-10-7)

thiopyridyl chloroformate

1-hydroxybenzotriazole (2592-95-2)

4-dimethylaminopyridine (1122-58-3)

S-tert-BUTYL CYCLOHEXANECARBOTHIOATE, Cyclohexanecarbothioic acid, S-(1,1-dimethylethyl) ester (54829-37-7)

N,N-carbonyldiimidazole (530-62-1)

4-tert-butyl-N-isopropylimidazole-2-thiol

2-fluoro-N-methylpyridinium tosylate (58086-67-2)

Thallium(I) 2-methylpropane-2-thiolate

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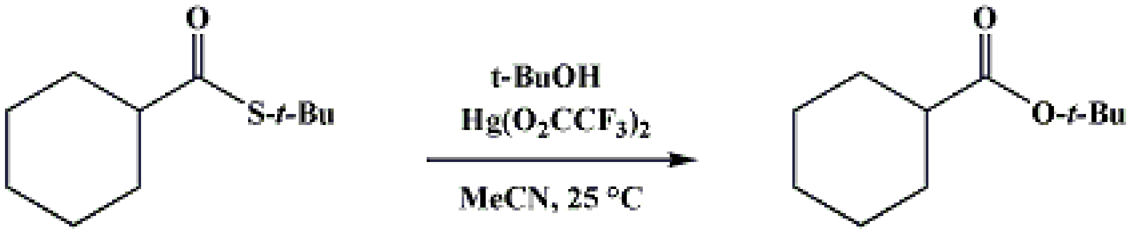
Organic Syntheses, CV 7, 87

PREPARATION OF *O*-ESTERS FROM THE CORRESPONDING THIOL ESTERS: *tert*-BUTYL CYCLOHEXANECARBOXYLATE

[Cyclohexanecarboxylic acid, 1,1-dimethylethyl ester]



Submitted by Wan Kit Chan[1], S. Masamune[1], and Gary O. Spessard[2].
Checked by Trina Kittredge and Robert V. Stevens.

1. Procedure

A 500-mL, round-bottomed flask equipped with a magnetic stirring bar is flushed with nitrogen. The flask is then charged with 5.56 g (0.028 mol) of *S*-*tert*-butyl cyclohexanecarbothioate (Note 1), 5.55 g (0.075 mol) of *tert*-butyl alcohol, and 250 mL of anhydrous acetonitrile (Note 2). The mixture is stirred vigorously and 23.7 g (0.056 mol) of mercury(II) trifluoroacetate (Note 3) is added in one portion. The resulting mixture is stirred vigorously for 45 min and then concentrated to approximately 50–75 mL on a rotary evaporator (Note 4). To this concentrated mixture is added 250 mL of hexane and the orange solid that forms is removed by filtration. The filter pad is then washed with 50 mL of hexane. The filtrate and washings are combined and washed with a 50 mL portion of aqueous saturated sodium chloride, dried over anhydrous sodium sulfate, and concentrated on a rotary evaporator to give a pale-yellow liquid (Note 4).

The crude product is purified by passing it through a column (4.5 cm × 30 cm) of neutral alumina (Note 5) using chloroform as eluant. The desired product moves with the solvent front, and the first 300–350 mL of eluant contains all of the product. Removal of the solvent gives 4.96 g. The product, which contains a small amount of *tert*-butyl alcohol, can be further purified by distillation through a short-path apparatus to give 4.6 g (90%) of pure *O*-ester, bp 91°C (25 mm) (Note 4) and (Note 6).

2. Notes

1. This compound is prepared according to *Org. Synth., Coll. Vol. VII* **1990**, 81.
2. Acetonitrile, obtained from J. T. Baker Chemical Co., was refluxed overnight with phosphorus pentoxide and then distilled under nitrogen onto freshly

activated Linde 4A molecular sieves. The acetonitrile was stored over the molecular sieves for 24 hr before use.

3. Although mercury(II) trifluoroacetate may be obtained commercially, the submitters recommend that it be freshly prepared. A mixture of red mercury(II) oxide (108.3 g, 0.5 mol) (obtained from BDH Chemicals Ltd.) and freshly distilled trifluoroacetic acid (137.0 g, 1.2 mol) (purchased from J. T. Baker Chemical Co.) was heated at 80°C for 30 min. The excess trifluoroacetic acid and the water formed in the reaction were removed under reduced pressure. The white crystaline residue was then dried (50°C, 0.01 mm) for 48 hr to give a quantitative yield of product.

4. The temperature of the water bath was kept below 28°C during evaporation of the acetonitrile.

5. Woelm neutral alumina, activity grade 1, (300 g) was used. The column was packed using hexane.

6. The spectral properties of the product are as follows: IR (neat) cm^{-1}: 1735 (strong); ^1H NMR ($CDCl_3$) δ: 1.38 [singlet, 9 H, $C(CH_3)_3$] 1.0–2.4 (multiplet, 11 H, cyclohexane protons).

3. Discussion

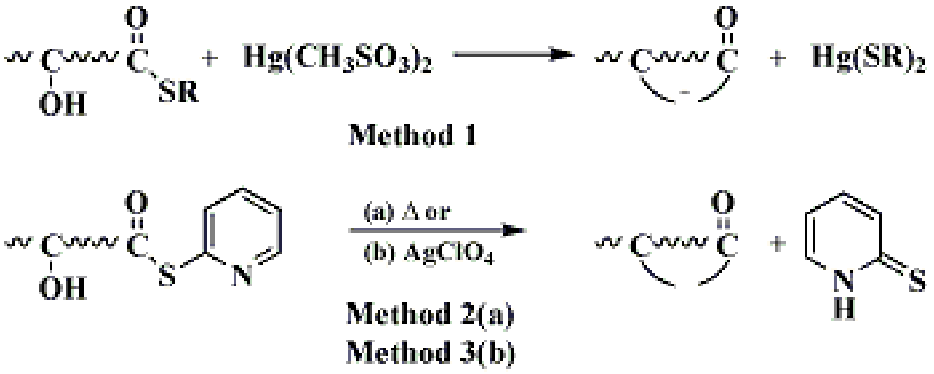
In recent years much attention has been directed toward efficient ester (and lactone) formation in connection with the synthesis of naturally occurring macrolides.[3 4 5 6 7 8; 9; 10; 11 12 13; 14 15; 16 17 18 19 20 21 22 23] Four principal methods for such a reaction have emerged from these studies:

Method 1. Use of a thiophilic metal ion to activate an alkane- or arenethiol ester for nucleophilic displacement by an alcohol is applicable to both ester and lactone formation.[24]

Method 2. Corey's "double activation" method for lactone formation is patterned after Mukaiyama's procedure for peptide formation and involves refluxing a solution of the 2-pyridinethiol ester of a hydroxy acid in a high-boiling solvent for a prolonged period of time.[25]

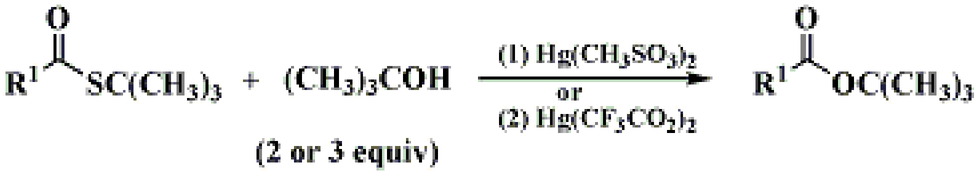
Method 3. Gerlach's modification of Method 2 uses $AgClO_4$ or $AgBF_4$ to catalyze the cyclization.[26]

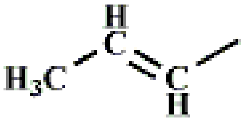
Method 4. Mitsunobu's method uses a combination of diethyl azodicarboxylate and triphenylphosphine as a condensing agent.[27]

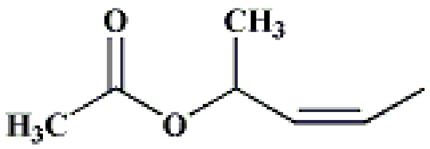


Method 1 offers some distinct advantages. First, an ester such as the 1,1-dimethylethylthiol ester serves as an excellent protective group, surviving both relatively mild alkaline and acid conditions, and has been used successfully in the synthesis of many macrolide natural products.[7,12,15,19,20,22] Second, reaction of a metal ion such as Hg (II) with the thiol ester formally creates a highly reactive trivalent sulfur species, and thus ester (and lactone) formation proceeds very rapidly at room temperature or below. More importantly, bulky substituents or double bonds located near the reaction centers (i.e., near the hydroxy and acyl groups) do not impede the reaction (see Table I).[15] Thus *tert*-

TABLE I

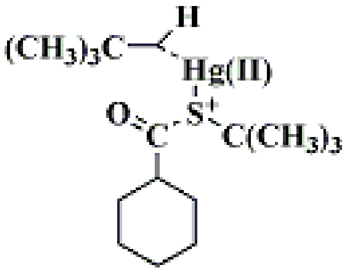


R^1	Reagent	Buffer	Yield (%)[a]
c-C_6H_{11}-	1 or 2	Na_2HPO_4 (or none)	100
$(CH_3)_3C$-	1		90
 (*E*)-CH_3CH=CH-	1 or 2		85

 (*Z*)-$CH_3CO_2C(CH_3)=CH$-	1	Na_2HPO_4	90

[a]The yields are estimated by GC analysis.

butyl pivalate and *tert*-butyl crotonate are prepared in excellent yields. In the absence of alcohols, *tert*-butyl cyclohexanecarbothioate reacts with $Hg(CF_3CO_2)_2$ to form cyclohexanecarboxylic trifluoroacetic anhydride. Reaction of this anhydride with *tert*-butyl alcohol to give the ester, however, proceeds ca. 10 times more slowly than the Hg (II)-catalyzed ester formation described above.[28] The intermediacy of the corresponding ketene has been eliminated by use of an appropriately deuterated compound[28] and pivalic acid. Thus the metal-catalyzed ester formation appears to proceed for the most part through coordination of the alcohol to the metal, as shown in a possible intermediate (**1**), followed by collapse into the ester and mercuric salts with retention of stereochemistry at the carbon atom alpha to the carboxy group.

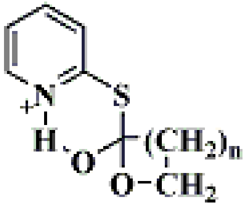


1

This method is not free from disadvantages: the electrophilicity of Hg(II) toward reactive alkenes may sometimes be a problem. However, in most cases the reactivity of Hg(II) with sulfur significantly exceeds that with ordinary or electron-deficient (C=C-C=O) double bonds, and other combinations of thiol esters and thiophilic metals may be used to overcome this problem. The more acidic the reacting thiol, the less thiophilic is the metal needed to effect the reaction, and in some cases Cu(I), Cu(II), and Ag(I) are superior to Hg(II). For example, the combination of $Ag(I)CF_3CO_2$ [but not $Ag(I)ClO_4$ or $Ag(I)BF_4$] and a benzenethiol ester is very efficient for ester formation. The presence of electron-withrawing groups such as the C=C bond and protected hydroxy groups somewhat retards the ester formation. A few examples are shown in Table II.[15] All these observations appear to conform with the hard and soft acid and base principle of Pearson. Further, it is clear that Gerlach's report of the use of Ag(I) to activate 2-pyridinethiol esters (Method 3) is fully in accord with this trend.

Corey's "double activation" procedure (Method 2) does not use an external reagent to activate the functional group, but effects cyclization by heating a solution of the 2-

pyridinethiol ester of a hydroxy acid for a prolonged period. Several pieces of evidence point to the intermediacy of **2** in this lactonization.[29] If one accepts this intermediate, it follows that a hydroxy(2-pyridinethiol)ester, heavily substituted near the reaction centers (i.e., near the hydroxyl and acyl groups), would encounter a high energy barrier in the process leading to **2**. This inference has been confirmed by measuring the approximate rates of reaction of 2-pyridine- and 2-benzothiazolethiol esters of cyclohexanecarboxylic acid with primary, secondary, and tertiary alcohols.[3,28] This steric retardation of the reaction may constitute a major drawback to Method 2. A marked improvement has been made, however, and the latest version of this method[30] involves use of the 1-methyl- or 1-isopropyl-4-*tert*-butylimidazole-2-thiol ester of the hydroxy acid which undergoes cyclization 100 times faster than the corresponding 2-pyridinethiol ester. This improved method has been used in syntheses of erythronolide A[18] and B.[16]



2

Lactonization of aliphatic hydroxy acids proceeds with the aid of two reagents, diethyl azodicarboxylate and triphenylphosphine. This fourth procedure has been selected as a method of choice for the final cyclization to yield vermiculine[14] and pyrenophorin.[13]

Several other methods to effect ester and lactone formation are now available. Mukaiyama uses 2-chloro-*N*-methylpyridinium iodide and its derivatives as a condensing agent.[31; 32; 33; 34; 35] Staab's imidazole method,[36] successfully utilized in a synthesis of pyrenophorin[8] and a model study for erythronolide B,[37] requires a catalytic amount of strong base, and thus is applicable only to compounds stable under such conditions. The mixed anhydride of a hydroxycarboxylic acid and 2,4,6-trichlorobenzoic acid is efficiently cyclized to provide the corresponding lactone.[37,38; 39] Similarly, the use of a reactive phosphoric acid anhydride intermediate is equally effective.[40] Some other methods for carboxyl activation, using dibutyltin oxide,[41; 42] distannoxane,[43] *N*,*N*,*N'*,*N'*-tetramethylchloroformamidinium chloride,[44] and the combination of dicyclohexylcarbodiimide (DCC), 4-dimethylaminopyridine (DMAP), and DMAP hydrochloride,[45] have also appeared.

TABLE II

R^1	R^2	MX	Solvent	Time	Yield (%)
c-C_6H_{11}-	-C_6H_5	$Cu(CF_3SO_3)$	C_6H_6/THF	10 min	95
c-C_6H_{11}-		$Ag(CF_3CO_2)$	C_6H_6	10 min	100
(*E*)-CH_3CH=CH-	-C_6H_5	$Cu(CF_3SO_3)$	C_6H_6/THF	5 hr	80
		$Cu(CF_3SO_3)_2$	CH_3CN	1.5 hr	24
(*E*)-C_6H_5=CH-	-C_6H_5	$Ag(CF_3CO_2)$	C_6H_6(Δ)	1.5 hr	100
		$AgBF_4$	C_6H_6(Δ)	1 hr	<5
		$Ag(CF_3CO_2)$	C_6H_6(Δ)	1.5 hr	100
C_6H_5-		$Cu(CF_3SO_3)$	C_6H_6/THF	5 hr	90
		$Cu(CF_3SO_3)_2$	CH_3CN	30 min	100

The preceding discussion is a summary of the lactonization methods known at present; newer methods continue to be explored. The selection of a method for an individual case depends to a large extent on the structure and functionalities of the substrate.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 81
- Org. Syn. Coll. Vol. 8, 254
- Org. Syn. Coll. Vol. 8, 350

References and Notes

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2. Department of Chemistry, Saint Olaf College, Northfield, MI 55057.
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alumina

red mercury(II) oxide

$AgClO_4$

$AgBF_4$

Na_2HPO_4

$Hg(CF_3CO_2)_2$

cyclohexanecarboxylic trifluoroacetic anhydride

vermiculine

pyrenophorin

erythronolide B

N,N,N',N'-tetramethychloroformamidinium chloride

DMAP hydrochloride

acetonitrile (75-05-8)

chloroform (67-66-3)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

sulfur (7704-34-9)

carbon (7782-42-5)

Cyclohexanecarboxylic acid (98-89-5)

Pivalic acid (75-98-9)

diethyl azodicarboxylate (1972-28-7)

hexane (110-54-3)

hydroxycarboxylic acid (463-79-6)

tert-butyl alcohol (75-65-0)

trifluoroacetic acid (76-05-1)

triphenylphosphine (603-35-0)

dicyclohexylcarbodiimide (538-75-0)

mercury(II) trifluoroacetate (13257-51-7)

4-dimethylaminopyridine (1122-58-3)

Cyclohexanecarboxylic acid, 1,1-dimethylethyl ester, tert-Butyl cyclohexanecarboxylate (16537-05-6)

butyl pivalate

2,4,6-trichlorobenzoic acid (50-43-1)

dibutyltin oxide (818-08-6)

distannoxane

phosphorus pentoxide (1314-56-3)

S-tert-BUTYL CYCLOHEXANECARBOTHIOATE (54829-37-7)

tert-butyl crotonate (79218-15-8)

tert-butyl cyclohexanecarbothioate

2-chloro-N-methylpyridinium iodide (14338-32-0)

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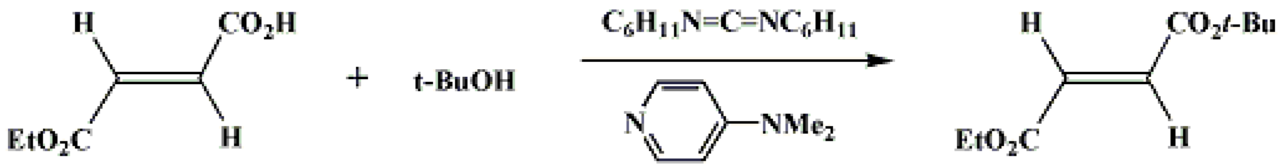
Organic Syntheses, CV 7, 93

ESTERIFICATION OF CARBOXYLIC ACIDS WITH DICYCLOHEXYLCARBODIIMIDE/4-DIMETHYLAMINOPYRIDINE: *tert*-BUTYL ETHYL FUMARATE

[(*E*)-2-Butenedioic acid, ethyl 1,1-dimethylethyl ester]



Submitted by B. Neises and Wolfgang Steglich[1].
Checked by Cheryl Stubbs and Robert V. Stevens.

1. Procedure

Caution! Dicyclohexylcarbodiimide is a potent allergen and should be handled with gloves.

A 500-mL, one-necked flask equipped with a calcium chloride drying tube is charged with 28.83 g (0.20 mol) of monoethyl fumarate (Note 1), 200 mL of dry dichloromethane (Note 2), 44.47 g (0.60 mol) of *tert*-butyl alcohol (Note 3), and 2.00 g (0.16 mol) of 4-dimethylaminopyridine (Note 4). The solution is stirred and cooled in an ice bath to 0°C while 45.59 g (0.22 mol) of dicyclohexylcarbodiimide (Note 5) is added over a 5-min period. After a further 5 min at 0°C the ice bath is removed and the dark-brown reaction mixture is stirred for 3 hr at room temperature. The dicyclohexylurea that has precipitated is removed by filtration through a fritted Büchner funnel (G3), and the filtrate is washed with two 50-mL portions of 0.5 *N* hydrochloric acid (Note 6) and two 50-mL portions of saturated sodium bicarbonate solution. During this procedure some additional dicyclohexylurea is precipitated, which is removed by filtration of both layers to facilitate their separation. The organic solution is dried over anhydrous sodium sulfate and concentrated with a rotary evaporator. The concentrate is distilled under reduced pressure, affording, after a small forerun, 30.5–32.5 (76–81%) of *tert*-butyl ethyl fumarate, bp 105–107°C (12 mm) (Note 7).

2. Notes

1. Monoethyl fumarate was purchased from Ega-Chemie, D-7924 Steinheim, Germany.
2. Dichloromethane was freshly distilled over P_4O_{10}.
3. *tert*-Butyl alcohol was purchased from E. Merck, D-6100 Darmstadt, Germany, and used without further purification.
4. 4-Dimethylaminopyridine was obtained from Schering AG, D-1000 Berlin, Germany. 4-Pyrrolidinopyridine, which is equally well suited as a catalyst in this reaction may be purchased from Ega-Chemie, D-7924 Steinheim, Germany.
5. Dicyclohexylcarbodiimide was freshly distilled with a Kugelrohr apparatus (Büchi GKR-50), bp 135–140°C (0.5 mm). It may be either added in crystalline form or dissolved in 50 mL of dry dichloromethane.

6. For esters more sensitive to acids, the use of concentrated aqueous citric acid solution is advisable.

7. The proton magnetic resonance spectrum of the product in chloroform-d shows the following absorptions: δ 1.30 [t, 3 H, *J* = 7.5, CH_3CH_2), 1.50 (s, 9 H, $C(CH_3)_3$], 4.23 (q, 2 H, *J* = 7.5, CH_3CH_2), 6.77 (s, 2 H, CH=CH). *tert*-Butyl ethyl fumarate may be easily converted into ethyl fumarate by alkaline hydrolysis.

3. Discussion

This procedure offers a convenient method for the esterification of carboxylic acids with alcohols[2,3,4] and thiols[2] under mild conditions. Its success depends on the high efficiency of 4-dialkylaminopyridines as nucleophilic catalysts in group transfer reactions.[5] The esterification proceeds without the need of a preformed, activated carboxylic acid derivative, at room temperature, under nonacidic, mildly basic conditions. In addition to dichloromethane other aprotic solvents of comparable polarity such as diethyl ether, tetrahydrofuran, and acetonitrile can be used. The reaction can be applied to a wide variety of acids and alcohols, including polyols,[2,4,6] α-hydroxycarboxylic acid esters,[7] and even very acid labile alcohols such as vitamin A.[8] It has also been used for the esterification of urethane-protected α-amino acids with polymeric supports carrying hydroxy groups.[9] In this case, however, some racemization of the amino acid is observed because of 2-alkoxyoxazolin-5-one formation.[10] Racemization can be decreased by shortening the coupling time[10] or completely avoided by working with *N*-(*p*-nitrophenylsulfenyl)amino acids.[11]

With increasing steric hindrance, the rate of esterification is decreased and the formation of *N*-acylureas may become a serious side reaction. This is indicated by the decrease in yield in the esterification of 2,5-cyclohexadiene-1-carboxylic acid with different alcohols: MeOH (95%), EtOH (84%), i-PrOH (75%), c-$C_6H_{11}OH$ (65%), *t*-BuOH (65%).[12] Diminished acidity because of the influence of electron-donating substituents in aromatic carboxylic acids can also lead to low yields.

The dicyclohexylcarbodiimide/4-dialkylaminopyridine method is also well suited to the synthesis of a wide variety of thiol esters.[2,13]

4-Dimethylaminopyridine also catalyzes the formation of esters and thiol esters in the reaction of mixed carboxylic anhydrides[14] or 2,4,6-trinitrophenyl esters[15] with alcohols and thiols. 1-Acyl-4-benzylidene-1,4-dihydropyridines have been introduced recently as promising reagents for the synthesis of sterically hindered esters.[16] The current methods available for ester and thiol ester formation have been reviewed recently by Haslam.[17]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

P_4O_{10}

hydrochloric acid (7647-01-0)

diethyl ether (60-29-7)

acetonitrile (75-05-8)

citric acid (77-92-9)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

ethyl fumarate, monoethyl fumarate (2459-05-4)

dichloromethane (75-09-2)

Tetrahydrofuran (109-99-9)

tert-butyl alcohol (75-65-0)

dicyclohexylcarbodiimide (538-75-0)

dicyclohexylurea

2,5-Cyclohexadiene-1-carboxylic acid (4794-04-1)

4-dimethylaminopyridine (1122-58-3)

4-Pyrrolidinopyridine (2456-81-7)

tert-Butyl ethyl fumarate, (E)-2-Butenedioic acid, ethyl 1,1-dimethylethyl ester (100922-16-5)

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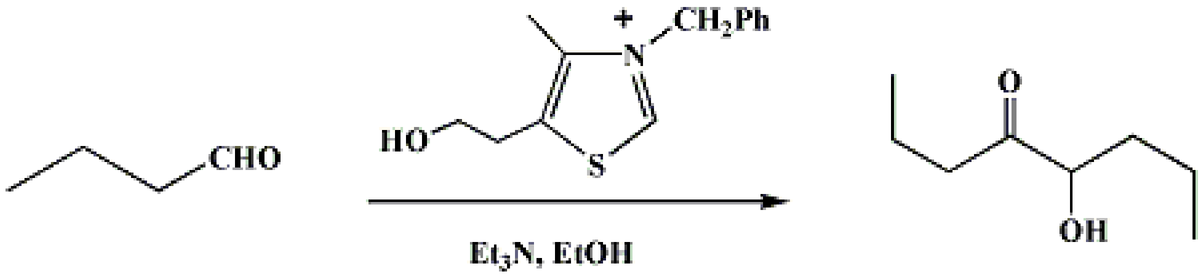
Organic Syntheses, CV 7, 95

ACYLOIN CONDENSATION BY THIAZOLIUM ION CATALYSIS: BUTYROIN

[4-Octanone, 5-hydroxy-]



Submitted by H. Stetter and H. Kuhlmann[1].
Checked by Sharbil J. Firsan and Robert M. Coates.

1. Procedure

A 500-mL, three-necked, round-bottomed flask is equipped with a mechanical stirrer, a short gas inlet tube, and an efficient reflux condenser fitted with a potassium hydroxide drying tube. The flask is charged with 13.4 g (0.05 mol) of 3-benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium chloride (Note 1), 72.1 g (1.0 mol) of butyraldehyde (Note 2), 30.3 g (0.3 mol) of triethylamine (Note 2), and 300 mL of absolute ethanol. A slow stream of nitrogen (Note 3) is begun, and the mixture is stirred and heated in an oil bath at 80°C. After 1.5 hr the reaction mixture is cooled to room temperature and concentrated by rotary evaporation. The residual yellow liquid is poured into 500 mL of water contained in a separatory funnel, and the flask is rinsed with 150 mL of dichloromethane which is then used to extract the aqueous mixture. The aqueous layer is extracted with a second 150-mL portion of dichloromethane. The combined organic phases are washed with 300 mL of saturated sodium bicarbonate and with 300 mL of water. The dichloromethane is removed by rotary evaporation under slightly diminished pressure. Distillation through a 20-cm Vigreux column gives 51–54 g (71–74%) of product as a colorless to light-yellow liquid, n_D^{20} 1.4309, bp 90–92°C (13–14 mm) (Note 4) and (Note 5).

2. Notes

1. The catalyst, 3-benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium chloride, is supplied by Fluka AG, Buchs, Switzerland, and by Tridom Chemical, Inc., Hauppauge, New York. The thiazolium salt may also be prepared as described below[2 3] by benzylation of 5-(2-hydroxyethyl)-4-methyl-1,3-thiazole, which is commercially available from E. Merck, Darmstadt, West Germany, and Columbia Organic Chemicals Co., Inc., Columbia, SC. The acetonitrile used by

the checkers was dried over Linde 3A molecular sieves[4] and distilled under nitrogen, bp 77–78°C. The same yield of thiazolium salt was obtained by the checkers when benzyl chloride and acetonitrile from commercial sources were used without purification.
A 250-mL, three-necked, round-bottomed flask is equipped with a mechanical stirrer, a reflux condenser fitted with a drying tube, and a stopper. The flask is charged with 14.3 g (0.1 mol) of 5-(2-hydroxyethyl)-4-methyl-1,3-thiazole, 12.7 g (0.1 mol) of freshly distilled benzyl chloride, and 50 mL of dry acetonitrile. The mixture is heated at reflux for 24 hr and cooled to room temperature. Crystallization is induced by scratching or seeding. The solid is collected by suction filtration, washed colorless with two 50-mL portions of acetonitrile, and dried partially in the air. Drying is completed under reduced pressure by gentle rotation on a rotary evaporator heated with a water bath at about 90°C. The yield of thiazolium salt, mp 141–143°C, is 18.2–19.6 g (67–73%).

2. Butyraldehyde is supplied by Aldrich Chemical Co., Inc. and Eastman Organic Chemicals. The aldehyde was freshly distilled before use. Triethylamine was dried over potassium hydroxide pellets and distilled.

3. The submitters recommend that the nitrogen stream be passed through a bubbler and that the flow rate be adjusted to ca. one bubble per second. If the nitrogen flow is too fast, some of the butyraldehyde will be swept out of the flask.

4. The procedure may be conducted on a larger scale, in which case the proportion of catalyst and base are reduced. The submitters report that they obtained 169 g (78%) of butyroin from 216.3 g (3.0 mol) of butyraldehyde, 26.8 (0.1 mol) of thiazolium catalyst, 60.6 g (0.6 mol) of triethylamine, and 600 mL of absolute ethanol. Although the scale may be increased further, appropriate precautions should be taken to control the reaction. For example, the aldehyde may be added in portions or the flask may be cooled initially.

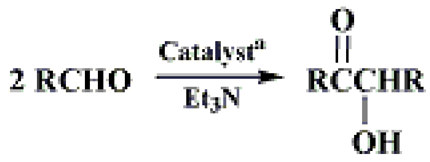
5. The product obtained by the checkers boiled at 86–87.5°C (15–16 mm). A boiling point of 85–87°C (12–13 mm) and an index of refraction n_D^{20} 1.4325 have been recorded for butyroin.[5] The product exhibits the following spectral characteristics: IR (neat) cm^{-1}: 3505 and 1704; ^1H NMR (CCl_4) δ: 0.94 (unsymmetrical t, 6 H, 2 CH_3), 1.18–1.56 (m, 4 H, 2 CH_2), 1.64 (sextet, 2 H, J = 7, CH_2CH_2C=O), 2.41 (t, 2 H, J = 7, CH_2C=O), 3.31 (s, 1 H, OH), 3.98 (m, 1 H, C*H*OH).

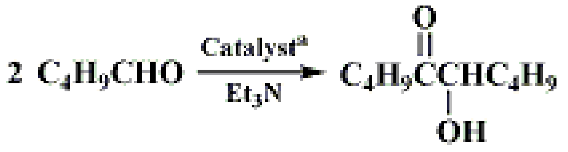
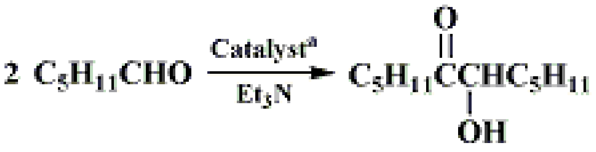
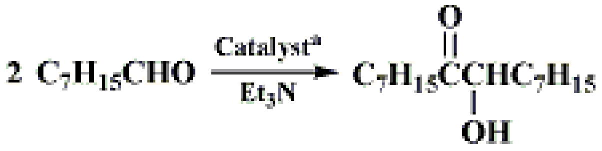
3. Discussion

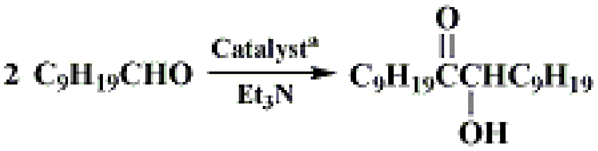
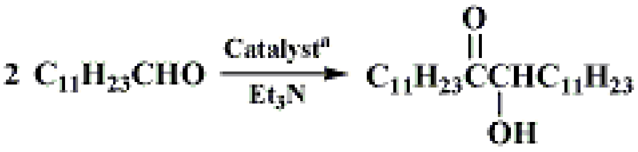
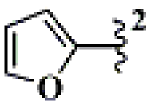
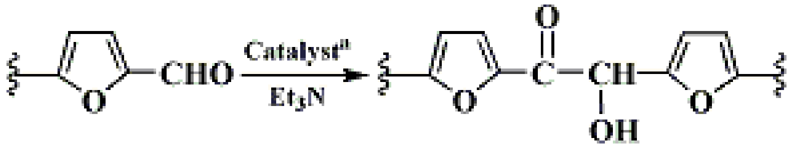
This procedure is representative of a new general method for the preparation of noncyclic acyloins by thiazolium-catalyzed dimerization of aldehydes in the presence of weak bases (Table I).[6] The advantages of this method over the classical reductive coupling of esters[7,8] or the modern variation, in which the intermediate enediolate is trapped by silylation,[5,9] are the simplicity of the procedure, the inexpensive materials used, and the purity of the products obtained. For volatile aldehydes such as

acetaldehyde and propionaldehyde the reaction is conducted without solvent in a small, heated autoclave. With the exception of furoin the preparation of benzoins from aromatic aldehydes is best carried out with a different thiazolium catalyst bearing an *N*-methyl or *N*-ethyl substituent, instead of the *N*-benzyl group.[6] Benzoins have usually been prepared by cyanide-catalyzed condensation of aromatic and heterocyclic aldehydes.[10,11,12] Unsymmetrical acyloins may be obtained by thiazolium-catalyzed cross-condensation of two different aldehydes.[13] The thiazolium ion-catalyzed cyclization of 1,5-dialdehydes to cyclic acyloins has been reported.[14]

TABLE I
ACYLOINS PREPARED BY THIAZOLIUM ION-CATALYZED CONDENSATION OF ALDEHYDES[6]



R	Yield (%)	Bp or mp (°C)
C_4H_9	 79	83 (2.2 mm)
C_5H_{11}	 81	90 (1.5 mm)
C_7H_{15}	 83[b]	39

C_9H_{19}		53
	85[b]	
$C_{11}H_{23}$		62
	83[b]	
		136
	80[c,d]	

[a] 3-Benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium chloride.

[b] The product was isolated by pouring the ethanolic solution into well-stirred, ice-cold water, filtering, and recrystallizing from aqueous ethanol. The solutions should be ice-cold for the isolation of the low-melting acyloins. The products may also be isolated by extraction as described for butyroin.

[c] In this case furoin crystallized from the ethanolic solution on cooling.

[d] The following somewhat simpler procedure may also be used. A solution of 13.4 g (0.05 mol) of catalyst, 96.1 g (1.0 mol) of 2-furaldehyde, 300 mL of absolute ethanol, and 30.3 g (0.3 mol) of triethylamine is stirred at room temperature for 12 hr. The product (84.5 g, 88%) crystallizes directly from solution and is isolated by filtration.

Although the catalysts of the dimerization of aldehydes to acyloins by thiazolium ion

has been known for some time,[15 16 17] the development of procedures using anhydrous solvents which give satisfactory yields of acyloins on a preparative scale was first realized in the submitters' laboratories.[6] The mechanism proposed by Breslow[15] for the thiazolium ion-catalyzed reactions is similar to the Lapworth mechanism[18] for the benzoin condensation with a thiazolium ylide replacing the cyanide ion. Similar mechanisms are involved in many important enzyme-catalyzed transformations that require thiamine as a cofactor. The combination of thiazolium salts and weak bases has also been utilized to catalyze the conjugate addition of aldehydes to electron-deficient double bonds.[2,3]

Butyroin has been prepared by reductive condensation of ethyl butyrate with sodium in xylene,[8] or with sodium in the presence of chlorotrimethylsilane,[9] and by reduction of 4,5-octanedione with sodium 1-benzyl-3-carbamoyl-1,4-dihydropyridine-4-sulfinate in the presence of magnesium chloride,[19] or with thiophenol in the presence of iron polyphthalocyanine as electron transfer agent.[20] This acyloin has also been obtained by oxidation of (*E*)-4-octene with potassium permanganate[21] and by reaction of propylmagnesium bromide with nickel tetracarbonyl.[22]

Acyloins are useful starting materials for the preparation of a wide variety of heterocycles (e.g., oxazoles[23] and imidazoles[24]) and carbocyclic compounds (e.g., phenols[25]). Acyloins lead to 1,2-diols by reduction, and to 1,2-diketones by mild oxidation.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 620

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

iron polyphthalocyanine

ethanol (64-17-5)

acetaldehyde (75-07-0)

acetonitrile (75-05-8)

sodium bicarbonate (144-55-8)

potassium permanganate (7722-64-7)

Propionaldehyde (123-38-6)

nitrogen (7727-37-9)

Benzoin (119-53-9)

potassium hydroxide pellets (1310-58-3)

sodium (13966-32-0)

benzyl chloride (100-44-7)

butyraldehyde (123-72-8)

xylene (106-42-3)

2-Furaldehyde (98-01-1)

dichloromethane (75-09-2)

Thiophenol (108-98-5)

Butyroin, 4-Octanone, 5-hydroxy- (496-77-5)

magnesium chloride

triethylamine (121-44-8)

CHLOROTRIMETHYLSILANE (75-77-4)

nickel tetracarbonyl

propylmagnesium bromide

3-benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium chloride

5-(2-hydroxyethyl)-4-methyl-1,3-thiazole (137-00-8)

furoin (552-86-3)

thiamine (59-43-8)

ethyl butyrate (105-54-4)

4,5-octanedione (5455-24-3)

sodium 1-benzyl-3-carbamoyl-1,4-dihydropyridine-4-sulfinate

(E)-4-octene (14850-23-8)

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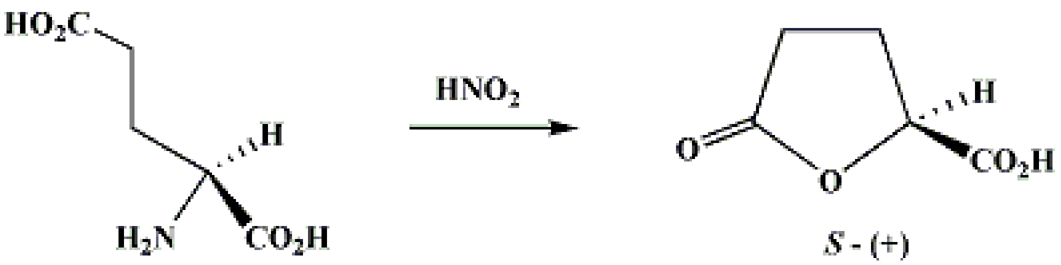
Organic Syntheses, CV 7, 99

(*S*)-(+)-γ-BUTYROLACTONE-γ-CARBOXYLIC ACID

[2-Furancarboxylic acid, tetrahydro-5-oxo-, (*S*)-]



Submitted by Olivier H. Gringore and Francis P. Rouessac[1].
Checked by Matthew F. Schlecht, Howard Drossman, and Clayton H. Heathcock.

1. Procedure

Caution! This procedure should be conducted in a well-ventilated hood to avoid inhalation of poisonous NO_2 vapors. To protect the operator the distillation must be carried out with the usual precautions associated with vacuum distillation.

A 6-L Erlenmeyer flask which contains a large magnetic stirring bar is charged with 294 g (2 mol) of L-glutamic acid (Note 1) and 2 L of distilled water. The suspension is stirred vigorously while solutions of 168 g (2.4 mol) of sodium nitrite in 1.2 L of water and 1.2 L of aqueous 2 *N* sulfuric acid are added simultaneously from separatory funnels (Note 2). After the addition is complete (Note 3), the solution is stirred at room temperature for an additional 15 hr. The water is then removed by heating below 50°C under reduced pressure with a rotary evaporator (Note 4). The resulting pasty solid is triturated with 500 mL of boiling acetone and the hot solution is filtered and set aside to cool. This operation is repeated four times (Note 5) and (Note 6). Removal of solvent with a rotary evaporator affords 312 g of crude (+)-γ-butyrolactone-γ-carboxylic acid as a slightly yellow oil (Note 7) and (Note 8).

A 250-mL, round-bottomed flask is equipped with a magnetic stirring bar and charged with 100 g of the foregoing crude lactone acid (Note 9). The flask is fitted with a Claisen distillation apparatus and connected to a vacuum pump (Note 10) and (Note 11). The flask is gradually heated with an oil bath (160°C) until gas evolution ceases (Note 12). At this point the oil bath is removed and the black, viscous oil is distilled with the use of a flame (Note 13). The product, 58 g (70%), is collected as a colorless oil at 146–154°C (0.03 mm). The distillate crystallizes in the receiver, mp 66–68°C (Note 14) and (Note 15).

2. Notes

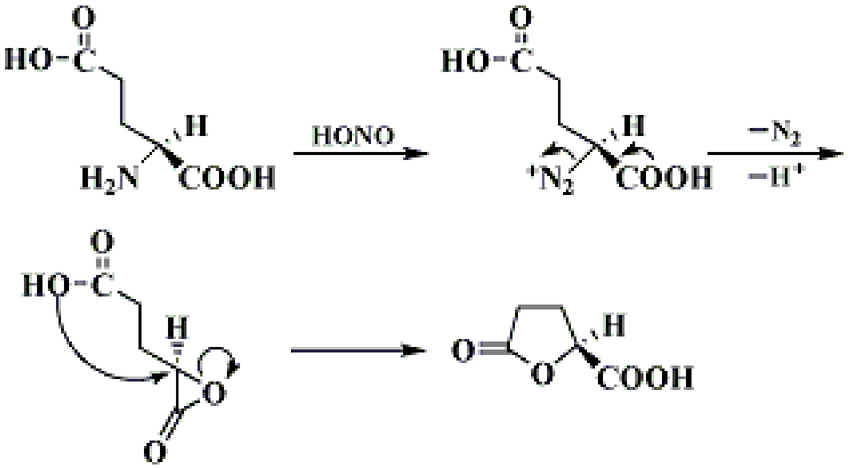
1. This material was purchased from the Aldrich Chemical Company Inc., $[\alpha]^{23}_{D}$ +29° (6 *N* HCl, *c* 1).
2. The addition requires about 30 min. During addition the reaction mixture should warm to 30–35°C and smooth evolution of NO_2 and N_2 should occur. If the solutions of $NaNO_2$ and H_2SO_4 are added too rapidly, more gas appears to be generated and a reduction in yield occurs.
3. At this point the reaction mixture is clear and colorless. Residual brown gas usually remains in the flask.
4. If a conventional aspirator pump is employed, concentration can require several days. The checkers employed a rotary evaporator that was evacuated to approximately 3 mm by a vacuum pump. Two traps, one cooled in an ice–salt bath and the other in an acetone–dry-ice bath, were inserted between the rotary evaporator and the vacuum pump. In this way, the reaction mixture can be concentrated to a paste in about 16–20 hr.
5. Repetitive extraction may also be performed in a flask heated with a water bath to 65°C; acetone is removed by decantation. Ethyl acetate has also been used for the extraction.[2]
6. The checkers found that a higher recovery is obtained if the pasty solid is vigorously agitated during trituration with five 750-mL portions of boiling acetone.
7. The crude yield reported is in excess of the theoretical yield (260 g). The checkers obtained crude yields of 243–259 g, probably because water was more efficiently removed in the concentration step.
8. Although this material is sufficiently pure for some applications, it is advisable to purify it further before use. Distillation[2] and crystallization[3] have been described. The submitters recommend purification by the distillation procedure given. By direct crystallization of 101 g of crude lactone acid from ether–petroleum ether, the checkers obtained 36.5 g (35%) of material, mp 72–74°C.
9. If the distillation is carried out on a larger scale, the yield is lower.
10. The submitters recommend a short-path distillation apparatus with large sections (i.e., wide bore) since the distillate partially crystallizes in the condenser during the distillation. It is important that the distillation apparatus have a Claisen head because the viscous material tends to bump.
11. The vacuum pump should be protected by a soda–lime trap.
12. During this heating period the system pressure should rise from 0.03 to 0.5 mm and the crude lactone acid should become black. When gas evolution ceases, the pressure decreases to its initial value.
13. Distillation should be carried out briskly. If a simple bunsen burner with a low flame is used, distillation requires several hours. The checkers used a hot flame, about 13 cm in length, from a gas–air torch. In this way, the distillation requires only about 15 min. Distillation is discontinued when colored vapors appear.
14. The checkers distilled crude lactone acid obtained in approximately quantitative yield (259 g). When this material was used, distillation of 100-g

portions gave 64.3–66.4 g (65–66% yield).
15. The submitters report that recrystallization from ethyl acetate–petroleum ether raises the melting point to 73°C. The product obtained is analytically pure, $[\alpha]_D^{21}$ + 16° (EtOH, *c* 2). When the checkers used ethyl acetate–petroleum ether they often obtained an oily product.
The spectrum of the lactone acid is as follows: ^1H NMR (CD_3COCD_3) δ: 2.1–2.9 (m, 4 H), 4.85–5.15 (m, 1 H), 5.1 (s, 1 H, COOH).

3. Discussion

The (*S*)-(+)-γ-butyrolactone-γ-carboxylic acid is a useful intermediate for the synthesis of pheromones,[4] natural lignans,[5] and other derivatives.[6] In the same manner, but starting with D-glutamic acid, the (*R*)-(−)-lactone acid may be prepared.[7] Lactonization occurs with full retention of configuration at the chiral center.[8,9] Recently, authors have described an efficient method that allows the formation of derivatives of the (*R*)-(−)-lactone from the more available (*S*)-(+) counterpart.[10]

The procedure is a detailed description of the Austin–Howard preparation.[2] The mechanism presumably involves anchimeric assistance of the carboxy group in decomposition of an intermediate diazonium ion, leading to a labile α-lactone:[4]



The title compound has also been prepared[11] using hydrochloric acid instead of sulfuric acid, and ethyl acetate instead of acetone. In the hands of the submitters, this procedure gave a lower yield.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

sulfuric acid (7664-93-9)

hydrochloric acid, HCl (7647-01-0)

ethyl acetate (141-78-6)

ether (60-29-7)

sodium nitrite (7632-00-0)

acetone (67-64-1)

Glutamic Acid (56-86-0)

(+)-γ-butyrolactone-γ-carboxylic acid (21461-84-7)

D-Glutamic acid (617-65-2)

(S)-(+)-γ-Butyrolactone-γ-carboxylic acid, 2-Furancarboxylic acid, tetrahydro-5-oxo-, (S)- (53558-93-3)

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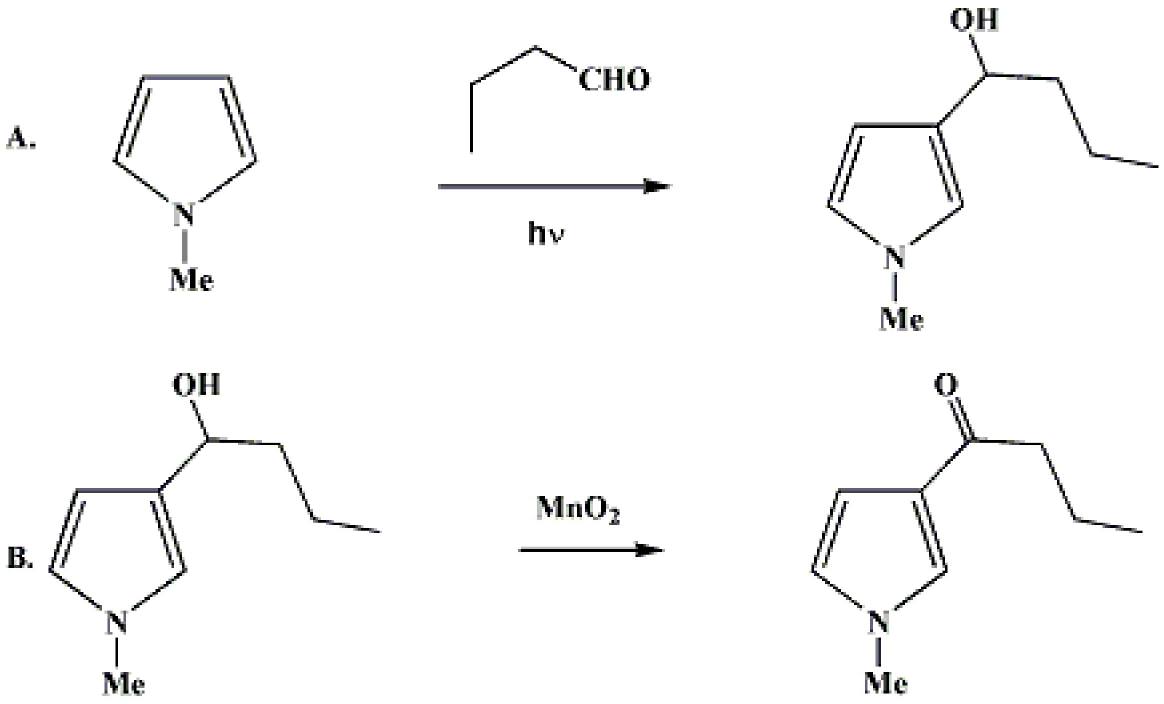
Organic Syntheses, CV 7, 102

3-(1-HYDROXYBUTYL)-1-METHYLPYRROLE AND 3-BUTYROYL-1-METHYLPYRROLE

[1 *H*-Pyrrole-3-methanol, 1-methyl-α-propyl- and 1-Butanone, 1-(1-methyl-1*H*-pyrrol-3-yl)-]



Submitted by H. M. Gilow and G. Jones, II[1].
Checked by Steven M. Pitzenberger, Richard A. Hayes, and Orville L. Chapman.

1. Procedure

A. *3-(1-Hydroxybutyl)-1-methylpyrrole* **(1)**. A photochemical quartz immersion well (220 mm length) (Note 1) equipped with 450-W Hanovia medium-pressure mercury lamp and a Vycor filter, cooled with water, is used. To a 125-mL Pyrex reaction vessel (230 mm long, 64 mm i.d.) equipped with a gas inlet and outlet is added 60 mL (55 g, 0.676 mol) of 1-methylpyrrole (Note 2) and 65 mL (54 g, 0.936 mol) of butyraldehyde (Note 3). Dry nitrogen is slowly bubbled through the solution during 48 hr of photolysis (Note 4).

The solution is concentrated under reduced pressure. The remaining oil is distilled under reduced pressure using a simple distillation apparatus. After a small forerun, 27 g (0.179 mol, 26% yield) (Note 5) of **1** is collected, as a light yellow oil, bp 90–94°C/0.05 mm (Note 6). Further purification is accomplished by a second distillation under reduced pressure, bp 90.2°C/0.05 mm (Note 7) and (Note 8).

B. *3-Butyroyl-1-methylpyrrole* **(2)**. A 100-mL, one-necked, round-bottomed flask is fitted with an efficient reflux condenser and arranged for magnetic stirring and heating. The flask is charged with 50 mL of pentane (Note 9) and 2.0 g (13 mmol) of 1 (Note 10). To the rapidly stirred solution is added 16 g (180 mmol) of activated manganese(IV) oxide (Note 11) in small portions over 5 min. The solution is heated at reflux for 18 hr and then an additional 8 g (90 mmol) of activated manganese(IV) oxide is added in portions (Note 12). After being heated at reflux for 24 hr, the reaction mixture is filtered through a 2-cm Celite filter pad. The filtered manganese oxides are thoroughly washed with about 200–300 mL of dichloromethane. Evaporation of solvent from the combined filtrates leaves 1.4–1.6 g of a light yellow oil. Bulb-to-bulb distillation at 100°C/0.1 mm (Note 13) gives 1.27–1.40 g (8.4–9.3 mmol, 64–71% yield) of an oil **(2)** (Note 14).

2. Notes

1. The photochemical quartz immersion well was obtained from Ace Glass Inc.
2. 1-Methylpyrrole was obtained from Aldrich Chemical Company, Inc. and distilled before use, bp 112–112.5°C.
3. Butyraldehyde was obtained from Aldrich Chemical Company, Inc. and distilled before use, bp 74.5–75.5°C. It is important that a freshly distilled sample, free of trimer, be used, or the final product will be contaminated with trimer.
4. When the reaction mixture was monitored by GLC (500-mm × 3.2-mm column, packed with 5% OV 101 on chromosorb G, HP, 100/120 mesh) most of the product was formed in the first 24 hr of photolysis, as shown by the following profile:

Time of Photolysis (hr)	% of Alcohol (Based on Starting Pyrrole)
2	4
19	18
24	23
48	25

5. The checkers found that the distillate contained 15–30% butyraldehyde (as monitored by NMR), which depended on the efficiency of the distillation. A 10-cm column packed with glass helices was the most efficient, but the yield of distilled product dropped drastically.
6. The susceptibility of 3-(1-hydroxybutyl)-1-methylpyrrole to air oxidation and decomposition with acid requires that prolonged storage be done in tightly capped containers in a refrigerator.
7. The spectral properties of 3-(1-hydroxybutyl)-1-methylpyrrole are as follows: ^{1}H NMR ($CDCl_3$) δ: 0.90 (t, 3 H, CH_3-C), 1.10–1.80 (m, 4 H, -CH_2CH_2-), 2.88

(s, 1 H, H-O-), 3.51 (s, 3 H, (CH_3N-), 4.50 (t, 1 H, HC-), 5.9 (t, 1 H, 4-pyrrole) and 6.41 (d, 2 H, 2,5-pyrrole). IR (neat)cm^{-1}: 3400 (H-O stretch) and 1175 (C=O stretch).

8. The reaction can also be carried out using smaller amounts of 1-methylpyrrole (0.113 mol), butyraldehyde (0.113 mol), and a solvent (245 mL acetonitrile, ACS grade) in a somewhat larger reaction vessel. After 17 hr of photolysis, and after removal of the volatile material and distillation of the remaining oil under reduced pressure, 4–5 g of the alcohol is isolated.

9. The submitters used dichloromethane. The checkers found that use of pentane[2] resulted in increased yields for the oxidation.

10. When the alcohol **(1)** is contaminated with small amounts of butyraldehyde, oxidation proceeds with a much lower yield of product.

11. Activated manganese(IV) oxide was purchased from Alfa Products, Morton Thiokol, Inc.

12. Progress of the reaction can be monitored by taking an aliquot of the reaction and filtering it, removing the solvent in a vacuum, dissolving the residual oil in carbon tetrachloride, and observing the ^{1}H NMR spectrum. Relative integration of the proton resonances of the pyrrole 2-position (6.1 ppm for the alcohol and 7.2 ppm for the ketone) gives an indication of the percent conversion. The checkers found only 77% conversion after the first reflux period. A higher conversion, 90–97%, was achieved after a second addition of activated manganese(IV) oxide and subsequent heating at reflux.

13. The submitters used a short-path simple distillation apparatus, bp 85–87°C (0.2 mm).

14. The following spectral properties were recorded for 3-butyroyl-1-methylpyrrole, **2:** ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.97 (t, 3 H), 1.72 (sextet, 2 H), 2.68 (t, 2 H), 3.68 (s, 3 H), 6.6 (m, 2 H, 4,5-pyrrole), 7.23 (t, 1 H, 2-pyrrole); IR (neat) cm^{-1}: 1660 (C=O stretch); MS (70 eV) *m/e* (rel. int.): 151 (8.6, M^+), 123 (1.6), 108 (34), 28 (100). The submitters reported the following spectral data: ^{1}H NMR ($CDCl_3$) δ: 0.95 (t, 3 H), 1.65 (sextet, 2 H), 2.65 (t, 2 H), 3.63 (s, 3 H), 6.47 (m, 2 H), 7.15 (m, 1 H); IR (neat)cm^{-1}: 1700.

3. Discussion

This procedure provides a method for functionalizing the pyrrole ring in the 3-position, normally a difficult synthetic step when conventional electrophilic substitution is used.[3] The technique has been extended to addition of several aldehydes and acetone and to a number of pyrroles.[4] The generality includes photoaddition to imidazoles that are substituted in the 4-position. Pyrrole photoadduct alcohols are readily dehydrated to 3-alkenylpyrroles or oxidized to 3-acyl derivatives.

The precedent is strong for the involvement of oxetanes as intermediates in carbonyl additions to pyrroles.[5,6,7] NMR evidence has been obtained for an oxetane adduct of acetone and *N*-methylpyrrole.[4] The initial photoadduct was shown to rearrange readily

on workup to the 3-(hydroxyalkyl)pyrrole derivative.

Oxidation of the 3-(hydroxyalkyl)pyrrole derivative gives a pure 3-acylpyrrole derivative that is difficult to obtain by direct substitution in the pyrrole ring. Acylation of pyrrole yields 1- and/or 2-acetylpyrrole, whereas acylation of 1-methylpyrrole forms both 2- and 3-acetyl-1-methylpyrrole, the latter in smaller amount.[3] When a similar procedure was used, 3-(1-hydroxyethyl)-1-methylpyrrole was converted to 3-acetyl-1-methylpyrrole in (76% yield.[4] Recently the decarbonylation of 1-methyl-4-acetyl-2-pyrrolaldehyde was used as a method to prepare 3-acetyl-1-methylpyrrole.[8]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

1 H-Pyrrole-3-methanol, 1-methyl-α-propyl- and 1-Butanone, 1-(1-methyl-1H-pyrrol-3-yl)-

alcohol (64-17-5)

acetonitrile (75-05-8)

carbon tetrachloride (56-23-5)

nitrogen (7727-37-9)

acetone (67-64-1)

butyraldehyde (123-72-8)

manganese(IV) oxide (1313-13-9)

Pentane (109-66-0)

Oxetane (503-30-0)

dichloromethane (75-09-2)

Pyrrole (109-97-7)

3-(1-Hydroxybutyl)-1-methylpyrrole (70702-66-8)

3-Butyroyl-1-methylpyrrole (62128-46-5)

1-methylpyrrole, N-methylpyrrole (96-54-8)

2-acetylpyrrole (1072-83-9)

3-acetyl-1-methylpyrrole (932-62-7)

3-(1-hydroxyethyl)-1-methylpyrrole

1-methyl-4-acetyl-2-pyrrolaldehyde

1-acetylpyrrole

2-acetyl-1-methylpyrrole

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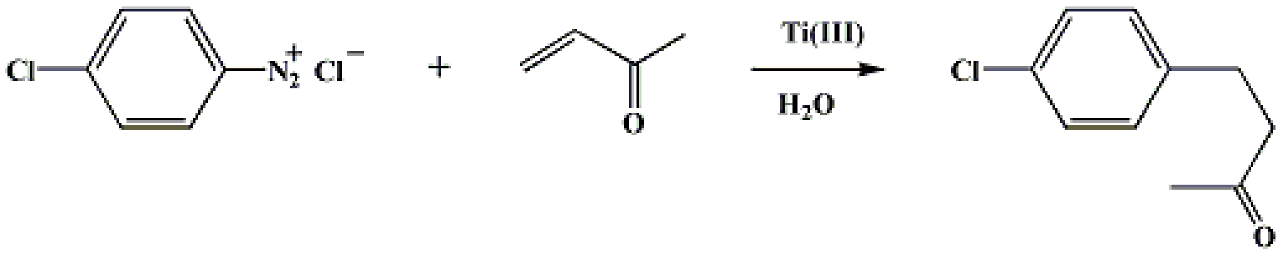
Organic Syntheses, CV 7, 105

REDUCTIVE ARYLATION OF ELECTRON-DEFICIENT OLEFINS: 4-(4-CHLOROPHENYL)BUTAN-2-ONE

[2-Butanone, 4-(4-chlorophenyl)-]



Submitted by Attilio Citterio
Checked by Robert Haessig, Leo Widler, and Dieter Seebach.

1. Procedure

Caution! Like all vinyl monomers, 3-buten-2-one is toxic and the preparation should be carried out in a well-ventilated hood.

A 500-mL, four-necked, round-bottomed flask equipped with a magnetic stirring bar, a thermometer, a gas inlet, an externally cooled, pressure-equalizing dropping funnel (Note 1), and a gas bubbler is charged with 15% aqueous titanium trichloride (92 mL, 0.109 mol) (Note 2). *N,N*-Dimethylformamide (Note 3) (70 mL) is added during 45 min with stirring and cooling (ice-bath; 0–5°C) while nitrogen is bubbled through the solution. Freshly distilled 3-buten-2-one (5.7 mL, 0.066 mol) is added at 0–5°C by syringe. The nitrogen flow is stopped, and 4-chlorobenzenediazonium chloride solution (0.044 mol) (Note 4) is added dropwise at 0–5°C from the dropping funnel. After 2–3 min, nitrogen evolution commences, and the rate of addition is adjusted so that 1–2 bubbles per second are vented through the bubbler. Nitrogen evolution continues for 20 min after the addition is complete (1.5 hr). The ice bath is removed and the solution stirred for 1 hr at room temperature. Ether, 50 mL, is added with stirring, and the organic phase is separated. The aqueous phase is extracted with ether (3 × 50 mL) and the combined organic extracts are washed with 3% aqueous Na_2CO_3 (2 × 30 mL) and water, dried over magnesium sulfate, and concentrated under reduced pressure. The residue is distilled to give 5.2–6.0 g (65–75% yield) of 4-(4-chlorophenyl)butan-2-one as a pale-yellow liquid, bp 90–91°C (0.5 mm) (Note 5).

2. Notes

1. The checkers used a dropping funnel with temperature-control jacket [Normag N 8055, Otto Fritz GmbH, Normschliff-Aufbaugeräte (Normag), D-6238 Hofheim am Taunus].
2. The 15% titanium trichloride solution was purchased from Carlo Erba Chemicals or from Merck & Company, Inc., but can also be prepared by dissolving metallic titanium in 20% aqueous hydrochloric acid[1] or by dissolving solid titanium trichloride in 1 *M* aqueous hydrochloric acid. Titanium(III) sulfate (from BDH Chemicals Ltd.) can also be used. All titanium(III) solutions were titrated with aqueous cerium(IV) sulfate prior to use.

3. *N,N*-Dimethylformamide from Carlo Erba Chemicals, from Fluka AG or from Merck & Company, Inc. was used as received. Other solvents (e.g., acetone, acetic acid, acetonitrile) can also be used.

4. The 4-chlorobenzenediazonium chloride solution is prepared as follows: finely powdered 4-chloroaniline (5.65 g, 0.044 mol) is suspended in 18 mL of 24% aqueous hydrochloric acid and cooled to 0°C. Sodium nitrite (3.2 g, 0.046 mol) in water (7 mL) is added dropwise during 45 min at 0–5°C to give a pale-yellow solution of the diazonium salt.

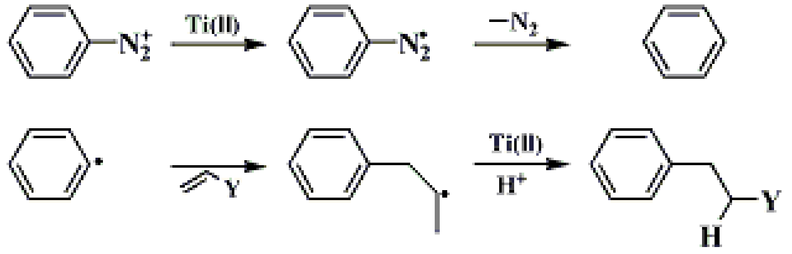
5. The physical properties of the product are as follows: n_D^{25} 1.5251; IR (liquid film) cm^{-1}: 1715; ^{1}H NMR ($CDCl_3$) δ: 2.0 (s, 3 H), 2.6–2.8 (m, 4 H), 6.8–7.3 (m, 4 H); mass spectrum *m/e*: 182 (M); semicarbazone, mp 165°C (164–165.5°C[2]). GLC analysis (glass capillary column, 20 m, pluronic L-64, program: 120–200°C at 5°C/min): >99% pure.

3. Discussion

This synthesis is only one example of a wide range of reactions that involve aryl (or alkyl) radical addition to electron-deficient double bonds resulting in reduction.[3,4,5] The corresponding oxidative reaction using aryl radicals is the well-known Meerwein reaction,[6] which uses copper(II) salts.

General arylation reactions are summarized by the following equations and some specific examples are presented in Table I.

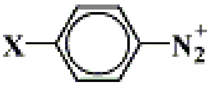
Homolytic cleavage of diazonium salts to produce aryl radicals is induced by titanium(III) salt, which is also effective in reducing the α-carbonylalkyl radical adduct to olefins, telomerization of methyl vinyl ketone, and dimerization of the adduct radicals. The reaction can be used with other electron-deficient olefins, but telomerization or dimerization are important side reactions.

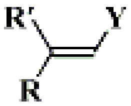


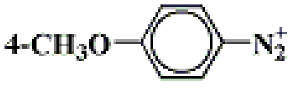
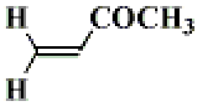
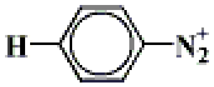
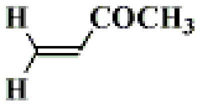
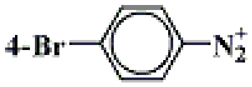
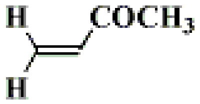
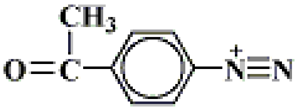
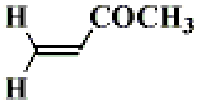
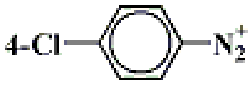
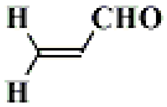
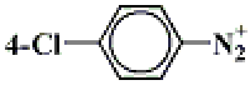
Other limitations of the reaction are related to the regioselectivity of the aryl radical addition to double bond, which is determined mainly by steric and radical delocalization effects.[7] Thus, methyl vinyl ketone gives the best results, and lower yields are observed when bulky substituents are present in the β-position of the alkene. However, the method represents complete positional selectivity because only the β-adduct radicals give reductive arylation products whereas the α-adduct radicals add to diazonium salts, because of the different nucleophilic character of the alkyl radical adduct.[7,8]

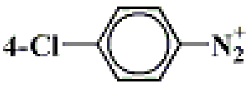
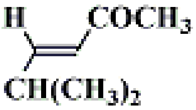
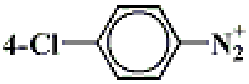
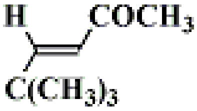
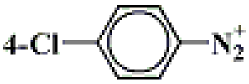
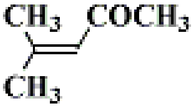
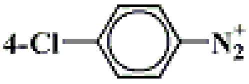
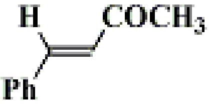
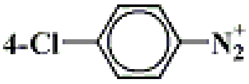
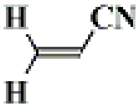
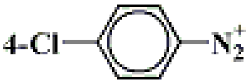
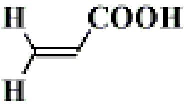
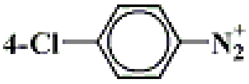
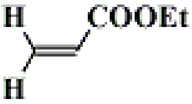
TABLE I

REDUCTIVE ARYLATION OF ELECTRON-DEFICIENT OLEFINS BY ARENEDIAZONIUM SALTS INDUCED BY TITANIUM(III) SALTS





X	R	R'	Y	Yield (%)[a]
 4-OCH_3	H	H	 $COCH_3$	65
 H	H	H	 $COCH_3$	75
 4-Br	H	H	 $COCH_3$	68
 4-$COCH_3$	H	H	 $COCH_3$	72
 4-Cl	H	H	 CHO	63
 4-Cl	CH_3	H	$COCH_3$	44

 4-Cl	$CH(CH_3)_2$	H	 $COCH_3$	28
 4-Cl	$C(CH_3)_3$	H	 $COCH_3$	14
 4-Cl	CH_3	CH_3	 $COCH_3$	12
 4-Cl	Ph	H	 $COCH_3$	18
 4-Cl	H	H	 CN	25[b]
 4-Cl	H	H	 COOH	33[b]
 4-Cl	H	H	 COOEt	32[b]

[a] From the diazonium salt.

[b] Telomers are formed; the reactions are carried out with twice the amount of titanium(III) salt.

The product described here, 4-(4-chlorophenyl)butan-2-one, was previously prepared in the following ways: (a) by reduction of the corresponding benzalacetone,[9] (b) by catalyzed decarbonylation of 4-chlorophenylacetaldehyde by $HFe(CO)_4$ in the presence of 2,4-pentanedione,[10] (c) by reaction of 4-chlorobenzyl chloride with 2,4-pentanedione under basic catalysis (K_2CO_3 in EtOH),[2] (d) by reaction of 4-chlorobenzyl chloride with ethyl 3-oxobutanoate under basic catalysis (LiOH),[11] and (e) by reaction of 3-(4-chlorophenyl)-propanoic acid with methyllithium.[12]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

$HFe(CO)_4$

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ether (60-29-7)

acetonitrile (75-05-8)

Na_2CO_3 (497-19-8)

nitrogen (7727-37-9)

sodium nitrite (7632-00-0)

acetone (67-64-1)

ethyl 3-oxobutanoate (141-97-9)

magnesium sulfate (7487-88-9)

2,4-pentanedione (123-54-6)

N,N-dimethylformamide (68-12-2)

methyl vinyl ketone, 3-buten-2-one (78-94-4)

Methyllithium (917-54-4)

cerium(IV) sulfate (13590-82-4)

4-Chloroaniline (106-47-8)

titanium(III)

titanium (7440-32-6)

titanium trichloride (7705-07-9)

4-(4-Chlorophenyl)butan-2-one, 2-Butanone, 4-(4-chlorophenyl)- (3506-75-0)

4-chlorobenzenediazonium chloride

Titanium(III) sulfate

4-chlorophenylacetaldehyde

4-chlorobenzyl chloride (104-83-6)

3-(4-chlorophenyl)-propanoic acid (2019-34-3)

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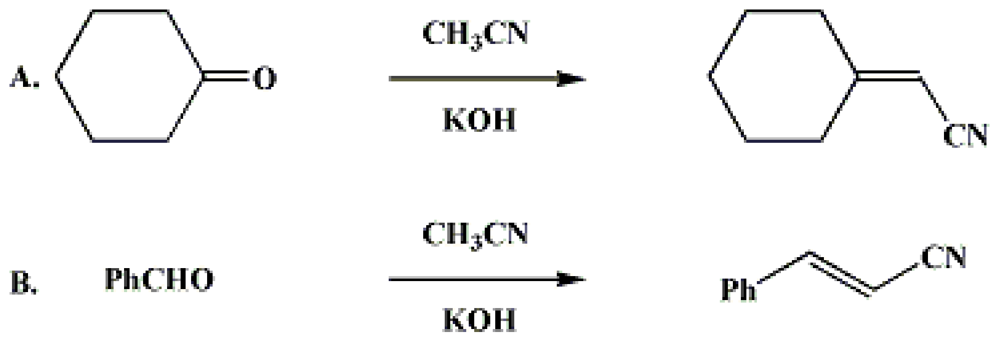
Organic Syntheses, CV 7, 108

SYNTHESIS OF α,β-UNSATURATED NITRILES FROM ACETONITRILE: CYCLOHEXYLIDENEACETONITRILE AND CINNAMONITRILE

[Acetonitrile, cyclohexylidene- and 2-propenenitrile, 3-phenyl, (*E*)- and (Z)-]



Submitted by Stephen A. DiBiase, James R. Beadle, and George W. Gokel[1].
Checked by Yumi Nakagawa and Robert V. Stevens.

1. Procedure

A. *Cyclohexylideneacetonitrile*. A 1-L three-necked, round-bottomed flask equipped with a reflux condenser, mechanical stirrer, and addition funnel is charged with potassium hydroxide (85% pellets, 33.0 g, 0.5 mol, (Note 1)) and acetonitrile (250 mL, (Note 2) and (Note 3)). The mixture is brought to reflux and a solution of cyclohexanone (49 g, 0.5 mol. (Note 4)) in acetonitrile (100 mL) is added over a period of 0.5–1.0 hr. Heating at reflux is continued for 2 hr (Note 5) after the addition is complete and the hot solution is then poured onto cracked ice (600 g). The resulting binary mixture is separated and the aqueous phase is extracted with ether (3 × 200 mL). The combined organic extracts are evaporated under reduced pressure, or may be placed in a 2-L Erlenmeyer flask containing several boiling chips and the volume reduced on a steam bath (internal temperature ca. 50°C). The resulting sweet-smelling, yellow to yellow–orange oil is transferred to a 1- or 2-L, three-necked, round-bottomed flask (depending on whether internal or external steam generation is used) and steam distilled (bp 81–99°C, (Note 6)). The distillate is extracted with three to five 200-mL portions of ether until the aqueous phase is clear (Note 7). The ether phase is washed with brine (2 × 100 mL), dried over sodium sulfate, and evaporated under reduced pressure to give a pale yellow oil (29–36 g, (48–60%) that consists of a mixture of isomers (α,β 80–83%, (β,γ 17–20%, (Note 8)).

Isolation of the pure α,β-*isomer.* A 250-mL Erlenmeyer flask equipped with a magnetic stirring bar is charged with the isomeric nitriles (20 g, 0.165 mol), prepared

in Section A above, and carbon tetrachloride (20 mL). A solution of bromine in carbon tetrachloride (1/9, v/v, ca. 25–30 mL) is added dropwise until the color of excess bromine persists. The reaction vessel is cooled in an ice bath for 30 min and filtered by gravity and the solvent evaporated under reduced pressure. The crude oil is distilled at reduced pressure (bp 40–42°C/0.15 mm) to give a colorless liquid (11–15 g, 55–75%) that is the pure α,β-isomer (Note 9) and (Note 10).

B. *Preparation of E- and Z-Cinnamonitrile*. A 1-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, reflux condenser, and addition funnel is charged with potassium hydroxide pellets (33 g, 0.5 mol, (Note 1)) and acetonitrile (400 mL, (Note 2)). The mixture is brought to reflux under nitrogen and a solution of benzaldehyde (53 g, 0.5 mol, (Note 4)) in acetonitrile (100 mL) is added in a stream (1–2 min). After addition, stirring is continued for 10 min (Note 5) and the hot solution is then poured onto 500 g of cracked ice in a 1-L beaker. After being cooled for a few minutes, the two-phase mixture is transferred to a 2-L, three-necked flask and steam-distilled (Note 11). The distillate is transferred to a separatory funnel, and the upper aqueous phase is separated and then extracted with two 500-mL portions of ether (Note 7). The combined organic material is dried briefly over Na_2SO_4 and the ether evaporated to yield pure cinnamonitrile (20–29 g, 31–45%) as a pale-yellow oil (*E/Z* ratio ca. 5.5; (Note 12)).

2. Notes

1. Potassium hydroxide (85% pellets, AR grade) should be as fresh as possible (see (Note 5)).
2. Acetonitrile (99%) was obtained from Aldrich Chemical Company, Inc. and may be used without purification.
3. The yield of product is dependent on concentration. An increase in the amount of acetonitrile in Step A to ca. 1000 mL increases the yield of the isomer mixture to 65–75% without affecting isomer distribution. Further dilution to ca. 5000 mL increases the yield to 80–85%.
4. Cyclohexanone and benzaldehyde were purchased from either Aldrich Chemical Company, Inc. or Eastman Organic Chemicals and used without additional purification.
5. The reaction time depends on the quality of the potassium hydroxide employed. An induction period is often observed when older potassium hydroxide samples are used, possibly because surface formation of carbonates reduces the solubility of the salt in acetonitrile. An attempt was made to monitor the cinnamonitrile reaction by GLC, following loss of starting material. Although formation of the product was observed and reached a maximum, the starting material peak never completely disappeared. Prolonged reaction times (>2 hr) resulted in failure to isolate any of the desired product. Reaction times of less than 30 min gave the expected yields. Undissolved potassium hydroxide was observed in the reaction vessel when these reactions were terminated. At a column temperature of 150°C and a gas flow rate of ca. 60 mL/min (5-ft × 0.25-

in. column, 10% SE-30 on firebrick), the retention times are as follows: cyclohexylideneacetonitrile and isomer, 2.8 min; *Z*-cinnamonitrile, 3.0 min; *E*-cinnamonitrile, 3.7 min). The reaction may also be monitored by a 2,4-dinitrophenylhydrazone spot test.
6. Distillation may be conducted using an apparatus designed for either internal or external steam generation. The first 1000-mL portion of distillate contains ca. 35 g of product. An additional 500 mL of distillate yields less than 1 g. Vacuum distillation gave product in 22% yield.
7. To facilitate phase separation, solid sodium chloride was added to the aqueous layer.
8. The product thus obtained is of high purity. The trace of color may be removed by distillation at reduced pressure (bp 50°C/0.5 mm).
9. Bromination can be monitored by ^1H NMR in CCl_4. The vinyl protons are observed at 5.08 (α,β-isomer) and 5.65 ppm.
10. The ^1H NMR spectra (in CCl_4) for the two isomers are as follows. Cyclohexylideneacetonitrile: δ 1.25-2.0 (m, 6 H), 2.0–2.8 (m, 4 H, methylene protons), 5.08 (m, 1 H, olefin); 2-(1-cyclohexenyl)acetonitrile: 1.25–2.0 (m, 4 H), 2.0–2.8 [m, 4 H, $-(CH_2)_4-$], 3.05 (pseudo-s, 2 H, $-CH_2CN$), 5.65 (m, 1 H, olefin).
11. Steam distillation may be conducted using apparatus designed either for internal or external steam generation. Using internally generated steam, 2.5 L of distillate was collected. The last 500 mL contained less than 1 g of product.
12. Isomer distribution and purity were assessed by GLC (see (Note 5)). The ^1H NMR spectra (in CCl_4) for the pure isomers are as follows: *E*-isomer: δ 5.71 [d, 1 H, *J* = 17, ArCH=CH-CN; 7.44 (d, 1 H, *J* = 17, ArCH=CHCN), 7.3 (pseudo-s, 5 H, aromatic protons). *Z*-Isomer: δ 5.31 (d, 1 H, *J* = 12, ArCH=CHCN), 6.98 (d, 1 H, *J* = 12, ArCH=CHCN), 7.3 (pseudo-s, 5 H, aromatic protons).

3. Discussion

Introduction of the two-carbon fragment is a cornerstone of synthetic methodology and many of the condensation reactions frequently used have been known for decades, if not for a century. Examples include the malonic ester[2] and acetoacetic ester[3] reactions, the Perkin[4] condensation, and the Doebner–Knoevenagel[5] reaction. Addition of the cyanomethyl group has been accomplished by a variety of methods,[6] mostly circuitous, and is certainly not in the group of classical reactions named above. The direct approach is found in a recent application of lithio trimethylsilylacetonitrile,[7] but the difference in expense and convenience between using this method and a mixture of potassium hydroxide and acetonitrile is manifest.

The direct synthesis of α,β-unsaturated nitriles can be accomplished by treating the appropriate carbonyl compound with potassium hydroxide in acetonitrile.[8] In order for direct condensation to succeed, acetonitrile must be deprotonated by the relatively weak base potassium hydroxide and the carbanion thus formed must add to the

carbonyl. The cyanohydrin is presumably dehydrated to leave the α,β-unsaturated compound, which may or may not isomerize in the medium. We have run this reaction with a large number of carbonyl compounds[8] and have found that it is most successful for aromatic aldehydes (36–86%) and other nonenolizable carbonyl compounds such as benzophenone (84%). Yields are also acceptable for most cyclic ketones with six or more carbons in the ring (e.g., 2-methylcyclohexanone, 78%; *cis*-octalone, 80%; cycloheptanone, 78%; cyclooctanone, 66%, cyclododecanone, 45%), and for aliphatic ketones having three or more carbons bonded on each side (e.g., diethyl ketone, 35%; di-*n*-propyl ketone, 65%, di-*n*-butyl ketone 65%). Ketones that are sterically hindered (camphor) or highly enolized (cyclopentanone) are not useful substrates in this reaction.

We present here examples of this condensation with an aromatic aldehyde and a cyclic ketone. Both of these examples are useful because, although other methods are available for their preparation, problems often attend these syntheses. In the synthesis of cyclohexylideneacetonitrile, for example, the standard method[9] results exclusively in the β,γ-isomer and none of the α,β-isomer. In Part A of this procedure, cyclohexanone is condensed with acetonitrile to give predominantly the conjugated isomer (80–83%), which is then separated from the nonconjugated isomer by selective bromination.

The procedures presented here are simple, inexpensive, and may be used on a large scale. The use of potassium hydroxide in this reaction may, however, prove incompatible with certain base-sensitive functional groups.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

brine

E- and Z-Cinnamonitrile

2,4-dinitrophenylhydrazone

cis-octalone

2-propenenitrile, 3-phenyl, (E)- and (Z)-

ether (60-29-7)

acetonitrile (75-05-8)

Cyclohexanone (108-94-1)

sodium chloride (7647-14-5)

bromine (7726-95-6)

sodium sulfate, Na_2SO_4 (7757-82-6)

carbon tetrachloride (56-23-5)

nitrogen (7727-37-9)

benzaldehyde (100-52-7)

potassium hydroxide, potassium hydroxide pellets (1310-58-3)

Benzophenone (119-61-9)

Cyclopentanone (120-92-3)

camphor (21368-68-3)

diethyl ketone (96-22-0)

2-methylcyclohexanone (583-60-8)

Cycloheptanone (502-42-1)

di-n-propyl ketone (123-19-3)

Cyclooctanone (502-49-8)

cyclododecanone (830-13-7)

Cinnamonitrile (4360-47-8)

Cyclohexylideneacetonitrile, Acetonitrile, cyclohexylidene- (4435-18-1)

Z-Cinnamonitrile

lithio trimethylsilylacetonitrile

di-n-butyl ketone (502-56-7)

E-cinnamonitrile (4360-47-8)

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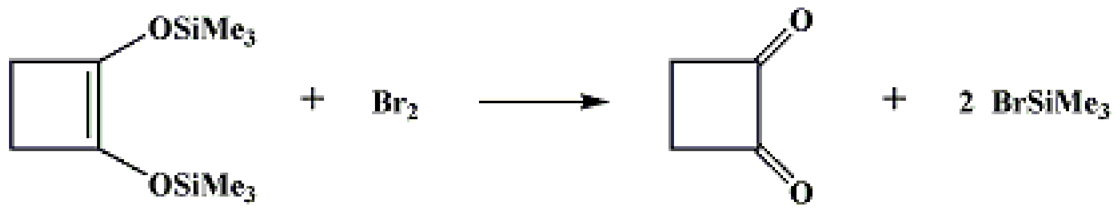
1,2-CYCLOBUTANEDIONE



Submitted by J. M. Denis, J. Champion, and J. M. Conia[1].
Checked by Robert V. Stevens and Steven R. Angle.

1. Procedure

Caution! This reaction should be carried out in a dark hood to prevent the photoinduced polymerization of the dione.

A 1-L, three-necked, round-bottomed flask equipped with a 500-mL dropping funnel, a nitrogen-inlet tube, a mechanical stirrer, a low-temperature thermometer, and a calcium chloride drying tube is charged with 172 g (0.75 mol) of 1,2-bis (trimethylsiloxy) cyclobutene (Note 1) and 375 mL of anhydrous pentane (Note 2). A dry nitrogen atmosphere is maintained in the system (Note 3) and the solution is cooled to –60°C by means of a dry ice-methanol bath. Then a solution of 120 g (0.75 mol) of bromine and 375 mL of anhydrous pentane is added dropwise with stirring over a period of 2 hr. When the addition is complete, the mixture must be heated to 40° C for 2 hr (Note 4) and concentrated by removing ca. 550 mL of solvent under reduced pressure (15 mm) at room temperature. To isolate the dione the residue is cooled to –60°C by immersion of the flask in a dry ice–methanol bath. The crystallized product is *quickly* filtered through a hermetically sealed (Note 3), 250-mL sintered-glass funnel (porosity 3), a dry nitrogen pressure being used to push down solvent. The yellow solid is washed with stirring with eight 25-mL portions of anhydrous pentane cooled to –60°C and sucked as dry as possible on the filter. The pentane used in the washing is concentrated under reduced pressure (15 mm) at room temperature to ca. 15 mL, then the flask is again cooled to –60°C. The crystallized product is washed with four 15-mL portions of anhydrous pentane cooled to –60°C as before. The two batches of crystals are of approximately equal purity. The yield of 1,2-cyclobutanedione is 42–46 g (70–73%), mp 65°C (Note 5).

2. Notes

1. The 1,2-bis(trimethylsiloxy)cyclobutene is prepared according to the procedure of Bloomfield.[2]
2. Pentane is distilled prior to use (bp 36°C/760 mm) and stored over sodium wire.

3. *Caution! Moisture must be avoided to prevent the ring contraction of the dione into 1-hydroxycyclopropanecarboxylic acid.*[2]

4. This heating is necessary to complete the reaction.[2]

5. The yellow product shows in the ^{1}H NMR (CCl_4) a single signal at 2.98 ppm indicating its high degree of purity. It can be sublimed under vacuum (15 mm) at room temperature, mp 65°C; IR (CCl_4) cm^{-1}: 1778 and 1810; UV (hexane) nm max ( ): 407 (4), 423 (8), 436 (10.5), 453 (19), 463 (17), 489 (42), and 500.5 (28). The dione can be stored at 0°C in a hermetically sealed flask in the dark for months.

3. Discussion

This method of preparation of the 1,2-cyclobutanedione is an adaptation of that independently described by Denis and Conia[3] and by Heine.[4] Acyloins, 1,2-cyclobutanediols, imidazole, thioimidazole, and amino- and cyanofuran derivatives are readily available[5,6] from bis(trimethylsiloxy)alkenes.

The bis(trimethylsiloxy)alkene bromination procedure is a large-scale preparation that gives excellent yields of cyclic and acyclic 1,2-diones; however, when enolizable 1,2-diketones are produced, some complications can be encountered.[7,8]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Acyloins

1,2-cyclobutanediols

amino- and cyanofuran derivatives

bis(trimethylsiloxy)alkenes

bis(trimethylsiloxy)alkene

cyclic and acyclic 1,2-diones

1,2-diketones

bromine (7726-95-6)

sodium wire (13966-32-0)

Pentane (109-66-0)

Imidazole (288-32-4)

hexane (110-54-3)

1,2-bis(trimethylsiloxy) cyclobutene, 1,2-bis(trimethylsiloxy)cyclobutene (17082-61-0)

1,2-Cyclobutanedione (33689-28-0)

1-hydroxycyclopropanecarboxylic acid (17994-25-1)

thioimidazole

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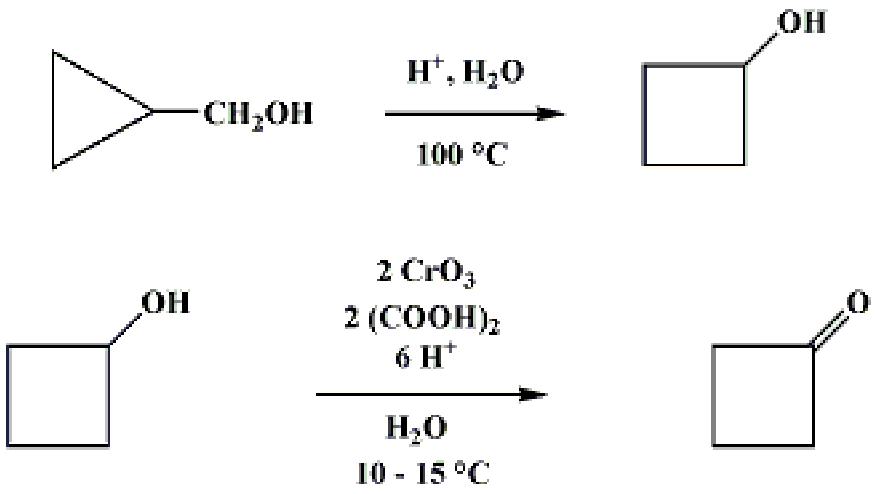
CYCLOBUTANONE



Submitted by Miroslav Krumpolc and Jan Rocek[1].
Checked by D. Seebach, R. Dammann, F. Lehr, and M. Pohmakotr.

1. Procedure

In a 2-L, three-necked, round-bottomed flask equipped with a reflux condenser are placed 250 mL of water, 48 mL (ca. 0.55 mol) of concentrated hydrochloric acid, and 49.5 g (0.65 mol) of cyclopropylcarbinol (Note 1); the reaction mixture is refluxed for ca. 100 min. The formation of cyclobutanol can be observed nearly instantaneously, as this alcohol is only partially soluble in water and soon separates (Note 2). The flask is then immersed in an ice bath equipped with a mechanical stirrer, a thermometer, and a dropping funnel (using a three-way adapter, parallel sidearm), and the reflux condenser is replaced by an ethanol–dry ice trap connected to a U-tube immersed in an ethanol–dry ice bath to ensure condensation of the very volatile cyclobutanone. The flask is charged with an additional 48 mL (ca. 0.55 mol) of concentrated hydrochloric acid in 200 mL of water and 440 g (3.5 mol) of oxalic acid dihydrate (Note 1). The heterogeneous mixture is stirred for ca. 15 min to saturate the solution with oxalic acid. A solution of 162 g (1.62 mol) of chromium trioxide in 250 mL of water is added dropwise with stirring at such a rate that the temperature of the reaction mixture is kept between 10°C and 15°C (NaCl–ice bath, –5°C to –10°C) and the generation of carbon dioxide remains gentle. The reduction of each drop of chromic acid is practically instantaneous. As the addition of the reagent proceeds (1.5–2 hr), oxalic acid gradually dissolves and a dark-blue solution containing chromium(III) salts results (Note 3). Just before the end of the oxidation (ca. 10 mL of the chromic acid solution left), the cyclobutanone (with traces of cyclobutanol) trapped in the U-tube (a few milliliters) is added to the reaction mixture. After the oxidation is completed, the ice bath is removed and stirring is continued for ca. 1 hr to bring the reaction mixture to room temperature and to reduce the amount of carbon dioxide in the solution.

The reaction mixture is poured into a 2-L separatory funnel and extracted with four 200-mL portions of methylene chloride (Note 4). The extracts (the lower phase) are combined, dried over anhydrous magnesium sulfate containing a small amount of anhydrous potassium carbonate (to remove traces of hydrochloric acid), and filtered, and the filtrate is concentrated by distillation through a vacuum-insulated silvered column (20-cm length, 1-cm i.d.) packed with glass helices (size 2.3 mm, Lab Glass, Inc.) and equipped with an adjustable stillhead, until the pot temperature rises to 80°C (Note 5). The crude product is then transferred to a 100-mL flask and distilled through the same column (reflux ratio 10:1) to give 14–16 g (0.20–0.23 mol), 31–35% overall yield (based on pure cyclopropyl carbinol) of cyclobutanone, bp 98–99°C, d_4^{25} 0.926, n_D^{25} 1.4190 (Note 6). The product is sufficiently pure (98–99%) for most purposes (Note 5), (Note 7), (Note 8), and (Note 9).

2. Notes

1. The following compounds were used as supplied: cyclopropylcarbinol (Aldrich Chemical Company, Inc. or Fluka AG, 95% pure), hydrochloric acid (Fisher Reagent, 36.5–38%), chromium trioxide (Fisher Certified), oxalic acid dihydrate (Fisher Certified), methylene chloride (Fisher Certified).

2. At this point cyclopropylcarbinol has been completely converted into a mixture of products containing ca. 80% cyclobutanol, 8% 3-butene-1-ol, and several additional products observable by GLC analysis in varying amounts. About 95–97% pure cyclobutanol (60–65% yield) can be obtained if the reaction mixture is neutralized with sodium hydroxide and sodium bicarbonate, saturated with magnesium sulfate, extracted with ether, and fractionally distilled on an efficient distillation column. The remaining impurities are extremely difficult to remove.

3. Oxalic acid is used in excess to ensure a rapid oxidation of the alcohol and to destroy the excess chromic acid when the cooxidation process is over. Part of the oxalic acid is consumed by chromium(III) to form oxalatochromium(III) complexes.

4. As cyclobutanone is considerably soluble in water, a thorough and vigorous agitation is recommended to ensure good extraction of the aqueous layer by methylene chloride. Oxalic acid is insoluble in this solvent.

5. The checkers used a silvered, vacuum-insulated column 30 cm in length with 1.5-cm i.d., filled with 4-mm × 4-mm helices; distillation of CH_2Cl_2 was first done from a 250-mL, two-necked flask with dropping funnel from which the dried extraction solution was continuously added. When ca. 50-mL total volume of solution remained (bath temperature ca. 90°C), it was transferred into a 100-mL, one-necked flask. Eight fractions of the cyclobutanone were collected at a 15–20:1 reflux ratio: bp/g/% purity of ketone (by VPC): 80–90/1.17/37, 90–95/4.3/53, 95–96/1.71/99.5, 96–97/1.41/—, 96–97.5/1.2/99.9, 97.5–98/3.95/99.9, 98/3.76/100, 98/1.78/99.8. The $n_D^{20.5}$ of fraction 7 was 1.4210.

6. The reported physical constants of cyclobutanone[2] are bp 99–100°C, d_4^{24}

0.924, n_D^{25} 1.4188.

7. Gas-liquid chromatography [1/8-in. × 6-ft, 10% diethylene glycol succinate (LAC-728) column, 70°C] of cyclobutanone (99.2% pure) revealed the presence of small amounts of methylene chloride (0.6%) and cyclobutanol (0.2%). No cleavage product, 4-hydroxybutyraldehyde, was found. The traces of water, detected by NMR spectroscopy using CD_3COCD_3 as a solvent, can be removed by drying over molecular sieves.

8. ^{1}H NMR (CCl_4) δ: 1.98, degenerate quintet (2 H, *J* = 8 Hz); 3.03, t (4 H, *J* = 8 Hz). IR (liquid film on KBr plates) cm^{-1}: 1783 (strong, C=O).

9. If the preparation of cyclobutanone from cyclopropylcarbinol is carried out in two steps, with cyclobutanol isolated first, somewhat higher yields can be achieved (70–80% based on cyclobutanol, 45–50% overall yield, purity 98–99%).

3. Discussion

Cyclobutanone has been prepared (1) by pyrolysis of 1-hydroxycyclobutane-1-carboxylic acid[3] (15% yield), (2) by reaction of diazomethane with ketene[4,5,6] (36% overall yield based on precursors used for the generation of both components[6]), (3) from pentaerythritol, the final step being the oxidative degradation of methylenecyclobutane[7,8] (30–45% overall yield), (4) by oxidation of cyclobutanol with chromic acid–pyridine complex in pyridine[9] (no yield is given), (5) by oxidative cleavage of 5,9-dithiaspiro[3.5]nonane, prepared via 2-(ω-chloropropyl)-1,3-dithiane[10,11] from 1,3-propanedithiol[12] (40% overall yield), (6) via solvolytic cyclization of 3-butyn-1-ol[13,14] (30% yield), (7) by epoxidation of methylenecyclopropane followed by ring expansion of resulting oxaspiropentane[15,16,17] (28% overall yield), (8) from 1,3-dibromopropane and methyl methylthiomethyl sulfoxide via cyclobutanone dimethyl dithioacetal *S*-oxide[18] (75% overall yield), and (9) from 4-chlorobutyraldehyde cyanohydrin, the final step being hydrolysis of cyclobutanone cyanohydrin[19] (45% overall yield).

The present procedure offers a simple and fast (2–3 days are required) preparation of pure cyclobutanone from cyclopropylcarbinol. The synthesis is carried out in one operation, without isolating the intermediate cyclobutanol. The first reaction, acid-catalyzed rearrangement of cyclopropylcarbinol, has been described by Caserio, Graham, and Roberts.[9] The novel feature is the preparation of cyclobutanone from cyclobutanol in the presence of oxalic acid. It is based on rapid cooxidation of two substrates proceeding via a three-electron oxidation–reduction mechanism[20,21] in which chromium (VI) is reduced directly to chromium (III). In the absence of oxalic acid the chromic acid oxidation of cyclobutanol gives along with cyclobutanone ca.

30–40% of 4-hydroxybutyraldehyde,[2] as the alcohol undergoes extensive carbon–carbon cleavage by chromium (IV).[2,21,22] The participation of oxalic acid in the reaction process serves to suppress the formation of a chromium (VI) intermediate; the only by-product formed is carbon dioxide.

Cyclobutanone is a versatile starting material used for numerous synthetic and theoretical studies in the chemistry of small rings. The preparation of this compound by the cooxidation process illustrates the synthetic utilization of three-electron oxidation–reduction reactions.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 117

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

oxalatochromium(III) complexes

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

1,3-dibromopropane (109-64-8)

Oxalic acid (144-62-7)

carbon dioxide (124-38-9)

pyridine (110-86-1)

chromic acid (7738-94-5)

Ketene (463-51-4)

methylene chloride (75-09-2)

Pentaerythritol (115-77-5)

magnesium sulfate (7487-88-9)

chromium trioxide (1333-82-0)

Diazomethane (334-88-3)

Cyclobutanone (1191-95-3)

cyclopropylcarbinol, cyclopropyl carbinol (2516-33-8)

3-butene-1-ol (627-27-0)

Cyclobutanol (2919-23-5)

3-butyn-1-ol (927-74-2)

1,3-propanedithiol (109-80-8)

methylenecyclobutane (1120-56-5)

5,9-dithiaspiro[3.5]nonane (15077-16-4)

Methylenecyclopropane (6142-73-0)

Oxaspiropentane (157-41-5)

2-(ω-chloropropyl)-1,3-dithiane

oxalic acid dihydrate (6153-56-6)

chromium(III), chromium (III)

4-hydroxybutyraldehyde (25714-71-0)

1-hydroxycyclobutane-1-carboxylic acid

methyl methylthiomethyl sulfoxide (33577-16-1)

4-chlorobutyraldehyde cyanohydrin

cyclobutanone cyanohydrin

chromium (VI)

chromium (IV)

cyclobutanone dimethyl dithioacetal S-oxide

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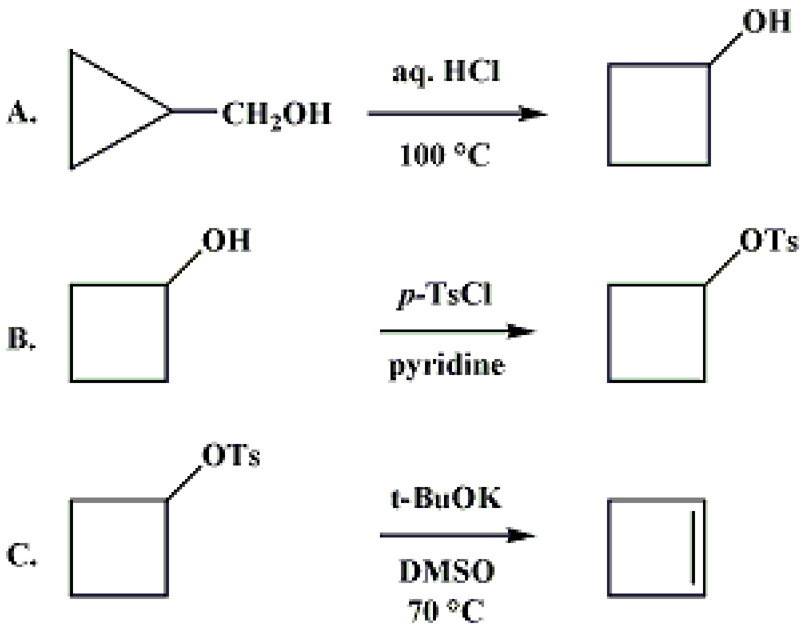
CYCLOBUTENE



Submitted by J. Salaün and A. Fadel[1].
Checked by Lawrence R. McGee and Bruce E. Smart.

1. Procedure

A. *Cyclobutanol.* A 1-L, three-necked, round-bottomed flask equipped with a reflux condenser and a magnetic stirring bar is charged with 600 mL of water, 57.5 mL (ca. 0.68 mol) of concentrated hydrochloric acid, and 57.7 g (0.80 mol) of cyclopropylcarbinol (Note 1). The reaction mixture is stirred and refluxed for 3 hr. Cyclobutanol is only partially soluble in water and soon separates. The reaction mixture is allowed to cool to room temperature, and the flask is then immersed in an ice bath. To the cold, stirred mixture is added 24 g (0.6 mol) of sodium hydroxide pellets, followed by 6.7 g (0.08 mol) of sodium bicarbonate to complete the neutralization. The mixture is saturated with sodium chloride and extracted for 30 hr with diethyl ether using a liquid–liquid continuous extraction apparatus. The ethereal extract is dried over anhydrous sodium sulfate and the drying agent is removed by filtration. The bulk of the solvent is distilled from the filtrate to give 55.0 g of residual liquid containing 88% cyclobutanol and 12% 3-buten-1-ol by gas chromatography (Note 2). The crude product is carefully distilled through spinning band columns to give 32.8 g (57%) of cyclobutanol, bp 122–124°C. Gas chromatographic analysis of the product shows it to be 95% pure (Note 2),(Note 3),(Note 4).

B. *Cyclobutyl tosylate.* A 500-mL, three-necked, round-bottomed flask fitted with a stirrer and a theromometer is charged with 200 mL of pyridine (Note 5) and 32.3 g (0.448 mol) of cyclobutanol. The solution is stirred and chilled to 0°C, and then 89.8 g

(0.471 mol) of *p*-toluenesulfonyl chloride (Note 6) is added in portions over a 20-min period. The reaction mixture is allowed to warm to room temperature and is stirred for 16 hr. The mixture is recooled to 0°C, and poured into 260 mL of concentrated hydrochloric acid in 800 mL of ice water. The mixture is extracted with three 300-mL portions of ether and the combined ethereal extracts are dried over anhydrous magnesium sulfate. The drying agent is removed by filtration and the filtrate is concentrated on a rotary evaporator. The residue is held under high vacuum (0.03 mm) at room temperature for 3 hr to give 93.3 g (92%) of cyclobutyl tosylate as a pale-yellow oil (Note 7).

C. *Cyclobutene*. A 500-mL, two-necked, round-bottomed flask is fitted with a 100-mL dropping funnel equipped with an argon-inlet tube, a magnetic stirring bar, and a water-cooled condenser. The outlet of the condenser is attached to an all-glass transfer manifold. Two weighed traps fitted with gastight stopcocks and immersed in dry ice–acetone baths are attached to the manifold. A calcium chloride drying tube is attached to the exit of the second trap. While the system is continuously purged with a slow stream of argon, the flask is charged with 33.6 g (0.30 mol) of potassium *tert*-butoxide and 120 mL of anhydrous dimethyl sulfoxide (Note 8), and a solution of 25.6 g (0.113 mol) of cyclobutyl tosylate in 30 mL of anhydrous dimethyl sulfoxide is placed in the dropping funnel. The potassium *tert*-butoxide suspension is stirred vigorously and heated to 70°C. The cyclobutyl tosylate solution is then added dropwise over a 10-min period (Note 9). After the addition is completed, the reaction mixture is stirred at 70°C for an additional 2 hr. The manifold system is closed off from the reaction vessel and the material collected in the first trap is slowly warmed. The product distills at ca. 2°C into the second dry-ice-cooled trap to give 4.3–5.1 g (70–84%) of cyclobutene [lit.[2] bp 2°C] (Note 10),(Note 11),(Note 12).

2. Notes

1. The checkers obtained cyclopropylcarbinol from the Aldrich Chemical Company, Inc. It can be readily prepared by the reduction of cyclopropanecarboxylic acid with lithium aluminum hydride.[3]
2. A 25-m × 0.3-mm HP Ultra Silicone capillary column at 70°C with 30–psi helium head pressure was used for the chromatographic analysis: retention times of 3-buten-1-ol and cyclobutanol are 1.19 and 1.35 min, respectively. The submitters used a 3-m × 0.3-cm 20 *M* carbowax column at 90°C/8 psi hydrogen and reported retention times of 13 and 20 min for 3-buten-1-ol and cyclobutanol, respectively.
3. The crude product was first distilled on a 50-cm × 0.8-cm spinning band column (reflux ratio 10:1) to give 19.6 g of cyclobutanol, bp 124°C. The forerun fractions, bp 66–123°C (23.0 g), were combined and redistilled on a 30-cm × 0.8-cm spinning band column (reflux ratio 25:1) to give an additional 13.2 g of cyclobutanol, bp 122–123°C. The major by-product, 3-buten-1-ol, boils at 112–114°C. Gas chromatographic analysis of the combined product fractions indicates a mixture of 95% cyclobutanol/3-buten-1-ol (99.7%/0.3%) and 5%

unidentified compounds.

4. Cyclobutanol shows the following ^{1}H NMR spectrum ($CDCl_3$): δ: 1.1–2.4 (m, 6 H), 4.16 (quintet, 1 H, *J* = 7.5), 4.54 (s, 1 H, OH).

5. The pyridine was distilled from calcium hydride and stored over potassium hydroxide.

6. The *p*-toluenesulfonyl chloride was obtained from the Aldrich Chemical Company, Inc., and was recrystallized from hexane prior to use.

7. The product is >99% pure by NMR and shows the following spectrum: ^{1}H NMR ($CDCl_3$) δ: 1.1–2.3 (m, 6 H), 2.47 (s, 3 H), 4.77 (quintet, 1 H, *J* = 7.5), 7.32 (d, 2 H, *J* = 9.0), 7.79 (d, 2 H, *J* = 9.0).

8. Potassium *tert*-butoxide was obtained from the Aldrich Chemical Company, Inc. The dimethyl sulfoxide was distilled from calcium hydride and stored under argon.

9. The reaction mixture turns green, then blue indigo, and finally dark pink during the addition.

10. The submitters report obtaining 5.2 g of 99.2% pure cyclobutene. The product obtained by the checkers was pure by NMR spectroscopy and shows the following ^{1}H NMR spectrum ($CDCl_3$) δ: 2.55 (s, 4 H), 6.00 (s, 2 H).

11. The cyclobutene can be converted to 1,2-dibromocyclobutane by distilling 4.3–7.3 g (0.079–0.135 mol) of cyclobutene into 100 mL of pentane chilled to −40°C, followed by adding a solution of 15.5–32.0 g (0.097–0.200 mol) of bromine in 30 mL of pentane. After the usual workup with aqueous sodium thiosulfate and distillation, 14.3–25.3 g (84–87.5%) of pure 1,2-dibromocyclobutane, bp 60°C (6 mm), is obtained. It shows the following ^{1}H NMR spectrum ($CDCl_3$) δ: 1.90–3.03 (m, 4 H), 4.27–4.70 (m, 2 H). The 1,2-dibromocyclobutane can be conveniently converted back to cyclobutene by debromination with zinc in ethanol.[4]

12. Cyclobutene can be prepared on a larger scale (25–37 g) simply by scaling up the reactants.

3. Discussion

Cyclobutene has been prepared (1) by pyrolysis of cyclobutyldimethylamine oxide[4,5,6] and cyclobutyltrimethylammonium hydroxide[4,6,7] (50–73% yield), which were prepared in eight steps from malonate esters (2.0–2.1% overall yield of cyclobutene contaminated with 1,3-butadiene), (2) by pyrolysis of the products of cycloaddition of dimethyl acetylenedicarboxylate with cyclooctatriene[8,9,10] (30–32% overall yield) or with cyclooctatetraene[11,12,13] (34–39% overall yield), (3) by photolysis of butadiene leading to cyclobutene (30% yield) and bicyclo[1.1.0]butane (5% yield),[14,15] (4) by oxidation of cyclobutylcarboxylic acid[16] with lead tetraacetate[17] (67% yield) (11.8% overall yield), (5) by fragmentation of 1,2-cyclobutyl thiocarbonate with trialkyl

phosphite[18] (68% yield based on *cis*-1,2-dihydroxycyclobutane), (6) by ring expansion of cyclopropylcarbene[19] (7) from cyclobutylidene[20 21] and (8) by base-induced ring expansion of cyclopropylmethyl tosylate with potassium *tert*-butoxide in dimethyl sulfoxide leading to a 1 : 1 mixture of cyclobutene and methylenecyclopropane.[22] None of these methods appears to be practical.

The present procedure offers in good yields a simple and ready preparation of pure cyclobutene from the easily available cyclopropylcarbinol. The product is free of the impurities (e.g., 1,3-butadiene, bicyclobutane, methylenecyclopropane) usually obtained with the various methods so far reported. The procedure described for the synthesis of cyclobutanol is patterned after the acid-catalyzed rearrangement of cyclopropylcarbinol reported by Roberts[23] and Rocek.[24]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

1,2-cyclobutyl thiocarbonate

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ether, diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

bromine (7726-95-6)

sodium sulfate (7757-82-6)

sodium thiosulfate (7772-98-7)

pyridine (110-86-1)

potassium hydroxide (1310-58-3)

zinc (7440-66-6)

Pentane (109-66-0)

magnesium sulfate (7487-88-9)

1,3-Butadiene, butadiene (106-99-0)

lithium aluminum hydride (16853-85-3)

cyclobutylcarboxylic acid (3721-95-7)

Cyclopropanecarboxylic acid (1759-53-1)

hexane (110-54-3)

dimethyl sulfoxide (67-68-5)

Dimethyl acetylenedicarboxylate (762-42-5)

calcium hydride (7789-78-8)

cyclobutene (822-35-5)

cyclopropylcarbinol (2516-33-8)

3-buten-1-ol (627-27-0)

Cyclobutanol (2919-23-5)

argon (7440-37-1)

Bicyclo[1.1.0]butane (157-33-5)

bicyclobutane

p-Toluenesulfonyl chloride (98-59-9)

Methylenecyclopropane (6142-73-0)

Cyclobutyl tosylate (10437-85-1)

1,2-dibromocyclobutane (89033-70-5)

cyclobutyldimethylamine oxide

cyclobutyltrimethylammonium hydroxide

cyclooctatriene (1871-52-9)

cyclooctatetraene

cyclopropylcarbene (19527-12-9)

cyclobutylidene

cyclopropylmethyl tosylate

potassium tert-butoxide (865-47-4)

cis-1,2-dihydroxycyclobutane (35358-33-9)

lead tetraacetate

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DEOXYGENATION OF EPOXIDES WITH LOWER VALENT TUNGSTEN HALIDES: *trans*-CYCLODODECENE

Submitted by Martha A. Umbreit and K. Barry Sharpless[1].
Checked by Ronald F. Sieloff, Michael F. Reinhard, and Carl R. Johnson.

1. Procedure

Caution! Concentrated butyllithium may ignite spontaneously on exposure to air or moisture. Manipulations with this reagent should be performed with great care.

A dry, 1-L, three-necked flask equipped with a thermometer, a mechanical stirrer, and a rubber septum is flushed with nitrogen (admitted through a hypodermic needle in the septum). A nitrogen atmosphere is maintained throughout the subsequent reaction. The flask is charged with 420 mL of tetrahydrofuran (Note 1), and the solvent is cooled to –62°C in an acetone–dry ice bath. Tungsten hexachloride (60g, 0.15 mol) (Note 2) is then introduced. While the cold suspension is stirred, 31 mL (0.30 mol) of 90% butyllithium in hexane (Note 3) is added slowly from a hypodermic syringe. The rate of addition (complete in ca. 5 min) is such that the temperature remains below –15°C. The resulting mixture is allowed to warm slowly to room temperature with stirring. The green-brown viscous suspension becomes a dark-brown homogeneous solution that eventually turns green at room temperature. Because the reaction with the epoxide is exothermic, the flask is momentarily returned to the acetone–dry ice bath while 14.8 g (0.081 mol) of *trans*-cyclododecene oxide (Note 4) and (Note 5) is introduced with a hypodermic syringe. The cooling bath is again removed and the reaction mixture is allowed to stir at room temperature. After 30 min (Note 6) the mixture is poured into 600 mL of an aqueous solution that is 1.5 *M* in sodium tartrate and 2 *M* in sodium hydroxide (Note 7), and extracted with 240 mL of hexane. The organic phase is washed with a mixture of 160 mL of water and 80 mL of aqueous saturated sodium chloride, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure with a rotary evaporator. The residual liquid is distilled under reduced pressure affording 10.5–10.8 g (78–82%) of cyclododecene as a colorless liquid, bp 92–98°C (4.1 mm) (Note 8), 92% *trans* and 8% *cis* by analysis on a -in. × 6-ft GLC column packed with 10% $AgNO_3$ and 5% Carbowax 20 M on 80–100 mesh

Chromosorb W at 110°C.

2. Notes

1. Reagent-grade tetrahydrofuran was freshly distilled from sodium and benzophenone and maintained under nitrogen. In small-scale experiments (1 mmol of tungsten hexachloride in 10 mL of solvent) anhydrous ether was equally effective, but did not give a homogeneous reaction solution.
2. Tungsten hexachloride, purchased from Pressure Chemical Company, was used without further purification. The dark blue-black crystals were pulverized in a dry box or glove bag under a nitrogen atmosphere prior to use. Upon exposure to air or moisture yellow or orange oxides form. Slight contamination from these products does not interfere with the deoxygenation.
3. A suspension of 90% butyllithium in hexane was purchased from Alfa Products, Morton Thiokol, Inc. and was not standardized. The suspension was shaken to obtain uniform density before it was taken up into the syringe. For smaller-scale reactions the submitters report that 15% (1.6 *M*) butyllithium in hexane or methyllithium in ether is convenient and effective.
4. *trans*-Cyclododecene oxide, purchased from Aldrich Chemical Company, Inc., was used without further purification. The purity of the cyclododecene oxide sold by Aldrich varies, but it is usually > 95% trans; in this case it was 98% trans and 2% cis by analysis on a 1/8-in. × 6-ft. GLC column packed with 3% OV-17 on 80–100-mesh Gas-Chrom Q at 140°C. It is not necessary to wait until the brown solution becomes green before adding the epoxide. After epoxide addition the solution is dark green and appears homogeneous.
5. Molar ratios of tungsten reagent to epoxide of less than 1.5 : 1 resulted in incomplete reaction, while ratios greater than 3 : 1 did not improve, and in some cases actually diminished, the yield of alkene. Ratios of ca. 2 : 1 proved generally effective for a variety of epoxides. Molar ratios of alkyllithium to tungsten hexachloride of less than 2 : 1 also gave incomplete reaction; ratios of 3 : 1 or 4 : 1 are believed to give rise to different reduced tungsten species, which may be used in other reductions.
6. The reaction may be monitored by quenching small aliquots in aqueous 20% sodium hydroxide, extracting into hexane, and analyzing by gas chromatography.
7. Aqueous alkali alone, unless in huge excess, produces an emulsion. The addition of a chelating agent such as tartrate permits a clean separation of phases in a workup of reasonable dimension. A minimum of 6 mol of tartrate and 6 mol of hydroxide per mole of tungsten hexachloride used is adequate to suppress emulsions.
8. An IR spectrum of the product was identical to that of an authentic sample of *trans*-cyclododecene. The ^{1}H NMR spectrum of the product was as follows: δ 1.4 (m, 16 H); 2.2 (m, 4 H, -CH_2-CH=CH-CH_2); 5.5 (m, -CH=CH-).

3. Discussion

This procedure illustrates a general, one-step method to deoxygenate di- or

trisubstituted epoxides to olefins in high yield and with high retention of stereochemistry.[2] Reductions are usually complete in less than 1 hr at room temperature or below. In certain cases yields and stereochemical retention have been maximized by using 3 equiv of alkyllithium for each equivalent of WCl_6, or by adding LiI.[2] The reagent is compatible with ethers and esters. It has been used to reductively couple aldehydes and ketones, but considerably longer reaction times and excess reagent are required for appreciable coupling.

Chlorohydrin salts are reduced by the reagent at elevated temperatures and extended reaction times, with complete loss of stereochemistry. Unlike the more highly substituted epoxides, terminal and unsubstituted cyclohexene epoxides appear to proceed, at least in part, via such intermediates, and must be refluxed for several hours to obtain olefins.

Epoxides have been converted to olefins stereoselectively and in good yield by preparation of the iodohydrins, which are then reduced with stannous chloride in the presence of phosphoryl chloride and pyridine.[3] A mild, stereoselective epoxide reduction can be achieved with sodium (cyclopentadienyl) dicarbonylferrate, after several in situ steps; however, the large steric demands of this reagent limit its use to terminal or very accessible epoxides.[4] Olefins of inverted stereochemistry have been obtained by the reaction of epoxides with lithium diphenylphosphide and methyl iodide, followed by cis elimination of the resulting betaine.[5] The reduced tungsten reagent complements these methods by reducing the more highly substituted epoxides with retention of stereochemistry. It should be especially useful when iodohydrin formation is sterically impeded or when conditions for the stereospecific iodohydrin reduction are objectionable.

Deslongchamps[6] and Masamune[7] have both encountered molecules in which the epoxide moiety was so severely shielded on the backside that any trans addition (e.g., iodohydrin formation) was inconceivable. Reduction with the tungsten reagent have excellent yields of olefin in both cases. Parker employed the tungsten reagent to selectively reduce the trisubstituted epoxides of the trisepoxide of humulene, in effect functionalizing the least reactive double bond of the parent triene.[8] Masamune and Parker found that other standard reagents for epoxide reduction failed in these cases; Deslongchamps did not try other methods.

A variety of reducing metals,[3,9] chromous salts,[10] and lower valent iron[11] and titanium[12] salts convert epoxides to olefins in one step, but yields are usually low or moderate and stereochemistry is largely or completely lost. Routes involving thionocarbonates,[13] episulfides,[14] and episelenides[15] have also been used to convert epoxides to olefins. Epoxides activated by adjacent carbonyl, ester, or hydroxy groups have been reduced by special methods.[16]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium (cyclopentadienyl) dicarbonylferrate

ether (60-29-7)

sodium hydroxide (1310-73-2)

iron (7439-89-6)

Cyclohexene (110-83-8)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

stannous chloride

pyridine (110-86-1)

Benzophenone (119-61-9)

sodium (13966-32-0)

hydroxide (14280-30-9)

Methyl iodide (74-88-4)

magnesium sulfate (7487-88-9)

tungsten (7440-33-7)

tartrate

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

hexane (110-54-3)

Methyllithium (917-54-4)

Cyclododecene (1501-82-2)

betaine (107-43-7)

phosphoryl chloride (10025-87-3)

lithium diphenylphosphide

titanium (7440-32-6)

Tungsten hexachloride

sodium tartrate (868-18-8)

cyclododecene oxide, trans-cyclododecene oxide (286-99-7)

trans-Cyclododecene (1486-75-5)

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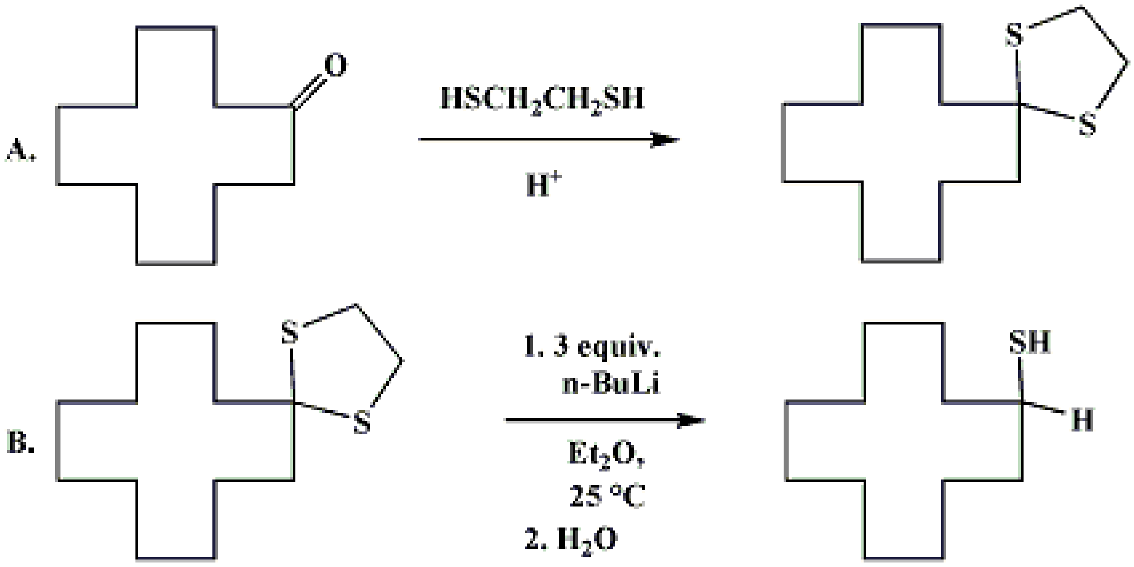
MERCAPTANS FROM THIOKETALS: CYCLODODECYL MERCAPTAN



Submitted by S. R. Wilson[1] and G. M. Georgiadis.
Checked by E. Vedejs, P. C. Conrad, and M. W. Beck.

1. Procedure

Caution! This procedure should be carried out in an efficient hood to prevent exposure to alkane thiols.

A. *1,4-Dithiaspiro[4.11]hexadecane*. A mixture of 46.5 g (0.26 mol) of cyclododecanone (Note 1), 24.1 g (21.5 mL, 0.26 mol) of 1,2-ethanedithiol (Note 1), and 0.75 g (0.004 mol) of *p*-toluenesulfonic acid monohydrate (Note 2), in 200 mL of toluene (Note 3) is placed in a 500-mL, three-necked reaction flask equipped for reflux under a water separator.[2] The mixture is heated at reflux for several hours until the theoretical amount of water (0.26 mol = 4.6 mL) has collected in the Dean-Stark trap. The reaction mixture is cooled and transferred to a separatory funnel. The mixture is washed with water, the toluene is removed on a rotary evaporator, and the residue is placed under reduced pressure (< 0.1 mm) for several hours to remove traces of solvent. Approximately 66 g (99%) of a white solid is recovered (0.26 mol, mp 84–86° C). The crude material is pure by GLC and TLC, and is used in the next step with no further purification.

B. *Cyclododecyl mercaptan*. In a 1-L, three-necked, round-bottomed flask equipped with a mechanical stirrer and nitrogen inlet and outlet stopcocks are placed 25.8 g (0.10 mol) of 1,4-dithiaspiro[4.11]hexadecane and 300 mL of ether, freshly distilled from sodium. The mixture is purged with nitrogen, cooled to 0°C with an ice bath, and 125 mL (0.30 mol, 2.4 *M* in hexane) of butyllithium is added by syringe (Note 4),

(Note 5) under a slow flow of nitrogen. The light-yellow mixture is then allowed to warm to room temperature and stirred overnight with nitrogen stopcocks closed (Note 6). The reaction mixture is cooled to 0°C and 50 mL of water is added slowly and very carefully (Note 7). The resulting light brown solution is poured into 200 mL of water in a separatory funnel and, after shaking, the organic layer is separated. The solution is dried over $MgSO_4$, concentrated (aspirator), and distilled through a 10-cm Vigreux column at 103–108°C (1 mm) to give 17.2–17.9 g (86–90%) of pure cyclododecyl mercaptan (Note 8), (Note 9). A small forerun, bp < 95°C, (ca. 2 mL) is discarded.

2. Notes

1. The submitters used cyclododecanone and 1,2-ethanedithiol obtained from Aldrich Chemical Company, Inc.
2. The submitters used *p*-toluenesulfonic acid monohydrate from MCB, Inc.
3. The submitters used benzene in place of toluene.
4. The submitters used butyllithium from Alfa Products, Ventron Corporation.
5. The reaction also occurs well with only 2 mol of butyllithium, but traces of starting material remain.
6. The reaction is complete in about 6 hr.
7. *Caution! Quenching of excess butyllithium is exothermic.*
8. By GLC analysis, the distilled cyclododecyl mercaptan is >95% pure. Sometimes the product is pale pink.
9. The distilled cyclododecyl mercaptan has the following spectral data: ^1H NMR (CCl_4) δ: 1.1 (d, 1 H, *J* = 6, S-*H*), 1.32 (broad s, 20 H), 1.64–1.82 (m, 2 H), 2.81 (m, 1 H, C*H*SH); IR (neat, •) 3.4, 6.82, 6.94. Anal. calcd. for $C_{12}H_{24}S$: C, 71.93; H, 12.07; S, 16.00. Found: C, 71.83; H, 12.19; S, 16.03.

3. Discussion

Mercaptans are generally prepared by displacement reactions.[3] However, secondary or hindered mercaptans are more difficult to obtain. The dithiolane cleavage reaction[4] is a convenient "in situ" generation of thioketones which are known to be reduced[5] with butyllithium to secondary mercaptans by β-hydrogen transfer. Table I shows a number of mercaptans prepared from *saturated* thioketals in 78–90% yields. The aryl example gives lower yields partly because of ring metalation.

TABLE I
MERCAPTANS FROM ETHYLENE THIOKETAL CLEAVAGE/REDUCTION

Ketone Thioketal	Bp/mp (°C)	Yield (%)
Cyclododecanone	103–108 (1 mm)	90

4-*tert*-Butylcyclohexanone	100 (0.5 mm)	90[a]
2-Adamantanone	mp 139–142	79
4-Heptanone	127–135 (760)	81
Acetophenone	70–75 (0.5 mm)	36[b]
Cyclohexanone	130–140 (760)	78[c]
Estrone	mp 170–175	90[d]
Pregnenolone	mp 108–113	65[d]
Undecan-5-one	110–120 (0.3 mm)	93

[a] Axial: equatorial ratio, 2:1.

[b] By extraction into KOH (purity = 85–93%).

[c] Distillation could not cleanly separate thiol from octane (formed from the butyllithium).

[d] Mixture of isomers.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Benzene (71-43-2)

ether (60-29-7)

Cyclohexanone (108-94-1)

nitrogen (7727-37-9)

Acetophenone (98-86-2)

toluene (108-88-3)

sodium (13966-32-0)

butyllithium (109-72-8)

octane (111-65-9)

hexane (110-54-3)

1,2-ethanedithiol (540-63-6)

4-Heptanone (123-19-3)

cyclododecanone (830-13-7)

2-adamantanone (700-58-3)

4-tert-Butylcyclohexanone (98-53-3)

Cyclododecyl mercaptan (7447-11-2)

1,4-Dithiaspiro[4.11]hexadecane (16775-67-0)

Ketone Thioketal

Estrone

Pregnenolone

Undecan-5-one (33083-83-9)

p-toluenesulfonic acid monohydrate (6192-52-5)

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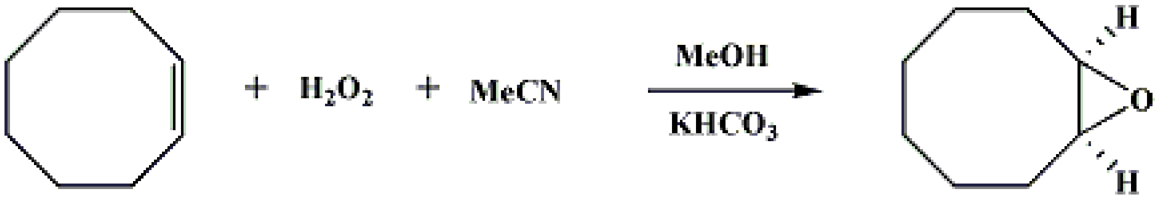
EPOXIDATION OF OLEFINS BY HYDROGEN PEROXIDE-ACETONITRILE: *cis*-CYCLOOCTENE OXIDE

[*cis*-9-Oxabicyclo [6.1.0] nonane]



Submitted by R. D. Bach and J. W. Knight[1].
Checked by K. W. Fowler and G. Büchi.

1. Procedure

Caution! Organic-soluble peroxides may be explosive (Note 4)!

In a 5-L, three-necked, round-bottomed flask fitted with a mechanical overhead stirrer, addition funnel, and thermometer are placed 484 g (4.4 mol) of *cis*-cyclooctene, 3 L of reagent methanol (Note 1), 330 g (8.04 mol) of acetonitrile, and 77 g (0.77 mol) of potassium bicarbonate (Note 2). To the resulting heterogeneous mixture is added dropwise 522 g (4.6 mol) of 30% hydrogen peroxide with cooling at a rate that maintains the temperature of the reaction at 25–35°C (Note 3). Following the addition of hydrogen peroxide, the ice bath is removed and the reaction mixture is allowed to stir at room temperature overnight. The reaction mixture is divided in half, and each portion is diluted with 500 mL of a saturated sodium chloride solution. Each portion is then extracted with four 500-mL portions of methylene chloride (Note 4). The organic phases are combined, dried over magnesium sulfate, and concentrated at reduced pressure by rotary evaporation. Short-path distillation of the crude product (Note 5) under reduced pressure gives 333–337 g (60–61%) of *cis*-cyclooctene oxide, bp 85–87°C (20 mm), as a white solid, mp 53–56°C (Note 6).

2. Notes

1. Omission of the methanol resulted in substantially reduced yields.
2. The reaction does not proceed well when sodium bicarbonate is used as the base.
3. The reaction is exothermic and caution should be exercised to keep the reaction temperature from rising. The time required for complete addition of the hydrogen peroxide is ca. 2–3 hr. The temperature is maintained at 25–35°C by employing an ice-water bath. When the hydrogen peroxide was added too

rapidly, the reaction temperature rose until the solvents refluxed.

4. To check for organic-soluble peroxides, add several milliliters of the methylene chloride solution to a solution containing ca. 1 mg of sodium dichromate, 1 mL of water, and 1 drop of dilute sulfuric acid. A blue color in the organic layer is a positive test for perchromate ion. The checkers found that the combined organic phases exhibited a positive test and therefore stirred them overnight with a solution of 100 g of sodium metabisulfite in 500 mL of water prior to drying.

5. Heat from an IR lamp or heat gun must be applied to the condenser to keep the product from solidifying. The distillation pot should not be taken to dryness because of the possibility of the presence of organic peroxides.

6. The crude product may be used in many cases without further purification. Sublimation of the distilled oxirane affords the product as white needles, mp 56–57°C. The checkers obtained a broader melting point of the distillate, but the product was pure by analytical VPC.

3. Discussion

cis-Cyclooctene oxide has been prepared from *cis*-cyclooctene by the action of perbenzoic acid,[2] hydrogen peroxide,[3] molybdenum hexacarbonyl and *tert*-butyl hydroperoxide,[4] peracetic acid,[5] chromic acid,[6] and polymer-supported peracids.[7]

Oxiranes are typically formed by the action of a peracid such as *m*-chloroperbenzoic acid[8] on an alkene.[9] The present method has the advantage of being useful for both large- and small-scale reactions. The actual epoxidizing agent is generated in situ from the addition of hydrogen peroxide to a nitrile, forming a peroxyimidic acid.[10] This procedure is an adaptation of the method of Payne that utilized an intermediate peroxyimidic acid derived from the reaction of hydrogen peroxide with acetonitrile[11] and benzonitrile.[12] The alkaline hydrogen peroxide-benzonitrile system has more recently been used with steroids,[13] and in the total synthesis of prostaglandin $F_{2\alpha}$.[14] The present method does not require the separation of benzamide from the product. In addition, the reagents are inexpensive and the method is convenient and safe since it does not require large-scale preparation and handling of an organic peracid. Recently, it has been shown that substitution of trichloroacetonitrile for acetonitrile produces an even more reactive reagent.[15]

This epoxide has been found to be particularly useful in the laboratory in the large-scale preparation of *trans*-cyclooctene using the procedure of Whitham.[16] *trans*-Cyclooctane-1,2-diol is obtained from *cis*-cyclooctene oxide on treatment with sodium acetate in acetic acid and alkaline hydrolysis of the intermediate *trans*-2-acetoxycyclooctanol. The *trans* diol is converted to its benzaldehyde acetal, which on treatment with butyllithium affords *trans*-cyclooctene in a stereospecific manner.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium metabisulfite

Oxiranes

peroxyimidic acid

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

methanol (67-56-1)

sodium acetate (127-09-3)

acetonitrile (75-05-8)

benzonitrile (100-47-0)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

benzamide (55-21-0)

chromic acid (7738-94-5)

oxirane (75-21-8)

sodium dichromate (7789-12-0)

hydrogen peroxide (7722-84-1)

methylene chloride (75-09-2)

trichloroacetonitrile (545-06-2)

magnesium sulfate (7487-88-9)

butyllithium (109-72-8)

peracetic acid (79-21-0)

potassium bicarbonate (298-14-6)

Perbenzoic acid (93-59-4)

tert-butyl hydroperoxide (75-91-2)

HYDROGEN PEROXIDE-ACETONITRILE

cis-Cyclooctene oxide (286-62-4)

molybdenum hexacarbonyl (13939-06-5)

benzaldehyde acetal

m-Chloroperbenzoic acid (937-14-4)

cis-cyclooctene (931-87-3)

trans-Cyclooctene (931-89-5)

trans-Cyclooctane-1,2-diol

trans-2-acetoxycyclooctanol

cis-9-Oxabicyclo [6.1.0] nonane (4925-71-7)

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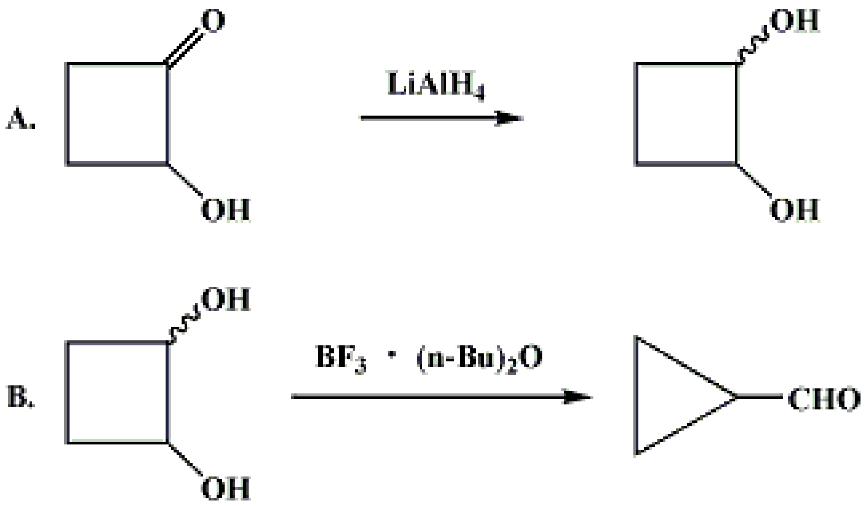
CYCLOPROPANECARBOXALDEHYDE



Submitted by J. P. Barnier, J. Champion, and J. M. Conia[1].
Checked by Robert V. Stevens and Steven R. Angle.

1. Procedure

A. *1,2-Cyclobutanediol.* A 2-L, three-necked, round-bottomed flask fitted with a 200-mL dropping funnel, a mechanical stirrer, a nitrogen-inlet tube, and a reflux condenser equipped with a calcium chloride drying tube is charged with 6.2 g (0.16 mol) of lithium aluminum hydride (Note 1) and (Note 2) and 200 mL of anhydrous diethyl ether (Note 3). The dropping funnel is charged with 42 g (0.48 mol) of 2-hydroxycyclobutanone (Note 4) and 150 mL of anhydrous diethyl ether. While the suspension of lithium aluminum hydride is gently stirred under a nitrogen atmosphere, the solution of 2-hydroxycyclobutanone is added dropwise at a rate maintaining a gentle reflux. When the addition is complete, the mixture is heated at reflux for 1 hr. After the mixture has returned to room temperature, 200 mL of anhydrous diethyl ether is added. The gray reaction mixture is hydrolyzed by addition, in small parts, of a sufficient amount of wet sodium sulfate (Note 5). The reaction mixture is filtered through a sintered-glass funnel (porosity 3). The organic layer is decanted and dried over sodium sulfate. The solid is extracted with anhydrous tetrahydrofuran (Note 6) by means of a Soxhlet apparatus over a period of 24 hr. The combined organic layers are concentrated by distillation of the solvent with a rotary evaporator. The yield of crude *cis*- and *trans*-1,2-cyclobutanediol (ca. 50:50) is 34–40 g (80–95%) (Note 7).

B. *Cyclopropanecarboxaldehyde.* A 50-mL distilling flask equipped with a receiver cooled to −20°C with a dry ice–methanol bath is charged with 34 g (0.39 mol) of a crude mixture of both *cis*- and *trans*-1,2-cyclobutanediol and 10 •L of boron trifluoride butyl etherate (Note 8). The mixture is heated to 230°C with a metal bath. Drops of liquid appear on the condenser, and the aldehyde and water distill into the receiver. The temperature of the distillate oscillates between 50 and 100°C. Each time the

distillation stops, 5–10 •L of boron trifluoride butyl etherate is added to the distilling flask (Note 9). The distillate is transferred into a separatory funnel and sodium chloride is added. The organic layer is decanted and the aqueous layer is extracted three times with 25-mL portions of methylene chloride. The combined organic solution is dried over sodium sulfate, and the solvent is removed by distillation through a 15-cm, helix-packed, vacuum-insulated column. The residue consists of practically pure cyclopropanecarboxaldehyde, 17.5–21.6 g (65–80%) (Note 10).

2. Notes

1. Lithium aluminum hydride is available from Prolabo—France or Alfa Products, Morton Thiokol, Inc.
2. On one occasion the checkers found it necessary to add more lithium aluminum hydride (0.3 g) for complete reaction.
3. The checkers used diethyl ether distilled from sodium–benzophenone.
4. The checkers prepared 2-hydroxycyclobutanone by the Bloomfield procedure.[2] The submitters prepared it by their aqueous hydrolysis procedure.[3] This procedure was checked also and proceeds in quantitative yield as described.[3]
5. Sodium sulfate is mixed with water to form a thick slurry. It is added to the reaction mixture with vigorous stirring to obtain a good dispersion of the slurry in the medium. The added amount of wet sodium sulfate is sufficient when the reaction effervescence ceases and the gray color of the mixture turns to yellow–white.
6. Tetrahydrofuran is purified by distillation from lithium aluminum hydride after 48-hr refluxing over potassium hydroxide (see *Org. Synth. Coll. Vol. V* **1973**, 976 for hazard warning).
7. The crude 1,2-cyclobutanediol is dried by azeotropic distillation with anhydrous benzene. The product is a mixture of *cis* and *trans* isomers (ca. 50:50) readily separable by gas chromatography on a 12-ft column containing 20% silicone SE 30 on Chromosorb W at 140°C. *cis*-1,2-Cyclobutanediol (mp 12–13°C): IR (CCl_4) cm^{-1}: hydroxyl absorption at 3625 and 3580; ^1H NMR (CCl_4) δ: multiplet at 1.98, multiplet at 4.20, and a singlet at 4.51 in a ratio 4:2:2, respectively. *trans*-1,2-Cyclobutanediol (mp 72°C): IR (CCl_4) cm^{-1}: hydroxyl absorption at 3620: ^1H NMR (CD_3COCD_3) δ: multiplet between 0.9 and 2.2, multiplet between 3.6 and 4.0, and singlet at 3.6 in a ratio of 4:2:2, respectively.
8. Boron trifluoride butyl etherate, purchased from Fluka AG, is chosen for its convenient boiling point.
9. In a typical run 10 •L of boron trifluoride butyl etherate is added every 10–15 min over a period of 3–4 hr.
10. The crude product is more than 99% pure as shown by gas chromatography; IR (CCl_4) cm^{-1}: carbonyl absorption at 1730; ^1H NMR (CCl_4) δ: doublet at 8.93, multiplet between 1.5 and 2.2, and a multiplet between 1.02 and 1.75 in

the ratio 1:1:4, respectively. The product has bp 95–98°C (760 mm).

3. Discussion

This method of preparation of cyclopropanecarboxaldehyde is an adaptation of that given by J. M. Conia and J. P. Barnier.[3] The various methods so far reported, which involve in the last step oxidation,[4] reduction,[5] or hydrolysis[6] of a suitable cyclopropane derivative, are tedious or require expensive starting materials. The other routes involve the direct ring contraction of cyclobutane derivatives into cyclopropanecarboxaldehyde starting from cyclobutene oxide[7] or from 2-bromo- or 2-tosyloxycyclobutanol.[8] The present procedure uses a particularly easy ring contraction, that of 1,2-cyclobutanediol, and it involves cheap, easily available starting materials. This method can be applied to symmetrical dialkylcyclobutane-1,2-diols, but it gives a mixture of two cyclopropyl carbonyl compounds from unsymmetrical diols.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

boron trifluoride butyl etherate

2-bromo- or 2-tosyloxycyclobutanol

Benzene (71-43-2)

diethyl ether (60-29-7)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

potassium hydroxide (1310-58-3)

Benzophenone (119-61-9)

sodium (13966-32-0)

methylene chloride (75-09-2)

cyclopropane (75-19-4)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

2-Hydroxycyclobutanone (17082-63-2)

Cyclopropanecarboxaldehyde (1489-69-6)

1,2-Cyclobutanediol, cis- and trans-1,2-cyclobutanediol (35358-34-0)

cyclobutene oxide

cis-1,2-Cyclobutanediol (35358-33-9)

trans-1,2-cyclobutanediol

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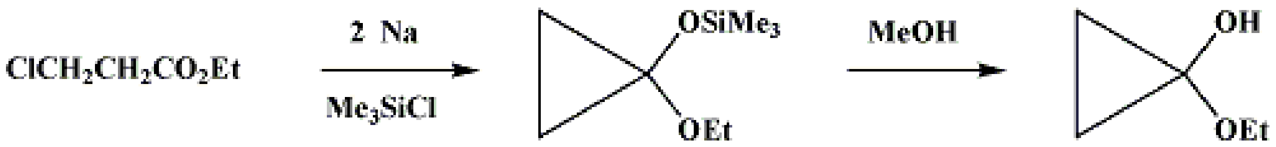
Organic Syntheses, CV 7, 131

CYCLOPROPANONE ETHYL HEMIACETAL FROM ETHYL 3-CHLOROPROPANOATE

[Cyclopropanol, 1-ethoxy-]



Submitted by J. Salaün and J. Marguerite[1].
Checked by Steven D. Young, Syun-ichi Kiyooka, and Clayton H. Heathcock.

1. Procedure

A. *1-Ethoxy-1-(trimethylsilyloxy) cyclopropane*. A 1-L, three-necked, round-bottomed flask is fitted with an efficient mechanical stirrer (Note 1), a reflux condenser provided with a calcium chloride tube, and a 500-mL pressure-equalizing dropping funnel equipped with a nitrogen inlet at the top. The flask is flushed with dry nitrogen, and 500 mL of anhydrous toluene (Note 2) and 52.9 g (2.3 g-atom) of sodium cut in small pieces (Note 3) are introduced. The mixture is brought to reflux by means of a heating mantle and the sodium is finely pulverized by vigorous stirring. Heating and stirring are stopped (Note 4), and the mixture is allowed to cool to room temperature. Toluene is removed under nitrogen pressure by means of a double-ended needle and replaced by 500 mL of anhydrous diethyl ether (Note 5) and (Note 6). At this point, 108.5 g (1 mol) of chlorotrimethylsilane (Note 7) is added to the flask. To the mixture, 136.58 g (1 mol) of ethyl 3-chloropropanoate is added dropwise with stirring at a rate sufficient to maintain a gentle reflux over a 3-hr period (Note 8). When about 0.3 mol of chloro ester has been added, a deep-blue precipitate appears (Note 9). When the addition is over, the reaction mixture is heated at reflux for 30 min. The contents of the flask are cooled and filtered through a sintered-glass funnel under a stream of dry nitrogen (Note 10). The precipitate is washed twice with 100 mL of anhydrous diethyl ether.

The colorless filtrate is transferred to a distilling flask and the solvent is distilled through a 25-cm vacuum-jacketed Vigreux column, and the residue is distilled under reduced pressure. After a small forerun (1–2 g), 1-ethoxy-1-(trimethylsilyloxy) cyclopropane is obtained at 43–45°C (12 mm) as a colorless liquid, 106 g (61%) (Note 11).

B. *Cyclopropanone ethyl hemiacetal*. Into a 500-mL Erlenmeyer flask fitted with a magnetic stirring bar is placed 250 mL of reagent-grade methanol. Freshly distilled 1-ethoxy-1-(trimethylsilyloxy) cyclopropane (100 g, 0.56 mol) is added all at once to the methanol and the solution is stirred overnight (12 hr) at room temperature (Note 12). An aliquot (50 mL) of the solution is concentrated by slow evaporation of methanol with a rotary evaporator at room temperature (Note 13) and formation of the methanolysis product is checked by NMR examination of the residue (Note 14). When the reaction is complete (Note 15), the solution

is concentrated by removal of the methanol (Note 16). Distillation of the residue through a 20-cm helix-packed, vacuum-insulated column under reduced pressure gives 52 g (89%) of 1-ethoxycyclopropanol, bp 60°C (20 mm) (Note 14) and (Note 17), which contains trace amounts of 1-methoxycyclopropanol (Note 18) and (Note 19).

2. Notes

1. An efficient stirrer is used at a spinning rate sufficient to disperse the molten sodium into small beads of a diameter of approximately 0.1 mm. The checkers found it necessary to use a mechanical stirrer equipped with a nichrome wire "beater" rather than a Teflon paddle. If the sodium sand particles are too large, the final product will be contaminated with starting chloro ester, from which it is very difficult to separate.
2. Toluene is freshly distilled from phosphorus pentoxide into the reaction flask.
3. Sodium pieces are washed in dry pentane or toluene to remove oil.
4. It is essential that stirring be discontinued before cooling is begun to prevent the molten sodium from coalescing into one gigantic lump.
5. Diethyl ether is dried by molecular sieves and distilled from lithium aluminum hydride.
6. To remove the toluene completely, the finely divided sodium is washed under nitrogen with anhydrous diethyl ether (3 × 50 mL).
7. Chlorotrimethylsilane, obtained from Aldrich Chemical Co. or Prolabo (France), is distilled from quinoline or calcium hydride.
8. For the acyloin condensation of diesters it has been recommended that the diester and chlorotrimethylsilane be added together to the sodium dispersion;[2] no difference has been noted with our procedure.
9. The deep-blue color seems to be indicative of a satisfactory reduction. When the color is yellow–green, the yield is usually poor.
10. *Caution! Because of the pyrophoric nature of finely divided alkali metal residues or production of free acid (HCl) from the chlorosilane, the products are sensitive to moisture. Unreacted sodium is destroyed by careful addition of ethanol to the residual solid.*
11. The yield varies from 60 to 85%, bp 50–52°C (18 mm); 60–62°C (35 mm); 66–68°C (40 mm); the proton magnetic resonance (PMR) spectrum (CCl_4 solution, $HCCl_3$ external reference) shows absorption at δ: 0.08 (s, 9 H), 0.70 (m, 4 H), 1.05 (t, 3 H, *J* = 7.11) and 3.55 (q, 2 H, *J* = 7.11); the IR spectrum (CCl_4) exhibits absorption at 3090 and 3010 (cyclopropane), 1250, 845, and 758 cm^{-1} ($-Si[CH_3]_3$).
12. After the solution is stirred for 5–10 min, the clear solution becomes slightly turbid for a few minutes and then turns clear again. When these changes are not observed, methanolysis has not occurred.
13. If some 1-ethoxy-1-(trimethylsilyloxy) cyclopropane is still present, it will be lost by too rapid evaporation of methanol.
14. The product has the following spectral properties: IR (CCl_4): 3600 and 3400 (hydroxyl), 3010 and 3090 cm^{-1} (cyclopropyl); ^1H NMR (CCl_4) δ: 0.84 (s, 4 H), 1.18 (t, 3 H, *J* = 7.11), 3.73 (q, 2 H, *J* = 7.11) and 4.75 (m, 1 H).
15. Lack of NMR absorption around δ 0.08 shows that the trimethylsilyloxy group has been completely removed.
16. If the reaction is not complete, as shown by the presence of a singlet around δ

0.08, a spatula tip full of pyridinium *p*-toluenesulfonate[3] is added and the mixture is stirred for 4 hr. Methanol is then removed, and the residue is dissolved in 200 mL of diethyl ether. The solution is washed with saturated sodium chloride until neutral, dried over anhydrous sodium sulfate, and concentrated. Addition of a drop of HCl or of chlorotrimethylsilane is also effective to complete the reaction. Then, the hydrochloric acid is removed with methanol. (Thus, it is not necessary to wash with saturated sodium chloride until neutral.)
17. The yield varies from 78 to 95%, bp 51°C (12 mm), 64°C (25 mm), 75°C (46 mm).
18. On standing with methanol at 25°C for 1 week, 65% of 1-ethoxycyclopropanol is converted into 1-methoxycyclopropanol; conversion appears to be complete after 15 days.[4] The spectral properties of the 1-methoxycyclopropanol are: IR (CCl_4): 3600 and 3400 (hydroxyl), 3010 and 3090 cm^{-1} (cyclopropyl); ^1H NMR (CCl_4) δ: 0.85 (s, 4 H) and 3.40 (s, 3 H).
19. Cyclopropanone hemiacetal can be kept unaltered for several months at 0°C in the refrigerator. On heating above 100°C or on standing in acidic solvents, it undergoes ring opening to give ethyl propionate.

3. Discussion

Cyclopropanone ethyl hemiacetal was first synthesized by the reaction of ketene and diazomethane in ether at −78°C in the presence of ethanol.[4] The yield is low (43%) and the reaction is hazardous, especially when a large-scale reaction is required. The method described in this procedure for the preparation of cyclopropanone ethyl hemiacetal from ethyl 3-chloropropanoate is an adaptation of that described previously;[5] the procedure described for the synthesis of 1-ethoxy-1-(trimethylsilyloxy) cyclopropane is patterned after the method reported by Rühlmann.[6]

Cyclopropanone ethyl hemiacetal is a molecule of considerable interest since its reactions appear to involve the formation of the labile cyclopropanone.[7] It readily undergoes nucleophilic addition of Grignard reagents,[4,5] azides,[4] and amines[8] to provide 1-substituted cyclopropanols in high yields. It has been reported that upon treatment with an equimolar amount of methylmagnesium iodide, the cyclopropanone ethyl hemiacetal is converted into iodomagnesium 1-ethoxycyclopropylate,[9] which can react with hydrides, organometallic reagents, cyanide carbanion, and phosphorus ylides[10] to provide useful synthons. The preparation of some challenging 2,3-disubstituted cyclopentanones including a total synthesis of the 11-deoxyprostaglandin has been reported from the cyclopropanone hemiacetal.[11] The ready availability of this compound should lead to other synthetic applications. For a recent review dealing with the chemistry of the cyclopropanone hemiacetals, see [12].

On the other hand, silylated cyclopropanols, such as 1-ethoxy 1-(trimethylsilyloxy) cyclopropane, work well as homoenolate anion precursors. They undergo ring opening reactions with a variety of metal halides ($TiCl_4$, $GaCl_3$, $SbCl_5$, $ZnCl_2$, $HgCl_2$ …). Thus, in

the presence of suitable catalysts, the zinc homoenolates of alkyl propionates undergo a variety of carbon-carbon bond forming reactions with a very high degree of chemoselectivity.[13]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 277
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

chloro ester

1-substituted cyclopropanols

cyanide carbanion

phosphorus ylides

2,3-disubstituted cyclopentanones

11-deoxyprostaglandin

silylated cyclopropanols

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

toluene (108-88-3)

sodium (13966-32-0)

hydroxyl (3352-57-6)

methylmagnesium iodide (917-64-6)

Quinoline (91-22-5)

Pentane (109-66-0)

Ketene (463-51-4)

cyclopropane (75-19-4)

Diazomethane (334-88-3)

ethyl propionate (105-37-3)

lithium aluminum hydride (16853-85-3)

calcium hydride (7789-78-8)

ETHYL 3-CHLOROPROPANOATE (623-71-2)

cyclopropyl (2417-82-5)

CHLOROTRIMETHYLSILANE (75-77-4)

chlorosilane (13465-78-6)

CYCLOPROPANONE (5009-27-8)

Cyclopropanone ethyl hemiacetal, Cyclopropanol, 1-ethoxy-, 1-ethoxycyclopropanol (13837-45-1)

1-ethoxy-1-(trimethylsilyloxy) cyclopropane, 1-ethoxy 1-(trimethylsilyloxy) cyclopropane (27374-25-0)

1-methoxycyclopropanol

Cyclopropanone hemiacetal

iodomagnesium 1-ethoxycyclopropylate

phosphorus pentoxide (1314-56-3)

pyridinium p-toluenesulfonate

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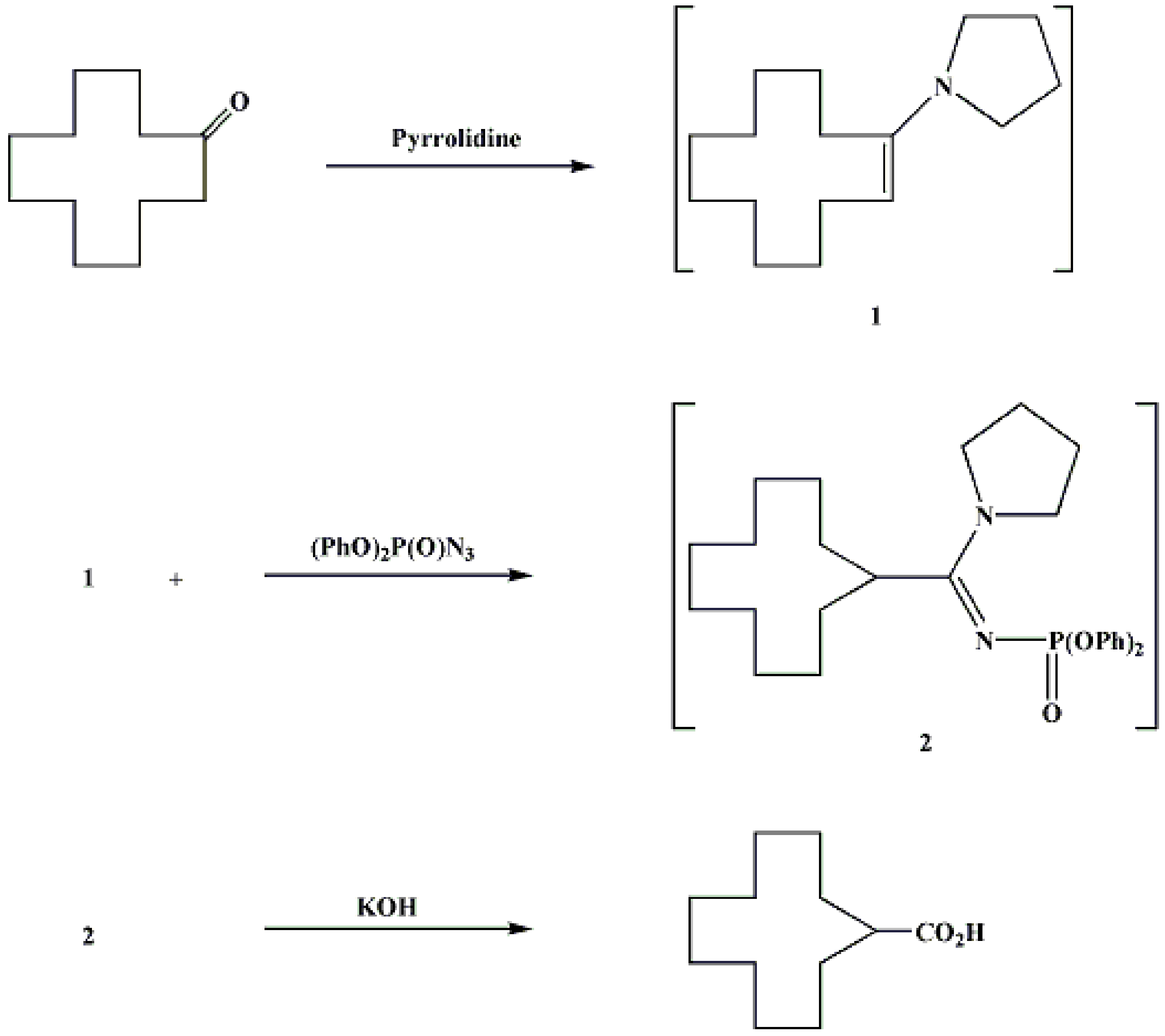
Organic Syntheses, CV 7, 135

CYCLOUNDECANECARBOXYLIC ACID



Submitted by Yasumasa Hamada and Takayuki Shioiri[1].
Checked by M. F. Semmelhack and E. Spiess.

1. Procedure

To a 300-mL, round-bottomed flask fitted with a water separator (Note 1) that contains 15 g of Linde 4A molecular sieve 1/16-in. pellets and is filled with toluene, are added 7.3 g (0.04 mol) of cyclododecanone, 11.4 g (0.16 mol) of pyrrolidine, 100 mL of toluene, and 0.57 g (0.004 mol) of boron trifluoride etherate. The solution is heated under reflux for 20 hr. The water separator is replaced by a distillation head, and about 90 mL of the toluene is removed by distillation at atmospheric pressure. The residue containing 1-(*N*-pyrrolidino)-1-cyclododecene **(1)** is used in the next step without further purification (Note 2).

The crude enamine **(1)** is dissolved in 20 mL of toluene, and the solution is transferred (Note 3) to a 100-mL, three-necked flask equipped with a magnetic stirring bar, a 50-mL dropping funnel, reflux condenser protected with a calcium chloride tube, and a thermometer immersed in the

solution. A solution of 13.2 g (0.048 mol) of diphenyl phosphorazidate ((Note 4); *Warning*) in 20 mL of toluene is added with stirring during 30 min while the reaction temperature is maintained at about 25°C. The mixture is stirred for 4 hr at 25°C and heated at reflux for 1 hr. The mixture is transferred to a 300-mL, round-bottomed flask and most of the toluene is removed under reduced pressure to yield 23.7 g of a reddish-brown oil, **2** (Note 5).

Ethylene glycol (200 mL) and 40 g (0.71 mol) of potassium hydroxide are added to the residual oil. The mixture is heated at reflux for 24 hr and then concentrated at 80–115°C (25 mm) (bath temperature ca. 190°C) until 100 mL of distillate is collected. The residue is dissolved in 300 mL of water and cooled to room temperature. Carbon dioxide is introduced as a gas until the pH of the solution reaches 9. The mixture is washed with three 80-mL portions of diethyl ether (Note 6). The aqueous layer is acidified with about 53 mL of concentrated hydrochloric acid and extracted with four 80-mL portions of benzene. The combined benzene extracts are washed with 50 mL of water and dried over anhydrous sodium sulfate. The solvent is removed under reduced pressure to give 4.5–5.5 g of a black-brown oil. Distillation of the oil at 110–115°C (0.1 mm) yields 3.5–3.8 g (40–48%) of cycloundecanecarboxylic acid as a colorless oil.

2. Notes

1. The apparatus described in *Organic Syntheses*[2] is satisfactory.
2. Pure 1-(*N*-pyrrolidino)-1-cyclododecene, bp 144°C (1.5 mm), may be isolated by distillation through a Vigreux column.
3. The original flask used for the enamine formation can be used after the attachment of a Y-shaped tube fitted with a dropping funnel and a reflux condenser protected with a tube packed with a drying agent such as anhydrous calcium chloride.
4. Diphenyl phosphorazidate is prepared by the action of sodium azide with diphenyl phosphorochloridate[3]. It is also available from Aldrich Chemical Co. and was used after purification by distillation at 134–136°C (0.2 mm). *Warning: Diphenyl phosphorazidate may produce explosive hydrogen azide when it is in contact with moisture for a long time. When diphenyl phosphorazidate, which has been stored for a long time, is used, it should be washed with saturated aqueous sodium bicarbonate and dried over sodium sulfate before distillation.*
5. Purification of 1 g of the crude oil was made by column chromatography using 50 g of Merck silica gel with 0.063–0.200-mm particles (catalog No. 7734) in a column 2.2-cm × 40-cm and 1:1 (v/v) ethyl acetate-hexane as eluant to give pure diphenyl (cycloundecyl-1-pyrrolidinylmethylene)phosphoramidate (2) as a colorless oil, 632 mg (78%). When a Merck precoated silica gel F254 thin layer plate, layer thickness 0.25 mm, is developed with 1:1 (v/v) ethyl acetate-hexane and visualized with ultraviolet light, the phosphoramidate appears at R_f 0.3. Thus the crude oil contained about 15 g of the phosphoramidate.
6. This procedure is designed primarily to remove phenol.

3. Discussion

Cycloundecanecarboxylic acid has been prepared by the bromination of cyclododecanone followed by the Favorskii rearrangement of 2-bromocyclododecanone.[4]

The present preparation illustrates a general and convenient method for ring contraction of cyclic ketones.[5] The first step is the usual procedure for the preparation of enamines. The second step

involves 1,3-dipolar cycloaddition of diphenyl phosphorazidate to an enamine followed by ring contraction with evolution of nitrogen. Ethyl acetate and tetrahydrofuran can be used as a solvent in place of toluene. Pyrrolidine enamines from various cyclic ketones smoothly undergo the reaction under similar reaction conditions. Diphenyl (cycloalkyl-1-pyrrolidinylmethylene) phosphoramidates with 5, 6, 7, and 15 members in the ring have been prepared in yields of 68–76%.

The third step is hydrolysis of the *N*-phosphorylated amidines, which is carried out by either acid or alkali depending on the substrate.

Similar reaction sequences can be used successfully to convert alkyl aryl ketones to α-arylalkanoic acids.[6]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ethyl acetate (141-78-6)

diethyl ether (60-29-7)

sodium bicarbonate (144-55-8)

phenol (108-95-2)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

potassium hydroxide (1310-58-3)

toluene (108-88-3)

ethylene glycol (107-21-1)

sodium azide (26628-22-8)

Tetrahydrofuran (109-99-9)

pyrrolidine (123-75-1)

boron trifluoride etherate (109-63-7)

hydrogen azide

cyclododecanone (830-13-7)

ethyl acetate-hexane (2639-63-6)

diphenyl phosphorochloridate (2524-64-3)

Cycloundecanecarboxylic acid (831-67-4)

Diphenyl phosphorazidate (26386-88-9)

diphenyl (cycloundecyl-1-pyrrolidinylmethylene)phosphoramidate (62914-02-7)

phosphoramidate

2-bromocyclododecanone

1-(N-Pyrrolidino)-1-cyclododecene (25769-05-5)

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Organic Syntheses, CV 7, 137

A GENERAL SYNTHETIC METHOD FOR THE PREPARATION OF METHYL KETONES FROM TERMINAL OLEFINS: 2-DECANONE

Submitted by Jiro Tsuji, Hideo Nagashima, and Hisao Nemoto[1].
Checked by Edwin Vedejs, J. Gegner, and T. K. Mallman.

1. Procedure

A 100-mL, three-necked, round-bottomed flask is fitted with a magnetic stirrer and a pressure-equalizing dropping funnel containing 1-decene (4.2 g, 30 mmol). The flask is charged with a mixture of palladium chloride (0.53 g, 3 mmol), cuprous chloride (2.97 g, 30 mmol) (Note 1), and aqueous dimethylformamide (DMF/H_2O = 7:1, 24 mL). With the other outlets securely stoppered and wired down, an oxygen-filled balloon (Note 2) is placed over one neck, and the flask is stirred at room temperature to allow oxygen uptake (Note 3). After 1 hr, 1-decene (4.2 g, 30 mmol) (Note 4) is added over 10 min (Note 5) using the dropping funnel, and the solution is stirred vigorously at room temperature under an oxygen balloon (Note 6). The color of the solution turns from green to black within 15 min and returns gradually to green. After 24 hr, the mixture is poured into cold 3 *N* hydrochloric acid (100 mL) and extracted with five 50-mL portions of ether. The extracts are combined and washed successively with 50 mL of saturated sodium bicarbonate solution, 50 mL of brine, and then dried over anhydrous magnesium sulfate. After filtration, the solvent is removed by evaporation and the residue is distilled using a 15-cm Vigreux column to give 2-decanone as a colorless oil (3.0–3.4 g, 65–73%, bp 43–50°C/1 mm (Note 7) and (Note 8).

2. Notes

1. Cupric chloride can be used, but it tends to chlorinate the products and cuprous chloride is preferable; reagent-grade dimethylformamide (DMF) was distilled before use.
2. The balloon was purchased at a toy shop; its inflated volume was approximately 500 mL.
3. The initial black solution gradually turns green by oxygen absorption.
4. The sample of 1-decene was obtained from the Aldrich Chemical Company, Inc. and distilled before use.
5. In cases where the alkene is soluble, up to 30% of the aqueous DMF can be mixed with the alkene to facilitate controlled addition. With 1-decene, DMF

forms a two-phase mixture.
6. The reaction is slightly exothermic.
7. The first fraction (bp 30–40°C) contains decenes that are formed by palladium-catalyzed isomerization of 1-decene (indicated by a broad signal at δ 5.2–5.5 in the ^{1}H NMR spectrum).
8. The spectral properties of 2-decanone are as follows: ^{1}H NMR (CCl_4) δ: 0.7–1.8 (15 H, complex), 2.02 (3 H, s), 2.37 (2 H, t, *J* = 7); IR (neat) 1722 cm^{-1}.

3. Discussion

Methyl ketones are important intermediates for the synthesis of methyl alkyl carbinols, annulation reagents, and cyclic compounds. A common synthetic method for the preparation of methyl ketones is the alkylation of acetone derivatives, but the method suffers limitations such as low yields and lack of regioselectivity. Preparation of methyl ketones from olefins and acetylenes using mercury compounds is a better method. For example, hydration of terminal acetylenes using $HgSO_4$ gives methyl ketones cleanly.[2] Oxymercuration of 1-olefins and subsequent oxidation with chromic oxide is another method.[3] Preparation of an epoxide from a 1-olefin and its rearrangement catalyzed by a cobalt catalyst to give methyl ketones has been reported briefly.[4]

Compared with these methods, the palladium-catalyzed oxidation of 1-olefins described here is more convenient and practical. The industrial method of ethylene oxidation to acetaldehyde using $PdCl_2–CuCl_2–O_2$ is the original reaction of this type.[5] The oxidation of various olefins has been carried out.[6,7,8,9]

Use of DMF as a solvent for the oxidation of 1-olefins has been reported by Clement and Selwitz.[6] The method requires only a catalytic amount of $PdCl_2$ and gives satisfactory yields under mild conditions. A small amount of olefin migration product is the only noticeable contaminant in the cases reported. The procedure can be applied satisfactorily to various 1-olefins with other functional groups. This useful synthetic method for the preparation of methyl ketones has been applied extensively in the syntheses of natural products such as steroids,[10] macrolides,[11,12] dihydrojasmone,[13] and muscone.[14] A comprehensive review article on the palladium-catalyzed oxidation of olefins has been published.[15]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

mercury compounds

METHYL KETONES

dimethylformamide (DMF)

acetaldehyde (75-07-0)

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium bicarbonate (144-55-8)

oxygen (7782-44-7)

cuprous chloride (7758-89-6)

cupric chloride (7758-89-6)

palladium chloride

magnesium sulfate (7487-88-9)

dimethylformamide (68-12-2)

cobalt (7440-48-4)

chromic oxide (1308-38-9)

2-Decanone (693-54-9)

1-decene (872-05-9)

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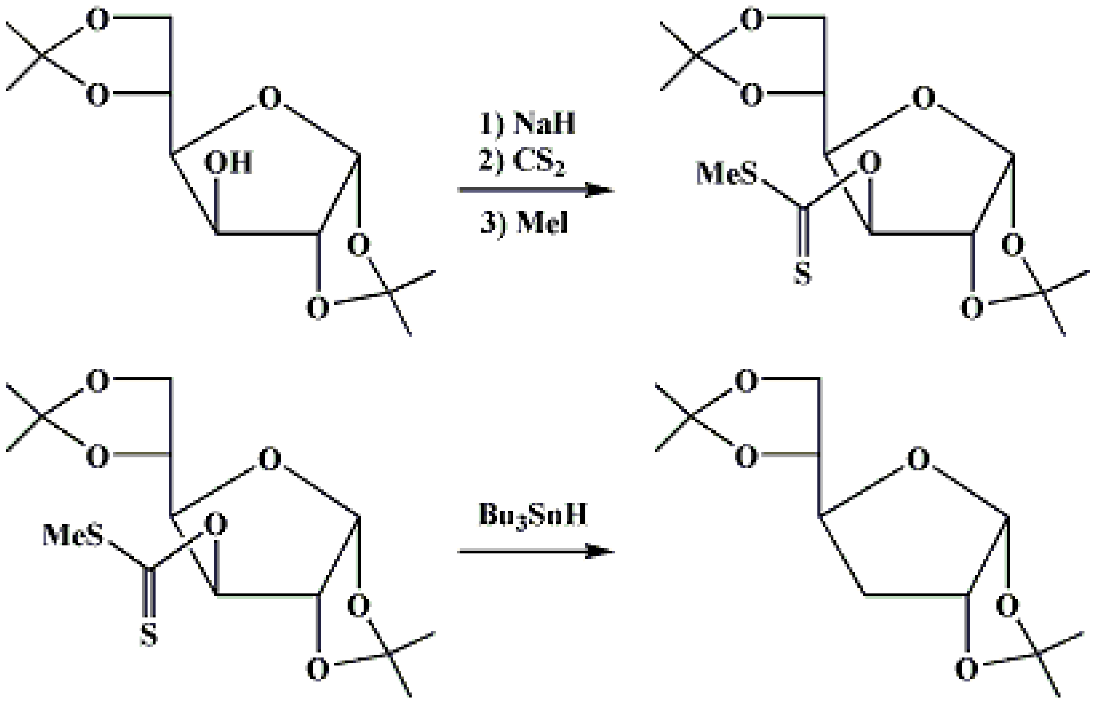
DEOXYGENATION OF SECONDARY ALCOHOLS: 3-DEOXY-1,2:5,6-DI-*O*-ISOPROPYLIDENE-α-d-*ribo*-HEXOFURANOSE

[α-d-*ribo*-Hexofuranose, 3-deoxy-1,2:5,6-bis-*O*-(1-methylethylidene)-]

A.

B.



Submitted by S. Iacono and James R. Rasmussen[1].
Checked by Peter J. Card and Bruce E. Smart.

1. Procedure

Caution! Carbon disulfide, iodomethane, and tributyltin hydride are poisonous and should be handled in a well-ventilated hood.

A. *1,2:5,6-Di-O-isopropylidene-3-O-(S-methyldithiocarbonate)*-α-D-*glucofuranose*. A 1-L, three-necked, round-bottomed flask equipped with a magnetic stirring bar, nitrogen-inlet adapter, pressure-equalizing addition funnel, and stopper is charged with 26.0 g (0.10 mol) of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose, 25 mg of imidazole (Note 1), and 400 mL of anhydrous tetrahydrofuran (Note 2). The reaction vessel is flushed with nitrogen and a nitrogen atmosphere is maintained during the ensuing steps. Over a 5-min period, 7.2 g (0.150 mol) of a 50% sodium hydride dispersion (Note 3) is added. Vigorous gas evolution is observed. After the reaction mixture is stirred for 20 min, 22.8 g (0.30 mol) of carbon disulfide is added all at once. Stirring is continued for 30 min, after which time 25.3 g (0.177 mol) of iodomethane is

added in a single portion. The reaction mixture is stirred for another 15 min, and 5.0 mL of glacial acetic acid is added dropwise to destroy excess sodium hydride. The solution is filtered (Note 4) and the filtrate is concentrated on a rotary evaporator. The semisolid residue is extracted with three 100-mL portions of ether, and the combined ether extracts are washed with two 100-mL portions of saturated sodium bicarbonate solution and two 100-mL portions of water. The ethereal solution is dried over anhydrous magnesium sulfate, the drying agent is removed by filtration, and the solvent is removed by rotary evaporation. The product is dried further at 0.05 mm overnight. The resulting orange syrup is distilled (Kugelrohr) to give 32.2–33.0 g (92–94%) of product, bp 153–160°C (0.5–1.0 mm) (Note 5).

B. *3-Deoxy-1,2:5,6-di-O-isopropylidene*-α-D-*ribo-hexofuranose*. A dry, 1-L, round-bottomed flask is equipped with a magnetic stirring bar and a reflux condenser to which a nitrogen inlet is attached. The apparatus is charged with 500 mL of anhydrous toluene (Note 6), 24.7 g (0.085 mol) of tributyltin hydride (Note 7) and 19.25 g (0.055 mol) of 1,2:5,6-di-*O*-isopropylidene-3-*O*-(*S*-methyldithiocarbonate)-α-D-glucofuranose. The reaction mixture is heated at reflux under a nitrogen atmosphere until TLC analysis indicates the disappearance of starting materials (4–7 hr) (Note 8). During this time the reaction solution changes from deep yellow to nearly colorless. The toluene is removed on a rotary evaporator to yield a thick, oily residue that is partitioned between 250-mL portions of petroleum ether and acetonitrile. The acetonitrile layer is separated and washed with three 100-mL portions of petroleum ether and is then concentrated on a rotary evaporator. The residual yellow oil is taken up in hexane-ethyl acetate (10 : 1) and filtered through a pad of silica gel (Note 9). The filtrate is concentrated and the residual oil is distilled to give 10.0 g (75%) of product as a colorless syrup, bp 72–73°C (0.2 mm); n_D^{25} 1.4474 (Note 10).

2. Notes

1. 1,2:5,6-Di-O-isopropylidene-α-D-glucofuranose and imidazole were purchased from Aldrich Chemical Company, Inc. and used without further purification. Alternatively, the glucofuranose starting material can be prepared by standard methods from D-glucose.[2]

2. Reagent-grade tetrahydrofuran was freshly distilled from a purple solution of sodium and benzophenone.

3. Sodium hydride, a 50% dispersion in mineral oil, was purchased from Alfa Products, Morton Thiokol, Inc. It is not necessary to remove the mineral oil before conducting the reaction.

4. The collected salts should be disposed of carefully by first rinsing with isopropyl alcohol to ensure that no sodium hydride remains.

5. The submitters report pure product with bp 135–136°C (0.07 mm). The material obtained by the checkers is pure by NMR analysis. It shows ^1H NMR ($CDCl_3$) δ: 1.35 (s, 6 H), 1.42 (s, 3 H), 1.55 (s, 3 H), 2.60 (s, 3 H), 3.90–4.40 (m, 4 H), 4.68 (d, 1 H), 5.85–6.0 (m, 2 H).

6. Reagent-grade toluene was dried by distilling the toluene–water azeotrope

and then cooling the remaining liquid under an atmosphere of nitrogen.
7. Tributyltin hydride was purchased from Aldrich Chemical Company, Inc. and stored under nitrogen at 4°C.
8. An E. Merck Silica Gel 60 F-254 0.25-mm plate was used for the TLC analysis.
9. Silica Woelm TSC, obtained from Woelm Pharma, was used.
10. The product is pure by NMR and TLC analyses and shows ^{1}H NMR ($CDCl_3$) δ: 1.27 (s, 3 H), 1.31 (s, 3 H), 1.38 (s, 3 H), 1.46 (s, 3 H), 1.60–1.90 (m, 1 H), 2.05–2.30 (dd, 1 H), 3.65–4.25 (m, 4 H), 4.71 (t, 1 H), 5.77 (d, 1 H).

3. Discussion

This procedure illustrates a simple, general method for the deoxygenation of secondary hydroxyl groups. It is particularly useful for reducing hindered alcohols. The method was first described by Barton and McCombie,[3] who have reviewed a number of other examples.[4]

A variety of thiocarbonyl derivatives, in addition to xanthate esters, undergo reductive homolytic cleavage when treated with tributyltin hydride. These include thiobenzoates,[3] thiocarbonylimidazolides,[3,5] and phenyl thionocarbonate esters.[6] The *S*-methyl xanthate ester is a particularly convenient intermediate to prepare because of its ease of formation and the low cost of the reagents. Its use is precluded, however, by the presence of base-labile protecting groups and, in such cases, the thiocarbonylimidazolide or phenyl thionocarbonate ester will generally prove satisfactory. Additional methods for the radical deoxygenation of alcohols are described in a review by Hartwig.[7]

The tributyltin hydride reduction usually proceeds without complications. The most common byproduct is starting alcohol, which is postulated to be derived from a mixed thioacetal.[3] Use of the phenyl thionocarbonate ester has been reported to minimize this side reaction in cases where it is a problem.[6]

3-Deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranose has been prepared by a variety of other methods, the most widely used of which is the Raney nickel reduction of the 3-*S*-[(methylthio)carbonyl]-3-thioglucofuranose derivative.[8]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

3-Deoxy-1,2:5,6-di-O-isopropylidene-α-D-ribo-hexofuranose

thioacetal

1,2:5,6-Di-O-isopropylidene-3-O-(S-methyldithiocarbonate)-α-D-glucofuranose

3-S-[(methylthio)carbonyl]-3-thioglucofuranose

acetic acid (64-19-7)

ether (60-29-7)

acetonitrile (75-05-8)

sodium bicarbonate (144-55-8)

nitrogen (7727-37-9)

Raney nickel (7440-02-0)

toluene (108-88-3)

Benzophenone (119-61-9)

sodium (13966-32-0)

isopropyl alcohol (67-63-0)

carbon disulfide (75-15-0)

iodomethane (74-88-4)

d-Glucose (492-62-6)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

sodium hydride (7646-69-7)

Imidazole (288-32-4)

tributyltin hydride (688-73-3)

phenyl thionocarbonate

thiocarbonylimidazolide

S-methyl xanthate

1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (582-52-5)

thiobenzoate

α-d-ribo-Hexofuranose, 3-deoxy-1,2:5,6-bis-O-(1-methylethylidene)- (4613-62-1)

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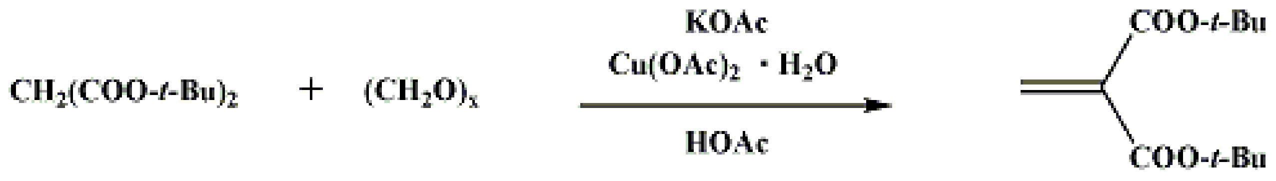
DI-*tert*-BUTYL METHYLENEMALONATE

[Propanedioic acid, methylene-, bis(1,1-dimethylethyl)ester]



Submitted by Paloma Ballesteros and Bryan W. Roberts[1].
Checked by Doreen L. Weller and James D. White.

1. Procedure

Caution! This reaction should be carried out in an efficient hood to prevent exposure to formaldehyde and acetic acid.

A 250-mL, one-necked, round-bottomed flask is equipped with a magnetic stirrer and a reflux condenser protected by a calcium chloride drying tube. Into the flask are placed 30.0 g (0.14 mol) of di-*tert*-butyl malonate (Note 1), 8.4 g (0.28 mol) paraformaldehyde (Note 2), 1.4 g (0.014 mol) of potassium acetate, 1.4 g (0.007 mol) of cupric acetate monohydrate, and 70 mL of glacial acetic acid. The resulting green–white suspension is placed in an oil bath preheated to 90–100°C and stirred for 2 hr (Note 3). The reaction mixture is allowed to cool to room temperature, and the reflux condenser is replaced with a short-path distillation apparatus, the vacuum outlet of which is connected in sequence to a trap cooled in acetone–dry ice, a potassium hydroxide trap, another trap cooled in acetone–dry ice, and a vacuum pump. The receiving flask is cooled in acetone–dry ice, and the system is evacuated over approximately 1 hr to remove acetic acid and other volatile material (Note 4). The bath temperature is increased to 40–50°C for 15 min and then is rapidly raised to 140–150°C to drive over crude product, which is collected over a boiling-point range of 60–82°C (Note 5). When distillate ceases to come over, the bath temperature is increased to 170°C and distillate is collected over the same boiling-point range until the reaction mixture turns from blue to green–brown. The total amount of crude product collected is 24.3 g. This material is dissolved in 50 mL of ether and washed with saturated aqueous sodium bicarbonate solution (4 × 20 mL) and water (25 mL). The combined aqueous fractions are extracted with 50 mL of ether, and the combined ether extracts are dried over magnesium sulfate for 10 min (Note 6). Filtration and evaporation on a rotary evaporator give 20.0 g of crude product, which is distilled through an 8-cm Vigreux column. The di-*tert*-butyl methylenemalonate is collected at 60–67°C/0.1 mm and weighs 15.3 g (48%) (Note 7). The product is somewhat unstable and should be stored in Pyrex in the refrigerator.

2. Notes

1. Di-*tert*-butyl malonate was prepared according to the procedure of Johnson; see

Org. Synth., Coll. Vol. IV **1963**, 261.

2. Paraformaldehyde was obtained from Aldrich Chemical Company, Inc., and stored in a desiccator over phosphorus pentoxide.

3. After approximately 25 min, the suspension dissolves and the reaction mixture becomes blue–green.

4. At the beginning of the evaporation, the pressure is controlled to minimize bumping of the vigorously boiling mixture.

5. During this operation the pressure varies between 0.3 and 1.5 mm. As the temperature is raised, the reaction mixture turns blue and gas evolution is observed.

6. The procedure can be interrupted at this point and the ether extracts dried over magnesium sulfate overnight in the refrigerator.

7. The bath temperature should not exceed 100°C in order to prevent contamination of the product with the bis(hydroxymethyl) derivative of di-*tert*-butyl malonate. The product exhibits single peaks in the ^{1}H NMR spectrum ($CDCl_3$, 250 MHz) at 1.51 and 6.25 ppm and contains approximately 6% of di-*tert*-butyl malonate as indicated by a peak at 1.47 ppm. Contamination by the bis(hydroxymethyl) derivative is indicated by a peak at 1.48 ppm.

3. Discussion

Methylenemalonate esters are potentially useful activated alkenes that can serve as electrophilic partners in the Michael and cycloaddition reactions and, in the process, introduce a *gem*-diester functionality for further synthetic transformation. The simple esters, however, have a marked propensity toward spontaneous polymerization and, as a consequence, have been used only sparingly in the Michael reaction,[2 3 4 5] the Diels–Alder reaction,[6 7 8] [2 + 2] cycloaddition,[9] and [3 + 2] cycloaddition.[10 11 12 13 14 15] The recently prepared di-*tert*-butyl analog[16] is advantageous in being longer lived and suitable for conventional synthetic operations, and in introducing a readily cleaved diester moiety. In its most useful application thus far, the compound has been found to react under mild conditions with enamines with no added catalyst or with enol ethers and acetates under Lewis acid catalysis to give either cyclobutanes or Michael adducts, depending on alkene structure.[17]

Di-*tert*-butyl methylenemalonate was originally prepared by phenylsulfenylation of di-*tert*-butyl methylmalonate and thermal elimination of the related sulfoxide.[16] Because methylenemalonate esters are customarily prepared by Knoevenagel-type condensation of malonic esters with formaldehyde equivalents, the considerably more convenient procedure described herein was subsequently adapted from Bachman and Tanner's study using paraformaldehyde under metal-ion catalysis.[6] The approximately 6% di-*tert*-butyl malonate accompanying the product has presented no interference in the aforementioned reactions with nucleophilic alkenes under neutral or acidic conditions, but its presence should be taken into consideration in other applications.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

cyclobutanes

methylenemalonate esters

acetic acid (64-19-7)

ether (60-29-7)

formaldehyde (630-08-0)

sodium bicarbonate (144-55-8)

magnesium sulfate (7487-88-9)

potassium acetate (127-08-2)

cupric acetate monohydrate (6046-93-1)

Propanedioic acid, methylene-, bis(1,1-dimethylethyl)ester, Di-tert-butyl methylenemalonate (86633-09-2)

phosphorus pentoxide (1314-56-3)

Di-tert-butyl malonate (541-16-2)

di-tert-butyl methylmalonate

paraformaldehyde (30525-89-4)

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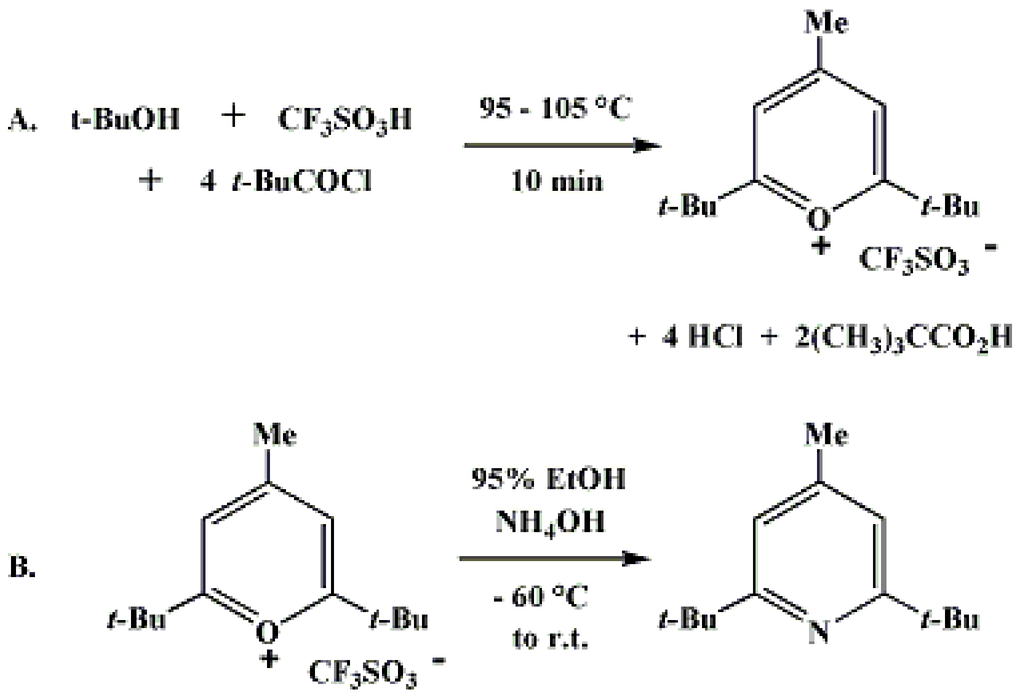
2,6-DI-*tert*-BUTYL-4-METHYLPYRIDINE

[Pyridine, 2,6-bis(1,1-dimethylethyl)-3-methyl-]



Submitted by Albert G. Anderson[1] and Peter J. Stang[2].
Checked by Mark T. DuPriest and George Büchi.

1. Procedure

Caution! The reaction described in Step A should be conducted in a hood, since some carbon monoxide is generated by partial decarbonylation of pivaloyl chloride.

A. *2,6-Di-*tert*-butyl-4-methylpyrylium trifluoromethanesulfonate* **(1)**. The center neck of a 5-L, three-necked, round-bottomed flask equipped with a thermometer port, magnetic stirrer bar coated with Teflon, and heating mantle is fitted with a 125-mL pressure-equalizing dropping funnel. The two side necks are fitted with 7 cm (diam) × 27 cm dry ice condensers vented through oil-filled bubblers into traps containing aqueous 1 *N* sodium hydroxide (Note 1). A thermometer is placed in the thermometer port to extend nearly to the bottom of the flask without contacting the stirrer bar. The apparatus is purged with dry nitrogen, the nitrogen flow is stopped, and to the flask are added 300 g (2.5 mol) of pivaloyl chloride and 46 g (0.62 mol) of anhydrous *tert*-butyl alcohol (Note 2). The condensers are charged with isopropyl alcohol-dry ice and, with stirring, the reaction mixture is warmed to 85°C. Heating is discontinued, and the mantle is allowed to remain in place. Then 187.5 g (109 mL, 1.25 mol) of trifluoromethanesulfonic acid is added with stirring during a period of 2–3 min (Note 3). After the addition is complete, the temperature is maintained at 95–105°C for 10 min with the heating mantle. The mantle is removed, and the brown reaction mixture

is first allowed to spontaneously cool to 50°C and finally cooled to −10°C with an isopropyl alcohol-dry-ice bath. On addition of 1 L of cold diethyl ether (Note 4), a precipitate forms immediately and is collected, washed with three 300-mL portions of diethyl ether, and air-dried on a medium-porosity fritted-glass filter to give 118–137 g (53–62%) of light tan 2,6-di-*tert*-butyl-4-methylpyrylium trifluoromethanesulfonate, mp 153–164°C (Note 5).

B. *2,6-Di-*tert*-butyl-4-methylpyridine* **(2)**. To 119–128 g (0.33–0.36 mol) of crude pyrylium salt in a 5-L, three-necked, round-bottomed flask equipped with a mechanical stirrer is added 2 L of 95% ethanol. The mixture is cooled to −60°C with an isopropyl alcohol-dry ice bath and to the fine slurry is added, with stirring, in one portion 1 L of concentrated (*d* 0.90) ammonium hydroxide also cooled to −60°C. The yellow reaction mixture is held at −60°C for 30 min, then allowed to warm to −40°C and maintained at that temperature for 2 hr, during which time the slurry dissolves. The mixture is then allowed to spontaneously warm to room temperature (Note 6). The reaction mixture is divided into two portions. Each portion is poured into a 4-L separatory funnel, 1 L of aqueous 10% sodium hydroxide is added, and the mixture is extracted with four 250-mL portions of pentane (Note 7). The extracts from both portions are combined and washed with 100 mL of saturated aqueous sodium chloride solution. The pentane is removed on the rotary evaporator (Note 8), leaving a residual light-yellow oil that is dissolved in 150 mL of pentane and introduced slowly during 20–30 min onto the top of a 40 × 4.5 cm water-jacketed chromatography column (Note 9) containing 300 g of activated alumina (Note 10). After the solution has been added, the column is filled with pentane and a 1-L constant-pressure addition funnel, also filled with pentane, is fitted to the top of the column to provide a slight head pressure. The elution is completed in ca. 90 min. All the pyridine is obtained in the first 2 L of eluant (Note 11). The pentane is removed on the rotary evaporator to yield 62.7–66.3 g (90–93%) of a colorless, odorless oil that solidifies on cooling or standing, mp 31–32°C (Note 12).

2. Notes

1. Since gas evolution at the onset of the reaction is quite vigorous, the operator should check to see that the passage of gas is unobstructed. Gas entering the sodium hydroxide trap should be passed over the solution, not bubbled through it, to guard against the possibility of sodium hydroxide solution being drawn back into the reaction flask.
2. *tert*-Butyl alcohol was obtained from Eastman Organic Chemicals and was used as received. The checkers also used *tert*-butyl alcohol freshly distilled from potassium with equal results. Pivaloyl chloride was obtained from Aldrich Chemical Company, Inc.
3. Trifluoromethanesulfonic acid FC-24 was obtained directly from the manufacturer, Minnesota Mining and Manufacturing Co. (3M), 15 Henderson Dr., West Caldwell, NJ 07006. Adherence to both the time and temperature during the addition is critical for best results.

4. The diethyl ether is conveniently cooled to −10°C by addition of some dry ice.
5. The crude salt darkens somewhat on standing because of further polymerization of impurities, but this does not affect the preparation of the base. It may be further purified by two recrystallizations at −30°C from isopropyl alcohol (8.7 mL/g) to give colorless needles (94% recovery), mp 168–169°C. The salt is not hygroscopic and may be stored indefinitely at room temperature. It is characterized by NMR [$(CD_3)_2SO$] δ: 1.45 (s, 18 H), 2.72 (s, 3 H), 8.10 (s, 2 H).
6. The submitters state that the reaction may be monitored by the formation of a brilliant-yellow intermediate that fades on completion of the reaction.[3] The checkers found it most convenient to remove the cold bath and allow the reaction to stir overnight at room temperature. If the reaction is worked up before completion, a yellow impurity is formed which cannot be removed by subsequent chromatography.
7. Phillips Petroleum Company pentane was used as received. Other brands required distillation to remove small amounts of higher-boiling compounds.
8. Ethanol should not be removed by distillation or use of a rotary evaporator since considerable amounts of product codistil with the ethanol.
9. The water-jacketed chromatography column shown in f.htmigure 1 is useful when low-boiling solvents or heat-sensitive compounds are chromatographed. Considerable heat is generated when the pentane solution containing the pyridine is introduced onto the column. This may cause boiling of the pentane and separation of the alumina. A flow of cold water through the jacket avoids separation of the alumina. The column was packed by slowly adding the alumina to the column half filled with pentane.

Figure 1. Not drawn to scale. (*A*) 29/26 joint; (*B*) hose connection; (*C*) water jacket; (*D*) 40 mm Kimflow fritted disk, size 40-C (coarse), Lab Glass LG28280; (*E*) Teflon Stopcock 2-mm plug bore, Lab Glass LG9605T.

Figure 1. Not drawn to scale. (A) 29/26 joint; (B) hose connection; (C) water jacket; (D) 40 mm Kimflow fritted disk, size 40-C (coarse), Lab Glass LG28280; (E) Teflon Stopcock 2-mm plug bore, Lab Glass LG9605T.

10. Aluminum oxide, activated, acidic, was obtained from Aldrich Chemical Company, Inc., and used as received.
11. The progress of the elution may be monitored by occasionally spotting a fluorescent TLC plate and examining the plate under short-wave UV light; the pyridine appears as a dark-blue spot. Attempts to completely remove colored impurities by distillation, acid-base extraction, or activated charcoal were

unsuccessful.
12. Additional physical constants are bp 148–153°C (95 mm), 223°C (760 mm); $HPtCl_6$ salt mp 213–214°C (decomp), CF_3SO_3H salt mp 202.5–203.5°C (from CH_2Cl_2); NMR (CCl_4) δ: 1.29 (s, 18 H), 2.25 (s, 3 H), 6.73 (s, 2 H); pK_a in 50% ethanol: 4.41[4] vs. 4.38 for pyridine in the same solvent.[5] Approximately 0.1% of an impurity, identified by gas chromatography–mass spectrum as 2,6-di-*tert*-butyl-4-neopentylpyridine, is also present; this arises by acid-catalyzed dimerization of isobutylene generated in situ during formation of the pyrylium salt.

3. Discussion

2,6-Di-*tert*-butyl-4-methylpyrylium salts previously have been prepared in yields of 4–40% starting with the chloride or anhydride of pivalic acid and employing various counterions, such as ClO_4^-, $FeCl_4^-$, or $AlCl_4^-$.[6] A more recent multistep preparation yields 33% of the perchlorate.[7] The pyrylium salt has been used to prepare pyrylotrimethinecyanine compounds.[8] 2,6-Di-*tert*-butyl-4-methylpyridine has been prepared in 44% yield by treating 4-picoline with a 10 molar excess of *tert*-butyl lithium[4] or by an anionic condensation reaction.[9] The present procedure is essentially that of Anderson and Stang.[3]

The pyrylium trifluoromethanesulfonate salt is nonexplosive. The resulting pyridine possesses the ability to distinguish between Lewis and Brπnsted acids.[3,5] It will not react with metal cations[10] or BF_3. The combination of 2,6-di-*tert*-butyl-4-methylpyridine and methyl trifluoromethanesulfonate results in improved yields under very mild conditions of methylated carbohydrates containing acid- or base-labile groups.[11] This pyridine was used as a hindered base in the synthesis of an antigenic bacterial hexasaccharide from *Salmonella newington*.[12] The base has also found use in silylation studies.[13,14] The hindered pyridine makes possible Friedel-Crafts alkylation of aromatic rings under basic conditons.[15,16] Substitution of pyridine by the hindered base results in substantially improved yields of a variety of vinyl esters.[16] The use of the sterically hindered base was essential for the preparation of 1-(ethynyl)vinyl trifluoromethanesulfonates.[17] After use the protonated base can be economically recovered in greater than 95% yield by addition of the pyridinium salt to a two-phase mixture of aqueous 50% sodium hydroxide and pentane followed by elution of the pentane solution through an unactivated silica gel column.[17]

Recently, 2,6,-di-*tert*-butyl-4-methylpyridine was incorporated into a polymer[18] via the 4-methyl group and the resulting polymer bound 2,6-di-*tert*-butylpyridine used in vinyl triflate synthesis. It has also been shown[19] that unlike 2,6-dimethyl and 2,4,6-trimethylpyridine, the 2,6-di-*tert*-butyl-4-methylpyridine does not react with triflic

anhydride, $(CF_3SO_2)_2O$, and this might account for the advantageous use of this nonnucleophilic base when preparing reactive triflates.[20]

Because of its ease of preparation and ready availability in quantity 2,6-di-*tert*-butyl-4-methylpyridine continues to be the base of choice in variety of applications when nonnucleophilic basic reaction conditions are required.[21,22]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 506
- Org. Syn. Coll. Vol. 8, 97
- Org. Syn. Coll. Vol. 8, 126
- Org. Syn. Coll. Vol. 9, 67

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alumina

pyrylium salt

chloride or anhydride of pivalic acid

1-(ethynyl)vinyl trifluoromethanesulfonates

2,6-dimethyl and 2,4,6-trimethylpyridine

ethanol (64-17-5)

diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

carbon monoxide (630-08-0)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

isopropyl alcohol (67-63-0)

ammonium hydroxide (1336-21-6)

potassium (7440-09-7)

Pentane (109-66-0)

aluminum oxide (1344-28-1)

isobutylene (9003-27-4)

tert-butyl alcohol (75-65-0)

trifluoromethanesulfonic acid (1493-13-6)

pivaloyl chloride (3282-30-2)

triflic anhydride (358-23-6)

4-picoline (108-89-4)

Pyridine, 2,6-bis(1,1-dimethylethyl)-3-methyl-

methyl trifluoromethanesulfonate (333-27-7)

tert-butyl lithium (594-19-4)

2,6-Di-tert-butyl-4-methylpyridine, 2,6,-di-tert-butyl-4-methylpyridine (38222-83-2)

2,6-Di-tert-butyl-4-methylpyrylium trifluoromethanesulfonate (59643-43-5)

2,6-di-tert-butyl-4-neopentylpyridine

2,6-di-tert-butylpyridine (585-48-8)

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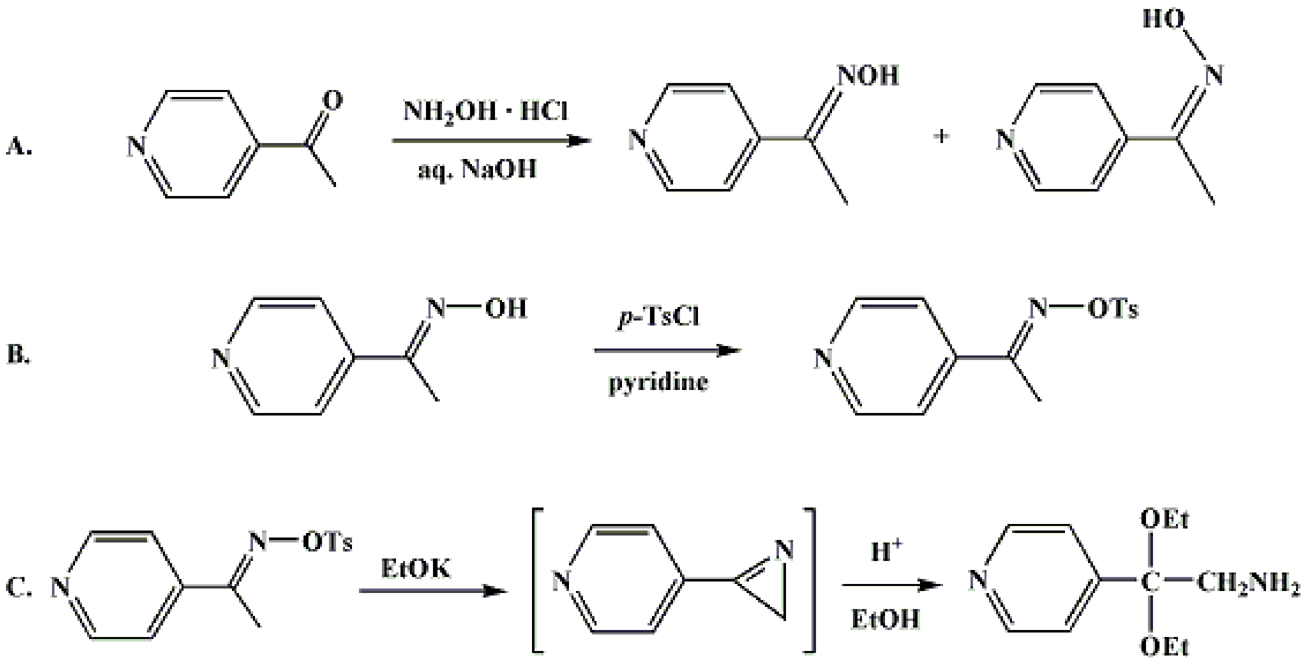
Organic Syntheses, CV 7, 149

α-AMINO ACETALS: 2,2-DIETHOXY-2-(4-PYRIDYL) ETHYLAMINE

[4-Pyridineethanamine, β,β-diethoxy]



Submitted by John L. LaMattina and R. T. Suleske[1].
Checked by Paul Hebeisen and Andrew S. Kende.

1. Procedure

It has been reported by workers at Pfizer Global R&D that oxime tosylates in this series are thermally very sensitive at temperatures slightly above their melting points (Chem. Eng. News ***2001****, October 1). It has also been reported that the 3-isomer demonstrated low-level shock sensitivity (Tetrahedron Lett.* ***1999****, 40. 6739). While this sensitivity was not observed during the checking of this procedure, extreme caution should be taken when handling these materials.*

A. *4-Acetylpyridine oxime*. Hydroxylamine hydrochloride (25.0 g, 0.36 mol) (Note 1) is dissolved in 50 mL of water, and the solution is added to 70 mL of 20% aqueous sodium hydroxide in a 500-mL Erlenmeyer flask. To this magnetically stirred solution is added at one time 4-acetylpyridine (36.3 g, 0.30 mol) (Note 2); a precipitate forms rapidly. The reaction mixture is stirred at 0–5°C for 2 hr; then the precipitate is collected by suction filtration and washed with 500 mL of cold water.

The product, (mp 122–146°C, 33–36 g, 81–88%) can be shown from its ^{1}H NMR spectrum (Note 3) to be a 5:1 mixture of the *E*- and *Z*-isomers of 4-acetylpyridine oxime. To obtain pure *E*-isomer (Note 4), the product is recrystallized twice as follows. The crude product is dissolved in 600 mL of hot water in a 2-L Erlenmeyer flask, the hot solution is decanted from any undissolved residue, and the supernatant liquid is allowed to cool slowly to 30°C during 2–3 hr by placing the flask on a cork ring. The precipitate is collected at this temperature by suction filtration. A second crystallization by the same procedure yields pure *E*-oxime, which is dried under reduced pressure over Drierite to constant weight. The yield of *E*-4-acetylpyridine oxime, mp 154–157°C (Note 5), is 27.1–28.3 g (66–69%).

B. *4-Acetylpyridine oxime tosylate*. Pure *E*-oxime (27.1 g, 0.20 mol) and *p*-toluenesulfonyl chloride (47.9

g, 0.22 mol) (Note 6) are added to 100 mL of anhydrous pyridine (Note 7) in a 1-L, round-bottomed flask fitted with a drying tube and a large magnetic stirring bar. The reaction mixture is stirred at 25°C for 24 hr; a precipitate of pyridine hydrochloride forms. A 500-mL portion of ice water is added with continued stirring. the initial precipitate dissolves, and a voluminous white precipitate soon forms. This is collected by suction filtration, washed with three 150-mL portions of cold water and dried under reduced pressure and over Drierite to constant weight. The yield of pure tosylate, mp 79–81°C (Note 8), is 55.1 g (95%).

C. *2,2-Diethoxy-2-(4-pyridyl)ethylamine*. To a 2-L, round-bottomed flask containing 80 mL of absolute ethanol (Note 9) and fitted with a magnetic stirrer and a reflux condenser with a drying tube, potassium metal (7.60 g, 0.19 mol) is slowly added (Note 10). When the metal has dissolved, the solution is cooled to 0–5°C and (*E*)-4-acetylpyridine tosylate (55.1 g, 0.19 mol) dissolved (with gentle warming) in 320 mL of absolute ethanol is added over 15 min through a dropping funnel to the stirred solution at 0–5°C. During this period a precipitate of potassium *p*-toluenesulfonate forms. The temperature of the stirred mixture is allowed to rise to room temperature for 1 hr. The mixture is diluted with 1 L of anhydrous ether and filtered by suction. The precipitate is quickly washed with 150 mL of anhydrous ether. The ether filtrates are combined, and hydrogen chloride gas is bubbled through the ether solution for 15 min. A precipitate forms immediately. The precipitate is collected by suction filtration, washed with three 170-mL portions of anhydrous ether, and dried briefly under reduced pressure. The dihydrochloride thus obtained is dissolved in 200 mL of water, and powdered sodium carbonate is added until the mixture reaches a pH of >10. The mixture is extracted four times with 125-mL portions of chloroform. The combined chloroform extracts are dried over anhydrous magnesium sulfate and concentrated at reduced pressure to an oil. This orange–red oil is distilled at 0.2 mm to yield 29.7 g (74.5%) of the amine as a colorless oil, bp 93–95°C (Note 11).

2. Notes

1. Hydroxylamine hydrochloride 97% (mp 155–157°C), available from Aldrich Chemical Company, Inc. or Fisher Scientific Company, is suitable for use without further purification.
2. 4-Acetylpyridine (98%) from Aldrich Chemical Company, Inc. was distilled under reduced pressure (bp 103–104°C/14–16 mm) prior to use.
3. In dimethyl sulfoxide-d_6, the *E* and *Z* isomers show OH proton resonances at δ 11.65 and 10.97, respectively.
4. Use of the isomer mixture prevents isolation of oxime tosylate in crystalline form at the next step and leads to reduced overall yield of pure amine.
5. The lit.[2] melting point for the oxime is 158°C.
6. *p*-Toluenesulfonyl chloride was purified prior to use by the procedure of L. Fieser and M. Fieser in "Reagents for Organic Synthesis."[3]
7. Pyridine AR (Mallinckrodt, Inc.) was used directly.
8. The lit.[2] mp for this compound is 80°C.
9. Ethanol was dried by reflux over magnesium ribbon.
10. For the safe handling and disposal of potassium metal, see *Org. Synth., Coll. Vol. IV* **1963**, 134.
11. This compound has the following 90-MHz ^1H NMR spectrum ($CDCl_3$) δ: 0.75 (br s, 2 H, NH_2), 1.20 [t, 6 H, *J* = 7, $(CH_3CH_2O)_2$], 2.97 (s, 2 H, CH_2NH_2), 3.41 [m, 4 H, $(OCH_2CH_3)_2$], 7.37 (d of d, 2 H, *J* = 2, 4.5, pyridine H_3 and H_5), 8.58 (d of d, 2 H, *J* = 2, 4.5, pyridine H_2 and H_6). Anal. calcd. for $C_{11}H_{18}N_2O_2$: C, 62.83; H, 8.63; N, 13.32. Found: C, 62.63; H, 8.52; N, 13.20.

3. Discussion

α-Amino ketones are useful intermediates for the preparation of a variety of heterocycles, including imidazoles,[4] oxazoles,[5] and pyrazines.[6] Unfortunately, pyrazine formation can be a complicating side reaction because of the tendency of α-amino ketones to dimerize. One way to avoid this problem is to

generate these intermediates in a protected form, specifically, as α-amino acetals.[7] Such derivatives allow one to manipulate the amino moiety as desired. The acetal can then be hydrolyzed at the appropriate interval to complete the synthesis.

α-Amino acetals can be prepared from α,α-dialkoxynitriles either via catalytic hydrogenation[8] or by reaction with organometallic reagents.[9] However, these methods are limited by the availability of the appropriate starting material. The procedure here offers a more simple approach that involves the Neber rearrangement. Although this reaction is generally used to prepare α-amino ketones, use of an anhydrous ethanol medium readily results in acetal formation. A summary of other α-amino acetals prepared using this procedure appears in Table I.

This reaction, like all Neber rearrangements, is limited by the availability of the appropriate oxime tosylate.[10] Substrates in which the aryl group contains an electrondonating function are unstable, since they have a propensity to undergo Beckmann rearrangement. However, this difficulty can be resolved by subsequent conversion of the α-amino acetals. For example, catalytic hydrogenation of 2,2-diethoxy-2-(p-bromophenyl)ethylamine yields the known parent compound 2,2-diethoxy-2-phenylethylamine; (these two α-amino acetals readily undergo hydrolysis and should be protected from moisture). Other approaches to α-aminoacetals include reduction of α-azidoacetals,[11] reaction of α-haloketimines with alcohol,[12] and reaction of *N*,*N*-dichloroamines with sodium ethoxide.[13]

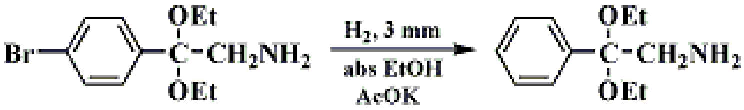
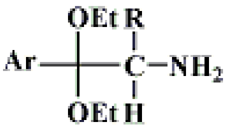
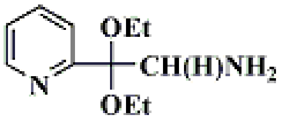
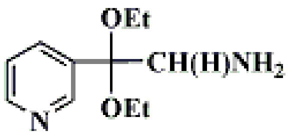
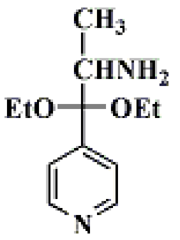
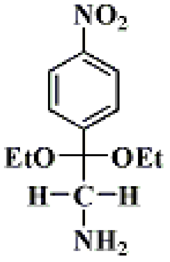
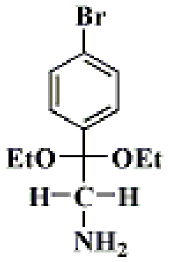


TABLE I

PREPARATION OFα-AMINOACETALS



Ar	R	Yield (%)	bp (°C/mm)	mp (°C), HCl salt
2-Pyridyl	H	 58	82/0.2	150 (dec)[a]
3-Pyridyl	H	 53	84/0.2	187–188[a]

4-Pyridyl	CH_3[b]	 40	98/0.2	129–130[a]
4-O_2N-C_6H_4	H	 78	—[c]	116 (dec)
4-Br-C_6H_4	H	 92	—[d]	

[a]Dihydrochloride salt.

[b]For the preparation of this material in Step C, gaseous HCl is bubbled into the ethereal filtrate for 3 hr. Presumably the longer reaction time is necessary for steric reasons.

[c]This material decomposes on distillation and is purified by column chromatography (silica gel–chloroform).

[d]This material decomposes on distillation and hydrolyzes when chromatographed on silica gel. However, ^{1}H-NMR analysis indicates that it is >95% pure.

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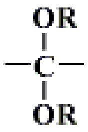
7. According to IUPAC Nomenclature of Organic Chemistry, Rule C-331.1: "Compounds containing the group



are termed acetals (the name ketal is abandoned)."
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Drierite

dimethyl sulfoxide-d_6

ethanol (64-17-5)

hydrogen chloride, HCl (7647-01-0)

ether (60-29-7)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

magnesium (7439-95-4)

sodium carbonate (497-19-8)

pyridine (110-86-1)

sodium ethoxide (141-52-6)

potassium (7440-09-7)

Hydroxylamine hydrochloride (5470-11-1)

magnesium sulfate (7487-88-9)

pyridine hydrochloride (628-13-7)

p-Toluenesulfonyl chloride (98-59-9)

2,2-Diethoxy-2-(4-pyridyl)ethylamine, 4-Pyridineethanamine, β,β-diethoxy (74209-44-2)

4-acetylpyridine (1122-54-9)

4-acetylpyridine oxime (1194-99-6)

2,2-diethoxy-2-(p-bromophenyl)ethylamine

2,2-diethoxy-2-phenylethylamine

potassium p-toluenesulfonate

E-4-acetylpyridine oxime

4-Acetylpyridine oxime tosylate (74209-52-2)

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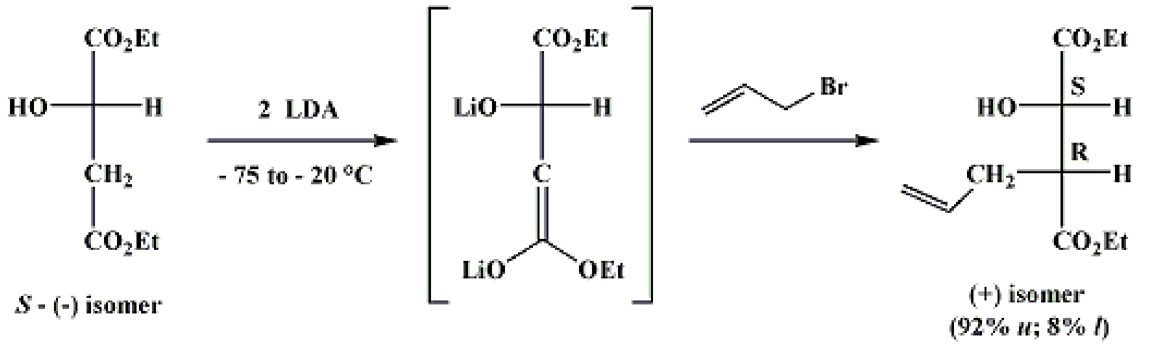
Organic Syntheses, CV 7, 153

DIASTEREOSELECTIVE α-ALKYLATION OF β-HYDROXYCARBOXYLIC ESTERS THROUGH ALKOXIDE ENOLATES: DIETHYL (2*S*, 3*R*)-(+)-3-ALLYL-2-HYDROXYSUCCINATE FROM DIETHYL (*S*)-(–)-MALATE

[Butanedioic acid, 2-hydroxy-3-(2-propenyl)-, diethyl ester, [*S*-(*R*,*S*)]]



Submitted by Dieter Seebach, Johannes Aebi, and Daniel Wasmuth[1].
Checked by Brian Maxwell and Clayton H. Heathcock.

1. Procedure

A 500-mL, three-necked flask containing a magnetic stirring bar is equipped with a 100-mL pressure-equalizing and serum-capped dropping funnel, a three-way stopcock, and a low-temperature thermometer (Note 1). The dry apparatus is filled with argon and kept under an inert gas pressure of ca. 100 mm against the atmosphere until the aqueous workup (Note 2); see f.htmigure 1.

Figure 1

Figure 1

The flask is charged through serum cap B with 17 mL (120 mmol) of diisopropylamine (Note 3) and 200 mL of tetrahydrofuran (THF) (Note 4), using syringe techniques. It is cooled to –75°C in a dry ice bath. With stirring, exactly 100 mmol of butyllithium (hexane solution) (Note 5) is introduced from the dropping funnel (Note 6) within 10 min, followed after 0.5 hr, by a mixture of 9.51 g (50 mmol) of (–)-diethyl (*S*)-malate (Note 7) and 5 mL of THF, which is added dropwise through cap B at such a rate that the temperature does not rise above –60°C. The addition takes approximately 10 min (Note 8). The dry ice cooling bath is replaced by an ice–salt bath (ca. –15°C) in which the contents of the flask warm to –20°C within 0.5 hr. The solution is stirred at –20°C ± 2°C for 0.5 hr and then is cooled to –75°C.

To the solution of the alkoxide enolate thus prepared is added by syringe within 5 min 10.7 mL (124 mmol) of neat 3-bromo-1-propene (Note 9) at such a rate that the

temperature of the reaction mixture does not rise above −70°C. Stirring is continued, first for 2 hr at −75°C, and then overnight while the temperature rises to −5°C (Note 10).

The reaction mixture is quenched by adding a solution of 12 g (200 mmol) of glacial acetic acid in 20 mL of diethyl ether at −50°C and is then poured into a 1-L separatory funnel containing 500 mL of ether and 70 mL of water. The organic layer is washed successively with 40 mL each of saturated sodium bicarbonate and sodium chloride solution, and the aqueous phases are extracted with two 200-mL portions of ether. The combined ethereal solutions are dried by vigorous stirring with dry $MgSO_4$ for 15 min. Removal of the solvent first with a rotary evaporator at a bath temperature no higher than 35°C and then at room temperature under oil pump vacuum (0.1 mm) furnishes 10.4 g of a yellow oil consisting, according to capillary gas chromatography (GC) (Note 11), of 81.3% of the desired allylated (2S,3R) product (73.5% yield), 8.5% of the (2S,3S) diastereoisomer (90.5% ds[2]), and 6.3% of the starting diethyl malate (Note 12).

The product is purified by flash chromatography (Note 13),(Note 14),(Note 15). A flash column of 7-cm diameter is charged with 450 g of silica gel (Kieselgel 60, Merck, Korngrösse 0.040–0.063 mm, 230–400 mesh ASTM) and 10.4 g of the crude product. A 1 : 1 mixture of ether and pentane is used for elution, with a running rate of 5-cm column length per minute (pressure 1.25 atm). After a 200-mL forerun, 33-mL fractions are collected. No attempt is made to separate the two diastereoisomers; fractions 22–40 are combined to give 8.0 g (70%) of pure allylated product [ratio of diastereoisomers 92 : 8 (Note 11)], after removal of the solvent; $[\alpha]_D^{20}$ + 11.2° (chloroform, *c* 2.23) (Note 16).

2. Notes

1. A Pt-100 thermometer (Testoterm KG, Lenzkirch, Germany) was used by the submitters. This is preferred to a conventional thermometer because it is more accurate and more convenient to read. Careful temperature control is essential for the present procedure. Unless stated otherwise, all temperatures given are those of the reaction mixture. The checkers found that a +30 to −100°C alcohol thermometer is satisfactory.
2. The glass components of the apparatus are dried overnight in a 170°C oven and allowed to cool in a desiccator over a drying agent before assembly. The apparatus is filled with argon by evacuating and pressurizing several times through the three-way stopcock, as described previously.[3]
3. Diisopropylamine was freshly distilled from calcium hydride.
4. Tetrahydrofuran (THF) was first distilled under an inert atmosphere from KOH and then from the blue solution obtained with potassium and benzophenone, as described previously.[3] [However, see warning notice, *Org. Synth., Coll. Vol. V* **1973**, 976–977.]
5. Before use, the commercial 1.6 *M* solution of butyllithium in hexane was titrated acidimetrically using diphenylacetic acid as an indicator.[4]
6. The dropping funnel was calibrated before use in this procedure. With standard graduated dropping funnels and syringes, the submitters noticed up to 10% deviation from true volumes! Syringe techniques were applied; the dropping funnel was rinsed with ca. 5 mL of dry THF.
7. Commercial (*S*)-(−)-malic acid was esterified under standard conditions, following a procedure by Fischer and Speier.[5] The freshly distilled ester employed by the submitters had an $[\alpha]_D^{20}$ −10.5° (neat) (d_{20}^{4} = 1.128 g/cm^3), which corresponds to an optical purity of 100%.[6]
8. The flask, in which the ester/THF mixture was prepared, and the syringe are rinsed with a total of ca. 5 mL of dry THF.
9. Commercial allyl bromide was distilled before use.
10. The submitters used a 2-L Dewar cylinder holding, besides the flask, ca. 1 L of ethanol as a cooling liquid. If no excess dry ice was present at the beginning of the warm-up period, it took ca. 12 hr to reach −5°C.
11. GLC-analysis were performed using the following column and conditions: 0.3-mm × 20-m glass capillary column Pluronic L 64, program 120°C, (3 min), 10° C/min up to 200°C, temperature of injector and detector 200°C, carrier gas: hydrogen (1.3 atm).

12. A total of ca. 4% of four minor side products with longer retention times is also present.

13. This is the fastest method, although it consumes large amounts of solvent and of silica gel. The procedure is that of Still et al.[7] Conventional chromatography is also possible but is more time-consuming.

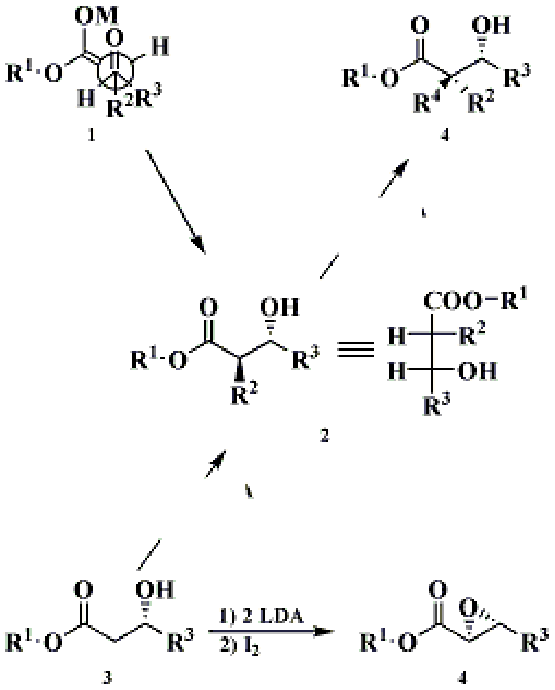
14. Kugelrohr distillation does not separate the starting material, diethyl malate. Distillation through a 30-cm Vigreux column (silvered vacuum jacket) leads to loss of material (only 40% yield, diastereoisomer ratio 90 : 10, free of starting material).

15. Hydrolysis of the crude product yields, after recrystallization, pure (2*S*,3*R*)-3-allyl-2-hydroxysuccinic acid, mp 96.0–97.5°C, $[\alpha]_D^{20}$ +14.7° (acetone, *c* 1.69).

16. The boiling point is 77–78°C (0.07 mm). Previously, a specific rotation of $[\alpha]_D^{25}$ + 11.9° (chloroform, *c* 1.77) was reported.[8] The ^{13}C NMR spectrum ($CDCl_3$) of the (2*S*, 3*R*) isomer shows the following signals δ (off-resonance multiplicity, assignment): 14.12 (q, $CO_2CH_2CH_3$), 32.21 (t, C(3) CH_2), 48.25 [d, C (3)], 60.86 and 61.81 (2 t, $CO_2CH_2CH_3$), 70.36 [d, C(2)], 117.78 [t, C(3)$CH_2CH=CH_2$], 134.94 [d, C(3)$CH_2CH=CH_2$], 171.92 and 173.48 (2 s, $CO_2CH_2CH_3$).

3. Discussion

The compound described here had not been known prior to our first synthesis of it.[8 9 10] Generally, aldol derivatives of this configuration are prepared by the addition of E enolates of esters to aldehydes,[11,12] **1** **2** in Scheme 1.



The method of preparing α-branched β-hydroxy esters by alkylation of dianion derivatives of the parent compounds was first discovered by Herrmann and Schlessinger.[13] It is highly diastereoselective[14] and applicable without racemization to optically active derivatives, as first demonstrated independently by Fráter with β-

hydroxybutanoate[15] and by us with malate[8 9 10,16 17 18] (see **3** □ **2** and **3** □ **5** in Scheme 1). In the meantime, many applications have been published.[19 20,21] A related method of preparing derivatives belonging to the same diastereoisomeric series is the alkylation of β-lactone enolates.[22]

Examples of alkylation of malic esters are listed in Table I, together with those of double alkylation, which can also be achieved, see **2** □ **4** in Scheme 1. Since the (*S*) and the (*R*) forms of malic acid are both readily available,[23] the enantiomers of all structures shown in Table I can be prepared as well. The method is also applicable to β-hydroxy γ-lactones of type **6**, the alkylations of which lead[24 25 26] to derivatives of opposite configuration **8**, see **6** □ **7** in Scheme 2. Finally, the dilithio derivative **9** of di-*tert*-butyl *N*-formylaspartate is alkylated (□ **10**; see Scheme 2)[27] with the same relative topicity,[28] **ul**, as the malate dianion derivative (Table I).

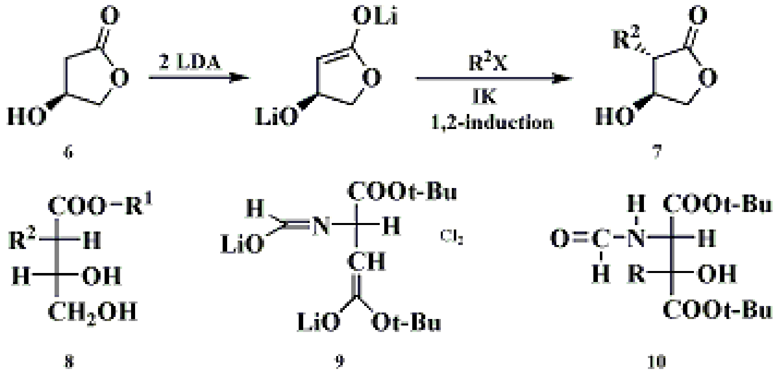
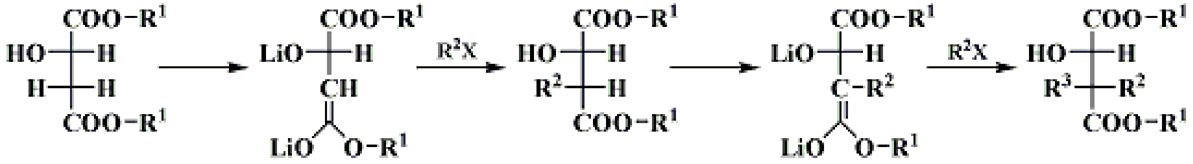
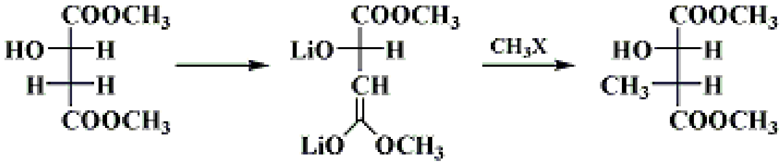
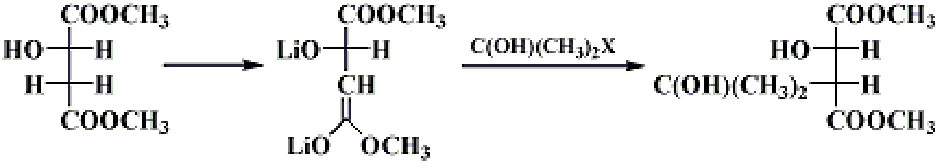
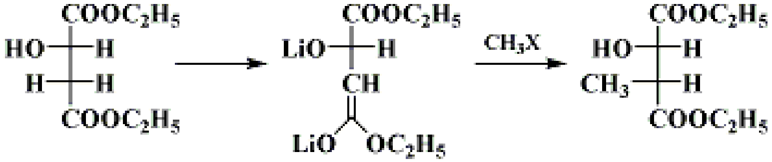
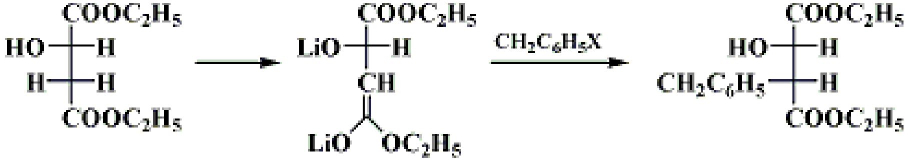


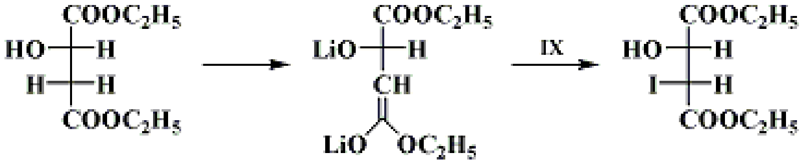
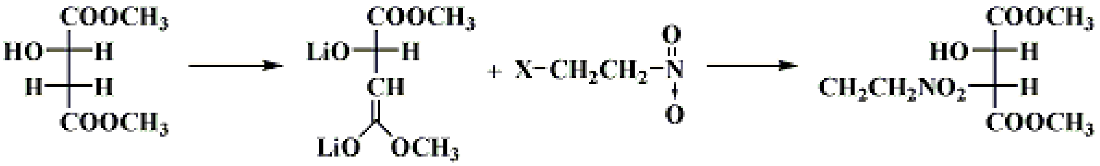
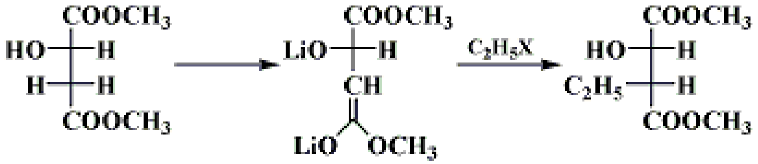
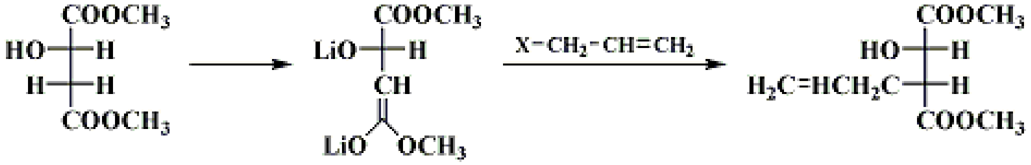
TABLE I

PRODUCTS OF MONO- AND DIALKYLATION WITH RELATIVE TOPICITY ul[a] OF (S)-MALIC ESTERS THROUGH ALKOXIDE ENOLATES. THE RATIOS OF DIASTEREOISOMERS (SEE % ds) WAS DETERMINED BY ^{1}H or ^{13}C NMR SPECTROSCOPY OR BY GC ANALYSIS.

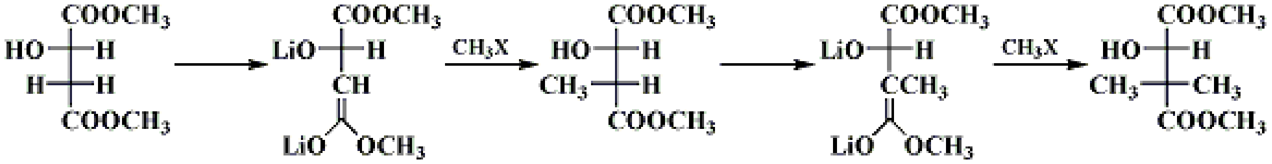
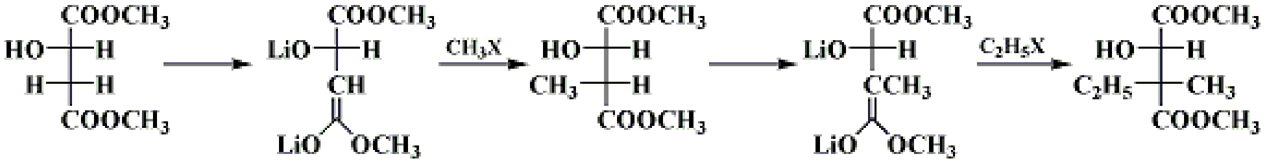
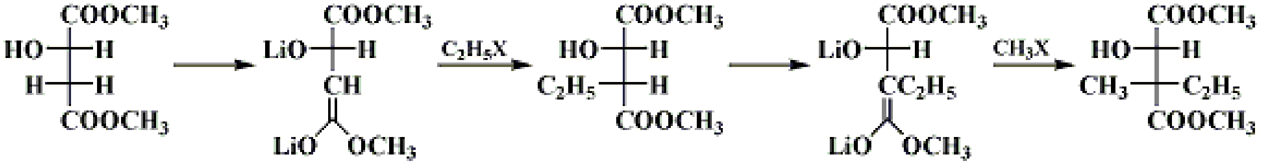
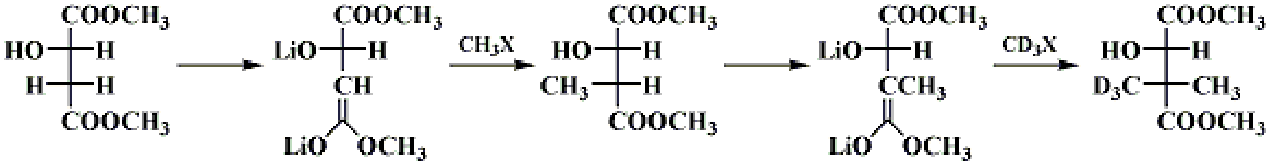
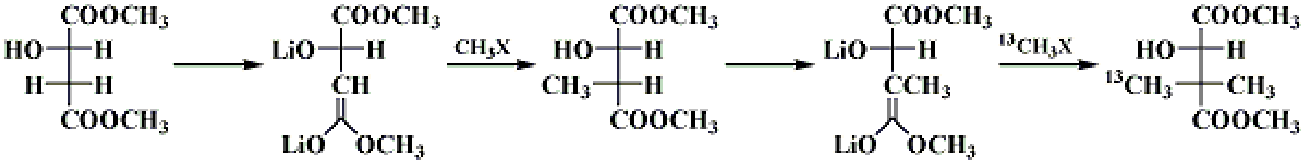


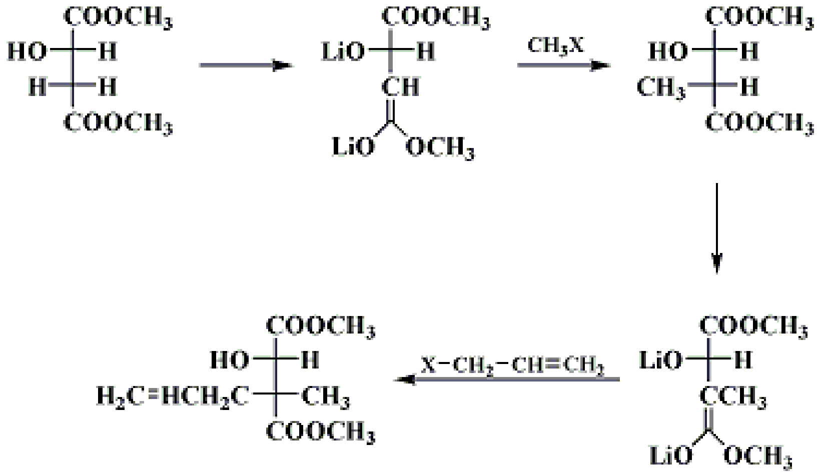
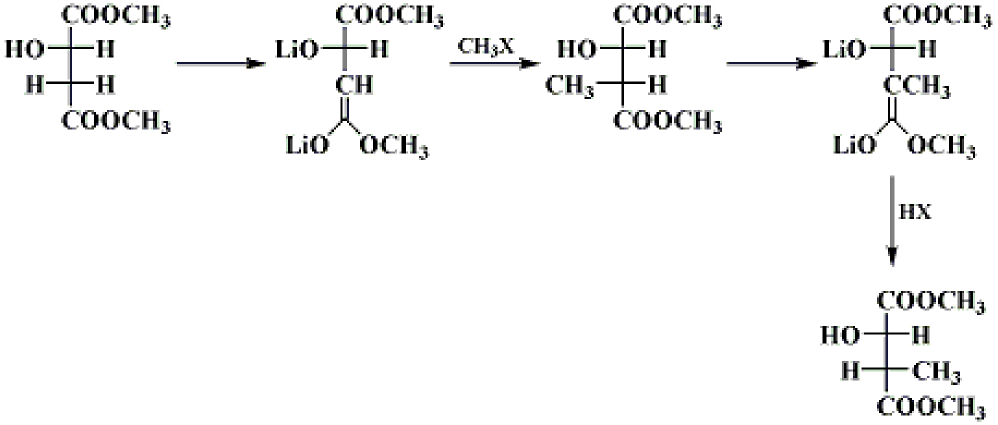
Product	R^1	R^2	R^3	Yield (%)	% ds[b]	Ref.
				(*Malate* □ ***a***)		

				65		
a	CH_3	CH_3	—		91	[8,17]
				55		
	CH_3	$C(OH)(CH_3)_2$	—		75	[8]
				88		
	C_2H_5	CH_3	—		91	[8]
				48		
	C_2H_5	$CH_2C_6H_5$	—		91	[8]

			80		
C_2H_5	I	—		67	8
			31		
CH_3	$CH_2CH_2NO_2$	—		85	16
			64		
CH_3	C_2H_5	—		90	17
			63		
CH_3	$CH_2CH=CH_2$	—		93	8b,14c

(***a*** ***b***)

				94		
b	CH_3	CH_3	CH_3		—	17
				36		
	CH_3	CH_3	C_2H_5		95	17
	CH_3	C_2H_5	CH_3		72	17
				92		
	CH_3	CH_3	CD_3		89	17
				81		
	CH_3	CH_3	$^{13}CH_3$		88	17

			74		
CH_3	CH_3	$CH_2CH{=}CH_2$		95	[18]
			>98		
CH_3	CH_3	H		67	[18]

[a]See [28].

[b]See [2].

In Table II, a series of useful chiral building blocks is shown, which are accessible through alkylations of malic acid derivatives; the table also contains some natural products that were synthesized from such building blocks.

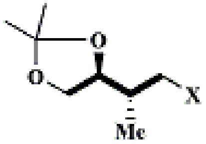
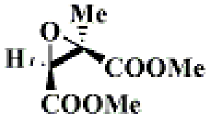
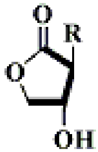
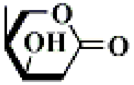
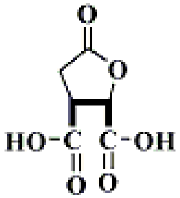
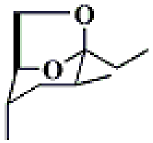
The alkylation of doubly deprotonated β-hydroxy esters, an example of which is described in the procedure above, is not just a useful alternative to the diastereoselective aldol-type addition, but can supply enantiomerically pure products from appropriate precursors, and it can be used for the preparation of α,α-disubstituted derivatives (see **4** in Scheme 1). These were hitherto not available stereoselectively from enolates of α-branched esters and aldehydes.[29,30]

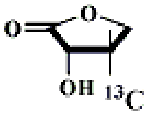
This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 420

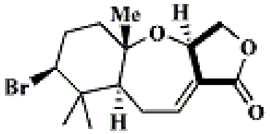
TABLE II
CHIRAL, NONRACEMIC BUILDING BLOCKS AND NATURAL PRODUCTS SYNTHESIZED THROUGH ALKYLATION OF MALIC ACID DERIVATIVES[a]

Products and Intermediates from (*S*)-Malic Acid

 ref. 15b, 22	ref. 8b	ref. 14c
 ref. 14c	 R = Me, et, higher alkyl allyl, benzyl; ref. 19	R = Me, allyl, benzyl (by oxidative degradation after alkylation); ref. 8c
 ref. 23	 (+)-isocitric acid ref. 8b	 (−)-d-multistratin ref. 15b, 22



(+)-pantolactone
ref. 14b



(–)-aplysistatin
ref. 19c

[a]The four-carbon unit of the structure derived from malic acid is indicated by heavy lines.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

DIETHYL (S)-(−)-MALATE

(−)-diethyl (S)-malate

allylated product

(S)-(−)-malic acid

(S) and the (R) forms of malic acid

ethanol (64-17-5)

acetic acid (64-19-7)

ether, diethyl ether (60-29-7)

hydrogen (1333-74-0)

chloroform (67-66-3)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

Allyl bromide, 3-bromo-1-propene (106-95-6)

acetone (67-64-1)

Benzophenone (119-61-9)

potassium (7440-09-7)

Diphenylacetic acid (117-34-0)

Pentane (109-66-0)

$MgSO_4$ (7487-88-9)

malic acid (617-48-1)

malate

butyllithium (109-72-8)

Tetrahydrofuran, THF (109-99-9)

hexane (110-54-3)

calcium hydride (7789-78-8)

argon (7440-37-1)

diisopropylamine (108-18-9)

diethyl malate (626-11-9)

β-hydroxybutanoate

DIETHYL (2S, 3R)-(+)-3-ALLYL-2-HYDROXYSUCCINATE (73837-97-5)

Butanedioic acid, 2-hydroxy-3-(2-propenyl)-, diethyl ester, [S-(R,S)]

(2S,3R)-3-allyl-2-hydroxysuccinic acid

(S)-Malic Acid (97-67-6)

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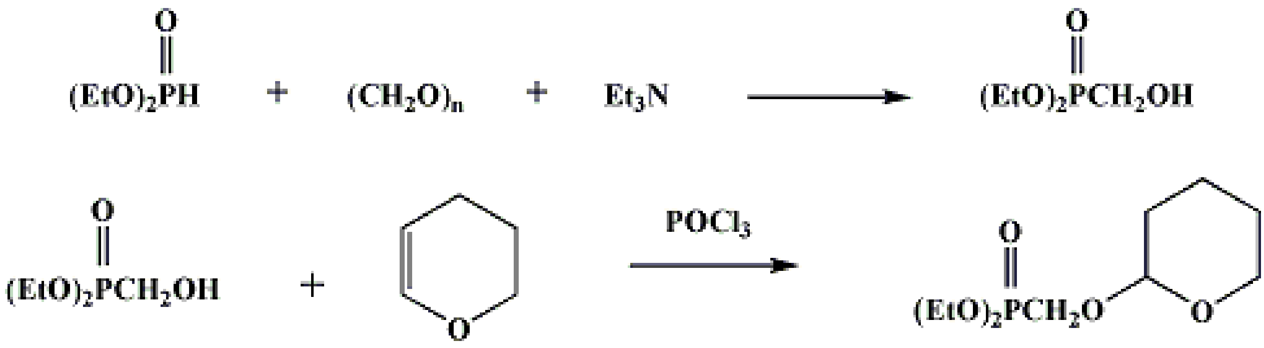
DIETHYL [(2-TETRAHYDROPYRANYLOXY)METHYL] PHOSPHONATE

[Phosphonic acid, [(tetrahydro-2 *H*-pyran-2-yl)oxy]methyl-, diethyl ester]



Submitted by Arthur F. Kluge[1]
Checked by Ronaldo A. Pilli, Kenneth S. Kirshenbaum, Clayton H. Heathcock, and K. Barry Sharpless.

1. Procedure

A. *Diethyl hydroxymethylphosphonate*. To a 250-mL, round-bottomed flask equipped with a magnetic stirring bar and an efficient reflux condenser are added 69 g (64.4 mL, 0.5 mol) of diethyl phosphite (Note 1), 15 g (0.5 mol) of paraformaldehyde, and 5.1 g (0.05 mol) of triethylamine. The mixture is placed in an oil bath preheated to 100–120°C. The temperature is increased to 120–130°C, and the mixture is stirred at this temperature for 4 hr. The stirring bar is removed, the flask is transferred to a rotary evaporator, and most of the triethylamine is removed by heating under reduced pressure of ca. 15 mm and with a bath temperature of ca. 80°C. Kugelrohr distillation at 125°C (0.05 mm) (Note 2) gives 41.4–54.9 g (49–65%) of material of sufficient purity for the next step (Note 3) and (Note 4).

B. *Diethyl [(2-tetrahydropyranyloxy)methyl]phosphonate*. A mixture of 33.63 g (0.2 mol) of diethyl hydroxymethylphosphonate, 21 g (0.25 mol) of dihydropyran, and 150 mL of diethyl ether is placed in a stoppered flask, and 20 drops of phosphorus oxychloride is added while the contents are swirled manually. After 3 hr at room temperature the reaction is monitored by TLC (Note 5). The mixture is diluted with diethyl ether, transferred into a separatory funnel, and shaken successively with 100 mL of saturated sodium bicarbonate solution, 100 mL of water, and 100 mL of saturated sodium chloride solution. The ether solution is dried over $MgSO_4$, filtered, and the ether is removed with a rotary evaporator. Kugelrohr distillation of the residue (110°C, 0.05 mm) gives 42.4–46.9 g (84–93%) of material of sufficient purity for use in homologation reactions (Note 6) and (Note 7).

2. Notes

1. Diethyl phosphite, paraformaldehyde, and triethylamine were obtained from Aldrich Chemical Company, Inc. Dihydropyran was obtained from MCB, Inc.
2. Attempted isolation of diethyl hydroxymethylphosphonate by standard vacuum-distillation technique is accompanied by extensive decomposition. The use of Kugelrohr apparatus allows the isolation to be accomplished at a lower temperature, and therefore the product is obtained in higher yield. Alternatively, the checkers found that distillation using a 2-in. wiped-film molecular still. (Pope Scientific, Inc.) significantly raised product yields, especially when the reaction was performed on a larger scale (Note 3) and (Note 6).
3. The checkers found that reactions run on up to four times the present scale and rectified using a molecular still (wall temperature 110–120°C, 0.10 mm) gave yields of 89–94%. *Warning: On this larger scale (i.e., four times the present scale) a brief runaway was experienced and some material that escaped from the condenser was caught in a trap; however, the yield was still excellent (94%).*
4. On TLC [silica, visualization with 1.5% phosphomolybdic acid spray and heating] the product has a retardation factor of ca. 0.1 with ethyl acetate development and ca. 0.3 with methanol–dichloromethane [5:95] development. The ^{1}H NMR spectrum ($CDCl_3$) is as follows δ: 1.31 (t, 6 H, *J* = 6.8), 3.87 (d, 2 H, *J* = 7), 4.13 (m, 4 H), 5.34 (br s, 1 H, OH).
5. Five drops of reaction mixture is added to a mixture of 20 drops of diethyl ether and 1 drop of triethylamine. On TLC (Note 4) the product has R_f 0.4 with ethyl acetate development. If TLC indicates the presence of diethyl hydroxymethylphosphonate an additional 5 g of dihydropyran and 10 drops of phosphorus oxychloride are added. The reaction is checked by TLC for completeness after 1 hr and is worked up at that time.
6. The checkers found that reactions run on up to nine times the present scale could be effected with only a small reduction in yield. Molecular still distillation (wall temperature 105–115°C, 0.10 mm) gave yields of 81–83%.
7. GLC analysis (0.5 × 200 cm 3% OV-17, 170°C, helium flow = 30 mL/min) shows the product with a retention time of 5 min and a purity greater than 97% The ^{1}H NMR spectrum ($CDCl_3$) is as follows δ: 1.35 (t, 6 H, *J* = 7), 1.4–1.9 (m, 6 H), 3.4–4.45 (m, 8 H), 4.7 (m, 1 H).

3. Discussion

Diethyl [(2-tetrahydropyranyloxy)methyl]phosphonate is useful in the Wittig–Horner synthesis of enol ethers, which are intermediates in one-carbon homologations of carbonyl compounds.[2] This procedure is an adaptation of a general method for preparing dialkyl hydroxymethylphosphonates.[3] An *O*-tetrahydropyranyl derivative also has been prepared from dibutyl hydroxymethylphosphonate, and diethyl hydroxymethylphosphonate has been *O*-silylated with *tert*-butylchlorodimethylsilane and imidazole.[2] Another useful congener in this series has been prepared by an Arbuzov reaction of methoxyethoxymethyl (MEM) chloride and triethyl phosphite.[2]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 18

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

methoxyethoxymethyl (MEM) chloride

ether, diethyl ether (60-29-7)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

Phosphorus Oxychloride (21295-50-1)

$MgSO_4$ (7487-88-9)

dihydropyran

Imidazole (288-32-4)

triethylamine (121-44-8)

Triethyl phosphite (122-52-1)

diethyl phosphite (762-04-9)

helium (7440-59-7)

phosphomolybdic acid (51429-74-4)

Diethyl [(2-tetrahydropyranyloxy)methyl]phosphonate, Phosphonic acid, [(tetrahydro-2 H-pyran-2-yl)oxy]methyl-, diethyl ester (71885-51-3)

Diethyl hydroxymethylphosphonate (3084-40-0)

dibutyl hydroxymethylphosphonate

tert-butylchlorodimethylsilane (18162-48-6)

paraformaldehyde (30525-89-4)

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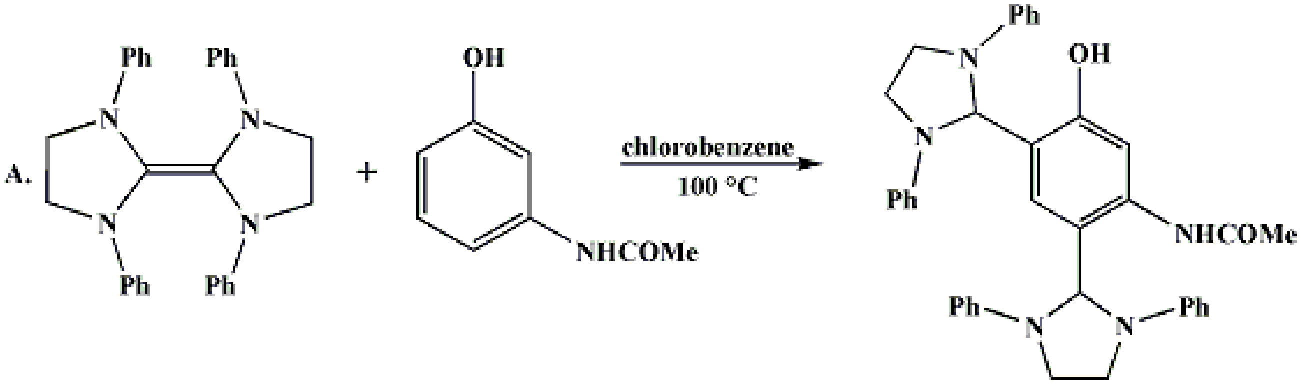
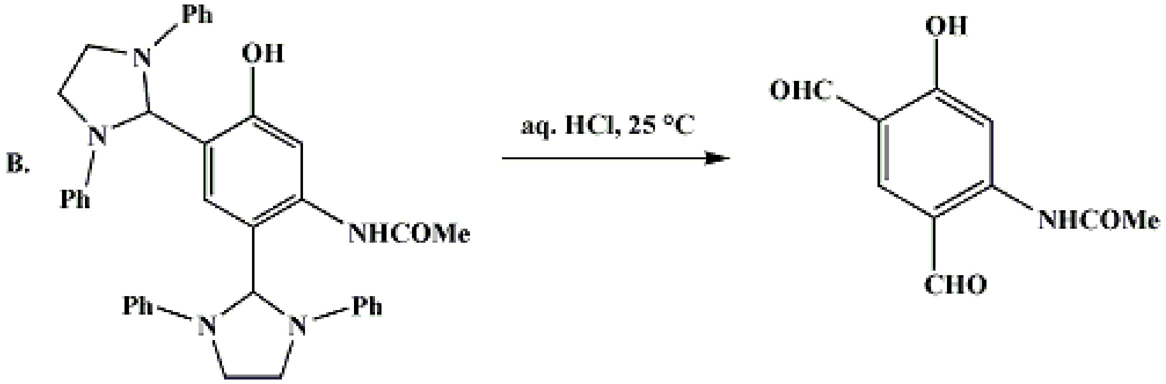
N-(2,4-DIFORMYL-5-HYDROXYPHENYL)ACETAMIDE

[Acetamide, *N*-(2,4-diformyl-5-hydroxyphenyl)-]





Submitted by Jürgen Hocker and Henning Giesecke[1].
Checked by G. Saucy, Harvey Gurien, and Gerald Kaplan.

1. Procedure

A. *N-[2,4-Bis(1,3-diphenylimidazolidin-2-yl)-5-hydroxyphenyl]acetamide.* A 500-mL, three-necked flask equipped with nitrogen inlet, mechanical stirrer, reflux condenser, and thermometer is charged with 88.8 g (0.2 mol) of 1,1',3,3'-tetraphenyl-2,2'-biimidazolidinylidene (Note 1) and 30.2 g (0.2 mol) of 3-acetamidophenol (Note 2). The system is flushed with and maintained under nitrogen, and 100 mL of chlorobenzene (Note 3) is added. The suspension is stirred at 100°C for 6 hr (Note 4). 2-Propanol (250 mL) is added to the hot mixture, which is then allowed to cool to room temperature. A pale-yellow solid precipitates which is filtered and washed with 200 mL of 2-propanol. Drying in vacuum affords 84.6–93.2 g (71–78%) of *N*-[2,4-bis(1,3-diphenylimidazolidin-2-yl)-5-hydroxyphenyl]acetamide, mp 254–256°C (Note 5).

B. *N-(2,4-Diformyl-5-hydroxyphenyl)acetamide.* A suspension of 95 g of the phenol (prepared as described under Section A) (Note 6) in 1 L of aqueous 10% hydrochloric acid is stirred for 2 hr at room temperature. The colorless solid (Note 7) is filtered by suction and twice suspended in water at 40°C. Final filtration is followed by a water wash (1 L, 40°C), and the solid is sucked down on the filter. Crystallization from 800 mL of acetonitrile affords 21.8–22.3 g (66–67.5%) of *N*-(2,4-diformyl-5-hydroxyphenyl)acetamide, mp 215–217°C (Note 8).

2. Notes

1. This material was prepared by the procedure of H. W. Wanzlick, *Org. Synth., Coll. Vol. V* **1973**, 115.
2. The checkers purchased 3-acetamidophenol from Aldrich Chemical Company, Inc.
3. The chlorobenzene was dried by azeotropic distillation.
4. The submitters checked the reaction progress by adding chloroform to an aliquot of the reaction mixture and observing it under long-wavelength UV light (350 mm). A bright fluorescence indicated incomplete reaction. The checkers found that further heating did not eliminate the fluorescence or improve the yield. Adding 1-g quantities of the phenol resulted in quenching of the fluorescence but a lower yield.
5. The product showed the following spectroscopic properties: ^{1}H NMR (d_7-DMF) δ: 1.92 (s, CH_3), 3.5–4.1 (m, 8 H, NCH_2), 6.05 (s, 1 H), 6.36 (s, 1 H), 6.5–7.5 (m, 23 H), 9.13 (s, 1 H).
6. The phenol should be ground in a mortar to eliminate lumps.
7. The checkers always obtained pale-yellow material.
8. The product had the following spectroscopic properties: IR (KBr) cm^{-1}: 1659, 1644, 1620; ^{1}H NMR (d_7-DMF) δ: 2.24 (s, CH_3), 8.22 (s, 1 H), 8.24 (d, $J < 1$ Hz, 1 H), 9.87 (d, $J < 1$ Hz, 1 H), 10.16 (s, 1 H), 11.35, 12.05 (2s, OH, NH).

3. Discussion

The reaction of 1,1',3,3'-tetraphenyl-2,2'-biimidazolidinylidene with phenols illustrated in this procedure is a general method for the preparation of phenolaldehydes.[2] Table I gives the aldehydes that have been prepared by conditions similar to those described here.

Nitrogen-containing heterocyclic compounds such as indoles and imidazoles are also formylated by the electron-rich olefin. 3-Methylimidazole-5-carboxaldehyde can be prepared from 2-methylimidazole (yield 83%) and 2-phenylindole-3-carboxaldehyde from 2-phenylindole (yield 64%).

TABLE I
ALDEHYDES FROM PHENOLS AND 1,1',3,3'-TETRAPHENYL-2,2'-BIIMIDAZOLIDINYLIDENE

	Yield (%)	
Aldehyde	Imidazolidin-2-yl-phenol	Hydrolysis
4-Hydroxybenzaldehyde	55	88
4-Hydroxy-3,5-dimethylbenzaldehyde	58	80
3-Cyclohexyl-5-methylsalicyladehyde	43	80
4-Dimethylamino-5-methylsalicylaldehyde	65	54
4-Dimethylaminosalicylaldehyde	52	90
Resorcinol-2,4,6-tricarboxaldehyde	43	96
4-Hydroxy-5-methoxyisophthalaldehyde	55	81
4-Hydroxy-6-methoxyisophthalaldehyde	57	87
Pyrogallol-4,6-dicarboxaldehyde	82	50
8-Hydroxyquinoline-7-carboxaldehyde	76	69

The formylation of phenols with the electron-rich olefin to give imidazolidin-2-yl-phenols is very selective and avoids mixtures of *o*- and *p*-isomers, which are frequently obtained by methods commonly employed for the synthesis of phenolaldehydes. Para substitution of the cyclic aminal group in the phenol is preferred. If the *p*-position is blocked or sterically hindered, the reaction proceeds via the *ortho*-aminals to salicylaldehydes. Incorporation of more than one aldehyde group in the benzene nucleus is often achieved with hydroxy- and aminophenols.

Reaction of phenols bearing strong electron-withdrawing substituents such as dichlorophenols and nitrophenols with 1,1',3,3'-tetraphenyl-2,2'-biimidazolidinylidene results in poor yields. Oxidation of the electron-rich olefin by nitro compounds is also possible.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

indoles

imidazoles

3-Cyclohexyl-5-methylsalicyladehyde

imidazolidin-2-yl-phenols

salicylaldehydes

dichlorophenols

nitrophenols

hydrochloric acid (7647-01-0)

acetonitrile (75-05-8)

chloroform (67-66-3)

phenol (108-95-2)

nitrogen (7727-37-9)

chlorobenzene (108-90-7)

2-propanol (67-63-0)

2-Phenylindole (948-65-2)

3-acetamidophenol (621-42-1)

3-Methylimidazole-5-carboxaldehyde

4-Hydroxybenzaldehyde (123-08-0)

4-Hydroxy-3,5-dimethylbenzaldehyde (2233-18-3)

4-Dimethylamino-5-methylsalicylaldehyde

4-Dimethylaminosalicylaldehyde

Resorcinol-2,4,6-tricarboxaldehyde

4-Hydroxy-5-methoxyisophthalaldehyde

4-Hydroxy-6-methoxyisophthalaldehyde

Pyrogallol-4,6-dicarboxaldehyde

8-Hydroxyquinoline-7-carboxaldehyde

2-methylimidazole (693-98-1)

2-phenylindole-3-carboxaldehyde (25365-71-3)

N-(2,4-Diformyl-5-hydroxyphenyl)acetamide, Acetamide, N-(2,4-diformyl-5-hydroxyphenyl)- (67149-23-9)

N-[2,4-Bis(1,3-diphenylimidazolidin-2-yl)-5-hydroxyphenyl]acetamide (67149-22-8)

1,1',3,3'-tetraphenyl-2,2'-biimidazolidinylidene (2179-89-7)

Imidazolidin-2-yl-phenol

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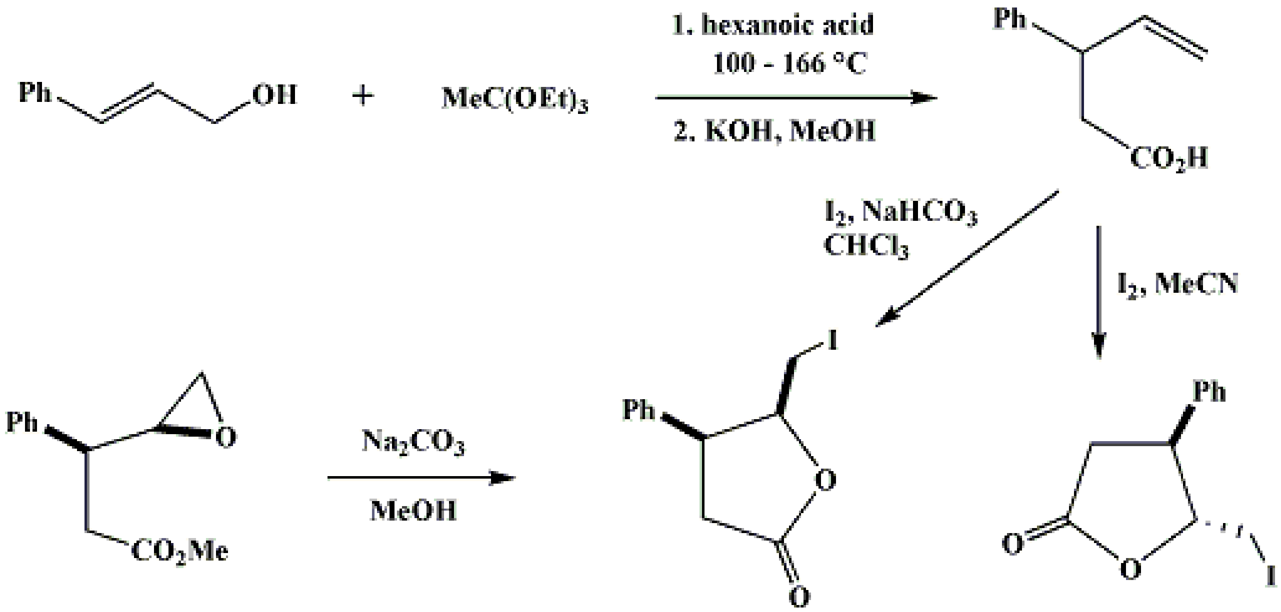
STEREOCONTROLLED IODOLACTONIZATION OF ACYCLIC OLEFINIC ACIDS: THE *trans* AND *cis* ISOMERS OF 4,5-DIHYDRO-5-IODOMETHYL-4-PHENYL-2(3*H*)-FURANONE



Submitted by F. Bermejo Gonzalez and Paul A. Bartlett[1].
Checked by Pauline J. Sanfilippo and Andrew S. Kende.

1. Procedure

A. *3-Phenyl-4-pentenoic acid*. A mixture of 33.7 g (0.25 mol) of cinnamyl alcohol (Note 1), 46.1 mL (0.25 mol) of triethyl orthoacetate (Note 1), and 0.19 mL (1.5 mmol) of hexanoic acid (Note 2) is placed in a 250-mL, round-bottomed flask equipped with a thermometer, Claisen head, and condenser. The solution is heated in an oil bath with distillation of ethanol. After 3 hr, distillation of ethanol slows and another 0.1-mL portion of hexanoic acid is added. Additional portions (0.1 mL) of the catalyst are added again at 3.5 and 4.5 hr. After 6 hr, a total of 27 mL of ethanol, out of a theoretical 29.2 mL, has been collected, and GC analysis (Note 3) indicates that no cinnamyl alcohol remains. Over this 6-hr period the internal temperature rises from 100 to 166°C.

The solution is allowed to cool, and 19.7 g (0.35 mol) of potassium hydroxide in 25 mL of water and 75 mL of methanol is added. The mixture is heated under reflux for 1 hr under nitrogen. After the alkaline solution is allowed to cool to room temperature, it is washed with ether and acidified with concentrated HCl. The acidic solution is extracted with three 50-mL portions of ether, and the organic layer is dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The yield of crude 3-phenyl-4-pentenoic acid is 38–39 g (86–88%). This material is essentially pure by NMR analysis and can be used directly as starting material for the following iodolactonization reactions. The acid can be further purified by crystallization from hexane (86% recovery in two crops) to give product melting at 44–46°C.

B. *Thermodynamically controlled formation of the trans (4RS,5SR) isomer of 4,5-dihydro-5-iodomethyl-4-phenyl-2(3H)-furanone*. In a 500-mL, round-bottomed flask equipped with a mechanical stirrer (Note 4) and immersed in an ice bath is placed a solution of 10 g (0.057 mol) of 3-phenyl-4-pentenoic acid in 200 mL of acetonitrile (Note 5). Solid iodine (44.5 g, 0.18 mol) (Note 6) is added, and the mixture is protected from light and stirred at 0°C under nitrogen for 24 hr. The mixture is partitioned between 100 mL of ether and 100 mL of saturated aq $NaHCO_3$. The organic layer is washed with 10% aqueous $Na_2S_2O_3$ until colorless, and with water and brine. It is then dried over $MgSO_4$, the solvent is removed at reduced pressure, and the crude trans iodolactone is obtained as a thick oil; weight 14.5–15.6 g (85–91%). NMR analysis indicates that the trans : cis ratio is at least 95 : 5 (Note 7).

C. *Kinetically-controlled formation of the cis (4RS,5RS) isomer of 4,5-dihydro-5-iodomethyl-4-phenyl-2(3H)-furanone*. A mixture of 10 g (0.057 mol) of 3-phenyl-4-pentenoic acid, 9.1 g (0.11 mol) of $NaHCO_3$ and 200 mL of water is placed in a 1000-mL round-bottomed flask equipped with a mechanical stirrer (Note 4) and stirred until a homogeneous solution is obtained. Chloroform (200 mL) is added, the mixture is cooled in an ice bath, and 28.4 g (0.112 mol) (Note 8) of iodine is added. The mixture is stirred at 0°C for 6 hr, the layers are separated, and the organic phase is washed with 10% aqueous $Na_2S_2O_3$ until colorless, and with water and brine. The organic layer is dried over $MgSO_4$, the solvent is removed under reduced pressure, and the crude *cis*-iodolactone is obtained as a semisolid: weight 15.5–16.3 g (91–95%), mp 75–90°C (Note 9). Direct recrystallization of this material from diisopropyl ether (Note 10) affords 9.0–9.5 g (52–55%) of material, mp 103–104°C, with a cis : trans ratio of 15–16 : 1. Further recrystallization from diisopropyl ether gives (in two crops) 8.3–8.9 g (48–52%) of product, mp 104–105°C, with a purity of ≥98%. Additional product can be obtained from the mother liquors.

2. Notes

1. The reagents employed were obtained from Aldrich Chemical Company, Inc. and used as received.
2. Propionic acid may also be used as catalyst; however, its boiling point (141°C) is below that of the reaction temperature at the end of the reaction. The use of *o*-nitrophenol as catalyst resulted in a lower yield in this case.
3. Gas chromatographic analysis was performed on a Varian model 940 gas chromatograph equipped with a 6-in. × 1/8-in. column of 5% OV-101 on Gas-Chrom Q at a column temperature of 155°C.
4. A magnetic stirrer is not recommended because the mixture becomes very thick.
5. Mallinckrodt Inc. analytical reagent-grade acetonitrile was used.
6. Two equivalents of iodine are required by the stoichiometry of the reaction, because of formation of HI_3. In our experience, however, the reaction does not proceed to completion without additional reagent.
7. The crude trans isomer obtained in this way is of suitable purity for conversion to the epoxy ester, as described below (see Discussion). It may be further purified by column chromatography; however, attempted vacuum distillation leads to considerable decomposition.
8. Two equivalents of iodine are required because of formation of NaI_3.
9. NMR analysis of the crude iodolactone indicates that the cis : trans ratio is about 3.4:1.
10. The recrystallization is performed using ca. 15 mL of diisopropyl ether per gram of crude product. Dichloromethane, 1–2%, is also added to the hot mixture to effect

complete solution before cooling.

3. Discussion

Iodolactonization has become a useful reaction for the stereocontrolled introduction of chiral centers in both cyclic[2] and acyclic[3,4,5,6,7,8,9] systems. Depending on the reaction conditions, the cyclization can be carried out under either kinetic or thermodynamic control.[3,10] The contrast between the stereochemical course of the two procedures is not always as dramatic as with 3-phenyl-4-pentenoic acid, as illustrated by the examples in Table I.[11] A procedure for obtaining high 1,3-asymmetric induction in formation of valerolactones by cyclization of *N,N*-dimethylamides has been reported,[12] and the tendency for an oxygen substituent in the allylic position to control the stereochemistry of electrophilic cyclization has been addressed.[13]

Conversion of iodolactones into the corresponding epoxy esters is often one of the major steps in their utilization for the purposes of stereocontrol.[3,4,5,6,7,14] Methanolysis of the cis isomer of 4,5-dihydro-5-iodomethyl-4-phenyl-2(3*H*)-furanone to methyl (3*RS*,4*RS*)-4,5-epoxy-3-phenylpentanoate is a representative procedure for this transformation.

A mixture of 5.0 g (16.6 mmol) of (4*RS*,5*RS*)-4,5-dihydro-5-iodomethyl-4-phenyl-2(3*H*)-furanone (cis isomer), 75 mL of methanol, and 1.8 g (17.0 mmol) of finely powdered, anhydrous Na_2CO_3 is placed in a 250-mL, round-bottomed flask equipped with a mechanical stirrer and heated under nitrogen at reflux for 8 hr. The resulting solution is concentrated under reduced pressure to a volume of 50 mL and partitioned between 100 mL of water and 100 mL of ether. The organic layer is washed with water and brine, dried over $MgSO_4$, and evaporated to give 3.1 g (91%) of crude product. This material, which shows only minor impurities by NMR spectroscopy, can be further purified by chromatography (silica gel/1 : 1 ether : hexane) (98% recovery) and bulb-to-bulb distillation (78°C/0.045 mm) (82% recovery).

TABLE I
IODOLACTONIZATION OF OLEFINIC ACIDS

	Trans : Cis Ratio [Yield (%)]	
Substrate	"Thermodynamic Control"	"Kinetic Control"
3-Methyl-4-pentenoic acid	10 : 1 (84)	1 : 3 (82)
4-Methyl-5-hexenoic acid	10 : 1 (77)	1 : 2.3 (83)
3-Methyl-5-hexenoic acid	1 : 6 (81)	1 : 3 (97)
2-Methyl-5-hexenoic acid	1.1 : 1 (68)	1.8 : 1 (78)
(2*RS*,4*SR*)-2,4-Dimethyl-5-hexenoic acid	20 : 1 (89)	3.5 : 1

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

trans AND cis ISOMERS OF 4,5-DIHYDRO-5-IODOMETHYL-4-PHENYL-2(3H)-FURANONE

$Na_2S_2O_3$

trans iodolactone

cis-iodolactone

HI_3

NaI_3

valerolactones

N,N-dimethylamides

iodolactones

cis isomer of 4,5-dihydro-5-iodomethyl-4-phenyl-2(3H)-furanone

(4RS,5RS)-4,5-dihydro-5-iodomethyl-4-phenyl-2(3H)-furanone (cis isomer)

(2RS,4SR)-2,4-Dimethyl-5-hexenoic acid

ethanol (64-17-5)

HCl (7647-01-0)

methanol (67-56-1)

ether (60-29-7)

acetonitrile (75-05-8)

chloroform (67-66-3)

$NaHCO_3$ (144-55-8)

propionic acid (79-09-4)

Na_2CO_3 (497-19-8)

oxygen (7782-44-7)

nitrogen (7727-37-9)

iodine (7553-56-2)

potassium hydroxide (1310-58-3)

hexanoic acid (142-62-1)

dichloromethane (75-09-2)

o-nitrophenol (88-75-5)

$MgSO_4$ (7487-88-9)

cinnamyl alcohol (104-54-1)

diisopropyl ether (108-20-3)

hexane (110-54-3)

triethyl orthoacetate (78-39-7)

3-Phenyl-4-pentenoic acid (5703-57-1)

4,5-Dihydro-5-iodomethyl-4-phenyl-2(3H)-furanone

3-Methyl-4-pentenoic acid

4-Methyl-5-hexenoic acid

3-Methyl-5-hexenoic acid

2-Methyl-5-hexenoic acid

Methyl (3RS,4RS)-4,5-epoxy-3-phenylpentanoate (107445-25-0)

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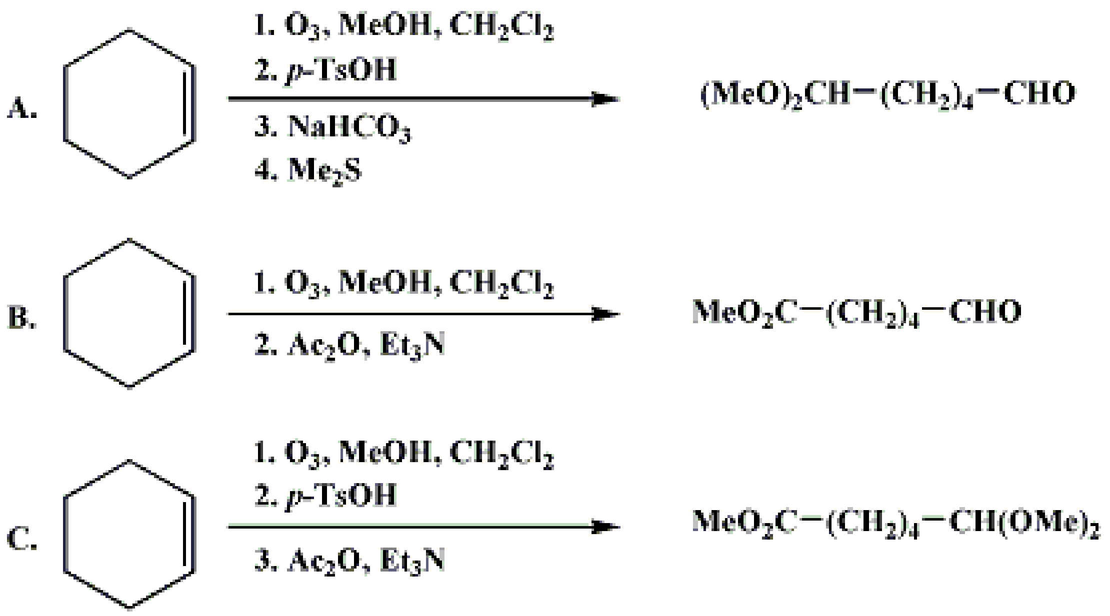
Organic Syntheses, CV 7, 168

OZONOLYTIC CLEAVAGE OF CYCLOHEXENE TO TERMINALLY DIFFERENTIATED PRODUCTS: METHYL 6-OXOHEXANOATE, 6,6-DIMETHOXYHEXANAL, METHYL 6,6-DIMETHOXYHEXANOATE

[Hexanoic acid, 6-oxo-, methyl ester; hexanal, 6,6-dimethoxy-; hexanoic acid, 6,6-dimethoxy-, methyl ester]



Submitted by Ronald E. Claus and Stuart L. Schreiber[1].
Checked by Nakcheol Jeong and Martin F. Semmelhack.

1. Procedure

Caution! The ozonolysis reaction produces peroxidic intermediates that can present a potential explosion hazard. Accordingly, it is recommended that the following experiments be carried out in a hood and behind a safety shield.

A. A 500 mL, three-necked, round-bottomed flask is fitted with a glass tube to admit ozone, a calcium chloride drying tube, a glass stopper, and a magnetic stirring bar and is charged with 6.161 g of cyclohexene (0.075 mol), 250 mL of dichloromethane, and 50 mL of methanol (Note 1). The flask is cooled to ca. −78°C (2-propanol–dry ice), and ozone (Note 2) is bubbled through the solution with stirring. When the solution turns blue, ozone addition is stopped. Nitrogen is passed through the solution until the blue color is discharged (Note 3) and then the cold bath is removed. The drying tube and ozone inlet are replaced with a stopper and rubber septum, and 1.215 g of *p*-toluenesulfonic acid (TsOH) (10% w/w) (Note 4) is added. The solution is allowed to

warm to room temperature as it stirs under an atmosphere of nitrogen for 90 min. Anhydrous sodium bicarbonate (2.147 g, 4 mol-equiv) is added to the flask and the mixture is stirred for 15 min, and then 12 mL of dimethyl sulfide (0.150 mol) (Note 5) is added. After being stirred for 12 hr, the heterogeneous mixture is concentrated to approximately 50 mL by rotary evaporation. Dichloromethane (100 mL) is added and the mixture is washed with 75 mL of water (Note 6). The aqueous layer is extracted with two more 100-mL portions of dichloromethane, and the combined organic layers are washed with 100 mL of water. After extracting the aqueous layer with 100 mL of dichloromethane, the organic layers are dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation. Short-path distillation of the crude product (Note 7) gives 8.2–8.4 g of 6,6-dimethoxyhexanal, 68–70%, bp 80–82°C/1.75 mm (Note 8) and (Note 9).

B. A round-bottomed flask equipped as in Step A is charged with 6.161 g of cyclohexene (0.075 mol), 250 mL of dichloromethane, 50 mL of methanol, and 2.0 g of anhydrous sodium bicarbonate (Note 1) and (Note 10). After the apparatus is cooled to ca. –78°C. ozone (Note 2) is bubbled through the solution as it is stirred. Ozone addition is stopped when the solution turns blue. Nitrogen is passed through the solution until the blue color is discharged (Note 3) and then the cold bath is removed. The solution is filtered into a l-L, round-bottomed flask and 80 mL of benzene is added. The volume is reduced to approximately 50 mL by rotary evaporation (Note 11). After dilution with 225 mL of dichloromethane the flask is cooled to 0°C and 16 mL of triethylamine (0.113 mol) and 21.24 mL of acetic anhydride (0.225 mol) are added via syringe (Note 12), and the solution is stirred under a nitrogen atmosphere for 15 min. The ice bath is removed and stirring is continued for 4 hr. The solution is washed with 150-mL portions of aqueous 0.1 *N* hydrochloric acid, aqueous 10% sodium hydroxide, and water. The organic layer is dried over anhydrous magnesium sulfate and filtered, and the solvent is removed by rotary evaporation. Short-path distillation of the crude product yields methyl 6-oxohexanoate, (7.0–7.8 g, 65–72%), bp 83–86°C/1.5 mm (Note 13).

C. Cyclohexene, 6.161 g (0.075 mol), is stirred with ozone in dichloromethane and methanol, as above. The resulting solution is treated with *p*-toluenesulfonic acid and subsequently neutralized with sodium bicarbonate, as described in Procedure A. The solution is filtered into a 1-L, round-bottomed flask, 80 mL of benzene is added, and the volume is reduced to approximately 50 mL by rotary evaporation (Note 11). Dilution with dichloromethane, treatment with triethylamine and acetic anhydride, and workup as described in Procedure B followed by short-path distillation provides methyl (6,6-dimethoxy)hexanoate, (11.2–11.8 g, 78–83%), bp 87–91°C/1.5 mm (Note 14).

2. Notes

1. Cyclohexene was purchased from Aldrich Chemical Company, Inc. and used

without purification. Dichloromethane was distilled from calcium hydride. Methanol was distilled from magnesium. The methanol–dichloromethane solvent combination may be replaced with 100% methanol (250 mL) with comparable results.

2. Ozone was produced by a Welsbach Corporation Ozonator, style T-709, with the voltages set at 100 V and oxygen pressure at 7 psi to give approximately 2% ozone concentration. The input oxygen was passed through a column of Hammond Drierite to ensure dryness.

3. The blue color indicates that cleavage of the olefin is complete. Excess ozone is removed to prevent overoxidation

4. Although the ozonolysis product exists in oligomeric form, the amount of acid used was calculated by assuming a theoretical yield of the corresponding monomeric aldehyde–methoxy hydroperoxide. *p*-Toluenesulfonic acid monohydrate, purchased from Aldrich Chemical Company, Inc., was not purified further.

5. The solution is neutralized to prevent bisacetal formation on subsequent reduction. Dimethyl sulfide was purchased from Aldrich Chemical Company, Inc. and used without purification.

6. An aqueous workup facilitates the removal of dimethyl sulfoxide produced by the reduction of the peroxide.

7. Typically 12.4–13.0 g of crude product is obtained after solvent removal. Material of this quality is satisfactory for most subsequent reactions.

8. The distilled product is similar in purity to the crude material. A small amount of dimethyl sulfoxide and minor impurities remain. Purification of the crude product by flash chromatography (1:1 ether:hexanes) affords 6,6-dimethoxyhexanal that is pure by ^{1}H and ^{13}C NMR in 90–95% yield.

9. The following spectral properties of the product were observed: ^{1}H NMR ($CDCl_3$), δ: 1.4–1.7 (m, 6 H), 2.4 (t, 2 H, *J* = 7), 3.3 (s, 6 H), 4.3 (t, 1 H, *J* = 5.3), 9.7 (t, 1 H, *J* = 2.5). ^{13}C NMR ($CDCl_3$), δ: 21.4, 23.7, 31.8, 43.2, 52.1, 103.9, 201.6. IR (film), cm^{-1}: 2700, 1720, 1100. MS, *m/e* (rel. %): 113(95), 57 (100).

10. Sodium bicarbonate serves to buffer the solution and prevent acetal formation.

11. Benzene is added to facilitate the removal of methanol. Although an aqueous wash will remove the methanol, azeotropic removal with benzene is simpler and provides a slightly higher yield.

12. Triethylamine purchased from Aldrich Chemical Company, Inc., was distilled from calcium hydride. Acetic anhydride as supplied by Mallinckrodt, Inc. was distilled from phosphorus pentoxide.

13. The following spectral properties were observed: ^{1}H NMR ($CDCl_3$), δ: 1.5–1.7 (m, 4 H), 2.2–2.4 (m, 4 H), 3.6 (s, 3 H), 9.7 (t, 1 H, *J* = 2.5). ^{13}C NMR ($CDCl_3$), δ: 21.1, 24.0, 33.2, 42.9, 51.0, 173.1, 201.4. IR (film), cm^{-1}: 2700, 1720, 1150. MS: *m/e* (rel. %): 159(1), 29(3), 75(100).

14. The following spectral properties were observed: ^{1}H NMR ($CDCl_3$), δ: 1.0–

1.6 (m, 6 H), 2.15 (t, 2 H, *J* = 8), 3.2 (s, 6 H), 3.6 (s, 3 H), 4.25 (t, 1 H, *J* = 5.5). ^{13}C NMR ($CDCl_3$), δ: 23.7, 24.3, 31.8, 33.4, 50.7, 52.0, 103.9, 173.1. IR (film), cm^{-1}: 1735, 1050, MS: *m/e* (rel. %): 159(10), 127(30), 75(100).

3. Discussion

This procedure illustrates a recently published method for the ozonolytic cleavage of cycloalkenes to terminally differentiated products.[2] Other examples of the unsymmetrical cleavage of olefins have been reported.[3] In addition, the title compounds have been prepared by other routes. Methyl 6-oxohexanoate has been synthesized from the acid chloride of the half-ester of adipic acid.[5] It has also been prepared from ε-caprolactone by methanolysis followed by oxidation.[5] Lead tetraacetate treatment of 2-hydroxycyclohexanone in methanol and subsequent acidification produces methyl 6,6-dimethoxyhexanoate.[6] A three-step route from cyclohexanone enol acetate (ozonolysis in methanol and reaction with dimethyl sulfide, then with trimethyl orthoformate) has been reported.[4] 6,6-Dimethoxyhexanal has been made by a multistep route.[7].

The present method utilizes commercially available cycloalkenes and proceeds under mild conditions to provide synthetically useful products. The method was shown to be general in the series of cycloalkenes investigated. Yields range from moderate (cyclopentene) to excellent (higher homologues).

The ozonolytic cleavage of cycloalkenes in the presence of methanol produces a chain with an aldehyde and a methoxy hydroperoxide group at the termini.[8] The unsymmetrical ozonolysis product is manipulated in several ways. Dehydration of the methoxy hydroperoxide group affords an ester (Step B). Alternatively, the aldehyde moiety is protected as an acetal. Under these conditions, the methoxy hydroperoxide is reduced[9] (Procedure A) or dehydrated (Step C).

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 18

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

p-toluenesulfonic acid (TsOH)

ACETAL (105-57-7)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

methanol (67-56-1)

acetic anhydride (108-24-7)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

magnesium (7439-95-4)

Adipic acid (124-04-9)

Cyclohexene (110-83-8)

oxygen (7782-44-7)

nitrogen (7727-37-9)

dichloromethane (75-09-2)

ozone (10028-15-6)

magnesium sulfate (7487-88-9)

Cyclopentene (142-29-0)

dimethyl sulfide (75-18-3)

dimethyl sulfoxide (67-68-5)

triethylamine (121-44-8)

calcium hydride (7789-78-8)

2-hydroxycyclohexanone

p-toluenesulfonic acid (104-15-4)

trimethyl orthoformate (149-73-5)

Methyl 6-oxohexanoate, Hexanoic acid, 6-oxo-, methyl ester (6654-36-0)

6,6-Dimethoxyhexanal, hexanal, 6,6-dimethoxy- (55489-11-7)

hexanoic acid, 6,6-dimethoxy-, methyl ester, methyl (6,6-dimethoxy)hexanoate, Methyl 6,6-dimethoxyhexanoate (25176-55-0)

ε-caprolactone (502-44-3)

cyclohexanone enol acetate

phosphorus pentoxide (1314-56-3)

p-toluenesulfonic acid monohydrate (6192-52-5)

lead tetraacetate

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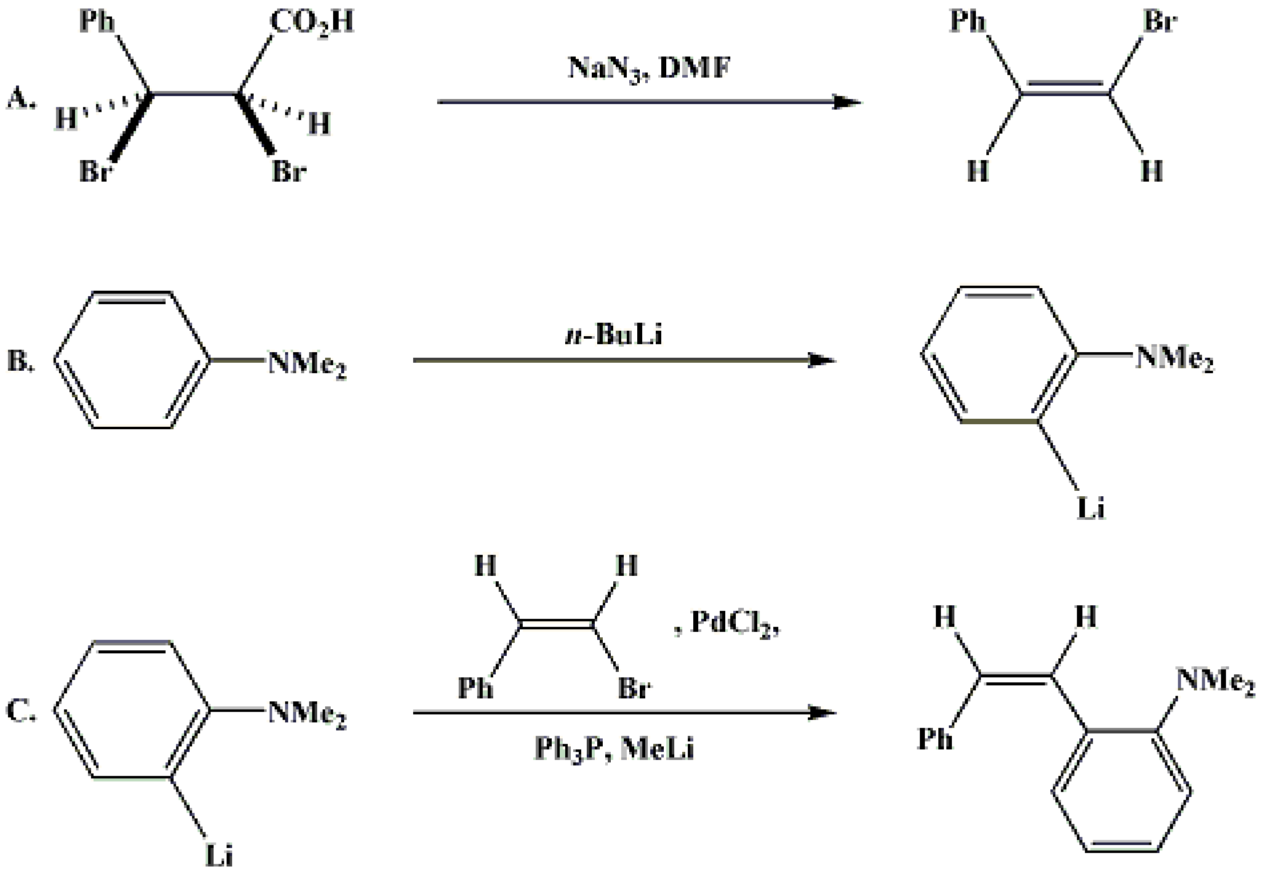
PALLADIUM-PHOSPHINE-COMPLEX-CATALYZED REACTION OF ORGANOLITHIUM COMPOUNDS AND ALKENYL HALIDES: (*Z*)-β-[2-(*N*,*N*-DIMETHYLAMINO)PHENYL]STYRENE

[Benzenamine, *N*,*N*-dimethyl-2-(2-phenylethenyl)-, (*Z*)-]



Submitted by Shun-Ichi Murahashi, Takeshi Naota, and Yoshio Tanigawa[1].
Checked by Joseph Fortunak and Ian Fleming.

1. Procedure

Caution! The reaction described in Section (Step) A (Note 1) should be carried out in a well-ventilated hood because bromine is toxic.

A. *(Z)-β-Bromostyrene.* In a 1-L, round-bottomed flask equipped with a magnetic stirring bar are placed 30.8 g (0.100 mol) of *erythro*-α,β-dibromo-β-phenylpropionic acid (Note 1), 13.0 g (0.200 mol) of sodium azide (Note 2), and 500 mL of dry *N*,*N*-dimethylformamide (Note 3). The reaction mixture is stirred at room temperature for 8 hr and poured into a mixture of 300 mL of ether and 300 mL of water. The organic layer is separated, washed with three 100-mL portions of water, dried over magnesium

sulfate, and filtered. After evaporation of the filtrate with a rotary evaporator, the residual liquid is distilled under reduced pressure, giving 13.5–13.9 g (74–76%) of (*Z*)-β-bromostyrene, bp 54–56°C (1.5 mm) (Note 4).

B. *2-(N,N-Dimethylamino)phenyllithium.* A 100-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar and a reflux condenser connected to a nitrogen-inlet tube is capped with serum stoppers and flushed with nitrogen. The flask is charged with 18.2 g (0.150 mol) of *N,N*-dimethylaniline (Note 5) and 33.4 mL (0.050 mol) of a 1.50 *M* solution of butyllithium in hexane (Note 6). While a continuous positive nitrogen pressure is maintained, the solution is heated at reflux (in a 90–95°C bath) with stirring for 20 hr and then cooled to room temperature (Note 7).

C. *(Z)-β-[2-(N,N-Dimethylamino)phenyl]styrene.* A 1-L. three-necked, round-bottomed flask equipped with a magnetic stirring bar, a reflux condenser connected to a nitrogen-inlet tube, and a 300-mL, pressure-equalizing dropping funnel is capped with serum stoppers. The flask is flushed with nitrogen and charged with 0.433 g (0.0025 mol) of palladium chloride (Note 8), 2.62 g (0.010 mol) of triphenylphosphine (Note 9) and 300 mL of benzene (Note 10). While a continuous positive nitrogen pressure is maintained, the mixture is stirred at gentle reflux for 30 min, and then 4.25 mL (0.0060 mol) of a 1.41 *M* solution of methyllithium in ether (Note 11) is added with a syringe. After an additional 10 min at reflux, 9.15 g (0.050 mol) of (*Z*)-β-bromostyrene as prepared in Section A is added in one portion with syringe, and the mixture is heated at reflux for 10 min. The solution of 2-(*N,N*-dimethylamino)phenyllithium prepared as described in Section B is transferred to the dropping funnel with a syringe and diluted by adding 150 mL of benzene (Note 10) and (Note 12). The resulting solution is then added dropwise to the mixture with stirring at reflux over a period of 30 min (Note 13). After additional stirring for 10 min, the resulting red solution is cooled to room temperature with the help of an ice bath and quenched by adding 100 mL of saturated aqueous ammonium chloride. The organic layer is separated, washed successively with 100 mL of water and 100 mL of saturated aqueous sodium chloride, and then dried over magnesium sulfate and filtered. The solvent is evaporated with a rotary evaporator, and the residue is distilled under reduced pressure to give a forerun (ca. 11 g) of excess *N,N*-dimethylaniline, bp 31–51°C (1 mm), followed by 7.4–7.5 g (66–67%) of (*Z*)-β-[2-(*N,N*-dimethylamino)phenyl]styrene, bp 90.0–92.0°C (0.035 mm), 82–84°C (0.01 mm), as a pale-yellow liquid (Note 14).

2. Notes

1. *erythro*-α,β-Dibromo-β-phenylpropionic acid is prepared from *trans*-cinnamic acid (mp 133–134°C) (Nakarai Chemicals, Japan) by the method used for ethyl α,β-dibromo-β-phenylpropionate (Abbott T. W.; Althousen, D. *Org. Synth., Coll. Vol. II* **1943**, 270) in 83% yield, mp 199–200°C. The checkers used benzene (400 mL per mol) in place of the carbon tetrachloride, because the

mixture was then easier to stir and the reaction was more reproducible. The yield before purification was 89% (mp 174–191°C); the yield after recrystallization was 81% (mp 198–199°C). Crude material could be used without appreciable loss of yield.

2. Sodium azide from Wako Pure Chemical Ind., Japan, was used without purification.

3. *N,N*-Dimethylformamide is distilled over calcium hydride.

4. Gas chromatographic analysis of the distillate (10% PEG-20M on 60–80-mesh, Celite 545 AW, 1-m × 4-mm column, column temperature 100–220°C, injection temperature 200°C) shows that the product is 100% isomerically pure. The spectral properties of the (*Z*)-β-bromostyrene are as follows: IR (neat) cm^{-1}: strong absorptions at 3095, 3040, 1620, 1500, 1450, 1333, 1032, 930, 920, 830, 770, and 700; ^{1}H NMR ($CHCl_3$) δ: 6.43 (doublet, 1 H, *J* = 8, PhCH=C), 7.08 (doublet, 1 H, *J* = 8, PhC=CHBr), 7.22–7.85 (multiplet, 5 H, aromatic). The checkers also purified the residual oil before distillation by filtration in 250 mL of pentane through three times its weight of silica gel (70–230-mesh) followed by evaporation. The yield before distillation was then reproducibly 84%, distillation was avoided, and the next step proceeded with undiminished yield.

5. *N,N*-Dimethylaniline from Nakarai Chemicals was dried over calcium hydride and freshly distilled. Three molar equivalents of *N,N*-dimethylaniline are used to achieve complete conversion of the butyllithium, because in the present particular case free butyllithium, if present, causes the isomerization of the (*Z*)-alkene to the (*E*)-isomer.

6. A solution of butyllithium in hexane was obtained from Aldrich Chemical Company, Inc. Before use the solution is titrated with a 1 *M* solution of 2-butanol in xylene according to the procedure of Watson and Eastham[2] (see Gall, M.; House, H. O. *Org. Synth. Coll. Vol. VI* **1988**, 121) with 2,2'-biquinoline as indicator.

7. The resulting cloudy, yellowish orange solution should be used within 3–4 hr.

8. Palladium chloride from Inuisho Precious Metal Company, Japan, was used without purification.

9. Triphenylphosphine from Nakarai Chemicals, Japan, was used without purification.

10. Benzene is distilled over benzophenone ketyl and stored under a nitrogen atmosphere.

11. A solution of methyllithium in ether is prepared from lithium wire and methyl bromide according to the literature procedure[3] and titrated by the same method as (Note 6). The checkers used 1.1 *M* methyllithium from Aldrich Chemical Co., Inc.

12. Without the dilution, (*Z*)-1,4-diphenyl-1-buten-3-yne is detected, apparently formed from the cross-coupling with phenylacetylide, derived from lithiation of β-bromostyrene, followed by E2cB elimination or Fritsch–Butlenberg–Wiechell-type rearrangement.

13. Prolonged reaction time causes the isomerization of (*Z*)-β-[2-(*N,N*-

dimethylamino)phenyl]styrene to the (*E*)-isomer.

14. Gas chromatographic analysis of the product (5% silicone SE 30 on 80–100-mesh Chromosorb W AB, 0.5-m × 4-mm column, column temperature 100–250°C, injection temperature 180°C) shows that the product is at least 98% (*Z*)-isomer. The spectral properties of the (*Z*)-alkene are as follows; IR (neat) cm^{-1}: strong absorptions at 3070, 3025, 2950, 2870, 2835, 2780, 1600, 1490, 1450, 1320, 1190, 1160, 1140, 1100, 1050, 950, 780, 750, and 690; ^{1}H NMR (CCl_4) δ: 2.76 (singlet, 6 H, CH_3-N), 6.38 (doublet, 1 H, *J* = 12.3, PhC=CH), 6.63 (doublet, 1 H, *J* = 12.3, PhCH=C), 6.50–7.30 (multiplet, 9 H, aromatic).

3. Discussion

The starting materials, (*Z*)-β-bromostyrene[4] and 2-(*N*,*N*-dimethylamino)phenyllithium[5] have been prepared in satisfactory yields by known procedures after slight modifications. The azide procedure[4] gives higher stereospecificity than the earlier procedure using sodium bicarbonate.[6]

This procedure illustrates a general method for the preparation of alkenes from the palladium(O)-catalyzed reaction of vinyl halides with organolithium compounds,[7] which can be prepared by various methods, including direct regioselective lithiation of hydrocarbons.[8] The method is simple and has been used to prepare a variety of alkenes stereoselectively. Similar stoichiometric organocopper reactions sometimes proceed in a nonstereoselective manner[9] and in low yields.[10] Nickel catalysts can be used efficiently for the reaction of alkenyl halides with Grignard reagents but not with organolithium compounds.[11] Highly reactive zerovalent palladium catalyst can be directly generated in situ from $PdCl_2$–PPh_3–CH_3Li. Tetrakis(triphenylphosphine)palladium can be used alternatively. Grignard reagents undergo the reaction as well with vinyl halides. Organolithium compounds require the limited reaction conditions under which the elimination of alkenyl halides producing lithium acetylides is slower than the cross-coupling reaction.[7] The choice of benzene as a solvent and the dilution of the solution satisfy the above conditions. The palladium-catalyzed alkylation of aryl halides with organolithium compounds proceeds efficiently without such difficulty.[7] Similar reactions with lithium thiolates give the corresponding alkenyl sulfides.[7] Representative reactions of organolithium compounds are shown in Table I.

This preparation is referenced from:

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TABLE I
Palladium-CatalyzedReactionofOrganolithiumCompoundsandAlkenylHalides[a]

Halides	Products	Ratio	Yield (%)
(Z)-ClCH=CHBr			85
(E)-ClCH=CHCl			94
			66–67
(E)-ClCH=CHSC			
(Z)-ClCH=CHSC			
(E)-ClCH=CHBr			85
			89

[a] The reaction was carried out on a 1.0–1.5-mmol scale.

[b] Determined by gas chromatography.

[c] Tetrakis(triphenylphosphine)palladium was used.

[d] Isolated yield.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

benzophenone ketyl

erythro-α,β-Dibromo-β-phenylpropionic acid

(Z)-$C_6H_5CH=CHBr$

CH_3Li

C_4H_9Li

C_6H_5SLi

(Z)-$C_6H_5CH=CHSC_6H_5$

C_2H_5SLi

(Z)-$C_6H_5CH=CHSC_2H_5$

(E)-$C_6H_5CH=CHBr$

Benzene (71-43-2)

ether (60-29-7)

ammonium chloride (12125-02-9)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

bromine (7726-95-6)

carbon tetrachloride (56-23-5)

nitrogen (7727-37-9)

nickel (7440-02-0)

palladium (7440-05-3)

methyl bromide (74-83-9)

xylene (106-42-3)

N,N-dimethylaniline (121-69-7)

Pentane (109-66-0)

sodium azide (26628-22-8)

β-bromostyrene (103-64-0)

palladium chloride, palladium dichloride

Lithium wire (7439-93-2)

magnesium sulfate (7487-88-9)

Ethyl α,β-dibromo-β-phenylpropionate (5464-70-0)

butyllithium (109-72-8)

N,N-dimethylformamide (68-12-2)

hexane (110-54-3)

Methyllithium (917-54-4)

calcium hydride (7789-78-8)

triphenylphosphine, triphenyl phosphine (603-35-0)

2-Butanol (78-92-2)

(Z)-β-Bromostyrene (103-64-0)

phenylacetylide

Tetrakis(triphenylphosphine)palladium (14221-01-3)

2,2'-biquinoline (119-91-5)

(Z)-β-[2-(N,N-Dimethylamino)phenyl]styrene, Benzenamine, N,N-dimethyl-2-(2-phenylethenyl)-, (Z)- (70197-43-2)

2-(N,N-Dimethylamino)phenyllithium

trans-cinnamic acid (140-10-3)

(Z)-1,4-diphenyl-1-buten-3-yne

cTetrakis-(triphenylphosphine)palladium

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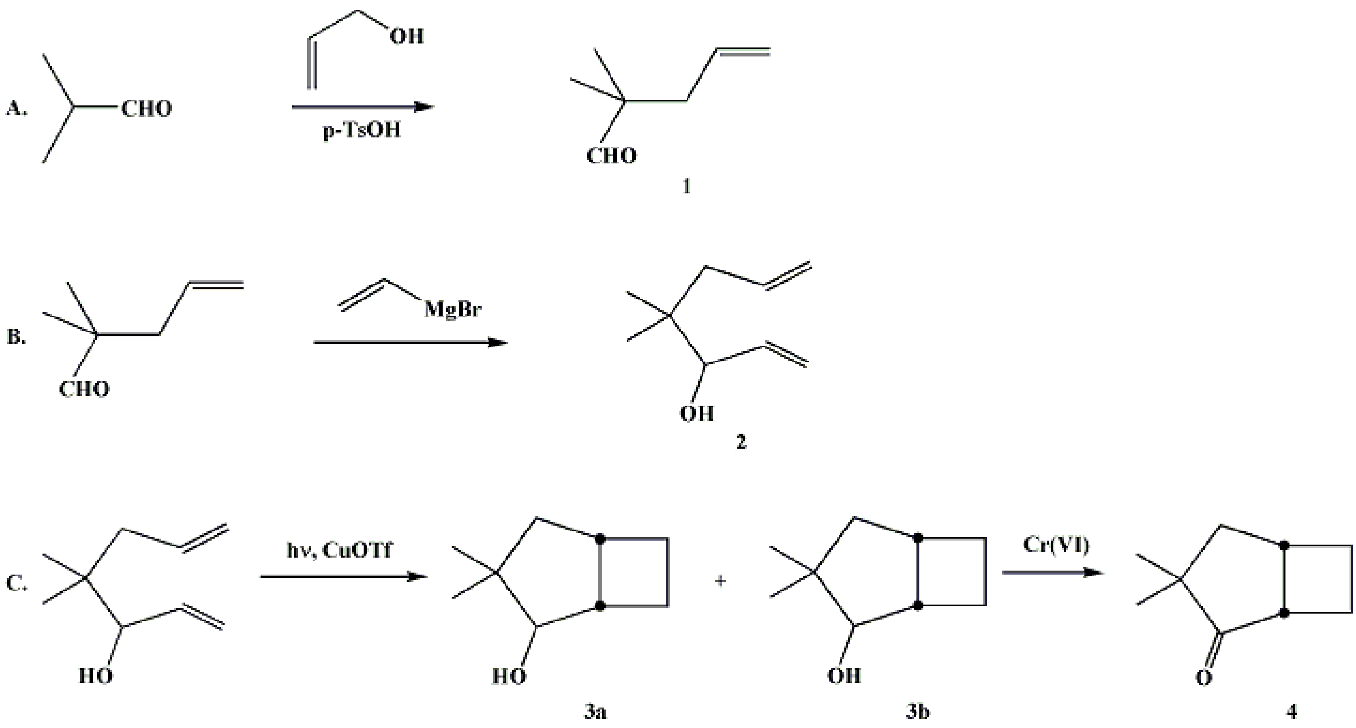
COPPER(I)-CATALYZED PHOTOCYCLOADDITION: 3,3-DIMETHYL-*cis*-BICYCLO [3.2.0]HEPTAN-2-ONE

[Bicyclo[3.2.0]heptan-2-one, 3,3-dimethyl-]



Submitted by Robert G. Salomon and Subrata Ghosh[1].
Checked by Daniel K. Jackson and Richard E. Benson.

1. Procedure

A. *2,2-Dimethyl-4-pentenal.* In a 500-mL, one-necked, round-bottomed flask that contains a magnetic stirring bar are placed 108 g (1.5 mol) of isobutyraldehyde (Note 1), 58 g (1.0 mol) of allyl alcohol (Note 1), 230 mL of *p*-cymene (Note 1), and 0.4 g (2 mmol) of *p*-toluenesulfonic acid monohydrate (Note 1). The mixture is heated with a mantle with stirring for 32 hr under a 50-cm fractionating column packed with 6-mm glass beads and topped by a Dean-Stark trap. The reaction mixture is then distilled through the packed column. The fraction that boils at 120–126°C is collected. The yield is 86.0–87.3 g (77–78%) of 2,2-dimethyl-4-pentenal (**1**) as a clear, colorless oil, n_D^{25} 1.4216 (Note 2).

B. *4,4-Dimethyl-1,6-heptadien-3-ol.* In a 1-L, three-necked, round-bottomed flask, fitted with mechanical stirrer, 500-mL pressure-equalizing addition funnel, and condenser topped with a gas inlet for maintaining an atmosphere of dry nitrogen, is placed 17 g (0.7 g-atom) of magnesium turnings (Note 3). The system is flushed with nitrogen, and methanol maintained at −20°C is circulated through the condenser (Note 4). From a solution of 70 g (0.65 mol) of vinyl bromide (Note 5) in 400 mL of tetrahydrofuran (Note 6), a 50-mL quantity is added by means of the addition funnel, and the resulting mixture is stirred mechanically. After a few minutes an exothermic reaction ensues, which subsides after several minutes of vigorous boiling (Note 7). The remainder of the vinyl bromide solution is added at such a rate as to maintain a gentle reflux. After stirring at room temperature for 12 hr, the resulting mixture is cooled with an ice–water bath, and 62 g (0.55 mol) of 2,2-dimethyl-4-pentenal (**1**) is added dropwise over 25–30 min through the addition funnel, which is then rinsed with 10 mL of dry tetrahydrofuran. The resulting mixture is stirred for 1 hr at 23°C and then poured into a mixture of 1 kg of ice, 200 mL of concentrated hydrochloric acid, and 400 mL of water. The resulting mixture is extracted with three 500-mL portions of ether. The combined extracts are washed successively with 400 mL of water, 400 mL of saturated aqueous sodium bicarbonate, and 400 mL of saturated aqueous sodium chloride and then dried over anhydrous sodium sulfate. The drying agent is removed by filtration and the ether is removed with a rotary evaporator. Distillation of the product through a 15-cm vacuum-jacketed Vigreux column gives 63.4–63.8 g (82–83% yield) of 4,4-dimethyl-1,6-heptadien-3-ol (**2**), bp 76–79°C (20 mm), n_D^{24} 1.4562 (Note 8).

C. *3,3-Dimethyl-cis-bicyclo[3.2.0]heptan-2-ol.* A 25-mL test tube is charged with 0.3–0.4 g (0.6–0.8 mmol) of bis(copper trifluoromethanesulfonate)benzene complex (Note 9) and sealed with a rubber septum under an atmosphere of dry nitrogen. A solution of 5 mL (4.3 g, 0.031 mol) of 4,4-dimethyl-1,6-heptadien-3-ol in 10 mL of ether (Note 10) is added by means of a syringe. The resulting solution is poured (Note 11) into a nitrogen-flushed Pyrex 250-mL annular reactor fitted with a magnetic stirrer, an internal concentric water-jacketed quartz immersion well, and a water-cooled reflux condenser topped with a gas inlet for maintaining an atmosphere of dry nitrogen. An additional 20 mL (17.4 g, 0.124 mol) of the hydroxydiene **2** in 200 mL of dry ether is added. The resulting solution is

stirred and irradiated for 15 hr with a 450-W medium-pressure Hanovia mercury are (Note 12) that is suspended in the immersion well. At the end of that time an opaque film of copper is wiped from the immersion well, and irradiation is then continued for an additional 7 hr. The resulting solution is shaken in a separatory funnel with a mixture of 100 g of ice and 100 mL of concentrated aqueous ammonium hydroxide. The organic phase is separated and the aqueous phase is extracted with 100 mL of ether. The organic phases are combined and washed with 100 mL of saturated aqueous sodium chloride and dried over anhydrous sodium sulfate. The solvent is removed by distillation using a rotary evaporator and the product is distilled through a 15-cm vacuum-jacketed Vigreux column to give 19.0–19.9 g (88–92% yield) of 3,3-dimethyl-*cis*-bicyclo[3.2.0]heptan-2-ol (**3**), bp 80–84°C (12 mm), n_D^{25} 1.4761–1.4783 (Note 13).

D. *3,3-Dimethyl-cis-bicyclo[3.2.0]heptan-2-one*. In a 500-mL Erlenmeyer flask containing a magnetic stirring bar is placed 35.1 g (0.25 mol) of 3,3-dimethyl-*cis*-2-bicyclo[3.2.0]heptanol and 200 mL of acetone (Note 14). The solution is cooled with an ice-water bath while 100 mL of 2.7 *M* Jones reagent (Note 15) is added in small portions over 15 min with vigorous stirring (Note 16). The ice–water bath is removed and the reaction mixture is stirred at 5–20°C for 2 hr. Then 400 mL of saturated aqueous sodium chloride is added, and the resulting mixture is extracted with three 500-mL portions of ether. The extractions are combined and washed successively with 400 mL of saturated aqueous sodium chloride and 200 mL of saturated aqueous sodium bicarbonate. The solvent is removed by means of a rotary evaporator, and the resulting product is transferred to a separatory funnel and separated from the water. The aqueous layer is extracted with 50 mL of ether. The product and the ether layer are combined and dried over anhydrous sodium sulfate. The ether is removed by distillation using a rotary evaporator and the product is distilled through a 15-cm vacuum-jacketed Vigreux column to give 28.7–32.2 g (83–93% yield) of 3,3-dimethyl-*cis*-bicyclo[3.2.0]heptan-2-one (**4**), bp 72–75°C (12 mm), n_D^{20} 1.4622 (Note 17).

2. Notes

1. Isobutyraldehyde, allyl alcohol, *p*-cymene, and *p*-toluenesulfonic acid monohydrate were purchased from Aldrich Chemical Company, Inc., and used as received.
2. The submitters state that the distilled product was about 97% pure as shown by GLC analysis on a 6.4-mm × 1.4-m column packed with 15% FFAP on Chromosorb W, 60–80 mesh, and operated at 140°C. The retention time is about 1.40 min. Two minor impurities with retention times of about 0.95 and 1.15 min were detected in roughly equal amounts. The product has the following spectral properties: IR (neat) cm^{-1}: 2965 (m), 2925 (m), 1725 (vs), 1465 (m), and 915 (m), together with numerous weaker absorption bands; ^1H NMR ($CDCl_3$) δ: 1.04 (s, 6 H), 2.22 (d, 2 H, *J* = 7.0), 4.9–5.3 (m, 2 H), 5.4–6.2 (m, 1 H), 9.40 (s, 1 H).
3. Reagent available from Fisher Scientific Company was used.
4. A Neslab ULT-80 refrigerated circulating bath was used. Alternatively, a Dewar condenser cooled with acetone–dry ice can be used.
5. Vinyl bromide, available from Aldrich Chemical Company, Inc., was used as received.
6. Tetrahydrofuran, anhydrous, 99.9% (water content <0.006%), was purchased from Aldrich Chemical Company, Inc., and used as received. The vinyl bromide solution was prepared in a 500-mL, round-bottomed flask fitted with a glass stopper. The stoppered flask containing the tetrahydrofuran was chilled to about 5°C and weighed. The vinyl bromide, also chilled to about 5°C, was rapidly poured into the tetrahydrofuran until the desired amount had been added. The flask was stoppered, the contents mixed by shaking, allowed to warm to about 16°C, and then added to the pressure-equalizing addition funnel.
7. The checkers found it necessary to initiate the reaction with a crystal of iodine.
8. The submitters state that the purity of the product is greater than 98% by gas chromatographic analysis on a 6.4-mm × 1.4-m column packed with 15% FFAP on Chromosorb W, 60–80 mesh, and operated at 140°C. The retention time is about 4.7 min. An impurity with a retention time of about 2.9 min was detected. The product has the following spectral properties: ^1H NMR ($CDCl_3$) δ: 0.84 (s, 3 H), 0.88, (s, 3 H), 1.80–2.30 (m, 2 H), 2.69 (s, 1 H), 3.78 (d, 1 H, *J* = 6), 4.87–5.33 (m, 4 H), 5.57–6.13 (m, 2 H).
9. The copper complex is available from Strem Chemicals, Inc., under the name "cuprous triflate" (benzene complex). The checkers recommend handling the material in a dry box because of its high sensitivity to moisture and air.
10. Anhydrous ether was distilled from lithium aluminum hydride under dry nitrogen immediately before use.
11. The submitters state that the copper(I) triflate is quite air-stable in solution in the presence of the allylic alcohol.
12. The checkers recommend the use of a relatively new are lamp. Substantially higher conversions were obtained with a new lamp because of an apparent bathochromic shift in the frequency of the light emitted as the lamp ages, thus lessening the intensity of light in the important absorption region for the reaction.
13. The submitters state that the purity of the product is greater than 97% by GLC analysis on a 6.4-mm × 1.4-m column packed with 15% FFAP on Chromosorb W, 60–80 mesh, and operated at 140°C. The retention time is about 8.0 min. The only impurity is unreacted diene with a retention time of about 4.7 min. The product is an epimeric mixture. TLC analysis by the submitters on 0.25-mm silica gel with 20% ethyl acetate in hexane shows major (>90%) and minor (<10%) epimers with R_f 0.32 and 0.23, respectively. The epimers are separable by column chromatography on silica gel with ethyl acetate–hexane mixtures as eluting solvents. A 3.1-g portion of the distilled isomer mixture was chromatographed by the checkers on 475 g of silica gel (Silica Woelm TSC—activity III/30 mm) using 5% ethyl acetate–hexane as eluent. The elution proceeded as follows: 1520 mL, nil; 1440 mL, 2.7 g of endo isomer; 1400 mL, nil; 2010 mL, 0.20 g of exo isomer. Analysis of the ^1H NMR spectrum of the distilled product confirms that the reaction is greater than 90% stereoselective in favor of the endo epimer. The major epimer, 3,3-dimethyl-*endo*-*cis*-bicyclo[3.2.0]heptan-2-ol, has the following spectral properties: ^1H NMR ($CDCl_3$) δ: 0.81 (s, 3 H), 1.13 (s, 3 H), 1.4–3.2 (m, 9 H), 3.66 (d, 1 H), *J* = 6.7; ^{13}CMR ($CDCl_3$) δ: 16.3 (t), 22.5 (q, CH_3), 26.0 (t), 27.8 (q, CH_3), 36.0 (d), 42.8 (d), 45.5 (t), 45.8 (s, C-3), 80.9 (d, C-2). The minor epimer, 3,3-dimethyl-*exo*-*cis*-bicyclo[3.2.0]heptan-2-ol, has the following spectral properties: ^1H NMR ($CDCl_3$) δ: 0.77 (s, 3 H), 1.08 (s, 3 H), 1.2–2.9 (m, 9 H), 3.80 (d, 1 H, *J* = 4.6); ^{13}CMR ($CDCl_3$) δ: 20.7 (q, CH_3), 24.0 (t), 26.5 (q, CH_3), 27.1 (t), 34.6 (d), 45.6 (s, C-3), 45.8 (d), 46.7 (t), 88.7 (d, C-2).
14. Certified ACS-grade acetone purchased from Fisher Scientific Company was used as received.
15. Eisenbraun, E. J. *Org. Synth., Coll. Vol. V* **1973**, 310–314.

16. Initially a gummy green precipitate is formed that is difficult to stir magnetically. Eventually, however, the inorganic by-products become more fluid. The use of a mechanical stirrer may be desirable.
17. The submitters state that the distilled product is <98% pure by GLC on a 6.4-mm × 1.4-m column packed with 15% FFAP on Chromosorb W, 60–80 mesh, operated at 140°C. The relative retention time is 2.3 versus an unidentified impurity at 1.0. The distilled product has the following spectral properties: IR (neat) cm^{-1}: 2960 (vs), 2940 (vs) and 1735 (vs), and other weaker bands. ^{1}H NMR (CCl_4) δ: 0.92 (s, 3 H), 1.12 (s, 3 H), 1.4–3.0 (m, 8 H); ^{13}CMR ($CDCl_3$), δ: 22.7, 24.1, 25.6, 26.4, 31.0, 43.9, 44.2, 48.4, 224.7.

3. Discussion

This procedure illustrates a general method for the preparation of 2-hydroxybicyclo[3.2.0]heptanes by copper(I)-catalyzed photobicyclization of 3-hydroxy-1,6-heptadienes[2] and a general route to the requisite dienes from allyl alcohols by conversion to 4-pentenals and treatment of the latter with vinyl Grignard reagents.

Compound **1**, 2,2-dimethyl-4-pentenal, has been prepared by the Claisen rearrangement route[3] described above and by reaction of isobutyraldehyde with allyl chloride in the presence of aqueous sodium hydroxide and a phase-transfer catalyst.[4] Both routes are applicable to the synthesis of a variety of substituted 4-pentenals.

cis-Bicyclo[3.2.0]heptan-2-ols have been prepared by reduction[5] of the corresponding *cis*-bicyclo[3.2.0]-heptan-2-ones, which have been prepared by photocycloaddition of alkenes with 2-cyclopentenones.[6] The synthetic strategy of the present procedure is complementary.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 208

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

bis(copper trifluoromethanesulfonate)benzene complex

2-hydroxybicyclo[3.2.0]heptanes

3-hydroxy-1,6-heptadienes

allyl alcohols

cis-Bicyclo[3.2.0]heptan-2-ols

cis-bicyclo[3.2.0]-heptan-2-ones

2-cyclopentenones

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

magnesium turnings (7439-95-4)

sodium chloride (7647-14-5)

ethyl (2025-56-1)

Allyl alcohol (107-18-6)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

allyl chloride (107-05-1)

copper (7440-50-8)

iodine (7553-56-2)

acetone (67-64-1)

ammonium hydroxide (1336-21-6)

p-cymene (99-87-6)

isobutyraldehyde (78-84-2)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

hexane (110-54-3)

vinyl bromide (593-60-2)

$^{24}_{D}$ (94-75-7)

copper(I) triflate, cuprous triflate

Bicyclo[3.2.0]heptan-2-one, 3,3-dimethyl- (71221-70-0)

2,2-Dimethyl-4-pentenal (5497-67-6)

4,4-Dimethyl-1,6-heptadien-3-ol (58144-16-4)

p-toluenesulfonic acid monohydrate (6192-52-5)

3,3-Dimethyl-cis-bicyclo[3.2.0]heptan-2-one

3,3-Dimethyl-cis-bicyclo[3.2.0]heptan-2-ol, 3,3-dimethyl-cis-2-bicyclo[3.2.0]heptanol, 3,3-dimethyl-endo-cis-bicyclo[3.2.0]heptan-2-ol, 3,3-dimethyl-exo-cis-bicyclo[3.2.0]heptan-2-ol (71221-67-5)

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Organic Syntheses, CV 7, 181

ANODIC OXIDATION OF ACIDS: DIMETHYL DECANEDIOATE

[Decanedioic acid, dimethyl ester]

Submitted by D. A. White[1]
Checked by Ronald F. Sieloff and Carl R. Johnson.

1. Procedure

The electrode assembly (Note 1) is constructed; the platinum electrodes are positioned vertically, parallel, and about 5 mm apart by careful bending of the lower platinum wire connections.

To a 500-mL, round-bottomed flask having a central 34/45 standard taper neck and two 24/40 standard taper necks are added 120 g (0.75 mol) of methyl hydrogen hexanedioate (Note 2), 250 mL of methanol, 4.1 g (0.075 mol) of sodium methoxide, 10 mL of pyridine, and a magnetic stirring bar. The electrode assembly is inserted so that the platinum electrodes are immersed in the solution. A thermometer and reflux water condenser are attached. The mixture is heated to 60°C and stirred until the sodium methoxide dissolves.

The mixture is electrolyzed with a constant current of 1.1 A (Note 3) until GLC analysis (Note 4) of the solution shows the absence of the peak due to methyl hydrogen hexanedioate. This requires about 23 hr; electrolysis is continued for an additional 2.5 hr at the same current (Note 5). Throughout the electrolysis the reaction mixture is maintained at 62–65°C by passage of the current. After about 1 hr of electrolysis, when conditions are stabilized, the reaction may be left unattended.

The yellow reaction mixture is allowed to cool and then is acidified with 20 mL of glacial acetic acid. The acidified solution is transferred with methanol washing to a 1-L round-bottomed flask and evaporated (70–80°C, 12 mm) to dryness. The solid residue is stirred with 500 mL of diethyl ether for 1 hr. Undissolved solids are removed by filtration and the residue is washed twice with 100-mL portions of diethyl ether. The combined filtrate and washings are washed with aqueous sodium carbonate until neutral and then three times with 200-mL portions of water. The ether solution is dried over anhydrous calcium sulfate. Filtration and evaporation of the ether afford a yellow oil that is distilled under reduced pressure through a Vigreux column (30 × 2.5 cm). This gives 6–7 g of dimethyl hexanedioate (bp 69–71°C, 0.02 mm), 3–4 g of a

mixed fraction (bp 72–105°C, 0.02 mm) (Note 6), and 60–61 g (70–71%) of dimethyl decanedioate (bp 105–107°C, 0.02 mm). The dimethyl decanedioate crystallizes on standing at room temperature, mp 26.5–27.2°C (Note 7) and (Note 8).

2. Notes

1. The electrode assembly shown (.htmFigure 1) is fairly versatile and has been used by the submitter in flasks with electrolyte volumes of ca. 40 mL to 4 L. Additionally, the platinum electrodes may be replaced by other electrodes that fit directly into the thermometer adaptor, e.g., commercially available in. graphite or stainless-steel rods. In the present example the electrodes are positioned vertically and are of opposite polarity. In other cases they may be positioned horizontally (parallel to a mercury cathode), and both are anodic.

Figure 1. Electrode assembly: (*A*) platinum wire; (*B*) mercury-filled 6-mm-o.d. glass tubing; (*C*) "thermometer" adapter, 10/18 standard taper joint, Teflon; (*D*) platinum electrodes 25 mm × 30 mm.

Figure 1. Electrode assembly: (A) platinum wire; (B) mercury-filled 6-mm-o.d. glass tubing; (C) "thermometer" adapter, 10/18 standard taper joint, Teflon; (D) platinum electrodes 25 mm × 30 mm.

The thermometer adaptors are available commercially (Ace Glass Company, Vineland, NJ). The platinum wire to platinum electrode connection was made by laying the wire on the foil, heating both parts to red heat with an oxygen–naturalgas flame, and forcing the two together with a sharp hammer blow.

2. Methyl hydrogen hexanedioate (adipic acid, monomethyl ester) was obtained from Aldrich Chemical Company, Inc.

3. The cell voltage, initially 25 V, increased slowly to 27 V. A power supply operating in a constant current mode was used to supply the current. [Since there is little change in cell voltage, a constant voltage power supply capable of delivering 24 V (e.g., two automobile batteries) could also be used.] The cell voltage is important only in connection with the amount of heat generated in the solution by the passage of current. This depends on the product of current and voltage. The voltage should not be so high that the reflux cannot cope with the heat generated or so low that the reflux temperature is not attained. It should be in the range 20–30 V. If the voltage should not fall within this range, the electrode separation should be adjusted. Decreasing the separation decreases the cell voltage. However, contact of the electrodes should not, of course, occur.

4. The column used was a 6 ft × 1/8 in. stainless-steel column packed with 5% OV17 on 100–120-mesh Chromosorb W. The column temperature was increased at 10°C per minute from 60 to 260°C.

5. The additional current passed is to allow for the conversion of that portion of the starting material that is converted to the sodium salt by the added sodium methoxide and that is not detected by gas chromatography.
6. The quantity of ester obtained (0.26 mol) theoretically requires 0.52*F*. Actual current passed was 28 A-hr [1.05*F* (Faradays)], corresponding to a current efficiency of 50%.
7. The melting point was determined by remelting the product and allowing it to cool with a thermometer inserted into it. Occasional stirring with the thermometer was necessary to prevent supercooling.
8. The product shows ^{1}H NMR ($CDCl_3$) δ: 1.2–1.8 (complex, 12, internal methylenes), 2.28 (4, α-CH_2), 3.65 (6, OCH_3).

3. Discussion

The present preparation is based on that of dimethyl tetradecanedioate,[2] with the inclusion of some pyridine into the electrolyte, which has been shown[3] to be effective in preventing anode coating. The reaction used is an example of the Crum Brown-Walker reaction[4] (anodic oxidation of half-esters of α,ω-dicarboxylic acids), which is itself an example of the Kolbe reaction (anodic oxidation of carboxylic acids). The latter is a very general reaction, and its scope and mechanism have been reviewed recently.[5,6] The particular example detailed here has some commercial interest and has been extensively examined. For example, the effects of current density (optimum 0.1–0.4 A/cm^2), degree of neutralization (optimum < 10%), nature of the base used for neutralization, and the nature of the solvent used have been examined.[7,8]. These optimized results were obtained [7,8]in a specially constructed cell with an electrode gap of ca. 0.15 mm. To obtain reasonable results with the larger electrode gap used in this example (ca. 5 mm; if the gap is made any smaller, inadvertent contact of the electrodes and short circuiting become a strong possibility) and maintain the cell voltage fairly low (within range of inexpensive power supplies), the current density used (0.14 A/cm^2) was kept toward the low end of the desirable range and the degree of neutralization (10%) at the highest value consistent with a good yield. In a small-gap cell a current efficiency of 66% together with a chemical yield of 85% has been obtained[7] in the same solvent and electrolyte system.

In addition to the route described here, dimethyl decanedioate has been prepared by esterification of decanedioic acid with methanol[9,10,11,12,13] or diazomethane,[14] hydrogenation of dimethyl 2,5,8-decatrienedioate,[15] and by thermal decomposition of bis(1-methoxy-1-cyclopentyl)pentoxide.[16]

The present procedure offers an alternative electrochemical setup to accomplish the Kolbe electrolysis of half esters to that reported earlier for the preparation of dimethyl octadecanedioate.[17] In the present case the apparatus offers general versatility and electrode coating is prevented by an additive (pyridine). In the earlier case periodic

current reversal was necessary.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 479

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

acetic acid (64-19-7)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

sodium carbonate (497-19-8)

platinum (7440-06-4)

calcium sulfate (7778-18-9)

sodium methoxide (124-41-4)

pyridine (110-86-1)

Diazomethane (334-88-3)

decanedioic acid (111-20-6)

methyl hydrogen hexanedioate, adipic acid, monomethyl ester (627-91-8)

Dimethyl decanedioate, Decanedioic acid, dimethyl ester (106-79-6)

dimethyl hexanedioate (627-93-0)

Dimethyl octadecanedioate (1472-93-1)

dimethyl tetradecanedioate (5024-21-5)

dimethyl 2,5,8-decatrienedioate

bis(1-methoxy-1-cyclopentyl)pentoxide

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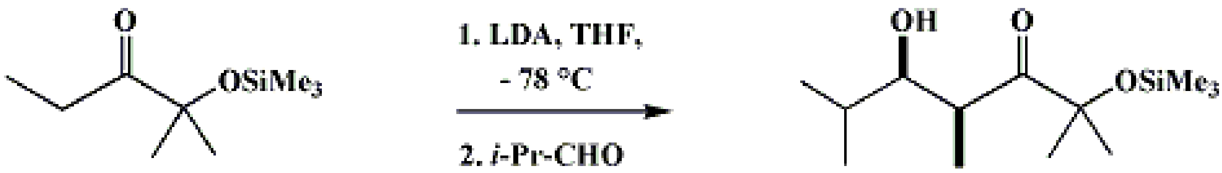
Organic Syntheses, CV 7, 185

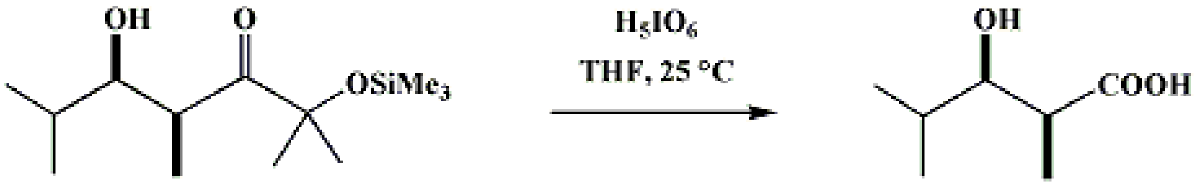
(2*SR*,3*RS*)-2,4-DIMETHYL-3-HYDROXYPENTANOIC ACID

[Pentanoic acid, 3-hydroxy-2,4-dimethyl-, (*R**,*S**)-(±)-]

A.



B.



Submitted by B. Bal, C. T. Buse, K. Smith, and Clayton H. Heathcock[1].
Checked by Joseph R. Flisak, Stan S. Hall, Hugh W. Thompson, and Gabriel Saucy.

1. Procedure

A. *5-Hydroxy-2,4,6-trimethyl-2-(trimethylsiloxy)heptan-3-one*. A dry, 1-L, four-necked (including a thermometer well), round-bottomed flask equipped with an efficient mechanical stirrer, thermometer, graduated 250-mL pressure-equalizing addition funnel sealed with a rubber septum, and a nitrogen inlet is charged with 125 mL of dry tetrahydrofuran (Note 1) and 31 mL (0.22 mol) of diisopropylamine (Note 2). The stirrer is started and 137 mL (0.20 mol) of 1.5 *M* butyllithium in hexane is transferred to the addition funnel by means of a 16-gauge cannula and argon pressure (Note 3). The reaction flask and its contents are cooled to below −5°C by immersion in a dry ice–acetone bath that is maintained at −10 to −15°C by the occasional addition of dry ice. The butyllithium is added dropwise over a period of 20 min. After the addition is complete 10 mL of dry tetrahydrofuran is added to the addition funnel with a syringe to rinse the walls of the funnel, and the rinse is then added to the pale-yellow solution. After the addition is complete, the solution is stirred for an additional 15 min and is then cooled to below −70°C (dry ice–acetone bath). While the reaction solution is cooling, a solution of 37.7 g (0.20 mol) of 2-methyl-2-(trimethylsiloxy)pentan-3-one (Note 4) in 10 mL of dry tetrahydrofuran is introduced through the septum into the addition funnel. When the lithium diisopropylamide (LDA) solution has cooled to below −70°C, the ketone is slowly added to the solution over a period of 20–25 min to ensure that the reaction temperature is maintained below −70°C. After the addition is complete 10 mL of dry tetrahydrofuran is added to rinse the walls of the addition funnel, the rinse is added, and the stirred reaction solution is maintained below −70°C for an additional 30–40 min. During this time the addition funnel is charged through the septum with a solution of 14.4 g (0.20 mol) of 2-methylpropanal (Note 5) in 10 mL of dry tetrahydrofuran. The aldehyde solution is added dropwise to the vigorously stirring yellow enolate solution at −70°C over a 15-min period,

and then the addition funnel is again rinsed with 10 mL of dry tetrahydrofuran and the rinse added to the reaction mixture. After 10–15 min 200 mL of a saturated aqueous ammonium chloride solution is added to the vigorously stirring, −70°C reaction mixture. At this point stirring is discontinued, the cooling bath is removed, and the partially frozen mixture is allowed to warm to room temperature. The contents of the reaction flask are introduced into a 2-L separatory funnel, 200 mL of ether is added to the flask, and the ether rinse is then transferred to the separatory funnel. The layers are shaken and then separated, and the aqueous phase is extracted again with 200 mL of ether. The combined organic phase is washed with 200 mL of water and 200 mL of saturated brine and then dried over magnesium sulfate. After removal of the drying agent by filtration the solvents are removed with a rotary evaporator at aspirator pressure to give 52.1–52.4 g of a pale-yellow oil that is a 63 : 37 mixture of the expected product and the starting material. Most of the starting material is then selectively removed by stirring (magnetic stirring bar) at 25°C at reduced pressure (vacuum pump, 0.1–0.08 mm) for 19 hr to yield 35.2 g of a 90 : 10 mixture (31.7 g, 61%), which is used without further purification for Step B (Note 6) and (Note 7).

B. *(2SR,3RS)-2,4-Dimethyl-3-hydroxypentanoic acid*. A dry, 500-mL, three-necked, round-bottomed flask equipped with a mechanical stirrer, thermometer, and a nitrogen inlet is flushed with nitrogen, charged with 12.5 g (55 mmol) of periodic acid (Note 8) and 150 mL of dry tetrahydrofuran (Note 1), and then sealed with a stoppered, 25-mL, pressure-equalizing addition funnel. The solution is stirred vigorously and cooled to 0–5°C with an ice–salt bath. During this time the addition funnel is charged with a solution of 12.0 g of 5-hydroxy-2,4,6-trimethyl-2-(trimethylsiloxy)heptan-3-one (10.8 g, 41 mmol of ketone from a 90 : 10 mixture from Part A) in 10 mL of dry tetrahydrofuran, which is then rapidly introduced (1 min) to the cold, stirring solution. After the addition is complete 5 mL of dry tetrahydrofuran is added to the addition funnel to rinse the walls of the funnel, and the rinse is then added to the reaction solution. The cooling bath is removed after 15 min and stirring is continued for 1.5 hr, during which time a white precipitate forms. In the meantime, 52 g (0.5 mol) of sodium bisulfite is mixed with 100 mL of distilled water in a 500-mL filtering flask with a side hose connection and cooled to 0–5°C with an ice–salt bath. The reaction mixture is filtered directly through filter paper with suction into the cold slurry of sodium bisulfite. The residue is rinsed with 50 mL of dry ether (Note 9), which is added to the filter funnel and drawn by suction into the yellow solution. After magnetic stirring of the cold mixture for 20 min the contents of the flask are introduced into a 500-mL separatory funnel and the layers are separated. The aqueous layer (pH 4.3) is extracted twice with 100 mL of ether and the combined yellow organic layer is washed with 125 mL of distilled water and separated (the pH of the wash is 2.6–3.5). The organic layer is dried over magnesium sulfate for 1 hr and filtered to remove the drying agent, and the solvents are removed with a rotary evaporator at aspirator pressure. Distillation of the dark-yellow oil affords 4.9–5.4 g (82–89%) of (2*SR*,3*RS*)-2,4-dimethyl-3-hydroxypentanoic acid, bp 85–89°C (0.01 mm), as a viscous, yellow–green liquid (Note 10). Crystallization from hexane using decolorizing carbon provides 4.6–5.0 g (77–83%) of pure hydroxy acid, mp 75–76°C, as white crystals (Note 11).

2. Notes

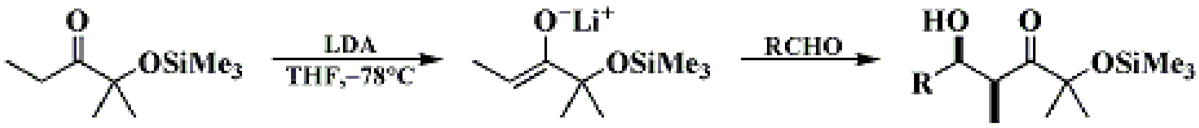
1. Tetrahydrofuran was distilled under a nitrogen atmosphere from sodium–benzophenone immediately prior to use.
2. Diisopropylamine was distilled, bp 85°C, under a nitrogen atmosphere from calcium hydride immediately prior to use.
3. *Caution! Concentrated butyllithium may ignite spontaneously on exposure to air or moisture. Manipulations with this reagent should be performed with care.* The submitters used fresh butyllithium from Foote Mineral Company, Johnsonville, Tennessee. The checkers used fresh butyllithium, 1.6 *M* in hexane under argon, from Aldrich Chemical Company, Inc. The butyllithium solutions may be standardized;[2 3] however, both the submitters and the checkers chose to use fresh reagents and forego the titration. Stainless-steel cannulas with deflected points (double-tip syringe needles) are available from Ace Glass, Inc. and Aldrich Chemical Company, Inc.
4. 2-Methyl-2-(trimethylsiloxy)pentan-3-one was prepared by the method of Young, Buse, and Heathcock, *Org. Synth., Coll. Vol. VII* **1990**, 381.
5. 2-Methylpropanal was freshly distilled; bp 64–65°C.
6. The submitters report that the starting material can be removed within 4 hr to give 38–42 g of the 90 : 10 mixture if the concentration is continued with the rotary evaporator rather than a stationary flask at 0.5–0.1 mm.
7. The ^{1}H NMR (200 MHz, $CDCl_3$) spectrum of the product (taken from a spectrum of a 90 : 10 mixture) is as follows δ: 0.18 (s, 9 H), 0.89 (d, 3 H, *J* = 6.7), 1.02 (d, 3 H, *J* = 6.5), 1.08 (d, 3 H, *J* = 7.1), 1.36 (s, 3 H), 1.37 (s, 3 H), 1.68 (d of septets, 1 H, *J* = 8.4 and 6.6), 2.95 (d, 1 H, *J* = 2.6, OH), 3.42 (dt, 1 H, *J* = 8.5, 2.6, and 2.6), 3.59 (dq, 1 H, *J* = 7.0 and 2.6). The IR spectrum (film) of a 93 : 7 mixture shows absorptions at 1700 and 3600–3300 cm^{-1}.
8. Fresh periodic acid was obtained from Aldrich Chemical Company, Inc. and stored in a desiccator.
9. Reagent-grade diethyl ether from a freshly opened container was used without further drying.
10. The checkers discovered that the desired hydroxy acid is sensitive to strong acid and heat. Early runs of Step B by the checkers using the original conditions recommended by the submitters involved stirring the bisulfite slurry at room temperature for 3–4 hr, simple partitioning without an aqueous backwash, and drying of the bisulfite oxidation mixture, and distillation of the product at 0.8 mm reduced pressure. These runs consistently resulted in acid-catalyzed transformation in either the workup or in distillation and led to mixtures contaminated with 2-methylpropanal produced by a retroaldol reaction, as well as with other unsaturated materials. Distillation of one of these runs, which had used a crude 58 : 42 mixture from Step A as starting material, afforded 13.4 g (53%) of α,γ,γ-trimethylbutyrolactone, bp 85–105°C (0.8 mm), as a yellow–green liquid by dehydration–lactonization. Crystallization from hexane provided 10.1 g (40%) of pure lactone, mp 50–51°C, as white crystals. The lactone had the following spectral properties: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.28 (d, 3 H, *J* = 7.1), 1.38 (s, 3 H), 1.46 (s, 3 H), 1.71 (superficial t, 1 H, *J* = ca. 12), 2.30 (dd, 1 H, *J* = 12.6 and 8.9), 2.83 (16-line m; 1 H, *J* = 11.2, 8.9, and 7.1); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 15.6, 27.0, 29.0, 35.6, 43.5, 81.8, 179.1; IR (CCl_4) cm^{-1}: 1780; mass spectrum, *m/z* (relative

intensity): 129 (M^+ + 1, 1), 113 (33), 84 (16), 69 (30), 59 (34), 43 (100).

11. The hydroxy acid showed the following spectral properties: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.89 (d, 3 H, *J* = 6.6), 1.02 (d, 3 H, *J* = 6.6), 1.21 (d, 3 H, *J* = 7.1), 1.71 (octet, 1 H, *J* = 6.7), 2.71 (dq, 1 H, *J* = 7.3 and 3.4), 3.64 (dd, 1 H, *J* = 8.1 and 3.4), 6.7 (br s, 2 H, OH and CO_2H); IR (CCl_4) cm^{-1}: 1700, 3600–2500.

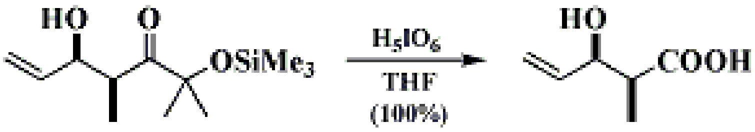
3. Discussion

The stereochemistry of the aldol addition reaction has been actively investigated in recent years, and several methods for achieving high stereoselectivity have been developed.[4,5,6] One of these utilizes the preformed lithium enolates of compounds such **1**.[7] Compound **1** gives a single enolate, which has the *Z*-configuration. This enolate reacts with aldehydes to give β-hydroxy ketones **(2)** with high stereoselectivity:

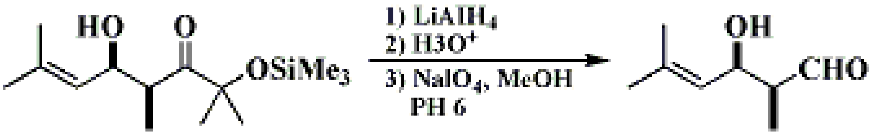


1 2

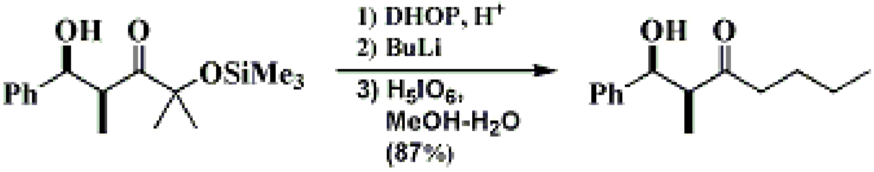
Compounds **2** may be directly cleaved with periodic acid to obtain β-hydroxy acids; for example:[7,8]



Alternatively, the carbonyl group may be reduced, the silyl group hydrolyzed, and the resulting vicinal diol cleaved with buffered sodium periodate to obtain the β-hydroxy aldehyde; for instance:[9,10]



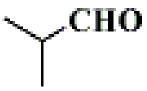
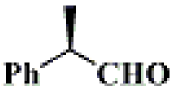
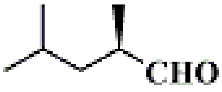
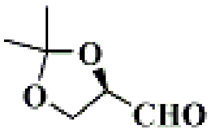
Finally, the hydroxy group may be protected as the tetrahydropyranyl ether, an aryl or alkyllithium reagent added to the carbonyl, and the resulting vicinal diol cleaved to obtain the corresponding β-hydroxy ketone; for example:[11]



Selected examples of the addition of ketone **1** to a variety of aldehydes are collected in Table I.

TABLE I

CONDENSATION OF KETONE 1 WITH ALDEHYDES (Equation 1)

Aldehyde	β-Hydroxy Ketone	β-Hydroxy Acid	Yield (%)	mp	Yield (%)	mpRef.
	80	oil	100	oil	8,12 9	
	97	oil	62	oil	12	
	99	oil	97	oil	12	
	43	oil	–	–	10	
	93	oil	61	73–75°C	7	
	51	oil	76	119–120°C	7	
PhCHO	78	oil	87	oil	7	
	100[a]	oil	65	134–135°C[d]	7	
	61[b]	oil	–	–	10	
	75[c]	oil	–	–	9	

[a]This is a 4 : 1 mixture of Cram : anti-Cram isomers.

[b]Major isomer.

[c]This is a 15 : 1 mixture of Cram : anti-Cram isomers.

[d]This is a 1.3 : 1 mixture of Cram : anti-Cram isomers.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 326

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

(2SR,3RS)-2,4-Dimethyl-3-hydroxypentanoic acid

Pentanoic acid, 3-hydroxy-2,4-dimethyl-, (R*,S*)-(±)-

lithium diisopropylamide (LDA)

ether, diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

nitrogen (7727-37-9)

sodium bisulfite (7631-90-5)

decolorizing carbon (7782-42-5)

Benzophenone (119-61-9)

sodium (13966-32-0)

magnesium sulfate (7487-88-9)

2-methylpropanal (78-84-2)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

hexane (110-54-3)

periodic acid

calcium hydride (7789-78-8)

argon (7440-37-1)

Sodium periodate (7790-28-5)

diisopropylamine (108-18-9)

2-methyl-2-(trimethylsiloxy)pentan-3-one (72507-50-7)

5-hydroxy-2,4,6-trimethyl-2-(trimethylsiloxy)heptan-3-one (64869-24-5)

α,γ,γ-trimethylbutyrolactone

tetrahydropyranyl ether

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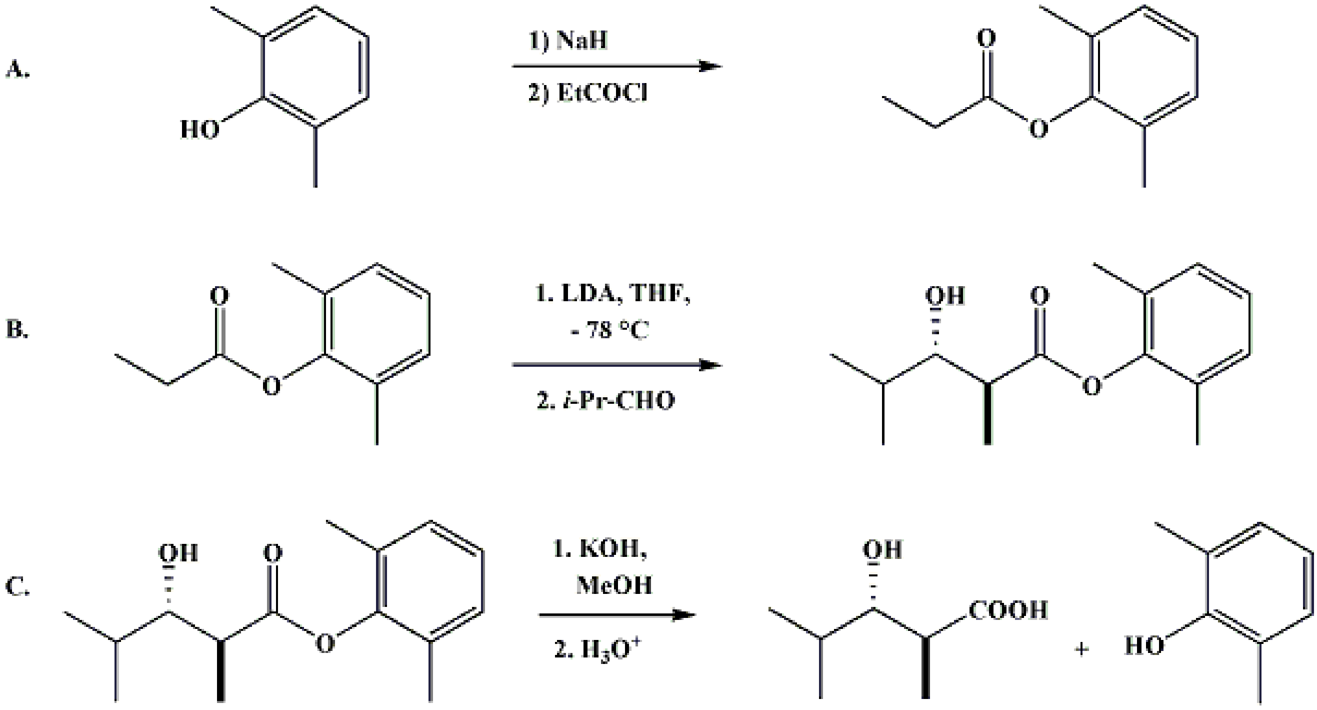
(2*SR*,3*SR*)-2,4-DIMETHYL-3-HYDROXYPENTANOIC ACID

[Pentanoic acid, 3-hydroxy-2,4-dimethyl-, (R*,R*)-]



Submitted by Stephen H. Montgomery, Michael C. Pirrung, and Clayton H. Heathcock[1].
Checked by Pauline J. Sanfilippo and Andrew S. Kende.

1. Procedure

A. *2,6-Dimethylphenyl propanoate*. To a 2-L, three-necked, round-bottomed flask is added 26.4 g (0.55 mol) of a 50% dispersion of sodium hydride in mineral oil (Note 1). The sodium hydride is washed several times by decantation with dry hexane and is then covered with 1 L of dry ether (Note 2). The flask is immersed in an ice bath and equipped with a dropping funnel, a mechanical stirrer, and a reflux condenser. A solution of 61.1 g (0.50 mol) of 2,6-dimethylphenol (Note 3) in 150 mL of dry ether is added dropwise over a 10-min period and the mixture is stirred for 5 min, during which time hydrogen evolution ceases. The cold solution is stirred continuously while a solution of 48 mL (50.9 g, 0.55 mol) of propanoyl chloride (Note 1) in 100 mL of dry ether is added dropwise over a 30-min period. After stirring for an additional hour the reaction mixture is poured into a 2-L separatory funnel containing 200 mL of water. The mixture is shaken vigorously and the ether layer is separated and washed successively with 200 mL of aqueous 10% sodium hydroxide, 200 mL of water, and 200 mL of 4% hydrochloric acid, then dried over magnesium sulfate. The ether is removed with a rotary evaporator and the residue distilled through a short, indented Claisen apparatus to obtain 85–86 g (96–97%) of 2,6-dimethylphenyl propanoate, bp 60–65°C (0.05 mm) (Note 4).

B. *2',6'-Dimethylphenyl (2SR,3SR)-2,4-dimethyl-3-hydroxypentanoate*. The reaction is carried out in a 2-L, three-necked, round-bottomed flask equipped with an efficient mechanical stirrer, a thermometer, and a 500-mL, pressure-equalizing dropping funnel. The dropping funnel is marked to hold 325 mL and is topped with a rubber septum pierced with a syringe needle attached to a source of dry nitrogen. The flask is charged with 300 mL of dry tetrahydrofuran (Note 2) and 69 mL (0.49 mol) of diisopropylamine (Note 1). Butyllithium (325 mL, 0.49 mol, 1.5 *M* in hexane) (Note 5) is transferred into the addition funnel with a cannula. The reaction flask and its contents are cooled to below −5°C by immersion in a bath of dry ice and isopropyl alcohol, which is maintained at −10 to −15°C by periodic additions of dry ice. The butyllithium is added dropwise at such a rate as to maintain the temperature of the reaction mixture in the range 0 to −5°C. After the addition is complete the mixture is stirred for an additional 15 min and is then cooled to −70°C. While the reaction mixture is cooling, the septum is

briefly removed and a solution of 85 g (0.48 mol) of 2,6-dimethylphenyl propanoate in 100 mL of dry tetrahydrofuran is added to the addition funnel, the septum is replaced, and nitrogen is passed through the apparatus in a slow stream for 5 min. The ester is then added to the lithium diisopropylamide solution at such a rate that the temperature of the reaction mixture does not exceed −65°C. The total addition time is 30–40 min. After the addition is complete the reaction mixture is kept at −70°C for an additional hour, during which time the dropping funnel is charged with a solution of 35.3 g (0.49 mol) of 2-methylpropanal (Note 1) in 100 mL of dry tetrahydrofuran. The aldehyde solution is added dropwise to the vigorously stirring enolate solution at such a rate as to maintain a reaction temperature of less than −65°C. After the addition is complete the reaction mixture is kept at −70°C for an additional 30 min. To the vigorously stirring solution is added 500 mL of saturated aqueous ammonium chloride. At this point stirring is discontinued, the cooling bath is removed, and the partially frozen mixture is allowed to warm to room temperature. The contents of the reaction flask are introduced into a large separatory funnel and diluted with 500 mL of ether. The layers are separated, and the organic phase is washed with 300 mL of water and 300 mL of saturated brine and then dried over magnesium sulfate. After removal of the drying agent the solvents are removed with a rotary evaporator to give 112–120 g of an oily semisolid, which is a 7 : 2 mixture of the β-hydroxy ester and 2,6-dimethylphenyl propanoate. This material may be crystallized from ether–hexane to provide 70 g (60%) of pure β-hydroxy ester, mp 75.5–76°C (Note 6). However, it is not necessary to purify the crude product before hydrolysis to the β-hydroxy acid (Note 7).

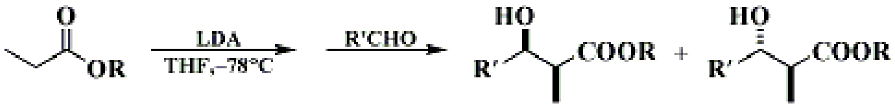
C. *(2SR,3SR)-2,4-Dimethyl-3-hydroxypentanoic acid*. The crude product from the foregoing preparation (112–120 g) is dissolved in 500 mL of methanol and placed in a 2-L Erlenmeyer flask. A solution of 112 g (2 mol) of potassium hydroxide in a mixture of 500 mL of water and 500 mL of methanol is added with stirring, whereupon the reaction mixture warms to about 40°C. After stirring for 15 min crushed dry ice is added in portions to the vigorously stirring mixture until the pH is 7–8. The resulting solution is concentrated to a volume of about 500 mL with a rotary evaporator and extracted with two 300-mL portions of methylene chloride, which are discarded. The aqueous phase is then acidified to pH 1–2 by addition of 75 mL of concentrated hydrochloric acid (vigorous evolution of CO_2) and extracted with two 500-mL portions of methylene chloride. The combined organic extracts are washed with 200 mL of saturated brine and dried over magnesium sulfate. After removal of the drying agent the solvent is removed with a rotary evaporator to obtain 36–53 g of (2*SR*,3*SR*)-2,4-dimethyl-3-hydroxypentanoic acid as a semisolid. Crystallization from hexane provides 30–43 g (41–60% overall yield) of pure hydroxy acid, mp 76–79°C (Note 8).

2. Notes

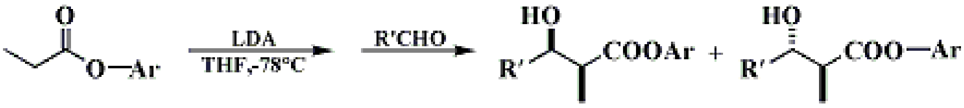
1. Sodium hydride was obtained from Ventron Corporation, Morton Thiokol Inc. 2,6-Dimethylphenol and propanoyl chloride were obtained from Aldrich Chemical Company, Inc. and used without further purification. Diisopropylamine was distilled from calcium hydride prior to use. 2-Methylpropanal was distilled prior to use.
2. Reagent-grade diethyl ether from a freshly opened container was used without further purification. Reagent-grade tetrahydrofuran was dried over sodium before use.
3. 2,6-Dimethylphenol is a corrosive, poisonous substance that is readily absorbed through the skin. All reactions should be carried out in an efficient hood, and appropriate protective apparel should be used.
4. The IR spectrum (neat) shows an absorption at 1755 cm^{-1}. The ^{1}H NMR spectrum ($CDCl_3$) is as follows δ: 1.27 (t, 3 H, *J* = 7), 2.13 (s, 6 H), 2.55 (q, 2 H, *J* = 7), 6.90 (s, 3 H).
5. Butyllithium was obtained from Foote Mineral Company, Johnsonville, Tennessee. It may be standardized by a double-titration procedure.[2]
6. The IR spectrum (neat) has absorptions at 3500 and 1750 cm^{-1}. The ^{1}H NMR spectrum is as follows δ: 1.00 (d, 3 H, *J* = 7), 1.07 (d, 3 H, *J* = 7), 1.40 (d, 3 H, *J* = 7), 2.20 (s, 6 H), 2.93 (quintet 1 H, *J* = 7), 3.50 (m, 2 H), 7.03 (s, 3 H).
7. The checkers found that hydrolysis of once-crystallized aldol (mp 74–75°C) gives a hydroxy acid that crystallizes readily from hexane, for an overall two-step yield of 32%. Hydrolysis of the crude aldol product gives the hydroxy acid as an oil that crystallizes with difficulty, for an overall two-step yield of 45%.
8. The IR spectrum (neat) has absorptions at 3500, 3300–2500, and 1695 cm^{-1}. The ^{1}H NMR spectrum is as follows δ: 0.93 (d, 3 H *J* = 7) 0.99 (d, 3 H, *J* = 7), 1.24 (d, 3 H, *J* = 7), 1.81 (octet, 1 H, *J* = 6), 2.69 (quintet, 1 H, *J* = 7), 3.44 (t, 1 H, *J* = 5.6), 7.4 (br s, 2 H, OH).

3. Discussion

A number of methods have been developed for accomplishing aldol addition reactions in a stereoselective manner.[3 4 5] The performed lithium enolates of alkyl esters normally react with aldehydes to give mixtures of the two diastereomeric β-hydroxy esters:[6]



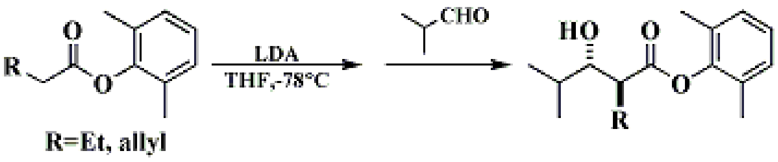
However, the enolates derived from certain aryl esters add to aldehydes to give largely one stereoisomeric product:[7 8]



1 2

The aryl groups that have been investigated are 2,6-dimethylphenyl (DMP), 2,6-di-*tert*-butyl-4-methylphenyl (BHT), and 2,6-di-*tert*-butyl-4-methoxyphenyl (DBHA). Selected examples are shown in Table 1. The most convenient reagents, because of the ease of their further manipulations, are the DMP esters. With aliphatic aldehydes branched at the α-carbon, the DMP esters give essentially one diastereomeric product, β-hydroxy ester **1**. With aromatic and α-unbranched aliphatic aldehydes, the DMP esters give predominantly, but not entirely, one isomer. In these cases the BHT or DBHA esters may be used. Acrolein gives a mixture of **1** and **2** even with the BHT and DBHA esters.

Aryl esters of other acids show similar stereoselectivity; examples are as follows:



In addition, the BHT esters of *O*-benzyllactic acid condense with aldehydes to give diastereomerically homogeneous adducts:[9]

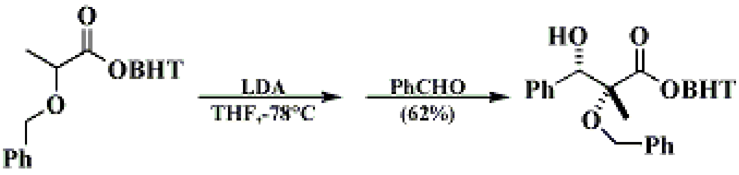


TABLE I

CONDENSATION OF ARYL ESTERS WITH ALDEHYDES

Ar Ester	R	1 : 2	mp (°C)	Yield (%)[a]
DMP	C_6H_5—	72	88/12	62–63[c]
DMP	n-C_5H_{11}	70	86/14	Oil
DMP	i-C_3H_7—	78	>98/2	76
DMP	t-C_4H_9—	82	>98/2	70–71
DMP	$C_6H_5(CH_3)CH$—	81	>98/2	Oil[d]
BHT	CH_2=CH—	88	85/15	64–67[e]
BHT	CH_2=C(CH_3)—	88	>98/2	70–71
BHT	C_6H_5—	96	>98/2	Oil
BHT	i-C_3H_7—	100[b]	>98/2	105–106

BHT	$C_6H_5(CH_3)CH$—	100[b]	>98/2	Oil[d]
DBHA	$CH_2=CH$—	90	87/13	65–72[f]
DBHA	C_6H_5—	75	>98/2	59–61
DBHA	n-C_5H_{11}—	70	>98/2	Oil
DBHA	i-C_3H_7—	79	>98/2	91–93
DBHA	t-C_4H_9—	77	>98/2	88–89

[a]All reactions were carried out on a 1-mmol scale. Unless otherwise noted, yields are for high-performance liquid chromatography (HPLC)-purified product. On a larger scale, such as is given in this procedure, yields are somewhat lower.

[b]This is the yield of crude product; these products were not purified by chromatography.

[c]Melting point given is that of the major diastereomer (1).

[d]Mixture of Cram's rule and anti-Cram's rule diastereomers: ratio = 4 : 1.

[e]Melting point given is for a 95 : 5 mixture of 1 : 2.

[f]Melting point given is for a 90 : 10 mixture of 1 : 2.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 326
- Org. Syn. Coll. Vol. 8, 420

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Pentanoic acid, 3-hydroxy-2,4-dimethyl-, (R*,R*)-

(2SR,3SR)-2,4-Dimethyl-3-hydroxypentanoic acid

2',6'-Dimethylphenyl (2SR,3SR)-2,4-dimethyl-3-hydroxypentanoate

2,6-dimethylphenyl (DMP)

2,6-di-tert-butyl-4-methylphenyl (BHT)

2,6-di-tert-butyl-4-methoxyphenyl (DBHA)

BHT esters of O-benzyllactic acid

hydrochloric acid (7647-01-0)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

Acrolein (107-02-8)

nitrogen (7727-37-9)

CO_2 (124-38-9)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

propanoyl chloride (79-03-8)

2-methylpropanal (78-84-2)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

sodium hydride (7646-69-7)

hexane (110-54-3)

calcium hydride (7789-78-8)

2,6-dimethylphenol (576-26-1)

lithium diisopropylamide (4111-54-0)

diisopropylamine (108-18-9)

2,6-Dimethylphenyl propanoate (51233-80-8)

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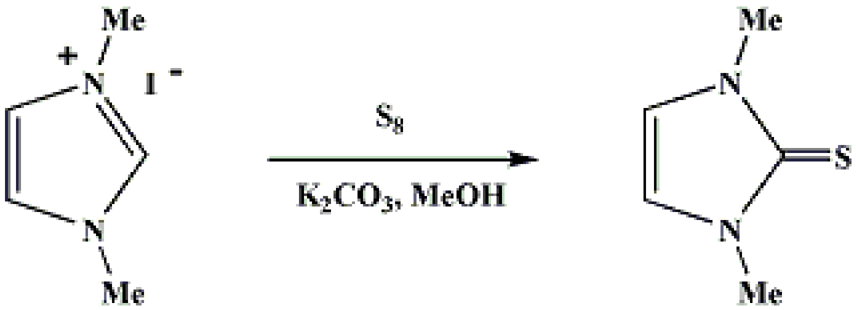
1,3-DIMETHYLIMIDAZOLE-2-THIONE

[2*H*-Imidazole-2-thione, 1,3-dihydro-1,3-dimethyl-]



Submitted by Brian L. Benac[1], Edward M. Burgess[2], and Anthony J. Arduengo, III[3].
Checked by David R. Brittelli, Joseph Buriak, Jr., and Bruce E. Smart.

1. Procedure

In a dry, 500-mL, round-bottomed flask, equipped with a magnetic stirrer and a drying tube are placed 44.8 g (0.20 mol) of 1,3-dimethylimidazolium iodide (Note 1), 35.0 g (0.25 mol) of anhydrous potassium carbonate, 6.5 g (0.20 mol) of sulfur (Note 2), and 300 mL of methanol (Note 3). The mixture is stirred for 40 hr at room temperature. The cloudy yellow mixture is filtered through a pad of Celite (Note 4) and the filter cake is washed with 80 mL of dichloromethane. The combined mother liquor and wash is evaporated to dryness on a rotary evaporator. The orange residue is dissolved in 500 mL of hot water and the hot solution is filtered to remove insoluble impurities. The aqueous filtrate is reheated and the product crystallizes on cooling. The white needles are collected by filtration, washed with 50 mL of cold water and air dried for 1 hr. The mother liquor is concentrated to yield a second crop of crystals to give a total of 15–16 g (58–62%) of pure 1, 3-dimethylimidazole-2-thione, mp 182–183.5°C (Note 5).

2. Notes

1. The imidazolium iodide salt is conveniently prepared by the following procedure. A 500-mL, three-necked, round-bottomed flask equipped with a dropping funnel, thermometer, water-cooled condenser, and magnetic stirrer is charged with 200 mL of anhydrous methylene chloride and 82.1 g (1.0 mol) of 1-methylimidazole (from the Aldrich Chemical Company, Inc.). The solution is cooled and maintained at 5°C while 143.0g (1.01 mol) of iodomethane in 75 mL of anhydrous methylene chloride is added dropwise over a 30-min period. When the addition is completed, the cooling bath is removed and the reaction mixture is stirred for 30 min at room temperature. Methylene chloride is removed on a

rotary evaporator to yield 213.6–216.7 g (95–97%) of 1,3-dimethylimidazolium iodide, mp 81–83°C, ^{1}H NMR (d_6-DMSO) δ: 3.89 (s, 6 H), 7.73 (s, 2 H), 9.16 (s, 1 H). The submitters report the following spectral data: ^{1}H NMR (d_6-DMSO) δ: 4.08 (s, 6 H), 7.75 (s, 2 H), 9.86 (s, 1 H); ^{13}C NMR (d_6-DMSO) δ: 36.10 (s), 123.04 (s), 136.69 (s). The submitters report that the bromide and methyl sulfate salts of the 1,3-dimethylimidazolium cation gave similar yields in the thione synthesis.

2. Lac (precipitated) sulfur gives the best results. The checkers found that with sublimed sulfur (Fisher Scientific Company, laboratory grade) the yield of thione product is 12.5–12.8 g (49–50%). Lac sulfur is prepared by boiling a suspension of 33 g of calcium oxide and 50 g of sublimed sulfur (Fisher Scientific Company) in 200 mL of water for 30 min, then filtering the hot solution and acidifying the clear filtrate to pH 5 with hydrochloric acid. The precipitated sulfur is collected, washed with water, and dried in a vacuum desiccator.

3. ACS-grade methanol from the Fisher Scientific Company was used without further purification. The submitters report that attempts to use ethanol or water as solvents were unsuccessful.

4. The reaction mixture has a distinct odor of sulfur and should be handled in a hood. The product is odorless.

5. The submitters report a melting point of 182–184°C for material that was recrystallized from water or sublimed under reduced pressure. The product shows the following ^{1}H NMR spectrum ($CDCl_3$) δ: 3.58 (s, 6 H), 6.71 (s, 2 H). The submitters report the following spectral data: ^{1}H NMR ($CDCl_3$) δ: 3.6 (s, 6 H), 6.68 (s, 2 H); ^{13}C NMR (d_6-DMSO) δ: 34.34 (s), 117.82 (s), 161.87 (s); IR ($CHCl_3$) cm^{-1}: 2940 (C-H), 1450, and 1380.

3. Discussion

1,3-Dimethylimidazole-2-thione was first reported by Ansell, Forkey, and Moore,[4] who studied the X-ray crystal structure of this thione. No detailed synthesis of the thione has appeared in the chemical literature. This unusual thione has been used as a precursor to unusual thione ylides,[5,6] tricoordinate sulfuranes[7] and as a desulfurizing agent for a thiirane.[6] The thione also has remarkable antioxidant properties.[8] Compared to tetramethylthiourea, 1,3-dimethylimidazole-2-thione is remarkably resistant to desulfurization.

This procedure has been used to synthesize a variety of 1,3-dialkylimidazole 2-thiones. Other imidazole-2-chalcogenones (Se, Te) can be synthesized by similar procedures.

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IL 61801.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

methanol (67-56-1)

sulfur (7704-34-9)

calcium oxide

iodomethane (74-88-4)

methylene chloride, dichloromethane (75-09-2)

thiirane (420-12-2)

1,3-Dimethylimidazole-2-thione, 2H-Imidazole-2-thione, 1,3-dihydro-1,3-dimethyl-, 1, 3-dimethylimidazole-2-thione (6596-81-2)

1,3-dimethylimidazolium iodide (4333-62-4)

1-methylimidazole (616-47-7)

tetramethylthiourea (2782-91-4)

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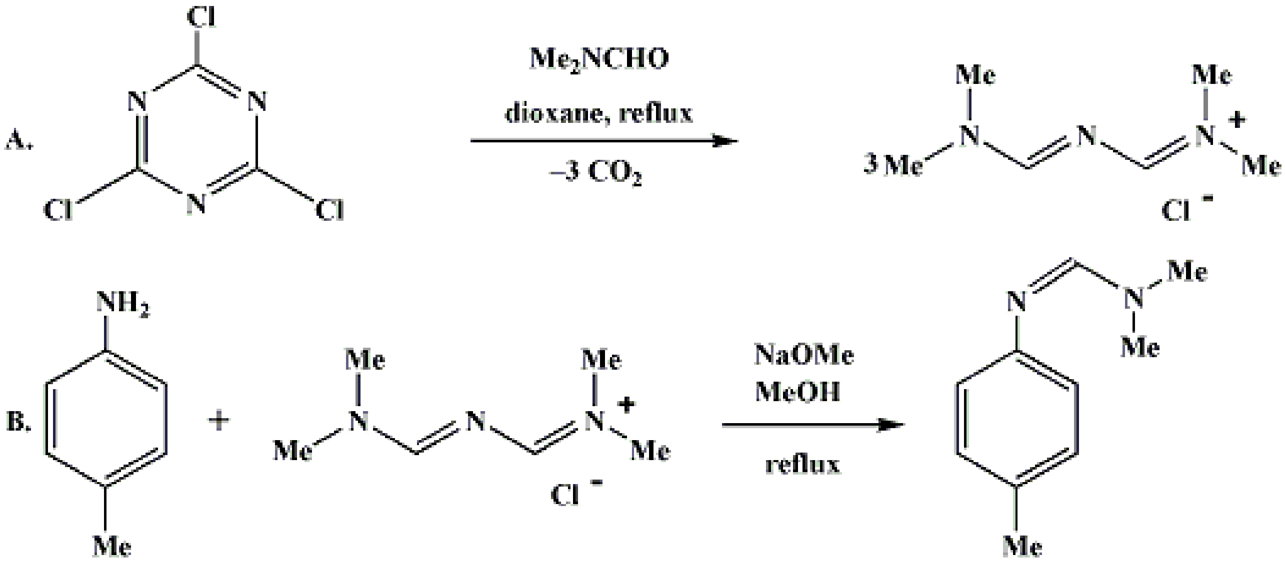
β-DIMETHYLAMINOMETHYLENATION: *N,N*-DIMETHYL-*N'-p-* TOLYLFORMAMIDINE

[Methanimidamide, *N,N*-dimethyl-*N'*-(4-methylphenyl)-]



Submitted by John T. Gupton and Steven A. Andrews[1].
Checked by T. V. RajanBabu and Bruce E. Smart.

1. Procedure

Caution! Cyanuric chloride is a lachrymator and causes burns on contact with the skin. All operations with this reagent should be carried out in a well-ventilated hood.

A. *[3-(Dimethylamino)-2-azaprop-2-en-1-ylidene]dimethylammonium chloride.* A 1-L, one-necked, round-bottomed flask is equipped with a Claisen adapter, mechanical stirrer, reflux condenser, and mineral oil bubbler (Note 1). The flask is charged with cyanuric chloride (73.8 g, 0.4 mol) (Note 2), *N,N*-dimethylformamide (175.4 g, 2.4 mol) (Note 3), and 1,4-dioxane (100 mL) (Note 4). The resulting solution is stirred and heated (at approximately 85°C) for 2–3 hr while a considerable amount of carbon dioxide is evolved (Note 5). When gas evolution is minimal, the reaction mixture is allowed to cool to room temperature; the product rapidly solidifies. The flask that contains the solid product is connected to an isopropyl alcohol–dry ice trap and the solvent is removed by evacuating the system to approximately 0.05 mm pressure. The crude product weighs 186–187 g (95%) and melts at 95–103°C (Note 6), (Note 7), (Note 8).

B. *N,N-Dimethyl-N'-p-tolylformamidine*. A 250-mL, three-necked, round-bottomed flask equipped with a reflux condenser and a magnetic stirring bar coated with Teflon is placed under a positive nitrogen pressure and charged with 100 mL of methanol (Note 9). Sodium metal (1.4 g, 0.06 mol) (Note 10) is then added in small portions. After all of the sodium has reacted, *p*-toluidine (6.4 g, 0.06 mol) (Note 11) is added and the resulting solution is stirred for 5 min. The iminium salt (10.6 g, 0.065 mol) produced in Step A is added in one portion and the resulting mixture is refluxed with stirring overnight. The reaction mixture is cooled to room temperature and the solvent is removed on a rotary evaporator. The residue is taken up in chloroform (100 mL) and extracted twice with a saturated, aqueous solution of sodium bicarbonate (2 × 30 mL).

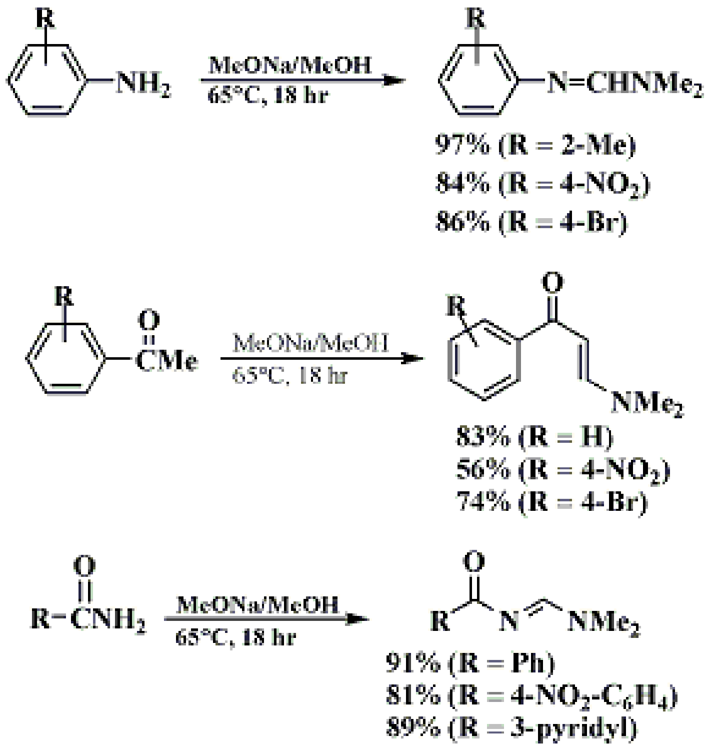
The chloroform phase is dried over anhydrous magnesium sulfate and filtered, and the solvent is removed on a rotary evaporator. The residual dark-brown liquid is distilled using a Kugelrohr apparatus (Note 12); the major fraction boils at 85–100°C (oven temperature), 0.4 mm, and yields 9.1–9.2 g (94–95%) of a pale-yellow liquid (Note 13) and (Note 14).

2. Notes

1. The bubbler is connected to the condenser to monitor carbon dioxide evolution.
2. Cyanuric chloride was purchased from Aldrich Chemical Co., Inc. and was used without additional purification.
3. *N,N*-Dimethylformamide was purchased from Aldrich Chemical Co., Inc. and was dried over Linde 3A molecular sieves prior to use.
4. The 1,4-dioxane was reagent-grade and obtained from Fisher Scientific Corp. It was dried over Linde 3A molecular sieves prior to use.
5. The reaction becomes very exothermic with substantial evolution of carbon dioxide within 30–45 min after heating is initiated. It may be necessary to cool the mixture with ice water if the evolution of gas becomes too vigorous.
6. The checkers obtained material free of *N,N*-dimethylformamide after drying for at least 18 hr. The checkers found variable melting points that depended on the rate of heating. The submitters obtained 195 g (99%) of product which melted at 81–83°C after drying overnight at 1–6 mm of pressure and indicated that the product may contain a small amount of *N,N*-dimethylformamide but is suitable for use without additional purification. [3-(Dimethylamino)-2-azaprop-2-en-1-ylidene]dimethylammonium chloride is reported to melt at 101–103°C.[2]
7. The product is very hygroscopic and should be handled under a moisture-free environment. If the iminium salt is kept dry, it will have a substantial shelf life. The submitters recommend storing the product in a desiccator over anhydrous calcium sulfate.
8. The product has the following spectral characteristics: IR ($CHCl_3$) cm^{-1}: 1610 (C=N); ^1H NMR ($CDCl_3$) δ: 3.27 (s, 6 H, 2 CH_3), 3.43 (s, 6 H, 2 CH_3), 9.57 (s, 2 H, -CH=N).
9. The methanol that was used was reagent-grade and was dried over Linde 3A molecular sieves.
10. Sodium metal was obtained from Fisher Scientific Corp.
11. *p*-Toluidine was reagent-grade and was obtained from the Eastman Chemical Co.
12. The Kugelrohr apparatus was obtained from the Aldrich Chemical Co.
13. The submitters obtained 8.3–9.1 g (86–94%) boiling at 85–107°C, 0.4 mm. The reported boiling point of *N,N*-dimethyl-*N'*-*p*-tolylformamidine is 163°C (30 mm).[3] A gas chromatographic analysis of the product using a -in. × 10-ft column packed with 5% Carbowax 20 M supported on 80–100-mesh chromosorb N exhibited a single peak with a retention time of 4.8 min at an oven temperature of 220°C with a flow rate of 60 cm^3/min. The checkers redistilled the product to obtain colorless material, bp 69.5°C (0.2 mm), which was analyzed. Anal. calcd. for $C_{10}H_{14}N_2$: C, 74.03; H, 8.70; N, 17.27. Found C, 73.57; H, 8.51; N, 17.50
14. The product has the following spectral characteristics: IR (neat) cm^{-1}: 3030 (aromatic CH), 1635 (C=N), 1600 (C=C), ^1H NMR ($CDCl_3$) δ: 2.23 (s, 3 H, aromatic CH_3), 2.87 [s, 6 H, -N(CH_3)$_2$], 6.83 (d, 2 H, J = 8, aromatic CH), 7.06 (d, 2 H, J = 8, aromatic CH), 7.43 (s, 1 H, -CH=N-).

3. Discussion

[3-(Dimethylamino)-2-azaprop-2-en-1-ylidene]dimethylammonium chloride ("Gold's reagent"),[4] the preparation of which is described in Step A of the procedure, is a general β-dimethylaminomethylenating agent that reacts successfully with amines (Equation 1) to produce amidines,[5] with ketones (Equation 2) to produce enaminones,[6] and with amides (Equation 3) to produce acylamidines.[7,8]



All reactions proceed in high yield and under mild conditions to produce relatively pure products. The most effective β-dimethylamino methylenating agents currently available are the formamide acetals,[9] some of which are available commercially.[10] They are, however, expensive, moisture- and heat-sensitive and require potent, mutagenic alkylating agents for their preparation. Under some circumstances they also necessitate high reaction temperatures and long reaction times. Alternatively, Gold's reagent is prepared in a single step, and in nearly quantitative yield, without purification, from inexpensive raw materials. The reaction of Gold's reagent with an amine or other substrate can be carried out at relatively low temperatures (65–90°C) and moderate reaction times (12-24 hr).

The significance of the aminomethylenated amines, ketones, and amides as important compounds and reaction intermediates is well-documented[5,6,7,8] and the use of Gold's reagent, therefore, provides an efficient, economical, and clean method[11] for obtaining such substances.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Cyanuric chloride

iminium salt

Gold's reagent

methanol (67-56-1)

chloroform (67-66-3)

sodium bicarbonate (144-55-8)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

calcium sulfate (7778-18-9)

sodium (13966-32-0)

magnesium sulfate (7487-88-9)

N,N-dimethylformamide (68-12-2)

p-toluidine (106-49-0)

1,4-dioxane (123-91-1)

[3-(Dimethylamino)-2-azaprop-2-en-1-ylidene]dimethylammonium chloride (20353-93-9)

N,N-DIMETHYL-N'-p- TOLYLFORMAMIDINE, Methanimidamide, N,N-dimethyl-N'-(4-methylphenyl)-, N,N-dimethyl-N'-p-tolylformamidine (7549-96-4)

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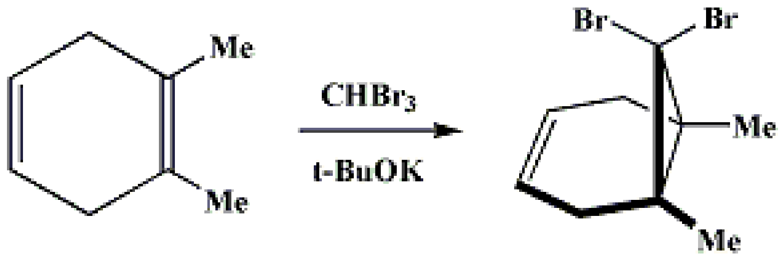
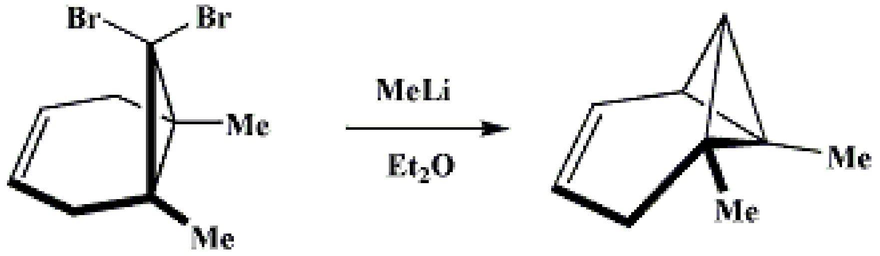
Organic Syntheses, CV 7, 200

1,6-DIMETHYLTRICYCLO[4.1.0.0^{2,7}]HEPT-3-ENE

A.



B.



Submitted by R. T. Taylor and L. A. Paquette[1].
Checked by David A. Cortes and M. F. Semmelhack.

1. Procedure

A. *7,7-Dibromo-1,6-dimethylbicyclo*[4.1.0]*hept-3-ene*. Into a 3-L, three-necked flask equipped with an overhead stirrer, 1-L addition funnel, and reflux condenser capped with a nitrogen-inlet tube are introduced 44.8 g (0.4 mol) of powdered potassium *tert*-butoxide (Note 1) and 1 L of olefin-free petroleum ether (bp 35–55°C; (Note 2)). To this stirred mixture is added a solution containing 38.0 g (0.35 mol) of 1,2-dimethyl-1,4-cyclohexadiene (Note 3) in 200 mL of the same solvent. With external cooling from an ice bath and under nitrogen, 102.4 g (0.4 mol) of bromoform in 400 mL of petroleum ether is added dropwise during 1 hr. The ice bath is removed and the resultant slurry is stirred at room temperature under nitrogen for 6 hr. Water (500 mL) is added and the mixture is poured into a 3-L separatory funnel containing 300 mL of benzene. The organic layer is washed with four 500-mL portions of water, dried over anhydrous magnesium sulfate, and concentrated on a rotary evaporator (Note 4). Further evacuation at 0.5 mm produces a solid that is recrystallized from ether–petroleum ether (1 : 3) to afford 55–62 g (56.5–63.5%) of colorless solid, mp 95–98°C (Note 5).

B. *1,6-Dimethyltricyclo*[4,1.0.0^{2,7}]*hept-3-ene*. A solution of 20.95 g (0.075 mol) of 7,7-dibromo-1,6-dimethylbicyclo[4.1.0]hept-3-ene in 500 mL of anhydrous ether is placed in a 1-L, three-necked flask equipped with a magnetic stirring bar, reflux condenser, addition funnel, and nitrogen-inlet tube. With stirring under nitrogen and external cooling in an ice bath, 50 mL of 1.6 *M* ethereal methyllithium (Note 6) in 70 mL of ether (0.08 mol) is introduced by dropwise addition during 30 min. The ice bath is

removed and the mixture is stirred at room temperature for 1 hr. After 100 mL of water has been cautiously introduced, the mixture is transferred to a separatory funnel and the organic layer is separated. This solution is washed with water (3 × 100 mL), dried over anhydrous sodium sulfate (Note 7), and carefully concentrated by slow distillation through a 40-cm Vigreux column at atmospheric pressure, heating at <60°C (Note 8). The residual liquid is distilled through a short, unpacked column to give 4.2–4.4 g (46–49%) of colorless oil, bp 48–49°C (23 mm) (Note 9). Under the proper conditions, this hydrocarbon can be stored for 2 weeks at −5°C without deterioration.

2. Notes

1. Potassium *tert*-butoxide can be obtained commercially from MSA Research Corporation, Callery, Pennsylvania. The checkers used a sample from Aldrich Chemical Company, Inc.
2. A liter of technical grade petroleum ether was treated in a separatory funnel with 200 mL of concentrated sulfuric acid, washed with water, and dried over anhydrous magnesium sulfate.
3. This diene was prepared by the procedure of Paquette and Barrett;[2] satisfactory results can be realized with material of 70–85% purity (15–30% contamination by *o*-xylene) since the aromatic impurity does not react subsequently and is easily removed.
4. Any residual *o*-xylene should be removed prior to crystallization because the dibromide is exceedingly soluble in aromatic solvents.
5. Further recrystallization is not necessary, but pure crystals, mp 107–108°C, can be obtained in the manner described by Vogel and co-workers.[3]
6. The ethereal methyllithium solutions were purchased from Alfa Inorganics. The concentration of methyllithium in such solutions may be conveniently determined by a procedure described elsewhere[4,5] in which the lithium reagent is titrated with *sec*-butyl alcohol, utilizing the charge transfer complex formed from bipyridyl or *o*-phenanthroline and the lithium reagent as indicator.
7. Anhydrous magnesium sulfate is too acidic for this purpose and promotes rearrangement of the hydrocarbon.
8. All glassware that is to contain the cyclized product should be washed in base and dried (where necessary) prior to use.
9. The checkers found bp 55–56°C/30 mm. Attempted distillation at ca. 50 mm (bp 75°C) led to significant rearrangement to a dimethylcycloheptatriene. The product exhibits the following ^{1}H NMR spectrum ($CDCl_3$) δ: 1.08 (s, 3 H, CH_3), 1.33 (d, 1 H, J = 2, methine C-*H*), 1.52 (s, 3 H, CH_3), 2.15–1.80 (m, 3 H, allylic methylene and methine), 5.50–5.15 (m, 1 H, olefinic C-*H*), 6.10–5.70 (m, 1 H, olefinic C-*H*).

3. Discussion

The tricyclo[4.1.0.0^{2,7}]hept-3-ene ring system, with its conjugated bicyclobutane ring

and double bond and its isomeric relationship to cycloheptatriene, has recently commanded attention as a precursor of yet more highly strained molecules. However, the preparation of the parent hydrocarbon by reaction of 7,7-dibromo-3-norcarene with methyllithium at 0°C, first reported by Klummp and Vrielink,[6] does not proceed in yields above 1–5%.[6,7] Placement of a single methyl group at a ring juncture position of the transient norcarenylidene intermediate is, however, adequate to promote efficient ring closure through C-H alpha insertion.[7,8] The procedure described above is exemplary. Although two alternative routes to tricyclo[4.1.0.0^{2,7}]hept-3-enes are currently available,[6,9] alkyllithium-promoted cyclization of readily available 7,7-dibromobicyclo[4,1.0]hept-3-enes constitutes the most direct and efficient approach. In addition, this procedure illustrates an entirely general method for converting norcarane derivatives to *endo,endo*-1,3-bridged bicyclobutanes.[10,11,12]

Exposure of tricyclo[4.1.0.0^{2,7}]hept-3-enes to catalytic amounts of Ag^+ leads instantaneously and quantitatively to cycloheptatriene derivatives.[7] Promise of their usefulness as synthetic intermediates is growing rapidly.[13,14]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

olefin-free petroleum ether

bipyridyl or o-phenanthroline

7,7-dibromobicyclo[4,1.0]hept-3-enes

endo,endo-1,3-bridged bicyclobutanes

sulfuric acid (7664-93-9)

Benzene (71-43-2)

ether (60-29-7)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

bromoform (75-25-2)

lithium (7439-93-2)

magnesium sulfate (7487-88-9)

Methyllithium (917-54-4)

cycloheptatriene (544-25-2)

1,2-Dimethyl-1,4-cyclohexadiene (17351-28-9)

sec-butyl alcohol (78-92-2)

1,6-Dimethyltricyclo[4.1.0.0^{2,7}]hept-3-ene (61772-32-5)

7,7-Dibromo-1,6-dimethylbicyclo[4.1.0]hept-3-ene (38749-43-8)

dimethylcycloheptatriene

7,7-dibromo-3-norcarene

norcarenylidene

o-Xylene (95-47-6)

potassium tert-butoxide (865-47-4)

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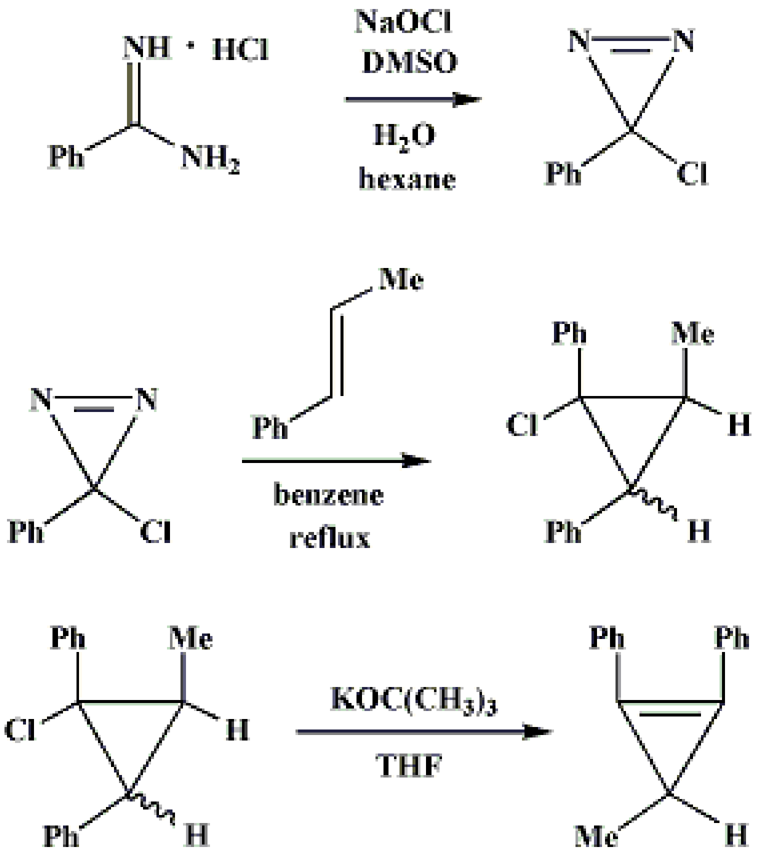
PREPARATION OF CHLOROPHENYLDIAZIRINE AND THERMAL GENERATION OF CHLOROPHENYL CARBENE: 1,2-DIPHENYL-3-METHYLCYCLOPROPENE

[Benzene, 1,1'-(3-methyl-1-cyclopropene-1,2-diyl)-bis-]



Submitted by Albert Padwa, Mitchell J. Pulwer, and Thomas J. Blacklock[1].
Checked by M. F. Semmelhack and A. Zask.

1. Procedure

Caution! Phenylchlorodiazirine is highly explosive (Note 6). It should always be handled with adequate shielding and normal protective equipment such as face shield and leather gloves.

Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A 3-L, three-necked, round-bottomed flask equipped with a high-speed mechanical stirrer and a 250-mL pressure-equalized dropping funnel is charged with 22.5 g (0.143

mol) of benzamidine hydrochloride (Note 1), 37.5 g (0.62 mol) of sodium chloride, 300 mL of hexane, and 400 mL of dimethyl sulfoxide. The flask is cooled at 0°C in an ice–salt bath (Note 2), and a mixture containing 15.5 g (2.65 mol) of sodium chloride in 1.2 L of aqueous 5.25% sodium hypochlorite solution (Note 3) is added with vigorous stirring over a 15-min period using the dropping funnel. After the addition is complete, stirring is continued for 15 min. At this time the organic phase is separated and the aqueous phase is extracted three times with 75-mL portions of ether. The ethereal extracts are combined with the organic phase and the mixture is washed successively four times with 125-mL portions of water and once with a 125-mL portion of saturated aqueous sodium chloride. The mixture is dried over anhydrous magnesium sulfate and concentrated to a volume of approximately 75 mL at 25°C under aspirator vacuum. The mixture is filtered through a 3-cm × 14-cm column of silica gel (Note 4) and eluted with 200 mL of anhydrous benzene (Note 5) into a 1-L, single-necked, round-bottomed flask. Concentration under reduced pressure at room temperature to a volume of approximately 50 mL yields a yellow solution (Note 6). The flask is equipped with a magnetic stirrer, heating mantle, and reflux condenser protected from the atmosphere by a calcium chloride drying tube and then charged with 600 mL of anhydrous benzene (Note 5) and 7.49 g (0.0634 mol) of *trans*-β-methylstyrene.

The reaction mixture is then heated at reflux for 3.5 hr and allowed to cool to 25°C. The benzene is removed at 25°C on a rotary evaporator to afford a dark-brown oil. This was diluted with 50 mL of ether, filtered through a 3-cm × 14-cm column of silica gel (Note 4), and eluted with an additional 175 mL of ether. Removal of the ether under reduced pressure yields ca. 21 g of an oily orange solid that consists of a mixture of diastereomeric 1-chloro-1,2-diphenyl-3-methylcyclopropanes (Note 7).

The crude mixture is transferred to a 1-L, one-necked flask equipped with a magnetic stirrer and a calcium chloride drying tube. To the flask is added 450 mL of anhydrous tetrahydrofuran (Note 8), and the mixture is cooled to −78°C in a dry ice–acetone bath. The drying tube is removed for a brief period, and 28.5 g (0.25 mol) of potassium *tert*-butoxide (Note 9) is quickly added in one portion using a powder funnel. The reaction is stirred for 1 hr at −78°C, warmed to 0°C, stirred for 3 hr, and then allowed to warm to room temperature and stirred for 12 hr. At the end of this time 60 mL of water is added slowly to the reaction mixture. The reaction mixture is concentrated on a rotary evaporator at 25°C to a volume of ca. 150 mL. The mixture is taken up in 160 mL of ether and washed successively with six 60-mL portions of water and one 60-mL portion of saturated aqueous sodium chloride. The ether layer is dried over anhydrous magnesium sulfate, and the solvent is removed under reduced pressure at room temperature. The resulting dark-brown oil is chromatographed through a 4-cm × 41-cm column of silica gel (Note 10) with eluting with hexane. Removal of the solvent under reduced pressure at 25°C affords 10.5–11.5 g (80–88%) of 1,2-diphenyl-3-methylcyclopropene as a pale yellow oil (Note 11).

2. Notes

1. Commercial benzamidine hydrochloride may be used without further purification.
2. Dimethylsulfoxide solidifies on the walls of the container but quickly dissolves on addition of the sodium hypochlorite solution.
3. Any commercial laundry bleach containing 5.25% by weight sodium hypochlorite is suitable.
4. Silica gel of 60–200-mesh was used (35 g).
5. Reagent-grade benzene was distilled from calcium hydride. The first 10% of the distillate was discarded.
6. Alternatively, to isolate the pure phenylchlorodiazirine, distillation through a 3-cm Vigreux column at 25°C (0.1 mm) affords 21.0–23.2 g (48–53%) of a pale-yellow oil; IR (cm^{-1}): 3067, 2967, 1706, 1567, 1490, 1437, 1332, 1258, 1200, 1081, 1013, 1001, 905, 758, 692. Foaming may occur during distillation as the residual solvent is removed under high vacuum. A water bath is employed to heat the distillation pot, and at no time should the pot temperature be allowed to rise above 35°C. The distillation receiving flask should be immersed in a cold bath at –60°C to avoid loss of phenylchlorodiazirine. Phenylchlorodiazirine is reputedly highly explosive and can be detonated by shock and/or elevated temperature.[2] The authors have encountered one such explosion due to a malfunctioning water bath thermostat that allowed the pot temperature to rise to 80°C. At this point the distillation mixture detonated. *In the pure form, phenylchlorodiazirine is considerately more shock-sensitive than nitroglycerine*.[3] Diluted with cyclohexane or benzene, it is not shock-sensitive.
7. The ^{1}H NMR spectrum shows the intermediate chlorocyclopropane to consist of a mixture of two stereoisomers in a 2 : 3 ratio resulting from the nonregio-specific addition of phenylchlorocarbene to *trans*-β-methylstyrene. Crystallization from hexane produced the major isomer as long white needles, mp 98–99°C, which was identified as (*S*)-1-chloro-(*S*,*S*)-1,2-diphenyl-(*R*)-3-methylcyclopropane; ^{1}H NMR ($CDCl_3$, 100 MHz) δ: 1.6 (d, 3 H, J = 6.0 Hz), 2.02 (dq, 1 H, J = 7.5 Hz and J = 6.0 Hz), 2.44 (d, 1 H, J = 7.5 Hz), and 6.6–7.2 (m, 10 H); IR (KBr) cm^{-1}: 3012, 2941, 2899, 2857, 1603, 1580, 1493, 1445, 1383, 1081, 1042, 987, 909, 853, 758, 751, 694. Successive crystallizations to remove the major isomer produced the minor component as a colorless oil identified as (S)-1-chloro-(*S*,*R*)-1,2-diphenyl-(*S*)-3-methylcyclopropane; ^{1}H NMR ($CDCl_3$, 100 MHz) δ: 0.96 (d, 3 H, J = 6.0 Hz), 2.02 (dq, 1 H, J = 7.5 Hz and J = 6.0 Hz), 2.44 (d, 1 H, J = 7.5 Hz), and 7.2–7.6 (*m*, 10 H); IR (neat, cm^{-1}): 3021, 2941, 2924, 1603, 1493, 1449, 1170, 1079, 1044, 1033, 913, 855, 758, 692.
8. Reagent-grade tetrahydrofuran was distilled from lithium aluminum hydride prior to use.
9. Commercial-grade potassium *tert*-butoxide (available from MSA Research Corporation, Evans City, PA 16033) was used without further purification.
10. Silica gel (200 g, 60–200 mesh) was used as the adsorbent. The eluant was

monitored by thin-layer chromatography with collection of only the first eluted component.

11. Distillation of 1,2-diphenyl-3-methylcyclopropene should not be attempted, as much decomposition occurs. The product is characterized by ^{1}H NMR ($CDCl_3$, 100 MHz) δ: 1.36 (d, 3 H, *J* = 5.0 Hz), 2.18 (q, 1 H, *J* = 5.0 Hz), and 7.1–7.8 (m, 10 H); IR (neat) cm^{-1}: 3049, 3012, 2907, 1815, 1603, 1490, 1370, 1348, 1087, 1073, 1030, 990, 755, 738, 685. 1,2-Diphenyl-3-methylcyclopropene decomposes slowly at 25°C.

3. Discussion

The formation of aryl-substituted cyclopropenes by the addition of phenylchlorocarbene to olefins followed by dehydrohalogenation is a general reaction. The reagent phenylchlorodiazirine decomposes readily to produce phenylchlorocarbene in high yield.[4,5,6,7] Phenylchlorocarbene adds to many olefins to give halocyclopropanes, which can easily eliminate hydrogen chloride on treatment with base. The reaction of phenylchlorodiazirine with acetylenes produces cyclopropenyl chlorides, which can readily be converted to the corresponding biscyclopropenyl ethers on treatment with aqueous alcohol.[4,8,9] 1,2-Diphenyl-3-methylcyclopropene has been used to prepare a wide assortment of 1,2-diphenyl-3,3-disubstituted cyclopropenes.[10,11]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

1-chloro-1,2-diphenyl-3-methylcyclopropanes

1,2-diphenyl-3,3-disubstituted cyclopropenes

hydrogen chloride (7647-01-0)

Benzene (71-43-2)

ether (60-29-7)

Benzamidine hydrochloride (1670-14-0)

sodium chloride (7647-14-5)

cyclohexane (110-82-7)

sodium hypochlorite (7681-52-9)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

hexane (110-54-3)

dimethyl sulfoxide, dimethylsulfoxide (67-68-5)

calcium hydride (7789-78-8)

phenylchlorocarbene

Chlorophenyldiazirine

CHLOROPHENYL CARBENE

1,2-Diphenyl-3-methylcyclopropene, Benzene, 1,1'-(3-methyl-1-cyclopropene-1,2-diyl)-bis- (51425-87-7)

Phenylchlorodiazirine

nitroglycerine

chlorocyclopropane

potassium tert-butoxide (865-47-4)

trans-β-methylstyrene (873-66-5)

(S)-1-chloro-(S,S)-1,2-diphenyl-(R)-3-methylcyclopropane

(S)-1-chloro-(S,R)-1,2-diphenyl-(S)-3-methylcyclopropane

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DIPHENYL PHOSPHORAZIDATE

[Phosphorazidic acid, diphenyl ester]

Submitted by Takayuki Shioiri[1] and Shun-ichi Yamada[2].
Checked by Christina Bodurow and M. F. Semmelhack.

1. Procedure

A mixture of 56.8 g (0.21 mol) of diphenyl phosphorochloridate (Note 1), 16.3 g (0.25 mol) of sodium azide, and 300 mL of anhydrous acetone (Note 2) in a 500-mL round-bottomed flask fitted with a calcium chloride tube is stirred at 20–25°C for 21 hr. The lachrymatory mixture is filtered in a hood, and the filtrate is concentrated under reduced pressure. The residue is distilled through a short Vigreux column (Note 3). The yield of diphenyl phosphorazidate, bp 134–136°C (0.2 mm), is 49–52 g (84–89%) (Note 4).

2. Notes

1. Diphenyl phosphorochloridate (diphenyl chlorophosphate), from Aldrich Chemical Company, Inc., was used after purification by distillation at 165–168°C (5 mm).
2. Commercial acetone was dried over anhydrous potassium carbonate and distilled.
3. The bath temperature should be kept below 200°C to minimize decomposition of diphenyl phosphorazidate.[3]
4. Diphenyl phosphorazidate is a colorless nonexplosive oil that can be kept for a long time without decomposition if it is protected against light[3] and moisture.

3. Discussion

The procedure described is essentially that of Shioiri and Yamada.[4] Diphenyl phosphorazidate is a useful and versatile reagent in organic synthesis.[5 6] It has been used for racemization-free peptide syntheses,[4,7,8] thiol ester synthesis,[9] a modified Curtius reaction,[7,10,11] *C*-acylation of active methylene compounds,[12] esterification of an α-substituted carboxylic acid,[13] formation of diketopiperazines,[14] an alkyl azide synthesis,[15] phosphorylation of alcohols and amines,[16] and polymerization of amino

acids and peptides.[17] Furthermore, diphenyl phosphorazidate acts as a nitrene source[3] and as a 1,3-dipole.[18,19] An example of the ring contraction of cyclic ketones to form cycloalkanecarboxylic acids is presented on page 135 in this volume.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 135
- Org. Syn. Coll. Vol. 8, 612

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Diphenyl phosphorochloridate (diphenyl chlorophosphate)

potassium carbonate (584-08-7)

acetone (67-64-1)

sodium azide (26628-22-8)

diphenyl phosphorochloridate (2524-64-3)

Diphenyl phosphorazidate, Phosphorazidic acid, diphenyl ester (26386-88-9)

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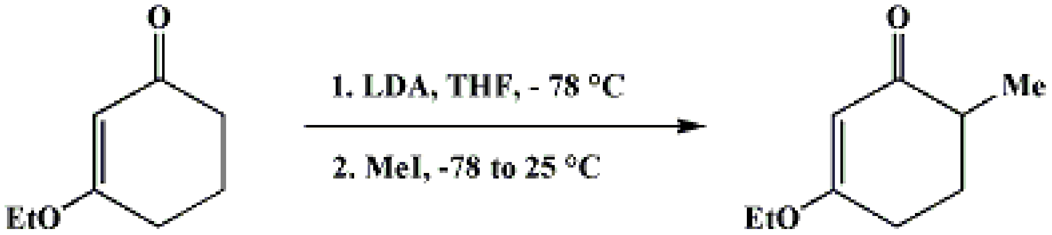
THE STORK–DANHEISER KINETIC ALKYLATION PROCEDURE: 3-ETHOXY-6-METHYL-2-CYCLOHEXEN-1-ONE

[2-Cyclohexen-1-one, 3-ethoxy-6-methyl-]



Submitted by Andrew S. Kende and Pawel Fludzinski[1].
Checked by P. Wovkulich, F. Barcelos, and Gabriel Saucy.

1. Procedure

A dry, 2-L, three-necked, round-bottomed flask is equipped with a magnetic stirrer and two 500-mL pressure-equalizing dropping funnels. One of the dropping funnels is fitted with a rubber septum and the air in the system is replaced with dry nitrogen (Note 1). The flask is charged with 400 mL of anhydrous tetrahydrofuran (Note 2) and 51.6 g (71.5 mL, 0.51 mol) of anhydrous diisopropylamine (Note 3). The flask is cooled to 0°C with an ice bath. A 1.7 *M* hexane solution of butyllithium (288 mL, 0.49 mol) is added dropwise with stirring over a 30-min period. The resulting lithium diisopropylamide is cooled to −78°C with a dry ice–acetone bath (Note 4). A solution of 53.9 g (0.385 mol) of 3-ethoxy-2-cyclohexen-1-one (Note 5) in 250 mL of anhydrous tetrahydrofuran is added dropwise with stirring at −78°C over a 1-hr period. The solution is stirred at −78°C for 30 min followed by the rapid addition of 114 g (50 mL, 0.80 mol) of methyl iodide (Note 6). After 5 min, the cooling bath is removed and the mixture is allowed to warm to room temperature and is stirred overnight. The reaction is quenched with 300 mL of water and the organic phase is separated. The aqueous phase is extracted four times with 75 mL of diethyl ether. The organic phases are combined and washed twice with 150 mL of water, once with 150 mL of brine, and dried over magnesium sulfate. Solvent removal on a rotary evaporator followed by distillation at reduced pressure affords 54–55 g (91–93%) of 3-ethoxy-6-methyl-2-cyclohexen-1-one as a colorless oil, bp 131–133°C (15 mm) (Note 7) and (Note 8).

2. Notes

1. The procedure described above is accomplished by alternately evacuating and filling the funnel with dry nitrogen two times; an oil bubbler is used to maintain a slight positive pressure throughout the reaction.

2. Tetrahydrofuran is freshly distilled from sodium and benzophenone.

3. Diisopropylamine is distilled from calcium hydride.

4. The flask is cooled with the dry ice–acetone bath for 1 hr before the next addition to ensure complete cooling of the solution.

5. *Org. Synth., Coll. Vol. V* **1973**, 539.

6. Methyl iodide was obtained from Eastman Organic Chemicals and used directly from a fresh bottle.

7. Spectroscopic data for 3-ethoxy-6-methyl-2-cyclohexen-1-one are as follows: ^{1}H NMR ($CDCl_3$) δ: 1.16 (d, 3 H, *J* = 7), 1.36 (t, 3 H, *J* = 6), 1.6–2.6 (m, 5 H), 3.92 (q, 2 H, *J* = 6), 5.32 (s, 1 H); IR (neat, cm^{-1}): 1670, 1600.

8. In the procedure as originally submitted, the authors used 1 equiv of base and distilled the product through a short-path distillation apparatus with 75–80% yields. The checkers used excess lithium diisopropylamide (suggested by Professor Clayton Heathcock) as specified in this procedure, and distilled the product through a 15-cm Vigreux column to afford 1.7–1.9 g of forerun (97–98.5% pure by GC) and 54.1–55.3 g (91.4–93.4% yield) of main fraction. The short-path distillation is probably quite adequate.

3. Discussion

The Stork-Danheiser[2] alkylation of 3-alkoxy-2-cyclohexenones under conditions of kinetic enolate formation at the 6-position has enjoyed extensive application in alicyclic synthesis. Such kinetic enolates have served as nucleophiles for a number of alkylations,[3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24] aldol condensations,[25,26,27] and Michael additions.[28,29] Reductive transposition of the resulting products to 4-substituted cyclohexenones has likewise found synthetic application.[30,31,32,33]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 241
- Org. Syn. Coll. Vol. 8, 235

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

brine

diethyl ether (60-29-7)

nitrogen (7727-37-9)

Benzophenone (119-61-9)

sodium (13966-32-0)

Methyl iodide (74-88-4)

magnesium sulfate (7487-88-9)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

hexane (110-54-3)

calcium hydride (7789-78-8)

3-ethoxy-2-cyclohexen-1-one (5323-87-5)

lithium diisopropylamide (4111-54-0)

diisopropylamine (108-18-9)

3-Ethoxy-6-methyl-2-cyclohexen-1-one, 2-Cyclohexen-1-one, 3-ethoxy-6-methyl- (62952-33-4)

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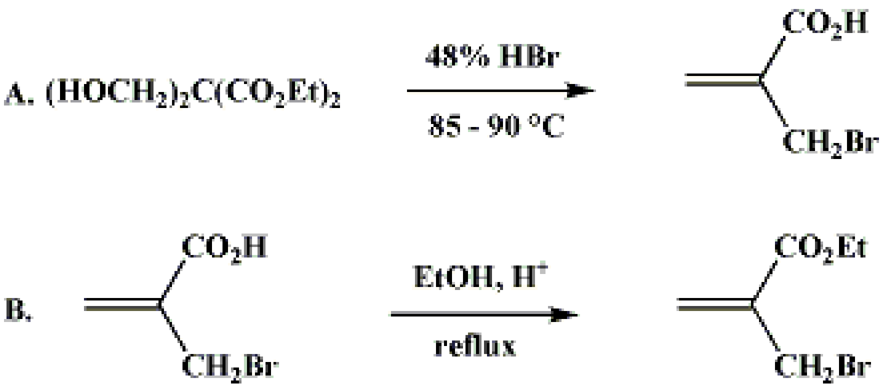
Organic Syntheses, CV 7, 210

ETHYL α-(BROMOMETHYL)ACRYLATE

[2-Propenoic acid, 2-(bromomethyl)-,ethyl ester]



Submitted by K. Ramarajan, K. Ramalingam, D. J. O'Donnell, and K. D. Berlin[1].
Checked by H. S. Shou, E. Tsou, R. A. Hayes, and Orville L. Chapman.

1. Procedure

Caution! Ethyl α-(bromomethyl) acrylate is a potent vesicant and lachrymator and should be handled with care. All operations should be carried out in an efficiently ventilated hood in order to avoid contact.

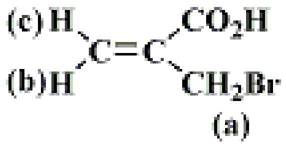
A. *α-(Bromomethyl)acrylic acid.* A 500-mL, three-necked, round-bottomed flask is equipped with a magnetic stirrer, fraction collector, cold-finger condenser, and two thermometers. Into the flask are placed 55.0 g (0.25 mol) of diethyl bis (hydroxymethyl)malonate (Note 1) and 142 mL (1.25 mol) of 47–49% hydrobromic acid (Note 2). The mixture is then heated and the temperature of the liquid maintained between 85 and 90°C. A mixture of ethyl bromide and water distills during the course of 1.5–2 hr. The residue is then boiled for 10 hr, maintaining the temperature between 85–90°C (Note 3). At the end of this period, the mixture is concentrated on a rotary evaporator at 65–70°C (10–15 mm). About 100 mL of water is removed. The residue is cooled in the refrigerator overnight. Crystals of α-(bromomethyl)acrylic acid are filtered in the cold (Note 4) to give, after drying (Note 5), 17.9 g (43%) of acid, mp 71–73°C (Note 6).

B. *Ethyl α-(bromomethyl)acrylate.* In a nitrogen-flushed, 1-L, round-bottomed flask equipped with a magnetic stirrer, Dean-Stark trap, and condenser are placed 42.0 g (0.25 mol) of α-(bromomethyl)acrylic acid and 300 mL of benzene. Approximately 50 mL of a binary azeotrope of benzene and water is distilled (Note 7). The Dean-Stark trap is removed and 100 mL of absolute ethanol (Note 8) and 1 mL of concentrated sulfuric acid are added slowly. The contents of the flask are boiled in a nitrogen

atmosphere for 36 hr, the condensate being passed through 100 g of molecular sieves (Linde 3A) before being returned to the flask. About 125 mL of a mixture of benzene and ethanol is removed from the reaction mixture by distillation (at 67°C). Then 100 mL of benzene is added and another 125 mL of benzene-ethanol mixture distilled (67–75°C). The residue is poured into 200 mL of water and neutralized with solid sodium bicarbonate (ca. 10–15 g) until CO_2 evolution ceases. The resulting solution is extracted with three 75-mL portions of ether, and the combined extracts are dried over anhydrous sodium sulfate for 3 hr. The ether is removed under reduced pressure in a rotary evaporator, and crude ester distilled to give a fraction at 39–40°C (0.9 mm) that weighs 33–34 g (71%). The ester is of high purity, as evidenced by spectral analysis (Note 9).

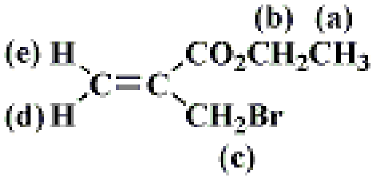
2. Notes

1. The checkers prepared this ester on a 0.7-mol scale by a modification of the previously published method.[2] The modification was effected as follows. The ethereal extract from the formaldehyde-diethyl malonate reaction, after drying over sodium sulfate for 3 hr, was concentrated in a rotary evaporator and the residue was stored in a refrigerator overnight. The crude ester was obtained as white crystals, mp 47–50°C; yield 85.6%. The checkers found that the ester prepared in this manner gave superior yields of the acrylic acid.
2. The submitters reported that the use of excess hydrobromic acid resulted in the formation of a mixture of dibromoisobutyric acid and α-(bromomethyl) acrylic acid as evidenced by NMR analysis.
3. Temperatures higher that 85–90°C gave a mixture of dibromoisobutyric acid and α-(bromomethyl)acrylic acid.
4. This was done at 4°C to improve the yield; otherwise considerable amounts of α-(bromomethyl)acrylic acid remain in solution.
5. The compound was air-dried for 3 days at room temperature.
6. The product was almost pure. It could be recrystallized from Skelly-solve-B (bp 60–80°C) and further purified by sublimation, mp 73–75°C (Anal. calcd. for $C_4H_5BrO_2$: C, 29.12; H, 3.05. Found: C, 29.07; H, 3.10). IR (KBr) cm^{-1}: 1689 (C=O), 1626 ($C=CH_2$), ^1H NMR ($CDCl_3$) δ: 4.18 (s, 2 H, H_a), 6.09 (s, 1 H, H_b), 6.49 (s, 1 H, H_c).



7. There was only about 1 mL of water in the distillate.
8. Absolute alcohol was prepared by boiling commercial absolute alcohol over magnesium turnings for 4 hr in a nitrogen atmosphere.
9. The spectral properties of ethyl α-(bromomethyl)acrylate are as follows: ^1H NMR ($CDCl_3$) δ: 1.26–1.40 (t, 3 H, H_a), 4.16–4.38 (quintet, 2 H, H_b), 4.19 (s, 2

H, H_c), 5.96 (s, 1 H, H_D), 6.32 (s, 1 H, H_e).



3. Discussion

The procedure described here is a modification of that of Ferris.[3] The overall yield has been increased from 17 to 30% by making changes as indicated in (Note 2) and (Note 3). In addition, the number of stages in the preparation of ethyl α-(bromomethyl) acrylate from diethyl malonate has been reduced from four to three.

Ethyl α-(bromomethyl)acrylate has proved to be an excellent reagent for conversion of aldehydes and ketones, both acyclic and cyclic, into the corresponding α-methylene-γ-butyrolactone derivatives[4,5,6,7,8,9] in a Reformatsky type reaction. The yield was excellent in the case of several spiro α-methylene-γ-butyrolactones.[10] Synthetic α-methylene-γ-butyrolactone derivatives have been shown to possess antitumor activity.[5,6,7,11,12,13] Ethyl α-(bromomethyl)acrylate has also proven of value in the synthesis of alkylated products of enol ethers of cyclohexane-1,3-dione.[14]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 265

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

formaldehyde-diethyl malonate

Skelly-solve-B

spiro α-methylene-γ-butyrolactones

enol ethers of cyclohexane-1,3-dione

alcohol, ethanol (64-17-5)

sulfuric acid (7664-93-9)

Benzene (71-43-2)

ether (60-29-7)

sodium bicarbonate (144-55-8)

magnesium turnings (7439-95-4)

HYDROBROMIC ACID (10035-10-6)

Ethyl bromide (74-96-4)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

CO_2 (124-38-9)

Acrylic acid (9003-01-4)

diethyl malonate (105-53-3)

benzene-ethanol (60-12-8)

Diethyl bis(hydroxymethyl)malonate (20605-01-0)

Ethyl α-(bromomethyl)acrylate, 2-Propenoic acid, 2-(bromomethyl)-,ethyl ester, Ethyl α-(bromomethyl) acrylate (17435-72-2)

α-(Bromomethyl)acrylic acid (72707-66-5)

dibromoisobutyric acid

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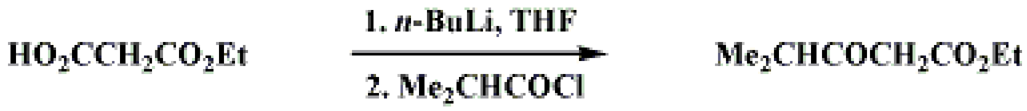
Organic Syntheses, CV 7, 213

ALIPHATIC AND AROMATIC β-KETO ESTERS FROM MONOETHYL MALONATE: ETHYL 2-BUTYRYLACETATE

[Pentanoic acid, 4-methyl-3-oxo-, ethyl ester]



Submitted by W. Wierenga and H. I. Skulnick[1].
Checked by Stefan Blarer, Daniel Wasmuth, and Dieter Seebach.

1. Procedure

Ethyl 2-butyrylacetate. In a 1-L, three-necked, round-bottomed flask fitted with a mechanical stirrer, dry nitrogen inlet, and thermometer is placed 19.8 g (0.150 mol) of monoethyl malonate (Note 1), 350 mL of dry tetrahydrofuran (THF, (Note 2)), and 5 mg of 2,2'-bipyridyl. The solution is cooled to approximately −70°C (in an isopropyl alcohol-dry ice bath) and a 1.6 *M* solution of butyllithium in hexane is added from a dropping funnel while the temperature is allowed to rise to approximately −10°C. Sufficient butyllithium is added (approx. 190 mL) until a pink color persists for several minutes (Note 3). The heterogeneous solution is recooled to –65°C and 7.90 mL (7.98 g, 75 mmol) of isobutyryl chloride (Note 4) is added dropwise over 5 min. The reaction solution is stirred for another 5 min (Note 5) and then poured into a separatory funnel containing 500 mL of ether and 300 mL of cold, 1 *N* hydrochloric acid (Note 6). The funnel is shaken, the layers are separated, and the organic phase is washed with two 150-mL portions of saturated aqueous sodium bicarbonate, followed by 150 mL of water, and dried over anhydrous sodium sulfate. Removal of the solvents under reduced pressure leaves 11.70 g (98%) of ethyl 2-butyrylacetate (Note 7). The crude product can be distilled at 70–74°C (7 mm) (80% yield, 96% purity by GLC).

2. Notes

1. The potassium salt of monoethyl malonate, available from the Aldrich Chemical Company, Inc., can be used after neutralization. Direct use of the potassium salt with only 1 equiv. of butyllithium gave substantially lower yields. Alternatively, monoethyl malonate can be conveniently prepared in high yield from diethyl malonate.[2]
2. For smaller-scale reactions, THF was dried and used directly by distillation from sodium–benzophenone, or first from KOH and then from $LiAlH_4$. The

checkers used only dry THF for the present, large-scale procedure as well.

3. Initially, butyllithium can be added rapidly (20 mL/min) while the cooling bath is removed. A slightly exothermic reaction is noted. Toward the end of the reaction, dropwise addition should be used; the pink color will form and then dissipate. The checkers found it more convenient to use the calculated amount of a freshly titrated[3] solution of butyllithium.

4. Isobutyryl chloride was used as purchased from Aldrich Chemical Company, Inc. or Fluka AG.

TABLE I
REACTION OF ACID CHLORIDES WITH DILITHIO MONOETHYL MALONATE

RCOCl → $RCOCH_2CO_2C_2H_5$

R	Reaction Time (min)/ Temperature (°C)	Yield (%) [a]
$CH_3CH_2CH_2$	5/–65	95
$PhCH_2$	5/–65	99
Ph	30/–65	97
4-$CH_3OC_6H_4$	60/–65	90
4-ClC_6H_4	30/–65	96
2-ClC_6H_4	30/–65	95
2-$C_{10}H_7$	30/–65	95
3-Furyl	15/–65, 60 to 0	97
2-Pyrazinyl	15/–65, 60 to 0	91

[a]The purity of all products isolated is higher than 90% as determined by GLC or ^{1}H NMR. The only contaminants appear to be hydrocarbons including *n*-octane.

5. Reaction times and temperatures vary, depending on the substrate acid chloride (see Table 1).

6. For acid chlorides that contain a basic nitrogen, the aqueous phase is adjusted to approximately pH 7 by limiting the concentration of the hydrochloric acid.

7. Gas chromatographic analysis using a 3-ft, 3% OV-17 column at 90°C indicated a purity of 92% (retention time was 3.2 min) with GC-mass spectrometric identification showing M^+ *m/e* 158 (27%) and the base peak (100%) at *m/e* 113 ($C_6H_9O_2$). The ^{1}H NMR spectrum of undistilled material indicates impurities with resonances in the aliphatic region (δ: 1.5–1.0). The checkers recommend distillation of the crude product.

3. Discussion

Since the β-keto ester group is often a key moiety in organic syntheses, a general and efficient route to these 1,3-dicarbonyl compounds is highly desirable. We feel that the one-pot preparation from monoethyl malonate described here[4] represents an attractive alternative to previous methods[5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22] because of the following characteristics: (1) the reaction is general, as demonstrated by the diversity of examples in Table I; (2) the starting materials, (monoethyl malonate and the acid chlorides) are readily available and inexpensive; (3) the yields are high and therefore omission of purification is possible in many instances; and finally (4) the reaction is simple and easy to scale up.

The optimum ratio for high yields of β-ketoester is 1.7 (monoethyl malonate: acid chloride). A nonstoichiometric reaction for optimum yield is not a serious drawback in this case since the reagent in excess is the inexpensive dilithio monoethyl malonate. Our results show that lowering the ratio also lowers the yield, whereas an increase in the ratio beyond 1.7 has little effect.

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Appendix

Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

KOH (1310-58-3)

Benzophenone (119-61-9)

sodium (13966-32-0)

diethyl malonate (105-53-3)

monoethyl malonate (1071-46-1)

isobutyryl chloride (79-30-1)

butyllithium (109-72-8)

Tetrahydrofuran, THF (109-99-9)

$LiAlH_4$ (16853-85-3)

n-octane (111-65-9)

hexane (110-54-3)

potassium salt of monoethyl malonate (6148-64-7)

2,2'-bipyridyl (366-18-7)

Ethyl 2-butyrylacetate (3249-68-1)

Pentanoic acid, 4-methyl-3-oxo-, ethyl ester (7152-15-0)

3-Furyl

dilithio monoethyl malonate

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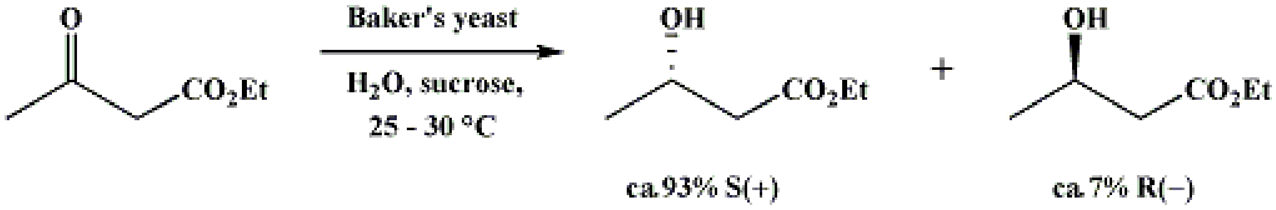
Organic Syntheses, *CV 7*, *215*

YEAST REDUCTION OF ETHYL ACETOACETATE: (*S*)-(+)-ETHYL 3-HYDROXYBUTANOATE

[Butanoic acid, 3-hydroxy-, ethyl ester, (*S*)]



Submitted by Dieter Seebach, Marius A. Sutter, Roland H. Weber, and Max F. Züger[1].
Checked by Terry Rosen and Clayton H. Heathcock.

1. Procedure

A 4-L, three-necked, round-bottomed flask equipped with mechanical stirrer, bubble counter, and a stopper is charged with 1.6 L of tap water, 300 g of sucrose (Note 1), and 200 g of baker's yeast (Note 2), which are added with stirring in this order. The mixture is stirred for 1 hr at about 30°C, 20.0 g (0.154 mol) of ethyl acetoacetate (Note 3) is added, and the fermenting suspension (Note 4) is stirred for another 24 hr at room temperature. A warm (ca. 40°C) solution of 200 g of sucrose (Note 1) in 1 L of tap water is then added, followed 1 hr later by an additional 20.0 g (0.154 mol) of ethyl acetoacetate (Note 3). Stirring is continued for 50–60 hr at room temperature. When the reaction is complete by gas chromatographic analysis (Note 5), the mixture is worked up by first adding 80 g of Celite and filtering through a sintered-glass funnel (porosity 4, 17-cm diam). After the filtrate is washed with 200 mL of water, it is saturated with sodium chloride and extracted with five 500-mL portions of ethyl ether (Note 6). The combined ether extracts are dried over magnesium sulfate, filtered, and concentrated with a rotary evaporator at 35°C bath temperature to a volume of 50–80 mL. This residue is fractionally distilled at a pressure of 12 mm through a 10-cm Vigreux column, and the fraction boiling at 71–73°C (12 mm) is collected to give 24–31 g (59–76%) of (*S*)-(+)-ethyl 3-hydroxybutanoate (Note 7) and (Note 8); the specific rotation $[\alpha]_D^{25}$ + 37.2° (chloroform, *c* 1.3) corresponds to an enantiomeric excess of 85% (Note 9).

The enantiomeric excess may be enhanced by several crystallizations of the 3,5-dinitrobenzoate derivative (Note 10) or else by using "starved" yeast (Note 11).

2. Notes

1. Commercially available sugar (sucrose) from a grocery store is used.
2. Commercially available baker's yeast can be used. The submitters used baker's yeast from E. Klipfel & Co. AG, CH-4310 Rheinfelden (Switzerland). The checkers used Fleischmann's yeast (cubes), obtained from a supermarket, or Red Star Baker's yeast (Universal Food Corporation), obtained from a bakery. The optical rotation of the final product was essentially the same for runs in which the two brands were employed.
3. Ethyl acetoacetate is freshly distilled before use (bp 65°C/12 mm).

4. One to two bubbles per second of CO_2 are developed.

5. A small sample (ca. 1 mL) is removed from the mixture and extracted with ethyl ether. The ether solution is analyzed for remaining ethyl acetoacetate by capillary gas chromatography: 0.3-mm × 20-m glass capillary column Carbowax 20 M, oven temperature 100°C, carrier gas: hydrogen (0.4 atm); retention time of ethyl acetoacetate: 450 sec, of (*S*)-(+)-ethyl 3-hydroxybutanoate: 610 sec. It is important that all the starting material be consumed. If small mounts of ethyl acetoacetate are detected, 100 g of sucrose is added and the mixture is stirred for a further period of 2 days. The checkers detected the presence of residual ethyl acetoacetate by TLC on 250-•m silica gel plates with 1 : 1 ether : hexane as eluant. Plates are developed by dipping the dried plate into a solution of 10% vanillin and 5% sulfuric acid in 95% ethanol and then gently warming over a hot plate; ethyl acetoacetate appears as an intense blue spot with R_f 0.45.

6. In the case of emulsions, addition of methanol may be helpful. The very fine and stable emulsion that still remains is included with the aqueous phase.

7. The spectral properties of (*S*)-(+)-ethyl 3-hydroxybutanoate are as follows: IR[2a] (film) cm^{-1}: 3440, 2980, 1730, 1375, 1300, 1180, 1030; ^1H NMR[2b] (CCl_4) δ: 1.15 (d, 3 H, *J* = 6.5, CH_3), 1.28 (t, 3 H, *J* = 7 Hz, CH_3), 2.35 (d, 2 H, *J* = 6.5, CH_2CO), 3.15 (s, 1 H, OH), 4.05 (q, 2 H, *J* = 7, CH_2O), 4.15 (m, 1 H, CHOH).

8. This ester should be stored in a refrigerator as there has been some indication that it may undergo a transesterification–oligomerization upon standing at room temperature.

9. The specific rotation $[\alpha]_D^{25}$ varies from +35.5° to +38° (82–87% enantiomeric excess). The enantiomeric purity can also be checked by formation of the ester with (*R*)-(+)-1-methoxy-1-trifluoromethylphenylacetyl (MTPA) chloride.[2] The ^{19}F NMR chemical shifts of the diastereomeric esters are 6.13 (*R*,*R*) and 6.01 (*R*,*S*) ppm downfield of external trifluoroacetic acid.

10. The procedure of enriching the (*S*)-(+)-enantiomer to 100% enantiomeric excess by the previously described crystallization method is tedious.[3] It provides optically pure ethyl (*S*)-(+)-3-(3',5'-dinitrobenzoyloxy)butanoate of $[\alpha]_D^{25}$ +26.3° (chloroform, *c* 2), which after cleavage gives enantiomerically pure (*S*)-(+)-ethyl 3-hydroxybutanoate of $[\alpha]_D^{25}$ + 43.5° (chloroform, *c* 1.0). This optically pure compound has recently become commercially available from Fluka AG, CH-9470 Buchs (Switzerland), but it is very expensive. After submission and checking of this procedure, it was shown[4] that the ee of the product can be increased to >95% by working under aerobic conditions and by adding the keto ester more slowly; see also (Note 11).

11. The analysis of the published procedures for reductions of β-keto esters by baker's yeast indicated[5] that aerobic conditions,[4] the presence of 5–15% ethanol in the medium,[4,6] and "aging" of the yeast[4] might be important for high selectivity. The optimum conditions—"starving" the yeast for at least 4 days in 5% aqueous ethanol aerobically—lead to an activation of the enzyme(s)[7] producing the *S*-enantiomer of ethyl-3-hydroxybutanoate.

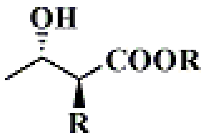
The procedure[5] was as follows. A suspension of 125 g of baker's yeast in 1000 mL of H_2O/EtOH (95 : 5) was shaken (120 rpm) at 30°C in a 2-L Erlenmeyer flask with indentations for 4 days. After the addition of 5 g (38 mmol) of ethyl acetoacetate the reaction was followed by GLC. When the reaction had reached completion (2–3 days), the mixture was centrifuged and the supernatant was extracted continuously with ether

(4 days). The organic layer was dried over magnesium sulfate, filtered, and concentrated with a rotary evaporator at 35°C bath temperature. The crude product was purified by bulb to bulb distillation to give ethyl 3-hydroxybutanoate, 3.54 g (70%), as a colorless liquid with an optical purity of 94% e.e. (enantiomeric excess).

3. Discussion

3-Hydroxybutanoic acid in both enantiomeric forms has been obtained by resolution of the racemic mixture.[8] Hydrogenation of methyl acetoacetate using a Raney nickel catalyst that had been treated with tartaric acid resulted in methyl 3-hydroxybutanoate with an enantiomeric excess of 83–88%.[9] Most recently it was found that enantiomerically pure (*R*-) or (*S*-)-ethyl 3-hydroxybutanoate is available by enantioselective hydrogenation with a chiral homogeneous ruthenium catalyst.[10] Furthermore, optically active 3-hydroxybutanoic acid has been obtained in good chemical and optical yield by condensation of chiral α-sulfinyl ester enolates with aldehydes followed by desulfurization.[11] (*R*-)-(–)-Ethyl 3-hydroxybutanoate in 100% enantiomeric excess resulted from depolymerization of poly-(*R*)-3-hydroxybutanoate, an intracellular storage product of *Alcaligenes eutrophus H 16*.[12] The method presented in the Seebach–Züger paper[12] is easy to perform. The (*S*)-(+)-ethyl 3-hydroxybutanoate obtained may be enriched to 100% enantiomeric excess by crystallization of its 3,5-dinitrobenzoate derivative, followed by alcoholysis.[3]

Optically active ethyl 3-hydroxybutanoate is a very useful chiral building block for natural product synthesis. Some applications are shown in Table 1. Alkylation of doubly deprotonated ethyl 3-hydroxybutanoate gives branched structures of the following type:[13,14]

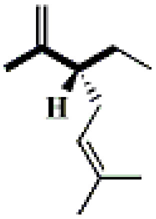


The yeast reduction is not limited to ethyl acetoacetate. It has been applied to other β-keto esters, α-keto esters, α-keto alcohols, α-keto phosphates, and some ketones (Table II). The reductions show a high degree of stereoselectivity. The absolute configuration of the product obtained by reduction of a carbonyl group containing a large group L and a small group S to the alcohol may be determined by application of Prelog's rule.[15,16]

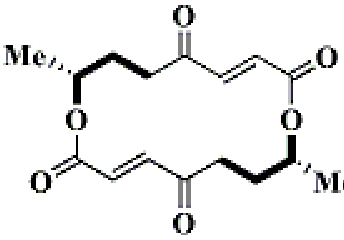
TABLE I

NATURAL PRODUCTS FROM (*S*)- OR (*R*)-ETHYL 3-HYDROXYBUTANOATE[a]

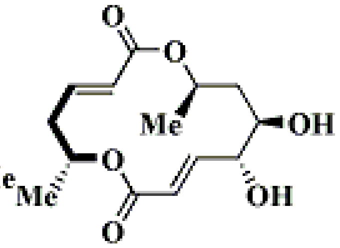
(S)-(+)-Sulcatol[12]



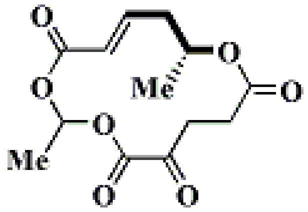
(R)-(–)-Lavandulol[13]



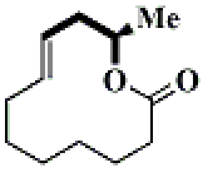
(R, R)-Pyrenophorin[14]



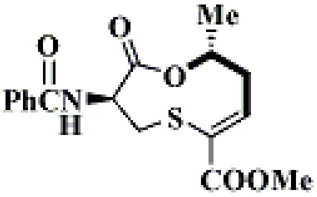
Colletodiol[15]



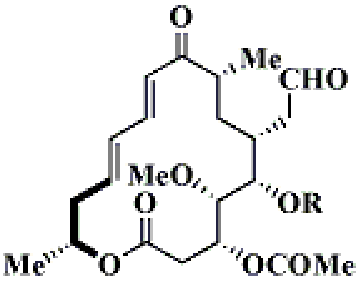
(R,R)-(–)-Grahamimycin A_1[15]



(R)-(+)-Recifeiolide[16]



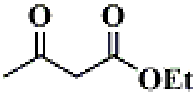
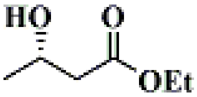
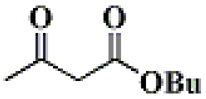
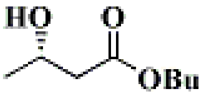
Griseoviridin precursor[17]

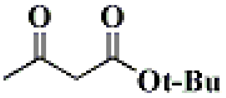
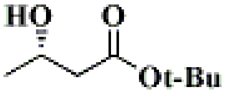
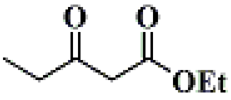
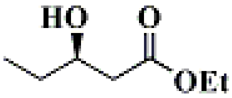
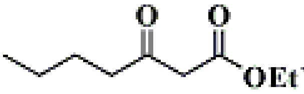
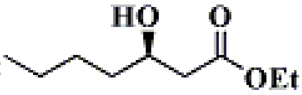
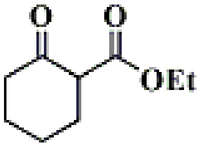
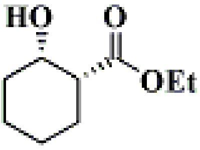
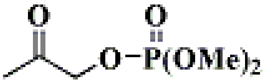
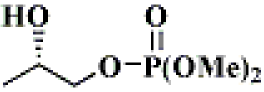
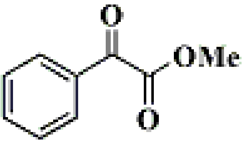
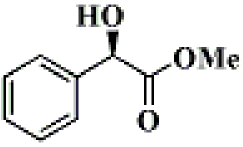
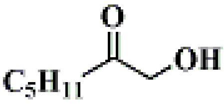
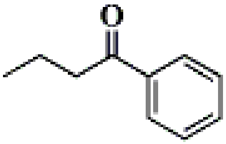
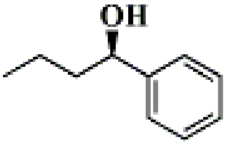
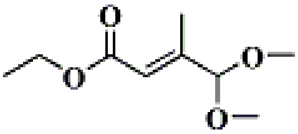
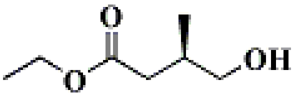


Carbomycin B[17]

[a]The skeleton of ethyl 3-hydroxybutanoate is indicated by heavy lines.

TABLE II
ENANTIOSELECTIVE PREPARATION OF ALCOHOLS FROM THE CORRESPONDING KETONE BY YEAST REDUCTION

Substrate	Product	Yield (%)	Enantiomeric Excess (%)	Ref.
		57-67	84-87	18, 19, 20
		58	90	12

		61	85	12
		67	40	13
			>90	13
		65	86	19, 21
		57	74	22
		59	>97	19
		56	100	23
		45	85-87	16
		34	>97	24

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 332

- Org. Syn. Coll. Vol. 8, 420
- Org. Syn. Coll. Vol. 9, 483
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31. See the Sadtler Standard Spectra; (a) no. 17507; (b) no. 4253 M.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

(R)-(+)-1-methoxy-1-trifluoromethylphenylacetyl (MTPA) chloride

(R-) or (S-)-ethyl 3-hydroxybutanoate

(R-)-(−)-Ethyl 3-hydroxybutanoate

(S)-(+)-Sulcatol

(R)-(−)-Lavandulol

(R,R)-(−)-Grahamimycin A_1

(R)-(+)-Recifeiolide

Griseoviridin precursor

Carbomycin B

ethanol, EtOH (64-17-5)

sulfuric acid (7664-93-9)

methanol (67-56-1)

ether, ethyl ether (60-29-7)

hydrogen (1333-74-0)

chloroform (67-66-3)

sodium chloride (7647-14-5)

CO_2 (124-38-9)

sucrose

Raney nickel (7440-02-0)

tartaric acid (87-69-4)

Ethyl acetoacetate (141-97-9)

magnesium sulfate (7487-88-9)

vanillin (121-33-5)

hexane (110-54-3)

Methyl acetoacetate (105-45-3)

trifluoroacetic acid (76-05-1)

ruthenium (7440-18-8)

ethyl-3-hydroxybutanoate, ethyl 3-hydroxybutanoate (5405-41-4)

3-Hydroxybutanoic acid (300-85-6)

methyl 3-hydroxybutanoate

Butanoic acid, 3-hydroxy-, ethyl ester, (S), (S)-(+)-ETHYL 3-HYDROXYBUTANOATE (56816-01-4)

ethyl (S)-(+)-3-(3',5'-dinitrobenzoyloxy)butanoate

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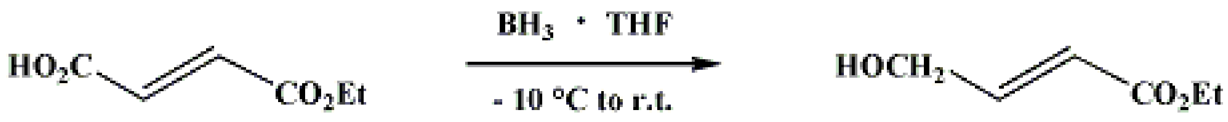
Organic Syntheses, *CV 7*, *221*

ETHYL 4-HYDROXYCROTONATE

[2-Butenoic acid, 4-hydroxy-, ethyl ester, (*E*)-]



Submitted by Andrew S. Kende and Pawel Fludzinski[1].
Checked by Cynthia McClure and Edwin Vedejs.

1. Procedure

A dry, 2-L, one-necked, round-bottomed flask is equipped with a 1-L pressure-equalizing funnel and a large magnetic stirring bar. The system is flame-dried under an internal atmosphere of dry nitrogen (Note 1). The flask is charged with 300 mL of anhydrous tetrahydrofuran (Note 2) and 100 g of monoethyl fumarate. The solution is then stirred under nitrogen and brought to about −5°C using an ice–salt/methanol bath (−10°C) (Note 3). A 1 *M* solution of 700 mL (0.70 mol) of borane–tetrahydrofuran complex (Note 4) is *cautiously* added dropwise (rapid H_2 evolution occurs) with rigorous temperature control to avoid an exothermic reaction. The ice–salt bath is maintained in position throughout the 90 min of addition. The stirred reaction mixture is then gradually allowed to warm to room temperature over the next 8–10 hr. The reaction is carefully quenched at room temperature by dropwise addition of 1 : 1 water : acetic acid (ca. 20 mL) with stirring until no more gas evolution occurs. The reaction is concentrated at room temperature and water pump pressure to a slurry by removal of most of the tetrahydrofuran. The slurry is carefully poured over a 20-min period into 300 mL of ice-cold, saturated sodium bicarbonate solution with mechanical stirring to avoid precipitation of solids, and the product is extracted with 300 mL of ethyl acetate. The aqueous layer is again extracted with 100 mL of ethyl acetate. The organic layers are combined, washed once with 200 mL of saturated sodium bicarbonate, then dried well with anhydrous magnesium sulfate.

Solvent removal at reduced pressure gives 61 g (67% yield) of essentially pure ethyl hydroxycrotonate (Note 5).

An analytical sample may be prepared by quick distillation (or Kugelrohr distillation) at 117–120°C (15 mm), but there is significant loss of material because of decomposition in the distillation pot. From 1 g of product, 0.72 g of pure material is obtained in this way, and recovery decreases as scale of distillation increases.

2. Notes

1. This is accomplished by passing a stream of dry nitrogen through the reaction

vessel. During the reaction, a slight positive pressure of nitrogen is maintained throughout the apparatus.

2. The tetrahydrofuran is freshly distilled from sodium and benzophenone.[2]

3. The flask is cooled with the ice–salt/methanol bath for 30 min before the next addition to insure complete cooling of the solution.

4. Borane-tetrahydrofuran is commercially available from Aldrich Chemical Company, Inc. When a fresh bottle is used, titration is not necessary.

5. ^{1}H NMR data for ethyl 4-hydroxycrotonate are as follows (100 MHz, $CDCl_3$): δ 1.30 (t, 3 H, *J* = 7), 3.58 (br s, 1 H), 4.17 (q, 2 H, *J* = 7), 4.30 (m, 2 H), 6.03 (dt, 1 H, *J* = 16), 6.98 (dt, 1 H, *J* = 16).

3. Discussion

Ethyl (or methyl) 4-hydroxycrotonate has previously been prepared in 51% yield by silver oxide-assisted solvolysis of methyl 4-bromocrotonate,[3] or in 94% yield by reaction of glycolaldehyde with (carbomethoxymethylene)triphenylphosphorane.[4] Both procedures require very expensive starting materials or reagents. Several multistep procedures for preparing the title compound have also been reported.[5 6 7 8] The procedure described above represents a convenient one-step alternative for preparing ethyl 4-hydroxycrotonate, requiring inexpensive starting materials and reagents. This procedure relies on the selective reduction of a carboxylic acid in the presence of a carboxylic ester with borane, which is well documented.[9]

Ethyl 4-hydroxycrotonate has proved to be a valuable intermediate in synthetic chemistry. It has been used in alkaloid synthesis[3] or as a dipolarophile in dipolar cycloadditions.[10] Furthermore, ethyl 4-hydroxycrotonate can be readily oxidized to ethyl 4-oxocrotonate,[4] which has also served as a valuable precursor in synthesis.[11 12]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Ethyl (or methyl) 4-hydroxycrotonate

acetic acid (64-19-7)

ethyl acetate (141-78-6)

sodium bicarbonate (144-55-8)

nitrogen (7727-37-9)

Benzophenone (119-61-9)

sodium (13966-32-0)

monoethyl fumarate (2459-05-4)

magnesium sulfate (7487-88-9)

borane (7440-42-8)

Tetrahydrofuran (109-99-9)

ethyl 4-oxocrotonate (2960-66-9)

glycolaldehyde (141-46-8)

Ethyl 4-hydroxycrotonate, ethyl hydroxycrotonate, 2-Butenoic acid, 4-hydroxy-, ethyl ester, (E)- (10080-68-9)

methyl 4-bromocrotonate (1117-71-1)

(carbomethoxymethylene)triphenylphosphorane (2605-67-6)

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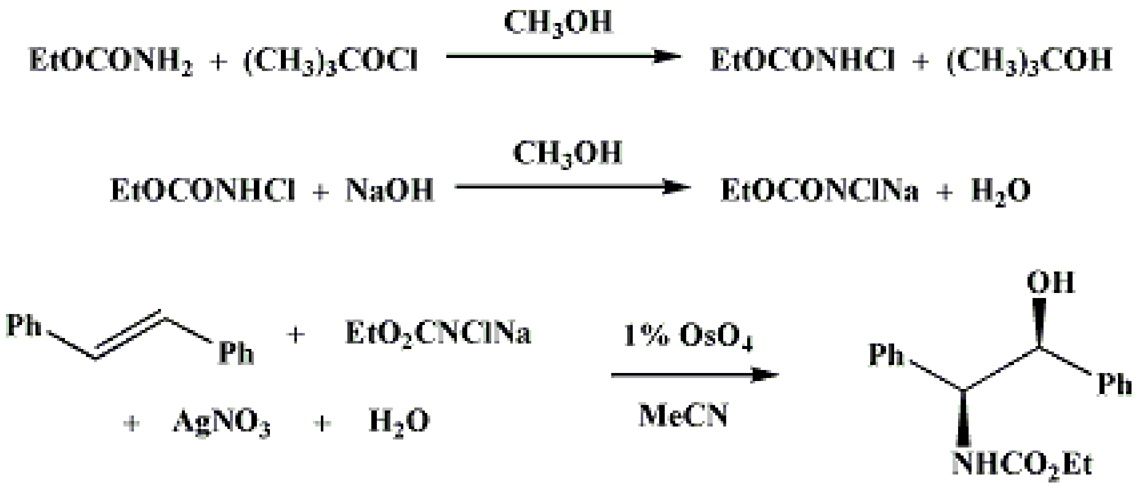
Organic Syntheses, CV 7, 223

OSMIUM-CATALYZED VICINAL OXYAMINATION OF OLEFINS BY *N*-CHLORO-*N*-ARGENTOCARBAMATES: ETHYL *threo*-[1-(2-HYDROXY-1,2-DIPHENYLETHYL)]CARBAMATE

[Carbamic acid (2-hydroxy-1,2-diphenylethyl),-ethyl ester, (*R***R**)-]



Submitted by Eugenio Herranz and K. Barry Sharpless[1].
Checked by Steven D. Young and Clayton H. Heathcock.

1. Procedure

A 1-L, one-necked, round-bottomed flask is equipped with a magnetic stirring bar and a 100-mL addition funnel. The flask is placed in an ice bath and charged with 13.36 g (0.15 mol) of ethyl carbamate (Note 1) and 100 mL of reagent-grade methanol. Vigorous stirring is begun and to the ice-cold solution is carefully added 16.9 mL (16.2 g, 0.15 mol) of *tert*-butyl hypochlorite (Note 2). Fifteen minutes after the addition of the *tert*-butyl hypochlorite is complete, a methanolic solution (75 mL) of sodium hydroxide (6.43 g, 0.158 mol) is added dropwise over a period of several minutes (Note 3). After addition of the sodium hydroxide is complete, the ice bath is removed and stirring is continued for a further 10 min. The solvent is removed using a rotary evaporator (bath <60°C) to give the crude ethyl *N*-chloro-*N*-sodiocarbamate as a white solid (Note 4). Addition of 400 mL of reagent-grade acetonitrile and 26.33 g (0.1 mol) of silver nitrate (Note 5) results in the gradual appearance of a brown suspension. The solution is stirred for 5 min at room temperature; 18.23 g (0.1 mol) of (*E*)-stilbene (Note 6), 10 mL (1.0 mmol) of a solution of OsO_4 in *tert*-butyl alcohol (Note 7), and 8.1 mL (0.45 mol) of water are then added. The milky brown suspension that results is stirred for 18 hr at room temperature. Filtration of the reaction mixture through a Celite mat on a sintered-glass funnel gives a yellow–brown solution (Note 8). The filtrate is refluxed for 3 hr with 200 mL of 5% aqueous sodium sulfite (Note

9). The resulting mixture is concentrated at aspirator pressure using a rotary evaporator until acetonitrile no longer distills. The residue, which is primarily aqueous, is extracted with two 60-mL portions of methylene chloride (Note 10). The organic phase is dried ($MgSO_4$) and concentrated to give 24.6 g of crude product as a pale-yellow solid. Crystallization from 50 mL of hot toluene affords 18.6–19.8 g (66–69%) of almost pure ethyl *threo*-1-(2-hydroxy-1,2-diphenylethyl)carbamate, mp 120–122°C (Note 11). Concentration of the mother liquors yields an additional 0.6–0.8 g of the hydroxy carbamate (Note 12).

2. Notes

1. Ethyl carbamate was obtained from the Aldrich Chemical Company, Inc.
2. *tert*-Butyl hypochlorite was obtained from Frinton Laboratories.
3. A 5% excess of sodium hydroxide was used to make sure that the *N*-chloro-*N*-sodiocarbamate was in a basic environment. The sodium hydroxide was obtained from J. T. Baker Chemical Company; it was 97.9% pure.
4. To remove the last traces of methanol the crude *N*-chloro-*N*-sodiocarbamate is placed under high vacuum (0.1 mm) for 15 min. Slightly higher yields of final product are obtained if the crude *N*-chloro-*N*-sodiocarbamate is purified by trituration with ether.
5. Silver nitrate was obtained from Apache Chemicals Inc.
6. (*E*)-Stilbene was used as obtained from Aldrich Chemical Company. The olefin should be added in small portions to avoid overheating of the reaction mixture.
7. Osmium tetroxide was supplied by Matthey-Bishop, Inc. in 1-g amounts in sealed glass ampuls. The procedure that we describe below should be followed to prepare the osmium tetroxide catalyst solution. Work in a well-ventilated hood. One ampul is scored in the middle, broken open, and the two halves are dropped into a clean, brown bottle containing 39.8 mL of reagent grade *tert*-butyl alcohol and 0.20 mL of 70 or 90% *tert*-butyl hydroperoxide (Aldrich). The bottle is capped (use caps with Teflon liners) and then swirled to ensure dissolution of the OsO_4. These solutions are stored in the hood at room temperature and seem to be very stable.
8. In this way the silver salts (AgCl) are removed from the reaction mixture. The precipitate is washed twice with 20-mL portions of acetonitrile.
9. The purpose of this sulfite treatment is to reduce and thereby remove the small amount of osmium that is bound to the organic products.
10. If an emulsion forms, addition of Celite and subsequent filtration through a sintered-glass funnel gives a clear separation of the two phases. The checkers found that extraction with three 100-mL portions of methylene chloride avoids emulsion formation.
11. Crystallization occurs at room temperature over a period of ca. 12 hr. The crystals are washed once with 15 mL of toluene or 50 mL of petroleum ether (bp 40–60°C). The product is quite pure. A product of higher purity, however, mp

122–123.5°C, can be obtained by a second crystallization from toluene.

12. After 24 hr at high vacuum (0.1 mm), some crystals appear. Addition of 15 mL of ether, filtration, and washing with 10 mL of ether gives more product, mp 110–121°C. The checkers found that a higher overall yield was obtained if the mother liquors from the first recrystallization were dissolved in 50 mL of boiling diethyl ether. The solution is then brought to cloudiness by addition of petroleum ether (bp 40–60°C). When this mixture is stored at 0°C overnight, brown crystals are deposited. Recrystallization of this material from 10 mL of hot toluene provides an additional 2.25–3.51 g of hydroxy carbamate, mp 114–117°C.

3. Discussion

This new procedure[2] for vicinal, cis addition of an oxygen and a nitrogen to an olefinic bond constitutes a major improvement over earlier methods, [3], [4] since the nitrogen is introduced bearing an easily removed protecting group. Although the procedure described here employs ethyl carbamate, both *tert*-butyl carbamate and benzyl carbamate can also be used. In fact, in most cases, higher yields are realized in oxyaminations using the latter carbamates.

N-Chloro-*N*-argentocarbamates are generated *in situ* by reaction of the corresponding *N*-chlorosodiocarbamates with silver nitrate in acetonitrile. The *N*-chlorosodiocarbamates are prepared from the carbamates according to the method of Campbell and Johnson.[5] There are conflicting statements in the literature about the stability of these *N*-chlorosodiocarbamates.[6] On one occasion, when EtOCONNaCl was prepared by the submitters on a 250-mmol scale, it decomposed rapidly (but not explosively), turning dark and releasing heat and gases. However, this same chloramine salt has been prepared on a 100-mmol scale without incident. The submitters have found that acidic conditions (which lead to contamination by the *N*-chlorocarbamate) are responsible for the spontaneous decomposition of these salts at room temperature. A simple modification of Campbell's procedure for preparing *N*-chloro-*N*-sodiocarbamates avoids this problem. By adding 5% more sodium hydroxide than the calculated amount, it is assured that all the *N*-chlorocarbamate in the reaction mixture is neutralized. No spontaneous decomposition has occurred in the batches of *N*-chloro-*N*-sodiocarbamates prepared in this way.

The regioselectivity of this new procedure toward terminal olefins is considerably better than that realized with the earlier catalytic oxyamination procedures based on chloramine-T[3]. However, the catalytic procedure cannot compete with the regiospecificity exhibited by the stoichiometric *tert*-alkyl imido osmium reagents.[3]

This new catalytic procedure shows a different range of reactivity when compared with the chloramine-T based procedures, being very effective for mono- and 1,2-disubstituted olefins, especially electron-deficient olefins such as dimethyl fumaratex and (*E*)-stilbene. However, when the steric hindrance of the olefin increases

(trisubstituted olefins), the oxyamination reaction proceeds slowly and affords mixtures of products. Very recently we have been able to oxyaminate trisubstituted olefins (2-methyl-2-heptene, 1-methylcyclohexene, 1-phenylcyclohexene, 3-methyl-2-cyclohexenone) using other *N*-chloro-*N*-metallocarbamates in conjunction with the addition of tetraethylammonium acetate (Et_4NOAc).[7]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

Ethyl threo-[1-(2-hydroxy-1,2-diphenylethyl)]carbamate

Carbamic acid (2-hydroxy-1,2-diphenylethyl),-ethyl ester, (R^*R^*)-

OsO_4

ethyl threo-1-(2-hydroxy-1,2-diphenylethyl)carbamate

methanol (67-56-1)

ether, diethyl ether (60-29-7)

acetonitrile (75-05-8)

sodium sulfite (7757-83-7)

sodium hydroxide (1310-73-2)

silver nitrate (7761-88-8)

oxygen (7782-44-7)

nitrogen (7727-37-9)

toluene (108-88-3)

methylene chloride (75-09-2)

$MgSO_4$ (7487-88-9)

1-phenylcyclohexene (771-98-2)

ethyl carbamate (51-79-6)

Benzyl carbamate (621-84-1)

osmium tetroxide (20816-12-0)

1-methylcyclohexene

tert-butyl alcohol (75-65-0)

Dimethyl fumarate (624-49-7)

3-methyl-2-cyclohexenone

osmium

tert-butyl hydroperoxide (75-91-2)

2-methyl-2-heptene (627-97-4)

tetraethylammonium acetate (67533-12-4)

(E)-stilbene (103-30-0)

tert-Butyl hypochlorite (507-40-4)

tert-Butyl carbamate (4248-19-5)

ethyl N-chloro-N-sodiocarbamate

N-chloro-N-sodiocarbamate

N-chlorocarbamate

chloramine-T

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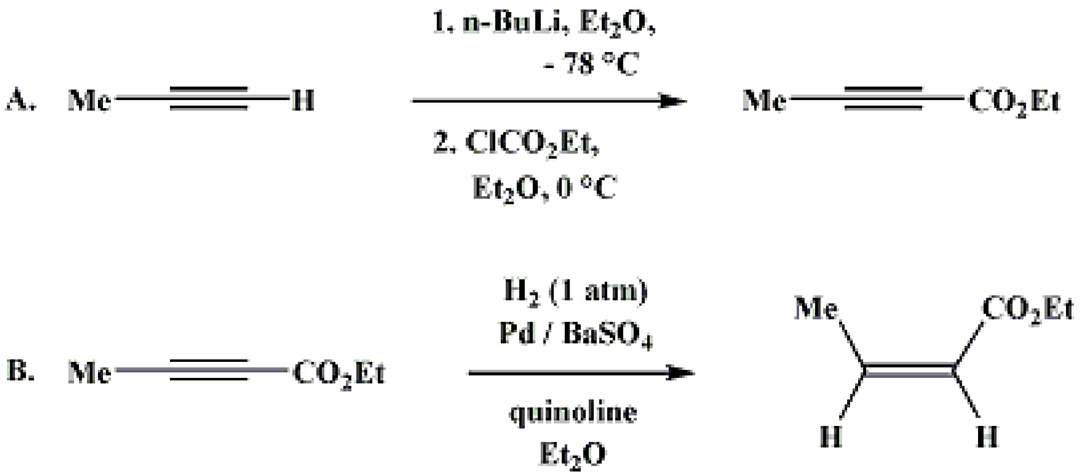
Organic Syntheses, CV 7, 226

ETHYL ISOCROTONATE

[Ethyl (*Z*)-crotonate]



Submitted by Michael J. Taschner, Terry Rosen, and Clayton H. Heathcock[1].
Checked by Judy Bolton and Ian Fleming.

1. Procedure

A. *Ethyl tetrolate*. A 3-L, three-necked, round-bottomed flask is equipped with an overhead mechanical stirrer and charged with 1000 mL of anhydrous ether (Note 1). One neck is fitted with a gas inlet joint connected to a nitrogen line equipped with a mineral oil bubbler. The second neck is fitted with a low-temperature thermometer, and the third is closed with a rubber serum cap after nitrogen has been passed through the flask for a few minutes. The flask is then immersed in a dry ice–acetone bath. While the ether is cooling, 85 mL (60.0 g, 1.50 mol) of propyne (Note 2) is condensed into a flask (Note 3). The stopper is removed briefly, the cold (−78°C) propyne is poured into the flask through a powder funnel inserted into the neck, and stirring is commenced. The stopper is replaced, and 667 mL of a 1.5 M solution of butyllithium in hexane is introduced by syringe at such a rate that the internal temperature does not exceed −65°C (Note 4)–(Note 6). During the butyllithium addition a copious white precipitate appears. The slurry is stirred at −78°C for 30 min, and 134 mL (152 g, 1.4 mol) of ethyl chloroformate (Note 7) is added. At this point, the acetone–dry ice bath is replaced by an ice bath and the reaction mixture is stirred overnight. During this time the ice bath will melt and the reaction mixture should eventually reach room temperature. The mixture is poured onto 400 g of crushed ice, the layers are separated, and the aqueous phase is extracted with two 200-mL portions of ether. The ether solutions are combined, washed with brine and dried over anhydrous $MgSO_4$. After filtration, the ether is removed with a rotary evaporator (Note 8). The residue is distilled at aspirator pressure to obtain 107–108 g (95–97%) of ethyl tetrolate, bp 60–

64°C (20 mm) [lit.[2] 105°C (90 mm)] (Note 9).

B. *Ethyl isocrotonate*. An oven-dried, 500-mL hydrogenation flask equipped with a sidearm fitted with a rubber serum cap and a magnetic stirring bar is charged with 0.4 g of 5% palladium on barium sulfate (Note 10), 0.4 g of quinoline, and 200 mL of anhydrous ether. The flask is attached to an atmospheric-pressure hydrogenation apparatus (Note 11) and flushed with hydrogen. Ethyl tetrolate (23.2 mL, 22.4 g, 0.2 mol) is introduced into the hydrogenation flask with a syringe, and stirring is commenced. The progress of the reaction may be monitored by the uptake of hydrogen (theoretical 4500 mL), by gas chromatography, or by removing aliquots that are concentrated and analyzed by ^{1}H NMR, monitoring the disappearance of the methyl singlet at δ 1.95; a total hydrogenation time of 10–15 hr is required (Note 12). After hydrogenation is complete, the catalyst is removed by filtration of the reaction mixture through a Celite pad. The ether is removed with a rotary evaporator (Note 8) to obtain 21.1–22.4 g (93–98%) of ethyl isocrotonate as a light-yellow liquid. This material contains traces of quinoline but is of a purity suitable for many uses (Note 6) and (Note 13). The quinoline may be removed, if desired, by washing the ether solution with 1 *M* aqueous acetic acid, followed by aqueous sodium carbonate, or by distillation at atmospheric pressure, bp 128–132°C [lit.[3] bp 129–130.5°C] (Note 14).

2. Notes

1. Although stirring can be done with a large magnetic stirring bar, the reaction mixture becomes rather thick as the 1-lithiopropyne is formed, and effective stirring is difficult. The checkers found that the yield in this step is only 77% when a magnetic stirrer is used.
2. Methylacetylene (technical grade) from Linde Division of the Union Carbide Corporation was employed. The checkers used Matheson Lecture bottles.
3. The propyne is passed directly from the tank or lecture bottle to a cold-finger condenser filled with a slush of isopropyl alcohol and dry ice. The condenser is attached to a 200-mL, three-necked flask equipped with a gas inlet adapter and a glass stopper. The flask has been previously calibrated to hold 85 mL of liquid.
4. Alternatively, the butyllithium solution may be forced into the reaction flask by means of an 18-gauge cannula inserted through the serum cap.
5. Butyllithium was obtained from Foote Mineral Co., Johnsonville, Tennessee. It may be standardized by a double titration procedure.[4]
6. If care is not taken in the formation of 1-lithiopropyne, the final product can be contaminated with as much as 10% of an impurity, which is presumed to be ethyl pentanoate. This impurity has a GLC retention time on conventional packed columns that is quite similar to that of ethyl (*E*)-crotonate. The by-product presumably results from the presence of butyllithium when the ethyl chloroformate is added. The submitters have not observed the formation of this product when care was taken to maintain the reaction temperature below –65°C during addition of the butyllithium to the propyne.

7. Ethyl chloroformate (practical grade) was obtained from MCB, Inc., Cincinnati, Ohio 45212, and used without purification.
8. It is important that the rotary evaporator bath be kept at 5–10°C, or some of the product will be lost by evaporation.
9. The IR spectrum (neat) has absorptions at 2250, 1700, and 1260 cm^{-1}. The ^1H NMR spectrum ($CDCl_3$) is as follows δ: 1.23 (t, 3 H, *J* = 7), 1.95 (s, 3 H), 4.07 (q, 2 H, *J* = 7).
10. The catalyst was obtained from The American Platinum Works, Newark, NJ.
11. The submitters employed an apparatus similar to that described by Wiberg.[5]
12. The hydrogenation can also be carried out without special apparatus by the following method. The ether solution is placed in a 500-mL, three-necked flask fitted with a fritted-gas inlet tube, a rubber serum cap, an oil bubbler, and a magnetic stirring bar. The catalyst, quinoline, and ethyl tetrolate are introduced, and the reaction flask is cooled in an ice bath. Hydrogen is bubbled through the cold solution at such a rate as to maintain atmospheric pressure in the flask as evidenced by the oil bubbler. When using this technique, it is necessary to monitor the course of hydrogenation by GLC or ^1H NMR. However, the rate of hydrogenation decreases rather abruptly after one molar equivalent has been absorbed, and there is little danger of overhydrogenation.
13. Capillary GLC analysis (12 m, cross-linked methyl silicone, programmed, 45°C, 3°C/min, retention time of ethyl (*Z*)-crotonate, 2.5 min). Ethyl (*E*)-crotonate has a retention time of 2.95 min under the same conditions. Careful quantitative analysis reveals that the ratio of *Z* and *E* isomers is reproducibly in the range 58 : 1 to 59 : 1.
14. The IR spectrum (neat) has absorptions at 3040, 1710, 1640, 1175, 1025, and 810 cm^{-1}. The ^1H NMR spectrum is as follows ($CDCl_3$) δ: 1.23 (t, 3 H, *J* = 7), 2.05 (dd, 3 H, *J* = 2, 7), 4.03 (q, 2 H, *J* = 7), 5.62 (dq, 1 H, *J* = 12, 2), 6.19 (dq, 1 H, *J* = 12, 7).

3. Discussion

A previous *Organic Syntheses* procedure for the preparation of isocrotonic acid involves the stereospecific Favorskii rearrangement of 1,3-dibromo-2-butanone.[6] However, the procedure is rather laborious and, in our hands, gives only a modest overall yield of acid. Isocrotonic acid has also been prepared by carbonation of *cis*-propenyllithium[7] and by sodium amalgam reduction of β-chloroisocrotonic acid.[8] The present procedure for semihydrogenation of ethyl tetrolate is based on early work of Bourguel[9] and of Allan, Jones, and Whiting.[10] The procedure for acylation of propyne is general and may be employed for the preparation of other α,β-acetylenic esters.[11]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 375

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

brine

methyl silicone

acetic acid (64-19-7)

ether (60-29-7)

hydrogen (1333-74-0)

sodium carbonate (497-19-8)

nitrogen (7727-37-9)

barium sulfate (7727-43-7)

sodium (13966-32-0)

isopropyl alcohol (67-63-0)

palladium (7440-05-3)

Quinoline (91-22-5)

ethyl chloroformate (541-41-3)

$MgSO_4$ (7487-88-9)

butyllithium (109-72-8)

hexane (110-54-3)

Ethyl (Z)-crotonate, ethyl (E)-crotonate (623-70-1)

propyne, methylacetylene (74-99-7)

Isocrotonic acid (503-64-0)

1,3-Dibromo-2-butanone (815-51-0)

Ethyl isocrotonate (6776-19-8)

Ethyl tetrolate (4341-76-8)

1-lithiopropyne (4529-04-8)

ethyl pentanoate (539-82-2)

β-chloroisocrotonic acid

cis-propenyllithium

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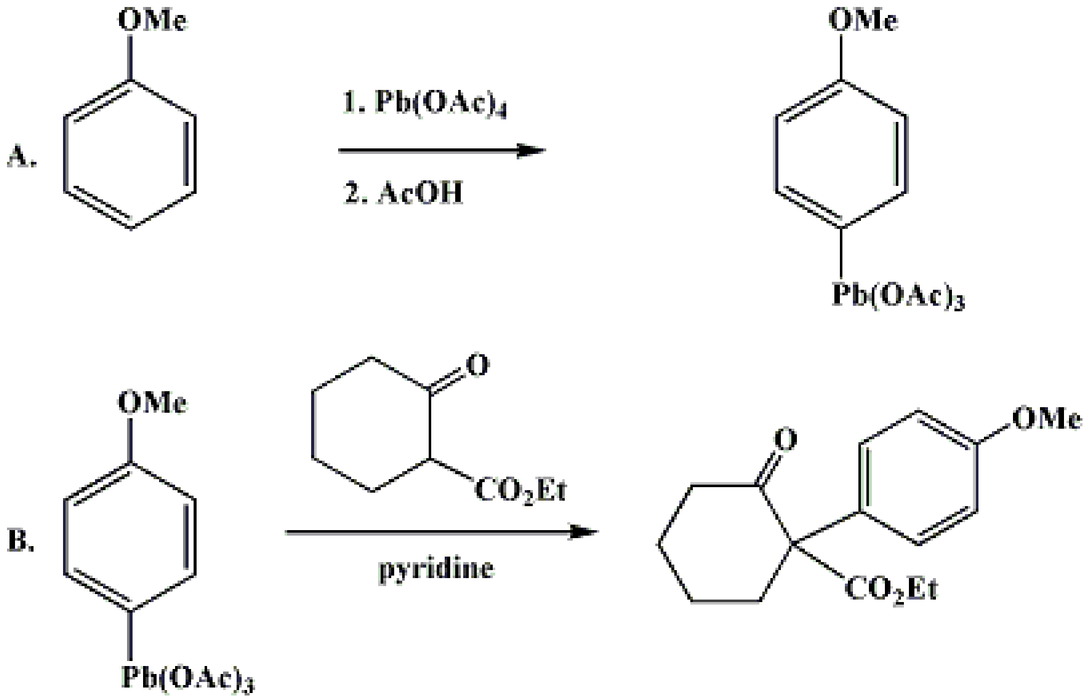
Organic Syntheses, *CV 7*, *229*

THE *C*-ARYLATION OF β-DICARBONYL COMPOUNDS: ETHYL 1-(*p*-METHOXYPHENYL)-2-OXOCYCLOHEXANECARBOXYLATE



Submitted by Robert P. Kozyrod and John T. Pinhey[1].
Checked by M. F. Semmelhack and David Ziering.

1. Procedure

A. *p-Methoxyphenyllead triacetate*. A 1-L Erlenmeyer flask, equipped with a magnetic stirring bar, is charged with 50 g (0.11 mol) of lead tetraacetate (Note 1), chloroform (200 mL), and 140 g (1.09 mol) of dichloroacetic acid (Note 2). To this solution is added 16 g (0.15 mol) of anisole (Note 3), and the mixture is stirred at 25°C until lead tetraacetate can no longer be detected (Note 4). The reaction mixture is washed with water (2 × 250 mL) and the chloroform solution is treated with 1.5 L of hexane (Note 5). The yellow precipitate (44 g) is collected by suction filtration and stirred with a mixture of glacial acetic acid (250 mL) and chloroform (200 mL) for 1 hr.

The chloroform solution is washed with water (2 × 250 mL) and stirred with glacial acetic acid (250 mL) for 1 hr (Note 6). The solution that results is washed with water (2 × 250 mL), and the chloroform phase is treated with 1.5 L of hexane and kept at 2°C for 48 hr. The material that precipitates is collected and dried at 0.1 mm in a desiccator (calcium chloride) for 5 hr to give *p*-methoxyphenyllead triacetate (20–22 g, 35–40%) as pale-yellow crystals, mp 138–139°C (Note 7). The product may be kept for at least 3 weeks if stored at 2°C in a sealed container.

B. *Ethyl 1-(p-methoxyphenyl)-2-oxocyclohexanecarboxylate*. A 250-mL, one-necked, round-bottomed flask, equipped with a magnetic stirring bar, is charged with 22.2 g (45 mmol) of p-methoxyphenyllead triacetate, 10.8 g (135 mmol) of pyridine (Note 8), and 70 mL of chloroform (Note 9). To this solution is added 7.0 g (41 mmol) of ethyl 2-oxocyclohexanecarboxylate (Note 10), a calcium chloride drying tube is put in place, and the mixture is stirred at 40°C (Note 11).

After 24 hr, the reaction mixture is diluted with chloroform (80 mL), and washed with water (150 mL) and 3 *M* sulfuric acid (2 × 150 mL). The water and sulfuric acid washings are each washed (Note 12) with 100 mL of chloroform. The combined chloroform extracts are washed with water (2 × 250 mL), dried with magnesium sulfate, and the solvent removed to give an orange–colored oil (10.3 g) that slowly crystallizes on standing. Crystallization from hexane (Note 5) gives 9.4 g (82%) of ethyl 1-(*p*-methoxyphenyl)-2-oxocyclohexanecarboxylate, mp 49–50°C.

2. Notes

1. Lead tetraacetate from Merck & Company, Inc. was used. Acetic acid was removed from the reagent at 0.1 mm for 24 hr, in the dark, in a desiccator containing potassium hydroxide pellets.
2. Dichloroacetic acid from Merck & Company, Inc. was used without further purification.
3. Anisole from Fluka AG was distilled before use.
4. A few drops of reaction mixture were shaken with water. A brown precipitate of PbO_2 indicates the presence of unreacted lead tetraacetate. For the quantities given, a reaction time of 1 hr at 15–20°C is adequate.
5. Hexanes, bp 60–69°C, certified by Fisher Scientific Company were used.
6. A second metathesis with glacial acetic acid is carried out to ensure complete conversion of the oligomer into the product.
7. It has been found that the yield of product is generally higher when the reaction is performed on a smaller scale. Reactions carried out on approximately one-third of the above scale have given yields of approximately 60%.
8. Pyridine from Merck & Company, Inc. was distilled and stored over potassium hydroxide pellets.
9. Chloroform was dried over calcium chloride and distilled prior to use.
10. The ethyl 2-oxocyclohexanecarboxylate used was Fluka AG practical grade and was distilled (bp 106–108°C/12 mm) before use.
11. The submitters report that after approximately 1 hr some lead(II) acetate is deposited as an orange–red gum that may temporarily restrict the motion of the stirring bar; this was not observed by the checkers. The material generally crystallizes after a short period as a white solid.
12. These washings are extracted separately in order to minimize formation of solid lead(II) sulfate.

3. Discussion

The procedure described here serves to illustrate a new, general method for effecting the α-arylation of β-dicarbonyl compounds by means of an aryllead triacetate under very mild conditions. Although the first synthesis of an aryllead triacetate was reported relatively recently, a wide range of these compounds can now be readily prepared.[2] The most direct route to these compounds is plumbation of an aromatic compound with lead tetraacetate, and in the procedure reported here *p*-methoxyphenyllead triacetate has been prepared in this way. It may also be obtained by reaction of the diarylmercury[3] or the corresponding aryltrialkylstannane[4] with lead tetraacetate; the latter provides a convenient and very general route to aryllead triacetates.

The first synthesis of *p*-methoxyphenyllead triacetate by direct plumbation was reported by Harvey and Norman,[5] who obtained the compound in 24% yield by heating anisole and lead tetraacetate in acetic acid at 80°C for 4 days. Recently it has been found[2] that a much faster reaction and higher yield of aryllead compounds can be achieved by use of a haloacetic acid in place of acetic acid, and this has allowed the synthesis of a greater range of aryllead triacetates by direct plumbation. The improved reaction rate is presumably due to an increase in electrophilicity of lead when acetate is exchanged for a more electron-withdrawing ligand. The choice of the haloacetic acid depends on the reactivity of the aromatic substrate; thus, while dichloroacetic acid has been found best for the plumbation of anisole, trichloroacetic acid is preferred in the case of toluene and biphenyl.[2]

Aryllead tricarboxylates have been shown to be intermediates in two new routes to phenols,[6, 7] and to have considerable potential as reagents for the *C*-arylation of carbon acids that are more acidic than diethyl malonate. A study of their reactions with β-diketones,[8] β-keto esters,[9] α-hydroxymethylene ketones,[10] derivatives of Meldrum's acid and barbituric acid,[11] and nitroalkanes[12] has established that such compounds, which contain only one replaceable hydrogen, undergo smooth arylation in high yield under the conditions outlined in this procedure. Compounds that contain two replaceable hydrogens are less predictable in their behavior. When a 1 : 1 ratio of substrate to aryllead compound is used, dimedone gave only diarylated product in high yield, while ethyl acetoacetate gave both mono- and diarylated products in only moderate yield.

Recently it has been shown that triphenylbismuth carbonate[13] and pentaphenyl-bismuth[14] can be used to achieve a similar arylation of β-dicarbonyl compounds. These reagents also react under very mild conditions and yields are generally high. Prior to the introduction of the organolead and organobismuth reagents, the most promising procedure for arylation of β-dicarbonyl compounds involved reaction of the enolate anion with a diaryliodonium salt, usually at 80–100°C.[15] Although only a limited range of substrates has been examined, it would appear that yields are only moderate, and in the case of dimedone a mixture of mono-, di-, and *O*-arylated

products is produced. A further method, which has obvious limitations, involves the copper-catalyzed substitution of bromine in 2-bromobenzoic acids by the enolate anion of a β-dicarbonyl compound.[16]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

PbO_2

haloacetic acid

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

hydrogen (1333-74-0)

chloroform (67-66-3)

bromine (7726-95-6)

Anisole (100-66-3)

pyridine (110-86-1)

potassium hydroxide pellets (1310-58-3)

toluene (108-88-3)

lead(II) acetate

Biphenyl (92-52-4)

Ethyl acetoacetate (141-97-9)

diethyl malonate (105-53-3)

dichloroacetic acid (79-43-6)

magnesium sulfate (7487-88-9)

Barbituric acid (67-52-7)

trichloroacetic acid (76-03-9)

dimedone (126-81-8)

ethyl 2-oxocyclohexanecarboxylate (1655-07-8)

hexane (110-54-3)

p-Methoxyphenyllead triacetate (18649-43-9)

lead(II) sulfate (7446-14-2)

triphenylbismuth carbonate

pentaphenyl-bismuth

ETHYL 1-(p-METHOXYPHENYL)-2-OXOCYCLOHEXANECARBOXYLATE (95793-86-5)

lead tetraacetate

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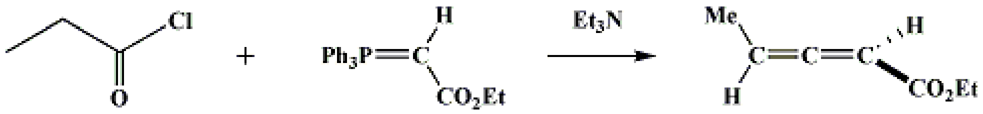
Organic Syntheses, CV 7, 232

α-ALLENIC ESTERS FROM α-PHOSPHORANYLIDENE ESTERS AND ACID CHLORIDES: ETHYL 2,3-PENTADIENOATE

[2,3-Pentadienoic acid, ethyl ester]



Submitted by Robert W. Lang[1] and Hans-Jürgen Hansen[2].
Checked by William F. Burgoyne and Robert M. Coates.

1. Procedure

A 1-L, three-necked, round-bottomed flask is equipped with a nitrogen inlet, a 250-mL, pressure-equalizing dropping funnel fitted with a gas outlet, and a Teflon-coated magnetic stirring bar. The flask is charged with 300 mL of dichloromethane (Note 1) and 34.8 g (0.10 mol) of ethyl (triphenylphosphoranylidene)acetate (Note 2) and flushed with nitrogen. The yellow solution is stirred at 25°C as a solution of 10.1 g (0.10 mol) of triethylamine (Note 3) in 100 mL of dichloromethane is added dropwise over 5 min. After 10 min, 9.25 g (0.10 mol) of propionyl chloride (Note 4) in 100 mL of dichloromethane is added dropwise to the vigorously stirred solution over 15 min (Note 5). Stirring is continued for an additional 0.5 hr (Note 6), after which the clear, yellow-tinted mixture is evaporated on a rotary evaporator at reduced pressure using a water bath maintained at 25°C (Note 7). A 500-mL portion of pentane (Note 8) is added to the semisolid residue, and the slurry is allowed to stand for 2 hr while it is shaken periodically to facilitate solidification and to complete the extraction of the product. The precipitate is removed by filtration through a coarse, sintered-glass Büchner funnel, and the filter cake is washed with a 50-mL portion of pentane. The filtrates are combined and concentrated at reduced pressure to approximately one-fourth of the original volume using a water bath maintained at 25°C. The mixture is filtered again to remove triphenylphosphine oxide, and the remaining solvent is then evaporated. Rapid distillation of the residual liquid in a short-path distillation apparatus under reduced pressure (Note 9) affords a small forerun amounting to 0.5 mL or less and 7.8–8.1 g (62–64%) of ethyl 2,3-pentadienoate, bp 57–59°C (12–14 mm) (Note 10) and (Note 11).

2. Notes

1. Dichloromethane was purified by percolation through Woelm activity grade 1 basic alumina and stored under nitrogen.
2. Ethyl (triphenylphosphoranylidene)acetate is available from Fluka AG and Tridom Chemical Inc. under the name (ethoxycarbonylmethylene)triphenylphosphorane and from Aldrich Chemical Company, Inc. under the name (carbethoxymethylene)triphenylphosphorane. The reagent may be prepared from triphenylphosphine and ethyl bromoacetate by the following procedure.[3]
A 1-L, two-necked, round-bottomed flask fitted with a dropping funnel and a mechanical stirrer is charged with 131.0 g (0.5 mol) of triphenylphosphine (Fluka AG, purum) and 250 mL of benzene (Merck, pro analysi). The solution is stirred vigorously while 83.5 g (0.5 mol) of ethyl bromoacetate (Fluka AG, practical-grade) is added dropwise at a rate that maintains the reaction mixture at, or slightly above, room temperature. After a total of 2 hr the reaction is complete and the colorless phosphonium salt is filtered. The salt is washed with 300 mL of cold benzene and 200 mL of pentane and then dissolved in 3 L of water at room temperature. Some further organic impurities are removed by extraction with ether, after which 2 drops of 2% alcoholic phenolphthalein are added. The aqueous solution is stirred vigorously and cooled in an ice bath as 2 *M* aqueous sodium hydroxide is added slowly until the pink endpoint is reached (pH 8–10). The crystalline phosphorane is collected by filtration, washed thoroughly with cold water, and dried, first with a rotary evaporator under reduced pressure at 60°C and then overnight in a drying oven at 180 mm and 70°C. The white to cream-colored crop of ethyl (triphenylphosphoranylidene)acetate, mp 124–126°C, weighs 150–156 g (86–90%) and may be used for the preparation of α-allenic esters without further purification.
3. Triethylamine was supplied by Fluka AG and Aldrich Chemical Company, Inc.
4. Propionyl chloride was purchased from Fluka AG and Aldrich Chemical Company, Inc. and was freshly distilled at 78–80°C (760 mm) prior to use.
5. The checkers maintained the temperature of the reaction mixture at ca. 25°C by cooling with a water bath during the addition of propionyl chloride.
6. The progress of the reaction may be followed by analytical thin-layer chromatography on alumina. The submitters used polygram precoated plastic sheets (Alox N/UV_{254}) purchased from Macherey-Nagel, Inc. The plates were developed with 1 : 1 hexane : ether and stained with basic permanganate. The retardation factor of the product is 0.56.

7. For the isolation of relatively volatile α-allenic esters such as ethyl 2,3-pentadienoate, the submitters recommend that the rotary evaporation be carried out with cooling in an ice bath. When this precaution was taken, the submitters obtained 8.5–9.5 g (67–75%) of product after distillation.

8. The checkers dried the pentane over sodium wire prior to use.

9. The checkers stirred the distilling liquid rapidly with a magnetic stirrer and maintained a bath temperature of 75–85°C throughout the distillation.

10. Ethyl 2,3-pentadienoate has the following spectral properties: IR (thin film) cm^{-1}: 1965, 1720, 1410, 1250, 1025, 865, 790; ^1H NMR (CCl_4) δ: 1.26 (t, 3 H, *J* = 7, OCH_2CH_3), 1.78 (m, 3 H, CH_3), 4.11 (q, 2 H, *J* = 7, OCH_2CH_3), 5.28–5.68 (m, 2 H, at C-2 and C-4).

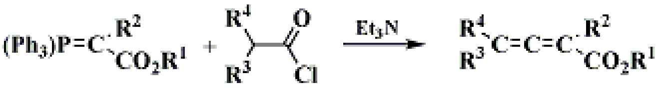
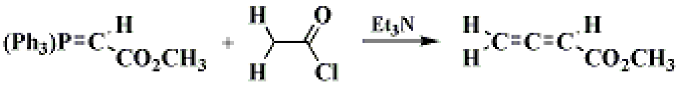
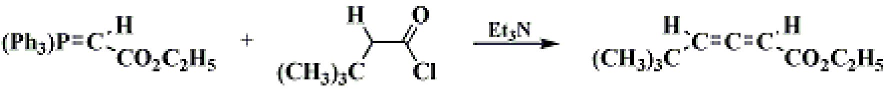
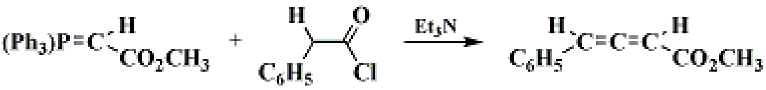
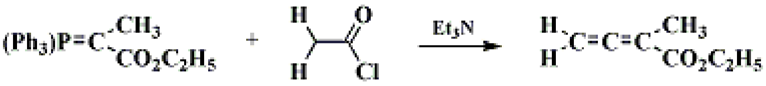
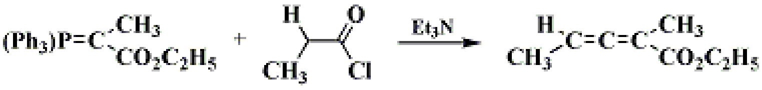
11. On 0.01-mol scale the yield of ethyl 2,3-pentadienoate is 0.79–0.93 g (64–74%). The product was purified by bulb-to-bulb distillation with a Kugelrohr apparatus at 12–14 mm with an oven temperature at 75–85°C.

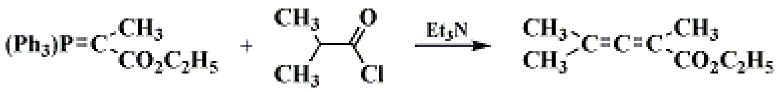
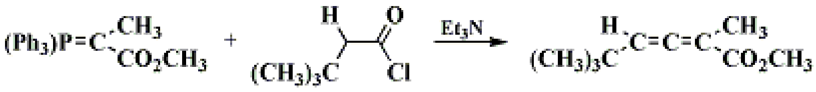
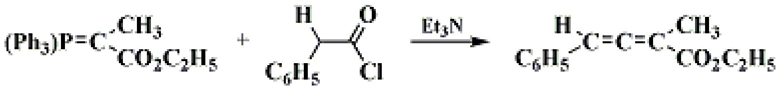
3. Discussion

The acylation of Wittig reagents provides the most convenient means for the preparation of allenes substituted with various electron-withdrawing substituents.[4] The preparation of α-allenic esters has been accomplished by the reaction of resonance-stabilized phosphoranes with isolable ketenes[5,6,7,8,9,10] and ketene itself[11] and with acid chlorides in the presence of a second equivalent of the phosphorane.[6] The disadvantages of the first method are the necessity of preparing the ketene and the fact that the highly reactive monosubstituted ketenes evidently cannot be used. The second method fails when the α-carbon of the phosphorane is unsubstituted.[12]

TABLE I

PREPARATION OF α-ALLENIC ESTERS BY THE WITTIG REACTION[13]

R^1	R^2	R^3	R^4	Solvent	Procedure[a]	Yield (%)
						
CH_3	H	H	H	CH_2Cl_2	A	 40
C_2H_5	H	$(CH_3)_3C$	H	CH_3CN	B	 55
CH_3	H	C_6H_5	H	CH_3CN	B	 23
C_2H_5	CH_3	H	H	CH_2Cl_2	A	 59
C_2H_5	CH_3	CH_3	H	CH_2Cl_2	A	 74

C_2H_5	CH_3	CH_3		$CH_3CH_2Cl_2$	B		39
CH_3	CH_3	$(CH_3)_3C$	H	CH_3CN	B		66
C_2H_5	CH_3	C_6H_5	H	CH_2Cl_2	A		70

[a]The reaction times varied from 10 min to 18 hr. Procedure: A—the corresponding phosphonium salt was used with the addition of 2 mol of triethylamine; B—the corresponding phosphorane was used with the addition of 1 mol of triethylamine.

The present procedure affords a general method for preparing α-allenic esters (Table I) that avoids the limitations of the previous methods.[12] Thus, α-allenic esters unsubstituted at C-2 are now available in generally satisfactory yields. Ethyl 2,3-pentadienoate, the title compound, had not been prepared prior to the development of this procedure by the submitters. The mild conditions (i.e., room temperature for relatively short times), avoid the base-catalyzed isomerization of the conjugated allenes to acetylenes.[14] The corresponding phosphonium salts may also be used directly in the reaction provided two equivalents of triethylamine are employed, obviating the lengthy process for drying the phosphorane.[15] Dichloromethane and acetonitrile have been used as solvents for the reaction.[12] The α-allenic esters are usually obtained in analytically pure form after bulb-to-bulb distillation. They may also be purified by column chromatography on alumina with 9 : 1 hexane : ether as eluant.[14]

The submitters have shown that these reactions proceed by dehydrochlorination of the acid chloride to the ketene, which is then trapped by reaction with the phosphorane. The resulting betaine decomposes to the allenic ester via an oxaphosphetane. In contrast, the reaction of acid chlorides with 2 equiv of phosphoranes involves initial acylation of the phosphorane followed by proton elimination from the phosphonium salt.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 436

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alumina

Benzene (71-43-2)

ether (60-29-7)

acetonitrile (75-05-8)

sodium hydroxide (1310-73-2)

nitrogen (7727-37-9)

sodium wire (13966-32-0)

Pentane (109-66-0)

dichloromethane (75-09-2)

phenolphthalein (77-09-8)

propionyl chloride (79-03-8)

Ethyl bromoacetate (105-36-2)

hexane (110-54-3)

triethylamine (121-44-8)

triphenylphosphine (603-35-0)

triphenylphosphine oxide (791-28-6)

betaine (107-43-7)

phosphorane (7723-14-0)

Ethyl 2,3-pentadienoate, 2,3-Pentadienoic acid, ethyl ester (74268-51-2)

ethyl (triphenylphosphoranylidene)acetate, (ethoxycarbonylmethylene)triphenylphosphorane, (carbethoxymethylene) triphenylphosphorane (1099-45-2)

oxaphosphetane

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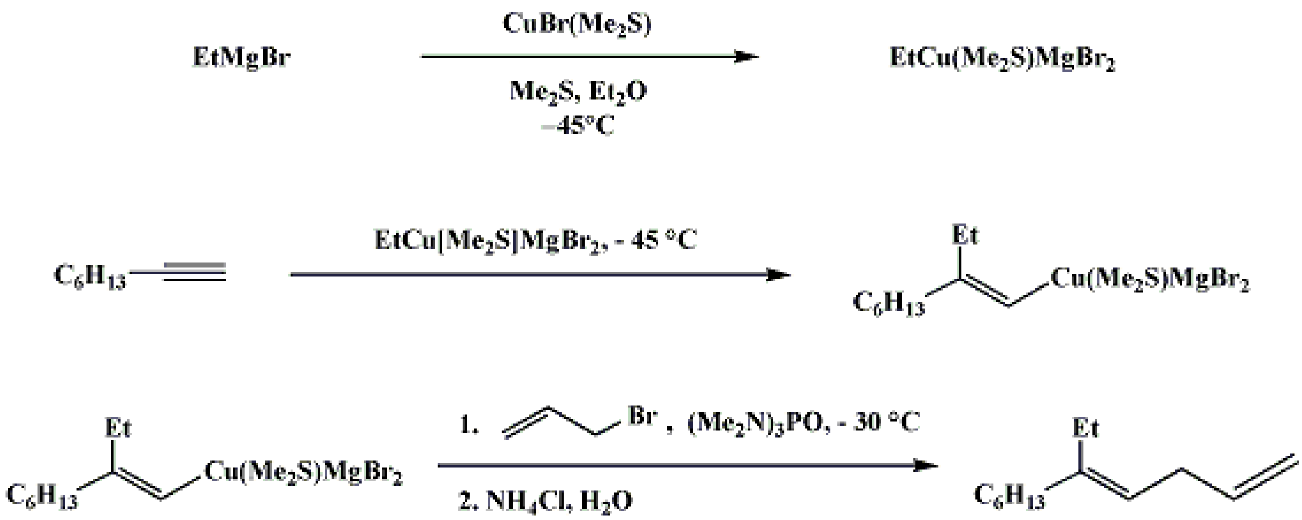
Organic Syntheses, CV 7, 236

ADDITION OF AN ETHYLCOPPER COMPLEX TO 1-OCTYNE: (*E*)-5-ETHYL-1,4-UNDECADIENE

[1,4-Undecadiene, 5-ethyl-, (*E*)-]



Submitted by Ramnath S. Iyer and Paul Helquist[1].
Checked by Brian H. Johnston and Andrew S. Kende.
Checked by Ronald C. Newbold and Andrew S. Kende.

1. Procedure

Caution! This experiment should be performed in an efficient fume hood because of the unpleasant odor of dimethyl sulfide.

A dry, 1-L, one-necked, round-bottomed flask is equipped with a Teflon-coated magnetic stirring bar and a three-way stopcock bearing a rubber septum (Note 1), and the flask is charged with 25.2 g (0.123 mol) of the dimethyl sulfide complex of cuprous bromide (Note 2). An argon or nitrogen (Note 3) atmosphere is established in the flask by repeated cycles of evacuation with an oil pump and refilling with the inert gas. Through use of a syringe or cannula, 150 mL of diethyl ether (Note 4) and 120 mL of dimethyl sulfide (Note 4)) are added. After the mixture is stirred for a few minutes at 25°C, the resulting clear and colorless solution is cooled to–45°C (Note 5) and (Note 6). A 2.73 *M* solution (45.0 mL, 0.123 mol) of ethylmagnesium bromide in ether (Note 7) is added dropwise with a syringe or cannula over a period of 10 min. The suspension of yellow–orange solid is stirred at–45°C for 2 hr, and 1-octyne (16.0 mL, 0.109 mol; (Note 4)) is added with a syringe or cannula over a period of 2 min. After the solution is stirred at –45°C for 2 hr, it is cooled to –78°C (Note 5) and maintained at this temperature during the successive additions of *N,N'*-dimethylpropyleneurea, DMPU (27.7 mL, 0.223 mol; (Note 8)) and allyl bromide (11.4 mL, 0.131 mol; (Note 4)). The mixture is immediately warmed to –30°C and stirred at–30°C for 12 hr; it is warmed to 0°C and quenched by the addition of 30 mL of a saturated, aqueous solution of ammonium chloride adjusted to pH 8 with ammonium hydroxide. The mixture is stirred at 25°C in the air for 1.5 hr (Note 9) and is then shaken in a separatory funnel with a mixture of additional diethyl ether (50 mL) and water (50 mL). The dark-blue aqueous layer is drawn off and the organic layer is washed with additional 50-mL portions of the ammonium chloride solution (pH 8) until the washings are colorless. The organic layer is washed separately with water (50 mL) and saturated aqueous sodium chloride solution (50 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation at 25°C (25 min). The residue consists of 15.9 g of yellow oil that is purified by distillation under reduced pressure

through a 15-cm Vigreux column to give 13.9 g (71%) (Note 10) of (*E*)-5-ethyl-1,4-undecadiene as a clear, colorless liquid, bp 56°C (0.70 mm; (Note 11)).

2. Notes

1. The stopcock is constructed as shown below so that a source of inert gas and vacuum may be attached to the horizontal tubulation and liquid reagents and solutions may be transferred into the reaction flask with a syringe needle or cannula inserted through a rubber septum placed over the end of the vertical tubulation. In order to avoid air leaks through the septum into the reaction flask when reagents are not being added, the stopcock is normally turned to close off the vertical tubulation, but to leave the flask open to the argon source.

2. This complex is prepared from cuprous bromide and dimethyl sulfide according to the procedure of House.[2] The complex must be pure white. Slightly impure samples will produce pinkish solutions that are unsatisfactory for this procedure. Normally, the complex is dark red when it is first prepared, but the required state of purity can be achieved by two or three recrystallizations under a nitrogen atmosphere as described by House.[2] We have found, however, that if the initially formed complex has a distinctly green appearance, it cannot be purified satisfactorily. Others have also been concerned about this matter of purification.[3,4]

3. The checkers found that the yields were diminished when the reaction was run under prepurified nitrogen, but they did obtain the reported yields using argon. The submitters, however, have never experienced difficulty using the prepurified nitrogen available in their laboratory.

4. Commercially obtained materials were purified before use as described below. Diethyl ether was distilled from a dark-blue or dark-purple solution of sodium benzophenone radical anion or dianion under nitrogen. This solution was obtained by dissolving 10 g of benzophenone in 1 L of commercial anhydrous ether, adding 10 g of freshly pressed sodium wire, and heating the mixture at reflux under nitrogen until the characteristic blue or purple color developed. Dimethyl sulfide (Aldrich Chemical Company, Inc.), 1-octyne (Chemical Samples Company or Albany International Chemicals), and allyl bromide (Columbia Organics) were distilled under nitrogen at atmospheric pressure. Dimethylpropyleneurea (DMPU) (Aldrich Chemical Company, Inc.) was distilled at aspirator pressure from calcium hydride.

5. Constant temperatures were maintained by using dry ice–acetone (−78°C) or dry ice–acetone/carbon tetrachloride baths (−25 to−45°C; the temperature tends toward the upper part of this range as the amount of acetone used is decreased) or more conveniently through the use of an acetone bath equipped with a Neslab CryoCool Model CC-100F low-temperature unit, a Cole-Parmer Versa-Therm Model 2158 temperature controller, and a 500-W immersible heating coil. The temperature of the alkenylcopper solution must not be allowed to exceed−15°C; above this temperature rapid coupling to give a diene occurs.

6. When the solution of the cuprous bromide complex is cooled, a portion of the reagent may precipitate, but this behavior does not affect the overall results of the experiment.

7. The ethylmagnesium bromide solution was obtained from Alfa Products, Morton Thiokol, Inc. and was titrated before use by the method of Watson and Eastham.[5]

8. (a) Checkers observed the freezing of some material on addition of DMPU and allyl bromide, making it difficult to maintain stirring. Vigorous, frequent shaking was performed to ensure good mixing. (b) The submitters used hexamethylphosphoric triamide, HMPA, in the original submission, but the Board of Editors of *Organic Syntheses* decided that, in view of the suspected carcinogenicity of this solvent, all procedures using it would be rechecked with DMPU. See (Note 10) for the effect of this substitution on the yield.

9. Stirring the mixture in the air simplifies the workup procedure because cuprous complexes are oxidized to cupric compounds that are highly soluble in water or the aqueous ammonia workup medium of this experiment.

10. This yield is approximately 14% lower than that reported using HMPA; however, this result is consistent with those reported by Seebach[6] for the substitution of DMPU.

11. The spectral characteristics of the final product are as follows: IR (neat) cm^{-1}: 3080, 2960, 2915, 2800, 1660, 1640, 1465, 1175, 940, and 910; H^1 NMR (80 MHz, $CDCl_3$) δ: 0.78–2.13 (several overlapping m, 18 H, other saturated C-H's), 2.63 (t, 2 H, J = 6.5, C=CH-CH_2-CH=CH_2), 4.70–5.20 (m, 3 H, other alkenyl C-H's), 5.50–6.05 (m, 1 H, alkenyl C-H); mass spectrum (70 eV) *m/e* (relative intensity) 181.1 (M + 1, 1.3), 180.1 (M, 9.2).

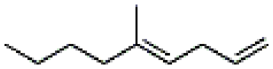
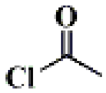
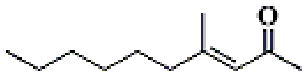
3. Discussion

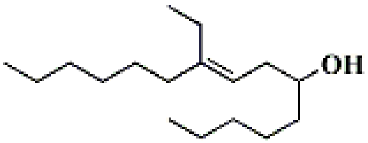
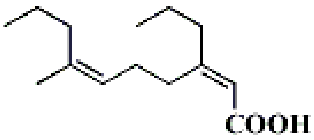
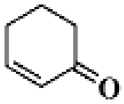
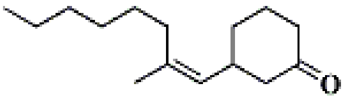
The procedure described above provides an approach to trisubstituted alkenes, compounds that are very common among natural products and that serve as key intermediates in the synthesis of other types of compounds.[7] The methods that have been developed for the preparation of trisubstituted alkenes are far too numerous to discuss to any significant extent here, but they have been the subject of previous review articles.[9 10 11 12] Very briefly, however, a large portion of the available methods may be divided among the following categories:[8] (1) elimination or cleavage reactions of organic halides and other compounds bearing leaving groups; (2) carbonyl condensation reactions of phosphonium ylides and other carbanionic or at least nucleophilic organic intermediates; (3) cleavage or rearrangements of other systems; (4) substitution reactions of alkenyl halides and related compounds; (5) reactions of various allylmetal and other allylic systems; (6) reactions of various alkenylmetal species; and (7) addition reactions to acetylenes, 1,3-dienes, and allenes.

The reaction of organocopper reagents with simple, unactivated acetylenes, an example of the last class of methods in the preceding list, serves as the basis of the procedure described here. This addition reaction was first reported by Normant in 1971[13] and has been investigated extensively since that time by not only Normant,[14] but also by Vermeer,[15] Helquist,[8] Levy,[16] and others.[4, 17 18 19 20 21 22 23 24 25 26 27 28 29 30,31] An important modification[8] of the reaction that has been incorporated in the present preparation is the use of dimethyl sulfide as a ligand and cosolvent, which permits much higher yields and a broader range of applicability than the originally reported procedure.[13]

The specific example reported here is one of several preparations that have been developed using the same general reaction sequence. A brief summary of other representative cases is given in Table I.[8, 32] Notice that the alkenylcopper intermediates react with a variety of electrophilic reagents in addition to alkyl halides. It is especially

TABLE I
TRISUBSTITUTED ALKENES FROM ADDITION OF GRIGNARD-DERIVED ALKYLCOPPER COMPLEXES TO ACETYLENES, FOLLOWED BY REACTION WITH ELECTROPHILIC REAGENTS

Grignard Reagent	Acetylene	Electrophile	Product	Overall Yield (%)^{a,b}
MeMgBr				84
MeMgBr				65

EtMgBr				94
		CO_2		50
				73

[a]Since yields are sensitive to traces of oxygen during the reactions, the use of an argon atmosphere is strongly recommended.

[b]See [9,10,11,12,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31].

noteworthy that the overall sequences leading to trisubstituted alkenes have been shown to proceed with greater than 99.9% stereoselectivity.[8] This unusually high degree of control of alkene configuration is of great value in natural products synthesis. The overall stereochemistry is indicative of *syn* addition of the alkylcopper complexes to acetylenes, a result which is observed for several types of carbometallation (or insertion) reactions.[14]

In summary, the procedure described in this chapter is representative of a very general, highly stereoselective approach to trisubstituted alkenes. The usefulness of this methodology has already been demonstrated in total synthesis.[8,21,22,24,27,29,30,31,32]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

dimethyl sulfide complex of cuprous bromide

sodium benzophenone

acetylene (74-86-2)

ammonia (7664-41-7)

ether, diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

sodium chloride (7647-14-5)

Allyl bromide (106-95-6)

oxygen (7782-44-7)

nitrogen (7727-37-9)

acetone (67-64-1)

Benzophenone (119-61-9)

sodium wire (13966-32-0)

cuprous bromide (7787-70-4)

ammonium hydroxide (1336-21-6)

ethylmagnesium bromide (925-90-6)

magnesium sulfate (7487-88-9)

dimethyl sulfide (75-18-3)

calcium hydride (7789-78-8)

hexamethylphosphoric triamide (680-31-9)

argon (7440-37-1)

1-OCTYNE (629-05-0)

dimethylpropyleneurea, N,N'-dimethylpropyleneurea (7226-23-5)

(E)-5-Ethyl-1,4-undecadiene, 1,4-Undecadiene, 5-ethyl-, (E)- (107445-19-2)

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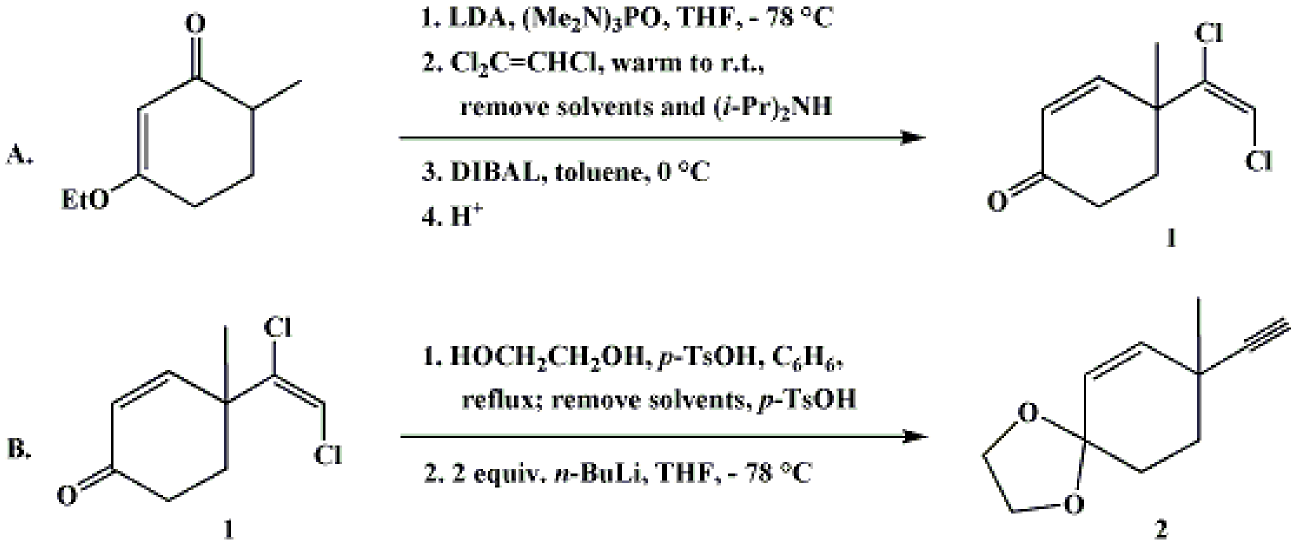
DICHLOROVINYLATION OF AN ENOLATE: 8-ETHYNYL-8-METHYL-1,4-DIOXASPIRO[4.5]DEC-6-ENE

[1,4-Dioxaspiro[4.5]dec-6-ene, 8-ethynyl-8-methyl-]



Submitted by Andrew S. Kende and Pawel Fludzinski[1].
Checked by P. Wovkulich, F. Barcelos, and Gabriel Saucy.

1. Procedure

Caution! Hexamethylphosphoric triamide and trichloroethylene are suspected carcinogens. All operations with either one should be performed in an efficient hood. The use of disposable gloves is highly recommended. Glassware should be rinsed with copious amounts of water into separate waste containers before removal from the hood.

A. *4-[(E)-1,2-Dichlorovinyl]-4-methyl-2-cyclohexen-1-one* **(1)**. A dry, 3-L, one-necked, round-bottomed flask is equipped with a magnetic stirrer and a 500-mL pressure-equalizing dropping funnel. The dropping funnel is fitted with a rubber septum and the air in the system is replaced with dry nitrogen (Note 1). The flask is charged with 1500 mL of anhydrous tetrahydrofuran (Note 2) and 38.9 g (54 mL, 0.38 mol) of diisopropylamine (Note 3). The flask is cooled to 0°C with an ice bath. A 1.51 *M* hexane solution of butyllithium (255 mL, 0.38 mol) is added dropwise with stirring over a 30-min period. The resulting lithium diisopropylamide is cooled to −78°C with a dry ice-acetone bath (Note 4). A solution of 57.8 g (0.38 mol) of 3-ethoxy-6-methyl-2-cyclohexen-1-one (Note 5) in 400 mL of anhydrous tetrahydrofuran is added dropwise with stirring at −78°C over a 90-min period, followed immediately by the addition of 68 g (66 mL, 0.38 mol) of neat hexamethylphosphoric triamide (Note 6) over a 5-min period. The solution is stirred at −78°C for 45 min, followed by the dropwise addition of 52.6 g (36 mL, 0.40 mol) of neat trichloroethylene (Note 7). The solution is allowed to warm to room temperature slowly over a 6-hr period. As the solution warms, the color changes from pale yellow to olive green, to pale red, and finally to black. After 6 hr (Note 8) the solution is quenched with 1000 mL of water and the organic phase is separated. The aqueous phase is extracted four times with 250 mL of diethyl ether. The organic phases are combined and washed four times with 750 mL of water and twice with 750 mL of brine and dried over magnesium sulfate. The solvent is removed on a rotary evaporator and recovered starting material is removed by fractional distillation at 91–93°C (1 mm) through a 15-cm Vigreux column. The residual crude 6-[(*E*)-1,2-dichlorovinyl]-3-ethoxy-6-

methyl-2-cyclohexen-1-one (Note 9) is dissolved in 400 mL of toluene and placed in a dry, 2-L, one-necked, round-bottomed flask, equipped with a mechanical stirrer; a 500-mL pressure-equalizing dropping funnel is fitted with a rubber septum and the air in the system is replaced with dry nitrogen (Note 1). The solution is cooled to 0°C with an ice bath. A 1 *M* hexane solution of diisobutylaluminum hydride (400 mL, 0.40 mol) (Note 10) is added dropwise with stirring at 0°C over a 1-hr period. The solution is stirred for 2 additional hr at 0°C. To quench the reaction 200 mL of methanol is carefully added to the stirred reaction mixture, followed slowly at first then more rapidly with 400 mL of water and then 300 mL of 10% sulfuric acid solution. After the mixture is stirred for 10 min, it is transferred to a separatory funnel and 500 mL of 10% sulfuric acid solution is added. The separatory funnel is shaken vigorously for 5 min and the organic phase is separated. The aqueous phase is extracted four times with 300 mL of diethyl ether. The organic phases are combined and washed twice with 300 mL of saturated sodium bicarbonate solution, twice with 300 mL of water, twice with 300 mL of brine, and dried over magnesium sulfate. Solvent removal on a rotary evaporator followed by short-path distillation at reduced pressure affords 31–34 g (40–44%, based on 3-ethoxy-6-methyl-2-cyclohexen-1-one) of 4-[(*E*)-1,2-dichlorovinyl]-4-methyl-2-cyclohexen-1-one (1) as a colorless oil, bp 75–78°C (0.1 mm) (Note 11).

B. *8-Ethynyl-8-methyl-1,4-dioxaspiro[4.5]dec-6-ene* **(2)**. A dry, 1-L, one-necked, round-bottomed flask is equipped with a magnetic stirrer, Dean-Stark trap, and reflux condenser. The flask is charged with 500 mL of benzene, 12.0 g (0.059 mol) of 4-[(*E*)-1,2-dichlorovinyl]-4-methyl-2-cyclohexen-1-one, 12.2 g (11 mL, 0.20 mol) of ethylene glycol and 40 mg (a catalytic amount) of *p*-toluenesulfonic acid. After the solution is refluxed for 24 hr, it is poured into 200 mL of saturated sodium bicarbonate solution. The organic phase is separated and the aqueous phase is extracted four times with 50 mL of diethyl ether. The organic phases are combined and washed twice with 100 mL of water and once with 100 mL of brine and are dried over magnesium sulfate. The solvent is removed on a rotary evaporator, and the resulting crude 8-[(*E*)-1,2-dichlorovinyl]-8-methyl-1,4-dioxaspiro[4.5]dec-6-ene (Note 12) is dissolved in 200 mL of anhydrous tetrahydrofuran and placed in a dry, 1-L, one-necked, round-bottomed flask equipped with a magnetic stirrer and a 500-mL pressure-equalizing dropping funnel. The dropping funnel is fitted with a rubber septum and the air in the system is replaced with dry nitrogen (Note 1). The solution is cooled to −78°C with a dry ice-acetone bath (Note 4). A 1.51 *M* hexane solution of butyllithium (76 mL, 0.12 mol) is added dropwise with stirring at −78°C over a 30-min period. The solution is stirred at −78°C for 2 hr, the cold bath is removed, and stirring is continued for 90 min. The solution is poured into 100 mL of water and the organic phase is separated. The aqueous phase is extracted four times with 25 mL of diethyl ether. The organic phases are combined and washed twice with 75 mL of water, twice with 75 mL of brine, and dried over magnesium sulfate. Solvent removal on a rotary evaporator followed by short-path distillation at reduced pressure yields 5.5-6.3 g (52–60%) of 8-ethynyl-8-methyl-1,4-dioxaspiro[4.5]dec-6-ene as a colorless oil, bp 88–90°C (1 mm) (Note 13).

2. Notes

1. This procedure is accomplished by alternatively evacuating and filling the funnel with dry nitrogen two times; an oil bubbler is used to maintain a slight positive pressure throughout the reaction.
2. Tetrahydrofuran is freshly distilled from sodium and benzophenone, as is all tetrahydrofuran used in this procedure.
3. Diisopropylamine is distilled from calcium hydride.
4. The flask is cooled with the dry-ice–acetone bath for 1 hr before the next addition to insure complete cooling of the solution.
5. See *Org. Synth. Coll. Vol. VII* **1990**, 208.
6. Hexamethylphosphoric triamide (HMPA) is freshly distilled from calcium hydride. Because

of the suspected carcinogenicity of HMPA, the editors of *Organic Synthesis* rechecked all procedures in which it has been used. In the case of the present procedure, it was found that the decrease in yield in Step A was very large (55% ρ 16%) and that the product was a mixture of **1** and the corresponding chloroalkyne. Thus DMPU, the suggested substitute solvent,[2] is unsatisfactory in the present case.

7. Trichloroethylene is freshly distilled from phosphorus pentoxide.

8. On a smaller scale, the reaction warms to room temperature more quickly and can be worked up after 4 hr. Extended reaction times (e.g., overnight) lead to the formation of by-products.

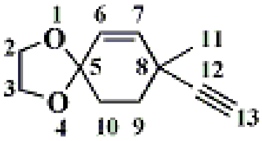
9. Distillation is not necessary at this point. Spectroscopic data for 6-[(*E*)-1,2-dichlorovinyl]-3-ethoxy-6-methyl-2-cyclohexen-1-one is as follows: ^{1}H NMR ($CDCl_3$) δ: 1.38 (t, 3 H, *J* = 6), 1.48 (s, 3 H), 1.8–2.7 (m, 4 H), 3.96 (q, 2 H, *J* = 6), 5.44 (s, 1 H), 6.36 (s, 1 H). A purified sample (bp 140–142°C, 1 mm) gave satisfactory analyses. Anal. calcd. for $C_{11}H_{14}Cl_2O_2$: C, 53.02; H, 5.68. Found: C, 53.20; H, 5.43.

10. Diisobutylaluminum hydride was purchased from Aldrich Chemical Company, Inc. Since the reagent is not titrated, excess is used to ensure complete reduction.

11. Spectroscopic data for 4-[(*E*)-1,2-dichlorovinyl]-4-methyl-2-cyclohexen-1-one are as follows: ^{1}H NMR ($CDCl_3$) δ: 1.50 (s, 3 H), 1.8-2.8 (m, 4 H), 5.92 (d, 1 H, *J* = 10), 6.34 (s, 1 H), 7.04 (d, 1 H, *J* = 10); ms (mass spectrum) (75 eV) *m/e* 204; IR ($CHCl_3$) cm^{-1}: 1680. Anal. calcd. $C_9H_{10}Cl_2O$: C, 52.71; H, 4.91. Found: C, 53.08, H, 5.03.

12. Spectroscopic data for 8-(*E*-1,2-dichlorovinyl)-8-methyl-1,4-dioxaspiro[4.5]dec-6-ene is as follows: ^{1}H NMR ($CDCl_3$) δ: 1.36 (s, 3 H), 1.6–2.6 (m, 4 H), 3.88–4.08 (m, 4 H), 5.56 (d, 1 H, *J* = 10), 6.08 (d, 1 H, *J* = 10), 6.28 (s, 1 H).

13. Spectroscopic data for 8-ethynyl-8-methyl-1,4-dioxaspiro[4.5]dec-6-ene are as follows: ^{1}H NMR ($CDCl_3$) δ: 1.32 (s, 3 H), 1.6–2.2 (m, 4 H), 2.12 (s, 1 H), 3.88–4.04 (m, 4 H), 5.64 (AB q, 2 H, *J* = 10); ms (75 eV) *m/e* 178; IR (neat) cm^{-1}: 3290, 2100. Anal. calcd. for $C_{11}H_{14}O_2$: (at C-11) C, 74.13; H, 7.92. Found: C, 73.96; H, 7.78. ^{13}C NMR ($CDCl_3$) δ: 28.1 (at C-11), 30.5 (at C-9 or C-10), 31.4 (at C-8), 34.6 (at C-9 or C-10), 64.0 (at C-2 or C-3), 64.3 (at C-2 or C-3), 68.4 (at C-13), 88.3 (at C-12), 104.5 (at C-5), 126.3 (at C-6), 137.0 (at C-7).



3. Dissusion

3. Discussion

Trichloroethylene serves as an effective reagent for the dichlorovinylation of lithium enolates of several conjugated ketones. Under similar reaction conditions, 2,6-dimethyl-cyclo-2-hexen-1-one and 2-ethyl-5-methoxy-1-tetralone give the analogous dichlorovinyl adduct in comparable yield.[3] This procedure represents an heretofore unknown, uncatalyzed[4] carbon–carbon bond forming reaction between enolates and a polychloroolefin that can subsequently provide access to α- and γ-acetylenic ketones.[5]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

brine

sulfuric acid (7664-93-9)

Benzene (71-43-2)

methanol (67-56-1)

diethyl ether (60-29-7)

sodium bicarbonate (144-55-8)

nitrogen (7727-37-9)

toluene (108-88-3)

Benzophenone (119-61-9)

sodium (13966-32-0)

ethylene glycol (107-21-1)

magnesium sulfate (7487-88-9)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

hexane (110-54-3)

trichloroethylene (79-01-6)

calcium hydride (7789-78-8)

diisobutylaluminum hydride (1191-15-7)

hexamethylphosphoric triamide (680-31-9)

p-toluenesulfonic acid (104-15-4)

lithium diisopropylamide (4111-54-0)

diisopropylamine (108-18-9)

3-Ethoxy-6-methyl-2-cyclohexen-1-one (62952-33-4)

8-Ethynyl-8-methyl-1,4-dioxaspiro[4.5]dec-6-ene, 1,4-Dioxaspiro[4.5]dec-6-ene, 8-ethynyl-8-methyl- (73843-26-2)

2,6-dimethyl-cyclo-2-hexen-1-one

2-ethyl-5-methoxy-1-tetralone

phosphorus pentoxide (1314-56-3)

4-[(E)-1,2-Dichlorovinyl]-4-methyl-2-cyclohexen-1-one (73843-27-3)

6-[(E)-1,2-dichlorovinyl]-3-ethoxy-6-methyl-2-cyclohexen-1-one (73843-25-1)

8-[(E)-1,2-dichlorovinyl]-8-methyl-1,4-dioxaspiro[4.5]dec-6-ene, 8-(E-1,2-dichlorovinyl)-8-methyl-1,4-dioxaspiro[4.5]dec-6-ene

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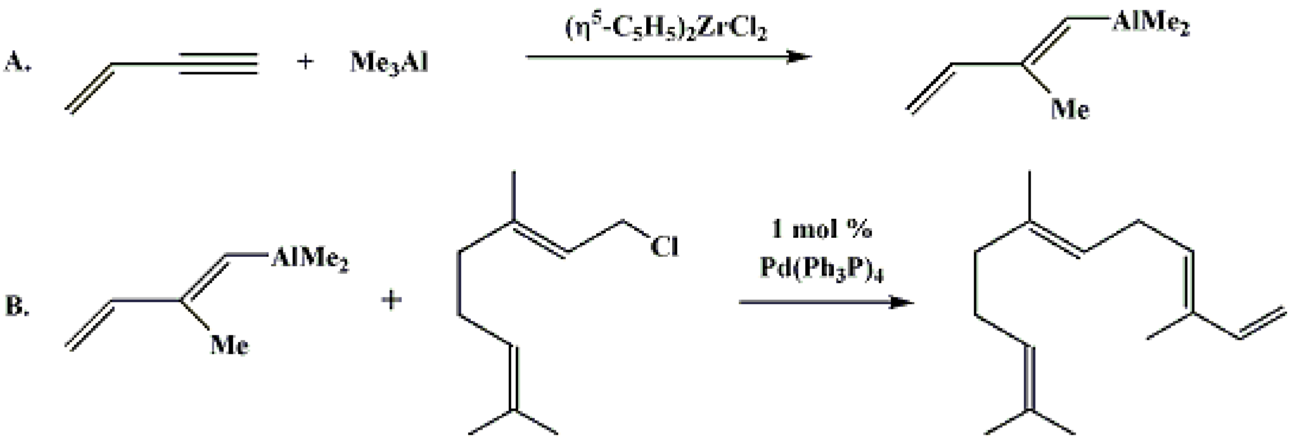
Organic Syntheses, CV 7, 245

PALLADIUM-CATALYZED SYNTHESIS OF 1,4-DIENES BY ALLYLATION OF ALKENYLALANES:α-FARNESENE

[1,3,6,10-Dodecatetraene, 3,7,11-trimethyl-]



Submitted by Ei-ichi Negishi[1] and Hajime Matsushita[2].
Checked by Pauline J. Sanfilippo and Andrew S. Kende.

1. Procedure

Caution! Trimethylalane (Note 1) is highly pyrophoric. It must be kept and used under a nitrogen atmosphere.

A. *(E)-(2-Methyl-1,3-butadienyl)dimethylalane*. An oven-dried, 1-L, two-necked, round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an outlet connected to a mercury bubbler is charged with 7.01 g (24 mmol) of dichlorobis (η5-cyclopentadienyl)zirconium (Note 2) and flushed with nitrogen. To this are added sequentially at 0°C 100 mL of 1,2-dichloroethane (Note 3), 12.48 g (120 mmol) of a 50% solution of 1-buten-3-yne in xylene (Note 4), and 120 mL (240 mmol) of a 2 *M* solution of trimethylalane in toluene (Note 1). The reaction mixture is stirred for 12 hr at room temperature and used in the next step without further treatment (Note 5).

B. *(3E, 6E)-3,7,11-Trimethyl-1,3,6,10-dodecatetraene (α-farnesene)*. To the solution of (E)-(2-methyl-1,3-butadienyl)dimethylalane prepared above are added 17.25 g (100 mmol) of geranyl chloride (Note 6) and 1.15 g (1 mmol) of tetrakis(triphenylphosphine)palladium (Note 7) dissolved in 100 mL of dry tetrahydrofuran (Note 8), while the reaction temperature is controlled below 25–30°C with a water bath. After the reaction mixture is stirred for 6 hr at room temperature, 250 mL of 3 *N* hydrochloric acid is slowly added at 0°C. The organic layer is separated and the aqueous layer is extracted twice with pentane. The combined organic layer is washed with water, saturated aqueous sodium bicarbonate, and water again. After the organic extract is dried over anhydrous magnesium sulfate, the solvent is removed thoroughly using a rotary evaporator (15–20 mm), and the crude product is passed through a short (15–20-cm) silica gel column (60–200 mesh) using hexane as an eluent (Note 9). After the hexane is evaporated using a rotary evaporator, the residue is distilled using a 12-cm Vigreux column to give 16.70 g (83% based on geranyl chloride) of α-farnesene as a colorless liquid, bp 63–65° (0.05 mm) (Note 10).

2. Notes

1. The submitters used trimethylalane available in a cylinder from Ethyl Corporation. Both neat trimethylalane and its 2 *M* solution in toluene gave comparable results. The toluene solution of trimethylalane is also available from Aldrich Chemical Company.

2. The submitters used dichlorobis(η^5-cyclopentadienyl)zirconium available from Aldrich Chemical Company. This chemical is sufficiently air-stable to be handled in air.

3. The 1,2-dichloroethane available from Aldrich Chemical Company was distilled from phosphorus pentoxide before use. Although less effective, dichloromethane may also be used in the carbometallation step.

4. The submitters used a 50% solution of 1-buten-3-yne in xylene, available from Chemical Samples Company. For transferring this solution, the following procedure may be recommended. An ampule containing the solution is cooled with an ice–salt bath, opened, and capped with a rubber septum. A weighed measuring flask capped with a rubber septum is cooled with the ice–salt bath. To this is introduced the cooled solution by means of a double-tipped needle, and the weighed solution is then introduced to the reaction flask by means of a double-tipped needle.

5. The reaction mixture containing (*E*)-(2-methyl-1,3-butadienyl)dimethylalane may be stored at room temperature for at least a few days. Although it appears to be stable at room temperature for a much longer period of time, its thermal stability has not been carefully determined. The cross-coupling reaction in Section B should require only one equivalent of the alkenylalane, and its yield by gas chromatographic examination is 90–100%. It is practical, however, to use ca. 20% excess of 1-buten-3-yne for preparing the alkenylalane so as to achieve a high-yield conversion of geranyl chloride into α-farnesene.

6. Geranyl chloride was prepared by treating geraniol, available from Aldrich Chemical Company, with carbon tetrachloride and triphenylphosphine according to an *Organic Syntheses* procedure (Calzada, J. G.; Hooz, J. *Org. Synth., Coll. Vol. VI* **1988**, 634).

7. Tetrakis(triphenylphosphine)palladium was prepared by treating palladium chloride, available from Matthey Bishop, Inc., with hydrazine hydrate in the presence of triphenylphosphine according to an *Inorganic Syntheses* procedure.[3] The submitters used a freshly prepared, shiny yellow, crystalline sample of the palladium complex. On standing for an extended period of time (more than a few weeks), its color gradually darkens. Even such samples are effective in many palladium-catalyzed cross-coupling reactions,[4 5] but have not been tested in this reaction. Tetrakis(triphenylphosphine)palladium is also available from Aldrich Chemical Company.

8. Tetrahydrofuran available from Aldrich Chemical Company was distilled from sodium and benzophenone.

9. The main purpose of this filtration is to remove traces, if any, of palladium-containing compounds that might induce undesirable transformations, such as isomerization and polymerization, during the subsequent distillative workup.

10. The submitters reported bp 73–75°C (0.05 mm). Gas chromatographic examination of the reaction mixture with a hydrocarbon internal standard indicates that α-farnesene is formed in 98% yield, based on geranyl chloride, essentially as a single product (>98%). The product obtained by this procedure shows the following properties: n_D^{23} 1.4977; IR (neat) cm^{-1}: 3080 (w), 2960(s), 2900(s), 1664(w), 1635(m), 1601(m), 981(m), 883(s); ^1H NMR [$CDCl_3$, $(CH_3)_4Si$] δ: 1.59 (s, 3 H), 1.63 (s, 3 H), 1.66 (s, 3 H), 1.74 (s, 3 H), 2.03 (m, 4 H), 2.82 (t, *J* = 6, 2 H); ^{13}C NMR [$CDCl_3$, $(CH_3)_4Si$] δ: 11.62, 16.07, 17.63, 25.69, 26.89, 27.35, 39.88, 110.37, 122.36, 124.50, 131.10, 131.74, 133.79, 135.55, 141.69.

3. Discussion

This procedure for the synthesis of α-farnesene[6] is representative of the palladium-catalyzed stereo-

and regiospecific coupling of allylic derivatives with alkenyl- and arylmetals.[7] The use of neryl chloride in place of geranyl chloride gives the 6-*Z* isomer of α-farnesene in 77% yield (>98% isomeric purity).[7] The high stereo- and regio-specificity (>98%) has been observed only with γ,γ-disubstituted allylic electrophiles. With γ-monosubstituted allylic derivatives, varying amounts of stereo- and regioisomers have been observed.[8]

Various allyl derivatives, such as those containing acyloxy, dialkylaluminoxy, and trialkylsilyloxy groups, also react with alkenylalanes in the presence of a palladium–phosphine catalyst,[8] and the synthesis of α-farnesene has been achieved by using geranyl acetate. Although the observed yields are ca. 20% lower than those observed with geranyl chloride, a careful comparison of the two derivatives has not been performed. In general, the order of reactivity of various leaving groups is: -Cl > -OAc > $-OPO(OR)_2$ > $-OSiR_3$.

In addition to alkenylalanes, readily obtainable by either hydroalumination[9] or carboalumination[10] of alkynes, alkenylzirconium derivatives,[7,11] obtainable by hydrozirconation[12] of alkynes, undergo a related alkenyl–allyl coupling reaction. In a related aryl–allyl coupling reaction catalyzed by palladium complexes, arylmetals containing magnesium, zinc, and cadmium, in addition to those containing aluminum and zirconium, give the expected cross-coupled products. The yields with zinc or cadmium tend to be higher than those with aluminum or zirconium, whereas magnesium, in this respect, is inferior to aluminum or zirconium.[8] Related reactions of alkenylboranes[13] and alkenylmercury compounds[14] are also known, but their applicability to the selective synthesis of 1,4-dienes of terpenoid origin, such as α-farnesene, is unknown.

The synthesis of 1,4-dienes via cross-coupling can, in principle, be achieved by either the reaction of allylmetals with alkenyl electrophiles or by the reaction of alkenylmetals with allyl electrophiles. The reaction of π-allylnickel derivatives with alkenyl halides[15] represents the former approach and can be highly regioselective. Stereo- and regiodefined alkenylmetals containing aluminum,[16] [17] [18] [19] boron,[20] silicon[21] and copper[22] [23] [24] [25] have been reported to react with allylic electrophiles producing 1,4-dienes. With the possible exception of the organocopper reaction, the scope of these uncatalyzed reactions is practically limited to γ-unsubstituted allylic halides. Finally, the nickel-catalyzed reaction of Grignard reagents with allylic electrophiles[26] is also known, but the reaction is generally nonselective. Nor does it appear that the reaction has been applied to the synthesis of 1,4-dienes.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

α-Farnesene

dichlorobis (η^5-cyclopentadienyl)zirconium

6-Z isomer of α-farnesene

(α-farnesene)

hydrochloric acid (7647-01-0)

sodium bicarbonate (144-55-8)

carbon tetrachloride (56-23-5)

1,2-dichloroethane (107-06-2)

nitrogen (7727-37-9)

toluene (108-88-3)

Benzophenone (119-61-9)

sodium (13966-32-0)

xylene (106-42-3)

hydrazine hydrate (7803-57-8)

Pentane (109-66-0)

dichloromethane (75-09-2)

palladium chloride

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

1-Buten-3-yne (689-97-4)

hexane (110-54-3)

geraniol (106-24-1)

triphenylphosphine (603-35-0)

Trimethylalane (75-24-1)

Geranyl chloride (5389-87-7)

neryl chloride

Tetrakis(triphenylphosphine)palladium (14221-01-3)

1,3,6,10-Dodecatetraene, 3,7,11-trimethyl-

(E)-(2-Methyl-1,3-butadienyl)dimethylalane

geranyl acetate (105-87-3)

phosphorus pentoxide (1314-56-3)

(3E, 6E)-3,7,11-Trimethyl-1,3,6,10-dodecatetraene (502-61-4)

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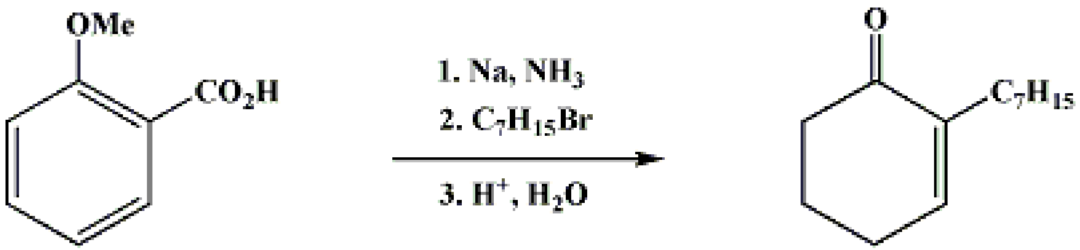
ALKYLATION OF THE ANION FROM BIRCH REDUCTION OF *o*-ANISIC ACID: 2-HEPTYL-2-CYCLOHEXENONE



Submitted by D. F. Taber, B. P. Gunn, and I-Ching Chiu[1].
Checked by M. F. Semmelhack and E. Stelter.

1. Procedure

Caution! Liquid ammonia should be used only in a well-ventilated hood.

2-Heptyl-2-cyclohexenone. A 1-L, three-necked, round-bottomed flask is charged with 15.2 g (0.1 mol) of *o*-anisic acid (Note 1) and 100 mL of tetrahydrofuran (Note 2). An acetone–dry ice condenser and mechanical stirrer are put in place, the flask is immersed in an acetone–dry ice bath, and 400 mL of ammonia is distilled in (Note 3), (Note 4). The resulting thick white suspension (the ammonium salt of the acid) is stirred mechanically. Sodium, washed sequentially with xylenes and ether, is added in small pieces. The suspension dissolves to give a pale yellow solution which, upon introduction of more sodium, changes to the characteristic blue color of excess sodium. When the deep blue color persists, a mixture of 1-bromoheptane (21.49 g, 0.12 mol) and 1.0 mL (2.4 mmol) of 1,2-dibromoethane is added in one portion. The blue color is discharged immediately, leaving a yellow solution. The acetone–dry ice bath and the condenser are removed, and the ammonia is allowed to evaporate under a gentle stream of nitrogen.

The residue is diluted with 700 mL of water, and the resulting aqueous solution is washed with three 40-mL portions of dichloromethane, acidified with cold concentrated HCl, and extracted with five 40-mL portions of 1,2-dichloroethane. The combined 1,2-dichloroethane extracts are placed in a 500-mL, one-necked, round-bottomed flask bearing a reflux condenser; water (50 mL), concentrated HCl (50 mL), and hydroquinone (300 mg) are added; and the mixture is heated at reflux under a positive pressure of nitrogen for 30 min. The mixture is cooled to 25°C, the layers are separated, and the organic layer is washed with 60 mL of 0.5 *M* aqueous sodium bicarbonate solution. The organic phase is dried over anhydrous potassium carbonate, concentrated by rotary evaporation at aspirator vacuum, and distilled through a 10-cm Vigreux column to yield a center cut, bp 100–104°C (0.02 mm), 9.0–11.5 g (46–59%)

(Note 5),(Note 6),(Note 7).

2. Notes

1. *o*-Anisic acid was obtained from Aldrich Chemical Company, Inc.
2. Tetrahydrofuran was dried and made oxygen-free by boiling over sodium/ benzophenone ketyl under argon, and distilling just before use.
3. Reduction in refluxing liquid ammonia (−33°C) led to substantial cleavage of the methoxyl group with resultant formation of alkylated dihydrobenzoic acid.
4. Arrangements for cooling or condensing the liquid ammonia over sodium in a preliminary drying operation could be made, but were not necessary. The results reported here were achieved by simply passing ammonia gas from a cylinder into the cold reaction system through heavy Tygon tubing.
5. The spectral properties of 2-heptyl-2-cyclohexenone are as follows: IR (CCl_4) cm^{-1}: 2920, 2860, 1670, 1455, 1435, 1370, 1170, 1120, 1095, 905; ^1H NMR ($CDCl_3$) δ: 0.85 (br t, 3 H, *J* = 7), 1.28 (br s, 10 H), 1.8–2.6 (m, 8 H), 6.70 (br s, 1 H); n_D^{26} 1.4738.
6. Before distillation, the crude enone contained substantial amounts of the β,γ-isomer. As an alternative to equilibrium on distillation, this mixture could be converted to the α,β-isomer by stirring with 0.1 *M* sodium methoxide in methyl alcohol under nitrogen at 0°C for 2 hr.
7. Professor L. N. Mander has advised us that addition of 1.0 equivalent of potassium *t*-butoxide prior to addition of sodium metal significantly improved the yield of this procedure: Hoole, J. M.; Mander, L. N.; Woolias, M. *Tetrahedron Lett.* **1982**, *23*, 1095.

3. Discussion

Cyclohexenones with 2-alkyl substituents are usually prepared by alkylation of dihydroresorcinol followed by enol ether formation, reduction, and hydrolysis.[2] A variety of other approaches have been employed.[3 2 4 5 6 7 8] The procedure outlined here is simple, occurring in essentially one pot, using commercially available starting materials. The alkylating agent can equally well be an alkyl iodide or *p*-toluenesulfonate ester. A variety of other alkylating agents have been employed using an earlier, unoptimized version of this procedure.[9]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

potassium carbonate (584-08-7)

HCl (7647-01-0)

ammonia (7664-41-7)

methyl alcohol (67-56-1)

ether (60-29-7)

hydroquinone (123-31-9)

sodium bicarbonate (144-55-8)

1,2-dichloroethane (107-06-2)

nitrogen (7727-37-9)

sodium methoxide (124-41-4)

sodium (13966-32-0)

1,2-dibromoethane (106-93-4)

dichloromethane (75-09-2)

1-bromoheptane (629-04-9)

Tetrahydrofuran (109-99-9)

Dihydroresorcinol

argon (7440-37-1)

2-Heptyl-2-cyclohexenone (87588-68-9)

dihydrobenzoic acid

potassium t-butoxide (865-47-4)

o-ANISIC ACID (579-75-9)

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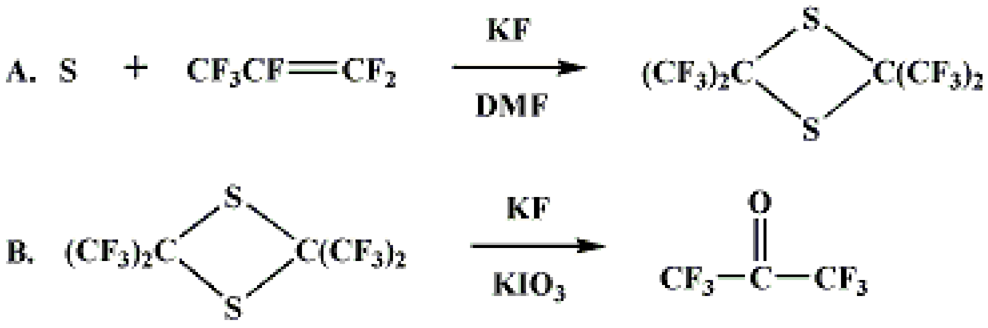
Organic Syntheses, CV 7, 251

HEXAFLUOROACETONE

[2-Propanone, 1,1,1,3,3,3-hexafluoro-]



Submitted by Michael Van Der Puy and Louis G. Anello[1].
Checked by Evan D. Laganis and Bruce E. Smart.

1. Procedure

Caution! Hexafluoroacetone and its precursor are toxic. Both procedures should be conducted in an efficient hood.

A. *2,2,4,4-Tetrakis(trifluoromethyl)-1,3-dithietane*. A 500-mL, three-necked flask is fitted with a good magnetic stirring bar, thermometer, water-cooled condenser, and a fritted gas inlet tube (Note 1). The outlet of the condenser is attached to a tared −78°C cold trap and the inlet tube is connected via flexible tubing to a graduated −78°C cold trap into which 60 mL (96 g, 0.64 mol) of hexafluoropropene has been condensed under nitrogen. The flask is charged with 3 g of potassium fluoride and is flamed gently under vacuum. The apparatus is cooled while purging with nitrogen. Sulfur (23 g, 0.72 mol) and 200 mL of dry dimethylformamide are then added (Note 2). The reaction mixture is heated to 40–45°C with stirring. The heat source is removed, the stopcock on the trap containing the hexafluoropropene is opened, and the trap is gently thawed. The rate of hexafluoropropene bubbling into the reaction mixture is adjusted to about 0.6 mL (1 g) / min by cooling or warming the trap containing the hexafluoropropene (Note 3),(Note 4),(Note 5). When all the hexafluoropropene has been added, the reaction mixture is cooled to −20°C to −30°C and quickly filtered under suction (Note 6). The filtercake is transferred to an Erlenmeyer flask and is allowed to melt. Water (50 mL) is added, and the mixture is filtered. The lower liquid phase is separated, washed with 50 mL of water, and distilled through a 20-cm Vigreux column at atmospheric pressure to give 93.0–99.4 g (80–85%) of product, bp 106–108°C (Note 7).

B. *Hexafluoroacetone*. A 1-L, three-necked flask is fitted with a sealed mechanical stirrer, thermometer, and condenser. A −78°C glass trap is attached to the condenser via flexible tubing. While the system is purged with nitrogen, 3 g of potassium

fluoride is added and the flask and potassium fluoride are flame-dried (Note 8). After the flask has cooled, 300 mL of dry dimethylformamide, 80 g (0.374 mol) of powdered potassium iodate, and 60 g (0.165 mol) of 2,2,4,4-tetrakis(trifluoromethyl)-1,3-dithietane are added (Note 9). The stirrer and water condenser are started and the reaction mixture is heated over a 45-min period to 149°C and is kept at 149°C for an additional 15 min. The heat source is then removed, and a slow stream of nitrogen is used to flush any remaining product gas into the cold trap (Note 8). The condensate is transferred under vacuum to a tared, evacuated-gas cylinder (Note 10). The cylinder contains 37.0–39.9 g (68–73%) of material (Note 11). This material is distilled to give 35.0–37.6 g (64–69%) of pure product, bp −28°C [lit.[2] bp −27°C] (Note 12).

2. Notes

1. The checkers dried the glassware overnight at 150°C in an oven and assembled it hot under a nitrogen purge.
2. The checkers obtained potassium fluoride, potassium iodate, dimethylformamide (reagent grades), and sulfur (sublimed) from Fisher Scientific Co. The submitters purchased hexafluoropropene from PCR Research Chemicals, Inc.; the checkers used hexafluoropropene from E. I. du Pont de Nemours & Company, Inc. The potassium fluoride was predried overnight in a vacuum oven at 110°C. The sulfur was dried in a vacuum desiccator and the dimethylformamide was distilled from P_2O_5 prior to use.
3. The mixture of dimethylformamide, sulfur, and potassium fluoride turns brown prior to the addition of hexafluoropropene, which quickly brings the color back to bright yellow. The submitters report that the reaction mixture will turn blue or green prior to the addition of hexafluoropropene, if the dimethylformamide is dry (less than ca. 0.05% water).
4. The reaction is moderately exothermic. The temperature rises to about 55°C and remains there as the reaction proceeds.
5. With good stirring, the reaction proceeds as fast as the hexafluoropropene is added. The dry ice trap attached to the condenser should be checked periodically, however. When the required amount of hexafluoropropene is added, little or no undissolved sulfur remains.
6. 2,2,4,4-Tetrakis(trifluoromethyl)-1,3-dithietane melts at 24°C. Thus, this operation must be done quickly to minimize product loss.
7. The product is more than 99% pure by GLPC (6 ft × 1/8 in. 20% FS-1265 on 60/80 Gaschrome R, 50–200°C) and by ^{19}F NMR ($CDCl_3$) ϕ: −73.3 (s). The submitters report that they obtained 78–90 g of 98% pure product, bp 110°C.
8. The nitrogen initially should come from the cold trap, itself cooled under a nitrogen flush. At the end of the reaction, the flow of nitrogen should be reversed. This can be done by replacing the thermometer with a gas inlet tube.
9. The submitters report that a ratio of KIO_3 to 2,2,4,4-tetrakis(trifluoromethyl)-1,3-dithietane of 2.26 is near the optimum since a ratio of 2.5 did not increase the yield, whereas a ratio of 2.0 gave 5–10% lower yields.

10. This transfer is best done on a vacuum manifold system equipped with a manometer. The trap and a stainless-steel cylinder of 100–300-mL capacity are attached via vacuum tubing to the manifold system, cooled in liquid nitrogen baths, and evacuated to 0.5–1 mm. The system is closed and the trap is removed from its cold bath and is slowly thawed. The volatile material in the trap is transferred to and condensed in the cylinder at such a rate that no positive pressure builds up in the closed system.
11. The submitters report collecting 45–50 g of product (98% pure or better by GLPC on a 10-ft × 1/8-in. Porapak P column) in the cold trap attached to reaction vessel. The checkers found that the trap contained relatively nonvolatile material, principally dimethylformamide, in addition to the desired product.
12. The checkers used a 30-cm jacketed, low-temperature spinning band column for this distillation. The IR spectrum of the distilled product is identical to that of an authentic sample; IR (vapor) cm^{-1}: 1806 (C=O).

3. Discussion

Earlier methods of preparing 2,2,4,4-tetrakis(trifluoromethyl)-1,3-dithietane (hexafluorothioacetone dimer, HFTA dimer) include the reaction of hexafluoropropene (HFP) and sulfur over a carbon bed at 425°C[3] and the reaction of HFP and sulfur in tetramethylene sulfone at 120°C in the presence of potassium fluoride (autoclave).[4] Dimethylformamide appears to be a far superior solvent for this reaction, permitting the use of atmospheric pressure and modest temperatures, as well as affording a cleaner product.

The generation of hexafluoroacetone (HFA) from HFTA dimer has been accomplished by the hot-tube oxidation with nitric oxide at 650°C (high temperature converts dimer into monomer).[5] The present method uses the more convenient interconversion of dimer to monomer effected by potassium fluoride in dimethylformamide. This permits many reactions to be conducted on the very reactive monomer without actually isolating it.

For occasional laboratory synthesis of HFA, the present method offers distinct advantages of convenience (cost, workup, standard equipment) over other known methods. These include the epoxidation of HFP followed by isomerization of the epoxide to HFA,[6,7] the high-temperature halogen exchange of hexachloroacetone with Cr^{3+} /HF,[8] and permanganate oxidation of the extraordinarily toxic perfluoroisobutylene.[9]

Hexafluoroacetone is a reactive electrophile. It reacts with activated aromatic compounds (e.g., phenol), and can be condensed with olefins, dienes, ketenes, and acetylenes. It forms adducts with many compounds containing active hydrogen (e.g., H_2O or HCN). Reduction of HFA with $NaBH_4$ or $LiAlH_4$ affords the useful solvent hexafluoroisopropyl alcohol. The industrial importance of HFA arises largely from its

use in polymers and as an intermediate in monomer synthesis.[10]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

P_2O_5

KIO_3

2,2,4,4-tetrakis(trifluoromethyl)-1,3-dithietane (hexafluorothioacetone dimer, HFTA dimer)

Cr^{3+} /HF

hydrogen (1333-74-0)

phenol (108-95-2)

nitrogen (7727-37-9)

sulfur (7704-34-9)

carbon (7782-42-5)

nitric oxide

potassium fluoride (7789-23-3)

$LiAlH_4$ (16853-85-3)

dimethylformamide (68-12-2)

$NaBH_4$ (16940-66-2)

tetramethylene sulfone (126-33-0)

perfluoroisobutylene (382-21-8)

hexachloroacetone (116-16-5)

Hexafluoroacetone, 2-Propanone, 1,1,1,3,3,3-hexafluoro- (684-16-2)

potassium iodate (7758-05-6)

hexafluoropropene (116-15-4)

2,2,4,4-Tetrakis(trifluoromethyl)-1,3-dithietane (791-50-4)

hexafluoroisopropyl alcohol (920-66-1)

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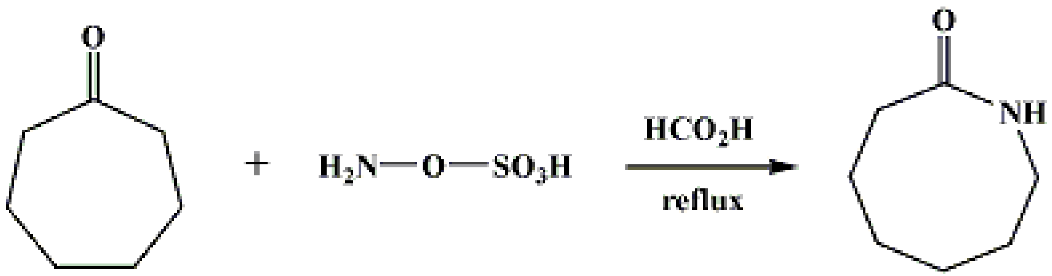
Organic Syntheses, CV 7, 254

HEXAHYDRO-2-(1*H*)-AZOCINONE

[2(1*H*)-Azocinone, hexahydro-]



Submitted by George A. Olah and Alexander P. Fung[1].
Checked by David Varie and Edwin Vedejs.
Checked by Scott Thompson and Clayton H. Heathcock.

1. Procedure

A 100-mL, three-necked flask is equipped with a magnetic stirring bar, a pressure-equalizing dropping funnel, and a reflux condenser connected to a nitrogen flow line. The system is dried with a heat gun while it is flushed with dry nitrogen. The reaction vessel is then cooled in a water bath while a light positive pressure of nitrogen is maintained. The flask is charged with hydroxylamine-*O*-sulfonic acid[2] (8.48 g, 0.075 mol) (Note 1) and 95–97% formic acid (45 mL) (Note 2). A solution of cycloheptanone (5.61 g, 0.05 mol) (Note 3) in 15 mL of 95–97% formic acid is added with stirring over a 3-min period. After addition is complete, the reaction mixture is heated under reflux for 5 hr and then cooled to room temperature. The reaction mixture is quenched with 75 mL of ice–water. The aqueous solution is slowly neutralized to pH 7 with 6 *N* sodium hydroxide (Note 4) and extracted with three 100-mL portions of chloroform. The combined organic layers are dried with anhydrous magnesium sulfate. After removal of the solvent on a rotary evaporator, the product hexahydroazocinone is purified by distillation to give 4.6 g (72%), bp 94–96°C/0.2 mm, (short-path apparatus), lit[3] bp 133–135°C/4 mm (Note 5).

2. Notes

1. The hydroxylamine-*O*-sulfonic acid used by the submitters was purchased from Ventron Corporation and used directly. However, it can be readily prepared in the laboratory.[4,3]
2. Formic acid 95–97% was obtained from the Aldrich Chemical Company.
3. Commercial cycloheptanone (bp 179°C) obtained from MCB, Inc. was used directly.
4. An external ice–salt bath is used.

5. The product exhibits the following spectra: ^{1}H NMR ($CDCl_3$) δ: 1.6–1.8 (m, 6 H, CH_2), 2.40 (3 H, m), 2.57 (m, 2 H, CH_2CO), 3.31 (m, 2 H, CH_2-N), 7.16 (br, 1 H, NH); IR (cm^{-1}): 3270, 3200, 1650; GLC analysis: 20% SE-30, 60/80 on Chrom-W, 1/8-in × 20-ft column, 180°C: one peak.

3. Discussion

The procedure described here is a one-step conversion of cycloheptanone into hexahydro-2(1*H*)-azocinone. The method is general and is characterized by good yields, mild conditions, and easy preparation of the product in pure form from readily available starting materials. Several methods are described in the patent literature for simultaneous oximation of ketones and rearrangement of the corresponding oxime, including the use of hydroxylamine and sulfuric acid,[5,6] or by employing primary nitroparaffins as a source of hydroxylamine.[7,8] The present method has been shown[9] to be applicable to a wide variety of lactams (C_5 □ C_{12}). In the specific case of hexahydroazocinone, the yield from cycloheptanone (60–63%) appears lowers than for the conventional two-step method,[10,11] but the latter requires isolation of the intermediate oxime.

12

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

formic acid (64-18-6)

nitrogen (7727-37-9)

magnesium sulfate (7487-88-9)

Cycloheptanone (502-42-1)

Hydroxylamine-O-sulfonic acid (2950-43-8)

hexahydroazocinone (673-66-5)

Hexahydro-2-(1H)-azocinone, 2(1H)-Azocinone, hexahydro-, hexahydro-2(1H)-azocinone (673-66-5)

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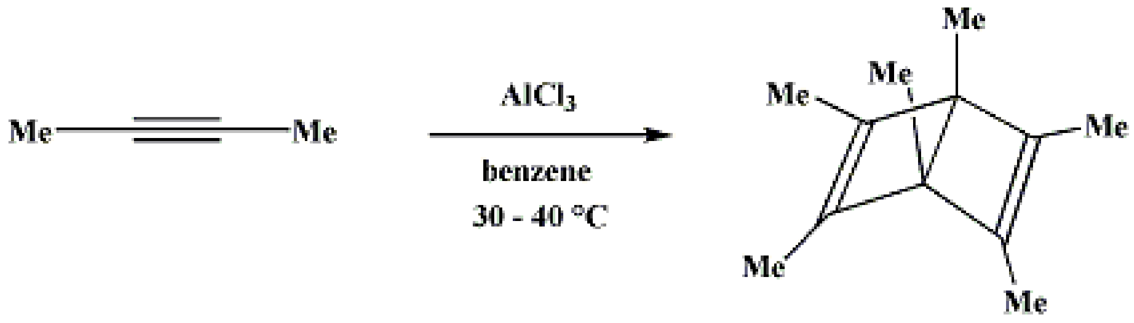
Organic Syntheses, CV 7, 256

HEXAMETHYL DEWAR BENZENE

[Bicyclo[2.2.0]hexa-2,5-diene, 1,2,3,4,5,6-hexamethyl-]



Submitted by Sami A. Shama and Carl C. Wamser[1].
Checked by Reto Naef, Dieter Seebach, and Beat Weidmann.

1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A 250-mL, three-necked, round-bottomed flask containing a 2.5-cm magnetic stirring bar is equipped with a Dewar-type reflux condenser containing ice, a dropping funnel, and a gas inlet tube. A calcium chloride drying tube is attached to the condenser and the apparatus is flushed with dry deoxygenated nitrogen (Note 1). The gas inlet tube is then replaced by a thermometer, and a suspension of 5.0 g of aluminum trichloride in 50 mL of benzene is introduced into the flask (Note 2). A solution of 100 g (1.85 mol) of 2-butyne (Note 3) and (Note 4) in 50 mL of cold dry benzene is added, with vigorous stirring, through the dropping funnel, over a period of 1 hr. During the addition, the temperature of the reaction mixture is kept between 30 and 40°C through the use of a water bath. Stirring is continued for 5 hr at 30–40°C after the addition has been completed. The catalyst is then decomposed by pouring the mixture onto 50 g of crushed ice in a 500-mL separatory funnel, whereupon the dark brown color turns pale yellow. When the ice has melted completely, the organic layer is separated, washed with two 25-mL portions of cold water, dried over anhydrous potassium carbonate, and filtered. Benzene and unreacted butyne (Note 5) are removed in a rotary evaporator using a water bath at 40°C and a water aspirator vacuum. The residual liquid is distilled through a short-path distillation head under reduced pressure using a capillary. The yield is 38–50 g (38–50%) of hexamethyl Dewar benzene, bp 43°C/10 mm, mp 7–8°C, n_D^{20} 1.4480 (Note 6) and (Note 7).

2. Notes

1. Commercial nitrogen is deoxygenated by bubbling it through a trap containing an alkaline pyrogallol solution.[2] The gas is then dried by passing it through a potassium hydroxide tower. The checkers used argon as an inert atmosphere.
2. Aluminum trichloride is purified by sublimation under reduced pressure and the benzene is dried over sodium wire before use. The checkers used sublimed $AlCl_3$ as supplied by Merck (Darmstadt).
3. 2-Butyne was purchased from Chemical Samples Company or from Fluka AG.
4. The bottle containing 2-butyne (bp 27°C) should be chilled thoroughly before opening.
5. About 20 g of 2-butyne may be collected in an ice-cooled receiver if the dried solution is concentrated by distillation through a 25-cm Vigreux column rather than by evaporation. The checkers do not recommend this mode of workup, nor did they use a column for distilling the Dewar benzene, to avoid prolonged heating of the bicyclic system.
6. The spectral properties of hexamethyl Dewar benzene are as follows: ^{1}H NMR ($CDCl_3$) δ: 1.07 (s, 6 H), 1.58 (s, 12 H).
7. Hexamethyl Dewar benzene undergoes thermal isomerization[3,4] and reacts with acids[5] and transition-metal ions.[6] It should be stored in a freezer in a tightly sealed bottle. Hexamethyl Dewar benzene is reportedly a carcinogen,[7] and care must be taken to avoid contact with the skin or inhalation of its vapor.

3. Discussion

The present procedure is that of Schäfer[8,9] and is the first method available for large-scale preparation of a Dewar benzene. Other syntheses of compounds containing the Dewar benzene skeleton have generally involved photochemical isomerization of the corresponding benzene isomer.[10]

The present procedure represents a novel reaction, bicyclotrimerization. The intermediate dimeric complex of $AlCl_3$ with tetramethylcyclobutadiene has been isolated, and addition of different alkynes to this complex provides a synthetic route to a variety of substituted Dewar benzenes.[11]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

$AlCl_3$

potassium carbonate (584-08-7)

Benzene (71-43-2)

nitrogen (7727-37-9)

aluminum trichloride (3495-54-3)

sodium wire (13966-32-0)

pyrogallol (87-66-1)

butyne (107-00-6)

2-butyne (503-17-3)

tetramethylcyclobutadiene

argon (7440-37-1)

Hexamethyl Dewar benzene, Bicyclo[2.2.0]hexa-2,5-diene, 1,2,3,4,5,6-hexamethyl- (7641-77-2)

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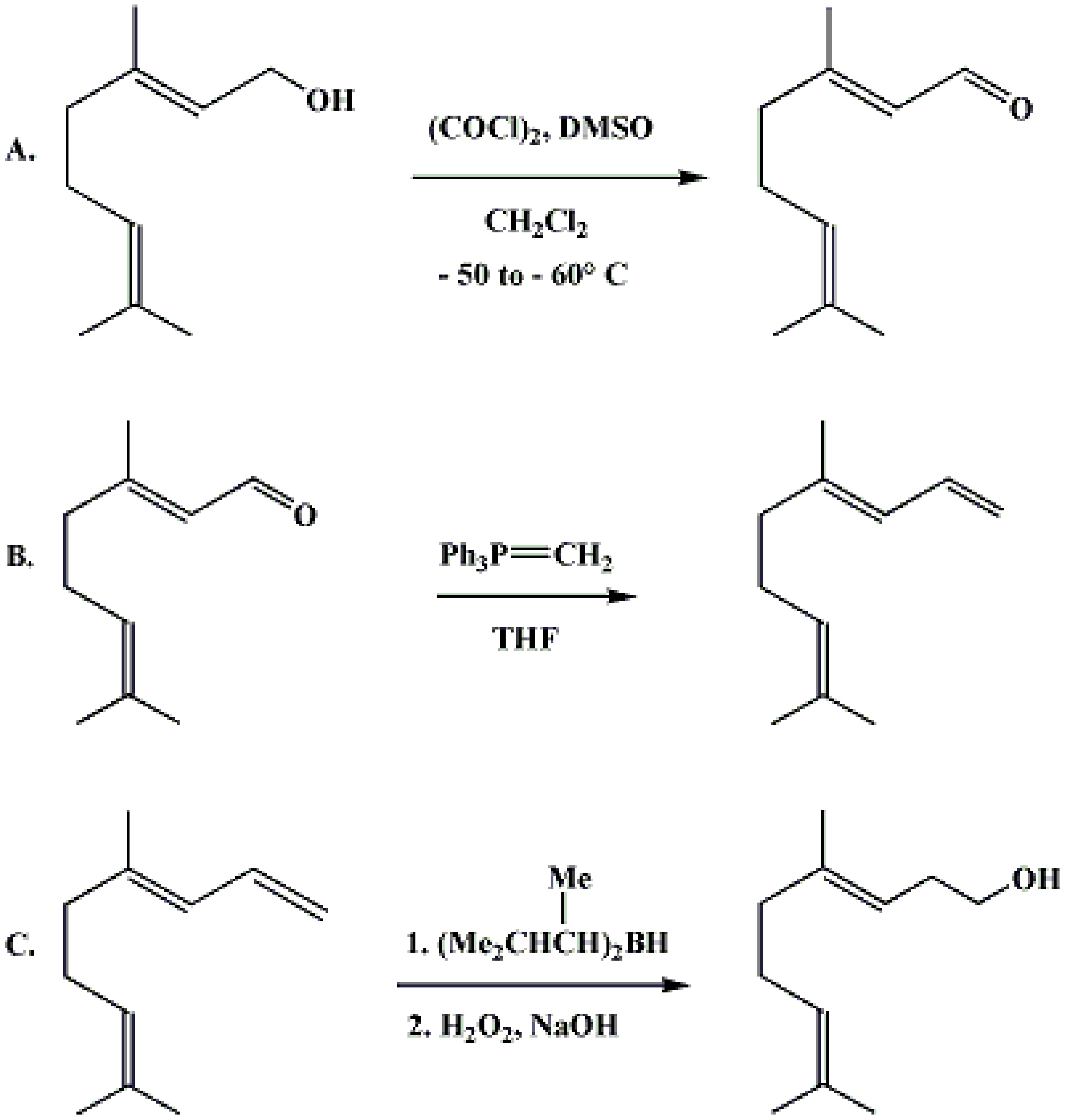
Organic Syntheses, CV 7, 258

SELECTIVE HYDROBORATION OF A 1,3,7-TRIENE: HOMOGERANIOL

[3,7-Nonadien-1-ol, 4,8-dimethyl-, (*E*)-]



Submitted by Eric J. Leopold[1]
Checked by Shridhar Hegde and Robert M. Coates.

1. Procedure

A. *Geranial*. A 2-L, three-necked, round-bottomed flask is dried in an oven and equipped with a mechanical stirrer, a thermometer, a Claisen adapter, and two pressure-equalizing dropping funnels. The flask is charged with 500 mL of dichloromethane (Note 1) and 20 mL (29.2 g, 0.23 mol) of oxalyl chloride (Note 2). The solution is stirred and cooled at −50 to −60°C as 34 mL (37.5 g, 0.48 mol) of dimethyl sulfoxide (Note 3) in 100 mL of dichloromethane is added dropwise at a

rapid rate. After 5 min 30.8 g (0.2 mol) of geraniol (Note 4) is added dropwise over 10 min maintaining the temperature at –50 to –60°C. After another 15 min, 140 mL of triethylamine is added dropwise while keeping the temperature at or below –50°C. Stirring is continued for 5 min, after which time the mixture if allowed to warm to room temperature and 700 mL of water is added. The aqueous layer is separated and extracted with two 300-mL portions of dichloromethane. The organic layers are combined, washed with two 100-mL portions of saturated sodium chloride, and dried over anhydrous magnesium sulfate. The filtered solution is concentrated to 500 mL by rotary evaporation and washed successively with 1% hydrochloric acid until it is no longer basic. The dichloromethane solution is washed with water, 5% sodium carbonate, water, and saturated sodium chloride before drying over anhydrous magnesium sulfate. Rotary evaporation of the solvent gives ca. 30 g of crude product. Distillation in a Kugelrohr apparatus (Note 5) with an oven temperature of 80–85°C (1 mm) affords 27.3–28.5 g (90–94%) of geranial, n_D^{24} 1.4870 (Note 6).

B. *(E)-4,8-Dimethyl-1,3,7-nonatriene*. A 1-L, three-necked, round-bottomed flask equipped with a pressure-equalizing dropping funnel, thermometer, magnetic stirring bar, and serum caps (Note 7) is charged with 50 g (0.12 mol) of methyltriphenylphosphonium iodide (Note 8) and 320 mL of tetrahydrofuran (Note 9) and is flushed with argon. The flask is cooled in an ice bath and the suspension is stirred under a positive pressure of argon, while about 0.2–0.6 mL of 2.05 *M* phenyllithium in 30 : 70 ether: cyclohexane (Note 10) and (Note 11) is added dropwise until the suspension develops a permanent yellow color (Note 12). Then 56 mL (0.115 mol) of 2.05 *M* phenyllithium is added dropwise over 10 min. The ice bath is removed, and the orange suspension containing excess phosphonium salt is stirred at room temperature for 30 min. The reaction mixture is stirred and cooled at 0–5°C, and 17.2 g (0.11 mol) of geranial in 50 mL of tetrahydrofuran is added dropwise over 10 min. The dropping funnel is rinsed with a small amount of tetrahydrofuran. The mixture is stirred at room temperature for 2 hr. The light-orange mixture is hydrolyzed by adding 2 mL of methanol, and most of the solvent is removed on a rotary evaporator until a slurry results (Note 13). The slurry is diluted with 200 mL of petroleum ether (bp 60–68°C), and the supernatant solution is decanted and filtered through 150 g of Celite on a Büchner funnel. The solids remaining in the flask are heated with three 100-mL portions of hot petroleum ether, and the supernatant solutions are also filtered through Celite. The filtrate is concentrated by rotary evaporation to a yellowish liquid that is filtered through 150 g of Florisil on a Büchner funnel, and the Florisil is washed with 300 mL of petroleum ether. Rotary evaporation of the eluate provides ca. 15 g of clear liquid, which on distillation in a Kugelrohr apparatus with an oven temperature of 60–70°C (2 mm) gives 13.1–13.5 g (77–80%) of the triene, n_D^{22} 1.4871 (Note 14) and (Note 15).

C. *Homogeraniol*. A 250-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, thermometer, pressure-equalizing dropping funnel, and a gas inlet tube to maintain a positive argon pressure within the apparatus (Note 7). The flask is charged with 102 mL (94.8 mmol) of 0.93 *M* diborane in tetrahydrofuran

(Note 16), and the contents are cooled to −30°C. The diborane solution is stirred as 22.1 mL (0.21 mol) of 2-methyl-2-butene (Note 17) is added rapidly. Stirring is continued for 2 hr while maintaining the temperature at 0–2°C. A 500-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, thermometer, pressure-equalizing dropping funnel, and a gas inlet tube to keep a positive pressure of argon (Note 7) is charged with 13.0 g (86.7 mmol) of (*E*)-4,8-dimethyl-1,3,7-nonatriene and 35 mL of tetrahydrofuran (Note 9). The contents are stirred and cooled at 0°C as the solution of disiamylborane in the first flask is transferred via a cannula to the pressure-equalizing dropping funnel attached to the second flask. After approximately 20 mL of disiamylborane is transferred to the dropping funnel via a cannula, the dropwise addition of the disiamylborane is started while the transfer continues. The remainder of the disiamylborane solution in the first flask is kept at 0°C. After the 1-hr addition is completed, stirring is continued for 1 hr at 0°C and overnight at room temperature (15 hr). Excess disiamylborane is destroyed by adding 2 mL of ethanol, the mixture is cooled to 0°C, and 33 mL of 3 *M* sodium hydroxide is added rapidly. Stirring and cooling at −10°C are continued as 33 mL of chilled 30% hydrogen peroxide is slowly added (Note 18). The reaction mixture is stirred at room temperature for 3 hr, the layers are separated, and the aqueous layer is extracted with two 75-mL portions of ether (Note 19). The combined organic layers are washed with two 25-mL portions of saturated sodium chloride and dried over anhydrous magnesium sulfate. Evaporation of the solvent gives ca. 21 g of crude product that is purified by chromatography on 400 g of silica gel packed in a 7.5-cm × 20-cm column. The column is eluted with dichloromethane and 100-mL fractions are collected, the first two of which are discarded. Elution is continued by collecting the 100-mL fractions in a weighed flask and evaporating the solvent under reduced pressure until a constant weight of product is obtained (nine 100-mL fractions). Distillation of the residue in a Kugelrohr apparatus with an oven temperature of 150°C (0.02 mm) gives 12.6–13.2 g (88–91%) of homogeraniol, n_D^{21} 1.4740 (Note 20).

2. Notes

1. Dichloromethane was distilled from calcium hydride and stored over Linde 4A molecular sieves.
2. Oxalyl chloride was distilled immediately before use.
3. Dimethyl sulfoxide was distilled from calcium hydride and stored over Linde 3A molecular sieves.
4. Geraniol was obtained from Aldrich Chemical Company, Inc. (Gold Label) and used without purification.
5. Kugelrohr ovens are available from Rinco Instrument Co., Inc., 5035 Prairie St., P.O. Box 167, Greenville, IL 62246.
6. Thin-layer chromatographic analysis of the product by the submitter on silica gel with 20% ethyl acetate in hexane as developing solvent showed one spot, R_f 0.5. Gas chromatographic analysis showed the presence of 1.5% of the cis isomer by coinjection with 40 : 60 cis: trans citral mixture available from Aldrich Chemical Company, Inc. The ^{1}H NMR spectral data for the product are

as follows δ: 1.61 (s, 3 H, CH_3), 1.69 (s, 3 H, CH_3), 2.17 (s, 3 H, CH_3), 2.19–2.23 (m, 4 H, CH_2CH_2), 5.06 (br s, 1 H, vinyl H at C-6), 5.88 (d, 1 H, *J* = 8, vinyl H at C-2), 9.99 (d, *J* = 8, CHO).

7. The glassware was dried in an oven at 150°C, assembled while still hot, and alternately evacuated and flushed with argon.

8. Methyltriphenylphosphonium iodide was prepared by the following procedure. Triphenylphosphine was recrystallized from ethanol and dried over phosphorus pentoxide under reduced pressure for 12 hr. A solution of 39 g (0.15 mol) of triphenylphosphine and 10.0 mL (22.8 g, 0.16 mol) of iodomethane in 105 mL of benzene was allowed to stir at room temperature for 12 hr. The precipitate was filtered, washed with benzene, and dried over phosphorus pentoxide under reduced pressure for 12 hr. The yield was 57 g (94%), mp 189°C (lit.[2] mp 182°C). The reagent is also available from Aldrich Chemical Company, Inc.

9. Tetrahydrofuran was distilled from sodium–benzophenone ketyl.

10. The phenyllithium solution was purchased from Aldrich Chemical Company, Inc. The checkers used 64 mL (0.115 mol) of 1.8 *M* phenyllithium in 75 : 25 benzene : ether, which was purchased from Alfa Products, Morton Thiokol, Inc.

11. The submitter states that the slight excesses of phenyllithium (5%) and methyltriphenylphosphonium iodide (10%) specified ensure complete conversion of the aldehyde and simplify the purification of the product since the excess phosphonium salt is readily removed during filtration through Florosil.

12. The addition of 0.2–0.6 mL of the phenyllithium solution presumably destroys small amounts of moisture or other impurities.

13. The submitter cautions against evaporating all the solvent; the triphenylphosphine oxide will tenaciously occlude the product, and the yield will be reduced.

14. A gas chromatographic analysis of the product by the submitter on a 15 M capillary column coated with silicone oil SE-54 at 70°C exhibited one peak (98%).

15. An index of refraction of 1.4826 at 20°C is reported[3] for the product. The spectral properties of the product are as follows: IR (neat) cm^{-1}: 3080, 1645, 1600, 1345, 990, 900; ^1H NMR ($CDCl_3$) δ: 1.61 (3 H, CH_3), 1.68 (s, 3 H, CH_3), 1.76 (s, 3 H, CH_3 at C-4), 1.95–2.12 (broad, 4 H, CH_2CH_2), 4.80–5.15 (broad, 3 H, vinyl H), 5.85 (d, 1 H, *J* = 10, vinyl H at C-3), 6.55 (3 d, *J* = 10, 10, 17, vinyl H at C-2).

16. The diborane solution was obtained from Aldrich Chemical Company, Inc. It was titrated[4] before use, although the submitter states that this is not necessary. The solution was transferred from the stock solution to the reaction flask via a cannula. The checkers first transferred the diborane solution via a cannula into a graduated cylinder that was capped with a rubber septum and purged with nitrogen. The specified volume was then transferred into the reaction vessel.

17. 2-Methyl-2-butene was obtained from Aldrich Chemical Company, Inc. and was distilled from calcium hydride.
18. The oxidation of organoboranes is exothermic, and efficient cooling and slow addition are necessary to keep the temperature near 0°C.[5].
19. The checkers observed the separation of a heavy, white precipitate presumed to be a borate salt during the addition of hydrogen peroxide. After the three-phase mixture had been stirred at room temperature for 3 hr, the liquid layers were decanted into a separatory funnel. The solid remaining in the flask was washed with two 75-mL portions of ether and these washings were used to extract the aqueous layer.
20. Indices of refraction of 1.4722 at 22°C and 1.4718 at 26°C are reported for homogeraniol.[6,7] The spectral properties of the product are as follows: IR (neat) cm^{-1}: 3330, 2960 (sh), 2920, 1448, 1435 (sh, m), 1374 (m), 1108 (w), 1045 (s), 875 (w); ^{1}H NMR ($CDCl_3$) δ: 1.60 (s, 3 H, CH_3 at C-4), 1.64 (s, 3 H, CH_3), 1.68 (s, 3 H, CH_3 at C-4), 1.95–2.15 (s, 4 H, CH_2CH_2), 2.30 (m, 2 H, CH_2CH_2OH), 3.60 (t, 2 H, *J* = 7, CH_2OH), 4.95–5.25 (m, 2 H, vinyl H).

3. Discussion

Homogeraniol is an important intermediate in syntheses of squalene,[6] aplysistatin[8] dendrolasin,[9] and juvenile hormone analogs.[10] [11] The present procedure affords an efficient, stereoselective method for preparing (*E*)-homogeraniol, contaminated by at most 1–2% of the *Z* isomer.

In Step A geraniol is oxidized to geranial (citral) by Swern's modification of the Moffat oxidation.[12] The stereoisomeric purity of the product is at least 98%. This procedure is readily conducted on a large-scale and requires only a 4-hr time period, including distillation of oxalyl chloride. The oxidation of geraniol to pure (*E*)-geranial may also be accomplished by Collin's oxidation with chromium trioxide–dipyridine complex,[13] or by use of activated manganese dioxide.[14] However, these methods require large amounts of reagents and solvents for 0.2-mol-scale preparations.

The Wittig methylenation of geranial to (*E*)-4,8-dimethyl-1,3,7-nonatriene is best carried out with phenyllithium in tetrahydrofuran as described in Section B. The use of butyllithium in tetrahydrofuran or ether–hexane[3] affords the triene in only 50–60% yield. When the ylide was generated with sodium hydride or potassium *tert*-butoxide in dimethyl sulfoxide by the submitter, the Wittig reaction gave triene containing 10–20% of the *Z* isomer. Step C illustrates the selective hydroboration of a diene with disiamylborane.[15] [16] The reaction is best carried out by adding preformed disiamylborane to the triene. Lower yields of homogeraniol were obtained by the submitter when the triene was added to the borane reagent.

Homogeraniol has been prepared by reduction of homogeranic acid with lithium

aluminum hydride,[6] by cyclopropylcarbinol rearrangement to homogeranyl bromide and subsequent displacement of the bromide,[17] by zirconium-catalyzed syn addition of trimethylaluminum to an acetylene precursor followed by reaction with ethylene oxide,[7] and by hydroxymethylation of geranyl chloride with diisopropoxymethylsilylmethyl Grignard reagent.[18] Homogeranic acid has been prepared by base-catalyzed hydrolysis of the nitrile,[6,9,19 20 21] copper-catalyzed S_N2-type alkylation of β-isopropenyl-β-propiolactone with dimethylallyl Grignard reagent,[22] alkylation of methoxy(phenylthio)methyllithium with geranyl chloride and subsequent chromic acid oxidation,[23] and carboxylation of geranyl phenyl sulfone followed by reductive desulfonation.[24] Although homogeranic acid prepared by nitrile hydrolysis and by β-isopropenyl-β-propiolactone alkylation[22] is a 70 : 30 mixture of *E* and *Z* isomers,[9,25] the *E* form may be isolated by crystallization at −10°C[6] or by preparative gas chromatography of their *tert*-butyl esters.[26] Homogeraniol prepared by acid-catalyzed cyclopropylcarbinyl to homoallyl rearrangement[17] is also a mixture of *E* and *Z* isomers.[27]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

benzophenone ketyl

diborane

disiamylborane

Homogeraniol

aplysistatin

dendrolasin

(E)-homogeraniol

homogeranic acid

homogeranyl bromide

dipyridine

ethanol (64-17-5)

acetylene (74-86-2)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

nitrogen (7727-37-9)

cyclohexane (110-82-7)

sodium (13966-32-0)

chromic acid (7738-94-5)

Ethylene oxide (75-21-8)

hydrogen peroxide (7722-84-1)

manganese dioxide (1313-13-9)

iodomethane (74-88-4)

dichloromethane (75-09-2)

Phenyllithium (591-51-5)

magnesium sulfate (7487-88-9)

chromium trioxide (1333-82-0)

borane (7440-42-8)

2-methyl-2-butene (513-35-9)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

oxalyl chloride (79-37-8)

lithium aluminum hydride (16853-85-3)

sodium hydride (7646-69-7)

hexane (110-54-3)

citral (5392-40-5)

geraniol (106-24-1)

dimethyl sulfoxide (67-68-5)

triethylamine (121-44-8)

calcium hydride (7789-78-8)

triphenylphosphine (603-35-0)

tert-BUTYL (1605-73-8)

triphenylphosphine oxide (791-28-6)

argon (7440-37-1)

trimethylaluminum (75-24-1)

squalene

Geranyl chloride (5389-87-7)

Geranial, (E)-geranial

methyltriphenylphosphonium iodide (2065-66-9)

diisopropoxymethylsilylmethyl

β-isopropenyl-β-propiolactone

dimethylallyl (29791-12-6)

methoxy(phenylthio)methyllithium

geranyl phenyl sulfone

cyclopropylcarbinyl

homoallyl (2154-62-3)

phosphorus pentoxide (1314-56-3)

potassium tert-butoxide (865-47-4)

3,7-Nonadien-1-ol, 4,8-dimethyl-, (E)- (459-88-1)

(E)-4,8-Dimethyl-1,3,7-nonatriene (19945-61-0)

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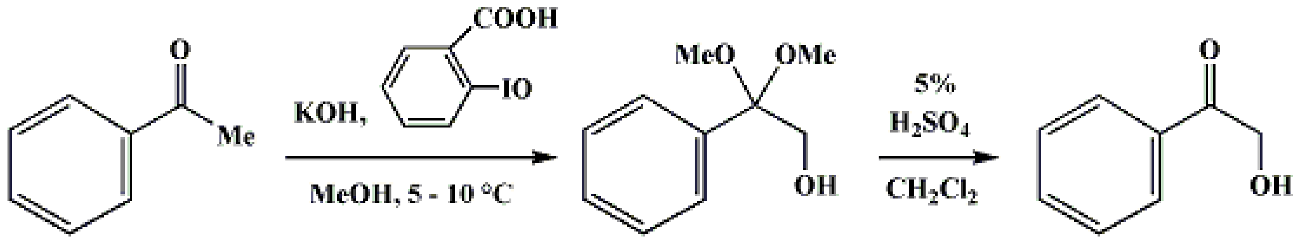
α-HYDROXYLATION OF A KETONE USING *o*-IODOSYLBENZOIC ACID: α-HYDROXYACETOPHENONE VIA THE α-HYDROXY DIMETHYLACETAL

[Ethanone, 2-hydroxy-1-phenyl-]



Submitted by Robert M. Moriarty, Kwang-Chung Hou, Indra Prakash, and S. K. Arora[1].
Checked by Janice Klunder and K. Barry Sharpless.

1. Procedure

A 250-mL, two-necked, round-bottomed flask is equipped with a magnetic stirring bar, 100-mL pressure-equalized addition funnel to which is attached a drying tube, and a stopper. Anhydrous methanol (80 mL) (Note 1) is added to the flask, which is cooled to 5–10°C. Stirring is begun and 8.4 g (0.15 mol) of powdered potassium hydroxide is added. Acetophenone (6.0 g; 0.05 mol) (Note 2) dissolved in 20 mL of methanol is added dropwise over a period of 10 min. After the solution is stirred for 15 min, 14.52 g (0.055 mol) of *o*-iodosylbenzoic acid (Note 3) is added during 30 min. The ice bath is removed and the resultant yellow-colored slurry is stirred overnight at room temperature to give a clear red solution (Note 4). The mixture is concentrated under reduced pressure in a rotary evaporator until one-half of the methanol is removed, and then 30 mL of water is added followed by extraction with four 50-mL portions of dichloromethane. The combined dichloromethane extracts are washed with two 10-mL portions of water, and the combined organic extracts are dried over anhydrous magnesium sulfate for 1 hr. After filtration, the methylene chloride is removed under reduced pressure in a rotary evaporator, and the crude acetal is distilled to give a fraction at 73–76°C (0.4 mm) weighing 6.0 g (65%) (Note 5). The acetal is of high purity, as shown by spectral analysis (Note 6).

α-Hydroxyacetophenone. In a 500-mL, round-bottomed flask equipped with a magnetic stirrer are placed 6.0 g (0.33 mol) of α-hydroxy dimethylacetal and 100 mL of dichloromethane. Stirring is begun and the flask is cooled to about 10°C with ice water. Aqueous 5% sulfuric acid (100 mL) is added dropwise from a pressure-equalized addition funnel and the mixture is stirred for another 30 min. The dichloromethane layer is separated and the aqueous layer is extracted twice with 25-mL portions of dichloromethane. The combined extracts are washed with two 10-mL portions of water and dried over anhydrous magnesium sulfate, and the solvent is removed under reduced pressure using a rotary evaporator. The resulting yellow crystalline solid is recrystallized from carbon tetrachloride to give a white crystalline material, mp 86–87.5°C (lit.[2] mp 86–87°C), yield 3.7 g (83%) (Note 7).

2. Notes

1. Anhydrous methanol is obtained by treatment with magnesium methoxide, obtained by refluxing 50 mL of methanol, 5 g of magnesium turnings, and 0.5 g of sublimed iodine together

until the iodine color disappears. The 1 L of methanol is added and the system is kept at reflux for 1 hr and distilled to yield purified methanol (bp 64.5°C).

2. Acetophenone was used as purchased from Fisher Scientific Company.

3. *o*-Iodosylbenzoic acid was used as purchased from Sigma Chemical Company.

4. TLC (ethyl acetate:hexane) shows residual starting material.

5. The α-hydroxy dimethylacetal obtained must be used immediately in the next step because at room temperature it undergoes a dimerization reaction by loss of two molecules of methanol.

6. The spectral properties of the product are as follows: IR (neat) cm^{-1}: 3470 (-OH): ^{1}H NMR ($CDCl_3$) δ: 1.83 (s, 1 H, OH), 3.23 (s, 6 H, $(OCH_3)_2$), 3.73 (s, 2 H, CH_2), 7.27–7.67 (m, 5 H, Ar H); ^{13}C NMR ($CDCl_3$) δ: 139.3 (s), 128.4 (d), 127.4, (d) 102.4 (s), 65.3 (t) 49.1 (q); mass spectrum: *m/e* 151 (M^+-OCH_3 100%), 105 (29.7%), 91 (31.7%), 77 (7.0%).

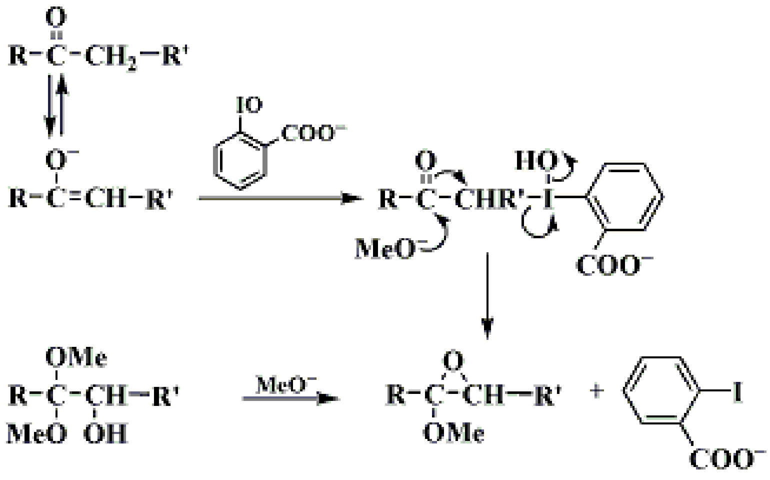
7. The product has the following spectral properties: ^{1}H NMR ($CDCl_3$) δ: 3.63 (s, 1 H, OH), 4.86 (s, 2 H, CH_2), 7.25–7.90 (m, 5 H, Ar H); ^{13}C NMR ($CDCl_3$) δ: 198.6 (s), 134.4 (s), 129.1 (d), 127.8 (d), 65.6 (t).

3. Discussion

The procedure reported here provides a convenient method for the α-hydroxylation of ketones that form enolates under the reaction conditions. The reaction has been applied successfully to a series of para-substituted acetophenones, 1-phenyl-1-propanone, 3-pentanone, cyclopentanone, cyclohexanone, cycloheptanone, cyclododecanone, 2-methylcyclohexanone, 2-norbornanone, and benzalacetone.[3] In the case of a steroidal example it was shown that a carbon–carbon double bond and a secondary hydroxyl group are not oxidized.[4] A primary amino function, as in the case of *p*-aminoacetophenone, is not affected.[5] Similarly, a tertiary amino ketone such as tropinone undergoes the α-hydroxylation reaction.[5]

The present procedure using *o*-iodosylbenzoic acid is an improvement over our original method, which uses either iodosylbenzene or diacetoxyphenyliodine(III).[6,7,8] The advantage of the present method is the solubility of the product iodobenzoic acid under the basic reaction conditions. Thus the α-hydroxy dimethylacetal may be isolated by direct extraction. Using the original procedure, both carboxylic acids and esters underwent high yield α-hydroxylation.[8]

The pathway by which the reactions are considered to occur involves attack of the enolate anion at the I=O bond of *o*-iodosylbenzoic acid followed by reductive elimination of *o*-iodobenzoic acid upon addition of methoxide to the carbonyl group. Ring opening of the epoxide thus formed yields the hydroxy dimethylacetal:



Other methods for α-hydroxy ketone synthesis are as follows: addition of $^3O_2$ to an enolate followed by reduction of the α-hydroperoxy ketone using triethyl phosphite;[9] the molybdenum peroxide–pyridine/HMPA oxidation of enolates;[10] photooxygenation of enol ethers followed by triphenylphosphine reduction;[11] the epoxidation of trimethylsilyl enol ethers by peracid;[12] the oxidation of trimethylsilyl enol ethers by osmium tetroxide in *N*-methylmorpholine *N*-oxide;[13] and, finally, the classical method of hydrolysis of an α-bromo ketone.[14]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 132

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

α-HYDROXY DIMETHYLACETAL

hydroxy dimethylacetal

HMPA

sulfuric acid (7664-93-9)

ethyl acetate (141-78-6)

methanol (67-56-1)

magnesium turnings (7439-95-4)

Cyclohexanone (108-94-1)

carbon tetrachloride (56-23-5)

iodine (7553-56-2)

Benzalacetone (122-57-6)

Acetophenone (98-86-2)

pyridine (110-86-1)

potassium hydroxide (1310-58-3)

Cyclopentanone (120-92-3)

magnesium methoxide

iodobenzoic acid, o-iodobenzoic acid (88-67-5)

methylene chloride, dichloromethane (75-09-2)

1-phenyl-1-propanone (93-55-0)

magnesium sulfate (7487-88-9)

α-Hydroxyacetophenone, Ethanone, 2-hydroxy-1-phenyl- (582-24-1)

3-pentanone (96-22-0)

osmium tetroxide (20816-12-0)

iodosylbenzene (536-80-1)

hexane (110-54-3)

2-methylcyclohexanone (583-60-8)

Cycloheptanone (502-42-1)

Triethyl phosphite (122-52-1)

triphenylphosphine (603-35-0)

cyclododecanone (830-13-7)

tropinone (532-24-1)

2-Norbornanone (497-38-1)

diacetoxyphenyliodine(III)

molybdenum peroxide

N-methylmorpholine N-oxide (80913-66-2)

p-aminoacetophenone (99-92-3)

o-IODOSYLBENZOIC ACID (304-91-6)

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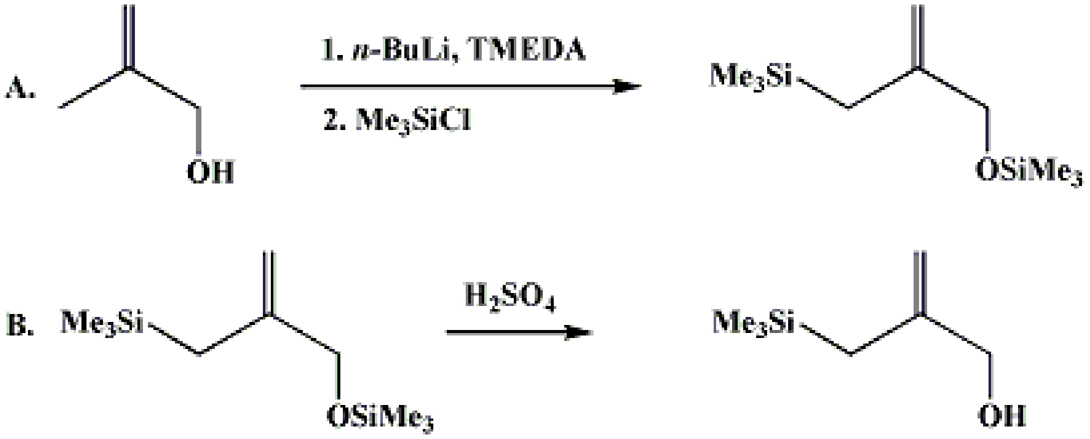
Organic Syntheses, CV 7, 266

SILYLATION OF 2-METHYL-2-PROPEN-1-OL DIANION: 2-(HYDROXYMETHYL) ALLYLTRIMETHYLSILANE



Submitted by Barry M. Trost, Dominic M. T. Chan, and Thomas N. Nanninga[1].
Checked by Paul R. Jenkins and Ian Fleming.

1. Procedure

Caution! Part A should be carried out in an efficient hood, since the reagents are noxious.

A. *2-(Trimethylsiloxymethyl)allyltrimethylsilane.* An oven-dried (Note 1) 2-L, three-necked, round-bottomed flask is equipped with an airtight mechanical stirrer (Note 2), a 500-mL pressure-equalizing dropping funnel (Note 3), and a reflux condenser. The top of the condenser is connected to a three-way stopcock with one branch connected to a nitrogen source and the other to a variable pressure oil pump with a dry ice trap (Note 4). The apparatus is flamed dry under a steady stream of nitrogen. The flask is charged with 836 mL (1.07 mol) of a 1.28 *M* solution of butyllithium in hexane (Note 5). The bulk of the hexane is removed at reduced pressure with stirring until a thick oil is obtained (Note 6). The system is carefully recharged with nitrogen. Alternatively, the use of 107 mL of 10 *M* butyllithium in hexanes is more convenient and gives similar yields (Note 7). The butyllithium is then cooled in an ice bath and 500 mL of anhydrous ether is added (Note 8), followed by 160 mL of tetramethylethylenediamine (Note 9). The mixture is stirred for a few minutes and 34 mL, 29.14 g (0.404 mol) of 2-methyl-2-propen-1-ol (Note 10) is added dropwise via a syringe over 22 min (Note 11). An immediate, vigorous reaction occurs and the lithium alkoxide precipitates as a white solid. Approximately 350 mL of tetrahydrofuran (Note 12) is added and the resultant slightly cloudy yellow solution is allowed to warm to room temperature over ca. 4 hr (Note 13). The reaction is stirred for 39 hr (Note 14), at which time the dianion separates as a dark-red gummy material from the deep orange solution. The mixture is

cooled to ca. –30°C (Note 15) and 230 mL (1.81 mol) of chlorotrimethylsilane (Note 16) is added all at once over ca. 20 sec. The reaction turns milky white (Note 17). After 5 min, the dry ice bath is removed and the mixture is stirred for a further 15 min at room temperature. The reaction mixture is added in two portions with swirling to 1.5 L of ether in two 2-L conical flasks, after which 1 L of saturated aqueous sodium bicarbonate is added very carefully to destroy excess chlorotrimethylsilane (Note 18). The two layers are separated and the aqueous phase is extracted with a further 1.5 L of ether. The combined organic layer is then washed with 1 L of water, two 1-L portions of saturated aqueous copper sulfate solution, and 400 mL of water. The solution is dried over anhydrous potassium carbonate and the solvent is removed by atmospheric distillation (Note 19). Careful distillation of the residual oil through a 27-cm Vigreux column at reduced pressure gives a forerun of 4.25 g, bp 29–57°C (4 mm), and 45.8 g (52%) of 2-(trimethylsiloxy)allyltrimethylsilane as a colorless liquid, bp 57–59°C (4 mm) (Note 20).

B. *2-(Hydroxymethyl)allyltrimethylsilane.* A 500-mL round-bottomed flask equipped with a magnetic stirring bar is charged with 21.10 g (0.0975 mol) of 2-(trimethylsiloxymethyl)allyltrimethylsilane in 170 mL of tetrahydrofuran (Note 12) and 44 mL of ca. 1 *N* aqueous sulfuric acid (Note 21). The resultant two-phase mixture is then stirred vigorously for 1.5 hr at room temperature. Solid anhydrous potassium carbonate is added carefully until bubbling subsides. The layers are separated and the aqueous layer is extracted with 100 mL of ether. The combined organic layers are dried over anhydrous potassium carbonate and distilled at atmospheric pressure to remove the solvents (Note 19). The remaining liquid is distilled at reduced pressure to give a forerun, 0.4 g, bp 22–54°C (4 mm), and 10.95 g (78%) of 2-(hydroxymethyl) allyltrimethylsilane as a colorless liquid, bp 54–56°C (2 mm) (Note 22).

2. Notes

1. All glassware was dried in an oven at over 100°C overnight.
2. The use of a magnetic stirrer is not advisable since the formation of the gum-like dianion prevents efficient stirring. A mechanical stirrer with a ground-glass shaft bearing lubricated with mineral oil is recommended.
3. The funnel is capped with a rubber septum. For ease of operation, volume markings, corresponding to the amounts of reagents to be added, are put on the addition funnel.
4. The function of the trap is to condense the hexane from the butyllithium solution. The checkers used a 1-L three-necked flask fitted with a short delivery tube (a quick-fit air-bleed tube was used), stopper, and rubber tubing connection. The submitters used a water aspirator and a 1-L filter flask with a drying tower between.
5. Butyllithium in hexane was purchased by the checkers from Pfizer Chemicals Ltd., UK, and manufactured by the Lithium Corporation of America. It was titrated using the double titration method with dibromoethane and transferred to the addition funnel using a cannula. The submitters used a 1.58 *M* solution from

the Foote Mineral Company; they found that the yield of product was reduced to ca. 42% when only 2 equiv of the lithium reagent was used.

6. One should try to remove as much hexane as possible from the butyllithium solution (i.e. greater than 90%) because the purity of the product depends on the polarity of the reaction medium. A warm-water bath was used to facilitate solvent removal. The checkers used a variable pressure oil pump with the vacuum adjusted to ca. 10–20 mm.

7. Butyllithium as a 10 *M* solution in hexanes is supplied by Aldrich Chemical Company, Inc. The procedure for its use in place of solutions of lower concentration is identical to that in the text except for deletion of the solvent evaporation step. As 10 *M* butyllithium is quite viscous and pyrophoric it should be handled with large-bore needles.

8. Ether was distilled from sodium ketyl of benzophenone. The dissolution of butyllithium in ether was slightly exothermic.

9. Tetramethylethylenediamine was obtained from Aldrich Chemical Company and distilled from calcium hydride before use.

10. 2-Methyl-2-propen-1-ol, purchased from Aldrich Chemical Company, was distilled from anhydrous potassium carbonate. It was added directly to the butyllithium solution using a long needle. The checkers quickly replaced the pressure-equalizing dropping funnel with a serum cap to carry out this addition. The funnel was fitted to a small dry flask to prevent the introduction of moisture during the addition period and replaced on the reaction flask immediately afterward.

11. The reaction of the alcohol with butyllithium is quite vigorous with evolution of butane.

12. Tetrahydrofuran was distilled from sodiumketyl of benzophenone.

13. The checkers renewed the ice bath when additions were complete and allowed the flask to remain in the ice bath without addition of fresh ice.

14. Dianion formation appears to be essentially complete within 24 hr. However, a reaction time of 36 hr is recommended by the submitters to ensure complete reaction.

15. An extremely violent reaction is observed if the dianion is quenched above 0°C, with ether boiling off at an uncontrollable rate. The submitters observed that if the chlorotrimethylsilane addition is performed at a lower temperature, the reaction temperature will remain below that of the boiling point of ether. A dry-ice bath made up of 80 : 20 (v/v) ethanol : water was used; the checkers measured a bath temperature of −55°C and kept the reaction in the bath for 15 min before adding chlorotrimethylsilane.

16. Chlorotrimethylsilane was distilled from tributylamine before use. Both of these reagents were obtained from the Aldrich Chemical Company.

17. The submitters observed the appearance of a brown color at this point. The checkers obtained a brown color only after the reaction mixture was added toether. In a run at half scale the reaction mixture remained milky white for 35 min and turned brown only when ether (500 mL) was added to it.

18. The submitters observed more precipitate on dilution with ether and recommended that the aqueous workup be performed in a hood.

19. The submitters distilled most of the solvent using a bath temperature increasing up to 100°C. The checkers used a rotary evaporator with a hot water bath.

20. A variable pressure oil pump was used in this distillation. Approximately 10 g of a volatile component, consisting mostly of hexamethyldisiloxane, was obtained at room temperature (15 mm) before the foreun. The forerun contained the desired product and mineral oil from the butyllithium solution. The pot residue was about 5 g. The submitters find the disilyl compound thus obtained is contaminated with a trace amount of mineral oil and 4–6% of a vinylsilane, probably 2-methyl-1-trimethylsiloxy-3-trimethylsilyl-2-propene. This impurity becomes quite significant if the reaction medium is less polar than the one described (e.g., too much hexane from butyllithium is allowed to remain behind). The spectral properties of the desired product determined by the checkers are as follows: IR (neat) cm^{-1}: 2955, 1643, 1636, 1250, 1085, 885–830; ^{1}H NMR (chloroform-*d*, 90 MHz) δ: 0.03 [s, 9 H, $CH_2Si(CH_3)_3$], 0.14 [s, 9 H, $OSi(CH_3)_3$], 1.50 [broad s, 2 H, CH_2-$Si(CH_3)_3$], 3.93 [broad s, 2 H, CH_2-$OSi(CH_3)_3$], 4.62 (m, 1 H, vinyl H), 4.92 (m, 1 H, vinyl H). The checkers observed small NMR peaks assigned to mineral oil at δ 0.9 and 1.28 and peaks assigned to 2-methyl-1-trimethylsiloxy-3-trimethylsilyl-2-propene at δ 1.87 and 4.1. When the reaction was carried out at half scale the quantity of the latter impurity was not measurable from the NMR integral; however, a run at full scale gave about 10% of the impurity as estimated from the NMR integral. The product from the run at half scale had bp 56–57°C (2 mm); the submitters, bp 65°C (5.5 mm).

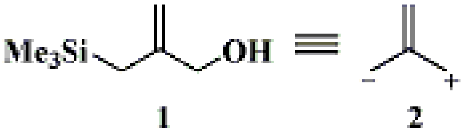
21. The acid solution was prepared by adding 13.5 mL of concentrated sulfuric acid to 500 mL of distilled water.

22. A variable-pressure pump is used for the distillation. The forerun consisted of mineral oil contaminant and product. The allylic alcohol is not very stable at room temperature but can be maintained indefinitely in the refrigerator at 0 to –6°C. The spectral properties of the alcohol were determined by the checkers as follows: IR (neat) cm^{-1}: 3600–3100, 2950, 1643, 1637, 1247, 1050, 885–830; ^{1}H NMR (chloroform-*d*), 90 MHz) δ: 0.02 [s, 9 H, $CH_2Si(CH_3)_3$], 1.51 [s, 2 H, CH_2-$Si(CH_3)_3$], 2.16 (broad s, 1 H, OH), 3.92 (broad s, 2 H, CH_2-OH), 4.62 (m, 1 H, vinyl H), 4.98 (m, 1 H, vinyl H). The checkers observed small NMR peaks assigned to mineral oil at δ 0.82 and 1.51 and peaks assigned to 2-methyl-1-trimethylsiloxy-3-trimethylsilyl-2-propene at δ 0.10, 1.87, and 4.1. When the reaction was carried out at half scale the quantity of the latter impurity was reduced; the product from the run at half scale had bp 54–55°C (3 mm); submitters, bp 53–54°C (1.6 mm).

3. Discussion

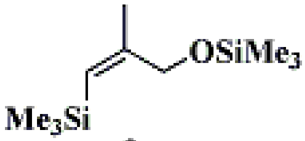
Compound **1**, 2-(hydroxymethyl)allyltrimethylsilane, represents a conjunctive reagent that can be considered as the equivalent of zwitterion **2**, possessing a nucleophilic allylanion synthon and an electrophilic allyl cation synthon in the same molecule. It

has been employed in a three-carbon condensative ring-expansion reaction,[2] a [3 + 2] annulation with cyclic enones,[3,4] and the total synthesis of coriolin.[5] Acetylation of the allylic alcohol gives 2-(acetoxymethyl)allyltrimethylsilane, which undergoes palladium (0) catalyzed annulation with electron-deficient olefins to produce methylenecyclopentanes via the trimethylenemethane–palladium complex. This cycloaddition has served as a key step in synthetic approaches directed toward natural products such as brefeldin A[6] and albene,[7] and the polyquinanes.[8] Additions to heteroatom unsaturation can also be induced to occur to form oxygen and nitrogen heterocycles[9] as well as carbocycles.[10] It has also been employed to generate the TMM complex of transition metals other than palladium.[11]



The present procedure provides a convenient two-step route to 2-(hydroxymethyl)allyltrimethylsilane using relatively inexpensive reagents. Other approaches require additional steps and expensive chloromethyltrimethylsilane.[3,12]

Dianion formation from 2-methyl-2-propen-1-ol seems to be highly dependent on reaction conditions. Silylation of the dianion generated using a previously reported method[13] was unsuccessful in our hands. The procedure described here for the metalation of the allylic alcohol is a modification of the one reported for formation of the dianion of 3-methyl-3-buten-1-ol.[14] The critical variant appears to be the polarity of the reaction medium. In solvents such as ether and hexane, substantial amounts (15–50%) of the vinylsilane **3** are observed. Very poor yields of the desired product were obtained in dimethoxyethane and hexamethylphosphoric triamide, presumably because of the decomposition of these solvents under these conditions. Empirically, the optimal solvent seems to be a mixture of ether and tetrahydrofuran in a ratio (v/v) varying from 1.4 to 2.2; in this case **3** becomes a very minor component.



3

A similar procedure has been employed to silylate the dianion of 3-methyl-3-buten-2-ol (67% yield).[15] In systems where such internal activation is not possible (e.g., 2-methyl-2-cyclohexen-1-ol), dianion formation can be performed in hexane to give a 75% yield of the corresponding disilyl compound.[16]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

lithium alkoxide

sodium ketyl of benzophenone

sodiumketyl of benzophenone

ethanol (64-17-5)

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

ether (60-29-7)

sodium bicarbonate (144-55-8)

allylic alcohol (107-18-6)

allyl (1981-80-2)

oxygen (7782-44-7)

nitrogen (7727-37-9)

copper sulfate (7758-98-7)

palladium, palladium(0) (7440-05-3)

lithium (7439-93-2)

butane (106-97-8)

3-methyl-3-buten-2-ol (10473-14-0)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

2-methyl-2-propen-1-ol (513-42-8)

hexane (110-54-3)

calcium hydride (7789-78-8)

dimethoxyethane (534-15-6)

trimethylenemethane (287-23-0)

tributylamine (102-82-9)

hexamethylphosphoric triamide (680-31-9)

CHLOROTRIMETHYLSILANE (75-77-4)

hexamethyldisiloxane (107-46-0)

tetramethylethylenediamine (20485-44-3)

2-METHYL-2-PROPEN-1-OL DIANION

2-(Hydroxymethyl)allyltrimethylsilane (81302-80-9)

2-(trimethylsiloxy)allyltrimethylsilane

2-(Trimethylsiloxymethyl)allyltrimethylsilane

dibromoethane (557-91-5)

vinylsilane (7291-09-0)

2-methyl-1-trimethylsiloxy-3-trimethylsilyl-2-propene

2-(acetoxymethyl)allyltrimethylsilane (72047-94-0)

chloromethyltrimethylsilane (2344-80-1)

3-methyl-3-buten-1-ol (763-32-6)

2-methyl-2-cyclohexen-1-ol

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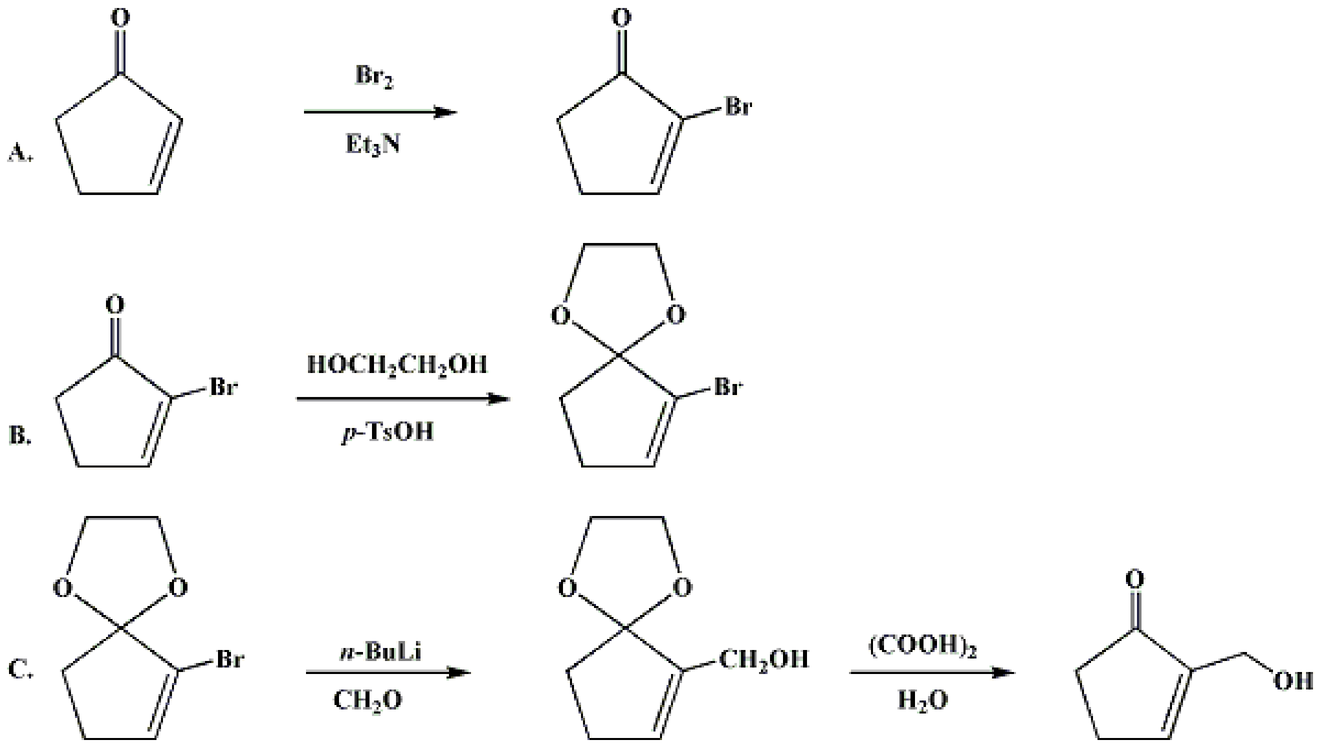
Organic Syntheses, CV 7, 271

2-HYDROXYMETHYL-2-CYCLOPENTENONE



Submitted by Amos B. Smith III, Stephen J. Branca, Michael A. Guaciaro, Peter M. Wovkulich, and Abner Korn[1].
Checked by F. Pigott and G. Saucy.

1. Procedure

A. *2-Bromo-2-cyclopentenone*. In a well-ventilated hood, a solution of 18.98 g (231.2 mmol) of 2-cyclopentenone (Note 1) in 150 mL of carbon tetrachloride is added to a 1-L, three-necked, round-bottomed flask fitted with a mechanical stirrer, thermometer, and an addition funnel. The solution is chilled to 0°C with an ice bath and a solution of 40.5 g (253.4 mmol, 13.0 mL) of bromine in 150 mL of carbon tetrachlorideis added dropwise during 1 hr. Then a solution of 35.1 g (346.8 mmol, 48.3 mL) of triethylamine in 150 mL of carbon tetrachloride is added dropwise over 1 hr with vigorous stirring while the reaction is held at 0°C. Stirring is continued for an additional 2 hr at room temperature; the resulting dark suspension is filtered with suction and the filtercake washed with carbon tetrachloride. The filtrate and washings are combined and washed with two 100-mL portions of 2 *N* hydrochloric acid, one 100-mL portion of saturated sodium bicarbonate solution, one 100-mL portion of water, and one 100-mL portion of saturated sodium chloride solution. The resultant solution is dried over anhydrous magnesium sulfate, filtered, and the solvent removed under reduced pressure. Distillation of the resultant oil (69–78°C, 1.0 mm) afforded 23.7 g (147.2 mmol, 64%) (Note 2) of a white crystalline solid, mp 36–37°C, (lit.[2] mp 39–39.5°C) (Note 3).

B. *2-Bromo-2-cyclopentenone ethylene ketal*. A solution of 22.00 g (136.7 mmol) of freshly distilled 2-bromo-2-cyclopentenone, 21.80 g (351.2 mmol) of ethylene glycol, 1.5 L of benzene (Note 4), and 60 mg of *p*-toluenesulfonic acid monohydrate is heated at reflux for 64 hr (Note 5), with azeotropic removal of water, in a 3-L, round-bottomed flask, equipped with a Dean-Stark trap, condenser, and Drierite drying tube. The solution is cooled to room temperature, dried with potassium carbonate, and filtered by vacuum through 15 g of Celite. The filtercake is washed with 150 mL of benzene. Removal of the solvent under reduced pressure yields a mobile yellow oil. Distillation (65–67°C, 0.7 mm) affords 22.4 g (109.0 mmol, 80%) (Note 6) of the ketal (Note 7).

C. *2-Hydroxymethyl-2-cyclopentenone*. The apparatus, as illustrated in f.htmigure 1 (Note 8), is flame-dried

while dry nitrogen is passed through. Paraformaldehyde (13 g, 433 mmol) (Note 9) is then added to the 250-mL flask (the generator) and 19.4 g (94.6 mmol) of freshly distilled 2-bromo-2-cyclopentenone ethylene ketal in 300 mL of dry tetrahydrofuran containing 2 mg of 2,2'-bipyridyl (Note 10) is added to the 500-mL flask (the reaction flask). The reaction flask is chilled to −78°C with an acetone/dry ice bath and 46.0 mL (105.8 mmol) of butyllithium (2.3 *M* in hexane) (Note 11) is added dropwise by syringe through the rubber septum during 1 hr. The resultant red solution is stirred for 1 hr and then warmed to −30°C using a methanol–water (2 : 3)/dry ice bath. An oil bath previously heated to 160°C is applied to the generator and the monomeric formaldehyde thus generated is bubbled into the reaction mixture via a steady stream of dry nitrogen until the red color of the indicator is discharged (approximately 45 min). The reaction is quenched by the addition of 10 mL of saturated ammonium chloride solution and the resultant mixture is poured into 100 mL of a saturated sodium chloride solution. This mixture is extracted four times with 100-mL portions of methylene chloride; the methylene chloride extracts are combined and dried over magnesium sulfate. After filtration, evaporation of the solvent under reduced pressure affords 8.1–10.7 g (Note 12) of crude 2-hydroxymethyl-2-cyclopentenone ethylene ketal as a viscous liquid (Note 13).

Figure 1

Figure 1

Without purification, 8.1 g of the above crude ketal is added to a solution consisting of 1.0 g of oxalic acid, 5 mL of water, and 40 mL of methylene chloride. The resultant mixture is stirred for 5 hr at room temperature. At the end of this period the solution is filtered through 50 g of magnesium sulfate impregnated with 1.0 g of potassium carbonate (Note 14). Evaporation of the solvent from the filtrate affords a solid which, after purification by short-path distillation (70–80°C, 0.1 mm) (Note 15), gives 4.9 g (46%, based on bromoketal) (Note 16) of pure 2-hydroxymethyl-2-cyclopentenone, mp 68–69°C (off-white crystals) (Note 17) and (Note 18).

2. Notes

1. Cyclopentenone is commercially available from the Aldrich Chemical Company, Inc., or may be prepared according to the procedure of DePuy; see *Org. Synth., Coll. Vol. V* **1973**, 326.
2. The checkers obtained somewhat higher yields (i.e., 66 and 77%).
3. Pure 2-bromo-2-cyclopentenone obtained by recrystallization from diethyl ether-hexane[2] displayed the following spectroscopic properties: IR (CCl_4) cm^{-1}: 1720 (s), 1595 (m); ^{1}H NMR (CCl_4, 60 MHz) δ: 2.35–2.60 (m, 2H), 2.60–2.91 (m, 2 H), 7.40 (t, 1 H, *J* = 2).
4. *Caution: Benzene is a potential carcinogen!*
5. The reaction progress was monitored by TLC analysis (silica gel) using hexane-ethyl acetate (4 : 1, v/v) with 3.5% methanolic phosphomolybdic acid as indicator: bromoketal, R_f 0.37, bromoketone, R_f 0.15.
6. The bromoketal appears to be somewhat unstable and should be used as soon as possible after preparation. Some decomposition was observed during distillation.
7. Pure 2-bromo-2-cyclopentenone ethylene ketal displayed the following spectroscopic properties: IR (CCl_4) cm^{-1}: 2975 (s), 2950 (s), 2880 (s), 1615 (w); ^{1}H NMR (CCl_4, 60 MHz) δ: 1.95–2.55 (m, 4 H), 3.71–4.01 (m, 2 H), 4.01–4.33 (m, 2 H), 6.05 (t, 1 H, *J* = 2).
8. The checkers found that it is important to employ tubing of wide bore (6-mm o.d.) to conduct the gaseous formaldehyde from the generation flask into the reaction flask to avoid the possibility of the tube becoming plugged.
9. Prior to use paraformaldehyde was dried overnight in high vacuum (0.1 mm) over phosphorus pentoxide.
10. The reagent 2,2'-bipyridyl, available from the Aldrich Chemical Company, Inc., appears red in solutions containing organolithium and organomagnesium reagents[3] and is thereby an excellent indicator. Its use here allows addition of the precise amount of gaseous formaldehyde.
11. Butyllithium is available commercially from Alfa Products, Morton Thiokol, Inc.
12. The checkers found this crude product to contain 84.5% of the desired ketal, based on GC analysis.
13. Although 2-hydroxymethyl-2-cyclopentenone ethylene ketal could be purified by Kugelrohr

distillation (88–100°C, 0.10 mm) this was not necessary for successful completion of the subsequent hydrolysis step. Pure 2-hydroxymethyl-2-cyclo-pentenone ethylene ketal possesses the following spectroscopic properties: IR (CCl_4) cm^{-1}: 3470–3500 (s), 1616 (w); ^1H NMR (CCl_4, 60 MHz) δ: 1.68–2.17 (m, 2 H), 2.17–2.58 (m, 2 H), 2.58–2.93 (br s, 1 H), 3.87 (s, 4 H), 3.98–4.16 (m, 2 H), 5.81–6.03 (m, 1 H).

14. The function of the potassium carbonate is to neutralize the oxalic acid as the solution passes through.

15. The short-path distillation of 2-hydroxymethyl-2-cyclopentenone is carried out without a water condenser. Furthermore, to prevent solidification of the distillate in the condenser, gentle warming of the condenser with a heat gun may be necessary.

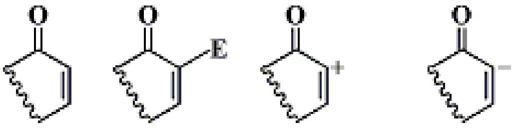
16. The submitters had obtained a 70% yield for this two-step sequence, the crucial step being the reaction with formaldehyde.

17. Pure 2-hydroxymethyl-2-cyclopentenone displayed the following spectroscopic properties: IR ($CHCl_3$) cm^{-1}: 3400–3450 (s), 1680 (s), 1630 (m); ^1H NMR ($CDCl_3$, 60 MHz) δ: 2.27–2.84 (m, 4 H), 3.00 (br s, 1 H), 4.33 (d, 2 H, J = 1), 7.60 (m, 1 H).

18. The overall yield from cyclopentenone to 2-hydroxymethyl-2-cyclopentenone over a number of runs was found to be in the range of 23–28%. The submitters had obtained 34.5%.

3. Discussion

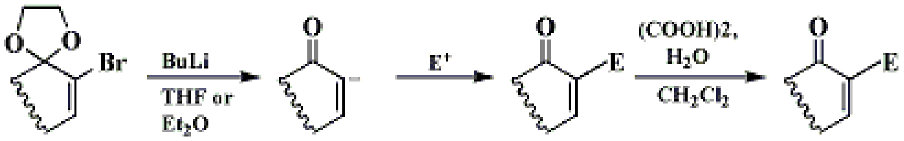
The procedure reported here provides an efficient method for the construction of a wide variety of α,β-unsaturated ketones directly from the parent enone (i.e., **1** **2**), which does not require intervention of the thermodynamic dienolate. To our knowledge, a *general* solution for this recurring synthetic problem is unavailable, although Corey et al.,[4] Fuchs,[5] and Stork and Panaras[6] have independently developed a reverse polarity (umpolung) strategy for α-arylation of α,β-unsaturated ketones. Central to their approach was the generation of an effective latent equivalent for α-ketovinyl cation **3**. Such a strategy, however, is limited in that it depends critically upon the availability of the requisite alkyl or aryl organocuprate or magnesium reagent.



1 2 3 4

α-Ketovinyl cation α-Ketovinyl antion

A more versatile, as well as a more direct approach for the conversion of **1** to **2** employs the ethylene ketal of α-bromo-α,β-enones (e.g., **5**) as a latent equivalent of α-ketovinyl anion **4**.[7] Indeed, independent studies by Ficini and Depezay,[8] House and McDaniel,[9] and Manning et al.[10] as well as our own[11] suggested that such a general strategy would be viable. To illustrate this approach, we record here the preparation of the very useful synthon α-hydroxymethyl-2-cyclopentenone:



5 6 7 8

The overall efficiency of this sequence demonstrates, we believe, the considerable promise that α-bromoketals of α,β-enones hold as latent α-ketovinyl anion equivalents. In particular, we note the feasibility of introducing the very useful trimethylsilyl, tri-*n*-butyltin, and phenylselenenyl substituents.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 495
- Org. Syn. 75, 69

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ethyl acetate (141-78-6)

methanol (67-56-1)

ammonium chloride (12125-02-9)

formaldehyde (630-08-0)

sodium bicarbonate (144-55-8)

magnesium (7439-95-4)

sodium chloride (7647-14-5)

bromine (7726-95-6)

carbon tetrachloride (56-23-5)

Oxalic acid (144-62-7)

nitrogen (7727-37-9)

ethylene glycol (107-21-1)

ethylene (9002-88-4)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

hexane (110-54-3)

bromoketone (593-95-3)

triethylamine (121-44-8)

2-Cyclopentenone, cyclopentenone (930-30-3)

2,2'-bipyridyl (366-18-7)

trimethylsilyl (16571-41-8)

phenylselenenyl

phosphomolybdic acid (51429-74-4)

tri-n-butyltin (688-73-3)

2-Hydroxymethyl-2-cyclopentenone (68882-71-3)

2-Bromo-2-cyclopentenone (10481-34-2)

2-Bromo-2-cyclopentenone ethylene ketal (68241-78-1)

2-Hydroxymethyl-2-cyclopentenone ethylene ketal, 2-hydroxymethyl-2-cyclo-pentenone ethylene ketal (80963-19-5)

diethyl ether-hexane

α-hydroxymethyl-2-cyclopentenone

phosphorus pentoxide (1314-56-3)

p-toluenesulfonic acid monohydrate (6192-52-5)

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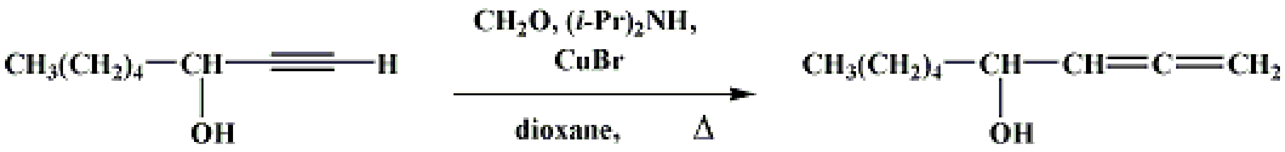
Organic Syntheses, CV 7, 276

ONE-STEP HOMOLOGATION OF ACETYLENES TO ALLENES: 4-HYDROXYNONA-1,2-DIENE

[1,2-Nonadien-4-ol]



Submitted by Pierre Crabbé, Bahman Nassim, and Maria-Teresa Robert-Lopes[1].
Checked by Jeffrey S. Stults and Edwin Vedejs.

1. Procedure

In a 500-mL, three-necked flask, equipped with a thermometer, stirrer, and a reflux condenser with drying tube, are placed 12.6 g (0.1 mol) of 1-octyn-3-ol, 154 mL of dioxane, 7.24 g (0.0504 mol) of cuprous bromide, 7.4 g of paraformaldehyde, and 18.54 g (0.183 mol) of diisopropylamine (Note 1). The resulting mixture is gently refluxed and stirred for 2 hr and then cooled to room temperature and filtered through a Celite plug. The dark-brown filtrate is concentrated under vacuum (Rotavapor) to a gummy residue and then diluted with 50 mL of water followed by 100 mL of ether and acidified with 6 *N* hydrochloric acid to pH 2. The ether–water layers are decanted from any residue, the ether layer is separated, and the aqueous solution is extracted with ether (5 × 50 mL). The ether extracts are combined and washed with small portions of water until pH 6.5 is reached. The organic layer is then washed with saturated sodium chloride solution and dried over anhydrous $MgSO_4$. After removal of ether by distillation through a 20-cm Vigreux column (water aspirator vacuum) while heating on a water bath, ≤40°C, the residual liquid is fractionated under reduced pressure through a 10-cm Vigreux column. The main fraction is collected at 41–42.5°C (0.15 mm) to give 8.65 g of pure allene (Note 2), with additional fractions of a less pure material.

2. Notes

1. Cuprous bromide and 1-octyn-3-ol were used as supplied by the Aldrich Chemical Company, Inc. Dioxane was dried over sodium–benzophenone and distilled, and diisopropylamine was distilled from barium oxide.

2. The spectral properties of 4-hydroxynona-1,2-diene are as follows: IR (neat) cm^{-1}: 3500 (OH), 1960 (C=C=C), 850 (=CH), 2900–2850 (CH). ^1H NMR ($CDCl_3$) δ: 0.65–1.7 (m); 4.15 (1 H, m); 4.8 (2 H, d of d, *J* = 2.6 Hz); 5.22, (1 H, q, *J* = 6 Hz).

3. Discussion

Although allenes were characterized long ago as a distinct class of organic substances, they have only recently received proper attention from chemists, in particular for their potential in organic synthesis.[2 3 4] A number of methods are known for the transformation of acetylenes into allenes,[5] but few are known to allow the homologation of an acetylenic group into a propadiene functionality.

A general procedure for the homologation of acetylenic compounds into allenes is described. The

reaction conditions are mild and appear to be general, so that they can be applied to plain acetylenic substances as well as to acetylenic alcohols, ethers, and esters. This procedure is essentially a one-step reaction. As such, it is simpler and faster than the previously reported technique that involves the conversion of an acetylenic compound into the Mannich base, the formation of its quaternary ammonium salt and the reduction of this salt with lithium aluminum hydride.[6] Of great advantage over previously available methodology are the mild conditions, as well as the clean and fast procedure, which make this a method of choice for an efficient conversion of acetylenes to allenes.[7 8 9]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium chloride (7647-14-5)

barium oxide

Benzophenone (119-61-9)

sodium (13966-32-0)

cuprous bromide (7787-70-4)

$MgSO_4$ (7487-88-9)

dioxane (5703-46-8)

propadiene (463-49-0)

lithium aluminum hydride (16853-85-3)

diisopropylamine (108-18-9)

4-Hydroxynona-1,2-diene, 1,2-Nonadien-4-ol (73229-28-4)

1-octyn-3-ol (818-72-4)

paraformaldehyde (30525-89-4)

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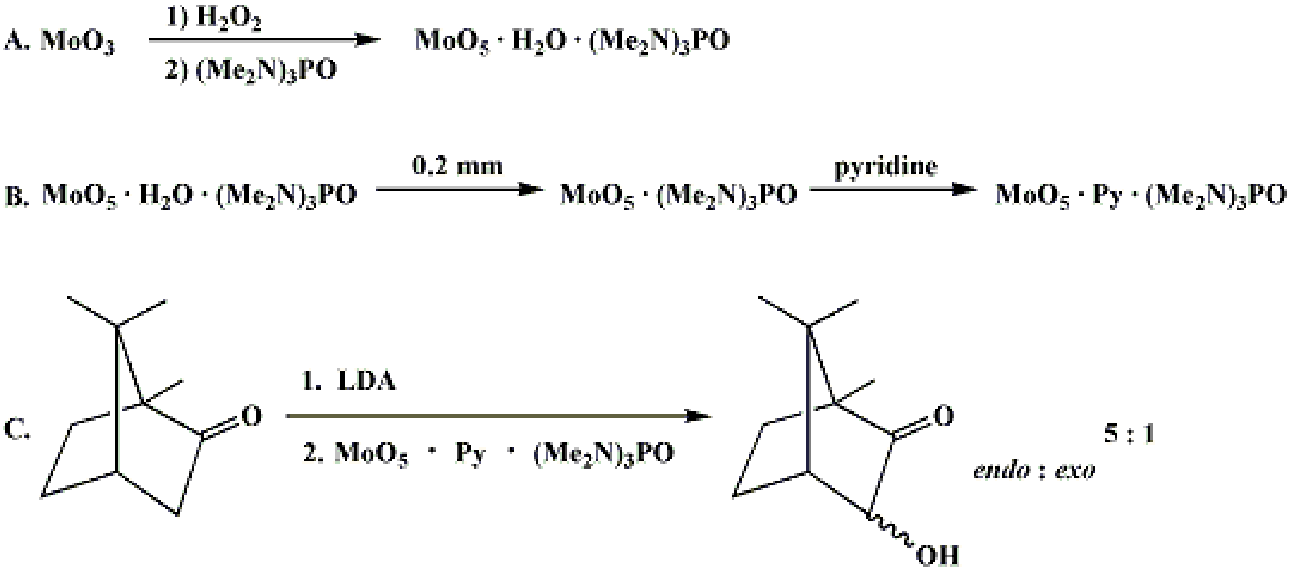
Organic Syntheses, CV 7, 277

HYDROXYLATION OF ENOLATES WITH OXODIPEROXYMOLYBDENUM(PYRIDINE)(HEXAMETHYLPHOSPHORIC TRIAMIDE), MoO_5·Py·HMPA (MoOPH): 3-HYDROXY-1,7,7-TRIMETHYLBICYCLO[2.2.1]HEPTAN-2-ONE

[Bicyclo[2.2.1]heptan-2-one, 3-hydroxy-1,7,7-trimethyl-]



Submitted by Edwin Vedejs and S. Larsen[1].
Checked by Gordon Hill and K. Barry Sharpless.

1. Procedure

Caution! Reactions using peroxides should be performed behind a safety shield to minimize explosion hazards (Note 1). Hexamethylphosphoric triamide (HMPA) and methanol are toxic and must be handled in a hood (Note 2).

A. *Oxodiperoxymolybdenum(aqua)(hexamethylphosphoric triamide), $MoO_5{\cdot}H_2O{\cdot}HMPA$.*[2] A 500-mL, three-necked flask is fitted with an internal thermometer and a mechanical paddle stirrer. The flask is charged, with stirring, with 30 g (0.2 mol) of molybdenum oxide (MoO_3) (Note 3) and 150 mL of 30% hydrogen peroxide (H_2O_2) (Note 4). An oil bath equilibrated at 40°C is placed under the rection mixture and heating is continued until the internal temperature reaches 35°C. The heating bath is removed and replaced by a water bath to control the mildly exothermic reaction so that an internal temperature of 35–40°C is maintained. After the initial exothermic period (approximately 30 min), the reaction flask is placed in the 40°C oil bath and stirred a total of 3.5 hr to form a yellow solution with a small amount of suspended white solid (Note 5).

After cooling to 20°C, the solution is filtered through a 1-cm mat of Celite pressed into a coarse-porosity sintered-glass filter. The yellow filtrate is cooled to 10°C (with an ice bath and magnetic stirring) and 37.3 g (0.21 mol) of hexamethylphosphoric triamide (HMPA) (Note 2) is added dropwise over 5 min, resulting in the formation of a yellow crystalline precipitate. Stirring is continued for a total of 15 min at 10°C, and the product is filtered using a Büchner funnel and

pressed dry with a spatula. After 30 min in the funnel (aspirator vacuum), the filtercake is transferred to a 1-L Erlenmeyer flask. Methanol (20 mL) is added and the mixture is stirred in the 40°C bath. More methanol is slowly added until the crystals have dissolved. Cooling the saturated solution in the refrigerator gives yellow needles. The crystal mass is broken up with a spatula, the product is filtered and washed with 20–30 mL of cold methanol to give $MoO_5 \cdot H_2O \cdot HMPA$, 46–50 g (59–64%) (Note 5) and (Note 6).

B. *Oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide) $MoO_5 \cdot Py \cdot HMPA = MoOPH$.*[2] The recrystallized product from above is dried over phosphorus oxide (P_2O_5) in a vacuum desiccator, shielded from the light, for 24 hr at 0.2 mm to give a somewhat hygroscopic yellow solid, $MoO_5 \cdot HMPA$. A 36.0-g (0.101 mol) portion of $MoO_5 \cdot HMPA$ is dissolved in 150 mL of dry tetrahydrofuran (THF) (Note 7) and the solution is filtered through a Celite mat, if needed, to remove a small amount of amorphous precipitate. The filtrate is then stirred magnetically in a 20°C water bath while 8.0 g (0.101 mol) of dry pyridine (Note 8) is added over 10 min. The crystalline, yellow product is collected on a Büchner funnel, washed with dry tetrahydrofuran (25 mL) and anhydrous ether (200 mL) and dried in a vacuum desiccator (1 hr, 0.2 mm) to yield 36–38 g (51–53% overall from MoO_3) of finely divided yellow crystalline $MoO_5 \cdot Py \cdot HMPA$ (Note 9).

The product is stored in a dark glass jar inside a second container partly filled with Drierite, and the container is kept in the refrigerator. Before opening the jar, the container is allowed to warm to room temperature to avoid condensation of moisture inside. Properly stored MoOPH is a freely flowing crystalline powder and can be used over a period of several months (Note 10).

C. *Hydroxylation of camphor*: *1,7,7-trimethyl-3-hydroxybicyclo[2.2.1]-heptan-2-one*. A solution of lithium diisopropylamide (LDA) is prepared as follows: A 250-mL, three-necked flask and magnetic stirrer are flame-dried under a slow stream of nitrogen. After cooling, the flask is charged with 40 mL of approximately 1.5 *M* butyllithium in hexane (Note 11) under nitrogen flow using a syringe. The flask is cooled in a dry ice–acetone bath and 9.2 mL (66 mmol) of diisopropylamine (Note 8) is added by syringe, followed by 40 mL of dry THF (Note 7). The resulting LDA solution is allowed to reach room temperature under a slow flow of nitrogen. For titration, 0.312 g (2 mmol) of menthol is dissolved in 5 mL of dry THF with a few crystals of phenanthroline (Note 12) under nitrogen flow at –70°C. The LDA solution is added dropwise (using a nitrogen-purged syringe) to the stirred menthol solution until the yellow color of menthoxide–phenanthroline turns to the rust color of LDA–phenanthroline (2.67 mL of LDA solution is needed, 0.75 M).

An aliquot of 47.1 mL (35.3 mmol) of LDA solution is transferred by nitrogen-filled syringe into a nitrogen-swept, 500-mL, three-necked flask equipped with a magnetic stirrer and a device for addition of solid MoOPH. The latter is an L-shaped glass tube with male joints at each end. A round-bottomed flask containing 20.9 g (48.1 mmol) of MoOPH is wired to the L-tube, which is wired to the reaction vessel at such an angle that rotation of the L-tube causes addition of MoOPH to the enolate. The MoOPH container is temporarily suspended using clamps, and the entire apparatus is maintained under a slow flow of nitrogen. After the LDA solution is cooled in a dry ice–acetone bath, 4.88 g (32.1 mmol) of camphor (Note 13) in 200 mL of dry THF is added dropwise with stirring over 0.5 hr. Then 10 min later the reaction is placed in a dry ice–carbon tetrachloride bath and after 15 min the MoOPH is added over 1–2 min by rotating the L-tube and gently tapping it to dislodge the powder. The reaction immediately turns orange and eventually fades to a pale tan (Note 14). Stirring is continued at approximately –23°C for 20 min, and the reaction is quenched by adding 100 mL of saturated aqueous sodium sulfite (Na_2SO_3). Vigorous stirring is maintained and the mixture is allowed to warm to room temperature. After 10 min at 20°C, the mixture is shaken with 100 mL of saturated sodium chloride solution, and the aqueous layer is extracted twice with 70 mL of ether. The combined organic layers are washed once with a mixture of 50 mL of 10%

aqueous hydrochloric acid and 50 mL of saturated sodium chloride solution. The hydrochloric acid–sodium chloride aqueous layer is back-extracted with 50 mL of ether, and the combined organic layers are dried over $MgSO_4$, filtered, and evaporated under an aspirator to yield a blue–green oil. Residual molybdenum salts are removed by filtration over 100 g of silica gel (Note 15) in a 2.5-cm column wet-packed and eluted with 1:1 ether–hexane. The product is eluted with approximately 750 mL of ether–hexane. Evaporation (aspirator) yields a white semisolid, which is crystallized from 15 mL of hexane at −20°C and collected by washing with hexane cooled to −70°C. The mother liquors are crystallized in a similar manner from 2-4 mL of hexane to give a total of five crops, 4.14 g (77%) of colorless needles, mp 170–183°C, a 5:1 mixture of endo : exo isomers (Note 16). Recrystallization did not affect the isomer ratio (literature mp; endo, 192–195°C, exo, 210–211°C).[3]

2. Notes

1. There are no reports that $MoO_5 \cdot H_2O \cdot HMPA$, $MoO_5 \cdot HMPA$, or $MoO_5 \cdot Py \cdot HMPA$ are shock-sensitive. On heating on a hot plate, the crystalline solids ignite and burn, but do not detonate. These compounds can be stored in a refrigerator with precautions to exclude light. Prolonged storage at room temperature in the light may cause decomposition with gas evolution and an exotherm sufficient to crack a glass container.
2. Hexamethylphosphoric triamide is toxic and a suspected carcinogen.
3. Molybdenum oxide was obtained from Mallinckrodt, Inc.
4. Hydrogen peroxide was obtained from Mallinckrodt, Inc.
5. Failure to maintain the internal temperature below 40°C results in formation of amorphous, insoluble products.
6. The purity of this material is decisive because the quality of subsequent products cannot be improved by recrystallization because of some decomposition.
7. Tetrahydrofuran was distilled from sodium–benzophenone and stored under nitrogen.
8. Pyridine was distilled from barium oxide.
9. The product melts with vigorous evolution of gas at 103–105°C.
10. Prolonged exposure to light, or failure to control exothermic reactions in prior steps, results in a sticky product that smells of pyridine. No method for purifying partly decomposed MoOPH has been found, and "sticky" product should not be used for enolate hydroxylation. Suspect material can be decomposed by stirring with aqueous sodium sulfite (Na_2SO_3) solution.
11. Butyllithium was obtained from the Foote Mineral Company.
12. Menthol and phenanthroline were obtained from the Aldrich Chemical Company, Inc.
13. Camphor was obtained from Eastman Organic Chemicals.
14. The colors are somewhat substrate-dependent. Some enolate hydroxylations acquire a green–blue color.
15. Silica gel, 60–200 mesh, was obtained from Davison Chemical Division.
16. The endo : exo ratio is determined by comparing the NMR CHOH signal areas of the endo (4.21 ppm, d, J = 4.8 Hz) and exo (3.75 ppm, br s) isomers.

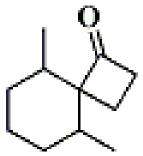
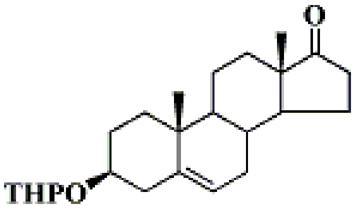
3. Discussion

Enolate hydroxylation is a problem of long standing. Direct oxygenation succeeds with the fully substituted enolates of certain α,α-disubstituted ketones[4] and a variety of carboxylic acid derivatives (ester anions, acid dianions, amide anions),[5] but the reaction of enolates, $RCH{=}C(O^-)R'$ or $CH_2{=}C(O^-)R'$, with oxygen results in complex products of overoxidation. The stable molybdenum peroxide reagent $MoO_5 \cdot Py \cdot HMPA$ (MoOPH),[2] first prepared by Mimoun, allows the conversion of RCH=C

(OLi)R' into RCH(OH)COR' in generally good yields (Table I).[6] In some cases, the α-diketone is formed as a by-product. The MoOPH reagent also hydroxylates branched or unbranched ester, amide, and nitrile anions.[6,7] For unknown reasons, MoOPH hydroxylations seldom give complete conversion of enolates into products, and recovery of 5–15% of the starting carbonyl substrate is to be expected.

Methyl ketone enolates are hydroxylated by MoOPH, but the products tend to undergo condensation with the starting enolate, resulting in poor yields.[6] Methyl ketone hydroxylation has been described by Moriarty, using $C_6H_5I{=}O/CH_3OH/OH^-$.[8]

TABLE I
CONVERSION OF RCH=C(OLi)R' INTO RCH(OH)COR'

Ketone	Oxidation Temperature (°C)	α-Hydroxy Ketone (%)	α-Diketone (%)
Valerophenone	−22	60	13
	−44	62	<2
Deoxybenzoin	−44	34	26
Isobutyrophenone	−22	65	
α-Tetralone	−22	48	
Camphor	−22	77	<2
	−22 □ 60, 16 hr	44	11
4,4-Diphenylcyclo-hexanone	−22	46	
2-Phenylcyclohexanone	−44	70	<5
	−22	81	
	−44	75 (16 α-OH)	

Several indirect methods for conversion of enolates into α-hydroxycarbonyl compounds are known. The most versatile is the reaction of enol silanes with *meta*-chloroperbenzoic acid developed by Rubottom.[9] This technique is often successful with substrates that are oxidized inefficiently by the MoOPH technique. Another alternative is to use the oxaziridine reagents developed by Davis et al.[10]

The method described for MoOPH hydroxylation of the camphor enolate is representative for ketone enolate hydroxylations, but optimization in each individual case to determine the best temperature and concentration is recommended. Large-scale oxidations may benefit from addition of reagent in several portions over time, and enolates that are sensitive to self-condensation may give higher yields if enolate is added slowly to excess MoOPH.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

Oxodiperoxymolybdenum(aqua)(hexamethylphosphoric triamide), $MoO_5{\cdot}H_2O{\cdot}HMPA$

molybdenum oxide (MoO_3)

hydrogen peroxide (H_2O_2)

$MoO_5{\cdot}H_2O{\cdot}HMPA$

Oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide) $MoO_5{\cdot}Py{\cdot}HMPA$=MoOPH

$MoO_5{\cdot}HMPA$

$MoO_5{\cdot}Py{\cdot}HMPA$

MoOPH

LDA

$MoO_5{\cdot}Py{\cdot}HMPA$ (MoOPH)

meta-chloroperbenzoic acid

OXODIPEROXYMOLYBDENUM(PYRIDINE)(HEXAMETHYLPHOSPHORIC TRIAMIDE), $MoO_5{\cdot}Py{\cdot}HMPA$(MoOPH)

menthoxide

hydrochloric acid (7647-01-0)

methanol (67-56-1)

ether (60-29-7)

sodium sulfite (7757-83-7)

sodium chloride (7647-14-5)

oxygen (7782-44-7)

barium oxide

nitrogen (7727-37-9)

pyridine (110-86-1)

Benzophenone (119-61-9)

sodium (13966-32-0)

hydrogen peroxide (7722-84-1)

menthol (15356-60-2)

$MgSO_4$ (7487-88-9)

camphor (21368-68-3)

butyllithium (109-72-8)

Tetrahydrofuran, THF (109-99-9)

α-Tetralone (529-34-0)

hexane (110-54-3)

deoxybenzoin (451-40-1)

2-phenylcyclohexanone (1444-65-1)

oxaziridine

phenanthroline

hexamethylphosphoric triamide (680-31-9)

isobutyrophenone (611-70-1)

lithium diisopropylamide (4111-54-0)

diisopropylamine (108-18-9)

3-Hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one, Bicyclo[2.2.1]heptan-2-one, 3-hydroxy-1,7,7-trimethyl-, 1,7,7-trimethyl-3-hydroxybicyclo[2.2.1]-heptan-2-one (21488-68-6)

molybdenum oxide

phosphorus oxide (1314-56-3)

molybdenum peroxide

Valerophenone (1009-14-9)

4,4-Diphenylcyclo-hexanone (4528-68-1)

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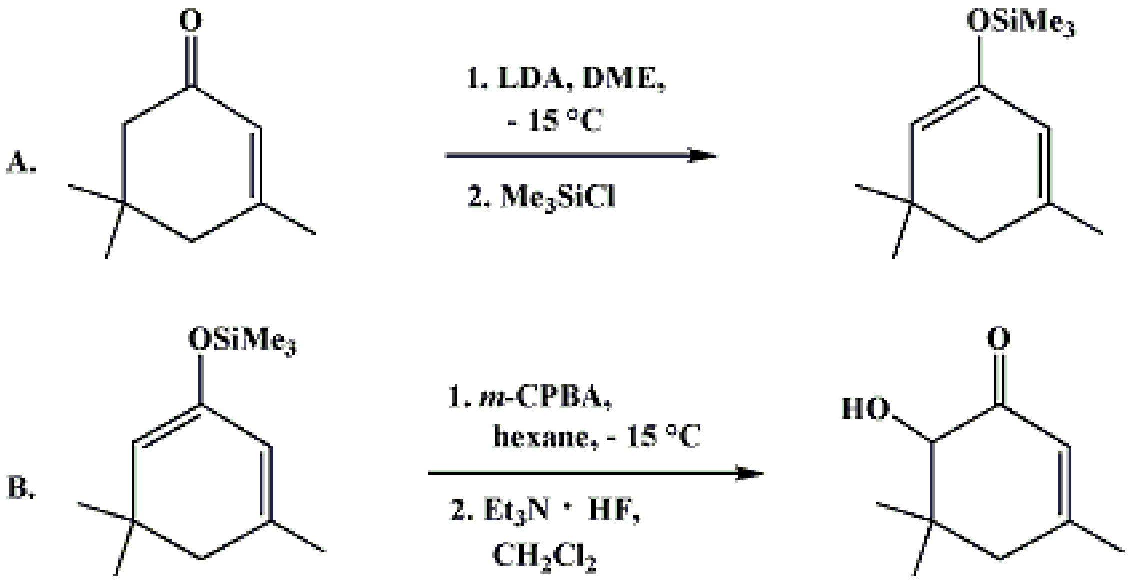
α-HYDROXY KETONES FROM THE OXIDATION OF ENOL SILYL ETHERS WITH *m*-CHLOROPERBENZOIC ACID: 6-HYDROXY- 3,5,5-TRIMETHYL-2-CYCLOHEXEN-1-ONE

[2-Cyclohexen-1-one, 6-hydroxy-3,5,5-trimethyl-]



Submitted by George M. Rubottom, John M. Gruber, Henrik D. Juve, Jr., and Dan A. Charleson[1].
Checked by Judy Bolton and Ian Fleming.

1. Procedure

A. *4,6,6-Trimethyl-2-trimethylsiloxycyclohexa-1,3-diene*. A 500-mL, three-necked, round-bottomed flask is fitted with a reflux condenser (center neck), Teflon-covered magnetic stirring bar, ground-glass stopper, and rubber septum. The apparatus is connected, through the reflux condenser, to a nitrogen source and a bubbler (Note 1). After the flask is flushed with nitrogen, it is charged with 150 mL of dry dimethoxyethane (DME) (Note 2) and 11.25 mL (80.4 mmol) of freshly distilled diisopropylamine (Note 3). The flask is immersed in a methanol–ice bath and cooled to an external temperature of –15°C. Over a period of about 5 min, butyllithium, 49.8 mL (79.6 mmol) (Note 4), is added, with continuous stirring, with a syringe through the septum. After an additional 15 min of stirring, 10.0 g (72.4 mmol) of freshly distilled isophorone (Note 5) is added neat over a 10-min period. The bright-yellow solution is stirred for an additional 10 min at –15°C. At this point, 17.5 mL (137.6 mmol) of freshly distilled chlorotrimethylsilane (TMSCL) (Note 6) is rapidly introduced through the septum. After the addition is complete (ca. 20 sec), the white

slurry is stirred for an additional 2 hr at room temperature. The apparatus is then dismantled, the two outside necks of the flask are stoppered with ground-glass stoppers, and the center neck is attached to a rotary evaporator. Solvent is removed under reduced pressure and the residue is treated with 100 mL of pentane. The slurry is filtered through a sintered-glass filter and the filtrate is concentrated on a rotary evaporator. The residue is distilled at reduced pressure to give 13.5–13.9 g (88–91%) of pure 4,6,6-trimethyl-2-trimethylsiloxycyclohexa-1,3-diene, bp 54–57°C (1.5 mm), 37–39°C (0.01 mm) [lit.[2] bp 45–49°C (0.05 mm)] (Note 7).

B. *6-Hydroxy-3,5,5-trimethyl-2-cyclohexen-1-one*. A 500-mL, three-necked, round-bottomed flask is fitted with an adapter with a stopcock connected to a nitrogen source and a bubbler (center neck), two ground-glass stoppers, and a Teflon-covered magnetic stirring bar (Note 1). After the system is flushed with nitrogen, the flask is charged with 300 mL of dry hexane (Note 8) and 10.0 g (47.5 mmol) of 4,6,6-trimethyl-2-trimethylsiloxycyclohexa-1,3-diene. The flask is immersed in a methanol–ice bath and cooled to an external temperature of −15°C and then, with stirring, the solution is treated with a slurry which contains 10.6 g (52.3 mmol) of *m*-chloroperbenzoic acid (MCPBA) (Note 9) and 50 mL of dry hexane (Note 10). When the addition is complete (ca. 1.5 min), the resulting slurry is stirred at −15°C for 20 min and then at 30°C (water bath) for 2 hr. The mixture is filtered through a sintered-glass filter into a 500-mL, round-bottomed flask and the solvent is removed under reduced pressure using a rotary evaporator. If solid remains in the residue, 10–15 mL of pentane is added, filtration is repeated, and solvent is again removed under reduced pressure. The flask is fitted with a Teflon-covered stirring bar and the residue is treated with 150 mL of dry methylene chloride (Note 11) and 11.5 g (95.0 mmol) of triethylammonium fluoride (Et_3NHF) (Note 12). After the solution is stirred for 2 hr at room temperature, it is transferred to a separatory funnel and extracted with saturated aqueous sodium bicarbonate solution (2 × 100 mL), 100 mL of 1.5 *N* hydrochloric acid, and saturated aqueous sodium bicarbonate solution (2 × 50 mL). The organic layer is dried with anhydrous magnesium sulfate, and filtered, and solvent is removed from the filtrate using a rotary evaporator. The residue is then freed of the last traces of solvent by pumping, with stirring, at reduced pressure (ca. 2.0 mm) (Note 13); the residue solidifies. The round-bottomed flask is attached to a short-path distillation apparatus and the residue is distilled at reduced pressure. After a small forerun, the main fraction, bp 73–75°C (1.3 mm), is collected (Note 14). This fraction solidifies and is triturated with 3–5 mL of petroleum ether (bp 30–60°C) at −15°C (ice–methanol) to remove traces of isophorone. When the crystalline residue is dried in a stream of nitrogen, pure 6-hydroxy-3,5,5-trimethyl-2-cyclohexen-1-one is obtained: 4.8–5.1 g (66–70%), mp 44.5–45°C [lit.[3] mp 45–46°C]. The forerun and the material left in the still head after distillation are combined (Note 15) and treated with the petrolum ether that was used to triturate the main fraction. Crystallization gives an additional 0.2–0.3 g (3–4%) of the hydroxy ketone, mp 44.5–45°C. Thus the total weight of the 6-hydroxy-3,5,5-trimethyl-2-cyclohexen-1-one is 5.1–5.4 g (70–73%) (Note 16).

2. Notes

1. All glassware was dried in an oven for 2 hr at 110°C before use. All reactions were carried out under an atmosphere of nitrogen. The checkers used a balloon filled with nitrogen rather than a bubbler.

2. Dimethoxyethane (DME) (Aldrich Chemical Company, Inc.) was dried over lithium aluminum hydride and distilled just before use. The submitters have found that DME is the solvent of choice in this reaction and is preferred over the more commonly used tetrahydrofuran (THF).

3. Diisopropylamine, bp 80–80.5°C (699 mm), (Aldrich Chemical Company, Inc.) was distilled under a static atmosphere of nitrogen just prior to use.

4. Butyllithium (Aldrich Chemical Company, Inc.) was a 1.6 *M* solution in hexane. The submitters used the method of Ronald[4] to check titer. It is essential to the success of the reaction that this value be checked with accuracy.

5. Isophorone, bp 85–87°C (10 mm), (Aldrich Chemical Company, Inc.) was distilled immediately before use.

6. Chlorotrimethylsilane (TMSCl), bp 54–55°C (699 mm), (Aldrich Chemical Company, Inc.) was distilled under a static atmosphere of nitrogen just prior to use.

7. The product has the following spectroscopic properties: n_D^{25} 1.4509; IR (neat) cm^{-1}: 3040 (vinyl CH), 1660 (C=COTMS), 1610 (C=C); ^1H NMR ($CDCl_3$) δ: 0.21 [s, 9 H, $Si(CH_3)_3$], 0.98 (s, 6 H, 2 CH_3), 1.75 (broad s, 2 H, vinyl CH_3), 1.92 (broad s, 2 H, CH_2), 4.52 (broad s, 1 H, vinyl H on carbon 1), 5.40 (multiplet, 1 H, vinyl H on C-3); mass spectrum, *m/z* (relative abundance using 15 eV): 210 (M^+, 28), 196 (17), 195 (100), 179 (9); metastable (m^*): 164.3 (195 □ 179). Anal. calcd. for $C_{12}H_{22}OSi$: C, 68.50; H, 10.54. Found: C, 68.50; H, 10.52. A gas chromatographic analysis using a 0.25-in. × 6.0-ft column packed with 12.5% SE-52 at a column temperature of 130°C and gas flow rate of 90 mL/min showed the purity of the product to be greater than 95%. The impurities present were a small amount of unreacted isophorone and a trace of an unidentified material.

8. Hexane was purified in 1.5-L batches by sequential washing with concentrated sulfuric acid (5 × 50 mL) and water (3 × 100 mL), drying ($CaCl_2$), and distillation. The pure hexane is stored over Linde 4A molecular sieves.

9. *m*-Chloroperbenzoic acid (MCPBA) (Aldrich Chemical Company, Inc.) containing 15% *m*-chlorobenzoic acid was obtained commercially and used without purification.

10. It is convenient to stir the 85% MCPBA in hexane while the flask is being charged with the diene. Addition of the slurry with a pipette is the method used by the submitters. The checkers poured it in directly from a beaker, and washed the beaker with 10 mL of hexane.

11. Methylene chloride is dried by distillation from calcium chloride.

12. Triethylammonium fluoride is prepared by the method of Hünig.[5] The purity

of this reagent seems to determine the amount of color that results in the crude hydroxy ketone. Stirring for a period of time greater than 2 hr results in lower yields and is to be avoided.

13. Stirring is crucial to prevent serious bumping when the crude hydroxy ketone solidifies. The checkers simply swirled the flask continuously without incident.

14. Taking a small forerun serves to concentrate residual isophorone in this fraction. Care must also be taken not to overcoolthe distillation head which may cause crystallization of the hydroxy ketonethroughout the system.

15. A small amount of methylene chloride is used to wash the still head. This solvent is then removed (rotary evaporator) prior to the addition of the petroleum ether. Petroleum ether is used if recrystallization is needed.

16. The product has the following spectroscopic properties: IR (Nujol mull) cm^{-1}: 3360 (OH), 3040 (vinyl CH), 1670, 1635 (C=C=C=O); ^1H NMR ($CDCl_3$) δ: 0.79 (s, 3 H, CH_3 on C-5 trans to OH), 1.14 (s, 3 H, CH_3 on C-5 cis to OH), 1.88 (s, 3 H, vinyl CH_3), 2.13 (d, 1 H, *J* = 18, AB doublet for H on C-4), 2.35 (d, 1 H, *J* = 18, AB doublet for H on C-4), 3.52 (d, 1 H, *J* = 2, OH), 3.78 (d, 1 H, *J* = 2, H on C-6), 5.70 (broad s, 1 H, vinyl H); mass spectrum, *m/z* (relative abundance using 15 eV): 154 (M^+, 24), 125 (10), 111 (14), 83 (100), 82 (96), 72 (44); metastables (m^*): 101.5 (154 125), 80.0 (154 111). Anal. calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.81; H, 9.50. A gas chromatographic analysis using a 0.25-in. × 6.0-ft column packed with 12.5% SE-52 at a column temperature of 158°C and a gas flow rate of 90 mL per minute showed the purity of the product to be greater than 98%. In some runs, a trace of isophorone could be detected (ca. 2%).

3. Discussion

The preparation of α-hydroxy carbonyl compounds has been accomplished by the oxidation of enolates using both oxygen[6] and MoO_5 · Py · HMPA · (MoOPH).[7] Acyl anion equivalents offer another route to this useful class of compounds.[8] The procedure presented here for the synthesis of 6-hydroxy-3,5,5-trimethyl-2-cyclohexen-1-one illustrates the use of MCPBA oxidation of an enol silyl ether as a method for obtaining an α-hydroxy enone. The procedure is a scale-up of a published synthesis.[9]

4,6,6-Trimethyl-2-trimethylsiloxycyclohexa-1,3-diene has been reported by Conia,[2] who used the standard "kinetic method" of House[10] for synthesis of the compound. The current method adapts this synthesis by employing DME as solvent and by using a nonaqueous workup which was previously noted by Ainsworth for the preparation of silyl ketene acetals.[11] These changes lead to higher yields of pure enol silyl ethers in general, and are recommended as a standard method.

6-Hydroxy-3,5,5-trimethyl-2-cyclohexen-1-one has been prepared in 22% yield by lead (IV) acetate oxidation of isophorone followed by hydrolysis of the resulting acetate.[3]

The MCPBA method gives high yields of both α-hydroxy enones[12 13] and ketones[14 15] and is extremely general in scope. The method is also viable for the synthesis of α-hydroxy acids[16] and α-hydroxy esters.[17] The method fails with the enol silyl ethers of both lactones[17]15 and aldehydes.[18]

Since the double-bond placement in enol silyl ethers is predictable and controllable,[14,15] the method allows the regiospecific introduction of α-hydroxy groups. Omission of the fluoride treatment permits isolation of α-trimethylsiloxy carbonyl compounds,[19 20 21] while treatment of enol silyl ethers, first with MCPBA, then with triethylammonium fluoride–acetic anhydride gives the corresponding α-acetoxy carbonyl compounds.[9] The probable mechanism of the MCPBA oxidation of enol silyl ethers has also been discussed.[22]

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Appendix

Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

m-chloroperbenzoic acid (MCPBA)

petrolum ether

DME

drying ($CaCl_2$)

MoO_5 · Py · HMPA · (MoOPH)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic anhydride (108-24-7)

sodium bicarbonate (144-55-8)

oxygen (7782-44-7)

nitrogen (7727-37-9)

Pentane (109-66-0)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

hexane (110-54-3)

dimethoxyethane (534-15-6)

fluoride (16984-48-8)

isophorone

diisopropylamine (108-18-9)

CHLOROTRIMETHYLSILANE (75-77-4)

6-HYDROXY- 3,5,5-TRIMETHYL-2-CYCLOHEXEN-1-ONE, 2-Cyclohexen-1-one, 6-hydroxy-3,5,5-trimethyl-, 6-Hydroxy-3,5,5-trimethyl-2-cyclohexen-1-one (61592-66-3)

4,6,6-Trimethyl-2-trimethylsiloxycyclohexa-1,3-diene (54781-28-1)

triethylammonium fluoride

lead(IV) acetate (546-67-8)

m-Chloroperbenzoic acid, MCPBA (937-14-4)

m-chlorobenzoic acid (535-80-8)

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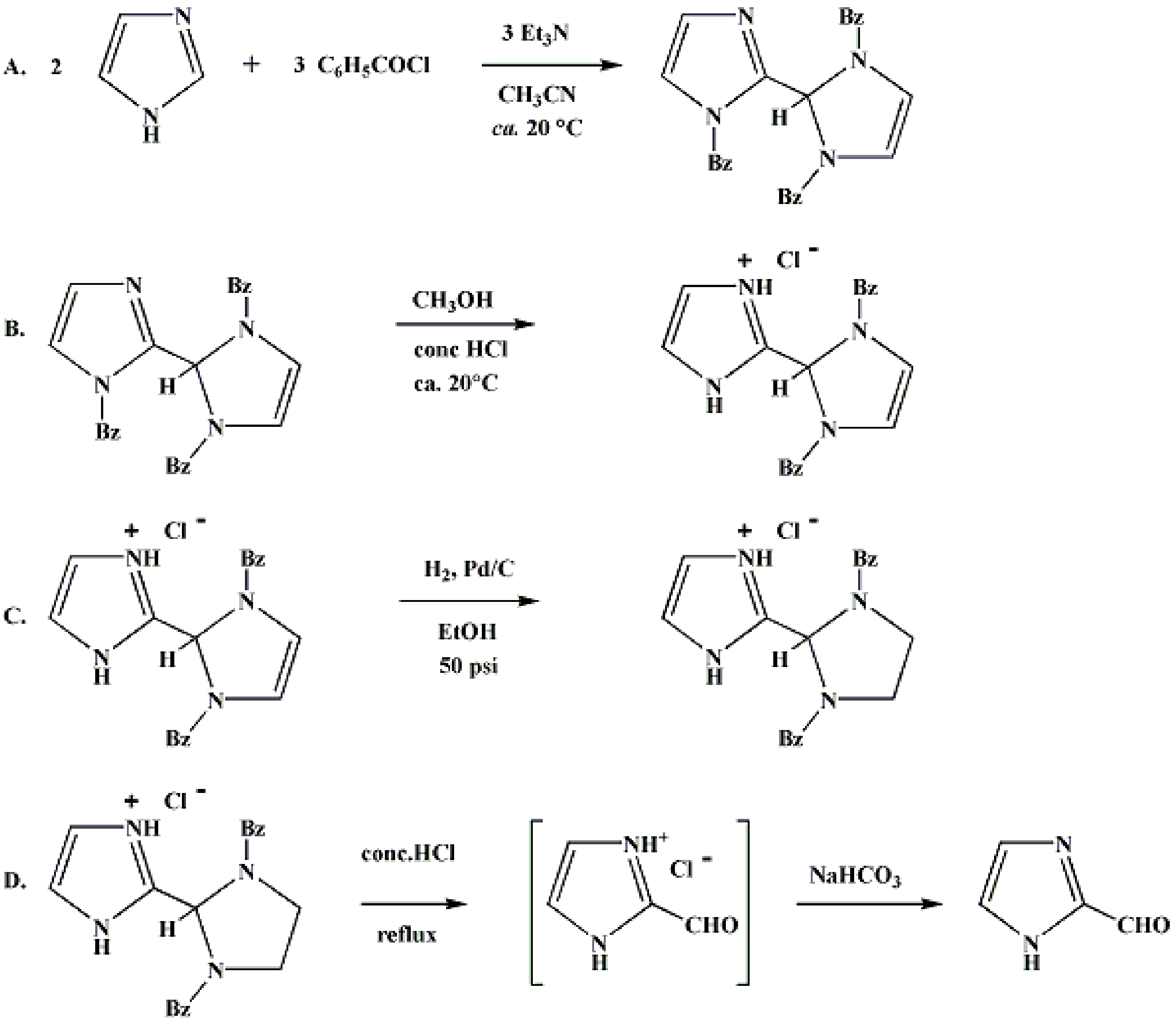
IMIDAZOLE-2-CARBOXALDEHYDE

[1*H*-Imidazole-2-carboxaldehyde]



Submitted by Leonard A. M. Bastiaansen, Pieter M. Van Lier, and Erik F. Godefroi[1].
Checked by Nancy Acton and Arnold Brossi.

1. Procedure

A. *1-Benzoyl-2-(1,3-dibenzoyl-4-imidazolin-2-yl)imidazole*.[2] A 12-L, wide-mouthed, round-bottomed vessel fitted with an efficient air-driven stirrer and thermometer is charged with 68 g (1.0 mol) of imidazole (Note 1), 202 g (2 mol) of triethylamine (Note 2), and 1000 mL of acetonitrile (Note 3). To the mixture is added dropwise over a 1-hr period and with external cooling 281 g (2.0 mol) of benzoyl chloride (Note 2), the temperature is maintained at 15–25°C. After addition is complete, stirring is continued for another hour at ambient temperature. With continued stirring 1 L of ether and 5 L of water are introduced, whereupon the temperature is brought to 5°C. The crystalline product is removed by filtration and is sucked dry with the aid of a rubber dam. Rinsing of the filtercake with, successively, water, acetone, and ether gives, on air-drying, 181–190 g (80–85%) of product, mp 197–198°C (Note 4). This product (5 g), taken up in 50 mL of boiling 90% dimethylformamide diluted while hot with water to the cloud point, gives, on cooling, 4.5 g of analytically pure stout prisms, mp 202–203° C (Note 5).

B. *2-(1,3-Dibenzoyl-4-imidazolin-2-yl)imidazole hydrochloride.*[3] Into a 3-L beaker equipped with an air-driven stirrer are successively introduced 150 g (0.335 mol) of dry, unrecrystallized 1-benzoyl-2-(1,3-dibenzoyl-4-imidazolin-2-yl) imidazole, 500 mL of technical-grade methyl alcohol, and 30 mL of concentrated hydrochloric acid. The mixture is stirred as the solids gradually dissolve. After 1 hr a clear yellow solution results, which is allowed to stand for another 5 hr, during which time white solid product begins to precipitate. Technical diethyl ether (1500 mL) is next added, and the mixture is allowed to stand overnight. Filtration and rinsing of the crystals with fresh ether and ultimate air drying furnish 114–119 g (89–93%) of product, mp 238–239° C (Note 6). Analytically pure material, obtained on recrystallizing a small sample from methyl alcohol-ether, has mp 240–241° C

C. *2-(1,3-Dibenzoylimidazolidin-2-yl)imidazole hydrochloride.*[3] A 1000-mL Parr hydrogenation bottle is charged with 38.0 g (0.10 mol) of dry, unrecrystallized 2-(1,3-dibenzoyl-4-imidazolin-2-yl)imidazole hydrochloride suspended in 300 mL of 95% reagent-grade ethyl alcohol. Then 2 g of 10% palladium on carbon (Note 7) is cautiously added (Note 8). The reaction vessel is now attached to the Parr hydrogenator and, after alternate evacuation and flushing with hydrogen gas, is shaken under a 50-psi atmosphere of hydrogen. Gas uptake ceases after absorption of 1 mol-equiv per mole of substrate; this requires ca. 2 hr. The catalyst is removed by vacuum filtration through Hyflow, the filtercake is rinsed with three portions of 95% ethyl alcohol (Note 9), and the filtrate is stripped to leave solid, impure product. This is triturated with 200 mL of ice-cold acetone; filtration and rinsing of the solids with fresh acetone and ultimately with ether yield 33.2–35.8 g (87–94%) of air-dried material, mp 225–226°C (Note 10). An analytically pure sample from isopropyl alcohol-ether melts at 225–226°C.

D. *Imidazole-2-carboxaldehyde.*[3] A solution of 19.1 g (0.05 mol) of dry, unrecrystallized 2-(1,3-dibenzoylimidazolidin-2-yl) imidazole hydrochloride in 200 mL of concentrated hydrochloric acid is refluxed for 22 hr (Note 11). The mixture is then chilled on ice, causing deposition of benzoic acid, which is removed by filtration (Note 11). The filtrate, on evaporation, leaves a residue that is first digested with 100 mL of 95% ethyl alcohol and then cooled on ice. The remaining solids are essentially pure ethylenediamine dihydrochloride and are filtered off (Note 12). Filtrate solvent is again removed under reduced pressure to leave solid residue. This is dissolved in 40 mL of water. Addition of solid sodium bicarbonate until foaming ceases causes imidazole-2-carboxaldehyde to crystallize. The mixture is chilled on ice, and the product is filtered and washed with ice-water to give, after thorough drying, 3.2–3.7 g (67–77%) of beige crystals, mp 206–207°C. Analytical material, prepared from water, has mp 206–207°C (Note 13).

2. Notes

1. Imidazole is a bulk chemical available from the Badische Anilin- & Sodafabrik AG, 6700 Ludwigshafen/Rhein, West-Germany. The checkers used Aldrich imidazole, 99%, from Aldrich Chemical Company, Inc.
2. Triethylamine and benzoyl chloride, both 99.5% pure, were purchased from Fluka. The checkers used material from Aldrich Chemical Company, Inc.
3. Acetonitrile, 99%, was obtained from Aldrich-Europe, B-2340 Beerse, Belgium.
4. Observing the theoretical stoichiometry, i.e., 2 equiv of imidazole and 3 equiv each of benzoyl chloride and triethylamine, resulted in significantly lower product yields.
5. The ^{1}H NMR spectrum ($CDCl_3$) corresponded to that in the literature[2]: δ 6.43 (s, 2, vinyl protons), 7.07 (t, 2, imidazole protons), 8.05 (s, 1, methine proton). Analysis calculated for $C_{27}H_{20}N_4O_3$: C, 72.31; H, 4.49; N, 12.49. Found: C, 72.27; H, 4.54; N, 12.53.
6. The checkers obtained variable melting points that were accompanied by decomposition and depended on the rate of heating. ^{1}H NMR (CD_3OD) δ: 6.57 (s, 2), 7.50 (m, 13, aromatic protons). Analysis calculated for $C_{20}H_{16}N_4O_2 \cdot HCl$: C, 63.07; H, 4.56; N, 14.71. Found: C, 63.02; H, 4.60; N, 14.79.
7. Merck-Schuchardt "Hydrierkatalisator," purchased from E. Merck, Darmstadt. The checkers used Pd/C from Alfa Products, Morton Thiokol Inc.
8. Direct introduction of a dry hydrogenation catalyst into an alcoholic system has been known to bring about spontaneous ignition. This risk may be obviated by addition of a slurry of 2.0 g of catalyst in 15 mL of water to the substrate in 285 mL of absolute ethyl alcohol.

9. Filtercakes of fresh, spent hydrogenation catalysts are known to be pyrophoric and should not be sucked completely dry.
10. The checkers obtained an oily foam that remained oily on adding cold acetone. The oily material became solid on adding and evaporating benzene (2 × 100 mL). The checkers obtained variable melting points accompanied by decomposition. ^{1}H NMR (CD_3OD) included an *AA′ BB′* system centered around δ 4.17 (4, CH_2CH_2). Analysis calculated for $C_{20}H_{18}N_4O_2 \cdot HCl$: C, 62.74; H, 5.00; N, 14.64. Found: C, 62.96; H, 4.98, N, 14.42.
11. Benzoic acid sublimes into the condenser and will plug a small-bore condenser.
12. The benzoic acid and ethylenediamine dihydrochloride isolated after the cited reaction time amount to ca. 90%.
13. Imidazole-2-carboxaldehyde has been reported to melt at 204°C,[4] 195–205°C,[5] 195°C,[6] 202°C,[7] and 190–196°C.[8] The material prepared has an ^{1}H NMR spectrum corresponding to that of the literature[8]: δ 7.43 (s, 2, imidazole protons), 9.67 (s, 1, CHO). Analysis calculated for $C_4H_4N_2O$: C, 49.99; H, 4.19; N, 29.16. Found: C, 50.05; H, 4.26; N, 28.96.

3. Discussion

Synthesis of imidazole-2-carboxaldehyde has previously been reported by manganese dioxide oxidation of the corresponding carbinol,[4] by acid-promoted cyclization of *N*-(2,2-diethoxyethyl)-2,2-diethoxyacetamidine,[5] and by methods centering around formylation of appropriately protected 2-imidazolelithium reagents.[6,7] The present method constitutes an optimization of the route recently reported from our laboratories.[3] Inexpensive, commercially available bulk chemicals are utilized to give imidazole-2-carboxaldehyde via high-yield processes mostly in open vessels and at ambient temperatures.All products are isolated directly from the reaction mixtures in a high state of purity without resorting to extractions, distillations, or recrystallizations. The by-products, benzoic acid and ethylenediamine dihydrochloride, are recovered in nearly quantitative yields. Waste and environmental pollution are kept to a minimum.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethyl alcohol (64-17-5)

hydrochloric acid, HCl (7647-01-0)

Benzene (71-43-2)

methyl alcohol (67-56-1)

ether, diethyl ether (60-29-7)

hydrogen (1333-74-0)

acetonitrile (75-05-8)

sodium bicarbonate (144-55-8)

Benzoic acid (65-85-0)

acetone (67-64-1)

carbon (7782-42-5)

benzoyl chloride (98-88-4)

isopropyl alcohol (67-63-0)

palladium (7440-05-3)

manganese dioxide (1313-13-9)

dimethylformamide (68-12-2)

Imidazole (288-32-4)

triethylamine (121-44-8)

Imidazole-2-carboxaldehyde, 1H-Imidazole-2-carboxaldehyde (10111-08-7)

1-benzoyl-2-(1,3-dibenzoyl-4-imidazolin-2-yl) imidazole, 1-Benzoyl-2-(1,3-dibenzoyl-4-imidazolin-2-yl) imidazole (62457-77-6)

2-(1,3-dibenzoyl-4-imidazolin-2-yl)imidazole hydrochloride (65276-00-8)

2-(1,3-dibenzoylimidazolidin-2-yl) imidazole hydrochloride, 2-(1,3-Dibenzoylimidazolidin-2-yl)imidazole hydrochloride (65276-01-9)

ethylenediamine dihydrochloride (333-18-6)

2-imidazolelithium

N-(2,2-diethoxyethyl)-2,2-diethoxyacetamidine

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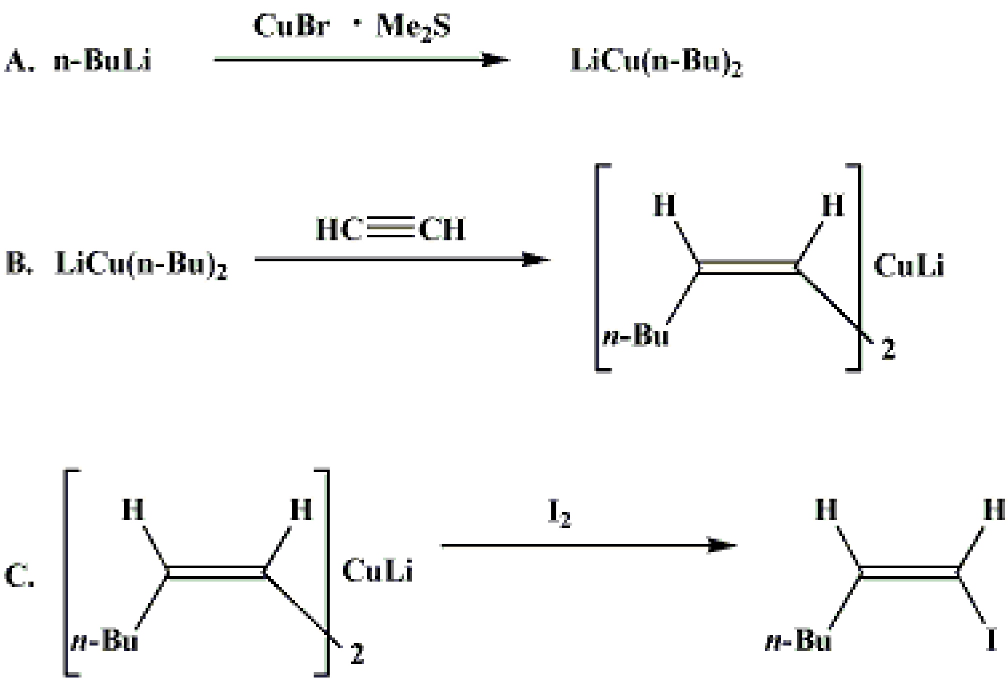
Organic Syntheses, *CV 7*, *290*

Z-1-IODOHEXENE

[1-Hexene, 1-iodo-, (Z)-]



Submitted by A. Alexakis, G. Cahiez, and J. F. Normant[1].
Checked by J. Gabriel, P. Knochel, and Dieter Seebach.

1. Procedure

A. *Preparation of an ether solution of lithium dibutylcuprate*. A 500-mL flask (.htmFigure 1) with a side arm is equipped with a magnetic stirring bar, rubber septum, and three-way stopcock, on top of which is attached a rubber balloon, D. A Pt-100-thermometer, E, is inserted into the flask through the septum (Note 1). The air in the flask is replaced by dry nitrogen (Note 2). The flask is charged with 10.8 g (0.0525 mol) of cuprous bromide–dimethyl sulfide complex (Note 3) and 100 mL of ether, then immersed in a bath at −50°C; 0.10 mol of butyllithium, ca. 1.6 *M* solution in hexane (Note 4), is added dropwise, with stirring, via a syringe inserted through the rubber septum, at such a rate that the temperature of the reaction mixture does not exceed −20°C.

Figure 1

Figure 1

After the addition is complete, stirring is continued at −30°C for 10 min to produce a gray–blue or dark-blue solution of the cuprate (Note 5).

B. *Preparation of a solution of lithium di(Z-hexenyl)cuprate*. A needle connected to an acetylene supply (Note 6) is introduced through the rubber septum of the flask, with its end at least 1 cm below the surface of the cuprate solution. The stopcock is fully opened toward the balloon, the solution is cooled to –50°C, and 2.64 L (0.11 mol) of acetylene (Note 6) is bubbled into the stirred cuprate solution, the temperature of which should not rise above –25°C. The gas inlet is removed and the greenish solution is stirred at –25°C for 30 min.

C. *Preparation of Z-iodohexene*. A dry, 100-mL flask with a sidearm is charged with 26.7 g (0.105 mol) of iodine, equipped with a stirring bar, three-way stopcock, and rubber septum, and flushed with argon as described above (Section A). The iodine is dissolved by introducing, with stirring, 30 mL of tetrahydrofuran through the septum with a syringe. Flask A, which contains the iodine solution, is connected to flask B, which contains the vinyl cuprate solution as shown in f.htmigure 1. The cuprate solution is kept between –60° and –50°C while the iodine solution is pushed through the Teflon tubing, C. Then the cooling bath is removed and the temperature is allowed to rise to –10°C, whereupon a precipitate of copper(I) iodide is formed and the mixture turns yellow. After 10 min at –10°C, a mixture of 100 mL of saturated aqueous ammonium chloride and 10 mL of saturated sodium bisulfite is added with vigorous stirring. The mixture is filtered by suction through 10 g of Celite on a sintered-glass funnel (No. 3), the contents of the funnel are washed twice with 50 mL of ether, and the filtrate is separated into two layers (Note 7). The inorganic layer is washed twice with 50 mL of pentane, and the combined organic layers are washed with aqueous sodium bisulfite (Note 8) and saturated ammonium chloride solution and dried over anhydrous $MgSO_4$. The solvents are removed by distillation through a 20-cm Vigreux column at atmospheric pressure. A spatula of copper powder is added to the residue, and the stirred mixture is distilled under reduced pressure through a 10-cm Vigreux colum to give 13.5–15.5 g (65–75%) of Z-1-iodohexene, bp 47°C/(15 mm) (Note 9) and (Note 10).

2. Notes

1. The technique used here has been described previously by the checkers.[2] Instead, the submitters used a dry 500-mL, three-necked flask equipped with a variable-speed mechanical stirrer, a 100-mL pressure-equalizing dropping funnel topped by a gas inlet and a Claisen head containing a low-temperature thermometer (–70°C to +35°C), and a bubbler. A stream of nitrogen followed from the gas inlet.
2. This manipulation is described in detail in *Org. Synth., Coll. Vol. VI* **1988**, 869.

3. This complex[3] should be used when the organolithium is in solution in a hydrocarbon solvent. For organolithium reagents prepared in ether (see (Note 4)), the same complex may be used or, more conveniently, copper iodide (CuI)

can be used. The CuI purchased from Prolabo or Merck & Company, Inc. may be used directly. Other commercial sources of CuI (Fluka, Aldrich Chemical Company, Inc., Alfa Products, Morton Thiokol, Inc.) furnish a salt that affords better results when purified. First 1 mol of CuI is stirred for 12 hr with 500 mL of anhydrous tetrahydrofuran, then filtered on a sintered-glass funnel (No. 3), washed twice with 50 mL of anhydrous tetrahydrofuran, once with 50 mL of anhydrous ether, and finally dried under reduced pressure (0.1 mm) for 4 hr.

4. Butyllithium was used as purchased from Aldrich Chemical Company, Inc., Fluka, or Metallgesellschaft (Frankfurt). Ethereal solutions of butyllithium may also be used. Other organolithium compounds are easily prepared in ether; the following is representative.

Under an atmosphere of argon, a solution of butyl bromide (137 g, 1 mol) in anhydrous ether (500 mL) is added with stirring to small chips of lithium containing 1–2% of sodium (15.5 g, 2.2 g-atom) in ether (150 mL). The reaction starts after the addition of about 40 mL of butyl bromide solution at room temperature. The temperature rises and the lithium metal becomes bright. If the reaction does not start, the addition of a small amount of 1,2-dibromoethane (1 mL) is often effective. Then the reaction mixture is cooled (–5°C to –10°C) and addition of the butyl bromide solution is continued slowly (about 4 hr). At the end of the addition, the solution is stirred for 2 hr at –5 to –10°C; then the reaction mixture is allowed to warm to room temperature. After 2 hr, excess lithium metal is removed. For many purposes, the use of a clear solution, obtained after the reaction mixture has stood overnight at 0 to –5°C, is preferable. Butyllithium in ether can be stored under an argon atmosphere without decomposition for 15 days at 0°C or for 2 months at –15°C.

5. During all of the operations, the rate of stirring is adjusted to avoid splashing the wall of the flask; above –10°C, thermal decomposition of the cuprate occurs. This is indicated by the presence of a black suspension, which is also formed if a copper(I) salt of insufficient purity is used, or when oxygen gets into the reaction flask.

6. The proper volume of acetylene is measured with a water gasometer as described in *Org. Synth., Coll. Vol. I* **1941**, 230, with two modifications: (a) Two traps immersed in an acetone–dry ice bath at –65°C are placed between the acetylene tank and the gasometer in order to remove acetone; (b) the washing bottles between the gasometer and the reaction flask are replaced by a drying tube (2-cm × 30-cm column packed with anhydrous $CaCl_2$). The apparatus must be flushed with acetylene in order to remove all traces of oxygen. Acetylene dissolved in acetone is most appropriate. Acetylene obtained from tanks that contain solvents such as dimethylformamide (or other solvents) gave lower yields of carbocupration.

7. If a precipitate appears in the filtrate, filtration is repeated until two layers can be clearly distinguished.

8. A mixture of 10 mL of saturated sodium bisulfite and 50 mL of water is used. One or more washings with sodium bisulfite solution are necessary if iodine is

present.

9. The sample thus obtained is >99% pure by GC analysis (3% OV 101 in a 2-m × 4-mm glass column, on Chromosorb G, with an injection temperature of 175° C, raised 100°C in 5 min, then 5°C/min).

10. The ^{1}H NMR spectrum of *Z*-1-iodohexene (in CCl_4) is as follows: δ: 0.94 (m, 3 H), 1.42 (m, 4 H, $-CH_2-$), 2.12 (m, 2 H, $-CH_2-C=$), 6.12 (m, 2 H).

3. Discussion

1-Iodoalkenes of the *Z* configuration are usually prepared by hydroboration of 1-iodoalkynes. The present method affords a product of higher configurational purity and constitutes an easier way to obtain such compounds in high yield, starting from less expensive reagents. In addition, the reaction can be performed easily on a larger scale (the submitters have prepared up to 1.8 mol of dialkenyl cuprate). The *Z*-1-iodo-1-alkenes shown in Table I have been prepared by the submitters.

TABLE I

EXAMPLES OF ALKENYL IODIDE PREPARATION FROM CARBOCUPRATION

Entry	Organolithium	Product[a]	Yield (%)
1	EtLi	EtCH=CHI	72
2	*n*-$C_5H_{11}Li$	(*n*-C_5H_{11})CH=CHI	89
3	*n*-$C_7H_{15}Li$	(*n*-C_7H_{15})CH=CHI	90
4	$EtCH=CHCH_2CH_2Li$	$EtCH=CHCH_2CH_2CH=CHI$	79
5	$RO(CH_2)_3Li$[b]	$HO(CH_2)_3CH=CHI$[c]	58
6	$RO(CH_2)_8Li$[b]	$HO(CH_2)_8CH=CHI$[c]	70

[a]All alkenes, reactants and products, are *Z*.

[b]*R* = CHMeOEt.

[c]After acid hydrolysis.

This reaction illustrates a stereoselective preparation of (*Z*)-vinylic cuprates,[4,5] which are very useful synthetic intermediates. They react with a variety of electrophiles such as carbon dioxide.[5,6] epoxides,[5,6] aldehydes,[6] allylic halides,[7] alkyl halides,[7] and acetylenic halides;[7] they undergo conjugate addition to α,β-unsaturated esters,[5,6] ketones,[6] aldehydes,[6] and sulfones.[8] Finally, they add smoothly to activated triple bonds[6] such as HC C-OEt, HC C-SEt, and HC C-CH(OEt)$_2$. In most cases these cuprates transfer both alkenyl groups. The uses and applications of the carbocupration reaction have been reviewed recently.[9] The configurational purity in

the final product is at least 99.9% *Z* in the preceding transformations.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 295

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

vinyl cuprate

copper iodide (CuI)

CuI

acetylene (74-86-2)

ether (60-29-7)

ammonium chloride (12125-02-9)

Butyl bromide (109-65-9)

oxygen (7782-44-7)

nitrogen (7727-37-9)

sodium bisulfite (7631-90-5)

carbon dioxide (124-38-9)

copper powder (7440-50-8)

iodine (7553-56-2)

acetone (67-64-1)

sodium (13966-32-0)

1,2-dibromoethane (106-93-4)

cuprous bromide (7787-70-4)

Pentane (109-66-0)

copper(I) iodide (7681-65-4)

lithium (7439-93-2)

$MgSO_4$ (7487-88-9)

dimethyl sulfide (75-18-3)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

dimethylformamide (68-12-2)

hexane (110-54-3)

argon (7440-37-1)

Z-1-IODOHEXENE, 1-Hexene, 1-iodo-, (Z)- (16538-47-9)

lithium dibutylcuprate

lithium di(Z-hexenyl)cuprate

Z-iodohexene

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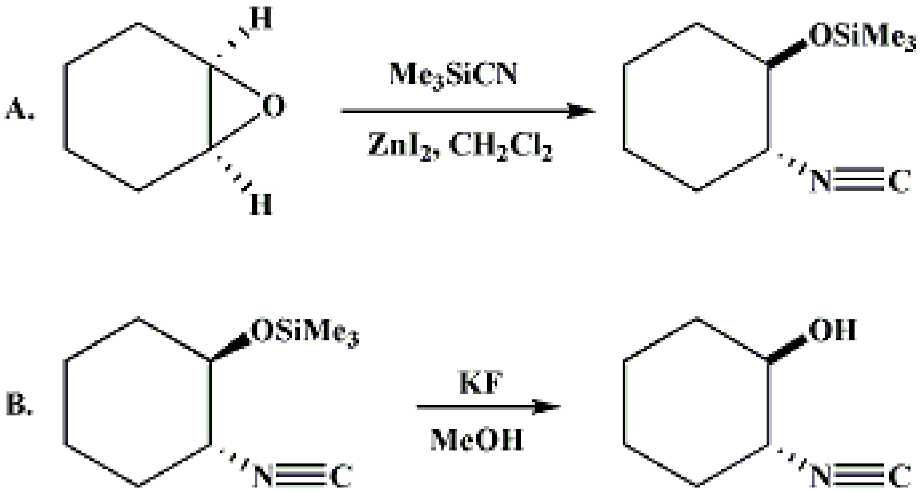
CONVERSION OF EPOXIDES TO β-HYDROXY ISOCYANIDES: *trans*-2-ISOCYANOCYCLOHEXANOL

[Cyclohexanol, 2-isocyanato-, *trans*-]



Submitted by Paul G. Gassman and Thomas L. Guggenheim[1].
Checked by Curtis E. Adams and K. Barry Sharpless.

1. Procedure

Caution! Trimethylsilyl cyanide is very toxic. All reactions in this sequence should be carried out in a hood.

A. *[(trans-2-Isocyanocyclohexyl)oxy]trimethylsilane*. A 100-mL, three-necked flask equipped with a reflux condenser, constant-pressure dropping funnel, magnetic stirring bar, and drying tube is charged with 20.2 g (204 mmol) of trimethylsilyl cyanide (Note 1), 60 mg (0.19 mmol) of anhydrous zinc iodide (Note 2), and 5 mL of dry methylene chloride (Note 3). The constant-pressure dropping funnel is charged with 10.0 g (102 mmol) of cyclohexene oxide (Note 4) and 5 mL of dry methylene chloride. The reaction mixture is heated to reflux and the cyclohexene oxide–methylene chloride solution is added dropwise to the refluxing reaction mixture over a 30-min period. After the addition is complete, the reaction mixture is refluxed for 4 hr and then allowed to cool to room temperature. The reaction mixture is transferred to a one-necked flask and the solvent and the excess trimethylsilyl cyanide are removed under reduced pressure on a rotary evaporator (Note 5). The residue is vacuum-distilled through a 3-in. Vigreux distillation column to yield 15.74 g (78%) of [(*trans*-2-isocyanocyclohexyl)oxy]trimethylsilane, bp 69–70°C (1.5 mm) (Note 6).

B. *trans-2-Isocyanocyclohexanol*. A 250-mL, one-necked, round-bottomed flask is charged with 13.72 g (70 mmol) of [(*trans*-2-isocyanocyclohexyl)oxy]trimethylsilane, 12.12 g (210 mmol) of potassium fluoride (Note 7), and 100 mL of methanol. The

reaction mixture is stirred magnetically for 5 hr at room temperature (23°C). The methanol is removed under reduced pressure on a rotary evaporator to yield a white slurry. This slurry is added to the top of a 250-g, 60–200-mesh silica gel chromatography column and the column is eluted with 20% ethyl acetate–80% hexane solvent mixture (Note 8). The solvent is removed from those fractions containing the product under reduced pressure on a rotary evaporator to afford an oil that is redissolved in methylene chloride, and the solution is filtered. The methylene chloride is removed from the filtrate under reduced pressure on a rotary evaporator to yield 8.46 g (68 mmol, 97%) of white, crystalline *trans*-2-isocyanocyclohexanol, mp 57.0–59.5°C (Note 9).

2. Notes

1. Trimethylsilyl cyanide was prepared shortly before use according to the procedure of Livinghouse, T. *Org. Synth., Coll. Vol. VII*, **1990**, 517. The checkers used trimethylsilyl cyanide as supplied from Aldrich Chemical Company, Inc.
2. Anhydrous zinc iodide was purchased from Alfa Products, Morton Thiokol, Inc., and used without further purification. In one run the checkers used 0.25 mmol of ZnI_2 and obtained a better yield than when they used 0.19 mmol of ZnI_2 (84% yield instead of 73%).
3. Commercial methylene chloride is dried by distillation from calcium hydride prior to use.
4. Cyclohexene oxide was purchased from Aldrich Chemical Company, Inc., and was used without purification.
5. The checkers also carried out this process in a fume hood. All glassware was rinsed afterward with 10% KOH solution or rinsed with acetone and the rinses mixed with 10% KOH. The resulting KOH solutions were treated with Chlorox overnight before being discarded.
6. This pure, colorless liquid showed the following physical properties: IR (neat) cm^{-1}: 2950, 2870, 2145, 1454, 1267, 1255, 1144, 1114, 1065, 1028, 931, 894, 884, 844, and 758; ^1H NMR (60 MHz, $CDCl_3$/TMS) δ: 0.17 (s, 9 H), 0.95–2.30 (br m, 8 H), 3.00–3.73 (br m, 2 H); ^1H NMR (250 MHz, $CDCl_3$) δ: 0.15 (s, 9 H), 1.25 (m, 3 H), 1.56 (m, 1 H), 1.67 (m, 2 H), 1.86 (m, 1 H), 2.13 (m, 1 H), 3.28 (m, 1 H), 3.56 (m, 1 H); density 0.882 g/mL.
7. Potassium fluoride was purchased from the Fisher Scientific Company.
8. Approximately 100-mL fractions are collected. The progress of the chromatography is followed by analysis of the eluting fractions with thin-layer chromatography developed with iodine vapor. The checkers achieved equal success using 120 g of 70–230-mesh silica in a 30-mm × 250-mm column.
9. The product showed the following physical properties: IR (KBr) cm^{-1}: 3470, 3400, 2965, 2945, 2870, 2175, 1450, 1376, 1328, 1302, 1240, 1123, 1090, 1081, 1007, 919, 856, and 851; ^1H NMR (60 MHz, $CDCl_3$/TMS) δ: 0.70–2.40 (br m, 8 H), 2.85 (d, 1 H, J = 5), 3.00–3.90 (br m, 2 H); ^1H NMR (250 MHz, $CDCl_3$) δ:

1.27 (m, 3 H), 1.56 (m, 1 H), 1.71 (m, 2 H), 2.02 (m, 1 H), 2.16 (m, 1 H), 2.35 (d, 1 H, *J* = 4), 3.30 (m, 1 H), 3.60 (m, 1 H).

3. Discussion

This method of preparation of *trans*-isocyanocyclohexanol is a version of our literature procedure.[2] It represents a general procedure that gives comparable yields with a wide variety of epoxides.[2] The method described is a new approach to the synthesis of isocyanides. Traditionally, isocyanides have been prepared by dehydration of formamides, the reaction of dihalocarbenes with primary amines, and the reaction of active halides and olefins with cyanides.[3,4,5]

Isocyanides are useful intermediates because of their diverse reactivity.[4] The β-hydroxy isocyanides, which are prepared readily by our general procedure, are particularly useful because of their straightforward conversion to β-amino alcohols in acids and their catalyzed cyclization to oxazolines.[2]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ZnI_2

ethyl acetate (141-78-6)

methanol (67-56-1)

iodine (7553-56-2)

acetone (67-64-1)

KOH (1310-58-3)

Cyclohexene oxide (286-20-4)

methylene chloride (75-09-2)

potassium fluoride (7789-23-3)

hexane (110-54-3)

calcium hydride (7789-78-8)

zinc iodide

Trimethylsilyl cyanide (7677-24-9)

trans-2-ISOCYANOCYCLOHEXANOL (83152-97-0)

Cyclohexanol, 2-isocyanato-, trans-

[(trans-2-isocyanocyclohexyl)oxy]trimethylsilane (83152-87-8)

trans-isocyanocyclohexanol

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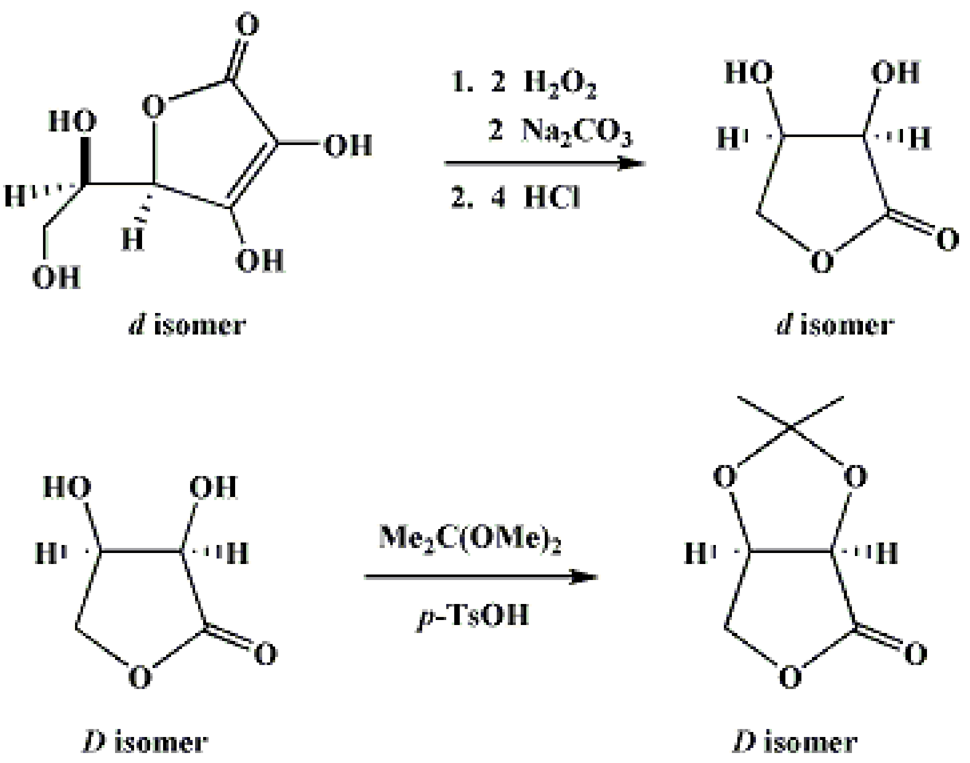
Organic Syntheses, CV 7, 297

2,3-*O*-ISOPROPYLIDENE-D-ERYTHRONOLACTONE

[Furo[3,4-*d*]-1,3-dioxol-4(3*aH*)-one, dihydro-2,2-dimethyl-(3*aR*-*cis*)-]



Submitted by Noal Cohen, Bruce L. Banner, Anthony J. Laurenzano, and Louis Carozza[1].
Checked by Lee A. Flippin and Clayton H. Heathcock.

1. Procedure

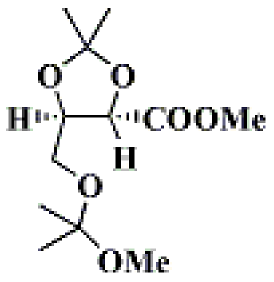
A 1-L, three-necked, round-bottomed flask fitted with a thermometer, addition funnel, and an air motor-driven paddle stirrer is charged with 35.2 g (0.20 mol) of erythorbic acid (Note 1) and 500 mL of deionized water. The solution is stirred with ice bath cooling (Note 2), and 42.4 g (0.40 mol) of anhydrous, powdered sodium carbonate (Note 3) is added in small portions (Note 4). The resulting yellow solution (Note 5) is stirred with ice-bath cooling while 44 mL (0.45 mmol) of 31.3% by weight aqueous hydrogen peroxide (Note 6) is added dropwise over a 10-min period. The internal temperature rises from 6 to 19°C (Note 7). The solution, containing a few solid particles, is stirred for 5 min with ice bath cooling, during which time the internal temperature continues to rise to 27°C. The flask is now immersed in a water bath that is heated to 42°C. The solution is stirred for 30 min, during which time the internal temperature reaches a maximum of 42°C (Note 8). Norit A (8 g) is added in portions over 10 min to decompose the excess peroxide and the mixture is heated on a steam bath with continued stirring for 30 min, at which point gas evolution has essentially ceased and a negative starch–iodide test is observed. The internal temperature reaches

and is kept at 75–78°C. The hot mixture is filtered with suction on a Celite pad into a 2-L, three-necked, round-bottomed flask and the filtercake is washed, in several small portions, with a total of 100 mL of deionized water. The combined filtrate and washes are acidified to pH 1 by the *cautious* (Note 9) addition of 150 mL (0.90 mol) of 6 *N* aqueous hydrochloric acid, in portions, with swirling. The acidic solution is concentrated with a rotary evaporator at 50°C/water aspirator pressure. The residue is dried at 50°C/0.2 mm to give 84.6 g of a pale-yellow solid residue containing D-erythronolactone, oxalic acid, and sodium chloride (Note 10) and (Note 11). To this material is added 175 mL of acetone (Note 13) and the mixture is swirled to loosen the solids caked on the sides of the flask. A 50-g portion of anhydrous, powdered magnesium sulfate (Note 14) is now added and the mixture is stirred by means of an air motor-driven paddle stirrer as 350 mL (2.85 mol) of 2,2-dimethoxypropane (Note 15) is added in one portion. To the stirred mixture is added 0.42 g (0.0022 mol) of *p*-toluenesulfonic acid monohydrate at room temperature. The slurry is blanketed with nitrogen and stirred at room temperature for 18 hr. In a 2-L, three-necked, round-bottomed flask fitted with a thermometer and an air motor-driven paddle stirrer, a mixture of 500 mL of anhydrous ether and 61.3 mL (0.44 mol) of triethylamine (Note 16) is cooled in an ice bath to 5°C. The reaction mixture is decanted into this solution. The residual solids are rinsed with 60 mL of ether, which is also decanted into the triethylamine solution. After being stirred for a few minutes (Note 17), the mixture is filtered with suction on a 600-mL, coarse, sintered-glass funnel. The solids are washed thoroughly with a total of 300 mL of anhydrous ether by slurrying three times on the funnel with the vacuum turned off; the vacuum is then applied to draw the wash ether through the funnel. The filtrate and washes are combined and concentrated with a rotary evaporator at water aspirator pressure, and the residue is dried at 45°C/0.5 mm to give 34.3 g of a pale-yellow solid (Note 18). This material is dissolved in approximately 150 mL of 1 : 1 hexanes : ethyl acetate and the solution (Note 19) is adsorbed on a column of 200 g of silica gel (Note 20) packed in 1 : 1 hexanes : ethyl acetate. The column is eluted with a total volume of 2 L of 1 : 1 hexanes : ethyl acetate (Note 21). The eluate is concentrated with a rotary evaporator at aspirator pressure and the solid residue is dried under high vacuum to afford 27.3 g of a colorless solid. This material, contained in a 1-L, one-necked, round-bottomed flask, is treated with 150 mL of anhydrous ether and the mixture is refluxed on a steam bath for 5 min to dissolve all the solid. The solution is removed from the steam bath and treated with 225 mL of hexanes. An immediate precipitate results. The mixture is refrigerated (0°C) for 3.5 hr and then filtered with suction. The solid is washed with a total of 100 mL of hexanes, in small portions, and then dried under high vacuum at 20°C. There is obtained 23.6 g (74.7%) of 2,3-*O*-isopropylidene-D-erythronolactone as a white solid, mp 65.5–66°C, $[\alpha]_D^{25}$ −113.8° (*c* 1.11 H_2O) (Note 22),(Note 23),(Note 24),(Note 25).

2. Notes

1. Erythorbic acid is the same compound as D-isoascorbic acid, available from the Aldrich Chemical Company, Inc. This substance is also known as *araboascorbic acid*.

2. The internal temperature is 6°C initially.
3. Sodium carbonate was obtained from the Fisher Scientific Company.
4. Vigorous evolution of carbon dioxide is observed. The internal temperature rises to 8°C.
5. A few particles of undissolved sodium carbonate may remain.
6. Aqueous hydrogen peroxide was obtained from the Fisher Scientific Company. The lot analysis given on the bottle is used to calculate the volume of hydrogen peroxide solution required. Approximately 10% molar excess of peroxide appears to be required to provide a clean product.
7. The oxidation is quite exothermic. Attempts to increase the concentrations of the reactants led to an exotherm that was difficult to control and was complicated by the precipitation of solids, which hampered stirring.
8. A small amount of gas evolution is noted during this period.
9. Evolution of carbon dioxide is vigorous.
10. It is essential that all the water be removed at this point and that a constant weight of approximately 84 g be obtained.
11. If desired, D-erythronolactone can be isolated at this point by treatment of the residue with boiling ethyl acetate. On this scale, the solid is triturated at reflux with 325 mL of ethyl acetate for 5 min. The solution is decanted and the trituration is repeated with 130 mL of ethyl acetate. The combined solutions are cooled to 5°C and filtered. The solid is washed in portions with a total of 400 mL of cold ethyl acetate. After air drying, there is obtained 15.4 g (77.0%) of D-erythronolactone as a white solid, mp 97.5–99.5°C, $[\alpha]_D^{25}$ −72.8° (H_2O, c 0.498) (Note 12).
12. The physical properties of D-erythronolactone are as follows: Lit.[2] mp 104–105°C, $[\alpha]_D^{20}$ −73.2° (H_2O, c 0.533).
13. Acetone was obtained from Fisher Scientific Company.
14. The drying agent is added to remove any residual moisture and to facilitate the subsequent filtration.
15. 2,2-Dimethoxypropane was obtained from the Aldrich Chemical Company, Inc.
16. Triethylamine was obtained from Eastman Chemical Products, Inc.
17. The mixture is alkaline to pH paper.
18. TLC analysis of the crude product (1 : 3 hexane : ethyl acetate, EM Silica Gel 60 F-254 plates) reveals the desired acetonide lactone to be the major component (R_f 0.6) with one minor, less polar impurity and several minor, more polar impurities. The ^1H NMR and IR spectra of a pure sample of the less polar impurity (an oil) were compatible with the following structure: ^1H NMR (100 MHz, $CDCl_3$) δ: 1.31 (2 s, 6 H, $(CH_3)_2C$), 1.39 (s, 3 H, C_2-CH_3), 1.59 (s, 3 H, C_2-CH_3), 3.20 (s, 3 H, OCH_3), 3.41 (dd, 1 H, J = 6, 10.5, CH_2O), 3.57 (dd, 1 H, J = 4.5, 10.5, CH_2O), 3.76 (s, 3 H, CO_2CH_3), 4.49 (m, 1 H, H_5), 4.67 (d, 1 H, $J_{4,5}$ = 7, H_4); IR ($CHCl_3$) cm^{-1}: 1760, 1735 (ester C=O).



19. A small amount of insoluble material is present.
20. EM Silica Gel 60, 0.063–0.2 mm was used. The column dimensions are approximately 1.75 in. × 14 in.
21. TLC is utilized to ensure that all of the desired product is eluted from the column. This procedure removes the minor, polar impurities present in the crude product that appear at or near the origin of the TLC plate.
22. This material is homogeneous on TLC analysis; ^{1}H NMR (100 MHz, $CDCl_3$) δ: 1.37 (s, 3 H, C_2-CH_3), 1.46 (s, 3 H, C_2-CH_3), 4.42 (d, 2 H, $J_{6,6a}$ = 2, H_6), 4.75 (d, 1 H, $J_{3a,6a}$ = 6, H_{3a}), 4.89 (dt, 1 H, $J_{3a,6a}$ = 6, $J_{6,6a}$ = 2, H_{6a}); IR ($CHCl_3$) cm^{-1}: 1786 (γ-lactone C=O).
23. The physical properties are as follows: lit.[3] mp 68–68.5°C, $[\alpha]_D^{20}$ −112° (H_2O, *c* 1.5).
24. The reaction sequence has been run on a 176-g (1.0-mol) scale with no loss in yield.
25. The checkers obtained 22.5 g (71.1%) of product as a white solid, mp 68.0–68.5°C, $[\alpha]_D^{20}$ −123.4° (H_2O, *c* 0.96). It is important that crystallization from the ether–hexane mixture be carried out at 0°C. In one run in which crystallization was carried out at 8°C, the checkers obtained only 15.3 g (48.4%) of product, mp 65.5–66.0°C.

3. Discussion

2,3-*O*-Isopropylidene-D-erythronolactone and the corresponding lactol, 2,3-*O*-isopropylidene-D-erythrose, are useful chiral synthons in the total synthesis of certain natural products such as the leukotrienes[4] and pyrrolizidine alkaloids.[5] The lactol is readily available from the lactone, in excellent yield, by reduction with diisobutylaluminum hydride.[4,5,6] 2,3-*O*-Isopropylidene-L-erythrose has been employed as the starting material in an enantioselective synthesis of (+)-15*S*-prostaglandin A_2.[7] Optically pure, selectively protected, polyfunctional C_4-units such as these have great potential in synthesis if readily available, in substantial quantity, from inexpensive members of the pool of chiral starting materials.[8]

D-Erythronolactone and/or its isopropylidene derivative have been prepared starting from L-rhamnose,[9] D-ribose,[10] D-ribonolactone,[3] potassium D-glucuronate,[11] D-glucose,[12] and erythorbic acid,[2] by optical resolution of racemic erythronolactone,[13] and asymmetric total synthesis.[14] 2,3-*O*-Isopropylidene-D-erythrose has been obtained

from D-arabinose by a route that does not involve the intermediacy of the lactone.[15] All of these processes suffer from either relatively low overall yields or the requirement of a large number of individual stages. The procedure described here, which is based on a similar oxidative degradation of L-ascorbic acid (vitamin C) to L-threonic acid,[16] is undoubtedly the most expeditious route to the acetonide of D-erythronolactone available. In addition, the starting material, erythorbic acid, is an inexpensive and readily available substance, commonly used as a food preservative. It is pertinent to note that recently L-ascorbic acid has itself found synthetic utility as a precursor to (*R*)-glycerol acetonide, an important C_3 chiral synthon.[17]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

H_2O

hexanes

erythorbic acid

(+)-15S-prostaglandin A_2

(R)-glycerol acetonide

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

ether (60-29-7)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

Oxalic acid (144-62-7)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

d-ARABINOSE (28697-53-2)

acetone (67-64-1)

Norit A (7782-42-5)

hydrogen peroxide (7722-84-1)

d-Glucose (492-62-6)

magnesium sulfate (7487-88-9)

hexane (110-54-3)

triethylamine (121-44-8)

diisobutylaluminum hydride (1191-15-7)

2,2-dimethoxypropane (77-76-9)

L-ascorbic acid

ERYTHRONOLACTONE, D-Erythronolactone

D-isoascorbic acid

D-ribose (50-69-1)

D-ribonolactone

p-toluenesulfonic acid monohydrate (6192-52-5)

2,3-O-isopropylidene-D-erythronolactone, Furo[3,4-d]-1,3-dioxol-4(3aH)-one, dihydro-2,2-dimethyl-(3aR-cis)- (25581-41-3)

2,3-O-isopropylidene-D-erythrose

2,3-O-Isopropylidene-L-erythrose

L-rhamnose

potassium D-glucuronate

L-threonic acid

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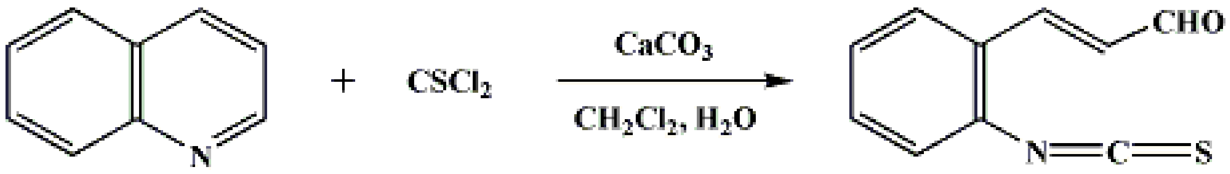
Organic Syntheses, CV 7, 302

o-ISOTHIOCYANATO-(*E*)-CINNAMALDEHYDE

[2-Propenal, 3-(2-isothiocyanatophenyl)-, (*E*)-]



Submitted by R. Farrand and R. Hull[1].
Checked by K. E. Fahrenholtz and G. Saucy.

1. Procedure

Caution! This reaction should be carried out in a good hood because of the toxicity of thiophosgene.

A 1000-mL (Note 1), multinecked flask is provided with an efficient stirrer, vented outlet, thermometer, and 250-mL dropping funnel. The flask is surrounded by an ice–water bath and charged with 62.5 mL (68.4 g, 0.53 mol) of quinoline, 250 mL of dichloromethane, 55 g (0.55 mol) of finely powdered calcium carbonate, and 250 mL of water. The mixture is stirred vigorously, cooled to 10°C, and maintained at 10–15°C as a solution of 37.5 mL (56.5 g, 0.49 mol) of thiophosgene (Note 2) in 120 mL of dichloromethane is added over 15 min. There is very little exotherm or foaming. The cooling bath is removed and the reaction mixture is stirred vigorously at ambient temperature overnight. The reaction is then filtered through a bed of filter aid. The layers are separated and the aqueous layer is extracted with 50 mL of dichloromethane. The combined organic layers are washed twice with 150 mL of 2 *N* hydrochloric acid (Note 3), then with 150 mL of water, and dried over anhydrous magnesium sulfate. Concentration under reduced pressure gives 95–103 g of crude material (Note 4). This is dissolved with heating in 400 mL of cyclohexane, decolorizing carbon is added, and the mixture is filtered through a bed of filter aid. The filtrate is heated under reflux for 2 hr (Note 5) and allowed to cool with stirring (Note 6). The resulting solid is isolated by filtration, washed with cyclohexane, and dried in a vacuum oven at 40°C to give 78–83 g (84–89%) of *o*-isothiocyanato-(*E*)-cinnamaldehyde as cream crystals, mp 77–79°C (Note 7).

2. Notes

1. The reaction has been carried out on 10 times these quantities with no difficulty.
2. The checkers used an older bottle of thiophosgene and obtained an 84% yield (based on thiophosgene). A subsequent run was carried out with Aldrich "85%

in CCl_4" thiophosgene found by analysis to contain 63% thiophosgene (therefore 89.4 g was used) and an 89% yield was obtained. A subsequent run on an unanalyzed bottle of the same lot number using 89.4 g gave a 100% yield (92% based on quinoline). It is suggested that thiophosgene be analyzed before use (Note 8).

3. These two washes remove unreacted quinoline.

4. The crude material consists of a mixture of *Z* and *E* isomers, with *Z* predominating. If workup of the reaction is delayed, more of the less soluble *E* isomer is formed, complicating subsequent filtration.

5. This additional heating completes the isomerization of the *Z* to the *E* isomer.

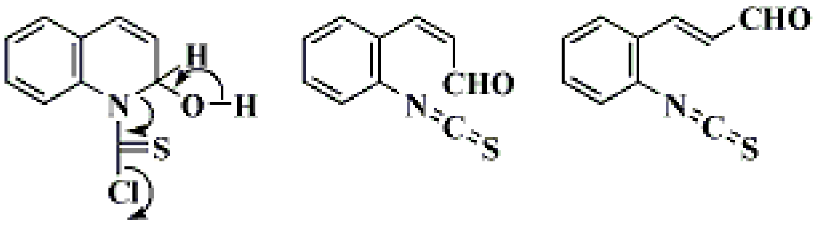
6. Subsequent breakup and filtration of the solid are facilitated if this solution is transferred and allowed to cool with stirring in a large-mouth container such as a beaker.

7. Melting points were taken in open capillaries on a Thomas-Hoover melting point apparatus. The crude material can be purified by dissolving it in dichloromethane, passing the solution over a plug of silica gel, and concentrating the solution with the addition of ether. The recrystallized material has essentially the same melting point and is colorless. The spectral properties of *o*-isothiocyanato-(*E*)-cinnamaldehyde are as follows: IR (Nujol) cm^{-1}: 2075 (NCS) and 1670 (conjugated CHO); ^1H NMR ($CDCl_3$) δ: 6.75 (d of d, 1 H, *J* = 16 and 7.5, CH=C*H*CHO), 7.4 (m, 4 H, aromatic H), 7.8 (d, 1 H, *J* = 16, ArC*H*=CH), 9.78 (d, 1 H, *J* = 7.5, C*H*O).

8. Thiophosgene mixed with CCl_4 can be analyzed as follows: a 0.5-mL aliquot of the reagent is mixed with a warm mixture of 15 mL of 30% hydrogen peroxide and 15 mL of 1 *N* sodium hydroxide. The mixture is shaken occasionally during 20 min (overnight gives the same titer) and diluted to 200 mL with water. Liberated Cl^- is then titrated with mercuric nitrate.

3. Discussion

This procedure is an example of a simple fission reaction of *N*-heterocyclic compounds by thiophosgene and base[2] wherein the dihydro intermediate **1** undergoes ring fission to yield the *Z*-isothiocyanate **2**, which isomerizes in situ to the *E*-isomer **3**. The reaction may be applied to certain substituted quinolines,[3,4] isoquinoline,[2] pyridine,[5] benzoxazole,[6] benzimidazole,[6,7] and oxazole[8] derivatives, but not to benzothiazole.[6]



1 2 3

The ortho-substituted isothiocyanates are valuable intermediates for the preparation of a variety of heterocyclic compounds; for example, *o*-isothiocyanato-(*E*)-cinnamaldehyde with sodio diethyl malonate undergoes facile cyclization to 3-formylquinoline-2(1*H*)-thione,[9] which in turn may be used for the preparation of tricyclic[9,10] and large ring heterocyclic compounds.[11]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium hydroxide (1310-73-2)

CCl_4 (56-23-5)

cyclohexane (110-82-7)

calcium carbonate (471-34-1)

decolorizing carbon (7782-42-5)

hydrogen peroxide (7722-84-1)

Thiophosgene (463-71-8)

Quinoline (91-22-5)

dichloromethane (75-09-2)

mercuric nitrate

magnesium sulfate (7487-88-9)

benzothiazole (95-16-9)

sodio diethyl malonate

o-Isothiocyanato-(E)-cinnamaldehyde, 2-Propenal, 3-(2-isothiocyanatophenyl)-, (E)- (19908-01-1)

3-formylquinoline-2(1H)-thione

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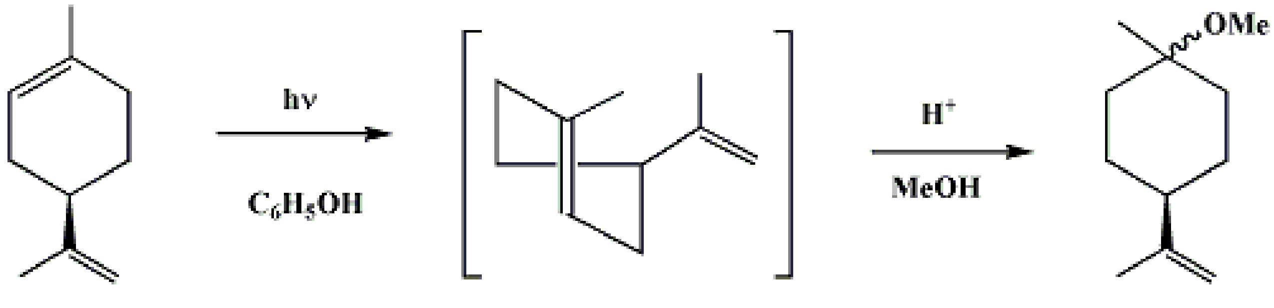
Organic Syntheses, CV 7, 304

PHOTOPROTONATION OF CYCLOALKENES: LIMONENE TO *p*-MENTH-8-EN-1-YL METHYL ETHER

[Cyclohexane, 1-methoxy-1-methyl-4-(1-ethenyl-1-methyl-)]



Submitted by F. P. Tise and P. J. Kropp[1].
Checked by R. L. Amey and R. E. Benson.

1. Procedure

A 250-mL photochemical reactor (see f.htmigure 1) is fitted with a cylindrical Vycor filter sleeve, a 450-W Hanovia mercury lamp, and a watercooled condenser which is connected to a mineral oil bubbler. Tubing attachments are made so that water is circulated through the condenser and then through the Vycor filter sleeve. The tube leading from the bottom of the reaction vessel and containing the glass frit is connected in series to a trap fitted with a fritted filter stick and then to a trap that is connected to a nitrogen source. The system is flushed with nitrogen, and sufficient anhydrous methanol is placed in the trap containing the fritted stick to provide for a methanol-saturated gas stream during the course of the reaction (Note 1).

Figure 1

Figure 1

The nitrogen-flushed reactor is charged with a solution of 20.0 g (147 mmol) of (+)-limonene (Note 2), 5.0 g (53 mmol) (Note 3) of phenol, and 5 drops of concentrated sulfuric acid in 210 mL (167 g, 5.2 mol) of anhydrous methanol (Note 4). Water flow through the condenser is started (Note 5), and the nitrogen flow is adjusted to provide good agitation of the contents of the vessel. After 15 min, irradiation is started and the reaction followed by GLC (Note 6), with 48 hr being the approximate time needed for essentially complete conversion (Note 7).

The solution is poured into 900 mL of 5% aqueous sodium hydroxide solution containing 125 g of sodium chloride, and the mixture is extracted with two 100-mL portions of ether. The ether layers are combined, washed with 50 mL of saturated sodium chloride solution, and dried over anhydrous sodium sulfate. The drying agent is removed by filtration and the

filtrate is concentrated with a Büchi rotary evaporator. After a preliminary distillation to separate the product from a small amount of nonvolatile material, the liquid is distilled at reduced pressure through a Teflon spinning band column (47 cm × 7 mm). The material that distills at 90–95°C (10 mm) is collected to give 12.8–13.2 g (52–53%) of a mixture of *cis*- and *trans*-*p*-menth-8-en-1-yl methyl ether (Note 8),(Note 9),(Note 10).

2. Notes

1. The submitters used a reactor with a joint that was capped with a rubber septum fitted with two syringe needles, which were attached by means of a Y-tube to a single nitrogen line. To one of these needles is attached a piece of 1.70-mm-o.d. polyethylene tubing of sufficient length to reach to the bottom of the reaction vessel. By use of pinchcocks, nitrogen can be passed through either of the two needles. The solution was stirred with a magnetic stirring bar.
2. (+)-Limonene was obtained from Aldrich Chemical Company, Inc. and distilled before use.
3. The checkers used reagent available from Fisher Scientific Company.
4. The checkers used fresh, acetone-free, absolute methanol available from Fisher Scientific Company.
5. For best results the cooling water should pass through the condenser first and then through the immersion well. This arrangement lessens evaporation of methanol.
6. The submitters used a 3-m × 3.2-mm stainless steel column packed with 20% SF-96 on Chromasorb W (60–80 mesh) and a He flow rate of 60 mL/min. With a temperature program of 4 min at 50°C followed by an increase of 10°C/min to a maximum of 200°C, the retention times were 17.9 and 18.7 min.
7. The checkers found that the reaction was impeded by the formation of a yellow film on the immersion well with very little further conversion occurring after 30 hr of irradiation.
8. The checkers used a 2.4-m × 3.2-mm column packed with 7% SE-30 and 3% Silar on Chromasorb W (60–80 mesh) at 160°C. The retention time was 1.56 min for the trans isomer and 1.81 min for the cis isomer at a He flow rate of 55 mL/min.
9. The spectral properties of the product (approximately 60% cis:40% trans isomers) are as follows: IR (neat) cm^{-1}: 3080 (=C-H); 2964, 2939, 2860, 2825, (C-H); 1645 (C=C); 1464, 1453, and 1442 (overlapping peaks); 1370, 1124, and 1082 (C-OC); 885 (=CH). ^{1}H NMR ($CDCl_3$) δ: 1.10 [s, 3 H, CH_3 (trans)], 1.19 [s, 3 H, CH_3 (cis)], 1.30–2.00 (8 H, -CH_2–), 1.71 [s, 3 H, CH_3 (cis/trans)], 3.14 [s, 3 H, OCH_3 (trans)], 3.21 [s, 3 H, OCH_3 (cis)], 4.69 [s, 2 H, =CH_2 (cis/trans)].
10. The submitters state that similar irradiation of 20.0 g of cyclohexene, 5.0 g of phenol, and 1.5 mL of concentrated sulfuric acid for 24 hr afforded cyclohexyl methyl ether in 70% yield.

3. Discussion

Acid-catalyzed, ground-state additions to limonene generally afford a mixture of products resulting from competing protonation of both double bonds.[2] In one case in which selective reaction was observed, attack occurred at the acyclic C_8-C_9 double bond.[3]

The photoprotonation of cycloalkenes, described in this procedure, is believed to proceed via

initial light-induced cis □ trans isomerization of the alkene.[4] The resulting highly strained trans isomer undergoes facile protonation. This procedure permits the protonation of cyclohexenes and cycloheptenes under neutral or mildly acidic conditions.[5] Since the process is irreversible, high levels of conversion to addition products can be achieved.

Photoprotonation is generally specific for cyclohexenes and cycloheptenes. Smaller-ring cycloalkenes are incapable of undergoing cis □ trans isomerization, and the trans isomers of larger-ring or acyclic analogues have insufficient strain to undergo ready protonation. Thus, in addition to facilitating protonation of cycloalkenes, the procedure affords a means of selectively protonating a double bond contained in a six- or seven-membered ring in the presence of another double bond contained in an acyclic, exocyclic, or larger-ring cyclic environment.[6] When conducted in non-nucleophilic media, the photoprotonation procedure is also useful for effecting the isomerization of 1-alkylcyclohexenes and -heptenes to their exocyclic isomers.[4]

References and Notes

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5. There is a fine balance between the acidity of the alcohol and the basicity of the trans olefin. For example, 1-methylcyclohexenes undergo photoprotonation in methanol whereas cyclohexenes require the addition of small amounts of acid. In the present example, the addition of a small quantity of acid reduces the competing formation of the exocyclic isomer, *p*-mentha-1(7),8-diene.
6. For an earlier report on the photoprotonation of (+)-limonene, see Kropp, P. J. *J. Org. Chem*. **1970**, *35*, 2435–2436.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

methanol (67-56-1)

ether (60-29-7)

sodium hydroxide (1310-73-2)

phenol (108-95-2)

Cyclohexene (110-83-8)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

CYCLOHEXYL METHYL ETHER (931-56-6)

LIMONENE, (+)-limonene

Cyclohexane, 1-methoxy-1-methyl-4-(1-ethenyl-1-methyl-)

p-Menth-8-en-1-yl methyl ether, cis- and trans-p-menth-8-en-1-yl methyl ether (24655-71-8)

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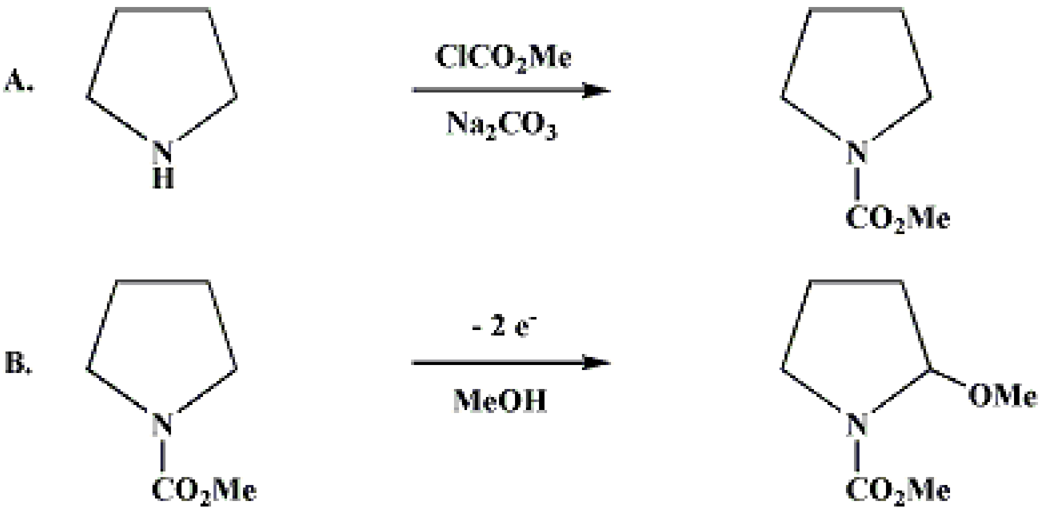
Organic Syntheses, CV 7, 307

ANODIC OXIDATION OF *N*-CARBOMETHOXYPYRROLIDINE: 2-METHOXY-*N*-CARBOMETHOXYPYRROLIDINE

[1-Pyrrolidinecarboxylic acid, 2-methoxy-, methyl ester]



Submitted by T. Shono, Y. Matsumura, and K. Tsubata[1].
Checked by B. Schaer, G. Reymond, V. Toome, and Gabriel saucy.

1. Procedure

A. *N-Carbomethoxypyrrolidine*. A 1-L, three-necked, round-bottomed flask is equipped with a 200-mL pressure-equalizing dropping funnel, a Graham condenser protected by a calcium chloride tube, and a mechanical stirrer. The flask is charged with 200 g (1.89 mol) of sodium carbonate (Note 1), 400 mL of methylene chloride (Note 2), and 71 g (1 mol) of pyrrolidine (Note 3). The dropping funnel is charged with 103 g (1.1 mol) of methyl chlorocarbonate (Note 3), which is added with stirring over a 2-hr period at a rate that sustains a gentle reflux. After the addition of methyl chlorocarbonate is completed, the reaction mixture is stirred overnight at room temperature. The white precipitate is filtered with suction through a coarse Büchner funnel and washed three times with 100 mL of methylene chloride. The filtrate is concentrated on a vacuum rotary evaporator at a bath temperature of 30°C. The crude oily product is distilled under reduced pressure through a Claisen flask to yield 119–121 g (92–94%) of *N*-carbomethoxypyrrolidine, bp 64°C/1.3 mm.

B. *2-Methoxy-N-carbomethoxypyrrolidine*. A solution of *N*-carbomethoxypyrrolidine (12.7 g, 0.098 mol) and tetraethylammonium *p*-toluenesulfonate (0.83 g, 0,0027 mol) (Note 3) in 83 mL of methanol (Note 2) is added into an undivided jacketed cell (Note 4) equipped with two graphite-rod anodes and two graphite-rod cathodes, (Note 5) a thermometer, an exit tube for venting purposes, and a magnetic stirring bar. The

carbon rods (0.6 cm in diameter, immersed 5.5 cm into the solution, resulting in a working electrode surface of 21.3 cm^2 and a current density of 46.9 mA/cm^2) are spaced 4.5 mm apart. The anode rods and the two cathode rods are connected with No. 22 copper wire as shown in f.htmigure 1. During the electrolysis (Note 6), the temperature of the reaction mixture is maintained at 10–15°C (Note 7) by cooling with tap water. After 2.34F/mol of electricity (1 A, 6 hr; the voltage between the anode and cathode was 19–24 V for the example in f.htmigure 1) has been passed through, (Note 8) the current is stopped and the solvent is removed under reduced pressure. The residue is dissolved in 120 mL of methylene chloride and washed with aqueous NaCl (20 mL). The aqueous NaCl wash is reextracted with methylene chloride (2 × 30 mL). The methylene chloride phases are combined and dried over magnesium sulfate. The solvent is evaporated and the residue is distilled, employing a 5 cm Vigreux column and an oil bath at 80–90°C (Note 9). The yield is 12.3–13.0 g (78–83%), bp 48–55°C/0.2–0.5 mm (Note 10).

Figure 1. Electrolysis cell for methoxylation.

Figure 1. Electrolysis cell for methoxylation.

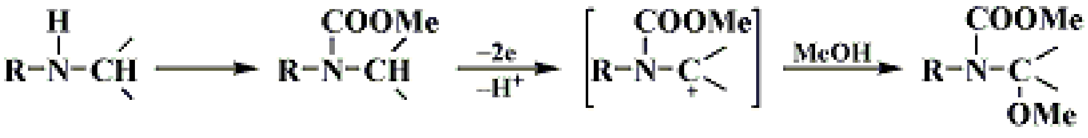
2. Notes

1. Sodium carbonate, anhydrous powder, supplied by J. T. Baker Chemical Company, is used directly.
2. Methylene chloride was purchased from Fisher Scientific Co.
3. Pyrrolidine and methyl chlorocarbonate were purchased from the Aldrich Chemical Company, and used without further purification.
4. The cell is shown in f.htmigure 1.
5. The electrodes were purchased from Princeton Applied Research (PAR); spectroscopic grade, Lot#174/78. This grade is not necessarily the best type of graphite for electrochemical purposes, but it was the only one immediately available. The submitters used graphite plates, purchased from Tokai Carbon Company, Inc., as electrodes, but they note that these are not the only electrode material usable in this reaction.
6. Princeton Applied Research (PAR) Potentiostat-Galvanostat, Model 173/179 was used.
7. According to the submitters, the temperature should be kept below 50°C; otherwise lower yields are observed.
8. According to the submitters, if more than 2.2–2.5F/mol of electricity is passed *N*-carbomethoxy-2,5-dimethoxypyrrolidine forms. The by-product can be separated by distillation (bp 64–65°C/1.0 mm).
9. An oil bath temperature higher than 100°C results in the formation of unsaturated carbamate formed by the elimination of methanol from the methoxylated carbamate. Accordingly, in the anodic methoxylation of carbamates having high boiling points, the product must be purified by column chromatography in order to avoid formation of the unsaturated carbamates.

10. The product has the following spectral properties: IR (liquid film) cm^{-1}: 2940, 2880, 1685, 1440, 1370, 1185, 1080, 950, 825, 770; ^{1}H NMR (CCl_4) δ: 1.48–2.21 (m, 4 H, CH_2 at C_3 and C_4 of pyrrolidine ring), 3.25 (s, 3 H, methoxy CH_3), 3.08–3.52 (m, 2 H, CH_2 at C_5 of pyrrolidine ring), 3.64 (s, 3 H, ester CH_3), 5.06 (m, 1 H, CH at C_2 of pyrrolidine ring).

3. Discussion

This procedure describes anodic α-methoxylation of carbamates (**2**), which are derived from primary and secondary amines (**1**).[2,3]



1 2 3 4

The intermediate cations (**3**) are trapped with methanol to yield α-methoxycarbamates, **4**, which are sufficiently stable to be stored for a long period. Table I shows other examples of anodic synthesis of **4**.

The high regioselectivity in the methoxylation of unsymmetrical carbamates is remarkable (see 2-pipecoline carbamate and N-carbomethoxyproline methyl ester in Table **I**). The methoxylation always takes place in the order of CH_3

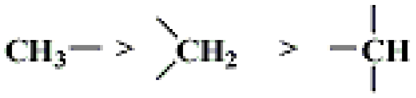


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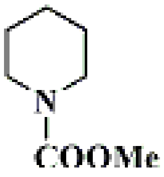
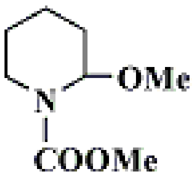
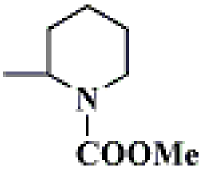
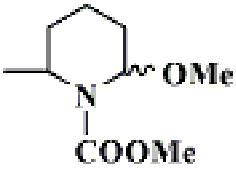
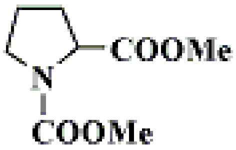
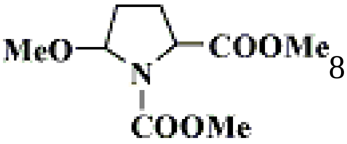
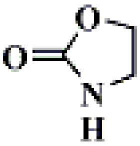
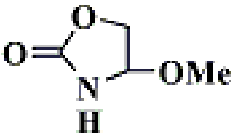
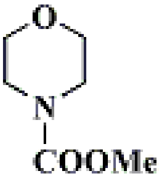
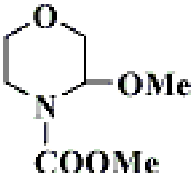
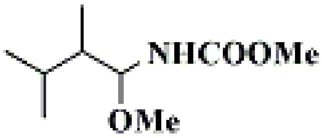
TABLE I
ANODIC SYNTHESES OF α-METHOXYCARBAMATES

	Electricity Passed (F/mol)	Carbamate	α-Methoxycarbamate	Yield (%)
	2.7		86	

	2.6		69
	2.5		87
	3.0		89
	2.7		55
	4.85		83
	10.2		88
	6.0		70
	7.1		77

	2.1		72
	3.2		94

α-Methoxycarbamates (**4**) are useful intermediates in organic syntheses, since treatment of **4** with Lewis acids or Brønsted acids regenerates **3** which can be trapped with a variety of nucleophiles. Thus, physiologically active compounds such as alkaloids,[3] amino acids,[4] nitrogen-containing phosphorus compounds,[5] and pyridoxine[6] can be synthesized using **4** as key starting compounds. f.htmigure 2 summarizes the transformations.[3,4,5,6,7]

Figure 2

Figure 2

References and Notes

1. Department of Synthetic Chemistry, Faculty of Engineering, Kyoto University, Yoshida, Sakyo, Kyoto 606, Japan.
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6. Shono, T.; Matsumura, Y.; Tsubata, K.; Takata, J. *Chem. Lett*. **1981**, 1121.
7. Shono, T.; Matsumura, Y.; Tsubata, K.; Sugihara, Y.; Yamane, S.; Kanazawa, T.; Aoki, T. *J. Am. Chem. Soc*. **1982**, *104*, 6697.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

methanol (67-56-1)

NaCl (7647-14-5)

sodium carbonate (497-19-8)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

methyl chlorocarbonate (79-22-1)

pyrrolidine (123-75-1)

carbamate

1-Pyrrolidinecarboxylic acid, 2-methoxy-, methyl ester, 2-Methoxy-N-carbomethoxypyrrolidine (56475-88-8)

2-pipecoline carbamate

α-Methoxycarbamate

N-Carbomethoxypyrrolidine (56475-80-0)

tetraethylammonium p-toluenesulfonate (733-44-8)

N-carbomethoxy-2,5-dimethoxypyrrolidine

N-carbomethoxyproline methyl ester

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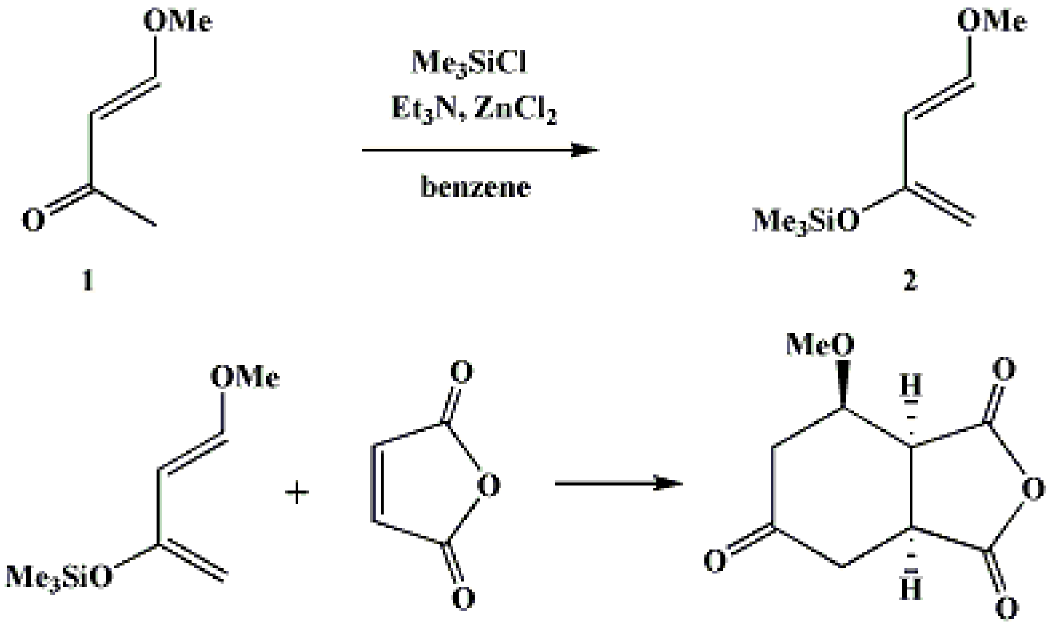
Organic Syntheses, CV 7, 312

PREPARATION AND DIELS–ALDER REACTION OF A HIGHLY NUCLEOPHILIC DIENE: *trans*-1-METHOXY-3-TRIMETHYLSILOXY-1,3-BUTADIENE AND 5β-METHOXYCYCLOHEXAN-1-ONE-3β,4β-DICARBOXYLIC ACID ANHYDRIDE

[Silane, [(3-methoxy-1-methylene-2-propenyl)oxy]trimethyl-]



Submitted by Samuel Danishefsky, Takeshi Kitahara, and Paul F. Schuda[1].
Checked by Dennis Golob, John Dynak, and Robert V. Stevens.

1. Procedure

*Caution! Benzene (see Section B) has been identified as a carcinogen; **OSHA** has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.*

A. *Preparation of the zinc chloride*. Reagent-grade zinc chloride (50 g) is placed in an evaporating dish and heated in a fume hood with a Fisher burner until no more water vapor is driven off. The hot dish is rapidly transferred to a glove bag that has been maintained under nitrogen. After the zinc chloride has cooled to a transparent glassy solid, it is ground to a fine powder with a mortar and pestle. The solid is transferred to a tightly stoppered bottle and stored in a desiccator over Drierite.

B. *Preparation of 1-methoxy-3-trimethylsiloxy-1,3-butadiene*. Triethylamine (575 g, 5.7 mol) is stirred mechanically in a three-necked flask (Note 1). To this is added 10.0 g (0.07 mol) of zinc chloride prepared as described above. The mixture is stirred at

room temperature under nitrogen for 1 hr. A solution of 250 g (2.50 mol) of 4-methoxy-3-buten-2-one (from Aldrich Chemical Company, Inc.) in 750 mL of benzene is added all at once. Mechanical stirring is continued for 5 min. Chlorotrimethylsilane (542 g, 5.0 mol) is added rapidly. The reaction mixture first turns pink, then red, and finally brown. Heat is evolved and the reaction is kept below 45°C by cooling in an ice bath. After 30 min, the mechanically stirred solution is heated by a heating mantle to 43°C (Note 2). This temperature is maintained for 12 hr. The reaction mixture becomes very thick during this time. After the mixture cools to ambient temperature, it is poured, with mixing, into 5 L of ether. The solid material is filtered through Celite. The Celite and solid material are removed and stirred with 4 L more of ether and refiltered through Celite. The combined ether washings are evaporated under reduced pressure (rotary evaporator) to a brown, sweet-smelling oil. The oil is transferred to a 1-L, single-necked flask equipped with an 18-in. Vigreux column (Note 3). Careful fractional distillation under water vacuum affords a forerun of approximately 16 g that boils at 70–78°C (22 mm). This fraction consists of impure diene that contains 4-methoxy-3-buten-2-one. The main fraction boils at 78–81°C (23 mm) and consists of 245 g of diene (Note 4) with approximately 5–10% of 4-methoxy-3-buten-2-one (Note 5). This material is suitable for most purposes. If higher purity is desired, the second fraction may be redistilled under reduced pressure through an 18-in. Vigreux column to afford 200 g (46%) of *trans*-1-methoxy-3-trimethylsiloxy-1,3-butadiene (Note 6).

C. *5β-Methoxycyclohexan-1-one-3β,4β-dicarboxylic acid anhydride*. To 3.00 g (0.174 mol) of 1-methoxy-3-trimethylsiloxy-1,3-butadiene at 0°C (ice bath) is added a total of 980 mg (0.01 mol) of freshly sublimed maleic anhydride in portions of 70–80 mg each over a period of 25 min. When the addition is complete, the ice bath is removed and the clear solution is stirred for 15 min at room temperature (Note 7). Three 5-mL portions of a solution of tetrahydrofuran (35 mL) and 0.1 *N* hydrochloric acid (15 mL) are added and the solution is stirred for 1 min. The remaining acid solution (35 mL) is added all at once and the resulting solution is poured into 100 mL of chloroform and treated with 25 mL of water. The organic layer is separated and the aqueous layer is extracted four times with 100-mL portions of chloroform. The extracts are combined and dried over anhydrous magnesium sulfate. The solvent is then removed under reduced pressure (Note 8) to provide 2.0 g of an oil which solidifies. Pentane (10 mL) is added to the oily solid and small portions of ether (total of 6 mL) are added; trituration is continued until the crystals become free flowing. The crystals are isolated by filtration and washed with 10 mL of 2 : 1 pentane/ether to afford 1.75 g (90%) of the anhydride, mp 87–89°C. Further recrystallization affords an analytically pure sample, mp 97–98°C.

2. Notes

1. The checkers dried all reagents by allowing them to stand over molecular sieves (Type 4A), with the exception of triethylamine, which was dried over potassium hydroxide pellets. The reaction flask was flame-dried. Because of

evolution of triethylamine hydrochloride that was encountered during addition of the chlorotrimethylsilane and in the workup, the reaction should be carried out in a hood.

2. The checkers did not cool the reaction, which allowed the temperature to rise to 55°C. After 30 min, the solution was heated overnight with a heating mantle. After 12 hr, the reaction temperature was 67°C.

3. A 16-in. Widmer column packed with 3-mm glass helices may also be used for the distillation.

4. *Caution! When the temperature begins to drop, heating must be stopped. Otherwise, on occasion, a violent reaction may occur with formation of a gas and rapid expansion of the residual tars.*

5. The checkers performed this distillation at a lower pressure (1–10 mm) through a similar Vigreux column to yield 225 g of clear liquid containing fluffy white material (triethylamine hydrochloride) that could not be removed by filtration. The purity of this distillate, determined by NMR, was 90 : 10 (diene : ketone). No forerun was obtained which contained more than 15% ketone.

6. The checkers carefully redistilled the impure distillate through the same previously mentioned distillation apparatus under water vacuum. Six fractions of various amounts were collected and combined to yield (1) a forerun of 64 g, bp 70–78°C (23–25 mm), purity 77 : 23 (diene : ketone); and (2) 145 g of pure diene, bp 78–81°C (23–25 mm). This second distillation seemed to remove the triethylamine hydrochloride from the product.

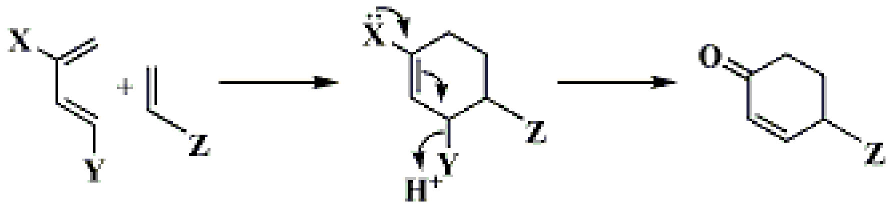
7. The reaction mixture is initially yellow, but turns colorless when the solution is warmed to room temperature.

8. When the chloroform extract is concentrated, care must be exercised to avoid overheating. The temperature should be no greater than 40°C.

3. Discussion

The procedure described here is a scale-up of the published method[2] for the preparation of 1-methoxy-3-trimethylsiloxy-1,3-butadiene (**2**) from readily available reagents. The preparation of this diene has recently been complemented by a report of the preparation of 1,3-bis(trimethysiloxy)-1,3-butadiene,[3] and earlier by a reported synthesis of a 1,3-dialkoxy-1,3-butadiene.[4]

The electron-donating nature of this diene confers high reactivity and orientational specificity in its reaction with unsymmetrical dienophiles.[5] This fact, coupled with the readily available conversion to the α,β-unsaturated ketone from the imparted functionality, makes 1-methoxy-3-trimethylsiloxy-1,3-butadiene (**2**) a potentially very valuable reagent in organic synthesis. The general reaction scheme is illustrated below:



The high reactivity of the diene is shown by reaction with notoriously unreactive dienophiles such as 1-carbomethoxycyclohexene, 2,5-dihydrobenzoic acid methyl ester,[6] and 2-methylcyclohex-2-en-1-one to give, after mild work-up, the corresponding α,β-unsaturated ketones in quite respectable yields.[5]

The Diels–Alder reaction with maleic anhydride is illustrative of the high reactivity and potential utility of this diene.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 38
- Org. Syn. 78, 152

References and Notes

1. Department of Chemistry, University of Pittsburgh, Pittsburgh, PA 15260. Current address of S.D.: Department of Chemistry, Yale University, New Haven, CT 06520.
2. Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc*. **1974**, *96*, 7807.
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

1,3-bis(trimethysiloxy)-1,3-butadiene

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether (60-29-7)

chloroform (67-66-3)

nitrogen (7727-37-9)

potassium hydroxide (1310-58-3)

zinc chloride (7646-85-7)

Pentane (109-66-0)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

maleic anhydride (108-31-6)

2-methylcyclohex-2-en-1-one (1121-18-2)

triethylamine (121-44-8)

Triethylamine hydrochloride (554-68-7)

4-methoxy-3-buten-2-one

CHLOROTRIMETHYLSILANE (75-77-4)

Silane, [(3-methoxy-1-methylene-2-propenyl)oxy]trimethyl-, 1-Methoxy-3-trimethylsiloxy-1,3-butadiene

1-carbomethoxycyclohexene

trans-1-METHOXY-3-TRIMETHYLSILOXY-1,3-BUTADIENE (59414-23-2)

5β-Methoxycyclohexan-1-one-3β,4β-dicarboxylic acid anhydride (87334-37-0)

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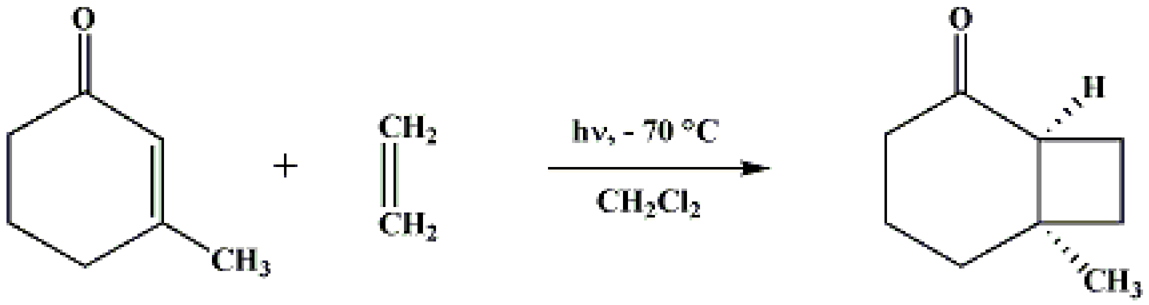
Organic Syntheses, CV 7, 315

PHOTOCYCLIZATION OF AN ENONE TO AN ALKENE: 6-METHYLBICYCLO[4.2.0]OCTAN-2-ONE

[Bicyclo[4.2.0]octan-2-one, 6-methyl-]



Submitted by R. L. Cargill[1], J. R. Dalton, G. H. Morton, and W. E. Caldwell[1].
Checked by Barry A. Wexler, Amos B. Smith III, and Carl R. Johnson.

1. Procedure

The irradiation apparatus (Note 1) is charged with a solution of 25.0 g (0.277 mol) of 3-methyl-2-cyclohexenone (Note 2) in reagent-grade dichloromethane (Note 3). A gas outlet tube to an efficient hood is placed in one 14/20 standard taper joint; in the other, there is a stopper that can be removed for periodic sampling. The cooling water is turned on (Note 4) and the apparatus is immersed in a dry-ice/2-propanol bath while the chilled solution is saturated with ethylene (Note 5). The lamp is inserted into the well and turned on (Note 6). Progress of the irradiation is conveniently followed by gas chromatography (Note 7). After about 8 hr, most of the starting material has reacted. At this time, the lamp is turned off and the apparatus removed from the cooling bath. The reaction mixture is degassed with a slow stream of nitrogen while it warms to room temperature, dried over magnesium sulfate, and concentrated with a rotary evaporator at a temperature below 30°C (Note 8). The product is isolated by distillation to afford 27–28 g (86–90%) of 6-methylbicyclo[4.2.0]octan-2-one, bp 62–65°C (3.5 mm) (Note 9) and (Note 10).

2. Notes

1. The apparatus is similar to one described earlier.[2] A triple-walled Dewar is constructed of Pyrex according to f.htmigure 1. For further discussion concerning this immersion well, contact Joel M. Babbitt, Glassblower, Department of Chemistry, University of South Carolina, Columbia, SC 29208. The evacuated jacket permits the safe use of circulating tap water as a lamp coolant even when irradiations are conducted in a dry ice bath. A further advantage is that three layers of Pyrex constitute an effective filter for light in the 280–300-nm region so that secondary photolysis of cycloadducts is not

usually observed. The irradiation flask is a cylindrical vessel of suitable volume fitted with a coarse, fritted disc for gas dispersion and a flanged lip. The light source is either a GE H1000-A36-15, Westinghouse H-36GV-1000, or equivalent lamp with the outer globe removed, used in conjunction with a GE 35-9627-6009 ballast. These lamps are available from the General Electric Company, Lamp Division, Charlotte, North Carolina.

Figure 1. Irradiation vessel.

Figure 1. Irradiation vessel.

2. This material can be purchased from Aldrich Chemical Company or prepared from Hagemann's ester.[3]

3. The volume of solution will vary depending on the exact volume of the apparatus, the temperature, and the miscibility of gaseous reactant in the solvent. The solution should completely surround the lamp, but should not overflow the vessel. The submitters used a volume of 1100 mL, and the checkers used 200 mL.

4. If the flow of cooling water is stopped while the apparatus is cold, the water may freeze and crack the immersion well. The vacuum jacket provides greater insurance against this problem than is available in the commercially available wells used with the usual 450 watt lamps.[2]

5. CP-grade ethylene (Matheson) was used without purification. A flow of ca. 100 mL/min of ethylene for 2–3 hr is adequate for saturation. Gas flow is continued throughout the irradiation in order to maintain a high concentration of ethylene and for stirring.

6. The lamp will not start if it is too cold or too hot. The practice of blowing nitrogen over the lamp to remove ozone is not recommended as this cools the lamp and decreases its output significantly, resulting in an unnecessarily long irradiation period.

7. The submitters used a Varian 1200 FID chromatograph with a 7% Carbowax 20 M on Chromosorb Q, 8-ft × 0.125-in. column, a carrier gas (N_2) flow rate of 40 mL/min; column, 160°C; injector, 220°C; and detector, 215°C. Retention times were 3-methyl-2-cyclohexenone, 4.2 min, and 6-methylbicyclo[4.2.0] octan-2-one, 3.9 min, respectively.

8. If the solvent is removed without care, a considerable amount of volatile product may be lost.

9. This material is contaminated with 10% of 3-methylcyclohexenone. Material of greater purity can be obtained by extending the time of irradiation, carrying out an efficient distillation of product, or decomposing starting material with potassium permanganate prior to distillation.

10. The product has the following spectral properties: IR (CCl_4) cm^{-1}: 1700; ^{1}H NMR (CCl_4) δ: 1.21 (s, 3 H, methyl), 1.9 (m, 11 H, all other protons); ^{13}C NMR (C_6D_6) δ (based on δ C_6D_6 128.00): 211.63, 51.34, 40.86, 39.45, 35.26, 31.20, 28.84; 21.45, 20.35; mass spectrum (*m/e*) 138.1041 (parent ion).

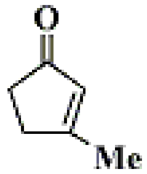
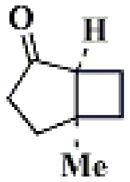
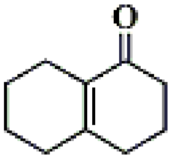
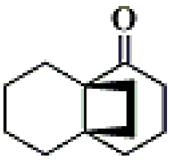
3. Discussion

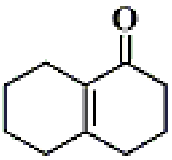
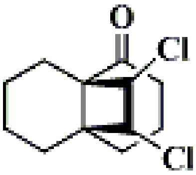
Although photochemical cycloadditions have gained acceptance in synthetic chemistry,[4] most such reactions are limited to a relatively small scale. The use of a 1000-W street lamp permits the irradiation of up to 1 mol of substrate in less time than 0.2 mol can be irradiated with the conventional 450-W lamps. Thus, under optimum conditions, the submitters were able to add ethylene to 3-methylcyclohexenone on a 20-g scale in 48 hr (80%) with a 450-W lamp; with the apparatus described here 94 g of this enone was condensed with ethylene in 8 hr (91%).

Some general points regarding photochemical cycloadditions deserve mention: (1) since the reaction is first-order in olefin, the concentration of olefin (especially gaseous olefins) is of critical importance; therefore, the cycloadditions are carried out at low temperature (in some cases, however, low temperature can be detrimental[5]); (2) since lamp output deteriorates with lamp age, the rates of otherwise identical cycloadditions are unlikely to be the same; therefore, it is of critical importance that the progress of each photochemical reaction be followed by some suitable means (GLC, IR, UV, NMR, etc); and (3) as long as all the incident light of appropriate wavelength is absorbed by the enone, the reaction proceeds at a rate independent of enone concentration; thus, the highest concentration of enone at which dimerization can be avoided is optimal.

Several examples of preparative cycloadditions are listed in Table I.

TABLE I
PREPARATIVE-SCALECYCLOADDITIONS

Entry	Enone	Weight (g)	Olefin	Time (hr)	Product(s)	Yield (%)	Ref.
1.		25	C_2H_4	12		90	6
2.		10	C_2H_4	6		71	7

3.		20	ClHC=CHCl	10		93[a]	8

[a]A mixture of cis and trans olefins was used; a mixture of diastereomeric products was obtained. Both olefins give similar mixtures.

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

potassium permanganate (7722-64-7)

nitrogen (7727-37-9)

ethylene (9002-88-4)

dichloromethane (75-09-2)

ozone (10028-15-6)

magnesium sulfate (7487-88-9)

3-methyl-2-cyclohexenone, 3-methylcyclohexenone

6-Methylbicyclo[4.2.0]octan-2-one, Bicyclo[4.2.0]octan-2-one, 6-methyl- (13404-66-5)

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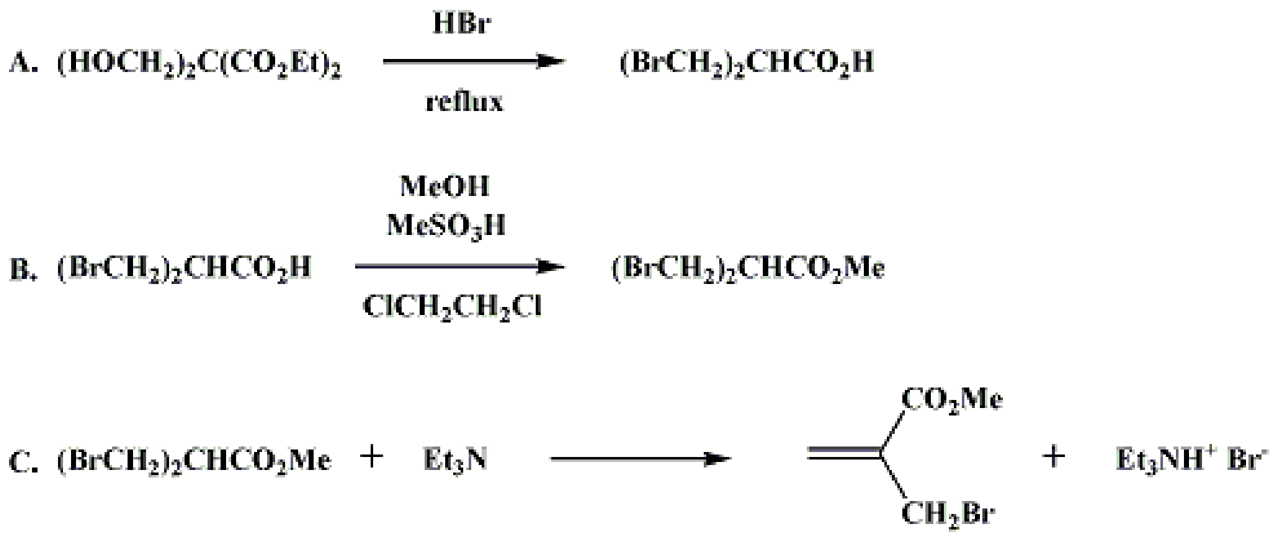
Organic Syntheses, *CV 7*, *319*

METHYL α-(BROMOMETHYL)ACRYLATE

[2-Propenoic acid, 2-(bromomethyl)-, methyl ester]



Submitted by John M. Cassady, Gary A. Howie, J. Michael Robinson, and Ioannis K. Stamos[1].
Checked by Paul R. West and Orville L. Chapman.

1. Procedure

Caution! Methyl α-(bromomethyl) acrylate is a potent vesicant and lachrymator and should be handled with care. All operations should be carried out in an efficient hood in order to avoid contact.

A. *β,β'-Dibromoisobutyric acid*. To a 5-L, single-necked flask, equipped with a heating mantle, 22-cm Vigreux distillation head, thermometer, 30-cm water-cooled condenser with adapter, and 1-L, ice-cooled receiving vessel (Note 1) is added 440 g (2.0 mol) of diethyl bis(hydroxymethyl)malonate (Note 2)[2] and (Note 3) and 3540 mL of concentrated aqueous hydrobromic acid (Note 4). Heating for 6 hr at vigorous reflux gives 2400 mL of aqueous distillate (Note 5). The undistilled concentrate is poured into a 3-L beaker, cooled overnight at −15°C (Note 6), and filtered through a 500-mL fritted-glass Büchner funnel using aspirator vacuum. After suction air drying for 6 hr, drying is continued for 6 days in a vacuum desiccator containing active Drierite and under 10 mm of initial vacuum (Note 7) to give 332 g (67.5%) of β,β'-dibromoisobutyric acid as a brown solid. Distillation of the filtrate to remove an additional 850 mL of aqueous hydrobromic acid (Note 8), followed by cooling and filtration, gives an additional 34.0 g (6.9%) of solid. Crude product, obtained in 74–85% yield (Note 9)[3], is suitable for use without further purification (Note 10).

B. *Methyl β,β'-dibromoisobutyrate*. In a 200-mL, round-bottomed flask fitted with a reflux condenser are placed 61.5 g (0.25 mol) of β,β'-dibromoisobutyric acid, 25 g (0.78 mol) of

commercial methanol, 75 mL of ethylene dichloride, and 0.2 mL of methanesulfonic acid (Note 11)[4] and (Note 12). The reaction mixture is heated under reflux for 24 hr. The solution is cooled to room temperature, diluted with about 200 mL of methylene chloride, and neutralized with dilute, cold sodium bicarbonate solution (Note 13). The organic layer is dried over anhydrous sodium sulfate and concentrated on a rotary evaporator to remove most of the methylene chloride. Fractional distillation of this residue under reduced pressure (the receiver is cooled with an ice–salt mixture) yields 48.8 g (75%) of product, bp 64–65°C (0.3 mm).[3,5,6]

C. *Methyl α-(bromomethyl)acrylate*. In a dry, 250-mL three-necked flask, equipped with a mechanical stirrer, reflux condenser, and an addition funnel, 20 g (0.077 mol) of methyl β,β'-dibromoisobutyrate (Note 14)[5,6] in 50 mL of anhydrous benzene (Note 15)[7] is stirred vigorously. Triethylamine (Note 16)[8] and (Note 17) (7.7 g, 0.076 mol) in 50 mL of benzene is introduced dropwise at a rate of about 3 mL per min. After the addition is complete the mixture is stirred for an additional 1 hr at room temperature, refluxed for 1 hr, and then cooled to 20°C. The reaction mixture is filtered with suction and the amine salt washed twice with 20 mL of benzene. The filtrate and washings are combined in a round-bottomed flask and concentrated on a rotary evaporator at 30–35°C to remove most of the benzene. The residue is transferred to a small distillation apparatus and fractionally distilled at reduced pressure using an oil bath at 50–55°C. The yield of ester collected at bp 35–37°C (1.3 mm) is 11.0 g (80%) (Note 18),(Note 19),(Note 20),(Note 21).

2. Notes

1. Cooling the receiving vessel greatly reduces loss of ethyl bromide.
2. Diethyl bis(hydroxymethyl)malonate was prepared up to an 8.0-mol scale by the method of Block.[2] After suction filtration to remove the drying agent, the dried diethyl ether extracts were concentrated directly on a Büchi rotary evaporator at aspirator vacuum using a bath temperature of 50°C; concentration was continued for ca. 2 hr after removal of the ether. The crude, oily diethyl bis(hydroxymethyl) malonate, obtained in 94–96% yield, solidified on standing and was suitable for use without further purification. The malonate can be stored at room temperature with no special precautions.
3. The checkers ran this reaction on a 20% scale [starting with 88 g (0.4 mol) of diethyl bis(hydroxymethyl)malonate]. At this scale, yields between 63 and 75% were realized.
4. Initial experiments used commercial 48% aqueous hydrobromic acid. In subsequent runs no decrease in yields was apparent when recovered distillate boiling at or above 110°C was substituted for the commercial acid.
5. Approximately 45 additional min of heating was required to reach distillation temperature. The first 780 mL (excluding ethyl bromide) of aqueous distillate boiled below 110°C and was discarded. The remaining distillate was recycled as described in (Note 4).
6. Cooling in a refrigerator freezing compartment is satisfactory. The beaker should be sealed (e.g., using Saran Wrap) to prevent escape of corrosive fumes.

7. After the solid was dried in the desiccator, weight reductions of up to 10% were observed.
8. Special care must be used toward the end of the distillation to avoid overheating caused by removal of too much solvent. Overheating can result in an intractable gummy residue.
9. Failure to distill the maximum amount of concentrated hydrobromic acid, higher crystallization temperatures, and/or washing with water may account for the lower (66%) reported[3] yield.
10. Storage at room temperature (under nitrogen or in a filled, sealed container) for periods in excess of 1 year resulted in no significant deterioration of the crude acid as judged by its suitability for use in step B. Preparation of acid was done on a 0.5–3.4-mol scale with no significant variation in yield.
11. These conditions are patterned after a general procedure for esterification reported by Clinton and Laskowski.[4]
12. The checkers ran this reaction on a 50% scale [starting with 30.75 g (0.125 mol) of β,β'-dibromoisobutyric acid] and obtained yields ranging from 66 to 67%.
13. A brown, emulsified layer, which separates on long standing, is formed between the organic and aqueous layers. This layer can also be taken up with an additional 200 mL of methylene chloride and dried with a sufficient amount of anhydrous sodium sulfate to recover the organic layer.
14. It is recommended that methyl β,β'-dibromoisobutyrate[5,6] that has been purified by fractional distillation be used, since the presence of acidic compounds reduces the yield and the presence of any hydroxyl function gives a product mixture that cannot be purified by simple distillation.
15. The preparation of anhydrous benzene has been described.[7]
16. Commercial triethylamine is conveniently purified by two distillations from a 2% solution of phenyl isocyanate.[8]
17. In a parallel experiment, ethyldiisopropylamine (9.82 g, purified as in (Note 16)) was mixed with a solution of 20 g of methyl β,β'-dibromoisobutyrate in 100 mL of dry benzene. The reaction mixture was stored at room temperature for 10 hr and gently refluxed for 1 hr under nitrogen in the dark. After workup and distillation the yield of the product was 80%.
18. Distillation at higher temperatures results in viscous residues with considerably reduced yields of the product. The receiver should be immersed in an acetone-dry ice bath in order to prevent loss of the product to the trap of the vacuum line.
19. The product is stable for long periods of time if kept under an inert atmosphere in the absence of light and in the refrigerator.
20. Ethyl α-(bromomethyl)acrylate is prepared similarly, bp 38–42°C (0.8 mm).
21. The checkers obtained a 76% yield.

3. Discussion

Although methyl and ethyl α-(bromomethyl)acrylate are used extensively as synthetic intermediates in the preparation of a variety of organic compounds,[9,10,11,12,13,14,15,16] many of biological importance, they are not commercially available and their preparation in good yield on a large scale is therefore of interest. The procedures outlined above

represent useful modifications of published literature routes to these compounds.

The procedure for the elimination of HBr from the dibromo ester is a modification of the method of Lawton and co-workers for sui generis generation of the methyl[5,9] or ethyl ester[10] during a reaction. Methyl α-(bromomethyl)acrylate has also been prepared by bromination of methyl methacrylate in 700°C steam[17] and by dehydrohalogenation with sodium acetate in acetic acid.[6] Ethyl α-(bromomethyl)acrylate has been prepared by dehydrohalogenation with the monosodium salt of ethylene glycol[3,18] and ethyl diisopropylamine.[11] The latter reaction was reported by Öhler et al. with no experimental details for the elimination reaction. The use of triethylamine as reported in this procedure appears to be the most efficient and convenient method for dehydrobromination to these acrylate esters.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

acetic acid (64-19-7)

Benzene (71-43-2)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

sodium acetate (127-09-3)

sodium bicarbonate (144-55-8)

HYDROBROMIC ACID (10035-10-6)

Ethyl bromide (74-96-4)

sodium sulfate (7757-82-6)

ethylene dichloride (107-06-2)

nitrogen (7727-37-9)

methylene chloride (75-09-2)

phenyl isocyanate (103-71-9)

triethylamine (121-44-8)

methanesulfonic acid (75-75-2)

Diethyl bis(hydroxymethyl)malonate (20605-01-0)

methyl methacrylate (80-62-6)

ethyldiisopropylamine, ethyl diisopropylamine (7087-68-5)

Ethyl α-(bromomethyl)acrylate (17435-72-2)

METHYL α-(BROMOMETHYL)ACRYLATE, 2-Propenoic acid, 2-(bromomethyl)-, methyl ester, Methyl α-(bromomethyl) acrylate, Methyl a-(bromomethyl)acrylate (4224-69-5)

β,β'-Dibromoisobutyric acid

Methyl β,β'-dibromoisobutyrate

monosodium salt of ethylene glycol

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Organic Syntheses, CV 7, 323

METHYL DIFORMYLACETATE

[2-Propenoic acid, 2-formyl-3-hydroxy-, methyl ester]

Submitted by C. R. Hutchinson, M. Nakane, H. Gollman, and P. L. Knutson[1].
Checked by David J. Wustrow and Andrew S. Kende.

1. Procedure

A. *Potassium monomethyl malonate*. Dimethyl malonate ((Note 1), 264.2 g, 2.0 mol) is dissolved in anhydrous methanol ((Note 2), 1150 mL) contained in a dry, 3-L, one-necked flask containing a large magnetic stirring bar and protected from atmospheric moisture with a calcium sulfate-filled drying tube. The solution is stirred magnetically and cooled to ice-water bath temperature. Potassium hydroxide pellets (112.2 g 2.0 mol) are added rapidly to the cold solution and the reaction mixture is allowed to warm to room temperature with stirring overnight. The colorless crystals of potassium monomethyl malonate that form are recovered by suction filtration through a Büchner funnel and washed with anhydrous diethyl ether. The combined filtrate and diethyl ether wash are concentrated at 30°C to a volume of ca. 750 mL on a rotary evaporator. The resulting crystalline precipitate is recovered as before by filtration and washing and combined with the first crop of crystals to give 220 g (71%) of potassium monomethyl malonate as fine colorless needles, mp 204–207°C. These crystals are dried under vacuum (0.1 mm) before use in the following reaction.

B. *Methyl diformylacetate*. Freshly distilled phosphorus oxychloride (612 g, 4 mol) is added dropwise with constant stirring at ambient temperature (Note 3) to dimethylformamide (1460 g) contained in a 3-L, three-necked flask equipped with a mechanical paddle stirrer, immersion thermometer, and a 500-mL pressure-equalizing addition funnel fitted with a calcium chloride-filled drying tube. The reaction mixture warms up and turns to a dark reddish-brown color during addition of the phosphorus oxychloride and formation of the Vilsmeier reagent [$(CH_3)_2N^+$=CHCl Cl^-]. The addition funnel is replaced with a 10-in. long West condenser (Note 4), and then the reaction mixture is cooled to 0°C by immersing the reaction flask in an ice-salt water bath. The cooling bath is removed and potassium monomethyl malonate (206 g, 1.32 mol) is added to the stirred reaction mixture in ten equal portions over a 30 min period (Note 3) and (Note 5), keeping the temperature of the mixture below 90°C. The dark-brown mixture then is stirred and heated on a water bath at 90°C for 4 hr. Gas (CO_2 plus HCl) evolves initially from the reaction on heating (Note 6). The thermometer is replaced with a glass

stopper, the condenser is fixed for distillation by addition of a distilling head and vacuum distillation receiver, and the reaction solvent is removed from the flask by distillation at ca. 2 mm on a steam bath (Note 7). The resulting dark-brown liquid is poured onto ice (4 kg, (Note 3)). A saturated aqueous solution of potassium carbonate (1.3 kg) is added slowly to the ice-cold crude reaction product with constant stirring until the pH of the mixture stabilizes at ca. 1 l. Considerable foaming and gas evolution (CO_2) occur during the addition of the base. The resulting basic solution is stirred magnetically at ambient temperature for 48 hr and then extracted with ethyl acetate in four 1-L portions. The organic phases are discarded, and the aqueous phase is saturated with potassium chloride (500 g) by stirring at ambient temperature until no more salt dissolves. This mixture is mixed with ice (1 kg), slowly acidified to pH 1 with ice-cold 12 *N* hydrochloric acid, and then thoroughly extracted with four 2-L portions of diethyl ether (Note 8). The combined cold ether extracts are washed with a saturated aqueous solution of potassium chloride (4 L) and dried over anhydrous sodium sulfate (500 g) for 1 hr. The solution is decanted from the desiccant, combined with a 500-mL diethyl ether wash of the desiccant, concentrated under reduced pressure to ca. 500 mL, and redried over anhydrous sodium sulfate. After removal of the desiccant by gravity filtration, the diethyl ether is removed by rotary evaporation at water aspirator pressure and 25°C. Fractional distillation of the resulting liquid residue at 2 mm with a N_2 bleed capillary through a Claisen head first gives a little dimethylformamide. When dimethylformamide ceases to distill (Note 9), the receiver is cooled in a dry ice–ethanol bath and the methyl diformylacetate distilled at 58–61°C to give 86–94 g (50–55%) of a colorless, solid distillate, which melts at about 10°C (Note 10) and (Note 11). Methyl diformylacetate prepared in this way is stable for at least 6 months if stored at –20°C.

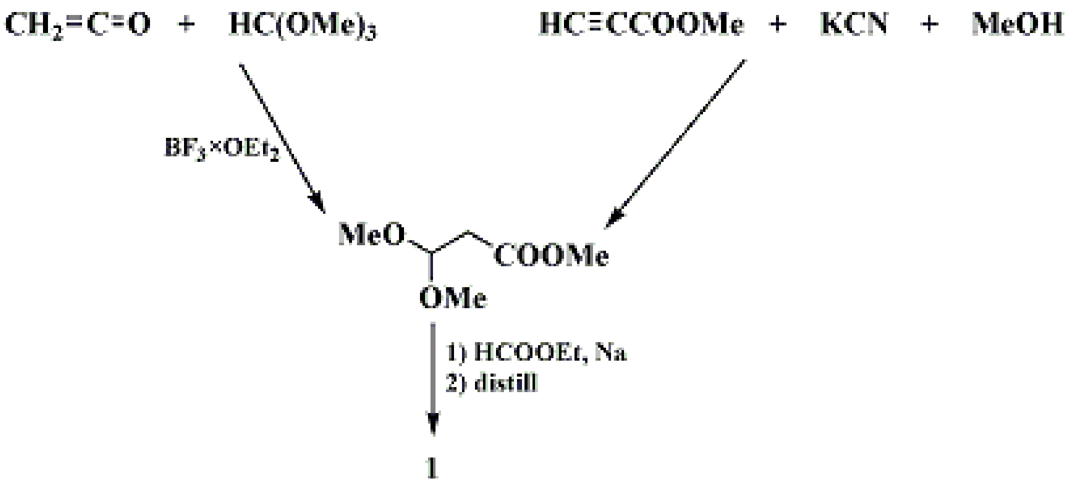
2. Notes

1. All reagents are used as received from commercial suppliers unless stated otherwise.
2. Reagent grade methanol is made anhydrous by refluxing over $Mg(OCH_3)_2$ according to the method of Vogel.[2]
3. All the following operations must be done in a hood.
4. The desiccant in the drying tube should be replaced with fresh calcium chloride and the drying tube fitted onto the top of the condenser.
5. The salt is added by replacing the condenser with a glass powder funnel, quickly pouring the crystalline solid through the funnel into the flask, and then replacing the powder funnel with the condenser.
6. The condenser can be cooled to prevent loss of solvent that is carried out of the reaction mixture by the escaping gases.
7. The volume of dimethylformamide distillate is ca. 1000 mL, and distillation is stopped when no more liquid distills from the reaction mixture.
8. The solvent extractions and washings should be done as rapidly as is possible since the crude methyl diformylacetate is not stable to small amounts of acid or base over long periods.
9. Dimethylformamide ceases to distill at a temperature less than 30°C.
10. Considerable product is lost if the receiver is not chilled to a low temperature.

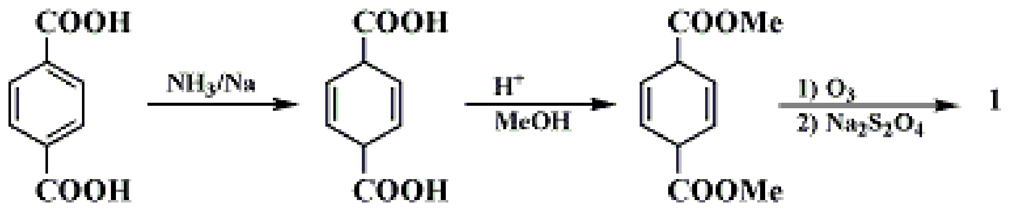
11. The submitters have obtained the same yield when this procedure was done on scales from 0.5 to 1.3 mol.

3. Discussion

Methyl diformylacetate can be prepared from ketene and trimethyl orthoformate,[3] or methyl propiolate and methanol,[4] via formylation of the methyl 3,3-dimethoxypropanoate intermediate (equation 1). The present procedure is better because it avoids the tedious preparation of ketene,[3] affords a superior yield,[3] or is much cheaper[4] than the other two methods. A fourth method[5] for its preparation (equation 2) should permit the preparation of any ester of diformylacetic acid that is stable to Birch reduction and ozonolysis conditions. However, this method is not convenient for use above a 0.1-mol scale, nor recommended for reasons of safety because of the amount of an O_2/O_3, mixture needed at larger scales.



(1)



(2)

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 254

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2536.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

$Mg(OCH_3)_2$

calcium chloride (10043-52-4)

potassium carbonate (584-08-7)

hydrochloric acid, HCl (7647-01-0)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

sodium sulfate (7757-82-6)

CO_2 (124-38-9)

Phosphorus Oxychloride (21295-50-1)

potassium hydroxide pellets (1310-58-3)

potassium chloride (7447-40-7)

dimethylformamide (68-12-2)

methyl propiolate (922-67-8)

trimethyl orthoformate (149-73-5)

dimethyl malonate (108-59-8)

Methyl diformylacetate

2-Propenoic acid, 2-formyl-3-hydroxy-, methyl ester (39947-70-1)

potassium monomethyl malonate (38330-80-2)

methyl 3,3-dimethoxypropanoate (7424-91-1)

diformylacetic acid

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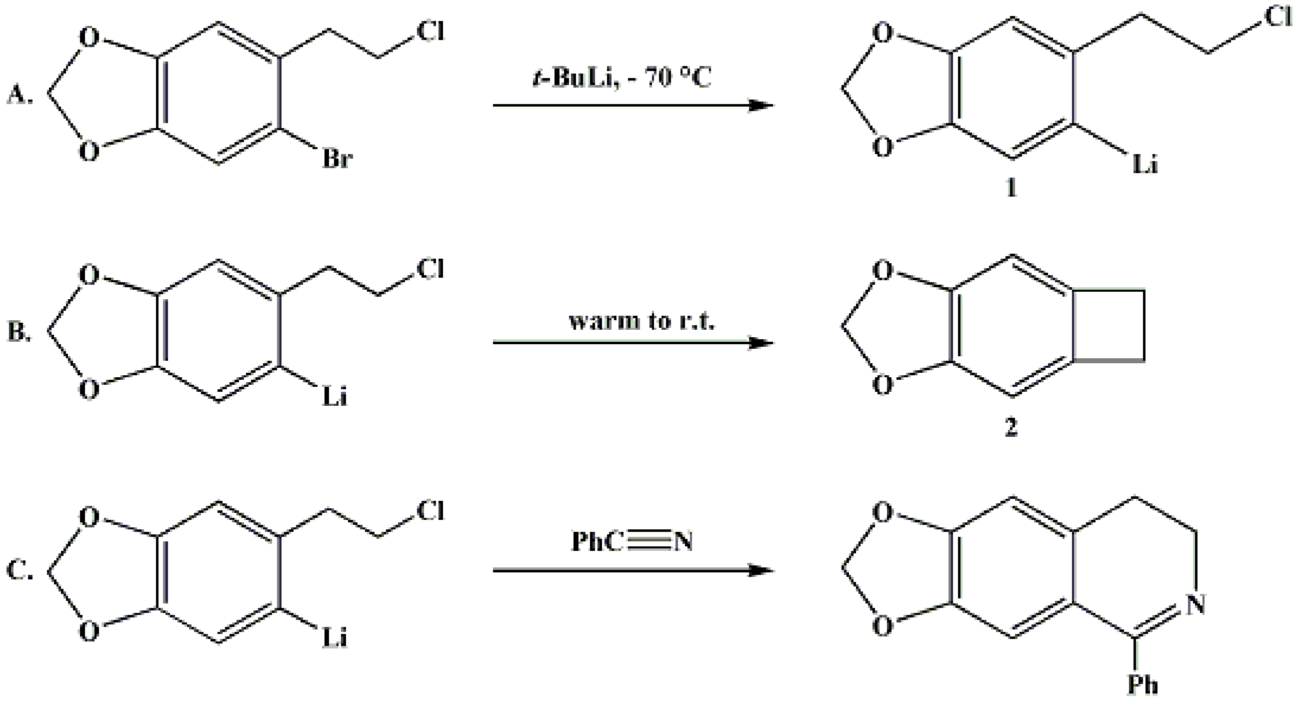
SELECTIVE HALOGEN-LITHIUM EXCHANGE REACTIONS OF 2-(2'-HALOPHENYL)ETHYL HALIDES: SYNTHESIS OF 4,5-METHYLENEDIOXYBENZOCYCLOBUTENE AND 1-PHENYL-3,4-DIHYDRO-6,7-METHYLENEDIOXYISOQUINOLINE

[Cyclobuta[*f*]-1,3-benzodioxole, 5,6-dihydro- and 1,3-dioxolo [4,5-*g*] isoquinoline, 7,8-dihydro-5-phenyl-]



Submitted by Dennis J. Jakiela, Paul Helquist[1], and Lawrence D. Jones[2].
Checked by Neville D. Emslie and Ian Fleming.

1. Procedure

A. *2-(2'-Lithio-4',5'-methylenedioxyphenyl)ethyl chloride*. A 500-mL, three-necked, round-bottomed flask, equipped with a magnetic stirring bar, 50-mL pressure-equalizing addition funnel (Note 1), low-temperature thermometer, and a three-way stopcock having a vertically oriented tube capped with a rubber septum and a horizontal tube connected to a source of dry nitrogen and vacuum, is charged with 10.0 g (37.9 mmol) of 2-(2'-bromo-4',5'-methylenedioxyphenyl)ethyl chloride (Note 2). The assembled apparatus is evacuated and refilled with nitrogen three times. Freshly distilled diethyl ether (200 mL) (Note 3) is added to the flask by means of a double-ended needle (0.5 m in length) inserted through the vertical tube of the stopcock while a slight vacuum is applied to the apparatus. A slightly positive pressure of nitrogen is then maintained in the apparatus throughout the course of the reaction. The solution is cooled in a dry ice–acetone bath (Note 4). The glass jacket (or styrofoam cup) (Note 1), which surrounds the addition funnel, is filled with powdered dry ice, and 33 mL of a 2.3 *M* solution of *tert*-butyllithium (76 mmol) in pentane (Note 5) is added to the addition funnel by means of a syringe. After 10 min the lithium reagent is added dropwise to the flask over a period of 1 hr, while the temperature of the reaction mixture is maintained below −60°C. The solution of the resulting aryllithium reagent **1** is then used in either of the two reactions described below.

B. *4,5-Methylenedioxybenzocyclobutene*. The reaction mixture from Step A is simply allowed to warm to room temperature over a period of several hours, during which time a white precipitate forms. After 18 hr, 100 mL of water is slowly added and the mixture is transferred to a 500-mL separatory funnel. As the mixture is shaken, the solid dissolves in the aqueous phase, which becomes light brown. The aqueous layer is extracted with two 75-mL portions of diethyl ether, and the combined organic layers are reduced in volume to 150 mL by rotary evaporation, washed with 75 mL of water and then 75 mL of saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered, and concentrated to dryness by rotary evaporation to give 5.6 g of pale-yellow solid (Note 6). This crude product is transferred to a large, dry ice-cooled sublimation apparatus (Note 7) and sublimed over a 6-hr period at 35°C (0.07 mm), at which time a dark-brown oil remains in the bottom of the apparatus. The vacuum is released by filling the apparatus with nitrogen, and the cooled portion of the apparatus is allowed to warm to room temperature. Pure 4,5-methylenedioxybenzocyclobutene, **2** (5.1–5.2 g, 91–93%) is obtained as colorless crystals, mp 60–62°C (Note 8).

C. *1-Phenyl-3,4-dihydro-6,7-methylenedioxyisoquinoline*. The reaction mixture containing the aryllithium intermediate is stirred for 15 min (internal temperature –65 to –68°C), and then 4.3 mL (42 mmol) of distilled benzonitrile is added quickly. The mixture is allowed to warm gradually to room temperature and the stirring is continued overnight. The yellow solution (Note 9) is diluted with 25 mL of ether, the mixture is poured into a 1-L separatory funnel, and the reaction flask is rinsed with an additional 75 mL of ether. The combined ether solutions are washed with 150 mL of water and then extracted with three 75-mL portions of 10% (w / w) hydrochloric acid. The combined acid extracts are rendered basic by the addition of 100 mL of 20% (w / w) aqueous sodium hydroxide solution, and the resulting milky white mixture is extracted with three 75-mL portions of dichloromethane. The combined organic extracts are washed with 50 mL of water and 50 mL of saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated to dryness by rotary evaporation, to give 8.96 g (94% crude yield) of orange-tan solid. This material is purified by recrystallization from ethyl acetate : acetone 2 : 1 (v : v) to give a first crop (6.8 g), and by flash chromatography[3] of the residue from the mother liquor, using 150 g of 230–400-mesh silica gel (Merck), a 40-mm diameter column, and elution with 10 : l (v : v) ethyl acetate : methanol. A fast-moving orange band and a slower moving lemon–yellow band can be seen clearly on the column. The lemon-yellow band is collected from the column and evaporation gives a second crop (1.4 g) of comparably pure material. The total yield of the pale-yellow isoquinoline is 8.2 g (86%), mp 135–137°C (Note 10).

2. Notes

1. The checkers used a home-made, glass-jacketed funnel sealed with a rubber septum. The submitters cut one side and part of the bottom of a styrofoam cup and held this in place with tape around the lower part of the addition funnel.
2. This starting material is prepared in three steps from commercially available (from Research Organic/Inorganic Chemical Corp., Belleville, NJ) 3,4-methylenedioxyphenylacetic acid according to well-established procedures that have been applied to similar compounds.[4 5 6 7 8 9] As an alternative starting material that could be used in a closely related fashion, 3,4-methylenedioxyphenylacetonitrile is available from Aldrich Chemical Company, Inc. First, 16.0 g (88.8 mmol) of the acid, recrystallized from chloroform, is dissolved in 50 mL of tetrahydrofuran, and the solution is added to a suspension of 5.98 g (158 mmol) of lithium aluminum hydride powder in 225 mL of distilled diethyl ether (Note 3) at 0°C. *(Caution: Lithium aluminum hydride is very sensitive to mechanical shock and very reactive toward moisture and other protic substances; its dust is very irritating to skin and mucous membranes.*

It should not be allowed to come into contact with metallic species of apparatus, including metal spatulas, because of the potential danger of metal ion-promoted detonation.) The mixture is stirred at 25°C for 16 hr and is then quenched[10] by the careful, dropwise addition of 6 mL of 15% aqueous sodium hydroxide, and finally 18 mL of water. *(Caution: The reaction of excess lithium aluminum hydride with water is very exothermic and produces a large volume of hydrogen gas.)* The resulting mixture is stirred for 1 hr and is then subjected to vacuum filtration. The white solid that is retained is washed with three 50-mL portions of diethyl ether, and the combined filtrates are concentrated by rotary evaporation to give 13.1 g (89%) of 2-(3',4'-methylenedioxyphenyl)ethanol as a clear yellow oil, bp 136–140°C (0.003 mm). Next, 12.7 g (76.5 mmol) of this compound and 7.4 mL (91.5 mmol) of pyridine are dissolved in 200 mL of dichloromethane at 0°C, and 4.3 mL (83.9 mmol) of neat bromine is added to the solution over a 4-min period. After the solution has been stirred at 25°C for 16 hr, it is washed with three 50-mL portions of 2 *N* hydrochloric acid, two 50-mL portions of saturated aqueous sodium sulfite, two 50-mL portions of water, and 50 mL of saturated aqueous sodium chloride. The organic layer is then dried over anhydrous magnesium sulfate and concentrated by rotary evaporation to give 18.6 g (99.5%) of yellow solid. Recrystallization from a mixture of 160 mL of hexane and 60 mL of ethyl acetate gives 14.6 g (78%) of 2-(2'-bromo-4',5'-methylenedioxyphenyl)ethanol as light yellow needles, mp 93–94°C. Finally, 9.95 mL (123 mmol) of distilled pyridine and 8.75 mL (120 mmol) of distilled thionyl chloride are added separately to a solution of 14.4 g (58.8 mmol) of the preceding product and 180 mL of chloroform at 25°C. The mixture is heated at reflux for 18 hr, cooled to 25°C, washed with 40 mL *N* hydrochloric acid, 40 mL of 5% aqueous sodium carbonate, two 40-mL portions of water, and 40 mL of saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and concentrated by rotary evaporation to give 14.0 g (90%) of brown crystals. Distillation gives 13.0 g (84%) of an oil (bp 130–134°C at 0.006 mm), which solidifies to give the final product as colorless crystals: ^{1}H-NMR ($CDCl_3$) δ: 3.08 (t, 2 H, J = 6.8), 3.67 (t, 2 H, J = 6.8), 5.95 (s, 2 H), 6.74 (s, 1 H), and 6.98 (s, 1 H); mp 47.0–47.5°C (corrected).

3. Commercially available anhydrous diethyl ether is distilled under nitrogen from a solution of the sodium benzophenone radical anion generated by treating a solution of 10 g of benzophenone and 1 L of ether with 10 g of sodium ribbon until a dark-blue or purple color persists.

4. Although the dry ice–acetone bath itself attains a temperature of −78°C, the lowest temperature achieved by the solution within the flask is only −68°C.

5. *Caution: tert-Butyllithium is pyrophoric in air; excess quantities of the reagent in the syringe should be discarded very carefully.* The checkers used the reagent available from Aldrich Chemical Company Ltd., England and standardized it by double titration with ethylene dibromide and hydrochloric acid.[11]

6. The submitters also ran the reaction on smaller scales using from 0.5 to 5.0 g of starting material and regularly obtained a crude yield of 98–105% at this stage.

7. The sublimation apparatus should have a least a 1-cm separation between the upper surface of the crude solid to be sublimed and the bottom of the cooling surface in order to avoid splattering of the oily residue onto the purified product near the end of the sublimation procedure.

8. The product showed the following spectral properties: ^{1}H NMR ($CHCl_3$) δ: 3.00 (s, 4 H), 5.75 (s, 2 H), and 6.50 (s, 2 H).

9. At this stage, the submitters had a brick-red reaction mixture that became yellow on dilution with ether.

10. The product showed the following spectral properties: ^{1}H-NMR ($CDCl_3$) δ: 2.67 (t, 2 H, J = 7.5), 3.73 (t, 2 H, J = 7.5), 5.83 (s, 2 H), 6.63 (s, 2 H), and 7.37 (m, 5 H).

3. Discussion

The halogen–metal exchange reaction was pioneered by Gilman and coworkers,[12] who established that substituted aryl bromides would exchange efficiently with butyllithium and that the reaction was of synthetic value provided the substituent was not reactive toward alkyl- or aryllithium reagents. More recently, Parham[8,13 14 15] and others[9,16 17 18 19 20 21 22] further defined the scope and limitations of this reaction by demonstrating that haloarenes substituted with electron-withdrawing (CO_2H, CN, CO_2R) or electron-donating [OR, OCH_2O, $(\text{-}CH_2\text{-})_nX$, where X = Br, Cl] functional groups would selectively exchange with alkyllithium reagents at low temperature. While a detailed mechanistic evaluation is not within the scope of this discussion, the halogen–metal exchange reaction has been shown to be reversible and rapid at −75°C, and in the exchange of alkyllithium with a haloarene, the equilibrium reaction favors formation of the lithioarene.[12,23,24]

As exemplified in the present procedure, the reaction has been optimized and extended in scope; it affords functionalized benzocyclobutenes as well as substituted isoquinolines in high yields. Benzocyclobutenes have been used as intermediates in the synthesis of many naturally occurring alkaloids,[25] steroids,[26 27 28 29 30] polycyclic terpenoids,[31] and anthracycline antibiotics.[32] The traditional routes leading to the preparation of benzocyclobutenes have been reviewed[33] and have involved (1) Cava's cyclization of *o*-quinodimethane intermediates (via reaction of sodium iodide with α,α,α',α'-tetrabromo-*o*-xylene) (2) thermal extrusion of sulfur dioxide from 1,3-dihydroisothianaphthene 2,2-dioxide, (3) dehydrogenation of the Diels–Alder adducts of 1,4-butadienes and cyclobutenes, and (4) Wolff rearrangement of α-diazoindanones. More recent methods include (1) thermal rearrangement of *p*-tolylcarbene,[34] (2) thermal decomposition of 3-isochromanones,[25] and (3) cobalt-catalyzed cyclizations of acetylenic compounds.[35] Many of these methods for synthesizing functionalized benzocyclobutenes involve (a) multistep routes, (b) unusual or relatively unavailable starting materials, (c) low overall yields, or (d) special apparatus. The method of halogen–metal exchange demonstrates a high degree of selectivity for formulation of the lithioarene intermediate, is broad in scope without loss of procedural simplicity, and provides a high-yield route to benzocyclobutenes of general synthetic utility by direct cyclization of readily available 2-(2'-lithiophenyl)ethyl chlorides.[8,9,17]

The lithioarene intermediate has also been shown to be of use in the synthesis of the isoquinoline ring system. This ring system is common to a variety of natural products that possess useful physiological activity. Several methods have been developed for the synthesis of isoquinolines; the most commonly used routes are the Bischler–Napieralski and the Pictet–Spengler reactions.[36 37 38 39 40,41 42 43 44] These methods involve electrophilic, aromatic substitution in the key ring-forming steps with the limitation that best results are obtained only when the aromatic ring bears electron-donating substituents. The present method permits use of substrates either with or without electron-donating groups on the aromatic nucleus since generation of the lithioarene has been shown to be relatively independent of the nature of the substituents.[13,d]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

2-(2'-Lithio-4',5'-methylenedioxyphenyl)ethyl chloride

2-(2'-bromo-4',5'-methylenedioxyphenyl)ethyl chloride

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

hydrogen (1333-74-0)

benzonitrile (100-47-0)

sodium sulfite (7757-83-7)

sodium hydroxide (1310-73-2)

thionyl chloride (7719-09-7)

chloroform (67-66-3)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

bromine (7726-95-6)

sulfur dioxide (7446-09-5)

nitrogen (7727-37-9)

acetone (67-64-1)

pyridine (110-86-1)

Benzophenone (119-61-9)

sodium ribbon (13966-32-0)

ethylene dibromide (106-93-4)

sodium iodide (7681-82-5)

Pentane (109-66-0)

dichloromethane (75-09-2)

lithium (7439-93-2)

magnesium sulfate (7487-88-9)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride, lithium aluminum hydride powder (16853-85-3)

hexane (110-54-3)

isoquinoline (119-65-3)

4,5-Methylenedioxybenzocyclobutene

1-Phenyl-3,4-dihydro-6,7-methylenedioxyisoquinoline, 1,3-dioxolo [4,5-g]isoquinoline, 7,8-dihydro-

5-phenyl- (55507-10-3)

3,4-methylenedioxyphenylacetic acid (2861-28-1)

3,4-methylenedioxyphenylacetonitrile (4439-02-5)

tert-Butyllithium (594-19-4)

1,3-dihydroisothianaphthene 2,2-dioxide

Cyclobuta[f]-1,3-benzodioxole, 5,6-dihydro- (61099-23-8)

o-quinodimethane

p-tolylcarbene

α,α,α',α'-tetrabromo-o-xylene (13209-15-9)

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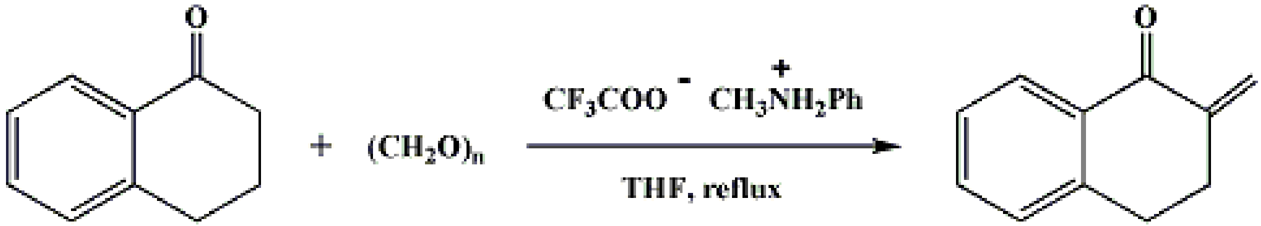
Organic Syntheses, CV 7, 332

METHYLENE KETONES AND ALDEHYDES BY SIMPLE, DIRECT METHYLENE TRANSFER: 2-METHYLENE-1-OXO-1,2,3,4-TETRAHYDRONAPHTHALENE

[1(2*H*)-Naphthalenone, 3,4-dihydro-2-methylene-]



Submitted by Jean-Louis Gras[1]
Checked by Kerry J. Gombatz and George Büchi.

1. Procedure

A 250-mL flask equipped with a reflux condenser is charged with 6.75 g (0.225 mol) of paraformaldehyde (Note 1) and 16.57 g (0.075 mol) of *N*-methylanilinium trifluoroacetate (Note 2). A solution of 7.30 g (0.05 mol) of α-tetralone (Note 3) in 50 mL of dry tetrahydrofuran (Note 4) is added at room temperature. The *N*-methylanilinium trifluoroacetate dissolves, and the magnetically stirred mixture is refluxed for 4 hr under a nitrogen atmosphere (Note 5). During this time a red color develops and the paraformaldehyde dissolves after 2 hr. After 4 hr the heating oil bath is removed and the red solution allowed to cool for 10 min. Diethyl ether (100 mL) is gradually added under efficient magnetic stirring, which induces the separation of a red gum. The ethereal solution is decanted from the red gum into a separatory funnel and washed with 50 mL of half-saturated sodium bicarbonate solution. The red gum is triturated with 50 mL of diethyl ether, and the resulting ethereal solution is then used to extract the washing water (Note 6). The combined organic layers are dried over magnesium sulfate. Filtration and concentration of the extract, first on a rotary evaporator then under high vacuum, afford 8.05–8.6 g of a heavy red oil (Note 7). Trituration of this oil with 70 mL of diethyl ether precipitates impurities and causes some polymerization. Filtration through Celite and concentration under high vacuum give 6.8–7.2 g (86–91%) of material that solidifies in a freezer (Note 8). Further purification by column chromatography over silica gel affords analytically pure material (mp 46–46.5°C) but lowers the yield to 70–82%.

2. Notes

1. Paraformaldehyde is sometimes sold commercially under the label "polyoxymethylene," and commercial polyoxymethylene (Prolabo—France) was used.

2. This crystalline white salt can be obtained by adding dropwise 1 mol of commercial trifluoroacetic acid (Fluka AG) to a stirred solution of 1 mol of commercial *N*-methylaniline (Fluka AG) in 1 L of dry diethyl ether in a nitrogen atmosphere with cooling in an ice bath. After addition the solution is stirred magnetically for 1 hr. The white precipitate that forms is filtered, washed with 100 mL of pentane, and dried overnight in a desiccator under high vacuum. The salt (195 g, 88%) thus obtained had mp 66.5°C.
3. Commercial α-tetralone, 95% pure, was purchased from Fluka AG and used without purification.
4. Tetrahydrofuran was distilled from the ketyl prepared from benzophenone and sodium, but the reaction does not suffer from moisture. Dioxane can also be used, but the iminium salt polymerizes rapidly at the reflux temperature of this solvent (101°C). To avoid polymerization the *N*-methylanilinium trifluoroacetate should be added in portions to the reaction mixture.
5. The reaction can be monitored by TLC. The α-methylene ketones exhibit higher R_f values than starting material when eluted in a diethyl ether-pentane (1 : 1) solvent system.
6. Workup and isolation should be completed in minimum time to avoid polymerization of the product. The heavy red gum thus obtained is soluble in methylene chloride and contains some β-methylene-α-tetralone.
7. A TLC analysis reveals a major component accompanied by two minor, more polar impurities. Because of the relative instability of α-methylene carbonyl compounds, isolation of these substances is associated with dimerization or polymerization. This crude material exhibits satisfactory NMR and IR data and can be used as such for many synthetic purposes.
8. The checkers found that storage of this material at room temperature results in the total conversion to polymer in less than 12 hr. The stability of the product is greatly increased if it is stored at temperatures below –5°C. The spectral properties are as follows: IR (CCl_4) cm^{-1}: 3065, 3030, 1680, 1620, 1604, 918; ^{1}H NMR (CCl_4) δ: 2.9 (singlet, 4), 5.37 (thin multiplet, 1), 6.17 (thin multiplet, 1), 7.3 (multiplet, 3), 8.07 (multiplet, 1).

3. Discussion

The procedure described herein demonstrates a general synthetic method to form α-methylene ketones by direct methylene transfer. A number of methods have been previously described and reviewed.[2,3] The advantages of direct methylene transfer for the formation of α-methylene ketones are the aprotic, nearly neutral conditions utilized. Although the reaction is not regiospecific, it is highly sensitive to steric hindrance, and transfer occurs at the less hindered site of unsymmetrical ketones. The reaction has been applied to cyclic and acyclic ketones[4] and extended to the synthesis of vinyl ketones[5] and α-methylenealdehydes. It is not applicable to γ- or δ-lactones, or strained cyclic ketones such as norcamphor or cyclobutanone. With cyclohexanone, cyclopentanone,[6] or aldehydes as substrates, preformation of the iminium intermediate

is recommended prior to the addition of the carbonyl compound. This can be achieved by heating the reagents to reflux in tetrahydrofuran for 20 min, followed by the addition of the carbonyl compound at reflux temperature or lower, if necessary. When higher reflux temperatures are required, dioxane can be used as a solvent. Addition in portions of *N*-methylanilinium trifluoroacetate to the reaction mixture minimizes polymerization of the iminium intermediate. In some cases, large-scale experiments may suffer from polymerization; it is recommended that the reaction be quenched before completion.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

polyoxymethylene

diethyl ether (60-29-7)

sodium bicarbonate (144-55-8)

Cyclohexanone (108-94-1)

nitrogen (7727-37-9)

Benzophenone (119-61-9)

sodium (13966-32-0)

Cyclopentanone (120-92-3)

Pentane (109-66-0)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

dioxane (5703-46-8)

methylene (2465-56-7)

N-Methylaniline (100-61-8)

Tetrahydrofuran (109-99-9)

α-Tetralone (529-34-0)

trifluoroacetic acid (76-05-1)

Cyclobutanone (1191-95-3)

Norcamphor (497-38-1)

diethyl ether-pentane

2-Methylene-1-oxo-1,2,3,4-tetrahydronaphthalene, β-methylene-α-tetralone, 1(2H)-Naphthalenone, 3,4-dihydro-2-methylene- (13203-73-1)

N-methylanilinium trifluoroacetate

paraformaldehyde (30525-89-4)

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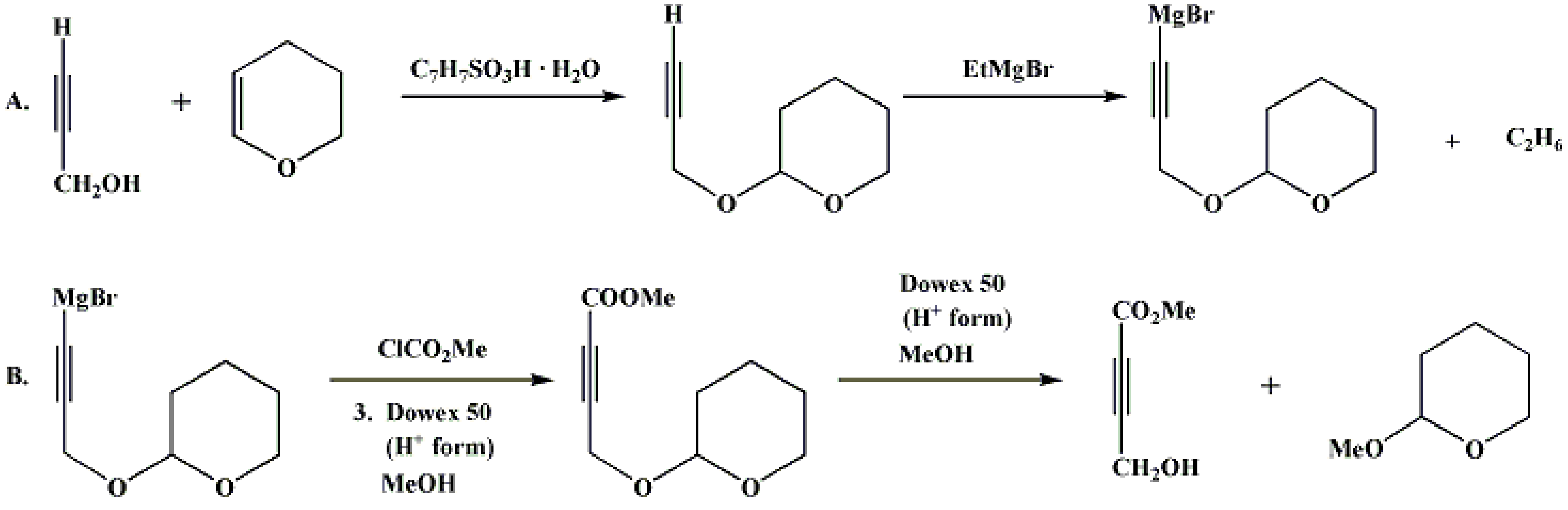
Organic Syntheses, CV 7, 334

METHYL 4-HYDROXY-2-BUTYNOATE

[2-Butynoic acid, 4-hydroxy-, methyl ester]



Submitted by R. A. Earl[1] and L. B. Townsend[2].
Checked by G. Saucy and G. Weber.

1. Procedure

Caution! Acetylenic compounds are potentially explosive and methyl 4-hydroxy-2-butynoate is a potent vesicant (Note 1).

A. *Tetrahydropyranyl derivative of propargyl alcohol* [*tetrahydro-2-(2-propynyloxy)-2H-pyran*]. Two crystals (ca. 10 mg) of *p*-toluenesulfonic acid monohydrate are added to 268 g (291.3 mL, 3.2 mol) of warm (60°C) dihydropyran (Note 2) in a 1-L, three-necked, round-bottomed flask equipped with a magnetic stirring bar, a thermometer, a dropping funnel containing 168 g (174.5 mL, 3.0 mol) of propargyl alcohol (Note 2) and a reflux condenser fitted with a drying tube. Stirring is started, and the propargyl alcohol is added (Note 3) as a thin stream during a period of ca. 30 min. The reaction is mildly exothermic, and the temperature is maintained at 60–65°C by

controlling the rate of addition of the propargyl alcohol and by occasional external cooling with an ice bath. After the addition is completed, the temperature is monitored for another 30 min; slight cooling is sometimes necessary to keep the temperature in the range of 60–65°C. The reaction mixture is stirred for a total of 1.5 hr after the addition is completed, and then 0.5 g of powdered sodium bicarbonate is added and the mixture stirred for another hour. The mixture is then gravity-filtered into a 1-L, round-bottomed flask. The reaction mixture is distilled through a 45-cm Vigreux column under reduced pressure (Note 15). A small forerun (ca. 40 mL) with a bp of 45°C (15–20 mm) is followed by the product, bp 47–50°C (3.5–5 mm), 330–355 g (78–92%) (Note 15); n_D^{22} 1.4559 (Note 16); ^{1}H NMR (90 MHz, neat) δ: 1.18–1.93 (br m, 6, $H_{2',2''}$, $H_{3',3''}$, $H_{4',4''}$); 2.47 (t, 1, *J* = 2, C□C-*H*), 3.17–3.84 (m, 2, $H_{5',5''}$), 4.03 (d, 2, *J* = 2, C□C-CH_2O), 4.63 (s, 1, H_1); IR (neat) cm^{-1}: 3300 (C□C-*H*), 2117 (C□C stretch).

B. *Methyl 4-hydroxy-2-butynoate*. One mole of ethylmagnesium bromide (Note 4) in diethyl ether is poured into a dry (Note 5) 2-L, three-necked, round-bottomed flask fitted with a mechanical stirrer and a glass stirrer bearing (Note 6), a dropping funnel fitted with a nitrogen-inlet tube, and an efficient condenser fitted with a drying tube. Stirring is started, and a solution of 140 g (1.0 mol, 141 mL) of the tetrahydropyranyl derivative of propargyl alcohol in 1-L of dry (Note 7) tetrahydrofuran is added during ca. 30 min (Note 8). Stirring is continued for an additional 1.5 hr, during which time a dry 3-L, three-necked flask is fitted with a mechanical stirrer, immersion thermometer, and dropping funnel. The 3-L flask is charged with a solution of 104 g (1.10 mol, 85.4 mL) of methyl chloroformate (Note 2) in 250 mL of tetrahydrofuran and the contents stirred and cooled to −20°C with a dry ice-acetone bath. Under gentle nitrogen pressure the acetylenic Grignard reagent is transferred portionwise through a □-in. polypropylene tube to the dropping funnel attached to the 3-L, three-necked flask (Note 9). The acetylenic Grignard reagent is then added dropwise during 1.5 hr to the well-stirred solution of methyl chloroformate in tetrahydrofuran while the temperature is maintained at −15 to −20°C by external cooling. After the addition is completed, the light-brown reaction mixture is stirred another 30 min at −15°C, followed by another 1.5 hr at ice temperature. The reaction mixture is then stored without stirring for 12 hr at +3°C, during which time the remaining magnesium salts separate from solution. The salts are removed by filtration (Note 10) and washed with three 150-mL portions of cold (0°C), dry toluene. The supernatant and washings are combined and concentrated (Note 11) to ca. 500-mL volume. The dark-brown solution is then washed five times with 100-mL portions of saturated brine followed by drying over anhydrous sodium sulfate. The solution is concentrated to remove the toluene and then dissolved (Note 12) in 1 L of anhydrous methanol; 25 mL of Dowex 50-X4 cation resin (H^+ form, prewashed with anhydrous methanol) is then added and the mixture stirred for 1.5 hr at 25°C. The ion-exchange resin is removed by filtration through a sintered-glass filter and is then washed with two 50-mL portions of anhydrous methanol. Solvent and 2-methoxytetrahydropyran are removed by concentration using a water aspirator and then an oil pump at 0.5-mm pressure. The residue from the concentration is then treated a second time (Note 13) with 1 L of anhydrous methanol and 25 mL of Dowex 50, followed by concentration as before. The residue is then distilled through a Claisen head to give methyl 4-hydroxy-2-butynoate (Note 14), 69–74 g (60–65%), by 66–69°C/0.2 mm, n_D^{22} 1.4684 (Note 17); ^{1}H NMR [$(CD_3)_2SO$] δ: 3.79 (s, 3, OCH_3), 4.31 (d, 2, CH_2, *J* = 6), 5.57 (t, 1, OH); IR (neat) cm^{-1}: 3410 (OH), 2240 (-C□C-), 1715 (ester).

2. Notes

1. Acetylenic compounds are potentially explosive, and all concentrations and distillations should be carried out behind a safety shield. Methyl 4-hydroxy-2-butynoate is a potent vesicant that causes painful burns on contact with skin. All operations should be carried out in an efficient fume hood and gloves should be worn at all times.
2. As supplied by Aldrich Chemical Company, Inc. (97% purity).
3. The general method of Robertson,[3] whereby toluenesulfonic acid monohydrate is added to a mixture of an alcohol and dihydropyran, is not recommended for this preparation since the reaction is rather exothermic. Reaction temperatures below 60°C are to be avoided for the same reason since unreacted reagents accumulate and the reaction may suddenly get out of hand with resulting boiling and colorization of the reaction mixture.
4. Ethylmagnesium bromide was obtained from Aldrich Chemical Company, Inc. in the form of a 3 *M* solution in diethyl ether containing 133.3 g of ethylmagnesium bromide. Alternately, the ethylmagnesium bromide could be prepared by a standard procedure.[4]
5. Glassware was dried in an oven at 110°C, assembled while still hot, and flushed with dry nitrogen as the assembly cooled to room temperature. All reactions involving the Grignard reagents were carried out under an atmosphere of dry nitrogen and in a fume hood.
6. The bearing was lubricated with mineral oil.
7. Anhydrous tetrahydrofuran from MCB, Inc. was used for the reactions. Freshly opened bottles gave no effervescence when mixed with powdered calcium hydride. If smaller amounts of tetrahydrofuran are used, the acetylenic Grignard reagent often crystallizes out of the reaction mixture.
8. Vigorous gas evolution (highly flammable ethane gas) and boiling take place during the addition.
9. This type of transfer technique[5] is preferred to open-air transfer to minimize losses due to hydrolysis by atmospheric moisture.
10. Filtration and subsequent washing of the hygroscopic salts are best carried out by replacing the dropping funnel in the reaction vessel with a sintered-glass filter stick. The reaction mixture is kept under a slightly positive nitrogen pressure while the supernatant is led from the filter stick through a polypropylene tube to a suction flask that is kept under a slightly negative pressure with the help of an aspirator.
11. Concentrations were carried out using a rotary evaporator and at a pressure of 12–15 mm and a temperature not exceeding 35°C unless otherwise noted.
12. The crude product at this stage shows the following ^{1}H NMR ($CDCl_3$) δ: 1.22–1.97 (m, 6 H, $H_{2',2''}$, $H_{3',3''}$, $H_{4',4''}$), 3.26–4.08 (m, 2, $H_{5',5''}$), 3.76 (s, 3, OCH_3), 4.36 (s, 2, C C-CH_2), 4.81 (bs, 1, H_1).
13. Distillation of the residue after the first treatment with Dowex 50 and methanol gives a product containing 7–10% of the tetrahydropyranyl derivative of methyl 4-hydroxy-2-butynoate. Removal of the by-product 2-methoxytetrahydropyran and

retreatment with Dowex 50 and methanol gives a product containing only 0.5–1.5% of the undeblocked alcohol.

14. The distillate often turns a light pink or yellow color in the receiver flask.

15. The checkers found that distillation at a pressure of 15–20 mm (submitters) gave a somewhat lower yield (78–84%). A slight yield improvement (78–94%) was obtained by the checkers by using lower pressure in the distillation.

16. The submitters reported n_D^{22} 1.4595.

17. The submitters reported n_D^{22} 1.4720.

3. Discussion

The preparation of the tetrahydropyranyl derivative of propargyl alcohol is a modification of a published[3] general procedure that is simple and useful for large-scale preparations.

Methyl 4-hydroxy-2-butynoate has been prepared[6] in 83% yield by treatment of 4-hydroxy-2-butynoic acid with 2% sulfuric acid in methanol and in 65% yield by carboxylation in an autoclave of the Grignard reagent of 1-(tetrahydropyran-2'-yloxy)prop-2-yne followed by treatment with 10% sulfuric acid in methanol. 4-Hydroxy-2-butynoic acid has been prepared[6] in 65% yield by treating the Grignard reagent of propargyl alcohol with carbon dioxide in an autoclave for 24 hr followed by acidic hydrolysis with aqueous 10% sulfuric acid. 4-Hydroxy-2-butynoic acid has also been prepared[7] in an unspecified yield by bubbling carbon dioxide for 14 days through a suspension of the Grignard derivative of propargyl alcohol in ether.

The first part of the procedure illustrates a method for the preparation of the tetrahydropyranyl derivative of an alcohol which requires no extraction or wash procedures during the workup of the product.

The second part of the preparation illustrates a very efficient, mild method for the preparation of a highly reactive α,β-acetylenic ester via the carbomethoxylation of the Grignard reagent of a terminal acetylenic compound with methyl chloroformate. This preparation of methyl 4-hydroxy-2-butynoate obviates the necessity[6] of carrying out the carboxylation of an acetylenic Grignard reagent in an autoclave. This procedure also eliminates the necessity[6] of carrying out the continuous ether extraction of 4-hydroxy-2-butynoic acid from an aqueous phase.

The use of a mixture of a strongly acidic cation-exchange resin and methanol to remove a tetrahydropyranyl protecting group offers a very mild method of deblocking that does not require the use of a base during the workup.

Methyl 4-hydroxy-2-butynoate has been used[6] as a starting material for the preparation of a δ-hydroxy-α,β-acetylenic ester. It has also

been employed[8] as a dipolarophile in a 1,3-dipolar cycloaddition reaction that resulted in the first synthesis of 8-aza-3-deazaguanosine.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

brine

Tetrahydropyranyl derivative of propargyl alcohol

tetrahydropyranyl derivative of methyl 4-hydroxy-2-butynoate

1-(tetrahydropyran-2'-yloxy)prop-2-yne

sulfuric acid (7664-93-9)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

toluene (108-88-3)

ethylmagnesium bromide (925-90-6)

ethane (74-84-0)

Tetrahydrofuran (109-99-9)

methyl chloroformate (79-22-1)

dihydropyran

calcium hydride (7789-78-8)

toluenesulfonic acid monohydrate

propargyl alcohol (107-19-7)

Methyl 4-hydroxy-2-butynoate, 2-Butynoic acid, 4-hydroxy-, methyl ester (31555-05-2)

2-methoxytetrahydropyran (6581-66-4)

4-hydroxy-2-butynoic acid

p-toluenesulfonic acid monohydrate (6192-52-5)

tetrahydro-2-(2-propynyloxy)-2H-pyran (6089-04-9)

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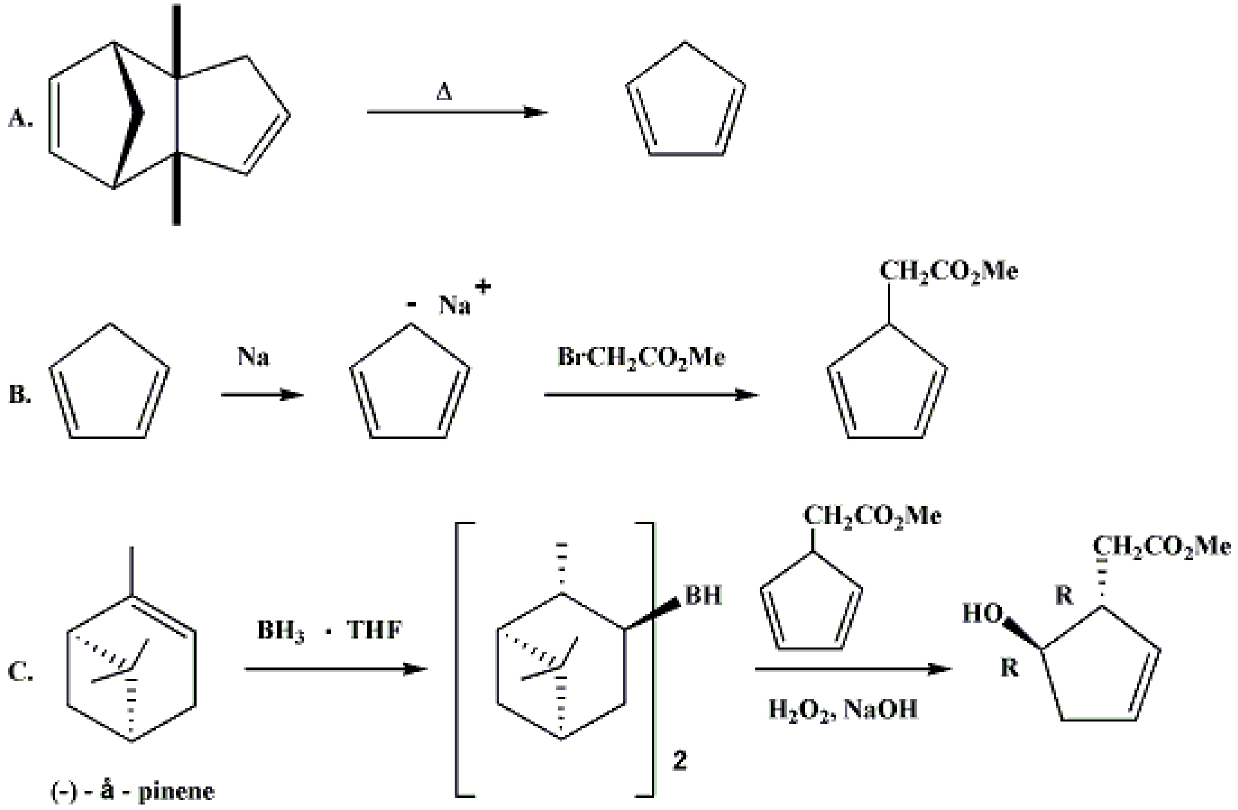
ASYMMETRIC HYDROBORATION OF 5-SUBSTITUTED CYCLOPENTADIENES: SYNTHESIS OF METHYL (1 *R*,5*R*)-5-HYDROXY-2-CYCLOPENTENE-1-ACETATE

[2-Cyclopentene-1-acetic acid, 5-hydroxy-, methyl ester, (1*R*-*trans*)-]



Submitted by John J. Partridge, Naresh K. Chadha, and Milan R. Uskokovic[1].
Checked by Bai Dong-Lu and Clayton H. Heathcock.

1. Procedure

Caution! Methyl bromoacetate, used in Step B, is intensely irritating to eyes and skin. The preparation of the ester should be carried out in an efficient hood.

A. *Pyrolysis of dicyclopentadiene to form cyclopentadiene*. Cyclopentadiene is prepared from its dimeric form by distillation according to the method of Moffett.[2]

The apparatus for the distillation is assembled as shown in f.htmigure 1. The equipment consists of a 250-mL flask, a Friedrichs condenser fitted with a Haake Model FE hot water circulator, a Claisen head, a thermometer, a gas inlet tube, and a collection receiver that is cooled to −78°C in a dry ice–acetone bath.

Figure 1. Apparatus for producing cyclopentadiene.

Figure 1. Apparatus for producing cyclopentadiene.

In the 250-mL flask is placed 100 mL of dicyclopentadiene (Note 1). The material is heated at reflux (bath temperature 200–210°C) under a nitrogen atmosphere (Note 2). After a 5-mL forerun is collected and discarded, the collection receiver is cooled to −78°C and 25 mL (0.30 mol) of cyclopentadiene is rapidly distilled at bp 36–42°C. A slight positive pressure of nitrogen is maintained throughout the distillation to prevent moisture from entering the system.

The distilled cyclopentadiene is stored at −78°C until it is used (Note 3). Residual dicyclopentadiene can be reused until it solidifies on cooling.

B. *Preparation in situ of methyl 2,4-cyclopentadiene-1-acetate (Note 4).* Cyclopentadienylsodium is prepared by modification of the methods of King[3] and Hafner[4] (Note 5).

In a 500-mL, three-necked Morton flask fitted with a condenser, mechanical stirrer, and gas inlet tube is placed 8.6 g (0.375 g-atom) of sodium and 75 mL of dry xylene (Note 6); the unstirred mixture is heated at reflux under a nitrogen atmosphere. After the xylene has reached its boiling point and the sodium has melted, the solution is rapidly stirred to produce a very fine-grained sodium sand. Quickly the heating mantle is removed and stirring stopped (Note 7). After cooling, the xylene is pipetted or siphoned away from the sodium sand and stored for future use.

The sand is washed with 3 × 25 mL of dry tetrahydrofuran (Note 8) and then is layered with 100 mL of dry tetrahydrofuran, and the mixture is cooled to −10°C (Note 9) under a nitrogen atmosphere. A solution of 25 mL (0.30 mol) of cyclopentadiene in 25 mL of tetrahydrofuran is added dropwise using a dropping funnel. After the addition is complete, the mixture is stirred overnight at room temperature, by which time hydrogen evolution has ceased. In the absence of air, the solution ranges from near colorless to bright pink (Note 10).

In a 1-L, three-necked flask fitted with a 200-mL pressure-equalizing dropping funnel, mechanical stirrer, and a gas inlet tube is placed 45.9 g (0.30 mol) of methyl bromoacetate (Note 11) and 75 mL of tetrahydrofuran and the mixture is cooled to −78°C in an inert atmosphere.

The solution of ca. 0.30 mol of cyclopentadienylsodium is decanted from residual sodium sand with a U-tube into the dropping funnel (Note 12) and is added dropwise over a 2-hr period (Note 13). A white precipitate of sodium bromide forms during the addition. The heterogeneous solution is stirred overnight at −78°C to ensure complete formation of methyl 2,4-cyclopentadiene-1-acetate.

C. *Asymmetric hydroboration with (+)-di-3-pinanylborane to form methyl (1R,5R)-5-hydroxy-2-cyclopentene-1-acetate (Note 4).* The (+)-di-3-pinanylborane is prepared from (−)-α-pinene by a modification[5,6] of the method of Brown[7] (Note 14).

In a 2-L, three-necked flask fitted with a condenser, mechanical stirrer, and a gas inlet tube is placed 90.0 g (0.66 mol) of (−)-α-pinene (Note 15). The flask is

cooled to 0°C and under an inert atmosphere a total of 300 mL (0.30 mol) of 1 *M* borane in tetrahydrofuran (Note 16) is added dropwise over a 1-hr period. The solution is stirred for 18 hr at 0°C, during which time a white precipitate of (+)-di-3-pinanylborane forms. This solution is then cooled to −78°C. The ca. 0.30 mol solution of methyl 2,4-cyclo-pentadiene-1-acetate (Section B) is transferred at −78°C to a 500-mL pressure-equalizing dropping funnel through a U-tube in an inert atmosphere and is added rapidly, in one portion, to the stirring solution of di-3-pinanylborane at −78°C. After this mixture is stirred for 6 hr at −78°C, the bath temperature is allowed to rise to 0°C and the mixture is stirred for 16 hr at 0°C to complete the hydroboration reaction.

To the reaction mixture is added dropwise 90 mL of 3 *N* aqueous sodium hydroxide, followed by 90 mL of 30% hydrogen peroxide (Note 17). The mixture is stirred for 30 min to complete the oxidation process. A total of 3 g of sodium bisulfite, 5 g of sodium chloride, and 125 mL of ether are added and the mixture is stirred for 10 min (Note 18). On standing, the reaction mixture separates into two layers, which are separated with a 1-L separatory funnel. The organic layer is washed with brine (2 × 50 mL). The water layer and the brine washes are combined and extracted with ether (3 × 125 mL). All the organic layers are then combined and dried over anhydrous magnesium sulfate. Filtration and removal of solvent under reduced pressure yield 110 g of a pale-yellow oil containing the desired product as well as (+)-isopinocampheol, and (−)-α-pinene (Note 19). The product mixture is dissolved in 250 mL of ether and is extracted with 1 *M* aqueous silver nitrate solution (3 × 100 mL). The aqueous layers are combined and back-extracted once with 50 mL of ether. The ether layers containing (+)-isopinocampheol are discarded.

The aqueous layers containing the silver(I) complex of methyl (1*R*,5*R*)-5-hydroxy-2-cyclopentene-1-acetate are then treated with an excess of saturated brine to precipitate silver chloride and free the desired product. After precipitation is complete, the water layer is decanted from the solid silver chloride. The solids are washed with ether (4 × 100 mL) and each ether layer is used to extract the water layer (Note 20). The combined ether layers are washed with 50 mL of brine and dried over anhydrous magnesium sulfate. Filtration and removal of solvent under reduced pressure yield 16–19 g of crude product. The product is distilled through a 4-in.-Vigreux column at 0.1 mm pressure to yield 12.8–14.7 g (27–31%) of methyl (1*R*,5*R*)-5-hydroxy-2-cyclopentene-1-acetate, bp 74–78°C at 0.1 mm, $[\alpha]_D^{25}$ −132° (CH_3OH, *c* 1.06) (Note 21) and (Note 22).

2. Notes

1. Dicyclopentadiene was obtained from Ace Scientific (TX 315), practical grade, 95%.
2. The Haake water circulator was employed with the circulating water temperature at 50°C. This allows only cyclopentadiene to distill.
3. Cyclopentadiene is stable at −78°C but dimerizes readily at room temperature.
4. Steps B and C must be run concurrently.
5. The efficient formation of cyclopentadienylsodium is of paramount importance for the entire reaction sequence. Variations in the yield of methyl 2,4-cyclopentadiene-1-acetate have been traced to the degree of efficiency in producing a fine sodium sand that is used to produce cyclopentadienylsodium. In the alkylation reaction of cyclopentadienylsodium with methyl bromoacetate, the entire process must be carried out in an inert dry atmosphere at −78°C. At higher temperatures, the desired product can undergo undesired dimerization and double-bond migration side reactions. Methyl 2,4-cyclopentadiene-1-acetate, once formed, is used immediately.
6. Xylene was obtained from Fisher Scientific Company. The xylene is initially dried over sodium and is saved and reused in making additional batches of sodium sand.
7. If stirring continues while the xylene cools, the sodium sand coagulates into a large lump.
8. Tetrahydrofuran was obtained from Fisher Scientific Company. The tetrahydrofuran employed was freshly distilled from lithium aluminum hydride. Care

should be exercised in drying tetrahydrofuran; cf. *Org. Synth., Coll. Vol. V* **1973**, 976. The checkers also examined the use of tetrahydrofuran that had been dried by distillation from sodium–benzophenone ketyl. When material that has been purified in this manner is used, the fine sodium sand coagulates, giving small porous lumps. No such coagulation occurs when tetrahydrofuran that has been dried by distillation from lithium aluminum hydride is used. However, the method of drying had no effect on overall yield of final product.

9. A bath of carbon tetrachloride containing a little dry ice is used for cooling.

10. The efficient formation of cyclopentadienylsodium was found to be the product-limiting step for the reaction sequence. *If air is present or if the sodium sand is not fine-grained, quantitative formation of cyclopentadienylsodium cannot be assumed.* Residual sodium sand may be washed with tetrahydrofuran, dried in a nitrogen atmosphere, and weighed to determine approximately the extent of cyclopentadienylsodium formation.

11. Methyl bromoacetate was obtained from Ace Scientific (MX 755).

12. Care must be taken during this transfer to minimize exposure of the cyclopentadienylsodium to air. Trace amounts of oxygen cause the formation of a dark brown color and brown solid in the solution.

13. The drip rate should be adjusted so that the dropping funnel is not plugged by crystalline cyclopentadienylsodium.

14. After the asymmetric hydroboration–oxidation sequence is completed, the desired product is separated via its silver(I) complex from (+)-isopinocampheol. The desired product can also be isolated by column chromatography.

15. (−)-α-Pinene was obtained from Chemical Samples Company. The (−)-α-pinene was distilled from sodium metal: bp 155–156°C; $[\alpha]_D^{25}$ −47° (neat).

16. Borane–tetrahydrofuran was obtained from Alfa Products, Morton Thiokol Inc.

17. The hydrogen peroxide oxidation is a very exothermic process and efficient cooling and stirring are necessary.

18. After the addition of ether, some inorganic salts precipitate. The checkers found it advantageous to remove this solid by suction filtration. The solid was washed with ether, which was combined with the organic solution.

19. Vacuum distillation does not effectively purify the desired product from the other impurities.

20. Methyl (1*R*,5*R*)-5-hydroxy-2-cyclopentene-1-acetate is found in both the aqueous layer and occluded with the solid silver chloride.

21. In like manner and employing (+)-α-pinene [bp 155–156°C; $[\alpha]_D^{25}$ +47° (neat)], the sequence affords the methyl (1*S*,5*S*)-5-hydroxy-2-cyclopentene-1-acetate, bp 74–77°C (0.1 mm); $[\alpha]_D^{25}$ +131° (CH_3OH, *c* 1.03).

22. The checkers used (−)-α-pinene (bp 155°C, $[\alpha]_D^{22}$ −42° (neat)) from Aldrich Chemical Company, Inc. and obtained a product having bp 75–80°C (0.15 mm) and $[\alpha]_D^{21}$ −126° (CH_3OH, *c* 0.039).

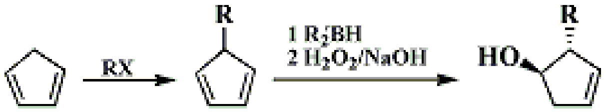
3. Discussion

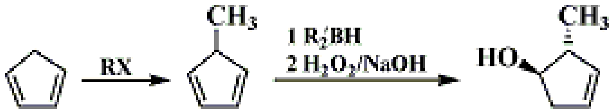
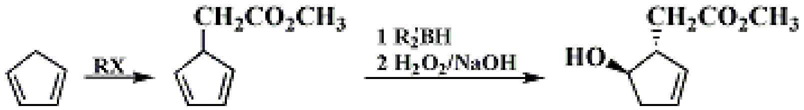
Several highly enantioselective asymmetric hydroboration reactions with prochiral olefins have been reported[8] with the di-3-pinanylborane reagents (diisopinocamphenyl-boranes) discovered by Brown and Zweifel.[9] Recently, alternative reagents such as the mono-3-pinanylboranes (monoisopinocamphenyl boranes)[10,11] and (+)-dilongifolyl-borane[12] have been used in effecting asymmetric hydroborations on prochiral olefins. With the di-3-pinanylborane reagents, the cis-disubstituted olefins[8,9] and 5-substituted cyclopentadienes[5,6] yield alcohols of high optical purity (80–95% e.e.). Lower asymmetric inductions (20–40% e.e.) occur when 1,1-disubstituted, trans-disubstituted, or trisubstituted olefins are employed as substrates. However, significantly higher enantioselective hydroborations occur when these olefins are treated with the mono-3-pinanylboranes[10,11] and (+)-longifolylborane.[12] Tetrasubstituted olefins have not successfully been asymmetrically hydroborated with any of these reagents.

Several racemic *cis*- or *trans*-2-alkyl-3-cyclopenten-1-ols have been prepared by multistep sequences from cyclopentadiene[13,14,15,16] or from substituted 1,3-dienes.[17] However, optically active *cis*- and *trans*-2-alkyl-3-cyclopenten-1-ols have been prepared directly by asymmetric hydroboration reactions using prochiral 5-substituted cyclopentadienes as substrates.[5,6] This asymmetric hydroboration method, described above, gives moderate yields of highly optically active *trans*-2-alkyl-3-cyclopenten-1-ols (94–96% e.e.), which are readily converted into the corresponding cis isomers.[5,6] Several of these substances are intermediates in the synthesis of such natural products as the monoterpene glycoside loganin,[5] the carbohydrate daunosamine,[18] and the prostaglandins such as $PGF_{2\alpha}$[6]

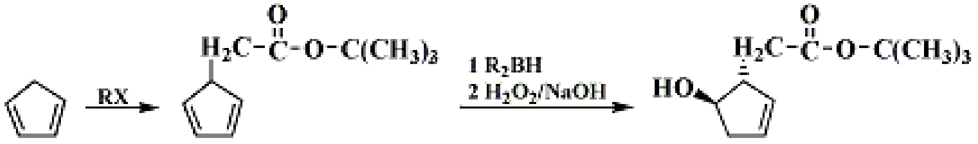
TABLE I

ASYMMETRIC HYDROBORATION OF 5-SUBSTITUTED CYCLOPENTADIENES



Substituent	Alkylating Agent	Hydroborating Agent	Yield (%)	Absolute Stereochemistry	Enantiomeric Excess (%)[a]	Reference
R = CH_3	CH_3I	(+)-Di-3-pinanylborane	40–50	*R,R*	94–96	5,21
	CH_3I	(−)-Di-3-pinanylborane	40–50	*S,S*	94–96	5,21
	$(CH_3)_2SO_4$	(+)-Di-3-pinanylborane	2	*R,R*	—	21
R = $CH_2CO_2CH_3$	$BrCH_2CO_2CH_3$	(+)-Di-3-pinanylborane	40–50	*R,R*	94–96	6,21
	$BrCH_2CO_2CH_3$	(−)-Di-3-pinanylborane	40–50	*S,S*	94–96	6,21
	$ClCH_2CO_2CH_3$	(+)-Di-3-pinanylborane	Trace	*R,R*	—	21

R = CH_2CO_2-*t*-Bu

	$BrCH_2CO_2$-*t*-Bu	(+)-Di-3-pinanylborane	Trace	*R,R*	—	21

[a]The percent enantiomeric excess was determined by HPLC analysis of products esterified with pure (S)-α-methoxy-α-trifluoromethylphenylacetyl chloride (Mosher Reagent).[19,20]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 186

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

benzophenone ketyl

brine

(−)-α-pinene

silver(I) complex of methyl (1R,5R)-5-hydroxy-2-cyclopentene-1-acetate

diisopinocamphenyl-boranes

mono-3-pinanylboranes

monoisopinocamphenyl boranes

(+)-dilongifolyl-borane

(+)-longifolylborane

METHYL (1 R,5R)-5-HYDROXY-2-CYCLOPENTENE-1-ACETATE

ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

silver chloride (7783-90-6)

silver nitrate (7761-88-8)

sodium bromide (7647-15-6)

oxygen (7782-44-7)

nitrogen (7727-37-9)

sodium bisulfite (7631-90-5)

sodium (13966-32-0)

hydrogen peroxide (7722-84-1)

xylene (106-42-3)

magnesium sulfate (7487-88-9)

borane (7440-42-8)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

CYCLOPENTADIENE (542-92-7)

dicyclopentadiene

cyclopentadienylsodium

methyl bromoacetate (96-32-2)

(+)-isopinocampheol (27779-29-9)

(+)-α-pinene

Di-3-pinanylborane, (+)-di-3-pinanylborane, (+)-di-3-pinanylborane (21947-87-5)

methyl 2,4-cyclopentadiene-1-acetate, methyl 2,4-cyclo-pentadiene-1-acetate (37455-98-4)

Methyl (1R,5R)-5-hydroxy-2-cyclopentene-1-acetate, 2-Cyclopentene-1-acetic acid, 5-hydroxy-, methyl ester, (1R-trans)- (49825-99-2)

methyl (1S,5S)-5-hydroxy-2-cyclopentene-1-acetate

(S)-α-methoxy-α-trifluoromethylphenylacetyl chloride (20445-33-4)

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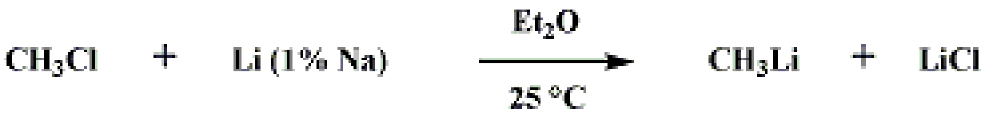
PREPARATION OF LOW-HALIDE METHYLLITHIUM

[Lithium, methyl-]



Submitted by Michael J. Lusch, William V. Phillips, Ronald F. Sieloff, Glenn S. Nomura, and Herbert O. House[1].
Checked by Gregory S. Bisacchi and Robert V. Stevens.

1. Procedure

Caution! The fine lithium dispersion used in this preparation, once washed to remove the mineral oil coating, will ignite spontaneously if exposed to air. Also, the methyl chloride and ether used are very volatile and highly flammable. The entire preparation, including the disposal of any residual lithium, should be performed in an efficient hood with a safety shield in front of the apparatus. A suitable dry-powder fire extinguisher should be kept at hand to extinguish any fires resulting from the accidental spillage of the washed lithium dispersion or of the methyllithium solution.

A dry, 1-L, three-necked, round-bottomed flask equipped with a large Teflon-covered magnetic stirring bar, a thermometer, and a dry ice condenser (Note 1) is flushed with argon (Note2), then capped with a serum stopper, and subsequently maintained under a positive pressure of argon (Note 2). A 30% dispersion of lithium metal (in mineral oil) containing 1% sodium (13.9 g, 2.00 g-atom of lithium) (Note 3) is rapidly weighed and transferred to the flask.

The lithium is washed three times by transferring approximately 150-mL portions of anhydrous ethyl ether (Note 4) into the flask through the serum stopper by forced siphon through a stainless-steel cannula, stirring the resulting suspension of lithium briefly, allowing the lithium to rise to the surface, and finally withdrawing the major part of the underlying ether by forced siphon through a cannula. Anhydrous ethyl ether (500 mL) is added to the resultant oil-free lithium. Methyl chloride gas (bp −24°C, $d_{-24°C}$ 0.99 g/mL) from a compressed gas cylinder is passed through a flask containing Linde 4A molecular sieves and into a dry, 100-mL Pyrex graduated cylinder equipped with a 24/40 standard taper joint attached to a Claisen adapter and dry ice condenser, and cooled to −24°C with a bath of dry ice–acetone (.htmFigure 1). When 52.7 mL (52.5 g, 1.04 mol) of liquid methyl chloride has been collected, the adapter and condenser are removed, several boiling chips are added to the cold (–24°C) graduated cylinder, and the cylinder is stoppered with a rubber septum through which is inserted

a stainless-steel cannula. The other end of this cannula is inserted through the rubber septum of the flask so that its tip is just above the liquid surface of the reaction flask. Dry ice–acetone is then added to the condenser attached to the reaction flask. Vigorous stirring of the ethereal lithium dispersion is begun and the methyl chloride is added over approximately a 1.5-hr period. The rate at which methyl chlorideis distilled into the reaction vessel is controlled by slight cooling or warming of the graduated cylinder that contains the liquid methyl chloride. During addition, the initial grey suspension changes to a brown to purple suspension; by the end of the addition, little, if any, lithium metal should be seen floating on the surface of the ether solution when stirring is interrupted. After the addition of methyl chloride is complete, the reaction mixture is stirred at 25°C for an additional 0.5–1 hr and then allowed to stand overnight or longer (Note 5) at 25°C under a static argon atmosphere, whereupon the precipitated lithium chloride settles to the bottom of the flask. The dry ice condenser and thermometer are removed from the flask and replaced with rubber septa. The supernatant methyllithium solution is transferred by forced siphon using a large-gauge cannula through a glass wool pad (Note 6) into a receiving flask previously flushed with an inert gas (.htmFigure 2). The receiving flask, which contains the filtrate, a pale-yellow solution of methyllithium, is removed (Note 7) and stored in a refrigerator for 12–24 hr during, which time an additional small quantity of lithium chloride separates as fine crystals. The resulting supernatant solution is transferred with a stainless-steel cannula and a slight positive pressure of argon or nitrogen into one or more suitable oven-dried, nitrogen-filled storage bottles capped with rubber septa. Two 1-mL aliquots of the solution are removed with a hypodermic syringe for a modified Gilman titration (Note 8) and a 5-mL aliquot is removed with a hypodermic syringe to determine the halide concentration (Note 9). The solution contains 1.40–1.77 *M* methyllithium accompanied by 0.07–0.09 *M* lithium chloride corresponding to a 70–89% yield of methyllithium. If this solution is protected from oxygen and moisture, it may be stored at 0–25°C for several months (and remain active).

Figure 1. Condensing the methyl chloride.

Figure 1. Condensing the methyl chloride.

Figure 2. Decanting the methyllithium solution.

Figure 2. Decanting the methyllithium solution.

2. Notes

1. The dry ice condenser used with the apparatus should have sufficient condensing capacity to prevent the loss of significant amounts of methyl chloride; a condenser 38 cm long and 3.8 cm in diameter was suitable.

Since finely divided lithium floats on the surface of the solvent and will be in contact with the atmosphere in the reaction vessel, an argon atmosphere, rather than a nitrogen atmosphere, should be used to avoid formation of the insoluble reddish-brown lithium nitride.

2. A slight positive pressure of argon was maintained in the vessel throughout the reaction by using an argon line connected to both a bubbler containing Nujol and the inlet on the dry ice condenser.

3. A dispersion in mineral oil of 30% (by weight) of lithium containing 1% by weight of sodium is marketed by Alfa Products, Morton Thiokol, Inc. This oilcoated dispersion may be exposed to the air during transfer and weighing and is conveniently transferred from its container by pouring through a wide-mouth funnel. Small quantities of the dispersion that adhere to the apparatus may be disposed of by rinsing in a stream of warm water to lower the viscosity of the oil and allow the suspended lithium to react with water at a controlled rate. To dispose of large quantities of this dispersion (or any quantity of lithium powder no longer coated with oil), the material should be suspended in anhydrous ether under an argon atmosphere and *tert*-butyl alcohol should be added dropwise to the suspension until all of the lithium metal has been consumed. Since hydrogen is liberated during these disposal procedures, they should be performed in an efficient hood.

4. Anhydrous ethyl ether was distilled from lithium aluminum hydride immediately before use.

5. Although most of the lithium chloride separates from the ether solution as a finely divided solid during the reaction, additional small quantities of lithium chloride continue to separate for 12–14 hr. After standing overnight, a typical reaction contains a precipitate of finely divided brownish-pink solid below a clear, pale-yellow solution.

6. A convenient filter was constructed by packing glass wool, previously dried in an oven, into a 20-mL Luer-Lok syringe barrel fitted with a 15-gauge needle. The syringe barrel was capped with a serum stopper. A large-diameter cannula (at least 15 gauge) should be used to transfer the methyllithium solution from the flask to the filter since smaller-gauge cannulas are frequently plugged by solid particles.

7. As soon as the receiver containing the methyllithium solution has been removed and stoppered, the residual solids in the reaction flask and the filtration apparatus should be rinsed into another receiver with anhydrous ether under an atmosphere of argon or nitrogen. The ether slurry of solids, which may contain some unchanged lithium metal, should be treated cautiously in a hood with *tert*-butyl alcohol to consume any residual lithium metal before the mixture is discarded.

8. One 1-ml aliquot is added to 1.0 mL of freshly distilled 1,2-dibromoethane (bp 132°C) in an oven-dried flask that contains a static atmosphere of nitrogen or argon. After the resulting solution has been allowed to stand at 25°C for 5 min, it is diluted with 10 mL of water and titrated for base content (residual base) to a phenolphthalein endpoint with standard 0.100 *M* hydrochloric acid.

The second 1-mL aliquot is added cautiously to 10 mL of water and then titrated for base content (total base) to a phenolphthalein endpoint with standard aqueous 0.100 *M* hydrochloric acid. The methyllithium concentration is the difference between the total base and residual base concentrations.[2 3] Alternatively, the methyllithium concentration may be determined by titration with a standard solution of *sec*-butyl alcohol employing 2,2'-bipyridyl as an indicator.[4 5]

9. To determine the concentration of chloride ion,[6 7] a 5-mL aliquot of the methyl-lithium solution is cautiously added to 25 mL of water and the resulting solution is acidified with concentrated sulfuric acid and then treated with 2–3 mL of ferric ammonium sulfate [$Fe(NH_4)(SO_4)_2$ 12 · H_2O] indicator solution and 2–3 mL of benzyl alcohol. The resulting mixture is treated with 10.0 mL of standard aqueous 0.100 *M* silver nitrate solution and then titrated with standard aqueous 0.100 *M* potassium thiocyanate solution to a brownish-red endpoint.

3. Discussion

Although ethereal solutions of methyllithium may be prepared by the reaction of lithium wire with either methyl iodide[8] or methyl bromide[9] in ether solution, the molar equivalent of lithium iodide or lithium bromide formed in these reactions remains in solution and forms, in part, a complex with the methyllithium.[10] Certain of the ethereal solutions of methyllithium currently marketed by several suppliers including Alfa Products, Morton Thiokol, Inc., Aldrich Chemical Company, and Lithium Corporation of America, Inc., have been prepared from methyl bromide and contain a full molar equivalent of lithium bromide. In several applications such as the use of methyllithium to prepare lithium dimethylcuprate[11 12] or the use of methyllithium in 1,2-dimethyoxyethane to prepare lithium enolates from enol acetates or trimethylsilyl enol ethers,[5] the presence of this lithium salt interferes with the titration and use of methyllithium. There is also evidence indicating that the stereochemistry observed during addition of methyllithium to carbonyl compounds may be influenced significantly by the presence of a lithium salt in the reaction solution.[13] For these reasons it is often desirable to use ethereal solutions of methyllithium that do not contain an equivalent amount of lithium iodide or lithium bromide.

The reaction of lithium with methyl chloride in ether solution produces a solution of methyllithium from which most of the relatively insoluble lithium chloride precipitates. Ethereal solutions of "halide-free" methyllithium, containing 2–5 mol % of lithium chloride, were formerly marketed by Foote Mineral Company and by Lithium Corporation of America, Inc., but this product has been discontinued by both companies. Comparable solutions are also marketed by Alfa Products and Aldrich Chemical Company; these solutions have a limited shelf life and older solutions have often deteriorated badly even before the container is opened. Since an ether solution of

methyl chloride reacts very slowly with lithium wire used in reactions with methyl bromide or methyl iodide, the present procedure[14] uses a finely divided suspension of lithium metal containing 1% (by weight) of sodium[10,15] to achieve a rapid reaction with methyl chloride. The finely divided lithium containing 1% sodium is marketed as a 30% (by weight) dispersion in mineral oil and must be washed free of this protective hydrocarbon diluent before use in order to avoid contamination of the final methyllithium reagent with a substantial amount of a mixture of high molecular weight hydrocarbons. Since lithium is less dense than common organic solvents such as diethyl ether or pentane, the washing procedure must be done with special care to avoid starting a fire with the pyrophoric, finely divided lithium.[3] Finely divided lithium with somewhat higher or lower percentages of sodium are expected to work equally well.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 226

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

H_2O

1,2-dimethyoxyethane

trimethylsilyl enol ethers

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ether, ethyl ether, diethyl ether (60-29-7)

hydrogen (1333-74-0)

silver nitrate (7761-88-8)

oxygen (7782-44-7)

nitrogen (7727-37-9)

methyl chloride (74-87-3)

acetone (67-64-1)

sodium (13966-32-0)

Benzyl alcohol (100-51-6)

1,2-dibromoethane (106-93-4)

methyl bromide (74-83-9)

Methyl iodide (74-88-4)

potassium thiocyanate (333-20-0)

Pentane (109-66-0)

phenolphthalein (77-09-8)

lithium (7439-93-2)

lithium aluminum hydride (16853-85-3)

Methyllithium, Lithium, methyl-, methyl-lithium (917-54-4)

Lithium chloride (7447-41-8)

tert-butyl alcohol (75-65-0)

lithium iodide (10377-51-2)

argon (7440-37-1)

sec-butyl alcohol (78-92-2)

2,2'-bipyridyl (366-18-7)

lithium dimethylcuprate

lithium bromide (7550-35-8)

lithium nitride (26134-62-3)

ferric ammonium sulfate

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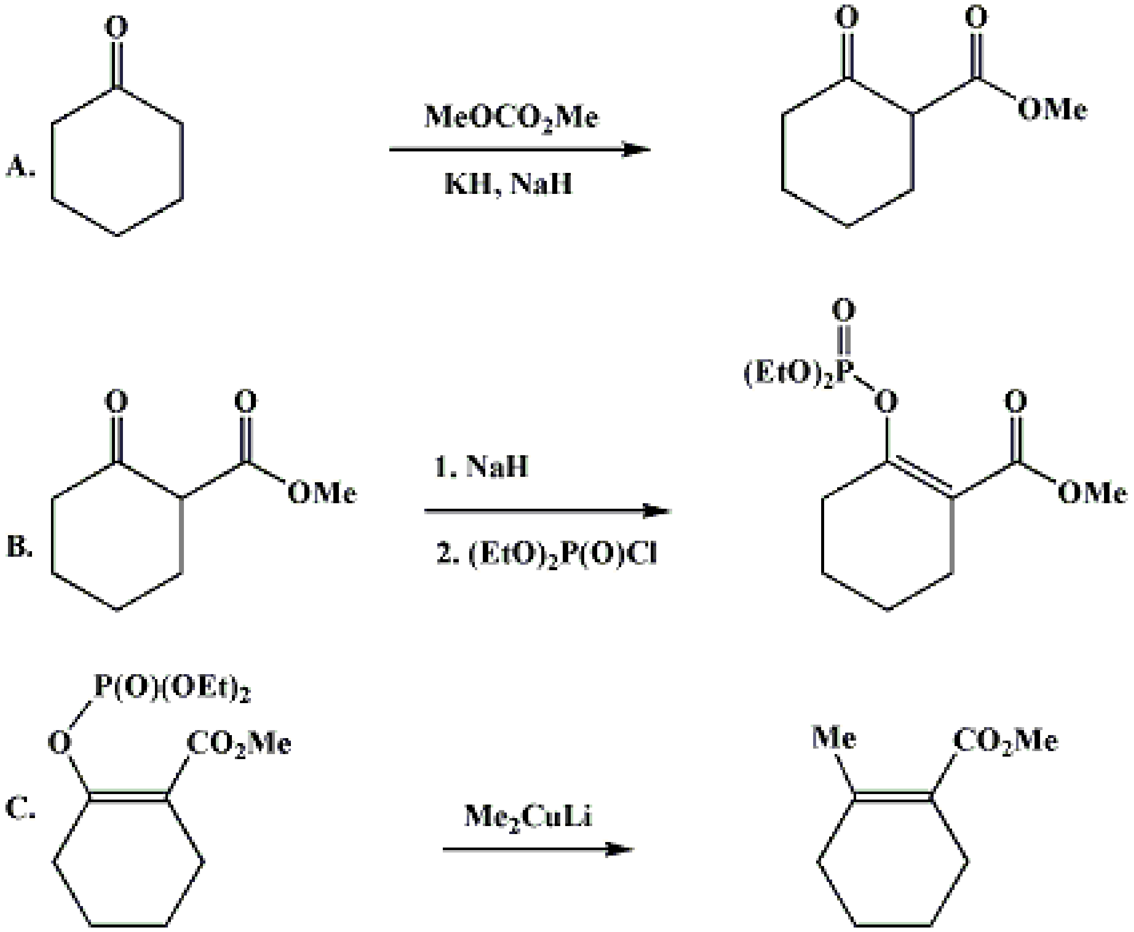
β-ALKYL-α,β-UNSATURATED ESTERS FROM ENOL PHOSPHATES OF β-KETO ESTERS: METHYL 2-METHYL-1-CYCLOHEXENE-1-CARBOXYLATE

[1-Cyclohexene-1-carboxylic acid, 2-methyl, methyl ester]



Submitted by Margot Alderdice, F. W. Sum, and Larry Weiler[1].
Checked by Stephen P. Ashburn, Clark H. Cummins, and Robert M. Coates.

1. Procedure

A. *Methyl 2-oxocyclohexanecarboxylate*. A 500-mL, three-necked, round-bottomed flask is equipped with a mechanical stirrer, a reflux condenser, and a pressure-equalizing dropping funnel bearing a nitrogen inlet (Note 1). The flask is flushed with nitrogen and charged with 18.02 g (0.20 mol) of dimethyl carbonate, 50 mL of anhydrous tetrahydrofuran, and 6.12 g (0.25 mol) of sodium hydride (Note 2). The suspension is stirred and heated to reflux temperature, at which time the slow, dropwise addition of 7.80 g (0.080 mol) of cyclohexanone in 20 mL of dry tetrahydrofuran is begun. After 2 min, 0.306 g (0.0076 mol) of powdered potassium hydride *(Caution! Dry potassium hydride is pyrophoric.)* (Note 3) is added to initiate

the reaction. The addition of cyclohexanone is continued over a 1-hr period. The mixture is stirred and heated at reflux for another 30 min, cooled in an ice bath for 15–20 min, and hydrolyzed by slowly adding 75 mL of 3 *M* aqueous acetic acid. The contents of the flask are poured into 100 mL of aqueous sodium chloride, and the aqueous mixture is extracted with four 150-mL portions of chloroform. The organic layers are combined, dried with anhydrous sodium sulfate, and concentrated at room temperature with a rotary evaporator. Distillation of the residual liquid under reduced pressure gives 9.8–10.8 g (79–87%) of methyl 2-oxocyclohexanecarboxylate as a colorless liquid, bp 53–55°C (0.35 mm) (Note 4).

B. *Methyl 2-(diethylphosphoryloxy)-1-cyclohexene-1-carboxylate*. A 250-mL, two-necked, round-bottomed flask is equipped with a magnetic stirring bar, a rubber septum, and a gas inlet tube connected to a nitrogen source and a mineral oil bubbler (Note 1). The flask is flushed with nitrogen and charged with 1.58 g (0.0329 mol) of a 50% dispersion of sodium hydride in mineral oil (Note 5). The sodium hydride is freed from the mineral oil by washing with four 40-mL portions of anhydrous diethyl ether (Note 6) and withdrawing the supernatant solvent with a syringe, after which 120 mL of anhydrous ether is added. The mixture is stirred and cooled in an ice bath as 4.68 g (0.0300 mol) of methyl 2-oxocyclohexanecarboxylate (Note 7) in 10 mL of ether is added at a moderately rapid rate such that vigorous but controlled evolution of hydrogen occurs (Note 8). The resulting creamy suspension is stirred at 0°C for another 30 min, after which time 4.5 mL (5.37 g, 0.031 mol) of diethyl chlorophosphate (Note 9) is injected through the septum with a syringe. The ice bath is removed, the mixture is stirred at room temperature for an additional 3 hr, and 0.6 g of solid ammonium chloride is added. Stirring is continued for 30 min, and the salts are then separated by suction filtration through a medium porosity fritted-glass funnel. Concentration of the filtrate under reduced pressure affords 8.18–8.63 g of the enol phosphate that is used in Step C without purification (Note 10).

C. *Methyl 2-methyl-1-cyclohexene-1-carboxylate*. A 250-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, a rubber septum, a pressure-equalizing addition funnel, and an inlet tube connected to a nitrogen source and a mineral oil bubbler (Note 1). The flask is charged with 8.03 g (0.042 mol) of copper(I) iodide (Note 11) and 50 mL of dry diethyl ether (Note 6), flushed with nitrogen, and cooled in an ice bath. The mixture is stirred and cooled as 92.7 mL (0.084 mol) of 1.1 *M* methyllithium in diethyl ether (Note 12) is added quickly through the septum by means of a syringe. The resulting clear and colorless, or light tan, solution of lithium dimethylcuprate is then cooled in a carbon tetrachloride–dry ice slush bath maintained at −23°C (Note 13). A solution of 8.18–8.63 g (ca. 0.028–0.030 mol) of the enol phosphate in 35 mL of dry ether is added from the addition funnel over 5–10 min. Stirring and cooling are continued for 3 hr, after which time the dark-purple solution is poured into a 1-L Erlenmeyer flask containing 75 mL of ice-cold 5% hydrochloric acid saturated with sodium chloride (Note 14). The mixture is stirred, or shaken vigorously, and cooled in an ice bath for 5–10 min to complete the hydrolysis. A 150-mL portion

of 15% aqueous ammonia is added to the gray suspension and the mixture is swirled vigorously for a few minutes until the organic layer becomes clear and the aqueous layer turns bright blue. The mixture is transferred to a separatory funnel, the aqueous layer is withdrawn, and the organic phase is washed with 50 mL of 15% aqueous ammonia. The aqueous layers are combined and extracted with one 100-mL portion of ether. The combined ethereal layers are washed with two 50-mL portions of saturated sodium chloride, dried with anhydrous magnesium sulfate, and concentrated by rotary evaporation. Distillation of the remaining 4.25–5.47 g of liquid in a short-path distillation apparatus affords 3.99–4.17 g (86–90% based on β-keto ester) of methyl 2-methyl-1-cyclohexene-1-carboxylate, bp 96–97°C (27 mm) (Note 15),(Note 16),(Note 17).

2. Notes

1. The glassware was dried in an oven at 125°C and assembled while warm.
2. Dimethyl carbonate is available from Aldrich Chemical Company, Inc. The checkers dried the tetrahydrofuran immediately before use by distillation from the sodium ketyl of benzophenone under a nitrogen atmosphere. The submitters purchased sodium hydride (50% oil dispersion) from Alfa Products, Morton Thiokol, Inc. The checkers used 12.24 g of a 50% dispersion of sodium hydride in mineral oil obtained from the same supplier. The dispersion was washed with three portions of pentane to remove the mineral oil and the remaining sodium hydride was allowed to dry under nitrogen.
3. The submitters used a 35% dispersion of potassium hydride in mineral oil supplied by Alfa Products, Morton Thiokol, Inc.; the mineral oil was separated by washing the dispersion with five portions of dry hexane. The checkers used a 25% dispersion of potassium hydride in mineral oil obtained from the same source but without removing the mineral oil. The oil remained in the distillation pot when the product was distilled.
4. A boiling point of 68°C (0.8 mm) and a melting point of 25°C have been reported for methyl 2-oxocyclohexanecarboxylate.[2] The spectral properties of the product are as follows: IR (liquid film) cm^{-1}: 1745, 1715, 1615; ^{1}H NMR ($CDCl_3$) δ: 1.62 (m, 4 H, 2 CH_2), 2.22 (m, 4 H, 2 CH_2), 3.37 (t, 0.25 H, J = 7 Hz, CH at C-2 in keto form), 3.74 (s, 3 H, CH_3), 12.10 (s, 0.75 H, enol OH).
5. The sodium hydride-mineral oil dispersion was purchased from Alfa Products, Morton Thiokol, Inc.
6. Diethyl ether was dried by the submitters by refluxing over lithium aluminum hydride and was distilled immediately before use. The checkers distilled diethyl ether from the sodium ketyl of benzophenone before use.
7. A mixture of methyl and ethyl 2-oxocyclohexanecarboxylate, available from Aldrich Chemical Company, Inc., may also be used. The product obtained is a mixture of methyl and ethyl 2-methylcyclohexene-1-carboxylates.
8. No gas evolution was observed by the checkers in some runs in which an older lot of sodium hydride was used. In this case, the cooling bath was removed

and the mixture was allowed to stir at room temperature until the bubbling ceased.

9. Diethyl chlorophosphate, supplied by Aldrich Chemical Company, Inc., was used by the submitters without purification and was handled in a glove bag under an atmosphere of dry nitrogen in a well-ventilated hood. The reagent was distilled and stored under nitrogen by the checkers. Aliquots were withdrawn with a syringe as needed.

10. The spectral properties of the enol phosphate are as follows: IR ($CHCl_3$) cm^{-1}: 1715, 1660, 1290, 1030; 90 MHz ^1H NMR ($CDCl_3$) δ: 1.3–1.9 (m, 4 H, CH_2CH_2), 1.35 (t, 6 H, J = 7 Hz, OCH_2CH_3), 2.3 (m, 4 H, allylic CH_2), 3.68 (s, 3 H, OCH_3), 4.15 (quintet, 4 H, J = 7 Hz, OCH_2CH_3).

11. Copper(I) iodide, supplied by either MC and B Manufacturing Chemists or Fisher Scientific Company, was purified by recrystallization from water saturated with potassium iodide.[3,4 5] The wet powder was washed successively with ethanol, acetone, and ether, and dried by heating overnight at 100°C in an evacuated drying pistol containing phosphorus pentoxide.[4,6] The submitters advise that the compound should not be dried by heating in air.[6] When oven-dried copper(I) iodide was used in this procedure, the yield of product was somewhat lower (77–88%) and as much as 10–20% of 1-acetyl-2-methylcyclohexene was formed. It is probable that the presence of small amounts of copper(II) impurities is responsible for the increased proportion of this by-product.[5,7] Purified copper(I) iodide may be stored under nitrogen without change for several months.[4]

12. Ethereal methyllithium (as the lithium bromide complex) was obtained by the submitters from Aldrich Chemical Company, Inc. The checkers used 1.19 *M* methyllithium–lithium bromide complex in ether supplied by Alfa Products, Morton Thiokol, Inc. The concentration of the methyllithium was determined by titration with 1.0 *M tert*-butyl alcohol in benzene using 1,10-phenanthroline as indicator.[8] The submitters report that ethereal methyllithium of low halide content purchased from Alfa Products, Morton Thiokol, Inc., gave similar results.

13. The coupling reaction between lithium dimethylcuprate and acyclic enol phosphates must be carried out between −47 and −98°C for stereoselective formation of β-methyl-α,β-unsaturated esters.

14. The submitters have found that the reaction may also be hydrolyzed with a solution of 60 mL of saturated ammonium chloride and 15 mL of concentrated aqueous ammonia. The ethereal layer is then washed with 15% aqueous ammonia until the aqueous layer is no longer blue. When lithium di-*n*-butylcuprate is used, the yields are often improved by adding 1-bromobutane to the reaction mixture before hydrolysis with aqueous ammonium chloride.

15. The product exhibits the following spectral properties: IR ($CHCl_3$) 1720, 1640, 1080 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.3–1.7 (m, 4 H, CH_2CH_2), 1.8–2.4 (m,

4 H, allylic CH_2), 1.97 (s, 3 H, CH_3), 3.69 (s, 3 H, OCH_3); MS (70 eV) *m / e* (assignment, relative intensity): 154 (M^+, 50%), 95 (-CO_2CH_3, 100%).

16. The purity of the product was determined by the checkers by GLC analysis using the following column and conditions: 3-mm × 1.8-m column, 5% free fatty acid phase (FFAP) on acid-washed Chromasorb W (60–80 mesh) treated with dimethyldichlorosilane, 90°C (1 min) then 90° to 200°C (15°C / min). The chromatogram showed a major peak for methyl 2-methyl-1-cyclohexene-1-carboxylate preceded by two minor peaks for methyl 1-cyclohexene-1-carboxylate and 1-acetyl-2-methylcyclohexene. The areas of the two impurity peaks were 5–6% and 0.5–2% that of the major peak. The purity of the product seems to depend on careful temperature control during the reaction. The total amount of the two impurities was 14–21% in runs conducted at about −15 to −20°C or at temperatures below −23°C.

17. The submitters purified the product by distillation in a Kugelrohr apparatus with an oven temperature of 85–88°C (20 mm) and obtained 3.80–3.85 g (88–89%). The purity of the product was 93–96% according to GLC analysis. The major impurity (2–6%) was 1-acetyl-2-methylcyclohexene.The product may also be purified by flash chromatography[9] using 19 / 1 (v / v) petroleum ether, (bp 30–60°C) / ethyl acetate as eluant. A column of 2-cm diameter was packed to a height of 25 cm with Kieselgel 60 (230–400 mesh) supplied by BDH Chemicals Ltd. In one run chromatography of 4.19 g of crude product afforded 3.70 g (88%) of the α,β-unsaturated ester that was completely free of the more polar by-product, 1-acetyl-2-methylcyclohexene. However, the checkers found that the other by-product, methyl 1-cyclohexene-1-carboxylate, is not readily separated by flash chromatography.

3. Discussion

This procedure illustrates a new method for the preparation of β-alkyl-α,β-unsaturated esters by coupling lithium dialkylcuprates with enol phosphates of β-keto esters.[10] The procedure for the preparation of methyl 2-oxocyclohexanecarboxylate described in Section A is based on one reported by Ruest, Blouin, and Deslongchamps.[2] Methyl 2-methyl-1-cyclohexene-1-carboxylate has been prepared by esterification of the corresponding acid with diazomethane[11] and by reaction of methyl 2-chloro-1-cyclohexene-1-carboxylate with lithium dimethylcuprate.[12]

The formation of β-alkyl-α,β-unsaturated esters by reaction of lithium dialkylcuprates or Grignard reagents in the presence of copper(I) iodide, with β-phenylthio-,[13,14,15] β-acetoxy-,[16,17,18,19] β-chloro-,[12,20] and β-phosphoryloxy-α,β-unsaturated esters[10] has been reported. The principal advantage of the enol phosphate method is the ease and efficiency with which these compounds may be prepared from β-keto esters. A wide variety of cyclic and acyclic β-alkyl-α,β-unsaturated esters has been synthesized from the corresponding β-keto esters.[10] However, the method is limited to primary

dialkylcuprates. Acyclic β-keto esters afford (Z)-enol phosphates that undergo stereoselective substitution with lithium dialkylcuprates with predominant retention of stereochemistry (usually >85–98%). It is essential that the cuprate coupling reaction of the acyclic enol phosphates be carried out at lower temperatures (−47 to −98°C) to achieve high stereo-selectivity. When combined with the γ-alkylation of methyl acetoacetate dianion,[21] this method provides a facile means of isoprenoid chain extension.[22 23 24] The procedures have been employed to advantage in syntheses of (*E*, *E*)-10-hydroxy-3, 7-dimethyldeca-2, 6-dienoic acid,[22] latia luciferin,[23] and mokupalide.[24] β-Diketones may be converted to β-alkyl-α,β-unsaturated ketones in a similar manner.[10]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium ketyl of benzophenone

methyl and ethyl 2-oxocyclohexanecarboxylate

methyl and ethyl 2-methylcyclohexene-1-carboxylates

1.0 M tert-butyl alcohol

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ammonia (7664-41-7)

Benzene (71-43-2)

ethyl acetate (141-78-6)

ether, diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

hydrogen (1333-74-0)

chloroform (67-66-3)

Cyclohexanone (108-94-1)

sodium chloride (7647-14-5)

1-bromobutane (109-65-9)

sodium sulfate (7757-82-6)

potassium iodide (7681-11-0)

nitrogen (7727-37-9)

acetone (67-64-1)

Pentane (109-66-0)

copper(I) iodide (7681-65-4)

magnesium sulfate (7487-88-9)

Diazomethane (334-88-3)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

sodium hydride (7646-69-7)

hexane (110-54-3)

Methyllithium (917-54-4)

Methyl 2-oxocyclohexanecarboxylate (41302-34-5)

diethyl chlorophosphate (814-49-3)

copper(II)

lithium dimethylcuprate

1,10-phenanthroline (66-71-7)

dimethyldichlorosilane (75-78-5)

potassium hydride (7693-26-7)

lithium bromide (7550-35-8)

phosphorus pentoxide (1314-56-3)

Methyl 2-methyl-1-cyclohexene-1-carboxylate, 1-Cyclohexene-1-carboxylic acid, 2-methyl, methyl ester (25662-38-8)

dimethyl carbonate (616-38-6)

1-acetyl-2-methylcyclohexene

methyl 1-cyclohexene-1-carboxylate

methyl 2-chloro-1-cyclohexene-1-carboxylate

lithium di-n-butylcuprate

(E,E)-10-hydroxy-3, 7-dimethyldeca-2, 6-dienoic acid

Methyl 2-(diethylphosphoryloxy)-1-cyclohexene-1-carboxylate (71712-64-6)

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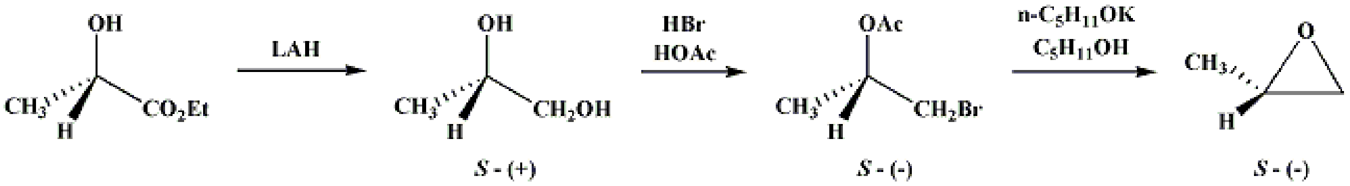
OPTICALLY ACTIVE EPOXIDES FROM VICINAL DIOLS VIA VICINAL ACETOXY BROMIDES: (*S*)-(−)- and (*R*)-(+)-METHYLOXIRANE



Submitted by Martin K. Ellis and Bernard T. Golding[1].
Checked by Stephen H. Montgomery and Clayton H. Heathcock.

1. Procedure

A. *(S)-(+)-Propane-1,2-diol*. Into a three-necked, 500-mL, round-bottomed flask fitted with a mechanical stirrer, dropping funnel and reflux condenser are placed 10.8 g (0.284 mol) of lithium aluminum hydride and 200 mL of dry ethyl ether. To this slurry is added, from the dropping funnel, 33 g (0.28 mol) of ethyl L-(−)-lactate (Note 1) in 150 mL of dry ethyl ether at a rate that maintains a steady reflux. The heterogeneous mixture is stirred for 3 hr. Then 25 mL (1.39 mol) of water is carefully added and stirring is continued for a further 1.5 hr. The mixture is filtered and the white solid (LiOH) is washed well with ether and dichloromethane. The organic phases are combined, dried over magnesium sulfate, and concentrated at reduced pressure with a rotary evaporator to give a portion of the crude product (3 g). Aqueous 1 *M* sulfuric acid is added to the solid until the milky suspension is just acidic (pH 6–6.5). The suspension is subjected to continuous extraction with twice its volume of dichloromethane (about 500 mL) for 168 hr. The dichloromethane layer is dried over magnesium sulfate and concentrated at reduced pressure with a rotary evaporator. The crude products are combined and distilled at reduced pressure to obtain 14.4–15.6 g (68–73%) of (*S*)-(+)-propane-1,2-diol, bp 52–56°C (0.5 mm), as a colorless liquid (Note 2).

B. *(S)-(−)-2-Acetoxy-1-bromopropane*. A three-necked, 100-mL, round-bottomed flask fitted with a magnetic stirring bar, dropping funnel, and reflux condenser is charged with 7.6 g (0.1 mol) of (*S*)-(+)-propane-1,2-diol. A solution of 45% w/v hydrogen bromide–acetic acid (71 g, 0.3 mol) (Note 3) is added from the dropping funnel with cooling over ca. 5 min. The homogeneous solution is stirred at room temperature for 45 min, after which time it is added to 200 mL of water and the mixture neutralized immediately with solid sodium carbonate (Note 4). The neutral solution is extracted three times with 150 mL of ethyl ether, the organic phases are combined, dried over magnesium sulfate, and concentrated at reduced pressure with a rotary evaporator. Distillation of the crude product at reduced pressure affords 14.1–15.4 g (78–85%) of (*S*)-(−)-2-acetoxy-1-bromopropane, bp 54–57°C (7 mm), as a colorless liquid (Note 5).

C. *(S)-(−)-Methyloxirane*. To a three-necked, 100-mL, round-bottomed flask equipped with a magnetic stirring bar, pressure-equalizing dropping funnel, and 10-cm Vigreux column connected to an efficiently cooled condenser and receiver are added 9.05 g (50 mmol) of the acetoxybromopropane and 20 mL of dry 1-pentanol. The solution is stirred at room temperature and 41.66 mL (50 mmol) of 1.2 *M* potassium pentoxide in 1-pentanol (Note 6) is added from the dropping funnel over ca. 20 min. A white precipitate of potassium bromide is observed. After addition is complete, the flask is warmed in an oil bath at ca. 130–145°C to attain distillation (Note 7). The product, (*S*)-(−)-methyloxirane, 2.0–2.35 g (69–81%), is collected as a colorless liquid, bp 34–35°C (Note 8).

2. Notes

1. Ethyl L-(−)-lactate was purchased from Fluka AG, Buchs, Switzerland and was used directly. Checkers found that fresh ethyl lactate purchased from Fluka is only 97–98% e.e. by ^{19}F NMR spectroscopy on the Mosher ester.

2. An optical rotation of $[\alpha]_D^{16}$ +20.3 (H_2O, *c* 7.5), [lit.[2] $[\alpha]_D^{20}$ +20.7° (H_2O, *c* 7.5))] was observed for this product. It had the following spectral properties: IR (liquid film, polystyrene reference) cm^{-1}: 3350 (s), 2970 (m), 2930 (m), 2870 (m), 1455 (m), 1375 (m); ^1H NMR ($CDCl_3$) δ: 1.15 (d, 3 H, $-CH_3$), 3.40 [q, 1 H, $H_2C(OH)-$] and 3.59 [q, 1 H, $H_2C(OH)-$], 3.89 [m, 1 H, -CH (OH) CH_3], -OH resonances variable.

3. Hydrogen bromide–acetic acid, 45%, was purchased from BDH Chemicals Ltd., Poole, England. The checkers used hydrobromic acid (30–32% in acetic acid, 4.1 *M*) from Fisher Scientific, 711 Forbes Ave., Pittsburgh, PA 51219.

4. Approximately 80 g of sodium carbonate is required. On addition of solid sodium carbonate a considerable amount of frothing occurs. To prevent the loss of product, the addition of the reaction mixture to the water and subsequent neutralization with solid sodium carbonate is performed in a 2-L beaker.

5. An optical rotation of $[\delta]_D^{20}$ −13.7° ($CHCl_3$, *c* 5.8), [lit.[2] $[\alpha]_D^{23}$ −13.55 ($CHCl_3$, *c* 5.8)] was observed for (*S*)-(−)-2-acetoxy-1-bromopropane. (*R*)-(+)-2-Acetoxy-1-bromopropane, obtained from (*R*)-(−)-propane-1,2-diol,[3,4] gave an optical rotation of $[\alpha]_D^{18}$ +14.1° ($CHCl_3$, *c* 5.8). Both enantiomers of acetoxybromopropane had the following spectral properties: IR

(liquid film, polystyrene ref.) cm^{-1}: 2980 (w), 2937 (w), 1735 (s), 1450 (w), 1425 (w), and 1370 (s); ^{1}H NMR (CCl_4) δ: 1.34 (d, 3 H, CH_3), 2.10 (s, 3 H, -$OCOCH_3$), 3.38 (d, 2 H, -CH_2Br), and 4.97 [m, 1 H, -CH($OCOCH_3$)CH_3] due to 2-acetoxy-1-bromopropane (94% by integration) and 1.70 (3 H) and 4.16 (3 H) due to 1-acetoxy-2-bromopropane (6%).

6. Potassium pentoxide in 1-pentanol is prepared by dissolving freshly cut potassium in dry, freshly distilled 1-pentanol under nitrogen. The molarity of this solution may be determined by titration against standard aqueous acid.

7. The oil bath is preheated to 120–130°C. It is then transferred to a prewarmed heater with stirrer on a lab jack below the reaction flask. The oil bath can then be moved into position with the aid of the lab jack.

8. An optical rotation of $[\alpha]_D^{20}$ −18.7° (CCl_4, *c* 5.83), [lit.[2] $[\alpha]_D^{22}$ −18.55° (CCl_4, *c* 5.84)] was observed for (*S*)-(−)-methyloxirane. (*R*)-(+)-Methyloxirane, obtained from (*R*)-(+)-acetoxybromopropane (Note 5), gave an optical rotation of $[\alpha]_D^{18}$ +19.13° (CCl_4, *c* 5.66), [lit.[2] $[\alpha]_D^{18}$ +18.7° (CCl_4, *c* 5.83)], bp 34–35°C, and a range of yields within the limits of those obtained for (*S*)-(−)-methyloxirane. Both enantiomers of methyloxirane had the following spectral properties; ^{1}H NMR (CCl_4) δ: 1.27 (d, 3 H, -CH_3), 2.27 (q, 1 H, -CH(O)CH_2), 2.59 [t, 1 H, -CH(O)CH_2] and 2.83 [m, 1 H, H_3C-CH(O)CH_3] ppm.

3. Discussion

This procedure illustrates the stereospecific conversion of 1,2-diols into vicinal acetoxy bromides by hydrogen bromide in acetic acid.[2] The acetoxy bromides that are formed are easily transformed into epoxides by base treatment. In the examples presented, the base is used in a high-boiling solvent to facilitate isolation of epoxide by direct distillation from the reaction mixture (see also [5,6,7,8]). For other examples, a solvent may be used that is either more volatile than the epoxide (e.g., methanol[2]) or easily removed by aqueous workup and solvent extraction of the epoxide (e.g., ethane-1,2-diol[9]). The hydrogen bromide–acetic acid method is superior to the preparation of epoxides from 1,2-diols via 1-*O*-sulfonate esters, because any contaminating 2-*O*-sulfonate ester will detract from the optical purity of the epoxide.[10] The optical purities of the samples of (*R*)- and (*S*)-methyloxirane prepared as described were better than 98%, according to complexation chromatography and ^{1}H NMR analysis with chiral shift reagent.[11,12] Other procedures for preparing (*R*)-[13,14] and (*S*)-methyloxirane have been described.[15,16,17] These compounds are valuable starting materials for preparing a variety of optically active natural products (nonactin,[18] sulcatol,[19] recifeiolide,[20] methyl-1,6-dioxaspiro[4.5]decanes[21]), drugs (e.g., *N*-2-hydroxypropyl-6,7-benzomorphans[22]) and for studies of stereoregular polymerizations.[23]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 434

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

H_2O

(S)-(–)- and (R)-(+)-METHYLOXIRANE

ethyl L-(–)-lactate

(LiOH)

(S)-(–)-2-Acetoxy-1-bromopropane

(S)-(–)-Methyloxirane

(R)-(–)-propane-1,2-diol

Potassium pentoxide in 1-pentanol

nonactin

sulcatol

recifeiolide

N-2-hydroxypropyl-6,7-benzomorphan

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

methanol (67-56-1)

ether, ethyl ether (60-29-7)

HYDROBROMIC ACID, hydrogen bromide (10035-10-6)

sodium carbonate (497-19-8)

methyloxirane (75-56-9)

nitrogen (7727-37-9)

ethane-1,2-diol (107-21-1)

potassium bromide (7758-02-3)

potassium (7440-09-7)

dichloromethane (75-09-2)

ethyl lactate (687-47-8)

1-pentanol (71-41-0)

magnesium sulfate (7487-88-9)

lithium aluminum hydride (16853-85-3)

acetoxybromopropane, (R)-(+)-acetoxybromopropane

potassium pentoxide

(R)-Methyloxirane, (R)-(+)-Methyloxirane (15448-47-2)

(S)-(+)-Propane-1,2-diol (4254-15-3)

(R)-(+)-2-Acetoxy-1-bromopropane

(S)-methyloxirane (16088-62-3)

methyl-1,6-dioxaspiro[4.5]decane

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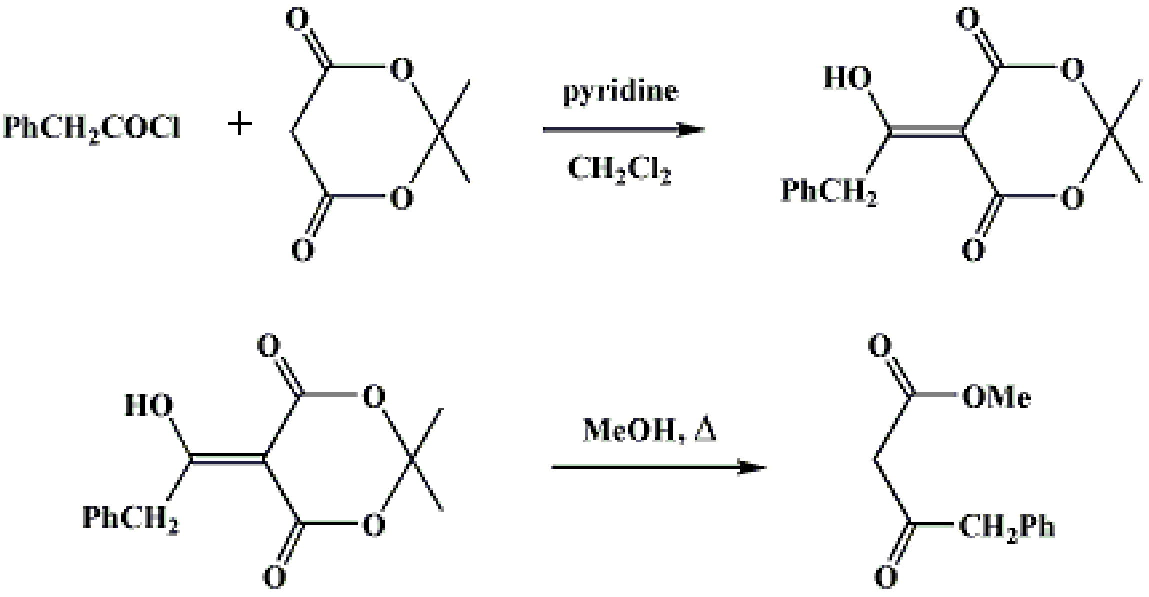
METHYL PHENYLACETYLACETATE FROM PHENYLACETYL CHLORIDE AND MELDRUM'S ACID

[Benzenebutanoic acid, β-oxo-, methyl ester]



Submitted by Y. Oikawa, T. Yoshioka, K. Sugano, and Osamu Yonemitsu[1].
Checked by Michael J. Taschner, Hans P. Märki, and Clayton H. Heathcock.

1. Procedure

Into a 300-mL, round-bottomed flask equipped with a dropping funnel and a magnetic stirrer is placed a solution of 23.75 g (0.165 mol) of recrystallized Meldrum's acid (Note 1) in 65 mL of anhydrous dichloromethane. The flask and its contents are cooled in an ice bath, and 32.5 mL (0.40 mol) of anhydrous pyridine (Note 2) is added with stirring under an argon atmosphere over a 10-min period. To the resulting colorless clear solution is added a solution of 25.0 g (0.16 mol) of freshly distilled phenylacetyl chloride (Note 3) in 50 mL of anhydrous dichloromethane over a 2-hr period. After the addition is complete, the resulting orange, cloudy reaction mixture is stirred for 1 hr at 0°C, then for an additional 1 hr at room temperature. The reaction mixture is diluted with 35 mL of dichloromethane, and then poured into 100 mL of 2 *N* hydrochloric acid containing crushed ice. The organic phase is separated and the aqueous layer extracted twice with 25-mL portions of dichloromethane. The organic phase and the extracts are combined, washed twice with 25-mL portions of 2 *N* hydrochloric acid and 30 mL of saturated sodium chloride solution, and dried over anhydrous sodium sulfate. The solvent is removed with a rotary evaporator to yield an acyl Meldrum's acid (Note 4) as a pale-yellow solid.

The solid acyl Meldrum's acid, without purification, is refluxed in 250 mL of anhydrous methanol for 2.5 hr. The solvent is removed with a rotary evaporator, and the residual oil is distilled under reduced pressure to give 25.2 g (82%) of methyl phenylacetylacetate as a colorless liquid, bp 126–128°C/(0.6 mm).

2. Notes

1. Meldrum's acid, 2,2-dimethyl-1,3-dioxane-4,6-dione, is available from the Aldrich Chemical Company, Inc. It may also be prepared from malonic acid and acetone.[2] It is used in this preparation after recrystallization from acetone or from acetone–hexane. The checkers found that a final product of significantly lower purity is obtained if the Meldrum's acid is not recrystallized.
2. The checkers used pyridine that had been distilled from calcium hydride.
3. Phenylacetyl chloride is supplied by Wako Pure Industries, Ltd. (Japan) and the Aldrich Chemical Company, Inc. It is distilled before use, bp 95–96°C/(12 mm). The checkers found the distilled commercial material to be slightly pink. However, material of this quality gave a good yield of pure product.
4. The product, 2,2-dimethyl-5-phenylacetyl-1,3-dioxane-4,6-dione, is isolated in its enol form in 97% yield. If desired, it may be further purified by recrystallization from ether–hexane to give pale-yellow prisms, mp 96–97°C (dec). The checkers recrystallized the material from dichloromethanehexane and obtained 65% yield of material, mp 94–96°C (dec) and 7%, mp 84–90°C. The ^{1}H NMR spectrum of this compound has absorptions at δ 1.65 (s, 6 H), 4.30 (s, 2 H), 7.20 (s, 5 H), and 15.0 (br s, 1 H).

3. Discussion

Because β-keto esters are among the most important intermediates in organic synthesis, many methods have been developed for their synthesis.[3] However, it is still desirable to have a general and practical method for preparation of β-keto esters of the general type $RCOCH_2CO_2R'$, and thence by alkylation with alkyl halides compounds of the type $RCOCHR''CO_2R'$.[4] The available synthetic methods can be classified broadly in three categories: those involving acetoacetic esters,[5] those involving mixed malonic esters,[6] and those involving malonic acid half esters.[7] The procedure described herein[8] may be classified as one of the malonic ester methods. The procedure consists of two simple steps and utilizes readily accessible starting materials. When the carboxylic acid chloride is not available, the carboxylic acid may be condensed with Meldrum's acid in the presence of a condensing agent such as ethyl phosphorocyanidate.[9]

Methanolysis or ethanolysis of an acyl Meldrum's acid is performed simply by refluxing in methanol or ethanol solution. The products are methyl or ethyl β-keto esters, and they can usually be purified by distillation. When a higher ester (such as

benzyl, *tert*-butyl, or trichloroethyl) is required, it is easily prepared by refluxing the acyl Meldrum's acid in benzene containing about 3 equiv of the appropriate alcohol.

Recently, Melillo and co-workers applied this Meldrum's acid method with some modifications to the synthesis of thienamycin. A carboxylic acid was treated with carbonyldiimidazole, followed by treatment with Meldrum's acid to give an acyl Meldrum's acid, which was converted to a β-keto *p*-nitrobenzyl ester by refluxing in acetonitrile containing *p*-nitrobenzyl alcohol.[10]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ester

benzyl, tert-butyl, or trichloroethyl

acyl Meldrum's acid

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

methanol (67-56-1)

ether (60-29-7)

acetonitrile (75-05-8)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

acetone (67-64-1)

pyridine (110-86-1)

dichloromethane (75-09-2)

Malonic acid (141-82-2)

phenylacetyl chloride (103-80-0)

hexane (110-54-3)

calcium hydride (7789-78-8)

CARBONYLDIIMIDAZOLE

argon (7440-37-1)

p-Nitrobenzyl alcohol (619-73-8)

Methyl phenylacetylacetate, Benzenebutanoic acid, β-oxo-, methyl ester (37779-49-0)

2,2-dimethyl-1,3-dioxane-4,6-dione, MELDRUM'S ACID (2033-24-1)

2,2-Dimethyl-5-phenylacetyl-1,3-dioxane-4,6-dione

dichloromethanehexane

ethyl phosphorocyanidate

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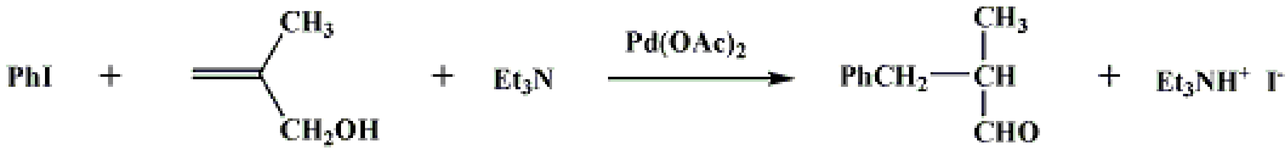
2-METHYL-3-PHENYLPROPANAL

[Benzenepropanal, α-methyl-]



Submitted by S. A. Buntin and R. F. Heck[1].
Checked by C. M. Tice and C. H. Heathcock.

1. Procedure

A 250-mL, three-necked, round-bottomed flask, equipped with a mechanical stirrer and a reflux condenser, is charged with 0.49 g (2.2 mmol) of palladium acetate (Note 1), 20.4 g (100 mmol) of iodobenzene, 9.0 g (125 mmol) of 2-methyl-2-propen-1-ol, 12.6 g (125 mmol) of triethylamine, and 32.5 mL of acetonitrile (Note 2). The reaction vessel is placed in an oil bath at 100°C and the solution is heated to reflux for 11 hr under a nitrogen atmosphere. The reaction mixture is allowed to cool to room temperature and transferred to a 500-mL separatory funnel with the aid of 100 mL of ether and 100 mL of water. The organic layer is washed five times with 100 mL portions of water. The combined aqueous layers are reextracted with 100 mL of ether. The organic layers are combined, dried over anhydrous sodium carbonate, and filtered. The organic layer is concentrated and distilled under reduced pressure. The product, 2-methyl-3-phenyl-propanal, 12.05 g (82%), has a boiling range of 52–58°C at 0.40 mm (Note 3).

2. Notes

1. Palladium acetate was prepared by the method of Stephenson et al.[2] A suitable material is also available from the Strem Chemical Company or Alfa Inorganics.
2. Iodobenzene, 2-methyl-2-propen-1-ol, and triethylamine were obtained from the Aldrich Chemical Company, Inc. Acetonitrile was obtained from the J. T. Baker Chemical Company. All these reagents were used as received.
3. The 2-methyl-3-phenylpropanal is 90% pure by GLC. The product mixture contains 6% of another isomer, 2-methyl-2-phenylpropanal, and a small amount of 2-phenyl-2-propen-1-ol. A completely pure sample of the aldehyde is readily obtained by stirring the crude aldehyde with excess saturated aqueous sodium bisulfite solution for several hours, filtering the solid bisulfite adduct, washing with ether, and liberating the aldehyde with excess aqueous sodium bicarbonate. Redistillation gives the completely pure aldehyde in about 60% yield.

3. Discussion

The reaction of allylic alcohols and aryl halides in the presence of a palladium catalyst has been used in the past to prepare various β-arylaldehydes. The procedure described here is essentially that of Heck and Melpolder.[3] A similar reaction has been carried out with bromobenzene and 2-methyl-2-propen-1-ol in hexamethylphosphoric triamide (HMPT) as solvent with sodium

bicarbonate as base. A variety of other bases have also been used.[4] 2-Methyl-3-phenylpropanal has been prepared by reacting palladium acetate and phenylmercuric acetate with 2-methyl-2-propen-1-ol.[5]

The aldehyde is also obtained by the hydroformylation of allylbenzene.[6] An alternative method involves benzylation of 2-ethylthiazoline followed by reduction with aluminum amalgam and cleavage with mercuric chloride.[7] A sixth method of preparation is the phenylation of 2-vinyl-5,6-dihydro-1,3-oxazine with phenylmagnesium bromide followed by methylation and hydrolysis.[8] Finally, arylation of 2-methyl-2-propen-1-ol with phenyldiazonium salts catalyzed by zero-valent palladium complexes gives the title aldehyde.[9]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ether (60-29-7)

acetonitrile (75-05-8)

sodium bicarbonate (144-55-8)

sodium carbonate (497-19-8)

nitrogen (7727-37-9)

aluminum (7429-90-5)

sodium bisulfite (7631-90-5)

palladium (7440-05-3)

bromobenzene (108-86-1)

mercuric chloride (7487-94-7)

Phenylmagnesium bromide (100-58-3)

phenylmercuric acetate

Iodobenzene (591-50-4)

2-methyl-2-propen-1-ol (513-42-8)

triethylamine (121-44-8)

allylbenzene (300-57-2)

hexamethylphosphoric triamide (680-31-9)

palladium acetate (3375-31-3)

Benzenepropanal, α-methyl-, 2-Methyl-3-phenylpropanal, 2-methyl-3-phenyl-propanal (5445-77-2)

2-ethylthiazoline

2-vinyl-5,6-dihydro-1,3-oxazine

2-methyl-2-phenylpropanal

2-phenyl-2-propen-1-ol

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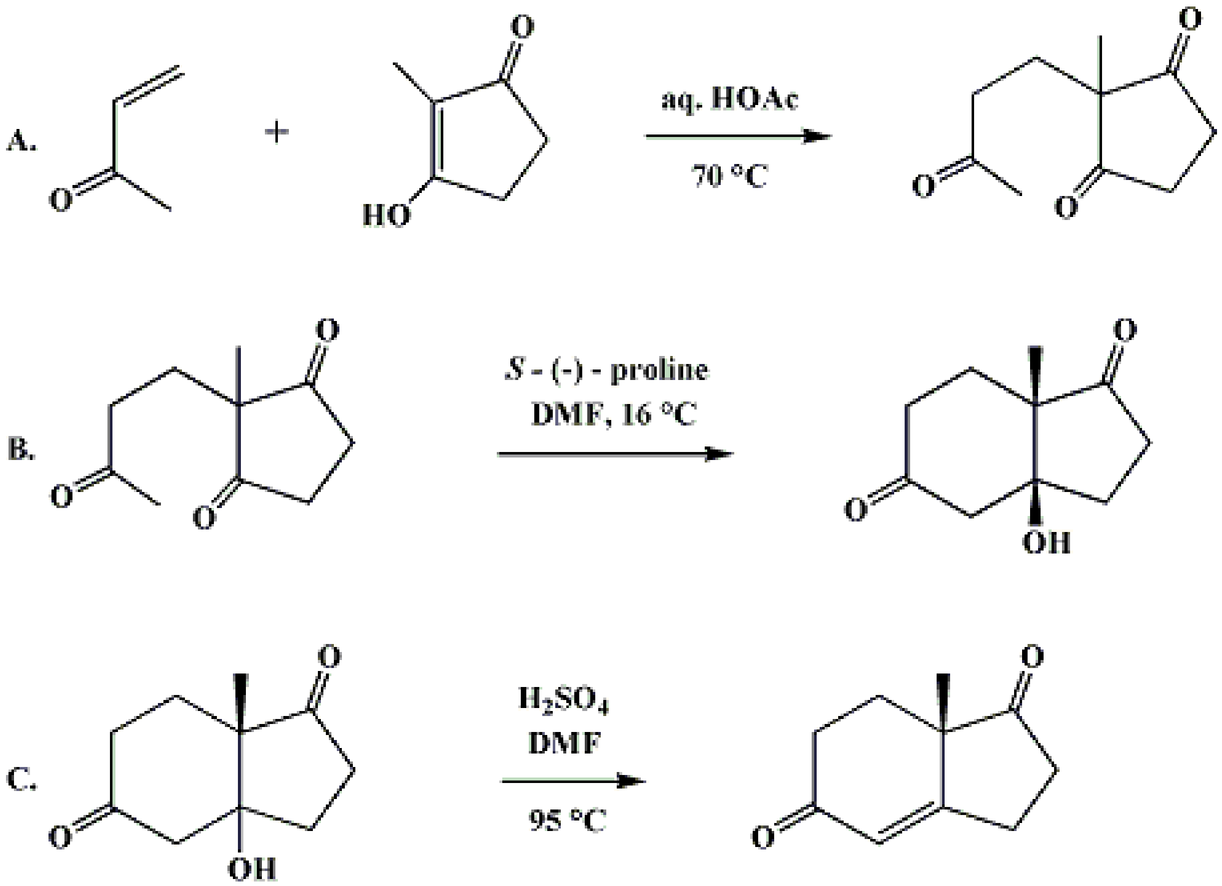
(+)-(7*aS*)-7a-METHYL-2,3,7,7a-TETRAHYDRO-1 *H*-INDENE-1,5-(6*H*-DIONE

[1 *H*-Indene-1,5(6 *H*)-dione, 2,3,7,7a-tetrahydro-7a-methyl-, (*S*)-]



Submitted by Zoltan G. Hajos[1] and David R. Parrish[2].
Checked by Stuart Remington, David Lust, and Gabriel Saucy.

1. Procedure

Caution! Part A should be performed in a well-ventilated hood because methyl vinyl ketone is a lachrymator.

A. *2-Methyl-2-(3-oxobutyl)-1,3-cyclopentanedione*. A 1.0-L, three-necked, round-bottomed flask equipped with a condenser, magnetic stirring bar, and thermometer is charged with 112.1 g (1.0 mol) of 2-methyl-1,3-cyclopentanedione (Note 1), 230 mL of deionized water, 3.0 mL of glacial acetic acid, and 140 mL (120.96 g, 1.72 mol) of methyl vinyl ketone (Note 2). The system is shielded from light with aluminum foil and placed under a slight positive pressure of nitrogen. The flask is placed in an oil bath and the temperature is raised to 70°C. The reaction is monitored by gas chromatography (GLC, (Note 3)) until complete (1–2 hr). The mixture is cooled,

transferred to a separatory funnel, and extracted with 500 mL and then two 100-ml portions of dichloromethane. The combined extracts are washed with 500 and 100 mL of saturated brine. The combined brine wash is extracted with a further two 100-mL portions of dichloromethane. The total dichloromethane extract is dried over sodium sulfate and filtered. The solvent is removed on a rotary evaporator at 45°C (70 mm). Drying on the rotary evaporator at 40–45°C (0.03 mm) for 16 hr gives 181.8 g (100%) of the desired triketone as an orange oil (Note 4) and (Note 5).

B. *(+)-(3aS,7aS)-2,3,3a,4,7,7a-Hexahydro-3a-hydroxy-7a-methyl-1 H-indene-1,5 (6H)-dione*. A 500-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar and a nitrogen inlet is charged with 188 mL of *N,N*-dimethyl-formamide (Note 6) and 863 mg (7.5 mmol) of *S*-(–)-proline (Note 7) and (Note 8). The mixture is degassed four times by alternate evacuation and refilling with nitrogen. The system is shielded from light with aluminum foil and the contents of the flask are stirred in a 15–16°C bath (Note 9) for 1.0 hr. To the resultant suspension is added 45.5 g (0.25 mol) of the 2-methyl-2-(3-oxobutyl)-1,3-cyclopentanedione prepared in Step A. A total of 62.5 mL of *N,N*-dimethylformamide is used to ensure complete transfer. The degassing procedure is repeated four times and stirring at 15–16°C (Note 10) is continued for 40–120 (Note 11) as the mixture becomes yellow and then brown. The reaction is monitored for completeness by TLC (Note 12). The solution of the desired ketol (Note 13) is used directly in Step C.

C. *(+)-(7aS)-7a-Methyl-2,3,7,7a-tetrahydro-1H-indene-1,5(6H)-dione*. A 100-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, pressure-equalizing dropping funnel, and nitrogen inlet is charged with 50 mL of *N,N*-dimethylformamide (Note 6). The contents of the flask are cooled to −20°C with a dry ice–acetone bath and 2.70 mL (4.97 g, 48.6 mmol) of concentrated sulfuric acid is added over 5–10 min at a rate to maintain a temperature of –15 to –20°C (Note 14).

The flask containing the solution of the (+)-(3a*S*,7a*S*)-2,3,3a,4,7,7a-hexahydro-3a-hydroxy-7a-methyl-1*H*-indene-1,5(6*H*)-dione in *N,N*-dimethylformamide is placed in an oil bath and heated to 95°C. When the temperature reaches 70–75°C, an 18.8-mL aliquot of the concd sulfuric acid in *N,N*-dimethylformamide solution is added in one portion. The reaction mixture is heated to 95°C for 3.0 hr. After 1.0 hr, an additional 7.5-mL aliquot of the concd sulfuric acid in *N,N*-dimethylformamide solution is added in one portion. The reaction is monitored for completeness by GLC (Note 15) and cooled. The solvent is removed on a rotary evaporator at 45°C (0.3–0.5 mm) to give a brown oil. The material is taken up in 375 mL of dichloromethane. The solution is washed with two 190-mL portions of 2.0 *N* sulfuric acid solution that have been saturated with sodium chloride, two 190-mL portions of saturated sodium bicarbonate solution that have been saturated with sodium chloride, and 190 mL of saturated brine. Each aqueous wash is extracted, in turn, with the same two 190-mL portions of dichloromethane. The combined dichloromethane solutions are dried over sodium sulfate and filtered, and the solvent is removed on a rotary evaporator at 40°C (70 mm)

to give 38.8–39.6 g of oily, brown semisolid. This material is taken up in 78 mL of ethyl acetate and the solution is applied to a dry column of 78 g of silica gel (Note 16). The column is eluted with 600 mL of ethyl acetate, and the total eluate is stripped of solvent on a rotary evaporator at 40°C (70 mm) to give 37.2–38.8 g of tan crystalline solid. The solid is subjected to bulb-to-bulb distillation[3] (Note 17) at 120–135°C (0.1 mm) to give 35.9–36.9 g of a slightly yellowish (cream white) solid, mp 56–61°C, $[\alpha]^{25}_{D}$ +324–329° (toluene, *c* 1.0) (Note 18),(Note 19),(Note 20). This material is taken up in 74 mL of ether at reflux. The solution is brought at reflux to the point of turbidity with 19 mL of hexanes. The mixture is seeded, allowed to stand at ambient temperature for 2 hr, and then chilled in a 17°C water bath for 30 min (Note 21). The solid is collected by filtration on medium porosity sintered glass, washed with two 12-mL portions of cold (3°C) 1 : 1 v/v ether : hexanes and dried at 20°C (70 mm) to give 28.7–31.3 g (70–76%) of white crystalline solid (Note 22), mp 64–66°C, $[\alpha]^{25}_{D}$ +347.5–349° (toluene, *c* 1.0) (Note 23), purity by GLC 99.4–99.5% (Note 24),(Note 25),(Note 26).

2. Notes

1. 2-Methyl-1,3-cyclopentanedione, 98%, purchased from the Aldrich Chemical Company, Inc., was used. Material prepared according to Hengartner, U.; Chu, V. *Org. Synth., Coll. Vol. VI* **1988**, 774 was determined by the checkers to be equally satisfactory.
2. Methyl vinyl ketone, technical grade, purchased from the Aldrich Chemical Company, Inc., was fractionally distilled into ca. 1% w/v hydroquinone shortly before use. The fraction boiling at 33–36°C (120 mm) was used.
3. Analyses were carried out on a Hewlett Packard HP 5840 A gas chromatograph operated isothermally at 150°C. A 25-m capillary column packed with cross-linked phenylmethylsilicone was employed. 2-Methyl-1,3-cyclopentanedione and 2-methyl-2-(3-oxobutyl)-1,3-cyclopentanedione had retention times of ca. 7 min 12.5 min, respectively.
4. If desired, pure triketone can be isolated by distillation of the crude triketone through a Vigreux column. The yield of light yellow oil, bp 115–120°C (0.2–0.3 mm), is 80–89%.
5. The triketone has the following spectral properties: IR (neat) cm^{-1}: 1770, 1725; ^{1}H NMR ($CDCl_3$) δ: 1.12 (s, 3 H, CH_3), 2.22 (s, 3 H, CH_3CO), 2.8 (m, 4 H, $COCH_2CH_2CO$).
6. *N,N*-Dimethylformamide, purchased from the Fisher Scientific Co., was mixed with 10% v/v toluene and distilled at atmospheric pressure. After all of the toluene had been distilled (head temperature to 148°C), vacuum was cautiously applied. The fraction of *N,N*-dimethylformamide that distilled at 78–82°C (56–65 mm) was collected and stored under nitrogen prior to use.
7. L-(−)-Proline [(*S*)-configuration], 99^{+}%, purchased from the Aldrich Chemical Company, Inc., was employed. The material was finely ground in a mortar and pestle immediately before use.

8. The L-(−)-proline was established by the checkers to be of >99.8% (estimated level of detection) enantiomeric purity by conversion to *N*-pentafluoropropionyl-L-(−)-proline isopropyl ester and GLC analysis on a 50-m glass capillary column containing the chiral phase, Chirasil-Val (Quadrex, Inc.). Analyses were performed on a Hewlett-Packard HP 5710 A instrument operated isothermally at 140°C. Racemic proline was used as a control.

9. The checkers used a flask with a built-in jacket. Water at 15–16°C was continuously circulated through the jacket.

10. Temperature control in this reaction is critical. At higher temperatures, the enantioselectivity of the reaction drops off significantly, while at lower temperatures, the reaction time becomes unacceptably long.

11. The reaction time varied substantially from run to run, but generally complete conversion was observed in 48–72 hr.

12. E. Merck silica gel F-254 plates were used, with 20 : 1 v/v dichloromethane : methanol as eluent. The plates were developed by drying, spraying with 9 : 1 v/v deionized water : concentrated sulfuric acid, light drying with a hot air gun, spraying with 3% w/v vanillin solution in ethanol, and strong heating with the hot air gun. The approximate R_f values observed were 0.67 (starting triketone) and 0.37 (product ketol). In addition, a minor spot at R_f 0.59 (enone arising from dehydration of the ketol) was seen.

13. If desired, the ketol can be isolated as follows. The reaction mixture from 18.0 g of distilled 2-methyl-2-(3-oxobutyl)-1,3-cyclopentanedione is evaporated on a rotary evaporator at 45°C (0.3 mm) to give 22.0 g of brown oil. A solution of this material in 200 mL of ethyl acetate is filtered through 80 g of J. T. Baker silica gel. Elution with ca. 1.3 L of ethyl acetate in 200-mL fractions is monitored by TLC (Note 12). The fractions containing the desired product are combined and stripped of solvent on a rotary evaporator at 45°C (70 mm). Final drying on the rotary evaporator at 45°C (0.3 mm) gives 18.0 g (100%) of crude ketol as a slightly oily, brown solid having the following spectral properties: IR ($CHCl_3$) cm^{-1}: 3600, 3500–3300, 1742, 1722; ^1H NMR ($CDCl_3$) δ: 1.26 (s, 3 H, CH_3), 2.63 (s, 2 H, $COCH_2COH$). Further purification of the compound by crystallization from ether (ca. 50% recovery) gives material of mp 118–119°C, $[\alpha]_D^{25}$ +59.8° (lit.[4] mp 119–119.5°C, $[\alpha]_D^{25}$ +60.4°).

14. The solution is prepared immediately before use and kept at −20°C.

15. The GLC system described in (Note 3) was employed. The intermediate ketol and product enone had retention times of ca. 23 and 16.5 min, respectively. A trace of ketol (<1%) is observed at the end of the reaction.

16. E. Merck silica gel 60 (70–230 mesh) was used. The column dimensions were 3.2 cm × 60 cm.

17. A Kugelrohr apparatus purchased from the Aldrich Chemical Company, Inc. was used. The receiving bulb was cooled with an ice–water bath. The temperature indicated is that of the oven air bath.

18. The ratio of rotations obtained in toluene and benzene has been determined to be 1.00 : 1.03. The rotation of enantiomerically pure material in toluene,

based on the accepted[5] value of +362° in benzene, is 351°. The enantiomeric purity at this stage is thus 92–94% (Note 19).

19. Attempts by both the submitters and checkers to find a method other than optical rotation to determine the enantiomeric purity have been unsuccessful.

20. Material of this purity is satisfactory for many synthetic purposes; see [3].

21. Further cooling results in a higher recovery of material. However, the melting point and rotation of the samples thus obtained are lower.

22. The compound is somewhat unstable. It is best stored in an amber bottle under nitrogen at 3°C.

23. The enantiomeric purity of the purified material is thus 99.0–99.4% (see (Note 18)).

24. GLC analysis was carried out on a Hewlett Packard HP 5710 A gas chromatograph operated isothermally at 155°C. A 50-m capillary column of OV-17 on fused silica was employed. The enone had a retention time of ca. 14.5 min.

25. The material has the following spectral properties: UV (CH_3OH) λ 235 nm (ε = 11,200); IR ($CHCl_3$) cm^{-1}: 1746, 1665; ^{1}NMR ($CDCl_3$) δ: 1.31 (s, 3 H), 7a-CH_3), 5.97 (broad, S, 1 H, vinylic-H).

26. Steps B and C have been scaled up to the 2.0-mol level with no loss in yield or enantiomeric purity.

3. Discussion

The (*S*)-(–)-proline-catalyzed asymmetric aldol cyclization of the triketone to the optically active bicyclic aldol product, followed by dehydration to the optically active enedione, (+)-7a-methyl-(7a*S*)-2,3,7,7a-tetrahydro-1*H*-indene-1,5(6*H*)-dione, has been described, and two alternative reaction mechanisms have been suggested by the submitters.[4] The exact mechanism of the extremely high asymmetric induction in the crucial conversion of the prochiral triketone to the optically active ketol still needs to be clarified.[6] [7] [8]

The synthesis of the triketone has been included (Step A of the procedure), since identification of the crystalline compound originally claimed[9] to be the triketone has been shown to be in error.[10] After completion of our work, the triketone was correctly characterized by another research group.[11]

Asymmetric aldol cyclization of the triketone with (*S*)-(–)-proline can also be effected in solvents other than *N,N*-dimethylformamide; acetonitrile is outstanding.[4]

Of the asymmetric amino acid reagents investigated, (*S*)-(–)-proline gave the highest optical yield (93.4%); (–)-*trans*-4-hydroxyproline gave 73.1%, and (*S*)-(–)-azetidinecarboxylic acid gave 63.9% optical yields in the asymmetric synthesis of the optically active bicyclic ketol.

The use of (*R*)-(+)-proline in acetonitrile induced the asymmetric aldol cyclization of

the triketone to the enantiomeric ketol, (−)-(3*aR*,7*aR*)-2,3,3a,4,7,7a-hexahydro-3a-hydroxy-7a-methyl-1*H*-indene-1,5(6*H*)-dione.[12]

The ethyl homolog of the triketone, 2-ethyl-2-(3-oxobutyl)-1,3-cyclopentanedione, has been converted with (*S*)-(−)-proline in *N*,*N*-dimethylformamide to (+)-(3*aS*, 7*aS*)-7a-ethyl-2,3,3a,4,7,7a-hexahydro-3a-hydroxy-1*H*-indene-1,5(6*H*)-dione in good yield.[4] This, in turn, could be dehydrated to the homologous bicyclic enedione, (+)-(7*aS*)-7a-ethyl-2,3,7,7a-tetrahydro-1*H*-indene-1,5(6*H*)-dione.[4]

Circular dichroism studies of the 7a-methyl bicyclic ketol suggested, and a single-crystal X-ray diffraction study of the racemic compound confirmed, the cis conformation with an axial 7a-methyl and an equatorial 3a-hydroxy group in the six-membered ring of the bicyclic system. On the other hand, similar measurements of the 7a-ethyl bicyclic keto established the alternate possible cis conformation to avoid the 1,3-diaxial inter-actions between the angular ethyl group and the C-4 and C-6 axial hydrogens.

Dehydration of the optically active bicyclic ketols in refluxing benzene with a little *p*-toluenesulfonic acid could readily be effected without loss of optical purity.[4] It has been shown by a research group at Schering A. G., Berlin, Germany that the triketone can be converted directly to the optically active enedione with 0.5 eq. of (*S*)-(−)-proline and 0.25 equiv. of 1 *N* aqueous $HClO_4$ in refluxing acetonitrile.[13]

The optically active bicyclic enedione, (+)-7a-methyl-(7*aS*)-2,3,7,7a-tetrahydro-1*H*-indene-1,5(6*H*)-dione, was prepared first by microbiological means,[5] and its absolute stereochemistry has been established.[14] The compound was later prepared by optical resolution.[15]

The products of this highly efficient asymmetric synthesis are important intermediates in natural product chemistry, such as the total synthesis of steroids and prostaglandins.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 368

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

hexanes

brine

(+)-(7aS)-7a-METHYL-2,3,7,7a-TETRAHYDRO-1 H-INDENE-1,5-(6H-DIONE

phenylmethylsilicone

(–)-trans-4-hydroxyproline

(S)-(–)-azetidinecarboxylic acid

(–)-(3aR,7aR)-2,3,3a,4,7,7a-hexahydro-3a-hydroxy-7a-methyl-1H-indene-1,5(6H)-dione

$HClO_4$

ethanol (64-17-5)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

Benzene (71-43-2)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether (60-29-7)

acetonitrile (75-05-8)

hydroquinone (123-31-9)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

toluene (108-88-3)

dichloromethane (75-09-2)

vanillin (121-33-5)

triketone

proline, S-(−)-proline, L-(−)-Proline, (S)-(−)-proline (147-85-3)

N,N-dimethylformamide, N,N-dimethyl-formamide (68-12-2)

methyl vinyl ketone (78-94-4)

2-Methyl-1,3-cyclopentanedione (765-69-5)

p-toluenesulfonic acid (104-15-4)

2-Methyl-2-(3-oxobutyl)-1,3-cyclopentanedione (25112-78-1)

2-ethyl-2-(3-oxobutyl)-1,3-cyclopentanedione

(R)-(+)-proline (344-25-2)

1 H-Indene-1,5(6 H)-dione, 2,3,7,7a-tetrahydro-7a-methyl-, (S)-, (+)-(7aS)-7a-Methyl-2,3,7,7a-tetrahydro-1H-indene-1,5(6H)-dione, (+)-7a-methyl-(7aS)-2,3,7,7a-tetrahydro-1H-indene-1,5(6H)-dione (17553-86-5)

(+)-(3aS,7aS)-2,3,3a,4,7,7a-Hexahydro-3a-hydroxy-7a-methyl-1 H-indene-1,5(6H)-dione, (+)-(3aS,7aS)-2,3,3a,4,7,7a-hexahydro-3a-hydroxy-7a-methyl-1H-indene-1,5(6H)-dione (33879-04-8)

(+)-(3aS, 7aS)-7a-ethyl-2,3,3a,4,7,7a-hexahydro-3a-hydroxy-1H-indene-1,5(6H)-dione

(+)-(7aS)-7a-ethyl-2,3,7,7a-tetrahydro-1H-indene-1,5(6H)-dione

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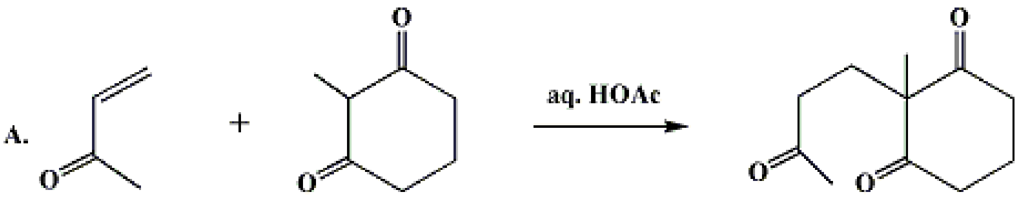
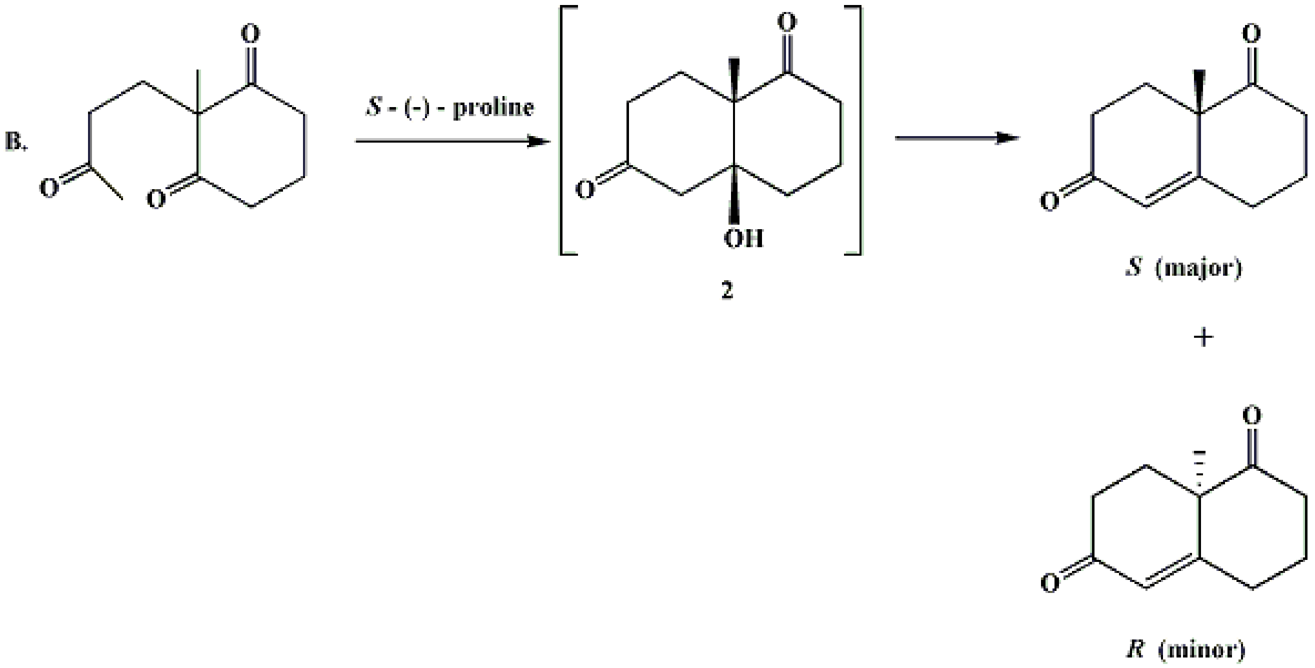
(*S*)-8a-METHYL-3,4,8,8a-TETRAHYDRO-1,6(2*H*, 7*H*)-NAPHTHALENEDIONE

[1,6(2*H*, 7*H*)-Naphthalenedione, 3,4,8,8a-tetrahydro-8a-methyl-, (*S*)-]



1



Submitted by Paul Buchschacher[1], A. Fürst[1], and J. Gutzwiller[1].
Checked by P. S. Belica, P. S. Manchand, and Gabriel Saucy.

1. Procedure

Caution! Part A should be performed in a well-ventilated hood because methyl vinyl ketone is a lachrymator.

A. *2-Methyl-2-(3-oxobutyl)-1,3-cyclohexanedione*. A 1-L, round-bottomed flask equipped with a thermometer and a reflux condenser capped with an argon-inlet tube is charged with 126.1 g (1 mol) of 2-methyl-1,3-cyclohexanedione (Note 1) and 300 mL of distilled water. To the well-stirred suspension are added 3 mL of acetic acid, 1.1 g of hydroquinone, and 142 g (167 mL, 2 mol) of freshly distilled methyl vinyl ketone (Note 2). The reaction mixture is stirred under argon at 72–75°C for 1 hr, cooled to room temperature, treated with sodium chloride (103 g), and poured into a separatory funnel containing ethyl acetate (400 mL). The organic phase is collected and the aqueous phase is reextracted twice with ethyl acetate (150 mL each time). The combined extracts are washed with two 200-mL portions of saturated brine, dried over anhydrous magnesium sulfate, and filtered, and the filtrate is evaporated at 40°C under reduced pressure (water aspirator) on a rotary evaporator. The residue is kept under high vacuum (1.0 mm) at 40°C for 30 min to give 210.8 g of crude 2-methyl-2-(3-oxobutyl)-1,3-cyclohexanedione (**1**, "trione") as a pale-yellow oil, homogeneous by thin-layer chromatography (Note 3). This crude material is used in Step B.

B. *(S)-8a-Methyl-3,4,8,8a-tetrahydro-1,6(2H, 7H)-naphthalenedione (3-S)*. A 3-L, one-necked, round-bottomed flask, equipped with an argon-inlet tube and containing a magnetic stirrer, is charged with 5.75 g (0.05 mol) of finely ground L-proline (Note 4) and a solution of 210.8 g of crude trione **1** (from Step A) in 1 L of anhydrous dimethyl sulfoxide (Note 5). The mixture is stirred at room temperature (ca. 25°C) under argon for 120 hr, the magnetic bar is removed, and the solvent is removed under high vacuum (1.0 mm) at 65°C (Note 6) on a rotary evaporator to give 206.9 g of a dark reddish-violet oil. The oil is dissolved in toluene (100 mL) and is absorbed on a column (9 cm X 60 cm) of silica gel (1.5 kg, 70–230 mesh) (Note 7), which was previously packed in hexane. Elution is carried out under a slight positive pressure of argon (ca. 1 atm) (Note 8) initially with 1 L of hexane: ethyl acetate (5 : 1) and then with a 3 : 2 mixture of hexane : ethyl acetate taking 300-mL fractions. The progress of the purification is monitored by thin-layer chromatography (Note 9): no product is observed until ca. 5 L of eluant is collected. Fractions containing the product are combined, and the solvents are removed under reduced pressure (water aspirator) at 45–50°C. The residue is then kept under high vacuum (0.1 mm) at 40°C for 30 min to give 154.2 g of an orange-colored oil, which became glassy and sometimes crystalline on standing at room temperature, $[\alpha]_D^{25}$ + 68° (toluene, *c* 1.5) (Note 10). This material is dissolved in 535 mL of ether and is filtered through a fluted filter paper to remove small particles. The flask is rinsed with 500 mL of ether, and this is passed through the filter paper. After cooling to 3°C, the combined filtrates are seeded with a few crystals of pure 3-S (Note 11), and the mixture is left undisturbed at −20°C for 18 hr. Most of the supernatant liquid is carefully decanted without agitation, and the crystals are collected by filtration. The flask is rinsed with cold (0°C) 50% ether in hexane and the rinse is used to wash the crystals. The crystals are dried for 16 hr under high vacuum at room temperature to yield 85.9 g of (*S*)-enedione (first crop), mp 49–50°C, $[\alpha]_D^{25}$ + 96.9° (toluene, *c* 1.2). The combined filtrate and washings are evaporated to give 67.1 g of an orange-colored oil, which is dissolved in 604 mL of ether, cooled to 3°C, and seeded with (*R,S*)-enedione (Note 12). The mixture is left at −20°C for 18 hr, and the supernatant liquid is carefully decanted (no agitation). The wet crystals are then collected by filtration, washed with cold (0°C) 50% ether in hexane, and dried under reduced pressure at room temperature to give 36.3 g of racemic material (3*R* + 3*S*). The filtrate and washing are evaporated to give 30.6 g of an oil, which is dissolved in 100 mL of ether, and filtered through a fluted filter paper. The flask is rinsed with 114 mL of ether, and filtered through the fluted filter paper, and the combined filtrates are cooled to 3°C and seeded with crystals of the pure 3-S. The mixture is left at −20°C overnight, the supernatant liquid is carefully decanted without much agitation and the wet crystals are collected by filtration and washed with cold (0°C) 50% hexane in ether. After drying 15.3 g of light amber-colored crystals (second crop), (mp 49–50°C, (or $[\alpha]_D^{25}$ + 97.3° (toluene, *c* 1.0). The total yield of (*S*)-enedione is 101.2 g (56.8%) (Note 13).

2. Notes

1. 2-Methyl-1,3-cyclohexanedione[2] was obtained from Aldrich Chemical Company, Inc. or Fluka and had mp 208–210°C.
2. Methyl vinyl ketone, bp 34°C/120 mm, was obtained from Aldrich Chemical Company, Inc. or Fluka.
3. Thin-layer chromatography was performed on silica gel with ethyl acetate : hexane (3 : 2). Visualization of the spots was achieved by spraying the plates with 10% ceric sulfate in 10% sulfuric acid, heating the plates to ca. 120°C, and spraying again with 10% phosphomolybdic acid in isopropyl alcohol. The product has R_f 0.50; 2-methyl-1,3-cyclohexanedione has R_f 0.30.
4. *S*-(–) Proline was obtained from Aldrich Chemical Company, Inc. It is also available from Ajinomoto GmbH or Degussa.
5. Dimethyl sulfoxide was dried over Linde 4A molecular sieves. Anhydrous, deaerated *N,N*-dimethylformamide was preferred by the submitters (Note 14).[3]
6. The temperature should be kept below 70°C.
7. Silica gel was purchased from EM Reagents, E. Merck, Darmstadt, Germany. The submitters preferred to do the preliminary purification by fractional vacuum distillation using a Hickman-type short-path distillation head. The main fraction distills as a light orange oil, bp 126–130°C (0.02 mm) (Note 14).
8. The procedure of W. C. Still[4] is used.
9. Silica gel and 60% ethyl acetate in hexane were used. The product, R_f 0.40, is visible under short-wavelength UV light, whereas the starting trione, also R_f 0.40, is not. Visualization is achieved as

described in (Note 3).

10. The material was melted at 55°C under reduced pressure (12 mm) on a rotary evaporator prior to sampling in order to measure the optical rotation on a homogeneous sample.

11. Compound 3-S was obtained from material having (or $[\alpha]_D^{25}$ + 68° (toluene, *c* 1.5) that was prepared in another experiment. Thus, 28.2 g of this (*S*)-enedione is dissolved in 90 mL of ether and the solution is left at −20°C for 18 hr. The crystals are collected by filtration without much agitation, washed with 30 mL of cold (0°C) 50% ether in hexane, and redissolved in 117 mL of ether. The solution is left at −20°C for 18 hr, and the crystals are collected by filtration, washed with 30 mL of cold (0°C) 50% ether in hexane, and dried under reduced pressure (1.0 mm) at room temperature to give 12.0 g of (*S*)-enedione, mp 50°C, $[\alpha]_D^{25}$ + 100° (benzene, *c* 1.5); $[\alpha]_D^{25}$ + 97° (toluene, *c* 1.0). It should be possible to prepare seed crystals from a small aliquot, but this was not attempted by the checkers.

12. Racemic Wieland-Miescher ketone was obtained from Aldrich Chemical Company, Inc. or prepared according to the procedure of Ramachandran and Newman.[5]

13. ^{1}H NMR studies (100 MHz, $CDCl_3$) using the shift reagent tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato] europium(III) (purchased from Aldrich Chemical Company, Inc.) indicated that the two crops were enantiomerically pure. Under identical conditions (10 mg of reagent per 9.6 mg of substrate), absorption due to the vinyl proton at 5.86 in the racemate appeared as two peaks (1-Hz separation) of equal intensity.

14. The submitters' procedure using dimethylformamide in Step B and using distillation for isolation of the enantiomerically enriched ketone was checked by K. Job, A. K. Beck, and D. Seebach and proved equally satisfactory.

3. Discussion

Racemic 8a-methyl-3,4,8,8a-tetrahydro-1,6(2*H*, 7*H*)-naphthalenedione (the Wieland-Miescher ketone)[5,6] is a versatile building block for the synthesis of steroids[7] and terpenoids.[8] The (*S*)-enantiomer, 3-S, was first obtained by microbiological means[9] and by classical resolution via a derived hemiphthalate.[10] The present synthesis[3] of 3-S is based[11 12] on the asymmetric intramolecular aldolization of the prochiral triketone 1 using *S*-(−)-proline catalytically. The product is obtained in 56% yield (from **2**) and is enantiomerically pure on the basis of optical rotation and NMR spectroscopy determined in the presence of a chiral shift reagent. Despite numerous synthetic investigations and modifications of this asymmetric Robinson annulation,[13 14 15] the mechanism of enantio-differentiation is still not fully understood;[16 17 18] see discussion in this volume, p. 367, relating to the asymmetric synthesis of the corresponding *S*-(+)-tetrahydro-7-methylindenedione.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

brine

tris[3-(heptafluoropropylhydroxymethylene)-d-camphorato] europium(III)

Wieland-Miescher ketone

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

ethyl acetate (141-78-6)

ether (60-29-7)

hydroquinone (123-31-9)

sodium chloride (7647-14-5)

toluene (108-88-3)

isopropyl alcohol (67-63-0)

magnesium sulfate (7487-88-9)

triketone

L-proline, S-(–) Proline, S-(–)-proline (147-85-3)

N,N-dimethylformamide, dimethylformamide (68-12-2)

hexane (110-54-3)

methyl vinyl ketone (78-94-4)

vinyl (2669-89-8)

dimethyl sulfoxide (67-68-5)

ceric sulfate (13590-82-4)

argon (7440-37-1)

8a-methyl-3,4,8,8a-tetrahydro-1,6(2H, 7H)-naphthalenedione (20007-72-1)

2-Methyl-1,3-cyclohexanedione (1193-55-1)

2-Methyl-2-(3-oxobutyl)-1,3-cyclohexanedione (5073-65-4)

phosphomolybdic acid (51429-74-4)

(S)-8a-METHYL-3,4,8,8a-TETRAHYDRO-1,6(2H, 7H)-NAPHTHALENEDIONE, (S)-8a-Methyl-3,4,8,8a-tetrahydro-1,6(2H, 7H)-naphthalenedione (3-S), 1,6(2H, 7H)-Naphthalenedione, 3,4,8,8a-tetrahydro-8a-methyl-, (S)- (33878-99-8)

S-(+)-tetrahydro-7-methylindenedione

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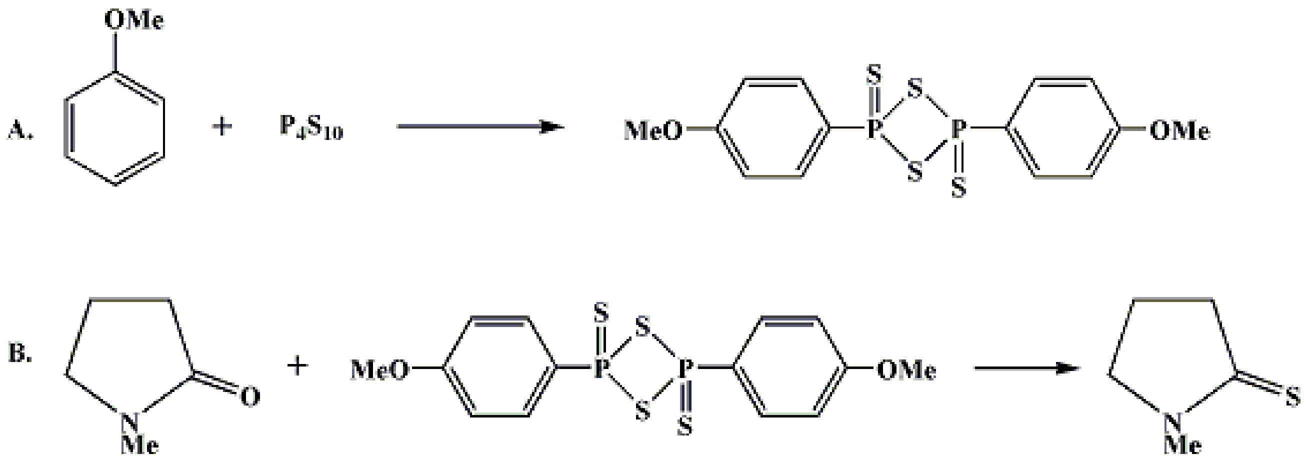
Organic Syntheses, CV 7, 372

THIATION WITH 2,4-BIS(4-METHOXYPHENYL)-1,3,2,4-DITHIADIPHOSPHETANE 2,4-DISULFIDE: *N*-METHYLTHIOPYRROLIDONE

[2-Pyrrolidinethione, 1-methyl-]



Submitted by I. Thomsen, K. Clausen, S. Scheibye, and S.-O. Lawesson[1].
Checked by Clayton H. Heathcock, Mark Sanner, and Terry Rosen.

1. Procedure

Caution! Preparation of 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide must be carried out in an efficient hood because hydrogen sulfide is evolved. Also, benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A. *2,4-Bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide (1)*. A dry 1-L, three-necked, round-bottomed flask, fitted with a reflux condenser, mechanical stirrer, and ground-glass stopper, is charged with 111.0 g (0.25 mol) of phosphorus sulfide, P_4S_{10} (Note 1) and 270 g (2.5 mol) of anisole (Note 1). Stirring is commenced and the mixture is heated at reflux temperature by use of a heating mantle. After 1 hr, the solution is homogeneous and after a second hour 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide (**1**) begins to precipitate. The reaction mixture is allowed to cool to room temperature and the precipitate is filtered (Note 2) and washed with anhydrous ether (2 × 50 mL) and 50 mL of anhydrous chloroform (free of alcohols) to yield 160–165 g (79–82%) of pale-yellow crystals, mp 228°C (Note 3) and (Note 4).

B. *N-Methylthiopyrrolidone* (**2**). A 200-mL, three-necked, round-bottomed flask is fitted with a rubber septum, thermometer, magnetic stirring bar, and reflux condenser equipped with a nitrogen bubbler. The flask is charged with 19.8 g (19.3 mL, 0.20 mol) of *N*-methylpyrrolidone (Note 5) and 40.4 g (0.10 mol) of **1**, whereupon the temperature of the reaction mixture increases to 75–80°C. After 5 min, 35 mL of benzene (Note 6) is added by syringe and the mixture is stirred while being brought to reflux (Note 7). The mixture is heated at reflux for 2 hr (Note 8) and then cooled to room temperature, whereupon it again becomes heterogeneous. The benzene is removed with the aid of a rotary evaporator and the resulting yellow slurry is distilled under reduced pressure through a 5-cm Vigreux column to provide 23.0 g (100%) of *N*-methylthiopyrrolidone (**2**) as a yellow liquid, bp 94–97°C/0.03 mm (Note 9).

2. Notes

1. Commercial phosphorus sulfide, P_4S_{10}, is used without purification. Checkers used P_4S_{10} from Matheson, Coleman and Bell and from Alfa Products, Morton Thiokol, Inc. Best results (yield, melting point) were obtained with the Alfa sample, mp 291–295°C.
2. Excess anisole (137 g) can be recovered by distillation of the filtrate.
3. The product is somewhat hygroscopic and should be stored in an airtight container. It is also available as Lawesson's reagent from Aldrich, Fluka, and from Merck–Schuchard.
4. The checkers obtained 176 g (87%) of **1**, mp 228–231°C.
5. Commercial material from the Aldrich Chemical Company was stored over Linde 4A molecular sieves.
6. Benzene was distilled from and stored over sodium wire.
7. During this operation most of the yellow solid gradually dissolves, affording a clear yellow solution with small amounts of suspended solid. When reflux begins, the internal temperature of the reaction mixture is 95°C.
8. The reaction time can be decreased to 3 min by the use of toluene as solvent.
9. The purified product freezes when stored in a refrigerator. The spectral properties are as follows: ^1H NMR ($CDCl_3$) δ: 2.07 (quintet, 2 H, *J* = 7), 3.03 (t, 2 H, *J* = 7), 3.29 (s, 3 H), 3.77 (t, 2 H, *J* = 7). IR (neat): 1520 cm^{-1}.

3. Discussion

A variety of thiating reagents are known: H_2S,[2] H_2S/HCl,[3] H_2S_2/HCl,[4] $(Et_2Al)_2S$,[5] $(EtAlS)_n$,[6] SiS_2,[7] B_2S_3,[7] $PCl_5/Al_2S_3/Na_2SO_4$,[8] Na_2S/H_2SO_4,[9] P_2S_5[10] P_2S_5/Pyridine,[11] P_2S_5/NEt_3,[12] $P_2S_5/NaHCO_3$,[13] RPS$(OR^1)_2$[14] $PSCl_x$ $(NMe_2)_{3-x}$ (X = 0–3),[15] and SCNCOOEt.[16] The reagent described here, 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide (**1**),[17] offers a number of advantages as a thiating reagent. It is easily prepared in a simple one-step procedure employing commercially available starting materials. It has a satisfactory shelf life, provided it is protected from moisture. In contrast to commercial P_4S_{10}, compound **1** is a well-defined reagent that gives reproducible results, usually in high yield. Under defined conditions, certain selectivity has been observed.[18,19,20] Other methods for the preparation of analogs of **1** have been described.[21,22,23]

The thiation procedure described here[24] is an example of a general synthetic method for the conversion of carbonyl to thiocarbonyl groups. Similar transformations have been carried out with ketones,[25] carboxamides,[26,27,28,29,30] esters,[31,32] thioesters,[31] lactones,[18,33] thiolactones,[18] imides,[24] enaminones,[34] and protected peptides.[35]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Benzene (71-43-2)

ether (60-29-7)

chloroform (67-66-3)

hydrogen sulfide (7783-06-4)

Anisole (100-66-3)

toluene (108-88-3)

sodium wire (13966-32-0)

N-methylpyrrolidone (872-50-4)

2-Pyrrolidinethione, 1-methyl-, N-Methylthiopyrrolidone (10441-57-3)

2,4-BIS(4-METHOXYPHENYL)-1,3,2,4- DITHIADIPHOSPHETANE 2,4-DISULFIDE, 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide (19172-47-5)

phosphorus sulfide

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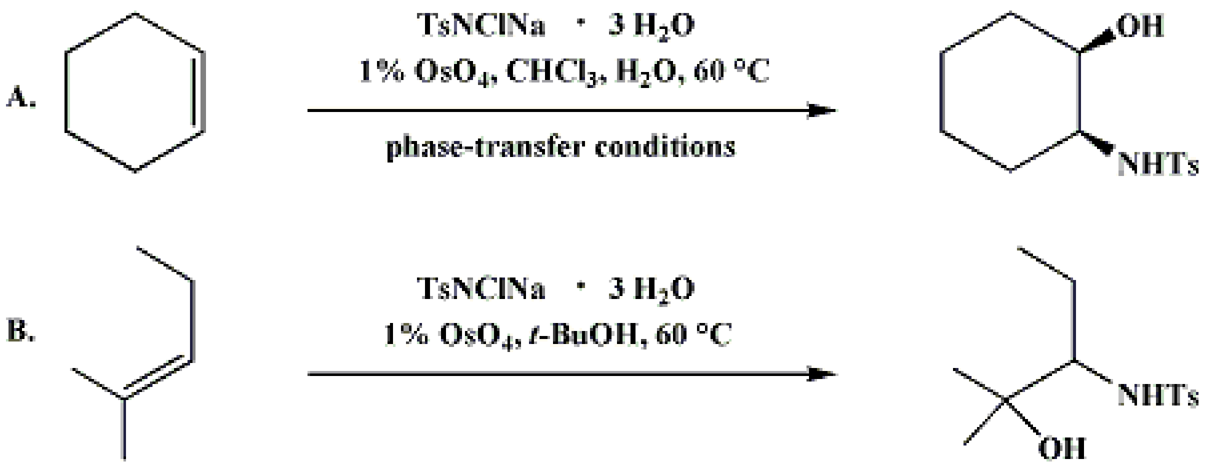
Organic Syntheses, CV 7, 375

OSMIUM-CATALYZED VICINAL OXYAMINATION OF OLEFINS BY CHLORAMINE-T: *cis*-2-(*p*-TOLUENESULFONAMIDO)CYCLOHEXANOL AND 2-METHYL-3-(*p*-TOLUENESULFONAMIDO)-2-PENTANOL

[Benzenesulfonamide, *N*-(2-hydroxycyclohexyl)-4-methyl-, *cis* and Benzenesulfonamide, *N*-(1-ethyl-2-hydroxy-2-methylpropyl)-4-methyl-]



Submitted by Eugenio Herranz and K. Barry Sharpless[1].
Checked by Rita Locher, Thomas Weller, and Dieter Seebach.

1. Procedure

Caution! Because of the volatility and toxic nature of OsO_4, these reactions should be carried out in a well-ventilated hood.

A. *cis-2-p(Toluenesulfonamido)cyclohexanol*. A 1-L, three-necked, round-bottomed flask is equipped with an efficient mechanical stirrer, thermometer, and reflux condenser. The flask is charged with 8.2 g (0.1 mol) of cyclohexene (Note 1), 250 mL of reagent grade chloroform (Note 2), and 10 mL (1 mmol) of osmium tetroxide catalyst solution (Note 3). To the resulting black solution is added a solution of 35.2 g (0.125 mol) of chloramine-T trihydrate (Note 4) and 1.1 g (5 mmol) of benzyltriethylammonium chloride (Note 5) in 250 mL of distilled water. Vigorous stirring is begun, and the reaction mixture is brought to 55–60°C by means of a heating mantle.

After 10 hr at 55–60°C, 14.2 g (0.1 mol) of sodium sulfite (Note 6) is added and the

mixture is refluxed for 3 hr. The hot reaction mixture (Note 7) is transferred to a 1-L separatory funnel and allowed to stand for 10 min. The organic layer is collected in a 500-mL, round-bottomed flask. The aqueous layer is extracted once with 25 mL of $CHCl_3$ that is then combined with the original organic layer. Removal of solvent with a rotary evaporator provides a residue (Note 8) that is transferred to a 350-mL fritted-glass funnel and triturated successively with 200 mL and 100 mL of saturated sodium chloride solution containing 1% sodium hydroxide (Note 9) and finally with two 50-mL portions of distilled water.

The resulting solid is placed in a 500-mL Erlenmeyer flask and dissolved in a mixture of 250 mL of $CHCl_3$ and 25 mL of CH_3OH. Anhydrous magnesium sulfate (ca. 8–10 g) is added and the resulting suspension is stirred magnetically for 5 min. Filtration of this suspension through a Celite mat on a sintered-glass funnel (Note 10), followed by evaporation of the solvent, affords (after drying under reduced pressure) 20.3–22 g (75–81.2%) of almost pure *cis*-2-(*p*-toluenesulfonamido)cyclohexanol, mp 155–157°C (Note 11). The oxyaminated product may be purified further by washing with toluene to give 20–21.8 g (74.3–80.9%); mp 157–158°C (Note 12).

B. *2-Methyl-3-(p-toluenesulfonamido)-2-pentanol*. A 500-mL, three-necked, round-bottomed flask is equipped with an efficient mechanical stirrer, thermometer, and reflux condenser. The flask is charged with 8.4 g (0.1 mol) of 2-methyl-2-pentene (Note 1), 100 mL of reagent-grade *tert*-butyl alcohol (Note 2), 10 mL (1 mmol) of osmium tetroxide catalyst solution (Note 3), and 35.2 g (0.125 mol) of chloramine-T trihydrate (Note 4). Vigorous stirring is begun, and the reaction mixture is brought to 55–60°C by means of a heating mantle.

After ca. 20 hr at 55–60°C, the mixture is cooled to room temperature using a water bath, and then 1.1 g (0.03 mol) of sodium borohydride is added (Note 6). Stirring is continued at room temperature for about 1 hr. Removal of the solvent on a rotary evaporator gives an oil that is taken up in 100 mL of ethyl acetate and washed once with a solution that is prepared by mixing 100 mL of saturated sodium chloride solution containing 1% sodium hydroxide (Note 13) with 25 mL of distilled water. The organic layer is washed twice more with 200 mL of saturated sodium chloride solution containing 1% sodium hydroxide and finally with 100 mL of saturated sodium chloride solution (Note 9) and (Note 14). Addition of anhydrous magnesium sulfate, filtration through a column of 75 g of silica gel (Note 15), elution with ethyl acetate (Note 16), and evaporation of the solvent on a rotary evaporator provides 21.5 g of the crude oxyaminated product (Note 17). The solid is then washed twice with ether (Note 18) to give 13.8–14.9 g (51–55%) of white, crystalline 2-methyl-3-(*p*-toluenesulfonamido)-2-pentanol, mp 96–97°C. Concentration of the ether yields an additional 4.0–5.0 g (15–18%) of oxyaminated product, mp 95–97°C (Note 19).

2. Notes

1. Cyclohexene and 2-methyl-2-pentene were used as commercially available.

2. The amount of solvent used is not critical. Several experiments have been performed at higher and lower concentrations and in all cases the yields were very much alike.
3. Osmium tetroxide was supplied commercially in 1-g amounts in sealed glass ampuls. The procedure we describe below should be followed to prepare the osmium tetroxide catalyst solution. Work in a well-ventilated hood. One ampul is scored in the middle, broken open, and the two halves are dropped into a clean brown bottle containing 39.8 mL of reagent grade *tert*-butyl alcohol and 0.20 mL of 70 or 90% *tert*-butyl hydroperoxide. The bottle is capped (use caps with Teflon liners) and then swirled to ensure dissolution of the OsO_4. Each milliliter of this stock solution contains 25 mg (ca. 0.1 mmol) of OsO_4. These solutions are stored in the hood at room temperature and seem to be very stable. We have also prepared five times more dilute solutions of OsO_4 in *tert*-butyl alcohol, which we use for small-scale experiments.[2]
4. Chloramine-T trihydrate (CT) was obtained commercially. Excess chloramine-T is used because we have observed traces of the α-ketosulfonamide in those cases where the oxyaminated product contains a secondary hydroxyl group. We have also observed that these α-ketosulfonamides are further oxidized under the reaction conditions in a process that consumes several moles of chloramine-T.
5. Benzyltriethylammonium chloride was used as purchased.
6. The rates of reduction of the osmate esters vary considerably. We found that, although the sulfite method (in the past we have also used sodium bisulfite) would reduce osmate esters from monosubstituted and 1,2-disubstituted olefins, osmate esters derived from trisubstituted and 1,1-disubstituted olefins were more inert to this treatment. Sodium borohydride reduces even these more hindered osmate esters rapidly at room temperature.
7. The oxyaminated product derived from cyclohexene is highly crystalline and begins to crystallize if the chloroform phase is allowed to cool.
8. The residue is dried under reduced pressure to remove the last traces of chloroform and *tert*-butyl alcohol, and then pulverized with a mortar and pestle.
9. In this way the *p*-toluenesulfonamide by-product along with some other impurities are removed from the oxyaminated product.
10. This treatment removes the suspended osmium particles from the solution.
11. GLC analysis revealed a purity of 99%.
12. The product obtained by this procedure is pure enough for most purposes. Its melt, however, is faintly cloudy. A product of higher purity, giving a clear melt, mp 158–159°C, can be obtained by recrystallization from about 10 mL of $CHCl_3$ per gram of oxyaminated product. The structural characterization of *cis*-2-(*p*-toluenesulfonamido)cyclohexanol, mp 158–159°C, is as follows. Anal. calcd. for $C_{13}H_{19}NO_3S$: C, 57.97; H, 7.11; N, 5.20. Found: C, 57.81; H, 6.98; N, 5.19. ^1H NMR ($CDCl_3$) δ: 1.2–1.9 (m, 8 H, C*H*), 2.26 (d, 1 H, *J* = 4, O*H*), 2.44 (s, 3 H, Ar CH_3), 3.30 (m, 1 H, NC*H*), 3.80 (m, 1 H, OC*H*), 5.30 (d 1 H, *J* = 7, N*H*), 7.55 (AA'BB' pattern, 4 H, *J* = 8, Ar*H*); IR (KBr pellet) cm^{-1}: 3420, 3150, 1305, 1285, 1145, 1085, 550 all (s); 2920, 2850, 1440, 970, 930, 890, 815, 660

all (m): 1590, 1370, 1250, 1195, 1185, 1060, 1000 all (w). GC analysis was carried out using the following conditions: 6-ft × 2-mm glass column, packed with 5% OV-17 on 80/100 GasChrom Q, at 70 ρ 250°C (32°C/min), retention time 9.50–9.60 min.

13. First a 1% solution of NaOH is prepared and then sodium chloride is added until saturation is reached. For the first washing, 25 mL of distilled water is added to 100 mL of the above solution in order to dissolve the inorganic salts present in the reaction mixture.

14. When ethyl acetate is used as the extracting solvent, rapid separation of the two phases was achieved. If a slight emulsion forms at the interphase during the last wash, the addition of celite and subsequent filtration improves the separation.

15. Silica Gel 60 (70–230 mesh ASTM) was used as obtained commercially. A column 50 cm long by 3.5 cm in diameter was used.

16. Approximately 700 mL of EtOAc was necessary to elute all the oxyaminated product from the silica gel column (monitoring by TLC elution with EtOAc is continued until a UV active spot does not appear on TLC). To speed up filtration, a slight pressure of 4 psi is applied.

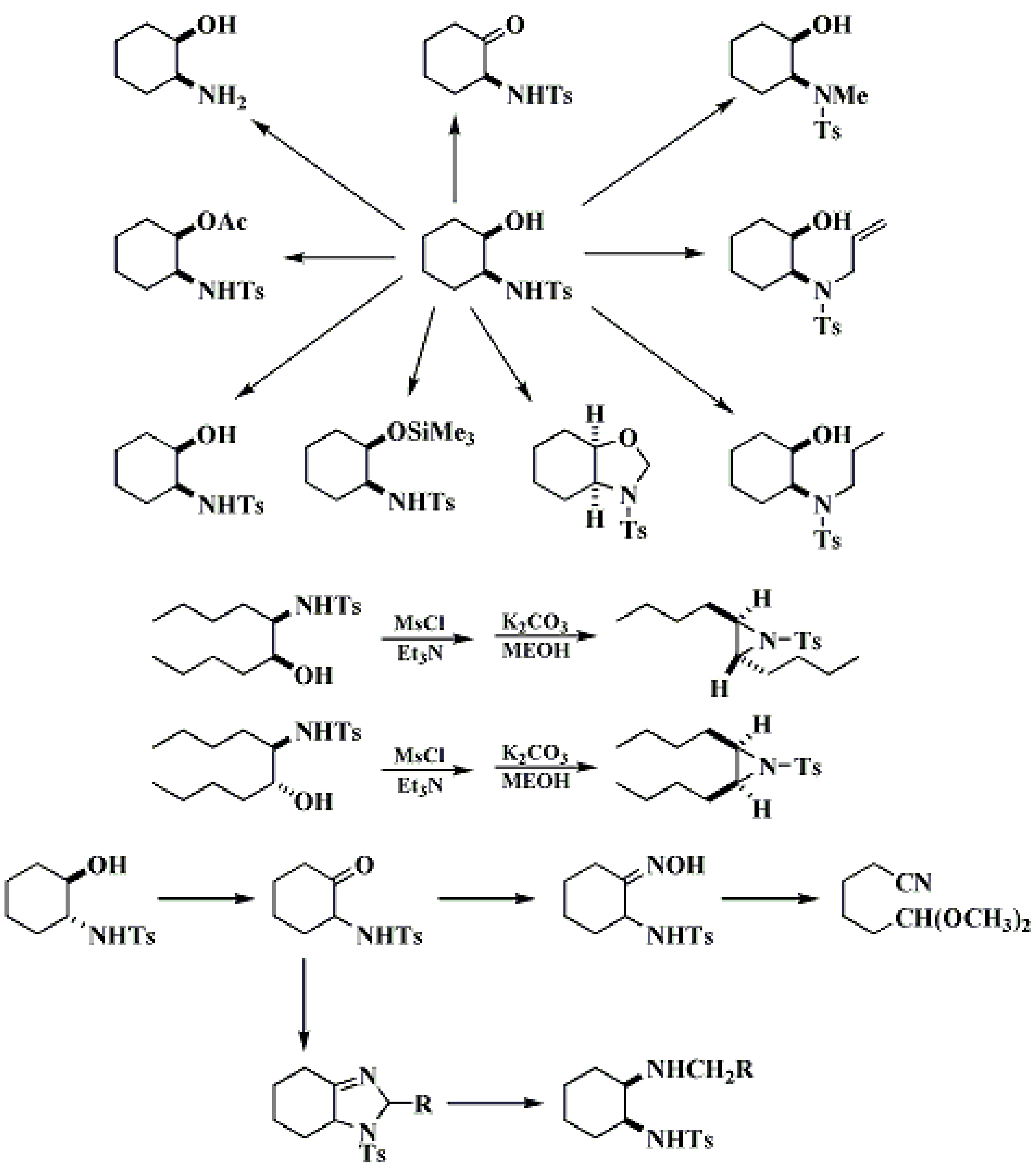
17. The product is a yellowish-brown solid that usually crystallizes when the last traces of EtOAc are removed on the rotary evaporator. If problems are encountered in inducing crystallization, either high vacuum or addition of ether followed by concentration should yield the desired solid.

18. The solid was washed in a 60-mL, sintered-glass funnel, the first time with 30 mL of ether and the second time with 25 mL.

19. The product obtained by this procedure is relatively pure. However, a product of higher purity, giving a clear melt, mp 99–100°C, can be obtained by recrystallization from about 1 mL of toluene per gram of oxyaminated product.

3. Discussion

This osmium-catalyzed procedure provides the first practical and direct means for the cis addition of a hydroxyl group and an arylsulfonamido moiety ($ArSO_2NH$) to an olefinic bond. The resulting vicinal hydroxy arylsulfonamides may in some cases be useful in their own right, but they are easily transformed in a variety of selective and potentially useful ways. Some of the interesting transformations that we[3] have observed are shown below:



Procedure (Step) A is very effective for most monosubstituted and 1,2-disubstituted olefins. This method,[2] using phase-transfer conditions (PTC), has been developed recently in our laboratory and represents a substantial improvement over our former procedures.[4 5 6] Cyclooctene, (*Z*)-5-decene, stilbene, ethyl crotonate, and 1-decene are among the olefins that are readily oxyaminated under the conditions described in Procedure A.

It is important to point out that the work-up we have used in the case of cyclohexene is a peculiar one because of the exceptional crystallinity of the oxyamination product. Generally, removal of the *p*-toluenesulfonamide is accomplished by shaking the chloroform layer with a saturated sodium chloride solution containing 1% sodium

hydroxide.

The chloramine derivatives ($ArSO_2NClNa$) of a variety of other arylsulfonamides (Ar = phenyl, *o*-tolyl, *p*-chlorophenyl, *p*-nitrophenyl, and *o*-carboalkoxyphenyl) have been used successfully in these catalytic oxyaminations. Since only chloramine-T (Ar = *p*-tolyl) and chloramine-B (Ar = phenyl) are commercially available, we have developed a convenient procedure for generating the chloramines in situ for use in the modification involving phase-transfer catalysis. One simply stirs a suspension of the arylsulfonamide with an equivalent of sodium hypochlorite (Clorox) until a homogeneous solution is obtained. When this solution is used in the PTC method (see 2 for experimental details), the yields of oxyaminated product are comparable with those obtained with isolated chloramine salts.

The PTC method gives poor results with trisubstituted and 1,1-disubstituted olefins. The oxyamination product may still form, but it is accompanied by a number of by-products. Fortunately, this class of olefins is successfully oxyaminated by the alternative procedure (B). Methylcyclohexene, α-methylstyrene, 2-methyl-2-hepten-6-one, and its ketal are examples of olefins that give oxyamination products in good yield following Procedure B.

Addition of a phase-transfer catalyst such as dicyclohexyl-18-*crown*-6 to the reaction mixture (in Procedure B) results in a faster reaction rate. However, there are no significant changes in the final yield of oxyamination product.

We have carried out experiments on a 1-mol scale in the case of cyclohexene and α-methylstyrene (in the cyclohexene 1-mol experiment, the reaction mixture was 2.5 times more concentrated than described here), and have realized 70–80% and 65–75% yields, respectively, of the oxyaminated products.

Procedure A does not succeed with diethyl fumarate and 2-cyclohexen-1-one. Both chloramine-T and part of the olefin are consumed, but the oxyamination product has not been detected in the reaction mixtures. It seems likely that it forms, but is unstable to the reaction conditions. Both of these olefins do form isolable oxyamination products under the milder conditions (room temperature) of a more recent oxyamination procedure.[7 8]

Procedure B does not succeed with tetramethylethylene and cholesterol, and it seems reasonable to anticipate negative results with most hindered tri- and tetrasubstituted olefins. No reaction occurs, and chloramine-T is not consumed.

The sulfonamide protecting group on the nitrogen may be undesirable in some cases. For this reason we have developed an analogous osmium-catalyzed procedure that effects cis addition of hydroxyl and carbamate (ROCONH) moieties across the olefinic linkage.[7,8] β-Amino alcohols with benzyloxycarbonyl (Z or CBZ) and *tert*-butoxycarbonyl (BOC) protecting groups on the nitrogen are accessible directly from the corresponding olefins by the new method.[7,8]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 223

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

OsO_4

cis-2-p(Toluenesulfonamido)cyclohexanol

CH_3OH

ethyl acetate, EtOAc (141-78-6)

ether (60-29-7)

sodium sulfite (7757-83-7)

sodium hydroxide, NaOH (1310-73-2)

chloroform, $CHCl_3$ (67-66-3)

Cyclohexene (110-83-8)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

sodium bisulfite (7631-90-5)

toluene (108-88-3)

diethyl fumarate (623-91-6)

sodium hypochlorite (7681-52-9)

tetramethylethylene (563-79-1)

magnesium sulfate (7487-88-9)

Cholesterol (57-88-5)

stilbene

osmium tetroxide (20816-12-0)

ethyl crotonate (623-70-1)

Methylcyclohexene

tert-butyl alcohol (75-65-0)

α-methylstyrene (98-83-9)

sodium borohydride (16940-66-2)

cyclooctene

2-cyclohexen-1-one (930-68-7)

benzyltriethylammonium chloride (56-37-1)

tert-butyl hydroperoxide (75-91-2)

2-methyl-2-hepten-6-one (110-93-0)

1-decene (872-05-9)

2-methyl-2-pentene (625-27-4)

p-toluenesulfonamide (70-55-3)

cis-2-(p-Toluenesulfonamido)cyclohexanol (58107-40-7)

2-Methyl-3-(p-toluenesulfonamido)-2-pentanol, Benzenesulfonamide, N-(1-ethyl-2-hydroxy-2-methylpropyl)-4-methyl- (87291-33-6)

Benzenesulfonamide, N-(2-hydroxycyclohexyl)-4-methyl-, cis

chloramine-T trihydrate

(Z)-5-decene

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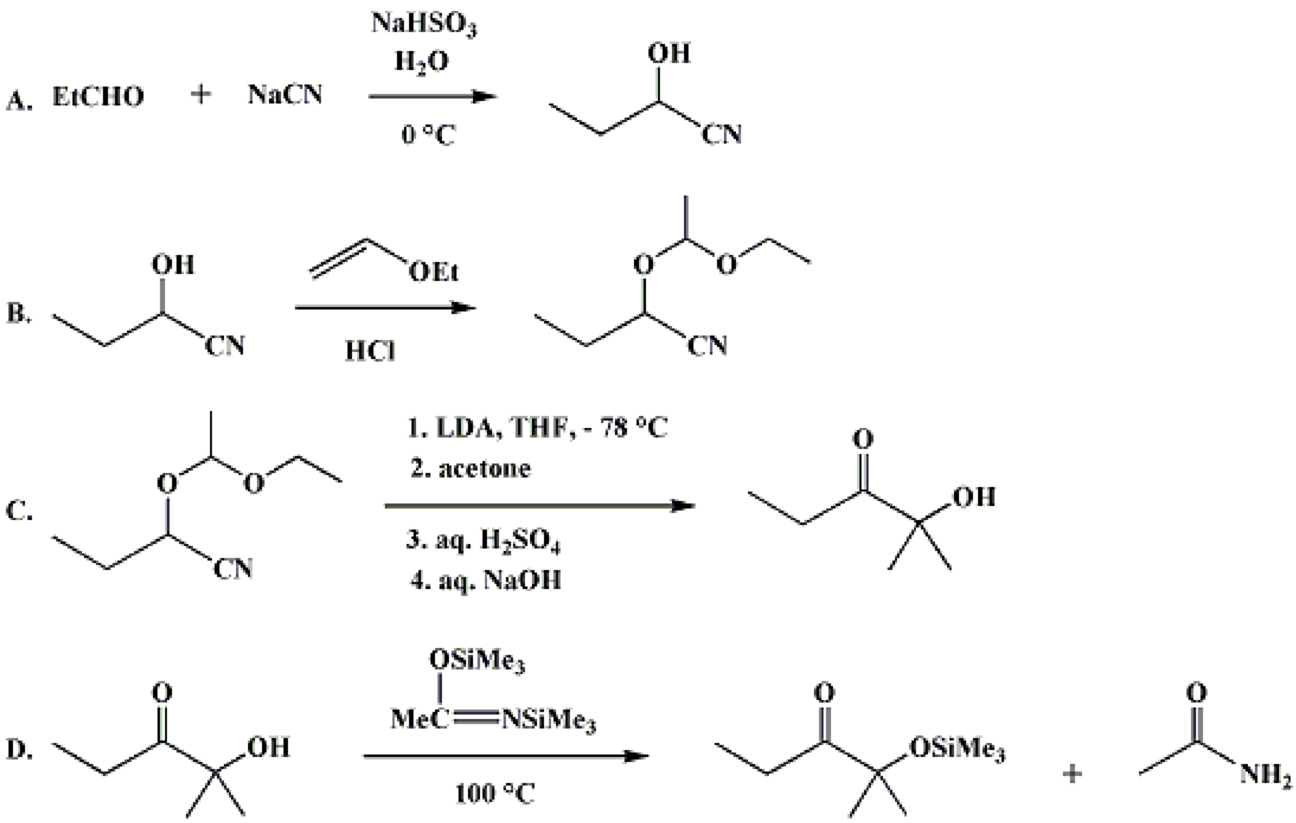
Organic Syntheses, CV 7, 381

2-METHYL-2-(TRIMETHYLSILOXY)PENTAN-3-ONE

[3-Pentanone, 2-methyl-2-[(trimethylsilyl)oxy]-]



Submitted by Steven D. Young, Charles T. Buse, and Clayton H. Heathcock[1].
Checked by Joseph R. Flisak, Sami Farahat, Stan S. Hall, Hugh W. Thompson, and Gabriel Saucy.

1. Procedure

A. *2-Hydroxybutanenitrile*. A 3-L, three-necked, round-bottomed flask is fitted with a mechanical stirrer and thermometer and charged with 312 g (3.0 mol) of sodium bisulfite and 1050 mL of water. The stirrer is started and after the sodium bisulfite has dissolved, the flask is placed in an ice–salt bath. A solution of 147 g (3.0 mol) of sodium cyanide (Note 1) in 450 mL of water and 174 g (3.0 mol) of propanal (Note 2) are separately cooled to 0°C in ice–salt baths. When the temperature of the vigorously stirring sodium bisulfite solution has stabilized at 0°C the cold propanal is added in one portion. The temperature of the reaction solution immediately increases to ca. 35°C and then returns to ca. 0°C. After 30 min the cold sodium cyanide solution is added in one portion. The reaction mixture again warms to ca. 15°C and then returns to ca. 0°C. This mixture is stirred for 2 hr at 0°C, during which time a thick white precipitate of sodium sulfite forms. The supernatant liquid is decanted into a 4-L separatory funnel and the precipitate is washed with 1 L of ice–water. The combined aqueous solution is extracted with three 1-L portions of ethyl ether. The combined ether extracts are washed with 1 L of saturated brine and dried by stirring (magnetic stirring bar) over magnesium sulfate for 2 hr. The solution is filtered through a coarse, sintered-glass funnel and the ether is removed with a rotary evaporator at water aspirator pressure. After the pH of the residue is adjusted to 5 with a few drops of concentrated hydrochloric acid (Note 3), the residue is distilled to give 154–192 g (60–75%) of 2-hydroxybutanenitrile, bp 108–114°C (30 mm), as a colorless liquid

(Note 4).

B. *2-[(1'-Ethoxy)-1-ethoxy]butanenitrile*. A 1-L, three-necked, round-bottomed flask is equipped with a condenser topped with a calcium chloride drying tube, a magnetic stirring bar, a 500-mL pressure-equalizing addition funnel, and a thermometer. The flask is charged with 174 g (2.05 mol) of 2-hydroxybutanenitrile to which 0.5 mL of concentrated hydrochloric acid has been added. The addition funnel is charged with 221 g (3.07 mol) of ethyl vinyl ether (Note 5), which is then added dropwise to the stirring cyanohydrin at such a rate that the temperature is maintained at ca. 50°C. When the addition is complete, the mixture is heated to 90°C for 4 hr. The condenser is replaced with a distillation head and the dropping funnel and thermometer are replaced with stoppers. Direct distillation of the gold–yellow solution from the reaction flask yields 226–277 g (70–86%) of nearly pure 2-[(1'-ethoxy)-1-ethoxy]butanenitrile, bp 85–84°C (30 mm), as a colorless liquid (Note 6).

C. *2-Hydroxy-2-methylpentan-3-one*. A dry, 5-L, three-necked (including a thermometer well), round-bottomed flask is equipped with a mechanical stirrer, low-temperature thermometer, nitrogen inlet, rubber septum, and a 1-L, graduated, pressure-equalizing addition funnel that is sealed with a rubber septum. The flask is charged with 775 mL of dry tetrahydrofuran (Note 7) and 166 g (1.64 mol) of dry diisopropylamine (Note 8). The contents of the flask are cooled to −10°C (dry ice–acetone bath) and 1095 mL (1.6 mol) of 1.5 *M* butyllithium in hexane (Note 9), which has been transferred to the addition funnel by means of a 16-gauge cannula and argon pressure, is slowly added to the stirring solution at such a rate as to maintain a temperature of −10°C. After the addition is complete, 50 mL of dry THF is added to the addition funnel with syringe to rinse the walls of the funnel; the rinse is added, and then the mixture is cooled to −75°C. The addition funnel is charged by syringe with 246 g (1.6 mol) of 2-[(1'-ethoxy)-1-ethoxy]butanenitrile, which is then added at such a rate that the temperature does not exceed −70°C. The mixture is stirred for 10 min and 104 g (1.8 mol) of dry acetone (Note 10) is added by syringe over a 30-min period at such a rate that the temperature of the reaction mixture does not exceed −70°C. When the addition is complete, the cooling bath is removed and the reaction mixture is allowed to warm to 0°C. The solution is poured into 1 L of water and the resulting mixture is concentrated at aspirator pressure with a rotary evaporator (30°C water bath) to remove the volatile organic compounds. The aqueous residue is extracted with three 1-L portions of methylene chloride. The organic extracts are combined and washed with two 500-mL portions of water and then concentrated with a rotary evaporator (25°C water bath) at aspirator pressure to obtain a yellow syrupy residue. This material is stirred with 680 mL of methanol and 340 mL of aqueous 5% sulfuric acid overnight at room temperature. The methanol is evaporated with a rotary evaporator (30°C water bath) at aspirator pressure and the yellow residue is extracted with three 1-L portions of ethyl ether. The combined ether extracts are shaken in a 4-L separatory funnel with 210 mL of 10 *N* aqueous sodium hydroxide for 15 min (Note 11). The layers are separated, and the ether layer is washed with 500 mL of brine and dried by stirring (magnetic stirring bar) over magnesium sulfate for 2 hr. The drying agent is removed by filtration through a coarse sintered-glass funnel and the ether is removed with a rotary evaporator (water bath below 40°C) at aspirator pressure. The yellow-orange liquid residue is distilled to obtain 82–115 g (45–63%) of 2-hydroxy-2-methylpentan-3-one, bp 57–65°C (15 mm), as a paleyellow liquid (Note 12) and (Note 13).

D. *2-Methyl-2-(trimethylsiloxy)pentan-3-one*. A dry, 500 mL, three-necked, round-bottomed flask equipped with a mechanical stirrer, reflux condenser with a nitrogen inlet, and a thermometer is charged with 84 g (0.72 mol) of 2-hydroxy-2-methylpentan-3-one and 74 g (0.36 mol) of *N,O*-bis(trimethylsilyl)acetamide (Note 14). The mixture is heated at 100°C for 12 hr with stirring and then cooled to room temperature, at which point the mixture becomes a semisolid as the acetamide crystallizes. The semisolid mixture is diluted with 50 mL of water and stirred at room temperature for 1 hr (Note 15). After the stirring is stopped, 200 mL of hexane is added and the layers are separated. The aqueous layer is extracted with 100 mL of hexane. The combined hexane extracts are washed

with four 100-mL portions of water and then dried over magnesium sulfate for 2 hr. After removal of the drying agent by filtration through a coarse sintered-glass funnel, the hexane is evaporated with a rotary evaporator (25°C water bath) at aspirator pressure. The crude, pale-yellow oil is distilled to afford 105–112 g (75–80%) of 2-methyl-2-(trimethylsiloxy)pentan-3-one, bp 71–75°C (15 mm), as a colorless liquid (Note 16).

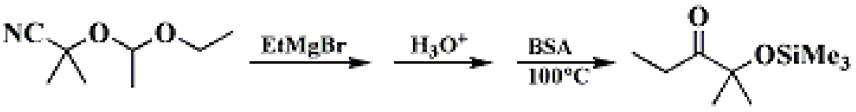
2. Notes

1. *1. Caution! Sodium cyanide and 2-hydroxybutanenitrile are extremely toxic. Great care should be taken when using these materials. Reactions should be carried out in a well-ventilated hood and suitable protective clothing should be worn at all times.*
2. Propanal was obtained from Aldrich Chemical Company and was used without further purification.
3. If HCl is omitted, the cyanohydrin reverts to HCN and propanal on attempted distillation. The checkers found it necessary to ensure that the residue was acidic by adjusting the pH to 5 by testing the residue with wet pH paper.
4. The IR spectrum (neat) shows absorption at 3420, 2960, 2310, and 1460 cm^{-1}.
5. Ethyl vinyl ether was obtained from Aldrich Chemical Company and was used without further purification.
6. The IR spectrum (neat) shows absorption at 2970, 1425, and 1385 cm^{-1}. The C N absorption is not observed.
7. Tetrahydrofuran is distilled under a nitrogen atmosphere from sodium–benzophenone immediately prior to use.
8. Diisopropylamine is distilled under a nitrogen atmosphere from calcium hydride prior to use. It may be stored under nitrogen for 1 week without redistillation.
9. *Concentrated butyllithium may ignite spontaneously on exposure to air or moisture. Manipulations with this reagent should be performed with care.* The submitters used butyllithium, 1.5 *M* in hexane from Foote Mineral Company, and measured it by transferring the solution to a 2-L, graduated cylinder stoppered with a rubber septum with a 15-gauge cannula and argon. The solution was then transferred directly to the reaction vessel by the same procedure. The checkers used fresh butyllithium, 1.55 *M* in hexane under argon, from Aldrich Chemical Company. Stainless steel cannulas with deflected points (double-tip syringe needles) are available from Ace Glass, Inc. and Aldrich Chemical Co.
10. ACS Certified acetone was obtained from Fisher Chemical Company and distilled from Linde 3A molecular sieves immediately prior to use.
11. Periodic shaking (once every 3 min) is sufficient to effect cyanohydrin hydrolysis.
12. The ^{1}H NMR (200 MHz, $CDCl_3$) spectrum is as follows δ: 1.12 (t, 3 H, *J* = 7.2), 1.39 (s, 6 H), 2.59 (q, 2 H, *J* = 7.2), 3.85 (s, 1 H). The IR spectrum (neat) shows absorption at 3450, 2960, and 1705 cm^{-1}.
13. In one run, the checkers, at this point obtained 241 g, bp 116–120°C (12 mm) of the protected cyanohydrin (NMR), which had not been deprotected and hydrolyzed, rather than the expected product. In this case, the entire distillate was resubjected to the acid and base sequence, which afforded the desired product in a 61% overall isolated yield.
14. *N,O*-Bis(trimethylsilyl)acetamide was obtained from Aldrich Chemical Company and used without further purification.
15. This process is necessary to ensure hydrolysis of any unreacted *N,O*-bis(trimethylsilyl) acetamide, which inevitably contaminates the product if the step is omitted.
16. The ^{1}H NMR spectrum (200 MHz, $CDCl_3$) is as follows: δ: 0.15 (s, 9 H), 1.02 (t, 3 H, *J* = 7.2), 1.33 (s, 6 H), 2.67 (q, 2 H, *J* = 7.2). The IR spectrum (neat) shows absorptions at 2980 and 1720 cm^{-1}.

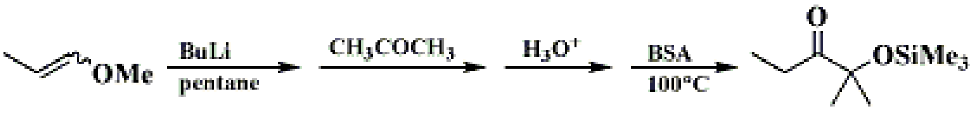
3. Discussion

2-Methyl-2-(trimethylsiloxy)pentan-3-one (**1**) is the prototype member of a series of α-trimethylsiloxy ketones that are useful for stereoselective aldol addition reactions (Equation 1).[2] β-Hydroxy ketones **2** may be converted into β-hydroxy acids,[2] β-hydroxy aldehydes,[3] and other β-hydroxy ketones.[4]

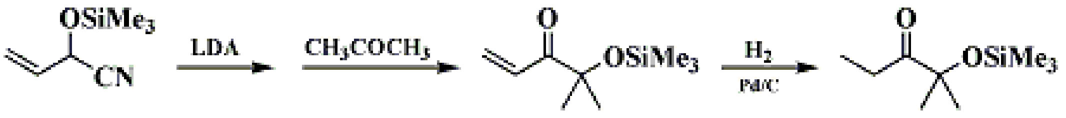
Compound **1** has also been prepared by the following methods. Addition of ethylmagnesium bromide to the protected cyanohydrin of acetone, followed by hydrolysis and silylation provides **1** in 40% yield (Equation 2).[2] Metallation of 1-methoxypropene by butyllithium in pentane[5] gives 1-lithio-1-methoxypropene, which reacts with acetone to give, after hydrolysis and silylation, ketone **1**



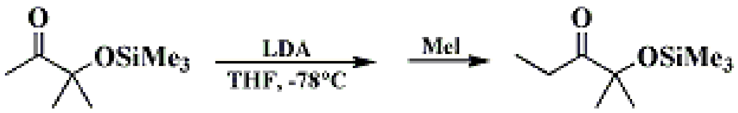
in 25–30% overall yield (Equation 3).[6] The trimethylsilyl ether of acrolein



cyanohydrin, prepared by the method of Hünig,[7] may be metallated and added to acetone to provide an enone which is hydrogenated to **1** (Equation 4).[8] Although the



overall yield in this sequence can be quite high, the intermediate enone **3** polymerizes very readily, and the procedure is not reliable on a large scale. Compound **1** has also been prepared by methylation of the lithium enolate of the lower homolog, **4**, (Equation 5).[9] Although this alkylation provides



1 in 60% yield on a 2-mmol scale, the desired product is accompanied by a significant quantity of the dimethylated product, from which it is not easily separated.[8]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 185

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

brine

2-[(1'-Ethoxy)-1-ethoxy]butanenitrile

HCN

sulfuric acid (7664-93-9)

hydrochloric acid, HCl (7647-01-0)

methanol (67-56-1)

ether, ethyl ether (60-29-7)

sodium sulfite (7757-83-7)

sodium hydroxide (1310-73-2)

sodium cyanide (143-33-9)

propanal (123-38-6)

nitrogen (7727-37-9)

sodium bisulfite (7631-90-5)

acetone (67-64-1)

Benzophenone (119-61-9)

sodium (13966-32-0)

Pentane (109-66-0)

methylene chloride (75-09-2)

ethylmagnesium bromide (925-90-6)

magnesium sulfate (7487-88-9)

butyllithium (109-72-8)

Tetrahydrofuran, THF (109-99-9)

hexane (110-54-3)

ethyl vinyl ether (109-92-2)

calcium hydride (7789-78-8)

argon (7440-37-1)

diisopropylamine (108-18-9)

2-methyl-2-(trimethylsiloxy)pentan-3-one, 3-Pentanone, 2-methyl-2-[(trimethylsilyl)oxy]- (72507-50-7)

2-Hydroxybutanenitrile (4476-02-2)

2-Hydroxy-2-methylpentan-3-one (2834-17-5)

1-methoxypropene (4188-68-5)

1-lithio-1-methoxypropene

N,O-bis(trimethylsilyl)acetamide

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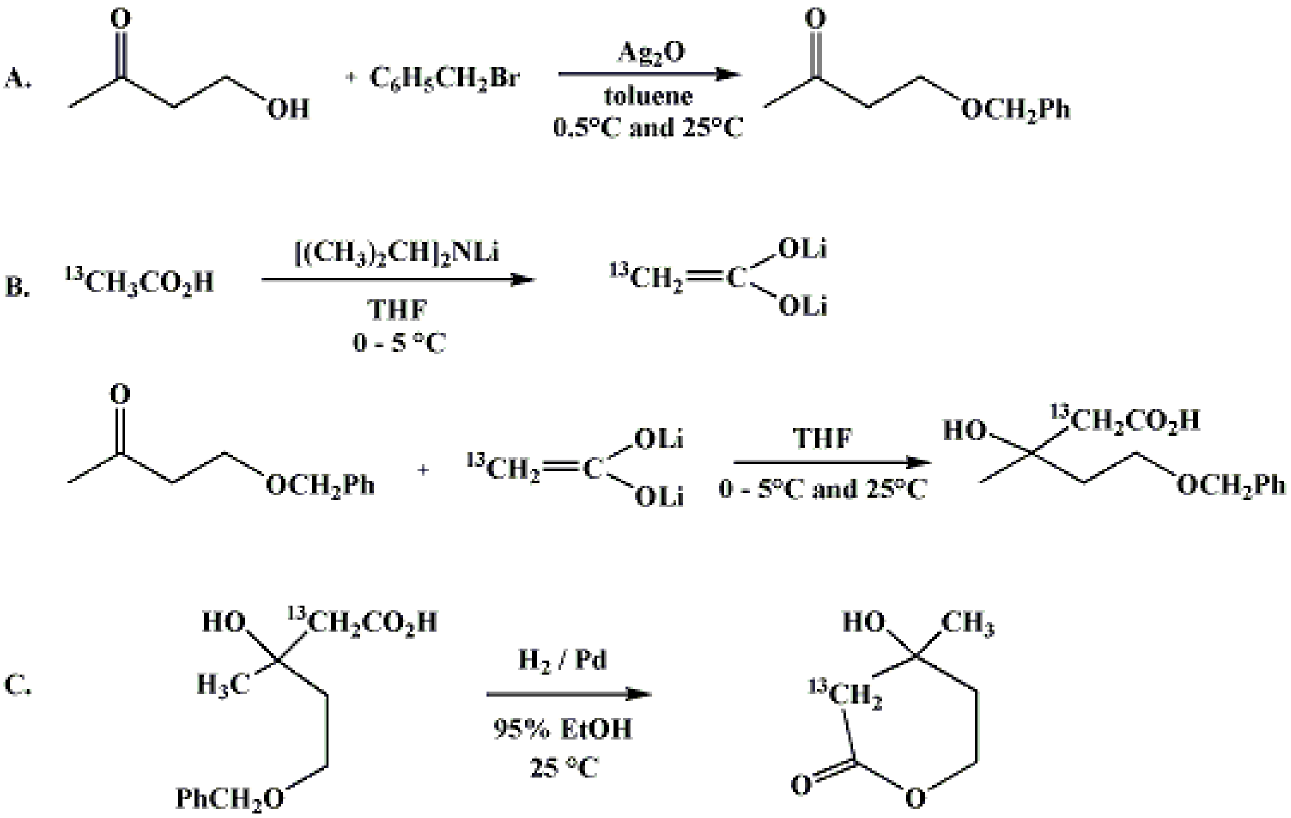
(*R*,*S*)-MEVALONOLACTONE-2-^{13}C

[2*H*-Pyran-2-one-^{13}C, tetrahydro-4-hydroxy-4-methyl-]



Submitted by Masato Tanabe and Richard H. Peters[1].
Checked by Paula M. Roach, Sung W. Rhee, and Robert M. Coates.

1. Procedure

Benzyl bromide is a lachrymator. This procedure should be conducted in a ventilated hood.

A. *4-Benzyloxy-2-butanone*. A 100-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, a condenser mounted with a nitrogen inlet, and a pressure-equalizing dropping funnel (Note 1). The flask is charged with 4.40 g (0.050 mol) of 4-hydroxy-2-butanone (Note 2), 50 mL of dry toluene (Note 3), and 13.9 g (0.060 mol) of freshly prepared silver oxide (Note 4). The suspension is stirred and cooled in an ice bath while 12.0 g (0.070 mol) of benzyl bromide (Note 5) is added over ca. 5 min. The ice bath is removed, and the mixture is allowed to stir for 18 hr at room temperature (Note 6). The suspension is filtered through Celite, the filter cake is washed with two 50-mL portions of toluene, and the combined filtrates are evaporated under reduced pressure. The remaining liquid, which weighs 9.6–10.4 g, is dissolved in 15 mL of 5% tetrahydrofuran in hexane. The cloudy solution is applied to a 5-cm × 47.5-cm column prepared with 380–385 g of silica gel (Note 7) packed in 5% tetrahydrofuran in hexane. The column is eluted with 5% tetrahydrofuran in hexane, and 250-mL fractions are collected and analyzed by TLC (Note 8). A total of 12 or 13 fractions (3–3.25 L) is collected first to separate benzyl bromide, dibenzyl ether, and other minor by-products. The product is then eluted with 0.5–1.0 L of tetrahydrofuran, the solvent is evaporated, and the remaining 6.0–6.5 g of liquid is distilled under reduced pressure. After separation of a 0.7–

1.0 g forerun, bp 30–68°C (0.2 mm), consisting mainly of benzyl alcohol, 3.87–4.33 g (43–49%) of 4-benzyloxy-2-butanone, bp 77–79°C (0.2 mm), n_D^{25} 1.5018 is collected (Note 9).

B. *5-Benzyloxy-3-hydroxy-3-methylpentanoic-2-^{13}C acid*. A 50-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, a rubber septum, a condenser connected to a nitrogen inlet, and a pressure-equalizing dropping funnel. The apparatus is purged with nitrogen and dried (Note 1), and the flask is charged with 1.79 g (2.4 mL, 0.0177 mol) of freshly distilled diisopropylamine and 6.5 mL of dry tetrahydrofuran (Note 10). The solution is stirred and cooled in an ice bath while 7.22 mL (0.0169 mol) of 2.34 *M* butyllithium in hexane (Note 11) is added from the dropping funnel over 30 min. After 30 min a solution of 0.439 g (0.00720 mol) of acetic acid-2-^{13}C (Note 12) in 3 mL of tetrahydrofuran is added by syringe over ca. 10 min. The solution is stirred and cooled in an ice bath for 3.5 hr, after which 1.30 g (0.0073 mol) of 4-benzyloxy-2-butanone in 4 mL of tetrahydrofuran is added by syringe over 15 min. Stirring is continued for 2 hr at 0°C and 18 hr at room temperature. The reaction mixture is cooled in an ice bath, hydrolyzed by adding 4.5 mL of water, and concentrated under reduced pressure to remove most of the tetrahydrofuran. The remaining aqueous suspension is basified by addition of 6 mL of aqueous 4% sodium hydroxide and extracted with 30 mL of diethyl ether. The ethereal layer is extracted with 40 mL of 4% sodium hydroxide, the combined alkaline extracts are cooled and acidified to pH 3 with ca. 10 mL of 18% hydrochloric acid, and the aqueous mixture is extracted with three 25-mL portions of ether. The combined ethereal extracts are dried over anhydrous sodium sulfate and evaporated. The remaining viscous, yellow liquid weighs 0.95–1.01 g (55–59%) and is used in part C without further purification (Note 13).

C. *Mevalonolactone-2-^{13}C*. In a 250-mL Parr hydrogenation bottle are placed 50 mL of 95% ethanol, 0.107 g (0.001 mol) of palladium black (Note 14), and 0.519 g (0.00217 mol) of 5-benzyloxy-3-hydroxy-3-methylpentanoic acid-2-^{13}C. The bottle is attached to a Parr hydrogenation apparatus (Note 15), charged to 50 psig with hydrogen and shaken at room temperature for 2 hr. The hydrogen is flushed from the bottle with nitrogen, and the suspension is filtered by gravity through a layer of Celite with a medium-porosity sintered-glass Büchner funnel to separate the catalyst. *The palladium is pyrophoric and must always be kept wet with ethanol during filtration to prevent contact with air* (Note 16). The bed of Celite and adhering catalyst is rinsed with three 5-mL portions of ethanol. The combined filtrates are returned to the Parr bottle, 0.107 g (0.001 mol) of fresh palladium black is added, and the hydrogenation is continued for another 8 hr. The catalyst is separated by filtration as previously described, and the combined filtrates are evaporated under reduced pressure. Distillation of the residual liquid with a Kugelrohr apparatus at 90–100°C and 0.01 mm affords 0.235–0.249 g (83–88%) of mevalonolactone-2-^{13}C as a slightly yellow oil (Note 17).

2. Notes

1. The apparatus was dried in an oven at 125°C and allowed to cool while a stream of nitrogen was passed through the condenser and out the dropping funnel. Alternatively the apparatus may be flushed with nitrogen and flamed dry. A nitrogen atmosphere was maintained within the apparatus during the subsequent operations.
2. 4-Hydroxy-2-butanone was purchased from Chemical Samples Company by the checkers and distilled, bp 56–58°C (5.0 mm). The submitters obtained the material from BASF Wyandotte Corporation, Parsippany, NJ 07054.
3. Toluene was dried over sodium wire for 36 hr.
4. The silver oxide was prepared by the following procedure. A solution of 6.9 g (0.172 mol) of sodium hydroxide in 200 mL of water was heated to 80–90°C and added to a solution of 30

g (0.177 mol) of silver nitrate in 200 mL of water, also heated to 80–90°C. The resulting hot suspension was quickly filtered, and the filter cake was washed with 200 mL of hot water, 200 mL of 95% ethanol, and 200 mL of absolute ethanol. The silver oxide was dried at 1 mm and weighed 17.8–18.3 g (87–89%).

5. Benzyl bromide was distilled before use, bp 89°C (14 mm).

6. The reaction is mildly exothermic, and the mixture becomes warm after the ice bath is removed. The checkers monitored the progress of the reaction by TLC on silica gel with 5% methanol in chloroform as developing solvent. After 2 hr the spot at R_f 0.42 for the starting alcohol has disappeared, and the formation of the spots at R_f 0.70 and 0.47 for the product and benzyl alcohol, respectively, appeared to be complete.

7. The checkers used silica gel 60 having particle sizes from 0.05 to 0.2 mm (70–270-mesh ASTM), supplied by Brinkmann Instruments, Inc., Westbury, NY. The submitters used 450 g of silica gel with 90–200 mesh purchased from Gallard-Schlesinger Chemical Manufacturing Corp., Carle Place, NY 11514.

8. Thin-layer chromatograms were performed by the checkers on plates coated with silica gel using chloroform as developing solvent. The R_f values for benzyl bromide, dibenzyl ether, 4-benzyloxy-2-butanone, and benzyl alcohol were 0.72, 0.61, 0.20, and 0.09, respectively. Chromatograms of the crude product showed spots for these four components and in addition three minor spots at R_f 0.44, 0.40, and 0.36. The first six fractions (1.5 L) were combined and evaporated, affording 0.6–1.5 g of material judged to be mainly benzyl bromide. The following six or seven fractions (1.5–1.75 L) provided 1.6–3.2 g of material composed largely of dibenzyl ether.

9. The submitters obtained 4.5 g (51%) of product, bp 95°C (0.8 mm), n_D^{27} 1.5029. A boiling point of 88–91°C (0.5 mm) and a refractive index of n_D^{28} 1.5040 are reported for 4-benzyloxy-2-butanone.[2] The product was analyzed by the checkers. Anal. calcd. for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 73.87; H, 8.09. The product has the following spectral characteristics: IR (liquid film) cm^{-1}: 1725 and 1710 (split C=O), 1360, 1175, 1110, 1090, 740, 700; ^1H NMR ($CDCl_3$) δ: 2.17 (singlet, 3, CH_3), 2.70 (triplet, 2, J = 6, C$H_2$$CH_2$O), 3.78 (triplet, 2, J = 6, CH_2CH_2O), 4.50 (singlet, 2, C$H_2$$C_6H_5$), 7.32 (singlet, 5, C_6H_5).

10. Diisopropylamine was dried over potassium hydroxide pellets and distilled from barium oxide before use. The submitters purified tetrahydrofuran by distillation from lithium aluminum hydride. For a warning concerning the potential hazards of this procedure, see *Org. Synth., Coll. Vol. V,* **1973**, 976. The checkers distilled the solvent from the sodium ketyl of benzophenone.

11. Butyllithium in hexane is available from Alfa Products, Morton Thiokol, Inc. The submitters standardized the butyllithium solution by titration of diphenylacetic acid in tetrahydrofuran.[3] The concentration of the butyllithium solution was determined by the checkers by titration of a 1-mL aliquot in 10 mL of benzene with 1 *M* 2-butanol in xylene using 1,10-phenanthroline as indicator.[4]

12. Acetic acid-2-^{13}C of 90% isotopic purity was purchased by the checkers from Stohler Isotope Chemicals, Rutherford, NJ, and dried by distillation from phosphorus pentoxide in the following manner. A 0.5-g portion of the labeled acetic acid was transferred to a 5-mL flask containing 0.1 g of phosphorus pentoxide. The flask (A) was attached to a vacuum system (see f.htmigure 1), chilled with a dry ice-acetone bath until the mixture solidified, and evacuated to 0.01 mm. The stopcock was closed, the cooling bath was moved to the receiver (flask B), and flask A was allowed to warm to room temperature. The distillation was completed by heating flask A to 60°C. Nitrogen was introduced into the system and flask B

removed and stoppered. The recovery of acetic acid-2-^{13}C was 0.42–0.44 g (84–86%).

Figure 1

Figure 1

13. The submitters carried out the procedure in Section B at five times the scale described with 1.96 g (0.0321 mol) of acetic acid-2-^{13}C and obtained 4.01 g (56%) of product. The spectral properties of the product are as follows: IR (liquid film) cm^{-1}: 1710 (C=O); ^{1}H NMR ($CDCl_3$) δ: 1.31 (doublet, ca. 2.4, J = 4.5, $^{13}CH_2CCH_3$), 1.31 (singlet, ca. 0.6, $^{12}CH_2CCH_3$), 1.89 (multiplet, 2, CH_2CH_2O), 2.55 (doublet, ca. 1.6, J = 128, $^{13}CH_2CO_2H$), 2.55 (singlet, ca. 0.4, $^{12}CH_2CO_2H$), 3.70 (triplet, 2, J = 6, CH_2CH_2O), 4.52 (singlet, 2, $C_6H_5CH_2$), 7.35 (singlet, 5, C_6H_5). The product may be purified further by Kugelrohr distillation with an oven temperature of 100–110°C (0.015 mm).

14. The palladium black was purchased from Engelhard Industries Division, Engelhard Minerals and Chemicals Corporation, Iselin, NJ 08830. The checkers found that the hydrogenolysis may also be effected with 5% palladium on carbon, although 20 hr was required to achieve complete reaction.

15. The hydrogenation apparatus is available from Parr Instrument Company, Inc., Moline, IL 61265.

16. As a further precaution the checkers chilled the suspension in an ice bath prior to filtration.

17. The product was further purified by the checkers by recrystallization from ca. 1.5 mL of ether at 0°C. The recovery of white, crystalline mevalonolactone-2-^{13}C, mp 24–26°C, was 90–92%. The reported[2] melting point is 27–28°C. The spectral properties of the product are as follows: IR (liquid film) cm^{-1}: 3300 (OH), 1730 (C=O); 220–MHz ^{1}H NMR ($CDCl_3$) δ: 1.40 (doublet, ca. 2.4, J = 4.5, $^{13}CH_2CCH_3$), 1.40 (singlet, ca. 0.6, $^{12}CH_2CCH_3$), 1.90 (multiplet, 2, CH_2CH_2O), 2.54 and 2.67 (eight-line *ABX* multiplet, ca. 1.6, J_{AB} = 17, J_{AX} = 132, J_{BX} = 127, $^{13}CH_AH_B$), 2.54 and 2.67 (*AB* doublet, 0.4, J = 17, $^{12}CH_AH_B$), 4.47 (multiplet, 2, CH_2CH_2O).

3. Discussion

The important role of mevalonate is the biosynthesis of terpenes and sterols has been the impetus for the development of numerous syntheses of the parent mevalonolactone[5,6,7,8,9,10,11] and a host of labeled analogs.[7,8,9,10,11] Mevalonolactone has been prepared by reduction of dimethyl or diethyl 3-hydroxy-3-methylglutarate in two stages with lithium aluminum hydride and hydrogen[12] or sodium borohydride[13 14]; by reduction of monomethyl 3-hydroxy-3-methylglutarate with lithium borohydride[15,16] or sodium in liquid ammonia[16]; by reduction of mevaldic acid or its esters with borohydride,[13,17 18,19] hydrogen,[18] or NADPH in enzyme preparations[20 21 22]; by reduction of *N*-(diphenylmethyl)-3,4-epoxy-5-hydroxy-3-methylpentanamide with lithium borohydride followed by hydrolysis;[23] by oxidation of 3,5-dihydroxy-3-methylpentanal and its derivatives with hydrogen peroxide in acetic acid,[24 25] or formic acid,[8] or with aqueous bromine;[26] by oxidation of 3-methyl-1,3,5-pentanetriol with chromium trioxide[27] or silver carbonate;[28] by ozonolysis of 3-methyl-1-tetrahydropyranyloxy-5-hexen-3-ol;[6,29] by hydrolysis of 3,5-dihydroxy-3-methylpentanenitrile;[30] by degradation of linalool;[31] and by Reformatsky reactions of acetate with a variety of 4-substituted 2-butanones.

The Reformatsky reactions of methyl or ethyl bromoacetate with 4-acetoxy-,[2,32 33] 4-benzyloxy-,[2] 4-tetrahydropyranyloxy-,[2] 4-chloro-,[6] and 4,4-dimethoxy-2-butanone[17,18,24,25] have been carried out. The adducts were converted to mevalonolactone by hydrolysis and, in the case of the acetal reactant, by appropriate reduction and oxidation procedures. The same Reformatsky-type syntheses of mevalonolactone have also been performed using the lithium and magnesium carbanions of acetate esters[5,26,34,35] and the dianion of acetic acid[35,36] instead of the usual zinc reagent. The intramolecular Reformatsky reaction of 4-(bromoacetoxy)-2-butanone gives mevalonolactone directly.[37] A related route to mevalonolactone involves boron trifluoride-catalyzed cycloaddition of ketene to 4-acetoxy-2-butanone followed by hydrolysis.[24]

Many of the procedures given above have been utilized for the preparation of mevalonolactone labeled with isotopes of carbon, hydrogen, and oxygen.[7,8,9,10,11] Mevalonolactone-^{14}C has been prepared with the label at all six positions: 1-,[7,38] 2-,[7,17,32,33] 3-,[14] 3'-,[27,39] 4-,[7,24] and 5-^{14}C.[26] Preparations of singly and doubly labeled mevalonolactone-^{13}C have been reported recently: 2-,[35,40] 3-,[41] 4-,[42 43] 3',4-,[7,24] 3,4-,[35,43] and 4,5-^{13}C.[44] The procedure described here[35] for the preparation of mevalonolactone-2-^{13}C is both convenient and economical compared to the usual Reformatsky methods since acetic acid-2-^{13}C is utilized directly in the condensation reaction, rather than methyl or ethyl bromoacetate. The overall yield of mevalonolactone-2-^{13}C is 46–52% based on acetic acid-2-^{13}C.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

palladium black

sodium ketyl of benzophenone

dimethyl or diethyl 3-hydroxy-3-methylglutarate

methyl or ethyl bromoacetate

2H-Pyran-2-one-^{13}C, tetrahydro-4-hydroxy-4-methyl-

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ammonia (7664-41-7)

Benzene (71-43-2)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

silver oxide (20667-12-3)

silver nitrate (7761-88-8)

bromine (7726-95-6)

sodium sulfate (7757-82-6)

oxygen (7782-44-7)

formic acid (64-18-6)

barium oxide

nitrogen (7727-37-9)

carbon (7782-42-5)

potassium hydroxide pellets (1310-58-3)

toluene (108-88-3)

zinc (7440-66-6)

sodium, sodium wire (13966-32-0)

palladium (7440-05-3)

Benzyl alcohol (100-51-6)

Dibenzyl ether (103-50-4)

hydrogen peroxide (7722-84-1)

xylene (106-42-3)

Diphenylacetic acid (117-34-0)

chromium trioxide (1333-82-0)

boron trifluoride (7637-07-2)

benzyl bromide (100-39-0)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

4-hydroxy-2-butanone (590-90-9)

silver carbonate (534-16-7)

hexane (110-54-3)

4,4-dimethoxy-2-butanone (5436-21-5)

sodium borohydride (16940-66-2)

2-Butanol (78-92-2)

1,10-phenanthroline (66-71-7)

diisopropylamine (108-18-9)

Linalool (78-70-6)

phosphorus pentoxide (1314-56-3)

4-Benzyloxy-2-butanone (6278-91-7)

mevalonolactone

monomethyl 3-hydroxy-3-methylglutarate

lithium borohydride (16949-15-8)

3,5-dihydroxy-3-methylpentanal

3-methyl-1,3,5-pentanetriol (7564-64-9)

3-methyl-1-tetrahydropyranyloxy-5-hexen-3-ol

3,5-dihydroxy-3-methylpentanenitrile

4-(bromoacetoxy)-2-butanone

4-acetoxy-2-butanone (10150-87-5)

N-(diphenylmethyl)-3,4-epoxy-5-hydroxy-3-methylpentanamide

5-Benzyloxy-3-hydroxy-3-methylpentanoic-2-^{13}C acid, 5-benzyloxy-3-hydroxy-3-methylpentanoic acid-2-^{13}C (57830-65-6)

acetic acid-2-^{13}C

Mevalonolactone-2-^{13}C

Mevalonolactone-^{14}C

(R,S)-Mevalonolactone-2-^{13}C

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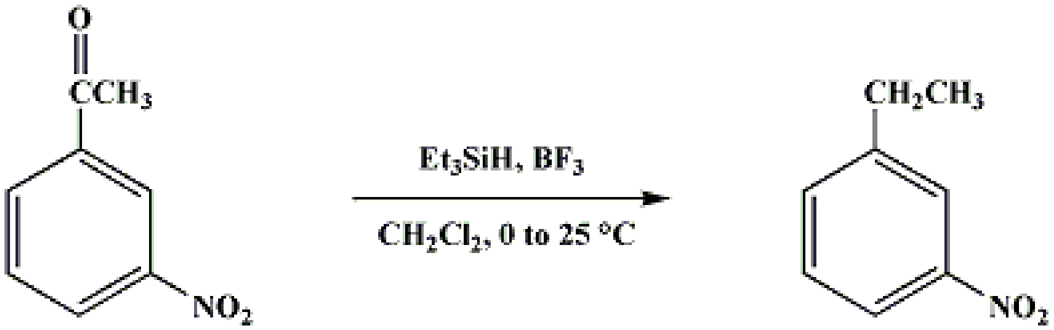
REDUCTION OF KETONES TO HYDROCARBONS WITH TRIETHYLSILANE: *m*-NITROETHYLBENZENE

[Benzene, 1-ethyl-3-nitro-]



Submitted by James L. Fry, Steven B. Silverman, and Michael Orfanopoulos[1].
Checked by Jack W. Muskopf and Robert M. Coates.

1. Procedure

Caution! Boron trifluoride gas is highly corrosive; this preparation should be conducted in a well-ventilated hood.

A dry, 250-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, a gas-inlet tube (Note 1), a pressure-equalizing dropping funnel, and a Dewar condenser cooled with ice-water and fitted with a drying tube containing anhydrous calcium sulfate (Drierite). A solution of 20.9 g (0.180 mol) of triethylsilane (Note 2) in 80 mL of dichloromethane (Note 3) is placed in the flask. The solution is stirred rapidly and cooled in an ice bath while boron trifluoride gas (Note 4) is introduced below the surface of the liquid at a moderate rate. The first appearance of white fumes at the exit of the drying tube (Note 5) indicates that the solution is saturated and the apparatus is filled with boron trifluoride. The flow of boron trifluoride is adjusted to a level sufficient to maintain a slight emission of white fumes from the drying tube, and a solution of 10.0 g (0.0606 mol) of *m*-nitroacetophenone (Note 6) in 30 mL of dichloromethane is added dropwise during 10 min. Stirring and cooling are continued for 30 min, after which the flow of boron trifluoride gas is stopped and the cooling bath is removed. The mixture is stirred at room temperature for 20 min, cooled again with the ice bath, and hydrolyzed by adding 20 mL of aqueous saturated sodium chloride. The upper organic layer is decanted from the salts, which are then dissolved in 50 mL of water. The aqueous solution is extracted with two 25-mL portions of pentane, which are combined with the original organic layer. The organic solution is washed with two 25-mL portions of saturated sodium chloride and dried with anhydrous sodium sulfate. Distillation at atmospheric pressure through

a 10-cm Vigreux column serves to separate solvent and ca. 15 g of a mixture of primarily triethylsilane and triethylfluorosilane, bp 106–109°C (Note 7). The remaining liquid is distilled in a short-path distillation apparatus under reduced pressure, affording 8.33–8.38 g (91–92%) of pale yellow *m*-nitroethylbenzene, bp 120–121°C (15 mm), 134–135°C (22 mm), n_D^{25} 1.5330 (Note 8).

2. Notes

1. A Pasteur pipet clamped in an O-ring thermometer adapter served as a convenient, adjustable gas-inlet tube. The large end of the pipet was fitted with a small rubber septum, through which a syringe needle was passed for introducing the boron trifluoride gas.

2. Triethylsilane was purchased from either Petrarch Systems, Inc., or PCR Research Chemicals, Inc. The reagent was dried with anhydrous sodium sulfate and distilled before use, bp 107–108°C.

3. Reagent-grade dichloromethane was extracted repeatedly with concentrated sulfuric acid, washed twice with water, dried with anhydrous calcium chloride, and distilled from phosphorus pentoxide before use.[2]

4. A cylinder of boron trifluoride gas was purchased from Linde Division, Union Carbide Chemical Corporation. The gas was passed through Teflon tubing to a 250-mL gas-washing bottle equipped with a fritted-glass inlet and containing a saturated solution of boric anhydride (ca. 16 g) in 150 mL of concentrated sulfuric acid. Another section of Teflon tubing was connected to the exit port of the gas-washing bottle and to the barrel of a 2-mL, gastight syringe that fitted into the syringe needle in the septum. Boric anhydride (boron oxide) is available from Fisher Scientific Company. The purpose of the boric anhydride-sulfuric acid scrubber is to remove hydrogen fluoride.[3] All ground-glass joints in the system were lined with Nalgene or Teflon standard-taper sleeves to prevent them from sticking together. Nalgene standard-taper sleeves are supplied by Nalge Sylron Corporation. Any stopcocks used should be Teflon. The checkers placed one empty 250-mL trap in the gas line before the gas-washing bottle and another after it.

5. The submitters recommend that the effluent gases be directed toward a water trap to reduce the amount of boron trifluoride and hydrogen fluoride released into the atmosphere.

6. *m*-Nitroacetophenone was supplied by Aldrich Chemical Company, Inc. and recrystallized from ethanol, mp 76–78°C. The compound may also be prepared by the method of Corson and Hazen.[4]

7. If desired, the mixture of triethylsilane and triethylfluorosilane can be reconverted into triethylsilane by reduction with lithium aluminum hydride.[5]

8. The product was analyzed by the checkers. Anal. calcd. for $C_8H_9NO_2$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.51; H, 6.17; N, 9.04. The spectral properties of the product are as follows: IR (CCl_4) cm^{-1}: 3100, 3075, 2975,

2940, 2880, 1532, 1348, 1095, 895; ^{1}H NMR ($CDCl_3$) δ: 1.27 (triplet, 3, *J* = 7.5, CH_3), 2.74 (quartet, 2, *J* = 7.5, CH_2), 7.3–8.1 (multiplet, 4, aromatic *H*); ^{13}C NMR ($CDCl_3$) δ: 14.7, 28.2, 120.4, 122.2, 128.8, 133.9, 145.9, 148.2.

3. Discussion

This procedure illustrates a method for the selective reduction of a carbonyl group to a methylene group in compounds having other potentially reducible functional groups. The method is applicable to the reduction of aryl aldehydes without electron-withdrawing ring substituents, aryl alkyl ketones, diaryl ketones, and dialkyl ketones.[6] Under the above conditions, aryl aldehydes having strongly electron-withdrawing ring substituents (viz., NO_2, CN) and alkyl aldehydes yield alcohols. Benzylic alcohols and secondary or tertiary aliphatic alcohols are also reduced to hydrocarbons under these reaction conditions,[7] as are some epoxides.[8] Functional groups that are not affected during ketone reductions include nitro, cyano, ether, ester, carboxylate, and ring halogens.

The effectiveness of this reduction procedure is related to the ability of free boron trifluoride to coordinate strongly to the carbonyl oxygen and to the strong driving force provided by the formation of the silicon-fluorine bond.[6] Similar carbonyl reductions using organosilicon hydrides in conjunction with Brønsted acids[9,10] or boron trifluoride etherate[11] are generally only successful with aryl ketones and aldehydes bearing electrondonating ring substituents; with other carbonyl substrates by-products other than hydrocarbons become the predominant products.

Other carbonyl reduction methods include the familiar Clemmensen[12] and Wolff-Kishner[13] reactions. These are usually conducted for extended periods of time at elevated temperatures under strongly acidic or basic conditions, respectively. Mixed metal hydride-Lewis acid reagents constitute strong reducing systems that are often effective in the deoxygenation of diaryl ketones and some aryl alkyl ketones. However, even the mixed lithium aluminum hydride-aluminum chloride[14] and sodium borohydride-boron trifluoride[15] reagents reduce dialkyl ketones only to the corresponding alcohols, often with the formation of significant amounts of olefinic by-products. *m*-Nitroethylbenzene has been prepared by reductive deamination of 4-amino-3-nitroethylbenzene[16] and by nitration of ethylbenzene and subsequent fractional distillation to separate the isomers.[17]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

lithium aluminum hydride-aluminum chloride

ethanol (64-17-5)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

hydrogen fluoride (7664-39-3)

calcium sulfate (7778-18-9)

ethylbenzene (100-41-4)

Pentane (109-66-0)

dichloromethane (75-09-2)

boric anhydride

boron trifluoride (7637-07-2)

lithium aluminum hydride (16853-85-3)

boron trifluoride etherate (109-63-7)

sodium borohydride (16940-66-2)

phosphorus pentoxide (1314-56-3)

TRIETHYLSILANE (617-86-7)

Benzene, 1-ethyl-3-nitro- (7369-50-8)

triethylfluorosilane (358-43-0)

boron oxide

boric anhydride-sulfuric acid

4-amino-3-nitroethylbenzene

m-Nitroacetophenone (121-89-1)

m-Nitroethylbenzene (6125-24-2)

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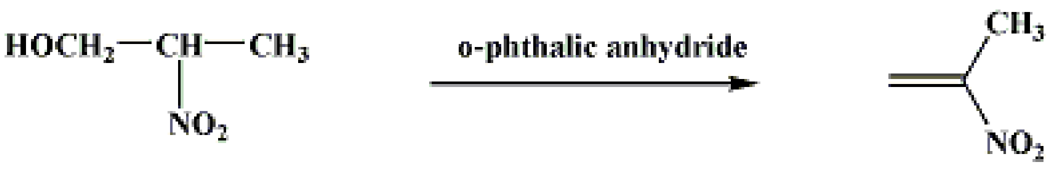
2-NITROPROPENE

[1-Propene, 2-nitro]



Submitted by Masaaki Miyashita, Tetsuji Yanami, and Akira Yoshikoshi[1].
Checked by D. Seebach, H. Siegel, and E. Wilka.

1. Procedure

Caution! This procedure should be carried out in a hood since 2-nitropropene is a powerful lachrymator. Nitroolefins have a tendency to undergo "fume-offs" (which can be like explosions) near the end of a distillation, particularly if air is let in on a hot distillation residue (from a vacuum distillation).

A 250 mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar is charged with 96.5 g (0.65 mol) of phthalic anhydride (Note 1) and 52.5 g (0.50 mol) of 2-nitro-1-propanol (Note 2). A 10-cm vacuum-insulated Vigreux column, a stillhead fitted with a thermometer, a condenser, a 50-mL, round-bottomed receiving flask, and a water aspirator are installed in due order, and the reaction vessel is placed in an oil bath and evacuated to 110 mm (Note 3). The bath temperature is raised to 150°C and maintained for 30 min while the phthalic anhydride melts to give a homogeneous solution. The receiving flask is immersed in an ice bath, stirring is started, and the bath temperature is raised to 180°C. As the reaction mixture darkens, green-colored 2-nitropropene is gradually distilled off with water, bp 50–65°C (110 mm). The bath temperature is held at 180–185°C until the distillation ceases (ca. 1 hr). The distillate is transferred into a 50-mL separatory funnel, and the lower layer is separated from water (Note 4) and dried over anhydrous magnesium sulfate. Redistillation under reduced pressure through a 10-cm vacuum-insulated Vigreux column (Note 5) gives 25.0–31.4 g (57–72%) of 2-nitropropene, which is collected in an ice-cooled receiving flask as a transparent green liquid, bp 56–57°C (86 mm), n_D^{20} 1.4348 [lit.[2] bp 58°C (90 mm), n_D^{19} 1.4292, d^{20}1.0492] (Note 5). The distilling flask is cooled to room temperature before the vacuum is released.

2. Notes

1. Commercial phthalic anhydride, purchased from Wako Pure Chemical Industries, Ltd. (Japan) or from Fluka AG, Buchs (Switzerland), was used without purification.
2. The checkers purchased 2-nitro-1-propanol (ca. 98% purity) from EGA-

Aldrich and used it without further purification. The submitters prepared this reagent from nitroethane and formalin according to the procedure of Feuer,[3] yield 70–75%, bp 79–80°C (5 mm).

3. Lower pressure may cause a loss of the product because of its volatility.

4. The layers sometimes do not separate well. In this case a small amount of magnesium sulfate should be added.

5. It is important that the bath temperature be kept as low as possible to avoid fume-off decompositions. In the checked procedure the bath temperature was never allowed to exceed 80°C. Toward the end of the distillation the pressure was reduced to ca. 60 mm to achieve complete distillation. Although pure 2-nitropropene may be stored in a freezer as a low-melting solid for several weeks, it is recommended to prepare it immediately before use since it tends to polymerize and to darken slowly on storage. 2-Nitropropene polymerizes readily in the presence of a trace of alkali.

3. Discussion

The procedure described is essentially the same as that of Buckley and Scaife.[2] The yield has been increased from 55.5% up to 72% by using 1.3 mol eq of phthalic anhydride and by carefully controlling the pressure and cooling the receiving flask. Although 2-nitropropene has previously been prepared by pyrolysis of 2-nitro-1-propyl benzoate in 72% overall yield from 2-nitro-1-propanol,[4] the present method is preferred for its preparation since the procedure is much simpler and the product is directly obtainable from 2-nitro-1-propanol without first preparing its ester. It is also applicable to the preparation of 1-nitro-1-propene (58%),[5,6] 2-nitro-1-butene (82%),[7] and 2-nitro-2-butene (60%).[6,7] In general, aliphatic nitroolefins have the tendency to polymerize readily with alkali.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 414

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

formalin (630-08-0)

phthalic anhydride (85-44-9)

magnesium sulfate (7487-88-9)

nitroethane (79-24-3)

2-Nitropropene, 1-Propene, 2-nitro (4749-28-4)

2-nitro-1-propanol (2902-96-7)

2-nitro-1-propyl benzoate

1-nitro-1-propene

2-nitro-1-butene

2-nitro-2-butene

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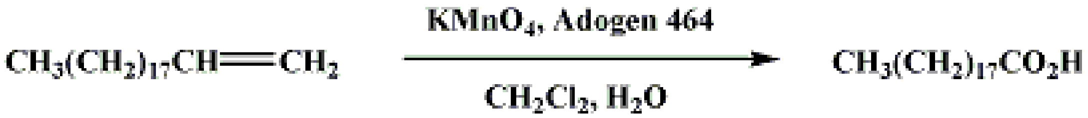
CARBOXYLIC ACIDS FROM THE OXIDATION OF TERMINAL ALKENES BY PERMANGANATE: NONADECANOIC ACID



Submitted by Donald G. Lee, Shannon E. Lamb, and Victor S. Chang[1].
Checked by Dennis P. Lorah and Andrew S. Kende.

1. Procedure

A 5-L, three-necked, round-bottomed flask fitted with a mechanical stirrer is placed in an ice bath and charged with 1000 mL of distilled water, 120 mL of 9 *M* sulfuric acid, 3.0 g of Adogen 464 (Note 1), 20 mL of glacial acetic acid, 1000 mL of methylene chloride, and 50 g of 1-eicosene (Note 2). The solution is rapidly stirred and 80 g (0.544 mol) of potassium permanganate is added in small portions over a 3-hr period (Note 3). Stirring is continued for an additional 18 hr at room temperature. The mixture is cooled in an ice bath, and 60 g of sodium bisulfite is added in small portions to reduce any precipitated manganese dioxide. The solution is acidified, if basic, with sulfuric acid and separated. The aqueous layer is extracted with two 400-mL portions of methylene chloride. The organic extracts are combined, washed with two 400-mL portions of water, washed once with brine, and concentrated to 400 mL on a rotary evaporator. The resulting mixture is heated to dissolve any precipitated product, a small amount of amorphous solid is removed by filtration, and the filtrate is cooled to 0°C. A first crop of white crystals (33–36 g, mp 67–68°C) is collected by suction filtration and washed with a minimum amount of ice-cold methylene chloride. Concentration of the mother liquor to 150 mL and cooling to 0°C yields a second crop of crystals (7–12 g). The combined products are dissolved, with heating, in 400 mL of methylene chloride and the pale-yellow solution is allowed to cool to room temperature, then *slowly* to –10°C. The white crystals (36–37 g) are collected, washed with a small amount of cold methylene chloride, and dried in vacuum overnight (mp 68–68.5°C, lit[2] 67–68°C). The yield is 75–77% (Note 4).

2. Notes

1. Adogen 464, a methyl trialkylammonium (C_8-C_{10}) chloride, was obtained from Ashland Chemical Co.
2. Technical 1-eicosene was obtained from the Aldrich Chemical Company, Inc. and used without further purification. Analysis by quantitative catalytic hydrogenation over Pd-C and NMR spectroscopy indicated that it contained about 10% unreactive, saturated hydrocarbon material.

3. Potassium permanganate was "Baker Analyzed" reagent. About 7.5 g was added every 15 min.
4. The yield was calculated by assuming that the starting material contained 90% 1-eicosene (see (Note 2)).

3. Discussion

Potassium permanganate is the preferred reagent for the oxidative cleavage of carbon-carbon double bonds.[3] Because of its low solubility in nonpolar solvents, however, the reactions have traditionally been carried out in polar organic solvent systems. For example, the use of aqueous *tert*-butyl alcohol[4] and acetic anhydride[5] for this purpose has been described. An alternative approach involves the use of phase-transfer agents to solubilize permanganate ion in organic solvents and several examples of this approach have been reported.[6] Although benzene has often been used as the solvent,[2] it has been observed that methylene chloride is a superior solvent[7]; better yields are obtained and because of its greater volatility it is more easily removed at the conclusion of the reaction. In addition, methylene chloride is more resistant to oxidation by solubilized permanganate. Adogen 464 was used as the phase-transfer agent because the yields compared well with those obtained when other agents[8] were used and because it is both inexpensive and readily available. The solutions were maintained acidic to neutralize hydroxide ions formed during the reduction of permanganate ($MnO_4^- + 2H_2O$ ρ $MnO_2 + 4OH^-$). In the absence of acetic acid the accumulation of base promotes certain side reactions and increases the stickiness of the manganese(IV) oxides which precipitate as the reaction proceeds.

TABLE I
PHASE-TRANSFER-ASSISTEDPERMANGANATEOXIDATIONS OFTERMINALALKENES

Alkene[a]	Product (Yield)[b]	Purification Method	mp or bp (°C)
1-Docosene	Heneicosanoic acid (84%)	Recrystallization (acetone)	72–74° (75°, 82°)[c]
1-Eicosene	Nonadecanoic acid(80%)	Recrystallization (methylene chloride)	68–68.5° (67–68°)[d]
1-Octadecene	Heptadecanoic acid (81%)	Recrystallization (pet. ether)	60–62° (60–61°)[e]
1-Hexadecene	Pentadecanoic acid (84%)	Recrystallization (ethanol-water)	52–53° (53°)[e]

1-Tetradecene	Tridecanoic acid (83%)	Recrystallization (acetone-water)	43–44° (44.5–45.5°)[e]
1-Decene	Nonanoic acid (92%)	Vacuum distillation	109–111°/2.4 mm (121°/4 mm)[e]
1-Octene	Heptanoic acid (70%)	Vacuum distillation	107–108°/7 mm (115–116°/11 mm)[e]
Styrene	Benzoic acid (96%)	Recrystallization (water)	121–122° (122°)[e]

[a]The alkenes were obtained from the Aldrich Chemical Company, Inc. Purity ranged from 99 to 87%.

[b]The purity of the starting material was taken into consideration in yield calculations.

[c]"Handbook of Chemistry and Physics," The Chemical Rubber Co., 52nd ed.

[d]2.

[e]"Dictionary of Organic Compounds," Eyre and Spottiswoode, 4th ed.

The results obtained with a number of other representative terminal alkenes have been summarized in Table I.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

brine

Adogen 464

manganese(IV) oxides

ethanol (64-17-5)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

Benzene (71-43-2)

acetic anhydride (108-24-7)

potassium permanganate (7722-64-7)

Benzoic acid (65-85-0)

sodium bisulfite (7631-90-5)

acetone (67-64-1)

manganese dioxide (1313-13-9)

methylene chloride (75-09-2)

styrene (100-42-5)

Tridecanoic acid (638-53-9)

Pentadecanoic acid (1002-84-2)

Heptanoic acid (111-14-8)

1-hexadecene (629-73-2)

Nonanoic acid (112-05-0)

tert-butyl alcohol (75-65-0)

1-octene (111-66-0)

1-octadecene (112-88-9)

1-decene (872-05-9)

Nonadecanoic acid (646-30-0)

1-eicosene (3452-07-1)

1-Docosene (1599-67-3)

1-Tetradecene (1120-36-1)

Heneicosanoic acid (2363-71-5)

Heptadecanoic acid (506-12-7)

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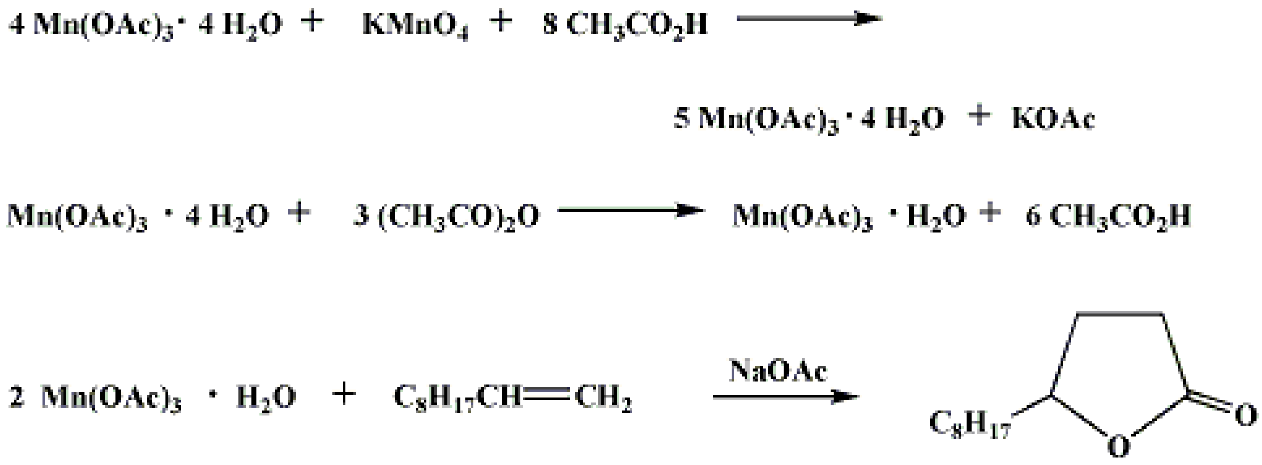
Organic Syntheses, CV 7, 400

SUBSTITUTED γ-BUTYROLACTONES FROM CARBOXYLIC ACIDS AND OLEFINS: γ-(*n*-OCTYL)-γ-BUTYROLACTONE

[2(3*H*)-Furanone, dihydro-5-octyl-]



Submitted by E. I. Heiba, R. M. Dessau, A. L. Williams, and P. G. Rodewald[1].
Checked by Gerald E. Lepone and Orville L. Chapman.

1. Procedure

Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A 1-L, four-necked flask is fitted with a nitrogen inlet tube, stirrer, dropping funnel, and thermometer. Acetic acid (558 g) is introduced and 107.6 g (0.439 mol) of manganese acetate tetrahydrate (Note 1) is added with stirring and heating under nitrogen. When the temperature reaches 90°C, 16.5 g of solid potassium permanganate (0.104 mol) is added. After the temperature has again fallen to 90°C, 175 mL (189 g, 1.86 mol) of acetic anhydride (Note 2) is added. When the temperature rise has ceased, 44.0 g of 1-decene (0.312 mol) (Note 3) is introduced, followed at once by 250 g of anhydrous sodium acetate. The reaction mixture is then heated to reflux (134°C pot temperature). After 2 hr of reflux under nitrogen the reaction mixture, now clear yellow, is diluted with 1 L of water. The crude product is extracted into 200 mL of benzene, and the aqueous layer again washed with 100 mL of benzene. Benzene is distilled from the combined extracts to give 55.1 g of lactone and 1-decene. 1-Decene is removed by vacuum distillation, followed by the lactone, which distills at 98–99°C (0.05 mm) (Note 4). The yield of γ-(*n*-octyl)-γ-butyrolactone is 34.1 g (66% based on potassium permanganate. However, the lactone yield based on olefin consumed is greater than 95%.)

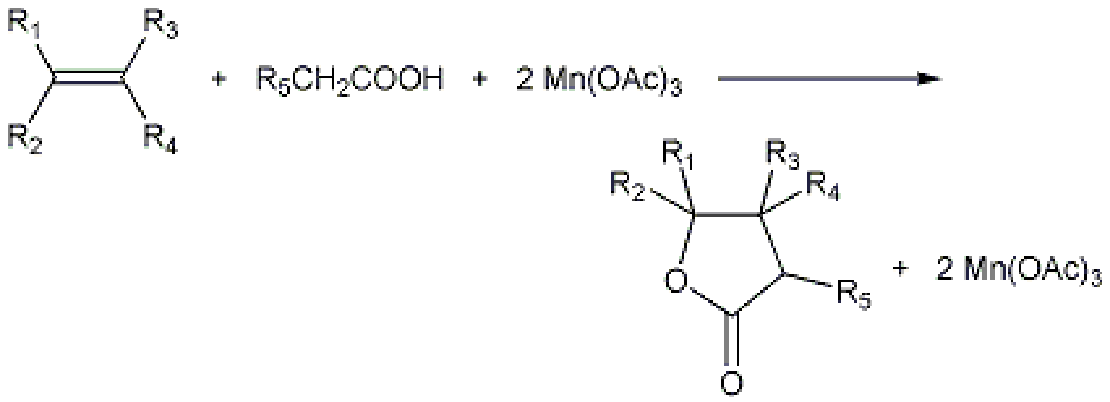
2. Notes

1. The checkers used manganous acetate tetrahydrate obtained from Fisher Scientific Company. This compound is more readily available than manganous acetate dihydrate used by the submitters and obtained from the Harshaw Chemical Company.
2. If the dihydrate is used, only 76.7 g (0.751 mol) of acetic anhydride is required.
3. 1-Decene was used as obtained from the Humphrey Chemical Company.
4. The checkers found the yield based upon olefin consumed to be 85%. This discrepancy could be accounted for by losses due to the high volatility of 1-decene at reduced pressure.

3. Discussion

This method has the advantage that it does not require the preparation and purification of solid manganic acetate dihydrate. Dehydration by various ratios of acetic anhydride to manganese shows that in this procedure the yield (35%) from the monohydrate is greater than that from the manganic acetate dihydrate. Further removal of all water from the manganic acetate by means of acetic anhydride does not improve the yield (66%).

This general procedure can be used to prepare a wide variety of substituted γ-butyrolactones that depend on the structure of the olefin and the aliphatic acid used. The free-radical mechanism and scope of this reaction are described in detail in a paper by Heiba, Dessau, and Rodewald.[2]



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2. Heiba, E. I.; Dessau, R. M.; Rodewald, P. G. *J. Am. Chem. Soc.* **1974**, *96*, 7977–7981.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

acetic acid (64-19-7)

Benzene (71-43-2)

acetic anhydride (108-24-7)

sodium acetate (127-09-3)

potassium permanganate (7722-64-7)

nitrogen (7727-37-9)

manganese (7439-96-5)

monohydrate (7732-18-5)

1-decene (872-05-9)

dihydro-5-octyl-

manganese acetate tetrahydrate, manganous acetate tetrahydrate (6156-78-1)

manganous acetate dihydrate

manganic acetate dihydrate (19513-05-4)

manganic acetate

2(3H)-Furanone

γ-(n-OCTYL)-γ-BUTYROLACTONE (2305-05-7)

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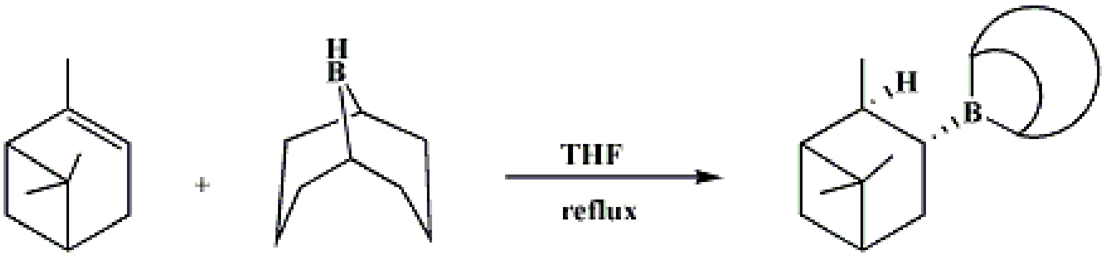
Organic Syntheses, CV 7, 402

ASYMMETRIC REDUCTION OF α,β-ACETYLENIC KETONES WITH *B*-3-PINANYL-9-BORABICYCLO[3.3.1]NONANE: (*R*)-(+)-1-OCTYN-3-OL

[1-Octyn-3-ol, (*R*)-]

A.



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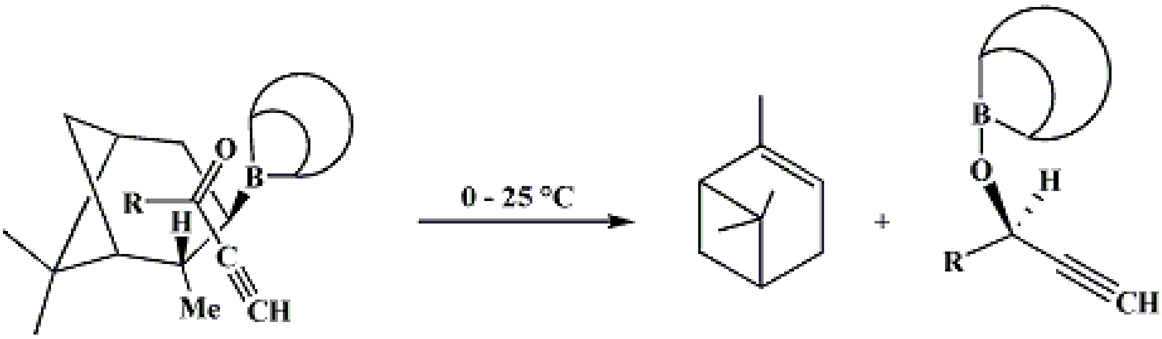
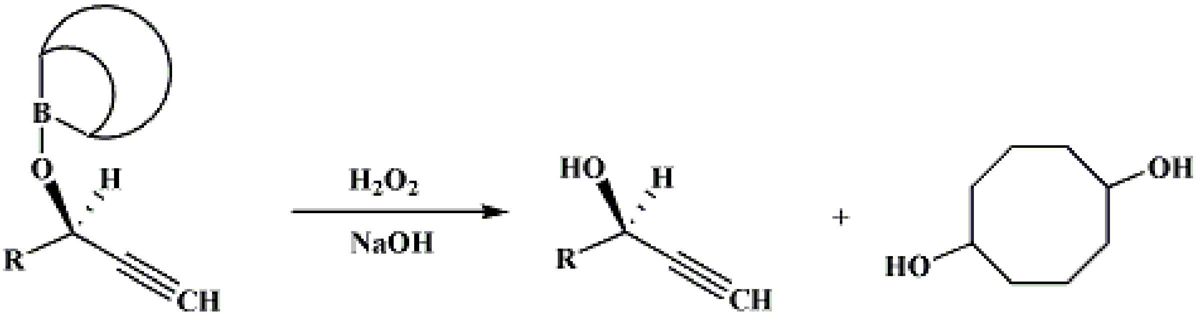


C.



Submitted by M. Mark Midland and Richard S. Graham[1].
Checked by Joel M. Hawkins and K. Barry Sharpless.

1. Procedure

A. A 2-L, round-bottomed flask equipped with a septum-capped sidearm, magnetic stirring bar, reflux condenser, and stopcock adapter connected to a mercury bubbler is flame-dried while being flushed with nitrogen. A nitrogen atmosphere is maintained during the procedure through the oxidation step. After the apparatus is cooled, it is charged, via a double-ended needle,[2] with 800 mL of a 0.5 M tetrahydrofuran (THF) solution of 9-borabicyclo[3.3.1]nonane (9-BBN, 0.4 mol, (Note 1)). Then 61.3 g (71.5 mL, 0.45 mol) of (+)-α-pinene (Note 2) is added. After the solution is refluxed for 4 hr, the excess α-pinene and THF are removed by vacuum (Note 3) to provide a thick clear oil of neat B-3-pinanyl-9-borabicyclo[3.3.1]

nonane, **1** (Note 4).

B. The flask is cooled to 0°C (ice bath) and 35.3 g (0.285 mol) of 1-octyn-3-one (Note 5) is added. After an initially exothermic reaction, the reaction is allowed to warm to room temperature. The reduction can be monitored by gas chromatography (Note 6), but generally 8 hr is required for completion. The color of the reaction mixture is initially light yellow and darkens to red at the end of the reduction.

C. Excess **1** is destroyed by adding 22 mL (0.3 mol) of freshly distilled propionaldehyde and stirring for 1 hr at room temperature. Liberated α-pinene is then removed by vacuum (Note 7). Tetrahydrofuran, 200 mL, is added, followed by 150 mL of 3 *M* aqueous NaOH. Hydrogen peroxide (150 mL, 30%) is added dropwise (see *Caution* in (Note 8)). Oxidation is complete in 3 hr at 40°C. The reaction mixture is transferred to a separatory funnel and extracted with three 50-mL portions of ethyl ether. The ether layers are combined and dried with copious amounts of anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation to give an oil. Distillation at 60–65°C (3.0 mm) yields 31 g (0.245 mol) of 1-octyn-3-ol, 86% yield (Note 9). The distillation pot residue is a thick oil consisting for the most part of *cis*-1,5-cyclooctanediol. An NMR lanthanide shift study showed the alcohol to be 93% (R) and 7% (S), 86% e.e. (Note 10) and (Note 11).

2. Notes

1. A 0.5 *M* THF solution of 9-BBN is available from Aldrich Chemical Company in 800 mL bottles.
2. (+)-α-Pinene (90–92% e.e.) is available from Aldrich Chemical Company. The pinene was distilled from lithium aluminum hydride before use.
3. Most of the THF is removed by water aspirator vacuum. Excess pinene (0.05 mol, 8 mL) is removed by applying a 0.05-mm vacuum for 2 hr while warming to 40°C with a water bath. The vacuum should be bled with nitrogen to maintain an inert atmosphere in the reaction flask. Recently Brown's group[3] has shown that reduction occurs at an enhanced rate with neat organoborane **1**. Excess **1**, 1.4 equiv per equivalent of l-octyn-3-one, is used to provide a slight excess of reducing agent to increase the rate for this bimolecular process.
4. *B*-3-Pinanyl-9-borabicyclo[3.3.1]nonane, **1**, is also available from Aldrich Chemical Company under the tradename "R-Alpine-Borane."
5. 1-Octyn-3-one was obtained by standard Jones oxidation[4] of racemic 1-octyn-3-ol (in 80% yield). Racemic 1-octyn-3-ol is available from Aldrich Chemical Company. It is essential to check the ketone for unreacted starting alcohol since racemic alcohol will contaminate the final, optically active product.
6. GLC can be used to monitor the disappearance of the acetylenic ketone. 1-Octyn-3-one is eluted just after α-pinene from a SE-30 6-ft column at 80°C. The checkers followed the disappearance of ketone by TLC (15% ethyl acetate in hexane).
7. This is the most convenient time for removal of α-pinene since α-pinene and 1-octyn-3-ol have similar boiling points, making separation by distillation difficult. Application of a 0.05-mm vacuum while the flask is warmed to 40°C for several hours will remove most of the α-pinene (0.4 mol, 63.5 mL). Because of the volume of α-

pinene, cold traps in the vacuum system may become plugged; therefore, the traps will have to be emptied several times. This provides a convenient method for recovery of liberated (+)-α-pinene.

8. Hydrogen peroxide oxidation of organoboranes is exothermic. Careful, dropwise addition of 30% hydrogen peroxide to the organoborane will provide sufficient heating to maintain a reaction temperature in the 40–50°C range.

9. 1-Octyn-3-ol has the following properties: bp 60–65°C (3.0 mm); IR (neat) cm^{-1}: 3315, 2950, 2860, 2120, 1475, 1380, 1120, 1060, 1025, 650; ^{1}H NMR ($CDCl_3$) δ: 0.86 (t, 3 H, *J* = 6.6, CH_3), 1.3-1.4 (m, 6 H), 1.65 (m, 2 H), 2.42 (d, 1 H, *J* = 2, C C-H), 3.0 variable (broad, 1 H, OH), 4.33 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ: 72.6 (C-1), 85.1 (C-2), 62 (C-3), 37.4 (C-4), 31.3 (C-5), 24.6 (C-6), 22.4 (C-7), 13.9 (C-8); $[\alpha]_D^{25}$ + 7.50° (neat, density 0.864 g/mL). It has been shown that optical rotation is an unreliable criterion of enantiomer purity of 1-octyn-3-ol.[5]

10. Commercially available Eu $(hfc)_3$, tris [3-(heptafluoropropylhydroxy-methylene)-*d*-camphorato]europium III, NMR shift reagent, was used as received from Aldrich Chemical Company. The proton on the chiral carbinol carbon was shifted downfield to 11 ppm in $CDCl_3$. The R isomer was shifted 0.5 ppm further downfield than the *S* isomer.

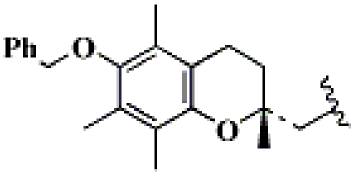
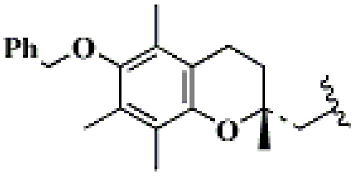
11. Optically pure (+)-1-octyn-3-ol may be obtained by recrystallization of the half-acid phthalate with (+)-α-methylbenzylamine (Aldrich Chemical Company). The half-acid phthalate salt is made by heating equal molar amounts of 1-octyn-3-ol and phthalic anhydride. This half acid phthalate derivative is a waxy solid that does not lend itself to recrystallization. Attempts to form crystalline salts of the phthalate derivative with achiral alkyl amines only lead to waxy solids or thick oils. The phthalic amine salt made with racemic 1-octyn-3-ol requires three to four recrystallizations from methylene chloride to resolve enantiomers.[6] The first recrystallization may take several days, with successive recrystallizations becoming easier. If the 86% e.e. 1-octyn-3-ol is used to make the phthalic amine salt only one facile recrystallization is needed to provide optically-pure alcohol. The pure amine salt melts at 132–134°C. The enantiomeric purity of the salt may be determined by NMR by observing the ethynyl hydrogen doublets at δ 2.48 (minor) and 2.52 (major) ($CDCl_3$ solvent).

3. Discussion

In this procedure, we describe a general method for the synthesis of alkynyl alcohols of high enantiomeric purity. The one-pot asymmetric reduction of 1-octyn-3-one with *B*-3-pinanyl-9-borabicyclo[3.3.1]nonane provides a mild and efficient method for the preparation of optically active 1-octyn-3-ol. The reduction occurs in good chemical yield and is virtually (>95%) stereospecific (correcting for the use of 90% e.e. α-pinene). The availability of optically pure α-pinene is a limiting factor in this method, but recently Brown's group has developed a process that provides enantiomerically pure α-pinene.[7] The reduction can be applied to prepare both enantiomers of 1-octyn-3-ol, since both enantiomers of α-pinene are commercially available; although commercial (–)-α-pinene is only 81.3% e.e.,[7] (–)-α-pinene of 92% e.e. is easily obtained by isomerizing commercial (–)-β-pinene (92% e.e.).[8 9]

(Reducing agent **1**, made with (–)-α-pinene, will provide (*S*)-(–)-1-octyn-3-ol). The α-pinene liberated (by β-hydride elimination) in the reduction may be recycled without loss of optical purity. Another attractive feature of this reduction is that organoborane **1** is a mild reagent and seldom affects other functional groups present within the acetylenic ketone. For base-sensitive systems that cannot tolerate the standard sodium hydroxide–hydrogen peroxide oxidation, an alternative workup using ethanolamine is available.[10] Table I illustrates the application of this reduction to other propargyl ketones.[10] In these cases, tetrahydrofuran was not removed prior to reduction. Removal of tetrahydrofuran provides a faster reaction and slightly higher optical purity.[3].

TABLE I
REDUCTIONS OF ALKYNYL KETONES WITH B-(3)-α-PINANYL-9-BBN

Ketone RCOC≡CR'			
R	R'	Yield (%)[a]	Enantiomeric Excess (%)[b]
Ph	Bu	72	89[c]
Me	Ph	98	72(78)
Pr	C_6H_{13}	68	77[c]
2-Pr	H	78	91(99)
	Me	77	85:15[d]
	H	75	91:9[d]
Me	COOEt	59	71(77)
C_5H_{11}	COOEt	72	85(92)
Ph	COOEt	64	92(100)
t-Bu	Me	0	
Me	*t*-Bu	62	73[c]

[a] Isolated yield based on starting ketone.

[b] Determined by analysis of the Eu(dcm)$_3$ shifted NMR spectrum. The numbers in parentheses are corrected for 92% e.e. α-pinene.

[c] 100% optically pure (+)-α-pinene was used.

[d] Diastereomeric ratio (*R*,*R* to *R*,*S*) determined by LC or NMR analysis of the mixture.

The most popular methods of preparing optically active 1-octyn-3-ol involve asymmetric reduction of 1-octyn-3-one with optically active alcohol complexes of lithium aluminum hydride or aluminum hydride.[11 9 12 13] These methods give optical purities and chemical yields similar to the method reported above. A disadvantage of these metalhydride methods is that some require exotic chiral alcohols that are not readily available in both enantiomeric forms. Other methods include optical resolution of the racemic propargyl alcohol (100% e.e.)[6] (and (Note 11)) and microbial asymmetric hydrolysis of the propargyl acetates (15% e. e. for 1-heptyn-3-ol).[14]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 95

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

9-BBN

propargyl acetates

tris [3-(heptafluoropropylhydroxy-methylene)-d-camphorato]europium III

ethyl acetate (141-78-6)

ethyl ether (60-29-7)

sodium hydroxide, NaOH (1310-73-2)

Propionaldehyde (123-38-6)

nitrogen (7727-37-9)

phthalic anhydride (85-44-9)

hydrogen peroxide (7722-84-1)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

ethanolamine (141-43-5)

(+)-α-methylbenzylamine (3886-69-9)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

hexane (110-54-3)

propargyl alcohol (107-19-7)

aluminum hydride

propargyl (2932-78-7)

9-borabicyclo[3.3.1]nonane (280-64-8)

α-pinene, (+)-α-pinene

pinene (18172-67-3)

1-octyn-3-ol, (+)-1-octyn-3-ol (818-72-4)

B-3-Pinanyl-9-borabicyclo[3.3.1]nonane (73624-47-2)

1-octyn-3-one, l-octyn-3-one

1-heptyn-3-ol (7383-19-9)

1-Octyn-3-ol, (R)-, (R)-(+)-1-OCTYN-3-OL (32556-70-0)

cis-1,5-cyclooctanediol

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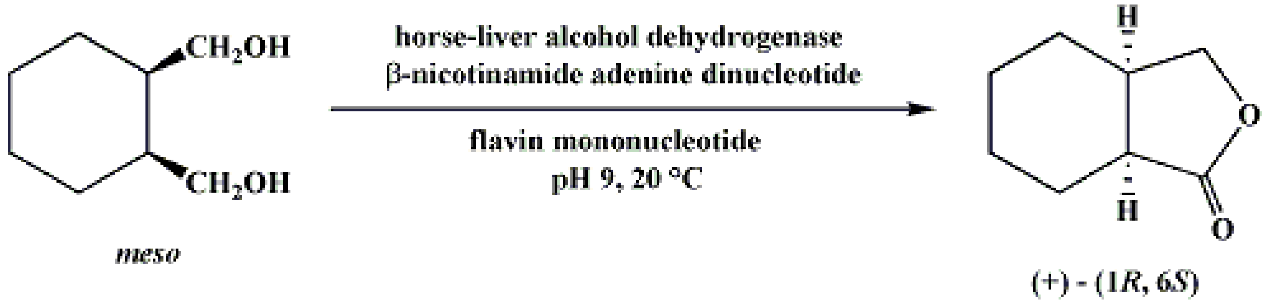
Organic Syntheses, CV 7, 406

PREPARATION OF CHIRAL, NONRACEMIC γ-LACTONES BY ENZYMECATALYZED OXIDATION OF *meso*-DIOLS: (+)-(1*R*,6*S*)-8-OXABICYCLO[4.3.0]NONAN-7-ONE

[1(3*H*)-Isobenzofuranone, hexahydro-, (3*aS*-*cis*)-]



Submitted by J. Bryan Jones and Ignac J. Jakovac[1].
Checked by Roland H. Weber, Max F. Züger, and Dieter Seebach.

1. Procedure

In a 1-L Erlenmeyer flask are placed 475 mL of distilled water (Note 1) and 3.75 g (0.05 mol) of reagent-grade glycine, and the pH is adjusted to 9 by the careful addition of aqueous 10% sodium hydroxide. In the buffer solution thus obtained are dissolved 2.00 g (13.87 mmol) of *cis*-1,2-bis(hydroxymethyl) cyclohexane (Note 2), 0.58 g (0.852 mmol) of β-NAD (Note 3), and 7.8 g (16.2 mmol) of FMN (Note 4). To the clear orange solution obtained is added 80 units of horse-liver alcohol dehydrogenase (Note 5). After the solution is gently swirled for 1 min, the pH is readjusted to 9 and the mixture is kept at room temperature (Note 6) with the mouth of the flask loosely covered by a watchglass. After a few minutes the color of the solution begins to darken and after several hours becomes an opaque green-brown. The pH is readjusted to 9 after 6, 12, 24, 48, and 72 hr by the careful addition of aqueous 10% sodium hydroxide since the pH of the mixture drops progressively as the reaction proceeds. After 4 days (Note 7), the mixture is brought to a pH of ca. 13.3 by the addition of 20 mL of aqueous 50% sodium hydroxide solution. After 1 hr, the mixture is continuously extracted with chloroform for 10 hr (Note 8). The chloroform extract is discarded. The aqueous layer is acidified to pH 3 with concentrated hydrochloric acid and again extracted continuously for 15 hr with chloroform. To the green–orange solution are added charcoal (0.5 g), and magnesium sulfate. The dried and partially decolorized mixture is filtered through a bed of Celite, and the chloroform is removed under reduced pressure using a rotatory evaporator. The residual orange–green oil is distilled in a Kugelrohr apparatus to give 1.4–1.5 g (72–77% yield, (Note 9)) of (+)-(1*R*,6*S*)-8-oxabicyclo[4.3.0]nonan-7-one (>97% e.e., (Note 10)) as a colorless oil, bp 85–100°C (0.1–0.05 mm), mp 26–29°C, $[\alpha]_D^{22}$ + 51.3° ($CHCl_3$, *c* 1.1) (Note 11).

2. Notes

1. It is not necessary to use doubly distilled or deionized water in this buffer preparation.
2. *cis*-1,2-Bis(hydroxymethyl)cyclohexane was purchased from Aldrich Chemical Company, Inc. (or EGA, D-Steinheim).
3. β-NAD is the standard biochemical abbreviation for the coenzyme β-nicotinamide adenine dinucleotide. The β-NAD used was of 95% purity and was purchased from Kyowa Hakko (USA), New York. It is also available from Sigma Chemical Company.
4. FMN is the standard biochemical abbreviation for flavin mononucleotide (or riboflavin phosphate). The sodium salt (95–97% pure) of FMN is used. This grade is inexpensive and is available from Sigma Chemical Company. Its purpose is to effect recycling[2] of the catalytic amount used of the much more costly NAD. A larger than stoichiometric amount of FMN is employed in order to ensure rapid recycling of the NAD.
5. Horse-liver alcohol dehydrogenase (HLADH or LADH, also called "equineliver alcohol dehydrogenase") is the crystalline preparation (>98% protein) sold by Sigma Chemical Company. It is also available from Worthington and Boehringer. The amount added is quoted in units of activity since the activity of the enzyme from different sources can vary. For example, the Sigma enzyme is sold as having an activity of 1–2 units per milligram of protein. The enzyme used in this preparation had 1.5 units of activity per milligram. We have used Worthington–Boehringer enzyme with equal success. The activity of the enzyme diminishes slowly on prolonged storage, even at −20°C. For controlled results, the enzymatic activity may be determined prior to use and the requisite number of units used.

The assay method of Dalziel[3] is convenient. In a recording UV spectrophotometer set at 340 nm is placed a 3-mL quartz cuvette containing 2.4 mL of 0.10 *M* glycine–sodium hydroxide buffer solution, pH 9, 500 •L of a 54 m*M* solution of ethanol in the same buffer, and 100 •L of a 15 m*M* solution of NAD, also in the same pH 9 buffer. The volume is made up to 3.0 mL, and the assay initiated by the addition of 10 •L of a 1 mg/mL solution of HLADH in 0.10 M "Trishydrochloric acid buffer," pH 7.4. The change in optical density at 340 nm is monitored at 25°C and the activity calculated from the following equation:

$$\text{Units of activity/mg protein} = \frac{\Delta OD_{340}/\text{min}}{6.23 \times \text{mg HLADH/mL of assay volume}}$$

If the preceding assay concentrations are followed exactly, this becomes:

$$\text{Units/mg protein} = \Delta OD_{340}\text{min}/20.75$$

6. Ambient temperatures of up to 30°C can be employed but the reaction temperature should not be allowed to fall below 20°C.
7. The end of the reaction is checked by gas chromatography using 3% QF-1 or OV-101 on Chromosorb columns. The checkers used an OV-101, at 190°C oven temperature. A sample is extracted with ether. The organic layer is analyzed. At 20°C the reaction usually goes to completion within 4 days.
8. This removes residual starting material and other nonacidic impurities.
9. Scaling up the preparation is easily accomplished. It is best done by increasing the number of reaction vessels rather than by increasing the reaction volume. For

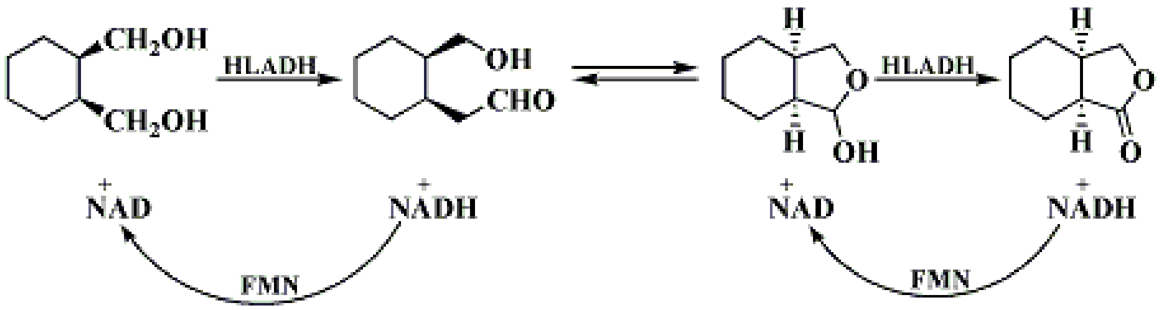
example, 10 g of the *cis*-diol substrate can be oxidized simultaneously using 2.5 g in each of four 1-L Erlenmeyer flasks as described in the procedure described above. After 4 days, the reaction mixtures are combined prior to the chloroform extraction and the lactone is isolated.

10. The absolute configuration and optical purity of the lactone was established by its hydrolysis and epimerization to (1*R*,2*R*)-*trans*-2-hydroxymethylcyclohexanecarboxylic acid followed by lithium aluminum hydride reduction to (1*R*,2R)-*trans*-1,2-bis(hydroxymethyl)cyclohexane.[4] By ^{1}H NMR,[5] the e. e. was >97%.

11. The spectral properties of the product obtained were as follows: IR (thin film): C=O at 1770 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 0.9–2.8 (m, 10 H, all cyclohexane H), 3.87–4.34 (m, 2 H, CH_2-O).

3. Discussion

Horse-liver alcohol degydrogenase is a well-documented enzyme capable of operating with high stereoselectivity on a broad structural range of alcohol and carbonyl substrates.[6] The present reaction proceeds via the pathway shown below, where NAD and NADH represent the oxidized and reduced forms, respectively, of the nicotinamide adenine dinucleotide coenzyme.

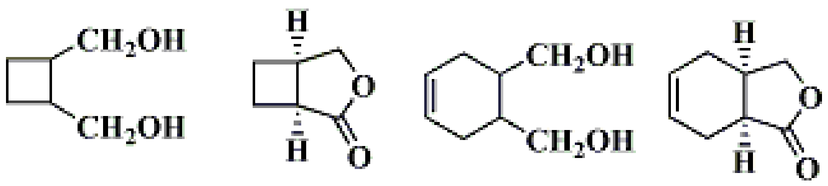


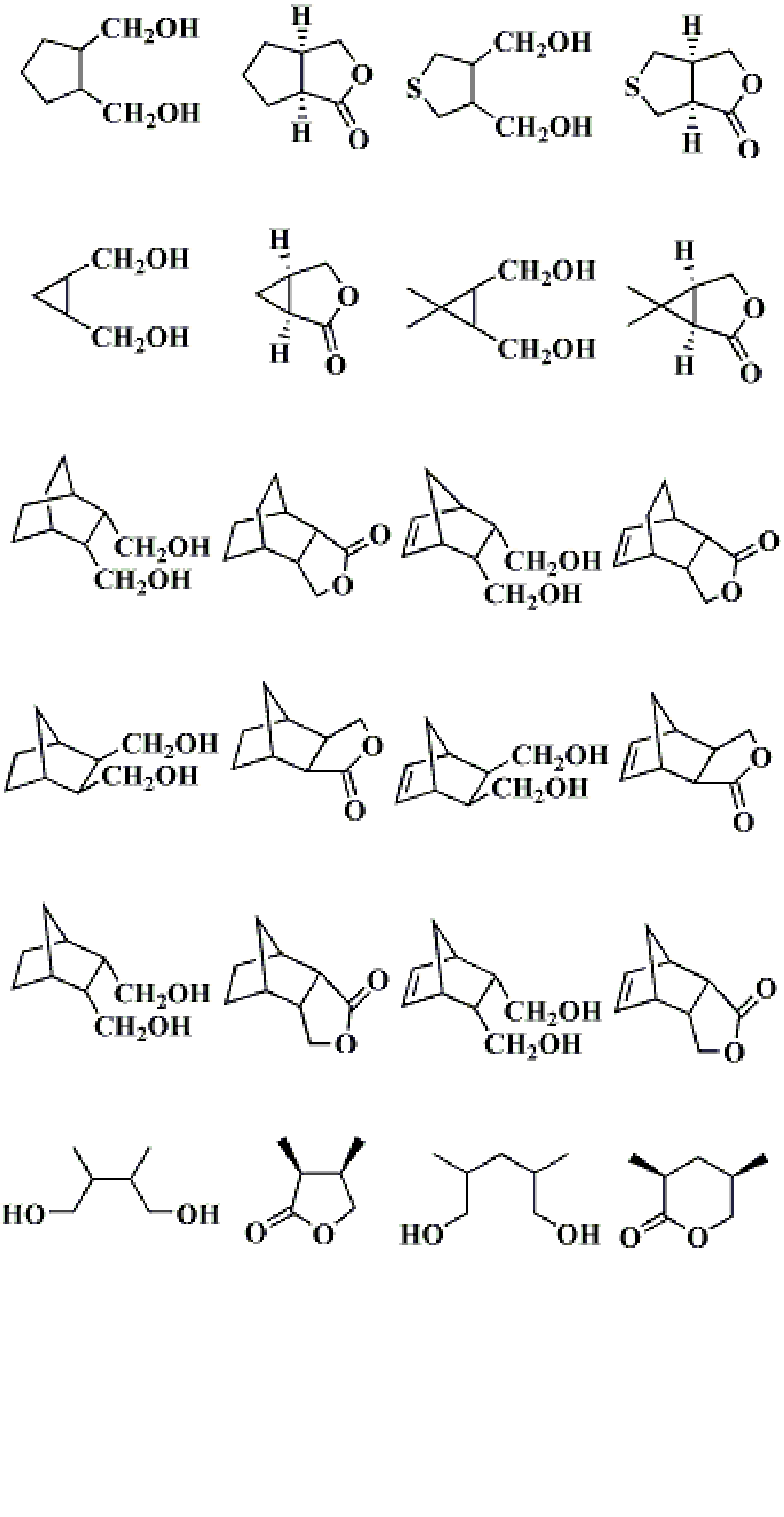
Chemical oxidations of diols to racemic lactones can be achieved by a broad spectrum of oxidizing agents.[7] At the present time, however, only the enzymatic route described can provide a versatile, one-step, access to such a wide range of highly enantiomerically enriched γ-lactones, useful as chiral building blocks for syntheses.

The lactones thus far obtained by this route have been assembled in Table I. Each oxidation proceeds in high chemical yield (65–90%) to give products of >97% enantiomeric excess.[5]

TABLE I

PREPARATION OF γ-LACTONES BY HLADH-CATALYZED OXIDATIONS OF *meso*-DIOLS (YIELD ref.)[a]





[a] The optical purities and/or enantiomeric excesses were determined by ^{1}H NMR to be >97%;[5] **2** was obtained with 85% e. e.

The maximum reaction time required for any one of the substrates shown in Table I is 7 days. In reaction mixtures that contain lactones **4** and **5**, minor amounts of the hemiacetal intermediates are present; they are removed during the extraction at pH 13. After chromatographic separation from any unreacted diols, they can be readily converted to the corresponding lactones by chemical oxidation with silver carbonate on Celite.[8]

The lactones shown in the Table include several representatives of recognized or potential value as starting materials in natural product synthesis. Lactone **1** is a precursor of grandisol,[9,10] lactone **3** of some pyrethroids,[9,11] lactone **6** of some prostaglandins,[9,12] and lactone **7** of multistriatin,[13] methynolide,[14] and monensin.[15]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 332

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

nicotinamide adenine dinucleotide coenzyme

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

Glycine (513-29-1)

magnesium sulfate (7487-88-9)

lithium aluminum hydride (16853-85-3)

silver carbonate (534-16-7)

cis-1,2-bis(hydroxymethyl) cyclohexane, cis-1,2-Bis(hydroxymethyl)cyclohexane (5059-76-7)

(+)-(1R,6S)-8-OXABICYCLO[4.3.0]NONAN-7-ONE

(1R,2R)-trans-2-hydroxymethylcyclohexanecarboxylic acid

(1R,2R)-trans-1,2-bis(hydroxymethyl)cyclohexane

1(3H)-Isobenzofuranone, hexahydro-, (3aS-cis)- (65376-02-5)

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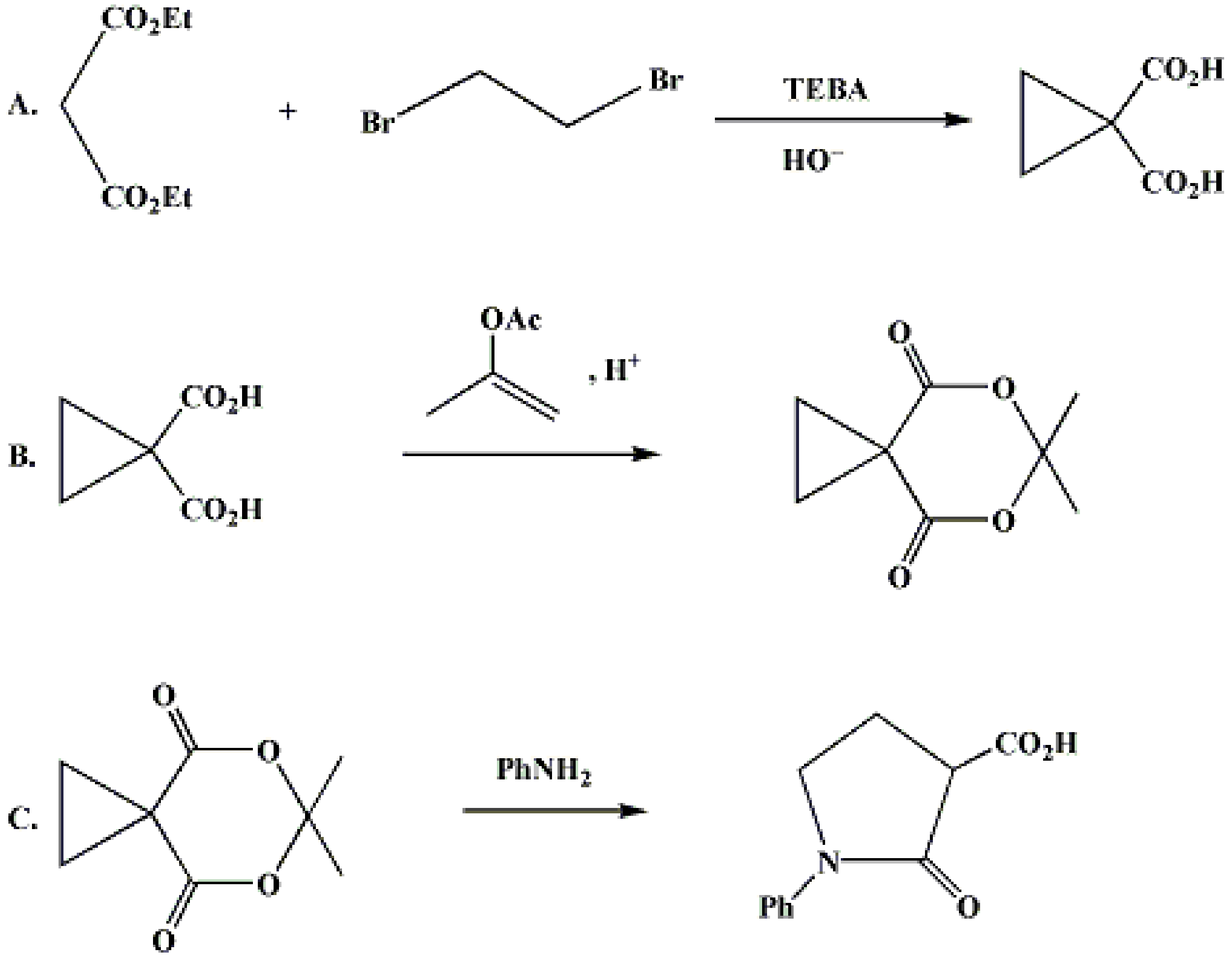
Organic Syntheses, CV 7, 411

HOMOCONJUGATE ADDITION OF NUCLEOPHILES TO CYCLOPROPANE-1,1-DICARBOXYLATE DERIVATIVES: 2-OXO-1-PHENYL-3-PYRROLIDINECARBOXYLIC ACID

[3-Pyrrolidinecarboxylic acid, 2-oxo-1-phenyl-]



Submitted by Rajendra K. Singh and Samuel Danishefsky[1].
Checked by M. R. Czarny and M. F. Semmelhack.

1. Procedure

A. *Preparation of cyclopropane 1,l-dicarboxylic acid (**1**)*. To a 1-L solution of aqueous 50% sodium hydroxide (Note 1), mechanically stirred in a 2-L, three-necked flask, was added, at 25°C, 114.0 g (0.5 mol) of triethylbenzylammonium chloride (Note 2). To this vigorously stirred suspension was added a mixture of 80.0 g (0.5 mol) of diethyl malonate and 141.0 g (0.75 mol) of 1,2-dibromoethane all at once. The reaction mixture was vigorously stirred for 2 hr (Note 3). The contents of the flask

were transferred to a 4-L Erlenmeyer flask by rinsing the flask with three 75-mL portions of water. The mixture was magnetically stirred and cooled with an ice bath to 15°C, and then carefully acidified by dropwise addition of 1 L of concentrated hydrochloric acid. The temperature of the flask was maintained between 15 and 25°C during acidification. The aqueous layer was poured into a 4-L separatory funnel and extracted three times with 900 mL of ether. The aqueous layer was saturated with sodium chloride and extracted three times with 500 mL of ether. The ether layers were combined, washed with 1 L of brine, dried ($MgSO_4$), and decolorized with activated carbon. Removal of the solvent by rotary evaporation gave 55.2 g of a semisolid residue. The residue was triturated with 100 mL of benzene. Filtration of this mixture gave 43.1–47.9 g (66–73%) of **1** as white crystals, mp 137–140°C.

B. *6,6-Dimethyl-5,7-dioxaspiro[2.5]octane-4,8-dione* (2). A suspension of 39.0 g (0.30 mol) of 1 and 33.0 g (0.33 mol) of freshly distilled isopropenyl acetate was stirred vigorously (magnetic stirrer). To this suspension was added dropwise over a period of 30 min, 0.5 mL of concentrated sulfuric acid. While being stirred for an additional 30 min, the solution became clear yellow, and then partly solidified after being kept at 5°C for 24 hr. After addition of 50 mL of cold water, the precipitated solid was filtered, washed with 10 mL of cold water, and air-dried to give 30.9 g of crude spiroacylal **2**. The filtrate was extracted three times with 50-mL portions of ether. The combined organic layers were carefully washed with 50 mL of brine, dried ($MgSO_4$), and decolorized with activated carbon. Evaporation of the solvent gave an additional 7.8 g of spiroacylal **2** as a yellow solid. The combined samples of crude spiroacylal (38.7 g) were recrystallized from 110 mL of hexane and 25 mL of benzene to give 28.7–31.5 g (55–61%) of **2** as colorless needles, mp 65–67°C. Concentration of the above mother liquor to ca. 40 mL gave 0.80 g of a second crop of spiroacylal **2** as slightly yellow crystals, mp 58–60°C.

C. *2-Oxo-1-phenyl-3-pyrrolidinecarboxylic acid* (**3**). To 1.70 g (10 mmol) of spiroacylal 2 was added 2.79 g (3 mmol) of aniline. The mixture became a homogeneous orange solution after 15 min and was allowed to stir at room temperature for 12 hr. The resulting crystalline mass was diluted with 150 mL of chloroform, washed three times with 10 mL of aqueous 10% hydrochloric acid, washed once with 20 mL of brine, dried ($MgSO_4$), and decolorized with a small amount of activated carbon. Concentration of the organic layer by rotary evaporation gave 5.27 g of a brown residue, which was recrystallized from chloroform-hexane to afford 4.86–5.07 g (79–82%) of the pyrrolidinone **3** as white crystals, mp 146–148°C (dec) (Note 4).

2. Notes

1. Aqueous 50% sodium hydroxide was prepared by dissolving 500 g of sodium hydroxide pellets in water and diluting to 1 L.
2. This compound is commercially available from Aldrich Chemical Company, Inc. Alternatively, it can be made very cheaply and simply by mixing benzyl

chloride (1 equiv) with triethylamine (2.5 equiv). The mixture is allowed to stand for 4–7 days at room temperature. Filtration of the solid and drying in vacuum give triethylbenzylammonium chloride suitable for use in nearly quantitative yield.

3. Some exothermicity results on mixing, causing the temperature to rise to ca. 65°C.

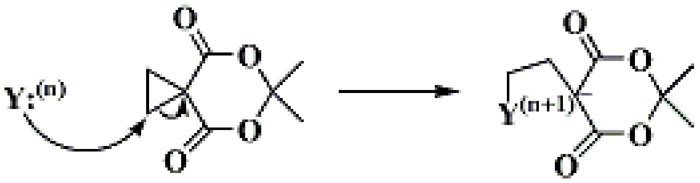
4. At this temperature, after a few minutes, the lactam acid **3** suffers smooth decarboxylation to afford *N*-phenyl-2-pyrrolidinone. Alternatively, the acid can be esterified (methanol-hydrochloric acid), and the resulting 1-phenyl-3-carbomethoxypyrrolidin-2-one can be used for the introduction of other functionality at the 3-position.

3. Discussion

Previously cyclopropane-1,1-dicarboxylic acid had been prepared[2,3,4] by hydrolysis of the corresponding diester. The preparation of 1,1-dicarboalkoxycyclopropanes by a conventional double alkylation of diethyl malonate with 1,2-dibromoethane was severely complicated by the recovery of unreacted diethylmalonate. This required a rather difficult distillation to separate starting material and product. In fact, many commercially offered lots of cyclopropane diester contain extensive amounts of diethyl malonate. Furthermore, preparation of the diacid required a separate and relatively slow saponification of the diester.[5]

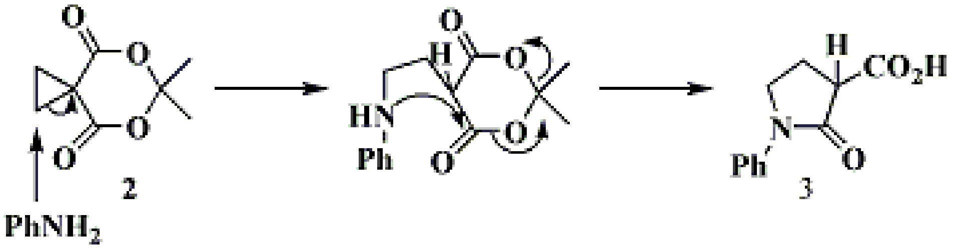
The procedure described here for compound **1** is a scale-up of a published method.[6] Phase-transfer catalysis[7] and concentrated alkali are used to effect a one-pot conversion of diethyl malonate to the cyclopropane diacid, which is easily obtained by crystallization. Apparently alkylation of the malonate system occurs either at the diester or monocarboxylate, monoester stage since the method fails when malonic acid itself is used as the starting material. This method of synthesizing doubly activated cyclopropanes has been extended to the preparation of 1-cyanocyclopropanecarboxylic acid (86%) by the use of ethyl cyanoacetate and 1-acetylcyclopropanecarboxylic acid (69%) by use of ethyl acetoacetate.[6]

The spiroacylal **2** is potentially a valuable agent in organic synthesis.[8] It is readily attacked by a variety of nucleophiles, including pyridine, to give ring-opened products bearing a stabilized carbanion. It is thus seen to be a synthetic equivalent of CH_2-CH_2-$CH(CO_2H)_2$ and $CH_2(CH_2)_2$-CO_2H, i.e., a homo-Michael acceptor. The general reaction is



2

where Y = aniline, piperidine, pyridine, mercaptide, enolate, etc. Spiroacylal **2** was designed under the rationale that the constraint of the carbonyl groups into a conformation in which overlap of their π-orbitals with the "bent bonds" of the cyclopropane is assured should dramatically increase the vulnerability of the cyclopropane toward nucleophilic attack.[8] Experimental support for this notion is abundant.[8] Spiroacylal **2** is considerably more reactive than 1,1-dicarbethoxycyclopropane in such reactions. For instance, reaction of **2** with piperidine occurs at room temperature. The corresponding reaction in the case of the diester is conducted at 110°C.[5] Reactions with enolates also occur under mild conditions.[8] Compound **2** reacts with the weak nucleophile pyridine at room temperature to give a betaine.[8] An illustrative mechanism for the reaction of the acylal **2** with aniline to afford 2-oxo-1-phenyl-3-pyrrolidinecarboxylic acid (**3**) is



2 3

The synthesis of the spiroacylal **2** from the diacid **1** follows a procedure used by Scheuer in a different context.[9]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

brine

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

methanol (67-56-1)

ether (60-29-7)

aniline (62-53-3)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium chloride (7647-14-5)

carbon (7782-42-5)

pyridine (110-86-1)

piperidine (110-89-4)

benzyl chloride (100-44-7)

1,2-dibromoethane (106-93-4)

Ethyl cyanoacetate (105-56-6)

Ethyl acetoacetate (141-97-9)

diethyl malonate (105-53-3)

Malonic acid (141-82-2)

cyclopropane (75-19-4)

$MgSO_4$ (7487-88-9)

isopropenyl acetate (108-22-5)

Cyclopropane-1,1-dicarboxylic acid (598-10-7)

hexane (110-54-3)

triethylamine (121-44-8)

betaine (107-43-7)

triethylbenzylammonium chloride (56-37-1)

CYCLOPROPANE-1,1-DICARBOXYLATE

2-Oxo-1-phenyl-3-pyrrolidinecarboxylic acid, 3-Pyrrolidinecarboxylic acid, 2-oxo-1-phenyl- (56137-52-1)

6,6-Dimethyl-5,7-dioxaspiro[2.5]octane-4,8-dione (5617-70-9)

chloroform-hexane

1-phenyl-3-carbomethoxypyrrolidin-2-one

diethylmalonate

1-cyanocyclopropanecarboxylic acid (6914-79-0)

1-acetylcyclopropanecarboxylic acid

1,1-dicarbethoxycyclopropane (1559-02-0)

mercaptide (18496-25-8)

N-phenyl-2-pyrrolidinone (4641-57-0)

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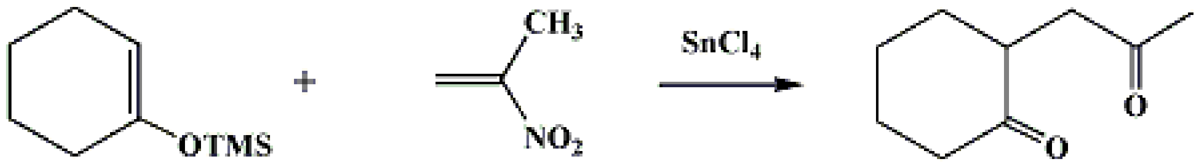
Organic Syntheses, CV 7, 414

SYNTHESIS OF 1,4-DIKETONES FROM SILYL ENOL ETHERS AND NITROOLEFINS: 2-(2-OXOPROPYL) CYCLOHEXANONE

[Cyclohexanone, 2-(2-oxopropyl)]



Submitted by Masaaki Miyashita, Tetsuji Yanami, and Akira Yoshikoshi[1].
Checked by Donald Hilvert, Stefan Kwiatkowski, and Dieter Seebach.

1. Procedure

Caution! This preparation should be carried out in a hood since 2-nitropropene is a powerful lachrymator and anhydrous stannic chloride is a skin irritant.

A 1-L, three necked, round-bottomed flask is fitted with a magnetic stirring bar and a pressure-equalizing dropping funnel to which is attached an oil bubbler, a rubber septum, and an argon or nitrogen inlet to maintain a static inert gas atmosphere in the reaction vessel throughout the reaction. The flask and dropping funnel are charged with 500 mL of dry methylene chloride and 40 mL (34 g, 0.20 mol) of 1-trimethylsiloxy-1-cyclohexene (Note 1), respectively. The flask is flushed with dry inert gas and immersed in a cooling bath at ca. −78°C (acetone or 2-propanol-dry ice). Stirring is started and 23 mL (52.1 g, 0.20 mol) of anhydrous stannic chloride (Note 2) is added rapidly through the rubber septum by means of a syringe. Then 20.0 mL (21.0 g, 0.23 mol) of 2-nitropropene (Note 3) is added through the rubber septum by a syringe over a period of 5–10 min, giving a green solution. The reaction mixture is further stirred at −78°C for 20 min, and then the silyl enol ether is added dropwise to the mixture over 1 hr, giving a faint yellow solution. After completion of the addition the resulting solution is stirred at ca. −78°C for an additional hour; then the bath temperature is gradually warmed to −5°C over a period of 3–3.5 hr while the stirring is continued (Note 4). The inert gas flow is stopped, the dropping funnel is replaced by a condenser, the magnetic stirrer is removed, and the flask is equipped with a heating mantle and an overhead stirring device. Then 280 mL of water are added, and the resulting heterogeneous mixture is vigorously stirred at reflux for 2 hr (Note 5). The mixture is subsequently cooled to room temperature and then poured into a 1-L separatory funnel and the methylene chloride layer is separated from the water. The aqueous layer is extracted once with 100 mL of methylene chloride, and the combined organic layers are washed twice with 160-mL portions of cold water (Note 6) and once

with saturated brine, dried over anhydrous magnesium sulfate, and filtered. The solvent is removed on a rotary evaporator and the residual oil is distilled through a 10-cm Vigreux column under reduced pressure to yield 18.7–21.5 g (61–70%) of 2-(2-oxopropyl)cyclohexanone as a fragrant yellow liquid, bp 84–85°C (0.8 mm), n_D^{19} 1.4671 [lit.[2] bp 91–93°C (1.1 mm), n_D^{25} 1.4655] (Note 7).

2. Notes

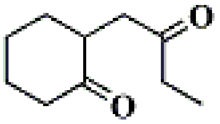
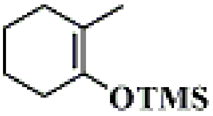
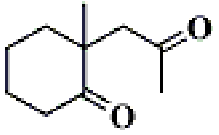
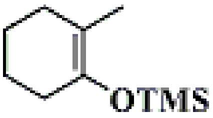
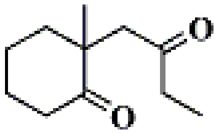
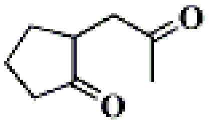
1. This silyl enol ether was prepared according to the procedure of House,[3] 80%, bp 75°C (21 mm) [lit.[3] 74–75°C (20 mm)].
2. A fresh bottle of commercial anhydrous stannic chloride purchased from Wako Pure Chemical Industries, Ltd., Japan, or from Fluka AG, Buchs, Switzerland, was used without purification.
3. 2-Nitropropene[4] was freshly prepared before use.
4. The yellow solution becomes green on warming and finally turns yellow.
5. On addition of water the mixture turns purple, and after refluxing it becomes brown.
6. Although an insoluble white substance appears in the aqueous washings, it is discarded.
7. The checkers found refractive indices n_D^{19} 1.468 and 1.4665 or n_D^{25} 1.4657 and 1.4649.

3. Discussion

This procedure illustrates a recently published, simple, general method for the synthesis of 1,4-diketones from silyl enol ethers and nitroolefins.[5] 2-(2-Oxopropyl)cyclohexanone has been prepared by the reaction of the pyrrolidine enamine of cyclohexanone with bromoacetone (40%)[2] and by several other multistep processes.[6,7,8] However, the overall yields obtained by these routes have never exceeded 50% and some of the methods are laborious for large-scale preparations. The present method illustrates a mild and convenient one-pot reaction for the preparation of 1,4-diketones. In addition, the starting materials are readily accessible, the reaction proceeds regioselectively, and the yields of product are generally high. This process consists of the initial Michael addition of silyl enol ethers to nitroolefins, followed by a Nef reaction of the nitronate esters.[5] The scope of the reaction is shown in Table I. The 1,4-diketones thus obtained have been converted into corresponding cyclopentenones in high yields.[5]

TABLE I
1,4-DIKETONES PREPARED FROM SILYL ENOL ETHERS AND NITROOLEFINS

Silyl Enol Ether	Nitroolefin	Lewis Acid	1,4-Diketone	Yield (%)

	2-Nitro-1-butene	$TiCl_4$		76
	2-Nitropropene	$TiCl_4$		70
	2-Nitro-1-butene	$TiCl_4$		82
	2-Nitropropene	$SnCl_4$		70

9

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

brine

pyrrolidine enamine of cyclohexanone

methylene chloride (75-09-2)

Bromoacetone (598-31-2)

stannic chloride (7646-78-8)

magnesium sulfate (7487-88-9)

1-trimethylsiloxy-1-cyclohexene (6651-36-1)

2-Nitropropene (4749-28-4)

2-nitro-1-butene

2-(2-Oxopropyl)cyclohexanone, Cyclohexanone, 2-(2-oxopropyl) (6126-53-0)

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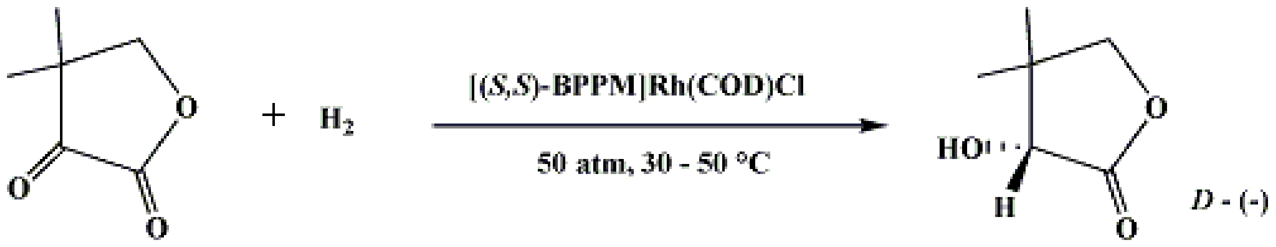
Organic Syntheses, CV 7, 417

ASYMMETRIC HYDROGENATION OF KETOPANTOYL LACTONE: D-(–)-PANTOYL LACTONE

[2(3*H*)-Furanone, dihydro-3-hydroxy-4,4-dimethyl-]



Submitted by I. Ojima, T. Kogure, and Y. Yoda[1].
Checked by Larry K. Truesdale, Stanley D. Hutchings, and Gabriel Saucy.

1. Procedure

A. *Preparation of catalyst solution*. A 250-mL, round-bottomed flask fitted with a septum and magnetic stirring bar is charged with 486.9–488.2 mg (Note 1) (0.985–0.990 × 10^{-3} mol) of chloro(1,5-cyclooctadiene)rhodium(I) dimer (Note 2) and, under argon (Note 3), with 1.20 g (2.15 × 10^{-3} ml) of (2*S*, 4*S*)-*N*-*tert*-butyloxycarbonyl-4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidine, (*S*,*S*)-BPPM (Note 4). The sealed flask is charged by cannula, under argon, with 150 mL of degassed benzene (Note 5) and stirred under argon for 15 min at room temperature. The catalyst is transferred by cannula, under argon, into the autoclave (see below).

B. *Asymmetric hydrogenation*. A stainless steel stirred autoclave with a total volume of 500 mL is charged with 25.6 g (0.2 mol) of ketopantoyl lactone (Note 6),(Note 7),(Note 8),(Note 9). The autoclave is flushed with argon and the catalyst solution (see above) is added by cannula, under argon. The autoclave is sealed and hydrogenation is carried out at 40°C, 750-psig hydrogen and 950–1050 rpm for 48 hr (Note 10). Care should be taken to flush all the lines before connecting to the autoclave. After the autoclave is cooled to room temperature, it is vented and opened. The reaction mixture is then transferred to a 500-mL, round-bottomed flask and most of the solvent is removed by rotary evaporator. Distillation (Note 11) of this reddish solid affords 24–25.6 g (92–98%) (Note 1) of D-(–)-pantoyl lactone: bp 90–110°C (4 cm); $[\alpha]_D^{25}$ –39.3° to –42.4° (*c* 2, H_2O) (Note 12) (78 to 84% e.e.) (Note 1) and (Note 10).

The pantoyl lactone thus obtained (25.41 g), $[\alpha]_D^{25}$ –40.8° (80.5% e.e.) (Note 13) is refluxed with 75 mL benzene and 290 mL of UV-grade hexanes. The cloudy solution is stirred briskly overnight as solids form. Filtration of the solids and drying for 3 hr at 0.25 mm, 30°C in a vacuum oven affords 21.51 g of product; $[\alpha]_D^{25}$ –47.7° (94.27% e.e.). This material is again refluxed and crystallized (Note 14) from 30 mL of benzene and 116 mL of UV-grade hexanes to afford 19.97 g (77%) of product; $[\alpha]_D^{25}$ –49.87° (98.5% e.e.). Anal. calcd. for $C_6H_{10}O_3$: C, 55.37; H, 7.75. Found: C, 55.34; H, 7.57 (Note 15).

2. Notes

1. The reaction was done four times at this scale. The range represents the high and low amounts of catalyst precursor used over the four reactions.
2. Chloro(1,5-cyclooctadiene)rhodium (I) dimer is commercially available from Strem Chemicals, Inc., Newburyport, MA.
3. The addition and measurement of (*S*,*S*)-BPPM is most conveniently done in a dry box or glove bag under argon. A Schlenk tube apparatus can be used if these are not available.
4. (2*S*,4*S*)-*N*-*tert*-Butyloxycarbonyl-4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidine, (*S*,*S*)-BPPM,[2,3] is commercially available from E. Merck, Darmstadt, West Germany and Kanto Chemical Company, Tokyo, Japan.
5. The submitters claim that tetrahydrofuran can also be used giving D-(–)-pantoyl lactone with 83.3–84.8% e.e. This was not checked.
6. (a) Ketopantoyl lactone is readily prepared by the oxidation of *d*,*l*-pantoyl lactone (Note 8) with bromine as follows.[4] Into a 500-mL, round-bottomed flask fitted with a mechanical stirrer, dropping funnel, condenser, and thermometer is charged 13.0 g (0.1 mol) of *d*,*l*-pantoyl lactone (Note 7) and 150 mL of carbon tetrachloride. The mixture is stirred and heated to reflux. Bromine (16.5 g, 0.103 mol) in 100 mL of carbon tetrachloride is slowly added from the dropping funnel over 3 hr. After 8 hr, generation of hydrogen bromide subsides and the red color of bromine almost disappears, indicating completion of the reaction. Dry air is bubbled through the solution to remove the remaining hydrogen bromide and the small quantity of bromine. The solvent is removed with a rotary evaporator and further evacuated with a vacuum pump to afford 12.8 g (100%) (Note 9) of almost pure ketopantoyl lactone. One recrystallization from 150 mL of carbon tetrachloride (heat to reflux and then cool to –10°C) affords 11.6–12.2 g (90–95%) of pure ketopantoyl lactone, mp 66–67.5°C. (b) An alternative procedure preferred by the checkers to prepare highly pure ketopantoyl lactone follows. A 5-L, round-bottomed flask equipped with a mechanical stirrer, condenser, thermometer, and dropping funnel is charged with 700 g of $Ca(OCl)_2$ (analyzed as 20% active chlorine) and 1.5 L of acetonitrile dried overnight over Linde 4A molecular sieves. *d*,*l*-Pantoyl lactone (165 g) (Note 7) is dissolved in 500 mL of dried acetonitrile. The $Ca(OCl)_2$ slurry is stirred while 1/7 of the pantoyl lactone solution is added. The temperature of the exothermic reaction is controlled with an ice bath to below 35°C. The remainder of the pantoyl lactone solution is added in 75-mL aliquots over 25–30 min while taking care to control the temperature. The ice bath is removed and stirring is continued. After 3.5 hr, GLC analysis indicates 94% product. The reaction mixture is filtered and the solids are rinsed with acetonitrile. The crude product is dried on a rotary evaporator and further evacuated overnight to yield 105.6 g. The material is dissolved in methylene chloride, dried over Na_2SO_4, filtered through Celite, and concentrated under reduced pressure. The crude product (94.1 g) is then purified by refluxing and stirring overnight with 500 mL of ethyl ether. The slurry is allowed to stand at 5°C. The solids are filtered, washed with cold ether, and dried in a vacuum oven at room temperature for 6 hr to afford 80.8 g (86% recovery) of pure ketopantoyl lactone. Ketopantoyl lactone has also been reported to be easily prepared by the oxidation of *d*,*l*-pantoyl lactone with alkaline metal hypochlorite[5] or by reaction

of sodium dimethylpyruvate with formaldehyde in the presence of potassium carbonate.[6]

7. *d,l*-Pantoyl lactone is very hygroscopic. Care must be taken during this oxidation that dry starting material is used and that water does not contaminate the reaction; the yield will fall drastically probably because of hydrolysis.

8. *d,l*-Pantoyl lactone is commercially available from Sigma Chemical Company, St. Louis, MO 63178.

9. GLC analysis indicates 97–98% yield. A simple GLC system to determine the relative completion of the reaction is a 3-ft × 1/8-in column packed with 10% Carbowax 20 M on Anakrom Q 90/100. With this column a program of 150 to 210°C at 8°/min and a 7-min hold gives baseline separation of ketopantoyl lactone at 2.75–3.2 min and pantoyl lactone at 3.7–3.95 min. The flow rate of the carrier gas is 20 mL/min.

10. When ketopantoyl lactone prepared by method 6b was used, the reaction was complete in 2 hr.

11. A bulb-to-bulb distillation using a Kugelrohr apparatus is most convenient.

12. The reported maximum rotation, $[\alpha]_D^{25}$, max, for pure D-(–)-pantoyl lactone is –50.7° (*c* 2.05, H_2O).[7,8]

13. The enantiomeric excess and the speed of reduction are both greatly influenced by impurities that are not detectable by GLC. Digestion in ether seems to remove these impurities better than recrystallization from CCl_4.

14. This recrystallization is very temperature-sensitive; for example, this purification was done at ambient temperature (28–30°C). The first recrystallization removes 3.7 g of *d,l*-pantoyl lactone and 0.2 g of D-(–)-pantoyl lactone. When the recrystallization was done at 5°C, twice as much solvent served to remove only 4.2 g of *d,l*-pantoyl lactone and none of the D-isomer.

15. The procedure described is a scaled-up version (20 ×) of the original submission worked out by the checkers.

3. Discussion

D-(–)-Pantoyl lactone is a key intermediate for the synthesis of pantothenic acid, which is a member of the vitamin B complex and is an important constituent of Coenzyme A. Although D-(–)-pantoyl lactone has been obtained by classical optical resolution using quinine, ephedrine, and other chiral amines, catalytic asymmetric synthesis appears to be more effective from a practical point of view.[9,10] One problem of the present approach was the availability of ketopantoyl lactone, but the recent method developed by Hoffmann–La Roche,[6] consisting in the condensation of sodium dimethylpyruvate with formaldehyde, may open a commercial route to ketopantoyl lactone. Thus, asymmetric reduction of ketopantoyl lactone now becomes an important route to D-(–)-pantoyl lactone. Asymmetric reduction of ketopantoyl lactone can also be achieved with micro-organisms. For example, microbial reduction of ketopantoyl lactone using baker's yeast was reported to give ca. 72% e.e.,[11] and the specific strain of an ascomycete, *Byssochlamys fulva*, was reported to give D-(–)-pantoyl lactone with 95–100% e.e.[11] However, the isolation procedure from aqueous media in these microbial reductions—specifically: extraction, recovery of raw materials, and purification—is very troublesome because of the high solubility of the product in water. Consequently, the present method has considerable advantages from a synthetic point of view; for instance, (a)

the yield of the reaction is virtually 100% and (b) isolation of the product is simple and convenient since the reaction is carried out in small amounts of nonaqueous media.

The present method has been successfully applied[12] to the asymmetric reduction of various α-keto carboxylates and α-keto lactones.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

H_2O

hexanes

chloro(1,5-cyclooctadiene)rhodium(I) dimer

(2S, 4S)-N-tert-butyloxycarbonyl-4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidine, (S,S)-BPPM

Chloro(1,5-cyclooctadiene)rhodium (I) dimer

(S,S)-BPPM

(2S,4S)-N-tert-Butyloxycarbonyl-4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidine, (S,S)-BPPM

D-(−)-pantoyl lactone

$Ca(OCl)_2$

potassium carbonate (584-08-7)

Benzene (71-43-2)

ether, ethyl ether (60-29-7)

hydrogen (1333-74-0)

acetonitrile (75-05-8)

formaldehyde (630-08-0)

hydrogen bromide (10035-10-6)

bromine (7726-95-6)

Na_2SO_4 (7757-82-6)

carbon tetrachloride, CCl_4 (56-23-5)

chlorine (7782-50-5)

methylene chloride (75-09-2)

Tetrahydrofuran (109-99-9)

argon (7440-37-1)

Ephedrine (90-82-4)

sodium dimethylpyruvate (3715-29-5)

pantothenic acid

quinine (130-95-0)

ketopantoyl lactone (13031-04-4)

pantoyl lactone, d,l-pantoyl lactone, 2(3H)-Furanone, dihydro-3-hydroxy-4,4-dimethyl- (79-50-5)

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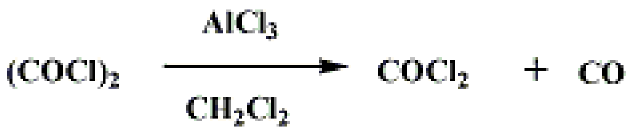
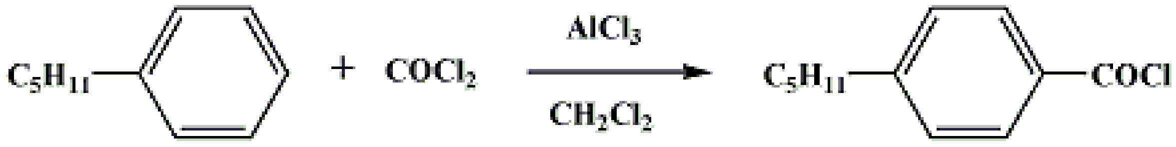
Organic Syntheses, CV 7, 420

PREPARATION OF 4-ALKYL-AND 4-HALOBENZOYL CHLORIDES: 4-PENTYLBENZOYL CHLORIDE

[Benzoyl chloride, 4-pentyl-]





Submitted by Mary E. Neubert and D. L. Fishel[1].
Checked by Vinay Chowdhry and R. E. Benson.

1. Procedure

Caution! Operations prior to vacuum distillation of the product should be done in a good hood since phosgene, carbon monoxide, and hydrogen chloride are present (Note 1). Rubber gloves should also be used to avoid contact with the reagents.

A 100-mL, three-necked, round-bottomed flask is fitted with a mechanical stirrer, 100-mL pressure-equalized addition funnel (Note 2) to which is attached a drying tube (Note 3), and a rubber septum. Dry methylene chloride (27 mL, (Note 4)) and 8.9 g (0.067 mol) of aluminum chloride (Note 5) are added to the flask, stirring is begun, and 17.1 g (11.5 mL, 0.135 mol) of oxalyl chloride (Note 6) is added over 5 min by means of a syringe introduced through the septum (Note 7). The septum is replaced by a thermometer and a solution of 10 g (11.6 mL, 0.067 mol) of amylbenzene (Note 8) in 40 mL of dry methylene chloride is added dropwise over 1 hr with stirring while the temperature is maintained at 20–25°C. The reaction mixture is reduced to about half of the original volume by distillation of solvent and excess oxalyl chloride and/or phosgene (Note 9). Approximately 40 mL of fresh dry methylene chloride is added to the flask and the solution is cooled to 0°C in an ice-salt bath. The cold solution is slowly poured onto a stirred mixture of 170 g of crushed ice and 10 g of calcium chloride at a rate to maintain the temperature below 5°C (Note 10). The organic layer is rapidly separated from the aqueous layer and dried over anhydrous sodium sulfate. The mixture is filtered and the solvent is removed by distillation at reduced pressure. The residual liquid is dissolved in 50 mL of ether, and the resulting solution is cooled to 0°C, extracted with 5 mL of cold (0°C) 5% potassium hydroxide solution, and then

washed twice with 15-mL portions of cold (0°C) water (Note 11). The ether solution is separated and dried over anhydrous sodium sulfate. The mixture is filtered and the solvent is removed by distillation at reduced pressure (Note 12). Distillation through a Vigreux column affords a small forerun and then 7.80–7.82 g (55%) of pure 4-pentylbenzoyl chloride, bp 95°C (0.20 mm) (Note 13) and (Note 14). The acid chloride is stable if kept in a sealed container to prevent hydrolysis.

2. Notes

1. Both phosgene and carbon monoxide were identified in IR spectra of gases generated from an equimolar mixture of oxalyl chloride and aluminum chloride at room temperature.
2. The submitters used a constant addition funnel.
3. Molecular sieves 4A available from Davison Chemical Co. were used.
4. The submitters state that the use of predried methylene chloride (stored overnight over 4A molecular sieves) gave the best results.
5. Use of either an excess of aluminum chloride or partially hydrolyzed aluminum chloride gives larger amounts of the by-product diaryl ketone at the expense of the acid chloride. The checkers used freshly opened containers of the anhydrous material available from Fisher Scientific.
6. Oxalyl chloride should be distilled if it is colored or contains solid. Studies by the submitters have shown that an excess of oxalyl chloride is needed for maximum conversion of the alkylbenzene to acid chloride. The checkers used oxalyl chloride available from Eastman Organic Chemicals.
7. The submitters added the oxalyl chloride through the funnel used to add amylbenzene.
8. The checkers used product available from Aldrich Chemical Company, Inc.
9. If excess oxalyl chloride (and/or phosgene) is not removed, the vigorous reaction with water during decomposition of the aluminum chloride complex contributes to hydrolysis of the product acid chloride by increasing the time needed to complete this step. The more dilute solution achieved by additional solvent helps to prevent this hydrolysis as does maintenance of a low temperature during decomposition of the complex.
10. The calcium chloride-ice mixture helps to maintain a low temperature.
11. Changing the solvent to ether prior to the base extraction step (to remove carboxylic acid formed by hydrolysis) inhibits emulsion formation, particularly with the higher alkyl-substituted products.
12. The procedure may be interrupted at this point if the crude acid chloride is protected from moisture, although highest yields are obtained if distillation is done at once. Failure to remove water (even that associated with the sodium sulfate drying agent) before storage may result in anhydride formation during distillation because of the presence of free carboxylic acid.
13. Infrared analysis (neat, film) shows a carbonyl doublet at 1740, 1770 cm^{-1}, typical of 4-substituted benzoyl chlorides and thought to be due to Fermi resonance.[2,3] Contamination of the product with the anhydride can be detected

by a doublet at 1720 and 1780 cm^{-1}, with the ketone by a singlet at 1650 cm^{-1}, and with the acid by a singlet at 1690 cm^{-1}.

14. The submitters obtained the product in 75% yield.

3. Discussion

This method is based on that of Fahim,[4] who isolated 4-alkylbenzoic acids in 40–60% yields by hydrolysis of the corresponding acid chlorides. The present improved procedure includes those conditions believed to be optimum for a one-step synthesis of 4-substituted benzoyl chlorides in good yields and apparently free of positional isomers, as indicated by gas chromatography/mass spectroscopy as well as ^{1}H and ^{13}C NMR analyses. The procedure has been used successfully for the synthesis of 4-halobenzoyl chlorides and several other aryl acid chlorides,[5,6] as well as for 4-alkylbenzoyl chlorides up through the decyl derivative. Some of these results are summarized in Table I. The reaction has been run on a 1-mol scale by the submitters with no difficulty.

The major by-product that can be isolated (3–6%) from the residue after distillation is the 4,4'-disubstituted benzophenone; formation of the ketone is minimized by using excess oxalyl chloride and by slow addition of a dilute solution of the alkylbenzene to the acylating agent. Ambient temperatures (20–25°C) appear to give optimum results; higher temperatures favor ketone formation and lower temperatures result in incomplete reaction for reasonable reactions times. Numerous additional reactions using 4-alkyl-benzenes indicate that the alkylbenzene solution can be added more rapidly as long as the temperature is maintained at 20–25°C. Maximum yields are obtained when the addition time is 30–60 min, apparently because longer times lead to loss of phosgene and reaction of the acid chloride with the alkylbenzene to give the ketone.

This method cannot be used to prepare acid chlorides of aromatic systems that contain substituents strongly activating for electrophilic substitution such as alkoxy groups (the major product is ketone), deactivating ring substituents (no reaction), or those that form stable acylium ions (major product is carboxylic acid). Mesitoic acid rather than the acid chloride was isolated from the acylation of mesitylene using these conditions, which confirms the results previously reported using similar conditions.[7]

TABLE I
4-SUBSTITUTED BENZOYL CHLORIDES FROM SUBSTITUTED BENZENES

Substituent	Yield (%)	bp (°C)(mm)
C_4H_9	66.5	113 (1.7)
i-C_4H_9	77.5	115 (1.6)
C_5H_{11}	75.3	136 (3.2)

C_6H_{13}	80.3	143 (1.3)
C_7H_{15}	79.3	160 (5)
C_9H_{19}	71.8	182 (2.6)
$C_{10}H_{21}$	68.0	169 (0.6)
F	84.4	50 (1.1)
Cl	77.7	86 (2.1)
Br	75.9	103 (2.5)
I	74.1	100 (0.7)

Previously, the most widely used method for preparation of 4-alkylbenzoyl chlorides on a laboratory scale has been from the benzoic acids obtained by oxidation of aromatic ketones, usually 4-alkylacetophenones.[8,9,10,11,12,13,14] The latter are usually prepared by acylating alkylbenzenes. Although this sequence gives high yields, it is lengthy (three completely separate steps) and the scale is restricted in the second step because of the large volumes required. The submitters state that they were unable to repeat the reported alkylation of toluic acid.[15] Methods that lead to formation of ortho and para isomeric intermediates are inconvenient since they require that the isomers be separated.[16,17,18,19]

This method provides easy access to 4-alkylbenzoyl chlorides, which are useful intermediates in the preparation of diaryl esters that have mesomorphic properties.[20] Benzoyl chlorides substituted in the 4-position also serve as starting materials for the preparation of aromatic aldehydes[21] and nitriles,[6,22] whereas the acids, derivable quantitatively from the acid chlorides, are good precursors via the Schmidt reaction to 4-substituted anilines.[23] This method has been used to prepare deuterated liquid crystalline anils from the anilines obtained by Schmidt rearrangement of 4-alkylbenzoic acids[24] and 4'-cyanobiphenyls[25] but was not successful in an attempt to prepare 2-alkyl-7-cyanofluorenes.[26]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

4,4'-disubstituted benzophenone

Benzoyl chlorides

calcium chloride (10043-52-4)

hydrogen chloride (7647-01-0)

ether (60-29-7)

carbon monoxide (630-08-0)

sodium sulfate (7757-82-6)

aluminum chloride (3495-54-3)

potassium hydroxide (1310-58-3)

phosgene (75-44-5)

Mesitylene (108-67-8)

methylene chloride (75-09-2)

Amylbenzene (538-68-1)

oxalyl chloride (79-37-8)

Mesitoic acid (480-63-7)

toluic acid (99-94-5)

4-Pentylbenzoyl chloride, Benzoyl chloride, 4-pentyl- (49763-65-7)

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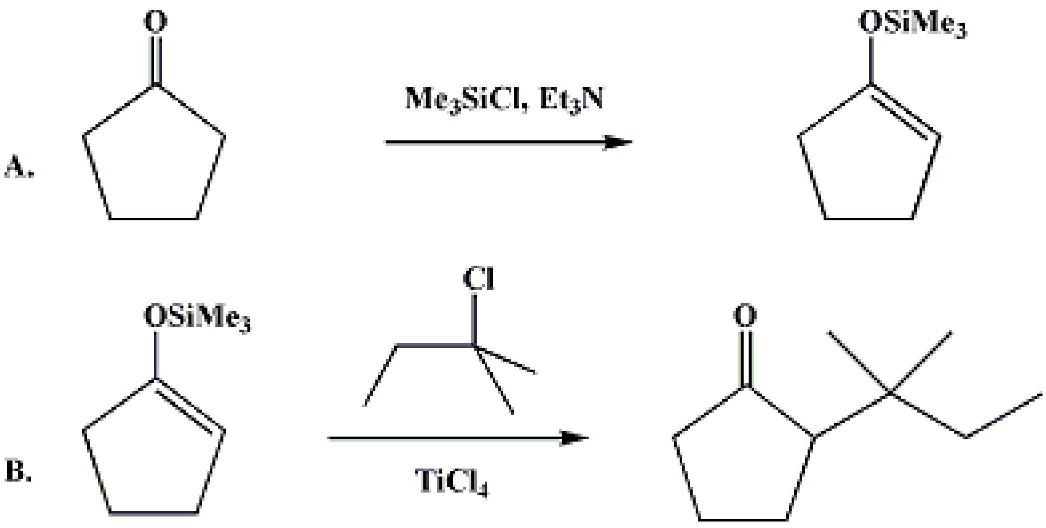
Organic Syntheses, CV 7, 424

α-*tert*-ALKYLATION OF KETONES: 2-*tert*-PENTYLCYCLOPENTANONE

[Cyclopentanone, 2-*tert*-pentyl-]



Submitted by M. T. Reetz, I. Chatziiosifidis, F. Hübner, and H. Heimbach[1].
Checked by Kevin Kunnen and Carl R. Johnson.

1. Procedure

A. *1-Trimethylsiloxycyclopentene*.[2] A 1-L, two-necked, round-bottomed flask is equipped with a mechanical stirrer and a reflux condenser having a drying tube (calcium chloride). The flask is charged with 200 mL of dimethylformamide (Note 1), 45 g (0.54 mol) of cyclopentanone (Note 2), 65.5 g (0.6 mol) of chlorotrimethylsilane (Note 2), and 185 mL (1.33 mol) of triethylamine (Note 1), and the mixture is refluxed for 17 hr (Note 3). The mixture is cooled, diluted with 350 mL of pentane, and washed four times with 200-mL portions of cold saturated aqueous sodium hydrogen carbonate. The aqueous phases are extracted twice with 100-mL portions of pentane and the combined organic phases are washed rapidly with 100 mL of ice–cold aqueous 2 *N* HCl and immediately thereafter with a cold saturated solution of sodium hydrogen carbonate. After the mixture has been dried over anhydrous magnesium sulfate, the pentane is removed by rotary evaporation. Distillation of the oily residue at 60°C (12 mm) using a 20-cm Vigreux column affords 50.1–51.6 g (60–62%) of 1-trimethylsiloxycyclopentene (**1**) as a colorless liquid (Note 4).

B. *2-tert-Pentylcyclopentanone*. A dry, 250-mL, three-necked, round-bottomed flask is fitted with a gas inlet, a gas bubbler, rubber septum, and magnetic stirrer. The apparatus is flushed with dry nitrogen or argon and charged with 120 mL of dry dichloromethane (Note 5), 15.6 g (0.10 mol) of 1-trimethylsiloxycyclopentene and

11.7 g (0.11 mol) of 2-chloro-2-methylbutane (Note 6). The mixture is cooled to −50°C (Note 7) and a cold (−50°C) solution of 11 mL (0.10 mol) of titanium tetrachloride (Note 8) in 20 mL of dichloromethane is added within 2 min through the rubber septum with the aid of a syringe. During this operation rapid stirring and cooling in maintained. Sunlight should be avoided. The reddish-brown mixture is stirred at the given temperature for an additional 2.5 hr and is then rapidly poured into 1 L of ice–water (Note 9). After the addition of 400 mL of dichloromethane, the mixture is vigorously shaken in a separatory funnel; the organic phase is separated and washed twice with 400-mL portions of water. The aqueous phase of the latter two washings is extracted with 200 mL of dichloromethane; the organic phases are combined and dried over anhydrous sodium sulfate. The mixture is concentrated using a rotary evaporator and the residue is distilled at 80°C (12 mm) (Note 10) to yield 9.2–9.5 g (60–62%) (Note 11) of 2-*tert*-pentylcyclopentanone as a colorless oil (Note 12).

2. Notes

1. Dimethylformamide and triethylamine were purchased from Baker (Baker Analyzed Reagent) and used without further purification.
2. Cyclopentanone and chlorotrimethylsilane were purchased from Aldrich Chemical Company and used without further purification.
3. According to the original procedure of House,[2] only 4 hr is needed, affording a 59% yield. However, the submitters found that an increase in reaction time raises the yield.
4. The spectral properties of the compound are as follows: ^{1}H NMR (CCl_4) δ: 0.2 (s, 9 H), 1.6–2.4 (m, 6 H), 4.4 (m, 1 H); IR (film) 1645 cm^{-1} (lit.[2] 1645 cm^{-1}).
5. Reagent-grade dichloromethane is dried by passing over a column of aluminum oxide (activity I).
6. The submitters purchased 2-chloro-2-methylbutane from Eastman Kodak Company. The checkers prepared the halide as follows. A separatory funnel was charged with 21.5 mL (0.2 mol) of 2-methyl-2-butanol and 100 mL of concentrated hydrochloric acid. The mixture was shaken vigorously with periodic venting for 10 min. The layers were separated and the 2-chloro-2-methylbutane layer (upper) was washed several times with equal volumes of cold water. The product was dried over calcium chloride and distilled, bp 85°C.
7. The precise temperature is not critical. The checkers observed that the reaction proceeds in about the same time and yield at −78°C. However, at temperatures above −40°C a drop in yield may occur.
8. The titanium tetrachloride should be clean, colorless, and free of hydrogen chloride. The checkers used material freshly distilled in an argon atmosphere.
9. If sodium bicarbonate is used, large amounts of titanium oxide-containing emulsions tend to form that hamper the purification of the product.
10. The by-products consist of volatile cyclopentanone and an unknown high-boiling material, so that rapid vacuum transfer at room temperature and 0.02

mm is also possible. Extremely slow distillation at high temperatures should be avoided. The value of 72°C (2.2 mm) cited in the literature[3] seems to be in slight error.

11. The submitters ran the reaction on a 0.5 scale and reported yields of 63–68%.

12. The product is >96% pure as checked by gas chromatography (4% UCON LB 550X, Chromasorb G, AW-DMCS 80–100 mesh, 130°C). The spectral properties are as follows: IR (neat) cm^{-1}: 3050–2800, 1735, 1460, 1150; ^{1}H NMR (CCl_4) δ: 0.80 (J = 6 Hz, CH_3 of the ethyl group, which partially overlaps with the signals of the other two diastereotopic methyl groups), 0.82 (s), 0.92 (s), 1.15–2.25 (m); ^{13}C NMR ($CDCl_3$) δ: 7.78, 19.87, 23.72 (slightly broad), 25.57, 32.62, 34.70, 40.02, 55.39, 219.57.

3. Discussion

This procedure solves the long-pending problem of α-*tert*-alkylation of ketones. The generality is shown by the fact that a wide variety of structurally different ketones can be alkylated via the corresponding silyl enol ethers with good yields.[4] Variation of the alkylating agent is also possible, branched and cyclic tertiary alkyl halides reacting position specifically without signs of rearrangement.[4] Chemoselectivity studies reveal that esters, aromatic groups, and primary alkyl halide moieties are tolerated.[4] In the case of a sensitive enol ether such as that derived from acetone, titanium tetrachloride should be replaced by more mild Lewis acids such as zinc chloride, although the yields are lower.[5] Finally, it should be noted that any S_Nl-reactive alkyl halide is likely to be a suitable alkylating agent in Lewis acid-promoted α-alkylation of carbonyl compounds. Indeed, aryl-activated secondary alkyl halides and acetates react in the same way.[6] Heteroatom substituted alkyl halides and acetates also react smoothly with enol silanes in the presence of ZnX_2.[4,6] Generally, such alkylating agents are unsuitable in classical enolate chemistry because of the ease of hydrogen halide elimination and/or the failure to react regiospecifically. The methods are thus complementary.

A related *tert*-butylation procedure in which the silyl enol ether is added to a mixture of titanium tetrachloride and *tert*-butyl chloride gives rise to distinctly lower yields.[7,8] This is also the case if the tertiary halide is added to a mixture of silyl enol ether and titanium tetrachloride.[5]

A number of alternative multistep procedures for the synthesis of α-*tert*-alkyl ketones are known, none of which possess wide generality. A previous synthesis of 2-*tert*-pentylcyclopentanone involved reaction of *N*-1-cyclopentenylpyrrolidine with 3-chloro-3-methyl-1-butyne and reduction of the resulting acetylene (overall yield 46%).[3] However, all other enamines tested afford much lower yields.[3] Cuprate addition to unsaturated ketones may be useful in certain cases.[9] Other indirect methods have been briefly reviewed.[5]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

calcium chloride (10043-52-4)

acetylene (74-86-2)

hydrogen chloride, hydrochloric acid, HCl (7647-01-0)

sodium bicarbonate, sodium hydrogen carbonate (144-55-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

acetone (67-64-1)

zinc chloride (7646-85-7)

tert-Butyl chloride (507-20-0)

Cyclopentanone (120-92-3)

Pentane (109-66-0)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

2-Methyl-2-butanol (75-85-4)

dimethylformamide (68-12-2)

titanium tetrachloride (7550-45-0)

triethylamine (121-44-8)

argon (7440-37-1)

2-chloro-2-methylbutane (594-36-5)

CHLOROTRIMETHYLSILANE (75-77-4)

1-Trimethylsiloxycyclopentene (19980-43-9)

2-tert-Pentylcyclopentanone, Cyclopentanone, 2-tert-pentyl- (25184-25-2)

N-1-cyclopentenylpyrrolidine

3-chloro-3-methyl-1-butyne (1111-97-3)

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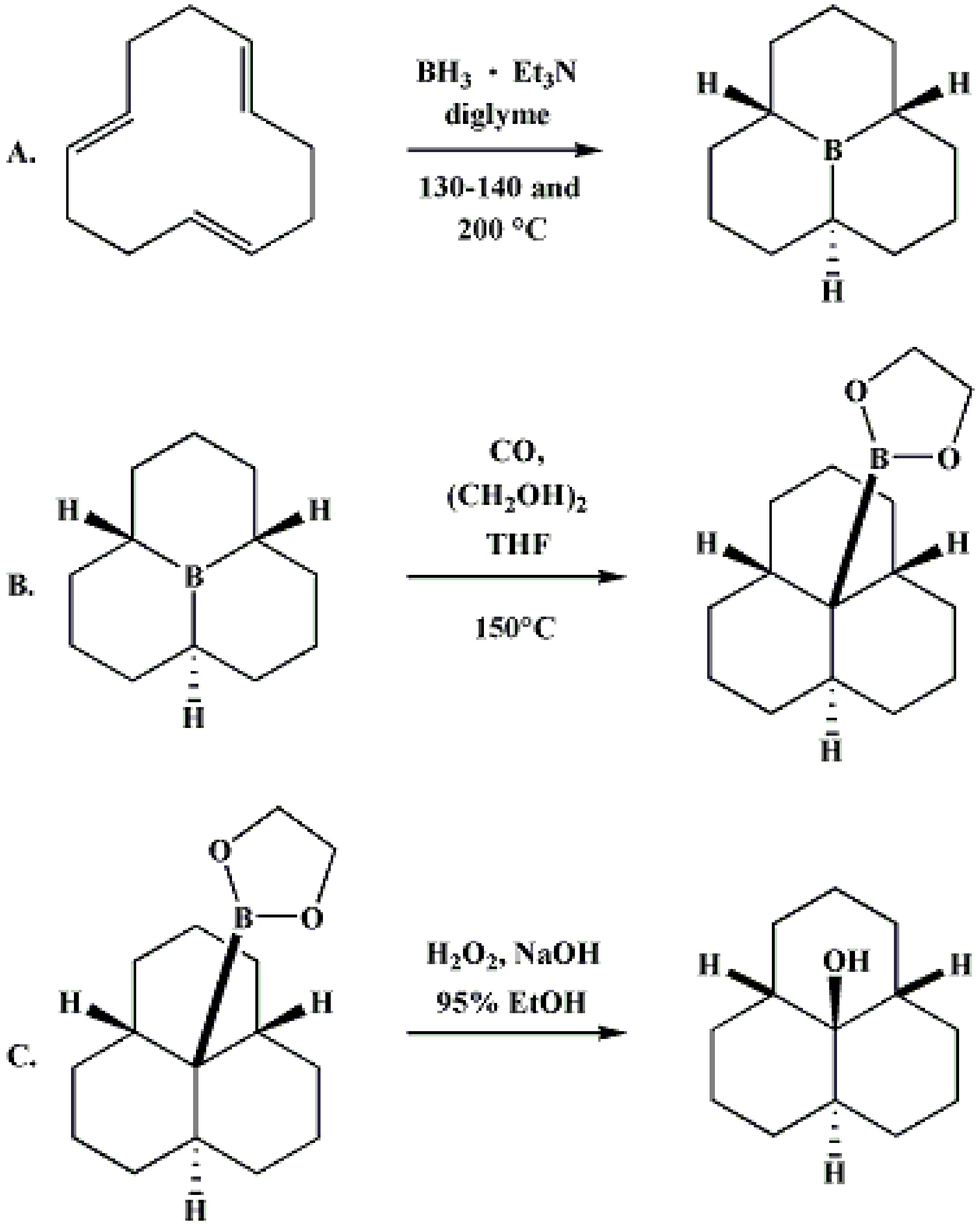
Organic Syntheses, CV 7, 427

PERHYDRO-9b-BORAPHENALENE AND PERHYDRO-9b-PHENALENOL

[9b-Boraphenalene, dodecahydro- and Phenalen-9bα(2*H*)-ol, 3,3aα,4,5,6,6aα,7,8,9,9aβ-decahydro-]



Submitted by Ei-ichi Negishi[1,3] and Herbert C. Brown[2,3].
Checked by A. J. Cocuzza and R. E. Benson.

1. Procedure

Caution! The products used and formed in Step A are extremely pyrophoric. Great

care should be taken in conducting this step.

A. *cis,trans-Perhydro-9b-boraphenalene.* A 1-L, three-necked, round-bottomed flask is fitted with a septum, thermometer, magnetic stirring bar, and a 12-cm Vigreux column. A 2-L, two-necked receiving flask is attached to the Vigreux column and fitted with a nitrogen-inlet tube that is attached to a mercury bubbler device to permit a positive pressure on the system (Note 1). The entire system is flushed with nitrogen and, while the system is maintained under a static pressure of nitrogen, 500 mL (0.050 mol) of a 1.0 *M* solution of borane in tetrahydrofuran (THF, (Note 2)) is added to the reaction flask by means of a syringe. The flask is immersed in an ice–water bath, stirring is begun, and 50.6 g (0.50 mol) of triethylamine (Note 3) is added slowly over 15 min. After the addition is completed, the THF is removed by distillation at atmospheric pressure and 300 mL of dry diglyme (Note 4) is added. The resulting solution is heated to 130–140°C and a solution of 81 g (0.50 mol) of *trans,trans,trans*-1,5,9-cyclododecatriene (Note 5) in 100 mL of dry diglyme (Note 6) is added over 2 hr. At the end of this time, the diglyme is removed by distillation at atmospheric pressure and the residual oil is heated at 200°C for 6 hr (Note 7). After the reaction is cooled, the thermally treated product is used directly in Step B (Note 8). Product free of polymeric impurity can be obtained by distillation (Note 9) and (Note 10).

B. *cis,cis,trans-2-(Perhydro-9'b-phenalyl)-1,3,2-dioxaborole*. The 250-mL pressure vessel (Note 11) is fitted with a cap bearing a rubber septum. Two hypodermic needles are inserted into the vessel through the septum, one with the end close to the bottom of the vessel and the other with the end close to the top. The vessel is flushed with nitrogen, with the exit gas passing through a mercury bubbler device. One-fifth of the thermally treated, undistilled product obtained from Step A is dissolved in 50 mL of dry THF (Note 12) and added to the vessel by means of a syringe while a static pressure of nitrogen is maintained on the vessel. Ethylene glycol (18.6 g, 16.8 mL, 0.30 mol) (Note 13) is then added. The rubber septum is removed and the vessel is quickly connected to a cylinder of carbon monoxide (Note 14) and placed in a heating device capable of agitation. The vessel is agitated and the pressure increased with carbon monoxide to ca. 70 atm (ca. 1000 psi); the temperature is raised to 150°C. The vessel is maintained at this temperature for 2 hr and then cooled to room temperature and opened to the air. The contents of the vessel are transferred to a flask; the vessel is rinsed with two 50-mL portions of pentane, and the pentane is added to the product. The resulting solution is washed with 50 mL of water and dried over magnesium sulfate. The drying agent is removed by filtration, and the pentane removed by distillation to give 19.4 g of *cis,cis,trans*-2-(perhydro-9'b-phenalyl)-1,3,2-dioxaborole, a solid that can be further purified by recrystallization from pentane, mp 101–102°C (Note 15).

C. *cis,cis,trans-Perhydro-9b-phenalenol.* A 500-mL, three-necked, round-bottomed flask is fitted with a septum, thermometer, magnetic stirring bar, and a reflux condenser, which is connected to a nitrogen inlet and a mercury bubbler device. The system is flushed with nitrogen, and 50 mL of THF, 100 mL of 95% ethanol, and 19.4

g (0.0782 mol) of *cis,cis,trans*-2-(perhydro-9'b-phenalyl)-1,3,2-dioxaborole from Step B are added to the flask together with 37 mL (0.220 mol, 120% excess) of 6 *N* sodium hydroxide. The solution is stirred and, by means of a dropping funnel, 37 mL (0.326 mol) of 30% hydrogen peroxide (Note 16) is added at such a rate that the temperature of the reaction mixture does not exceed 40°C. After the initial reaction has subsided, the reaction mixture is heated for 2 hr at 50°C to assure complete oxidation (Note 17). At the end of this time, 300 mL of pentane is added. The mixture is transferred to a separatory funnel, and the organic layer is separated and washed three times with 50-mL portions of water and then dried over magnesium sulfate. The mixture is filtered, and the solvent is removed by distillation to yield a solid (Note 18) which is recrystallized from cold pentane to give 10.9 g (71.7%) of *cis,cis,trans*-perhydro-9b-phenalenol, mp 75–76°C (Note 19).

2. Notes

1. All joints must be well greased and securely clamped. Even a minor leak is a fire hazard.
2. The checkers used a reagent available from Aldrich Chemical Company, Inc. Borane–THF was prepared by the submitters.[2] The direct use of borane–THF for hydroboration results in the formation of a polymeric, insoluble intermediate, which can be depolymerized by heating.
3. The checkers refluxed triethylamine, available from Eastman Organic Chemicals, with phenyl isocyanate and then isolated the amine by distillation. The submitters used a reagent available from Aldrich Chemical Company, Inc.
4. The checkers used a reagent available from Aldrich Chemical Company, Inc. The diglyme was distilled from sodium benzophenone ketyl prior to use. The submitters used a reagent available from the same source and distilled it from lithium aluminum hydride prior to use.
5. The checkers and the submitters used reagent available from Chemical Samples Co. The submitters state that other isomers such as *trans,trans,cis*-1,5,9-cyclododecatriene or a mixture of isomers can be used.[3] In this case a slightly different isomer distribution is observed, and the yields of isolated product are somewhat lower. The checkers confirmed this observation, using trans,trans,cis reagent available from Aldrich Chemical Company, Inc.
6. A syringe pump was used with the syringe well greased with a polyhalo hydrocarbon lubricant. Alternatively, a pressure-equalizing dropping funnel can be used.
7. It is essential to heat the initially formed product to 200°C to achieve isomerization of the other isomers present to *cis,trans*-perhydro-9b-boraphenalene. When this thermal treatment is omitted, the desired product is contaminated with one major (30–40%) and several minor, unidentified, isomeric substances.
8. Perhydro-9b-boraphenalene is highly flammable. The transfer must be carried out with caution. The use of gloves is recommended to avoid direct contact with the organoborane. The transfer is most conveniently done under a slightly

positive pressure of nitrogen using a broad-gauge (18-gauge), double-tipped needle.

9. The crude product is diluted with a small amount of dry THF and the solution transferred to a 100-mL distillation flask. Distillation through a 12-cm Vigreux column gives 58.0–60.1 g (66–68% yield) of a mixture of *cis,trans*- and *cis,cis*-perhydro-9b-boraphenalene, bp 113–114°C (9.5 mm), ^{1}H NMR ($CDCl_3$) δ: 0.7–2.2.

10. The submitters state that the composition of the distillate is 92 : 8 cis,trans : cis,cis isomer, based on GC analyses using an SE-30 column. The assigned stereochemistry is supported by the ^{1}H NMR spectrum of the pyridine complex.[3]

11. The checkers used a 250-mL Hastelloy pressure vessel. The submitters used a 250-mL autoclave available from American Instrument Co.

12. The checkers used a reagent available from Fisher Scientific Company. The submitters used a reagent available from Aldrich Chemical Company, Inc.

13. The checkers distilled the reagent available from E. I. du Pont de Nemours & Co. The submitters used a reagent available from Aldrich Chemical Company, Inc.

14. The checkers and submitters used a reagent available from Matheson Gas Products.

15. The checkers obtained the product in 87% crude yield using distilled boraphenalene. Recrystallization from pentane gave product in 66% yield, mp 101–102°C, with the following spectral characteristics: IR (KBr) cm^{-1}: 1185, 1200, 1250, 1310, 1385, 2860, and 2900–2950; ^{1}H NMR ($CDCl_3$) δ: 1.0–1.9 (m, 21 H), 4.11 (s, 4 H). The structure of the product has been confirmed by X-ray crystallography.[3]

16. The checkers and the submitters used reagent available from Fisher Scientific Company.

17. The submitters state that oxidation of the dioxaborole is unusually sluggish and urge the use of ethanol as a cosolvent and an excess of 6 *N* sodium hydroxide. They also urge monitoring of the reaction by GC. The checkers monitored the reaction by both GC and TLC analyses. GC analysis by the checkers was conducted using the following column and conditions: 3.2-mm × 2-m column, 7% SE 30/3% Silar on Gas Chrom Q (60–80 mesh), 170°C, 50 mL of nitrogen per min. The retention times for the perhydrophenalenol and dioxaborole are 6.4 and 15.2 min, respectively. For TLC analyses, Analtech silica gel plates bearing the material were eluted by 1 : 2 methylene chloride–petroleum ether, and visualized with phosphomolybdic acid: perhydrophenalenol, R_f 0.4; dioxaborole, R_f 0.9. The checkers found that the reaction was essentially complete after addition of the hydrogen peroxide. Additional heating did not lower the yield of product.

18. The submitters state that GC analysis of the solid indicates a 92 : 8 mixture of the cis,cis,trans and cis,cis,cis isomers.

19. Using recrystallized dioxaborole from Step B, the checkers obtained product, recrystallized from pentane, mp 75–76°C, in 85% yield, having the following spectral characteristics: IR (KBr) cm^{-1}: 1450 (s), 2860 (m), 2930 (s),

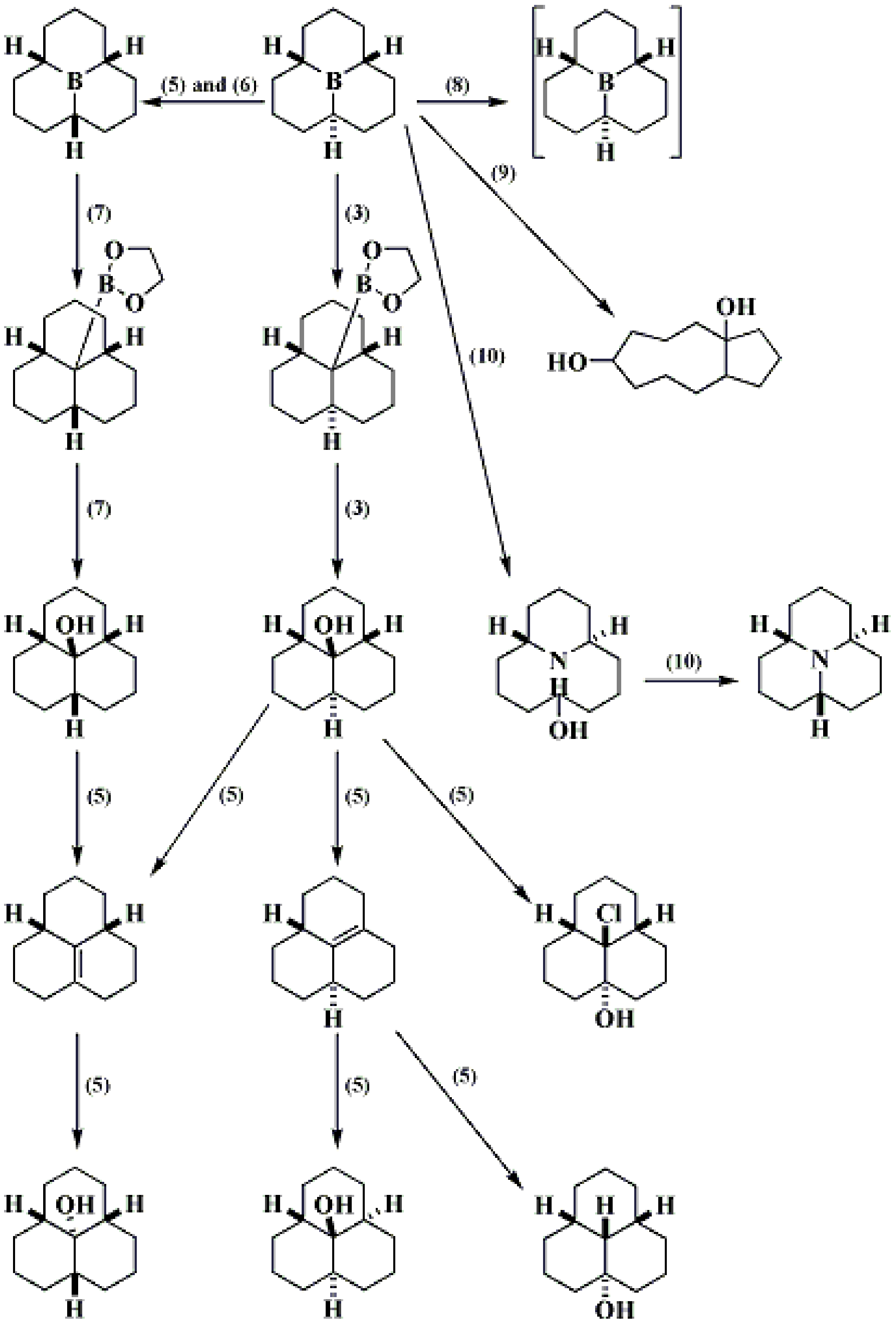
and 3460 (m); ^{1}H NMR ($CDCl_3$) δ: 1.0–2.3; ^{13}C NMR ($CDCl_3$) δ: 21.25 (t), 26.52 (t), 27.42 (t), 29.79 (t), 29.12 (t), 33.86 (d), 44.32 (d), 73.24 (s) (undecoupled spectrum).

3. Discussion

Preparation of the two stereoisomers of perhydro-9b-boraphenalene was originally reported by Köster and Rotermund,[5] and the present procedure (Step A) is largely based on the procedure described by these authors. However, the original stereochemical assignment was incorrect and has been reversed.[3,6] Furthermore, these authors did not use the thermal treatment described above, which appears essential to achieve isomerization of other constitutional isomers into perhydro-9b-boraphenalene.[3] The original procedure for isomerization of the cis,trans isomer to the all cis isomer has been satisfactory. Contrary to the claim made by these authors,[5] however, this isomerization does not lead quantitatively to the all cis isomer, but reaches an equilibrium, which consists of the all cis and cis,trans isomers in the ratio of 88 : 12; this ratio was also confirmed by reverse isomerization of the pure all cis isomer.[7]

cis,trans-Perhydro-9b-boraphenalene has been converted to lithium *cis,cis,trans*-perhydro-9b-boraphenalyl hydride by reaction with lithium hydride.[8] The tricyclic organoborane reported here has been converted to bicyclo[7.3.1]dodecane-1,5-diol[9] and *trans*-13-azabicyclo[7.3.1]tridecan-5-ol.[10] The latter has been converted to *cis, trans*-perhydro-9b-azaphenalene.[10]

The procedure reported here (Steps B and C) has been applied with minor modifications to the syntheses of the cis,cis,cis isomers of the 1,3,2-dioxaborole and perhydro-9b-phenalenol.[6] The two other stereoisomers, cis,trans,trans and trans,trans, trans, have been prepared from *cis,cis,trans*-perhydro-9b-phenalenol via the cis and trans isomers of $\Delta^{3a,9b}$-perhydrophenalene.[7] In addition, a few isomers of perhydrophenalenol and of perhydrophenalene and *cis,cis,trans*-9b-chloroperhydrophenalene have also been prepared from *cis,cis,trans*-perhydro-9b-phenalenol.[7] Some of the representative transformations are summarized in Scheme 1. (The numbers in parentheses refer to references.)



References and Notes

1. Department of Chemistry, Syracuse University, Syracuse, NY 13210. The current address is the same as [2].
2. Richard B. Wetherill Laboratory, Purdue University, West Lafayette, IN 47907.
3. The results described here were previously reported as a Communication: Brown, H.

C.; Negishi, E. *J. Am. Chem. Soc*. **1967**, *89*, 5478–5480. A similar procedure has also been described elsewhere.[4]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

sodium benzophenone ketyl

cis,trans- and cis,cis-perhydro-9b-boraphenalene

lithium cis,cis,trans-perhydro-9b-boraphenalyl hydride

bicyclo[7.3.1]dodecane-1,5-diol

ethanol (64-17-5)

sodium hydroxide (1310-73-2)

carbon monoxide (630-08-0)

nitrogen (7727-37-9)

ethylene glycol (107-21-1)

hydrogen peroxide (7722-84-1)

Pentane (109-66-0)

methylene chloride (75-09-2)

phenyl isocyanate (103-71-9)

magnesium sulfate (7487-88-9)

borane (7440-42-8)

Tetrahydrofuran, THF (109-99-9)

lithium aluminum hydride (16853-85-3)

triethylamine (121-44-8)

diglyme (111-96-6)

lithium hydride (7580-67-8)

phosphomolybdic acid (51429-74-4)

Perhydro-9b-boraphenalene, 9b-Boraphenalene, dodecahydro-, cis,trans-perhydro-9b-boraphenalene (16664-33-8)

Perhydro-9b-phenalenol, Phenalen-9bα(2H)-ol, 3,3aα,4,5,6,6aα,7,8,9,9aβ-decahydro- (16664-34-9)

boraphenalene

perhydrophenalenol

trans,trans,cis-1,5,9-cyclododecatriene

trans,trans,trans-1,5,9-cyclododecatriene (676-22-2)

cis,cis,trans-perhydro-9b-phenalenol

trans-13-azabicyclo[7.3.1]tridecan-5-ol

cis,trans-perhydro-9b-azaphenalene

cis,cis,trans-9b-chloroperhydrophenalene

cis,cis,trans-2-(perhydro-9'b-phenalyl)-1,3,2-dioxaborole

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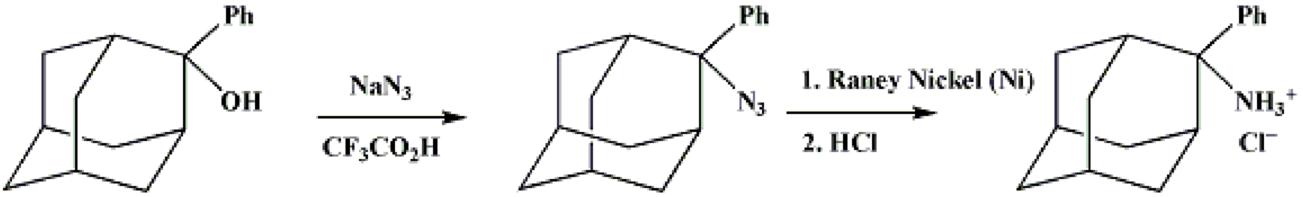
Organic Syntheses, CV 7, 433

2-PHENYL-2-ADAMANTANAMINE HYDROCHLORIDE

[Tricyclo[3.3.1.1^{3,7}]decan-2-amine, 2-phenyl, hydrochloride]



Submitted by Asher Kalir and David Balderman[1].
Checked by Carl R. Johnson and Debra L. Monticciolo.

1. Procedure

Caution! The reaction should be carried out in a good hood.

A. *2-Azido-2-phenyladamantane*. A 500-mL, three-necked, round-bottomed flask equipped with a mechanical stirrer, a pressure-equalizing dropping funnel, and a thermometer is charged with 125 mL of chloroform and 13 g (0.2 mol) of sodium azide. The mixture is cooled with an ice–salt bath to −5°C to 0°C, and 37.5 mL (0.5 mol) of trifluoroacetic acid is added, followed after 5–10 min with 22.8 g (0.1 mol) of 2-phenyl-2-adamantanol (Note 1). The resulting slurry is stirred for 4 hr at 0°C and then allowed to reach room temperature overnight. The mixture is cautiously neutralized with a slight excess of 12–15% aqueous ammonia solution and transferred to a separatory funnel. The chloroform layer is separated, and the aqueous solution is extracted with 50 mL of chloroform. The combined organic extracts are washed with 50 mL of water, separated, and dried over magnesium sulfate. The solvent is removed in a rotary evaporator. The oily residue solidifies on cooling. The yield is 23.6–24.8 g (93–98%), mp 42–45°C. Recrystallization of a sample from 2-propanol raises the melting point to 47–48°C (Note 2).

B. *2-Phenyl-2-adamantanamine hydrochloride*. A solution of 24 g (0.095 mol) of the crude 2-azido-2-phenyladamantane in 75 mL of 2-propanol is placed in a 1-L beaker fitted with a mechanical stirrer, and heated in a water bath that can be removed quickly. Wet, active Raney nickel (Note 3) and (Note 4) is added in portions at 60–70°C with stirring until the evolution of nitrogen ceases (Note 5). The mixture is heated for an additional 10 min, filtered through a Büchner funnel, and washed with 75 mL of 2-propanol in such a manner that the catalyst is always covered with liquid (Note 6). The filtrate is concentrated in a rotary evaporator under reduced pressure. The crude residue is dissolved in 75 mL of toluene and treated with 22 mL of concentrated hydrochloric acid while stirring. The 2-phenyl-2-adamantanamine hydrochloride is collected, triturated with 50 mL of warm acetone, filtered again, and air-dried. The yield is 22.5–24.0 g (90–96%), and the product melts at 293–296°C (closed capillary) (Note 7) and (Note 8).

2. Notes

1. 2-Phenyl-2-adamantanol[2] is prepared by adding 25 g (0.167 mol) of 2-adamantanone (Note 3) in several portions to phenylmagnesium bromide, obtained from 40 g of bromobenzene and 6.5 g of magnesium turnings in 200 mL of diethyl ether. The solution is stirred for 1 hr and worked up with aqueous ammonium chloride. The organic layer is separated, dried over magnesium sulfate, concentrated, and the oily residue is crystallized from petroleum ether. The yield is 25.5 g (67%) of crystals melting at 77–78°C. The crude oily residue may be used in the next step without purification.
2. The product is characterized by IR (CCl_4) cm^{-1}: 2075; ^1H NMR (CCl_4) δ: 1.72 and 2.40 (s, 14 H), 7.20 (s, 5 H).
3. 2-Adamantanone was obtained from Aldrich Chemical Company, Inc. Active Raney nickel catalyst

was obtained from W. R. Grace Company.

4. The amount of Raney nickel depends on its hydrogen content. Usually 25–35 g is sufficient.

5. A large vessel is required because of excessive frothing. The frothing may be controlled by adding a little cold 2-propanol, by removing the heating, or by stopping the stirrer.

6. *Caution! Dry catalyst is pyrophoric.*

7. The free 2-phenyl-2-adamantanamine may be liberated from the salt by adding a solution of ammonia or sodium hydroxide, extracting with toluene, concentrating, and distilling under reduced pressure; bp 120–122°C (0.15 mm); n_D^{17} 1.5850; ^1H NMR (CCl_4) δ: 1.30 (s, 2H, NH_2), 1.68 and 2.26 (br s, 14 H, adamantane protons), 7.1 (m, 5H, Ph).

8. Similarly, 2-butyl-2-adamantanamine hydrochloride, mp 300–305°C, is obtained from 2-butyl-2-adamantanol[3] in 30% yield.

3. Discussion

The present procedure is an example of preparation of tertiary phenylcarbinylamines, and is in many cases superior to methods based on the Ritter reaction,[4] and Hofmann[5] or Curtius degradation.[6] The availability of starting materials, fair yields of products, and the simplicity of operations (there is no need to isolate any intermediates or to use a hydrogenation apparatus) are the main advantages of this procedure. The azide synthesis is adapted from procedures described for the preparation of 1,1-diphenyl-2-azidoethane[7] and 1-phenyl-1-azidocyclohexane.[8] The azides are quite stable and could be distilled under reduced pressure. The amines and their substitution products are physiologically active agents.[4,9]

A number of compounds have been prepared by this method (the isolation of hydrochloride can be omitted), as listed in Table I.[10]

TABLE I
AMINES FROM TERTIARY ALCOHOLS

Alcohol	Azide[a] Bp (°C) (mm Hg)	Amine Bp (°C) (mm Hg)	Amine Yield (%)	Starting Material
2-Phenyl-2-propyl	106 (22)	100 (22)	66	α-Methylstyrene
1-Phenylcyclo-pentyl	139–140 (38)	128–130 (20)	40	Cyclopentanone
1-Phenylcyclo-hexyl		115–120 (5)	38	Cyclohexanone
2-Methyl-1-phenyl-cyclohexyl	90–91 (0.25)	150–153 (23)	66	2-Methyl-1-phenyl-cyclohexanol
1-Phenylcyclo-heptyl	153–155 (23)	163–165 (25)	45	Cycloheptanone
2-Phenyl-2-norbornyl	150–155 (25)	163–165 (28)	51	2-Norbornanone

[a] The azides contain up to 15–20% of the corresponding phenylalkenes.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

amine

alcohol (64-17-5)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

magnesium turnings (7439-95-4)

Cyclohexanone (108-94-1)

nitrogen (7727-37-9)

Raney nickel (7440-02-0)

acetone (67-64-1)

toluene (108-88-3)

2-propanol (67-63-0)

bromobenzene (108-86-1)

Cyclopentanone (120-92-3)

Phenylmagnesium bromide (100-58-3)

sodium azide (26628-22-8)

magnesium sulfate (7487-88-9)

Cycloheptanone (502-42-1)

trifluoroacetic acid (76-05-1)

α-methylstyrene (98-83-9)

2-Norbornanone (497-38-1)

2-adamantanone (700-58-3)

2-Phenyl-2-adamantanamine hydrochloride, Tricyclo[3.3.1.1^{3,7}]decan-2-amine, 2-phenyl, hydrochloride (73032-81-2)

2-phenyl-2-adamantanol (29480-18-0)

2-Azido-2-phenyladamantane (65218-96-4)

2-phenyl-2-adamantanamine

2-butyl-2-adamantanamine hydrochloride

2-butyl-2-adamantanol

1,1-diphenyl-2-azidoethane

1-phenyl-1-azidocyclohexane

2-Phenyl-2-propyl (16804-70-9)

1-Phenylcyclo-pentyl

1-Phenylcyclo-hexyl

2-Methyl-1-phenyl-cyclohexyl

2-Methyl-1-phenyl-cyclohexanol

1-Phenylcyclo-heptyl

2-Phenyl-2-norbornyl

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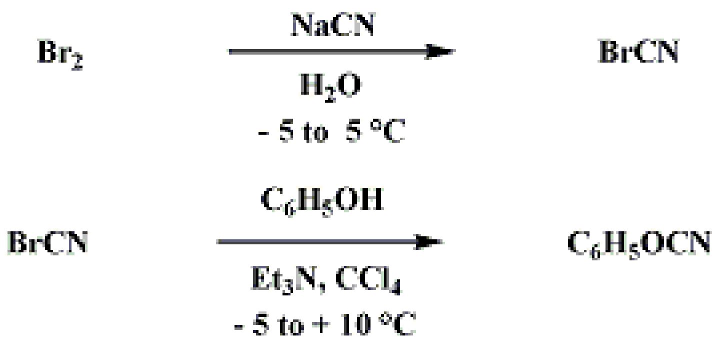
Organic Syntheses, CV 7, 435

CYANIC ACID ESTERS FROM PHENOLS: PHENYL CYANATE

[Cyanic acid, phenyl ester]



Submitted by D. Martin[1] and M. Bauer.
Checked by E. R. Holler, Jr. and R. E. Benson.

1. Procedure

Caution! These operations, which involve toxic reagents, should be conducted in an efficient hood.

A 1-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, thermometer, and a 200-mL pressure-equalizing dropping funnel with a stopper is charged with 160 g (50.9 mL, 1.0 mol) of bromine (Note 1) and 150 mL of water. The mixture is stirred rapidly while cooling in an ice–salt bath to −5°C, and a solution of 49.0 g (1.0 mol) of sodium cyanide in 150 mL of water is added dropwise over a 40–50 min period while maintaining the temperature of the reaction mixture at −5 to 5°C. The resulting solution is stirred an additional 5–10 min (Note 2). A solution of 89.5 g (0.95 mol) of phenol in 300 mL of tetrachloromethane (Note 3) is added in one portion to the flask. The resulting mixture is stirred vigorously while 96.0 g (131 mL, 0.95 mol) of triethylamine is added dropwise over a 30–40-min period at such a rate that the temperature does not exceed 5–10°C. After an additional 15 min of stirring, the mixture is transferred to a separatory funnel, the organic phase is separated and the aqueous layer is extracted twice with 50-mL portions of tetrachloromethane. The organic phases are combined and washed three times with 50-mL portions of water and then dried over polyphosphoric anhydride (P_2O_5) (Note 4). The drying agent is removed by filtration and the solvent is removed by distillation under reduced pressure using a rotary evaporator at 20°C (25 mm). A few drops of polyphosphate ester (Note 5) are added to the remaining liquid and the product is distilled through a 20-cm Vigreux column to give 85–96 g (75–85%) of phenyl cyanate, bp 77–79° (13 mm), n_D^{20} 1.5094–1.5100, d_4^{20} 1.096. The product is a colorless liquid with a pungent odor (Note 6).

2. Notes

1. The chemicals used were commercially available products and were used without further purification. The checkers used sodium cyanide, phenol, and tetrachloromethane from Fischer Scientific Company, bromine from Matheson, Coleman and Bell, phosphoric anhydride from J. T. Baker Chemical Co., and triethylamine from Eastman Organic Chemicals.
2. The solution should develop a yellowish color.
3. The procedure can also be conducted using other water immiscible solvents such as ether, trichloromethane, and benzene.[2]
4. Other drying agents such as anhydrous calcium chloride can also be used. The desiccation must be done carefully since water is soluble in the product in the presence of phenol and may cause trimerization of the cyanate to a 1,3,5-triazine derivative.
5. A few drops of polyphosphate ester are a good drying agent and stabilizer.[3] The ester may be prepared by heating polyphosphoric anhydride in dry ether and trichloromethane for 40 hr followed by removal of the solvent.[4] The checkers found that the use of polyphosphate ester was essential to obtain the described yield.
6. The spectral properties of phenyl cyanate are as follows. IR (CCl_4) cm^{-1}: 2235 (m), 2261 (m), 2282 (S) ($\nu_{C \square N}$).[5] UV (cyclohexane) nm max (log ε): 216 (3.21), 256 (2.58), 262 (2.75), and 268 (2.67).[6] The product was further characterized by vapor-phase chromatography analysis using a 200-cm column containing 10% SE 52 on Chromosorb W/AW/DMCS at 140°C with a hydrogen flow rate of 70 mL/min and a retention time of 1.47 min.

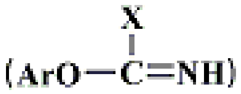
3. Discussion

Although isocyanates have been known for some time, the isomeric cyanates were unknown until 1964. The latter were first prepared almost simultaneously by two different methods: (1) thermolysis of 5-aryl- or 5-alkyloxy-1,2,3,4-thiatriazoles[6,7] and (2) by reaction of phenols or alcohols with cyanogen halides.[8] Since their synthesis, cyanates have acquired considerable synthetic significance.[9,10,11,12,13,14] The simplified procedure described here for preparation of phenyl cyanate is a combination of the preparation of cyanogen bromide[15] and the cyanation of phenol in the presence of a base.[8] This procedure is also applicable to many other phenols, bisphenols, naphthols, and some acidic alcohols. Examples are given in Table I.

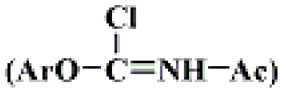
TABLE I
CYANATES FROM HYDROXY COMPOUNDS

Hydroxy Compound	Cyanate	mp(°C) (bp, °C/mm)	Yield (%)
$2\text{-}CH_3C_6H_4OH$	$2\text{-}CH_3C_6H_4OCN$	(88–90/10)	81
$4\text{-}CH_3C_6H_4OH$	$4\text{-}CH_3C_6H_4OCN$	(90–91/10)	87
$4\text{-}CH_3OC_6H_4OH$	$4\text{-}CH_3OC_6H_4OCN$	22–26(118–119/10)	91
$2\text{-}ClC_6H_4OH$	$2\text{-}ClC_6H_4OCN$	(112–113/13)	81
$4\text{-}ClC_6H_4OH$	$4\text{-}ClC_6H_4OCN$	38–39(100–101/10)	87
$2\text{-}CH_3OCOC_6H_4OH$	$2\text{-}CH_3OCOC_6H_4OCN$	58–60	84
2-Naphthyl-OH	2-Naphthyl-OCN	(162–164/12)	95
$4\text{-}NCOC_6H_4OH$	$4\text{-}NCOC_6H_4OCN$	107–109	98
CCl_3CH_2OH	CCl_3CH_2OCN	(77–78/10)	75
CF_3CH_2OH	CF_3CH_2OCN	(29–30/13)	81

Aryl cyanates have activated cyano groups and undergo many reactions.[14] They are effective dehydrating and hydrogen sulfide-bonding agents in organic synthesis.[9,10,11,13,14] *N*-, *O*-, and *S*-nucleophiles (HX) add to the carbon atom of the cyano group to form the corresponding carbonic acid imide esters



.[9,10,11,13,14] Transfer of the cyano group to a number of carbon nucleophiles also occurs.[9,10,11,13,14] Acyl halides (AcCl) add to the nitrogen atom of the cyano group to give *N*-acylated carbonic acid imide chlorides



.[12,13,14] These compounds are useful starting materials for syntheses of heterocyclic compounds. The cyanates also undergo 1,3- and 1,4-dipolar cycloadditions involving the cyano group to give substituted azoles and azines.[9,10,11,13,14] Polycyclic trimerization of dicyanates to poly-*s*-triazines is of considerable importance.[16,17,18]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

polyphosphoric anhydride (P_2O_5)

polyphosphoric anhydride

polyphosphate ester

2-$CH_3C_6H_4OH$

4-$CH_3C_6H_4OH$

4-$CH_3OC_6H_4OH$

4-$CH_3OC_6H_4OCN$

2-ClC_6H_4OH

2-ClC_6H_4OCN

4-ClC_6H_4OH

4-ClC_6H_4OCN

2-$CH_3OCOC_6H_4OH$

2-$CH_3OCOC_6H_4OCN$

2-Naphthyl-OH

2-Naphthyl-OCN

4-$NCOC_6H_4OH$

4-$NCOC_6H_4OCN$

CCl_3CH_2OH

CCl_3CH_2OCN

CF_3CH_2OH

CF_3CH_2OCN

calcium chloride (10043-52-4)

Benzene (71-43-2)

ether (60-29-7)

hydrogen (1333-74-0)

trichloromethane (67-66-3)

phenol (108-95-2)

sodium cyanide (143-33-9)

bromine (7726-95-6)

tetrachloromethane (56-23-5)

nitrogen (7727-37-9)

carbon (7782-42-5)

Cyanogen bromide (506-68-3)

phosphoric anhydride (2466-09-3)

triethylamine (121-44-8)

PHENYL CYANATE, Cyanic acid, phenyl ester (1122-85-6)

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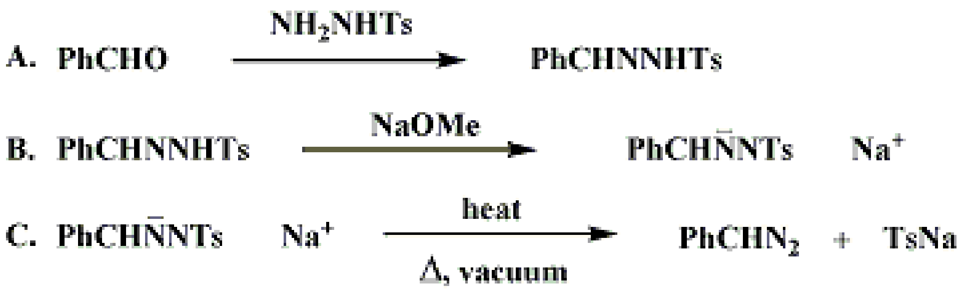
Organic Syntheses, *CV 7*, *438*

TOSYLHYDRAZONE SALT PYROLYSES: PHENYLDIAZOMETHANES

[Benzenes, diazomethyl-]



Submitted by Xavier Creary[1]
Checked by Weyton W. Tam, Kim F. Albizati, and Robert V. Stevens.

1. Procedure

Caution! Diazo compounds are presumed to be highly toxic and potentially explosive. All manipulations should be carried out in a hood. Although in numerous preparations we have never observed an explosion, all pyrolyses and distillations should routinely be carried out behind a safety shield.

A. *Benzaldehyde tosylhydrazone.* A 14.6-g sample (0.078 mol) of *p*-toluenesulfonylhydrazide (Note 1) was placed in a 125-mL Erlenmeyer flask and 25 mL of absolute methanol was added. The slurry was swirled as 7.50 g (0.071 mol) of freshly distilled benzaldehyde was added rapidly. A mildly exothermic reaction ensued and the *p*-toluenesulfonylhydrazide dissolved. Within a few minutes, the tosylhydrazone began to crystallize. After 15 min the mixture was cooled in an ice bath. The product was collected on a Büchner funnel, washed with a small amount of cold methanol, and dried under an aspirator vacuum. The dry benzaldehyde tosylhydrazone, mp 124–125°C, weighed 16.97–18.19 g (87–93%) and was not purified further.

B. *Phenyldiazomethane (Vacuum pyrolysis method)*. In a 200-mL, single-necked, round-bottomed flask is placed 13.71 g (0.05 mol) of benzaldehyde tosylhydrazone. A 1.0 *M* solution (51 mL) of sodium methoxide in methanol (0.051 mol) (Note 2) is added via syringe and the mixture is swirled until dissolution is complete (Note 3). The methanol is then removed by a rotary evaporator. The last traces of methanol are removed by evacuation of the flask at 0.1 mm for 2 hr. The solid tosylhydrazone salt is broken up with a spatula and the flask is fitted with a vacuum take-off adapter and a 50-mL receiver flask. The system is evacuated at 0.1 mm and the receiver flask is cooled in a dry ice–acetone bath to about −50°C. The flask containing the salt is immersed in an oil bath and the temperature is raised to 90°C. (We recommend the use

of a safety shield.) At this temperature, red phenyldiazomethane first begins to collect in the receiver flask. The temperature is raised to 220°C over a 1-hr period (Note 4). During this time red phenyldiazomethane collects in the receiver flask (Note 5). The pressure increases to 0.35 mm over the course of the pyrolysis. On completion of the pyrolysis the pressure drops to less than 0.1 mm.

The apparatus is disconnected and the 50-mL receiver flask that contains the crude phenyldiazomethane is fitted with a water-cooled short-path distillation head and a receiver flask cooled to about −50°C in a dry ice–acetone bath. The pressure is lowered to 1.5 mm and a trace of methanol collects in the receiver. A new receiver flask is connected and cooled to −50°C and the pressure is lowered to less than 0.2 mm. Red phenyldiazomethane distills below room temperature (Note 6). The yield of phenyldiazomethane, which is a liquid above −30°C, is 4.50–4.70 g (76–80%). The product should be used immediately or stored at a low temperature (−20 to −80°C) under nitrogen or argon (Note 7),(Note 8),(Note 9),(Note 10),(Note 11); it is explosive at room temperature.

2. Notes

1. *p*-Toluenesulfonylhydrazide was obtained from Aldrich Chemical Company, Inc. and used without further purification.
2. The sodium methoxide solution was prepared by dissolving 2.30 g of sodium in absolute methanol and diluting it to 100 mL. If commercial sodium methoxide powder is used, it must be of high quality; otherwise the yield of phenyldiazomethane is lower.
3. Powdered sodium hydroxide can be used in place of sodium methoxide with no appreciable change in yield. Sodium hydroxide dissolves less readily in methanol.
4. When carried out on a small scale, pyrolysis is complete at lower temperatures (160–200°C).
5. Phenyldiazomethane solidifies at dry ice temperature. Care must be taken not to plug the vacuum take-off adapter; this occurs if the temperature of the receiver flask is too low. The receiver bath was maintained manually at about −50°C by addition of small pieces of dry ice to an acetone bath. We prefer to use this procedure rather than a chloroform–dry ice bath, which freezes at −63°C, because of the toxic nature of chloroform and the disposal problems associated with this solvent.
6. Slight warming with an oil bath at 30°C allows distillation to proceed at a reasonable rate. The bath should not be heated above this temperature. Gutsche and Jason[2] report a boiling point of 37–41°C at 1.5 mm. Although we have never experienced any difficulty in numerous distillations, Gutsche and Jason[2] report that phenyldiazomethane "sometimes detonated violently during purification" by distillation. Therefore, we emphatically recommend that distillation be carried out below room temperature, behind a safety shield. On completion of the distillation, only a small amount of nonvolatile residue

remained.
7. The checkers reported that a sample that was allowed to stand at room temperature for approximately 1 hr and then exposed to air decomposed violently after 5 min. In numerous preparations, when distilled phenyldiazomethane was immediately stored at –20°C or at –80°C under nitrogen, we never experienced any difficulty. We emphasize the need to keep phenyldiazomethane cold, and under nitrogen.
8. In runs on smaller scales, yields ranged from 84 to 91%.
9. The IR spectrum (CCl_4) shows an intense band at 4.83 •m (2060 cm^{-1}); ^1H NMR (CCl_4) δ: 4.79 (s, 1 H), 6.7–7.6 (m, 5 H).
10. Phenyldiazomethane shows no appreciable change on storage at –80°C for 3 months. Storage at –20°C led to significant decomposition after 2 weeks.
11. Traces of diazo compounds should be destroyed by addition to acetic acid.

3. Discussion

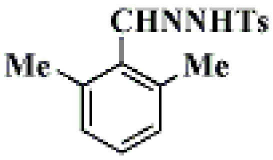
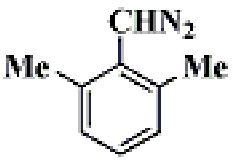
Diazo compounds have previously been prepared by a variety of methods. Some of these methods include hydrazone oxidations,[3] the reaction of diazomethane with acid chlorides,[4] the reaction of activated methylene compounds with tosyl azide,[5] decomposition of *N*-nitroso compounds,[6] diazotization of amines,[7] and pyrolysis of tosylhydrazone salts.[8,9,10,11,12,13] The present procedure for the preparation of phenyldiazomethane illustrates the vacuum pyrolysis method introduced by Shechter[12] for carrying out the Bamford–Stevens reaction.[9]

Phenyldiazomethane has been prepared by reaction of base with ethyl *N*-nitroso-*N*-benzylcarbamate,[13] *N*-nitroso-*N*-benzylurea,[14] and *N*-nitroso-*N*-benzyl-*N'*-nitroguanidine.[15] Staudinger's preparation[16] and that of Gutsche and Jason[2] employed mercuric oxide oxidation of benzaldehyde hydrazone. Yates and Shapiro[17] prepared phenyldiazomethane by basic cleavage of azibenzil. Bamford and Stevens[9] prepared phenyldiazomethane by solution pyrolysis of the salt of benzaldehyde tosylhydrazone. Closs and Moss[10] and Farnum[11] used variations of this solution pyrolysis method for the preparation of phenyldiazomethane. The vacuum pyrolysis method employed by Shechter[12] has also been used to prepare phenyldiazomethane.

The present procedure uses sodium methoxide in methanol for generation of the tosylhydrazone salt. This procedure gives the highest reported yield and, unlike other procedures, also gives pure diazo compounds free from solvents. This vacuum pyrolysis method appears applicable to the formation of relatively volatile aryldiazomethanes from aromatic aldehydes. Table I gives yields of diazo compounds produced by this vacuum pyrolysis method. The yields have not been optimized. The relatively volatile diazo esters, ethyl α-diazopropionate[18] and ethyl α-diazobutyrate,

can also be prepared by this method.

TABLE I
FORMATION OF DIAZO COMPOUNDS BY VACUUM PYROLYSIS OF SODIUM SALTS OF TOSYLHYDRAZONES

Tosylhydrazone	Product	Yield (%)
p-$MeC_6H_4CHNNHTs$	p-$MeC_6H_4CHN_2$	52
m-$MeC_6H_4CHNNHTs$	m-$MeC_6H_4CHN_2$	55
		69
p-$FC_6H_4CHNNHTs$	p-$FC_6H_4CHN_2$	69
m-$FC_6H_4CHNNHTs$	m-$FC_6H_4CHN_2$	59
Me–C(=NNHTs)–COOEt	Me–C(=N_2)–COOEt	87
Et–C(=NNHTs)–COOEt	Et–C(=N_2)–COOEt	65

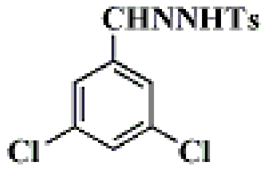
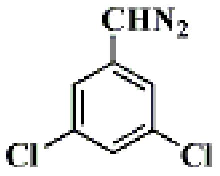
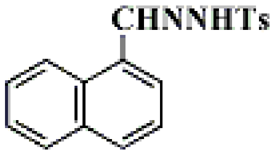
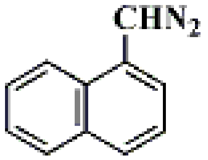
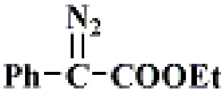
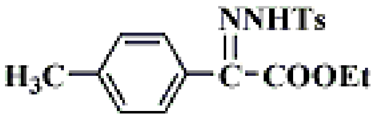
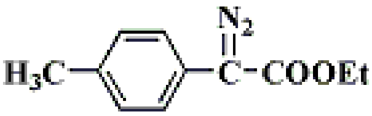
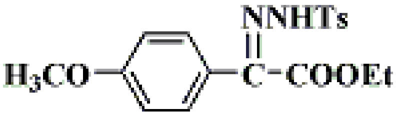
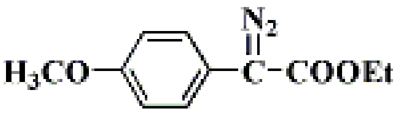
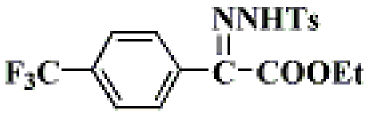
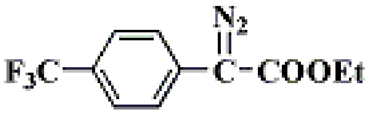
The major limitation of the vacuum pyrolysis method appears to be thermal decomposition of less volatile diazo compounds during the pyrolysis. The vacuum pyrolysis method was unsuccessful for the preparation of 1-naphthyldiazomethane and 3,5-dichlorophenyldiazomethane. However, such diazo compounds could be prepared from the corresponding tosylhydrazone salts by pyrolysis in ethylene glycol and extraction of the aryldiazomethane into hexane or ether. This procedure, as described by Goh,[19] permits the periodic extraction of the potentially labile diazo compound into an organic solvent while leaving the unreacted tosylhydrazone salt dissolved in the immiscible ethylene glycol phase. This solution pyrolysis method can also be used to prepare aryl diazo esters in high yields. This method is quite useful since the starting keto esters can be readily prepared in large quantities by reaction of the corresponding arylmagnesium bromides with diethyl oxalate.[20]

In a typical procedure, 0.14 g of sodium was dissolved in 10 mL of ethylene glycol by heating to 70°C and 0.0041 mol of tosylhydrazone was added. After heating with vigorous stirring for 5 min at 70–80°C, the mixture was cooled to about 35°C and 15 mL of hexane or ether was added with continued stirring. The organic extract was

removed by pipette and the procedure was repeated a total of 5 times. The combined organic extracts were washed with 30 mL of 5% sodium hydroxide solution, with a saturated sodium chloride solution, and dried over magnesium sulfate. After filtration, the solvent was removed on a rotary evaporator to leave the diazo compound. Table II gives yields of diazo compounds prepared by this solution pyrolysis method.

TABLE II

FORMATION OF DIAZO COMPOUNDS BY PYROLYSIS OF SODIUM SALTS OF TOSYLHYDRAZONES IN ETHYLENE GLYCOL

Tosylhydrazone	Temperature (°C)	Product	Yield (%)
	70[a]		90
	80[a]		77
	70[b]		86
	70[b]		88
	70[b]		76
	70[b]		94

[a] The salt in ethylene glycol was heated at this temperature, cooled, and extracted periodically with hexane.

[b] Ether extraction.

[c] This product was further purified by distillation at less than 0.1 mm. The other products were *not* distilled.

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20. Unpublished work from this laboratory. See also Nimitz, J. S.; Mosher, H. S. *J. Org. Chem.* **1981**, 46, 211–213 for a synthesis of keto esters.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

PHENYLDIAZOMETHANES

Benzenes, diazomethyl-

salt of benzaldehyde tosylhydrazone

SODIUM SALTS OF TOSYLHYDRAZONES

p-$MeC_6H_4CHNNHTs$

p-MeC_6H_4

m-$MeC_6H_4CHNNHTs$

m-$MeC_6H_4CHN_2$

p-$FC_6H_4CHNNHTs$

p-$FC_6H_4CHN_2$

m-$FC_6H_4CHNNHTs$

m-$FC_6H_4CHN_2$

tosylhydrazone

SODIUM SALTS OF TOSYLHYDRAZONES IN ETHYLENE GLYCOL

acetic acid (64-19-7)

methanol (67-56-1)

ether (60-29-7)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

mercuric oxide (21908-53-2)

benzaldehyde (100-52-7)

sodium methoxide (124-41-4)

sodium (13966-32-0)

ethylene glycol (107-21-1)

magnesium sulfate (7487-88-9)

Diazomethane (334-88-3)

hexane (110-54-3)

diethyl oxalate (95-92-1)

Ethyl N-nitroso-N-benzylcarbamate (6558-76-5)

phenyldiazomethane (766-91-6)

ethyl α-diazopropionate

argon (7440-37-1)

tosyl azide (941-55-9)

Benzaldehyde tosylhydrazone (1666-17-7)

benzaldehyde hydrazone

ethyl α-diazobutyrate

1-naphthyldiazomethane

3,5-dichlorophenyldiazomethane

p-Toluenesulfonylhydrazide (1576-35-8)

N-nitroso-N-benzylurea

N-nitroso-N-benzyl-N'-nitroguanidine

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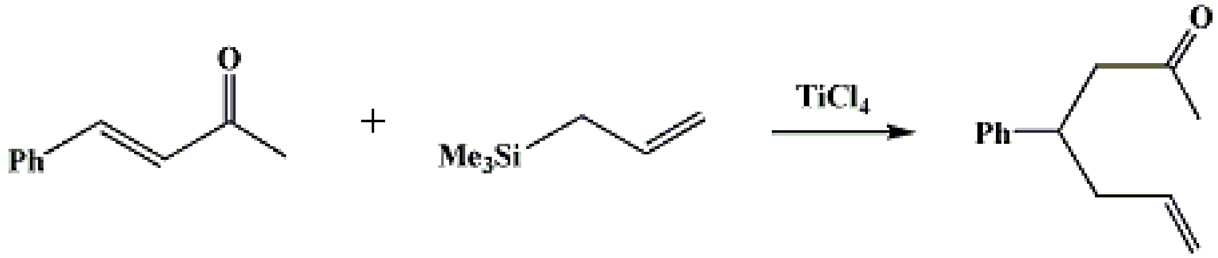
Organic Syntheses, CV 7, 443

CONJUGATE ALLYLATION OF α,β-UNSATURATED KETONES WITH ALLYLSILANES: 4-PHENYL-6-HEPTEN-2-ONE

[6-Hepten-2-one, 4-phenyl-]



Submitted by Hideki Sakurai, Akira Hosomi, and Josabro Hayashi[1].
Checked by Todd A. Blumenkopf and Clayton H. Heathcock.

1. Procedure

A 2-L, three-necked, round-bottomed flask is fitted with a dropping funnel (Note 1), mechanical stirrer, and reflux condenser attached to a nitrogen inlet. In the flask are placed 29.2 g (0.20 mol) of benzalacetone (Note 2) and 300 mL of dichloromethane (Note 3). The flask is immersed in a dry ice–methanol bath (−40°C) and 22 mL (0.20 mol) of titanium tetrachloride (Note 4) is slowly added by syringe to the stirred mixture. After 5 min, a solution of 30.2 g (0.26 mol) of allyltrimethylsilane (Note 5) and (Note 6) in 300 mL of dichloromethane is added dropwise with stirring over a 30-min period. The resulting red–violet reaction mixture is stirred for 30 min at −40°C (Note 7), hydrolyzed by addition of 400 mL of H_2O, and, after the addition of 500 mL of ethyl ether with stirring, allowed to warm to room temperature. The nearly colorless organic layer is separated and the aqueous layer is extracted with three 500-mL portions of ethyl ether. The organic layer and ether extracts are combined and washed successively with 500 mL of saturated sodium bicarbonate and 500 mL of saturated sodium chloride, dried over anhydrous sodium sulfate, and evaporated at reduced pressure. The residue is distilled under reduced pressure through a 6-in. Vigreux column to give 29.2–30.0 g (78–80%) of 4-phenyl-6-hepten-2-one, bp 69–71°C (0.2 mm), n_D^{20} 1.5156, as a colorless liquid (Note 8).

2. Notes

1. A 500-mL dropping funnel, with pressure-equalizing arm, is used.
2. Benzalacetone is purchased from Wako Pure Chemical Ind., Ltd. or Aldrich Chemical Company, Inc.
3. Dichloromethane is dried over anhydrous calcium chloride, distilled, and

stored over Linde 5A molecular sieves before use. The checkers distilled dichloromethane from calcium hydride immediately before use.

4. Titanium tetrachloride, purchased from Junsei Chemical Co., Ltd. is distilled before use. The checkers purchased titanium tetrachloride from the Fisher Scientific Company and distilled it from copper powder before use.

5. The starting allyltrimethylsilane can be prepared in satisfactory yield by the procedure of Sommer.[2] It can also be purchased from PCR, Inc.; Aldrich Chemical Company, Inc.; Fluka A. G., Petrarch Systems, Inc.; and Tokyo Kasei Kogyo Co., Ltd. The checkers employed material from Petrarch.

6. The use of more than 1.2 equiv of allyltrimethylsilane is essential for shortening the reaction time as well as to avoid contamination of the product by unreacted benzalacetone.

7. Disappearance of benzalacetone and appearance of product can be readily monitored by thin-layer or gas chromatographic analysis on a 1-m column packed with 20% Silicone SE-30 at 180°C. The reaction should be stopped as soon as disappearance of benzalacetone is confirmed.

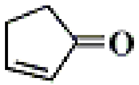
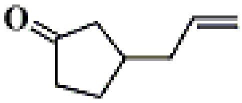
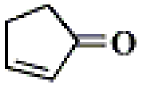
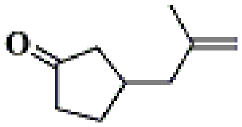
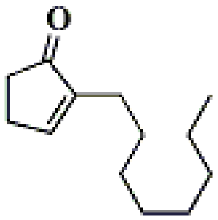
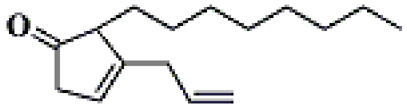
8. Gas chromatographic analysis of the product on a 1-m column packed with 20% Silicone SE-30 at 180°C should give a single peak. The product has the following spectral properties: IR (film) cm^{-1}: 1710, 1630 (C=C); ^{1}H NMR ($CDCl_3$) δ: 1.97 (s, 3 H, CH_3CO), 2.35 (t, 2 H, J = 7.5, CH_2C=C), 2.72 (d, 2 H, J = 7.5, CH_2CO), 3.27 (quintet, 1 H, J = 7.5, PhCH), 4.8–5.1 (m, 2 H, CH_2=C), 5.4–5.9 (m, 1 H, CH=C), 7.0–7.4 (m, 5 H, aromatic).

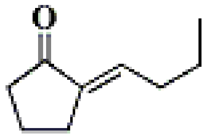
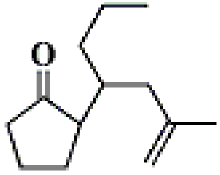
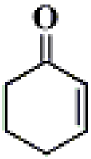
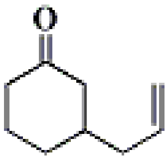
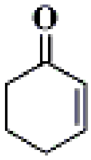
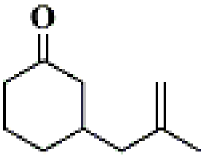
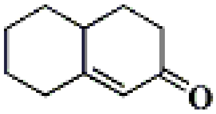
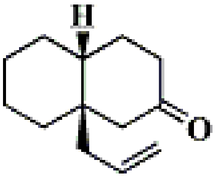
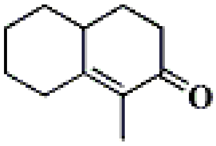
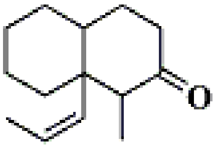
3. Discussion

This procedure is general for the conjugate allylation of α,β-unsaturated ketones with allysilanes.[3] Some representative examples are listed in Table I. The main advantages of the method are its wide generality and the ready availability of the necessary starting materials. The procedure is often useful for the preparation of δ,ε-unsaturated ketones that cannot be obtained in satisfactory yield by the use of allylcuprate (e.g., entry 13) reagents.[4] Another useful aspect of the reaction is the regiospecific coupling of the allyl group. Examples of this feature can be seen in entries 2 and 5. Although cyclic as well as acyclic α,β-unsaturated ketones give satisfactory results, the reaction is slower in sterically hindered systems (entries 13 and 14). However, even in these cases, good yields are obtained by using excess allylsilane and by conducting the reaction at higher temperature. Since the allyl group can be modified by the regioselective addition of various reagents to the double bond,[5,6] the method is applicable to the synthesis of a wider variety of compounds than are shown in the Table. By oxidation of the double-bond 1,5-diketones may be obtained.[7] Conjugate allylation with allylsilanes can be used in conjunction with a suitable electrophile to achieve "one-pot" double alkylation at the adjacent vinyl position of an α,β-unsaturated ketone.[8] The method has also been utilized in the synthesis of perhydroazulenones.[9] Allylsilanes also undergo regioselective, Lewis acid-catalyzed reaction with carbonyl compounds,[10] acetals,[11] α,β-unsaturated acetals,[12] acyl

halides,[13] tertiary alkyl halides,[14] and oxiranes.[14] Such allylations can also be achieved by using allystannanes.[15]

TABLE I
CONJUGATE ALLYLATION OF α,β-ENONES WITH ALLYLSILANES PROMOTED BY TITANIUM TETRACHLORIDE[a]

Entry	Allylsilane	α,β-Enone	Conditions Temp., °C, time	δ,ε-Enone	Yield (%)[b]
1	I[c]	$CH_2{=}CHCOCH_3$	–78, 1 min	$CH_2{=}CH(CH_2)_3COCH_3$	59
2	II[d]	$CH_2{=}CHCOCH_3$	–78, 3 hr	$CH_2{=}C(CH_3)_2CH_2CH_2COCH_3$	79
3	I	$(CH_3)_2C{=}CHCOCH_3$	25, 5 min	$CH_2{=}CHCH_2C(CH_3)_2CH_2COCH_3$	87
4	III[e]	$PhCH{=}CHCOCH_3$[f]	–78, 0.5 min	$CH_2{=}C(CH_3)CH_2CH(Ph)CH_2COCH_3$	69
5	IV[g]	$PhCH{=}CHCOCH_3$	–78, 5 hr	$CH_2{=}CHCH(CH_3)CH(Ph)CH_2COCH_3$	76
6	I	$PhCH{=}CHCOPh$	–78, 1 min	$CH_2{=}CHCH_2CH(Ph)CH_2COCH_3$	96
7	I		–78, 2 hr		70
8	III		–78, 10 min		70
9	I		–78, 2 hr		54

10	III		−78, 30 min		82[h]
11	I		−78, 1 hr		80[i]
12	III		−78, 10 min		99[j]
13	I		−78, 18 hr then −30, 5 hr		85[k]
14	I		−78, 2 hr then 0, 15 min		88

[a] The reaction was carried out on a 1–20-mmol scale in dichloromethane.

[b] Yields after isolation by distillation or thin-layer chromatography.

[c] I = $Me_3SiCH_2CH=CH_2$.

[d] II = $Me_3SiCH_2CH=C(CH_3)_2$.

[e] III = $Me_3SiCH_2C(CH_3)=CH_2$.

[f] Three equivalents of the allylsilane were used.

[g] IV = *trans*-$Me_3SiCH_2CH=CHCH_3$.

[h] A [2 + 2] cycloadduct assigned the structure 1-methyl-1-trimethylsilylmethyl-3-*n*-propylspiro[3,4]octan-5-one was obtained in 19% yield.

[i] BP 56–60°C (3 mm), n_D^{20} 1.4719.

[j] Two equivalents of the allylsilane were used.

[k] Bp 83–85°C (0.6 mm), n_D^{20} 1.5111. A diallylated product, assigned the structure 2,8a-diallyl-3,4,4a,5,6,7,8,8a-octahydronaphthalene, was obtained as a forerun in less than 5% yield.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

H_2O

perhydroazulenones

$Me_3SiCH_2CH=CH_2$

$Me_3SiCH_2CH=C(CH_3)_2$

$Me_3SiCH_2C(CH_3)=CH_2$

trans-$Me_3SiCH_2CH=CHCH_3$

$CH_2=CHCOCH_3$

$CH_2=C(CH_3)_2CH_2CH_2COCH_3$

$(CH_3)_2C=CHCOCH_3$

$CH_2=CHCH_2C(CH_3)_2CH_2COCH_3$

$PhCH=CHCOCH_3$

$CH_2=C(CH_3)CH_2CH(Ph)CH_2COCH_3$

$CH_2=CHCH(CH_3)CH(Ph)CH_2COCH_3$

PhCH=CHCOPh

$CH_2=CHCH_2CH(Ph)CH_2COCH_3$

calcium chloride (10043-52-4)

ether, ethyl ether (60-29-7)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

copper powder (7440-50-8)

Benzalacetone (122-57-6)

dichloromethane (75-09-2)

titanium tetrachloride (7550-45-0)

calcium hydride (7789-78-8)

4-Phenyl-6-hepten-2-one, 6-Hepten-2-one, 4-phenyl- (69492-29-1)

allyltrimethylsilane (762-72-1)

allylcuprate

allylsilane (18191-59-8)

2,8a-diallyl-3,4,4a,5,6,7,8,8a-octahydronaphthalene

1-methyl-1-trimethylsilylmethyl-3-n-propylspiro[3,4]octan-5-one

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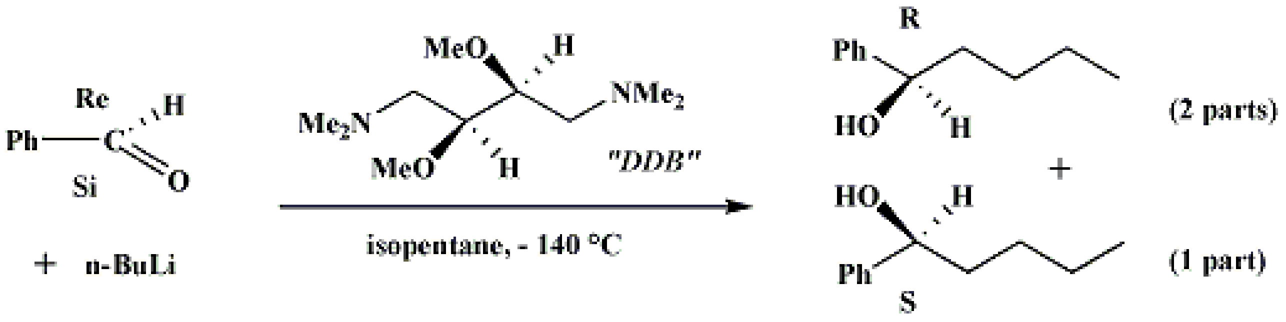
Organic Syntheses, CV 7, 447

ENANTIOSELECTIVE ADDITION OF BUTYLLITHIUM IN THE PRESENCE OF THE CHIRAL COSOLVENT DDB: (*R*)-(+)-1-PHENYL-1-PENTANOL

[Benzenemethanol, α-butyl-, (*R*)-]



Submitted by Dieter Seebach and August Hidber[1].
Checked by M. F. Semmelhack and Charles Shuey.

1. Procedure

As shown in f.htmigure 1, a dry, 1-L, three-necked flask is equipped with an overhead stirrer bearing a four-bladed propeller of ca. 2.5-cm diameter driven by a strong, safely connected motor A (Note 1), a rubber septum, and a three-way stopcock. The air in the flask is replaced by dry argon or nitrogen, the pressure of which is maintained during the reaction at ca. 50 mm above atmospheric pressure with a mercury bubbler (Note 2). A second stirrer (m.htmotor B, Figure 1) to agitate the bath is attached next to the flask with the propeller just below the bottom of the flask. Finally, a 4.5-cm × 20-cm test tube is held next to the bath stirrer. The entire apparatus (.htmFigure 1) is mounted well above the bench to allow for immersion of the flask, bath stirrer, and tube into cooling baths and for exchange of bulky bath containers with the aid of a lab jack. The flask is charged (Note 3) with 400 mL of 2-methylbutane (isopentane) (Note 4) and 24.6 g (27.5 mL, 0.12 mol) of (*S*,*S*)-(+)-*N*,*N*,*N'*,*N'*-tetramethyl-1,4-diamino-2,3-dimethoxybutane (DDB) (Note 5). A methanol–dry ice bath is raised to immerse the flask and cool the contents to −78°C with slow stirring, whereupon 0.021 mol of butyllithium (13.5 mL of a 1.56 *M* solution in hexane) (Note 6) is added within a few minutes. A second cooling bath is prepared in a ca. 7-L Dewar cylinder (Note 7) by pouring liquid nitrogen into a stirred (glass rod) mixture of methylcyclohexane/isopentane (3 : 2) (Note 8) until about half of the liquid has solidified and a slush has been formed, the temperature of which is ca. −140°C (Note 9). The reaction flask is cooled to the lower temperature by exchanging baths and waiting for 15 min with bath stirring. The bath is temporarily lowered and cooled until again half frozen by pouring in liquid nitrogen and manual agitation (Note 10). From then on, cooling is kept constant by filling the tube in the stirred bath at intervals with liquid nitrogen (Note 10). A solution of 2.12 g (0.020 mol) of benzaldehyde (Note 11) in 20 mL of isopentane (Note 4) is added dropwise (Note 12) over 15 min to the vigorously stirred (ca. 1000 rpm) reaction mixture. After completion of the addition (ca. 0.5 hr), the bath is removed, the flask is warmed to ca. 0°C (Note 13), and the contents are poured into a 1-L separatory funnel containing 150 mL of ice-cold 2 *N* aqueous hydrochloric acid. The aqueous layer is extracted twice with 70 mL of hexane

and saved for recovery of the chiral auxiliary agent DDB (Note 14). The combined organic layers are sequentially washed with saturated aqueous bicarbonate and sodium chloride solutions and concentrated in a rotary evaporator to ca. 200 mL. The solution is then transferred to a 500-mL separatory funnel and vigorously shaken with 40 mL of a saturated aqueous sodium bisulfite solution to precipitate the bisulfite adduct of unreacted benzaldehyde (Note 15). After filtration (if necessary) the residue and the aqueous phase are washed with hexane. The combined organic solution is dried over anhydrous magnesium sulfate and concentrated by rotary evaporation. Simple distillation yields 2.60–2.95 g (80–90%) of 1-phenyl-1-pentanol, bp 54–56°C (0.02 mm), $[\alpha]_D$ = 6.13° (neat), (Note 16), optical yield 30% (Note 17).

Figure 1

Figure 1

2. Notes

1. The checkers used a conventional, flat, crescent-shaped Teflon blade, 8 cm long.
2. This is done as previously described in *Organic Syntheses* procedures: Seebach, D.; Beck, A. K. *Org. Synth., Coll. Vol. VI* **1988**, 869; Enders, D.; Pieter, R.; Seebach, D. *Org. Synth., Coll. Vol. VI* **1988**, 542. All connections should be securely fastened.
3. All additions of solvents and reagents are carried out through the rubber septum with dry, appropriately sized, and argon-flushed syringes with hypodermic needles. Because of its low boiling point, it is advantageous to force isopentane into the 100-mL syringe by applying pressure to the storage flask.
4. Isopentane (bp 28°C, 95% 2-methylbutane), was purchased from Fluka AG, freshly distilled from P_2O_5, and stored under inert gas pressure.
5. DDB is presently available from Aldrich Chemical Company, Inc. For its preparation, see p. 000 in this volume. DDB is hygroscopic and must be refluxed for some time and freshly distilled from lithium aluminum hydride (bp 38°C/0.01 mm) prior to use. The submitters used material with $[\alpha]_D$ 14.7°; the checkers' sample showed $[\alpha]_D$ 14.3°.
6. Butyllithium was purchased from Metallgesellschaft, Frankfurt, and titrated for active alkyllithium using diphenylacetic acid as an indicator: Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879.
7. If no such Dewar container is available, two appropriately sized plastic buckets with a layer of styrofoam particles between the inner and outer bucket can be used.
8. The mixture was used as purchased from Fluka AG. The submitters have occasionally used, as a bath liquid, petroleum ether (bp 40–60°C) of unknown composition or pure isopentane (mp −160°C). In such cases, temperature control is necessary; it was achieved with a platinum temperature sensor inside the reaction mixture.
9. The checkers used a thermocouple to verify the temperature of the cooling bath.
10. The coolant must not be poured directly into the bath, because local overcooling can cause partial freezing of the reaction mixture, which is clear and homogeneous before addition of the aldehyde. If freezing should occur, the flask is temporarily warmed slightly by removing the bath.
11. Benzaldehyde was obtained from Fluka AG or Aldrich Chemical Company, Inc., and freshly distilled under reduced pressure (40°C/3 mm).
12. Clear drops of the aldehyde solution must fall from the tip of the needle directly into the reaction mixture. If the needle is inserted too far, the aldehyde can freeze and clog the needle; it is thawed by extracting the needle tip into the upper, warmer part of the neck.

13. A slow method is to wait until the ice that has condensed on the walls of the flask has all melted. Alternatively, the flask may be immersed in a methanol bath.
14. The combined aqueous layers of several runs are saturated with potassium hydroxide by adding KOH pellets with cooling. DDB separates on top of the aqueous phase and is extracted with ether. Distillation leads to 90% recovery (bp 42–43°C/0.05 mm).
15. The checkers observed no precipitate formation at this point.
16. In five runs carried out by the submitters at temperatures between –140 and –150°C, the specific rotations of phenylpentanol (d_4^{20} 0.967) ranged from $[\alpha]_D$ 5.95 to 7.0° (29–34% optical yield; see (Note 17)). At dry ice temperature, the optical yields are only half as high.[2] The checkers obtained specific rotations of $[\alpha]_D$ 5.87° and 6.05° (28 and 29% optical yield).
17. For optically pure 1-phenyl-1-pentanol a specific rotation of $[\alpha]_D^{25}$ 20.7° (neat) is reported.[3]

3. Discussion

The optically active form of 1-phenyl-1-pentanol has been prepared by a variety of methods.[4] [5] [6],[7] The present procedure is a modification and extended description of our previously published[2],[8] chiral solvent method. DDB and other auxiliary agents from tartaric acid lead to a wide range of optically active products from achiral components with prochiral centers (enantioselective syntheses). A list of examples of DDB applications is found in the accompanying procedure describing its preparation from tartaric acid.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 153

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

P_2O_5

(S,S)-(+)-N,N,N',N'-tetramethyl-1,4-diamino-2,3-dimethoxybutane (DDB)

DDB

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

sodium bisulfite (7631-90-5)

benzaldehyde (100-52-7)

potassium hydroxide, KOH (1310-58-3)

tartaric acid (87-69-4)

Diphenylacetic acid (117-34-0)

methylcyclohexane (108-87-2)

magnesium sulfate (7487-88-9)

isopentane, 2-methylbutane (78-78-4)

butyllithium (109-72-8)

lithium aluminum hydride (16853-85-3)

hexane (110-54-3)

argon (7440-37-1)

1-phenyl-1-pentanol (583-03-9)

phenylpentanol (10521-91-2)

Benzenemethanol, α-butyl-, (R)-, (R)-(+)-1-PHENYL-1-PENTANOL (19641-53-3)

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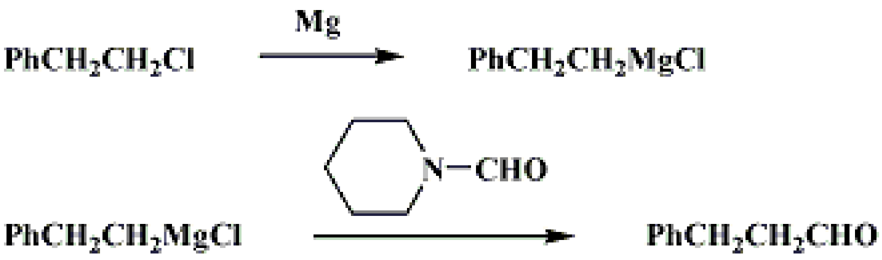
Organic Syntheses, *CV 7*, *451*

FORMYL TRANSFER TO GRIGNARD REAGENTS WITH *N*-FORMYLPIPERIDINE: 3-PHENYLPROPIONALDEHYDE



Submitted by George A. Olah and Massoud Arvanaghi[1].
Checked by David Heiler and Martin F. Semmelhack.

1. Procedure

Magnesium (2.88 g, 0.12 mol), 300 mL of anhydrous tetrahydrofuran (Note 1), and 10 mg of iodine are placed in a 1-L, three-necked, round-bottomed flask fitted with a stirrer, dropping funnel with a pressure-equalizing tube, and a reflux condenser connected to a nitrogen flow line. Nitrogen is passed through the solvent for 15 min and a constant flow of nitrogen is maintained throughout the reaction. A solution of 14.06 g (0.1 mol) of (2-chloroethyl)benzene (Note 2) in 50 mL of tetrahydrofuran is placed in the dropping funnel. About 2 mL of this solution is added to the reaction mixture and the reaction is initiated by gently heating the flask (with a heat gun). Once the reaction has started, as evidenced by the disappearance of iodine color, the rest of the (2-chloroethyl)benzene solution is added dropwise at such a rate that a gentle reflux is maintained throughout the addition. The resulting solution is stirred for an additional 1 hr at 23°C, followed by heating at reflux for 8 hr. The reaction vessel is cooled to 0°C and a solution of 13.56 g (0.12 mol) of *N*-formylpiperidine (Note 3) in 50 mL of dry tetrahydrofuran is added dropwise (Note 4). The mixture is brought to 23°C and stirred for another 15 min.

The reaction mixture is quenched by the addition of 25 mL of ice water and slowly acidified to pH 2 with 75 mL of 3 *N* hydrochloric acid. The organic layer is separated and the aqueous layer is extracted with three 75-mL portions of ether. The extracts are combined with the original ether layer, washed successively with 50 mL of water, two 50-mL portions of aqueous 10% sodium bicarbonate, and 50 mL of saturated sodium chloride solution, and dried over anhydrous magnesium sulfate. After the magnesium sulfate is removed by filtration, the solvent is removed at aspirator vacuum on a rotary evaporator and the residue is distilled through a short column to give 8.8–10.2 g (66–76%) of 3-phenylpropionaldehyde, bp 87°C (1.0 mm) (Note 5),(Note 6),(Note 7).

2. Notes

1. Technical-grade tetrahydrofuran was predried for a few days over sodium hydroxide. It was then heated under reflux over sodium wire with benzophenone until a permanent blue color developed and distilled with exclusion of atmospheric moisture. *(Caution: See p. 976 of Org. Synth., Coll. Vol. V for a warning regarding purification of tetrahydrofuran.)*
2. The (2-chloroethyl)benzene was purchased from Eastman Organic Chemicals and used without further purification.
3. *N*-Formylpiperidine was obtained from Reilly Tar and Chemicals or from Aldrich Chemical Company and used without further purification.
4. Too rapid addition of *N*-formylpiperidine should be avoided as it can result in a cake-like solid that hinders mixing of the reaction mixture. Efficient stirring is crucial to optimum yields.
5. The reported[2] boiling point for 3-phenylpropionaldehyde is 104–105°C (13 mm).
6. The spectral properties of the product are as follows: ^{13}C NMR ($CDCl_3$) δ: 27.9 (t, -CH_2-CH_2-CHO), 45.1 (t, -CH_2-CHO), 126.1 (d, *para*), 128.2 (d, *ortho*), 128.5 (d, *meta*), 140.2 (s, *ipso*), 201.4 (d, -CHO); ^1H NMR ($CDCl_3$) δ: 2.77 (m, -CH_2-CHO); 2.95 (m, -CH_2-CH_2-CHO), 7.16–7.33 (m, aromatic), 9.80 (t, -CHO); IR cm^{-1}: 2700, 1710.
7. (2-Bromoethyl)benzene can be used instead of (2-chloroethyl)benzene; anhydrous diethyl ether is used as the solvent instead of tetrahydrofuran.

3. Discussion

The procedure described here is a one-step conversion of (2-chloroethyl)benzene to 3-phenylpropionaldehyde. The method is general and characterized by good yields, mild conditions, and easy preparation of 3-phenylpropionaldehyde in pure form from readily available starting materials. Several methods are described in the literature for the preparation of 3-phenylpropionaldehyde, including dry distillation of calcium formate with calcium hydrocinnamate,[3] sodium amalgam reduction, and deprotection of cinnamaldehyde dimethyl acetal,[4] or formation from heterocyclic system.[5,6] The present method has been shown[7] to be applicable to a wide variety of organolithium and Grignard reagents.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 328
- Org. Syn. Coll. Vol. 9, 707

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

ether, diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

magnesium (7439-95-4)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

iodine (7553-56-2)

Benzophenone (119-61-9)

sodium wire (13966-32-0)

(2-chloroethyl)benzene (622-24-2)

magnesium sulfate (7487-88-9)

(2-bromoethyl)benzene (103-63-9)

calcium formate (544-17-2)

Tetrahydrofuran (109-99-9)

N-FORMYLPIPERIDINE (2591-86-8)

3-Phenylpropionaldehyde (104-53-0)

cinnamaldehyde dimethyl acetal

calcium hydrocinnamate

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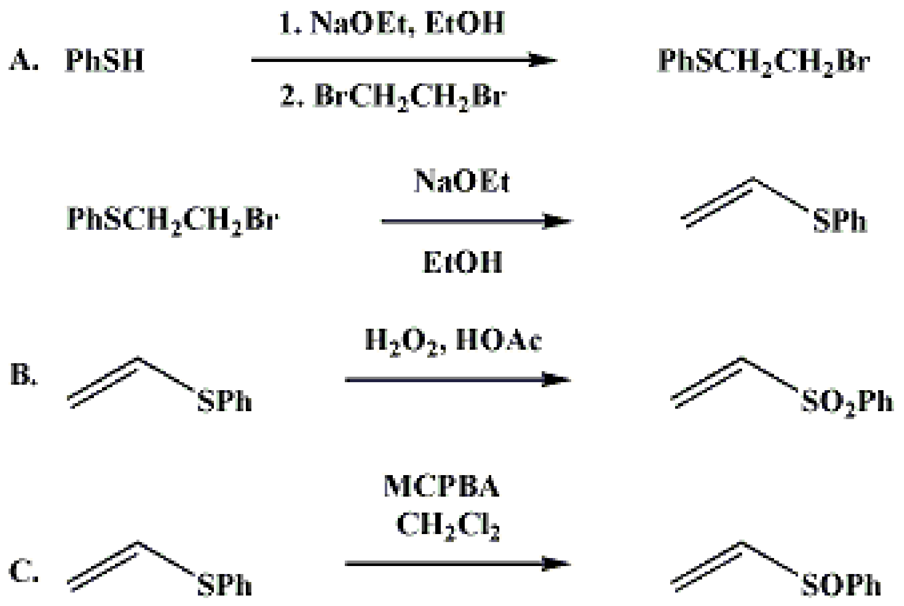
Organic Syntheses, CV 7, 453

PHENYL VINYL SULFONE AND SULFOXIDE

[Benzene, (ethenylsulfonyl)- and benzene, (ethenylsulfiny)-]



Submitted by Leo A. Paquette and Richard V. C. Carr[1].
Checked by Wayne Schnatter and Martin F. Semmelhack.

1. Procedure

Caution! 1-Phenylthio-2-bromoethane is a powerful alkylating agent that causes severe skin blistering. Although the present one-pot procedure eliminates the cumbersome handling of this intermediate, due care must be exercised to avoid exposure to this substance.

A. *Phenyl vinyl sulfide.* In a 1-L, three-necked, round-bottomed flask fitted with magnetic stirrer, condenser, addition funnel, and nitrogen-inlet tube is placed 400 mL of ethanol. Sodium metal (23 g, 1 g-atom), cut into small pieces, is added with stirring. When conversion to sodium ethoxide is complete (5–15 min), the stopper of the addition funnel is removed under a positive flow of nitrogen, and benzenethiol (110 g, 1 mol) is poured into the addition funnel. The stopper is put in place, and the benzenethiol is added over 15–20 min to the cloudy, gray sodium ethoxide solution. The reaction mixture warms spontaneously and becomes clear brown. At 25°C this solution is transferred by stainless-steel cannula (Note 1) over 45 min to a stirred solution of 1,2-dibromoethane (272 g, 1.45 mol) in ethanol (28 mL) contained in a 2-L, three-necked round-bottomed flask equipped with a mechanical stirrer, addition funnel, reflux condenser, nitrogen-inlet tube, and internal thermometer (Note 2). The reaction temperature is maintained at 25–30°C by cooling with an ice bath. The mixture is stirred under nitrogen for 30 min and treated for an additional 30 min with

ethanolic sodium ethoxide prepared from 40 g (2.17 g-atom) of sodium and 800 mL of ethanol (Note 3). The resulting mixture is stirred at reflux for 8 hr (Note 4), cooled, and treated with 750 mL of benzene and 750 mL of water. The organic layer is separated, washed with water (2 × 50 mL) and brine (100 mL), and concentrated by rotary evaporation. The yellow oil that results is distilled to give 70–87 g (50–65%) of phenyl vinyl sulfide, bp 91–93°C/20 mm (Note 5) and (Note 6).

B. *Phenyl vinyl sulfone*. In a 250-mL, three-necked, round-bottomed flask fitted with a magnetic stirrer, condenser, addition funnel, and thermometer is placed 19.7 g(0.145 mol) of phenyl vinyl sulfide dissolved in 70 mL of glacial acetic acid. Hydrogen peroxide (30%, 56 mL, 0.5 mol) is added slowly at such a rate to maintain a reaction temperature of 70°C (Note 7). The reaction mixture is heated at reflux for 20 min, cooled, and treated with ether (150 mL) and water (200 mL). The organic phase is separated, washed with water (50 mL) and brine (50 mL), and concentrated at 70°C/0.3 mm for 3 hr to afford 18–19 g (74–78%) of phenyl vinyl sulfone as a colorless solid, mp 64–65°C. Although this material is sufficiently pure for most purposes, recrystallization from hexane affords colorless crystals, mp 66–67°C (Note 8).

C. *Phenyl vinyl sulfoxide*. A 500 mL, three-necked, round-bottomed flask equipped with a dropping funnel and magnetic stirrer is charged with 20 g (0.147 mol) of phenyl vinyl sulfide and 250 mL of dichloromethane. The solution is stirred and cooled to −78°C while a solution of *m*-chloroperbenzoic acid (25.4 g, 1.0 equiv) in 200 mL of dichloromethane is added dropwise during a 30-min period. The mixture is stirred and warmed to room temperature for 1 hr in a water bath at 30°C. The mixture is then poured into 300 mL of saturated sodium bicarbonate solution, and the mixture is extracted with three 250-mL portions of dichloromethane. The combined organic extracts are washed with three 250-mL portions of water and dried over anhydrous magnesium sulfate. The solvent is removed by rotary evaporation and the residual liquid is distilled to afford 15–16 g (68–70%) of phenyl vinyl sulfoxide as a colorless liquid, bp 98°C/0.6 mm (Note 9) and (Note 10).

2. Notes

1. The cannula is a stainless-steel tube, 16-gauge, sharpened to a needle at both ends, and 60 cm long. One end is placed through a rubber septum into the flask containing the 1,2-dibromoethane solution, while the other end is positioned under the surface of the benzenethiolate solution. Control of the nitrogen pressure allows slow transfer of the benzenethiolate solution.
2. The yield in the previously published method for the preparation of this sulfide is low, affording chiefly 1,2-bis(phenylthio)ethane.[2] The problem is overcome here by utilization of an inverse addition procedure.
3. Alternatively, dry powered sodium ethoxide may be substituted with a corresponding reduction of the reaction volume.
4. Thin-layer chromatographic analysis at this stage shows that 1-phenylthio-2-

bromoethane is absent.

5. This product has the following spectral properties: IR (neat) cm^{-1}: 3040, 1585, 1475, 1435, 1085, 1020, 950, 735, and 680; ^{1}H NMR (chloroform-*d*) δ: 5.25 (superimposed doublets, 2 H, *J* = 12 and 18, terminal vinyl), 6.50 (dd, 1 H, *J* = 12 and 18, olefinic,), 7.32 (m, 5 H, aromatic).

6. When stored at room temperature, phenyl vinyl sulfide becomes yellow-colored within 1 day and a black syrup after 1 week. This decomposition can be substantially retarded by storage under a nitrogen or argon atmosphere in a freezer.

7. The submitter observed the temperature increase to 70°C during addition of the first 10 mL of hydrogen peroxide. The checkers noted that the mixture never rose in temperature to 70°C.

8. This product has the following spectral properties: IR ($CHCl_3$) cm^{-1}: 3020, 1445, 1380, 1315, 1145, 1080, and 965; ^{1}H NMR (chloroform-*d*) δ: 5.96 (d, 1 H, *J* = 10, olefinic), 6.33 (d, 1 H, *J* = 17, olefinic), 6.75 (dd, 1 H, *J* = 10 and 17, olefinic), 7.55 (m, 3 H, aromatic), 7.85 (m, 2 H, aromatic).

9. Earlier citations[3] report bp 105–110°C (1.5 mm) and 93–95°C (0.2 mm).

10. This product has the following spectral properties: IR (neat) cm^{-1}: 3025, 1720, 1680, 1480, 1440, 1045, 750, and 690; ^{1}H NMR (chloroform-*d*) δ: 5.63–6.17 (m, 2 H, olefinic H), 6.44–6.87 (m, 1 H, olefinic H), 7.10–7.55 (m, 5 H, aromatic H).

3. Discussion

The procedure for oxidation of the sulfide to the sulfone is based on that reported earlier by Bordwell and Pitt.[4] The synthetic utility of phenyl vinyl sulfone and sulfoxide derives not only from their ability to serve as excellent Michael acceptors toward such reagents as enolate anions and organometallics[5,6,7,8,9,10,11,12] but also as moderately reactive dienophiles in Diels–Alder reactions.[13,14,15,16] The resulting adducts, in turn, can be chemically modified so that these electron-deficient olefins serve as useful synthons for acetylene,[13] ethylene,[14] terminal olefins,[15] vinylsilanes,[17] and ketene[18] in [4 + 2] cycloadditions. Phenyl vinyl sulfone undergoes ready cycloaddition to Danishefsky's diene in the first step of a protocol for the regiospecific γ-alkylation of 2-cyclohexenones.[19] Furthermore, the ready lithiation of phenyl vinyl sulfones[20] and sulfoxides[21] represents a convenient route to α-(phenylsulfonyl) and α-(phenylsulfinyl)vinyllithium reagents.

The method described here for the preparation of phenyl vinyl sulfoxide is superior to that involving reaction of ethyl phenyl sulfinate with vinylmagnesium bromide.[13]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 107

- Org. Syn. Coll. Vol. 9, 656
- Org. Syn. Coll. Vol. 9, 662

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

brine

PHENYL VINYL SULFONE AND SULFOXIDE

benzene, (ethenylsulfiny)-

2-cyclohexenones

ethanol (64-17-5)

acetylene (74-86-2)

acetic acid (64-19-7)

Benzene (71-43-2)

ether (60-29-7)

sodium bicarbonate (144-55-8)

nitrogen (7727-37-9)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

ethylene (9002-88-4)

1,2-dibromoethane (106-93-4)

hydrogen peroxide (7722-84-1)

Ketene (463-51-4)

dichloromethane (75-09-2)

Benzenethiol (108-98-5)

magnesium sulfate (7487-88-9)

hexane (110-54-3)

vinylmagnesium bromide (1826-67-1)

argon (7440-37-1)

Phenyl vinyl sulfone, Benzene, (ethenylsulfonyl)- (5535-48-8)

1-Phenylthio-2-bromoethane (4837-01-8)

Phenyl vinyl sulfide (1822-73-7)

Phenyl vinyl sulfoxide (20451-53-0)

benzenethiolate

1,2-bis(phenylthio)ethane (622-20-8)

ethyl phenyl sulfinate

m-Chloroperbenzoic acid (937-14-4)

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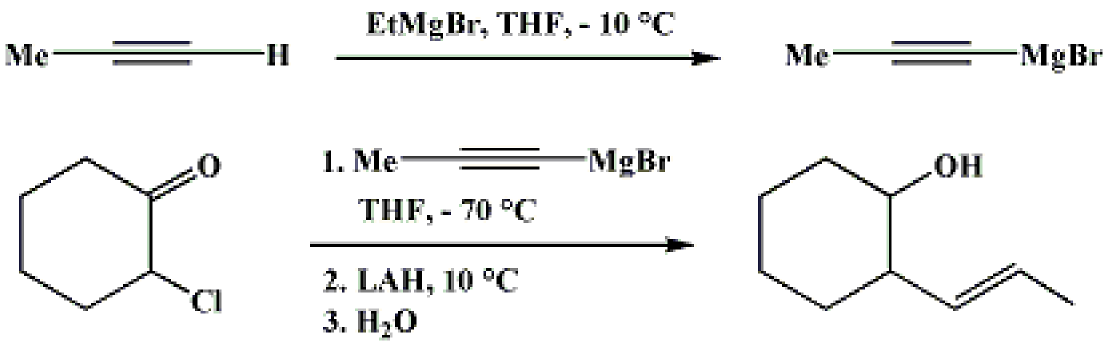
Organic Syntheses, CV 7, 456

2-ALKENYL CARBINOLS FROM 2-HALO KETONES: 2-*E*-PROPENYLCYCLOHEXANOL

[Cyclohexanol, 2-(1-propenyl)-, (*E*)-]



Submitted by P. A. Wender, D. A. Holt, and S. Mc N. Sieburth[1].
Checked by Peggy A. Radel and Clayton H. Heathcock.

1. Procedure

A dry, 5-L, four-necked, round-bottomed flask is equipped with an air-driven stirrer (Note 1), 250-mL pressure-equalizing dropping funnel, thermometer, rubber septum, and a nitrogen-inlet tube that, by means of a T-tube, is also connected to a gas bubbler. After being charged with 1200 mL of anhydrous tetrahydrofuran (Note 2), the flask is swept with dry nitrogen and maintained under an atmosphere of nitrogen throughout the remainder of the reaction. A solution of ethylmagnesium bromide in diethyl ether (1.1 mol, 380 mL, 2.9 *M*) is transferred to the flask and the flask is then cooled to below 10°C by means of an ice–water bath (Note 3). Propyne is bubbled through the cooled, stirred solution (Note 4) at such a rate that a small amount escapes through the nitrogen inlet–gas bubbler. Propyne addition is continued for 2.5 hr, at which time approximately 100 g (2.5 mol) of propyne has been used (Note 5) and the internal temperature has risen 5–10°C. The ice–water bath is then replaced with a dry ice–acetone bath and the mixture is cooled to ca. –70°C. A solution of 2-chlorocyclohexanone (1 mol, 132.6 g) (Note 6) in 50 mL of tetrahydrofuran is added dropwise from the addition funnel over 1.5 hr so as to maintain the temperature below –65°C (Note 7). After stirring for an additional 1.5 hr at –70°C (Note 8), the dry ice–acetone bath is replaced with an ambient-temperature water bath and the reaction mixture is allowed to warm slowly. When the temperature reaches 10°C, a solution of lithium aluminum hydride in tetrahydrofuran (1 mol, 1000 mL, 1 *M*) is added by cannula (Note 9). After addition of the lithium aluminum hydride, the mixture is stirred at ambient temperature for 3–5 hr, at which time the solids have dissolved and reaction is complete (Note 10) and (Note 11). The solution is then cooled to 5°C by means of an ice–water bath. The reaction is quenched by careful, dropwise addition of 38 mL of water over 2 hr to maintain the temperature below 20°C. The solution

becomes somewhat cloudy at this point and 2000 mL of hexanes is added. The addition of 38 mL of aqueous 15% sodium hydroxide solution over 15 min is followed by the addition of 100 mL of water over 5 min. Some frothing occurs during the last addition of water and a large amount of white aluminum salts precipitates. After 5 min of stirring, 100 g of anhydrous sodium sulfate is added and stirring is continued for another 5 min. The thick mixture is then filtered by suction through Celite using a 200-mm-diameter Büchner funnel. The solids are removed from the funnel, thoroughly washed with 1500 mL of hot tetrahydrofuran (Note 12), and refiltered. This wash is repeated twice and the combined organic solutions are concentrated with a rotary evaporator (15 mm). The residual yellow liquid is distilled under reduced pressure to yield 118.8 g (85%) of 2-*E*-propenylcyclohexanol as a clear colorless liquid, bp 49–54°C (1 mm) (Note 13).

2. Notes

1. The use of a magnetic stirrer is more convenient than a mechanical stirrer for reactions conducted on small scale (<0.2 mol) or at low concentrations (<0.5 *M*). However, because of the difficulty encountered in stirring the sometimes thick suspensions associated with concentrated (e.g., 1 *M*) reaction mixtures, and because of the potentially disastrous results if a stir bar should fracture the flask wall during a large-scale preparation, the submitters strongly recommend the use of an air-driven overhead mechanical stirrer for such large-scale reactions. At a later stage in the reaction, when the propynylmagnesium bromide is cooled to −70°C, the THF solution becomes viscous and rather difficult to stir. The checkers recommend the use of a heavy-duty, air-driven stirrer such as the Fisher Scientific Model 14-508.5. An electrically driven overhead stirrer should not be used, as the hydrogen released during the quench represents a considerable explosion hazard.
2. The submitters used "Baker Analyzed" tetrahydrofuran (0.005% H_2O) without further purification or drying.
3. The submitters used ethylmagnesium bromide solution purchased from Aldrich Chemical Company, Inc. and found it most convenient to measure the required amount by transferring the solution by cannula to a nitrogen-flushed graduated cylinder fitted with a rubber septum. This measured amount of solution is then transferred to the flask by cannula. (See [2] for general techniques for handling air-sensitive reagents in this manner.) Some of the Grignard reagent precipitates at this temperature and concentration. There is a tendency for the ethylmagnesium bromide to clog the cannula. The checkers found it convenient to use a cannula made from 2-mm stainless-steel tubing.
4. Propyne of 99.96% purity, purchased from Liquid Carbonic Company in a lecture bottle, was used without purification and was introduced to the flask by means of a Tygon tube that was attached to a 9-in., 18-gauge hypodermic needle.
5. The amount of propyne used is conveniently determined by weighing the lecture bottle before and after addition. In this case the submitters used an excess of alkyne to ensure complete consumption of the Grignard reagent. In cases where nongaseous, nonvolatile alkynes are to be used, stoichiometric

amounts suffice.
6. The submitters used 2-chlorocyclohexanone purchased from Aldrich Chemical Company, Inc. without further purification. Alternatively, this compound can be easily prepared by chlorination of cyclohexanone.[3]
7. A flask should be used that is constructed in such a manner that the chloro ketone solution drips directly from the addition funnel into the reaction mixture. Any portion that flows along the sides of the flask will freeze.
8. Chloro alkoxide formation is essentially complete at this time and can be conveniently monitored by quenching a small aliquot and subjecting it to GLC analysis. Using a 50-m × 0.2-mm OV-1 capillary column at 110°C and a flow rate of 0.87 mL/min (H_2 carrier), the submitters found retention times of 3.2 min for 2-chlorocyclohexanone and 6.7 min and 7.2 for *trans*- and *cis*-1-propynyl-2-chlorocyclohexanols, respectively.
9. Lithium aluminum hydride in tetrahydrofuran was purchased from Aldrich Chemical Company, Inc. and was handled in the fashion described above for the Grignard solution (see (Note 3)). While solid lithium aluminum hydride can be used (with appropriate changes in the amount of solvent initially used), the hazards of handling this flammable and even explosive reagent (see [4] and [5]) can be reduced by using the preprepared solution. An excess of hydride reagent is necessary to facilitate complete reaction in a reasonable time. When only the stoichiomeric amounts of hydride reagent are used, the reaction is not complete even after several days at room temperature.
10. In reactions run at high concentration the reaction has a tendency to become slightly exothermic at some point, with the temperature increasing by as much as 30°C. Although the reaction is usually complete in less time, and with no reduction in yield of product, this exothermic reaction can be prevented by keeping the flask in a large ambient-temperature water bath, thus buffering temperature changes that apparently initiate the exothermic reaction. The progress of the reaction can be conveniently monitored by TLC or GLC analysis of a quenched aliquot. Using the same GLC conditions as described in Note 8, the retention times for *cis*- and *trans*-2-*E*-propenylcyclohexanols are 4.1 min and 3.9 min, respectively.
11. The checkers noted that a homogeneous solution occurs after about 2 hr. However, TLC and GLC analysis showed that reaction was not complete until 3.5–5 hr.
12. The tetrahydrofuran used for washing the filtercake should be tested for peroxides before use, since the final distillation is carried out almost to dryness.
13. GLC analysis indicated a purity greater than 98% and a cis : trans ratio of 1 : 2. These isomers can be separated by column chromatography and give the following ^{1}H NMR spectra: ($CDCl_3$) δ: cis: 1.1–2.0 (m, 12 H, CH_2, CH_3, OH), 2.2 (m, 1 H, allylic CH), 3.75 (m, 1 H, carbinol CH), 5.4–5.6 (m, 2 H, CH=CH); trans: 1.0–2.2 (m, 10 H, CH_2, OH, allylic CH), 1.70 (d, 3 H, J = 4.9, CH_3), 3.1 (m, 1 H, carbinol CH), 5.0–5.8 (m, 2 H, CH-CH).

3. Discussion

A variety of approaches have been employed to effect the preparation of α-alkenyl ketones and carbinols, including reactions of metallo alkenes with epoxides,[6 7] α-halo ketones,[8 9 10 11] or enolonium ion equivalents[12 13] and the reactions of ketone enolates with vinyl cation equivalents.[14 15 16 17 18 19 20 21 22 23 24 25 26 27] The procedure described here offers several advantages over existing methodology. Starting materials and reagents are all commercially available at low cost. Manipulations are simple, and the procedure can be carried out in a single operation, in a single flask, on a small or large (1-mol) scale and in high yield. In addition, as described in more detail elsewhere,[28] this method permits the use of cyclic as well as acyclic halo ketones, bromo ketones instead of chloro ketones, a variety of alkynes including acetylene, conjugated alkynes, 3-silyloxy functionalized alkynes, and other aluminum hydride reagents such as diisobutylaluminum hydride and lithium trimethoxyaluminum hydride. Furthermore, the method provides for complete control over alkene geometry and easy access to trisubstituted alkenes of defined stereochemistry.

Mechanistically, the reaction proceeds through an alkynyl chloro alkoxide, which, when treated with the reducing agent, is hydroaluminated to yield the vinyl alanate, which subsequently undergoes a facile pinacol-like 1,2-rearrangement. Excess hydride reagent reduces the intermediate alkenyl ketone and the resulting 2-alkenyl carbinol is isolated on aqueous workup (Scheme 1). Table I contains representative examples.

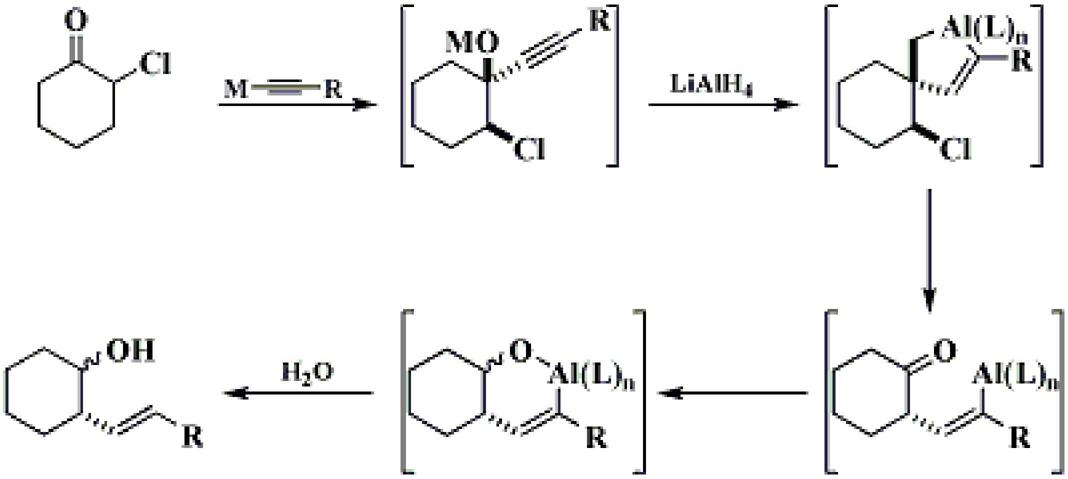
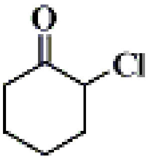
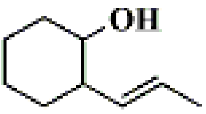
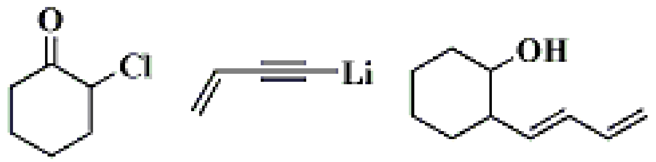


TABLE I
PREPARATION OF ALKENYL CARBINOLS

Carbonyl	Alkynylide	Alkenyl Carbinol	Yield(%)
			85



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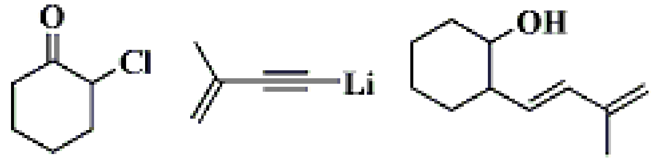

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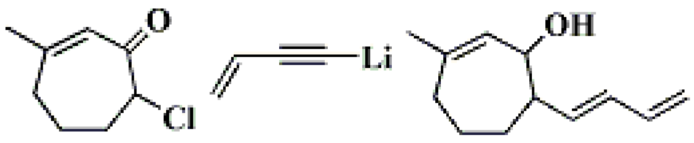

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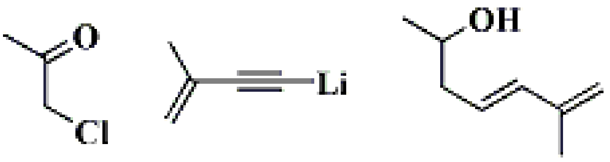

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

H_2O

trans- and cis-1-propynyl-2-chlorocyclohexanols

cis- and trans-2-E-propenylcyclohexanols

acetylene (74-86-2)

diethyl ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

Cyclohexanone (108-94-1)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

ethylmagnesium bromide (925-90-6)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

2-Chlorocyclohexanone (822-87-7)

propynylmagnesium bromide

hydride

diisobutylaluminum hydride (1191-15-7)

propyne (74-99-7)

aluminum hydride

vinyl cation

lithium trimethoxyaluminum hydride

vinyl alanate

2-E-PROPENYLCYCLOHEXANOL

Cyclohexanol, 2-(1-propenyl)-, (E)-

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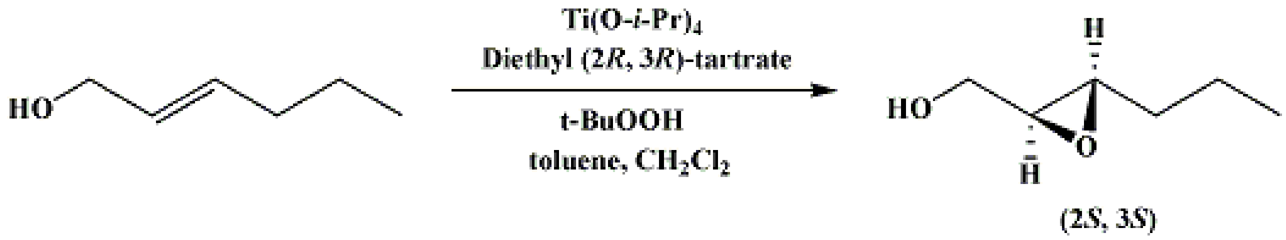
Organic Syntheses, CV 7, 461

ENANTIOSELECTIVE EPOXIDATION OF ALLYLIC ALCOHOLS: (2*S*,3*S*)-3-PROPYLOXIRANEMETHANOL

[Oxiranemethanol, 3-Propyl-, (2*S*,3*S*)-]



Submitted by J. Gordon Hill[1], K. Barry Sharpless[1], Christopher M. Exon[2], and Ronald Regenye[2].
Checked by Mark H. Norman and Clayton H. Heathcock.

1. Procedure

A 2-L, three-necked, round-bottomed flask equipped with a mechanical stirrer with Teflon blades, thermometer, and nitrogen inlet is charged with 1.00 L of methylene chloride (Note 1) and 39.9 mL (38.1 g, 0.134 mol) of titanium(IV) isopropoxide (Note 2). The flask content is stirred and cooled under nitrogen in a dry ice–ethanol bath to −70°C. To the flask is then added 33.1 g (27.5 mL, 0.161 mol) of diethyl (2*R*,3*R*)-tartrate (Note 3) and 25.0 g (0.25 mol) of *E*-2-hexen-1-ol (Note 4). A small volume of methylene chloride is used to ensure complete transfer of each material to the reaction flask. To the flask is then added 184.5 mL (0.50 mol) of 2.71 *M* anhydrous *tert*-butyl hydroperoxide in toluene (Note 5) that has been precooled to −20°C (Note 6). The addition causes a temperature increase to −60°C; the temperature of the reaction mixture is allowed to come to 0°C over a 2.0-hr period (Note 7).

A 4-L beaker equipped with a magnetic stirring bar and thermometer is charged with a solution of 125 g of ferrous sulfate and 50 g of tartaric acid in a total volume of 500 mL of deionized water. The solution is stirred and cooled by means of an ice–water bath to 10°C. When the epoxidation reaction mixture reaches 0°C, it is immediately (Note 8) poured into the stirred contents of the beaker. The resulting reaction is mildly exothermic, causing a temperature rise to ca. 20°C (Note 9). After the exothermic reaction has subsided and the temperature has begun to drop (ca. 5 min), the cooling bath is removed and the mixture is stirred at ambient temperature for 30 min. The contents of the beaker are transferred to a 2-L separatory funnel and the aqueous phase is separated and extracted with two 250-mL portions of ether. The combined organic layers are dried over sodium sulfate and filtered. The solvent is removed with a rotary evaporator at 35°C (70 mm) to give 85.9–89.9 g (Note 10) of pale-amber oil.

A 2-L, three-necked, round-bottomed flask equipped with a thermometer and a mechanical stirrer with Teflon blades is charged with a solution of the reaction product in 750 mL of ether. The contents of the flask are cooled in an ice–water bath to 3°C. To the flask is added a precooled (3°C) solution of 20 g (0.50 mol) of sodium hydroxide in 500 mL of brine (Note 11). The two-phase mixture is stirred vigorously for 1 hr with continued cooling (Note 12) and then is transferred to a separatory funnel. The aqueous phase is separated and extracted with two 150-mL portions of

ether (Note 13) and (Note 14). The combined organic solution (Note 15) is dried over sodium sulfate and filtered. Solvent removal with a rotary evaporator at 35°C (70 mm) followed by concentration with the rotary evaporator at 35°C (12 mm) for 1.0 hr gives 24.7–25.0 g of crude (2*S*,3*S*)-3-propyloxiranemethanol as a pale-amber oil (Note 16).

The crude product is distilled through a 10-cm Vigreux column (the receiving flask is cooled in an ice–water bath) to yield 22.45–22.84 g (80–81%) of (2*S*,3*S*)-3-propyloxiranemethanol as a colorless liquid, bp 31–33°C (0.30–0.40 mm). Analysis by GC indicates a chemical purity of 89–93% (Note 17). The material is fractionally distilled through a 20-cm vacuum-jacketed Vigreux column to obtain 17.69–19.44 g (63–69%), $[\alpha]_D^{22}$ –38.1 to –38.6° (neat), $[\alpha]_D^{23}$ –46.2 to –48.6° ($CHCl_3$, *c* 1.0) of a colorless liquid. Analysis by GC indicates a chemical purity of 96–98% (Note 17). An enantiomeric purity of 96.4–97.5% is determined by ^1H NMR analysis of the derived acetate using Eu(*hfc*)$_3$, tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato] europium (III), (Note 18) as the chiral shift reagent (Note 19). The enantiomeric purity may also be determined by GC analysis (Note 20) of the derived α-methoxy-α-(trifluoromethyl)phenylacetic acid esters[3] (Note 21) and (Note 22). An alternative to the distillation method is purification by preparative HPLC (Note 23) and (Note 24) and bulb-to-bulb distillation (Note 25) to give 21.85 g (78%) of (2*S*,3*S*)-3-propyloxiranemethanol as a white solid, mp 19°C, $[\alpha]_D^{25}$ –46.6° ($CHCl_3$, *c* 1.0). Analysis by GC of material purified in this manner indicates a chemical purity of >99% (Note 14) and an enantiomeric purity of 96.8% (Note 20),(Note 21),(Note 22).

2. Notes

1. Fisher Scientific Company methylene chloride, certified ACS grade containing 0.02% water was used; a fresh bottle was used for each run.
2. Titanium(IV) isopropoxide is available from the Aldrich Chemical Company, Inc.
3. (+)-Diethyl L-tartrate was obtained from the Aldrich Chemical Company, Inc.
4. trans-2-Hexen-1-ol was obtained from Alfa Products, Morton Thiokol, Inc. Analysis by GC (Hewlett-Packard HP 5710A; 50-m × 0.25-mm capillary column of bonded CPS-2 on fused silica; 120°C isothermal) with appropriate standards indicated an *E*-2-hexen-1-ol content of 96.1% with 0.9% *Z*-2-hexen-1-ol and 2.9% hexanol as impurities. *trans*-2-Hexen-1-ol from the Aldrich Chemical Company, Inc., could also be used. This material was of similar composition: 95.4% *E*-2-hexen-1-ol, 0.8% *Z*-2-hexen-1-ol and 3.2% hexanol.

5. Anhydrous *tert*-butyl hydroperoxide in toluene[4] was prepared starting with Aldrich Chemical Company, Inc. 70% aqueous *tert*-butyl hydroperoxide. A 500-g lot of this material was swirled in a separatory funnel with 1.0 L of toluene. The aqueous phase was removed and discarded. The organic solution was heated at reflux under nitrogen for 4 hr in a flask equipped with a Dean–Stark trap for water separation (for greater detail, see [4]). The solution was cooled and stored under nitrogen at –20°C (Note 6). The content of *tert*-butyl hydroperoxide was determined by ^1H NMR according to the equation Molarity = $X / 0.1X + 0.32Y$ where X = integration of *tert*-butyl resonance; Y = integration of methyl resonance.

6. Storage of the solution at –20°C is not necessary.[4] It does, however, provide a convenient method of precooling the material.
7. Addition of dry ice to the cooling bath was stopped. If the rate of temperature increase was too slow, the ethanol bath was lowered.
8. If the mixture is allowed to stand at 0°C or to warm above this temperature, undesired by-products (TLC) are formed.

9. The temperature should be kept ≤20°C. In some cases, the addition of small amounts of ice to the reaction is necessary.
10. This weight can vary substantially, depending on the extent to which the solvents, especially toluene, have been stripped from the solution. Concentration need only be carried out until the weight is < 100 g.
11. This mixture is prepared by dissolving the sodium hydroxide in the brine at ambient temperature and then cooling the total to 3°C. The resultant cloudy, supersaturated suspension is used in toto. The use of this reagent ensures complete extraction (vide infra) of the somewhat water-soluble product. In addition, it minimizes contact of this material with the aqueous base, conditions which can lead to the Payne rearrangement.[5]
12. Saponification serves to remove the diethyl tartrate as well as to liberate any product which has been transesterified to form a tartrate ester.
13. GC analysis (Note 14) of a third extract showed no product.
14. GC analysis was performed on a column with the following properties: Hewlett-Packard HP 5702A, 2-m × 0.63-cm OV-101 column, programmed 70–200°C at 8°C/min.
15. GC analysis (Note 14) shows no diethyl (2*R*,3*R*)-tartrate, indicating that the saponification was complete.
16. Material of this quality is suitable for many synthetic purposes.
17. The properties of the column are as follows: Hewlett-Packard HP 5790A, 12-m × 0.2-mm cross-linked methyl silicone (fast analysis) column, programmed from 35 to 140°C at 3°C/min.
18. The shift reagent was obtained from the Aldrich Chemical Company, Inc. Drying the $Eu(hfc)_3$ overnight with a drying pistol at 56°C (refluxing acetone) under vacuum afforded optimum results.
19. The analytical sample of the acetate derivative is prepared as follows. Into a 5-mL, round-bottomed flask equipped with a magnetic stirring bar are placed 2 drops of the reaction product, 16 drops of acetic anhydride, and 32 drops of pyridine. The solution is stirred at ambient temperature for 2 hr, and the mixture is then transferred to a separatory funnel with the aid of 10 mL of methylene chloride. The methylene chloride solution is washed with two 10-mL portions of 1 *M* phosphoric acid, the organic layer is dried over $MgSO_4$, and the filtered solution is concentrated with a rotary evaporator to give approximately 20 mg of acetate as a colorless oil. A 5-•L sample of this crude acetate is dissolved in 0.5 mL of benzene-d_6 and transferred to an NMR tube. A solution of 75 mg of $Eu(hfc)_3$ in 0.5 mL of benzene-d_6 is prepared. A 50-•L portion of the shift reagent solution is added to the acetate sample, the mixture is shaken well, and the ^1H NMR spectrum is recorded. Additional portions of shift reagent are added in 10-•L portions until the acetate methyl resonance (originally at δ = 1.65 ppm) shifts downfield to the region 2.3–3.1 ppm and shows baseline resolution of the resonances from the two enantiomers. A total of 50–90 •L of the shift reagent solution should be required to achieve the desired shift, at which point a chemical-shift difference of about 0.2 ppm should be obtained. The %ee is obtained by integration of the two acetate peaks.
20. The column had the following properties: Hewlett-Packard HP 5710A, 50-m × 0.25-mm capillary column of OV-17 (bonded) on fused silica; 175°C isothermal.
21. The analytical sample of α-methoxy-α-(trifluoromethyl)phenylacetic acid ester is prepared as follows. Into a 5-mL, capped, amber vial equipped with a magnetic stirring bar are placed 20 mg of the reaction product, 1.0 mL of methylene chloride, 87 mg of (+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (Note 22), 4 drops of triethylamine, and 1 crystal of 4-dimethylaminopyridine. The mixture is stirred at ambient temperature for 1.5 hr, at which point TLC (Note 26) indicates complete conversion to the ester. Addition of 4 drops of *N*,*N*-dimethyl-1,3-propanediamine and concentration on a rotary evaporator at 35°

C (70 mm) affords a yellow oil. This material is filtered through 10 g of E. Merck silica gel 60 (70–230 mesh) with 9 : 1 hexanes–ethyl acetate until TLC analysis indicates no further product elution. The total eluate is concentrated on a rotary evaporator at 35°C (70 mm). The resultant colorless oil is subjected to GC analysis. A sample of *E*-2-hexen-1-ol in methylene chloride was epoxidized at 20°C with *m*-chloroperoxybenzoic acid. The resultant racemic epoxy alcohol, on conversion to the diastereomeric (+)-α-methoxy-α-(trifluoromethyl) phenylacetic acid esters in the manner described above, provided a GC standard for determination of the enantiomeric excess obtained in the asymmetric epoxidation.

22. The acid chloride was prepared[3] from (+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid, which was used as obtained from Aldrich Chemical Company, Inc.

23. Purification by preparative HPLC is accomplished as follows. The crude product is taken up in 60 mL of 4 : 1 hexanes : ethyl acetate. The solution is subjected to preparative HPLC (Note 24) using the same solvent system. Chromatography is monitored by TLC (Note 26) and the appropriate fractions are combined. Solvent removal with a rotary evaporator at 35°C (12 mm) gives a colorless oil. This material is subjected to bulb-to-bulb distillation at 75–90°C (8 mm).

24. A Waters Associates Prep LC/System 500 with two cartridges (1.0 kg) of PrepPak-500/ Silica was used. The course of the chromatography was followed with a refractive index detector. Approximately 3.6 L of solvent was eluted prior to the product band.

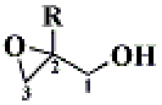
25. A Kugelrohr apparatus purchased from the Aldrich Chemical Company, Inc. was used. The receiving bulb was cooled with an ice–water bath. The temperature indicated is the oven temperature.

26. E. Merck silica gel F-254 plates were used, with 2 : 1 hexanes : ethyl acetate as eluent. Visualization was effected by spraying with a 10% phosphomolybdic acid in ethanol solution followed by heating with a hot air gun. (2*S*,3*S*)-3-Propyloxiranemethanol had an R_f of 0.3.

3. Discussion

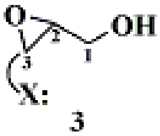
Both the synthetic[6] and mechanistic[7] aspects of this asymmetric epoxidation process have been reviewed recently. While the process has great scope regarding the allylic alcohol substrate, two classes of substrates present difficulties. These limitations will be best appreciated by reference to the recent reviews;[6,7] however, the main problems are worth mentioning here. When difficulties arise, they are almost never due to the failure of the asymmetric epoxidation process itself but can be traced instead to the nature of the epoxy alcohol product.

Water-soluble products (e.g., 3- and 4-carbon epoxy alcohols) present obvious isolation problems that have been only partly solved. The other troublesome class of products includes those epoxy alcohols that are unstable under the epoxidation and/or isolation conditions. This latter class consists of the three main types shown below:



1

2



3

Type **1** is sensitive to nucleophilic opening at the primary epoxide carbon (C-3). Type **2** represents cases where the substituent Y facilitates opening at carbon-3 through resonance stabilization of the incipient carbonium ion. Finally, type **3** includes those cases in which the product bears a heteroatom substituent (X) placed so that a five- or six-membered ring results

from anchimerically assisted opening of the epoxide at carbon-3. Not even these structural features (i.e., as in **1, 2**, and **3**) are always fatal, for some representatives of types **1, 2**, and **3** afford good yields of the desired epoxy alcohols.[6,7] Furthermore, when the structure of a given case is marginal, we have found that modification of the epoxidation and/or isolation procedures can lead to substantially improved yields. With such sensitive epoxy alcohols, milder isolation procedures are always employed (see [6] and [8] for a discussion of these modified work up methods). However, certain substrates of types **1, 2**, and **3** still fail completely with all current procedures. The best we have been able to do in these difficult cases is to use a strategy that actually takes advantage of the facile epoxide opening process.[6,7,10]

Questions are often asked concerning the catalytic nature of the asymmetric epoxidation. One notes that the present procedure calls for 50% catalyst. With very favorable substrates, one can realize complete conversion and >95% e.e. using as little as 2% catalyst.[6,7] In the present case, the reaction stops at about 80% conversion using 2% catalyst and almost reaches completion with 10% catalysis.[11] The selection of 50% catalyst is a compromise aimed at rendering the procedure applicable to a wider range of substrates. In the literature, most applications of asymmetric epoxidation use 100% catalyst. This is rarely necessary, but ensures rapid and complete epoxidation in small-scale reactions where cost of the reagents is not an issue. The cases yielding epoxy alcohols that are sensitive to opening require the most catalyst, because the open-diol products are potent inhibitors of the epoxidation catalysis.[6] If one wished to produce molar amounts of a given epoxy alcohol, it would be worthwhile to determine the optimum catalyst loading for the case at hand. In addition to the cost incentive, the isolation procedure becomes simpler as the amount of catalyst is decreased.

The aqueous tartaric acid workup procedure described here is the simplest method for removing the titanium species, but it should be used only with relatively stable epoxy alcohols that are not water-soluble. In this regard, the six-carbon epoxy alcohol made here probably represents the lower limit, as it is on the verge of water solubility. Of course, one cannot assume that this work up will succeed with all six-carbon or larger epoxy alcohols, for in addition to limited water solubility, the product must be fairly resistant to acid-catalyzed epoxide opening processes. *For water-soluble and/or acid-sensitive epoxy alcohols, the "sodium sulfate workup" is generally preferred*.[6,8] When making a particularly sensitive epoxy alcohol, one should not only use this sodium sulfate workup but also modify the initial stage of the epoxidation process so that the reaction mixture only warms to −20°C rather than to 0°C.

Finally, two other practical points are worth mentioning. The early procedures for asymmetric epoxidation called for dilute solutions of sodium hydroxide to effect tartrate ester hydrolysis. For the reasons given in Note 11, one should always (unless one is certain that the epoxy alcohol is completely insoluble in water) use, instead, NaOH in brine. In this procedure, the excess *tert*-butyl hydroperoxide (TBHP) was destroyed early in the workup ($FeSO_4$), although this is not essential because dilute solutions of TBHP are not dangerous. Other methods for removing excess TBHP in these epoxidations have been reviewed.[6] One of the simplest is to remove it as the azeotrope with toluene. We have removed up to 0.5 mol of TBHP by this means.[12]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 356

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8. The "sodium sulfate workup" should be used in place of the "tartaric acid workup," employed in the present procedure, whenever one is dealing with a water-soluble and/or acid-sensitive epoxy alcohol. The early stages of this alternate workup are as follows. The reaction mixture is removed from the freezer (ca. −20°C), and, while it is stirred (magnetic or mechanical depending on the scale), ether is added to the cold reaction mixture, followed immediately by a saturated sodium sulfate solution (no cooling bath is used at this stage and the ether is not precooled). We use 1 mL of saturated Na_2SO_4 solution per mmol of Ti(*O*-*i*-Pr)$_4$. (Note that this is about 3.3 times more than was recommended in an earlier[9] procedure.) The volume of ether added should be at least 1 mL per milliliter of saturated Na_2SO_4 solution used, and more ether is beneficial. The heterogeneous mixture that results is stirred vigorously for about 2 hr at room temperature. It is then filtered through a Celite pad and the resulting orange–yellow paste is washed with several portions of anhydrous ether until the paste becomes somewhat granular. The orange–yellow layer is scraped off the Celite pad into an Erlenmeyer flask. Ethyl acetate is added along with a magnetic stirring bar and the resulting suspension is stirred vigorously for 5 min in boiling ethyl acetate. The slurry is then filtered through the same Celite pad, and the orange–yellow solid is washed once with hot ethyl acetate. Treatment of the filtrand in this manner is a key improvement that *usually increases the total isolated yield by 10–15%*. The combined filtrates are concentrated to afford crude product along with the tartrate diester and any excess TBHP. This material is ready for the next stage of the work-up, which involves removal of the tartrate ester. The present preparation describes (vide supra) hydrolysis of the ester with NaOH/brine. For alternate ways of separating the epoxy alcohols from the tartrate ester see [6]. (This reference also describes several ways for removing the TBHP.)
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12. Hill, J. G., unpublished results.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

benzene-d_6

hexanes

brine

Eu(hfc)$_3$, tris[3-(heptafluoropropylhydroxymethylene)-d-camphorato] europium(III)

α-methoxy-α-(trifluoromethyl)phenylacetic acid esters

α-methoxy-α-(trifluoromethyl)phenylacetic acid ester

ethanol (64-17-5)

ethyl acetate (141-78-6)

ether (60-29-7)

acetic anhydride (108-24-7)

sodium hydroxide (1310-73-2)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

ferrous sulfate (13463-43-9)

pyridine (110-86-1)

toluene (108-88-3)

phosphoric acid (7664-38-2)

tartaric acid (87-69-4)

hexanol (111-27-3)

methylene chloride (75-09-2)

triethylamine (121-44-8)

tert-BUTYL (1605-73-8)

N,N-dimethyl-1,3-propanediamine (109-55-7)

phosphomolybdic acid (51429-74-4)

tert-butyl hydroperoxide (75-91-2)

diethyl tartrate, (+)-Diethyl L-tartrate

4-dimethylaminopyridine (1122-58-3)

titanium(IV) isopropoxide (546-68-9)

(+)-α-methoxy-α-(trifluoromethyl) phenylacetic acid, (+)-α-methoxy-α-(trifluoromethyl) phenylacetic acid (56135-03-6)

trans-2-Hexen-1-ol, E-2-hexen-1-ol (928-95-0)

(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride

epoxy alcohol

m-chloroperoxybenzoic acid (937-14-4)

diethyl (2R,3R)-tartrate (87-91-2)

Oxiranemethanol, 3-Propyl-, (2S,3S)-, (2S,3S)-3-Propyloxiranemethanol (89321-71-1)

Z-2-hexen-1-ol (928-94-9)

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Organic Syntheses, CV 7, 467

ACID CHLORIDES FROM α-KETO ACIDS WITH α,α-DICHLOROMETHYL METHYL ETHER: PYRUVOYL CHLORIDE

[Propanoyl chloride, 2-oxo-]

Submitted by Harry C. J. Ottenheijm and Marianne W. Tijhuis[1].
Checked by Larry A. Last and Robert M. Coates.

1. Procedure

A 100-mL, two-necked, round-bottomed flask is equipped with a magnetic stirrer, pressure-equalizing dropping funnel, and a 1.2- × 24-cm vacuum-jacketed Vigreux column that is connected to a condenser, vacuum-take-off adapter, and fraction collector with three receiving flasks (Note 1). The vacuum-take-off adapter is attached to a calcium chloride drying tube which is connected to a water aspirator, and the flask is charged with 35.2 g (28.6 mL, 0.40 mol) of pyruvic acid (Note 2). The pyruvic acid is stirred at room temperature as 46.4 g (36.1 mL, 0.40 mol) of α,α-dichloromethyl methyl ether (Note 3) is added slowly over 30 min. Evolution of hydrogen chloride begins after a few minutes. When the addition is complete, the dropping funnel is removed and replaced by a glass stopper. The solution is stirred and heated at 50°C in an oil bath for 30 min (Note 4) while a few drops of methyl formate are collected as the first fraction (Note 5). The condenser is then cooled to –30°C (Note 6) and the receiving flasks are cooled to –50°C with chilled acetone. The aspirator is turned on and the pressure is adjusted to 190 mm. With the oil bath at 50°C, a second fraction, bp 25–35°C (190 mm), is collected. As soon as the head temperature begins to drop, the pressure is reduced to 120 mm and the temperature of the oil bath is raised slowly to 75°C. A third fraction, bp 35–40°C (120 mm), consisting mainly of pyruvoyl chloride is collected (Note 7) and (Note 8). The second and third fractions are combined to give 33–41 g of a mixture of pyruvoyl chloride and methyl formate, which is redistilled through a 1.4- by 18-cm vacuum-jacketed Vigreux column (Note 1). The condenser and the receiving flasks are cooled to –5°C with chilled acetone. The first fraction, weighing 2.3–11.4 g and consisting mainly of methyl formate, is collected at 25–30°C (190 mm) with an oil bath temperature of 60°C. When the pressure is reduced to 120 mm and the oil bath is maintained at 60°C, 18.6–21.2 g (44–50%) of pyruvoyl chloride, bp 43–45°C (120 mm), distills into the receiver as a light yellow liquid, n_D^{20} 1.4165 (Note 9) and (Note 10).

2. Notes

1. The glassware was dried for 16 hr in an oven at ca. 125°C and assembled while still warm. The checkers used a 27-cm Vigreux column insulated with glass wool instead of the vacuum-jacketed column.
2. Pyruvic acid, supplied by Aldrich Chemical Company, Inc., was freshly distilled: bp 59–62°C (14 mm).
3. α,α-Dichloromethyl methyl ether was purchased from Aldrich Chemical Company, Inc., and redistilled prior to use: bp 83–84°C. The reagent may also be prepared from methyl

formate and phosphorus pentachloride.[2] Unlike chloromethyl methyl ether and bis (chloromethyl) ether, α,α-dichloromethyl methyl ether is reported to have no significant carcinogenic activity.[3] However, as a precaution, the compound should be handled with care in a well-ventilated hood.
4. At this temperature the intermediate, chloromethoxymethyl pyruvate, decomposes to pyruvoyl chloride and methyl formate.[4]
5. The submitters made no effort to collect methyl formate quantitatively. The checkers did not observe the formation of any condensate at this point.
6. This was accomplished by the checkers by passing acetone chilled with dry ice slowly through the condenser jacket. The coolant was contained in a 1-L separatory funnel which was connected to the condenser inlet with a section of Tygon tubing. The effluent was collected in a beaker and periodically returned to the separatory funnel reservoir.
7. Fractions 2 and 3 weighed 10.1–13.4 and 23.6–30.0 g, respectively. Proton NMR spectra of fraction 2 indicated a composition of 70–84% of methyl formate, 16–20% of pyruvoyl chloride, and 0–10% of unreacted starting materials. The composition of fraction 3 was 21–28% of methyl formate, 60–70% of pyruvoyl chloride, and 1–20% of starting materials. The two fractions collected by the checkers boiled at 25–26°C (190 mm) and 40–46°C (120 mm).
8. For some reactions, such as simple esterification, it is not necessary to distill the acid chloride. The crude reaction mixture may be used provided the hydrogen chloride present is neutralized with an appropriate base.[5]
9. The submitters found that pyruvoyl chloride may be stored at −20°C in carbon tetrachloride solution or as the pure liquid in a sealed tube.
10. The product obtained by the checkers boiled at 48–51°C (120 mm) and was contaminated with ca. 5–10% of methyl formate and unreacted starting materials. The spectral properties of the product are as follows: IR (liquid film) cm^{-1}: 2900 (w), 1770 (s, broad), 1415 (m), 1355 (s), 1195 (s), 1130 (m), 1095 (m), 1005 (s), 875 (s); ^{1}H NMR ($CDCl_3$) δ: 2.51 (s, 3 H). The compound may be characterized as the *p*-nitroanilide derivative.[6]

3. Discussion

Most of the conventional reagents for the synthesis of acid chlorides from carboxylic acids are unsatisfactory for the preparation of α-keto acid chlorides. For example, the reaction of pyruvic acid with phosphorus halides does not give pyruvoyl chloride[7] whereas the use of phosgene[8] or oxalyl chloride[9,10] affords ether solutions of the acid chloride in low yield. Recently a useful preparation of pyruvoyl chloride from trimethylsilyl pyruvate and oxalyl chloride has been described.[11]

The use of α,α-dichloromethyl alkyl ethers for the conversion of carboxylic acids to acid chlorides was first reported by Heslinga et al. in 1957.[4] The submitters have found that the readily available α, α-dichloromethyl methyl ether[2] is the reagent of choice for the preparation of pyruvoyl chloride.[6] This simple and economical procedure has been used in other laboratories,[5,12,13] and the submitters have applied the method to the preparation of three other α-keto acid chlorides: 2-oxobutanoyl chloride (32%), 3-methyl-2-oxobutanoyl chloride (10%), and phenylglyoxylyl chloride (78%).[6]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrogen chloride (7647-01-0)

ether (60-29-7)

phosphorus pentachloride (10026-13-8)

carbon tetrachloride (56-23-5)

acetone (67-64-1)

phosgene (75-44-5)

methyl formate (107-31-3)

bis(chloromethyl) ether (542-88-1)

chloromethyl methyl ether (107-30-2)

Pyruvic acid (127-17-3)

oxalyl chloride (79-37-8)

phenylglyoxylyl chloride (532-27-4)

α,α-dichloromethyl methyl ether (4885-02-3)

Pyruvoyl chloride, Propanoyl chloride, 2-oxo- (5704-66-5)

chloromethoxymethyl pyruvate

trimethylsilyl pyruvate

2-oxobutanoyl chloride

3-methyl-2-oxobutanoyl chloride

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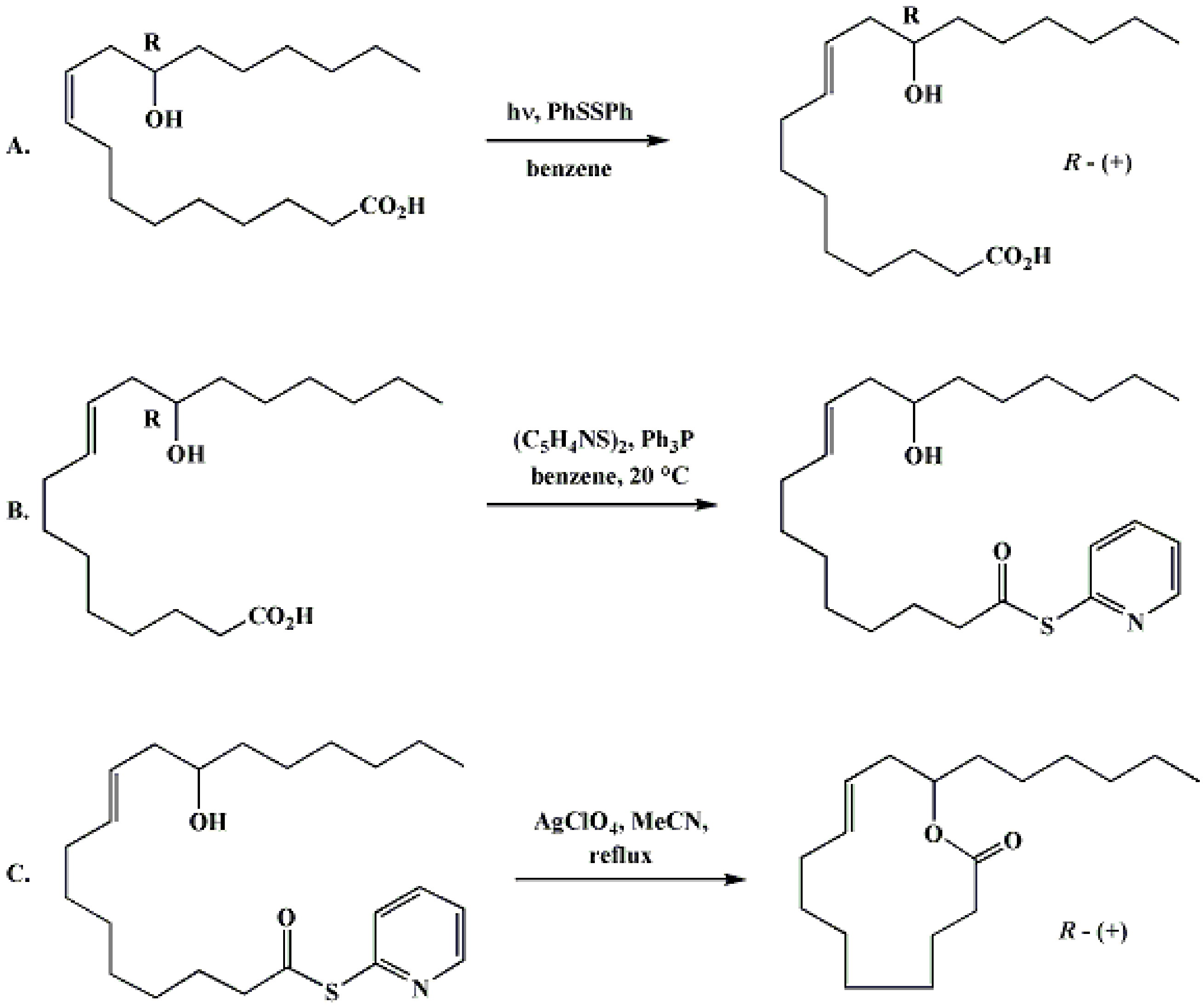
Organic Syntheses, CV 7, 470

RICINELAIDIC ACID LACTONE

[9-Octadecenoic acid, 12-hydroxy-, [(+)-(*R*)-*trans*]-, lactone]



Submitted by Adolf Thalmann, Konrad Oertle, and Hans Gerlach[1].
Checked by James R. Pribish and Edwin Vedejs.

1. Procedure

A. *Ricinelaidic acid*. Ricinoleic acid (Note 1) (39.75 g, 0.106 mol) and 586 mg (2 mol %) of diphenyl disulfide dissolved in 1000 mL of hexane are placed in a photochemical reactor (Note 2) and irradiated for 3 hr with a Philips HP(L) 250-W medium-pressure mercury lamp. After irradiation the solvent is removed under reduced pressure and the semisolid residue is recrystallized from 185 mL of hexane to yield 11.3 g of crude ricinelaidic acid, mp 39–43°C. The irradiation is repeated with the mother liquor under the same conditions to yield, after removal of the solvent and recrystallization of the residue from 135 mL of hexane, an additional 7.2 g, mp 38–42°C; total yield of crude ricinelaidic acid is 18.5 g (58%). The product after recrystallization from 220 mL of hexane weighs 15.6 g (49%), mp 43–45°C, and is suitable for the following step. Repeated recrystallization from hexane yields ricinelaidic acid with mp 51.0–51.5°C (Note 3) and (Note 4).

B. *Ricinelaidic acid S-(2-pyridyl)carbothioate.* In a dry, stoppered, 10-mL flask containing a magnetic

stirring bar are placed 360 mg (1.2 mmol) of ricinelaidic acid (see above), 308 mg (1.4 mmol) of 2,2'-dipyridyl disulfide (Note 5), 1 mL of benzene, and 367 mg (1.4 mmol) of triphenylphosphine, and the mixture is stirred for 30 min. The resulting slurry is then dissolved in 55 mL of dry acetonitrile (Note 6).

C. *Ricinelaidic acid lactone*. Dry acetonitrile (100 mL), 3.5 mL of 1 *M* silver perchlorate in toluene (Note 7) and (Note 8), and a magnetic stirring bar are placed in a 500-mL flask equipped with a reflux condenser that carries a Hershberg dropping funnel. The solution is heated in an oil bath so that the boiling acetonitrile returns from the condenser at the rate of 5–10 drops per second (Note 9). Then the acetonitrile solution of the ricinelaidic acid *S*-(2-pyridyl)carbothioate is added dropwise during 1 hr through the condenser to the magnetically stirred refluxing silver perchlorate solution (Note 9). The slightly turbid mixture is boiled for an additional 15 min and the solvent is removed under reduced pressure in a rotary evaporator. The residue is diluted with 30 mL of 0.5 *M* potassium cyanide solution and the mixture containing suspended solids is extracted with three 50-mL portions of benzene. The benzene extracts are washed with 30 mL of water, dried with anhydrous magnesium sulfate, and filtered, and the solvent is removed under reduced pressure. Crude product is obtained as an oil (710 mg). It can be purified by chromatography on 40 g of silica gel (Note 10) with benzene as eluant. Fractions of 10 mL are collected at 30-min intervals. Fractions 7–19 contain 283–296 mg (84–88%) of ricinelaidic acid lactone (Note 11).

2. Notes

1. Technical-grade (80%) ricinoleic acid was obtained from Fluka AG Buchs, Switzerland or from Tridom Chemicals, Inc. Saponification of methyl ricinoleate[2] also gives suitable material.
2. The photochemical reactor used is quite similar to the one described in *Org. Synth., Coll. Vol. V* **1973**, 298.
3. The purity of the products has been checked by capillary gas liquid chromatography of the corresponding methyl ester obtained with ethereal diazomethane solution (Carlo Erba Fractovap 20-m glass capillary coated with UCON HB at 160°C). Ricinelaidic acid, mp 49–50°C, contains 4%, that with mp 51.0–51.5°C, less than 1% of ricinoleic acid. Submitters obtained higher yields (58%, mp 49–50°C), perhaps due to better quality starting material.
4. (+)-(*R*)-Ricinelaidic acid, mp 51.0–51.5°C, has an optical rotation of $[\alpha]_D$ +6.6° (C_2H_5OH, *c* 10).
5. 2,2'-Dipyridyl disulfide obtained from Fluka AG, Buchs, Switzerland, was recrystallized from hexane (30 mL/g) to yield a suitable product, mp 58–59°C.
6. Commercially available acetonitrile is distilled over phosphorus pentoxide.
7. Silver perchlorate monohydrate (9 g) (obtained from Fluka AG) is suspended in 110 mL of toluene together with a Teflon-coated magnetic stirring bar. The solution is magnetically stirred and heated in an oil bath until 70 mL of toluene has distilled.
8. The silver perchlorate solution may be substituted by 8.5 mL of 0.4 *M* silver trifluoromethanesulfonate (Fluka) in toluene.
9. This reflux rate is crucial for predilution of the carbothioate in the condenser. Lower reflux rates require an accordingly slower addition of the *S*-(2-pyridyl)carbothioate during 2–4 hr.
10. Silica gel 60 Merck in a 2.5-cm-diameter column was used.
11. The product distills at 110°C (0.01 mm) in a Kugelrohr distillation apparatus and has an optical rotation of $[\alpha]_D$ +42° ($CHCl_3$, *c* 1).

3. Discussion

The silver ion-promoted lactonization of hydroxy-*S*-(2-pyridyl)carbothioates was introduced by the submitters[3] as a mild method for the synthesis of naturally occurring macrolides as, for example, nonactin[4] and recifeiolide[5] from the corresponding hydroxy acids. If the method of Mukaiyama et al.[6] is used for the formation of the *S*-(2-pyridyl)carbothioate, no protection of the hydroxyl group is needed in this step. The cited examples show that silver ion-promoted lactonization can be used to effect ring closure of base-sensitive and unsaturated acid-sensitive hydroxy acids in good yield.

Similar methods to effect lactonization have been proposed by Corey et al.[7] and Masamune et al.[8] The first consists of prolonged heating of hydroxy-*S*-(2-pyridyl)carbothioates in boiling xylene; the second is the mercury trifluoroacetate-promoted cyclization of a hydroxy-*S*-*tert*-butyl carbothioate.

Ricinelaidic acid was selected for the submitted procedure because it has a moderately complex structure and can be prepared easily from commercially available technical grade ricinoleic acid. This conversion represents an example of the facile cis–trans interconversion of olefins[9] caused by photochemically generated phenylthiyl radicals leading to the thermodynamic equilibrium.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 87

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

2,2'-dipyridyl disulfide

Benzene (71-43-2)

acetonitrile (75-05-8)

potassium cyanide (151-50-8)

toluene (108-88-3)

xylene (106-42-3)

magnesium sulfate (7487-88-9)

ricinoleic acid

methyl ricinoleate (141-24-2)

Diazomethane (334-88-3)

hexane (110-54-3)

triphenylphosphine (603-35-0)

diphenyl disulfide (882-33-7)

phosphorus pentoxide (1314-56-3)

Ricinelaidic acid lactone, 9-Octadecenoic acid, 12-hydroxy-, [(+)-(R)-trans]-, lactone (79894-06-7)

Ricinelaidic acid, (+)-(R)-Ricinelaidic acid (540-12-5)

silver perchlorate (7783-93-9)

Silver perchlorate monohydrate (14242-05-8)

silver trifluoromethanesulfonate (2923-28-6)

Ricinelaidic acid S-(2-pyridyl)carbothioate (100819-69-0)

hydroxy-S-tert-butyl carbothioate

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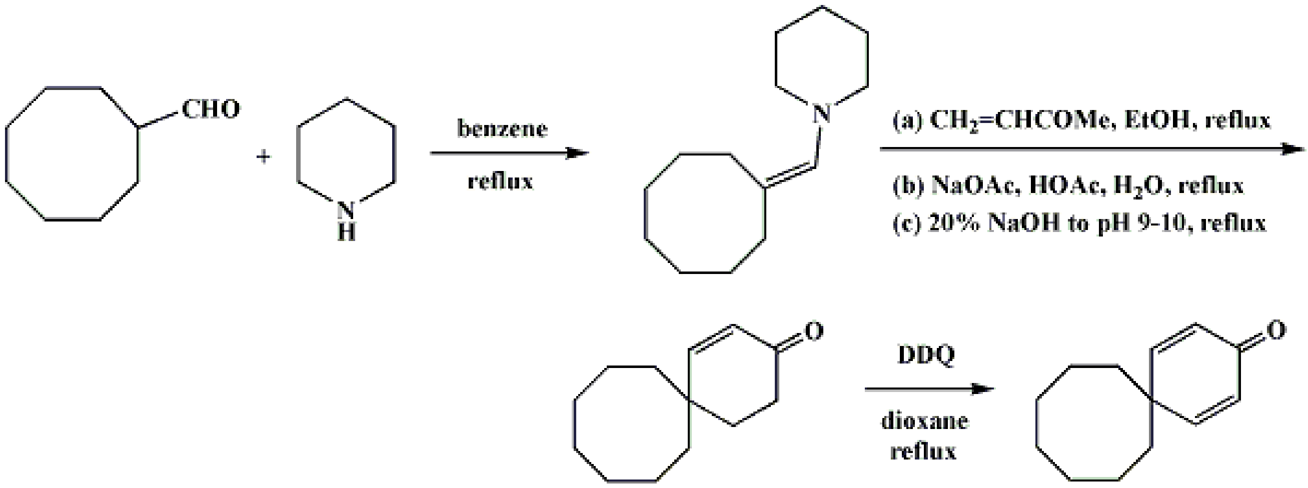
Organic Syntheses, CV 7, 473

SPIRO[5.7]TRIDECA-1,4-DIEN-3-ONE



Submitted by Vinayak V. Kane and Maitland Jones Jr[1].
Checked by R. V. Stevens and R. P. Polniaszek.

1. Procedure

Caution! The following reactions should be performed in an efficient hood to protect the experimentalist from noxious vapors (piperidine and methyl vinyl ketone).

A. *1-(Cyclooctylidenemethyl)piperidine.* Cyclooctanecarboxaldehyde (12.5 g, 0.089 mol) (Note 1) and piperidine (8.35 g, 0.098 mol) are dissolved in 115 mL of toluene and placed in a 250-mL, one-necked flask equipped with a magnetic stirring bar and Dean-Stark water separator, on top of which is a condenser fitted with a nitrogen-inlet tube. The reaction mixture is placed under a nitrogen atmosphere, then brought to and maintained at reflux with stirring for 6 hr, at which time the theoretical amount of water (1.75 mL) has been collected. The reaction mixture is cooled and fractionally distilled under reduced pressure (Note 2); toluene and excess piperidine are removed at 40°C (0.5 mm), and the enamine product is distilled as a colorless liquid to yield 17.30 g (0.084 mol, 93.6%) of 1-(cyclooctylidenemethyl)piperidine, bp 81–83°C (0.5 mm).

B. *Spiro[5.7]tridec-1-en-3-one.* A dry, 1-L, three-necked flask is equipped with a Teflon stirring bar, condenser, pressure-equalizing dropping funnel, and nitrogen-inlet tube. To this flask are introduced absolute ethanol (460 mL) (Note 3) and 1-(cyclooctylidenemethyl)piperidine (17.3 g. 0.084 mol). After the solution has been stirred for 5 min, methyl vinyl ketone (6.44 g, 0.092 mol) (Note 4) is added dropwise over a period of 5 min. The solution is refluxed for 20 hr using a heating mantle. The mixture is cooled and anhydrous sodium acetate (15.0 g), acetic acid (25.5 mL), and water (46 mL) are added. The mixture is brought to and maintained at reflux for 8 hr. The heat is removed and the solution is cooled with ice water; aqueous sodium hydroxide (20% solution, approximately 65 mL) is added until pH 9–10 is attained. The solution is refluxed for another 15 hr; at the end of this period the reaction mixture is cooled. The reaction mixture (600 mL) is divided equally into two 2-L separatory funnels and each portion is diluted with 600 mL of ice-cold water. Each separatory funnel is extracted with ether (3 × 125 mL). The ether extract is washed successively with aqueous 5% hydrochloric acid (125 mL) and saturated brine (3 × 170 mL), dried over anhydrous magnesium sulfate, and filtered. The solvent is removed on a rotary evaporator and the product is distilled under vacuum (Note 5) as a colorless liquid to yield 7.05–7.75 g (44–49%) of spiro[5.7]tridec-1-en-3-one, bp 95–125°C (0.5 mm) (Note 6).

C. *Spiro[5.7]trideca-1,4-dien-3-one.* Spiro[5.7]tridec-1-en-3-one (3.63 g, 0.0189 mol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (8.90 g, 0.0392 mol) (Note 7) are dissolved in 50 mL of dioxane (Note 8) in a 250-mL, one-necked flask equipped with a magnetic stirring bar and fitted with a condenser and drying tube. The reaction mixture is brought to and maintained at reflux with stirring for 6 hr. The mixture is cooled, filtered, and the dioxane removed in a rotary evaporator. The product is taken up in ether (125 mL), and the ether layer is washed with aqueous sodium hydroxide (15%, 4 × 60 mL). The combined aqueous layers are further extracted

with ether (3 × 60 mL). The ether layers are combined and washed with saturated sodium chloride (4 × 60 mL), dried over anhydrous magnesium sulfate and filtered. The solvent is removed on the rotary evaporator to afford a crude yellow liquid. To this crude product are added silica gel (6.25 g) (Note 9) and enough ether to cover the silica gel. The ether is removed with a rotary evaporator so as to absorb the crude product on the silica gel. This silica gel dry powder is poured onto a column (12 in. long × 1.0 in. diameter) containing silica gel (50 g) in hexane. The column is eluted with hexane (70 mL) and then with an increasing amount of ethyl acetate/hexane (Note 10). The desired fractions are combined (Note 11) and solvent is removed under vacuum to afford spiro[5.7]trideca-1,4-dien-3-one (2.65 g, 73.7%), (Note 12).

2. Notes

1. Cyclooctanecarboxaldehyde was obtained from Aldrich Chemical Company, Inc. and used without purification.
2. 1-(Cyclooctylidenemethyl)piperidine is typical of most enamines in that it discolors rapidly when exposed to air and therefore must be handled under an inert atmosphere, preferably nitrogen.
3. Absolute ethanol, distilled and stored over molecular sieves, was used.
4. Methyl vinyl ketone (bp 35–36°C at 140 mm) was obtained from Aldrich Chemical Company, Inc. and distilled immediately before use.
5. A heating mantle was used for this distillation. A forerun of 25–95°C (0.5 mm) was discarded. The exact boiling point of spiro[5.7]tridec-1-en-3-one is 86°C (0.1 mm).
6. The product has the following spectral properties: ^{1}H NMR (CCl_4) δ: 1.62 (s, 14 H), 1.85 (br d, 2 H), 2.25 (m, 2 H), 5.68 (d, 1 H, J = 10 Hz), 6.75 (d, 1 H, J = 10 Hz).
7. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone, supplied by Aldrich Chemical Company, Inc. was used without further purification.
8. Dioxane was refluxed over potassium hydroxide pellets, distilled, and stored over molecular sieves.
9. silica gel analytical reagent (60–200 mesh) was obtained from the J. T. Baker Chemical Co.
10. The silica gel column was eluted starting with hexane (70 mL), followed by 2% ethyl acetate–hexane (100 mL); 5% ethyl acetate–hexane (100 mL); 10% ethyl acetate–hexane (600 mL). The fractions were monitored with 20% ethyl acetate–hexane, using silica 7 GF plates (purchased from Analtech, Inc.), thickness 250 •m, 20 cm long × 5 cm wide. The plates were sprayed with 3% ceric sulfate and heated at 350°C to detect dienone and monoenone. Alternatively, silica gel 60 F-254 plates (purchased from EM Laboratories, Inc.), thickness 25 mm, 20 cm long × 5 cm wide may be used. Detection may be made with ultraviolet light. The ratio of 1 g of crude dienone to 15 g of silica gel is adequate for obtaining pure spiro[5.7]trideca-1,4-dien-3-one.
11. When 20% ethyl acetate/hexane is used, the monoenone, R_f 0.57, and the dienone, R_f 0.47 (Analtech Uniplate–Silica 7 GF), are obtained.
12. The product has the following spectral properties: ^{1}H NMR (CCl_4) δ: 1.65 (s, 14 H), 6.10 (d, 2 H), J = 10 Hz), 6.98 (d, 2 H, J = 10 Hz).

3. Discussion

This procedure illustrates a general method for preparing a wide range of spirocyclohexenones and hence spirocyclohexadienones. A number of intramolecular and intermolecular reactions are known to give spirodienones; however, these methods have limited synthetic application.[2] This procedure is superior[3] to that developed by Bordwell and Wellman[4] for side reactions such as aldol condensation of the aldehyde and polymerization of methyl vinyl ketone are avoided. These spirodienones are useful intermediates in the synthesis of paracyclophanes.[5,6]

Cyclopentanecarboxaldehyde (47%), cyclohexanecarboxaldehyde (41%), 1,2,5,6-tetrahydrobenzaldehyde (43%), cycloheptanecarboxaldehyde (41%), cyclooctanecarboxaldehyde (42%), cycloundecanecarboxaldehyde (36%), 5-norbornene-2-carboxaldehyde (32%), adamantanecarboxaldehyde (20%), and 1,2,3,4-tetrahydro-1-naphthylaldehyde (40%) gave corresponding spiroenones.[7] Spiroenones obtained from cyclohexanecarboxaldehyde, cycloheptanecarboxaldehyde and cyclooctanecarboxaldehyde were converted to the corresponding dienones using the dichlorodicyanobenzoquinone (DDQ). The yields for all three dienones are

in the range of 56 to 58%.

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7. Yields are for the overall conversion.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

brine

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ethyl acetate (141-78-6)

ether (60-29-7)

sodium acetate (127-09-3)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

potassium hydroxide (1310-58-3)

toluene (108-88-3)

piperidine (110-89-4)

magnesium sulfate (7487-88-9)

dioxane (5703-46-8)

hexane (110-54-3)

methyl vinyl ketone (78-94-4)

Cyclohexanecarboxaldehyde (2043-61-0)

Cyclopentanecarboxaldehyde (872-53-7)

ceric sulfate (13590-82-4)

2,3-dichloro-5,6-dicyano-1,4-benzoquinone, dichlorodicyanobenzoquinone

1,2,5,6-tetrahydrobenzaldehyde

Spiro[5.7]trideca-1,4-dien-3-one (41138-71-0)

Cyclooctanecarboxaldehyde (6688-11-5)

1-(Cyclooctylidenemethyl)piperidine (65226-88-2)

Spiro[5.7]tridec-1-en-3-one (60033-39-8)

cycloheptanecarboxaldehyde

cycloundecanecarboxaldehyde

5-norbornene-2-carboxaldehyde

adamantanecarboxaldehyde

1,2,3,4-tetrahydro-1-naphthylaldehyde

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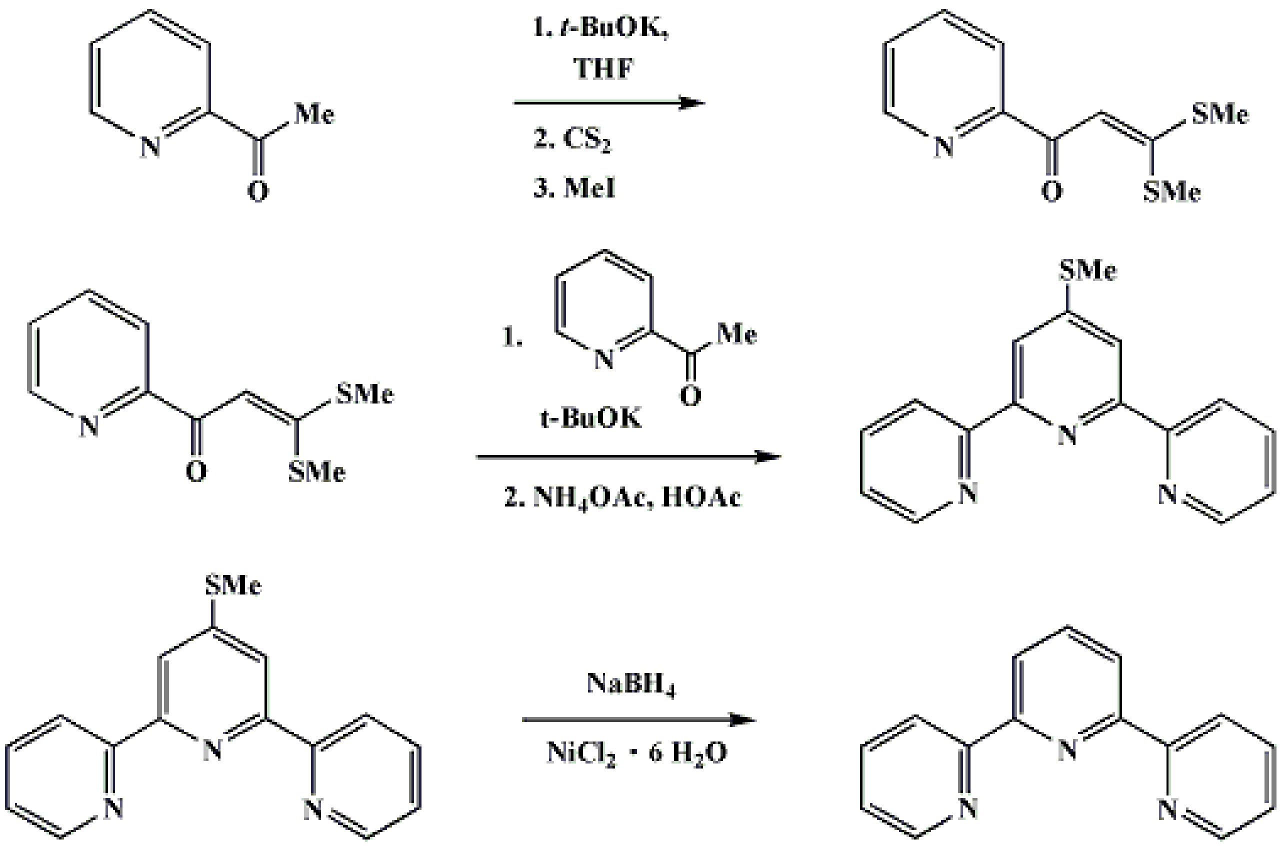
Organic Syntheses, CV 7, 476

2,2' : 6',2' -TERPYRIDINE



Submitted by Kevin T. Potts, Philip Ralli, George Theodoridis, and Paul Winslow[1].
Checked by B. L. Chenard and Bruce E. Smart.

1. Procedure

A. *3,3-Bis(methylthio)-1-(2-pyridinyl)-2-propen-1-one*. A 3-L, three-necked flask is equipped with an efficient mechanical stirrer, pressure-equalizing dropping funnel with needle valve, and a reflux condenser fitted with a nitrogen gas inlet tube that is attached to a mineral oil bubbler. The system is flushed with nitrogen, and while the system is maintained under a static pressure of nitrogen, the flask is charged with 1000 mL of dry tetrahydrofuran (Note 1) and 96.5 g (0.86 mol) of potassium *tert*-butoxide (Note 2). Freshly distilled 2-acetylpyridine (50.0 g, 0.41 mol) (Note 3) is then added dropwise over a period of 5–10 min (Note 4). To the resulting reaction mixture 32.7 g (0.43 mol) of carbon disulfide is added over a period of 30–35 min. After the addition is completed, 122.1 g (0.86 mol) of methyl iodide is added over 1 hr to the viscous, heterogeneous orange reaction mixture. After the tan reaction mixture is stirred for 12 hr at room temperature, it is poured into 2 L of iced water and allowed to stand for 4 hr. The solid that precipitates is collected by filtration and air-dried to give 56 g (61%) of yellow crystals, mp 106–107°C. The filtrate is diluted with water to a total volume of 4 L, and chilled to afford an additional 16.5 g (18%) of product, mp 104–107°C (Note 5).

B. *4'-(Methylthio)-2,2' : 6',2''-terpyridine (Note 6)*. A 1-L, three-necked round-bottomed flask fitted with a mechanical stirrer and a gas inlet tube is flushed with nitrogen and charged with 500 mL of anhydrous tetrahydrofuran and 22.4 g (0.20 mol) of potassium *tert*-butoxide. Freshly

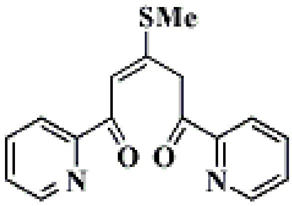
distilled 2-acetylpyridine (12.1 g, 0.10 mol) (Note 3) is added, the solution is stirred for 10 min, and 22.5 g (0.1 mol) of 3,3-bis(methylthio)-1-(2-pyridinyl)-2-propen-1-one is then added. The mixture is stirred for 12 hr at room temperature, during which time it turns bright red and a red solid precipitates (Note 7). The mixture is next treated with 77 g (1.0 mol) of ammonium acetate and 250 mL of glacial acetic acid. A distillation head fitted with a thermometer is attached to the flask and the tetrahydrofuran is removed by distillation over a 2-hr period. The residual brown solution is chilled to 15°C, treated with 400 g of ice, and allowed to stand for 3 hr. Water (400 mL) is added, the mixture is chilled to 15°C, and the gray material that precipitates is collected by filtration, washed with iced water (3 × 200 mL), and air-dried. The crude product is taken up in 250 mL of boiling ethanol and filtered. The filtercake is rinsed with 50 mL of hot ethanol, and the hot filtrates are combined, diluted with 150 mL of water, concentrated to a volume of 400 mL, and allowed to cool to room temperature. After the mixture is thoroughly chilled in an ice bath, the precipitate is collected by filtration, washed with 50% aqueous ethanol, and dried under reduced pressure (23°C, 0.1 mm) to give 20.6–21.4 g (74–77%) of 4'-(methylthio)-2,2' : 6',2"-terpyridine as gray needles, mp 118–119°C (Note 8). This material is sufficiently pure for use in the following step.

C. *2,2' : 6',2"-Terpyridine*. A 1-L, four-necked flask equipped with a mechanical stirrer, pressure-equalizing dropping funnel, thermometer, and a condenser fitted with a nitrogen gas inlet tube is flushed with nitrogen and charged with 300 mL of ethanol, 5.0 g (0.018 mol) of 4'-(methylthio)-2,2' : 6',2"-terpyridine and 42.8 g (0.180 mol) of finely ground nickel chloride hexahydrate (Note 9). The resultant green heterogeneous mixture is chilled in an ice bath while the system is maintained under a static pressure of nitrogen. To this chilled (0–5°C) mixture, a solution of 20.4 g (0.54 mol) of sodium borohydride in 128 mL of 40% aqueous sodium hydroxide is added dropwise over 4 hr (Note 10). After the addition is completed and the evolution of hydrogen subsides, the dark reaction mixture is refluxed for 12 hr. The hot mixture is then filtered through a Celite pad, and the pad is washed with hot ethanol (3 × 100 mL). The filtrates are combined and evaporated to dryness under reduced pressure to yield a gray solid residue (Note 11). This solid is suspended in 300–400 mL of water and chilled in an ice bath for 4 hr. The cold suspension is filtered and the gray solid is air-dried. The crude product is taken up in 100 mL of boiling hexane and filtered. The filtrate is concentrated to 50 mL, chilled in an ice bath, and filtered to give 2.48–2.53 g (59–60%) of 2,2' : 6',2"-terpyridine as cream-colored prisms, mp 84–86°C [lit.[2] mp 85–86°C] (Note 12) and (Note 13). The mother liquor is concentrated to 10 mL to give a second crop of 0.37–0.40 g (8.8–9.5%), mp 81–84°C.

2. Notes

1. The checkers used tetrahydrofuran that was distilled from lithium aluminum hydride *(Caution: See Org. Synth., Coll. Vol. V* ***1973****, 976)* and stored with a chip of sodium metal. Distillation from sodium/benzophenone is preferable.
2. Potassium *tert*-butoxide was obtained from the Aldrich Chemical Company, Inc.
3. The checkers obtained 2-acetylpyridine from the Aldrich Chemical Company, Inc. The submitters thank Reilly Tar & Chemical Corp. for a generous gift of 2-acetylpyridine used in their work.
4. A light yellow solid precipitates during this addition.
5. The product is pure by ^{1}NMR ($CDCl_3$) δ: 2.55 (s, 3 H), 2.65 (s, 3 H), 7.40 (d of d of d, 1 H, *J* = 1.5, 5.6, 7.5), 7.65 (s, 1 H), 7.85 (d of t, 1 H, *J* = 7.5, 2.0), 8.20 (d of t, 1 H, *J* = 7.5, 1.5), 8.65 (d of m, 1 H *J* = 7.5); IR (KBr) cm^{-1}: 1484, 1471. Analytically pure material, mp 108–109°C, may be obtained by recrystallization from ethanol.

6. Recently, it has been shown that this product may be prepared without isolation of the precursors obtained in Step A.[3]
7. This solid is the potassium salt of the enedione intermediate.



8. The checkers also obtained material with mp 116–118°C. The submitters report product of unspecified purity with mp 120–122°C. The material obtained by the checkers shows the following ^{1}H NMR ($CDCl_3$) δ: 2.0 (s, impurity), 2.67 (s, 3 H), 7.30 (d of d of d, 2 H *J* = 1.8, 5.6, 8.0), 7.80 (d of t, 2 H, *J* = 1.8, 8.0), 8.35 (s, 2 H), 8.4–8.78 (m, 4 H). Mass spectrum *m/e* calculated: 279.0830. Found: 279.0815. IR (KBr) cm^{-1}: 1558, 1390. The combustion analyses for the products obtained by the checkers were within accepted limits for H, but off about 2% for C, and 0.6–0.8% for N.
9. Nickel chloride hexahydrate was obtained from the Fisher Scientific Company.

10. This reaction, which generates nickel boride,[4] is exothermic and evolves hydrogen. Frothing is prevented by keeping the reaction mixture at 0–5°C during addition of the sodium borohydride.
11. The submitters report obtaining tan material.
12. This material is analytically pure. Anal. calcd. for $C_{15}H_{11}N_3$:C, 77.23;H, 4.75; N, 18.01. Found C: 76.82; H, 4.69; N, 18.17. The product shows ^{1}H NMR ($CDCl_3$) δ: 7.33 (d of d of d, 2 H *J* = 1.5, 5.0, 8.0), 7.86 (d of t, 2 H, *J* = 2.0, 8.0), 7.96 (t, 1 H, *J* = 8.0 H), 8.45 (d, 2 H *J* = 8.0), 8.62 (d, 2 H, *J* = 8.0), 8.71 (d of m, 2 H).
13. The submitters report that 4'-(methylthio)-2,2' : 6',2"-terpyridine also can be conveniently reduced to 2',2" : 6',2"-terpyridine with Raney nickel in ethanol. The checkers found, however, that this procedure invariably gave product contaminated with 4'-ethoxy-2,2' : 6',2"-terpyridine. Raney nickel which was exhaustively washed with water to remove base still gave 15% of this by-product.

3. Discussion

The procedure described here is by far the most efficient synthesis of terpyridine.[5] Previous preparations include the dehydrogenation of pyridine with ferric chloride,[2] the Ullman reaction of 2-bromopyridine and 2,6-dibromopyridine,[6] the action of copper on 2-bromopyridine and 6-bromo-2,2'-dipyridyl,[6] the reaction of iodine or ferric chloride with 2,2'-bipyridyl,[6] and the reaction of 2,2'-bipyridyl with 2-lithiopyridine (40% yield).[7]

Terpyridine is a very effective chelating agent.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium/benzophenone

nickel boride

2',2" : 6',2"-terpyridine

6-bromo-2,2'-dipyridyl

ethanol (64-17-5)

acetic acid (64-19-7)

ammonium acetate (631-61-8)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

nitrogen (7727-37-9)

copper (7440-50-8)

nickel (7440-02-0)

iodine (7553-56-2)

pyridine (110-86-1)

sodium (13966-32-0)

carbon disulfide (75-15-0)

ferric chloride (7705-08-0)

Methyl iodide (74-88-4)

nickel chloride hexahydrate (7791-20-0)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

2-Bromopyridine (109-04-6)

hexane (110-54-3)

sodium borohydride (16940-66-2)

2,2'-bipyridyl (366-18-7)

TERPYRIDINE

2-acetylpyridine (1122-62-9)

3,3-bis(methylthio)-1-(2-pyridinyl)-2-propen-1-one (78570-34-0)

2,6-dibromopyridine (626-05-1)

2-lithiopyridine

potassium tert-butoxide (865-47-4)

2,2' : 6',2' -TERPYRIDINE, 2,2' : 6',2"-Terpyridine (1148-79-4)

4'-(Methylthio)-2,2' : 6',2"-terpyridine (78570-35-1)

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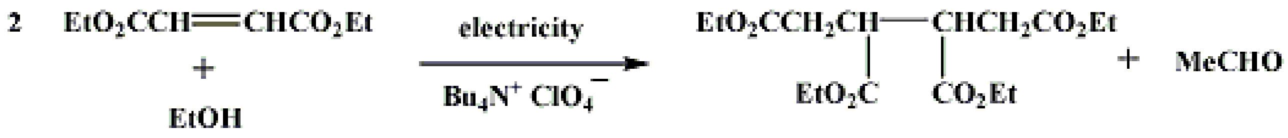
Organic Syntheses, CV 7, 479

ELECTROHYDRODIMERIZATION OF AN ACTIVATED ALKENE: TETRAETHYL 1,2,3,4-BUTANETETRACARBOXYLATE

[1,2,3,4-Butanetetracarboxylic acid, tetraethyl ester]



Submitted by D. A. White[1]
Checked by Carl R. Johnson and Debra L. Monticciolo.

1. Procedure

The cell consists of a commercially available four-necked, 500-mL, round-bottomed flask equipped with a 34/45 standard-taper joint electrode assembly (Note 1), a 24/40 standard-taper joint purge and vent assembly, a mercury pool cathode (Note 2), a cathode contact (Note 3), a magnetic stirring bar (Note 4), and thermometer (inserted in a 10/18 standard-taper joint neck). The two platinum anodes of the electrode assembly (Note 1) are positioned in a horizontal plane ca. 1 cm above (Note 4) the mercury (cathode) surface.

To the cell are added diethyl fumarate (172 g, 1.0 mol) (Note 5), absolute ethanol (200 mL), and tetrabutylammonium perchlorate (3.41 g, 0.1 mol) (Note 6). The mixture is allowed to stand for 0.5 hr to allow complete dissolution of the tetrabutylammonium perchlorate. The cell is placed in a flowing-water bath in a hood.

The solution is electrolyzed with continuous magnetic stirring and nitrogen purging at a constant current (Note 7) until the theoretical quantity of electricity (1.0*F* 1e⁻ per mole of diethyl fumarate) has been passed. The rate at which the cooling water in the bath flows is adjusted to maintain the electrolyte solution at 35°C during the first 2 hr of the electrolysis. It is then kept constant for the remainder of the electrolysis. After conditions have stabilized (ca. 1–2 hr of electrolysis), the reaction does not need constant attention, and may be allowed to run overnight.

The reaction mixture is transferred to a 2-L, round-bottomed flask with ethanol washing and the ethanol is removed by rotatory evaporation. Diethyl ether (1 L) is added to precipitate the electrolyte salt, which is collected by filtration and washed with ether. The crude electrolyte is obtained as a white solid (32–32.5 g, theory 34.1 g). The filtrate and washings were combined and evaporated to give a viscous brown oil, which was vacuum-distilled through a short Vigreux column (15 cm × 2.5 cm). After a forerun of 70 mL of material boiling below 150°C (0.15 mm), the product (92–96 g, 53–56%), bp 150–155°C (0.1 mm), is collected (Note 8) and (Note 9). The forerun contained diethyl maleate, diethyl fumarate, diethyl succinate, and diethyl ethoxysuccinate. The product is a mixture of diastereomers; on standing some meso isomer, mp 74–75°C, crystallizes.

2. Notes

1. The electrode assembly has been described (see synthesis of dimethyl decanedioate, Note 1 and Figure 1, p. 182). In this case the electrodes have the same polarity and are electrically connected with a platinum wire dipping into the mercury contacts.
2. About 65 mL (860 g) of mercury was used, giving a pool with a surface diameter of ca. 6 cm.
3. A mercury-filled 6-mm o.d. glass tube with a platinum wire sealed through the lower end was used. The tube was bent to fit the contour of the flask. It was connected to the flask through a 24/40 standard-taper joint Teflon thermometer adapter (Ace Glass, Vineland, NJ). Contact to the mercury was made with a platinum wire as shown (Figure 1, p. 183).
4. A 20-cm × 0.5-cm Teflon coated stirring bar was used. This thickness (0.5 cm) is close to the maximum usable with an electrode gap of 1 cm. The rate of stirring was the maximum possible without breaking the mercury surface into droplets.
5. Diethyl fumarate, obtained from Aldrich Chemical Company, Inc., was used without prior purification. The submitters used diethyl maleate.
6. Tetrabutylammonium perchlorate, obtained from Eastman Organic Chemicals, was recrystallized from aqueous methanol (75%) and dried in vacuo.
7. The checkers used a Heath Schlumberger Model SP-2711 (30 V, 3 A) power supply at a current of 1.5 A. The cell voltage, initially 25 V, slowly rose to 30 V at the end of the electrolysis and the current dropped to ca. 1 A. The electrolysis required 17–24 hr. The submitters used a current of 1.0 A.
8. The submitters reported a yield of 135 g (78%). In part the reduced yields found by the checkers were caused by mechanical losses during distillation.
9. The product showed ^{1}H NMR ($CDCl_3$) δ: 1.25 (t, 12 H, CH_3), ca. 2.6 (m, 4 H,-$COCH_2$), ca. 3.3 (m, 2 H, C*H*), 4.2 (two overlapping q, 8 H, OCH_2). Analysis calculated for $C_{16}H_2O_8$: C, 55.5; H, 7.6%. Found: C, 55.5; H, 7.8. Molecular weight calculated: 346. Found (osmometrically in $CHCl_3$): 340, 338.

3. Discussion

This synthesis is an example of electrohydrodimerization of activated alkenes, the scope and mechanism of which have been recently reviewed.[2,3] The individual reactions combining to give the overall result. are the cathodic reduction of the alkene to a dimer dianion (in the general case there are two major mechanisms by which the dianion may be formed and these are discussed in the references cited[2,3]), the protonation of the dianion by ethanol, and the anodic oxidation of ethanol.

In addition to providing an anode reaction (a suitable reaction at the "other" electrode is a necessity in any electrochemical reaction), reaction (4) also maintains the pH constant by producing protons to neutralize the ethoxide ions originating from reaction (3).

The present synthesis is an adaptation of a previously reported synthesis[4] in a divided cell (i.e., separate anode and cathode compartments). The overriding consideration in making this modification has been to simplify the operations involved and render the synthesis more attractive to chemists not well acquainted with electrochemical procedures. The main simplification achieved is that the pH is controlled internally via the anodic generation of protons as noted above (in the reported procedure,[4] this is achieved by periodic addition of acetic acid to the cathode compartment). A further simplification has been to run the reaction with a constant current rather than at controlled cathode potential. After the electrolysis has been initiated, the

reaction requires no special attention. A small price is paid for the simplicity of the present synthesis in that the yield is somewhat lower than that obtained previously.[4] The major by-product formed is diethyl succinate, which results from a 2e⁻ reduction of diethyl fumarate or diethyl maleate: [cf. (2), which consumes 1e⁻ per mole of ester]. The occurrence of reaction (5) leads to incomplete consumption of ester after passage of the theoretical quantity of electricity (there may also be contributions from other sources).

The by-product, diethyl 2-ethoxybutanedioate, may be formed via base-catalyzed reaction in the vicinity of the cathode, where conditions may become quite basic.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

acetic acid (64-19-7)

methanol (67-56-1)

diethyl ether (60-29-7)

mercury (7439-97-6)

platinum (7440-06-4)

diethyl fumarate (623-91-6)

diethyl maleate (141-05-9)

ethoxide

Diethyl succinate (123-25-1)

Dimethyl decanedioate (106-79-6)

Tetraethyl 1,2,3,4-butanetetracarboxylate, 1,2,3,4-Butanetetracarboxylic acid, tetraethyl ester (4373-15-3)

tetrabutylammonium perchlorate (1923-70-2)

diethyl ethoxysuccinate, diethyl 2-ethoxybutanedioate

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Organic Syntheses, CV 7, 482

INDIRECT ELECTROLYSIS: TETRAMETHYL 1,1,2,2-ETHANETETRACARBOXYLATE

[1,1,2,2-Ethanetetracarboxylic acid, tetramethyl ester]

$$2 \quad (MeO_2C)_2CH_2 \xrightarrow[\text{MeOH, NaI}]{\text{electricity}} (MeO_2C)_2CHCH(CO_2Me)_2 \quad + \quad H_2$$

Submitted by Donald A. White[1]
Checked by Carl R. Johnson and Robert C. Elliott.

1. Procedure

The preparation is carried out in a 500-mL, three-necked flask equipped with two graphite rod electrodes (Note 1). To the flask are added 132 g (1.0 mol) of dimethyl 1,3-propanedioate (Note 2), 15 g (0.10 mol) of sodium iodide, and 300 mL of methanol. A thermometer and reflux condenser are attached; the mixture is stirred and the solution formed is heated to 60°C. The heat source is removed. The solution is electrolyzed with a constant current of 2.0 A (Note 3) for 13.5 hr (Note 4) with gentle magnetic stirring. After a few minutes of electrolysis, the electrolyte begins to reflux gently and reflux is maintained throughout the electrolysis period by the heating effect of current passage (Note 5). Small granular crystals of the product begin to separate toward the end of the electrolysis period.

After electrolysis the reaction mixture is allowed to cool to room temperature and is filtered (Note 6). The crystalline residue is washed three times with 100-mL portions of methanol, dried by suction on the filter, and finally dried under vacuum. The product (88.4–91 g, 67–69%) is obtained as a white solid, mp 134–135°C.

2. Notes

1. The electrodes are 12 × in. graphite rods such as those used by glassblowers in shaping softened glass. They are attached as shown on page 183 via thermometer adaptors (Ace Glass Company, Vineland, NJ) and a specially made glass adaptor having two 10/18 and one 34/45 standard-taper joints. The electrodes should extend as far as possible into the electrolyte without interfering with the operation of the magnetic stirrer.
2. Dimethyl 1,3-propanedioate (dimethyl malonate) was obtained from Aldrich Chemical Company, Inc., and used as supplied.
3. A Heath/Schlumberger dc power supply, Model SP-2711, 30 V, 3 A, operating in its constant current mode, was used.
4. The current passed is 1.01*F* (1 faraday = 26.8 A-hr) and this is sufficient to convert 75–80% of the starting material to product. At higher conversions

further oxidation occurs, leading to formation of tetramethyl ethenetetracarboxylate and hexamethyl 1,1,2,2,3,3-propanehexacarboxylate. The latter has solubility properties similar to those of the desired product. The product may be contaminated with the propanehexacarboxylate ester if the reaction is taken to higher conversions.

5. The cell voltage was initially 15 V and rose to 18 V at the end of the electrolysis. The cell voltage should be in the range 15–20 V so that the heat generated can be controlled by reflux. Since the cell voltage changes only slightly during the course of the electrolysis, a constant-voltage power supply could be used.

6. The filtrate contains only 2–5 g of the desired product; recovery is not worthwhile. The filtrate can, however, be reused as the electrolyte for conversion of further propanedioate ester.

7. The product may be recrystallized (from methanol), which gives material with mp 135–136°C.

8. The product gave an acceptable C,H analysis; the molecular weight by osmometry in chloroform was found to be 258 ($C_{10}H_{14}O_8$ in theory 262). The product showed ^{1}H NMR ($CDCl_3$) δ: 3.8, 4.2.

3. Discussion

The propanedioate (malonate) carbanion can be oxidized directly at an anode to give ethanetetracarboxylate esters, presumably via a radical intermediate.[2,3,4] Competing oxidation of solvent leads to a mixture of products[3,4] and for preparative purposes it is advantageous to carry out the reaction via indirect electrolysis as reported here. Indirect electrolysis refers to the continuous generation and regeneration of a reagent at an electrode, which interacts with substrate, as opposed to direct reaction of the substrate at the electrode. In the present case iodine is generated at the anode (1) and reacts with the cathodically generated (2) carbanion as shown (3) to give the desired overall reaction (4):

The present procedure is based on literature reports[5,6] using indirect electrolysis involving electrogenerated halogens. Ethanetetracarboxylate esters have also been prepared by the chemical reaction of propanedioate carbanions with halogens.[7,8,9] The present procedure has the advantage of providing in situ generation of both the carbanion and the halogen from a small amount of added sodium halide. In other work it has been shown that the anodic formation of ethanetetracarboxylate ester can be paired with cathodic conversion of propenoate (acrylate) to hexanedioate (adipate) esters[10,11] In addition to these routes based on propanedioate esters, ethanetetracarboxylate esters have been obtained by electrocarboxylation of *cis*-butenedioate (maleate) esters.[12,13]

14

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Dimethyl 1,3-propanedioate (dimethyl malonate)

methanol (67-56-1)

chloroform (67-66-3)

iodine (7553-56-2)

sodium iodide (7681-82-5)

dimethyl 1,3-propanedioate (108-59-8)

Tetramethyl 1,1,2,2-ethanetetracarboxylate, 1,1,2,2-Ethanetetracarboxylic acid, tetramethyl ester (5464-22-2)

tetramethyl ethenetetracarboxylate (1733-15-9)

hexamethyl 1,1,2,2,3,3-propanehexacarboxylate

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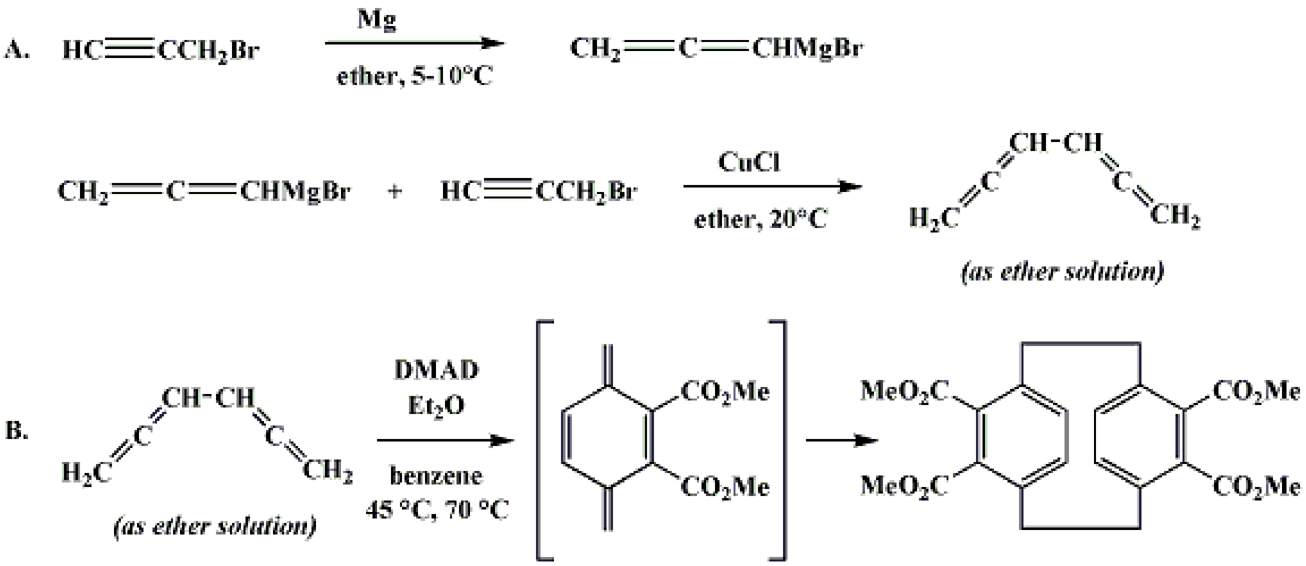
Organic Syntheses, CV 7, 485

DIELS-ALDER REACTION OF 1,2,4,5-HEXATETRAENE: TETRAMETHYL[2.2]PARACYCLOPHANE-4,5,12,13-TETRACARBOXYLATE

[Tricyclo[8.2.2.2^{4,7}]hexadeca-4,6,10,12,13,15-hexaene-5,6,11,12-tetracarboxylic acid, tetramethyl ester]



Submitted by Henning Hopf, Ingrid Böhm, and Jürgen Kleinschroth[1].
Checked by Paul F. Sherwin and Robert M. Coates.

1. Procedure

Caution! Propargyl bromide is poisonous and should be handled in a well-ventilated hood. Benzene has been identified as a carcinogen; OSHA has issued emergency standards for its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A. *1,2,4,5-Hexatetraene in ether solution.* A 2-L, four-necked, round-bottomed flask is equipped with a mechanical stirrer, a reflux condenser fitted with a drying tube containing anhydrous calcium sulfate (Drierite), a dropping funnel, and a thermometer (Note 1). The flask is charged with 0.5 g (0.002 mol) of mercury(II) chloride and 29.2 g (1.2 mol) of magnesium turnings that have been crushed with a mortar and pestle, and the apparatus is flushed with nitrogen while being heated externally with a Bunsen burner to remove traces of moisture. In the cooled flask are placed 160 mL of anhydrous ethyl ether (Note 2) and 7.6 g (5.0 mL, 0.064 mol) of propargyl bromide (Note 3). The ether begins to reflux within 1 min, indicating that formation of the Grignard reagent has begun (Note 4). The mixture is cooled to 5° in an ice-salt bath and stirred vigorously as a solution of 135 g (89 mL, 1.13 mol) of propargyl bromide in 560 mL of anhydrous ether is added. The addition rate is adjusted so as to maintain the internal temperature between 5° C and 10°C (Note 5). The cooling bath is removed, and the dark green mixture is stirred for 45 min at room temperature (Note 6). A 2-g (0.02 mol) portion of finely pulverized, dry copper(I) chloride (Note 7) is added, and the mixture, which becomes a chocolate-brown color after 2–3 min, is stirred for 15 min at room temperature and cooled again to 5°C with either an ice-water bath or an ice-salt bath. Stirring is continued while a solution of 128 g (85 mL, 1.08 mol) of propargyl bromide in 100 mL of ether is added at a rate such that the internal temperature is kept at ca. 20°C (Note 8). The mixture becomes almost black, and two phases are discernible when the stirrer is stopped, especially toward the end of the addition. The cooling bath is removed and stirring is continued for 15 min at room temperature to complete the dimerization. The

reaction mixture is cooled to 0°C with an ice-salt bath and stirred vigorously as 200 mL of 1 *N* aqueous hydrochloric acid is added (Note 9). The two-phase mixture is warmed to room temperature, and another 100 mL of 1 *N* hydrochloric acid is added. The ether layer is separated and washed with three 100-mL portions of water (Note 10). A few crystals (0.2–0.5 g) of hydroquinone are added to stabilize the reddish solution, which is then dried with anhydrous potassium carbonate. The drying agent is filtered, and the filtrate is concentrated to a volume of ca. 400 mL by distillation under nitrogen at atmospheric pressure with a 40-cm Vigreux column and a heating bath kept at 40–45°C. The concentrate is purified by vacuum transfer (Note 11), and the now colorless solution, which contains ca. 25–30 g (30–36%) of 1,2,4,5-hexatetraene, is stabilized by adding another 0.1–0.5 g of hydroquinone (Note 12) and (Note 13).

B. *Tetramethyl[2.2]paracyclophane-4,5,12,13-tetracarboxylate*. The 1-L flask from Step A containing ca. 25–30 g (0.32–0.38 mol) of 1,2,4,5-hexatetraene in ether solution is equipped with a magnetic stirring bar and a 40-cm Vigreux column for distillation at atmospheric pressure. A solution of 69.4 g (60 mL, 0.49 mol) of dimethyl acetylenedicarboxylate (Note 14) in 220 mL of benzene (Note 15) is added. The resulting solution is stirred and heated at 45°C for 5–7 hr and at 70°C for 20 hr (Note 16). The ether distils slowly at 45°C and rather rapidly at 70°C, the color of the solution changes from yellow to red–orange, and a white solid is gradually deposited. The mixture is cooled and filtered. Recrystallization of the solid from 600–800 mL of toluene affords 27–35 g of white crystalline product, mp 201.5–203°C. The original benzene filtrate and the toluene mother liquor, when evaporated to dryness and crystallized separately from 40–70 mL of toluene, provide 3–4 g and 2–3 g of product, respectively, having essentially the same melting point. The combined yield is 33–41 g (40–50% based on 1,2,4,5-hexatetraene) (Note 17) and (Note 18).

2. Notes

1. The checkers used a three-necked flask equipped with a Claisen adapter. The straight branch of the adapter was fitted with a thermometer, and the curved branch was mounted with a condenser bearing a nitrogen inlet. After the nitrogen-filled apparatus had been flamed dry and cooled, the dropping funnel was capped with a rubber septum. A nitrogen atmosphere was maintained in the apparatus at all times, and liquids were placed in the dropping funnel via syringe.
2. The checkers dried the ether by distillation from sodium benzophenone ketyl immediately before use.
3. Propargyl bromide may be purchased from Fluka. The reagent may also be prepared by the procedure of Gaudemar.[2] Propargyl bromide (97%) supplied by Tridom Chemical Inc. was dried by the checkers prior to use by stirring over Linde-type 4A molecular sieves under a nitrogen atmosphere for 2–3 days. The volumetric quantities given in the procedure are for 97% propargyl bromide, which has a density of 1.56 at 20°C according to a catalog from Tridom Chemical Inc.
4. The submitters initiated Grignard formation by adding a few milliliters of a solution of 142.8 g (1.2 mol) of propargyl bromide in 560 mL of anhydrous ether. If the reaction does not begin, they suggest that the flask be heated with a warm stream of air from a "heat gun."
5. The checkers found that the addition time varied from ca. 1 to 4 hr, depending on the temperature of the cooling bath and the extent to which it was stirred.
6. Some unreacted magnesium turnings remain in the flask at this time. However, the submitters recommend against heating the mixture to achieve further conversion, since the initially formed allenylmagnesium bromide will isomerize to 1-propynylmagnesium bromide.
7. The submitters used copper(I) chloride purchased from E. Merck, Darmstadt, which had a greenish tinge attributed to slight contamination by copper(II) salts. The reagent used by the checkers was supplied by J. T. Baker Chemical Company.
8. The checkers, using an ice-salt cooling bath, maintained the internal temperature between 7°C and 12°C. The addition time varied from 15 to 75 min depending on the efficiency of the cooling.
9. The internal temperature was maintained at 10–15°C by the submitters and 5–12°C by the checkers. The time required for the hydrolysis was reduced by the checkers by prior chilling of the hydrochloric acid.
10. Since the product is unstable to oxygen, the checkers tried to keep the ethereal solution under a nitrogen atmosphere during transfer and extractions.

11. The crude solution of 1,2,4,5-hexatetraene may also be employed in part B. However, yields are lower, and the purification of the product becomes tedious owing to the presence of insoluble by-products. The vacuum transfer may be accomplished with a simple distillation apparatus equipped with a magnetic stirring bar and a 1-L, round-bottomed flask as receiver in the following manner. The crude ethereal solution is chilled to a glass with a liquid nitrogen bath, and the apparatus is evacuated to a pressure of 1–3 mm with a vacuum pump. The apparatus is isolated from the vacuum pump, the cooling bath is removed, and the ether glass is allowed to warm until it becomes mobile. The freeze–evacuate–thaw cycle is repeated two more times to complete the degassing process. The solution is again chilled with liquid nitrogen, the apparatus is evacuated to 1–3 mm, and the system is then isolated from the vacuum pump. The receiving flask is cooled with a liquid nitrogen or dry ice-isopropyl alcohol bath, the cooling bath is removed from the distilling flask, and the ether solution is stirred and allowed to warm to room temperature in the closed system. Once the ether solution becomes mobile, the flask may be warmed cautiously with a water bath at room temperature to speed up the vacuum transfer.

12. Pure 1,2,4,5-hexatetraene polymerizes readily when exposed to air at room temperature. However, solutions of the purified compound are stable for months at 0°C, especially if protected by an inert gas. Contact with air should be minimized to avoid inducing polymerization.

13. The amount of 1,2,4,5-hexatetraene in solution was estimated by the submitters from ^{1}H NMR spectra and GC analyses. The major product of the dimerization reaction is 1,2-hexadien-5-yne. The submitters have shown that this hydrocarbon does not interfere with the cycloaddition in Step B.

14. Dimethyl acetylenedicarboxylate is supplied by Aldrich Chemical Company, Inc.; E. Merck, Darmstadt; and Fluka. The reagent, bp 110–112°C (15 mm), was distilled before use.

15. The checkers carried out one run on one-tenth scale using toluene instead of benzene in part B. The yield of tetramethyl[2.2]paracyclophane-4,5,12,13-tetracarboxylate, mp 202.5–204°C, was 2.91 g (35% based on 1,2,4,5-hexatetraene in part A).

16. The conditions and isolation procedure given are those used by the checkers. The submitters heated the solution first to 45°C, after which the temperature was gradually increased to 70°C over several hours. The solution was then heated at 70°C overnight, and the solvents were removed by rotary evaporation. The semisolid, yellow-orange residue was recrystallized from benzene or methanol. Concentration of the mother liquor afforded additional crops of crystalline product. The total yield of the tetraester was 25–30 g (30–36% based on 1,2,4,5-hexatetraene), mp 206–207°C.

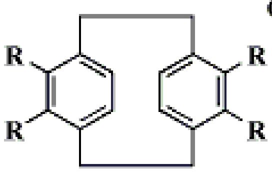
17. The melting point of the product obtained by the checkers increased only slightly to 202–203.5°C on recrystallization from toluene, benzene, or methanol. The once-recrystallized product was analyzed by the checkers. Anal. calcd. for $C_{24}H_{24}O_8$: C, 65.45; H, 5.49. Found: C, 65.51; H, 5.49. The submitters obtained material of analytical purity by sublimation at 180°C (0.001 mm).

The spectral properties of the product are as follows: IR (potassium bromide) cm^{-1}: 1715, 1260, 1195, 1125, 1005, 870; ^{1}H NMR ($CDCl_3$) δ: 2.93–3.43 (nine-line *AA'BB'* multiplet, 8, two CH_2CH_2), 3.83 (singlet, 12, four CO_2CH_3), 6.80 (singlet, 4, four aryl C*H*); proton-decoupled ^{13}C NMR ($CDCl_3$) δ (assignment): 33.27 (CH_2), 52.25 (OCH_3), 131.51 (CCO_2CH_3), 134.98 (CCH_2), 139.68 (CH), 168.40 (CO_2CH_3).

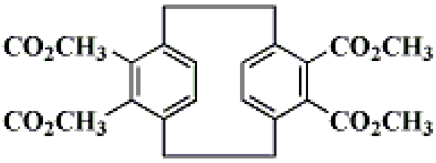
TABLE I

[2.2]Paracyclophanes Prepared by Diels-Alder Reaction of Disubstituted Acetylenes with 1,2,4,5-Hexatetraene[3, 4]

R	mp (°C)	Yield (%)

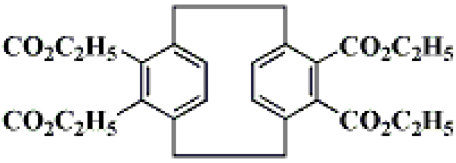


CO_2CH_3



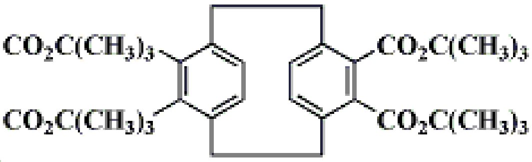
203 47

$CO_2C_2H_5$



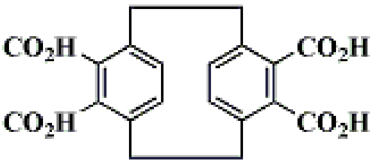
133.5 30

$CO_2C(CH_3)_3$



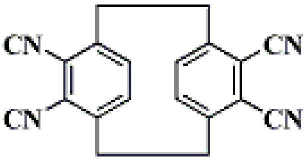
205 20

CO_2H



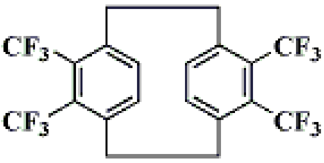
365 (dec) 5

CN



320 (dec) 37

CF_3



174 21

18. The submitters have scaled up this procedure to prepare as much as 60 g of the paracyclophane in one run. However, since the volumes of solvents and flasks are quite large, the operations become rather cumbersome.

3. Discussion

[2.2]Paracyclophanes have been recognized for some time as interesting structures for stereochemical studies and for unusual intra- and intermolecular π-electron interactions.[5; 6; 7; 8; 9; 10,11,12,13] The nonplanar, boatlike benzene rings[14] of these compounds have attracted the attention of numerous synthetic organic chemists[5,6,7,8,9,10,11,12,13] as well as theoreticians[15,16] and spectroscopists.[13,17]

The principal methods used previously for the preparation of [2.2]paracyclophanes have been reviewed several times[5,6,7,8,9,10,11,12,13] and include (1) intramolecular Wurtz coupling of appropriately substituted dihalides at high dilution; (2) ring contraction of cyclophanes having larger bridges by sulfone pyrolysis (the most versatile procedure currently known), Stevens rearrangement, and other extrusion reactions; and (3) the dimerization of transient *p*-quinodimethane intermediates (*p*-xylylenes), usually generated from *p*-xylene precursors by elimination reactions.[18] A *p*-quinodimethane is presumably also formed initially in Step B of this procedure. This cycloaddition route to *p*-quinodimethanes and [2.2]paracyclophanes, discovered for the first time in the submitters' laboratories, is attractive on account of the availability of the starting materials, the simplicity of the procedure, and the relatively large quantities of product that may be obtained. The approach appears to be fairly general, since both the bisallene and acetylene components may be varied (Table I).[19,3,4] However, methyl 2-butynoate, 2-butyne, diphenylacetylene, and bistrimethylsilylacetylene failed to react with 1,2,4,5-hexatetraene. Another limitation is the exclusive formation of [2.2]paracyclophanes with the *anti* configuration from disubstituted acetylenic dienophiles.

The substituted [2.2]paracyclophanes prepared by the present procedure have proven to be useful starting materials for the synthesis of cyclophanes with extended aromatic ring systems,[20] additional ethano bridges,[21,22] and chromium tricarbonyl complexes.[23]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium benzophenone ketyl

TETRAMETHYL[2.2]PARACYCLOPHANE-4,5,12,13-TETRACARBOXYLATE

chromium tricarbonyl complexes

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

methanol (67-56-1)

ether, ethyl ether (60-29-7)

hydroquinone (123-31-9)

magnesium turnings (7439-95-4)

sulfone (7446-09-5)

oxygen (7782-44-7)

nitrogen (7727-37-9)

toluene (108-88-3)

mercury(II) chloride (7487-94-7)

copper(I) chloride (7758-89-6)

Diphenylacetylene (501-65-5)

1-propynylmagnesium bromide

Dimethyl acetylenedicarboxylate (762-42-5)

2-butyne (503-17-3)

propargyl bromide (106-96-7)

1,2,4,5-Hexatetraene (29776-96-3)

allenylmagnesium bromide

1,2-hexadien-5-yne (33142-15-3)

methyl 2-butynoate (23326-27-4)

bistrimethylsilylacetylene (14630-40-1)

p-quinodimethane

Tricyclo[8.2.2.2^{4,7}]hexadeca-4,6,10,12,13,15-hexaene-5,6,11,12-tetracarboxylic acid, tetramethyl ester

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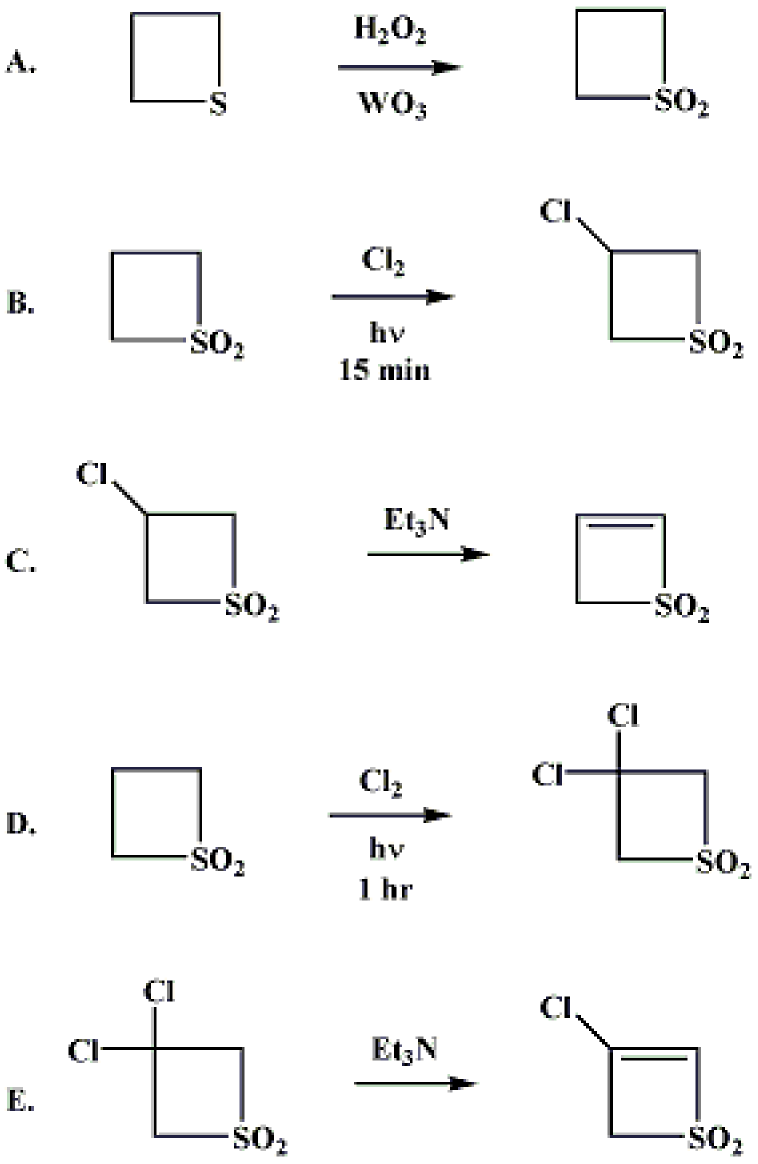
Organic Syntheses, CV 7, 491

THIETE 1,1-DIOXIDE AND 3-CHLOROTHIETE 1,1-DIOXIDE

[2*H*-Thiete 1,1-dioxide and 2*H*-thiete, 3-chloro- 1,1-dioxide]



Submitted by Thomas C. Sedergran and Donald C. Dittmer[1].
Checked by M. F. Semmelhack, Elena M. Bingham, William A. Sheppard, and Joseph J. Bozell.

1. Procedure

A. *Thietane 1,1-dioxide*. The pH of a solution of tungstic acid ($WO_3 \cdot H_2O$) (1.1 g, 0.044 mol) (Note 1) in 280 mL of distilled water is adjusted to 11.5 by addition of 10% aqueous sodium hydroxide; the white suspension of the tungstate catalyst is added to a 1-L, round-bottomed flask fitted with a mechanical stirrer and a pressure-

equalizing addition funnel. The tungstic acid–water mixture is cooled to 0–10°C by means of an ice–salt bath; glacial acetic acid (50 mL) and trimethylene sulfide (thietane) (47.5 g, 0.641 mol, *d* 1.028) (Note 2) are added. The chilled mixture is stirred, and 30% hydrogen peroxide (189 mL) is added carefully by means of the addition funnel over a period of 2 hr (Note 3). The mixture is stirred at 0–10°C for an additional hour, transferred to an evaporating dish, and heated to near dryness on a steam bath. The resulting solid material is triturated five times with 100-mL portions of hot chloroform; any catalyst is removed by filtration. The chloroform solutions are combined and dried over anhydrous magnesium sulfate and the solvent is removed via a rotary evaporator to give a white solid (60.3–63.7 g, 0.57–0.60 mol, 88.7–93.7%), mp 74–76°C (lit.[2] mp 75.5–76°C).

B. *3-Chlorothietane 1,1-dioxide*. Thietane 1,1-dioxide (14.0 g, 0.132 mol) is placed in a three-necked, 500-mL, round-bottomed flask fitted with a magnetic stirrer, reflux condenser and a chlorine bubbler. *Caution! (Since chlorine is poisonous, the reaction involving it should be done in a good hood.)* Carbon tetrachloride (300 mL) is added to the flask (Note 4) and the suspension is irradiated by a 250-W sunlamp positioned as close as possible to the reaction flask without touching it (Note 5) while chlorine is bubbled through the solution for 15 min at a moderate rate (Note 6). A copious white precipitate forms and irradiation and addition of chlorine must be stopped at this point (or 10 min after the first appearance of a precipitate) to avoid dichlorination. The reaction mixture is cooled to room temperature and filtered to give a white, fluffy product (5.4–8.1 g, 30–44%) that is crystallized from chloroform, mp 136–137°C (lit.[3] mp 136.5–137.5°C).

C. *Thiete 1,1-dioxide.* A sample of 3-chlorothietane 1,1-dioxide (8.0 g, 0.057 mol) is dissolved in dry toluene (300 mL) (Note 7) in a 500-mL, two-necked, round-bottomed flask equipped with a reflux condenser, magnetic stirrer, heating mantle (or silicone oil bath), and thermometer. The reaction is heated to 60°C and triethylamine (28.7 g, 0.28 mol, 39.5 mL) is added through the condenser. The reaction mixture is stirred for 4 hr and triethylamine hydrochloride is removed by filtration and washed with toluene (100 mL). Toluene is removed on a rotary evaporator and the residue is recrystallized from diethyl ether–ethanol (Note 8) to give a white solid (4.5–4.8 g, 75–81%); mp 49–50°C (lit.[3] mp 52–54°C).

D. *3,3-Dichlorothietane 1,1-dioxide*. Thietane 1,1-dioxide (5.0 g, 0.047 mol) is placed in a 500-mL, three-necked, round-bottomed flask equipped with a reflux condenser, magnetic stirrer, and chlorine gas bubbler. Carbon tetrachloride (350 mL) is added and the solution is irradiated with a 250-W sunlamp (Note 5) while chlorine is bubbled through the stirred mixture for 1 hr (Note 9). Irradiation and chlorine addition are stopped and the reaction mixture is allowed to cool to room temperature. The product is collected by filtration as a white solid (4.0–4.4 g, 49–53%), mp 156–158°C[4] (Note 10). the product can be used without further purification or recrystallized from chloroform.

E. *3-Chlorothiete 1,1-dioxide.* A solution of 3,3-dichlorothietane 1,1-dioxide (4.0 g, 0.023 mol) in toluene (150 mL) is placed in a 250-mL, round-bottomed, two-necked flask equipped with a heating mantle (or silicone oil bath), magnetic stirrer, reflux condenser, and thermometer. The solution is heated to 60°C and triethylamine (2.54 g, 0.025 mol, 3.5 mL) is added dropwise through the condenser over a 10-min period. The solution is stirred for 2 hr at 60°C and cooled to room temperature. The triethylamine hydrochloride is collected by filtration and washed with hot toluene (50 mL). Removal of toluene on a rotary evaporator gives a white solid (2.7–3.0 g, 84–93%) that is recrystallized from chloroform-hexane, mp 118–120°C[4] (Note 11).

2. Notes

1. The tungstic acid was used as supplied by the Eastman Kodak Company.
2. The trimethylene sulfide was used as supplied by the Aldrich Chemical Company.
3. The addition rate of the hydrogen peroxide must be adjusted so that the temperature of the reaction mixture does not rise above 10°C. The yield is reduced if the temperature is allowed to rise above that point. The endpoint of the reaction, when excess peroxide is present, can be determined with potassium iodide–starch test paper. The yield also is reduced if more than a slight excess of hydrogen peroxide is used.
4. The sulfone is not completely dissolved at this point. The prescribed ratio of sulfone to carbon tetrachloride (0.0467 g mL) is important. If it is less (i.e., more carbon tetrachloride relative to sulfone), considerable 3,3-dichlorothietane 1,1-dioxide will be formed.
5. Any commercial sunlamp is satisfactory and should be used with eye protection. Carbon tetrachloride boils gently because of the heat from the lamp.
6. The submitters suggested adding the chlorine at such a rate that a constant yellow color is maintained in the solution or suspension. The checkers found that, depending on the rate of chlorine introduction, it took from 10 to 35 min for the appearance of the white precipitate. In each run, the monochlorinated product was contaminated with a small amount (5–10% by NMR integration) of either starting material or dichlorinated product. The checkers found that the optimum yield of monochlorinated product was obtained when the chlorine was bubbled into the solution through a -in. glass tube at a rate estimated to be between 5–15 bubbles per second. The suspended sulfone dissolves as the reaction proceeds.
7. Toluene was dried over Linde 4A molecular sieves. Benzene may be used also.
8. The product is heated in about 25–30 mL of diethyl ether, and ethanol is added dropwise until a solution is obtained. The checkers found that the thiete sulfone could also be crystallized by gently heating the crude material in diethyl ether (100 mL) until it dissolves, followed by cooling to −15°C.
9. If the reaction time is less than 1 hr, a mixture of monochloro- and

dichlorosulfone is obtained.

10. The spectral properties of the product are as follows: IR (KBr disk) cm^{-1}: 2950 (m), 1370 (m, SO_2), 1310 (m), 1210 (m), 1140 (m, SO_2), 970 (m), 940 (m), 820 (w); ^{1}H NMR (chloroform-*d*) δ: 5.0 (s, 4 H, $CH_2SO_2CH_2$).

11. The spectral properties of the product are as follows: IR (KBr disk) cm^{-1}: 1540 (m, $>C=C<$), 1400 (w), 1300 (s, SO_2), 1210 (s), 1140 (s, SO_2), 1020 (m), 770 (m); ^{1}H NMR (chloroform-*d*) δ: 4.6 (s, 2 H, CH_2-SO_2), 6.8 (s, 1 H, CH=C).

3. Discussion

This preparation of thiete 1,1-dioxide is more direct and less tedious than previous methods.[3,5,6]

Oxidation of trimethylene sulfide catalyzed by tungstic acid[7] is preferred to the uncatalyzed reaction; yields are better and the reaction time is shortened by elimination of an induction period.

Selective chlorination of the 3-position of thietane 1,1-dioxide may be a consequence of hydrogen atom abstraction by a chlorine atom. Such reactions of chlorine atoms are believed to be influenced by polar effects, with preferential hydrogen abstraction occurring remotely from an electron withdrawing group.[8] The free-radical chain reaction may be propagated by attack of the 3-thietanyl 1,1-dioxide radical on molecular chlorine.

Conversion of 3-chlorothietane 1,1-dioxide to the 3-(*N*,*N*-dimethylamino) derivative followed by reduction, quaternization, and Hofmann elimination affords a convenient route to the highly reactive thiete (thiacyclobutene).[5,9]

The following compounds have been obtained from thiete 1,1-dioxide: substituted cycloheptatrienes,[10] benzyl α-toluenethiosulfinate,[11] pyrazoles,[12] naphthothiete 1,1-dioxides,[13] and 3-substituted thietane 1,1-dioxides.[14] It is a dienophile in Diels–Alder reactions[10,13,15] and undergoes cycloadditions with enamines, dienamines, and ynamines.[16] Thiete 1,1-dioxide is a source of the novel intermediate, vinylsulfene (CH_2=CHCH=SO_2), which undergoes cycloadditions to strained olefinic double bonds,[17] reacts with phenol to give allyl sulfonate derivatives[18] or cyclizes unimolecularly to give an unsaturated sultene.[18] Platinum[19] and iron[20] complexes of thiete 1,1-dioxide have been reported.

3-Chlorothiete 1,1-dioxide is a useful intermediate for the preparation of other 3-substituted thiete 1,1-dioxides via addition–elimination reactions.[4] It also undergoes Diels–Alder reactions with 1,3-butadiene and with 1,3-diphenylisobenzofuran.[4]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

H_2O

monochloro- and dichlorosulfone

thiete (thiacyclobutene)

ethanol (64-17-5)

acetic acid (64-19-7)

Benzene (71-43-2)

diethyl ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

iron (7439-89-6)

phenol (108-95-2)

carbon tetrachloride (56-23-5)

platinum (7440-06-4)

chlorine (7782-50-5)

toluene (108-88-3)

hydrogen peroxide, peroxide (7722-84-1)

magnesium sulfate (7487-88-9)

1,3-Butadiene (106-99-0)

triethylamine (121-44-8)

Triethylamine hydrochloride (554-68-7)

chloroform-hexane

Thiete 1,1-dioxide, 2H-Thiete 1,1-dioxide (7285-32-7)

3-Chlorothiete 1,1-dioxide, 2H-thiete, 3-chloro- 1,1-dioxide (90344-86-8)

tungstic acid

trimethylene sulfide, thietane (287-27-4)

Thietane 1,1-dioxide (5687-92-3)

3-Chlorothietane 1,1-dioxide (15953-83-0)

3,3-Dichlorothietane 1,1-dioxide (90344-85-7)

benzyl α-toluenethiosulfinate

allyl sulfonate

1,3-diphenylisobenzofuran (5471-63-6)

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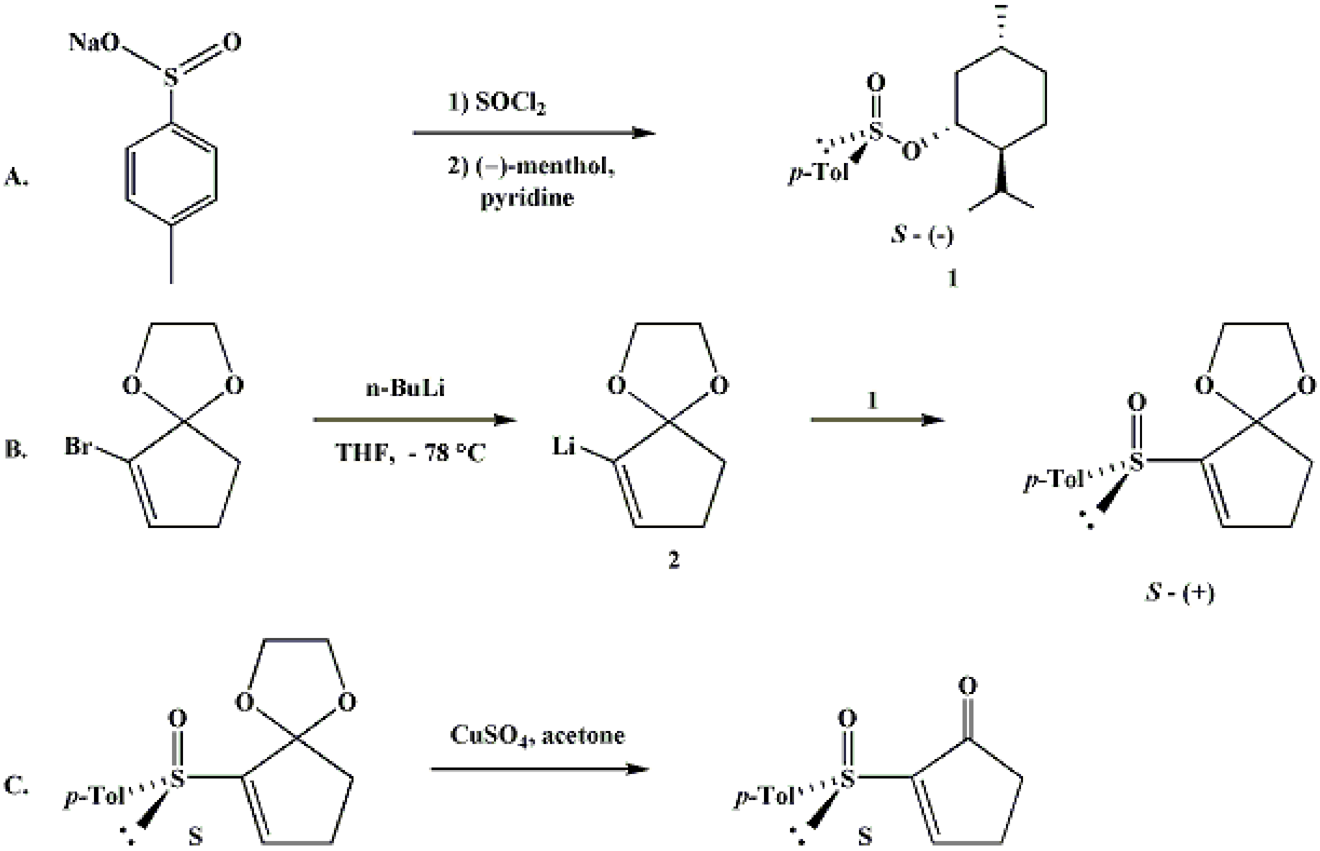
Organic Syntheses, CV 7, 495

(*S*)-(+)-2-(*p*-TOLUENESULFINYL)-2-CYCLOPENTENONE: PRECURSOR FOR ENANTIOSELECTIVE SYNTHESIS OF 3-SUBSTITUTED CYCLOPENTANONES

[2-Cyclopenten-1-one, 2-[(4-methylphenyl)sulfinyl]-, (*S*)-]



Submitted by Martin Hulce, John P. Mallomo, Leah L. Frye, Timothy P. Kogan, and Gary H. Posner[1].
Checked by Ernest B. Clark, Michel Crevoisier, Han Young, and Robert M. Coates.

1. Procedure

Caution! Part A should be conducted in an efficient fume hood to avoid exposure to sulfur dioxide generated in the reaction. Benzene has been identified as a carcinogen; OSHA has issued emergency standards for its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A. (*S*)-(–)-*Menthyl p-toluenesulfinate*. In a dry, 250-mL, three-necked, round-bottomed flask equipped with a nitrogen inlet are placed a magnetic stirring bar and 65 g (40 mL, 0.55 mol) of thionyl chloride (Note 1). The liquid is stirred under a nitrogen atmosphere as 35.6 g (0.200 mol) of anhydrous sodium *p*-toluenesulfinate (Note 2) is added in portions over about 1 hr (Note 3). The solution immediately develops a yellow-green tinge as sulfur dioxide is liberated. After about three-fourths of the sulfinate has been added, 30 mL of benzene is added to facilitate stirring. The greenish slurry is stirred for another 1.5 hr, after which time 75 mL of benzene is added. The mixture is transferred to a 500-mL, round-bottomed flask, along with 75 mL of benzene used to rinse the flask. Excess thionyl chloride and benzene are removed by rotary evaporation and gentle heating. Four 150-mL portions of benzene are added to the residue, and each portion is evaporated to complete the removal of the thionyl chloride. The flask is equipped with a magnetic stirring bar and a 125-mL, pressure-equalizing dropping funnel. The crude *p*-toluenesulfinyl chloride, sodium chloride, and residual benzene are dissolved in 150 mL of anhydrous diethyl ether. The resulting ethereal suspension is stirred and cooled in an ice bath as 31.3 g (0.200 mol) of (–)-menthol (Note 1) in 25 mL of pyridine is added over ca. 2 min. The mixture is allowed to stir overnight, after

which 70 g of ice is added. The layers are separated and the aqueous layer is extracted with one 100-mL portion of ether. The ethereal solutions are combined, washed three times with 50-mL portions of 20% aqueous hydrochloric acid, and dried with a mixture of anhydrous sodium sulfate and potassium carbonate. Filtration to separate the drying agents and rotary evaporation until a pressure of 3 mm is sustained leaves 57.5 g of crude methyl *p*-toluenesulfinate as a clear liquid admixed with white crystals. The less soluble (*S*)-(−) diastereomer (**1**) is isolated in several crops by crystallization from 1.2 volumes of reagent-grade acetone at −20°C. After the first crop has been collected, 3 drops of concd hydrochloric acid is added to the acetone mother liquor to effect equilibration of the sulfinate diastereomers. A total of 40.9–42.2 g of crystalline sulfinate is obtained in six crops. Recrystallization from acetone affords two crops of (*S*)-(−)-methyl *p*-toluenesulfinate, mp 105–106°C, $[\alpha]_D^{25}$ −199.4 (acetone, *c* 1.5), weighing 36.9–38.2 g (63–65%) (Note 4).

B. *(S)-(+)-2-(p-Toluenesulfinyl)-2-cyclopentenone ethylene ketal.* A 250-mL, three-necked, round-bottomed flask equipped with two rubber septa, a nitrogen inlet, 125-mL pressure-equalizing dropping funnel, and a magnetic stirring bar is flame-dried under nitrogen. After the apparatus cools to room temperature, the flask is charged with 70 mL of anhydrous tetrahydrofuran (Note 5) and cooled in an isopropyl alcohol–dry ice bath. Stirring is begun as 42 mL (60.8 mmol) of 1.45 *M* butyllithium in hexane (Note 6) is added slowly through the dropping funnel over 10–30 min. After another 10 min. a solution of 11.3 g (55.1 mmol) of 2-bromo-2-cyclopentenone ethylene ketal (Note 7) is added from the dropping funnel over 30 min. The colorless or pale-yellow solution is stirred and cooled at −78°C for 1.5 hr. A 1-L, three-necked, round-bottomed flask equipped with a magnetic stirring bar, two rubber septa, and a stopcock connected to a bubbler gas exit is flushed with nitrogen and charged with 24.4 g (82.9 mmol) of (*S*)-(−)-menthyl *p*-toluenesulfinate and 460 mL of anhydrous tetrahydrofuran. The sulfinate suspension is stirred vigorously (Note 8) and cooled at −78°C as the vinyllithium reagent (**2**) in the first flask in then transferred into the second flask through a cooled cannula by means of nitrogen pressure (Note 9). As the 50-min transfer proceeds, the sulfinate suspension becomes yellow. The mixture is stirred for another 15 min at −78°C, the cooling bath is removed, and 125 mL of saturated aqueous sodium dihydrogen phosphate is added. When the contents have warmed to room temperature, the tetrahydrofuran is removed by rotary evaporation. The residue is partitioned between 300 mL of water and 200 mL of chloroform. The aqueous layer extracted with three 100-mL portions of chloroform. The chloroform extracts are combined and dried over anhydrous potassium carbonate. Filtration of the drying agent and evaporation of the chloroform gives 40–55 g of a viscous brown oil consisting of the sulfinyl ketal, menthol, menthyl sulfinate, minor by-products, and residual chloroform. The sulfinyl ketal is isolated by modified flash chromatography on 500 g of Woelm silica gel (32–64 •m) packed in dry diethyl ether in a 6.5-cm × 45-cm column (Note 10). The crude product is applied to the column in 25 mL of chloroform and the column is eluted with ether under sufficient compressed air pressure to achieve a flow of 60 mL per min. After thirty 60-mL fractions are collected, the solvent is changed to ethyl acetate, and another forty 60-mL fractions are collected and analyzed by thin-layer chromatography (Note 11). Combination and evaporation of fractions 40–60 provides 9.05–9.75 g (62–67%) of crude (*S*)-(+)-2-(*p*-toluenesulfinyl)-2-cyclopentenone ethylene ketal as a pale-yellow oil, $[\alpha]_D^{25}$ +78° ($CHCl_3$, *c* 0.25) (Note 12).

C. *(S)-(+)-2-(p-Toluenesulfinyl)-2-cyclopentenone.* A magnetic stirring bar, 100 g of anhydrous copper(II) sulfate, and a solution of 9.05–9.75 g of the sulfinyl ketal in 300 mL of acetone are placed in a 500-mL Erlenmeyer flask. The flask is flushed with nitrogen and stoppered. The suspension is stirred vigorously overnight, the copper sulfate is separated by filtration, and the filtercake is washed thoroughly with 500–700 mL of acetone. Concentration of the combined filtrates by rotary evaporation gives 7.36–7.58 g of tan crystals. Recrystallization is carried out by dissolving the product in a minimum volume of ethyl acetate (ca. 80 mL) at room temperature, treating with Norite, diluting with an equal volume of diethyl ether, and cooling to −20°C. After the resulting crystals are collected, the mother liquor is evaporated under reduced pressure at room temperature, and the procedure is repeated twice. The mother liquor is again evaporated and the residue (1.4–1.8 g) is purified by flash chromatography on 110 g of Woelm silica gel using ethyl acetate as eluant (Note 13). Combination of appropriate fractions, evaporation, and recrystallization affords two additional crops of crystalline product (0.4–0.7 g). The yield of (*S*)-(+)-2-(p-toluenesulfinyl)-2-cyclopentenone, mp 125–126°C, $[\alpha]_D^{25}$ + 148° ($CHCl_3$, *c* 0.11), is 6.02–6.60 g (50–54% based on bromo ketal) (Note 14) and (Note 15).

2. Notes

1. This reagent was purchased from Aldrich Chemical Company, Inc.

2. Sodium p-toluenesulfinate hydrate, purchased from Aldrich Chemical Company, Inc., was dried overnight in a vacuum oven at 140°C to remove the water of hydration. The weight loss amounts to 19–21%.
3. The checkers added the sodium sulfinate from a 100-mL, three-necked flask via a bent sidearm fitted to the reaction vessel. A stream of nitrogen flowing through the 100-mL flask prevented backflow of fumes from the reaction and caking of the sodium sulfinate powder.

4. The spectral properties of the (*S*)-(-) sulfinate are as follows: IR (CCl_4) cm^{-1}: 2958 (s), 2924 (s), 2870 (s), 1455 (m), 1135 (s), 961 (s), 919 (s), 853 (s); ^1H NMR (90 MHz, $CDCl_3$) δ: 0.72 (d, 3 H, *J* = 6, $CHCH_3$), 0.94 and 0.86 [2 d, 6 H, *J* = 7, CH $(CH_3)_2$], 2.37 (s, 3 H, $ArCH_3$), 4.08 (t of d, 1 H, *J* = 5, 10, $CHOSO_2$), 7.26 and 7.56 (2 d, 4 H, *J* = 8, ArH).
5. Tetrahydrofuran was dried by distillation from sodium–benzophenone ketyl before use.
6. Butyllithium in hexane is available from Aldrich Chemical Company, Inc. and Alfa Products, Morton Thiokol, Inc. The reagent was titrated with anhydrous diphenylacetic acid as described in the literature.[2]

7. 2-Bromo-2-cyclopentenone ethylene ketal was prepared according to a published procedure.[3] The compound is quite unstable and should be purified by distillation before use to remove impurities. The submitters stored the bromo ketal at –20°C over Linde 3Å molecular sieves and redistilled a portion in a Kugelrohr apparatus with an oven temperature of 38°C (0.1 mm) immediately before use. The checkers found it necessary to distill the bromo ketal a second time to increase its purity. The compound was stored at –20°C and used in Step B the next day.
8. The submitters caution that rapid stirring is essential to avoid local heating from the exothermic reaction and, as a consequence, diminished yields.
9. The checkers used a 61-cm, 16-gauge cannula with a single loop ca. 6 cm in diameter immersed in an isopropyl alcohol–dry ice bath. The submitters report that lower yields were obtained when the vinyllithium reagent was allowed to warm above −78°C briefly during the transfer.
10. The submitters purified the product by medium-pressure liquid chromatography on a 60-cm × 5-cm column packed with 230–400-mesh silica gel 60 purchased from E. Merck. Ethyl acetate was used as eluant at a flow rate of 4.0 mL per min. Fractions (20 mL) were collected and analyzed by thin-layer chromatography.
11. Thin-layer chromatograms were obtained with silica gel as absorbent and ethyl acetate as developing solvent. The order of elution and R_f values of the major components are as follows: menthyl sulfinate (0.65). menthol (0.59), sulfinyl ketal (0.30).

12. The ^1H NMR spectral characteristics of the ketal are as follows ($CDCl_3$) δ: 2.0–2.2 (m, 2 H, CH_2), 2.3–2.6 (m, 2 H, $C{=}CCH_2$), 2.37 (s, 3 H, CH_3), 3.7–3.9 (m, 4 H, OCH_2CH_2O), 6.67 (t, 1 H, *J* = 2, C=CH), 7.24 (2 d, 4 H, *J* = 8, aryl H).

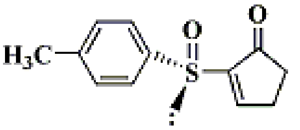
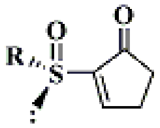
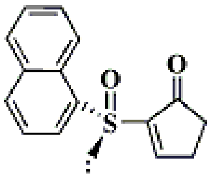
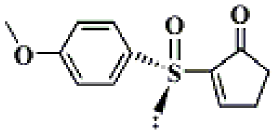
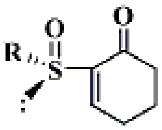
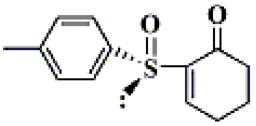
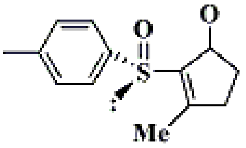
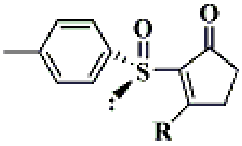
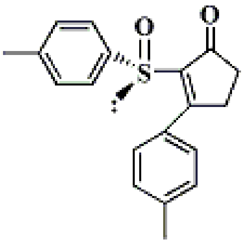
13. Flash chromatography was carried out according to a procedure in the literature.[4]
14. The spectral properties of the sulfinyl enone are as follows: IR (CCl_4) cm^{-1}: 2924 (m), 1715 (s), 1287 (m), 1152 (s), 1083 (s), 1054 (s), 728 (m), ^1H NMR ($CDCl_3$) δ: 2.2–2.5 (m, 2 H, CH_2), 2.30 (s, 3 H, CH_3), 2.6–2.8 (m, 2 H, $C{=}CCH_2$), 7.19 and 7.58 (2 d, 4 H, *J* = 8, aryl H), 8.03 (t, 1 H, *J* = 2, C=CH); mass spectrum (70 eV), *m/z* (relative intensity): 220 (M^+, 30), 172 (100), 139 (48), 129 (72). The product was analyzed by the submitters: Anal. calcd. for $C_{12}H_{12}SO_2$: C, 65.43; H, 5.49; S, 14.56. Found: C, 65.53; H, 5.51; S, 14.72.
15. The submitters report that the sulfinyl ketone may be stored in vials in a desiccator at 0°C for more than 1 year without evidence of decomposition. Although storage under an inert atmosphere is not necessary, the checkers found that product exposed to the atmosphere at room temperature became discolored after several weeks.

3. Discussion

Enantiomerically pure β-substituted carbonyl compounds serve as useful intermediates in the synthesis of many chiral organic compounds. The enantioselective synthesis of acyclic β-substituted carboxylic acids has been reported by Meyers,[5,6] Mukaiyama,[7] and Koga.[8,9] However, no effective, general method for the enantio-controlled preparation of β-substituted cycloalkanones was available prior to the investigations by the submitters.[10] For example, poor enantioselectivity was observed in conjugate additions of organometallic reagents to cyclic α,β-enones in the presence of optically active solvents[11] or chiral ligands.[12] In contrast, the submitters have found that conjugate addition to chiral cyclic α-sulfinyl α,β-enones occurs with high

enantioselectivity.[13,14,15,16,17,18] Thus, the title compound is a useful intermediate for the synthesis of a variety of β-substituted cyclopentanones.

TABLE I
ENANTIOMERICALLYPUREα-SULFINYL-α,β-ENONESPREPAREDFROMETHYLENEKETALSOFα-BROMO-α,β-ENONES

Sulfinyl Enone	R	Product	Yield (%)	mp (°C)	$[\alpha]_D^{25}$
	p-MeC$_6$H$_4$		50–54	125–126	+142°
	1-Naphthyl		65	96.5–97.0	+292°
	p-MeOC$_6$H$_4$		76	120.5–121.5	+141°
	*p*-MeC$_6$H$_4$		66	101–102	+210°
	Me		38	90.5–91.0	+21.0°
	*p*-MeC$_6$H$_4$		35	132–133	–322°

The preparation of (*S*)-(–)menthyl *p*-toluenesulfinate described in Step A is based upon the procedure reported by Solladié.[19] 2-Bromo-2-cyclopentenone ethylene ketal is available from 2-cyclopentenone by the procedure of Smith and co-workers.[3] The present procedure has been used by the submitters to prepared analogous chiral α-sulfinyl α,β-enones (Table I).[13,14,15,16,17,18] The utility of these chiral synthons is enhanced by their stability, the facility of their conjugate addition reactions, and the capability of producing either enantiomeric β-substituted adduct by varying the reaction conditions.[20] Similar methodology has allowed conversion of some enantiomerically pure butenolide sulfoxides into the corresponding β-substituted butyrolactones.[21]

Both (*S*)-(−)- and (*R*)-(+)-menthyl 4-toluenesulfinates are now available from the Aldrich Chemical Company, Inc.

This preparation is referenced from:

- Org. Syn. 77, 50

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

benzophenone ketyl

sulfinyl ketal

(S)-(−)menthyl p-toluenesulfinate

(S)-(−)- and (R)-(+)-menthyl 4-toluenesulfinates

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ethyl acetate (141-78-6)

ether, diethyl ether (60-29-7)

thionyl chloride (7719-09-7)

chloroform (67-66-3)

sulfur dioxide (7446-09-5)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

copper sulfate, copper(II) sulfate (7758-98-7)

acetone (67-64-1)

pyridine (110-86-1)

sodium (13966-32-0)

Diphenylacetic acid (117-34-0)

menthol (15356-60-2)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

sodium sulfinate

hexane (110-54-3)

sodium dihydrogen phosphate (7558-80-7)

2-Cyclopentenone (930-30-3)

vinyllithium (917-57-7)

2-Bromo-2-cyclopentenone ethylene ketal (68241-78-1)

Menthyl p-toluenesulfinate

Sodium p-toluenesulfinate hydrate (824-79-3)

menthyl sulfinate

methyl p-toluenesulfinate

Sodium p-toluenesulfinate

p-toluenesulfinate

2-Cyclopenten-1-one, 2-[(4-methylphenyl)sulfinyl]-, (S)-, (S)-(+)-2-(p-TOLUENESULFINYL)-2-CYCLOPENTENONE (79681-26-8)

p-toluenesulfinyl chloride, sodium chloride

(S)-(+)-2-(p-Toluenesulfinyl)-2-cyclopentenone ethylene ketal (82136-15-0)

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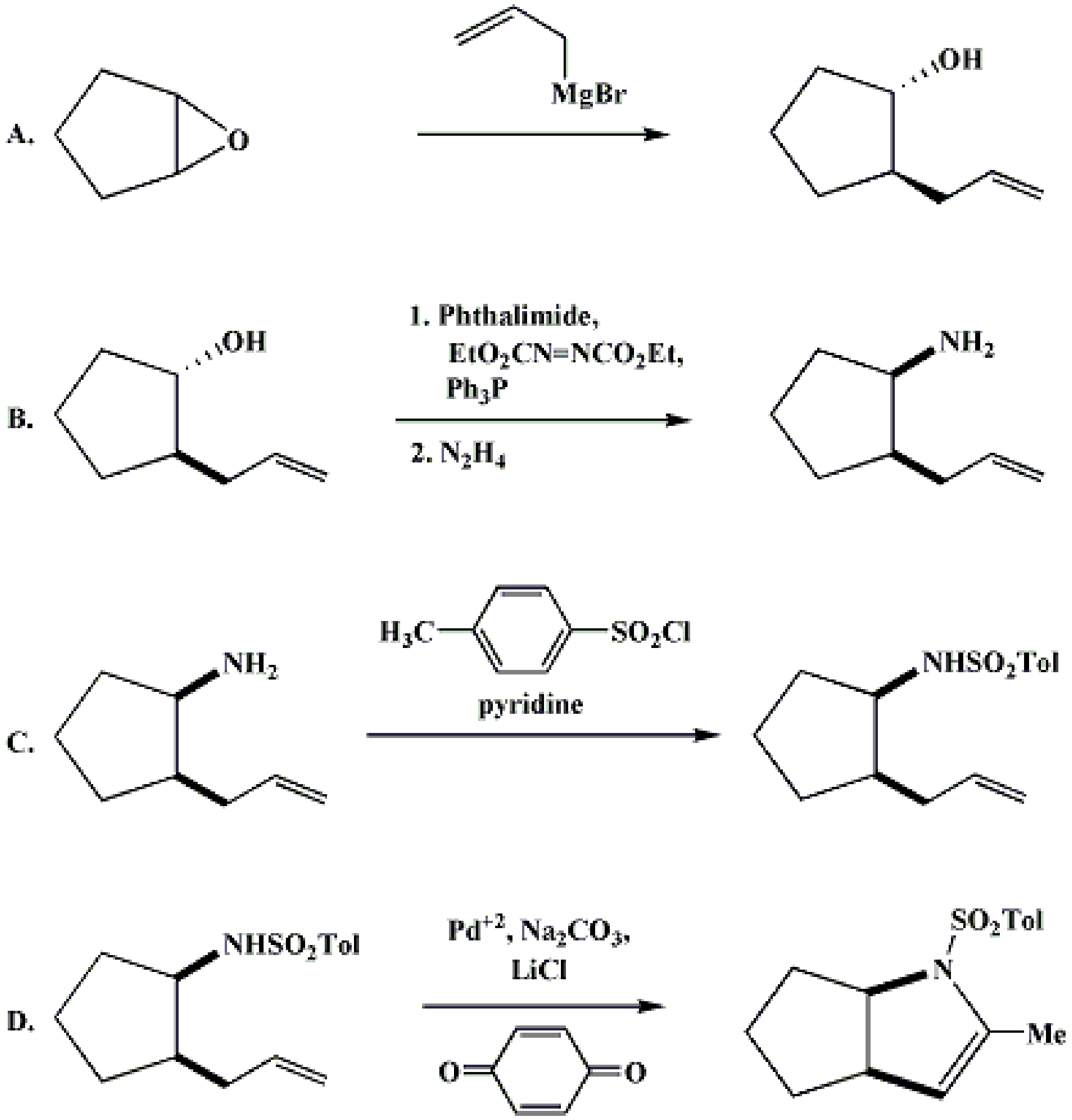
Organic Syntheses, CV 7, 501

cis-*N*-TOSYL-3-METHYL-2-AZABICYCLO[3.3.0]OCT-3-ENE

[Cyclopenta[*b*]pyrrole, 1,3a,4,5,6,6a-hexahydro-2-methyl-1-[4-methylphenyl)sulfonyl]-, *cis*-]



Submitted by Louis S. Hegedus, Michael S. Holden, and James M. McKearin[1].
Checked by Christoph Nubling and Ian Fleming.

1. Procedure

A. *trans-2-(2-Propenyl)cyclopentanol.* A 500-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, reflux condenser with a stopcock, and a 250-mL

addition funnel is charged with 18.3 g (750 mmol) of magnesium turnings (Note 1). The system is evacuated and placed under argon, then 100 mL of ethyl ether (Note 2) is added to the system via cannula. The system is placed in an ice–water bath, and 2 mL of allyl bromide (Note 3) is added via syringe to the magnesium suspension to initiate Grignard formation. The addition funnel is charged with 45.5 g (375 mmol) of allyl bromide and 30 mL of ethyl ether. Another 100 mL of ethyl ether is added to the reaction flask. Stirring is begun, and the allyl bromide–ethyl ether mixture is added dropwise to the cooled reaction flask over a period of about 2 hr. After the addition is complete, the dark-gray solution is stirred for several hours at ambient temperature (Note 4). Meanwhile, a 500-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, a reflux condenser with a stopcock, and a 60-mL addition funnel is evacuated and placed under argon. The Grignard solution is transferred, via a cannula, into the flask, and 16.8 g (200 mmol) of cyclopentene oxide (Note 5) is placed in the addition funnel. While the solution is stirred, the epoxide is added dropwise to the Grignard reagent at a rate sufficient to maintain a mild reflux. After the solution is stirred for several hours or overnight, the flask containing the dark gray reaction mixture is placed in an ice–water bath, and excess Grignard reagent is hydrolyzed with 40 mL of a saturated aqueous ammonium chloride solution. The fine white precipitate is allowed to settle (Note 6), and the liquid is decanted into a 500-mL separatory funnel. The precipitate is washed with ethyl ether (4 × 50 mL) (Note 7), and all the ethyl ether solutions are combined, washed with saturated aqueous sodium bicarbonate solution (3 × 20 mL), then with saturated aqueous sodium chloride (2 × 20 mL). The aqueous layers are combined and washed with ethyl ether (2 × 20 mL). The ether layers are combined and dried over anhydrous potassium carbonate. The desiccant is removed by gravity filtration, and the solvent removed under reduced pressure to give 24.1–26.4 g (96–105%) of a yellow oil. Distillation (43°C, 0.250 mm) yields **1** (19.8–23.0 g, 78–91%) as a clear, colorless oil (Note 8).

B. *cis-2-(2-Propenyl)cyclopentylamine*. A 1000-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, two addition funnels, and a stopcock is charged with 41.5 g (158 mmol) of triphenylphosphine (Note 9) and 23.3 g (158 mmol) of phthalimide (Note 10). The system is evacuated and placed under argon. To one addition funnel, 20.0 g (158 mmol) of *trans*-2-(2-propenyl)cyclopentanol is added; 27.5 g (158 mmol) of diethyl azodicarboxylate (Note 11) is added to the other. Tetrahydrofuran, 500 mL (Note 12), is added to the flask via cannula, and stirring is begun. The substrate and diethyl azodicarboxylate are simultaneously added dropwise, slowly over about 30 min (Note 13), with stirring; the solution turns clear and yellow (Note 14). The reaction is permitted to proceed for 2 days at room temperature; the solution is then transferred to a 1000-mL, one-neck, round-bottomed flask, and the solvent is removed under reduced pressure, to leave a yellow–white semisolid. A magnetic stirring bar is added to the flask and the semisolid is taken up in 250 mL of reagent-grade methyl alcohol. To this, 10.1 g (316 mmol) of hydrazine (Note 15) is added. A reflux condenser is attached to the flask, stirring is begun, and the system is brought to reflux (Note 16). A large amount of clumpy white solid forms in a yellow-to-orange solution. After 4 hr at reflux, the solution is allowed to cool to room

temperature; a mixture of 20 mL of hydrochloric acid (Note 17) and 65 mL of methyl alcohol is added, and the system is refluxed overnight. The resulting reaction mixture is filtered to remove the precipitate, and the solvent is removed under reduced pressure to yield a white-to-pink solid, which is taken up in 800 mL of water and 28 mL of hydrochloric acid. The solution is filtered, and the solid washed with water (2 × 200 mL) and hydrochloric acid (20 mL). The liquids are combined, placed in a 2000-mL separatory funnel, and washed with chloroform (3 × 250 mL), and ethyl ether (1 × 250 mL). The aqueous layer is transferred to a 2000-mL Erlenmeyer flask and cooled in an ice–water bath. A saturated aqueous sodium hydroxide solution is used to make the solution basic, to approximately pH 14, whereupon the solution turns dark olive green. The basic solution is extracted with ethyl ether (10 × 250 mL or by continuous extraction overnight) and the combined organic layers are dried over a mixture of anhydrous sodium sulfate and anhydrous potassium carbonate. Filtration and solvent removal at atmospheric pressure yields a green–yellow oil. Distillation (52–58°C, 8–11 mm) gives **2** (11.8–12.5 g, 60–63%) as a clear, colorless oil (Note 18).

C. *cis-1-N-Tosyl-2-(2-propenyl)cyclopentylamine*. A 100-mL, one-necked, round-bottomed flask equipped with a sidearm, a magnetic stirring bat, stopcock, and a serum cap on the sidearm, is charged with 8.00 g (64 mmol) of *cis*-2-(2-propenyl)cyclopentylamine. The system is evacuated and placed under argon. Via cannula, 50 mL of pyridine (Note 19) is added. The flask is cooled in an ice–water bath, the stopcock removed, 12.58 g (66 mmol) of *p*-toluenesulfonyl chloride (Note 20) is added to the reaction mixture, and the stopcock replaced. The reaction mixture immediately turns orange; it is allowed to stir at 0°C overnight, during which time the reaction mixture turns deep purple. The reaction mixture is then poured into a separatory funnel, 60 mL of distilled technical grade ethyl acetate is added, and the solution is washed with 100-mL portions of 1 : 1 2 N HCl: saturated aqueous sodium chloride until the washings are acidic. The organic layer is washed with saturated aqueous sodium chloride (2 × 60 mL), and dried over anhydrous magnesium sulfate. Gravity filtration and solvent removal under reduced pressure yield a dark red–brown solid. This is purified by recrystallization from 250 mL of ethyl alcohol: water (4 : 1); crystallization is completed in the refrigerator to give **3** (12.7–13.9 g, 71–78%) as off-white plates, mp 109–110°C (Note 21).

D. *cis-N-Tosyl-3-methyl-2-azabicyclo[3.3.0]oct-3-ene*. A 500-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar and reflux condenser is charged with 5.159 g (18.49 mmol) of *cis*-1-*N*-tosyl-2-(2-propenyl)cyclopentylamine, 1.998 g (18.49 mmol) of *p*-benzoquinone (Note 22), 0.096 g (0.370 mmol, 2 mol%) of $PdCl_2(CH_3CN)_2$ (Note 23), 3.920 g (92.46 mmol, 500 mol%) of lithium chloride (Note 24), and 1.960 g (18.49 mmol) of sodium carbonate (Note 25). Tetrahydrofuran (100 mL) (Note 12) is added and stirring is begun. The yellow–orange solution is heated at reflux until thin-layer chromatography (3 : 1 hexane : ethyl acetate, SiO_2) shows that no starting material remains (about 3–4 hr); it is then poured into a 500-mL separatory funnel and 100 mL of ethyl acetate is added. This is washed with 100-mL portions of 1 : 1 saturated aqueous sodium chloride : sodium hydroxide (1%) until the aqueous

layer is clear; then the yellow–green organic layer is washed with saturated aqueous sodium chloride (2 × 50 mL). The organic layer is dried over anhydrous magnesium sulfate, filtered by gravity, and passed through a short column (approximately 5 cm) of neutral alumina, and the column is washed with 100 mL of ethyl acetate. The combined solvents are removed under reduced pressure to give 4.9–5.1 g (94–99%) of a tan solid. The product is recrystallized from 100 mL of methyl alcohol : water (4 : 1) to yield **4** (3.9–4.45 g, 76–87%) as white needles, mp 91–92°C (Note 26) and (Note 27).

2. Notes

1. Magnesium turnings, purified for Grignard reactions, are purchased from J. T. Baker Chemical Company and used without further purification.
2. Ethyl ether is freshly distilled from sodium/benzophenone ketyl at atmospheric pressure under nitrogen.
3. Allyl bromide, purchased from Aldrich Chemical Company, Inc., is distilled and stored in a brown bottle away from light.
4. Successful reactions have been run with this induction period lasting from 1 hr to overnight.
5. Cyclopentene oxide is purchased from Arapahoe Chemicals, Boulder, CO, and used without purification. The checkers bought cyclopentene oxide from Lancaster Synthesis.
6. The fine precipitate may take several hours to settle. Filtration is often ineffective, but settling can be accelerated by centrifuging.
7. Since the efficiency of this washing is dependent on the degree of settling, the checkers recommend that washing with 50-mL batches of ether be continued until the smell of the alcohol is no longer detectable on a sample of the dry salts.
8. The spectral properties are as follows: ^{1}H NMR ($CDCl_3$) δ: 1.0–2.4 (m, 9 H); 3.0–3.3 (br s, 1 H, O-H); 3.7–4.1 (m, 1 H, CH-O); 4.8–5.3 (m, 2 H, $=CH_2$); 5.5–6.2 (m, 1 H, -CH=).
9. Anhydrous triphenylphosphine is purchased from Sigma Chemical Company and is used without further purification
10. Phthalimide, 98%, is purchased from Aldrich Chemical Company, Inc. and is used without further purification.
11. Diethyl azodicarboxylate is purchased from Aldrich Chemical Company, Inc. and is used without further purification.
12. Tetrahydrofuran is freshly distilled from sodium/benzophenone ketyl at atmospheric pressure under nitrogen.
13. Too rapid a rate of addition may cause the solution to boil.
14. The solution does not become homogeneous until it is warmed by the heat of the reaction.
15. Anhydrous hydrazine, ≥97%, is purchased from Matheson, Coleman and Bell, No wood, OH 45212 and is used without further purification.
16. *Caution! Because of the dangerous nature of hydrazine, a safety shield should always be in place during this reaction.*

17. ACS reagent hydrochloric acid is purchased from Fisher Scientific Company and used without further purification.
18. The spectral properties are as follows: ^{1}H NMR ($CDCl_3$) δ: 0.8 (s, 2 H, NH_2); 1.3–2.4 (m, 9 H, CH_2, CH); 3.1–3.4 (m, 1 H, HC-N); 4.8–5.2 (m, 2 H, $=CH_2$); 5.4–6.1 (m, 1 H, HC=).
19. Pyridine is distilled from CaH_2 and stored over CaH_2 under argon.
20. *p*-Toluenesulfonyl chloride is purchased from J. T. Baker Chemical Company and purified by dissolving 20 g in 50 mL of chloroform, adding 250 mL of hexane, filtering, and removing solvent under reduced pressure.[2]
21. The spectral properties are as follows: ^{1}H NMR ($CDCl_3$) δ: 1.0–2.3 (m, 9 H, CH_2, CH); 2.41 (s, 3 H, CH_3); 3.4–3.8 (m, 1 H, CHN); 4.7–5.1 (m, 3 H, $=CH_2$, NH); 5.2–6.1 (m, 1 H, =CH); 7.25 (d, 2 H, J = 8, ArH); 7.8 (d, 2 H, J = 8 ArH).
22. *p*-Benzoquinone, ≥98%, is purchased from the Aldrich Chemical Company, Inc., sublimed at 60°C/15 mm, and stored under argon. The checkers used it as supplied.
23. Palladium(II) chloride–acetonitrile complex is formed by placing 8.00 g of $PdCl_2$ in 200 mL of acetonitrile and stirring for 2 days or refluxing for 3 hr. The complex (11.43 g, 97.8%) is collected by filtration, washed, and dried.
24. Lithium chloride is purchased from Fisher Scientific Company and used without further purification.
25. Sodium carbonate is purchased from Aldrich Chemical Company, Inc. and used without further purification.
26. The spectral properties are as follows: ^{1}H NMR ($CDCl_3$) δ: 1.40–2.00 (m, 6 H, CH_2); 2.10 (m, 3 H, CH_3C=); 2.40 (s, 3 H, $ArCH_3$); 2.80–3.20 (m, 1 H) 4.20–4.50 (m, 1 H, CHN); 4.70 (m, 1 H, CH=); 7.30 (d, 2 H, J = 8, ArH); 7.70 (d, 2 H, J = 8, ArH).
27. The checkers also carried out the entire sequence on three times the scale with slightly better yields.

3. Discussion

Synthesis of the title compound is representative of a number of syntheses of non-aromatic nitrogen heterocycles via Pd(II)-catalyzed amination of olefins.[3] These tosylated enamines are not readily available by standard synthetic methods and show potential for further functionalization of the heterocycle.[4] The saturated amine can be synthesized from the title compound by hydrogenation of the double bond followed by photolytic deprotection.[3]

In terms of cost, the effectiveness of the catalytic cycle in the ring closure makes this process economical in palladium. The first three steps in the reaction sequence—ring opening of an epoxide by a Grignard reagent,[5] conversion of an alcohol to an amine with inversion,[6] and sulfonamide formation from the amine[7]—are all standard synthetic processes.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

benzophenone ketyl

Cyclopenta[b]pyrrole, 1,3a,4,5,6,6a-hexahydro-2-methyl-1-[4-methylphenyl) sulfonyl]-, cis-

cis-1-N-Tosyl-2-(2-propenyl)cyclopentylamine

ethyl alcohol (64-17-5)

potassium carbonate (584-08-7)

hydrochloric acid, HCl (7647-01-0)

ethyl acetate (141-78-6)

methyl alcohol (67-56-1)

ether, ethyl ether (60-29-7)

ammonium chloride (12125-02-9)

acetonitrile (75-05-8)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium bicarbonate (144-55-8)

magnesium, magnesium turnings (7439-95-4)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

Allyl bromide (106-95-6)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

pyridine (110-86-1)

sodium (13966-32-0)

palladium (7440-05-3)

Phthalimide (85-41-6)

hydrazine (302-01-2)

p-benzoquinone (106-51-4)

palladium(II) chloride

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

diethyl azodicarboxylate (1972-28-7)

hexane (110-54-3)

Lithium chloride (7447-41-8)

triphenylphosphine (603-35-0)

argon (7440-37-1)

p-Toluenesulfonyl chloride (98-59-9)

Cyclopentene oxide (285-67-6)

tosyl-2-(2-propenyl)cyclopentylamine

cis-N-Tosyl-3-methyl-2-azabicyclo[3.3.0]oct-3-ene (81097-07-6)

trans-2-(2-Propenyl)cyclopentanol (74743-89-8)

cis-2-(2-Propenyl)cyclopentylamine (81097-02-1)

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Organic Syntheses, *CV 7*, *506*

TRIFLOROACETYL TRIFLATE

[Acetic acid, trifluoro-, anhydride with trifluoromethanesulfonic acid]

$$CF_3CO_2H + CF_3SO_3H \xrightarrow{P_2O_5} CF_3CO_2SO_2CF_3$$

Submitted by Stephen L. Taylor, T. R. Forbus, Jr., and J. C. Martin[1].
Checked by Thomas W. Panunto and Edwin Vedejs.

1. Procedure

Caution! The volatile product reacts rapidly with water to give corrosive strong acids. It also reacts rapidly with other nucleophiles. Care should therefore be exercised to avoid inhalation of its vapors. It should be handled in a well-vented fume hood.

To a 1-L flask containing 160 g (1.13 mol) of powdered phosphorus oxide (P_2O_5), thoroughly mixed with an equal volume of dried fine sand (Note 1), is added a mixture of 85.5 g (0.75 mol) of trifluoroacetic acid (TFA) (Note 2) and 56.5 g (0.750 mol) of triflic acid (TfOH) at –20°C (Note 3). The stoppered flask (Note 4) is vigorously shaken for 5 min and then fitted for simple distillation, with the receiving flask cooled to –78°C, and allowed to stand at room temperature under a dry nitrogen atmosphere for 2.5 hr. The liquid is removed from the solid mixture by simple distillation at a bath temperature of 240°C (Note 5) for 3.5 hr (Note 6). The distillate is then carefully fractionally distilled (Note 7) from 5 g of powdered P_2O_5 (Note 8) with the receiving flasks cooled at –78°C. The colorless liquid collected at 62.5–63°C (760 mm) (Note 9), 69 g (75%) of trifluoroacetyl triflate (TFAT), is of 99% purity (Note 10), as determined by fluorine magnetic resonance (Note 11).

2. Notes

1. In recent synthetic applications of this method the powdered phosphorus oxide was mixed with *twice* as much volume of dried fine sand. The increased volume of sand makes it easier to remove the TFAT by distillation and reduces the probability that the flask will be broken after the distillation.
2. The 99% TFA obtained from Aldrich Chemical Company, Inc. was used without further purification.
3. Triflic acid (TfOH), obtained from Minnesota Mining & Manufacturing Company, (3M), in kilogram quantities was used without further purification.
4. Ground-glass joints were connected using Teflon sleeves or a chlorofluorocarbon stopcock grease.
5. High temperatures are needed to distill the products from P_2O_5. The use of temperatures higher than 250°C, however, causes the round-bottomed flask to

break when the temperature is lowered to near room temperature. On completion of the reaction, the P_2O_5 sand mixture can be removed from the flask by careful, slow addition of water. The checkers used an equilibrated bath of sand in a large heating mantle; the flask always broke after distillation (see (Note 1)).

6. The nitrogen outlet from the distillation apparatus should be well vented.
7. An 8-mm × 1-m jacketed column packed with a coiled tantalum wire was used by the submitters. The checkers used a Vigreux column of similar size.
8. Since the distillate contains 1–3% of the starting acids, P_2O_5 is added to prevent the reaction of TFA and TFAT, which gives trifluoroacetic anhydride (TFAA) and TfOH.
9. The first fraction is TFAA, bp 38.5–41°C (760 mm).
10. The impurity is TFAA.
11. The reactants and products show only singlets in their fluorine magnetic resonance spectra with the following chemical shifts (downfield from fluorotrichloromethane internal standard) δ: TFA, –76.3; TfOH, –77.3; TFAT, –73.3 and –74.8; TFAA, –75.9; triflic anhydride, –72.6 ppm.

3. Discussion

Trifluoroacetyl triflate is probably the most powerful trifluoroacetylating agent known, as evidenced by its reactivity toward several types of nucleophiles under mild conditions. A sterically hindered base, 2,6-di-*tert*-butyl-4-methylpyridine,[2] may be used to scavenge the triflic acid produced in the reactions, since it does not react with TFAT under these conditions.

Trifluoroacetylation occurs at carbon in activated arenes such as anthracene[3] under milder conditions using TFAT than when using T FAA. Trifluoroacetate esters are formed from alcohols and phenols,[4] while ketones are acylated at oxygen to yield enol trifluoroacetates.[3] Amines[4] give the corresponding amides on reaction with 1 equiv of TFAT or imides on reaction with 2 equiv. Some covalent halides (fluorides[5] and chlorides[3]) are acylated at halogen by TFAT to yield the very volatile trifluoroacetyl halides and ionic triflates. It was recently reported that TFAT reacts with a thioketone to give a stable cation.[6] Reaction of TFAT with the methyl ester of glutaconic acid gives 2,6-dimethoxypyrylium triflate, the first member of a new class of pyrylium salts[4] with alkoxy groups at positions-2 and -6.

The high reactivity of TFAT limits the number of solvents that can be used for its reactions. We have found that TFAT is unreactive towards saturated hydocarbons, benzene, and common halogenated solvents. It reacts only very slowly with nitromethane, but reacts relatively rapidly with ether, tetrahydrofuran, ethyl acetate, and acetonitrile.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 144

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

TRIFLOROACETYL TRIFLATE

Triflic acid (TfOH)

trifluoroacetic anhydride (TFAA)

Benzene (71-43-2)

ethyl acetate (141-78-6)

ether (60-29-7)

acetonitrile (75-05-8)

oxygen (7782-44-7)

carbon (7782-42-5)

anthracene (120-12-7)

Nitromethane (75-52-5)

Tetrahydrofuran (109-99-9)

fluorotrichloromethane (75-69-4)

trifluoroacetic acid (76-05-1)

Acetic acid, trifluoro-, anhydride (407-25-0)

trifluoromethanesulfonic acid, triflic acid (1493-13-6)

triflic anhydride (358-23-6)

TFA

phosphorus oxide (1314-56-3)

Trifluoroacetyl triflate (68602-57-3)

2,6-dimethoxypyrylium triflate

2,6-Di-tert-butyl-4-methylpyridine (38222-83-2)

methyl ester of glutaconic acid

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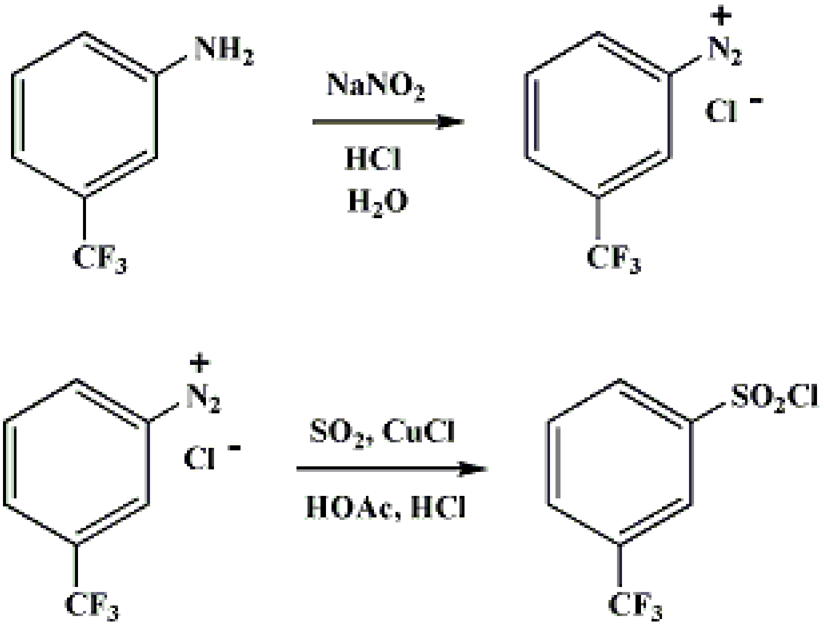
Organic Syntheses, *CV 7*, *508*

m-TRIFLUOROMETHYLBENZENESULFONYL CHLORIDE

[Benzenesulfonyl chloride, *m*-(trifluoromethyl)-]



Submitted by R. V. Hoffman[1]
Checked by G. Saucy, G. P. Roth, and J. W. Scott.

1. Procedure

Caution! All operations should be carried out in a hood! m-Trifluoromethylbenzenesulfonyl chloride is a lachrymator. Spills should be treated with saturated sodium carbonate.

α,α,α-Trifluoro-*m*-toluidine (*m*-aminobenzotrifluoride) (96.7 g, 0.6 mol) (Note 1) is added in one portion to a mixture of concentrated hydrochloric acid (200 mL) and glacial acetic acid (60 mL) in a 1000-mL beaker arranged for efficient mechanical stirring (Note 2). The white hydrochloride salt precipitates (Note 3). The beaker is placed in a dry ice-ethanol bath and, when the temperature of the stirred mixture has reached −10°C, a solution of sodium nitrite (44.8 g, 0.65 mol) in water (65 mL) is added dropwise at such a rate that the temperature does not exceed −5°C (Note 4). After all the sodium nitrite solution has been added, the mixture is stirred for 45 min while the temperature is maintained between −10°C and −5°C (Note 5).

While the diazotization is being completed, glacial acetic acid (600 mL) is placed in a 4000-mL beaker and stirred magnetically. Sulfur dioxide is introduced by a bubbler tube with a fritted end immersed below the surface of the acetic acid until saturation is

evident (Note 6). Cuprous chloride (15 g) (Note 7) is added to the solution. The introduction of sulfur dioxide is continued until the yellow–green suspension becomes blue-green. Most of the solids dissolve during this time (20–30 min). The mixture is then placed in an ice bath and cooled with stirring. When the temperature approaches 10°C, the diazotization reaction mixture (Note 8) is added in portions over a 30-min period to the sulfur dioxide solution. Considerable foaming occurs after each addition, and this can be disrupted with a few drops of ether. The temperature rises during the addition, but it should not exceed 30°C. After all the diazonium salt mixture has been added, the mixture is poured into ice water (1 : 1, 2000 mL), stirred magnetically until the ice has melted, and added to a 4000-mL separatory funnel. The product separates as a yellow oil that is drawn off. The reaction mixture is extracted with 200-mL portions of ether until the ether washings are colorless (Note 9), and these washings are added to the initial product. The combined organic fraction is washed with saturated aqueous sodium bicarbonate until neutral (Note 10), then with water, and is then dried with magnesium sulfate. The solvent is removed with a rotary evaporator, and the residue is distilled (bp 54–55°C, 0.1 mm) through a 10-cm vacuum-jacketed Vigreux column to give *m*-trifluoromethylbenzenesulfonyl chloride (100–115 g, 68–79%) as a colorless or slightly yellow, clear liquid (Note 11), (Note 12).

2. Notes

1. α,α,α-Trifluoro-*m*-toluidine was obtained from Aldrich Chemical Company, Inc. The checkers distilled this material prior to use (bp 187–189°C).
2. A chain beaker clamp is very satisfactory for supporting the beaker, as it can later be used as a handle to pour the diazonium solution. For efficient stirring the blade of the stirrer was made by trimming the ends of a large Teflon stirring paddle to the diameter of the beaker. The paddle was inverted (straight edge on bottom) and should rotate 1–1.5 cm from the bottom of the beaker.
3. If solid amines are used, they should be thoroughly crushed in a mortar and pestle before adding to the acid mixture.
4. Temperature control during the sodium nitrite addition is essential to the success of the preparation. The temperature can go as low as −15°C but must not exceed −5°C. The addition takes ca. 1 hr. At temperatures greater than −5°C, dark-red by-products form which lower the yield.
5. Temperature control is conveniently accomplished by raising and lowering the dry-ice bath. It does not seem to matter if longer reaction times are employed, but the temperature should be lowered to −10°C or below after 45 min.
6. Saturation, which requires 15–30 min, is conveniently noted by observing that most sulfur dioxide bubbles reach the surface of the acetic acid.
7. The original literature[2] suggests that copper(II) chloride dihydrate can be used as a catalyst, since it is reduced by the sulfur dioxide to copper(I). It has been noted on several occasions that catalytically inactive mixtures result. If copper (II) chloride dihydrate is used, it is expedient to add copper(I) chloride (1 g) to ensure efficient catalysis in the early stages of reaction.

8. This mixture should be a pale tan suspension, and it should be cooled between additions.
9. The first portion of ether may be larger (400 mL) since much dissolves in the aqueous mixture. A total of 1000 mL of ether is usually sufficient.
10. A considerable amount of acid is present in the ether extracts, so vigorous gas evolution occurs during the sodium bicarbonate extraction. Caution must be exercised at this point.
11. The product is sufficiently pure for most purposes. A second distillation affords a colorless product (lit.[3] bp 88–90°C, 6 mm).
12. With many anilines used as precursors in this reaction, the sulfonyl chloride product is a solid and an alternate workup procedure is used. After the reaction is quenched with ice water, the solid product is filtered with suction and washed copiously with cold water. The crude product tends to occlude water and copper salts, which may be detrimental in later reactions. A good washing protocol involves rinsing the solid on the filter with water (200 mL), then suspending the solid in cold water (1000 mL), stirring briskly, and filtering with suction. The latter process should be repeated three times. The final water wash should be only very slightly yellow. After air drying the product can be recrystallized from an appropriate solvent.

3. Discussion

m-Trifluoromethylbenzenesulfonyl chloride has been prepared by treatment of *m*-trifluoromethylbenzenediazonium chloride with sulfur dioxide and hydrochloric acid[4] and by conversion of benzotrifluoride to *m*-trifluoromethylbenzenesulfonic acid with oleum, followed by chlorination with phosphorus pentachloride.[3] Derivatives of this compound, such as esters and amides, are quite useful in that they display reactivities similar to *p*- and *m*-nitrobenzenesulfonyl compounds but have greatly improved solubilities.

The described procedure essentially follows that described by Meerwein et al.[2] as modified slightly by Yale and Sowinski.[4] This same method can be used for a great variety of substituted anilines with good results. As evident in Table I, good yields are obtained in most cases, and the reaction works better for anilines with electron-withdrawing substituents. The identical procedure has been used to prepare many other examples, such as *m*-F, *o*-F, 3,5-di-CF_3.[5] This method readily provides many unavailable arylsulfonyl chlorides; it is experimentally straightforward, and the products are isolated without complications.

There are two general routes to arylsulfonyl chlorides. The first involves the conversion of an already sulfur-substituted aromatic compound to the sulfonyl chloride. Thus arylsulfonic acids or their alkali metal salts yield sulfonyl chlorides by treatment with a variety of chlorinating agents such as phosphorus pentachloride, thionyl chloride, phosgene, and chlorosulfonic acid. Alternatively, substituted thiophenols or aryl disulfides can be oxidized by chlorine-water to the sulfonyl

chloride.[6]

TABLE I
CONVERSION OFARYLAMINES TOARYLSULFONYLCHLORIDES

Amine, $XC_6H_4NH_2$, X =	Yield (%) of $XC_6H_4SO_2Cl$
m-CF_3	72
p-NO_2	68
m-NO_2	86
p-Cl	90
p-CO_2CH_3	90
3,5-di-NO_2	81
m-CH_3	71
H	53
p-OCH_3	27

The second route utilizes the introduction of the chlorosulfonyl substituent directly onto the aromatic nucleus. The reaction of substituted benzenes with chlorosulfonic acid gives good yields of arylsulfonyl chlorides; however, the aryl substituent dictates the position of attachment of the chlorosulfonyl function in this electrophilic aromatic substitution.[7] The method described herein allows replacement of a diazotized amine function by the chlorosulfonyl group. The ready availability of substituted anilines makes this the method of choice for the preparation of arylsulfonyl chlorides.

Arylsulfonyl chlorides are pivotal precursors for the preparation of many diverse functional types including sulfonate esters,[8] amides,[4] sulfones,[9] sulfinic acids,[10] and others.[11] Furthermore, sulfonyl fluorides are best prepared from sulfonyl chlorides.[12] The sulfonyl fluorides have many uses, among which is their utilization as active site probes of chymotrypsin and other esterases.[13] The trifluoromethyl group also plays valuable roles in medicinal chemistry.[14]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfonyl chloride

amine

p- and m-nitrobenzenesulfonyl

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ether (60-29-7)

chlorosulfonic acid (7790-94-5)

phosphorus pentachloride (10026-13-8)

thionyl chloride (7719-09-7)

sodium bicarbonate (144-55-8)

sodium carbonate (497-19-8)

sulfur dioxide (7446-09-5)

sodium nitrite (7632-00-0)

phosgene (75-44-5)

cuprous chloride, copper(I) chloride (7758-89-6)

magnesium sulfate (7487-88-9)

copper(I)

benzotrifluoride (98-08-8)

copper(II) chloride dihydrate (10125-13-0)

m-aminobenzotrifluoride, α,α,α-Trifluoro-m-toluidine (98-16-8)

m-Trifluoromethylbenzenesulfonyl chloride, Benzenesulfonyl chloride, m-(trifluoromethyl)- (777-44-6)

m-trifluoromethylbenzenediazonium chloride

m-trifluoromethylbenzenesulfonic acid

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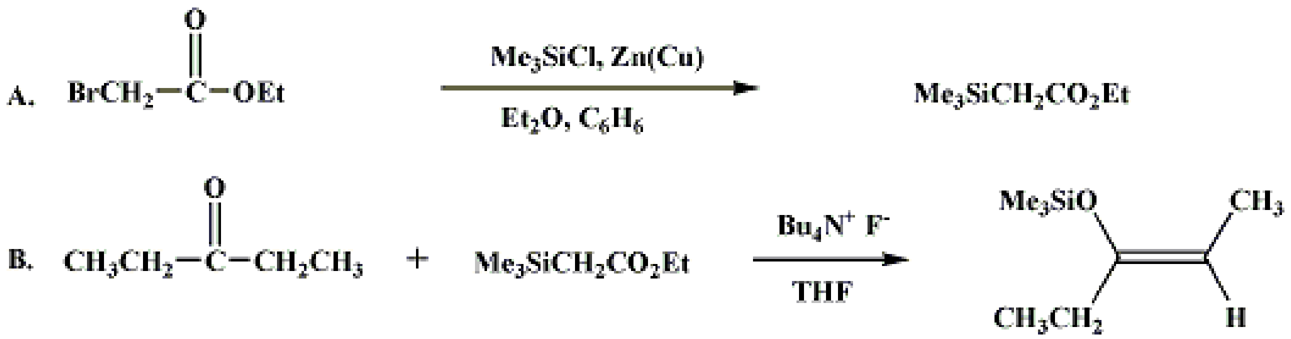
Organic Syntheses, CV 7, 512

SILYLATION OF KETONES WITH ETHYL TRIMETHYLSILACETATE: (Z)-3-TRIMETHYLSILOXY-2-PENTENE

[Silane, [(1-ethyl-1-propenyl)oxyl]trimethyl-, (Z)-]



Submitted by Isao Kuwajima, Eiichi Nakamura, and Koichi Hashimoto[1].
Checked by Peter J. Card and Richard E. Benson.

1. Procedure

Caution! Ethyl bromoacetate is intensely irritating to eyes and skin. The preparation of this ester should be carried out in an efficient hood. Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A. *Ethyl trimethylsilylacetate* (Note 1). In a 3-L, three-necked flask fitted with a 1-L, pressure-equalizing dropping funnel, mechanical stirrer, and efficient condenser that is connected to a nitrogen source are placed 97.5 g (1.5 mol) of zinc powder (Note 2) and 14.9 g (0.15 mol) of cuprous chloride (Note 3). After the reaction vessel is flushed with nitrogen, a static nitrogen atmosphere is maintained for the remainder of the reaction. A mixture of 150 mL of benzene (Note 5) is added to the flask, and the resulting mixture is refluxed with stirring for 30 min with the aid of an electric heating mantle. Heating is discontinued and a solution of 109 g (128 mL, 1.0 mol) of chlorotrimethylsilane (Note 6) and 184 g (123 mL, 1.1 mol) of ethyl bromoacetate (Note 7) in a mixture of 90 mL of ether and 350 mL of benzene is promptly added through the dropping funnel at such a rate as to maintain the reaction at gentle reflux. The addition takes about 1 hr. After the addition is complete, the mixture is heated at reflux for 1 hr and then cooled in an ice bath. While the mixture is stirred, 300 mL of aqueous 5% hydrochloric acid is added through the dropping funnel over a 10-min period. The liquid layer is decanted into a 3-L separatory funnel and the flask is washed with two 100-mL portions of ether. The ether solutions are added to the separatory funnel, the organic layer is separated, and the aqueous layer is extracted with two 200-mL portions of ether. The organic phases are combined and washed twice with 200-mL portions of saturated aqueous sodium chloride, twice with 200-mL portions of saturated aqueous sodium bicarbonate, and finally with 200 mL of saturated aqueous sodium chloride. The organic layer is dried over anhydrous magnesium sulfate, the mixture is filtered, and the filtrate is concentrated on a rotary evaporator to a volume of about 400 mL. The residual yellow liquid is distilled in a 30-cm vacuum-jacketed Vigreux column at atmospheric pressure until the boiling point is 90°C. The remaining liquid is distilled at reduced pressure to give, after a small forerun, 101–108 g (63–

74%, (Note 8)) of ethyl trimethylsilylacetate, bp 93–94°C (104 mm), n_D^{20} 1.4152–1.4154 (Note 9).

B. *(Z)-3-Trimethylsiloxy-2-pentene.* In a dry, 200-mL flask (Note 10) equipped with a Teflon-coated magnetic stirring bar and a three-way stopcock, one exit of which is capped with a small rubber septum, is quickly placed 1.5 g (ca. 6 mmol) of dried tetrabutylammonium fluoride hydrate (Note 11). With the aid of a hypodermic syringe, 50 mL of dry tetrahydrofuran (THF, (Note 12) is added through the septum, and the clear solution is stirred. After 5 min, the reaction vessel is immersed in a hexane/dry ice bath, and 38.4 g (0.240 mol) of ethyl trimethylsilylacetate is added during 10 min through a syringe that is rinsed with 15 mL of dry THF. After 10 min a solution of 17.2 g (0.200 mol) of 3-pentanone (Note 13) in 15 mL of dry THF is introduced during 10 min to the stirred solution with the aid of a syringe, which is then rinsed with 5 mL of dry THF. The clear solution is stirred for 3 hr, then warmed gradually to 0°C over about 1 hr and finally the temperature is held at 0°C for 2–4 hr (Note 14). Meanwhile, 400 mL of pentane (Note 15) in a dry, nitrogen-filled, 1-L flask equipped with a drying tube and a magnetic stirring bar is cooled with stirring in a hexane/dry ice bath, and the dark-orange reaction mixture is poured into it. The reaction vessel is rinsed with three 50-mL portions of pentane. The pentane rinses are added to the reaction solution and the resulting mixture is filtered through a pad of Hyflo Super Cell on a sintered-glass filter, and the filtrate is washed with 100 mL of saturated aqueous sodium bicarbonate and 100 mL of saturated aqueous sodium chloride. The organic layer is dried over magnesium sulfate, the drying agent is remove by filtration, and the resulting solution is concentrated on a rotary evaporator at room temperature to a volume of 150 mL. The remaining liquid is distilled through a 10-cm Vigreux column. After a very small amount of forerun (< 1 g), 21.9–24.1 g (69–76%) of 3-trimethylsiloxy-2-pentene is obtained, bp 139–142°C; n_D^{20} 1.4133–1.4135 (Note 16).

2. Notes

1. This procedure is based on a report by Fessenden and Fessenden.[2] Cuprous chloride[3] is a more efficient initiator than iodine as specified in the original procedure.
2. The submitters used zinc powder purchased from Koso Chemical (Japan) without any purification. The checkers used product available from Fisher Scientific Company. It is essential to use excess zinc to ensure complete consumption of ethyl bromoacetate, which interrupts the catalytic cycle in Step B of the present silylation reaction.
3. The submitters used cuprous chloride purchased from Koso Chemical Co. Ltd. without purification. The checkers used cuprous chloride available from Fisher Scientific Company.
4. The submitters used diethyl ether, obtained from Showa Ether, after distillation from sodium wire. The checkers distilled the product obtained from Fisher Scientific Company from lithium aluminum hydride.
5. Benzene was distilled over sodium wire before use
6. The submitters used chlorotrimethylsilane obtained from Nakarai Chemical. The material was distilled from calcium hydride or sodium wire before use. The checkers used product available from Aldrich Chemical Company, Inc.
7. The submitters used ethyl bromoacetate (GR grade) obtained from Tokyo Kasei and distilled it before use in an efficient hood. The checkers used product available from Aldrich Chemical Company, Inc.
8. The submitters state that the yield ranged from 68 to 70% for runs made on a 1.5-mol scale.
9. Ethyl trimethylsilylacetate is stable to the usual manipulations, and can be stored in glass

containers for years without change of physical and spectral properties. IR (liquid film) cm^{-1}: 1720, characteristic of α-silyl esters. The reported physical constants are bp 76–77°C (40 mm), n_D^{25} 1.4136,[2] n_D^{20} 1.4149.[4] ^{1}H NMR (CCl_4) δ: 0.17 (s, 9 H, CH_3Si), 1.31 (t, 3 H, J = 7, CH_3CH_2), 1.88 (s, 2 H, $SiCH_2$), and 4.14 (q, 2 H, J = 7, CH_2O).

10. Tetrabutylammonium fluoride is very hygroscopic. A drybox may be used to avoid rapid manipulation of the fluoride in the atmosphere and exposure of the reagent in the storage vessel to moisture. Alternatively, hydrated tetrabutylammonium fluoride (Note 11) can be dried in the reaction vessel and used directly.

11. Tetrabutylammonium fluoride trihydrate obtained from Fluka AG was dried over phosphorus pentoxide for 48 hr at a pressure of 0.1 mm. The hygroscopic fluoride was pulverized with the aid of a spatula in a dry atmosphere. The checkers prepared the dry salt by this method using material obtained from Tridom Chemical, Inc.

Alternatively, the fluoride can be prepared as follows: A 10–40% aqueous or alcoholic solution of tetrabutylammonium hydroxide available from several sources is placed in a glass flask fitted with a Teflon-coated magnetic stirring bar and stirred gently. The pH of the solution is adjusted to about 8 by rapid addition of an almost theoretical amount of 48% aqueous hydrofluoric acid with the aid of a plastic pipette. *Caution! Hydrofluoric acid in contact with the skin produces extremely painful burns. Long, acid-resistant gloves should be worn.* Final adjustment of the pH to 7–8, measured with a pH meter, is achieved by addition of 5% aqueous acid. The bulk of the solvent is removed by distillation on a rotary evaporator at 30°C (1 mm). The resulting white paste is further dried as described above to give the salt as a white mass.

The submitters state that in some cases, probably depending on the source of the hydroxide, the dried salt did not solidify. On such an occasion, the aqueous solution was diluted with deionized water to obtain a 0.5 *M* aqueous solution. The resulting solution was cooled to 5–10°C and allowed to stand to give a white clathrate. The supernatant liquid was removed by a pipette and the clathrate was washed once with cold water. When the clathrate was dried as described above the fluoride was obtained as a solid.[5]

12. Tetrahydrofuran was distilled successively from cuprous chloride and sodium wire,[6] and further purified by distillation from sodium benzophenone ketyl in a recycling still. The checkers used product obtained from Fisher Chemical Company that was distilled from lithium aluminum hydride prior to use.

13. 3-Pentanone obtained form Tokyo Kasei (GR grade) was distilled before use. The checkers used product available from Aldrich Chemical Company, Inc.

14. The reaction is normally complete at −78°C, affording a product of 99.5% isomeric purity. It is advisable, however, to raise the reaction temperature finally to 0°C, since some unknown factors occasionally retard this catalyzed reaction. Development of an orange-to-red color of the mixture usually indicates the progress of the reaction.

15. Pentane was stored over sodium wire. The checkers used product available from Eastman Organic Chemicals.

16. The spectral properties of 3-trimethylsiloxy-2-pentene are as follows: ^{1}H NMR (CCl_4) δ: 0.18 (s, 9 H, $SiCH_3$), 1.03 (t, 3 H, J = 7, CH_3CH_2), 1.48 (d of t, 3 H, CH_3C=CH, J = 1 and 6.5), 2.02 (unresolved quartet, 2 H, CH_2CH_3, J = 7), 4.47 (q, 1 H, J = 7, CH_3CH=C). IR spectrum (liquid film) cm^{-1}: 1678, 1250, and 835. The isomeric purity was 96–99.5% of *Z* isomer as determined by the submitters by GLC comparison with an authentic *E*-[7,8] or *Z*-enriched[8] mixture. The GLC analysis was carried out using the following column and conditions: 3-mm × 6-m stainless steel column, 5% XE-60 on 60–80-mesh Chromosorb P (AW), 80°C, 45 mL of nitrogen per min. The retention times for the *E*-isomer, the *Z*-

isomer, 3-pentanone, and ethyl trimethylsilylacetate are 5.2, 5.6, 6.2, and 15.9 min, respectively.

3. Discussion

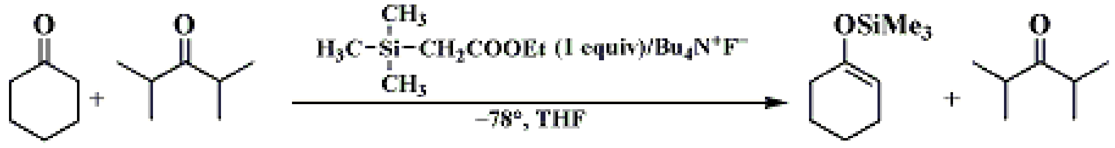
Enol trimethylsilyl ethers belong to a most important class of enol derivatives[9] and serve as good precursors of isomerically pure enolate anions.[8,10] The double bond also resembles that of electron-rich olefins in reactions with electrophiles and sometimes is reactive in electrocyclic reactions.

Among the methods for their preparations, two reactions described by House have been employed widely:[8] a thermodynamically controlled silylation with chlorotrimethylsilane/triethylamine in hot dimethylformamide or a kinetically controlled reaction that involves lithiation with a lithium dialkylamide followed by quenching with the chlorosilane. Each method has its own merits and drawbacks with respect to three important factors: regio-, stereo-, and chemoselectivities.

The present silylation reaction[11] represents a new procedure based on metathetical generation of reactive enolate species,[12] and some characteristic features described below make this reaction complementary to the previous methods.

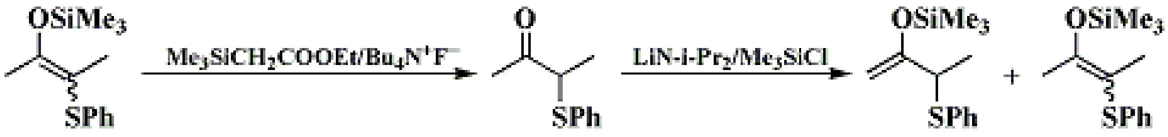
The excellent stereoselectivity as described in the present example is one of the advantages that merits attention.[11] The reaction affords only *Z*-enol silyl ethers when applied to acyclic ketones. For instance, silylation of 5-nonanone and 2-octanone gave (*Z*)-5-trimethylsiloxy-4-nonene and (*Z*)-2-trimethylsiloxy-2-octene (together with 14% of its regio isomer), both in 91% yield.

Chemoselectivity of the reaction constitutes another point of interest. Ketones can be silylated in the presence of functional groups that include oxiranes, esters, nitriles,[11] and even ketones. Thus silylation of one ketone can be performed in the presence of another. The equation shown below illustrates this selectivity.[13]



Alkyl halides[12] and aldehydes[14] are not compatible with the present silylation reaction.

Kinetic selectivity of the silylation reaction is high with methyl isopropyl ketone (99.5% of the less highly substituted isomer),[13] and methyl isobutyl ketone (90%), and fair with 2-methylcyclohexanone (80%).[11] The nature of the regioselectivity of this reaction appears different from that with lithium dialkylamide for which steric factors may influence the regioselectivity. In fact, silylation of 3-phenylthio-2-butanone with ethyl trimethylsilylacetate at 0°C produced 2-phenylthio-3-trimethylsiloxy-2-butene, whereas treatment with lithium diisopropylamide followed by quenching with chlorortrimethylsilane gave mainly the less highly substituted regioisomer.[13]



7 : 3

Since the only by-product of the reaction is ethyl acetate, the silylated product can be employed for further reactions without purification. Examples include the fluoridecatalyzed aldol reaction[15] and bromination with *N*-bromosuccinimide.[11]

The present reaction can be applied to a variety of ketones including four- to eight-membered and twelve-membered cycloalkanones and acyclic and α,β-unsaturated ketones.[11] It has also been used for primary, secondary, and tertiary alcohols,[16] alkanethiols,[16] phenols,[16] and arylacetylenes.[11]

Ethyl trimethylsilylacetate has also been used for the synthesis of α,β-unsaturated esters.[17] The chemistry of tetrabutylammonium fluoride as a base with mild reactivity has been reviewed.[18]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium benzophenone ketyl

chlorortrimethylsilane

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ethyl acetate (141-78-6)

ether, diethyl ether (60-29-7)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

hydrofluoric acid (7664-39-3)

iodine (7553-56-2)

zinc, zinc powder (7440-66-6)

sodium wire (13966-32-0)

cuprous chloride (7758-89-6)

Pentane (109-66-0)

Methyl isobutyl ketone (108-10-1)

2-Octanone (111-13-7)

magnesium sulfate (7487-88-9)

Ethyl bromoacetate (105-36-2)

Methyl isopropyl ketone (563-80-4)

Tetrahydrofuran (109-99-9)

3-pentanone (96-22-0)

lithium aluminum hydride (16853-85-3)

dimethylformamide (68-12-2)

N-bromosuccinimide (128-08-5)

2-methylcyclohexanone (583-60-8)

calcium hydride (7789-78-8)

lithium diisopropylamide (4111-54-0)

CHLOROTRIMETHYLSILANE (75-77-4)

phosphorus pentoxide (1314-56-3)

ETHYL TRIMETHYLSILACETATE

(Z)-3-TRIMETHYLSILOXY-2-PENTENE, Silane, [(1-ethyl-1-propenyl)oxyl]trimethyl-, (Z)- (51425-54-8)

Ethyl trimethylsilylacetate (4071-88-9)

tetrabutylammonium fluoride hydrate (22206-57-1)

3-Trimethylsiloxy-2-pentene

Tetrabutylammonium fluoride (429-41-4)

Tetrabutylammonium fluoride trihydrate (87749-50-6)

tetrabutylammonium hydroxide (2052-49-5)

5-nonanone (502-56-7)

3-phenylthio-2-butanone

2-phenylthio-3-trimethylsiloxy-2-butene

(Z)-5-trimethylsiloxy-4-nonene

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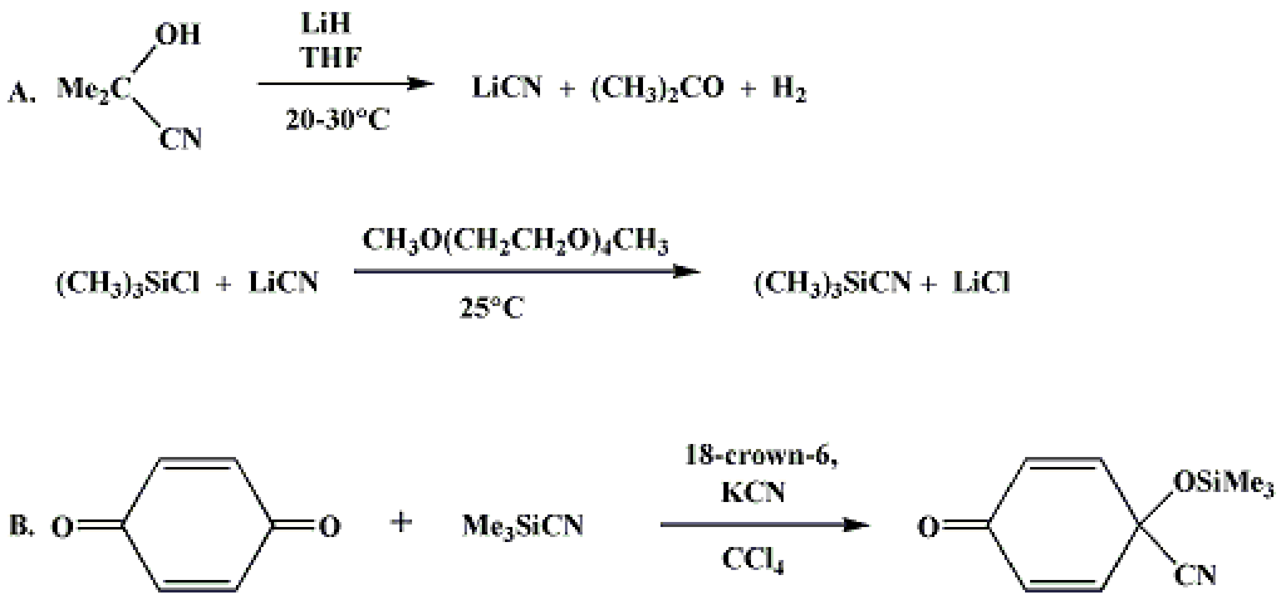
Organic Syntheses, CV 7, 517

TRIMETHYLSILYL CYANIDE: CYANOSILATION OF *p*-BENZOQUINONE

[Silanecarbonitrile, trimethyl]



Submitted by Tom Livinghouse[1]
Checked by Tod Holler, Kevin J. Carlin, and G. Büchi.

1. Procedure

Caution! Trimethylsilyl cyanide is very toxic. All reactions in this sequence should be carried out in a hood.

A. *Trimethylsilyl cyanide.* A 1-L, round-bottomed flask equipped with a magnetic stirrer, nitrogen inlet, and a 60-mL addition funnel is charged with 5.0 g (0.624 mol) of lithium hydride (Note 1) and 500 mL of anhydrous tetrahydrofuran (Note 2). The stirred suspension is cooled in an ice bath and 42.6 g of acetone cyanohydrin (45.7 mL, 0.501 mol) (Note 3) is added dropwise over 15 min. After the addition is complete, the ice bath is removed and the mixture stirred for 2 hr at room temperature (Note 4). The magnetic stirring bar is removed and the solvent evaporated as completely as possible on a rotary evaporator. The white lithium cyanide is then dried in vacuo for 3 hr (Note 5) and (Note 6). The lithium cyanide is freed from the sides of the flask and broken up with a spatula (Note 7). A 250-mL round-bottomed flask equipped with an ice bath, magnetic stirrer, thermometer, and nitrogen inlet is charged with 54.32 g (63.46 ml, 0.500 mol) of trimethylchlorosilane (Note 8) and 100 mL of bis[2-(2-methoxyethoxy)ethyl] ether (Note 9). The lithium cyanide is added to this stirred solution over 15 min through Gooch tubing (Note 10). After the addition is complete, the ice bath is removed and the milky suspension stirred overnight at room temperature. The Gooch tubing and the thermometer are then removed from the reaction flask and a stillhead equipped for downward vacuum distillation is attached. A 100-mL, round-bottomed flask immersed halfway in an acetone-dry ice slush bath (Note 11) is employed as the receiver. The volatile

compounds are distilled under a pressure of 50 mm (bp 25–55°C) by heating the contents of the pot using an oil bath (Note 12). The distillate is carefully redistilled through a well-insulated 15-cm column packed with glass helices under an inert atmosphere. A 25–40 mL forerun (bp 66–113°C), consisting primarily of tetrahydrofuran and hexamethyldisiloxane, is first collected. The second fraction, containing 29–41 g (59–82%) of trimethylsilyl cyanide, bp 114–117°C, n_D^{25} 1.3902 (Note 13), then distills. A purity of ca. 97% was established by GC analysis (Note 14) and (Note 15); the product is suitable for synthetic use without further purification.

B. *Cyanosilylation of p-benzoquinone.* A 100-mL, round-bottomed flask equipped with a magnetic stirrer, West condenser, and a nitrogen inlet is charged with 6.30 g (58.2 mmol) of *p*-benzoquinone (Note 16), 10 mL of dry carbon tetrachloride, and 8 mL (63.03 mmol) of trimethylsilyl cyanide. The stirred suspension is heated to a gentle reflux by means of a heat gun to dissolve all the *p*-benzoquinone. It is then allowed to cool slowly until the crystallization of the *p*-benzoquinone starts (Note 17), at which time 5 mg of the 1 : 1 complex between potassium cyanide and 18-*crown*-6 (Note 18) is added through the top of the condenser. An immediate vigorous reflux sets in and continues for 1–2 min (Note 19). The stirred reaction mixture is permitted to cool slowly to room temperature, whereupon the condenser is removed and 3 g of Florisil (Note 20) is added. After stirring for an additional 15 min, 10 mL of dry carbon tetrachloride is added. The suspension is then filtered and the filtercake leached with three 5-mL portions of carbon tetrachloride. The solvent is evaporated from the filtrate as completely as possible on a rotary evaporator, at which point crystallization of the residue usually begins (Note 21). The last traces of solvent and trimethylsilyl cyanide are then removed in vacuo over 20 hr at 50 • to afford 12.0–12.2 g of crude product. The trimethylsilyl cyanohydrin is recrystallized by dissolving the crude material in 25 mL of hot hexane and allowing the resulting solution to cool slowly to room temperature (Note 22). After collection by filtration the product is rinsed with two 5-mL portions of hexane and airdried to yield 7.54–9.77 g (63%–81%) of white to buff-colored needles, mp 65–67°C (Note 23) and (Note 24).

2. Notes

1. Commercial lithium hydride (Alfa Products, Morton Thiokol, Inc.) was used.
2. Commercial tetrahydrofuran was distilled from sodium benzophenone ketyl immediately before use.
3. Commercial acetone cyanohydrin (Aldrich Chemical Company, Inc.) was used without further purification.
4. A vigorous evolution of hydrogen gas occurs during the addition of the acetone cyanohydrin. Hydrogen evolution virtually ceases after stirring at room temperature for 2 hr.
5. It is essential to exclude atmospheric moisture as much as possible during this operation.
6. A small quantity of tetrahydrofuran remains complexed in the solid lithium cyanide and is separated later in the preparation.
7. This operation must be performed rapidly to avoid water absorption by the hygroscopic lithium cyanide.
8. Commercial trimethylchlorosilane (Silar Laboratories, Inc.) was distilled from calcium hydride immediately before use.

9. Commercial bis[2-(2-methoxyethoxy)ethyl] ether, "tetraglyme" (Eastman Organic Chemicals), was dried over Linde 4A molecular sieves for 24 hr before use.
10. The internal temperature is maintained at or below 35°C during this operation by periodic cooling with an ice bath.
11. Trimethylsilyl cyanide solidifies in the receiver during the course of the distillation. *It is absolutely necessary that the receiver be immersed no more than halfway in the slush bath*. Further immersion may cause the product to solidify in the end of the condenser. This necessitates cessation of the distillation to unclog the apparatus.
12. The temperature of the oil bath is raised from 25 to 110°C over 45 min and then maintained at the upper temperature until no more product distills.
13. The product exhibits the following properties: ^{1}H NMR (CCl_4 with $CHCl_3$ internal standard) δ: 0.4 [s, $Si(CH_3)_3$]; IR (neat) cm^{-1}: 2200 (-CN).
14. The GC analysis was performed on an 8-ft column packed with 5% OV-17 on Anachrome ABS.
15. Trimethylsilyl cyanide hydrolyzes rapidly in moist air and is best stored under an inert atmosphere.
16. Commercial *p*-benzoquinone (Matheson, Coleman, and Bell, Inc.) was recrystallized from 95% ethanol before use.
17. The initiation of crystallization indicates the optimum reaction temperature for the catalyzed cyanosilylation of *p*-benzoquinone. The use of higher temperatures results in excessive darkening of the product and a decrease in yield.
18. The 1 : 1 complex is conveniently prepared by dissolving 0.652 g (10 mmol) of pulverized potassium cyanide and 2.640 g (10 mmol) of commercial 18-*crown*-6 (Aldrich Chemical Company, Inc.) in 45 mL of anhydrous methanol by swirling and warming. The methanol is then evaporated at a rotary evaporator and the white complex dried in vacuo over night.
19. *Caution! Extreme care must be taken during the addition of the catalyst. The addition of too much catalyst or the use of higher reaction temperatures may result in the reaction mixture boiling over.*
20. Florisil obtained from Matheson, Coleman, and Bell, Inc. was used.
21. Crystallization of the residue may also be induced by the addition of a seed crystal or scratching with glass rod.
22. In some instances addition of a seed crystal during cooling is necessary.
23. *p*-Benzoquinone monotrimethylsilyl cyanohydrin darkens on prolonged exposure to light and air. It is best stored under nitrogen in the dark.
24. An analytically pure sample, mp 67–67.5°C, may be obtained by a second recrystallization from cyclohexane: ^{1}H NMR (CCl_4) δ: 0.30 (s, 9, CH_3), 6.30 (d, 1, J = 10, C=CH), 6.83 (d, 1, J = 10, C=CH); IR (CCl_4) cm^{-1}: 1678 (C=O), 1252, 845 (Si-CH_3).

3. Discussion

Trimethylsilyl cyanide is a useful reagent for the preparation of β-amino alcohols,[6] α-amino nitriles,[2] and α-trimethylsiloxyacrylonitriles[3] from the corresponding ketones, imines, and ketenes. The reagent adds rapidly to the carbonyl of aldehydes at 25°C,[6] and the resulting adducts have proved useful precursors for the preparation of carbonyl anion synthons.[4] Enones give exclusively the products derived from 1,2-addition.[6]

Trimethylsilyl cyanide has been prepared in modest yield by the action of hexamethyldisilazane on hydrogen cyanide[5] and the reaction of silver cyanide with trimethylchlorosilane.[5,7] It has been prepared in good yield by the treatment of preformed lithium cyanide (from LiH and HCN) with trimethylchlorosilane in ether.[7] The procedure described here not only affords trimethylsilyl cyanide in good yield, but also avoids the use of hydrogen cyanide and the need for Schlenk ware.

Table I illustrates the cyanosilylation of several representative ketones and aldehydes.

TABLE 1
CYANOSILYLATIONOFKETONESANDALDEHYDES

Substrate	Silylcyanohydrin	Yield (%)	Ref.
Benzophenone	(78)[a]	98	6
Crotonaldehyde	(88)[a]	98	6
Furfural		99	6
Cyclooctanone		94	7
Cyclododecanone		94	7
Camphor		>95[b]	7
α-Tetralone		>95[b]	7
3-Methyl-3-penten-2-one		91	7

[a] No catalyst employed; zinc iodide catalyst used in all other cases.

[b] Yield determined by GLC analysis.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 20
- Org. Syn. Coll. Vol. 7, 294

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium benzophenone ketyl

Florisil

ethanol (64-17-5)

methanol (67-56-1)

ether (60-29-7)

hydrogen (1333-74-0)

hydrogen cyanide (74-90-8)

carbon tetrachloride (56-23-5)

nitrogen (7727-37-9)

potassium cyanide (151-50-8)

cyclohexane (110-82-7)

Benzophenone (119-61-9)

Furfural (98-01-1)

p-benzoquinone (106-51-4)

Acetone cyanohydrin (75-86-5)

camphor (21368-68-3)

Tetrahydrofuran (109-99-9)

α-Tetralone (529-34-0)

silver cyanide (506-64-9)

hexane (110-54-3)

crotonaldehyde (123-73-9)

calcium hydride (7789-78-8)

zinc iodide

Cyclooctanone (502-49-8)

cyclododecanone (830-13-7)

lithium hydride (7580-67-8)

Trimethylsilyl cyanide, Silanecarbonitrile, trimethyl (7677-24-9)

trimethylchlorosilane (75-77-4)

hexamethyldisiloxane (107-46-0)

hexamethyldisilazane

lithium cyanide

bis[2-(2-methoxyethoxy)ethyl] ether (143-24-8)

3-Methyl-3-penten-2-one

p-Benzoquinone monotrimethylsilyl cyanohydrin (40861-57-2)

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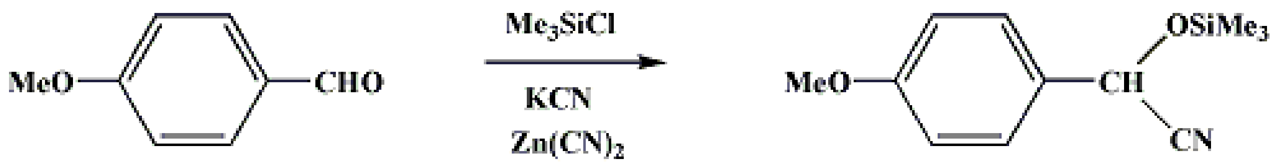
Organic Syntheses, *CV 7*, *521*

in situ CYANOSILYLATION OF CARBONYL COMPOUNDS: *O*-TRIMETHYLSILYL-4-METHOXYMANDELONITRILE

[Benzeneacetonitrile, 4-methoxy-α-[(trimethylsilyl)oxy]-]



Submitted by J. K. Rasmussen and S. M. Heilmann[1].
Checked by M. F. Semmelhack and Raj N. Misra.

1. Procedure

Caution! Potassium cyanide is highly toxic. Care should be taken to avoid direct contact of the chemical or its solutions with the skin, and impervious gloves should be worn to handle the reagent.

In a 1-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, a reflux condenser fitted with a nitrogen-inlet tube, and a rubber septum (Note 1) are placed 97.5 g (1.5 mol) of finely ground potassium cyanide (Note 2), 81.4 g (0.75 mol, 95.2 mL) of chlorotrimethylsilane (Note 3), 68 g (0.5 mol) of *p*-anisaldehyde (Note 4), 100 mL of dry acetonitrile (Note 5), and 0.5 g (4.25 mmol) of zinc cyanide (Note 6). The reaction mixture is blanketed with dry nitrogen (Note 7), stirring is begun, and the temperature is raised (heating mantle) to maintain gentle reflux. Heating is continued under these conditions for 30 hr (Note 8), with the occasional removal of small samples by syringe for monitoring by GLC (Note 9). On completion of the reaction, the mixture is cooled to ambient temperature and filtered. The filtercake is washed twice with 50 mL of dry acetonitrile and the combined filtrates are concentrated on a rotary evaporator. The residue is distilled at reduced pressure (Note 10). The yield of the colorless liquid (Note 10), which boils at 93–98°C (0.15 mm), amounts to 105–115 g (90–98% based on *p*-anisaldehyde).

2. Notes

1. All glassware was oven-dried overnight at 130°C, assembled hot, and allowed to cool under a flow of dry nitrogen.
2. Reagent-grade potassium cyanide was purchased from Matheson, Coleman and Bell, and dried at 115°C (0.5 mm) for 24 hr. The checkers found it necessary to use newly purchased potassium cyanide. The use of potassium cyanide which was several years old gave incomplete reaction even at extended reaction times. The large excess of potassium cyanide is used simply to obtain convenient reaction times. For comparison, use of 1.5 equiv of KCN gave 38% conversion under conditions where 3 equiv produced 100% conversion.

3. Chlorotrimethylsilane was supplied by Petrarch Systems, Inc. and used without further purification.
4. *p*-Anisaldehyde (4-methoxybenzaldehyde), 95%, was used as supplied by Aldrich Chemical Co.
5. Acetonitrile, 99%, supplied by Aldrich Chemical Co., was dried over Linde 4A molecular sieves for 12 hr and decanted.
6. Technical-grade zinc cyanide was used as supplied by MCB, Inc. Other Lewis acids, notably aluminum chloride, zinc bromide, and zinc iodide, may be used as catalysts for the reaction.
7. To "blanket with nitrogen," the checkers simply prepared the reaction mixture with the flask open, introduced a flow of nitrogen over the surface for a few minutes, and then closed the system with an exit through a mercury bubbler to maintain a positive pressure.
8. The reaction time required depends on the catalyst. Zinc iodide, zinc cyanide, and zinc bromide produce essentially complete conversion under these conditions in approximately 16.5, 28, and 30 hr, respectively, probably reflecting solubility differences. When zinc iodide is used, the distilled product is often colored because of the formation of small amounts of iodine.
9. This may be done using a simple boiling-point column. We have employed either 10% UCW-98 on Chromasorb W or SP-2100 on 80/100 Supelcoport G2642. The checkers did not monitor the reaction except to extract a small sample after 30 hr in order to verify the absence of starting aldehyde by ^{1}H NMR spectroscopy.
10. Distillation should be below 100°C. In some instances, at distillation temperatures in excess of 100°C, reversion to the starting aldehyde and trimethylsilyl cyanide has been observed. The pure compound shows the following spectral data: ^{1}H NMR (CCl_4): δ 0.28 (s, 9 H), 3.86 (s, 3 H), 5.35 (s, 1 H), 6.83 (d, J = 9, 2 H), 7.35 (d, J = 9, 2 H); IR (film) cm^{-1}: 2965, 1614, 1512, 1258, 1180, 1089, 878, 850. The purity of the crude product is generally such that a distillation forecut need not be taken.

3. Discussion

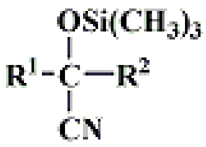
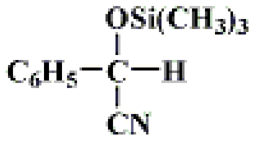
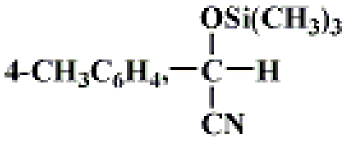
Cyanosilylations have generally been accomplished by addition of a trialkylsilyl cyanide to the corresponding aldehyde or ketone.[2,3,4,5] Although this method is straight-forward and proceeds in good to excellent yield, use of preformed trialkylsilyl cyanides has a number of disadvantages, particularly when one considers larger-scale preparations. Trialkylsilyl cyanides can be prepared[6] by treatment of the corresponding silyl chlorides with either silver cyanide or lithium cyanide generated in situ by reaction of lithium hydride with hydrogen cyanide. The former procedure involves the use of stoichiometric quantities of a rather expensive reagent, while the latter involves handling fairly large quantities of hydrogen cyanide gas. In addition, both procedures require relatively long reaction times and distillation of the silyl cyanide, and produce only moderate to good yields. More recently, improved syntheses of trimethylsilyl cyanide have appeared.[7,8] Commercially available tremethylsilyl cyanide is also rather expensive.

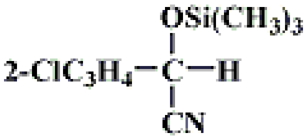
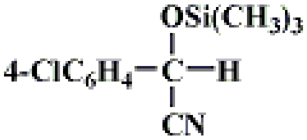
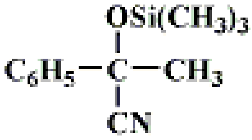
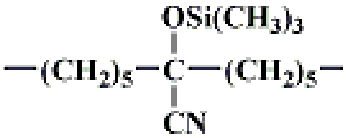
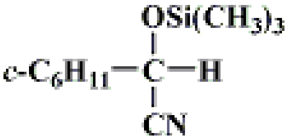
Silylated cyanohydrins have also been prepared via silylation of cyanohydrins themselves[9] and by the addition of hydrogen cyanide to silyl enol ethers.[10] Silylated cyanohydrins have

proved to be quite useful in a variety of synthetic transformations, including the regiospecific protection of *p*-quinones,[11] as intermediates in an efficient synthesis of α-aminomethyl alcohols,[6] and for the preparation of ketone cyanohydrins themselves.[12] The silylated cyanohydrins of heteroaromatic aldehydes have found extensive use as acyl anion equivalents, providing general syntheses of ketones[13] and acyloins.[14] Acyloins are also readily prepared via addition of Grignard reagents to silylated cyanohydrins followed by hydrolysis of the magnesium imine intermediate.[15] Alternatively, reduction of this same intermediate with borohydride provides a general synthesis of aminoalcohols.[16] Tetronic acids may be produced on reaction of silylated cyanohydrins with Reformatsky reagents.[17]

The in situ cyanosilylation of *p*-anisaldehyde is only one example of the reaction that can be applied to aldehydes and ketones in general.[18] The simplicity of this one-pot procedure, coupled with the use of inexpensive reagents, are important advantages over previous methods. The silylated cyanohydrins shown in Table I were prepared under conditions similar to those described here. Enolizable ketones and aldehydes have a tendency to produce silyl enol ethers as by-products in addition to the desired cyanohydrins. The problem can be overcome by using a modified procedure in which dimethylformamide is employed as solvent.[18]

TABLE I
InSituCyanosilylationofCarbonylCompounds

	Distilled Yield (%)	bp (°C) (pressure, mm)
$R^1 = C_6H_5$, $R^2 = H$		
	95–98	93–95 (1.75)
$R^1 = 4\text{-}CH_3C_6H_4$, $R^2 = H$		
	91	87 (0.45)

R^1 = 2-ClC_6H_4, R^2 = H		
	99	92–93 (0.45)
R^1 = 4-ClC_6H_4, R^2 = H		
	93	100 (0.45)
R^1 = C_6H_5, R^2 = CH_3		
	93	73–75 (0.9)
R^1, R^2 = $(-CH_2-)_5$		
	89	96 (15)
R^1 = *c*-C_6H_{11}, R^2 = H		
	87	106–108 (6.5)

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

tremethylsilyl cyanide

acetonitrile (75-05-8)

hydrogen cyanide (74-90-8)

nitrogen (7727-37-9)

potassium cyanide (151-50-8)

iodine (7553-56-2)

aluminum chloride (3495-54-3)

dimethylformamide (68-12-2)

silver cyanide (506-64-9)

zinc bromide (7699-45-8)

zinc cyanide (557-21-1)

zinc iodide

lithium hydride (7580-67-8)

Trimethylsilyl cyanide (7677-24-9)

CHLOROTRIMETHYLSILANE (75-77-4)

lithium cyanide

Benzeneacetonitrile, 4-methoxy-α-[(trimethylsilyl)oxy]- (66985-48-6)

4-methoxybenzaldehyde, p-anisaldehyde (123-11-5)

silyl cyanide

O-Trimethylsilyl-4-methoxymandelonitrile

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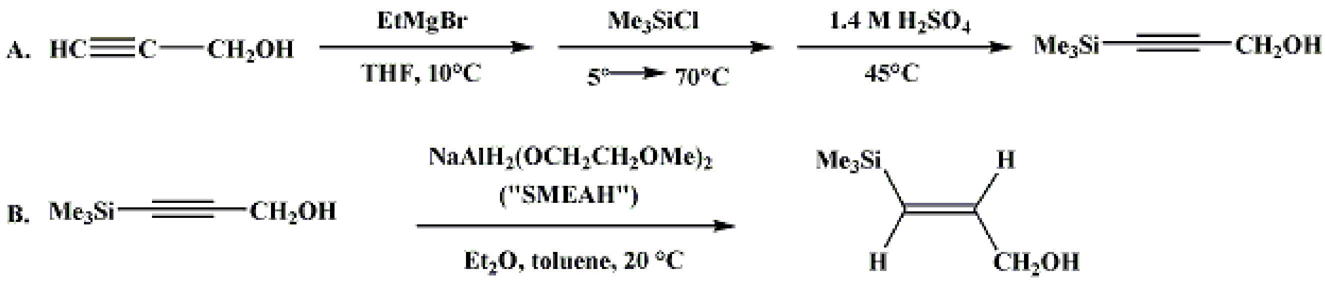
Organic Syntheses, CV 7, 524

STEREOSPECIFIC REDUCTION OF PROPARGYL ALCOHOLS: (*E*)-3-TRIMETHYLSILYL-2-PROPEN-1-OL

[2-Propen-1-ol, 3-(trimethylsilyl)-, (*E*)-]



Submitted by Todd K. Jones and Scott E. Denmark[1].
Checked by Steven M. Viti and K. Barry Sharplpess.

1. Procedure

A. *3-Trimethylsilyl-2-propyn-1-ol.* A 3-L, three-necked, round-bottomed flask (equipped with a mechanical stirrer and a thermometer) is fitted with a Claisen adapter on which is mounted a 250-mL pressure-equalizing addition funnel and a reflux condenser (Note 1). The apparatus is flushed with nitrogen and then charged with 48.7 g (2.0 mol) of magnesium turnings and 1 L of dry tetrahydrofuran (Note 2). To the stirred suspension is added dropwise 149.5 mL (218.3 g, 2.0 mol) of bromoethane over 3 hr while maintaining the temperature at 50°C or less. After complete addition, the gray–green solution is heated at 50°C for 1 hr and then cooled to 5°C on ice. A solution of 41.6 mL (40.5 g, 0.72 mol) of propargyl alcohol (Note 3) in 42 mL of tetrahydrofuran is cautiously added dropwise to the gray suspension over 2.25 hr while maintaining the temperature at 10°C or less (Note 4). The addition funnel is rinsed with 25 mL of tetrahydrofuran and the gray–green suspension is stirred overnight. The resulting solution is cooled to 5°C on ice and the addition funnel is charged with 254 mL (217 g, 2.0 mol) of chlorotrimethylsilane (Note 5). This is added dropwise to the stirred solution over 1 hr while maintaining the temperature at 25°C or less by external cooling with ice. After complete addition, the mixture is heated to reflux for 2 hr with a heating mantle (Note 6). The suspension is cooled to 20°C on ice and then 800 mL of 1.4 *M* aqueous sulfuric acid is cautiously added over 0.75 hr so that the temperature remains below 45°C. The resulting solution is stirred for 5 min and then 600 mL of ether is added. Both phases are transferred to a 4-L separatory funnel and the layers are separated. The aqueous phase is extracted twice with 400-mL portions of ether and all ether layers are individually washed in series with two 1-L portions of water and once with 800 mL of saturated sodium chloride solution. The combined organic extracts are dried over magnesium sulfate and concentrated by rotary evaporation. The yellow–brown residue is purified by short path distillation to afford 82–86 g (91–94% yield) of 3-trimethylsilyl-2-propyn-1-ol as a clear, colorless liquid (Note 7), bp 76°C (20 mm) (Note 8).

B. *(E)-3-Trimethylsilyl-2-propen-1-ol.* A three-necked, 2-L, round-bottomed flask fitted with a thermometer, nitrogen inlet, 250-mL pressure-equalizing addition funnel, and magnetic stirring bar is charged with 147 mL of a 3.4 *M* solution of sodium bis(2-methoxyethoxy)aluminum hydride (SMEAH, (Note 9)) and 200 mL of anhydrous ether (Note 10). The SMEAH solution is cooled to 3°C on ice and then treated dropwise from the addition funnel with a solution of 40 g (0.31 mol) of 3-trimethylsilyl-2-propyn-1-ol in 180 mL of ether over 1.25 hr, while maintaining the temperature at 5°C or less. Then 10 min after complete addition, the ice bath is removed and the reaction is complete within 1 hr (Note 11). The mixture is cooled to 0°C and then quenched by the addition of 1 L of 3.6 *M* aqueous sulfuric acid (Note 12). The layers are separated in a separatory funnel and the aqueous phase is extracted twice with 200-mL portions of ether. All ether layers are individually washed in series with two 200-mL portions of water and once with 200 mL of saturated sodium chloride. The combined organic extracts are dried over magnesium sulfate and concentrated by rotary evaporation. Distillation of the yellow residue with a capillary bleed affords 27.7–29.0 g (68–71%) of (*E*)-3-trimethylsilyl-2-propen-1-ol (Note 13) as a clear, colorless liquid, bp 73–75°C (20 mm) (Note 14).

2. Notes

1. It is not necessary to flame or oven-dry this apparatus, but a nitrogen inlet on the reflux condenser is desirable. The size of the stirring paddle is critical because of the viscous nature of the solution during this protection step. A paddle at least 11 cm in length is recommended to ensure complete mixing.
2. Magnesium turnings and bromoethane are Mallinckrodt AR grade and are used without purification. Tetrahydrofuran is Aldrich Gold Label and is distilled from sodium benzophenone ketyl prior to use.
3. Propargyl alcohol is obtained from Aldrich Chemical Company, Inc. and is distilled from potassium carbonate.
4. Evolution of ethane can conveniently be monitored with a Nujol bubbler in the nitrogen line by turning off the nitrogen flow.
5. Chlorotrimethylsilane is purchased from Silar and used as received.
6. The progress of the reaction can be monitored by gas chromatography. Column: 5% Carbowax 12 M on acid-washed Chromosorb W, 6 ft × one-eighth in; temperature program: 70°C (2 min), 20°C/min, 200°C (5 min). Retention times: propargyl alcohol, 2.4 min; 3-trimethyl-2-propyn-1-ol, 4.8 min.
7. *Caution! The distillation pot may ignite if it is exposed to air before it is allowed to cool.* The product thus obtained is 94–98% pure by GC analysis and is of suitable purity for reduction. Further purification can be effected by distillation through a 6-in. Vigreux column.
8. The product has the following spectral characteristics: ^{1}H NMR (90 MHz, $CDCl_3$) δ: 0.27 [s, 9 H, $(CH_3)_3Si$], 1.65 (s, 1 H, OH), 4.28 [s, 2 H, 2 H-C(1)].
9. Sodium bis(2-methoxyethoxy)aluminum hydride is obtained as a 70% solution in toluene from Aldrich Chemical Company, Inc. (Red-Al). Iodometric titration gives a 3.6 *M* concentration.
10. Anhydrous ether is obtained from Mallinckrodt, Inc. (AR grade) and used without purification.
11. The reaction can be monitored by gas chromatography (Note 6), temperature program: 70°C (2 min), 20°C/min, 150°C (2 min). Retention times: (*E*)-3-trimethylsilyl-2-propen-1-ol, 4.2 min; 3-trimethylsilyl-2-propyn-1-ol, 6.1 min.
12. A vigorous evolution of hydrogen accompanies the addition of the first milliliters of sulfuric acid. The reaction mixture becomes gelatinous and unstirable but clarifies on further addition of acid.
13. The product is 100% E geometry by GC analysis.
14. The product has the following spectral characteristics: ^{1}H NMR(90 MHz, $CDCl_3$) δ: 0.23 [s, 9 H, $(CH_3)_3Si$], 1.5 (t, 1 H, *J* = 6, OH), 4.22 [d of d, 2 H, *J* = 6 and 4, 2 H-C(1)], 5.93 [d, 1 H, *J* = 18, H-C(3)], 6.23 [d of t, 1 H, *J* = 18 and 4, H-C(2)].

3. Discussion

The silylation of propargyl alcohol dianion[2] described here is a further modification of the procedure recently reported.[3] By replacing ether with tetrahydrofuran the reaction mixture is more manageable and the silyl ether can be hydrolyzed in situ obviating an unnecessary workup and distillation. The yield correspondingly improves by up to 91–94%. Silylation of the dilithium salt in ether is reported[4] to proceed in 86% yield.

Reduction of 3-trimethylsilyl-2-propyn-1-ol exemplifies the problem of stereoselectivity in hydride reduction of acetylenic alcohols to *E*-allyl alcohols.[5 6] Early reports[7 8] that lithium aluminum hydride stereoselectively reduced acetylenic alcohols gave way to closer scrutiny, which revealed a striking solvent dependence of the stereochemistry.[9] Specifically, the percentage of trans reduction is seen to increase with increasing Lewis basicity of solvent. Similarly, the addition of less Lewis acidic cations to the reducing mixture leads to improved trans : cis ratios.[10 11] Sodium bis(2-methoxyethoxy)aluminum hydride (SMEAH)[12 13 14] makes use of these phenomena simultaneously (even in ether–toluene mixtures) and leads to completely stereospecific trans reduction where lithium aluminum hydride in various solvents or with sodium methoxide is less selective.[3,15,16 17] The use of SMEAH to reduce stereospecifically other acetylenic alcohols has been reported.[18 19]

(*E*)-3-Trimethylsilyl-2-propen-1-ol is a versatile intermediate used to introduce organosilicon functional groups into organic molecules.[15,20] The corresponding aldehyde has found use in the preparation of β-silyl divinyl ketones[21 22 23 24] and as a precursor for 1-trimethylsilyl-substituted dienes.[16,17,25]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 510

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium benzophenone ketyl

PROPARGYL ALCOHOLS

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

ether (60-29-7)

hydrogen (1333-74-0)

magnesium turnings (7439-95-4)

sodium chloride (7647-14-5)

bromoethane (74-96-4)

nitrogen (7727-37-9)

sodium methoxide (124-41-4)

toluene (108-88-3)

magnesium sulfate (7487-88-9)

ethane (74-84-0)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

acetylenic alcohols (32038-79-2)

propargyl alcohol (107-19-7)

CHLOROTRIMETHYLSILANE (75-77-4)

3-Trimethylsilyl-2-propyn-1-ol (5272-36-6)

sodium bis(2-methoxyethoxy)aluminum hydride

3-trimethyl-2-propyn-1-ol (590-38-5)

(E)-3-Trimethylsilyl-2-propen-1-ol, 2-Propen-1-ol, 3-(trimethylsilyl)-, (E)- (59376-64-6)

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Organic Syntheses, CV 7, 528

TRIS(DIMETHYLAMINO)SULFONIUM DIFLUOROTRIMETHYLSILICATE

[Sulfur(1+), tris(*N*-methylmethanaminato)-, difluorotrimethylsilicate(1-)]

Submitted by William J. Middleton[1]
Checked by Fred G. West and Edwin Vedejs.

1. Procedure

Caution! This procedure should be conducted in an efficient hood to avoid exposure to the toxic gas sulfur tetrafluoride.

A dry, 500-mL, four-necked flask equipped with a magnetic stirrer, dry ice condenser, thermometer (–100° – 50°C) and a gas inlet tube is assembled as shown in f.htmigure 1 (connections were all-glass or polyethylene tubing). The system is flushed with nitrogen through three-way stopcocks A and B, the four-necked flask is charged with 150 mL of dry ether (Note 1), and the dropping funnel is charged with 46.9 g (0.40 mol) of *N*,*N*-dimethylaminotrimethylsilane (Note 2). The reaction vessel is maintained under a positive nitrogen pressure using a bypass nitrogen stream and bubbler. Stopcock A is connected to the sulfur tetrafluoride (SF_4) tank (Note 3) and stopcock B is turned to vent directly into a nitrogen bypass line and bubbler. While the graduated cylinder C is cooled in acetone-dry ice, SF_4 is slowly passed into the cylinder until 7 mL (13 g at –70°C, 0.12 mol) of liquid SF_4 have condensed. Stopcock A is closed and B is vented directly into the three-necked flask. Removal of the cooling bath from graduated cylinder C allows distillation of SF_4 into the cooled reaction vessel.

Figure 1

Figure 1

A slow stream of nitrogen is passed into the reaction vessel through stopcock B and the *N*,*N*-dimethylaminotrimethylsilane is added to the stirred SF_4 solution at a rate sufficiently slow to keep the temperature below –60°C (about 30 min). The cooling bath is removed, the mixture is allowed to warm to room temperature, and the entire system is placed inside a nitrogen-flushed glove bag. The dropping funnel and condenser are replaced by stoppers, stopcock B is closed, and the closed system is stirred for 3 days with constant nitrogen flow through the glove bag (Note 4). During

this time, the product separates as fine crystals. The crystals are collected in a nitrogen pressure filter, washed with 50–100 mL of dry ether, and dried by passing a stream of dry nitrogen through them to give 23–26 g (71–78% yield) of tris(dimethylamino) sulfonium difluorotrimethylsilicate as hygroscopic (Note 5), colorless needles, mp 98–101°C (Note 6).

2. Notes

1. It is important that the ether be very dry (distilled from Na/benzophenone). Otherwise, the quality of the product and the yield will be substantially lower.
2. *N,N*-Dimethylaminotrimethylsilane is available from Petrarch Systems, Inc. Care should be taken to assure that there is no free dimethylamine present. Commercial samples can be purified by distillation through a 6-in. Vigreux column, bp 86–87°C. The submitters used a spinning band column for removal of hexamethyl-disiloxane, bp 99–100°C, which is present as a contaminant.
3. Sulfur tetrafluoride is available from Air Products and Chemicals, Inc. or Matheson Gas Products. Commercial SF_4 was used without purification. In a more convenient modification of this procedure, dimethylaminosulfur trifluoride (methyl DAST), available from Carbolabs, Inc., can be substituted for SF_4. Dimethylaminosulfur trifluoride (1 mol) is mixed with dry ether and dimethylaminotrimethylsilane (2.1 mol) is added over a one-half–2 hr period with the temperature held below 20°C. After this addition, all other aspects of the run are carried out in the same manner as those of the procedure using SF_4.
4. The submitters obtained good yields without a glove bag, but the checkers encountered 30–40% yield reduction without this precaution. A drybox is also suitable. More than 3 days may be required for the reaction to go to completion if the laboratory temperature drops below 20°C.
5. Because tris(dimethylamino)sulfonium difluorotrimethylsilicate is very hygroscopic, it is best transferred in a dry atmosphere of nitrogen or argon (dry box or glove bag).
6. Even a brief exposure to moist air will cause the product to react with the available water vapor to give $(Me_2N)_3S^+ HF_2^-$ and $(Me_3Si)_2O$, and the presence of these products will appreciably lower the melting point. A melting point as low as 58–62°C can be obtained after a brief exposure.

3. Discussion

Tris(dimethylamino)sulfonium difluorotrimethylsilicate is a source of soluble organic fluoride ion of high anionic reactivity. Fluoride ion from this salt and other tris (dialkylamino)sulfonium difluorotrimethylsilicates has been used to displace halogen from carbon[2] and to cleave Si-O[3,4,5,6,7] and Si-C=O[7,8] bonds. Since these salts can be prepared in a rigorously anhydrous state, they have an advantage over quaternary ammonium fluorides, which usually contain some water. Tris(dialkylamino)sulfonium difluorotrimethylsilicates have also been used to prepare other sulfonium salts with

high nucleophilic reactivity, including $(R_2N)_3S^+$ enolates,[6] phenoxide,[5] cyanide, azides, and cyanates.[2]

This method has been used to prepare several different tris(dialkylamino)sulfonium difluorotrimethylsilicates, including salts with greater organic solubility such as the tris (diethylamino)sulfonium[2,3] and tris(pyrrolidino)sulfonium[2] difluorotrimethylsilicates. The tris(dimethylamino)sulfonium salt, however, is highly crystalline and thus has an advantage in ease of preparation and purification over these other salts.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 326

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Sulfur(1+), tris(N-methylmethanaminato)-, difluorotrimethylsilicate(1-)

SF_4

ether (60-29-7)

nitrogen (7727-37-9)

carbon (7782-42-5)

Benzophenone (119-61-9)

Na (13966-32-0)

dimethylamine (124-40-3)

sulfur tetrafluoride (7783-60-0)

argon (7440-37-1)

hexamethyl-disiloxane (107-46-0)

dimethylaminosulfur trifluoride (3880-03-3)

Tris(dimethylamino)sulfonium difluorotrimethylsilicate (59218-87-0)

dimethylaminotrimethylsilane, N,N-dimethylaminotrimethylsilane (2083-91-2)

phenoxide

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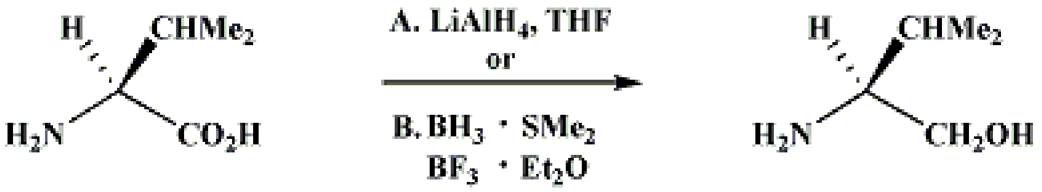
Organic Syntheses, CV 7, 530

REDUCTION OF α-AMINO ACIDS: L-VALINOL

[1-Butanol, 2-amino-3-methyl-, (S)-]



Submitted by D. A. Dickman[1], A. I. Meyers[1], G. A. Smith[2], and R. E. Gawley[2].
Checked by (A) Karl M. Smith, Clayton H. Heathcock, (B) Alan T. Johnson, Kraig M. Yager, and James D. White.

1. Procedure

Caution! A. Because of the hydrogen gas evolved during this reaction, this procedure should be carried out in an efficient fume hood.

An oven-dried, 3-L, three-necked flask equipped with a mechanical stirrer, a Friedrich condenser, and a nitrogen-inlet tube is flushed with nitrogen, and then charged with a suspension of lithium aluminum hydride (47.9 g, 1.26 mol) in 1200 mL of tetrahydrofuran (THF) (Note 1). The mixture is cooled (10°C, ice bath) and L-valine (100 g, 0.85 mol) is added in portions over a 30-min period from a 200-mL round-bottomed flask connected to the reaction flask via a flexible plastic sleeve so as not to produce too vigorous an evolution of hydrogen (Note 2). After the addition is complete, the plastic sleeve is replaced by a stopper, the ice bath is removed, and the reaction mixture is warmed to room temperature and then refluxed for 16 hr. The reaction mixture is then cooled again (10°C, ice bath) and diluted with ethyl ether (1000 mL) (Note 3). The reaction is quenched over a 30-min period with water (47 mL) (*Caution! See (Note 4)*, aqueous 15% sodium hydroxide (47 mL, over 20 min), and water (141 mL, over 30 min). The solution is stirred for 30 min and the white precipitate is filtered. The filter cake is washed with ethyl ether (3 × 150 mL) and the organic filtrates are combined, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. Distillation of the residue under vacuum affords L-valinol (63.9–65.7 g, 73–75%) (Note 5) as a clear liquid: bp 63–65°C (0.9 mm) (Note 6): $[\alpha]^{20}_{D}$ + 14.6° (neat); n^{20}_{D} 1.455; IR (neat) cm^{1}: 3300, 1590; ^{1}H NMR ($CDCl_3$) δ: 0.92 (d, 6 H), 2.38–2.74 (m, 4 H), 3.13–3.78 (m, 2 H).

B. *Caution! Because of the foul odor of the methyl sulfide given off, this procedure, up to the methanol quench, should be carried out in a hood.*

A 2-L, three-necked, round-bottomed flask is equipped with a mechanical stirrer, heating mantel, 250-mL graduated addition funnel, and an 8-in., air-cooled reflux

condenser (West type) topped with a water-cooled distillation head and a 1-L receiving flask. It is connected to a nitrogen line through the still head. The glassware is either oven-dried and cooled in a desiccator or flame-dried and assembled while still hot. The assembly is flushed with nitrogen and charged with 200 g of L-valine (1.7 mol), 400 mL of tetrahydrofuran (THF) (Note 1), and 210 mL of freshly distilled boron trifluoride etherate (242 g, 1.7 mol). The mixture is heated at a rate sufficient to cause the THF to reflux gently (Note 7) and 188 mL (1.88 mol) of borane–methyl sulfide complex (BMS) (Note 8) is added dropwise over the course of 2 hr (Note 9). The solution is then refluxed for 18 hr. The methyl sulfide that has collected at the stillhead is discarded (Note 10), and the reaction mixture is cooled to 0°C and quenched by the slow addition of 200 mL of methanol. The addition funnel is replaced by a glass stopper, and the air-cooled condenser is removed, leaving the flask equipped for distillation of solvent through the distillation head. The reaction mixture is concentrated under reduced pressure with heating and stirring. The distillation head is replaced by a water-cooled reflux condenser, and the residue is dissolved in 1 L of 6 *M* sodium hydroxide and refluxed for 4 hr. The mixture is saturated with potassium carbonate (ca. 400 g); cooled; filtered through a Celite pad on a coarse, fritted funnel; and extracted with three 1-L portions of chloroform. The combined extracts are washed with three portions of saturated sodium chloride (500 mL each), stirred over anhydrous potassium carbonate for 24 hr, and concentrated under reduced pressure to give a yellow oil. The crude material is vacuum distilled to give 77.5 g (44%) of purified L-valinol, bp 62–67°C/2.5 mm(Note 6); $[\alpha]_D^{20}$ + 14.6° (neat), n_D^{20} 1.455; IR (neat film) cm^{-1}: 3300 (OH), and 1590 (NH_2); NMR δ: 0.92 (d, 6 H), 1.54 (m, 1 H), 2.38–2.74 (m, 4 H), 3.13–3.78 (m, 2 H).

2. Notes

1. Tetrahydrofuran is dried by distillation from sodium/benzophenone ketyl.
2. The hydrogen gas released during the addition of the amino acid should be vented through the nitrogen inlet to a bubbler at the back of the fume hood, well away from the mechanical stirrer motor and any other source of electrical spark.
3. Dilution is necessary to keep the reaction mixture from becoming too thick during the quench. Dilution with THF results in significantly lower yields.
4. An addition funnel was used for the dropwise addition of water. Care *must* be taken during this quench to ensure that all the escaping hydrogen gas is vented to the back of the fume hood through the nitrogen bubbler.
5. The submitters reported a yield of 73.7 g (84%).
6. The checkers found that L-valinol (mp 29–31°C) solidifies on distillation and will clog a water-cooled condenser. The use of a heat gun is recommended to avoid obstruction of the distillation pathway.
7. The temperature is maintained sufficiently high so that THF refluxes in the aircooled condenser while ether and methyl sulfide distill through the short-path distillation head.
8. The borane–methyl sulfide complex is available from Aldrich Chemical Company, Inc.

9. It is important that gentle reflux be maintained throughout the addition. If the solution is not heated during this period, an exothermic reaction occurs when the solution is refluxed.
10. Methyl sulfide should be destroyed by slowly pouring the volatile distillate into I gallon of household bleach (5% sodium hypochlorite). After 30 min, the bleach solution may be discarded in the drain.

3. Discussion

The reduction of amino acids to the corresponding amino alcohols via their ethyl ester hydrochlorides has been reported using lithium aluminum hydride[3] and sodium borohydride.[4] The reduction of several amino acids with borane–methyl sulfide (BMS) has also been reported.[5] The reduction of proline to prolinol with lithium aluminum hydride in THF was reported by Enders[6] and of valine to valinol by Meyers.[7] Procedure A (see Section A) is adapted from the latter work. The submitters have used the same procedure to reduce alanine to alaninol (70% yield), phenylglycine to phenylglycinol (76% yield), phenylalanine to phenylalaninol (87% yield), and *N*-benzoylvaline to *N*-benzylvalinol (76% yield).

Procedure A using LAH is faster and more convenient than the BMS procedure (B). Both procedures are general for the reduction of amino acids to amino alcohols. If functional group incompatibility is precluded, lithium aluminum hydride reduction is preferable.

The borane procedure (B) is a hybrid of two methods, Lane's procedure for BMS/trimethyl borate reduction of anthranilic acid,[8] and Brown's procedure for enhanced-rate reductions of several functional groups with BMS by distilling off the methyl sulfide during the course of the reaction.[9] The submitters have obtained a 97% crude yield (44–51% yield after distillation) of prolinol using this procedure. Lane reports that the following additional amino acids can be reduced using BMS/BF_3 etherate: leucine, phenylalanine, and 6-aminocaproic acid.[5] Meyers has added phenylglycine to the list, and has confirmed the optical purity of the amino alcohols obtained by preparation of the Mosher amides.[10]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 204
- Org. Syn. Coll. Vol. 8, 528

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

benzophenone ketyl

BMS

BF_3 etherate

potassium carbonate (584-08-7)

methanol (67-56-1)

ethyl ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium chloride (7647-14-5)

alanine (56-41-7)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

sodium (13966-32-0)

Anthranilic Acid (118-92-3)

sodium hypochlorite (7681-52-9)

6-aminocaproic acid (60-32-2)

borane (7440-42-8)

methyl sulfide (75-18-3)

phenylalanine (63-91-2)

proline (147-85-3)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

leucine (61-90-5)

valine (72-18-4)

phenylglycine (103-01-5)

boron trifluoride etherate (109-63-7)

sodium borohydride (16940-66-2)

trimethyl borate (121-43-7)

L-Valinol, 1-Butanol, 2-amino-3-methyl-, (S)-, valinol (2026-48-4)

prolinol (23356-96-9)

alaninol (2749-11-3)

phenylglycinol (7568-93-6)

phenylalaninol (3182-95-4)

N-benzoylvaline

N-benzylvalinol

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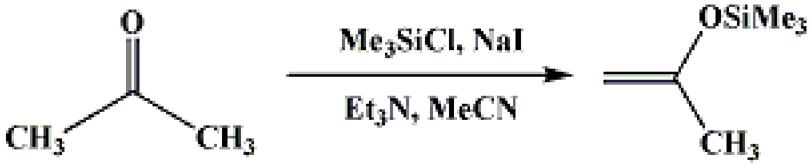
Organic Syntheses, CV 8, 1

ACETONE TRIMETHYSILYL ENOL ETHER

[Silane trimethyl[(1-methylethenyl)oxy]-]



Submitted by Nigel D. A. Walshe, Graham B. T. Goodwin, Graham C. Smith, and Frank E. Woodward[1].
Checked by V. A. Palaniswamy and James D. White.

1. Procedure

To a 5-L, four-necked flask, equipped with a mechanical stirrer, a reflux condenser with a nitrogen inlet, a thermometer, and a pressure-equalizing dropping funnel, are added 150 g (2.6 mol) of acetone (Note 1) and 192 g (1.9 mol) of triethylamine (Note 2) under a nitrogen atmosphere. To this mixture, stirred at room temperature under nitrogen, is added via the dropping funnel 200 g (1.84 mol) of chlorotrimethylsilane over 10 min (Note 3). The flask is then immersed in a water bath and the contents are warmed to 35°C. The water bath is removed and the dropping funnel is charged with a solution of 285 g (1.9 mol) of sodium iodide (Note 4) in 2.14 L of acetonitrile (Note 5). This solution is added to the stirred mixture in the flask at such a rate that the temperature of the reaction is maintained at 34–40°C without external heating or cooling (Note 6). The addition requires approximately 1 hr. When addition is complete, the reaction mixture is stirred for a further 2 hr at room temperature. The contents of the flask are then poured into 5 L of ice-cold water, and the aqueous mixture is extracted with two 1-L portions of pentane, and once with 500 mL of pentane. The combined pentane extracts are dried over anhydrous potassium carbonate, and filtered into a 3-L, round-bottomed flask. This is arranged for distillation at atmospheric pressure, incorporating a 30-cm Vigreux fractionating column. The pentane is distilled off at atmospheric pressure, until a head temperature of 88°C is attained. The crude material is transferred to a 500-mL flask, and the product is then distilled at atmospheric pressure through a 20-cm Vigreux column. A forerun of 20 g is collected between room temperature and 94°C. The product is the fraction boiling at 94–96°C, the yield of which is 116–130 g (48–54%) (Note 7).

2. Notes

1. "AnalaR"-grade acetone, as supplied by BDH, was used.
2. Triethylamine was dried over potassium hydroxide pellets for at least 24 hr.
3. Commercial chlorotrimethylsilane was used without purification. When it was added to the acetone/triethylamine mixture, only a very mild exothermic

reaction occurred (ca. 2°C). Dense white fumes formed, and a turbid solution was obtained.

4. Sodium iodide was reagent grade. It is essential to dry this material thoroughly. Heating at 140°C for 8 hr under reduced pressure (ca. 20 mm) is satisfactory. The loss of weight on drying is roughly 5%. If this is not done, hexamethyldisiloxane is the principal product.

5. Acetonitrile was reagent grade, dried by passage through 1 kg of neutral alumina (grade 1), and then stored over Linde 3A molecular sieves.

6. A copious white precipitate forms at this stage. If the reaction is not mildly exothermic, then very poor yields of product are obtained.

7. The yield is based on chlorotrimethylsilane. Two small-scale runs—0.124 and 0.37 mol, also based on chlorotrimethylsilane—gave yields of 60 and 61%, respectively, which the submitters also reported on the larger scale. The material from the large-scale run was 92% pure by gas-chromatographic analysis. The impurities, identified by NMR, are triethylamine (0.5%) and hexamethyldisiloxane (7.5%). The product has the following spectral characteristics; IR (film) cm^{-1}: 1650, 1280, 1260, 1050; ^{1}H NMR ($CDCl_3$) δ: 0.13 (s, 9 H, $SiCH_3$), 1.69 (br s, 3 H, $=CCH_3$), 3.92 (m, 2 H, $=CH_2$).

3. Discussion

Trimethylsilyl enolates of aldehydes and ketones are now established as highly useful synthetic intermediates.[2] In particular, their Lewis-acid-catalyzed reactions (e.g., alkylation[3] and mild, regiospecific aldol condensations[4]) provide useful alternatives to classical, base-generated metal enolate chemistry. This new methodology would be ideal for the introduction of the commonly encountered acetonyl residue. However, the required silyl enol ether of acetone is not commercially available, nor is a simple, reliable, and economical synthesis adequately described in the literature. The above procedure is an adaptation of a literature method,[5] and relies on the generation of iodotrimethylsilane in situ. We have found that the precautions described in (Note 4) and (Note 6) are crucial to the success of the preparation. This procedure makes available a useful reagent by a cheap, reliable route, starting from readily available materials, and in large or small quantity. The trimethylsilyl enol ether of acetone has been prepared previously in good yield by reaction of acetone with trimethylsilyl triflate and triethylamine.[6] However, the silyl triflate reagent is expensive for large-scale work. Another route[7] involves the mercuric iodide-catalyzed rearrangement of α-trimethylsilylacetone (obtained from trimethylsilylmethylmagnesium chloride and acetic anhydride). This is a laborious, low-yield process. Other methods include a synthesis from acetone, chlorotrimethylsilane, and triethylamine[8] (yields and exact procedure unspecified); or reaction of acetone with hexamethyldisilazane,[9] or bis (trimethylsilyl)acetamide,[10] and a catalytic amount of sodium in the presence of hexamethylphosphoric triamide. Two authors[11] who used the method of House[12] (no

experimental details supplied) note that their product always contained about 30% of hexamethyldisiloxane, which could not be separated by fractional distillation.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 323

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ACETONE TRIMETHYSILYL ENOL ETHER

Silane trimethyl[(1-methylethenyl)oxy]-

silyl enol ether of acetone

potassium carbonate (584-08-7)

acetic anhydride (108-24-7)

acetonitrile (75-05-8)

nitrogen (7727-37-9)

acetone (67-64-1)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

sodium iodide (7681-82-5)

Pentane (109-66-0)

triethylamine (121-44-8)

hexamethylphosphoric triamide (680-31-9)

CHLOROTRIMETHYLSILANE (75-77-4)

hexamethyldisiloxane (107-46-0)

Iodotrimethylsilane (16029-98-4)

hexamethyldisilazane

trimethylsilyl triflate (27607-77-8)

silyl triflate

α-trimethylsilylacetone, trimethylsilyl enol ether of acetone

Trimethylsilylmethylmagnesium chloride (13170-43-9)

bis(trimethylsilyl)acetamide

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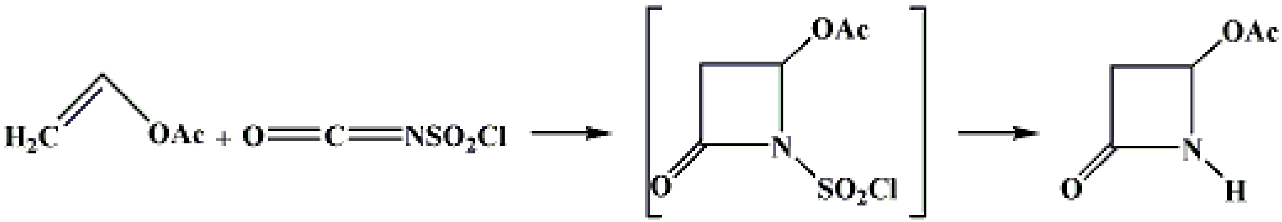
Organic Syntheses, CV 8, 3

SYNTHESIS OF A KEY β-LACTAM INTERMEDIATE BY A [2 + 2] CYCLOADDITION ROUTE: 4-ACETOXYAZETIDIN-2-ONE

[2-Azetidinone, 4-(acetyloxy)-]



Submitted by Stuart J. Mickel[1], Shi-Nung Hsiao, and Marvin J. Miller[2].
Checked by Daniel A. Aguilar, John Czepiel, and Gabriel Saucy.

1. Procedure

A 500-mL, four-necked, round-bottomed flask equipped with a mechanical stirrer, rubber septum with a nitrogen source, a thermometer, and a pressure-equalized dropping funnel is charged with 150 mL (140 g, 1.63 mol) of vinyl acetate (Note 1) and (Note 2). Stirring is initiated and the flask content is cooled in an ice–water bath to 3°C. Chlorosulfonyl isocyanate (25 mL, 40 g, 0.28 mol) (Note 2) and (Note 3) is added as rapidly as possible from the addition funnel while maintaining the temperature at less than 5°C. The cooling bath is removed and the temperature is allowed to rise to 10°C. At this point an exothermic reaction begins. Intermittent cooling is required as the temperature is kept at 10–15°C for 40 min. The dark-red mixture is then cooled to –40°C in a dry ice–acetone bath.

A 1.0-L, three-necked flask equipped with a thermometer, a mechanical stirrer, and a septum cap is charged with a mixture of 67 g (0.80 mol) of sodium bicarbonate, 71.5 g (0.69 mol) of sodium bisulfite, and 200 mL of water. This mixture is cooled in a dry ice–acetone bath to –20° C with vigorous stirring. Immediately (Note 4) the reaction mixture is added dropwise via cannula at a rate such that the temperature remains at –10°C. This addition takes 30–40 min. When approximately half of the reaction solution has been added, an additional 35.7 g (0.34 mol) of sodium bisulfite is added to the aqueous quench mixture. After the addition is complete, the mixture is stirred for an additional 40 min at –10°C. The light-yellow mixture (pH 7) is extracted with three 500-mL portions of chloroform (Note 5). The combined extracts are dried over magnesium sulfate and concentrated on a rotary evaporator at 40°C at 70 mm (Note 6). Final solvent removal with a vacuum pump gives a two-phase, oily mixture. The mixture is stirred with three 100-mL portions of hexane, and the hexane extracts are decanted (Note 7) and discarded. Removal of the final traces of solvent with a vacuum pump gives 16.1–22.8 g (44–62% yield based on chlorosulfonyl isocyanate) of a light-orange oil that slowly solidifies on standing at –20°C. The resulting solid melts at 34°C (Note 8).

2. Notes

1. Commercial vinyl acetate (Aldrich Chemical Company, Inc.) was used directly without

purification. The checkers observed that distilled vinyl acetate afforded slightly higher yields and improved product purity (Note 7).

2. The volume of reagents used was determined by cannulation into the graduated addition funnel before charging into the reaction flask.

3. Aldrich Chemical Company, Inc. chlorosulfonyl isocyanate was used directly without purification.

4. The mixture tended to freeze if allowed to stand at −20°C.

5. Filtration of the mixture through sintered glass aided in breaking emulsions.

6. Room temperature is even more satisfactory, although the concentration takes longer. Heat leads to decomposition of the product.

7. The hexane-soluble impurity is believed to originate in the vinyl acetate. This purification may not be necessary in all cases.

8. The material prepared by this route contains a trace of a yellow impurity (vinyl acetate polymer?). However, the impurity is not detected in the ^{1}H NMR, ^{13}C NMR, or mass spectrum of the product. Very careful column chromatography is required to remove the color and in the hands of the submitters 4-acetoxyazetidin-2-one,[3] prepared by the preceding method, is adequate for any further manipulation. High-vacuum distillation may be employed to obtain a colorless sample (bp 80–82°C at 10^{-3} mm); however, extensive losses occur. The spectra are as follows: IR ($CHCl_3$) cm^{-1}: 3350 (NH), 1790 (β-lactam C=O), 1730 (acetate C=O); ^{1}H NMR ($CDCl_3$) δ: 2.03 (s, 3 H, $OCOCH_3$), 3.00 (d of d, 1 H, $J_{3b\text{-}3}$ = 15.0, $J_{3b\text{-}4}$ = 1.5), 3.28 (d of d, 1 H, $J_{3a\text{-}3b}$ = 15.0, $J_{3a\text{-}4}$ = 4.6, H_{3a}), 5.81 (d of d, 1 H, $J_{4\text{-}3a}$ = 4.6, $J_{4\text{-}3b}$ = 1.6), 7.4–7.1 (br, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ (off-resonance multiplicity, assignment): 45.0 (t, C3), 73.2 (d, C4), 166.4 (s, C2).

Thin-layer chromatographic analysis of 4-acetoxyazetidin-2-one was carried out on E. Merck Silica gel F254 plates by elution with ethyl acetate. The hexanesoluble impurity (R_f 0.67) was detected by shortwave UV. 4-Acetoxyazetidin-2-one (R_f 0.38) was detected by exposure of the plate for 5 min to chlorine gas followed by spraying with TDM solution (Note 9) and heating with a hot air gun.

9. TDM spray solution was prepared as follows. Solution A: 2.5 g of 4,4'-tetramethyldiaminodiphenylmethane (TDM) was dissolved in 10 mL of glacial acetic acid and diluted with 50 mL of H_2O. Solution B: 5 g of potassium iodide was dissolved in 100 mL of H_2O. Solution C: 0.3 g of ninhydrin was dissolved in 90 mL of H_2O diluted with 10 mL of glacial acetic acid. Solutions A and B and 1.5 mL of solution C were mixed and stored in a brown bottle.

3. Discussion

Within the current synthetic effort in β-lactam chemistry, 4-acetoxyazetidin-2-one and its derivatives play an important role in the total synthesis of many conventional β-lactams and their analogs.[4,3,5,6] There is therefore a requirement for a simple large-scale preparative method for this key intermediate. This synthesis is a modification of that reported by Clauss et al.[7]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

acetic acid (64-19-7)

ethyl acetate (141-78-6)

chloroform (67-66-3)

sodium bicarbonate (144-55-8)

potassium iodide (7681-11-0)

sodium bisulfite (7631-90-5)

chlorine (7782-50-5)

magnesium sulfate (7487-88-9)

vinyl acetate (108-05-4)

hexane (110-54-3)

CHLOROSULFONYL ISOCYANATE (1189-71-5)

ninhydrin (938-24-9)

4-Acetoxyazetidin-2-one, 2-Azetidinone, 4-(acetyloxy)- (28562-53-0)

4,4'-tetramethyldiaminodiphenylmethane

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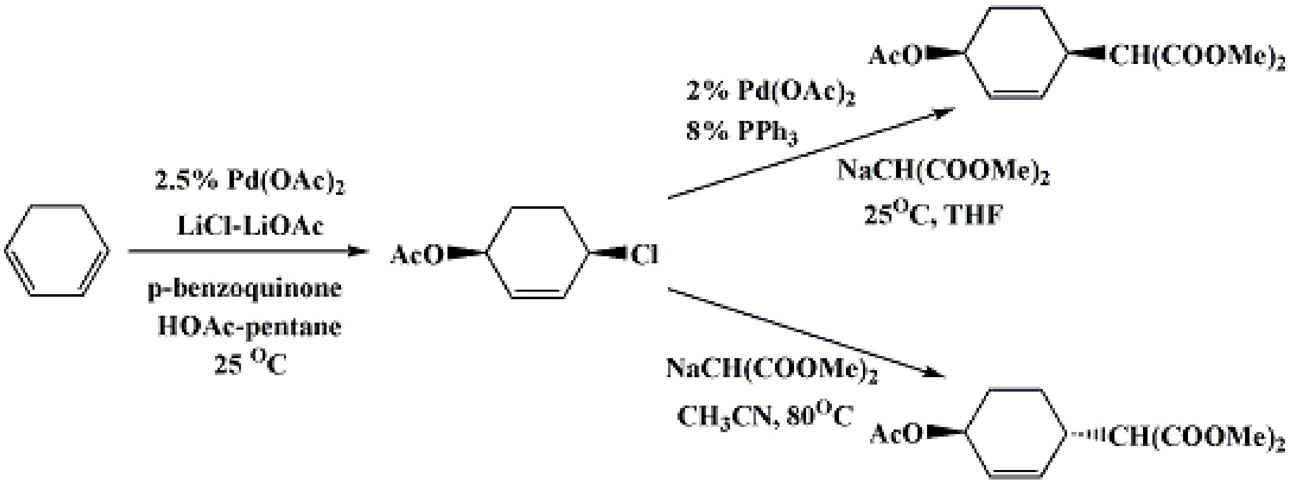
STEREOSELECTIVE 1,4-FUNCTIONALIZATIONS OF CONJUGATED DIENES: *cis*- AND *trans*-1-ACETOXY-4-(DICARBOMETHOXYMETHYL)-2-CYCLOHEXENE

[Propanedioic acid, [4-(Acetyloxy)-2-cyclohexen-1-yl]-, dimethyl ester, *cis*- and *trans*-]



Submitted by Jan-E. Bäckvall and Jan O. Vågberg[1].
Checked by Michael R. Sestrick and Albert I. Meyers.

1. Procedure

A. *cis-1-Acetoxy-4-chloro-2-cyclohexene.* A 1-L, one-necked, round-bottomed flask equipped with a magnetic stirring bar is charged with 200 mL of acetic acid, 5.1 g (0.12 mol) of lithium chloride, 12.2 g (0.12 mol) of lithium acetate dihydrate, 0.67 g (3 mmol) of palladium acetate, and 12.9 g (0.12 mol) of *p*-benzoquinone. The contents of the flask are stirred at room temperature until all components are dissolved, and 300 mL of pentane is added. To the pentane phase of the biphasic system formed is added 4.82 g (60 mmol) of 1,3-cyclohexadiene (Note 1). The reaction mixture is stirred at a moderate rate (Note 2) at room temperature and after 4 hr, 2.87 g (33 mmol) of manganese dioxide (Note 3) is added. After the flask is stirred for another 4 hr at room temperature, the organic phase is separated and saved, and 2.87 g (33 mmol) of manganese dioxide and 20 mL of acetic acid are added to the remaining acetic acid, which is vigorously stirred for 30 min. To the mixture are added 2.6 g (60 mmol) of lithium chloride and 300 mL of pentane. A new portion of 4.82 g (60 mmol) of 1,3-cyclohexadiene is added and the reaction mixture is stirred at a moderate rate (Note 1) at room temperature overnight (12–15 hr). To the reaction mixture is added 70 mL of saturated sodium chloride solution and the organic phase is separated and saved. The aqueous phase is filtered and extracted with pentane (2 × 300 mL). The combined organic phases are washed with water (2 × 120 mL), 120 mL of saturated aqueous sodium carbonate, 120 mL of 2 *M* sodium hydroxide, 120 mL of water, and 120 mL of saturated sodium chloride solution. The organic phase is dried over magnesium sulfate and the solvent is removed by rotary evaporation at reduced pressure, giving 16.5–17.5 g (79–84%) of a yellow oil. Kugelrohr distillation (95–105°C, 1 mm) of the crude product affords 14.6–15.6 g (71–75%) of pure *cis*-1-acetoxy-4-chloro-2-cyclohexene (>98% *cis*). Analysis by HPLC and GLC [high-performance (pressure) liquid and gas chromatograph] shows about 1% contamination of diacetate as the only impurity. No dichloride can be detected (<0.5%).

B. *cis-1-Acetoxy-4-(dicarbomethoxymethyl)-2-cyclohexene.* A 2-L, two-necked, round-bottomed flask equipped with a magnetic stirrer, a nitrogen-vacuum inlet, and a rubber septum is charged with 17.5 g (0.1 mol) of *cis*-1-acetoxy-4-chloro-2-cyclohexene, 0.49 g (2.2 mol) of palladium acetate and 2.4 g (9.0 mmol) of triphenylphosphine (Note 4). The flask is flushed with nitrogen (Note 5). To the flask is added 550 mL of a 0.2 *M* solution (0.11 mol) of sodium dimethyl malonate in tetrahydrofuran (THF) by syringe (Note 6). The flask is again flushed with nitrogen and the reaction mixture, which now has turned yellow, is stirred at room temperature for 2 hr (Note 7). The flask is opened and 200 mL of saturated aqueous sodium bicarbonate is added. The stirring is continued for 20 min, and then 100 mL of water and 200 mL of ether are added. The contents of the flask are transferred into a 2-L separatory funnel and the organic phase is separated. The remaining aqueous phase is extracted with ether (3 × 300 mL). The combined organic phases are washed with 200 mL of saturated brine, dried over anhydrous magnesium sulfate, concentrated on a rotary evaporator to approximately 400 mL, and then filtered through a short silica gel column (Note 8). Removal of the rest of the solvent by rotary evaporation at reduced pressure gives 30.4–31.3 g of a light-brown oil. Excess dimethyl malonate is removed by Kugelrohr distillation at 100°C (1 mm). Kugelrohr distillation (140°C, 0.2 mm) of the remaining crude product affords 25.9–26.7 g (91%) of *cis*-1-acetoxy-4-(dicarbomethoxymethyl)-2-cyclohexene as a light-brown oil. Analysis by GLC indicates a chemical purity of 95–98%.

C. *trans-1-Acetoxy-4-(dicarbomethoxymethyl)-2-cyclohexene.* In a 1-L, two-necked flask equipped with a reflux condenser, a nitrogen gas inlet, and a magnetic stirring bar are placed 8.73 g (50 mmol) of *cis*-1-acetoxy-4-chloro-2-cyclohexene and 400 mL of a 0.18 *M* solution (72 mmol) of sodium dimethyl malonate in acetonitrile (Note 9). The flask is flushed with nitrogen and then heated in an oil bath at reflux for 21 hr. The reaction mixture is cooled to room temperature and 5 g of solid sodium hydrogen carbonate is added. The mixture is stirred for 2 hr, poured into 800 mL of ether, and the resulting mixture is filtered. The organic phase is collected and the solvent is removed on a rotary evaporator to afford 16.1 g of the product together with dimethyl malonate. The excess dimethyl malonate is removed by Kugelrohr distillation at 70°C (0.2 mm). The residual crude yellow oil was dissolved in a minimal amount of ethyl acetate and passed through a short silica plug (30–35g, Alfa silica) gel (53 •m) eluting with a small amount of fresh ethyl acetate. Removal of ethyl acetate on a rotary evaporator and further concentration at 0.2 mm overnight yielded 11.6–12.2 g (86–90%) of *trans*-1-acetoxy-4-(dicarbomethoxymethyl)-2-cyclohexene as a clear oil, essentially pure (99% by GLC) (Note 10).

2. Notes

1. 1,3-Cyclohexadiene was obtained from Aldrich Chemical Company, Inc. and distilled before use. It can also be synthesized according to *Org. Synth., Coll. Vol. V*, **1973**, 285.
2. A stirring rate 5–10 revolutions per second (rps) was used (only a small vortex was present).
3. Commercial, active manganese dioxide from Merck-Schuchardt was used.
4. Palladium acetate and triphenylphosphine generate the active tri- or tetrakis (triphenylphosphine)palladium(0) catalyst on addition of sodium dimethyl malonate.
5. A manifold system connected to a vacuum line and a nitrogen line was used.
6. Sodium dimethyl malonate was prepared from equimolar amounts of sodium hydride and dimethyl malonate.
7. The reaction is usually over after 30 min. The reaction was checked by GLC or TLC to confirm completion.
8. This filtration was done in order to remove remaining palladium species and phosphine oxide. A column (4 × 8 cm) packed with Alfa silica gel (58 •m) was used.
9. Acetonitrile was stirred overnight with calcium hydride and then distilled onto freshly

activated Linde 4A molecular sieves.
10. All GLC analyses were performed on a 2.4-m × 6-mm glass column packed with 5% SE-30 on Chromosorb W or crosslinked 50% phenylmethylsilicone.

3. Discussion

This procedure for stereoselective 1,4-functionalization of 1,3-dienes is based on 1,4-acetoxychlorination[2 3] and allows the preparation of 1,4-disubstituted 2-cyclohexenes with full stereocontrol of the carbon–carbon bond formation in the 4-position. It is also highly regioselective. Other procedures[4,5] for obtaining 4-alkyl-substituted 3-cyclohexenol derivatives use 1,3-cyclohexadiene monoepoxide as starting material. None of the previous methods allow the selective preparation of both stereoisomers as shown here.

The present procedure uses palladium catalysis in the first step and in one of the second steps. These reactions occur under very mild conditions (room temperature), and the catalyst used is commercial palladium acetate.

Since the title compounds can be stereoselectively functionalized in the 1-position by metal-catalyzed nucleophilic substitutions of the acetoxy group, a great number of 1,4-disubstituted 2-cyclohexenes with defined 1,4-relative stereochemistry are available.

While this process works for a great number of conjugated dienes, a few, such as 1,3-cyclopentadiene and those acyclic dienes that have an oxygen substituent in an allylic position, did not give a chloroacetoxylation product.[2] Control of the 1,4-relative stereochemistry and preparation of compounds analogous to the title compounds also work for acyclic dienes,[2,6] This process was used to obtain remote stereocontrol in acyclic systems and applied to the synthesis of a pheromone.[6]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Propanedioic acid, [4-(Acetyloxy)-2-cyclohexen-1-yl]-, dimethyl ester, cis- and trans-

saturated brine

acetic acid (64-19-7)

ethyl acetate (141-78-6)

ether (60-29-7)

acetonitrile (75-05-8)

sodium hydroxide (1310-73-2)

sodium bicarbonate, sodium hydrogen carbonate (144-55-8)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

nitrogen (7727-37-9)

palladium (7440-05-3)

manganese dioxide (1313-13-9)

Pentane (109-66-0)

p-benzoquinone (106-51-4)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

sodium hydride (7646-69-7)

Lithium chloride (7447-41-8)

1,3-cyclopentadiene (542-92-7)

calcium hydride (7789-78-8)

triphenylphosphine (603-35-0)

1,3-Cyclohexadiene (592-57-4)

phosphine oxide

palladium acetate (3375-31-3)

dimethyl malonate (108-59-8)

tetrakis (triphenylphosphine)palladium(0) (14221-01-3)

lithium acetate dihydrate (6108-17-4)

sodium dimethyl malonate

1,3-cyclohexadiene monoepoxide

trans-1-ACETOXY-4-(DICARBOMETHOXYMETHYL)-2-CYCLOHEXENE (82736-53-6)

cis-1-Acetoxy-4-chloro-2-cyclohexene (82736-39-8)

cis-1-acetoxy-4-(dicarbomethoxymethyl)-2-cyclohexene

cis- and trans-1-Acetoxy-4-(dicarbomethoxymethyl)-2-cyclohexene

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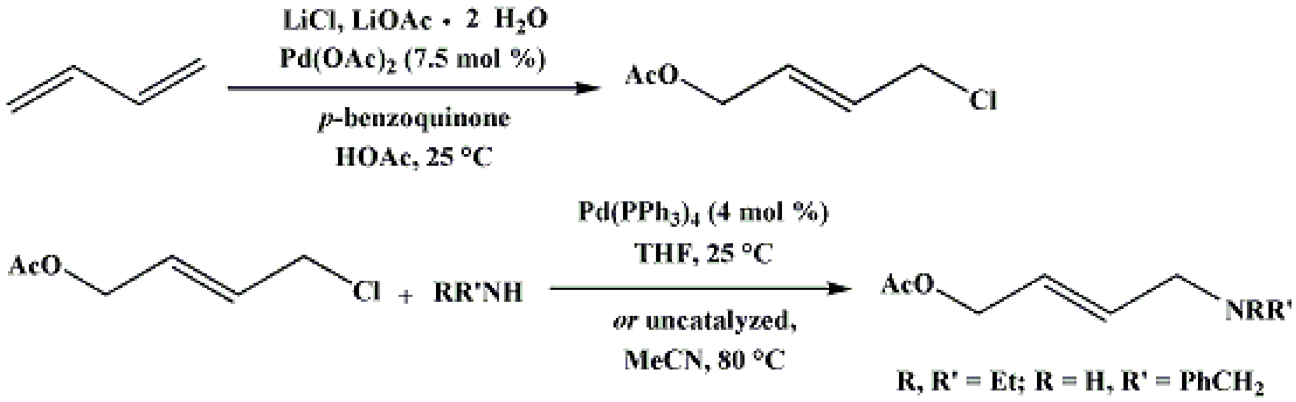
Organic Syntheses, CV 8, 9

1,4-FUNCTIONALIZATION OF 1,3-DIENES VIA PALLADIUM-CATALYZED CHLOROACETOXYLATION AND ALLYLIC AMINATION: 1-ACETOXY-4-DIETHYLAMINO-2-BUTENE AND 1-ACETOXY-4-BENZYLAMINO-2-BUTENE

[2-Buten-1-ol, 4-(diethylamino)-, acetate ester and 2-Buten-1-ol, 4-[(phenylmethyl)amino]-, acetate ester]



Submitted by J. E. Nyström, T. Rein, and J. E. Bäckvall[1].
Checked by Marvin M. Hansen and Clayton H. Heathcock.

1. Procedure

A. *1-Acetoxy-4-chloro-2-butene.* In a 2-L, two-necked, round-bottomed flask equipped with a 5-cm egg-shaped magnetic stirring bar and a pressure-reducing outlet (Note 1) is placed 800 mL of pentane (Note 2). The flask is cooled with an ice bath and 5.4 g (0.1 mol) of butadiene is dissolved with stirring (0–5° C) by addition through one of the inlets from a Fluka low-pressure bottle of butadiene (Note 3). The pressure-reducing outlet is removed and a freshly prepared solution of 1.68 g (7.5 mmol) of palladium acetate, $Pd(OAc)_2$, 8.4 g (0.2 mol) of lithium chloride, 20.4 g (0.2 mol) of lithium acetate dihydrate ($LiOAc \cdot 2H_2O$), and 21.6 g (0.2 mol) of *p*-benzoquinone in 400 mL of acetic acid is added (Note 4). The cooling bath is removed and the two-phase system is stirred at a moderate rate (Note 5) at 25°C for 26 hr. A saturated sodium chloride solution (300 mL) is added and after the mixture is stirred for 5 min; it is filtered using a Büchner funnel with an intermediate paper filter using aspirator vacuum. The organic phase is separated and the aqueous phase is extracted with three 300-mL portions of pentane–ether (80 : 20). The combined organic phases are washed with two 75-mL portions of water, two 100-mL portions of saturated potassium carbonate solution, three 100-mL portions of 2 *M* sodium hydroxide solution, and finally with 50 mL of saturated sodium chloride solution. The organic phase is dried over anhydrous magnesium sulfate, filtered, and concentrated to a volume of 20–30 mL by distilling off the solvent at atmospheric pressure. The remaining solvent is removed with a rotary evaporator at aspirator vacuum to give 13–15 g of crude product, which is distilled (10 mm, 70–90°C) to yield 9.7–12.0 g (65–81%) of a light-yellow liquid consisting of 91% of 1-acetoxy-4-chloro-2-butene (*E/Z* = 90/10) and 9% of 4-acetoxy-3-chloro-1-butene. The chloroacetate is contaminated with approximately 1% of 5,8-dihydronaphthoquinone (Note 6).

Further purification is achieved by the following procedure. The chloroacetate from above is dissolved in 150 mL of ether. This solution is stirred together with a 10-mL aqueous solution saturated with sodium borohydride. The stirring is continued until the yellow color of the organic phase disappears

(ca. 15 min). The organic phase is separated and washed with 5 mL of 2 *M* sodium hydroxide solution and 5 mL of a saturated sodium chloride solution, dried over magnesium sulfate, and concentrated by distilling off the solvent at atmospheric pressure. The solvent that remains is removed with a rotary evaporator to afford 9.5–10.5 g (64–70%) of chloroacetate, with the same composition as above, but which is now completely free from 5,8-dihydronaphthoquinone (Note 7).

B1. *1-Acetoxy-4-diethylamino-2-butene*. *Method 1.* In a 500-mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar, nitrogen-vacuum inlet, and a rubber septum, is placed 2.77 g (2.4 mmol) of tetrakis(triphenylphosphine)palladium, $Pd(PPh_3)_4$ (Note 8). The flask is closed, evacuated, and filled with nitrogen. This flushing procedure is repeated twice (Note 9). A solution of 8.91 g (0.06 mol) of the chloroacetate from Procedure A in 180 mL of dry tetrahydrofuran (Note 10) is added through the membrane with the aid of a 50-mL syringe. With the same syringe 21.9 g (0.30 mol) of diethylamine (Note 11) in 120 mL of dry tetrahydrofuran is added. The mixture is stirred at ambient temperature and the reaction is followed by gas chromatography. When the starting material has been consumed, which takes approximately 4 hr (Note 12), 600 mL of ice-cooled ether and 600 mL of ice-cooled saturated aqueous sodium carbonate solution are added and the mixture is shaken in a separatory funnel (Note 13). The aqueous phase is extracted with ether (2 × 300 mL).

The combined organic phases are washed with 50 mL of saturated potassium carbonate solution and dried over solid potassium carbonate. Evaporation with a rotary evaporator affords 13.7 g of crude product. The residue is put on a column (silica, 3 × 10 cm) and eluted with 600 mL of ether–pentane–triethylamine (47.5 : 47.5 : 5) (Note 14). The main fractions are collected to give 8.15 g (73%) of essentially pure *E*-1-acetoxy-4-diethylamino-2-butene (>94% *E*). No 1,2-isomer could be detected. The product is further purified by Kugelrohr distillation to afford 7.81–8.21 g (70–74%) (Note 15).

B2. *1-Acetoxy-4-benzylamino-2-butene*. *Method 2.* In a 250-mL, one-necked, round-bottomed flask are placed in order 8.91 g (0.06 mol) of the chloroacetate from Method A, 100 mL of acetonitrile, and 19.3 g (0.18 mol) of benzylamine (Note 6). The flask is equipped with a reflux condenser and the solution is refluxed for 2 hr using an oil bath at 100–110°C. The reaction mixture is cooled and 150 mL of ether and 100 mL of a saturated sodium carbonate solution are added. The mixture is shaken in a separatory funnel and the organic phase is collected. The aqueous phase is extracted with 50 mL of ether. The combined organic phases are dried over potassium carbonate. The solvent and excess benzylamine are removed by rotary evaporation and Kugelrohr distillation at 50°C (1 mm). Kugelrohr distillation of the crude product gives 9.1–9.9 g (70–76%) of 1-acetoxy-4-benzylamino-2-butene as a 90 : 10 mixture of the *E* and *Z* isomers (Note 17).

2. Notes

1. The pressure-reducing outlet can be a U-shaped tube filled with oil or a thick-walled rubber balloon.
2. Light petroleum, boiling point 40°C, can also be used.
3. The amount of butadiene added is determined by weighing the Fluka bottle and double-checked by weighing the reaction flask before and after addition. The checkers purchased butadiene from Matheson and measured it by condensation into a 25-mL flask cooled to −10°C. The cooled material was then transferred by cannula into the reaction vessel containing the pentane, cooled to 0–5°C.
4. *p*-Benzoquinone, 200 mol%, is needed for a rapid and efficient reaction.
5. A stirring rate of approximately 5 rps (revolutions per second) is used. The reaction tolerates a variation of 3–10 rps, which gives essentially the same result.
6. 5,8-Dihydronaphthoquinone is the oxidized Diels–Alder adduct between butadiene and benzoquinone.
7. The spectral properties are as follows: ^1H NMR ($CDCl_3$, 250 MHz) δ: 2.09 (s, 3 H), 4.06 (m, 2

H), 4.59 (m, 2 H), 5.90 (m, 2 H).

8. Tetrakis(triphenylphosphine)palladium, $Pd(PPh_3)_4$, is commercially available but is readily prepared according to [2] (or [3]). Palladium acetylacetonate, $Pd(acac)_2$, together with 4 PPh_3, can be used in place of $Pd(PPh_3)_4$ and gives essentially the same result.

9. A manifold system connected to a vacuum line and a nitrogen line is used.

10. Tetrahydrofuran is distilled under nitrogen from potassium benzophenone.

11. Commercial diethylamine (BDH) is used without further purification.

12. The rate of the reaction varies slightly depending on the quality of the catalyst.

13. The solution is kept cold to avoid hydrolysis of the acetoxy group.

14. The checkers observed that, on placing the crude product on the top of the silica gel column, the residual $Pd(PPh_3)_4$ precipitates. However, the presence of this solid residue does not interfere with the progress of the chromatography or affect the yield of product.

15. The spectral properties are as follows: ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 1.03 (t, 6 H, J = 7.2), 2.07 (s, 3 H), 2.51 (q, 4 H, J = 7.2), 3.10 (br d, 2 H), 4.55 (br d, 2 H), 5.64–5.90 (m, 2 H).

16. Benzylamine (Fluka) is dried over NaOH and distilled over sodium. The three-fold excess of benzylamine is used to depress the dialkylation product.

17. The spectral properties are as follows: ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 1.20–1.60 (br s, 1 H), 2.06 (s, 3 H), 3.28 (br d, 2 H, J = 5.7), 3.78 (s, 2 H), 4.55 (br d, 2 H, J = 5.8), 5.74 (dt, 1 H, J = 15.5, 5.8), 5.88 (dt, 1 H, J = 15.7, 5.7), 7.20–7.45 (m, 5 H).

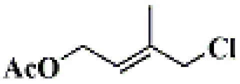
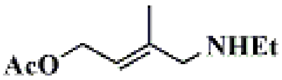
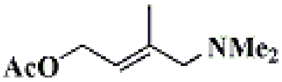
3. Discussion

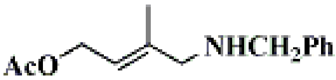
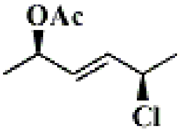
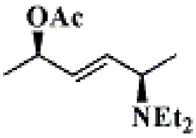
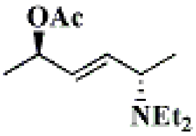
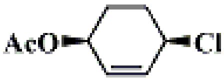
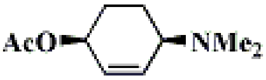
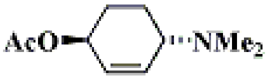
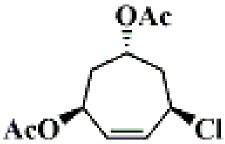
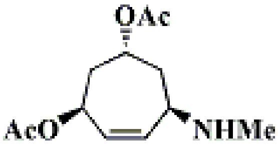
The procedure reported here provides an efficient method for the preparation of 4-amino-2-alken-1-ol derivatives. It is based on the palladium-catalyzed 1,4-acetoxy-chlorination of 1,3-dienes[4,3] and palladium-catalyzed amination of allylic substrates.[5] Compared to other methods,[6] this method is more convenient and more general. It allows complete control of the 1,4-relative configuration when the carbons bearing nitrogen and oxygen are stereogenic. In these cases the chloride is replaced with *retention* according to Procedure B1 but with *inversion* according to Procedure B2.[3,7]

Procedure A is very effective for a range of acyclic and cyclic conjugated dienes.[4,3] The major side reaction in the chloroacetoxylation is Diels–Alder addition of *p*-benzoquinone to the diene. The purpose of the pentane phase is to ensure a low concentration of diene in the acetic acid phase, which represses the Diels–Alder reaction. The reaction can also be performed without the pentane phase with slow addition of the diene using a syringe pump.

Some representative examples of the amination reaction according to Procedure B are shown in Table I.

TABLE I

Chloroacetate[a]	Amine	Procedure	Aminoacetate	Yield(%)
	Et_2NH	B1 B2		87[b] 75
	$EtNH_2$	B2		89
	Me_2NH	B2		76

	$PhCH_2NH_2$	B2		89
	Et_2NH	B1		80
		B2		70
	Me_2NH	B1		95
		B2		93
	$MeNH_2$	B1		87

[a]The chloroacetates were prepared from the corresponding dienes according to Procedure A or the modified version without the pentane phase (see discussion).

[b]From a small-scale experiment with acid extraction in the workup.

[c]*E/Z* = 3.5/1.

[d]>94% R^*R^*.

[e]>90% R^*S^*.

[f]>98% *cis.*

[g]>98% *trans.*

[h]>95% β, β, α

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Palladium acetylacetonate

potassium benzophenone

potassium carbonate (584-08-7)

acetic acid (64-19-7)

ether (60-29-7)

acetonitrile (75-05-8)

sodium hydroxide, NaOH (1310-73-2)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

oxygen (7782-44-7)

nitrogen (7727-37-9)

chloroacetate (79-11-8)

sodium (13966-32-0)

diethylamine (109-89-7)

Pentane (109-66-0)

benzoquinone, p-benzoquinone (106-51-4)

magnesium sulfate (7487-88-9)

benzylamine (100-46-9)

butadiene (106-99-0)

Tetrahydrofuran (109-99-9)

Lithium chloride (7447-41-8)

triethylamine (121-44-8)

sodium borohydride (16940-66-2)

acetoxy

palladium acetate (3375-31-3)

Tetrakis(triphenylphosphine)palladium (14221-01-3)

lithium acetate dihydrate (6108-17-4)

1-Acetoxy-4-diethylamino-2-butene, 2-Buten-1-ol, 4-(diethylamino)-, acetate ester (82736-47-8)

1-Acetoxy-4-benzylamino-2-butene, 2-Buten-1-ol, 4-[(phenylmethyl)amino]-, acetate ester (130892-14-7)

4-acetoxy-3-chloro-1-butene (96039-67-7)

5,8-dihydronaphthoquinone

E-1-acetoxy-4-diethylamino-2-butene

1-Acetoxy-4-chloro-2-butene (34414-28-3)

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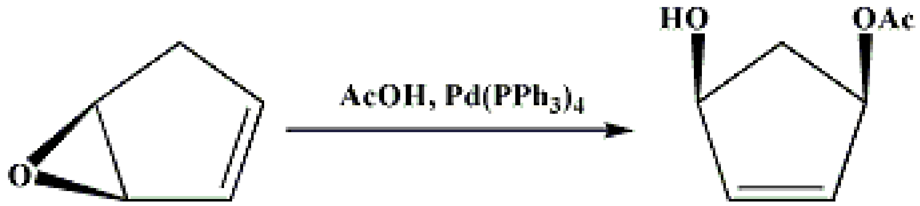
Organic Syntheses, CV 8, 13

PALLADIUM(0)-CATALYZED *syn*-1,4-ADDITION OF CARBOXYLIC ACIDS TO CYCLOPENTADIENE MONOEPOXIDE: *cis*-3-ACETOXY-5-HYDROXYCYCLOPENT-1-ENE

[4-Cyclopentene-1,3-diol, monoacetate, *cis*-]



Submitted by Donald R. Deardorff and David C. Myles[1].
Checked by Helmut Grebe and Ekkehard Winterfeldt.

1. Procedure

An oven-dried, 300-mL, two-necked, round-bottomed flask is equipped with a Teflon-coated magnetic stirring bar, a pressure-equalizing dropping funnel, and a rubber septum with an 18-gauge needle connected to a dry-nitrogen source. The nitrogen-flushed apparatus is charged with 125 mL of dry tetrahydrofuran (Note 1) and 0.28 g (0.24 mmol, 0.2 mol%) of tetrakis(triphenylphosphine)palladium(0) (Note 2). The mixture is stirred at room temperature until all of the palladium catalyst dissolves (Note 3). The solution is cooled in an ice–water bath and 7.0 mL (7.3 g, 122 mmol) of acetic acid (Note 4) is added via syringe. At this point a slight darkening of the solution is observed. A room temperature solution containing 10.9 g of 92% cyclopentadiene monoepoxide (10.0 g, 122 mmol, (Note 5)) in 40 mL of tetrahydrofuran is added over 10 min with the aid of the addition funnel. The original pale-yellow color gives way to a deeper transparent orange. After 5 min (Note 6), the solution is concentrated at ambient temperature under reduced pressure and the resulting reddish-brown oil is passed through a plug of silica gel (50 g, (Note 7) with 450 mL of ethyl ether (Note 8). The slightly cloudy filtrate is washed through a plug of anhydrous magnesium sulfate (60 g, 5 × 7-cm coarse glass frit) with an additional 150 mL of ether (Note 9) The solvent is removed under reduced pressure to yield a pale-yellow oil. The material is distilled through a short-path apparatus at 73–75°C (0.15 mm) to afford 12.5–13.2 g (72–76%) of colorless oil that crystallizes upon refrigeration (mp 36–39°C) . The material is homogeneous by TLC and ^{1}H NMR (Note 10), but can be further purified by recrystallization from an ether–hexane mixture to give colorless crystals, mp 38.5–41°C (Note 11).

2. Notes

1. Tetrahydrofuran was predried over potassium hydroxide *Caution! See Org. Synth., Coll. Vol. V, **1973**, 976 for possible hazard.*), then dried by distillation from sodium/benzophenone ketyl under nitrogen.
2. Tetrakis(triphenylphosphine)palladium(0) was purchased from Aldrich Chemical Company, Inc., and used without further purification. No special precautions were taken in handling the catalyst.
3. Dissolution takes approximately 2–3 min.
4. Glacial acetic acid was purchased from J. T. Baker Chemical Company (Baker Analyzed Reagent) and distilled prior to use.
5. Cyclopentadiene monoepoxide was prepared from cyclopentadiene and peracetic acid according to the well-established procedure of Korach et al.[2] However, the submitters report that epoxidation of cyclopentadiene under conditions developed by Knapp et al.[3] for cyclohexadiene increased their isolated yields from 40% to 62%. The major impurity in distilled cyclopentadiene monoepoxide is 3-cyclopentenone. This by-product can be conveniently assayed by ^{1}H NMR integration of the four methylene protons that appear as a broad singlet at 2.80 δ. Epoxide purity can be determined by GLC analysis on a 25 M Carbowax capillary column operated at 50°C.
6. TLC analysis using Baker Si250F precoated glass plates with a hexane–ethyl acetate (1 : 1) solvent system indicates that all of the starting material is consumed.
7. Baker Analyzed Reagent silica gel 60–200 mesh was used in a 4.5 × 9.0-cm column. This step removes most palladium-containing compounds from the reaction mixture. In order to ensure that the palladium is efficiently separated, itis important that all tetrahydrofuran be removed from the crude oil prior to filtration.
8. Anhydrous ether (purified) was purchased from J. T. Baker Chemical Company and used without additional purification.
9. This step removes the final traces of palladium. It is imperative that all catalyst be removed prior to distillation since, on heating, this metal catalyzes the decomposition of *cis*-3-acetoxy-5-hydroxycyclopent-1-ene into isomeric cyclopentenones and acetic acid.
10. *cis*-3-Acetoxy-5-hydroxycyclopent-1-ene has the following spectral characteristics: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.59 (dt, 1 H, J = 4.0 and 14.5, CH_2), 2.00 (s, 3 H, CH_3), 2.38 (br s, 1 H, OH), 2.76 (quintet, overlapping dt, 1 H, J = 7.4 and 14.5, CH_2), 4.67 (m, 1 H, CHOH), 5.45 (m, 1 H, CHOAc), 5.92 (m, 1 H, CH=CH), 6.05 (m, 1 H, CH=CH); IR (neat) cm^{-1}: 3410 (s), 1720 (s), 1250 (s).
11. 4-Acetoxy-2-cyclopentenone could be prepared in 85% yield by treatment of 1 equiv of this alcohol with 1.1 equiv of pyridinium chlorochromate in methylene chloride for 1 hr at room temperature, followed by washing with water, concentration, and distillation.

3. Discussion

Functionalized cyclopentenoids have been used extensively as key building blocks for the synthesis of many biologically active molecules.[4] This procedure details the facile preparation of one such versatile intermediate: *cis*-3-acetoxy-5-hydroxycyclopent-1-ene. Although important in its own right, this material also serves as a one-step precursor to the highly useful synthetic substrate 4-acetoxy-2-cyclopenten-1-one.[4] Only the acetic acid adduct with cyclopentadiene monoepoxide is described here. However, this palladium-catalyzed reaction appears to be general for other acidic substrates as well.[5,6] For example, the corresponding benzoate and phenyl ether adducts have been successfully prepared[5] from both benzoic acid and phenol in yields of 87 and 82%, respectively. Moreover, the reaction is not limited to just the monoprotected versions of *cis*-cyclopentene-3,5-diol. The corresponding diesters can be similarly prepared by replacement of the carboxylic acid component with an anhydride. This minor modification permits direct synthetic access to either the dibenzoate or diacetate in equally good yields (74 and 79%, respectively). Recently, silyl carboxylates and silyl phenoxides were also found to react analogously with cyclopentadiene monoepoxide in the presence of Pd(0) catalyst.[7] It should be stressed that in each case only the *cis*-1,4-adducts are observed, despite the fact that three other stereoisomers are possible. This remarkable stereo- and regiospecificity is undoubtedly a manifestation of an intermediate palladium π-allyl complex.[8]

Racemic *cis*-monoesters of cyclopentene-3,5-diol were previously prepared by the selective acylation[9 10 11] of the *meso*-diol and the copper-mediated[12] addition of carboxylic acid salts to cyclopentadiene monoepoxide. Optically active monoacetates can be accessed by enzymatic hydrolysis[13 14 15 16 17] of the corresponding diester. The present method offers four principal advantages over the earlier reports: (1) it is operationally simple; (2) it requires a much shorter reaction time; (3) it gives better yields; and (4) it has widespread applicability, since reactants other than carboxylic acids may be employed with equally good results.

A major disadvantage with the acylation method[9,10,11] is that the starting material, *cis*-cyclopentene-3,5-diol, is not readily available and must be prepared via photoxygenation procedures.[18] Furthermore, acylation occurs with the concomitant formation of diacylated product, which results in reduced yields and associated purification problems. The copper-mediated[12] and palladium-catalyzed procedures share some similarities in that both use cyclopentadiene monoepoxide as their starting material and deliver the desired product in good yield. But, unlike the palladium-catalyzed method, copper-mediated reactions require two full equivalents of carboxylate salt, much lower reaction temperatures (–78°C), and substantially longer reaction times. Finally, the enantioselective hydrolysis[13,14,15,16,17] of *cis*-3,5-diacetoxycyclopent-1-ene by hydrolase enzymes is an effective two-step method for generating optically enriched product.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 132
- Org. Syn. Coll. Vol. 9, 136
- Org. Syn. Coll. Vol. 9, 487

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

sodium/benzophenone ketyl

Racemic cis-monoesters of cyclopentene-3,5-diol

acetic acid (64-19-7)

ethyl acetate (141-78-6)

ether, ethyl ether (60-29-7)

phenol (108-95-2)

nitrogen (7727-37-9)

Benzoic acid (65-85-0)

potassium hydroxide (1310-58-3)

palladium (7440-05-3)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

peracetic acid (79-21-0)

hexane (110-54-3)

CYCLOPENTADIENE (542-92-7)

cyclohexadiene (592-57-4)

pyridinium chlorochromate (26299-14-9)

tetrakis(triphenylphosphine)palladium(0) (14221-01-3)

CYCLOPENTADIENE MONOEPOXIDE

3-cyclopentenone

4-Acetoxy-2-cyclopentenone, 4-Acetoxy-2-cyclopenten-1-one (768-48-9)

cis-3-Acetoxy-5-hydroxycyclopent-1-ene (60410-16-4)

cis-3,5-diacetoxycyclopent-1-ene (54664-61-8)

4-Cyclopentene-1,3-diol, monoacetate, cis- (60410-18-6)

cis-cyclopentene-3,5-diol

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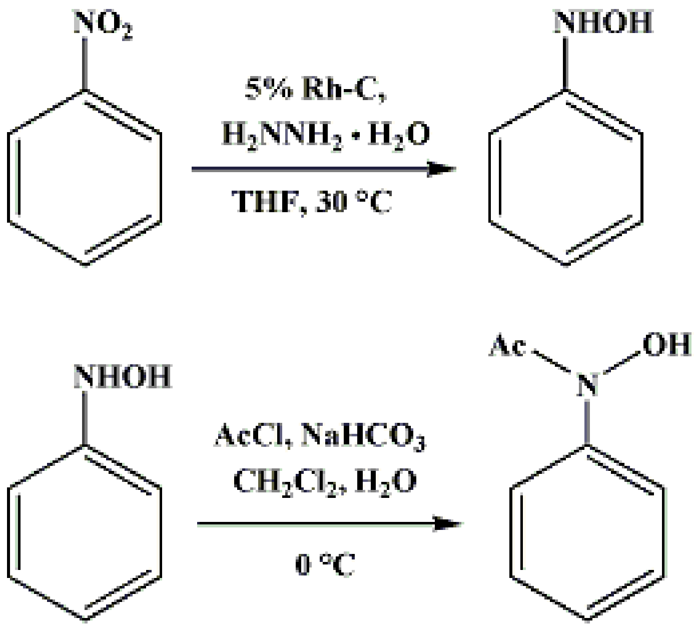
Organic Syntheses, CV 8, 16

N-ACETYL-*N*-PHENYLHYDROXYLAMINE VIA CATALYTIC TRANSFER HYDROGENATION OF NITROBENZENE USING HYDRAZINE AND RHODIUM ON CARBON

[Acetamide, *N*-hydroxy-*N*-phenyl-]



Submitted by P. W. Oxley, B. M. Adger, M. J. Sasse, and M. A. Forth[1].
Checked by Soo Y. Ko and K. Barry Sharpless.

1. Procedure

Caution! Nitrobenzene and hydrazine are both toxic. Phenylhydroxylamine and N-acetyl-N-phenylhydroxylamine are both suspected carcinogens.

A. *N-Phenylhydroxylamine.* Wet, 5% rhodium on carbon (1.1 g) (Note 1), tetrahydrofuran (200 ml) (Note 2), and nitrobenzene (41.0 g) (Note 3) are introduced into a 500-mL, three-necked, round-bottomed flask fitted with a mechanical stirrer, a thermometer, and a condenser. The mixture is cooled to 15°C and hydrazine hydrate (17.0 g) (Note 4) is introduced into the reaction mixture from a pressure-equalized addition funnel over 30 min. The temperature of the mixture is maintained at 25–30°C throughout the addition by means of an ice–water bath. After the mixture is stirred for a further 2 hr at 25–30°C, the reaction is complete (Note 5). The mixture is filtered and the catalyst washed with a little tetrahydrofuran. The solution is used immediately in the acylation step (Note 6).

B. *N-Acetyl-N-phenylhydroxylamine.* To the *N*-phenylhydroxylamine solution in a 1000-mL, three-necked, round-bottomed flask fitted with a mechanical stirrer and a thermometer is added a slurry of sodium bicarbonate (42 g) in water (40 mL). The mixture is cooled to −4°C in an ice–salt bath before acetyl chloride (26.0 g) (Note 7) is introduced into the well-stirred mixture over 1 hr (Note 8) while the temperature is maintained below 0°C. Stirring is then continued for 30 min before a solution of sodium hydroxide (20.0 g) in water (200 mL) is added, keeping the temperature below 20°C. The aqueous phase is separated, the tetrahydrofuran phase is diluted with an equal volume of petroleum ether, the aqueous phase is separated again, and the organic phase is extracted with aqueous 10% sodium hydroxide solution (2 × 50 mL). The combined aqueous phases are washed with methylene chloride (200 mL) and then neutralized with concentrated hydrochloric acid (cooling employed). The mixture is extracted with methylene chloride (3 × 100 mL) and the extracts are combined, dried over magnesium sulfate, filtered, and concentrated at reduced pressure (about one-fifth volume) (Note 9). After the solution is cooled to 40°C, 100 mL of petroleum ether (bp 60–80°C) is added. The mixture is stirred at 10°C for 39 min before filtering and washing with additional petroleum ether. The material is dried at room temperature to afford 39.3–40.1 g (79–80%) of *N*-acetyl-*N*-phenylhydroxylamine as a white crystalline solid, mp 66–67°C (lit.[2] mp 67–67.5°C) (Note 10).

2. Notes

1. The 5% rhodium on carbon used was purchased dry from Engelhard Industries Ltd. The checkers purchased it from Aldrich Chemical Company, Inc. The catalyst is used wet (40–50% water) to reduce the risk of fire when the solvent is added.
2. Tetrahydrofuran was from a bulk supply purchased from Blagden Campbell. The checkers obtained it from EM Science. The solvent was tested for peroxides prior to use.
3. Nitrobenzene was supplied by BDH Chemicals Ltd., and was used as received. The checkers obtained it from Aldrich Chemical Company, Inc. Nitrobenzene should be handled only with gloves and in an efficient fume hood.
4. Hydrazine hydrate was purchased from FBC Industrial Chemicals and was used as supplied. The checkers obtained it from Aldrich Chemical Company, Inc. Hydrazine is a severe poison and should be handled only with gloves in an efficient fume hood.
5. An HPLC system was used to monitor the reduction and to determine the end of the reaction. The HPLC monitoring was not employed by the checker. However, TLC indicated that the reduction was almost complete after stirring for 2 hr at 25–30°C. If only a slight excess (1.03 equiv) of hydrazine is employed, the reaction is generally complete in 2 hr and excessive overreduction cannot occur.
The HPLC system consisted of a Waters C_{18} •-Bondapak column, a mobile phase consisting of 15% acetonitrile, 85% 0.05 *M* aqueous ammonium acetate using a flow rate of 2 mL/min and a UV wavelength detector for 235 nm. The

relative response factors of nitrobenzene and aniline were 1.75 and 0.66, respectively.

6. *N*-Phenylhydroxylamine, mp 83.5–85°C, can be isolated at this stage in 75–85% yields if desired, but it should be borne in mind that *N*-phenylhydroxylamine is not very stable. The isolation can be carried out by adding an equal volume of methylene chloride to the tetrahydrofuran solution, which is then dried over magnesium sulfate and concentrated to low volume under reduced pressure. Addition of a little petroleum ether precipitates *N*-phenylhydroxylamine, which is then filtered and washed with petroleum ether.

7. Acetyl chloride was obtained from Hoechst and was used as supplied. The checkers obtained it from Fluka Chemical Corporation. The quantity of acetyl chloride used is 1.05 equiv based on the HPLC yield. (The checkers simply used the amount specified.) Acetyl chloride should be handled only with gloves in an efficient fume hood.

8. No vigorous, exothermic reaction is seen during the addition of acetyl chloride, but the addition should be slow because of the heterogeneous nature of the reaction and the need to destroy efficiently hydrogen chloride as it is formed. The product, like *N*-phenylhydroxylamine, is sensitive to acid and undergoes the Bamberger rearrangement.[3]

9. Excessive heating causes decomposition of the product. This method also affords an easily handled crystalline solid of good purity.

10. The following analytical data have been obtained: ^{1}H NMR ($CDCl_3$, 100 MHz) δ: 2.11 (s, 3 H acetylmethyl); 7.40 (m, 5 H, aromatics); 8.90 (board, 0.6 H, NOH); IR (Nujol) cm^{-1}: 3140, 2930, 2860, 1630, 1595, 1460, 1380. Anal. calcd. for $C_8H_9NO_2$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.48; H, 5.99; N, 9.21. Nonaqueous titration (Bu_4NOH), 98.3%.

3. Discussion

This preparation illustrates a convenient reduction of nitrobenzene under catalytic transfer hydrogenation conditions to give *N*-phenylhydroxylamine in high yield and demonstrates a monoacylation method to afford the *N*-acetyl derivative in high yield. Some work has been done in this area by Johnstone et al.[4] A number of other reductive methods described in the literature were tried,[5,6,7] but these were not as good as the procedure described here. Phenylhydroxylamine is thermally unstable, can undergo a Bamberger rearrangement,[3] and deteriorates on storage, so its isolation is undesirable. The material was therefore converted directly, without isolation, to its more stable *N*-acetyl derivative. Other acylation methods led to mixtures of mono and diacylated products.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

hydrogen chloride, hydrochloric acid (7647-01-0)

ammonium acetate (631-61-8)

aniline (62-53-3)

acetonitrile (75-05-8)

sodium hydroxide (1310-73-2)

acetyl chloride (75-36-5)

sodium bicarbonate (144-55-8)

carbon (7782-42-5)

Nitrobenzene (98-95-3)

Phenylhydroxylamine, N-Phenylhydroxylamine (100-65-2)

hydrazine hydrate (7803-57-8)

hydrazine (302-01-2)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

rhodium (7440-16-6)

N-Acetyl-N-phenylhydroxylamine, Acetamide, N-hydroxy-N-phenyl- (9032-75-1)

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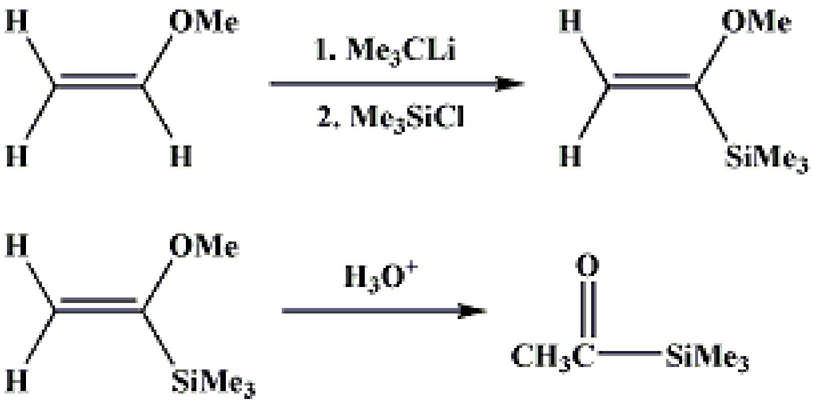
Organic Syntheses, CV 8, 19

ACETYLTRIMETHYLSILANE

[Silane, acetyltrimethyl-]



Submitted by John A. Soderquist[1]
Checked by Edward D. White III and James D. White.

1. Procedure

Caution! Persons following these procedures should be thoroughly familiar with the handling of air-sensitive solutions (Note 1).

A dry (Note 2), 2-L, round-bottomed flask containing a magnetic stirring bar and equipped with a rubber septum inlet is flushed with dry nitrogen and charged with 450 mL of purified tetrahydrofuran (Note 3). After the contents of the flask are cooled using a dry ice–acetone bath, 72 g (1.2 mol) of methyl vinyl ether is distilled into the flask from a commercial cylinder (Note 4). The septum is replaced, under a positive pressure of nitrogen gas, with a 500-mL, pressure-equalizing addition funnel equipped with a rubber septum inlet. The stirred contents of the flask are continuously cooled while 1.0 mol of *tert*-butyllithium in pentane solution *(Caution! Solutions of this reagent are pyrophoric and extreme care should be exercised when carrying out this manipulation!)* (Note 5) is transferred to the addition funnel and subsequently added to the mixture dropwise over ca. 1.5 hr. The resulting yellow slurry is allowed to warm slowly to 0°C over ca. 3 hr (Note 6). With the addition of dry ice to the bath, the near-colorless solution is recooled to ca. –78°C and 84.6 g (0.78 mol) of chlorotrimethylsilane (Note 7) is transferred to the addition funnel and subsequently added dropwise to the stirred mixture. The cold bath is removed and, after the mixture has reached room temperature, is allowed to stir for an additional 1 hr (Note 8). The contents of the flask are carefully poured into a 2-L separatory funnel which contains ca. 400 g of ice and ca. 200 mL of saturated ammonium chloride solution (Note 9). After separation of the aqueous layer, the organic solution is washed with water (12 × 250 mL) (Note 10), dried over anhydrous potassium carbonate, filtered, and distilled to

give 89–95 g (88–94%) of 1-(methoxyvinyl) trimethylsilane (bp 102–104°C, 760 mm), n_D^{20} 1.4173 (Note 11) and (Note 12).

A 50-mL, round-bottomed flask is charged with 65 g (0.50 mol) of 1-(methoxyvinyl) trimethylsilane and 300 mL of a 4:1 v/v mixture of acetone and 1.0 *M* aqueous hydrochloric acid (Note 13). After the pale-yellow-green solution is stirred for 1 hr at room temperature, it is transferred to a 1-L separatory funnel and 150 mL each of water and diethyl ether are added. After separation, the aqueous layer is washed with diethyl ether (2 × 50 mL), and these extracts are combined with the organic material. The ethereal solution is washed with water (3 × 300 mL), dried over anhydrous magnesium sulfate, filtered, and distilled to give 45–48 g (78–83%) of acetyltrimethylsilane (bp 112°C, 760 mm), n_D^{20} 1.4125 (lit.[2] 1.4113) (Note 14) and (Note 15).

2. Notes

1. For a detailed description of the general techniques used in the handling of air-sensitive solutions, consult [3]. Alternatively, a useful pamphlet describing these techniques is available from Aldrich Chemical Company, Inc., on request.
2. All of the glassware used in the preparation of 1-(methoxyvinyl) trimethylsilane was dried for at least 4 hr at 110°C, assembled hot, and allowed to cool under a nitrogen atmosphere.
3. Reagent-grade tetrahydrofuran (Aldrich Chemical Company, Inc.) was distilled under a nitrogen atmosphere from sodium/benzophenone prior to use.
4. Commercial cylinders of methyl vinyl ether were obtained from Matheson Gas Products, East Rutherford, NJ, and were fitted with a standard needle-valve regulator adapted to connect to a 24-in. 16-gauge syringe needle (Aldrich Chemical Company, Inc.). Unwanted, nonvolatile impurities from the cylinder were removed by employing a second flask, which was empty and septum-sealed, between the cylinder and the cold reaction flask. The gaseous reagent is transferred, through the needle, into the empty flask and through a double-ended needle (Aldrich Chemical Company, Inc.) into the reaction flask. The weight of the added methyl vinyl ether was periodically determined from the difference between the initial tare weight of the flask plus the contents and the total weight at each new weighing. However, the amount of this reagent added can be varied by at least ±10% without significantly affecting the product yield.
5. This reagent was obtained either from Aldrich Chemical Company, Inc., or Lithium Corporation of America, Bessemer City, NC. A technical data sheet is available from the suppliers. Solutions of ca. 2 *M* were titrimetrically analyzed for active alkyllithium by the tosylhydrazone method.[4] It is advisable to make certain that the organolithium reagent to be used was prepared in pentane solution. This evaluation can be easily accomplished by the gas-chromatographic analysis of the organic layer obtained from the hydrolysis, under a nitrogen atmosphere, of the *tert*-butyllithium solution to be used. Isobutane and pentane should comprise essentially all of the volatile material

observed. Recently, from the latter supplier, we found that the solvent used was a petroleum distillate that contained some higher-boiling components. As a consequence, the distillative isolation of the product was more difficult and the yield was lower (i.e., 80%).

6. The slow warm-up is accomplished conveniently by the removal of the solid dry ice from the cold bath. This process minimizes the formation of acetylenic byproducts. The warm-up period can vary with the amount of coolant used. We have consistently obtained good results using sufficient coolant to match the liquid level of the reaction mixture.

7. Chlorotrimethylsilane was purchased from Petrarch. Inc., Levittown, PA and was distilled from calcium hydride prior to use.

8. Lithium chloride precipitates during the warm-up procedure.

9. *Caution! The reaction mixture contains low boiling components and care must be exercised to prevent product loss.*

10. This procedure effectively removes the tetrahydrofuran, thus simplifying the distillative isolation of the product. This operation must be done carefully to prevent the loss of product.

11. A Nester–Faust Model NFT-50 annular spinning-band distillation unit was used to obtain the reported product yields in >99% Chemical purity by gas-chromatographic analysis (Perkin–Elmer Model Sigma 1B Instrument using a 6-ft × 1/8-in. 5% SE-30 on silylated Chromosorb W column). Lower product yields (84–86%) of similar chemical purity were obtained using a 200-mm column packed with glass helices.

12. This product gave a satisfactory combustion analysis for $C_6H_{14}OSi$ and exhibited the following spectroscopic data: ^1H NMR ($CDCl_3$) δ: 0.09 (s, 9 H), 3.50 (s, 3 H), 4.28 (d, 1 H, *J* = 2.0), 4.59 (d, 1 H, *J* = 2.0); ^{13}C NMR ($CDCl_3$) δ: –2.3 ($Si–CH_3$), 54.0 (OCH_3), 93.3 (C-2), 170.1 (C-1); IR (film) cm^{-1}: 1590 (C=C); 1257 (TMS); 1227, 1050 (C=C-OR); MS:*m/z* 130 (6%), 115 (20%), 89 (47%), 73 (100%), 59 (29%), 44 (11%), 42 (15%).

13. Exposure to direct sunlight was routinely avoided because of the known photochemical reactivity of acylsilanes.[5]

14. Distillation and gas-chromatographic analysis of this compound was carried out as described in (Note 11).

15. This product gave a satisfactory combustion analysis for $C_5H_{12}OSi$ and exhibited the following spectroscopic data: ^1H NMR ($CDCl_3$) δ: 0.09 (s, 9 H), 2.16 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ: –3.5 ($Si–CH_3$), 35.2 (CH_3), 246.8 (C=O); IR (film) cm^{-1}: 1645 (C=O); MS: *m/z* 116 (13%), 101 (11%), 73 (100%), 59 (6%), 44 (34%), 42 (15%). The ultraviolet spectrum of this material in cyclohexane solution exhibits absorbances at 381, 365, 356, and 344 nm with molar extinction coefficients of 91, 123, 97, and 60, respectively. In addition, shorter-wavelength shoulders are observed. For a detailed discussion of the spectroscopic properties of acylsilanes, consult [6].

3. Discussion

Acylsilanes have been known since 1957, when Brook described the synthesis of benzoyltriphenylsilane.[7] Their unique reactivity has made them very useful reagents for organic syntheses.[8] The simplest known member of this class of compounds, acetyltrimethylsilane, has been prepared from the oxidation of 1-trimethylsilylethanol,[6] the hydrolysis of 2-methyl-2-trimethylsilyl-l,3-dithiane,[2] the silylation–hydrolysis of *N*-acetylimidazole,[9] the lithiation–silylation–hydrolysis of ethyl vinyl ether,[10] the pyrolysis of 2,4,4-trimethyl-2-trimethylsilyl-1,3-oxathiolane 3,3-dioxide,[11] and the silylation of acid chlorides.[12]

The present preparation[13] utilizes the simple deprotonation of methyl vinyl ether first reported by Baldwin and co-workers to obtain 1-(methoxyvinyl)lithium,[14] which functions as a very useful reagent for nucleophilic acylation.[15] After detailed studies of the processes involved, this approach has been applied to the syntheses of a number of acyl derivatives of silicon, germanium, and tin.[16] This procedure also overcomes the hydrolysis problems encountered in a previous study.[10] The vinyl ether approach to such acylmetalloids has been demonstrated to provide access to systems that cannot be prepared using other acyl anion equivalents.[17] In the present case, the simple two-step process from commercially available reagents gives the highest reported overall yield of pure acetyltrimethylsilane from chlorotrimethylsilane (69–78%). Moreover, the reaction sequence can be scaled up or down without encountering difficulties.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

1-(methoxyvinyl)lithium

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

nitrogen (7727-37-9)

cyclohexane (110-82-7)

acetone (67-64-1)

Pentane (109-66-0)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

Lithium chloride (7447-41-8)

methyl vinyl ether (9003-09-2)

ethyl vinyl ether (109-92-2)

calcium hydride (7789-78-8)

isobutane (75-28-5)

CHLOROTRIMETHYLSILANE (75-77-4)

tert-Butyllithium (594-19-4)

Acetyltrimethylsilane, Silane, acetyltrimethyl- (13411-48-8)

1-(methoxyvinyl) trimethylsilane, 1-(methoxyvinyl)trimethylsilane (79678-01-6)

benzoyltriphenylsilane

2,4,4-trimethyl-2-trimethylsilyl-1,3-oxathiolane 3,3-dioxide

N-acetylimidazole (2466-76-4)

1-trimethylsilylethanol (13246-39-4)

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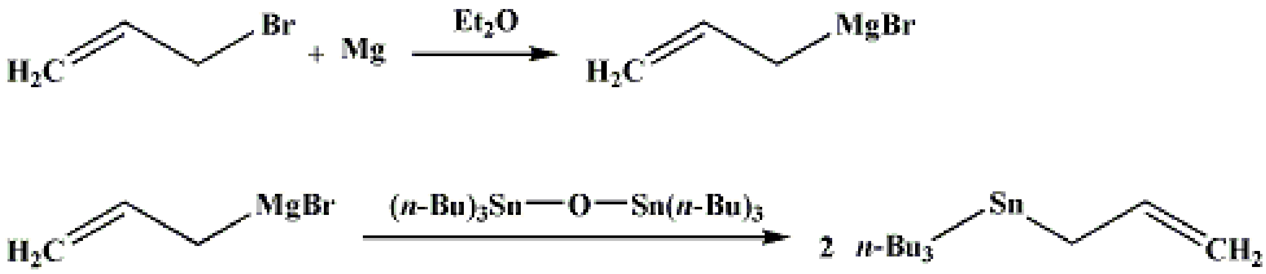
ALLYLTRIBUTYLTIN

[Stannane, tributyl-2-propenyl-]



Submitted by Noreen G. Halligan and Larry C. Blaszczak[1].
Checked by Christophe M. G. Philippo and Leo A. Paquette.

1. Procedure

Magnesium turnings (72.6 g, 3 g-atom) and 1000 mL of anhydrous ethyl ether are placed under argon in a dry, 3-L, three-necked flask equipped with a mechanical stirrer, a 500-mL pressure-equalizing dropping funnel, a Claisen adapter, a thermometer, an ice–water-cooled condenser, and an argon inlet. The dropping funnel is charged with allyl bromide (158 mL, 1.8 mol) (Note 1) in 150 mL of anhydrous ether. Stirring is initiated and a 10–12-mL portion of the allyl bromide solution is run into the reaction flask. The resulting mixture is treated with a few crystals of iodine, whereupon a rise in temperature and clouding of the reaction mixture occurs, indicating that the reaction has begun (Note 2). The remainder of the allyl bromide solution is added dropwise with continued stirring at such a rate as to maintain a gentle reflux. The addition requires approximately 1.5 hr. The mixture is then refluxed for an additional 1.5 hr.

While the Grignard solution is being refluxed, the dropping funnel is charged with bis (tributyltin) oxide (371 g, 0.62 mol) (Note 1) in 150 mL of anhydrous ether. After the reflux, heating is stopped and the bis(tributyltin) oxide solution is added at such a rate as to maintain a reaction temperature of 36–38°C. The addition requires approximately 1 hr. After the addition is complete, the reaction mixture is refluxed for 1.5 hr and then stirred overnight at room temperature.

The reaction mixture is cooled in a water–ice bath, and a saturated aqueous ammonium chloride solution is added at such a rate as to maintain the temperature below 35°C. Ammonium chloride solution is added in portions until addition produces no further exothermic reaction (Note 3). The supernatant solution is decanted through glass wool onto 400 g of ice in a 4-L separatory funnel. The residual solids are washed with three portions of hexane, approximately 1000 mL total, and the washes are decanted into the separatory funnel. After the phases are separated, the aqueous phase is washed with an additional 500-mL portion of hexane. The combined organic extracts are washed with 500 mL of saturated ammonium chloride, and then with 500 mL of brine. The organic layer is

dried over anhydrous magnesium sulfate and filtered. Most of the solvent is removed by a rotary evaporator and the residual oil is distilled at reduced pressure using an ice–water-cooled fraction cutting head. After a small forerun, approximately 390–392 g (94% of theory) is collected as a colorless oil, bp 116°C at 1.6 mm (lit. 155°C at 17 mm).[2]

2. Notes

1. Allyl bromide and bis(tributyltin) oxide were obtained from Aldrich Chemical Company, Inc.
2. Initiation of the reaction required about 1 min of sonication in an ordinary laboratory cleaner.
3. Approximately 190 mL of saturated aqueous ammonium chloride is required.

3. Discussion

Within the last decade, organotin chemistry has become a major source of new and highly selective reagents for effecting carbon–carbon bond formation. Transmetalation, nucleophilic substitution, stereoselective carbonyl addition, and transition-metal- or radical-mediated substitution reactions have all been accomplished using allyltributyltin. Because of the broad range of selective reactivities under which the synthetically versatile allyl group may be transferred to a highly functionalized substrate, allyltin compounds have secured a position on the modern chemist's list of indispensable reagents.

Transmetalation of allyltributyltin with organolithium species[3] has been used for the generation of allyllithium solutions free of the coupling by-products that often result from reduction of allylic halides with lithium metal. These solutions may then be used directly for the preparation of Gilman reagents and other reactive modifications of the parent allyllithium.

The use of allyltributyltin in combination with a Lewis acid has been used to effect both nucleophilic substitution[4] and stereoselective carbonyl addition[5] reactions. These reactions occur with a high degree of selectivity because of the reagent's nucleophilic, completely nonbasic character in the presence of a sufficiently reactive carbon electrophile. Allyltin reagents appear to be more useful than the corresponding allylsilanes for these purposes.

By far the most generally useful synthetic application of allyltributyltin is in the complementary set of transition-metal- and radical-mediated substitution reactions. When the halide substrates are benzylic, allylic, aromatic, or acyl, transition-metal catalysis[6] is usually the method of choice for allyl transfer from tin to carbon. When the halide (or halide equivalent) substrate is aliphatic or alicyclic, radical chain conditions[7] are appropriate, as β-hydrogen elimination is generally not a problem in these cases.

Allyltriorganotin compounds have been prepared by the reaction of allyl Grignard[8] or allyllithium reagents with triorganotin halides as well as by the procedure described. This procedure is an adaptation of that used by Rosenberg[9] for the preparation of

vinyltrialkyltin compounds. Allyltriorganotin compounds in which the allyl group bears complex substituents can be prepared by desulfurization of allylic sulfides, sulfoxides, or sulfones with triorganotin hydrides.[10]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 707
- Org. Syn. 75, 12

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

brine

ether, ethyl ether (60-29-7)

ammonium chloride (12125-02-9)

magnesium turnings (7439-95-4)

Allyl bromide (106-95-6)

tin (7440-31-5)

iodine (7553-56-2)

carbon (7782-42-5)

lithium (7439-93-2)

magnesium sulfate (7487-88-9)

hexane (110-54-3)

allyltin

Allyllithium

Allyltributyltin, Stannane, tributyl-2-propenyl- (24850-33-7)

bis(tributyltin) oxide (56-35-9)

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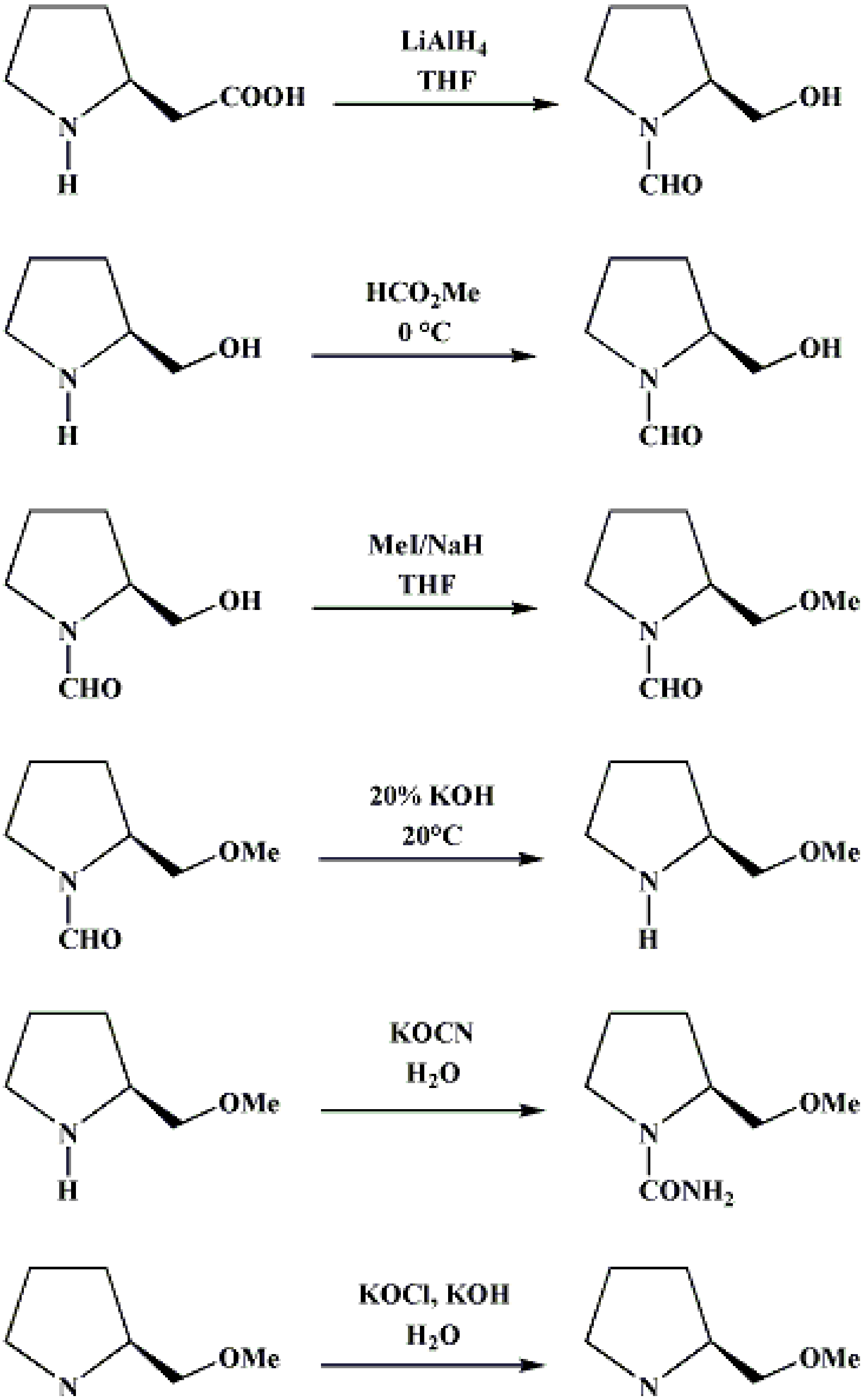
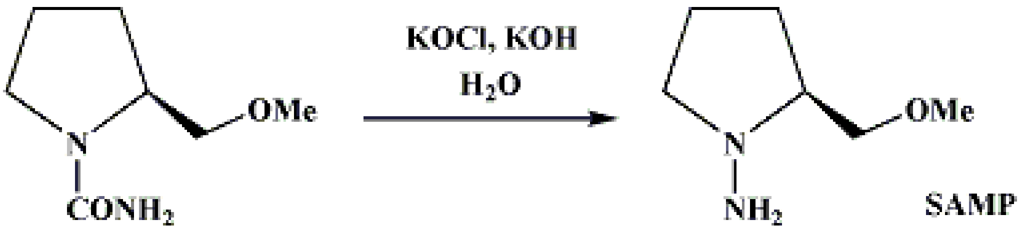
(*S*)-(–)-1-AMINO-2-METHOXYMETHYLPYRROLIDINE (SAMP) AND (*R*)-(+)-1-AMINO-2-METHOXYMETHYLPYRROLIDINE (RAMP), VERSATILE CHIRAL AUXILIARIES

[1-Pyrrolidinamine, 2-(methoxymethyl)-, (*S*) 1-Pyrrolidinamine, 2-(methoxymethyl)-, (*R*)]





Submitted by Dieter Enders, Peter Fey, and Helmut Kipphardt[1].
Checked by Akira Yanagisawa and Ryoji Noyori.

1. Procedure

A. *(S)-(+)-2-Hydroxymethylpyrrolidine.* In a 4-L, three-necked, round-bottomed flask equipped with a heating mantle (Note 1), an overhead stirrer bearing a two-bladed propeller (ca. 2.5-cm diameter), an effective reflux condenser with a drying tube packed with silica gel, and a plastic stopper are placed 2.5 L of anhydrous tetrahydrofuran (THF, (Note 2)) and 60 g (1.56 mol) of lithium aluminum hydride ($LiAlH_4$, (Note 3)). The suspension is heated under reflux for 15 min, the heating mantle is switched off, and 115.1 g (1 mol) of powdered (*S*)-proline (Note 4) is added in small portions (ca. 2 g, (Note 5)) to the boiling mixture at such a rate as to maintain reflux. The addition requires ca. 45 min and the contents of the flask are kept boiling for an additional 1 hr. Excess lithium aluminum hydride is then decomposed by cautiously adding a solution of 28 g of potassium hydroxide in 112 mL of water (without external heating) through a pressure-equalizing dropping funnel to the boiling mixture. On hydrolysis, white salts precipitate and stirring becomes difficult. After the addition is complete (ca. 25 min), the mixture is refluxed for 15 min and the hot solution is filtered by suction through a large Büchner funnel (18-cm diameter). The precipitate is pressed dry with a beaker. Any remaining prolinol is extracted from the precipitate by refluxing with 1.5 L of tetrahydrofuran for 1 hr under mechanical stirring, followed again by suction filtration. The combined filtrates are concentrated in a 2-L flask at 390°C (Note 6) under reduced pressure to yield 115–125 g of the crude hydroxymethylpyrrolidine as a pale-yellow oil.

B. *(S)-(−)-1-Formyl-2-hydroxymethylpyrrolidine.* The 2-L flask containing the crude hydroxymethyl derivative (ca. 1 mol) is equipped with a dropping funnel and a magnetic stirring bar and cooled to 0°C. Eighty milliliters (1.3 mol) of methyl formate (Note 7) is added over a period of 20 min and stirring is continued for 30 min at 0°C to give a green-colored solution. Excess methyl formate is evaporated at 30°C, affording a dark oil, which is taken up in 600 mL of dichloromethane and dried twice by stirring over a sufficient amount of anhydrous sodium sulfate. The drying agent is removed by suction filtration through Celite (Note 8), using a large column, and the filtrate is concentrated under reduced pressure at 30°C. Any remaining traces of solvents are removed by stirring under reduced pressure using and oil pump (20°C at 1 mm). This procedure takes about 2 hr and yields ca. 130 g (ca. 1 mol) of the dry, crude *N*-formyl compound, which is used in the next step without further purification.

C. *(S)-(−)-1-Formyl-2-methoxymethylpyrrolidine.* A 4-L, three-necked flask, fitted

with a magnetic stirrer, a reflux condenser, a low-temperature thermometer, and a mineral oil bubbler is charged with a solution of the crude formyl derivative in 1.5 L of dry tetrahydrofuran (Note 9) and flushed with argon. The solution is cooled to −50 to −60°C (internal temperature, acetone–dry ice), the cooling bath is removed, and 81 mL (1.3 mol) of methyl iodide is added. Then 28.8 g (1.2 mol) of sodium hydride (Note 10) is introduced carefully in one portion.

Caution! To prevent contact of sodium hydride with the cooling medium, it is absolutely necessary to remove the cooling bath before adding the sodium hydride. In addition, argon bubbling is stopped to avoid sodium hydride dust from being blown out of the flask.

The apparatus is flushed again with argon and allowed to warm to room temperature. During this period hydrogen gas evolves and a gray solid precipitates, which causes stirring to become difficult. At about 0°C the precipitate dissolves exothermally under strong evolution of hydrogen. The thermometer is replaced by a pressure-equalizing dropping funnel, and the solution is refluxed for 15 min and quenched by slow addition of 90 mL of 6 *N* hydrochloric acid, without external heating. Tetrahydrofuran is removed under reduced pressure to yield the crude *O*-methylated compound in water.

D. *(S)-(+)-2-Methoxymethylpyrrolidine.* A solution of 180 g of potassium hydroxide in 720 mL of water is added to the crude product and the mixture is vigorously stirred under argon overnight. Saturation with potassium carbonate (500 g) causes precipitation of potassium salts, which are filtered off by suction (large Büchner funnel) and washed with ether. The filtrate is extracted with ether (3 × 300 mL) (Note 11), and the ether layer is acidified with 100 mL of 12 *N* hydrochloric acid under ice cooling in a hood (evolution of fumes) and extracted twice with 100 mL of water to yield an aqueous solution of the hydrochloride of 2-methoxymethylpyrrolidine (Note 12).

E. *(S)-(−)-1-Carbamoyl-2-methoxymethylpyrrolidine.* The aqueous amine hydrochloride solution is adjusted to a pH of 2.8–3.2 (Note 13) with aqueous 50% potassium hydroxide. A solution of 80 g (1 mol) of potassium cyanate (Note 14) in 140 mL of water is then added all at once at 15°C and the mixture is allowed to stir for at least 12 hr at 20°C.

F. *(S)-(−)-1-Amino-2-methoxymethylpyrrolidine (SAMP).* A 4-L, three-necked flask containing the crude urea is cooled to −5°C (internal temperature) by means of an ice–salt bath and treated with a chilled (−5°C) solution of 168 g of potassium hydroxide in 150 mL of water. After addition of 685 mL (1.3 mol) of 1.9 *N* potassium hypochlorite solution (Note 15), precooled to −5°C, the temperature rises within 10 min to 30–40°C and the cooling bath is removed after the mixture reaches room temperature (Note 16). Stirring is continued for a total of 12–15 hr. Excess potassium hypochlorite is destroyed with a freshly prepared solution of sodium bisulfite (20 g $NaHSO_3$ in 50 mL

of H_2O) and the mixture is acidified (pH 2) with a minimum amount of 12 *N* hydrochloric acid (ca. 350 mL) under ice cooling. A strong evolution of carbon dioxide occurs. The mixture is allowed to stir for an additional 15 min at ambient temperature, made alkaline (pH 9) with ca. 100 mL of aqueous 50% potassium hydroxide, and saturated with potassium carbonate (500 g). Precipitated potassium salts are filtered off by suction through a large Büchner funnel and washed twice with ethanol; the filtrate is extracted with a 1 : 1 chloroform/ethanol mixture (1 × 800 mL and 2 × 400 mL). During extraction salt precipitation again occurs and the salts should be filtered off as mentioned above. The organic layers are collected, concentrated under reduced pressure at 30°C (Note 17), taken up in 500 mL of chloroform, and dried twice over sodium sulfate. The drying agent is removed by suction filtration through Celite and the solvent is stripped off as mentioned above to give 80–90 g of a dark oil. Immediate distillation through a 40-cm vacuum-jacketed Vigreux column (the receiver should be cooled with ice to prevent loss of substance) yields a small forerun containing 2-methoxymethylpyrrolidine, followed by SAMP as a colorless liquid, bp 42°C at 1.8 mm (80°C bath temperature), $[\alpha]_D^{20}$ −79.6° (neat). Overall yields of SAMP range from 65 to 75 g (50–58%). A purity of ca. 95% was established by GLC analysis (Note 18). The optical antipode RAMP, $[\alpha]_D^{20}$ + 79.8° (neat), can be prepared likewise, starting from (*R*)-proline (Note 19).

2. Notes

1. The heating mantle should be covered with aluminum foil to prevent contact with lithium aluminum hydride and proline.
2. Peroxide-free tetrahydrofuran (for precautions, see *Org. Synth., Coll. Vol. V,* **1973**, 976) was refluxed over potassium hydroxide pellets for 2 hr, distilled, and dried by addition of ca. 1 g of lithium aluminum hydride prior to use. *Failure to heed the precautions can result in a serious explosion!* Drying the THF over sodium–benzophenone is generally recommended for safety reasons.
3. Lithium aluminum hydride (100%) was used as purchased from Metallgesellschaft AG, Frankfurt, Germany, or Wako Pure Chemical Industries, Ltd., Japan.
4. Both (*S*)- and (*R*)-proline (≥99.5% ee) were obtained from Degussa AG, Hanau, Germany. The checkers used (*S*)-proline (guaranteed reagent) purchased from Wako Pure Chemical Industries, Ltd.
5. A convenient technique is to add the proline portionwise with a spoon that is inserted as far as possible into the flask to prevent the proline from being blown-off the spoon by hydrogen generated during the reaction. The flask is immediately stoppered after every addition.
6. The temperature of the heating bath should not exceed 30°C to avoid significant loss of product. To prevent oxidation the rotary evaporator is flushed with argon.
7. Methyl formate (reagent grade) was used as purchased from Riedel de Haen, Seelze, Germany. The checkers used the product (guaranteed reagent) of Wako Chemical Industries, Ltd.

8. Celite was supplied by Fluka AG, Buchs, Switzerland, or Manville Products Corporation, USA.
9. This time, tetrahydrofuran (Note 2) is made anhydrous by adding ca. 2 g of sodium hydride.
10. Methyl iodide was purchased from Merck-Schuchardt, Hohenbrunn, Germany, or Wako Pure Chemical Industries, Ltd., Japan. Because of its volatility and possible carcinogenicity it should be handled in a well-ventilated hood. Sodium hydride was supplied by Riedel de Haen, Seelze, Germany, or Wako Pure Chemical Industries, Ltd., Japan. In a 1-L, round-bottomed flask 50 g of 80% sodium hydride (mineral oil dispersion) is washed free of oil by stirring with pentane (4 × 300 mL). After the supernatant liquid is decanted for the fourth time, the remaining solvent is removed by evaporation (20°C at 1 mm).
11. After the usual workup, the amine can be obtained pure merely by distilling through a 40-cm Vigreux column, bp 75–77°C/40 mm.
12. The ether layer contains a small amount of the starting material and is discarded.
13. The pH of the solution should be exactly calibrated by means of a pH meter in order to prevent side reactions. The use of pH paper is not recommended.
14. Potassium cyanate (technical grade) was supplied by Degussa AG, Hanau, Germany. Alternatively, sodium cyanate may be used. The checkers used the practical-grade reagent purchased from Wako Pure Chemical Industries, Ltd., Japan.
15. The optimized preparation of an aqueous potassium hypochlorite solution is a modification of an *Organic Syntheses* procedure.[2] Two hundred grams of HTH [commercially available as swimming-pool sanitizer from Olin Chemicals, 120 Long Ridge Road, Stamford, CT 06904, USA, ca. 68% $Ca(OCl)_2$, or Nippon Soda Co., Japan, 70% $Ca(OCl)_2$] is vigorously shaken with 600 mL of water (ca. 10 min), a solution (20°C) of 40 g of potassium hydroxide and 140 g of potassium carbonate in 250 mL of water is added, and shaking is continued for at least 10 min to yield a semifluid gel. The gel is filtered off by suction and thoroughly pressed dry to give 650–770 mL of a yellow potassium hypochlorite solution. These solutions are 1.8–2.2 *M* according to simple iodometric titration (see *Org. Synth., Coll. Vol. VI,* **1988**, 968, (Note 3).)
16. Temperatures lower than those mentioned above inhibit the exothermic reaction, and the reaction time is extended to approximately 24 hr. Less efficient cooling results in warming to 70–80°C, which causes decarboxylation of the intermediate carboxylate and/or simple oxidation by potassium hypochlorite.
17. If the temperature of the water bath exceeds 30°C, significant amounts of product are lost. To prevent oxidation, the rotary evaporator is flushed with argon.
18. The checkers observed contamination of the final product by ca. 4% 2-methoxymethylpyrrolidine according to 270 MHz NMR.
19. The chiral hydrazines are stable over months if stored in a refrigerator under argon. The spectra are as follows. IR (film) cm^{-1}: 3360 (NH_2), 3150, 2980,

2880, 2820, 1610, 1465, 1200, 1120, 960, 920; ^{1}H NMR ($CDCl_3$, 90 MHz) δ: 1.4–2.1 (m, 4 H, CH_2), 2.1–2.6 (m, 2 H, CH_2N), 3.1 (m, 3 H, NH_2, NCH), 3.3 (s, 3 H, OCH_3), 3.4 (m, 2 H, CH_2O); mass spectrum (70 eV) *m/e* (relative intensity): M^+ 130.1100 (6.7%) (calcd. 130.1106); 97.07 (3.9); 86.07 (8.9); 85.07 (100.0); 83.06 (4.1); 71.06 (16.3); 68.05 (31.3); 57.04 (5.6); 56.05 (4.6); 45.03 (10.7); 43.03 (12.1); 42.04 (3.4); 41.04 (28.9); 39.02 (5.5).

3. Discussion

The previously reported preparation of SAMP and its enantiomer RAMP involved hazardous nitrosamine intermediates.[3,4,5] The new procedure described here circumvents this problem by *N*-amination via Hofmann degradation[6] (step F). The procedure, which required an optimization of the synthesis of the known intermediates,[7,8] is characterized by good yields, mild conditions and readily available starting materials. The entire sequence of six steps can be performed in a week.

The enantiomerically pure hydrazines SAMP and RAMP are versatile chiral auxiliaries with a wide range of applications in asymmetric synthesis.[9] For a detailed description of the SAMP/RAMP–hydrazone method see page 403.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 403

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

(S)-(−)-1-AMINO-2-METHOXYMETHYLPYRROLIDINE (SAMP)

(R)-(+)-1-AMINO-2-METHOXYMETHYLPYRROLIDINE (RAMP)

(S)-(−)-1-Formyl-2-hydroxymethylpyrrolidine

(S)-(−)-1-Formyl-2-methoxymethylpyrrolidine

(S)-(−)-1-Carbamoyl-2-methoxymethylpyrrolidine

(S)- and (R)-proline

ethanol (64-17-5)

potassium carbonate (584-08-7)

hydrochloric acid, hydrochloride (7647-01-0)

ether (60-29-7)

hydrogen (1333-74-0)

chloroform (67-66-3)

sodium sulfate (7757-82-6)

aluminum (7429-90-5)

sodium bisulfite (7631-90-5)

carbon dioxide (124-38-9)

potassium hydroxide (1310-58-3)

Benzophenone (119-61-9)

sodium (13966-32-0)

Methyl iodide (74-88-4)

Pentane (109-66-0)

methyl formate (107-31-3)

dichloromethane (75-09-2)

potassium cyanate (590-28-3)

potassium hypochlorite

proline, (S)-proline (147-85-3)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

sodium hydride (7646-69-7)

sodium cyanate (917-61-3)

argon (7440-37-1)

prolinol, (S)-(+)-2-Hydroxymethylpyrrolidine (23356-96-9)

1-Pyrrolidinamine, 2-(methoxymethyl)-, (S) (72748-99-3)

1-Pyrrolidinamine, 2-(methoxymethyl)-, (R) (59983-39-0)

hydroxymethylpyrrolidine

2-methoxymethylpyrrolidine

(R)-proline (344-25-2)

(S)-(+)-2-Methoxymethylpyrrolidine (63126-47-6)

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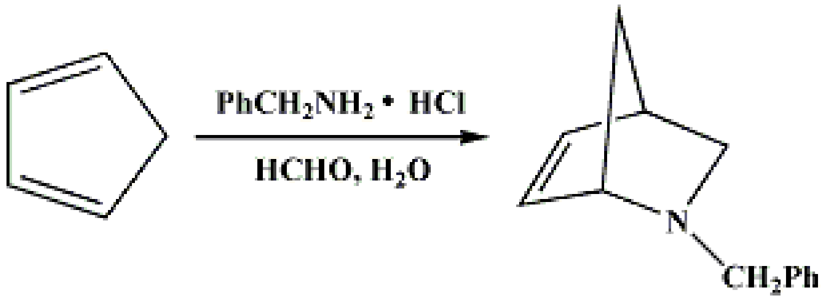
Organic Syntheses, CV 8, 31

IMINIUM ION-BASED DIELS–ALDER REACTIONS: *N*-BENZYL-2-AZANORBORNENE

[2-Azabicyclo[2.2.1]hept-5-ene, 2-(phenylmethyl)-]



Submitted by Paul A. Grieco and Scott D. Larsen[1].
Checked by V. Ramamurthy and Bruce E. Smart.

1. Procedure

A 100-mL, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar is charged with 24 mL of deionized water and 8.6 g (60.0 mmol) of benzylamine hydrochloride (Note 1). To this homogeneous solution is added 6.3 mL (84 mmol) of 37% aqueous formaldehyde solution (Note 2) followed by 9.9 mL (120 mmol) of freshly prepared cyclopentadiene (Note 3). The flask is stoppered tightly (Note 4) and stirred vigorously at ambient temperature. After 4 hr, the reaction mixture is poured into 50 mL of water and washed with ether–hexane, 1 : 1 (2 × 40 mL). The aqueous phase is made basic by the addition of 4.0 g of solid potassium hydroxide and extracted with ether (3 × 60 mL). The combined ether extracts are dried over anhydrous magnesium sulfate and filtered. The solvent is removed under reduced pressure (15–20 mm) to give 11.2 g (100%) of *N*-benzyl-2-azanorbornene as a very-pale-yellow oil (Note 5). The crude product is distilled at 80–85°C (0.05 mm) (Note 6) through a short-path apparatus to provide 10.1–10.2 g (91–92%) of pure product (Note 7) as a colorless oil (Note 8).

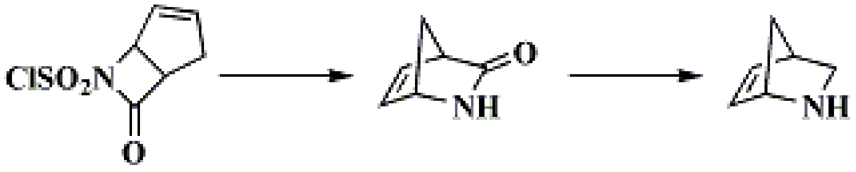
2. Notes

1. Benzylamine hydrochloride is commercially available from Aldrich Chemical Company, Inc.
2. Aqueous formaldehyde solution (37%) is commercially available from Mallinckrodt, Inc.
3. Cyclopentadiene is prepared by heating commercial dicyclopentadiene (available from Aldrich Chemical Company, Inc.) at 160°C in a distillation apparatus,. Cyclopentadiene distills smoothly at 39–45°C.[2]
4. The heterogeneous reaction mixture is stoppered tightly to avoid loss of

cyclopentadiene.
5. This crude material is essentially pure product contaminated by trace amounts of ether. *N*-Benzyl-2-azanorbornene has the following spectrum: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.42 (dm, 1 H, *J* = 8), 1.52 (dd, 1 H, *J* = 2, 8.5), 1.64 (dm, 1 H, *J* = 8), 2.94 (bs, 1 H), 3.18 (dd, 2 H, *J* = 3, 8.5), 3.34, 3.58 (AB, 2 H, *J* = 13), 3.83 (m, 1 H), 6.09 (dd, 1 H, *J* = 2, 6), 6.38 (ddd, 1 H, *J* = 2, 3, 6), 7.2–7.4 (m, 5 H).
6. Attempted distillation at 15–20 mm resulted in extensive decomposition.
7. The submitters obtained 10.8 g (97%) of analytically pure product, bp 80–85° C (0.05 mm). Anal. calcd. for $C_{13}H_{15}N$: C, 84.28; H, 8.16; N, 7.56. Found: C, 84.68; H, 8.36; N, 7.59.
8. On prolonged standing in air at room temperature discoloration of the product accompanied by slow evolution of cyclopentadiene takes place.

3. Discussion

Simple unactivated iminium salts generated in situ from formaldehyde and primary alkyl amines undergo a facile aza Diels–Alder reaction with cyclopentadiene at ambient temperature[3] to afford novel *N*-alkylated 2-azanorbornenes. The procedure described above is general and can be applied to a number of primary alkyl amines. Yields of *N*-alkyl substituted 2-azanorbornenes are good to excellent. Use of ammonium chloride and formaldehyde in the above reaction produces 2-azanorbornene in modest (40–50%) yield. 2-Azanorbornene **(3)** has been previously prepared[4] by reaction of cyclopentadiene with chlorosulfonyl isocyanate, which provides a single *N*-chlorosulfonyl β-lactam **(1)**. Exposure of **1** to an aqueous solution of sodium sulfite gives rise (25–30%) to 2-azanorbornen-3-one **(2)** which upon reduction with lithium aluminum hydride affords (ca. 80%) 2-azanorbornene **(3)**.



1 2 3

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ether (60-29-7)

ammonium chloride (12125-02-9)

sodium sulfite (7757-83-7)

formaldehyde (630-08-0)

potassium hydroxide (1310-58-3)

magnesium sulfate (7487-88-9)

lithium aluminum hydride (16853-85-3)

hexane (110-54-3)

CYCLOPENTADIENE (542-92-7)

dicyclopentadiene

CHLOROSULFONYL ISOCYANATE (1189-71-5)

2-Azabicyclo[2.2.1]hept-5-ene, 2-(phenylmethyl)-, N-Benzyl-2-azanorbornene (112375-05-0)

benzylamine hydrochloride (3287-99-8)

2-azanorbornene

2-azanorbornen-3-one

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Organic Syntheses, CV 8, 33

MIXED HIGHER-ORDER CYANOCUPRATE-INDUCED EPOXIDE OPENINGS: 1-BENZYLOXY-4-PENTEN-2-OL

[4-Penten-2-ol, 1-(phenylmethoxy)-]

Submitted by Bruce H. Lipshutz[1], Robert Moretti, and Robert Crow.
Checked by Gary L. Bolton, Steven G. Toske, and James D. White.

1. Procedure

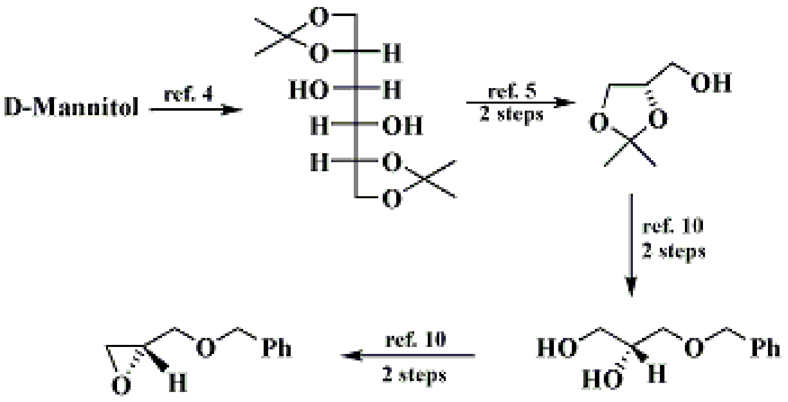
A 100-mL, two-necked, round-bottomed flask (Note 1) equipped with a stirring bar and a rubber septum is evacuated and flame-dried under vacuum, then flushed with dry argon. This process is repeated 3 times. Anhydrous tetrahydrofuran (36 mL, (Note 2)) and distilled thiophene (3.05 g, 2.91 mL, 36.3 mmol, (Note 3)) are injected via syringe and the resulting solution is cooled to −78°C. Butyllithium in hexanes (12.8 mL, 2.83 *M*, 36.3 mmol, (Note 4)) is added dropwise via syringe. The resulting light-yellow solution is warmed to −20°C using a solid dry ice–carbon tetrachloride bath and stirred for 20 min.

A 500-mL, two-necked, round-bottomed flask equipped with a stirring bar and a rubber septum is charged with copper(I) cyanide (2.95 g, 33.0 mmol, (Note 5)). The flask is evacuated and gently flame-dried under vacuum (Note 6), then flushed with dry argon. The process is repeated 3 times. Anhydrous tetrahydrofuran (33 mL) is injected and the resulting slurry is cooled to −78°C. At this time, the previously prepared solution of 2-lithiothiophene in tetrahydrofuran (at −20°C) is added via cannula to the stirring slurry. At the end of the addition, the acetone–dry ice bath is exchanged for an ice bath. After 5 min (Note 7), the flask is again placed in a dry ice–acetone bath. Vinyllithium in tetrahydrofuran (16.7 mL, 1.98 *M*, 33.0 mmol, (Note 8)) is added dropwise after 15 min. Then the −78°C bath is exchanged for an ice bath. After 5 min, the reaction mixture is recooled to −78°C and a cooled (−20°C) solution of benzyl 2,3-epoxypropyl ether (4.93 g, 30.0 mmol, (Note 9)) in anhydrous tetrahydrofuran (30 mL) is added to the cuprate solution via cannula over a 10-min period. The reaction mixture is warmed to 0°C (Note 10). After 3 hr at 0°C, it is warmed to ambient temperature and stirred for an additional 1 hr. It is then cooled to −78°C and poured on to a solution of saturated aqueous ammonium chloride (135 mL) and concentrated aqueous ammonium hydroxide (15 mL). The mixture is stirred for an additional 15 min while the temperature of the system is allowed to rise. The mixture is filtered through Celite. The flask and the filter cake are rinsed with tetrahydrofuran (2 × 20 mL). The tetrahydrofuran is evaporated using a rotary evaporator, and the resulting aqueous layer is extracted with ethyl acetate (2 × 150 mL). Each organic layer is washed with water (75 mL) and brine (75 mL). The combined organic layers are dried over anhydrous sodium sulfate and concentrated with a rotary evaporator. The residue is purified by column chromatography on silica gel (Note 11), using a 6 : 1 mixture of petroleum ether and ethyl acetate as eluant (Note 12), to afford an oil (5.7 g, 29.6 mmol, 99%), which is distilled through a short-path distillation apparatus to give 4.20 g of an oil (26.1 mmol, 73%) (Note 13) as a colorless liquid, bp 85°C at 0.1 mm; IR (neat) cm^{-1}: 3400, 3070, 3030, 1640, 1100, 740, 700; ^1H NMR ($CDCl_3$) δ: 2.26 (t, 2 H, *J* = 6.9), 2.41 (d, 1 H, *J* = 3.3), 3.4–3.6 (m, 2 H), 3.90 (m, 1 H), 4.55 (s, 2 H), 5.1 (m, 2 H), 5.75–5.90 (m, 1 H), 7.33 (s, 5 H); mass spectrum, *m/e* (relative intensity): 192 (M^+, 1.06), 92 (24.89), 91 (100); high-resolution mass spectrum. Calcd. for $C_{12}H_{16}O_2$: 192.1150. Found: 192.1161.

2. Notes

1. All glassware, needles, and syringes are stored in an oven at 120°C overnight and assembled while hot.

2. Tetrahydrofuran is distilled from sodium–benzophenone before use.
3. Thiophene is purchased from the Aldrich Chemical Company, Inc. and distilled from calcium hydride before use.
4. Butyllithium in hexanes (2.5 *M*) is purchased from the Aldrich Chemical Company, Inc. and titrated with 2-pentanol in ether, using 1,10-phenanthroline as indicator before use.[2] Use of lower concentrations of butyllithium for the metalation of thiophene under these conditions results in incomplete lithiation.
5. Copper(I) cyanide is purchased from the Aldrich Chemical Company, Inc. and is dried in an Abderhalden apparatus at 56°C for ca. 2 days before use. *Caution: Copper(I) cyanide is very toxic.*
6. *Caution should be exercised during this operation. Overheating can result in partial decomposition of the copper(I) cyanide.*
7. At this point, all of the copper(I) cyanide has been consumed and the reaction appears as a brown solution.
8. Vinyllithium in tetrahydrofuran is purchased from Organometallics, Inc., and titrated[2] before use (see (Note 4)).
9. The starting material was prepared by the benzylation of glycidol, with benzyl bromide in tetrahydrofuran according to the following procedure. A 500-mL, two-necked, round-bottomed flask, equipped with a stirring bar and a rubber septum, is evacuated and flame-dried under vacuum, then flushed with dry argon. This process is repeated 3 times. A solution of distilled glycidol (4.0 g, 3.58 mL, 54 mmol, obtained from Aldrich Chemical Company, Inc. and distilled before use) in anhydrous tetrahydrofuran (139 mL) is injected via syringe and the resulting clear solution is cooled to 0°C. Sodium hydride (2.24 g of a 60% dispersion in mineral oil, 56 mmol, obtained from Aldrich Chemical Company, Inc.) is added portionwise and the resulting gray mixture is stirred at 0°C for 30 min. Solid tetrabutylammonium iodide (0.21 g, 0.56 mmol, obtained from Aldrich Chemical Company, Inc.) is then introduced all at once. Distilled benzyl bromide (9.54 g, 6.63 mL, 55.8 mmol) is added (neat) dropwise via syringe. [Benzyl bromide was purchased from the Aldrich Chemical Company, Inc. and dried over $MgSO_4$, filtered, and distilled before use. (*Caution: Benzyl bromide is light-sensitive and is a potent lachrymator.*)] The solution is stirred at 0°C for 5 min, then warmed to ambient temperature and stirred for 1 hr. The mixture is quenched with aqueous ammonium chloride and extracted with ethyl acetate (2 × 200 mL). Each organic phase is washed with water (100 mL) and brine (2 × 100 mL). The combined organic layers are dried over sodium sulfate and concentrated using a rotary evaporator. The remaining yellow residue is purified by flash chromatography,[3] using a 5 : 1 mixture of petroleum ether and ethyl acetate as eluent, to afford chromatographically pure (±)-benzyl 2,3-epoxypropyl ether (7.34 g, 44.7 mmol, 83%), which can be distilled through a short-path distillation apparatus to give 6.52 g of the epoxide (39.7 mmol, 74%) as a colorless liquid, bp 105°C at 0.4 mm. Optically active (*S*)-benzyl 2,3-epoxypropyl ether can be obtained in quantity in seven steps from D-mannitol according to literature procedures.[4] Modified routes to D-glyceraldehyde acetonide in bulk are also available,[5] as are other experimental changes for yield enhancements.[6] Reviews on the use of both (*R*)/(*S*)-2,3-*O*-isopropylidene glyceraldehyde[7] and nonracemic glycidol and derivatives[8] provide excellent sources of additional information.



10. At this point, the color of the solution turns from brown to light green, and darkens with time.

11. The technique of Still[3] (flash chromatography) is used, with silica gel purchased from ICN Biomedicals (ICN Silica 21-63).

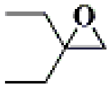
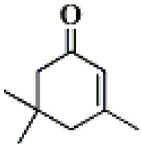
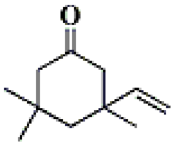
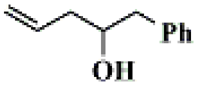
12. For TLC analyses, Merck silica gel F-254 TLC plates were used, with 1 : 1 petroleum ether–ether as eluent. Visualization was effected by spraying with a 5% phosphomolybdic acid in ethanol solution followed by heating at ca. 250°C on a hot plate. (*R*)-1-Benzyloxy-4-penten-2-ol has an R_f of ca. 0.35 in this solvent system.

13. The checkers found that there was consistently 10–12% of 1-benzyloxyheptan-2-ol in the reaction mixture resulting from coupling of "residual" butyllithium (which forms *N*-Bu(Th)Cu(CN)Li_2) with the epoxide.

3. Discussion

This procedure is an illustration of the use of mixed, higher-order (H.O.) cyanocuprates containing a nontransferable or "dummy" ligand for epoxide opening.[9] H.O. cuprates of general stoichiometry R_T(2-thienyl)Cu(CN)Li_2 can also be used to effect substitution reactions with halides, as well as conjugate additions to unhindered α,β-unsaturated ketones (see Table I).[9]

TABLE I
REACTIONS OF VARIOUS SUBSTRATES WITH (VINYL)(2-THIENYL)CU(CN)LI_2

Substrate	Equiv. of cuprate	Conditions	Product	Yield(%)
	1.20	THF/Et_2O room temp. 4 hr		71[a]
	1.50	THF, 31° 18 hr		67[b]
	1.10	THF/Et_2O 1.1 eq. BF_3 −78°, 1 hr		98[b]
	1.25	THF/Et_2O 0°, 1 hr		90[a]

[a]Isolated yield of chromatographically pure material.

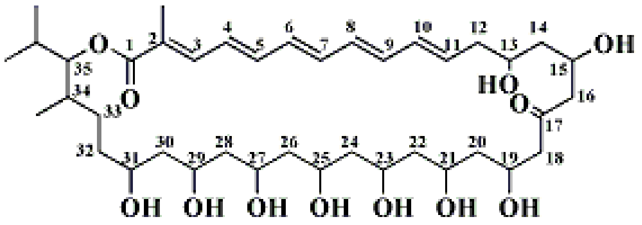
[b]By quantitative GC analysis.

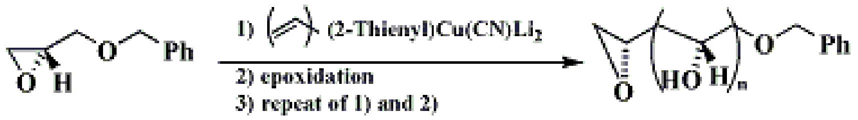
The lower order (L.O.) cyanocuprate (2-Th)Cu(CN)Li has an excellent shelf life, thereby providing a highly stable precursor to higher-order cuprates.[10] Tetrahydrofuran solutions of this L.O. cuprate are available commercially (from Aldrich Chemical Company, Inc.), thus allowing further simplification of this procedure.

The often greater reactivity of H.O. cuprates[11,12] as compared to their L.O. counterparts to exemplified by this method. When $(vinyl)_2CuLi$ (from 2 vinyllithium + 1 CuI, a Gilman-type reagent)[13] was used for the

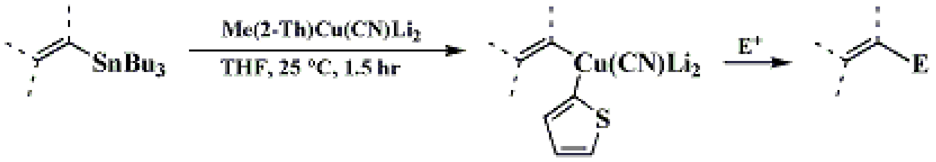
same transformation, a yield of 73% was observed, along with recovered starting material.[14] The L.O. cyanocuprate (vinyl)Cu(CN)Li gave only 11% of the desired product.[9] Significantly, in the procedure described only 1.1 equiv of H.O. cuprate are necessary for complete consumption of the epoxide.

The (*R*)-1-benzyloxy-4-penten-2-ol produced using enantiomerically enriched starting material in this reaction is a useful precursor in the synthesis of the polyol section of the polyene macrolide antibiotic roflamycoin (Scheme 1). This molecule has an array of 1,3-secondary hydroxyl groups, assumed to bear an all-*syn* relationship to each other, for which a synthetic strategy has been devised.[14,15,16] Thus, a reiterative two-step protocol involving epoxide opening with a H.O. vinylcyanocuprate, followed by stereoselective homoallylic alcohol epoxidation, reforms the functionality (i.e., an epoxide) from which it was originally derived (Scheme 2).

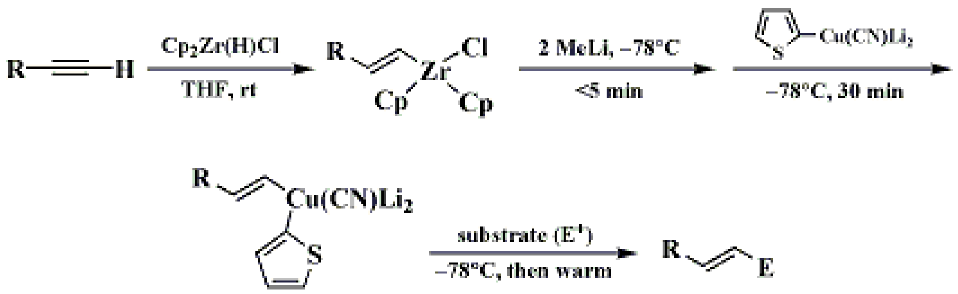




As an alternative to the preparation of $(CH_2{=}CH\text{-})(2\text{-thienyl})Cu(CN)Li_2$ from vinyllithium (or a substituted vinyllithium), 2-lithiothiophene, and CuCN, mixed reagents of this type can be formed via transmetallation processes involving vinylstannanes and $Me(2\text{-thienyl})Cu(CN)Li_2$ in THF at ambient temperatures.[17] Double-bond geometry is strictly maintained, and thus the intermediacy of vinylic organolithium species is avoided.



As additional development concerns the use of vinylzirconium intermediates, formed in the usual manner by hydrozirconation of 1-alkynes. Treatment of these species at −78°C with $MeLi/Me_2Cu(CN)Li_2$ effects ligand exchange, thereby forming a mixed cyanocuprate $(vinylic)MeCu(CN)Li_2$, which selectively delivers the vinyl residue to α,β-unsaturated ketones in high yields.[18,19 20] Alkylations can be effected using $MeLi/Me(2\text{-thienyl})Cu(CN)Li_2$ to arrive at $(vinylic)(2\text{-Th})Cu(CN)Li_2$.[21]



This preparation is referenced from:

- Org. Syn. 75, 12

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

hexanes

brine

D-glyceraldehyde acetonide

$(vinyl)_2CuLi$

(vinyl)Cu(CN)Li

$Me(2\text{-thienyl})Cu(CN)Li_2$

$MeLi/Me_2Cu(CN)Li_2$

$(vinylic)MeCu(CN)Li_2$

$MeLi/Me(2\text{-thienyl})Cu(CN)Li_2$

$(vinylic)(2\text{-Th})Cu(CN)Li_2$

ethanol (64-17-5)

ethyl acetate (141-78-6)

ether (60-29-7)

ammonium chloride (12125-02-9)

sodium sulfate (7757-82-6)

copper(I) cyanide (544-92-3)

Benzophenone (119-61-9)

sodium (13966-32-0)

ammonium hydroxide (1336-21-6)

2-Pentanol (6032-29-7)

Thiophene (110-02-1)

benzyl bromide (100-39-0)

butyllithium (109-72-8)

Tetrahydrofuran, THF (109-99-9)

sodium hydride (7646-69-7)

calcium hydride (7789-78-8)

argon (7440-37-1)

vinyllithium (917-57-7)

phosphomolybdic acid (51429-74-4)

1,10-phenanthroline (66-71-7)

2-lithiothiophene

1-Benzyloxy-4-penten-2-ol, 4-Penten-2-ol, 1-(phenylmethoxy)- (58931-16-1)

Benzyl 2,3-epoxypropyl ether, (±)-benzyl 2,3-epoxypropyl ether (2930-05-4)

glycidol (556-52-5)

tetrabutylammonium iodide (311-28-4)

mannitol (69-65-8)

1-benzyloxyheptan-2-ol

vinylcyanocuprate

vinylzirconium

(R)/(S)-2,3-O-isopropylidene glyceraldehyde (15186-48-8)

(S)-benzyl 2,3-epoxypropyl ether (16495-13-9)

(R)-1-Benzyloxy-4-penten-2-ol

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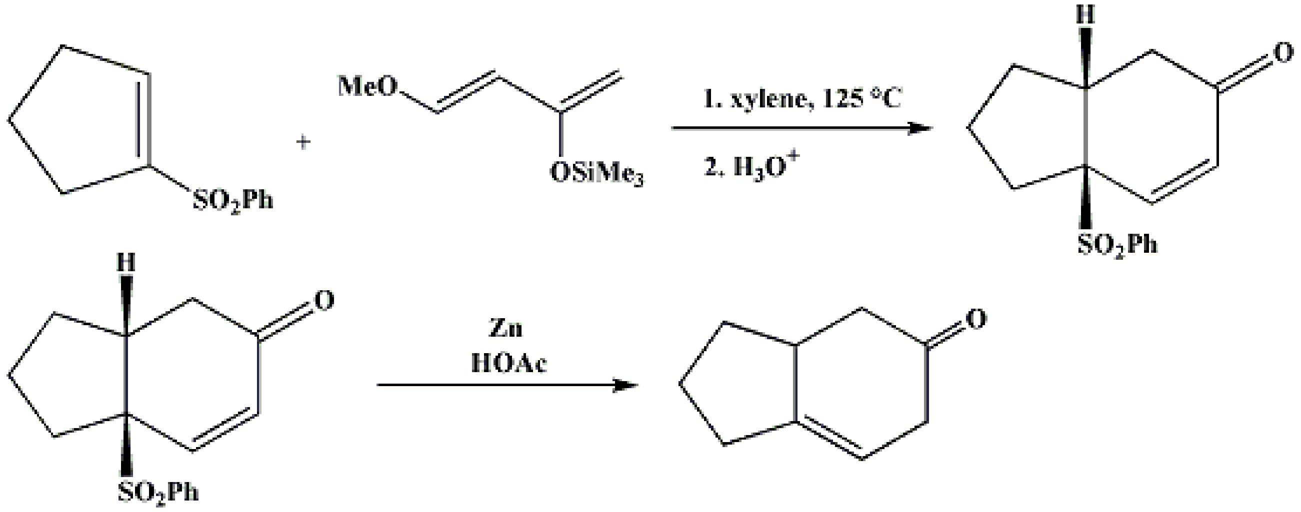
REDUCTIVE ANNULATION OF VINYL SULFONES: BICYCLO [4.3.0.]NON-1-EN-4-ONE

[5*H*-Inden-5-one, 1,2,3,3a,4,6-hexahydro-]



Submitted by Ho-shen Lin and Leo A. Paquette[1].
Checked by Edward J. Adams and Edwin Vedejs.

1. Procedure

A. *4-Oxo-1-(phenylsulfonyl)-cis-bicyclo[4.3.0]non-2-ene.* A 250-mL, one-necked flask equipped with a Teflon-coated magnetic stirring bar, a condenser, and a nitrogen inlet tube is charged with 8.76 g (42.1 mmol) of 1-(phenylsulfonyl)cyclopentene (Note 1), 8.75 g (50.9 mmol) of 1-methoxy-3-(trimethylsiloxy)-1,3-butadiene and 8 mL of xylene (Note 2). The stirred reaction mixture is blanketed with nitrogen and heated in an oil bath at 123–125°C in the dark for 3 days. After the solution is cooled, it is diluted with 80 mL of tetrahydrofuran and 30 mL of 2 *N* hydrochloric acid and heated at the reflux temperature for 24 hr. Most of the tetrahydrofuran is removed on a rotary evaporator. The residue is transferred to a 1-L separatory funnel and diluted with ether (200 mL) and dichloromethane (100 mL). The organic phase is washed with two 50-mL volumes of half-saturated sodium bicarbonate solution and a mixed solution of saturated sodium bicarbonate (10 mL) and half-saturated sodium chloride (40 mL). The organic layer is dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue is subjected to flash column chromatography on silica gel (250 g). Elution with a mixture of ethyl acetate–dichloromethane–petroleum ether (1 : 25 : 25) returns 3.56 g (41%) of unreacted 1-(phenylsulfonyl)cyclopentene. Subsequent increase in the solvent polarity to 3 : 25 : 25 provides the cycloadduct as a yellowish solid. This material is dissolved in the minimum amount of dichloromethane to which is added 25 mL of ether; 4.33 g of colorless crystals precipitate. Concentration of the filtrate and crystallization from ether–petroleum ether afford an additional 0.77–1.34 g of light-yellow crystals (combined yield of 44–49%) (Note 3).

B. *Bicyclo[4.3.0]non-1-en-4-one.* The preceding enone (5.64 g, 20.4 mmol) is dissolved with magnetic stirring in 120 mL of glacial acetic acid contained in a 500-mL, one necked flask. Zinc powder (13.3 g, 0.203 mol) (Note 4) is introduced and the capped reaction mixture is stirred vigorously at room temperature for 1 hr. The zinc is removed by suction filtration through a Celite pad (Büchner funnel) and washed with 200 mL of ether. The combined filtrates are transferred to a 2-L separatory funnel, diluted with 300 mL of petroleum ether, and washed with 200 mL of water. The aqueous phase is

reextracted with 300 mL of a 1 : 1 mixture of ether and petroleum ether. Finally the combined organic layers are washed with 100 mL of water and 200 mL of saturated sodium bicarbonate solution prior to drying over anhydrous magnesium sulfate and filtration. The solvents are removed on a rotary evaporator to leave a pale-yellow oil that is purified by chromatography on silica gel (elution with 14% ethyl acetate in petroleum ether). There is isolated 1.81–1.98 g (65–71%) of the β,γ-enone as a colorless oil (Note 5) and (Note 6).

2. Notes

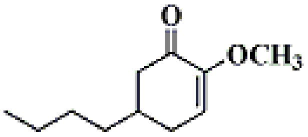
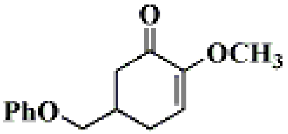
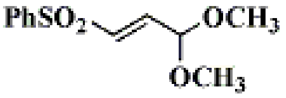
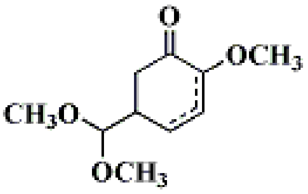
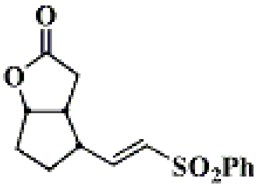
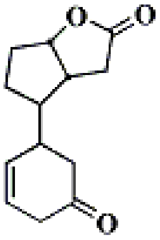
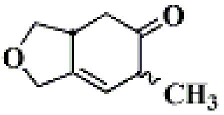
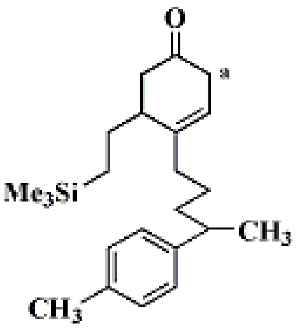
1. See *Org. Synth., Coll. Vol. VIII*, **1993**, 543 for preparation of this intermediate.
2. The reagents were purchased from the Aldrich Chemical Company, Inc.; the diene was used without further purification, and xylene was dried by azeotropic removal of water and distillation from calcium hydride. 1-Methoxy-3-trimethylsiloxy-1,3-butadiene can be prepared by the method of *Org. Synth., Coll. Vol. VII*, **1990**, 312.
3. The product can be further purified by crystallization from dichloromethane and ether. The crystalline modification that is obtained melts at 122.5–126°C. Melting and resolidification provides a second modification that melts at 122.5–123.2°C. The product has the following spectral properties: IR (CH_2Cl_2) cm^{-1}; 1680, 1310, 1150, 1090; ^1H NMR ($CDCl_3$) δ: 1.27–1.49 (m, 1 H), 1.55–1.87 (m, 3 H), 1.95–2.15 (m, 1 H), 2.16–2.31 (m, 2 H), 2.59–2.76 (m, 1 H), 2.93–3.13 (m, 1 H), 6.08 (d, 1 H, *J* = 10.2), 6.49 (dd, 1 H, *J* = 10.0, 1.7), 7.53 (br t, 2 H, *J* = 7.3), 7.64 (br t, 1 H, *J* = 7.2), 7.83 (br d, 2 H, *J* = 7.2); ^{13}C NMR ($CDCl_3$) δ: 22.76, 32.34, 35.68, 37.91, 38.73, 70.46, 129.05, 129.64, 131.89, 134.19, 136.38, 143.54, 196.27; *m/z* calcd. for M^+-$C_6H_5SO_2$: 135.0801. Found: 135.0835. Anal. calcd. for $C_{15}H_{16}O_3S$: C, 65.19; H, 5.84. Found: C, 65.28, H, 6.85.
4. Fresh Mallinckrodt zinc dust was used without purification.
5. The product has the following spectral properties: IR (CH_2Cl_2) cm^{-1}: 2960, 2880, 1710; ^1H NMR ($CDCl_3$) δ: 1.08–1.35 (m, 1 H), 1.43–1.68 (m, 1 H), 1.68–1.91 (m, 1 H), 1.91–2.15 (m, 2 H), 2.15–2.38 (m, 2 H), 2.38–2.65 (m, 2 H), 2.65–2.94 (m, 2 H), 5.38–5.53 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ: 24.86, 29.78, 33.80, 39.09, 40.40, 45.07, 113.22, 146.32, 211.05; *m/z* calcd. for $C_9H_{12}O$: 136.0888. Found: 136.0896.
6. The product may be isolated by distillation, although two complications arise. First, because of the volatility of the enone, some material loss is incurred (yields of 57–60% result), bp 68–78°C (19 mm). More critically, heating induces some equilibration (generally ca. 10–15%) to the α,β-enone isomer. Thus, distillation should be avoided if pure β,γ-enone is desired. The spectral properties of the conjugated ketone, which can be obtained in a pure state by silica gel chromatography, are as follows: IR (CH_2Cl_2) cm^{-1}: 2950, 2875, 1670; ^1H NMR ($CDCl_3$) δ: 1.31–1.49 (m, 1 H), 1.57–2.08 (m, 5 H), 2.40 (dd, 1 H, *J* = 17.8, 7.4), 2.47–2.62 (m, 2 H), 2.72–2.84 (m, 1 H), 5.92 (dd, 1 H, *J* = 10.2, 2.1), 6.70 (dd, 1 H, *J* = 10.2, 3.5); *m/z* calcd. for $C_9H_{12}O$: 136.0888. Found: 136.0864.

3. Discussion

As a group, annulation reactions have been exceedingly valuable to the synthetic organic chemist. Unfortunately, processes of this type involving simple alkenes and cycloalkenes are few. However, the facility with which unactivated olefins can be transformed into vinyl sulfones,[2,3] the high degree to which α,β-unsaturated sulfones are captured regioselectively by unsymmetrical dienes[4] such as those developed by Danishefsky,[5 6 7 8] and the ease with which reductive desulfonylation can be effected[9,10] combine to permit convenient synthetic entry to substituted cyclohexenones. Several representative examples can be found in Table I.

TABLE I

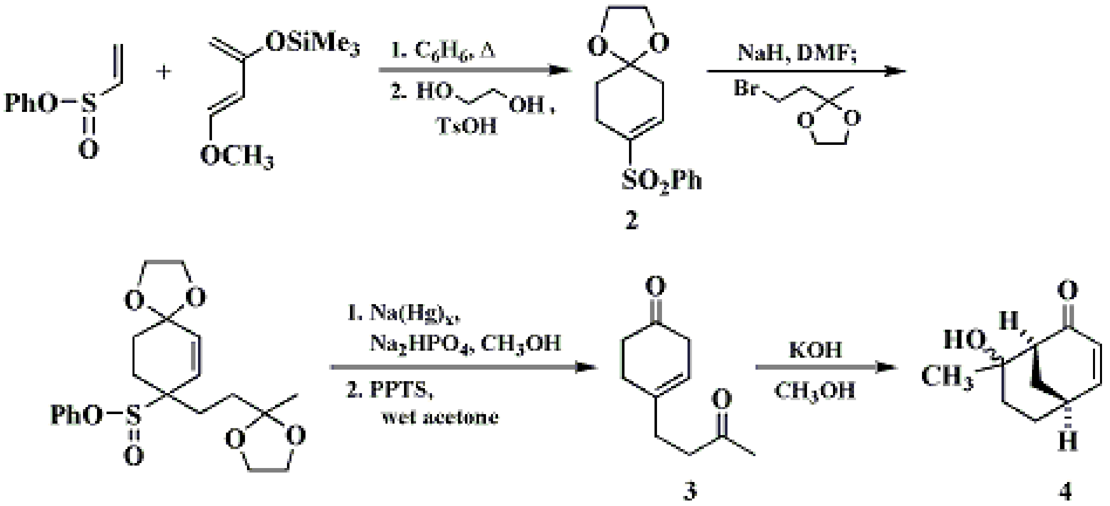
REDUCTIVE ANNULATION OF VINYL SULFONES[4]

Starting material	Diene	Product	α,β:β,γ Ratio
	1b		100:0
	1b		100:0
	1b		60:40
	1a		0:100
	1b		0:100
	1a	 a	0:100

[a]Including an intermediate alkylation step.

Other variants on this theme are possible. Thus, if the initially formed Diels–Alder adduct is directly ketalized as in **2**, the derived α-sulfonyl carbanion can be alkylated. Reductive desulfonylation and acidic hydrolysis [with pyridinium *p*-toluenesulfonate (PPTS)] then deliver a 4-substituted

cyclohexenone (e.g., **3**), which in many cases can be made to undergo further useful synthetic transformations (e.g., **4**).[4]



The expendability of the scheme allows one to prepare 4-substituted and 4,5-disubstituted 2(and 3)-cyclohexenones where the nature of the side chains can be widely varied.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

petroleum ether

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ethyl acetate (141-78-6)

ether (60-29-7)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

zinc (7440-66-6)

xylene (106-42-3)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

calcium hydride (7789-78-8)

1-Methoxy-3-trimethylsiloxy-1,3-butadiene, 1-methoxy-3-(trimethylsiloxy)-1,3-butadiene

BICYCLO[4.3.0.]NON-1-EN-4-ONE, 5H-Inden-5-one, 1,2,3,3a,4,6-hexahydro-, Bicyclo[4.3.0]non-1-en-4-one (131712-16-8)

1-(Phenylsulfonyl)cyclopentene (64740-90-5)

pyridinium p-toluenesulfonate

4-Oxo-1-(phenylsulfonyl)-cis-bicyclo[4.3.0]non-2-ene (131712-15-7)

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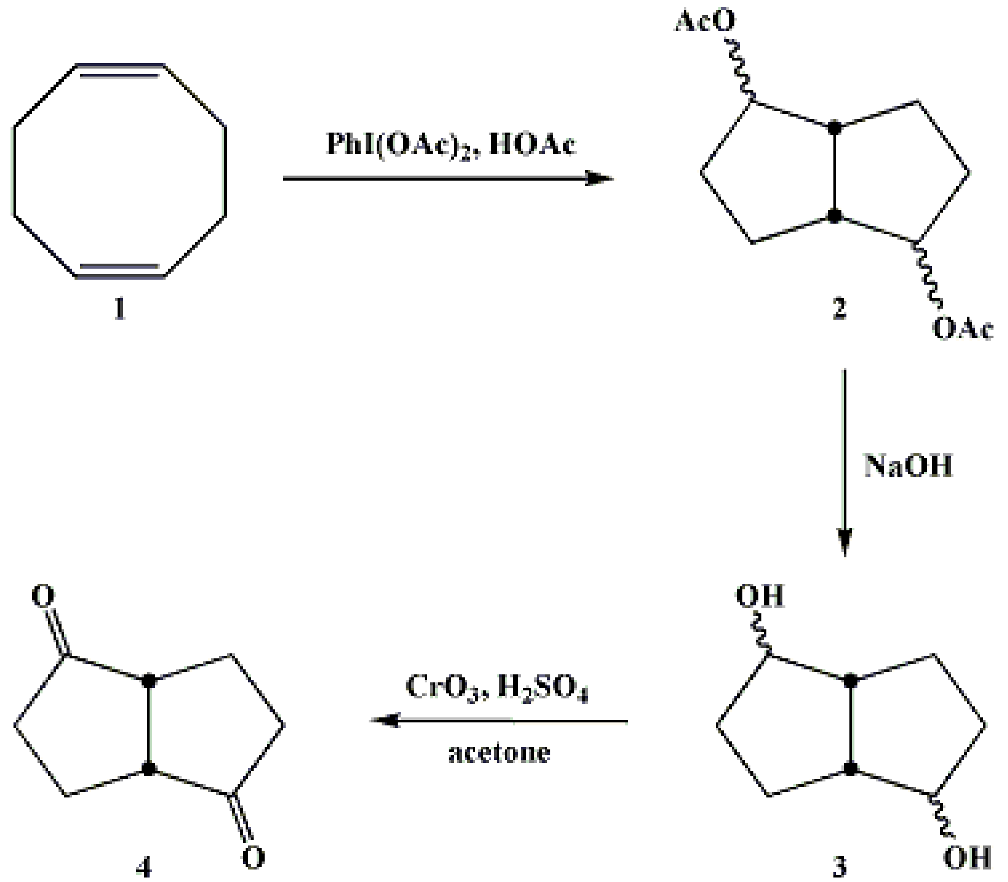
INTRAMOLECULAR CYCLIZATION OF *cis,cis*-1,5-CYCLOOCTADIENE USING HYPERVALENT IODINE: BICYCLO[3.3.0]OCTANE-2,6-DIONE

[1,4-Pentalenedione, hexahydro-]



Submitted by Robert M. Moriarty[1], Michael P. Duncan[1], Radhe K. Vaid[1], and OM Prakash[2].
Checked by Deng Bing and Ekkehard Winterfeldt.

1. Procedure

A. *2,6-Diacetoxybicyclo[3.3.0]octane.* (Compound **2**; (Note 1) and (Note 2).) An ovendried. 1-L round-bottomed flask, equipped with a magnetic stirring bar, a reflux condenser, and a drying tube (Drierite), is charged with iodosobenzene diacetate (IBD) (100 g. 0.31 mol) and 300 mL of glacial acetic acid. To this stirred mixture, 25 g (0.23 mol) of *cis,cis*-1,5-cyclooctadiene (COD) is added. The resulting mixture is then heated to reflux for 16 hr (Note 3), at which time the colorless solution has become brown-orange. At the end of this time the acetic acid is evaporated using a rotary evaporator (15 mm). Reduced-pressure distillation (74–84°C at 0.060 mm) yields 29.1–

30.5 g (56–58%) of 2.6-diacetoxybicyclo[3.3.0]octane, as a pale-yellow liquid (lit.[3] bp 84–88°C at 0.2 mm) (Note 4).

B. *Bicyclo[3.3.0]octane-2,6-diol.* (Compound **3**; (Note 5).) An ice-cooled aqueous 10% solution of sodium hydroxide (100 mL) is placed in a 250-mL, round-bottomed flask equipped with a magnetic stirring bar and a stopper. To this ice-cooled solution 27.8 g of diacetate 2<.htm/A> (0.123 mol) is added dropwise over a few minutes. The cooled solution is slowly allowed to warm to room temperature (1 hr) and stirring is continued for 15 hr. at which time the colorless solution has become yellow-orange (Note 6).

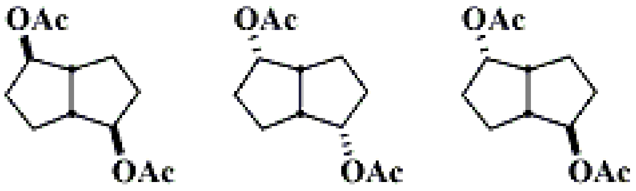
The reaction mixture is then extracted continuously with ether for a 3 days. After extraction the ether is removed by rotary evaporation. The crude viscous liquid that results after evaporation (Note 7) is distilled (Note 8) under reduced pressure (106–111°C at 0.06 mm) (lit.[3] bp 90–96°C at 0.3 mm) to yield 14.5–16.2 g (83–93%) of **3**, pure bicyclo[3.3.0]octane-2,6-diol, as a yellow viscous liquid (Note 9).

C. *Bicyclo[3.3.0]octane-2,6-dione.* (Compound **4**; (Note 10).) Diol 3<.htm/A>, 12.6 g (0.089 mol), is placed in a 250-ml, three-necked, round-bottomed flask equipped with a mechanical stirrer and a reflux condenser. Acetone (125 mL) is added and the mixture is cooled to 0°C. A 2.7 *M* solution of Jones reagent (Note 11) (70 mL) is slowly added dropwise over 10 min at 0°C. The solution is allowed to warm slowly to room temperature (1 hr) and stirring is continued for an additional 15 hr.

After 15 hr the acetone is removed on a rotary evaporator and water (125 mL) is added. The dark-green aqueous mixture is extracted continuously with ether for 3 days. The ether is removed by rotary evaporation, which results in a yellow oil. The oil is then distilled under reduced pressure (74–79°C at 0.06 mm) to yield analytically pure bicyclo[3.3.0]octane-2,6-dione, **4** (6.4–7.1 g, 52–58%) as a white crystalline solid, mp 45–46°C (lit.[4] mp 45.1–46.3°C) (Note 12) and (Note 13).

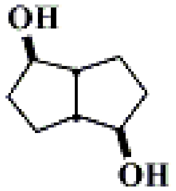
2. Notes

1. *cis,cis*-1,5-Cyclooctadiene (COD) and iodosobenzene diacetate (IBD) are purchased from Aldrich Chemical Company, Inc.
2. The diacetate **(2)** is a mixture of three difficultly separable stereoisomers [the di-*exo*-diacetate **(2a)**, di-*endo*-diacetate **(2b)**, and the *exo*–*endo*-diacetate **(2c)**]. The major isomer is the di-*exo*-diacetate **(2a)** based on ^{13}C-NMR of the known di-*exo*-diol (Note 9).



2a 2b 2c

3. This solution of iodosobenzene, acetic acid, and *cis,cis*-1,5-cyclooctadiene should continue to be stirred and should not be allowed to react for more than 20 hr (at refluxing temperature) to prevent decomposition of the product diacetate.
4. The ^{1}H NMR spectrum ($CDCl_3$) is as follows δ: 1.60 (m, 8 H, CH_2), 1.97 (s, 6 H, OAc), 2.55 (br, s, 2 H, CH), 4.90 (br, s, 2 H, CHOAc). The IR spectrum (neat) shows a carbonyl peak at 1738 cm^{-1}.
5. This procedure for the preparation of the diol is an adapted version of that by Cantrell and Strasser.[3] It is a procedure superior to that of Crandall and Mayer.[5]
6. The checkers monitored the reaction by TLC using ethyl acetate as the developing solvent.
7. This viscous liquid **(3)** is easily transferred to a distilling flask by using acetone.
8. The use of a heat gun aids the distillation because the product is extremely viscous.
9. The ^{1}H NMR spectrum ($CDCl_3$) is as follows δ: 1.70 (m, 8 H, CH_2), 2.61 (m, 2 H, CH), 3.05 (s, 2 H, OH), 3.90 (m, 2 H, CHOH). The IR spectrum shows a broad peak at 3500 cm^{-1}. The major peaks in the ^{13}C NMR spectrum ($CDCl_3$) are δ: 27.41 (C-4), 33.81 (C-3), 50.64 (C-1), 79.54 (C-2). The ^{13}C NMR indicates that the major stereoisomer is **3a**, the *exo,exo*-2,6-dihydroxy-*cis*-bicyclo[3.3.0]octane [lit.[6] ^{13}C NMR δ: 27.8 (C-4), 34.2 (C-3), 51.0 (C-1), 79.9 (C-2)].



3a

10. Other oxidation procedures were used, including pyridinium chlorochromate (Corey's reagent),[7] and dipyridine Cr(VI) oxide (Collins' reagent),[8] but did not produce yields comparable to the Jones method.
11. Jones reagent was prepared by the method in Fieser and Fieser:[9] Dissolve 13.36 g of chromium trioxide in 11.5 mL of concd sulfuric acid, and carefully dilute this cooled solution (0°C) with water to 50 mL.
12. The ^{1}H NMR spectrum ($CDCl_3$) is as follows δ: 2.23 (m, 8 H, CH_2), 3.00 (m, 2 H, CH). The IR spectrum (Nujol) shows a carbonyl peak at 1745 cm^{-1}.
13. GLC analysis shows that the product is contaminated by small amounts of diol. If desired, purer material could be obtained by sublimation at 35–40°C at

0.01 mm onto a cold finger kept at 0°C.[4]

3. Discussion

The preparation of bicyclo[3.3.0]octane-2,6-dione has been accomplished by intermolecular reactions,[4,10] intramolecular reactions,[3,11] and degradation reactions.[5,12]

Bicyclo[3.3.0]octane-2,6-dione has been known since 1934,[10] but extant procedures for large-scale multigram synthesis of this versatile intermediate are cumbersome, except for the recently published results of Hagedorn and Farnum.[4] Whitesell and Matthews[6] have shown that bicyclo[3.3.0]octanes are valuable intermediates for the total synthesis of natural products.

We now report a simple, three-step synthesis of the dione, which uses simple procedures and inexpensive starting materials, to procure multigram amounts of bicyclo[3.3.0]octane-2,6-dione in reasonable yields.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

ethyl acetate (141-78-6)

ether (60-29-7)

sodium hydroxide (1310-73-2)

iodine (7553-56-2)

acetone (67-64-1)

chromium trioxide (1333-82-0)

Iodosobenzene diacetate (3240-34-4)

pyridinium chlorochromate (26299-14-9)

Bicyclo[3.3.0]octane-2,6-dione, 1,4-Pentalenedione, hexahydro- (77483-80-8)

2.6-diacetoxybicyclo[3.3.0]octane, 2,6-Diacetoxybicyclo[3.3.0]octane (17572-85-9)

Bicyclo[3.3.0]octane-2,6-diol (17572-86-0)

iodosobenzene, acetic acid

cis,cis-1,5-cyclooctadiene

exo,exo-2,6-dihydroxy-cis-bicyclo[3.3.0]octane

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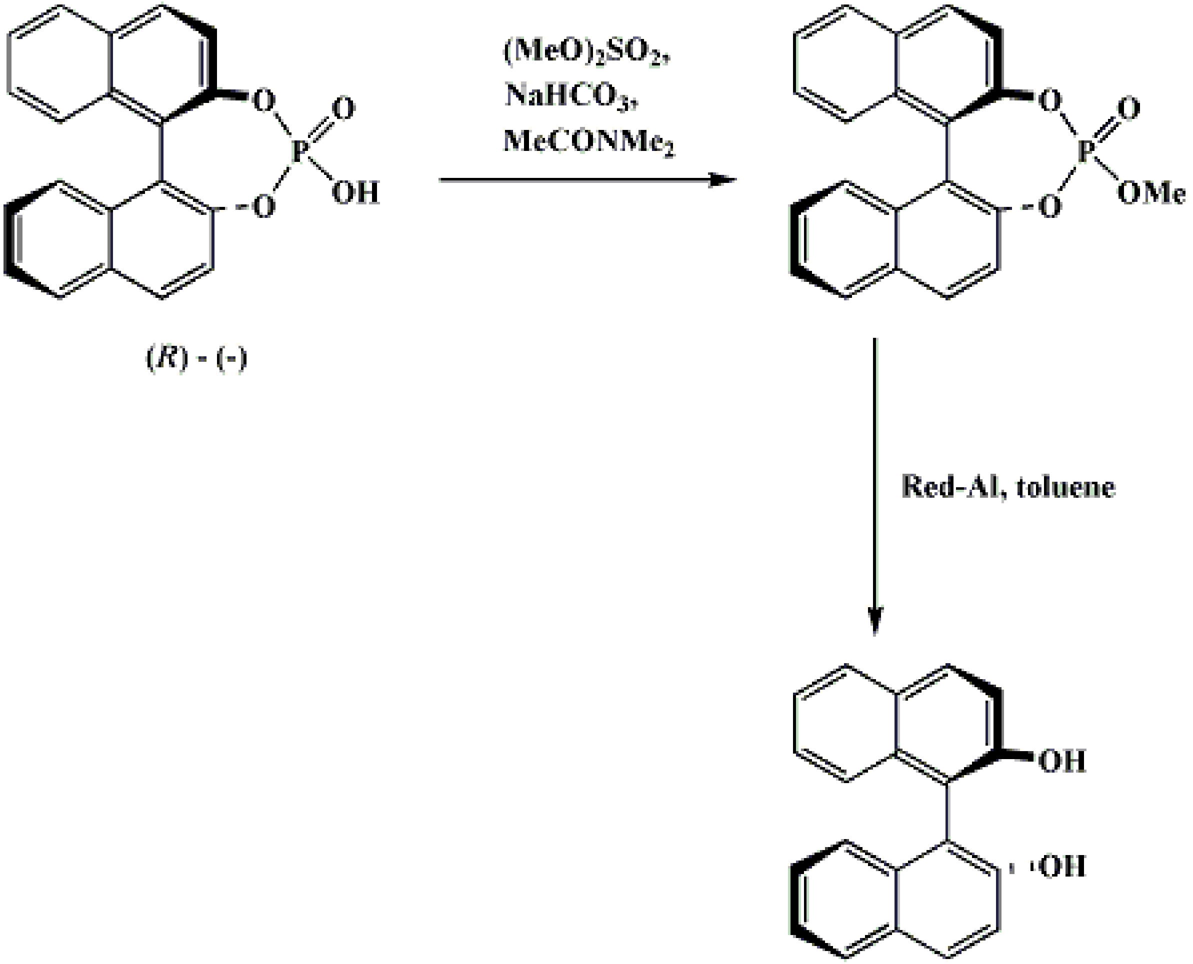
(*R*)-(+)-1,1'-BINAPHTHALENE-2,2'-DIOL

[1,1'-Binaphthalene]-2,2'-diol,(*R*)-]



Submitted by Larry K. Truesdale[1]
Checked by Georg W. Schröder and K. Barry Sharpless.

1. Procedure

A. *(R)-(−)-Methyl 1,1'-binaphthyl-2,2'-diylphosphate.* A 200-mL, three-necked flask equipped with a magnetic stirrer and a gas bubbler is charged with 20.0 g (57.4 mmol) of (*R*)-(−)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate (Note 1), 40 mL of *N,N*-dimethylacetamide, and 10.0 mL (105.7 mmol) of dimethyl sulfate (Note 2). The resulting pale-yellow oil is then treated cautiously in small portions with 10.4 g (123.8 mmol) of sodium bicarbonate. The addition causes gas evolution and foaming. Foaming subsides after ca. 20 min, and the resulting turbid yellow solution is stirred overnight at room temperature (Note 3).

The reaction mixture is poured into a mixture of 300 mL of toluene and 100 mL of ethyl acetate. The resulting milky solution is washed twice with 100-mL portions of

deionized water and twice with 100-mL portions of brine and then dried over anhydrous sodium sulfate. The drying agent is removed by filtration and the filtrate is concentrated on a rotary evaporator under reduced pressure in a 50°C bath. The semisolid residue is slurried in 55 mL of ether and then collected by filtration on a sintered-glass funnel. After the solid is washed 4 times with 10 mL of ether, it is set aside and the filtrate is evaporated to dryness. The residue is slurried in 10 mL of ether. The solid is collected on a glass frit and washed twice with 10 mL of ether. Both solids are combined and dried under reduced pressure to give 16.4 g (45.2 mmol) (79%) of phosphate as an off-white powder, mp 215–217°C; $[\alpha]_D^{25}$ –526.8° (THF, c 1.16) (Note 4).

B. *Crude (R)-(+)-1,1'-binaphthalene-2,2'-diol.*

[Caution! Gases evolved in this step create a stench and are toxic. The use of an efficient fume hood is imperative (Note 5).]

A 2-L, three-necked flask equipped with Y-tube, magnetic stirrer, dropping funnel topped with gas bubbler, thermometer, and drying tube is charged with 14.7 g (40.6 mmol) of crude (*R*)-(–)-methyl 1,1'-binaphthyl-2,2'-diyl phosphate and 350 mL of dry toluene. The mixture is stirred under nitrogen and heated with a steam bath until dissolution occurs (44°C). The solution is then cooled in an ice–water bath to 10°C. The cooling bath is removed and a solution of 27.0 mL (91.8 mmol) of Red-Al (Note 6) in 35 mL of toluene is added from the dropping funnel over a 90-min period. The mixture turns yellow, evolves a gas, and heats up to 26°C. Gas evolution ceases 20 min after the addition is completed. TLC analysis (silica gel plate developed with ethyl acetate) indicates that the reaction is complete.

The entire reaction mixture is poured into 430 mL of 10% hydrochloric acid (mild exothermic reaction). The organic layer is separated and washed with another 430-mL portion of 10% hydrochloric acid. After further washes with 150 mL of brine and 160 mL of deionized water, all aqueous layers are combined and back-extracted with a 550-mL portion of 3 : 2 toluene : methanol and two 300-mL portions of toluene. The combined organic layers are dried over anhydrous sodium sulfate, and filtered. The solvent is removed on a rotary evaporator under reduced pressure in a 45°C bath to give 11.4 g (98%) of crude product as a bright-yellow microcrystalline solid, mp 203–205°C.

C. *Recrystallization of (R)-(+)-1,1'-binaphthalene-2,2'-diol.* A 200-mL flask with a reflux condenser is charged with 11.4 g of crude (*R*)-(+)-1,1'-binaphthalene-2,2'-diol and 1.5 g of Norit A, and refluxed for 5 min. The hot solution is filtered through a pad of 5 g of Celite on a glass frit. The Celite and Norit A from the frit are slurried together with 1.5 g of Norit A in 70 mL of toluene, refluxed for 5 min, and filtered hot through a pad of 5 g of Celite on a glass frit. The Celite is washed with 70 mL of hot toluene. The combined filtrates are warmed to 50°C to dissolve the precipitated crystals and filtered once again while warm through a pad of 5 g of Celite on a glass frit, which is then washed with 40 mL of hot toluene. The filtrate is freed from solvent

on a rotary evaporator and the residue is recrystallized from 75 mL of toluene with stirring. The mixture is stirred overnight at ambient temperature. The resulting suspension is filtered and the filter cake is washed with two 10-mL portions of toluene. The recrystallized product is then dried under reduced pressure (high vacuum) to give 9.62 g of white, microcrystalline material in the first crop. This material melts at 207–209°C, $[\alpha]_D^{25}$ +33.6° (THF, c 1.11) (Note 7) and (Note 8).

Concentration of the filtrate and toluene washings under reduced pressure to ca. 11 mL affords, after cooling, collecting, washing 3 times with 3 mL of toluene, and drying the solid material, a second crop of product that weighs 1.04 g. This crop is an off-white microcrystalline powder, mp 204–206°C and $[\alpha]_D^{25}$ + 33.6° (THF, c 1.12) (Note 9).

The two crops (10.66 g) represent 94% recovery on recrystallization. The yield of recrystallized product is 92% in the reductive cleavage of the phosphate ester and 73% overall.

2. Notes

1. The starting material was prepared by the method described in the companion procedure of Fouquey and Jacques (*Org. Synth., Coll. Vol. VIII*, **1993**, 50) and had $[\alpha]_D^{25}$ –704.7 (MeOH, c 1.0).
2. Dimethyl sulfate was obtained from Aldrich Chemical Company, Inc. It is highly toxic and carcinogenic, and it should be handled only in a well-ventilated hood.
3. The reaction was complete by TLC (silica gel plate) analysis. The consumption of starting material and the formation of product can be monitored using a 5 : 2 (v : v) mixture of ethyl acetate : hexane as the solvent.
4. The enantiomeric excess of this product was determined to be >99.5% using a chiral stationary phase HPLC (preparative Regis Pirkle Type 1-A, 10 × 250 mm id., 7.5 mL/min flow rate, 100-psi pressure, 10% 2-propanol in hexane, detector at 284 nm). The *R*-(–)-enantiomer is eluted first and the peaks are well separated.[2] Another batch of phosphate ($[\alpha]_D^{25}$ –507.7°C, THF, c 1.17) was shown to have 96.5% ee using the same conditions. The same reaction was also checked on a slightly smaller scale, using 18.8 g (54.0 mmol) of (*R*)-(–)-1,1'-binaphthyl-2,2'-diyl phosphate. The yield was 81%. The submitters report a yield of 80% for the reaction run on a 1.6-mol scale.
5. The phosphorus hydride that evolves is highly toxic and creates a stench. Therefore, the checkers recommend that this reaction as well as the workup be performed in an efficient fume hood. The checkers found it advantageous to scrub the phosphorus hydride that formed in a trap (shown below) by bubbling the evolving gases through a solution of 250 mL of bleach (5% sodium hypochlorite in water). During the reaction a constant flow of nitrogen was applied to avoid contamination of the reaction flask with wet gases from the traps.

6. Red-Al is the Aldrich Chemical Company, Inc., brand of sodium bis(2-methoxyethoxy)aluminum hydride in 3.4 *M* toluene solution.
7. The enantiomeric excess of this product was determined to be >99.5% using the same conditions as mentioned in (Note 4). The peaks are well separated and the *R*-(+)-enantiomer is eluted second.[2] Another batch obtained from reduction of phosphate having 96.5% ee had mp 207–209°C and $[\alpha]_D^{25}$ +33.5° (THF, c 1.12). This material had an enantiomeric excess of >99.5%, determined under the same conditions as described in (Note 4). The submitters report $[\alpha]_D^{25}$ +24.7° (THF, c 1.035) for material with mp 207–209°C [lit.[3] mp 206.5–207.5° C, $[\alpha]_D^{25}$ +34.3° (THF, c 1.1)].
8. The product has the following spectral properties: ^{1}H NMR (1 : 1 $CDCl_3$: d_6-DMSO) δ: 7.04 (d, 2H, *J* = 8.8), 7.20–7.35 (m, 4 H), 7.40 (d, 2H, *J* = 8.8), 7.92 (d, 2 H, *J* = 8.8), 9.21 (s, 2 H).
9. The enantiomeric excess of this product was determined to be >99.5% using the same conditions as mentioned in (Note 4). The second crop obtained from the reduction of phosphate having 96.5% ee had mp 200–204°C and $[\alpha]_D^{25}$ +20.7° (THF, c 1.13). This (second crop) material had an enantiomeric excess of 86.5%, determined under the same conditions as described in (Note 4). The submitters report $[\alpha]_D^{25}$ +33.5° (THF, c 0.775) for material with mp 204–206°C.

3. Discussion

Enantiomerically pure 1,1'-binaphthalene-2,2'-diols are used in various types of asymmetric syntheses, for example, as chiral auxiliaries in a method for the asymmetric reduction of ketones.[4].

The previously published method[5,3] for the liberation of the diol from the resolved 1,1'-binaphthyl-2,2'-diyl hydrogen phosphate entailed esterification with diazomethane and reductive cleavage with lithium aluminum hydride. The procedure presented here is felt to be safer in that it circumvents the hazards associated with using diazomethane and lithium aluminum hydride on a large scale.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 50
- Org. Syn. Coll. Vol. 9, 77
- Org. Syn. 76, 1

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

brine

(R)-(+)-1,1'-BINAPHTHALENE-2,2'-DIOL

(R)-(–)-Methyl 1,1'-binaphthyl-2,2'-diylphosphate

(R)-(–)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate

Crude (R)-(+)-1,1'-binaphthalene-2,2'-diol

(R)-(–)-methyl 1,1'-binaphthyl-2,2'-diyl phosphate

Red-Al

(R)-(–)-1,1'-binaphthyl-2,2'-diyl phosphate

1,1'-Binaphthalene]-2,2'-diol,(R)-

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether (60-29-7)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

dimethyl sulfate (77-78-1)

Norit A (7782-42-5)

toluene, M toluene (108-88-3)

2-propanol (67-63-0)

sodium hypochlorite (7681-52-9)

Diazomethane (334-88-3)

lithium aluminum hydride (16853-85-3)

hexane (110-54-3)

phosphate

N,N-dimethylacetamide (127-19-5)

sodium bis(2-methoxyethoxy)aluminum hydride

phosphorus hydride (7723-14-0)

1,1'-binaphthyl-2,2'-diyl hydrogen phosphate (39648-67-4)

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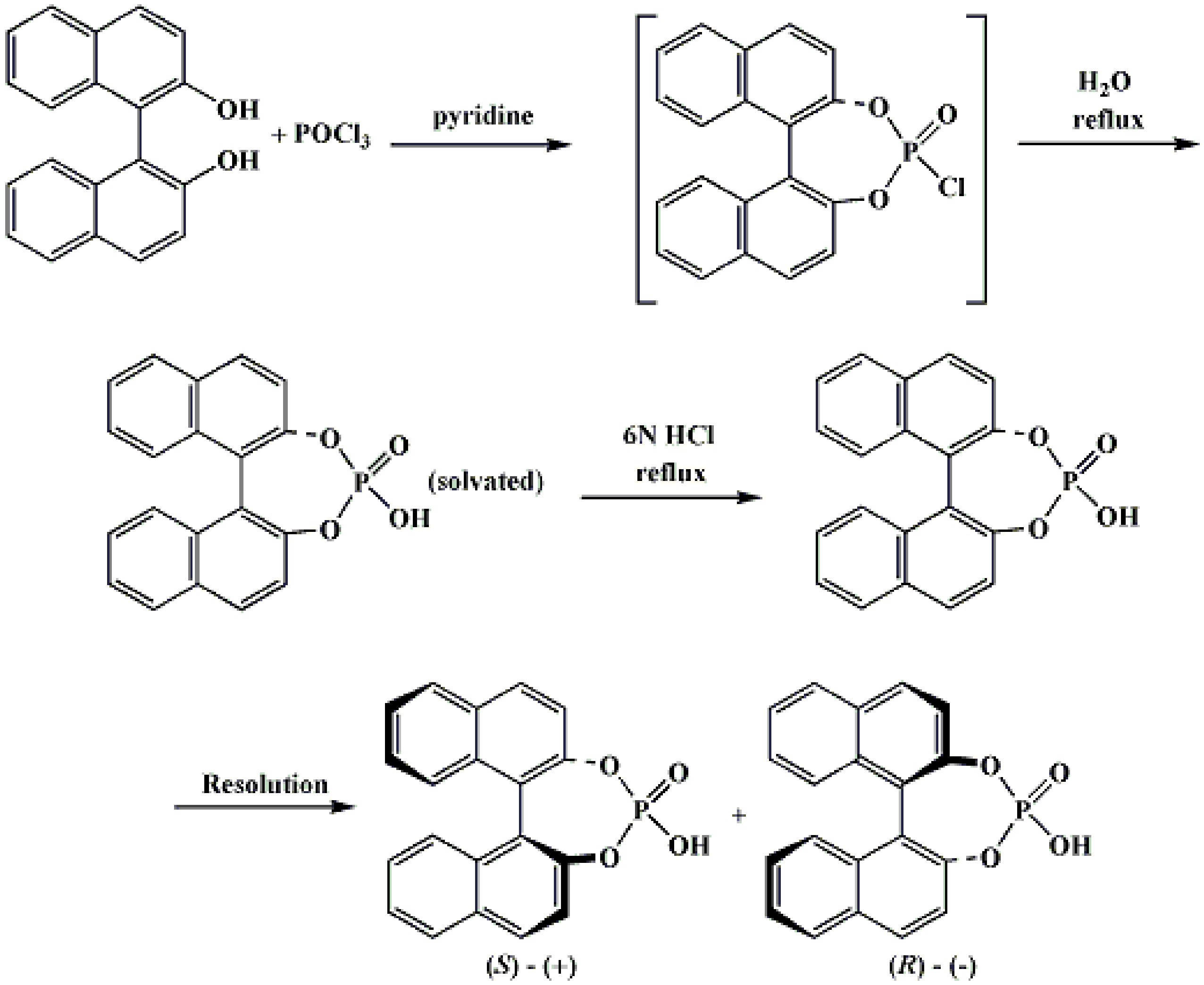
ENANTIOMERIC (*S*)-(+)- AND (*R*)-(–)-1,1'-BINAPHTHYL-2,2'-DIYL HYDROGEN PHOSPHATE

[Dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin, 4-hydroxy-, 4-oxide]



Submitted by J. Jacques and C. Fouquey[1].
Checked by P. R. Carlier and K. Barry Sharpless.

1. Procedure

Caution! Part A of this procedure should be carried out in an efficient hood to avoid exposure to noxious vapors (pyridine, phosphorus oxychloride).

A. *(±)-Binaphthylphosphoric (BNP) acid.* A 1-L, three-necked flask, fitted with a magnetic stirring bar, a pressure-equalizing dropping funnel, a reflux condenser topped by a calcium chloride drying tube, and a thermometer, is charged with 450 mL of pyridine and, while stirring, with 100 g (0.35 mol) of (±)-1,1'-bi-2-naphthol (Note 1).

To this stirred suspension, 73.6 g (0.48 mol) of freshly distilled phosphorus oxychloride is added dropwise, whereupon the temperature rises to about 80°C, most of the binaphthol dissolves, and

pyridine hydrochloride crystals form. Complete dissolution is achieved by heating to 90°C. The stirred solution is allowed to cool to 50–60°C. (Crystallization occurs at about 85°C.) To the stirred suspension, 40 mL of water is added dropwise *(Caution! Exothermic reaction!)*, which raises the temperature to the boiling point (ca. 118°C). The resulting solution, cooled to about 60°C, is transferred to a l-L dropping funnel and the flask is rinsed with pyridine (2 × 20 mL). The solution and rinse are combined and added dropwise with vigorous stirring to 900 mL of 6 *N* hydrochloric acid (Note 2), which gives a precipitate of pyridine-solvated binaphthylphosphoric (BNP) acid (Note 3). This crude product is collected by suction filtration. The wet cake is transferred to a 2-L, large-necked flask and stirred with 300 mL of 6 *N* hydrochloric acid. The suspension is heated to boiling (possible foaming!) and immediately cooled. The solid is thoroughly filtered by suction, washed twice with 20 mL of water (Note 4), and air-dried to afford 114–119 g (94–99%) of (±)-binaphthylphosphoric acid. This compound, which decomposes without melting at about 300°C (Note 5), is pure enough to be resolved. Analytical crystalline samples can be obtained from ethanol.

B. *(S)-(+)- and (R)-(–)-BNP acid*. In a 2-L flask 95.2 g (0.27 mol) of racemic binaphthylphosphoric (BNP) acid and 80.4 g (0.27 mol) of (+)-cinchonine (Note 6) are dissolved in 985 mL of hot methanol (Note 7). To the hot (65°C) solution is added 420 mL of hot water via a dropping funnel over the course of 20 min. During the addition the solution is vigorously stirred and maintained at 65–70°C. At the end of the addition, the flask is transferred to another (cool) stirring plate. Crystallization starts at approximately 60°C, and stirring is maintained until the solution has reached room temperature (Note 8). The crystals are collected, washed with a 2 : 1 methanol–water mixture (3 × 45 mL), and air-dried to afford 76.6 g of salt consisting of 91% p salt [(+)-acid, (+)-base] and 9% n salt [(–)-acid, (+)-base], $[\alpha]_{546}^{25}$ + 424° (methanol, c 0.99) (Note 9) and (Note 10).

(*S*)-(+)-BNP ACID. A 2-L, three-necked flask, equipped with addition funnel, reflux condenser, magnetic stirring bar, and thermometer, is charged with 76.6 g of the above-mentioned salt and 500 mL of ethanol. The salt is dissolved by heating to reflux, and 570 mL of 6 *N* hydrochloric acid is added with vigorous stirring over the course of 30 min. The temperature is maintained at 75–80°C during the addition, and the acid begins to precipitate. Once the addition is complete, the solution is allowed to cool without stirring to room temperature. The solid is collected, washed with water (5 × 90 mL), and air-dried to afford 26.7 g of (*S*)-(+)-BNP acid, $[\alpha]_{546}^{25}$ + 712° (methanol, c 0.98) (Note 11). The yield based on enantiomer present in the racemate is 56%. The product is free from contamination by cinchonine, as shown by ^{1}H NMR (Me_2SO, 250 MHz), and elemental analysis. HPLC analysis of the methyl ester derivative employing a chiral stationary phase (Note 12) shows the acid to be greater than 99.4% ee. Partially resolved samples, recovered by adding water to the filtrates, may be purified by crystallization from ethanol or by digestion in hot methanol (Note 13).

(*R*)-(–)-BNP ACID. The filtrate from the initial crystallization of the cinchonine salt is evaporated nearly to dryness to give 107 g of crude salt, $[\alpha]_{546}^{25}$ –113° (methanol, c 0.95), consisting of approximately 81% n salt and 19% p salt (Note 14) and (Note 10). A 2-L, three-necked flask equipped with addition funnel, reflux condenser, magnetic stirring bar, and thermometer is charged with 107 g of the crude salt and 700 mL of ethanol. The salt is dissolved by heating to reflux, and 790 mL of 6 *N* hydrochloric acid is added with vigorous stirring over the course of 30 min. The temperature is maintained at 75–80°C during the addition, and the acid begins to precipitate. Once the addition is complete, the solution is allowed to cool without stirring to room temperature. The solid is collected, washed with water (5 × 100 mL), and air-dried to afford 23.3

g of (–)-BNP acid, $[\alpha]_{546}^{25}$ –717° (methanol, c 1.00) (Note 11). The yield based on enantiomer present in the racemate is 49%. The product is free from contamination by cinchonine, as shown by ^{1}H NMR (Me_2SO, 250 MHz) and elemental analysis. HPLC analysis of the methyl ester derivative employing a chiral stationary phase (Note 12) shows the acid to be 100.0% ee.

2. Notes

1. Commercial dry pyridine, stored over Linde 4A molecular sieves, was used without further purification. The 1,1'-bi-2-naphthol is commercially available from Aldrich Chemical Company, Inc. The submitters prepared it by oxidizing a hot aqueous suspension of commercial 98% pure 2-naphthol (Merck-Schuchardt) with ferric chloride[2] to obtain crude colored binaphthol (80–90% yield). Unless this material is purified and decolorized by successive crystallization and digestion in hot toluene, the color will be retained in the binaphthylphosphoric acid (60–65% overall yield).
2. The reverse addition of 6 *N* hydrochloric acid to the pyridine solution results in the formation of a thick and syrupy precipitate, which prevents stirring.
3. Regardless of the conditions of precipitation or crystallization, a polymorphic solvate is obtained that consists of 2 BNP acid : 1 pyridine : 1 H_2O, according to elemental analyses. Pyridine peaks are apparent in the ^{1}H NMR spectrum (δ 8.71 and 8.78 in d_6-DMSO). Desolvation occurs at 210–230°C on the Kofler bench or by heating to reflux in 6 *N* hydrochloric acid.
4. The solubility of BNP acid in water is about 2 g/L at 20°C.
5. The BNP acid is polymorphic. A metastable form, identical with the enantiomers and therefore a conglomerate,[3] was sometimes obtained when working above 40°C; the usual stable form is a racemic compound.[3] The IR spectrum (Nujol, cm^{-1}) of the racemate is as follows: 950 (strong), 1025 (strong, broad), 1185 (medium), 1200 (strong), 1220 (strong); of conglomerate: 1050 (strong, broad), 1200 (medium), 1230 (strong), 1255 (medium).
6. Commercial (+)-cinchonine (Aldrich Chemical Company, Inc.), $[\alpha]_{D}^{25}$ +288° (ethanol, c 0.5), was used without further purification.
7. The checkers observed coloration of this solution and stirred it with 10 g of Norit activated carbon, followed by filtration through a Celite pad. The pad was washed with hot methanol (2 × 50 mL). The submitters did not report any coloration.
8. In order to achieve an efficient resolution it is imperative that the addition of water be even and slow; otherwise premature precipitation or oiling of the cinchonine salt may occur. Likewise, stirring must be maintained during the cooling period to achieve high yields and to avoid the formation of oils. The salt is collected as soon as the mixture cools to room temperature, because the more soluble salt deposits as an oil on standing. The submitters suggest that the yield may be improved by carrying out the crystallization in a cold bath until the solution reaches room temperature. It should be noted that the checkers did not observe crystallization until a packet of seed crystals was opened in their laboratory.
9. The submitters obtained 78.5 g of salt composed of 97% p and 3% n salts, $[\alpha]_{546}^{25}$ +471° (methanol, c 0.9).
10. The p and n salts, prepared from the pure (+)- or (–)-acids and cinchonine and crystallized from methanol–ethyl acetate and methanol–acetone–ethyl acetate, respectively, exhibit the following rotations (±3%) in methanol:

	$[\alpha]_{\lambda}^{25}$				
Salt	589 nm	578 nm	546 nm	436 nm	
p	+409°	+428	+492	+890	(c 0.7)
n	−211	−222	−256	−474	(c 0.8)

11. Two crystallizations from ethanol did not change the optical rotations of (+)- and (−)-BNP acid, which are as follows:

	$[\alpha]_{\lambda}^{25}$				
	589 nm	578 nm	546 nm	436 nm	365 nm
Methanol	595° ± 7	624 ± 7	720 ± 8	1328 ± 15	2050 ± 25
Ethanol	574 ± 16	602 ± 17	694 ± 20	1267 ± 25	1828 ± 40

Both enantiomers decompose without melting above 300°C. The solid-state IR spectra of the enantiomers and the racemate (conglomerate) are identical. The checkers obtained a rotation of −705° at 546 nm.

12. The methyl ester derivatives were prepared by treating BNP acid with diazomethane in methanol–ether. A Regis Pirkle Type 1-A preparative column (25 cm × 10 mm i.d.) was used and the conditions were as follows: 10% 2-propanol/hexanes, 8.0 mL/min, detector at 284 nm. The (*R*)-(−) enantiomer is eluted first and the peaks are well separated (α = 1.24).[4]

13. BNP acid, racemate and enantiomers are sparingly soluble in water and organic solvents, except alcohols. Their solubilities at 25 ± 0.5°C in methanol and 95% ethanol, expressed in g/100 mL of solvent and g/100 mL of solution (in brackets) are as follows:

	Racemate	Enantiomer
Ethanol	10.3 ± 0.5 (11.5)	5.7 ± 0.2 (6.7)
Methanol	2.5 ± 0.1 (3.1)	2.1 ± 0.1 (2.6)

As shown by these data, the racemate is approximately twice as soluble as the enantiomers in ethanol, whereas in methanol, the solubilities are nearly the same. This is because the racemate forms a crystalline compound (solvate) with methanol as shown by IR and NMR (Me_2SO) spectra, and by elemental analysis. The racemate dissolves more rapidly in refluxing methanol than do the enantiomers. Accordingly, partially resolved samples having an enantiomeric excess of 80–90% can be conveniently purified by merely digesting them for 10–15 min in refluxing methanol. In general, partially resolved BNP acid can be purified by crystallization from ethanol. In this case, the dissolution rate is particularly slow and the desired solution is obtained by using solvent in excess, then concentrating the solution.

14. The submitters obtained 103 g of material consisting of about 85% n and 15% p salts, $[\alpha]_{546}^{25}$ −150° (methanol, c 0.8).

3. Discussion

Marschalk[5] first prepared BNP acid by the action of phosphorous oxychloride on binaphthol without any solvent, followed by hydrolysis of the isolated acid chloride. The procedure herein described was only briefly mentioned, without any experimental details, in a paper describing the

resolution of BNP acid and its use as a resolving agent.[6]

The BNP acid has also been prepared by Cram and co-workers[7] from binaphthol and phosphorus oxychloride, although under quite different conditions, which involved isolation of the intermediate acid chloride and its hydrolysis by aqueous tetrahydrofuran, and extraction of BNP acid with ethyl acetate. In our hands, this extraction could not be carried out without using larger volumes of solvent and water than those reported. More recently, it has also been prepared by Japanese authors who used a slightly modified method.[8]

The resolution of BNP acid by crystallizing the (+)-acid–cinchonine salt, then the (−)-acid–cinchonidine salt, was first mentioned in a short paper and subsequently described in a patent.[6]

A modification of this procedure was used by Cram et al.,[7] who likewise obtained the (+)-BNP acid via its cinchonine salt, but they isolated the (−)-enantiomer directly from the more soluble salt, without using cinchonidine, in 59% and 46% respective yields. Both enantiomers, precipitated by 6 *N* hydrochloric acid from their cinchonine salt solutions, had to be purified by successive digestions with hot 6 *N* hydrochloric acid and water in order to decompose any remaining cinchonine salt. These purifications are avoided by using the procedure described herein.

BNP acid has also been resolved via some other salts: with strychnine,[9] 2-amino-1,2-diphenylethanol,[10] 2-aminobutanol,[11] 2-amino-1-(4-nitrophenyl)-1,3-propanediol in the presence of acetone, which forms an oxazolidine with the chiral base.[12] A chromatographic resolution of BNP acid was unsuccessfully attempted with natural polymers.[13]

Some physical properties of BNP acid have been studied (triplet-state circular dichroism,[14] luminescence, photoracemization.[15]).

Derivatives have been prepared: methyl esters (enantiomers and racemate)[6,9,10,11,12,13] and D-glucopyransoyl ester.[16]

Enantiomeric (*S*)-(+)- and (*R*)-(−)-BNP acids are useful resolving agents, which give well-crystallized, easily separated salts with a variety of amines. They have been used in the preparation of the enantiomers of biologically and therapeutically active compounds, such as α-difluoromethyl-α-aminovaleric acid,[17] cephalosporin,[18] dibenzothiepin,[19] benzodiazepine derivatives[20] and 3-hydroxyphenyl-*N*-propylpiperidine,[21] 7-phenylquinolizidine,[22] barbituric acid derivative,[23] and thiazepinones,[24] among others. BNP acid also has been used for the direct resolution of underivatized *o*-tyrosine.[25]

(+)-BNP acid, linked to silica gel, has been used in HPLC resolution of helicenes.[26]

BNP acid was tried as an auxiliary for asymmetric synthesis of carboxylic acids.[27] It was used as a NMR chiral complexing agent for amine purity determination.[28]

Chiral recognition of *R*- and *S*-BNP acids by permethylated β-cyclodextrins was described,[29] and chirality of secondary carbinols was determined by CD (circular dichroic) measurements of their

R- or *S*-BNP esters.[30]

Reduction of (*S*)-(+)-and (*R*)-(–)-BNP methyl esters[6] or acids[7] by lithium aluminum hydride, or by Red-Al (this volume, p. 46) yields respectively the known (*S*)-(–)- and (*R*)-(+)-binaphthol, thus establishing the BNP acids' absolute configuration. This is a convenient access to optically active binaphthols, used by Cram and co-workers[31] to prepare macrocyclic polyethers and by Japanese authors[8] in asymmetric synthesis of cyclic binaphthyl esters.

Racemic and optically active BNP acids (as well as binaphthols) are also available commercially from Aldrich Chemical Company, Inc.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 46
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hexanes

(S)-(+)- AND (R)-(−)-1,1'-BINAPHTHYL-2,2'-DIYL HYDROGEN PHOSPHATE

(±)-Binaphthylphosphoric (BNP) acid

pyridine-solvated binaphthylphosphoric (BNP) acid

(S)-(+)- and (R)-(−)-BNP acid

binaphthylphosphoric (BNP) acid

(S)-(+)-BNP acid

(R)-(−)-BNP ACID

(−)-BNP acid

(+)- and (−)-BNP acid

cephalosporin

o-tyrosine

(S)-(−)- and (R)-(+)-binaphthol

methyl ester derivatives

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether (60-29-7)

2-naphthol (135-19-3)

acetate

acetone (67-64-1)

carbon (7782-42-5)

Phosphorus Oxychloride (21295-50-1)

pyridine (110-86-1)

toluene (108-88-3)

2-propanol (67-63-0)

ferric chloride (7705-08-0)

cinchonidine

pyridine hydrochloride (628-13-7)

Diazomethane (334-88-3)

strychnine

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

phosphorous oxychloride

pyridine, phosphorus oxychloride

binaphthol

(+)-cinchonine, cinchonine

binaphthylphosphoric acid, (±)-binaphthylphosphoric acid

2-amino-1,2-diphenylethanol

2-aminobutanol (13054-87-0)

2-amino-1-(4-nitrophenyl)-1,3-propanediol (119-62-0)

α-difluoromethyl-α-aminovaleric acid

dibenzothiepin

1,1'-bi-2-naphthol, (±)-1,1'-bi-2-naphthol (18531-99-2)

3-hydroxyphenyl-N-propylpiperidine

Dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin, 4-hydroxy-, 4-oxide (39648-67-4)

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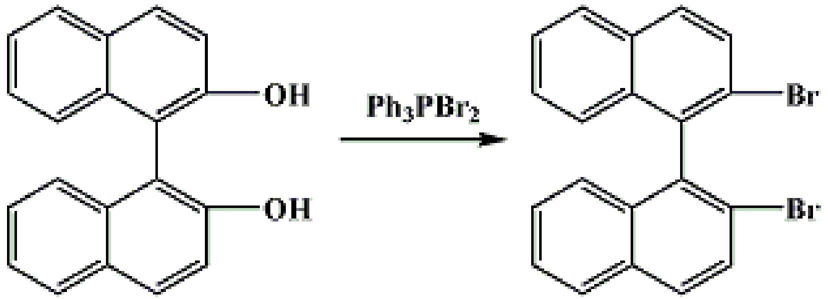
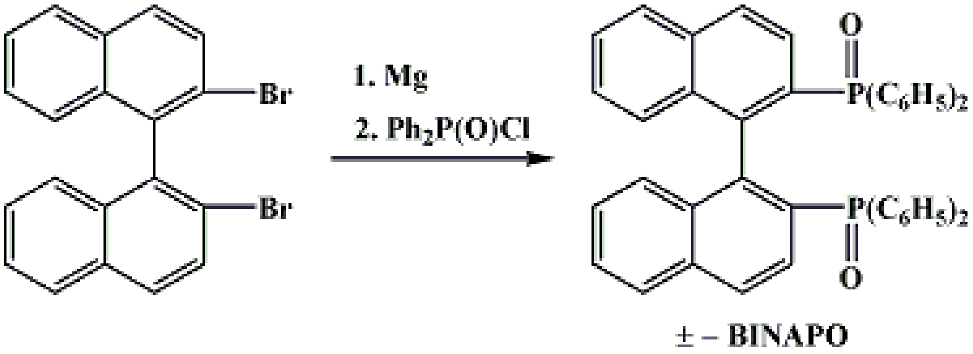
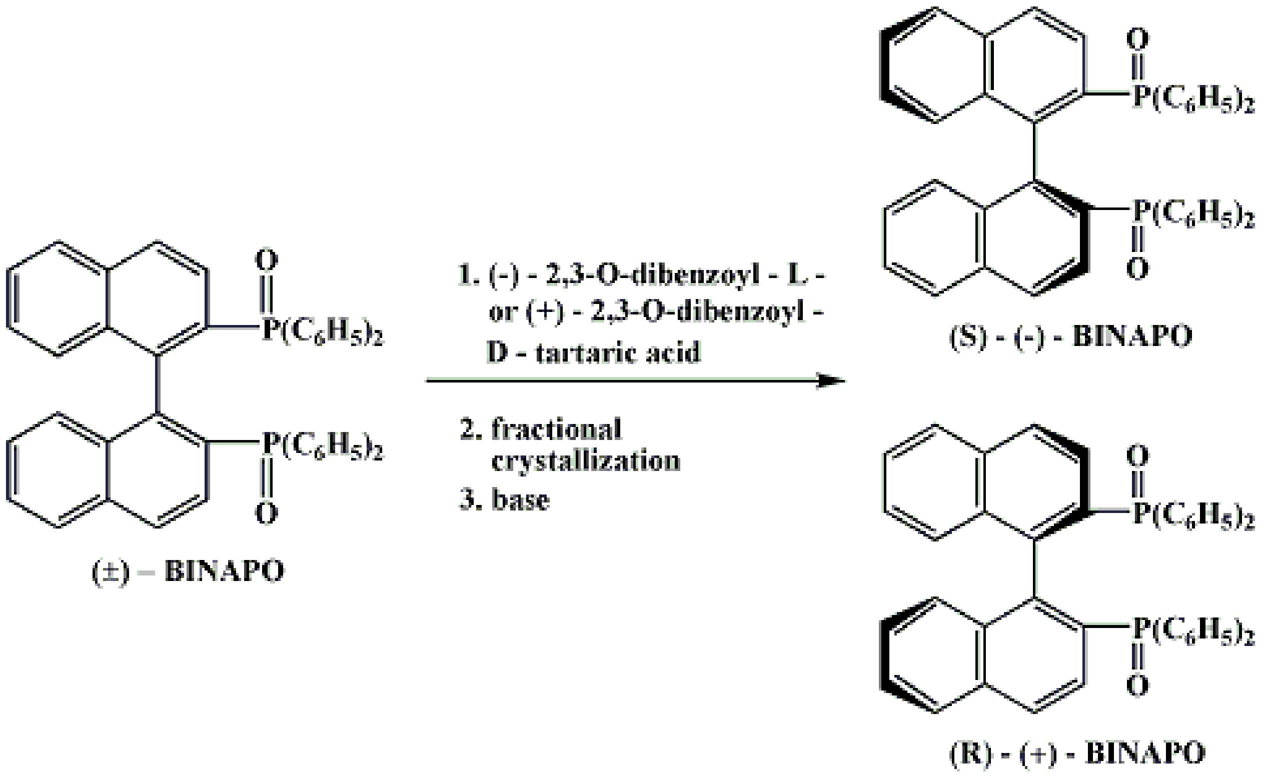
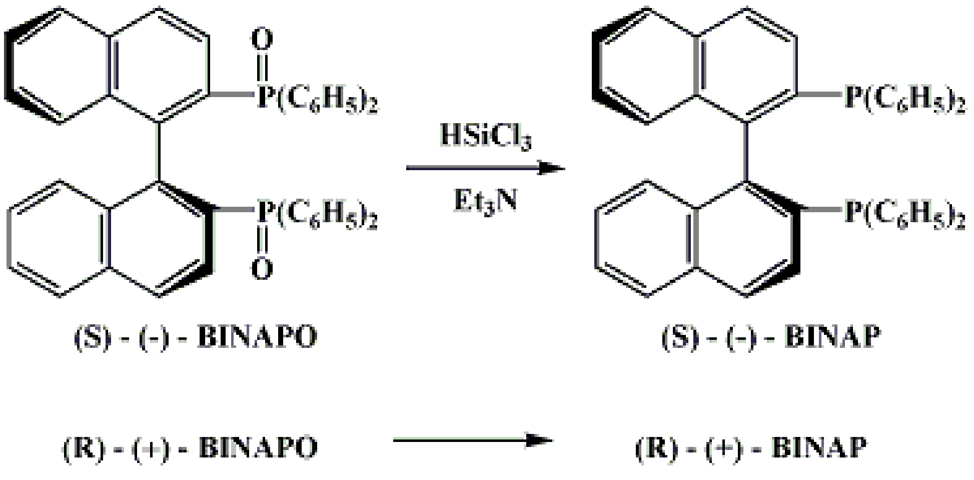
(*R*)-(+)- AND (*S*)-(–)-2,2'-BIS(DIPHENYLPHOSPHINO)-1,1'-BINAPHTHYL (BINAP)

[Phosphine, [1,1'-binaphthalene]-2,2'-diylbis[diphenyl-, (*R*)- or (*S*)-]









Submitted by Hidemasa Takaya[1], Susumu Akutagawa[2], and Ryoji Noyori[3].
Checked by Marco Cereghetti, Alain Rageot, Max Vecchi, and Gabriel Saucy.

1. Procedure

Caution! These operations, which involve toxic reagents, should be conducted in an efficient hood.

A. *2,2'-Dibromo-1,1'-binaphthyl*. A 2-L, three-necked, round-bottomed flask is equipped with an efficient mechanical stirrer, a thermometer, and a dropping funnel. The flask is charged with 240 g (0.915 mol) of triphenylphosphine and 500 mL of dry acetonitrile (Note 1). Stirring is begun and the solid is dissolved by warming the flask with hot water. The solution is then cooled with an ice–water mixture, and to this is added dropwise with stirring 155 g (50 mL, 0.969 mol) of bromine over a 1-hr period. The ice–water bath is removed and 120 g (0.420 mol) of 2,2'-dihydroxy-1,1'-binaphthyl is added to the solution (Note 2). The viscous slurry is stirred at 60°C for 30 min. The flask is now fitted for a simple distillation, and most of the solvent is removed by applying partial vacuum. The last trace of acetonitrile is removed at aspirator vacuum using a bath temperature of 100°C. The temperature of the resulting mass is raised carefully by means of a heating mantle (Note 3) to 240–260°C over a period of 1 hr, at which temperature an exothermic reaction occurs (Note 4), with evolution of hydrogen bromide. After the exothermic reaction subsides, the reaction mixture is further stirred at 260–270°C for 1 hr, and then the temperature is gradually raised and kept at 310–320°C for 30 min to complete the reaction. The reaction mixture, a homogenous melt, is allowed to cool to ca. 200°C with stirring and to this is added 1000 mL of Celite with stirring (Note 5). After the mixture is cooled below 70°C, it is extracted with 500 mL of a boiling 1 : 1 mixture of benzene and hexane. The solid material, separated by filtration through a sintered-glass funnel, is extracted further with three 200-mL portions of a boiling 1 : 1 mixture of benzene and hexane. The combined extracts are evaporated to give an orange-yellow viscous oil, which is dissolved in 200 mL of ethanol. The solution is left in a refrigerator for 2 days (Note 6). 2,2'-Dibromo-1,1'-binaphthyl precipitates and is collected on a sintered-glass funnel to give 90 g of the crude product. Recrystallization from ethanol affords the pure dibromide (78.0 g, 45% yield) as pale-yellow, fine crystals (Note 7).

B. *(±)-2,2'-Bis(diphenylphosphinyl)-1,1'-binaphthyl* [*(±)-BINAPO*]. A 1-L, three-necked,

round-bottomed flask is provided with a mechanical stirrer, an addition funnel, a thermometer, and a reflux condenser, the top of which is connected with a bubbler and an argon line by way of a three-way stopcock. The flask is flushed with argon and charged with 2.84 g (0.117 g-atom) of magnesium turnings, 50 mL of dry, degassed tetrahydrofuran (Note 8), 50 mg of iodine, and 0.5 mL of 1,2-dibromoethane. The mixture is stirred at room temperature until the color of iodine fades and evolution of ethylene ceases. The flask is placed in an oil bath, the reaction mixture is stirred and heated at 50–70°C, and 20.0 g (50.0 mmol) of 2,2'-dibromo-1,1'-binaphthyl in 400 mL of dry, degassed toluene (Note 9) is added over a period of 3.5 hr. The mixture is stirred at 75°C for 2 hr and then cooled to 10°C. To this is added dropwise over a 20-min period a solution of 28.4 g (120 mmol) of diphenylphosphinyl chloride (Note 10) in 35 mL of toluene (Note 9) while the temperature is held at 10–15°C. After the addition is completed, the mixture is further stirred at 60°C for 2 hr, and then cooled to 15°C. To the solution is added dropwise 350 mL of 10% aqueous ammonium chloride and the mixture is stirred for another 10 min at 60°C. The organic layer is separated, washed successively with 150 mL of 10% aqueous ammonium chloride, two 150-mL portions of 1 *N* sodium hydroxide, and finally with two 150-mL portions of water. The toluene layer is dried for a short time over anhydrous sodium sulfate (Note 11), filtered, and concentrated under reduced pressure to give 38.8 g of a pale-yellow solid. This crude product is stirred with 150 mL of boiling toluene for a few minutes, and to this is added 100 mL of heptane. The mixture is allowed to stand at room temperature overnight. The solid product is separated by filtration through a sintered-glass funnel and dried at 70°C (0.05 mm) for 2 hr to give 24.5 g (75%) of (±)-BINAPO as a slightly-pale-yellow solid (Note 12). Concentration of the filtrate and recrystallization of the residue twice from 30-mL portions of toluene gives an additional 3.6 g (11%) of (±)-BINAPO. This product is suitable for use in Part C without further purification.

C. *Optical resolution of (±)-BINAPO.* A 2-L, round-bottomed flask is equipped with a magnetic stirring bar and a reflux condenser. The flask is charged with 10.5 g (16.0 mmol) of racemic BINAPO and 700 mL of chloroform (Note 13). The solid is dissolved by heating at reflux temperature with stirring, followed by rapid addition of a warm solution of 6.0 g (16.0 mmol) of (−)-2,3-*O*-dibenzoyl-L-tartaric acid monohydrate [(−)-DBT monohydrate] (Note 14) in 460 mL of ethyl acetate (Note 13). The mixture is stirred under reflux for 2–3 min and then allowed to stand at room temperature overnight. The crystals formed are collected on a sintered-glass funnel and the filtrate is stored for recovery of (*R*)-(+)-BINAPO (see below). The solid product is dried at room temperature (0.05 mm) for 6 hr to give 7.2 g (89% of theory) of a 1 : 1 complex of (*S*)-BINAPO and (−)-DBT, mp 238–240°C (dec), $[\alpha]_D^{25}$ −170° (ethanol, c 0.503) (Note 15).

This complex (7.1 g, 7.0 mmol) is treated with 150 mL of 0.75 *N* aqueous sodium hydroxide and the mixture is extracted with two 150-mL portions of chloroform. The combined organic layers are washed with 100 mL of 0.75 *N* sodium hydroxide and water and dried over anhydrous sodium sulfate. The drying agent is removed by filtration and the solvent is evaporated. The residue is washed with 20 mL of cold ethyl acetate to furnish 5.3 g of white solid, which is dried at 80°C (0.05 mm) overnight to give 4.6 g (100% based on the complex used) of (*S*)-BINAPO, mp 256–258°C, $[\alpha]_D^{25}$ −392°

(benzene, c 0.530) (Note 16).

The mother liquor and the filtrate from the first resolution (see above) are combined and concentrated to dryness to give 9.0 g of solid material ((*R*)-BINAPO and (−)-DBT) after being dried at 80°C (0.05 mm) for 3 hr, mp 228–230°C (dec). This solid is treated with 150 mL of 0.75 *N* aqueous sodium hydroxide and extracted with two 150-mL portions of chloroform. The combined extract is washed with 70 mL of 0.75 *N* sodium hydroxide, two 100-mL portions of water, and dried over sodium sulfate. The drying agent is removed by filtration and the filtrate is evaporated to give 7.7 g of colorless solid, which is dried at 80°C overnight to afford 5.9 g (9.0 mmol) of crude (*R*)-BINAPO, mp 249–251°C, $[\alpha]_D^{20}$ +304° (benzene, c 0.522). This recovered (*R*)-BINAPO is dissolved in 350 mL of refluxing chloroform, and to this added is added with stirring a solution of 3.4 g (9.0 mmol) of (+)-DBT monohydrate in 280 mL of warm ethyl acetate. The mixture is stirred at reflux temperature for 5 min and then allowed to stand at room temperature overnight. The white precipitates are collected on a sintered-glass funnel, washed with two 20-mL portions of cold ethyl acetate, and dried at 70°C (0.05 mm) for 12 hr to give 7.5 g [92% yield based on the initially used (*R*)-BINAPO] of the (*R*)-BINAPO-(+)-DBT-complex, mp 235–236°C (dec), $[\alpha]_D^{25}$ +172° (ethanol, c 0.527).

This complex (7.3 g, 7.2 mmol) is treated with 200 mL of 0.75 *N* aqueous sodium hydroxide and extracted twice with 150-mL portions of chloroform. The combined chloroform layer is washed with 60 mL of 0.75 *N* aqueous sodium hydroxide and two 100-mL portions of water and is dried over anhydrous sodium sulfate, and filtered. Evaporation of the filtrate affords 5.25 g of colorless solid that is dried at 80°C (0.05 mm) to give 4.65 g (99% yield based on the complex used) of (*R*)-BINAPO, mp 256–258°C, $[\alpha]_D^{25}$ +388° (benzene, c 0.514) (Note 17).

D. *Reduction of (S)-(−)-BINAPO to (S)-(−)-BINAP*. In a 300-mL, three-necked flask, fitted with a magnetic stirring bar, a thermometer, and a reflux condenser which is connected through a three-way stopcock to an argon inlet tube and a bubbler, is placed 4.5 g (6.9 mmol) of (*S*)-BINAPO. The flask is flushed with argon followed by the addition of 100 mL of dry, degassed xylene (Note 9), 4.2 mL of triethylamine (3.1 g, 30 mmol) (Note 9), and 3.0 mL (4.0 g, 29 mmol) of trichlorosilane (Note 13) by means of syringes. The mixture is stirred and heated at 100°C for 1 hr, at 120°C for 1 hr, and finally at refluxing temperature for 6 hr (Note 18). After the solution is cooled to room temperature, 70 mL of 30% aqueous sodium hydroxide solution is carefully added. The mixture is then stirred at 60°C until the organic and aqueous layers become clear, and it is transferred into a 300-mL separatory funnel. The organic layer is separated, and the aqueous layer is extracted with two 50-mL portions of warm toluene. The combined organic layer is washed with 70 mL of 30% sodium hydroxide solution and three 100-mL portions of water, and then dried over anhydrous sodium sulfate. The organic layer is concentrated under reduced pressure to a volume of about 15 mL, and to this added 15 mL of degassed methanol. The precipitates are collected on a sintered-glass funnel, washed with 15 mL of methanol, and dried at 80°C (0.05 mm) for 6 hr to give 4.2 g (97% yield) of (*S*)-BINAP as colorless solid, mp 236–238°C, $[\alpha]_D^{25}$ −223° (benzene, c 0.502) (Note 19) and (Note 20).

2. Notes

1. Reagent-grade acetonitrile was dried over Linde 3A molecular sieves and then heated at reflux for several hours over calcium hydride and distilled under dry argon.
2. Commercial reagent grade 2,2'-dihydroxy-1,1'-binaphthyl from Aldrich Chemical Company, Inc. (1,1'-bi-2-naphthol) was used as obtained. It also can be prepared by the oxidative coupling of β-naphthol with ferric chloride[4] and used after recrystallization from ethanol and then benzene.
3. In order to obtain a homogeneous melt, the checkers had to raise the bath temperature to 300–335°C. They preferred a Woods metal bath.
4. Temperature should be carefully controlled. Too rapid heating can result in an uncontrollably vigorous reaction.
5. This facilitates the smooth extraction of the products.
6. This procedure removes triphenylphosphine oxide.
7. The product melts at 184–185°C (lit.[5] mp 180°C), R_f 0.50 (E. Merck Kieselgel 60 PF_{254}, 1 : 4 benzene–hexane).
8. Reagent-grade tetrahydrofuran was distilled from sodium benzophenone ketyl under argon before use.
9. Commercial guaranteed-grade solvents were distilled over finely powdered calcium hydride under argon before use.
10. Commercial reagent-grade diphenylphosphinyl chloride from Aldrich Chemical Company, Inc. was used as obtained. This compound can be prepared either by oxidation of diphenylphosphinous chloride with dimethyl sulfoxide[6] or by the treatment of diphenylphosphinic acid with phosphorus pentachloride.[7]
11. Prolonged standing of the solution at room temperature may cause precipitation of (±)-BINAPO. In such a case, warm chloroform can be used to dissolve the solid.
12. The checkers obtained first crops ranging from 76 to 84%, mp 295.5–297°C. The submitters report mp 299–300°C. An analytically pure sample was obtained by recrystallization from a mixture of hexane and toluene, mp 304–306°C. One gram of (±)-BINAPO dissolves in 28 mL of boiling toluene.
13. Commercial reagent-grade chemicals were used.
14. Guaranteed-grade (–)-2,3-*O*-dibenzoyl-L-tartaric acid monohydrate and its enantiomer were purchased from Tokyo Kasei Kogyo Co., Ltd., and used without further purification.
15. The checkers had yields ranging from 69 to 90%. They determined the enantiomeric purity of the *S*-BINAPO component, $[\alpha]_D^{20}$ –168° (ethanol, c 0.5), to be 99.6/0.4 using a Pirkle column (Note 16). The submitters report that recrystallization from a 1 : 2 mixture of ethyl acetate and chloroform gave an analytically pure sample, mp 240–241°C (dec), $[\alpha]_D^{24}$ –174° (ethanol, c 0.523).
16. The checkers obtained first crops of 87% and 75.8%, mp 263–263.5°C, $[\alpha]_D^{20}$ –389° (benzene, c 0.5), and mother liquors of 11% and 13.5%, respectively. These materials were analyzed on a Pirkle column (Baker bond II) with hexane/ethanol

mixtures and found to have *S/R* ratios of 99.7/0.3 (first crop) and 93/1.7 (mother liquor). The submitters report obtaining analytically pure (*S*)-BINAPO by recrystallization from a mixture of hexane and toluene, mp 261–262°C, $[\alpha]_D^{24}$ –396° (benzene, c 0.467).

17. The submitters obtained analytically pure (*R*)-BINAPO by recrystallization from a mixture of hexane and toluene, mp 262–263°C, $[\alpha]_D^{24}$ +399° (benzene, c 0.500). See (Note 16) for determination of optical purity. The checkers found an *R/S* ratio of 98.8/1.2 for unrecrystallized material, mp 261–263°C, $[\alpha]_D^{20}$ +379° (benzene, c 0.5).

18. During this period a white solid forms at the bottom of the reflux condenser. Use of a ground-glass joint as large as possible is recommended to avoid clogging.

19. GLC analysis (OV-101, capillary column, 5 m, 200–280°C) indicates that the product has a purity of 97%. Trace amounts of BINAPO and the monooxide of BINAP were detected by TLC analysis (E. Merck Kieselgel 60 PF_{254}, 1 : 19 methanol-$CHCl_3$); R_f 0.42 (BINAPO), 0.67 (monooxide of BINAP), and 0.83 (BINAP). The submitters report that recrystallization from a 1 : 1 mixture of toluene and ethanol affords optically pure (*S*)-BINAP, mp 241–242°C, $[\alpha]_D^{25}$ –229° (benzene, c 0.312). The checkers oxidized a sample of first-crop material, mp 241–242.5°C, $[\alpha]_D^{20}$ –221° (benzene, c 0.5), for Pirkle analysis (see (Note 16)). This gave an *S/R* ratio of 98.2/1.7.

20. The checkers also reduced (*R*)-(+)-BINAPO to (*R*)-(+)-BINAP by this procedure. In the best of two runs, first-crop material (94.8%), mp 241–242°C, $[\alpha]_D^{20}$ +217° (benzene, c 0.5), with an *R/S* ratio of 99.0/0.8 was obtained.

3. Discussion

BINAP is a new type of fully aryl-substituted diphosphine with only an axial element of chirality. Optically pure BINAP was first synthesized by the optical resolution of (±)-BINAP using optically active di-•-chlorobis[(*S*)-*N,N*-dimethyl-α-phenylethyl-amine-2*C,N*]dipalladium.[8 9] The phosphine is also obtained by stereospecific transformation of optically active 2,2'-dibromo-1,1'-binaphthyl.[9,10] The procedure outlined here,[11] however, is the best preparative-scale synthesis of both enantiomers of BINAP in an optically pure state starting from easily accessible racemic 2,2'-dihydroxy-1,1'-binaphthyl. This method is applicable to various BINAP analogues.[11] The absolute configuration of (+)-BINAP was determined to be *R* by X-ray analysis of the complex [Rh((+)-binap)(norbornadiene)]ClO_4.[12] BINAP serves as an excellent ligand for the Rh(I)-catalyzed asymmetric hydrogenations of α-(acylamino)acrylic acids and esters.[8,9] The ligand has also been successfully applied to the Rh(I)-catalyzed asymmetric isomerization of diethylnerylamine or diethylgeranylamine into citronellal (*E*)-*N,N*-diethylenamine (this volume, p. 183).[13 14 15] This reaction is now used for commercial production of (–)-methanol. In addition, BINAP-based Ru(II) complexes[16] catalyze highly enantioselective hydrogenation of alkyl- or aryl-substituted acrylic acids,[17 18] enamides leading to isoquinoline alkaloids,[19 20] allylic and homoallylic alcohols,[21 22] β-

keto esters,[23 24 25 26 27] other functionalized ketones,[28 29] and other compounds.[30 31]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 183
- Org. Syn. Coll. Vol. 9, 169
- Org. Syn. Coll. Vol. 9, 589
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium benzophenone ketyl

(R)-(+)- AND (S)-(−)-2,2'-BIS(DIPHENYLPHOSPHINO)-1,1'-BINAPHTHYL (BINAP)

(±)-2,2'-Bis(diphenylphosphinyl)-1,1'-binaphthyl [(±)-BINAPO]

(±)-BINAPO

BINAPO

(−)-2,3-O-dibenzoyl-L-tartaric acid monohydrate [(−)-DBT monohydrate

(R)-(+)-BINAPO

(S)-BINAPO

(−)-DBT

((R)-BINAPO

(−)-DBT)

(R)-BINAPO

(+)-DBT monohydrate

(R)-BINAPO-(+)-DBT-complex

(S)-(−)-BINAPO

(S)-BINAP

(−)-2,3-O-dibenzoyl-L-tartaric acid monohydrate

S-BINAPO

R)-(+)-BINAPO

(R)-(+)-BINAP

BINAP

(±)-BINAP

di-•-chlorobis[(S)-N,N-dimethyl-α-phenylethyl-amine-2C,N]dipalladium

(+)-BINAP

citronellal (E)-N,N-diethylenamine

Phosphine, [1,1'-binaphthalene]-2,2'-diylbis[diphenyl-, (R)- or (S)-

ethanol (64-17-5)

Benzene (71-43-2)

ethyl acetate (141-78-6)

methanol (67-56-1)

ammonium chloride (12125-02-9)

acetonitrile (75-05-8)

sodium hydroxide (1310-73-2)

phosphorus pentachloride (10026-13-8)

chloroform (67-66-3)

magnesium turnings (7439-95-4)

hydrogen bromide (10035-10-6)

bromine (7726-95-6)

sodium sulfate (7757-82-6)

β-naphthol (135-19-3)

iodine (7553-56-2)

toluene (108-88-3)

ethylene (9002-88-4)

1,2-dibromoethane (106-93-4)

ferric chloride (7705-08-0)

xylene (106-42-3)

Tetrahydrofuran (109-99-9)

heptane (142-82-5)

phosphine (7723-14-0)

hexane (110-54-3)

dimethyl sulfoxide (67-68-5)

triethylamine (121-44-8)

calcium hydride (7789-78-8)

triphenylphosphine (603-35-0)

triphenylphosphine oxide (791-28-6)

homoallylic alcohols (627-27-0)

argon (7440-37-1)

diphenylphosphinous chloride (1079-66-9)

TRICHLOROSILANE (10025-78-2)

diphenylphosphinyl chloride (1499-21-4)

diphenylphosphinic acid (1707-03-5)

diethylnerylamine (40137-00-6)

diethylgeranylamine (40267-53-6)

1,1'-bi-2-naphthol, 2,2'-dihydroxy-1,1'-binaphthyl (18531-99-2)

(S)-(–)-BINAP (76189-56-5)

2,2'-Dibromo-1,1'-binaphthyl (74866-28-7)

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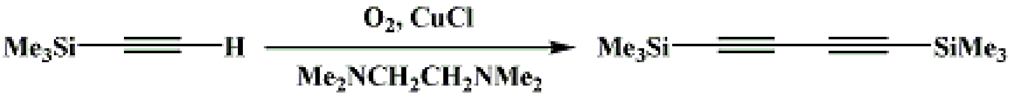
1,4-BIS(TRIMETHYLSILYL)BUTA-1,3-DIYNE

[Silane, 1,3-butadiyne-1,4-diylbis[trimethyl-]]



Submitted by Graham E. Jones, David A. Kendrick, and Andrew B. Holmes[1].
Checked by James Armstrong and Clayton H. Heathcock.

1. Procedure

A. *Copper(I) chloride–tetramethylethylenediamine complex.* A 200-mL, three-necked, round-bottomed flask equipped with magnetic stirring bar, rubber septum, nitrogen inlet tube, and bubbler is charged with acetone (90 mL) and copper(I) chloride (5 g, 51 mmol) (Note 1). After the flask is purged with nitrogen, the mixture is stirred and *N,N,N',N'*-tetramethylethylenediamine (TMEDA) (2.5 mL, 16.6 mmol) (Note 2) is added. Stirring is maintained for 30 min, and the solid material is then allowed to settle, leaving a clear deep-blue-green solution of the CuCl–TMEDA catalyst that is used in the oxidative coupling reaction.

B. *1,4-Bis(trimethylsilyl)buta-1,3-diyne (BTMSBD).* A 1-L, four-necked flask, equipped with a mechanical stirrer (Note 3), a dry-ice cold-finger condenser (Note 4), sintered gas inlet, and a swan-neck adapter that supports a thermometer and a rubber septum is charged with acetone (300 mL) and trimethylsilylacetylene (50 g, 0.51 mmol) (Note 5). The reaction mixture is agitated and a rapid stream of oxygen is passed through the solution (Note 6). The supernatant solution containing the CuCl–TMEDA catalyst is transferred by syringe in 5-mL portions into the reaction vessel. The temperature rises as the catalyst is added and should have reached 35°C after about 75% of the catalyst has been added. When this temperature is reached, external ice cooling is applied to moderate the exothermic reaction (Note 7). The remaining catalyst is added and the temperature is maintained in the range of 25–30°C for 2.5 hr (Note 8). When the reaction is complete, there should be no evidence of trimethylsilylacetylene condensing on the cold trap. Agitation and oxygenation are then stopped.

The acetone is removed by evaporation with a rotary evaporator, and the residue is dissolved in petroleum ether (bp 30–40°C, 150 mL) (Note 9) and shaken in a separatory funnel with 3 *M* aqueous hydrochloric acid (150 mL). The phases are separated and the aqueous phase is washed with petroleum ether (bp 30–40°C, 3 × 150 mL). The combined organic layers are washed with saturated aqueous sodium chloride (50 mL), dried (Na_2SO_4), and evaporated to dryness with a rotary evaporator. The solid residue is dissolved in hot methanol (400 mL) to which has been added 3 *M* aqueous hydrochloric acid (4 mL). The solution may be filtered at this stage if it is necessary to remove colored insoluble impurities. Water is then added dropwise until recrystallized material is permanently present. The solution is allowed to cool, finally in ice, and crystalline bis(trimethylsilyl)butadiyne (BTMSBD) is collected. The material is washed with a small portion of ice-cold methanol–water (50 : 50 v/v; 50 mL), and air-dried to give bis(trimethylsilyl)butadiyne (31–35 g, 68–76%), mp 111–112°C (lit.[2,3] 107–108°C) (Note 10). A further 3–5 g (6–10%) of the product is obtained from the mother liquors (Note 11) and (Note 12).

2. Notes

1. Copper(I) chloride, standard laboratory reagent (SLR) grade, was used as supplied by Fisons

Scientific Apparatus Ltd. Best results are obtained with fresh samples of copper(I) chloride which usually contains ≤2% copper(II) chloride. Further purification[4] did not improve the yield of BTMSBD. The checkers used Mallinckrodt Chemical Company, analytical reagent-grade copper (I) chloride, without further purification.

2. *N,N,N',N'*-Tetramethylethylenediamine (TMEDA) (98%) was used as supplied by B. D. H. The checkers used 99% TMEDA, as supplied by Aldrich Chemical Company, Inc.

3. Mechanical stirring is adequate for a 50-g scale, as described herein, and magnetic stirring is sufficient for a 5-g scale. The submitters ran the procedure on a 200-g scale, and found that use of a Vibro-mixer is essential to obtain satisfactory oxygenation of the reaction mixture. The Vibro-mixer model E-1 was supplied by Chemap AG, Alte Landstr. 415, CH-8708, Mannedorf, Switzerland.

4. The reactant is sufficiently volatile in the fast oxygen stream that substantial loss of material occurs unless a cold-finger condenser with a large contact area, charged with dry ice–2-propanol, is used. The use of a short Vigreux column between the dry-ice condenser and the reaction vessel is strongly recommended to provide additional protection against loss of material as an aerosol.

5. Trimethylsilylacetylene is prepared by silylation of ethynylmagnesium chloride as described elsewhere in this volume (*Org. Synth., Coll. Vol. VIII*, **1993**, 606). It is also commercially available from the Aldrich Chemical Company, Inc.

6. *Caution! Although no hazard has been encountered in this reaction, due care should be taken with acetylenic compounds in an atmosphere of oxygen.* The experiment should be conducted in a well-ventilated hood behind a safety shield and away from any source of ignition. Dilution of exit gases (T-joint) with nitrogen is strongly advised.

7. On two occasions the temperature was observed by the checkers to reach 35°C well before 75% of the catalyst had been added. The temperature should be monitored closely during this addition. If ice cooling is necessary, it is important to lower the temperature only to 25°C; otherwise the reaction will become too sluggish. After the internal temperature is brought to 25°C, further cooling is not needed during addition of the remaining catalyst.

8. A deep-blue-green coloration should be evident throughout the addition of the catalyst. The color is determined by the rate of oxygen flow. Too high a flow rate can lead to overoxidation, producing a black precipitate, whereas too low a flow rate can lead to overreduction of the catalyst, with the green color fading to be replaced by an orange-red precipitate. Both factors reduce the yield of BTMSBD.

9. The checkers used pentane instead of petroleum ether.

10. The checkers observed mp 109–110°C for all crops.

11. Yields of 95% on a 5-g scale and 70–75% on a 200-g scale were reproducibly obtained by the submitters.

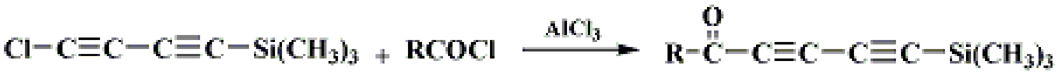
12. Pure bis(trimethylsilyl)butadiyne exhibits the following spectroscopic data: IR (CCl_4) cm^{-1}: 2080 (s), 1250 (s), and 650 (s); UV (C_6H_{12}) nm max(ε): 224 (80), 235 (150), 248 (260), 262 (345), and 278 (250); ^1H NMR ($CDCl_3$, 250 MHz) δ: 0.22 (18 H).

3. Discussion

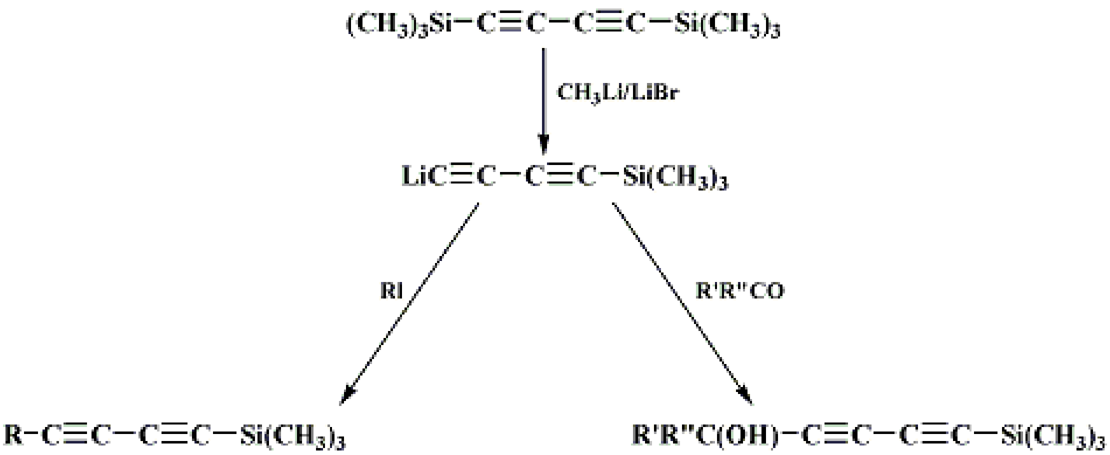
Oxidative coupling of terminal acetylenes in the presence of copper(I) catalysts is the best method of preparing symmetrically substituted butadiyne derivatives,[5] and has been applied to the coupling of trimethylsilylacetylene.[6] Better yields are obtained using the Hay procedure in which the catalyst is the TMEDA complex of copper(I) chloride.[7] The procedure submitted here is an improved version of Walton and Waugh's synthesis of BTMSBD by the Hay coupling of trimethylsilylacetylene.[2] BTMSBD has also been prepared by silylation of butadiynedimagnesium bromide[3] and chloride[8] in moderate yield, and more recently from the dilithium derivative in good yield.[9]

BTMSBD is a very convenient source of butadiyne, an extremely useful, but dangerously explosive

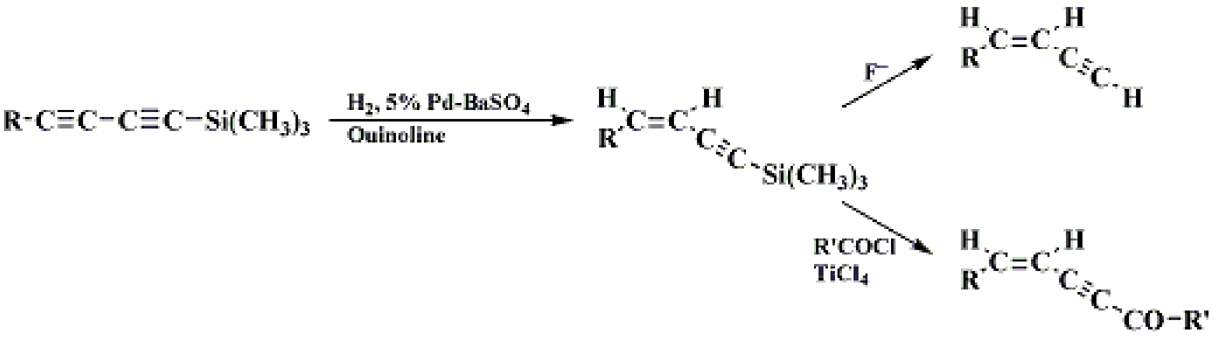
chemical.[10] It is also a synthon for the vinylacetylene anion. A single trimethylsilyl group can selectively be replaced by reaction with electrophiles (Friedel–Crafts reaction) to give trimethylsilylbutadiynyl ketones.[2]

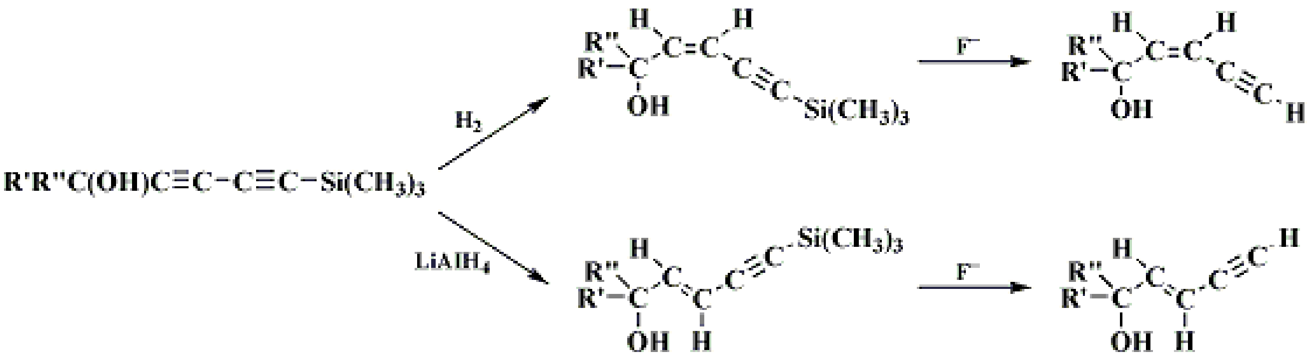


Alternatively, a more nucleophilic anionic reagent can be generated by selective cleavage of a single trimethylsilyl group with methyllithium–lithium bromide complex.[11] This lithiobutadiyne derivative will react with electrophiles such as carbonyl compounds[11,12] or primary alkyl iodides.[13]



Regio- and stereoselective reduction of the nonsilylated triple bond by either partial catalytic hydrogenation[13,14,15,16] or lithium aluminum hydride reduction of the propargylic alcohols,[12,17,18] affords (after desilylation), respectively, terminal (*Z*)- and (*E*)-enynes. Furthermore, the remaining trimethylsilyl group in both silylated diynes and enynes may be replaced by another electrophile in a second Friedel–Crafts reaction.[19]





Such reactions have found a variety of applications in natural product synthesis.[12,14,15,17,18,20]

BTMSBD reacts with a variety of nucleophiles to give novel heterocycles such as selenophen,[21] tellurophen,[22] and pyrazoles.[23] It has also been used in [2 + 4] cycloaddition/cycloreversion sequences to prepare ethynyl-substituted pyridazines[24] and furans.[25]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

(Na_2SO_4)

TMEDA

CuCl

hydrochloric acid (7647-01-0)

methanol (67-56-1)

sodium chloride (7647-14-5)

oxygen (7782-44-7)

nitrogen (7727-37-9)

acetone (67-64-1)

2-propanol (67-63-0)

copper(I) chloride (7758-89-6)

copper(II) chloride (7758-89-6)

Pentane (109-66-0)

lithium aluminum hydride (16853-85-3)

Methyllithium (917-54-4)

copper(I)

butadiyne (460-12-8)

tetramethylethylenediamine (20485-44-3)

lithium bromide (7550-35-8)

1,4-BIS(TRIMETHYLSILYL)BUTA-1,3-DIYNE, bis(trimethylsilyl)butadiyne (4526-07-2)

Silane, 1,3-butadiyne-1,4-diylbis[trimethyl-]

Trimethylsilylacetylene (1066-54-2)

Ethynylmagnesium chloride

butadiynedimagnesium bromide

selenophen (288-05-1)

tellurophen (288-08-4)

N,N,N',N'-tetramethylethylenediamine (110-18-9)

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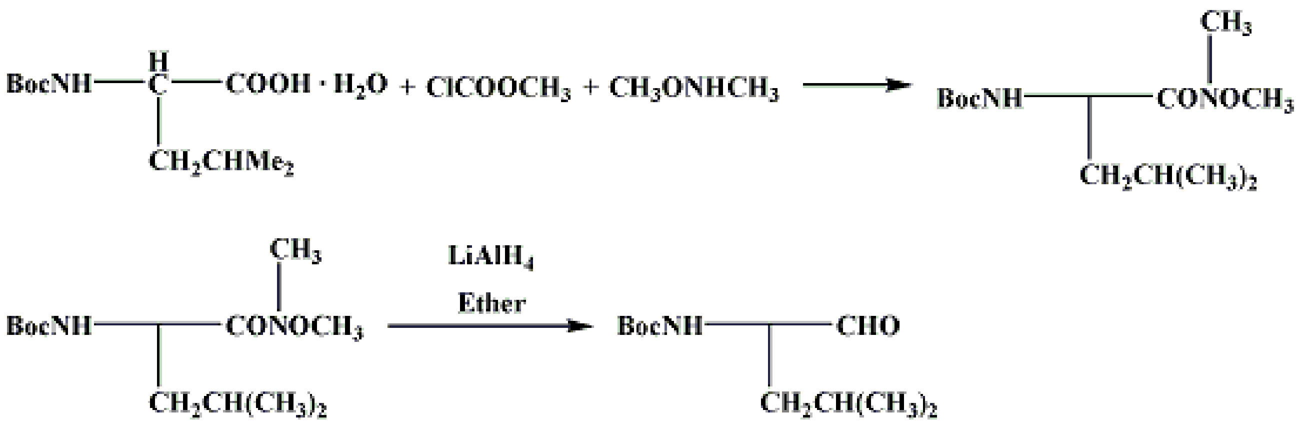
N-tert-BUTOXYCARBONYL-L-LEUCINAL

[Carbamic acid, (1-formyl-3-methylbutyl)-, 1,1-dimethylethyl ester, (*S*)-]



Submitted by O. P. Goel, U. Krolls, M. Stier, and S. Kesten[1]..
Checked by Susumu Ohira and James D. White.

1. Procedure

A. *Boc-*L*-leucine N-methyl-O-methylcarboxamide.* A 1-L, three-necked, round-bottomed flask is equipped with a mechanical stirrer, an electronic digital thermometer, and a graduated addition funnel. The flask is charged with 39.1 g (0.4 mol) of *N,O*-dimethylhydroxylamine hydrochloride (Note 1) and 236 mL of methylene chloride (Note 2). The suspension is stirred and cooled to 2°C with an ice–water bath. *N*-Methylpiperidine. (Note 3), 48.8 mL (0.41 mol), is placed in the addition funnel and added dropwise while the temperature is maintained at 2° ± 2°C. A clear colorless solution results which is kept cold and used in the following reaction.

A 5-L, three-necked, round-bottomed flask is equipped with a mechanical stirrer, a thermometer, and an addition funnel with drying tube. The flask is charged with 100 g (0.4 mol) of Boc-L-leucine hydrate (Note 4), 458 mL of tetrahydrofuran (Note 2), and 1.8 L of methylene chloride. A clear solution results on stirring, which is cooled to −20° ± 2°C by immersing the flask in a dry ice–2-propanol bath. *N*-Methylpiperidine, 48.8 mL (0.41 mol), is placed in the addition funnel and added rapidly to the mixture, while the temperature is allowed to rise to −12° ± 2°C. Methyl chloroformate (Note 5), 31 mL (0.4 mol), is then placed in the addition funnel and added rapidly to the mixture with good stirring, while the temperature is kept at −12° ± 2°C. Two minutes later the solution of *N,O*-dimethylhydroxylamine, prepared as described earlier, is added. The cooling bath is removed and the clear solution allowed to warm to room temperature over 4 hr (Note 6). The solution is again cooled to 5°C and extracted with two 500-mL portions of aqueous 0.2 *N* hydrochloric acid and two 500-mL portions of aqueous 0.5 *N* sodium hydroxide (Note 7). The solution is washed with 500 mL of saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated on a rotary evaporator at a bath temperature of 30–35°C. The residue is further evacuated on an oil pump to constant weight. The residual colorless syrup weighs 100–102 g (91–93%), $[\alpha]_D^{23}$ −24 to −25° (1.5% in methanol) (Note 8).

B. *N-tert-Butoxycarbonyl-*L*-leucinal*: *Boc-*L*-leucinal*. A 5-L, four-necked, round-bottomed flask is equipped with an efficient mechanical stirrer, a thermometer, a pressure-equalizing addition funnel, and an air-cooled condenser fitted with an argon blanket adapter. The flask is charged under an argon blanket with 17.7 g (95% pure, 0.44 mol) of lithium aluminum hydride (Note 9), and 1.5 L of

anhydrous ethyl ether (Note 10). The gray suspension is stirred at room temperature for 1 hr or until most of the solid is finely dispersed. The flask is immersed in a dry ice–2-propanol bath and the suspension cooled to −45°C. A solution of the Boc-L-leucine *N*-methyl-*O*-methycarboxamide, obtained in Part A, in 300 mL of anhydrous ethyl ether is placed in the addition funnel and added to the lithium aluminum hydride suspension in a steady stream (Note 11) while the reaction temperature is maintained −35° ± 3°C. The cooling bath is removed and the mixture is stirred and allowed to warm to +5°C. The mixture is once again cooled to −35°C and a solution of 96.4 g (0.71 mol) of potassium bisulfate (Note 12) in 265 mL of deionized water is placed in the addition funnel. This is added cautiously at first and then rapidly, while the temperature is allowed to rise to −2° ± 3°C. The cooling bath is removed and the mixture stirred for 1 hr. The reaction mixture is filtered through a 2-in. pad of Celite (Note 13). The filter cake is washed with two 500-mL portions of ethyl ether. The combined ether layers are washed in sequence with three 350-mL portions of cold (5°C) 1 *N* hydrochloric acid, two 350-mL portions of saturated aqueous sodium bicarbonate solution, and 350 mL of saturated sodium chloride solution. The organic solution is dried over magnesium sulfate and evaporated on a rotary evaporator (bath at 30°C). The residual, slightly cloudy syrup weighs 69–70 g (87–88%), $[\alpha]^{23}$ −49 to −51° (1.65% in methanol) (Note 14). The product is stored in a freezer (−17°C) prior to use. It solidifies readily at 5°C (Note 15).

2. Notes

1. *N*,*O*-Dimethylhydroxylamine hydrochloride was obtained from the Aldrich Chemical Company, Inc., and used as received.
2. Methylene chloride and tetrahydrofuran were obtained from the Fisher Scientific Company.
3. *N*-Methylpiperidine was obtained from the Aldrich Chemical Company, Inc., and used as received.
4. Bachem Inc. was the source of Boc-L-leucine hydrate. It was not necessary to prepare anhydrous Boc-L-leucine. The yield and quality of the product were unaffected by the presence of water during the reaction.
5. Methyl chloroformate was obtained from the Aldrich Chemical Company, Inc.
6. The reaction mixture may be stirred overnight for convenience.
7. The organic solution should be kept at 5–15°C during extractions.
8. The crude product is 96–99% pure by HPLC and is satisfactory for use in the next reaction. HPLC was carried out on a Varian 5500 instrument using a 250-cm × 4.6-mm-i.d. Alltech C-18 column with 60 : 40 methanol : 0.5 *M* $NH_4H_2PO_4$ (pH 3) as the mobile phase, UV detector at 210 nm. Thin-layer chromatography on silica gel plates (EM) and development with hexane : EtOAc (3 : 1) indicates that the major product spot is at R_f = 0.32. Starting Boc-L-leucine, if present, appears at R_f = 0.16; detector: ninhydrin and gradual warming on a hot plate. The physical properties are as follows: IR (liquid film) cm^{-1}: 2960(s), 1714(s), 1665(s); ^1H NMR (200 MHz, $CDCl_3$) δ: 0.92 [2d appear as t, 6 H, *J* = 6.8, $CH(CH_3)_2$], 1.40, [s, 9 H, $C(CH_3)_3$], 1.38–1.44 (m, 2 H, C_3-H), 1.59–1.76 (m, 1 H, C_4-H), 3.17, and 3.14 (s and a rotamer singlet, 3 H, N-CH_3), 3.76 and 3.67 (s, and a rotamer singlet, 3 H, O-CH_3), 4.7 (m, 1 H, C_2-H), 5.06 (m, 1 H, N-H).
9. Lithium aluminum hydride was obtained from Alfa Products, Morton/Thiokol Inc.
10. Ethyl ether was obtained from the Fisher Scientific Co.
11. The lithium aluminum hydride suspension should be cooled to −45°C prior to addition of the amide. Higher initial temperatures (−30°C and above) lead to an impurity as shown by TLC.
12. Potassium bisulfate was obtained from the Matheson, Coleman and Bell Co. A saturated aqueous solution is obtained after stirring overnight. Aqueous potassium bisulfate will react vigorously if tetrahydrofuran is the reaction medium in place of ethyl ether.
13. A gel-like precipitate is formed from the inorganic by-products. A thick Celite pad helps to

prevent clogging of the filter funnel.

14. Consistently higher optical rotations than reported were obtained.[2] NMR and capillary gas-chromatographic analyses indicated chemical purity of 98–99%. Varian 6000, RSL-310, 15-m, fused silica column, 0.25 mm i.d., film thickness 0.25 •m, at 60°C for 4 min and then 60–220°C at 10°C/min, H_2 as carrier gas at 10 psi. TLC under the conditions described in Note 8 shows the major spot at R_f = 0.53. The spectral properties are as follows: IR (liquid film) cm^{-1}: 2961(s), 1736(s), 1698(b); ^1H NMR (200 MHz, $CDCl_3$) δ: 0.96 (d, 6 H, *J* = 6.4, CH $(CH_3)_2$), 1.45 (s, 9 H, $C(CH_3)_3$), 1.48–1.81 (m, 3 H, C_3-H, C_4-H): 4.24 (m, 1 H, C_2-H); 4.92 (broad singlet, 1 H, N-H); 9.59 (s, 1 H, C_1-H).

15. Boc-L-leucinal racemizes if stored at room temperature. Although it solidified in the cold it became liquid at room temperature. It is very soluble in pentane at room temperature, but crystallizes from pentane at −30°C. It is reported[2] to melt at 63–66°C.

3. Discussion

Boc-L-leucinal is a useful chiral synthon in the preparation of the natural amino acid statine[3] [*S*-(*R**, *R**)]-4-amino-3-hydroxy-6-methylheptanoic acid (3*S*,4*S*). The procedure reported here is based on the method of Fehrentz and Castro[2] for the preparation of optically active Boc amino aldehydes from α-amino acids. It is satisfactory on a kilogram scale. Boc-L-leucinal has also been prepared by the reduction of Boc-L-leucine methyl ester with diisobutylaluminum hydride[4] or oxidation of Boc-L-leucinol.[5] The reaction conditions described here differ from those in the literature.[2] The *N*-methoxy-*N*-methylamide is prepared simply and in high yield by the mixed anhydride method[6] rather than with the very expensive reagent benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate. In addition, the amide can be added to a cold lithium aluminum hydride suspension rather than inversely as recommended.[2] This is an important consideration for scale-up. Reduction of this amide with bis(2-methoxy-ethoxy)aluminum hydride solution (Red-Al) gave a substantially impure aldehyde.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Boc-L-leucine N-methyl-O-methycarboxamide

N-methoxy-N-methylamide

hydrochloric acid (7647-01-0)

methanol (67-56-1)

ether, ethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

potassium bisulfate (7646-93-7)

Pentane (109-66-0)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

methyl chloroformate (79-22-1)

lithium aluminum hydride (16853-85-3)

hexane (110-54-3)

diisobutylaluminum hydride (1191-15-7)

N-Methylpiperidine (626-67-5)

ninhydrin (938-24-9)

benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (56602-33-6)

bis(2-methoxy-ethoxy)aluminum hydride

N,O-dimethylhydroxylamine hydrochloride (6638-79-5)

Carbamic acid, (1-formyl-3-methylbutyl)-, 1,1-dimethylethyl ester, (S)-, N-tert-BUTOXYCARBONYL-L-LEUCINAL, Boc-L-leucinal (58521-45-2)

N,O-dimethylhydroxylamine (1117-97-1)

Boc-L-leucine N-methyl-O-methylcarboxamide

Boc-L-leucine hydrate

Boc-L-leucine

Boc-L-leucine methyl ester

Boc-L-leucinol

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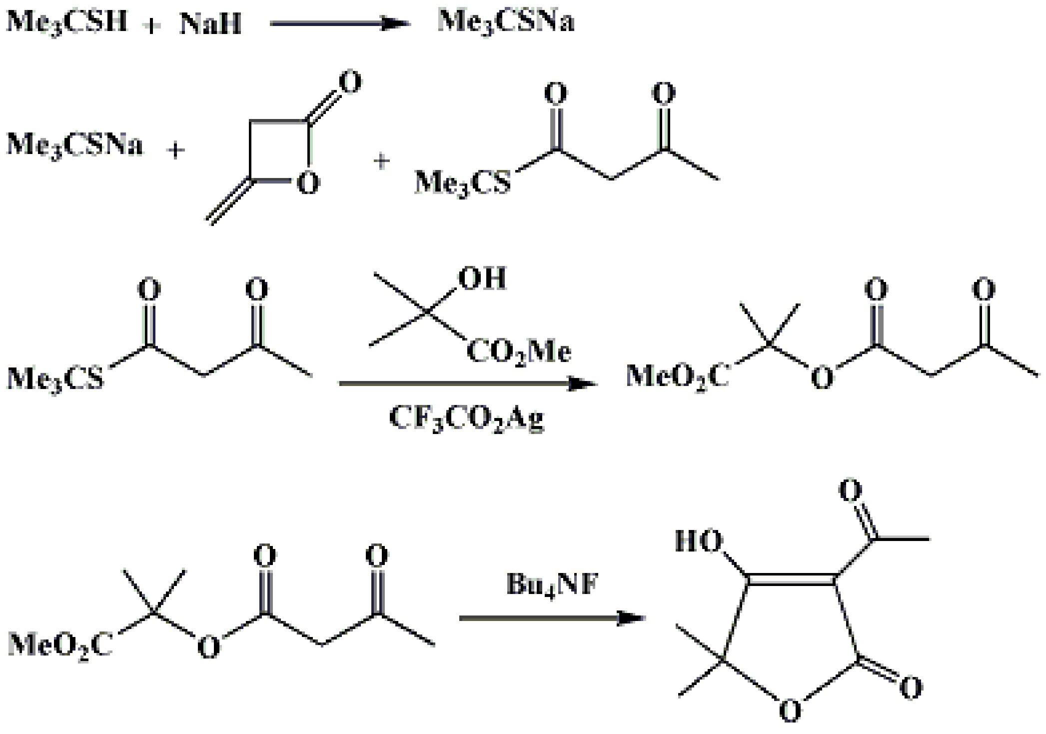
tert-BUTYL ACETOTHIOACETATE AND ITS USE IN SYNTHESIS: 3-ACETYL-4-HYDROXY-5,5-DIMETHYLFURAN-2(4*H*)-ONE

[Acetoacetic acid, 1-thio-, *S*-*tert*-butyl ester]



Submitted by Christina M. J. Fox and Steven V. Ley[1].
Checked by Anura P. Dantanarayana and James D. White.

1. Procedure

Caution! 2-Methylpropane-2-thiol should be handled in an efficient fume hood because of its odor.

A. *S-tert-Butyl 3-oxobutanthioate.* A dry, 2-L, three-necked, round-bottomed flask (Note 1) fitted with a 100-mL pressure-equalizing dropping funnel, a thermometer, a magnetic stirring bar, and an argon inlet is charged with 9.8 g (0.24 mol) of sodium hydride as a 60% dispersion in oil (Note 2). The system is flushed with, and kept under, dry argon. The sodium hydride is washed with two 40-mL portions of sodium-dried pentane and the system is purged with dry argon to remove traces of pentane. To the flask is then added 900 mL of dry tetrahydrofuran (Note 3).

The flask is cooled in an ice–salt bath to –5°C and a solution of 20 g (25 mL, 0.22 mol) of 2-methylpropane-2-thiol (Note 2) in 20 mL of dry tetrahydrofuran is added at

such a rate as to maintain a steady evolution of hydrogen. The slightly exothermic reaction causes the temperature to rise to 0°C and the colorless solution is stirred at this temperature for 15 min to ensure complete formation of the thiolate. The reaction mixture is then recooled to −5°C and 20.3 g (18.8 mL, 0.24 mol) of diketene (Note 2) is added over 15 min to give a yellow-green solution. The cooling bath is removed and the solution allowed to warm to room temperature.

The reaction is quenched and excess sodium hydride is destroyed by careful addition of 300 mL of saturated ammonium chloride solution. The two-phase mixture is transferred to a 2-L separatory funnel charged with 400 mL of ether. The layers are separated and the organic phase is washed with 300-mL portions of water, saturated sodium bicarbonate solution, and Brine. The aqueous washes are reextracted with a 400-mL portion of ether and the combined organic layers are dried over anhydrous sodium sulfate. The solvent is removed with a rotary evaporator to give the crude product as a deep-red oil. Bulb-to-bulb distillation (Note 4) at 95–100°C (0.9 mm) gives 22 g (57%) of *S-tert*-butyl 3-oxobutanthioate as a colorless oil (Note 5).

B. *1-Carbomethoxy-1-methylethyl 3-oxobutanoate.* A 500-mL, round-bottomed flask equipped with a magnetic stirring bar is charged with 10 g (0.085 mol) of methyl 2-hydroxyisobutyrate (Note 2), 17.7 g (0.102 mol) of *S-tert*-butyl 3-oxobutanthioate, and 250 mL of dry tetrahydrofuran. The flask is placed in the dark and 22.5 g (0.102 mol) of freshly prepared silver(I) trifluoroacetate (Note 6) is added in two portions. The resulting dark-brown suspension is stirred for 15 min (Note 7) and then concentrated to approximately 50 mL with a rotary evaporator. The concentrated mixture is diluted with 200 mL of hexane and the resulting orange-brown precipitate is removed by filtration. The filtered solid is washed with two 50-mL portions of hexane and the combined filtrate and washings concentrated with a rotary evaporator to give an orange-brown oil.

The crude product is chromatographed on 350 g of silica (Note 8) using 1 : 1 ether-petroleum ether (40–60) as eluant. The chromatography is monitored by TLC (Note 9) and the appropriate fractions are combined. Removal of the solvent with a rotary evaporator gives a pale-orange oil (Note 10), which was further purified by distillation to give 11.7 g (68%) of the *O*-ester, bp 69–72°C (0.2 mm) (Note 11).

C. *3-Acetyl-4-hydroxy-5,5-dimethylfuran-2(5H)-one.* A 100-mL, round-bottomed flask equipped with a 50-mL pressure-equalizing dropping funnel and a magnetic stirring bar is charged with 5 g (0.025 mol) of the acetoacetate and 37 mL (0.037 mol) of tetrabutylammonium fluoride (1 *M* solution in THF) (Note 2) is added over 5 min. The resulting solution is stirred vigorously for 3 hr (Note 12) and then transferred to a 250-mL separatory funnel containing 50 mL of 6 *M* hydrochloric acid. The acidified mixture is extracted with three 30-mL portions of ether, each extract being washed with 10 mL of Brine. The combined organic extracts are dried over anhydrous sodium sulfate and concentrated with a rotary evaporator to give 4.3 g of the crude tetronic acid as a yellow solid. Recrystallization from 25 mL of hot 5% ether–petroleum ether

gives 1.9 g of the tetronic acid as pale-yellow plates, mp 66–67°C (lit.[2]: mp 64–65°C) (Note 13). Concentration of the mother liquor affords a second crop of 0.4 g, mp 63–65°C, giving a combined yield of 54%.

2. Notes

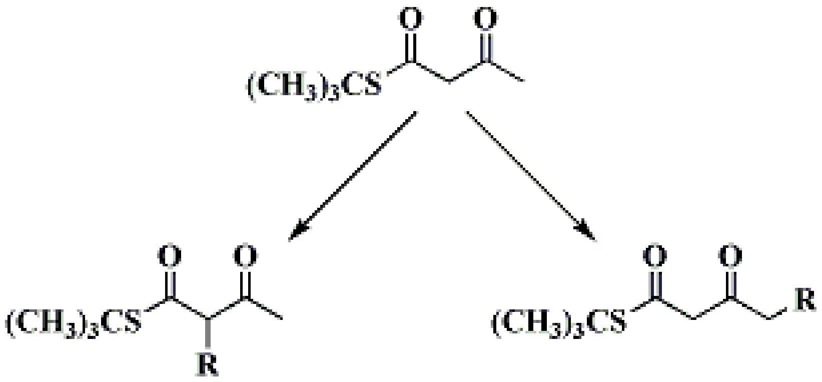
1. The apparatus was oven-dried, assembled while hot, and cooled under a stream of dry argon.
2. Sodium hydride, 2-methylpropane-2-thiol, diketene, methyl 2-hydroxyisobutyrate, and tetrabutylammonium fluoride were purchased from Aldrich Chemical Company, Inc. Diketene was distilled prior to use to remove polymeric species.
3. Tetrahydrofuran was refluxed over and distilled from sodium/benzophenone immediately prior to use.
4. A Kugelrohr apparatus was used for the distillation. The reported temperature is the oven temperature.
5. The checkers found that the yield of this material was substantially higher (83%) when the reaction was conducted at scale. Spectral properties of the product[3][4] are as follows: IR (neat) cm^{-1}: 1712, 1676, 1621; ^{1}H NMR (60 MHz, $CDCl_3$) δ: 1.5 (s, 9 H, $(CH_3)_3C$), 2.3 (s, 3 H, $COCH_3$), 3.6 (s, 2 H, $COCH_2CO$), 5.3 (s, COCH=C(OH)).
6. Silver(I) trifluoroacetate may be obtained commercially, but it is recommended that it be freshly prepared.[5] Trifluoracetic acid (18 mL, 0.24 mol) is added to silver(I) oxide (0.12 mol), freshly precipitated from silver nitrate (20 g, 0.12 mol) and sodium hydroxide (4.7 g, 0.12 mol) in water (30 mL). The solution is filtered and evaporated to dryness under reduced pressure. The crude product is purified by dissolving it in ether (150 mL), filtering through decolorizing charcoal and evaporation to give the product as a white crystalline solid (19.3 g, 74%).
7. The time reported represents the average reaction time. The reaction can be followed by TLC, visualizing with iodine and 10% phosphomolybdic acid in ethanol followed by heating on a hot plate.
8. Merck Kieselgel 60 silica gel (230–400 mesh) was used.
9. Merck precoated silica gel 60 F-254 plates were used, visualizing with iodine.
10. In some cases, the product is contaminated with a yellow solid even after chromatography. This is removed prior to distillation by filtering through a short pad of Celite.
11. The spectral properties of the product[2] are as follows: IR (neat) cm^{-1}: 1745, 1720; ^{1}H NMR δ (90 MHz, $CDCl_3$): 1.57 (s, 6 H, $(CH_3)_2C$), 2.28 (s, 3 H, $COCH_3$), 3.44 (s, 2 H, $COCH_2CO$), 3.72 (s, 3 H, CO_2CH_3).
12. The reaction is monitored by TLC and quenched when starting material has been consumed.
13. Spectral properties of the product[2] are as follows: IR (KBr) cm^{-1}: 1758,

1685, 1610; ^{1}H NMR (60 MHz, $CDCl_3$) δ: 1.50 and 1.51 [2 s, 6 H, $C(CH_3)_2$], 2.5 (s, 3 H, $COCH_3$), 9.25 (br s, 1 H, OH).

3. Discussion

Selective alkylation of β-keto esters via either anions or dianions is an important synthetic transformation.[6] Equally, thioesters may be transesterified in the presence of thiophilic metal cations.[7] These two features can be usefully combined in one substrate, *tert*-butyl acetothioacetate, the subject of this Organic Syntheses procedure.

Alkylation at the 2-position can be achieved by formation of the anion with sodium hydride in 1,2-dimethyoxyethane (DME) at 0°C followed by reaction with an alkyl halide at room temperature. Alternatively, selective alkylation at C-4 involves sequential treatment with sodium hydride (at −10°C) and butyllithium in DME (at −40°C) to form the dianion, followed by kinetic alkylation with an alkyl halide (or carbonyl compound).[8]



The choice of DME as solvent in these reactions is important as other ether solvents are much less successful and lead to unwanted side products.

Transesterification of the resulting alkylated β-keto thioesters to the corresponding oxo esters is readily achieved using alcohols under various metal catalysis.[7]

The alcohols used may also contain fairly sensitive functional groups, such as esters, halides, and silyl ethers. In this work, therefore, *tert*-butyl acetothioacetate is behaving as a synthetic equivalent to diketene. When this methodology is used, it is possible to devise very short syntheses of acyl tetronic acids[8] and novel macrocyclic structures.[9]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

brine

1,2-dimethyoxyethane

sodium/benzophenone

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ether (60-29-7)

ammonium chloride (12125-02-9)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

silver(I) oxide (20667-12-3)

silver nitrate (7761-88-8)

sodium sulfate (7757-82-6)

iodine (7553-56-2)

diketene (674-82-8)

Pentane (109-66-0)

acetoacetate

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

sodium hydride (7646-69-7)

hexane (110-54-3)

Trifluoracetic acid (76-05-1)

silver(I) trifluoroacetate (2966-50-9)

argon (7440-37-1)

phosphomolybdic acid (51429-74-4)

2-methylpropane-2-thiol (75-66-1)

Tetrabutylammonium fluoride (429-41-4)

methyl 2-hydroxyisobutyrate (2110-78-3)

tetronic acid (4971-56-6)

tert-BUTYL ACETOTHIOACETATE

3-ACETYL-4-HYDROXY-5,5-DIMETHYLFURAN-2(4H)-ONE

S-tert-butyl 3-oxobutanthioate (15925-47-0)

1-Carbomethoxy-1-methylethyl 3-oxobutanoate (110451-07-5)

3-Acetyl-4-hydroxy-5,5-dimethylfuran-2(5H)-one (22609-93-4)

Acetoacetic acid, 1-thio-, S-tert-butyl ester

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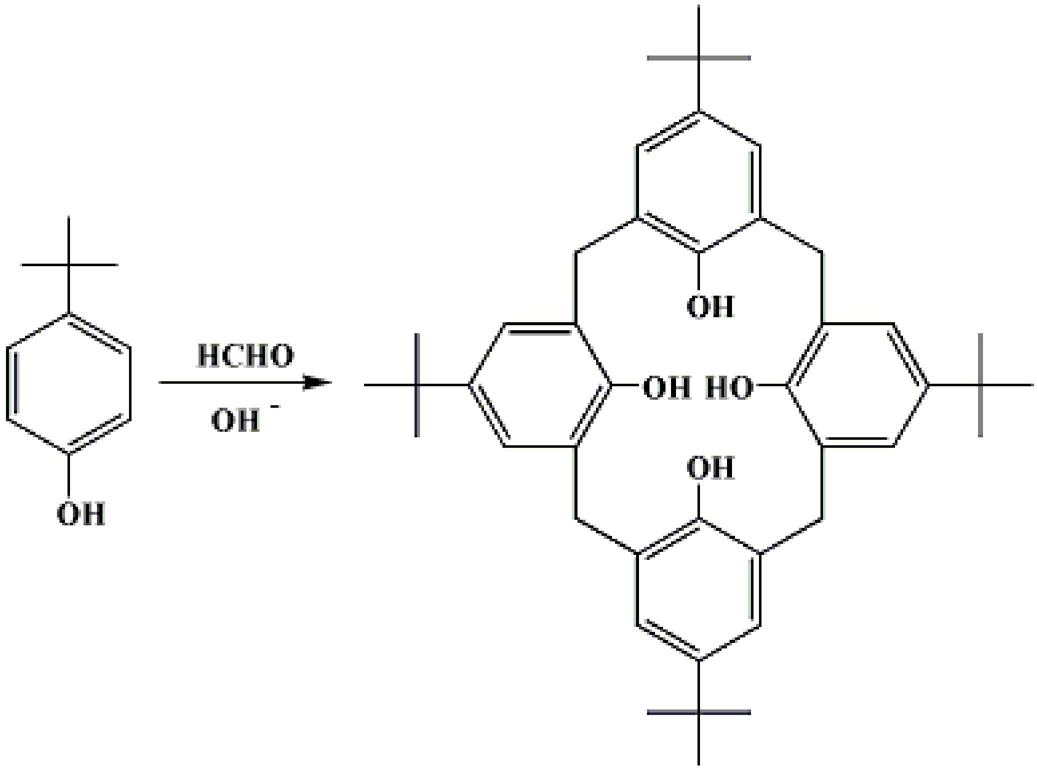
p-tert-BUTYLCALIX[4]ARENE



Submitted by C. D. Gutsche and M. Iqbal[1].
Checked by Anthony T. Watson and Clayton H. Heathcock.

1. Procedure

A. *Preparation of "precursor."* A mixture of 100 g (0.666 mol) of *p-tert*-butylphenol, 62 mL of 37% formaldehyde solution (0.83 mol of HCHO), and 1.2 g (0.03 mol) of sodium hydroxide (corresponding to 0.045 equiv with respect to phenol) (Note 1) in 3 mL of water is placed in a 3-L, three-necked, round-bottomed flask equipped with a mechanical stirrer. The contents of the open flask are allowed to stir for 15 min at room temperature, and then heated for 2 hr at 100–120°C by means of a heating mantle (Note 2). The reaction mixture, which is clear and colorless at the beginning, becomes light yellow after 30 min, a somewhat deeper yellow after 2 hr, and eventually changing to a thick slurry as the water evaporates and finally turning to a deep yellow or brown-yellow very viscous mass. During this period there is considerable frothing, and the reaction mixture fills most of the flask before shrinking back to the original volume. Stirring is discontinued, the reaction vessel is removed from the heating mantle, and the reaction mixture is allowed to cool to room temperature. To dissolve the residue 800–1000 mL of warm diphenyl ether (Note 3) is added to the flask and the contents are stirred, the process generally requiring at least 1 hr.

B. *Pyrolysis of the precursor.* The 3-L, three-necked flask is fitted with a nitrogen

inlet. The contents of the flask are stirred and heated (110–120°C) with a heating mantle while a stream of nitrogen is blown rapidly over the reaction mixture to facilitate the removal of the water as it is evolved. During this period the color of the solution changes from yellow to a gray or a light brown. When the evolution of water subsides and a solid starts to form (prior to attaining the reflux temperature) (Note 4), the flask is fitted with a condenser, and the contents of the flask are stirred and heated to ca. 150–160°C (Note 5) for a few minutes and then at reflux for 3–4 hr under a gentle flow of nitrogen (Note 6). During this phase of the reaction the solid dissolves, and a clear dark-brown to grayish-black solution is formed. The reaction mixture is cooled to room temperature (some solid separates), and the product is precipitated by the addition of 1.5 L of ethyl acetate. The resulting mixture is stirred for 15–30 min and allowed to stand for at least 30 min (Note 7). Filtration yields material that is washed twice with 100-mL portions of ethyl acetate, once with 200 mL of acetic acid, twice with 100-mL portions of water, and twice with 50-mL portions of acetone to yield ca. 66 g (61%) of crude product (Note 8). The white-to-beige-colored crude product is dissolved in ca. 1600–1800 mL of boiling toluene that is concentrated to ca. 700–900 mL. On cooling, 61 g (49%) of product is obtained as glistening white rhombic crystals, mp 342–344°C (Note 9) and (Note 10).

2. Notes

1. *p-tert*-Butylphenol from Aldrich Chemical Company, Inc., mp 98–101°C, and 37% formaldehyde solution from Fisher Chemical Company, Certified ACS grade, were used.
2. Care should be taken not to allow the heating mantle to get so hot as to char the solid material on the walls of the flask. Submitters have used an oil bath.
3. Diphenyl ether recovered from previous preparations of *p-tert*-butylcalix[4]arene can be used, resulting in some cases in slightly higher yields of product.
4. Stirring accelerates the rate of water removal, but is not necessary.
5. In some cases a solid does not form, and the solution remains clear throughout.
6. Cyclic octamer rather than cyclic tetramer has occasionally been reported as the major product, probably the result of insufficiently strenuous pyrolysis conditions (e.g., diphenyl ether not at reflux or too rapid a flow of nitrogen).
7. It may be convenient to transfer the contents of the three-necked flask to an Erlenmeyer flask prior to the addition of ethyl acetate.
8. The crude material is usually pure enough to be used in subsequent reactions without recrystallization.
9. The product of crystallization from toluene is a 1 : 1 complex of *p-tert*-butylcalix[4]arene and toluene, from which the toluene can be removed by drying under high vacuum (< 1 mm) and high temperature (> 140°C) for an extended period of time (48 hr).
10. The melting point is measured in an evacuated melting-point tube.

3. Discussion

A prototype of this procedure was first published in 1941 by Zinke and Ziegler,[2] although the unambiguous identity of the product was not established until some years later.[3] A few other *p*-alkylcalix[4]arenes have been prepared by this procedure, but for practical purposes it appears to be restricted to *p*-alkylphenols in which the *p*-alkyl group is highly branched at the position adjacent to the phenyl ring. Thus, *p-tert*-pentylcalix[4]arene and *p*-(1,1,3,3-tetramethylbutyl)calix[4]arene[4] are among the few other phenols that yield a tractable product in reasonable yield.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

p-tert-Butylcalix[4]arene

HCHO

p-tert-pentylcalix[4]arene

p-(1,1,3,3-tetramethylbutyl)calix[4]arene

acetic acid (64-19-7)

ethyl acetate (141-78-6)

sodium hydroxide (1310-73-2)

formaldehyde (630-08-0)

phenol (108-95-2)

nitrogen (7727-37-9)

acetone (67-64-1)

toluene (108-88-3)

diphenyl ether (101-84-8)

p-tert-butylphenol (98-54-4)

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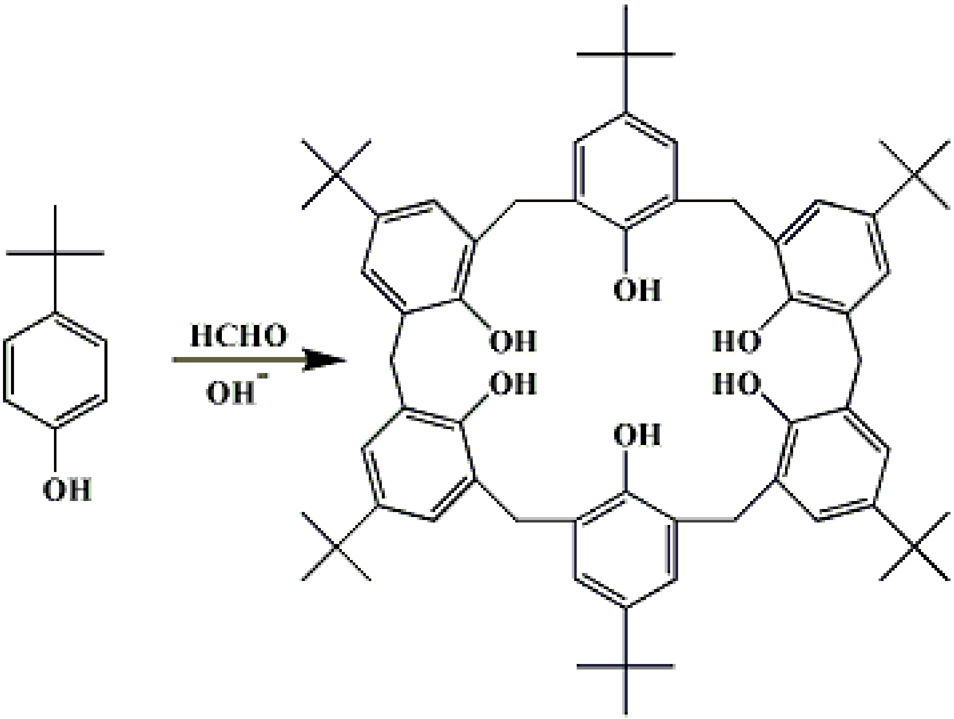
p-tert-BUTYLCALIX[6]ARENE



Submitted by C. D. Gutsche, B. Dhawan, M. Leonis, and D. Stewart[1].
Checked by Roger J. Butlin and James D. White.

1. Procedure

A 2-L, three-necked, round-bottomed flask equipped with a nitrogen inlet, a mechanical stirrer, and a Dean–Stark trap and condenser (Note 1) is placed in a Glas-Col heating mantle. To the flask are added 100 g (0.665 mol) of *p-tert*-butylphenol, 135 mL of 37% formalin solution (1.8 mol of HCHO), and 15 g (0.227 mol) of potassium hydroxide pellets (corresponding to 0.34 equiv of the phenol) (Note 2) and (Note 3). Heating and stirring are begun, and after 15 min nitrogen is blown across the reaction mixture at a brisk rate and out through the condenser on top of the Dean–Stark trap (Note 4); the reaction mixture is heated and stirred for 2 hr (Note 5). As the reaction progresses, the originally clear solution turns bright lemon yellow and, as water is removed, the reaction mixture eventually changes to a thick, golden-yellow mass of taffylike consistency (Note 6). During this period some frothing occurs, and the reaction mixture expands somewhat before shrinking to the original volume. Xylene (1 L) is now added to the flask to dissolve the semisolid mass and give a yellow solution that is brought quickly to reflux by increasing the temperature of the heating mantle (Note 7). After 30 min a precipitate begins to form, and the color of the reaction mixture changes from yellow to orange. Refluxing is continued for 3 hr, the heating mantle is removed, and the mixture is allowed to cool to room temperature. The mixture is filtered, and the precipitate is washed with xylene and dried on a Büchner funnel to yield 105–110 g of crude, almost colorless product. This material is

powdered, placed in an Erlenmeyer flask, dissolved in 2.5 L of chloroform (not completely soluble), and treated with 800 mL of 1 *N* hydrochloric acid. After 10–15 min the stirred solution turns yellow to light orange; stirring is continued for an additional 10 min, and the mixture is transferred to a separatory funnel. The chloroform layer is drawn off, the aqueous layer is extracted with an additional 250 mL of chloroform, and the combined chloroform extracts are washed once with water and dried over magnesium sulfate. Magnesium sulfate is removed by filtration, the chloroform solution is concentrated to ca. 1 L by boiling, and 1 L of hot acetone is added to the boiling chloroform solution. The mixture is allowed to cool and is then filtered to give 90–95 g (83–88%) of product as a white powder: mp 372–374°C (Note 8),(Note 9),(Note 10).

2. Notes

1. It is not essential that a Dean–Stark trap be used. However, it provides a convenient way for monitoring this stage of the reaction and for collecting the aqueous formaldehyde mixture that is evolved.
2. *p-tert*-Butylphenol from Aldrich Chemical Company, Inc., mp 98–101°C, and 37% formaldehyde solution from Fisher Chemical Company, Certified ACS grade, were used. The potassium hydroxide (KOH) pellets are ca. 85% KOH and 15% water. When sodium hydroxide or lithium hydroxide is used instead of potassium hydroxide the yield of product is considerably lower.
3. Sometimes the reaction between the phenol and formaldehyde proceeds with sufficient speed after mixing that considerable warming takes place. The ultimate outcome of the reaction is the same regardless of whether spontaneous warming occurs.
4. Typically, the rate of nitrogen flow is ca. 200 bubbles per minute, as measured by a bubbler attached to the condenser outlet. Although a rapid flow of nitrogen is not essential, it facilitates the removal of water and formaldehyde from the reaction mixture; this should amount to ca. 85 mL in the lower layer of the Dean–Stark trap.
5. Stirring is not absolutely necessary, but it accelerates the rate of removal of water. In unstirred reaction mixtures the frothing contents may fill the entire flask. Stirring reduces the amount of frothing.
6. As the reaction mixture becomes more viscous it is necessary to increase the torque on the stirring motor to keep the taffylike mass in motion while heating is continued. It is important to remove as much of the water as possible in this first stage of the reaction by continuing the stirring as long as possible (see (Note 7)). When stirring becomes very difficult or when the yellow mass no longer sticks to the sides of the flask, xylene is added. Care should be taken not to scorch the reaction mixture at this point. As a further aid to rapid removal of water it is recommended that the upper portion of the reaction flask as well as the Dean–Stark trap be covered with insulating material such as cotton or glass wool.
7. Incomplete removal of water and/or too slow removal of water can result in the formation of a significant amount of cyclic octamer, which is difficult to separate from the cyclic hexamer. It is important, therefore, to bring the reaction

mixture to reflux (10–15 min) and to remove all the water. In addition to the ca. 85 mL of H_2O/HCHO removed in the first phase of the reaction, an additional ca 10 mL (as a cloudy, lower layer in the Dean–Stark trap) is removed in the second phase.
8. HPLC analysis of this product usually shows it to contain less than 1% of other calixarenes. If these are present in greater amounts (usually the cyclic tetramer, cyclic heptamer, or cyclic octamer), their content can be reduced to less than 1% by triturating the product with hot acetone. The purity of the product can be qualitatively checked with TLC using a petroleum ether (30–60° C)/methylene chloride mixture (1 : 1) as eluant. The R_f of the cyclic hexamer is ca. 0.65, and the appearance of any spots with $R_f > 0.1$ indicates the presence of other calixarenes.
9. The melting point is measured in an evacuated and sealed melting-point tube.
10. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) δ: 1.29 (s, 54 H), 3.90 (s, 12 H), 7.16 (s, 12 H), 10.42 (s, 6 H).

3. Discussion

p-tert-Butylcalix[6]arene was first prepared by Gutsche et al.[2] by the reaction of *p-tert*-butylphenol and paraformaldehyde in the presence of rubidium hydroxide (RbOH). A few other *p*-substituted calix[6]arenes have been prepared, including *p*-phenylcalix[6]arene[3] and *p*-isopropylcalix[6]arene.[4]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

HCHO

p-tert-Butylcalix[6]arene

H_2O/HCHO

p-phenylcalix[6]arene

p-isopropylcalix[6]arene

hydrochloric acid (7647-01-0)

sodium hydroxide (1310-73-2)

formaldehyde, formalin (630-08-0)

chloroform (67-66-3)

phenol (108-95-2)

nitrogen (7727-37-9)

acetone (67-64-1)

potassium hydroxide (1310-58-3)

xylene (106-42-3)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

lithium hydroxide (1310-65-2)

rubidium hydroxide (1310-82-3)

p-tert-butylphenol (98-54-4)

paraformaldehyde (30525-89-4)

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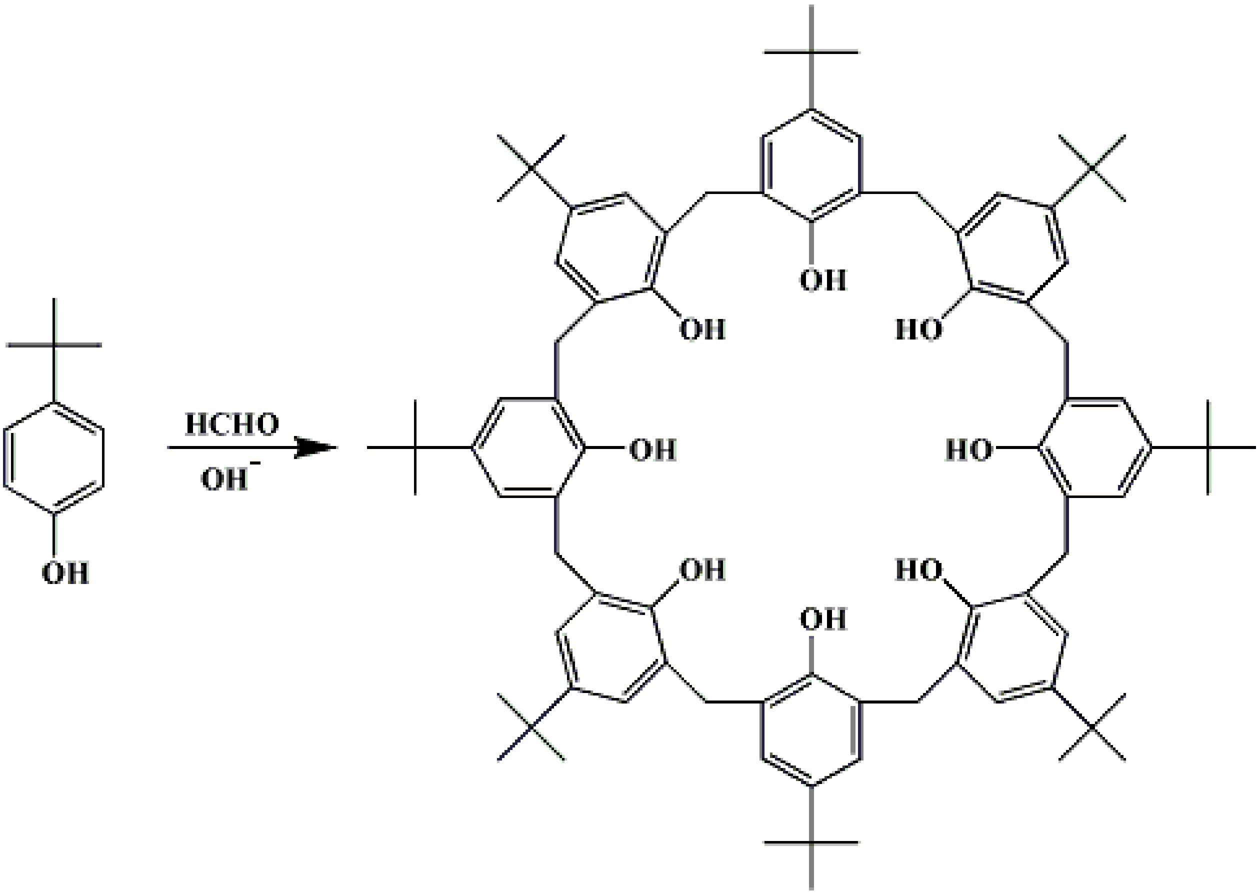
p-tert-BUTYLCALIX[8]ARENE



Submitted by J. H. Munch[1] and C. D. Gutsche[2].
Checked by Daniel T. Daly and James D. White.

1. Procedure

A slurry prepared from 100 g (0.67 mol) of *p-tert*-butylphenol, 35 g (ca. 1.1 mol) of paraformaldehyde (Note 1), and 2.0 mL (0.02 mol) of 10 *N* sodium hydroxide (Note 2) in 600 mL of xylene is placed in a 2-L, round-bottomed, three-necked flask fitted with a Dean–Stark water collector and a mechanical stirrer. The air in the flask is replaced with nitrogen, and the stirred contents of the flask are heated to reflux by means of a heating mantle. After 30 min a homogeneous solution is obtained, and after 1 hr a white precipitate begins to form. The reaction mixture is refluxed for 4 hr, the heating mantle is removed, the mixture is allowed to cool to room temperature, and the precipitate is removed by filtration. The crude product is washed, in succession, with 400-mL portions of toluene, ether, acetone, and water and is then dried under reduced pressure. It is dissolved in ca. 1600 mL of boiling chloroform. The chloroform is concentrated to ca. 1200 mL, the solution is cooled to room temperature, and the precipitate is collected by filtration to yield 67–70 g (62–65%) of a colorless powder, dec 418–420°C (Note 3) and (Note 4).

2. Notes

1. *p-tert*-Butylphenol from Aldrich Chemical Company, Inc., mp 98–101°C, and paraformaldehyde from Fisher Chemical Company, Certified ACS grade, were used.
2. Other bases, including KOH, RbOH, and CsOH, also work with approximately the same results, but LiOH is considerably inferior.
3. The (solvated) product can be obtained in crystalline form but, on standing in air for a few minutes, the colorless, glistening needles change to a white powder as the result of loss of solvent of crystallization. Considerable variation in the melting point of this material is noted. The product generally melts above 400°C, but sometimes the melting point falls to ca. 395°C or even lower. Undoubtedly, this is due to impurities such as metal ions and/or other cyclic oligomers that are incompletely removed in the recrystallization (see (Note 4)).
4. Evaporation of the xylene filtrate and trituration of the residue with methylene chloride yields ca. 11 g of solid that consists mainly of cyclic hexamer and cyclic tetramer. The methylene chloride contains, inter alia, cyclic pentamer, cyclic heptamer, and bishomo compound, and these can be obtained as pure samples in low yield by fractional crystallization procedures. The composition of the reaction mixtures can be qualitatively established by TLC by means of the following R_f values in 9 : 1 petroleum ether/acetone and 1 : 1 petroleum ether/methylene chloride, respectively: (a) cyclic octamer—0.54, 0.85, (b) cyclic heptamer—0.40, 0.78, (c) cyclic hexamer—0.54, 0.76, (d) cyclic pentamer—0.74, 0.68, (e) cyclic tetramer—0.63, 0.66, and (f) bishomooxa compound—0.66, 0.56.

3. Discussion

This method for preparing *p-tert*-butylcalix[8]arene was first described in the patent literature[3] by chemists of the Petrolite Corporation, St. Louis, MO and, therefore, is often referred to as the "Petrolite procedure." It was introduced into journal literature by Gutsche et al.[4] Although the procedure is restricted to phenols substituted in the *p*-position with electronically neutral groups, it is more general in its application than the accompanying procedures for the calix[4]arenes and calix[6]arenes and has been used with *p*-isopropylphenol,[5] *p-tert*-pentylphenol,[5] *p*-(1,1,3,3-tetramethylbutyl)phenol,[6] and *p*-phenylphenol.[7]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

p-tert-Butylcalix[8]arene

ether (60-29-7)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

nitrogen (7727-37-9)

acetone (67-64-1)

toluene (108-88-3)

xylene (106-42-3)

methylene chloride (75-09-2)

p-phenylphenol (92-69-3)

p-tert-butylphenol (98-54-4)

p-isopropylphenol (99-89-8)

p-tert-pentylphenol (80-46-6)

p-(1,1,3,3-tetramethylbutyl)phenol (140-66-9)

paraformaldehyde (30525-89-4)

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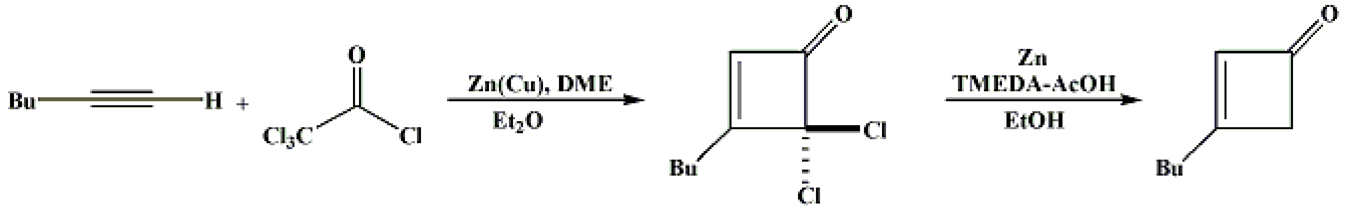
3-BUTYLCYCLOBUTENONE

[2-Cyclobuten-1-one, 3-butyl-]



Submitted by Rick L. Danheiser[1], Selvaraj Savariar, and Don D. Cha[2].
Checked by Reinhard Kratzberg and Ekkehard Winterfeldt.

1. Procedure

A. *3-Butyl-4,4-dichlorocyclobutenone.* A 1-L, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, two glass stoppers, and a 250-mL pressure-equalizing addition funnel fitted with a nitrogen inlet adapter (Note 1). The flask is charged with 39.23 g (0.60 mol) of zinc–copper couple (Note 2), 400 mL of diethyl ether (Note 3), and 23.0 mL (0.20 mol) of 1-hexyne (Note 4). The dropping funnel is charged with a solution of 44.6 mL (0.40 mol) of trichloroacetyl chloride (Note 5) in 125 mL of dimethoxyethane (Note 6), and this solution is then added dropwise to the reaction mixture over 1 hr. After 18 hr, the resulting brown mixture is filtered through a sintered-glass Büchner funnel, and the black solid that is separated is thoroughly washed with 200 mL of hexane. The filtrate is washed successively with 200 mL each of ice-cold 0.5 *N* hydrochloric acid, ice-cooled 5% sodium hydroxide solution, and saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and then concentrated at reduced pressure using a rotary evaporator. The residual brown oil is transferred to a 100-mL, round-bottomed flask and distilled through a 10-cm Vigreux column to afford 29.5–30.0 g (76–78%) of 3-butyl-4,4-dichlorocyclobutenone as a colorless liquid, bp 68.5–70°C (0.3 mm) (Note 7).

B. *3-Butylcyclobutenone.* A 1-L, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, two glass stoppers, and a 125-mL pressure-equalizing dropping funnel fitted with a nitrogen inlet adapter (Note 1). The flask is charged with 52.6 g (0.805 mol) of zinc dust (Note 8), 121 mL of tetramethylethylenediamine (Note 9), and 270 mL of absolute ethanol, and cooled with an ice bath while 46 mL of glacial acetic acid is added dropwise over 5 min. The reaction mixture is maintained at 0°C while a solution of 26.59 g (0.138 mol) of 3-butyl-4,4-dichlorocyclobutenone in 27 mL of absolute ethanol is added over 10 min via the dropping funnel. After 15 min the ice bath is removed, and the reaction mixture is stirred for 2.5 hr and then filtered through a sintered-glass Büchner funnel with the aid of 1.5 L of a 1 : 1 mixture of diethyl ether and pentane. The filtrate is washed successively with 500 mL of 1 *N* hydrochloric acid, 500 mL of water, 800 mL of saturated sodium bicarbonate solution, and 500 mL of saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered, and concentrated at reduced pressure using a rotary evaporator. The residual yellow oil is transferred to a 100-mL, round-bottomed flask fitted with a short-path distillation head (Note 10) and a pear-shaped receiver flask that is cooled below –75°C with a dry ice–acetone bath. Distillation at 0.001 mm (bath temperature 50–70°C) (Note 11) provides 3-butylcyclobutenone (13.4–16.2 g, 78–86% yield) as a clear, colorless liquid, bp 33°C (0.001 mm) (Note 12).

2. Notes

1. The glass components of the apparatus are dried overnight in a 120°C oven and then assembled and maintained under an atmosphere of nitrogen during the course of the reaction.
2. To a stirred mixture of 65.38 g (1.0 mol) of zinc dust (purchased from Mallinckrodt, Inc.) and 100 mL of water in a 1-L Erlenmeyer flask is added at 30-sec intervals two solutions of 7.6 g of copper sulfate, ($CuSO_4 \cdot 5H_2O$) in 50 mL of water. After 1 min the mixture is filtered through a sintered-glass Büchner funnel and the zinc–copper couple is washed with two 50-mL portions of water, two 50-mL portions of acetone, and 50 mL of diethyl ether. The resulting dark-gray powder is dried at 100°C at 1 mm for 4 hr and then stored under nitrogen.
3. Diethyl ether was distilled from sodium benzophenone ketyl immediately before use.
4. 1-Hexyne was obtained from Aldrich Chemical Company, Inc., and distilled from calcium hydride before use.
5. Trichloroacetyl chloride was purchased from Fluka Chemical Corporation and distilled before use.
6. Dimethoxyethane was obtained from Aldrich Chemical Company, Inc., and distilled from sodium benzophenone ketyl immediately before use.
7. The product exhibits the following spectral properties: IR (film) cm^{-1}: 2970, 2940, 2880, 1800, 1585, 1475, 1415, 1390, 1260, 1210, 1045, 850, and 630; UV (isooctane) nm max (ε): 306 (33) and 215 (9530); ^1H NMR (300 MHz,

$CDCl_3$) δ: 0.96 (t, 3 H, *J* = 7), 1.45 (apparent sextet, 2 H, *J* = 7), 1.72 (apparent quintet, 2 H, *J* = 7), 2.69 (dt, 2 H, *J* = 2, 7), and 6.20 (t, 1 H, *J* = 2); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 13.5, 22.3, 25.9, 27.6, 91.9, 135.6, 179.2, 186.1.

8. Zinc dust was purchased from Mallinckrodt, Inc. and used without further purification.

9. Tetramethylethylenediamine (TMEDA) was obtained from Aldrich Chemical Company, Inc., and distilled from calcium hydride before use.

10. The delivery tube of the short-path distillation head is fitted with a 5-cm length of Teflon tubing that extends nearly to the bottom of the receiving flask.

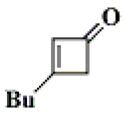
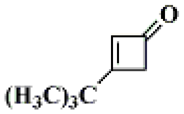
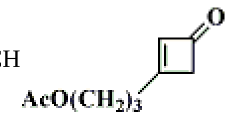
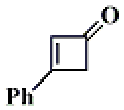
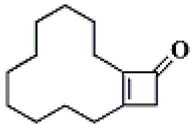
11. Substantial decomposition of the product was observed when the bath temperature was allowed to exceed 80°C or when distillation was attempted using a short Vigreux column.

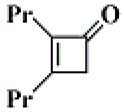
12. 3-Butylcyclobutenone displays the following spectral properties: IR (film) cm^{-1}: 2970, 2940, 2860, 1770, 1590, 1470, 1420, 1385, 1310, 1280, 1220, 1180, 1100, 1030, 990, 925, 850; UV (isooctane) nm max (ε): 306 (36) and 220 (6860); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.93 (t, 3 H, *J* = 7), 1.38 (apparent sextet, 2 H, *J* = 7), 1.58 (apparent quintet, 2 H, *J* = 7), 2.54 (t, 2 H, *J* = 7), 3.12 (s, 2 H), and 5.86 (s, 1 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 13.5, 22.2, 27.9, 31.6, 50.5, 133.8, 181.2, 187.6.

3. Discussion

The procedure described above illustrates a general two-step method for the preparation of 3-substituted and 2,3-disubstituted cyclobutenones.[3,4] The first step in the procedure involves the [2+2] cycloaddition of an acetylene with dichloroketene, which is best carried out using a modification of the method originally reported by Hassner and Dillon.[5] Under these conditions dichloroketene combines smoothly with a variety of alkyne derivatives in contrast to ketene itself which fails to add to unactivated acetylenes. The 4,4-dichlorocyclobutenone cycloadducts produced in the first step are then subjected to reductive dechlorination with zinc dust to afford the desired cyclobutenones. Although it has previously been reported that this reductive dechlorination reaction cannot be accomplished reliably,[5] recent studies[3,4] have shown that under carefully controlled conditions the desired transformation is in fact a feasible and efficient process. As summarized in Table I, this strategy is applicable to the synthesis of a variety of substituted cyclobutenones.

TABLE I
SYNTHESIS OF CYCLOBUTENONES FROM ALKYNES

Case	Alkyne	Cyclobutenone	Isolated Yield (%)
1	Bu-C≡CH		70
2	tBu-C≡CH		54
3	$AcO(CH_2)_3$-C≡CH		56
4	Ph-C≡CH		66–77
5	Cyclododecyne		75

6 Pr-C C-Pr  73

The preparation of 3-butyl-4,4-dichlorocyclobutenone described here represents an optimized procedure for the [2+2] cycloaddition of dichloroketene with acetylenes. Previously there was some disagreement over the efficacy of phosphorus oxychloride ($POCl_3$) as a sequestering agent for the zinc chloride generated in the course of the reaction. Hassner and Dillon[5] have reported that the inclusion of phosphorus oxychloride is crucial to the success of these reactions, and that in its absence tarry products are produced that are difficult to purify. Dreiding and co-workers,[4] however, report that these conditions lead to the production of the desired cycloadducts contaminated with significant amounts of the corresponding 2,4-dichloro isomers. Dreiding consequently suggests that these cycloadditions are best carried out in the absence of phosphorus oxychloride employing short reaction times (< 15 min).

We have found that the method used to prepare the zinc–copper couple is an important variable in determining the efficiency and rate of these reactions. Optimal results are achieved using a couple prepared by brief (2 min) exposure of commercial zinc dust to twice the amount (0.06 equiv) of copper sulfate employed in the previous studies.[4,5] We have also found that the cycloadditions proceed with equal efficiency and more conveniently by employing dimethoxyethane[6] in place of phosphorus oxychloride as a zinc chloride sequestering agent. Under these optimized conditions a variety of terminal acetylenes are smoothly converted to 4,4-dichlorocyclobutenones in high yield. Although cycloadditions involving disubstituted acetylenes lead to the desired 4,4-dichlorocyclobutenones contaminated with varying amounts of isomeric 2,4-dichloro isomers, the formation of these by-products can be suppressed (to < 10%) simply by carrying out the cycloaddition at temperatures between 10 and 15°C.

Under conventional dechlorination conditions (20 equiv of zinc dust, acetic acid, 25 or 50°C) the reduction of 4,4-dichlorocyclobutenones affords complex mixtures of products that include the desired cyclobutenones as well as significant amounts of partially reduced by-products. We have found that the desired transformation can be accomplished cleanly provided that the reduction is carried out at room temperature in alcoholic solvents (preferably ethanol) in the presence of 5 equiv each of acetic acid and a tertiary amine (preferably tetramethylethylenediamine). Zinc dust has proved to be somewhat superior to zinc–copper couple for this reduction. The desired cyclobutenones are obtained in somewhat higher yield using this procedure as compared to the related conditions reported by Dreiding [Zn(Cu), 4 : 1 AcOH–pyridine, 50–60°C] for the same transformation.[4]

The most efficient synthetic route to 3-butylcyclobutenone reported previously[7 8] involves the addition of butylmagnesium bromide[9] or butyllithium[10] to 3-ethoxycyclobutenone followed by acid hydrolysis. 3-Ethoxycyclobutenone is itself available in modest yield via the addition of ketene to ethoxyacetylene. This procedure provides 3-butylcyclobutenone in only 20% overall yield and requires the use of a ketene generator and the rather unstable ethoxyacetylene as starting material.

Cyclobutenones serve as versatile intermediates for the preparation of α,β-butenolides,[11] cyclopentenones,[11] and a variety of substituted cyclobutane derivatives. We have shown that cyclobutenones also function as four-carbon annulation components in routes to eight-membered carbocycles[10] and highly substituted aromatic compounds.[12 13]

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Appendix

Compounds Referenced (Chemical Abstracts Registry Number)

amine

sodium benzophenone ketyl

Bu-C□CH

tBu-C□CH

$AcO(CH_2)_3$-C□CH

Ph-C□CH

Pr-C□C-Pr

phosphorus oxychloride ($POCl_3$)

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

copper sulfate (7758-98-7)

copper (7440-50-8)

acetone (67-64-1)

Phosphorus Oxychloride (21295-50-1)

zinc (7440-66-6)

zinc chloride (7646-85-7)

Pentane (109-66-0)

Butylmagnesium bromide (693-03-8)

magnesium sulfate (7487-88-9)

butyllithium (109-72-8)

hexane (110-54-3)

1-Hexyne (693-02-7)

Ethoxyacetylene (927-80-0)

calcium hydride (7789-78-8)

dimethoxyethane (534-15-6)

cyclobutane (287-23-0)

cyclododecyne (1129-90-4)

trichloroacetyl chloride (76-02-8)

tetramethylethylenediamine (20485-44-3)

3-Butylcyclobutenone, 2-Cyclobuten-1-one, 3-butyl- (38425-48-8)

3-butyl-4,4-dichlorocyclobutenone (72284-70-9)

4,4-dichlorocyclobutenone

Cyclobutenone

3-ethoxycyclobutenone

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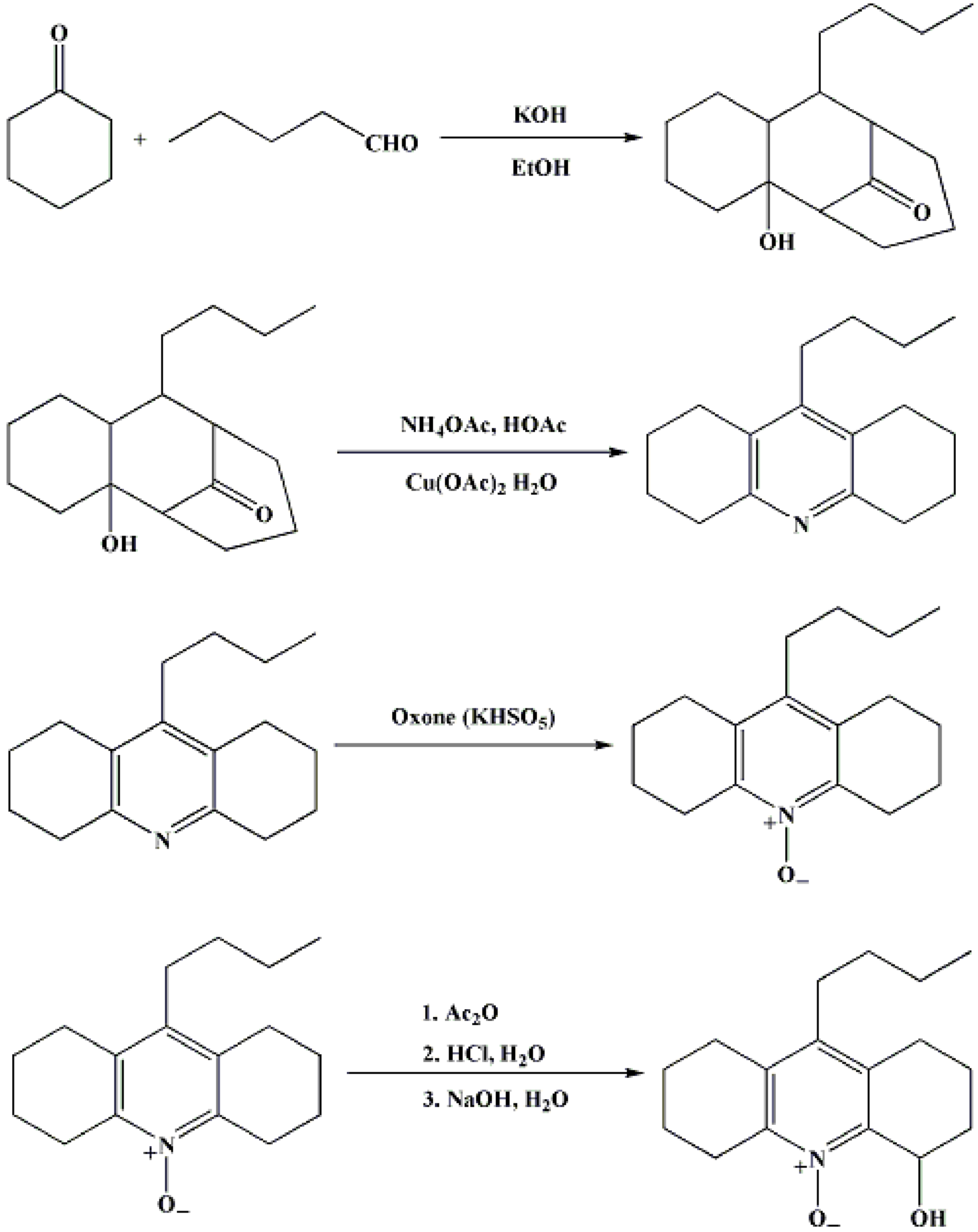
Organic Syntheses, CV 8, 87

9-*n*-BUTYL-1,2,3,4,5,6,7,8-OCTAHYDROACRIDIN-4-OL

[4-Acridinol; 9-butyl-1,2,3,4,5,6,7,8-octahydro]



Submitted by Thomas W. Bell, Young-Moon Cho, Albert Firestone, Karin Healy, Jia Liu, Richard Ludwig, and Scott D. Rothenberger[1].

Checked by Edward R. Holler, Jr. and Bruce E. Smart.

1. Procedure

A. *8-n-Butyl-2-hydroxytricyclo[7.3.1.0*^{2,7}]tridecan-13-one. A 2-L, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, a thermometer, a 500-mL pressure-equalizing dropping funnel, and a reflux condenser fitted with a nitrogen gas inlet tube that is attached to a mineral oil bubbler. The flask is flushed with nitrogen and then charged with 1.0 L (947 g, 9.65 mol) of cyclohexanone (Note 1). The cyclohexanone is stirred and heated to 70–75°C under nitrogen, a solution of 9.0 g (0.14 mol) of potassium hydroxide (Note 2) in 150 mL of absolute ethanol is added in one portion, and then a solution of 150 mL (122 g, 1.4 mol) of pentanal (Note 3) in 140 mL of absolute ethanol is added dropwise over a 8-hr period while maintaining the reaction mixture at 70–75°C. The reaction mixture is stirred and held at 70–75°C for an additional 12 hr, and then allowed to cool to room temperature. The reaction flask is immersed in an ice bath, the inner wall of the flask is scratched with a glass rod to initiate crystallization, and the mixture is kept at 0°C for 4 hr to complete the crystallization. The colorless crude product is collected by vacuum filtration and washed with 200 mL of cold ether. The filtrates are combined and concentrated to approximately 200 mL with a rotary evaporator. The precipitated white solid is collected by filtration and washed with water (2 × 200 mL) and 200 mL of cold ether to give a second crop of crude product. The two crops ae combined and recrystallized by dissolving in hot methanol (3 mL per gram of solid), boiling until cloudiness occurs and cooling slowly to room temperature, then to 0°C. The white crystals are collected by vacuum filtration to give 228–230 g (61–62%) of 8-*n*-butyl-2-hydroxytricyclo[7.3.1.0^{2,7}]tridecan-13-one, mp 140–141°C (Note 4).

B. *9-n-Butyl-1,2,3,4,5,6,7,8-octahydroacridine.* A 2-L, three necked flask equipped with a mechanical stirrer, a glass stopper, and a reflux condenser is charged with 70 g (0.91 mol) of ammonium acetate, 309 g (1.55 mol) of cupric acetate monohydrate (Note 5) and 750 mL of glacial acetic acid. The mixture is stirred and heated at reflux for 15 min under nitrogen. The resulting solution is allowed to cool below reflux and 200 g (0.76 mol) of 8-*n*-butyl-2-hydroxytricyclo-[7.3.1.0^{2,7}]-tridecan-13-one is added in several portions. The blue-green reaction mixture is then refluxed under nitrogen for 3 hr with efficient stirring to control foaming. The mixture is allowed to cool to room temperature and then chilled in an ice bath for 3 hr (Note 6). The precipitated cuprous acetate is collected by vacuum filtration using a medium porosity fritted glass funnel and washed with 200 mL of ether. The combined filtrates are mixed with 500 g of ice in a 4-L beaker and stirred rapidly as 1600 mL of concentrated ammonium hydroxide is added slowly along with additional ice (ca. 300 g) to avoid local heating and boiling of the ether (final pH 10–11). The resulting mixture is separated and the aqueous layer is extracted with ether (400 mL, then 2 × 200 mL). The combined ether layers are washed with 200 mL of 20% aqueous ammonium hydroxide, followed by 200 mL of saturated aqueous sodium chloride, and dried over anhydrous magnesium sulfate. The drying agent is removed by filtration and washed with 200 mL of ether. The combined filtrates are concentrated to minimum volume with a rotary evaporator and the resulting solid is dried to constant weight under vacuum (1 mm) to give 173–177 g (91–96%) of beige solid, mp 36–38°C (Note 7). The product may be used directly in procedure C or further purified by adding a solution of material in dichloromethane to a column of Woelm neutral alumina and eluting with dichloromethane. The solvent is

removed on a rotary evaporator to give 148 g (86%) of white crystalline solid, mp 41–43°C (Note 7).

C. *9-n-Butyl-1,2,4,5,6,7,8-octahydroacridine N-oxide.* A 2-L, round-bottomed flask equipped with a mechanical stirrer or a powerful magnetic stirrer and a reflux condenser fitted with a nitrogen inlet tube is flushed with nitrogen and charged with 38.0 g (0.16 mol) of 9-*n*-butyl-1,2,3,4,5,6,7,8-octahydroacridine, 42.7 g (0.51 mol) of sodium bicarbonate, and 890 mL of methanol. The resulting mixture is stirred as 110 g (0.18 mol) of Oxone® (Note 8) is added, followed by 360 mL of distilled water. The suspension is stirred under nitrogen at 48–50°C for 12–24 hr (Note 9). The mixture is cooled to room temperature and filtered, and the filter cake is washed with methanol (2 × 50 mL). The methanol is removed from the combined filtrates with a rotary evaporator, and the resulting mixture (volume: ca 200 mL) is extracted with dichloromethane (3 × 100 mL). The combined extracts are washed with water (2 × 50 mL) and dried over magnesium sulfate. The drying agent is removed by filtration, the filtrate is concentrated with a rotary evaporator, and the residual solid is dried under vacuum (0.1–0.5 mm) to give 40.0 g (99%) of 9-*n*-butyl-1,2,3,4,5,6,7,8-octahydroacridine-*N*-oxide as a cream colored solid, mp 92–94°C (Note 10),(Note 11),(Note 12).

D. *9-n-Butyl-1,2,3,4,5,6,7,8-octahydroacridin-4-ol.* Crude 9-*n*-butyl-1,2,3,4,5,6,7,8-octahydroacridine-*N*-oxide (38.9 g, 0.15 mol) is placed in a 1-L, three-necked, round-bottomed flask equipped with a magnetic stirrer, a glass stopper, and a reflux condenser fitted with a nitrogen inlet tube and a 500-mL addition funnel. Acetic anhydride (300 mL) is placed in the addition funnel, deaerated by sparging with helium for 30 min, and then added rapidly to the nitrogen-purged reaction flask. The reaction mixture is stirred and heated in a 100–110°C oil bath for 2 hr. The reflux condenser is replaced by a simple distillation head and approximately 280 mL of acetic anhydride is removed by distillation at water-aspirator pressure (25–35 mm). To the brown residue is added 470 mL of 3 *M* aqueous hydrochloric acid, and the resulting mixture is refluxed under nitrogen for 1.5 hr. The mixture is allowed to cool to room temperature, chilled in an ice bath, and made alkaline (pH 12–13) by slowly adding about 550 mL of cold 4 *M* aqueous sodium hydroxide. The resulting cloudy mixture is extracted with chloroform (3 × 150 mL) and the combined extracts are dried over anhydrous sodium sulfate. The drying agent is removed by filtration and the filtrate is concentrated to dryness with a rotary evaporator. The brown residue is recrystallized from 75 mL of ethyl acetate, and the collected product is recrystallized again from 50 mL of ethyl acetate (Note 13) to give 26–28 g (67–72%) of 9-*n*-butyl-1,2,3,4,5,6,7,8-octahydroacridin-4-ol as a light beige solid, mp 105–106°C (Note 14).

2. Notes

1. Cyclohexanone (99.8%) was obtained from Aldrich Chemical Company, Inc. and was used without purification.
2. Certified-grade potassium hydroxide (86.6%) from Fisher Scientific was used.
3. Pentanal (99%) was obtained from Aldrich Chemical Company, Inc., redistilled under a static atmosphere of nitrogen (bp 103°C), and used immediately.
4. The product has the following spectroscopic properties: ^1H NMR (300 MHz, $CDCl_3$) δ: 0.89 (t, 3 H, *J* = 6, CH_3), 1.1–2.3 (m, 23 H, CH_2, CH), 2.44 (m, 1 H, CH_2),

2.72 (s, 1 H, OH); IR (KBr) cm^{-1}: 3413 (s), 2931 (s), 2857 (s), 1703 (s), 1455 (m), 1406 (m), 1378 (m), 1352 (m), 1285 (m), 1267 (m), 1206 (m), 1140 (m), 968 (m), 931 (m); mass spectrum *m/z* (relative abundance, 70 eV): 264 (M^+, 10), 167 (85), 166 (100). The submitters report that a second recrystallization gives analytically pure material, mp 141–142°C. Anal. calcd. for $C_{17}H_{28}O_2$: C, 77.22; H, 10,67. Found: C, 77.34; H, 10.51.

5. Ammonium acetate (99 + %) and copper(II) acetate monohydrate (98 + %) were obtained from Aldrich Chemical Company, Inc.

6. Alternatively, the stoppered reaction flask may be allowed to stand overnight in a refrigerator or freezer. In this case the flask should stand at room temperature for 0.5–1 hr prior to filtration in order to partially melt the acetic acid.

7. The product is pure by TLC analysis (Alumina GF Uniplate from Analtec, Inc., 1 : 1 ethyl acetate: hexane solvent, R_f = 0.79) and ^{1}H NMR analysis. The product has the following spectroscopic properties: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.96 (t, 3 H, *J* = 6, CH_3), 1.42 (m, 4 H, $CH_2CH_2CH_3$), 1.7–1.9 (m, 8 H, H2, H3, H6, H7), 2.49 (m, 2 H, $ArCH_2$), 2.68 (m, 4 H, $ArCH_2$), 2.85 (m, 4 H, $ArCH_2$); IR (neat) cm^{-1}: 2932 (s), 2858 (s), 1565 (m), 1438 (m), 1409 (m), 1246 (w); mass spectrum, *m/z* (relative abundance 70, eV): 243 (M^+, 51), 228 (6), 214 (16), 201 (64), 200 (56), 186 (100). The submitters obtained an analytically pure sample by bulb-to-bulb distillation of the initial beige product. Anal. calcd. for $C_{17}H_{25}N$: C, 83.89; H, 10.35; N, 5.75. Found: C, 83.58; H, 10.07; N, 5.40.

8. Oxone®, the Du Pont Company trade name for potassium peroxymonosulfate, has the composition $2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$, and was purchased from Aldrich Chemical Company, Inc.

9. Oxidation may be monitored by thin-layer chromatography (Alumina GF Uniplate, 1 : 1 ethyl acetate : hexane). The R_f values of the *N*-oxide product and starting material are 0.3 and 0.8, respectively. The reaction is approximately 99% complete after 12 hr, but reaction times varied with different lots of Oxone®

10. The submitters report obtaining 39 g (96%) of pale-yellow product, mp 89–92°C, when the beige starting material from Part B, mp 36–39°C, was used without further purification. The checkers, however, obtained only an 80% yield of *N*-oxide, mp 87–91°C, when crude starting material was used.

11. The product is sufficiently pure to be used directly in Part D, but may be further purified by recrystallization from ethyl acetate : hexane (1 : 6) to give colorless material, mp 99–101°C. The product has the following spectral properties : ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.97 (t, 3 H, *J* = 6, CH_3), 1.42 (m, 4 H, $CH_2CH_2CH_3$), 1.7–1.9 (m, 8H, H2, H3, H6, H7), 2.53 (m, 2 H, 9-CH_2), 2.69 (m, 4 H, H1, H8), 2.97 (m, 4 H, H4, H5); IR (KBr) cm^{-1}: 2942 (s), 2857 (s), 1477 (m), 1444 (m), 1424 (m), 1398 (m), 1350 (m), 1322 (m), 1286 (s), 1236 (m), 1096 (s).

12. The submitters provided the following alternative procedure for conducting the oxidation with *m*-chloroperoxybenzoic acid (MCPBA) in place of Oxone®. Into a 1-L, round-bottomed flask equipped with a magnetic stirrer, a reflux condenser, and a 250-mL addition funnel are placed 56.3 g (0.26 mol) of MCPBA (80%) and 350 mL of dichloromethane. The suspension is stirred and a solution of 38.0 g (0.16 mol) of 9-*n*-butyl-1,2,3,4,5,6,7,8-octahydroacridine in 120 mL of dichloromethane is added rapidly (exotherm). When the reaction mixture ceases to boil gently from the heat of reaction, it is heated to extend the reflux period to a total of 2.5 hr. The reaction

mixture is cooled to room temperature, extracted with 0.5 *M* aqueous sodium hydroxide (4 × 450 mL), and dried over anhydrous sodium sulfate. The drying agent is removed by filtration, the filtrate is concentrated with a rotary evaporator, and the residual solvent is removed at 0.1-mm pressure to afford 40 g (99%) of yellow crystalline product, mp 96–100°C.

13. For both recrystallizations, the solid is taken up in boiling ethyl acetate, rapidly filtered, and the filtrate is allowed to cool slowly to room temperature. It then is stored at –5°C overnight in a refrigerator prior to collecting the crystals.

14. The product (R_f = 0.47) contains a trace of 9-*n*-butyl-1,2,3,4,5,6,7,8-octahydroacridine (R_f = 0.79) by TLC analysis (Alumina GF Uniplate, 1 : 1 ethyl acetate : hexane). The checkers chromatographed a 10-g sample on a Woelm neutral alumina column (75 × 28 mm) using 300 mL of warm ethyl acetate as eluent to give 9.2 g of colorless product, mp 107–109°C. The original and chromatographed products have identical spectroscopic properties: ^{1}NMR (300 MHz, $CDCl_3$) δ: 0.96 (t, 3 H, *J* = 7, CH_3), 1.41 (m, 4 H, $CH_2CH_2CH_3$), 1.7–1.9 (m, 6 H, H2, H6, H7), 2.03 (m, 1 H, H3), 2.27 (m, 1 H, H3), 2.50 (m, 2 H, 9-CH_2), 2.70 (m, 4 H, H1, H8), 2.84 (m, 2 H, H5), 4.63 (m, 1 H, H4), 4.76 (s, 1 H, OH); IR (KBr) cm^{-1}: 3174 (s, br), 2942 (s), 2713 (m), 1569 (s), 1432 (s), 1407 (s), 1377 (m), 1338 (s), 1307 (s), 1253 (m), 1216 (m), 1169 (m), 1155 (s), 1094 (s), 1081 (s), 1005 (s), 962 (s), 939 (m), 893 (m). The submitters obtained an analytical sample, mp 104–105°C, by recrystallization from ethyl acetate and drying for 6 hr at room temperature (0.1 mm). Anal. calcd. for $C_{17}H_{25}NO$: C, 78.72; H, 9.71; N, 5.40. Found: C, 78.81, H, 9.53, N, 5.19.

3. Discussion

Taken together, Steps A and B of this procedure describe the most expedient, large-scale approach to 9-*n*-butyl-1,2,3,4,5,6,7,8-octahydroacridine, which is prepared in about 60% overall yield from inexpensive starting materials. This heterocycle is an important building block for "hexagonal lattice" receptors, which are relatively rigid, planar hosts for metal ions and organic molecules.[2 3 4 5 6 7 8 9]

Several methods exist for preparing pyridines that are annelated to nonaromatic rings in the [*b*,*e*]-positions,[10,11 12 13 14 15 16,17 18,19 20 21 22] but most do not also introduce an alkyl group in the 4-position. *n*-Butyl groups are found to lend solubility to higher molecular weight hexagonal lattice receptors. Step A of this procedure is a modification of the method of Tilichenko, who has reported the condensation of cyclohexanone with various aldehydes.[23] The reaction involves the following sequence: aldol condensation to form 2-pentylidenecyclohexanone, Michael addition of cyclohexanone enolate, and intramolecular aldol condensation of the resulting 1,5-diketone. Many aldol products are formed and the yield of keto alcohol depends strongly on (1) reaction temperature, (2) use of a large excess of cyclohexanone, and (3) prolonged addition of the aldehyde. The ease of product isolation is particularly dependent on its crystallinity and solubility.

If a substituent is not required in the 4-position of the new pyridine ring, then viable alternatives to the current procedure include trimethylhydrazonium-salt pyrolysis[17,18] and various methods for condensing ketones or enamines with formaldehyde or

methyleneammonium salts.[11,16,22] The latter methods often involve isolation of the intermediate 1,5-diketone, which is condensed with ammonia or ammonium salts to form the pyridine ring.[12,13,14,16] The yield of this cyclization is limited by disproportionation of the intermediate dihydropyridine.[24] Hydrazine[15] or hydroxylamine[2,11] may also be used, but yields are similar to those obtained with ammonium acetate in acetic acid. The cupric acetate/ ammonium acetate method described in Step B nearly quantitatively gives annelated pyridines from various 1,5-diketone equivalents.[24] Cupric acetate appears to be the oxidant of choice for intercepting dihydropyridines before disproportionation can occur.

Step C describes a method for oxidizing a pyridine to its *N*-oxide with Oxone® (potassium hydrogen persulfate). The more traditional oxidant, *m*-chloroperoxybenzoic acid (MCPBA), works equally well, but the availability of 80–85% pure MCPBA is now limited. Pyridine *N*-oxides may also be prepared with hydrogen peroxide in acetic acid,[25,26] but reaction time is variable and removal of acetic acid is inconvenient for large-scale preparations. Potassium hydrogen persulfate (Oxone®) is an inexpensive alternative to MCPBA in many oxidation reactions.[27 28 29 30 31 32] The oxidation procedure given here avoids the formation of volatile peroxides, which occurs in ketone-catalyzed *N*-oxidation of pyridine by persulfate.[28,31] A 50% excess of Oxone® is used, assuming 100% activity. The submitters used Oxone® of 67–68% purity by iodometric titration. Less oxidant leads to incomplete reaction or inconveniently long reaction times.

Synthesis of annelated polypyridines or hexagonal lattice receptors from 1,2,3,4,5,6,7,8-octahydroacridines requires oxidative functionalization of the 4-position (CH_2 group bonded to the pyridine 2-position). In Step D this is accomplished by "Katada" or "Boekelheide" rearrangement of the *N*-oxide. This general reaction is commonly used for selective oxidation of alkylated pyridines, although the mechanism for conversion of the acetylated *N*-oxide to the 2-acetoxyalkylpyridine has not been fully elucidated.[33 34] The current procedure reflects an empirical finding that deoxygenation of the acetic anhydride prior to addition results in slightly higher yields. Condensation of 2-alkylpyridines with benzaldehyde, followed by ozonolysis of the benzylidene intermediate, is a general, alternative route to 2-oxoalkylpyridines.[35] The *N*-oxide rearrangement described here is superior when monofunctionalization is required, because condensation of 9-*n*-butyl-1,2,3,4,5,6,7,8-octahydroacridine with 1 equiv of benzaldehyde gives a mixture of monobenzylidene and dibenzylidene derivatives.[2,3,4,5,6,7,8,9] Recent work by Tilichenko has shown that 1,5-diketones may be converted to monobenzylidene derivatives before forming the pyridine ring,[36] but overall yields are lower than those for the current procedure.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

pyridine N-oxides

potassium peroxymonosulfate

m-chloroperoxybenzoic acid (MCPBA)

1,2,3,4,5,6,7,8-octahydroacridines

4-Acridinol; 9-butyl-1,2,3,4,5,6,7,8-octahydro

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ammonia (7664-41-7)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether (60-29-7)

ammonium acetate (631-61-8)

acetic anhydride (108-24-7)

sodium hydroxide (1310-73-2)

formaldehyde (630-08-0)

chloroform (67-66-3)

oxone (37222-66-5)

sodium bicarbonate (144-55-8)

Cyclohexanone (108-94-1)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

benzaldehyde (100-52-7)

pyridine (110-86-1)

potassium hydroxide (1310-58-3)

hydrogen peroxide (7722-84-1)

ammonium hydroxide (1336-21-6)

cupric acetate (142-71-2)

benzylidene

hydrazine (302-01-2)

hydroxylamine (7803-49-8)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

Ammonium (14798-03-9)

persulfate (13445-49-3)

cupric acetate monohydrate, copper(II) acetate monohydrate (6046-93-1)

hexane (110-54-3)

dihydropyridine

helium (7440-59-7)

methyleneammonium

cuprous acetate (598-54-9)

pentanal (110-62-3)

2-pentylidenecyclohexanone

cyclohexanone enolate

potassium hydrogen persulfate

m-chloroperoxybenzoic acid (937-14-4)

9-n-BUTYL-1,2,3,4,5,6,7,8-OCTAHYDROACRIDIN-4-OL (99922-91-5)

8-n-Butyl-2-hydroxytricyclo[7.3.1.0^{2,7}]tridecan-13-one (24133-22-0)

9-n-butyl-1,2,3,4,5,6,7,8-octahydroacridine (99922-90-4)

9-n-butyl-1,2,3,4,5,6,7,8-octahydroacridine-N-oxide (136528-61-5)

9-n-Butyl-1,2,4,5,6,7,8-octahydroacridine N-oxide

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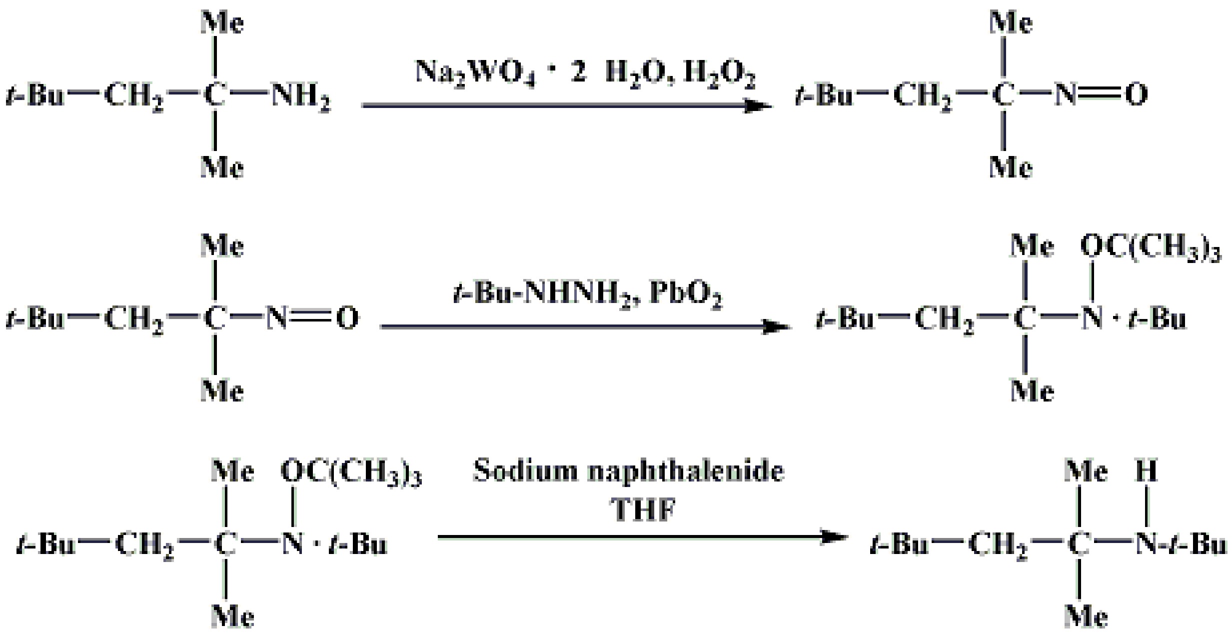
Organic Syntheses, CV 8, 93

tert-BUTYL-*tert*-OCTYLAMINE

[2-Pentanamine, *N*-(1,1-dimethylethyl)-2,4,4-trimethyl-]



Submitted by E. J. Corey and Andrew W. Gross[1].
Checked by Axel H. K. Paul and Clayton H. Heathcock.

1. Procedure

A. *Nitroso-tert-octane*.[2] To a 1-L, three-necked flask equipped with an addition funnel, a mechanical stirrer, and a thermometer are added 120 mL of methanol, 51.7 g of *tert*-octylamine (0.4 mol), and 90 mL of water containing 1.2 g (0.0028 mol) of the tetrasodium salt of ethylenediaminetetraacetic acid and 2.52 g (0.0076 mol) of sodium tungstate dihydrate. The solution is cooled to 15°C in an ice bath and hydrogen peroxide (361 mL of a 16% solution, 1.7 mol) (Note 1) and (Note 2) is added over 5 hr. The blue reaction mixture is stirred for an additional 16 hr and the product is extracted with petroleum ether (3 × 50 mL). Unreacted amine is removed by washing twice with 2 *N* hydrochloric acid. After the blue organic layer is washed with brine, it is dried over $MgSO_4$. Petroleum ether is removed by distillation at atmospheric pressure. Continued distillation of the product affords 29.7 g of nitroso-*tert*-octane (52%), bp 45–55°C, 18 mm. On standing, the product crystallizes as the colorless dimer, mp 63–65°C. For use in the subsequent reaction the required amount of the dimer is stirred for 1 hr in hexane to establish monomer–dimer equilibrium (Note 3) and (Note 4).

B. *N-tert-Butyl-N-tert-octyl-O-tert-butylhydroxylamine.* Into a 1-L, three-necked flask equipped with a dropping funnel, a mechanical stirrer, and a gas inlet tube is placed a

solution of 22.8 g (0.16 mol of monomer) of nitroso-*tert*-octane in 500 mL of hexane. After the mixture is stirred for 1 hr, lead dioxide (132 g, 0.55 mol) (Note 5) is added. To the rapidly stirring mixture is added 48.8 g (0.55 mol) of *tert*-butylhydrazine (Note 6) dropwise at such a rate as to give brisk but controlled nitrogen evolution (approximately 30 min). Cooling is provided by an ice bath so as to maintain the reaction temperature between 15 and 25°C. Progress of the reaction is monitored visually by the disappearance of the blue nitroso monomer color (Note 7). After the blue color has disappeared (about 1.5 hr), the lead oxides are removed by filtration through a pad of Celite and the residue is washed with ether/hexane (1 : 1). The filtrate and washes are combined and the solvents are removed at reduced pressure with a rotary evaporator to give a 6 : 1 mixture of *N*-*tert*-butyl-*N*-*tert*-octyl-*O*-*tert*-butylhydroxylamine and *N*-*tert*-octyl-*O*-*tert*-butylhydroxylamine (Note 8) and (Note 9).

C. *tert-Butyl-tert-octylamine.* In a dry, 500-mL, three-necked flask equipped with a mechanical stirrer, an addition funnel, and a nitrogen inlet are placed 25.6 g (0.20 mol) of naphthalene, 250 mL of dry tetrahydrofuran (THF), and 10.8 g (0.47 mol) of sodium pieces. The mixture is stirred at room temperature for 30 min. To the blue-green sodium naphthalenide solution is added the hydroxylamine mixture (Note 10) in 50 mL of THF over 20 min. *(Caution! Exothermic reaction.)* The mixture is stirred for 2.5 hr at room temperature (Note 11). The reaction mixture is carefully decanted from excess sodium and the excess reducing agent is cautiously quenched with isopropyl alcohol. After dilution with 150 mL of hexane, the mixture is acidified with 300 mL of ice-cold 2 *N* hydrochloric acid, the aqueous layer is separated, and the organic layer extracted twice more with 100-mL portions of 2 *N* hydrochloric acid. The combined acidic extracts are washed with 80 mL of petroleum ether (Note 12), neutralized with 4 *N* sodium hydroxide, and extracted with ether (3 × 100 mL). The ether extract is dried over $MgSO_4$ and the solvent is removed with a rotary evaporator. Distillation of the residue gives a small forerun, followed by 18–19 g of *tert*-butyl-*tert*-octylamine, bp 79°C (17 mm). The yield is 60–64% based on nitroso-*tert*-octane (Note 13).

2. Notes

1. Mallinckrodt 30% H_2O_2 was diluted with water to give a solution of 16% H_2O_2 in water.
2. Although it is used in excess, the amount of H_2O_2 used seems to be critical. The checkers found that the use of 2.1 mol of H_2O_2 results in considerable overoxidation to nitro-*tert*-octane, resulting in a yield of nitroso-*tert*-octane of only 40%.
3. Nitroso-*tert*-octane may also be prepared by oxidation of *tert*-octylamine with peracetic acid in ethyl acetate, obtained by the submitters from the Union Carbide Corporation.[3] To a 1-L, three-necked flask equipped with a mechanical stirrer and an addition funnel are added 51.7 g of *tert*-octylamine (0.4 mol), 50

mL of water, and 50 mL of ethyl acetate. The flask is placed in an ice bath and the contents are stirred until the temperature reaches 0–5°C. A solution of peracetic acid in ethyl acetate (3.15 *M* solution, 51 mL, 0.16 mol) is added dropwise over a 30-min period. The blue reaction mixture is stirred at 0°C until the absence of peroxy acid is indicated by starch–iodide test paper. The reaction mixture is transferred to a separatory funnel and diluted with 200 mL of hexane. Unreacted *tert*-octylamine is removed by washing with 4 *N* hydrochloric acid. The aqueous washes are backwashed until colorless with 50-mL portions of hexane. The combined, blue organic fractions are dried over sodium sulfate and used directly in the next step. When the nitroso compound is prepared in this manner, isolation is unnecessary. The checkers did not employ this procedure because the peracetic acid/ethyl acetate solution is not commercially available.

4. Care should be taken in distilling the nitroso compound because it is thermally unstable; its half-life is less than 5 min at 150°C.[2]

5. If technical-grade lead dioxide (Fisher Scientific Company) is used, a somewhat greater amount must be added to compensate for the decreased Pb (IV) content.

6. *tert*-Butylhydrazine is conveniently liberated from its hydrochloride (Aldrich Chemical Company, Inc.) by distillation from 40% KOH (bp 104–107°C). The distillate consists of a mixture of *tert*-butylhydrazine and water. On addition of several grams of KOH pellets, the distillate separates into two layers. The upper layer, consisting of slightly wet *tert*-butylhydrazine, is dried over KOH pellets.

7. Additional lead dioxide and/or *tert*-butylhydrazine may be necessary to complete the reaction.

8. The spectral properties are as follows. *N*-*tert*-Butyl-*N*-*tert*-octyl-*O*-*tert*-butylhydroxylamine ^{1}H NMR ($CDCl_3$) δ: 1.00 (s, 9 H), 1.26 (s, 12 H), 1.30 (s, 3 H), 1.31 (s, 9 H), 1.76 (s, 2 H); *N*-*tert*-octyl-*O*-*tert*-butylhydroxylamine ^{1}H NMR ($CDCl_3$) δ: 1.01 (s, 9 H), 1.12 (s, 6 H), 1.15 (s, 9 H), 1.40 (s, 2 H), 4.44 (s, 1 H).

9. The trisubstituted hydroxylamine is sensitive to both acid and heat.

10. The yield of product is greatly reduced if the hydroxylamine mixture is not rigorously freed of solvent from the previous reaction.

11. The submitters report that the sodium naphthalenide color is discharged on addition of the hydroxylamine mixture, and that completion of the reduction is indicated by reappearance of the characteristic blue-green color of the reagent. The checkers did not observe disappearance of the reagent color.

12. If the acidic solution is not extracted at this point, the final product will be contaminated with 2–3% naphthalene.

13. The ^{1}H NMR spectrum of *tert*-butyl-*tert*-octylamine is as follows ($CDCl_3$) δ: 1.02 (s, 9 H, CH_3), 1.19 (s, 9 H, CH_3), 1.24 (s, 6 H, CH_3), 1.44 (s, 2 H, CH_2).

3. Discussion

In addition to the procedure given here for the oxidation of *tert*-octylamine to nitroso-

tert-octane,[2] the oxidation may be carried out with *m*-chloroperoxybenzoic acid[4] or with a solution of peroxyacetic acid in ethyl acetate.[3] The lead dioxide oxidation of alkylhydrazines to alkyl radicals appears to have general application. In addition to *tert*-butylhydrazine, various secondary alkylhydrazines (e.g., bornylhydrazine and menthylhydrazine) have been used to good effect. The reduction of tri-*tert*-alkylhydroxylamine to the di-*tert*-alkylamine has also been achieved with sodium in ammonia, but the insolubility of the hydrophobic substrate makes this procedure difficult. The use of sodium naphthalenide[5] gives higher yields and is more reproducible.

In addition to the commercially available 2,2,6,6-tetramethylpiperidine,[6] di-*tert*-alkylamines have been prepared by Rathke[7] by the copper-catalyzed coupling of acetylenic amines with acetylenic chlorides in an improvement of the procedure of Hennion.[8] Di-*tert*-butylamine has been synthesized by the reaction of 2-methyl-2-nitropropane with sodium, followed by reduction.[9]

The three-step procedure described here illustrates a convenient, general route to di-*tert*-alkylamines. Extensive purification or isolation of intermediates is not required. The reactions are easily monitored. Only in the final step is the exclusion of air and moisture necessary. It should be noted that *tert*-butyl-*tert*-octylamine is considerably more hindered than 2,2,6,6-tetramethylpiperidine. *tert*-Butyl-*tert*-octylamine is inert to methyl iodide, while 2,2,6,6-tetramethylpiperidine gives a white precipitate of the pentamethylammonium iodide within minutes on treatment with methyl iodide at room temperature. The extreme hindrance of this amine has been exploited in the selective deprotonation of carbon acids and in other reactions.[10]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

amine

brine

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

sodium (13966-32-0)

isopropyl alcohol (67-63-0)

Naphthalene (91-20-3)

hydrogen peroxide (7722-84-1)

Methyl iodide (74-88-4)

Tetrahydrofuran (109-99-9)

peracetic acid, peroxyacetic acid (79-21-0)

hexane (110-54-3)

2-Methyl-2-nitropropane (594-70-7)

2,2,6,6-tetramethylpiperidine (768-66-1)

ethylenediaminetetraacetic acid (60-00-4)

Nitroso-tert-octane (31044-98-1)

sodium tungstate dihydrate (10213-10-2)

sodium naphthalenide

bornylhydrazine

menthylhydrazine

pentamethylammonium iodide

m-chloroperoxybenzoic acid (937-14-4)

lead dioxide

tert-octylamine

tert-Butyl-tert-octylamine

2-Pentanamine, N-(1,1-dimethylethyl)-2,4,4-trimethyl- (90545-94-1)

tert-butylhydrazine (32064-67-8)

N-tert-Butyl-N-tert-octyl-O-tert-butylhydroxylamine (90545-93-0)

N-tert-octyl-O-tert-butylhydroxylamine

nitro-tert-octane

Di-tert-butylamine (21981-37-3)

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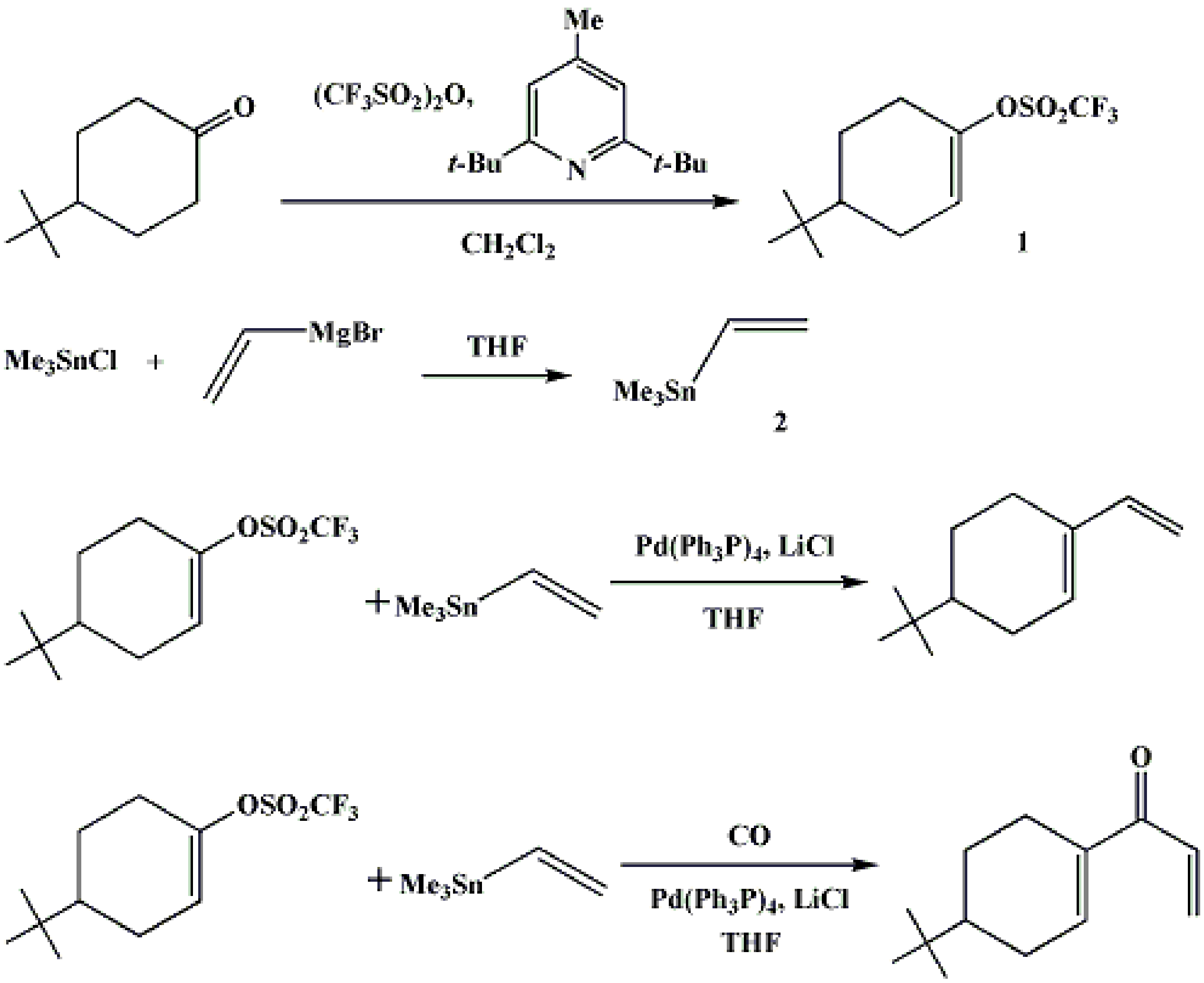
Organic Syntheses, *CV 8*, *97*

PALLADIUM-CATALYZED COUPLING OF VINYL TRIFLATES WITH ORGANOSTANNANES: 4-*tert*-BUTYL-1-VINYLCYCLOHEXENE AND 1-(4-*tert*-BUTYLCYCLOHEXEN-1-YL)-2-PROPEN-1-ONE

[Cyclohexene, 4-(1,1-dimethylethyl)-1-ethenyl- and 2-propen-1-one, 1-[4-(1,1-dimethylethyl)-1-cyclohexen-1-yl]]



Submitted by William J. Scott[1], G. T. Crisp[2], and J. K. Stille[3].
Checked by Dean R. Lagerwall and Leo A. Paquette.

1. Procedure

Caution! Many organotin compounds are toxic.[4] Their preparation and use should be carried out in a well-ventilated hood.

A. *4-tert-Butylcyclohexen-1-yl trifluoromethanesulfonate*. A dry, 2-L, three-necked, round-bottomed flask equipped with a magnetic stirring bar, an argon inlet, and a condenser (Note

1) is charged with 33.0 g (0.214 mol) of 4-*tert*-butylcyclohexanone (Note 2), 1.5 L of dichloromethane (Note 3), and 49.5 g (0.241 mol) of 2,6-di-*tert*-butyl-4-methylpyridine (Note 4). The solution is stirred under a static argon atmosphere and cooled to 0°C, at which time the dropwise addition of 40.0 mL (0.238 mol) of trifluoromethanesulfonic anhydride (Note 5) is begun. After the addition is complete, the brown mixture is allowed to warm slowly to room temperature and is stirred at that temperature for 10 hr. At this point, the consumption of starting ketone is verified by thin-layer chromatography (hexane; silica gel). If the reaction is incomplete, more trifluoromethanesulfonic anhydride is added and additional time is allowed. The solvent is removed by distillation and the resulting light-tan material is treated with 1 L of pentane and heated to reflux for 30 min. The tan salts thus obtained are removed by filtration and washed with five 100-mL portions of pentane (Note 6). The combined pentane solutions are washed with two 250-mL portions each of a 10% hydrochloric acid solution, a 10% sodium hydroxide solution, and a saturated sodium chloride solution, dried with magnesium sulfate, filtered through a 6 × 4-cm pad of silica gel (Note 7), and concentrated by distillation. Bulb-to-bulb distillation (Note 8) of the resulting yellow oil at 75–80°C (0.5 mm) gives 43–45 g (70–73%) of the product as a colorless oil (Note 9).

B. *Trimethylvinyltin*. To a dry, 1-L, three-necked, round-bottomed flask, equipped with a Dewar-type condenser cooled to –78°C, a magnetic stirring bar and a gas inlet leading to a static supply of dry argon (Note 1) are added 11.4 g (0.469 mol) of clean magnesium turnings, 50 mL of dry tetrahydrofuran (Note 10), 3 mL of vinyl bromide, and 0.3 mL of methyl iodide to initiate formation of vinylmagnesium bromide. To this is added a solution of 41 mL (0.624 mol or 66.7 g total) of vinyl bromide in 125 mL of dry tetrahydrofuran via cannula at a rate that maintains a gentle reflux. After addition the mixture is heated to reflux for 1 hr with an oil bath and then cooled to 60°C.

To the resulting slurry of vinylmagnesium bromide (with the condenser still maintained at –78°C) is added via cannula a solution of 61.3 g (0.307 mol) of trimethyltin chloride (Note 11) in 50 mL of dry tetrahydrofuran at a rate suitable to maintain a gentle reflux. The temperature is maintained at 60°C for 5 hr and then the mixture is cooled to room temperature. With the condenser still maintained at –78°C, 200 mL of a saturated ammonium chloride solution is added by syringe at a rate that maintains a gentle reflux, followed by 200 mL of water. The resulting solution is transferred to a separatory funnel with the aid of 200 mL of pentane and the organic layer is washed with 250 mL of a saturated ammonium chloride solution. The combined aqueous layers are back-extracted twice with 250 mL of pentane, and the combined organic layers are washed 5 times with 250 mL of saturated ammonium chloride, 10 times with a 10% hydrochloric acid solution, and twice with a saturated sodium chloride solution, and then gravity-filtered through a 9 × 4-cm pad of silica gel (Note 7) to give approximately 500 mL of a slightly yellow solution. Pentanes are removed by distillation using a 16-cm Vigreux column and a short-path stillhead (Note 12). Continued distillation affords a fraction boiling from 60–90°C, which contains a mixture of 4.9 g of trimethylvinyltin in 16.3 g of tetrahydrofuran (Note 13). At this point the still is cooled to room temperature, the Vigreux column is removed, and the remaining oil is distilled at 95–100°C to give 38–39 g (64–66% purified yield) of trimethylvinyltin (Note 14).

C. *4-tert-Butyl-1-vinylcyclohexene*. A dry, 2-L, one-necked, round-bottomed flask equipped with a magnetic stirring bar, an argon inlet, and a condenser (Note 1) is charged with 1.18 g (1.02 mmol) of tetrakis(triphenylphosphine)palladium(0) (Note 15), 12.9 g (0.305 mol) of lithium chloride (Note 16), and 500 mL of tetrahydrofuran (Note 10). This mixture is stirred for 15 min under a static argon atmosphere; then a solution of 28.0 g (0.0979 mol) of 4-*tert*-butylcyclohexen-1-yl trifluoromethanesulfonate and 19.0 g (0.0997 mol) of trimethylvinyltin in 250 mL of tetrahydrofuran is added, followed by an additional 250 mL of tetrahydrofuran. The resulting, almost colorless solution is heated to a gentle reflux for 48 hr (Note 17). The mixture is cooled to room temperature and partitioned between 500 mL of water and 250 mL of pentane. The aqueous layer is back-extracted with two 200-mL portions of pentane. The combined organic layers are washed with two 250-mL portions each of a concentrated sodium bicarbonate solution, water, and a concentrated sodium chloride solution, dried over magnesium sulfate, filtered through a 4 × 4-cm pad of silica gel (Note 7) and concentrated by distillation using a 10-cm Vigreux column. Bulb-to-bulb distillation (Note 8) of the resulting yellow oil at 65–68°C (0.55 mm) gives 12.6–12.8 g (78–79%) of the coupled product (Note 18).

D. *1-(4-tert-Butylcyclohexen-1-yl)-2-propen-1-one*. To a dry, 2-L, round-bottomed flask, equipped with a magnetic stirring bar, a condenser, and a gas inlet connected to a static argon atmosphere (Note 1), are added 1.12 g (0.968 mmol) of tetrakis(triphenylphosphine) palladium(0) (Note 15), 13.2 g (0.312 mol) of lithium chloride (Note 16), and 500 mL of tetrahydrofuran (Note 10), followed by a solution of 28.6 g (0.100 mol) of 4-*tert*-butylcyclohexen-1-yl trifluoromethanesulfonate and 19.1 g (0.100 mol) of trimethylvinyltin in 250 mL of tetrahydrofuran, and then an additional 250 mL of tetrahydrofuran. A gas bag (Note 19) filled with carbon monoxide is attached to the gas inlet and the apparatus is flushed with carbon monoxide. The gas bag is refilled with carbon monoxide and reattached to the gas inlet. The mixture is then heated to 55°C (Note 20). After 2–4 hr, a large amount of the carbon monoxide has been absorbed into solution and the gas bag is refilled and reattached to the gas inlet. After a total of 40 hr, the reaction mixture darkens and is cooled to room temperature (Note 21). This solution is transferred to a 2-L separatory funnel, diluted with 500 mL of pentane, and washed successively with two 300-mL portions each of water, saturated sodium bicarbonate solution, water again, and saturated sodium chloride solution. The resulting yellow solution is dried over magnesium sulfate, filtered through a 6 × 4-cm pad of silica gel (Note 7), and concentrated using a rotary evaporator. Slow bulb-to-bulb distillation (Note 8) and (Note 22) of the brown oil at 85–95°C (0.35 mm) gives 14.3–14.5 g (74–75%) of the product as a colorless oil (Note 23).

2. Notes

1. The glassware is dried in an oven at 140°C overnight and assembled warm under a static argon atmosphere.
2. 4-*tert*-Butylcyclohexanone is purchased from the Aldrich Chemical Company, Inc.
3. Dichloromethane is freshly distilled from calcium hydride.
4. 2,6-Di-*tert*-butyl-4-methylpyridine can be purchased from the Aldrich Chemical Company, Inc. or prepared from pivaloyl chloride.[5]

5. Trifluoromethanesulfonic anhydride can be purchased from the Aldrich Chemical Company, Inc. or prepared from trifluoromethanesulfonic acid.[6]

6. The solids can range in color from off-white to brown. 2,6-Di-*tert*-butyl-4-methylpyridine can be recovered by separation of the tan solids between 500 mL of pentane and 650 mL of a 1.2 *N* sodium hydroxide solution. The aqueous layer is extracted with two 200-mL portions of pentane. The combined organic phases are washed with two 200-mL portions of water and two 200-mL portions of a saturated sodium chloride solution dried with sodium sulfate, filtered through a 6 × 4-cm pad of silica gel (Note 7), and concentrated using a rotary evaporator. Bulb-to-bulb distillation (Note 8) of the yellow oil at 65–75°C (0.55 mm) with trapping of the distillate in two connected receiving flasks cooled to −78°C gives 42.1–48.1 g (85–97%) of colorless oil, which solidifies on standing.

7. Woelm 230–400-mesh silica gel is used.

8. An Aldrich Chemical Company, Inc. Kugelrohr apparatus is used.

9. 4-*tert*-Butylcyclohexen-1-yl trifluoromethanesulfonate has the following properties: mp 17°C; TLC R_f (hexanes): 0.65; IR (neat) cm^{-1}: 1698, 1440, 1425, 1250, 1225; ^{1}H NMR ($CDCl_3$, 270 MHz) δ: 0.89 (s, 9 H), 1.26–1.38 (m, 3 H), 1.90–2.18 (m, 2 H), 2.23–2.39 (m, 2 H), 5.73–5.75 (m, 1 H): ^{13}C NMR ($CDCl_3$, 68 MHz) δ: 23.9, 25.4, 27.2 (3C), 28.6, 32.0, 43.1, 118.3, 118.7 (q, J = 319, CF_3), 149.3.

10. Tetrahydrofuran is freshly doubly distilled from potassium.

11. Trimethyltin chloride can be purchased from Strem Chemicals, Inc. or prepared by the reaction of tetramethyltin with tin tetrachloride as follows. To a 100-mL, round-bottomed flask, equipped with a magnetic stirring bar, a septum, and a gas inlet connected to a static argon atmosphere, containing 41.2 g (0.230 mol) of tetramethyltin cooled to −20°C with a dry ice–carbon tetrachloride slurry, is added 9.0 mL (0.0768 mol) of tin tetrachloride at a slow dropwise rate. After the addition is complete, the mixture is heated to 60°C for 16 hr. The mixture is cooled to room temperature to afford 61.3 g (100% yield) of a colorless solid.

12. In order to maximize the yield of trimethylvinyltin, pentanes should be removed as carefully as possible. The authors employed only 14/20-ground glassware in the distillation and carefully controlled the oil bath temperature to maintain a collection rate of approximately 0.3 mL per min.

13. The ratio of trimethylvinyltin to tetrahydrofuran is determined by NMR. The trimethylvinyltin/THF solution may be used in palladium-catalyzed coupling reactions without further purification.

14. Trimethylvinyltin is >97% pure as shown by gas chromatography on a 1/8-in. × 6-ft column packed with 6% SP-2100 on Supelcoport, 80–100 mesh, operated at 50°C. The relative retention times are 1.9 min for tetrahydrofuran, 4.0 min for trimethylvinyltin, and 7.0 min for trimethyltin chloride (not seen). The distilled product has the following properties: ^{1}H NMR ($CDCl_3$, 270 MHz) δ: 0.12 (s, 9 H), 5.66 (dd, 1 H, J = 3.4, 20.5), 6.11 (dd, 1 H, J = 3.6, 13.9), 6.52 (dd, 1 H, J = 13.9, 20.5); ^{13}C NMR ($CDCl_3$, 68 MHz) δ: −9.9 (3C) 133.2, 140.0

15. Tetrakis(triphenylphosphine)palladium(0) can be purchased from Strem Chemicals, Inc. or prepared from palladium chloride.[7] On standing for a period of time (at least a few weeks) the catalyst gradually darkens, turning tan in the absence

of oxygen or turning green in the presence of oxygen. However, the coupling reactions run equally well with catalyst that has aged for a year.

16. Lithium chloride is dried at 140°C for 24 hr prior to use.

17. The progress of the reaction is conveniently monitored by gas chromatography using a 1/8-in. × 6-ft column packed with 6% SP-2100 on Supelcoport, 80–100 mesh. operated at 50°C for 4 min, then heated at 15°C/min to 250°C. The relative retention times are 4.0 min for trimethylvinyltin, 6.5 min for trimethyltin chloride, 12.0 min for 4-*tert*-butyl-1-vinylcyclohexene, and 13.1 min for 4-*tert*-butylcyclohexen-1-yl trifluoromethanesulfonate. Because of the extreme volatility of trimethylvinyltin, it may be necessary to add additional small amounts in order to drive the reaction to completion.

18. 4-*tert*-Butyl-1-vinylcyclohexene has the following properties: bp 45°C (0.1 mm); TLC R_f (hexanes): 0.74; IR (neat) cm^{-1}: 3100, 3020, 1650, 1610, 1395, 1365, 985, 890; ^{1}H NMR ($CDCl_3$, 270 MHz) δ: 0.87 (s, 9 H), 1.08–1.34 (m, 3 H), 1.84–2.36 (m, 4 H), 4.88 (d, 1 H, J = 10.7), 5.04 (d, 1 H, J = 17.5), 5.73–5.75 (m, 1 H), 6.35 (dd, 1 H, J = 10.7, 17.5); ^{13}C NMR ($CDCl_3$, 68 MHz) δ: 23.8, 25.3, 27.2 (3C), 27.4, 32.2, 44.4, 109.7, 129.8, 136.0, 139.7.

19. The gas bag can be purchased from the Fisher Scientific Company and is filled to approximately 5 psig (pounds per square inch gauge) with carbon monoxide.

20. Refluxing conditions must be avoided in order to maximize the amount of carbon monoxide in solution.

21. The progress of the reaction is conveniently monitored by gas chromatography on a 1/8-in. × 6-ft column packed with 6% SP-2100 on Supelcoport, 80–100 mesh, operated at 50°C for 4 min, then heated at 15°C/min to 250°C. The relative retention times are 4.0 min for trimethylvinyltin, 6.5 min for trimethyltin chloride, 13.1 min for 4-*tert*-butylcyclohexen-1-yl trifluoromethanesulfonate, and 14.7 min for 1-(4-*tert*-butylcyclohexen-1-yl)-2-propen-1-one. Because of the extreme volatility of trimethylvinyltin, it may be necessary to add additional small amounts of this reagent in order to drive the reaction to completion.

22. The purification procedure occasionally leads to product contaminated with organotins. The submitters have found that careful washing with water minimizes this problem. The checkers found that distillation of product at a slow rate allows the unwanted tin to escape to the cold trap.

23. 1-(4-*tert*-Butylcyclohexen-1-yl)-2-propen-1-one has the following properties: bp 75°C (0.1 mm); IR (neat) cm^{-1}: 1665, 1645, 1612; ^{1}H NMR ($CDCl_3$, 270 MHz) δ: 0.81 (s, 9 H), 1.21–2.65 (m, 7 H), 5.58 (d, 1 H, J = 9.0), 6.14 (d, 1 H, J = 17.2), 6.75–7.00 (m, 2 H); ^{13}C NMR ($CDCl_3$, 68 MHz) δ: 23.3, 24.6, 26.9 (3C), 27.8, 32.0, 43.4, 127.1, 131.5, 139.4, 141.1, 190.8.

3. Discussion

The conversion of a ketone into a substituted olefin is classically achieved by the addition of a Grignard reagent to a ketone, followed by the dehydration of the resulting alcohol. Such a scheme can often lead to a mixture of regioisomers. By converting the ketone into a vinyl iodide,[8] followed by a cuprate coupling reaction,[9] it is possible to form selectively the less-hindered, substituted olefin. Group 10[10]-catalyzed coupling reactions of vinyl iodides also

lead to the formation of olefins in good yields.[11,12,13] However, the synthesis of the more hindered vinyl iodides can be quite difficult.

A number of enolate derivatives have recently been offered as alternatives to vinyl iodides. The advantage to such a scheme lies in the ability to form regioselectively either the kinetic or the thermodynamic enolate using known methodology,[14] and then to trap that enolate to give the required derivative. In general, enolate derivatives, such as methyl vinyl ethers,[15] silyl enol ethers,[16] and enol phosphates,[17] have undergone coupling only in the presence of nickel catalysts, thus requiring the use of very strong nucleophiles. However, such nucleophiles severely restrict the functionality that may be present in either the enolate derivative or the nucleophile.

Vinyl trifluoromethanesulfonates[18] have provided a solution to this problem. Vinyl trifluoromethanesulfonates can be formed by the action of trifluoromethanesulfonic anhydride with a ketone.[6,18] Enolates may be trapped using *N*-phenyltrifluoromethanesulfonimide to form selectively either the kinetic or thermodynamic derivative.[9,10,11,12,13,14,15,16,17,18,19,20,21] The resulting enolate derivatives couple readily with organocuprates.[22] Palladium-catalyzed coupling reactions may also be run to give directly coupled products,[21] Heck-type coupled products,[23,24,25] or reduced products.[21,22,23,24,25,26] Direct coupling reactions of vinyl trifluoromethanesulfonates have been used in the synthesis of pleraplysillin-1,[21] the synthesis of cardenolides,[24] the synthesis of vinylstannanes,[27,28,29] and in intramolecular cyclization reactions.[30,31,32]

The synthesis of ketones is very important to the organic chemist. Two common methods involve the addition of Grignard reagents to aldehydes, followed by oxidation of the secondary alcohol, and the addition of organolithium reagents to carboxylic acids.[33] In addition, acid chlorides have been coupled with Grignard reagents,[34,35] organoaluminum reagents,[36] organocadmium reagents,[35] organocuprates,[9] or organozinc reagents[35] to give the corresponding ketone. More recently, the palladium-catalyzed coupling of acid chlorides with organozinc reagents,[37] organostannanes,[38] or organomercury reagents[39] has provided a very mild method for ketone synthesis.

In order to avoid the necessity of using acid chlorides in the coupling reactions, the palladium-catalyzed coupling of electrophiles in the presence of carbon monoxide was developed.[40,41] Again, the necessity of using vinyl iodides limits this methodology. On palladium-catalyzed coupling of vinyl trifluoromethanesulfonates in the presence of lithium chloride, the desired enones are formed in good yield.[42,43] The carbonylative coupling reaction has been used in the synthesis of (±)-$\Delta^{9,12}$-capnellene.[42]

References and Notes

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2. Department of Organic Chemistry, University of Melbourne, Parkville, Victoria, 3052, Australia;
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Pentanes

vinyl iodides

methyl vinyl ethers

silyl enol ethers

Vinyl trifluoromethanesulfonates

N-phenyltrifluoromethanesulfonimide

pleraplysillin-1

vinylstannanes

hydrochloric acid (7647-01-0)

ammonium chloride (12125-02-9)

sodium hydroxide (1310-73-2)

carbon monoxide (630-08-0)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

oxygen (7782-44-7)

tin (7440-31-5)

nickel (7440-02-0)

potassium (7440-09-7)

Methyl iodide (74-88-4)

Pentane (109-66-0)

dichloromethane (75-09-2)

palladium chloride

tin tetrachloride (7646-78-8)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

hexane (110-54-3)

Lithium chloride (7447-41-8)

vinyl bromide (593-60-2)

vinylmagnesium bromide (1826-67-1)

calcium hydride (7789-78-8)

argon (7440-37-1)

trifluoromethanesulfonic acid (1493-13-6)

4-tert-Butylcyclohexanone (98-53-3)

pivaloyl chloride (3282-30-2)

Trifluoromethanesulfonic anhydride (358-23-6)

tetrakis(triphenylphosphine)palladium(0) (14221-01-3)

4-tert-Butyl-1-vinylcyclohexene, Cyclohexene, 4-(1,1-dimethylethyl)-1-ethenyl- (33800-81-6)

2-propen-1-one, 1-[4-(1,1-dimethylethyl)-1-cyclohexen-1-yl], 1-(4-tert-Butylcyclohexen-1-yl)-2-propen-1-one (92622-56-5)

trimethyltin chloride (1066-45-1)

Trimethylvinyltin (754-06-3)

tetramethyltin (594-27-4)

vinyl iodide (593-66-8)

2,6-Di-tert-butyl-4-methylpyridine (38222-83-2)

4-tert-Butylcyclohexen-1-yl trifluoromethanesulfonate (77412-96-5)

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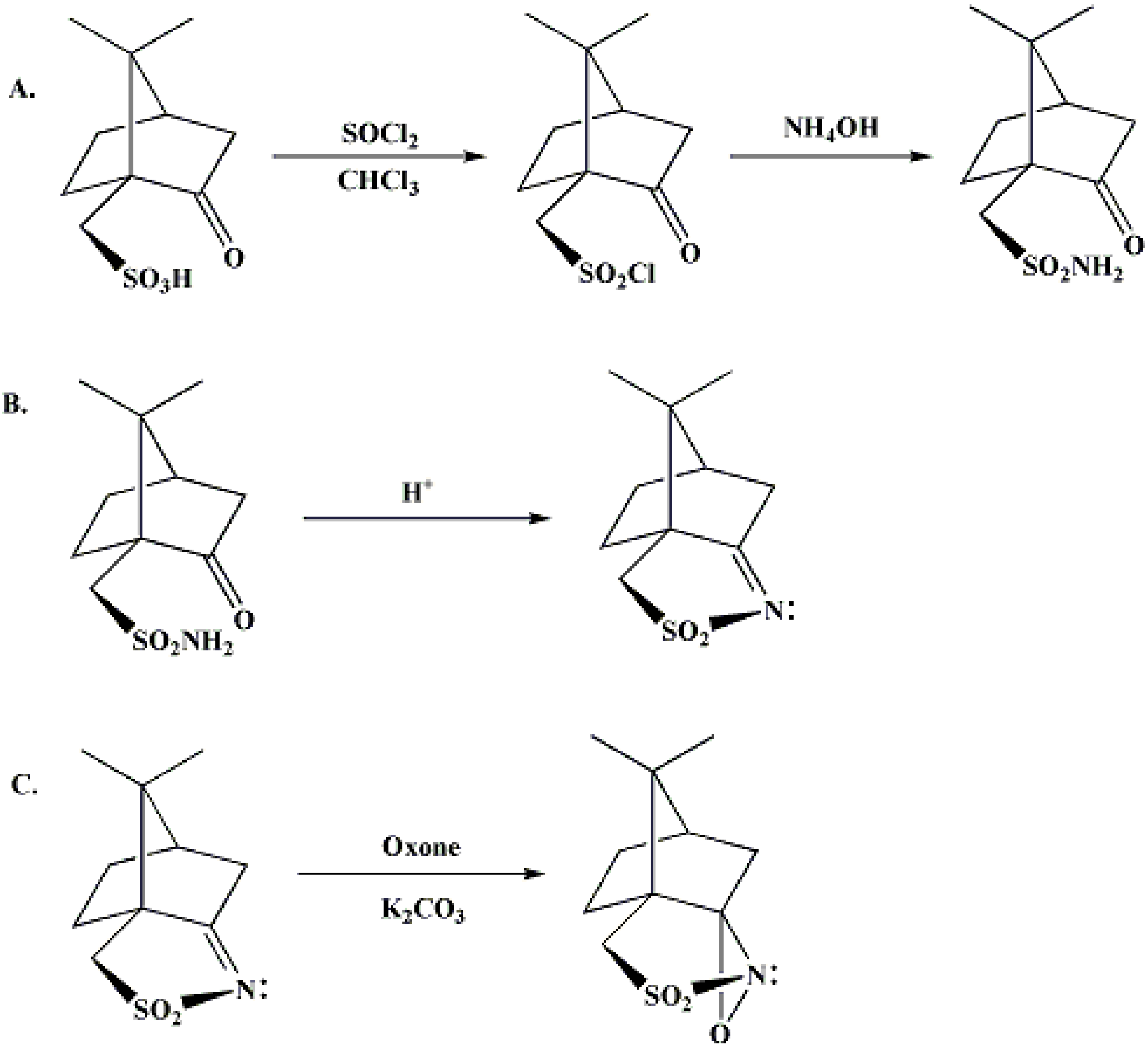
(+)-(2*R*,8a*S*)-10-(CAMPHORYLSULFONYL)OXAZIRIDINE

[4H-4A,7-Methanooxazirino[3,2-*i*][2,1]benzisothiazole, tetrahydro-9,9-dimethyl-, 3,3-dioxide, [4a*S*-(4aα,7α,8a*R**)]]



Submitted by James C. Towson, Michael C. Weismiller, G. Sankar Lal, Aurelia C. Sheppard, Anil Kumar, and Franklin A. Davis[1].
Checked by David I. Magee and Robert K. Boeckman, Jr..

1. Procedure

A. *(+)-(1S)-10-Camphorsulfonamide*. Into a 2-L, two-necked, round-bottomed flask, equipped with a 250-mL dropping funnel, a magnetic stirring bar, and a reflux condenser fitted with an outlet connected to a disposable pipette dipped in 2 mL of chloroform in a test tube for monitoring gas evolution, were placed 116 g (0.5 mol) of camphorsulfonic acid (Note 1) and 750 mL of reagent-grade chloroform. The suspension of camphorsulfonic acid was heated to reflux and 71.4 g (43.77 mL, 0.6 mol, 1.2 equiv) of freshly distilled thionyl chloride was added dropwise over a 1-hr period. Heating was continued until gas evolution (sulfur dioxide and hydrogen chloride) had ceased (approximately 9–10 hr). The resultant solution of

camphorsulfonyl chloride in chloroform was converted to camphorsulfonamide without further purification.

In a 5-L, two-necked, round-bottomed flask fitted with a 250-mL dropping funnel and a mechanical stirrer was placed a solution of 1.6 L of reagent-grade ammonium hydroxide solution and the flask was cooled to 0°C in an ice bath. The solution of the crude camphorsulfonyl chloride, prepared in the preceding section, was added dropwise to the ammonium hydroxide solution at 0–10°C over a period of 1 hr. The reaction mixture was warmed to room temperature, stirred for 4 hr, the organic layer separated, and the aqueous layer was extracted with methylene chloride (3 × 250 mL). The combined organic layers were washed with brine (250 mL) and dried over anhydrous magnesium sulfate. Removal of the solvent on the rotary evaporator gave 104.0 g (90%) of the crude camphorsulfonamide (Note 2) and (Note 3).

B. *(−)-(Camphorsulfonyl)imine.* A 1-L, round-bottomed flask is equipped with a 2-in. egg-shaped magnetic stirring bar, a Dean–Stark water separator, and a double-walled condenser containing a mineral oil bubbler connected to an inert gas source. Into the flask are placed 5 g of Amberlyst 15 ion-exchange resin (Note 4) and 41.5 g of the crude (+)-(1*S*)-camphorsulfonamide in 500 mL of toluene. The reaction mixture is heated at reflux for 4 hr. After the reaction flask is cooled, but while it is still warm (40–50°C), 200 mL of methylene chloride is slowly added to dissolve any (camphorsulfonyl)imine that crystallizes. The solution is filtered through a 150-mL sintered glass funnel of coarse porosity an the reaction flask and filter funnel are washed with an additional 75 mL of methylene chloride.

Isolation of the (−)-(camphorsulfonyl)imine is accomplished by removal of the toluene on the rotary evaporator. The resulting solid is recrystallized from absolute ethanol (750 mL) to give white crystals, 34.5–36.4 g (90–95%), mp 225–228°C; $[\alpha]_D$ −32.7° ($CHCl_3$, c 1.9) (Note 5).

C. *(+)-(2R, 8aS)-10-Camphorylsulfonyloxaziridine*. A 5-L, three-necked, round-bottomed Morton flask is equipped with an efficient mechanical stirrer, a 125-mm Teflon stirring blade, a Safe Lab stirring bearing (Note 6), and a 500-mL addition funnel. Into the flask are placed the toluene solution of (−)-(camphorsulfonyl)imine (39.9 g, 0.187 mol) prepared in Step B and a room-temperature solution of 543 g (3.93 mol, 7 equiv based on oxone) of anhydrous potassium carbonate dissolved in 750 mL of water. The reaction mixture is stirred vigorously and a solution of 345 g (0.56 mol, 6 equiv of $KHSO_5$) of oxone dissolved in 1250 mL of water is added dropwise in three portions over 45 min (Note 7) and (Note 8). Completion of the oxidation is determined by TLC (Note 9) and the reaction mixture is filtered through a 150-mL sintered-glass funnel of coarse porosity to remove solids. The filtrate is transferred to a 3-L separatory funnel, the toluene phase is separated and the aqueous phase is washed with methylene chloride (3 × 100 mL). The filtered solids and any solids remaining in the Morton flask are washed with an additional 200 mL of methylene chloride. The organic extracts are combined and washed with 100 mL of saturated sodium sulfite, dried over anhydrous magnesium sulfate for 15–20 min, filtered, and concentrated on the rotary evaporator. The resulting white solid is crystallized from approximately 500 mL of hot 2-propanol to afford, after drying under vacuum in a desiccator, 35.9 g (84%) of white needles, mp 165–167°C, $[\alpha]_D$ +44.6° ($CHCl_3$, c 2.2) (Note 10) and (Note 11).

(−)-(2*S*,8a*R*)-10-(camphorylsulfonyl)oxaziridine is prepared in a similar manner starting from (−)-10-camphorsulfonic acid; mp 166–167°C, $[\alpha]_D$ +43.6° ($CHCl_3$, c 2.2).

2. Notes

1. (1*S*)-(+)-10-Camphorsulfonic acid was purchased from Aldrich Chemical Company, Inc.
2. The crude sulfonamide is contaminated with 5–10% of the (camphorsulfonyl)imine, the yield of which increases on standing.
3. The ^{1}H NMR spectrum of (+)-(1*S*)-10-camphorsulfonamide is as follows: ($CDCl_3$) δ: 0.93 (s, 3 H, CH_3), 1.07 (s, 3 H, CH_3), 1.40–2.50 (m, 7 H), 3.14 and 3.53 (AB quartet, 2 H, CH_2-SO_2, *J* = 15.1), 5.54 (br s, 2 H, NH_2).
4. Amberlyst 15 ion-exchange resin is a strongly acidic, macroreticular resin purchased from Aldrich Chemical Company, Inc.
5. The spectral properties of (–)-(camphorsulfonyl)imine are as follows: ^{1}H NMR ($CDCl_3$) δ: 1.03 (s, 3 H, CH_3), 1.18 (s, 3 H, CH_3), 1.45–2.18 (m, 6 H), 2.65 (m, 1 H), 3.10 and 3.28 (AB quartet, 2 H, CH_2-SO_2, *J* = 14.0); ^{13}C NMR ($CDCl_3$) δ: 19.01 (q, CH_3), 19.45 (q, CH_3), 26.64 (t), 28.44 (t), 35.92 (t), 44.64 (d), 48.00 (s), 49.46 (t), 64.52 (s), 195.52 (s); IR ($CHCl_3$) cm^{-1}: 3030, 2967, 1366. Checkers obtained material having identical melting point and $[\alpha]_D$ –32.3° ($CHCl_3$, c 1.8).
6. The SafeLab Teflon bearing can be purchased from Aldrich Chemical Company, Inc. A glass stirring bearing lubricated with silicone grease is unsatisfactory because the dissolved salts solidify in the shaft, causing freezing.
7. Efficient stirring is important and indicated by a milky white appearance of the solution.
8. Occasionally batches of oxone purchased from Aldrich Chemical Company, Inc., have exhibited reduced reactivity in this oxidation. Oxone exposed to moisture prior to use also gives reduced reactivity in this oxidation. If this occurs, oxone is added until oxidation is complete as determined by TLC (Note 9). Potassium carbonate is added as needed to maintain the pH at approximately 9.0. Oxone stored in the refrigerator under an inert atmosphere has shown no loss in reactivity for up to 6 months.
9. Oxidation is generally complete after addition of the oxone solution. The oxidation is monitored by TLC as follows. Remove approximately 0.5 mL of the toluene solution from the nonstirring solution, spot a 250-•m TLC silica gel plate, elute with methylene chloride, and develop with 10% molybdophosphoric acid in ethanol and heating (camphorsulfonyl) imine R_f = 0.28 and (camphorylsulfonyl)oxaziridine R_f = 0.62. If (camphorsulfonyl)imine is detected, stirring is continued at room temperature until the reaction is complete (see (Note 8)). If the reaction mixture takes on a brownish color after addition of oxone and has not gone to completion after 30 min, the reaction mixture is filtered through a 150-mL sintered-glass funnel of coarse porosity, and the solids are washed with 50 mL of methylene chloride. The aqueous/organic extracts are returned to the 5-L Morton flask and stirred vigorously and 52 g (0.08 mol, 1 equiv $KHSO_5$) of oxone is added over 5 min and stirring continued until oxidation is complete (approximately 10–15 min).
10. The submitters employed a toluene solution of crude imine prepared in Part B and obtained somewhat higher yields (90–95%). However, the checkers obtained yields in this range on one half the scale using isolated sulfonylimine.
11. The spectral properties of (+)-(camphorsulfonyl)oxaziridine are as follows: ^{1}H NMR ($CDCl_3$) δ: 1.03 (s, 3 H, CH_3), 1.18 (s, 3 H, CH_3), 1.45–2.18 (m, 6 H), 2.65 (d, 1 H), 3.10 and 3.28 (AB quartet, 2 H, CH_2-SO_2, *J* = 14.0); ^{13}C NMR ($CDCl_3$) δ: 19.45 (q, CH_3), 20.42 (q, CH_3), 26.55 (t), 28.39 (t), 33.64 (t), 45.78 (d), 48.16 (s), 48.32 (t), 54.07 (s), 98.76 (s). The checkers obtained material (mp 165–167°C) having $[\alpha]_D$ +44.7° ($CHCl_3$, c 2.2).

3. Discussion

Camphorsulfonamide, required for the preparation of the (camphorsulfonyl)imine, was previously prepared in two steps. The first step involved conversion of camphorsulfonic acid to the sulfonyl chloride with PCl_5 or $SOCl_2$. The isolated sulfonyl chloride was converted in a second step to the sulfonamide by reaction with ammonium hydroxide. This modified procedure is more efficient because it transforms camphorsulfonic acid directly to camphorsulfonamide, avoiding isolation of the camphorsulfonyl chloride.

(Camphorsulfonyl)imine has been reported as a by-product of reactions involving the camphorsulfonamide.[2,3,4,5] Reychler in 1898 isolated two isomeric camphorsulfonamides,[2] one of which was shown to be the (camphorsulfonyl)imine by Armstrong and Lowry in 1902.[3] Vandewalle, Van der Eycken, Oppolzer, and Vullioud described the preparation of (camphorsulfonyl)imine in 74% overall yield from 0.42 mol of the camphorsulfonyl chloride.[6] The advantage of the procedure described here is that, by using ammonium hydroxide, the camphorsulfonyl chloride is converted to the sulfonamide in >95% yield.[7] The sulfonamide is of sufficient purity that it can be used directly in the cyclization step, which, under acidic conditions, is quantitative in less than 4 hr. These modifications result in production of the (camphorsulfonyl) imine in 86% overall yield from the sulfonyl chloride.

In addition to the synthesis of enantiomerically pure (camphorylsulfonyl)oxaziridine[7] and its derivatives,[8] the (camphorsulfonyl)imine has been used in the preparation of (−)-2,10-camphorsultam (Oppolzers' auxiliary),[6,9] (+)-(3-oxocamphorysulfonyl) oxaziridine,[10] and the *N*-fluoro-2,10-camphorsultam, an enantioselective fluorinating reagent.[11]

The *N*-sulfonyloxaziridines are an important class of selective, aprotic oxidizing reagents.[12 13 14] Enantiomerically pure *N*-sulfonyloxaziridines have been used in the asymmetric oxidation of sulfides to sulfoxides (30–91% ee),[15] selenides to selenoxides (8–9% ee).[16] disulfides to thiosulfinates (2–13% ee),[5] and in the asymmetric epoxidation of alkenes (19–65% ee).[17,18] Oxidation of optically active sulfonimines ($R^*SO_2N=CHAr$) affords mixtures of *N*-sulfonyloxaziridine diastereoisomers requiring separation by crystallization and/or chromatography.[3]

(+)-(Camphorylsulfonyl)oxaziridine described here is prepared in four steps from inexpensive (1*S*)-(+)- or (1*R*)-(+)-10-camphorsulfonic acid in 77% overall yield.[7] Separation of the oxaziridine diastereoisomers is not required because oxidation is sterically blocked from the exo face of the C-N double bond in the (camphorsulfonyl)imine. In general, (camphorsulfonyl) oxaziridine exhibits reduced reactivity compared to other *N*-sulfonyloxaziridines. For example, while sulfides are asymmetrically oxidized to sulfoxides (3–77% ee), this oxaziridine does not react with amines or alkenes.[7] However, this oxaziridine is the reagent of choice for the hydroxylation of lithium and Grignard reagents to give alcohols and phenols because yields are good to excellent and side reactions are minimized.[19] This reagent has also been used for the stereoselective oxidation of vinyllithiums to enolates.[20]

The most important synthetic application of the (camphorylsulfonyl)oxaziridines is the asymmetric oxidation of enolates to optically active α-hydroxy carbonyl compounds.[14,21,22,23,24]

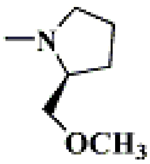
Chiral, nonracemic α-hydroxy carbonyl compounds have been used extensively in asymmetric synthesis, for example, as chiral synthons, chiral auxiliaries, and chiral ligands. This structural array is also featured in many biologically active natural products. This oxidizing reagent gives uniformly high chemical yields regardless of the counterion, and stereoselectivities are good to excellent (50–95% ee).[9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24] Since the configuration of the oxaziridine three-membered ring controls the stereochemistry, both α-hydroxy carbonyl optical isomers are readily available. Representative examples of the asymmetric oxidation of prochiral enolates by (+)-(2*R*,8a*S*)-camphorylsulfonyl)oxaziridine are given in Tables I and II.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 110
- Org. Syn. Coll. Vol. 9, 212

TABLE I

ASYMMETRIC OXIDATION OF LITHIUM ENOLATES OF ESTERS AND AMIDES USING (+)-(2*R*,8a*S*)-10-(CAMPHORYLSULFONYL)OXAZIRIDINE

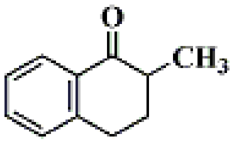
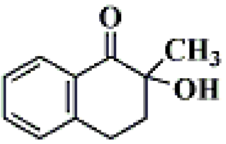
	RC(R')=C(OLi)X					Product		
Entry	R	R'	X	Cosolvent	Temp. (°C)	Yield (%)[a]	% ee (Config.)	Ref.
1	Ph	H	$OCMe_3$	—	–90	82	71 (*R*)	21
2	$PhCH_2$	H	OMe	—	–90	73	58 (*R*)	21
				HMPA	–90	63	85 (*R*)	
3	Ph	Me	OMe	—	–78	61	45 (*R*)	21
4	Ph	H	NC_4H_8	—	–78	70	30 (*S*)	21
				HMPA	–78	74	50 (*R*)	
5	Ph	Me	NC_4H_8	—	–78	40	35 (*S*)	21
				HMPA	–78	35	20 (*R*)	
6	Ph	Me		—	–78	53	48 (*S*)	23
7				HMPA	–78	65	89 (*S*)	

[a]Isolated yields.

TABLE II

ASYMMETRIC OXIDATION OF KETONE-DERIVED ENOLATES USING (+)-(2*R*,8a*s*)-10-(CAMPHORYLSULFONYL)OXAZIRIDINE

	α-Hydroxy Ketone

Entry	Ketone	Base/ Cosolvent	Temp. (°C)	Yield (%)[a]	% ee (Config.)	Ref.
1	$PhC(O)CH_2Ph$	LDA	0	70	68 (*S*)	22
2		LDA/ HMPA	0	64	6 (*S*)	
3		NHMDS[b]	–78	84	95 (*S*)	
4	$PhC(O)CH_2Me$	LDA	0	51	43 (*S*)	22
5		NHMDS	–78	73	62 (*S*)	
6	$Me_3CC(O)CH_2Me$	LDA	0	55	32 (*R*)	25
7		NHMDS	–78	71	89 (*R*)	
8	$PhCH_2C(O)Me$	NHMDS	–78	70	40 (*S*)	25
9		NHMDS/ HMPA	–78	76	76 (*R*)	25
	 					
10		LDA	0	75	30 (*R*)	25
11		NHMDS	0	80	16 (*R*)	25

[a]Isolated yields.

[b]Bis (trimethylsilyl) amide.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfonyl chloride

brine

(+)-(2R,8aS)-10-(Camphorylsulfonyl)oxaziridine

4H-4A,7-Methanooxazirino[3,2-i][2,1]benzisothiazole, tetrahydro-9,9-dimethyl-, 3,3-dioxide, [4aS-(4aα,7α,8aR*)]

(−)-(Camphorsulfonyl)imine

(camphorsulfonyl)imine

(−)-(2S,8aR)-10-(camphorylsulfonyl)oxaziridine

(−)-10-camphorsulfonic acid

sulfonamide

camphorsulfonamides

(−)-2,10-camphorsultam

(+)-(3-oxocamphorysulfonyl) oxaziridine

N-sulfonyloxaziridines

N-sulfonyloxaziridine

(1S)-(+)- or (1R)-(+)-10-camphorsulfonic acid

(camphorylsulfonyl)oxaziridines

α-hydroxy carbonyl

(+)-(2R,8aS)-camphorylsulfonyl)oxaziridine

ethanol (64-17-5)

potassium carbonate (584-08-7)

hydrogen chloride (7647-01-0)

sodium sulfite (7757-83-7)

thionyl chloride (7719-09-7)

chloroform (67-66-3)

oxone (37222-66-5)

sulfur dioxide (7446-09-5)

toluene (108-88-3)

2-propanol (67-63-0)

ammonium hydroxide (1336-21-6)

methylene chloride (75-09-2)

lithium (7439-93-2)

magnesium sulfate (7487-88-9)

oxaziridine

camphorsulfonic acid (5872-08-2)

camphorsulfonyl chloride (6994-93-0)

Molybdophosphoric acid (51429-74-4)

camphorsulfonamide

(camphorylsulfonyl)oxaziridine, (+)-(camphorsulfonyl)oxaziridine, (+)-(Camphorylsulfonyl) oxaziridine, (camphorsulfonyl)oxaziridine, (+)-(2R, 8aS)-10-Camphorylsulfonyloxaziridine (104322-63-6)

sulfonylimine

(+)-(1S)-camphorsulfonamide, (+)-(1S)-10-Camphorsulfonamide (60933-63-3)

(1S)-(+)-10-Camphorsulfonic acid (3144-16-9)

N-fluoro-2,10-camphorsultam

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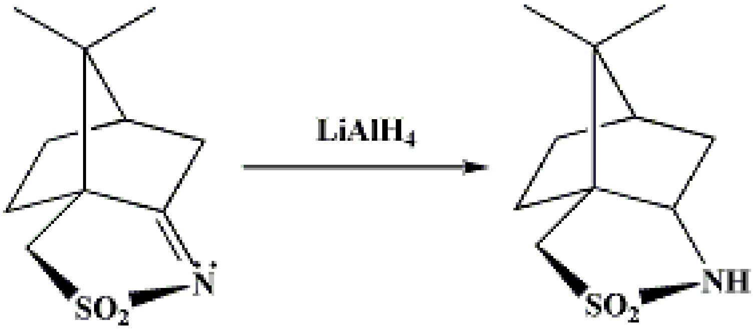
Organic Syntheses, CV 8, 110

(–)-D-2,10-CAMPHORSULTAM

[3*H*-3a,6-Methano-2,1-benzisothiazole, 4,5,6,7-tetrahydro-8,8-dimethyl-2,2-dioxide, (3a*S*)-]



Submitted by Michael C. Weismiller, James C. Towson, and Franklin A. Davis[1].
Checked by David I. Magee and Robert K. Boeckman, Jr..

1. Procedure

(–)-2,10-Camphorsultam. A dry, 2-L, three-necked, round-bottomed flask is equipped with a 1.5-in egg-shaped Teflon stirring bar, a 250-mL addition funnel, and a 300-mL Soxhlet extraction apparatus equipped with a mineral oil bubbler connected to an inert-gas source. The flask is charged with 600 mL of dry tetrahydrofuran (THF) (Note 1) and 6.2 g (0.16 mol) of lithium aluminum hydride (Note 2). Into the 50-mL Soxhlet extraction thimble is placed 35.0 g (0.16 mol) of (–)-(camphorsulfonyl)imine (Note 3) and the reaction mixture is stirred and heated at reflux. After all of the (camphorsulfonyl)imine has been siphoned into the reaction flask (3–4 hr), the mixture is allowed to cool to room temperature. The unreacted lithium aluminum hydride is cautiously hydrolyzed by dropwise addition of 200 mL of 1 *N* hydrochloric acid via the addition funnel (Note 4). After the hydrolysis is complete the contents of the flask are transferred to a 1-L separatory funnel, the lower, silver-colored aqueous layer is separated, and the upper layer placed in a 1-L Erlenmeyer flask. The aqueous phase is returned to the separatory funnel and washed with methylene chloride (3 × 100 mL). After the reaction flask is rinsed with methylene chloride (50 mL), the organic washings are combined with the THF phase and dried over anhydrous magnesium sulfate for 10–15 min. Filtration through a 300-mL sintered-glass funnel of coarse porosity into a 1-L round-bottomed flask followed by removal of the solvent on a rotary evaporator gives 33.5 g (95%) of the crude (–)-2,10-camphorsultam. The crude sultam is placed in a 250-mL Erlenmeyer flask and crystallized from approximately 60 mL of absolute ethanol. The product is collected on a 150-mL sintered-glass funnel of coarse porosity and dried in a vacuum desiccator to give 31.1 g (88%) of the pure sultam. A second crop of crystals can be gained by evaporating approximately half the filtrate; the residue is crystallized as above to give 1.4 g (4%). The combined yield of

white crystalline solid, mp 183–184°C, $[\alpha]_D$ –30.7° ($CHCl_3$, c 2.3) is 92% (Note 5) and (Note 6).

2. Notes

1. Tetrahydrofuran (Aldrich Chemical Company, Inc.) was distilled from sodium benzophenone.
2. Lithium aluminum hydride was purchased from Aldrich Chemical Company, Inc.
3. (–)-(Camphorsulfonyl)imine, [(7*S*)-(–)-10,10-dimethyl-5-thia-4-azatricyclo [5.2.1.0^{3,7}]dec-3-ene 5,5-dioxide] was prepared by the procedure of Towson, Weismiller, Lal, Sheppard, and Davis, *Org. Synth., Coll. Vol. VIII*, **1993**, 104.
4. The addition must be very slow at first (1 drop/5 sec) until the vigorous reaction has subsided.
5. The NMR spectrum of (–)-2,10-camphorsultam is as follows: ^{1}H NMR ($CDCl_3$) δ: 0.94 (s, 3 H, CH_3), 1.14 (s, 3 H, CH_3), 1.33 (m, 1 H), 1.47 (m,, 1 H), 1.80–2.05 (5 H), 3.09 (d, 1 H, *J* = 14), 3.14 (d, 1 H, *J* = 14), 3.43 (m, 1 H), 4.05 (br s, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ: 20.17 (q, CH_3), 26.51 (t), 31.55 (t), 35.72 (t), 44.44 (d), 47.15 (s), 50.08 (t), 54.46 (s), 62.48 (d).
6. Checkers obtained material having the same mp (183–184°C) and $[\alpha]_D$ –31.8° ($CHCl_3$, *c* 2.3).

3. Discussion

(–)-2,10-Camphorsultam was first prepared by the catalytic hydrogenation of (–)-(camphorsulfonyl)imine over Raney nickel.[2] Lithium aluminum hydride reduction was used by Oppolzer and co-workers in their synthesis of the sultam.[3,4] However, because of the low solubility of the sultam in tetrahydrofuran, a large amount of solvent was required.[4] In the procedure described here the amount of solvent is significantly reduced by using a Soxhlet extractor to convey the imine slowly into the reducing medium.[5]

Oppolzer's chiral auxiliary,[6] (–)-2,10-camphorsultam, is useful in the asymmetric Diels–Alder reaction,[3,4] and for the preparation of enantiomerically pure β-substituted carboxylic acids[7] and diols,[8] in the stereoselective synthesis of Δ^2-isoxazolines,[9] and in the preparation of *N*-fluoro-(–)-2,10-camphorsultam, an enantioselective fluorinating reagent.[10]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium benzophenone

(–)-(Camphorsulfonyl)imine

(camphorsulfonyl)imine

(–)-2,10-camphorsultam

(–)-D-2,10-CAMPHORSULTAM

3H-3a,6-Methano-2,1-benzisothiazole, 4,5,6,7-tetrahydro-8,8-dimethyl-2,2-dioxide, (3aS)-

N-fluoro-(–)-2,10-camphorsultam

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

Raney nickel (7440-02-0)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

Tetrahydrofuran, THF (109-99-9)

lithium aluminum hydride (16853-85-3)

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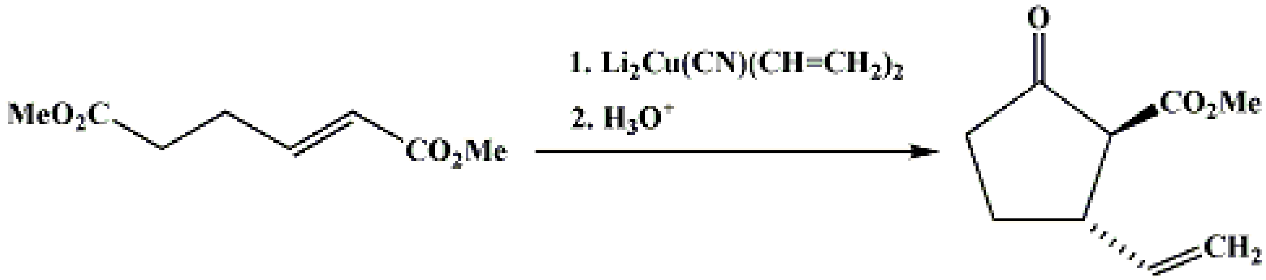
Organic Syntheses, CV 8, 112

CONJUGATE ADDITION–CYCLIZATION OF A CYANOCUPRATE: 2-CARBOMETHOXY-3-VINYLCYCLOPENTANONE

[Cyclopentanecarboxylic acid, 2-ethenyl-5-oxo-, methyl ester]



Submitted by William A. Nugent and Frank W. Hobbs, Jr.[1].
Checked by David J. Wustrow and Andrew S. Kende.

1. Procedure

A. *Dimethyl (E)-2-hexenedioate.*[2] A 100-mL, one-necked, round-bottomed flask is capped by a septum, swept with dry nitrogen and flame-dried. The flask is charged with methyl acrylate (50 mL, 0.55 mol, (Note 1)), then anhydrous lithium tetrafluoroborate (9 g, 0.096 mol, (Note 2)), and finally tetrakis(acetonitrile)palladium tetrafluoroborate (1.33 g, 0.003 mmol, (Note 3)). The mixture is stirred briefly until homogeneous. It is warmed under nitrogen in a 40°C oil bath for 72 hr (Note 4) and then allowed to cool to room temperature. The mixture is added to saturated aqueous sodium bicarbonate (100 mL) and extracted with ether (3 × 50 mL). The combined ether extracts are dried over anhydrous magnesium sulfate, filtered, and concentrated to an oil with a rotary evaporator. The residue is distilled through a 10-cm Vigreux column to give dimethyl (*E*)-2-hexenedioate (38.6 g, 81%, (Note 5)) as a colorless liquid, bp 100°C (1.1 mm).

B. *2-Carbomethoxy-3-vinylcyclopentanone.* A 1-L, three-necked, round-bottomed flask is fitted with a 125-mL pressure-equalizing addition funnel capped with a septum, an overhead stirrer, and a septum. The apparatus is flame-dried and purged with dry nitrogen. The flask is charged through the addition funnel with tetravinyltin (12.48 g, 0.055 mol, (Note 6)) and anhydrous ether (250 mL). The solution is cooled to 0°C under nitrogen, and low-halide methyllithium in ether (133 mL, 1.5 *M*, 0.20 mol, (Note 7)) is slowly added directly by syringe to the stirred solution. After 15 min, the vinyllithium mixture is cooled in a dry ice–acetone bath to −78°C for 20 min. The septum on one neck

is briefly removed, and copper(I) cyanide (9.31 g 0.107 mol, (Note 8)) is added all at once. The septum is replaced by a low-temperature thermometer in an adapter. The bath and reaction are allowed to warm under nitrogen slowly, with stirring, so that the internal temperature is −30°C after 1 hr (Note 9). The addition funnel is charged with dimethyl (*E*)-2-hexenedioate (6.89 g, 0.040 mol) and anhydrous ether (16 mL). The contents of the addition funnel are added dropwise over 30 min to the cuprate at −30°C, and stirring is continued under the nitrogen atmosphere for an additional 30 min at that temperature. A mixture of saturated aqueous ammonium chloride (80 mL) and water (80 mL) is added dropwise over 20 min through the addition funnel while the temperature of the system is allowed to rise. After the mixture is stirred for an additional 90 min it is filtered through a medium-porosity glass frit. The flask and filter cake are rinsed with water (2 × 30 mL) and ether (2 × 30 mL). The ether layer is separated, and the aqueous layer is further extracted with ether (2 × 75 mL). The combined organic layers are washed with water (25 mL), dried over anhydrous magnesium sulfate, and concentrated with a rotary evaporator (Note 10). The residue (Note 11) is distilled through a short-path distillation apparatus to afford 2-carbomethoxy-3-vinylcyclopentanone (5.39 g, 80%, (Note 12)) as a colorless liquid, bp 65–70°C at 0.4 mm (Note 13).

2. Notes

1. Reagent-grade methyl acrylate from Fisher Scientific Company, containing *p*-methoxyphenol as inhibitor, was used as received.
2. Anhydrous 98% pure lithium tetrafluoroborate ($LiBF_4$) from Alfa Products, Morton/Thiokol, Inc. was used as received.
3. The palladium complex was purchased from Strem Chemical Company and was used as received. Alternatively, material prepared from palladium sponge and nitrosonium tetrafluoroborate in acetonitrile[3] worked equally well.
4. The grayish precipitate which begins to appear after ca. 40 hr is the 1 : 1 adduct of the product with lithium tetrafluoroborate.
5. Submitters find that the product typically contains 95% of 2-hexenedioates as measured by capillary column GLC (30-m DB17 column, 120°C isothermal). Retention times for the isomeric hexenedioates were (*Z*)-2 (2.44 min), (*Z*)-3 (2.75 min), (*E*)-3 (3.08 min), (*E*)-2 (3.44 min). TLC (30 : 70 ethyl acetate/hexane, UV) for some runs shows, in addition to the product at R_f = 0.36, a weak spot due to an intensely UV-active impurity at R_f = 0.41. The spectra are as follows: ^{1}H NMR ($CDCl_3$) δ: 2.45–2.58 (m, 4 H), 3.69 (s, 3 H), 3.73 (s, 3 H), 5.87 (d, 1 H, *J* = 16), 6.96 (dt, 1 H, *J* = 16, 6); IR (CCl_4) cm^{-1}: (C=O) 1743 s, 1730 s, (C=C) 1661 m.
6. The submitters obtained tetravinyltin from Columbia Organic Chemicals Company; it was used as received. The checkers obtained it from K&K Laboratories, ICN Biomedicals Inc., Plainview, NY. It may also be synthesized by literature methods.[4 5]
7. Low-halide methyllithium in ether from Alfa Products, Morton/Thiokol, Inc. or Aldrich Chemical Company, Inc. was used as received. A single run using methyllithium/lithium bromide complex gave a significantly reduced yield (53%). Use of commercial vinyllithium in tetrahydrofuran gave a product contaminated

with starting dimer, requiring chromatographic purification.
8. Copper (I) cyanide from Alfa Products, Morton/Thiokol, Inc. was used as received. *Caution! Copper(I) cyanide is severely toxic.* Care should be taken not to expose cyanide-containing wastes to strong acid, thus liberating hydrogen cyanide. Prior to disposal, insoluble wastes should be treated overnight with a strong alkaline solution containing calcium hypochlorite.
9. If the internal temperature is allowed to rise too quickly, rapid exothermic cuprate formation can occur with resultant decomposition of the reagent.
10. Tetramethyltin (bp 78°C) is a potentially hazardous side product of this reaction. This workup should therefore be done with gloves in a well-ventilated hood. Most of the tetramethyltin ends up in the condensate from the rotary evaporator; the condensate should be disposed of by incineration.
11. In two cases submitters have observed that the residue separated into two layers. The upper layer consists of a heavy oil apparently because of incomplete washing of the lithium suspension used in manufacturing methyllithium. When this happens it is necessary to remove the oil with a pipette prior to distillation. Failure to do so gives a product that appears pure by TLC but is substantially impure according to elemental analysis (1 % high in carbon).
12. Submitters find that the product is homogeneous by TLC (30 : 70 ethyl acetate/hexane, I_2, R_f = 0.43). Capillary column GLC analysis (30-m DB17 column, 120°C isothermal) is complicated by some thermal decarboxylation on the column. However, using a clean injection port liner and 180°C injection port, 95% of the product is eluted as a single, somewhat broad peak at 3.0-min retention time. The spectra are as follows: ^{1}H NMR ($CDCl_3$) δ: 1.72 (m, 1 H), 2.1–2.6 (m, 3 H), 3.05 (d, 1 H, J = 11), 3.1–3.3 (m, 1 H), 3.75 (s, 3 H), 5.09 (d, 1 H, J = 11), 5.16 (d, 1 H, J = 17), 5.75–5.85 (m, 1 H); IR (CCl_4) cm^{-1}: (C=O) 1762 s, 1735 s, 1662 m, 1618 m; (C=C) 1644 w.
13. The submitters have carried out these steps on twice the scale given here. On that scale their yields for Step A were 91–93%; for step B, 77–85%.
The checkers found that the diastereomeric purity of the product was much greater than 90% based on its 300 MHz ^{1}H and fully decoupled ^{13}C NMR spectra. Based on the proton–proton coupling constant (J = 11), *trans* geometry has been assigned.

3. Discussion

This procedure illustrates a general route to the 3-substituted 2-carbomethoxycyclopentanones, which are versatile intermediates for the preparation of a variety of cyclopentanoid products. For example, the product of this procedure, 2-carbomethoxy-3-vinylcyclopentanone, has been utilized in the synthesis of methyl dihydrojasmonate[6] and 18-hydroxyestrone.[7] This conjugate addition–cyclization approach (utilizing "Gilman reagents" prepared from copper(I) iodide) has been applied[8] to the synthesis of the methyl-, butyl-, *sec*-butyl-, neopentyl-, and phenyl-substituted 2-carbomethoxycyclopentanones. The present procedure takes advantage of the greater stability of higher order cyanocuprates[9] ("Lipshutz reagents") to overcome the moderate yield of the vinyl analog due to cuprate decomposition as reported in earlier studies.[8] With either the Gilman or Lipshutz reagents, Michael addition to dimethyl (*E*)-2-

hexenedioate produces an enolate that undergoes Dieckmann cyclization faster than proton transfer. Therefore, no 4-substituted cyclopentanones are formed. This approach has now been extended to the synthesis of the corresponding cyclopentenones by using dimethyl 2-hexynedioate as the Michael acceptor.[10]

Alternatively, 3-substituted 2-carbomethoxycyclopentanones have been prepared by Michael addition to 2-carbomethoxycyclopentenone.[11,12,13] However, this Michael acceptor is unstable, is difficult to prepare, and polymerizes in the presence of many nucleophiles.[12] A longer synthesis of 2-carbomethoxy-3-vinylcyclopentanone has been reported.[6] The general route to 2-carbomethoxy-3-vinylcyclopentanones developed by Trost[14] has the advantage of producing these compounds in optically active form.

Several catalyst systems have been described for the tail-to-tail dimerization of methyl acrylate.[15,16,17,18,19,20] Advantages of the dimerization procedure described here are its mild conditions, efficient use of the catalyst, and high selectivity for the Δ^2 isomer. Tetrakis(acetonitrile)palladium tetrafluoroborate, $Pd(NCMe)_4(BF_4)_2$, also efficiently catalyzes dimerization of ethyl acrylate and methyl methacrylate. The presence of lithium tetrafluoroborate in the reaction mixture increases the rate of the reaction and prolongs catalyst life. Dimerization of methyl acrylate can be effected without lithium tetrafluoroborate if the reaction is performed in nitromethane.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

18-hydroxyestrone

ethyl acetate (141-78-6)

ether (60-29-7)

ammonium chloride (12125-02-9)

acetonitrile (75-05-8)

sodium bicarbonate (144-55-8)

hydrogen cyanide (74-90-8)

nitrogen (7727-37-9)

copper(I) cyanide, Copper (I) cyanide (544-92-3)

carbon (7782-42-5)

palladium sponge (7440-05-3)

ethyl acrylate (140-88-5)

Nitromethane (75-52-5)

copper(I) iodide (7681-65-4)

methyl acrylate (96-33-3)

magnesium sulfate (7487-88-9)

calcium hypochlorite (7778-54-3)

Tetrahydrofuran (109-99-9)

hexane (110-54-3)

Methyllithium (917-54-4)

p-methoxyphenol (150-76-5)

vinyllithium (917-57-7)

methyl methacrylate (80-62-6)

nitrosonium tetrafluoroborate (14635-75-7)

cyanocuprate

tetramethyltin (594-27-4)

2-Carbomethoxy-3-vinylcyclopentanone, Cyclopentanecarboxylic acid, 2-ethenyl-5-

oxo-, methyl ester (75351-19-8)

lithium tetrafluoroborate (14283-07-9)

tetrakis(acetonitrile)palladium tetrafluoroborate

tetravinyltin (1112-56-7)

dimethyl 2-hexynedioate

2-carbomethoxycyclopentenone

Dimethyl (E)-2-hexenedioate (113327-79-0)

methyl dihydrojasmonate

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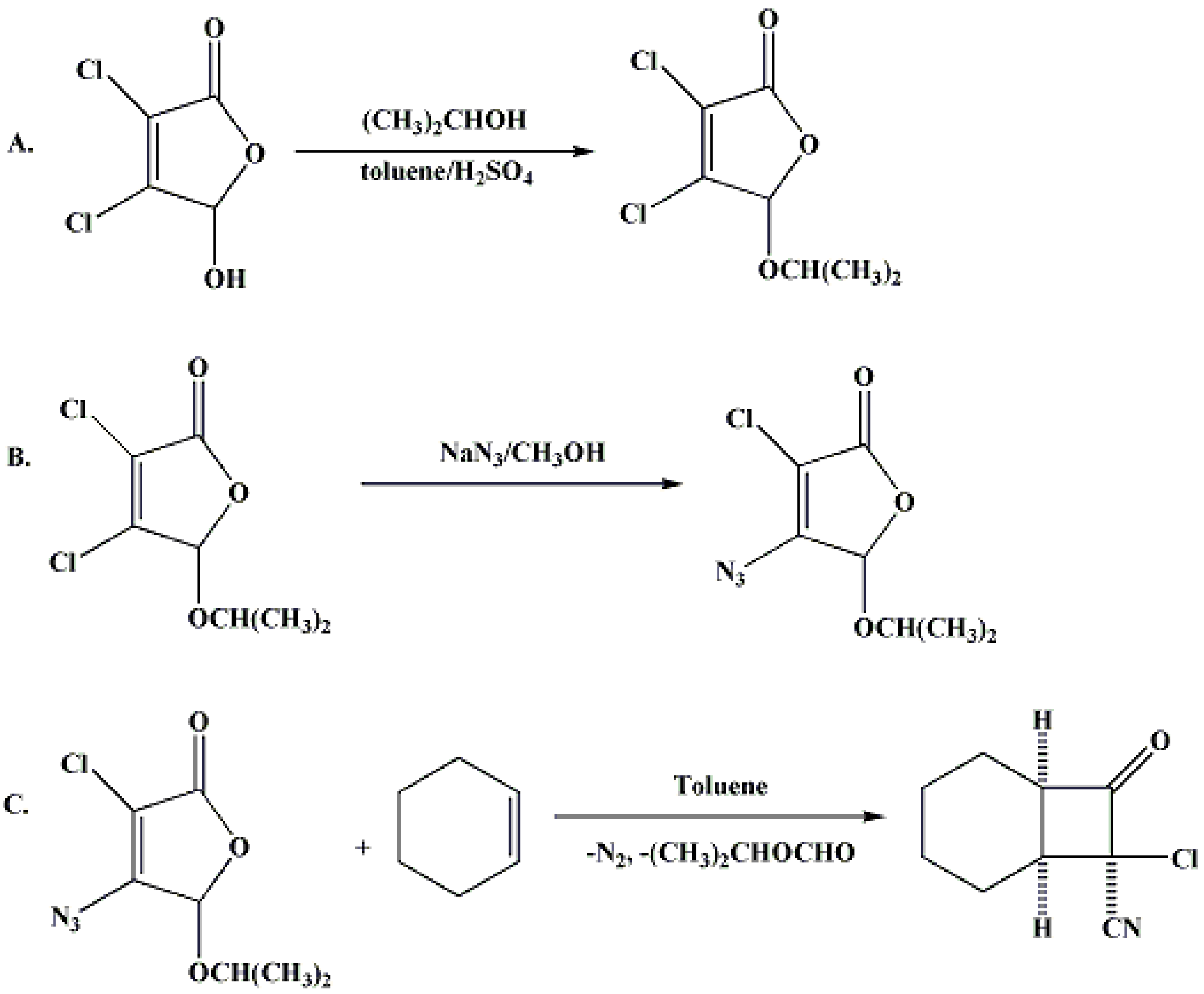
Organic Syntheses, CV 8, 116

7-CHLORO-7-CYANOBICYCLO[4.2.0]OCTAN-8-ONE

[(Prepared from Chlorocyanoketene) (Bicyclo[4.2.0]octane-7-carbonitrile, 7-chloro-8-oxo-, (1α,6α,7β)-)]



Submitted by Paul L. Fishbein and Harold W. Moore[1].
Checked by Steven Wolff and David L. Coffen.

1. Procedure

A. *3,4-Dichloro-5-isopropoxy-2(5H)-furanone.*[2] A 1-L, round-bottomed flask equipped with a Dean–Stark trap, a condenser, an argon bubbler, and a magnetic stirrer is charged with 50.7 g (0.30 mol) of mucochloric acid (Note 1), 46 mL (0.60 mol) of isopropyl alcohol, 300 mL of toluene, and 20 drops of concentrated sulfuric acid. The mixture is heated to reflux with stirring overnight (18 hr) with separation of water. The solution is cooled, washed with saturated sodium bicarbonate solution and brine, and dried with magnesium sulfate. After removal of the solvent under reduced pressure, the residue is distilled to give 60.88 g (96%) of the furanone as a clear colorless liquid (bp 90–91°C, 1.5-mm; lit.[2] mp 23–24°C, bp 109–111°C, 6 mm).

B. *7-Chloro-7-cyanobicyclo[4.2.0]octan-8-one.* To a 250-mL Erlenmeyer flask is added 20.0 g (94.8 mmol) of 3,4-dichloro-5-isopropoxy-2(5*H*)-furanone and 120 mL of methanol. The flask is cooled in an ice bath with stirring and 7.5 g (115.4 mmol) of sodium azide is added. The ice bath is removed after 15 min and the mixture is stirred for an additional 50 min. After dilution with 600 mL of water, the reaction mixture is extracted with one 100-mL and two 50-mL portions of toluene. The combined organic layers are washed with water (2 × 100 mL) and with 100 mL of brine and are dried with magnesium sulfate. TLC analysis (1 : 1 ether:hexane, SiO_2) indicates only one component (R_f = 0.38) and no remaining dichlorofuranone (R_f = 0.45) (Note 3).

A 2-L, three-necked flask fitted with condenser, argon bubbler, thermometer, and addition funnel is charged with 700 mL of toluene (freshly distilled and dried over Linde 4A molecular sieves) and 20 mL (Note 4) of cyclohexene (freshly distilled). With magnetic stirring, the mixture is heated to 105°C and the azidofuranone solution prepared above is added over a period of 20 min (Note 5). On completion, the reaction mixture is heated for an additional 1.25 hr at 105°C. The solution is cooled and concentrated under reduced pressure to yield a yellow-brown residue that is distilled using a short-path apparatus to give 13.3 g (76%) (bp 85–90°C, 0.5 mm) of the cyclobutanone as a very pale-yellow oil that solidifies (mp 34–35°C) on standing at 4°C (Note 6) and (Note 7).

2. Notes

1. Practical-guide mucochloric acid obtained from Aldrich Chemical Company, Inc. (mp 125–128°C) was used. Unless otherwise stated, all reagents and solvents were of commercial grade. The checkers used mucochloric acid obtained from Eastman Organic Chemicals.
2. The spectral properties are as follows: IR (CCl_4) cm^{-1}: 1795, 1652; ^1H NMR ($CDCl_3$) δ: 1.31 (d, 6 H, *J* = 6.2), 4.14 (heptet, 1 H, *J* = 6.2), 5.87 (s, 1 H); MS (EI): 195 (39), 151 (100), 95 (25); MS (Cl): 211 (M^+ + 1), 100. Anal. calcd. for $C_7H_8Cl_2O_3$: C, 39.84; H, 3.82. Found: C, 39.55; H, 3.84.
3. The submitters isolated and characterized the azidofuranone as a white crystalline solid after recrystallization from petroleum ether (bp 35–60°C), with mp 51.5–52.5°C. The spectral properties are as follows: IR (CCl_4) cm^{-1}: 2130, 1814, 1664; ^1H NMR ($CDCl_3$) δ: 1.33 (d, 6 H, *J* = 6.2), 4.17 (heptet, 1 H, *J* = 6.2), 5.99 (s, 1 H); MS (EI): 217 (M^+, 6), 158 (34), 119 (28, $C_3ClNO + H_2O$), 101 (77), 73 (100); MS (Cl): 218 (M^+ + 1, 55), 120 (10, $C_3HClNO + H_2O$), 102 (100). Anal. calcd. for $C_7H_8ClN_3O_3$: C, 38.64; H, 3.71. Found: C, 38.67; H, 3.65. The azidofuranone decomposes at about 80°C, so caution must be exercised when working with it.
4. If an alkene less volatile than toluene is used, 1.1–1.2 equiv of the alkene are satisfactory.
5. The ketene must be generated in situ since it is exceptionally reactive and will undergo self-condensation if permitted.
6. Recrystallization from petroleum ether (35–60°C) in a dry ice/acetone bath afforded colorless crystals with mp 39.5–40.5°C. The spectral properties are as follows: IR (CCl_4) cm^{-1}: 2340, 1838: ^1H NMR ($CDCl_3$) δ: 1.66 (m, 8 H), 3.03 (m, 1 H), 3.96 (m, 1 H); ^{13}C NMR ($CDCl_3$): 20.72, 21.20, 21.41, 24.25, 36.26, 55.33, 64.17, 115.90, 189.91; MS (EI): 183 (M^+, 6), 148 (46), 119 (13), 109 (33), 81 (100); MS (Cl): 184 (M^+ + 1, 84), 156 (100). Anal. calcd. for $C_9H_{10}ClNO$: C, 58.87; H, 5.49. Found: C, 58.58; H, 5.71.
7. Since chlorocyanocyclobutanones are readily hydrolyzed, protic recrystallization solvents and silica gel chromatography should be avoided. Short-path distillation is the method of choice for the purification of most of the cyclobutanones.

3. Discussion

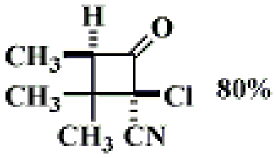
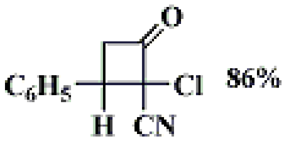
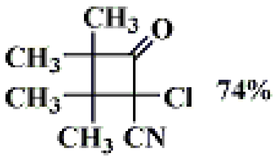
Chlorocyanoketene has been prepared previously by the thermal decomposition of the pseudomethyl ester of the azidofuranone.[3 4 5] This azide has been used extensively without complication. However, all azides are capable of detonation. The ratio (C + O/N) has been suggested as a threshold value for detonation, which may occur when this ratio is lower than 3:1.[6] The ratio for the previously used azide is 2.7, while that for the isopropyl analog is 3.3:1.

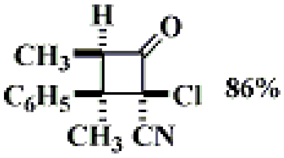
The synthesis of chlorocyanoketene presented here has advantages over other routes such as dehydrohalogenation of the appropriate acid chloride.[7] The most obvious advantage is that the ketene is generated slowly during thermolysis. Thus, its concentration is always low. In addition, since it is generated by pyrolytic means, the presence of *tert*-amines and/or metals is avoided. No other method for the synthesis of chlorocyanoketene has been reported. However, we have found that it can be prepared with difficulty from chlorocyanoacetyl chloride.

Chlorocyanoacetyl chloride can be made from the extremely hygroscopic acid. It is quite unstable, with 1 g decomposing in 1 hr at room temperature. If a mixture of an imine and triethylamine is treated with the acyl chloride, only a dark tar is obtained. However, if the acyl chloride is first treated with the imine, the reaction allowed to subside, and the mixture then treated with triethylamine, the resulting 2-azetidinone is formed in 63% yield. This is in comparison with the 96% yield obtained by using the azidofuranone.

Other cyclobutanones that can be made with chlorocyanoketene and their respective yields are shown in Table I.

TABLE I
OTHERCYCLOBUTANONES FROMCHLOROCYANOKETENE[4c]

	80%
	86%
	74%



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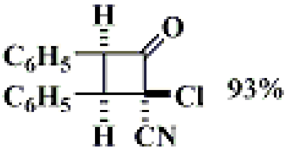

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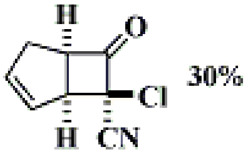

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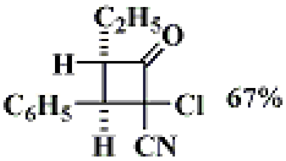

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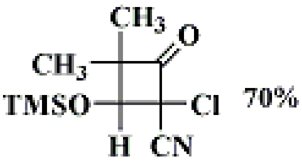

70%

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

brine

SiO_2

Bicyclo[4.2.0]octane-7-carbonitrile, 7-chloro-8-oxo-, (1α,6α,7β)-)

sulfuric acid (7664-93-9)

methanol (67-56-1)

ether (60-29-7)

sodium bicarbonate (144-55-8)

Cyclohexene (110-83-8)

toluene (108-88-3)

isopropyl alcohol (67-63-0)

sodium azide (26628-22-8)

magnesium sulfate (7487-88-9)

hexane (110-54-3)

triethylamine (121-44-8)

2-azetidinone (930-21-2)

7-Chloro-7-cyanobicyclo[4.2.0]octan-8-one (89937-15-5)

Chlorocyanoketene

mucochloric acid

azidofuranone

chlorocyanoacetyl chloride

3,4-Dichloro-5-isopropoxy-2(5H)-furanone (29814-12-8)

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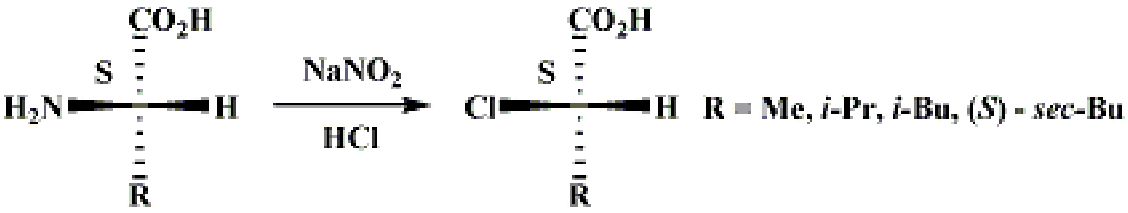
(*S*)-2-CHLOROALKANOIC ACIDS OF HIGH ENANTIOMERIC PURITY FROM (*S*)-2-AMINO ACIDS: (*S*)-2-CHLOROPROPANOIC ACID

[Propanoic acid, 2-chloro-, (*S*)-]



Submitted by Bernhard Koppenhoefer and Volker Schurig[1].
Checked by G. Nagabhushana Reddy and James D. White.

1. Procedure

(S)-2-Chloropropanoic acid. In a 4-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, a 500-mL dropping funnel, and a two-necked adapter fitted with a thermometer and a reflux condenser (Note 1), 89.1 g (1 mol) of (*S*)-alanine (Note 2) is dissolved in 1300 mL of 5 *N* hydrochloric acid (Note 3). The mixture is cooled to 0°C in an ice/sodium chloride bath (Note 4) and a precooled solution of 110 g (1.6 mol) of sodium nitrite in 400 mL of water is added dropwise at a rate of about 2 mL/min under vigorous stirring and efficient cooling so that the temperature of the reaction mixture is kept below 5°C. After 5 hr, the bath is removed and the reaction is allowed to stand overnight at room temperature (Note 5). The reflux condenser is connected with a water aspirator and the flask is carefully evacuated with stirring for 3 hr to remove nitrogen oxides, whereupon the color changes from yellowish brown to pale yellow. While the mixture is stirred vigorously, 100 g of solid sodium carbonate is added carefully in small portions so as to prevent excessive foaming. The reaction mixture is extracted with four portions of 400 mL of diethyl ether. The combined ether layers are concentrated to ca. 300 mL using a rotary evaporator at atmospheric pressure. The solution is washed with 50 mL of saturated brine, which thereafter is reextracted with three portions of 100 mL of diethyl ether. The combined ethereal solutions are dried for 10 hr over calcium chloride. The ether is distilled off with a rotary evaporator at atmospheric pressure (bath temperature 40–50°C). The oily residue is transferred into a distillation flask (rinsing the remainder with small portions of ether) and then fractionally distilled at reduced pressure, the main fraction boiling within a range of 2–3°C (i.e., bp 75–77°C at 10 mm) (Note 6) to give 63–71 g (58–65%) of an oil. The colorless oil is sufficiently pure for most purposes (Note 7) and (Note 8). On prolonged standing in a refrigerator, the oil tends to solidify partially or totally, but the white crystals formed have no sharp melting point. This procedure can be employed for other α-amino acids (see Table I and the Discussion).

2. Notes

1. If the procedure is carried out under an atmosphere of nitrogen, oxidation of nitrogen monoxide to nitrogen dioxide is prevented and the reaction mixture remains colorless, but the yield is not improved.

2. The checkers used (*S*)-alanine of 97% optical purity, purchased from Aldrich Chemical Company, Inc. The enantiomeric purities of the (*S*)-amino acids were checked by preparing the corresponding *N*-trifluoroacetylamino acid methyl esters, which are resolved into enantiomers by gas–liquid chromatography on glass capillary columns coated with the chiral stationary phase "Chirasil-Val"[2] (see Table I). For this purpose, an aliquot of the aqueous solution, containing about 0.1–1 mg of the amino acid, is transferred to a 1-mL vial. Water is removed by a stream of nitrogen and the residue is transformed to the methyl ester hydrochloride (15% hydrochloric acid in methanol, 110°C, 30 min) and finally (after drying in a stream of nitrogen) to the *N*-trifluoroacetyl derivative (trifluoroacetic anhydride, 110°C, 10 min). This material is dried and dissolved in dichloromethane for GLPC analysis. The commercially available (*S*)-amino acids alanine, valine, leucine, and isoleucine usually contained only negligible amounts (a few parts/thousand) of the (*R*)-antipode, but occasionally up to 2.5% of the (*R*)-enantiomer has been detected in (*S*)-alanine and (*S*)-valine. The (*R*)-enantiomer is almost completely removed by one recrystallization from water.

3. Concentrated hydrochloric acid is diluted by its own volume with water. Hydrochloric acid (2.4 L, 5 *N*) is employed for the less soluble (*S*)-amino acids valine, leucine, and isoleucine.

4. A precipitate of the amino acid hydrochloride that formed on cooling is dissolved during the reaction.

5. The less soluble chloroalkanoic acids (*R* larger than methyl) separate from the solution as an oil.

6. Sometimes a brownish forerun is observed (bp ≤ 70°C/10 mm for 2-chloropropanoic acid), turning green in a refrigerator and occasionally undergoing vigorous decomposition. It is therefore recommended that distillation be interrupted and the flask containing the forerun removed.

7. Redistillation is recommended; overall yields are given in Table I. Enantiomeric purities were determined after conversion to *tert*-butyl amides (catalyzed by dicyclohexylcarbodiimide, 30 min at 0°C in dichloromethane) by gas–liquid chromatography on Chirasil-Val.[3] The specific rotation is adulterated by traces of water (determined by GLC on Porapak using a thermal conductivity detector) and unidentified brownish impurities. The chiroptical data (see Table I) are taken from double-distilled (*S*)-2-chloroalkanoic acids. Azeotropic removal of water from (*S*)-2-chloro-3-methylbutanoic acid by refluxing for 24 hr with dichloromethane in a water separator, followed by repeated spinning band distillation, yielded specific rotation values of up to –1.79°C.

8. The spectral properties of (*S*)-2-chloropropanoic acid were as follows: ^{1}H NMR ($CDCl_3$) δ: 1.66 (d, 3 H, *J* = 6.7), 4.40 (q, 1 H, *J* = 6.7), 12.0 (s, 1 H; this

signal may be broadened and shifted upfield due to minimal amounts of water); ^{13}C NMR ($CDCl_3$) δ: 20.9, 52.0, 176.0.

3. Discussion

The present procedure is based on the method published by Fu et al.[4] The yields are increased by the very slow addition of an aqueous solution of sodium nitrite to the reaction mixture as well as by a modified workup procedure, specifically, careful removal of nitrogen oxides and the final decomposition of their adducts with carboxylic acids by buffering with sodium carbonate.

By using high-efficiency capillary gas chromatography with chiral stationary phases [i.e., Chirasil-Val[2] and (*R*)-*N*-lauroyl-1-(1-naphthyl)ethylamine;[5] see also recent publications on permethylated β-cyclodextrin[6]], it has been possible for the first time to determine the degree of racemization during the substitution reaction that proceeds with overall retention of configuration because of double inversion via an unstable α-lactone.[7] Thus, the maximum degree of inversion amounts to approximately 2.2%, resulting in a 2-chloroalkanoic acid of ee 95.6% (see Table I) if racemization occurs in the diazotization reaction, and not in the conversion of the free chloroalkanoic acid to the *tert*-butylamide employed for analysis of the enantiomeric composition.[3,5,6] The enantiomeric yields given in Table I represent the lowest values found in various experiments. The degree of racemization at carbon atom 2 is strongly affected by the alkyl group R (see Table I). Racemization is more pronounced in the case of less hindered primary and secondary carbon atoms adjacent to the stereocenter. It is interesting to note that the degree of racemization observed in the diazotization reaction runs parallel to the degree of racemization observed in aqueous solutions of the amino acids at pH 7.6 at elevated temperature.[8]

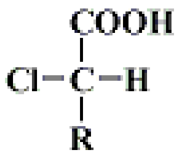
The diazotization in 5 *N* hydrochloric acid is superior to that in aqua regia,[9] where up to 10% inversion has been observed.[10]

The method described may also be used for the preparation of the corresponding (*R*)-2-chloroalkanoic acids when starting from unnatural (*R*)-2-amino acids. For instance, (*R*)-2-aminodecanoic acid has been obtained in high enantiomeric yield by enzymatic cleavage of the racemic *N*-chloroacetyl derivative.[11] For amino acids containing large alkyl side chains, diazotization at higher dilution is recommended. For the synthesis of racemic 2-chloroalkanoic acids, the diazotization method described here appears more convenient than the direct chlorination of alkanoic acids.[12]

2-Chloroalkanoic acids bearing chiral side groups are useful starting materials for the synthesis of chiral alcohols of high enantiomeric purity. Thus, (3*S*)-3-methylpentanol-1 has been obtained from (2*S*,3*S*)-isoleucine via exhaustive lithium aluminum hydride reduction of the chloro acid.[13 14] Similarly, (3*S*)-1,3-butanediol has been obtained from (2*S*,3*S*)-allothreonine.[15] The time-controlled lithium aluminum hydride reduction

of 2-chloroalkanoic acids leads to 2-chloro-1-alkanols (chlorohydrins), which can be cyclized to alkyloxiranes of high enantiomeric purity.[16]

TABLE I
(2*S*)-2-CHLOROALKANOICACIDS



Reactant	Substituent R	Yield (%)	bp (°C/mm)	ee (%) of Chloro Acid[a]	d_4^{20} (g/cm^3)	$[\alpha]_D^{20}$ (°)[e]
(*S*)-Alanine	-CH_3	64 ± 6	75–77/10	95.6[b]	1.265	–13.98
(*S*)-Valine	-$CH(CH_3)_2$	62 ± 5	103–105/10	97.7[b]	1.140	–1.44
(*S*)-Leucine	-$CH_2CH(CH_3)_2$	58 ± 4	113–115/10	95.8[c]	1.082	–31.73
(2*S*)-Isoleucine	(3*S*)-$CH(CH_3)CH_2CH_3$	59 ± 6	111–112/10	98.3[c,d]	1.115	–4.78

[a]In each case the starting amino acid was ≥99.8% optically pure, as shown by gas chromatography of the trifluoroacetyl methyl esters on Chirasil-Val (Note 2).

[b]By gas chromatography on the *tert*-butyl amides on Chirasil-Val (Note 7).

[c]By gas chromatography of the *tert*-butyl amides on (*R*)-*N*-lauroyl-1-(1-naphthyl)ethylamine ([5],[6]).

[d]Diastereomeric excess, referring to (2*R*,3*S*)-2-chloro-3-methylpentanoic acid. Total composition: 99.0% 2*S*,3*S*; 0.8% 2*R*,3*S*; 0.2% 2*S*,3*R*; approximately 0% 2*R*,3*R*. The starting amino acid was contaminated with 0.2% of the 2*S*,3*R*.

[e]Rotations were measured on the neat liquids; specific rotations are given for material of the indicated enantiomeric excess.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 434

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

nitrogen oxides

brine

permethylated β-cyclodextrin

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

alanine, (S)-alanine (56-41-7)

2-chloropropanoic acid (598-78-7)

sodium carbonate (497-19-8)

nitrogen (7727-37-9)

sodium nitrite (7632-00-0)

nitrogen monoxide

nitrogen dioxide (10102-44-0)

dichloromethane (75-09-2)

lithium aluminum hydride (16853-85-3)

isoleucine, (2S)-Isoleucine, (2S,3S)-isoleucine (73-32-5)

leucine, (S)-Leucine (61-90-5)

valine, (S)-valine (72-18-4)

dicyclohexylcarbodiimide (538-75-0)

trifluoroacetic anhydride (407-25-0)

(2S,3S)-allothreonine (28954-12-3)

(S)-2-Chloropropanoic acid, Propanoic acid, 2-chloro-, (S)- (29617-66-1)

(S)-2-chloro-3-methylbutanoic acid

(R)-2-aminodecanoic acid

(3S)-3-methylpentanol-1

(3S)-1,3-butanediol

(2R,3S)-2-chloro-3-methylpentanoic acid

(R)-N-lauroyl-1-(1-naphthyl)ethylamine

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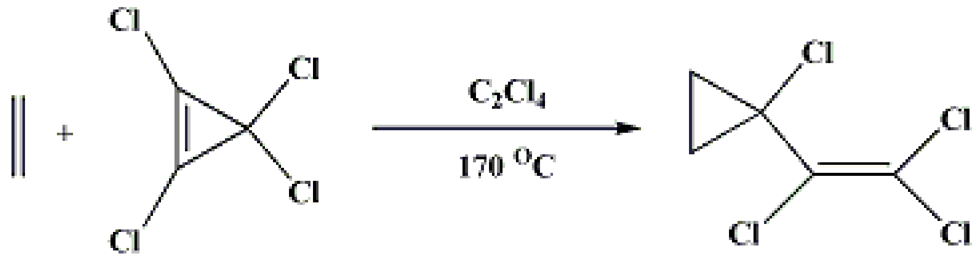
1-CHLORO-1-(TRICHLOROETHENYL) CYCLOPROPANE

[Cyclopropane, 1-chloro-1-(trichloroethenyl)-]



Submitted by Thomas Liese, Frank Jaekel, and Armin de Meijere[1].
Checked by John R. Berry, James S. Piecara, and Bruce E. Smart.

1. Procedure

A 1-L Hastelloy C-276 shaker tube (Note 1) fitted with a temperature sensor, a rupture-disk safety device, and a gas inlet valve attached to an ethylene cylinder is charged with 120.0 g (0.675 mol) of freshly distilled tetrachlorocyclopropene (Note 2), 350 mL of dry tetrachloroethylene (Note 3), and 10 g of anhydrous sodium carbonate (Note 4). The tube is pressurized to 20 atm with ethylene and shaken for 3 hr. The ethylene cylinder is disconnected, and the pressure vessel is gradually heated to 170°C over a 30-min period and is shaken at this temperature for 19.5 hr. The vessel is allowed to cool to room temperature, and the excess ethylene is slowly released and bubbled through a wash bottle containing methylene chloride (Note 5). The light-brown liquid in the shaker tube is decanted and the remaining solid washed twice with 50 mL of methylene chloride. The organic phases are combined and the methylene chloride is removed by distillation. The residual liquid is distilled at water-aspirator vacuum through a 40-cm Vigreux column. The solvent tetrachloroethylene, bp 35°C (27 mm), is collected (Note 6), followed by 104.1–105.6 g (75–76%) of 1-chloro-1-(trichloroethenyl)cyclopropane as a colorless liquid, bp 81–83°C (27 mm) (Note 7).

2. Notes

1. The submitters used a 1-L autoclave lined with Hastelloy C-4. Hastelloy C materials are high nickel alloys. A highly resistant alloy is employed to avoid possible side reactions.
2. Tetrachlorocyclopropene was prepared from sodium trichloroacetate and trichloroethylene.[2,3] It is also available from the Aldrich Chemical Company, Inc., Eastman Organic Chemicals, and the Merck-Schuchardt Company (in Europe).
3. Tetrachloroethylene was obtained from the Aldrich Chemical Company, Inc.

and distilled from phosphorus pentoxide prior to use.
4. Anhydrous sodium carbonate was obtained from the J. T. Baker Chemical Company and dried under vacuum at 130°C.
5. The wash bottle serves to trap any product carried with the ethylene vapors, to monitor and control the release of ethylene pressure and to indicate when no excess pressure remains, and to diminish the release of toxic materials.
6. The receiver was cooled in an ice bath to avoid loss of the tetrachloroethylene distillate.
7. The submitters obtained 111–116 g of product, bp 72–75°C (14–18 mm). The spectral properties of 1-chloro-1-(trichloroethenyl)cyclopropane are as follows; IR (neat) cm^{-1}: 3100 (CH), 3020 (CH), 1585 (C=C), 1415, 1170, 1040, 1015, 940, 910, 875, 800, 750, 645; ^1H NMR ($CDCl_3$) δ: 1.42 (m, 2 H), 1.52 (m, 2 H).

3. Discussion

Tetrachlorocyclopropene has been known for some time to be a reasonably reactive dienophile.[4] Its thermal ring opening to perchlorovinyl carbene is in accord with the behavior of other cyclopropenes under thermolytic conditions,[5] but the efficiency with which this vinyl carbene intermolecularly adds to a wide variety of olefins[6,7] is unprecedented. The resulting 1-chloro-1-(trichloroethenyl)cyclopropanes[6,7] can be reductively dechlorinated to vinylcyclopropanes,[6] transformed into variously substituted cyclopropylacetylenes[7,8] or cyclopropylidenacetates.[9] The simple cyclopropyl derivatives, accessible from the reported 1-chloro-1-(trichloroethenyl)cyclopropane, like methyl 2-chloro-2-cyclopropylidenacetate (see accompanying procedure) and 1-trimethylsilyl-1-(trimethylsilylethynyl)cyclopropane (prepared by reductive silylation with magnesium/chlorotrimethylsilane in tetrahydrofuran[10]), are especially useful building blocks for the construction of complex organic molecules.[11,12,13]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 373

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

magnesium (7439-95-4)

sodium carbonate (497-19-8)

ethylene (9002-88-4)

methylene chloride (75-09-2)

tetrachloroethylene (127-18-4)

Tetrahydrofuran (109-99-9)

trichloroethylene (79-01-6)

sodium trichloroacetate (650-51-1)

CHLOROTRIMETHYLSILANE (75-77-4)

tetrachlorocyclopropene

phosphorus pentoxide (1314-56-3)

1-CHLORO-1-(TRICHLOROETHENYL)CYCLOPROPANE, Cyclopropane, 1-chloro-1-(trichloroethenyl)- (82979-27-9)

perchlorovinyl carbene

Methyl 2-chloro-2-cyclopropylidenacetate (82979-45-1)

1-trimethylsilyl-1-(trimethylsilylethynyl)cyclopropane

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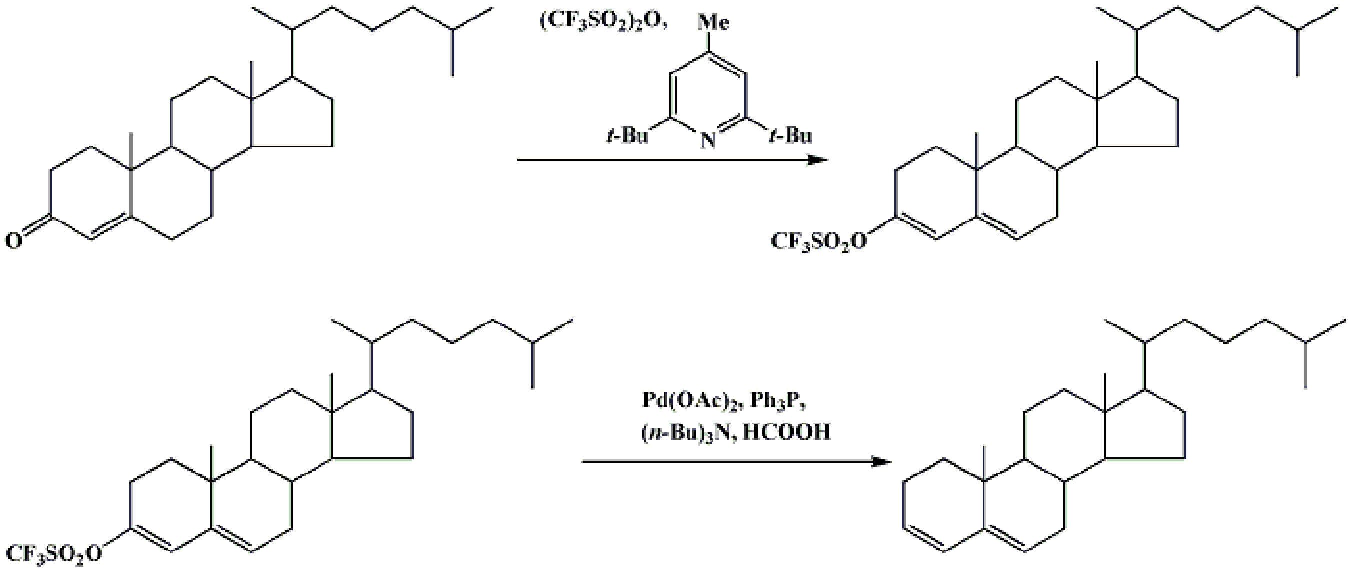
Organic Syntheses, CV 8, 126

PALLADIUM-CATALYZED REDUCTION OF VINYL TRIFLUOROMETHANESULFONATES TO ALKENES: CHOLESTA-3,5-DIENE



Submitted by Sandro Cacchi[1], Enrico Morera[2], and Giorgio Ortar[2].
Checked by Sean Kerwin, Christopher Schmid, and Clayton H. Heathcock.

1. Procedure

A. *Cholesta-3,5-dien-3-yl trifluoromethanesulfonate.* A dry, 250-mL, two-necked, round-bottomed flask, equipped with a magnetic stirring bar, a rubber septum, and a pressure-equalizing 100-mL dropping funnel fitted with a calcium chloride drying tube, is charged with 4.62 g (22.5 mmol) of 2,6-di-*tert*-butyl-4-methylpyridine (Note 1) and 60 mL of dry dichloromethane (Note 2). Then 3.08 mL (18.75 mmol) of trifluoromethanesulfonic anhydride (Note 3) is added rapidly from a syringe and 5.77 g (15 mmol) of cholest-4-en-3-one (Note 4) diluted 40 mL of dry dichloromethane is added through the dropping funnel, dropwise and with stirring, during 15–20 min. The mixture is stirred for an additional 1 hr at room temperature. During this period the solution turns slightly pink and a white precipitate separates. The solvent is removed with a rotary evaporator and the residue is combined with 100 mL of diethyl ether. The white pyridinium trifluoromethanesulfonate salt is filtered off and washed with additional diethyl ether (3 × 50 mL). The ethereal solution is washed with cold 2 *N* hydrochloric acid (2 × 100 mL) and saturated sodium chloride solution (3 × 100 mL), dried over anhydrous potassium carbonate, and concentrated at reduced pressure. The solid residue (7.21–7.40 g) is recrystallized from hexane to give 6.46–6.72 g (83–87%) of cholesta-3,5-dien-3-yl trifluoromethanesulfonate as white crystals (Note 5), mp 125–126°C (Note 6).

B. *Cholesta-3,5-diene.* A 50-mL, two-necked, round-bottomed flask, equipped with a magnetic stirring bar and a reflux condenser with a nitrogen inlet at the top, is charged with 5.00 g (9.68 mmol) of cholesta-3,5-dien-3-yl trifluoromethanesulfonate (1), 6.92 mL (29.03 mmol) of tributylamine (Note 7), 0.043 g (0.19 mmol) of palladium acetate, 0.100 g (0.38 mmol) of triphenylphosphine, and 20.2 mL of *N,N*-dimethylformamide. The mixture is gently flushed with nitrogen for 1–2 min. and capped with a rubber septum. Formic acid, 99%, 0.73 mL (19.42 mmol), is added from a syringe dropwise and with swirling during 2–3 min. The resulting mixture is warmed in an oil bath at 60°C for 1 hr with continuous stirring under nitrogen. During this period the mixture becomes black. The contents of the flask are poured into 50 mL of 2 *N* hydrochloric acid and extracted with two 75-mL portions of ethyl ether. The combined organic phases are then washed with 50 mL of 2 *N* hydrochloric acid, 15 mL of saturated sodium bicarbonate solution, and two 10-mL portions of saturated sodium chloride solution, and are then dried over anhydrous magnesium sulfate. The drying agent is removed by filtration, the ether is evaporated at reduced pressure, and the solid residue (3.92–4.16 g) is purified by open-column chromatography on 100 g of basic aluminum oxide (Note 8) using hexane as eluent to give 3.12–3.22 g of nearly pure cholesta-3,5-diene, which is recrystallized from acetone to give a first crop (2.92–3.00 g) as white needles (Note 9), mp 81.5–82.5°C (lit.[3] mp 79.5–80°C) (Note 6) and a second crop (0.11–0.15 g, 85–88% overall yield), mp 79.5–80.5°C (Note 6).

2. Notes

1. A commercial sample of 2,6-di-*tert*-butyl-4-methylpyridine from Fluka AG was purified through a short column of silica gel by eluting with hexane. Alternatively, it may be prepared according to the procedure reported in *Organic Syntheses.*[4]
2. Reagent-grade dichloromethane is dried by passing over a column of aluminum oxide (activity I).
3. Trifluoromethanesulfonic anhydride from Fluka AG was stirred over phosphorus pentoxide for 18 hr and distilled. It can

also be prepared from trifluoromethanesulfonic acid (Fluka AG) according to the procedure described in *Organic Syntheses.*[5]

4. Cholest-4-en-3-one was purchased from Fluka AG and used without further purification.

5. Spectral data are as follows: ^{1}H NMR (90 MHz, $CDCl_3$) δ: 0.69 (s, 3 H, 13-CH_3), 0.82 (s, 3 H, 10-CH_3), 5.62 (m, 1 H, C-6 H), 6.02 (m, 1 H, C-4 H); MS *m / e*: 516 (M^+).

6. Melting points are uncorrected and were determined with a Köfler hot-stage apparatus.

7. Tributylamine, palladium acetate, triphenylphosphine from Fluka AG and *N*,*N*-dimethylformamide, and formic acid from Farmitalia Carlo Erba Chemicals were used without further purification.

8. Basic aluminum oxide (activity I) is available from Merck & Company, Inc.

9. This compound has the following physical properties: ^{1}H NMR (90 MHz, $CDCl_3$) δ: 0.69 (s, 3 H, 13-CH_3), 0.82 (s, 3 H, 10-CH_3), 5.4 (m, 1 H, C-6 H), 5.59 (m, 1 H, C-3 H), 5.71 (d, 1 H, *J* = 10, C-4 H); $[\alpha]_D$ ($CHCl_3$, 1%) −115° (lit.[3] $[\alpha]_D$ −123°).

3. Discussion

The present preparation illustrates a general and convenient method for a two-step deoxygenation of carbonyl compounds to olefins.[6] Related procedures comprise the basic decomposition of *p*-toluenesulfonylhydrazones,[7] the hydride reduction of enol ethers,[8] enol acetates,[9] enamines,[10] the reduction of enol phosphates (and/or enol phosphorodiamidates) by lithium metal in ethylamine (or liquid ammonia),[11] the reduction of enol phosphates by titanium metal under aprotic conditions,[12] the reduction of thioketals by Raney nickel,[13] and the reduction of vinyl sulfides by Raney nickel in the presence of isopropylmagnesium bromide.[14]

Following our first report on the palladium-catalyzed reaction of vinyl triflates with olefins[15] (Heck-type reaction), oxidative insertion of palladium(0) into the carbon–oxygen bond of easily available vinyl and aryl triflates[16] has proved to be a general method for the generation of σ-vinyl and σ-aryl palladium intermediates that can react with a variety of nucleophiles such as olefins,[15 17 18 19] 1-alkynes,[20] disubstituted alkynes,[21] allenes,[22] dialkyl phosphites,[23] triphenylphosphine,[24] silyloxycyclopropanes,[25] cyanide,[26] carbon monoxide in the presence of alcohols,[27] amines,[27] alkynes,[28] and silyloxycyclopropanes.[29]

Palladium-catalyzed cross-coupling of vinyl and aryl triflates with organotion,[30] organozinc,[31] organoboron,[32] organoaluminum,[33] and organosilicon[34] reagents has also been reported.

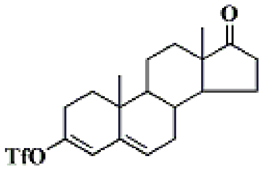
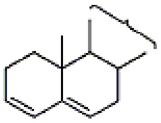
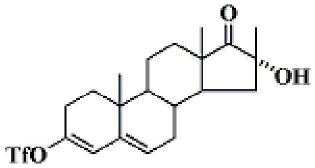
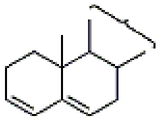
Reviews dealing with some aspects of the palladium chemistry of vinyl and aryl triflates have been published.[35]

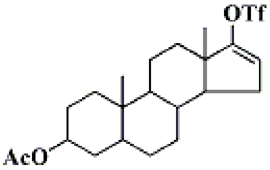
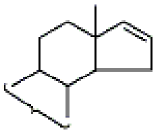
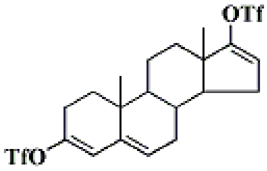
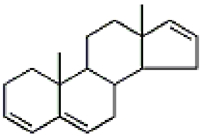
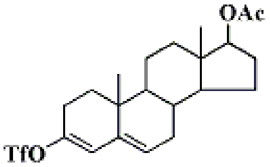
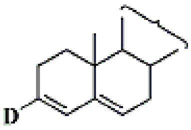
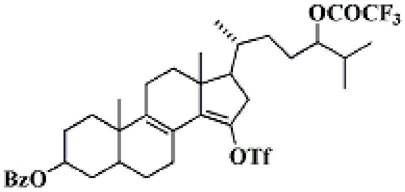
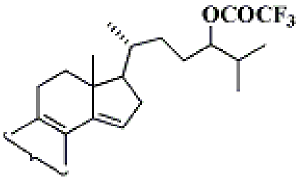
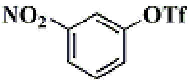
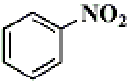
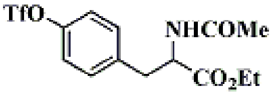
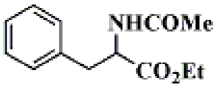
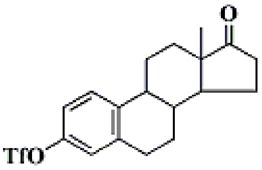
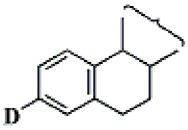
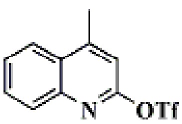
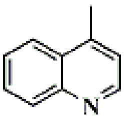
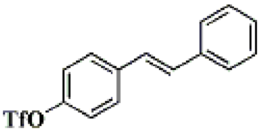
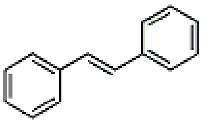
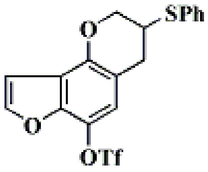
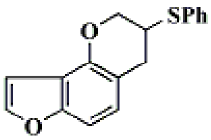
σ-Vinyl palladium triflates are smoothly reduced to alkenes with trialkylammonium formate, usually in high yield. Some advantages of this reduction procedure should be noted. The trialkylammonium formate–palladium reducing system is very simple to use.[36] Clean reduction of vinyl triflates to olefins is observed, and no overreduction is detected. Since vinyl triflates with defined regiochemistry can be easily synthesized,[37] the method is of use in the regioselective synthesis of alkenes and dienes. Ketones, alcohols, ethers, aromatic systems, and presumably a variety of other functional groups are unaffected by the reduction conditions. When the reaction is carried out by using DCOOD, this method allows the regioselective and quantitative introduction of a deuterium atom.

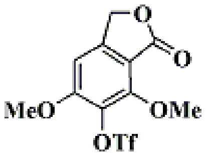
The reaction has been successfully extended to the reduction of aryl triflates[38,39,40,41] and fluoroalkanesulfonates[39,42] to arenes.

Some selected examples of palladium-catalyzed reduction of vinyl and aryl triflates are summarized in Table I.

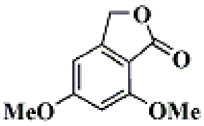
TABLE I
PALLADIUM-CATALYZED REDUCTION OF VINYL AND ARYL TRIFLATES

Substrate	Catalyst	Product	% yield
	$Pd(OAc)_2(PPh_3)_2$		81[6]
	$Pd(OAc)_2(PPh_3)_2$		93[6]

	$Pd(OAc)_2(PPh_3)_2$		85[6]
	$Pd(OAc)_2(PPh_3)_2$		95[6]
	$Pd(OAc)_2(PPh_3)_2$[a]		87[6]
	$Pd(OAc)_2(PPh_3)_2$[a]		95[43]
	$Pd(OAc)_2$/dppf[b]		79[38]
	$Pd(OAc)_2$/dppf[b]		94[38]
	$Pd(OAc)_2$/dppf[a]		87[38]
	$Pd(OAc)_2$/dppf		82[38]
	$Pd(OAc)_2(PPh_3)_2$		91[38]
	$Pd(OAc)_2(PPh_3)_2$		90[40]



$PdCl_2(PPh_3)_2$/dppp[c]



76[41]

[a]DCOOD was used.

[b]DPPF refers to 1, 1'-bis(diphenylphosphino)ferrocene.

[c]DPPP refers to 1,3-bis(diphenylphosphino)propane.

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

p-toluenesulfonylhydrazones

vinyl triflates

silyloxycyclopropanes

σ-Vinyl palladium triflates

$Pd(OAc)_2(PPh_3)_2$

$Pd(OAc)_2$/dppf

$PdCl_2(PPh_3)_2$/dppp

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ether, ethyl ether, diethyl ether (60-29-7)

carbon monoxide (630-08-0)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

formic acid (64-18-6)

nitrogen (7727-37-9)

Raney nickel (7440-02-0)

acetone (67-64-1)

palladium(0) (7440-05-3)

dichloromethane (75-09-2)

lithium (7439-93-2)

magnesium sulfate (7487-88-9)

aluminum oxide (1344-28-1)

isopropylmagnesium bromide (920-39-8)

N,N-dimethylformamide (68-12-2)

hexane (110-54-3)

Cholest-4-en-3-one (601-57-0)

ethylamine (75-04-7)

triphenylphosphine (603-35-0)

tributylamine (102-82-9)

trifluoromethanesulfonic acid (1493-13-6)

Trifluoromethanesulfonic anhydride (358-23-6)

1,3-bis(diphenylphosphino)propane (6737-42-4)

deuterium (7782-39-0)

palladium acetate (3375-31-3)

titanium (7440-32-6)

phosphorus pentoxide (1314-56-3)

Cholesta-3,5-diene (747-90-0)

Cholesta-3,5-dien-3-yl trifluoromethanesulfonate (95667-40-6)

2,6-Di-tert-butyl-4-methylpyridine (38222-83-2)

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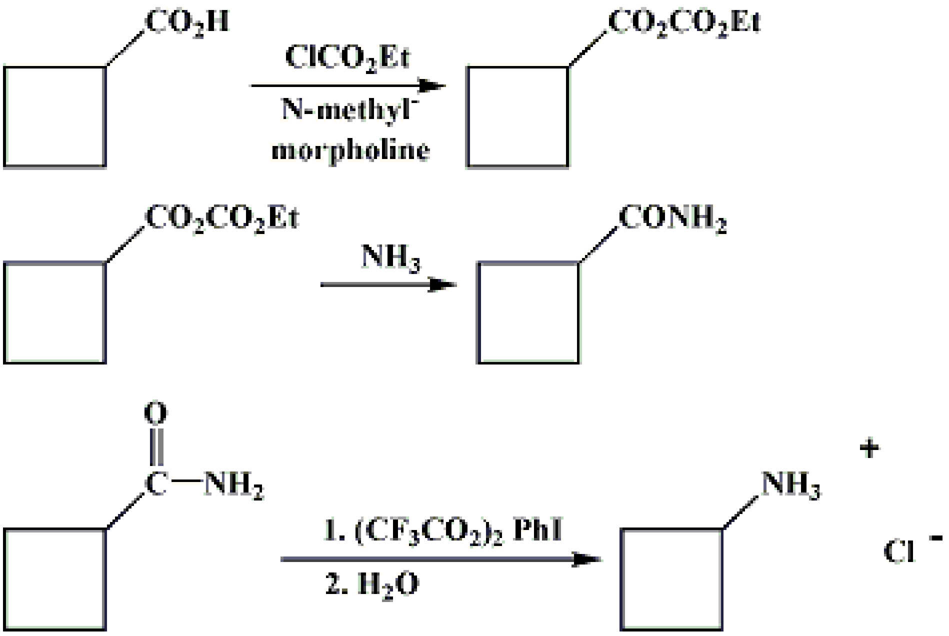
Organic Syntheses, CV 8, 132

HOFMANN REARRANGEMENT UNDER MILDLY ACIDIC CONDITIONS USING [I,I-BIS (TRIFLUOROACETOXY)]IODOBENZENE: CYCLOBUTYLAMINE HYDROCHLORIDE FROM CYCLOBUTANECARBOXAMIDE

[Cyclobutanamine hydrochloride]



Submitted by Merrick R. Almond, Julie B. Stimmel, E. Alan Thompson, and G. Marc Loudon[1].
Checked by C. Eric Schwarta and Edwin Vedejs.

1. Procedure

A. *Cyclobutanecarboxamide.* (See (Note 1).) A 250-mL, round-bottomed flask, equipped with a mechanical stirrer and a drying tube (Drierite), is flame-dried and allowed to cool to room temperature. The flask is equipped with a punctured rubber septum, through which is inserted a –90° thermometer. The flask is subjected to a nitrogen atmosphere by inserting a syringe needle connected to a nitrogen bubbler through the septum along with a second syringe needle used as an outlet. Under a flow of nitrogen the flask is charged via syringe with cyclobutanecarboxylic acid (6.0 g, 59.9 mmol, (Note 2)), 60 mL of dry tetrahydrofuran (Note 2), and *N*-methylmorpholine (6.6 mL, 59.9 mmol, (Note 2)). Stirring is commenced, and the solution is cooled to an internal temperature of –15°C using a dry ice–isopropyl alcohol bath at –20° to –25°C. Ethyl chloroformate (5.7 mL, 59.9 mmol; (Note 2) and (Note 3)) is added and the solution is stirred for 5 min. The addition of ethyl

chloroformate results in an internal temperature rise to +8 to +10°C and the precipitation of a white solid. Following the precipitation the continuously stirred mixture, still in the dry ice–isopropyl alcohol bath, is allowed to reach an internal temperature of −14°C. Anhydrous ammonia (Note 2), introduced into the flask via a syringe needle, is vigorously bubbled through the solution for 10 min with manual stirring; the internal temperature rises abruptly to 25°C. With the flask still in the cooling bath, stirring is continued for an additional 30 min, and the reaction mixture is stored in the freezer at −15°C overnight (Note 4).

The slurry is stirred with tetrahydrofuran (100 mL) at room temperature for 5 min and ammonium salts are removed by suction filtration through a Büchner funnel. After the solids are rinsed with tetrahydrofuran (20 mL), the filtrate is passed through a plug of silica gel (65 g Merck 60 230-400 mesh) in a coarse porosity sintered-glass filter funnel with aspirator suction. The funnel is further washed with acetonitrile (750 mL) and the combined filtrates are evaporated (rotary evaporator) to give a white solid. This material is recrystallized by heating (steam bath) with 8 : 1 ether : ethanol (70 mL); if necessary, ethanol is added dropwise to obtain a homogeneous solution. Cooling to room temperature results in white flakes that are collected by filtration (ether wash), 2.93 g. Two more crops (1.3 g total) are obtained by repeating the process for a total of 4.23 g (71%), mp 152–153°C (lit.[2] 155°C). In several similar runs, the yield of amide was 4.23–4.49 g (71–76%).

B. *Cyclobutylamine hydrochloride.* A 500-mL, round-bottomed flask is equipped with a magnetic stirring bar and covered with aluminum foil. To the flask is added a solution of [I,I-bis(trifluoroacetoxy)iodo]benzene (16.13 g, 37.5 mmol; (Note 5)) in 37.5 mL of acetonitrile, and the resulting solution is diluted with 37.5 mL of distilled deionized water. Cyclobutanecarboxamide (2.48 g, 25 mmol) is added; the amide quickly dissolves. Stirring is continued for 4 hr, and the acetonitrile is removed with a rotary evaporator. The aqueous layer is stirred with 250 mL of diethyl ether; to the stirring mixture is added 50 mL of concd hydrochloric acid (Note 6). The mixture is transferred to a separatory funnel and the layers are separated. The aqueous layer is extracted with two 125-mL portions of ether. The organic fractions are combined and extracted with 75 mL of 2 *N* hydrochloric acid. The aqueous fractions are combined and concentrated with a rotary evaporator using a vacuum pump. Benzene (50 mL, (Note 2)) is added to the residue and the solution is concentrated with the rotary evaporator, again using a vacuum pump. Addition of benzene and concentration is repeated five more times. The crude solid is dried under reduced pressure over sulfuric acid overnight. To the product is added 5 mL of absolute ethanol and 35 mL of anhydrous ether, and the solution is heated at reflux on a steam bath. Ethanol is added slowly to the mixture, with swirling, until all the material is dissolved; the solution is cooled to room temperature. Anhydrous ether is added slowly until crystallization just begins. The flask is placed in the freezer and the product is allowed to crystallize. Filtration of the product and drying overnight under reduced pressure over phosphorus pentoxide yields 1.86–2.06 g of cyclobutylamine hydrochloride (69–77%), mp 183–

185°C (lit.[3 4] 183–184°C).

2. Notes

1. The method used here for preparing the amide gives superior yields to two literature methods that employ the acid chloride as an intermediate.[3,4]
2. Sources and purification of reagents are as follows. Cyclobutanecarboxylic acid, 98%, is from Aldrich Chemical Company, Inc., and is vacuum-distilled before use. Tetrahydrofuran is freshly distilled from sodium–benzophenone under nitrogen. *N*-Methylmorpholine, 99%, is from Aldrich Chemical Company, Inc., and is predried over barium oxide, distilled from ninhydrin, and stored over sodium hydroxide pellets. Ethyl chloroformate, 97%, is from Aldrich Chemical Company, Inc., and is freshly distilled prior to use under a nitrogen atmosphere. Anhydrous ammonia (99.99% min) is from a Matheson lecture bottle. The silica gel used for flash chromatography is Davidson grade 62, 60–200 mesh. Acetonitrile is from Fisher Scientific Company, HPLC grade. Benzene, spectral grade, is from J. T. Baker.
3. The submitters have repeated this preparation with isobutyl chloroformate substituted for ethyl chloroformate with no increase in yield.
4. The submitters purified the product by flash chromatography as follows. Tetrahydrofuran is removed on a rotary evaporator. Silica gel (20 g) and 80 mL of acetonitrile (Note 2) are added to the flask. The resulting slurry is concentrated with a rotary evaporator to a dry solid. The material is scraped from the flask and loaded onto a flash-chromatography column (50-mm diameter) containing 250 g of silica gel, prepared according to the method of Still.[7] The column is eluted with acetonitrile (Note 2) at a flow rate of 0.5 in./min (Note 7). The first 500 mL of eluent is measured with a graduated cylinder and discarded, and then fractions (80 × 23 mL) are collected in test tubes. A small aliquot (5 •L) is taken from every other tube and these aliquots are spotted in successive lanes on a silica gel TLC plate (E. Merck No. 5735), which is developed with acetonitrile. The plate is dried and the product detected by the chlorine/starch-potassium iodide procedure (Note 8). This thin-layer analysis reveals that early fractions from the flash chromatography column contain a small amount of ethyl carbamate impurity at R_f = 0.53; another unidentified impurity (R_f = 0.37) follows. The product cyclobutanecarboxamide emerges next, beginning at about fraction 14 (R_f = 0.26). The product appears as a blue-black spot on a faint blue background. There is some overlap between the second impurity and the product. The fractions containing only product are pooled and concentrated in a 1-L, round-bottomed flask with a rotary evaporator to a white crystalline solid. This product is dried under reduced pressure overnight to yield cyclobutanecarboxamide (4.52 g, 76.1%), mp 156–157.5°C (lit.[2] 155°C).
5. [I,I-Bis(trifluoroacetoxy)iodo]benzene is prepared by dissolving, with heating, a given number of grams of (I,I-diacetoxyiodo)benzene(iodobenzene

diacetate, Aldrich Chemical Company, Inc.; see also *Org. Synth., Coll. Vol. V,* **1973**, 660) in twice that number of milliliters of trifluoroacetic acid that has been distilled from a small amount of phosphorus pentoxide. For example, 40 g of (I,I-diacetoxyiodo)benzene is dissolved in 80 mL of trifluoroacetic acid in an Erlenmeyer flask, which is allowed to stand in a dark drawer. The [I,I-bis(trifluoroacetoxy)iodo]benzene crystallizes and is isolated by suction filtration within 2 hr (53–70% yield). If crystallization does not occur, it can be induced by scratching or seeding. It has been the submitters' experience that if a dark-yellow trifluoroacetic acid supernatant is obtained, the yield of the rearrangement reaction carried out with the resulting reagent is invariably poor; the supernatant solution is normally very lightly colored. If the proportion of trifluoroacetic acid is reduced, a greater weight of crystals is obtained; however, this material gives considerably lower yields in the rearrangement. Upon standing, particularly in the light, [I,I-bis(trifluoroacetoxy)iodo]benzene turns yellow; this reagent also gives poor yields in the rearrangement and yellow reaction mixtures; the reaction mixtures of satisfactory rearrangements are water-white. The reagent should be stored in a dark bottle under nitrogen or argon. The submitters have also found that the rearrangement can be effected with (I,I-diacetoxyiodo)benzene or iodobenzene and two equivalents of trifluoroacetic acid.

6. Hydrochloric acid not only provides the chloride counterion for the final product, but also effects the removal of any uncreated (I,I-bis(trifluoroacetoxy)iodo)benzene as the ether-soluble (I,I-dichloroiodo)benzene (iodobenzene dichloride).

7. A nitrogen regulator has to be set at 8 psi to achieve a pressure sufficient to maintain a flow rate of 0.5 in./min. A slower flow rate results in poor resolution.

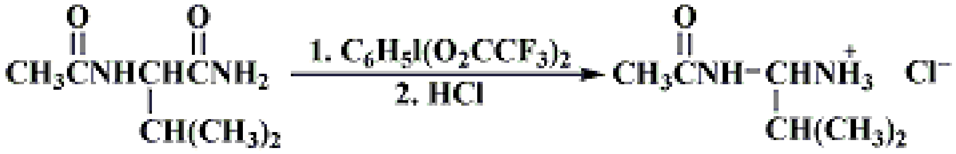
8. The thin-layer plate is chlorinated for 1 min by placing it in a chamber with potassium chlorate to which a few drops of hydrochloric acid are added. The plate is dried in air for 10 min and then sprayed with aqueous 1% starch-1% potassium iodide solution.

3. Discussion

Hypervalent iodine reagents have been used recently for a variety of organic transformations,[8] including α-hydroxylation of ketones.[5,6] (I,I-Dicarboxyiodo)benzene derivatives have also found a variety of uses.[9] The use of (I,I-diacetoxyiodo)benzene for the conversion of amides to carbamates in alcohol solvents was studied by Smith and Baumgarten,[10] and the "acidic Hofmann rearrangement" utilized in this preparation, in which amides are converted directly into the corresponding amines in partially aqueous solution, was developed by Loudon et al.[11,12] and applied to a variety of amides; the mechanism of the rearrangement has also been studied.[13] The rearrangement occurs with retention of stereochemical configuration at the migrating alkyl group,[10,12,14] and the relative rates of rearrangement generally follow the migratory preferences observed in the Lossen rearrangement, Baeyer–Villiger

reaction, and similar migrations to electron-deficient centers.

A particularly interesting application of this reagent is the preparation of "geminal amino amides," a novel class of compounds that have surprising stability in aqueous solution.[15 16 17] These derivatives have found application in the construction of *retro-inverso*-peptides,[18 19] in the design of a novel class of prodrugs,[20 21] and as intermediates in a carboxyl-terminal peptide degradation.[22 23]



Although iodine(III) reagents attack double bonds, the rearrangement of the amide group is, at least in some cases, more rapid than electrophilic attack on alkenes. Thus 3-cyclohexene-1-carboxamide rearranges smoothly to the corresponding amine as long as only one equivalent of [I,I-bis(trifluoroacetoxy)iodo]benzene is used.

The acidic nature of the reagent is important; the trifluoracetic acid liberated in the reaction catalyzes hydrolysis of the intermediate isocyanate, and also ensures that the amine which is formed is protonated and cannot react with the isocyanate to give urea by-products. The reaction can be accelerated by addition of pyridine to an observed pH of about 3.5, and is retarded by added acid or trifluoroacetate ion.[12,13] In the present procedure pyridine was not employed, since the reaction in its absence proceeds with a satisfactory rate.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

starch

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

Benzene (71-43-2)

ether, diethyl ether (60-29-7)

acetonitrile (75-05-8)

sodium hydroxide (1310-73-2)

barium oxide

potassium iodide (7681-11-0)

nitrogen (7727-37-9)

pyridine (110-86-1)

chlorine (7782-50-5)

Benzophenone (119-61-9)

sodium (13966-32-0)

potassium chlorate (3811-04-9)

urea (57-13-6)

Iodobenzene (591-50-4)

ethyl chloroformate (541-41-3)

ethyl carbamate (51-79-6)

Tetrahydrofuran (109-99-9)

iodobenzene dichloride (2401-21-0)

Cyclobutanecarboxylic acid (3721-95-7)

trifluoroacetic acid, Trifluoracetic acid (76-05-1)

Cyclobutanecarboxamide (1503-98-6)

argon (7440-37-1)

ninhydrin (938-24-9)

isobutyl chloroformate (543-27-1)

phosphorus pentoxide (1314-56-3)

Cyclobutylamine hydrochloride, Cyclobutanamine hydrochloride (6291-01-6)

iodobenzene diacetate (3240-34-4)

N-methylmorpholine (109-02-4)

[I,I-BIS(TRIFLUOROACETOXY)]IODOBENZENE, [I,I-bis(trifluoroacetoxy)iodo]benzene, (I,I-bis(trifluoroacetoxy)iodo)benzene (2712-78-9)

(I,I-diacetoxyiodo)benzene (3240-34-4)

(I,I-dichloroiodo)benzene

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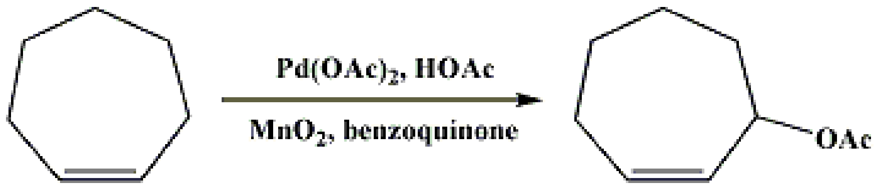
ALLYLIC ACETOXYLATION OF CYCLOALKENES: 2-CYCLOHEPTEN-1-YL ACETATE

[2-Cyclohepten-1-ol, acetate]



Submitted by A. Heumann[1], B. Åkermark[2], S. Hansson[2], and T. Rein[2].
Checked by Joe Guiles and Albert I. Meyers.

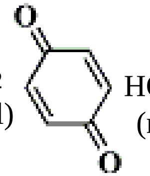
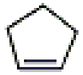
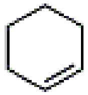
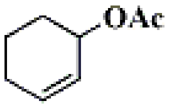
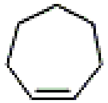
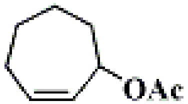
1. Procedure

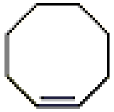
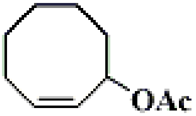
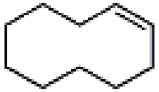
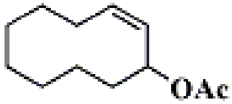
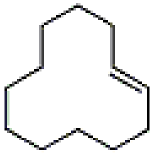
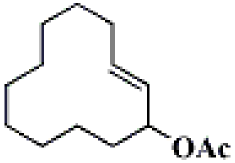
Palladium acetate (1.12 g, 0.005 mol), benzoquinone (2.16 g, 0.02 mol), manganese dioxide (10.44 g, 0.12 mol), and anhydrous acetic acid (250 mL) (Note 1) are placed in a 1-L, round-bottomed flask equipped with a reflux condenser and a magnetic stirring bar. This heterogeneous mixture is equilibrated by efficient stirring for 30–60 min. Cycloheptane (9.61 g, 0.1 mol) (Note 2) is added, and the stirring is continued at 60°C for 28 hr (Note 3). After the solution is cooled to room temperature, 250 mL of pentane/ether (1 : 1) is added and the mixture is stirred for another 30 min. The two-phase mixture is filtered with suction through a Büchner funnel, which contains a layer of Celite (5–10 mm). The Celite layer is washed successively with 250 mL of pentane/ether (1 : 1), 250 mL of water, 100 mL of pentane/ether (1 : 1), and 250 mL of water. After the organic phases are separated, the aqueous phase is extracted 3 times with 250 mL of pentane/ether (1 : 1). The combined organic phases are washed successively with 250 mL of water, 250 mL and then 100 mL of aqueous sodium hydroxide (2 *N*) (Note 4), 250 mL of water, and finally dried over anhydrous magnesium sulfate. After evaporation or distillation of the solvent, the product is purified by distillation (Note 5) to give 2-cyclohepten-1-yl acetate (11.25 g, 73%), bp 61–62°C (5 mm), lit.[3] bp 70°C (6 mm) (Note 6).

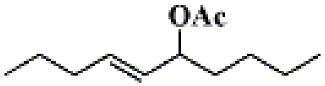
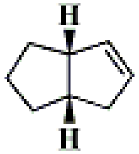
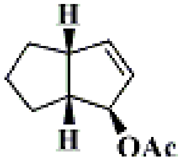
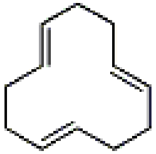
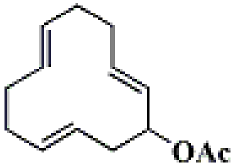
2. Notes

1. All the reagents used are analytical-grade, commercially available products, which are used without further purification. Darkened benzoquinone was purified by sublimation. Activated grade manganese dioxide was used; however, it was not shown that "activation" of manganese dioxide is necessary for the reaction.
2. Reaction conditions for other olefins are shown in Table I.

TABLE I
ALLYLIC ACETOXYLATION OF OLEFINS

Olefin (mmol)	Pd(OAc)$_2$ (mmol)	MnO_2 (mmol)	 (mmol)	HOAc (mL)	Temp. (°C)	Time (hr)	Yield (%)	Product[a]	bp (°C) (mm)	Optimized Conversion (Note 3)
 **(100)** (100)	5	120	20	250	50	16	66		79–82 (58)	>95[b]
 **(100)** (100)	0.5	110	10	250	60	50	77		68 (15)	95
 **(100)** (100)	5	120	20	250	60	28	73		61–62 (5)	98

 (100)	5	200	20	250	60	90	35[c]		63–64 (3)	60	
 (20)	1	24	4	50	60	300	78		Flash (Note 5)	93	
 (20)	1	24	4	50	60	43	72[a]		Flash (Note 5)	77	
(2)	0.1	2.4	0.4	5	60	72	>80[e]		Flash (Note 5)	—	
(20)	1	40	4	50	60	68	74		Flash (Note		

(20)									5)	95	
 (100) (100)	5	120	20	250	50	30	76		60–62 (3)	98	
 (20) (20)	1	40	4	50	40	72	60		Flash (Note 5)	85	

[a]Some of the products contain small amounts of the homoallylic isomer (5% or less).

[b]The conversion was determined by NMR.

[c]The yield was not corrected; yield based on consumed starting material is 39%.

[d]Based on consumed olefin the yield is 90%. The starting olefin was a mixture of approximately 62% *trans* and 32% *cis* isomer together with 6% cyclododecane. After the reaction about 20% of the starting material could be recovered, now as a mixture of 20% *trans*, 50% *cis* olefin, and 30% cyclododecane.

[e]This is a GLC yield using *n*-decane as internal standard.

[f]The product was a 1:1 mixture.

3. The time for optimized conversion has been determined by GLC for all olefins. It is crucial for all reactions to be stopped at optimum conversion, because slow decomposition of the allylic product occurs during the reaction. To obtain optimum yields one should follow the reaction by GLC. Optimized conversion is defined as allylic acetate/allylic acetate plus remaining olefin.
4. *Caution should be observed during the alkaline washings because they are exothermic.*
5. The crude reaction products can easily be purified by distillation or by flash chromatography, with hexane/ether (95 : 5) as eluant.
6. The product exhibits the following NMR spectra: ^{1}H (200 MHz, $CDCl_3$) δ: 1.30–2.30 (m, 8 H), 2.05 (s, 3 H), 5.40 (m, 1 H), 5.65 (m, 1 H), 5.82 (m, 1 H); ^{13}C (50.3 MHz, $CDCl_3$) δ: 21.20, 26.43, 26.48, 28.33, 32.70, 74.13, 131.38, 133.56, 170.24.

3. Discussion

Allylic acetates are usually prepared by esterification from allylic alcohols. However, the corresponding alcohols are often only accessible by the fairly expensive hydride reduction of carbonyl compounds. Consequently, direct allylic functionalization of easily available olefins has been intensively investigated.[4] Most of these reactions involved peroxides[5] or a variety of metal salts.[6,7] However, serious drawbacks of these reactions, (e.g., toxicity of some metals, stoichiometric reaction conditions, or nongenerality) may be responsible for their infrequent use for the construction of allylic alcohols or acetates.

Allylic acetoxylation with palladium(II) salts is well known;[8] however, no selective and catalytic conditions have been described for the transformation of an unsubstituted olefin. In the present system use is made of the ability of palladium acetate to give allylic functionalization (most probably via a palladium–π-allyl complex) and to be easily regenerated by a co-oxidant (the combination of benzoquinone–manganese dioxide). In contrast to copper(II) chloride ($CuCl_2$) as a reoxidant,[8] our catalyst combination is completely regioselective for alicyclic alkenes; with aliphatic substrates, evidently, both allylic positions become substituted. As yet, no allylic oxidation reagent is able to distinguish between the two allylic positions in linear olefins; this advantage is overcome when the allylic acetates are to be used as precursors for π-allyl complexes (e.g., in palladium-catalyzed substitution reactions).

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

acetic acid (64-19-7)

ether (60-29-7)

sodium hydroxide (1310-73-2)

manganese dioxide (1313-13-9)

copper(II) chloride (7758-89-6)

Pentane (109-66-0)

benzoquinone (106-51-4)

magnesium sulfate (7487-88-9)

hexane (110-54-3)

n-DECANE (124-18-5)

cyclododecane (294-62-2)

palladium acetate (3375-31-3)

2-Cyclohepten-1-yl acetate, 2-Cyclohepten-1-ol, acetate (826-13-1)

Cycloheptane (291-64-5)

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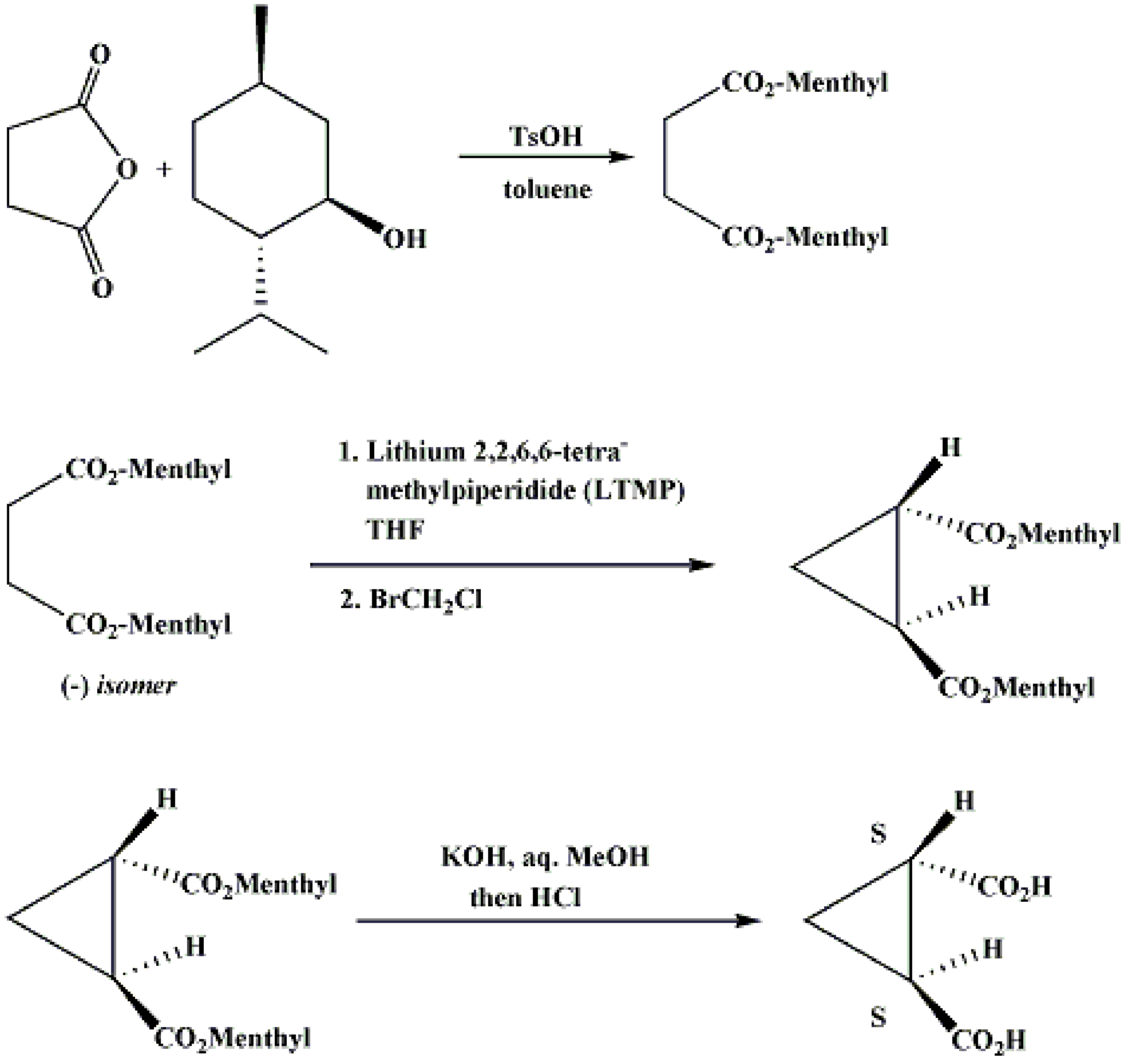
CONDENSATION OF (–)-DIMENTHYL SUCCINATE DIANION WITH 1,ω-DIHALIDES: (+)-(1*S*,2*S*)-CYCLOPROPANE-1,2-DICARBOXYLIC ACID

[1,2-Cyclopropanedicarboxylic acid, (1*S*,2*S*)-(+)-]



Submitted by Kyoji Furuta, Kiyoshi Iwanaga, and Hisashi Yamamoto[1].
Checked by Ichiro Mori and Clayton H. Heathcock.

1. Procedure

A. *(–)-Dimenthyl succinate.* A 300-mL. one-necked, round-bottomed flask is equipped with a magnetic stirrer, a Dean–Stark trap, and a reflux condenser. The flask is charged with 20 g (0.2 mol) of succinic anhydride, 62.5 g (0.4 mol) of *l*-menthol, 250 mg (1.3 mmol) of *p*-toluenesulfonic acid monohydrate, and 150 mL of toluene (Note 1). The mixture is heated under reflux in an oil bath (about 140°C) for 24 hr. During this period the

theoretical amount of water (3.6 mL) is collected. The mixture is allowed to cool to ambient temperature, diluted with 200 mL of hexane, and poured into a mixture of 250 mL of aqueous saturated sodium bicarbonate, 100 mL of methanol, and 200 mL of water. The organic phase is separated and the aqueous phase is extracted twice with 100 mL of hexane. The organic phases are combined, washed once with 200 mL of saturated brine, and dried over sodium sulfate. The solvent is removed with a rotary evaporator, and the resulting crude product is dissolved in 100 mL of methanol. After the solution stands in a refrigerator overnight, colorless crystals appear in the mixture and are collected by filtration with suction (Note 2). This material (ca. 70 g in two crops) is purified by recrystallization from methanol to afford 66 g (84%) of pure (–)-dimenthyl succinate, mp 63–64°C (Note 3).

B. *(–)-Dimenthyl (1S,2S)-cyclopropane-1,2-dicarboxylate.* A dry, 500-mL, three-necked, round-bottomed flask containing a magnetic stirring bar is equipped with a 100-mL pressure-equalizing dropping funnel, a rubber septum, and a three-way stopcock with a nitrogen inlet. The air in the system is replaced with dry nitrogen. The flask is charged with 180 mL of dry tetrahydrofuran and cooled with an ice bath; 74.1 mL of a 1.7 *M* hexane solution of butyllithium (126 mmol) (Note 4) is added. This solution is stirred while 21.3 mL (126 mmol) of 2,2,6,6-tetramethylpiperidine (Note 5) is added dropwise with a syringe through the septum over a 10-min period. The resulting solution of lithium 2,2,6,6-tetramethylpiperidide (LTMP) is cooled to −78°C with a dry ice–methanol bath (Note 6) and stirred. A solution of 23.7 g (60 mmol) of (–)-dimenthyl succinate in 50 mL of dry tetrahydrofuran is then added dropwise through the addition funnel over a 1-hr period. The wall of the funnel is rinsed with 10 mL of dry tetrahydrofuran and the rinse is added to the solution. The resulting yellow solution of succinate dianion is stirred for 1 hr. To the solution is added dropwise 3.9 mL (60 mmol) of bromochloromethane (Note 7) with a syringe through the septum over a 10-min period. After the reaction mixture is stirred for 2 hr (Note 8), 2.2 mL (24 mmol) of isobutyraldehyde (Note 9) is added dropwise to quench any unreacted anions (Note 10). After being stirred for an additional 30 min, the reaction mixture is poured into 250 mL of ice-cooled 1 *N* hydrochloric acid and the product is extracted 3 times with 150 mL of ether. The combined organic phases are washed with 250 mL of brine, dried over sodium sulfate, filtered, and concentrated with a rotary evaporator. The residue is chromatographed on 700 g of silica gel (Note 11) packed in a 9.5-cm-diameter column using a mixture of ether and hexane (1 : 18) as eluant. The appropriate fractions are collected and concentrated to give 11.5 g (47%) of (–)-dimenthyl (1*S*,2*S*)-cyclopropane-1,2-dicarboxylate as colorless crystals. Analysis by GC indicates a diastereomeric ratio of 96 : 4 (Note 12). Recrystallization of this material from 25 mL of methanol affords 9–10 g (38–40%) (Note 13) of optically pure product, mp 95–96°C (Note 14).

C. *(+)-(1S,2S)-Cyclopropane-1,2-dicarboxylic acid.* (–)-Dimenthyl (1*S*,2*S*)-cyclopropane-1,2-dicarboxylate (4.06 g, 10 mmol, $[\alpha]_D^{25}$ + 17.8°) is dissolved in 20 mL of a 10% potassium hydroxide solution in 9 : 1 methanol/water in a 50-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar. The solution is heated at 60°C with an oil bath. Progress of the reaction is monitored by TLC on silica gel, using 1 : 1 hexane/ethyl acetate as eluant (Note 15). After about 4 hr the resulting two-phase mixture is

diluted with 20 mL of water and extracted with three 40-mL portions of ether (Note 16). The aqueous layer is acidified by the addition of 20 mL of ice-cold 6 *N* hydrochloric acid, saturated with ca. 5 g of sodium chloride, and extracted with five 40-mL portions of ether. The combined organic layers are dried over sodium sulfate, diluted with 5 mL of hexane, and concentrated with a rotary evaporator. Filtration provides 1.17 g (90%) of (+)-(1*S*,2*S*)-cyclopropane-1,2-dicarboxylic acid, mp 172–173°C, $[\alpha]_D^{25}$ +228° (ethanol, *c* 1.01) [lit.[2] mp 169.5–170°C, $[\alpha]_D^{25}$ +227.9° (ethanol, *c* 2.342)] (Note 17).

2. Notes

1. Succinic anhydride and *p*-toluenesulfonic acid monohydrate were purchased from Wako Pure Chemical Industries, Ltd. (Japan). Guaranteed-grade *l*-(–)-menthol was purchased from Tokyo Kasei Kogyo Company, Ltd. (Japan). Reagent-grade toluene was dried and stored over sodium metal. The checkers obtained *p*-toluenesulfonic acid from Eastman Kodak and succinic anhydride and *l*-(–)-menthol from the Aldrich Chemical Company, Inc.
2. In the first trial the checkers experiences difficulty in crystallization at this point, even after keeping the solution in a 5°C refrigerator for 4 days. Crystallization was induced by cooling the crude product (ca. 80 g of oil) to −78°C in a methanol–dry ice bath. Ether (5 mL) was added to the resulting glass, the cooling bath was removed, and the surface of the solid material was scratched continuously with a spatula. At about 0°C the glass began to melt and small white spots appeared. Continued stirring of the viscous material as it warmed resulted in crystallization of the entire mass. The crystalline mass was dried under vacuum and a small portion kept as seed crystals. The remainder was dissolved in 100 mL of warm methanol. After the solution was cooled to room temperature, a small quantity of the seed material was added and the solution was placed in a 5°C refrigerator overnight. Approximately 68 g of crystalline (–)-dimenthyl succinate was obtained. The filtrate was condensed with a rotary evaporator and cooled again to give another 2.6 g. In subsequent trials, the foregoing procedure was not necessary as the crude diester crystallized spontaneously, giving a similar yield in two crops.
3. The submitters report mp 65–66°C. The physical properties are as follows: ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 0.70–2.02 (complex, 18 H), 0.75 (d, 6 H, *J* = 6.9), 0.89 (d, 12 H, *J* = 6.4), 2.60 (s, 4 H), 4.70 (dt, 2 H, *J* = 4.4, 10.8); $[\alpha]_D^{25}$ −88.7° ($CHCl_3$, *c* 1.02).
4. Tetrahydrofuran was freshly distilled from sodium–benzophenone. Butyllithium was obtained from Wako Pure Chemical Industries, Ltd. or Foote Mineral Company. It was titrated with anhydrous 2-butanol using 1,10-phenanthroline as an indicator.
5. 2,2,6,6-Tetramethylpiperidine, purchased from Tokyo Kasei Kogyo Company, Ltd. or Aldrich Chemical Company, Inc., was used. The use of this sterically hindered lithium amide is crucial for high diastereoselectivity. If lithium diisopropylamide is used, the diastereoselectivity of the reaction is reduced significantly.[3]
6. The flask was cooled with a dry ice–methanol bath for 30 min before subsequent addition.
7. Bromochloromethane was purchased from Tokyo Kasei Kogyo Company, Ltd. or

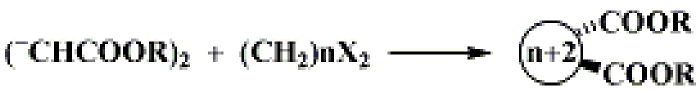
from Aldrich Chemical Company, Inc. and was used without purification.
8. TLC (ether–hexane) showed residual starting material.
9. Isobutyraldehyde was obtained from Wako Pure Chemical Industries, Ltd. or from Aldrich Chemical Company, Inc. and was used without purification.
10. This procedure was not essential but facilitated the subsequent chromatographic separation of desirable product from residue.
11. Silica gel (70–200 mesh) purchased from Fuji Davison Chemical (BW-820 MH) was used. The checkers used silica gel (230–400 mesh) purchased from Merck (Kieselgel 60).
12. GC analysis was performed with a capillary column (PEG, 0.25 mm × 25 m) purchased from Gaskuro Kogyo Company, Ltd. (Japan). The checkers used a 0.2-mm × 25-m Carbowax 20 M capillary column. The diastereomeric excess ranged from about 80–92%. In all cases, however, essentially pure material could be obtained by a subsequent single recrystallization. The diastereomeric ratio can be further improved by reducing the amount of added bromochloromethane. This may be due to the stereochemical purity of the enolates. On treatment with lithium 2,2,6,6-tetramethylpiperidide, the succinate affords mainly the *E*,*E*-enolate and only a slight amount of *Z*,*Z*-enolate; the latter may induce the opposite stereochemistry in the product. Fortunately, the *E*,*E*-enolate is more reactive, and therefore, the undesirable reaction with *Z*,*Z*-enolate can be suppressed, kinetically by reducing the amount of halide. Thus the use of 0.5 equivalent of bromochloromethane compared to starting ester results in over 99% diastereoselectivity with comparable chemical yield, based on the halide. The procedure described in the text is, however, recommended from a practical point of view.
13. This yield ranges from 38 to 57% in several experiments. Recrystallization was accomplished by dissolving the crude diester in warm methanol and then allowing this solution to cool to room temperature. The checkers found that, if crystallization was induced by cooling the methanol solution in a refrigerator, the crystalline diester was accompanied by an oily by-product. A second recrystallization was then necessary to purify the material.
14. The submitters report mp 99–100°C. The physical properties are as follows: ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 0.70–2.02 (complex, 20 H), 0.76 (d, 6 H, J = 7.0), 0.90 (d, 12 H, J = 6.8), 2.12. (dd, 2 H, J = 7.4, 7.2), 4.68 (dt, 2 H, J = 5.4, 10.9); $[\alpha]_D^{25.5}$ + 17.8° ($CHCl_3$, c 1.0).
15. During the course of the saponification, a spot with R_f intermediate between that of the reactant and product (presumably the monoester) was observed.
16. The combined organic layer may be washed with 50 mL of brine, dried over sodium sulfate, and evaporated to recover 3.45 g of crude menthol.
17. The checkers note that in the paper by Inouye et al.[2] the diacid was prepared by ozonolysis of (+)-*trans*-2-phenylcyclopropanecarboxylic acid having 96.3% optical purity. The product diacid was purified by sublimination and recrystallization from water to obtain material giving the cited physical properties. Although the original publication[2] claims an optical purity of 96.3% for this diacid, it is probably optically pure because of the recrystallization step.

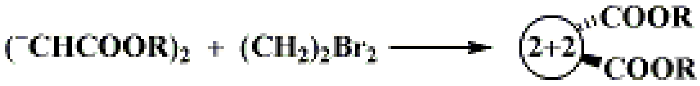
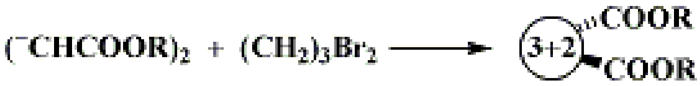
3. Discussion

The procedure described here provides a simple and general method for the construction of

optically active *trans*-cycloalkane-1,2-dicarboxylic acids.[3] The reaction has been applied successfully to a series of dihalides and ditosylates (Table I).

TABLE I
ASYMMETRIC SYNTHESIS OF CYCLOALKANE DICARBOXYLATES



Electrophile				
X	*n*	Yield (%)	Diastereomeric Excess (%)	Configuration
 Br	2	72	—[a,b]	—[c]
 Br	3	77	65	*S,S*
OTs	3	63	92	*S,S*
OTs	3	64	88	*R,R*[d]
Cl[e]	3	57	83[a]	—[c]

4 61 75 *S,S*

OTs

[a]Reaction first at –100°C, and then warming to –20°C.

[d]Not determined. $[\alpha]_D^{25}$ –51.7° ($CHCl_3$, *c* 1.0).

[c]Not determined.

[d]*d*-Menthyl ester was used.

[e]3-Chloro-2-chloromethyl-1-propene.

A few methods are described in the literature for the preparation of optically active dialkyl *trans*-cyclopropane-1,2-dicarboxylates,[2] including a Michael addition–condensation sequence of menthyl chloroacetate and menthyl acrylate,[4] and cobalt(0) or nickel(0) complex-catalyzed cyclopropanation of dimenthyl fumarate with dibromomethane.[5] The present method is characterized by good chemical and high optical yields, simple operation, preparation of both enantiomers with equal ease, and the ready availability of the starting materials.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Lithium 2,2,6,6-tetramethylpiperidide

brine

(−)-Dimenthyl succinate

(–)-Dimenthyl (1S,2S)-cyclopropane-1,2-dicarboxylate

lithium 2,2,6,6-tetramethylpiperidide (LTMP)

l-(–)-menthol

trans-cycloalkane-1,2-dicarboxylic acids

d-Menthyl ester

trans-cyclopropane-1,2-dicarboxylates

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether (60-29-7)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

nickel(0) (7440-02-0)

potassium hydroxide (1310-58-3)

toluene (108-88-3)

Benzophenone (119-61-9)

sodium (13966-32-0)

menthol, l-menthol (15356-60-2)

dibromomethane (74-95-3)

Succinic anhydride (108-30-5)

isobutyraldehyde (78-84-2)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

SUCCINATE DIANION

lithium amide (7782-89-0)

hexane (110-54-3)

cobalt(0) (7440-48-4)

2-Butanol (78-92-2)

p-toluenesulfonic acid (104-15-4)

lithium diisopropylamide (4111-54-0)

1,10-phenanthroline (66-71-7)

2,2,6,6-tetramethylpiperidine (768-66-1)

bromochloromethane (74-97-5)

(+)-(1S,2S)-Cyclopropane-1,2-dicarboxylic acid, 1,2-Cyclopropanedicarboxylic acid, (1S,2S)-(+)- (14590-54-6)

3-Chloro-2-chloromethyl-1-propene (1871-57-4)

menthyl chloroacetate

menthyl acrylate

dimenthyl fumarate

p-toluenesulfonic acid monohydrate (6192-52-5)

(+)-trans-2-phenylcyclopropanecarboxylic acid (939-90-2)

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Organic Syntheses, CV 8, 146

TRIPLE-BOND ISOMERIZATIONS: 2- TO 9-DECYN-1-OL

Submitted by Suzanne R. Abrams and Angela C. Shaw[1].
Checked by Maurizio Taddei and Ian Fleming.

1. Procedure

Caution! This preparation should be carried out in an efficient hood and the operator should wear gloves to protect against spillage of corrosive 1,3-diaminopropane.

A 1-L, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, a thermometer, a pressure-equalizing dropping funnel to which an argon inlet is attached, and a condenser fitted with a drying tube filled with potassium hydroxide pellets (Note 1). The flask is charged with lithium (4.2 g, 0.6 mol, (Note 2)) and 1,3-diaminopropane (300 mL, (Note 3)). The mixture is stirred at room temperature for 30 min. A slight exothermic reaction takes place as the lithium dissolves.

The mixture is stirred and heated in an oil bath at 70°C until the blue color discharges (ca. 3 hr), affording a white suspension of the lithium amide. The reaction mixture is cooled to room temperature, and potassium *tert*-butoxide (44 g, 0.4 mol, (Note 4)) is added to the flask using a powder funnel. The resultant pale yellow solution is stirred for 20 min at room temperature, and then 2-decyn-1-ol (15.4 g, 0.1 mol, (Note 5)) is added over 10 min by means of the dropping funnel (Note 6). Residual 2-decyn-1-ol is washed into the flask with 1,3-diaminopropane (20 mL). The reddish-brown mixture is stirred for 30 min and then poured into 1 L of ice water and extracted 4 times with 500-mL portions of hexane. The hexane extracts are combined and washed succesively with 1 L each of water, 10% hydrochloric acid, and saturated sodium chloride solution. The hexane solution is dried over anhydrous sodium sulfate, filtered, and concentrated with a rotary evaporator. The crude product is distilled under reduced pressure to give 9-decyn-1-ol (12.8–13.5 g, 83–88%) (Note 7) and (Note 8), as a colorless oil, bp 86–88°C/0.5 mm.

2. Notes

1. All glassware should be previously dried in an oven at 110°C for at least 2 hr.
2. Lithium wire (3.2-mm diameter, 0.02% Na, Alfa Products, Morton/Thiokol Inc.) is cut into 1-cm pieces, then washed with hexane and quickly weighed into a tared beaker of hexane. The checkers also used lithium shot (BDH); the lithium did not all dissolve at room temperature, and heating at 70°C for 6 hr was necessary to discharge the blue color.
3. 1,3-Diaminopropane (97%, Aldrich Chemical Company, Inc.) was distilled at atmospheric pressure under nitrogen from barium oxide and stored over molecular sieves (Linde 4A).

4. Potassium *tert*-butoxide (Aldrich Chemical Company, Inc.) was used without further purification, and was added over 1–2 min.
5. 2-Decyn-1-ol (Farchan Labs., Lancaster Synthesis) was used without further purification. On addition of 2-decyn-1-ol to the reaction mixture slight warming is observed. The temperature is maintained at 25–30°C using a water bath.
6. The checkers used a syringe, injecting through a rubber septum.
7. The submitters used a Kugelrohr apparatus with an oven temperature of 80–90°C/0.05 mm.
8. The isomeric purity of the product is greater than 99% as determined by GLC of the trimethylsilyl ether. 9-Decyn-1-ol (n_D^{26} 1.4552) has the following spectroscopic characteristics: ^{1}H NMR ($CDCl_3$) δ: 1.1–1.7 (m, 12 H), 1.9 (t, *J* = 1.5, $C\equiv CH$), 2.1 (m, 2 H, $CH_2C\equiv C$), 3.6 (t, 2 H, *J* = 6, OCH_2); IR (film) ν_{max} cm^{-1}: 3400 (br), 3300 (s), 2100 (w), 1050 (s).

3. Discussion

In 1975 Brown and Yamashita[2] reported that a triple bond in any position of a straight-chain hydrocarbon or acetylenic alcohol, when treated with a sufficiently strong base, could be isomerized exclusively to the free terminus of the chain. The "zipper reaction" thus provides a general solution to the problem of remote functionalization of a long hydrocarbon chain. Isomerizations along chains of 30 carbon atoms have been achieved. Isomerization is blocked by alkyl or hydroxyl branches; the triple bond then migrates to the free terminus.

The base employed by Brown and Yamashita was the potassium salt of 1,3-diaminopropane, prepared by reaction of potassium hydride with the solvent of the reaction, 1,3-diaminopropane. The reagent is very effective, and yields of isomerically pure products are high, but potassium hydride is hazardous, expensive and difficult to handle.

We and others have developed alternative methods for preparing the isomerization reagent.[3,4,5,6] Hommes and Brandsma[3] first prepared potassium or sodium amide in liquid ammonia and then replaced the solvent with 1,3-diaminopropane. Kimmel and Becker[4] treated molten potassium or sodium with 1,3-diaminopropane in a flask immersed in an ultrasonic bath at 90°C. We[5,6] found that sodium hydride reacts with 1,3-diaminopropane, or 1,2-diaminoethane, on warming. All of these methods produce effective isomerization reagents with comparable conversions and yields. The lithium salt alone is a poor isomerization reagent; however, addition of potassium *tert*-butoxide affords a reagent that very effectively isomerizes triple bonds. This procedure, presented here, is our most refined method.[7] It is straightforward, gives reproducibly high yields, employs inexpensive reagents, and can be safely carried out on a large scale.

It is not satisfactory to employ 1,2-diaminoethane in place of 1,3-diaminopropane. The reagent is not as stable; addition of potassium *tert*-butoxide results in the immediate formation of a deep-purple solution. Isomerizations proceed to completion, but yields are somewhat reduced (by about 10% in the case of the rearrangement of 2- to 9-decyn-1-ol).

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

2- to 9-decyn-1-ol

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

barium oxide

nitrogen (7727-37-9)

carbon (7782-42-5)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

potassium (7440-09-7)

lithium (7439-93-2)

sodium amide (7782-92-5)

lithium amide (7782-89-0)

sodium hydride (7646-69-7)

1,2-diaminoethane (107-15-3)

hexane (110-54-3)

acetylenic alcohol (32038-79-2)

argon (7440-37-1)

trimethylsilyl ether (107-46-0)

potassium hydride (7693-26-7)

9-Decyn-1-ol (17643-36-6)

1,3-diaminopropane (109-76-2)

2-decyn-1-ol (4117-14-0)

potassium salt of 1,3-diaminopropane

potassium tert-butoxide (865-47-4)

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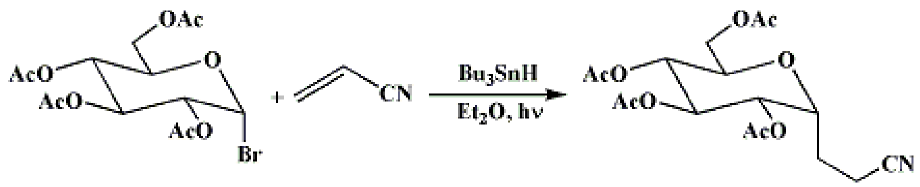
Organic Syntheses, CV 8, 148

1-DEOXY-2,3,4,6-TETRA-*O*-ACETYL-1-(2-CYANOETHYL)-α-D-GLUCOPYRANOSE

[D-glycero-D-ido-Nononononitrile, 4,8-anhydro-2,3-dideoxy-, 5,6,7,9-tetraacetate]



Submitted by Bernd Giese, J. Dupuis, and Marianne Nix[1].
Checked by John P. Daub and Bruce E. Smart.

1. Procedure

Caution! Acrylonitrile is an OSHA-regulated carcinogen and appropriate precautions should be taken in handling this substance.

A 250-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, a dry-nitrogen inlet, a reflux condenser, and a septum is flushed with nitrogen and charged with 20.6 g (50 mmol) of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (Note 1) and 100 mL of anhydrous ether. The mixture is brought to reflux with a heat gun. A nitrogen atmosphere is maintained over the reaction mixture during this and the ensuing steps. When the 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide dissolves, 13.5 g (250 mmol) of acrylonitrile and 16.0 g (55 mmol) of tributyltin hydride (Note 2) are added by means of a syringe. The refluxing solution is irradiated with a sunlamp positioned 2.5–3.8 cm from the reaction flask (Note 3). The heat from the sunlamp maintains a vigorous reflux. After 4 hr, the irradiation is stopped and the reaction mixture is cooled and filtered to collect the precipitated crystals (Note 4). The filtrate is reintroduced under nitrogen into the reaction vessel. An additional 6.6 g (120 mmol) of acrylonitrile and 5.8 g (20 mmol) of tributyltin hydride are added and irradiation is resumed for another 4 hr until the starting bromide is completely reacted (Note 5). After the reaction mixture is cooled, it is filtered, the filtrate is saved, and the filter cake (Note 6) is combined with the crystals collected above. The solids are stirred with 250 mL of hot isopropyl alcohol and filtered. The hot filtrate is concentrated to a total volume of 75 mL, allowed to cool and filtered to give 7.8–8.6 g (40–45%) of 1-deoxy-2,3,4,6-tetra-*O*-acetyl-1-(2-cyanoethyl)-α-D-glucopyranose as long, colorless crystals, mp 121–122°C, $[\alpha]_D^{25}$ +66.2 ($CHCl_3$, *c* 0.7) (Note 7). The isopropyl alcohol mother liquor is set aside. The above filtrate from the crude reaction mixture is concentrated, taken up in 50 mL of acetonitrile, and extracted 3 times with 50-mL portions of pentane. The acetonitrile phase is combined with the isopropyl alcohol mother liquor and concentrated. The resulting syrup is flash-chromatographed on silica gel using ethyl acetate/hexane (1 : 1) eluent to afford an additional 2.2–2.5 g of pure 1-deoxy-2,3,4,6-tetra-*O*-acetyl-1-(2-cyanoethyl)-α-D-glucopyranose after separation of by-products (Note 8) and (Note 9). The combined yield of pure product is 53–56%

2. Notes

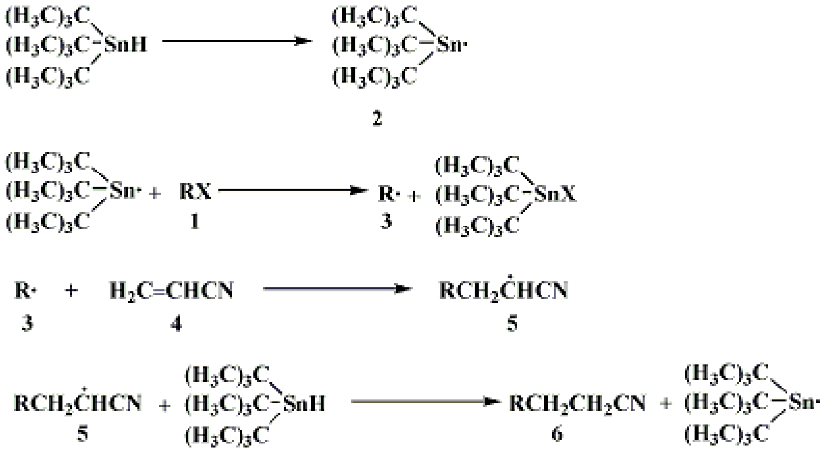
1. This material was obtained from the Sigma Chemical Company and was recrystallized from ethyl ether/pentane before use. It also can be prepared by the procedure of Redemann, C. E.; Niemann, C. *Org. Synth., Coll. Vol. III*, **1955**, 11.
2. Acrylonitrile and tributyltin hydride were obtained from the Aldrich Chemical Company, Inc. and used without further purification. The use of a large excess of acrylonitrile reduced the amount of reduction by-product (2,3,4,6-tetraacetyl-1,5-anhydroglucitol). Because tributyltin hydride also reacts with acrylonitrile, a small excess must be used.
3. The checkers used a 275-W General Electric sunlamp. The submitters indicate that the type of sunlamp is not critical and that a 125-W Philips E99/2 sunlamp or a 125-W Philips 57203 high-pressure mercury lamp are suitable. If the heat from the sunlamp does not maintain reflux, the reaction flask should be about one-fourth submerged into a hot oil bath.
4. During the reaction the amount of precipitate gradually increases until the light from the sunlamp is totally blocked and the reaction stops.
5. The reaction can be followed by TLC using 0.25-mm silica gel 60 F-254 plates (E. Merck & Company) and ethyl acetate/hexane (1 : 1) eluent: 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (R_f = 0.39); 2,3,4,6-tetra-*O*-acetyl-1,5-anhydroglucitol (R_f = 0.28); 1-deoxy-2,3,4,6-tetra-*O*-acetyl-1-(2-cyanoethyl)-β-D-glucopyranose (R_f = 0.20); 1-deoxy-2,3,4,6-tetra-*O*-acetyl-1-(2-cyanoethyl)-α-D-glucopyranose (R_f = 0.16).
6. This solid contains a large amount of insoluble polymer in addition to product.
7. The product is analytically pure. Anal. calcd. for $C_{17}H_{23}NO_9$: C, 52.98; H, 6.02; N, 3.63. Found: C, 52.80; H, 6.01; N, 3.63; ^{1}H NMR ($CDCl_3$, 360 MHz): 1.84–1.95 (m, 1 H, CCH_2), 2.05 (s, 6 H, 2 OAc), 2.09 (s, 3 H, OAc), 2.11 (s, 3 H, OAc), 2.05–2.22 (m, 1 H, CCH_2), 2.46 (m, 2 H, CH_2CN), 3.88 (ddd, 1 H, H_5, $J_{5,6}$ = 5.80, $J_{5,6'}$ = 2.88, $J_{4,5}$ = 8.30), 4.12 (dd, 1 H, $H_{6'}$, $J_{6,6'}$ = 12.24), 4.23 (m, 1 H, H_1), 4.32 (dd, 1 H, H_6), 4.98 (t, 1 H, H_4, $J_{3,4}$ = 8.30), 5.09 (dd, 1 H, H_2, $J_{1,2}$ = 5.23, $J_{2,3}$ = 8.30), 5.23 (t, 1 H, H_3); IR (KBr) cm^{-1}: 2240 (C≡N), 1745 (C=O).
8. E. Merck 230–400 mesh Kieselgel 60 silica gel was used in the flash chromatography. The first fraction contained 3.5 g

(21%) of the tetra-*O*-acetyl-1,5-anhydroglucitol by-product; the second fraction contained 0.95–1.00 g (5%) of pure 1-deoxy-2,3,4,6-tetra-*O*-acetyl-1-(2-cyanoethyl)-β-D-glucopyranose: mp 91–93°C, 117–119°C (two forms); $[\alpha]_D^{25}$ –19.6 ($CHCl_3$, *c* 1.01). The final fraction contained the desired product. The ratio of α : β isomers based on isolated yields is 11 : 1. The submitters report a ratio of 14 : 1 based on chromatographic analysis of the crude reaction mixture.

9. 1-Deoxy-2,3,4,6-tetra-*O*-acetyl-1-(2-cyanoethyl)-β-D-glucopyranose shows IR (KBr) cm^{-1}: 2240 (C≡N), 1745 (C=O); ^1H NMR ($CDCl_3$, 360 MHz) δ: 1.79 (br m, 1 H, CCH_2), 1.92 (br m, 1 H, CCH_2), 2.00 (s, 3 H, OAc), 2.03 (s, 3 H, OAc), 2.07 (s, 3 H, OAc), 2.09 (s, 3 H, OAc), 2.52 (m, 2 H, CH_2CN), 3.56 (dt, 1 H, H_1, $J_{1,2}$ = 9.6, J = 9.6, 2.6), 3.68 (ddd, 1 H, H_5, $J_{4,5}$ = 9.9, $J_{5,6}$ = 5.0, $J_{5,6'}$ = 2.1), 4.11 (dd, 1 H, $H_{6'}$, $J_{6,6'}$ = 12.2), 4.24 (dd, 1 H, H_6), 4.88 (t, 1 H, H_2, $J_{2,3}$ = 9.6), 5.05 (t, 1 H, H_4, $J_{3,4}$ = 9.4), 5.20 (t, 1 H, H_3). Anal. calcd. for $C_{17}H_{23}NO_9$: C, 52.98; H, 6.02; N, 3.63. Found: C, 52.85; H, 6.09; N, 3.70.

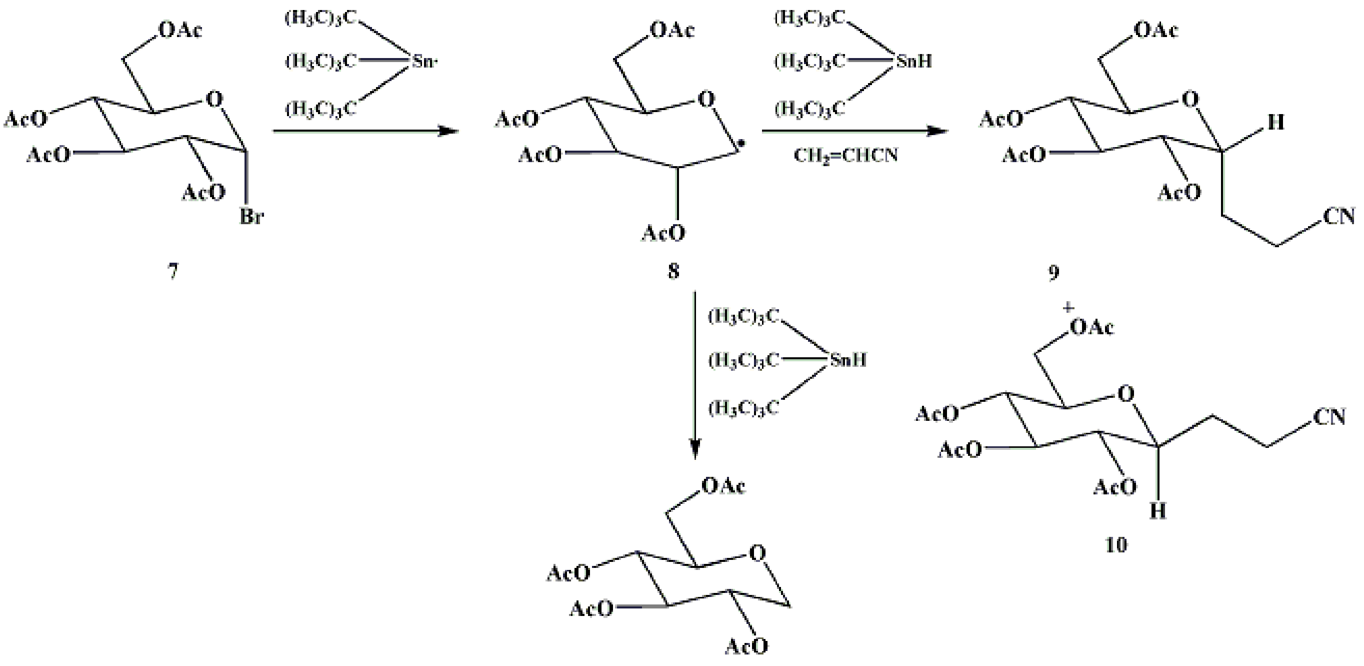
3. Discussion

The formation of the C-C bond occurs in a radical chain reaction[2] (Scheme 1). Bromine abstraction from halide **1** by tin radicals **2**[3] leads to carbon radicals **3** that react with alkenes **4** to give product radicals **5**. Trapping of **5** by tributyltin hydride yields products **6** and the tin radical **2**.



In contrast to anionic 1,4-addition methods, the radical procedure tolerates an acetoxy group adjacent to the reactive center (radical-bearing carbon). In applying this general method to tetraacetylglucosyl bromide **7**,[4] products **9**, with an axial C-C bond, and **10** are obtained in a ratio of ca. 10 : 1. ESR experiments show that the radical intermediate has the boat conformation **8**.[5] The attack that leads to the axial product **9** is, therefore, the favored pseudoequatorial attack,[6] assuming that the transition state is also boatlike **8**. Some of the radical **8** is trapped directly by tributyltin hydride to give the simple reduction product **11**. This is a common side reaction in tin hydride-initiated radical coupling reactions.

This method has been applied also to mannosyl bromide and galactosyl bromide.[4] Because alkoxyalkyl radicals are nucleophilic radicals, only alkenes with electron-withdrawing substituents can be used.[7] The 1,5-anhydroglycitol side product **11** is formed in amounts that increase with the decreasing reactivity of alkene **4**.



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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

1-Deoxy-2,3,4,6-tetra-O-acetyl-1-(2-cyanoethyl)-α-D-glucopyranose

(2,3,4,6-tetraacetyl-1,5-anhydroglucitol)

2,3,4,6-tetra-O-acetyl-1,5-anhydroglucitol

1-deoxy-2,3,4,6-tetra-O-acetyl-1-(2-cyanoethyl)-β-D-glucopyranose

tetra-O-acetyl-1,5-anhydroglucitol

mannosyl bromide

D-glycero-D-ido-Nononitrile, 4,8-anhydro-2,3-dideoxy-, 5,6,7,9-tetraacetate

ethyl acetate (141-78-6)

ether, ethyl ether (60-29-7)

acetonitrile (75-05-8)

bromine (7726-95-6)

nitrogen (7727-37-9)

tin (7440-31-5)

carbon (7782-42-5)

isopropyl alcohol (67-63-0)

Pentane (109-66-0)

acrylonitrile (107-13-1)

hexane (110-54-3)

tributyltin hydride (688-73-3)

tetraacetylglucosyl bromide

galactosyl bromide

2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide

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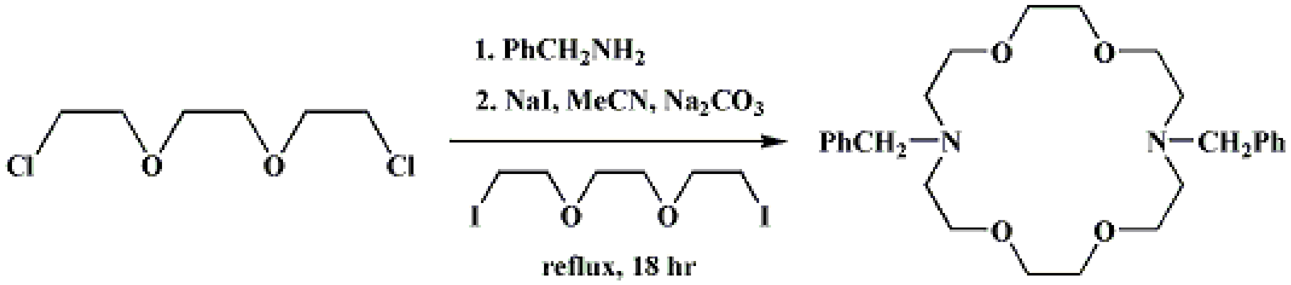
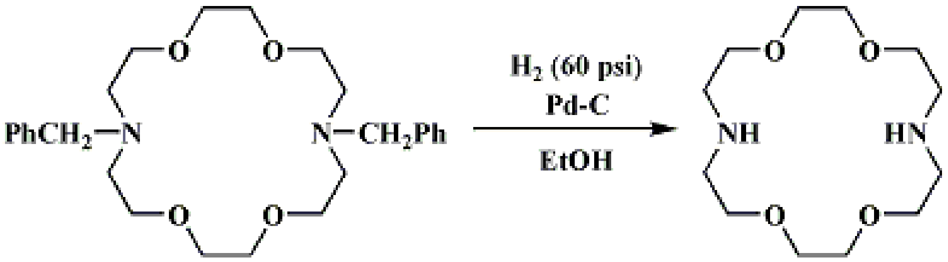
Organic Syntheses, *CV 8*, *152*

4,13-DIAZA-18-CROWN-6

[1,4,10,13-Tetraoxa-7,16-diazacyclooctadecane]





Submitted by Vincent J. Gatto, Steven R. Miller, and George W. Gokel[1].
Checked by P. C. Prabhakaran and James D. White.

1. Procedure

A. *1,10-Dibenzyl-4,7-dioxa-1,10-diazadecane.* A solution of benzylamine (172 g, 1.6 mol) (Note 1) and 1,2-bis(2-chloroethoxy)ethane (18.7 g, 0.1 mol) (Note 2) is stirred and heated at 120°C for 28 hr. The reaction is cooled to room temperature, sodium hydroxide pellets (8.0 g, 0.2 mol) are added, and the mixture is heated at 120°C, with stirring, for 1 hr. The reaction is cooled and excess benzylamine is removed by vacuum distillation (Note 3) using a water aspirator (Note 4). The resulting oil is dissolved in chloroform (100 mL), filtered, and washed with water (50 mL) to remove salts. The organic phase is dried (Na_2SO_4) and concentrated under reduced pressure. Bulb-to-bulb distillation using a Kugelrohr apparatus (175–177°C, 0.2 mm) gives 27.9–31.2 g (85–95%) of 1,10-dibenzyl-4,7-dioxa-1,10-diazadecane (Note 5) as a slightly yellow oil that is sufficiently pure to be used for the preparation of *N,N'*-dibenzyl-4,13-diaza-18-crown-6.

B. *N,N'-Dibenzyl-4,13-diaza-18-crown-6.* In a 3-L, round-bottomed flask fitted with a mechanical stirrer and an efficient reflux condenser are placed 1,10-dibenzyl-4,7-dioxa-1,10-diazadecane (28.2 g, 86 mmol), 1,2-bis(2-iodoethoxy)ethane (39.3 g, 106 mmol) (Note 6), anhydrous sodium carbonate (45.3 g, 427 mmol), and sodium iodide (6.4 g, 43 mmol) in acetonitrile (1700 mL). The resulting solution is stirred mechanically (Note 7) and heated at reflux for 21 hr. The reaction is cooled, filtered, and concentrated under reduced pressure (Note 8). The crude solid is dissolved in a refluxing solution of acetone–dioxane (175 mL each) and allowed to crystallize in a freezer. The crystals (a mixture of sodium iodide and the sodium iodide complex of the product) are dried and taken up in 500 mL of water and 400 mL of chloroform. The phases are separated and the aqueous portion is extracted with chloroform (3 × 75 mL). The combined organic phases are dried ($MgSO_4$) and concentrated under reduced pressure. Recrystallization (hexanes, 500 mL, followed by

absolute ethanol, 110 mL) affords 25.6–27.0 g (67–71%) of *N,N'*-dibenzyl-4,13-diaza-18-crown-6 as a white solid (mp 80–81°C): ^{1}H NMR ($CDCl_3$) δ: 2.82 (t, 8 H, NCH_2); 3.64 and 3.70 (t, s, s, 2 CH, OCH_2 and CH_2Ph); 7.37 (s, 10 H, Ar); IR (KBr) cm^{-1}: 2960, 2900, 2880, 1500, 1460, 1120, 1060, 1050, 750, 700 (Note 9) and (Note 10).

C. *4,13-Diaza-18-crown-6. N,N'*-Dibenzyl-4,13-diaza-18-crown-6 (25.0 g, 56 mmol) (Note 11), 10% Pd/C catalyst (1.0 g), and absolute ethanol (300 mL) are shaken in a Parr series 3900 hydrogenation apparatus at 60-psi hydrogen pressure and 25°C for 72 hr. The mixture is filtered through a pad of Celite and concentrated under reduced pressure. The yield of pure 4,13-diaza-18-crown-6 after recrystallization (hexanes, 1 g/35 mL) is 13.5 g (91%). The white solid (mp 114–115°C) possesses physical properties identical to those previously reported:[2] ^{1}H NMR ($CDCl_3$) δ: 2.06 (bs, 2 H, NH); 2.72 (t, 8 H, CH_2N); 3.54 (5, s, 16 H, CH_2); IR (KBr) cm^{-1}: 3330.

2. Notes

1. Benzylamine was obtained from Aldrich Chemical Company, Inc., and was used without further purification.
2. 1,2-Bis(2-chloroethoxy)ethane was obtained from Eastman Kodak Company, and was used without further purification.
3. The excess benzylamine, recovered from the distillation step, can be reused if redistilled from calcium oxide.
4. If an efficient water aspirator is used (<20 mm), the benzylamine should distill between 60 and 70°C.
5. The product has the following spectral characteristics: ^{1}H NMR ($CDCl_3$) δ: 1.82 (s, 2 H, NH), 2.72 (t, 4 H, NCH_2), 3.58 (s and t, 8 H, CH_2), 3.72 (s, 4 H, benzyl), and 7.28 ppm (s, 10 H, Ar).
6. 1,2-Bis(2-iodoethoxy)ethane was prepared as described by Kulstad and Malmsten.[3] 1,2-Bis(2-chloroethoxy)ethane (21.3 g, 0.114 mol) and sodium iodide (37.0 g, 0.247 mol) in acetone (55 mL) were heated at reflux while stirring magnetically during 3 days. The reaction mixture was allowed to cool and was filtered, and the filtrate was evaporated under reduced pressure. The residue was dissolved in methylene chloride (200 mL), washed with aqueous 10% sodium thiosulfate solution (2 × 100 mL), dried over magnesium sulfate, and evaporated under reduced pressure. The residual methylene chloride was removed by high-vacuum evaporation at ambient temperature and the resulting 1,2-bis(2-iodoethoxy)ethane (40 g, 95%) was used without further purification. The proton NMR spectrum (δ, $CDCl_3$) is as follows: 3.25 (t, 4 H); 3.68 (s, 4 H); 3.78 (t, 4 H).
7. This reaction must be stirred vigorously (120–150 rpm using a 60-mm paddle) for best results.
8. The acetonitrile in this step can be reused without any further purification.
9. Wester and Voegtle[4] reported mp 80°C.
10. When this reaction is run on twice the reported scale, the percent yield is the same.
11. The *N,N'*-dibenzyl-4,13-diaza-18-crown-6 must be freshly recrystallized from absolute ethanol for the hydrogenolysis to proceed at a reasonable rate.

3. Discussion

During the past two decades, a relatively few macrocyclic polyethers have played central roles in numerous research programs. Examples are 18-crown-6, dibenzo-18-crown-6, and aza-15-crown-5.

4,13-Diaza-18-crown-6 and its derivatives are compounds of considerable current interest despite the parent's high price and limited availability. 4,13-Diaza-18-crown-6 is a key compound in the study of two-armed macrocycles since it may readily be alkylated or acylated to afford a variety of symmetric, *N,N'*-disubstituted derivatives.

4,13-Diaza-18-crown-6 has been prepared in a variety of ways.[2,3,5,6,7,8,9] Lehn first reported its preparation by reaction of 1,2-bis(2-aminoethoxy)ethane with triglycolic acid dichloride, followed by lithium aluminum hydride or diborane reduction of the resulting bislactam.[2] Kulstead and Malmsten have condensed 1,2-bis(2-aminoethoxy)ethane with 1,2-bis(2-iodoethoxy)ethane to give 4,13-diaza-18-crown-6.[3] Recently, we have reported that a single-step reaction of benzylamine with 1,2-bis(2-iodoethoxy)ethane, followed by hydrogenation of the resulting *N,N'*-dibenzyl-protected crown, gives 4,13-diaza-18-crown-6.[5] The latter, single-step cyclization reaction is more direct than the present procedure, but the yield is substantially lower and the manipulations are less convenient.

The method described here offers three advantages over the previously published procedures.[2,3,5,6,7,8,9] First, the cyclization reaction does not require the use of high-dilution conditions in order to obtain satisfactory yields of product. This is a substantial improvement over the procedure of Lehn,[2] which requires large volumes of dry solvents and slow addition rates. Second, purification of all the intermediates is straightforward, involving either vacuum distillation using a Kugelrohr apparatus or recrystallization. This is an important advantage when the sequence is scaled up because it allows the preparation of large sample sizes in relatively short periods of time. We have prepared as much as 40 g of 4,13-diaza-18-crown-6 in less than 1 week. Third, the benzyl protecting groups are easily removed by hydrogenolysis over H_2/Pd–C in ethanol. Previous preparations of 4,13-diaza-18-crown-6 are more difficult because they involve the hydrolysis or reduction of *N*-tosyl protected nitrogens.[5,6,7,8] We should also note that our own previously published,[5] single-step preparation for *N,N*-disubstituted-4,13-diaza-18-crown-6 derivatives is more convenient than the present preparation because it involves a single-step reaction, but the yields are always inferior to those obtained using the present, multistep approach.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hexanes

N-tosyl

ethanol (64-17-5)

acetonitrile (75-05-8)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium carbonate (497-19-8)

sodium thiosulfate (7772-98-7)

acetone (67-64-1)

calcium oxide

sodium iodide (7681-82-5)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

dioxane (5703-46-8)

benzylamine (100-46-9)

lithium aluminum hydride (16853-85-3)

18-Crown-6 (17455-13-9)

1,2-bis(2-chloroethoxy)ethane (112-26-5)

DIBENZO-18-CROWN-6 (14187-32-7)

4,13-Diaza-18-crown-6, 1,4,10,13-Tetraoxa-7,16-diazacyclooctadecane (23978-55-4)

1,10-Dibenzyl-4,7-dioxa-1,10-diazadecane (66582-26-1)

1,2-bis(2-iodoethoxy)ethane (36839-55-1)

aza-15-crown-5

1,2-bis(2-aminoethoxy)ethane (929-59-9)

N,N'-dibenzyl-4,13-diaza-18-crown-6 (69703-25-9)

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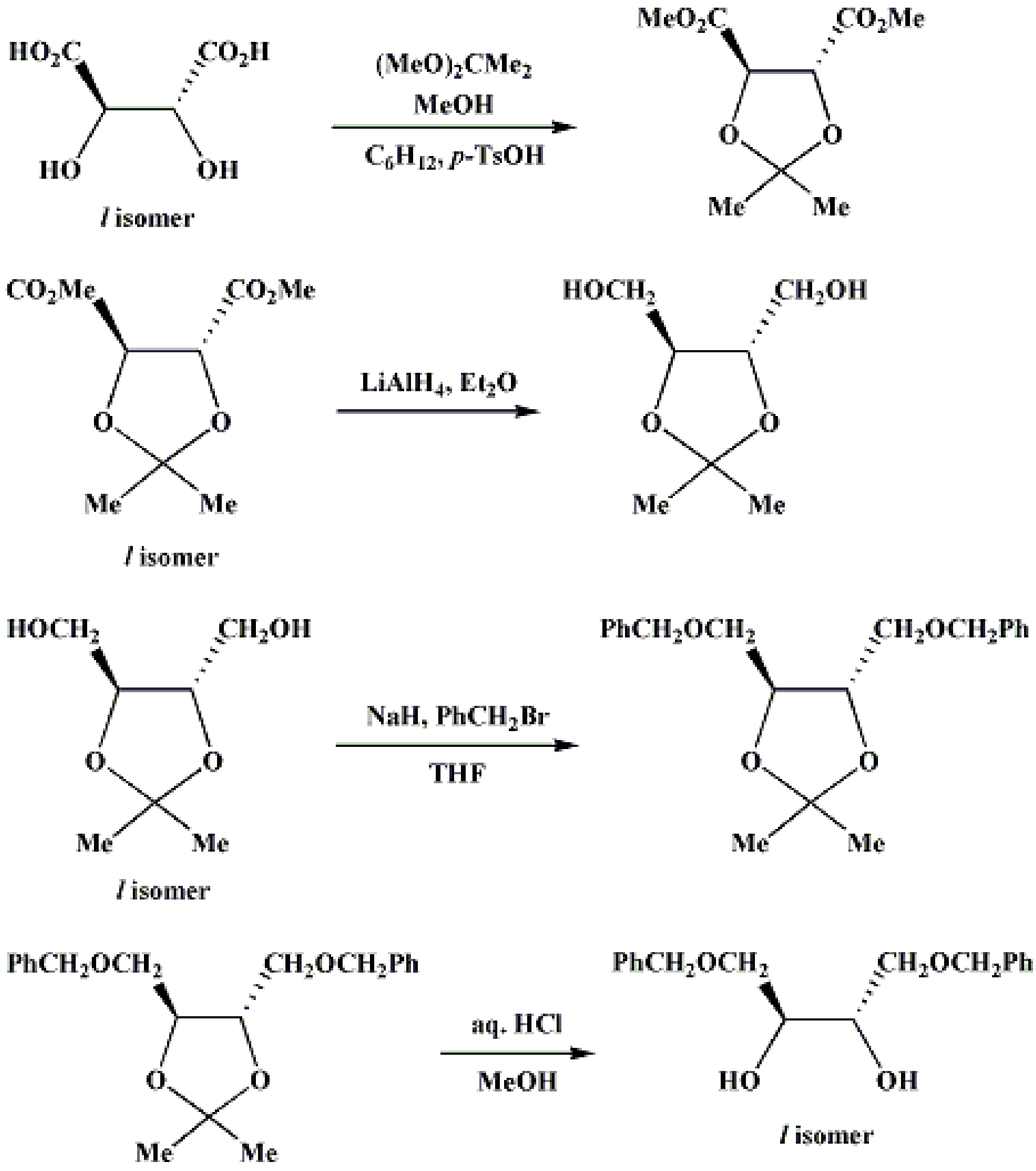
Organic Syntheses, CV 8, 155

1,4-DI-*O*-ALKYL THREITOLS FROM TARTARIC ACID: 1,4-DI-*O*-BENZYL-L-THREITOL

[2,3-Butanediol, 1,4-bis(phenylmethoxy)- [*S*-(*R**,*R**)]-]



Submitted by Eugene A. Mash, Keith A. Nelson, Shawne Van Deusen, and Susan B. Hemperly[1].
Checked by Peter D. Theisen and Clayton H. Heathcock.

1. Procedure

A. *Dimethyl 2,3-O-isopropylidene-L-tartrate*. (See (Note 1).) In a 1-L, one-necked, round-bottomed flask fitted with a reflux condenser and a large magnetic stirring bar under argon, a mixture of L-tartaric acid (101 g, 0.673 mol) (Note 2), 2,2-dimethoxypropane (190 mL, 161 g, 1.54 mol) (Note 3), methanol (40 mL) (Note 4), and *p*-toluenesulfonic acid monohydrate (0.4 g, 2.1 mmol) (Note 5) is warmed on a steam bath with occasional swirling until a dark-red homogeneous solution is obtained (Note 6). Additional 2,2-dimethoxypropane (95 mL, 80.5 g, 0.77 mol) and cyclohexane (450 mL) (Note 7) are added and the flask is fitted with a 30-cm Vigreux column and a variable reflux distilling head. The mixture is heated to reflux with internal stirring and the acetone–cyclohexane and methanol–cyclohexane azeotropes are slowly removed (Note 8). Additional 2,2-dimethoxypropane (6 mL, 5.1 g, 49 mmol) is then added and the mixture heated under reflux for 15 min (Note 9). After the mixture has cooled to room temperature, anhydrous potassium carbonate (1 g, 7.2 mmol) is added and the mixture is stirred until the reddish color has abated (Note 10). Volatile material is removed under reduced pressure (water aspirator) and the residue is fractionally distilled under vacuum to afford the product as a pale-yellow oil, bp 94–101°C (0.5 mm); 125–135 g (0.57–0.62 mmol, 85–92% yield) (Note 11) and (Note 12).

B. *2,3-Di-O-isopropylidene-L-threitol*. (See (Note 13).) In a dry, 2-L, three-necked, round-bottomed flask equipped with a 500-mL pressure-equalized addition funnel, a reflux condenser, a thermometer, and a large magnetic stirring bar is suspended lithium aluminum hydride (36 g, 0.95 mol) (Note 14) in diethyl ether (600 mL) (Note 15) under argon. The mixture is stirred and heated to reflux for 30 min. Heating is discontinued while a solution of dimethyl 2,3-*O*-isopropylidene-L-tartrate (123 g, 0.564 mol) in diethyl ether (300 mL) (Note 15) is added dropwise over 2 hr. Heating is then resumed and the mixture is refluxed for an additional 3 hr. The mixture is cooled to 0–5°C (Note 16) and *cautiously* treated with water (36 mL), 4 *N* sodium hydroxide solution (36 mL), and water (112 mL) (Note 17). The mixture is then stirred at room temperature until the gray color of unquenched lithium aluminum hydride has completely disappeared (Note 18). The mixture is filtered on a Büchner funnel and the inorganic precipitate is extracted with ether in a Soxhlet apparatus (Note 19). The combined ethereal extracts are dried over anhydrous magnesium sulfate and filtered, and volatile material is removed under reduced pressure (water aspirator). The residue is fractionally distilled under vacuum to afford the product as a colorless to pale-yellow oil, bp 94–106°C (0.4 mm); 50.2–60.3 g (0.31–0.37 mmol, 54–66% yield) (Note 20) and (Note 21).

C. *1,4-Di-O-benzyl-2,3-O-isopropylidene-L-threitol*. In a 2-L, three-necked, round-bottomed flask equipped with a large magnetic stirring bar under argon is placed fresh sodium hydride (33.6 g of a 55% dispersion in oil; 18.5 g, 0.77 mol) (Note 22). The oil is removed by washing with hexanes (3 × 100 mL) (Note 23) and (Note 24). The flask is fitted with a 500-mL pressure-equalized addition funnel, a reflux condenser, and a stopper. Tetrahydrofuran (250 mL) (Note 25) is added under argon. A solution of 2,3-di-*O*-isopropylidene-L-threitol (55 g, 0.34 mol) in tetrahydrofuran (250 mL) is then

added dropwise with stirring at room temperature (Note 26). Benzyl bromide (91 mL, 130.8 g, 0.76 mol) (Note 27) is then added dropwise via the addition funnel (Note 28). After stirring for 12 hr at room temperature, the mixture is heated at reflux for 2 hr, cooled in an ice bath, and quenched by addition of water until a clear solution results. Tetrahydrofuran is removed under reduced pressure (water aspirator); the residue is diluted with water (500 mL) and extracted with diethyl ether (3 × 500 mL). The extracts are combined, dried over anhydrous magnesium sulfate, and filtered. Removal of volatile material under reduced pressure (water aspirator) gives crude 1,4-di-*O*-benzyl-2,3-*O*-isopropylidene-L-threitol as an oil (115–116 g).

D. *1,4-Di-O-benzyl-L-threitol*. The crude ketal is dissolved in methanol (300 mL), 0.5 *N* hydrochloric acid (30 mL) is added, and the resulting mixture is heated to reflux. Acetone and methanol are slowly distilled off (Note 29). Additional methanol (50 mL) and 0.5 *N* hydrochloric acid (20 mL) are added and the mixture is kept at room temperature until ketal hydrolysis is complete. The mixture is diluted with saturated sodium bicarbonate solution (500 mL) and extracted with ether (3 × 500 mL). The ether extracts are combined, dried over anhydrous magnesium sulfate, and filtered. Removal of volatile material under reduced pressure gives crude 1,4-di-*O*-benzyl-L-threitol as a pale-yellow solid. This solid is recrystallized twice from chloroform/hexanes to provide 59–65 g (195–215 mmol, 57–63% yield) of pure diol, mp 54–55°C (Note 30) and (Note 31). Concentration of the mother liquors from the recrystallizations gives a yellow solid that is chromatographed on 70–230-mesh silica gel 60 (500 g) (Note 32), and eluted with 50% ethyl acetate/hexanes, to provide an additional 20–26 g (66–86 mmol, 19–25% yield) of diol, mp 56–57°C (Note 33).

2. Notes

1. Dimethyl 2,3-*O*-isopropylidene-L-tartrate is also commercially available from Fluka Chemical Corporation.
2. L-tartaric acid, 99 + %, mp 170–172°C, $[\alpha]_D^{20}$ + 12.4° (water, *c* 20), from Aldrich Chemical Company, Inc., was used as obtained.
3. 2,2-Dimethoxypropane, 98%, from Aldrich Chemical Company, Inc., was distilled before use. The checkers used this material directly from the bottle without adverse effects.
4. Methanol was distilled from sodium methoxide before use. The checkers used absolute methanol from Fisher Chemical Company directly from the bottle without adverse effects.
5. *p*-Toluenesulfonic acid monohydrate, 99%, from Aldrich Chemical Company, Inc., was used as obtained.
6. This procedure normally requires 1–2 hr.
7. Reagent-grade cyclohexane, from MCB Manufacturing Chemists Inc., was used as obtained.
8. Removal over a 2-day period (10–15 mL/hr) is satisfactory. After approximately 600 mL of distillate has been collected, the temperature at the solvent head is approximately 79°C.

9. The checkers omitted this final addition and 15-min reflux period without adverse effects.
10. This normally occurs within 1–2 hr, leaving a yellow solution.
11. This product was ≥88% pure based on recovery of an analytical sample from chromatography on silica gel 60 eluted with 30% ethyl acetate/hexanes. Physical properties and spectral data are as follows: $[\alpha]_D^{24}$ −42.6° ($CHCl_3$, *c* 5.1), lit. $[\alpha]_D^{20}$ −49.4° (neat);[2] IR (neat) cm^{-1}: 2992, 2956, 1759, 1438, 1384, 1213, 1111, 1013, 858, 749; ^1H NMR ($CDCl_3$) δ: 1.49 (s, 6 H), 3.83 (s, 6 H), 4.81 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ: 25.98, 52.42, 76.68, 113.49, 169.75. The checkers found this material to be 91–94% pure by gas chromatography.
12. Dimethyl 2,3-*O*-isopropylidene-D-threitol was prepared similarly.
13. 2,3-*O*-Isopropylidene-L-threitol is also commercially available from Aldrich Chemical Company Inc. and from Fluka Chemical Corporation.
14. Lithium aluminum hydride, ≥95%, from Aldrich Chemical Company, Inc., was used as obtained.
15. Diethyl ether was distilled from sodium immediately prior to use.
16. An ice–salt or ice–acetone bath is employed.
17. Dropwise addition via a funnel is recommended. During the quenching procedure, stirring becomes difficult for a time and manual swirling may be necessary. Use of a stirrer with a powerful magnet is recommended.
18. *Cautious* scraping of the sides of the flask to expose isolated pockets of unquenched lithium aluminum hydride may be expeditious at this point.
19. The checkers obtained a greater yield by carrying out the Soxhlet extraction with tetrahydrofuran instead of ether.
20. This product was ≥80% pure based on recovery of an analytical sample from chromatography on silica gel 60 eluted with 80% ethyl acetate/hexanes. Physical properties and spectral data are as follows: $[\alpha]_D^{24}$ +2.78° ($CHCl_3$, *c* 4.67), lit. $[\alpha]_D^{20}$ +4.1° ($CHCl_3$, *c* 5);[3] IR (neat) cm^{-1}: 3413, 2987, 2934, 1455, 1372, 1218, 1166, 1057, 986, 882, 844, 801, 756; ^1H NMR ($CDCl_3$) δ: 1.42 (s, 6 H), 3.73 (m, 6 H), 3.94 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ: 26.75, 62.06, 78.32, 109.08. The checkers found this material to be 95–97% pure by gas chromatography.
21. 2,3-Di-O-isopropylidene-D-threitol was prepared similarly.
22. Sodium hydride, 55–60% dispersion in mineral oil, from Alfa Products, Morton/Thiokol, Inc., was used as obtained.
23. Hexanes were distilled from calcium hydride prior to use.
24. The hexane washes can be decanted into a larger beaker containing isopropyl alcohol and dry ice. The last traces of hexanes can be removed under vacuum, followed by reintroduction of an argon atmosphere.
25. Tetrahydrofuran was distilled from sodium immediately prior to use.
26. Toward the end of this addition stirring becomes increasingly difficult. Use of a stirrer with a powerful magnet is recommended.
27. Benzyl bromide from Fluka Chemical Corporation was used as obtained.
28. If magnetic stirring is impossible at this point, manual swirling of the flask

may be necessary for a time. As the alkylation proceeds, the mixture becomes less viscous.

29. This procedure requires 3–5 hr. Progress of this hydrolysis can be monitored by thin-layer chromatography on 0.25-mm silica gel 60 plates eluted with 50% ethyl acetate/hexanes; R_f ketal 0.59, R_f diol 0.21.

30. Physical properties and spectral data for 1,4-di-*O*-benzyl-L-threitol are as follows: $[\alpha]_D^{24}$ −5.85° ($CHCl_3$, *c*, 5.15), lit. $[\alpha]_D^{25}$ −5.0 ($CHCl_3$, *c* 5);[4] IR ($CHCl_3$) cm^{-1}: 3562, 3065, 3014, 2867, 1495, 1453, 1361, 1233, 1101, 1027; ^1H NMR ($CDCl_3$) δ: 2.93 (br s, 2 H), 3.54–3.60 (m, 4 H), 3.83–3.87 (m, 2 H), 4.47–4.57 (m, 4 H), 7.23–7.36 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ: 70.45, 71.85, 73.45, 127.70, 128.37, 137.66.

31. 1,4-Di-*O*-benzyl-D-threitol was prepared similarly; $[\alpha]_D^{24}$ +6.16° ($CHCl_3$, *c* 3.83).

32. E. Merck 70–230-mesh silica gel 60 from Curtin-Matheson Scientific was employed.

33. The checkers found that the solid obtained by recrystallization from chloroform/hexanes occludes a large amount of solvent. To obtain pure, dry material, it is necessary to press the moist solid while it is still on the Büchner funnel and then to dry it under vacuum (room temperature, 0.05 mm, 12–18 hr). Only 35 g of pure material was obtained in this manner. Repetition of the process with the mother liquors yielded another 35 g of material. The remaining product (ca. 20 g) was obtained by chromatography. Recrystallization from ethyl acetate/hexanes gave a product that is easier to dry.

3. Discussion

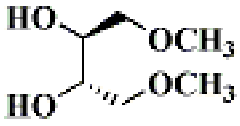
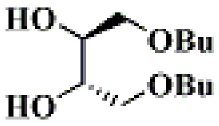
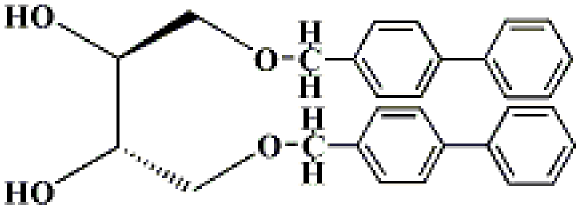
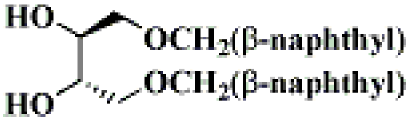
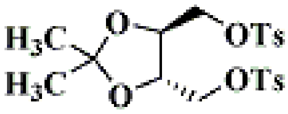
Homochiral molecules readily available from inexpensive sources are useful synthetic building blocks and chiral auxiliaries. 1,4-Di-*O*-benzyl-L-threitol has been used in construction of homochiral crown ethers that are useful as enzyme model systems.[5 6 7] Topologically controlled diastereoselective delivery of the Simmons–Smith reagent for 2-cycloalken-1-one 1,4-di-*O*-benzyl-L-threitol ketals was recently reported.[8 9 10]

A number of other enantioselective processes are known to depend on homochiral acetal or ketal participation.[11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26] Diols used in these reactions include tartrate esters, tartramides, propanediols, butanediols, and pentanediols. 1,4-Di-*O*-benzyl-L-threitol may prove superior to other diols since it (a) can be produced inexpensively in quantity in either enantiomeric form; (b) is an amorphous solid; (c) contains a UV chromophore, making derivatives easy to monitor; (d) can be introduced directly or via transketalization; and (e) provides "functionalized arms" which can be chemically manipulated after ketalization.

The preparation of 1,4-di-*O*-benzyl-L-threitol described here from L-tartaric acid via 2,3-*O*-isopropylidene-L-threitol is adapted from work by Carmack,[2] Feit,[3] and Inouye.[4] This general route has been employed by the submitters and by others for the

production of a number of synthetically useful L-threitol derivatives (Table I). The corresponding D-threitol derivatives are as easily prepared from commercially available D-tartaric acid.

TABLE I

Electrophile	Threitol Derivative	Yield, %[a]	Reference
Methyl iodide		62	27
Butyl iodide		37	27
4-(Chloromethyl) biphenyl		53	28
2-(Bromomethyl) naphthalene		83	28
p-Toluenesulfonyl chloride		82–90	1, 27, 29
Methanesulfonyl chloride		75–82	2, 30

This preparation is referenced from:

- Org. Syn. 76, 12
- Org. Syn. 76, 101

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

2,3-Butanediol, 1,4-bis(phenylmethoxy)- [S-(R*,R*)]-

hexanes

2-cycloalken-1-one 1,4-di-O-benzyl-L-threitol

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium bicarbonate (144-55-8)

cyclohexane (110-82-7)

acetone (67-64-1)

sodium methoxide (124-41-4)

sodium (13966-32-0)

isopropyl alcohol (67-63-0)

tartaric acid, L-tartaric acid (87-69-4)

Methyl iodide (74-88-4)

magnesium sulfate (7487-88-9)

benzyl bromide (100-39-0)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

sodium hydride (7646-69-7)

hexane (110-54-3)

2-(Bromomethyl)naphthalene (939-26-4)

calcium hydride (7789-78-8)

Methanesulfonyl chloride (124-63-0)

2,2-dimethoxypropane (77-76-9)

argon (7440-37-1)

p-Toluenesulfonyl chloride (98-59-9)

THREITOL, D-threitol (6968-16-7)

Butyl iodide (542-69-8)

4-(Chloromethyl)biphenyl (1667-11-4)

p-toluenesulfonic acid monohydrate (6192-52-5)

D-tartaric acid (147-71-7)

2,3-O-isopropylidene-L-threitol (50622-09-8)

2,3-Di-O-isopropylidene-L-threitol (50622-09-8)

Dimethyl 2,3-O-isopropylidene-L-tartrate

1,4-Di-O-benzyl-L-threitol (17401-06-8)

1,4-di-O-benzyl-2,3-O-isopropylidene-L-threitol (68394-39-8)

Dimethyl 2,3-O-isopropylidene-D-threitol

2,3-Di-O-isopropylidene-D-threitol

1,4-Di-O-benzyl-D-threitol

L-threitol

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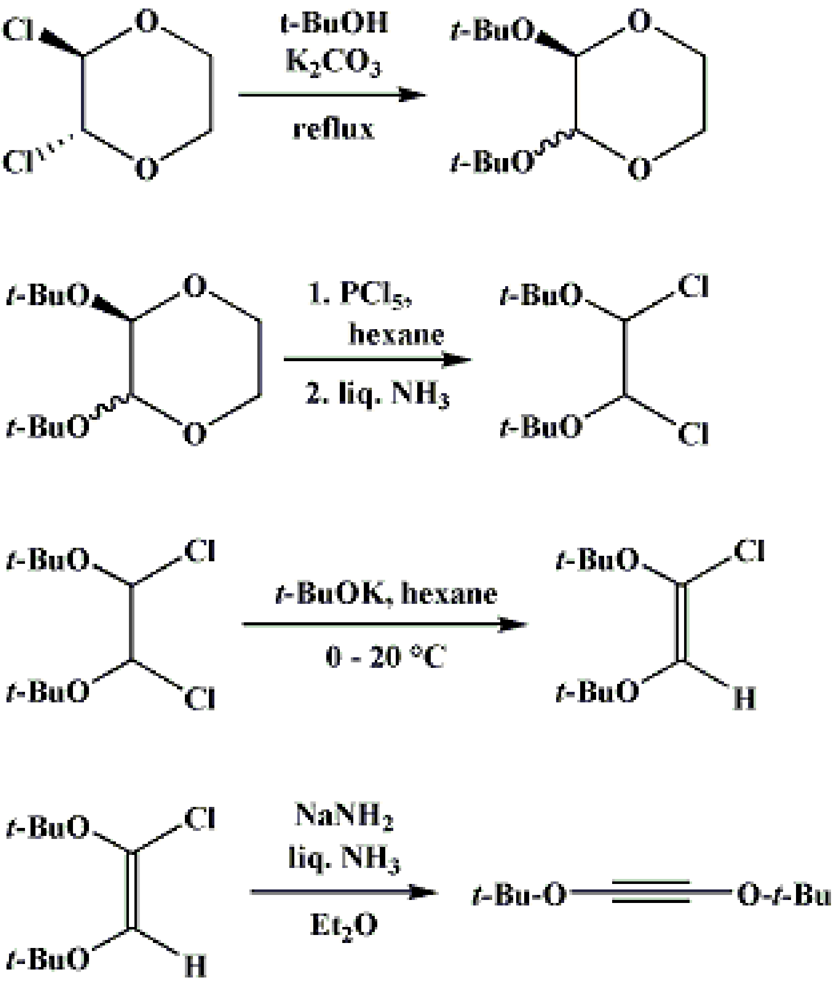
Organic Syntheses, CV 8, 161

DIALKOXYACETYLENES: DI-*tert*-BUTOXYETHYNE, A VALUABLE SYNTHETIC INTERMEDIATE

[Propane, 2,2'-j[1,2-ethynediylbis(oxy)]bis[2-methyl-]



Submitted by Anna Bou, Miquel A. Pericàs, Antoni Riera, and Fèlix Serratosa.
Checked by Terry Singleton, Jae Chan Park, Martin F. Semmelhack, Sean M. Kerwin, and Clayton H. Heathcock.

1. Procedure

A. (1) *Preparation of trans-2,3-dichloro-1,4-dioxane*. (See (Note 1).) To a 2-L, three-necked, round-bottomed flask, equipped with two inlet tubes (with sintered-glass diffusers at the end) connected to a chlorine cylinder, and a reflux condenser connected to an outlet tube immersed in a potassium hydroxide solution, are added 1200 g (13.64 mol) of anhydrous dioxane (*free of peroxides!*) and 8 g (0.03 mol) of iodine. A stream of chlorine is passed through the dioxane/iodine solution heated at 90° C, and the reaction is monitored by NMR spectroscopy. After 9 hr, the conversion is 50% complete (Note 2); after 33 hr, about 90% complete. At this point, the stream of chlorine is interrupted. *Reinitiation of the chlorine stream after some hours (next*

morning, for example) may be dangerous because it was observed in one case the mixture inflamed spontaneously! The reaction mixture is allowed to cool to room temperature, 500 mL of ether is added, and the solution is washed with aqueous sodium thiosulfate solution. The organic layer is separated, dried over sodium sulfate, the ether is evaporated under reduced pressure, and the residue is distilled through a 20-cm Vigreux column, to yield 1200–1300 g of *trans*-2,3-dichloro-1,4-dioxane, bp 89°C/16 mm (lit.[1] bp 82.5°C/14 mm; mp 31°C) (Note 3).

(2) *2,3-Di-tert-butoxy-1,4-dioxane.* To a 2-L, three-necked, round-bottomed flask, equipped with a mechanical stirrer, a reflux condenser protected from moisture by a drying tube, and an inlet tube for dry nitrogen, are added 103.6 g (0.66 mol) of *trans*-2,3-dichloro-1,4-dioxane, 979.1 g (13.23 mol) of anhydrous *tert*-butyl alcohol (distilled from CaH_2), and 365.1 g (2.64 mol) of potassium carbonate (ground with a mortar and pestle and activated at 250°C for 3 hr) (Note 4). The mixture is stirred vigorously and heated under reflux for 24–30 hr, the progress of the reaction being monitored by ^{1}H NMR spectroscopy. Once the singlet at δ 5.95, corresponding to the methine protons of the starting material, has completely disappeared, the reaction mixture is allowed to cool to room temperature, and poured into 500 mL of ether, and enough water (750–850 mL) is added to dissolve all of the inorganic salts. The organic layer is separated, and the aqueous layer is extracted with two 200-mL portions of ether. The combined ether extracts are dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 128–147 g of an oily residue (Note 5). Hexane (250 mL) is added and the solution is allowed to stand in a refrigerator. The resulting crystals are separated by suction filtration and washed thoroughly with 150–250 mL of hexane. The residue of 3–6 g of crystalline product, mp 106–107°C, which remains insoluble, is identified as *trans*-2-*tert*-butoxy-3-hydroxy-1,4-dioxane (Note 6). The filtrate (which contains approximately a 25 : 75 mixture of *cis* and *trans* isomers) is evaporated under reduced pressure to one-half its volume and is cooled to 0°C. Massive crystals appear, which are collected by suction filtration. The crystallization process is repeated once more to give 40–60 g of *trans*-2,3-di-*tert*-butoxy-1,4-dioxane, mp 64–65°C. The hexane solution is evaporated under reduced pressure and the oily residue distilled at 50–57°C/0.25 mm to give 54–84 g of a mixture of *cis*- and *trans*-2,3-di-*tert*-butoxy-1,4-dioxane (115–124 g combined; 75–81% yield) (Note 7).

B. *1,2-Di-tert-butoxy-1,2-dichloroethane.* To a 250-mL, round-bottomed flask, equipped with a pressure-equalizing dropping funnel protected from moisture by a drying tube, and a magnetic stirring bar, are added 43.2 g (0.21 mol) of phosphorus pentachloride and 50 mL of hexane, and the flask is cooled with an ice–salt bath. While the solution is stirred, a solution of 30 g (0.13 mol) of 2,3-di-*tert*-butoxy-1,4-dioxane in 100 mL of hexane is added dropwise. After the addition is complete, the cooling bath is removed and the mixture is stirred at room temperature for 90–180 min until no starting material is observed in the NMR spectrum of a sample (Note 8); the reaction mixture is then filtered through a sintered-glass filter to remove excess

phosphorus pentachloride. The resulting hexane solution (200 mL), which contains 1,2-di-*tert*-butoxy-1,2-dichloroethane, 2-chloroethyl dichlorophosphate, 1,2-dichloroethane, phosphorus oxychloride, and traces of phosphorus pentachloride, is transferred into a 1-L, three-necked, round-bottomed flask, equipped with a magnetic stirrer, a dry-ice condenser protected from moisture by a potassium hydroxide tube, and a short inlet tube connected to an ammonia cylinder. The reaction flask is cooled with a dry ice–acetone bath and, while the solution is stirred (Note 9), a fast stream of gaseous ammonia is introduced. A vigorous reaction takes place and a copious white precipitate forms. The stream of gaseous ammonia is continued for 15–60 min (Note 10). The cooling bath and condenser are removed, the reaction flask is connected to an ordinary aspirator line through a potassium hydroxide drying trap, and the ammonia is evaporated under aspirator vacuum with efficient stirring. The ammonia-free solution is filtered through a sintered-glass filter and the precipitate is washed with hexane. The resulting hexane solution (400–500 mL), which contains 25–26 g (0.12 mol) of pure 1,2-di-*tert*-butoxy-1,2-dichloroethane, is suitable for the next operation (yields, calculated from an aliquot, are 95–97%) (Note 11).

C. *(E)-1,2-Di-tert-butoxy-1-chloroethene.* The solution prepared above is placed in a 1-L, round-bottomed flask, equipped with a magnetic stirring bar and a Liebig condenser (protected from moisture by a drying tube) and cooled with an ice bath; 28.9 g (0.258 mol) of solid potassium *tert*-butoxide is added in small portions through the condenser over a 30-min period. After addition, the cooling bath is removed and stirring is continued for 90–120 min until no more starting material is detected in the ^{1}H NMR spectrum of a sample; enough ice water is then added to just dissolve all the inorganic salts. The organic layer is separated and the aqueous layer is extracted with hexane (2 × 100 mL). The combined hexane extracts are dried over anhydrous sodium sulfate, filtered, and concentrated at aspirator vacuum. The residue is distilled at 40°C/0.2 mm, with the collection flask at −78°C, to give a center cut of (*E*)-1,2-di-*tert*-butoxy-1-chloroethene (15.4–17.0 g, 58–63% yield from 2,3-di-*tert*-butoxy-1,4-dioxane) (Note 12) and (Note 13).

D. *Di-tert-butoxyethyne.* In a 2-L, three-necked, round-bottomed flask, equipped with a magnetic stirring bar (Note 14), a dry-ice condenser protected from moisture by a potassium hydroxide tube, and a pressure-equalizing dropping funnel, 0.5 mol of sodium amide is prepared in 500 mL of liquid ammonia (Note 15), and 20 g (0.0968 mol) of (*E*)-1,2-di-*tert*-butoxy-1-chloroethene dissolved in 150 mL of anhydrous ether is added in a 5-min period with efficient stirring. After the addition, stirring is continued for 80 min. The reaction mixture is diluted with 200 mL of cold pentane (−20 to −30°C), and 400 mL of cold water is added very cautiously. The organic layer is washed with 50 mL of a 0.1 *M* buffered phosphate solution (NaH_2PO_4/Na_2HPO_4), dried over anhydrous sodium sulfate (Note 16), filtered, and concentrated at aspirator vacuum without heating to give 10–12 g (78–86% yield) of di-*tert*-butoxyethyne as a pale-yellow oil. The product is sufficiently pure for further reactions (Note 17), but it may be distilled at 30°C/0.05 mm; freezing point 8.5°C.

2. Notes

1. This procedure was reported by J. J. Kucera and D. C. Carpenter.[1,2]
2. These data were obtained by the checkers. The submitters report conversion of 76–80% after only 9 hr. It seems likely that the rate of the reaction may be sensitive to the dimensions and mechanical features of the chlorine introduction system, and/or an induction period. It is easy and important to monitor the process.
3. *trans*-2,3-Dichloro-1,4-dioxane has the following spectra: IR (CCl_4) cm^{-1}: 2990, 2940, 2885, 1455, 1385, 1375, 1337, 1160, 1115, 1032, 900, 875, 670; ^1H NMR (CCl_4)[2b] δ: 3.40–4.57 (AA'BB', 4 H, CH_2), 5.95 (s, 2 H, ClCHO).
4. The yields of this reaction are very sensitive to the presence of traces of moisture and to the ratio of reagents. If one works without a nitrogen atmosphere and with *tert*-butyl alcohol that has not been previously dried over calcium hydride, with a 1 : 10 ratio of dichloro derivative/alcohol, the yields drop to 65%.
5. *Caution should be exercised in evaporation of the ether, as the di-tert-butoxy compounds are appreciably volatile at reduced pressure. If a rotary evaporator is used for the concentration, the water bath should be kept at or below room temperature, and the residue should not be pumped after it is clear that the bulk of the ether has been evaporated.*
The submitters report ca. 130 g of oily residue at this stage. Treatment of the oily residue with 105 mL of ether leads to partial crystallization. During washing of the crystals in a Büchner filter with more ether, an almost complete solubilization takes place, but eventually 0.1–0.5 g of *cis*-2,3,7,10-tetraoxabicyclo[4.4.0]decane remains as an insoluble residue. This compound was prepared for the first time in 1931;[3] the *cis* configuration was established only in 1966.[4] It has the following properties: mp 136°C; IR (CCl_4) cm^{-1}: 2980, 2955, 2930, 2910, 2875, 1460, 1350, 1285, 1260, 1250, 1150, 1140, 1095, 1080, 1025, 910, 870, 780; ^1H NMR (CCl_4) δ: 3.30–4.20 (AA'BB', 8 H CH_2), 4.60 (s, 2 H, OCHO).
6. The crystalline trans isomer epimerizes in chloroform solution to give a nearly 70 : 30 mixture of *cis* and *trans* isomers. The *trans* isomer, mp 106–107° C, shows the following spectroscopic properties: IR (KBr) cm^{-1}: 3450, 2980, 2935, 2890, 1445, 1390, 1370, 1335, 1280, 1260, 1200, 1135, 1105, 1060, 1045, 1035, 1020, 910, 855, 780; ^1H NMR (CCl_4) δ: 1.27 (s, 9 H, CH_3), 3.33–4.13 (ABCD + OH, 4 H + 1 H) 4.57 (br, 2 H, OCHO). Anal. calcd. for $C_8H_{16}O_4$: C, 54.53; H, 9.15. Found: C, 54.53; H, 9.29.
7. *trans*-2,3-di-*tert*-butoxy-1,4-dioxane has the following spectra: IR (CCl_4) cm^{-1}: 2975, 2930, 1390, 1367, 1190, 1145, 1100, 1060, 1040, 857; ^1H NMR (CCl_4) δ: 1.19 (s, 18 H, CH_3), 3.05–4.20 (m, AA'BB', 4 H, CH_2), 4.30 (s, 2 H, OCHO). *cis*- + *trans*-2,3-Di-*tert*-butoxy-1,4-dioxane have the following

additional signals: IR (CCl_4) cm^{-1}: 1170, 1130, 1120, 1080, 1020, 1000, 960, 879; ^1H NMR (CCl_4) δ: 4.43 (s, 2 H, OCHO, *cis*).

8. The peaks corresponding to 2,3-di-*tert*-butoxy-1,4-dioxane overlap with those of the methylene protons of 2-chloroethyl dichlorophosphate, a by-product from the reaction, but the absence of the acetal protons of the starting material is clear from the symmetry of the multiplet.

9. The solution is thick at −78°C. Dilution with additional hexane may be necessary.

10. The end of the reaction can be easily detected because, when all of the 2-chloroethyl dichlorophosphate has been destroyed, the reaction mixture *does not crackle* any more when condensed ammonia drops on the stirred mixture, or, much more easily, when the reaction mixture becomes basic to pH paper.

11. The crude reaction mixture is, in fact, an approximately 30 : 70 mixture of *dl*- and *meso*-1,2-di-*tert*-butoxy-1,2-dichloroethane. Although the ^1H NMR spectrum at 60 MHz (CCl_4) shows only one singlet at 5.6 ppm, the 200-MHz spectrum ($CDCl_3$) shows two sharp singlets separated by 1.8 Hz. The pure meso compound could be isolated by crystallization and purified by sublimation at 40° C/0.05 mm; mp 77–78° (dec). The spectra are as follows: IR (CCl_4) cm^{-1}: 2975, 2925, 1470, 1458, 1390, 1368, 1310, 1250, 1180, 1130, 1025, 850, 650; ^1H NMR at 200 MHz ($CDCl_3$) δ: 1.36 (s, 9 H, CH_3), 5.73 (s, 1 H, OCHCl).

12. In later fractions, small amounts (0.2–0.5%) of (*Z*)-1,2-di-*tert*-butoxy-1-chloroethane have been detected: ^1H NMR (CCl_4) δ: 1.25 (s, 9 H, CH_3), 1.33 (s, 9, H, CH_3), 6.03 (s, 1 H, = CH).

13. (*E*)-1,2-Di-*tert*-butoxy-1-chloroethene has the following properties: n_D^{25} 1.4410–1.4415; UV (cylohexane): 217.7 nm (log ε = 3.7); IR (CCl_4) cm^{-1}: 2972, 1670, 1470, 1390, 1366, 1290, 1260, 1240, 1180, 1140, 1070, 1025, 935; ^1H NMR (CCl_4) δ: 1.26 (s, 9 H, CH_3), 1.33 (s, 9 H, CH_3), 5.91 (s, 1 H, = CH).

14. The stirring bar must be glass-covered, since sodium in ammonia solution attacks Teflon.

15. The method used for the preparation of sodium amide is a modification of the procedure described by Nieuwland et al.[5] In a 3-L, three-necked, round-bottomed flask, equipped with a magnetic stirring bar (Note 14), a dry-ice condenser protected from moisture by a potassium hydroxide tube, and an inlet tube connected to the ammonia cylinder, is condensed 500 mL of liquid ammonia. A slow stream of dry oxygen is initiated through the inlet tube and 11.5 g (0.5 mol) of sodium in small pieces is slowly introduced. The addition of sodium requires 4–5 hr, since the blue color must be discharged before each new addition of sodium. In this way, a completely white suspension of sodium amide is obtained, which allows the formation of crude di-*tert*-butoxyethyne, free from any iron impurities.

16. It is best to minimize exposure of di-*tert*-butoxyethyne to light.

17. Eventually, if a more concentrated solution of (*E*)-1,2-di-*tert*-butoxy-1-

chloroethene in ether is used, the formation of 1,2,3-tri-*tert*-butoxy-3-cyano-1-propene [^{1}H NMR (CCl_4) δ: 6.05 (s, 1 H), 4.98 (s, 1 H), 1.28 (br, 27 H)] and 1,2,3-tri-*tert*-butoxy-1-cyano-1-propene [^{1}H NMR (CCl_4) δ: 4.03 (s, 2 H), 1.28 (b, 27 H)] is observed. The by-products may be eliminated by column chromatography on neutral alumina (40 g, 100–125 mesh, activity 1), using a column refrigerated at 0°C and protected from the light, and eluting with pentane under nitrogen pressure. From the first 750 mL of eluant, 9–12 g of pure di-*tert*-butoxyethyne is obtained.

18. Di-*tert*-butoxyethyne has the following properties: n_D^{25} 1.4365; IR (CCl_4) cm^{-1}: 2972, 2922, 1470, 1450, 1390, 1367, 1301, 1263, 1245, 1150, 825; ^{1}H NMR (CCl_4) δ: 1.31 (s, CH_3).

3. Discussion

The present procedure for the preparation of di-*tert*-butoxyethyne is an improvement of a method previously reported by the submitters,[6] who have also reported the preparation from glyoxal via 1,2-dichloro-1,2-dimethoxyethane.[6]

Although acetylenic diethers are thermodynamically stable compounds, they show a high kinetic instability that induces polymerization even at low temperatures.[7]

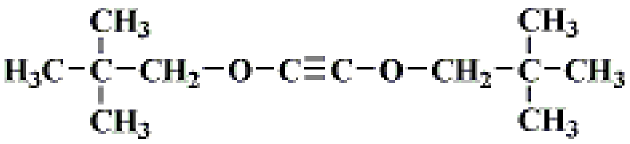
Different acetylenic diethers have been prepared, either from glyoxal (method B) or from dioxane (method A); their stability correlates well, in a qualitative way, with Charton's ν steric parameter,[8] based on effective Van der Waals radii for the corresponding alkoxy groups (Table I).

TABLE I
ACETYLENIC DIETHERS

$RO-C\equiv C-OR$

RO-C C-OR

-OR	Method	ν	t Order of magnitude (by NMR)
$H_3CO-C\equiv C-OCH_3$ $-OCH_3$	B9	0.38	Seconds (0°C, soln.)

$-OC_2H_5$	B_7	0.48	Seconds (0°C, soln.)
 $-OCH_2C(CH_3)_3$	A[10]	0.70	Minutes (RT,[a] soln.)
$-OCH(CH_3)_2$	A,B[6]	0.75	Minutes (RT, soln.)
$-OC(CH_3)_3$	A,B[6]	1.22	Days (RT, neat)

[a] Room temperature

.

As shown above, di-*tert*-butoxyethyne is the only acetylenic diether prepared so far whose stability allows its use as a synthetic intermediate. It has been used in the synthesis of all the members of the series of monocyclic oxocarbons (deltic, squaric, croconic, and rhodizonic acids),[9 10 11 12] as well as in the synthesis of semisquaric acid, the parent compound of the natural mycotoxins, *moniliformins.*[10]

Di-*tert*-butoxyethyne, like other acetylenic ethers having hydrogen atoms β to oxygen, is thermally unstable, and when a benzene solution is heated under reflux, elimination occurs to give isobutene and *tert*-butoxyketene. *tert*-Butoxyketene then reacts with the parent acetylene to afford 2,3,4-tri-*tert*-butoxycyclobutenone, which is the precursor of squaric and semisquaric acid.[9,10] This thermal instability prevents the use of di-*tert*-butoxyethyne in those reactions that proceed at temperatures higher than 40–50°C.

On the other hand, di-*tert*-butoxyethyne is prone to undergo a variety of reactions with transition-metal complexes [$PdCl_2CH_3CN$, $Co_2(CO)_8$, $CpCo(CO)_2$, $Ni(CO)_4$], to afford new, transient, intermediate complexes which are the actual precursors of oxocarbons.[13]

141516

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

dl- and meso-1,2-di-tert-butoxy-1,2-dichloroethane

Propane, 2,2'-j[1,2-ethynediylbis(oxy)]bis[2-methyl-

ACETAL (105-57-7)

potassium carbonate (584-08-7)

acetylene (74-86-2)

ammonia (7664-41-7)

Benzene (71-43-2)

ether (60-29-7)

hydrogen (1333-74-0)

glyoxal (107-22-2)

phosphorus pentachloride (10026-13-8)

chloroform (67-66-3)

iron (7439-89-6)

sodium sulfate (7757-82-6)

oxygen (7782-44-7)

sodium thiosulfate (7772-98-7)

1,2-dichloroethane (107-06-2)

nitrogen (7727-37-9)

iodine (7553-56-2)

methine (7782-42-5)

Phosphorus Oxychloride (21295-50-1)

chlorine (7782-50-5)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

Pentane (109-66-0)

dioxane (5703-46-8)

methylene (2465-56-7)

isobutene (9003-27-4)

sodium amide (7782-92-5)

hexane (110-54-3)

tert-butyl alcohol (75-65-0)

calcium hydride (7789-78-8)

phosphate

trans-2,3-Dichloro-1,4-dioxane (3883-43-0)

2-chloroethyl dichlorophosphate (1455-05-6)

1,2-dichloro-1,2-dimethoxyethane

potassium tert-butoxide (865-47-4)

Di-tert-butoxyethyne (66478-63-5)

trans-2-tert-butoxy-3-hydroxy-1,4-dioxane

trans-2,3-di-tert-butoxy-1,4-dioxane

2,3-Di-tert-butoxy-1,4-dioxane, cis- and trans-2,3-di-tert-butoxy-1,4-dioxane (68470-79-1)

1,2-Di-tert-butoxy-1,2-dichloroethane (68470-81-5)

(E)-1,2-Di-tert-butoxy-1-chloroethene (70525-93-8)

cis-2,3,7,10-tetraoxabicyclo[4.4.0]decane

(Z)-1,2-di-tert-butoxy-1-chloroethane

1,2,3-tri-tert-butoxy-3-cyano-1-propene

1,2,3-tri-tert-butoxy-1-cyano-1-propene

tert-butoxyketene

2,3,4-tri-tert-butoxycyclobutenone

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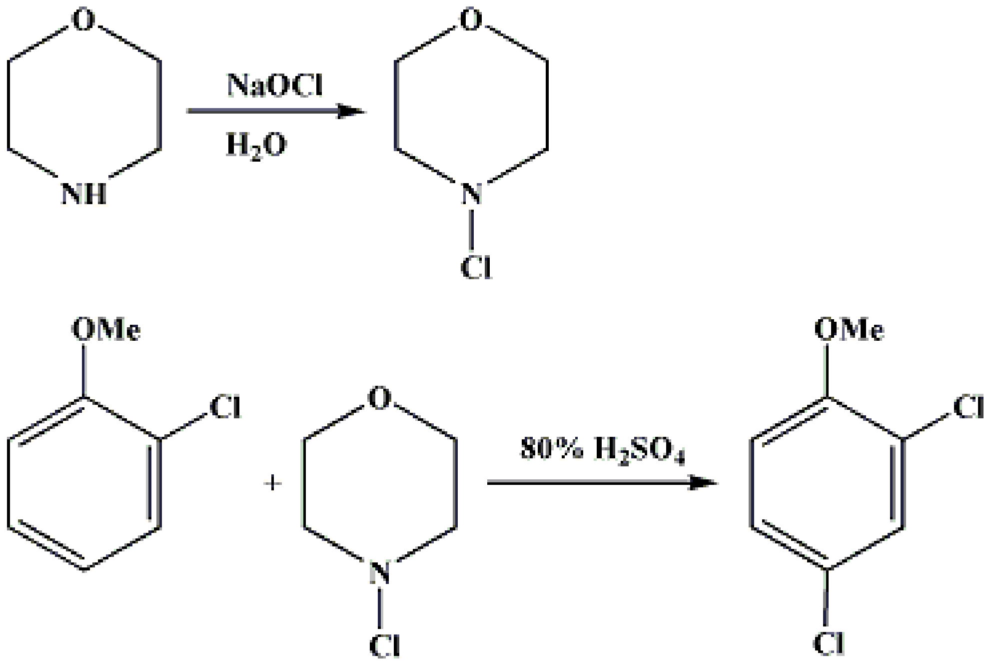
4-CHLORINATION OF ELECTRON-RICH BENZENOID COMPOUNDS: 2,4-DICHLOROMETHOXYBENZENE

[Benzene, 2,4-dichloro-1-methoxy-]



Submitted by John R. Lindsay Smith, Linda C. McKeer, and Jonathan M. Taylor[1].
Checked by Yasushi Morita and Ryoji Noyori.

1. Procedure

A. *N-Chloromorpholine.* A 500-mL, three-necked, round-bottomed flask equipped with a dropping funnel, a mechanical stirrer, and a thermometer is charged with 250 mL of 1.5 *M* sodium hypochlorite solution (Note 1). The solution is stirred and the temperature is maintained below 10°C while 30 mL (0.34 mol) of morpholine (Note 2) is added dropwise. The resulting mixture is stirred for 5 min before the *N*-chloromorpholine is extracted with four 50-mL portions of diethyl ether. The combined ether extracts are dried over anhydrous magnesium sulfate and concentrated with a rotary evaporator (Note 3). The concentrate is distilled at reduced pressure (Note 4) to afford 35.5–36.5 g (86–88%) of *N*-chloromorpholine, bp 63–64°C (36–38 mm) (Note 5).

B. *2,4-Dichloromethoxybenzene.* A 500-mL, three-necked, round-bottomed flask equipped with a dropping funnel, a mechanical stirrer, and a thermometer is charged with 250 mL of 80% (v/v) sulfuric acid (Note 6) and cooled in an ice bath before 16 g

(0.11 mol) of 2-chloromethoxybenzene (Note 7) is added with stirring. The stirring and cooling are maintained while 14.5 g (0.12 mol) of *N*-chloromorpholine is added dropwise (Note 8). The cooling bath is removed and stirring is continued for 1 hr. The reaction mixture is carefully poured into a mixture of 150 mL of distilled water and 100 g of crushed ice in a 1-L flask cooled at 0°C (Note 9). The aromatic products are extracted with a 100-mL portion, followed by four 50-mL portions, of diethyl ether. The combined ether extracts are washed with 100 mL of water containing 0.5 g of potassium iodide, 2 g of sodium thiosulfate and 2 mL of acetic acid (Note 10) followed by 50 mL of 8% (w/v) aqueous sodium hydroxide (Note 11), dried over anhydrous magnesium sulfate, and concentrated with a rotary evaporator. The concentrate is distilled under reduced pressure to afford 15.2–16.0 g (77–81%) of 2,4-dichloromethoxybenzene, bp 110–111°C (10 mm) [lit.[2] bp 125°C (10 mm), 233°C (740 mm)]. The product after distillation is 98.9–99.2% pure; the major impurities are 2,6-dichloromethoxybenzene (0.4–0.5%) and 2,4,6-trichloromethoxybenzene (0.4–0.6%) (Note 12) and (Note 13). If this above purity is insufficient, it can be improved to >99.9% by recrystallization (Note 14) and (Note 15).

2. Notes

1. Solutions of sodium hypochlorite of different concentrations can be used with a corresponding change in the volume. The submitters purchased sodium hypochlorite solution from BDH Chemicals Ltd., England. The material initially contains 10–14% available chlorine, but it deteriorates on standing over a period of weeks. The checkers used the material (chlorine content 9–14%) purchased from Nakarai Chemicals, Ltd., Japan.
2. Gold Label-grade morpholine (≥99%) was obtained from Aldrich Chemical Company, Inc., and used as supplied.
3. Since *N*-chloromorpholine has a low boiling point, the water-bath temperature should not exceed 30°C.
4. It is recommended that a water or oil bath, or a hot-air blower, be used for this distillation to avoid the risk of local overheating.
5. *N*-Chloromorpholine should be handled with extreme care at all times. On standing at room temperature it slowly decomposes, forming crystals of morpholine hydrochloride. However, it can be stored for several weeks at −18°C. Vigorous decomposition of *N*-chloromorpholine has been reported when it is distilled at atmospheric pressure.[3] The checkers removed the small quantity of salt contamination by filtration through a glass filter and used the pure liquid in the subsequent chlorination reaction.
6. Trifluoroacetic acid, 100 mL, obtainable from Aldrich Chemical Company, Inc., can be used instead of aqueous sulfuric acid (see Discussion).
7. 2-Chloromethoxybenzene was obtained from Aldrich Chemical Company, Inc., and was distilled prior to use, bp 195–196°C or 112°C (41 mm).
8. Since the dissolution of *N*-chloromorpholine in sulfuric acid (or trifluoroacetic acid) and the subsequent reaction between protonated *N*-

chloromorpholine and 2-chloromethoxybenzene are both exothermic processes, the addition of the chloramine should be carried out at such a rate as to keep the reaction temperature below 5°C. The checkers found that a reaction run at 8°C gave product of only 93% purity.

9. If the reaction is carried out in trifluoroacetic acid, the product mixture is made basic by adding it cautiously, with cooling and stirring, to a cold solution of 50 g of sodium hydroxide in 150 mL of distilled water. The aromatic products are then extracted with diethyl ether as described in the main text.

10. If trifluoroacetic acid is used, more acetic acid may be required to ensure that the aqueous layer is acidic. Should any iodine remain, more sodium thiosulfate should be added until all of the iodine has been converted to iodide.

11. The aqueous layer should remain basic after washing with sodium hydroxide. If it is still acidic, this wash should be repeated.

12. If trifluoroacetic acid is used as solvent, the purity is 98–99% and the impurities are mainly 2,6-dichloro- and 2,4,6-trichloromethoxybenzene.

13. The purity of the product can be determined by gas–liquid chromatography using a column packed with 10% (w/w) Carbowax 20 M on Celite (80–100 mesh) at 195°C, nitrogen carrier gas flow rate 35 mL/min.

14. Eighteen grams of 2,4-dichloromethoxybenzene is dissolved in 20 mL of light petroleum ether and chilled to −18°C. Crystallization can be induced by either scratching or seeding. The mixture is kept at −18°C for 1 hr to maximize the yield before the crystals are filtered with a Büchner funnel and washed with 10 mL of chilled light petroleum ether. The crystals are sucked dry, and then dried in a vacuum desiccator. The recrystallized yield of 2,4-dichloromethoxybenzene is 12.8 g (55–58% overall), mp 25.5–26.5°C, lit.[2] mp 28°C.

15. The product had the following spectral properties: IR (neat) cm^{-1}: 1483, 1288, 1254, 1055, 700; ^{1}H NMR (CCl_4, 60 MHz) δ: 3.77 (s, 3 H, OCH_3), 6.70 (d, 1 H, J = 9.0, H_6), 7.05 (dd, 1 H, J = 9.0 and 2.5, H_5), 7.27 (d, 1 H, J = 2.5, H_3); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ: 56.2 (q), 112.7 (d), 123.3 (s), 125.6 (s), 127.5 (d), 129.9 (d), 153.9 (s); mass spectrum (70 eV) *m/e* (relative intensity): 178 (M^+ + 2, 66), 176 (M^+, 100), 163 (47), 161 (58), 135 (23), 133 (43). Mass spectrum calcd, for $C_7H_6OCl_2$ (M^+): 175.9797. Found: 175.9809.

3. Discussion

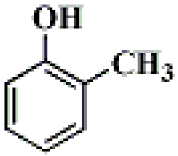
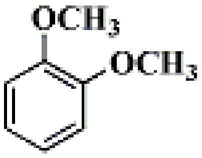
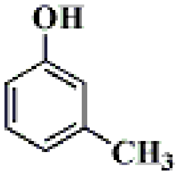
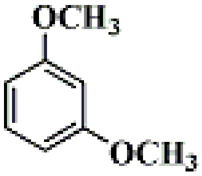
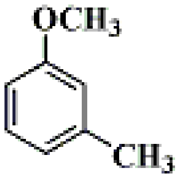
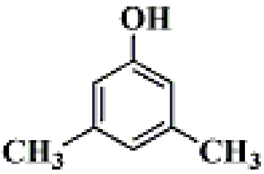
Chlorine or hypochlorous acid has been used traditionally for the chlorination of aromatic compounds and, when required, the reactivity of these reagents can be increased with a Lewis or protic acid, respectively.[4] However, these reactions are rarely selective for one monochlorinated product (site-selective[5]) and, furthermore, with some substrates di- and polychlorination can also occur. The increasing need for isomerically pure chloroaromatics in recent years has led to the development of more selective chlorinating agents, particularly for electron-rich aromatic compounds (e.g.,

phenol).[6] In this respect the submitters have found that *N*-chlorodialkylamines in strongly acidic solution are efficient and very selective monochlorinating agents for aromatic compounds containing a π-donor (+ M) substituent.[7] Thus, normally the addition of the *N*-chloramine to an equimolar quantity of the substrate in acid leads rapidly and almost exclusively to the *para*-chlorinated product (Table I). Although most of the reactions have been studied on a small scale (< 1 g of substrate) for reasons of economy, the submitters have had no difficulty in scaling up the chlorinations to use 20 g of substrate. The two acidic media that have been used with success are trifluoroacetic acid and aqueous sulfuric acid [commonly 80% (v/v) sulfuric acid]. The advantages of the former are that the reactions are homogeneous and can, if necessary, be carried out at low temperature (< 0°C) and can be monitored readily by ^{1}H NMR spectroscopy. However, trifluoroacetic acid is relatively expensive and is highly toxic. (The reactions must be carried out in a well-ventilated hood.) In situations where these disadvantages outweigh the advantages, aqueous sulfuric acid is generally a cheap and less toxic alternative. The fact that the reactions in aqueous sulfuric acid are not homogeneous is not a serious problem. Thus, with efficient stirring the chlorinations occur rapidly; furthermore, solid substrates can be added as solutions in diethyl ether (e.g., with *N*-chloromorpholine, phenol gave 93% of 4-chloro- and 7% of 2-chlorophenol, and 2-methylphenol gave 95% of 4-chloro- and 5% of 6-chloro-2-methylphenol). The major disadvantage in the use of aqueous sulfuric acid arises with the most reactive substrates (e.g., some phenols) from competing aromatic sulfonation. However, this can be reduced to a minor side reaction by keeping the reaction mixture cold (below 8°C the 80% sulfuric acid reaction mixtures will begin to freeze) and by minimizing the time between the addition of the substrate and of the chloramine to the aqueous sulfuric acid.

TABLE I

YIELD AND PRODUCT DISTRIBUTIONS FROM THE CHLORINATION OR AROMATIC COMPOUNDS IN TRIFLUOROACETIC ACID[a]

Substrate	Chlorinating Agent	Yield[b] (%)	Product	Product Distribution (%)
C_6H_5OMe	NCP[c]	97	2-Chloromethoxybenzene	1
			4-Chloromethoxybenzene	99
C_6H_5OH	NCP	98	2-Chlorophenol	3
			4-Chlorophenol	97

	NCP	84	6-Chloro-2-methylphenol	1.5
			4-Chloro-2-methylphenol	98.5
	NCTA[d]	80	4-Chloro-1,2-dimethoxybenzene	100
	NCP	89	4-Chloro-3-Methylphenol	98
			4,6-Dichloro-3-methylphenol	2
	NCP	79	4-Chloro-1,3-dimethoxybenzene	91
			4,6-Dichloro-1,3-dimethoxybenzene	9
	NCP	85	4-Chloro-3-methylmethoxybenzene	100
	NCTA[e]	95	4-Chloro-3,5-dimethylphenol	96
			2,4-Dichloro-3,5-dimethylphenol	4

[a]Equimolar quantities of substrate and *N*-chloro compound

[b]Yield of products isolated from reaction, based on *N*-chloro compound

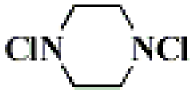
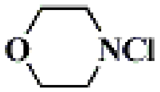
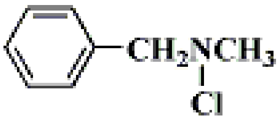
[c]NCP = *N*-chloropiperidine

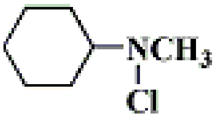
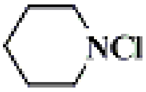
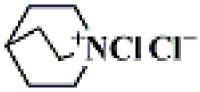
[d]NCTA = *N*-chlorotriethylammonium chloride.[8]

[e]Twofold excess of substrate, reaction temperature −17°C

The structure of the *N*-chlorodialkylamine markedly affects its reactivity and to a lesser extent its selectivity (Table II). Thus with 2-chloromethoxybenzene as substrate, *N*-chloromorpholine is approximately 17,000 times more reactive than *N*-chloropiperidine and yet it is only slightly less selective for *para*-chlorination of methoxybenzene. For most substrates the shorter reaction times (less chance of other side reactions) of the more reactive *N*-chloroamines more than compensates for any small decrease in selectivity.

TABLE II
RELATIVE REACTIVITY AND SELECTIVITY OF *N*-CHLORINATED AMINES IN TRIFLUOROACETIC ACID

N-Chloro Compound	Reactivity Relative to NCP[a]	Ratio of 4- to 2-Chlorination[b]
	160,000	6.0
	17,000	20
	200	48

	9	66
	1	99
	0.2	500

[a]Determined from chlorination of 2-chloromethoxybenzene.
NCP = *N*-chloropiperidine

[b]From the chlorination of methoxybenzene

References and Notes

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3. Henry, R. A.; Dehn, W. M. *J. Am. Chem. Soc.* **1950**, *72*, 2280.
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7. Lindsay Smith, J. R.; McKeer, L. C. *Tetrahedron Lett.* **1983**, *24*, 3117; Lindsay Smith, J. R.; McKeer, L. C.; Taylor, J. M. *J. Chem. Soc., Perkin Trans. II*, **1987**, 1533; **1988**, 385; and **1989**, 1529.
8. Fuller, S. E.; Lindsay Smith, J. R.; Norman, R. O. C.; Higgins, R. *J. Chem. Soc., Perkin Trans. II*, **1981**, 545.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

2,6-dichloro- and 2,4,6-trichloromethoxybenzene

93% of 4-chloro- and 7% of 2-chlorophenol

95% of 4-chloro- and 5% of 6-chloro-2-methylphenol

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

ether, diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

phenol (108-95-2)

potassium iodide (7681-11-0)

sodium thiosulfate (7772-98-7)

nitrogen (7727-37-9)

methoxybenzene (100-66-3)

iodine (7553-56-2)

chlorine (7782-50-5)

hypochlorous acid (7790-92-3)

2-methylphenol (95-48-7)

sodium hypochlorite (7681-52-9)

chloro

magnesium sulfate (7487-88-9)

2-chlorophenol (95-57-8)

iodide (20461-54-5)

chloramine, N-chloramine (10599-90-3)

morpholine (110-91-8)

trifluoroacetic acid (76-05-1)

2-chloromethoxybenzene, 4-Chloromethoxybenzene

4-Chlorophenol (106-48-9)

N-Chloropiperidine (2156-71-0)

2,4-Dichloromethoxybenzene, Benzene, 2,4-dichloro-1-methoxy- (553-82-2)

2,6-dichloromethoxybenzene (1984-65-2)

2,4,6-trichloromethoxybenzene (87-40-1)

6-chloro-2-methylphenol (87-64-9)

4-Chloro-2-methylphenol (1570-64-5)

4-Chloro-1,2-dimethoxybenzene (16766-27-1)

4-Chloro-3-Methylphenol (59-50-7)

4,6-Dichloro-3-methylphenol (1124-07-8)

4-Chloro-1,3-dimethoxybenzene (7051-13-0)

4,6-Dichloro-1,3-dimethoxybenzene

4-Chloro-3-methylmethoxybenzene (3260-85-3)

4-Chloro-3,5-dimethylphenol (88-04-0)

2,4-Dichloro-3,5-dimethylphenol (133-53-9)

N-Chloromorpholine (23328-69-0)

N-chlorotriethylammonium chloride

morpholine hydrochloride

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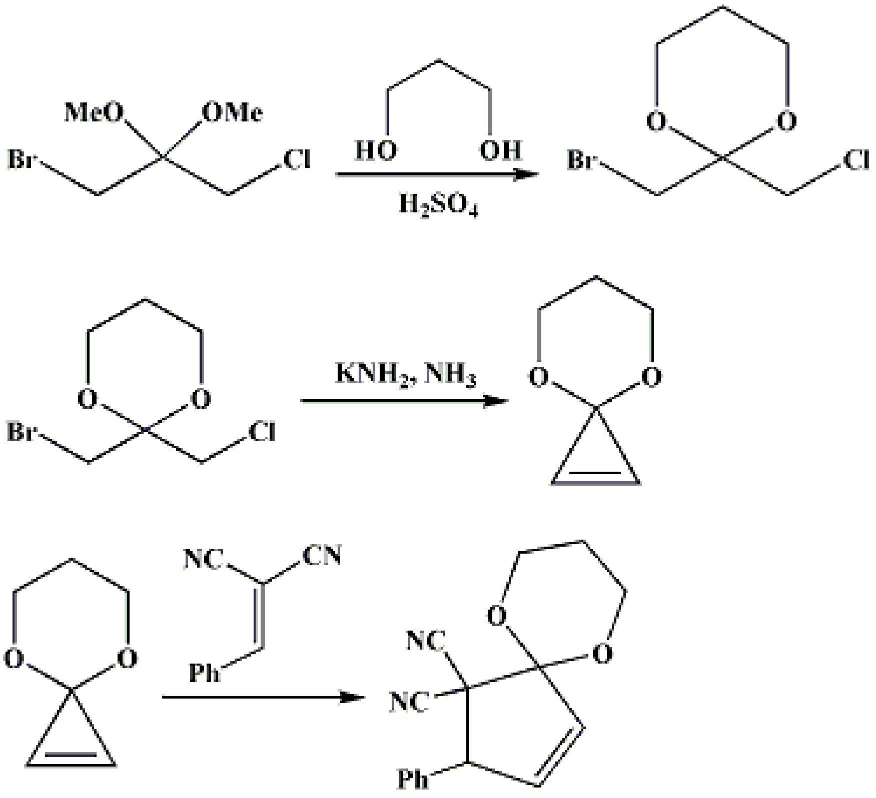
PREPARATION AND THREE-CARBON + TWO-CARBON CYCLOADDITION OF CYCLOPROPENONE 1,3-PROPANEDIOL KETAL: 5,5-DICYANO-4-PHENYL-2-CYCLOPENTEN-1-ONE 1,3-PROPANEDIOL KETAL

[4,8-Dioxaspiro[2.5]oct-1-ene and 6,10-Dioxaspiro[4.5]dec-3-ene-1,1-dicarbonitrile, 2-phenyl-]



Submitted by Dale L. Boger, Christine E. Brotherton, and Gunda I. Georg[1].
Checked by Steven K. Davidsen Clayton and H. Heathcock.

1. Procedure

A. *2-(Bromomethyl)-2-(chloromethyl)-1,3-dioxane*.[2] A 100-mL, round-bottomed flask is equipped with a 10-mL Dean–Stark apparatus and a condenser. The flask is charged with 30.0 g (0.138 mol) of 1-bromo-3-chloro-2,2-dimethoxypropane (Note 1), 10.0 mL (0.138 mol) of 1,3-propanediol (Note 2), and 3 drops of concentrated sulfuric acid. The resulting solution is heated (bath temperature 140°C) for 8 hr (Note 3) with distillative removal of methanol (ca. 11 mL). The mixture is allowed to cool to room temperature and the crude product is partitioned in 150 mL of pentane and 40 mL of water. The organic phase is dried with magnesium sulfate and the solvent is removed under reduced pressure (Note 4). Distillation (1 mm, 90–95°C) yields 25.5–27.7 g (81–88%) of 2-(bromomethyl)-2-(chloromethyl)-1,3-dioxane, mp 57–59°C (Note 5).

B. *Cyclopropenone 1,3-propanediol ketal*.[3] A 1000-mL, three-necked, round-bottomed flask is equipped with a gas inlet, an acetone–dry ice condenser with a drying tube containing potassium hydroxide pellets, a stopper, and a magnetic stirring bar. The flask is placed in an acetone–dry ice bath and anhydrous ammonia (Note 6) is condensed into the flask (400 mL). A small piece of potassium

metal (ca. 0.5 g) is added to the liquid ammonia and the cooling bath is removed. A catalytic amount of anhydrous ferric chloride (0.1 g) is added and the reaction mixture is allowed to warm to reflux temperature, at which time the deep blue color turns to gray. The remaining potassium metal (12.2 g, 0.31 g-atom total) is added in 0.5-g pieces over ca. 30 min. The reaction mixture is allowed to stir until a gray suspension results (20–30 min). A −50°C cooling bath is placed under the flask and the stopper is replaced with a 125-mL, pressure-equalized dropping funnel containing 22.9 g (0.1 mol) of 2-(bromomethyl)-2-(chloromethyl)-1,3-dioxane in 50 mL of anhydrous ether. This solution is added dropwise to the solution of freshly generated potassium amide over 15 min while the temperature is maintained at −50°C (Note 7). After the solution is stirred for 3 hr at −50° to −60°C, solid ammonium chloride is added slowly to quench the excess potassium amide (Note 8). The cooling bath is removed and the ammonia is allowed to evaporate. During the course of the evaporation, anhydrous ether (350 mL total) is added dropwise through the addition funnel to replace the ammonia. After the temperature has reached 0°C, the brown reaction mixture is filtered by suction through a coarse fritted-glass filter to remove the inorganic salts and the salts are washed twice with 25 mL of anhydrous ether. The combined ethereal filtrate and washes are concentrated under reduced pressure (80–100 mm, 30°C) to constant weight (ca. 4–5 hr) (Note 9). The residue is transferred to a 50-mL, round-bottomed flask fitted with a water-cooled, short-path distillation head, and the product is distilled (1.25 mm; 30–35°C) into an ice-cooled receiver. Cyclopropenone 1,3-propanediol ketal is obtained as a colorless liquid (6.1–7.8 g, 55–70% yield, (Note 10)).

C. *5,5-Dicyano-4-phenyl-2-cyclopenten-1-one 1,3-propanediol ketal*. Benzylidenemalononitrile (Note 2) (3.85 g, 25 mmol) and cyclopropenone 1,3-propanediol ketal (5.6 g, mmol) are combined in 25 mL of dry distilled toluene (Note 11) in a sealed tube (Note 12) with a magnetic stirring bar. The reaction mixture is heated at 80°C for a 6.5 hr with stirring. The crude reaction mixture is filtered through a short plug of glass wool and applied to a Waters Associates Prep LC/System 500, eluting with 2.5 : 1 hexane/ethyl acetate (Note 13). The fractions containing product are combined and concentrated under reduced pressure to give 4–4.2 g (60–64%) of 5,5-dicyano-4-phenyl-2-cyclopenten-1-one 1,3-propanediol ketal as a white solid: mp 139–141°C (ethanol, (Note 14)).

2. Notes

1. The preparation[4] of this material has been described in detail: Breslow, R.; Pecoraro, J.; Sugimoto, T. *Org. Synth., Coll. Vol. VI* **1988**, 361.
2. The submitters employed material available from Aldrich Chemical Company, Inc. without further purification.
3. Shorter reaction times result in incomplete transketalization.
4. The checkers found that the product crystallizes, either on removal of solvent or in the condenser during the following distillation. To prevent the condensers tube becoming plugged by the crystalline product, an air-cooled, rather than a water-cooled, condenser jacket should be used.
5. The product has the following spectral properties: ^{1}H NMR ($CDCl_3$) δ: 1.78 (m, 2 H, CH_2), 3.70 (s, 2 H, CH_2Cl), 3.80 (s, 2 H, CH_2Br), 3.96 (t, 4 H, J = 6, OCH_2); IR ($CHCl_3$) cm^{-1}: 3030, 3000, 2900, 1485, 1430, 1245, 1202, 1158, 1135, 1105 (s), 1020.
6. Commercial anhydrous ammonia is employed without further drying.
7. Crystals that may form at the tip of the addition funnel are scraped off and allowed to drop into the reaction flask.
8. The checkers added a total of 25 g of solid ammonium chloride in portions of approximately 2 g with a spatula.
9. The checkers removed the solvent with a rotary evaporator at 20 mm and 25°C; under these conditions only 1 hr is required to concentrate the solution to a constant weight.
10. This material should be stored under an argon atmosphere below 0°C. The product has the following spectral properties: ^{1}H NMR ($CDCl_3$) δ: 1.83 (m, 2 H, CH_2), 4.01 (t, 4 H, J = 6,

OCH_2), 7.84 (s, 2 H, CH=CH); ^{13}C NMR ($CDCl_3$) δ: 25.4 (CH_2), 65.6 (OCH_2), 80.5 (OCO), 125.1 (C=C); IR (film) cm^{-1}: 3101, 2980, 2870, 1600, 1475, 1460, 1435, 1370, 1300, 1275, 1155, 1090, 1030, 935, 910, 865, 740.

11. Toluene was distilled from calcium hydride under a nitrogen atmosphere.

12. The resealable glass tube was fabricated from an Ace Glass medium-walled straight tube. The tube was permanently sealed on one end, and the other end remained internally threaded. The tube was sealed with a solid Teflon plug fitted with a FETFE O-ring. Various sizes of such tubes are now available from Ace Glass.

13. The submitters used medium pressure chromatography[5] on 25 × 1000 mm of 230–400 mesh silica gel with a 25 × 250-mm scrubber column. The eluant (3 : 1 : 1 hexane : ethyl acetate: methylene chloride) was passed through the column at a rate of 15 mL/min, collecting 15-mL fractions. The checkers were unable to obtain pure product using a gravity column or flash chromatography.

14. The product has the following spectral properties: ^{1}H NMR ($CDCl_3$) δ: 1.71 (dt, 1 H, J = 13.8, J = 3.8, $OCH_2CH_2CH_2O$), 2.1–2.3 (broad m, 1 H, $OCH_2CH_2CH_2O$), 3.9–4.3 (m, 4 H, $OCH_2CH_2CH_2O$), 4.63 (t, 1 H, J = 2.3, allylic CH), 6.25 (dd, 1 H, J = 6.3, J = 2.0, CH-CH=CH-C), 6.62 (dd, 1 H, J = 6.3, J = 2.6, CH-CH=CH-C), 7.3–7.5 (m, 5 H, phenyl); IR ($CHCl_3$) cm^{-1}: 3070, 2920, 2290 (C[illegible]N), 1510, 1465, 1350, 1260, 1210, 1175, 1140, 1100, 1080, 1040, 870, 705.

3. Discussion

Although a number of multistep procedures are available for the introduction of five-membered carbocycles, their direct formation in a thermal cycloaddition is rare.[6] Interest in the potential application of such a three-carbon + two-carbon cyclopentane cycloaddition has been derived from the expectation that such a process could prove to be an effective complement to the four-carbon + two-carbon Diels–Alder reaction, which is used extensively in the regio- and stereocontrolled preparation of functionalized six-membered carbocycles.

Cyclopropenone ketals, of which cyclopropenone 1,3-propanediol ketal (**1**) is a representative and unusually stable example, have proved to be useful equivalents of the 1,3-dipole (**i**) in a regiospecific three-carbon + two-carbon cycloaddition with electron-deficient olefins (Eq. 1). Table I shows representative results of a study of this reaction.[7]

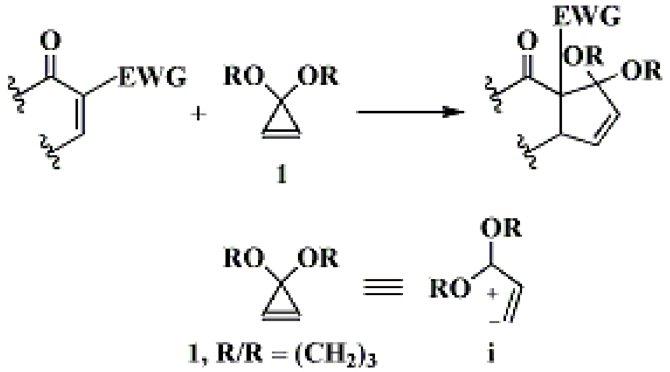
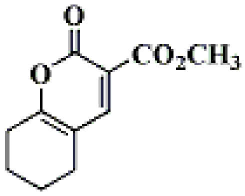
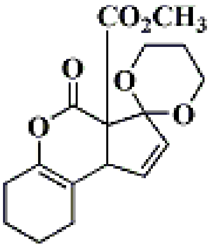
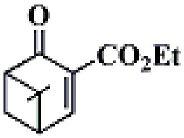
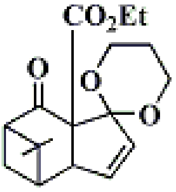
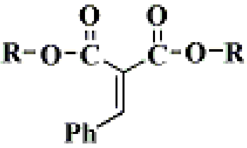
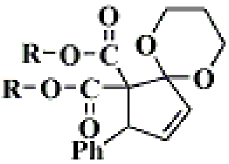
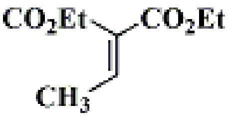
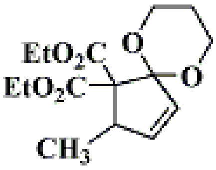
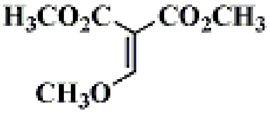
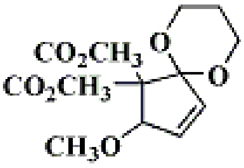
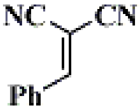
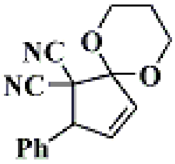


TABLE I

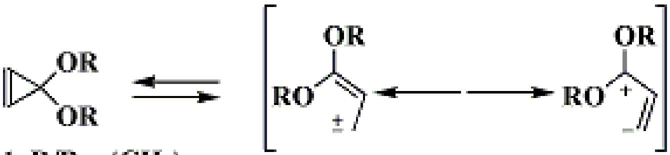
REACTIONS OF CYCLOPROPENONE KETAL 1 WITH ELECTRON-DEFICIENT OLEFINS

Substrate	Conditions[a] equiv 1, temp. °C(time hr)	Product	% Yield

	1.0–2.0, 80 (12)		42%
	1.0, 75 (13)		45%
	R = Et 1.5, 75 (13)		53%
	R = Me 2.5, 75 (32)		60%
	1.5, 75 (15)		57%
	2.0, 80 (5)		84%
	2.0, 80 (4)		60–64%

[a] All reactions were run in benzene (0.5–2.0 *M* in substrate) under nitrogen unless otherwise noted.

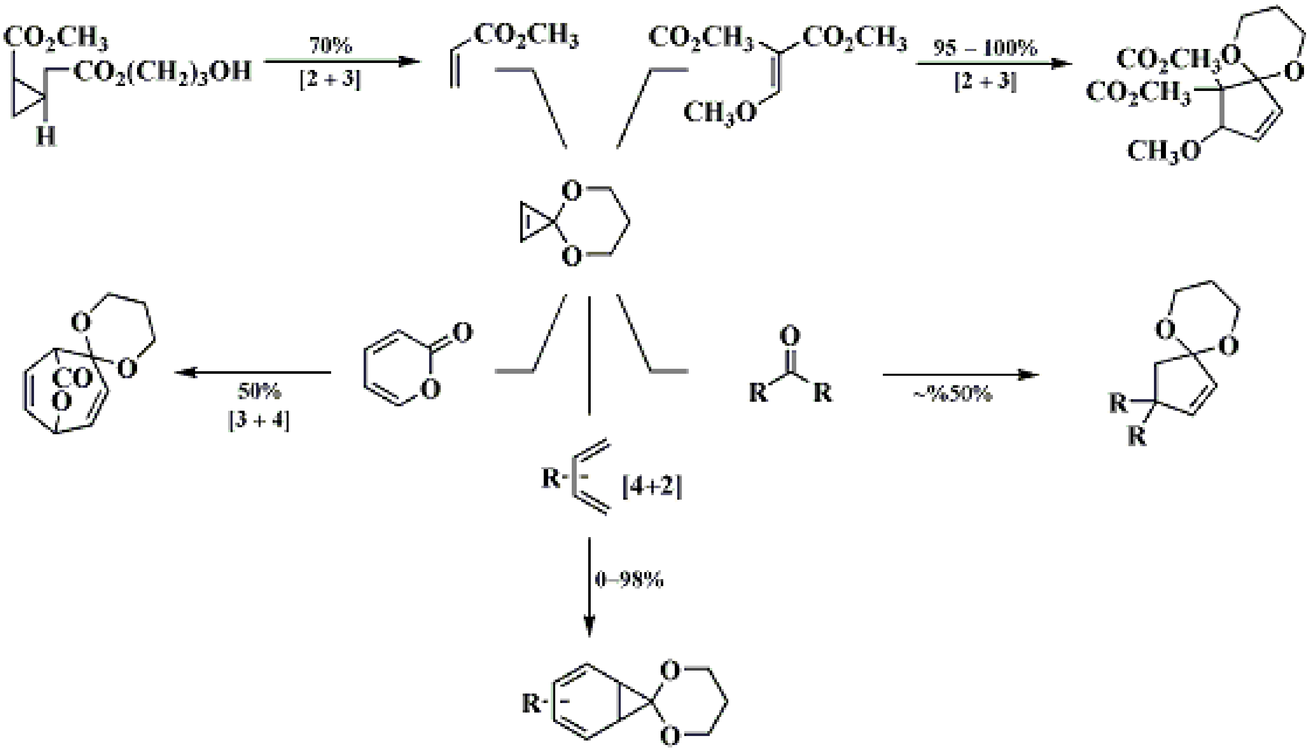
Studies have defined the scope of the thermal reactions of cyclopropenone ketals which are characterized by their thermal, reversible ring opening to provide reactive intermediates best represented as delocalized singlet vinyl carbenes, three-carbon 1,1-/1,3-dipoles without octet stabilization (Eq. 2).



1, R/R = $(CH_2)_3$

In addition to the representative [3 + 2] cycloaddition reactions shown in Table I, the delocalized singlet vinyl carbenes have been shown to participate as $\pi 2_a$ components of nonlinear cheletropic [$\pi 2_s$

+ $\pi 2_a$] cycloadditions to provide cyclopropanes with an observable endo effect,[8] and as $\pi 2_s$ components of [$\pi 4_s$ + $\pi 2_s$] cycloadditions with selected dienes to provide cycloheptadienes[9,10] (Scheme 1). This thermal reactivity of cyclopropenone ketals complements their dual participation as strained olefins in normal ($HOMO_{diene}$ controlled) and inverse electron demand ($LUMO_{diene}$ controlled) Diels–Alder reactions with electron-rich, electron-deficient, and neutral dienes under room temperature, thermal, and pressure-promoted Diels–Alder conditions.[11,12,13]



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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Cyclopropenone 1,3-propanediol ketal

5,5-Dicyano-4-phenyl-2-cyclopenten-1-one 1,3-propanediol ketal

ethanol (64-17-5)

sulfuric acid (7664-93-9)

ammonia (7664-41-7)

Benzene (71-43-2)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether (60-29-7)

ammonium chloride (12125-02-9)

1,3-propanediol (504-63-2)

nitrogen (7727-37-9)

toluene (108-88-3)

ferric chloride (7705-08-0)

potassium (7440-09-7)

Pentane (109-66-0)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

potassium amide

hexane (110-54-3)

calcium hydride (7789-78-8)

cyclopentane (287-92-3)

argon (7440-37-1)

1-Bromo-3-chloro-2,2-dimethoxypropane (22089-54-9)

4,8-Dioxaspiro[2.5]oct-1-ene (60935-21-9)

6,10-Dioxaspiro[4.5]dec-3-ene-1,1-dicarbonitrile, 2-phenyl- (88442-12-0)

2-(Bromomethyl)-2-(chloromethyl)-1,3-dioxane (60935-30-0)

Benzylidenemalononitrile (2700-22-3)

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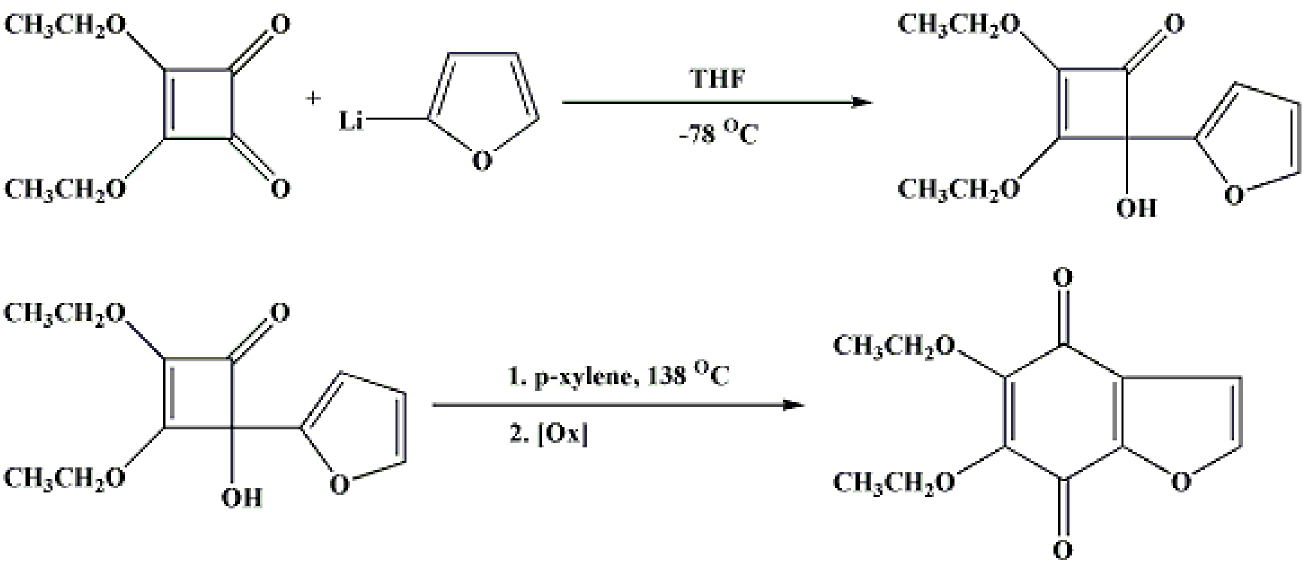
Organic Syntheses, CV 8, 179

REARRANGEMENT OF 4-ARYL-4-HYDROXY-2,3-DIALKOXYCYCLOBUTENONES TO ANNULATED HYDROQUINONES AND QUINONES: 5,6-DIETHOXYBENZOFURAN-4,7-DIONE



Submitted by S. T. Perri, P. Rice, and H. W. Moore[1].
Checked by Ho-Jung Kang and Leo A. Paquette.

1. Procedure

A 500-mL, round-bottomed flask is flame-dried and flushed with nitrogen. The flask is equipped with a magnetic stirring bar and a rubber septum and charged with 4.14 g (60.9 mmol) of furan (Note 1) and 300 mL of dry tetrahydrofuran (Note 2). The solution is stirred and cooled in an ethylene glycol–dry ice bath (–15°C) and 24.17 mL (55.6 mmol) of 2.3 *M* butyllithium is added slowly by means of a syringe pump (rate = 1.5 mL/min). After complete addition, the solution is stirred for an additional 30 min. The ethylene glycol–dry ice bath is replaced with an ice bath and the solution stirred for 1.5 hr at 0°C. The flask is then cooled to −78°C in a dry ice–acetone bath.

A 1000-mL, round-bottomed flask is flame-dried and flushed with nitrogen. The flask is equipped with a magnetic stirring bar and a rubber septum and charged with 9.00 g (52.9 mmol) of diethyl squarate (Note 3) and 450 mL of dry tetrahydrofuran (Note 2). The solution is stirred and cooled in a dry ice–acetone bath at −78°C. The solution of 2-lithiofuran is transferred dropwise via cannula to the flask containing the diethyl squarate, which is stirred rapidly. After complete addition (45 min), the solution is stirred for 20 min and quenched by pouring the cold solution into a separatory funnel containing 150 mL of aqueous 10% ammonium chloride and 100 mL of diethyl ether. The separatory funnel is shaken vigorously until phase separation is achieved and all of the ice has melted. The aqueous phase is separated from the organic phase and the aqueous layer is extracted twice with 40-mL portions of diethyl ether. The combined organic layer is washed with 125 mL of brine solution and dried over solid anhydrous potassium carbonate (Note 4) for 5 min with gentle swirling.

The solution is decanted from the potassium carbonate (Note 5) and concentrated on a rotary evaporator (bath temperature = 23–40°C) to approximately 150 mL in a 1000-mL round-bottomed flask. Then 400 mL of dry *p*-xylene (Note 6) is added and the flask is placed on the rotary evaporator at a bath temperature of 40°C to remove the remaining tetrahydrofuran and diethyl ether. The flask containing the remaining *p*-xylene solution of the cyclobutenone is fitted with a reflux condenser and heated at reflux for 3 hr under nitrogen.

The flask is cooled to ambient temperature and the solvent is removed on a rotary evaporator fitted with a bump trap at a bath temperature of 70°C to give a red oil.

The oil is dissolved in 500 mL of diethyl ether and washed with three 200-mL portions of an ethanolic ferric chloride solution (Note 7). The aqueous layers are separated from the organic phase and extracted with four 100-mL portions of diethyl ether. The combined organic layer is washed with saturated sodium bicarbonate solution (Note 8) until the aqueous wash is no longer acidic. The resulting neutralized aqueous extracts are combined and extracted with three 30-mL portions of diethyl ether. The organic extracts are combined, washed with 150 mL of brine solution, and dried over magnesium sulfate. The solution is filtered and concentrated on a rotary evaporator to give the quinone as a red solid. The solid is recrystallized from methanol to yield 10.4–10.5 g of the quinone as orange needles in two or three crops (83–84% based on diethyl squarate), mp 54–55°C (Note 9).

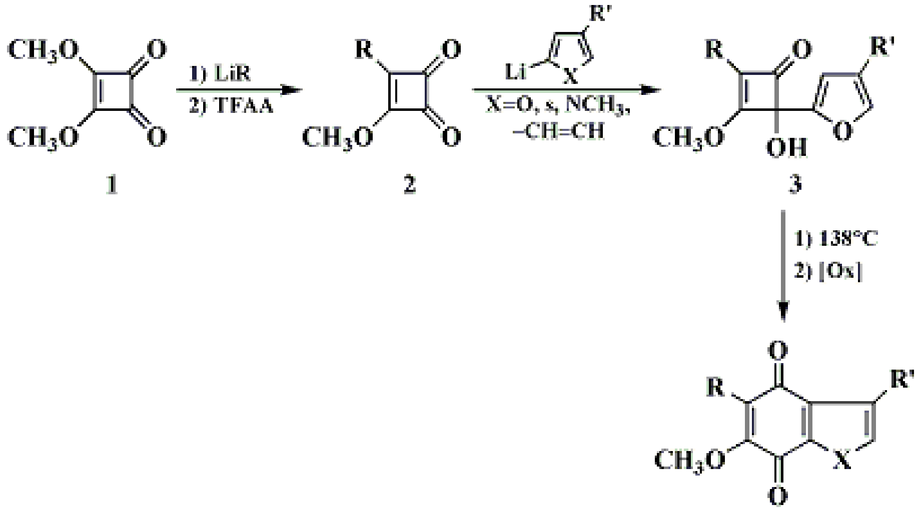
2. Notes

1. Furan was purchased from Aldrich Chemical Company, Inc., and used as such.
2. Tetrahydrofuran was distilled under argon from benzophenone ketyl.
3. 3,4-Diethoxy-3-cyclobutene-1,2-dione is commercially available from Aldrich Chemical Company, Inc. *Caution: This substance was found to cause severe skin rashes, and extreme care should be exercised in handling it.* The dimethoxy analog appears to be safer. Diethyl squarate has the following spectral properties: IR (neat) cm^{-1}: 1830, 1741, 1609; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.47 (t, 6 H, *J* = 2.9), 4.47 (q, 4 H, *J* = 7.1).
4. Prolonged drying of the cyclobutenone over potassium carbonate resulted in product decomposition. Anhydrous magnesium sulfate was found to hydrolyze the product during the thermolysis step.
5. The cyclobutenone was pure enough to use in the next step without purification. This compound is stable for a few hours in solution while kept cold (< 5°C) and anhydrous.
6. Certified *p*-xylene was purchased from Fisher Scientific Company and used as such.
7. Ferric chloride was purchased from Mallinckrodt, Inc. A saturated solution of 80 g of ferric chloride in 500 mL of water was diluted with 500 mL of ethanol, filtered, and used as such. The oxidation could be followed by TLC using Engel stain.
8. Quinones are generally sensitive to bases, and some decomposition may occur if the product is exposed for a prolonged period of time to sodium bicarbonate. Therefore the neutralization wash was carried out quickly.
9. The spectral properties of the product are as follows: IR ($CHCl_3$) cm^{-1}: 2980, 1667, 1480, 1370, 1290, 1250, 1179; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.42 (2 overlapping t, 6 H, two CH_3), 4.30 (2 overlapping q, 4 H, two CH_2), 6.81 (d, 1 H, *J* = 1.9), 7.67 (d, 1 H, *J* = 1.8); ^{13}C NMR ($CDCl_3$) δ: 15.7, 15.8, 70.2, 70.3, 108.3, 126.7, 145.7, 146.6, 148.5, 150.1, 172.7, 178.8; EI–MS (70 eV): *m/z* = 236 (19%), 208 (21), 193 (8), 180 (24), 163 (7), 152 (100), 123 (9).

3. Discussion

This procedure describes a synthetic route to annulated hydroquinones and quinones. The example represents a general, convergent, regiospecific and usually high-yielding method. This is further elaborated by the generalized scheme given below. Specifically, dialkoxycyclobutenediones (e.g., dimethyl squarate, **1**) are easily converted to unsymmetric cyclobutenediones **2** on treatment with an organolithium reagent (R = alkyl, aryl, alkenyl, alkynyl, −78°C, THF) followed by treatment with trifluoroacetic anhydride (−78°C, TFAA) and an aqueous workup.[2,3,4] Treatment of **2** with an aryllithium reagent results in the regiospecific formation of the cyclobutenones **3** via 1,2-addition to the more nucleophilic carbonyl group. These adducts then undergo facile rearrangement to the corresponding annulated hydroquinones in refluxing *p*-xylene. The product is usually isolated as the quinone **4** after an oxidative workup.[5,6,7] It is noted that alkenyl lithium reagents as well as alkynyl analogs also add regiospecifically to the cyclobutenediones **2** to give the corresponding cyclobutenones. The alkenyl adducts, like the aryl analogs, also rearrange to the

corresponding hydroquinones. The alkynyl adducts rearrange directly to the corresponding quinones via a unique pathway involving migration of the alcoholic proton of the 4-hydroxycyclobutenone to the quinone ring nucleus of the product.[8,9]



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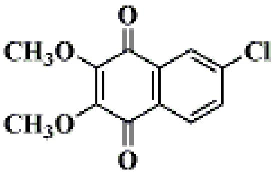
Compounds **5–10** are specific examples of annulated products that have been prepared by the method outlined here.



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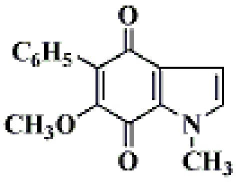

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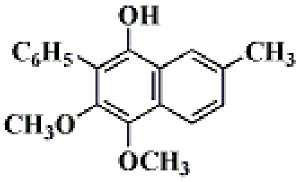

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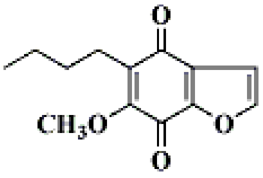

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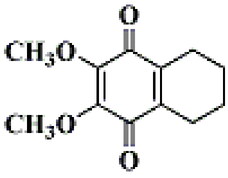

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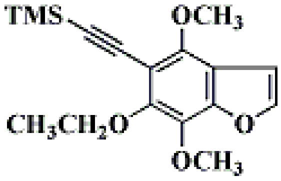

10
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

benzophenone ketyl

brine

ethanolic ferric chloride

ethanol (64-17-5)

potassium carbonate (584-08-7)

methanol (67-56-1)

diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

sodium bicarbonate (144-55-8)

nitrogen (7727-37-9)

ferric chloride (7705-08-0)

p-xylene (106-42-3)

Furan (110-00-9)

magnesium sulfate (7487-88-9)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

trifluoroacetic anhydride (407-25-0)

argon (7440-37-1)

5,6-Diethoxybenzofuran-4,7-dione (138225-13-5)

diethyl squarate, 3,4-Diethoxy-3-cyclobutene-1,2-dione

2-Lithiofuran

4-hydroxycyclobutenone

DIMETHYL SQUARATE (5222-73-1)

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Organic Syntheses, CV 8, 183

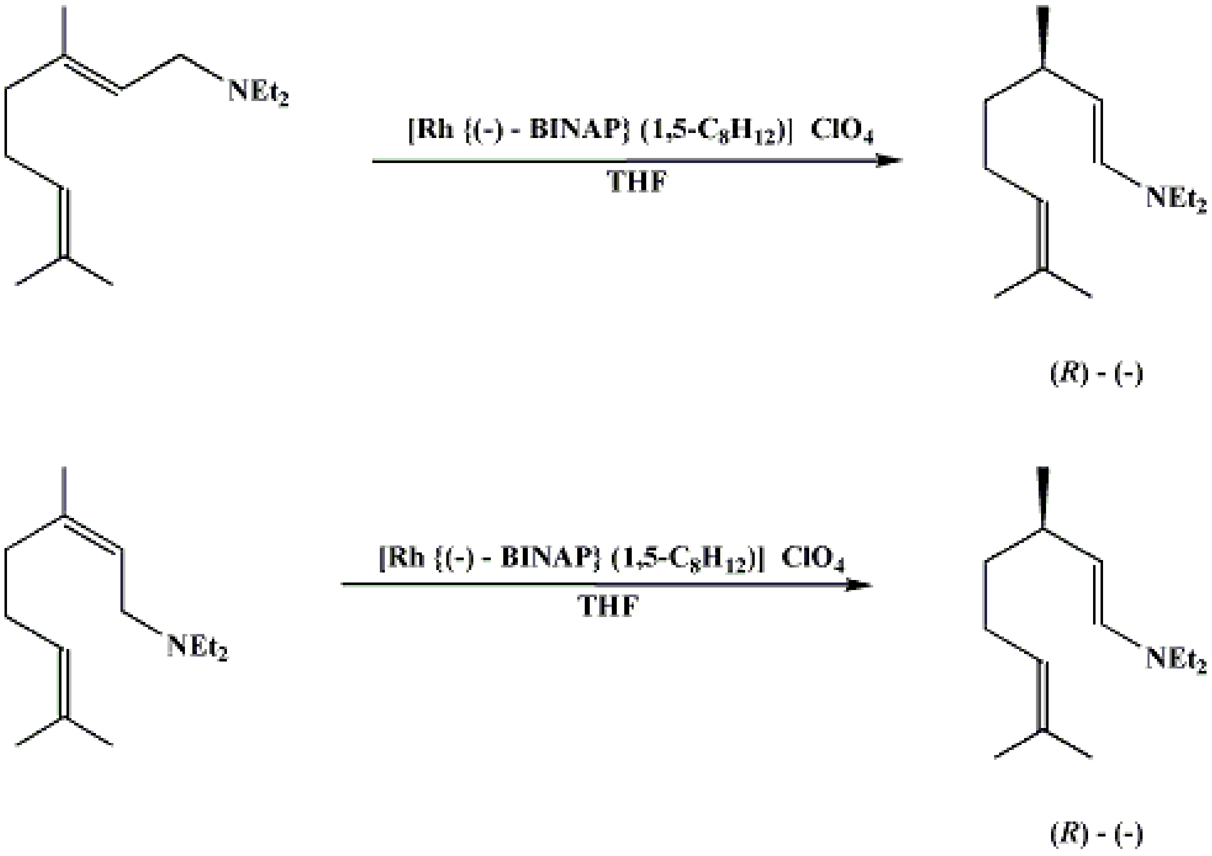
(*R*)-(–)-*N*,*N*-DIETHYL-(*E*)-CITRONELLALENAMINE AND (*R*)-(+)-CITRONELLAL VIA ISOMERIZATION OF *N*,*N*-DIETHYLGERANYLAMINE OR *N*,*N*-DIETHYLNERYLAMINE

[1-(*E*), 6-Octadienamine, (*R*)-(–)-*N*,*N*-diethyl-3,7-dimethyl- and 6-octenal, 3,7-dimethyl-, (*R*)-(+)-]

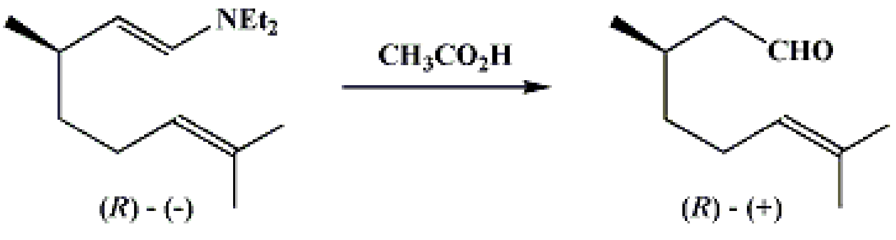
A. $[RhCl(1,5\text{-}C_8H_{12})]_2 + 2\ (+)\text{-BINAP} \xrightarrow[\text{acetone}]{AgClO_4} [Rh\{(+)\text{-BINAP}\}(1,5\text{-}C_8H_{12})]\,ClO_4$

$[RhCl(1,5\text{-}C_8H_{12})]_2 + 2\ (-)\text{-BINAP} \xrightarrow[\text{acetone}]{AgClO_4} [Rh\{(-)\text{-BINAP}\}(1,5\text{-}C_8H_{12})]\,ClO_4$

B.



C.



Submitted by Kazuhide Tani[1], Tsuneaki Yamagata[1], Sei Otsuka[1], Hidenori Kumobayashi[2], and Susumu Akutagawa[2].
Checked by David Coffen, Louis A. Portland, Bryant Rossiter, and Gabriel Saucy.

1. Procedure

Caution! All manipulations for the preparation of the transition-metal complexes and the catalytic isomerization should be carried out under dry nitrogen or argon. All solvents used are distilled under dry nitrogen over metallic sodium, or after drying over calcium sulfate (in the case of acetone) immediately before use.

A. [*(+)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl*]-*(η⁴-1,5-cyclooctadiene) rhodium(I) perchlorate*. [*Rh{(+)-BINAP} (1,5-C_8H_{12})*] *ClO_4*. A dry, 250-mL Schlenk flask, filled with dry nitrogen or argon and equipped with a magnetic stirring bar, is charged with 0.53 g (1.08 mmol) of chloro-(1,5-cyclooctadiene)rhodium(I) dimer (Note 1). Then 40 mL of dry acetone is added using an airtight syringe. The flask is protected from light by wrapping it with aluminum foil and 0.45 g (2.17 mmol) of silver perchlorate is added to the stirred suspension. The mixture is stirred for 1 hr at ambient temperature. The colorless precipitate of silver chloride is removed by suction filtration under argon through a stainless-steel cannula fitted with a filter tip (Note 2). The precipitates are washed with 5 mL of acetone. To the pale-orange filtrate and the washings is added 1.34 g (2.16 mmol) of (+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl [(+)-BINAP] (Note 3) and the resulting dark-red solution is stirred under argon for 18 hr at ambient temperature. The reaction mixture is concentrated under reduced pressure (60 mm) to ca. 3 mL. Then 30 mL of ether is slowly added with a syringe. The resulting mixture is stirred at ambient temperature for 18 hr. The orange solid is filtered off under argon and washed with 5 mL of ether. The crude product is dissolved in 50 mL of dry acetone and the solution is concentrated to ca. 3 mL under 60 mm pressure. Dry ether (30 mL) is slowly added and the mixture is stirred for 18 hr. The deep-orange crystals are collected by filtration, washed with 5 mL of dry ether, and dried under vacuum to afford 2.07 g of recrystallized product, 230–235°C (dec) (Note 4).

[*(–)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl*] *(η⁴-1,5-cyclooctadiene) rhodium(I) perchlorate*: [*Rh{(–)-BINAP}(1,5-C_8H_{12})*] ClO_4 is similarly prepared from 0.53 g (1.08 mmol) of chloro-(1,5-cyclooctadiene)rhodium(I) dimer, 0.45 g (2.17 mmol) of silver perchlorate, and 1.34 g (2.16 mol) of (–)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl [(–)-BINAP] (Note 5) in acetone. The crude product is recrystallized from acetone–ether as above to give 2.02 g of orange powder, mp 230°C (dec) (Note 6).

B. *(R)-(–)-N,N-Diethyl-(E)-citronellalenamine* [*(R)-(–)-N,N-Diethyl-3,7-dimethyl-1(E),6-octadienylamine*]. *From N,N-diethylgeranylamine*. A 500-mL, three-necked, round-bottomed flask equipped with a magnetic stirrer, a reflux condenser and an argon inlet is charged with 373 mg (0.40 mmol) of [(–)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl](η⁴-1,5-cyclooctadiene) rhodium(I) perchlorate. The flask is evacuated and refilled with argon 4 times. Another 500-mL, three-necked, round-bottomed flask is charged with 83.8 g (0.40 mol) of N,N-diethylgeranylamine (Note 7) and 250 mL of distilled tetrahydrofuran (Note 8) under an argon blanket. This solution is transferred under argon by cannula to the flask containing the catalyst, which is then evacuated and refilled with argon twice. The reaction mixture is stirred and heated at reflux for 21 hr (Note 9). The solution is cooled to room temperature and the solvent is removed under vacuum (60 mm) at 45°C. The residue is vacuum-distilled through a 10-cm

Vigreux column to give 78.7 g (93.9%) of *(R)-(−)-N,N*-diethyl-(*E*)-citronellalenamine as a colorless liquid, bp 84–85°C (1.1 mm), $[\alpha]_D^{25}$ −66.5° (hexane, *c* 10.2). The product is 97.2% chemically pure by GLC analysis (Note 10),(Note 11),(Note 12).

From N,N-diethylnerylamine. Similarly, 83.8 g (0.40 mol) of *N,N*-diethylnerylamine (Note 13) is isomerized with 373 mg (0.40 mmol) of [(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl](η^4-1,5-cyclooctadiene)rhodium(I) perchlorate catalyst in 250 mL of THF (Note 8) at reflux for 70 hr (Note 9) to give 77.2 g (92.1%) of (*R*)-(–)-*N,N-diethyl*-(*E*)-citronellalenamine, $[\alpha]_D^{25}$ −66.9° (hexane, *c* 10.7). The chemical purity of the product is 91.7% by GLC (Note 10), (Note 12), and (Note 14).

C. *(R)-(+)-Citronellal*. [*(R)-(+)-3,7-Dimethyl-6-octanal*]. A 500-mL, round-bottomed flask equipped with a magnetic stirrer and an ice bath is charged with 33.4 g (0.16 mol) of (*R*)-(–)-*N*, *N*-diethyl-(*E*)-citronellalenamine in 80 mL of ether at 0°C. To this stirred solution is added 80 mL of a 1 : 4 glacial acetic acid–deionized water solution in one portion (Note 15). The reaction mixture is stirred for 5 min at 0°C and then at room temperature for 25 min. The ether layer is separated and washed successively with 50 mL of water, two 50-mL portions of saturated aqueous sodium bicarbonate solution, 50 mL of water, and 50 mL of saturated brine. The ether layer is dried over anhydrous sodium sulfate and filtered (Note 16). The ether solution is concentrated at 40°C under reduced pressure (60 mm) to a pale-yellow liquid. The liquid is distilled through a 10-cm Vigreux column to give 22.5 g (91.4%) of (+)-citronellal as a colorless liquid, bp 79–80°C (7 mm), $[\alpha]_D^{25}$ +15.7° (neat, d 0.851). The product is 99.4% chemically pure by GLC and has an optical purity of 95.2% (Note 17).

2. Notes

1. Chloro(η^4-1,5-cyclooctadiene)rhodium(I) dimer [RhCl(1,5-C_8H_{12})] can be prepared according to the method described in *Inorganic Syntheses*.[3] The checkers used material purchased from the Aldrich Chemical Company, Inc.
2. This can also be done as previously described in *Inorganic Syntheses*.[4]
3. (*R*)-(+)-2,2'-Bis(diphenylphosphino)-1,1'-binapthyl was prepared according to Takaya, H.; Akutagawa, S.; Noyori, R. *Org. Synth., Coll. Vol. VIII,* **1993**, 57.
4. The submitters obtained 1.5–1.7 g of analytically pure material with mp 164°C (dec). The ^{1}H NMR (CD_2Cl_2) of this product showed signals at δ: 2.00–2.62 (m, 8 H, -CH_2-), 4.58 (br signal, 2 H, -CH=), 4.84 (br signal, 2 H, -CH=), 6.42–8.22ppm (m, 32 H, aromatic). Anal. calcd. for ($C_{52}H_{44}ClO_4Rh$): C, 66.93; H, 4.75; Cl, 3.80. Found: C, 66.66; H, 4.89; Cl, 3.92.
5. (*S*)-(–)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl was prepared according to the *Organic Syntheses* procedure; see (Note 3).
6. The submitters used THF–ether for recrystallization, in which case the product was obtained as a THF-solvated complex, [Rh{(–)-BINAP} (1,5-C_8H_{12})]ClO_4 THF, in the form of deep-orange crystals, mp 153°C (dec). Its ^{1}H NMR (CD_2Cl_2) spectrum clearly showed the presence of the solvating tetrahydrofuran; δ: 1.60–2.00 (m. 4 H, -CH_2- of THF), 2.00–2.62 (m, 8 H, -CH_2-), 3.40–3.80 (m, 4 H, -CH_2O- of THF), 4.58 (br signal, 2 H, -CH=), 4.82 (br, signal, 2 H, -CH=), 6.40–7.97 (m, 32 H, aromatic). Anal. calcd. for ($C_{52}H_{44}ClO_4RhC_4H_8O$): C, 66.90; H, 5.21; Cl, 3.53. Found: C, 66.55; H, 5.62; Cl, 3.68.
7. *N,N*-Diethylgeranylamine was prepared according to the method described in *Org.*

Synth., Coll. Vol. VIII, **1993**, 188. The submitters used material of 99.7% purity (determined by GLC; Hitachi 063 with OV-101 in fused silica, 0.2-mm × 25-m column) that was obtained by careful distillation through a column with one hundred theoretical plates, bp 70°C (2 mm), and redistilled over calcium hydride before use. The checkers used a 32-cm Goodloe column and collected the amine at 105°C (2.4 mm), which had a purity of 100% (GLC).

8. Acetone or methanol also may be used. However, tetrahydrofuran gives the best results. The solvents should be strictly dry because water deactivates the catalyst.

9. The submitters ran the reaction at 60°C for 24 hr.

10. Purity of the product and progress of the isomerization can be determined by GLC (Triton X 305 packed in a 0.2 mm × 30 m glass column from Gasukuro Kogyo Co. Ltd., or a column-crosslinked 5% phenylmethyl silicone, 25-m high-performance capillary column supplied by Hewlett Packard. Starting temperature, 125°C; rate 3°/min; final temperature, 180°C). The product enamine is 100% (*E*)-isomer. The spectral properties of the product are as follows: IR (neat) cm^{-1}: 3045, 2960, 2915, 2860, 2720, 1660, 1655, 1450, 1377, 1298, 1245, 1196, 1100, 985, 937, 886, 830, 784, 740; ^{1}H NMR (acetone d_6) δ: 0.96 (d, 3 H, *J* = 7.2), 1.01 (t, 6 H, *J* = 7.1), 1.1–1.4 (m, 2 H), 1.58 (br s, 3 H), 1.66 (br s, 3 H), 1.8–2.1 (m, 3 H), 2.92 (q, 4 H, *J* = 7.1), 3.93 (d of d, 1 H, *J* = 14.6, 8.4), 5.11 (br t, 1 H, *J* = 7.3), 5.79 (d of d, 1 H, *J* = 14.6, 0.8).

11. The submitters report 92–96% yields of 98% chemically pure product, bp 80–82°C (1 mm), $[\alpha]_D^{25}$ −74.3° (hexane, *c* 10.0). The specific rotation was corrected for this purity (Note 12). A specific rotation of $[\alpha]_D^{25}$ −77.6° (hexane) is estimated for the pure enamine.

12. The product is very moisture sensitive and should be handled under dry nitrogen or argon. Despite this precaution, the product is always contaminated by small amounts of (+)-citronellal, which has an optical rotation opposite to that of the enamine. To determine the optical purity of the product enamine, the specific rotation measured therefore must be corrected for the (+)-citronellal impurity. It is more reliable to base optical purity on the specific rotation of the citronellal obtained by hydrolysis of the enamine (Part C). The absolute method using HPLC of the diastereomeric amide derivative[5] also may be useful as a check of the optical purity.

13. *N,N*-Diethylnerylamine was prepared according to the method described in *Org. Synth., Coll. Vol. VIII,* **1993**, 190, and distilled over calcium hydride and stored under nitrogen below −20°C. GLC–MS analysis (Hitachi 063 and Hitachi RMU-6MG with OV-101 in fused silica, 0.2-mm × 25-m column) of *N,N*-diethyl-nerylamine used by the submitters showed a purity of 94.9%, and contained *N,N*-diethyl-2-ethylede-6-methyl-5-heptenylamine (0.2%), *N,N*-diethyl-2,7-dimethyl-2,6-octadienylamine (1.5%), *N,N*-diethyl-3-methylene-7-methyl-6-octenylamine (2.1%), and unidentifiable products (1.3%) as impurities, but not the (*E*)-isomer, *N,N*-diethylgeranylamine. The checkers distilled the nerylamine through a 32-cm Goodloe column, bp 102°C (3 mm), and achieved a purity of 98.6%.

14. The submitters obtained 90–95% yields of 94% chemically pure product, $[\alpha]_D^{24}$ −73.1° (hexane, *c* 10.0; corrected for the citronellal impurity).

15. The submitters conducted the hydrolysis step in a mixture of 2 *N* sulfuric acid and toluene. The acid is added dropwise at 0°C at a rate that keeps the pH of the mixture at 4–5. Control of pH is critical.

16. Rapid workup after the acid hydrolysis is desirable.

17. A specific rotation of $[\alpha]_D^{25}$ +16.5° (neat) is reported for optically pure citronellal.[6]

3. Discussion

(*R*)-(+)-Citronellal is a useful, key intermediate for the preparation of several important, optically active compounds such as citronellol, 1-menthol,[6] muscone,[7] and α-tocopherol.[8] The optical purity of citronellal from natural sources is at most 77% ee, however. This new procedure gives (*R*)-(+)-citronellal of high optical purity (> 95% ee).

The intermediate enamine, (*R*)-(–)-*N*,*N*-diethyl-(*E*)-citronellalenamine, is also a key intermediate for preparation of useful, optically active compounds, such as (+)-7-hydroxydihydrocitronellal.[9]

Isomerization of *N*,*N*-diethylnerylamine with [Rh{(–)-BINAP} (1,5-C_8H_{12})] ClO_4 and *N*,*N*-diethylgeranylamine with [Rh{(+)-BINAP} (1,5-C_8H_{12})] ClO_4 under conditions similar to those described in the text ([substrate]/[Rh] = 100, in THF, 40°C, 23 hr) proceed equally efficiently to give (+)-*N*,*N*-diethyl-(*E*)-citronellalenamine in good chemical (97 and 95%, respectively) and optical yields (92 and 96%, respectively). Thus, unnatural (*S*)-(–)-citronellal with high optical purity (> 95% ee) can also be prepared by the new procedure. The substrates must be geometrically pure and the chiral ligands enantiomerically pure in order to achieve optimal results.

If extreme care is taken to purify the substrate and the solvent, the [substrate]/[Rh] ratio can be raised much higher. For example, *N*,*N*-diethylgeranylamine can be isomerized in tetrahydrofuran in the presence of 0.00125 mol% of [Rh{(–)-BINAP} (1,5-C_8H_{12})] ClO_4 at 100°C in a glass autoclave during 3–7 hr to give (–)-*N*,*N*-diethyl-(*E*)-citronellalenamine with 97% ee in almost quantitative yield.

With the same catalyst systems, other prochiral *N*-alkyl- or *N*,*N*-dialkylallylamines can also be isomerized efficiently to the corresponding optically active imines or (*E*)-enamines, respectively. For example, with [Rh{(+)-BINAP} (1,5-C_8H_{12})] ClO_4, ([substrate]/[Rh] = 100, in THF, 40°C, 23 hr) a secondary allylamine, *N*-cyclohexylgeranylamine, and an allylamine with styrene-type conjugation, *N*,*N*-dimethyl-3-phenyl-2(*E*)-butenylamine, are isomerized to give (*S*)-(–)-*N*-cyclohexylcitronellalimine (chemical yield, 100%; optical yield, 96%) and (*R*)-(–)-*N*,*N*-dimethyl-3-phenyl-1(*E*)-butenylamine (chemical yield, 84%; optical yield, 90%), respectively.

Under similar conditions, various kinds of *N*,*N*-dialkylamines with substituents at δ-or γ-positions; for example, *N*,*N*-dimethyl-2-propenylamine, *N*,*N*-dimethyl-2(*E*)-butenylamine, *N*,*N*-dimethyl-2-methyl-2-propenylamine, and *N*,*N*-dimethyl-3-methyl-2-butenylamine can also be isomerized to the corresponding (*E*)-enamine in medium to good yields (60, 52, 97, and 100%). However, *N*,*N*-dimethyl-2(*E*)-butenylamine and *N*-phenyl- or *N*,*N*-diphenylgeranylamine were found to be poor substrates.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 57

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1. Department of Chemistry, Faculty of Engineering Science, Osaka University, Toyonaka, Osaka, 560 Japan;

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

brine

(R)-(–)-N,N-DIETHYL-(E)-CITRONELLALENAMINE

1-(E), 6-Octadienamine, (R)-(–)-N,N-diethyl-3,7-dimethyl- and 6-octenal, 3,7-dimethyl-, (R)-(+)-

[Rh{(+)-BINAP} (1,5-C_8H_{12})] ClO_4

chloro-(1,5-cyclooctadiene)rhodium(I) dimer

(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl [(+)-BINAP]

[Rh{(–)-BINAP}(1,5-C_8H_{12})] ClO_4

(–)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl [(–)-BINAP]

(R)-(–)-N,N-Diethyl-(E)-citronellalenamine [(R)-(–)-N,N-Diethyl-3,7-dimethyl-1(E),6-octadienylamine]

[Rh{(–)-BINAP} (1,5-C_8H_{12})]ClO_4 THF

N,N-diethyl-2-ethylede-6-methyl-5-heptenylamine

muscone

(+)-7-hydroxydihydrocitronellal

[Rh{(–)-BINAP} (1,5-C_8H_{12})] ClO_4

(S)-(–)-citronellal

(–)-N,N-diethyl-(E)-citronellalenamine

N-phenyl- or N,N-diphenylgeranylamine

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

methanol (67-56-1)

ether (60-29-7)

sodium bicarbonate (144-55-8)

silver chloride (7783-90-6)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

calcium sulfate (7778-18-9)

acetone (67-64-1)

toluene (108-88-3)

sodium (13966-32-0)

Allylamine (107-11-9)

Tetrahydrofuran, THF (109-99-9)

hexane (110-54-3)

calcium hydride (7789-78-8)

argon (7440-37-1)

1,5-cyclooctadiene

citronellal, (+)-citronellal (106-23-0)

silver perchlorate (7783-93-9)

N,N-Diethylnerylamine, N,N-diethyl-nerylamine (40137-00-6)

N,N-Diethylgeranylamine (40267-53-6)

rhodium(I) perchlorate

citronellol (106-22-9)

1-menthol

α-tocopherol (59-02-9)

cyclohexylcitronellalimine

(R)-(+)-2,2'-Bis(diphenylphosphino)-1,1'-binapthyl, (S)-(−)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl (76189-56-5)

(R)-(+)-Citronellal (2385-77-5)

N,N-diethyl-2,7-dimethyl-2,6-octadienylamine

N,N-diethyl-3-methylene-7-methyl-6-octenylamine

(+)-N,N-diethyl-(E)-citronellalenamine

N-cyclohexylgeranylamine

N,N-dimethyl-3-phenyl-2(E)-butenylamine

dimethyl-3-phenyl-1(E)-butenylamine

N,N-dimethyl-2-propenylamine (2155-94-4)

N,N-dimethyl-2(E)-butenylamine

N,N-dimethyl-2-methyl-2-propenylamine

N,N-dimethyl-3-methyl-2-butenylamine

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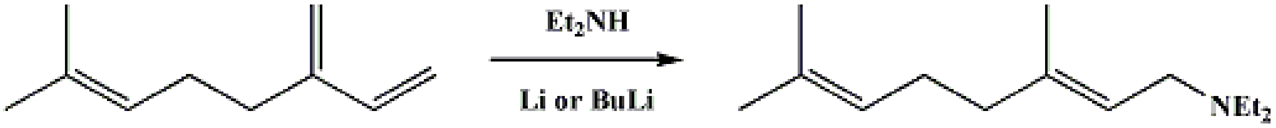
ADDITION OF DIALKYLAMINES TO MYRCENE: *N,N*-DIETHYLGERANYLAMINE

[2,6-Octadien-1-amine, *N,N*-diethyl-3,7-dimethyl-, (*E*)-]



Submitted by Kunihiko Takabe[1], Takao Katagiri[1], Juntaro Tanaka[1], Tsutomu Fujita[2], Shoji Watanabe[2], and Kyoichi Suga[2].
Checked by Alan J. Chalk, Laszlo V. Wertheimer, and Gabriel Saucy.

1. Procedure

In a 50-mL, round-bottomed glass reactor equipped with a magnetic stirring bar are placed 13.60 g (74 mmol) of myrcene (Note 1), 10.29 g (141 mmol) of diethylamine (Note 2), and 0.185 g (0.0267 g-atom) of metallic lithium cut into small pieces. The vessel is flushed with dry nitrogen, and is sealed. The solution is heated to 55°C in a water bath, and is stirred for 5 hr. The vessel is cooled to room temperature and the contents are poured into 30 mL of ice–water. The upper organic layer is separated, and the aqueous layer is extracted with 20-mL portions of diethyl ether. The combined organic layer is washed with aqueous sodium sulfate solution, dried over anhydrous sodium sulfate, and evaporated under reduced pressure. Distillation (Note 3) of the residual liquid affords 1.2–2.0 g of unreacted myrcene and 12.66–13.28 g (74–77%) of the product as a colorless liquid, bp 67–68°C (0.5 mm). GLC analysis indicated that the product contained 91.2–92.5% of *N,N*-diethylgeranylamine and other isomers (Note 4).

The checkers found that the use of benzene (20 mL) as a solvent increased the selectivity for *N,N*-diethylgeranylamine to 94% (Note 5) and (Note 6).

A similar reaction of myrcene with dipropylamine (50°C, 20 hr) afforded *N,N-dipropylgeranylamine* (80%; bp 93–94°C, 1 mm).

2. Notes

1. Myrcene, obtained from SCM Organic Chemicals (also available from Takasago Perfumery Company, Ltd., in Japan), was distilled (bp 69–70°C, 20 mm) prior to use. GLC analysis (Triton X-305, 0.28 mm × 30 m, 80–120°C) showed that the fraction contained 74% myrcene. The submitters used 80% pure myrcene.
2. Diethylamine, obtained from Aldrich Chemical Company, Inc. (also available from Nakarai Chemicals, Ltd., in Japan), was distilled from calcium hydride before use.
3. A short-path distillation apparatus was used in order to prevent loss of the product.
4. GLC analysis (Triton X-305; 0.28 mm × 30 m, 80–160°C) showed a composition of 92% *N,N*-diethylgeranylamine and other isomers that were identified by the checkers.[3]
The spectral properties of *N,N*-diethylgeranylamine are as follows: IR (neat) cm^{-1}: 1660, 1200, 1165, 1050, 830; ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 0.96 (t, 6 H, J = 7), 1.44–1.67 (m,

6 H), 1.85–2.15 (m, 4 H), 2.40 (q, 4 H, *J* = 7), 2.92 (d, 2 H, *J* = 6.5), 4.77–5.30 (m, 2 H).

5. The submitters preferred butyllithium in hexane in place of lithium metal. In a 50-mL, round-bottomed flask equipped with a magnetic stirring bar are placed 4.08 g (24 mmol) of myrcene and 3.29 g (45 mmol) of diethylamine under nitrogen. The mixture is cooled to 0°C using an ice bath, and 3.0 mL (4.8 mmol) of a 1.60 *M* solution of butyllithium in hexane is added dropwise by syringe while stirring for 15 min. The flask is sealed, and the solution is warmed to 50°C and stirred for 4 hr. The vessel is cooled to room temperature, and the contents are poured into 20 mL of cold water. The vessel is washed with 30 mL of diethyl ether and 10 mL of water. The upper layer is separated and the aqueous layer is extracted twice with 20 mL of diethyl ether. The combined organic layers are washed with brine, dried over anhydrous sodium sulfate, and evaporated under reduced pressure. Distillation (Note 3) of the residual liquid affords a 0.31–0.42-g forerun of unreacted myrcene and 4.06–4.37 g of the product (77–83%) as a colorless liquid, bp 84–86°C (1.5); composition by GLC: 95.3% *N,N*-diethylgeranylamine and 4.5% other isomers.

6. The submitters report that sodium naphthalenide can be used in place of butyllithium. Using tetrahydrofuran as a solvent, they obtained *N,N*-diethylgeranylamine in 56% yield.

3. Discussion

N,*N*-Dialkylgeranylamines have been prepared by the reaction of dialkylamines with geranyl halides.[4,5] The procedure described here is a modification of one we reported earlier.[4,6] It is a simple, one-step synthesis of *N*,*N*-dialkylgeranylamines from myrcene and dialkylamines, which are readily available bulk chemicals. The reaction proceeds stereoselectively, and yields are high.

N,N-Diethylgeranylamine is a key intermediate for the synthesis of industrially important acyclic monoterpenes such as geranyl acetate,[7] linalool,[8] citral,[9] and citronellal.[10]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 183

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

brine

MYRCENE

Benzene (71-43-2)

diethyl ether (60-29-7)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

diethylamine (109-89-7)

lithium (7439-93-2)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

hexane (110-54-3)

citral (5392-40-5)

calcium hydride (7789-78-8)

Linalool (78-70-6)

citronellal (106-23-0)

geranyl acetate (105-87-3)

N,N-Diethylgeranylamine, 2,6-Octadien-1-amine, N,N-diethyl-3,7-dimethyl-, (E)- (40267-53-6)

sodium naphthalenide

dipropylamine (142-84-7)

N,N-dipropylgeranylamine

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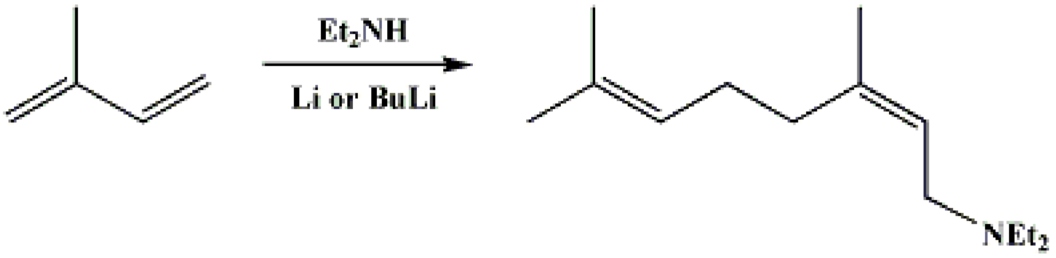
TELOMERIZATION OF ISOPRENE WITH DIALKYLAMINE: *N,N*-DIETHYLNERYLAMINE

[2,6-Octadien-1-amine, *N,N*-diethyl-3,7-dimethyl-, (*Z*)-]



Submitted by Kunihiko Takabe[1], Takashi Yamada, Takao Katagiri[1], and Juntaro Tanaka[1].
Checked by Alan J. Chalk, Laszlo V. Wertheimer, and Gabriel Saucy.

1. Procedure

A 100-mL glass autoclave (Note 1) is charged with 34 g (0.50 mol) of isoprene (Note 2) and 7.3 g (0.10 mol) of diethylamine (Note 3) under nitrogen (Note 4). The contents are cooled to 3–5°C using an ice–salt bath, and 3.7 mL (0.006 mol) of a 1.62 *M* solution of butyllithium in hexane (Note 5) is added dropwise by syringe while stirring. The resulting slightly yellow solution is blanketed carefully with dry nitrogen, and the vessel is sealed. The solution is heated to 65°C and stirred for 13 hr. The vessel is then cooled using an ice–salt bath, the contents are poured into 15 mL of water, and the organic layer is separated. The aqueous phase is extracted with 30 mL of diethyl ether. The organic layers are combined, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure with a rotary evaporator. The residual liquid is distilled under reduced pressure (Note 6) to afford 16.1–18.0 g (77–86%) of *N,N*-diethylnerylamine as a colorless liquid, bp 83–84°C (1.5 mm) (Note 7) and (Note 8).

2. Notes

1. The glass autoclave must be used with appropriate precaution. A pressure of about 20 psi is generated, so a low-positive-pressure reactor, such as a shielded Fischer-Porter Bottle (Fischer and Porter Company, Lab-Coest Division, Warminster, PA18974), can be used instead. Alternatively, the reaction may be carried out without pressure equipment in 3 days.[2]
2. Isoprene, obtained from Aldrich Chemical Company, Inc. (also available from Nakarai Chemicals, Ltd. in Japan), was dried over Linde 4A molecular sieves for at least 1 day and freshly distilled prior to use.
3. Diethylamine, obtained from Aldrich Chemical Company, Inc., was distilled

from calcium hydride before use.
4. A slow stream of dry nitrogen was passed through an inverted funnel that was placed over the vessel.
5. Butyllithium in hexane was obtained from Aldrich Chemical Company, Inc. (also available from Nakarai Chemicals, Ltd. in Japan), and titrated before use.[3] Lithium (0.055 g, 0.0079 g-atom), cut into small pieces (ca. 2 mm), can be used in place of the butyllithium-hexane solution.
6. A forerun (1.4–0.6 g) boiling at 52–56°C (16 mm) consists mainly of *N,N*-diethyl-2-methyl-2-butenylamine and *N,N*-diethyl-3-methyl-2-butenylamine.
7. GLC analysis (7% Apiezon L on 60–80-mesh Gaschrom Q, 3 mm × 3 m, 170°C) showed that the product is over 99% isomerically pure. The spectral properties of *N,N*-diethylnerylamine are as follows: IR (neat) cm^{-1}: 1660, 1200, 1165, 1050, 830; ^1H NMR ($CDCl_3$) δ: 1.03 (t, 6 H, *J* = 7, CH_3-), 1.45–1.7 (m, 6 H, CH_3-C=), 2.02–2.2 (m, 4 H, -CH_2-C=), 2.50 (q, 4 H, *J* = 7, -N-CH_2-), 3.05 (d, 2 H, *J* = 6.5, -N-CH_2-C=), 4.9–5.5 (m, 2 H, -CH=).
8. The submitters report that similar reactions of isoprene with dimethylamine (55°C, 10 hr) and dipropylamine (65°C, 15 hr) afforded *N,N*-dimethylnerylamine (69%), bp 85–86°C (9 mm) and *N,N*-dipropylnerylamine (77%), bp 86–87°C (1 mm), respectively.

3. Discussion

The procedure described here is essentially that reported earlier[4] and modified by subsequent experience.[5] It is a simple, general method for the synthesis of an *N,N*-dialkylnerylamine from isoprene and a dialkylamine. *N,N*-Dialkylnerylamines can also be prepared by the reaction of a dialkylamine with neryl chloride[6] by a modification of Sandler's method.[7] However, pure nerol, the starting material of neryl chloride, is expensive, and not easily available commercially. The present method illustrates a mild and convenient one-step reaction for the preparation of an *N,N*-dialkylnerylamine. In addition, the starting materials are readily accessible, the reaction proceeds stereoselectively, and the yields of the product are generally high. This process consists of the initial addition of lithium dialkylamide to isoprene, followed by the propagation of the resulting intermediate, and the termination by dialkylamine.

N,N-Dialkylnerylamines serve as convenient precursors for naturally occurring acyclic monoterpenes such as linalool,[8] citronellal,[9] and citral.[10]

This preparation is referenced from:

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

diethyl ether (60-29-7)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

diethylamine (109-89-7)

lithium (7439-93-2)

dimethylamine (124-40-3)

butyllithium (109-72-8)

ISOPRENE (78-79-5)

hexane (110-54-3)

citral (5392-40-5)

calcium hydride (7789-78-8)

Linalool (78-70-6)

neryl chloride

nerol

citronellal (106-23-0)

N,N-Diethylnerylamine, 2,6-Octadien-1-amine, N,N-diethyl-3,7-dimethyl-, (Z)- (40137-00-6)

dipropylamine (142-84-7)

butyllithium-hexane

N,N-diethyl-2-methyl-2-butenylamine

N,N-diethyl-3-methyl-2-butenylamine

N,N-dimethylnerylamine

N,N-dipropylnerylamine

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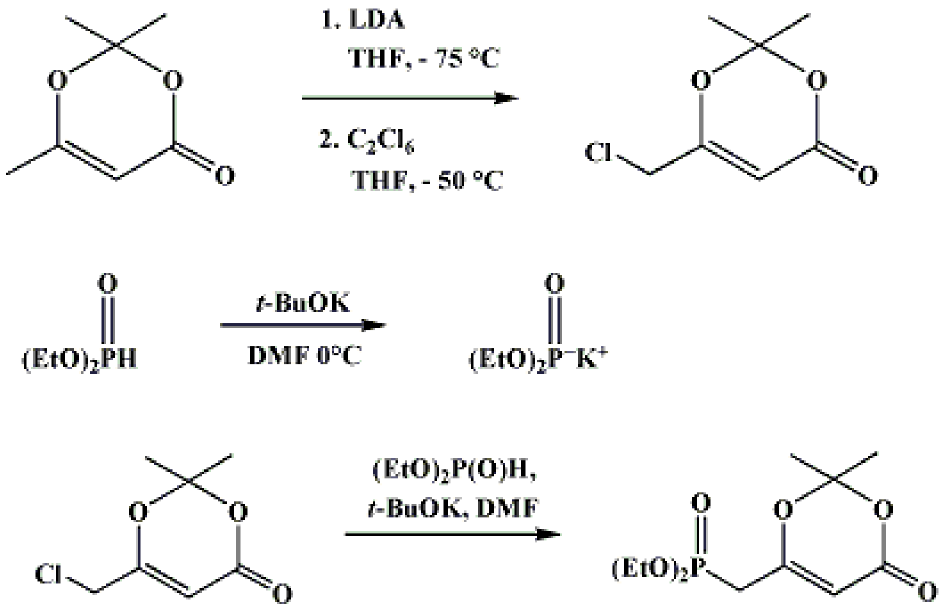
Organic Syntheses, CV 8, 192

6-DIETHYLPHOSPHONOMETHYL-2,2-DIMETHYL-1,3-DIOXEN-4-ONE

[Phosphonic acid, [(2,2-dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)methyl]-, diethyl ester]



Submitted by Robert K. Boeckman, Jr., Robert B. Perni, James E. Macdonald, and Anthony J. Thomas[1].
Checked by Stacey C. Slater and James D. White.

1. Procedure

A. *6-Chloromethyl-2,2-dimethyl-1,3-dioxen-4-one.* A three-necked, 500-mL, round-bottomed flask is fitted with a nitrogen inlet, a rubber septum, and a 125-mL dropping funnel. The flask is flame-dried, flushed with nitrogen and charged with diisopropylamine (22.0 mL, 0.16 mol) and 100 mL of tetrahydrofuran (THF) (Note 1). This solution is cooled in an ice bath, and the dropping funnel is charged with a solution of butyllithium (80.0 mL of a 1.88 *M* solution in hexane, 0.15 mol), which is added dropwise over 15 min (Note 2). The resulting solution is cooled to approximately −75°C in a dry ice–acetone bath and treated with a solution of 2,2,6-trimethyl-1,3-dioxen-4-one[2] (16.0 g, 0.11 mol) in tetrahydrofuran (20 mL) dropwise over 20 min (Note 3). During the addition, a fine yellow suspension forms. The enolate solution is stirred at −75°C for an additional 15 min and then transferred via cannula to a 1-L flask containing hexachloroethane[3 4; 5] (39.0 g, 0.16 mol) (Note 4) in tetrahydrofuran (150 mL) at −50 to −55°C (dry ice–acetone bath) over 30 min. When the addition is complete, any residual enolate is transferred with an additional portion of tetrahydrofuran (20 mL). The resulting reaction mixture is allowed to warm slowly to −25°C over 30 min and poured into ice-cold aqueous 10% hydrochloric acid (200 mL), and the mixture is briefly shaken to discharge the red color. The organic layer is separated, and the aqueous layer is extracted with ether (2 × 100 mL). The combined organic extracts are washed with saturated aqueous sodium bicarbonate solution (100 mL), saturated aqueous sodium chloride solution (100 mL), dried over sodium sulfate, and concentrated under reduced pressure to afford 31.50–35.50 g of an oily solid. Column chromatography on Florisil (100–200 mesh, 400 g) (Note 5) and elution with hexane (1 L) and 20% ethyl acetate–hexane (2 L), gives 12.17–12.67 g (63–65%) of the desired product as a yellow oil (Note 6),(Note 7),(Note 8).

B. *6-Diethylphosphonomethyl-2,2-dimethyl-1,3-dioxen-4-one.* A 500-mL, three-necked flask is outfitted as

above, flushed with nitrogen, and charged with potassium *tert*-butoxide (21.0 g, 0.187 mol) and dimethylformamide (200 mL) (Note 9). The stirring mixture is cooled in an ice bath and treated with diethyl phosphite (26.7 g, 0.193 mol). The resulting solution is stirred in the ice bath for 20–40 min and then treated dropwise with a solution of 6-chloromethyl-2,2-dimethyl-1,3-dioxen-4-one (11.00 g, 0.062 mol) in tetrahydrofuran (50 mL) over 20 min. The resulting purple solution is stirred for an additional 15 min at 0°C and treated with concentrated hydrochloric acid dropwise until the purple color is discharged (ca. 6 mL). The resulting mixture is filtered by suction through Celite (Note 10), and the collected solids are washed with tetrahydrofuran (50 mL). The combined organic portions are treated with several grams of anhydrous potassium carbonate and filtered, and the tetrahydrofuran is removed with a rotary evaporator. Dimethylformamide and excess diethyl phosphite are removed by distillation at 0.4 mm with the bath temperature maintained below 50°C (Note 11). The residue is diluted with ethyl acetate (200 mL) and placed in the refrigerator at 0°C overnight. The solid that precipitates is removed by filtration, and the filtrate is concentrated under reduced pressure to ca. 75 mL and purified by flash chromatography (Note 12) and (Note 13) on 700 g of Florisil (9 × 22-cm column). Elution with 3 L of 1 : 1 ethyl acetate–hexane, 3 L of 3 : 1 ethyl acetate–hexane, and then 3 L of 100% ethyl acetate affords 8.30–8.56 g (48–50%) of 6-diethylphosphonomethyl-2,2-dimethyl-1,3-dioxen-4-one (Note 14) and (Note 15). Mixed fractions may be rechromatographed to afford an additional 2–4% of product.

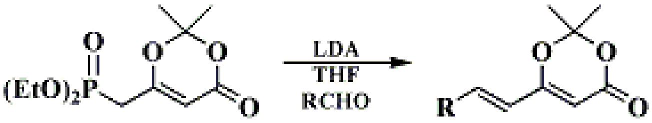
2. Notes

1. Tetrahydrofuran was distilled under a nitrogen atmosphere from sodium benzophenone ketyl. Diisopropylamine was distilled under a nitrogen atmosphere from calcium hydride.
2. A solution of butyllithium in hexane (ca. 1.8 *M*) was obtained from Lithcoa and standardized by titration against 2,5-dimethoxybenzyl alcohol.[6]
3. 2,3,6-Trimethyl-1,3-dioxen-4-one is commercially available from the Aldrich Chemical Company, Inc. and may be used without further purification.
4. Hexachloroethane was obtained from the Aldrich Chemical Company, Inc. and used without further purification.
5. Florisil is a magnesium silicate adsorbent obtained from the Floridin Company.
6. Substantial amounts of unreacted hexachloroethane may be recovered from early fractions.
7. The reaction may be carried out equally well on a 32-g scale.
8. The NMR and IR spectral data of the chloride are as follows: ^{1}H NMR ($CDCl_3$) δ: 1.74 (s, 6 H), 4.02 (s, 2 H), 5.53 (s, 1 H), IR (film) cm^{-1}: 2970, 1730, 1640, 1390, 1280, 1210, 1024.
9. Dimethylformamide (DMF) was distilled under reduced pressure (20 mm) from calcium hydride. Diethyl phosphite may be used directly from a freshly opened bottle or redistilled before use.
10. This filtration is very slow, and a wide sintered-glass funnel is recommended.
11. The product phosphonate decomposes to diethylphosphonoacetone above 50°C, and care must be taken during the distillation and concentration of chromatography fractions that heating baths do not exceed this temperature.
12. The procedure of W. C. Still was utilized.[7]
13. Chromatographic fractions were analyzed by TLC by elution with ethyl acetate, and were visualized with a permanganate spray. The phosphonate had R_f = 0.35.
14. The NMR and IR spectral data of the phosphonate are as follows: ^{1}H NMR ($CDCl_3$) δ: 1.37 (t, 6 H), 1.72 (s, 6 H), 2.81 (d, 2 H), 4.16 (m, 4 H), 5.40 (d, 1 H); IR (film) cm^{-1}: 2980, 1720, 1630, 1370, 1255. The absence of residual hexachloroethane was confirmed by ^{13}C NMR spectroscopy.
15. The phosphonate should be stored at 0°C. Under these conditions the purified product is stable for at least several months.

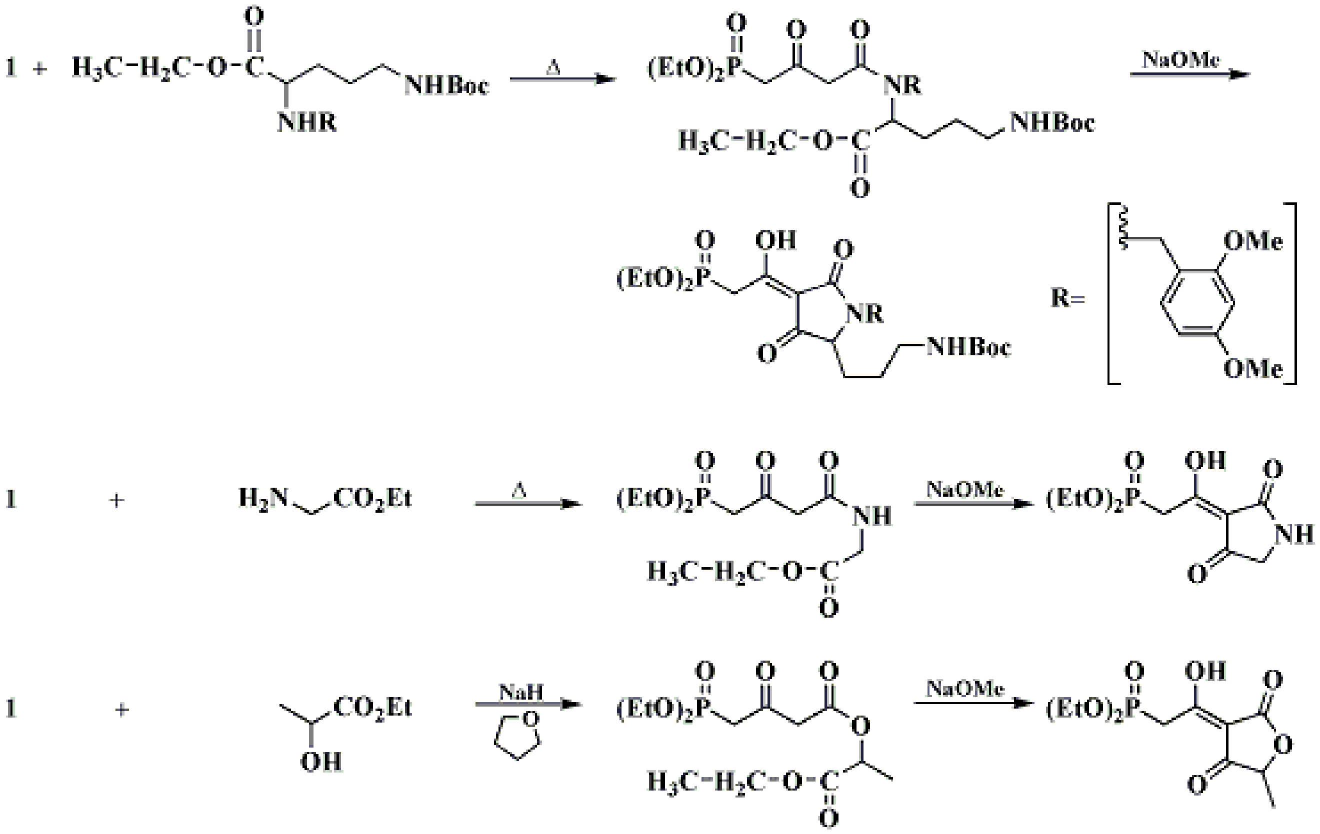
3. Discussion

This procedure is a modification of the previously-published procedure by Boeckman and Thomas.[8] The acetone diketene adduct serves as a versatile, activated β-keto ester equivalent.[2,3,4,5,9] Conversion of this

material to the phosphonate by the procedure described above affords an even more versatile synthon that is useful for the preparation of protected analogues of the Nazarov reagents by means of a Wadsworth–Emmons olefination.[10,11]

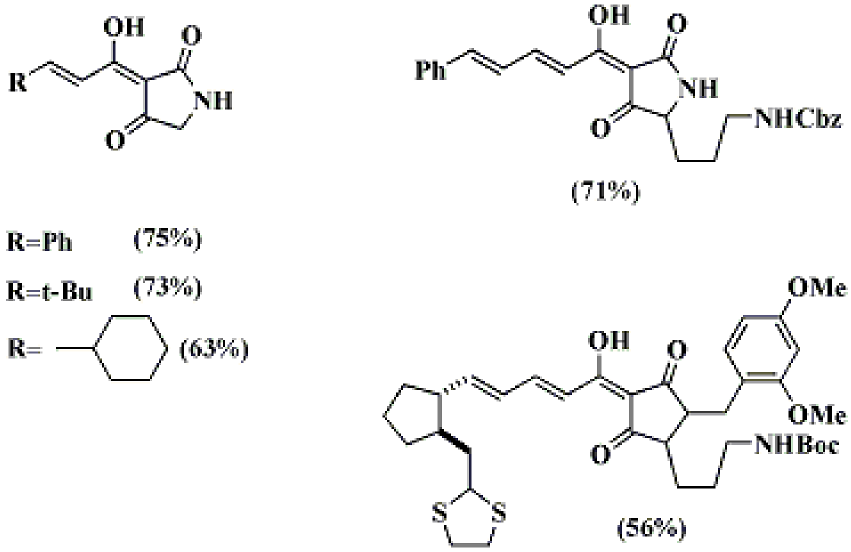


The title phosphonate and related substances undergo thermal decomposition to β-acyl ketenes at temperatures in excess of 50°C.[12] Thus thermolysis in the presence of alcohols, amines, α-hydroxy esters, and α-amino esters affords the corresponding β-keto esters and amides; the latter two classes can be cyclized upon subsequent base treatment to unsaturated tetronic and tetramic acids and the related phosphonate reagents.[8,13]



For sensitive amino acids prone to thermal dimerization to the related diketopiperazines, the reaction can be conducted in refluxing tetrahydrofuran solution in the presence of *p*-toluene- or camphorsulfonic acid as catalyst. Where possible the non acid-catalyzed thermal procedure is preferred since it generally provides cleaner products in higher yields.

The resulting tetramic and tetronic acid phosphonate reagents undergo the Wadsworth–Emmons olefination[11] with a variety of aldehydes to afford (*E*)-α,β-unsaturated and diene acyl tetramic and tetronic acids in good to excellent yields on treatment with potassium *tert*-butoxide (2 equiv) in tetrahydrofuran. For readily enolizable substrates use of the *N*-protected systems is generally required. The following compounds have been prepared, in the indicated yields, in this manner:



Two alternative methods for the preparation of phosphorus-activated tetramic acid reagents have recently been described.[14] [15] These reagents have served to provide a workable solution to the problem of construction of the dienoyl tetramic acid unit required for the synthesis of tirandamycin-A.[16],[17],[18],[19].

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium benzophenone ketyl

6-Diethylphosphonomethyl-2,2-dimethyl-1,3-dioxen-4-one

6-Chloromethyl-2,2-dimethyl-1,3-dioxen-4-one

2,2,6-trimethyl-1,3-dioxen-4-one

2,3,6-Trimethyl-1,3-dioxen-4-one

tetramic and tetronic acid phosphonate

tirandamycin-A

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

ether (60-29-7)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

p-toluene (108-88-3)

permanganate

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

dimethylformamide (68-12-2)

hexane (110-54-3)

calcium hydride (7789-78-8)

diethyl phosphite (762-04-9)

camphorsulfonic acid (5872-08-2)

hexachloroethane (67-72-1)

diisopropylamine (108-18-9)

2,5-dimethoxybenzyl alcohol (33524-31-1)

magnesium silicate

diethylphosphonoacetone (1067-71-6)

potassium tert-butoxide (865-47-4)

Phosphonic acid, [(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)methyl]-, diethyl ester (81956-28-7)

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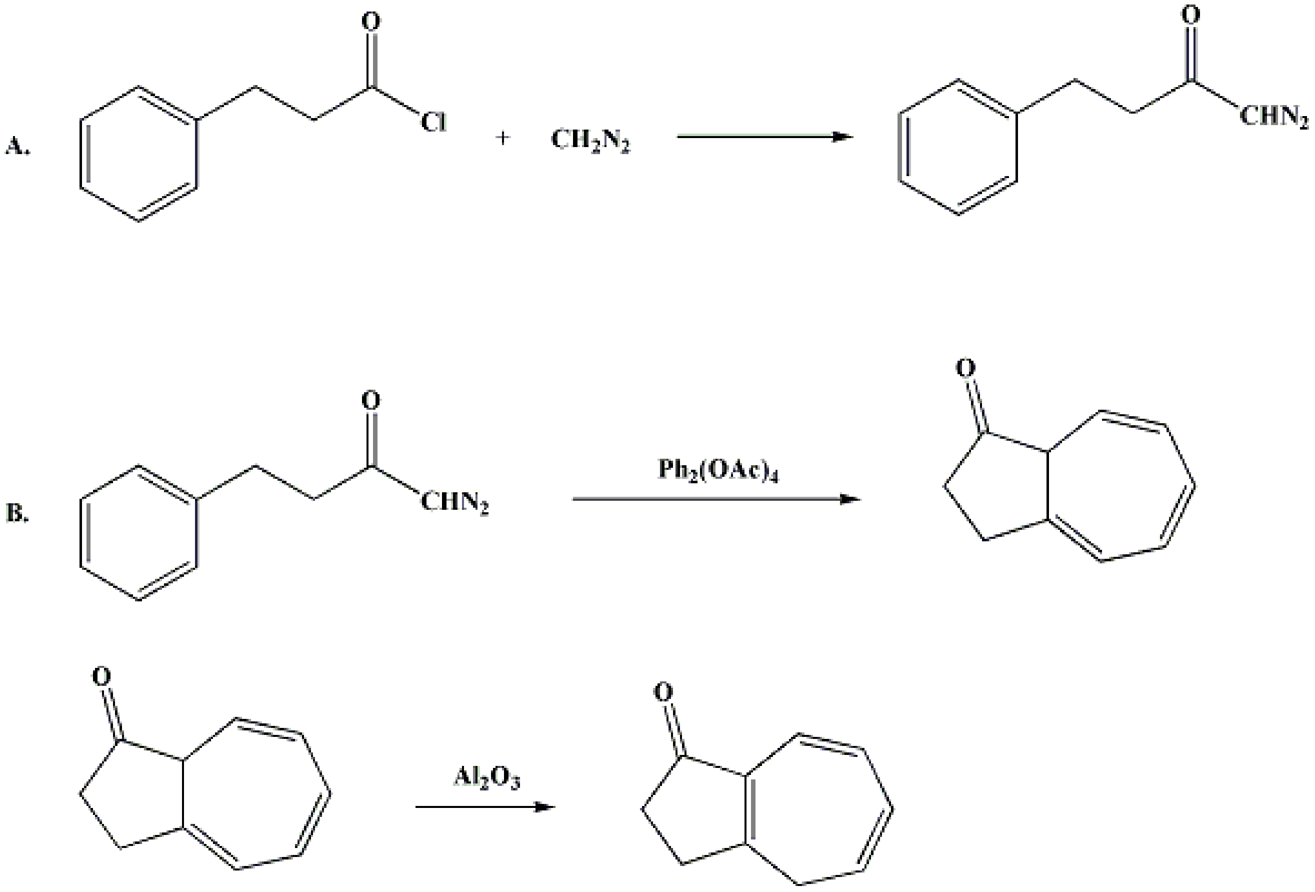
DIAZO KETONE CYCLIZATION ONTO A BENZENE RING: 3,4-DIHYDRO-1(2*H*)-AZULENONE

[1(2*H*)-Azulenone, 3,4-dihydro-]



Submitted by Lawrence T. Scott and Chris A. Sumpter[1].
Checked by John M. Fevig and Larry E. Overman.

1. Procedure

Caution! Diazomethane is toxic and explosive; all operations should be carried out in a well-ventilated hood with adequate shielding. (See (Note 1).)

A. *1-Diazo-4-phenyl-2-butanone*. A 1-L Erlenmeyer flask equipped with a two-in. magnetic stirring bar and a two-hole rubber stopper fitted with a 125-mL Teflon stopcock separatory funnel (Note 2) and a drying tube filled with potassium hydroxide (Note 3) is charged with a solution of 200 mmol (3.4 equiv) of diazomethane (Note 4) in 600 mL of dry ether. The solution is cooled to 0°C and stirred at high speed (Note 5). To this cooled solution, 10.0 g (59 mmol) of hydrocinnamoyl chloride (3-phenylpropionyl chloride) (Note 6) diluted to 125 mL with anhydrous ether is added dropwise over a 1-hr period. The resulting reaction mixture is stirred cold for an additional 0.5 hr and then at room temperature for 1 hr. After this period of time the reaction is complete, and excess diazomethane is removed by evacuating the Erlenmeyer flask with a water aspirator pump in the hood (Note 7). The Erlenmeyer flask is evacuated by connecting the aspirator to a one-hole stopper that has been fitted with a plastic or fire-polished glass tube. After the diazomethane has been removed, the remaining ethereal solution is concentrated by rotary evaporation to give 10.5–10.6 g (> 100% crude yield) of 1-diazo-4-phenyl-2-butanone as a yellow oil (Note 8). This oil is used without purification for the next reaction.

B. *3,4-Dihydro-1(2H)-azulenone*. A 250-mL, one-necked, round-bottomed flask is equipped with an egg-shaped magnetic stirring bar and a high dilution trident (.htmFig. 1)[2] (Note 9). The high-dilution trident is further equipped with a 100-mL pressure-equalizing addition funnel attached to a nitrogen inlet and an efficient reflux condenser attached to a nitrogen outlet. The round-bottomed flask is charged with 100 mL of dry freshly distilled methylene chloride and 12 mg of rhodium diacetate dimer (Note 10). This heterogeneous mixture is stirred at high speed (Note 11) and heated to a rapid reflux without bumping. The addition funnel is charged with a solution of 8.7 g (50 mmol) of 1-diazo-4-phenyl-2-butanone (Note 12) diluted to 50 mL with methylene chloride. As soon as the high-dilution trident reservoir (20 mL) fills up and begins to overflow back into the round-bottomed flask, dropwise addition of the diazo ketone solution is initiated (1:20, one drop of diazo ketone solution to every 20 drops of solvent entering the trident reservoir from the condenser). After the addition is complete (2.5–3 hr), the reaction mixture is allowed to reflux for an additional 1 hr. The reaction mixture is then cooled, and the yellow-green solution of the initially formed unstable trienone (Note 13) is suction-filtered through 110 g of neutral alumina (Note 14) in a 250-mL fritted-glass funnel to isomerize the β, γ double bond into conjugation with the carbonyl group and to remove the rhodium diacetate dimer. The alumina is then washed with 100 mL of ethyl acetate, and the combined organic filtrates are concentrated by rotary evaporation to give a yellow oil. Vacuum distillation of this oil through a short-path distillation head gives 5.5–5.7 g (75–78% yield) of a colorless to slightly green oil that solidifies at 0°C, bp 73–75°C/0.2 mm (Note 15). This material is sufficiently pure for most purposes (Note 16). Recrystallization from hexane (80 mL per gram of trienone) yields colorless needles, mp 28.5–29.0°C (Note 17).

Figure 1

Figure 1

2. Notes

1. See full warning in *Org. Synth., Coll. Vol. II* **1943**, 165, and *ald.htmrichimica Acta* **1983**, *16(1)*, 3–10.
2. Ground glass can cause explosions; therefore, a Teflon stopcock must be used.
3. Potassium hydroxide must be used as the drying agent since calcium sulfate and other drying agents can react with diazomethane and cause an explosion.
4. Diazomethane is prepared as described in *Org. Synth., Coll. Vol. IV* **1963**, 250, with 50 g of Diazald (from Aldrich Chemical Company, Inc.) in 300 mL of ether added to 15 g of KOH in 25 mL of water, 30 mL of ether, and 50 mL of 2-(2-ethoxyethoxy)ethanol. One equivalent of diazomethane becomes incorporated in the reaction product, and the remainder serves as a scavenger for the HCl produced as a reaction by-product. The excess of diazomethane called for in this procedure is necessary to inhibit the undesired formation of 1-chloro-4-phenyl-2-butanone. The submitters report that this reaction can be performed on twice this scale with comparable results.
5. The high rate of stirring reduces the production of 1-chloro-4-phenyl-2-butanone, a by-product of this reaction.
6. This compound can be purchased from Aldrich Chemical Company, Inc. or prepared according to standard methods.[3]
7. Two hundred milliliters of ether and diazomethane are removed before transfer for rotary evaporation. Diazomethane in a rotary evaporator can cause explosions.
8. A pure sample of diazo ketone can be obtained by chromatography on silica gel using 15% ethyl acetate/hexane as an eluent, $R_f = 0.37$. The checkers estimate the purity of the crude diazo ketone to be 90–91% based on careful column chromatography of 1.0-g aliquots. They further estimate that approximately 5–6% of 1-chloro-4-phenyl-2-butanone is also produced in the reaction. The spectral properties of 1-diazo-4-phenyl-2-butanone are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.59–2.64 (m, 2 H), 2.95 (t, 2 H, $J = 7$), 5.20 (broad s, 1 H), 7.17–7.31 (m, 5 H).
9. The high-dilution trident in this example dilutes the diazo ketone solution to 10^{-3}–10^{-4} M before it reaches the reaction mixture.
10. The rhodium diacetate dimer is used in catalytic amounts; 0.132% (weight of dimer/weight of diazo ketone) has worked out to be the best ratio for this reaction.
11. The high-speed stirring minimizes undesired bimolecular reactions.

12. The submitters report that this step can be performed on a 0.5-mol scale (87 g of diazo ketone) in 86.5–94.9% yield. This amount of diazo ketone was prepared in multiple batches as described in Step A. The submitters were reluctant to prepare and handle diazomethane on scale large enough to make 0.5 mol of diazo ketone in one batch.
13. The initially formed trienone isomerizes quantitatively to β-tetralone on treatment with catalytic amounts of trifluoroacetic acid. This acid sensitivity precludes chromatography of the crude product on normal silica gel.
14. F20 Alumina (60–200 mesh) from Schoofs, Inc. was used. The checkers used chromatography grade neutral alumina (100–125 mesh) supplied by Fluka.
15. The oil bath temperature maximum must be maintained below 120°C or the yield of product drops.
16. The checkers found that on this scale a bulb-to-bulb (Kugelrohr) distillation could also be employed. The distilled product is contaminated with approximately 4–5% of 1-chloro-4-phenyl-2-butanone, which was produced in Step A. This impurity is easily removed by recrystallization from hexane. Alternatively, this impurity can be removed at the diazo ketone stage by column chromatography. The use of purified diazo ketone in Step B affords purer distilled product, but this modification has no significant effect on the overall yield.
17. The spectral properties of 3,4-dihydro-1(2*H*)-azulenone are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.50 (narrow m, 2 H), 2.70 (narrow m, 2 H), 2.78 (apparent d, 2 H, J = 6), 5.38 (dt, 1 H, J = 9.6, 6.3), 6.09 (dd, 1 H, J = 9.2, 6.2), 6.47 (dd, 1 H, J = 11, 5.7), 6.68 (d, 1 H, J = 11); IR (film) cm^{-1}: 1697.

3. Discussion

The cyclopropanation of alkenes, alkynes, and aromatic compounds by carbenoids generated in the metal-catalyzed decomposition of diazo ketones has found widespread use as a method for carbon–carbon bond construction for many years, and intramolecular applications of these reactions have provided a useful cyclization strategy. Historically, copper metal, cuprous chloride, cupric sulfate, and other copper salts were used most commonly as catalysts for such reactions; however, the superior catalytic activity of rhodium(II) acetate dimer has recently become well established.[4] This commercially available rhodium salt exhibits high catalytic activity for the decomposition of diazo ketones even at very low catalyst : substrate ratios (< 1%) and is less capricious than the old copper catalysts. We recommend the use of rhodium(II) acetate dimer in preference to copper catalysts in all diazo ketone decomposition reactions. The present synthesis describes a typical cyclization procedure.

A special feature of the synthesis described here is the glass apparatus used to achieve high-dilution reaction conditions (.htmFig. 1).[2] This "trident" is simple but effective and can be fabricated quite easily from standard parts. The one shown here is designed to accept an overhead mechanical stirrer.

The product of this synthesis is an especially useful, highly functionalized hydroazulene that is not available commercially. We have used it as a synthetic precursor to homoazulene,[5 6] and to a variety of homoazulene derivatives,[7 8] bridged homotropylium cations,[9 10] and azulene quinones.[11 12] It could undoubtedly serve as a precursor to numerous natural products. The cyclization reaction tolerates electron-donating substituents[4,13,14] but not halogens[15] on the aromatic ring.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

rhodium diacetate dimer

rhodium(II) acetate dimer

HCl (7647-01-0)

ethyl acetate (141-78-6)

ether (60-29-7)

cupric sulfate (7758-98-7)

copper (7440-50-8)

calcium sulfate (7778-18-9)

potassium hydroxide, KOH (1310-58-3)

cuprous chloride (7758-89-6)

methylene chloride (75-09-2)

Diazomethane (334-88-3)

hydrocinnamoyl chloride, 3-phenylpropionyl chloride (645-45-4)

hexane (110-54-3)

trifluoroacetic acid (76-05-1)

β-Tetralone (530-93-8)

2-(2-ethoxyethoxy)ethanol (111-90-0)

1-Diazo-4-phenyl-2-butanone (10290-42-3)

1-chloro-4-phenyl-2-butanone

3,4-Dihydro-1(2H)-azulenone, 1(2H)-Azulenone, 3,4-dihydro- (52487-41-9)

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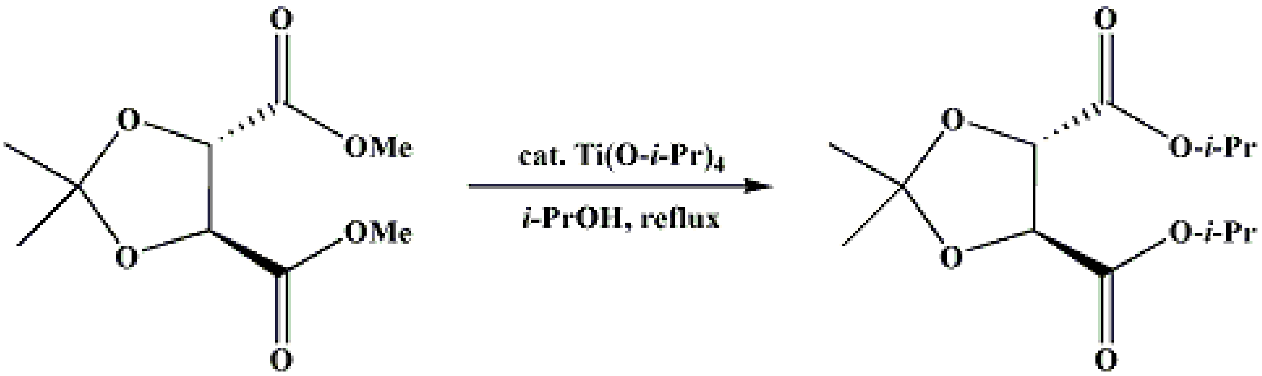
Organic Syntheses, CV 8, 201

DIISOPROPYL (2*S*,3*S*)-2,3-*O*-ISOPROPYLIDENETARTRATE

[1,3-Dioxolane-4,5-dicarboxylic acid, 2,2-dimethyl-, bis(1-methylethyl) ester, (4*R*-*trans*)-]



Submitted by René Imwinkelried, Martin Schiess, and Dieter Seebach[1].
Checked by Isao Kurimoto and Ryoji Noyori.

1. Procedure

A dry, 500-mL, two-necked flask equipped with a magnetic stirrer and a reflux condenser is flushed with nitrogen and charged with 8.4 mL (45.8 mmol) of dimethyl (2*S*,3*S*)-2,3-*O*-isopropylidenetartrate (Note 1) and 250 mL of absolute 2-propanol (Note 2). To the resulting solution is added with a plastic syringe and hypodermic needle 1.35 mL (4.6 mmol) of tetraisopropyl titanate (Note 1). The mixture is refluxed with stirring for 2 hr. To remove the methanol formed, the flask is transferred to a rotary evaporator, and the contents are concentrated to 10–12 mL. The oily residue is once more dissolved in 250 mL of absolute 2-propanol (Note 2) and refluxed for 2 hr. The solvent is removed again in a rotary evaporator, and the resulting yellow oil is dissolved in 100 mL of diethyl ether. After addition of 5 mL of water (Note 3) the pale mixture is vigorously stirred for 10 min and then dried over anhydrous magnesium sulfate. The flaky suspension is filtered and the filter cake washed with three 25-mL portions of ether. The ether solution is concentrated in a rotary evaporator. The residue, 12.5–13.1 g of a slightly yellow oil, solidifies on standing. This solid is freed from small amounts of solvent by an oil-pump vacuum (ca. 0.01 mm) at room temperature for 2 hr. Further purification by short-path distillation at 91–93°C/0.05 mm furnishes 11.5–12.0 g (91–95%) of a slightly yellow solid, which turns colorless on crushing, mp 41.5–42.5°C, $[\alpha]_D^{RT}$ +42 ± 0.3° ($CHCl_3$, c 4).

2. Notes

1. Commercial (Fluka purum) (−)-or (+)-dimethyl 2,3-*O*-isopropylidenetartrate and tetraisopropyl titanate can be used without further purification.

2. 2-Propanol was heated at reflux over $CaSO_4$, distilled, and redistilled with addition of tetraisopropyl titanate (ca. 10 g/L).
3. This is done to hydrolyze titanium alkoxides. Part of the titanium alkoxides is removed during evaporation of the solvents in the rotatory evaporator [Ti(OCHMe$_2$)$_4$, bp 78°C/12 mm].

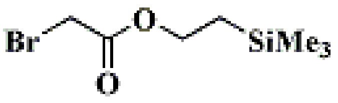
3. Discussion

Normally, transesterifications are acid- or base-catalyzed (e.g., sulfuric acid, *p*-toluenesulfonic acid, and potassium or sodium alkoxides in the appropriate alcohols).[2] These methods fail with molecules containing acid- or base-labile functional groups. The titanate-mediated esterifications, deacylations, and transesterifications of rather simple, monofunctional substrates are described in the patent literature; see the references in a recent article.[3] Recently, Seebach et al.[3,4,5] have demonstrated that this method is applicable also to substrates with additional functional groups that would not survive acid- or base-catalyzed transesterification conditions, such as C□C and C□N bonds, acetals, β-hydroxy and β-acyloxy esters, β-lactams, *tert*-butyldimethylsilyloxy groups, BOC,[6] and other carbamate protecting groups. The possible applications of this transesterification are illustrated in s.htmcheme 1, and some characteristic examples are given in Table I. Of course, the method can only establish equilibrium conditions. Therefore, depending on the particular case, components of the equilibria have to be removed (see procedure above) or used in large excess to drive the conversion to the desired products.

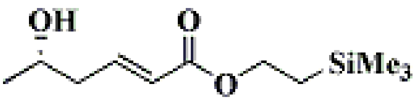
Scheme 1. Titanate-mediated transesterifications. X = functional group (see accompanying text); (a) transesterification in alcoholic solvents, with removal of acyl protecting groups and exchange of the alcohol component of ester groups in the substrate; (b) transesterification in ester solvents, with acylation of hydroxy groups and exchange of the alcohol or of the acid component of ester groups in the substrate.

Scheme 1. Titanate-mediated transesterifications. X = functional group (see accompanying text); (a) transesterification in alcoholic solvents, with removal of acyl protecting groups and exchange of the alcohol component of ester groups in the substrate; (b) transesterification in ester solvents, with acylation of hydroxy groups and exchange of the alcohol or of the acid component of ester groups in the substrate.

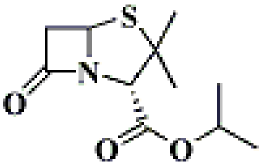
TABLE I
PRODUCTS OF TRANSESTERIFICATION WITH TITANATE CATALYSIS[3,4,5,6]



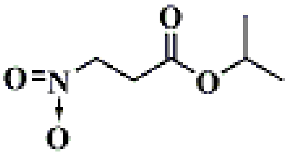
71% from ethyl ester and 2-trimethylsilylethanol



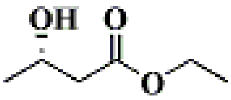
74% from methyl ester and 2-trimethylsilylethanol



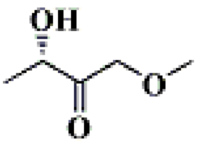
91% from methyl ester and 2-propanol



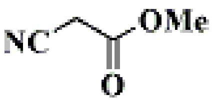
50% from methyl ester and 2-propanol



90% from 0-3,5-dinitrobenzoate and ethanol

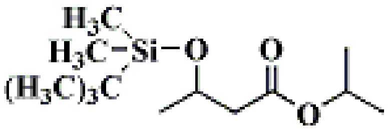


60% from O-propanoyl derivative and ethanol



88% from ethyl ester
and methanol

70% from alcohol
and ethyl acetate



83% from ehtyl ester
and 2-propanol

89% from methyl ester
and benzyl alcohol

91% from athyl ester
and 2-propanol

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 495

References and Notes

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2. Patai, S., Ed. "The Chemistry of Acid Derivatives," Supplement B, Part 1; Interscience Publishers: New York, 1979.
3. Seebach, D.; Hungerbühler, E., Naef, R.; Schnurrenberger, P.; Weidmann, B.; Züger, M. F. *Synthesis* **1982**, 138.
4. Schnurrenberger, P.; Züger, M. F.; Seebach, D. *Helv. Chim. Acta* **1982**, *65*, 1197.Seebach, D.; Züger, M. *Helv. Chim. Acta* **1982**, *65*, 495.
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6. Rehwinkel, H.; Steglich, W. *Synthesis* **1982**, 826.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

(–)-or (+)-dimethyl 2,3-O-isopropylidenetartrate

$CaSO_4$

$Ti(OCHMe_2)_4$

sulfuric acid (7664-93-9)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

2-propanol (67-63-0)

magnesium sulfate (7487-88-9)

p-toluenesulfonic acid (104-15-4)

BOC

tetraisopropyl titanate

Diisopropyl (2S,3S)-2,3-O-isopropylidenetartrate (81327-47-1)

1,3-Dioxolane-4,5-dicarboxylic acid, 2,2-dimethyl-, bis(1-methylethyl)ester, (4R-trans)-

dimethyl (2S,3S)-2,3-O-isopropylidenetartrate (37031-30-4)

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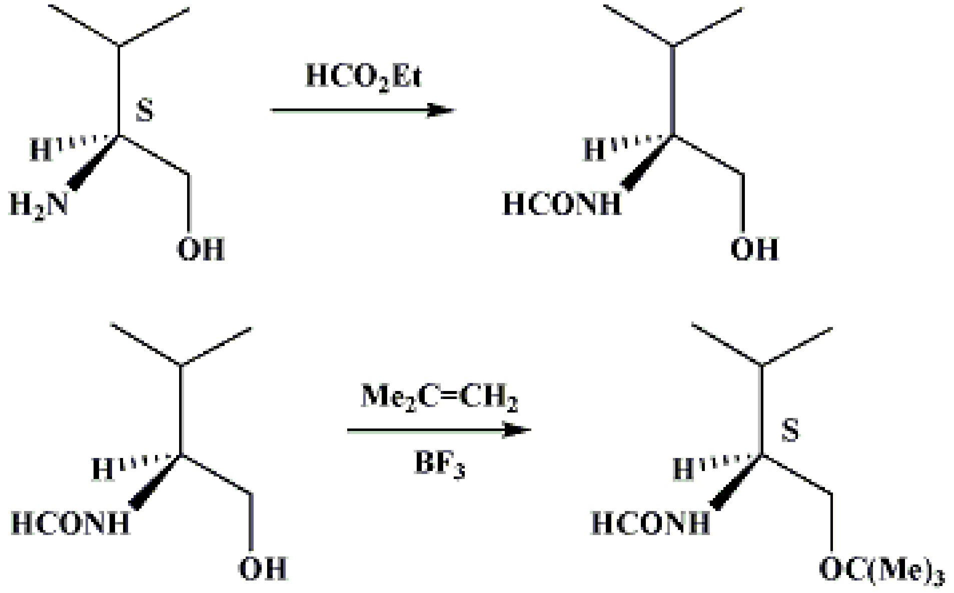
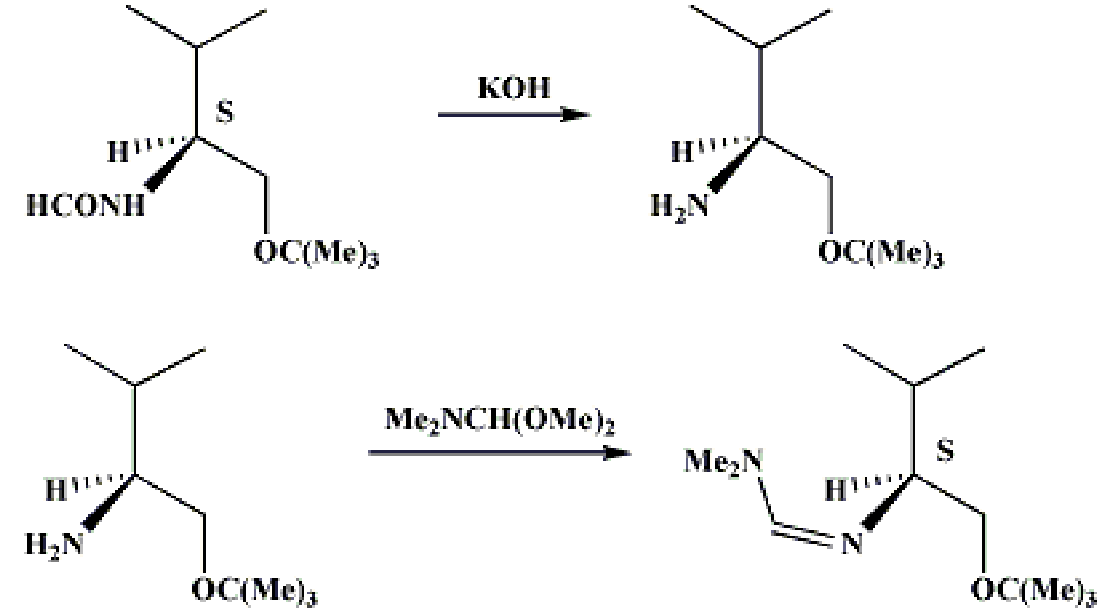
(*S*)-*N*,*N*-DIMETHYL-*N'*-(1-*tert*-BUTOXY-3-METHYL-2-BUTYL)FORMAMIDINE

[Methanimidamide, *N'*-[1-[(1,1-dimethylethoxy)methyl]-2-methylpropyl]-*N*,*N*-dimethyl-, (*S*)-]

A.



B.



Submitted by Daniel A. Dickman, Michael Boes, and Albert I. Meyers[1].
Checked by Jeffrey Romine and Leo A. Paquette.

1. Procedure

A. *(S)-N-Formyl-O-tert-butylvalinol (**1**)*. In a 100-mL, round-bottomed flask, 20.6 g

(200 mmol) of (*S*)-valinol (Note 1) and 16 g (216 mmol) of ethyl formate (Note 2) are heated at reflux under a nitrogen atmosphere for 1 hr. Excess ethyl formate is removed under reduced pressure and the oil is triturated with dry ether until a yellow solid appears. This material is dissolved in 260 mL of dry dioxane (Note 3) in a 1000-mL pressure bottle (Note 4) equipped with a magnetic stirring bar and immersed in an ice–water bath. The bottle is immediately charged with ca. 260 mL of liquid isobutene (Note 5) and 75 mL of boron trifluoride etherate is rapidly added. The pressure bottle is sealed with a stopper, removed from the ice bath, and stirred at room temperature for 3 hr (Note 6). In a fume hood, excess isobutene is removed from the resulting clear solution by carefully cracking the seal of the stopper. When the gas ceases to discharge, the stopper is removed and the solution is poured into a 1000-mL separatory funnel containing 250 mL of 2 *N* sodium hydroxide and is extracted twice with 100 mL of dichloromethane. The organic layer is washed with 100 mL of brine and dried over anhydrous magnesium sulfate. The organic solvent is removed and the residue is distilled (Kugelrohr tube, 0.05 mm, 80–85°C bath temperature) to give 27–36 g (75–95%) of *N*-formyl-*O*-*tert*-butylvalinol **(1)** as a clear oil (Note 7).

B. *(S)-N,N-Dimethyl-N'-(1-tert-butoxy-3-methyl-2-butyl)formamidine* ***(2)***. In a 500-mL, round-bottomed flask 26 g (140 mmol) of the formamide from Part A is dissolved in 100 mL of ethanol and 200 mL of a 50% aqueous potassium hydroxide solution is added. The mixture is heated at reflux overnight; on cooling, the reaction separates into colorless aqueous and organic layers. The two layers are extracted 3 times with 100 mL of ether and the combined organic layers are washed with 100 mL of brine. After the solution is dried over anhydrous potassium carbonate and filtered, the ether and ethanol are carefully removed under aspirator vacuum at ambient temperature. The crude amine is treated with 25 g (210 mmol) of *N,N*-dimethylformamide dimethyl acetal (Note 8) and the reaction mixture is heated under argon at 40°C for 1 hr. The solution is concentrated under reduced pressure and the crude product is distilled bulb-to-bulb (0.05 mm, 55–65°C) to give 25.7–27 g (86–91.5%) of (*S*)-*N,N*-dimethyl-*N'*-(1-*tert*-butoxy-3-methyl-2-butyl)formamidine **(2)** as a colorless liquid (Note 9).

2. Notes

1. (L)- or (*S*)-Valinol was purchased from Aldrich Chemical Company, Inc. and used without further purification. The preparation of (L)-valinol has been described: Smith, G. A.; Gawley, R. E. *Org. Synth., Coll. Vol. VII* **1990**, 530.
2. Ethyl formate was purchased from J. T. Baker Chemical Company.
3. Dioxane was distilled from lithium aluminum hydride.
4. A Kimble bottle (#15096) purchased from VWR Scientific (Cat. No. 16267-101) was employed.
5. Isobutene was purchased from Matheson Gas Products.
6. The two-layer system became a clear solution within 15 min.
7. The physical properties are as follows: IR (neat) cm^{-1}: 3300, 1660; ^1H NMR ($CDCl_3$, 300 MHz) δ: 0.79–0.88 (m, 6 H), 1.07 (s, 9 H), 1.82 (m, 1 H), 3.3 (m, 2

H), 3.75 (m, 1 H), 7.94 (d, 1 H, *J* = 12), 8.13 (d, 1 H, *J* = 1); $[\alpha]_D^{25}$ −59.6° (EtOH, c 3.5).

8. *N*,*N*-Dimethylformamide dimethyl acetal was purchased from Aldrich Chemical Company, Inc.

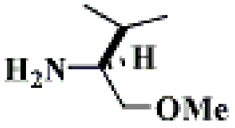
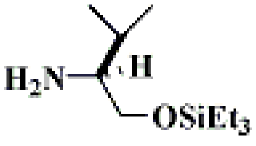
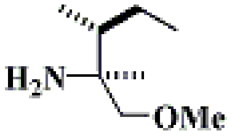
9. The physical properties are as follows: IR (neat) cm^{-1}: 1660; ^1H NMR ($CDCl_3$, 300 MHz) δ: 0.77 (d, 3 H, *J* = 6.5), 0.79 (d, 3 H, *J* = 6.5), 1.07 (s, 9 H), 1.72 (m, 1 H), 2.6–3.5 (m, 3 H), 2.73 (s, 6 H), 7.14 (s, 1 H); $[\alpha]_D^{25}$ −15.9° (THF, c 0.98).

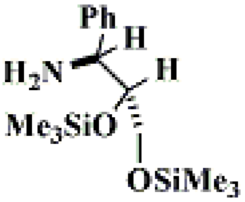
3. Discussion

This procedure for the synthesis of *N*,*N*-dimethyl-*N'*-alkylformamidines is representative for both chiral and achiral alkyl groups. These compounds are used to activate a wide range of secondary amines toward metalation and alkylation and may be removed to furnish the α-alkylated amines.[2 3]

N,*N*-Dimethyl-*N'*-alkylformamidines may be prepared from dimethylformamide dimethyl acetal and a primary amine by heating for 1–5 hr[4] (Eq. 1, Table 1).

TABLE I
PREPARATION OF *N*,*N*-DIMETHYL-*N'*-ALKYLFORMAMIDINES

RNH_2	% yield
	95
	98
	98



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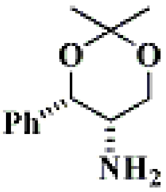
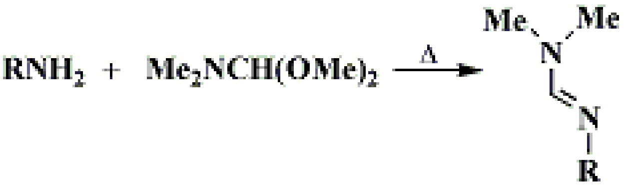
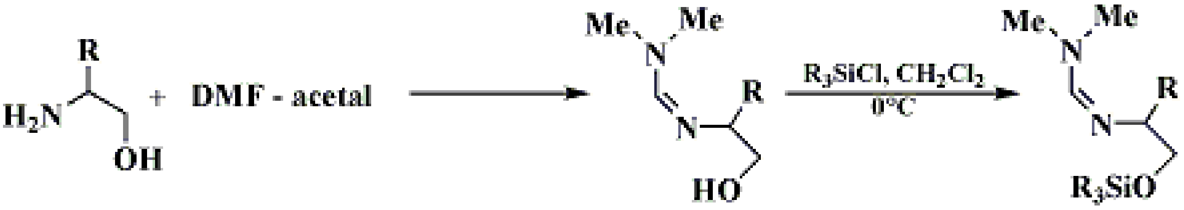


98



It is also possible to simply heat "DMF-acetal" with an amino alcohol (e.g., valinol, leucinol) and obtain the hydroxy formamidine, which can be directly silylated with Et_3SiCl, Me_3SiCl, or *tert*-$BuMe_2SiCl$ at 0°C in dichloromethane (Eq. 2).[2] If these *N*,*N*-dimethylformamidines are required, this procedure has the advantage of eliminating the sometimes troublesome cleavage of a silyl ether during reaction with CMF–acetal.



In addition to the exchange reaction[5] described previously,[6] formamidines derived from secondary amines can be prepared by forming the *N*-formyl derivative, which is treated successively with boron trifluoride etherate and the appropriate primary amine[2] (Eq. 3, Table II). However, this method is not satisfactory if sensitive groups (e.g., Me_3Si) are present on the amine since they are cleaved by the Meerwein reagent.

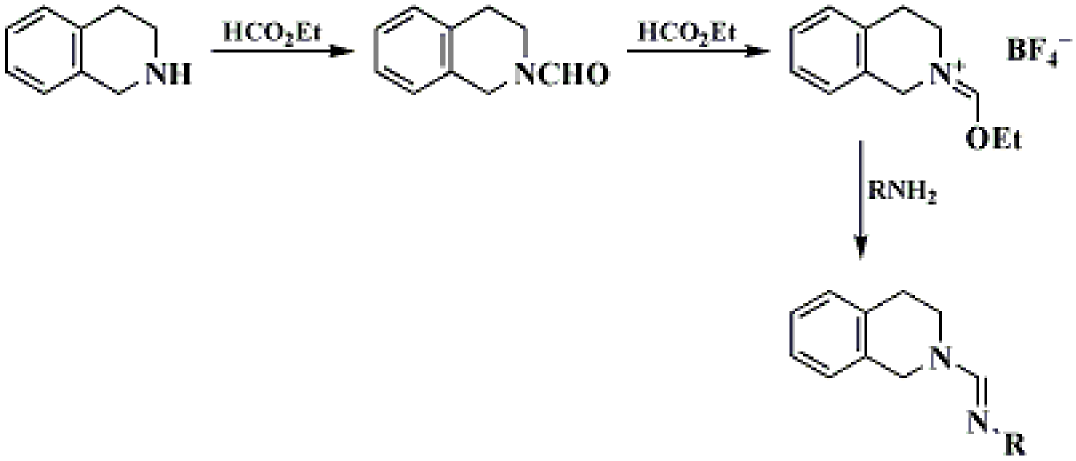
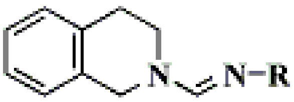
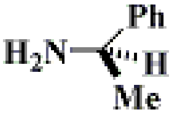
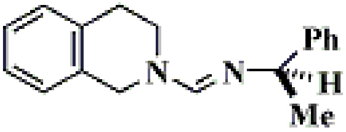
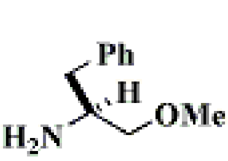
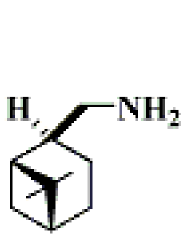
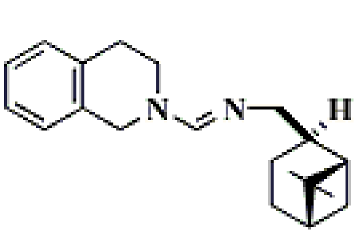
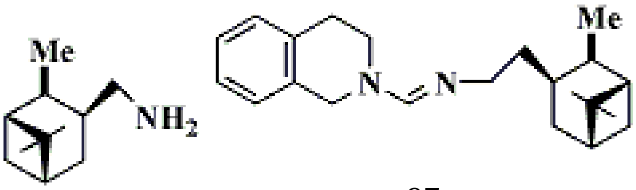


TABLE II
PREPARATION OF FORMAMIDINES VIA *N*-FORMYL DERIVATIVES

RNH_2	(%) 
	 98
	94
	 98



97

The main advantages of using the *tert*-butyl ether of the valinol formamidine are its stability to reaction conditions used in the asymmetric alkylation of amines and its ready recovery from these reactions for further use.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 573

References and Notes

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2. Meyers, A. I.; Fuentes, L. M.; Kubota, Y. *Tetrahedron* **1984**, *40*, 1361;
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6. Meyers, A. I.; Boes, M., Dickman, D. A. *Org. Synth., Coll. Vol. VIII* **1993**, 573.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

brine

(S)-N-Formyl-O-tert-butylvalinol (1)

(S)-N,N-Dimethyl-N'-(1-tert-butoxy-3-methyl-2-butyl)formamidine (2)

(L)- or (S)-Valinol

Et_3SiCl

Me_3SiCl

tert-$BuMe_2SiCl$

N,N-dimethylformamidines

ethanol (64-17-5)

potassium carbonate (584-08-7)

ether (60-29-7)

formamide (75-12-7)

sodium hydroxide (1310-73-2)

nitrogen (7727-37-9)

potassium hydroxide (1310-58-3)

ethyl formate (109-94-4)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

dioxane (5703-46-8)

isobutene (9003-27-4)

lithium aluminum hydride (16853-85-3)

boron trifluoride etherate (109-63-7)

argon (7440-37-1)

silyl ether (13597-73-4)

valinol, (S)-valinol, (L)-valinol (2026-48-4)

leucinol

dimethylformamide dimethyl acetal, N,N-dimethylformamide dimethyl acetal (4637-24-5)

hydroxy formamidine

valinol formamidine

tert-butyl ether (6163-66-2)

N-formyl-O-tert-butylvalinol (90482-04-5)

(S)-N,N-DIMETHYL-N'-(1-tert-BUTOXY-3-METHYL-2-BUTYL) FORMAMIDINE, Methanimidamide, N'-[1-[(1,1-dimethylethoxy)methyl]-2-methylpropyl]-N,N-dimethyl-, (S)- (90482-06-7)

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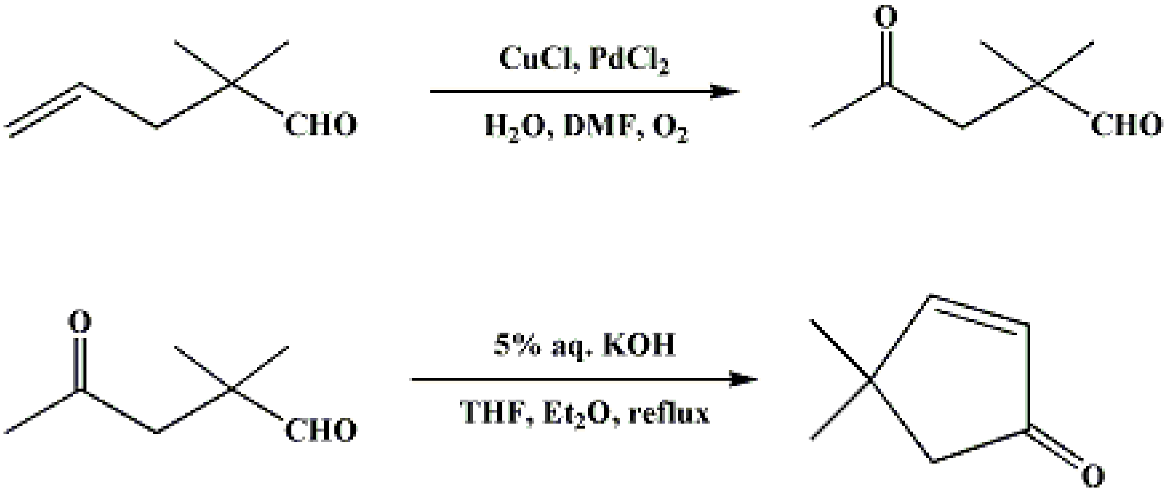
Organic Syntheses, CV 8, 208

4,4-DIMETHYL-2-CYCLOPENTEN-1-ONE

[2-Cyclopenten-1-one, 4,4-dimethyl-]



Submitted by David Pauley, Frank Anderson, and Tomas Hudlicky[1].
Checked by David M. Fink and Andrew S. Kende.

1. Procedure

A. *2,2-Dimethyl-4-oxopentanal.* (See (Note 1).) Oxygen is bubbled for 2 hr through a stirred solution of copper(I) chloride (32.8 g, 0.33 mol), palladium(II) chloride (1.19 g, 0.007 mol), 829 mL of dimethylformamide, and 331 mL of water in a 2-L, three-necked, round-bottomed flask cooled in a water bath. 2,2-Dimethyl-4-pentenal (185.6 g, 1.66 mol) (Note 2) is added to the solution and oxygen is bubbled through for an additional 60 hr at room temperature. The solution is acidified to litmus with 10% hydrochloric acid and extracted 4 times with 200 mL of ethyl ether. The combined organic layers are washed 3 times with 200 mL of saturated sodium chloride solution and dried over sodium sulfate. The ether is removed first by rotary evaporation and then under reduced pressure (0.2 mm). In this way 133.6 g (1.04 mol) of keto-aldehyde is obtained in 62.7% yield. The original aqueous layer is saturated with sodium chloride and extracted 5 times with 200 mL of anhydrous ethyl ether. The combined organic layers are washed 3 times with 200 mL of saturated sodium chloride solution and dried over sodium sulfate. Solvent is removed by rotary evaporation and vacuum pump. An additional 31.5 g (0.25 mol) of keto-aldehyde is recovered to give a total yield of 78% (Note 3), bp 32°C (0.3 mm) (Note 4).

B. *4,4-Dimethyl-2-cyclopenten-1-one.* A 3-L, round-bottomed flask, containing a solution of 600 mL of aqueous 5% potassium hydroxide, 300 mL of tetrahydrofuran, 1350 mL of ethyl ether, and 165.1 g (1.29 mol) 2,2-dimethyl-4-oxopentanal, is equipped with a mechanical stirrer and a reflux condenser. The solution is heated under reflux for 66 hr under a nitrogen atmosphere. On completion, the organic layer

is washed 3 times with 200 mL of saturated sodium chloride solution and dried over sodium sulfate. The aqueous layer is extracted 3 times with 200 mL of anhydrous ethyl ether. The resulting organic layers are washed 3 times with saturated sodium chloride solution and dried over sodium sulfate. All organic layers are evaporated using aspirator vacuum and a rotary evaporator and combined. The residual ether is removed under reduced pressure to yield 89.7 g (63%) of 4,4-dimethyl-2-cyclopenten-1-one, bp 32°C (0.3 mm) (Note 5),(Note 6),(Note 7).

2. Notes

1. This procedure was originally described by Magnus.[2]
2. 2,2-Dimethyl-4-pentenal was prepared as described in *Org. Synth., Coll. VII* **1990**, 177.
3. The product is sufficiently pure to be used in the next reaction without purification.
4. The spectral properties of the product are as follows: IR (neat) cm^{-1}: 2990, 2730, 1740, 1485, 1380; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.12 (s, 6 H), 2.14 (s, 3 H), 2.7 (s, 2 H), 9.52 (s, 1 H).
5. This product is volatile. The checkers found one-third of the product in a vacuum trap after 24 hr at ca. 5 mm.
6. The checkers distilled the product (Kugelrohr 8 mm, 80°C) and obtained yields of 83% (one-third scale) and 79% (two-thirds scale).
7. The spectral properties of the product are as follows: IR (neat) cm^{-1}: 2970, 2890, 1730, 1600, 1480, 1430; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.20 (s, 6 H), 2.21 (s, 2 H), 5.97 (d, 1 H, J = 6), 7.46 (d, 1 H, J = 6).

3. Discussion

4,4-Dimethyl-2-cyclopenten-1-one is a valuable starting material in terpenoid synthesis and in cases where a *gem*-dimethylcyclopentane unit needs to be introduced. It is useful as a starting material in further functionalization. Its preparation by the method of Magnus[2] is amenable to large scale synthesis.

Acknowledgment

The authors thank Professor P. D. Magnus for permission to use his method for the scale up reported here.

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

ether, ethyl ether (60-29-7)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

oxygen (7782-44-7)

nitrogen (7727-37-9)

potassium hydroxide (1310-58-3)

copper(I) chloride (7758-89-6)

palladium(II) chloride

Tetrahydrofuran (109-99-9)

dimethylformamide (68-12-2)

2,2-Dimethyl-4-pentenal (5497-67-6)

4,4-Dimethyl-2-cyclopenten-1-one, 2-Cyclopenten-1-one, 4,4-dimethyl- (22748-16-9)

2,2-Dimethyl-4-oxopentanal (61031-76-3)

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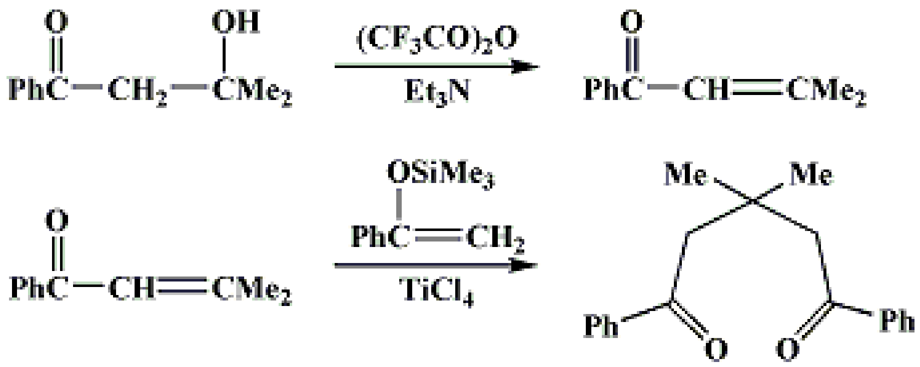
3,3-DIMETHYL-1,5-DIPHENYLPENTANE-1,5-DIONE

[1,5-Pentanedione, 3,3-dimethyl-1,5-diphenyl-]



Submitted by Koichi Narasaka[1]
Checked by David E. Uehling and Clayton H. Heathcock.

1. Procedure

A. *Isopropylideneacetophenone.* A 1-L, three-necked flask is fitted with a 100-mL pressure-equalizing dropping funnel, a mechanical stirrer, and a condenser equipped with a two-way stopcock leading to a balloon of argon gas. To the flask is added a solution of 18.4 g of 3-hydroxy-3-methyl-1-phenyl-1-butanone (Note 1) in 60 mL of dry methylene chloride. The flask is cooled in an ice bath and 28.5 g of triethylamine, a catalytic amount of 4-(*N*,*N*-dimethylamino)pyridine, and 20 mL of methylene chloride are added. A solution of 25.8 g of trifluoroacetic anhydride (Note 2) in 40 mL of methylene chloride is added dropwise over a period of 15 min, and the mixture is stirred for 2.5 hr.

The ice bath is removed and the mixture is stirred for 21 hr at room temperature (about 30°C). Under vigorous stirring, 100 mL of saturated aqueous sodium carbonate, 100 mL of water, and 300 mL of ether are added to the mixture. The organic layer is separated and the water layer is extracted with 100 mL of ether. The combined ether extracts are washed with brine and dried over magnesium sulfate. The ether solution is condensed using a rotary evaporator and the residue is distilled under reduced pressure to give 14.5–16.0 g (88–97% yield) of isopropylideneacetophenone (Note 3).

B. *3,3-Dimethyl-1,5-diphenylpentane-1,5-dione.* A 500-mL, three-necked flask is fitted with a mechanical stirrer, a rubber septum, and a two-way stopcock equipped with a balloon of argon gas (Note 4). To the flask is added 100 mL of dry methylene chloride, and the flask is cooled in a dry ice–acetone bath. Titanium tetrachloride (7.7 mL) (Note 5) is added by syringe through the septum. The septum is removed and replaced with a 100-mL pressure-equalizing dropping funnel containing a solution of 11.2 g of isopropylideneacetophenone in 30 mL of methylene chloride. This solution

is added over a 3-min period, and the mixture is stirred for 4 min. A solution of 13.5 g of the silyl enol ether of acetophenone (Note 1) in 40 mL of methylene chloride is added dropwise with vigorous stirring over a 4-min period, and the mixture is stirred for 7 min. The reaction mixture is poured into a solution of 22 g of sodium carbonate in 160 mL of water with vigorous magnetic stirring (Note 6). The resulting white precipitate is removed by filtration through a Celite pad and the precipitate is washed with methylene chloride.

The organic layer of the filtrate is separated and the aqueous layer is extracted with two 40-mL portions of methylene chloride. The combined organic extracts are washed with 60 mL of brine and dried over sodium sulfate. The methylene chloride solution is concentrated with a rotary evaporator and the residue is passed through a short column of silica gel (Baker 200 mesh, 400 mL) using 1.5 L of a 9 : 1 (v/v) mixture of hexane and ethyl acetate (Note 7). The eluent is condensed and distilled; the first fraction (bp 81–85°C/0.6 mm, 2.04 g) is a mixture of isopropylideneacetophenone and acetophenone; the second fraction (bp 85–172°C/0.6 mm, 0.42 g) is a mixture of the above-mentioned substances and the desired product; the third fraction (bp 172–178°C/0.6 mm) gives 14.0–15.2 g (72–78%) of 3,3-dimethyl-1,5-diphenylpentane-1,5-dione (Note 8).

2. Notes

1. See *Org. Synth., Coll. Vol. VIII* **1993**, 324.
2. Attempted dehydration using an acid catalyst or iodine failed, giving mainly acetophenone. When acetic anhydride is employed instead of trifluoroacetic anhydride, the reaction proceeds very slowly. Dehydration with excess methanesulfonyl chloride and triethylamine gives the product in high yield; however, the distilled product has a strong odor of sulfur compound.
3. The physical properties are as follows: bp 73–75°C/0.4 mm; the NMR spectrum (CCl_4) shows singlets at δ 1.93 (3 H) and 2.13 (3 H) and multiplets at 6.63 (1 H), 7.16–7.48 (3 H) and 7.71–7.91 (2 H).
4. All the apparatuses should be well dried before use.
5. Freshly distilled titanium tetrachloride (bp 136.4°C) is used.
6. Stirring should be continued until the organic and aqueous layers show no acidity.
7. The submitters used Wako gel C-200.
8. The physical properties are as follows. Anal. calcd. for $C_{19}H_{20}O_2$: C, 81.39; H. 7.19. Found: C, 81.34; H, 7.16. The ^1H NMR spectrum ($CDCl_3$) shows singlets at δ 1.22 (6 H, CH_3) and 3.26 (4 H, CH_2), and multiplet signals between 7.17–8.03 (10 H, aromatic CH).

3. Discussion

The preparation of 3,3-dimethyl-1,5-diphenylpentane-1,5-dione has also been achieved from 3,3-dimethylglutaric acid and phenyllithium.[2]

The present method gives 3,3-dimethyl-1,5-diphenylpentane-1,5-dione in better yield and is widely applicable to the preparation of various 1,5-diketones.[3] In addition, when silyl enol ethers of esters are employed instead of those of ketones. δ-keto esters can be obtained.[4]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

brine

silyl enol ether of acetophenone

ethyl acetate (141-78-6)

ether (60-29-7)

acetic anhydride (108-24-7)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

iodine (7553-56-2)

methylene chloride (75-09-2)

Phenyllithium (591-51-5)

magnesium sulfate (7487-88-9)

hexane (110-54-3)

titanium tetrachloride (7550-45-0)

triethylamine (121-44-8)

3,3-dimethylglutaric acid (4839-46-7)

Methanesulfonyl chloride (124-63-0)

trifluoroacetic anhydride (407-25-0)

argon (7440-37-1)

4-(N,N-dimethylamino)pyridine (1122-58-3)

3,3-Dimethyl-1,5-diphenylpentane-1,5-dione, 1,5-Pentanedione, 3,3-dimethyl-1,5-diphenyl- (42052-44-8)

3-Hydroxy-3-methyl-1-phenyl-1-butanone (43108-74-3)

Isopropylideneacetophenone (5650-07-7)

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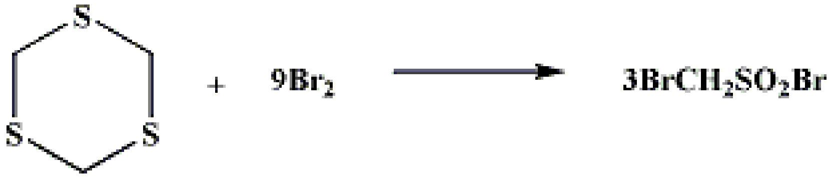
Organic Syntheses, CV 8, 212

A GENERAL SYNTHETIC METHOD FOR THE PREPARATION OF CONJUGATED DIENES FROM OLEFINS USING BROMOMETHANESULFONYL BROMIDE: 1,2-DIMETHYLENECYCLOHEXANE

[Cyclohexane, 1,2-bis(methylene)-]

A.



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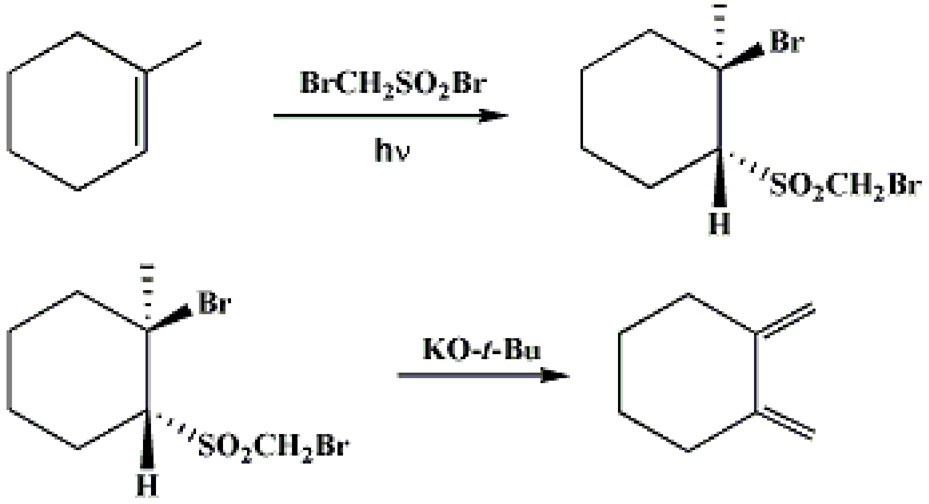


Submitted by Eric Block and Mohammad Aslam[1].
Checked by Jeffrey C. Weber and Leo A. Paquette.

1. Procedure

A. *Bromomethanesulfonyl bromide.* A 3-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, a pressure-equalized dropping funnel, and a thermometer is charged with 100 g (0.73 mol) of *sym*-trithiane (Note 1) suspended in 600 mL of water. Bromine (1136 g, 7.1 mol) is added with stirring while keeping the flask temperature around 40°C (Note 2). After the addition of half of the bromine, 600 mL of water is added and bromine addition is continued. After all of the bromine has been added, the reaction mixture is stirred for 0.25 hr. The mixture is transferred to a 4-L separatory funnel, the lower organic layer is separated, and the aqueous layer is extracted with two 200-mL portions of methylene chloride (Note 3). The organic extracts are combined, washed with one 100-mL portion of cold 5% sodium bisulfite solution and with 100 mL of water, dried over anhydrous magnesium sulfate, and

concentrated at room temperature with a rotary evaporator to a light-yellow oil. Distillation using a short Vigreux column affords 218–249 g (42–48%) of bromomethanesulfonyl bromide as a light-yellow oil, bp 68–69°C (0.55 mm) (Note 4) and (Note 5).

B. *1-Bromo-1-methyl-2-(bromomethylsulfonyl)cyclohexane.* Four Pyrex test tubes (2.5 × 20 cm) are charged with 1-methylcyclohexene (5.0 g per test tube; total weight 20.0 g, 0.21 mol) (Note 6). Methylene chloride (12 mL) is added to each test tube, which is cooled in ice. An ice-cold solution of bromomethanesulfonyl bromide (13.6 g of bromomethanesulfonyl bromide per test tube; total weight 54.4 g, 0.23 mol) in methylene chloride (12 mL) is added to each test tube with mixing at 0°C (Note 7). The test tubes are attached with the help of several rubber bands to a Pyrex immersion well equipped with a 45-W mercury lamp (Note 8). The immersion well is cooled by circulation of ice water (Note 9) and immersed in a cooling bath maintained at −15°C. The reaction mixture is irradiated for 2 hr. Solid potassium carbonate (1.5 g) is added to each test tube and the contents of the test tubes are filtered through a small column with a glass wool plug into a 250-mL round-bottomed flask. Methylene chloride is removed, first on a rotary evaporator and then with a vacuum pump (1 mm), to give an oil that gradually solidifies (68.3 g, 98%). Recrystallization from 95% ethanol (100 mL) gives white crystals (54.3 g, 78%) (Note 10), mp 59–61°C (Note 11).

C. *1,2-Dimethylenecyclohexane.* An oven-dried, 1-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, a pressure-equalized dropping funnel, and a stopper is charged with potassium *tert*-butoxide (59.5 g, 0.53 mol) (Note 12) dissolved in *tert*-butyl alcohol–tetrahydrofuran (9:1, 400 mL total) (Note 13) and cooled in ice. A solution of 1-bromo-1-methyl-2-(bromomethylsulfonyl)cyclohexane (54.0 g, 0.16 mol) in *tert*-butyl alcohol–tetrahydrofuran (9:1, 100 mL) (Note 14) is added dropwise over a 1-hr period. After the addition is complete the reaction mixture is stirred at room temperature for 0.5 hr and then poured into a 2-L separatory funnel containing 500 mL of water. This solution is extracted with two 150-mL portions of pentane. The combined pentane extracts are washed 8 times with water (500 mL) (Note 15), dried over anhydrous magnesium sulfate, and filtered. The pentane is removed by distillation at atmospheric pressure using an efficient Vigreux column and the residue is distilled under reduced pressure to give 11.4 g (65%) of 1,2-dimethylenecyclohexane as a colorless liquid, bp 69–70° (90 mm) (lit.[2] 60–61°C, 90 mm) (Note 16) and (Note 17).

2. Notes

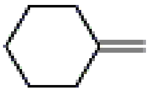
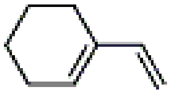
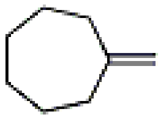
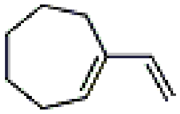
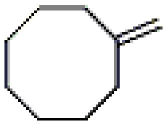
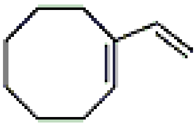
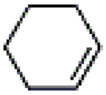
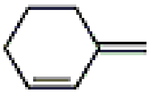
1. *sym*-Trithiane is prepared as described by Bost and Constable[3] and is used without purification. It can be purchased from Aldrich Chemical Company, Inc.
2. This is an exothermic reaction; no outside heating is required. If the temperature goes above 40°C, the flask is cooled by ice–water.
3. In the first of these extractions, the upper phase is the organic one. In the

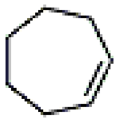
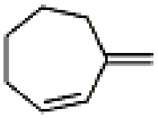
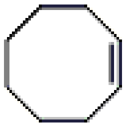
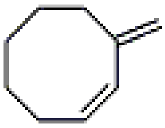
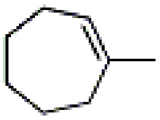
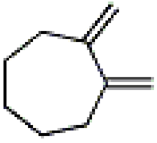
second extraction, the organic layer is at the bottom.
4. The product has refractive index n_D^{20} 1.5706 and spectral properties as follows: IR (neat) cm^{-1}: 3040 (vs), 2960 (vs), 1362 (vs), 1205 (s), 1160 (vs), 1105 (m), 830 (s), 680 (s); ^1H NMR ($CDCl_3$, 60 MHz) δ: 5.05 (s).
5. The product can be synthesized on a much smaller scale with no loss in yield simply by reducing the quantities as desired.
6. 1-Methylcyclohexene was obtained from the Aldrich Chemical Company, Inc. and was distilled before use.
7. On occasion bromomethanesulfonyl bromide undergoes spontaneous, exothermic addition to olefins. While this problem was not encountered with 1-methylcyclohexene, it is desirable to mix the reagents at low temperature to avoid a possible vigorous spontaneous reaction and to maximize the yield of adduct.
8. The apparatus should be shielded to avoid exposure to ultraviolet light. The immersion well, lamp, and the requisite transformer are available from Hanovia Lamp Division, Canrad-Hanovia Inc., 100 Chestnut Street, Newark, NJ 07105. The test tubes are positioned so as to be as close as possible to the lamp.
9. A "Little Giant" submersible pump (available from Little Giant Pump Co., Oklahoma City, OK) is used to circulate ice water through the immersion well.
10. The first crop (47.0 g) is followed by two other crops (5.2 and 2.1 g) obtained by concentrating and cooling the mother liquor.
11. The spectral properties are as follows: IR (KBr disk) cm^{-1}: 2960 (s), 1450 (m), 1380 (s), 1315 (vs), 1205 (s), 1140 (vs), 1090 (vs), 745 (s); ^1H NMR (300 MHz, $CDCl_3$) δ: 1.56–1.82 (m, 4 H, CH_2), 2.08–2.41 (m, 4 H, CH_2), 2.15 (s, 3 H, CH_3), 3.96 (dd, 1 H, $CHSO_2$), 4.58 (AB quartet, 2 H, J_{AB} = 11, CH_2Br); ^{13}C NMR ($CDCl_3$) δ: 22.66, 23.25, 24.27, 29.72, 43.69, 44.39, 65.81, 67.21.
12. Potassium *tert*-butoxide can be obtained from Aldrich Chemical Company, Inc.
13. The *tert*-butyl alcohol and tetrahydrofuran are distilled from calcium hydride prior to use.
14. Warming is required to dissolve the solid in this solvent.
15. The first four washings are done with gentle agitation to avoid emulsion formation.
16. The first cut of the distillate (ca. 1–2 mL) coming below 60°C was discarded.
17. The physical properties of the product are as follows: n_D^{20} 1.4722; IR (liquid film) cm^{-1}: 3090 (s), 2940 (s), 2870 (s), 1635 (s), 1440 (s), 895 (vs); ^{13}C NMR ($CDCl_3$) δ: 26.85, 35.37, 107.78, 149.68; GLC analysis (50 m OV-101 fused silica capillary column obtained from Perkin Elmer, Inc.) showed the product to be 90–93% pure. The material has an ^1H NMR spectrum corresponding to that reported in the literature:[4] (300 MHz, $CDCl_3$) δ: 1.62–1.66 (m, 4 H, CH_2), 2.24–2.27 (m, 4 H, CH_2), 4.64–4.65 (m, 2 H, vinyl CH), 4.92–4.93 (m, 2 H, vinyl CH).

3. Discussion

This procedure illustrates a recently published, simple, general method for the synthesis of conjugated dienes from olefins.[5] The scope of the reaction is shown in Table I.[5] In most of these examples hydrogen bromide elimination can be effected by stirring a solution of the olefin–bromomethanesulfonyl bromide adduct in methylene chloride with 1 equiv of triethylamine at room temperature. Only 2 equiv of the more costly potassium *tert*-butoxide are then needed in the second elimination step; the yields using the two-base procedure are generally superior to that obtained using only potassium *tert*-butoxide.

TABLE I
DIENE SYNTHESIS VIA THE VINYLOGOUS RAMBERG–BÄCKLUND REACTION

	Olefin	Product (Isomer Ratio[a])	Yield, %[b]
1	$C_4H_9CH{=}CH_2$	$C_3H_7CH{=}CHCH{=}CH_2$ (2:1)	38
2	$C_6H_{13}CH{=}CH_2$	$C_5H_{11}CH{=}CHCH{=}CH_2$ (2:1)[c]	61
3	(E)-$C_4H_9CH{=}CHC_4H_9$	(E)-$C_3H_7CH{=}CHC(C_4H_9){=}CH_2$	68[d]
		(E)-$C_4H_9CH{=}CHC(CH_3){=}CH_2$	52
4	(E)-$C_5H_{11}CH{=}CHCH_3$	(E)-$C_4H_9CH{=}CHC(CH_3){=}CH_2$ + $CH_2{=}CHC(C_5H_{11}){=}CH_2$	15
5			53
6			74
7			75
8			41[e]

9			31[e]
10			49[e]
11			43>[e]
12	$PhCH_2CH{=}CH_2$	$PhCH{=}CHCH{=}CH_2$ (1:8)	85
13	$PhOCH_2CH{=}CH_2$	$PhOCH{=}CHCH{=}CH_2$ (9:1)	54
14	$HO(CH_2)_9CH{=}CH_2$	$HO(CH_2)_8CH{=}CHCH{=}CH_2$ (5:1)	86
15	$(CH_3)_3SiCH_2CH{=}CH_2$	$(CH_3)_3SiCH{=}CHCH{=}CH_2$ (1:10)	41
16	$CH_2{=}CH(CH_2)_6CH{=}CH_2$	$CH_2{=}CH(CH_2)_5CH{=}CHCH{=}CH_2$	49[f,g,h]
17	$CH_2{=}CH(CH_2)_6CH{=}CH_2$	$CH_2{=}CHCH{=}CH(CH_2)_4CH{=}CHCH{=}CH_2$	40[i,j]
18	$(CH_3)_2Si(CH_2CH{=}CH_2)_2$	$(CH_3)_2Si(CH{=}CHCH{=}CH_2)_2$	38[i]

[a] (*Z*):(*E*) ratio.

[b] Overall yield of distilled product.

[c] (*Z*):(*E*) ratios 5:1 and 1:16 from (*E*)- and (*Z*)-1-octenylbromomethyl sulfones, respectively (59–61% overall distilled yields).[2]

[d] Analysis by GLC indicated < 1% (*Z*)-isomer.

[e] Et_3N step omitted.

[f] Isomers not resolved by GLC.

[g] Two equivalents of diene used.

[h]Includes [illegible]5% of 1,3,9,11-dodecatetraene.

[i]Two molar equivalents of 1 used.

[j][illegible]80% (*Z.Z*).

1,2-Dimethylenecyclohexane, a useful diene for Diels–Alder reactions,[6,7,8] has previously been synthesized in 11–77% yield in multistep procedures from *cis*-1,2-cyclohexanedicarboxylic anhydride[6] or acid,[7] from diethyl phthalate,[2] or from cyclohexanone.[4]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

$C_4H_9CH{=}CH_2$

$C_3H_7CH{=}CHCH{=}CH_2$

$C_6H_{13}CH{=}CH_2$

(E)-$C_4H_9CH{=}CHC_4H_9$

(E)-$C_3H_7CH{=}CHC(C_4H_9){=}CH_2$

(E)-$C_5H_{11}CH=CHCH_3$

(E)-$C_4H_9CH=CHC(CH_3)=CH_2$

$CH_2=CHC(C_5H_{11})=CH_2$

$PhCH_2CH=CH_2$

$PhCH=CHCH=CH_2$

$PhOCH_2CH=CH_2$

$PhOCH=CHCH=CH_2$

$HO(CH_2)_9CH=CH_2$

$HO(CH_2)_8CH=CHCH=CH_2$

$(CH_3)_3SiCH_2CH=CH_2$

$(CH_3)_3SiCH=CHCH=CH_2$

$CH_2=CH(CH_2)_6CH=CH_2$

$CH_2=CH(CH_2)_5CH=CHCH=CH_2$

$CH_2=CHCH=CH(CH_2)_4CH=CHCH=CH_2$

$(CH_3)_2Si(CH_2CH=CH_2)_2$

$(CH_3)_2Si(CH=CHCH=CH_2)_2$

ethanol (64-17-5)

potassium carbonate (584-08-7)

Cyclohexanone (108-94-1)

hydrogen bromide (10035-10-6)

bromine (7726-95-6)

sodium bisulfite (7631-90-5)

Pentane (109-66-0)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

diethyl phthalate (84-66-2)

1-methylcyclohexene

triethylamine (121-44-8)

tert-butyl alcohol (75-65-0)

calcium hydride (7789-78-8)

tert-BUTYL (1605-73-8)

Bromomethanesulfonyl bromide (54730-18-6)

1,2-Dimethylenecyclohexane, Cyclohexane, 1,2-bis(methylene)- (2819-48-9)

1-Bromo-1-methyl-2-(bromomethylsulfonyl)cyclohexane (120696-44-8)

1,3,9,11-dodecatetraene

potassium tert-butoxide (865-47-4)

sym-Trithiane (291-21-4)

cis-1,2-cyclohexanedicarboxylic anhydride

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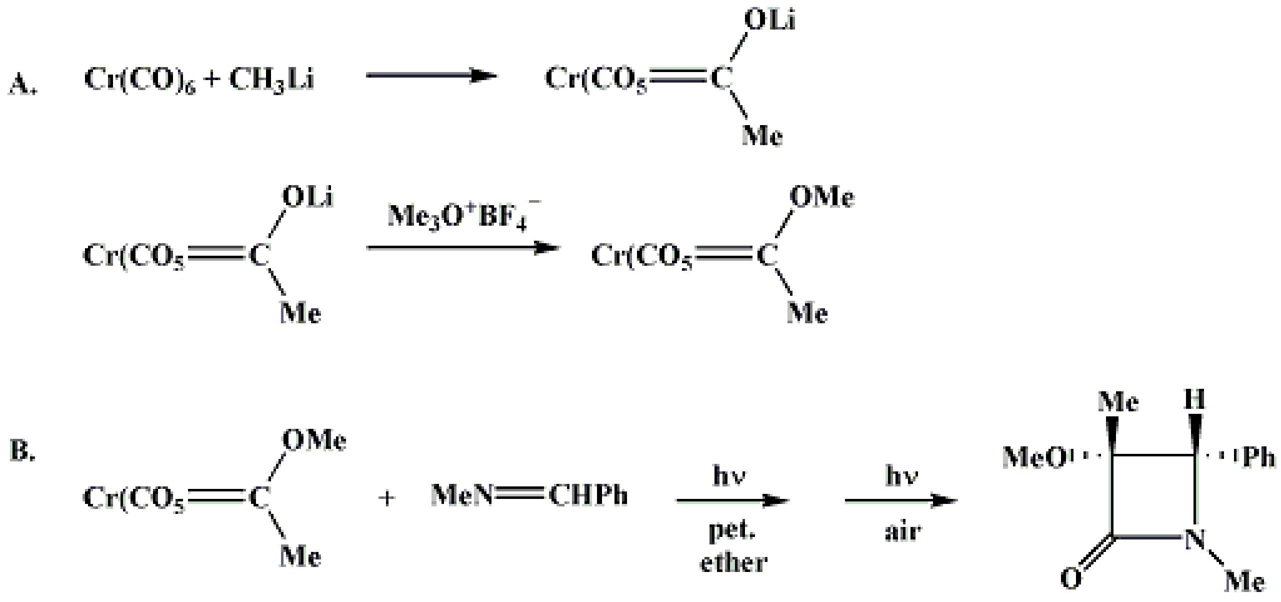
1,3-DIMETHYL-3-METHOXY-4-PHENYLAZETIDINONE

[2-Azetidinone, 3-methoxy-1,3-dimethyl-4-phenyl-]



Submitted by Lous S. Hegedus, Michael A. McGuire, and Lisa M. Schultze[1].
Checked by Ming Chang P. Yeh and Martin F. Semmelhack.

1. Procedure

A. [*(Methyl)(methoxy)carbene*]*pentacarbonyl chromium(0)*.[2] A 1-L, two-necked, round-bottomed flask equipped with magnetic stirring bar, 100-mL addition funnel, reflux condenser, and gas inlet is charged with 17.8 g (0.085 mol) of chromium hexacarbonyl (Note 1). The apparatus is evacuated (oil pump) and filled with argon (four cycles), and a positive pressure is maintained with an argon-filled balloon on a T-tube. Dry diethyl ether (500 mL) is transferred via cannula into the flask and stirring is commenced. The addition funnel is charged with 60 mL (1.42 *M* in ether, 0.085 mol) of methyllithium via cannula and rapid dropwise addition is begun. The methyllithium is added over a 15-min period, during which time the solution turns from bright yellow to dark brown. The solution is heated at reflux for approximately 1.5 hr. After the solution is cooled, the solvent is removed by rotary evaporation. The dark-brown residual solid is taken up in 80 mL of water (in air), and 13.0 g (0.088 mol) of trimethyloxonium tetrafluoroborate (Note 2) is added over a 30-min period with stirring (Note 3). The mixture is extracted several times with 200-mL portions of cold pentane (Note 4). The combined pentane layers are dried over anhydrous magnesium sulfate and filtered through a bed of Celite. The solution is concentrated by rotary evaporation to approximately 60 mL and is cooled to –20°C under argon. After 1 hr the resulting bright-yellow crystals (17.6 g, 83%) are collected and dried at 25°C under reduced pressure for 10 min (Note 5).

B. *1,3-Dimethyl-3-methoxy-4-phenylazetidinone.* A 250-mL Pyrex Erlenmeyer flask is charged with 1.25 g (5.0 mmol) of [(methyl)(methoxy)carbene]pentacarbonyl chromium(0)]. The flask is fitted with a rubber septum, evacuated, and filled with argon (four cycles). Dry

petroleum ether (175 mL) is transferred via cannula into the flask to produce a dark-yellow solution. The solution is charged with 0.59 g (5.0 mmol) of *N*-methylbenzylidenimine (Note 6). The flask is irradiated with six 20-W Vitalites (Note 7). The solution turns brown and heterogeneous within an hour. After 3 days (Note 8) the solution is filtered through a bed of Celite, the precipitate is washed with dry petroleum ether, and the now lighter-yellow solution is sealed in a flask, degassed, and irradiated as before. After 5 days of further irradiation, the mixture is filtered and the filtrate is exposed to air and irradiated again until a colorless solution is obtained (ca. 1 day). Filtration through a bed of Celite and removal of solvent by rotary evaporation affords colorless crystals of essentially pure β-lactam **2**. Recrystallization from hexane gives 0.67–0.76 g (65–74% yield), mp 76–77°C (Note 9).

2. Notes

1. Chromium hexacarbonyl was obtained by the checkers from Pressure Chemical Company, Pittsburgh, PA. and used without purification. It can be weighed in air as it is relatively nonvolatile and air-stable. The usual precautions appropriate for a potentially toxic metal carbonyl should be employed, but the low volatility makes handling relatively easy.
2. The checkers obtained trimethyloxonium tetrafluoroborate from Alfa Products, Morton/Thiokol, Inc.
3. Meerwein's reagent was added until the pH of the solution was slightly acidic.
4. The carbene complex is slightly air-sensitive in solution. The pentane was cooled to 0°C and nitrogen was bubbled through the solvent before use.
5. Longer drying resulted in loss of carbene complex by sublimation. The carbene complex was stored under argon at −20°C. The pure product shows ^{1}H NMR ($CDCl_3$) δ: 4.60 (s, 3 H, OCH_3) and 2.90 (s, 3 H, CH_3).
6. The checkers obtained *N*-methylbenzylidenimine from Aldrich Chemical Company, Inc. and used it without purification. It was added as a neat liquid, via syringe.
7. Vitalites were obtained by the checkers from a local hardware store. They were arranged horizontally, in banks of two in a way to provide maximum illumination of the flask. Aluminum foil was used generously around the outside of the lights in order to minimize light loss.
8. Precipitate forms and reduces light intensity in the solution. The complete conversion of reactants can be accelerated by more frequent filtration and by using sunlight in place of the Vitalites. The submitters were successful using the Vitalites with five filtrations over a 72-hr period. The checkers found that the reaction was incomplete under these conditions and the β-lactam must be purified by chromatography (silica gel column, elution with 1 : 1 ethyl acetate : hexane) in order to remove residual benzaldehyde and other minor impurities.
9. The product has the following spectral properties: ^{1}H NMR ($CDCl_3$) δ: 1.60 (s, 3 H, CH_3); 2.80 (s, 3 H, NCH_3); 3.03 (s, 3 H, OCH_3); 4.35 (s, 1 H, CH); 7.28 (s, 5 H, ArH); IR ($CHCl_3$) cm^{-1}: 1750.

3. Discussion

The procedure described is an efficient conversion of imines to β-lactams.[3] It is very general, and imines such as thiazolines, benzothiazines, dihydroisoquinoline, and quinoline itself, as well as simple aldehyde and ketone imines, are converted to β-lactams in fair to good yield.

The reaction is stereospecific, producing only one diastereoisomer of the β-lactam. The chromium carbene complex is easy to prepare on a large scale, to store, and to handle, since it is air-stable as a solid. The β-lactam forming reaction proceeds under very mild conditions and requires only the most simple glassware and either sunlight or commercially available fluorescent tubes that duplicate the spectrum of sunlight (e.g., Vitalite). Product isolation consists of simple filtration and solvent removal. The procedure produces β-lactams containing heteroatom substituents at the 3-position. It is complementary or superior to existing methods for the conversion of imines to β-lactams involving ketenes,[4 5 6] acid chlorides and base,[7 8 9 10 11] or ketene silyl acetals.[12 13]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 1

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

[(Methyl)(methoxy)carbene]pentacarbonyl chromium(0)

[(methyl)(methoxy)carbene]pentacarbonyl chromium(0)]

thiazolines

benzothiazines

ethyl acetate (141-78-6)

ether, diethyl ether (60-29-7)

nitrogen (7727-37-9)

benzaldehyde (100-52-7)

Quinoline (91-22-5)

Pentane (109-66-0)

magnesium sulfate (7487-88-9)

hexane (110-54-3)

Methyllithium (917-54-4)

N-methylbenzylidenimine (622-29-7)

argon (7440-37-1)

Trimethyloxonium tetrafluoroborate (420-37-1)

dihydroisoquinoline

1,3-Dimethyl-3-methoxy-4-phenylazetidinone, 2-Azetidinone, 3-methoxy-1,3-dimethyl-4-phenyl- (82918-98-7)

chromium hexacarbonyl (13007-92-6)

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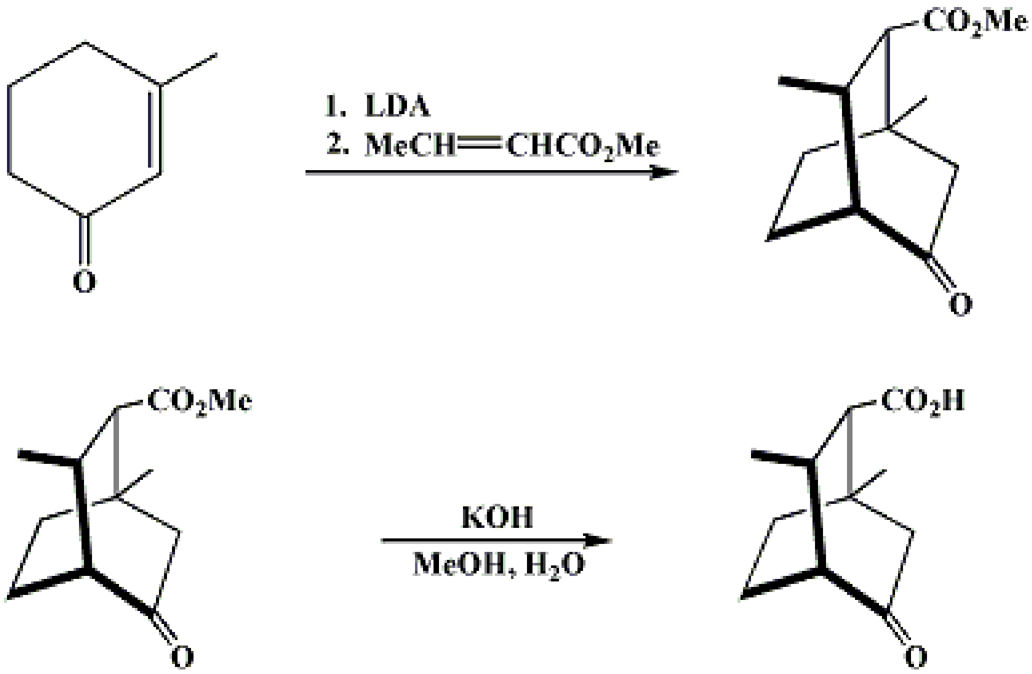
Organic Syntheses, CV 8, 219

APROTIC DOUBLE MICHAEL ADDITION: 1,3-DIMETHYL-5-OXOBICYCLO[2.2.2]OCTANE-2-CARBOXYLIC ACID

[Bicyclo[2.2.2]octane-2-carboxylic acid, 1,3-dimethyl-5-oxo-]



Submitted by Dietrich Spitzner and Anita Engler[1].
Checked by Michael P. Trova, Mary A. Kinsella, and Leo A. Paquette.

1. Procedure

A. *Methyl 1,3-dimethyl-5-oxobicyclo[2.2.2]octane-2-carboxylate.*[2] An oven-dried, 250-mL, round-bottomed flask equipped with a stirring bar and a rubber septum is charged with 100 mL of dry tetrahydrofuran and 5.56 g (55 mmol) of anhydrous diisopropylamine. The flask is flushed with argon via a needle inlet–outlet and cooled to −78°C with a dry ice–isopropyl alcohol bath (Note 1),(Note 2),(Note 3). To the stirred solution is added dropwise with a syringe 30 mL (54 mmol) of a 1.8 *M* solution of butyllithium in hexane (Note 4) to form lithium diisopropylamide, followed after 30 min by a solution of 5.50 g (50 mmol) of 3-methyl-2-cyclohexen-1-one (Note 5) in 60 mL of dry tetrahydrofuran via a flex-needle over a 15-min period. Stirring and cooling is continued for an additional 30 min. To the resulting yellow solution of the lithium dienolate, 10.0 g (0.1 mol) of methyl (*E*)-crotonate (Note 6) is added with a syringe within 2 min. The cooling bath is removed and the reaction mixture is allowed to warm to room temperature (Note 7). Stirring is continued at room temperature for 2 hr. The reaction mixture is quenched by adding 1 *N* hydrochloric acid until the mixture

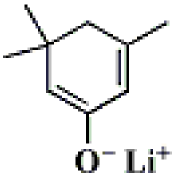
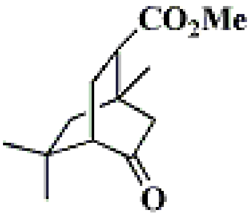
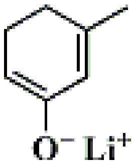
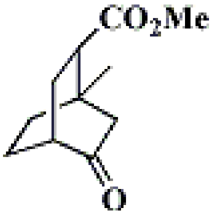
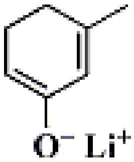
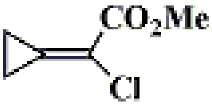
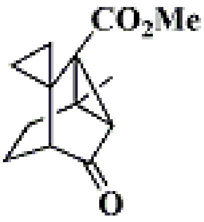
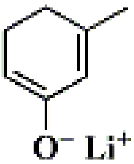
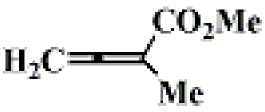
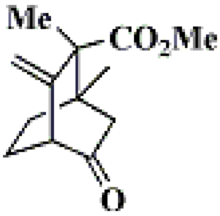
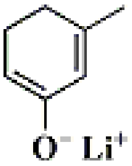
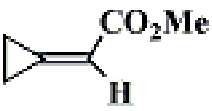
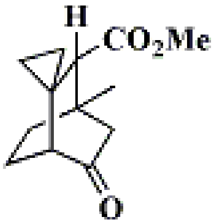
turns acidic. Extraction with three 80-mL portions of dichloromethane followed by evaporation of the solvent yields a light-yellow oil that is taken up in 100 mL of diethyl ether. This solution is filtered through 100 g of silica gel to remove polymers and water. Elution with diethyl ether and evaporation of the solvent gives a yellow oil that is distilled in a Kugelrohr distillation apparatus (Note 8) under reduced pressure. After a small forerun (ca. 0.5 g of unreacted 3-methyl-2-cyclohexen-1-one) at 50°C, 0.05 mm, the main fraction is collected at 110–120°C (oven temperature), 0.05 mm to give 8.25–9.43 g (78–90%) of a colorless oil, which solidifies on standing in the freezer. One recrystallization from cold pentane (approximately 10 mL of pentane per 8 g of ester mixture) gives 6.0 g of product as white crystals, mp 37°C (Note 9), of approximately 97% isomeric purity (Note 10).

B. *1,3-Dimethyl-5-oxobicyclo[2.2.2]octane-2-carboxylic acid*. A mixture of 11.2 g (53.4 mmol) of the foregoing crude ester in 40 mL of methanol and 8.0 g (143 mmol) of potassium hydroxide in 16 mL of water is refluxed under argon until the ester is no longer present when monitored by TLC (Note 7). This takes about 1 day. Methanol is removed with a rotary evaporator, and the remaining dark solution is extracted with ether (2 × 50 mL), acidified to pH 1 with dilute sulfuric acid, and extracted with dichloromethane (4 × 50 mL). The organic layer is filtered through 100 g of silica gel and eluted with ether to remove most of the dark impurities. Concentration under reduced pressure gives 10.0 g of acid mixture. Distillation in a Kugelrohr apparatus at 180°C, 0.03 mm and one recrystallization from ether-pentane gives 7.0 g (67%) of pure bicyclic acid (isomeric purity >98%) as white crystals, mp 130–131°C (Note 11).

2. Notes

1. All glassware, syringes, and flex needles were baked in an oven at 120°C overnight and assembled while hot.
2. Tetrahydrofuran was purified by passing it through activated (12 hr at 450°C) neutral aluminum oxide purchased from ICN and distilling it fresh from lithium aluminum hydride.
3. Diisopropylamine was distilled from calcium hydride prior to use.
4. Butyllithium in hexane was purchased from Metallgesellschaft AG, Frankfurt, Germany and standardized by titration with diphenylacetic acid.[3]
5. 3-Methyl-2-cyclohexen-1-one was purchased from Aldrich-Europe, but is easily prepared from ethyl acetoacetate and paraformaldehyde.[4]
6. Methyl crotonate may polymerize to some extent under these conditions. An excess is used in order to insure complete formation of the product. Unreacted methyl crotonate is easily removed by distillation.
7. The reaction was monitored by TLC (silica gel 60PF254, Merck, Darmstadt, Germany; 1 : 1 diethyl ether : pentane as the mobile phase, 2,4-dinitrophenyl-hydrazine as revealing reagent) and by GLC (N_2, 3% SE30 rubber on Volaspher A2, Merck, Darmstadt, Germany, 140°C isotherm). The Michael reaction is very slow at −78°C, and the optimum temperature depends on the acceptor (Table I).

TABLE I
EXAMPLES OF CARBOCYCLIC ESTERS PREPARED BY THE APROTIC DOUBLE MICHAEL ADDITION

Dienolate	Acceptor	Product	Yield (%)	Ref.
			98	6
			90	7
			64	10
			75	11
			61	5

8. A Büchi rotary evaporator was used.

9. The spectra are as follows: IR (neat) cm^{-1}: 1730 (ester, ketone); EI-GCMS (70 eV): *m/e* = 210 (M^+, 5%), 110 (100), 95 (30); ^{1}H NMR (250 MHz, $CDCl_3$,

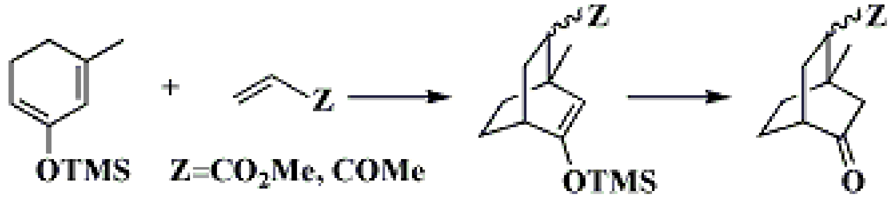
TMS) δ: 0.94 (s, Me, 3 H), 1.10 (d, 3 H, *J* = 7), 1.30–2.35 (m, 8 H), 2.75 (dd, 1 H, *J* = 3 and 19), 3.67 (s, OMe).

10. The oily product contains approximately 8% of the *exo* isomer (estimated by ^{1}H NMR on the basis of the ester methyl at 3.70 ppm (major) and at 3.67 ppm (minor)).

11. An additional 1.2 g (9.5%) of pure acid may be recovered from the mother liquor. The spectra are as follows: ^{13}C NMR (62.88 MHz, $CDCl_3$) δ: 17.3 (t), 17.4 (q), 23.7 (q), 31.8 (d), 33.9 (t), 35.7 (s), 44.9 (t), 47.9 (d), 50.9 (q), 54.5 (d), 174.8 (s), 214.1 (s); >^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.05 (s, 3 H), 1.15 (d, 3 H, *J* = 6.8), 1.35–2.15 (m, 8 H), 2.32 (m, 1 H), 2.81 (dd, 1 H, *J* = 19, 3), 11.2 (broad s, 1 H); EI–MS (70eV): *m/z* = 196 (M^+, 40%), 178 (5), 110 (100), 95 (45); IR (CH_2Cl_2) cm^{-1}: 3480 (m), 2920 (s), 1725 (s), 1705 (s).

3. Discussion

The aprotic double Michael addition was discovered by R. A. Lee[6] and used[7,8,9,10,11] to synthesize functionalized bicyclo[2.2.2]octanes, which may serve as starting materials in natural products syntheses (Table I). These bicyclo[2.2.2]octanes can also be obtained by a Diels–Alder cycloaddition of 2-trimethylsiloxy-substituted cyclohexadienes and dienophiles:[12]



But there are many cases known where the (4 + 2) cycloaddition fails even with siloxy-activated dienes; for example, methyl (*E*)-crotonate does not react with diene **1** at normal pressure and elevated temperature (110°C), whereas the aprotic double Michael addition does give the desired bicyclo[2.2.2]octane in high yield. This reaction[13] gives mainly (92%) bicyclic esters with the *endo* configuration.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

potassium hydroxide (1310-58-3)

Diphenylacetic acid (117-34-0)

Ethyl acetoacetate (141-97-9)

Pentane (109-66-0)

dichloromethane (75-09-2)

2,4-dinitrophenyl-hydrazine (119-26-6)

aluminum oxide (1344-28-1)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

hexane (110-54-3)

calcium hydride (7789-78-8)

methyl crotonate, methyl (E)-crotonate (623-43-8)

argon (7440-37-1)

3-methyl-2-cyclohexen-1-one

lithium diisopropylamide (4111-54-0)

diisopropylamine (108-18-9)

1,3-Dimethyl-5-oxobicyclo[2.2.2]octane-2-carboxylic acid, Bicyclo[2.2.2]octane-2-carboxylic acid, 1,3-dimethyl-5-oxo- (121829-82-1)

bicyclo[2.2.2]octane (280-33-1)

Methyl 1,3-dimethyl-5-oxobicyclo[2.2.2]octane-2-carboxylate (121917-73-5)

paraformaldehyde (30525-89-4)

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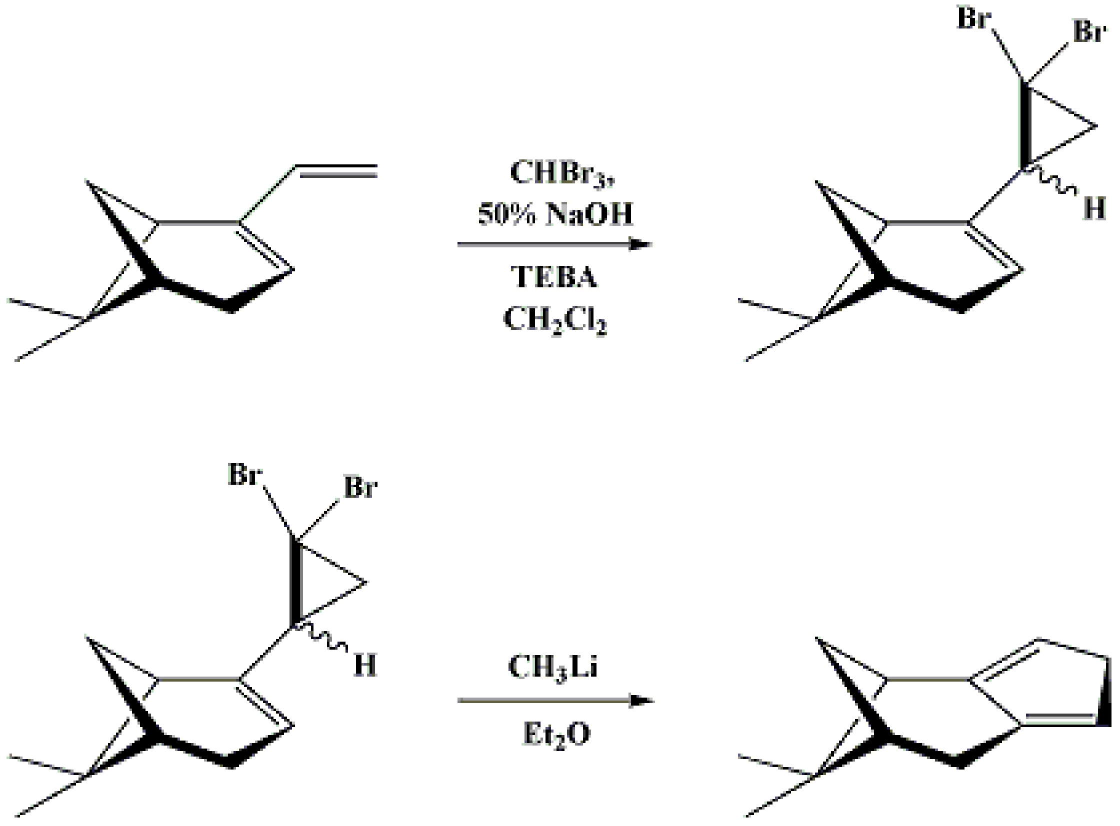
CYCLOPENTADIENE ANNULATION VIA THE SKATTEBØL REARRANGEMENT: (1*R*)-9,9-DIMETHYLTRICYCLO-[6.1.1.0^{2,6}]DECA-2,5-DIENE



Submitted by Leo A. Paquette and Mark L. McLaughlin[1].
Checked by Nanine van Draanen and Clayton H. Heathcock.

1. Procedure

A. *Dibromocarbene addition to (1R)-nopadiene.* A 250-mL, three-necked flask is equipped with a mechanical stirrer, a nitrogen inlet, and a serum cap. The flask is charged with 26.2 mL (0.30 mol) of bromoform (Note 1), 29.6 g (0.20 mol) of (1*R*)-nopadiene (Note 2), 1.0 g (4.4 mmol) of benzyltriethylammonium chloride (TEBA), 0.8 mL of ethanol, and 20 mL of dichloromethane (Note 3). The suspension is stirred and cooled in an ice bath while 100 mL of 50% sodium hydroxide solution is added over 10 min from a dropping funnel. The reaction mixture is stirred at room temperature for 24 hr and poured into 250 mL of water. The lower layer is separated and the aqueous phase is extracted with three 25-mL portions of dichloromethane. The combined organic layers are washed with three 100-mL portions of water, dried over magnesium sulfate, and concentrated under reduced pressure to give a brown-black oil. The oil is dissolved in an equal volume of hexane and filtered through a 2-in. bed of silica with hexane (1.5 L) as eluant. The solvent is evaporated and the orange oil is

distilled in an apparatus protected from light (Note 4) at 85–95°C and 0.08 mm. The yellow distillate is redistilled through a 4-in. Vigreux column to give 32.0–33.6 g (50–53%) of the diastereomeric dibromocyclopropanes (Note 5).

B. *(1R)-9,9-Dimethyltricyclo[6.1.1.0^{2,6}]deca-2,5-diene.* A flame-dried, 3-L flask is equipped with a large magnetic stirring bar and a serum cap and charged with 17.6 g (55.0 mmol) of the dibromide. A total of 2 L of anhydrous ether (Note 6) is transferred into the flask via cannula. The stirred solution is cooled in an ice bath and 147 mL of 1.5 *M* methyllithium in ether (220 mmol) is introduced via a second cannula (Note 7). The ice bath is removed and stirring is maintained for 10 hr before the solution is transferred by cannula into 1 L of ice-cold water. The ether layer is separated and the aqueous phase is extracted with two 200-mL portions of ether. The combined ethereal solutions are dried and concentrated (Note 8). The residual yellow oil is immediately diluted with an equal volume of hexane and passed through a short column of neutral alumina (Note 9). The solvent is carefully removed and the yellow oil is subjected to bulb-to-bulb distillation at 90°C and 5 mm (Note 10). The yield of colorless hydrocarbon is 6.9–7.1 g (78–80%) (Note 11) and (Note 12).

2. Notes

1. The submitters used a purified grade of bromoform purchased from the Fisher Chemical Company.
2. The (1*R*)-nopadiene is prepared from commercially available (Aldrich Chemical Company, Inc.) (1*R*)-(−)-nopol according to the following procedure.[2] A 1000-mL, three-necked flask is equipped with a mechanical stirrer, internal thermometer and nitrogen inlet. The flask is charged with 125 g (0.752 mol) of (1*R*)-(−)-nopol and 500 mL of pyridine. Stirring is begun and the solution is cooled to −10°C in an ice–salt bath under nitrogen. *p*-Toluenesulfonyl chloride (175 g, 0.918 mol) is added in one portion under an inert atmosphere via Gooch tubing (the checkers used a powder funnel for the addition). The temperature rises to 40°C for 15–20 min, but returns to 5°C, where it is maintained for 2 hr. Twenty 1-mL portions of water are next introduced at such a rate that the temperature does not exceed 5°C. The reaction mixture is poured into 1 L of ether and extracted with ice-cold 5 *M* sulfuric acid until the aqueous layer remains acidic, then with saturated $CuSO_4$ solution until the aqueous layer remains blue. The ethereal phase is washed with two 200-mL portions each of water and 5% sodium bicarbonate solution prior to drying over magnesium sulfate and solvent evaporation. A solid residue is obtained. If this material is dark, it may be dissolved in hexane and filtered through a pad of Celite to remove the black impurity. The tosylate is recrystallized by dissolving it in 500 mL of hot hexane and cooling to −78°C. Six such recrystallizations give material with mp 51.0–51.8°C and $[\alpha]_D^{25}$ −25.6° (C_2H_5OH, c 0.03). The yield is 62–72%. A 2000-mL, three-necked flask is equipped with a mechanical stirrer, an internal thermometer, and a nitrogen inlet. The flask is charged with 200 g (0.624 mol) of (1*R*)-nopyl tosylate and 1000 mL of dimethyl sulfoxide

that has been freshly distilled from calcium hydride at 40 mm. The stirring solution is cooled briefly in a cold-water bath and 69.0 g (0.615 mol) of freshly sublimed potassium *tert*-butoxide is added rapidly while nitrogen is flowing above the solution (the checkers used potassium *tert*-butoxide from a freshly opened bottle). (The base must be the limiting reagent to offset isomerization of the product diene.) The temperature rises to approximately 45°C, and a brown color develops. As the reaction proceeds, the color dissipates to a light yellow. After the initial exotherm subsides, the mixture is heated at 75°C for 10 hr, cooled to room temperature, and diluted with 800 mL of hexane. The lower layer, mostly dimethyl sulfoxide, is diluted with 1 L of water and extracted with two 100-mL portions of hexane. The combined hexane layers are washed with water (5 × 200 mL), dried over magnesium sulfate, and rotary-evaporated at 40 mm and 25°C to leave a yellow oil. Distillation through a 5-in. Vigreux column gives 69.4–74.0 g (75–80%) of (1*R*)-nopadiene as a clear, colorless oil, bp 78–79°C/25 mm.

3. These phase-transfer conditions are adapted from experimental procedures described earlier.[3,4]

4. The dibromocyclopropane is light-sensitive when hot. Exposure to light during distillation produces colored impurities that cause autocatalytic decomposition of the product when subsequently stored in the cold.

5. Both distillations must be performed with a pot temperature below 150°C in order to avoid thermal decomposition; ^{1}H NMR indicates the product to be a 4 : 1 mixture of diastereomers. All available evidence denotes that both are transformed efficiently into the cyclopentadiene.

6. The ether was freshly distilled from sodium benzophenone ketyl. The checkers used anhydrous ether from a freshly opened can.

7. The methyllithium was purchased from the Aldrich Chemical Company, Inc. and contains lithium bromide.

8. Solvent evaporation was accomplished at 40 mm and 25°C in order to counter product volatility.

9. The checkers used a 1 × 1-in. plug of alumina. The experience of the submitters has been that the use of silica gel at this point causes some decomposition.

10. The checkers found foaming to be a serious problem in this distillation. The problem is ameliorated by use of a ≥50-mL distillation flask.

11. Purified diene polymerizes within 24 hr if stored neat. Its lifetime can be indefinitely prolonged by storage as a 10% by weight solution in hexane under an argon atmosphere.

12. The product exhibits $[\alpha]_D^{24}$ −21.9° (C_2H_5OH, c 1.8) and the following ^{1}H NMR spectrum at 300 MHz in $CDCl_3$ solution δ: 0.72 (s, 3 H), 1.24 (m, 1 H), 1.33 (s, 3 H), 1.60 (s, 1 H), 2.11 (m, 1 H), 2.60 (m, 1 H), 2.70 (m, 2 H), 2.99 (s, 2 H), 5.77 (s, 1 H), 5.99 (s, 1 H).

3. Discussion

Experience has shown[5,6] that cyclopentadiene annulation of 2,3-dimethylenebicyclo [2.2.2]octanes can be efficiently realized by means of the Skattebøl procedure.[7] However, the added strain in 2,3-dimethylenenorbornanes reroutes the rearrangement instead into vinylallene formation.[4] This phenomenon has been attributed to an inability on the part of the torsionally constrained empty carbene *p* orbital to interact with the flanking double bond.[8] This structural inhibition is entirely alleviated by positioning the cyclopropyl carbene completely external to the norbornene ring as in the present example. The heightened conformational maneuverability of the carbenoid center is conducive to exclusive cyclopentadiene ring formation.

(1*R*)-9,9-Dimethyltricyclo[6.1.1.0^{2,6}]deca-2,5-diene is a chiral, optically active homolog of isodicyclopentadiene, a molecule that has been extensively studied with regard to π-facial selectivity in cycloaddition reactions.[9] The response of the title compound to similar dienophiles has been described[10] and its complexation to various transition metals reported.[10,11] The steric contributions of the *gem*-dimethyl substituents relegate bonding to the opposite surface of the cyclopentadiene ring.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium benzophenone ketyl

Dibromocarbene addition to (1R)-nopadiene

(1R)-(−)-nopol

$CuSO_4$

(1R)-Nopadiene

2,3-dimethylenenorbornanes

ethanol (64-17-5)

sulfuric acid (7664-93-9)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

nitrogen (7727-37-9)

pyridine (110-86-1)

bromoform (75-25-2)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

hexane (110-54-3)

Methyllithium (917-54-4)

dimethyl sulfoxide (67-68-5)

CYCLOPENTADIENE (542-92-7)

calcium hydride (7789-78-8)

argon (7440-37-1)

Dibromocyclopropane

p-Toluenesulfonyl chloride (98-59-9)

benzyltriethylammonium chloride (56-37-1)

lithium bromide (7550-35-8)

cyclopropyl carbene (19527-12-9)

vinylallene (10563-01-6)

potassium tert-butoxide (865-47-4)

(1R)-9,9-DIMETHYLTRICYCLO-[6.1.1.$0^{2,6}$]DECA-2,5-DIENE (108404-79-1)

(1R)-nopyl tosylate (81600-63-7)

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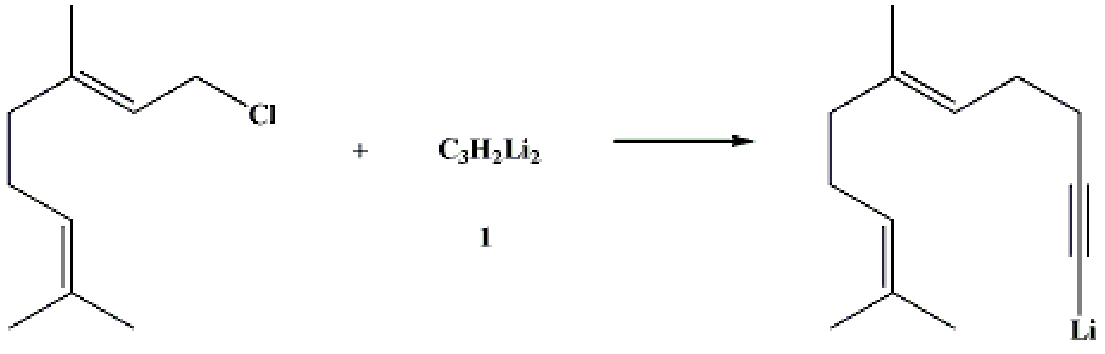
Organic Syntheses, CV 8, 226

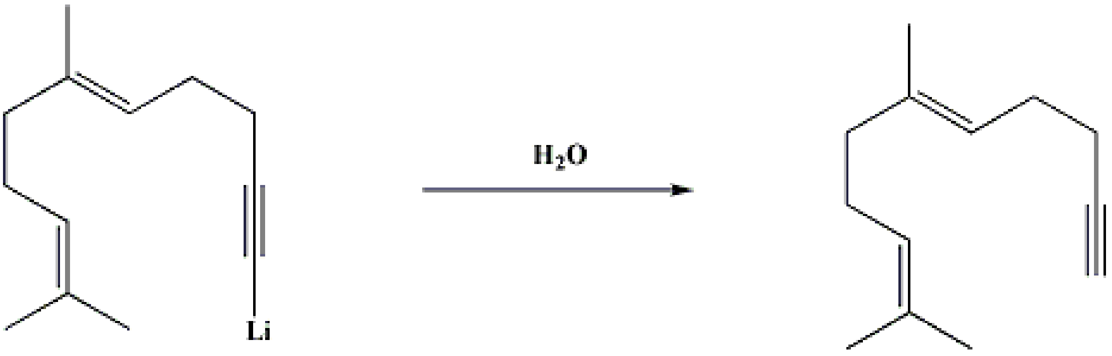
PROPARGYLATION OF ALKYL HALIDES: (*E*)-6,10-DIMETHYL-5,9-UNDECADIEN-1-YNE AND (*E*)-7,11-DIMETHYL-6,10-DODECADIEN-2-YN-1-OL

[5,9-Undecadien-1-yne, 6,10-dimethyl-, (*E*)- and 6,10-Dodecadien-2-yn-1-ol, 7,11-dimethyl-, (*E*)-]

A.

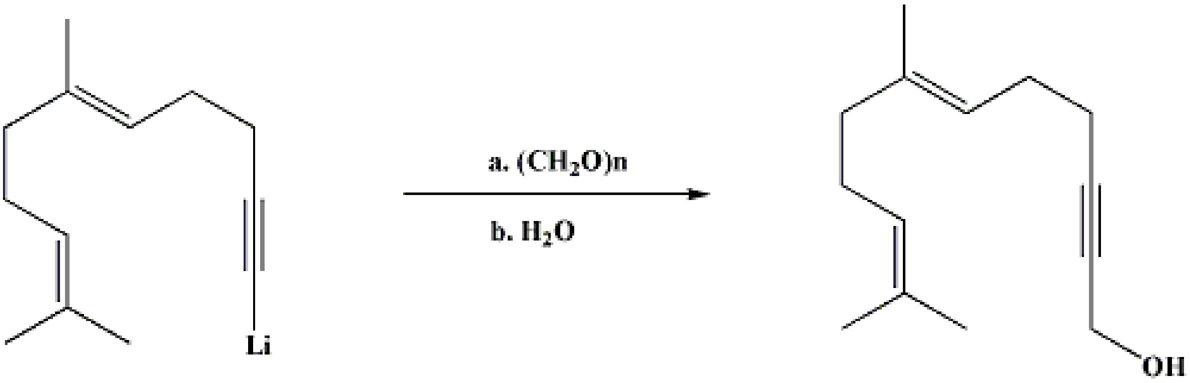


2



2

B.



2

Submitted by John Hooz[1], Jorge Cabezas[2], Sergio Musmanni[2], and Jose Calzada[2].
Checked by Hanno Wild, Andreas Weier, and Larry E. Overman.

1. Procedure

Caution! Allene and ethyl ether are highly volatile and flammable. Paraformaldehyde is a noxious material. The entire operation should be conducted in an efficient fume hood.

A. *(E)-6,10-Dimethyl-5,9-undecadien-1-yne.* An oven-dried (Note 1), 1-L, three-necked, round-bottomed flask is equipped with a large magnetic stirring bar (Note 2), a 250-mL pressure-equalizing addition funnel capped by a rubber septum (Note 3), a dry-ice condenser capped by a rubber septum, and a rubber septum (capping the central neck) bearing a stainless-steel cannula that serves as an argon inlet. The flask is charged with 190 mL of anhydrous ethyl ether (Note 4) and cooled to ca. −78°C using a dry ice–acetone bath. On a separate assembly (Note 5), allene gas (*d* at −40°C = 0.67 g/mL) from a compressed-gas cylinder (Note 6) is condensed into a dry, 100-mL Pyrex graduated cylinder equipped with a 24/40 standard taper joint attached to a Claisen adapter and dry-ice condenser (containing a slurry of dry ice–acetone) and cooled to −78°C with a bath of dry ice–acetone (Note 7). After 22.5 mL (375 mmol) of liquid allene has been collected, the adapter and the condenser are removed and the graduated cylinder is capped with a rubber septum through which is inserted a cannula. The other end of this cannula is inserted through the rubber septum on the central neck to reach just below the surface of the cooled solvent. The allene is then transferred to the reaction vessel by removing the cylinder from the cooling bath. The temperature of the reaction vessel is maintained at −78°C, and a solution of 190 mL of 1.37 *M* butyllithium (260 mmol) in hexane (Note 8) is added dropwise over 1 hr through the addition funnel, which is then rinsed with 5 mL of dry ether. The reaction mixture is allowed to warm gradually (over ca. 30 min) to −15°C and the white precipitate that forms is stirred an additional 15 min under an argon atmosphere. A solution of 12.9 g (75 mmol) of geranyl chloride (Note 9) in 40 mL of dry ether is added dropwise over 303 min through the addition funnel while maintaining the temperature at −15°C. Then the stirred mixture is allowed to warm to room temperature over 1 hr (Note 10). The resulting white suspension containing the lithium acetylide **2** is carefully poured into 450 mL of ice-water slurry, the aqueous layer is saturated with sodium chloride, and the product is extracted with four 100-mL portions of ether. The combined extracts are dried over anhydrous magnesium sulfate, the drying agent is removed by filtration, and the solvent is distilled at atmospheric pressure using a 25-cm Vigreux column. The residue is distilled through a short-path distillation apparatus to afford 10.5–11.2 g (79–89% yield) of (E)-6,10-dimethyl-5,9-undecadien-1-yne, bp 103–107°C (10 mm) (Note 11).

B. *(E)-7,11-Dimethyl-6,10-dodecadien-2-yn-1-ol.* To the suspension containing the acetylide intermediate **2**, as prepared in Part A, is added 14 g (460 mmol) of paraformaldehyde (Note 12) in portions (Note 13) over 10 min (Note 14). After stirring the mixture for 24 hr, the resulting suspension is poured into 450 mL of ice-cold water (Note 15), the aqueous layer is saturated with sodium chloride, and the product is extracted with four 100-mL portions of ether. The combined organic extracts are dried over magnesium sulfate, the drying agent is removed by filtration, and the solvent is removed at room temperature on a rotary evaporator. The residue is distilled through a short-path distillation apparatus to provide a forerun of 2-butyn-1-ol (bp 42–46°C, 6 mm), followed by 10.5 g (68% yield) of (*E*)-7,11-dimethyl-6,10-dodecadien-2-yn-1-ol as a colorless liquid, bp 120–124°C (0.5 mm) (Note 16).

2. Notes

1. All glassware is dried in an oven at 125°C and assembled while warm.
2. Although the reaction mixture will become heterogeneous, mechanical stirring is unnecessary on this scale.
3. A stainless-steel cannula inserted through this septum is connected by means of tygon tubing to a mercury bubbler.

4. Ethyl ether is freshly distilled from the sodium ketyl of benzophenone.
5. This is an adaptation of the method used to condense methyl chloride, illustrated in figure.htm 1 of an *Organic Syntheses* procedure (Lusch, M. J.; Phillips, W. V.; Sieloff, R. F.; Normura, G. S.; House, H. O. *Org. Synth., Coll. Vol. VII* **1990**, 347).
6. The submitters used allene purchased from Matheson Gas Products, Inc. The checkers found that an old lecture bottle of allene from this source gave unsatisfactory results, affording a crude product that contained up to 20% of unchanged geranyl chloride. Other lecture bottles of allene from Matheson or Pfaltz and Bauer were satisfactory.
7. All temperatures recorded are external bath temperatures.
8. A solution of butyllithium in hexane was purchased from Foote Mineral Company. Before use the concentration is determined by titration according to the procedure of Watson and Eastham.[3]
9. Geranyl chloride was prepared by treating geraniol, available from Aldrich Chemical Company, Inc., with carbon tetrachloride and triphenylphosphine according to an *Organic Syntheses* procedure.[4]
10. If dienyne product containing less than 1% of geranyl chloride is required, the checkers suggest the following treatment at this point to destroy any remaining geranyl chloride. The addition funnel is removed and a gentle stream of argon is bubbled through the stirred reaction mixture for 15 min to remove excess allene. Additional butyllithium (40 mmol in hexane) is added and the resulting mixture is stirred for 3 hr at room temperature prior to hydrolytic workup. If this modification is employed, the subsequent hydrolysis step should be done slowly. The Erlenmeyer flask (1 L) containing the ice–water mixture is best cooled externally with an ice bath during the hydrolysis. The checkers also report that (*E*)-6,10-dimethyl-5,9-undecadien-1-yne containing <1% geranyl chloride is produced in 78–90% yield when 2.0 mmol of butyllithium per millimole of allene is employed.
11. Capillary GC analysis of the product using a 25-m fused-silica DB-5 column shows the presence of 5% geranyl chloride, which is eluted at a slightly shorter retention time than the enyne product. Similar analysis of the product produced (in 89% yield) by the modification reported in Note 10 showed that the product was >96% pure and contained <1% of geranyl chloride. Spectral properties for (*E*)-6,10-dimethyl-5,9-undecadien-1-yne are as follows: IR (thin film) cm^{-1}: 3312, 2119, 1665; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.58 (s, 3 H), 1.60 (s, 3 H), 1.66 (s, 3 H), 1.97–2.14 (m, 4 H), 2.22 (narrow m, 4 H), 5.11 (m, 2 H), 5.19 (m, 1 H).
12. Paraformaldehyde is dried over P_2O_5 in a vacuum desiccator for 24 hr prior to use.
13. The dropping funnel is removed and replaced by a 250-mL Erlenmeyer flask containing the paraformaldehyde. This is connected to the reaction vessel by rubber tubing. The cannula previously attached to the mercury bubbler is inserted through the septum of the dry-ice condenser.
14. The reaction with paraformaldehyde has an induction period of approximately 7–10 min, when the solvent suddenly begins to boil. The dry-ice condenser should be kept charged with dry ice–acetone to avoid loss of solvent.
15. In some runs the checkers found that the slurry became too thick to stir. In these cases, the ice-cold water (450 mL) was added to the reaction flask while stirring the solid mass with a large spatula. The final yield of the alcohol product was similar in these runs. Alternatively the reaction flask can be stirred mechanically.
16. The purity of the product was determined to be 92–94% by capillary GLC analysis using a fused-silica 25-m × DB-5 column, 70–280°C (10°C/min). The spectral properties of the product are as follows: IR (thin film) cm^{-1}: 3334, 2287, 2224, 1670, 1020; ^1H NMR (500 MHz, $CDCl_3$) δ: 1.50 (t, 1 H, J = 10.8), 1.60 (s, 3 H), 1.61 (s, 3 H), 1.68 (s, 3 H), 1.99 (m, 2 H), 2.07 (m, 2 H), 2.22 (narrow m, 4 H), 4.25 (d, 2 H, J = 10.8), 5.09 (m, 1 H), 5.16 (m, 1 H). Vinylic signals for minor impurities are apparent at δ 4.7–4.9.

3. Discussion

The highly useful three-carbon homologation, RX RCH$_2$C CH, often employed in isoprenoid-related syntheses (e.g., sirenin,[5] C_{18}-Cecropia juvenile hormone,[6] 16,17-dehydroprogesterone[7]) is frequently difficult to accomplish cleanly because of the tendency of ambident propargylic nucleophiles, R-C C-CH$_2$M, **3**, to produce troublesome mixtures of both the allenic and acetylenic products.[8,9,10] Propargyl alanates **3** [M = Al(i-C_4H_9)$_3$], for example, couple with allyl bromide to produce mainly the corresponding allene (<4% acetylene), whereas the analogous borate complex **3** [M = B(*sec*-C_4H_9)$_3$] produces an 83 : 17 mixture of the corresponding allene : acetylene.[11] The "propargyl" Grignard reagent[12] also couples with allylic halides[7,13,14] to produce acetylenic–allenic mixtures, for which a separation procedure has been developed based on trimethylsilylation of the crude product mixture.[13] An indirect procedure employing lithio-1-trimethylsilylpropyne initially produces the trimethylsilyl-protected acetylene (50–55%), from which the required homologated alkyne is liberated by reaction with ethanolic silver nitrate followed by sodium cyanide.[15] 1,3-Dilithiopropyne in either tetramethylethylenediamine or 1,4-diazabicyclo[2.2.2]octane is reported to couple with simple halides[16] to form acetylenes in moderate yield, although it fails to couple cleanly with allylic halides.[17]

The present procedure, based on the controlled lithiation of allene, produces the operational equivalent of a propargyl dianion **1** ($C_3H_2Li_2$), and provides a convenient single-step route to propargylated derivatives. Lithiation of allene is deceptively complex, and the extent of metalation (i. e., mono-, di-, tri-, tetra-) and the regiochemical outcome of subsequent alkylation (allenic vs. acetylenic) is highly dependent on reaction conditions. Metalation by butyllithium (1 equiv, THF, –70°C) followed by alkylation with octyl iodide produced an 87 : 13 mixture of the corresponding allene and acetylene,[18] whereas an allene : C_4H_9Li ratio of 1 : 2 (THF, –50°C) followed by trimethylsilylation, produced a mixture comprised of mono-, di-, tri-, and tetra-silylated products.[19] In the current procedure, the solvent ratio (v/v) of ether : hexane of 1 : 1, as well as the stoichiometry and temperature, were empirically determined, and under these conditions there was no detectable evidence (NMR, GLPC) of isomeric allene formation in any of the alkylations examined, for either simple or allylic halides.[20] An additional advantage is that the initially formed lithium acetylide intermediate (e.g., **2**) may be further transformed to other useful functional derivatives in situ, as illustrated by the hydroxymethylation procedure.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

P_2O_5

C_4H_9Li

sodium ketyl of benzophenone

trimethylsilyl-protected acetylene

acetylene (74-86-2)

ether, ethyl ether (60-29-7)

sodium cyanide (143-33-9)

sodium chloride (7647-14-5)

silver nitrate (7761-88-8)

Allyl bromide (106-95-6)

carbon tetrachloride (56-23-5)

methyl chloride (74-87-3)

magnesium sulfate (7487-88-9)

Allene (463-49-0)

octyl iodide (629-27-6)

butyllithium (109-72-8)

hexane (110-54-3)

geraniol (106-24-1)

2-Butyn-1-ol (764-01-2)

triphenylphosphine (603-35-0)

argon (7440-37-1)

1,4-diazabicyclo[2.2.2]octane (280-57-9)

tetramethylethylenediamine (20485-44-3)

Geranyl chloride (5389-87-7)

Lithium acetylide (6867-30-7)

lithio-1-trimethylsilylpropyne

1,3-Dilithiopropyne

(E)-6,10-Dimethyl-5,9-undecadien-1-yne, 5,9-Undecadien-1-yne, 6,10-dimethyl-, (E)- (22850-55-1)

(E)-7,11-Dimethyl-6,10-dodecadien-2-yn-1-ol, 6,10-Dodecadien-2-yn-1-ol, 7,11-dimethyl-, (E)- (16933-56-5)

paraformaldehyde (30525-89-4)

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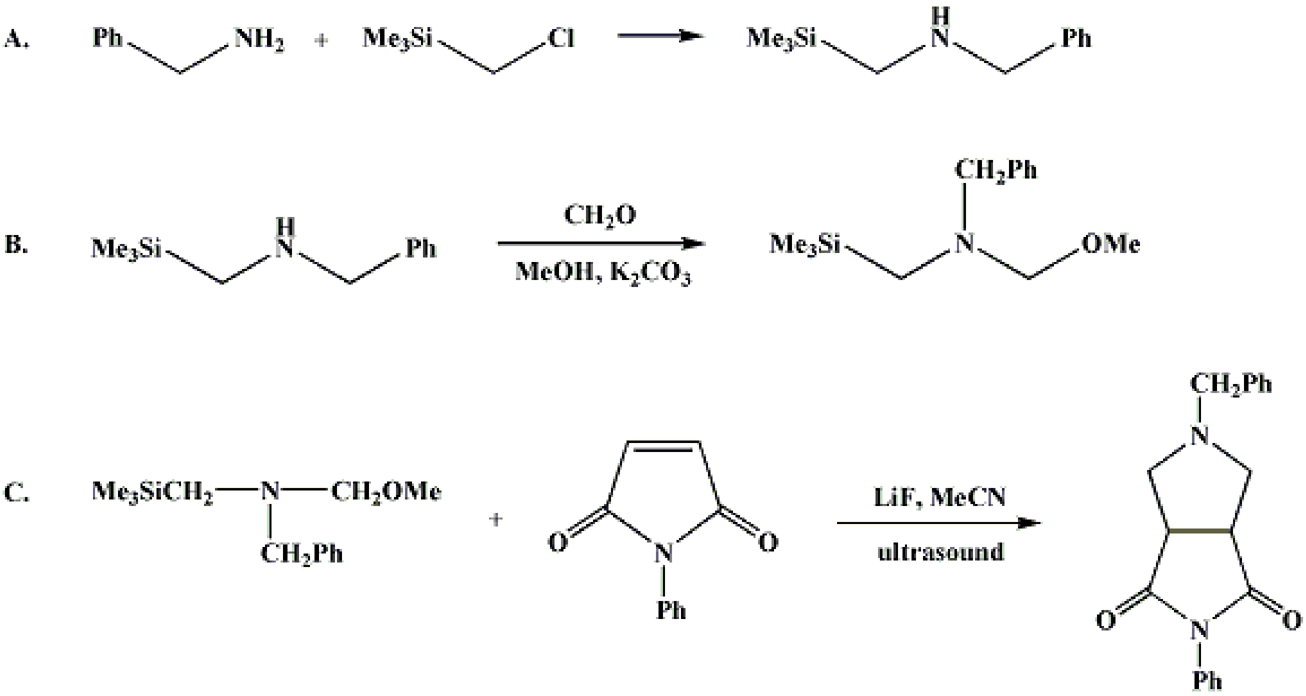
N-BENZYL-*N*-METHOXYMETHYL-*N*-(TRIMETHYLSILYL) METHYLAMINE AS AN AZOMETHINE YLIDE EQUIVALENT: 2,6-DIOXO-1-PHENYL-4-BENZYL-1,4-DIAZABICYCLO[3.3.0]OCTANE

[Pyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione, tetrahydro-2-phenyl-5-(phenylmethyl)-, *cis*-]



Submitted by Albert Padwa and William Dent[1].
Checked by Bruce Lefker and Albert I. Meyers.

1. Procedure

A. *N-Benzyl-N-(trimethylsilyl)methylamine*. An oven-dried, 100-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar and a reflux condenser is charged with 12.58 g (0.1 mol) of chloromethyltrimethylsilane (Note 1). Benzylamine (Note 2) (33.1 g, 0.3 mol) is added with stirring and the resulting solution is heated at 200°C for 2.5 hr. At the end of this time a 0.1 *N* sodium hydroxide solution is added in order to hydrolyze the white organic salt that had formed. The mixture is extracted with ether and the ether layer is dried over magnesium sulfate and concentrated under reduced pressure. The residue is distilled under reduced pressure through a 6-in. Vigreux column to give 11.6–15.3 g (58–72%) of *N*-benzyl-*N*-(trimethylsilyl)methylamine, bp 68–72°C (0.7–0.8 mm) (Note 3).

B. *N-Benzyl-N-methoxymethyl-N-(trimethylsilyl)methylamine*. A 25-mL, round-bottomed flask equipped with a stirring bar is charged with 6.0 g (74 mmol) of a 37% aqueous formaldehyde solution (Note 4). The solution is cooled to 0°C and 10.0 g (51.7 mmol) of *N*-benzyl-*N*-(trimethylsilyl)methylamine is added dropwise with stirring. After the solution is stirred for 10 min at 0°C, 6 mL (0.15 mol) of methanol (Note 5) is added in one portion. Potassium carbonate (4.0 g) is added to the mixture to absorb the aqueous phase. The mixture is stirred for 1 hr, the nonaqueous phase is decanted, an additional 2.0 g of potassium carbonate is added, and the mixture is stirred at 25°C for 12 hr. Ether is added to the mixture and the solution is dried over potassium carbonate, filtered, and concentrated under reduced pressure (Note 6). The residue is distilled at reduced pressure to give 6.8–8.6 g (54–69%) of *N*-benzyl-*N*-methoxymethyl-*N*-(trimethylsilyl) methylamine as a colorless liquid, bp 77–80°C (0.5 mm) (Note 7).

C. *2,6-Dioxo-1-phenyl-4-benzyl-1,4-diazabicyclo[3.3.0]octane*. An oven-dried, 250-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar is charged with 10.0 g (0.042 mol) of *N*-benzyl-*N*-methoxymethyl-*N*-(trimethylsilyl)methylamine and 100 mL of anhydrous acetonitrile (Note 8). *N*-Phenylmaleimide (Note 9) (7.3 g, 0.042 mol) is added, followed by 1.7 g (0.063 mol) of lithium fluoride (Note 10). The reaction mixture is sonicated (Note 11) for 3 hr and poured into 100 mL of water. The mixture is extracted with three 100-mL portions of ether. The organic extracts are combined and washed with 100 mL of saturated sodium chloride solution, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue is chromatographed on a silica gel column (300 g) using a 35% ethyl acetate:hexane mixture (ca. 1500 mL) as the eluant to give 9.2–9.6 g (72–75%) of 2,6-dioxo-1-phenyl-4-benzyl-1,4-diazabicyclo[3.3.0]octane as a pale yellow solid, mp 97–98°C (Note 12).

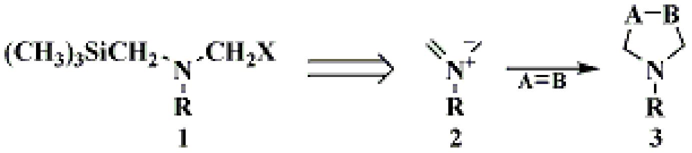
2. Notes

1. Chloromethyltrimethylsilane is purchased from Petrarch Systems, Inc. and is used without purification.
2. Benzylamine, purchased from Aldrich Chemical Company, Inc., is distilled and stored over potassium hydroxide.
3. The submitters report bp 89–90°C (5 mm). The ^{1}H NMR spectrum ($CDCl_3$, 90 MHz) is as follows δ: 0.10 (s, 9 H), 2.00 (s, 2 H), 3.78 (s, 2 H) and 7.28 (s, 5 H).
4. Formaldehyde (37% solution in water) is purchased from Aldrich Chemical Company, Inc. Sufficient aqueous 10% sodium hydroxide solution (1–5 drops) is added until the pH reaches 7.
5. Purified-grade methanol, purchased from Fisher Scientific Company, is used.
6. The submitters found it easier to pump down the crude mixture overnight under reduced pressure to ensure that all the methanol is removed. If not, the residue tends to bump uncontrollably upon distillation.
7. The spectral properties are as follows: IR (neat) cm^{-1}: 3095, 3064, 3030, 2900, 1605, 1495, 1450, 1422, 1385, 1362, 1245, 1070, 925, 845, 740, 700; ^{1}H NMR ($CDCl_3$, 90 MHz) δ: 0.10 (s, 9 H), 2.13 (s, 2 H), 3.20 (s, 3 H), 3.72 (s, 2 H), 3.95 (s, 2 H) and 7.22 (m, 5 H).
8. Anhydrous acetonitrile, purchased from Aldrich Chemical Company, Inc., is distilled over calcium hydride and stored over Linde 4A molecular sieves.
9. *N*-Phenylmaleimide is purchased from Aldrich Chemical Company, Inc., and used without purification.
10. Lithium fluoride is purchased from Fisher Scientific Company.
11. A Branson ultrasonic cleaner (2.8 L, 13 × 23 × 10 cm), purchased from Fisher Scientific Company, is used for sonication. Without sonication, the yield drops by ca. 10–15%.
12. The spectral properties are as follows: IR (neat) cm^{-1}: 3145, 3000, 2950, 2900, 2800, 1760, 1700, 1575, 1490, 1445, 1380, 1310, 1200, 1155, 880, 840, 740, 700; ^{1}H NMR ($CDCl_3$, 90 MHz) δ: 2.3–2.7 (m, 2 H), 3.2–3.6 (m, 4 H), 3.60 (s, 2 H), 7.0–7.7 (m, 10 H).

3. Discussion

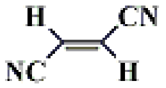
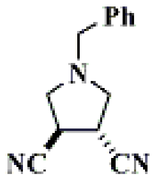
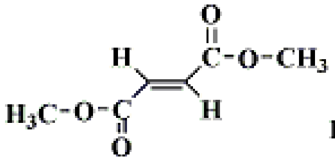
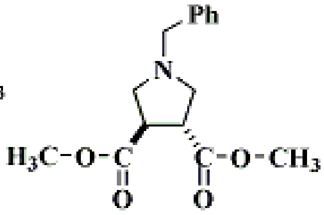
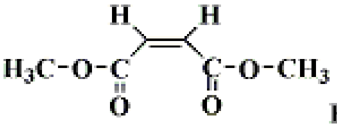
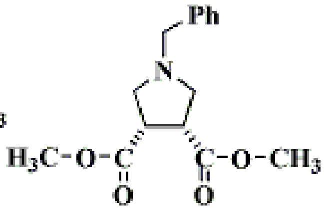
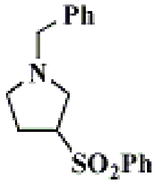
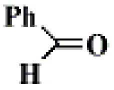
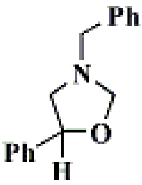
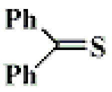
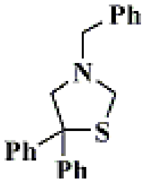
The preparation of pyrrolidines has received extensive attention by synthetic chemists in recent years, in part because of the interesting biological activities exhibited by several polysubstituted pyrrolidines.[2] Little attention has been given to one of the most conceptually simple ways of pyrrolidine formation: a 1,3-dipolar cycloaddition of an azomethine ylide with an olefin. This is not surprising since few methods exist for the preparation of nonstabilized azomethine ylides.[3,4,5,6,7,8,9,10,11,12,13] Silyl-substituted amines of type 1 represent conjunctive reagents that can be considered as the equivalent of a nonstabilized azomethine ylide. These reagents have recently been found to undergo 1,3-dipolar cycloaddition to olefins to give pyrrolidine derivatives in good yield.[14,15,16] The present procedure provides a convenient route for the synthesis of a variety of five-membered ring nitrogen heterocycles using different dipolarophiles. Some representative examples are given in Table I. Advantages of the present method over existing methodologies include mild conditions, high yield, and simplicity of the cycloaddition. Trimethylsilyl triflate or trimethylsilyl iodide can

also be used.[12] However, these reagents are expensive and require longer reaction times.



X = CN, SPh, OMe

TABLE I
CYCLOADDITION OF 1 WITH ELECTRON-DEFICIENT DIPOLAROPHILES

Dipolarophile	Product	% Yield
		90
		90
		90
		92
		80
		91

We have found that sonication of the reaction mixture decreases the time needed for reaction and also substantially increases the yield. This is probably related to an increase in the solubility of lithium fluoride in acetonitrile or is a consequence of surface effects on the metal.

N-Benzyl-*N*-methoxymethyl-*N*-(trimethylsily)methylamine undergoes stereospecific cycloaddition with dimethyl maleate and fumarate. The cycloaddition behavior of an unsymmetrically substituted α-methoxysilylamine has also been examined and found to occur with high overall regioselectivity. The stereospecificity and regioselectivity of the reaction is consistent with a concerted 1,3-dipolar cycloaddition reaction.[17]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

potassium carbonate (584-08-7)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether (60-29-7)

acetonitrile (75-05-8)

sodium hydroxide (1310-73-2)

formaldehyde (630-08-0)

sodium chloride (7647-14-5)

potassium hydroxide (1310-58-3)

magnesium sulfate (7487-88-9)

benzylamine (100-46-9)

pyrrolidine (123-75-1)

hexane (110-54-3)

calcium hydride (7789-78-8)

Dimethyl fumarate (624-49-7)

N-Phenylmaleimide (941-69-5)

trimethylsilyl iodide (16029-98-4)

chloromethyltrimethylsilane (2344-80-1)

trimethylsilyl triflate (27607-77-8)

2,6-Dioxo-1-phenyl-4-benzyl-1,4-diazabicyclo[3.3.0]octane

lithium fluoride (7789-24-4)

dimethyl maleate (624-48-6)

α-methoxysilylamine

N-BENZYL-N-METHOXYMETHYL-N-(TRIMETHYLSILYL)METHYLAMINE (93102-05-7)

N-benzyl-N-(trimethylsilyl)methylamine

Pyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione, tetrahydro-2-phenyl-5-(phenylmethyl)-, cis- (87813-00-1)

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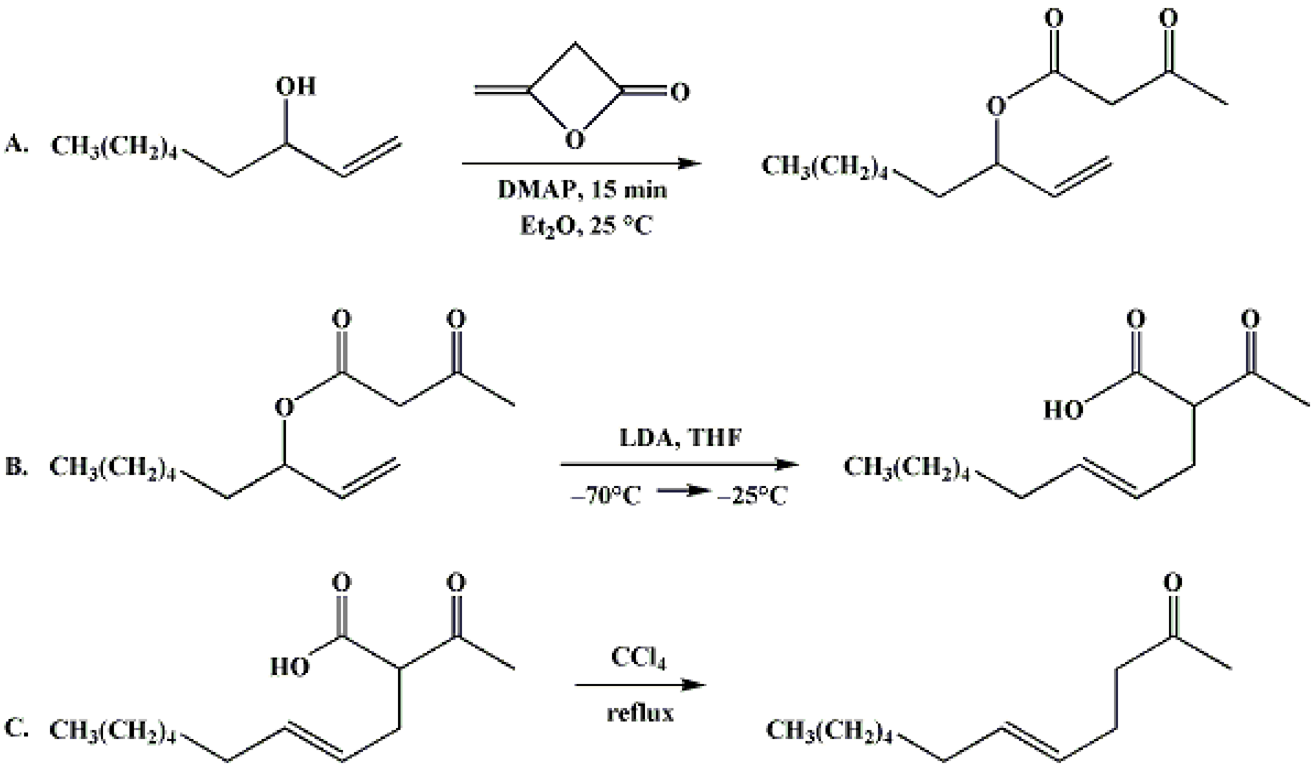
THE CARROLL REARRANGEMENT: 5-DODECEN-2-ONE

[5-Dodecen-2-one, (*E*)-]



Submitted by Stephen R. Wilson and Corinne E. Augelli[1].
Checked by T. R. Vedananda and James D. White.

1. Procedure

A. *(1-Ethenyl)heptanyl 3-ketobutanoate.* 3-Hydroxy-1-nonene ((Note 1), 7.5 g, 0.053 mol) is stirred in 250 mL of anhydrous ether (Note 2) in a 500-mL, three-necked, round-bottomed flask, fitted with a thermometer, a nitrogen/mineral oil bubbler, a Teflon-covered magnetic stirring bar, and a rubber septum. A constant flow of nitrogen is maintained throughout the reaction. To this clear homogeneous solution, diketene ((Note 3), 5.04 g, 0.060 mol) is added in one portion by syringe, followed by 4-dimethylaminopyridine (DMAP) (0.591 g, 0.0049 mol, (Note 4)). A slightly exothermic reaction (to 32°C) is observed. After 15 min, the reaction is complete (Note 5). The reaction mixture is quenched with 100 mL of 0.1% sodium hydroxide solution and 100 mL of anhydrous ether. The layers are separated and the organic phase is washed once with 50 mL of 0.1% sodium hydroxide solution and once with brine. Drying over magnesium sulfate and concentration under reduced pressure affords 11.3 g (0.05 mol, 94%) of a pale-yellow oil. The β-keto ester is of high purity, as shown by TLC, GLC, and spectral analyses (Note 6); however, distillation (bp 113–114°C/1.4 mm) leads to a colorless oil.

B. *2-Carboxy-5-dodecen-2-one.* A solution of lithium diisopropylamide (LDA, (Note 7)) in 150 mL of tetrahydrofuran (Note 8) is prepared from 0.199 mol (20.12 g) of diisopropylamine (Note 9) and 0.181 mol of butyllithium (Note 10) and (Note 11). The solution is cooled to −78°C (acetone–dry ice) and a solution of 10.0 g (0.044 mol) of (1-ethenyl)heptanyl 3-ketobutanoate in 50 mL of tetrahydrofuran (Note 8) is added via a 12-mL, pressure-equalizing dropping funnel at −78°C over a 15-min period. After the addition is complete, the reaction mixture is stirred at −78°C for 45 min and is then allowed to warm gradually to room temperature. When the reaction mixture finally reaches 25°C (about 2 hr), it has a deep-red color. After the mixture is stirred for 18 hr at room temperature, the reaction is complete (Note 12). To this mixture, 100 mL of water and 100 mL of pentane are added in portions with stirring, maintaining the temperature below 25°C with an ice bath. As the deep-red reaction mixture is quenched, an orange heterogeneous mixture results. The layers are separated and

the pentane layer is extracted 2 times with 50 mL of 0.1% sodium hydroxide solution (Note 13). All aqueous layers are combined in a 800-mL beaker equipped with a Teflon-covered magnetic stirring bar. A 100-mL aliquot of pentane is added to this aqueous mixture, which is stirred vigorously, and then 100 mL of 10% hydrochloric acid solution is added in 10-mL portions until pH 2 is reached (Note 14). The heterogeneous solution is poured into a 1-L separatory funnel and the layers are quickly separated. The aqueous layer is extracted 3 times more, each time with 50 mL of pentane. The combined organic layers (ca. 250–300 mL) are dried ($MgSO_4$), and evaporated at reduced pressure without heating, to give 9.6 g (0.04 mol, 97%) of a red-orange oil. This carboxylic acid is of high purity as shown by TLC and spectral analyses (Note 15).

C. *5-Dodecen-2-one.* The 3-carboxy-5-dodecen-2-one (9.0 g, 0.040 mol) is stirred in 150 mL of carbon tetrachloride (Note 16) in a 500-mL, three-necked, round-bottomed flask that is fitted with a reflux condenser, a thermometer, a Teflon-covered magnetic stirrer, and a ground-glass stopper. After the orange-yellow solution is heated at reflux for 1 hr, TLC analysis shows the reaction to be complete (Note 17). The reaction mixture is concentrated under reduced pressure with warming to afford 7.1 g (0.039 mol, 98%) of a red-orange oil. The product is sufficiently pure for most purposes. It may be purified by vacuum distillation at 105–107°C/2.7 mm (5.2 g, 0.03 mol, 71%), which yields a pale-yellow oil (Note 18).

2. Notes

1. 3-Hydroxy-1-nonene was prepared by the following procedure. First, 0.219 mol (25.0 g) of heptaldehyde (Eastman Kodak Co.), distilled prior to use, was stirred in 450 mL of anhydrous ether (Note 2) under a nitrogen atmosphere. The solution was cooled to 0°C with an ice bath and 0.260 mol (260.4 mL) of vinylmagnesium bromide (1.0 *M* solution in tetrahydrofuran, Aldrich Chemical Company, Inc., 1.2 equiv) was then added dropwise over a 0.5-hr period. The reaction mixture was allowed to warm gradually to room temperature and was stirred for 0.5 hr. The reaction mixture was added, in portions with stirring, to 400 mL of a saturated ammonium chloride solution, maintaining the temperature below 25°C with an ice bath. This quenched reaction mixture was stirred for 15 min. The layers were separated and the aqueous layer was extracted 2 times, each time with 200 mL of ether. The combined organic layers were extracted with 200 mL of brine, dried ($MgSO_4$), and concentrated under reduced pressure with warming to afford a yellow oil in quantitative yield. The allylic alcohol was distilled (bp 185°C/760 mm, 25 g, 0.158 mol, 73%) before use. Silica gel TLC showed one spot: R_f = 0.34 (20% ethyl acetate/ligroin). GLC: retention time, 4.56 min. Program: 40°C/1 min; 20°C/1 min to 320°C; 2% OV-101, 0.2% Carbowax on Chromosorb. This program and column were used throughout the entire sequence of reactions. IR (neat) cm^{-1}: 3610 (OH); 3000 (C-H, alkenes); 1650 (C=C); 1000 (C-O). Mass spectrum: *m/e* 57 [100% M^+-$CH_2(CH_2)_4CH_3$], 85 (7.7% M^+-CHOHCH=CH_2), 113 (2.5% M^+-CH_2CH_3). ^{1}H NMR ($CDCl_3$) δ: 0.91 (t, 1 H, *J* = 6.9), 1.54–1.31 (m, 11 H), 4.12 (q, 1 H, *J* = 6.3), 5.27–5.11 (m, 1 H), 5.95–5.84 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ: 14.0, 22.6, 25.4, 29.3, 31.9, 37.1, 72.9, 114.0, 141.5.

2. Anhydrous ether (Fisher Scientific Company) was used without further drying.

3. Diketene (Aldrich Chemical Company, Inc.) was distilled immediately prior to use.

4. 4-Dimethylaminopyridine (DMAP) was purchased from Aldrich Chemical Company, Inc. A catalytic amount of 4-dimethylaminopyridine is necessary for this reaction to proceed.

5. Reaction progress can be monitored by GLC analysis of the disappearance of diketene.

6. Silica gel TLC shows one spot at R_f = 0.45 (20% ethyl acetate/ligroin); GLC shows >95% purity of the β-keto ester. The β-keto ester undergoes partial cleavage to the corresponding allylic alcohol under the following GLC conditions. Retention time, 7.8 [(1-ethenyl)heptanyl 3-ketobutanoate]; retention time, 4.88 (3-hydroxy-1-nonene). Mass spectrum for the β-keto ester: *m/e* 43 (100% M^+-$COCH_3$), 85 [46.5% $(CH_2)_5CH_3$], 141 (13.3% M^+-$COCH_2COCH_3$). Mass spectrum for allylic alcohol: *m/e* 57 [100% M^+-$CH_2(CH_2)_4CH_3$], 85 (8.7% M^+-CHOHCH=CH_2), 113 (2.8% M^+-CH_2CH_3). IR (neat) cm^{-1}: 3000 (C-H, alkenes); 1725 (C=O); 1650 (C=C); ^{1}H NMR ($CDCl_3$) δ: 0.89 (t, 3 H), 1.30–1.64 (m, 10 H), 2.3 (s, 3 H), 3.47 (s, 2 H), 5.19–5.31 (m, 3 H), 5.72–5.84 (m, 1 H). Anal. calcd. for $C_{13}H_{22}O_3$: C, 68.99; H, 9.8. Found: C, 69.25; H, 10.06.

7. Lithium diisopropylamide (LDA) was prepared by the method described in *Org. Synth., Coll. Vol. VII* **1990**, 208.

8. Tetrahydrofuran was distilled from lithium aluminum hydride immediately prior to use.
9. Diisopropylamine, purchased from Aldrich Chemical Company, Inc., was distilled immediately prior to use.
10. Butyllithium, 2.5 *M* solution, in hexanes was purchased from Aldrich Chemical Company, Inc. Butyllithium was titrated with diphenylacetic acid[2] before each use.
11. An amount of 4.1 equiv of lithium diisopropylamide (LDA) is absolutely necessary for this reaction to go to completion. An equilibrium exists between the formation of the second anion of the β-keto ester and the formation of lithium diisopropylamide from diisopropylamine.
12. Reaction progress can be followed most accurately by silica gel TLC and GLC analysis. In TLC analysis, one sees the disappearance of (1-ethenyl)heptanyl 3-ketobutanoate, R_f = 0.45 (20% ethyl acetate/ ligroin) and the appearance of baseline material that is indicative of the corresponding carboxylic acid salt. In GLC analysis, an aliquot (3 drops of reaction mixture, 3 drops of ether, 3 drops of 10% hydrochloric acid) will show complete disappearance of peaks at R_t = 7.44 and 4.56 [which correspond to (1-ethenyl)heptanyl 3-ketobutanoate and cleavage of this β-keto ester under GLC conditions to the 3-hydroxy-1-nonene, respectively] and appearance of a peak at R_t = 7.04 that corresponds to 5-dodecen-2-one. The 3-carboxy-5-dodecen-2-one decarboxylates upon injection yielding the GLC spectrum of the ultimate product.
13. Sodium hydroxide (0.1%) is used to extract all of the carboxylate from the ether layer in the form of the sodium salt.
14. A slight exotherm was noted from 25 to 32°C. Acidification is necessary to extract all of the desired carboxylate from the aqueous layer into the organic layer.
15. Silica gel TLC shows one major spot at the baseline (20% ethyl acetate/ligroin) with a very slight impurity (<5%) at R_f = 0.47. Mass spectrum of 5-dodecen-2-one: *m/e* 43 (100% $COCH_3$), 97 [6.1% M^+-$CH_2(CH_2)_4CH_3$], 125 (1.7% M^+-CH_2COCH_3). IR (neat) cm^1: 3000 (COOH); 1725 (COOH, RCOR); ^1H NMR ($CDCl_3$) δ: 0.90 (t, 3 H, *J* = 6.3); 1.28 (m, 8 H); 2.00 (m, 2 H); 2.31 (s, 3 H); 2.60 (t, 2 H, *J* = 6.9); 3.48–3.59 (m, 1 H); 5.27–5.44 (m, 1 H, *trans J* = 15.3); 5.49–5.61 (m, 1 H, *trans J* = 15.3).
16. Carbon tetrachloride was used as purchased from Fisher Scientific Company.
17. Reaction progress was followed most accurately by TLC analysis. The disappearance of the baseline material (i.e., 3-carboxy-5-dodecen-2-one) and appearance of the desired ketone at R_f = 0.33 (10% ethyl acetate/ligroin) indicates the completeness of the reaction.
18. Silica gel TLC shows one spot at R_f = 0.33 (10% ethyl acetate/ligroin). GLC shows >95% purity; one peak at R_t = 7.04. Mass spectrum: *m/e* 43 (100% $COCH_3$), 97 [6.3% M^+-$CH_2(CH_2)_4CH_3$], 125 (2.0% M^+-CH_2COCH_3). IR (neat) cm^{-1}: 1700 (R'COR); ^1H NMR ($CDCl_3$) δ: 0.90 (t, 3 H, *J* = 6.5), 1.28 (m, 8 H), 1.98 (q, 2 H, *J* = 6.3), 2.16 (s, 3 H), 2.28 (q, 2 H, *J* = 6.6), 2.51 (t, 2 H, *J* = 7.4), 5.34–5.51 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ: 14.0, 22.6, 26.9, 28.8, 29.5, 29.8, 31.7, 32.5, 43.6, 128.2, 131.5, 207.9. Anal. calcd. for $C_{12}H_{22}O$: C, 79.06; H, 12.17. Found: C, 78.79; H, 12.10.

3. Discussion

The Carroll rearrangement,[3,4] an old and well-established thermal rearrangement, involves the rearrangement of allylic esters to β-keto acids followed by decarboxylation to provide γ,δ-unsaturated methyl ketones. Even though the Carroll rearrangement is a versatile complement to the Claisen rearrangement,[5] it is not of widespread use. This may be due to (a) the lack of a convenient, high-yield method for the formation of β-keto esters and (b) the harsh conditions required to effect rearrangement.[6] Often, procedures involve direct conversion of allylic alcohols to the rearranged and decarboxylated products in one step and low yield.

The method of preparation of 5-dodecen-2-one presented here is a version of the literature procedure published earlier.[10] It offers several advantages over existing methodology:

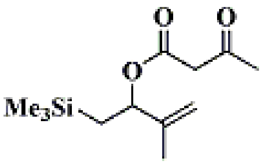
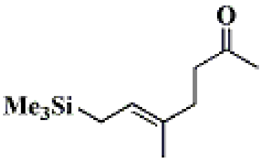
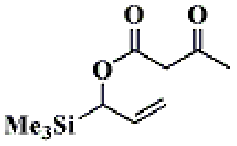
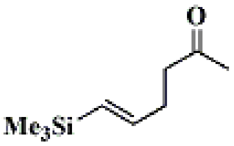
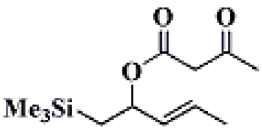
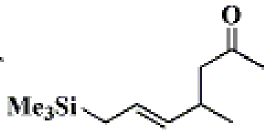
1. The ester enolate modification of the Carroll rearrangement provides the allylic acetoacetates via a mild, fast, and high-yield synthesis. This procedure represents a significant improvement over other routes.[7 8 9]
2. Dianions of the allylic acetoacetates rearrange at room temperature and the resulting β-keto acids can be

readily isolated. Isolation of the acetoacetic acids adds to the versatility of the synthesis of γ,δ-unsaturated methyl ketones and makes purification much more simple than pyrolysis method.

3. Finally, the general pyrolysis procedure, although one step, leads to side products and low yields (typically 10–40%). For example, pyrolysis of (1-ethenyl)heptanyl 3-ketobutanoate[4] gives two major products, 5-dodecen-2-one and 3-hydroxy-1-nonene, whereas the method of preparation described here yields only the desired γ,δ-unsaturated methyl ketone.

Table I contains representative examples of the method of preparation described here.

TABLE I
PREPARATION OF γ,δ-UNSATURATED METHYL KETONES

SUBSTRATE	PRODUCT	YIELD(%)	REF.
		40	10
		80	10
		84	10

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6. Rearrangement is normally carried out at temperatures of 130–220°C by heating the β-keto ester neat or in a high-boiling solvent (xylene, diphenyl ether), usually *in situ* after preparation of the β-keto ester.
7. Acetoacetate formation has previously been carried out by using the following. (a) Et_3N: Kato, T.; Chiba, T. *Chem. Pharm. Bull.* **1975**, *23*, 2263;
8. NaOR: see [4];
9. *p*-TsOH: Boese, A. B., Jr. *Ind. Eng. Chem.* **1940**, *32*, 16.
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ligroin

brine

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

ether (60-29-7)

ammonium chloride (12125-02-9)

sodium hydroxide (1310-73-2)

carbon tetrachloride (56-23-5)

nitrogen (7727-37-9)

diketene (674-82-8)

Diphenylacetic acid (117-34-0)

Pentane (109-66-0)

magnesium sulfate, $MgSO_4$ (7487-88-9)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

vinylmagnesium bromide (1826-67-1)

heptaldehyde (111-71-7)

lithium diisopropylamide (4111-54-0)

diisopropylamine (108-18-9)

4-dimethylaminopyridine (1122-58-3)

5-Dodecen-2-one

(1-Ethenyl)heptanyl 3-ketobutanoate (133538-60-0)

3-Carboxy-5-dodecen-2-one (133538-61-1)

3-Hydroxy-1-nonene (21964-44-3)

5-Dodecen-2-one, (E)- (81953-05-1)

2-Carboxy-5-dodecen-2-one

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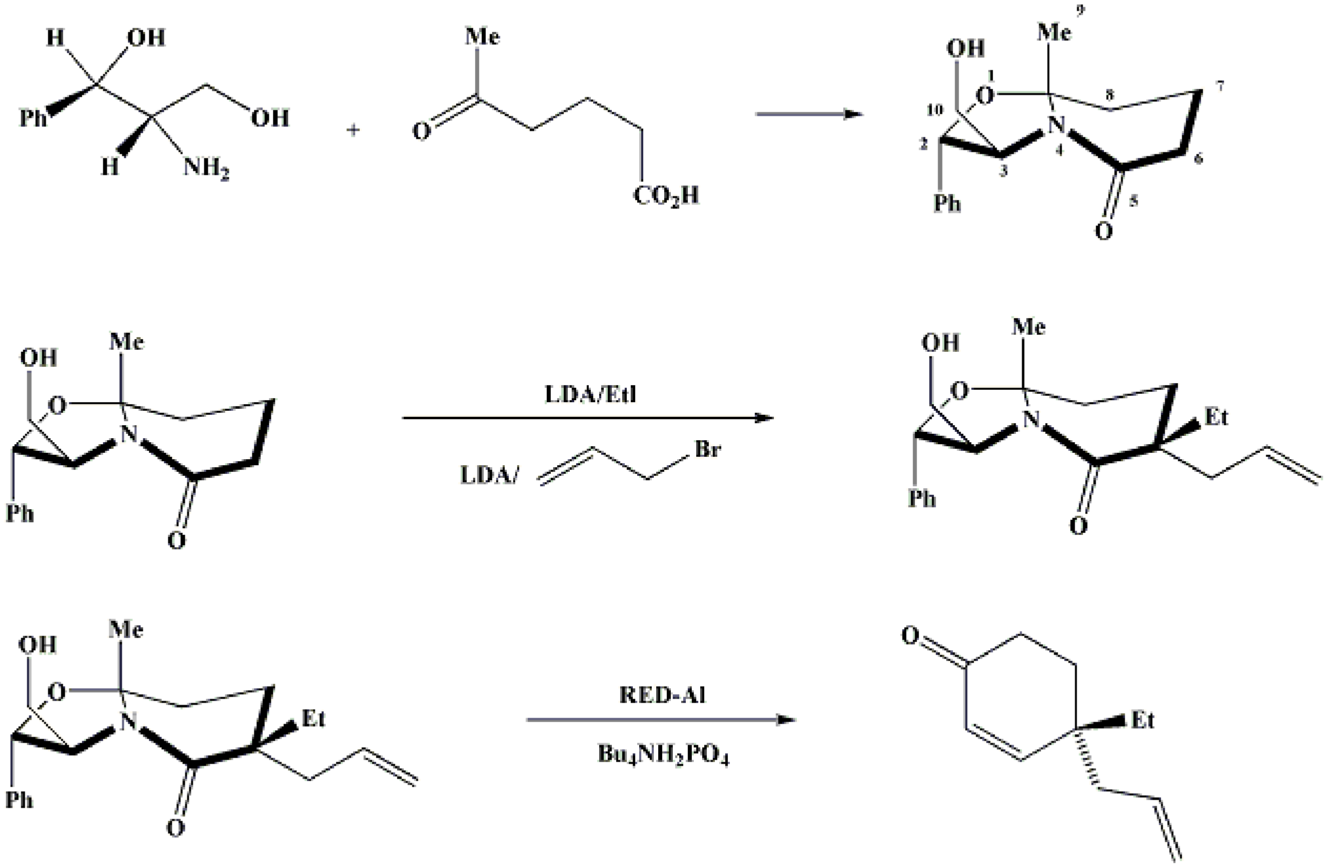
Organic Syntheses, CV 8, 241

ASYMMETRIC SYNTHESIS OF 4,4-DIALKYLCYCLOHEXENONES FROM CHIRAL BICYCLIC LACTAMS: (*R*)-4-ETHYL-4-ALLYL-2-CYCLOHEXEN-1-ONE



Submitted by Albert I. Meyers and Daniel Berney[1].
Checked by P. B. Madan, A. Schwartz, and David L. Coffen.

1. Procedure

A. *Hexahydro-3-(hydroxymethyl)-8a-methyl-2-phenyl[2S,3S,8aR]-5-oxo-5H-oxazolo[3,2-a]pyridine (Bicyclic lactam)*. To a warm solution of (1*S*,2*S*)-(+)-2-amino-1-phenyl-1,3-propanediol (32.4 g, 194 mmol) (Note 1) in toluene (800 mL), 5-oxohexanoic acid (25 g, 912 mmol) (Note 2) is added with stirring. The stirred mixture is heated to reflux under argon with azeotropic removal of water for 18 hr. The reaction mixture is cooled, washed with 0.5 *N* hydrochloric acid (100 mL) and with saturated sodium bicarbonate solution (50 mL), dried over magnesium sulfate, and evaporated to dryness. The residue is crystallized from methylene chloride/hexane in the cold. The crystals are collected by filtration and washed with cold ether to give 35.9–37.2 g (71–74% yield) of the bicyclic lactam in two crops (Note 3).

B. *Hexahydro-6-ethyl-3-(hydroxymethyl)-6-allyl-2-phenyl[2S,3S,6S,8aR]-5-oxo-5H-oxazolo[3,2-a]pyridine*. In an oven-dried, 500-mL, round-bottomed flask, containing a magnetic stirring bar, is placed 14.4 g (55.2 mmol) of dry bicyclic lactam prepared as described in Part A. The flask is flushed with argon and filled with 150 mL of anhydrous tetrahydrofuran (Note 4) and then sealed with a rubber septum. The air in the flask is further replaced by argon (Note 5). After dissolution of the bicyclic lactam, the flask is cooled in dry ice–acetone and the solution is stirred while preparing lithium diisopropylamide (LDA).

To an oven-dried, 200-mL, conical flask (Note 6) with air replaced by argon, containing 50 mL of dry tetrahydrofuran (THF) and sealed with a rubber septum, 13.9 g (19.3 mL, 137.4 mmol) of diisopropylamine (Note 7) is added with a syringe. The flask is placed in an ice–water bath. After 15 min, 84 mL (134.4 mmol) of 1.6 *M* butyllithium in hexane (Note 8) is slowly added with a syringe and with gentle swirling of the flask. The solution is kept for 5 min at this

temperature.

The lithium diisopropylamide solution prepared as described above is transferred dropwise, via a cannula, into the bicyclic lactam solution. The dry ice–acetone bath is replaced by an ice–water bath, where the reaction mixture is kept for 40 min to complete formation of the lithium enolate. The reaction mixture is cooled again (30 min) with a dry ice–acetone bath. Freshly distilled ethyl iodide (25.8 g, 13.4 mL, 165.4 mmol) (Note 9) is added slowly, via syringe, to the mixture and stirring is continued for 55 min in a dry ice–acetone bath. The cooling bath is replaced by an ice–water bath, and the mixture is stirred for exactly 40 min (Note 10) and is poured immediately into a separatory funnel containing 400 mL of 1.0 *N* hydrochloric acid. The resulting emulsion is extracted once with 400 mL of ether and the organic layer is washed with 200 mL of a 1 : 1 mixture of brine and a saturated solution of sodium bicarbonate. The ether extract is dried over magnesium sulfate and evaporated to dryness in a 500-mL round-bottomed flask. The residue is dissolved in 60 mL of dry toluene and evaporated again using a water bath (60°C for 45 min) to remove all traces of water and toluene. The product (17.2 g, > 100%) is used in the next step without further purification.

The 500-mL flask containing the crude dry product (17.2 g) is filled with argon and dry tetrahydrofuran (150 mL), a magnetic stirring bar is added, the flask is sealed with a rubber septum, and argon is introduced once again. The flask is gently swirled until the viscous oil is totally dissolved and then the flask is immersed in a dry ice–acetone bath.

Another portion of LDA is prepared as described above except that this time 12.6 g of diisopropylamine (17.6 mL, 124.6 mmol) in THF (50 mL) and 78.0 mL (124.8 mmol) of 1.6 *M* butyllithium/hexane are used. The LDA solution is added, through a cannula, to the ethylated bicyclic lactam solution and the mixture is allowed to warm to 0°C; it is kept at this temperature for 3.0 hr (Note 11). The solution is cooled to −75° to −80°C in a dry ice–acetone bath. A solution of 9.4 g of freshly distilled allyl bromide (6.8 mL, 77.6 mmol) (Note 12) in dry THF (50 mL) is prepared in a 100-mL, oven-dried conical flask flushed with argon and sealed with a rubber septum. This solution is cooled in a dry ice–acetone bath and slowly added to the reaction mixture through a cannula (Note 13). After addition of the allyl bromide, the mixture is kept in a dry ice–acetone bath for 2.5 hr; then the bath is replaced by acetone at −50°C, which is allowed to warm to −30°C within a period of 45 min (Note 14). The reaction is terminated by pouring it into 1 *N* hydrochloric acid (as above), extracting with ether, washing with sodium bicarbonate–brine, drying over magnesium sulfate, and evaporating the solvents. The viscous or solid residue is dissolved in methylene chloride (10 mL), and petroleum ether (30–60°C) (140 mL) is added. The product is allowed to crystallize at room temperature for 1 hr, then at −15°C overnight, to give 13.5 g (74%, mp 90–92°C) of a 9 : 1 mixture of diastereoisomers.

This mixture is recrystallized three times with the same mixture of solvents and the product is collected after 1 hr at 0°C to give 8.7 g (47.9%, mp 101–103°C) of a 25 : 1 mixture of diastereoisomers (values based on the 8a-methyl signal integration on NMR spectra) (Note 15).

C. *(R)-4-Ethyl-4-allyl-2-cyclohexen-1-one*. In an oven-dried, 500-mL, round-bottomed flask, containing dry toluene (300 mL) and a magnetic stirring bar, is placed the dialkylated lactam (7.8 g, 23.7 mmol). The solution is cooled in a dry ice–acetone bath and a 1 *M* solution of Red-Al in toluene (55 mL, 55.0 mmol) is slowly added (Note 16). The flask is flushed with argon and sealed with a rubber septum which is connected by a hypodermic needle to a rubber balloon filled with argon. The reaction mixture is allowed to warm to room temperature and stirred for 3 days. The septum is removed, the reaction mixture is cooled to 0°C, and methanol (10 mL) is cautiously added with stirring to destroy excess Red-Al. The solution is poured over 1 *M* aqueous potassium hydroxide (500 mL) in a 2-L separatory funnel and thoroughly shaken with ether (200 mL) until both layers become almost clear. The aqueous layer is extracted twice more with ether (2 × 100 mL), and, after the ethereal layers are combined, the ethereal solution is dried over magnesium sulfate and evaporated to dryness in a 500-mL flask.

The residue is dissolved in ethanol (250 mL), a 1 *M* aqueous solution of tetrabutylammonium dihydrogen phosphate (80 mL) (Note 17) is added, and the mixture is stirred under reflux for 24 hr. After the solution is cooled, it is partly evaporated on a rotary evaporator with a bath temperature not exceeding 40°C (Note 18) to remove most of the ethanol. Water is added (500 mL) and the solution is extracted twice with chloroform (200 mL). The chloroform extracts are washed with a 1 : 1 mixture of brine and 1 *N* hydrochloric acid and then with brine and saturated sodium bicarbonate solutions. Both aqueous phases are extracted twice with chloroform and the extracts are combined, dried over magnesium sulfate, and evaporated to dryness to give 5.8 g of crude 4,4-disubstituted cyclohexenone. The product is distilled rapidly in a Kugelrohr apparatus at 3.5 mm and 115°C to give 3.0 g (77%) of highly pure cyclohexenone (Note 19).

2. Notes

1. The amino diol was purchased from Aldrich Chemical Company, Inc. and was recrystallized before use from methanol/ethyl acetate (the material used had mp 111–113°C).

2. 5-Oxohexanoic acid was purchased from Aldrich Chemical Company, Inc. and was used without further purification.

3. The bicyclic lactam thus prepared has the following physical properties: mp 98–99°C; $[\alpha]_D^{21}$ + 13.54° (EtOH, c 1.55); IR (KBr) cm^{-1}: 3360, 2950, 1625, 1500, 1395; ^{1}H NMR (270 MHz, $CDCl_3$) δ: 3.75 (dd, C_{10}H, *J* = 11.3, 8.5), 3.90 (dd, C_{10}H, *J* = 11.3, 1.9), 4.07 (dt, C_3H, *J* = 8.5, 1.9), 4.79 (d, C_2H, *J* = 8.6), 4.89 (br s, 1 H, OH), 7.38 (s, 5 H, phenyl) and unresolved signals.

4. THF was distilled from a blue solution of benzophenone ketyl obtained by refluxing THF in the presence of a sodium dispersion in paraffin and benzophenone.

5. All reactions were done under argon atmosphere. The argon was introduced through hypodermic needles at a pressure below 50 mm across the rubber septum. An exhaust line was also provided to remove air or excess pressure.

6. A conical flask was used in order to allow efficient transfer of the LDA solution.

7. Commercial diisopropylamine wa distilled over calcium hydride and stored over potassium hydroxide or Linde 4A molecular sieves.

8. 1.6 *M* Butyllithium in hexane was purchased from Aldrich Chemical Company, Inc.

9. Ethyl iodide was distilled over anhydrous potassium carbonate and stored in the refrigerator over copper turnings.

10. If the reaction mixture is kept for longer than 40 min in the ice-water bath, undesirable amounts of the diethylated product are produced.

11. This is the minimum time to allow complete enolate formation.

12. Allyl bromide was distilled over anhydrous potassium carbonate and stored in the refrigerator over Linde 4A molecular sieves.

13. The allyl bromide solution was allowed to cool efficiently by dripping it against the cold walls of the flask. It is important that allyl bromide reach the reaction mixture at the lowest possible temperature in order to obtain an optimal stereo-selective alkylation. The cannula was protected against heat exchange with air by coating it with a fine rubber tubing.

14. Dry ice was removed, leaving only acetone in the Dewar vessel. The temperature was then adjusted to −50°C by adding warm (room temperature) acetone; the temperature was allowed to rise slowly to −30°C by adding small portions of acetone.

15. The physical properties for the dialkylated bicyclic lactam are as follows: $[\alpha]_D^{21}$ +38.89° (EtOH, c 1.77); IR (KBr) cm^{-1}: 3250, 2490, 1600, 1450, 1370, 1330, 1070, 890, 750; ^{1}H NMR (270 MHz, $CDCl_3$) δ: 0.91 (t, 3 H, C_{12}H, *J* = 7.3), 1.57 (s, 3 H, C_9H); 2.42 (ddd, 2 H, C_{13}H, *J* = 63.6, 13.4, 7.4), 3.65 (br, 1 H, OH), 3.75 (dd, C_{10}H, *J* = 11.3, 8.8), 3.90 (dd, C_{10}H, *J* = 11.2, 2.5), 4.13 (dt, C_3H, *J* = 8.8, 2.5), 4.78 (d, C_2H, *J* = 8.5), 5.11–5.16 (m, 2 H, C_{15}H), 5.73–5.88 (m, C_{14}H), 7.37 (s, 5 H, phenyl) and unresolved signals. Anal. calcd. for $C_{20}H_{27}NO_3$: C, 72.91: H, 8.26; N, 4.25. Found: C, 72.77; H, 8.25; N, 4.24.

16. 1 *M* Red-Al is prepared, by diluting to 100 mL with toluene, 29.5 mL of commercially available 3.4 *M* Red-Al solution in toluene (Aldrich Chemical Company, Inc.; the checkers used Vitride brand supplied by Hexcel Corp.). Before use, this solution should be warmed to room temperature since it tends to separate into two layers at low temperatures. The first milliliter of Red-Al produces a vigorous evolution of gas; therefore, the flask should be kept open until the Red-Al addition is complete. Then the reaction vessel is sealed as described.

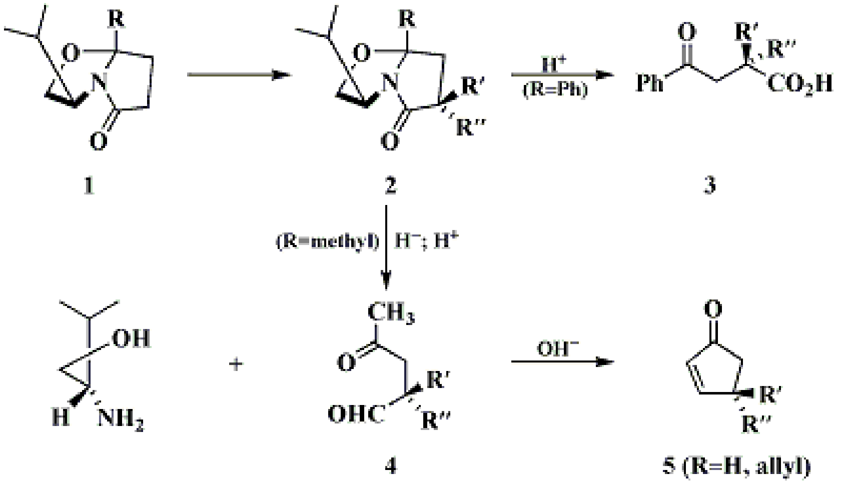
17. 1 *M* Tetrabutylammonium dihydrogen phosphate aqueous solution was purchased from Aldrich Chemical Company, Inc.

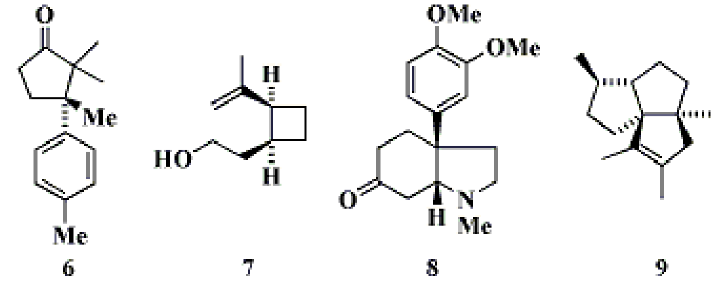
18. The product has a high vapor pressure and can easily be lost by evaporation. Thus, the yields will vary because of this property. The more caution exerted in the evaporation and distillation step, the higher will be the yield of product.

19. If the distillation is performed slowly, a substantial amount of the product may polymerize, resulting in lower yield. The physical data are as follows: $[\alpha]_D^{21}$ −23.12° (EtOH, c, 1.67); IR (film) cm^{-1}: 2960, 1680, 1450, 1380, 1210; ^{1}H NMR (270 MHz, $CDCl_3$) δ: 0.95 (t, 3 H, C_8H, *J* = 7.6), 1.49–1.57 (m, 2 H, C_3H), 1.87 (t, 2H, C_5H, *J* = 6.8), 2.23 (d, 2 H, C_9H, *J* = 6.6), 2.45 (t, 2 H, C_6H, *J* = 6.8), 5.07–5.14 (m, C_{11}H), 5.65–5.82 (m, C_{10}H), 5.94 (d, C_2H, *J* = 10.3), 6.71 (d, C_3H, *J* = 10.3). Anal. calcd. for $C_{11}H_{16}O$: C, 80.45; H, 9.82. Found: C, 79.67; H, 10.05. By GLC analysis, the product is 93–95% pure with 5–7% of diethylcyclohexenone detectable by GLC–MS.

3. Discussion

Chiral bicyclic lactams such as those described here are useful in reaching a variety of chiral quaternary carbon derivatives. Thus, **1** can be doubly alkylated to the bicyclic lactam **2** in high diastereoselectivity. Acidic hydrolysis leads to α,α-substituted γ-keto acids **3**,[2] whereas reduction and hydrolysis furnish the chiral keto aldehydes **4**. Base-catalyzed aldolization affords chiral cyclopentenones **5**.[3] In addition, several total syntheses of natural products have been accomplished, further demonstrating the synthetic usefulness of these bicyclic lactams **1**. Thus, (−)-α-cuparenone **(6)**,[4] (−)-grandisol **(7)**,[5] (+)-mesembrine **(8)**,[6] and (−)-silphiperfol-6-ene (**9**)[7] have been prepared in high enantiomeric excess.





To reach chiral cyclohexenones, we have found that the bicyclic lactam **10**, derived from 5-oxohexanoic acid and the commercially available amino diol, gave excellent results. A number of examples were obtained (Table I).[8]

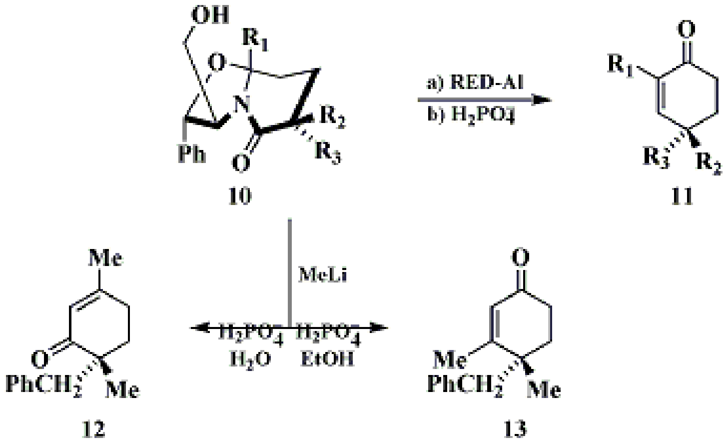
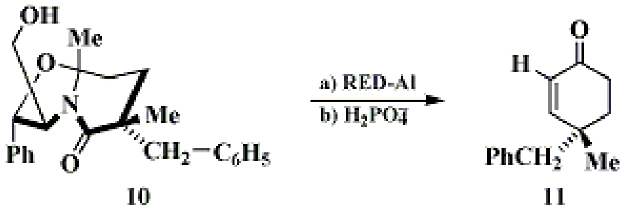
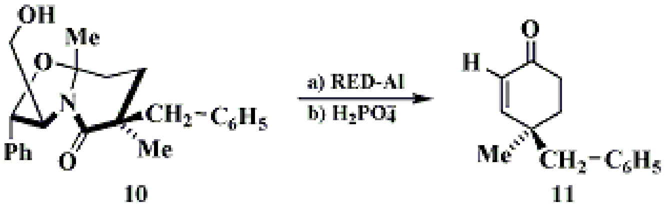
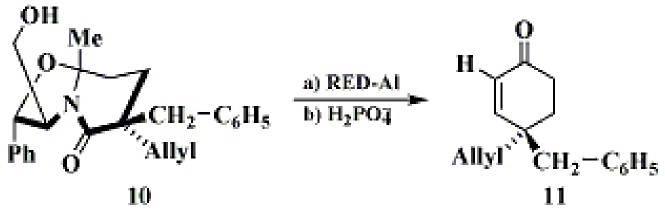
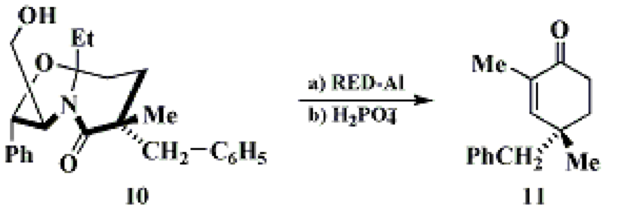
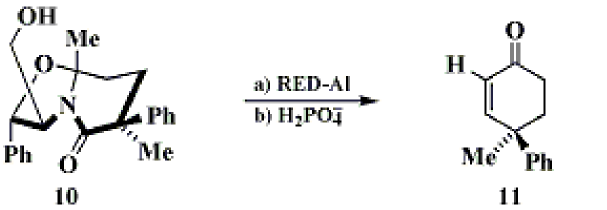


TABLE I

CHIRAL 4,4-DIALKYLCYCLOHEXENONES (11)[a]

10			11				
R_1	R_2	R_3	R_1	R_2	R_3	Yield(%)	$[\alpha]_D$

Me	Me	$PhCH_2$	H	ME	$PhCH_2$		–65.6°	53
Me	$PhCH_2$	Me	H	$PhCH_2$	Me		+64.8°	68
Me	$PhCH_2$	Allyl	H	$PhCH_2$	Allyl		+48.9°	47
Et	Me	$PhCH_2$	Me	Me	$PhCH_2$		–39.7°	66
Me	Ph	Me	H	Ph	Me		+122.2°	47

[a]Yields refer to reduction and hydrolysis of **10** to **11**. All products are 99% optically pure (see [8]).

Furthermore, in place of reduction of **10** it was possible to add organolithium reagents such that the resulting alkyl carbinolamine, after hydrolysis, gave either **12** or **13** depending on hydrolysis conditions.[6] In summary, these bicyclic lactams have provided a route to a variety of chiral, nonracemic cyclohexenones and cyclopentenones containing quaternary stereocenters.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 457
- Org. Syn. Coll. Vol. 9, 530

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

benzophenone ketyl

brine

Red-Al

Hexahydro-3-(hydroxymethyl)-8a-methyl-2-phenyl[2S,3S,8aR]-5-oxo-5H-oxazolo[3,2-a]pyridine (Bicyclic lactam)

ethanol (64-17-5)

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether (60-29-7)

chloroform (67-66-3)

sodium bicarbonate (144-55-8)

Allyl bromide (106-95-6)

allyl (1981-80-2)

copper turnings (7440-50-8)

acetone (67-64-1)

potassium hydroxide (1310-58-3)

toluene (108-88-3)

Benzophenone (119-61-9)

sodium (13966-32-0)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

Ethyl iodide (75-03-6)

butyllithium (109-72-8)

Tetrahydrofuran, THF (109-99-9)

hexane (110-54-3)

calcium hydride (7789-78-8)

argon (7440-37-1)

lithium diisopropylamide (4111-54-0)

diisopropylamine (108-18-9)

5-oxohexanoic acid (3128-06-1)

tetrabutylammonium dihydrogen phosphate (5574-97-0)

(R)-4-Ethyl-4-allyl-2-cyclohexen-1-one (122444-62-6)

(1S,2S)-(+)-2-amino-1-phenyl-1,3-propanediol

Hexahydro-6-ethyl-3-(hydroxymethyl)-6-allyl-2-phenyl[2S,3S,6S,8aR]-5-oxo-5H-oxazolo[3,2-a]pyridine

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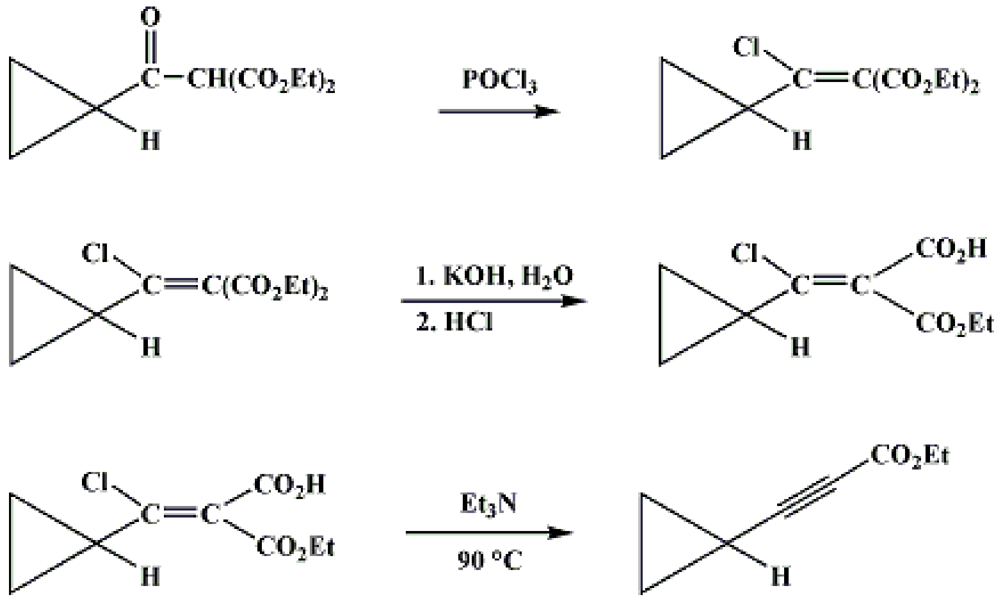
Organic Syntheses, CV 8, 247

UTILIZATION OF β-CHLORO ALKYLIDENE/ARYLIDENE MALONATES IN ORGANIC SYNTHESIS: ETHYL CYCLOPROPYLPROPIOLATE

[2-Propynoic acid, 3-cyclopropyl-, ethyl ester]



Submitted by Osmo Hormi[1]
Checked by David Oare and Clayton Heathcock.

1. Procedure

A. *Diethyl 2-chloro-2-cyclopropylethene-1,1-dicarboxylate*. A 1-L, two-necked flask equipped with magnetic stirrer, reflux condenser, and dropping funnel is charged with 166 g (0.73 mol) of diethyl cyclopropylcarbonylmalonate (Note 1) and 0.5 kg of phosphorus oxychloride (Note 2). The flask is cooled with a water bath, stirring is started and 135 g (0.73 mol) of tributylamine (Note 3) is added from the dropping funnel. The reaction is exothermic. When the addition is complete, the dropping funnel is replaced by a glass stopper and the water bath is replaced by an oil bath. The mixture is heated at 110°C with stirring for 5–6 hr.

Excess phosphorus oxychloride is removed as well as possible with a rotary evaporator under reduced pressure. The residue is cooled to room temperature and 300 mL of diethyl ether is added. The mixture is poured into a separatory funnel. Hexane is added until the two phases separate cleanly and the funnel is shaken vigorously. The phases are separated and the lower layer is extracted with three 250-mL portions of ether (Note 4). The combined organic layers are washed with 300 mL of cold aqueous 10% hydrochloric acid and 200 mL of aqueous 5% sodium hydroxide (Note 5) and then concentrated carefully with a rotary evaporator to give 136–156 g (70–87%) of crude diethyl 2-chloro-2-cyclopropylethene-1,1-dicarboxylate.[2]

B. The crude chloromalonate is dissolved in 100 mL of 95% ethanol and transferred to a 1-L, round-bottomed flask equipped with a magnetic stirring bar. Stirring is begun and a solution of potassium hydroxide in 350 mL of 95% ethanol (0.0035 mol of potassium hydroxide per gram of chloromalonate) (Note 6) is added dropwise from an additional funnel. A slightly exothermic reaction is noted. After the addition is complete, the mixture is stirred for 3 hr (or until the mixture is neutral to litmus; (Note 7)). Excess ethanol is removed with a rotary evaporator under reduced pressure and the residue is dissolved in

300 mL of water and extracted with 350 mL of ether (Note 8). The phases are separated and some ice is added to the aqueous phase. The cooled aqueous phase is acidified with concentrated hydrochloric acid and extracted with three 300-mL portions of ether. The ether phase is dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure with a rotary evaporator to give 72–94 g (70–80%) of crude monoester.

C. *Ethyl cyclopropylpropiolate*. The crude product is transferred to a 500-mL, round-bottomed flask equipped with a magnetic stirring bar and a reflux condenser. A solution of 0.70 mL of triethylamine (Note 9) per gram of crude monoester from Part B in about 200 mL of toluene is added. The mixture is heated using an oil bath at 90°C with stirring until the evolution of carbon dioxide has subsided, and is then heated for another hour (Note 10). The mixture is cooled to room temperature, and washed with 300 mL of aqueous 10% hydrochloric acid (Note 11) and finally with 300 mL of aqueous 5% sodium carbonate. The organic layer is dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure with a rotary evaporator. Fractional distillation of the residue gives the product, 87–95°C at 10 mm. The yield of the final step is 30–46 g (66–78%); the overall yield is 33–54% (Note 12).

2. Notes

1. Diethyl cyclopropylcarbonylmalonate is prepared by the procedure of Price and Tarbell[3] or Reynolds and Hauser.[4] On scale-up the checkers found that a slight modification is necessary. The procedure of Price and Tarbell was used:[3] 45 g (1.9 mol) of magnesium turnings, 1 mL of carbon tetrachloride, and approximately 20 mL of a solution of 281 mL (269 g, 1.9 mol) of diethyl malonate in 148 mL of absolute ethanol were combined. After the reaction begins, the addition of diethyl malonate solution is completed so that the reaction is maintained at a fairly vigorous rate. If the reaction subsides prior to the completion of the addition of the diethyl malonate solution, the addition is interrupted and a portion (300–400 mL) of the specified 550 mL of dry ether is added cautiously until the reaction resumes, whereupon the addition of the diethyl malonate solution is resumed. After the remainder of the diethyl malonate solution has been added and the reaction mixture cooled, the remaining dry ether is added cautiously and the mixture is worked up as described[3] using 350 mL of dry benzene. The residue is dissolved in 550 mL of dry ether and treated as described by Reynolds and Hauser[4] with 168 mL (194 g, 1.9 mol) of cyclopropanecarboxylic acid chloride in 230 mL of dry ether. After the addition is completed, an additional 40 mL of dry ether is added and the mixture is cooled and worked up as described[4] using 2 L of aqueous 25% sulfuric acid, 800 mL of ether, 600 mL of saturated aqueous sodium bicarbonate, 200 mL of water, and 100 mL of brine. The crude product is distilled (85–95°C; 0.05 mm) and 362 g (1.6 mol, 86%) of a clear liquid is obtained. ^{1}H NMR δ: 1.01 (m, 2 H), 1.20 (m, 2 H), 1.31 (t, 6 H, J = 7.1), 2.12 (tt, 1 H, J = 4.5, 7.8), 4.28 (q, 4 H, J = 7.1), 4.58 (s, 1 H).
2. Commercial phosphorus oxychloride was used without purification.
3. Commercial tributylamine was used without purification.
4. Extraction with a mixture of ether and hexane is repeated until ether and the lower layer readily separate.
5. Tributylamine is liberated from the lower layer by addition of sodium hydroxide.
6. Commercial potassium hydroxide (minimum 85.5% of potassium hydroxide) was used. The yield is based on potassium hydroxide.
7. Dilution of 1 mL of the mixture in 5 mL of water gave pH 7–8.
8. The ether phase is dried with anhydrous sodium sulfate, filtered, and concentrated with a rotary evaporator to give 32–46 g of recovered starting material.
9. Commercial triethylamine was used without purification.
10. The checkers found that this process requires approximately 24 hr.
11. Triethylamine is liberated from the water phase by addition of sodium hydroxide.
12. Cyclopropylpropiolic acid ethyl ester has the following spectra: ^{1}H NMR (CCl_4) δ: 0.84 and

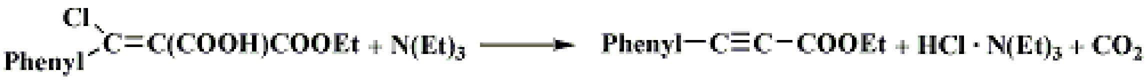
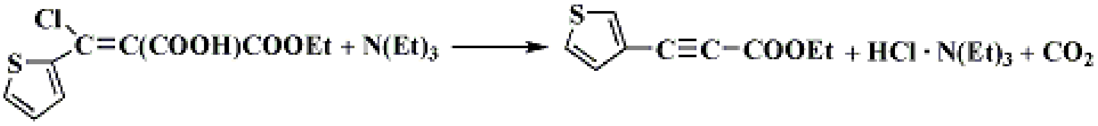
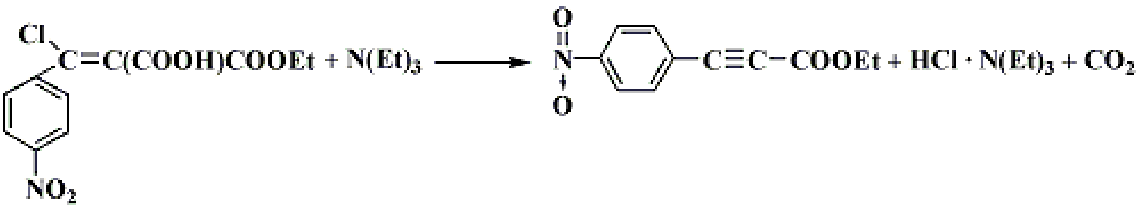
0.93 (4 H, ring CH_2), 1.25 (t, 3 H, CH_3 ester), the ring–CH is hidden under the ester CH_3-triplet, 4.05 (q, 2 H, CH_2 ester); IR (CCl_4) cm^{-1}: 2220 (C□C), m, 1710 (C=O), s, 1255 (C-O-C), s, 1030–1040 two bands (cyclopropyl), m, and 860–880 two bands (cyclopropyl), w; MS: M (calculated for $C_8H_{10}O_2$) 138.068, M^+ is not readily detected, 94 (20%), 93 (100%), 66 (65%), 65 (53%), 63 (10%), 53 (15%), 40 (10%).

3. Discussion

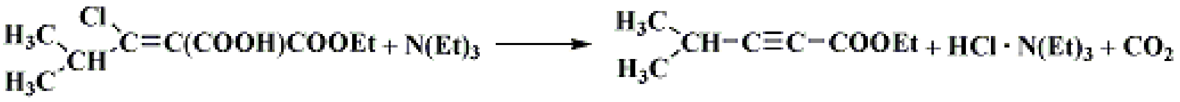
Substituted cyclopropyl rings conjugated with a triple-bond system have recently received attention as C_5 building blocks.[5] The procedure described here is a modification of the decarboxylation–elimination reaction for the preparation of α,β acetylenic acids from enol sulfonates of acyl malonates.[6,7,8] Addition of aqueous alkali to the enol sulfonate of diethyl cyclopropylcarbonylmalonate gives cyclopropylpropiolic acid, but the yield is low.

The major advantages of this procedure over the enol sulfonate procedure lie in the availability of diethyl 2-chloro-2-cyclopropylethene-1,1-dicarboxylate from the corresponding acylmalonate and phosphorus oxychloride, and the fast, homogeneous, decarboxylative elimination reaction of the triethylamine salt of the half-ester in dry organic solvents. The conditions described here, with slight modifications (overnight treatment), have been used for a variety of β-chloro alkylidene/arylidene malonates as shown in Table I.

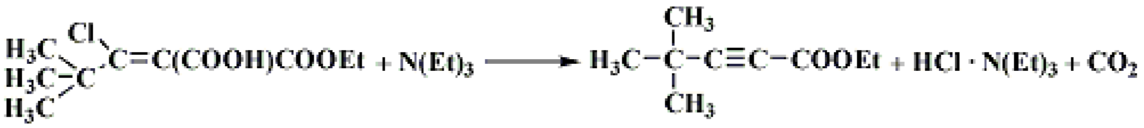
TABLE I
α,β-ACETYLENICESTERS FROMβ-CHLOROALKYLIDENEMALONATES

R	Yield (%)
Phenyl	
	80
2-Thienyl	
	90
p-NO_2-C_6H_4	
	70

Isopropyl

 67

tert-Butyl

 70

Sometimes the acetylenic ester rearranges to the corresponding allenic ester. For example, when the triethylamine salt of 3-chloro-2-ethoxycarbonyl-4-phenyl-2-hexenoic acid is refluxed in toluene, the allenic ester and acetylenic ester are obtained in a ratio of 3 : 7 (total yield 70%). There are alternative routes to cyclopropylpropiolic acids and esters, such as adding butyllithium to corresponding acetylenes and treating the product with carbon dioxide or methyl chloroformate.[5]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

brine

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether, diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

magnesium turnings (7439-95-4)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

carbon tetrachloride (56-23-5)

carbon dioxide (124-38-9)

Phosphorus Oxychloride (21295-50-1)

potassium hydroxide (1310-58-3)

toluene (108-88-3)

diethyl malonate (105-53-3)

butyllithium (109-72-8)

methyl chloroformate (79-22-1)

hexane (110-54-3)

triethylamine (121-44-8)

tributylamine (102-82-9)

Ethyl cyclopropylpropiolate, 2-Propynoic acid, 3-cyclopropyl-, ethyl ester (123844-20-2)

diethyl cyclopropylcarbonylmalonate (7394-16-3)

Diethyl 2-chloro-2-cyclopropylethene-1,1-dicarboxylate (123844-18-8)

cyclopropanecarboxylic acid chloride (4023-34-1)

cyclopropylpropiolic acid

triethylamine salt of 3-chloro-2-ethoxycarbonyl-4-phenyl-2-hexenoic acid

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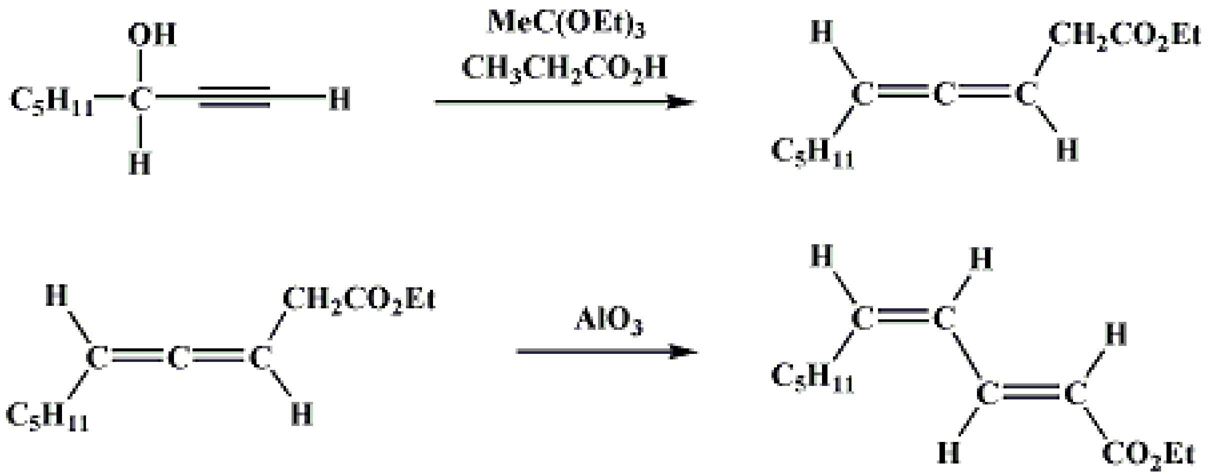
Organic Syntheses, CV 8, 251

ETHYL (*E*,*Z*)-2,4-DECADIENOATE

[2,4-Decadienoic acid, ethyl ester, (*E*,*Z*)-]



Submitted by S. Tsuboi, T. Masuda, S. Mimura, and A. Takeda[1].
Checked by Mark A. Henderson and Clayton H. Heathcock.

1. Procedure

Caution! See benzene warning, Org. Synth., Coll. Vol. VI ***1988***, *68.*

A. *Ethyl 3,4-decadienoate* ***(1)***.[2] A 300-mL, round-bottomed flask equipped with a reflux condenser is charged with 12.1 g (0.096 mol) of 1-octyn-3-ol (Note 1), 100 g (0.616 mol) of triethyl orthoacetate (Note 2), and 0.24 g (3.2 mmol) of propionic acid. The solution is heated at 140–150°C in an oil bath. Every 2 hr, the ethanol produced is removed under reduced pressure with a rotary evaporator, and then 10 g (0.0562 mol) of triethyl orthoacetate and 0.024 g (0.32 mmol) of propionic acid are added. The mixture is heated until the starting material is consumed (6–8 hr) (Note 3). Excess triethyl orthoacetate is removed under reduced pressure (Note 4). The residue is distilled under reduced pressure to give 15.4–17.2 g (82–91%) of **1** (Note 5) as a clean oil, bp 80–85°C (0.3 mm).

B. *Ethyl (E,Z)-2,4-decadienoate* ***(2)***. A dry, 500-mL, round-bottomed flask is charged with 50 g of aluminum oxide (Note 6) and heated at 200°C for 2 hr under reduced pressure (0.05 mm). The flask is fitted with a reflux condenser connected to a nitrogen line and a heavy magnetic stirring bar is added (Note 7); the flask is flushed with nitrogen. With positive nitrogen pressure, the flask is charged with 200 mL of benzene (Note 8) and 15.4–17.2 g (78–88 mmol) of allenic ester 1. The mixture is heated at reflux temperature with vigorous stirring for 5 hr. The aluminum oxide is removed by filtration with suction through a sintered-glass funnel of medium porosity and

thoroughly washed with 100 mL of ethyl acetate (Note 9). The combined filtrate is concentrated with a rotary evaporator to afford 11.6–13.6 g (75–88%) of nearly pure **2** as a clean oil (Note 10) and (Note 11), bp 83–88°C (0.1 mm).

2. Notes

1. 1-Octyn-3-ol was used as supplied by Aldrich Chemical Company, Inc. (96% purity).
2. Triethyl orthoacetate was used as supplied by Aldrich Chemical Company, Inc. (97% purity) or by Tokyo Kasei Kogyo Co., Ltd. (98% purity).
3. The checkers removed the ethanol with a rotary evaporator and replaced it with fresh triethyl orthoacetate (10 g) and propionic acid (0.024 g) after 2, 4, and 6 hr.
4. The checkers removed excess triethyl orthoacetate under reduced pressure (0.05 mm) overnight. The recovered material may be easily purified by distillation and reused.
5. The product might contain trace amounts of triethyl orthoacetate, but it can be used for the next step since aluminum oxide adsorbs triethyl orthoacetate. The product[2] is characterized by IR (neat) cm^{-1}: 1970 and 1740; ^1H NMR (CCl_4) δ: 0.92 (t, 3 H, $CH_3(CH_2)_4$), 1.29 (t, 3 H, OCH_2CH_3), 1.32 (m, 6 H, $CH_3(CH_2)_3$), 1.91 (m, 2 H, CH_2CH=), 2.90 (m, 2 H, CH_2CO_2Et), 4.08 (q, 2 H, $CO_2CH_2CH_3$), 5.09 (m, 2 H, CH=C=CH).
6. Weakly basic alumina[3] (200–300 mesh) for column chromatography is used. The checkers used Alumina Woelm-B, Akt. 1.
7. Efficient stirring is essential to the success of this reaction.
8. Aprotic solvents such as xylene, chlorobenzene, and toluene can be used instead of benzene. If the boiling point of the product is close to that of the solvent, the mixture of aluminum oxide and the allene may be heated to distil at ca. 150°C under an atmosphere of nitrogen.
9. The checkers found that the use of more than 100 mL of ethyl acetate gives a less pure final product.
10. Gas-chromatographic analysis (capillary column coated Thermon-1000, 30 m, 140°C) indicated that the product was ca. 93% pure. Impurities consisted of the 2*E*, 4*E* isomer (5%) and an unidentified compound (2%).
11. The proton magnetic resonance spectrum is as follows (CCl_4) δ: 0.90 (t, 3 H, J = 6, $CH_3(CH_2)_4$), 1.28 (t, 3 H, J = 7, $CO_2CH_2CH_3$), 1.40 (m, 6 H, $CH_3(CH_2)_3CH_2$), 1.9–2.6 (m, 2 H, CH_2CH=CH), 4.12 (q, 2 H, J = 7, $CO_2CH_2CH_3$), 5.4–6.3 (m, 3 H, CH=CH-CH=$CHCO_2Et$), 7.46 (dd, 1 H, J = 10 and 15, CH=$CHCO_2Et$); n_D^{25} 1.4895.

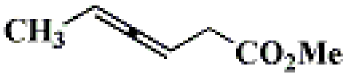
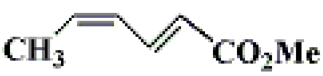
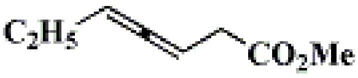
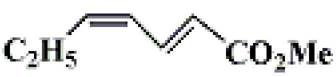
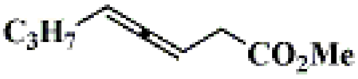
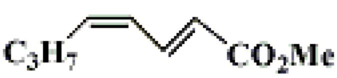
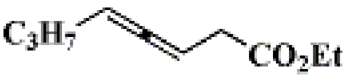
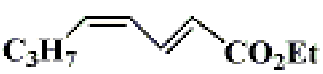
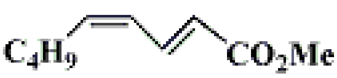
3. Discussion

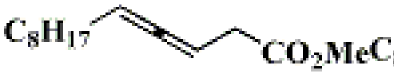
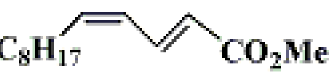
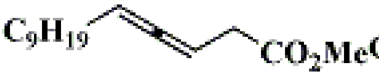
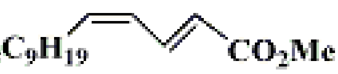
Ethyl (*E*,*Z*)-2,4-decadienoate has been prepared in several ways: (a) the addition of lithium di-(*Z*)-1-heptenylcuprate to ethyl propiolate[4] [90% yield, 95% purity; 27–32%

overall yield based on (*Z*)-1-bromoheptene],[5] (b) the reaction of 1-heptneylmagnesium bromide with ethyl (*E*)-β-(*N*,*N*-diethylamino)acrylate (32% yield, 89% purity),[6] and (c) the Wittig reaction of hexyltriphenylphosphonium bromide with ethyl (*E*)-4-oxo-2-butenoate (68% yield, 85% purity).[7] These known methods involving the use of organometallic reagents need anhydrous conditions at low temperatures (−8 to −40°C). Occasionally the separation of triphenylphosphine oxide from the reaction mixture in a Wittig reaction is not easy.

The present procedure offers an experimentally simple and less expensive preparation of ethyl (*E*,*Z*)-2,4-decadienoate under essentially neutral conditions. It allows large-scale preparation since the starting materials are not sensitive to air or moisture. In addition, the reaction proceeds stereoselectively, and the yields of product are generally high. Several examples are listed in Table I to show the scope of the method.

TABLE I
REARRANGEMENT OF β-ALLENIC ESTERS TO (*E*,*Z*)-2,4-DIENOIC ESTERS WITH ALUMINA[2]

Starting Material	Product	Yield (%)[a]	Purity (%)[b]
		57	90
		82	96
		80	96
		69	93
		87	93
		82	99

		87	91
		70	96

[a]Isolated yield.

[b]Purity determined by gas chromatography.

There are many compounds containing a conjugated (*E*,*Z*)-diene structure in naturally occurring compounds such as flavors,[3,8] insect pheromones,[3,9] and leukotrienes.[10] The present procedure has been used for the syntheses of bombykol,[3] megatomoic acid,[11] (±)-leukotriene A_4 methyl ester,[12] and (*E*,*Z*)-2,4-dienamides.[13]

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9. For example, see: Rossi, R. *Synthesis* **1977**, 817.
10. For example, see: Rokach, J.; Adams, J. *Acc. Chem. Res.* **1985**, *18*, 87; Hashimoto, S.; Toda, M. *Yuki Gosei Kagaku Kyokaishi* **1983**, *41*, 221; *Chem. Abstr.* **1983**, *98*, 191841*f*.
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alumina

1-heptneylmagnesium bromide

ethanol (64-17-5)

Benzene (71-43-2)

ethyl acetate (141-78-6)

propionic acid (79-09-4)

nitrogen (7727-37-9)

chlorobenzene (108-90-7)

toluene (108-88-3)

xylene (106-42-3)

aluminum oxide (1344-28-1)

ethyl (E)-4-oxo-2-butenoate (2960-66-9)

triethyl orthoacetate (78-39-7)

ethyl propiolate (623-47-2)

(E,Z)-2,4-D (94-75-7)

triphenylphosphine oxide (791-28-6)

1-octyn-3-ol (818-72-4)

Ethyl 3,4-decadienoate (36186-28-4)

Ethyl (E,Z)-2,4-decadienoate, 2,4-Decadienoic acid, ethyl ester, (E,Z)- (3025-30-7)

hexyltriphenylphosphonium bromide (4762-26-9)

lithium di-(Z)-1-heptenylcuprate

(Z)-1-bromoheptene

ethyl (E)-β-(N,N-diethylamino)acrylate

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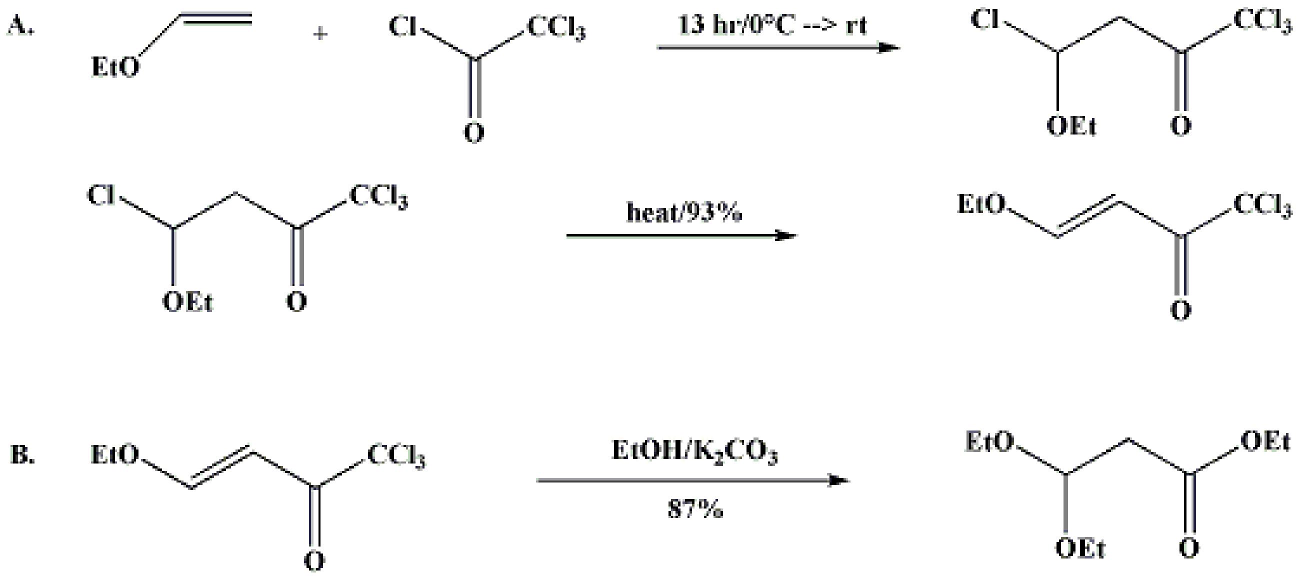
SYNTHESIS OF ALKYL PROPANOATES BY A HALOFORM REACTION OF A TRICHLORO KETONE: ETHYL 3,3-DIETHOXYPROPANOATE

[Propanoic acid, 3,3-diethoxy-, ethyl ester]



Submitted by L. F. Tietze, E. Voss, and U. Hartfiel[1].
Checked by Daniel Romo and Albert I. Meyers.

1. Procedure

A. *1,1,1-Trichloro-4-ethoxy-3-buten-2-one* ***(4)***.[2] A 500-mL, two-necked, round-bottomed flask equipped with a pressure-equalizing addition funnel with drying tube, nitrogen inlet, and magnetic stirring bar is charged with trichloroacetyl chloride, **2** (173 g, 0.96 mol) (Note 1). Under nitrogen the flask is cooled with an ice bath to 0°C and ethyl vinyl ether (137 g, 181 mL, 1.90 mol, (Note 2)) is added within 1 hr to the well-stirred mixture. Stirring is continued for 12 hr, allowing the mixture to warm to room temperature without removing the cooling bath (Note 3). The addition funnel is replaced by a short Vigreux column and excess ethyl vinyl ether is removed at 20°C under reduced pressure (20 mm). The bath temperature is raised (to ca. 140°C) under reduced pressure (20 mm) to start elimination of hydrogen chloride, which is accompanied by formation of a deep black color and requires 1–2 hr for completion. Distillation of the residue under reduced pressure affords 193 g (92%) of **4**,[3] as a bright-yellow oil that fades to pale yellow on standing, bp 116–118°C/13 mm, n_D^{24} 1.5129 (Note 4) and (Note 5).

B. *Ethyl 3,3-diethoxypropanoate* ***(5)***. A 500-mL, two-necked, round-bottomed flask equipped with magnetic stirring bar, a reflux condenser with a drying tube, and a 250-mL pressure-equalizing addition funnel is charged with dry ethanol (200 mL, 3.4 mol) and anhydrous potassium carbonate (12 g, 87 mmol) and cooled with an ice–water bath. The addition funnel is charged with 1,1,1-trichloro-4-ethoxy-3-buten-2-one, 4 (200 g, 0.92 mol) and the addition is performed with stirring during 30 min. Stirring is continued for 10 hr at room temperature, petroleum ether or pentane (300 mL) is added, and the potassium carbonate is filtered off. After concentration under reduced pressure the residue is distilled through a short Vigreux column to yield 153 g (87%) of **5**, bp 92–95°C/15 mm,

n_D^{24} 1.4117 (Note 6) and (Note 7).

2. Notes

1. Trichloroacetyl chloride (obtained from Fluka Chemical Corporation) was distilled immediately before use.
2. Ethyl vinyl ether (obtained from Fluka Chemical Corporation) was used from a freshly opened bottle containing a stabilizer (0.1% diethylaniline) without purification. The stabilizer seems to be important (see (Note 7)).
3. An exothermic reaction was observed after removing the ice bath.
4. Distillation should not be performed at a lower pressure.
5. The synthesis of **4** can be carried out on a large scale: a run using 1.8 kg of trichloroacetyl chloride gave **4** in 97% yield. The spectral properties are as follows: IR (neat) cm^{-1}: 2990 (C-H), 1710 (C=O), 1600 (C=C), 835 (C-Cl); ^1H NMR (60 MHz, $CDCl_3$) δ: 1.38 (t, 3 H, *J* = 7, OCH_2CH_3), 4.08 (q, 2 H, *J* = 7, OCH_2CH_3), 6.13 (d, 1 H, *J* = 12.4, 3-H), 7.87 (d, 1 H, *J* = 12.4, 4-H).
6. Distillation should be performed only within the indicated temperature range. Approximately 20 mL of a dark residue remains after distillation. The spectral properties are as follows: IR (neat) cm^{-1}: 2990, 2940 (C-H), 1740 (C=O), 1115, 1060 (C-O); ^1H NMR (60 MHz, $CDCl_3$) δ: 1.18 (t, 6 H, *J* = 7, OCH_2CH_3), 1.25 (t, 3 H, *J* = 7, $CO_2CH_2CH_3$), 2.62 (d, 2 H, *J* = 6, 2-H), 3.30–3.80 (2 AB systems, 4 H, 2 OCH_2CH_3), 4.13 (q, 2 H, *J* = 7, $CO_2CH_2CH_3$), 4.93 (t, 1 H, *J* = 6, 3-H).
7. In a similar way, methyl 3,3-dimethoxypropanoate can be prepared using trichloroacetyl chloride and methyl vinyl ether as starting materials. However, in this case, using methyl vinyl ether without a stabilizer, it is necessary to perform the reaction in the presence of pyridine; otherwise extensive polymerization of the vinyl ether takes place.
Procedure. A 1000-mL, three-necked, round-bottomed flask equipped with a pressure-equalizing addition funnel with drying tube, intensive condenser (cryostat temp., –5°C) with nitrogen inlet, and mechanical stirrer, is charged with 2 (270 g, 1.48 mol); pyridine (117 g, 1.48 mol) is added within 15 min under vigorous stirring at room temperature. Under nitrogen, the flask is cooled with an ice bath to −10°C and liquid methyl vinyl ether (112 g, ca. 145 mL, 1.93 mol) is added through a coolable addition funnel (ca. −10°C) within 30 min to the well-stirred mixture. Stirring is continued for 12 hr, allowing the mixture to warm to room temperature without removing the cooling bath. After addition of water (250 mL) and extraction with diethyl ether (2 × 200 mL), the combined organic layers are washed with brine (2 × 50 mL), dried (Na_2SO_4), and the solvent evaporated under reduced pressure. Distillation (20-cm Vigreux column) of the residue under reduced pressure affords 267 g (88%) of 1,1,1-trichloro-4-methoxy-3-buten-2-one as a colorless liquid, bp 102°C at 10 mm, n_D^{20} 1.5238. The spectral properties are as follows: IR (neat) cm^{-1}: 2940, 2840 (C-H), 1710 (C=O), 1600 (C=C); ^1H NMR (60 MHz, $CDCl_3$) δ: 3.80 (s, 3 H, OCH_3), 6.03 (d, 1 H, *J* = 12, 3-H), 7.77 (d, 1 H, *J* = 12, 4-H). Solvolysis of 1,1,1-trichloro-4-methoxy-3-buten-2-one with methanol to give methyl 3,3-dimethoxypropanoate can be performed according to the procedure given for **5**.

3. Discussion

The synthesis of ethyl 3,3-diethoxypropanoate **(5)** described here implies acylation of an enol ether followed by a haloform reaction. The procedure is superior to other methods, which afford mixtures of acetals and acrylates,[4] give only moderate yields,[5,6,7] require the troublesome use of ketene[8] or expensive ethyl propiolate,[9,10,11] need palladium(II) catalysis,[12] or equipment for electrochemical

reactions.[13]

Ethyl 3,3-diethoxypropanoate **(5)** is the stable, protected derivative of the unstable 3-formylpropanoate. It can be stored at room temperature for several months without decomposition. It is a useful starting material, especially for the synthesis of heterocycles such as coumarins,[14] isoxazoles,[15] pyrimidines,[16] porphyrins,[17] and thiadiazines.[18] Also spermine metabolites,[19] steroids,[20] herbicides,[21] antihypertensives,[22] photographic sensitizers,[23] cephalosporins,[24] lycopodium alkaloids,[25] nucleic acids,[5] and pentaerythritol[26] as well as related alcohols can be obtained from **5**. Thus ester **5** can be reduced to the corresponding alcohol, which yields 3-hydroxypropanal with acidic conditions;[26] elimination of ethanol gives 3-ethoxyacrylate.[27] Of great interest is also the formylation of **5** to give ethyl 2-formyl-3-oxopropanoate or, starting from methyl 3,3-dimethoxypropanoate, methyl 2-formyl-3-oxopropanoate.[10,28] The latter compound has been used in the synthesis of iridoids,[28] ipecacuanha alkaloids,[29] 1,4-dihydropyridines,[29] NADH analogs,[30] dihydropyrans,[31] and branched amino sugars.[32]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

ethanol (64-17-5)

potassium carbonate (584-08-7)

hydrogen chloride (7647-01-0)

methanol (67-56-1)

diethyl ether (60-29-7)

Na_2SO_4 (7757-82-6)

nitrogen (7727-37-9)

pyridine (110-86-1)

Pentane (109-66-0)

Pentaerythritol (115-77-5)

diethylaniline (91-66-7)

methyl vinyl ether (9003-09-2)

ethyl vinyl ether (109-92-2)

ethyl propiolate (623-47-2)

trichloroacetyl chloride (76-02-8)

vinyl ether (109-93-3)

methyl 2-formyl-3-oxopropanoate

methyl 3,3-dimethoxypropanoate (7424-91-1)

Palladium(II)

Ethyl 3,3-diethoxypropanoate, Propanoic acid, 3,3-diethoxy-, ethyl ester (10601-80-6)

1,1,1-Trichloro-4-ethoxy-3-buten-2-one (83124-74-7)

1,1,1-trichloro-4-methoxy-3-buten-2-one (138149-14-1)

3-formylpropanoate

3-hydroxypropanal (2134-29-4)

3-ethoxyacrylate

ethyl 2-formyl-3-oxopropanoate

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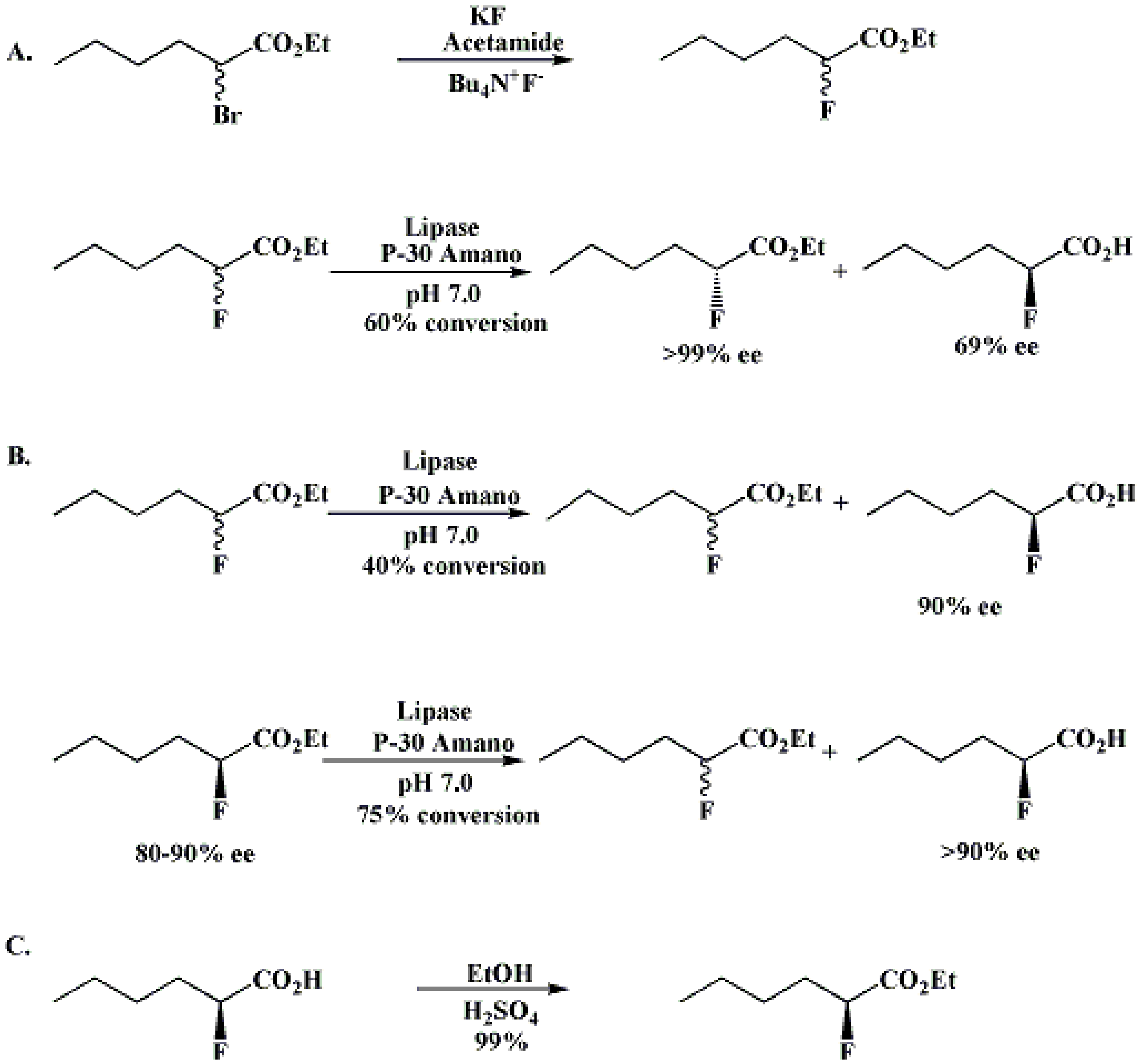
ENANTIOMERICALLY PURE ETHYL (*R*)- AND (*S*)- 2-FLUOROHEXANOATE BY ENZYME-CATALYZED KINETIC RESOLUTION

[Hexanoic acid, 2-fluoro-, ethyl ester, (*R*)- and (*S*)-]



Submitted by P. Kalaritis and R. W. Regenye[1].
Checked by Ronan Guevel and Leo A. Paquette.

1. Procedure

For preparation of ethyl 2-fluorohexanoate (Note 1), a 1-L flask equipped with a mechanical stirrer, thermometer, condenser and a gas adapter is charged under an atmosphere of argon with 38.5 g of acetamide and 80 g (0.36 mol) of ethyl 2-bromohexanoate (Note 2). The mixture is heated to 80°C until solution is effected and 38.6 g (0.65 mol) of potassium fluoride (Note 3) is added to it followed by 2.7 mL of tetra-*n*-butylammonium fluoride (Note 4). The resulting

mixture is heated at 140°C with rapid stirring for 4–5 (Note 5). The reaction mixture is allowed to cool to 90°C and then is poured into 600 mL of ice. The reaction flask is rinsed with 100 mL of water and 100 mL of dichloromethane, which are added to the ice mixture. The aqueous phase is extracted with dichloromethane (4 × 200 mL). The combined organic layers are dried over anhydrous sodium sulfate and filtered. The dichloromethane solution is then cooled to 5°C and treated under an atmosphere of argon with 15 mL of bromine (Note 6). The reaction is judged complete after ca. 3 hr. It is quenched by adding 200 mL of saturated sodium thiosulfate solution. The two phases are separated and the organic phase is successively partitioned with saturated aqueous sodium bicarbonate solution (2 × 150 mL) and then with 200 mL of brine. It is finally dried over anhydrous sodium sulfate and concentrated to an oil at 40°C / 7 mm (Note 7). Vacuum distillation at 36–37°C / 0.8-0.9 mm affords 26.2–31.4 g (45–54% yield) of pure ethyl 2-fluorohexanoate as a colorless liquid (Note 8).

Method A. *Enantiomerically pure ethyl (R)-2-fluorohexanoate (60% hydrolysis)*. A 1-L Morton flask equipped with a mechanical stirrer, a glass baffle, an electrode connected to a pH control unit, and an addition tube connected to a syringe pump is charged with 300 mL of 0.05 *M* aqueous phosphate buffer (pH 7.0) (Fisher), 300 mL of deionized water, and 70 g (0.43 mol) of ethyl 2-fluorohexanoate. The resulting mixture is stirred for several minutes and the pH is adjusted to 7.0 with the addition of a few drops of 0.1 *N* sodium hydroxide solution. Then 0.43 g of Pseudomonas lipase enzyme (P-30, Amano International Enzyme Co., Inc., Troy, VA) is added and the hydrolysis is allowed to proceed at 5°C with stirring (reaction time ca. 2 hr). The pH is kept constant at 7.0 by adding 0.1 *N* sodium hydroxide solution via the syringe pump, which is activated by the pH control unit. The hydrolysis is discontinued when 260 mL of 1.0 *N* sodium hydroxide solution has been added (60% conversion, (Note 9)). The mixture is extracted with diethyl ether (5 × 300 mL). The combined organic layers are dried over anhydrous potassium carbonate, filtered, and concentrated at 40°C / 70 mm. Vacuum distillation at 36–38°C / 0.7–0.8 mm gives 24.0 g (34% yield, 85% of theory, (Note 10)) of pure ethyl (*R*)-2-fluorohexanoate, which is 97.5–99% enantiomerically pure, $[\alpha]_D^{25}$ + 13.0 to + 13.2° ($CHCl_3$, *c* 1.3) (Note 9). The aqueous layer is acidified to pH 2 with 3 *N* hydrochloric acid and extracted with diethyl ether (3 × 500 mL). The combined organic layers are dried over anhydrous sodium sulfate, filtered, and concentrated at 40°C / 70 mm. The residue is distilled at 71–72°C / 0.7 mm to give 30.9 g (53% yield: 89% of theory) of (*S*)-2-fluorohexanoic acid, which is 53–68% enantiomerically pure (Note 11) $[\alpha]_D^{25}$ −6.8 to −8.7° ($CHCl_3$, *c* 1.3).

Method B. *Enantiomerically pure ethyl (S)-2-fluorohexanoate*. A 1-L, three-necked flask equipped with a mechanical stirrer, a glass baffle, an electrode connected to a pH control unit, and an addition tube connected to a syringe pump is charged with 300 mL of deionized water, 300 mL of 0.05 *M* phosphate buffer (pH 7.0) (Fisher), and 80 g (0.49 mol) of racemic ethyl 2-fluorohexanoate. The pH is adjusted to 7.0 with a few drops of 1 *N* aqueous sodium hydroxide solution, and 23 mg of Pseudomonas lipase enzyme (P-30, Amano International) is added to the mixture. The hydrolysis is allowed to proceed at 5–10°C with stirring. The pH is maintained at 7.0 by adding adequate 1 *N* aqueous sodium hydroxide solution via the syringe pump. The hydrolysis is discontinued when 197 mL (40% conversion) of 1 *N* aqueous sodium hydroxide solution has been added (total reaction time: 2.5 hr). The reaction mixture is immediately transferred to an extractor containing 750 mL of ethyl ether. The mixture is agitated for 5 min and the two phases are separated. The aqueous phase is extracted with ethyl ether (3 × 400 mL). The combined organic layers are dried over anhydrous potassium carbonate, filtered, and concentrated at 30°C/70 mm to afford 47.2 g (98% of theory) of

optically active ethyl (*R*)-2-fluorohexanoate. The aqueous phase is transferred back into the extractor and carefully acidified to pH 2.0 with concentrated hydrochloric acid. It is subsequently extracted with diethyl ether (4 × 500 mL). The combined organic layers are dried over anhydrous sodium sulfate and concentrated at 30°C/70 mm to provide 26.1 g (39% yield; 98% of theory) of (*S*)-2-fluorohexanoic acid (81–86% ee).

Optical Purity Enhancement. A 1-L, three-necked flask equipped as described above is charged with 28.4 g (0.175 mol) of ethyl (*S*)-2-fluorohexanoate (81% ee) (Note 12), 300 mL of deionized water and 300 mL of 0.05 *M* phosphate buffer (pH 7.0). The pH is adjusted to 7.0 with a few drops of 1 *N* aqueous sodium hydroxide solution and 36 mg of Pseudomonas lipase enzyme (P-30, Amano International) is added to the mixture. The hydrolysis is allowed to proceed at 5°C. The pH is kept at 7.0 by adding adequate 1 *N* aqueous sodium hydroxide solution via the syringe pump. The hydrolysis is discontinued when 131.3 mL (75% conversion) of 1 *N* aqueous sodium hydroxide solution has been added (total reaction time: 4 hr). The mixture is quickly extracted with ethyl ether (3 × 500 mL). The combined organic layers are dried over anhydrous potassium carbonate and concentrated at 35°C/70 mm to provide 5.66 g of nearly racemic ethyl 2-fluorohexanoate. The aqueous phase is acidified to pH 2.0 with concentrated hydrochloric acid and extracted with ethyl ether (4 × 500 mL). The combined organic layers are dried over anhydrous sodium sulfate and concentrated at 35°C/70 mm to give 16.8 g (71% yield; 95.5% of theory) of (*S*)-2-fluorohexanoic acid. This acid is distilled at 67°C/0.4–0.5 mm to give 14.2 g of enantiomerically pure (*S*)-2-fluorohexanoic acid as a colorless oil: $[\alpha]_D^{25}$ −13.8° ($CHCl_3$, *c* 1.7) (Note 11) and (Note 13).

Method C. *Esterification of (S)-2-fluorohexanoic acid*. A 250-mL flask is charged with 13.8 g of (*S*)-2-fluorohexanoic acid, 200 mL of ethanol, and 2 mL of concentrated sulfuric acid. The solution is heated at reflux for 4 hr. Most of the ethanol is distilled slowly at atmospheric pressure and the residue is dissolved in 200 mL of dichloromethane after allowing it to cool to 23°C. The solution is partitioned with 200 mL of saturated aqueous sodium bicarbonate solution and the aqueous layer is back-extracted with 100 mL of dichloromethane. The combined organic layers are washed with 100 mL of brine, dried over anhydrous potassium carbonate, and concentrated at 30°C/70 mm to afford 15.6 g (93% yield) of enantiomerically pure (Note 11) ethyl (*S*)-2-fluorohexanoate as a colorless liquid: $[\alpha]_D^{25}$ −13.8° ($CHCl_3$, *c* 1.0), chemical purity 100% (GC analysis).

2. Notes

1. This procedure was originally used by P. Rosen, G. Holland, and R. J. Karasiewicz at Hoffmann-La Roche. A similar procedure has appeared in the literature.[2]
2. Ethyl 2-bromohexanoate was purchased from Aldrich Chemical Company, Inc.
3. Potassium fluoride was purchased from Fluka and was ground to a fine powder prior to use.
4. Tetra-*n*-butylammonium fluoride was purchased from Aldrich Chemical Company, Inc.
5. The progress of the reaction was monitored by gas chromatography on an OV-17 column at 100–250°C (20°/min).
6. Bromine was added dropwise keeping the temperature below 10°C at all times. The progress of the reaction was monitored by gas chromatography as described in (Note 4). Bromine was added to brominate the α,β-unsaturated ester that was present as a product

in the crude material. This procedure simplified the isolation of the ethyl 2-fluorohexanoate by distillation.

7. Some yellow solids appeared on removing the solvent; they were filtered prior to distillation.

8. The purity of ethyl 2-fluorohexanoate was determined by gas chromatography as described above. The reaction yield varied from 42 to 70%.

9. Percent conversion is based on the amount of base added.

10. Percent theoretical yield is based on percent conversion.

11. The enantiomeric excess (% ee) of these compounds was determined by the submitters as follows. The ester and acids were first reduced to the corresponding alcohols with DIBAL and LAH, respectively. The alcohols were then allowed to react with 100% excess of (*S*)-(+)-α-methoxy-α-trifluoromethylphenylacetyl chloride (Mosher's reagent) in (1 : 1) pyridine–carbon tetrachloride for 18 hr. The diastereomeric ratio of these derivatives was finally determined by isothermal gas chromatography on a capillary OV-17 column at 160°C.

12. This ester was prepared from the optically active (*S*)-2-fluorohexanoic acid isolated above, by the esterification method described in this procedure.

13. The checkers have noted that the 2-fluorohexanoic acid crystallizes when allowed to stand at room temperature. This material can be recrystallized from pentane at low temperature. The crystals liquify on standing in the open air at room temperature.

3. Discussion

In recent years there has been an increasing interest in the use of enzymes and microorganisms to produce optically active compounds by means of either a kinetic resolution or stereospecific chemical transformations (e.g., reductions, oxidations, epoxidations, hydroxylations).[3] Hydrolases in general have been used to effect kinetic resolutions of racemic esters and alcohols via their corresponding esters.[4] Lipases, a subclass of hydrolases, are commercially available and relatively inexpensive. As a result, they constitute a very attractive class of catalysts for effecting kinetic resolutions, some of which might be difficult by other means.

Lipase P-30 Amano (ex *Pseudomonas fluorescens*) has been found to be synthetically useful in catalyzing very effectively kinetic resolutions of both racemic alcohols and racemic acids via their corresponding esters. This property is seldom observed with other enzymes and, therefore, makes this particular enzyme of greater synthetic utility. The enzyme can tolerate high concentrations of substrates and their hydrolysis products. The rates of the hydrolyses have usually been fast and the enantiomeric excesses achieved high. In most cases, the hydrolyses have been carried out in water and in the absence of cosolvents. These resolutions can be easily accomplished in multikilogram scale. A wide variety of substrates have been resolved enantioselectively with this lipase.[5]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

brine

ETHYL (R)- AND (S)- 2-FLUOROHEXANOATE

Hexanoic acid, 2-fluoro-, ethyl ester, (R)- and (S)-

ethanol (64-17-5)

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

Acetamide (60-35-5)

ethyl ether, diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

bromine (7726-95-6)

sodium sulfate (7757-82-6)

sodium thiosulfate (7772-98-7)

Pentane (109-66-0)

dichloromethane (75-09-2)

potassium fluoride (7789-23-3)

argon (7440-37-1)

tetra-n-butylammonium fluoride (429-41-4)

Ethyl 2-fluorohexanoate (17841-31-5)

ethyl 2-bromohexanoate (615-96-3)

ethyl (R)-2-fluorohexanoate (124439-29-8)

ethyl (S)-2-fluorohexanoate (124439-31-2)

(S)-2-fluorohexanoic acid (113776-26-4)

2-Fluorohexanoic acid

(S)-(+)-α-methoxy-α-trifluoromethylphenylacetyl chloride (20445-33-4)

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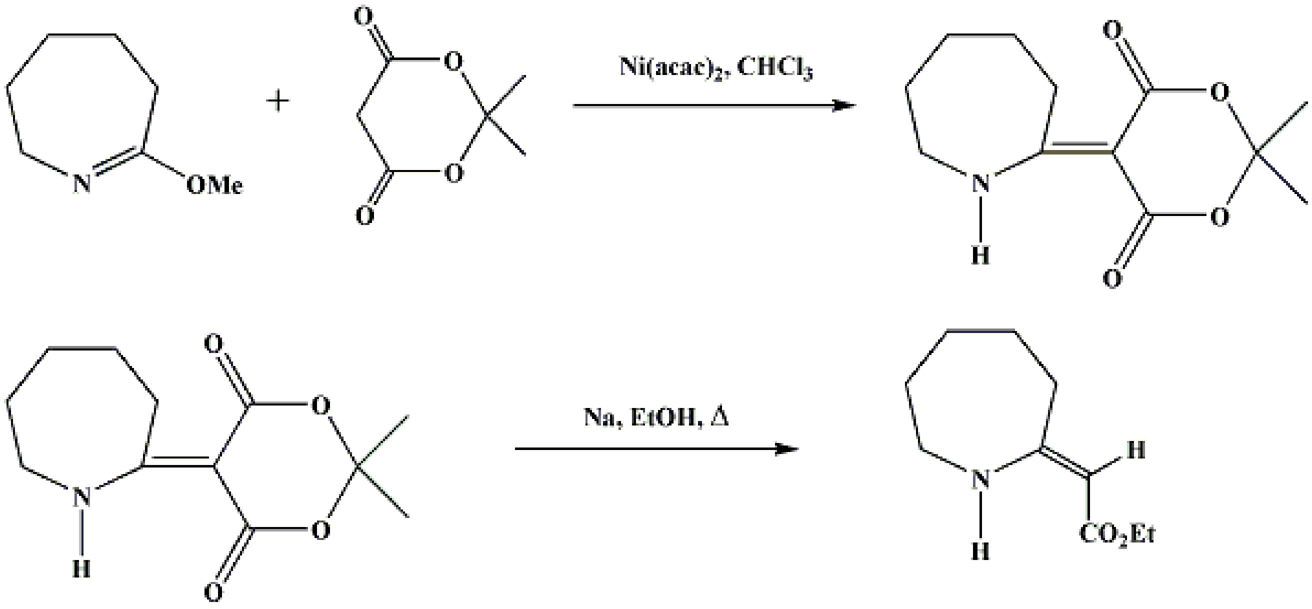
ETHYL α-(HEXAHYDROAZEPINYLIDENE-2)ACETATE FROM *O*-METHYLCAPROLACTIM AND MELDRUM'S ACID

[Acetic acid, (hexahydro-2*H*-azepin-2-ylidene)-, ethyl ester, (*Z*)-]



Submitted by J. P. Celerier, E. Deloisy-Marchalant, G. Lhommet, and P. Maitte[1].
Checked by Ting-Zhong Wang and Leo A. Paquette.

1. Procedure

A. *Isopropylidene α-(hexahydroazepinylidene-2)malonate*. In a 1-L, round-bottomed flask fitted with an efficient reflux condenser and equipped with a magnetic stirrer are placed 50.8 g (0.40 mol) of *O*-methylcaprolactim (Note 1), 57.6 g (0.40 mol) of Meldrum's acid (Note 2), and 0.25 g of nickel acetylacetonate monohydrate (Note 3) in 500 mL of anhydrous chloroform. The reaction mixture is refluxed for 12 hr. The solvent is removed with a rotary evaporator and the bright-yellow precipitate is recrystallized from absolute ethanol to give 77–78 g (81–82%) of pale-yellow crystals, mp 147–149°C (Note 4).

B. *Ethyl α-(hexahydroazepinylidene-2)acetate*. A solution of sodium ethoxide is prepared from 8.3 g (0.36 mol) of freshly cut sodium and 600 mL of freshly distilled absolute ethanol (Note 5) in a 1-L, round-bottomed flask equipped with a magnetic stirrer and fitted with a reflux condenser. To the stirred solution is added in one portion 71.7 g (0.30 mol) of freshly recrystallized isopropylidene α-(hexahydroazepinylidene-2)malonate. The mixture is refluxed and a white precipitate begins to appear. Refluxing is continued for 12 hr. The solvent is removed with a rotary evaporator and the white precipitate is placed in a 2-L beaker. Water (300 mL) is added and a 1 *N* hydrochloric solution is added dropwise to pH 6. The reaction mixture is extracted with four 100-mL portions of chloroform. The extracts are dried over anhydrous sodium sulfate and the solvent is removed with a rotary evaporator. The yellow solid residue is recrystallized from methanol to give 43–44 g (78–80%) of white powder, mp 55–56°C (Note 6).

2. Notes

1. *O*-Methylcaprolactim (1-aza-2-methoxy-1-cycloheptene) is available from the Janssen Chimica Society (France) and from the Aldrich Chemical Company, Inc. It may be also prepared from ε-caprolactam and dimethyl sulfate.[2]
2. Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) is available from the Janssen Chimica Society

(France) or can be prepared from malonic acid and acetone.[3] The checkers purchased Meldrum's acid from the Aldrich Chemical Company, Inc.

3. Nickel acetylacetonate monohydrate is a better basic catalyst than triethylamine for the condensation of Meldrum's acid and the lactim ether. The yields are higher and the product is easier to purify.

4. The submitters report mp 145–147°C.

5. Absolute ethanol must be freshly distilled to obtain good yields in the transesterification.

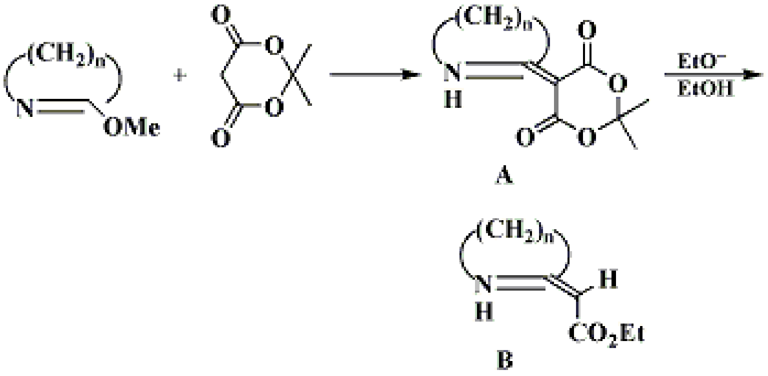
6. The submitters report mp 48–50°C. The product, ethyl α-(hexahydroazepinylidene-2)acetate, shows a *Z* geometry. The ^{1}H NMR (300 MHz) spectrum of this compound is as follows: δ: 1.22 (t, 3 H, *J* = 7.1), 1.65 (m, 6 H), 2.25 (m, 2 H), 3.25 (m, 2 H), 4.06 (q, 2 H, *J* = 7.1), 4.42 (s, 1 H), 8.83 (br s, 1 H).

3. Discussion

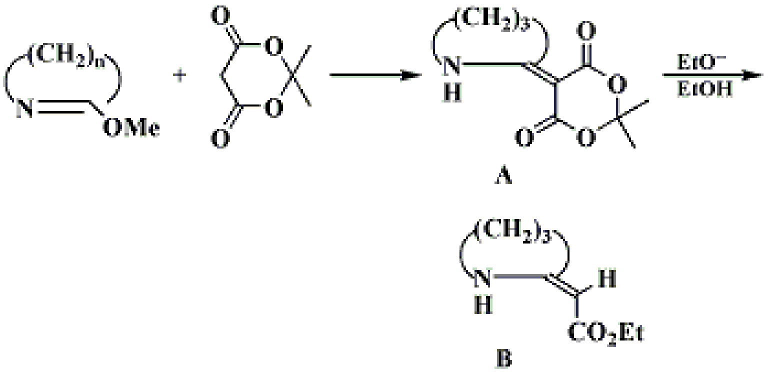
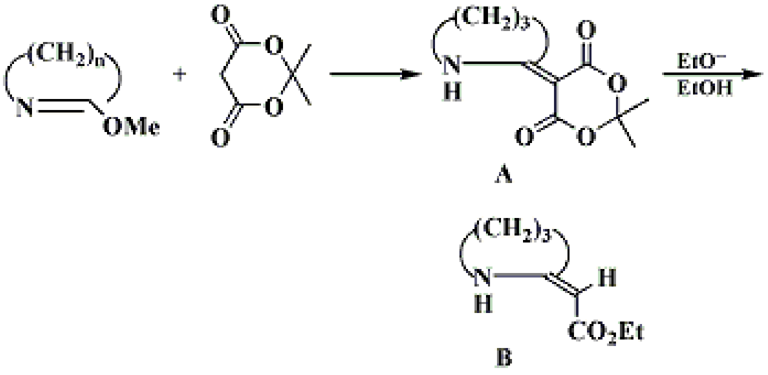
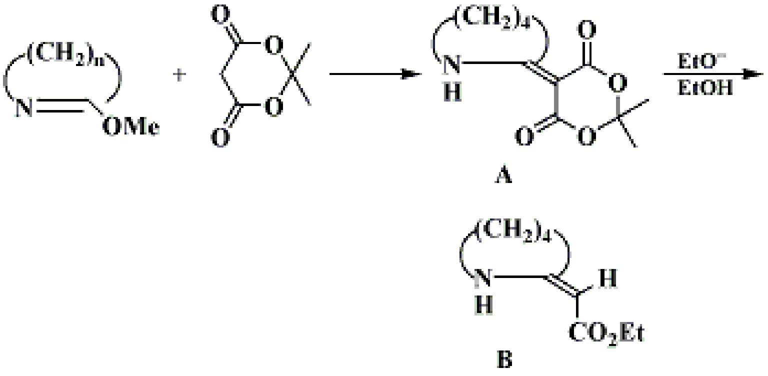
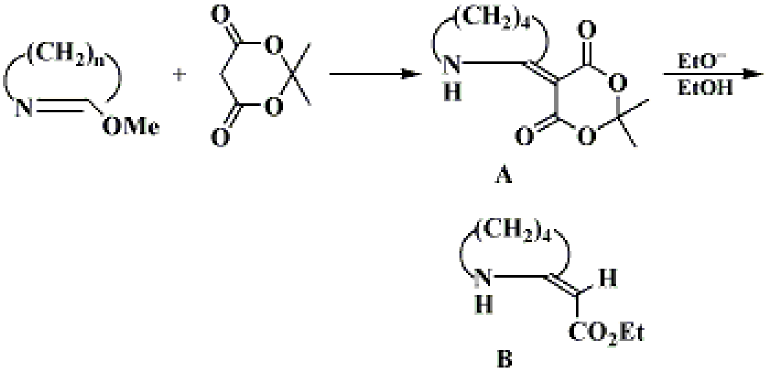
This procedure is representative of a general and versatile method for the preparation of cyclic β-enamino esters that are known to be precursors of many alkaloids such as camptothecin,[4] (±)-lamprolobine,[5] (±)-lupinine,[6] or isoretronecanol.[7]

Common synthetic methods for the preparation of cyclic β-enamino esters are the condensation between a lactim ether and benzyl cyanoacetate followed by hydrogenolytic decarboxylation,[8] or the imino ester carbon–carbon condensation with *tert*-butyl cyanoacetate followed by a trifluoroacetic acid treatment.[9] The use of a thiolactam condensed with ethyl bromoacetate gives, after sulfur extrusion by triphenylphosphine,[10] cyclic β-enamino esters. Compared with these methods, the Meldrum's acid condensation followed by the monodecarboxylating transesterification described here is more convenient and practical. An extension of this procedure permits preparation of smaller cyclic β-enamino esters in comparable yields.[11] The results are reported in Table I.

TABLE I
PREPARATION OF SMALL-RING β-ENAMINO ESTERS



Product	n	Yield (%)	mp (solvent) (°C) or bp (mm)	Ref.

 A	3	92–94	170–172°C (ethanol)	11
 B	3	85–87	61–63°C (hexane)	2,7,11
 A	4	90–92	118–120°C (ethanol)	11
 B	4	80–84	90–94°C / 0.1 mm	2,5,6,11

Only ethyl or methyl esters can be prepared by this procedure. However, pyrolysis of the cyclic β-enamino diesters at 225°C in the presence of different alcohols, thiols, or amines is a versatile and rapid method for preparing cyclic β-enamino esters, thioesters. or amides.[2]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

nickel acetylacetonate monohydrate

ethanol (64-17-5)

methanol (67-56-1)

chloroform (67-66-3)

sodium sulfate (7757-82-6)

sulfur (7704-34-9)

dimethyl sulfate (77-78-1)

acetone (67-64-1)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

Malonic acid (141-82-2)

ε-caprolactam (105-60-2)

Ethyl bromoacetate (105-36-2)

hexane (110-54-3)

triethylamine (121-44-8)

trifluoroacetic acid (76-05-1)

O-Methylcaprolactim (2525-16-8)

triphenylphosphine (603-35-0)

2,2-dimethyl-1,3-dioxane-4,6-dione, MELDRUM'S ACID (2033-24-1)

1-aza-2-methoxy-1-cycloheptene

benzyl cyanoacetate (14447-18-8)

tert-Butyl cyanoacetate (1116-98-9)

Ethyl α-(hexahydroazepinylidene-2)acetate

Acetic acid, (hexahydro-2H-azepin-2-ylidene)-, ethyl ester, (Z)- (70912-51-5)

Isopropylidene α-(hexahydroazepinylidene-2)malonate (70912-54-8)

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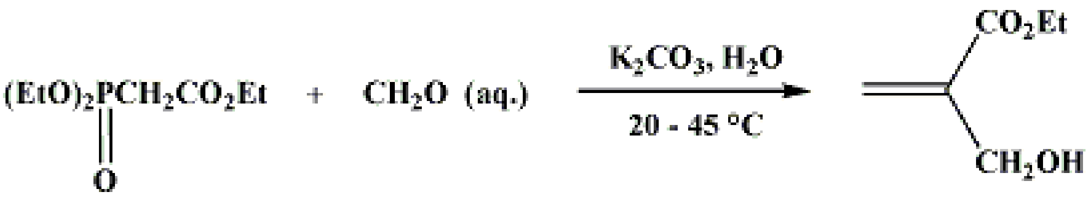
ETHYL α-(HYDROXYMETHYL)ACRYLATE

[2-Propenoic acid, 2-(hydroxymethyl)-, ethyl ester]



Submitted by J. Villieras and M Rambaud[1].
Checked by Christina M. J. Fox and James D. White.

1. Procedure

A. *Ethyl α-(hydroxymethyl)acrylate*. (See (Note 1)). A 1000-mL, four-necked, round-bottomed flask is fitted with mechanical stirrer, 250-mL equalizing funnel, condenser, and thermometer. Paraformaldehyde (48 g, 1.6 mol), 1 *N* phosphoric acid (4 mL), and water (110 mL) are heated at 90°C for 1.5 hr to form a clear aqueous formaldehyde solution. This solution is cooled to room temperature. Triethyl phosphonoacetate (89.6 g, 0.4 mol) is added to the flask and the solution is stirred at room temperature at 1000 rpm. A solution of potassium carbonate (60.7 g, 0.44 mol) in water (60 mL) is added at room temperature (first slowly: 10 mL in 10 min) and then more rapidly (40 min). The temperature reaches 35–40°C and must be maintained at this level (with a water bath if necessary). Stirring is continued for 5 min at 40°C after the end of the addition; then the mixture (liquid–liquid heterogenous mixture) must be cooled rapidly to room temperature using an ice bath (Note 2) while diethyl ether (200 mL) and brine (150 mL) are added. After decantation, the mixture is extracted with ether (three 100-mL portions). The combined organic layers are washed with brine (two 100-mL portions) (Note 3) and dried over magnesium sulfate; the solvents are evaporated under reduced pressure and the remaining oil is distilled to give a fraction at 65–70°C (1 mm) that weighs 38.5–41.6 g (74–80%), n_D^{20} 1.4494. The hydroxy ester is of high purity as shown by GLC analysis (25-m silica capillary OV-1 column) and spectral data (Note 4) and (Note 5).

2. Notes

1. All manipulations should be carried out in a well-ventilated hood. The preparation requires the use of formaldehyde solution and gives rise to ethyl acrylate as a secondary product, the amount of which increases if the addition of the carbonate solution, is too rapid and the temperature rises to 45°C. A freshly opened supply of paraformaldehyde purchased from Aldrich Chemical Company, Inc. was used by the checkers. The use of commercial formaldehyde solutions that now contain up to 15% methanol leads to the formation of several

by-products that cannot be separated by distillation from the α-(hydroxymethyl) acrylate.

2. This experimental procedure must be followed carefully to avoid partial decomposition of ethyl α-(hydroxymethyl) acrylate. The reaction is stopped rapidly after the addition of the carbonate solution (5 min) to prevent formation of high molecular weight by-products which result from transesterification and Michael addition, both of which occur in the basic medium. However, about 25% of the product is lost. Addition of diethyl ether during cooling minimizes side reactions.

3. Treatment with brine allows total elimination of base in the organic layer and prevents any side reaction during the distillation.

4. The spectral properties of ethyl α-(hydroxymethyl) acrylate are as follows: ^{1}H NMR (CCl_4) δ: 4.20 (2 H, CH_2-OH), 5.80 and 6.15 (2 H, CH_2=); ^{13}C NMR ($CDCl_3$) δ: 60.9 (CH_2OH), 124.8 (CH_2=C), 140.2 (CH_2=C), 166.5 (COOEt).

5. α-(Bromomethyl)-, α-(chloromethyl)-, α-(iodomethyl)-, and α-(fluoromethyl) acrylates are easily obtained from the α-(hydroxymethyl)acrylate[2] as illustrated in the following procedure.

A 500-mL, four-necked, round-bottomed flask is fitted with a mechanical stirrer, a 100-mL pressure-equalizing addition funnel, a reflux condenser capped with a drying tube (silica gel), and a thermometer (range –90° to +60°C). The flask is charged with a stirred solution of ethyl α-(hydroxymethyl)acrylate (33.84 g, 0.26 mol) in dry ether (250 mL) at –10°C. Phosphorus tribromide (34 g, 11.5 mL, 0.12 mol) is added slowly (15 min). The temperature is allowed to rise to 20°C and stirring is continued for 3 hr. Water (150 mL) is added at –10°C and the mixture is extracted with technical-grade hexane (three 50-mL portions). The organic phase is washed twice with a saturated sodium chloride solution (50 mL) and dried over magnesium sulfate. The solvents are removed with a rotary evaporator under reduced pressure, and the remaining oil is distilled to give ethyl α-(bromomethyl)acrylate, bp 85–87°C (20 mm), which weighs 43.8 g (87%), n_D^{20} 1.4502. The ester is of high purity as shown by GLC analysis on a capillary OV-1 column, and spectral data.

The spectral properties of ethyl α-(bromomethyl)acrylate are as follows: ^{1}H NMR (CCl_4) δ: 4.15 (2 H, CH_2Br), 5.90 and 6.22 (2 H, H_2C=); ^{13}C NMR ($CDCl_3$) δ: 29.2 (CH_2Br), 126.5 (CH_2=C), 137.8 (CH_2=C), 164.5 (COOEt).

3. Discussion

Ethyl α-(hydroxymethyl)acrylate can be used for the synthesis of chloro and bromomethyl acrylates. The fluoro and iodo compounds have been prepared easily by halogen exchange from ethyl α-(bromomethyl)acrylate.[2]

The same procedure can be applied to the synthesis of diethyl α-(bromomethyl) vinylphosphonate.[3,4] The keto analogs can be obtained in the same way.[5]

The procedure described here is relatively new and gives improved overall yields of 60–67% for the preparation of ethyl α-(bromomethyl)acrylate in two stages from commercially available starting materials. Other more complex and less productive procedures have been described.[6]

Ethyl α-(bromomethyl)acrylate has been used extensively for the synthesis of α-methylene lactones from ketones and aldehydes,[7] and α-methylene lactams, which are known for their cytotoxic activity,[7,8,9] from imines.[8]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

brine

potassium carbonate (584-08-7)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

formaldehyde (630-08-0)

sodium chloride (7647-14-5)

phosphorus tribromide (7789-60-8)

phosphoric acid (7664-38-2)

magnesium sulfate (7487-88-9)

keto

hexane (110-54-3)

triethyl phosphonoacetate (867-13-0)

Ethyl α-(bromomethyl)acrylate (17435-72-2)

Ethyl α-(hydroxymethyl)acrylate, 2-Propenoic acid, 2-(hydroxymethyl)-, ethyl ester, ethyl α-(hydroxymethyl) acrylate (10029-04-6)

diethyl α-(bromomethyl)vinylphosphonate

paraformaldehyde (30525-89-4)

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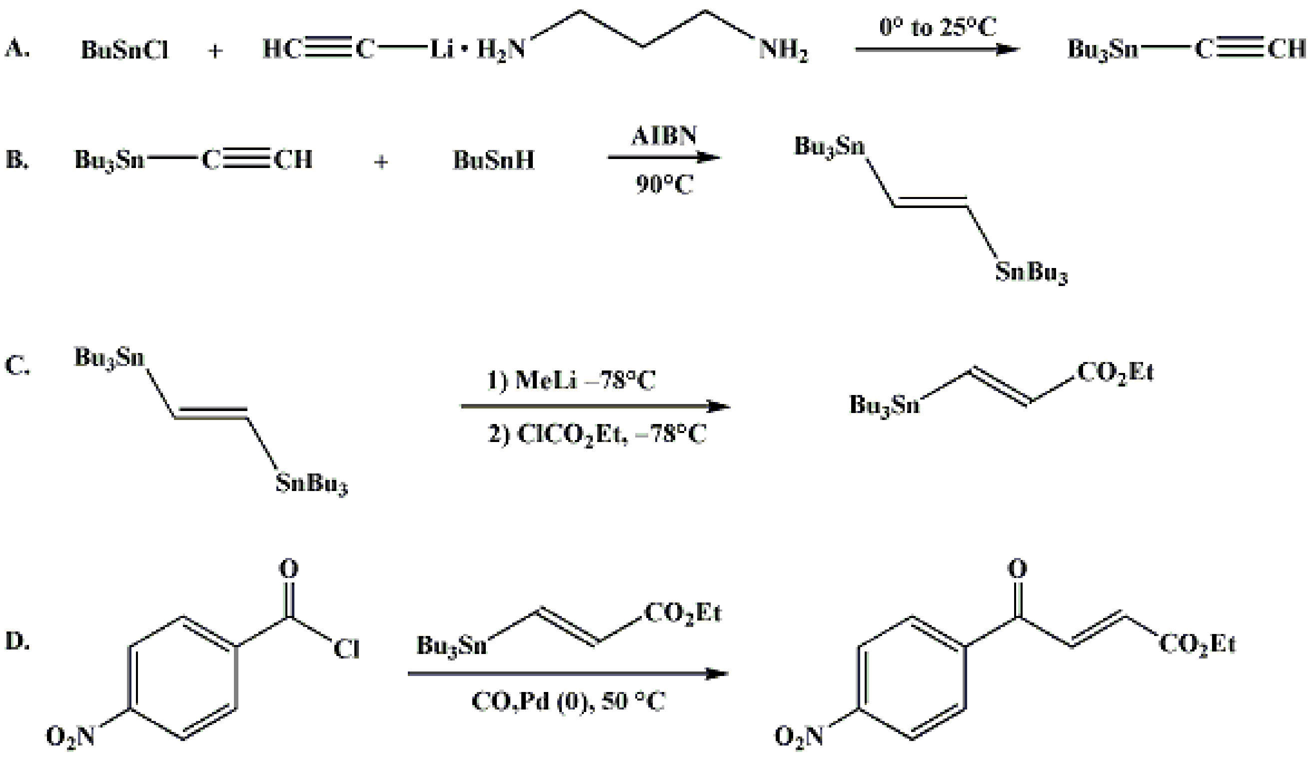
Organic Syntheses, CV 8, 268

PALLADIUM-CATALYZED COUPLING OF ACID CHLORIDES WITH ORGANOTIN REAGENTS: ETHYL (*E*)-4-(4-NITROPHENYL)-4-OXO-2-BUTENOATE

[2-Butenoic acid, 4-(4-nitrophenyl)-4-oxo-, ethyl ester, (*E*)-]



Submitted by A. F. Renaldo[1], J. W. Labadie, and J. K. Stille[2].
Checked by Robert Aslanian, Cynthia A. Smith, and Andrew S. Kende.

1. Procedure

Caution! Most tin compounds are toxic,[3]; [4]; [5] and their preparation should be carried out in a well-ventilated hood.

A. *Tributylethynylstannane.* An oven-dried, 2-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, a 100-mL addition funnel, and a nitrogen inlet is charged with 24.0 g (0.26 mol) of lithium acetylide-ethylenediamine complex (Note 1). The system is evacuated, placed under nitrogen, and 800 mL of tetrahydrofuran (Note 2) is added to the system via a cannula. The flask is cooled in an ice-water bath and 70.7 g (0.22 mol) of tributyltin chloride (Note 3) is added dropwise over 45 min. The ice bath is removed and the mixture is stirred for 18 hr at room temperature. The flask is placed in an ice water bath and excess lithium acetylide is hydrolyzed with 20 mL of water. The reaction mixture is concentrated under reduced pressure and washed with hexane (3 × 50 mL). The organic layers are combined and dried over anhydrous magnesium sulfate. Filtration and evaporation of the solvent at reduced pressure gives a colorless oil. Distillation yields 21.4–24.3 g (31–35%) of tributylethynylstannane, bp 90–94°C (0.5 mm) as a water-white liquid (Note 4), (Note 5),(Note 6).

B. *(E)-1,2-Bis(tributylstannyl)ethylene.* In a 200-mL, one-necked, round-bottomed flask containing a magnetic stirring bar and a nitrogen inlet are placed 20.6 g (0.066 mol) of tributylethynylstannane, 23.1 g (0.079 mol) of tributyltin hydride (Note 7), and 0.25 g (0.0016 mol) of 2,2'-azobis(2-methylpropionitrile)

(Note 8). The mixture is heated at 90°C with stirring for 6 hr. Distillation (170–186°C, 0.3 mm) yields 35.1–36.6 g (88–92%) of (*E*)-1,2-bis(tributylstannyl)ethylene as a clear, colorless oil (Note 9) and (Note 10).

C. *Ethyl (E)-3-(tributylstannyl)propenoate.* A flame-dried, 1-L, three-necked, round-bottomed flask equipped with a magnetic stirring bar, a 100-mL pressure-equalizing addition funnel (Note 11), and a nitrogen inlet is charged with 26.7 g (0.044 mol) of (*E*)-1,2-bis(tributylstannyl)ethylene. Tetrahydrofuran (100 mL) is added to the flask by cannula. The system is cooled in a dry ice-acetone bath and the addition funnel is charged, under nitrogen, with 44.8 mL of a 1.2 *M* solution of methyllithium (0.054 mol) in ethyl ether by means of a double-ended needle (Note 12) and (Note 13). After 10 min the lithium reagent is added dropwise to the flask over a 40-min period. After the addition is complete, the yellow solution is stirred for an additional 2 hr at −78°C during which time a 1-L, one-necked, round-bottomed flask, containing a magnetic stirring bar, is flame-dried under nitrogen. The 1-L, flask, capped with a rubber septum, is charged with a solution of 5.8 g (0.053 mol) of ethyl chloroformate (Note 14) in 150 mL of tetrahydrofuran and cooled to −78°C with a dry ice–acetone bath. Under gentle nitrogen pressure, the metallated reagent is transferred dropwise over a 2.0-hr period by means of a double-ended needle to the 1-L flask containing ethyl chloroformate while the temperature of both flasks is maintained at −78°C (Note 15). After the addition is complete, the reaction mixture is allowed to stir an additional 30 min at −78°C and then treated with 20 mL of methanol in one portion. After 10 min at −78°C the reaction mixture, while still cold, is transferred to a 1-L separatory funnel containing 200 mL of water and 100 mL of hexane. The organic layer is separated and the aqueous layer is washed with hexane (3 × 50 mL). The combined organic layers are dried over anhydrous sodium sulfate, filtered, and concentrated to give a dark-brown oil. The product is dissolved in hexane (30 mL) and purified by chromatography on a column of silica gel (600 g) (Note 16). Elution is carried out initially with hexane (Note 17) and then with hexane/ethyl acetate (95 : 5). Fractions containing the product are combined to give 10.2 g (59%) of ethyl (*E*)-3-(tributylstannyl)propenoate (Note 18),(Note 19),(Note 20) as a yellow oil.

D. *Ethyl (E)-4-(4-nitrophenyl)-4-oxo-2-butenoate.* A flame-dried, 150-mL, one-necked, round-bottomed flask containing a magnetic stirring bar and equipped with a side-arm is charged with 3.20 g (17.2 mmol) of *p*-nitrobenzoyl chloride (Note 21), 0.08 g (0.10 mmol) of benzyl(chloro)bis(triphenylphosphine)palladium(II) (Note 22), and 30 mL of chloroform (Note 23). The bright-yellow solution is evacuated and refilled with carbon monoxide (3 cycles) utilizing a gas bag (Note 24) and (Note 25). After an additional 10 min at room temperature a solution of 8.0 g (20.6 mmol) of ethyl (*E*)-3-(tributylstannyl)propenoate in 5 mL of chloroform is added to the flask by syringe. The stirring reaction mixture is heated to 50°C for 12 hr while a pressure of 1 atm of carbon monoxide is maintained (Note 26) and (Note 27). The reaction is cooled to room temperature and treated with 18 mL of a 1.2 *M* solution of pyridinium poly(hydrogen fluoride) (Note 28),(Note 29),(Note 30) along with 10 mL of pyridine. The reaction mixture is allowed to stir at room temperature overnight and then transferred to a 250-mL separatory funnel containing 75 mL of water. After addition of 30 mL of chloroform, the organic layer is washed successively with 10% hydrochloric acid (3 × 20 mL), saturated sodium bicarbonate (3 × 20 mL), water (25 mL), and brine (25 mL). The organic layer is dried over anhydrous sodium sulfate, filtered, and concentrated to give a dark-brown solid. The product is dissolved in chloroform and 15 g of silica gel (Note 16) is added to the solution. Concentration under reduced pressure gives a brown powder of silica coated with product, which is immediately placed on the top of a column of silica gel (50 g) (Note 16). Elution is carried out with ethyl acetate and the fractions are combined and concentrated under reduced pressure (Note 31). The crude product is again placed on a column of silica gel (250 g). Elution is carried out with hexane/ethyl acetate (90 : 10). Fractions containing the product (obtained by collecting the bright yellow band on the column) are combined to give 3.42 g (80%) of ethyl (*E*)-4-(4-nitrophenyl)-4-oxo-2-butenoate as yellow-green crystals, mp 69–71°C (Note 32).

2. Notes

1. Lithium acetylide-ethylenediamine complex is purchased from Aldrich Chemical Company, Inc. and used without purification.
2. Tetrahydrofuran is freshly distilled from sodium/benzophenone ketyl at atmospheric pressure under nitrogen.

3. Tributyltin chloride, purchased from Alfa Products, Morton/Thiokol, Inc., is distilled immediately before use (bp 128–130°C, 3 mm).

4. This procedure is a modification of that reported by Seitz.[6]

5. The remaining fraction of the mixture after distillation was bis(tributylstannyl)acetylene, which could be recycled for the preparation of tributylethynylstannane.

6. The spectral properties are as follows: ^{1}H NMR (270 MHz, $CDCl_3$) δ: 0.88 (t, 9 H, *J* = 7.3), 0.93–1.02 (m, 6 H), 1.25–1.38 (m, 6 H), 1.49–1.60 (m, 6 H), 2.17 (s, 1 H). The infrared spectrum (neat) shows absorption at 3260 and 2000 cm^{-1}.

7. Tributyltin hydride is prepared by the procedure of Hayashi[7] in 75% yield on a 0.3-mol scale. The checkers used material from Alfa Products, Morton/Thiokol, Inc., which was vacuum-distilled before use (bp 75–78°C, 0.7 mm).

8. 2,2'-Azobis(2-methylpropionitrile), purchased from Alfa Products, Morton/Thiokol, Inc., is recrystallized from chloroform prior to use.

9. The submitters report bp 180–218°C (0.5 mm). The spectral properties are as follows: ^{1}H NMR (270 MHz, $CDCl_3$) δ: 0.75–1.02 (m, 30 H), 1.21–1.43 (m, 12 H), 1.48–1.63 (m, 12 H), 6.85 (s, 2 H). The infrared spectrum (neat) shows absorption at 1425 and 1020 cm^{-1}.

10. (*E*)-1,2-Bis(tributystannyl)ethylene has been prepared by an alternative procedure using lithium chloroacetylide.[8]

11. The funnel is capped with a rubber septum. For ease of operation, volume markings, which correspond to the amount of methyllithium to be added, are put on the addition funnel.

12. *Caution! Methyllithium is pyrophoric in air; excess quantities of the reagent should be discarded very carefully,*

13. Methyllithium is purchased from Aldrich Chemical Company, Inc. Although butyllithium could also be used in the metallation step, a cleaner product is obtained with methyllithium.

14. Ethyl chloroformate, purchased from Aldrich Chemical Company, Inc., is distilled at atmospheric pressure prior to use, discarding the first 25 mL.

15. The solution in the flask which contains the ethyl chloroformate is bright yellow and gradually becomes dark red on the addition of the metallated reagent.

16. The checkers used Kieselgel 60 (230–400 mesh), purchased from E. Merck. The submitters used silica gel (32–63 mesh) purchased from Universal Scientific, Inc.

17. Hexane removes the methyltributyltin.

18. The spectral properties are as follows: ^{1}H NMR (270 MHz, $CDCl_3$) δ: 0.78–0.99 (m, 12 H), 1.01–1.49 (m, 18 H), 4.11 (q, 2 H *J* = 7.3), 6.22 (d, 1 H, *J* = 19.7), 7.65 (d, 1 H, *J* = 19.6). The infrared spectrum (neat) shows absorption at 1715, 1580, and 1200 cm^{-1}.

19. Attempts to purify the product by vacuum distillation, bp 110–138°C (0.05 mm), result in 7–8% isomerization to ethyl (*Z*)-3-(tributylstannyl)propenoate [based on ^{1}H NMR (270 MHz) analysis].

20. The product should be stored under nitrogen at 0°C to prevent decomposition.

21. *p*-Nitrobenzoyl chloride, purchased from Aldrich Chemical Company, Inc., is recrystallized from hexane prior to use.

22. Benzyl(chloro)bis(triphenylphosphine)palladium(II) is prepared from tetrakis(triphenylphosphine) palladium(0)[9] (also available from Aldrich Chemical Company, Inc.) by the procedure of Fitton.[10]

23. Chloroform is freshly distilled at atmospheric pressure under nitrogen and filtered through a plug of neutral alumina.

24. The bright-yellow color of the solution changes to light green after saturation with carbon monoxide. The presence of carbon monoxide prevents decarbonylation of the acylpalladium complex and thus the formation of ethyl *p*-nitrocinnamate.

25. The gas bag is purchased from Fisher Scientific.

26. The pressure of 1 atm is maintained by use of the gas bag.

27. The reaction changes color from light green to bright orange.

28. Pyridinium poly(hydrogen fluoride) is purchased from Aldrich Chemical Company, Inc.

29. The solution of pyridinium poly(hydrogen fluoride) in tetrahydrofuran and pyridine is prepared according to the procedure of Trost.[11] Pyridine is freshly distilled over calcium hydride at atmospheric

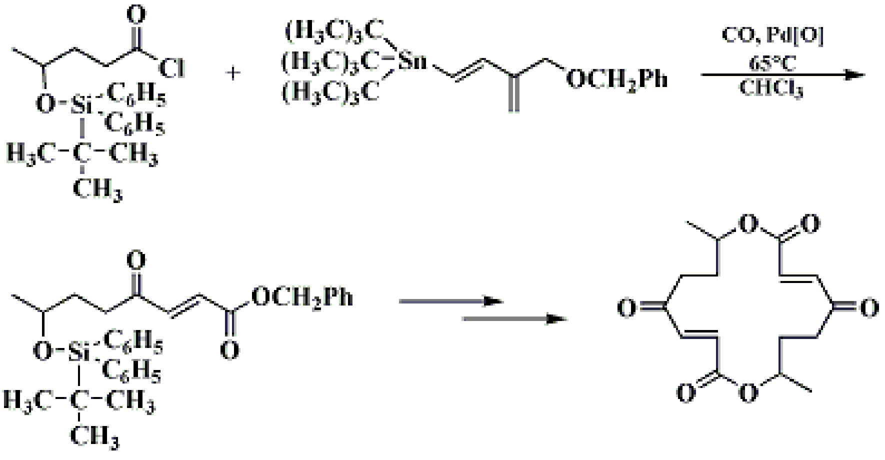
pressure and stored over Linde 4A molecular sieves.
30. The orange reaction mixture changes to deep red and the reaction becomes slightly exothermic (50–60°C).
31. The initial filtration with silica gel is necessary to remove most of the tributyltin fluoride.
32. The spectral properties are as follows: ^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.34 (t, 3 H, *J* = 7.2), 4.30 (q, 2 H, *J* = 7.2), 6.92 (d, 1 H, *J* = 15.6), 7.85 (d, 1 H, *J* = 15.6), 8.13 (d, 2 H, *J* = 8.9), 8.35 (d, 2 H, *J* = 8.8); ^{13}C NMR (68 MHz, $CDCl_3$) δ: 14.2, 61.7, 124.1, 129.9, 134.3, 135.5, 141.4, 151.0, 165.1, 188.4. The infrared spectrum (Nujol) shows the following absorption cm^{-1}: 1690, 1660, 1590, 1300, 990, 970, 710.

3. Discussion

The procedure for synthesis of the title compound is representative of the palladiumcatalyzed coupling of acid chlorides with organotin reagents.[12 13 14 15] The formation of ketones by Grignard reagents,[16] organocuprates,[17 18] and organoborates[19] has been reported. The principal advantage of the palladium-catalyzed organotin coupling method lies in the broad range of functionality that can be introduced in the product. The reaction can be carried out under mild, neutral conditions with functional groups on the acid chloride such as nitro, nitrile, haloaryl, methoxy, ester, and even aldehyde.[15] Solvents other than chloroform, such as tetrahydrofuran, hexamethylphosphorictriamide, and dichloromethane, can be used in this reaction.

The unsymmetric tetraorganotin reagent has been demonstrated to transfer selectively the vinyl group rapidly without butyl transfer occurring. By using a tributyl or trimethyl organotin reagent (e.g., Bu_3SnR or Me_3SnR), the order of transfer of the R groups is RC≡C- > RCH=CH- > Ar- > RCH=CH-CH_2- > ArCH_2- > CH_3OCH_2- > C_nH_{2n+1}.[20 21]

A number of functionalized organotin derivatives have been used in palladium-catalyzed coupling to produce aromatic heterocyclic ketones,[22] acetylenic ketones,[23] and vinyl ketones.[24 25 26] The organotin coupling method has been used effectively in the preparation of a key methyl ketone intermediate in the total synthesis of (±)-quadrone[27] and in the preparation of **5**, a key precursor in the synthesis of the antibiotic pyrenophorin **6** (Eq. 1).[21]



5 **6**

The organotin reagents are very stable since they can withstand distillation as well as chromatography on silica gel. The procedure for preparation of tributylethynylstannane **(1)** in Part A is based on one reported by Bottaro et al.[6] Bis(tributylstannyl)ethylene **(2)** has been prepared from lithium chloroacetylide[8] and tributylethynylstannane.[28 29] Although ethyl *(E)*-3-(tributylstannyl)propenoate **(3)** is produced from transmetallation[30] of **2** or hydrostannation[31] of ethyl propiolate, other known procedures to synthesize **3** include conjugate addition to tributylstannylcuprate[32 33] to ethyl propiolate, and tributylstannylcopper to β-

substituted acrylates.[34]

In most cases the trimethyltin reagents are preferred since the by-product, trimethyltin chloride, can easily be removed by water extraction. In the case of the water-insoluble tributyltin chloride it is necessary to add an aqueous solution of potassium fluoride to an ethereal solution of the product, thereby forming insoluble tributyltin fluoride, which can be separated by filtration.[20,21,35] However, a completely homogeneous and neutral fluoride source, pyridinium hydrofluoride,[11] is used in this procedure, making the filtration unnecessary and simplifying the subsequent chromatography step.

References and Notes

1. Correspondence should be sent to A. F. R., IBM Corporation, E88/142, 5600 Cottle Road, San Jose, CA 95190;
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

benzophenone ketyl

pyrenophorin

lithium acetylide-ethylenediamine

pyridinium poly(hydrogen fluoride

(E)-1,2-Bis(tributystannyl)ethylene

pyridinium poly(hydrogen fluoride)

(±)-quadrone

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

methanol (67-56-1)

ethyl ether (60-29-7)

carbon monoxide (630-08-0)

chloroform (67-66-3)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

tin (7440-31-5)

pyridine (110-86-1)

sodium (13966-32-0)

dichloromethane (75-09-2)

ethyl chloroformate (541-41-3)

lithium (7439-93-2)

magnesium sulfate (7487-88-9)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

potassium fluoride (7789-23-3)

hexane (110-54-3)

Methyllithium (917-54-4)

calcium hydride (7789-78-8)

ethyl propiolate (623-47-2)

hexamethylphosphorictriamide (680-31-9)

tributyltin hydride (688-73-3)

tetrakis(triphenylphosphine)palladium(0) (14221-01-3)

trimethyltin chloride (1066-45-1)

Lithium acetylide, Lithium acetylide-ethylenediamine complex (6867-30-7)

tributyltin chloride (1461-22-9)

Tributylethynylstannane (994-89-8)

benzyl(chloro)bis(triphenylphosphine)palladium(II)

bis(tributylstannyl)acetylene (994-71-8)

lithium chloroacetylide

methyltributyltin (1528-01-4)

tributyltin fluoride

Bis(tributylstannyl)ethylene

tributylstannylcuprate

tributylstannylcopper

pyridinium hydrofluoride

p-Nitrobenzoyl chloride (122-04-3)

Ethyl (E)-4-(4-nitrophenyl)-4-oxo-2-butenoate, 2-Butenoic acid, 4-(4-nitrophenyl)-4-oxo-, ethyl ester, (E)- (131504-53-5)

(E)-1,2-Bis(tributylstannyl)ethylene (14275-61-7)

Ethyl (E)-3-(tributylstannyl)propenoate (106335-84-6)

ethyl (Z)-3-(tributylstannyl)propenoate

ethyl p-nitrocinnamate

2,2'-azobis(2-methylpropionitrile)

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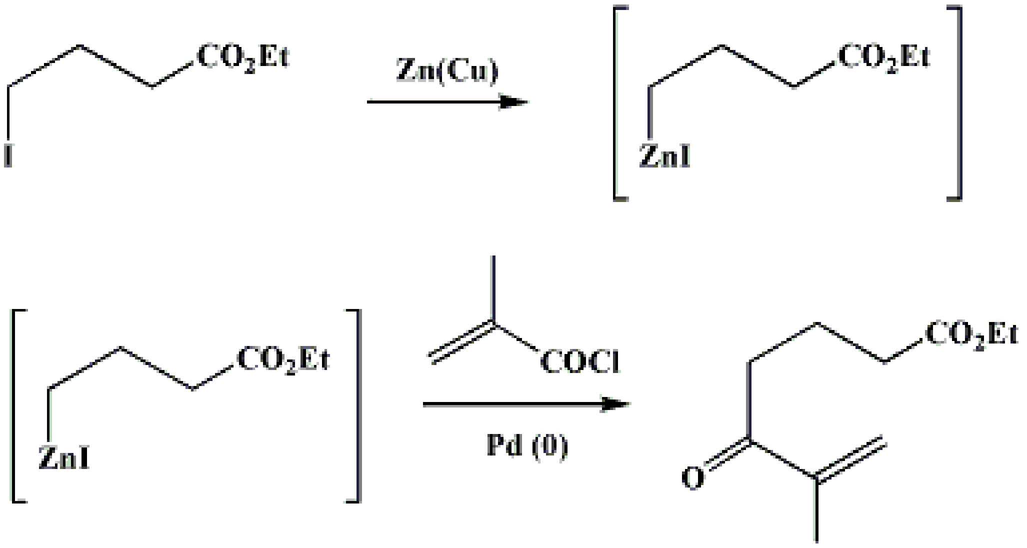
Organic Syntheses, CV 8, 274

ETHYL 5-OXO-6-METHYL-6-HEPTENOATE FROM METHACRYLOYL CHLORIDE AND ETHYL 4-IODOBUTYRATE

[6-Heptenoic acid, 6-methyl-6-oxo-, ethyl ester]



Submitted by Yoshinao Tamaru, Hirofumi Ochiai, Tatsuya Nakamura, and Zen-ichi Yoshida[1].
Checked by Kevin B. Kunnen and Albert I. Meyers.

1. Procedure

A 300-mL, four-necked, round-bottomed flask containing a magnetic stirring bar is fitted with a serum cap, a thermometer, a 100-mL serum-capped pressure-equalizing addition funnel, and a reflux condenser equipped at the top with a nitrogen inlet. The dry apparatus is flushed with nitrogen and 5.6 g (85.5 mmol) of zinc–copper couple (Note 1) and 20 mL of benzene are introduced (Note 2). A mixture of 13.8 g (57 mmol) of ethyl 4-iodobutyrate (Note 3), 9 mL of *N*,*N*-dimethylacetamide (Note 4), and 70 mL of benzene is transferred into the addition funnel by cannulation techniques and added to the stirred Zn(Cu) suspension over 3 min at room temperature. The mixture is vigorously stirred for 1 hr at room temperature (Note 5) and then heated at gentle reflux with an oil bath for 4.5 hr (Note 6). After the mixture is cooled to 60°C, a solution of 0.58 g (0.5 mmol) of tetrakis(triphenylphosphine)palladium(0) (Note 7) in 15 mL of benzene is added over 1 min through the addition funnel and stirring is continued for 5 min at the same temperature. The oil bath is removed, a solution of 5.23 g (50 mmol) of methacryloyl chloride (Note 8) in 10 mL of benzene is added through the addition funnel over a period of 5 min, and stirring is continued for 1 hr (Note 9). The mixture is filtered with suction through a Celite pad on a medium-fritted funnel and the filter cake is washed with 200 mL of diethyl ether. The filtrate is

washed successively with 50 mL of 1 *N* ammonium chloride, 10 mL of saturated sodium hydrogen carbonate and 50 mL of saturated sodium chloride. The aqueous phases are extracted with 100 mL of diethyl ether. The combined organic extracts are dried over magnesium sulfate and the solvents are removed with a rotary evaporator to yield a deep-brown mobile oil. This is purified by chromatography on 200 g of silica gel with a hexane–diethyl ether gradient (10 : 1, 400 mL; 5 : 1, 400 mL, and 2 : 1, 600 mL) (Note 10), followed by distillation in the presence of hydroquinone (10 mg) in a Kugelrohr apparatus to give 8.0–8.1 g (87–88%) of the product as a colorless liquid, bp 185°C (20 mm) (Note 11).

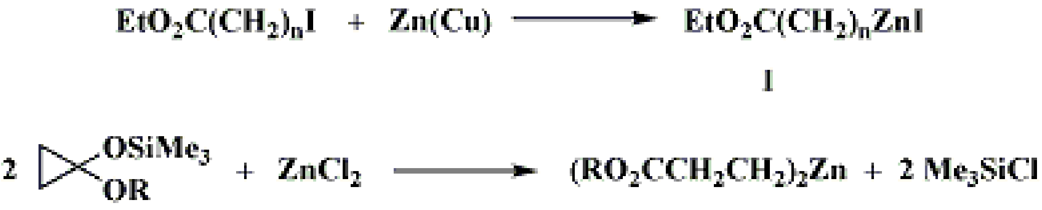
2. Notes

1. Zinc–copper couple was prepared according to the literature procedure[2] and kept in a desiccator over phosphorus pentoxide under nitrogen.
2. Benzene is dried by distillation from sodium/benzophenone ketyl.
3. Ethyl 4-iodobutyrate, bp 65°C (2.5 mm), was obtained according to the literature procedure[3] (80–90% yield). A mixture of 50 g (0.26 mol) of ethyl 4-bromobutyrate, available from Aldrich Chemical Company, Inc., and 190 g (1.26 mol) of sodium iodide was heated in 500 mL of acetone at 60°C for 24 hr.
4. *N,N*-Dimethylacetamide (DMA) is dried by distillation under reduced pressure from calcium hydride. The use of DMA is essential to promote metallation.[4] [5] The metallation is also successful with *N,N*-dimethylformamide as a cosolvent, but the yield of product is significantly lowered (60–70%) because of formation of acid anhydride.[5]
5. The metallation is only slightly exothermic.
6. It is difficult to judge the completion of the metallation by appearance. Although the metallation is reproducible, it is recommended that a reaction aliquot be checked by VPC or TLC after quenching with 1 *N* hydrochloric acid.
7. Tetrakis(triphenylphosphine)palladium(0) is available from Aldrich Chemical Company, Inc.
8. Methacryloyl chloride, obtained from Aldrich Chemical Company, Inc., is distilled from calcium chloride under nitrogen at atmospheric pressure into a flask containing a small amount of hydroquinone monomethyl ether.
9. The reaction is moderately exothermic, and the temperature rises to about 65°C after the addition of methacryloyl chloride and then gradually falls to ambient temperature.
10. The reaction mixture gives only one spot on silica gel TLC (R_f = 0.5, hexane/ethyl acetate = 4 : 1 using iodine or saturated 2,4-dinitrophenylhydrazine in 2 *N* hydrochloric acid as an indicator). This column purification is undertaken to help the smooth distillation of the product. Silica gel 60 Merck in a 5.5-cm-diameter column was used.
11. The submitters report bp 100°C (6 mm). The product shows the correct elemental analysis and has the following physical and spectral properties: n_D^{20}

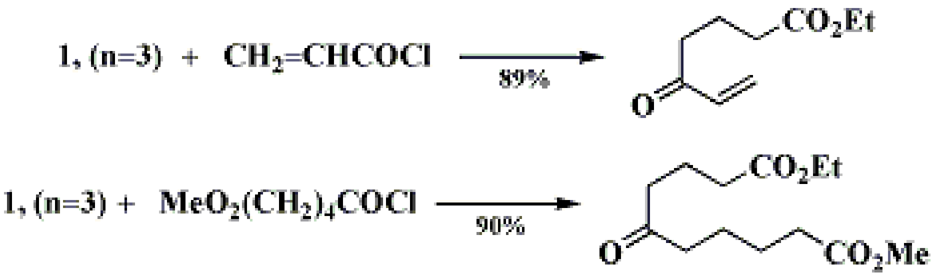
1.4512; IR (liquid film) cm^{-1}: 3100 (w), 2970 (m), 1730 (s), 1680 (s), 1630 (m), 940 (m); ^{1}H NMR ($CDCl_3$) δ: 1.25 (t, 3 H, *J* = 7.1), 1.75–2.11 (m, 5 H), 2.35 (t, 2 H, *J* = 6.8), 2.76 (t, 2 H, *J* = 7.1), 4.13 (q, 2 H, *J* = 7.1), 5.77 (br, s, 1 H), 5.96 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ: 13.9, 17.2, 19.3, 33.0, 36.0, 59.9, 124.1, 144.1, 172.7, 200.6; VPC analysis: 20% Silicone DC550 on celite (Nishio Kogyo Co.), 3-mm × 1-m column, constant temperature increase 8°C/min from 100°C, one peak of impurity (retention time 1.8 min), and the peak of the product (retention time 9.0 min, 99.5% purity).

3. Discussion

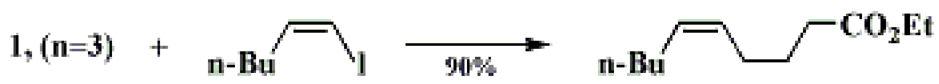
α-Metallocarbonyl compounds, so-called enolates, are among the most widely used reagents for organic syntheses. Undoubtedly, β-, γ-, and δ-metallocarbonyl compounds are also of great synthetic value. The use of these organometallics, however, has been limited mainly because of the lack of a convenient preparative method. Herein are described the preparation of a γ-metallo ester, 3-carboethoxypropylzinc iodide (**1**, *n* = 3; Eq. 1) and its reaction with acid chlorides to yield δ-keto esters. According to the same procedure, it is possible to generate 2-carboethoxyethylzinc iodide (**1**, *n* = 2) and 4-carboethoxybutylzinc iodide (**1**, *n* = 5)[6] with similar efficiency. 2-Carboalkoxyethylzinc may be prepared by a cyclopropane ring-opening procedure (Eq 2).[7,8]



These organozincs, **1** (*n* = 2, 3, and 4), react with diverse acid chlorides to yield γ-, δ-, and ε-keto esters, respectively, in good yields. Two typical examples are shown in Equations 3 and 4. The product of Equation 3, ethyl 5-oxo-6-heptenoate, may be prepared by laborious, multistep methods.[9,10] The title compound, ethyl 5-oxo-6-methyl-6-heptenoate, is a new compound.



Another use of **1** (*n* = 3) is the coupling with vinyl iodides or triflates, which furnish δ, ε-unsaturated esters.[11] One example is shown in Equation 5. The reaction proceeds with retention of the double-bond geometry.



This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 502

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

benzophenone ketyl

vinyl iodides

6-Heptenoic acid, 6-methyl-6-oxo-, ethyl ester

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ethyl acetate (141-78-6)

diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

hydroquinone (123-31-9)

sodium hydrogen carbonate (144-55-8)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

copper (7440-50-8)

iodine (7553-56-2)

acetone (67-64-1)

zinc (7440-66-6)

sodium (13966-32-0)

sodium iodide (7681-82-5)

magnesium sulfate (7487-88-9)

2,4-Dinitrophenylhydrazine (119-26-6)

N,N-dimethylformamide (68-12-2)

hexane (110-54-3)

calcium hydride (7789-78-8)

Ethyl 4-iodobutyrate (7425-53-8)

hydroquinone monomethyl ether (150-76-5)

ethyl 4-bromobutyrate (2969-81-5)

N,N-dimethylacetamide (127-19-5)

tetrakis(triphenylphosphine)palladium(0) (14221-01-3)

phosphorus pentoxide (1314-56-3)

Ethyl 5-oxo-6-methyl-6-heptenoate (130892-17-0)

METHACRYLOYL CHLORIDE (920-46-7)

3-carboethoxypropylzinc iodide

2-carboethoxyethylzinc iodide

4-carboethoxybutylzinc iodide

ethyl 5-oxo-6-heptenoate

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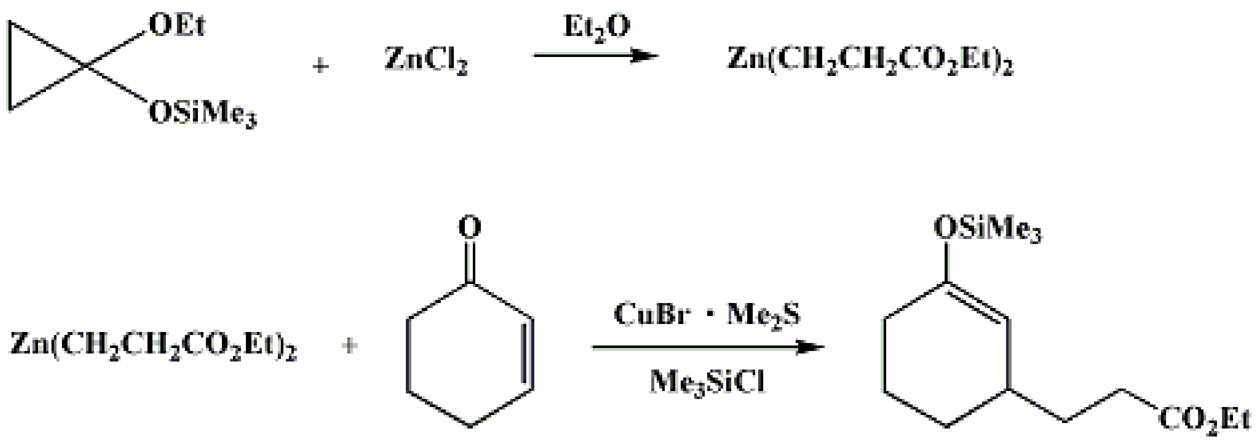
Organic Syntheses, CV 8, 277

COPPER-CATALYZED CONJUGATE ADDITION OF A ZINC HOMOENOLATE: ETHYL 3-[3-(TRIMETHYLSILYLOXY)CYCLOHEX-2-ENYL] PROPIONATE

[2-Cyclohexene-1-propanoic acid, 3-[(trimethylsilyl)oxy]-, ethyl ester]



Submitted by Eiichi Nakamura and Isao Kuwajima[1].
Checked by Tina M. Kravetz, Daniel Cheney, and Leo A. Paquette.

1. Procedure

In a tared 1-L, three-necked flask, two necks of which are covered with rubber septa and the other connected to a nitrogen-vacuum source, is placed 17.2 g of zinc chloride (Note 1). The flask is evacuated to approximately 2 mm and heated with a burner with swirling until practically all of the salt melts. The flask is cooled and filled with nitrogen. The dried salt weighs 16.4–17 g (ca. 0.12 mol) (Note 2). An efficient magnetic stirring bar and a Dimroth condenser in place of a rubber septum are set in position, and the flask is again flushed with nitrogen. Ether (300 mL) (Note 3) is introduced via the septum, and stirring is initiated and maintained throughout the reaction. The mixture is refluxed gently for 1 hr to aid dissolution of the solid state (Note 4). The flask is cooled, and 1-trimethylsilyloxy-1-ethoxycyclopropane (41.80 g, 0.24 mol) (Note 5) is introduced with the aid of a hypodermic syringe during 5 min. The cloudy mixture is stirred at room temperature for 1 hr; the more dense lower layer may have mostly disappeared at this point. The mixture is refluxed for 30 min to complete homoenolate formation. The clear, colorless solution of the zinc homoenolate and chlorotrimethylsilane is cooled in an ice bath, and cuprous bromide/dimethyl sulfide complex (0.4 g, 2 mmol) (Note 6) is added by removing the septum while nitrogen adequate to exclude air is introduced through the inlet. 2-Cyclohexen-1-one (9.62 g, 0.1 mmol) (Note 7) is introduced via the septum during 1 min, and then

hexamethylphosphoric triamide (HMPA) (34.8 mL, 0.2 mol) (Note 8) and (Note 9) is added during 5 min. A slightly exothermic reaction occurs initially and the bath is removed after 20 min. After 3 hr at room temperature, 40 g of silica gel (Note 10) and 300 mL of dry hexane (Note 11) are added while the mixture is stirred vigorously for 3 min. The supernatant liquid is decanted, and the residue is suspended in 60 mL of dry ether. Dry hexane (60 mL) is added and the supernatant liquid is decanted. This extractive procedure is repeated once and the combined organic phase is filtered through Celite (Note 12). After concentration with a rotary evaporator, the oily product is distilled under reduced pressure (ca. 2 mm). 1-Trimethylsilyloxy-1-ethoxycyclopropane (8–10 g) is recovered as the first fraction (bp 26°C at 2.3 mm). The majority of the HMPA remaining after workup distils at 80–120°C/2.3 mm. Finally, the desired product (18.9–20.5 g, 70–76%) is obtained as a fraction boiling at 130–132°C/2.3 mm (Note 13).

2. Notes

1. Zinc chloride was purchased from Koso Chemical Company and used as such (cf. *Org. Synth., Coll. Vol. VI,* **1988**, 692). Alfa's ultra pure-grade reagent resisted complete dissolution and appeared less suitable. The checkers used "Baker Analyzed" reagent zinc chloride with prior drying at 0.3 mm.
2. The amount of zinc chloride may be in slight excess of the theoretical amount (i.e., 0.5 equiv of the cyclopropane).
3. Ether was distilled from sodium benzophenone ketyl immediately before use.
4. A two-layer mixture results.
5. This cyclopropane was prepared according to an Organic Syntheses procedure (*Org. Synth., Coll. Vol. VII,* **1990**, 131).
6. Cuprous bromide/dimethyl sulfide complex was purchased from Aldrich Chemical Company, Inc. and used as such.
7. Cyclohexenone was purchased from Tokyo Kasei Chemical Company or Aldrich Chemical Company, Inc. and used after simple distillation at reduced pressure.
8. Hexamethylphosphoric triamide (HMPA) was purchased from Tokyo Kasei Chemical Company and used after distillation from calcium hydride under reduced pressure.
9. This step was also checked, substituting *N,N'*-dimethylpropyleneurea (DMPU),[2] supplied by Aldrich Chemical Company, Inc. or Fluka, for HMPA. The yield of final product dropped somewhat to 16.36–17.36 g (60–64%), but otherwise the reaction proceeded as described.
10. Ordinary silica gel (Wakogel C-300, Wako Chemical Company) was used.
11. Hexane was distilled from calcium hydride and stored over a potassium mirror. The checkers stored the redistilled hexane over molecular sieves.
12. Since the product has only moderate hydrolytic stability, the extractive procedure should be carried out rapidly under a flow of nitrogen. Operation in a nitrogen-filled plastic bag may eliminate the possibility of hydrolysis.

13. When the workup is performed as described (Note 11), the product may contain small amounts of residual HMPA and up to 5% (GLC estimation) of the keto ester resulting from hydrolysis of the enol silyl ether. Retardation factor values of the keto ester and the silyl ether or thin-layer analysis (Merck silica gel plates coated with a 0.25-mm layer of Kieselgel 60 F_{254}, developed with 30% ethyl acetate in hexane) were 0.4 and 0.8, respectively; gas-chromatographic (GLC) analysis (OV-101, capillary glass column of 0.25 mm × 20 m, 120°C) showed retention times of 2.56 and 4.96 min for these two compounds, respectively. GLC analysis also indicated the ratio of the regioisomers of the enol silyl ether as >99 : 1 (4.96 and 6.13 min, respectively). On a smaller scale where the product can readily be handled on silica gel chromatography, a yield over 85% may be attained. Correct elemental analysis has been obtained for a sample purified by chromatography and distillation. Spectral properties of the product are as follows: ^{1}H NMR (300 MHz, CCl_4) δ: 0.04 (s, 9 H), 1.10 (t, 3 H, *J* = 7.1), 1.3–2.2 (m, 11 H), 3.93 (q, 2 H, *J* = 7.1), 4.55 (br s, 1 H); IR (neat film) cm^{-1} 1730 (s), 1655 (s), 1445 (m), 1365 (s), 1245 (s), 1180 (vs), 840 (vs), 745 (s).

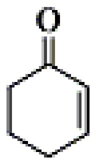
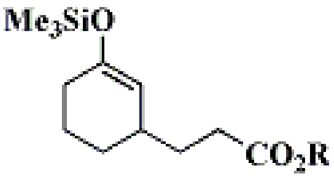
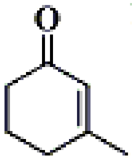
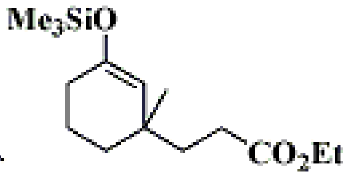
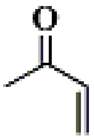
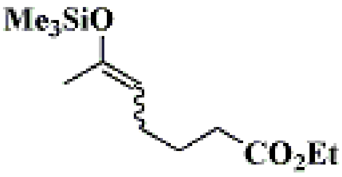
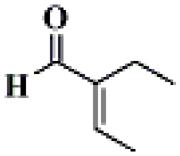
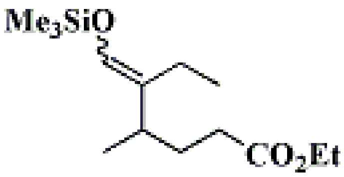
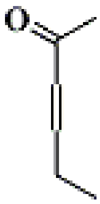
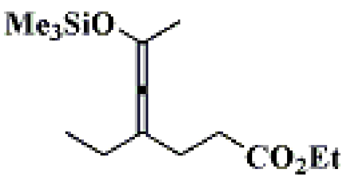
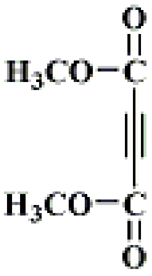
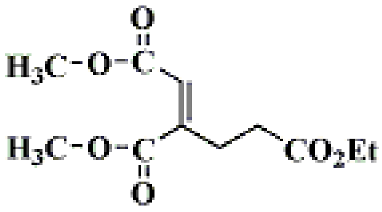
3. Discussion

Unlike their enolate counterparts, homoenolates have been underrated because of a prior lack of synthetic accessibility.[3] Many of the previously known homoenolates cyclize readily to the cyclopropanolate tautomer and behave chemically as the latter. 1-Alkoxy-1-silyloxycyclopropanes[4] have provided, for the first time, examples of reactive yet characterizable homoenolates (of alkyl propionates). A titanium homoenolate undergoes 1,2-addition to carbonyl compounds, providing an efficient synthetic route to γ-lactones.[4] The present procedure represents an unique and highly efficient method for the preparation of the zinc homoenolate of an alkyl propionate and illustrates its copper-catalyzed conjugate addition.[5] The reaction consists of two stages; the first part of the present procedure generates a mixture of the zinc homoenolate and chlorotrimethylsilane, from which the homoenolate can be isolated by removal of the volatile material under reduced pressure, and the second part involves the chlorotrimethylsilane-assisted conjugate addition of the transient copper homoenolate. Only one of the propionate moieties on the zinc metal is available for the conjugate addition. The reaction mechanism has already been discussed briefly.[6]

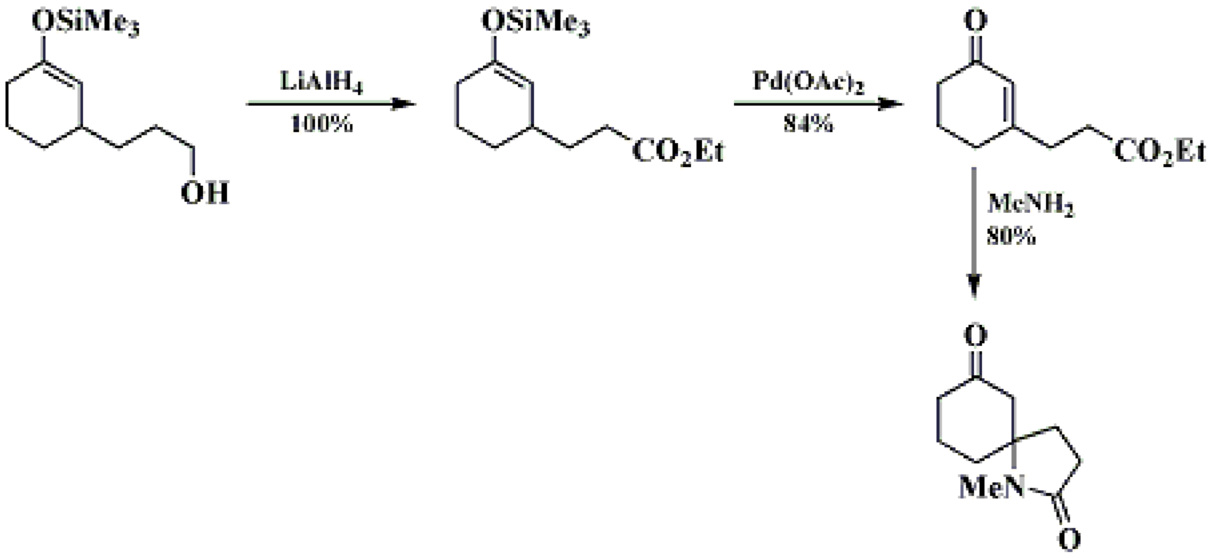
The reaction is applicable to a variety of enones, enals, and acetylenic carbonyl compounds (Table I). No 1,2-addition is seen under copper-catalyzed conditions since the zinc homoenolate does not generally undergo a 1,2-addition reaction to carbonyl compounds. The conjugate adduct is useful for organic synthesis as indicated by the scheme below. The enol silyl ether moiety acts either to protect or activate the ketone functionality. The ready hydrolytic generation of the keto ester from the conjugate adduct provides an efficient entry to 6-keto esters. Replacement of the enone with an acyl halide leads to 4-keto esters in high yield,[5] and the palladium-catalyzed reaction with aryl and vinyl halides gives 3-aryl- and 3-vinyl propionates.[7] The purified

homoenolate undergoes 1,2-addition to aldehydes in the presence of chlorotrimethylsilane.[8]

TABLE I
CONJUGATE ADDITION OF HOMOENOLATE OF ESTERS

Acceptor	Product	%Yield
		R= i-Pr 93 R = Et 76 R = Me 91
		92
		80
		75
		73
		63

No other synthetic method is known that achieves the equivalent transformation. Rather elaborate procedures using an allylic anion type of the homoenolate "equivalents"[6] or homoenolate radicals[9] have been reported, but their tolerance to the structure of the enone acceptor is much narrower.



This preparation is referenced from:

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

sodium benzophenone ketyl

dimethyl sulfide complex

ethyl acetate (141-78-6)

ether (60-29-7)

nitrogen (7727-37-9)

cuprous bromide (7787-70-4)

zinc chloride (7646-85-7)

cyclopropane (75-19-4)

dimethyl sulfide (75-18-3)

hexane (110-54-3)

calcium hydride (7789-78-8)

2-cyclohexen-1-one, cyclohexenone (930-68-7)

hexamethylphosphoric triamide (680-31-9)

CHLOROTRIMETHYLSILANE (75-77-4)

silyl ether (13597-73-4)

N,N'-dimethylpropyleneurea (7226-23-5)

1-trimethylsilyloxy-1-ethoxycyclopropane (27374-25-0)

ETHYL 3-[3-(TRIMETHYLSILYLOXY)CYCLOHEX-2-ENYL]PROPIONATE, 2-Cyclohexene-1-propanoic acid, 3-[(trimethylsilyl)oxy]-, ethyl ester (90147-64-1)

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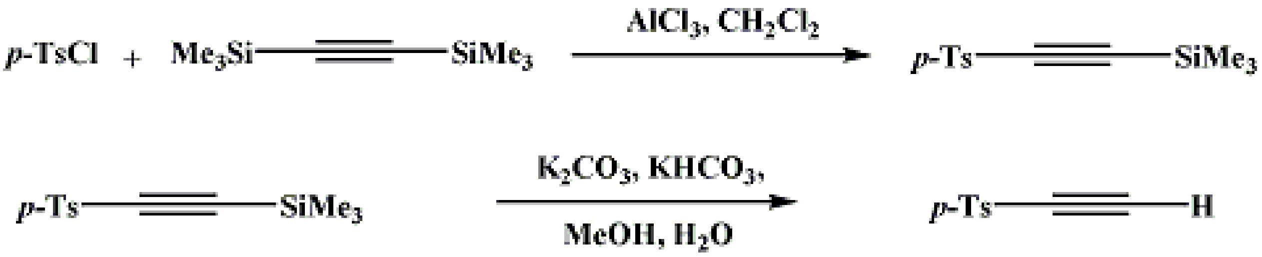
Organic Syntheses, CV 8, 281

ETHYNYL *p*-TOLYL SULFONE

[Benzene, 1-(ethynylsulfonyl)-4-methyl-]



Submitted by Liladhar Waykole and Leo A. Paquette[1].
Checked by Dirk A. Heerding and Larry E. Overman.

1. Procedure

A. *p-Tolyl 2-(trimethylsilyl)ethynyl sulfone.* In a flame-dried, 500-mL, three-necked, round-bottomed flask fitted with a nitrogen inlet and glass stoppers are placed 200 mL of dry dichloromethane (Note 1) and 29.4 g (0.22 mol) of freshly powdered anhydrous aluminum chloride. After the addition of *p*-toluenesulfonyl chloride (41.9 g, 0.22 mol), the resulting dark-brown mixture is shaken occasionally for 20 min at room temperature.

A 1-L, three-necked, round-bottomed flask equipped with a 500-mL addition funnel and a Teflon-coated stirring bar is flame-dried under a stream of dry nitrogen. The flask is charged with bis(trimethylsilyl)acetylene (34.0 g, 0.20 mol) (Note 2) and dry dichloromethane (200 mL) (Note 1) and the solution is cooled to 0°C in an ice–water bath.

The *p*-toluenesulfonyl chloride–aluminum chloride complex is quickly filtered through a glass wool plug (Note 3) into the addition funnel. The residue is washed rapidly with an additional 50 mL of dry dichloromethane and the funnel is quickly stoppered. The complex is added dropwise during 1 hr to the cold (0°C), magnetically stirred silylacetylene solution. On completion of the addition, the reaction mixture is allowed to warm to room temperature and is stirred for an additional 12 hr. The mixture is hydrolyzed by pouring it into a slurry of 20% hydrochloric acid (200 mL) and ice (200 g) (Note 4). The organic layer is separated, washed twice with water (150 mL), and dried over anhydrous sodium sulfate. Removal of solvent in a rotary evaporator gives a brown solid (Note 5) that is recrystallized from light petroleum ether (bp 40–60°C) to yield 39.7–40.4 g (79–80%) of *p*-tolyl 2-(trimethylsilyl)ethynyl sulfone as white crystals, mp 81–82°C (Note 6).

B. *Ethynyl p-tolyl sulfone.* A 1-L, three-necked, round-bottomed flask equipped with a thermometer, a 500-mL addition funnel, a nitrogen inlet, and a Teflon-coated magnetic stirring bar is charged with *p*-tolyl 2-(trimethylsilyl)ethynyl sulfone (25.2 g, 0.1 mol)

and 300 mL of reagent-grade methanol. After the mixture is stirred for 30 min, a clear solution is obtained. In the addition funnel is placed 350 mL of an aqueous solution containing potassium carbonate (6.2×10^{-3} *M*) and potassium bicarbonate (6.2×10^{-3} *M*); this buffer is added at a rate to maintain the reaction temperature at 30°C (Note 7) and (Note 8). The mixture is diluted with water (200 mL), and extracted with four 100-mL portions of chloroform. The combined organic phases are washed 3 times with water (100 mL) and twice with brine (100 mL) prior to drying over anhydrous sodium sulfate. Removal of solvent under reduced pressure leaves a creamy white solid, which is purified by either recrystallization from ethyl acetate–petroleum ether or silica gel chromatography using 10% ethyl acetate in petroleum ether as eluant (Note 9). There is obtained 15.0 g (83%) of colorless crystals, mp 74–75°C (Note 10) and (Note 11).

2. Notes

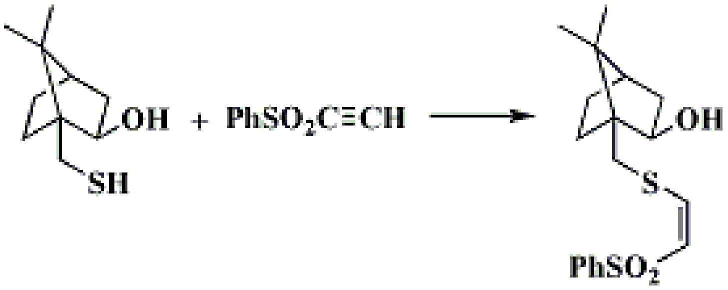
1. The submitters used dichloromethane freshly distilled from powdered calcium hydride.
2. This reagent was obtained from Petrarch Systems, Inc., Bartram Road, Bristol, PA 19007.
3. This mixture is rather hygroscopic and must be maintained under a nitrogen atmosphere as much as possible.
4. Stirring facilitates the hydrolysis. The reaction mixture should be added relatively slowly since the decomposition is exothermic.
5. Material of this purity may be used directly in the ensuing step. However, lower yields are realized.
6. Earlier citations[2,3] report mp 81–82°C. This product has the following spectral properties: IR (KBr) cm^{-1}: 2124, 1338, 1164, 854, 779; ^{1}H NMR ($CDCl_3$) δ: 0.22 (s, 9 H), 2.48 (s, 3 H), 7.40 (d, 2 H, *J* = 9), 7.91 (d, 2 H, *J* = 9). MS (CI, 70 eV, isobutane) 253 (M^+ + 1, 100). Anal. calcd. for $C_{12}H_{16}O_2SSi$: C, 57.10; H, 6.40; S, 12.70. Found: C, 57.84; H, 5.88; S, 12.85. The checkers found that treatment of the crude solid with activated charcoal is required to obtain colorless product.
7. The checkers found that the reaction is complete immediately after addition if the temperature is maintained accurately at 30°C. The reaction rate is dramatically dependent on the reaction temperature. The submitters report that considerable resinous material is obtained if the temperature goes above 30°C.
8. This period of reaction may vary depending on the scale of the reaction. Progress may be easily followed by isolating aliquots and obtaining ^{1}H NMR spectra. The disappearance of the trimethylsilyl singlet is the observable diagnostic.
9. The checkers found that an impurity with a characteristic ^{1}H NMR singlet at 3.74 ppm is readily removed by recrystallization, but cannot be removed by chromatography. They also report that small amounts of this impurity are formed during flash chromatography on silica gel.
10. The ^{1}H NMR spectral characteristics of this sulfone are as follows ($CDCl_3$) δ: 2.47 (s, 3 H), 3.52 (s, 1 H), 7.38 (dd, 2 H, *J* = 8.5, 0.6), 7.88 (d, 2 H, *J* = 8.5). Its IR spectrum (KBr) consists of the following bands (cm^{-1}): 3235, 2013, 1337,

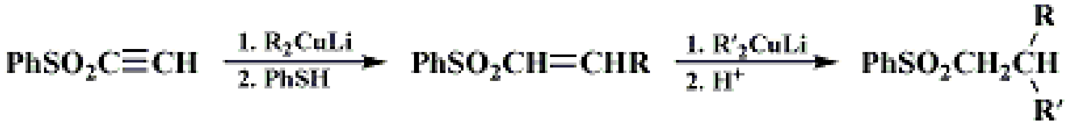
1156. MS (CI, 70 eV, isobutane) 181 (M^+ + 1, 100). Anal. calcd. for $C_9H_8SO_2$: C, 59.97; H, 4.47; S, 17.79. Found: C, 59.20; H, 4.55; S, 17.52.

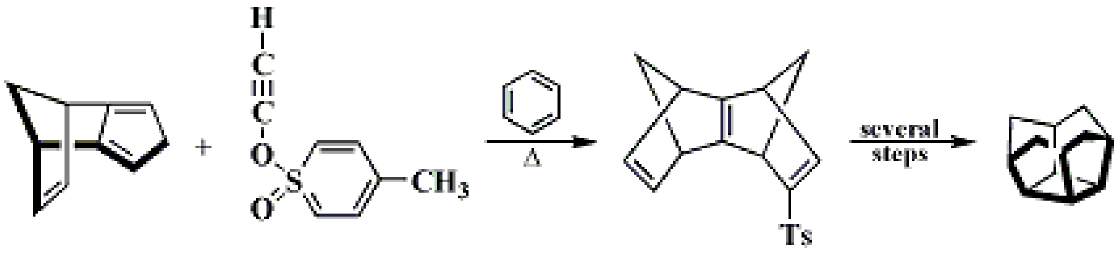
11. Further purification can be achieved if desired by recrystallization of this material from hexane–ethyl acetate (95 : 5). Shiny needles that melt at 75°C are thereby obtained.

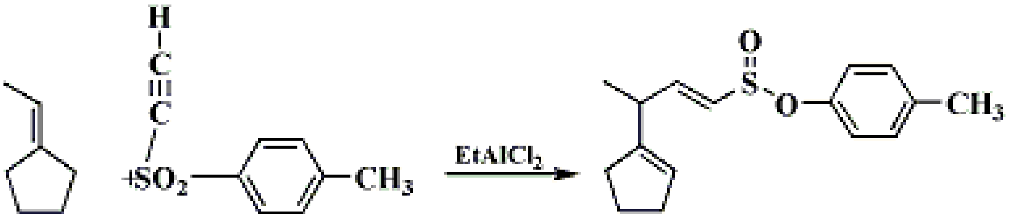
3. Discussion

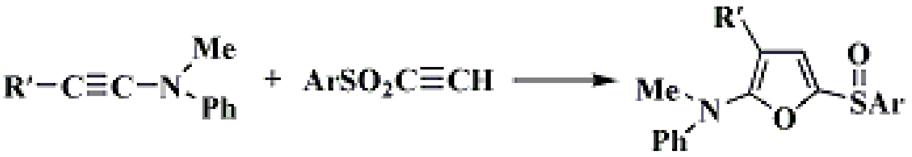
Interest in arylsulfonyl acetylenes arose initially because of their powerful Michael acceptor properties. Examples of facile nucleophilic addition involving thiolates (Eq. 1),[4,5,6,7] amines,[2] cuprates (Eq. 2),[8] malonate anions,[9] alkoxides,[10,11] hydroxylamines,[12,13] and azlactone enolates[14] abound. More recently, the dienophilic properties of this class of compounds have been used to advantage, such as use of the title compound as an acetylene synthon in Diels–Alder cycloadditions,[15,16] its [4+2] capture by *N*-methoxycarbonylpyrrole in a first step toward the elusive 7-azanorbornadiene,[17] and its pivotal role in a synthesis of [4]-peristylane (Eq. 3).[18] Ethynyl *p*-tolyl sulfone undergoes $EtAlCl_2$-catalyzed ene reactions with alkenes to give 1,4-dienyl *p*-tolyl sulfones (Eq. 4).[19] Condensations with ynamines to give 2-amino-5-arylsulfinylfurans (Eq. 5) have been reported.[20] α,β-Acetylenic sulfones also react with organolithium and Grignard reagents to give the correspondingly higher acetylene (Eq. 6).[21]

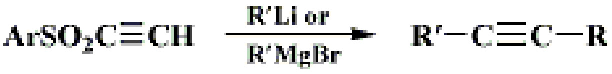












The procedures used most often for preparation of arylsulfonyl acetylenes involve oxidation of the corresponding ethynyl thio ether. The thio ethers are usually obtained via a two-step sequence beginning with twofold thiophenoxide displacement of chloride ion from *cis*-1,2-dichloroethylene, followed by elimination with n-butyllithium in the resultant *cis*-1,2-bisarylthioethylene.[19] Less well known methods involve diazotization of 4-arylsulfonyl-5-aminoisoxazoles,[22] dehydrobromination of *cis*- and *trans*-2-bromovinyl phenyl sulfone with fluoride ion,[23] and oxidative elimination of β-(phenylseleno)vinyl sulfones.[24] The method described here, which bypasses the need for strongly basic conditions, is adapted from the work of Bhattacharya et al.[3] The simplicity and mildness of the method suggest that it may be broadly useful.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

brine

potassium carbonate (584-08-7)

acetylene (74-86-2)

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

methanol (67-56-1)

chloroform (67-66-3)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

aluminum chloride (3495-54-3)

dichloromethane (75-09-2)

n-butyllithium (109-72-8)

hexane (110-54-3)

potassium bicarbonate (298-14-6)

calcium hydride (7789-78-8)

trimethylsilyl (16571-41-8)

p-Toluenesulfonyl chloride (98-59-9)

bis(trimethylsilyl)acetylene (14630-40-1)

Benzene, 1-(ethynylsulfonyl)-4-methyl-, ETHYNYL p-TOLYL SULFONE (13894-21-8)

silylacetylene

7-azanorbornadiene

cis-1,2-dichloroethylene (156-59-2)

p-Tolyl 2-(trimethylsilyl)ethynyl sulfone (34452-56-7)

N-methoxycarbonylpyrrole (4277-63-8)

trans-2-bromovinyl phenyl sulfone

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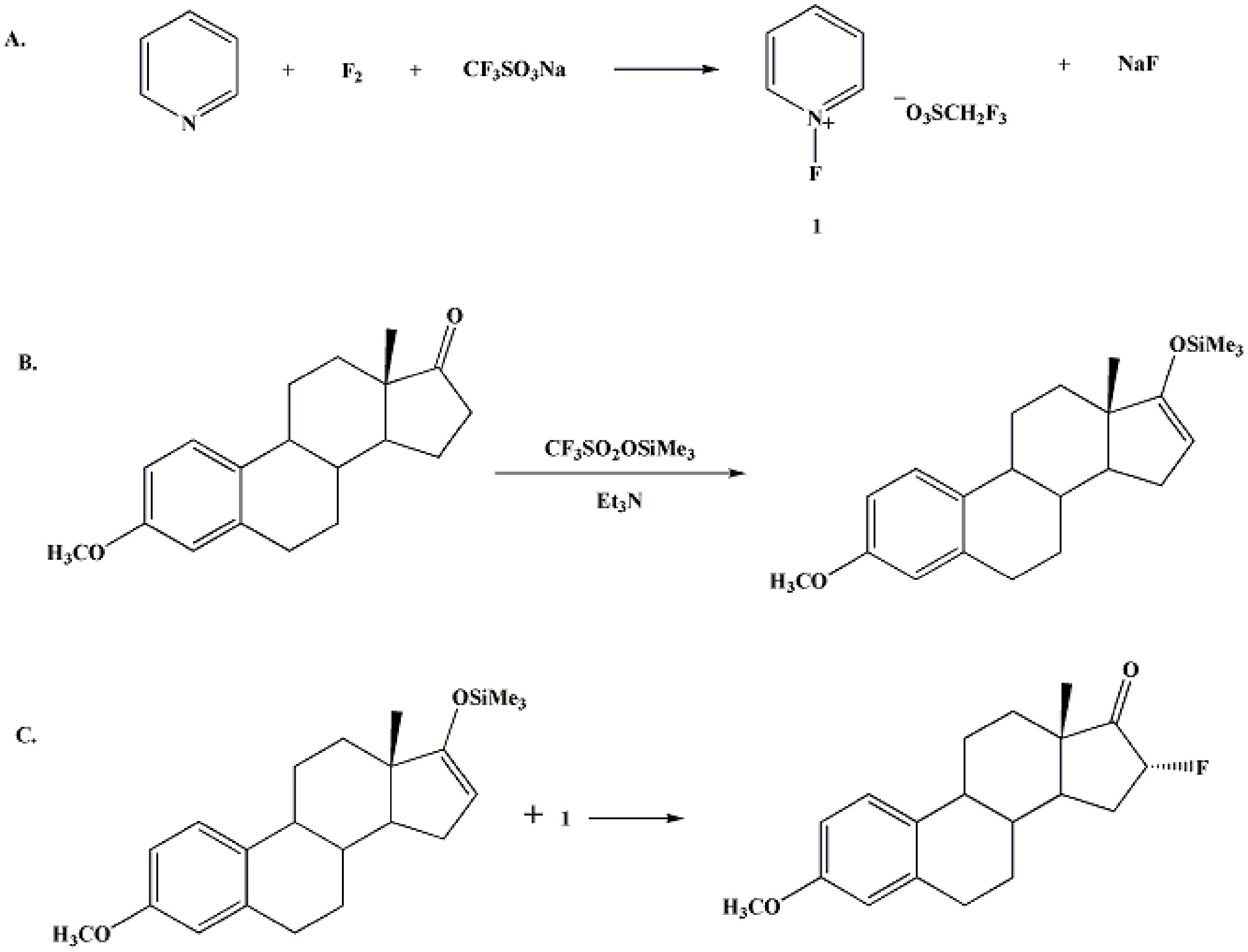
Organic Syntheses, CV 8, 286

N-FLUOROPYRIDINIUM TRIFLATE: AN ELECTROPHILIC FLUORINATING AGENT

[Pyridinium, 1-fluoro-, salt with trifluoromethanesulfonic acid (1:1)]



Submitted by Teruo Umemoto[1], Kyoichi Tomita[1,2], and Kosuke Kawada[1,2].
Checked by Shlomo Rozen and Bruce E. Smart.

1. Procedure

Caution! Molecular fluorine is a very toxic and corrosive gas. The following reaction should be carried out in an efficient fume hood, and the experimenter should be familiar with the precautions necessary for safe handling of fluorine.[3] Since molecular fluorine diluted with an inert gas is much safer to handle than pure fluorine, the use of a fluorinel nitrogen mixture comprising no more than 20% fluorine is recommended.

A. *N-Fluoropyridinium triflate* ***(1).*** The reaction is carried out in the apparatus shown in f.htmigure 1. The pressure regulator on the cylinder containing a mixture of 20% fluorine/80% nitrogen (Note 1), and the pressure gauge and flowmeter on the fluorine line are specifically designed for fluorine service (Note 2). The fluorine and nitrogen cylinders, pressure regulators, flowmeters, valves, and filters are connected with stainless-steel tubing. The Pyrex glass reaction vessel is connected to the metal tubing via Viton® tubing, and the fluorine gas is introduced into the vessel through a Pyrex glass tube (7 mm o. d.). The gas outlet from the reaction vessel is connected to a granular alumina trap which consumes molecular fluorine.

Figure 1. A—flowmeter (Matheson model 7825); B—flowmeter (Hastings model CST); C—alumina trap; D—reactor system; E—bubble counter containing perfluorotributylamine; F—pressure regulator (Matheson model 63–5512); G, I, K, O, P—stainless-steel values; H—pressure gauge (Matheson model 63–5512); J, N—stainless-steel filters; L—pressure regulator for nitrogen; M, Q, R, S—brass valves; T—Viton tubing; U—Teflon corks; V—Pyrex Claisen Adapter; W—Pyrex flask; X—Pyrex tube; Y—Teflon-coated stirring bar; Z— −40°C cooling bath.

Figure 1. A—flowmeter (Matheson model 7825); B—flowmeter (Hastings model CST); C—alumina trap; D—reactor system; E—bubble counter containing perfluorotributylamine; F—pressure regulator (Matheson model 63–5512); G, I, K, O, P—stainless-steel values; H—pressure gauge (Matheson model 63–5512); J, N—stainless-steel filters; L—pressure regulator for nitrogen; M, Q, R, S—brass valves; T—Viton tubing; U—Teflon corks; V—Pyrex Claisen Adapter; W—Pyrex flask; X—Pyrex tube; Y—Teflon-coated stirring bar; Z— –40°C cooling bath.

The 300-mL, round-bottomed reaction flask is charged with 4.74 g (0.06 mol) of pyridine (Note 3), 10.3 g (0.06 mol) of sodium triflate (Note 4), and 80 mL of dry acetonitrile (Note 5). The system is purged with nitrogen, and the reaction mixture is chilled and maintained at –40°C. The flow of dilute fluorine is started, and the flow rates from the nitrogen and fluorine cylinders are adjusted to introduce a 10% fluorine/90% nitrogen mixture at a rate of 90 mL/min just above the surface of the rapidly stirred solution (Note 6). When a total of 2.7 L of fluorine (0.12 mol) is introduced (Note 7), the flow of fluorine is discontinued and nitrogen only is flowed through the system at a rate of 45 mL/min for 30 min while keeping the reaction mixture at –40°C. The reaction mixture is then warmed to room temperature and filtered through a pad of Celite to remove the sodium fluoride. The filtrate is concentrated to dryness with a rotary evaporator without heating. The crystalline residue is washed with 30 mL of dry ethyl acetate to give 11.0–12.0 g (74–81%) of crude product, mp 178–181°C. The crude material is dissolved in 18 mL of dry acetonitrile at room temperature, and 36 mL of dry diethyl ether is added. The precipitated crystals are collected by filtration under nitrogen (Note 8) to give 10.0–10.3 g (68–70%) of pure *N*-fluoropyridinium triflate, mp 182°C (Note 9),(Note 10),(Note 11).

B. *3-Methoxy-17-trimethylsiloxy-1,3,5(10), 16-estratetraene.* A 125-mL, two-necked round-bottomed flask equipped with a reflux condenser and a magnetic stirrer is purged with argon and charged with 6.8 g (0.024 mol) of estrone 3-methyl ether (Note 12), 50 mL of dry benzene, and 4.0 mL (2.9 g, 0.029 mol) of triethylamine. The solution is stirred, 4.9 mL (5.6 g, 0.025 mol) of trimethylsilyl triflate (Note 13) is added through a syringe, and the mixture is refluxed for 1.5 hr. The reaction mixture is allowed to cool to room temperature, whereupon it separates into two layers. Dry hexane (40 mL) is added, and the upper hexane–benzene layer is separated, washed successively with saturated sodium bicarbonate and water, and then dried over magnesium sulfate. The drying agent is removed by filtration, and the filtrate is transferred to a 125-mL, round-bottomed, tared flask. The solution is evaporated to a constant weight with a rotary evaporator, initially at water-aspirator pressure and then at 0.5–1 mm, to leave 8.6 g (100%) of pale-yellow enol trimethylsilyl ether. This material is used immediately in Part C without purification (Note 14).

C. *16α-Fluoro-3-methoxy-1,3,5(10)-estratrien-17-one (16α-fluoroestrone 3-methyl ether).* The 125-mL, round-bottomed flask containing the enol silyl ether from Part B is purged with argon, and 50 mL of dry dichloromethane is added. *N*-Fluoropyridinium triflate **(1)** (6.5 g, 0.026 mol) is added in one portion, and the mixture is stirred at 20–25°C for 8 hr (Note 15). The reaction mixture is poured into water and extracted with three 60-mL portions of dichloromethane. The combined organic extracts are washed with saturated sodium bicarbonate and then with water, and dried over magnesium sulfate. The drying agent is removed by filtration and the solution is evaporated to dryness with a rotary evaporator. The resulting pale-yellow solid is column-chromatographed on silica gel (250 g, 60 × 4.5-cm column) using dichloromethane eluant (Note 16) to give 950 mg (14%) of estrone 3-methyl ether starting material and 4.8 g (66%) of 16α-fluoroestrone 3-methyl ether as a colorless solid, mp 157°C (Note 17),(Note 18),(Note 19).

2. Notes

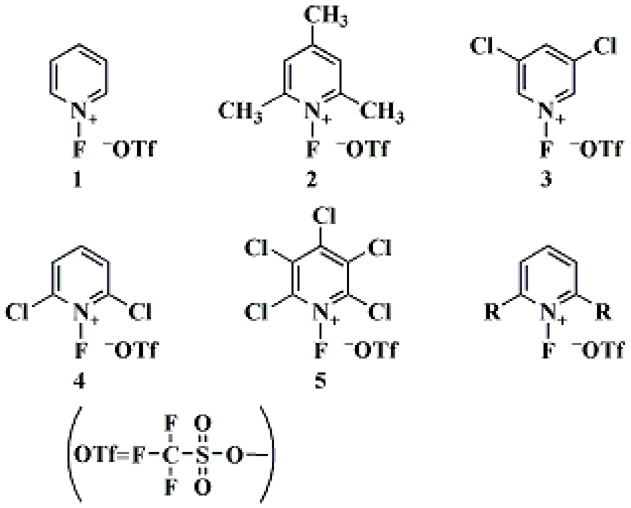
1. A cylinder containing 20% fluorine/80% nitrogen was obtained from Air Products & Chemicals, Inc.
2. The checkers used a Matheson model B15F-679 single-stage pressure regulator, a model 63-5512 pressure gauge, and a model 7825 flowmeter. Information on equipment designed to handle fluorine can be found in the bulletin Tech-Brief TB-115, published by Matheson Gas Products.
3. Anhydrous pyridine (≥99%) packaged under nitrogen was purchased from Aldrich Chemical Company, Inc., and used without further purification.
4. Sodium trifluoromethanesulfonate (triflate) was prepared from trifluoromethanesulfonic acid (Aldrich Chemical Company, Inc.) as follows. A solution of 26.5 g (0.66 mol) of sodium hydroxide in 50 mL of water was added dropwise to 100 g (0.67 mol) of triflic acid chilled in an ice bath. The solution was concentrated to dryness with a rotary evaporator, and the residual solid was recrystallized from 65 mL of acetonitrile. The collected solid is dried at 80°C under vacuum for 24 hr to give 90 g of pure sodium triflate.
5. Acetonitrile was distilled from calcium hydride under nitrogen immediately before use.
6. A powerful magnetic stirrer was used to obtain a stirring rate of about 80 rps. The checkers also used a VIBRO-Mixer E1 (Chemapec, Inc.). The checkers found that the yield was unaffected if the fluorine is introduced below rather than above the surface of the solution.
7. A substantial excess of fluorine over the theoretical, equimolar amount is needed to complete the reaction because of the low solubility of fluorine. The amount of fluorine required can vary depending on the scale of reaction, the flow rate, and the efficiency of mixing.
8. The submitters carried out the filtration procedure in air. Filtration in wet air should be avoided.
9. The submitters report obtaining 13.2 g of crude product, mp 181–184°C, and 12.0 g (81%) of recrystallized material, mp 185–187°C.
10. The product obtained by the checkers is pure by NMR analyses. *N*-Fluoropyridinium triflate **(1)** has the following spectral properties: ^{1}H NMR (CD_3CN) δ: 8.32 (m, 2 H), 8.77 (m, 1 H), 9.33 (dd, 2 H, *J* = 16.7); ^{19}F NMR (CD_3CN) δ: 48.8 (bs, 1 F, N-F), –77.6 (s, 3 F, CF_3): IR (Nujol on NaCl plate) cm^{-1}: 3140 (s), 3120 (s), 3080 (s), 3050 (s), 1600 (m), 1485 (s), 1475 (s), 1330 (w), 1270 (s), 1250 (s), 1220 (s), 1200 (s), 1175 (s), 1160 (s), 1090 (m), 1055 (w), 1020 (s), 805 (m), 770 (s), 755 (m), 630 (s).
11. *N*-Fluoropyridinium triflate is stable and can be stored indefinitely under a dry atmosphere. It slowly decomposes in water. The submitters report that it has a half-life of 13 days in D_2O at room temperature.
12. Estrone 3-methyl ether [3-methoxyestra-1,3,5(10)-trien-17-one] was purchased from Sigma Chemical Company.
13. Trimethylsilyl triflate was obtained from Aldrich Chemical Company, Inc. and used without further purification.
14. The product exhibits the following partial spectral data: ^{1}H NMR ($CDCl_3$) δ: 0.21 (s, 9 H, CH_3Si), 0.87 (s, 3 H, 18-CH_3), 3.77 (s, 3 H, OCH_3), 4.53 (m, 1 H, 16-H). This silyl enol ether is sensitive to hydrolysis, and the submitters recommend that it be isolated in the same flask that is used for its subsequent reaction in Part C.
15. Crystals of **1** gradually disappear as the reaction proceeds, and the mixture turns orange and finally becomes homogeneous when the reaction is completed.
16. Each fraction was monitored by thin-layer chromatography on silica gel (Merck Silica Gel 60 F-254). The R_f values (dichloromethane) of the product and starting estrone 3-methyl ether are 0.53 and 0.40, respectively.
17. The product has the following characteristic spectral properties: ^{1}H NMR (360 MHz, $CDCl_3$) δ: 0.95 (s, 3 H, 18-CH_3), 3.77 (s, 3 H, OCH_3), 5.13 (dd, 1 H, *J* = 50.6, 7.3, 16 β-H), 6.64 (d, 1 H, *J* = 2.7, 4-H), 6.72 (dd, 1 H, *J* = 8.6, 2.7, 2-H), 7.19 (d, 1 H, *J* = 8.6, 1-H); ^{19}F NMR ($CDCl_3$) δ: –192.7 (m); IR (KBr) cm^{-1}: 2900, 2850, 1750, 1600, 1500, 1460, 1440, 1310, 1240, 1030, 1000: MS *m/e* (relative intensity) 304 (2.7), 303 (21.5), 302 (M^+) (100), 301 (3.7).
18. The product contains about 4% of the 16β-fluoroestrone epimer; ^{1}H NMR (360 MHz, $CDCl_3$) δ: 4.76 (dt, *J* = 50, 8; 16α-H); ^{19}F NMR ($CDCl_3$) δ: –185.3 (dd, *J* = 50, 22; 16β-F).
19. Identical yields of recovered starting material and product were obtained when Parts B and C were run on 2.5 times the scale. The submitters report obtaining a 78% yield of product, mp 145–149°C (recrystallized from ethyl acetate/hexane after chromatography) containing a small but unspecified amount of its epimer, along with 11% recovered starting material and 12% 2-pyridyl triflate, which is a decomposition product of **1**. Anal. calcd. for $C_{19}H_{23}O_2F$: C, 75.47; H, 7.66. Found: C, 75.52; H, 7.81.

3. Discussion

Electrophilic fluorinating agents such as F_2,[4] CF_3OF,[5] $FClO_3$,[6] CF_3COOF,[7] CH_3COOF,[8] XeF_2,[9] and $CsSO_4F$[10] require the use of special equipment and techniques because of their explosive, toxic, unstable, or hygroscopic nature. *N*-Fluoroperfluoropiperidine,[11] *N*-fluoropyridone,[12] and *N*-fluoro-*N*-alkyltoluenesulfonamides[13] are easy to handle, but their low reactivity limits the scope of their applications. Recently, a variety of fluorinating agents have been developed; *N*-fluoroquinuclidinium salts,[14] *N*-fluorobis[(trifluoromethyl)sulfonyl]imide,[15] *N*-fluorosultams,[16] *N*-fluoro-3,3-dimethyl-2,3-dihydro-1,2-benzothiazole 1,1-dioxide,[17] perfluoro-[*N*-fluoro-*N*-(4-pyridyl)methanesulfonamide],[18] *N*-fluoro-*o*-

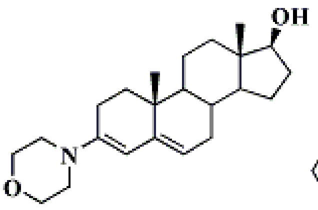
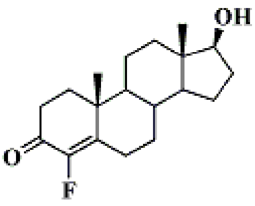
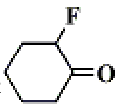
benzenedisulfonimide,[19] *N*-fluorobenzenesulfonimide,[20] and *N*-fluorotriethylenediammonium salts.[21]

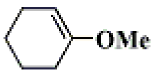
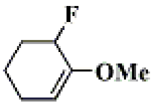
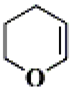
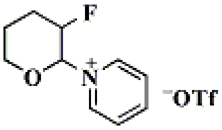
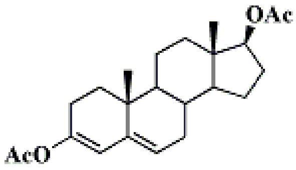
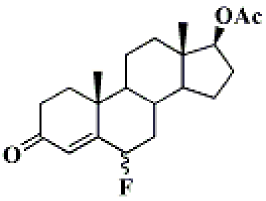
N-Fluoropyridinium trifluoromethanesulfonate (triflate) and its analogs are widely applicable, stable fluorinating agents with varying degrees of power and selectivity in fluorinations.[22 23 24 25 26 27 28 29 30 31] The procedure given here represents a general method for preparing substituted *N*-fluoropyridinium triflates. *N*-Fluoropyridinium salts with a different counter anion such as BF_4, PF_6, or ClO_4 can be prepared in good yields by the same method. However, depending on the ring substituents or counteranions, the modified or other methods should be adopted.[24,25] Counteranion-bound *N*-fluoropyridinium salts **6** and **7** are prepared in good yields by fluorination of the corresponding pyridinesulfonic acids with 10% F_2/N_2 in aqueous acetonitrile at −20°C.[24,25]



The reactivity of the *N*-fluoropyridinium salts can be adjusted by varying the substituents on the pyridine ring. Triflates **1–5**, whose fluorinating power increases in the order **2** < **1** < **3** < **4** < **5**, are the most generally useful reagents. Salts **6 and 7**, power order **6** < **7**, are the highly selective reagents. Other useful *N*-fluoropyridinium salts were described in the paper.[23] The reagents are all stable, crystalline materials and thus can be handled routinely. However, it should be noticed that the relative stability of the *N*-fluropyridinium salts decreases with increasing fluorinating power. Examples of fluorinations which illustrate their use are given in Table I. The weakest reagent, **2**, is most suited for fluorinating reactive or easily oxidized compounds, such as carbanions, enamines, and sulfides, whereas the most potent reagents **4** and **5** are preferred for fluorinating alkenes and aromatic rings. Salt **1** of intermediate reactivity is effective with moderately electron-rich substrates, such as enol alkyl ethers, enol silyl ethers, and activated vinyl acetates. Salt **3** is useful with activated aromatic compounds but an elevated reaction temperature is required.

TABLE I
ELECTROPHILIC FLUORINATIONS WITH *N*-FLUOROPYRIDINIUM TRIFLATES

Substrate	Reagent[a]	Conditions	Product	Yield (%)[b]			
n-$C_{12}H_{25}MgCl$	**2**	0°C, 30 min in Et_2O	*n*-$C_{12}H_{25}F$	75[c]			
$NaCH(COOEt)_2$	**2**	0°C, 0.1 hr in THF	$CHF(COOEt)_2$	73			
$CH_2(COOEt)_2$	**2**[d]	$AlCl_3$,[e] 80° C 24 hr in CH_2ClCH_2Cl	$CF_2(COOEt)_2$	76[f]	$CHF(COOEt)_2$	19[f]	
			p-$ClC_6H_4SCH_3$	**2**	RT, 8 hr in CH_2Cl_2	*p*-$ClC_6H_4SCH_2F$	76
	**2**	(1) −15°C, 1 hr in $CH_2Cl_2/CH_3CN(1/4)$		54	**1**	(2) RT, ca. 12 hr in conc. HCl/DMF	46
		1		RT, 7 hr in CH_2Cl_2		87[c]	

	**1**	60°C, 30 min in CH_2ClCH_2Cl		63[f]
 [g]	**1**	Reflux, 7 hr in CH_2Cl_2		86[h]
	**1**	Reflux, 10 hr in CH_2Cl_2		71[f]
PhH	**5**	Reflux, 2 hr in CH_2Cl_2	Ph-F	48[f]
PhOH	**4**	RT, 5 hr in CH_2Cl_2	$F\text{-}C_6H_4OH$ (*o*:*p*)	49[c,j] (1.3:1)
PhOH	**6**	Reflux, 1.5 hr in $CHCl_2CH_2Cl$	*o*-$F\text{-}C_6H_4OH$	45[c,j]
PhNHCOOEt	**3**	Reflux, 5.5 hr in CH_2ClCH_2Cl	$F\text{-}C_6H_4NHCOOEt$ (*o*:*p*)	51[j] (2.6:1)
PhNHCOOEt	**7**	Reflux, 72 hr in CH_2ClCH_2Cl	$F\text{-}C_6H_4NHCOOEt$ (*o*:*p*)	66[j] (12:1)
$PhCH{=}CH_2$	**5**	RT, 1 hr in AcOH	$PhCH(OAc)CH_2F$	72

[a]Equimolar *N*-fluoropyridinium triflate unless noted otherwise.

[b]Isolated yields unless noted otherwise. Yield calculations based on the used amounts of triflates.

[c]GLPC yields.

[d]2 Equivalents of **2.**

[e]0.4 Equivalents of $AlCl_3$.

[f]^{19}F NMR yields.

[g]1.5 Equivalents of dihydropyran.

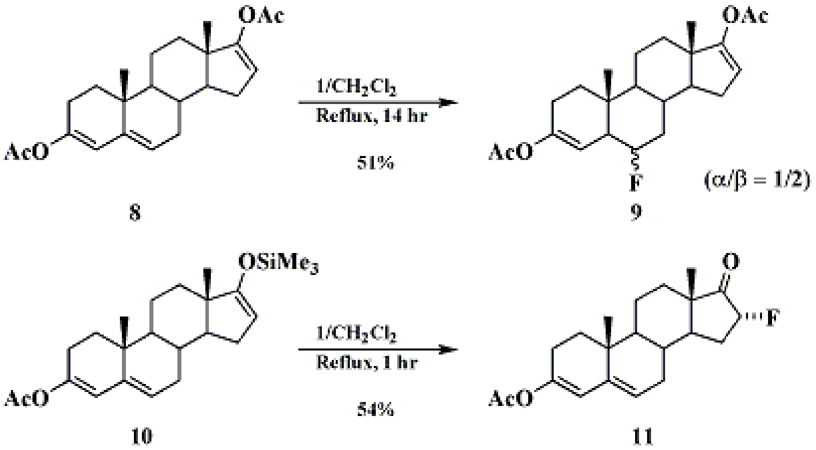
[h]*cis/trans* = 1/1.

[i]α/β = .

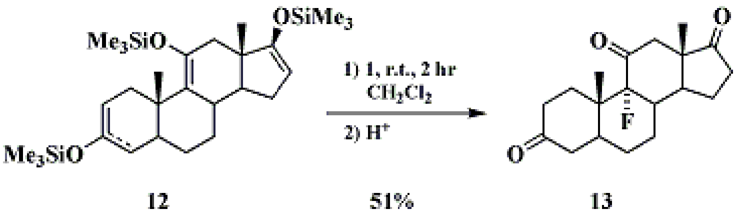
[j]A considerable amount of the starting substrate (16–38%) was recovered.

[j]α/β = .

N-Fluoropyridinium triflate shows high regioselectivity in its fluorinations, as evidenced by the results in Schemes 1 and 2. With steroids **8** and **10**, each having two reactive sites, **1** reacts to give exclusively the 6-fluoro steroid **9** and the 16-fluoro steroid **11**, respectively. Thus **1** can distinguish between a conjugated and a nonconjugated vinyl acetate, and between an enol silyl ether and a conjugated vinyl acetate in its fluorinations. The present procedure for converting estrone enol silyl ether to 16α-fluoroestrone also shows that **1** selectively reacts with an enol silyl ether moiety in the presence of an activated aromatic ring.



The fluorination of **12**, easily prepared from the corresponding triketo steroid, with an equimolar amount of **1** (Scheme 2) shows the remarkable ability of **1** to distinguish disubstituted from trisubstituted enol silyl ethers. The 9α-fluoro steroid **13** is produced in 51% yield (78% based on recovered triketo steroid) and the combined yield of the other products is only 4.6%.[23] It thus is apparent that **1** reacts almost exclusively with the trisubstituted enol ether moiety. The new, selective direct fluorination at the 9α-position holds considerable promise as a means to prepare biologically important 9α-fluoro steroids.[32]



Salt **6** or **7** affords exclusive or greatly preferential ortho-fluorination of phenol and aniline derivatives (Table I). Some fluorinations may be stereoselective. When allowed to react with 3, 17β-diacetoxy-3,5-androstadiene, **1** gives a 1 : 2 mixture of α- and β-fluorination at 6-position, while the bulky salt **2** affords a 1 : 8.5 mixture of them, resulting from less hindered fluorination.[23] A diastereoselective fluorination of a chiral enolate with salt **2** was reported.[30]

With the increasing importance of organofluorine compounds in the development of new materials, pharmaceuticals, and agricultural chemicals, *N*-fluoropyridinium salts should find extensive use as mild and selective fluorinating agents.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

fluorinel nitrogen

N-fluoro-o-benzenedisulfonimide

N-fluorobenzenesulfonimide

N-fluorotriethylenediammonium

9α-fluoro steroids

Pyridinium, 1-fluoro-, salt with trifluoromethanesulfonic acid (1:1)

Benzene (71-43-2)

ethyl acetate (141-78-6)

diethyl ether (60-29-7)

aniline (62-53-3)

acetonitrile (75-05-8)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

phenol (108-95-2)

Salt (7647-14-5)

nitrogen (7727-37-9)

pyridine (110-86-1)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

sodium fluoride (7681-49-4)

vinyl acetate (108-05-4)

dihydropyran

hexane (110-54-3)

vinyl (2669-89-8)

triethylamine (121-44-8)

calcium hydride (7789-78-8)

9α-fluoro

Fluorine (7782-41-4)

argon (7440-37-1)

triflate

trifluoromethanesulfonic acid, triflic acid (1493-13-6)

silyl (13765-44-1)

trimethylsilyl ether (107-46-0)

silyl ether (13597-73-4)

trimethylsilyl triflate (27607-77-8)

N-fluoropyridinium, N-fluropyridinium

sodium triflate, Sodium trifluoromethanesulfonate (2926-30-9)

perfluorotributylamine (311-89-7)

estrone 3-methyl ether, 3-methoxyestra-1,3,5(10)-trien-17-one

16α-Fluoro-3-methoxy-1,3,5(10)-estratrien-17-one, 16α-fluoroestrone 3-methyl ether (2383-28-0)

16β-fluoroestrone

2-pyridyl triflate (65007-00-3)

estrone enol silyl ether

16α-fluoroestrone

17β-diacetoxy-3,5-androstadiene

N-Fluoropyridinium triflate, N-Fluoropyridinium trifluoromethanesulfonate (107263-95-6)

N-Fluoroperfluoropiperidine (836-77-1)

N-fluoropyridone

N-fluoroquinuclidinium

N-fluoro-3,3-dimethyl-2,3-dihydro-1,2-benzothiazole 1,1-dioxide (124170-23-6)

perfluoro-[N-fluoro-N-(4-pyridyl)methanesulfonamide]

3-Methoxy-17-trimethylsiloxy-1,3,5(10), 16-estratetraene

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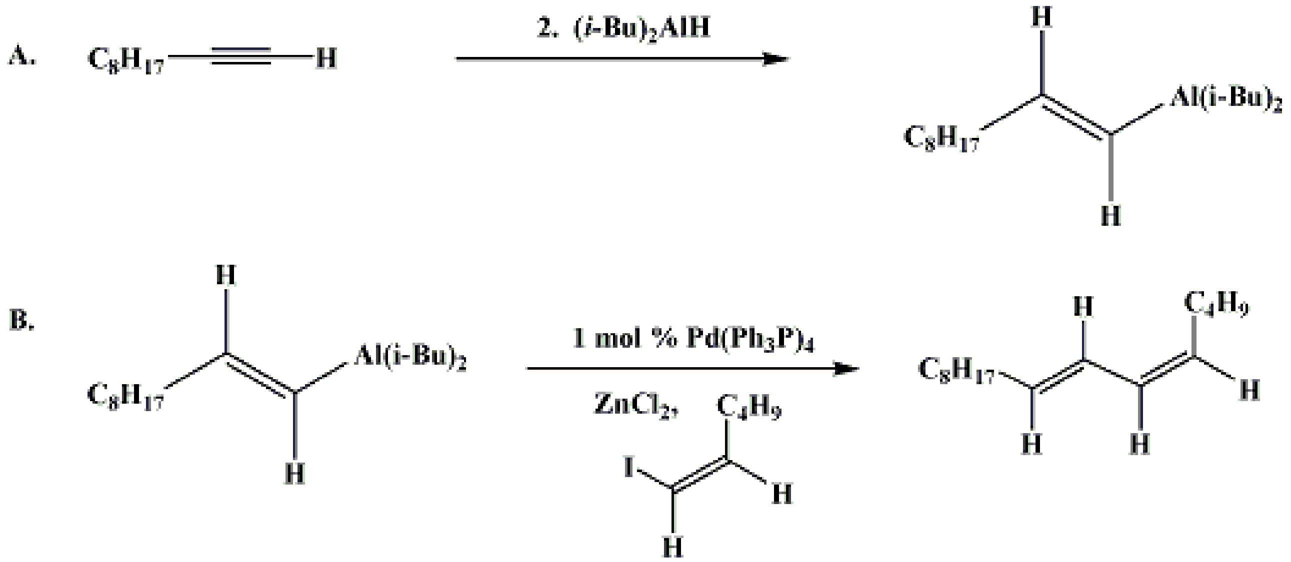
Organic Syntheses, *CV 8*, *295*

PALLADIUM-CATALYZED SYNTHESIS OF CONJUGATED DIENES: (5*Z*,7*E*)-5,7-HEXADECADIENE

[5,7-Hexadecadiene, (*Z*, *E*)-]



Submitted by Ei-Ichi Negishi, Tamotsu Takahashi, and Shigeru Baba[1].
Checked by Masako Ohta and Ryoji Noyori.

1. Procedure

Caution! Organoaluminum compounds are pyrophoric. They must be kept and used with caution under a nitrogen atmosphere.

A. *(E)-1-Decenyldiisobutylalane*. An oven-dried, 300-mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar, a rubber septum inlet, and an outlet connected to a mercury bubbler is flushed with nitrogen, immersed in a water bath kept at room temperature, and charged with 22.6 mL (125 mmol) of 1-decyne (Note 1) and 80 mL of hexane (Note 2). To this flask is added dropwise, with stirring, 22.3 mL (125 mmol) of diisobutylaluminum hydride (Note 3) using a syringe (Note 4). After the addition has been completed, the water bath is replaced with an oil bath kept at 50–60°C, and the reaction mixture is stirred for 6 hr at this temperature (Note 5).

B. *(5Z, 7E)-5,7-Hexadecadiene.* To a mixture of 21.0 g (100 mmol) of (*Z*)-1-hexenyl iodide (Note 6), 13.6 g (100 mmol) of zinc chloride (Note 7), and 1.15 g (1 mmol) of tetrakis (triphenylphosphine)palladium (Note 8) in 100 mL of tetrahydrofuran (Note 9) is added the solution of (*E*)-1-decenyldiisobutylalane prepared as described above, while the reaction temperature is controlled with a water bath at room temperature. After the reaction mixture is stirred for 6 hr at room temperature, it is slowly transferred into a mixture of 300 mL of ice-cooled 3 *N* hydrochloric acid and 100 mL of pentane via a double-ended needle under a positive pressure of nitrogen. The organic layer is separated, and the aqueous layer is extracted twice with 100 mL of pentane. The combined organic layer is washed with 100 mL of water, followed by 100 mL of saturated aqueous sodium bicarbonate, and then dried over anhydrous magnesium

sulfate. After filtration, the solvent is removed using a rotary evaporator. Hydroquinone (30 mg) is added and the residue is distilled (Note 10) to give 14.3–15.8 g [64–66% based on (*Z*)-1-hexenyl iodide] of (5*Z*,7*E*)-5,7-hexadecadiene as a colorless liquid, bp 116–119°C (1 mm) (Note 11) and (Note 12).

2. Notes

1. The submitters used 1-decyne from Farchan Laboratories, Inc. without further purification. The checkers used the material purchased from Aldrich Chemical Company, Inc. and Tokyo Kasei Kogyo Company.
2. Hexane available from Fisher Scientific Company was purified by distillation from sodium. The checkers used the solvent from Wako Pure Chemical Industries, Ltd. after distillation from sodium and benzophenone or calcium hydride under argon.
3. The submitters used neat diisobutylaluminum hydride obtained from Ethyl Corporation. The checkers used the material from Aldrich Chemical Company, Inc.
4. The submitters used a 50-mL syringe with a Luer-lock and a long (≥6-in.) 18-gauge needle, the plunger of which was lightly greased with a silicone grease. For a larger-scale operation, it is advisable to use a septum-capped graduated cylinder and a double-ended needle in place of a syringe.
5. GLC analysis of a small aliquot after iodinolysis with iodine dissolved in tetrahydrofuran indicated the formation of (*E*)-1-decenyldiisobutylalane (ca. 80%), 1-decynyldiisobutylalane (7–8%), and 1-decene (5%), together with 1-decyne (ca. 10%).
6. (*Z*)-1-Hexenyl iodide was prepared by treating acetylene with lithium dibutylcuprate followed by iodine according to an *Organic Syntheses* procedure.[2]
7. Zinc chloride available from Mallinckrodt, Inc. was flame-dried under a slow stream of nitrogen. The checkers used the material from Wako Pure Chemical Industries, Ltd. after heating under vacuum (1 mm).
8. Tetrakis(triphenylphosphine)palladium was prepared according to an *Inorganic Syntheses* procedure.[3] The submitters used a freshly prepared, shiny yellow crystalline sample of the palladium complex. On standing for an extended period of time (more than a few weeks), its color gradually darkens. The checkers used tetrakis(triphenylphosphine) palladium purchased from Aldrich Chemical Company, Inc.
9. Tetrahydrofuran available from Fisher Scientific Company or Wako Pure Chemical Industries, Ltd. was distilled from sodium and benzophenone.
10. Hydroquinone was added to avoid polymerization of the diene product.
11. Gas chromatographic examination of the reaction mixture using a 2-ft column of 20% SE-30 on Chromosorb W with undecane as an internal standard (200°C) indicates that (5*Z*,7*E*)-5,7-hexadecadiene is formed in 86–90% yield, based on (*Z*)-1-hexenyl iodide. The product obtained by this procedure shows the following properties: n_D^{23} 1.4662; IR (neat) cm^{-1}: 1630 (w), 1370 (w), 978 (m), 943 (m), 720 (m); ^1H NMR [CCl_4, $(CH_3)_4Si$] δ: 0.8–1.0 (m, 6 H), 1.15–1.5 (m, 16 H), 1.9–2.3 (m, 4 H) m, 5.15 (dt, 1 H, *J* = 10, 8), 5.61 (dt, 1 H, *J* = 14, 7) 5.92 (dd, 1 H, *J* = 10, 11), 6.30 (dd, 1 H, *J* = 11, 14).
12. (5*E*,7*E*)-5,7-Hexadecadiene can be prepared in the same manner as described except that (*E*)-1-hexenyl iodide is used in place of its (*Z*) isomer. The (*E*) iodide is obtainable by treating (*E*)-1-hexenyldiisobutylalane, prepared from 1-hexyne and diisobutylaluminum hydride, with iodine in tetrahydrofuran.[4] The (*E*,*E*) diene prepared by this procedure shows the following properties: n_D^{23} 1.4671; IR (neat) cm^{-1}: 1370 (w), 982 (m), 722 (m); ^1H

NMR [CCl_4, $(CH_3)_4Si$] δ: 0.89 (t, 6 H, *J* = 6), 1.15–1.7 (m, 16 H), 1.8–2.2 (m, 4 H), 5.2–6.15 (m, 4 H): ^{13}C NMR [$CDCl_3$, $(CH_3)_4Si$] δ: 13.93, 14.06, 22.34, 22.76, 29.40, 29.62, 31.16, 31.78, 32.03, 32.37, 32.72, 130.59, 132.19, 132.26.

3. Discussion

The procedure described here is based on two reports by Negishi and his co-workers.[5,6] The original procedure[5] did not use zinc chloride as the second catalyst and required ca. 5 mol% of Pd$(PPh_3)_4$. The preparation of (*E*)-1-alkenylalane via hydroalumination was first reported by Wilke and Müller.[7] The procedure used here is essentially that which was described by Zweifel.[8]

The first highly stereoselective and satisfactory syntheses of conjugated dienes of general applicability are those based on organoboron chemistry reported by Negishi for (*E*,*E*) dienes[9] and (*E*,*Z*) dienes[10] as well as by Zweifel for (*Z*,*Z*) dienes.[11]

The method described here represents the first highly selective and general cross-coupling procedure for preparing conjugated dienes.[5,6] Subsequently, several variations of the above-described method have been published by Negishi and others. Some salient features of these investigations are as follows. First, palladium–phosphine complexes, such as Pd$(PPh_3)_4$, are preferred to nickel complexes,[5] which tend to reduce stereoselectivity. Second, all three possible stereoisomers may be prepared using this methodology. Third, in addition to Al, Zr,[12] Mg,[13 14] B,[15] and Cu[16] have been shown to participate in Pd-catalyzed alkenyl–alkenyl cross-coupling. Fourth, the reaction is markedly accelerated by the addition of zinc and cadmium halides, such as $ZnCl_2$, $ZnBr_2$, and $CdCl_2$,[6] at least in cases where organometals containing Al,[6] Zr,[6] and Cu[16] are used. This and other observations suggest that alkenylzinc derivatives are probably the most reactive organometals in this reaction,[6] although no systematic comparisons have been made so far. Otherwise, the choice of metal depends on the stereochemistry of the desired product the required chemoselectivity, and other factors. For example, (*E*)-alkenyl metals are most directly available via hydroalumination,[8] carboalumination,[17 18] hydroboration,[19] or hydrozirconation[20] of alkynes. In cases where the use of such derivatives is desirable, Al. B. or Zr should be considered first. On the other hand, (*Z*)-alkenyl metals are often readily available via carbocupration[21] of alkynes, and they may be used directly or via formation of the corresponding (*Z*)-alkenyl iodide.

Together with the organoboron procedures mentioned above, the Pd-catalyzed cross coupling procedures have been applied to the synthesis of a wide variety of insect pheromones, terpenoids, and carotenoids.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

acetylene (74-86-2)

hydrochloric acid (7647-01-0)

hydroquinone (123-31-9)

sodium bicarbonate (144-55-8)

nitrogen (7727-37-9)

iodine (7553-56-2)

Benzophenone (119-61-9)

sodium (13966-32-0)

palladium (7440-05-3)

zinc chloride (7646-85-7)

1-Decyne (764-93-2)

Pentane (109-66-0)

magnesium sulfate (7487-88-9)

iodide (20461-54-5)

Tetrahydrofuran (109-99-9)

hexane (110-54-3)

1-Hexyne (693-02-7)

calcium hydride (7789-78-8)

diisobutylaluminum hydride (1191-15-7)

argon (7440-37-1)

undecane (1120-21-4)

1-decene (872-05-9)

Tetrakis(triphenylphosphine)palladium (14221-01-3)

(Z)-1-hexenyl iodide (16538-47-9)

lithium dibutylcuprate

1-decynyldiisobutylalane

(5Z,7E)-5,7-Hexadecadiene, (5Z, 7E)-5,7-Hexadecadiene, 5,7-Hexadecadiene, (Z, E)- (86883-79-6)

(E)-1-Decenyldiisobutylalane (107441-86-1)

(5E,7E)-5,7-Hexadecadiene

(E)-1-hexenyl iodide

(E)-1-hexenyldiisobutylalane

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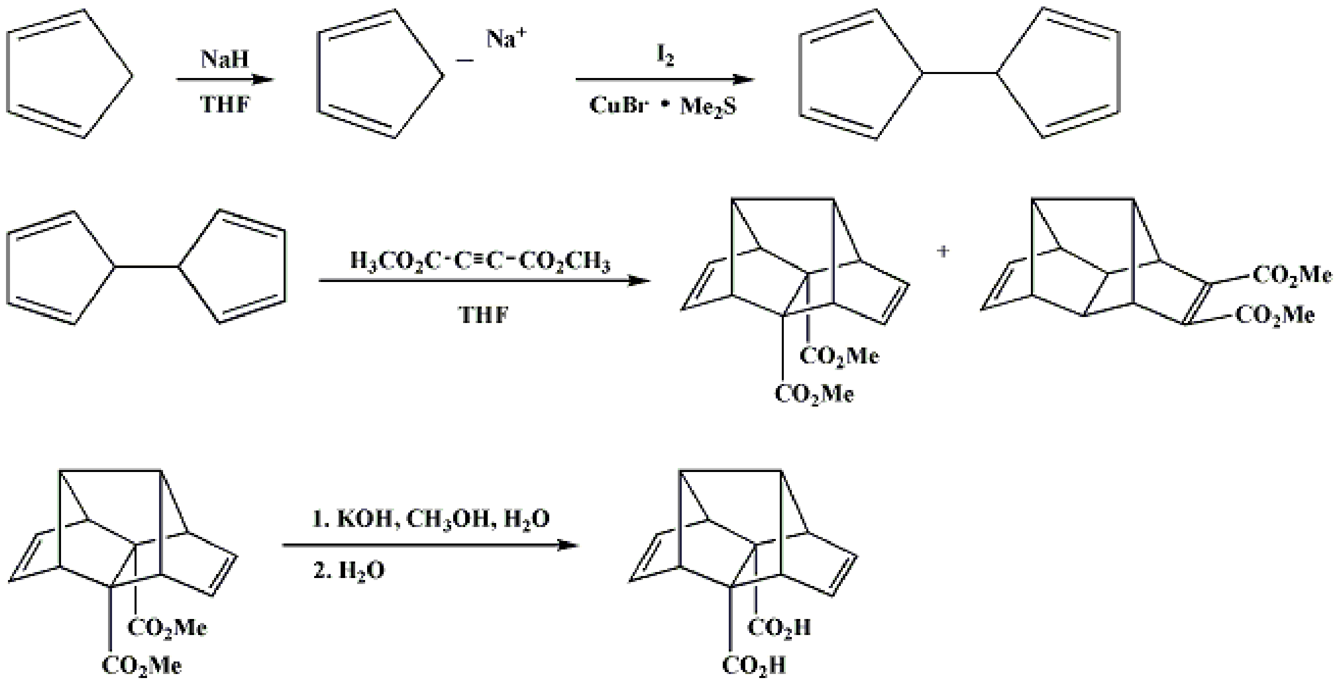
Organic Syntheses, CV 8, 298

DOMINO DIELS–ALDER REACTION: 3,3a,3b,4,6a,7a-HEXAHYDRO-3,4,7-METHENO-7*H*-CYCLOPENTA[*a*]PENTALENE-7,8-DICARBOXYLIC ACID

[3,4,7-Metheno-7*H*-cyclopenta[*a*]pentalene-7,8-dicarboxylic acid, 3,3a,3b,4,6a,7a-hexahydro]



Submitted by Richard T. Taylor[1], Michael W. Pelter[1], and Leo A. Paquette[2].
Checked by Katsunori Nagai and Ryoji Noyori.

1. Procedure

All apparatuses for Steps A and B should be dried overnight in an oven.

A. *9,10-Dihydrofulvalene.* A 5-L, three-necked, round-bottomed flask is fitted, while hot, with a Hirschberg stirrer, gas inlet, and stopper (Note 1). The assembled apparatus is flame-dried and allowed to cool to room temperature under a stream of dry, oxygen-free argon (Note 2). The stopper is replaced with a powder funnel and, under a sweep of positive argon, 100 g (4.17 mol) of dry sodium hydride (Note 3) is added followed by 2.0 L of dry tetrahydrofuran (Note 4). The powder funnel is replaced by a 500-mL, pressure-equalizing, jacketed addition funnel that is flushed with argon, then stoppered.

The stirred sodium hydride suspension is cooled by an external ice–water bath and the jacket of the addition funnel is cooled in a dry ice–isopropyl alcohol bath. Into the addition funnel is introduced 275 g (4.16 mol) of neat, freshly distilled cyclopentadiene (Note 5). The cyclopentadiene is added rapidly, dropwise over 30–40 min to the stirred slurry *(Caution: Avoid excess foaming.)* (Note 6). After the addition is complete, the cooling bath is removed and the solution is stirred for 1 hr at room temperature.

The jacketed addition funnel is removed and 1.5 g of cuprous bromide–dimethyl sulfide complex (Note 7) is added through a powder funnel. A 500-mL, pressure-equalizing addition funnel (long-tipped) is attached to the flask and flushed with argon. As the anion solution is cooled in a dry ice–isopropyl alcohol bath, a solution of 530 g (2.08 mol) of sublimed iodine in 500 mL of anhydrous tetrahydrofuran is placed in the addition funnel. This solution is added dropwise to the cooled slurry over approximately 90 min (Note 8). The solution is stirred for about 15 min at low temperature.

B. *Diels–Alder reaction.* A 500-mL, pressure-equalizing addition funnel containing 330 g (2.32 mol) of dimethyl acetylenedicarboxylate (Note 9) is placed in the flask and the ester is added rapidly dropwise over 10 min. The solution is stirred for 30 min, the cooling bath is removed, and stirring is maintained for 4 hr (Note 10).

The reaction solution is filtered through a Celite pad (ca. 5 cm thick on a 32-cm Büchner funnel), and the solid is washed repeatedly with tetrahydrofuran (1.5 L). The combined filtrates are concentrated under reduced pressure at a temperature

not above 30°C. To the concentrate is added 1.5 L of ether. The solution is stirred for 15 min, again filtered through Celite, and concentrated at 30°C (Note 11).

C. *Hydrolysis.* Into a three-necked, 5-L, round-bottomed flask equipped with mechanical stirrer, thermometer, and 500-mL addition funnel with gas inlet is placed the above concentrate and 2 L of methanol. The solution is cooled to −5 to 0°C by means of an ice–salt bath. A precooled (0°C) solution containing 220 g of 87.5% potassium hydroxide in 400 mL of water is added dropwise at such a rate as to keep the reaction temperature below 10°C. The reaction mixture is stirred for an additional 2 hr at 0°C and for 1 hr at room temperature prior to the addition of 100 mL of glacial acetic acid. Solid sodium carbonate is added to bring the pH to 8 and the solution is filtered through Celite. Concentration off the filtrate at 35°C and reduced pressure affords about 1 L of a dark liquid. The liquid is diluted with 2 L of water and extracted with petroleum ether (6 × 600 mL). The combined extracts are washed with aqueous sodium thiosulfate solution (800 mL) and dried (magnesium sulfate). Concentration at 30°C affords a clear red liquid (occasionally a yellow solid) which is almost pure internal diester (Note 12).

The diester is dissolved in 130 mL of methanol, placed in a 1-L, one-necked flask equipped with a magnetic stirring bar and reflux condenser, and treated with a solution containing 35 g of potassium hydroxide in 130 mL of water. The mixture is stirred at reflux temperature for 1 hr. Methanol is removed under reduced pressure and 250 mL of water is added. Heating is continued for another 5 hr. After the solution is cooled, 5 g of activated charcoal is added and the mixture is stirred for 8 hr at room temperature. Filtration through Celite is followed by cooling of the stirred filtrate in an ice bath with acidification to pH 1 (dropwise addition of concentrated hydrochloric acid). The tan solid is isolated by filtration and dried under vacuum at room temperature. On the average, the yield is 52–55 g (10–11%) but can vary from 42 to 68 g (8–13% yield) (Note 13).

2. Notes

1. A paste made from a 1 : 1 mixture of mineral oil and silicone grease is used to lubricate the stirrer.
2. Prepurified argon (Linde) can be used with no further treatment.
3. Dry sodium hydride is available from Aldrich Chemical Company, Inc., as a fine powder. In multiple runs, it is most convenient to weigh the bulk reagent into 100-g (one reaction) lots. Extreme care should be used in handling this moisture-sensitive, flammable solid.
4. Tetrahydrofuran is distilled from calcium hydride and then from sodium–benzophenone immediately prior to use.
5. This amount of cyclopentadiene can be prepared in 2–3 hr using any of a variety of procedures.[3,4,5]
6. The checkers transferred cyclopentadiene by using a stainless-steel cannula from a cooled (dry ice–methanol), 500-mL, round-bottomed flask to the reaction vessel.
7. The complex was purchased from Aldrich Chemical Company, Inc.
8. A bright emerald-green color (usually) develops as the addition proceeds. If the iodine is impure, a brown color develops with no decrease in yield.
9. While dimethyl acetylenedicarboxylate is available commercially, it is easily prepared by the procedure of Huntress et al.[6] Care should be taken with this compound as it is a severe lachrymator and vesicant.
10. A tan to white precipitate of sodium iodide forms and a gentle exotherm is observed.
11. This concentrate (a dark red oil) may be stored in a refrigerator if time does not permit further work.
12. While the Diels–Alder reaction affords a wide variety of products, all of the esters formed hydrolyze faster than the desired internal adduct. The above hydrolysis removes all byproducts through base extraction. The internal diester has spectral properties as follows: ^{1}H NMR ($CDCl_3$) δ: 2.50 (tt, 2 H, *J* = 2.0, 4.3), 3.30 (dd, 4 H, *J* = 2.0, 4.3), 3.59 (s, 6 H), 6.07 (t, 4 H, *J* = 2.0); ^{13}C NMR ($CDCl_3$) δ: 51.5, 58.8, 64.6, 69.5, 132.7, 172.7.
13. Spectral properties of the diacid are as follows: ^{1}H NMR (d_6-DMSO) δ: 2.36 (tt, 2 H, *J* = 1.5, 4.1), 3.21 (dd, 4 H, *J* = 1.5, 4.1), 5.95 (t, 4 H, *J* = 1.7).

3. Discussion

The present procedure is a modification of the method previously reported.[7 8] While the overall yield is similar, the method described here is simpler in that it avoids a cumbersome transfer of the sodium cyclopentadienide solution.

The first step leading to 9,10-dihydrofulvalene is adapted from the earlier work of Matzner.[9] The utility of this thermally labile hydrocarbon ranges from its ability to engage in multiple [4+2] cycloadditions[7,8,10] to its capacity for bonding to a pair of metal atoms.[11 12 13 14 15]

The product diacid has served as starting material for the synthesis of tetracyclo[7.2.1.0^{4,11}.0^{6,10}]dodeca-2,7-diene-5,12-dione,[16 17] C_{16}-hexaquinacene,[18 19 20 21] (C_s)-C_{17}-heptaquinane derivatives,[22 23] the parent dodecahedrane molecule,[24 25]

[26] and a number of substituted dodecahedranes.[27 28 29 30 31 32 33 34]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

9,10-Dihydrofulvalene

activated charcoal

C_{16}-hexaquinacene

(C_s)-C_{17}-heptaquinane

dodecahedrane

Dry Ice

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

methanol (67-56-1)

ether (60-29-7)

sodium carbonate (497-19-8)

oxygen (7782-44-7)

sodium thiosulfate (7772-98-7)

iodine (7553-56-2)

potassium hydroxide (1310-58-3)

Benzophenone (119-61-9)

sodium (13966-32-0)

sodium iodide (7681-82-5)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

sodium hydride (7646-69-7)

CYCLOPENTADIENE (542-92-7)

Dimethyl acetylenedicarboxylate (762-42-5)

calcium hydride (7789-78-8)

sodium cyclopentadienide (4984-82-1)

argon (7440-37-1)

3,3a,3b,4,6a,7a-Hexahydro-3,4,7-metheno-7H-cyclopenta[a]pentalene-7,8-dicarboxylic acid, 3,4,7-Metheno-7H-cyclopenta[a]pentalene-7,8-dicarboxylic acid, 3,3a,3b,4,6a,7a-hexahydro (61206-25-5)

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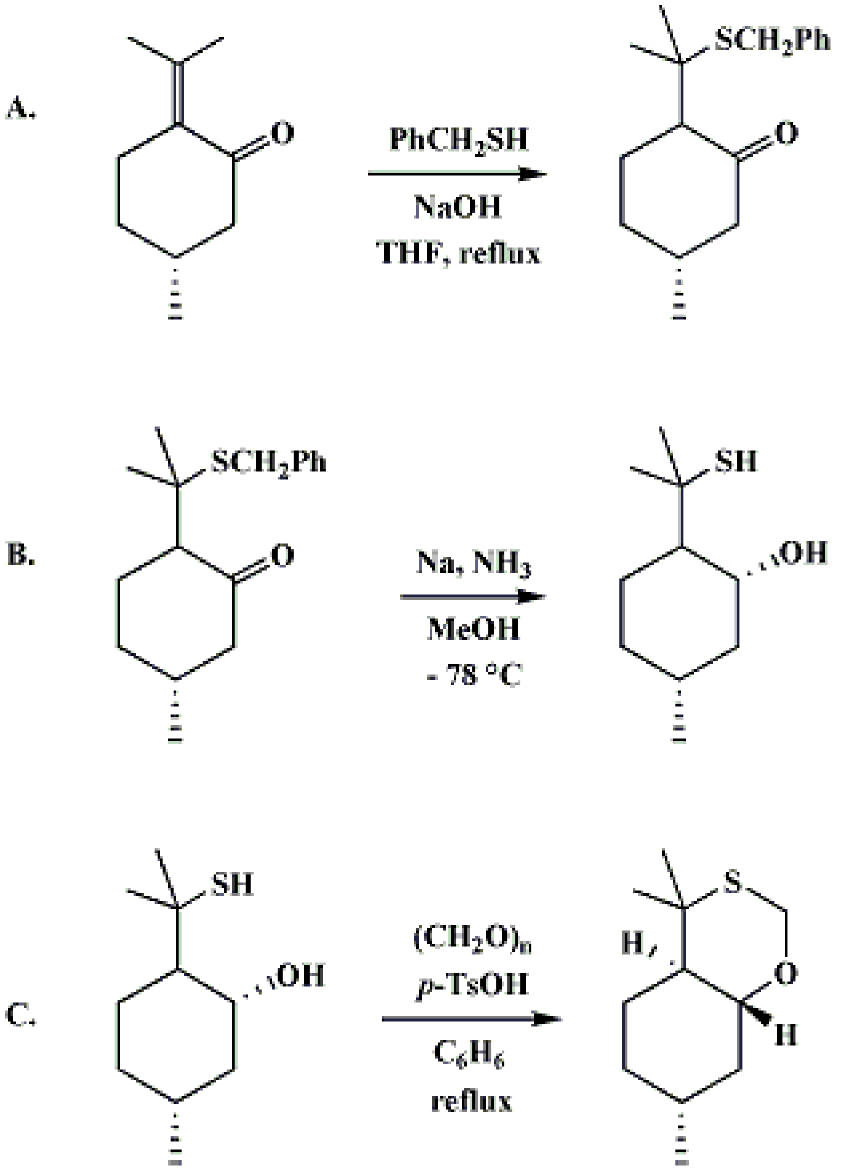
Organic Syntheses, *CV 8, 302*

CHIRAL 1,3-OXATHIANE FROM (+)-PULEGONE: HEXAHYDRO-4,4,7-TRIMETHYL-4*H*-1,3-BENZOXATHIIN

[4*H*-1,3-Benzoxathiin, hexahydro-4,4,7-trimethyl-]



Submitted by Ernest L. Eliel, Joseph E. Lynch, Fumitaka Kume, and Stephen V. Frye[1].
Checked by Leticia M. Diaz, Stan S. Hall, and Gabriel Saucy.

1. Procedure

Caution! Benzyl mercaptan (Part A) is a foul-smelling liquid. Benzyl mercaptan, the liquid ammonia required in Part B, and the benzene employed as a solvent in Part C

should be used only in a well-ventilated hood.

A. *cis- and trans-5-Methyl-2-[1-methyl-1-(phenylmethylthio)ethyl]cyclohexanone (7-benzylthiomenthone).* A 1-L, three-necked, round-bottomed flask equipped with a magnetic stirring bar and a Friedrich condenser connected by its upper joint to a mineral oil bubbler through which passes nitrogen gas is charged with 500 mL of tetrahydrofuran (Note 1), 202.0 g (1.33 mol) of (+)-pulegone (Note 2), and 181.0 g (1.46 mol) of benzyl mercaptan (Note 3). The flask is flushed with nitrogen, 10 mL of aqueous 10% sodium hydroxide is added, the flask is stoppered, and the mixture is heated to reflux under a static pressure of nitrogen. After 2 hr at reflux the pale-yellow solution is allowed to cool, transferred to a 2-L separatory funnel, and washed with two 500-mL portions of saturated aqueous sodium chloride. The combined sodium chloride layers, in turn, are extracted with three 250-mL portions of ether, and the combined organic layers are dried over magnesium sulfate for 2 hr, filtered and concentrated by rotary evaporation at aspirator vacuum. The residual liquid is distilled in a good vacuum to give a fraction of bp 167–174°C (0.4 mm) weighing 325–330 g (89–90%). The product is a mixture of *cis* and *trans* isomers otherwise highly pure as evidenced by spectral analysis (Note 4).

B. *2-(1-Mercapto-1-methylethyl)-5-methylcyclohexanol (7-thiomenthol).* A 5-L, three-necked, round-bottomed flask is equipped with a variable speed Hershberg stirrer and a 500-mL Dewar condenser filled with dry ice–acetone and connected by its upper joint to a mineral oil bubbler through which passes dry nitrogen gas. The flask is immersed in a dry ice–acetone bath, flushed well with nitrogen and 3000 mL of ammonia is condensed into the flask via a glass tube passed through a rubber septum in the remaining neck of the flask (Note 5). Clean sodium, 125 g (5.43 g-atom), is added slowly to the ammonia with slow stirring (Note 6). Then 250.3 g (0.906 mol) of 5-methyl-2-[1-methyl-1-(phenylmethylthio)ethyl]cyclohexanone and 72.5 mL (1.8 mol) of methanol in 625 mL of anhydrous ether (Note 7) are added dropwise via a pressure-equalized addition funnel over 5 hr to the vigorously stirred (ca. 500 rpm) solution (Note 8). Stirring is continued an additional 30 min following which 150 mL of methanol is added over 2.5 hr dropwise (to avoid a violent eruption). The solution is allowed to warm slowly (Note 9) and the addition funnel and the condenser are removed to allow the ammonia to evaporate overnight. The reaction flask is immersed in an ice bath and 700 mL of water is added cautiously over an hour to the yellow solid left by evaporation of the ammonia (Note 10). The solution is transferred to a 2-L separatory funnel and extracted with two 200-mL portions of ether, which are discarded. The aqueous layer is poured into a mixture of 500 mL of concentrated hydrochloric acid and 1000 g of ice, transferred to a 4-L separatory funnel, and extracted with four 200-mL portions of ether. The combined ether extracts are washed with 200 mL of water and 200 mL of saturated aqueous sodium chloride, dried over magnesium sulfate, and concentrated by rotary evaporation at aspirator vacuum. The residual liquid is placed under reduced pressure (0.2 mm) for 1 hr to remove the remaining solvent to give 137–140 g (80–82%) of an orange oil that is a diastereomeric mixture of which the major component constitutes 80%, as indicated

by ^{13}C NMR (Note 11).

C. *Hexahydro-4,4,7-trimethyl-4H-1,3-benzoxathiin.* To a 1-L, one-necked, round-bottomed flask equipped with a magnetic stirrer and charged with 325 mL of benzene (Note 12) is added 140.0 g (0.753 mol) of 5-methyl-2-(1-methyl-1-thioethyl) cyclohexanol, 26.0 g (0.87 mol) of paraformaldehyde (Note 13) and 1 g of p-toluenesulfonic acid monohydrate (Note 14). The flask is fitted with a Dean–Stark trap and a Friedrich condenser and the contents are refluxed for 4 hr, by which time the benzene distillate is clear. After the solution is cooled, 5 g of anhydrous potassium carbonate is added and the solution is stirred overnight, filtered, and concentrated by rotary evaporation and the residual liquid is distilled in a good vacuum to give a fraction of bp 69–94°C (0.1 mm), which weighs 130–134 g (86–89%) (Note 15). This fraction is dissolved in 250 mL of pentane, cooled to −25°C, and seeded with a crystal of the product (Note 16). Crystallization is allowed to proceed in a freezer, and collection and concentration of the mother liquor to half the original volume are carried out every other day to yield, after four crops of crystals are collected, 55–60 g (37–40%) of the spectrally pure product (Note 17).

2. Notes

1. Tetrahydrofuran was gold label from Aldrich Chemical Company, Inc.
2. (+)-Pulegone was obtained from SCM Corporation, Jacksonville, FL or Givaudan Corporation, Clifton, NJ; the specific rotation ranged from +21.85 to 22.6°. The material is also available from Aldrich Chemical Company, Inc. Pure pulegone has[2] $[\alpha]_D^{23}$ + 22.5°. The discrepancy, if any, is probably due to chemical impurities since the pulegone used has been shown to be enantiomerically pure.[3,4] The checkers used (+)-pulegone from Givaudan Corporation, $[\alpha]_D^{20}$ +25.7°, which was 94.4% pure (GLC) and contained 4.8% of isopulegone or carvone.
3. Benzyl mercaptan was used as received from Aldrich Chemical Company, Inc.
4. Spectral data; IR (film), cm^{-1}: 1708, 1620, 1500, 1458, 1382, 1363, 1120, 710, 695; ^{13}C NMR (50 MHz, $CDCl_3$) δ: 22.2, 23.8, 27.8, 29.6, 33.1, 34.5, 36.6, 48.0, 52.3, 57.8, 126.8, 128.4 (2 C), 128.9 (2 C), 138.7, and 210.2; ^{1}H NMR (200 MHz, $CDCl_3$) δ, partial: singlets at 1.38, 1.60, and 3.73, and an intense doublet at 0.97 (J = 5.9). The checkers noted that the product distillate was a pale-blue color, which turned pale yellow after a few minutes.
5. The submitters noted that at least 15 kg of dry ice was required for a reaction of this scale. Using the described apparatus the checkers found that the condensation of the ammonia required 8–10 hr, which could be reduced to ca. 5 hr by using the following assembly. An over-dried, 5-L, three-necked, round-bottomed flask was equipped with a glass stirrer shaft fitted with a sleeve joint and a large Teflon blade and the shaft was connected to an overhead motor drive. The flask was also connected to two 450-mL Dewar condensers with a large soda-lime drying tube attached to the tube connector of one condenser

while the tube connector of the other condenser was attached with Tygon tubing that led through a tower of solid potassium hydroxide pellets to a tank of anhydrous ammonia. While ammonia was slowly flushed through the entire assembly, the Dewar condensers were filled with dry ice–acetone, and a dry ice–acetone bath was raised to cool the vessel by immersion. The ammonia flow rate was increased to condense ca. 3000 mL of ammonia into the flask. The condenser with the inlet connection from the ammonia was removed and the flask sealed with a glass stopper.
6. Sodium was stored under mineral oil and washed with pentane before use. For convenience the checkers used 1/6– -in. sodium spheres (Matheson Coleman and Bell) that were weighed in mineral oil, then wiped free of oil, rinsed in hexane, cut in half, rinsed in hexane again, and immediately added to the reaction over a 2-hr period, during which time the dark-black mixture became extremely viscous.
7. At this point the checkers charged an oven-dried, 1000-mL pressure-equalizing addition funnel with the ketone in methanol and ether, and then quickly mounted the sealed funnel on the reaction flask by removing the flask's glass stopper.
8. Methanol was used as received from Fisher Scientific, Inc. Anhydrous ether was used as received from freshly opened containers from Mallinckrodt, Inc. and Fisher Scientific, Inc.
9. It is important to let the reaction mixture warm slowly; otherwise the ammonia will boil violently and carry some of the reaction material out of the flask.
10. This reaction is highly exothermic, and caution should be exercised since some active sodium may occasionally be left on the sides of the flask.
11. The intense ^{13}C NMR (50 MHz, $CDCl_3$) signals of the major isomer are at 21.9, 26.9, 29.0, 31.3, 34.5, 34.6, 45.4, 47.2, 54.6, and 72.9 ppm relative to TMS; ^{1}H NMR (200 MHz, $CDCl_3$) δ, partial: 0.91 (d, 3 H, J = 6.5), 1.40 (s, 3 H), and 1.52 (s, 3 H).
12. Benzene was used as received from Aldrich Chemical Company, Inc. *Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.*
13. Paraformaldehyde was used as received form Aldrich Chemical Company, Inc.
14. *p*-Toluenesulfonic acid monohydrate was used as received from Aldrich Chemical Company, Inc.
15. Excess paraformaldehyde may separate from the distillate. If this occurs, the liquid should be filtered prior to crystallization.
16. In the absence of seeding, crystallization may take several weeks. It is preferable to separate a small sample of the precursor thiomenthol from its stereoisomers by HPLC (3% ethyl acetate in hexane as eluant) and prepare a small amount of pure oxathiane from this material. Alternatively, a small amount of the product may be purified by GLC on a 5% FFAP column. The

melting point of pure material is 37–38°C. The checkers, who did not have seeding crystals, found that the early crops of crystals melted when the flask was allowed to warm to ambient temperature. Consequently, the cold supernatant liquid was withdrawn from the crystals with a Pasteur pipette while the flask was maintained at ca. 0°C (ice–water bath). The crystals were subsequently recrystallized several times in the same flask without filtration. By this technique, white crystals melting at 32–35°C were obtained; this material is spectrally pure and suitable for asymmetric synthesis. The supernatant liquid was also concentrated, as the submitters described, to obtain additional crops using this technique.

17. Spectral data; IR (film), cm^{-1}: 2970–2870, 1455, 1440, 1388, 1370, 1355, 1305, 1155, 1095, 1066, 985, 955, 900, 830, and 710; ^{13}C NMR (50 MHz, $CDCl_3$) δ: 21.8, 22.1, 24.4, 29.4, 31.3, 34.7, 41.8 (2 C), 51.5, 67.1, 76.7 ppm; ^{1}H NMR (200 MHz, $CDCl_3$) δ partial: 0.92 (d, 3 H, J = 6.5), 1.27 (s, 3 H), 1.43 (s, 3 H), 3.35 (td, 1 H, J = 10.5, 4.2, HCO), 4.69 (d, 1 H, J = 11.5, SCH_2O), 5.03 (d, 1 H, J = 11.5, SCH_2O).

3. Discussion

Hexahydro-4,4,7-trimethyl-4*H*-benzoxathiin is used as a chiral template in the asymmetric synthesis, in over 90% enantiomeric excess, of tertiary[3,5] and secondary[6] α-hydroxy aldehydes, RR'C(OH)CHO and the derived acids, $RR'C(OH)CO_2H$ and glycols, $RR'C(OH)CH_2OH$.[7] The present procedure is a slight modification of a published[5] one.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Dry Ice

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

Benzene (71-43-2)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

acetone (67-64-1)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

Pentane (109-66-0)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

hexane (110-54-3)

benzyl mercaptan (100-53-8)

TMS (16571-41-8)

carvone

1,3-OXATHIANE

(+)-PULEGONE, pulegone (89-82-7)

7-benzylthiomenthone

2-(1-Mercapto-1-methylethyl)-5-methylcyclohexanol

7-Thiomenthol

5-methyl-2-[1-methyl-1-(phenylmethylthio)ethyl]cyclohexanone, cis- and trans-5-Methyl-2-[1-methyl-1-(phenylmethylthio)ethyl]cyclohexanone

5-methyl-2-(1-methyl-1-thioethyl)cyclohexanol

p-toluenesulfonic acid monohydrate (6192-52-5)

isopulegone

thiomenthol

oxathiane (57917-36-9)

Hexahydro-4,4,7-trimethyl-4H-1,3-benzoxathiin, 4H-1,3-Benzoxathiin, hexahydro-4,4,7-trimethyl- (59324-06-0)

Hexahydro-4,4,7-trimethyl-4H-benzoxathiin

paraformaldehyde (30525-89-4)

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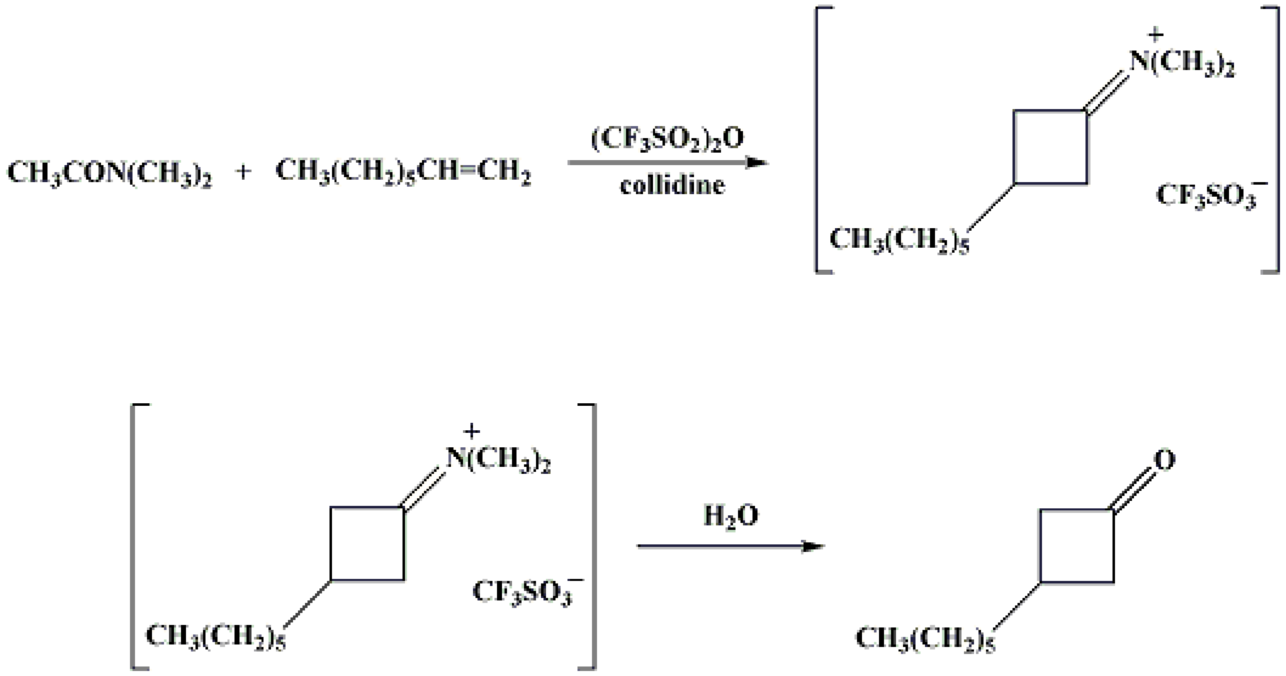
Organic Syntheses, CV 8, 306

A GENERAL SYNTHESIS OF CYCLOBUTANONES FROM OLEFINS AND TERTIARY AMIDES: 3-HEXYLCYCLOBUTANONE



Submitted by C. Schmit, J. B. Falmagne, J. Escudero, H. Vanlierde, and L. Ghosez[1].
Checked by Thomas J. Sowin and Albert I. Meyers.

1. Procedure

A 500-mL, three-necked flask is equipped with a rubber septum, a magnetic stirring bar, a gas inlet, and a reflux condenser. The top of the condenser is connected to a pressure-equalizing dropping funnel isolated from moisture by a sulfuric acid trap (Note 1). The flask is cooled to −15° C and charged with *N,N*-dimethylacetamide (3.26 g, 37.5 mmol) (Note 2) in 100 mL of 1,2-dichloroethane (Note 3). The dropping funnel is charged with 1-octene (16.8 g, 150 mmol) (Note 4) and 2,4,6-collidine (5.44 g, 45 mmol) (Note 5) in 50 mL of 1,2-dichloroethane. A slightly positive pressure of argon is maintained in the apparatus throughout the course of the reaction. Trifluoromethanesulfonic anhydride (12.69 g, 45 mmol) (Note 6) is added through the rubber septum into the solution of *N,N*-dimethylacetamide by means of a syringe. A precipitate is formed. The olefin–collidine solution is then added dropwise over a 20-min period. During these operations rapid stirring and cooling are maintained. The resulting mixture is refluxed for 17 hr (Note 7). The solvent is removed by rotary evaporation. The oily residue is washed with dry ether (3 × 20 mL) (Note 8). Then 20 mL of carbon tetrachloride (Note 9) and 20 mL of water are added to the crude cyclobutaniminium salt. The mixture is refluxed for 6 hr (Note 10). The organic phase is separated and the aqueous phase is extracted with carbon tetrachloride (3 × 20 mL). The combined organic phases are dried over anhydrous magnesium sulfate. The solvent is removed by distillation at atmospheric pressure (Note 11). Bulb-to-bulb distillation (bath temperature 100–110° C, water pump) gives 3.3 g (59%) of 3-hexylcyclobutanone (Note 12) and (Note 13).

2. Notes

1. The assembled apparatus is flame-dried under a slight pressure of argon.
2. *N,N*-Dimethylacetamide (Janssen Chimica, Beerse, Belgium) is distilled before use. The checkers used it as obtained from Aldrich Chemical Company, Inc.
3. 1,2-Dichloroethane (99%) is obtained from Janssen Chimica or Aldrich Chemical Company, Inc. It is distilled from calcium hydride.
4. 1-Octene (97%) is purchased from Janssen Chimica or Aldrich Chemical Company, Inc. and distilled.
5. 2,4,6-Collidine (99%, Janssen Chimica or Aldrich Chemical Company, Inc.) is distilled from calcium hydride and stored under argon in a brown bottle.
6. Trifluoromethanesulfonic anhydride is prepared just prior to use according to the procedure of Stang and Dueber.[2] The checkers obtained it from Aldrich Chemical Company, Inc.
7. During this period the solution turns dark brown and, after rotary evaporation, the residue is a thick, black oil. The progress of the reaction can be followed by IR (

$$(\nu_{C=N^{+}})\ cm^{-1}:$$

) cm^{-1}: 1730–1735, but the checkers found that it was complete in this 17-hr period.
8. Technical ether is dried over potassium hydroxide.
9. Technical carbon tetrachloride is used. Dichloromethane is preferred only when the cyclobutanone is too volatile.
10. The progress of the hydrolysis can be followed by IR, but the checkers found that it was complete in 6 hr.
11. Rotary evaporation or vacuum distillation can lead to a substantial loss of cyclobutanone.
12. The spectral properties of the compound are as follows: IR (CCl_4, $\nu_{C=O}$) cm^{-1} 1785; ^1H NMR (270 MHz, $CDCl_3$) δ: 0.840 (t, 3 H, CH_3), 1.226–1.243–1.302 (m, 8 H, CH_2), 1.513 (m, 2 H, CH), 2.300 (m, 1 H, CH), 2.610 (m, 2 H, CH), 3.079 (m, 2 H, CH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 13.98, 22.53, 23.78, 28.16, 29.02, 31.71, 36.29, 52.43, 208.61.
13. The physical properties of the semicarbazone are as follows: mp 148.5°C; Anal. calcd. for $C_{11}H_{21}N_3O$: C, 62.53; H, 10.02; N, 19.88; O, 7.57. Found: C, 62.63; H, 10.05; N, 19.95; O, 7.50.

3. Discussion

Cyclobutanones are important synthetic intermediates. A common synthetic method for their preparation is the [2+2] cycloaddition of olefins with ketenes often generated in situ from acid chlorides. However, that method suffers limitations especially when aldoketenes and unreactive olefins are used.

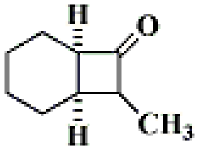
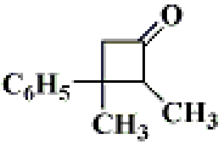
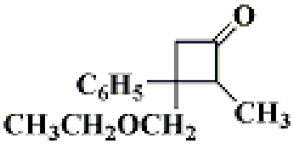
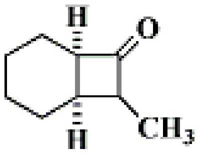
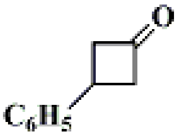
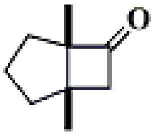
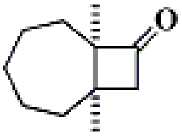
Keteniminium salts are more electrophilic than ketenes and are thus able to react with less nucleophilic olefins. Ketoketeniminium salts can be conveniently prepared from the corresponding α-chloroenamines and Lewis acids.[3 4 5 6] However, the method cannot be applied well to the preparation of the less stable aldoketeniminium salts.

The method described here which involves the in situ generation of keteniminium triflates is practical and more general. The best results were obtained with 2,4,6-collidine, but occasionally the more expensive 2,6-di-t-butyl-4-methylpyridine was superior. Pyridine gave satisfactory results in few cases only. Triethylamine always gave poor results. With the more reactive olefins

(e.g., styrene), reactions can be run in refluxing dichloromethane. The procedure described here usually gives better yields than that previously reported in a preliminary communication.[10] It has been used to prepare cyclobutanones as well as cyclobutenones[7,8 9] from a wide variety of olefins or acetylenes. A few examples are shown in Table I. The method works well for olefins or acetylenes bearing alkyl, alkenyl or aryl groups. It does not apply to enol ethers or enamines.

TABLE I

SYNTHESIS OF CYCLOBUTANONES FROM TERTIARY AMIDES AND OLEFINS

Amide	Olefin	Cyclobutanone	Yield (%)
$CH_3CH_2CON(CH_3)_2$	Cyclohexene		89[a]
$CH_3CH_2CON(CH_3)_2$	α-Methylstyrene		79[a]
$CH_3CH_2CON(CH_3)_2$	Allyl ethyl ether		56[a]
$CH_3CON(CH_3)_2$	Cyclohexene		46
$CH_3CON(CH_3)_2$	Styrene		71
$(H_3C)_2NCO-\underset{CH_3}{CH}(CH_2)_3CH{=}CH_2$			87[b]
$(H_3C)_2NCO(CH_2)_6CH{=}CH_2$			71[b]

[a] Mixture of *endo* + *exo* isomers.

[b] These reactions were performed under slightly different conditions.[10]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

$CH_3CH_2CON(CH_3)_2$

$CH_3CON(CH_3)_2$

$(H_3C)_2NCO(CH_2)_6CH=CH_2$

ether (60-29-7)

Cyclohexene (110-83-8)

carbon tetrachloride (56-23-5)

1,2-dichloroethane (107-06-2)

pyridine (110-86-1)

potassium hydroxide (1310-58-3)

dichloromethane (75-09-2)

styrene (100-42-5)

magnesium sulfate (7487-88-9)

2,4,6-collidine (108-75-8)

triethylamine (121-44-8)

calcium hydride (7789-78-8)

α-methylstyrene (98-83-9)

Cyclobutanone (1191-95-3)

argon (7440-37-1)

N,N-dimethylacetamide (127-19-5)

1-octene (111-66-0)

Trifluoromethanesulfonic anhydride (358-23-6)

3-Hexylcyclobutanone (138173-74-7)

Allyl ethyl ether (557-31-3)

2,6-di-t-butyl-4-methylpyridine (38222-83-2)

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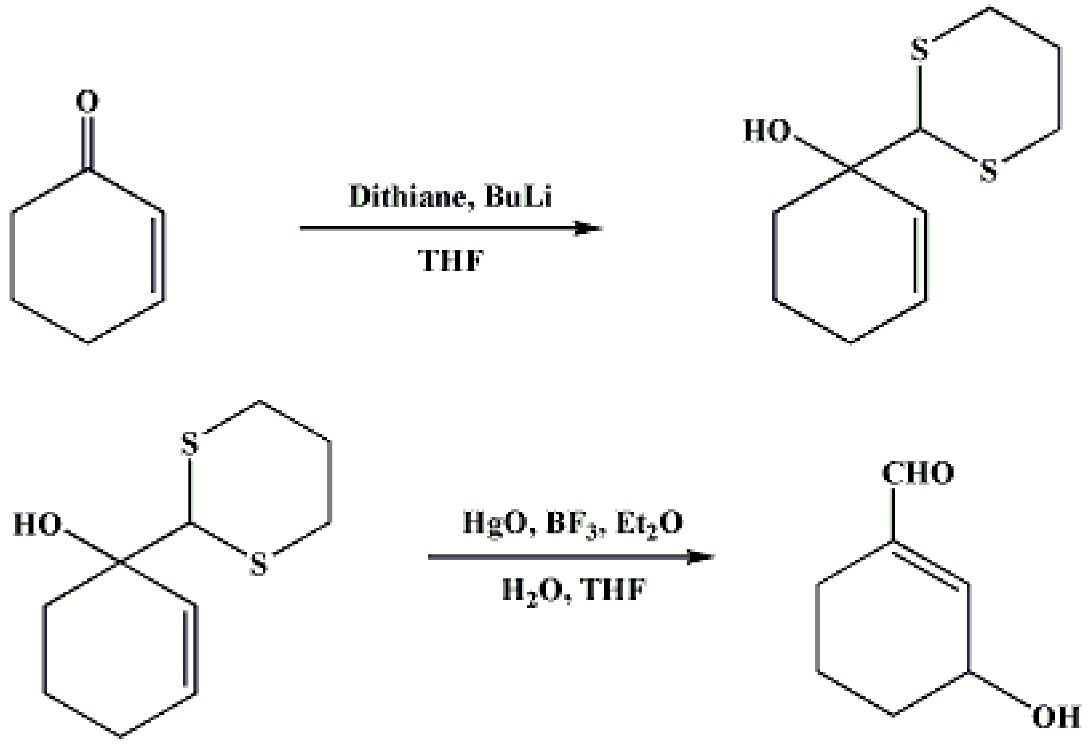
Organic Syntheses, CV 8, 309

3-HYDROXY-1-CYCLOHEXENE-1-CARBOXALDEHYDE

[1-Cyclohexene-1-carboxaldehyde, 3-hydroxy-]



Submitted by H. L. Rigby, M. Neveu, D. Pauley, B. C. Ranu, and T. Hudlicky[1].
Checked by Denis R. St. Laurent and Leo A. Paquette.

1. Procedure

A. *1-(1,3-Dithian-2-yl)-2-cyclohexen-1-ol (2)*. To a suspension of 1,3-dithiane (Note 1) (12 g, 0.1 mol) in dry tetrahydrofuran (100 mL) (Note 2) at –78°C is added butyllithium (40 mL, 2.5 *M*, 0.1 mol). The reaction is stirred for 2 hr. Initially the dithiane dissolves, followed by precipitation of the lithio salt. After 2 hr, 2-cyclohexen-1-one (9.6 g, 0.1 mol) (Note 3) in dry tetrahydrofuran (20 mL) is added dropwise. After about half of the cyclohexenone is added, the mixture becomes homogeneous. After the addition is complete, the reaction is stirred for an additional 30 min at –78°C and then stored for 18 hr at 0°C. The solution is concentrated to one-fourth volume under reduced pressure. Water (100 mL) is added and the mixture is extracted with ether (3 × 50 mL). The extract is dried over sodium sulfate and evaporated to give an oil that is vacuum-distilled to give 14.0–14.7 g (65–68%) of the protected aldehyde **2**, bp 149–153°C (0.8–1.0 mm) (Note 4).

B. *3-Hydroxy-1-cyclohexene-1-carboxaldehyde (3)*. The hydroxy thioacetal 2 (5.5 g,

0.025 mol) in 25 mL of tetrahydrofuran is added dropwise to a mechanically stirred suspension of red mercuric oxide (11 g, 0.051 mol) (Note 5) and boron trifluoride etherate (7.2 g, 0.051 mol) (Note 6) in refluxing 15% aqueous tetrahydrofuran (50 mL). After the addition is complete, the mixture is stirred (Note 7) at reflux for an additional 2 hr. Another 5.5 g of red mercuric oxide is added and the reaction is stirred at reflux for 1 hr. The reaction is cooled to room temperature and ether (150 mL) is added, followed by 50 mL of brine. The mixture is filtered and the residue washed with ether (3 × 50 mL). The organic layer is separated and washed with saturated sodium bicarbonate solution (2 × 50 mL) and brine (1 × 50 mL). The organic layer is dried over sodium sulfate and the solvent evaporated to leave a residual oil. This oil is purified by medium-pressure liquid chromatography (silica gel, elution with 40% ethyl acetate in hexane) to give 1.5–1.6 g (47–50%) of the aldehyde **3**, bp 125°C (0.075 mm) (Kugelrohr) (Note 8).

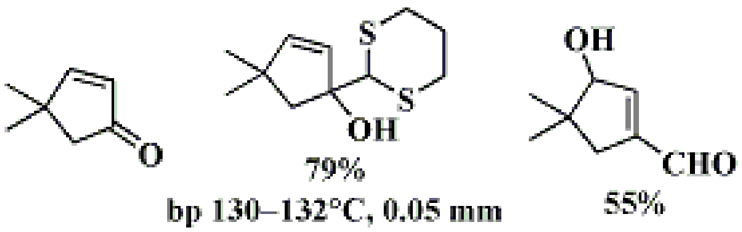
2. Notes

1. Dithiane was obtained from Aldrich Chemical Company, Inc. and was used without purification.
2. Tetrahydrofuran was distilled under nitrogen from potassium and benzophenone.
3. 2-Cyclohexen-1-one was obtained from Aldrich Chemical Company, Inc. and used as received.
4. The submitters report bp 157°C (1 mm). The spectral properties of 2 are as follows: IR (neat) cm^{-1}: 3450 (br), 3030, 2940, 2900 (sh), 2830, 1645 (w), 1425, 1280, 1185, 1085, 985; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.57–2.08 (m, 8 H), 2.40 (s, 1 H), 2.74–2.90 (m, 4 H), 4.17 (s, 1 H), 5.68 (d, 1 H, *J* = 10.05), 5.85–5.91 (m, 1 H); ^{13}C NMR ($CDCl_3$, 20 MHz) δ: 18.53, 24.98, 25.75, 30.35, 30.54, 33.03, 59.54, 71.75, 129.43, 132.18; MS: M^+ 198, 120, 119 (base), 97, 91 (no M^+ peak).
5. Mercuric oxide (red) was purchased from Aldrich Chemical Company, Inc. and used without purification.
6. Boron trifluoride etherate was distilled from calcium hydride at aspirator pressure.
7. Mechanical stirring was found to be essential, and in some cases addition of sea sand to the reaction mixture reduced clogging of the reagents and led to higher yields.
8. The submitters report bp 70°C (10^{-4} mm). The spectral properties of **3** are as follows: IR (neat) cm^{-1}: 3400 (br), 2950, 2870, 2720, 1675, 1435, 1305, 1180, 1135, 1070, 1045, 995, 965, 925; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.47–1.54 (m, 2 H), 1.71–1.79 (m, 1 H), 1.90–1.98 (m, 1 H), 2.06 (s, 2 H), 3.49 (br s, 1 H), 4.37 (br s, 1 H), 6.63 (s, 1 H), 9.34 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 18.54, 20.94, 31.35, 65.84, 77.43, 141.63, 150.88, 194.49; MS: M^+ 97 (base), 79, 69, 55, 41.

3. Discussion

Preparation of a compound such as **3** is useful where extensive functionalization of a cyclic enone is required. In addition to **3**, 4,4-dimethyl-3-hydroxy-1-cyclopentene-1-carboxaldehyde was prepared using the same procedure from 4,4-dimethyl-2-cyclopenten-1-one.[2] Table I gives yields and physical properties for this compound, which has been used as a starting material in the syntheses of coriolin and pentalenic acid.[3,4]

TABLE I
PREPARATION OF 4,4-DIMETHYL-3-HYDROXY-1-CYCLOPENTENE-1-CARBOXALDEHYDE

Enone	Dithiane	Hydroxy Aldehyde
		
	79% bp 130–132°C, 0.05 mm	55%

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

brine

red mercuric oxide

Mercuric oxide (red)

coriolin

Hydroxy Aldehyde

ethyl acetate (141-78-6)

ether (60-29-7)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

Benzophenone (119-61-9)

potassium (7440-09-7)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

hexane (110-54-3)

boron trifluoride etherate (109-63-7)

dithiane (505-20-4)

calcium hydride (7789-78-8)

2-cyclohexen-1-one, cyclohexenone (930-68-7)

1,3-Dithiane (505-23-7)

4,4-Dimethyl-2-cyclopenten-1-one (22748-16-9)

3-Hydroxy-1-cyclohexene-1-carboxaldehyde, 1-Cyclohexene-1-carboxaldehyde, 3-hydroxy- (67252-14-6)

1-(1,3-Dithian-2-yl)-2-cyclohexen-1-ol (53178-46-4)

4,4-dimethyl-3-hydroxy-1-cyclopentene-1-carboxaldehyde

pentalenic acid

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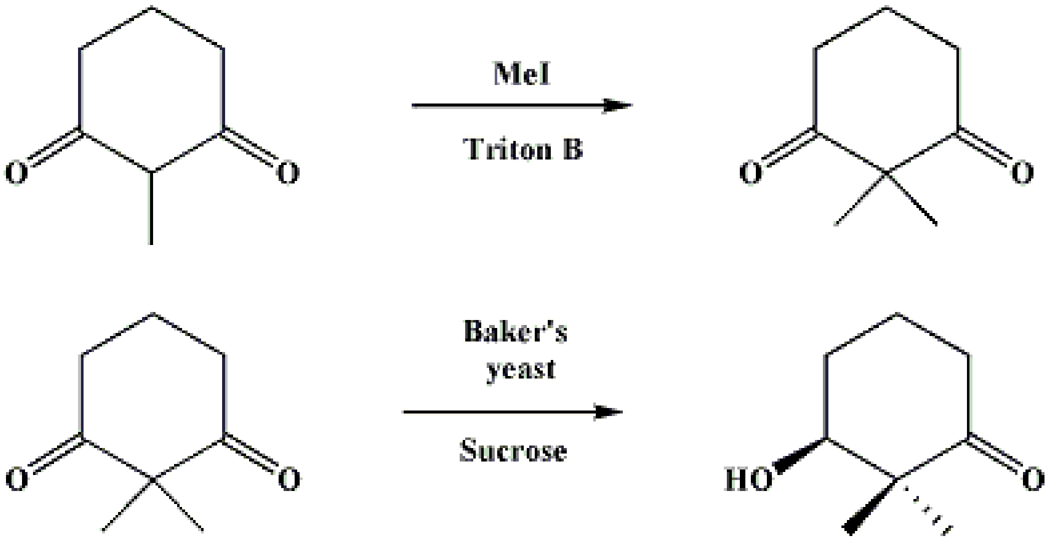
Organic Syntheses, CV 8, 312

YEAST REDUCTION OF 2,2-DIMETHYLCYCLOHEXANE-1,3-DIONE: (*S*)-(+)-3-HYDROXY-2,2-DIMETHYLCYCLOHEXANONE)

[Cyclohexanone, 3-hydroxy-2,2-dimethyl-, (*S*)-]



Submitted by Kenji Mori and Hideto Mori[1].
Checked by Mark Hopkins and Larry E. Overman.

1. Procedure

A. *2,2-Dimethylcyclohexane-1,3-dione*. In a 1-L, three-necked, round-bottomed flask equipped with a magnetic stirrer, a 200-mL pressure-equalizing dropping funnel, and a reflux condenser (the top of which is connected to a calcium chloride drying tube) are placed 50.4 g (0.4 mol) of 2-methylcyclohexane-1,3-dione[2] and 500 mL of dry methanol. To this stirred solution is added dropwise 168 mL of commercial Triton B (40% in methanol) (Note 1) and (Note 2). After the additional is complete, the resulting solution is stirred at room temperature for 10 min and 60.0 g (0.423 mol) of methyl iodide is added portionwise. This solution is then stirred and heated under reflux for 16–20 hr (Note 3). After the reaction mixture is cooled to room temperature, about 400 mL of methanol is removed by rotary evaporation. The residue is poured into a mixture of 100 mL (1.2 mol) of concentrated hydrochloric acid and about 100 g of ice to decompose the O-alkylated product (Note 4), and the mixture is stirred for 30 min. The precipitated solid (recovered starting material) is collected by filtration and the filtrate is extracted 4 times with 100 mL of ethyl acetate. The combined ethyl acetate extracts are washed with 5% sodium thiosulfate solution (4 × 100 mL), saturated sodium hydrogen carbonate solution (2 × 100 mL) and saturated sodium chloride solution (100 mL), dried over anhydrous magnesium sulfate, and filtered.

Ethyl acetate is removed by rotary evaporation and the residue is distilled to give 30–32 g (54–57%) of 2,2-dimethylcyclohexane-1,3-dione bp 92–97°C (4 mm) as a glassy solid (Note 5) and (Note 6).

B. *(S)-(+)-3-Hydroxy-2,2-dimethylcyclohexanone*. In a 5-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, a thermometer, and an air-reflux condenser are placed 3 L of tap water and 450 g of sucrose (Note 7). The mixture is stirred at 30°C, and 200 g of dry baker's yeast (Note 8) is added with stirring, whereupon brisk fermentation takes place (Note 2). This fermenting mixture is stirred at 30°C for 10 min and a solution of 15 g (0.107 mol) of 2,2-dimethylcyclohexane-1,3-dione in 95% ethanol (30 mL) and 0.2% Triton X-100 (120 mL) is added portionwise (Note 9). The mixture is stirred at 30°C for 40–48 hr (Note 10). Diethyl ether (about 200 mL) and Celite (about 50 g) are then added to the mixture and it is left to stand overnight. After the flocculated yeast cells are precipitated, the mixture is filtered through a pad of Celite (Note 11). The filter cake is washed with ethyl acetate (2 × 100 mL) and the combined filtrate and washings are saturated with sodium chloride and extracted 4 times with 100 mL of ethyl acetate. The combined ethyl acetate extracts are washed with saturated sodium hydrogen carbonate solution (200 mL) and saturated sodium chloride solution (200 mL), dried over anhydrous magnesium sulfate, and filtered. Ethyl acetate is removed by rotary evaporation and the residue (about 20 g) is chromatographed over 200 g of silica gel (Fuji Davison 820 MH gel) (Note 12). Elution with hexane–ethyl acetate (10 : 1–5 : 1) gives 5–6 g of recovered starting material. Further elution with hexane-ethyl acetate (5 : 1–1 : 2) gives 7.7–7.9 g (47–52%) of (*S*)-3-hydroxy-2,2-dimethylcyclohexanone. An analytical sample can be obtained by distillation, bp 85–87°C at 3.7 mm, $[\alpha]_D^{21}$ + 23.0° ($CHCl_3$, *c* 2.0) (Note 13),(Note 14),(Note 15).

2. Notes

1. The submitters used Triton B purchased from Tokyo Kasei Co., Ltd., whereas the checkers used material purchased from Aldrich Chemical Company, Inc. A rigorously moisture-free condition is not necessary. Even with ordinary methanol, the same result was obtained.

2. No temperature control is required because of the nonexothermic nature of this reaction.

3. The checkers found (GLC analysis using a 12.5-m, 5% methyl silicone capillary column) that the reaction was complete within 4–6 hr.

4. To ensure the complete decomposition of the O-alkylated product, this amount of hydrochloric acid is used. A smaller amount may result in incomplete decomposition of the by-product.

5. This material is sufficiently pure for use in the next step. Analysis by ^{13}C NMR indicates that 2–4% of an unknown impurity is present. Recrystallization from hexane–methylene chloride gives pure product melting at 37–38°C.

6. The spectra are as follows: ^1H NMR (250 MHz, $CDCl_3$) δ: 1.29 (s, 6 H), 1.93

(5 lines, 2 H, *J* = 6.5), 2.67 (t, 4 H, *J* = 6.9); ^{13}C NMR (76 MHz, $CDCl_3$) δ: 18.1, 22.3, 37.4, 61.8, 210.6.

7. Commercially available sucrose is used. The checkers employed deionized water.

8. The submitters used yeast purchased from the Oriental Yeast Co., Ltd., whereas the checkers used Fleischman's Dry Active Yeast.

9. The submitters used Triton X-100 purchased from Tokyo Kasei Co., Ltd., whereas the checkers used material purchased from Rohm & Haas Co.

10. To keep the temperature at 30°C, the flask is gently heated on a large water bath.

11. The checkers found that the use of coarse filter paper and a Büchner funnel was preferable to a sintered glass funnel.

12. The checkers found that the chromatography was best accomplished using 450 g of silica gel (E. Merck).

13. The spectral properties of (*S*)-(+)-3-hydroxy-2,2-dimethylcyclohexanone are as follows: IR ν_{max} (film) cm^{-1}: 3470 (s), 1705 (s), 1120 (m), 1055 (s), 985 (s), 965 (m); ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.11 (s, 3 H), 1.15 (s, 3 H), 1.60–1.71 (m, 1 H), 1.76–1.86 (m, 1 H), 1.96–2.05 (m, 2 H), 2.16 (br s, 1 H), 2.35–2.45 (m, 2 H), 3.69 (dd, 1 H, *J* = 7.6, 2.9); ^{13}C NMR (76 MHz, $CDCl_3$) δ: 19.7, 20.7, 22.9, 29.0, 37.3, 51.3, 77.8, 215.3.

14. The optical purity of (*S*)-(+)-3-hydroxy-2,2-dimethylcyclohexanone can be determined by HPLC analysis. The (*S*)-α-methoxy-α-trifluoromethylphenylacetate (MTPA ester) is prepared according to the reported procedure:[3] HPLC analysis (Column, Nucleosil® 50-5, 25 cm × 4.6 mm; eluant, hexane : THF = 30 : 1, 1.03 mL/min; detected at UV 256 nm) retention time 35.6 min (98.0–99.4%) and 29.6 min (0.6–(2.0%). Therefore, the optical purity is determined to be 96.0–98.8% ee.

15. Analysis of the MTPA ester of this product by 250 MHz ^{1}H NMR and capillary GLC (12.5 m, 5% methyl silicone column) failed to detect any more of the minor diastereomer than would have been expected from the purity (98% ee) of the MTPA-Cl employed.

3. Discussion

Microbial reduction of prochiral cyclopentane- and cyclohexane-1,3-diones was extensively studied during the 1960s in connection with steroid total synthesis.[4] Kieslich, Djerassi, and their coworkers reported the reduction of 2,2-dimethylcyclohexane-1,3-dione with *Kloeckera magna* ATCC 20109, and obtained (*S*)-3-hydroxy-2,2-dimethyl-cyclohexanone.[5] We found that the reduction of the 1,3-diketone can also be effected with conventional baker's yeast, and secured the hydroxy ketone of 98–99% ee as determined by an HPLC analysis of the corresponding (*S*)-α-methoxy-αtrifluoromethyl-phenylacetate (MTPA ester).[6,7] (*S*)-3-Hydroxy-2,2-dimethylcyclohexanone has been proved to be a versatile chiral nonracemic building block in terpene synthesis as shown in f.htmigure 1.

Figure 1. Natural products synthesized from (*S*)-3-hydroxy-2,2-dimethylcyclohexanone

Figure 1. Natural products synthesized from (S)-3-hydroxy-2,2-dimethylcyclohexanone

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

Triton B

Triton X-100

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

methanol (67-56-1)

diethyl ether (60-29-7)

sodium hydrogen carbonate (144-55-8)

sodium chloride (7647-14-5)

sodium thiosulfate (7772-98-7)

sucrose

Methyl iodide (74-88-4)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

THF (109-99-9)

hexane (110-54-3)

2-methylcyclohexane-1,3-dione (1193-55-1)

2,2-Dimethylcyclohexane-1,3-dione (562-13-0)

(S)-(+)-3-Hydroxy-2,2-dimethylcyclohexanone, Cyclohexanone, 3-hydroxy-2,2-dimethyl-, (S)-, (S)-3-hydroxy-2,2-dimethylcyclohexanone, (S)-3-hydroxy-2,2-dimethyl-cyclohexanone (87655-21-8)

(S)-α-methoxy-α-trifluoromethylphenylacetate, (S)-α-methoxy-αtrifluoromethyl-phenylacetate

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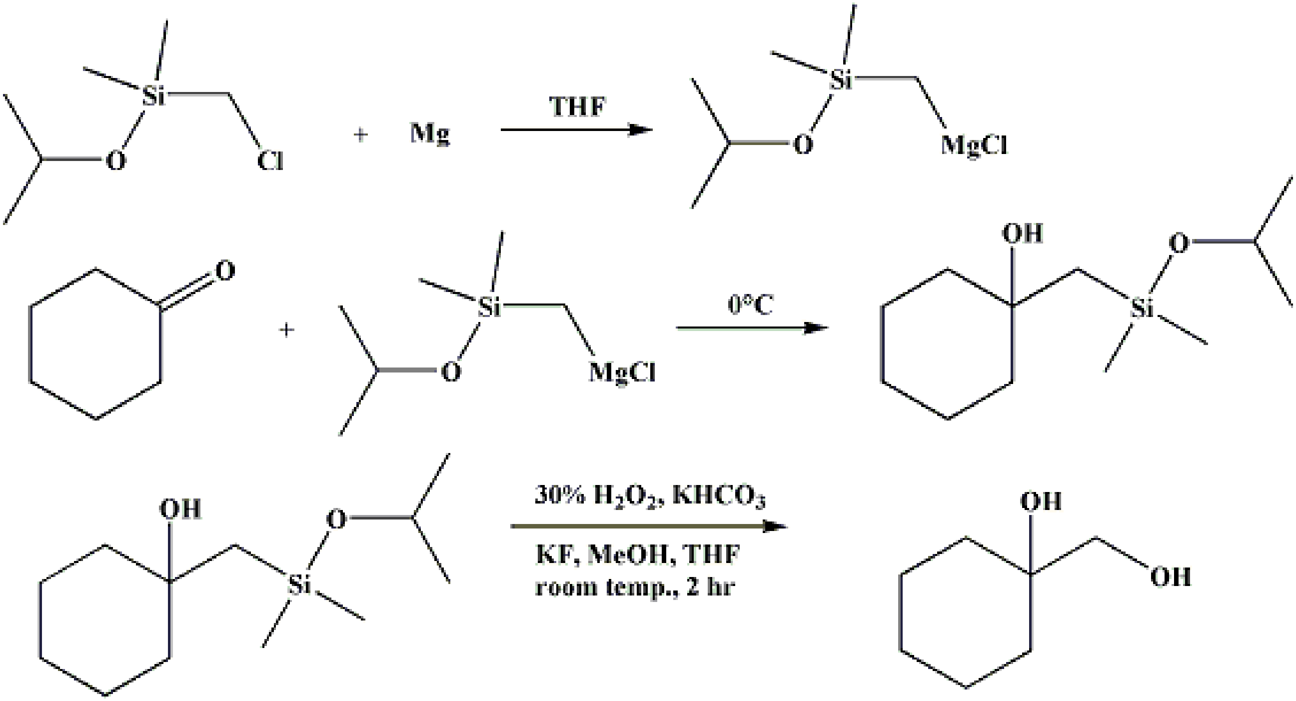
Organic Syntheses, CV 8, 315

NUCLEOPHILIC HYDROXYMETHYLATION BY THE (ISOPROPOXYDIMETHYLSILYL)METHYL GRIGNARD REAGENT: 1-(HYDROXYMETHYL)CYCLOHEXANOL FROM CYCLOHEXANONE

[Cyclohexanemethanol, 1-hydroxy-]



Submitted by Kohei Tamao, Neyoshi Ishida, Yoshihiko Ito, and Makoto Kumada[1].
Checked by Vinh D. Tran and Larry E. Overman.

1. Procedure

A. *1-[(Isopropoxydimethylsilyl)methyl]cyclohexanol*. A 500-mL, three-necked flask is equipped with a pressure-equalizing dropping funnel, a magnetic stirrer, a three-way stopcock, and a reflux condenser connected with a nitrogen bubbler. The flask is charged with magnesium turnings (2.43 g, 100 mg-atm) that are dried under a rapid stream of nitrogen with a heat gun. After the flask is cooled to room temperature, the rate of nitrogen flow is reduced. Several milliliters of a solution of (isopropoxydimethylsilyl)methyl chloride (16.67 g, 100 mmol) (Note 1) in dry tetrahydrofuran (THF) (120 mL) (Note 2) and about 50 •L of 1,2-dibromoethane are added. The mixture is stirred at room temperature and within a few minutes an exothermic reaction starts. The remaining solution is added dropwise at room temperature over ca. 45 min at such a rate as to maintain a gently exothermic reaction. After the addition is complete, the tan-gray mixture is refluxed for 0.5 hr and then cooled to 0°C with an ice bath. A solution of freshly distilled cyclohexanone (7.36 g, 75 mmol) in dry THF (30 mL) is added dropwise with stirring over 30 min. The resultant mixture is stirred at 0°C for another 30 min (Note 3) and then hydrolyzed by dropwise addition of an aqueous 10% solution of ammonium chloride (100 mL) at 0°C over 10 min. The organic layer is separated. The aqueous layer is extracted with four 40-mL portions of diethyl ether. The combined organic layer and extracts are washed once with aqueous saturated sodium chloride, dried over magnesium sulfate, filtered into a 500-mL round-bottomed flask and concentrated with a rotary evaporator below room temperature (Note 4) at water aspirator pressure. A colorless oil remains (Note 5).

B. *1-(Hydroxymethyl)cyclohexanol* The 500-mL, round-bottomed flask containing the crude 1-[(isopropoxydimethylsilyl)methyl]cyclohexanol is equipped with a magnetic stirrer and a thermometer, and is kept open to air throughout the reaction. The flask is charged with tetrahydrofuran (75 mL), methanol (75 mL) (Note 6), potassium hydrogen carbonate (7.5 g 75 mmol), and potassium fluoride (8.7 g, 150 mmol) (Note 7). To the stirred mixture is added 30% hydrogen peroxide (28.0 mL, 247.5 mmol) in one portion at room temperature. A somewhat cloudy organic layer and a milky-white, heavy inorganic layer result. After several minutes an exothermic reaction begins which is controlled by intermittent, brief cooling with a water bath to maintain the temperature at 40–50°C (Note 8). After about 30 min the exothermic reaction ceases. The mixture is then stirred at room temperature for 2 hr (Note 9). The remaining hydrogen peroxide is decomposed by careful dropwise addition (Note 10) of an aqueous 50% solution of sodium thiosulfate pentahydrate (ca. 30 mL) with stirring over 30 min, during which time the temperature is maintained near 30°C by intermittent cooling with an ice bath (Note 11). A negative starch-iodide test is observed (Note 12). A white precipitate forms and diethyl ether (ca. 100 mL) is added to ensure further precipitation. The mixture is filtered with suction and the filter cake is washed with three 20-mL portions of diethyl ether. The combined filtrate and washes are concentrated with a rotary evaporator at 50°C at water aspirator pressure until much of the water has been removed. The remaining oil is diluted with diethyl ether (ca. 200 mL), transferred to a separatory funnel, and washed with saturated aqueous sodium chloride solution to remove the remaining water. The organic layer is separated, dried over magnesium sulfate, filtered, and concentrated with a rotary evaporator to give a colorless solid. The solid is dissolved in a 10 : 1 mixture of hexane–ethyl acetate (75 mL) at reflux, and the hot solution is filtered. The filtrate is allowed to cool to room temperature and finally is kept at 0°C for 2 hr. The crystals are separated with suction, washed with cold hexane/ethyl acetate (10 : 1, 10 mL), and dried under high vacuum at room temperature. There is obtained 7.54 g (77%) of 1-(hydroxymethyl) cyclohexanol as white crystals, mp 76.0–76.2°C (Note 13) and (Note 14).

2. Notes

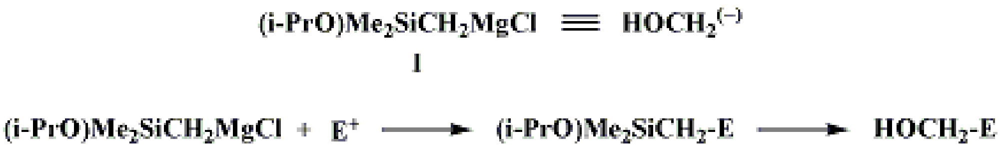
1. (Isopropoxydimethylsilyl)methyl chloride[2] is readily prepared from (chlorodimethylsilyl)methyl chloride by treatment with isopropyl alcohol (1.1 equiv) and triethylamine (1.1 equiv) in diethyl ether at room temperature (0.5 hr) and then at reflux temperature (0.5 hr). After filtration of the white salt, the filtrate is washed successively once with water, twice with 0.1 *N* hydrochloric acid, once with an aqueous 10% solution of sodium hydrogen carbonate and once with water, and then dried over sodium sulfate. Filtration and distillation give the product in 80% yield, bp 65–67°C at 50 mm, as an air-stable, colorless liquid. The checkers used commercially available material purchased from Aldrich Chemical Company, Inc.
2. Tetrahydrofuran (THF) was distilled from lithium aluminum hydride under nitrogen *(Caution: See Org. Synth., Coll. Vol. V, **1973**, 976 for a warning regarding the purification of tetrahydrofuran. The checkers employed THF that had been purified by distillation from sodium and benzophenone.)*.
3. The color of the mixture lightened slightly.
4. Care must be taken not to raise the temperature since β-elimination of the β-hydroxysilane can result.
5. The remaining oil appeared as one spot on silica gel TLC, R_f = 0.8 (hexane/ethyl acetate 1 : 1), and showed the following ^{1}H NMR spectrum ($CDCl_3$, 300 MHz) δ: 0.19 (s, 6 H, $Si(CH_3)_2$), 1.01 (s, 2 H, CH_2Si), 1.20 (d, 6 H, J = 6, $CH(CH_3)_2$), 1.38–1.75 (m, 10 H, $(CH_2)_5$), 3.5 (s, OH), 4.04 (septet, 1 H, J = 6, $OCH(CH_3)_2$).
6. Commercial reagent-grade THF and methanol are used without further purification.
7. Potassium fluoride of anhydrous grade was purchased from Nakarai Chemicals. Ltd. This must be weighed quickly because it is highly hygroscopic. The checkers used material purchased from Allied Chemical Company.
8. The oxidation is so exothermic that the temperature reaches 60–65°C in 10 min if no external

cooling is applied.
9. Completion of the oxidation was confirmed by TLC on silica gel: R_f of the product diol is 0.4 (hexane/ethyl acetate 1 : 1).
10. Care must be taken not to add the thiosulfate solution in one portion; otherwise a violent, uncontrollable reaction might suddenly occur.
11. The reaction temperature should be monitored carefully. If it falls below 10°C, the cooling bath should be removed to allow the mixture to warm to ca. 30°C.
12. If the test is still positive, thiosulfate solution should be added until a negative test is attained. The checkers found EM Quant Peroxide Test Strips obtained from EM Science to be more sensitive than conventional KI-Starch test paper.
13. The reported melting point is 75–76°C.[3]
14. 1-(Hydroxymethyl)cyclohexanol exhibits the following spectral properties: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.25–1.70 (broad m, 10 H, $(CH_2)_5$), 2.12 (s, 1 H, OH), 2.37 (t, 1 H, *J* = 6, OH), 3.45 (d, 2 H, *J* = 6, CH_2OH); IR (KBr) cm^{-1}: 3700–3020 (strong), 2920 (strong), 2845 (strong). Mass spectrum (24 eV): *m/z* (relative intensity) 130 (M^+, 0.3), 99 (100), 81 (67). High-resolution mass spectrum: calcd. for $C_7H_{14}O_2$, 130.0992; found, 130.0969.

3. Discussion

This procedure for the preparation of 1-(hydroxymethyl)cyclohexanol is a modification of that reported by the submitters.[4] While 1-(hydroxymethyl)cyclohexanol has been conventionally prepared from methylenecyclohexane by dihydroxylation[5a] or from cyclohexanone in three steps through the cyanohydrin,[5b] the present method consists of an alternative route from cyclohexanone via nucleophilic hydroxymethylation.

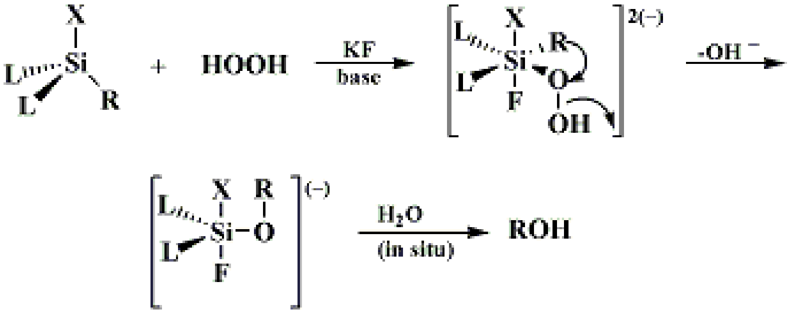
Although nucleophilic hydroxymethylating agents (hydroxymethyl anion synthons) or alkoxymethyl anions could be of great use in synthetic organic chemistry,[6] only a few agents of this type have been developed so far. They include $MeOH/TiCl_4/hv$,[7] $Bu_3SnCH_2OH/BuLi$,[8] *tert*-$BuOCH_2Li$,[9] $HSiR_3/CO/Co_2(CO)_8$,[10] $PhCH_2OCH_2Cl/SmI_2$,[11] $ArCO_2CH_2Li/LiAlH_4$,[12] $R_2BCH_2Li/[O]$,[13 14] and $(Me_3SiO)CH{=}C(OSiMe_3)_2$.[15] These methods are not as convenient or widely applicable as the method reported here. Two points deserve comment.



In addition to the (isopropoxydimethylsilyl)methyl Grignard reagent, $(isoPrO)Me_2SiCH_2MgCl$ (**1**), the (diisopropoxymethylsilyl)methyl counterpart, $(isoPro)_2MeSiCH_2MgCl$ (**2**), has also been used as a nucleophilic hydroxymethylating agent.[16] Despite labile alkoxy group(s) on silicon, the Grignard reagents are readily prepared in a normal manner in greater than 90% yields, and are sufficiently stable to be stored at room temperature for at least 2 days with little decrease in activity. The monoisopropoxy Grignard reagent (**1**) is recommended as the reagent of first choice. Its precursor, (isopropoxydimethylsilyl)methyl chloride, is readily available at lower cost, and the reaction products, $(iso\text{-}PrO)Me_2SiCH_2E$, are more stable not only to aqueous workup under weakly basic and acidic conditions but also to silica gel chromatography.

The present method is based on the oxidative cleavage reaction of the silicon–carbon bond by hydrogen peroxide.[17] The presence of at least one heteroatom on silicon is essential for the oxidative cleavage. Thus, the silicon-carbon bonds in hydro-, fluoro-, chloro-, alkoxy-, or aminosilanes are cleaved oxidatively to give the corresponding hydroxylated products. Although the oxidation may be performed

in several ways, the following conditions (involving weak base and fluoride ion) may be the most efficient and most widely applicable: 30% H_2O_2 (1.2 equiv/Si-C bond), $KHCO_3$ (1 molar equiv), KF (2 molar equiv), MeOH/THF (1 : 1), room temperature. Under these conditions, the reaction usually occurs exothermically and is typically complete in several hours. Functional groups such as olefin, aldehyde, ketone, ester, amine, ether, ketal and *tert*-butyldimethylsiloxy groups, and furan, thiophene, and pyridine rings are stable under the oxidation conditions. The oxidation proceeds with complete retention of configuration at an sp^3 carbon. The oxidation has been considered to proceed through intramolecular migration of an organic group from silicon to the adjacent oxygen atom in penta- or hexacoordinate hydroperoxysilicon intermediates, as shown in Scheme 1, where X stands for a functional group. The oxidation has found a variety of synthetic applications.[18]

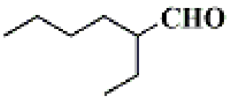
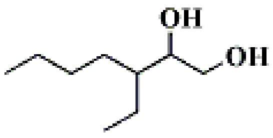
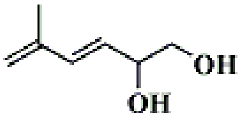
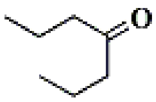
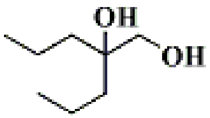


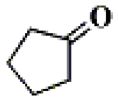
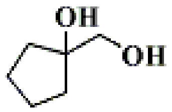
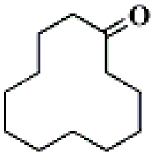
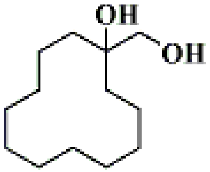
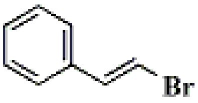
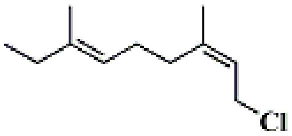
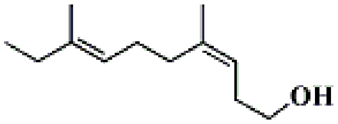
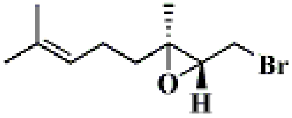
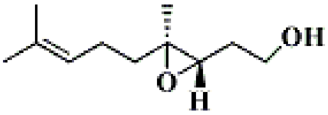
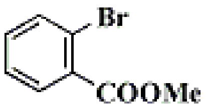
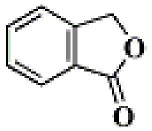
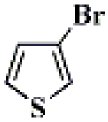
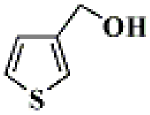
Several representative examples of nucleophilic hydroxymethylation of aldehydes, ketones, organic halides, tosylates, and epoxides are summarized in Table 1. The oxidation conditions given in the original literature are not necessarily optimum, and results may be improved by use of the oxidation method employed here. These results, summarized in Table I, demonstrate the general applicability of the silicon-based nucleophilic hydroxymethylation.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 493
- Org. Syn. Coll. Vol. 9, 539

TABLE I
NUCLEOPHILICHYDROXYMETHYLATION OFALDEHYDES,KETONES,ORGANICHALIDES, ALCOHOLS, ANDEPOXIDES[a]

Starting Material	Product	Overall isolated yield (%)	Ref.
		67	4
		75	19
		86	4

		65	4
		63	4
		79	16
		87	16
		52	20
		86	16
		65	16
(via tosylate)		67	21
		74	21

[a]Introduction of the silylmethyl group into organic halides, tosylates, and epoxides is achieved by nickel-, palladium-, or copper-catalyzed cross-coupling reactions.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

methanol, MeOH (67-56-1)

diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

sodium hydrogen carbonate (144-55-8)

magnesium (7439-95-4)

Cyclohexanone (108-94-1)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

Benzophenone (119-61-9)

sodium (13966-32-0)

isopropyl alcohol (67-63-0)

1,2-dibromoethane (106-93-4)

hydrogen peroxide (7722-84-1)

magnesium sulfate (7487-88-9)

Tetrahydrofuran, THF (109-99-9)

potassium fluoride (7789-23-3)

lithium aluminum hydride (16853-85-3)

hexane (110-54-3)

triethylamine (121-44-8)

potassium hydrogen carbonate (298-14-6)

Methylenecyclohexane (1192-37-6)

sodium thiosulfate pentahydrate

1-(Hydroxymethyl)cyclohexanol, Cyclohexanemethanol, 1-hydroxy- (15753-47-6)

1-[(Isopropoxydimethylsilyl)methyl]cyclohexanol (138080-23-6)

(Isopropoxydimethylsilyl)methyl chloride (18171-11-4)

(chlorodimethylsilyl)methyl chloride (1719-57-9)

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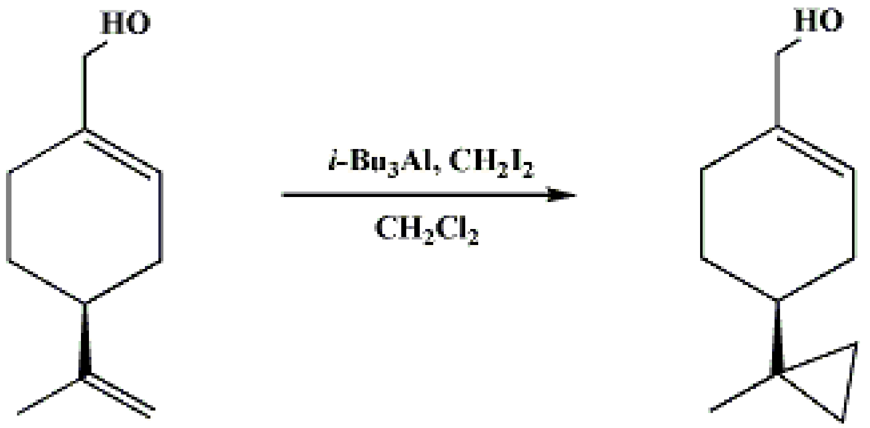
SELECTIVE CYCLOPROPANATION OF (*S*)-(–)-PERILLYL ALCOHOL: 1-HYDROXYMETHYL-4-(1-METHYLCYCLOPROPYL)-1-CYCLOHEXENE

[1-Cyclohexene-1-methanol, 4-(1-methylcyclopropyl)-]



Submitted by Keiji Maruoka, Soichi Sakane, and Hisashi Yamamoto[1].
Checked by Hisatoyo Kato and Ryoji Noyori.

1. Procedure

A dry, 1-L, three-necked, round-bottomed flask is equipped with a gas inlet, a 50-mL pressure-equalizing dropping funnel, a rubber septum, and a Teflon-coated magnetic stirring bar. The flask is flushed with argon, after which 10.65 g (0.07 mol) of (*S*)-(–)-perillyl alcohol (Note 1) followed by 350 mL of dichloromethane (Note 2) is injected through the septum into the flask. The solution is stirred and 37.3 mL (0.147 mol) of triisobutylaluminum (Note 3) is added from the dropping funnel over a 20-min period at room temperature (Note 4). After the mixture is stirred at room temperature for 20 min, 7.3 mL (0.091 mol) of diiodomethane (Note 5) is added dropwise with a syringe over a 10-min period. The mixture is stirred at room temperature for 4 hr, and poured into 400 mL of ice-cold 8% aqueous sodium hydroxide. The organic layer is separated, and the aqueous layer is extracted twice with 100-mL portions of dichloromethane. The combined extracts are dried over anhydrous sodium sulfate and concentrated with a rotary evaporator at ca. 20 mm. The residual oil is distilled under reduced pressure to give 10.64–11.13 g (92–96%) of 1-hydroxymethyl-4-(1-methylcyclopropyl)-1-cyclohexene as a colorless liquid, bp 132–134°C (24 mm) (Note 6) and (Note 7).

2. Notes

1. (*S*)-(–)-Perillyl alcohol is available from Aldrich Chemical Company, Inc.
2. Reagent-grade dichloromethane was dried and stored over Linde type 4A

molecular sieves.

3. Neat triisobutylaluminum of 97.6% purity was supplied in a metal cylinder from Toso-Akzo Chemical Company, Ltd. (Japan). This reagent is also available from Aldrich Chemical Company, Inc. Since neat triisobutylaluminum is pyrophoric and reacts violently with oxygen and water, the used syringe should be immediately washed with hexane.

4. During this operation an exothermic reaction took place.

5. Diiodomethane, available from Tokyo Kasei Kogyo Company, Ltd. (Japan), was used without any purification.

6. The spectral properties of the product are as follows: ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.22 and 0.26 (m, 4 H, cyclopropyl C-H), 0.80–0.92, 1.24–1.30, and 1.36–1.47 (m, 3 H, cyclohexenyl C-H), 0.93 (s, 3 H, CH_3), 1.77–1.83 (m, 1 H, cyclohexenyl =C-C-H), 1.91–2.16 (m, 4 H, OH, and cyclohexenyl =C-C-H), 3.99 (brt, 2 H, CH_2-O), 5.69 (br s, 1 H, =C-C-H); IR (liquid film) cm^{-1}: 3330, 2830–2960, 1423–1460, 1390, 1010, 1000.

7. Gas-chromatographic analysis of the trimethylsilyl ether using a 25-m PEG-HT capillary column at 100°C indicated a purity of 93% (retention time: 11.2 min). Under the present conditions, neither the starting perillyl alcohol nor the isomeric monocyclopropanation product (1-hydroxymethyl-4-isopropenylbicyclo [4.1.0]-heptane) were detected. Dicyclopropanation products amounted to less than 5%.

3. Discussion

This procedure illustrates a new method for selective cyclopropanation of unsaturated alcohols not obtainable with ordinary cyclopropanation reactions.[2] The selectivity in this trialkylaluminum-promoted cyclopropanation is complementary to that obtained in the Simmons–Smith reaction and its modifications,[3] which give facile hydroxyl-assisted cyclopropanations with perillyl alcohol to afford 1-hydroxymethyl-4-isopropenylbicyclo[4.1.0]heptane predominantly. A similar tendency was observed in the case of geraniol. Thus, cyclopropanation with the $i\text{-}Bu_3Al/CH_2I_2$ system takes place almost exclusively at the C(6)–C(7) olefinic site far from the hydroxyl group of geraniol, and the C(2)–C(3) olefinic bond is left intact.[2]

The present cyclopropanation using trialkylaluminum-methylene iodide may proceed via dialkyl(iodomethyl)aluminum as an active intermediate,[4] which also can be generated by the reaction of dialkylaluminum iodide with diazomethane.[5] In addition, reaction of diiodomethane with triisobutylaluminum (each 1 equiv) afforded nearly 1 equiv of isobutyl iodide as a product, suggesting the formation of diisobutyl (iodomethyl)aluminum in the solution.[2]

The combined use of a wide variety of trialkylaluminum compounds and alkylidene iodide serves as a highly convenient and versatile method for cyclopropanation of

simple olefins under mild conditions.[2] For example, treatment of 1-dodecene with CH_2I_2/R_3Al (R = Me, Et, *i*-Bu) in dichloromethane at room temperature for 3–8 hr gave decylcyclopropane in 96–98% yields.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

(S)-(−)-PERILLYL ALCOHOL

sodium hydroxide (1310-73-2)

sodium sulfate (7757-82-6)

oxygen (7782-44-7)

diiodomethane (75-11-6)

dichloromethane (75-09-2)

Diazomethane (334-88-3)

hexane (110-54-3)

geraniol (106-24-1)

triisobutylaluminum (100-99-2)

argon (7440-37-1)

trimethylsilyl ether (107-46-0)

1-Hydroxymethyl-4-(1-methylcyclopropyl)-1-cyclohexene, 1-Cyclohexene-1-methanol, 4-(1-methylcyclopropyl)- (98678-72-9)

perillyl alcohol

1-hydroxymethyl-4-isopropenylbicyclo[4.1.0]-heptane, 1-hydroxymethyl-4-isopropenylbicyclo[4.1.0]heptane

Isobutyl iodide (513-38-2)

diisobutyl(iodomethyl)aluminum

1-dodecene (112-41-4)

decylcyclopropane

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3-HYDROXY-3-METHYL-1-PHENYL-1-BUTANONE BY CROSSED ALDOL REACTION

[1-Butanone, 3-hydroxy-3-methyl-1-phenyl-]

Submitted by Teruaki Mukaiyama and Koichi Narasaka[1].
Checked by Kathleen Hug and Clayton H. Heathcock.

1. Procedure

A 500-mL, three-necked flask is fitted with a stirring bar, a rubber stopper, a 100-mL pressure-equalizing dropping funnel, and a three-way stopcock that is equipped with a balloon of argon gas (Note 1). The flask is charged with 140 mL of dry methylene chloride (Note 2) and cooled in an ice bath. Titanium tetrachloride (11.0 mL) (Note 3) is added by a syringe with stirring by a magnetic stirrer, and a solution of 6.5 g of acetone in 30 mL of methylene chloride is added dropwise over a 5-min period. On completion of this addition a solution of 19.2 g of acetophenone trimethylsilyl enol ether (Note 4) in 15 mL of methylene chloride (Note 5) is added dropwise over a 10-min period, and the mixture is stirred for 15 min.

The reaction mixture is poured into 200 mL of ice water with vigorous stirring and the organic layer is separated. The aqueous layer is extracted with two 30-mL portions of methylene chloride. The combined methylene chloride extracts are washed with two 60-mL portions of a 1 : 1 mixture of saturated aqueous sodium bicarbonate and water, and then with brine. The methylene chloride solution is dried over sodium sulfate and the methylene chloride is removed using a rotary evaporator.

The residue is dissolved in 30 mL of benzene, and the solution is transferred to a chromatographic column (50-mm diameter) consisting of 600 mL of silica gel. The product is eluted sequentially with (a) 1 L of 4 : 1 (v/v) hexane : ethyl acetate and (b) 1.5 L of 2 : 1 (v/v) hexane : ethyl acetate (flash chromatography) (Note 6).

The initial ca. 900 mL of the eluent is discarded. Concentration of the later fractions (ca. 1.3 L) under reduced pressure yields the pure product as an oil (Note 7). The total yield is 12.2–12.8 g (70–74%).

2. Notes

1. All apparatuses should be oven-dried before use.
2. Methylene chloride was purified by distillation from phosphorus pentoxide, then from calcium hydride, and was stored over Linde 4A molecular sieves.
3. Freshly distilled titanium tetrachloride (bp 152–153°C) was used. The checkers distilled the titanium tetrachloride from calcium hydride.
4. The silyl enol ether may be obtained from the Fluka Chemical Corp., 255 Oser Avenue, Hauppauge, NY 11788. Alternatively, it may be prepared by the following modification of the procedure of Walshe and co-workers.[2] The Walshe procedure is followed exactly with 36 g (0.30 mol) of acetophenone, 41.4 g (0.41 mol) of triethylamine, 43.2 g (0.40 mol) of chlorotrimethylsilane, 60 g (0.40 mol) of sodium iodide, and 350 mL of acetonitrile. After extraction, the organic layer is dried over potassium carbonate and then concentrated with a rotary evaporator under reduced pressure. The crude product is a mixture of 97% of the desired silyl enol ether and 3% of acetophenone, as shown by gas chromatography. The crude product is distilled in a Claisen flask at a pressure of about 40 mm. After a small forerun (ca. 3 g), 52.3 g (91%) of silyl enol ether, bp 124–125.5°C, is obtained. The purity of this material is approximately 98%, as judged by gas chromatography and ^{1}H NMR spectroscopy.
5. Submitters report using 60 mL of hexane.
6. 3-Hydroxy-3-methyl-1-phenyl-1-butanone is too unstable to be purified by distillation, and decomposes

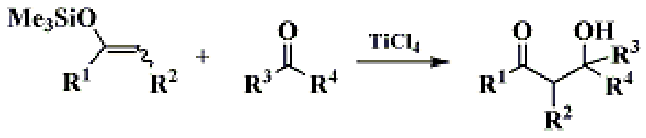
to acetophenone and acetone.

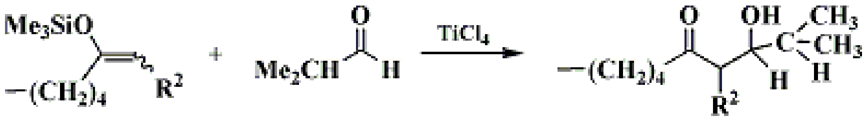
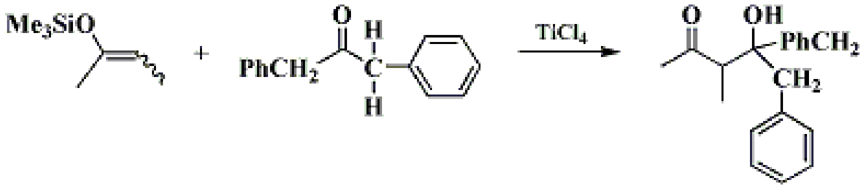
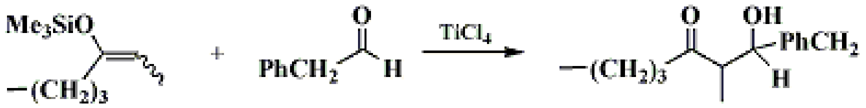
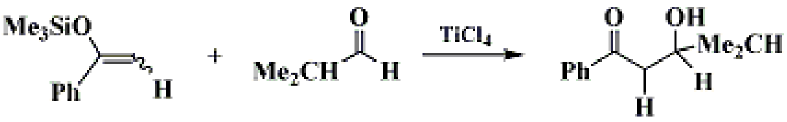
7. The initial fractions are sometimes contaminated with a less polar by-product. These fractions are condensed and purified again by column chromatography using 6 : 1 (v/v) hexane : ethyl acetate and then 2 : 1 (v/v) hexane : ethyl acetate as developing solvents. The NMR spectrum ($CDCl^{3}$) shows singlets at δ 1.33 (6 H, CH_3), 3.12 (2 H, CH_2), 4.12 (broad, OH) and complex signals between 7.24–8.01 (5 H).

3. Discussion

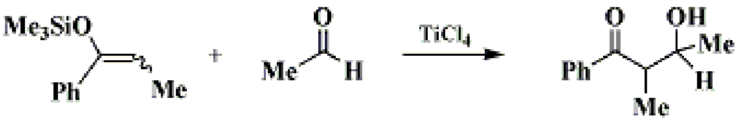
This procedure illustrates a general method for the preparation of crossed aldols. The aldol reaction between various silyl enol ethers and carbonyl compounds proceeds smoothly according to the same procedure (see Table 1). Silyl enol ethers react with aldehydes at –78°C, and with ketones near 0°C.[3] Note that the aldol reaction of silyl enol ethers with ketones affords good yields of crossed aldols, which are generally difficult to prepare using lithium or boron enolates. Lewis acids such as tin tetrachloride and boron trifluoride etherate also promote the reaction; however, titanium tetrachloride is generally the most effective catalyst.

TABLE I
PREPARATION OF CROSSED ALDOLS



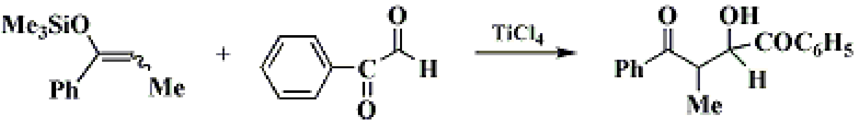
Substituents				
R^1	R^2	R^3	R^4	Yield of Aldols (%)
-$(CH_2)_4$-		Me_2CH	H	 92
		$PhCH_2$	$PhCH_2$	 64
-$(CH_2)_3$-		$PhCH_2$	H	 95
Ph	H	Me_2CH	H	 94

Ph Me Me H



92

Ph Me PhCO H



83

Ph Me Me $(CH_2)_2CO_2Me$

53

Ketene alkyl silyl acetals may also be used as nucleophiles for the formation of β-hydroxy esters.[4] The present reaction can be carried out equally well on large or small (mmole) scales. For small scale applications, it is convenient to prepare a stock solution of titanium tetrachloride in methylene chloride. (A rubber stopper is gradually destroyed by titanium tetrachloride; therefore, a Teflon stopper should be used.) Titanium tetrachloride also promotes the aldol-type reaction between silyl enol ethers and acetals to give β-alkoxy carbonyl compounds.[5].

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 210

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

brine

acetophenone trimethylsilyl enol ether

potassium carbonate (584-08-7)

Benzene (71-43-2)

ethyl acetate (141-78-6)

acetonitrile (75-05-8)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

acetone (67-64-1)

Acetophenone (98-86-2)

sodium iodide (7681-82-5)

methylene chloride (75-09-2)

tin tetrachloride (7646-78-8)

hexane (110-54-3)

titanium tetrachloride (7550-45-0)

triethylamine (121-44-8)

boron trifluoride etherate (109-63-7)

calcium hydride (7789-78-8)

argon (7440-37-1)

CHLOROTRIMETHYLSILANE (75-77-4)

phosphorus pentoxide (1314-56-3)

3-Hydroxy-3-methyl-1-phenyl-1-butanone, 1-Butanone, 3-hydroxy-3-methyl-1-phenyl- (43108-74-3)

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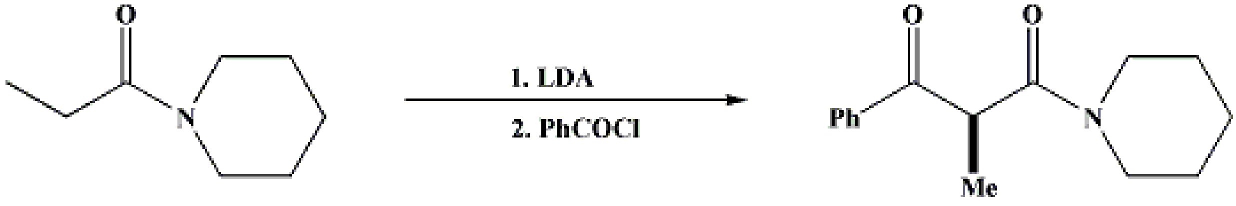
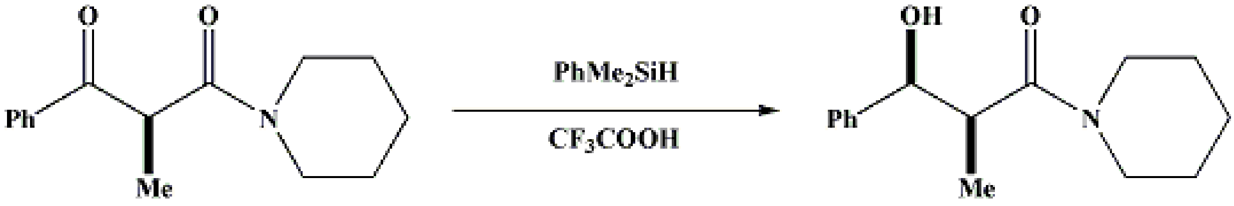
erythro-DIRECTED REDUCTION OF A β-KETO AMIDE: ERYTHRO-1-(3-HYDROXY-2-METHYL-3-PHENYLPROPANOYL) PIPERIDINE

[Piperidine, 1-(3-hydroxy-2-methyl-1-oxo-3-phenylpropyl)-, (*R**, *R**)-(±)-]

A.



B.



Submitted by M. Fujita and T. Hiyama[1].
Checked by Gregory P. Roth and Albert I. Meyers.

1. Procedure

A. *1-(2-Benzoylpropanoyl)piperidine*. A dry, 300-mL, two-necked, round-bottomed flask is equipped with a magnetic stirrer and charged with nitrogen. One neck is connected to a three-way stopcock equipped with a balloon filled with nitrogen, and the other neck is capped with a rubber septum. The flask is charged with 100 mL of anhydrous tetrahydrofuran (THE) (Note 1) and 10.1 g (14.1 mL, 0.100 mol) of diisopropylamine (Note 2) and immersed in an acetone–dry ice bath. A 1.68 *M* hexane solution of butyllithium (60 mL, 0.10 mol) (Note 3) is added dropwise with stirring over a 10-min period, and the stirring is continued for 1 hr at −78°C. To the resulting lithium diisopropylamide (LDA) solution is added dropwise 14.1 g (0.100 mol) of propanoylpiperidine (Note 4) with stirring over a 10-min period, and the stirring is continued for 2 hr at −78°C (Note 15). The rubber septum is replaced with a polyvinyl chloride (or Teflon) tube connected to another 300-mL, two-necked, round-bottomed flask, which is equipped with a magnetic stirrer and a three-way stopcock, charged with 100 mL of anhydrous THF and 13.5 g (16.3 mL, 0.110 mol) of benzoyl chloride (Note 6), and immersed in an acetone–dry ice bath. The balloon is taken off and nitrogen is passed through the two stopcocks so that the reaction mixture does not come in contact with air (see the apparatus shown in f.htmig. 1). By inclining the first flask, the THF solution of the lithium enolate of 1-propanoylpiperidine is added to the THF solution of benzoyl chloride in the second flask through the polyvinyl chloride tube over a 5-min period. After the solution is stirred for 0.5 hr at −78°C, it is allowed to warm to room temperature, diluted with 200 mL of dichloromethane, and washed with 200 mL of water. The organic layer is separated, and the aqueous layer is extracted with two 50-mL portions of diethyl ether. The combined organic layers are dried over anhydrous magnesium sulfate and concentrated with a rotary evaporator. Recrystallization from diethyl ether–hexane affords 12.5 g (51%) of 1-(2-benzoylpropanoyl)piperidine, mp 100–101°C (Note 7).

Figure 1

Figure 1

B. *erythrol-1-(3-Hydroxy-2-methyl-3-phenylpropanoyl)piperidine*. A 300-mL, two-necked, round-bottomed flask is equipped with a magnetic stirrer and charged with nitrogen. One neck is connected with a balloon charged with nitrogen, and the other neck is capped with a rubber septum. Into the flask are placed 50 mL of trifluoroacetic acid (Note 8) and 11.9 g of 1-(2-benzoylpropanoyl)piperidine (48.7 mmol) prepared as described in Part A; then the flask is immersed in an ice–water bath. To the flask is added 7.3 g of dimethylphenylsilane (8.24 mL, 54 mmol) (Note 9) over a 5-min period with the aid of a 10-mL syringe, and the resulting mixture is stirred for 4 hr in the ice bath. The mixture is diluted with 200 mL of dichloromethane and washed with 200 mL of water. After the organic layer is separated, the aqueous layer is extracted with two 50-mL portions of diethyl ether, and the combined organic layers are concentrated with a rotary evaporator (Note 10). The crude oil is placed in a 200-mL, one-necked flask and dissolved in 100 mL of methanolic 1 *M* sodium hydroxide. The solution is stirred for 1.5 hr at ambient temperature with a magnetic stirrer. The mixture is diluted with 200 mL of dichloromethane and washed with 50 mL of water. The organic layer is separated, and the aqueous layer is extracted with two 50-mL portions of diethyl ether. The combined organic layers are dried over anhydrous magnesium sulfate and concentrated by rotary evaporation (Note 11). The residual oil is subjected to column chromatography using 100 g of silica gel (Note 12). After the first fraction (800t mL) of hexane is eluted, the second fraction, eluted with 500 mL of diethyl ether, is collected and concentrated. Recrystallization of the resulting oil from diethyl ether–hexane gives 10.2 g of material, mp 85–86°C. The yield is 90% (Note 13).

The analogous threo derivatives can be made by use of tris(diethylamino)sulfonium difluorotrimethylsilicate as the catalyst (Note 14).

2. Notes

1. Tetrahydrofuran (THF) is freshly distilled over benzophenone ketyl.
2. Diisopropylamine is distilled over calcium hydride.
3. The hexane solution of butyllithium is purchased from Wako Pure Chemicals Industries, Ltd. and titrated before use.
4. Propanoylpiperidine is prepared from propanoyl chloride and piperidine according to a similar procedure described in [2].
5. The lithium enolate of (2-benzoylpropanoyl)piperidine should be handled below −20°C, as it decomposes above 0°C.
6. Benzoyl chloride of commercial grade is distilled before use.
7. Spectral characteristics are as follows: ^{1}H NMR ($CDCl_3$) δ: 1.46 (d, 3 H, *J* = 7.2), 1.3–1.7 (m, 6 H), 3.25–3.65 (m, 4 H), 4.40 (q, 1 H, *J* = 7.2), 7.25–7.65 (m, 3 H), 7.85–8.05 (m, 2 H); IR (KBr) cm^{-1}: 1696, 1620, 1450, 1204, 686; MS (50 eV) *m/z* rel intensity, 245 (M^+; 14), 140 (37), 105 (100), 84 (99), 77 (47). Anal. calcd. for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.22; H, 7.87; N, 5.69.
8. Trifluoroacetic acid was purchased from Aldrich Chemical Company, Inc. (also available from Tokyo Kasei Co. LTD, Japan), and used directly.
9. Dimethylphenylsilane was purchased from Aldrich Chemical Company, Inc. (also available from Shin-etsu Kagaku Co. LTD, Japan), and used directly.
10. About half of the product is trifluoroacetylated during the concentration procedure.
11. A 400-MHz ^{1}H NMR analysis of the crude oil showed exclusive formation of the erythro isomer of the material (>99:1).
12. A glass column (35 mm × 20 cm) packed with Wakogel C-200 is used.
13. Spectral characteristics are as follows: ^{1}H NMR ($CDCl_3$) δ: 1.03 (d, 3 H, *J* = 7), 1.3–1.7 (m, 6 H), 2.84 (dq, 1 H, *J* = 2.5, 3), 3.2–3.7 (m, 4 H), 4.30 (broad s, 1 H), 5.06 (d, 1 H, *J* = 2.5), 7.2–7.4 (m, 5 H); IR (KBr) cm^{-1}: 3350, 1606; MS (relative intensity) *m/z*, 247 (M^+; 7), 232 (20), 141 (100), 112 (26), 84 (43), 79 (20). Anal. calcd. for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.74; H, 8.69; N, 5.52.
14. *threo-1-(3-Hydroxy-2-methyl-3-phenylpropanoyl)piperidine*. A 300-mL, two-necked, round-

bottomed flask is equipped with a magnetic stirrer and charged with dry nitrogen. One neck is connected with a three-way stopcock, one arm of which is connected to a balloon filled with nitrogen. The other neck is capped with a rubber septum. The flask is evacuated with a vacuum pump under heating with a heat gun and nitrogen is admitted. This operation is repeated 3 times to replace the inner atmosphere of the flask completely with dry nitrogen. In the flask are placed 50 mL of hexamethylphosphoric triamide (Note 15), 12.3 g of 1-(2-benzoylpropanoyl)piperidine (50 mmol), and 8.2 g of dimethylphenylsilane (9.2 mL, 60 mmol) by syringe, and then the flask is immersed in an ice–water bath. To the flask is added dropwise 2.5 mL of a 1 *M* tetrahydrofuran (THF) solution of tris(diethylamino)sulfonium difluorotrimethylsilicate (TASF) (2.5 mmol) (Note 16) with the aid of a syringe, and the resulting mixture is stirred for 6 hr at ice-bath temperature. In order to complete the reaction, 3.4 g of dimethylphenylsilane (3.8 mL, 25 mmol) and 1.5 mL of a 1 *M* THF solution of TASF (1.5 mmol) are added and stirring is continued for an additional 6 hr at the same temperature. The mixture is quenched with 50 mL of 1 *M* hydrochloric acid, stirred for 1.5 hr at ambient temperature, and extracted with three 100-mL portions of diethyl ether. The organic layer is washed with 50 mL of water, dried over anhydrous magnesium sulfate, and concentrated with a rotary evaporator. The crude oil is subjected to column chromatography using 100 g of silica gel (Note 17). After the first fraction, eluted with 800 mL of hexane, is removed, the second fraction, eluted with 500 mL of diethyl ether, is concentrated (Note 18). Recrystallization of the residue from diethyl ether–hexane gives 8.03 g (65%) of material, mp 79–80°C (Note 19). The mother liquor is concentrated and again subjected to column chromatography (Note 20) to give the same material, which, after recrystallization from diethyl ether–hexane, melts at 77–79°C (1.5 g, 12%). The total yield amounts to 77%.

15. Hexamethylphosphoric triamide is distilled from calcium hydride under reduced pressure of nitrogen. In place of hexamethylphosphoric triamide, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)pyrimidinone (DMPU), which is dried and purified similarly,[3] can be used.

16. TASF was prepared according to the procedure described in [4]. Typically, diethylamino(trimethyl)silane (6.4 g, 8.3 mL, 44 mmol) is added drop by drop under a dry inert atmosphere to an ethereal solution (20 mL) of diethylaminosulfur trifluoride (DAST, purchased from Aldrich Chemical Company, Inc., and used directly) (3.2 g, 2.4 mL, 20 mmol) under cooling with a dry ice–acetone bath. The mixture is allowed to warm to room temperature and stirred for 72 hr at room temperature. The initial homogeneous solution separates into two layers. The upper layer is removed with the aid of a syringe. The lower layer is washed with dry ether (10 mL × 3) and dried under reduced pressure to afford TASF as a solid (6.0 g, 16.6 mmol, 83% yield). All the isolation operations should be carried out under an inert atmosphere such as nitrogen. The solid is dissolved in THF to give a 1 *M* solution (the volume of the solution is 16.6 mL) which is stored under a dry nitrogen atmosphere.

17. A glass column (35 mm × 20 cm) packed with Wakogel C-200 is used.

18. A 400-MHz ^{1}H NMR analysis of the crude oil showed exclusive formation of the threo isomer of the material (>99%).

19. Spectral characteristics are as follows: ^{1}H NMR ($CDCl_3$) δ: 1.22 (d, *J* = 7.3 H), 1.1–1.7 (m, 6 H), 2.8–3.8 (m, 5 H), 4.7–4.8 (m, 2 H), 7.31 (s, 5 H); IR (KBr) cm^{-1}: 3380, 1606; MS (relative intensity) *m/z* 247 (M^+; 6), 232 (16), 141 (100), 112 (23), 84 (39), 79 (15). Anal. calcd. for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.70; H, 8.63; N, 5.65.

20. A glass column (20 mm × 25 cm) packed with 50 g of Wakogel C-200 is used. After the first fraction, eluted with 300 mL of dichloromethane, was removed, the second fraction, eluted with 300 mL of dichloromethane–diethyl ether (1 : 4), was concentrated.

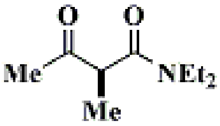
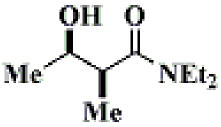
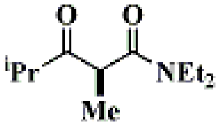
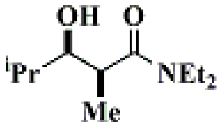
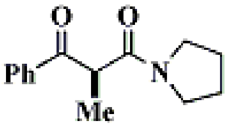
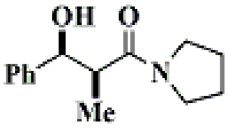
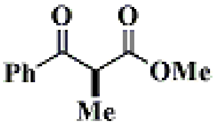
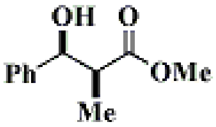
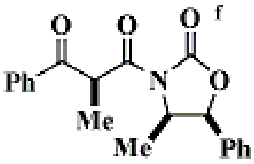
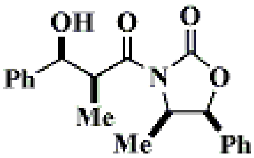
3. Discussion

Aldols of the *erythro* configuration are prepared by aldol condensation of various metal enolates.[5 6 7] An alternative approach is reduction of β-keto esters[8] or amides[9] with zinc borohydride. The hydrosilane-

based reduction described here provides *erythro* aldols under high stereocontrol and is practical because of the mild conditions and easy handling of readily available hydrosilanes.[3] The scope of this reduction is summarized in Table I. No epimerization at the chiral center is observed as shown in the last entry. The erythro-selective reduction with the $PhMe_2SiH/CF_3COOH$ reagent is also applicable to the reduction of 2-oxy or 2-amino ketones.[10,11]

TABLE I

***erythro*-SELECTIVE REDUCTION OF α-SUBSTITUTED β-KETO ACID DERIVATIVES WITH $PhMe_2SiH/H^+$ REAGENT[a]**

Substrate[b]	Time, hr	Product[c]	% Yield[d]	Threo: Erythro[e]
	3		94	2:98
	20		89	1:99
	3		99	1:99
	3		87	1:>99
 [f]	4		98	1:>99

[a]Carried out on a 0.5–1.0-mmol scale at 0°C employing $PhMe_2SiH$ (1.2 mol equiv) and CF_3COOH (1–2 mL/mmol).

[b]Racemates were employed unless noted.

[c]Major isomers are shown.

[d]Purified by silica gel chromatography.

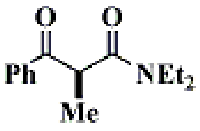
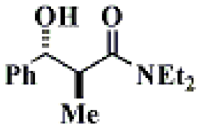
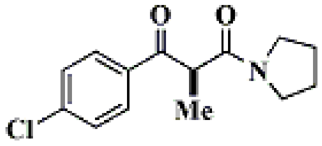
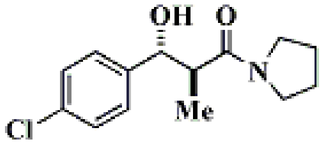
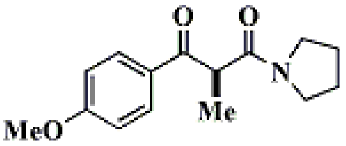
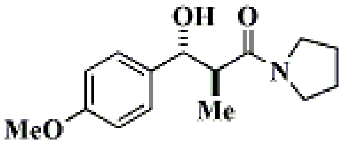
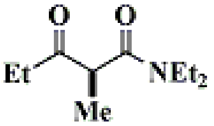
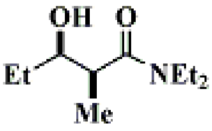
[e]The ratio was determined by 90 or 400 MHz ^{1}H NMR analysis.

[f]The optically pure substrate was prepared according to a known method: see Evans, D. A.; Ennis, M. D.; Le, T.; Mandel, N.; Mandel, G. *J. Am. Chem. Soc.* **1984**, *106*, 1154.

Preparation of *threo* aldols is sometimes a problem. For stereoselective synthesis by aldol condensation, propionate esters of mesitol must be employed.[12] A general, alternative approach to *threo* aldols is *threo*-directed reduction of β-keto esters.[13] Although the stereoselectivity of this reduction is usually low, reduction of β-keto amides with potassium triethylborohydride ($KBHEt_3$) is extremely selective.[14] The hydrosilane/F^- reduction of β-keto amides provides *threo* aldols of high diastereomeric purity when aroyl-substituted amides are employed.[3] The scope of this reduction is summarized in Table II. High *threo* selectivity is observed only for reduction of 2-aroylpropanoates, whereas the reduction of 2-alkanoylpropanoates proceeds with poor selectivity and gives *erythro* isomers as the major product.[15] The hydrosilane/F^- reduction is also applicable to the *threo*-selective reduction of α-oxy and α-amino ketones.[10]

TABLE II

THREO-SELECTIVE REDUCTION OF β-KETO AMIDES WITH $PhMe_2SiH/F^-$ REAGENT[a]

Substrate[b]	Time hr	Product[c]	% Yield[d]	Threo: Erythro[e]
	12		98	>99:1
	16		86	99:1
	16		92	99:1
	22		93	23:27

[a]Carried out on a 0.5–1.0-mmol scale at 0°C employing $PhMe_2SiH$ (1.2 mol equiv) and TASF (10 mol %).

[b]Racemates were employed.

[c]Major isomers are shown.

[d]Purified by silica gel chromatography.

[e]The ratio was determined by 90 or 400 MHz ^{1}H NMR analysis.

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

benzophenone ketyl

erythro-1-(3-Hydroxy-2-methyl-3-phenylpropanoyl)piperidine

Piperidine, 1-(3-hydroxy-2-methyl-1-oxo-3-phenylpropyl)-, (R*, R*)-(±)-

lithium enolate of 1-propanoylpiperidine

THF solution of benzoyl chloride

erythrol-1-(3-Hydroxy-2-methyl-3-phenylpropanoyl)piperidine

lithium enolate of (2-benzoylpropanoyl)piperidine

threo-1-(3-Hydroxy-2-methyl-3-phenylpropanoyl)piperidine

TASF

hydrochloric acid (7647-01-0)

ether, diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

nitrogen (7727-37-9)

benzoyl chloride (98-88-4)

piperidine (110-89-4)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

propanoyl chloride (79-03-8)

butyllithium (109-72-8)

Tetrahydrofuran, THF (109-99-9)

hexane, hexane solution of butyllithium (110-54-3)

calcium hydride (7789-78-8)

trifluoroacetic acid (76-05-1)

hexamethylphosphoric triamide (680-31-9)

lithium diisopropylamide (4111-54-0)

diisopropylamine (108-18-9)

Diethylaminosulfur trifluoride (38078-09-0)

diethylamino(trimethyl)silane (996-50-9)

1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)pyrimidinone (7226-23-5)

propanoylpiperidine

1-(2-Benzoylpropanoyl)piperidine (99114-34-8)

dimethylphenylsilane (766-77-8)

tris(diethylamino)sulfonium difluorotrimethylsilicate (59201-86-4)

zinc borohydride

potassium triethylborohydride

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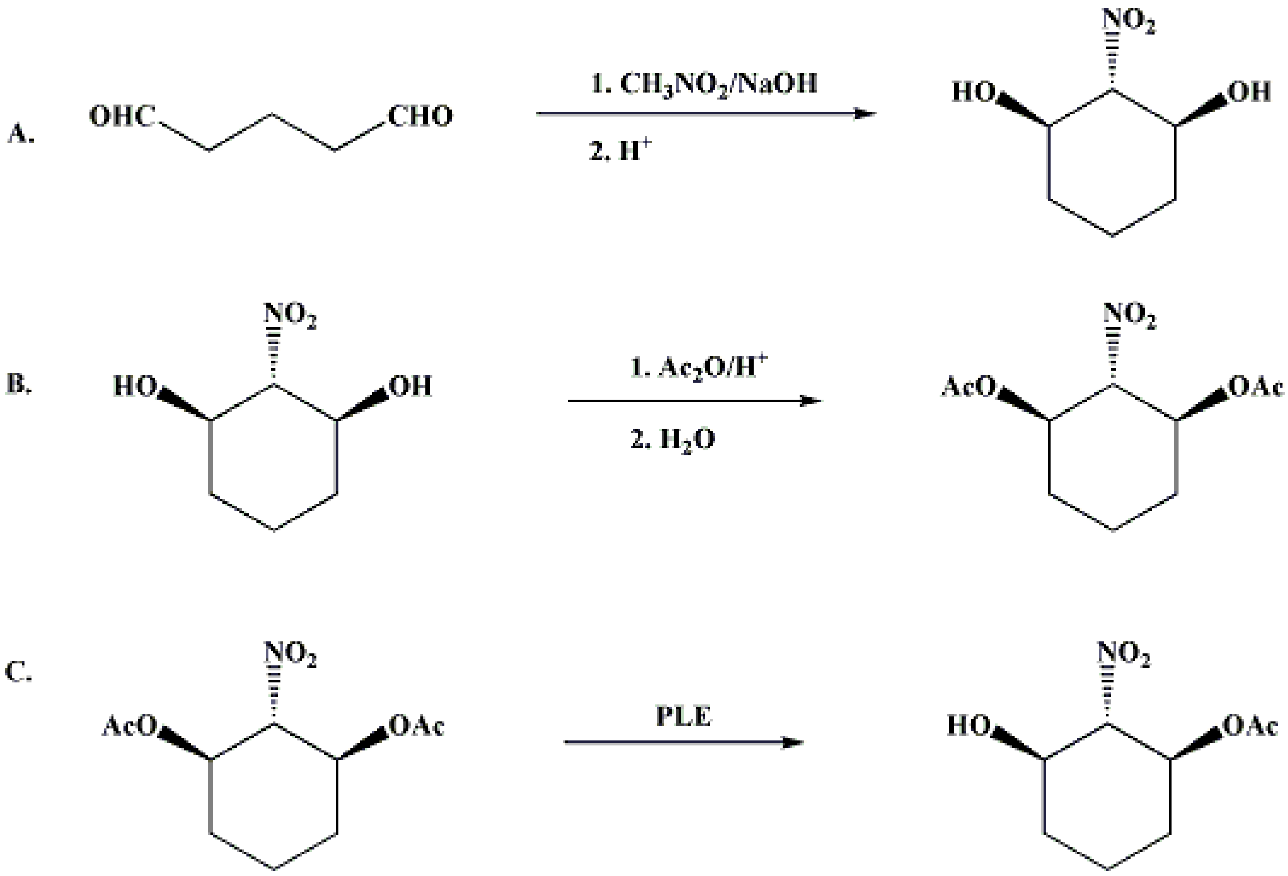
ENANTIOSELECTIVE SAPONIFICATION WITH PIG LIVER ESTERASE (PLE): (1*S*,2*S*,3*R*)-3-HYDROXY-2-NITROCYCLOHEXYL ACETATE

[1,3-Cyclohexanediol, 2-nitro-, 1-acetate, [1*S*-(1α, 2β, 3α]]



Submitted by Martin Eberle, Martin Missbach, and Dieter Seebach[1].
Checked by David L. Coffen

1. Procedure

A. *(1R,2r,3S)-2-Nitrocyclohexane-1,3-diol*. A 1-L, round-bottomed flask, equipped with a magnetic stirrer, a thermometer, and an ice–ethanol bath is charged with 175 mL (0.455 mol) of an aqueous 25% solution of glutaric dialdehyde, 38 mL (0.708 mol) of nitromethane, and 600 mL of methanol (Note 1). At 0–5°C 12 mL of aqueous 2 *M* sodium hydroxide is added gradually. The cooling bath is removed and the reaction mixture is stirred for 4 hr at room temperature. The resulting yellow solution is neutralized by adding 15 g of acidic cation-exchange resin and stirring for an additional 20 min (Note 2). The resin is filtered off and washed with a small volume of methanol. The filtrate is evaporated to a semisolid residue using reduced pressure and a 35°C water bath. The residue is dissolved in 100 mL of absolute ethyl alcohol with heating and diluted by gradual addition of 250 mL of toluene. The resulting two-phase mixture (Note 3) is again evaporated, with azeotropic removal of water. The resulting residue is again taken up in 100 mL of hot ethyl alcohol and diluted with 250 mL of toluene (Note 3). The almost colorless crystals are filtered and dried at high vacuum to yield 44–52 g (60–70%) of nitrodiol, mp 152–155°C (dec).

B. *(1R,2r,3S)-3-Acetoxy-2-nitrocyclohexyl acetate*. In a 1-L flask 52 g (0.323 mol) of the nitrodiol are suspended in 150 mL of acetic anhydride. Without cooling, 3–6 drops of concentrated sulfuric acid are added (Note 4). After 1 hr 500 mL of ice/water is rapidly added and stirring is continued for 60 min. The resulting colorless crystals are filtered, washed with water, and air-dried. The product thus obtained, 75.6 g (95.6%) of colorless crystals, is pure by TLC (4 : 1 hexane/ethyl acetate) and NMR, and melts at 89–90°C (Note 5).

C. *(1S,2S,3R)-3-Hydroxy-2-nitrocyclohexyl acetate*. A 500-mL flask equipped with a magnetic stirrer is charged with 10 g (41 mmol) of powdered nitrodiacetate and 300 mL of 0.2 *M* phosphate buffer of pH 7.0 prepared by dissolving 11 g of potassium dihydrogenphosphate and 3.3 g of potassium hydroxide in 300 mL of deionized (or distilled) water. To the stirred suspension is added 30 mg of purified PLE [Esterase (EC 3.1.1.1), suspended in 2.8 mL of 3.2 *M* ammonium sulfate buffer] (Note 6) and the mixture is stirred for 24 to 48 hr (Note 7). The continuously measured pH drops to about 5.6 during the reaction and then remains almost constant, while the mixture has turned to a practically clear, pale-yellow solution (Note 8). The solution is filtered through a paper filter and the filtrate is extracted 3 times with 100 mL of ether. The organic phase is dried over anhydrous magnesium sulfate and filtered. Removal of the solvent and of the acetic acid under reduced pressure leaves 7–8 g (85–95%) of colorless monoacetate as a crystalline solid (Note 9). Recrystallization by dissolving in 100 mL of ether and adding 250 mL of pentane gives 5–6 g (60–70%) of pure (1*S*,2*S*,3*R*)-3-hydroxy-2-nitrocyclohexyl acetate (Note 10), mp 90–91°C, $[\alpha]_D$ + 9.5° ($CHCl_3$, *c* 1.0) (Note 11). From the mother liquor, another 1–2 g (12–24%) of monoacetate, mp 89–90°C, can be obtained (Note 12).

2. Notes

1. Commercial-grade chemicals were used without further purification. The glutaric dialdehyde solution should be fresh.
2. The checkers used Amberlite IR-120 (plus) acid form, capacity 1.9 meq/mL supplied by the Aldrich Chemical Company, Inc.
3. Two layers will form unless the water content of the crude product is sufficiently reduced during the preceding evaporation; in that case, the evaporation is to be repeated.
4. The solution turns clear and the temperature rises to 60–70°C when the reaction has started. More sulfuric acid should be added if a sustained exotherm does not ensue.
5. The submitters recommend recrystallization from alcohol/water (2 : 1). This is essential if NMR and TLC analyses of the crude nitrodiacetate indicate the presence of monoacetate.
6. The checker used the contents of one 30-mg vial of Sigma material, rinsed in with ca. 1 mL of deionized water. The submitters originally developed the process with PLE purified according to a procedure they had published previously.[2]
7. The submitters used 45 mg of enzyme and observed the reaction to be complete in 11.5–12.5 hr.
8. In addition to the monoacetate, a small amount of diacetate and an even smaller amount of diol could be detected by TLC in the crude product.
9. The crude product is enantiomerically pure according to ^{19}F NMR of the corresponding Mosher ester (>97% ee). The checker observed lower $[\alpha]_D^{25}$ values (+8.72° and +8.61°) but confirmed the enantiomeric purity by HPLC analysis of the corresponding Mosher esters. By HPLC comparison with the diastereomeric mixture of Mosher esters prepared from a sample of racemic monoacetate (oily substance obtained by partial hydrolysis of diacetate), the (–)-enantiomer content appears to be less than 1%.
10. The absolute configuration of the product has been proved by X-ray analysis of the corresponding camphanic ester.[2,3]

11. The monoacetate shows the following ^{1}H NMR spectrum (90 MHZ) δ: 1.3–1.9 (m, 4 H), 2.0 (s, 3 H), 2.1–2.2 (m, 2 H), 2.7 (d, *J* = 5.5, OH), 4.1 (m, 1 H), 4.4 (apparent, t, *J* = 10.5, 1H), 5.1–5.3 (m, 1 H).

12. Recrystallization of this fraction gave another 0.75–1.5 g (10–18%) of pure product.

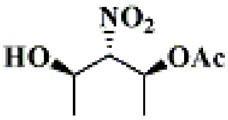
3. Discussion

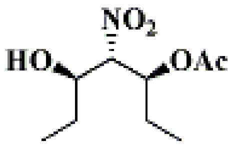
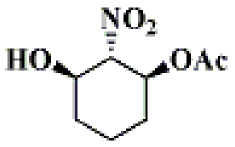
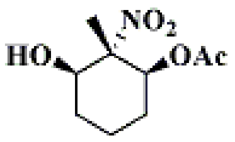
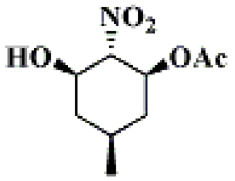
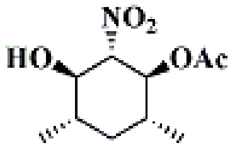
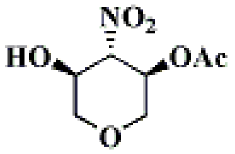
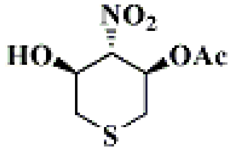
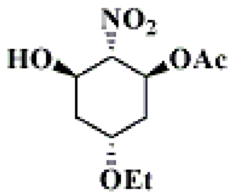
The use of ester-cleaving enzymes will probably be one of the most useful biological–chemical methods in the synthetic laboratory. No example of this type of reaction has hitherto been published in the *Organic Syntheses* series of procedures. So far, the only biological–chemical *Organic Syntheses* procedures are two yeast reductions,[4,5] one oxidation with horse liver alcohol dehydrogenase,[6] and a disaccharide synthesis catalyzed by emulsin.[7] The procedure described here is also applicable with crude enzyme powder, but the workup is a bit more complicated, because a continuous extractor must be used to overcome problems with emulsions. Both crude enzyme concentrate and purified PLE as a mixture of isoenzymes[8] are commercially available, but the crude concentrate can easily be prepared from fresh pig liver and is thus very cheap.[2] By using self-made PLE-powder, the submitters have produced amounts of 20–25 g of pure monoacetate per run.[2]

Several review articles containing discussions of enantioselective syntheses with ester-cleaving enzymes have appeared.[9,10,11,12,13] Of the many examples, the ones in which *meso* substrates are employed are most attractive since the theoretical yield is 100%. In many applications of PLE the enantiomeric excess (% ee) of the product depends crucially on the source of the enzyme. This effect has not been noticed in the enantioselective saponifications of nitrodiol diacetates, either because the reaction is insensitive to it, or because this complication is overcome by the great crystallization tendency of the products. The only problem we observed when the reaction was carried out with commercial crude PLE-powder (but not with the self made one) was the production of a certain amount of diol that could not be removed by simple recrystallization. In this case, filtration over a short silica gel column with methylene chloride as eluent gives after recrystallization pure monoacetate.

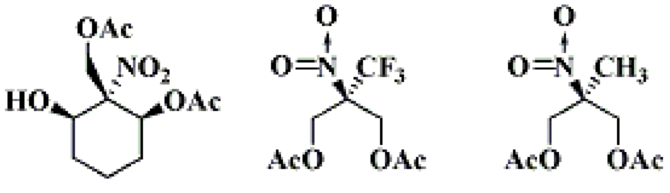
Other examples of enantiomerically pure monoacetates of *meso*-nitrodiols, which are available using the procedure described above, are collected in Table I. Entries 1 and 3 in Table I refer to runs following the above procedure, for all other cases the self made crude PLE-powder was used. Cases in which no reaction (a) or unsatisfactory selectivities (b) were observed, are shown below.

TABLE I
YIELDS, MELTING POINTS, AND SPECIFIC ROTATIONS OF NITRODIOL MONOACETATES PREPARED BY PROCEDURE C USING PLE-POWDER[2] INSTEAD OF PURIFIED ENZYME[a]

Entry No.		Yield (%)	Mp (°C)	$[\alpha]_D$ ($CHCl_3$, *c* 1)
1		50–70	58–60	−10.5

2		40–50	Oil	−10.7
3		60–70	90–91	+9.8
4		80–90	106–107	–9.4
5		70–80	91–92	+29.1
6		60–70	130–131	–1.3
7		20–30	111–112	+14.7
8		60–70	130–131 (dec)	+28.1
9		60–70	93–94	+6.0

[a]Entries 1 and 3 refer to runs following the above procedure; for all other cases the self made crude PLE-powder was used. The configuration and the sense of chirality of the products of entries 1, 3, and 4 were determined by x-ray crystal structure analysis of the camphanic esters, those of the other are inferred by analogy and by NMR comparison. The open-chain compounds (entries 1 and 2) were obtained using TES buffer at pH 6.5.

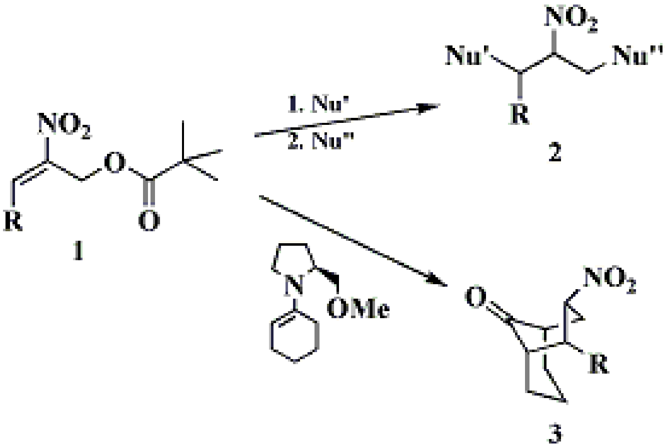


(a) (a) (b)

The *meso*-nitrodiol starting materials for the preparation of the PLE diacetate substrates are readily obtained from nitromethane or nitroethane and aldehydes or dialdehydes. They crystallize readily. The above procedures for the preparation of nitrocyclohexanediol and its diacetate from glutaraldehyde and nitromethane are modifications of published methods.[14,15]

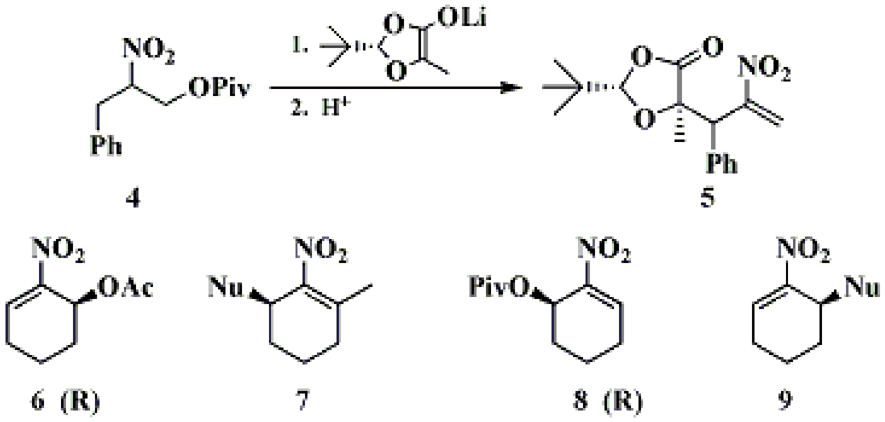
The chiral monoacetates now available are useful multiple coupling reagents[16,17,18] for syntheses of enantiomerically pure target molecules. They can be converted to nitroolefinic allylic esters, achiral or racemic analogs of which we have previously shown[16,17,18] to combine sequentially with two (different) nucleophiles (see **1** and **2** in Scheme 1).

In a first approach to an enantioselective version of this method, we employed[19] chiral enamines derived from proline,[20] (see **1–3** in Scheme 1). In this stoichiometric, enantioselective reaction, the valuable auxiliary used has to be recovered (i.e., recycled) in preparative-scale applications.[21]



We then used[22] nitroallylic pivalates for the alkylation of hydroxy acid-derived enolates to prepare enantiomerically pure compounds (EPC), (see **4** and **5** in Scheme 2), an example of the use of the pool of chiral building blocks for EPC syntheses.[23,24,25] Finally, the procedure described here allows for syntheses of EPC with a catalytic enantioselective step:[26] dehydration of the monoacetate from the PLE saponification leads to (*S*)-nitrocyclohexenyl acetate **6**, and pivaloylation followed by acetate hydrolysis and dehydration leads to the pivalate **8** of the enantiomeric alcohol. These compounds can be used for substitutions with a variety of

nucleophiles.[2,3,26] Thus, starting from the enantiomerically pure Michael acceptors **6** and **8**, 3-alkyl nitrocyclohexenes **7 9**, respectively, of high enantiomeric excess are available (see Scheme 2, Nu = methyllithium, phenyllithium and the morpholinoenamine of acetophenone):



Nu

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

methyllithium, phenyllithium and the morpholinoenamine of acetophenone

1,3-Cyclohexanediol, 2-nitro-, 1-acetate, [1S-(1α, 2β, 3α]

ethyl alcohol (64-17-5)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether (60-29-7)

acetic anhydride (108-24-7)

sodium hydroxide (1310-73-2)

potassium hydroxide (1310-58-3)

toluene (108-88-3)

ammonium sulfate (7783-20-2)

Pentane (109-66-0)

Nitromethane (75-52-5)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

potassium dihydrogenphosphate (7778-77-0)

proline (147-85-3)

hexane (110-54-3)

glutaraldehyde, glutaric dialdehyde (111-30-8)

nitroethane (79-24-3)

meso-nitrodiol

nitrocyclohexanediol

pivalate

(1S,2S,3R)-3-Hydroxy-2-nitrocyclohexyl acetate

(S)-nitrocyclohexenyl acetate

(1R,2r,3S)-2-Nitrocyclohexane-1,3-diol (38150-01-5)

(1R,2r,3S)-3-Acetoxy-2-nitrocyclohexyl acetate

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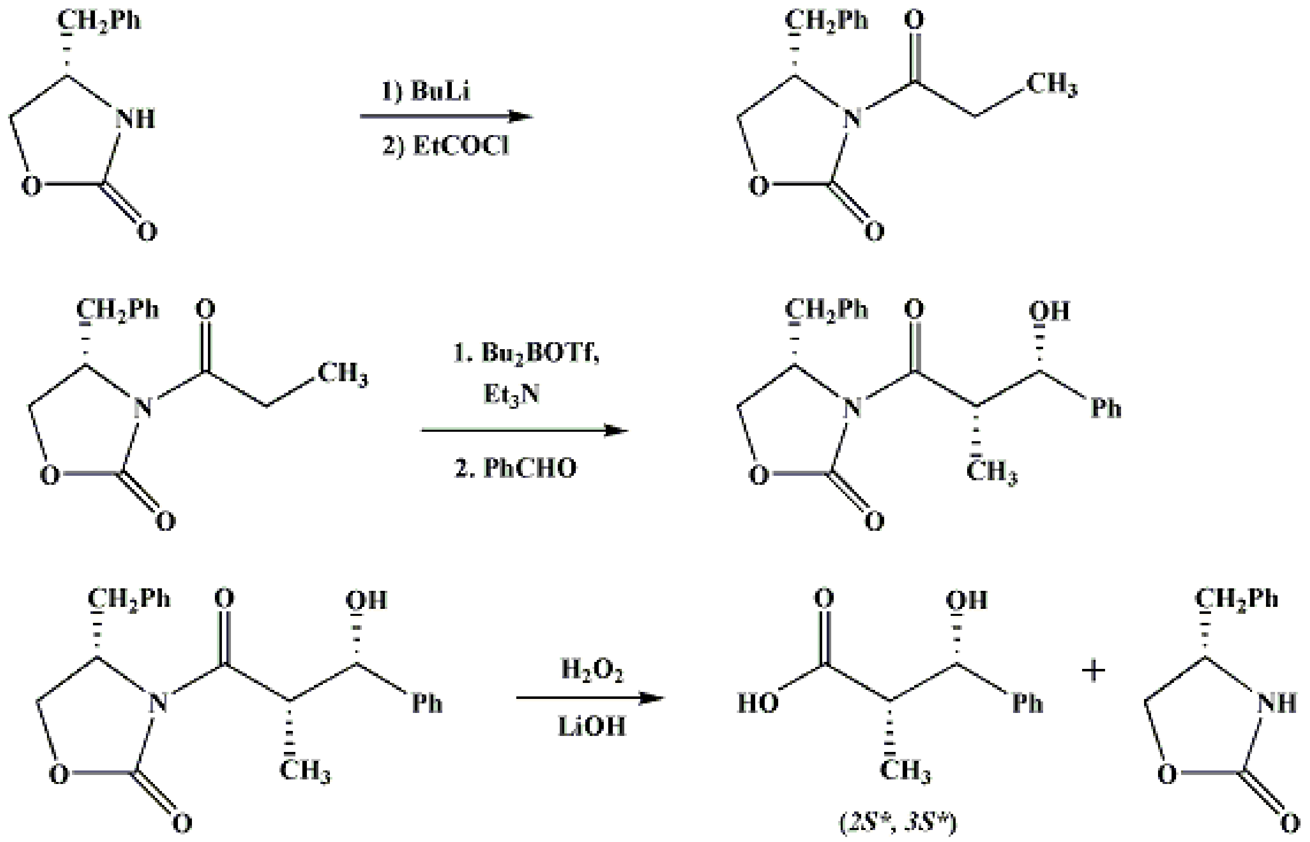
Organic Syntheses, CV 8, 339

DIASTEREOSELECTIVE ALDOL CONDENSATION USING A CHIRAL OXAZOLIDINONE AUXILIARY: (2*S**,3*S**)-3-HYDROXY-3-PHENYL-2-METHYLPROPANOIC ACID

[Benzenepropanoic acid, β-hydroxy-α-methyl-, [*S*-(*R**,*R**)]-]



Submitted by James R. Gage and David A. Evans[1].
Checked by Donald T. DeRussy and Leo A. Paquette.

1. Procedure

A. *(S)-3-(1-Oxopropyl)-4-(phenylmethyl)-2-oxazolidinone*. A dry, 500-mL flask equipped with a magnetic stirring bar is charged with 17.7 g (0.100 mol) of (*S*)-4-(phenylmethyl)-2-oxazolidinone,[2] capped with a rubber septum, and flushed with nitrogen. Anhydrous tetrahydrofuran, 300 mL (Note 1), is then added to the flask via cannula, and the resulting solution is cooled to −78°C in an acetone–dry ice bath. A solution of 68.3 mL (0.101 mol) of 1.47 *M* butyllithium in hexane (Note 2) is transferred via cannula first to a dry, septum-stoppered, 100-mL graduated cylinder with a ground-glass joint, and then to the reaction flask over a 10-min period. The solution may turn yellow and slightly cloudy. Freshly distilled propionyl chloride (9.6 mL, 0.11 mol, (Note 3) is added in one portion by syringe after completion of the addition of butyllithium. The resulting clear, nearly colorless solution is stirred for 30 min at −78°C, then allowed to warm to ambient temperature over a 30-min period. Excess propionyl chloride is quenched by the addition of 60 mL of saturated aqueous ammonium chloride. The bulk of the tetrahydrofuran and hexane is removed on a rotary evaporator (bath temp. ca. 25–30°C), and the resulting slurry is extracted with two 80-mL portions of dichloromethane. The combined organic extracts are washed with 75 mL of an aqueous 1 *M* sodium hydroxide solution and 75 mL of brine, dried over anhydrous sodium sulfate, and filtered. The solvent is removed by rotary evaporation, and the residue, a light-yellow oil, is placed in a refrigerator overnight to crystallize. The resulting crystalline solid is

pulverized and triturated with a minimum quantity of cold hexane. After filtration and drying 21.2–22.3 g (91–96%) of the desired product is obtained as a colorless crystalline solid, mp 44–46°C (Note 4) and (Note 5).

B. *The boron aldol reaction*. Into a dry, 2-L flask equipped with a large magnetic stirring bar is introduced 21.2 g (0.091 mol) of the acylated oxazolidinone. The flask is sealed with a rubber septum and swept with nitrogen. The solid is dissolved in 200 mL of anhydrous dichloromethane (Note 6), which is introduced via syringe. A thermometer is inserted through the rubber septum, and the contents of the flask are cooled to 0°C with an ice bath. To this cooled solution is added via syringe 27 mL (0.107 mol) of dibutylboron triflate followed by 16.7 mL (0.120 mol) of triethylamine (Note 7) dropwise at such a rate as to keep the internal temperature below +3°C. The solution may turn slightly yellow or green during the dibutylboron triflate addition, and then to light yellow when triethylamine is added. The ice bath is then replaced with a dry ice–acetone bath (Note 8). When the internal temperature drops below −65°C, 10.3 mL (0.101 mol) of freshly distilled benzaldehyde is added over a 5-min period via syringe. The solution is stirred for 20 min in the dry ice–acetone bath, then for 1 hr at ice-bath temperature. The reaction mixture is quenched by the addition of 100 mL of a pH 7 aqueous phosphate buffer and 300 mL of methanol. To this cloudy solution is added by syringe 300 mL of 2 : 1 methanol–30% aqueous hydrogen peroxide at such a rate as to keep the internal temperature below +10°C. After the solution is stirred for an additional 1 hr, the volatile material is removed on a rotary evaporator at a bath temperature of 25–30° C. The resulting slurry is extracted with three 500-mL portions of diethyl ether. The combined organic extracts are washed with 500 mL of 5% aqueous sodium bicarbonate and 500 mL of brine, dried over anhydrous magnesium sulfate, filtered, and concentrated on a rotary evaporator, to afford 35–36 g of a white solid (Note 9). The unpurified aldol adduct has a diastereomeric purity of >97% as determined by gas chromatography (Note 10). The solid is recrystallized from ca. 500 mL of 1 : 2 ethyl acetate–hexane to yield 25.8 g (84%) of the desired aldol adduct, mp 92–93°C (Note 12). The mother liquor is purified by flash chromatography (column dimensions: 8 × 20 cm) with flash-grade silica gel (Note 13).[3] On elution with 25% ethyl acetate-hexane, an additional 2.8 g (9%) of diastereomerically pure material is obtained.

C. *Chiral auxiliary removal*. A 500-mL flask fitted with a magnetic stirring bar is charged with 8.48 g (0.025 mol) of the aldol adduct and 125 mL of 4 : 1 tetrahydrofuran–distilled water. The flask is sealed with a rubber septum, purged with nitrogen, and cooled to 0°C in an ice bath. To this solution is added via syringe 10.2 mL (0.100 mol) of 30% aqueous hydrogen peroxide (Note 14) over a 5-min period, followed by 0.96 g (0.040 mol) of lithium hydroxide in 50 mL of distilled water. Some gas evolves from the clear solution. After the solution is stirred for 1 hr, the septum is removed, and 12.6 g (0.100 mol) of sodium sulfite in 75 mL of distilled water is added. The bulk of the tetrahydrofuran is removed on a rotary evaporator at a bath temperature of 25–30°C, and the resulting mixture (pH 12–13) is extracted with three 100-mL portions of dichloromethane to remove the oxazolidinone auxiliary. The aqueous layer is cooled in an ice bath and acidified to pH 1 by the addition of an aqueous 6 *M* hydrochloric acid solution. The resulting cloudy solution containing the β-hydroxy acid is then extracted with five 100-mL portions of ethyl acetate. The combined ethyl acetate extracts are dried over anhydrous magnesium sulfate, filtered, and concentrated, affording 5.1 g of a white crystalline solid, which is dissolved in approximately 200 mL of an aqueous 5% sodium bicarbonate solution. This solution is extracted with two 100-mL portions of dichloromethane and then acidified and extracted with ethyl acetate as before. The combined dichloromethane extracts are dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation to afford 4.35 g (99%) of the oxazolidinone auxiliary as a white crystalline solid. This solid is recrystallized from 50 mL of 2 : 1 ethyl acetate–hexane to give 3.95 g (89%) of the recovered oxazolidinone as white crystals, mp 85–87°C. The combined ethyl acetate extracts are dried over anhydrous magnesium sulfate, filtered, and concentrated to afford 4.50 g (100%) of the desired hydroxy acid as a white crystalline solid, which is recrystallized from ca. 20 mL of carbon tetrachloride to give 4.00–4.03 g (89–90%) of pure (2S*,3S*)-3-hydroxy-3-hydroxy-3-phenyl-2-methylpropanoic acid, mp 89.5–90°C (Note 15).

2. Notes

1. Reagent-grade tetrahydrofuran was purchased from Fisher Scientific Company and either freshly distilled from sodium metal and benzophenone or dried at least 3 days over activated Linde 4A molecular sieves before use in Reaction A. It was used as received for reaction C.
2. Butyllithium in hexane was purchased from Aldrich Chemical Company, Inc. and titrated prior to use.[4]
3. Propionyl chloride (d, 1.065) was obtained from Aldrich Chemical Company, Inc., and distilled prior to use.
4. Trituration by the checkers gave 21.2–22.3 g (91–96%) of acylated product of somewhat higher purity: mp 45–46°C; $[\alpha]_D^{22}$ +99.5° (ethanol, *c* 1.01). Alternatively, the acylated oxazolidinone can be isolated by distillation (Kugelrohr, 125°C, 12 mm). Isolated yields were 97–99%.
5. The product has the following spectroscopic properties: IR (solution in dichloromethane) cm^{-1}: 3030, 2980, 1780, 1705, 1455, 1385, 1245, 1210, 1080; ^1H NMR ($CDCl_3$) δ: 1.2 (t, 3 H, *J* = 7.2, CH_3), 2.8 (dd, 1 H, *J* = 13.3, 9.6, $CH_2C_6H_5$), 2.9 (m, 2 H, CH_2CH_3), 3.3 (dd, 1 H, *J* = 13.4, 3.3, $CH_2C_6H_5$), 4.1 (m, 2 H, $CHCH_2O$), 4.7 (m, 1 H, NCH), 7.1–7.5 (m, 5 H, ArH); $[\alpha]_D$ +92.9° (ethanol, *c* 1.01).
6. Dichloromethane was distilled from calcium hydride.
7. Dibutylboron triflate was prepared according to the method of Mukaiyama.[5] It is also available from Aldrich Chemical Company, Inc. as a solution in dichloromethane or diethyl ether, but results with this material are inconsistent. It should be used within 2 weeks of preparation or after redistillation. Triethylamine (Fisher Scientific Company) was distilled from calcium hydride immediately prior to use.
8. The entire reaction can be carried out at 0°C if desired. The ratio of diastereomers in the unpurified product mixture falls slightly to 97.6 : 0.2 : 2.2 (Note 10).
9. The checkers isolated a colorless viscous oil that crystallized on addition of 1 : 2 ethyl acetate–hexane. Care must be taken to avoid an excess of hexane, since oiling of the product can occur under these circumstances.
10. Diastereomer ratios were determined by gas chromatography. Since the aldol adduct undergoes retroaldol reaction on the column, it must be silylated prior to injection. Approximately 5 mg of the crude adduct is filtered through a short plug of silica gel to remove any trace metals. The material is taken up into 1–2 mL of dichloromethane in a 2-mL flask or small test tube. To this solution are added 4–5 drops of *N,N*-diethyl-1,1,1-trimethylsilylamine and a small crystal of 4-(*N,N*-dimethylamino)pyridine (Note 11). The solution is stirred for 2 hr and injected directly onto the column. (Column conditions: 30-m × 0.32-mm fused-silica column coated with DB 5, 14-psi hydrogen carrier gas, oven temperature 235°C.)
11. *N,N*-Diethyl-1,1,1-trimethylsilylamine and 4-(*N,N*-dimethylamino)pyridine were purchased from Aldrich Chemical Company, Inc.
12. The product has the following spectroscopic characteristics: IR (solution in dichloromethane) cm^{-1}: 3520, 3040, 2980, 1780, 1695, 1455, 1385, 1210, 1110; ^1H NMR ($CDCl_3$) δ: 1.2 (d, 3 H, *J* = 7.0, CH_3), 2.8 (dd, 1 H, *J* = 13.4, 9.5, 1 H $CH_2C_6H_5$), 3.1 (d, 1 H, *J* = 2.7, OH), 3.3 (dd, 1 H, *J* = 13.4, 3.4, $CH_2C_6H_5$), 4.1 (m, 3 H, $CHCH_2O$, $CHCH_3$), 4.6 (m, 1 H, NCH), 5.1 (m, 1 H, HOCH), 7.1–7.5 (m, 10 H, ArH); $[\alpha]_D$ +75.7° (dichloromethane, *c* 1.00).
13. Kieselgel 60 was purchased from EM Science, Cherry Hill, NJ, an affiliate of E. Merck, Darmstadt.
14. Hydrogen peroxide was obtained from Mallinckrodt, Inc.
15. The following spectroscopic characteristics were observed: IR (solution in dichloromethane) cm^{-1}: 3600, 3400–2300 broad hump, 3040, 3000, 1710, 1455, 1230; ^1H NMR ($CDCl_3$) δ: 1.2 (d, 3 H, *J* = 7.1, CH_3), 2.9 (m, 1 H, $CHCH_3$), 5.2 (d, 1 H, *J* = 3.9, C_6H_5CH), 7.2–7.4 (m, 5 H, ArH); $[\alpha]_D^{22}$ –26.4° (CH_2Cl_2, *c* 1.04). No epimerization was detected by NMR.

3. Discussion

This procedure demonstrates a particularly effective method for controlling the relative and absolute stereochemistry of the aldol reaction. It is quite general in scope.[6] Alkyl-, aryl, and α,β-unsaturated aldehydes all give good results. In addition to chiral propionates,[7] a range of related aldol reactions may be carried out. For example, the analogous aldol reactions of thioalkyl,[7] benzyloxy,[8] or haloacetate,[9] as well as succinate-[7] and crotonate-derived[10] carboximides, have been reported.

In addition to the high levels of asymmetric induction, two other attractive features of this sequence of reactions warrant comment. First, both acylation and hydrolysis of the chiral auxiliary are facile, high-yield reactions. Second, we have recently found that the lithium hydroperoxide hydrolysis protocol described in Part C is the method of choice for the *deacylation* process. This reagent exhibits remarkable regioselectivity for attack at the desired exocyclic acyl carbonyl moiety.[11]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

(2S*,3S*)-3-hydroxy-3-hydroxy-3-phenyl-2-methylpropanoic acid

(2S*,3S*)-3-HYDROXY-3-PHENYL-2-METHYLPROPANOIC ACID

Benzenepropanoic acid, β-hydroxy-α-methyl-, [S-(R*,R*)]-

brine

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

methanol (67-56-1)

diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

hydrogen (1333-74-0)

sodium sulfite (7757-83-7)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

carbon tetrachloride (56-23-5)

nitrogen (7727-37-9)

benzaldehyde (100-52-7)

Benzophenone (119-61-9)

sodium (13966-32-0)

hydrogen peroxide (7722-84-1)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

propionyl chloride (79-03-8)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

hexane (110-54-3)

triethylamine (121-44-8)

calcium hydride (7789-78-8)

lithium hydroxide (1310-65-2)

N,N-diethyl-1,1,1-trimethylsilylamine (996-50-9)

4-(N,N-dimethylamino)pyridine (1122-58-3)

dibutylboron triflate

lithium hydroperoxide

(S)-4-(Phenylmethyl)-2-oxazolidinone (90719-32-7)

(S)-3-(1-Oxopropyl)-4-(phenylmethyl)-2-oxazolidinone (101711-78-8)

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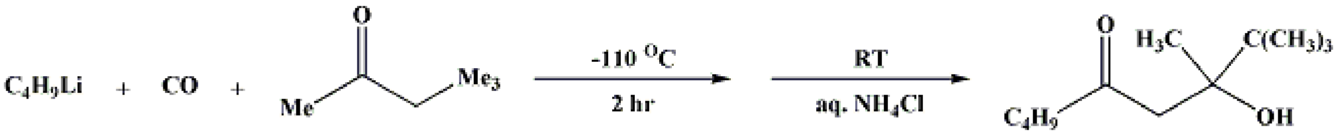
Organic Syntheses, CV 8, 343

DIRECT NUCLEOPHILIC ACYLATION BY THE LOW-TEMPERATURE, IN SITU GENERATION OF ACYLLITHIUM REAGENTS; α-HYDROXY KETONES FROM KETONES: 3-HYDROXY-2,2,3-TRIMETHYLOCTAN-4-ONE FROM PINACOLONE

[4-Octanone, 3-hydroxy-2,2,3-trimethyl-]



Submitted by Richard Hui and Dietmar Seyferth[1].
Checked by Hiroshi Koyano and Ryoji Noyori.

1. Procedure

A 2-L, three-necked flask was equipped with an overhead mechanical stirrer, a Claisen adapter that contained a low-temperature thermometer, and a no-air stopper that held a gas dispersion tube for the introduction of carbon monoxide (Note 1). The flask was charged with 400 mL each of tetrahydrofuran (THF) and diethyl ether, 100 mL of pentane, and pinacolone (7.92 g, 79.1 mmol) (Note 2). The reaction solution was cooled to −110°C (Note 3) and (Note 4) under an argon atmosphere and carbon monoxide (Note 5) was bubbled in for 30 min. Then a solution of butyllithium (2.53 *N* solution in pentane, 31.0 mL, 78.43 mmol) (Note 6) was added at 0.6–1.0 mL/min by means of a syringe pump (Note 7). The reaction mixture was orange after the addition had been completed. The reaction mixture was stirred at −110°C for 2 hr while the carbon monoxide stream was continued. The liquid nitrogen Dewar was removed, and the reaction mixture was allowed to warm to room temperature over the course of 1.5 hr, during which time the color changed to yellow. The reaction mixture subsequently was quenched by the addition of 300 mL of saturated ammonium chloride solution, which resulted in a light-yellow organic layer and a clear, colorless aqueous phase. The aqueous layer was separated and washed twice with 100 mL of pentane. The organic layers were combined, dried over anhydrous magnesium sulfate, and filtered. The solvents were removed by fractional distillation (9-in. Vigreux column). The residue was distilled through a 7-cm jacketed column to give 9.7–10.8 g (67–73%) of 3-hydroxy-2,2,3-trimethyloctan-4-one, 97% pure by GLC, bp 120–122°C (30 mm), and n_D^{20} 1.442 (Note 8).

2. Notes

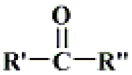
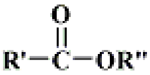
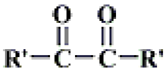
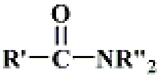
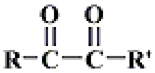
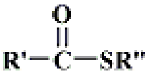
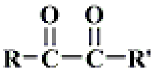
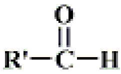
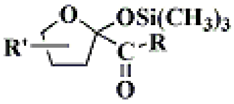
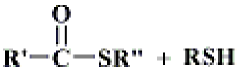
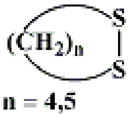
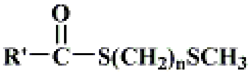
1. All glassware was dried for 15 hr in an oven at ca. 110°C and assembled while still warm.
2. Tetrahydrofuran (THF) and ether were distilled from sodium benzophenone ketyl. Pentane was distilled from lithium aluminum hydride and stored in bottles under a positive pressure of nitrogen. Pinacolone was distilled from potassium carbonate prior to use, bp 106°C (760 mm).
3. Total-immersion-type low-temperature pentane thermometers (Kessler) were used to measure the temperature in the partial immersion mode. The readings are usually 7–8°C higher compared to the actual temperature under our reaction conditions. The temperatures reported here are all corrected by subtracting 7°C from the thermometer readings. The checkers used a Delta MC-20R digital thermometer (Sato Keiryoki Co., Japan). Temperature control is very important to obtain a satisfactory yield.
4. The temperature was controlled by moving a liquid-nitrogen-filled Dewar flask up and down with a lab jack.
5. Carbon monoxide, purchased from Matheson Gas Products or Nihon Sanso Co., was used without further purification.
6. Butyllithium in pentane was purchased from Alfa Products, Morton/Thiokol, Inc. and was titrated by the method of Gilman and Cartledge.[2] The checkers used a 1.56 *N* hexane solution purchased from Mitsuwa Chemical Co. after titration by the Kofron–Baclawski procedure.[3]
7. Orion Research Inc., Model 341 was used. Alternatively, if a syringe pump is not available, the organolithium solution may be added manually by syringe, very slowly and at a reasonably constant rate.
8. GLC conditions were as follows: 2-m × 5-mm glass column packed with 20% silicone SE-30 on Chromosorb W AW; gas flow: 0.8 kg/cm^2; temperature program 100–275°C at 6°C per minute; retention times: n-C_9H_{20}, 4.9 min; 3-hydroxy-2,2,3-trimethyloctan-4-one, 12.5 min. Spectral properties of the product are as follows: IR(thin film, NaCl) cm^{-1}: 3350–3580 (br, s, ν_{OH}), 2985 (s), 2872 (m), 1695 (s, $\nu_{C=O}$), 1480 (m), 1465 (s), 1462 (s), 1395 (s), 1220 (m), 1170 (m), 1125 (s), 1040 (s), 990 (m), 910 (m); ^{1}H NMR (270 MHz, $CDCl_3$) δ: 0.92 (t, 3 H, J = 7.3, CH_2-CH_3), 0.97

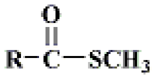
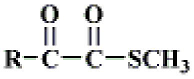
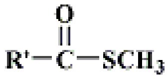
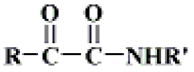
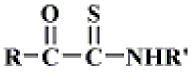
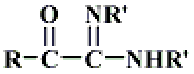
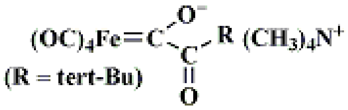
(s, 9 H, $C(CH_3)_3$), 1.33 (tq, 2 H, *J* = 7.3, 7.3, CH_2=CH_3), 1.34 (s, 3 H, CH_3), 1.60 (tt, 2 H, *J* = 7.6, 7.6, CH_2CH_2C (O)), 2.52 (dt, 1 H, *J* = 15.2, 7.6, a proton of $CH_2C(O)$), 2.60 (dt, 1 H, *J* = 15.2, 7.6, a proton of $CH_2C(O)$), 3.64 (s, 1 H, OH).

3. Discussion

In situ generated acyllithium reagents not only can acylate ketones, but also can acylate aldehydes,[11] esters,[12] lactones,[15] isocyanates and isothiocyanates,[17] carbodiimides,[18] carbon disulfide and carbonyl sulfide,[16] organic disulfides,[14] and trialkylchlorosilanes.[10] For reviews, see [4] and [13] This direct, nucleophilic acylation procedure, when applicable, makes unnecessary the usually applied method of "masked acyl anion equivalents" for nucleophilic acylation.[5 6 7 8] The present procedure finds only very limited applicability in the case of aryllithium/CO systems,[9] but seems to be generally applicable to alkyllithium systems.

TABLE I
LOW-TEMPERATURE, IN SIRU,DIRECTNUCLEOPHILICACYLATION WITH THERLi/CO REAGENT

Electrophile	Quench Reagent	Product	Reference
$(CH_3)_3SiCl$	H_2O		10
	H_2O		11,12
	H_2O		12
	H_2O		13
	H_2O		14
	H_2O		11
	$(CH_3)_3SiCl$		15
R'SSR'	H_2O		14
	CH_3I		14

S_8	CH_3I		14
COS	CH_3I		16
CS_2	CH_3I		16
R'NCO	H_2O		17
R'NCS	H_2O		17
	CH_3I		17
R'N=C=NR'	H_2O		18
$Fe(CO)_5$			19

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

benzophenone ketyl

$(CH_3)_3SiCl$

CH_3I

S_8

COS

CS_2

$Fe(CO)_5$

potassium carbonate (584-08-7)

ether, diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

carbon monoxide (630-08-0)

nitrogen (7727-37-9)

Pinacolone (75-97-8)

sodium (13966-32-0)

carbon disulfide (75-15-0)

Pentane (109-66-0)

magnesium sulfate (7487-88-9)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

hexane (110-54-3)

argon (7440-37-1)

3-Hydroxy-2,2,3-trimethyloctan-4-one, 4-Octanone, 3-hydroxy-2,2,3-trimethyl- (85083-71-2)

carbonyl sulfide

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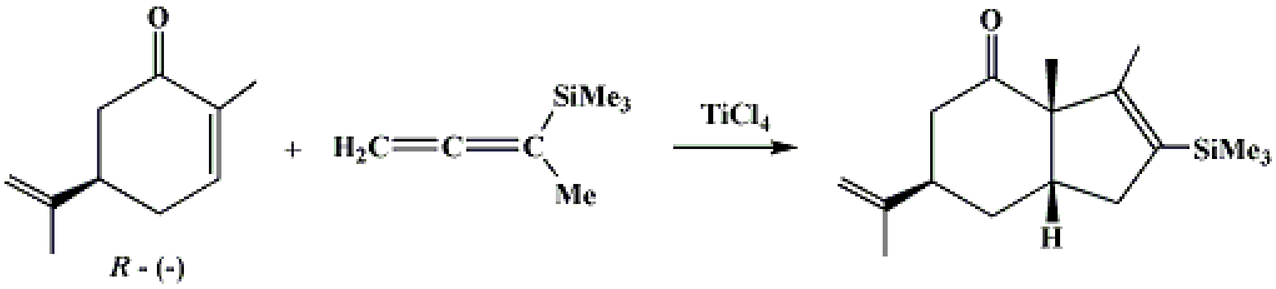
Organic Syntheses, CV 8, 347

A GENERAL [3+2] ANNULATION: *cis*-4-*exo*-ISOPROPENYL-1,9-DIMETHYL-8-(TRIMETHYLSILYL) BICYCLO[4.3.0]NON-8-EN-2-ONE

[4*H*-Inden-4-one, 1,3a,5,6,7,7a-hexahydro-3,3a-dimethyl-6-(1-methylethenyl)-2-(trimethylsilyl)-, (3aα,6α,7aα)-]



Submitted by Rick L. Danheiser, David M. Fink, and Yeun-Min Tsai[1].
Checked by Marianne Marsi and Bruce E. Smart.

1. Procedure

A 500-mL, three-necked, round-bottomed flask is equipped with a 25-mL pressure-equalizing dropping funnel, a mechanical stirrer, and a Claisen adapter fitted with a nitrogen inlet adapter and a low-temperature thermometer (Note 1). The flask is charged with 115 g (0.077 mol) of (*R*)-(−)-carvone (Note 2), 10.8 g (0.079 mol) of 1-methyl-1-(trimethylsilyl)allene (Note 3), and 180 mL of dry dichloromethane (Note 4), and then cooled below −75°C with a dry ice–acetone bath while a solution of 17.4 g (0.092 mol) of titanium tetrachloride (Note 5) in 10 mL of dichloromethane is added dropwise over 1 hr. After 30 min, the cold bath is removed, and the reaction mixture, which appears as a red suspension, is allowed to warm to 0°C over approximately 30 min. The resulting dark red solution is poured slowly into a 2-L Erlenmeyer flask containing a magnetically stirred mixture of 400 mL of diethyl ether and 400 mL of water (Note 6). The aqueous phase is separated and extracted with two 200-mL portions of ether. The combined organic phases are washed with 250 mL of water and 250 mL of saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated at reduced pressure using a rotary evaporator. The residual yellow liquid is distilled through a 15-cm Vigreux column at reduced pressure to afford 17.5 g (82%) of the bicyclonoenone **1** as a very-pale-yellow liquid, bp 98–101°C (0.03 mm), $[\alpha]_D^{20}$ −157.8 ± 0.8 (1.57, CH_2Cl_2) (Note 7) and (Note 8).

2. Notes

1. The apparatus is flame-dried under vacuum and then maintained under an atmosphere of nitrogen during the course of the reaction.

2. (*R*)-(−)-Carvone was purchased from Aldrich Chemical Company, Inc. and distilled before use.

3. 1-Methyl-1-(trimethylsilyl)allene (90% purity, contaminated with 10% 1-

trimethylsilyl-1-butyne) was prepared by the method of Danheiser, R. L.; Tasai, Y. M.; Fink, D. M. *Org. Synth., Coll. Vol. VIII*, **1993**, 471.

4. Dichloromethane was distilled from calcium hydride immediately before use.

5. Titanium tetrachloride (99.9%) was obtained from the Aldrich Chemical Company, Inc. and distilled before use. Lower yields (70–77%) resulted if the titanium tetrachloride was not distilled. Unreacted carvone is recovered if a small excess of titanium tetrachloride is not used.

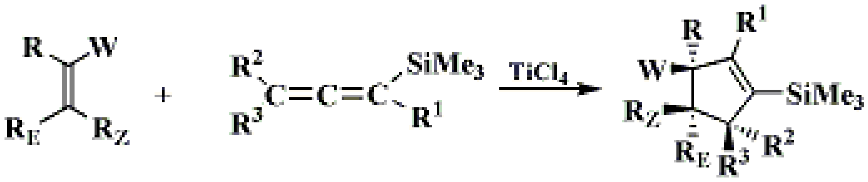
6. The two-phase mixture is vigorously stirred using a 7-cm Teflon-coated magnetic stirring bar.

7. The submitters report obtaining 18.8 g (88%) of product, bp 93–96°C (0.03 mm). The purity of the product was determined to be >99% by gas chromatographic analysis (10% OV-101 on 100-120 mesh Chromosorb W, 6 ft × 1/8 in., program: 200°C for 2 min and then 200–300°C at 32°C/min).

8. The product exhibits the following spectral properties: IR (neat) cm^{-1}: 3080, 2950, 2920, 1700, 1640, 1610, 1440, 1375, 1315, 1245, 1200, 830, 755, 680; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 0.08 (s, 9 H), 1.10 (s, 3 H), 1.65 (t, 3 H, *J* = 2.2), 1.68 (m, 3 H), 1.65–1.72 (m, 2 H), 2.10 (d of m, 1 H, *J* = 12.4), 2.15–2.25 (m, 1 H), 2.27–2.31 (m, 2 H), 2.45–2.57 (m, 2 H), 4.63 (m, 1 H), 4.72 (m, 1 H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ: –0.7, 14.4, 21.1, 21.3, 32.4, 39.8, 42.0, 43.9, 46.1, 64.8, 110.4, 136.1, 147.7, 151.5, 215.6.

3. Discussion

The procedure described here serves to illustrate a general [3 + 2] annulation method[2 3] for the synthesis of cyclopentane derivatives. A unique feature of this one-step annulation is its capacity to generate regiospecifically five-membered rings substituted at each position, and functionally equipped for further synthetic elaboration. As formulated in the following equation, the reaction proceeds with remarkably high stereoselectivity via the effective suprafacial addition of the three-carbon allene component to an electron-deficient olefin ("allenophile").

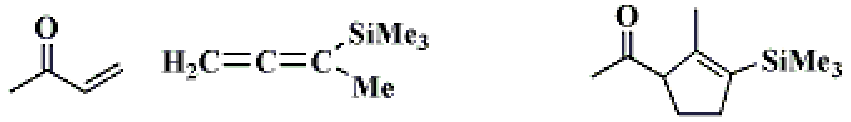


Some representative examples of the [3 + 2] annulation are listed in Table I. Both cyclic and acyclic allenophiles participate in the reaction. α-Alkylidene ketones undergo annulation to provide access to spiro-fused systems, and acetylenic allenophiles react to form cyclopentadiene derivatives. The reactions of (*E*)- and (*Z*)-3-methyl-3-penten-2-one illustrate the stereochemical course of the annulation, which proceeds with a strong preference for the suprafacial addition of the allene to the two-carbon allenophile. The high stereoselectivity displayed by the reaction permits the stereocontrolled synthesis of a variety of mono- and polycyclic systems.

TABLE I

[3 + 2] ANNULATIONSEMPLOYINGALLENYLSILANES

Allenophile	Allene	Annulation Product	Yield (%)



71-75

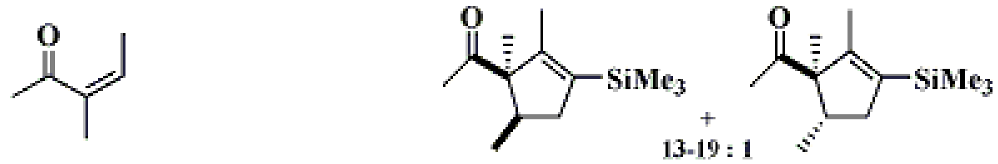
86

49

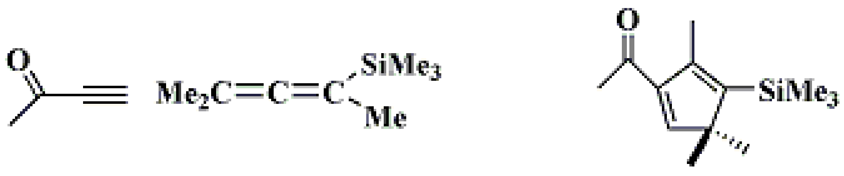
91

90

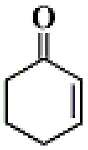
71

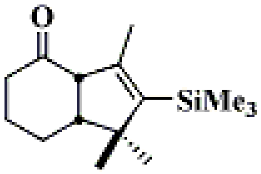


68



53





63

This preparation is referenced from:

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

(R)-(−)-carvone

(E)- and (Z)-3-methyl-3-penten-2-one

ether, diethyl ether (60-29-7)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

Allene (463-49-0)

titanium tetrachloride (7550-45-0)

calcium hydride (7789-78-8)

carvone

1-Methyl-1-(trimethylsilyl)allene (74542-82-8)

1-trimethylsilyl-1-butyne

cis-4-exo-Isopropenyl-1,9-dimethyl-8-(trimethylsilyl)bicyclo[4.3.0]non-8-en-2-one (77494-23-6)

4H-Inden-4-one, 1,3a,5,6,7,7a-hexahydro-3,3a-dimethyl-6-(1-methylethenyl)-2-(trimethylsilyl)-, (3aα,6α,7aα)-

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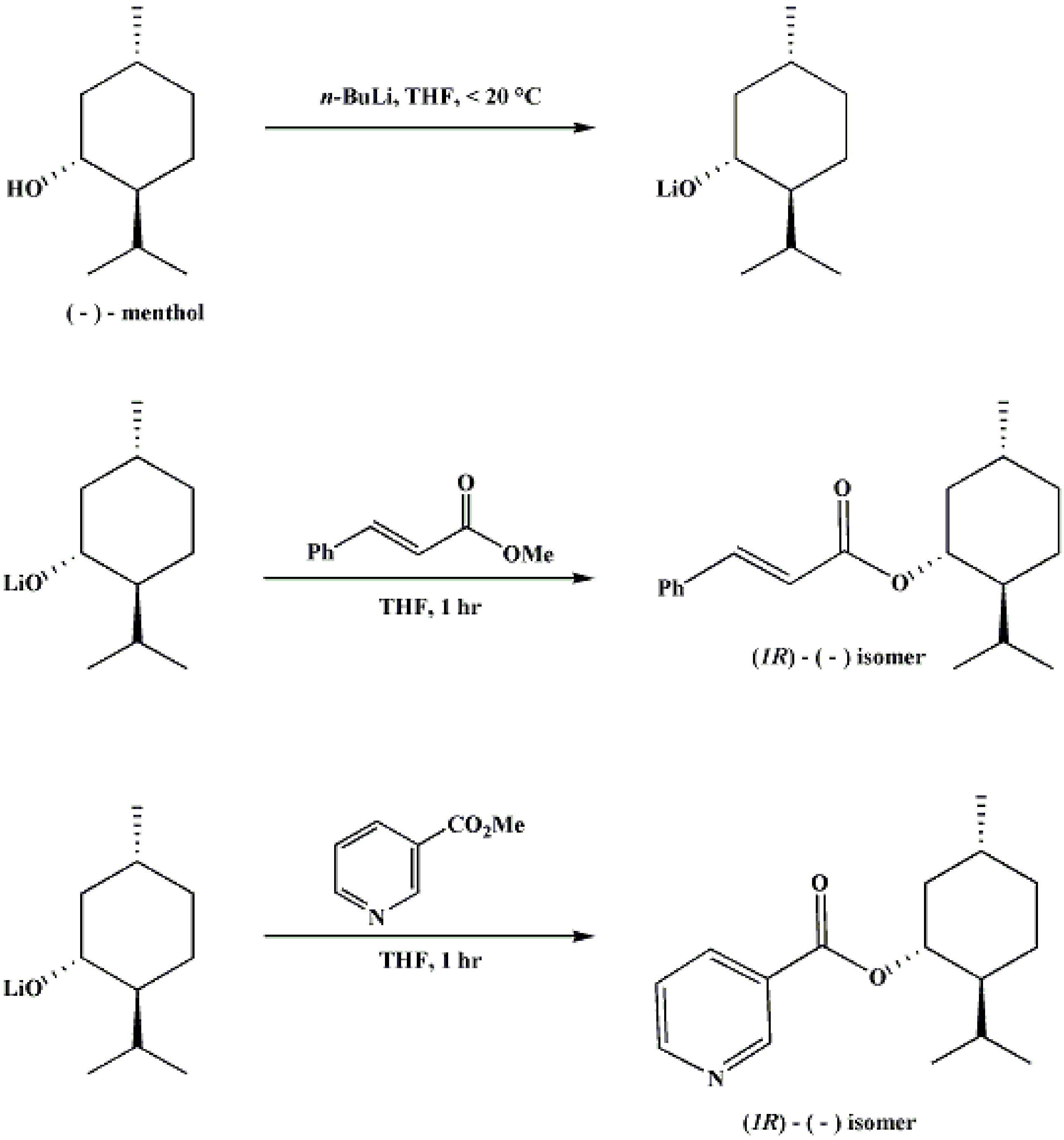
Organic Syntheses, CV 8, 350

TRANSESTERIFICATION OF METHYL ESTERS OF AROMATIC AND α,β-UNSATURATED ACIDS WITH BULKY ALCOHOLS: (–)-MENTHYL CINNAMATE AND (–)-MENTHYL NICOTINATE

[2-Propenoic acid, 3-phenyl-, 5-methyl-2-(1-methylethyl)cyclohexyl ester, [1*R*-(1α,2β,5α)]-] and [3-pyridinecarboxylic acid, 5-methyl-2-(1-methylethyl) cyclohexyl ester, [1*R*-(1α,2β,5α)]-]



Submitted by Otto Meth-Cohn[1]
Checked by Gladys Zenchoff, Hubert Maehr, and David Coffen.

1. Procedure

An oven-dried, 500-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, rubber septum inlet, an alcohol thermometer, and, through the center neck, a pressure-equalizing dropping funnel bearing a calcium chloride drying tube. The apparatus is flushed with argon (Note 1) and the flask is placed in an ice water bath. To the flask are added (−)-menthol (Note 2) (15.63 g, 100 mmol) and 150 mL of dry tetrahydrofuran (THF) (Note 3). To this stirred solution is added dropwise through the dropping funnel butyllithium in hexane (Note 4) (1.60 *M*, 55 mL, 88 mmol), transferred by syringe, at such a rate that the temperature does not rise above 20°C (about 10 min). When the addition is complete, the methyl ester [either methyl cinnamate (Note 5) (16.21 g, 100 mmol) or methyl nicotinate (Note 5) (13.71 g, 100 mmol)], dissolved in 30 mL of tetrahydrofuran, is added in one lot to the solution and washed in with an additional 20 mL of tetrahydrofuran. The resulting solution, which slowly becomes cloudy, is stirred for another hour (Note 6) and (Note 7) and then poured into 200 mL of water in a 1-L separatory funnel; the flask is washed out with 100 mL of diethyl ether. The aqueous layer is separated and the organic phase is washed twice with 200 mL of water. After the organic phase is dried with magnesium sulfate, the solvent is removed on a rotary evaporator and the residue is distilled from a 100-mL flask bearing a Vigreux column (Note 8) under reduced pressure (0.1–0.5 mm). After a forerun of 2–3 g (Note 9) the (1*R*)-(−)-menthyl ester is collected. (1*R*)-(−)-Menthyl cinnamate distills at 145–147°C (0.2 mm) and is greater than 99% pure by GLC (Note 10). The yield is 22.6–23.9 g (79–83%). (1*R*)-(−)-Menthyl nicotinate boils at 141–143°C (0.5 mm) and is greater than 99% pure by GLC (Note 10). The yield is 20.1–21.7 g (77–83%).

2. Notes

1. The submitter used a balloon attached by 1 in. of rubber pressure tubing to the barrel of a plastic disposable syringe bearing a 2-in. needle through the septum.
2. (−)-Menthol was obtained from Fluka Chemical Corporation (>99%, puriss. grade) and used directly.
3. Tetrahydrofuran was obtained from BDH Chemicals Ltd. and was distilled from sodium and benzophenone.
4. Butyllithium in hexane was purchased from Lithium Corporation of Europe. The checkers used material supplied by the Aldrich Chemical Company, Inc.
5. Methyl cinnamate (>99%) and methyl nicotinate (>99%) were used as supplied by Fluka Chemical Corporation.
6. The reactions may be monitored by TLC. The submitter used Merck Silica gel precoated plates, Silica gel 60 F-254, employing diethyl ether : hexane (1 : 5) for the cinnamate and (1 : 1) for the nicotinate transesterifications. After 5 min the reactions are already largely complete. On a small scale, purification by flash chromatography is most effective. Retardation factor R_f times of the reactants are as follows: methyl cinnamate, 0.47; menthyl cinnamate, 0.73; methyl nicotinate, 0.26; menthyl nicotinate, 0.47. Menthol was not visible under ultraviolet light as were the esters, but may be visualized with iodine or phosphomolybdic acid and heat: R_f 0.22 (1 : 4 ether : hexane).
7. The ice bath may be left in place after all of the reactants are added since the transesterifications are rapid, even below 10°C. If the reaction time is prolonged, only a small difference in product yields results.
8. The submitter used a 120 × 20-mm Vigreux column; the checkers used a 120 × 10-mm column.
9. The forerun contained a mixture of menthol and the methyl ester.
10. Capillary GLC analysis (50 m, OV17, He) gave the following retention times: Menthyl cinnamate 17.5 min (programmed 100–240°C, 5°C/min); menthyl nicotinate 20.2 min

(programmed 150–240°C, 5°C/min). The products showed the following properties. Menthyl cinnamate: $[\alpha]_D^{20}$ −57.8° ($CHCl_3$, *c* 0.20) [lit.[2] $[\alpha]_D^{25}$ −59.5° ($CHCl_3$, *c* 7.5)]; ^{1}H NMR ($CDCl_3$) δ: 0.6–2.25 (m, 18 H, aliphatic), 4.74 (dt, 1 H, *J* = 9.5 and 5, O-CH), 6.35 (d, 1 H, *J* = 17, olefinic), 7.2–7.6 (m, 5 H, aromatic), 7.83 (d, 1 H, *J* = 17, olefinic). Menthyl nicotinate: $[\alpha]_D^{20}$ −86.8° ($CHCl_3$, *c* 0.11); ^{1}H NMR ($CDCl_3$) δ: 0.6–2.35 (m, 18 H, aliphatic), 5.01 (dt, 1 H, *J* = 4.5 and 10.0, O-CH), 7.40 (ddd, 1 H, *J* = 0.8, 4.8 and 7.8, H-5), 8.32 (dt, 1 H, *J* = 1.8 and 7.8, H-4), 8.81 (dd, 1 H, *J* = 1.8 and 4.8, H-6), 9.30 (dd, 1 H, *J* = 0.8 and 2.1, H-2).
The optical rotations of the products showed a marked dependence on concentration. The submitters found $[\alpha]_D^{20}$ −60.7° ($CHCl_3$, *c* 0.11) for menthyl cinnamate and $[\alpha]_D^{20}$ −87.9° ($CHCl_3$, *c* 0.11) for menthyl nicotinate.

3. Discussion

The method described here is based on the general method for such transesterifications.[3] The best alcohol is bulky or tertiary, a feature disfavored by most other methods. Thus *tert*-butyl alcohol, *tert*-amyl alcohol, lanosterol, cholesterol, fenchol, and borneol are highly effective. If primary alcohols, (e.g., allyl alcohol) are used, it is better to employ 3–5 equiv for an efficient reaction. Alcohols bearing other hetero atoms that form complexes with lithium (e.g., carbohydrate derivatives) prove ineffective in the transesterification.

Methyl esters are always the preferred substrates, as conversions are lower with, for example, ethyl esters. Functional groups such as nitro, methoxy, alkenyl, and pyridyl are compatible with the reaction conditions. Diesters can be effective only if bistransesterification is desired, when an excess of the alcohol (e.g., 3–5 equiv) is necessary. Methyl acrylate tends to polymerize under the reaction conditions, but the use of an excess of the ester (3–5 equiv) and lower temperatures (−10°C) allows efficient isolation of the required ester.

Organolithium compounds other than butyllithium can be used with no change in the reaction efficiency; reduction of the molar ratio of organolithium to alcohol merely slows the transesterification. Even when one-sixth (0.166) of an equivalent is used, efficient but slow transesterification occurs. In no case has it been found necessary to leave reactions longer than 18 hr or to use temperatures higher than ambient. Ether solvents are far more effective than hydrocarbons, in which slower reactions occur.

There are very few known methods for transesterifications using bulky alcohols. Thiol esters undergo ready mercury(II) trifluoroacetate-catalyzed transesterifications with *tert*-butyl alcohol.[4] Potassium *tert*-butoxide in the presence of Linde 4A molecular sieves converts certain dimethyl malonates into methyl *tert*-butyl malonates.[5] The majority of published transesterification methods involve the use of primary or occasionally secondary alcohols and a catalyst, and either require a large excess of one reactant or continuous removal of a low-boiling component in the equilibrium. Catalysts include acids such as sulfuric[6] or *p*-toluenesulfonic acid,[7] Lewis acids such as boron tribromide,[8] or bases such as alkoxides.[4,9] Neutral catalysts, in particular titanates,[10] and potassium cyanide[11] have also been used.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

(−)-MENTHYL CINNAMATE

(−)-MENTHYL NICOTINATE

(1R)-(−)-Menthyl cinnamate

(1R)-(−)-Menthyl nicotinate

(−)-Menthol

ether, diethyl ether (60-29-7)

Allyl alcohol (107-18-6)

potassium cyanide (151-50-8)

iodine (7553-56-2)

Benzophenone (119-61-9)

sodium (13966-32-0)

menthol (15356-60-2)

methyl acrylate (96-33-3)

lithium (7439-93-2)

magnesium sulfate (7487-88-9)

Cholesterol (57-88-5)

tert-amyl alcohol (75-85-4)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

hexane (110-54-3)

tert-butyl alcohol (75-65-0)

boron tribromide (10294-33-4)

argon (7440-37-1)

p-toluenesulfonic acid (104-15-4)

phosphomolybdic acid (51429-74-4)

borneol (6627-72-1)

methyl cinnamate (103-26-4)

mercury(II) trifluoroacetate (13257-51-7)

methyl nicotinate (93-60-7)

menthyl cinnamate

menthyl nicotinate

fenchol

potassium tert-butoxide (865-47-4)

lanosterol

2-Propenoic acid, 3-phenyl-, 5-methyl-2-(1-methylethyl)cyclohexyl ester, [1R-(1α,2β,5α)]- (16205-99-5)

3-pyridinecarboxylic acid, 5-methyl-2-(1-methylethyl)cyclohexyl ester, [1R-(1α,2β,5α)]-

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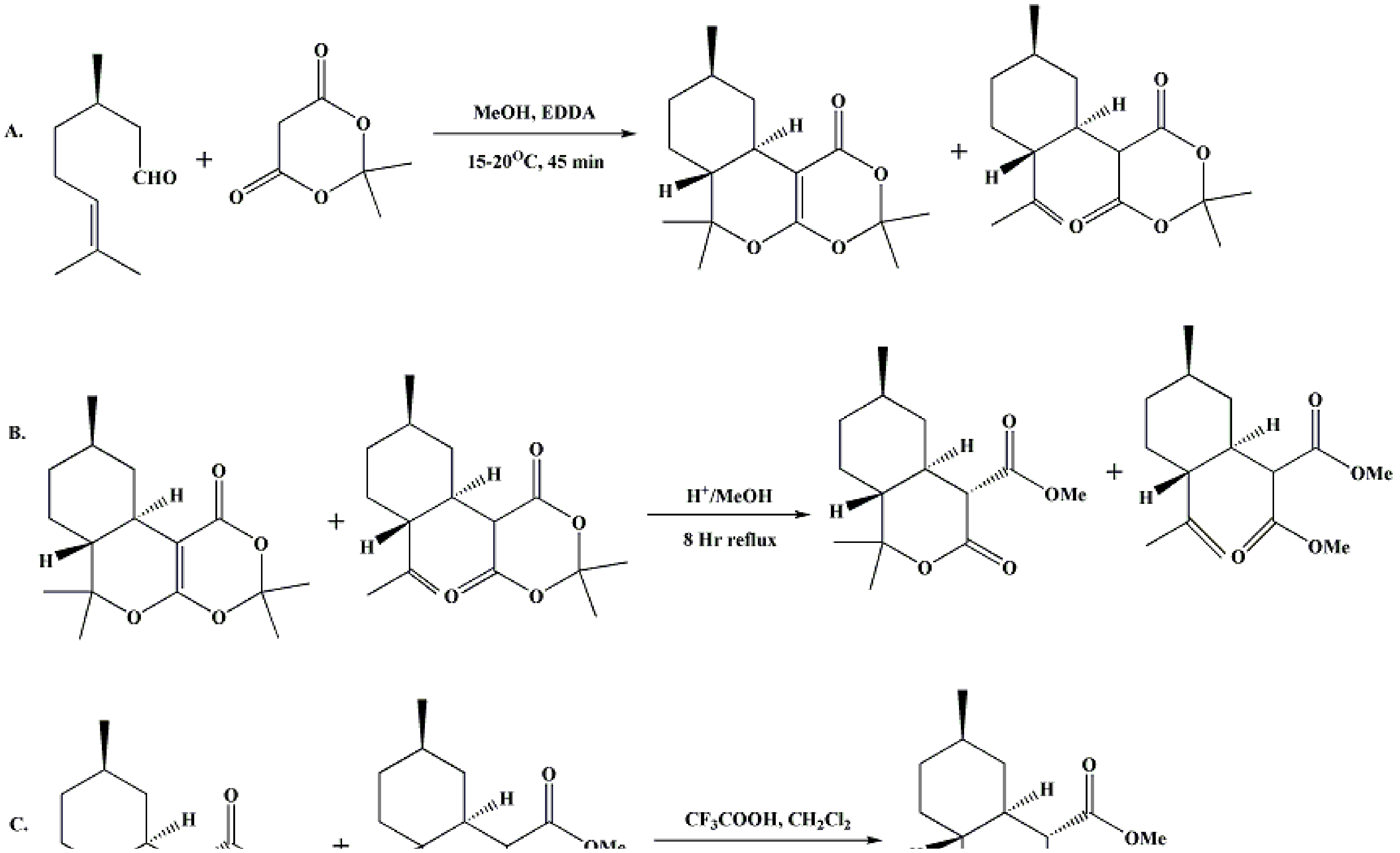
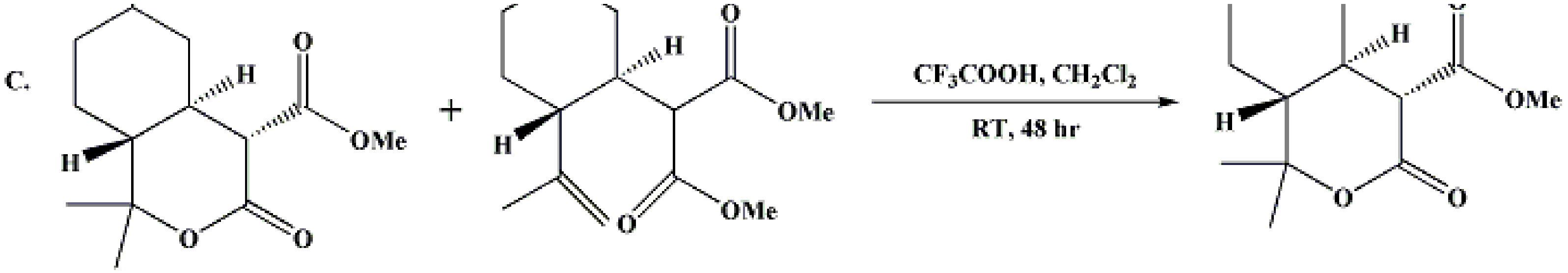
DIASTEROSELECTIVE FORMATION OF α-METHOXYCARBONYL LACTONES THROUGH AN INTRAMOLECULAR DIELS–ALDER REACTION: (4*RS*,4a*RS*,6*RS*,8a*RS*)-, (4*S*,4a*S*,6*S*,8a*S*)- AND (4*R*,4a*R*,6*R*,8a*R*)-4-METHOXYCARBONYL-1,1,6-TRIMETHYL-1,4,4A,5,6,7,8,8a-OCTAHYDRO-2,3-BENZOPYRONE [*rac*-5, (+)-5, AND (–)-5]





Submitted by L. F. Tietze, G. v. Kiedrowski, K.-G. Fahlbusch, and E. Voss[1].
Checked by Charles F. Marth and Edwin Vedejs.

1. Procedure

A. *Diels–Alder-adduct rac-3*.[2] A 250-mL, round-bottomed flask equipped with a pressure-equalizing addition funnel with a calcium-sulfate-filled drying tube, a nitrogen inlet, and a magnetic stirring bar is charged with 2,2-diamethyl-1,3-dioxane-4,6-dione **2** (Meldrum's acid) ((Note 1), 10.0 g, 69.4 mmol), a catalytic amount of ethylenediammonium diacetate (EDDA) ((Note 2), 500 mg, 2.77 mmol) and dry methanol (150 mL). (*R,S*)-Citronellal (*rac*-**1**, Sigma; dried over $MgSO_4$ and distilled) ((Note 3), 9.74 g = 11.4 mL, 63.1 mmol) is added under nitrogen (Note 4) over 15 min through the dropping funnel to the well-stirred mixture while the temperature is kept at 15–20°C by cooling the flask with a water bath. The solution is stirred for an additional 45 min at room temperature, the solvent is removed on a rotary evaporator (25°C), and the remaining yellow oil is dissolved in diethyl ether (300 mL). The organic layer is washed with water (50 mL), saturated sodium bicarbonate (2 × 50 mL) and brine (50 mL), and dried over anhydrous sodium sulfate. Filtration and removal of the solvent gives an 8 : 1 mixture (16.5 g) of the Diels–Alder adduct *rac*-**3** and the ene-product *rac*-**4** as a yellow oil (Note 5).

B. *Lactone* **5**. The crude mixture of *rac*-**3** and *rac*-**4** is dissolved in 300 mL of dry methanol (distilled from sodium) containing 10 drops of concentrated hydrochloric acid and heated under reflux for about 8 hr until the reactants can no longer be detected by thin-layer chromatography (Note 6). The solvent is removed on a rotary evaporator at 25°C and the remaining residue, which consists of an 8 : 1 mixture of lactone *rac*-**5** and dimethyl ester *rac*-**6**, is dissolved in dry dichloromethane (50 mL). The solution is acidified with trifluoroacetic acid (10 mL) and stirred at room temperature for about 48 hr, until the thin-layer chromatogram does not show any dimethyl ester *rac*-**6** (Note 6). The organic layer is washed with water (50 mL), saturated sodium bicarbonate solution (2 × 50 mL), water (50 mL), and brine (50 mL), dried over sodium sulfate, filtered, and concentrated on a rotary evaporator. Distillation of the remaining thick, yellow oil under reduced pressure in a short-path distillation apparatus with an air-cooled condenser gives 12.6 g (79%) of *rac*-**5**, bp 133–135°C at 0.001 mm. The colorless oil is dissolved in *tert*-butyl methyl ether (10 mL) and hexane (80 mL) and the solvent is allowed to evaporate over 2 days to about 15% of the original volume. Lactone *rac*-**5** (8.11 g, 53%) slowly crystallizes (mp 69–71°C) (Note 7) and (Note 8). If the above procedure is repeated with the mother liquor, a variable additional amount of *rac*-**5** (Note 8) is obtained.

With (*S*)-citronellal the (4*S*,4a*S*,6*S*,8a*S*)-lactone (+)-**5** is obtained; with (*R*)-citronellal the (4*R*,4a*R*,6*R*,8a*R*)-lactone (–)-**5** is obtained (Note 3) and (Note 7).

2. Notes

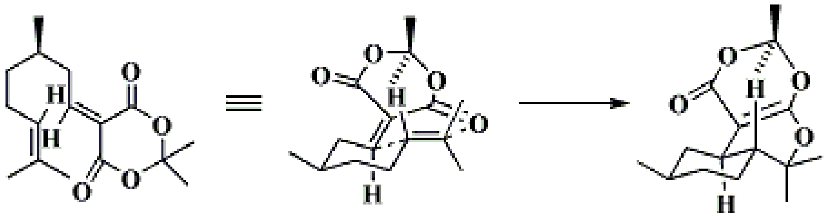
1. Meldrum's acid is commercially available from Merck-Schuchardt, Fluka, or Aldrich Chemical Company, Inc., or it can be prepared by the reaction of malonic acid with acetone.[3]

2. Ethylenediammonium diacetate (EDDA) is prepared as follows.[4] A 250-mL, round-bottomed flask with a stirring bar and a pressure-equalizing addition funnel with a calcium-sulfate-filled drying tube is charged with dry ethylenediamine (12.0 g. 0.20 mol) and dry ether (100 mL). Acetic acid (24.0 g, 0.40 mol) in dry ether (20 mL) is added through the dropping funnel to the stirred solution. The reaction mixture is left at 4°C for 14 hr and the crystals are collected by filtration and washed with ether. Recrystallization from methanol provides 19.8 g (83%) of pure EDDA, mp 114°C, as white needles; IR (KBr) cm^{-1}: 3500–2000 (NH), 2180 (MH_3^+), 1650 (C=O), 1600–1400 (CO_2^-); ^{1}H NMR ($CDCl_3$) δ: 1.90 (s, 6 H, CH_3), 3.20 (s, 4 H, CH_2), 5.75 (s, 6 H, NH_3^+).
EDDA is the best catalyst for the condensation. Piperidine acetate gives side products.
3. (*R,S*)-Citronellal can be purchased from BASF; and (*R*)-citronellal, from Dragoco, Fluka, or Takasgo Perfumery Co., Ltd., Japan. (*R*)-Citronellal can also be synthesized from pulegone with ee >99%.[5] (*S*)-Citronellal may be obtained by oxidation of (*S*)-citronellol,[6] which is accessible by different routes with ee 95%.[7] The optical purity of citronellal can be determined by GLC after conversion to the acetal of (–)-(2*R*,4*R*)-pentanediol.[8] For the reactions described, (*R, S*)-citronellal from BASF, (*R*)-citronellal from Dragoco, and (*S*)-citronellol from Fluka were used. (*R,S*)-Citronellal and (*S*)-citronellal were distilled under nitrogen before use (bp 83–85°C/11 mm), (*S*)-citronellal: $[\alpha]_D^{20}$ –11.5° (chloroform, *c* 0.1); (*R*)-citronellal ($[\alpha]_D^{20}$ + 13 ± 1°) and (*S*)-citronellal ($[\alpha]_D^{20}$ –4.9 ± 0.2°) were used as purchased.
4. The reaction can also be performed without using inert gas, but the yields may be lower.
5. The pure Diels–Alder adduct **3** can be obtained by crystallization of the crude reaction product from ether/hexane: white needles, mp 104–106°C; IR (KBr) cm^{-1}; 2950, 2930, 2860 (C-H), 1715 (C=O), 1615 (C=C), 1400, 1265; ^{1}H NMR ($CDCl_3$) δ: 0.40 (m, 1 H, 4 β-H), 0.7–2.5 (m, 7 H, CH + CH_2), 0.90 (d, 3 H, *J* = 7, CH_3), 1.23, 1.43, 1.70, 1.73 (s, 3 H, CH_3), 2.75 (dt, 1 H, J_1 = 12, J_2 = 2, 4-H). When the pure Diels–Alder adduct **3** is heated in dry methanol under reflux for 3 hr, **5** (mp 68–70°C) is obtained in 92% yield from **3**.
6. Macherey-Nagel Polygram SIL G/UV_{254}-plates were used with 2 : 5 v/v ether/hexane as eluant. The Diels–Alder product **3** (R_f = 0.29), is visible under short-wavelength ultraviolet light, whereas the detection of **4** (R_f = 0.33), *rac*-**5** (R_f = 0.22) and **6** (R_f = 0.47) is effected by development in an iodine chamber.
7. The physical properties of *rac*-**5**, (+)-**5**, and (–)-**5** are as follows: (+)-**5**, $[\alpha]_D^{20}$ +44.1° (chloroform, *c* 1.004); (–)-**5**, $[\alpha]_D^{20}$ –44.0°, (chloroform, *c* 0.995); IR (KBr) cm^{-1}: 2980, 2950, 2930, 2870, (CH), 1745, 1725 (C=O), 1450, 1320; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.74 (ddd, 1 H, *J* = 12, 12, 12, 5β-H), 0.86–1.7 (m, 5 H, 6, 7β, 8a, 8α, 8β-H), 0.95 (d, 3 H, *J* = 6.5, 6-CH_3), 1.36 (s, 3 H, 1α-CH_3), 1.7–1.9 (m, 2 H, 5α, 7α-H), 1.42 (s, 3 H, 1β-CH_3), 2.16 (dddd, 1 H, *J* = 3.5, 12, 12, 12, 4a-H), 3.09 (d, 1 H, *J* = 12, 4-H), 3.81 (s, 3 H, OCH_3); >^{13}C NMR (50.3 MHz, $CDCl_3$) δ: 22.0 (1α-CH_3), 23.3 (6-CH_3), 27.2 (C-7), 28.2 (1β-CH_3), 31.6, (C-6), 34.2 (C-8), 36.0 (C-8a), 40.5 (C-5), 45.9 (C-4a), 52.6 (OCH_3), 55.1 (C-4), 86.6 (C-1), 167.1 (C=O), 169.6 (C-3); MS (70 eV): *m/e* = 254 (1%, M^+), 239 (6%, M–CH_3), 223 (2%, M–OCH_3), 196 (50%, M–C_3H_6O), 168 (15%, 196-CO), 109 (22%, 168-CO_2CH_3), 101 (100%), 59 (55%, CO_2CH_3).
8. Crystallization of the crude material without distillation from *tert*-butyl methyl ether/hexane affords 56% of *rac*-**5**, mp 68–70°C, as pale-yellow crystals. The submitters obtained a second crop of 1.5 g from crystallization of distilled material; mp 68–78°C, starting from citronellal purchased from BASF. The checkers found that citronellal from Sigma required distillation and gave an impure second crop of **5** only with difficulty.

3. Discussion

Lactone **5** can be obtained in both enantiomeric forms or as racemate according to the described procedure. The reaction sequence includes the in situ formation of an alkylidene-1,3-dicarbonyl system **7**, which can act as a heterodiene in an intramolecular hetero-Diels–Alder addition. A small amount of the ene product **4** with diastereomeric excess (de) > 98% is formed at room temperature as well. The remarkable selectivity in formation of diastereomer **3** is explained by an energetically

more favorable *exo* transition state **8** with a pseudochair arrangement having the methyl group quasiequatorial. Polycyclic *cis*-fused compounds can also be synthesized by the procedure above,[9] and a related sequence to the cannabinoid skeleton has been described using appropriate 1,3-dicarbonyl reactants.[10]



7 **8** **3**

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

brine

(4RS,4aRS,6RS,8aRS)-, (4S,4aS,6S,8aS)- AND (4R,4aR,6R,8aR)-4-METHOXYCARBONYL-1,1,6-TRIMETHYL-1,4,4A,5,6,7,8,8a-OCTAHYDRO-2,3-BENZOPYRONE [rac-5, (+)-5, AND (−)-5]

2,2-diamethyl-1,3-dioxane-4,6-dione

(−)-(2R,4R)-pentanediol

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

chloroform (67-66-3)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

acetone (67-64-1)

sodium (13966-32-0)

dichloromethane (75-09-2)

Malonic acid (141-82-2)

$MgSO_4$ (7487-88-9)

ethylenediamine (107-15-3)

hexane (110-54-3)

piperidine acetate

trifluoroacetic acid (76-05-1)

citronellal (106-23-0)

MELDRUM'S ACID (2033-24-1)

pulegone (89-82-7)

ethylenediammonium diacetate

(S)-Citronellol (7540-51-4)

(R)-Citronellal, (R,S)-citronellal (2385-77-5)

tert-butyl methyl ether (1634-04-4)

(S)-citronellal

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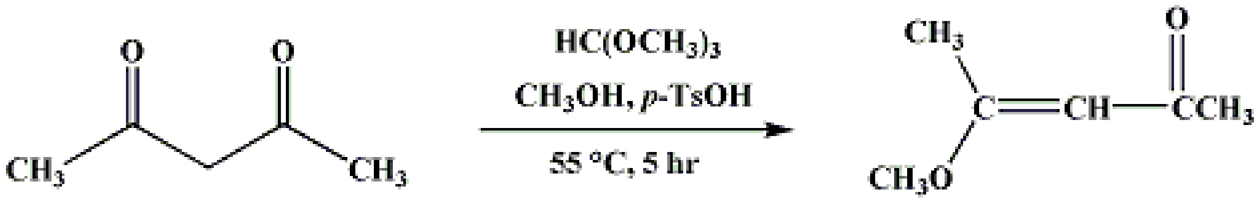
Organic Syntheses, CV 8, 357

4-METHOXY-3-PENTEN-2-ONE

[3-Penten-2-one, 4-methoxy-]



Submitted by George A. Kraus, Michael E. Krolski, and James Sy[1].
Checked by Yun Gao and K. Barry Sharpless.

1. Procedure

4-Methoxy-3-penten-2-one. A flame-dried, 250-mL, one-necked flask equipped with a condenser and a drying tube is charged with 2,4-pentanedione (Note 1) (25.0 g, 250 mmol), trimethyl orthoformate (Note 2) (26.53 g, 250 mmol), *p*-toluenesulfonic acid (0.54 g. 2.8 mmol), and methanol (Note 3) (62 mL). The flask is placed in an oil bath and heated at 55°C for 5 hr. The solution is cooled and concentrated under reduced pressure. Then 50 mL of CCl_4 is added and the solution is again concentrated under reduced pressure. The crude product is distilled via a short-path condenser and collected in a flask cooled in an ice bath (Note 4). The product distills at 43–47°C (4 mm) *at an oil-bath temperature of 60°C* (Note 5). The yield of pure product is 17.3–18.8 g (61–66%) (Note 6).

2. Notes

1. 2,4-Pentanedione was obtained from Aldrich Chemical Company, Inc. Its purity was greater than 99% and was used without purification.
2. The trimethyl orthoformate used in this experiment was obtained from Aldrich Chemical Company, Inc. Its purity was listed as 98% and was used without purification.
3. Methanol was obtained from Fisher Scientific. It was anhydrous-grade methanol.
4. The checkers used a dry ice–acetone cooling bath.
5. Use of higher temperature (>65°C) results in a much lower yield.
6. The spectral properties of 4-methoxy-3-penten-1-one are as follows: IR (neat) cm^{-1}: 1674, 1590, 1165, 922. NMR ($CDCl_3$) δ: 2.15 (s, 3 H), 2.28 (s, 3 H), 3.64 (s, 3 H), 5.41 (s, 1 H).

3. Discussion

4-Methoxy-3-penten-2-one has been prepared by Awang using methanol and sulfuric acid.[2] He also determined the stereochemistry by NMR solvent shift data and observation of nuclear Overhauser effects. Our preparation is a convenient, one-pot procedure. The title compound is useful for effecting the overall γ-alkylation of enones[3] and has been used in a synthesis of prostaglandins.[4]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfuric acid (7664-93-9)

methanol (67-56-1)

CCl_4 (56-23-5)

2,4-pentanedione (123-54-6)

p-toluenesulfonic acid (104-15-4)

trimethyl orthoformate (149-73-5)

4-Methoxy-3-penten-2-one, 3-Penten-2-one, 4-methoxy- (2845-83-2)

4-methoxy-3-penten-1-one

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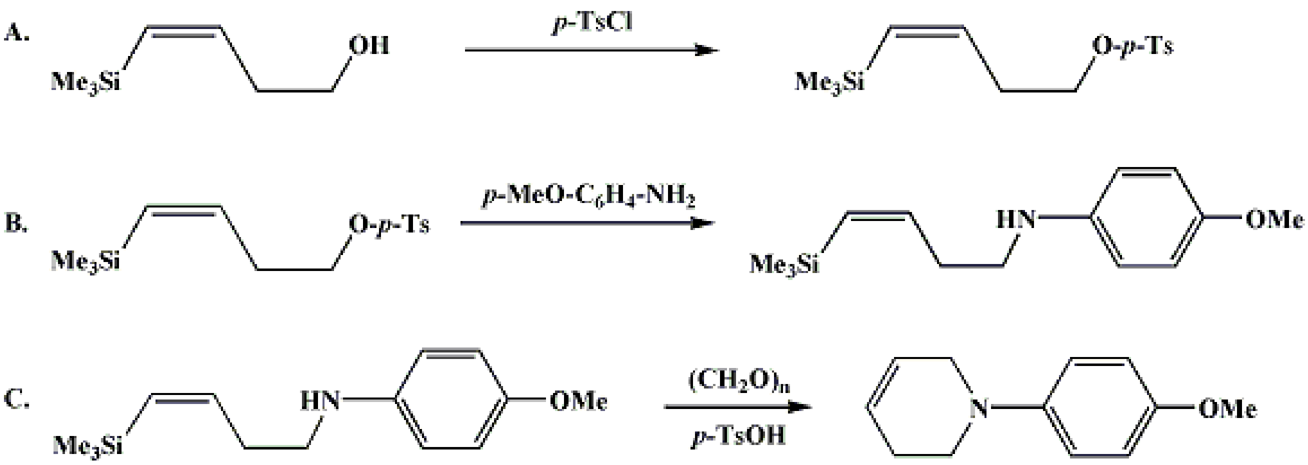
Organic Syntheses, *CV 8, 358*

REGIOSELECTIVE SYNTHESIS OF TETRAHYDROPYRIDINES: 1-(4-METHOXYPHENYL)-1,2,5,6-TETRAHYDROPYRIDINE

[Pyridine, 1,2,3,6-tetrahydro-1-(4-methoxyphenyl)-]



Submitted by Larry E. Overman, Chris J. Flann, and Thomas C. Malone[1].
Checked by Ronald C. Newbold and Andrew S. Kende.

1. Procedure

A. *Preparation of (Z)-4-(trimethylsilyl)-3-butenyl 4-methylbenzenesulfonate*. An oven-dried, 1-L, round-bottomed flask is equipped with a magnetic stirring bar and purged with dry argon or nitrogen. The flask is charged with 17.3 g (0.120 mol) of (Z)-4-(trimethylsilyl)-3-buten-1-ol (Note 1) and 290 mL of dry pyridine (Note 2). The reaction mixture is cooled to 0°C in an ice–water bath and 25.2 g (0.132 mol) of *p*-toluenesulfonyl chloride (Note 3) is added to the solution. When the *p*-toluenesulfonyl chloride is completely dissolved, the flask containing the reaction mixture is sealed and placed in a refrigerator at −20°C for 24 hr (Note 4). The reaction mixture is then poured into a rapidly stirring mixture of 200 g of ice and 200 mL of water contained in a 2-L Erlenmeyer flask. The resulting mixture is transferred to a 2-L separatory funnel and extracted with five 200-mL portions of ether. The combined organic phases are washed with five 200-mL portions of ice-cold aqueous 6 *N* hydrochloric acid (Note 5) and 200 mL of water. The organic phase is dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure using a rotary evaporator to give 29.2 g (82%) of crude (Z)-4-(trimethylsilyl)-3-butenyl 4-methylbenzenesulfonate as a light-yellow oil (Note 6).

B. *Preparation of N-(4-methoxyphenyl)-(Z)-4-(trimethylsilyl)-3-butenamine*. A 250-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, a 250-mL addition funnel, and a gas inlet tube. The flask is flushed with argon or nitrogen and charged with 41.5 g (0.337 mol) of 4-methoxyaniline (Note 7) and then heated to 65°C. The stirring melt is degassed (Note 8), 20.2 g (67.8 mmol) of (*Z*)-4-(trimethylsilyl)-3-butenyl 4-methylbenzenesulfonate is added over 15 min, and the resulting solution is maintained at 65°C for 3 hr. The reaction product is allowed to cool to ca. 50°C and is then transferred to a 500-mL separatory funnel using 250 mL of chloroform. The chloroform solution is washed with two 100-mL portions of 1 *M* sodium hydroxide and the combined aqueous phases are extracted with 500 mL of chloroform. The combined organic phases are dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure using a rotary evaporator. The crude residue is distilled through a 17-cm Vigreux column and excess 4-methoxyaniline is collected in the first fraction, bp 80–86°C (0.25 mm) (Note 9). Vacuum distillation is continued to give 10.6 g (63% yield) of *N*-(4-methoxyphenyl)-(Z)-4-(trimethylsilyl)-3-butenamine, bp 125–128°C (0.25 mm), as a pale-yellow oil (Note 10).

C. *Preparation of 1-(4-methoxyphenyl)-1,2,5,6-tetrahydropyridine*. An oven-dried, 250-mL, two-necked round-bottomed flask is equipped with a magnetic stirring bar, a reflux condenser, and an argon or nitrogen inlet. The flask is flushed with argon or nitrogen, charged with 6.62 g (26.5 mmol) of *N*-(4-methoxyphenyl)-(Z)-4-(trimethylsilyl)-3-butenamine, 7.45 g (260 mmol) of paraformaldehyde (Note 11), 4.8 g (25 mmol) of *p*-toluenesulfonic acid monohydrate (Note 12), and 100 mL of acetonitrile (Note 13). The reaction mixture is degassed (Note 8) and heated at reflux for 1 hr (Note 14). The reaction mixture is cooled to room temperature and the excess paraformaldehyde is removed by vacuum filtration. The reaction vessel is washed with two 25-mL portions of dichloromethane and the washings are clarified by filtration. The combined organic phases are concentrated under reduced pressure using a rotary evaporator, and the resulting solid residue is dissolved in dichloromethane and transferred to a 500-mL separatory funnel. The organic phase is washed with two 100-mL portions of 4 *M* sodium hydroxide and the aqueous washings are extracted with 50 mL of dichloromethane. The combined organic phases are then washed with 100 mL of water, dried over anhydrous potassium carbonate, filtered, and concentrated under reduced pressure using a rotary evaporator. The crude residue is dissolved in 9 : 1 hexane–ether and filtered through a 20-cm column (6-cm diameter) of silica gel. Evaporation of solvent gives 4.2 g (84% yield) of 1-(4-methoxyphenyl)-1,2,5,6-tetrahydropyridine as a white crystalline solid, mp 49–51°C (Note 15) and (Note 16).

2. Notes

1. The trimethylsilyl butenol was prepared as described in another *Organic Syntheses* procedure (*Org. Synth., Coll. Vol. VIII,* **1993**, 609).
2. Pyridine is freshly distilled from calcium hydride under an argon atmosphere.
3. *p*-Toluenesulfonyl chloride was purchased from Aldrich Chemical Company, Inc. and was purified by dissolving 100 g in 100 mL of chloroform, adding 1250 mL of hexane, filtering to remove insoluble impurities, and concentrating the filtrate under reduced pressure.[2]
4. During this time, pyridinium hydrochloride precipitates from the solution as white needles.
5. Caution must be exercised so that the ether layer does not become too warm during this extraction.
6. The sample has the following spectral characteristics: IR (neat) cm^{-1}: 1610, 1365, 1255, 1180. ^1H NMR ($CDCl_3$, 250 MHz) δ: 0.13 (s, 9 H, $SiCH_3$), 2.49–2.58 (m, 5 H), 4.14 (apparent t, 2 H, *J* = 6.9, CH_2OR), 5.69 (d, 1 H, *J* = 14.1, $R_3SiCH{=}CH$), 6.17 (overlapping dt, 1 H, *J* = 14.1 *J* = 7.2, $R_3SiCH{=}CH$), 7.40 (apparent d, 2 H, *J* = 7.8, aryl H), 7.85 (apparent d, 2 H, *J* = 8.3, aryl H). Gas-chromatographic analysis using a 25-m 5% methyl-phenylsilicone column showed that this sample was >92% pure and contained several unidentified impurities.
7. 4-Methoxyaniline (*p*-anisidine) was purchased from Aldrich Chemical Company, Inc.
8. This is done by applying a mild vacuum to the reaction vessel and then filling the vessel with argon or nitrogen. This operation was repeated 3 times.
9. The condenser is not cooled and the collector tip is at times gently heated with a heat gun to prevent crystallization of 4-methoxyaniline in the distillation apparatus.
10. The product had the following spectral characteristics: IR (neat) cm^{-1}: 3390, 2950, 1608, 1246, 1040, 838; ^1H NMR ($CDCl_3$, 250 MHz) δ: 0.14 (s, 9 H, $SiCH_3$), 2.42–2.51 (apparent q, 2 H, *J* = 7, $=CHCH_2$), 3.15 (t, 2 H, *J* = 6.8, CH_2NR), 3.76 (s, 3 H, $ArOCH_3$), 5.67 (d, 1 H, *J* = 14.1, $R_3SiCH{=}CH$), 6.32 (overlapping dt, 1 H, *J* = 14.1 and 7.3, $R_3SiCH{=}CH$), 6.59 (apparent d, 2 H, *J* = 9.0, aryl H), 6.76 (apparent d, 2 H, *J* = 9.0, aryl H). High-resolution mass spectrum (EI, 70 eV) 249.1548 (calcd. for $C_{14}H_{23}NOSi$: 249.1549). Gas-chromatographic analysis using a 25-m 5% methylphenylsilicone capillary column showed that this sample was >95% pure. Two impurities of similar retention time, presumed to be the (*E*)-stereoisomer and the corresponding alkane, constitute 1–3% of the product mixture depending on the run, while a third, longer-retention-time impurity, the corresponding tertiary amine, represents 2% of the product mixture.
11. Paraformaldehyde was purchased from Alpha Products, Morton/Thiokol, Inc.
12. *p*-Toluenesulfonic acid monohydrate was purchased from Aldrich Chemical Company, Inc. and is suitable for use after storage for 24 hr in a vacuum desiccator over phosphorus pentoxide.
13. Acetonitrile was purchased from Mallinkrodt, Inc.

14. During this time paraformaldehyde can be seen forming on the inside of the reflux condenser.

15. The sample thus obtained is 94–97% pure by capillary GC analysis using a 25-m 5% methylphenylsilicone capillary column. This material gave the following elemental analysis. Anal. calcd. for $C_{12}H_{15}NO$: C, 76.15; H, 7.99; N, 7.40. Found: C, 75.49; H, 8.15; N, 7.31.

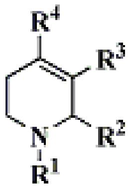
16. A purer sample may be obtained by vacuum sublimation at 60°C (0.3 mm). The material shows the following spectral characteristics: IR (KBr) cm^{-1}: 2831, 1514, 1249, 1210, 1190, 1035, 815; ^{1}H NMR (250 MHz) δ: 2.4–2.7 (m, 2 H), 3.27 (t, 2 H, *J* = 5.6), 3.58–3.65 (m, 2 H), 3.80 (s, 3 H, OCH_3), 5.7–5.9 (m, 2 H, RCH=CHR), 6.85–6.95 (m, 4 H, aryl H). Gas-chromatographic analysis using a 25-m 5% methylphenylsilicone column showed that this material was 98% pure and was contaminated with 1.8% of the starting secondary amine and 0.3% of the corresponding tertiary acyclic amine. This material melts at 50–52°C and gave the following elemental analysis. Anal. calcd. for $C_{12}H_{15}NO$: C, 76.15; H, 7.99; N, 7.40. Found: C, 76.18, H, 8.00; N, 7.40. The oxalate salt melts at 134–135°C and gave the following elemental analysis. Anal. calcd. for $C_{14}H_{17}NO_5$: C, 60.21; H, 6.09; N, 5.01. Found: C, 60.09; H, 6.16; N, 4.98.

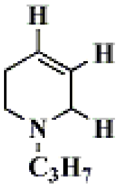
3. Discussion

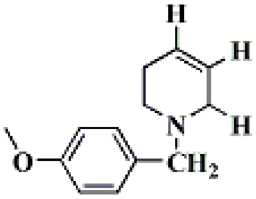
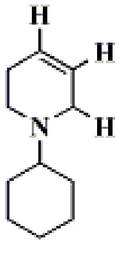
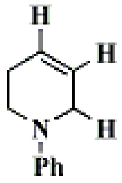
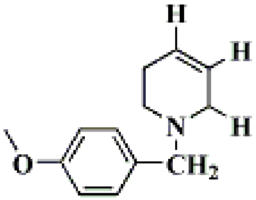
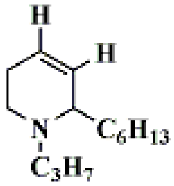
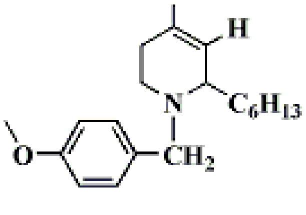
A variety of 1,2,5,6-tetrahydropyridines can be prepared by the reaction of (*Z*)-4-(trimethylsilyl)-3-butenamines with aldehydes.[3,4,5,6] Representative examples are summarized in Table I. Cyclizations with paraformaldehyde occur readily in refluxing acetonitrile, while cyclizations with other aldehydes require higher temperatures. Tetrahydropyridines with substituents at atoms −1, −2, −3, and −4 have been regioselectively prepared in this way. In no case was any trace of a regioisomeric tetrahydropyridine detected.

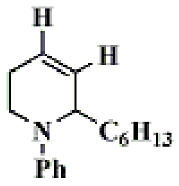
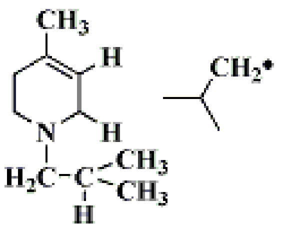
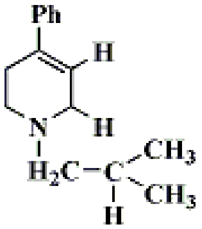
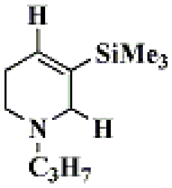
TABLE I

PREPARATION OF SUBSTITUTED 1,2,5,6-TETRAHYDROPYRIDINES[3,4]



				Cyclization Step	
R^1	R^2	R^3	R^4	Conditions (Temp., °C; Time, hr)	Yield (%)
C_3H_7	H	H	H	80; 1.5	 61

4-Methoxybenzyl	H	H	H	80; 1.5	 91
Cyclohexyl	H	H	H	110; 10	 54[a]
Ph	H	H	H	80; 0.7	 61
4-Methoxyphenyl	H	H	H	80; 1	 84
C_3H_7	C_6H_{13}	H	H	120; 48	 54
4-Methoxybenzyl	C_6H_{13}	H	H	120; 72	 64

Ph	C_6H_{13}	H	H	80; 3	 68
Iso-C_4H_9	H	H	CH_3	80; 2	 66
Iso-C_4H_9	H	H	Ph	80; 2	 83
C_3H_7	H	$SiMe_3$	H	80; 1.2	 82

[a]In this case the reaction of a cyanomethyl tertiary amine with silver trifluoroacetate in chloroform was used to initiate the cyclization instead of the reaction of an aldehyde with a secondary amine salt.

The 1,2,5,6-tetrahydropyridine ring is found in several natural products and numerous pharmacologically active materials.[5,6] This ring system is most commonly constructed by reduction of the corresponding pyridinium salt or from 4-piperidone precursors.[5] The cyclization approach reported here has the advantage of complete regiocontrol of the double-bond position. Moreover, this approach is of particular value for the synthesis of 1-aryl-substituted tetrahydropyridines that are difficult to access, since they are not generally available from pyridine precursors.

Iminium ion-vinylsilane cyclizations closely related to the one described here have been used to prepare indolizidine alkaloids of the pumiliotoxin A[7] and elaeokanine[3] families, indole alkaloids,[8] amaryllidaceae alkaloids,[9] and the antibiotic (+)-streptazolin.[10] The ability of the silicon substituent to control the position, and in some cases stereochemistry, of the unsaturation in the product heterocycle was a key feature of each of these syntheses.

Alternative methods of preparing 1-(4-methoxyphenyl)-1,2,5,6-tetrahydropyridine have not been reported.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 609

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

ether (60-29-7)

acetonitrile (75-05-8)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

pyridine (110-86-1)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

Indole (120-72-9)

hexane (110-54-3)

calcium hydride (7789-78-8)

silver trifluoroacetate (2966-50-9)

argon (7440-37-1)

p-Toluenesulfonyl chloride (98-59-9)

phosphorus pentoxide (1314-56-3)

p-toluenesulfonic acid monohydrate (6192-52-5)

1-(4-Methoxyphenyl)-1,2,5,6-tetrahydropyridine, Pyridine, 1,2,3,6-tetrahydro-1-(4-methoxyphenyl)- (133157-31-0)

(Z)-4-(Trimethylsilyl)-3-butenyl 4-methylbenzenesulfonate (87682-62-0)

(Z)-4-(Trimethylsilyl)-3-buten-1-ol (87682-77-7)

N-(4-Methoxyphenyl)-(Z)-4-(trimethylsilyl)-3-butenamine (133157-30-9)

4-methoxyaniline, p-anisidine (104-94-9)

pyridinium hydrochloride (628-13-7)

4-piperidone

paraformaldehyde (30525-89-4)

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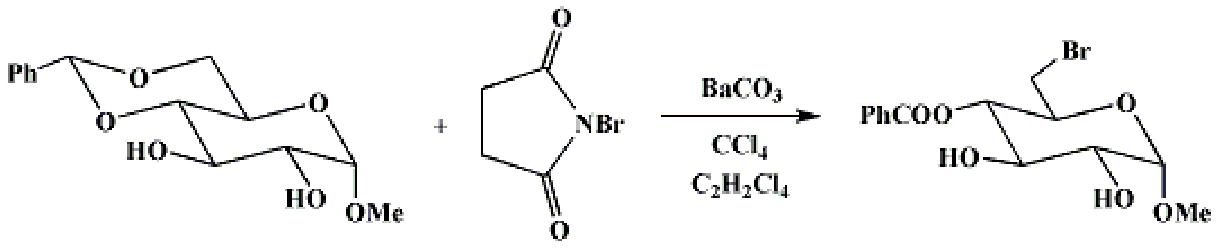
Organic Syntheses, *CV 8*, *363*

6-BROMO-6-DEOXY HEXOSE DERIVATIVES BY RING OPENING OF BENZYLIDENE ACETALS WITH *N*-BROMOSUCCINIMIDE: METHYL 4-*O*-BENZOYL-6-BROMO-6-DEOXY-α-D-GLUCOPYRANOSIDE

[Glucopyranoside, methyl 6-bromo-6-deoxy-, 4-benzoate, α-D-]



Submitted by S. Hanessian[1]
Checked by Janice Cammack and James D. White.

1. Procedure

To a suspension containing 20.5 g (72.61 mmol) of methyl 4,6-O-benzylidene-α-D-glucopyranoside (Note 1) in 1 L of carbon tetrachloride and 60 mL of 1,1,2,2-tetrachloroethane (Note 2) are added 15 g (84.27 mmol) of *N*-bromosuccinimide and 8 g (31.13 mmol) of barium carbonate (Note 3). The resulting suspension is heated at the reflux temperature of the mixture with mechanical stirring for a 2.5-hr period and filtered while hot. During the initial period of heating, a reddish orange color develops but fades before termination of the reaction. The yellowish gummy residue in the flask is washed with two 100-mL portions of hot carbon tetrachloride and the filtrate and washings are evaporated under reduced pressure to give a pale-yellow oil that is dissolved in 500 mL of ether. The solution is washed with three 60-mL portions of water, then dried over anhydrous sodium sulfate. Evaporation affords a pale-yellow oil that crystallizes (Note 4) on trituration with cold ether to yield 12.1 g of white crystals, mp 120–123°C. A second crop of 1.72 g is obtained from the mother liquors (Note 5). Recrystallization of 1 g of product by dissolution in a minimum volume of acetone and addition of ether, then pentane gives 0.9 g of white crystals, mp 131–132°C; $[\alpha]_D$ + 118° ($CHCl_3$, *c* 1).

2. Notes

1. The preparation of methyl 4,6-O-benzylidene-α-D-glucopyranoside follows essentially the procedure reported.[2] A mixture of 60 g (0.31 mol) of methyl α-D-glucopyranoside, 45 g of freshly fused and powdered zinc chloride, and 150 mL of benzaldehyde ("practical" grade) is stirred at room temperature for a period of 48 hr. The resulting pale-yellow, cloudy reaction mixture is poured slowly, with stirring, into 1.25 L of cold water, stirred for an additional 10 min, and refrigerated overnight. Hexane (75 mL) is added and the resulting mixture is stirred for 0.5 hr to aid in removing excess benzaldehyde. The product is separated on a Büchner funnel, washed twice with 100 mL of cold water, and dried under vacuum at room temperature overnight. Recrystallization from chloroform–ether affords 55 g (63% yield) of analytically pure material, mp 164–165°C.
2. Carbon tetrachloride (spectral grade) was passed through a thick layer of Woelm alumina (neutral). 1,1,2,2-Tetrachloroethane was used as a cosolvent to aid in the dissolution of the starting sugar derivative. In other instances carbon tetrachloride was the solvent.
3. Barium carbonate can be replaced by calcium carbonate in some cases; see Chretien, F.; Khaldi, M.; Chapleur, Y. *Syn. Commun.*, **1990**, *20*, 1589.
4. Crystallization did not occur if traces of tetrachloroethane were present. The checkers found it

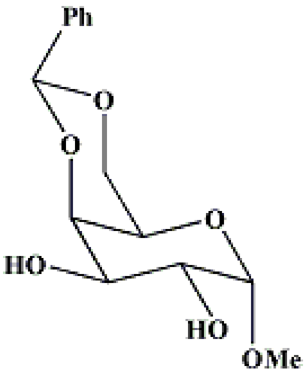
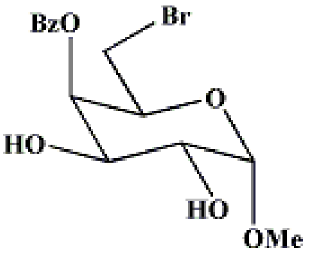
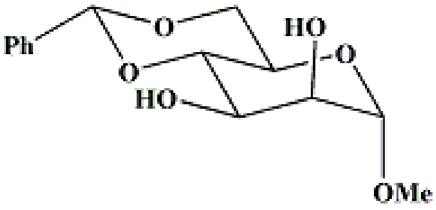
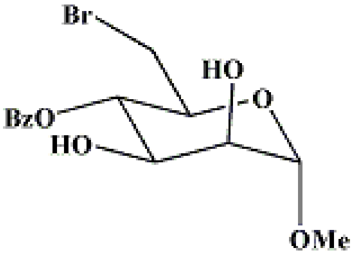
necessary to evaporate at 0.05 mm in a warm water bath for ca. 2 hr to remove residual solvent.

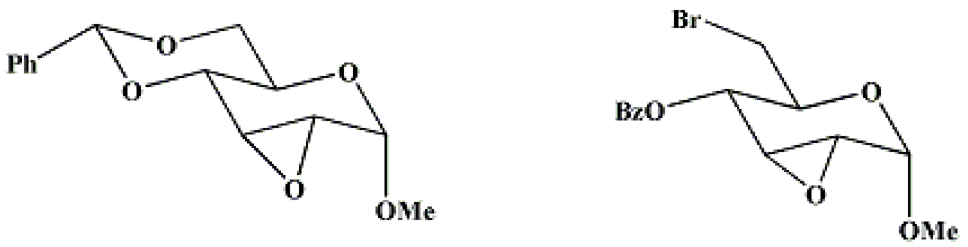
5. Evaporation of the mother liquors and flash-column chromatography (350 mL of silica gel; column height 28 cm; eluant 70% ethyl acetate–hexanes, fraction size, 30 mL), given additional (1.87 g) product that was eluted with fractions 25–36; total yield 15.69 g, (Silica gel, Kieselgel 60; E. Merck AG, Darmstadt, Germany.)

3. Discussion

Halogeno sugar derivatives are versatile intermediates for the preparation of aminodeoxy, deoxy, thio, and related analogs.[3] These transformations are easily achieved in the case of primary halides, which in turn can be prepared by a variety of methods. A number of 6-deoxy and 6-amino-6-deoxy hexoses are components of antibiotics and related natural products.[4,5] Benzylidene acetals of the 1,3-dioxane or 1,3-dioxolane type undergo a ring-opening reaction in the presence of *N*-bromosuccinimide to give the corresponding *O*-benzoylated bromohydrins.[6] This transformation has been known for a number of years in the carbohydrate series (Hanessian–Hullar reaction),[7] and has been used extensively in synthetic work. In the case of 4,6-*O*-benzylidene acetals, the products are the 6-bromo-6-deoxy-4-benzoates. Internal acetals of the 1,3-dioxolane type often undergo ring opening to give the two possible regioisomeric bromo benzoates. The reaction is compatible with a variety of functional and protecting groups (ester, ether, amide, halide, epoxide, etc.). It is also applicable to substrates containing free hydroxyl groups such as the example given above. A unique feature, which arises as a consequence of the nature of the ring opening, is seen in the case of methyl 4,6-*O*-benzylidene-α-D-galactopyranoside and its derivatives. In this series the benzoate group is found at the C-4 position which has an axial orientation. Hence one achieves halogenation at the primary position as well as an indirect benzoylation of an axial hydroxyl group in the parent sugar. Other applications have been found in amino sugars and nucleosides. Table I illustrates a selection of such ring-opening reactions. The reaction has also been applied with disaccharide acetals.[6,8]

TABLE I
REACTION OF *O*-BENZYLIDENE ACETALS WITH *N*-BROMOSUCCINIMIDE

Starting Acetal	Product(s)	Reference
		5
		5



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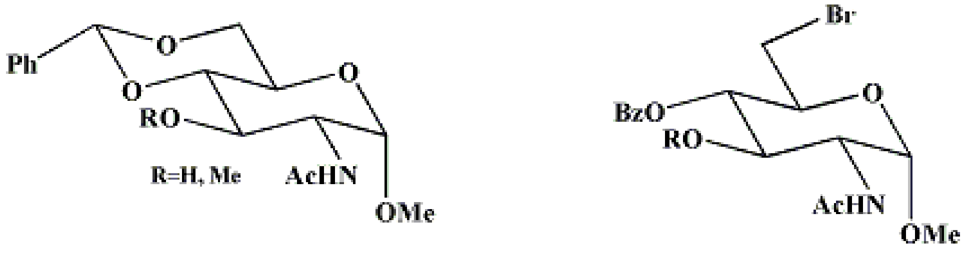

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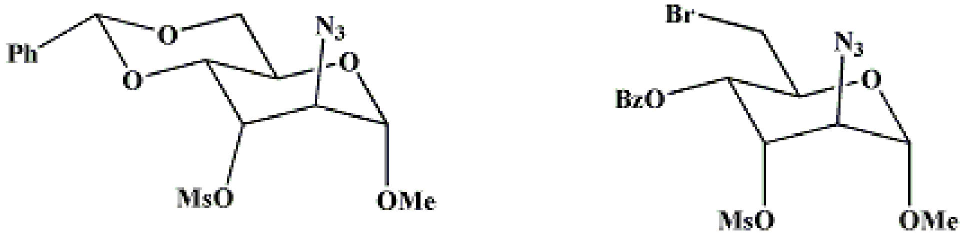

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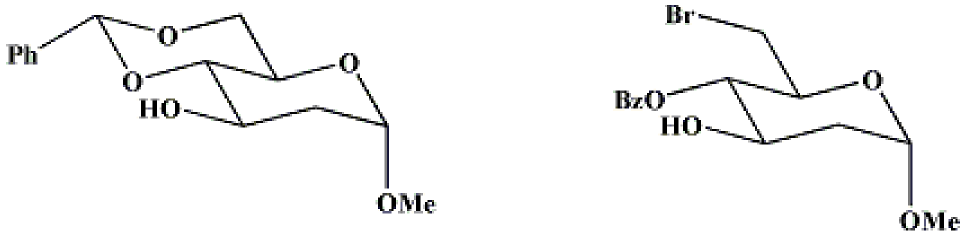

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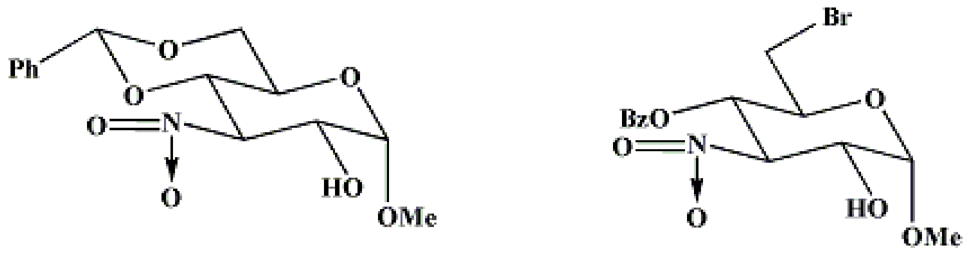

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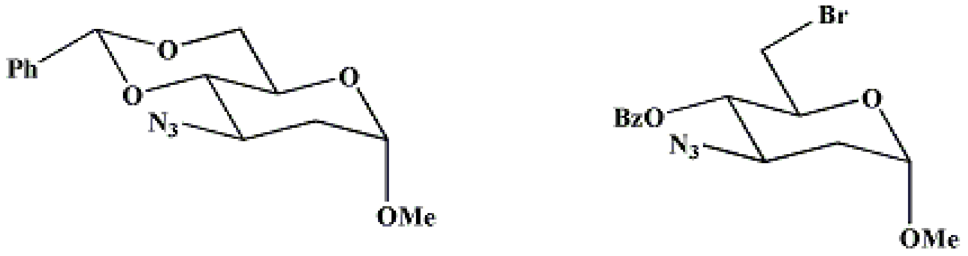

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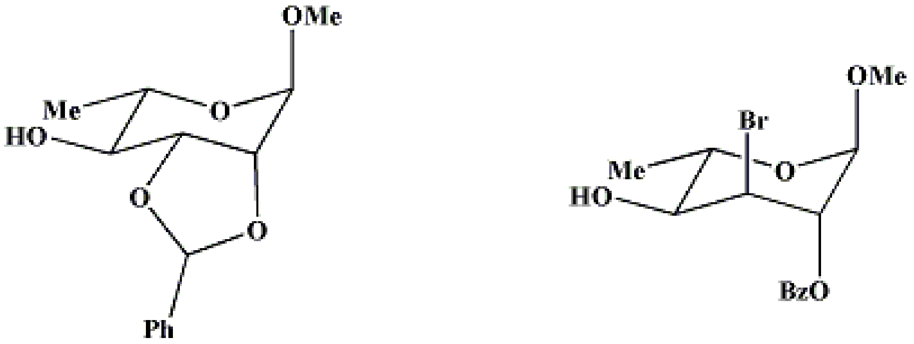

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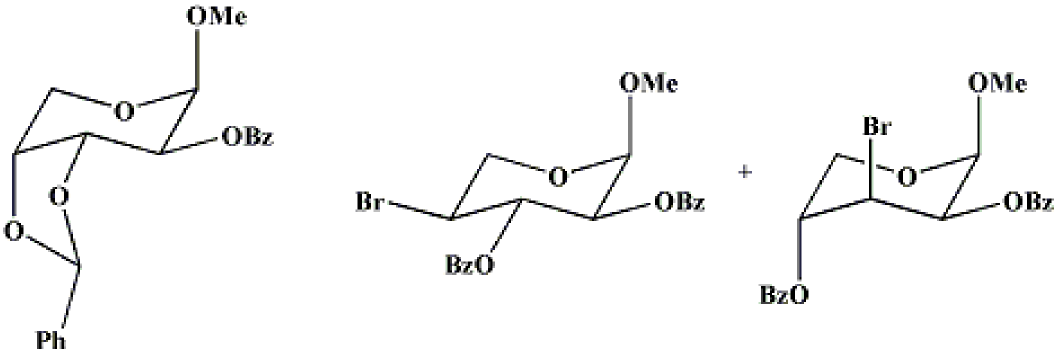

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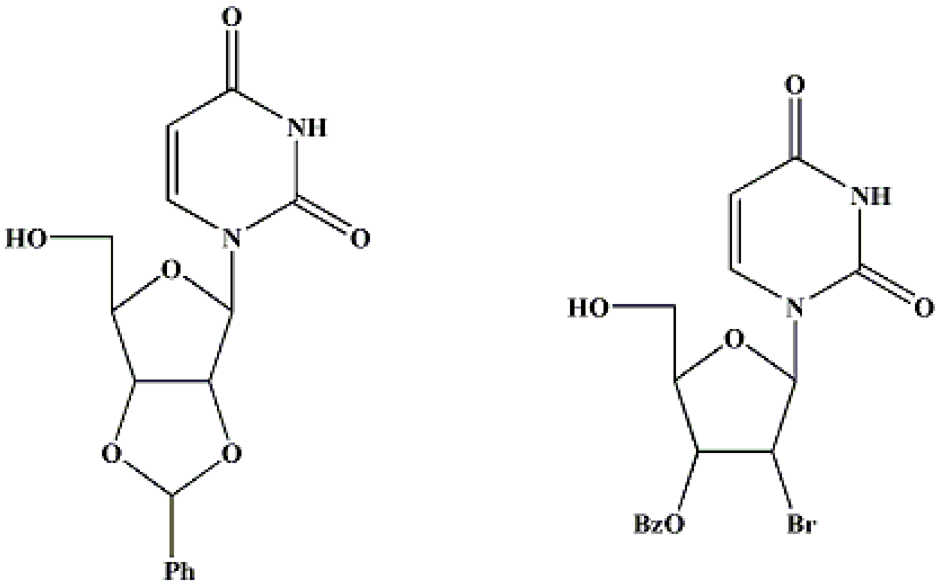

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Acknowledgments

The authors thanks Mrs. Ani Glamyan for valuable technical assistance.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

Glucopyranoside, methyl 6-bromo-6-deoxy-, 4-benzoate, α-D-

hexanes

ethyl acetate (141-78-6)

ether (60-29-7)

chloroform (67-66-3)

sodium sulfate (7757-82-6)

carbon tetrachloride (56-23-5)

benzaldehyde (100-52-7)

calcium carbonate (471-34-1)

acetone (67-64-1)

zinc chloride (7646-85-7)

barium carbonate (513-77-9)

Pentane (109-66-0)

tetrachloroethane (630-20-6)

N-bromosuccinimide (128-08-5)

hexane (110-54-3)

1,1,2,2-tetrachloroethane (79-34-5)

Methyl 4-O-benzoyl-6-bromo-6-deoxy-α-D-glucopyranoside (10368-81-7)

Methyl 4,6-O-benzylidene-α-D-glucopyranoside (3162-96-7)

methyl α-D-glucopyranoside (97-30-3)

methyl 4,6-O-benzylidene-α-D-galactopyranoside

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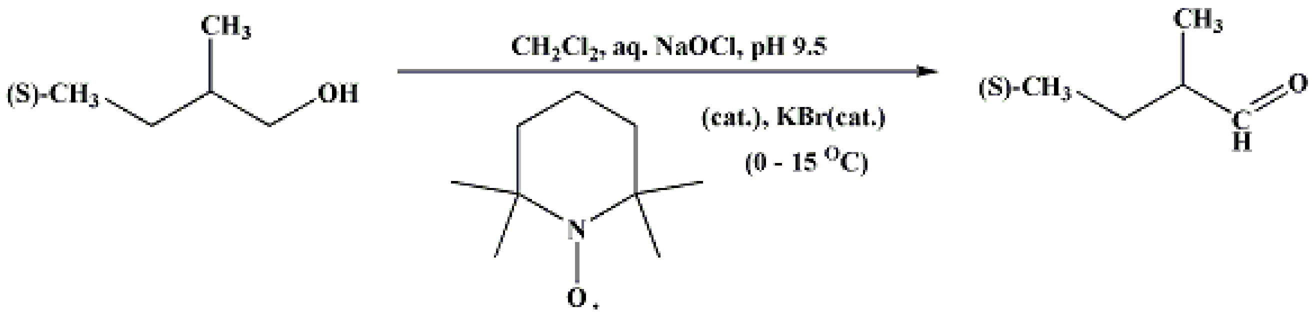
Organic Syntheses, CV 8, 367

A GENERAL SYNTHETIC METHOD FOR THE OXIDATION OF PRIMARY ALCOHOLS TO ALDEHYDES: (*S*)-(+)-2-METHYLBUTANAL

[Butanal, 2-methyl-, (*S*)-]



Submitted by Pier Lucio Anelli, Fernando Montanari, and Silvio Quici[1].
Checked by Katsumasa Nonoshita and Hisashi Yamamoto.

1. Procedure

A 1-L, three-necked, round-bottomed flask is fitted with a mechanical stirrer, pressure-equalizing dropping funnel, and a thermometer. The flask is charged with 44.05 g (0.50 mol) of (*S*)-(−)-2-methyl-1-butanol (Note 1), 0.78 g (5 mmol) of 2,2,6,6-tetramethylpiperidin-1-oxyl (Note 2), 170 mL of dichloromethane, and a solution of 5.95 g (0.050 mol) of potassium bromide in 25 mL of water (Note 3). The reaction mixture is vigorously stirred and cooled to −10°C with a salt–ice bath, then 550 mL (0.55 mol) of 1 *M* aqueous sodium hypochlorite (Note 4) at pH 9.5 (Note 5) is added over 15–20 min (Note 6), keeping the temperature of the reaction mixture between 10 and 15°C. The mixture is stirred for a further 3 min (Note 7). The orange organic phase is separated and the aqueous phase (Note 8) is extracted with 50 mL of dichloromethane. The combined organic extracts are washed with 100 mL of 10% aqueous hydrochloric acid containing 1.6 g (0.010 mol) of potassium iodide (Note 9), 60 mL of 10% aqueous sodium thiosulfate (Note 10), and 60 mL of water (Note 11). The organic phase is dried over anhydrous magnesium sulfate and then distilled at atmospheric pressure through a 20-cm Vigreux distilling column to give 35.3–36.3 g (82–84%) (Note 12) of (*S*)-(+)-2-methylbutanal as a colorless oil, bp 90–92°C (GC purity >99%) (Note 13), $[\alpha]_D^{22}$ +36.8° (acetone, *c* 2.5) (Note 14),(Note 15),(Note 16).

2. Notes

1. (*S*)-(−)-2-Methyl-1-butanol (GC purity >99.5%); $[\alpha]_D^{20}$ −6.6±0.3° (ethanol, *c* 10) was purchased from Fluka Chemie AG. Esterification with (*R*)-(+)-3,3,3-trifluoro-2-methoxy-2-phenylpropionic acid (Mosher's acid),[2] and subsequent ^{1}H and ^{19}F NMR analyses at 300 MHz of the resulting ester showed an enantiomeric purity of (*S*)-(−)-2-methyl-1-butanol >99%.
2. 2,2,6,6-Tetramethylpiperidin-1-oxyl from Nacalai Tesque, Inc., Kyoto, Japan, also available from Janssen Chimica, Beerse, Belgium, was used. 4-Methoxy-2,2,6,6-tetramethylpiperidin-1-oxyl, prepared according to the procedure of Endo,[3] can also be used.[4]
3. In the absence of potassium bromide longer reaction times are required.[4]
4. Concentrations of aqueous sodium hypochlorite in the range 0.3–2.0 *M* have been used successfully.
5. The pH (12.7) of fresh commercial 1 *M* aqueous sodium hypochlorite is adjusted to 9.5 by dissolving 17 g of sodium hydrogen carbonate per liter immediately before use.
6. If the reaction is carried out on a 1–10-mmol scale, the temperature is easily maintained at 0°C and

the reaction is over in a few minutes.[4] On a larger scale, a very efficient cooling system is required to maintain the temperature at about 0°C. When conventional laboratory equipment is used, the conditions described in this procedure are a reasonable compromise between two requirements: (a) fast addition of the aqueous sodium hypochlorite and (b) temperature in the reaction medium low enough to minimize the catalyst decomposition.[4] Longer reaction times increase slightly the formation of 2-methylbutanoic acid.

7. At this stage the reaction can be monitored by GC: 1 m × 3 mm OV 101 5% on Chromosorb HP 100–120-mesh column, 50°C (2 min), then 50–90°C (15°C/min).

8. (*S*)-(+)-2-Methylbutanoic acid, $[\alpha]_D^{20}$ +18.7° (ethanol, *c* 1.1) (lit.[5] $[\alpha]_D^{22}$ +16.3°, ethanol, *c* 1.1) (1.5–2.6 g, 3–5% yield) can be isolated by acidic workup of the aqueous phase.

9. Washing with hydrochloric acid and potassium iodide removes 2,2,6,6-tetramethylpiperidin-1-oxyl from the organic phase.[6] Because of its volatility, the catalyst cannot be eliminated in the distillation of crude aldehyde.

10. Washing with 10% aqueous sodium thiosulfate leads to a colorless organic phase, indicating total elimination of the catalyst.

11. The aqueous phase must be neutral. Acidic impurities catalyze trimerization of the anhydrous aldehyde[7,8] in the distillation stage.

12. Yields can be further increased with a more efficient separation of the (*S*)-(+)-2-methyl-1-butanal contained in the top fractions.

13. The spectral properties of (*S*)-(+)-2-methylbutanal are as follows: IR (film) cm^{-1}: 2970, 2940, 2890, 2820, 2710, 1725, 1460; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.94 (t, 3 H), 1.09 (d, 3 H), 1.33–1.54 (m, 1 H), 1.64–1.85 (m, 1 H), 2.18–2.33 (m, 1 H), 9.63 (d, 1 H).

14. Reduction with borane/tetrahydrofuran[9] regenerated enantiomerically pure (*S*)-(−)-2-methyl-1-butanol, as shown by esterification with Mosher's acid and subsequent NMR analysis of the ester (see (Note 1).

15. When practical, (*S*)-(−)-2-methyl-1-butanol (GC purity 95%); $[\alpha]_D^{20}$ −6.3 ± 0.5° (EtOH, *c* 10) from Fluka Chemie was used, and (*S*)-(+)-2-methylbutanal having $[\alpha]_D^{20}$ +33.1° (acetone, *c* 2.5) was obtained.

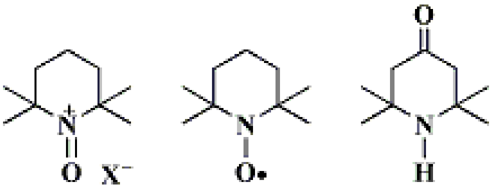
16. Oxidation of (*S*)-(−)-2-methyl-1-butanol to (*S*)-(+)-2-methylbutanal has been previously carried out in low yields by chromium oxidation,[10] under phase-transfer catalysis,[11] or by Swern oxidation in the presence of tributylamine.[12]

3. Discussion

Oxammonium salts **1** have been used extensively either in stoichiometric or in catalytic amounts[13] for the oxidation of primary and secondary alcohols to the corresponding carbonyl derivatives.

The catalytic procedure described here allows a fast, cheap, and highly selective conversion of primary alcohols into aldehydes, using sodium hypochlorite as the oxidant in a two-phase (dichloromethane–water) system. Aqueous sodium hypochlorite is buffered at pH 8.6–9.5 to ensure the presence of hypochlorous acid in the organic layer.[14]

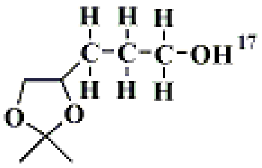
Oxammonium salt **1**, the effective oxidant species, is continuously generated from nitroxyl radical **2** by hypochlorous acid in the organic phase. Radical **2** is one of the most stable radicals known, and is easily prepared from the inexpensive triacetoneamine **3.**[15,16,17,18] The oxidation is very exothermic; for this reason scale-up of the reaction needs a very efficient cooling system to maintain the temperature in the optimum 0–15°C range. One one-hundredth (0.01) molar equivalent of nitroxyl radical **2** is generally used, but on this reaction scale the amount of catalyst can be reduced to 0.002 molar equivalent, without substantially affecting the reaction time. Sodium hypochlorite is used in only slight excess and is entirely consumed, an unusual occurrence for reactions carried out under aqueous, organic two-phase conditions.[19,20]



1 2 3

Conversion of saturated, primary alkyl and aryl alkyl alcohols into the corresponding aldehydes can be achieved by this method provided that the alcohols are entirely dissolved in the organic phase. Relatively unstable protective groups are not affected, as in the oxidation of the acetonide of 1,2,6-hexanetriol, whereas conjugated and isolated double bonds give rise to side reactions that considerably decrease selectivities and yields.[4] Some examples of aldehydes synthesized with this method are reported in Table I. Under the same conditions, secondary alcohols are oxidized to ketones. Addition of catalytic amounts of quaternary onium salts allows fast and total conversion of primary alcohols and aldehydes into carboxylic acids making this methodology very versatile.[4]

TABLE I
OXIDATION OF PRIMARY ALCOHOLS TO ALDEHYDES

Alcohol	Isolated Yield (%)
1-Heptanol	88
1-Octanol	92
1-Nonanol	92[4]
1-Undecanol	93[4]
	85
Benzyl alcohol	90[4]
p-Nitrobenzyl alcohol	89
m-Nitrobenyl alcohol	88
	75

When the limitations outlined above are considered, the procedure described here appears to be easier and cheaper than most methods in the condensed phase known to date.[21] Furthermore, alkali halides are almost the only contaminants in the waste water, making the scale up of this method very attractive.

The conditions reported for the preparation of *S*-(+)-2-methylbutanal also have been used for the oxidation of diols containing both primary and secondary hydroxyl groups into carbonyl derivatives; for example, 1,10-undecanediol can be converted into 10-hydroxyundecanal, or 10-oxoundecanal, or 10-oxoundecanoic acid depending on the amount of NaOCl used and on the presence of a phase-transfer catalyst.[22]

Very hydrophilic alcohols are conveniently oxidized under solid–liquid two-phase conditions (LiOCl–CH_2Cl_2) in the presence of $NaHCO_3$ and 0.01 molar equiv of 2,2,6,6-tetramethylpiperidin-1-oxyl or its 4-methoxy derivative.[22] Commercial solid LiOCl contains 7% of water so that the reaction conditions can be assimilated to those of a pseudo solid–liquid system.[23]

Under these conditions 1-butanol is converted into butanal in 80% yield in 20 min at 0°C, whereas the hydrophilic 1,4-butanediol and 1,5-pentanediol are readily oxidized into the corresponding lactones.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

(S)-(−)-2-methyl-1-butanol

(R)-(+)-3,3,3-trifluoro-2-methoxy-2-phenylpropionic acid (Mosher's acid)

Mosher's acid

acetonide of 1,2,6-hexanetriol

m-Nitrobenyl alcohol

alcohol, ethanol (64-17-5)

hydrochloric acid (7647-01-0)

sodium hydrogen carbonate, $NaHCO_3$ (144-55-8)

potassium iodide (7681-11-0)

sodium thiosulfate (7772-98-7)

1-butanol (71-36-3)

acetone (67-64-1)

Benzyl alcohol (100-51-6)

potassium bromide (7758-02-3)

butanal (123-72-8)

hypochlorous acid (7790-92-3)

1,5-Pentanediol (111-29-5)

1-heptanol (111-70-6)

sodium hypochlorite, NaOCl (7681-52-9)

dichloromethane (75-09-2)

2-methylbutanoic acid (600-07-7)

magnesium sulfate (7487-88-9)

chromium (7440-47-3)

borane (7440-42-8)

1-Octanol (111-87-5)

Tetrahydrofuran (109-99-9)

1,4-butanediol

tributylamine (102-82-9)

p-Nitrobenzyl alcohol (619-73-8)

2,2,6,6-tetramethylpiperidin-1-oxyl (2564-83-2)

4-Methoxy-2,2,6,6-tetramethylpiperidin-1-oxyl (95407-69-5)

1,10-undecanediol

10-hydroxyundecanal

10-oxoundecanal

10-oxoundecanoic acid

1-Nonanol (143-08-8)

1-Undecanol (112-42-5)

(S)-(+)-2-METHYLBUTANAL, Butanal, 2-methyl-, (S)-, (S)-(+)-2-methyl-1-butanal, S-(+)-2-methylbutanal (1730-97-8)

(S)-(+)-2-Methylbutanoic acid

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ALKOXYCARBONYLATION OF PROPARGYL CHLORIDE: METHYL 4-CHLORO-2-BUTYNOATE

[2-Butynoic acid, 4-chloro-, methyl ester]

Submitted by M. Olomucki and J. Y. Le Gall[1].
Checked by H. T. M. Le and M. F. Semmelhack.

1. Procedure

Caution! Propargyl chloride, methyl chloroformate, and methyl 4-chloro-2-butynoate are vesicants and lachrymators. This preparation should be conducted in a ventilated hood and protective gloves should be worn.

A 250-mL, round-bottomed flask is equipped with stirring bar (Note 1), thermometer, and pressure-equalizing dropping funnel (dried in an oven at 80°C, assembled while still hot), and the system is placed under argon (Note 2). Via syringe, 7.45 g (7.16 mL, 0.1 mol) of propargyl chloride (Note 3) and 35 mL of anhydrous diethyl ether (Note 4) are added. The solution is stirred and cooled to −50 to −60°C (Note 5) with an alcohol–dry ice bath (Note 6). Under gentle argon pressure, 72.4 mL of a 1.41 *M* solution of methyllithium in diethyl ether (Note 7) is added dropwise over ca. 20 min (Note 8). Stirring is continued for 15 min and 18.9 g (0.2 mol) (Note 9) of methyl chloroformate (Note 10) is added through the dropping funnel over ca. 10 min. The reaction mixture is allowed to warm slowly (3–4 hr) to 0 to −5°C, during which time a fine precipitate appears. Water (40 mL) is added dropwise with efficient stirring; the ether layer is separated and the aqueous layer is extracted 2 times with ether. The combined ether solutions are dried over anhydrous magnesium sulfate, and the ether is removed under reduced pressure with a rotary evaporator. The residual liquid is distilled in a simple distillation assembly under reduced pressure, affording 10.7–11.1 g (81–83%) of methyl 4-chloro-2-butynoate as a colorless liquid, bp 41°C (0.25 mm), n_D^{22} 1.4728 (Note 11).

2. Notes

1. The submitters specify a mechanical stirrer; the checkers find magnetic stirring to be more convenient and equally effective.
2. The system was alternately evacuated with an oil pump and then filled with argon 3 or more times, and a positive pressure was maintained throughout the reaction period. The submitters used nitrogen in place of argon.

3. Propargyl chloride (98% purity), obtained from Fluka AG, was used without further purification.
4. Ether was dried over sodium wire.
5. Although cooling to −20 to −30°C is sufficient, the addition of methyllithium is more convenient at lower temperatures.
6. The checkers used a constant temperature refrigerated bath (Cryocool).
7. Methyllithium in the form of solutions in diethyl ether is supplied by Aldrich Chemical Company, Inc. in rubber septum stoppered bottles, which should be stored in a refrigerator.
8. The solution of methyllithium was conveniently handled using techniques for the manipulation of air-sensitive reagents.[2]
9. Lower yields were obtained when less methyl chloroformate was used. Thus, the yield was about 55% when the reaction was performed with 1 equiv of methyl chloroformate, and 70–72% with 1.5 mol of the latter per mole of propargyl chloride.
10. Methyl chloroformate was used as supplied by Fluka AG (98% purity).
11. The product gives satisfactory elemental analysis and shows the following IR spectrum (film) cm^{-1}: 2267, 1725, 720.

3. Discussion

Methyl 4-chloro-2-butynoate has been prepared[3] in 54% yield by treatment of 4-chloro-2-butynoic acid with 10% sulfuric acid in methanol. 4-Chloro-2-butynoic (chlorotetrolic) acid has been prepared[3] in 40% yield by chromic acid oxidation of 4-chloro-2-butyn-1-ol (the latter obtained[4] in 45% yield by the reaction of 2-butyne-1,4-diol with thionyl chloride) or in 85% yield by treatment of the lithium derivative of propargyl chloride with carbon dioxide.[5]

The present synthesis illustrates a convenient preparation of chlorotetrolic esters that can be performed in one step starting from commercially available and inexpensive products; it is faster and gives better yields as compared with the overall yields of the multistep preparations described earlier. Since chlorotetrolic acid is not an intermediate in this synthesis, the necessity of distilling this explosive product is eliminated. In contrast to the acid, explosions were never observed during distillations of the lower-boiling chlorotetrolic esters.

Other 4-chloro-2-butynoic esters can be obtained by varying the alkyl chloroformates. Thus, ethyl 4-chloro-2-butynoate was prepared[6] in the same way in 60% yield, and *tert*-butyl 4-chloro-2-butynoate in 73% yield; the procedure could probably be further generalized. When butyllithium is used in these syntheses instead of methyllithium, much lower (ca. 30%) yields are obtained.

Chlorotetrolic esters are small, highly functionalized, reactive molecules; of particular interest is the possibility of using them as reagents for chemical modification of

biological macromolecules. Different protein nucleophiles react under mild conditions with methyl 4-chloro-2-butynoate by addition across the triple bond and/or substitution of chlorine[7] while the triple bond and the ester group are involved in the reaction of chlorotetrolic esters with nucleic acid bases.[8]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

4-Chloro-2-butynoic (chlorotetrolic) acid

lithium derivative of propargyl chloride

sulfuric acid (7664-93-9)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

thionyl chloride (7719-09-7)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

chlorine (7782-50-5)

sodium wire (13966-32-0)

chromic acid (7738-94-5)

magnesium sulfate (7487-88-9)

butyllithium (109-72-8)

methyl chloroformate (79-22-1)

Methyllithium (917-54-4)

argon (7440-37-1)

PROPARGYL CHLORIDE (624-65-7)

Methyl 4-chloro-2-butynoate, 2-Butynoic acid, 4-chloro-, methyl ester (41658-12-2)

4-chloro-2-butynoic acid, chlorotetrolic acid

4-chloro-2-butyn-1-ol

2-butyne-1,4-diol (110-65-6)

ethyl 4-chloro-2-butynoate

tert-butyl 4-chloro-2-butynoate

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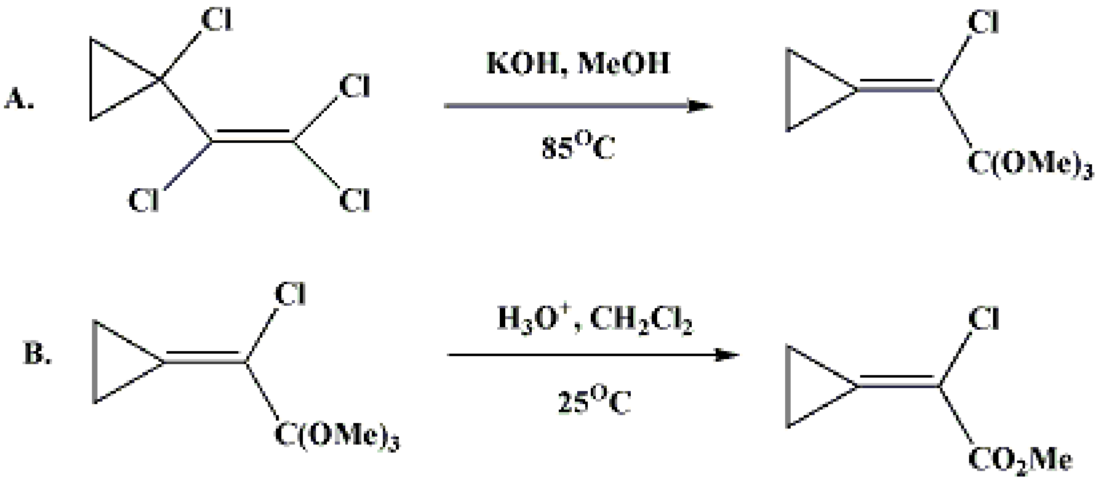
Organic Syntheses, CV 8, 373

METHYL 2-CHLORO-2-CYCLOPROPYLIDENACETATE

[Acetic acid, chlorocyclopropylidene-, methyl ester]



Submitted by Thomas Liese, Fereydoun Seyed-Mahdavi, and Armin de Meijere[1].
Checked by James S. Piecara and Bruce E. Smart.

1. Procedure

A. *Trimethyl 2-chloro-2-cyclopropylidenorthoacetate*. A 1-L, two-necked, round-bottomed flask equipped with a mechanical stirrer and a reflux condenser is charged with 40.0 g (0.19 mol) of 1-chloro-1-(trichloroethenyl)cyclopropane (Note 1), 120 g of potassium hydroxide, and 300 mL of methanol (Note 2). The mixture is stirred for 16–18 hr in an oil bath at 85°C. After the solution is cooled to room temperature, it is diluted with 1 L of ice water. The mixture is then transferred to a 3-L separatory funnel and extracted with three 200-mL portions of ether. The combined ether phases are washed with three 150-mL portions of saturated brine, dried over anhydrous magnesium sulfate, and filtered. The solvent is removed from the filtrate by distillation at atmospheric pressure, and the residue is distilled through a short-path column under water-aspirator vacuum to give 14.5–15.4 g (39–41%) of trimethyl 2-chloro-2-cyclopylidenorthoacetate bp 103–105°C (20 mm) (Note 3) and (Note 4).

B. *Methyl 2-chloro-2-cyclopropylidenacetate*. A 250-mL, one-necked, round-bottomed flask is charged with 60 mL of methylene chloride (Note 2), 3.5 g of a strongly acidic ion-exchange resin (Note 5), and 11.0 g (0.057 mol) of trimethyl 2-chloro-2-cyclopropylidenorthoacetate. The mixture is stirred for 12 hr at room temperature. The ion-exchange resin is removed by filtration and washed with three 10-mL portions of methylene chloride. The combined organic solutions are dried over anhydrous magnesium sulfate, filtered, and distilled at atmospheric pressure to remove

the solvent. The residue is distilled through a short-path column under reduced pressure to give 6.2–6.7 g (74–80%) of methyl 2-chloro-2-cyclopropylidenacetate, bp 95–97°C (10 mm) (Note 6),(Note 7)(Note 8).

2. Notes

1. 1-Chloro-1-(trichloroethenyl)cyclopropane was prepared from tetrachlorocyclopropene as described in *Org. Synth., Coll. Vol. VIII* **1993**, 124.
2. Methanol and methylene chloride were obtained from E. M. Science (Merck & Company, Inc.) and used without further purification.
3. The checkers obtained the same yields for 0.10-mol scale runs. The submitters report yields of 54–58%, however. The submitters report that the yields of 2-chloro-2-cyclopropylidenacetate are consistently better, when a larger excess of sodium methoxide (prepared by dissolving 20.1 g (0.87 mol) of sodium metal in 300 mL of dry methanol) is used. The reaction is monitored by thin layer chromatography; complete consumption of starting material may require up to 48 hr. The workup procedure was also modified. Instead of extracting with ether, the mixture is extracted with three 100-mL portions of methylene chloride. The combined methylene chloride extracts are washed with three 50-mL portions of saturated brine, dried over anhydrous magnesium sulfate, and filtered. The solution is concentrated under slightly reduced pressure in a closed system (rotary evaporator) to a volume of 100 mL. In Step B this solution is treated with 10 g of a strongly acidic ion-exchange resin and the rest of the procedure is followed as described.
4. The submitters report bp 107–109°C (20 mm). The spectral properties of 2-chloro-2-cyclopropylidenorthoacetate are as follows: IR (neat) cm^{-1}: 2840 (OCH_3), 1780 (C=C); ^1H NMR ($CDCl_3$) δ: 1.27–1.80 (m, 4 H), 3.23 (s, 9 H).
5. The checkers used analytical-grade AG 50W-X8 resin, which is strongly acidic polystyrene-gel-type resin, supplied by Bio-Rad Laboratories. The submitters used the large-pore, strongly acidic ion-exchange resin Lewatit SPC 118, supplied by Bayer AG.
6. The submitters report obtaining 7.0–7.5 g (84–90%) of product, bp 60–63°C (3.7 mm), and note that 4.7–5.0 g of analytically pure material, mp 33–34°C, can be obtained by crystallization at −20°C from 10–15 mL of pentane and the remaining 2.3–2.5 g of product can be recovered from the mother liquor by chromatography on silica gel (60 g) using a 5 : 1 mixture of pentane/diethyl ether as the eluent.
7. The product obtained by the checkers is pure by NMR analysis and shows the following spectral properties: IR (neat) cm^{-1}: 3080 (cyclopropyl CH), 1720 (C=O); ^1H NMR ($CDCl_3$) δ: 1.42–1.52 (m, 2 H), 1.69–1.78 (m, 2 H), 3.84 (s, 3 H).
8. The submitters report that the product can be obtained in higher yields without isolation of the intermediate orthoester according to the following procedure. To a solution of sodium methoxide, freshly prepared by dissolving 14.0 g (0.61 mol) of sodium metal in 200 mL of dry methanol, at 65°C is added

with stirring 30.0 g of 1-chloro-1-(trichloroethenyl)cyclopropane. The stirred mixture is refluxed (oil-bath temperature of 110°C) for 72 hr. After the solution is cooled to room temperature, 200 mL of ice water is added, and the mixture is extracted with three 200-mL portions of ether. The combined ether extracts are washed with three 50-mL portions of saturated brine, dried over anhydrous magnesium sulfate, and filtered. The solvent is removed from the filtrate by distillation at atmospheric pressure. The residue is dissolved in 100 mL of methylene chloride, 10 g of a strongly acidic ion-exchange resin is added (Note 5), and the mixture is stirred at room temperature for 48 hr. The resin is removed by filtration and is washed with three 10-mL portions of methylene chloride. The combined organic solutions are dried over anhydrous magnesium sulfate and filtered, and the solvent is removed from the filtrate by distillation at atmospheric pressure. The residual oil is taken up in 200 mL of pentane and the solution is refrigerated at 5°C. The precipitated crystals are collected by filtration to yield 11–13 g (51–60%) of 2-chloro-2-cyclopropylidenacetate. The checkers obtained a 50% yield of pure product, mp 40–41°C, when this procedure was repeated on about half the scale.

3. Discussion

This procedure is applicable to a number of substituted 1-chloro-1-(trichloroethenyl) cyclopropanes,[2] and in general gives good yields of methyl 2-chloro-2-cyclopropylidenacetates.[3] These are highly reactive Michael acceptors that react rapidly with nucleophiles to give 1'-substituted-2-chloro-2-cyclopropylacetates. The parent 2-chloro-2-cyclopropylidenacetate is a particularly useful building block in organic synthesis since it adds to cyclic dienolates to give complex skeletons in high yields.[4,5] In addition, it is a reactive dienophile[5,6] and can be further modified to 2-arylthio-substituted derivatives as well as to the parent methyl 2-cyclopropylidenacetate in high yields.[7] The corresponding ethyl 2-cyclopropylidenacetate has been prepared in poor yield by a Wittig–Horner–Emmons olefination of cyclopropanone hemiacetal magnesium salt (8%),[8] and more recently in vastly improved yield (87%) by the benzoic-acid-catalyzed Wittig olefination.[9]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 124

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

brine

trimethyl 2-chloro-2-cyclopylidenorthoacetate

cyclopropanone hemiacetal magnesium salt

methanol (67-56-1)

ether, diethyl ether (60-29-7)

sodium methoxide (124-41-4)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

Pentane (109-66-0)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

tetrachlorocyclopropene

1-CHLORO-1-(TRICHLOROETHENYL)CYCLOPROPANE (82979-27-9)

Methyl 2-chloro-2-cyclopropylidenacetate, Acetic acid, chlorocyclopropylidene-, methyl ester (82979-45-1)

Trimethyl 2-chloro-2-cyclopropylidenorthoacetate (82979-34-8)

methyl 2-cyclopropylidenacetate

ethyl 2-cyclopropylidenacetate

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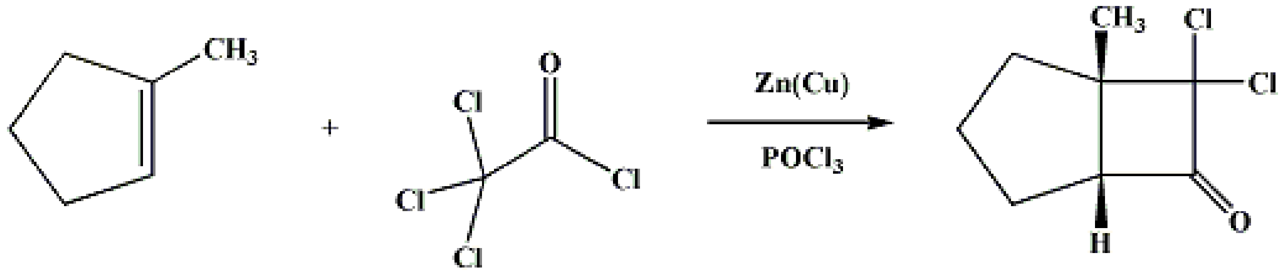
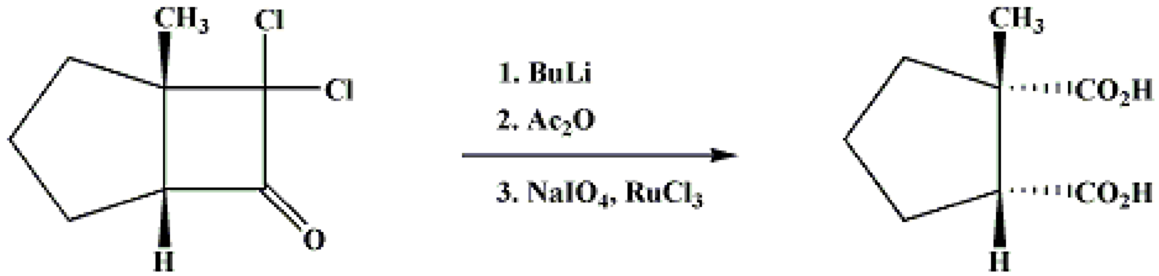
VICINAL DICARBOXYLATION OF AN ALKENE: *cis*-1-METHYLCYCLOPENTANE-1,2-DICARBOXYLIC ACID

[1,2-Cyclopentanedicarboxylic acid, 1-methyl-, *cis*-(±)-]





Submitted by Jean-Pierre Deprés and Andrew E. Greene[1].
Checked by Scott K. Thompson, Gregory A. Slough, and Clayton H. Heathcock.

1. Procedure

A. *7,7-Dichloro-1-methylbicyclo[3.2.0]heptan-6-one*. A 500-mL, two-necked, round-bottomed flask is equipped with a Teflon-covered magnetic stirring bar, a 250-mL pressure-equalizing addition funnel topped with a gas inlet, and a condenser connected to a Nujol-filled bubbler (Note 1). The system is flushed with nitrogen (Note 2). The flask is then charged with 10.0 g (ca. 150 mmol) of zinc–copper couple (Note 3), 200 mL of anhydrous ether (Note 4), and 10.5 mL (8.2 g, 100 mmol) of 1-methyl-1-cyclopentene (Note 5), and the addition funnel is filled with a solution of 13.4 mL (21.8 g, 120 mmol) of trichloroacetyl chloride (Note 5) and 11.2 mL (18.4 g, 120 mmol) of phosphorus oxychloride (Note 6) in 100 mL of anhydrous ether. Magnetic stirring is begun and the solution is added dropwise over 1 hr to the reaction flask at room temperature. After being stirred for an additional 14 hr, the reaction mixture is filtered under water pump pressure through 30 g of filter aid, which is then washed with 120 mL of ether. The filtrate is concentrated to ca. 100–120 mL, treated with 400 mL of hexane, and then briefly stirred to precipitate the zinc chloride. The supernatant solution is transferred to a separatory funnel and the viscous residue is washed with two 75-mL portions of 3 : 1 hexane–ether. The combined solution is washed successively with 200 mL of cold water, 200 mL of saturated aqueous sodium bicarbonate solution, and 2 × 50 mL of saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated to dryness by rotary evaporation at 25°C to give 17.0–17.8 g of a brown oil. Vacuum distillation of this material without fractionation provides 14.9–16.0 g (77–83%) of 7,7-dichloro-1-methylbicyclo[3.2.0]heptan-6-one as a clear, light-yellow oil, bp 38°C (0.2 mm), n_D^{20} 1.4970 (Note 7).

B. *cis-1-Methylcyclopentane-1,2-dicarboxylic acid*. A 1-L, one-necked, round-bottomed flask (Note 1) equipped with a Teflon-covered magnetic stirring bar is flushed with nitrogen and then charged with 300 mL of dry tetrahydrofuran (Note 4) and 14.5 g (75 mmol) of 7,7-dichloro-1-methylbicyclo[3.2.0]heptan-6-one. The flask is capped with a septum and connected to a Nujol bubbler and to a nitrogen line by means of syringe needles (Note 2). To the stirred solution cooled in a dry ice–acetone bath is added by syringe over 5 min 33.2 mL (83 mmol) of a 2.50 *M* solution of butyllithium in hexane (Note 8). After being stirred for 15 min with continued cooling, the reaction mixture is treated with 14.2 mL (150 mmol) of acetic anhydride all at once (Note 9). The cooling bath is removed and the reaction mixture is allowed to warm to room temperature and then stirred for an additional 1 hr. Most of the solvent and excess acetic anhydride are directly removed with a rotary evaporator at 25°C under water pump pressure (Note 10). The resulting solid residue is further dried for 15–30 min at 4 mm and then dissolved in a mixture of 100 mL of acetonitrile, 100 mL of carbon tetrachloride, and 150 mL of distilled water. The mixture is cooled in an ice bath and, with efficient stirring, treated with 40.1 g (187 mmol) of sodium periodate and 346 mg (1.5 mmol) of ruthenium(III) chloride hydrate (Note 11). After 15 min, the cooling bath is removed (Note 12) and stirring is continued for 5 hr, whereupon the thick mixture is treated with 200 mL of 10% aqueous sodium hydroxide solution and then extracted in a separatory funnel with 500 mL of 1 : 1 ether–hexane (Note 13). The phases are separated and to the aqueous phase is added 900 mL of 2 : 1 ether–ethyl acetate followed by a 2 *N* aqueous hydrochloric acid solution until a pH of 2–3 is obtained (Note 14). After being vigorously agitated, the phases are separated and the organic phase is washed successively with solutions of 3% aqueous sodium thiosulfate (Note 15) and saturated aqueous sodium chloride. All aqueous phases are mixed and, at pH 2 to 3, extracted with 1 L of 3 : 2 ether–ethyl acetate, which is then washed as before. The ether–ethyl acetate solutions are combined and dried over anhydrous sodium sulfate and the solvents are removed by rotary evaporation to leave a light-yellow solid, mp 123–126°C. Trituration of this material with 1 : 1 ethyl acetate–petroleum ether (Note 16) gives 7.9–8.0 g (61–62%) of *cis*-1-methylcyclopentane-1,2-dicarboxylic acid as a white solid, mp 123–124.5°C (Notes 16-19).

2. Notes

1. All glassware was dried overnight in an oven at 115°C and allowed to cool in a desiccator.
2. A slight positive pressure of nitrogen is maintained throughout the reaction.
3. A literature procedure[2] for the preparation of the zinc–copper couple was followed except for the use of slightly more (28%) than the indicated amount of copper sulfate. The checkers found that the kind of zinc used is critical. Zinc dust, 325-mesh, from Aldrich Chemical Company, Inc. (catalog no. 20,998-8) gave 7,7-dichloro-1-methylbicyclo[3.2.0]heptan-6-one in 80–89% yield. Zinc metal (dust) from Fisher Scientific Company (Lot 8744394) gave the dichloro ketone in yields of 37–61% (five trials). The Fisher zinc was of unknown mesh, but was much more finely-divided than the Aldrich Chemical Company, Inc. zinc.
4. Ether and tetrahydrofuran were distilled from the sodium ketyl of benzophenone.
5. 1-Methyl-1-cyclopentene (96% pure) and trichloroacetyl chloride (99% pure) were purchased from the Aldrich Chemical Company, Inc. The trichloroacetyl chloride was distilled prior to use.
6. Phosphorus oxychloride (99% pure) was obtained from the Aldrich Chemical

Company, Inc. and distilled from potassium carbonate prior to use.
7. This material was found to darken with time. Its spectral properties are the following: IR (film) cm^{-1}: 1805; ^{1}H NMR ($CDCl_3$, 80 MHz) δ: 1.57 (s, 3 H), 1.5–2.5 (m, 6 H), 3.50 (m, 1 H). These values are in accord with those reported in the literature.[3]
8. The solution of butyllithium in hexane was purchased from the Aldrich Chemical Company, Inc. and standardized with menthol and phenanthroline[4] before use.
9. Acetic anhydride was distilled prior to use.
10. A trap is used between the flask and the rotary evaporator as a precaution against possible bumping during the evaporation.
11. Sodium periodate was obtained from the Aldrich Chemical Company, Inc. and ruthenium(III) chloride hydrate (5–10% water) was purchased from Fluka. The more expensive periodic acid can replace sodium periodate; however, ruthenium(III) chloride appears to be somewhat more efficient than ruthenium(IV) oxide.
12. Should a noticeably exothermic reaction ensue, the cooling bath is replaced for a few minutes.
13. At this point the checkers filtered the mixture through a pad of 30 g of Celite to remove the green precipitate. This filtration reduces the problem of emulsions and clogging of the separatory funnel during subsequent extractions.
14. Iodine formation becomes substantial at lower pH.
15. Normally 50–100 mL of this solution is required.
16. This is done first with 20 mL and then with 8 mL. Product loss is minimized by storing the trituration flask overnight at –25°C prior to removal of the supernatant solution. On evaporation, the supernatant solution affords an oil containing the diacid and a small amount of the corresponding anhydride. Treatment of this oil with 10% aqueous NaOH at room temperature overnight and then processing the solution as before yields an additional 0.4 g (3%) of the diacid, mp 126–127°C.
17. The submitters report a crude yield of 11.5 g (89%) and a recrystallized yield of 9.0 g (70%), mp 128–129°C.
18. Melting points of 123–129°C have been reported for this compound.[5]; [6]; [7]; [8]; [9] Its spectral properties are the following: IR (Nujol) cm^{-1}: 2720, 2630, 1690; ^{1}H NMR ($CDCl_3$, 80 MHz) δ: 1.44 (s, 3 H), 1.5–2.5 (m, 6 H), 2.72 (pseudo-t, 1 H, J = 8), 10.8 (br s, 2 H).
19. Gas-chromatographic analysis (10%, Carbowax 20 M on 80–100 mesh Chromosorb W, 2.5 × 2 mm, column temperature 180°C, injection temperature 230°C, flow rate 10 mL/min, retention time 10 min) of the corresponding dimethyl ester, formed with ethereal diazomethane, indicated a purity of greater than 99%.

3. Discussion

This procedure serves to illustrate a relatively inexpensive, two-pot, stereoselective method for effecting vicinal dicarboxylation of alkenes that is more generally applicable and higher-yielding than the palladium-catalyzed carbonylation reaction and other more circuitous procedures.[10] Part A of this procedure is a slight modification of the dichloroketene–olefin cycloaddition method previously described by Krepski and Hassner.[2] Part B makes use of Sharpless and co-workers' ruthenium(III) chloride-catalyzed oxidation process[11] for the cleavage of the β-chloro enol acetate, which is formed on trapping the β-chloro enolate intermediate with acetic anhydride. A slightly different, nonoptimized version of this procedure has been used[10,12] for the vicinal dicarboxylation of 1-decene, *cis*- and *trans*-2-butene, 2-

methyl-2-butene, 2,3-dimethyl-2-butene, 1-methyl-1-cyclohexene, 1,6-dimethyl-1-cyclohexene, and 5α-cholest-2-ene with overall yields of 52–83%.

cis-1-Methylcyclopentane-1,2-dicarboxylic acid has been previously prepared by a variety of methods: by oxidative cleavage (HNO_3) of cyclobutanone[5] and cyclopentanone[6] precursors, through saponification and oxidation ($KMnO_4$) of a γ-butyrolactone intermediate,[7] and by anhydride formation and then hydrolysis starting from mixtures of the *cis*- and *trans*-diacids (obtained in about five steps).[8,9] Compared with these methods, the cycloaddition–cleavage procedure is much more efficient and practical. It requires only readily available reagents and easily affords, without any chromatographic separations, a product of high purity.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

sodium ketyl of benzophenone

copper couple

1,2-Cyclopentanedicarboxylic acid, 1-methyl-, cis-(±)-

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

ether (60-29-7)

acetic anhydride (108-24-7)

acetonitrile (75-05-8)

sodium hydroxide, NaOH (1310-73-2)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

carbon tetrachloride (56-23-5)

sodium thiosulfate (7772-98-7)

nitrogen (7727-37-9)

copper sulfate (7758-98-7)

iodine (7553-56-2)

Phosphorus Oxychloride (21295-50-1)

zinc, Zinc metal (dust) (7440-66-6)

palladium (7440-05-3)

zinc chloride (7646-85-7)

Cyclopentanone (120-92-3)

menthol (15356-60-2)

2,3-dimethyl-2-butene (563-79-1)

2-methyl-2-butene (513-35-9)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

hexane (110-54-3)

periodic acid

1-methyl-1-cyclohexene

γ-butyrolactone (96-48-0)

phenanthroline

Cyclobutanone (1191-95-3)

trichloroacetyl chloride (76-02-8)

Sodium periodate (7790-28-5)

ruthenium(III) chloride (14898-67-0)

cis- and trans-2-butene

1-decene (872-05-9)

1-methyl-1-cyclopentene

7,7-Dichloro-1-methylbicyclo[3.2.0]heptan-6-one (51284-43-6)

ruthenium(III) chloride hydrate (13815-94-6)

ruthenium(IV) oxide

1,6-dimethyl-1-cyclohexene

5α-cholest-2-ene

cis-1-Methylcyclopentane-1,2-dicarboxylic acid (70433-31-7)

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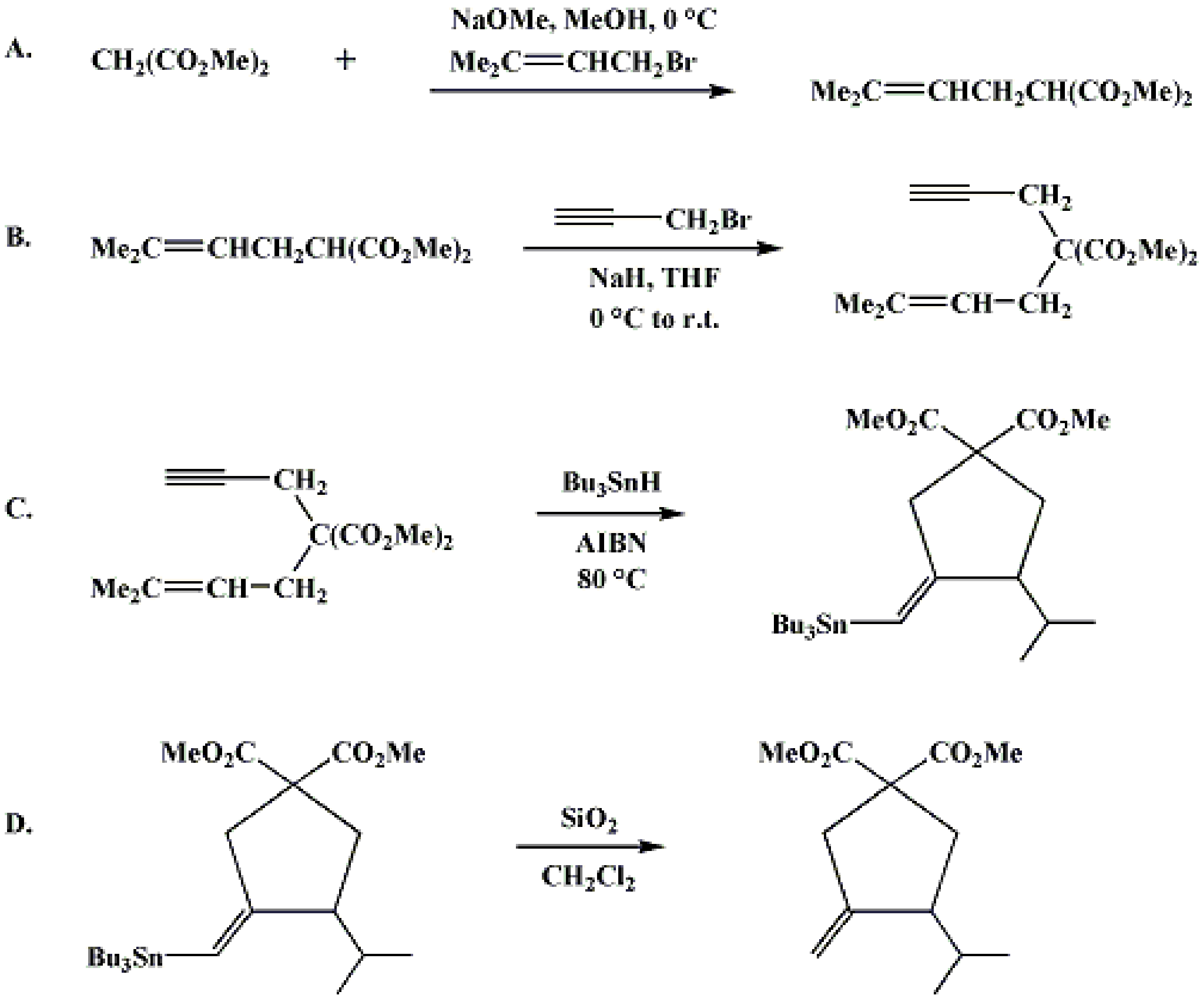
Organic Syntheses, CV 8, 381

VINYL RADICAL CYCLIZATION VIA ADDITION OF TIN RADICALS TO TRIPLE BONDS: 3-METHYLENE-4-ISOPROPYL-1,1-CYCLOPENTANEDICARBOXYLIC ACID, DIMETHYL ESTER

[1,1-Cyclopentanedicarboxylic acid, 3-methylene-4-(1-methylethyl)-, dimethyl ester]



Submitted by Robert Mook, Jr. and Philip Michael Sher[1].
Checked by Anthony G. Schaefer and Leo A. Paquette.

1. Procedure

A. *(3-Methyl-2-butenyl)propanedioic acid, dimethyl ester* ***(1)***. To a 500-mL, flame-dried, three-necked, round-bottomed flask under an argon atmosphere and fitted with a thermometer, a pressure-equalizing addition funnel, and a magnetic stirring bar is added 250 mL of methanol (Note 1). The flask is immersed in an ice bath, and 6.7 g (0.29 mol) of sodium is added cautiously (Note 2). After the sodium has dissolved, the ice bath is removed,

36.9 g (0.28 mol) of dimethyl malonate (Note 1) is added at room temperature, and the solution is stirred for 0.5 hr. The reaction mixture is cooled to 0°C, and 45.8 g (0.31 mol) of 3,3-dimethylallyl bromide (Note 1) is added dropwise while the temperature is maintained near 5°C (Note 3). After 1 hr (Note 4), the reaction mixture is transferred to a 1-L, one-necked, round-bottomed flask with the aid of a small amount of methanol and concentrated with a rotary evaporator. The white residue is taken up in 400 mL of ether and 300 mL of a saturated salt/saturated sodium bicarbonate (1 : 1) solution and is transferred to a separatory funnel. The ether layer is separated, and the aqueous layer is extracted with ether (1 × 200 mL). The ether layers are combined, dried over magnesium sulfate, filtered, and concentrated with a rotary evaporator. Distillation of the residue through a 6-in. Vigreux column (after a small forerun is collected) yields 43.9–44.5 g (78–79%) of **1**, bp 60–63°C (0.15 mm) (Note 5).

B. *(3-Methyl-2-butenyl)(2-propynyl)propanedioic acid, dimethyl ester* ***(2)***. To a 1-L, flame-dried, three-necked, round-bottomed flask, equipped with a magnetic stirring bar (Note 6) and under an argon atmosphere, is added 9.0 g (0.19 mol) of sodium hydride dispersion (Note 7). The sodium hydride is washed with petroleum ether (4 × 30 mL), removing the petroleum ether by pipette after the sodium hydride has settled. The flask is then fitted with a thermometer and an over-dried pressure-equalizing addition funnel and charged with 500 mL of tetrahydrofuran (Note 7). The heterogenous mixture is cooled with an ice bath, and 36.4 g (0.18 mol) of the monoalkyl diester (1.htm) is added dropwise at the rate of 1 drop/2–3 sec (Note 2). The cooling bath is removed when the addition is complete, and the solution is stirred until no more gas evolves (ca. 1 hr). The reaction mixture is recooled to 0°C, and 22 mL of propargyl bromide solution (0.20 mol) (Note 7) is added dropwise while the temperature is maintained at 0–10°C. Sodium bromide begins to precipitate within 20 min. The ice bath is removed, and the reaction mixture is stirred overnight (Note 8). After careful addition of 50 mL of water (Note 9) and removal of the stirring bar, the solution is transferred to a 1-L, one-necked, round-bottomed flask and concentrated with a rotary evaporator. The residue is taken up in 500 mL of ether and washed with water (3 × 300 mL) and saturated salt solution (1 × 100 mL). The aqueous layers are combined, saturated with salt, and extracted with ether (2 × 150 mL). The ether layers are combined, dried over magnesium sulfate, filtered, and concentrated with a rotary evaporator. The residue is distilled through a short-path distillation apparatus at 80°C (0.25 mm) to yield 34.0–34.2 g (79–80%) of (Note 10).

C. *(Z)-3-Tributylstannylmethylene-4-isopropyl-1,1-cyclopentanedicarboxylic acid, dimethyl ester* ***(3)***. A flame-dried, 100-mL, round-bottomed flask equipped with a magnetic stirring bar is charged with argon, and 23.8 g (0.100 mol) of dialkylmalonate diester (2.htm), 30.2 g (<0.104 mol) of tributyltin hydride (Note 11), and 40 mg (0.25 mmol) of azobisisobutyronitrile (AIBN) (Note 12) are added neat (Note 13) and (Note 14). The entire assembly is lowered into an oil bath maintained at 75–85°C, and the mixture is stirred. After an induction period of less than 30 min, an exothermic reaction occurs and produces a small amount of gas and a rise in the temperature of the oil bath (as much as 20°C for a small bath). After this point TLC shows that the reaction is essentially complete (Note 15)(Note 16) (Note 17). Unpurified 3 thus obtained is suitable for protodestannylation.

D. *3-Methylene-4-isopropyl-1,1-cyclopentanedicarboxylic acid, dimethyl ester* ***(4)***. Crude

vinylstannane (3) is transferred to a 2-L Erlenmeyer flask containing 1 L of dichloromethane, 350 g of silica (Note 18), and a large (7 × 3-cm, egg-shaped) stirring bar. The flask is stoppered, and the mixture is stirred for 24–48 hr (Note 19). The mixture is divided into three portions. Each portion is filtered under reduced pressure with a 600-mL glass frit, and the silica is washed with ethyl acetate (8 × 200 mL) to extract all of the desired product (Note 20). The solution is filtered through Celite and the solvent is removed with a rotary evaporator. Distillation through a short-path distillation apparatus (with no forerun) gives 19.8–20.5 g of **4** (83–85% overall from **2**), bp 80°–85°C (0.2 mm) (Note 21).

2. Notes

1. The use of less solvent can result in gel formation. Methanol was freshly distilled from calcium hydride or magnesium metal. Dimethyl malonate (Aldrich Chemical Company, Inc.) was distilled before use. 3,3-Dimethyallyl bromide may be purchased from Aldrich Chemical Company, Inc. or Wiley Organics.
2. The apparatus should be vented. Hydrogen gas formation causes vigorous bubling.
3. At higher temperature more dialkylation occurs.
4. The reaction can be monitored by TLC eluting with 10% ethyl acetate/petroleum ether.
5. The physical properties are as follows: IR (neat) cm^{-1}: 2980, 1730–1760, 1435, 1040; ^{1}H 200 MHz NMR ($CDCl_3$) δ: 1.62 (s, 3 H), 1.65 (s, 3 H), 2.56 (t, 2 H, J = 7), 3.34 (t, 1 H, J = 7), 3.70 (s, 6 H), 5.06 (bt, 1 H, J = 7).
6. Unless a sufficiently large stirring bar is used the precipitate may be impossible to stir. An overhead mechanical stirrer can be substituted.
7. Sodium hydride, 50% oil dispersion, was purchased from Alfa Products, Morton/Thiokol, Inc. Tetrahydrofuran was freshly distilled from sodium/benzophenone. Propargyl bromide (80% in toluene) was purchased from Aldrich Chemical Company, Inc. and used directly.
8. The reaction is generally complete sooner, but because it progress is difficult to monitor by TLC (since the starting material and product have similar R_f values) the submitters routinely allow more than enough time.
9. Trace amounts of sodium hydride may still be present. If the water is added too quickly, a vigorous reaction results.
10. The checkers observed a boiling point of 99–100°C (0.35 mm) for this material. The physical properties are as follows: IR (neat) cm^{-1}: 3290, 2960, 1740, 1440; ^{1}H 300 MHz NMR ($CDCl_3$) δ: 1.61 (s, 3 H), 1.65 (s, 3 H), 1.97 (t, 1 H, J = 3), 2.7 (m, 4 H), 3.69 (s, 6 H), 4.9 (t, 1 H J = 7).
11. Tributyltin hydride 97%, was purchased from Aldrich Chemical Company, Inc. and used directly. A minimal excess of this reagent is desired in order to ensure clean distillation of 4. If the product is to be purified by chromatography, a 10% excess of tributyltin hydride can be used.
12. Azobisisobutyronitrile (AIBN) was purchased from Aldrich Chemical Company, Inc. and recrystallized from chloroform. To exclude the possibility of a violent reaction, no more than twice this amount should be used on this scale.
13. These reactions can also be run in benzene, which is preferable in cases where transfer of hydrogen to the vinyl radical is competitive with cyclization.
14. The submitters routinely interposed a Vigreux column between the reaction flask

and the argon line to protect the argon line in the event of bumping.

15. The reaction mixture is routinely stirred hot for an additional 30 min to ensure complete conversion.

16. Vinylstannane (**3**) may protodestannylate on TLC, which could be confusing when monitoring Reaction C since dialkylmalonate diester (**2**) and protodestannylated product (**4**) have similar R_f values. The submitters found that TLC plates stored in the open air (as opposed to desiccator-stored plates) caused negligible protodestannylation.

17. Although vinylstannane **3** protodestannylates on silica, it may be isolated by flash chromatography in greater than 90% yield: IR (neat) cm^{-1}: 2960, 2930, 2880, 2860, 1740, 1615, 1465, 1435; ^{1}H 200 MHz NMR ($CDCl_3$) δ: 3.71 (s, 3 H), 3.73 (s, 3 H), 5.62 (bs, 1 H) with satellites.

18. The submitters employed Silica Woelm 32-63 purchased from Universal Scientific, Inc.; the checkers used Merck silica gel 60 (40–60 •m in size). Before use the silica was oven dried for several days at 160°C. Undried silica may be used, but larger quantities and/or longer reaction times are necessary.

19. TLC plates stored in the open air should be used (see (Note 16)) to monitor Reaction D accurately. Approximately 4% of noncyclized hydrostannylation product is produced in Reaction C. This material forms cospots with **3** (2.5% ethyl acetate in petroleum ether), but protodestannylates much more slowly. Therefore, by TLC Reaction D may appear not to go to completion.

20. A larger glass frit would obviate division of the mixture. In any case, the silica should be washed until by TLC the filtrate no longer contains **4**.

21. The checkers observed a boiling point of 98–105°C (0.35 mm) for this product: IR (neat) cm^{-1}: 3080, 2960, 2875, 1735, 1655, 1435, 1385, 1365, 890. MS (CI) M + l = 241; ^{1}H 300 MHz NMR ($CDCl_3$) δ: 0.75 (d, 3 H, J = 7), 0.85 (d, 3 H, J = 7), 1.80 (m, 2 H), 2.40 (m, 2 H), 2.84 (m, 2 H), 3.64 (s, 3 H), 3.65 (s, 3 H), 4.72 (bs, 1 H), 4.90 (bs, 1 H).

3. Discussion

Free-radical reactions are proving to be synthetically useful alternatives for producing carbon–carbon bonds.[2 3 4 5 6 7 8 9 10,11 12 13 14 15 16 17] Recently, Stork has shown that vinyl radicals are valuable in ring forming reactions since they place a double bond in a predictable position.[11,12,13,14,15,16,17] Their compatibility with many unprotected functional groups and their ability to form quarternary centers are additional features which make vinyl radical cyclization an attractive synthetic method.

Previously, vinyl radicals for cyclization reactions were produced by the reduction of vinyl halides with tributyltin hydride. In the present procedure vinyl radicals are produced by the addition of tin radicals to triple bonds.[18 19] These vinyl radicals undergo cyclization in an analogous fashion to those generated from vinyl halides. However, this approach provides vinylstannanes stereoselectively; these vinylstannanes may be utilized in a wide range of synthetic transformations.

Vinylstannanes[20 21 22 23 24 25 26 27 28 29 30 31] are versatile synthetic intermediates. They serve as a source of stereospecific vinyl anions and vinyl cuprates.[20,23,32 33 34] In the presence of Pd(0), vinylstannanes can be acylated[35,36] or alkylated.[37,38] Epoxidation followed by rearrangement converts vinylstannanes into carbonyl compounds.[39] Treatment

with halogens or *N*-halosuccinimides yields vinyl halides.[20,21,22,23,34,40] Deuterium-labeled olefins result from deuterolysis of vinyl stannanes with AcOD or DCl.[23] Olefins identical to those produced in vinyl halide reductions are obtained on protodestannylation with silica gel, which, unlike simple acid treatment, solves the problem of separation from tin residues.[41]

Many examples of radicals kinetically favoring addition to double bonds over triple bonds are known.[42 43 44 45] Yet, vinyl radical cyclization in the present procedure is initiated by the addition of a tin radical to a triple bond.[46] The apparent selectivity of the tin radical for the triple bond in the presence of a double bond is, at least in some cases, a result of reversible addition to both followed by selective cyclization of the vinyl radical.[18,19]

References and Notes

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46. The sterically less biased case of allylpropargyl malonate gives greater than 75% of analogous product.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

silica

3,3-Dimethyallyl bromide

Benzene (71-43-2)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether (60-29-7)

hydrogen (1333-74-0)

chloroform (67-66-3)

sodium bicarbonate (144-55-8)

magnesium (7439-95-4)

sodium bromide (7647-15-6)

toluene (108-88-3)

Benzophenone (119-61-9)

sodium (13966-32-0)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

sodium hydride (7646-69-7)

calcium hydride (7789-78-8)

argon (7440-37-1)

propargyl bromide (106-96-7)

tributyltin hydride (688-73-3)

dimethyl malonate (108-59-8)

3-Methylene-4-isopropyl-1,1-cyclopentanedicarboxylic acid, dimethyl ester, 1,1-Cyclopentanedicarboxylic acid, 3-methylene-4-(1-methylethyl)-, dimethyl ester (107473-16-5)

3,3-dimethylallyl bromide (870-63-3)

azobisisobutyronitrile (78-67-1)

(3-Methyl-2-butenyl)propanedioic acid, dimethyl ester (43219-18-7)

(3-Methyl-2-butenyl)(2-propynyl)propanedioic acid, dimethyl ester (107473-14-3)

(Z)-3-Tributylstannylmethylene-4-isopropyl-1,1-cyclopentanedicarboxylic acid, dimethyl ester

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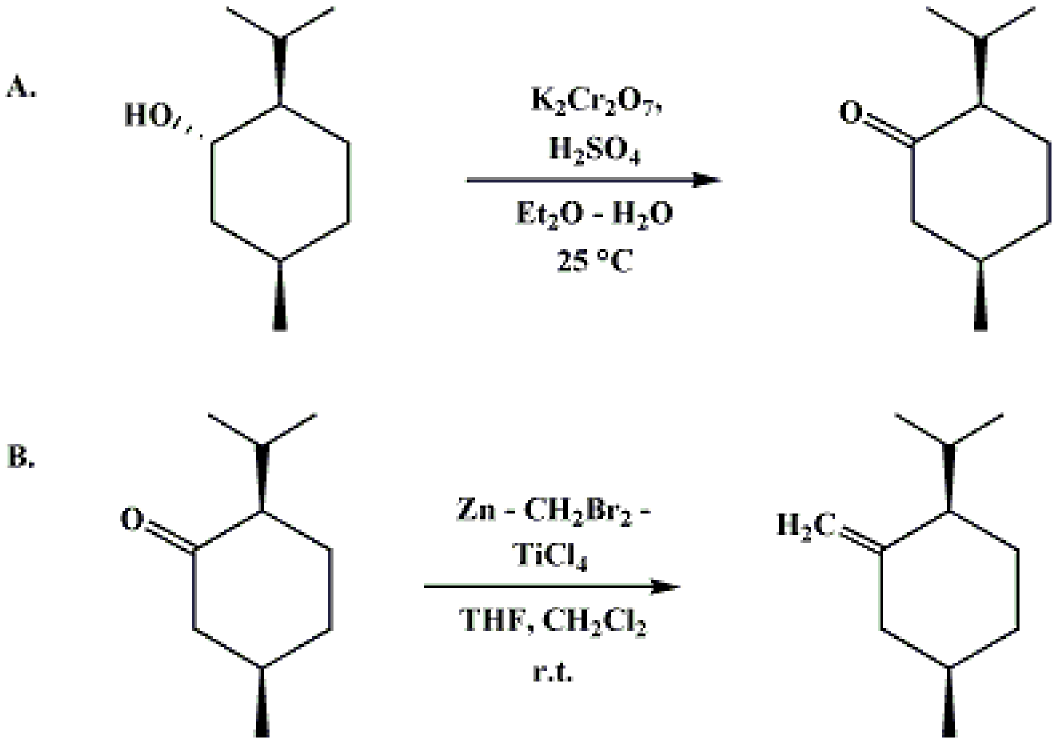
METHYLENATION OF CARBONYL COMPOUNDS: (+)-3-METHYLENE-*cis*-*p*-METHANE

[Cyclohexane, 4-methyl-2-methylene-1-(1-methylethyl)-, *R*,*R*-]



Submitted by Luciano Lombardo[1]
Checked by Mamoru Uchiyama and Ryoji Noyori.

1. Procedure

A. *(+)-Isomenthone*. Into a 1-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, a condenser, a thermometer, and a dropping funnel are placed 54.6 g (0.35 mol) of (+)-isomenthol (Note 1) and 350 mL of ether. A solution of chromic acid, prepared by mixing 56.7 g (0.23 mol) of potassium dichromate and 31.0 mL (0.58 mol) of 98% sulfuric acid and diluting to 200 mL with water, is added dropwise to maintain the reaction temperature at 25°C. The mixture is stirred for a further 2 hr. The ether layer is separated and the aqueous phase is extracted twice with 100-mL portions of ether. The combined ether extracts are washed with saturated sodium bicarbonate solution, dried over magnesium sulfate, and evaporated under reduced pressure to leave an oil. Distillation through a short Vigreux column gives the main fraction of (+)-isomenthone as a clear, colorless liquid (40.5 g), bp 64–64.5°C at 5 min; $[\alpha]_D^{16}$ +114° [$CHCl_3$, *c* 5.09].

B. *(+)-3-Methylene-cis-p-menthane*. Into a 1-L, round-bottomed flask fitted with a magnetic stirrer and a pressure-equalizing dropping funnel connected to a nitrogen line

are placed 28.75 g (0.44 mol) of activated zinc powder (Note 2), 250 mL of dry tetrahydrofuran (Note 3), and 10.1 mL (0.144 mol) of dibromomethane (Note 4). The mixture is stirred and cooled with a dry ice–acetone cooling bath at –40°C. To the stirred mixture is added dropwise 11.5 mL (0.103 mol) of titanium tetrachloride (Note 4) over 15 min. The cooling bath is removed and the mixture is stirred (Note 5) at 5°C (cold room) for 3 days under a nitrogen atmosphere. The dark-gray slurry (Note 6) is cooled with an ice–water bath and 50 mL of dry dichloromethane (Note 7) is added. To the stirred mixture is added 15.4 g (0.1 mol) of (+)-isomenthone in 50 mL of dry dichloromethane over a period of 10 min. The cooling bath is removed and the mixture is stirred at room temperature (20°C) for 1.5 hr. The mixture is diluted with 300 mL of pentane and a slurry of 150 g of sodium bicarbonate in 80 mL of water is added cautiously (Note 8) over 1 hr. The clear organic solution is poured of into a 1.5-L Erlenmeyer flask and the residue is washed 3 times with 50-mL portions of pentane. The combined organic solutions are dried over a mixture of 100 g of sodium sulfate and 20 g of sodium bicarbonate (Note 9) and filtered through a sintered-glass funnel (No. 2), and the solid desiccant is thoroughly washed with pentane. The solvent is removed at atmospheric pressure by flash distillation through a column (40 × 2.5 cm) packed with glass helices. The liquid residue is distilled (Note 10) to give the methylenated product as a clear, colorless liquid, bp 105–107°C at 90 mm, 13.6 g, 89% yield (Note 11), n_D^{24} 1.45321, $[\alpha]_D^{23}$ +7.7 to +8.6° [$CHCl_3$, *c* 4.0].

2. Notes

1. (+)-Isomenthol was purchased from the Aldrich Chemical Company, Inc. Oxidation was carried out according to the procedure of Brown.[2]
2. Zinc powder from Hopkin and williams Chemical Company or Nakarai Chemicals (GR grade) is activated according to Fieser and Fieser.[3]
3. Tetrahydrofuran is dried by distillation from sodium/benzophenone.
4. Dibromomethane from EGA-CHEMIE and titanium tetrachloride from E. Merck are used as supplied. The checkers used the products of Nakarai Chemicals. All residues of titanium tetrachloride are destroyed with acetone from a wash bottle.
5. As the reaction progresses the mixture thickens, and it is necessary to begin with a reasonably fast rate of stirring. However, too fast a stirring rate causes the mixture to splash up to the neck of the round-bottomed flask as the mixture thickens.
6. The reagent must be kept cold at all times because at room temperature the active reagent slowly decomposes and the mixture darkens considerably. Once prepared the reagent can be stored at –20°C (freezer) in a well-sealed flask without a significant loss of activity. A sample stored in this way for 1 year showed only a slight, ca. 5–10%, loss of activity. The molar activity of the active reagent is equivalent to the titanium tetrachloride ($TiCl_4$) molarity (determined by reaction with excess ketone followed by GLC analysis); however, an increase in the proportion of $TiCl_4$ makes no difference in the

molar activity.

7. Analytical-reagent ANALAR dichloromethane was dried by storing over Linde 4A sieves. The checkers purchased the EP-grade solvent from Wako Pure Chemical Industries.

8. It is necessary to add the slurry dropwise at the beginning, allowing the effervescence to subside after each drop. After the initial vigorous effervescence, larger portions can be added. During this part of the addition, the stirrer becomes ineffective and gentle shaking by hand is continued until effervescence ceases.

9. The organic solution is shaken with the drying agent for 10–15 min to remove the last traces of titanium salts.

10. The pressure is allowed to drop to ca. 40 mm for a few minutes when the oil-bath temperature has reached 50°C. This procedure removes any residual tetrahydrofuran that could be responsible for a small contaminated forerun. A considerable amount of product is collected at the end of the distillation as the temperature drops.

11. This is the first preparation of this compound (see [4] of discussion); the data obtained are as follows. Anal. calcd. for $C_{11}H_{20}$: C, 86.83, H, 13.48. Found: C, 86.76, H, 13.24. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.79 (d, 3 H, *J* = 7, $-CH_3$); 0.91 (d, 6 H, *J* = 7, $-CH_3$); 1.01–2.14 (m, 9 H, $-CH_2-$, -CH); 4.54, 4.60, (two s, 2 H, $=CH_2$); ^{13}C NMR ($CDCl_3$): 17.4, 18.3, 19.2, 22.6, 25.8, 26.5, 31.8, 37.3, 47.4, 104.6, 148.4.

3. Discussion

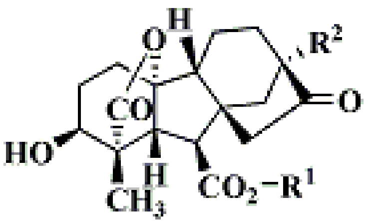
This new $Zn/CH_2Br_2/TiCl_4$ procedure[5] provides a mild, nonbasic method for the methylenation of ketones (a competitive pinacol dimerization occurs with aldehydes, but good yields of the olefin can still be achieved) and offers an important alternative to the standard Wittig[6] reaction. These characteristics are derived from two important observations:

1. Ketones are not enolized by the reagent and one important consequence is that adjacent enolizable chiral centers are not epimerized.
2. The reagent is compatible with a wide variety of functional groups, for example (Table I), THP ethers, *tert*-butyldimethylsilyl ethers, acetals, esters, carboxylic acids, alcohols, and lactones. Such selectivity makes it a valuable procedure in organic synthesis[7,8] and appreciably augments Wittig methodology.

TABLE I

METHYLENATION OF KETONES WITH $Zn/CH_2Br_2/TiCl_4$

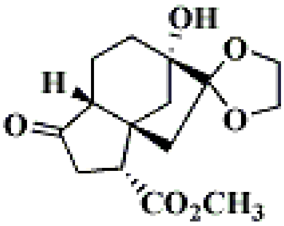
Substrate	Isolated Yield	Ref.



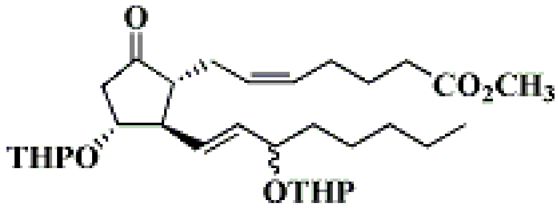
$R^1=R^2=H$ — 80%

$R^1=CH_3$, $R^2=H$ — 93%

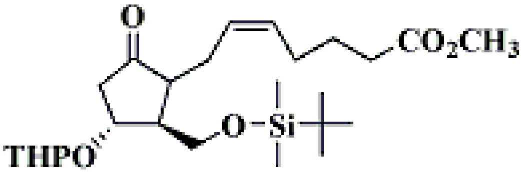
2



90% — 2



80% — 4b



81% — 4b

The corresponding Wittig reagent, $CH_2=PPh_3$, reacts smoothly with both aldehydes and ketones to give methylenated products in high yield but with one subtle limitation. The problem cannot be detected with aldehydes because they react rapidly even at temperatures as low at –78°C, but ketones react more slowly, and an adjacent enolizable chiral center can be epimerized as a result of competitive reversible enolization. This limitation of the Wittig procedure has been recognized for some time,[9] and new methylenation methods[9,10] that avoid enolization have been developed. However, the application of these methods is restricted either by low yields or by incompatibility with other functionality in the molecule. In the closest analogy to the present preparation of (+)-3-methylene-*cis*-*p*-menthane, one of these methods has been used for the methylenation of *l*-menthone,[4] but a yield of only 40% was obtained.

The $Zn/CH_2Br_2/TiCl_4$ procedure as originally reported[11] has not been widely used. The active reagent was generated and trapped by the carbonyl compound in situ at room temperature. Long reaction times were required and as a consequence the substrate was exposed for long periods to $TiCl_4$, severely limiting the usefulness of the

procedure. The discovery[5] that the active reagent was stable at low temperature and could be performed extends the utility and scope of the reaction enormously. This reagent reacts rapidly with ketones at room temperature with considerably improved yields and selectivities.

The nonbasic nature of the reagent makes it useful in other applications. It has, for example, also proved useful for the methylenation of the gibberellin norketone[5] (Table I) without the need for protection of the readily epimerized 3β-OH. The use of CD_2Br_2[5] allows the introduction of $=CD_2$ without scrambling of the label.

The $Zn/CH_2Br_2/TiCl_4$ reagent is superior to other nonbasic methylenation reagents. Furthermore, the long shelf life at low temperatures, together with the ease of workup, render it an appealing alternative to the Wittig method for the methylenation of ketones in general.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

(+)-3-METHYLENE-cis-p-METHANE

$TiCl_4$

$Zn/CH_2Br_2/TiCl_4$

sulfuric acid (7664-93-9)

ether (60-29-7)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

acetone (67-64-1)

Benzophenone (119-61-9)

zinc powder (7440-66-6)

sodium (13966-32-0)

chromic acid (7738-94-5)

Pentane (109-66-0)

potassium dichromate (7778-50-9)

(+)-isomenthol (15356-60-2)

menthone, (+)-Isomenthone, l-MENTHONE (1196-31-2)

dibromomethane (74-95-3)

dichloromethane (75-09-2)

pinacol (76-09-5)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

titanium tetrachloride (7550-45-0)

(+)-3-Methylene-cis-p-menthane

cis-p-menthane

Cyclohexane, 4-methyl-2-methylene-1-(1-methylethyl)-, R,R- (122331-74-2)

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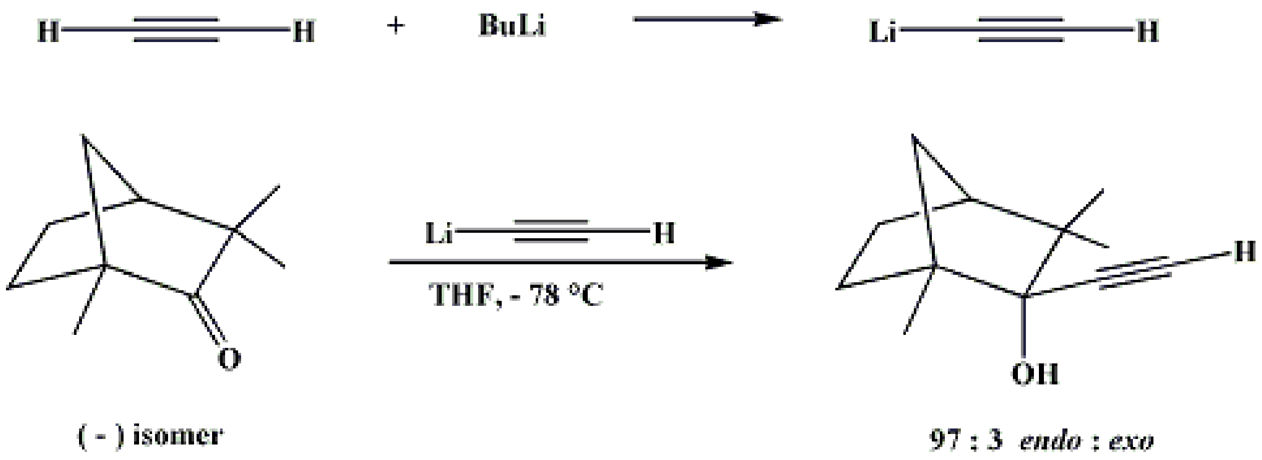
Organic Syntheses, CV 8, 391

PREPARATION AND USE OF LITHIUM ACETYLIDE: 1-METHYL-2-ETHYNYL-*endo*-3,3-DIMETHYL-2-NORBORNANOL

[Bicyclo[2.2.1]heptan-2-ol, 2-ethynyl-1,3,3-trimethyl-, (1*R*-*endo*)]



Submitted by M. Mark Midland, Jim I. McLoughlin, and Ralph T. Werley Jr[1].
Checked by Matthew J. Sharp and Larry E. Overman.

1. Procedure

An oven-dried (Note 1), 500-mL, septum-capped, round-bottomed flask is flushed with nitrogen, charged with 70 mL of tetrahydrofuran (THF) (Note 2), and cooled to −78°C. After the apparatus has cooled, 157 mL of a 2.1 *M* solution of butyllithium (0.330 mol) (Note 3) is added using a 50-mL syringe. The contents are mixed by swirling the flask and kept at −78°C until needed. An oven-dried, 2-L, round-bottomed flask, equipped with a magnetic stir bar and capped with a septum, is cooled under a nitrogen purge (Note 4). The flask is charged with 500 mL of THF and cooled to −78°C. A 100-mL graduated cylinder (Note 5) is fitted with a septum in which an 8-mm hole has been bored (Note 6). A 9-mm glass tube that can be connected to either a nitrogen or acetylene line through a three-way valve (Note 6) and (Note 7) is inserted through the septum of the graduated cylinder. A double-ended needle is used to connect the cylinder to the 2-L reaction flask. After the cylinder and reaction flask have been thoroughly purged with nitrogen, 70 mL of THF is introduced into the cylinder, and the cylinder is cooled to −78°C (Note 8). Acetylene (Note 7) and (Note 9) is introduced through the 9-mm tube into the bottom of the graduated cylinder at such a rate that 30 mL (Note 10) has been added in 20 min; excess acetylene that does not dissolve in the THF is allowed to flow through the double-ended needle to the 2-L reaction flask. The cold acetylene solution is transferred via the double-ended needle to the 2-L reaction flask. While the solution is cooling in the −78°C bath, nitrogen is blown over the surface to purge the system completely of acetylene (Note 11). The precooled butyllithium/THF solution is then slowly added by a

double-ended needle over a 1-hr period (Note 12). The clear solution of lithium acetylide is stirred for an additional 15 min at −78°C before 48.4 mL of (−)-fenchone (0.300 mol, (Note 13)) is slowly added via syringe. The solution immediately becomes yellow. After the addition is complete, the cold bath is removed and the mixture is stirred for 3 hr while it warms to room temperature. The flask is opened to the atmosphere and 400 mL of 1.0 *M* hydrochloric acid is added (Note 14). The quenched reaction is stirred for 20 min and then transferred to a 2-L separatory funnel. The aqueous material is separated and 200 mL of pentane is added. The organic layer is then sequentially washed with 100 mL of 1.0 *M* hydrochloric acid, 300 mL of water, and finally 100 mL of saturated brine. The combined aqueous material is extracted with 200 mL of ether. The organic extracts are combined, dried with magnesium sulfate, and filtered. Concentration (rotary evaporation, 40°C under aspirator pressure) provides a thick, yellow oil that is distilled to obtain 48.2 g (90%) of the alcohol as a pale-yellow oil (bp 51–55°C at 0.05 mm) (Note 15).

2. Notes

1. All glassware was oven-dried for at least 24 hr at 130°C, assembled hot, and cooled under a stream of nitrogen.[2] [3]
2. Tetrahydrofuran, THF, was obtained from Mallinckrodt Inc. and distilled from sodium/benzophenone ketyl immediately prior to use.
3. The checkers used butyllithium, purchased from Lithium Alkyls, which was standardized by titration with 2,5-dimethoxybenzyl alcohol. The submitters used butyllithium obtained from Aldrich Chemical Company, Inc. as a 1.55 *M* solution in hexanes that was measured by transfer to a septum-capped 250-mL graduated cylinder with a 15-gauge cannula and nitrogen back pressure.[2] This solution was then transferred to the flask containing THF in the same manner. The THF must be cooled prior to addition of the butyllithium. Stainless-steel double-ended needles of the type used by the submitters are available from Aldrich Chemical Company, Inc. and Ace Glass, Inc.
4. A slight positive pressure of nitrogen was maintained in the reaction vessel throughout the procedure until the reaction was quenched.
5. Graduated cylinders of various sizes with 24/40 standard taper joints are available from Ace Glass, Inc.; appropriate septa were obtained from Aldrich Chemical Company, Inc.
6. Both nitrogen and acetylene are introduced into the graduated cylinder through a 9-mm glass tube approximately 30 cm in length. An 8-mm hole bored through the septum allows for a good seal and for movement of the glass tube in order to adjust the height of the tube from the bottom of the graduated cylinder. A drawing of the apparatus employed is provided in f.htmigure 1.

Figure 1

Figure 1

7. Acetylene is obtained from Liquid Carbonics and is purified by passage through a −78°C cold trap, a liquid trap (to prevent aspiration of sulfuric acid), a gas washing bottle containing 100 mL of concentrated sulfuric acid, and a calcium

chloride drying tube before introduction into the graduated cylinder.[4] A bubbler and a three-way valve, in that order, are placed before the graduated cylinder. The bubbler with a head of 30 mm of mercury is connected to the system with a T-shaped connecting tube and serves as a relief valve to prevent overpressurization of the acetylene line. The three-way valve allows nitrogen to be flushed through the graduated cylinder and reaction flask for purging the apparatus and to provide back pressure for the transfer of the acetylene solution. (See f.htmig. 1 for drawing of the reaction apparatus.) *Caution: Reactions with acetylene should be carried out in the hood and all lines carrying exhaust from the bubblers must be vented to a fume hood!*

8. The graduated cylinder and its contents are cooled in a wide-mouth Dewar containing a dry ice–acetone slurry.

9. Acetylene is an explosive compound and reacts with metals (e.g., Cu, Ag).[5]

10. The amount of acetylene is approximated by assuming a density of 0.7 g/mL. Approximately 2.5–3.0 equiv of acetylene is used. THF is added to the graduated cylinder so that the final volume of the acetylene solution will be 100 mL. In this case, 30 mL of acetylene is measured to provide approximately 0.85 mol.

11. Acetylene gas must be removed from above the solution to prevent reaction with the concentrated butyllithium solution entering the flask. Such a reaction in the presence of excess butyllithium will result in the formation of dilithium acetylide on the needle tip. The formation of even small amounts of dilithium acetylide must be avoided; lithium acetylide readily disproportionates to dilithium acetylide and acetylene on warming or in the presence of excess butyllithium. The formation of a small amount of dilithium acetylide accelerates the rate of disproportionation (see (Note 12)).[6]

12. Butyllithium must be added slowly to an excess of the efficiently stirred acetylene solution at −78°C. Localized warming of the solution or rapid introduction of butyllithium to produce a local excess of base must be avoided in order to prevent the formation of the unreactive and insoluble dilithium acetylide, which will be observed as a cloudy suspension. Reaction of ketones or aldehydes with a cloudy suspension of dilithium acetylide results in substantially lowered yields of the carbinol products.[6]

13. (−)-Fenchone was obtained from Fluka Chemical Corporation and was used without additional purification.

14. After the solution is warmed to room temperature, substantial amounts of acetylene and butane may remain in solution. The reaction must be quenched in an efficient fume hood, and the first 10–20 mL of hydrochloric acid solution should be added slowly.

15. The product displays the following physical and spectral data: $[\alpha]^{25}_{D}$ +20.4° ($CHCl_3$, *c* 9); IR (neat film/NaCl plates) cm^{-1}: 3490, 2110, 1460, 1060; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.93 (s, 3 H), 1.0–1.15 (m, 2 H), 1.11 (s, 3 H), 1.17 (s, 3 H), 1.20–1.95 (m, 5 H), 1.99 (OH), 2.53 (s, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 17.84, 21.54, 25.77, 27.08, 29.81, 40.95, 42.90, 48.40, 53.06, 74.86, 80.45, 85.61; MS (EI, –70 eV): *m/z* calcd. for $C_{12}H_{18}O$: 178.1357, *m/z* found: 178.1355. The

product is a 97:3 mixture of endo : exo addition products based on capillary GC analysis. (A Hewlett-Packard 5880 Capillary Gas Chromatograph equipped with Supelcowax-10 30-m capillary column, available from Supelco, Inc., was used.)

3. Discussion

A general procedure for the preparation and use of monolithium acetylide is described. Monolithium acetylide is a useful reagent for the preparation of a variety of propargyl alcohols and terminal acetylenes.[7] The formation of monolithium acetylide is often complicated by the production of dilithium acetylide.[8,9] The reagent may be formed in liquid ammonia, which serves to stabilize the monoanion. Other amines, such as ethylenediamine, may be similarly added as a complexing agent.[10] However, it is often desirable to prepare the more reactive amine-free acetylide species.[6,9] Dilithium acetylide is an insoluble salt in tetrahydrofuran and is generally unreactive toward ketones, aldehydes, and other electrophiles. The slow addition of a dilute, cooled solution of butyllithium is critical for the reproducible preparation of a cleaner lithium acetylide solution. Solutions of monolithium acetylide must be kept colder, near −78°C, to prevent disproportionation to dilithium acetylide and acetylene. If the solution is warmed to 0°C, irreversible formation of dilithium acetylide as the white insoluble precipitate occurs.

Lithium acetylide adds in high yield to a variety of ketones and aldehydes. (Table I). Typically 1.1–1.2 equiv of lithium acetylide is employed Sterically hindered ketones react in higher yield when 2.0 equiv of lithium acetylide is used. Optimum yields are obtained with a concentration of monolithium acetylide of approximately 0.5 *M*; higher concentrations approaching 1.0 *M*, usually result in slightly lowered yields.[6] In all cases the reactions are essentially complete upon warming to room temperature. This method allows for a rapid and convenient preparation of propargyl alcohols. The procedure seems to be generally applicable to a wide variety of ketones and aldehydes.

TABLE I

ADDITION OF MONOLITHIUM ACETYLIDE TO ALDEHYDES AND KETONES

R	Ketone RCOR'	R'	Yield (%)[a]
CH_3		CH_3	94
$CH_3(CH_2)_4$		H	98
CH_3		$(CH_2)_3CH_3$	92
$CH_3CH(CH_3)CH_2$		$CH_3CH(CH_3)CH_2$	75,86[b]
$CH_3CH_2CH(CH_3)$		$CH_3CH_2CH(CH_3)$	89
$(CH_3)_3C$		$(CH_3)_3C$	66,98[b]
$PhCH_2$		CH_3	94
Ph		CH_3	75
Ph		H	93

Ph		Ph	(85)
PhCH=CH		H	96
$(CH_3)_2C$=CH		CH_3	86(77)
	β-Ionone		93
	cyclo-$(CH_2)_4$		94
	cyclo-$(CH_2)_5$		95
	cyclo-$(CH_2)_6$		90(83)
	cyclo-$(CH_2)_7$		86
	Norcamphor		97(92)[c]
	Cyclohexanecarboxaldehyde		98

[a]By VPC based on RCOR'. Isolated yields are given in parentheses.

[b]100% excess monolithium acetylide was used.

[c]The product was >99% 2-ethynyl-*endo*-2-norbornanol by VPC and ^{13}C NMR examination.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

brine

sodium/benzophenone ketyl

Tetrahydrofuran, THF

(−)-Fenchone

sulfuric acid (7664-93-9)

acetylene (74-86-2)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ether (60-29-7)

nitrogen (7727-37-9)

mercury (7439-97-6)

Pentane (109-66-0)

magnesium sulfate (7487-88-9)

butane (106-97-8)

butyllithium (109-72-8)

Tetrahydrofuran, THF (109-99-9)

ethylenediamine (107-15-3)

Cyclohexanecarboxaldehyde (2043-61-0)

Norcamphor (497-38-1)

acetylide

β-Ionone

2,5-dimethoxybenzyl alcohol (33524-31-1)

Lithium acetylide, dilithium acetylide (6867-30-7)

monolithium acetylide

1-Methyl-2-ethynyl-endo-3,3-dimethyl-2-norbornanol (131062-94-7)

Bicyclo[2.2.1]heptan-2-ol, 2-ethynyl-1,3,3-trimethyl-, (1R-endo)

2-ethynyl-endo-2-norbornanol

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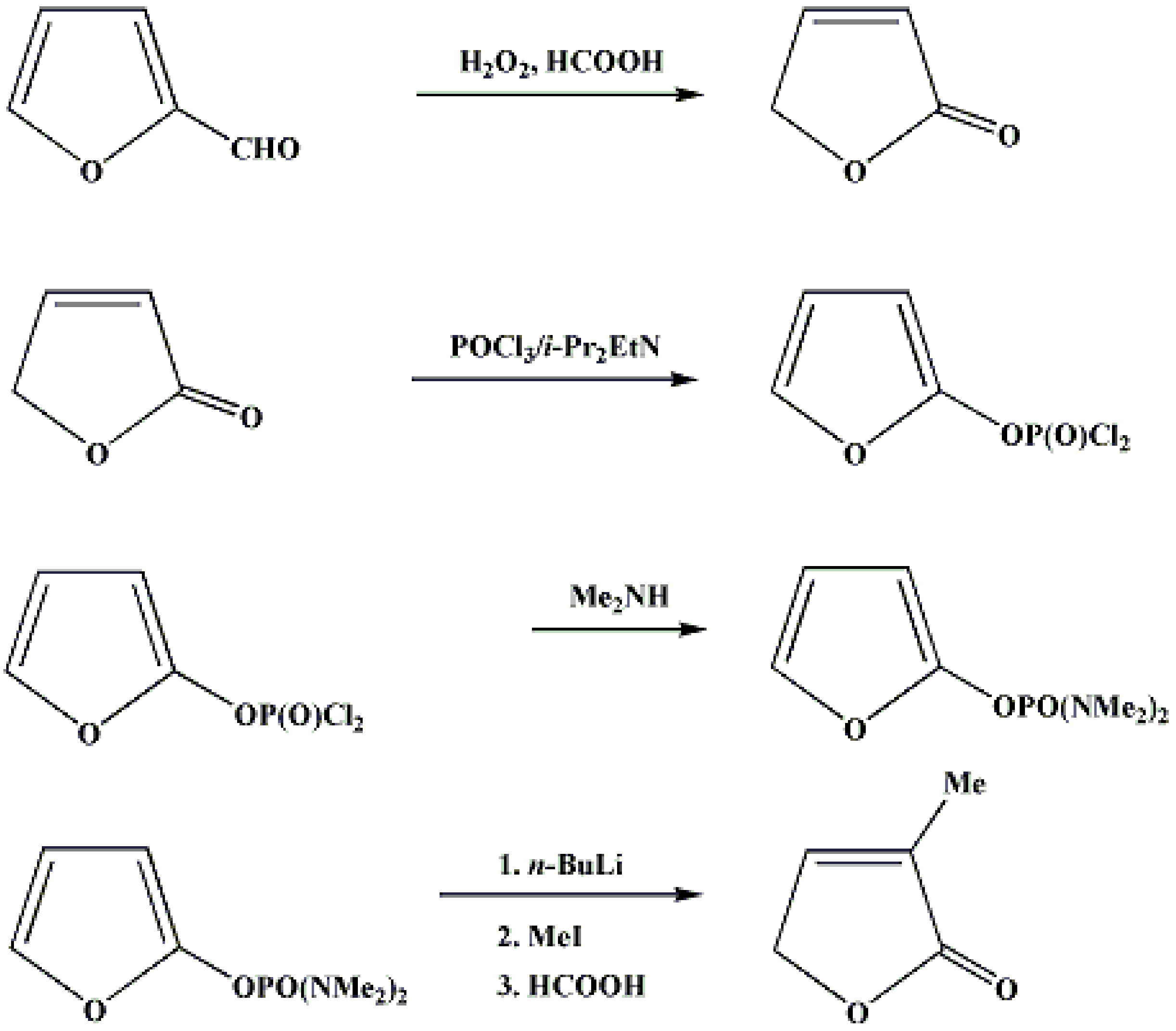
Organic Syntheses, CV 8, 396

3-METHYL-2(5*H*)-FURANONE

[2(5*H*)-Furanone, 3-methyl-]



Submitted by Jan H. Näsman[1]
Checked by Alan T. Johnson and James D. White.

1. Procedure

Caution! Hydrogen peroxide attacks the skin and may decompose violently. The first step should be carried out behind a safety screen, and the operator should wear safety glasses and rubber gloves. Air must not be admitted to the hot distillation residue in Step 2.

A. *2(5H)-Furanone.* A 6-L, three-necked, round-bottomed flask equipped with two condensers, a dropping funnel, and a 12 × 55-mm magnetic stirring bar is charged with 480 g (5 mol) of furfural (Note 1) and 2.0 L of methylene chloride. The addition of 200 g of sodium sulfate (Note 2) and 150 g of *N,N*-dimethylethanolamine (Note 3) in

one portion each is followed immediately by 460 g of formic acid (Note 4), carefully added in portions over a period of 2 min, after which 100 mL of 30% hydrogen peroxide (Note 5) is added in one portion. The mixture is stirred vigorously. After 5 min the mixture will reflux and another 800 mL of 30% hydrogen peroxide is added dropwise during 9 hr (Note 6) while stirring is continued. When the addition is complete, the mixture is vigorously stirred as long as it refluxes and then stirred gently overnight. The organic phase is separated, and the water phase is extracted with the 200 mL of methylene chloride that is used to wash out residues from the reaction flask.

The methylene chloride phase is washed with two 150-mL portions of saturated sodium disulfite solution (Note 7) and dried over magnesium sulfate and sodium sulfate. After a negative peroxide test (Note 8), the solvent is removed. The crude product (255 g) is fractionated through a 30-cm Vigreux column. The material boiling at 85–85°C (13 mm) is collected to give 210 g of butenolide, which is yellow because of some high-boiling residues. Redistillation through the 30-cm Vigreux column and collection of the material boiling at 100–102°C (30 mm), 95–97°C (19 mm), 89–91°C (16 mm), or 79–81°C (9 mm) gives colorless butenolide. In this way 170.2 g (41%) of pure butenolide is obtained.

B. *Furyl phosphorodichloridate.* A 1-L flask, protected from moisture by a calcium chloride tube, is charged with 42 g (0.5 mol) of 2(5*H*)-furanone, 85 g (0.55 mol) of phosphoryl chloride, and 100 mL of methylene chloride. A solution of 65 g (0.5 mol) of ethyldiisopropylamine in 60 mL of methylene chloride is added dropwise during 4 hr at ambient temperature (Note 9). The resulting mixture is stirred overnight (12 hr), after which 6.5 g of the amine in 10 mL of methylene chloride is added in one portion and stirring is continued for 20 hr (Note 10). The solvent is removed on a rotary evaporator and 200 mL of dry ether (Note 11) is added cautiously, followed by 100 mL of pentane (in that order), to the dark residue to precipitate the amine hydrochloride. The flask is stoppered and shaken for 1–2 min. The hydrochloride is filtered by suction and washed immediately with 100 mL of dry ether and 200 mL of pentane or petroleum ether (Note 12). The bottle is tightly stoppered and the filtrate is allowed to stand in the refrigerator (+4°C) overnight. The clear brown ethereal phase is decanted from a dark lower phase, and the solvent is evaporated. The residue (ca. 100 g) is distilled at the water pump. In order to obtain pure, color-stable, yellow dichloridate it is usually necessary to distill it twice. The first distillation is done rapidly, collecting the material that boils at 73–98°C (9 mm) to give 65–75 g of product, which usually darkens within a few days (Note 13) and (Note 14). Redistillation (Note 15), collecting the material that boils at 91–93°C (22 mm), 88–90°C (16 mm), or 73–76°C (9 mm), gives 60–65 g of pure product (Note 16). The yield is 60–65%.

C. *Furyl N,N,N',N'-tetramethyldiamidophosphate*. To 180 mL of dry diethyl ether, chilled to −30°C, is added 56.7 g (4.2 equiv) (1.26 mmol) of dimethylamine (Note 17). This solution is added—during 1–2 hr from a double-jacketed dropping funnel, protected from moisture by a calcium chloride tube and connected to a cryostat

regulated to –30°C—to a stirred mixture (Note 18) of 60 g (0.30 mol) of the freshly distilled furyl phosphorodichloridate and 250 mL of ether in a two-necked, 1-L flask equipped with a condenser, protected from moisture by a calcium chloride tube and connected to the cryostat. This flask is chilled in an ice bath during the addition of the first 2 equiv of the dimethylamine. After the addition of dimethylamine is complete, stirring is continued for 20 hr while the mixture is warmed on a water bath at 35°C. The hydrochloride that forms is carefully filtered off with suction and washed with two 70-mL portions of dry ether. The combined ether phases are evaporated to give ca. 65 g (99%) of crude product. Distillation, discarding a yellow forerun and collecting the fraction boiling at 149–152°C (20 mm) or 131–134°C (7 mm) (Note 19), affords 52–58 g (79–88%) of pure material (Note 20).

D. *3-Methyl-2(5H)-furanone.* To 10.9 g (50 mmol) of furyl tetramethyldiamidophosphate in 90 mL of tetrahydrofuran (THF) (Note 21), chilled to –75°C, is added 21.9 mL (55 mmol) of a 2.51 *M* hexane solution of butyllithium (Note 22) at a rate (6–10 min) such that the temperature reaches –60°C but does not exceed this level. The resulting mixture is chilled to –75°C for 10 min; then 8.9 g (63 mmol) of methyl iodide in 20 mL of tetrahydrofuran is added with a syringe during 7–8 min (Note 23) so that the temperature does not rise above –55°C. After the addition is complete, the temperature is raised to 0°C and the mixture is concentrated to ca. 40 mL. Water (30 mL) and ethyl acetate (50 mL) are added, the phases are separated, and the dark inorganic phase is extracted with two 50-mL portions of ethyl acetate. The combined, yellow organic phases are washed with brine and dried over magnesium sulfate. The solvent is evaporated to give 10.5 g of crude 2-(3-methylfuryl) tetramethyldiamidophosphate, which need not be purified for the next reaction (Note 24).

To the phosphate in a 250-mL flask on a water bath at 25°C (Note 25) is added 20 mL of 98–100% formic acid (Note 26), and the resulting mixture is stirred until bubbling has ceased (30–40 min). Benzene (50 mL) is added and most of the excess formic acid is removed on an evaporator. To the residue are added 50 mL of ethyl acetate and 30 mL of a sodium chloride–sodium carbonate solution (Note 27). The organic phase is washed twice with the latter solution (i.e., a total of 3 × 20 mL), the combined inorganic phases are extracted once with 50 mL of ethyl acetate, the combined organic phases are dried over magnesium sulfate, the solvent is removed, and the product is distilled to give 3.2 g (64%) of 3-methyl-2(5*H*)-furanone, bp 97–101°C (19 mm).

2. Notes

1. Practical-grade furfural from Fluka Chemical Corporation or Aldrich Chemical Company, Inc. was used without any purification. Very dark furfural can be used, but it foams at the beginning of the reaction and leads to lower yields.
2. Sodium sulfate is used to salt out the water phase; brine is not effective. The

yield without the sulfate is 5–10% lower.

3. *N,N*-Dimethylethanolamine (99% pure) was obtained from EGA CHEMIE or Aldrich Chemical Company, Inc. The role of the compound is to isomerize any 2(3*H*)-furanone formed.

4. Formic acid (98–100%), obtained from Merck & Company, Inc., was used.

5. "Perhydrol" (30%), obtained from Merck & Company, Inc., gave reproducible results without efforts to determine the activity of the peroxide. An excess is used.

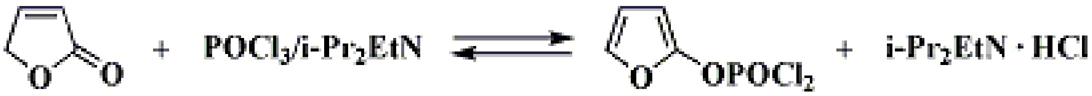
6. The process is a fine balance between oxidation and isomerization of the initially formed 2(3*H*)-furanone. Longer addition times produce better yields; however, the benefit is of marginal value.

7. Sodium disulfite, $Na_2S_2O_5$, from Merck & Company, Inc. was used. The saturated solution of disulfite should be the lower phase.

8. The mixture is tested for peroxide as follows. Prepare an approximately 1% solution of ferrous ammonium sulfate. Transfer 5 mL to each of two test tubes and add 0.5 mL of 0.5 *M* sulfuric acid and 0.5 mL of 0.1 *M* potassium thiocyanate solution to each tube. Add 5 mL of the methylene chloride solution to one of the test tubes and shake well. The aqueous phase in the methylene chloride tube should not develop a brown-red color when examined parallel to the blank.

9. Phosphoryl chloride from Fluka Chemical Corporation or Aldrich Chemical Company, Inc., and methylene chloride (purum) from Merck & Company, Inc., were used. Unless the contents of a freshly opened bottle were used, methylene chloride was distilled from phosphorus pentoxide (20 g/L) before use. The amine (Fluka or Aldrich) was distilled from and stored over potassium hydroxide. The best yields were obtained with once-recovered amine.

10. The reaction is reversible. In order to obtain pure (97–98%) dichloridate it is essential to add the 6.5 g of amine after the first equivalent has reacted.



11. Ordinary diethyl ether is stored over calcium chloride for 36 hr, filtered, and dried over sodium wire.

12. The use of more pentane or petroleum ether gave a product of better stability and purity.

13. Once-distilled product was usually not color-stable for prolonged periods.

14. The distillation flask is allowed to cool before air is passed into it. A vigorous polymerization may occur if air is passed into the hot residue, which may be safely discarded after the addition of acetone (an exothermic, but easily controlled reaction). Spectroscopic data for furyl phosphorodichloridate are as follows: ^{1}H NMR (60 MHz, $CDCl_3$, TMS) δ: 5.85 (m, 1 H, furan-*H*3), 6.30 (m, 1 H, furan-H4), 7.05 (m, 1 H, furan-H5); ^{13}C NMR ($CDCl_3$, TMS) δ: 92.5 ($^{3}J_{PC}$ = 7, furan-C3), 111.5 ($^{4}J_{PC}$ = 3, furan-C4), 137.1 ($^{4}J_{PC}$ = 3, furan-C5), 147.9

($^2J_{PC}$ = 12, furan-C2). MS *m / e* [relative intensity (rel. int.)]: 202 (16), 200 (26), 119 (4), 117 (6), 83 (100), 55 (31). M^+ 201.9160: calcd. 201.9167 for $C_4H_3Cl_2O_3P$; observed 199.9195. calcd. 199.9197. IR cm^{-1}: 1610 (s), 1300 (s), 980 (s), 890, 870. Anal. calcd. for $C_4H_3Cl_2O_3P$: C, 23.9, H, 1.5. Found: C, 23.8, H, 1.5.

15. Pure, pale-yellow dichloridate is stable for months without extensive change of color if stored in well-stoppered bottles in the refrigerator.

16. The purity of this product is 97–98%. It contains some butenolide; therefore an excess of dimethylamine is used in the subsequent step.

17. Dry dimethylamine from Fluka Chemical Corporation or MC and B Manufacturing Chemists was used as delivered.

18. A 12 × 55-mm heavy magnetic stirring bar is used for good stirring.

19. The monochloroamidate distills at 123°C (9 mm) and is identified in the ^1H NMR by its $^3J_{PH}$ = 13.5. *Distill slowly in the beginning!* The purity of the product is ≥99%. Redistill if a dark-yellow color develops; however, this color does not precluded successful lithiation.

20. The distilled diamide is a pale-yellow oil at room temperature; it freezes in the refrigerator (+4°C) if seeded within some hours. The first spontaneous crystalization took several weeks. It can also be obtained as snow-white crystals from diisopropyl ether/hexane, mp 15–16°C. Spectroscopic data for furyl tetramethyldiamidophosphate are as follows: ^1H NMR (400 MHz, $CDCl_3$ TMS) δ: 2.71 (d, 12 H, $^3J_{PH}$ = 10, two $N(CH_3)_2$), 5.62 (m, 1 H, furan-H3), 6.28 (m, 1 H, furan-H4), 6.95 (m, 1 H, furan-H5); ^{13}C NMR (15.03 MHz, $CDCl_3$, TMS) δ: 151.9 (d, $^2J_{PC}$ = furan-C2), 134.5 (s, furan-C5), 111.3 (s, furan-C4), 88.8 (d, $^3J_{PC}$ = 4, furan-C3), 36.6 (d, $^2J_{PC}$ = 4, $N(CH_3)_2$). Note that multiplicities s and d refer to C-P coupling. MS *m/e* (rel. int.): 218 (6), 136 (6), 135 (100), 127 (2), 111 (2), 92 (7), 90 (2), 83 (4), 69 (3). M^+ at 218.0822: calcd. 218.0820 for $C_8H_{12}N_2O_3P$; IR cm^{-1}: 2900, 2800, 1610, 1300, 990, 960.

21. Tetrahydrofuran (Merck) was distilled from sodium–benzophenone ketyl prior to use.

22. Butyllithium was obtained from Aldrich Chemical Company, Inc.; and methyl iodide, from Merck & Company, Inc. Butyllithium was titrated with phenanthroline as indicator prior to use according to the method of Watson and Eastham.[2] Fresh alkoxide-free butyllithium should be used to ensure pure product.

23. Methyl iodide should be added carefully in the beginning when the reaction mixture is mostly solid.

24. The phosphate can be crystallized from diisopropyl ether/hexane at −20°C in 80–85% yield; mp 42–44°C. Spectroscopic data for 2-(3-methylfuryl) tetramethyldiamidophosphate are as follows: ^1H NMR (400 MHz, $CDCl_3$, TMS) δ: 1.95 (dxt, 3 H, *J* = 0.4 and 2.2 CH_3), 2.73 (d, 12 H, $^3J_{PH}$ = 10.2, two $N(CH_3)_2$), 6.16 (dxdxq, 1 H, *J* = 0.4 and 2.2, furan-H4), 6.91 (dxdxq, 1 H, *J* = 0.4 and 2.2, furan-H5); ^{13}C NMR δ: 8.4 (sxq, CH_3), 36.6 (dsq, $^2J_{PC}$ = 4, $N(CH_3)_2$),

98.7 (dxs, $^3J_{PC}$ = 5, furan-C3), 113.8 (dxs, $^4J_{PC}$ = 2, furan-C4), 133.9 (dxd, $^4J_{PC}$ = 2 furan-C5), 147.8 (dxs, $^3J_{PC}$ = 8, furan-C2); multiplicities underlined in the ^{13}C spectrum refer to C-P coupling, the other to C-H coupling; MS *m*/*e* (rel. int.): 232 (7), 135 (100), 97 (3), 92 (5). M^+ at 232.0980: calcd. 232.0977 for $C_9H_{17}N_2O_3P$: Calcd. for $C_9H_{17}N_2O_3P$: C, 46.55, H, 7.33, N, 12.07. Found: C, 46.5, H, 7.6, N, 12.0.

25. The water bath can be removed after 5 min. The reaction is vigorous in the beginning, and chilling is necessary to avoid formation of dimethylformamide (DMF), which is formed at elevated temperatures.

26. Formic acid (98–100%), obtain from Merck & Company, Inc., was used.

27. *Warning: CO_2 evolution.* The sodium chloride–sodium carbonate solution was prepared from 185 g of sodium chloride and 110 g sodium carbonate dissolved in water to give a total volume of 1 L.

3. Discussion

The preparation of 2(5*H*)-furanone is the scaled-up and slightly modified procedure[3] based on the report of Badovskaya that furfural is oxidized with performic acid to give a mixture of furanones.[4] The preparation here is improved by the use of *N,N*-dimethylaminoethanol as a catalyst for the isomerization of 2(3*H*)-furanone to 2(5*H*)-furanone. The complex between this amino alcohol and formic acid does not enter the organic phase during workup, and the product is thus easily isolated simply by evaporation of the solvent.

The hitherto preferred method for preparation of the butenolide is that of Price and Judge,[5] which can be modified (by extraction of the bromolactone with methylene chloride and elimination of hydrogen bromide with triethylamine or preferably with diisopropylethylamine in toluene at 70°C) of give routinely 60% or greater overall yield on a 6-mol scale. However, the large amount of hydrogen bromide evolved is sometimes a nuisance, especially to inexperienced workers. The method reported here is fast and independent of scale (0.1–6 mol tried), the starting materials are cheap, and the product is easily isolated.

Substituted furfurals do not react at a synthetically useful rate when formic acid/ hydrogen peroxide is used. This suggests that the reaction takes place in the water phase and that substituted furfurals enter this phase only with difficulty.

The preparation of furyl phosphorodichloridate is based on a method for preparation of 2-chlorofuran (16% yield, Hormi, Näsman, unpublished). Later the preparation was extended to a general method to prepare furyl esters from carboxylic acid chlorides lacking α-hydrogens and alkyl furyl carbonates from primary (other than methyl) and secondary alkyl chloroformates.[6] Phosphoryl chloride was the only acid chloride except carbon analogs found to give a furyl ester by the amine-catalyzed reaction.

Regioselective β-metallation for π-excessive five-ring heterocycles is not a novel reaction.[7] Oxazoline[8 9 10 11] and pyridine[12] as well as carboxylate-[13] and carboxamide[14]-substituted heterocycles have been lithiated. From the point of synthetic utility thiophenes have been shown to be useful substrates after careful optimization of reaction conditions; furans have been of less utility.

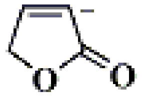
The generation of 2-(3-lithio)furyl tetramethyldiamidophosphate (≥95%) in tetrahydrofuran with a slight excess of butyllithium is a reliable procedure. The reagent usually forms a precipitate (active) when stored for prolonged times (3–12 hr) at –80°C and less than 35 mL of tetrahydrofuran/10 mmol of reagent is used.[7] The reagent darkens when warmed to –30°C. The reagent has been used on 100-mmol scales with no difficulties in methylation with methyl iodide. Methyl iodide is a very good electrophile for the reagent, whereas ethyl iodide does not react. Other good substrates for this unmodified reagent are ketones, aldehydes, and chloromethyl ethers. Alkylation is difficult unless strongly activated substrates are use. For example, benzyl chloride is unreactive, benzyl bromide reacts but not completely, and the corresponding iodide gives a complex mixture.

The reagent must be added to the electrophile when the leaving group is an alkoxide. For example, quenching with MeOD on larger scales yields products labelled also in the 5-position, whereas reverse addition with good stirring does not.

The furan products can be purified by flash chromatography[15] and should be used at once. A mixture of ethyl acetate and methylene chloride is a good solvent system for flash chromatography. Small residues of silica tend to partly decompose these furans within 2 weeks. The products are hygroscopic. Diisopropyl ether–diethyl ether–hexane is a useful solvent system for recrystallization of solid furans.

The formic acid reaction to convert furans to butenolides seems to be general, although heating may be necessary for acceptor-substituted furans; dimethylformamide (DMF) is then a byproduct.

In conclusion, furyl *N,N,N',N'*-tetramethylamidophosphate is the precursor to the d^3-synthon **1** for butenolide, which is difficult to generate by direct or other indirect methods;[16] however, [17] for a metal–halogen exchange reaction of 3- or 4-bromo-2-methoxy- or 2-trimethylsiloxyfurans.



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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

amine

benzophenone ketyl

brine

dimethylformamide (DMF)

butenolide

2-(3-methylfuryl) tetramethyldiamidophosphate

Perhydrol

bromolactone

2-(3-Lithio)furyl tetramethyldiamidophosphate

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrochloride (7647-01-0)

Benzene (71-43-2)

ethyl acetate (141-78-6)

ether, diethyl ether (60-29-7)

sodium chloride (7647-14-5)

hydrogen bromide (10035-10-6)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

formic acid (64-18-6)

acetone (67-64-1)

pyridine (110-86-1)

potassium hydroxide (1310-58-3)

toluene (108-88-3)

sodium (13966-32-0)

benzyl chloride (100-44-7)

hydrogen peroxide, peroxide (7722-84-1)

Methyl iodide (74-88-4)

potassium thiocyanate (333-20-0)

Furan (110-00-9)

Furfural (98-01-1)

Pentane (109-66-0)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

Ethyl iodide (75-03-6)

dimethylamine (124-40-3)

benzyl bromide (100-39-0)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

diisopropyl ether (108-20-3)

ferrous ammonium sulfate (10045-89-3)

dimethylformamide (68-12-2)

hexane (110-54-3)

oxazoline

triethylamine (121-44-8)

N,N-dimethylethanolamine, N,N-dimethylaminoethanol (108-01-0)

phenanthroline

2(5H)-Furanone (497-23-4)

phosphoryl chloride (10025-87-3)

diisopropylethylamine, ethyldiisopropylamine (7087-68-5)

phosphorus pentoxide (1314-56-3)

sodium disulfite

Furyl phosphorodichloridate (105262-70-2)

furyl tetramethyldiamidophosphate, Furyl N,N,N',N'-tetramethyldiamidophosphate, furyl N,N,N',N'-tetramethylamidophosphate (105262-58-6)

2-chlorofuran (3187-94-8)

2(3H)-Furanone

3-Methyl-2(5H)-furanone, 2(5H)-Furanone, 3-methyl- (22122-36-7)

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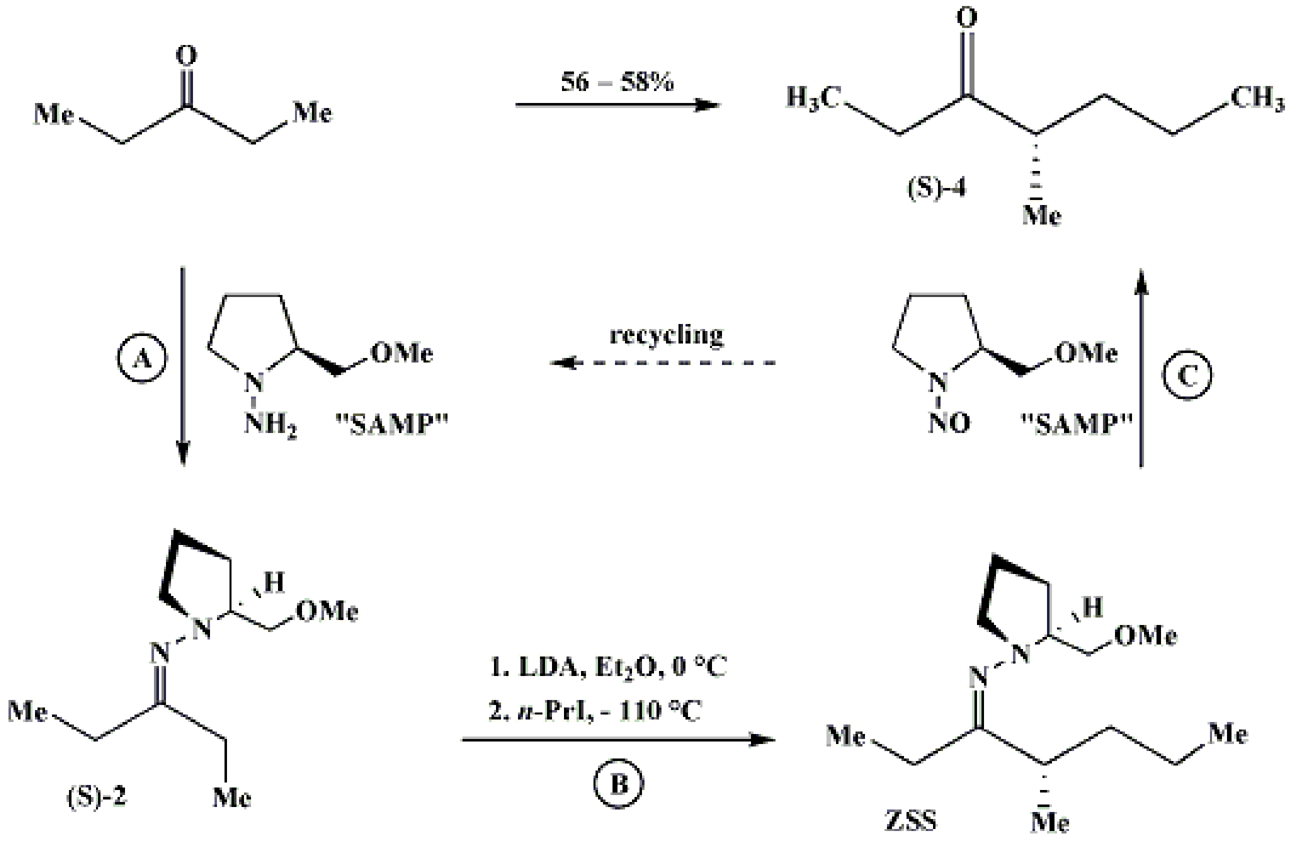
Organic Syntheses, CV 8, 403

ASYMMETRIC SYNTHESES USING THE SAMP-/RAMP-HYDRAZONE METHOD: (*S*)-(+)-4-METHYL-3-HEPTANONE

[3-Heptanone, 4-methyl, (*S*)-]



Submitted by Dieter Enders, Helmut Kipphardt, and Peter Fey[1].
Checked by Benjamin Guzmán, Stan S. Hall, and Gabriel Saucy.

1. Procedure

A. *3-Pentanone SAMP hydrazone [(S)-2]*. A 50-mL, one-necked, pear-snapped, flask equipped with a 10-cm Liebig condenser, a gas inlet tube, and a magnetic stirring bar is charged with 3.9 g (3.0 mmol) of SAMP (Note 1) and 3.79 mL (36 mmol) of 3-pentanone (Note 2) and the mixture is warmed at 60°C under argon overnight (Note 3). The crude product is diluted with 200 mL of ether in a 250-mL separatory funnel and washed with 30 mL of water. The organic layer is separated, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. Purification by short-path distillation yields 5.18 g (87%) of a colorless oil, bp 70–75°C at 0.5 mm, $[\alpha]_D^{20}$ +297° (benzene, *c* = 1). The SAMP-hydrazone (*S*)-**2** should be stored in a refrigerator under argon (Note 4).

B. *(S)-(+)-4-Methyl-3-heptanone SAMP hydrazone [(ZSS)-3]*. A flame-dried, one-necked 250-mL flask with side arm, rubber septum, and magnetic stirring bar is flushed with argon (Note 5). The flask is then cooled to 0°C and 110 mL of dry ether (Note 6) and 2.97 mL (21 mmol) of dry diisopropylamine (Note 7) are added, followed by dropwise addition of 21 mmol of butyllithium (13.1 mL of a 1.6 *N* solution in hexane (Note 8)). Stirring is continued for 10 min and a solution of

3.96 g (20 mmol) of SAMP-hydrazone (*S*)-**2** in 10 mL of ether is added to the stirred mixture over a 5-min period at 0°C. An additional 2 mL of ether is used to transfer all of the hydrazone (*S*)-**2** into the reaction flask. Stirring is continued for 4 hr at 0°C, while the lithiated hydrazone precipitates. The mixture is cooled to −110°C (pentane/liquid nitrogen bath) and kept for 15 min at this temperature. Then 2.15 mL (22 mmol) of propyl iodide (Note 9) is added dropwise, and the mixture is allowed to reach room temperature overnight. The contents of the flask are poured into a mixture of 300 mL of ether plus 50 mL of water in a 500-mL separatory funnel, the layers are separated, and the aqueous layer is extracted twice with 25 mL of ether. The combined organic layers are washed with 10 mL of water, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to yield 4.3 g (90%) of crude (*ZSS*)-**3** (Note 10).

C. *(S)-(+)-4-Methyl-3-heptanone [(S)-**4**]*. A 100-mL Schlenk tube, fitted with a gas inlet and Teflon stopcocks, is charged with 4.3 g (18 mmol) of crude (*ZSS*)-**3** dissolved in 50 mL of dichloromethane (Note 11), and cooled to −78°C (acetone/dry ice bath) under nitrogen. Dry ozone (Note 12) is passed through the yellow solution until a green-blue color appears (ca. 4 hr). The mixture is then allowed to come to room temperature while a stream of nitrogen is bubbled through the solution to give the yellow nitrosamine (*S*)-**5** (Note 13) and the title ketone (*S*)-**4**. The solvent is removed by distillation at 760 mm (60°C bath temperature) and the residue is transferred into a microdistillation apparatus (10-mL flask, 5-cm Vigreux column, spider, collector device, (Note 14)). After a small forerun (3–4 pale-yellow drops), a colorless liquid distills to afford 1.6–1.7 g (56–58% overall) of ketone (*S*)-**4**; bp 63–67°C at 40 mm (110–115°C bath temperature), GLC analysis 98.2%, $[\alpha]_D^{20}$ + 21.4° to + 21.7° (hexane, *c* = 2.2), $[\alpha]_D^{20}$ + 17.88° (neat) (Note 15). To recycle the chiral auxiliary SAMP, see (Note 16).

2. Notes

1. (*S*)-1-Amino-2-methoxymethylpyrrolidine (SAMP) and RAMP are commercially available from Merck-Schuchardt (Frankfurter Strasse 250, 6100 Darmstadt or Eduard-Buchner-Strasse 14-20, 8011 Hohenbrunn, Germany) and Aldrich Chemical Company, Inc., Milwaukee, Wisconsin. The submitters prepared SAMP from (*S*)-proline as described in *Org. Synth., Coll. Vol. VIII* **1993**, 26; the checkers used SAMP from Merck-Schuchardt.
2. Redistilled prior to use, 3-pentanone was obtained from Merck-Schuchardt (submitters) and Aldrich Chemical Company, Inc. (checkers).
3. The reaction was monitored by TLC. The TLC plates (SiO_2, F_{254}, 0.25 mm), commercially available from Merck, Darmstadt, Germany, were eluted with ether and developed by dipping into a 10% ethanolic solution of phosphomolybdic acid (Merck) and then heating.[2]
4. Partial ^1H NMR spectrum ($CDCl_3$, 200 MHz) δ: 1.06 (t, 3 H, *J* = 7.7, CH_3CH_2), 1.08 (t, 3 H, *J* = 7.5, CH_3CH_2), 3.34 (s, 3 H, CH_3O); IR (film) cm^{-1}: 1645.
5. This is done by alternately evacuating and filling the flask with argon 3 times. During the reaction a pressure of about 50 mm above atmospheric pressure is maintained using a mercury bubbler. All reagents are added via a glass syringe under rigorously anhydrous conditions. For a more detailed description of the metalation technique, see [3].
6. The submitters used ether that had been freshly distilled from sodium and benzophenone under an argon atmosphere. The checkers used anhydrous ether directly from freshly opened 500-g containers from Fisher Scientific Company, Springfield, NJ. In addition, the checkers charged the reaction flask with ether using a dry graduated cylinder, flushed the system with argon, and then sealed and cooled the vessel to 0°C before the sequential addition of

diisopropylamine and butyllithium.
7. Diisopropylamine from BASF AG, Ludwigshafen, Germany (submitters) and Aldrich Chemical Company, Inc. (checkers) was distilled from calcium hydride, and then stored under argon and over calcium hydride until use.
8. Butyllithium was purchased from Metallgesellschaft, Frankfurt, Germany, and titrated for active alkyllithium using diphenylacetic acid as an indicator.[4] The checkers used fresh butyllithium, 1.55 *M* in hexane under argon, from Aldrich Chemical Company, Inc. and omitted the titration.
9. Propyl iodide was obtained from Merck-Schuchardt, distilled over potassium carbonate, and stored over copper wire under argon. *Caution: Propyl iodide is a cancer suspect agent.* The checker's source was Aldrich Chemical Company, Inc.
10. Partial ^{1}H NMR spectrum ($CDCl_3$, 200 MHz) δ: 0.88 (t, 3 H, *J* = 6.9, CH_3CH_2), 1.02 (d, 3 H, *J* = 7.1, CH_3CH), 1.10 (t, 3 H, *J* = 7.5, CH_3CH_2), 3.33 (s, 3 H, CH_3O); IR (film) cm^{-1}: 1630. An ^{1}H-NMR experiment using the chiral shift reagent [$Eu(hfc)_3$, Aldrich] with crude **3** shows that only the (*ZSS*) isomer is present (sharp methoxy singlet). During the measurement a slow isomerization to the thermodynamically more stable (*ESS*) isomer takes place, but within the limit of detection of a 100-MHz spectrometer no (*SR*) diastereomer can be seen [diastereomeric excess (de) > 97%].[5 6]
11. Dichloromethane was distilled over potassium carbonate prior to use.
12. *Caution! Organic ozonides are highly explosive. The reaction should be carried out in a well-ventilated hood with a shatter-proof shield. Do not grease the ground-glass joints!* The submitters used a Fischer Model OZ II ozonizer from Fischer, Bad Godesberg, Germany. For detailed descriptions of a laboratory ozonizer see *Org. Synth., Coll. Vol. III,* **1955**, 673. The checkers used a Welsbach Model T-408 Laboratory Ozonizer, Welsbach Corp., Philadelphia, PA. The power setting was 100 V (AC) and the oxygen pressure setting was 8 psi 0.55 kg/cm^2) to produce 2–3% ozone at a gas flow rate (rotameter) of 2 L/min. The ozone production rate was measured by passing a measured amount of ozonized gas through a 2% potassium iodide solution (neutral), acidifying with 1 *M* sulfuric acid, and then titrating the liberated iodine with 0.1 *N* sodium thiosulfate. Using these conditions, the ozonolysis required at least 4 hr, rather than the 30 min suggested by the submitters.
13. *Caution! The nitrosamine (S)-**5** may be carcinogenic. All operations with (S)-**5** should be performed in a well-ventilated hood, and the operator should wear disposable gloves.* In order to destroy any nitrosamine traces, the glassware contaminated with (*S*)-**5** should be immersed in a bath of HBr/acetic acid.
14. To prevent any racemization during distillation, the apparatus is shaken with 1 mL of chlorotrimethylsilane (freshly distilled from calcium hydride), which is removed under reduced pressure. *Caution: Glassware, cleaned under alkaline conditions, will lead to spontaneous racemization!* The spider (three to four arms for liquid collection) should be cooled with an ice bath. To prevent bumping, the checkers performed the distillation with a Bunsen burner rather than with a bath.
15. The product has an optical purity of 97–98% by comparison with the reported optical rotation of $[\alpha]_D^{25}$ + 22.1 ± 0.4° (hexane, *c* = 1.0) of the naturally occurring pheromone[7] and an ee of ≥97% by comparison with the de of ≥97% of (*ZSS*)-**3** (Note 10); ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.90 (t, 3 H, *J* = 6.7, CH_3CH_2), 1.06 (d, 3 H, *J* = 6.9, CH_3CH) superimposed on 1.04 (t, 3 H, *J* = 7.2, CH_3CH_2), 2.45 (q, 2 H, *J* = 7.3, CH_2CH_3); IR (film) cm^{-1}: 1710.
16. The nitrosamine (*S*)-**5** (1.94 g, 67%) is obtained from the residue of the ketone distillation (bp 79–80°C/0.1 mm). Reduction with lithium aluminum hydride in tetrahydrofuran yields 1.47 g (49% overall) of SAMP[8 9] with an $[\alpha]_D^{20}$ −75.46° (neat).

3. Discussion

The title ketone (*S*)-**4**, which is 400 times more active than its enantiomer,[7,10] is the principal alarm pheromone of the leaf-cutting ant *Atta texana*. It has also been identified as an alarm pheromone in three other ant genera of the subfamily *Myrmicinae*,[7,11] as a component of the defensive secretion of the "daddy longlegs" *Leiobunum vittatum* (Opiliones),[12,13] and is produced by the elm bark beetles *Scolytus scolytus (F.)* and *S. multistriatus.*[14]

The ketone (*S*)-**4** and/or its enantiomer (*R*)-**4** have been prepared via resolution of an intermediate,[10] starting from (*R*)-citronellic acid,[15] by stoichiometric asymmetric synthesis[4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19] (76–88% ee), and by a microbiological method.[20]

The three-step procedure described here, using inexpensive, commercially available starting materials and the chiral auxiliary SAMP, illustrates the synthetic utility of the "SAMP-/RAMP-hydrazone method."[21,22,23,24,25] It is remarkable that the classical electrophilic substitution of a conformationally flexible, acyclic ketone **1** (*S*)-**4** occurs with virtually complete asymmetric induction. This demonstrates complete stereochemical control of the three critical operations: metalation, alkylation, and cleavage. Because deprotonated SAMP-/RAMP-hydrazones react with nearly the entire palette of electrophiles, this new methodology, a chiral version of the now widely used dimethylhydrazone (DMH) method,[3] opens an elegant and economical entry to a great variety of important classes of compounds with good overall chemical yields and excellent diastereo- and enantioselectivities. The following stereoselective reactions may be mentioned: α-alkylations or aldehydes[8,26] and ketones;[5,6,8,13] diastereo- and enantioselective aldol reactions;[9,27,28] diastereo- and enantioselective Michael additions to form β,γ-substituted δ-keto esters,[29,30] δ-lactones,[31] and various heterocycles, such as dihydropyridines, octahydroquinolinediones and hexahydroquinolinones;[32,33] α-alkylations of β-keto esters;[21,22,23,24,25] and, finally, asymmetric syntheses of α- and/or β-substituted primary amines[23,24] via alkylation–reductive amination of aldehydes and ketones[34] or nucleophilic addition to aldehyde-SAMP-/RAMP-hydrazones, followed by N-N bond cleavage.[35] This broad applicability is summarized in f.htmigure 1, and typical examples are listed in Table I.

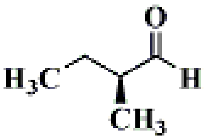
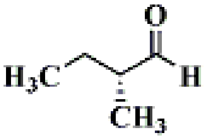
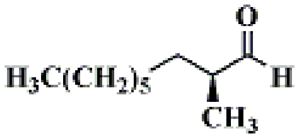
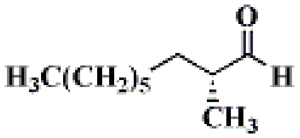
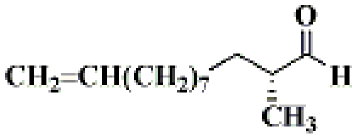
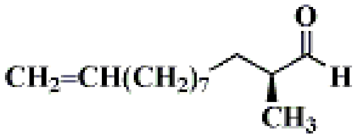
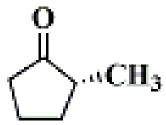
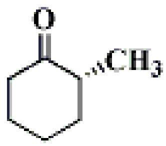
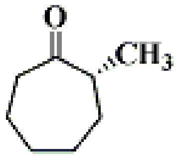
Figure 1. Optically active carbonyl compounds and amines.

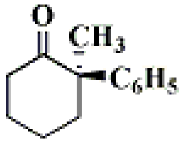
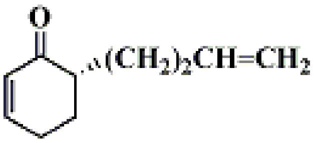
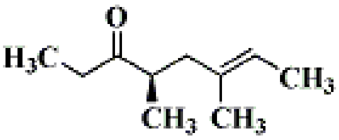
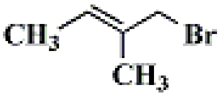
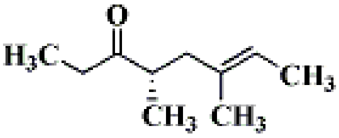
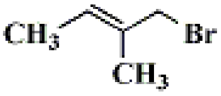
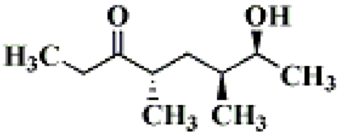
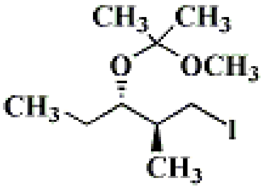
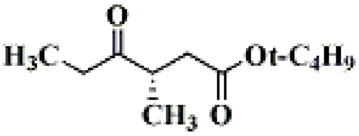
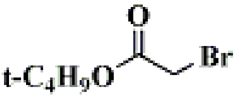
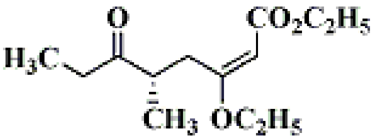
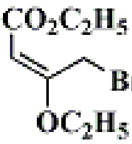
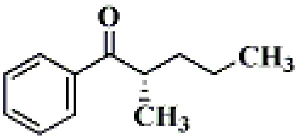
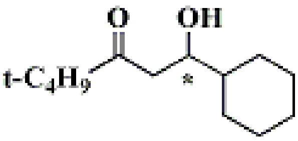
Figure 1. Optically active carbonyl compounds and amines.

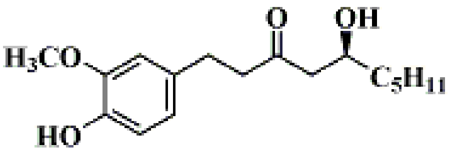
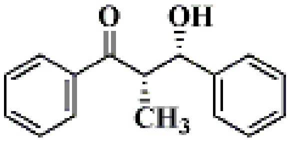
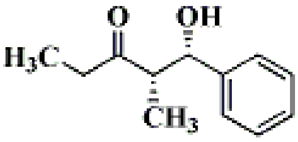
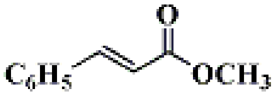
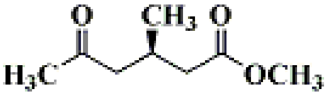
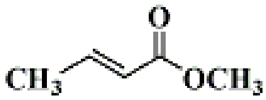
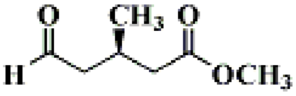
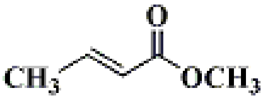
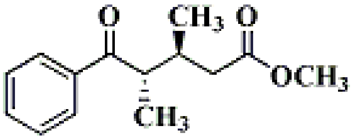
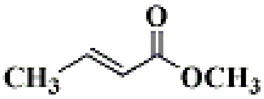
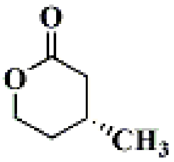
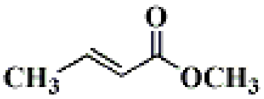
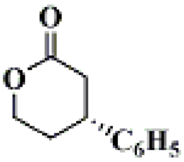
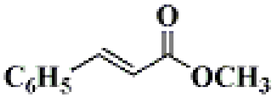
TABLE I

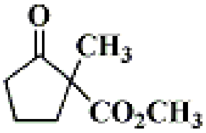
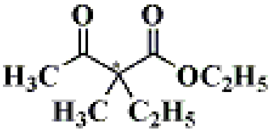
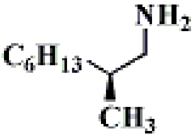
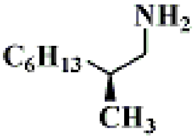
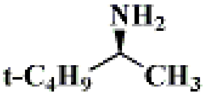
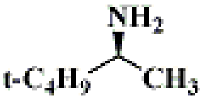
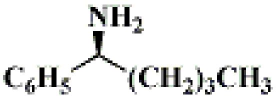
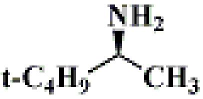
OPTICALLY ACTIVE CARBONYL COMPOUNDS AND AMINES PREPARED BY ASYMMETRIC SYNTHESIS USING THE SAMP/RAMP HYDRAZONE METHOD

Carbonyl Compound Amine	Electrophile	Cleavage[a]	Yield[b] [%]	ee[%] (Config.)	Lit.

	C_2H_5I	B	71	95 (S)	8,21
	CH_3I	A	65	95 (R)	8,21
	$C_6H_{13}I$	A	52	≥95 (S)	8,21
	CH_3I	A	61	95 (R)	8,21
	$(CH_3)_2SO_4$	B	65	95 (R)	21,36
	$(CH_3)_2SO_4$	B	51	95(S)[c]	21,36
	$(CH_3)_2SO_4$	A	66	86 (R)	8
	CH_3I	A	74	45 (R)	8
	$(CH_3)_2SO_4$	A	70	99 (R)	8
	CH_3I	A	70	67 (R)	8
	CH_3I	B	59	94 (R)	8

	CH_3I	C	43	93 (R)	21,23
	$H_2C{=}CH(CH_2)_2Br$	B	26	≥89 (R)	21,37
		B	61	≥97 (S)	13
		B	62	≥97 (R)[c]	13
		B	46	99 (S)	38
		A	53	>95 (S)	21,23
		A	80	≥95 (S)	21,23
	C_2H_5I	B	44	≥97 (S)	6
	c-$C_6H_{11}CHO$	D	32	62 (-) 100 (-)[e]	27

	$C_5H_{11}CHO$	E	75	39 (S)[c]	9
	C_6H_5CHO	A A	86 35	72 (SS) [de=67% (SS)] de=ee= 100 (SS)[f]	28
	C_6H_5CHO	A A	81 37	74 (SS) [de=66% (SS)] de=ee= 100 (SS)[f]	28
		A	62	≥99 (R)	29
		A	45	≥96 (R)	29
		A	46	≥95 (R)	31
		A	39	≥98 (SS) [de 100% (SS)]	30
		A	35[g]	≥95 (R)	31
		A	30[g]	≥95 (R)	31

	CH_3I	A	65	60 (-)	21,23
	C_2H_5I	A	52	27(+)	21,23
	CH_3I	h	56	>90 (R)	34
	$C_6H_{13}Br$	h	63	>95 (S)	34
		i	60	90 (S)	23,24
		j	47	88 (R)	23,24
		k	56	85 (R)	35
		l	41	87 (R)	35

[a](A) Oxidative cleavage by ozonolysis (O_3, CH_2Cl_2, −78°C). (B) Acidic hydrolysis [(i) excess MeI, 60°C; (ii) 5 *N* HCl/pentane]. (C) Acidic hydrolysis (12 *N* HCl/ether). (D) Oxidative cleavage ($^1O_2$, Me_2S, hydrolysis). (E) Oxidative cleavage (30% H_2O_2, MeOH, pH 7 buffer).

[b]Overall chemical yield.

[c]RAMP was used as chiral auxiliary.

[d]Diastereomeric excess of corresponding SAMP-hydrazone.

[e]After two recrystallizations of the ketol.

[f]After separation and cleavage of the corresponding crystalline SAMP-hydrazone.

[g]Overall yield, including reduction of the intermediate β-substituted aldehyde esters and lactonization.

[h]The primary amines are obtained by catechol–borane reduction of the SAMP-hydrazones, followed by N-N bond cleavage with Raney nickel.

[i]Obtained by $LiAlH_4$ reduction of 3,3-dimethyl-2-butanone-SAMP-hydrazone, followed by N-N bond cleavage.

[j]Obtained by catechol–borane reduction of 3,3-dimethyl-2-butanone-SAMP-hydrazone, followed by N-N bond cleavage.

[k]Obtained by addition of butyllithium to benzaldehyde-SAMP-hydrazone, followed by N-N bond cleavage.

[l]Obtained by addition of methyllithium to 2,2-dimethylpropanal-SAMP-hydrazone, followed by N-N bond cleavage.

In S_E2' front-type electrophilic substitutions via SAMP-/RAMP-hydrazones the less substituted α-carbon atom is regioselectively deprotonated. Under the standard reaction conditions (lithium diisopropylamide, 0°C, ether or THF) the intermediate aza enolates are formed as the $E_{CC}Z_{CN}$ species, as confirmed by spectroscopic[26,39 40] and numerous trapping experiments.[21,22,23] Because of the uniform diastereoface differentiation common for all asymmetric SAMP-/RAMP-hydrazone alkylations, the absolute configuration that will predominate in the final product can be predicted reliably. Furthermore, instead of changing from SAMP to the enantomeric RAMP as chiral auxiliary, it is possible to prepare both enantiomers of target molecules in excess using SAMP, simply by changing the building blocks used as nucleophile and electrophile. This opposite enantioselectivity through synthon control is demonstrated in the cases of 2-methylbutanal, 2-methyloctanal, and 2-methyl-1-octanamine (see Table I).

Another advantage of SAMP-/RAMP-hydrazones is the facile determination of the asymmetric induction by downfield shifting of the SAMP- or RAMP-hydrazone methoxy singlet [LIS-technique, $Eu(fod)_3$].

Besides the oxidative cleavage by ozonolysis, the optically active carbonyl compounds can be alternatively obtained by acidic hydrolysis of the corresponding SAMP-/RAMP-hydrazone methiodides in a two-phase system.[6,8]

The chiral auxiliary SAMP or RAMP may be recycled by lithium aluminum hydride reduction of the nitrosamine (*S*)-**5** formed during ozonolysis. Other very successful applications of the SAMP-/RAMP-hydrazone method in natural product synthesis have recently been reported by Nicolaou et al. [ionophore antibiotic X-14547A (indanomycine)][41 42], Pennanen (eremophilenolide, sesquiterpene),[37] Enders et al. (defensive substance of "daddy longlegs"),[13] Mori et al. (serricornin, cigarette beetle pheromone),[38] and Bestmann et al. (pheromone analogs).[36] Finally, it should be mentioned that the chiral auxiliaries SAMP and RAMP may also be used in the resolution of aldehydes[43] and ketones[44] and in the NMR spectroscopic determination of percent enantiomeric excess ee of chiral aldehydes.[45]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 26

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

SAMP-hydrazone (S)-2

3,3-dimethyl-2-butanone-SAMP-hydrazone

benzaldehyde-SAMP-hydrazone

2,2-dimethylpropanal-SAMP-hydrazone

3-Pentanone SAMP hydrazone

(S)-(+)-4-Methyl-3-heptanone SAMP hydrazone

SAMP

RAMP

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

HCl (7647-01-0)

Benzene (71-43-2)

ether (60-29-7)

oxygen (7782-44-7)

potassium iodide (7681-11-0)

sodium thiosulfate (7772-98-7)

nitrogen (7727-37-9)

copper (7440-50-8)

Raney nickel (7440-02-0)

iodine (7553-56-2)

Benzophenone (119-61-9)

sodium (13966-32-0)

Catechol (120-80-9)

Diphenylacetic acid (117-34-0)

Pentane (109-66-0)

dichloromethane (75-09-2)

ozone (10028-15-6)

magnesium sulfate (7487-88-9)

borane (7440-42-8)

butyllithium (109-72-8)

(S)-proline (147-85-3)

Tetrahydrofuran (109-99-9)

3-pentanone (96-22-0)

lithium aluminum hydride, $LiAlH_4$ (16853-85-3)

hexane (110-54-3)

Methyllithium (917-54-4)

nitrosamine (35576-91-1)

calcium hydride (7789-78-8)

argon (7440-37-1)

phosphomolybdic acid (51429-74-4)

lithium diisopropylamide (4111-54-0)

diisopropylamine (108-18-9)

CHLOROTRIMETHYLSILANE (75-77-4)

Propyl iodide (107-08-4)

(S)-1-Amino-2-methoxymethylpyrrolidine (72748-99-3)

2-methylbutanal (96-17-3)

2-methyloctanal (7786-29-0)

2-methyl-1-octanamine

(S)-(+)-4-Methyl-3-heptanone, 3-Heptanone, 4-methyl, (S)- (51532-30-0)

(R)-citronellic acid (18951-85-4)

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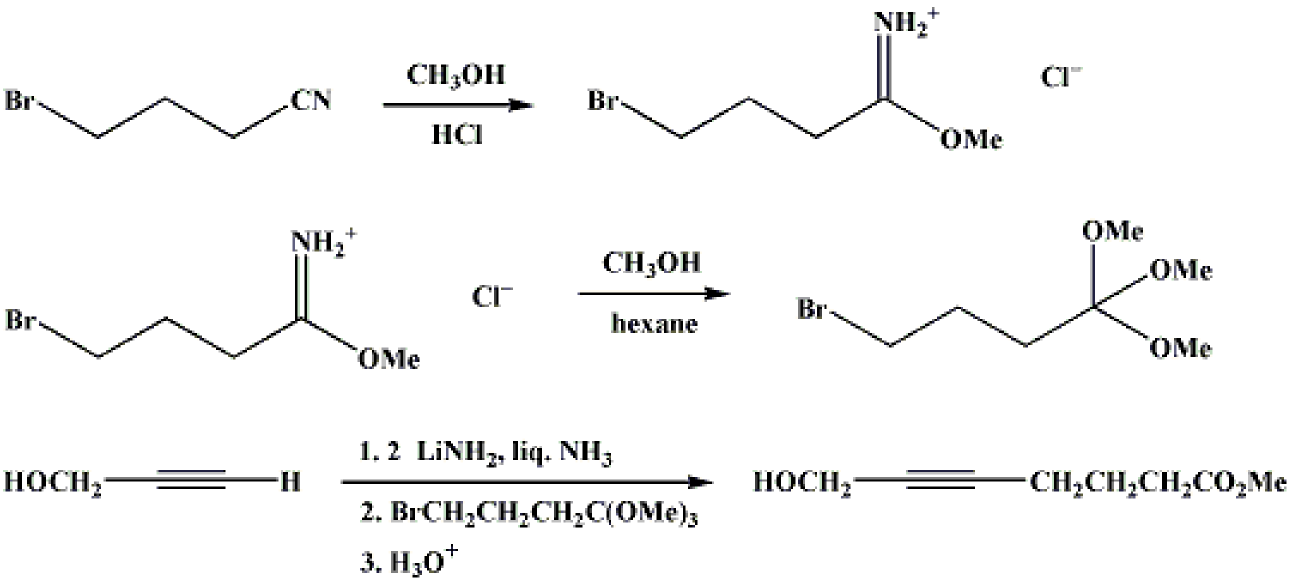
Organic Syntheses, *CV 8, 415*

METHYL 7-HYDROXYHEPT-5-YNOATE

[5-Heptynoic acid, 7-hydroxy-, methyl ester]



Submitted by Guy Casy[1], John W. Patterson[2], and Richard J. K. Taylor[1].
Checked by Friedhelm Balkenhohl and E. Winterfeldt.

1. Procedure

A. *Methyl 4-bromo-l-butanimidate hydrochloride.* A 500-mL, three-necked, round-bottomed flask is connected via neck A to a hydrogen chloride water trap using the arrangement shown in f.htmigure 1. A stream of nitrogen (Note 1) is introduced via neck C; the flask is flame-dried and allowed to cool. The stopper is removed from neck B and the flask is charged with 29.6 g (0.20 mol) of 4-bromobutanenitrile (Note 2), 200 mL of dry ether (Note 3) and 7.7 g (0.24 mol; 1.2 equiv based on 1.0 equiv of 4-bromobutanenitrile) of dry methanol (Note 3). The stopper is replaced, and the weight of the flask and its contents are recorded. The flask and its contents are cooled to −5°C by immersion in an ice–salt bath, the nitrogen source is removed, and the gas inlet tube is connected to the cylinder of hydrogen chloride. The cylinder tap is cautiously opened, and hydrogen chloride is allowed to bubble through the reaction mixture at a steady but controlled rate until 18.2 g (0.50 mol; 2.5 equiv based on 1.0 equiv of 4-bromobutanenitrile) has been absorbed (Note 4). A stopper is placed in each neck of the flask and a strip of Parafilm is bound around the edge of each ground-glass connection to ensure an airtight seal.

Figure 1

Figure 1

The flask is stored at 5°C (refrigerator) for between 48 hr and 5 days (Note 5), after which time a copious precipitate of the title compound is obtained. The mixture is filtered with suction through a dry 100-mm sintered-glass funnel. After all of the product is collected, a large inverted funnel connected to a nitrogen source is positioned about 15 cm above the sintered funnel to provide a blanket of dry, inert gas (Note 6). The product is washed thoroughly with several portions of dry ether, totaling 500 mL, and then dried to constant weight over solid potassium hydroxide in a

desiccator evacuated at 12–20 mm (water aspirator). There is obtained 39.0 g (90%) (Note 7) of methyl 4-bromo-1-butanimidate hydrochloride as fine white crystals, mp 95–97°C (Note 8).

B. *Trimethyl ortho-4-bromobutanoate.* A 1-L, two-necked, round-bottomed flask containing an efficient magnetic stirring bar is purged with nitrogen (Note 1) introduced via a pressure-equalizing glass bubbler (Note 9). The flask is charged with 38.9 g (0.18 mol) of methyl 4-bromo-1-butanimidate hydrochloride, 450 mL of dry hexane (Note 3), and 17.3 g (0.54 mol) of dry methanol (Note 3). A stopper is placed in one neck of the flask; the glass bubbler is removed from the other neck and immediately replaced with a gas outlet adapter to which is attached a balloon filled with nitrogen (Note 10). Finally, a strip of Parafilm is bound around the edge of each ground-glass connection to ensure an airtight seal. The reaction mixture is stirred at room temperature for 48 hr, then filtered with suction to remove the precipitated ammonium chloride. The filter cake is washed with two 30-mL portions of dry hexane, and the filtrate and washings are concentrated under reduced pressure (water aspirator) at 30–40°C by rotary evaporation to leave a slightly turbid, colorless liquid, to which is added 0.25 g of anhydrous potassium carbonate. This material is distilled under reduced pressure to afford 36.4–36.7 g (89–90%) (Note 11) of trimethyl *ortho*-4-bromobutanoate as a colorless oil, bp 65°C (0.5 mm) (Note 12).

C. *Methyl 7-hydroxyhept-5-ynoate.* A 2-L, three-necked, round-bottomed flask equipped with a dry-ice condenser and a mechanical stirring rod is charged with 750 mL of anhydrous ammonia, via a gas inlet tube, at −33°C (Note 13) under nitrogen (Note 1) and (Note 14). The gas inlet tube is removed, and about 0.1 g of lithium wire (Note 2) is added in small portions until a permanent blue color is obtained. Ferric nitrate (0.1 g) is added to discharge the blue color, and after the solution is stirred for 5 min, 4.24 g (0.611 mol; 2.5 equiv based on 1.0 equiv of propargyl alcohol) of lithium wire is added in small portions. After the addition is complete, the flask is fitted with a 100-mL pressure-equalizing, serum-capped dropping funnel. Stirring is continued for 20 min to obtain a gray suspension of lithium amide, to which is added slowly and dropwise a solution of 13.7 g (0.245 mol; 1.5 equiv based on 1.0 equiv of trimethyl *ortho*-4-bromobutanoate) of redistilled propargyl alcohol (Note 2) in 15 mL of dry ether (Note 3). After the solution is stirred for 20 min, a solution of 36.4 g (0.160 mol) of trimethyl *ortho*-4-bromobutanoate in 40 mL of dry ether is added dropwise. Stirring is continued for 3 hr, the reaction vessel is opened to the atmosphere, and its contents are allowed to warm to room temperature over 16–18 hr. The mixture is heated at 50°C on a water bath under a stream of nitrogen to remove any remaining ammonia. This furnishes a gray solid, which is cooled to 0°C, and 5% sulfuric acid is added in 100-mL portions until a pH of 1 is obtained (Note 15). The resulting suspension is stirred at room temperature for 30 min, and extracted with three 200-mL portions of ether. The combined organic extracts are washed with 200 mL of saturated sodium bicarbonate, dried over magnesium sulfate, and filtered. The filtrate is concentrated under reduced pressure (water aspirator) at 30–40°C by rotary evaporation, to leave 19.1 g (77%) of an essentially pure amber oil (Note 16). This material can be distilled under reduced pressure to afford 16.8 g (67%) (Note 17) of methyl 7-hydroxyhept-5-ynoate as a colorless oil, bp 100°C (0.05 mm) (Note 18) and (Note 19).

2. Notes

1. Oxygen-free nitrogen, dried by passage through activated molecular sieves, was used.
2. 4-Bromobutanenitrile was obtained from Lancaster Synthesis Ltd. Alternatively it can be prepared from 1,3-dibromopropane and potassium cyanide using the procedure of Derrick and Henry.[3] Lithium wire (3.2-mm diameter, containing ca. 0.01% sodium) and propargyl alcohol were obtained from the Aldrich Chemical Company, Inc. The latter was dried with potassium carbonate and then distilled prior to use.

3. Diethyl ether and hexane were freshly distilled from blue solutions obtained with sodium and benzophenone. Methanol was distilled from magnesium and iodine. The use of high-purity solvents (e.g., Mallinckrodt AR anhydrous ether, Nanograde hexane, and AR methanol) as received gave only small reductions in yield.
4. To monitor uptake of hydrogen chloride, the flask and its contents are periodically weighed. Typically, the process is complete within 5 min.
5. The progress of the reaction can be monitored by tilting the flask slightly to expose clear supernatant liquor. The flask is left in this position overnight, and if no further crystallization is apparent, the product may be isolated.
6. Alternatively, a dry-nitrogen glove box can be employed.
7. In several smaller-scale experiments (0.07–0.14 mol of 4-bromobutanenitrile) yields in the range 83–93% were achieved.
8. The product has the following spectroscopic properties: IR (Nujol) cm^{-1}: 1650, 1405, 1215, 875; ^{1}H NMR (TFA-d) δ: 2.08–2.64 (m, 2 H), 3.04 (t, 2 H, *J* = 7), 3.48 (t, 2 H, *J* = 6), 4.32 (s, 3 H), 9.52 (br s, 2 H); ^{13}C NMR (TFA-d) δ: 28.53, 30.82, 33.41, 60.77, 183.65.
9. The glassware was dried overnight at 150°C and assembled hot under nitrogen.
10. This arrangement is preferable to a continuous flow of nitrogen; otherwise the quantity of methanol in situ may be critically diminished.
11. In several smaller-scale experiments (0.05–0.12 mol of methyl 4-bromo-1-butanimidate hydrochloride) yields in the range 90–93% were achieved.
12. The product has the following spectroscopic properties: IR (neat) cm^{-1}: 2840, 1740, 1070; ^{1}H NMR ($CDCl_3$) δ: 1.77–2.03 (m, 4 H), 3.23 (s, 9 H), 3.33–3.60 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ: 26.54, 29.00, 33.87, 49.37, 115.31. This compound is now commercially available from Aldrich Chemical Company, Inc.
13. To minimize evaporation of liquid ammonia, a temperature of −33 ± 5°C was maintained until the workup by means of a Cryocool™–acetone cooling bath. (A dry ice–acetone cooling bath will suffice.) In addition, the dry-ice condenser was continually charged with a saturated dry ice–acetone mixture.
14. The apparatus is maintained under a slight positive nitrogen pressure until the workup. If this precaution is not taken, atmospheric moisture is drawn into the apparatus (see (Note 19).
15. A total volume of 500–600 mL of 5% sulfuric acid is normally required.
16. This material is essentially pure as indicated by TLC and ^{1}H NMR spectroscopic analyses, and by CH microanalysis. (Anal. calcd. for $C_8H_{12}O_3$: C, 61.5; H, 7.7. Found: C, 61.8; H, 7.9.)
17. On a smaller scale (0.109 mol of trimethyl *ortho*-4-bromobutanoate) in which a magnetic stirring bar was used to agitate the reaction mixture, a distilled yield of 71% (81% before distillation) was achieved.
18. The submitters report bp 120°C (0.06 mm). The product has the following spectroscopic properties: IR (neat) cm^{-1}: 3420, 1735, 1015; ^{1}H NMR ($CDCl_3$) δ: 1.63–2.63 (m, 6 H), 3.24 (s, 1 H), 3.67 (s, 3 H), 4.12–4.30 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ: 18.02, 23.54, 32.64, 50.73, 51.43, 79.32, 84.31, 173.60.
19. If moisture is drawn into the apparatus, this can diminish the quantity of the dilithio derivative of propargyl alcohol. If any *O*-lithio monoanion is present during the addition of trimethyl *ortho*-4-bromobutanoate, a quantity of the *O*-alkylated derivative, methyl 4-(2-propynyloxy)butanoate will be produced. The latter exhibits the following ^{1}H NMR ($CDCl_3$) spectrum: δ: 1.61–2.58 (m, 5 H), 3.52 (t, 2 H, *J* = 5.5), 3.65 (s, 3 H), 4.09 (d, 2 H, *J* = 2.5).

3. Discussion

Methyl 7-hydroxyhept-5-ynoate is an important precursor to alkylating agents that are used to

introduce the complete prostaglandin α-side chain.[4,5] It is normally prepared from propargyl alcohol using a six-step sequence originally introduced by Corey and Sachdev[6] with subsequent modifications.[7,8,9,10,11] Alternative routes to methyl 7-hydroxyhept-5-ynoate have also been reported[12,13] but appear less efficient than the one described here. The present route arose from the observation that whereas alkylations of propargyl alcohol-derived anions with 4-halobutanoates were unsuccessful,[13,14] the use of trimethyl ortho-4-bromobutanoate gave efficient alkylation.[4] Related reactions using ortho-ester protecting groups have been reported recently[15] and the preparation of such compounds from nitriles using the Pinner reaction, as described herein, is well established.[16] Trimethyl *ortho*-4-bromobutanoate is also the precursor to the useful four-carbon homologating reagent, trimethyl 4-lithioorthobutanoate.[17]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Trimethyl ortho-4-bromobutanoate

O-lithio monoanion

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

hydrogen chloride (7647-01-0)

ammonia (7664-41-7)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

sodium bicarbonate (144-55-8)

magnesium (7439-95-4)

1,3-dibromopropane (109-64-8)

nitrogen (7727-37-9)

potassium cyanide (151-50-8)

iodine (7553-56-2)

potassium hydroxide (1310-58-3)

Benzophenone (119-61-9)

sodium (13966-32-0)

lithium (7439-93-2)

magnesium sulfate (7487-88-9)

ferric nitrate

4-bromobutanenitrile (5332-06-9)

lithium amide (7782-89-0)

hexane (110-54-3)

propargyl alcohol (107-19-7)

Methyl 7-hydroxyhept-5-ynoate, 5-Heptynoic acid, 7-hydroxy-, methyl ester (50781-91-4)

Methyl 4-bromo-1-butanimidate hydrochloride, Methyl 4-bromo-l-butanimidate hydrochloride (21367-90-8)

methyl 4-(2-propynyloxy)butanoate

trimethyl 4-lithioorthobutanoate

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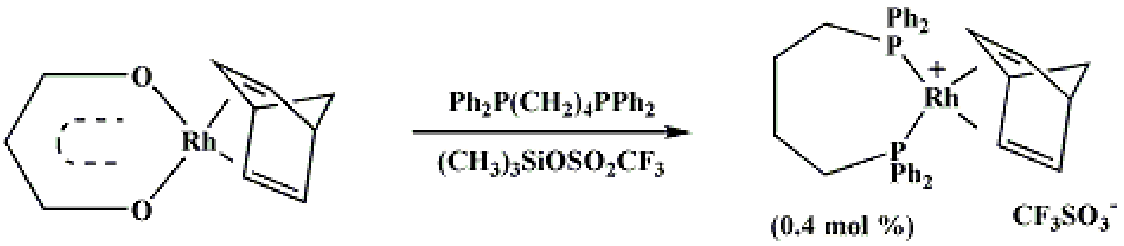
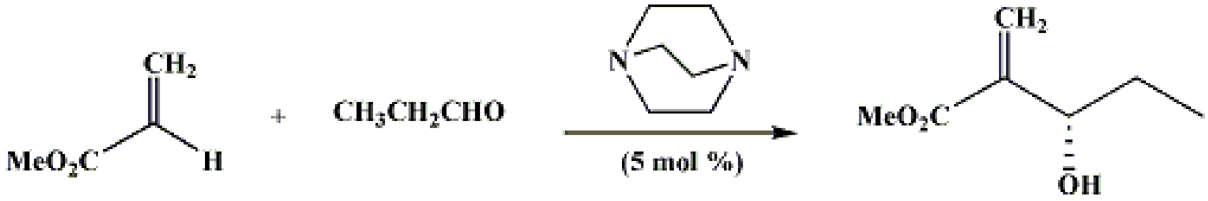
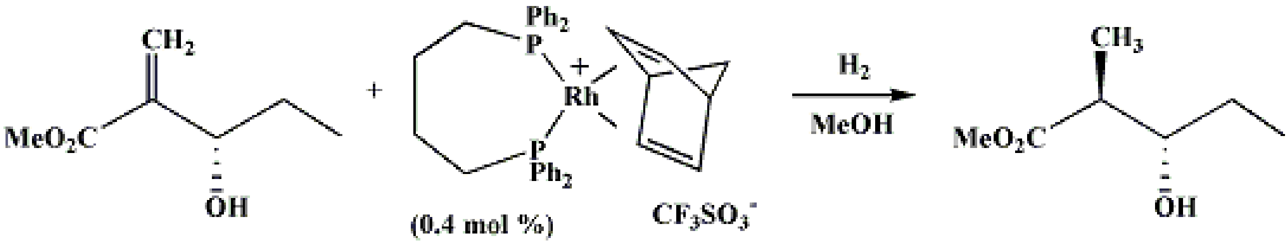
Organic Syntheses, CV 8, 420

DIRECTED HOMOGENEOUS HYDROGENATION: METHYL *anti*-3-HYDROXY-2-METHYLPENTANOATE

[Pentanoic acid, 3-hydroxy-2-methyl-, methyl ester, (*R**, *R**)-(±)-]







Submitted by John M. Brown, Phillip L. Evans, and Alun P. James[1].
Checked by Ulrike Eggert, H. M. R. Hoffmann, and Ekkehard Winterfeldt.

1. Procedure

A. *Bicyclo[2.2.1]hepta-2,5-diene 1,4-bis(diphenylphosphino)butanerhodium trifluoromethanesulfonate* **1.** A 250-mL, two necked, round-bottomed flask, equipped with a septum, two-way stopcock used as a gas inlet and outlet, and a magnetic stirrer, is charged with a solution of bicyclo[2.2.1]hepta-2,5-diene-2,4-pentanedionatorhodium (117.6 mg, 0.4 mmol) (Note 1) in dry tetrahydrofuran (2.5 mL) under a gentle stream of argon. Trimethylsilyl trifluoromethanesulfonate (97.8 mg, 0.44 mmol) (Note 2) is added in one portion by microsyringe via the septum, resulting in a color change from yellow to orange. Solid 1,4-bis(diphenylphosphino)butane (170.4 mg, 0.4 mmol) (Note 3) is added all at once, with removal and immediate replacement of the septum cap. The color of the solution darkens to a deep orange-red, and precipitation of an orange solid occurs over 1–2 min. Dry 30–40 petroleum ether (10 mL) is added with vigorous stirring. The mixture is allowed to settle, and the solvent is removed first by syringe and finally under reduced pressure with an oil pump. Argon is admitted and the catalyst is dried and stored under argon (Note 4) and (Note 5).

B. *Methyl 3-hydroxy-2-methylenepentanoate.* A 250-mL, round-bottomed flask is charged with methyl acrylate (50.0 mL, 0.556 mol), propionaldehyde (60.0 mL, 0.832 mol), and 1,4-diazabicyclo [2.2.2]octane (3.0 g, 26.8 mmol) (Note 6). After the solution is stirred briefly to ensure complete dissolution, the flask is stoppered and set aside at ambient temperature for 7 days. The reaction

mixture is then dissolved in dichloromethane (150 mL) and washed with 1 *M* hydrochloric acid (100 mL), and the organic layer is separated and dried over anhydrous magnesium sulfate. Solvent is removed under reduced pressure after filtration and the residue is fractionated through a 12-in. vacuum-jacketed Vigreux column. The main fraction boiling at 54°C (0.1 mm) is collected as a water-white liquid to afford 57 g (71%) of condensation product (Note 7). Care must be taken in the distillation to avoid contamination by high-boiling impurities that may inactivate the catalyst.

C. *Methyl dl-anti-3-hydroxy-2-methylpentanoate.* Freshly distilled methyl 3-hydroxy-2-methylenepentanoate (14.4 g, 0.1 mol) is added to the biphosphinorhodium catalyst (catalyst/substrate ratio 1/250) (Note 8) in the flask from Step A. Methanol [40 mL, distilled from $Mg(OMe)_2$] is added. The apparatus is sealed with a rubber septum, the side arm is connected to a burette line, and the apparatus is then transferred to a dry ice/2-propanol bath. The vessel is evacuated to 1 mm 3 times and filled with hydrogen (Note 9) each time, the burette being partially filled on the last occasion. The mixture is warmed to near-ambient temperature and transferred to a water bath at 12° ± 2°C (Note 10). When thermal equilibration is complete, the stirrer is started so as to create a deep vortex in the reaction solution, which darkens to a brick-red color with rapid uptake of hydrogen. The burette is recharged with hydrogen as necessary, and gas absorption occurs steadily until the reaction is complete, when ca. 2.5 L of hydrogen has been consumed (Note 11). Completion of reaction can be readily checked by addition of 50 •L of methyl 3-hydroxy-2-methylenepentanoate to the reaction solution by microsyringe, leading to a perceptible burst of gas absorption. At this stage the flask is disconnected from the hydrogen line and flushed with argon and the contents are transferred to a 250-mL, round-bottomed flask. Solvent is removed at ambient temperature on a rotary evaporator, and the residue is dissolved in diethyl ether (40 mL) and 30–40 petroleum ether (150 mL). The mixture is filtered through a small plug of silica (60 •m, Merck flash chromatography grade) that effectively retains the residual rhodium catalyst (Note 1). Solvents are removed on a rotary evaporator, and the colorless product (Note 12) is distilled in a Kugelrohr apparatus, bp 50°C (0.5 mm). The yield of methyl *dl-anti*-3-hydroxy-2-methylpentanoate is 13.3 g (91%), chemically and stereochemically pure by ^{13}C NMR (Note 13).

This procedure may be adapted for kinetic resolution of the reactant, employing an optically active biphosphinorhodium catalyst (Note 13).

2. Notes

1. The starting material for complex preparation is $RhCl_3 \cdot 3\ H_2O$, obtained as a loan from Johnson Matthey Co. Rhodium-containing reaction residues are collected for return. The synthesis of bicyclo[2.2.1]hepta-2,5-diene-2,4-pentanedionatorhodium has been described by Wilkinson,[2] and later by Green,[2] and may be carried out by the following modification: $RhCl_3 \cdot 3\ H_2O$ (0.68 g, 2.58 mmol) was dissolved in 90% ethanol (10 mL) and stirred with freshly distilled bicyclo[2.2.1]hepta-2,5-diene (1.95 mL) for 2 days under argon. The yellow precipitate was filtered, dried, and dissolved in tetrahydrofuran (10 mL) to which was added sodium 2,4-pentanedionate (0.314 g, 2.58 mmol) in one portion. The suspension was stirred vigorously for 4 hr and filtered and solvent was removed from the filtrate under reduced pressure. The resulting complex [530 mg, 70%, mp 172–175°C (lit.[2] 175–177°C)] is sufficiently pure to use, but may be sublimed under reduced pressure if desired. Alternatively, catalysts may be purchased from Chemical Products, Johnson Matthey Co., Royston, Cambridgeshire, England.
2. This toxic and corrosive reagent (Aldrich Chemical Company, Inc.) was transferred directly from the septum-sealed commercial sample.
3. This reagent was obtained from the Strem Chemical Company, Inc.
4. If it is desired to isolate and store the catalyst, an alternative procedure, preferred by the

submitters, may be used. A 25-mL Schlenk tube is used as a reaction flask. After addition of the petroleum ether, the resulting orange suspension is filtered by centrifugation in a Craig tube and dried under argon. The bright-orange solid (0.26–0.28 g), mp 211–212°C (dec), is indefinitely stable when stored in a −20°C freezer under argon.

5. Earlier work on directed hydrogenation used tetrafluoroborate salts.[3 4] Triflate salts seem superior in keeping properties, and their preparation is easy and convenient.

6. Methyl acrylate, 99% (stabilized with 200 ppm hydroquinone monomethyl ether); propionaldehyde, 97%; and 1,4-diazabicyclo[2.2.2]octane were purchased from the Aldrich Chemical Company, Inc. and used as supplied.

7. The Michael-induced condensation reaction between acrylates and aldehydes[5] is dramatically accelerated by high pressure, cutting the reaction time from several days to a few minutes.[6]

8. The submitters used a 1 : 500 catalyst/substrate ratio (H_2 uptake ca. 40 mL/min), but the checkers used the higher ratio to speed up the hydrogen uptake. If an accurate rate of hydrogen uptake is crucial to a user, the lower ratio may be preferred.

9. Hydrogen of 99.99% purity, supplied by the British Oxygen Company, was employed.

10. The diastereoselectivity of reduction increases with decreasing temperature, and the conditions chosen represent a compromise between rate and specificity.

11. On one occasion the submitters added an extra 15.0 g of starting material to the reaction vessel at this point. Hydrogenation proceeded to completion (i.e., 1000 turnovers, in total) but slowed appreciably in the latter stages of reaction.

12. The submitters fractionated the product through a short Vigreux column, collecting the main fraction boiling at 65°C (1 mm). The ^{13}C NMR spectrum of the bulk reaction product is as follows: ($CDCl_3$) δ: 8.89 (CH_3CH), 13.19 (CH_3CH_2), 26.41 (CH_2), 44.21 (OCH_3), 50.79 (CH-CO), 73.73 (CH-O), 175.63 (C=O). The *syn* isomer exhibits resonances at ($CDCl_3$) δ: 9.10, 13.19, 28.33, 44.21, 50.94, 71.53; it may be prepared by Pd/C/H_2 reduction of the starting material and separation of the diastereomers of product by preparative GLC (OV 225, 15', 150° C).

13. When (*R*,*R*)-1,2-bis(*o*-anisylphenylphosphino)ethanerhodium triflate ($DIPAMPRh^+$) was used as catalyst,[7] 5.0 g of starting material was hydrogenated with 0.1 g of catalyst in methanol at 0°C to 65% reaction (ca. 6 hr). Workup and isolation by preparative GLC (OV 225, 15', 150° C) gave 2.0 g of 2*R*,3*R*-(−)-methyl 3-hydroxy-2-methylpentanoate, $[\alpha]^{20}_{587}$ −6.4° (chloroform, *c* 4), and 0.8 g of recovered *S*-(−)-methyl 3-hydroxy-2-methylenepentanoate, $[\alpha]^{20}_{587}$ −20.3° (chloroform, *c* 2). The optical purity of the former is 57 ± 2% by chiral shift NMR [Eu(hfc)$_3$] and the latter is ≥97% optically pure. This represents an enantiomer rate ratio of 13 : 1.

3. Discussion

α-Substituted β-hydroxy esters are the formal product of an ester enolate aldol condensation. High *anti*-stereoselectivity in the reaction requires the lithium enolate of a reasonably bulky aryl ester and a sterically demanding aldehyde. The condensation between 2,6-dimethylphenyl propionate and 2-methylpropanal has been described in *Organic Syntheses*,[8] under conditions where the product is formed with 98% *anti*-selectivity. Recently the condensation of *E*-silylketene acetals derived from *N*-methylephedrine esters with aldehydes mediated by titanium(IV) chloride has been shown to occur with good *anti*-selectivity and in high ee.[9]

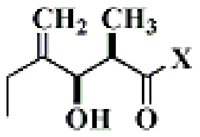
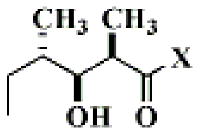
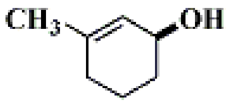
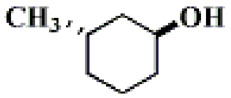
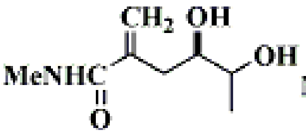
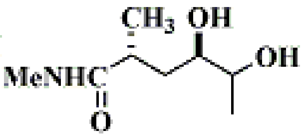
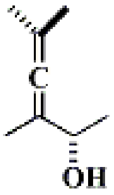
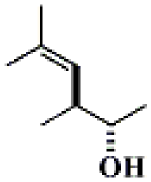
Alternatively, the *anti*-α-alkyl-β-hydroxy ester structure may be obtained by alkylation of the dianion of a β-hydroxy ester, which occurs with ≥95% stereoselectivity.[10] Since the starting materials are available in moderate to high optical purity by yeast reduction of β-keto esters,[11,12] this constitutes an

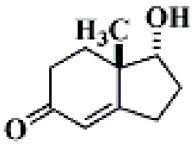
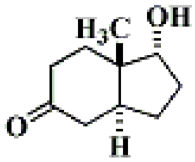
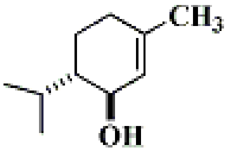
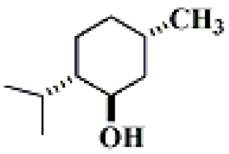
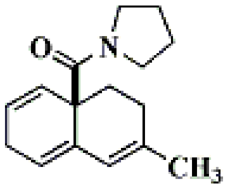
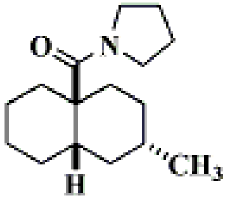
asymmetric synthesis.[13]

The present procedure involving homogeneous catalysis is operationally simple and takes advantage of the easy availability of 2-(1'-hydroxyalkyl)acrylic esters. A two-step procedure involving kinetic resolution of the racemic starting material with an optically active hydrogenation catalyst, followed by a further reduction with an achiral catalyst, leads to diastereomerically pure products in ≥97% ee.

Directed hydrogenation is applicable to olefins that are α'-disubstituted or trisubstituted with a polar functional group at an adjacent chiral center.[14] The latter must be capable of sustained coordination to the metal during the catalytic cycle, thereby exerting stereochemical control on hydride transfer to carbon. The presence of an electron-withdrawing group at the α'-position enhances both the reaction rate and stereoselectivity, making 2-(1'-hydroxyalkyl)acrylates highly suitable substrates for the reaction. The polar group is most commonly -OH, but CO_2Me, $CONR_2$, NHCOR, and $NHCO_2R$ have all been used. Other substituents, including OMe, OCOR, and NH_2, are much less effective. For acyclic cases where the reactant possesses conformational flexibility, cationic rhodium complexes derived from the seven-ring chelate of 1,4-bis(diphenylphosphino)butane have proved most effective. With cyclic reactants, cationic iridium catalysts of the type introduced by Crabtree and Morris[15] have generally been more successful, and the procedure is more tolerant of steric bulk in the reactant olefin. A series of examples is collected in Table I.

TABLE I
DIRECTED HOMOGENEOUS HYDROGENATION

Reactant	Product	Catalyst[a] (mol%)	Selectivity
		A(>2)	93[4]
		A(20)	99.6[3c]
		A(2)	96[16]
		A(3)	97[16]

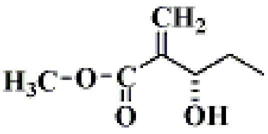
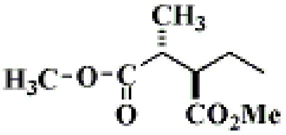
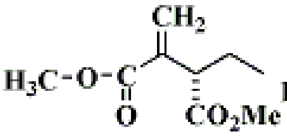
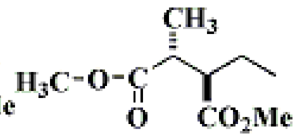
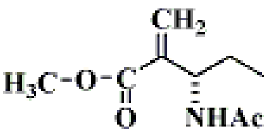
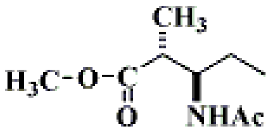
		B(20)	96[17]
		B(2.5)	99.7[18]
		B(5)	99.9[19]

[a]Catalyst A is complex **1** (see text); catalyst B is $(PCx_3)(py)(C_8H_{12})IrPF_6$.

Substituted acrylates (which resemble the enamide substrates employed in asymmetric hydrogenation)[16] may be deracemized by reduction with an optically active catalyst, especially $DIPAMPRh^+$. Selectivity ratios of 12 : 1–22 : 1 have been obtained for a variety of reactants; with compounds of reasonable volatility, separation of starting material and product may be effected by preparative GLC. Recovered starting material can then be reduced with an achiral catalyst to give the optically pure *anti* product. Examples of kinetic resolutions by this method are given in Table II. More recently very successful kinetic resolutions of allylic alcohols have been carried out with Ru(BINAP) catalysts.[13]

TABLE II

KINETIC RESOLUTIONS IN ACRYLATE HYDROGENATION[a]

Recovered reactant	Major product	% Reaction	Ee
		65	98[16]
		65	96[20]
		58	96[21]

[a] 1–4 mol % DIPAMPRh$^+$ in MeOH, usually at 0°C.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

H_2O

bicyclo[2.2.1]hepta-2,5-diene-2,4-pentanedionatorhodium

$RhCl_3 \cdot 3\ H_2O$

sodium 2,4-pentanedionate

2R,3R-(−)-methyl 3-hydroxy-2-methylpentanoate

S-(−)-methyl 3-hydroxy-2-methylenepentanoate

Pentanoic acid, 3-hydroxy-2-methyl-, methyl ester, (R^*, R^*)-(±)-

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

methanol (67-56-1)

diethyl ether (60-29-7)

hydrogen (1333-74-0)

chloroform (67-66-3)

Propionaldehyde (123-38-6)

carbon (7782-42-5)

dichloromethane (75-09-2)

methyl acrylate (96-33-3)

lithium (7439-93-2)

magnesium sulfate (7487-88-9)

tetrafluoroborate (14874-70-5)

2-methylpropanal (78-84-2)

Tetrahydrofuran (109-99-9)

titanium(IV) chloride (7550-45-0)

hydroquinone monomethyl ether (150-76-5)

bicyclo[2.2.1]hepta-2,5-diene

argon (7440-37-1)

triflate

iridium (7439-88-5)

rhodium (7440-16-6)

1,4-diazabicyclo[2.2.2]octane (280-57-9)

2,6-dimethylphenyl propionate (51233-80-8)

E-silylketene

Trimethylsilyl trifluoromethanesulfonate (27607-77-8)

Methyl anti-3-hydroxy-2-methylpentanoate, methyl dl-anti-3-hydroxy-2-methylpentanoate (100992-75-4)

1,4-bis(diphenylphosphino)butane (7688-25-7)

Methyl 3-hydroxy-2-methylenepentanoate (18052-21-6)

biphosphinorhodium

N-methylephedrine (42151-56-4)

Bicyclo[2.2.1]hepta-2,5-diene 1,4-bis(diphenylphosphino)butanerhodium tri-fluoromethanesulfonate

(R,R)-1,2-bis(o-anisylphenylphosphino)ethanerhodium triflate

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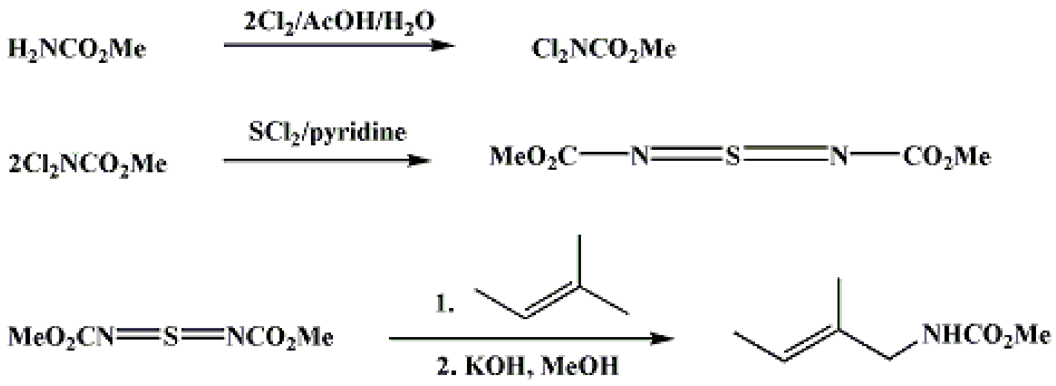
Organic Syntheses, *CV 8, 427*

ALLYLCARBAMATES BY THE AZA-ENE REACTION: METHYL *N*-(2-METHYL-2-BUTENYL)CARBAMATE

[Carbamic acid, (2-methyl-2-butenyl)-, methyl ester]



Submitted by Günter Kresze, Hans Braxmeier, and Heribert Münsterer[1].
Checked by N. Laxma Reddy and Ian Fleming.

1. Procedure

Caution! All three parts of this preparation should be performed in a well-ventilated hood. The reagents and the products of Parts A and B are toxic and unpleasant substances.

A. *Methyl N,N-dichlorocarbamate.* A 2-L, two-necked, round-bottomed flask equipped with a magnetic stirrer, a gas inlet, and a gas outlet is charged with 84 g (1.1 mol) of methyl carbamate, 210 g (2.6 mol) of sodium acetate, 21 g (0.35 mol) of glacial acetic acid, and 400 mL of water and cooled to −10 to −15°C (Note 1). About 175 g (2.5 mol) of chlorine is condensed in a calibrated Schlenk tube (Note 2) cooled with dry ice–methanol. The cooling bath is replaced by an ice–water bath (Note 3) and chlorine is passed slowly (Note 4) (over 2 hr, (Note 5)) at a constant rate into the solution, which is vigorously stirred with a magnetic stirrer. The mixture is transferred to a separatory funnel and the yellow oil which settles is run off. The yellow oil is washed with three subsequent 50-mL portions of a 20% aqueous sodium chloride solution and dried over anhydrous magnesium sulfate. The crude product is then transferred to a distillation apparatus, where it is kept under reduced pressure (11–15 mm) at room temperature for about 20 min. The bath temperature is slowly raised to a maximum of 60°C. The product distills at 43°C (11 mm) to give 102–118 g (63–73%, based on methyl carbamate) of a heavy yellow oil ((Note 6), (Note 7), (Note 8)).

B. *N^1,N^2-Bis(methoxycarbonyl)sulfur diimide.* A 250-mL, three-necked, round-bottomed flask, equipped with a gas outlet stopcock, a thermometer, and a pressure-equalizing dropping funnel and containing a magnetic stirring bar, is purged with dry nitrogen and charged with 53.0 g (0.37 mol) of methyl *N,N*-dichlorocarbamate and 0.2 mL of pyridine. The dropping funnel is filled with 20.6 g (0.2 mol) of freshly distilled sulfur dichloride (Note 9). The whole apparatus is closed and connected by way of the gas outlet to a paraffin-oil-filled valve (Note 10). About 2 mL of sulfur dichloride is then added dropwise into the stirred flask. When the evolution of chlorine has started (usually after about 5 min) (Note 11), the remainder of the sulfur dichloride is added at such a rate that three to five bubbles of chlorine per second are evolved (Note 12), without allowing the temperature of the reaction mixture to exceed 35°C for more than short intervals. The addition takes 1.5–2 hr. After the addition is completed and the evolution of gas has slowed down significantly, volatile materials are removed by stirring the mixture at 60°C under reduced pressure (11–15 mm) for about 10 min (Note 13). Further removal is accomplished at room temperature at 0.01–0.05 mm for approximately 1 hr. The product (33.0–35.0 g), a moisture-sensitive, viscous, yellow oil, is used directly without further purification (Note 14).

C. *Methyl N-(2-methyl-2-butenyl)carbamate.* A 250-mL, two-necked flask, equipped with a gas outlet stopcock and a pressure-equalizing dropping funnel, and containing a magnetic stirring bar, is flushed with dry nitrogen and charged with a solution of N^1,N^2-bis(methoxycarbonyl)sulfur diimide from Part B in 30 mL of dry chloroform. The solution is cooled with ice water, and 14.1 g (0.20 mol) of 2-methyl-2-butene is slowly dropped in with stirring over 1 hr. After the addition is completed, the reaction mixture is stirred for another 10 hr at room temperature. The funnel is replaced by a distillation unit and most of the solvent is removed (11–15 mm, bath temperature 30°C). To the residue are added 240 mL of a 10% solution of potassium hydroxide in methanol and about 10 mL of water. The mixture is stirred for 3 hr at room temperature, and any precipitate is filtered off (Note 15). The residue is washed with 50 mL of methanol, and the filtrate, a red solution, is concentrated at 40°C (11–15 mm). The residue is taken up in 450 mL of ether and washed with four 100-mL portions of water. The ethereal layer is dried with anhydrous magnesium sulfate and treated with charcoal until the color has changed from red to yellow, whereupon the solvent is removed under reduced pressure. The resultant oil is distilled at 70–75°C (3 mm), 62–64°C (0.2 mm) to give the colorless product, yield 10.7–13.7 g (43–52%, based on *N,N*-dichlorocarbamate) (Note 16) and (Note 17).

2. Notes

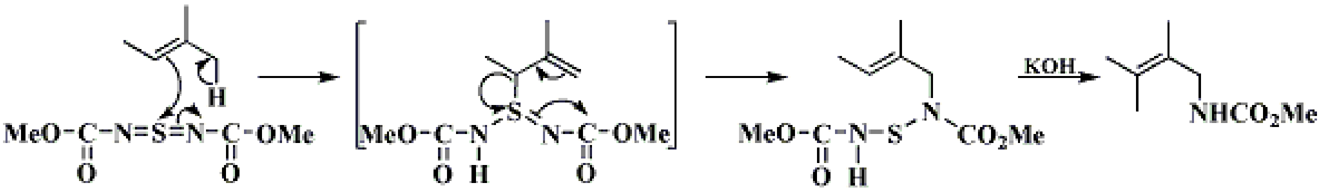
1. The solution of methyl carbamate, sodium acetate, and acetic acid is best prepared at room temperature. On cooling small amounts of precipitate form, but this precipitate dissolves again during the reaction.
2. An amount of 175 g of condensed chlorine corresponds to a volume of about 115 mL. A dry ice–acetone condenser is fitted above the Schlenk tube.
3. A safety flask of at least 1 L should be placed between the Schlenk tube and the reaction flask.
4. To prevent chlorine from escaping before reaction has taken place, the gas inlet tube is immersed as deeply as possible into the solution.
5. To follow the rate of evaporation of chlorine, it is helpful to have calibrated the Schlenk tube.
6. The crude product should not be stored, and the distilled product is best kept protected from light at –78°C.
7. During the distillation, the product is best kept cooled in an ice–water bath.
8. *The product is a powerful skin irritant. Protective gloves should be worn during the separation and when transferring the liquid to the distillation apparatus.*
9. Sulfur dichloride decomposes at its boiling point. It is best distilled at low pressure, condensing it in a cooled vessel.
10. The valve serves as a bubble counter for monitoring the evolution of gas.
11. Sometimes no significant evolution of chlorine occurs. In these cases the mixture is heated to 30–40°C with a water bath, which is removed after the reaction has started. The checkers found no delay in the evolution of chlorine.
12. This evolution should not be interrupted.
13. An aspirator and a water bath may be used for this purpose. A tube filled with anhydrous calcium chloride should be placed between the aspirator and the flask.
14. The product is best stored protected from light at –78°C. Even under these conditions, it is advisable to use it up within at least 1 month.
15. Sometimes no significant amount of precipitate is formed, in which case filtration may be omitted.
16. During distillation the receiving flask should be cooled with ice water in order to minimize losses. The product is a semisolid material at room temperature and solidifies completely when kept in a refrigerator.
17. The product has the following spectroscopic properties: IR (film) cm^{-1}: 3520 (NH), 1700 (CO) 1530; ^{1}H NMR (250 MHz, d_5-pyridine) δ: 1.50 (d, 3 H, J = 6.7, CH_3CH), 1.59 (s, 3 H, CH_3C=), 3.72 (s, 3 H, CH_3O), 3.90 (d, 2 H, J = 6, CH_2N), 5.48 (q, 1 H, J = 6.7, HC=), 8.00 (m, 1 H, HN), with long-range splitting evident in the fine structure. It appears to be a single stereoisomer (>97 : 3).

3. Discussion

The preparation of methyl *N,N*-dichlorocarbamate is based on work of Foglia and Swern,[2] and the preparation

of the sulfurdiimide is based on work of Levchenko.[3] In both cases, we have modified the method and added significant details.

The synthesis of primary allylamines up to 1983 has been reviewed.[4] Our method involves the ene reaction of various aza analogs of sulfur or selenium dioxide (**1** + **2** **3**), followed by [2,3]-sigmatropic rearrangement (**3** **4**). The use of *N*-tosyl activating groups, as in our earlier work[5] and that of Sharpless,[6,7,8] has the disadvantage that the *N*-sulfonyl group cannot easily be removed under mild conditions, as Sharpless observed in his synthesis of gabaculine.[8] In the present method, the methoxycarbonyl group is used in place of the sulfonyl group. It is easy to remove, but the diimide (**2**) is less reactive than the corresponding sulfonyl compound.[9] Nevertheless, it reacts at room temperature with a variety of alkenes, such as β-methylstyrene, 2-pentene, and cyclohexene, and more heavily substituted derivatives of these compounds.[10] The urethane group can easily be hydrolyzed or reduced (lithium aluminum hydride) to give the corresponding allylamines.[10]



2 3 4 5

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

calcium chloride (10043-52-4)

acetic acid (64-19-7)

methanol (67-56-1)

ether (60-29-7)

sodium acetate (127-09-3)

chloroform (67-66-3)

Cyclohexene (110-83-8)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

sulfur (7704-34-9)

pyridine (110-86-1)

chlorine (7782-50-5)

selenium dioxide (7446-08-4)

potassium hydroxide (1310-58-3)

2-Pentene (646-04-8)

β-methylstyrene

magnesium sulfate (7487-88-9)

sulfur dichloride (10545-99-0)

2-methyl-2-butene (513-35-9)

lithium aluminum hydride (16853-85-3)

Carbamic acid, (2-methyl-2-butenyl)-, methyl ester, Methyl N-(2-methyl-2-butenyl)carbamate (86766-65-6)

methyl carbamate (598-55-0)

bis(methoxycarbonyl)sulfur diimide (16762-82-6)

sulfurdiimide

Methyl N,N-dichlorocarbamate (16487-46-0)

N,N-dichlorocarbamate

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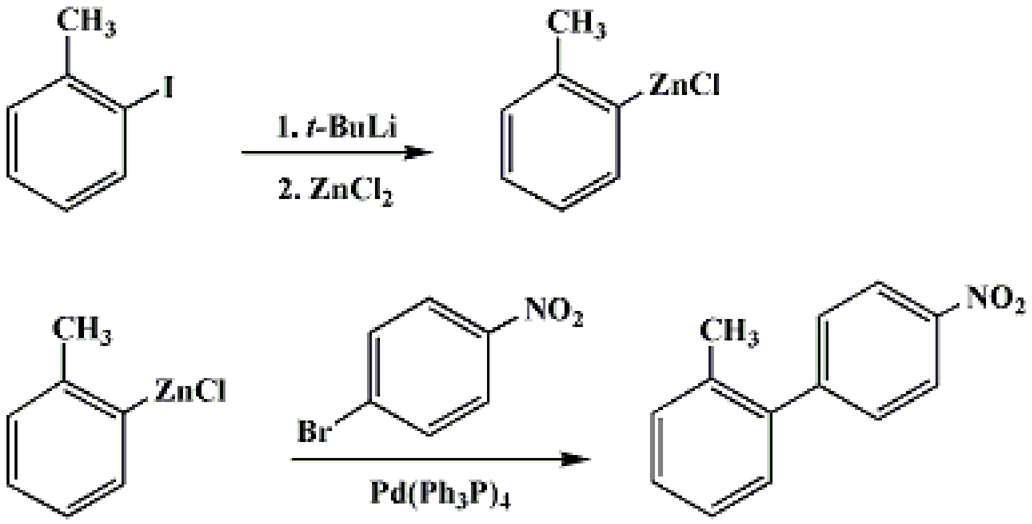
Organic Syntheses, CV 8, 430

SYNTHESIS OF BIARYLS VIA PALLADIUM-CATALYZED CROSS-COUPLING: 2-METHYL-4'-NITROBIPHENYL

[1,1'-Biphenyl, 2-methyl-4'-nitro-]



Submitted by Ei-Ichi Negishi, Tamotsu Takahashi, and Anthony O. King[1].
Checked by Koji Kawai and Ryoji Noyori.

1. Procedure

A. *o-Tolylzinc chloride.* An oven-dried, 500-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, a dropping funnel, a rubber septum inlet, and an outlet connected to a mercury bubbler is flushed with nitrogen, immersed in a dry-ice bath kept at −78°C, and charged with 26.2 g (120 mmol) of *o*-iodotoluene (Note 1) and 60 mL of ether (Note 2). To this solution is added dropwise, with stirring, 154 mL (1.56 *M*, 240 mmol) of a hexane solution of *tert*-butyllithium (Note 3). After the reaction mixture is stirred for 1 hr at −78°C, it is warmed to room temperature, stirred for 1 hr, and concentrated under diminished pressure using a water aspirator (ca. 15 mm) until most of the volatile solvents are evaporated. To this concentrate is added 80 mL of tetrahydrofuran (THF) (Note 4) and (Note 5). The mixture is, in turn, added to 16.3 g (120 mmol) of dry zinc chloride (Note 6) and 60 mL of tetrahydrofuran placed in a similarly equipped, 500-mL flask using a 16-gauge double-ended needle under a slight positive pressure of nitrogen; the resulting mixture is stirred for 1 hr at room temperature.

B. *2-Methyl-4'-nitrobiphenyl.* To a mixture of 1.16 g (1 mmol) of tetrakis (triphenylphosphine)palladium (Note 7), 100 mL of tetrahydrofuran and 20.2 g (100 mmol) of 1-bromo-4-nitrobenzene (Note 8) in a 500-mL flask, set up as described

above and immersed in a water bath, is added the *o*-tolylzinc chloride solution prepared above. The reaction mixture is stirred for 6 hr at room temperature and poured onto a mixture of 100 mL of ether and 300 mL of ice-cold 3 *N* hydrochloric acid. The organic layer is separated, and the aqueous layer is extracted with two 100-mL portions of ether. The combined organic layer is washed with saturated aqueous sodium bicarbonate and dried over anhydrous magnesium sulfate. After filtration, the solvent is removed using a rotary evaporator to give a light-brown solid. The solid is recrystallized from 300 mL of hexane to yield 16.0 g of yellow crystals. The second crop from 50 mL of hexane is 2.4 g. The combined product is recrystallized from 100 mL of ethanol to afford 16.0 g of light-yellow needles. Crystallization of the mother liquor from 25 mL of ethanol gives a second crop of 0.5 g. The total yield of 2-methyl-4'-nitrobiphenyl is 16.5 g (78% based on 1-bromo-4-nitrobenzene) (Note 9).

2. Notes

1. The submitters used *o*-iodotoluene from Aldrich Chemical Company, Inc. The checkers purchased it from Wako Chemical Industries, Ltd.
2. Ether available from Fisher Scientific Company or Sanraku Company was distilled from sodium and benzophenone.
3. The submitters used *tert*-butyllithium from Aldrich Chemical Company, Inc. after titration by the method of Watson and Eastham.[2] The checkers titrated it by the method of Lipton.[3]
4. Tetrahydrofuran from Fisher Scientific Company or Kishida Chemical Company was distilled from sodium and benzophenone.
5. Although somewhat more cumbersome, the following more economical procedure using lithium metal may also be used to generate *o*-tolyllithium. To 1.7 g (240 mg-atom) of freshly cut lithium in 35 mL of ether at 0°C is added dropwise 20.5 g (120 mmol) of *o*-bromotoluene in 25 mL of ether. After formation of *o*-tolyllithium, it is diluted with 60 mL of tetrahydrofuran before use.
6. Zinc chloride, available from Mallinckrodt, Inc., was flame-dried under a slow stream of nitrogen in the reaction flask. The checkers used zinc chloride from Wako Pure Chemical Industries, Inc. after fusion by flame-drying under reduced pressure for 20 min.
7. Tetrakis(triphenylphosphine)palladium was prepared according to the procedure of Coulson.[4]
8. The submitters used 1-bromo-4-nitrobenzene from Aldrich Chemical Company, Inc. without further purification. The checkers purchased it from Tokyo Kasei Kogyo Company.
9. Gas-chromatographic examination of another reaction mixture run on a 10-mmol scale with undecane as an internal standard indicates that 2-methyl-4'-nitrobiphenyl is formed in 90% yield based on 1-bromo-4-nitrobenzene. The product obtained by this procedure shows the following properties: mp 99–101°

C (lit.,[5] mp 103–105°C); IR (neat) cm^{-1}: 1600 (s), 1510 (s), 1480 (s), 1340 (s), 858 (s), 778 (s), 756 (s), 730 (s), 702 (s); ^{1}H NMR (90 MHz, $CDCl_3$) δ: 2.26 (s, 3 H), 7.15–7.40 (m, 4 H), 7.48 (d, 2 H, J = 8.5), 8.27 (d, 2 H, J = 8.5); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ: 20.30, 123.42, 126.16, 128.50, 129.42, 130.11, 130.75, 135.09, 139.67, 147.00, 148.85.

3. Discussion

The procedure described above is based on a paper reporting the Ni- or Pd-catalyzed reaction of arylzinc derivatives with aryl halides.[6] The Ni- or Pd-catalyzed cross-coupling reaction[7] represents one of the most general and satisfactory routes to unsymmetric biaryls.

The currently available data, such as those summarized in Table I, indicate the following. First, Ni-Phosphine and Pd-phosphine complexes may be used interchangeably in many cases (Entries 1 and 2). In cases where sterically hindered aryl reagents, such as mesitylzinc chloride, are used, Ni catalysts tend to lead to higher product yields than the corresponding Pd catalysts (Entries 11 and 12). The scope with respect to the halogen leaving group of aryl halides is broader with Ni catalysts than with Pd catalysts. As a general rule, Ni-catalyzed aryl–aryl cross-coupling proceeds smoothly with both aryl iodides and aryl bromides, whereas aryl bromides must be activated by an electron-withdrawing group in Pd-catalyzed cross-coupling. Palladium-catalyzed cross-coupling, however, is considerably more chemoselective than Ni-catalyzed cross-coupling. Thus, for example, the nitro group appears to be totally incompatible with Ni-phosphine catalysts (Entry 9), and the presence of an alkynyl group tends to lower significantly the yield of product.

TABLE I
PREPARATION OF BIARYLS BY THE Ni- OR Pd-CATALYZED REACTION OF ARYLMETALS WITH ARYL HALIDES[a]

Entry	Ar^1M[b]	ArX	Catalyst[c]	Amount (%)	Yield[d] (%)
1	PhZnCl	*p*-Iodoanisole	Ni	5	85
2	PhZnCl	*p*-Iodoanisole	Pd[e]	5	87
3	PhMgBr	*p*-Iodoanisole	Pd[e]	5	71
4	PhAl (i-Bu)$_2$	*p*-Iodoanisole	Pd[e]	5	72
5	PhZnCl	p-BrC_6H_4CN	Ni	5	90
6	PhZnCl	p-BrC_6H_4COOMe	Ni	5	70
7	PhZnCl	p-$IC_6H_4NO_2$	Pd[e]	5	90 (74)
8	*o*-TolZnCl	p-$BrC_6H_4NO_2$	Pd[e]	1	90 (70)
9	*o*-TolZnCl	p-$BrC_6H_4NO_2$	Ni	1	0
10	*m*-TolZnCl	m-$IC_6H_4CH_3$	Ni	5	95

11	MesZnCl[f]	*o*-$IC_6H_4CH_3$	Ni	5	93
12	MesZnCl	*o*-$IC_6H_4CH_3$	Pd	5	88
13	MesMgBr[g]	*o*-$IC_6H_4CH_3$	Ni	5	38
14	MesMgBr	*o*-$IC_6H_4CH_3$	Ni	5	92
15	PhZnCl	2-Furyl iodide	Pd	5	91
16	2-FurylZnCl	PhI	Pd	5	94 (89)
17	3-FurylZnCl	PhI	Pd	5	89 (85)
18	PhZnCl	2-Furyl bromide	Pd	5	0
19	2-ThienylZnCl	PhI	Pd	5	81 (75)
20	PhZnCl	2-Pyridyl bromide	Pd	5	99 (89)
21	PhZnCl	3-Pyridyl bromide	Pd	5	0

[a]The reactions are carried out in THF at room temperature. The time required for completion is usually less than several hours.

[b]Unless otherwise mentioned, arylzinc chlorides and arylalanes are prepared via in situ transmetalation of aryllithiums, while arylmagnesium halides are prepared by treating aryl halides with Mg. The molar ratio of an aryl metal to an aryl halide is 1–1.5.

[c]Ni = $Ni(PPh_3)_4$ prepared in situ by the reaction of $Ni(acac)_2$, PPh_3, and $(i\text{-Bu})_2AlH$ (1:4:1). Unless otherwise indicated, Pd = $Pd(PPh_3)_4$.

[d]By GLC. The numbers in parentheses are isolated yields.

[e]The Pd catalyst is prepared by treating $Cl_2Pd(PPh_3)_2$ with $(i\text{-Bu})_2AlH$ (2 equiv).

[f]Mes = mesityl.

[g]Generated in situ by treating MesLi with $MgBr_2$ generated from 1,2-dibromoethane and Mg.

Second, the choice of metal counterion is of critical importance. Except in some special cases, alkali metals such as Li, Na, and K are unsatisfactory, partly because arylmetals that contain these metals readily participate in halogen–metal exchange leading to cross–homo scrambling,[6] and also because these organometals are among the least chemoselective. Zinc appears to be among the most satisfactory metals from

the standpoint of (a) product yield, (b) cross/homo ratio, (c) chemoselectivity, and (d) ease of preparation of arylmetal reagents, although Mg has also been used successfully in many cases.[8,9] Results shown in Entries 11 and 13 indicate that the mesitylmagnesium reagent, generated in situ by treatment of mesityllithium with magnesium bromide, appears to be considerably inferior to mesitylzinc chloride generated in a similar manner. On the other hand, mesitylmagnesium bromide generated by treatment of mesityl bromide with Mg is as effective as mesitylzinc chloride (Entry 14). However, the yield of mesitylmagnesium bromide itself is in the range 50–60% and is substantially lower than that of mesitylzinc chloride (ca. 90%). Recent results obtained with arylboron derivatives[10] appear highly promising, although the preparation of arylboronic acids is, at present, more elaborate than that of Grignard reagents or in situ generation of arylzinc reagents. Various other metals, such as Cd,[11] Hg,[12] Al,[6] Sn,[12] Zr,[11] and Cu,[12] have been shown to participate in aryl–aryl cross-coupling. Their advantages over Zn or Mg are, however, largely unknown.

Third, the procedure described above has been applied to the preparation of various biaryls containing heteroaromatic rings (Entries 15–17, 19, 20). Although the number of papers reporting the use of the Ni- or Pd-catalyzed procedure for aryl–aryl coupling is still small, the synthesis of steganone by Raphael and his co-workers[13] is demonstrative of its synthetic potential.

This preparation is referenced from:

- Org. Syn. 75, 53

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium bicarbonate (144-55-8)

nitrogen (7727-37-9)

Benzophenone (119-61-9)

zinc (7440-66-6)

sodium (13966-32-0)

1,2-dibromoethane (106-93-4)

zinc chloride (7646-85-7)

magnesium bromide (7789-48-2)

lithium (7439-93-2)

magnesium sulfate (7487-88-9)

mesityl bromide (576-83-0)

o-Bromotoluene (95-46-5)

Tetrahydrofuran (109-99-9)

2-Pyridyl bromide (109-04-6)

o-iodotoluene (615-37-2)

hexane (110-54-3)

mesitylmagnesium bromide

3-Pyridyl bromide (626-55-1)

mesityl

undecane (1120-21-4)

Tetrakis(triphenylphosphine)palladium (14221-01-3)

tert-Butyllithium (594-19-4)

1-bromo-4-nitrobenzene (586-78-7)

2-Methyl-4'-nitrobiphenyl, 1,1'-Biphenyl, 2-methyl-4'-nitro- (33350-73-1)

mesitylzinc chloride

2-Furyl iodide

2-Furyl bromide

mesitylmagnesium

mesityllithium

p-Iodoanisole (696-62-8)

o-Tolyllithium

o-Tolylzinc chloride

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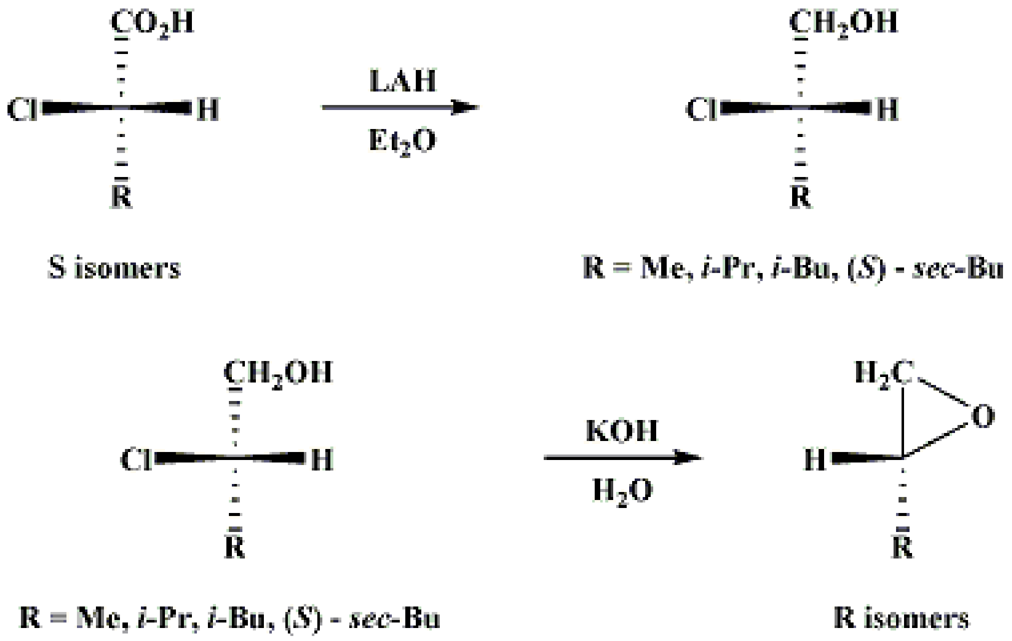
Organic Syntheses, *CV 8*, *434*

(*R*)-ALKYLOXIRANES OF HIGH ENANTIOMERIC PURITY FROM (*S*)-2-CHLOROALKANOIC ACIDS VIA (*S*)-2-CHLORO-1-ALKANOLS: (*R*)-METHYLOXIRANE

[Oxirane, methyl- (*R*)-]



Submitted by Bernhard Koppenhoefer and Volker Schurig[1].
Checked by G. Nagabhushana Reddy and James D. White.

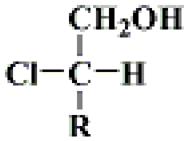
1. Procedure

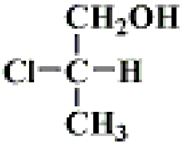
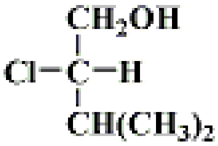
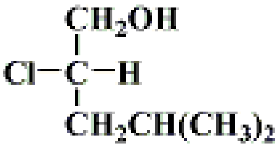
Caution! Methyloxirane is a suspected carcinogen for humans.

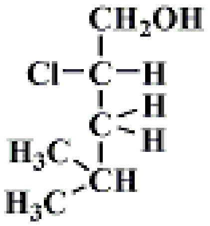
A. *(S)-2-Chloropropan-1-ol.* Into a 2-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, a 250-mL dropping funnel, a stopper (Note 1), and an efficient reflux condenser fitted with a calcium chloride drying tube is placed 9.1 g (0.24 mol) of lithium aluminum hydride; 400 mL of dry diethyl ether is added with caution. The slurry is cooled in an ice bath and a solution of 21.7 g (0.20 mol) of (*S*)-2-chloropropanoic acid (Note 2) in 150 mL of dry diethyl ether is added carefully with vigorous stirring over a 10-min period so that refluxing of the solvent is kept under control. After a total reaction time of 15 min (Note 3), the drying tube is removed and 20 mL of water is added drop by drop *(Caution: Vigorous evolution of hydrogen!)* with efficient stirring and cooling (Note 4). The precipitate is dissolved (Note 5) by addition of 0.6 L of 2 *N* sulfuric acid (Note 6). The layers are separated, and the aqueous layer is extracted with two 200-mL portions of diethyl ether. The combined

ether layers are washed with 50 mL of water, 50 mL of sodium carbonate solution (Note 4), and 50 mL of sodium bicarbonate solution, each aqueous layer being reextracted with two 50-mL portions of diethyl ether (Note 7). The combined ethereal layers are concentrated with a rotary evaporator at atmospheric pressure (bath temperature 40–50°C) to approximately 300 mL, dried over sodium sulfate, and concentrated to give an oily residue. Fractional distillation at reduced pressure (Note 8) affords 10.6–11.0 g (56–58%) of a colorless oil. This procedure can be applied to chlorohydrins with other alkyl residues (see (Note 3) and (Note 8), Table I).

TABLE I
(2*S*)-2-CHLOROALKAN-1-OLS(CHLOROHYDRINS)



Substituent R	Yield (%)	bp (°C/mm)	d_4^{20} (g/cm^3)	$[\alpha]_D^{20}$ (°)[a]
 $-CH_3$	56	131/725	1.110_1	+17.8
 $-CH(CH_3)_2$	70	91/50	1.044_2	+3.6
 $-CH_2CH(CH_3)_2$	64	92/30	1.005_3	–48.8

 (*S*)-$CH(CH_3)CH_2CH_3$	56	75/10	1.028_6	–7.6

[a] Rotations were measured on the neat liquids.

B. *(R)-Methyloxirane* (Note 9). The reaction is conveniently carried out in a special apparatus (see f.htmig. 1) in order to prevent loss of the volatile oxirane. A 50-mL, narrow-necked vessel (A) is equipped with a magnetic stirrer and a small Claisen stillhead (B), fitted with a thermometer and connected to a small receiver adapter with vacuum connection (C). A 25-mL or 50-mL flask (D) serves as a trap for the oxirane. To prevent clogging of the inlet pipe (E) by solidified reaction product, an appropriate flask (D) is chosen so that the distance between the inlet pipe (E) and the flask (D) is approximately 5–10 mm. The vacuum end of the adapter (C) is connected via a stopcock (F), a T-piece carrying a needle valve (G), and a manometer (H) to a water aspirator (I). The reaction vessel (A) is equipped with an ice bath, a thermometer, and a combined heater and magnetic stirrer that is placed on a jack. After the entire apparatus is connected (F closed), the trap (D) is air-cooled in a Dewar (K) that is partially filled with liquid nitrogen and heat-insulated at the top with cotton. A low-temperature thermometer (L) is placed at the same height near trap (D). The temperature of the trap (D) is controlled by moving the jack to the appropriate height to approximately –80°C. The pressure is adjusted by a needle valve (G) to 100 mm (F remains closed). A solution of 12.3 g (0.22 mol) of potassium hydroxide pellets in 12 mL of water is placed in the vessel (A) and cooled to 0°C. Neat (*S*)-2-chloropropan-1-ol, 11.8 g (0.125 mol), is poured at once into the alkaline solution (Note 10), and the reaction vessel is immediately fitted with a stillhead (B) and stirred vigorously with efficient cooling. The stopcock (F) is opened occasionally for a short period until the pressure in the closed system is reduced to 100 mm (Note 11). The ice bath is replaced by a water bath at 20°C. As the cyclization reaction proceeds, a white precipitate of potassium chloride is formed. After 10 min, the bath temperature is raised slowly to 30°C. Gentle boiling of the oxirane is maintained by cautiously opening the stopcock (F) from time to time, with attention paid to the reaction vessel. After a total reaction time of 40 min (Note 12), air is allowed to enter the closed system at the top of the stillhead, and the trap (D) is allowed to warm (Note 13) until two liquid phases are formed. The lower phase containing water is transferred via a Pasteur pipette into a small flask (Note 14). The flask (D) containing 5.9 g (81%) of crude (*R*)-methyloxirane is used in position (A) of the clean, dry apparatus (see f.htmig. 1) for redistillation of the oxirane from calcium hydride. At atmospheric pressure (stopcock F open), flask (A) is cooled to 0°C, whereas the trap (D) is kept at room temperature.

Calcium hydride is added in small portions over a period of 1–2 hr until evolution of hydrogen ceases. The stopcock (F) is closed, the trap (D) is cooled, and the oxirane is distilled as described. Reduced pressure is applied with great care to avoid too vigorous boiling; 4.7–5.0 g (65–70%) of anhydrous oxirane is obtained as a clear liquid. This procedure can be employed for other oxiranes with slight modifications (see (Note 12) and (Note 14) and Table II).

Figure 1. Apparatus for the preparation of (*R*)-methyloxirane.

Figure 1. Apparatus for the preparation of (R)-methyloxirane.

2. Notes

1. As a safeguard it is recommended that the reaction be performed under nitrogen using a gas inlet instead of the stopper. The flask should be dry and free of faults.
2. (*S*)-2-Chloroalkanoic acids are prepared according to the procedure described.[2]
3. A total reaction time of 30 min is needed for more sterically hindered (*S*)-2-chloroalkanoic acids. Prolonged reaction times should be avoided to prevent hydrogenolysis of the chlorine-carbon bond.
4. Prolonged exposure to alkaline conditions should be avoided to prevent oxirane formation at this step.
5. The aqueous phase is allowed to remain opalescent to avoid unnecessarily low pH-values.
6. Concentrated sulfuric acid, 60 g, is added to a beaker charged with 540 g of crushed ice. Precooled 2 *N* sulfuric acid is added to the reaction mixture.
7. Less than 5% of the chloroalkanoic acid is reisolated after acidification of the sodium carbonate phase and extraction with diethyl ether.
8. (*S*)-2-Chloropropan-1-ol is carefully distilled at atmospheric pressure using a 20-cm Vigreux column. (*S*)-2-Chloro-3-methylbutan-1-ol, (*S*)-2-chloro-4-methyl-pentan-1-ol, and (2*S*,3*S*)-2-chloro-3-methylpentan-1-ol are distilled under reduced pressure with a spinning-band column or a "Spaltrohr-column" (approximately 50 theoretical plates, supplier: W. G. Fischer, D-5309 Meckenheim, FRG); see Table I. The main fractions are >99% pure by GLC (OV 17 on Chromosorb P AW-DMCS). Because of the low boiling points of the oxiranes, diethyl ether should be completely removed from the chlorohydrins.
9. The synthesis should be carried out in a well-ventilated hood. *Caution: Methyl-oxirane is a suspected carcinogen for humans.*
10. The amount of chlorohydrin used is determined from the weight remaining in the original flask (ca. 1 g).
11. During the course of the reaction, the stopcock (F) should remain closed except for short periods in order to avoid loss of the volatile oxirane. There is no

danger of excess pressure in the closed system as long as the trap (D) is cooled efficiently.

12. The chlorohydrins show different rates of cyclization, reflecting the steric hindrance of residue R. The most vigorous reaction is observed in the case of (*S*)-2-chloropropan-1-ol (R = CH_3); only 30°C at 100 mm is required. For (*R*)-isopropyloxirane, the bath temperature is raised slowly to 50°C, and after 40 min to 60°C, while the pressure is reduced to 50 mm for an additional 5 min. For the higher-boiling oxiranes, such as (*R*)-isobutyloxirane and (*S*)-*sec*-butyl-(*R*)-oxirane [(2*R*,3*S*)-3-methyl-1,2-epoxybutane], the temperature is raised slowly to 60°C within 1 hr, while the pressure is reduced carefully to 30 mm.

13. Buildup of methyloxirane pressure is prevented by briefly opening the apparatus from time to time.

14. For methyloxirane, the binary system with water has been studied in detail.[3] By careful operation during the distillation, water is largely retained in the original flask (A). The racemate melts at −112°C, but the hydrate $C_3H_6O(H_2O)_{16}$ (mp −3°C) may solidify in the inlet tube (E). In the case of higher boiling oxiranes, substantial amounts of water are codistilled. After removal from the flask (D), the aqueous phase may be saturated with sodium chloride. Thereby a second portion of the oxirane (approximately 0.2 g) is separated and combined with the main portion in the flask (D).

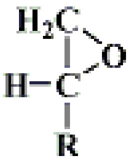
3. Discussion

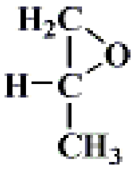
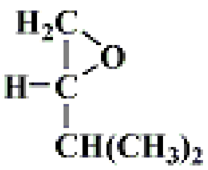
The method described here illustrates the transformation of optically active 2-chlorocarboxylic acids, which are readily available from 2-amino acids,[2] via 2-chloroalkan-1-ols to alkyloxiranes with inversion of configuration at the stereocenter. Thus (*R*)-methyloxirane is prepared from (*S*)-alanine, (*R*)-isopropyloxirane from (*S*)-valine, (*R*)-isobutyloxirane from (*S*)-leucine, and (*S*)-*sec*-butyl-(*R*)-oxirane from (2*S*,3*S*)-isoleucine, respectively. This useful three-step route complements the synthesis of (*S*)-alkyloxiranes from (*S*)-2-amino acids via (*S*)-2-hydroxy acids,[4,5] with retention of configuration at the stereocenter.

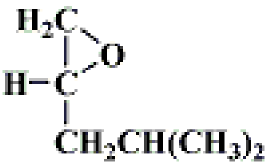
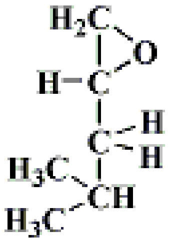
The stereoselective conversion of chlorohydrins into diols via oxiranes as intermediates in aqueous potassium hydroxide solution was originally described in Fickett et al.[6] In the present procedure, the oxiranes are distilled off as they are formed to prevent subsequent ring-opening. Among different reaction conditions investigated,[7] the procedure given here appears to be most convenient, and is accompanied by almost no racemization (Table II). The enantiomeric purities of the oxiranes are determined directly with high precision by complexation gas chromatography on optically active metal chelates [e.g., Ni(II) bis(2-heptafluorobutyryl-(*S*)-4-methylthujan-3-onate)[8] or Mn(II) bis(3-heptafluorobutyryl-(*R*)-camphorate),[7] respectively]. Depending on the chemical structure of the chloro acids used,[2] the degree of inversion of configuration is less than 0.5% for R = methyl, isopropyl, and (*S*)-sec-butyl, and approximately 1.5% for R = isobutyl. In the latter

case, prolonged exposure of the oxirane to the reaction mixture leads to increased racemization. Both (*R*)- and (*S*)-methyloxirane have been synthesized with retention of configuration from (*R*)- and (*S*)-propane-1,2-diol, respectively, by cyclization of the bromoacetates,[9,10,11] which seems to be superior to the route via bromohydrins.[12] Starting from commercially available (*S*)-ethyl lactate,[9] other groups have employed different routes to (*S*)-methyloxirane[13,14] [$[\alpha]_D$ –12.5° (neat)][13] and to (*R*)-methyloxirane[15,16] [$[\alpha]_D^{24}$ + 13.9° (neat),[15] $[\alpha]_D^{20}$ + 13.4° (neat),[17] $[\alpha]_D^{22}$ + 13.0° (neat),[16] $[\alpha]_D^{25}$ + 11.97° (neat)[18]]. The apparent deviations of these specific rotations from the maximum optical rotation extrapolated for the pure enantiomer may be ascribed to lack of enantiomeric purity of the substances described, and to inappropriate optical rotation measurements (error in the density, chemical impurities). Enantiomeric impurities in the oxirane can also originate from the starting material since variable fractions of (*R*)-ethyl lactate (up to 5%) have been detected in commercial (*S*)-ethyl lactate by gas chromatography on D-Chirasil-Val.[19] The enantiomeric purity of the chiral starting material must be established with certainty in any "chiral pool" transformation.

TABLE II
(2*R*)-ALKYLOXIRANES(1,2-EPOXYALKANES)



Substituent R	Yield (%)^a	bp (°C/mm)^b	ee (%)	d_4^{20} (g/cm^3)	$[\alpha]_D^{20}$ (°)^c
 $-CH_3$	81/67	34/728	94.6 ± 0.4^d	0.8309	+13.12
 $-CH(CH_3)_2$	93/87	82/730	97.4 ± 0.2^e	0.8201	–4.46

 $-CH_2CH(CH_3)_2$	84/78	108/730	93.0 ± 0.4[e]	0.8241	+20.47
 (*S*)-$CH(CH_3)CH_2CH_3$	79/73	109/726	97.4 ± 0.2[d,f]	0.7598	+14.4

[a] First number: crude reaction product (organic layer). Second number: final yield after redistillation.

[b] Determined in a separate experiment.

[c] Rotations were determined on neat samples; specific rotations are for material of the indicated enantiomeric excess.

[d] Determined by complexation gas chromatography on Ni(II) bis(2-heptafluorobutyryl-(S)-4-methylthujan-3-onate) ([8]).

[e] Determined as Mn(II) bis(3-heptafluorobutyryl-(R)-camphorate) ([7]).

[f] Diastereomeric excess, referring to (2*S*,3*S*)-1,2-epoxy-3-methylpentane, (*S*)-*sec*-butyl-(*R*)-oxirane as impurity. Composition: 98.5 ± 0.1% 2*R*,3*S*; 1.3 ± 0.1% 2*S*,3*S*; 0.2 ± 0.1% 2*R*,3*R*, approximately 0% 2*S*,3*R*.

The "chiral pool" approach appears at present to be superior to other methods of access to optically active alkyl-substituted oxiranes, such as enzymatic,[20,21,22] and

nonenzymatic[23] epoxidation of prochiral olefins, chromatographic resolution experiments,[11,24] and kinetic resolution methods.[8,25,26] Halohydrins and oxiranes of high enantiomeric purity have recently been obtained by diastereoselective synthesis.[27] As reviewed previously,[10] a variety of optically active compounds have been synthesized from (*R*)- and (*S*)-methyloxirane. Additional examples are macrolides,[28,29,30] alcohols,[31,32,33] amino alcohols,[20,34] 1-chloro-2-alkanols,[35] and thiiranes.[17,36] The potential of higher, alkyl-substituted oxiranes as building blocks in chiral synthesis awaits its full exploitation. (*S*)-Ipsenol has been synthesized from (*S*)-isobutyloxirane,[37,38] which is also available from D-mannitol.[38,39] By stereoselective ring-opening reactions, optically active oligomers (crown ethers)[40] and polymers are conveniently prepared.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 119

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

(R)- and (S)-methyloxirane

(S)-2-Chloroalkanoic acids

Ni(II) bis(2-heptafluorobutyryl-(S)-4-methylthujan-3-onate)

Mn(II) bis(3-heptafluorobutyryl-(R)-camphorate)

(R)- and (S)-propane-1,2-diol

S)-methyloxirane

R)-ethyl lactate

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

ether, diethyl ether (60-29-7)

hydrogen (1333-74-0)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

(S)-alanine (56-41-7)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

methyloxirane, Methyl-oxirane (75-56-9)

nitrogen (7727-37-9)

potassium hydroxide (1310-58-3)

oxirane (75-21-8)

potassium chloride (7447-40-7)

lithium aluminum hydride (16853-85-3)

(2S,3S)-isoleucine (73-32-5)

(S)-Leucine (61-90-5)

(S)-valine (72-18-4)

calcium hydride (7789-78-8)

chlorine-carbon

D-mannitol (69-65-8)

(S)-ethyl lactate (97-64-3)

(R)-Methyloxirane, Oxirane, methyl- (R)- (15448-47-2)

(S)-2-Chloropropanoic acid (29617-66-1)

(S)-2-Chloropropan-1-ol (19210-21-0)

(S)-2-Chloro-3-methylbutan-1-ol

(S)-2-chloro-4-methyl-pentan-1-ol

(2S,3S)-2-chloro-3-methylpentan-1-ol

(R)-isopropyloxirane, (2R,3S)-3-methyl-1,2-epoxybutane

(R)-isobutyloxirane

(S)-sec-butyl-(R)-oxirane

(2S,3S)-1,2-epoxy-3-methylpentane

(S)-isobutyloxirane

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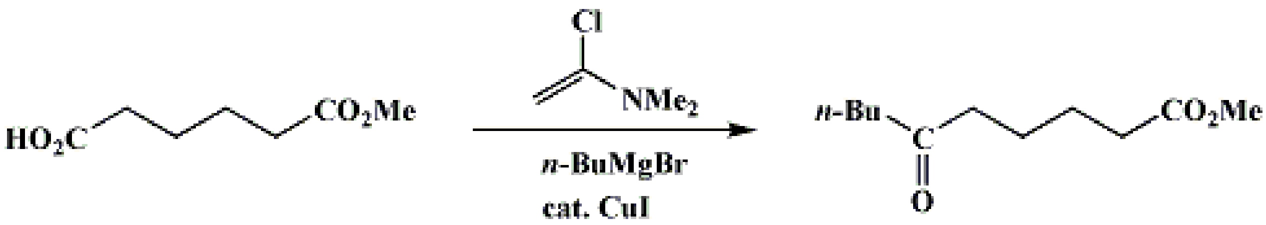
Organic Syntheses, CV 8, 441

KETONES FROM CARBOXYLIC ACIDS AND GRIGNARD REAGENTS: METHYL 6-OXODECANOATE

[Decanoic acid, 6-oxo-, methyl ester]



Submitted by Tamotsu Fujisawa and Toshio Sato[1].
Checked by Cynthia Smith and Andrew S. Kende.

1. Procedure

A 500-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, a thermometer, an addition funnel for solids (Note 1), and a rubber septum is flushed with nitrogen. The flask is charged with 50 mL of dichloromethane (Note 2) and 6.92 g (0.052 mol) of 1-chloro-*N*,*N*,2-trimethylpropenylamine (Note 3). The solution is stirred and cooled in an ice bath and 8.01 g (0.050 mol) of adipic acid monomethyl ester (Note 4) is added slowly by means of a syringe over 10 min. After the addition is complete, the cooling bath is removed and the contents of the flask are stirred for 30 min at room temperature (Note 5). The flask is cooled in an ice–salt bath to –15°C. Then 100 mL of tetrahydrofuran (Note 6) and 0.48 g (0.0025 mol) of copper(I) iodide (Note 7) are added to the flask through the septum and the funnel, respectively. To this stirred mixture is added 50.5 mL (0.052 mol) of a 1.03 *M* solution of butylmagnesium bromide (Note 8) in tetrahydrofuran over 1 hr using a syringe pump, while the internal temperature is maintained below –10°C. The reaction mixture is stirred for an additional hour at –15°C. After 100 mL of 2 *M* hydrochloric acid solution has been poured into the flask in one portion, the mixture is transferred to a separatory funnel and the organic layer is separated. The aqueous layer is extracted with two 100-mL portions of hexane. The combined organic extracts are washed with five 10-mL portions of 2 *M* hydrochloric acid solution (Note 9), 100 mL of 5% sodium thiosulfate solution, two 100-mL portions of saturated sodium bicarbonate solution, and 100 mL of brine, dried over anhydrous sodium sulfate, and filtered. The solvent is evaporated under reduced pressure and the residual liquid is distilled with a short-necked Claisen distillation flask. After separation of a small forerun (<0.3 g) (Note 10), 8.53–8.67 g (85–86%) of methyl 6-oxodecanoate is collected, bp 106–110°C (2.8 mm) (Note 11).

2. Notes

1. A simple bent glass tube is useful as an addition funnel for copper (I) iodide.
2. Dichloromethane was distilled over calcium hydride, and stored over Linde 4A

molecular sieves.

3. *N,N*-Dimethylisobutyramide (Gavrilov, N.; Koperina, A.; Klutcharova, M. *Bull. Soc. Chim. Fr.* **1945**, *12*, 773) was converted to 1-chloro-*N,N*,2-trimethylpropenylamine according to the procedure of *Org. Synth., Coll. Vol. VI,* **1988**, 282, in 61% yield, bp 118–121°C. Freshly distilled oxalyl chloride was used instead of phosgene. The propenylamine should be handled carefully in a syringe to avoid its rapid hydrolysis by moisture.

4. Adipic acid monomethyl ester was purchased from Nakarai Chemicals or Aldrich Chemical Company, Inc. and distilled before use, bp 155–158°C (7 mm).

5. In a separate experiment, formation of adipic acid monomethyl ester monochloride was observed.[2]

6. Tetrahydrofuran was freshly distilled from the sodium ketyl of benzophenone.

7. Copper(I) iodide purchased from Wako Chemicals was used without purification.

8. Butylmagnesium bromide was prepared from magnesium and butyl bromide in tetrahydrofuran at room temperature by a standard procedure (*Org. Synth., Coll. Vol. VI,* **1988**, 407), and titrated by the procedure of Watson and Eastham.[3]

9. The organic extracts must be washed 4 or 5 times to remove *N,N*-dimethylisobutyramide.

10. The forerun consisted of *N,N*-dimethylisobutyramide, other by-products, and methyl 6-oxodecanoate.

11. The reported physical constants are bp 149°C (13.5 mm),[4] 97–103°C (3.5 mm),[5] n_D^{20} 1.4377,[4] n_D^{25} 14376.[5] Gas-chromatographic analysis of the product using a 3 mm × 1-m stainless-steel column, 15% SE-30 on 60–80-mesh Chromosorb W (AW), 150°C, 50 mL of nitrogen per minute indicated a purity of 99.6% (the retention time is 6.9 min). The spectral properties of the product are as follows: IR (liquid film) cm^{-1}: 2960, 2870, 1740, 1714, 1454, 1435, 1415, 1370, 1200, 1175; ^1H NMR (60 MHz, CCl_4) δ: 0.9 (t, 3 H, J = 7, CH_3), 1.06–1.86 (m, 8 H, CH_2), 2.06–2.56 (m, 6 H, $CH_2C{=}O$), 3.60 (s, 3 H, OCH_3).

3. Discussion

The direct coupling of Grignard reagents with carboxylic acids is not generally useful for ketone synthesis because of the accompanying formation of tertiary alcohols. An exception is the recently published method using a nickel catalyst.[6] In order to accomplish such a chemoselective ketone synthesis, the method of activation of carboxylic acid in situ is important, and several activating reagents have been proposed for the purpose, such as a bulky acyl chloride,[7] dichlorotriphenylphosphorane,[8] or *N,N*-diphenyl-*p*-methoxyphenylchloromethylenammonium chloride,[9] which react with carboxylic acids to produce mixed anhydrides, carboxyphosphonium salts, or carboxymethylenammonium salts, respectively.

The present procedure, reported earlier by the submitters,[10] illustrates a general method for ketone synthesis in a one-pot operation using an α-chloroenamine as a condensation reagent. 1-Chloro-*N,N*,2-trimethylpropenylamine reacts with carboxylic acids to produce

the corresponding acyl chlorides,[2] which instantaneously couple with Grignard reagents in the presence of a copper catalyst to give ketones. The utility of the procedure is as follows: (a) an equimolecular amount of Grignard reagent is sufficient to complete the reaction of carboxylic acid and (b) the exceptionally high chemoselectivity of the reaction tolerates various kinds of functional groups such as nitrile, halide, ester and even ketone.[10]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 498

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

brine

sodium ketyl of benzophenone

Adipic acid monomethyl ester monochloride

α-chloroenamine

hydrochloric acid (7647-01-0)

sodium bicarbonate (144-55-8)

magnesium (7439-95-4)

Butyl bromide (109-65-9)

sodium sulfate (7757-82-6)

sodium thiosulfate (7772-98-7)

nitrogen (7727-37-9)

copper (7440-50-8)

nickel (7440-02-0)

phosgene (75-44-5)

Butylmagnesium bromide (693-03-8)

dichloromethane (75-09-2)

copper(I) iodide, copper (I) iodide (7681-65-4)

Tetrahydrofuran (109-99-9)

oxalyl chloride (79-37-8)

hexane (110-54-3)

adipic acid monomethyl ester (627-91-8)

calcium hydride (7789-78-8)

Dichlorotriphenylphosphorane (2526-64-9)

Methyl 6-oxodecanoate, Decanoic acid, 6-oxo-, methyl ester (61820-00-6)

1-Chloro-N,N,2-trimethylpropenylamine (26189-59-3)

N,N-dimethylisobutyramide (21678-37-5)

N,N-diphenyl-p-methoxyphenylchloromethylenammonium chloride

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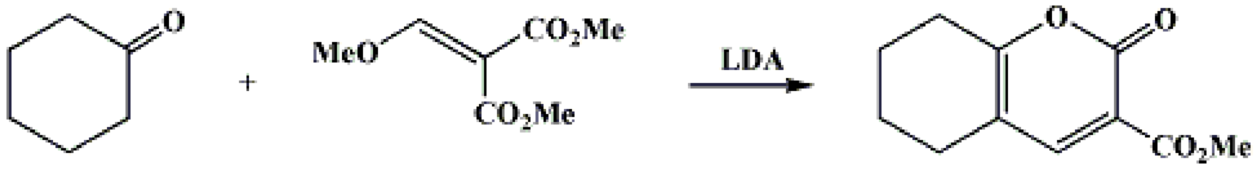
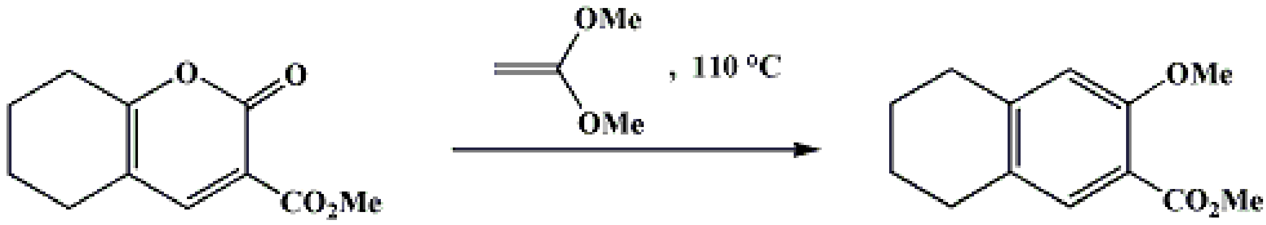
PREPARATION AND INVERSE-ELECTRON-DEMAND DIELS–ALDER REACTION OF AN ELECTRON-DEFICIENT DIENE: METHYL 2-OXO-5,6,7,8-TETRAHYDRO-2*H*-1-BENZOPYRAN-3-CARBOXYLATE AND 6-METHOXY-7-METHOXYCARBONYL-1,2,3,4-TETRAHYDRONAPHTHALANE

[2*H*-1-Benzopyran-3-carboxylic acid, 5, 6, 7, 8-tetrahydro-2-oxo-, methyl ester and 2-Naphthalenecarboxylic acid, 5, 6, 7, 8-tetrahydro-3-methoxy-, methyl ester]





Submitted by Dale L. Boger and Michael D. Mullican[1].
Checked by Drew B. Burns and K. Barry Sharpless.

1. Procedure

A. *Methyl 2-oxo-5,6,7,8-tetrahydro-2H-1-benzopyran-3-carboxylate.* A dry, 500-mL, round-bottomed flask with a side arm containing a magnetic stirring bar is fitted with a septum and a three-way stopcock equipped with an argon-filled balloon (Note 1). The air in the flask is replaced with argon (Note 2). Tetrahydrofuran (100 mL, (Note 3)) and diisopropylamine (4.7 g, 46 mmol, (Note 4)) are introduced into the flask through the septum using dry syringes (Note 5). The flask is immersed in an ice–water bath and a 2.8 M solution of butyllithium in hexane (17 mL, 46 mmol, (Note 6)) is added to the stirred solution using a syringe (10 min). The yellow solution is allowed to stir at 0°C for an additional 15 min. The resulting solution containing lithium diisopropylamide is immersed in a dry ice–2-propanol bath (−78°C) and a solution of cyclohexanone (3.74 g, 38.1 mmol, (Note 7)) in tetrahydrofuran (50 mL) is added using a syringe (30 min). The reaction is allowed to warm slowly to −5°C over 1.75 hr. The resulting solution containing the lithium enolate of cyclohexanone is recooled to −30 to −25°C and a solution of dimethyl methoxymethylenemalonate (8.1 g, 46 mmol, (Note 8)) in tetrahydrofuran (20 mL) is added using a syringe (15 min). The reaction is allowed to warm to ambient temperature

over 3.5 hr (Note 9). The reddish-orange solution is poured slowly onto aqueous 5% hyrochloric acid (300 mL) and the resulting yellow solution is extracted with methylene chloride (4 × 80 mL). The combined organic layers are dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to approximately 15 mL. The solution is applied to a medium pressure liquid chromatography column (25 × 500 mm, (Note 10)) packed with silica gel and 30% ethyl acetate-hexane. The eluant (30% ethyl acetate–hexane) is passed through the column at a rate of 20 mL/min; 20-mL fractions are collected (Note 11). The fractions are analyzed by thin-layer chromatography on analytical silica gel plates containing UV indicator (ethyl ether eluant). The fractions containing the product are combined and concentrated under reduced pressure to give 4.9 g (62%, 62–68%) of methyl 2-oxo-5,6,7,8-tetrahydro-2*H*-1-benzopyran-3-carboxylate as a white solid: mp 107–108°C (ethyl acetate–hexane, (Note 12)).

B. *6-Methoxy-7-methoxycarbonyl-1,2,3,4-tetrahydronaphthalene.* 1,1-Dimethoxyethylene (1.1 g, 12.5 mmol, (Note 13)) is added to a solution of methyl 2-oxo-5,6,7,8-tetrahydro-2*H*-1-benzopyran-3-carboxylate (507 mg, 2.44 mmol) in dry toluene (2.5 mL, (Note 14)) in a dry, 11 × 13-mm, resealable glass tube (Note 15). The tube is flushed with argon and sealed with a Teflon plug. The reaction is warmed at 110°C in an oil bath for 15 hr (Note 16). The reaction is cooled and concentrated under reduced pressure. Purification of the product is effected by gravity chromatography on a 1.5 × 16-cm column of silica gel (30% ethyl ether–hexane eluant) collecting 5-mL fractions (Note 17). The fractions are analyzed by thin-layer chromatography (50% ethyl ether–hexane eluant) and those containing the product are combined and concentrated under reduced pressure to give 451 mg (84%, 84–86%) of 6-methoxy-7-methoxycarbonyl-1,2,3,4-tetrahydronaphthalene as a white solid: mp 98.5–99.5°C (methanol–water, (Note 18)).

2. Notes

1. The flask containing the stirring bar was dried at 120°C in an oven for several hours. The warm flask was fitted with a septum and a three-way stopcock.
2. This procedure is described in detail in *Org. Synth., Coll. Vol. VI*, **1988**, 869.
3. Tetrahydrofuran was distilled from benzophenone ketyl under a nitrogen atmosphere.
4. Diisopropylamine was distilled from calcium hydride under a nitrogen atmosphere and stored over activated Linde 3A sieve pellets.
5. The hypodermic syringes and needles were dried for several hours in an oven at 120°C and allowed to cool to ambient temperature in a desiccator.
6. Butyllithium was purchased from Aldrich Chemical Company, Inc.
7. Cyclohexanone was distilled before use.
8. Technical-grade dimethyl methoxymethylenemalonate was purchased from Fluka Chemical Corporation and was purified by recrystallization from ether (2 times), mp 43.0–44.0°C. It can be prepared by the procedure described for diethyl ethoxymethylenemalonate.[2]
9. Gradual warming to room temperature over 3.5 hr is necessary to ensure reasonable yields. Shorter times result in significantly lower yields.
10. The use of medium pressure liquid chromatography is described by Meyers.[3]

11. The checkers found that MPLC can be replaced by ordinary flash chromatography (30% EtOAc–hexane eluant, 6-cm-i.d. column, ca. 200–240 g of flash-grade silica gel 230–400-mesh, 250-mL fractions). The crude product was dissolved in CH_2Cl_2 to which was added several grams of silica gel. This mixture was concentrated under reduced pressure and the resulting solid was applied to the top of the column.

12. The product has the following spectral properties: ^1H NMR ($CDCl_3$) δ: 1.80 (m, 4 H, CH_2CH_2), 2.46 (m, 4 H, CH_2CH_2C=), 3.86 (s, 3 H, -CO_2CH_3), 7.99 (s, 1 H, vinyl); IR ($CHCl_3$) cm^{-1}: 3040, 2975, 1765, 1745, 1555, 1270, 1220, 1155.

13. 1,1-Dimethoxyethylene was purchased from Wiley Organics and used without further purification.

14. Toluene was distilled from calcium hydride under a nitrogen atmosphere.

15. The resealable glass tube was fabricated from a chromatography column purchased from Ace Glass Company. The tube was permanently sealed on one end and the other end remained internally threaded. A solid, threaded, Teflon plug equipped with an O-ring was used to seal the tube. Various sizes of such tubes are now available from Ace Glass Company.

16. *Caution: The reaction should be run behind a shield in a fume hood for protection in case of explosion. Pressure will build up in the tube since 1,1-dimethoxyethylene boils at 89°C and carbon dioxide is formed.*

17. The checkers found that gravity chromatography can be replaced by ordinary flash chromatography (30% ethyl ether–hexane eluant, 2.5-cm-i.d. column, ca 40 g of flash-grade silica gel, 20-mL fractions). In at least one case, the checkers found that pure product could be isolated in high yield (98%) without recrystallization.

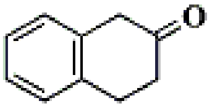
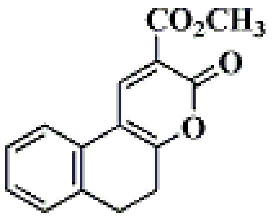
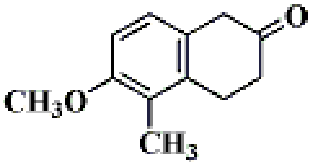
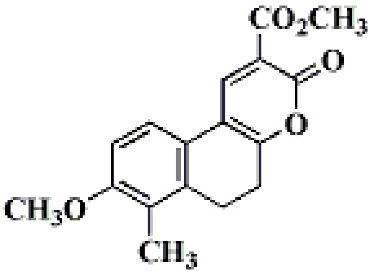
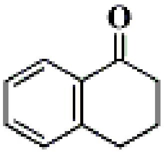
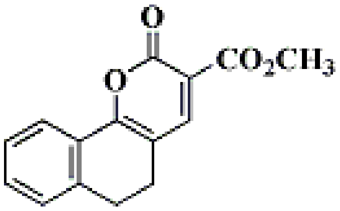
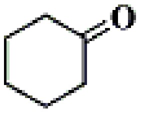
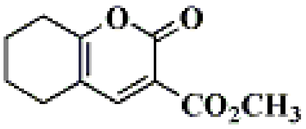
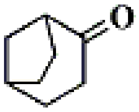
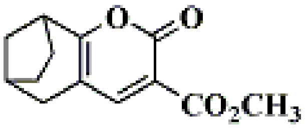
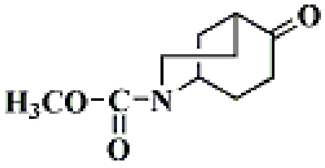
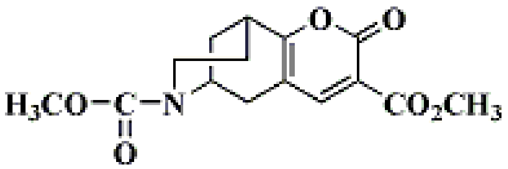
18. The product has the following spectral properties: ^1H NMR ($CDCl_3$) δ: 1.80 (m, 4 H, CH_2CH_2), 2.75 (m, 4 H, CH_2CH_2C=), 3.86 (s, 6 H, -OCH_3 and -CO_2CH_3), 6.65 (s, 1 H, C-5 H), 7.53 (s, 1 H, C-8 H); IR ($CHCl_3$) cm^{-1}: 3040, 2970, 1725, 1610, 1280, 1080; lit.[4] mp 99–100°C.

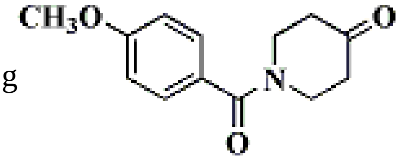
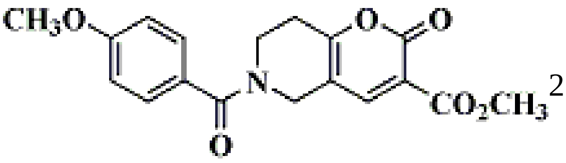
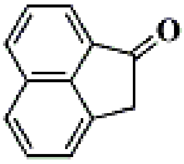
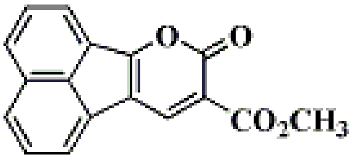
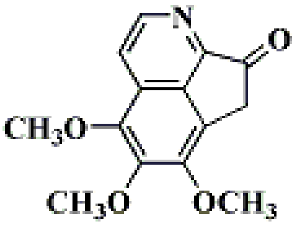
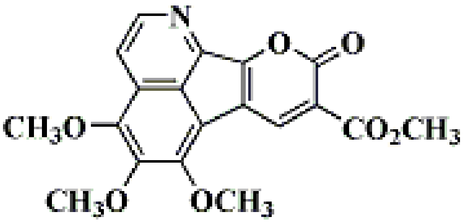
3. Discussion

This procedure describes the preparation and inverse electron demand [$LUMO_{diene}$ (lowest unoccupied molecular orbital) controlled][5] Diels–Alder reaction of an electron-deficient diene. While extensive studies on the preparative utility of the normal [$HOMO_{diene}$ (highest occupied molecular orbital) controlled][5] Diels–Alder reaction have been detailed, few complementary studies on the preparative value of the inverse-electron-demand Diels–Alder reaction have been described.[6 7 8 9 10 11] Table I details representative 3-carbomethoxy-2-pyrones that have been prepared by procedures similar to that described herein, and Tables II and III detail their inverse-electron-demand Diels–Alder reactions with electron-rich dienophiles.

TABLE I

PREPARATION OF3-CARBOMETHOXY-2-PYRONES[11]

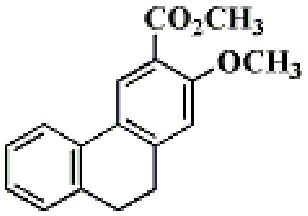
	Ketone	Method, Yield (%)	3-Carbomethoxy-2-pyrone	2
1a		A, 73%		2a
1b		A, 81%		2b
1c		B, 90%		2c
1d		B, 84%		2d
1e		B, 62%		2e
1f		B, 56%		2f

1g		B, 35% C, 59%		2g
1h		C, 47% D, 96%		2h
1i		D, 62%		2i

[a]Method A: The enolate of 1 was generated with 2.2 equiv of NaH in THF (0.2 *M*) at 0 to 25°C. Method B: The enolate of **1** was generated with 1.2 equiv of LDA in THF (0.2 *M*) at −78 to −5°C. Method C: the enolate of **1** was generated with 1.2 equiv of LDA in THF (0.2 *M*) at −78 to −5°C and closure to the α-pyrone was effected with acetic anhydride treatment at 100 to 130°C. Method D: the enolate of **1** was generated with 2.2 equiv of NaH in THF (0.2 *M*) at 0–25°C and closure to the α-pyrone was effected with catalytic p-toluenesulfonic acid treatment in refluxing toluene with distillative removal of methanol.

TABLE II

DIELS–ALDER REACTION OF 3-CARBOMETHOXY-2-PYRONES (2) WITH 1,1-DIMETHOXYETHYLENE: SALICYLATE FORMATION

3-Carbomethoxy-2-pyrone (2)	Conditions equiv time hr (temp., ° C)	Product	Yield (%)[11]
2a	8.5, 22(140)		59%

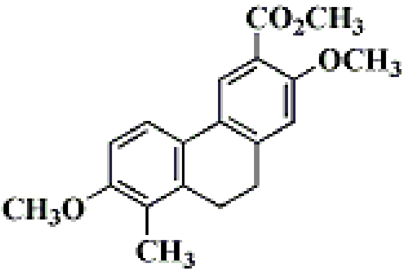
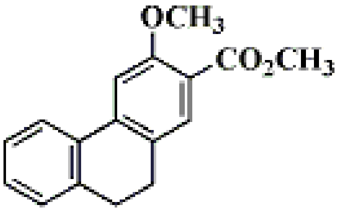
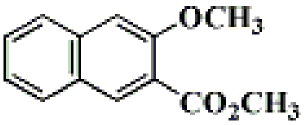
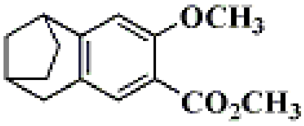
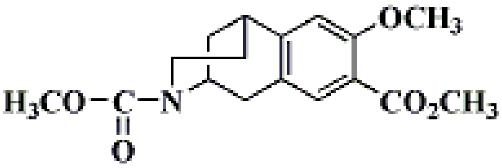
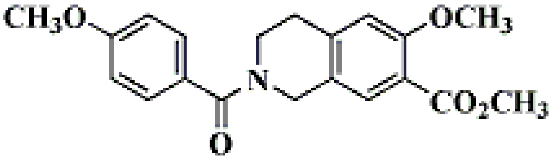
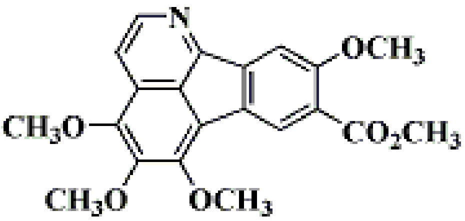
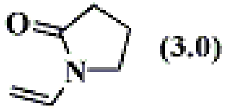
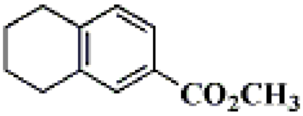
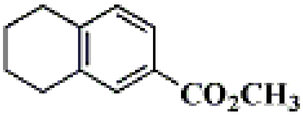
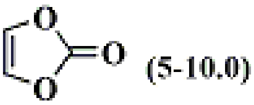
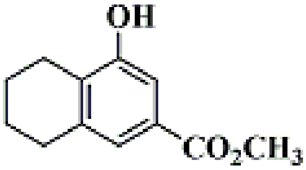
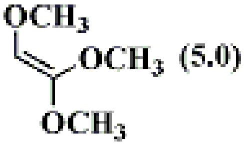
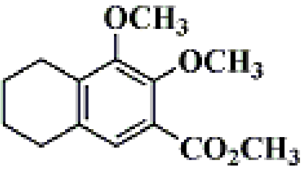
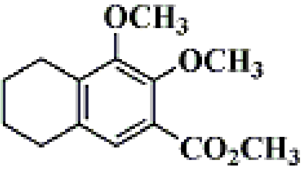
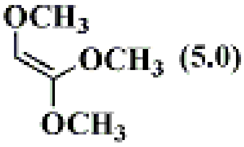
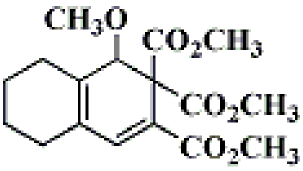
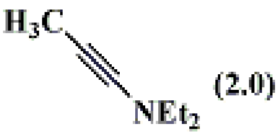
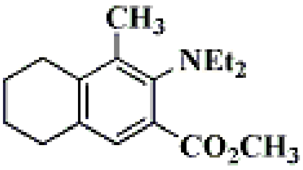
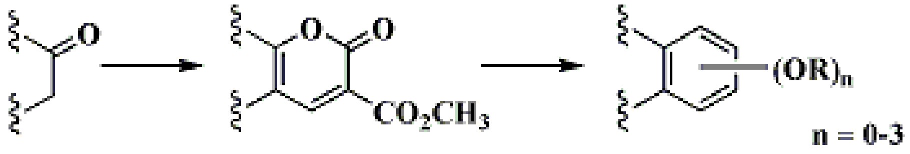
2b	10.0, 21 (140)		75%
2c	10.0, 15 (120)		78%
2d	5.5, 15(110) 5.0, 96(25), CH_2Cl_2 cat. Ni(acac)$_2$		86% 50%
2e	6.0, 12(95)		90%
2f	10.0, 13 (120)		80%
2g	10.0, 24 (120)		91%
2i	8.0, 5(120)		83%

TABLE III

DIELS–ALDER REACTIONS OF 3-CARBOMETHOXY-2-PYRONE (2d)[11]

Entry	Dienophile (equiv.)	Conditions [temp., °C (time, hr)]	Product(s)	Yield (%)
1	 (3.0)	160(42)		98%
2	(5.0)	145(43)		51%
3	 (5-10.0)	180(40)		83%
4	 (5.0)	150(78); cat. CH_3SO_3H or		57%
	(10.0)	150(84); cat. DBU 150(12)		51%
5	 (10.0)	120(59)		61%
6	 (2.0)	150(17)		43%

An application of the LUMO$_{diene}$ controlled Diels–Alder reactions of 3-carbomethoxy-2-pyrones in the preparation of a full range of oxygenated aromatics [e.g., benzene, 1-, 2-, or 3-phenol, symmetric and unsymmetric o-catechol, resorcinol, and pyrogallol introduction (Eq. 1)][11] as well as their application in the total synthesis of sendaverine, 6,7-benzomorphans, juncusol, imeluteine, and rufescine, has been described.[11]



References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

benzophenone ketyl

3-carbomethoxy-2-pyrones

sendaverine

6,7-benzomorphans

juncusol

imeluteine

rufescine

Benzene (71-43-2)

ethyl acetate, EtOAc (141-78-6)

methanol (67-56-1)

ether, ethyl ether (60-29-7)

acetic anhydride (108-24-7)

Cyclohexanone (108-94-1)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

toluene (108-88-3)

methylene chloride (75-09-2)

resorcinol (108-46-3)

pyrogallol (87-66-1)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

diethyl ethoxymethylenemalonate (87-13-8)

hexane (110-54-3)

calcium hydride (7789-78-8)

argon (7440-37-1)

α-Pyrone (504-31-4)

p-toluenesulfonic acid (104-15-4)

lithium diisopropylamide (4111-54-0)

diisopropylamine (108-18-9)

6-METHOXY-7-METHOXYCARBONYL-1,2,3,4-TETRAHYDRONAPHTHALANE

dimethyl methoxymethylenemalonate (22398-14-7)

1,1-Dimethoxyethylene (922-69-0)

6-Methoxy-7-methoxycarbonyl-1,2,3,4-tetrahydronaphthalene, 2-Naphthalenecarboxylic acid, 5, 6, 7, 8-tetrahydro-3-methoxy-, methyl ester (78112-34-2)

3-Carbomethoxy-2-pyrone

Methyl 2-oxo-5,6,7,8-tetrahydro-2H-1-benzopyran-3-carboxylate, 2H-1-Benzopyran-3-carboxylic acid, 5, 6, 7, 8-tetrahydro-2-oxo-, methyl ester (85531-80-2)

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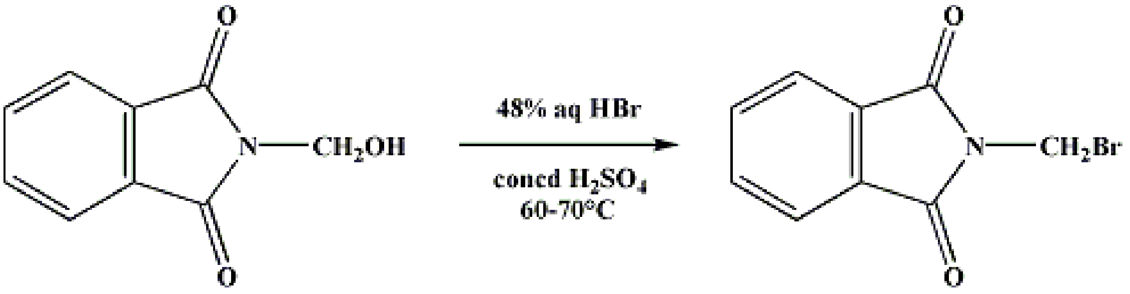
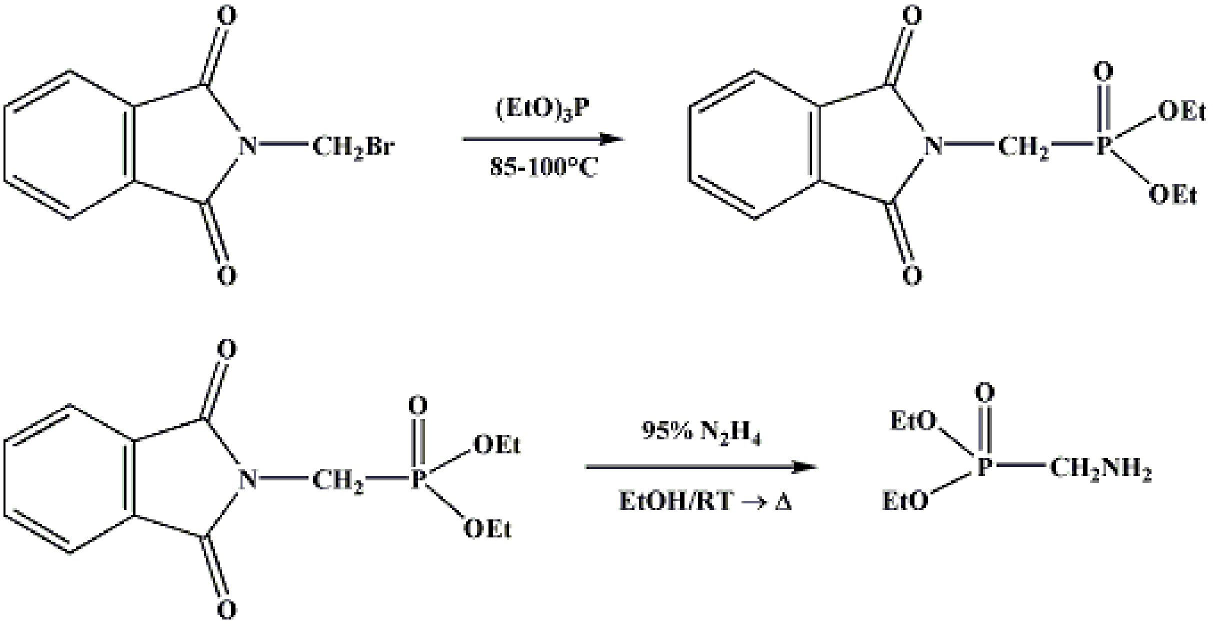
GEMINAL ACYLATION-ALKYLATION AT A CARBONYL CENTER USING DIETHYL *N*-BENZYLIDENEAMINOMETHYLPHOSPHONATE: 2-METHYL-2-PHENYL-4-PENTENAL

[4-Pentenal, 2-methyl-2-phenyl-]

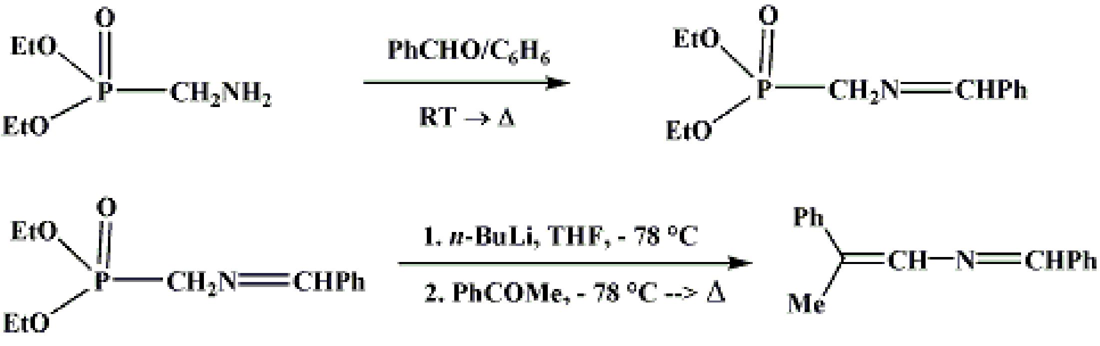
A.



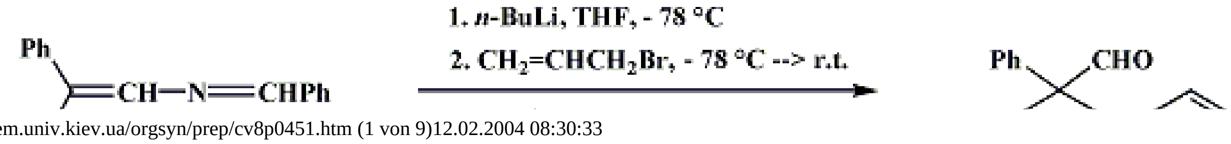
B.

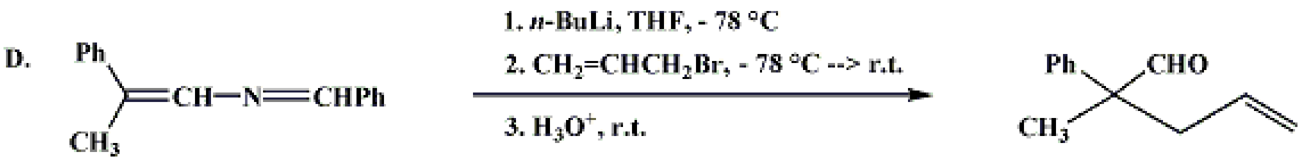


C.



D.





Submitted by Steven K. Davidsen, Gerald W. Phllips, and Stephen F. Martin[1].
Checked by Robert G. Aslanian, Max Tishler, and Andrew S. Kende.

1. Procedure

A. *N-Bromomethylphthalimide (2).* A 1-L, three-necked, round-bottomed flask is fitted with a mechanical stirrer, a 125-mL pressure-equalizing dropping funnel, and a thermometer. The flask is charged with 50.0 g (0.28 mol) of *N*-hydroxymethylphthalimide (Note 1) and 200 mL of 48% aqueous hydrobromic acid (Note 2). The flask is immersed in an ice bath, and 75 mL of concentrated sulfuric acid is added with stirring over a period of about 15 min (Note 3). On completion of the addition, the flask is removed from the ice bath, heated at 60–70°C for 5 hr, and then cooled overnight in a refrigerator. The solid is collected by suction filtration using a 125-mm glass funnel with a coarse frit. The crude product is washed thoroughly with three 100-mL portions of cold water, two 50-mL portions of cold 10% aqueous ammonium hydroxide, and finally with three 100-mL portions of cold water (Note 4). The crude product thus obtained is completely dried under reduced pressure at room temperature over phosphorus pentoxide to give 57.1–63.8 g (85–95%) of *N*-bromomethylphthalimide as a light-tan solid, mp 142–147°C. Although the material thus obtained may be used in the next step without further purification, it may also be recrystallized from dry acetone, mp 147–148°C (lit. mp 148°C,[2] 148–149°C[3]) (Note 5).

B. *Diethyl phthalimidomethylphosphonate (3).* A 500-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar and an efficient reflux condenser (ca. 80 cm long) is charged with 51.2 g (0.21 mol) of dry *N*-bromophthalimide (**2**) and 43.1 g (0.26 mol) of freshly distilled triethyl phosphite (Note 6). The mixture is immersed in an oil bath and the temperature of the oil bath gradually increased over about 15 min to 85–100°C, whereupon the solid dissolves and a vigorous, exothermic reaction ensues (Note 7). When the reaction has subsided, the oil bath is lowered and the condenser is removed. The flask is fitted for simple distillation, and ethyl bromide and other volatile materials are distilled from the reaction mixture over a period of 3–4 hr by continued heating at 115°C (oil bath). The resulting light-yellow oil is cooled to room temperature, whereupon it solidifies (Note 8). The crude product is collected by suction filtration and washed with three 100-mL portions of cold petroleum ether (bp 60–68°C) to give 50.1–56.3 g (80–90%) of diethyl phthalimidomethylphosphonate as white crystals, mp 60–63°C, which are used in the next step without further purification. Recrystallization of this material from diethyl ether/petroleum ether (bp 60–68°C) affords pure **3**, mp 65–67°C (lit.,[3] 67°C) (Note 9).

C. *Diethyl N-benzylideneaminomethylphosphonate (5).* A 2-L, two-necked, round-bottomed flask is equipped with a mechanical stirrer and a 125-mL pressure-equalizing dropping funnel fitted with a calcium chloride drying tube. The flask is charged with 50.0 g (0.17 mol) of diethyl phthalimidomethylphosphonate (**3**) dissolved in 750 mL of absolute ethanol (Note 10). To this solution is then added 6.4 g (0.19 mol) of 95% hydrazine (Note 11) in 50 mL of absolute ethanol, and the resulting mixture is stirred overnight at room temperature. The dropping funnel is replaced with a reflux condenser bearing a calcium chloride drying tube, and the mixture is heated at reflux for 4 hr and then cooled to 0–5°C in an ice bath. The precipitated phthalhydrazide is collected by suction filtration and thoroughly washed with three 125-mL portions of benzene. The excess solvents and hydrazine are completely removed under reduced pressure on a rotary evaporator and then under high vacuum (0.1 mm) (Note 12) and (Note 13). The crude diethyl aminomethylphosphonate (**4**)[4,5] (Note 14) thus obtained is dissolved in 350 mL of reagent-grade benzene, and the solution is cooled overnight in the refrigerator. Any additional phthalhydrazide that precipitates is removed by suction filtration and washed with two 25-mL portions of benzene. The filtrate and washings are combined in a 1-L, one-necked flask equipped with magnetic stirring bar, and the solution is cooled to 5–10°C, at which time 21.2 g (0.20 mol) of freshly distilled benzaldehyde is added in one portion with

stirring. The mixture is stirred for 4 hr at room temperature, the flask is fitted with a Dean–Stark trap and a reflux condenser and heated overnight at reflux with constant removal of water. The solution is cooled to approximately room temperature, and the excess solvents are removed under reduced pressure. The crude product is purified by vacuum distillation, bp 145–149°C (0.05 mm), to give 37.5–40.2 g (84–90%) of pure diethyl *N*-benzylideneaminomethylphosphonate (**5**)[6,7] as a light-yellow oil (Note 15).

D. *2-Methyl-2-phenyl-4-pentenal (7).* A dry, 100-mL, three-necked, round-bottomed flask with 14/20 joints is fitted with a magnetic stirrer, a reflux condenser, and a rubber septum (Note 16). The flask is charged with 50 mL of anhydrous tetrahydrofuran (Note 17) and cooled to −78°C in a dry ice–isopropyl alcohol bath, and a solution of butyllithium (12.0 mmol) in hexane (Note 18) is added with stirring. To this stirred solution is added dropwise via syringe a solution of 3.06 g (12.0 mmol) of diethyl *N*-benzylideneaminomethylphosphonate (**5**) in 5 mL of anhydrous tetrahydrofuran, and the colored solution is stirred an additional hour at −78°C. A solution containing 1.20 g (10.0 mmol) of freshly distilled acetophenone in 5 mL of anhydrous tetrahydrofuran is added dropwise, and the cooling bath is removed. The solution is stirred for 1 hr at room temperature and then at reflux for 2 hr. After the solution is cooled to room temperature, it is poured into a 250-mL, round-bottomed flask and the solvents are removed under reduced pressure on a rotary evaporator. The yellow residue is partitioned between 50 mL of ether and 50 mL of saturated sodium chloride. The layers are separated and the aqueous phase is extracted with three 25-mL portions of ether. The combined organic layers are washed with 50 mL of saturated sodium chloride and dried over magnesium sulfate. Magnesium sulfate is removed by filtration, and the excess solvents are then completely removed under reduced pressure on a rotary evaporator. The resulting yellow solid is dried under reduced pressure and transferred to a 100-mL, two-necked, round-bottomed flask that is fitted with a magnetic stirring bar, a nitrogen inlet, and a rubber septum. The flask is charged with 50 mL of anhydrous tetrahydrofuran and flushed thoroughly with dry nitrogen. The resulting solution of the 2-azadiene **6** (Note 20) is cooled to −78°C, and a solution of butyllithium (12.0 mmol) in hexane is added dropwise via syringe. The deeply colored solution is stirred at −78°C for 1 hr, at which time 1.81 g (15.0 mmol) of freshly distilled allyl bromide (Note 21) is added. The cooling bath is removed, and the solution is stirred for 2 hr at room temperature. The reaction is added to 50 mL of 3 *N* aqueous hydrochloric acid, and the resulting heterogeneous mixture is stirred vigorously for 18 hr at room temperature. After the addition of 50 mL of saturated sodium chloride, the layers are separated, and the aqueous layer is extracted with three 75-mL portions of ether. The combined organic layers are washed with 75-mL portions of saturated aqueous sodium bicarbonate and saturated sodium chloride, and the washings are back washed with a 50-mL portion of ether. The combined organic layers are dried over magnesium sulfate, and the excess solvents are removed under reduced pressure on a rotary evaporator. Distillation of the resulting yellow oil under reduced pressure gives 1.30–1.45 g (75–83%) of pure 2-methyl-2-phenyl-4-pentenal as a colorless liquid, bp 70–73°C (0.1 mm) (Note 22).

2. Notes

1. Although *N*-hydroxymethylphthalimide may be purchased from Aldrich Chemical Company, Inc., it may also be prepared from phthalimide and 37% aqueous formaldehyde.[8] Material prepared in this way should be dried at room temperature under reduced pressure over phosphorus pentoxide.
2. Aqueous 48% hydrobromic acid should be purchased either from Eastman Organic Chemicals or Mallinckrodt (AR) since that obtained from other sources tends to give, for unknown reasons, less satisfactory results.
3. The temperature should not be allowed to exceed 30°C during the addition.
4. Removal of *all* of the hydrobromic acid by washing is critical to the success of the next reaction. If the filtrate is not basic after washing with cold 10% aqueous ammonium hydroxide the washing should be continued until the filtrate is basic. Disconnection of the vacuum during each washing is recommended. The final aqueous wash should be no more basic than pH 8–9. Use of a rubber dam facilitates the filtration and washing.
5. The proton magnetic resonance spectrum of **2** exhibits the following absorptions ($CDCl_3$) δ: 5.42

(s, 2 H, CH_2Br), 7.65–7.91 (complex, 4 H, aromatic).

6. Triethyl phosphite was purchased from Aldrich Chemical Company, Inc.

7. The exothermic reaction usually commences after all of the solid has dissolved. It is important to allow this exothermic reaction, which lasts about 5 min, to run its course without cooling, since premature cooling results in lower yields of impure product which may be difficult to purify.

8. Use of impure *N*-bromomethylphthalimide or incomplete reaction may lead to the formation of a gummy or mushy residue at this stage, and the addition of petroleum ether (bp 60–68°C) might facilitate crystallization. Alternatively, the crude product may be purified by dissolving it in a minimum volume of anhydrous ether, addition of petroleum ether (bp 60–68°C) until the solution turns cloudy and then cooling. Scratching may be necessary to induce crystallization. Several crops of crystals may be collected, but the total yields thus obtained are generally lower than 80%.

9. The proton magnetic resonance spectrum of product **3** exhibits the following absorptions ($CDCl_3$) δ: 1.31 (t, 6 H, *J* = 7, CH_2CH_3), 3.83–4.26 (complex, 6 H, OCH_2, NCH_2P), 7.60–7.86 (complex, 4 H, aromatic).

10. Absolute ethanol was purchased from Aaper Alcohol and Chemical Company and used without further purification. Slight heating may be required to effect solution.

11. Hydrazine, 95%, was purchased from Eastman Organic Chemicals.

12. Since it may undergo reaction with benzaldehyde in the subsequent step to give benzaldehyde azine, it is advisable to remove the last traces of hydrazine by rotating the flask under reduced pressure. The submitters used an oscillating motor which operates on compressed air or vacuum and is commonly employed with Kugelrohr distilling units. One such motor is available from the Aldrich Chemical Company, Inc.

13. Diethyl aminomethylphosphonate undergoes decomposition on attempted distillation, but no deterioration of the product was observed if these operations were executed at temperatures not exceeding 30°C.

14. The proton magnetic resonance spectrum of crude **4** exhibits the following absorptions ($CDCl_3$) δ: 1.31 (t, 6 H, *J* = 7, CH_2CH_3), 2.68 (br s, 2 H, NH_2), 3.00 (d, 2 H, *J* = 10, PCH_2N), 3.95–4.27 (complex, 4 H, aromatic).

15. The proton magnetic resonance spectrum of **5** exhibits the following absorptions ($CDCl_3$) δ: 1.32 (t, 6 H, *J* = 7, CH_2CH_3), 3.85–4.24 (complex, 6 H, CH_2CH_3, PCH_2N), 7.24–7.40 (complex, 3 H, *para, meta* Ph CH), 7.64–7.75 (complex, 2 H, *ortho* Ph CH), 8.25 (d, 1 H, *J* = 5, N=CHPh). This material shows no significant tendency to deteriorate when stored under dry nitrogen at room temperature.

16. The apparatus was flame-dried under a flow of dry nitrogen and then kept under a slight positive pressure of nitrogen during the reactions by maintaining a slow flow of nitrogen through a mercury bubbler.

17. Tetrahydrofuran was distilled from the potassium ketyl of benzophenone. *(Caution: See Org. Synth., Coll. Vol. V, **1973**, 976 for a warning regarding the purification of tetrahydrofuran.)*

18. Butyllithium was prepared by dilution of 90% butyllithium obtained from Lithium Corporation of America with purified hexane or petroleum ether (bp 60–68°C) (Note 19). The normality was determined prior to use by titration according to the method of Watson and Eastham.[9]

19. Hexane was purified by preliminary stirring over concentrated sulfuric acid and then anhydrous potassium carbonate followed by distillation. The hexane thus obtained was then distilled from sodium wire.

20. The proton magnetic resonance spectrum of **6** exhibits the following absorptions ($CDCl_3$) δ: 2.52 (br s, 3 H, C-CH_3), 7.20–7.65 (complex, 9 H, aromatic), 7.86 (m, 2 H, aromatic), 8.33 (br s, 1 H, N=CHPh).

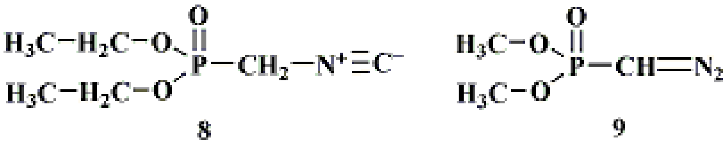
21. Allyl bromide was purchased from Aldrich Chemical Company, Inc. and distilled from pulverized calcium hydride and filtered through basic alumina (10 g) immediately prior to use.

22. The proton magnetic resonance spectrum of **7** exhibits the following absorptions ($CDCl_3$) δ: 1.32 (s, 3 H, CCH_3), 2.49 (d, 2 H, *J* = 7, $CH_2CH=CH_2$), 4.88 (m, 2 H, $CH=CH_2$), 5.45 (m, 1 H, $CH=CH_2$), 7.14 (m, 5 H, aromatic), 9.33 (s, 1 H, CHO).

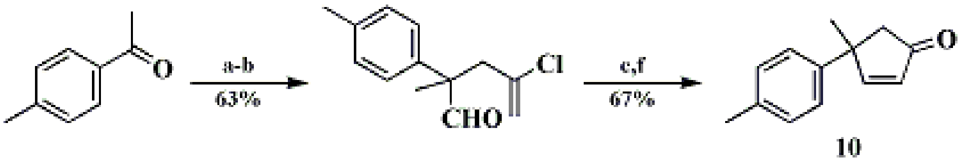
3. Discussion

The procedure in the present reaction sequence for the preparation of *N*-bromomethylphthalimide (**2**) is a modification of that reported by Pucher and Johnson.[2] *N*-Bromomethylphthalimide has also been prepared by treatment of *N*-hydroxymethylphthalimide with phosphorus tribromide.[3] The procedures for the syntheses of the phosphonates **3** and **4** represent modifications of those described by Yamauchi and co-workers.[3,4] Two other routes to **4** have recently been reported by Gross and co-workers.[5] Ratcliffe and Christensen have also recorded the preparation of diethyl *N*-benzylideneaminomethylphosphonate (**5**) by the condensation of benzaldehyde with **4** under conditions virtually identical to those detailed herein, but their route to **4** was completely different.[6] The submitters have found that the present method for the syntheses of **2–5** gives reproducibly higher yields and is more reliable and convenient than those alternative procedures.

Diethyl *N*-benzylideneaminomethylphosphonate (**5**) has been previously employed as an intermediate in the synthesis of β-lactam antibiotics[6] and as a reagent for the homologation of aldehydes and ketones via intermediate 2-azadienes.[7] Other derivatives of dialkyl aminomethylphosphonates have also emerged as useful synthetic reagents. For example, diethyl isocyanomethylphosphonate (**8**) may be employed for the conversion of aldehydes and ketones to α,β-unsaturated isocyano compounds.[10] Dimethyl diazomethylphosphonate (**9**)[11] has recently been shown to be an effective reagent for the elaboration of aldehydes or alkyl aryl ketones and diaryl ketones to alkynes[12] and for the conversion of dialkyl ketones into aldehydic enol ethers and enamines.[13]



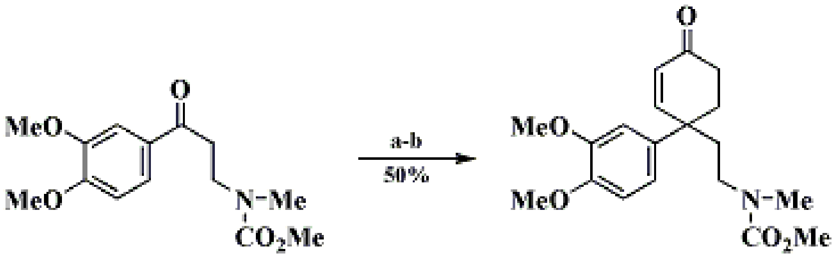
Part D of the present procedure represents a slight modification of a general method for effecting the net replacement of both of the carbon–oxygen bonds of a carbonyl group with an acyl group and a functionalized alkyl appendage; some typical examples of the original procedure are collected in Table I.[14] Moreover, when the electrophile employed for alkylation of the intermediate metalloenamine[15] is properly selected, it is possible to introduce geminal substituents at the carbonyl function that are suitably functionalized for subsequent conversion either to 4,4-disubstituted cyclopentenones (Eq. 1)[14] or 4,4-disubstituted cyclohexenones (Eq. 2).[15] The preparation of **10** represents a formal total synthesis of α-cuparenone. An annulation related to that depicted in Eq. 2, which was a key step in an efficient synthesis of mesembrine,[16] has also been featured in total syntheses of the Amaryllidaceae alkaloids lycoramine[17] and crinine.[18] Finally, the intermediate metalloenamines may be utilized as the nucleophilic partners in directed aldol reactions (Eq. 3), but it appears to be necessary to trap the intermediate β-oxidoimines by acylation or alkylation to avoid retroaldolization during the hydrolysis step.[14] Such a process has recently been exploited in the syntheses of the Amaryllidaceae alkaloids pretazettine and haemanthidine.[19]



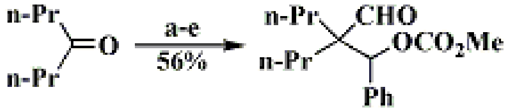
a. $(EtO)_2P(O)CHLiN=CHPh/THF/-78°C$ → reflux; b. BuLi/-78°C;

c. $CH_2=CClCH_2Cl/THF/HMPA/-78°C$ → reflux; d. H_3O^+; e. $Hg(OAc)_2/HCO_2H/RT$

f. KOH/aq MeOH/RT

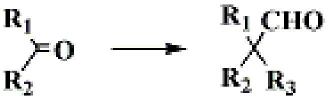


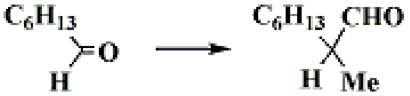
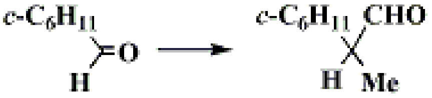
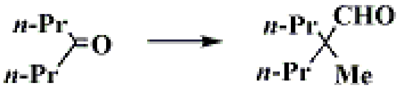
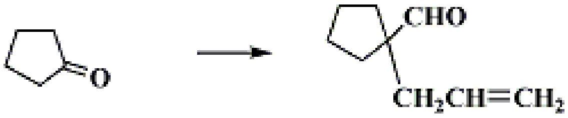
a. $(EtO)_2P(O)CHLiN{=}CHPh/THF/\text{-}78°C \rightarrow$ reflux; b. BuLi/-78°C;
c. $BrCH_2CH_2C(OCH_2CH_2O)CH_3/THF/HMPA/\text{-}78°C \rightarrow$ RT;
d. H_3O^+/RT; e. KOH/aq MeOG/RT

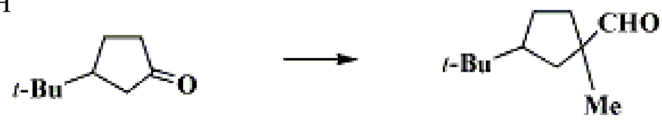
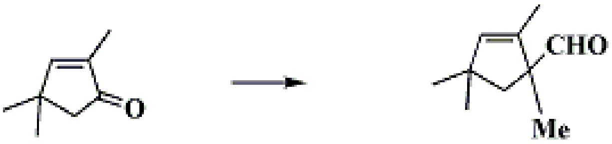
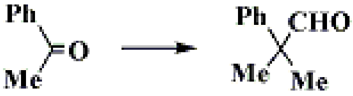


a. $(EtO)_2P(O)CHLiN{=}CHPh/THF/\text{-}78°C \rightarrow$ reflux; b. BuLi/78°C;
c. PhCHO; d. $MeOCOCl/\text{-}78°C \rightarrow$ RT; e. H_3O^+/RT

TABLE I
GEMINAL ACYLATION-ALKYLATION OF CARBONYL COMPOUNDS



Entry	R_1	R_2	R_3	Overall Yield (%)[a]
1	C_6H_{13}	H	Me 	34
2	c-C_6H_{11}	H	Me 	43
3	*n*-Pr	*n*-Pr	Me 	58
4		$-(CH_2)_5-$	$CH_2CH{=}CH_2$ 	51

5		-$(CH_2)_2$CH (*t*-Bu) $(CH_2)_2$-	Me		63[b]
6		-CH_2C (Me) $_2CH_2$C (Me)=CH-	Me		80
7	Ph	Me	Me		77

[a]Yields are of distilled products but are not optimized.

[b]As a 4 : 1 mixture of diastereoisomers.

It presently appears that this methodology is well suited for the construction of quaternary carbon atoms bearing substituted alkyl appendages containing a diverse array of functionality. In large measure this is because metalloenamines, which are the key synthetic intermediates, are highly nucleophilic and generally undergo regioselective reaction at carbon with a variety of weak and multifunctional electrophiles.

Moreover, numerous functional groups may be present on the starting aldehyde or ketone, but one report[20] suggests that carbonyl compounds bearing potential leaving groups on the carbon adjacent to the carbonyl group may not be good substrates. While a number of individual operations are required, it is frequently possible to execute the entire sequence of reactions in a single flask. In this particular preparation the sequence may also be performed in a single vessel, but purification of product 7 by simple distillation is more difficult because of the presence of lower-boiling impurities.

References and Notes

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20. For example, see Jarosz, S.; Fraser-Reid, B. *Tetrahedron Lett.*, **1981**, *22*, 2533.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

potassium ketyl of benzophenone

α-cuparenone

ethanol (64-17-5)

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether, diethyl ether (60-29-7)

formaldehyde (630-08-0)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

HYDROBROMIC ACID (10035-10-6)

Allyl bromide (106-95-6)

Ethyl bromide (74-96-4)

phosphorus tribromide (7789-60-8)

nitrogen (7727-37-9)

benzaldehyde (100-52-7)

acetone (67-64-1)

Acetophenone (98-86-2)

carbon (7782-42-5)

sodium wire (13966-32-0)

Phthalimide (85-41-6)

ammonium hydroxide (1336-21-6)

hydrazine (302-01-2)

magnesium sulfate (7487-88-9)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

Phthalhydrazide (1445-69-8)

hexane (110-54-3)

Triethyl phosphite (122-52-1)

calcium hydride (7789-78-8)

phosphorus pentoxide (1314-56-3)

2-Methyl-2-phenyl-4-pentenal, 4-Pentenal, 2-methyl-2-phenyl- (24401-39-6)

N-Bromomethylphthalimide (5332-26-3)

Diethyl phthalimidomethylphosphonate (33512-26-4)

Diethyl N-benzylideneaminomethylphosphonate (50917-73-2)

diethyl aminomethylphosphonate (50917-72-1)

diethyl isocyanomethylphosphonate (41003-94-5)

Dimethyl diazomethylphosphonate

N-hydroxymethylphthalimide (118-29-6)

N-bromophthalimide (2439-85-2)

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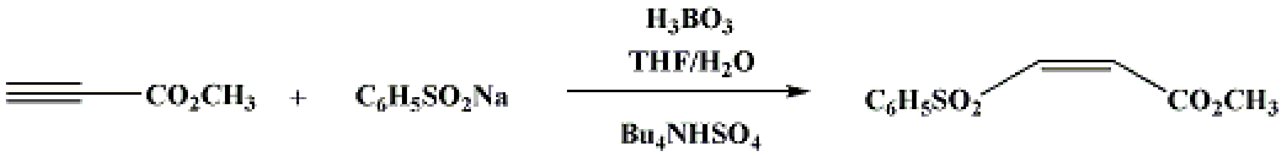
Organic Syntheses, CV 8, 458

METHYL (*Z*)-3-(PHENYLSULFONYL)PROP-2-ENOATE

[2-Propenoic acid, 3-(phenylsulfonyl)-, methyl ester, (*Z*)-]



Submitted by G. C. Hirst[1] and P. J. Parsons.
Checked by Annette Prelle and Ekkehard Winterfeldt.

1. Procedure

Caution! Methyl propiolate is a lachrymator and must be handled in a fume hood.

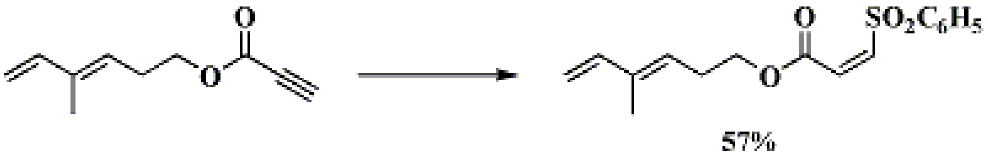
A two-phase mixture of methyl propiolate (5.0 g, 59.5 mmol), boric acid (5.5 g, 89 mmol), sodium benzenesulfinate (9.75 g, 59.5 mmol), and tetra-*n*-butylammonium hydrogen sulfate (3.0 g, 8.75 mmol) (Note 1) in tetrahydrofuran : water (200 mL, 1 : 1) is stirred vigorously at room temperature for 48 hr (Note 2). The solution is acidified to pH 4 (2 *N* hydrochloric acid) and extracted into diethyl ether (4 × 50 mL) (Note 3). The organic layer is dried ($MgSO_4$) and concentrated under reduced pressure to afford 13.75 g of yellow oil (Note 4), which is subjected to flash-column chromatography (1.5 : 1 hexanes : diethyl ether) to afford initially methyl (*E*)-3-(phenylsulfonyl)prop-2-enoate (400 mg, 2.9%) and then the desired *Z*-isomer (10.89 g, 81%) as a pale-yellow solid, pure by spectra study (Note 5).

2. Notes

1. All reagents were purchased from Aldrich Chemical Company, Inc. and were used without further purification.
2. A magnetic stirrer is usually adequate. An overhead stirrer was used for the larger scale reported here.
3. Slightly increased yields are observed if most of the organic material is removed under reduced pressure prior to extraction into ether.
4. Purity determines the structure of the product; the crude product is often a yellow solid at this point.
5. The isolated yield has ranged between 71 and 88%. The product has the following spectral and physical characteristics: mp 50.5–51.5°C (ether); IR (CH_2Cl_2) cm^{-1}: 3040 (m), 1732 (s), 1630 (m), 1440 (s), 1340 (s), 1310 (s), 1145 (s); ^1H NMR ($CDCl_3$, 360 MHz) δ: 3.92 (s, 3 H, CO_2CH_3), 6.52 (d, 1 H, *J* = 11.5), 6.57 (d, 1 H, *J* = 11.5), 7.55–8.05 (m, 5 H, Ar); ^{13}C NMR ($CDCl_3$, 90.56 MHz) δ: 52.43 (q), 127.93 (d), 129.23 (d), 131.5 (d), 133.95 (d), 135.50 (d), 139.42 (s), 164.22 (s); *m/z*: found, M^+ 226.02890; $C_{10}H_{10}O_4S$ requires M^+, 226.02998; 226 (M^+, 5), 195 (16), 161 (10), 131 (12), 77 (80), 51 (100).

3. Discussion

This procedure describes the short, one-pot, high-yield preparation of methyl (*Z*)-3-(phenylsulfonyl)prop-2-enoate. This route is shorter than a previously reported preparation.[2] We have been able to apply this technique to the preparation of a highly functionalized sulfonyl acrylate, although the generality of this reaction has not been studied (Eq. 1).[3]



Vinyl sulfones in general serve as excellent dienophiles in Diels–Alder reactions,[4] and we[5] and others[2,4] have found the resultant cyclohexene to contain very useful functionality for further manipulation. Hence the vinyl sulfone moiety can serve as a synthon for ethylene,[6] terminal olefins,[7] acetylene,[8] and vinylsilanes[9] in [4+2]-cycloadditions as well as valuable synthetic intermediates in general.[10]

References and Notes

1. Present address: Department of Medicinal Chemistry, Glaxo Group Research Ltd., Park Road, WARE, Hertfordshire, SG16 ODP, U.K. This work was carried out at the University of Southampton, Southampton, U.K. Support from the SERC is gratefully acknowledged.
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hexanes

acetylene (74-86-2)

hydrochloric acid (7647-01-0)

ether, diethyl ether (60-29-7)

ethylene (9002-88-4)

boric acid (10043-35-3)

$MgSO_4$ (7487-88-9)

Tetrahydrofuran (109-99-9)

methyl propiolate (922-67-8)

tetra-n-butylammonium hydrogen sulfate (32503-27-8)

sodium benzenesulfinate

Methyl (Z)-3-(phenylsulfonyl)prop-2-enoate, 2-Propenoic acid, 3-(phenylsulfonyl)-, methyl ester, (Z)- (91077-67-7)

methyl (E)-3-(phenylsulfonyl)prop-2-enoate

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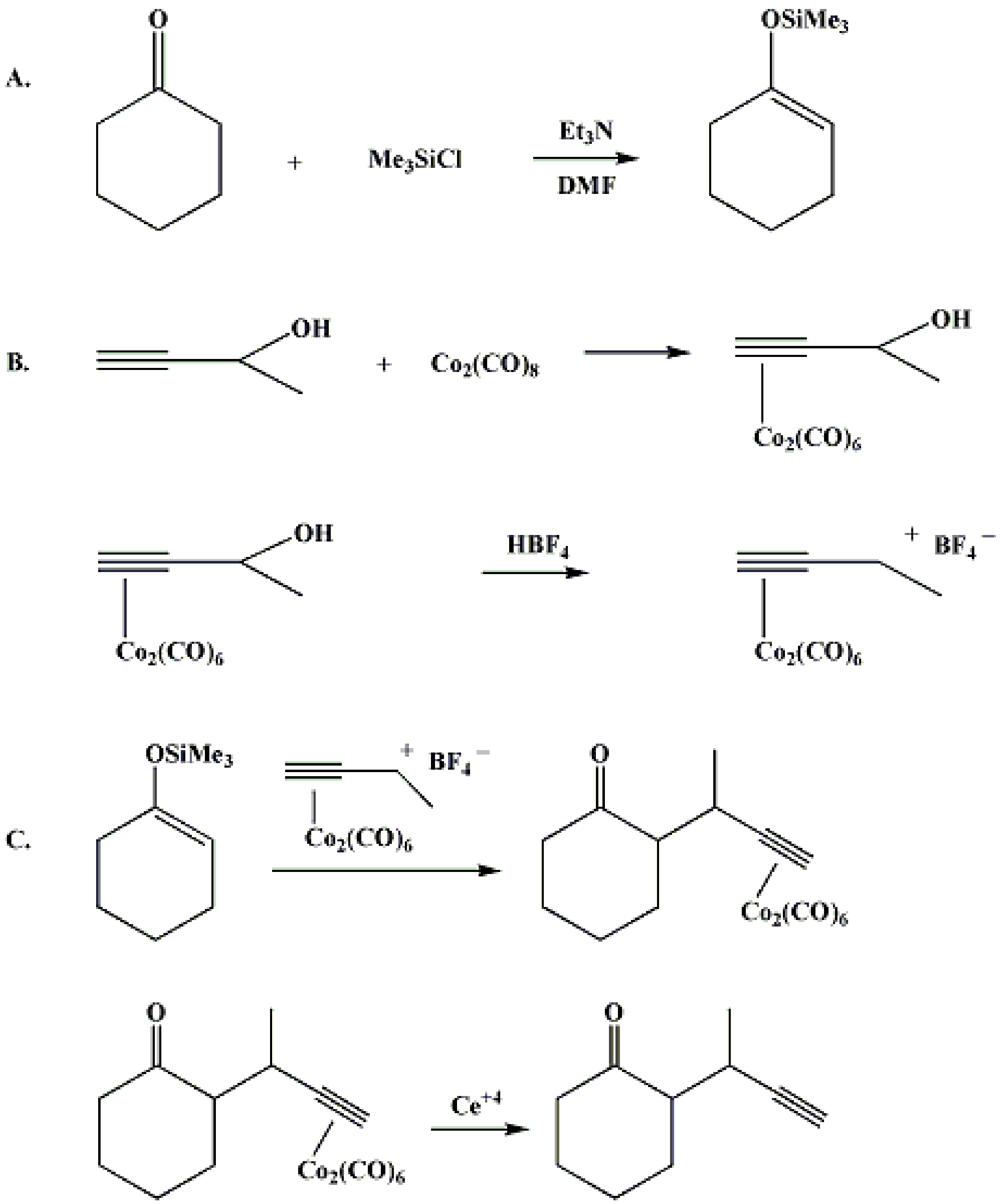
Organic Syntheses, CV 8, 460

ALKYLATIONS USING HEXACARBONYL (PROPARGYLIUM)DICOBALT SALTS: 2-(1-METHYL-2-PROPYNYL)CYCLOHEXANONE

[Cyclohexanone, 2-(1-methyl-2-propynyl)-, (*R**,*R**) and (*R**,*S**)-]



Submitted by Valsamma Varghese, Manasi Saha, and Kenneth M. Nicholas[1].

Checked by T. V. Rajanbabu, Leslie G. Upchurch, and Bruce E. Smart.

1. Procedure

Caution! Dicobalt octacarbonyl is highly toxic and air sensitive. All operations with this reagent should be carried out in an inert atmosphere and in a well-ventilated hood.

A. *1-Trimethylsiloxycyclohexene.*[2] A 1-L, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, a rubber septum, and a reflux condenser fitted with a nitrogen gas inlet tube that is attached to a mineral oil bubbler. The system is flushed with nitrogen and flame-dried, and while the system is maintained under a static pressure of nitrogen, the flask is charged with 300 mL of dry dimethylformamide (Note 1) and 110.3 g (1.1 mol) of triethylamine (Note 2); 58.3 (0.54 mol) of chlorotrimethylsilane (Note 3) is added by syringe. Cyclohexanone (40.0 g, 0.41 mol) (Note 4) is added and the mixture is refluxed with stirring for 48 hr. After the flask is cooled to room temperature, the contents are poured into 600 mL of pentane. The resulting mixture is transferred to a separatory funnel and washed with three 500-mL portions of cold aqueous sodium bicarbonate. The organic layer is washed rapidly in succession with 200 mL of cold 1.5*N* hydrochloric acid and 200 mL of cold aqueous sodium bicarbonate. The pentane solution is dried over sodium sulfate, filtered, and concentrated by rotary evaporation. The crude product is distilled through a short Vigreux column to give 53–54 g (76–77%) of 1-trimethylsiloxycyclohexene as a colorless liquid, bp 75–80°C (20–21 mm) (Note 5).

B. *Hexacarbonyl(1-methyl-2-propynylium)dicobalt tetrafluoroborate* (***1***). A 2-L, two-necked, round-bottomed flask fitted with a magnetic stirring bar, a stopper, and a gas inlet T-tube that is attached to a mineral oil bubbler is flame-dried under a flow of nitrogen. The flask is charged with 200 mL of dry dichloromethane (Note 6) and 13.0 g (0.185 mol) of 3-butyn-2-ol (Note 7). After the mixture is stirred for 15 min, 65.0 g (0.19 mol) of dicobalt octacarbonyl (Note 8) is added in portions over a few minutes while maintaining a slow stream of nitrogen. Vigorous gas evolution (*carbon monoxide!*) is observed. The mixture is stirred for 4–5 hr, and the solvent is then removed under reduced pressure (20–25 mm). The residual solid (alkyne)$Co_2(CO_6)$ complex is dissolved in 40 mL of propionic anhydride under nitrogen and cooled to –45°C in a dry ice–acetonitrile bath. Tetrafluoroboric acid–dimethyl etherate (37.3 g, 0.28 mol) (Note 9) is added with stirring. After 30 min, 600–800 mL of anhydrous diethyl ether is added with continuous stirring. The burgundy-red salt that precipitates is isolated by filtration under a flow of nitrogen (Note 10) and is thoroughly washed with anhydrous diethyl ether to give 60–61 g (76–77%) of hexacarbonyl(1-methyl-2-propynylium)dicobalt tetrafluoroborate. This material is used immediately in the following step.

C. *2-(1-Methyl-2-propynyl)cyclohexanone.* A 2-L, two-necked, round-bottomed flask

is equipped with a magnetic stirring bar, a stopper, and a pressure-equalizing dropping funnel fitted with a gas inlet T-tube that is connected to a mineral oil bubbler. The flask is flushed with nitrogen and charged with 150 mL of dry dichloromethane (Note 6) and 60.0 g (0.141 mol) of the salt from Part B. The mixture is stirred and cooled to −78°C in a dry ice/2-propanol bath, and 23.9 g (0.141 mol) of 1-trimethylsiloxycyclohexene (Part A) is added dropwise over a few minutes. The mixture is stirred at −78°C for 4 hr. After the solution is warmed to room temperature, dichloromethane is removed under reduced pressure and replaced with 400 mL of acetone. The dark-red solution of the alkyne complex is cooled to −78°C and 175 g (0.32 mol) of ceric ammonium nitrate (Note 11) is added in portions. The mixture is stirred until the gas evolution (carbon monoxide!) ceases (ca. 4 hr) (Note 12). The reaction mixture is warmed to room temperature, poured into 1 L of saturated brine solution, and extracted with four 250-mL portions of diethyl ether. The combined ether extracts are dried over magnesium sulfate, filtered, and concentrated on a rotary evaporator. The residual red oil is distilled at reduced pressure to afford 15.0–15.2 g (71–72%) of 2-(1-methyl-2-propynyl)cyclohexanone as a pale-yellow liquid, bp 57–60°C (10 mm) (Note 13).

2. Notes

1. Dimethylformamide, obtained from Aldrich Chemical Company, Inc., was vacuum distilled from calcium hydride, bp 44°C (25 mm), and stored over Linde 3A molecular sieves.
2. Triethylamine, obtained from the Aldrich Chemical Company, Inc., was distilled from potassium hydroxide prior to use.
3. Chlorotrimethylsilane, obtained from the Aldrich Chemical Company, Inc., was redistilled from calcium hydride before use.
4. Cyclohexanone was purchased from the Aldrich Chemical Company, Inc., redistilled, and stored over Linde 4A molecular sieves.
5. The product is over 99.5% pure by GLPC (6 ft × 1/8 in. 3% SP 2100 on 100–120-mesh Supelcoport column) and has the following spectral characteristics: ^{1}H NMR ($CDCl_3$) δ: 0.21 (s, 9 H), 1.55 (m, 2 H), 1.69 (m, 2 H), 2.05 (br d, 4 H), 4.88 (br s, 1 H).
6. Dichloromethane, obtained from the Aldrich Chemical Company, Inc., was distilled from calcium hydride and stored over Linde 4A molecular sieves.
7. 3-Butyn-2-ol was obtained from the Aldrich Chemical Company, Inc., and used without further purification.
8. Dicobalt octacarbonyl was obtained from Alfa Products, Morton/Thiokol, Inc. It is best weighed in a nitrogen-filled polyethylene glove bag or in a dry box.
9. Tetrafluoroboric acid–dimethyl etherate (d 1.38 g/mL) was purchased from the Aldrich Chemical Company, Inc. The submitters note that a tetrafluoroboric acid–acetic acid mixture, which is prepared by carefully adding 49% aqueous tetrafluoroboric acid (50 g, 0.28 mol) to ice-cold acetic anhydride (30.6 g, 0.30 mol), also can be used.

10. The filtration under nitrogen is conveniently carried out in a Schlenk filter flask.[3]
11. Ceric ammonium nitrate was obtained from the Aldrich Chemical Company, Inc.
12. The disappearance of the dark red (alkyne)$Co_2(CO)_6$ complex can be monitored by TLC on silica gel with a 1 : 9 diethyl ether : petroleum ether solvent mixture.
13. The product is obtained as a 2 : 1 diastereomeric mixture and is over 99% pure by GLPC (6 ft × 1/8 in. 3% SP 2100 on 100–120-mesh Supelcoport column). It has the following spectral characteristics: IR (CCl_4) 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 0.8–2.9 (br envelope, 10 H), 1.05 (d, 3 H, *J* = 7, minor diastereomer), 1.10 (d, 3 H, *J* = 7, major diastereomer), 2.15 (s, 1 H, both diastereomers); ^{13}C NMR ($CDCl_3$) δ: 16.3, 19.2, 24.2, 25.6, 24.7, 27.1, 28.4, 30.7, 41.7, 41.9, 54.1, 54.8, 68.2, 69.6, 86.3, 87.5, 209.7, 210.3; MS (70 eV) *m/e* 150, 121 (100%).

3. Discussion

In addition to their reactions with trimethylsilyl enol ethers, (propargylium)-$Co_2(CO)_6^+$ complexes react with a variety of other mild carbon nucleophiles including activated aromatic compounds,[4] β-dicarbonyl compounds,[5] other enol derivatives (enol acetates and ketones directly),[6] allylsilanes,[7] and alkyl- and alkynyl-aluminum reagents.[8,9] These reactions provide a flexible means of introducing the synthetically versatile propargyl function. Key features of propargylations using these complexes are (a) ready introduction and removal of the activating and directing -$Co_2(CO)_6$ group, (b) regiospecific attack by nucleophiles at the carbon α to the coordinated alkynyl group, giving propargyl products only (no allenic coproducts); and (c) very mild reaction conditions and good overall yields.

The method reported here appears to be the one of choice for the dependable, efficient α-propargylation of ketones. It can be applied to propargylate ketones regioselectively at either the less substituted α-position (via the trimethylsilyl enol ether) or the more substituted α-position (using the enol acetate or even the ketone directly[6]). The resulting α-propargylated ketones are very useful synthetic intermediates. They have been converted to chromanols,[10] furans,[11] other heterocycles,[11] and cyclohexenones,[12] and they undergo regiospecific hydration to 1,4-diketones that, in turn, can be converted to cyclopentenones.[13,14,15] More classical indirect ketone propargylations generally give low yields with substantial coproduction of allenic by-products, as with enamine[10,16] or acetoacetic ester propargylations.[11,17] Direct coupling of ketone enolates with propargyl halides or tosylates have rarely been attempted and can be expected to have the same limitations.

This preparation of 2-(1-methyl-2-propynyl)cyclohexanone appears to be the first reported.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

brine

dicobalt octacarbonyl

Cyclohexanone, 2-(1-methyl-2-propynyl)-, (R*,R*) and (R*,S*)-

dimethyl etherate

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ether, diethyl ether (60-29-7)

acetic anhydride (108-24-7)

carbon monoxide (630-08-0)

sodium bicarbonate (144-55-8)

Cyclohexanone (108-94-1)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

acetone (67-64-1)

carbon (7782-42-5)

potassium hydroxide (1310-58-3)

Pentane (109-66-0)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

propionic anhydride (123-62-6)

dimethylformamide (68-12-2)

triethylamine (121-44-8)

calcium hydride (7789-78-8)

CHLOROTRIMETHYLSILANE (75-77-4)

1-Trimethylsiloxycyclohexene (6651-36-1)

ceric ammonium nitrate

2-(1-Methyl-2-propynyl)cyclohexanone (130719-24-3)

3-butyn-2-ol (2028-63-9)

Hexacarbonyl(1-methyl-2-propynylium)dicobalt tetrafluoroborate (62866-98-2)

tetrafluoroboric acid (16872-11-0)

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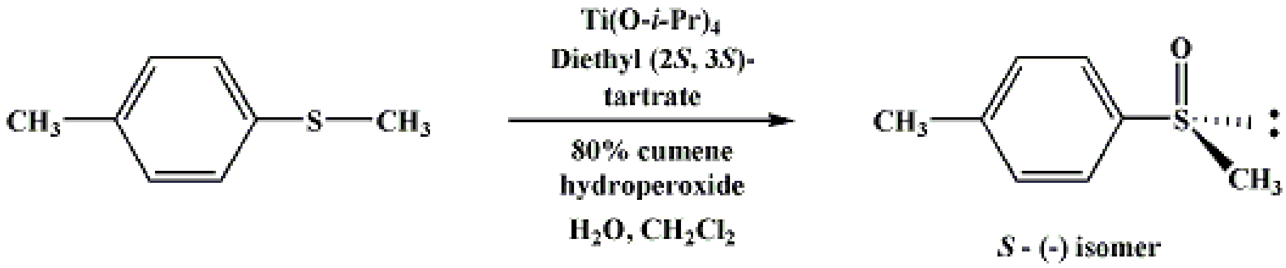
Organic Syntheses, CV 8, 464

ENANTIOSELECTIVE OXIDATION OF A SULFIDE: (*S*)-(–)-METHYL *p*-TOLYL SULFOXIDE

[Benzene, 1-methyl-4-(methylsulfinyl)-, (*S*)-]



Submitted by S. H. Zhao, O. Samuel, and H. B. Kagan[1].
Checked by Carl A. Busacca and Albert I. Meyers.

1. Procedure

Into a 1-L flask containing 125 mL of methylene chloride (Note 1) and a magnetic stirring bar (4-cm length) is added at room temperature (20°C) 5.35 mL, 6.19 g (0.030 mol) of (*S*,*S*)-(–)-diethyl tartrate (DET) (Note 2) by means of a 10-mL syringe. The flask is stoppered with a septum cap and purged with argon. Titanium(IV) isopropoxide, $Ti(OiPr)_4$, (4.48 mL, 0.015 mol) (Note 3) is introduced through the septum via a 10-mL syringe. The stirred limpid solution immediately turns yellow. After a few minutes distilled water (0.27 mL, 0.015 mol) is added dropwise using a calibrated syringe. Strong stirring is maintained until there is total dissolution of water and formation of a pale-yellow solution (after 25 min). Methyl *p*-tolyl sulfide (4.09 mL, 4.20 g, 0.030 mol) (Note 4) dissolved in 5 mL of methylene chloride is introduced with a 10-mL syringe that is then rinsed with 5 mL of methylene chloride. The flask is cooled (–30°C) with an acetone–dry ice bath while it is stirred for 40 min. At this point 5.54 mL of 80% cumene hydroperoxide (Note 5) (0.030 mol, 5.70 g) is added dropwise from a 10-mL syringe, with stirring, during 5 min. The reaction flask is kept in a freezer (–23°C) overnight (15 hr) (Note 6). Hydrolysis is then effected by adding 5.05 mL of water followed by vigorous stirring for 90 min at room temperature (20°C).

A large sintered-glass funnel (9-cm diameter, porosity grade 2) is partially filled with Celite (Celite height: 2.5 cm) and then impregnated with methylene chloride. The suspension resulting from hydrolysis is poured in portions onto the Celite under suction by a water pump. The Celite is washed many times with 50-mL portions of technical-grade methylene chloride. In order to accelerate filtration and to improve washing, the surface of the Celite is disturbed from time to time with a spatula. The filtration time is approximately 50 min. The filtrate (300 mL) is then vigorously stirred for 1 hr in a mixture of 80 mL of 2 *N* sodium hydroxide and 40 mL of saturated aqueous sodium chloride. The organic phase [negative test for peroxides using a Merck kit (Merkoquant 1001 l)] is decanted, dried (magnesium sulfate or sodium sulfate), filtered and concentrated in a Büchi apparatus (bath temperature: 45°C) to leave 10 g of an oily material that is a mixture of methyl *p*-tolyl sulfoxide, 2-phenyl-2-propanol, and some starting sulfide.

Optically pure sulfoxide is then easily isolated as follows. The crude product (10 g) is diluted with 4 mL of a solvent mixture (ethyl acetate/cyclohexane = 9 : 1). This solution is poured onto a column (75-mm diameter) filled with 120 g of silica gel (Merck 230–400 mesh) for flash chromatography. Elution is performed under gravity and requires ca. 200 mL of the above solvent

system, followed by ca. 200 mL of ethyl acetate. 2-Phenyl-2-propanol mixed with methyl *p*-tolyl sulfide is eluted in the first fraction (ca. 150 mL, monitored by TLC). The subsequent fractions are collected (ca. 300 mL) and evaporated, giving 4.0 g of methyl *p*-tolyl sulfoxide $[\alpha]_D$ –88° (acetone, *c* 1), 89% ee, 85% yield. This material is crystallized once from 60 mL of hot hexane, to afford, after 2 hr at 20°C, 3.14 g (68%) of enantiomerically pure (Note 7) (*S*)-(–)-methyl *p*-tolyl sulfoxide as needles, $[\alpha]_D$ –142° (acetone, *c* 1), mp 73–76°C (Reichert microscope with heating system).

The chemical purity of the compound is checked by ^{1}NMR (250 MHz) and thin-layer chromatography (silica gel, eluent: ethyl acetate), which show the complete absence of the corresponding sulfide and sulfone (Note 8).

2. Notes

1. Methylene chloride, technical grade (99.5%), was passed through a column of basic alumina (grade I) and then stored over molecular sieves (Linde 4A).
2. (–)-Diethyl (*S*,*S*)-tartrate was obtained from the Aldrich Chemical Company, Inc. and was distilled (bp 120°C at 2 mm).
3. Titanium(IV) isopropoxide, $Ti(OiPr)_4$ (Aldrich Chemical Company, Inc.) was distilled under an inert atmosphere (nitrogen or argon) and stored in a flask with a septum cap under argon (bp 85°C at 1.5 mm).
4. Methyl *p*-tolyl sulfide, available from Aldrich Chemical Company, Inc., was distilled (bp 95°C at 18 mm) before use.
5. Cumene hydroperoxide, obtained from Aldrich Chemical Company, Inc., technical grade (80%), was dried overnight over Linde 4A molecular sieves (pellets) prior to use.
6. A standard freezer without accurate temperature control was used; it is estimated that the temperature is –23 ± 1°C. One night is a convenient reaction time, but oxidation is in fact complete after a few hours.
7. Enantiomerically pure (*R*)-(+)-methyl *p*-tolyl sulfoxide, prepared from (–)-menthyl *p*-tolylsulfinate,[2,3,4] was described with the following specific rotations: $[\alpha]_D$ +145.5° (acetone),[3] $[\alpha]_D^{25}$ +168° (acetone, *c* 1.8),[4] $[\alpha]_D$ +189° ($CHCl_3$, *c* 1).[5] The submitters checked a sample prepared[3,4] and kindly provided by Professor G. Solladié (Strasbourg), which was recrystallized from hexane: $[\alpha]_D$ +146° ± 1 (acetone, *c* 1), mp 76–77°C. HPLC analysis carried out on a chiral stationary phase shows the absence of the enantiomer (Dr. Tambute, private communication). The same analysis shows that the product obtained by the procedure described above is of 99.5% ee.
8. The checkers attempted chromatography of the three-component mixture on a 150-mmol scale using 55- and 75-mm diameter columns. However, mixed fractions were obtained even with seemingly large R_f differences for the components.

3. Discussion

Both enantiomers of methyl *p*-tolyl sulfoxide are available from this procedure by selection of the appropriate diethyl tartrate. This procedure describes the preparation of (*S*)-(–)-methyl *p*-tolyl sulfoxide, which is not easy to prepare by the Andersen method[2,3,4] using (+)-menthol.

Cumene hydroperoxide was selected because it was recently observed[6] that it gives in many cases better ee values in asymmetric oxidation of sulfides than the original procedure with *t*-butyl

hydroperoxide.[7,8,9]

The enantiomeric purity of the crude (*S*)-methyl *p*-tolyl sulfoxide produced from the oxidation is close to 90% (measurement made on a sample of 200 mg of material purified by flash chromatography on silica gel; eluant: ethyl acetate : ethanol = 96 : 4). However, when oxidation is performed on a 10-mmol scale, enantioselectivity is improved (96% ee, 87% isolated yield).[6] We have no explanation for this optimum scale effect. It could be because of easier temperature control on a small scale (there is a decrease of enantioselectivity above –20°C or below –25°C).[7]

tert-Butyl hydroperoxide (anhydrous toluene solution prepared as described in [9]) was also used as the oxidant on a 0.11-mol scale in the presence of 0.10 mol of methyl *p*-tolyl sulfide and 0.053 mol of chiral titanium complex (Ti/DET/H_2O = 1 : 2 : 1). The procedure is identical to the one described above using cumene hydroperoxide. The ee of the crude sulfoxide is 84%. Pure (*S*)-methyl *p*-tolyl sulfoxide $[\alpha]_D$ –146° (acetone, *c* 1) is obtained without flash chromatography by three recrystallizations of the crude material from hexane in 50% yield (with respect to sulfide).

Preparation of various enantiomerically pure sulfoxides by oxidation of sulfides seems feasible in the cases where asymmetric synthesis occurs with ee values in the range of 90% giving crystalline products that can usually be recrystallized up to 100% ee. Aryl methyl sulfides usually give excellent enantioselectivity during oxidation[6,7,8,9] and are good candidates for the present procedure. For example, we have shown on a 10-mmol scale that optically pure (*S*)-(–)-methyl phenyl sulfoxide $[\alpha]_D$ –146° (acetone, *c* 1)[6] could be obtained in 76% yield after oxidation with cumene hydroperoxide followed by flash-chromatographic purification on silica gel and recrystallizations at low temperature in a mixed solvent (ether-pentane). Similarly, (*S*)-(–)-methyl *o*-methoxyphenyl sulfoxide, $[\alpha]_D$ –339° (acetone, *c* 1.5; 100% ee measured by HPLC), was obtained in 80% yield by recrystallizations from hexane.

The method with cumene hydroperoxide has recently been used with success[10] to prepare both enantiomers of methyl *p*-methoxyphenyl sulfoxide, which were then taken as starting material for the total synthesis of biological compounds. It also applies to transformation of some 1,3-dithianes into 1,3-dithiane 1-monoxides, with ee values up to 80%.[11] This enantioselectivity was achieved by optimization of reaction temperature; ee was maximum at –40°C.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

(S)-(−)-METHYL p-TOLYL SULFOXIDE

(S,S)-(−)-diethyl tartrate

(−)-Diethyl (S,S)-tartrate

(−)-menthyl p-tolylsulfinate

titanium complex

(S)-(−)-methyl phenyl sulfoxide

(S)-(−)-methyl o-methoxyphenyl sulfoxide

ethanol (64-17-5)

ethyl acetate (141-78-6)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

cyclohexane (110-82-7)

acetone (67-64-1)

Pentane (109-66-0)

(+)-menthol (15356-60-2)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

hexane (110-54-3)

argon (7440-37-1)

tert-butyl hydroperoxide, t-butyl hydroperoxide (75-91-2)

diethyl tartrate

titanium(IV) isopropoxide (546-68-9)

cumene hydroperoxide

2-phenyl-2-propanol (617-94-7)

methyl p-tolyl sulfide (623-13-2)

Benzene, 1-methyl-4-(methylsulfinyl)-, (S)-, (S)-methyl p-tolyl sulfoxide (5056-07-5)

methyl p-tolyl sulfoxide (1519-39-7)

(R)-(+)-methyl p-tolyl sulfoxide

methyl p-methoxyphenyl sulfoxide

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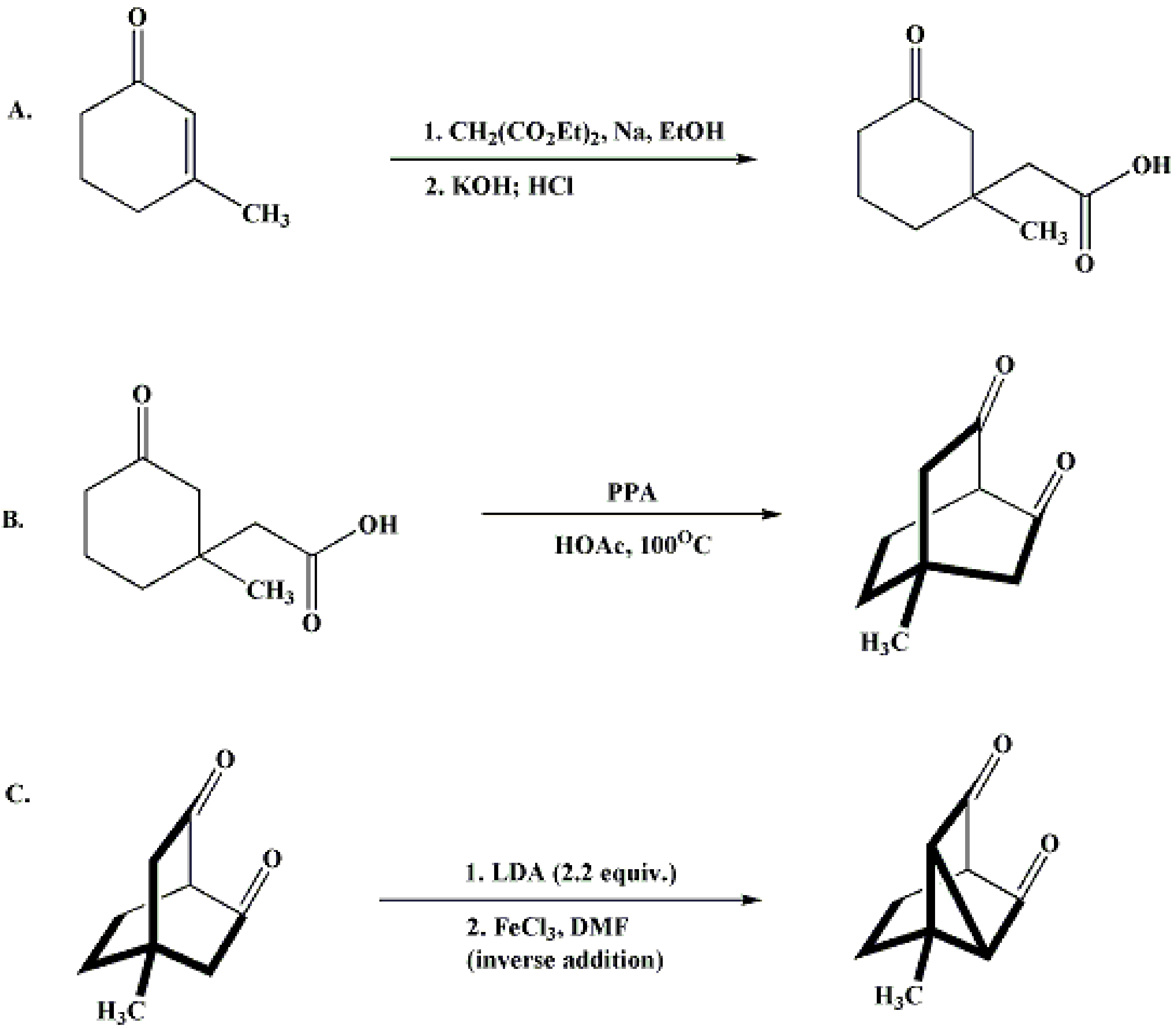
Organic Syntheses, CV 8, 467

INTRAMOLECULAR OXIDATIVE COUPLING OF A BISENOLATE: 4-METHYLTRICYCLO[2.2.2.0^{3,5}]OCTANE-2,6-DIONE

[Tricyclo[3.2.1.0^{2,7}]octane-6,8-dione, 2-methyl-]



Submitted by Marc-André Poupart, Gilbert Lassalle, and Leo A. Paquette[1].
Checked by L. A. Stolz and Robert K. Boeckman, Jr..

1. Procedure

A. *3-Methylcyclohexanone-3-acetic acid.* A 2-L, three-necked Morton flask fitted with a low-temperature thermometer, a 250-mL addition funnel, an exit tube attached to a calcium chloride drying tube, and a Teflon-coated magnetic stirring bar is charged with 1.1 L of anhydrous ethanol. The stirred solution is cooled to 0°C and 23 g (1 mol) of sodium cut into small pieces is added through the exit tube. During the addition, the temperature of the reaction mixture increases; therefore, cooling is applied (Note 1). After all of the sodium has completely reacted, 160.2 g (1 mol) of neat diethyl malonate is slowly added through the addition funnel while the temperature is

maintained at 0°C (Note 2). At this point, 110.2 g (1 mol) of 3-methyl-2-cyclohexen-1-one (Note 3) is gradually introduced through the addition funnel at 0°C. A white precipitate eventually appears. After 9 days of stirring, the brown reaction mixture is poured onto ice, brought to neutrality with concentrated hydrochloric acid while being vigorously stirred, and extracted with one 600-mL portion and four 300-mL portions of ether (Note 4). The combined organic layers are washed with three 250-mL portions of saturated brine and dried over anhydrous magnesium sulfate. After evaporation under reduced pressure to remove the solvent, the residual oil is distilled through a 20-cm Vigreux column under reduced pressure. The first fraction (bp <60°C at 0.15 mm) consists of a mixture of unreacted starting materials. The second fraction (bp 145–165°C at 1.5 mm), a mixture of diesters (Note 5), is a colorless oil: 202–205 g (74–76%).

In a 2-L, one-necked, round-bottomed flask fitted with a magnetic stirring bar is placed 99 g (0.366 mol) of the diesters. A 1.0-*M* solution of potassium hydroxide (750 mL, 0.75 mol) is added to the flask with stirring. The mixture is stirred overnight and subsequently heated to reflux for 1 hr. After the mixture is cooled, it is acidified with 100 mL of concentrated hydrochloric acid and gently boiled for 20 min. Following return to room temperature, the mixture is transferred to a 2-L separatory funnel and extracted with dichloromethane (6 × 100 mL). The combined organic layers are washed with saturated brine (100 mL) and dried over sodium sulfate. The solvent is removed in a rotary evaporator and the residue is distilled in a Kugelrohr apparatus (140–160°C and 0.3–0.5 mm) to provide 49.3 g (79%) of the keto acid (Note 6).

B. *4-Methylbicyclo[2.2.2]octane-2,6-dione.* A 2-L, three-necked, Morton flask fitted with a mechanical stirrer, a thermometer, and a reflux condenser is charged with 245.0 g of polyphosphoric acid (PPA, (Note 7)), 26.8 g (158 mmol) of the keto acid, and 427 mL of glacial acetic acid. The vigorously stirred mixture is heated at 100°C for 7 hr. After being cooled, the reaction mixture is diluted with 500 mL of saturated brine and extracted with four 200-mL portions of benzene (Note 8). The combined organic layers are washed with saturated sodium bicarbonate (4 × 100 mL) and brine (1 × 100 mL) solutions, and dried over anhydrous magnesium sulfate. After removal of the solvents on a rotary evaporator, the viscous residue is distilled under reduced pressure in a Kugelrohr apparatus, affording 11.0–13.3 g (46–55%) of cyclized diketone as a colorless liquid, bp 100°C at 0.1 mm, which may solidify on standing at room temperature (Note 9).

C. *4-Methyltricyclo[2.2.2.0^{3,5}]octane-3,5-dione.* A 500-mL, one-necked, round-bottomed flask fitted with a Teflon-coated magnetic stirring bar and a rubber septum is charged under nitrogen with a solution of 30.8 mL (220 mmol) of dry diisopropylamine in 170 mL of anhydrous tetrahydrofuran. The solution is cooled to 0°C (acetone–dry ice bath), and 137.5 mL (220 mmol) of a 1.6 *M* solution of butyllithium in hexanes is introduced over a 35-min period. The resulting colorless solution is stirred for 15 min at 0°C and then cooled to −78°C.

The diketone (15.20 g, 100 mmol) is dissolved in 27 mL of dry tetrahydrofuran in a 50-mL, round-bottomed flask and added dropwise through a 16-gauge cannula (nitrogen pressure) during 35 min to the lithium diisopropylamide solution. This mixture is stirred for 30 min at −78°C and is added in turn to 280.4 mL (300 mmol) of a 1.07 *M* solution of anhydrous ferric chloride (Note 10) in dry dimethylformamide, diluted with 39 mL of dry dimethylformamide and contained in a 1-L, three-necked, round-bottomed flask equipped with an efficient mechanical stirrer and cooled to −78°C (Note 11). This addition is accomplished as rapidly as possible through an 8-gauge cannula (nitrogen pressure). After the reaction mixture is stirred for 2 hr at −78°C, it is quenched by the dropwise addition of 24 mL of dry methanol and allowed to reach room temperature. Saturated brine (300 mL) is added and the entire mixture is filtered through Celite. The aqueous phase is extracted with four 250-mL portions of ether. The combined organic layers are washed with saturated brine (3 × 150 mL) and dried over anhydrous magnesium sulfate. After solvent evaporation under reduced pressure, the

residue is chromatographed (100 g of TLC-grade silica gel; eluant is 15% ethyl acetate in petroleum ether). There is isolated 6.4–6.5 g (43%, (Note 12)) of the cyclized diketone as a colorless oil (Note 13) and 1.11 g (7.3%) of starting material.

2. Notes

1. Cooling should be applied to moderate the reaction while maintaining a vigorous evolution of gas or the reaction time is prolonged unduly.
2. Cooling below 0°C will induce precipitation of the sodium diethyl malonate.
3. 3-Methyl-2-cyclohexen-1-one can be purchased from the Aldrich Chemical Company, Inc. or prepared according to a known procedure.[2] Checkers obtained material from Aldrich Chemical Company, Inc. and Lancaster Synthesis, Inc.
4. The checkers employed 600 mL of ether in the first extraction to ensure separation of the phases.
5. According to the literature,[3] these esters consist of the product of Michael addition to 3-methylcyclohexenone and of an isomer arising from rearrangement of this primary adduct.
6. The keto acid exhibits the following spectral properties: IR (neat) cm^{-1}: 3500–2500, 1730, 1705; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.07 (s, 3 H), 1.61–1.77 (m, 2 H), 1.77–1.97 (m, 3 H), 2.14–2.44 (m, 5 H), 8.4–10 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.8, 25.3, 35.7, 38.0, 40.7, 45.4, 53.0, 176.9, 179.7.
7. Polyphosphoric acid can be prepared by the addition of 200 g of phosphorus pentoxide (P_2O_5) to 100 mL of an 85% solution of phosphoric acid and heating to 170°C with vigorous stirring until all of the P_2O_5 is dissolved (ca. 6 hr).
8. Continuous extraction of the aqueous phase with toluene can also be applied for 3 days in order to yield 80% of the diketone after Kugelrohr distillation.
9. The pure diketone is a colorless solid, mp 75–76°C; IR (neat) cm^{-1}: 1735, 1710; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.17 (s, 3 H), 1.67–1.73 (m, 2 H), 2.07–2.13 (m, 2 H), 2.22 (ABq, 4 H, J_{AB} = 8.0, $\Delta\nu_{AB}$ = 35.05), 3.16 (t, 1 H, J = 2.9); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 22.7, 25.7, 31.0, 33.9, 50.4, 63.4, 206.6.
10. The 1.07 *M* anhydrous ferric chloride solution in dimethylformamide is prepared as follows: 178.43 g (1.1 mmol) of anhydrous solid ferric chloride is refluxed over 360 mL of thionyl chloride for 4 days at atmospheric pressure. After the solution is cooled, thionyl chloride is removed by distillation at 20 mm and trapped in a 1-L, round-bottomed flask cooled to −78°C. The sold residue is stirred for 1 hr at room temperature under reduced pressure (ca. 20 mm) and heated at 40°C for 1 hr under high vacuum (ca. 1 mm). Drying without heating is then continued overnight under high vacuum. The flask is filled with argon and cooled to 0°C. Approximately 600 mL of freshly distilled dimethylformamide is then slowly added (exothermic reaction). The entire dissolution of solid ferric chloride is achieved in an ultrasound bath during 24 hr. After decantation, the dark brown solution is transferred under argon to a 1-L volumetric flask and the required level is adjusted with freshly distilled dimethylformamide.
11. The checkers found that vigorous mechanical stirring was required because of the viscosity of the dimethylformamide solution at −78°C; otherwise, diminished yields were observed.
12. The yields obtained range from 40 to 54% depending principally on the rate of the inverse addition and the scale of the reaction.
13. The tricyclic diketone, a colorless oil which slowly solidifies, exhibits mp 34.5–35.0°C; IR (neat) cm^{-1}: 1760, 1710; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.26 (s, 3 H), 2.00–2.06 (m, 2 H), 2.27–2.30 (m, 2 H), 2.46–2.68 (m, 1 H), 2.68 (d, 2 H, J = 1.3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.3, 26.6, 30.9, 47.1, 48.9, 52.6, 203.5.

3. Discussion

The initial Michael addition step is a modified and improved version of a procedure originally developed by Farmer and Ross.[3] The second step involving acid-catalyzed dehydration of the cyclohexanone-3-acetic acid is adapted from earlier work developed for the desmethyl series.[4]

The intermolecular dimerization of ketone enolates to give 1,4-diketones has been accomplished earlier with cupric[5 6,7] and ferric salts.[8] These transition-metal salts have also been used to achieve intramolecular carbon–carbon bond formation.[7,9,10] However, Step C represents the only reported example[11] of cyclopropane construction via technology of this type.

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12. Unpublished results courtesy of Deeter, J. B. (Eli Liily Company).

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

brine

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether (60-29-7)

thionyl chloride (7719-09-7)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

potassium hydroxide (1310-58-3)

toluene (108-88-3)

sodium (13966-32-0)

phosphoric acid (7664-38-2)

ferric chloride (7705-08-0)

diethyl malonate (105-53-3)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

dimethylformamide (68-12-2)

argon (7440-37-1)

3-methyl-2-cyclohexen-1-one, 3-methylcyclohexenone

lithium diisopropylamide (4111-54-0)

diisopropylamine (108-18-9)

phosphorus pentoxide (1314-56-3)

4-Methyltricyclo[2.2.2.0^{3,5}]octane-2,6-dione, Tricyclo[3.2.1.0^{2,7}]octane-6,8-dione, 2-methyl- (119986-99-1)

sodium diethyl malonate

3-Methylcyclohexanone-3-acetic acid (119986-97-9)

4-Methylbicyclo[2.2.2]octane-2,6-dione (119986-98-0)

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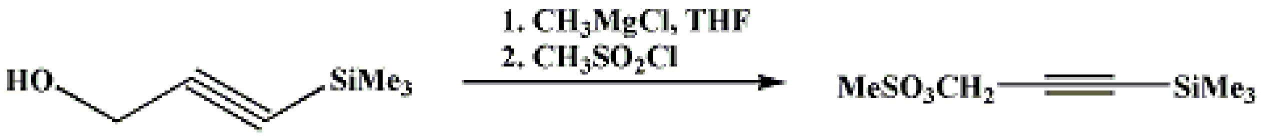
Organic Syntheses, CV 8, 471

A GENERAL METHOD FOR THE SYNTHESIS OF ALLENYLSILANES: 1-METHYL-1-(TRIMETHYLSILYL)ALLENE

[Silane, trimethyl(1-methyl-1,2-propadienyl)-]



Submitted by Rick L. Danheiser, Yeun-Min Tsai, and David M. Fink[1].
Checked by Marianne Marsi and Bruce E. Smart.

1. Procedure

A 500-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, a rubber septum, a low-temperature thermometer, and a 250-mL pressure-equalizing dropping funnel fitted with a nitrogen inlet adapter (Note 1). The flask is charged with 30.0 g (0.234 mol) of 3-trimethylsilyl-2-propyn-1-ol (Note 2) and 230 mL of dry tetrahydrofuran (Note 3), and then cooled with an ice bath while 84 mL of a 2.8 *M* solution of methylmagnesium chloride in tetrahydrofuran (Note 4) is added at such a rate that the internal temperature does not rise above 10°C. Approximately 1.5 hr is required for the addition, after which time the gray solution is stirred at 0°C for 30 min, and then cooled below −70°C with a dry ice–acetone bath. Methanesulfonyl chloride (26.8 g, 0.234 mol) (Note 5) is added over 10 min via syringe, and after 30 min the cold bath is removed and the pale-yellow reaction mixture is allowed to warm to room temperature over 2 hr.

A 2-L, three-necked, round-bottomed flask equipped with a vacuum adapter and two glass stoppers (Note 1) is charged with 21.4 g (0.246 mol) of anhydrous lithium bromide and 35.3 g (0.246 mol) of anhydrous cuprous bromide (Note 6). The reaction vessel is evacuated and the contents are briefly heated with a Bunsen burner flame. After 30 min the vacuum is replaced by nitrogen and the apparatus is equipped with a mechanical stirrer and two rubber septa. Dry tetrahydrofuran (260 mL) (Note 3) is added, and the resulting green solution containing a small amount of undissolved solid is cooled with an ice bath while 84 mL of a 2.8 *M* solution of methylmagnesium chloride in tetrahydrofuran (Note 4) is added rapidly via syringe over 1–2 min. After 20 min of further stirring at 0°C, the reaction mixture appears as a viscous yellow-green

suspension. The solution of the mesylate derivative of 3-trimethylsilyl-2-propyn-1-ol prepared above is now transferred via cannula over 45 min to the reaction mixture, which is cooled below –70°C with a dry ice–acetone bath. After 30 min, the cold bath is removed and the green reaction mixture is stirred at room temperature for 2 hr. The blue-gray mixture is then poured into a 2-L Erlenmeyer flask containing a magnetically stirred mixture of 400 mL of pentane, 200 mL of water, and 400 mL of saturated ammonium chloride solution. The organic phase is separated and washed successively with two 200-mL portions of saturated ammonium chloride solution, ten 1-L portions of water (Note 7), and 100 mL of saturated sodium chloride solution. The organic phase is dried over anhydrous sodium sulfate, and the drying agent is removed by filtration. The solvent is removed from the filtrate by atmospheric distillation through a 10-cm Vigreux column. The residual liquid is carefully distilled through a 12-cm column packed with glass helices to give 21.3–22.2 g, (72–75%) of 1-methyl-1-(trimethylsilyl)allene as a colorless liquid, bp 111°C (Note 8),(Note 9),(Note 10)(Note 11).

2. Notes

1. The apparatus is flame-dried at 20 mm pressure and then maintained under an atmosphere of nitrogen during the course of the reaction.

2. 3-Trimethylsilyl-2-propyn-1-ol was obtained from Petrarch Systems, Inc. and used as received. Alternatively, it can be prepared by the silylation of 2-propyn-1-ol.[2]

3. Tetrahydrofuran was distilled from sodium benzophenone ketyl immediately before use.

4. Methylmagnesium chloride in tetrahydrofuran was purchased from Aldrich Chemical Company, Inc.

5. Methanesulfonyl chloride was obtained from the Aldrich Chemical Company, Inc. and purified by distillation from phosphorus pentoxide before use.

6. Lithium bromide, obtained from Aldrich Chemical Company, Inc., and cuprous bromide, supplied by Fluka Chemical Corporation, were dried at 120°C (0.02 mm) for 8 hr before use. The checkers obtained lower yields (54–58%) with cuprous bromide that was supplied by other commercial sources.

7. This procedure conveniently removes tetrahydrofuran from the organic phase.

8. The submitters report bp 112–113°C and state that an additional 2.2 g (7%) of product, bp 54–56°C (90 mm), can be obtained by combining the distillation forerun with the pot residue and redistilling the mixture at reduced pressure.

9. The allenylsilane thus obtained was found by ^{1}H NMR analysis to be contaminated with 7–8% of 1-trimethylsilyl-1-butyne. This material is suitable for use in [3+2] annulations.[3] Efficient stirring during the formation of the mixed cuprate reagent is important in minimizing the amount of this impurity produced in the reaction.

10. The submitters note that if pure 1-methyl-1-(trimethylsilyl)allene is required, the mixture of allenylsilane and 1-trimethylsilyl-1-butyne is treated with 0.15 equiv of silver nitrate in 10:1 methanol–water at room temperature for 1 hr. Extraction with pentane and distillation furnishes the allenylsilane in 79% yield.

Gas-chromatographic analysis (0.2-mm × 10.5-m methyl silicone-coated fused silica capillary column, split ratio 100:1, column pressure 20 psi, temperature 20° C) indicates that this material contains none of the acetylenic side product.
11. The product exhibits the following spectral properties: IR (neat) cm^{-1}: 2955, 2920, 2900, 2860, 1935, 1440, 1400, 1250, 935, 880, 830, 805, 750, and 685; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 0.08 (s, 9 H), 1.67 (t, 3 H, J = 3.3), and 4.25 (q, 2 H, J = 3.3); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ: –2.1, 15.1, 67.3, 89.1, 209.1. The impurity, 1-trimethylsilyl-1-butyne, displays ^{1}H NMR peaks at 0.14 (s, 9 H), 1.15 (t, 3 H, J = 7), and 2.23 (q, 2 H, J = 7).

3. Discussion

Allenylsilanes serve as valuable three-carbon components in a general [3+2] annulation method for the synthesis of five-membered rings.[4 5]. A variety of general synthetic approaches to allenylsilanes have recently been developed,[6 7 8,9,10 11 12 13 14 15 16] and a number of specialized routes to various specific functionalized derivatives[17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39] are available as well. The present procedure involves a modification of the general method of Vermeer,[6] which is the most widely applicable route to substituted allenylsilanes. Advantages of this approach include its efficiency, high regioselectivity, and utility in the synthesis of a variety of mono-, di-, and trisubstituted allenylsilane derivatives.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 347
- Org. Syn. 76, 178

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium benzophenone ketyl

ammonium chloride (12125-02-9)

sodium chloride (7647-14-5)

silver nitrate (7761-88-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

cuprous bromide (7787-70-4)

Pentane (109-66-0)

Tetrahydrofuran (109-99-9)

Methanesulfonyl chloride (124-63-0)

2-propyn-1-ol (107-19-7)

lithium bromide (7550-35-8)

phosphorus pentoxide (1314-56-3)

3-Trimethylsilyl-2-propyn-1-ol (5272-36-6)

1-Methyl-1-(trimethylsilyl)allene, Silane, trimethyl(1-methyl-1,2-propadienyl)- (74542-82-8)

1-trimethylsilyl-1-butyne

methylmagnesium chloride (676-58-4)

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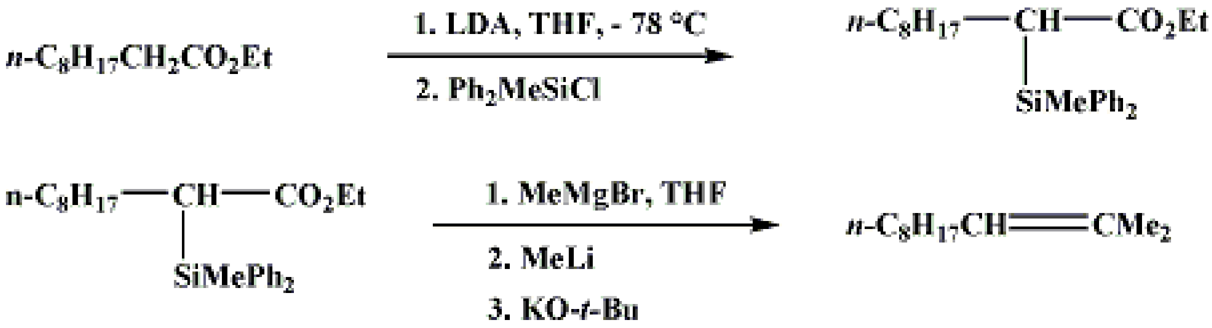
Organic Syntheses, CV 8, 474

α-DIPHENYLMETHYLSILYLATION OF ESTER ENOLATES: 2-METHYL-2-UNDECENE FROM ETHYL DECANOATE

[2-Undecene, 2-methyl-]



Submitted by Gerald L. Larson, Ingrid Montes de Lopez-Cepero, and Luis Rodriguez Mieles[1].
Checked by Choon Sup Ra and Leo A. Paquette.

1. Procedure

A. *Ethyl 2-(diphenylmethylsilyl)decanoate.* A 500-mL, three-necked, round-bottomed flask equipped with a magnetic stirrer, a nitrogen inlet, a 100-mL pressure-equalizing dropping funnel, and a no-air stopper is flame-dried under a vigorous flow of nitrogen, cooled under an atmosphere of nitrogen to −78°C with a dry ice–acetone bath, and charged with 39.2 mL (52.5 mmol) of a 1.34 *M* solution of butyllithium in hexane (Note 1). To this solution is added 7.4 mL (5.31 g; 52.5 mmol) of diisopropylamine (Note 2) in 7 mL of tetrahydrofuran (Note 3). The resulting solution is warmed to ambient temperature and held for 30 min. The solution is diluted with 50 mL of dry tetrahydrofuran and cooled again to −78°C. To this solution is added 11.6 mL (10.0 g; 50 mmol) of ethyl decanoate (Note 4) in 45 mL of tetrahydrofuran dropwise over a 30-min period. The mixture is kept at −78°C for 30 min to allow the enolate to form, and then 10.3 mL (11.6 g; 50 mmol) of diphenylmethylchlorosilane (Note 5) in 40 mL of tetrahydrofuran is added over a 5-min period. The reaction mixture is allowed to reach ambient temperature and stir at that temperature for 8 hr. It then is cooled to 0°C, diluted with hexane (150 mL), washed with cold water (2 × 100 mL), dried over magnesium sulfate, filtered, and concentrated at reduced pressure (Note 6). The crude product, which is ca. 95% pure (Note 7), is purified by rapid filtration through 50 g of silica gel (Note 8) with 1% ethyl acetate–hexane (Note 9) as eluant. There is obtained 18.4–18.7 g (93–94%) of ethyl 2-(diphenylmethylsilyl)decanoate (Note 10). Similar results are obtained on a larger scale (Note 11).

B. *2-Methyl-2-undecene*. A 1-L, three-necked, round-bottomed flask equipped with a magnetic stirrer, a nitrogen inlet, a 500-mL pressure-equalizing dropping funnel, and a no-air stopper is flame-dried under vacuum, cooled to room temperature under an atmosphere of nitrogen, and charged with 87 mL (260 mmol) of 3 *M* methylmagnesium bromide in ether (Note 12). This solution is cooled to 0°C (ice bath) and 52 g (130 mmol) of ethyl 2-(diphenylmethylsilyl)decanoate in 260 mL of tetrahydrofuran (Note 3) is added over an 8-min period. After the addition is complete, the reaction mixture is warmed to room temperature and heated to reflux for 24 hr. The reaction mixture is again cooled to 0°C and 244 mL (390 mmol) of 1.6 *M* methyllithium in tetrahydrofuran (Note 13) is added over a 30-min period. After the addition is complete, the reaction mixture is heated to reflux for 24 hr, cooled to 0°C (ice bath), and 29.2 g (260 mmol) of solid potassium *tert*-butoxide (Note 14) is added in three portions (Note 15). The reaction mixture is heated to reflux for 1 hr, cooled to 0°C, diluted with hexane (100 mL), and hydrolyzed by the dropwise addition of 1 *M* hydrochloric acid (240 mL), followed by about 150 mL of 3 *M* hydrochloric acid until a pH of 4 is reached (Note 16). The organic layer is separated and the aqueous layer is extracted with hexane (3 × 100 mL). The combined organic layers are dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure (Note 6) to give 55 g of crude material (Note 17). This material is diluted with 150 mL of dry hexane (Note 18) and applied to a silica gel column (Note 8). The product is obtained by eluting with hexane and collecting 200-mL fractions. This material, which contains small amounts of dimethyldiphenylsilane and diphenylmethylsilanol, is chromatographed under 3–5 psi on a silica gel column (50 × 2.8 cm) eluting with hexane (Note 19) to give 11.3 g (51.8%) of the olefin (Note 20).

2. Notes

1. Butyllithium was purchased from Foote Mineral Company and titrated by the method of Watson and Eastham.[2]
2. Diisopropylamine was purchased from Aldrich Chemical Company, Inc., and distilled from calcium hydride prior to use.
3. Tetrahydrofuran was a gift from Pfizer Pharmaceuticals of Puerto Rico purchased by them from Dupont Company. It was distilled from sodium/ benzophenone prior to use.
4. Ethyl decanoate was purchased from Aldrich Chemical Company, Inc. and used without further purification.
5. Diphenylmethylchlorosilane was purchased from Petrarch Systems, Inc., and distilled from calcium hydride (bp 85°C at 0.1 mm) prior to use. A 187.5-mmol-scale reaction using diphenylmethylchlorosilane purchased from Petrarch Systems and used without purification gave an 89% yield of the α-silyl ester.
6. A high-volume house vacuum system was used for this step.
7. The minor impurities are unreacted ethyl decanoate and diphenylmethylsilanol.
8. Chromatographic silica gel, 70–230 mesh, from Matheson-Coleman-Bell was

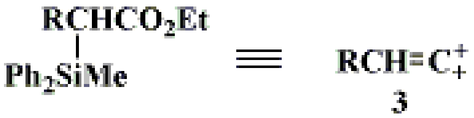
used.
9. Alternatively, the product can be distilled in an Aldrich Kugelrohr apparatus (pot temperature 130–135°C at 0.2 mm) to give slightly lower (80–90%) yields.
10. The physical properties are as follows: n_D^{20} 1.5190; IR (neat) cm^{-1}: 3068, 3045, 2950–2850, 1714, 1589, 1254, 790; ^1H NMR ($CDCl_3$, 80 MHz) δ: 0.66 (s, 3 H), 0.95 (t, 3 H, *J* = 1), 1.21 (brs, 14 H), 2.56 (m, 1 H), 3.86 (m, 2 H), 7.29–7.62 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ: 3.39, −5.57, 14.01, 22.63, 25.02, 27.56, 29.20, 29.35, 30.51, 31.87, 36.39, 59.75, 127.71, 129.50, 129.56, 134.32, 134.64, 134.78, 134.83, 175.02; MS 70 eV m/e (relative abundance) 398 (10), 397 (19), 396 (33), 353 (21), 351 (20), 319 (27), 298 (39), 297 (75), 284 (23), 227 (33), 199 (30), 198 (43), 197 (100), 195 (30), 183 (26), 181 (27), 121 (35), 105 (39), 93 (20), 73 (24), 69 (21), 55 (36), 53 (16). Anal. calcd. for $C_{25}H_{36}O_2Si$: C, 75.76, H, 9.09. Found: C, 75.59, H, 9.19.
11. The submitters report that a 187.5-mmol-scale reaction gave an 89% yield of product.
12. Methylmagnesium bromide was purchased from Columbia Organic Chemicals as a 3 *M* solution and used as obtained.
13. Methyllithium was purchased from Aldrich Chemical Company, Inc., and titrated prior to use.[2]
14. Potassium *tert*-butoxide was purchased from Aldrich Chemical Company, Inc., and used without further purification.
15. *Caution! Some foaming occurs because of an exothermic reaction.*
16. Litmus paper was used to determine the pH.
17. Gas-chromatographic analysis of this material (6 ft × 1/8 in. 10% SP-2401 on 100–120-mesh Supelcoport; 100–200°C program at 10°C/min; flow rate of 20 psi) showed the presence of ethyl decanoate, 2-undecanone, dimethyldiphenylsilane, and 2-methyl-2-undecanol in addition to the desired olefin. Small amounts of unidentified products were also present.
18. A mixture of hexanes (Mallinkrodt anhydrous) was used. If the crude product is placed directly on the silica gel column, the column plugs and the compound does not elute.
19. Attempts to purify the product by spinning-band distillation from the crude material gave only about 20% yield.
20. The product is greater than 97% pure by GLC (Note 17). It showed n_D^{20} 1.4360; ^1H NMR ($CDCl_3$, 80 MHz) δ: 0.88 (br t, 3 H), 1.28 (br s, 12 H), 1.61 (br s, 3 H), 1.69 (br s, 3 H), 1.93–2.00 (m, 2 H), 5.14 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ: 14.05, 17.62, 22.74, 25.64, 28.14, 29.41, 29.65, 29.99, 31.98, 125.08, 131.00; MS (70 eV) m/e (relative abundance) 169 (2), 168 (14), 112 (6), 84 (11), 83 (13), 82 (6), 70 (23), 69 (100), 68 (10), 67 (13), 57 (34), 56 (68), 55 (34), 53 (9).

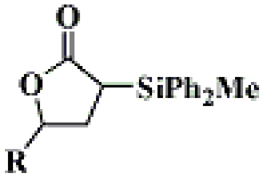
3. Discussion

Compound **1** represents one example of several α-(diphenylmethylsilyl) esters prepared by the method presented herein.[3] Other examples include the α-

diphenylmethylsilylated derivatives of ethyl acetate, ethyl propionate, ethyl 10-undecenoate, ethyl palmitate, and ethyl stearate, all obtained in greater than 70% yield. Other alcohols, principally methyl, isopropyl, *tert*-butyl and 1-menthyl, also have been employed in this reaction without marked differences. The reasons as to why the lithium enolates of esters are silylated at the carbon terminus with diphenylmethylchlorosilane as opposed to the usual silylation on the oxygen terminus is not clear. The direct *C*-silylation of the lithium enolates of α,β-disubstituted esters is not possible, except with ethyl cyclopropanecarboxylate and ethyl cyclobutanecarboxylate.[4]

The α-(diphenylmethylsilyl) esters have been shown to be vinyl dication equivalents 3, and as such are precursors to terminal olefins and deuterated olefins,[5] 1,1-disubstituted olefins,[6] and tri- and tetrasubstituted olefins.[7] They are precursors to β-ketosilanes and ketones,[8,9] wherein the overall transformation results in an ester to ketone conversion. They can also be deprotonated and the enolate anion condensed with aldehydes and ketones to give α,β-unsaturated esters,[10] in particular α-alkylated-α,β-unsaturated esters.[11] Their γ-lactone counterparts, α-(diphenylmethylsilyl)-γ-butyrolactone **4a** and α-(diphenylmethylsilyl)-γ-valerolactone **4b**, are precursors to 4-oxo acids,[12] 1,4-diketones[13] and α-ylidene-γ-lactones.[14]





4a R=H
4b R=Me

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 530

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

ether (60-29-7)

nitrogen (7727-37-9)

carbon (7782-42-5)

Benzophenone (119-61-9)

sodium (13966-32-0)

magnesium sulfate (7487-88-9)

ethyl propionate (105-37-3)

ethyl palmitate (628-97-7)

methylmagnesium bromide (75-16-1)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

hexane (110-54-3)

Methyllithium (917-54-4)

ethyl stearate (111-61-5)

calcium hydride (7789-78-8)

diisopropylamine (108-18-9)

2-Methyl-2-undecene, 2-Undecene, 2-methyl- (56888-88-1)

ETHYL DECANOATE (110-38-3)

diphenylmethylchlorosilane

Ethyl 2-(diphenylmethylsilyl)decanoate

dimethyldiphenylsilane (778-24-5)

diphenylmethylsilanol

2-methyl-2-undecanol

ethyl cyclopropanecarboxylate (4606-07-9)

ethyl cyclobutanecarboxylate (14924-53-9)

potassium tert-butoxide (865-47-4)

α-(diphenylmethylsilyl)-γ-butyrolactone

2-undecanone (112-12-9)

ethyl 10-undecenoate (692-86-4)

α-(diphenylmethylsilyl)-γ-valerolactone

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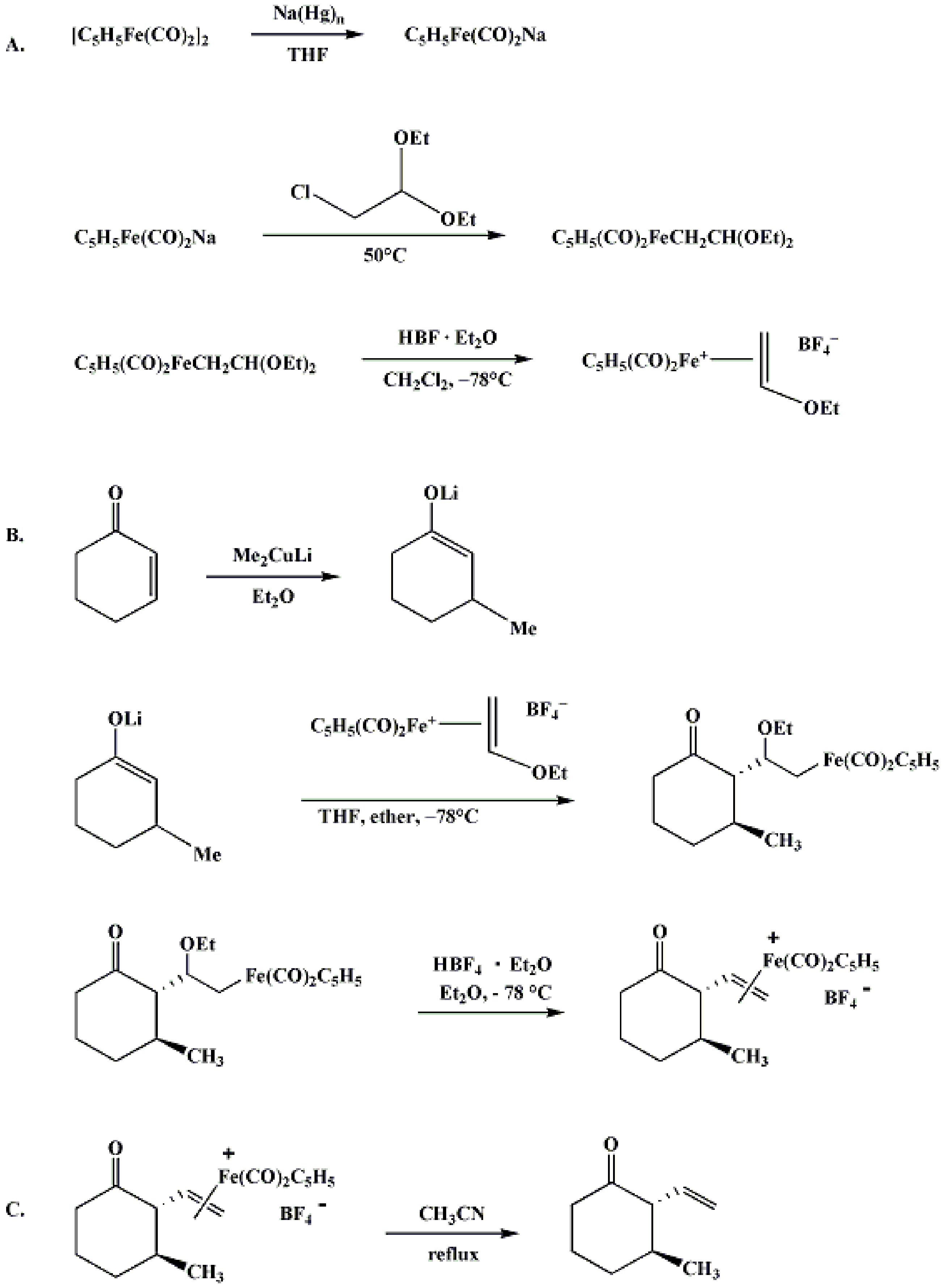
Organic Syntheses, CV 8, 479

VINYLATION OF ENOLATES WITH A VINYL CATION EQUIVALENT: *trans*-3-METHYL-2-VINYLCYCLOHEXANONE

[Cyclohexanone, 2-ethenyl-3-methyl-, *trans*-]



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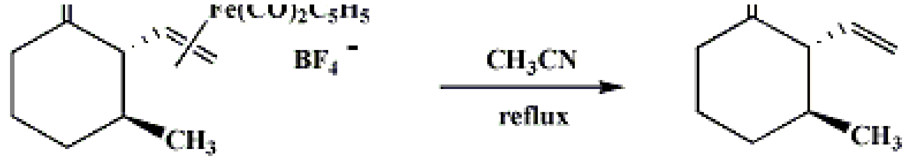


Submitted by Tony C. T. Chang[1], Myron Rosenblum[2], and Nancy Simms[2].
Checked by Ed Fewkes and Martin F. Semmelhack.

1. Procedure

Caution! Care should be exercised in the preparation of the sodium amalgam since the initial reaction is highly exothermic. This and all subsequent operations should be carried out in a well-ventilated hood. Chloroacetaldehyde diethyl acetal is an irritant and a mutagen. Care should be exercised in its handling.

A. *Dicarbonyl(cyclopentadienyl)(ethyl vinyl ether)iron tetrafluoroborate* (**1**). A 500-mL, three-necked flask, with a stopcock at the bottom, is fitted with a nitrogen inlet and a mechanical stirrer with a Teflon paddle. Nitrogen is passed through the flask while it is flame-dried (Note 1) and then 70 mL of mercury is introduced. The mercury is stirred vigorously as 7.2 g (0.31 mol) of sodium metal, cut into small pieces, and added slowly under a strong flow of nitrogen; after which the remaining neck is capped with a rubber septum. The amalgam is allowed to cool to room temperature and 100 mL of tetrahydrofuran is added (Note 2) and (Note 3). While the system is flushed with nitrogen, one septum is removed and 35.4 g (0.1 mol) of dicarbonyl(cyclopentadienyl)diiron $[(CO)_2CpFe]_2$ (Note 4) is added at once. Vigorous stirring is continued for 40 min. The mercury is drained through the stopcock, and the deep-yellow-red solution of sodium dicarbonyl(cyclopentadienyl)ferrate, which is ready for use without further purification, is transferred (Note 2) to a 500-mL, round-bottomed flask containing a magnetic stirrer. An additional 50 mL of tetrahydrofuran is used to rinse the amalgam flask.

Chloroacetaldehyde diethyl acetal (31.11 g, 0.20 mol) (Note 5) is added by syringe slowly, since the initial reaction is exothermic. The resulting solution is heated at 50°C with stirring for 2 hr. After the solution is cooled to room temperature, solvent is removed, first with a rotary evaporator and then with an oil pump overnight (Note 6). The residue is taken up in ethyl ether (Note 7), and filtered by suction through a 1-in. plug of Celite packed in a 250-mL, coarse-porosity, fritted Schlenk tube (Note 8) and (Note 9). The filtrate is collected in a 1-L, round-bottomed flask containing a magnetic stirring bar. The sodium chloride residue is washed several times with fresh ether until the washings are nearly colorless. The filter tube is removed and the flask is capped with a rubber septum and a nitrogen inlet; air is displaced by flushing the flask is capped with nitrogen.

The solution is cooled to −78°C in a dry ice–acetone bath, and 38.19 g (0.23 mol) of tetrafluoroboric acid–diethyl ether complex (Note 10) is added dropwise by syringe over a 30-min period. The solution is allowed to warm to room temperature. The yellow precipitate is filtered off and collected in a 250-mL Schlenk tube, washed with ether, and dried under a stream of nitrogen and finally under reduced pressure (oil pump). The bright-yellow salt **1** weighs 43.2–57.6 g (60–80%) and may be used without further purification (Note 11). It may be stored indefinitely under nitrogen at 0°C without decomposition.

B. *Dicarbonyl(cyclopentadientyl)(trans-3-methyl-2-vinylcyclohexanone)iron tetrafluoroborate* (**3**). Under a nitrogen atmosphere, cuprous iodide (Note 12) (24.76 g, 0.13 mol) and 150 mL of ether are placed in a 1-L, three-necked, round-bottomed flask containing a magnetic stirring bar, and cooled to 0°C in an ice–salt bath. First 172 mL (0.26 mol) of methyllithium in ether (Note 13) is added by syringe, then 12.60 g (0.13 mol) of 2-cyclohexen-1-one (Note 14) is added dropwise by syringe while the mixture is stirred at 0°C. A bright yellow precipitate forms immediately. After 15 min, 200 mL of tetrahydrofuran is added and the mixture is cooled to −78°C in a dry ice–acetone bath. While vigorous stirring and a strong flow of nitrogen are maintained, one septum is removed and 43.70 g (0.13 mol) of complex salt 1 is added at once. The septum is replaced and 50 mL of fresh tetrahydrofuran is used to wash solid **1** from the neck

and sides of the reaction vessel. After 1 hr at −78°C, the mixture is allowed to warm to room temperature while stirring is continued. Stirring is halted to allow insoluble copper salts to settle, leaving a red supernatant liquid. A 250-mL, coarse-frit, Schlenk filter is prepared with a Celite mat, topped with 2 in. of activity-IV neutral alumina (Note 15), which is further deactivated by washing in the Schlenk tube with 100 mL of diethyl ether. The supernatant solution is transferred to the Schlenk tube by cannula and filtered by suction into a 1-L, round-bottomed flask containing a magnetic stirring bar. The copper salts remaining in the reaction vessel are repeatedly washed with fresh ether until the filtered washings are nearly colorless. Removal of solvent from the filtrate leaves product **2** as a deep red oil (Note 16).

The oil is dissolved in 500 mL of diethyl ether under a nitrogen atmosphere, cooled to −78°C in a dry ice–acetone bath and 18 g (0.11 mol) of tetrafluoroboric acid–diethyl ether complex is added dropwise by syringe over a 30-min period, while the bath temperature is maintained at −78°C. The solution is allowed to warm to room temperature, and the powdery yellow solid is isolated by filtration through a 250-mL, coarse-frit, Schlenk filter tube. The product is washed several times with fresh ether and dried under a stream of nitrogen and then under reduced pressure (oil pump). The yield of salt **3** is 31–39.1 g (60–75%). The product may be used without further purification (Note 17) and may be stored under nitrogen of 0°C for several weeks with no observable decomposition (Note 18).

C. *trans-3-Methyl-2-vinylcyclohexanone* ***(4)***. Compound 3 (31.5 g) and 25 mL of acetonitrile (0.47 mol, 6-fold excess) (Note 19) are placed in a 100-mL round-bottomed flask (Note 20) fitted with a magnetic stirring bar and a reflux condenser. The mixture is heated to reflux for 2 hr under nitrogen, cooled to room temperature, and slowly added to 300 mL of diethyl ether. The acetonitrile complex **5** precipitates as a bright yellow solid, and may be removed by suction filtration (Note 21).

The filtrate is washed 3 times with distilled water to remove excess acetonitrile and then dried over anhydrous magnesium sulfate. Filtration followed by removal of ether leaves the product **4** as a yellow oil (7.1–7.6 g, 64–70%), which may be further purified by short path or bulb-to-bulb distillation (bp 30°C at 0.1 mm) to a colorless liquid (Note 22) and (Note 23).

2. Notes

1. All glassware, syringes, and cannulae were routinely flame- or oven-dried and cooled under dry nitrogen.
2. In general, transfers of dry solvent or of solutions are made by 2-mm cannulae inserted through rubber septa capping delivery and receiver vessels. Transfer is made by positive nitrogen pressure applied through a hypodermic needle, while a second needle in the receiver vessel is employed as a vent. Cannulae are available from Hamilton Company, P.O. Box 10030, Reno, NV 89510.
3. Tetrahydrofuran is predried over potassium hydroxide pellets, degassed with nitrogen, and freshly distilled under nitrogen from sodium benzophenone ketyl.[3]
4. Dicarbonyl(cyclopentadienyl)diiron can be readily prepared on a large scale from iron pentacarbonyl and dicyclopentadiene.[4] Alternatively it can be purchased from Alfa Products, Johnson Mathey Co. or from Strem Chemical Company.
5. Chloroacetaldehyde diethyl acetal was purchased from Aldrich Chemical Company, Inc. This substance is listed as an irritant. Proper care should be exercised when handling it.
6. It is important to stir the product continually to ensure effective removal of tetrahydrofuran. If appreciable solvent remains, the vinyl ether complex **1** may not crystallize readily.
7. Ethyl ether was freshly distilled from sodium benzophenone ketyl.
8. Schlenk tubes were purchased from Ace Glass Company, Catalog No. 7761-36.
9. Filtration is smoothly accomplished by allowing the sodium chloride to settle and filtering the clear supernatant liquor in small portions, transferring the solution to the filtering tube by cannula. If the Celite should become clogged, the surface may be scraped clean, under a strong stream of nitrogen, using a long spatula, in order to increase the filtration rate.

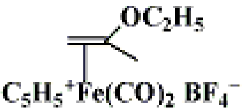
10. Tetrafluoroboric acid–diethyl ether complex was purchased from Columbia Organics Chemical Company, Inc.
11. The salt may be reprecipitated by dissolution in methylene chloride containing a small amount of ethanol, followed by the addition of ether. The product shows the following spectra: IR (CH_2Cl_2) cm^{-1}: 2095, 2045, 1545; NMR (CD_3NO_2) δ: 1.40 (t, 3 H, Me), 2.73 (dd, 1 H, *trans*-CH=), 3.00 (dd, 1 H, *cis*-CH=), 4.37 (q, 2 H, OCH_2), 5.50 (s, 5 H, Cp), 7.92 (dd, 1 H, CHOEt). The checkers realized the higher yield only when the preparation was carried out on one-tenth the scale specified here.
12. Cuprous iodide was purchased from Fisher Scientific Company, and purified by recrystallization from saturated aqueous potassium iodide.[5,6]
13. Methyllithium was purchased from Aldrich Chemical Company, Inc., and standardized by double titration with benzoic acid in aqueous ethanol and with allyl chloride.[7]
14. 2-Cyclohexen-1-one was purchased from Aldrich Chemical Company, Inc., and purified by vacuum distillation.
15. Alumina was purchased from Woelm and brought to activity IV as directed.
16. As in the preparation of the vinyl ether complex, **1**, it is very important to remove tetrahydrofuran effectively to promote facile crystallization of product. This is most easily done by removing most of the solvent with a rotary evaporator and then stirring the resulting oil under reduced pressure (oil pump) overnight. Mixing the oil with about 50 mL of ether followed by solvent removal under reduced pressure helped to facilitate removal of traces of tetrahydrofuran. Pure **2** may be obtained as a yellow crystalline solid, which decomposes on heating, by chromatographing the oil on basic alumina (activity IV), eluting with 5% ether in hexane. Compound **2** is characterized by the following spectra: IR (CH_2Cl_2) cm^{-1}: 2000, 1940, 1700; NMR ($CDCl_3$) δ: 1.17 (t, 6 H, CH_3), 1.43 (d, 2 H, $FeCH_2$), 1.65 (dd, 1 H, CHCO), 1.70–2.55 (m, 7 H, CH, CH_2), 3.41 (dq, 2 H, OCH_2), 3.76 (dt, 1 H, CHOEt), 4.87 (s, 5 H, Cp).
17. Compound **3** may be recrystallized by dissolution in a minimum volume of nitromethane at 0° C followed by the addition of diethyl ether. The crystalline material decomposes on heating. It is characterized by the following spectra: IR (CH_2CH_2) cm^{-1}: 2090, 2050, 1708; NMR (CD_3NO_2) δ: 1.1 (m, 3 H, CH_3), 1.4–2.6 (m, 8 H, CH, CH_2), 3.28 (d, 1 H, *trans*-CH_2=), 4.00 (d, 1 H, *cis*-CH_2=), 5.0 (m, 1 H, CH=), 5.65 (s, 5 H, Cp).
18. However, salt **3** is unstable at room temperature as a solid and in solution and rearranges to the isomeric complex in which the iron center is bound to the carbonyl group of the substituted cyclohexanone.
19. Acetonitrile is freshly distilled under nitrogen from calcium hydride.
20. Because of the ease with which product **4** isomerizes to the conjugated enone in the presence of base, it is imperative that the demetallation and subsequent purification steps be carried out in glassware that is free of basic residues.
21. An inert atmosphere is not necessary.
22. The considerable vapor pressure of **4** causes some loss during vacuum distillation. Although the color of the product is improved by distillation, both IR and NMR spectra of the product before and after distillation show little change.
23. Compound **4** is observed to darken on standing in air at room temperature for prolonged periods. Compound **4** is characterized by the following spectra: IR (neat) cm^{-1}: 1708; NMR ($CDCl_3$) δ: 0.99 (d,d, 1 H, CH_3), 1.3–2.8 (m, 8 H, CH, CH_2), 4.98 (dd, 1 H, *trans*-CH_2=), 5.2 (dd, 1 H, *cis*-CH_2=), 5.76 (m, 1 H, CH=).

3. Discussion

Few reagents are available to the synthetic organic chemist that function as vinyl cation synthons. At present, these include α-phenylseleneoacetaldehyde,[8] α-silyl aldehydes, and ketones,[9], α,β-epoxysilanes,[10] phenyl vinyl sulfoxide,[11] phenyl ethynyl sulfone,[12,13] phenyl 2-chlorovinyl sulfone,[13]

and activated vinyl halides or ethynyl halides.[14] With the exception of the first two, the use of these reagents is confined to reactions with tertiary enolates or organocuprates.

The procedure given here illustrates the use of readily prepared organoiron complex **1** for the vinylation of a secondary enolate. This salt may be prepared on a large scale from readily available starting materials and can be stored at 0°C without decomposition. The closely related isopropenyl ethyl ether and *cis*-propenyl ethyl ether–iron complexes, **6** and **7**, are similarly prepared from α-bromoacetone[15,16] and α-bromopropionaldehyde diethyl acetal[17] and have been used as isopropenylating[16] and *trans*-propenylating[18] reagents with enolates. Complex **8**, derived from ethyl 3-bromopyruvate, functions as an α-acrylic ester cation with enolates.[19,20]



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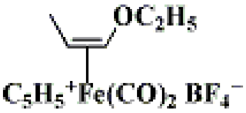

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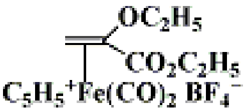
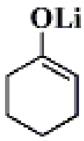
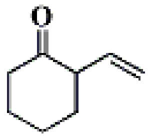
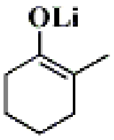
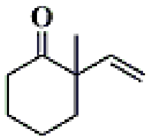
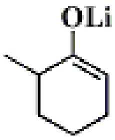
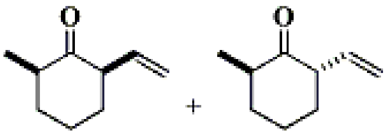
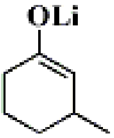
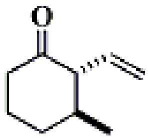


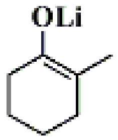
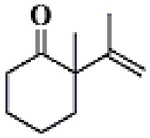
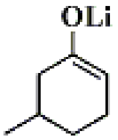
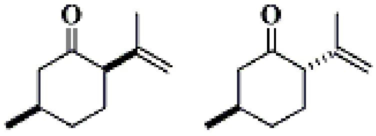
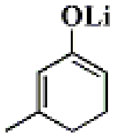
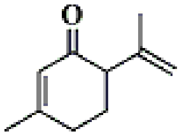
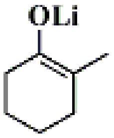
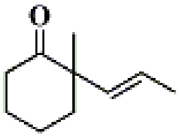
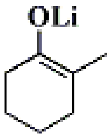
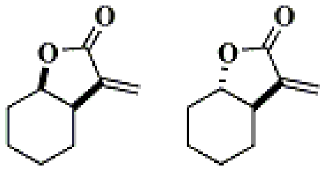
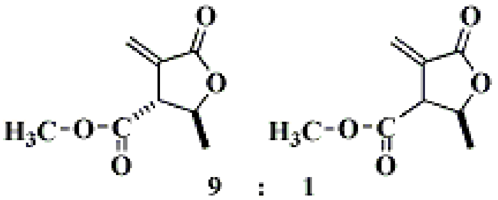
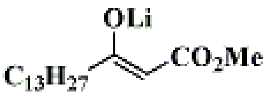
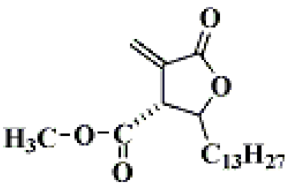
8

Because of their high reactivity, these complex salts react rapidly and regiospecifically, at low temperature, with a number of carbon and heteroatomic nucleophiles, including thiols, amines, and alcohols.[21] Finally, exposure of the double bond takes place under particularly mild conditions so that isomerization of the β,γ-unsaturated carbonyl system may be avoided. The present scope of reactions with these vinyl cation synthons is summarized in Table I.

TABLE I

VINYLATION OF ENOLATES WITH VINYL CATION EQUIVALENTS

Enolate	Enol Ether Complex	Vinylated Product	Yield%
	1		80
	1		80
	1	 1 : 1	80
	1		47[a]

	7		72
	7	 2 : 5	53
	7		91
	6		72
	8		44[b] 37[c]
	8	 9 : 1	65[b]
	8		(15)[d]

[a]From cyclohexenone.

[b]By reduction of the initial condensation product with L-Selectride.

[c]By reduction of the initial condensation product with sodium borohydride.

[d]By reduction of the initial condensation product with $LiAlH_4$ at −78°C.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium benzophenone ketyl

dicarbonyl(cyclopentadienyl)diiron

Dicarbonyl(cyclopentadientyl)(trans-3-methyl-2-vinylcyclohexanone)iron tetrafluoroborate

acetonitrile complex

α-phenylseleneoacetaldehyde

ethanol (64-17-5)

ether, ethyl ether, diethyl ether (60-29-7)

acetonitrile (75-05-8)

iron (7439-89-6)

sodium chloride (7647-14-5)

potassium iodide (7681-11-0)

nitrogen (7727-37-9)

allyl chloride (107-05-1)

Benzoic acid (65-85-0)

mercury (7439-97-6)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

Nitromethane (75-52-5)

methylene chloride (75-09-2)

cuprous iodide (7681-65-4)

α-bromoacetone (598-31-2)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

hexane (110-54-3)

Methyllithium (917-54-4)

dicyclopentadiene

isopropenyl ethyl ether (926-66-9)

chloroacetaldehyde diethyl acetal (621-62-5)

calcium hydride (7789-78-8)

sodium borohydride (16940-66-2)

iron pentacarbonyl

2-cyclohexen-1-one, cyclohexenone (930-68-7)

ethyl 3-bromopyruvate (70-23-5)

Phenyl vinyl sulfoxide (20451-53-0)

tetrafluoroboric acid (16872-11-0)

Sodium dicarbonyl(cyclopentadienyl)ferrate (12152-20-4)

trans-3-Methyl-2-vinylcyclohexanone, Cyclohexanone, 2-ethenyl-3-methyl-, trans- (110222-94-1)

phenyl ethynyl sulfone

phenyl 2-chlorovinyl sulfone

α-bromopropionaldehyde diethyl acetal

Dicarbonyl(cyclopentadienyl)(ethyl vinyl ether)iron tetrafluoroborate

cis-propenyl ethyl ether

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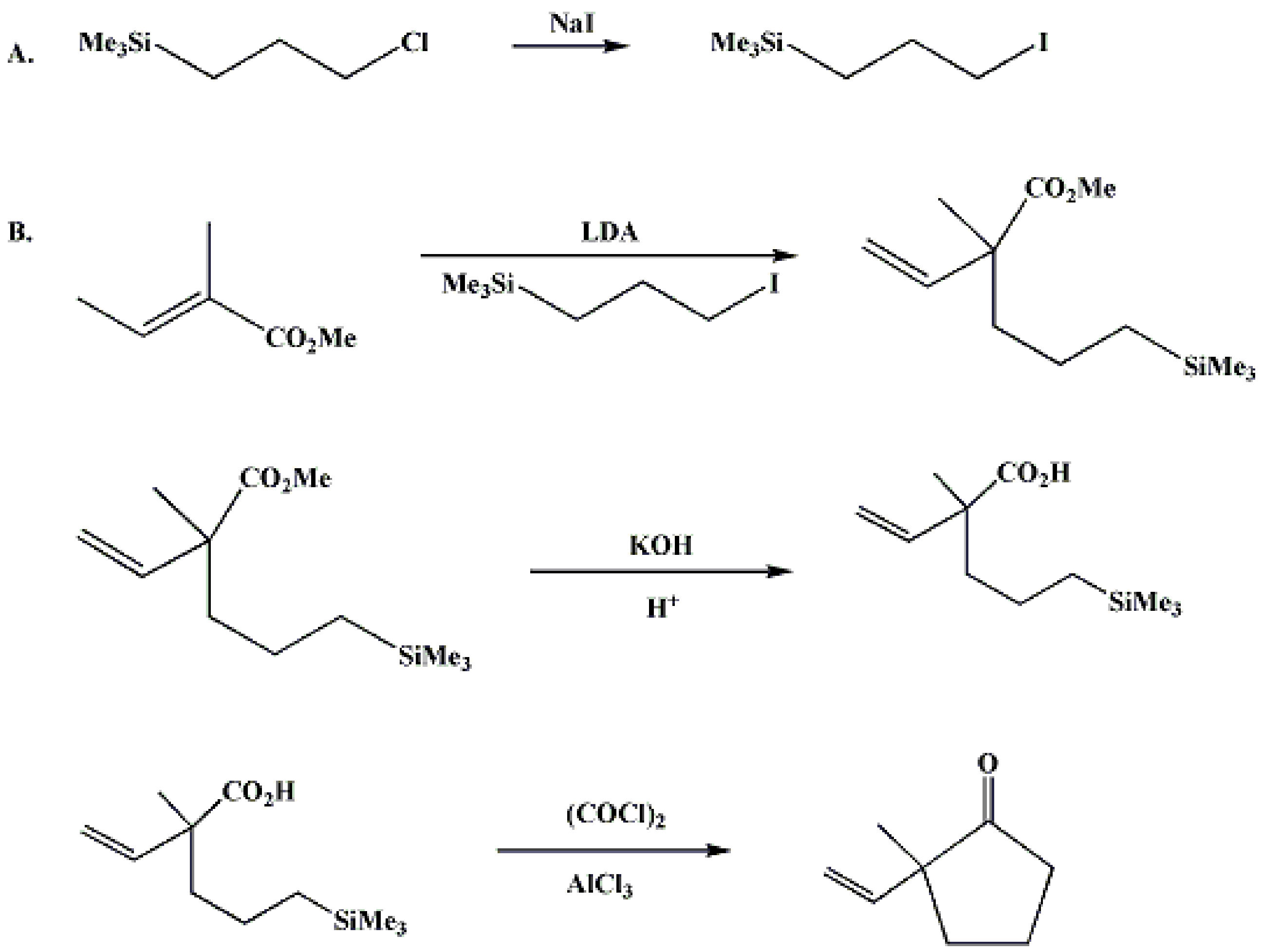
Organic Syntheses, CV 8, 486

CYCLOPENTANONES FROM CARBOXYLIC ACIDS VIA INTRAMOLECULAR ACYLATION OF ALKYLSILANES: 2-METHYL-2-VINYLCYCLOPENTANONE

[Cyclopentanone, 2-ethenyl-2-methyl-]



Submitted by Isao Kuwajima and Hirokazu Urabe[1].
Checked by Robert J. Ross and Leo A. Paquette.

1. Procedure

Caution! The following reactions should be performed in an efficient hood.

A. *1-Iodo-3-trimethylsilylpropane.* In a dry, 100-mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar, a reflux condenser, and a rubber septum is placed 15.0 g (0.10 mol) of sodium iodide. A nitrogen inlet tube is connected to the top of the reflux condenser and all the apparatus is kept under nitrogen. To this vessel are added 50 mL of acetone and 11.5 mL (10 g, 0.066 mol) of 1-chloro-3-trimethylsilylpropane (Note 1) with a hypodermic syringe through the septum; the resulting white suspension is stirred under reflux for 24 hr. The condenser is replaced with a Claisen head, and the bulk of the solvent is removed under ordinary pressure (Note 2) to give a white slurry. To this is added 60 mL of hexane and the inorganic salts are filtered off by suction. The filter cake is washed with five 10-mL portions of hexane. The hexane is distilled off from the

combined organic portions at atmospheric pressure. The residual oil is transferred to a 50-mL, round-bottomed flask fitted with a stirring bar and a Claisen head, and is distilled under reduced pressure to afford 1-iodo-3-trimethylsilylpropane **1** (11.5–13.1 g, 72–81%), bp 84–86°C (25 mm), as a clear liquid (Note 3) and (Note 4).

B. *2-Methyl-2-vinylcyclopentanone.* A 300-mL, two-necked, round-bottomed flask fitted with a magnetic stirring bar, a nitrogen inlet tube, and a rubber septum is kept under dry nitrogen. To this flask are introduced 8.3 mL (5.99 g, 0.0591 mol) of diisopropylamine and 120 mL of tetrahydrofuran (Note 5) with a syringe through the septum. The flask is cooled in a dry ice–hexane bath. To the solution is slowly added 38.7 mL of butyllithium (1.53 *M* in hexane, 0.0592 mol) with a syringe and the mixture is kept at 0°C (in an ice bath) for 10 min. The resulting solution of lithium diisopropylamide is again cooled in a dry ice–hexane bath (−78°C), and 11.2 mL (11.57 g, 0.0645 mol) of *N,N'*-dimethylpropyleneurea (DMPU) (Note 6) is added. After stirring for 30 min, 6.47 mL (6.15 g, 0.0539 mol) of methyl tiglate is injected drop by drop at −78°C. After the solution is stirred for an additional 20 min, 13.0 g (0.0537 mol) of 1-iodo-3-trimethylsilylpropane **1** is added with a syringe and the dry ice–hexane bath is replaced with an ice bath. The solution is stirred at about 0°C for 1 hr and then poured onto 150 mL of ice-cooled 3 *N* hydrochloric acid covered with 150 mL of hexane. The organic layer is separated and the aqueous layer is extracted with two 80-mL portions of hexane. The combined organic layers are washed successively with 50 mL of 3 *N* hydrochloric acid and 50 mL of saturated sodium bicarbonate solution and dried over anhydrous magnesium sulfate. The solvent is removed on a rotary evaporator to afford the crude ester **2** (ca. 13 g) (Note 7), which is sufficiently pure for the next operation.

In a two-necked, round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and a reflux condenser, the top of which is fitted with a nitrogen inlet tube, is placed 7.3 g (ca. 0.13 mol) of 85% pure potassium hydroxide. To the flask are added 4 mL of water and an ethanol solution (60 mL) of the crude ester **2** (ca. 13 g) with a syringe; the mixture is refluxed for 1 hr. The reflux condenser is replaced with a Claisen head and the bulk of the solvent is distilled off over 30 min (Note 8). The residue is cooled in an ice bath and 80 mL of 6 *N* hydrochloric acid is cautiously introduced. The mixture is extracted with 150 mL of hexane and the organic layer is separated. To the aqueous layer is added 40 mL of concentrated hydrochloric acid and the solution is again extracted with two 100-mL portions of hexane. The combined organic extracts are dried over anhydrous magnesium sulfate and concentrated under reduced pressure to afford the crude acid **3** (10.6–12.0 g) as a dark-colored oil (Note 9).

A 200-mL, two-necked, round-bottomed flask fitted with a magnetic stirring bar, a reflux condenser, and a rubber septum is flushed with nitrogen. To this flask is introduced a dry benzene solution (50 mL) of crude acid **3** through the septum. Then 8.9 mL (12.9 g, 0.101 mol) of oxalyl chloride is slowly added with stirring at room temperature. After the evolution of gas ceases, the solution is further heated in an oil bath maintained at 70°C for 30 min. The solvent, together with excess oxalyl chloride, is removed at room temperature first on a rotary evaporator and finally with a vacuum pump to leave the crude acid chloride of **3** as a dark-colored oil (Note 10).

In a 300-mL, three-necked, round-bottomed flask fitted with an nitrogen inlet tube, a dropping funnel, and a rubber septum are placed 7.45 g (0.0559 mol) of powdered aluminum chloride and a magnetic stirring bar. After 100 mL of dichloromethane (Note 11) is introduced, the crude acid chloride, dissolved in 50 mL of dichloromethane, is added via the dropping funnel to the stirred suspension of aluminum chloride at 0°C over 5 min, whereupon most of the aluminum chloride dissolves. After further stirring at 0°C for 15 min and at room temperature for 15 min, the flask is recooled in an ice bath and 100 mL of 3 *N* hydrochloric acid is cautiously added through the

dropping funnel. The organic phase is separated and the aqueous layer is extracted 3 times with 50-mL portions of dichloromethane. The combined organic layers are successively washed with 30 mL of 3 *N* hydrochloric acid and 50 mL of saturated sodium bicarbonate solution, and dried over anhydrous magnesium sulfate. The solvent is removed under ordinary pressure and the residue is distilled under reduced pressure to give 2-methyl-2-vinylcyclopentanone as a clear liquid (3.74–5.6 g, 56–84% yield based on the methyl tiglate), bp 104–124°C (110 mm) (Note 12), ca. 95% pure by GLC (Note 13).

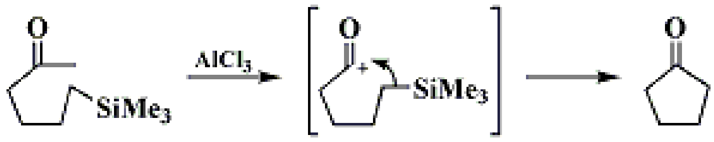
2. Notes

1. 1-Chloro-3-trimethylsilylpropane, obtained from Petrarch Systems, Inc., was used as received.
2. About 40 mL of distillate is collected.
3. 1-Iodo-3-trimethylsilylpropane has the following spectral properties: ^{1}H NMR (CCl_4, 3% benzene (δ 7.24) as an internal standard) δ: –0.03 (s, 9 H, $(CH_3)_3Si$), 0.34–0.74 (m, 2 H, CH_2Si), 1.47–2.04 (m, 2 H, CH_2), 3.07 (t, 2 H, *J* = 7, CH_2I); IR (neat) cm^{-1}: 2950, 1250, 860, 830.
4. 1-Iodo-3-trimethylsilylpropane can also be prepared by other methods; [2].
5. Tetrahydrofuran was used after distillation from sodium benzophenone ketyl under nitrogen.
6. The submitters used hexamethylphosphoric triamide (HMPA), but it was replaced for safety reasons by *N,N'*-dimethylpropyleneurea (DMPU),[3] obtained from Aldrich Chemical Company, Inc. or Fluka; no change in procedure was required and the yield was unaffected.
7. Alkylation of methyl tiglate was carried out according to a reported procedure.[4]
8. About 50 mL of distillate was collected.
9. Crude **3** exhibited the following spectral properties, which are virtually identical to those of an analytically pure sample: ^{1}H NMR (CCl_4, 3% benzene (δ 7.24) as an internal standard) δ: 0.16 (s, 9 H, $(CH_3)_3Si$), 0.44–0.77 (m, 2 H, CH_2Si), 1.1–2.0 (m, 4 H, CH_2CH_2), 1.41 (s, 3 H, CH_3), 4.91–5.31 (m, 2 H, $C{=}CH_2$), 6.04 (d of d, 1 H, *J* = 10 and 18, $CH{=}CH_2$), 11.34 (s, 1 H, CO_2H); IR (neat) cm^{-1}: 2950, 1700, 1400, 1250, 1180, 920, 840, 740, 680.
10. Conversion of the carboxylic acid to the acid chloride was based on a reported method.[5]
11. Dichloromethane was distilled from phosphorus pentoxide.
12. 2-Methyl-2-vinylcyclopentanone showed the following spectral properties: ^{1}H NMR (CCl_4) δ: 0.73 (s, 3 H, CH_3), 1.6–2.3 (m, 6 H, $(CH_2)_3$), 4.67–5.07 (m, 2 H, $C{=}CH_2$), 5.62 (d of d, 1 H, *J* = 8 and 18, $CH{=}CH_2$); IR (neat) cm^{-1}: 3070, 2950, 1730, 1640, 1450, 1400, 1150, 1060, 1040, 1000, 920.
13. Vapor-phase chromatography was performed on an OV 101, fused silica, 20-m capillary column.

3. Discussion

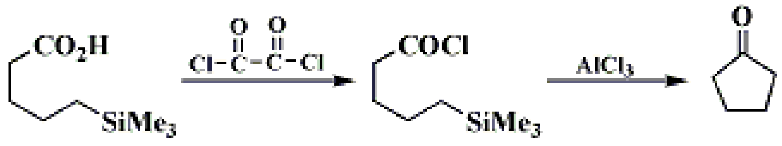
Cyclopentanones are widely found in natural products and are also useful intermediates in organic synthesis. Thus a facile construction of cyclopentanones from easily available acyclic precursors is particularly desirable. This method of preparation is based on an intramolecular acylation of 5-trimethylsilylalkanoyl chlorides previously reported by us.[2] The starting materials are generally prepared by alkylation of carboxylic acids with 3-trimethylsilylalkyl halides followed by their conversion to the corresponding acid chlorides. The cyclization of the acid chlorides proceeds cleanly with aluminum chloride. An acyl cation generated from the acid chloride and aluminum

chloride is trapped with the alkyl–silicon bond in the same molecule to yield a cyclopentanone selectively:

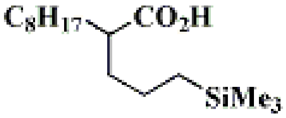
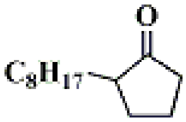
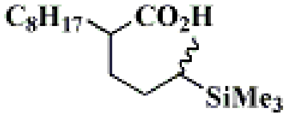
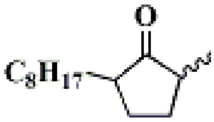
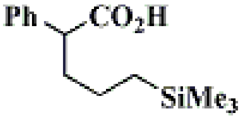
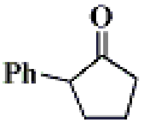
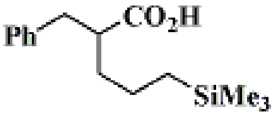
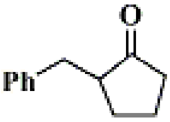
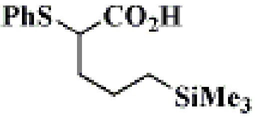
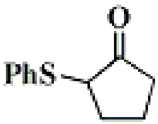


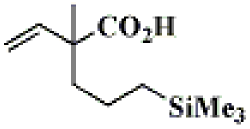
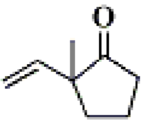
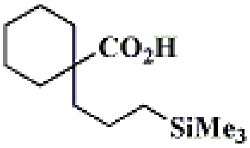
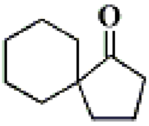
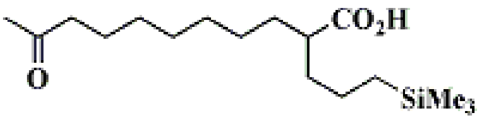
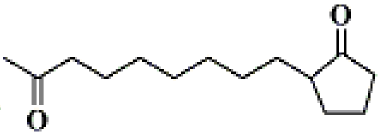
Other results are collected in Table I,[2] which shows that cyclopentanones having a variety of substituents can be prepared according to this procedure with substantial advantage over other methods, such as alkylation of 2-alkoxycarbonylcyclopentanone.

TABLE I
CYCLOPENTANONE SYNTHESIS BY INTRAMOLECULAR ACYLATION OF 5-TRIMETHYLSILYLALKANOYL CHLORIDES[a]



1 **2** **3**

Acid (**1**)	Product (**3**)	Yield(%)[b]
		92[c]
		83
		84
		85
		60[d]

		67
		70
		76[e]

[a]Reactions are carried out on 0.2–0.3-mmol scale with the reactant ratio 1/ $(COCl)_2/AlCl_3$ = 1 : 2 : 1.

[b]Overall yield from **1**. Products are isolated by chromatography.

[c]Reaction on 3.5-mmol scale; the product was isolated by Kugelrohr distillation.

[d]Reactant ratio: **1**/$(COCl)_2/AlCl_3$ = 1:1.5:0.75.

[e]Reactant ratio: **1**/$(COCl)_2/AlCl_3$ = 1:2:2.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium benzophenone ketyl

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

sodium bicarbonate (144-55-8)

nitrogen (7727-37-9)

acetone (67-64-1)

aluminum chloride (3495-54-3)

potassium hydroxide (1310-58-3)

sodium iodide (7681-82-5)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

oxalyl chloride (79-37-8)

hexane (110-54-3)

hexamethylphosphoric triamide (680-31-9)

lithium diisopropylamide (4111-54-0)

diisopropylamine (108-18-9)

N,N'-dimethylpropyleneurea (7226-23-5)

phosphorus pentoxide (1314-56-3)

2-Methyl-2-vinylcyclopentanone, Cyclopentanone, 2-ethenyl-2-methyl- (88729-76-4)

1-chloro-3-trimethylsilylpropane (2344-83-4)

1-Iodo-3-trimethylsilylpropane (18135-48-3)

methyl tiglate (6622-76-0)

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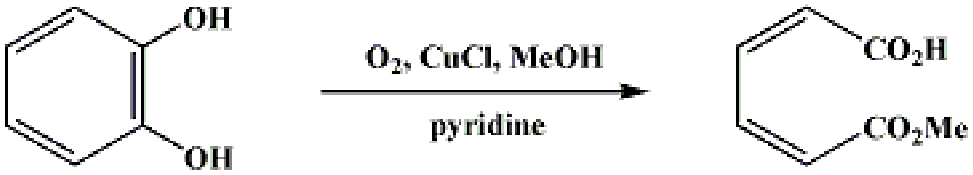
Organic Syntheses, CV 8, 490

OXIDATIVE CLEAVAGE OF AN AROMATIC RING: *cis,cis*-MONOMETHYL MUCONATE FROM 1,2-DIHYDROXYBENZENE

[2,4-Hexadienedioic acid, monomethyl ester, (*Z,Z*)-]



Submitted by Donald Bankston[1]
Checked by Won Hun Ham and Leo A. Paquette.

1. Procedure

A. *cis,cis-Monomethyl muconate.* A 1000-mL, three-necked, round-bottomed flask is equipped with a mechanical stirrer and an addition funnel ((Note 1), f.htmig. 1). The flask is charged with 400 mL of pyridine, 5 mL (0.12 mol) of methanol and 9.9 g (0.10 mol) of cuprous chloride under an atmosphere of nitrogen (Note 2). The resultant yellow solution is stirred vigorously at room temperature until the cuprous chloride dissolves (Note 3). The nitrogen is removed and oxygen is bubbled into the flask below the surface of the liquid for approximately 30 min (Note 4). A solution, composed of 1000 mL of pyridine, 5.5 g (0.05 mol) of 1,2-dihydroxybenzene (catechol), and 5 mL (0.12 mol) of methanol, is degassed and slowly added to the flask over a 2-hr period with efficient stirring (Note 5). The reaction mixture is stirred for an additional 30 min before the pyridine is removed at reduced pressure. The dark green residue is dissolved in 300 mL of ethyl ether (Note 6) and 300 mL of 6 *N* hydrochloric acid; this solution is stirred for 10 min and filtered over Celite, and the organic layer is isolated. The ether is removed at reduced pressure and the resultant brown residue is boiled sequentially with six 50-mL portions of hexane (Note 7). The hot liquid is carefully decanted, leaving behind most of the dark residue. The yellow-to-colorless solid is crystallized from hot hexane (or methanol) to yield 5.6–6.2 g (71–80%) of colorless needles, mp 80–81°C (Note 8).

Figure 1

Figure 1

2. Notes

1. The checkers employed an alternate device of the following type and

introduced the methanolic catechol solution subsequently via syringe.

2. Pyridine (Mallinckrodt Inc., reagent grade) was distilled over potassium hydroxide, bp 114–116°C. Cuprous chloride was prepared fresh,[2] washed with anhydrous methanol (distilled from magnesium metal), and dried under reduced pressure. Methanol (Fisher Scientific Company, purified grade) was dried over molecular sieves. The concentration of the methanol should be within the range of 3–8 mol/mol of catechol[3,4] and anhydrous conditions are necessary[4].
3. Dissolution requires 1.5–2 hr. If the solution is not properly degassed, it will turn green prematurely. The green color indicates that oxygen absorption by the cuprous chloride–pyridine complex has occurred, but it also means that any undissolved cuprous chloride has been oxidized. Therefore, nitrogen should be bubbled into the flask at a brisk rate and stirring should not commence until addition of the cuprous chloride is complete.
4. As oxygen is introduced into the flask the solution becomes dark green and slightly viscous.
5. Catechol was purchased from Fisher Scientific Company (resublimed). The addition funnel should be charged with a nitrogen atmosphere throughout addition to obviate oxidation of the catechol.
6. Ethyl ether was purchased from Mallinckrodt, Inc. (analytical grade); methylene chloride may be substituted, but the monomethyl ester is more soluble in ether. At least two other extractions will be necessary to optimize the yield when methylene chloride is used.
7. Hexane was purchased from Fisher Scientific Company (technical grade).
8. The spectral properties are as follows: ^{1}H NMR (300 MHz, CCl_4) δ: 3.74 (s, 3 H); 5.88–6.09 (m, 2 H); 7.75–8.26 (m, 2 H); 11.29 (s, 1 H).

3. Discussion

Phenol also undergoes oxidative cleavage in the presence of O_2/CuCl/pyridine and methanol to give *cis,cis*-monomethyl muconate, but the yield is not high.[4,5] It has also been observed that catechol, under anaerobic conditions, reacts with cupric methoxy chloride in pyridine containing water and methanol to give *cis,cis*-monomethyl muconate in high yield.[6] Catechol and phenol may also be converted to *cis,cis*-muconic acid by a metal-catalyzed peracetic acid oxidation;[7] subsequently, treatment with diazomethane gives the monomethyl or dimethyl ester.

References and Notes

1. Laboratory of J. C. Barborak, Department of Chemistry, University of North Carolina

at Greensboro, Greensboro, NC 27412. Present address: Burroughs Wellcome, Organic Chemistry Department, 3030 Cornwallis, Research Triangle Park, NC 27709.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

cupric methoxy chloride

CuCl

O_2

hydrochloric acid (7647-01-0)

methanol (67-56-1)

ether, ethyl ether (60-29-7)

magnesium (7439-95-4)

phenol (108-95-2)

oxygen (7782-44-7)

nitrogen (7727-37-9)

pyridine (110-86-1)

potassium hydroxide (1310-58-3)

Catechol, 1,2-DIHYDROXYBENZENE (120-80-9)

cuprous chloride (7758-89-6)

methylene chloride (75-09-2)

Diazomethane (334-88-3)

peracetic acid (79-21-0)

hexane (110-54-3)

cis,cis-Monomethyl muconate, 2,4-Hexadienedioic acid, monomethyl ester, (Z,Z)- (61186-96-7)

cis,cis-muconic acid (505-70-4)

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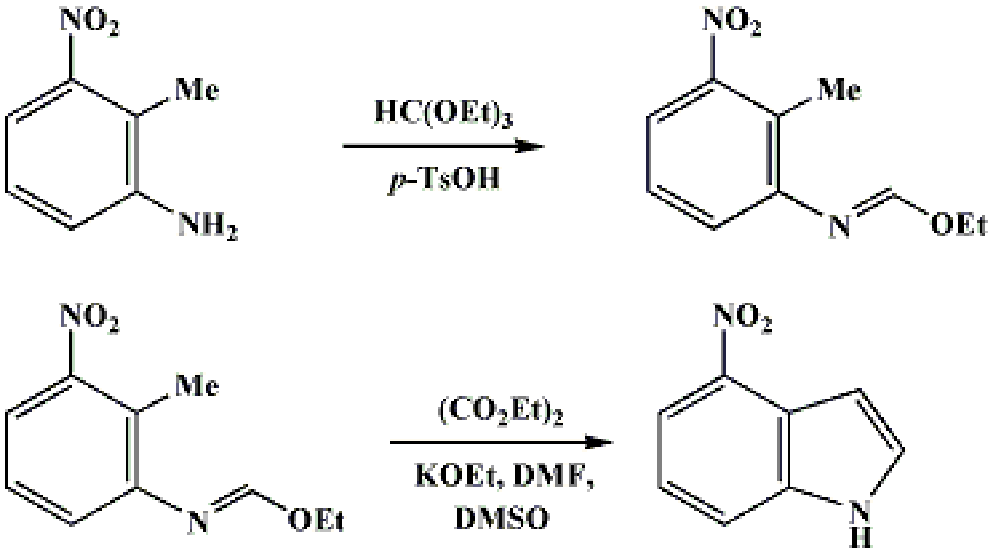
Organic Syntheses, CV 8, 493

4-NITROINDOLE

[Indole, 4-nitro-]



Submitted by Jan Bergman and Peter Sand[1].
Checked by Cynthia A. Smith and Andrew S. Kende.

1. Procedure

A. *Ethyl N-(2-methyl-3-nitrophenyl)formimidate.* A 1-L, one-necked, round-bottomed flask, fitted with a Claisen condenser protected from moisture with a drying tube, is charged with 200 g (1.35 mol) of freshly distilled triethyl orthoformate, 1 g of *p*-toluenesulfonic acid and 152 g (1 mol) of 2-methyl-3-nitroaniline (Note 1) and (Note 2). The solution is heated to 120°C and all of the ethanol formed is continuously distilled off during ca. 1 hr. Fractional vacuum distillation of the residue gives at 156–158°C/6 mm, the imidate ester, 184 g (88%), as a light-yellow, solidifying oil, mp 57–58°C.

B. *4-Nitroindole.* To a solution of 22 g (0.15 mol) of diethyl oxalate in 50 mL of dry dimethylformamide in a 200-mL beaker is added, under cooling, 11 g (0.13 mol) of potassium ethoxide with vigorous stirring (Note 3) and (Note 4). The solution is immediately (within a few seconds) poured into a 250-mL flask containing a solution of 20.8 g (0.10 mol) of ethyl *N*-(2-methyl-3-nitrophenyl)formimidate in 75 mL of dry dimethyl sulfoxide (Note 5). The resulting deep-red solution is stirred for 1 hr at ca. 40°C (Note 6) and (Note 7). The solution is then transferred into a 1-L beaker and water is added under stirring at a rate that gives smooth precipitation of 4-nitroindole. The product is filtered off and dried, giving 16.3 g (ca. 100%) of a brownish-yellow solid, mp 195–201°C [sublimation (subl.)], which is sublimed at 170°C/0.5 mm giving 11.5 g (71%) of yellow crystals, mp 204–205°C (subl.) (Note 8).

2. Notes

1. 2-Methyl-3-nitroaniline and triethyl orthoformate were purchased from Fluka AG.
2. Trimethyl orthoformate is not suitable for this preparation because of side-product formation.
3. Diethyl oxalate was purchased from Merck and Company, Inc., and was used without further purification. Potassium ethoxide was purchased from Alfa Products, Johnson Mathey Co. or preferably was prepared from potassium metal and absolute ethanol.
4. The diethyl oxalate/potassium ethoxide complex can also be prepared by adding the oxalic ester to an ethanolic solution of potassium ethoxide and evaporating the solvent. However, this complex is less active and is difficult to store.
5. Dimethyl sulfoxide (DMSO) prevents precipitation of intermediate salts, which can also be achieved by using a larger volume of dimethylformamide (DMF) (ca. 200 mL). Attempts to prepare the diethyl oxalate/potassium ethoxide complex in DMSO have not been successful (i.e., it is not active).
6. At elevated temperatures (e.g., above 40°C) by-products are formed.
7. The reaction can be monitored by TLC (CH_2Cl_2). The spots were developed with an ethanolic solution of *p*-dimethylaminobenzaldehyde/HCl. The product gave a bright-red spot at R_f 0.5, and the imidate ester gave a yellow spot at R_f 0.6. Addition of small portions of diethyl oxalate/potassium ethoxide complex was continued if the starting material was not consumed after the initial reaction period.
8. Crude 4-nitroindole can also be purified by recrystallization from methanol, ethanol, or acetonitrile giving brownish-yellow crystals, mp 204–206°C.

3. Discussion

This procedure illustrates the synthesis of 4-nitroindoles; the present method can easily be extended to the 2-alkyl derivatives (using other *ortho* esters), 5-, 6- and/or 7-substituted derivatives and 1-alkyl derivatives (from the corresponding *N*-alkylanilides).[2,3] Other published preparations of 4-nitroindole (e.g., [4]) are of no practical value.

The mechanism of the formation of 4-nitroindole parallels the Reissert indole synthesis[5] and is discussed in [2] and [3].

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

4-nitroindoles

ethanol (64-17-5)

HCl (7647-01-0)

methanol (67-56-1)

acetonitrile (75-05-8)

potassium (7440-09-7)

triethyl orthoformate (122-51-0)

potassium ethoxide (917-58-8)

dimethylformamide (68-12-2)

diethyl oxalate (95-92-1)

dimethyl sulfoxide (67-68-5)

p-Dimethylaminobenzaldehyde (100-10-7)

p-toluenesulfonic acid (104-15-4)

trimethyl orthoformate (149-73-5)

4-Nitroindole, Indole, 4-nitro- (4769-97-5)

2-methyl-3-nitroaniline (603-83-8)

Ethyl N-(2-methyl-3-nitrophenyl)formimidate (115118-93-9)

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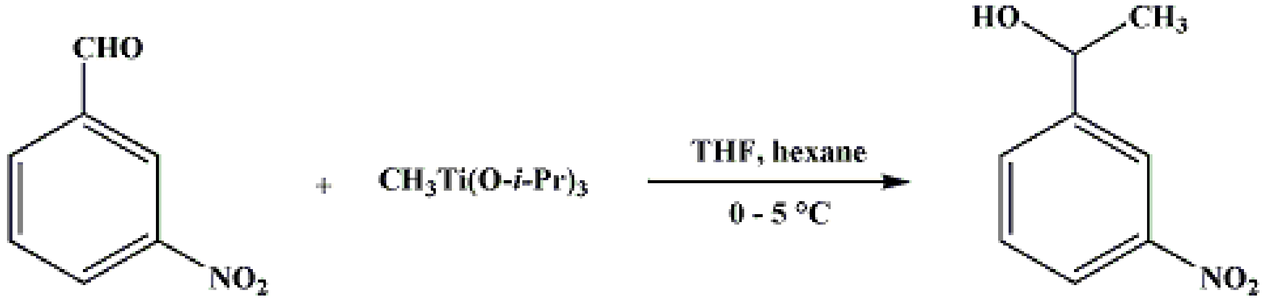
Organic Syntheses, CV 8, 495

3'-NITRO-1-PHENYLETHANOL BY ADDITION OF METHYLTRIISOPROPOXYTITANIUM TO *m*-NITROBENZALDEHYDE

[Benzenemethanol, α-methyl-3-nitro-]



Submitted by René Imwinkelried and Dieter Seebach[1].
Checked by Cheryl A. Martin and K. Barry Sharpless.

1. Procedure

A dry, 500-mL, three-necked flask equipped with pressure-equalizing 100-mL dropping funnel, argon inlet, and magnetic stirrer is evacuated and flushed with argon (three cycles). The flask is charged with 16.0 mL (57.7 mmol) of tetraisopropyl orthotitanate (Note 1) via a plastic syringe and hypodermic needle and 2.1 mL (19.2 mmol) of titanium tetrachloride is added over 5 min, with gentle cooling of the flask in an ice–water bath to give a viscous oil (Note 2). After the addition of 70 mL of tetrahydrofuran (Note 3), the clear solution is stirred at room temperature for 30 min. The dropping funnel is charged with 62 mL (77 mmol, 1.24 *M* in hexane) of methyllithium (Note 4), which is added to the cooled (ice bath) tetrahydrofuran solution over a period of 25–30 min. During the addition the resulting suspension changes from orange to bright yellow. After the mixture has stirred at ice–bath temperature for 1 hr, a solution of 10.6 g (70 mmol) 3-nitrobenzaldehyde (Note 5) in 60 mL of tetrahydrofuran (Note 3) is added from the dropping funnel within 20–25 min at the same temperature. The mixture is stirred at 0–5°C for 1 hr and then 60 mL of 2 *N* hydrochloric acid is added. The organic phase is separated in a separatory funnel and the aqueous phase is extracted with three 150-mL portions of diethyl ether. The combined organic phases are washed with 100 mL of saturated sodium bicarbonate solution and 100 mL of saturated sodium chloride solution and then dried over anhydrous magnesium sulfate. After filtration the solution is concentrated on a rotary evaporator and dried at 0.1 mm for 1 hr. The residue, 11.0–11.1 g (94–95%) of an orange-brown viscous oil, sometimes solidifies on standing (mp 55–60°C); the purity of the crude product is at least 95% (estimated by ^{1}H NMR). The product can be purified by short-path distillation at 120–125°C (0.15 mm) to give 9.9–10.4 g (85–89%) of a yellow oil, which solidifies on standing at room temperature or at −30°C in a freezer, mp 60.5–62.0°C (lit.[2] mp 62°C) (Note 6).

2. Notes

1. Commercial tetraisopropyl orthotitanate [Ti(O-*i*-Pr)$_4$] (Dynamit Nobel) and titanium tetrachloride (Fluka pract.) can be used without further purification. The checkers obtained Ti(O-*i*-Pr)$_4$ from Aldrich Chemical Company, Inc. and titanium tetrachloride from Fluka. Distillation of Ti(O-*i*-Pr)$_4$ did not improve the results.
2. If the mixture is overcooled, the resulting chlorotriisopropoxytitanium partially solidifies.
3. Tetrahydrofuran was distilled from potassium/benzophenone immediately before use.
4. The methyllithium solution was obtained from Metallgesellschaft, Frankfurt. The checkers used methyllithium (Aldrich Chemical Company, Inc.), salt-free 1.4 *M* in ethyl ether, with no significant difference observed in the reaction.
5. 3-Nitrobenzaldehyde is Fluka purum, used without further purification. The checkers obtained it from Aldrich Chemical Company, Inc.
6. The product obtained after distillation can be recrystallized from benzene/ petroleum ether (3:2, v : v) to give pale-yellow crystals (91–95% from distilled product) with a melting point of 61–63°C. Attempts by the checkers to crystallize the crude reaction mixture were unsuccessful. ^{1}H NMR ($CDCl_3$) δ: 1.54 (d, 3 H, *J* = 6.5, CH_3), 2.3 (br, 1 H, OH), 5.00 (q, *J* = 6.5, O-C-H), 7.5–7.7 (m, 2 H, arom. H), 8.0–8.25 (m, 2 H, arom. H); IR (KBr) cm^{-1}: 3260 (br, m), 2990 (m), 1580 (m), 1525 (s), 1340 (s), 1205 (m), 1170 (m), 810 (m), 740 (m), 690 (m).

3. Discussion

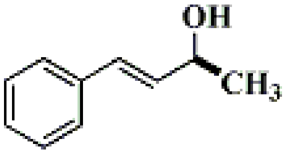
The addition of nucleophilic organometallic compounds (usually RLi or RMgX) to a carbonyl group—a key step in numerous syntheses—is not always straightforward. The addition reaction is complicated by the fact that aldehydes, ketones, and esters are not well differentiated; that other electrophilic functional groups, such as cyano, nitro, halo, and trialkylstannyl may interfere; and that proton abstraction or one electron-transfer processes rather than addition occur. For example, the addition of methyllithium or methylmagnesium iodide to 3-nitrobenzaldehyde under the same conditions used with $CH_3Ti(OCH(CH_3)_2)_3$ (this procedure) leads to a complex mixture of products with formation of only 10–30% of 3'-nitro-1-phenylethanol.[3] In many cases these complications can be remedied by using derivatives of titanium and zirconium, compounds that have become increasingly important in organic syntheses during the past decade. Several review articles discuss different aspects.[3]

The nucleophilic titanium and zirconium reagents are readily available by simple transmetallation of the organolithium or Grignard reagents with $(RO)_3TiCl$, $(RO)_3ZrCl$, or $(R_2N)_3TiX$. The trialkoxychloro compounds are prepared by mixing the inexpensive, industrially available, titanates, $Ti(OR)_4$, or zirconates, $Zr(OR)_4$, with the appropriate amount of $TiCl_4$ or $ZrCl_4$. In contrast to compounds of most other heavy metals, few toxic effects of $Ti(OR)_4$ and $Zr(OR)_4$ are known, partly because they are very rapidly

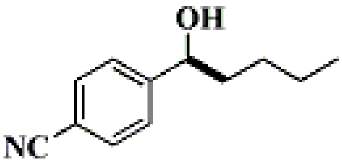
hydrolyzed by water and the resulting oxide–hydrates are insoluble (TiO_2 is a white pigment). Some of the reagents, $RTi(OR')_3$, can be isolated without difficulty. Thus, $CH_3Ti(O$-*i*-$Pr)_3$s can be obtained as a bright-yellow oil that distills without decomposition at 50°C/0.001 mm.[4]

The organotitanium and -zirconium compounds, for the most part generated in situ, react highly selectively with carbonyl compounds. For example, $CH_3Ti(O$-*i*-$Pr)_3$ reacts five orders of magnitude faster with benzaldehyde than with acetophenone at room temperature.[5] Reagents of the type $RTi(O$-*i*-$Pr)_3$ add smoothly to nitro- (see this procedure), iodo-, or cyanosubstituted benzaldehydes, and the reactions may be performed in chlorinated solvents or in acetonitrile (for some examples, see Table I). The zirconium analogs have particularly low basicity and add in high yield to α- and β-tetralones.[6] The inclusion of chiral OR* groups gives enantioselective reagents (up to ≥98% ee).[7,8,9] Allylic $(RO)_3Ti$ derivatives react diastereoselectively only at the more highly substituted carbon atom with aldehydes and even with unsymmetric ketones.[8,9,10] Titanates can be used as mild catalysts for the transesterification of compounds containing acid- or base-labile functional groups.[11]

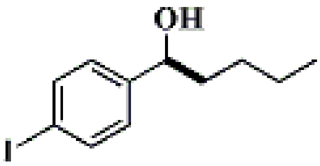
TABLE I
SOME PRODUCTS OF ORGANOTITANIUM TRIISOPROPOXIDES [RTi(OiPr)$_3$] WITH FUNCTIONALIZED CARBONYL COMPOUNDS[3,a]



90%



97%



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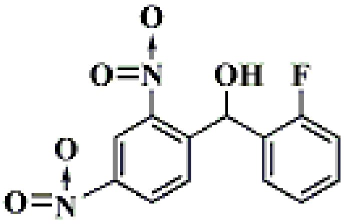
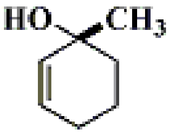


98%



80%

[a]The bonds formed during the reaction are drawn bold.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

3'-NITRO-1-PHENYLETHANOL

tetraisopropyl orthotitanate [$Ti(O-i-Pr)_4$] (Dynamit Nobel)

$CH_3Ti(OCH(CH_3)_2)_3$

$CH_3Ti(O-i-Pr)_3$

$Ti(O-i-Pr)_4$

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ethyl ether, diethyl ether (60-29-7)

acetonitrile (75-05-8)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

Acetophenone (98-86-2)

carbon (7782-42-5)

Benzophenone (119-61-9)

potassium (7440-09-7)

methylmagnesium iodide (917-64-6)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

hexane (110-54-3)

Methyllithium (917-54-4)

titanium tetrachloride (7550-45-0)

zirconium

argon (7440-37-1)

titanium (7440-32-6)

Methyltriisopropoxytitanium (18006-13-8)

Benzenemethanol, α-methyl-3-nitro- (5400-78-2)

tetraisopropyl orthotitanate (546-68-9)

3-nitrobenzaldehyde, m-Nitrobenzaldehyde (99-61-6)

chlorotriisopropoxytitanium

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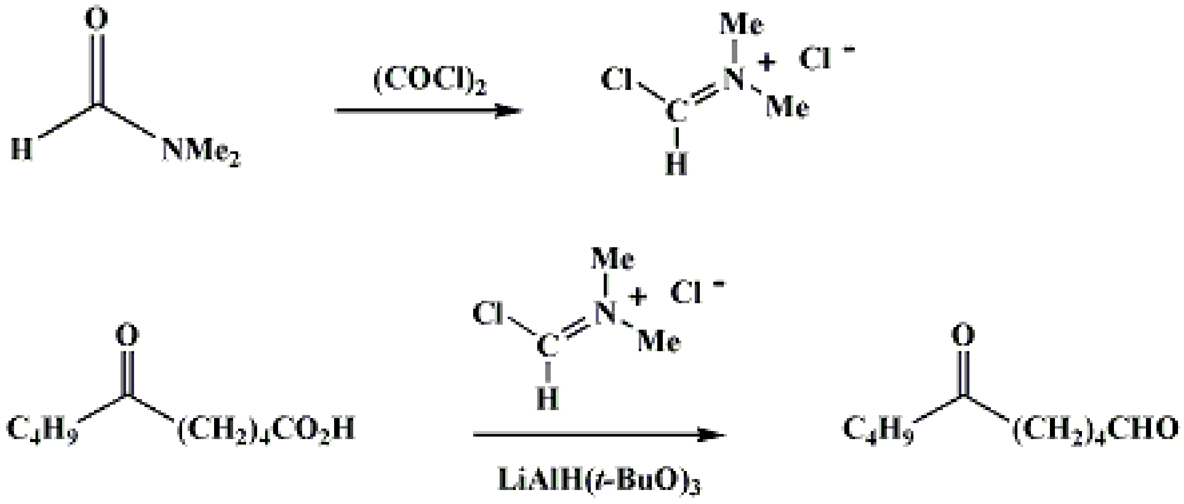
Organic Syntheses, CV 8, 498

REDUCTION OF CARBOXYLIC ACIDS TO ALDEHYDES: 6-OXODECANAL

[Decanal, 6-oxo-]



Submitted by Tamotsu Fujisawa and Toshio Sato[1].
Checked by Cynthia Smith and Andrew S. Kende.

1. Procedure

Caution! Oxalyl chloride is toxic. This preparation should be carried out in a well-ventilated hood.

A. *N,N-Dimethylchloromethylenammonium chloride.* A 500-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, a thermometer (Note 1), and a three-way stopcock fitted with a drying tube containing anhydrous calcium chloride and a rubber septum. The flask is charged with 50 mL of dichloromethane (Note 2) and 3.07 (0.042 mol) of *N,N*-dimethylformamide (Note 3) added through the septum from a syringe, and cooled in an ice bath. To the cooled mixture is slowly added 5.23 mL (0.06 mol) of oxalyl chloride (Note 4) by means of a syringe. The addition is accompanied by gas evolution and formation of a white precipitate. The reaction mixture is stirred for an additional hour at 0°C. Excess oxalyl chloride and solvent are removed under reduced pressure by first using a water aspirator and then a rotary pump at room temperature through the drying tube. The white solid remaining in the flask is *N,N*-dimethylchloromethylenammonium chloride, which is used directly in Part B.

B. *6-Oxodecanal.* The drying tube is removed and the flask is flushed with nitrogen. A nitrogen atmosphere is maintained throughout the subsequent reaction. A dropping funnel is attached and charged with 7.45 g (0.04 mol) of 6-oxodecanoic acid (Note 5),

3.32 g of pyridine (Note 6), and 80 mL of tetrahydrofuran (Note 7), which are mixed well by shaking. The flask is charged with 45 mL of acetonitrile (Note 8) and 80 mL of tetrahydrofuran and cooled (methanol–liquid nitrogen) to −30°C. The contents of the funnel are added to the flask at −30°C over 30 min. The reaction mixture is stirred at −30°C for an additional hour and at −20°C for 30 min. After the mixture is cooled to −90°C (Note 9), 34 mL (0.046 mol) of a 1.35 *M* solution of lithium tri(*tert*-butoxy) aluminum hydride in tetrahydrofuran (Note 10) is injected through the septum by means of a syringe over 30 min, while the internal temperature is kept below −85°C. Stirring is continued for an additional 30 min at −90°C. To the flask is added 50 mL of 2 *M* hydrochloric acid solution, and the cooling bath is immediately removed. The organic layer is separated and the aqueous layer is extracted with three 50-mL portions of ether. The combined organic extracts are washed with two 50-mL portions of saturated sodium hydrogen carbonate solution and 50 mL of brine, dried over anhydrous sodium sulfate, and filtered. The solvent is removed with a rotary evaporator and the residual liquid is distilled under reduced pressure to yield 5.78–6.35 g (85–93%) of 6-oxodecanal as a fragrant liquid, bp 85–90°C (1.4 mm) (Note 11).

2. Notes

1. The thermometer must be able to measure temperatures as low as –90°C.
2. Dichloromethane was distilled from calcium hydride and stored over Linde 4A molecular sieves.
3. *N,N*-Dimethylformamide was distilled under reduced pressure, bp 45–47°C (20 mm), and stored over Linde 4A molecular sieves.
4. Oxalyl chloride purchased from Wako Chemicals was used without purification. The checkers found that oxalyl chloride, purchased from Aldrich Chemical Company, Inc., gives better yields if freshly distilled.
5. 6-Oxodecanoic acid was obtained by hydrolysis of methyl 6-oxodecanoate prepared by the *Organic Syntheses*[2] method as follows: 20 g (0.100 mol) of methyl 6-oxodecanoate was treated with 200 mL of 1 *M* potassium hydroxide solution at room temperature overnight. The alkaline solution was washed with two 50-mL portions of ether, and acidified with 50 mL of 6 *M* hydrochloric acid solution at 0°C. The acidic layer was extracted with three 100-mL portions of ether. The ethereal extracts were dried over sodium sulfate and filtered. Removal of the solvent under reduced pressure and recrystallization of the residual white solid from hexane gave 17.85 g (96%) of 6-oxodecanoic acid, mp 45.0–45.5°C (lit.[3] mp 45–46°C).
6. Pyridine was distilled from calcium hydride, and stored over Linde 4A molecular sieves.
7. Tetrahydrofuran was freshly distilled from the sodium ketyl of benzophenone.
8. Acetonitrile was distilled from calcium hydride, and stored over Linde 4A molecular sieves.
9. The checkers used a 1 : 1 methanol : ethanol/liquid nitrogen bath.
10. Lithium tri(tert-butoxy)aluminum hydride was purchased from Kanto

Chemicals or Aldrich Chemical Company, Inc.
11. GLC analysis of the product using a 3-mm × 1-m stainless-steel column, 15% SE-30 on Chromosorb W (AW), 60–80 mesh, 150°C, 50 mL of nitrogen per minute showed a purity of 99.2% (the retention times is 4.0 min). The spectral properties of the product are as follows: IR (liquid film) cm^{-1}: 2950, 2930, 2870, 2720, 1710, 1455, 1410, 1370; ^{1}H NMR (60 MHz, CCl_4) δ: 0.87 (t, 3 H, *J* = 7, CH_3), 1.1–1.9 (m. 8 H, CH_2), 2.1–2.6 (m, 6 H, $CH_2C{=}O$), 9.73 (t, 1 H, *J.* = 1.4, H-C=O).

3. Discussion

Various reagents have been suggested for the conversion of carboxylic acids into aldehydes, such as modified aluminum hydride reagents,[4] Grignard reagents catalyzed by dichlorobis(π-cyclopentadienyl)titanium,[5] lithium in methylamine,[6] and boron hydride reagents.[7] However, these reagents have some drawbacks in availability, lack of chemoselectivity due to the high reactivity of the reagents, and isolation of products.

The present procedure, a modified one reported earlier by the submitters, illustrates a general method of aldehyde synthesis from carboxylic acids in a one-pot operation using the readily available, *N,N*-dimethylchloromethylenammonium chloride.[8] Strong activation of carboxylic acids by the iminium salt via the carboxymethylenammonium salt[9] and a weak reducing reagent, lithium tri(*tert*-butoxy)aluminum hydride, achieve the chemoselective reduction of carboxylic acids to aldehydes. The present procedure has several advantages: (a) easy availability of the reagents; (b) use of a slight excess of the hydride reagent; (c) high yields of both aliphatic and aromatic aldehydes; (d) high chemoselectivity, which tolerates nitrile, ester, halide, olefin, and even ketone; and (e) easy isolation of the product.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

brine

sodium ketyl of benzophenone

dichlorobis(π-cyclopentadienyl)titanium

hydrochloric acid (7647-01-0)

methanol (67-56-1)

ether (60-29-7)

acetonitrile (75-05-8)

sodium hydrogen carbonate (144-55-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

pyridine (110-86-1)

potassium hydroxide (1310-58-3)

methylamine (74-89-5)

dichloromethane (75-09-2)

lithium (7439-93-2)

boron hydride (7440-42-8)

Tetrahydrofuran (109-99-9)

oxalyl chloride (79-37-8)

N,N-dimethylformamide (68-12-2)

hexane (110-54-3)

calcium hydride (7789-78-8)

Methyl 6-oxodecanoate (61820-00-6)

6-Oxodecanal, Decanal, 6-oxo- (63049-53-6)

6-Oxodecanoic acid (4144-60-9)

Lithium tri(tert-butoxy)aluminum hydride

N,N-Dimethylchloromethylenammonium chloride

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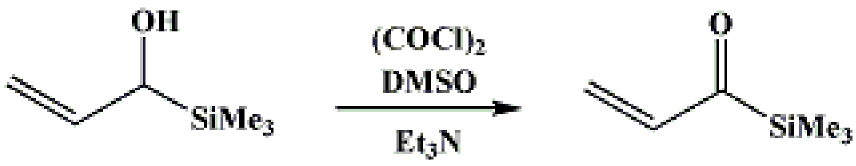
Organic Syntheses, CV 8, 501

(1-OXO-2-PROPENYL)TRIMETHYLSILANE

[Silane, trimethyl(1-oxo-2-propenyl)-]



Submitted by Rick L. Danheiser, David M. Fink, Kazuo Okano, Yeun-Min Tsai, and Steven W. Szczepanski[1].
Checked by Masahiko Hayashi and Ryoji Noyori.

1. Procedure

A. *(1-Hydroxy-2-propenyl)trimethylsilane.* A 2-L, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, two pressure-equalizing dropping funnels (250 and 500 mL), and a Claisen adapter fitted with an argon inlet adapter and a rubber septum (Note 1). The flask is charged with 20.0 g (0.344 mol) of allyl alcohol (Note 2), and 400 mL of dry tetrahydrofuran (Note 3), and then cooled below –75°C with a dry ice–acetone bath and maintained at that temperature while 157 mL (0.363 mol) of a 2.31 *M* solution of *n*-butyllithium in hexane (Note 4) is added dropwise over 1 hr. After 50 min, a solution of 39.3 g (0.362 mol) of chlorotrimethylsilane (Note 5) in 25 mL of tetrahydrofuran is added dropwise via syringe over 30 min, and the resulting colorless reaction mixture is stirred for 1 hr further, and then treated dropwise over 1.5 hr with 258 mL (0.415 mol) of a 1.61 *M* solution of *tert*-butyllithium in pentane (Note 4). After 2 hr of further stirring at –75°C the cold bath is removed, and 100 mL of saturated ammonium chloride solution is added in one portion to the yellow reaction mixture. The resulting solution is stirred for 5 min and then diluted with 50 mL of water and 300 mL of pentane. The organic phase is separated and washed successively with three 100-mL portions of water and two 100-mL portions of saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and concentrated by carefully distilling off the solvents at atmospheric pressure through a 10-cm Vigreux column. The residual pale yellow liquid is transferred to a 100-mL round-bottomed flask, and the remaining volatile impurities are removed by distillation at 15 mm through a 4-cm column packed with glass helices

(Note 6), leaving 35.1–39.7 g of (1-hydroxy-2-propenyl)trimethylsilane as a pale-yellow liquid (Note 7) and (Note 8) used in the next step without further purification.

B. *(1-Oxo-2-propenyl)trimethylsilane.* A 2-L, three-necked, round-bottomed flask is equipped with a mechanical stirrer and two 250-mL pressure-equalizing dropping funnels, one of which is fitted with an argon inlet adapter (Note 1). The flask is charged with 41.71 g (0.329 mol) of oxalyl chloride (Note 9) and 500 mL of dichloromethane (Note 10), and cooled below −75°C with a dry ice–acetone bath and maintained at that temperature while a solution of 55.82 g (0.715 mol) of dimethyl sulfoxide (Note 11) in 60 mL of dichloromethane is added dropwise over 1 hr. After 1 hr, a solution of the crude (1-hydroxy-2-propenyl)trimethylsilane in 100 mL of dichloromethane is added dropwise over 1.25 hr to the colorless reaction mixture, which is stirred at −75°C for 1 hr further, and then treated dropwise over 30 min with 150.38 g (1.486 mol) of triethylamine (Note 12). After 1 hr, the cold bath is removed and the reaction mixture is poured into 200 mL of water. The organic phase is separated and washed successively with five 100-mL portions of 10% hydrochloric acid, three 100-mL portions of water, and two 100-mL portions of saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and concentrated by carefully distilling off the solvents at atmospheric pressure through a 10-cm Vigreux column. The residual yellow oil is transferred to a 250-mL, round-bottomed flask containing 0.050 g of 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide (Note 13) and distilled through a 4-cm column packed with glass helices to afford 27.8–30.0 g (63–68% overall yield based on allyl alcohol) of (1-oxo-2-propenyl)trimethylsilane as a brilliant-yellow oil, bp 47–50°C (30 mm) (Note 14) and (Note 15).

2. Notes

1. The glass components of the apparatus are dried overnight in a 120°C oven, and then assembled and maintained under an atmosphere of argon during the course of the reaction.
2. Allyl alcohol was purchased from Aldrich Chemical Company, Inc. and distilled from calcium hydride prior to use.
3. Tetrahydrofuran was distilled from sodium benzophenone ketyl immediately before use.
4. *n*-Butyllithium was purchased from Aldrich Chemical Company, Inc. or Mitsuwa Pure Chemicals, *tert*-Butyllithium was obtained from Aldrich Chemical Company, Inc. These were titrated using the method of Watson and Eastham[2] submitters) or Lipton[3] (checkers).
5. Chlorotrimethylsilane was obtained from Petrarch Systems, Inc., or Shin-etsu Kagaku Co., and distilled from calcium hydride before use.
6. The heating bath temperature was not permitted to exceed 70°C during the course of the distillation.
7. The purity of this material was determined to be 95% by gas-chromatographic analysis (10% OV-101 on 100–120-mesh Chromosorb W, 6 ft × 1/8 in., program: 50°C for 2 min and then 50–250°C at 32°C/min).

8. The product exhibits the following spectral properties: IR (film) cm^{-1}: 3420, 2955, 2895, 2820, 1625, 1410, 1245, 1140, 1095, 990, 900, 840; ^{13}C NMR (67.9 MHz, $CDCl_3$) δ: –4.4, 68.9, 109.4, 139.9; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 0.05 (s, 9 H), 2.86 (br s, 1 H), 3.88 (m, 1 H), 4.86 (ddd, 1 H, *J* = 2, 2, 11), 4.98 (ddd, 1 H, *J* = 2, 2, 17), 5.89 (ddd, 1 H, *J* = 5.5, 11, 17); HRMS *m/e* calcd. for $C_6H_{14}OSi$ (M^+): 130.0814, Found: 130.0810.

9. Oxalyl chloride purchased from Aldrich Chemical Company, Inc. was fractionally distilled under argon before use.

10. Dichloromethane was distilled from calcium hydride immediately before use.

11. Dimethyl sulfoxide was distilled from calcium hydride immediately before use.

12. Triethylamine was distilled from calcium hydride before use.

13. 3-*tert*-Butyl-4-hydroxy-5-methylphenyl sulfide was purchased from Aldrich Chemical Company, Inc.

14. The purity of this material was determined to be >97% by gas-chromatographic analysis (10% OV-101 on 100–120-mesh Chromosorb W, 6 ft × 1/8 in., program: 50°C for 2 min and then 50–250°C at 32°C/min).

15. The product exhibits the following spectral properties: IR (film) cm^{-1}: 2960, 2900, 1635, 1600, 1590, 1415, 1390, 1255, 1185, 985, 960, and 845; ^{13}C NMR (67.9 MHz, $CDCl_3$) δ: –2.2, 128.5, 141.3, 237.9; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 0.23 (s, 9 H), 5.94 (dd, 1 H, *J* = 1, 11), 6.13 (dd, 1 H, *J* = 1, 18), 6.38 (dd, 1 H, *J* = 11, 18).

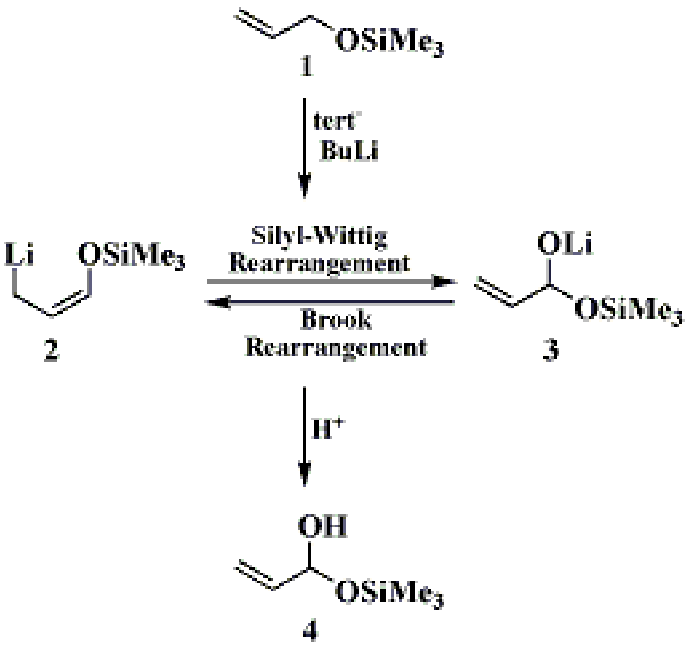
3. Discussion

(1-Oxo-2-propenyl)trimethylsilane has previously been prepared by Reich and co-workers in four steps beginning with propargyl alcohol.[4] This earlier synthesis proceeded in 45% overall yield and involved as key steps the metalation (at –90°C) and silylation of 1-(1-ethoxyethoxy)-1,2-propadiene, followed by careful hydrolysis of the resulting α-silyl allenyl ether.

The present method[5] offers a more efficient and convenient two-step route to the parent α,β-unsaturated acylsilane derivative. The first step in the procedure involves the conversion of allyl alcohol to allyl trimethylsilyl ether, followed by metalation[6 7 8 9 10 11] (in the same flask) with *tert*-butyllithium at –75°C. Protonation of the resulting mixture of interconverting lithium derivatives (**2** and **3**) with aqueous ammonium chloride solution furnishes (1-hydroxy-2-propenyl)trimethylsilane (**4**), which is smoothly transformed to (1-oxo-2-propenyl)trimethylsilane by Swern oxidation.[12] The acylsilane is obtained in 63–68% overall yield from allyl alcohol in this fashion.

α,β-Unsaturated acylsilanes serve as valuable building blocks for the synthesis of a variety of complex organic compounds. These α,β-unsaturated carbonyl derivatives participate in a number of carbon–carbon bond forming processes including

organocuprate conjugate additions,[4] $TiCl_4$-mediated conjugate allylations,[13] Diels–Alder reactions,[4] 1,3-dipolar cycloadditions,[14] and the [3+2] annulation method recently developed in our laboratory.[14] The utility of these reactions is enhanced by the fact that the product acylsilanes are subject to a variety of useful further transformations,[15 16] including, for example, Brook reactions,[4,17 18] oxidation to carboxylic acids,[19 20] and fluoride-promoted conversion to ketones and aldehydes.[20,21 22 23 24] The present procedure provides a practical method for the preparation of multigram quantities of the simplest α,β-unsaturated acylsilane.



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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium benzophenone ketyl

hydrochloric acid (7647-01-0)

ammonium chloride (12125-02-9)

sodium chloride (7647-14-5)

Allyl alcohol (107-18-6)

sodium sulfate (7757-82-6)

Pentane (109-66-0)

dichloromethane (75-09-2)

n-butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

oxalyl chloride (79-37-8)

hexane (110-54-3)

dimethyl sulfoxide (67-68-5)

triethylamine (121-44-8)

calcium hydride (7789-78-8)

propargyl alcohol (107-19-7)

argon (7440-37-1)

CHLOROTRIMETHYLSILANE (75-77-4)

tert-Butyllithium (594-19-4)

(1-Oxo-2-propenyl)trimethylsilane, Silane, trimethyl(1-oxo-2-propenyl)- (51023-60-0)

(1-Hydroxy-2-propenyl)trimethylsilane (95061-68-0)

1-(1-Ethoxyethoxy)-1,2-propadiene (20524-89-4)

allyl trimethylsilyl ether (18146-00-4)

3-tert-butyl-4-hydroxy-5-methylphenyl sulfide (96-66-2)

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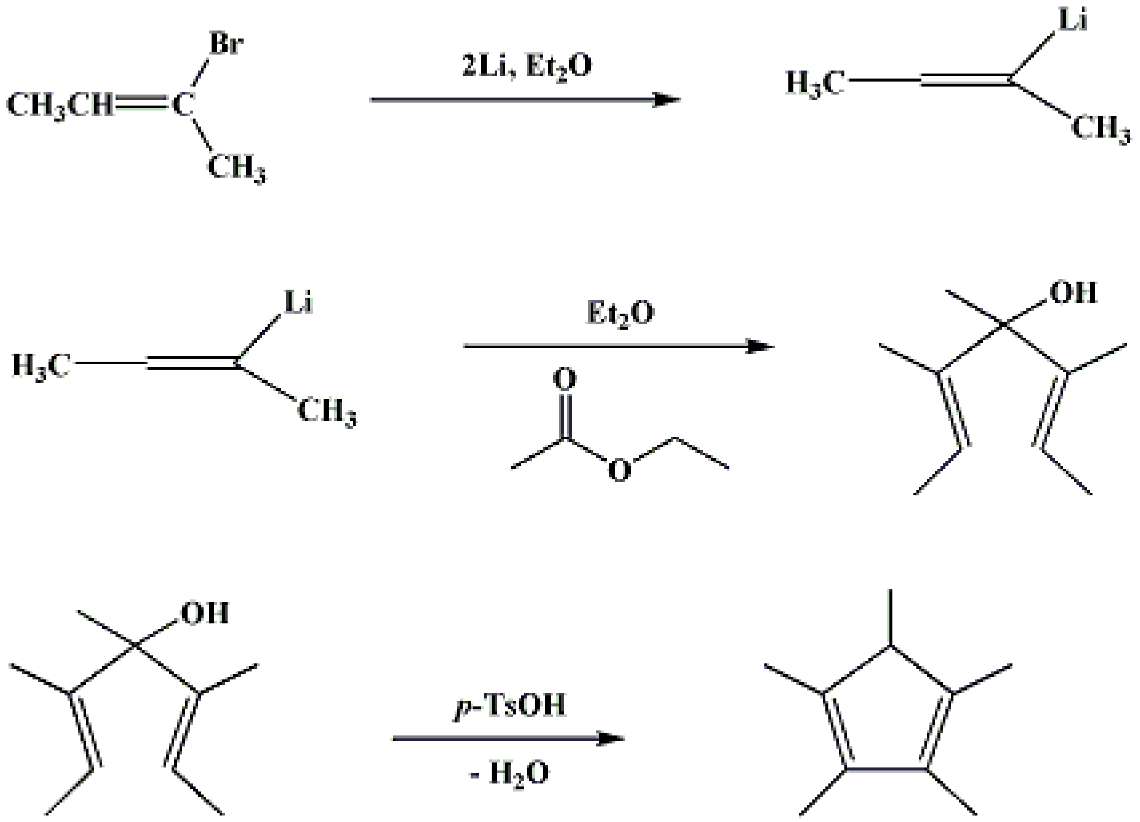
1,2,3,4,5-PENTAMETHYLCYCLOPENTADIENE

[1,3-Cyclopentadiene, 1,2,3,4,5-pentamethyl-]



Submitted by Richard S. Threlkel[1], John E. Bercaw[1], Paul F. Seidler[2], Jeffrey M. Stryker[2], and Robert G. Bergman[2].
Checked by David E. Hill and James D. White.

1. Procedure

A. *3,4,5-Trimethyl-2,5-heptadien-4-ol.* Lithium wire (1/8 in.) is cut up into approximately 1-cm lengths and washed with hexane (Note 1). A mixture of the cut-up lithium (21 g, 3.0 mol) in 100 mL of diethyl ether from a freshly opened can is stirred well under argon in a 2-L, three-necked, round-bottomed flask equipped with a reflux condenser and a 250-mL addition funnel. 2-Bromo-2-butene (*cis-trans* mixture) is purified and dried by passing it through a 2 × 15-cm column of basic alumina (Note 2). An addition funnel is charged with 2-bromo-2-butene (200 g, 1.48 mol) and a small amount of the alkene is added dropwise to the flask until reaction begins, as shown by warming of the reaction mixture and formation of bubbles on the surface of the lithium (Note 3). At this point the mixture is diluted with an additional 900 mL of fresh diethyl ether, and the remainder of the 2-bromo-2-butene is added at a rate sufficient to maintain gentle reflux. Stirring is continued for 1 hr following completion of this addition, after which ethyl acetate (66 g, 0.75 mol) diluted with an equal volume of

fresh diethyl ether is added dropwise via the addition funnel. The reaction mixture turns from yellow-orange to milky-yellow with this addition. It is then poured into 2 L of saturated aqueous ammonium chloride. The ethereal layer is separated, and the aqueous layer is adjusted to approximately pH 9 with hydrochloric acid. The aqueous layer is extracted three times with diethyl ether. The combined ethereal layers are dried over magnesium sulfate, filtered, and concentrated to 100–200 mL by rotary evaporation.

B. *1,2,3,4,5-Pentamethylcyclopentadiene.* A mixture of 13 g (0.068 mol) of *p*-toluenesulfonic acid monohydrate and 300 mL of diethyl ether is stirred under argon in a 1-L, three-necked, round-bottomed flask equipped with a reflux condenser and a 250-mL addition funnel. The concentrate from above is added as quickly as possible to the flask from the addition funnel, maintaining a gentle reflux. As the reaction proceeds, a water layer separates. The mixture is stirred for 1 hr after the addition is completed and then washed with saturated aqueous sodium bicarbonate until the washings remain basic. The ethereal layer is separated, and the combined aqueous layers are extracted three times with diethyl ether. The combined ethereal layers are dried over sodium sulfate. Diethyl ether is removed by rotary evaporation, and the crude product is distilled under reduced pressure (bp 55–60°C, 13 mm): yield 73–75 g (73–75%) (Note 4).

2. Notes

1. High-sodium lithium (1–2% sodium) is preferred in order to facilitate initiation of the reaction. (The checkers used 1% sodium in lithium wire purchased from Lithium Corporation of America, Bessemer City, NC.)
2. While published procedures have used samples of 2-bromo-2-butene as obtained from the supplier without further purification, impurities in some batches often make it difficult, if not impossible, to start the reaction safely.
3. *Caution! It is imperative to add only a few milliliters of the 2-bromo-2-butene and to patiently wait for the reaction with the lithium to begin. Addition of too much 2-bromo-2-butene too soon may lead to a violent reaction.*
4. Pentamethylcyclopentadiene has the following spectral properties; IR (neat) cm^{-1}: 2940, 2890, 2840, 2730, 1670, 1655, 1440, 1370; ^{1}H NMR ($CDCl_3$) δ: 1.00 (3 H, d, J = 7.6, CH_3CH), 1.8 (12 H, br s, CH_3C=), 2.45 (1 H, q, J = 6.5, $CHCH_3$).

3. Discussion

The procedure described here is a modification of that previously published.[3] Specifically, it is frequently insufficient to use the 2-bromo-2-butene as obtained from the supplier without purification using basic alumina I. Such purification assures facile reaction with lithium. Furthermore, the large volumes of diethyl ether used in the past are unnecessary and may inhibit initiation of the reaction of 2-bromo-2-butene with

lithium. Finally, while dry solvents and reagents are required, diethyl ether from a freshly opened can is sufficiently free of water, and distillation from lithium aluminum hydride is unnecessary.

1,2,3,4,5-Pentamethylcyclopentadiene is a useful aromatic building block for the preparation of other compounds. It can be converted to many salts of its conjugate base with alkali metals or strong bases such as butyllithium.[4] These pentamethylcyclopentadienyl anion salts as well as the diene itself can be transformed into η^5-pentamethylcyclopentadienyl ligands of organotransition metal complexes by many known methods.[4]

References and Notes

1. Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, CA 91125.
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

2-Bromo-2-butene (cis-trans mixture)

High-sodium lithium

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

sodium (13966-32-0)

lithium (7439-93-2)

magnesium sulfate (7487-88-9)

butyllithium (109-72-8)

lithium aluminum hydride (16853-85-3)

hexane (110-54-3)

argon (7440-37-1)

pentamethylcyclopentadiene, 1,2,3,4,5-Pentamethylcyclopentadiene, 1,3-Cyclopentadiene, 1,2,3,4,5-pentamethyl- (4045-44-7)

p-toluenesulfonic acid monohydrate (6192-52-5)

2-Bromo-2-butene

3,4,5-Trimethyl-2,5-heptadien-4-ol (64417-15-8)

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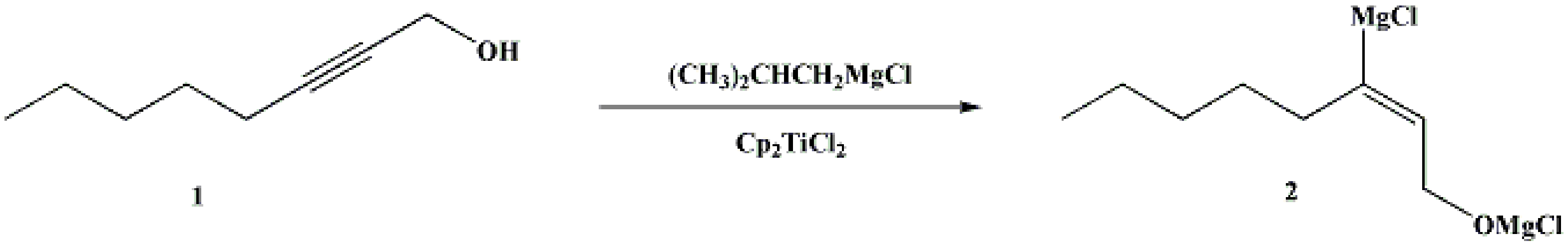
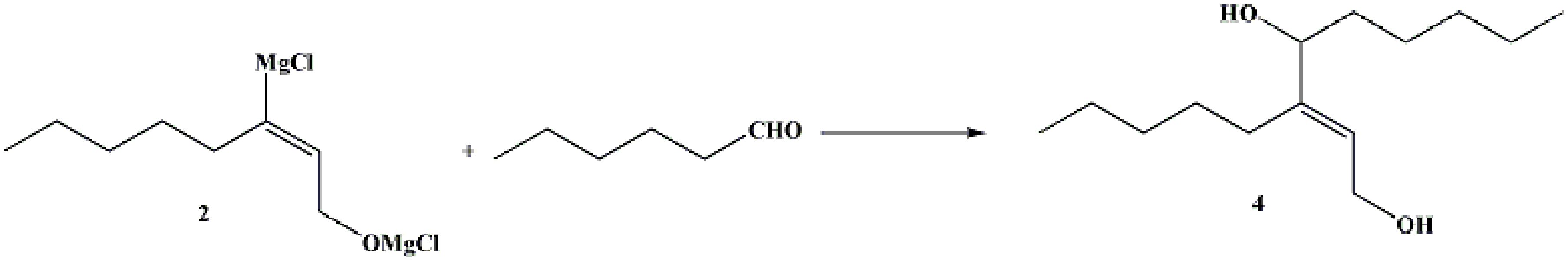
HYDROMAGNESIATION REACTION OF PROPARGYLIC ALCOHOLS: (*E*)-3-PENTYL-2-NONENE-1,4-DIOL FROM 2-OCTYN-1-OL

A.



B.



Submitted by Fumie Sato and Yuichi Kobayashi[1].
Checked by Zuliang Zhou and Ekkehard Winterfeldt.

1. Procedure

A. *The Grignard reagent* ***2.*** A dry, 500-mL, three-necked, round-bottomed flask containing a magnetic stirring bar is equipped with a 100-mL pressure-equalizing dropping funnel, a glass stopper, and a two-way stopcock to which is attached a T-piece connected at one end to a supply of nitrogen, and at the other to an oil bubbler (Note 1). The flask is charged with a solution of isobutylmagnesium chloride in ether (320 mL, 0.75 *M*, 240 mmol) (Note 2) and (Note 3) and immersed in an ice–water bath. Titanocene dichloride (1.3 g, 5.2 mmol) (Note 4) is added at once and the resulting solution is allowed to stir at 0°C for 10 min. A solution of 2-octyn-1-ol (**1**) (13.2 g, 105 mmol) (Note 5) in ether (30 mL) (Note 3) is placed in the dropping funnel and added dropwise to the flask over 20 min at 0°C. The solution is stirred at room temperature for 4 hr to complete the reaction, affording Grignard reagent **2** (Note 6),(Note 7),

(Note 8).

B. *(E)-3-Pentyl-2-nonene-1,4-diol* ***(4)***. Half the amount of the Grignard reagent **2** prepared according to Procedure A is diluted with ether (160 mL) and cooled in an ice–water bath to 0°C. A solution of hexanal (9.25 g, 92.5 mmol) (Note 9) dissolved in ether (30 mL) (Note 3) is added through the dropping funnel over 30 min with efficient stirring. After the addition is complete, the solution is stirred at 0–5°C for 2 hr and then poured into saturated ammonium chloride solution (300 mL). The mixture is stirred at 0°C for 1 hr. The resulting precipitate is removed by filtration through a pad of Celite (70 × 24 mm) under reduced pressure and the precipitate is washed with ethyl acetate (100 mL). The organic layer is separated and the aqueous phase is extracted with ethyl acetate (150 mL). The combined organic layers are dried over magnesium sulfate and concentrated under reduced pressure to leave an oil that is purified by column chromatography on silica gel (Note 10) and (Note 11) to afford **4** (7.0–7.4 g, 59–62% yield) (Note 12).

2. Notes

1. Reactions A and B are carried out under a nitrogen atmosphere. The submitters used argon.
2. A solution of isobutylmagnesium chloride in ether was prepared using isobutyl chloride (13.8 g, 150 mmol), magnesium turnings (4.05 g, 165 mg-atom), and ether (175 mL) according to the procedure for the preparation of *sec*-butylmagnesium chloride reported by Gilman and Kirby.[2] The checkers found that this solution contained about 145 mmol of isobutylmagnesium chloride.
3. Ether and tetrahydrofuran were distilled from benzophenone ketyl under an argon atmosphere.
4. Titanocene dichloride was purchased from Aldrich Chemical Company, Inc., and used without further purification.
5. Alcohol **1** was prepared according to the procedure of Rickards and Weiler[3] and distilled under reduced pressure (102–108°C at 15 mm) before use. This material is also commercially available from Farchan Laboratories, Inc. The checkers obtained it from Lancaster Chemical Co.
6. The checkers found that Grignard reagent **2** could not be obtained quantitatively although all of the isobutylmagnesium chloride had reacted. The end point of the reaction was determined by TLC analysis of a small amount of reaction mixture after hydrolysis. 2-Octyn-1-ol (**1**) and (*Z*)-2-octen-1-ol (**3**), have R_f values of 0.53 and 0.47, respectively (using Silica Gel 60 F_{254} precoated TLC aluminum sheets and benzene–ethyl acetate (1 : 1) as developing agent). If the reaction is not complete, an additional amount of titanocene dichloride should be added to the solution, which is cooled again to 0°C before the addition.
7. The submitters report that, if this solution is poured into 1 *N* hydrochloric acid and ice and worked up in the usual manner, (*Z*)-2-octen-1-ol (**3**) may be obtained in 86% yield by distillation, bp 97–101°C (12 mm). This product has the following spectra: IR (neat) cm^{-1}: 3290, 1457, 1014; ^1H NMR (90 MHz, CCl_4, $(CH_3)_4Si$, D_2O) δ: 0.88 (t, 3 H, J = 6), 1.05–1.57 (m, 6 H), 1.85–2.22 (m, 2 H), 4.03 (d, 2 H, J = 5), 5.27–5.65 (m, 2 H).
8. The submitters report that, if this solution is concentrated, then dissolved in tetrahydrofuran and treated with methyl iodide, (*Z*)-3-methyl-2-octen-1-ol (**5**) may be obtained after silica gel chromatography using hexane–ether as eluent. The product has the following spectra: IR (neat) cm^{-1}: 3305, 1447, 1000; ^1H NMR (90 MHz, CCl_4, $(CH_3)_4Si$, D_2O) δ: 0.88 (t, 3 H, J = 6), 1.1–1.6 (m, 6 H), 1.68 (s, 3 H), 1.9–2.2 (m, 2 H), 3.99 (d, 2 H, J = 6), 5.29 (t, 1 H, J = 6).
9. Hexanal was used as supplied by Tokyo Kasei Kogyo Co., Ltd. (Japan). The checkers obtained it from Aldrich Chemical Company, Inc.
10. Silica gel (100–200 mesh) was purchased from Wako Pure Chemical Industries, LTD (Japan).
11. A silica gel column (225 g, 60 × 210 mm) is used with a mixture of benzene and ethyl acetate as an eluent [R_f value (benzene–ethyl acetate = 1 :

1): **3**, 0.47; **4**, 0.23]. Distillation of product **4** under reduced pressure caused partial decomposition (bp 120–155°C/0.25 mm).

12. Diol **4** has the following spectra: IR (neat) cm^{-1}: 3300, 1468, 1020; ^1H NMR (90 MHz, $CDCl_3$, $(CH_3)_4Si$, D_2O) δ: 0.89 (t, 6 H, J = 6), 1.1–1.7 (m, 14 H), 1.9–2.2 (m, 4 H), 4.02 (m, 1 H), 4.20 (d, 2 H, J = 6), 5.63 (t, 1 H, J = 6). With D_2O exchange there is a change in the range of δ 1.9–2.2 (m, 2 H).

3. Discussion

In 1962 Cooper and Finkbeiner reported the titanium chloride ($TiCl_4$)-catalyzed exchange reaction of an alkyl Grignard reagent (RMgX) having β-hydrogen (s) with olefins (Eq. 1).[4] In this reaction, RMgX can be formally regarded as a source of HMgX that adds to the olefins, and hence this reaction is known as the hydromagnesiation reaction.

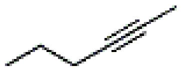
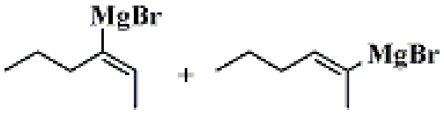
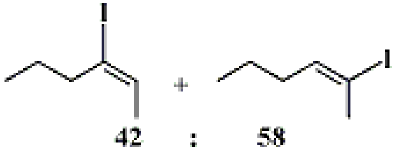
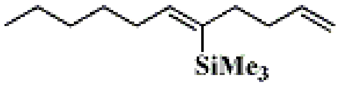
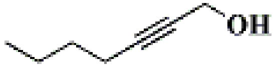
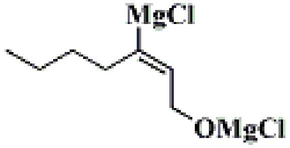
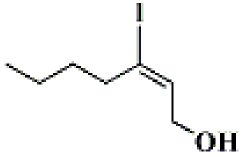
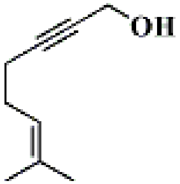
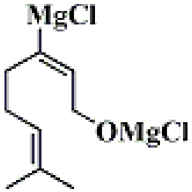
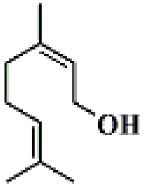
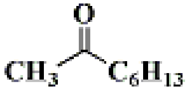
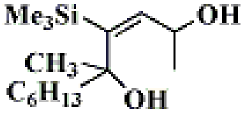
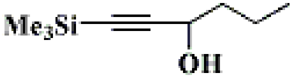
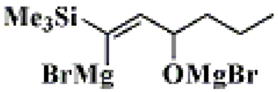
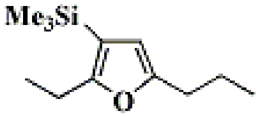
$$\mathrm{RMgX} + \mathrm{R'CH{=}CH_2} \xrightarrow{TiCl_4} \underset{(\mathrm{R''CH_2CH_2{=}R})}{\mathrm{R'CH{=}CH_2}} + \mathrm{R'CH_2CH_2MgX}$$

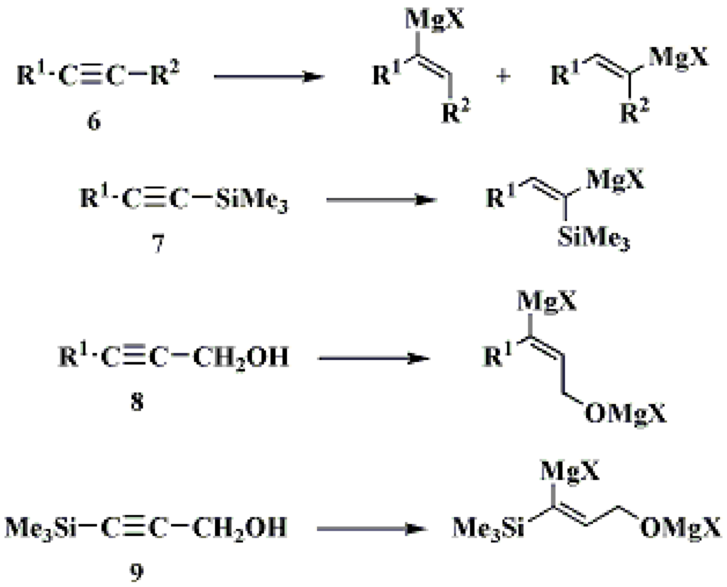
Since then, hydromagnesiation of other unsaturated hydrocarbons such as conjugated dienes and acetylenes has been investigated intensively.[5,6] Hydromagnesiation of 2-alkyl substituted 1,3-butadienes has been shown to proceed regiospecifically by using Cp_2TiCl_2 as a catalyst to afford the corresponding allylic Grignard reagent shown in Eq. 2 quantitatively.[7]

Cp_2TiCl_2-catalyzed hydromagnesiation of acetylenes with isobutyl Grignard reagents has also been shown to provide a convenient and practical method for preparation of various vinyl Grignard reagents. The acetylenes so far examined include 1,2-dialkylacetylenes **6** (Eq. 3), 1-(trimethylsilyl)acetylenes **7** (Eq. 4),[8] propargyl alcohols **8** (Eq. 5),[9] and 3-(trimethylsilyl)propargyl alcohol (**9**) (Eq. 6).[10] Although the reaction occurs with low regioselectivity for unsymmetric dialkylacetylenes **6**, high regioselectivity is attained in the case of **7, 8**, and **9**. Acetylenes **6, 7**, and **8** afford the corresponding vinylmagnesium halides in which HMgX adds in a *syn* pathway to the triple bond, while **9** affords the *anti*-addition product. In the latter case, hydromagnesiation follows the *syn* pathway to yield the corresponding (*Z*)-alkenyl Grignard reagent first, which, however, isomerizes rapidly under the reaction conditions to the (*E*)-alkenyl Grignard reagent. Since the hydromagnesiation reaction of **7, 8**, and **9** proceeds highly regio- and stereo-selectively, the reaction has become a powerful synthetic tool for utilization in organic syntheses. Some of the examples are given in Table I.

TABLE I

Starting Acetylene	i-BuMgX X	Vinylmagnesium Halide	Electrophile	Product	Yield %Ref.

	Br		I_2		70	8
	Br				86	11
	Cl		I_2		78-86	9
	Cl		MeI		95	9
	Br				83	12
	Br		EtCN		86	13



This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 510

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

benzophenone ketyl

Cp_2TiCl_2

1-(trimethylsilyl)acetylenes

Br

Cl

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ethyl acetate (141-78-6)

ether (60-29-7)

ammonium chloride (12125-02-9)

magnesium turnings (7439-95-4)

nitrogen (7727-37-9)

isobutyl chloride (513-36-0)

Methyl iodide (74-88-4)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

hexane (110-54-3)

titanium chloride (7550-45-0)

argon (7440-37-1)

Hexanal (66-25-1)

3-(trimethylsilyl)propargyl alcohol (5272-36-6)

2-OCTYN-1-OL (20739-58-6)

isobutylmagnesium chloride (5674-02-2)

Titanocene dichloride (1271-19-8)

(E)-3-Pentyl-2-nonene-1,4-diol (138149-15-2)

sec-butylmagnesium chloride (15366-08-2)

(Z)-2-octen-1-ol (26001-58-1)

(Z)-3-methyl-2-octen-1-ol (30804-78-5)

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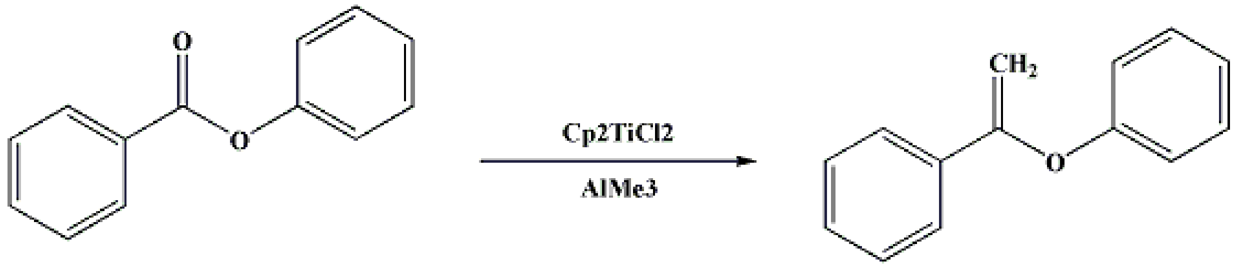
Organic Syntheses, CV 8, 512

ENOL ETHERS BY METHYLENATION OF ESTERS: 1-PHENOXY-1-PHENYLETHENE AND 3,4-DIHYDRO-2-METHYLENE-2*H*-1-BENZOPYRAN

[Ether, phenyl 1-phenylvinyl and 2*H*-1-benzopyran, 3,4-dihydro-2-methylene-]

A.



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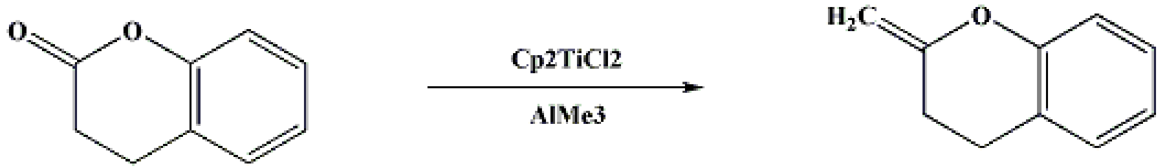

Submitted by Stanley H. Pine[1], Gia Kim[2], and Virgil Lee.
Checked by Roger B. Ruggeri and Clayton H. Heathcock.

1. Procedure

A. *1-Phenoxy-1-phenylethene.* To a 250-mL round-bottomed flask (Note 1) equipped with a magnetic stirring bar is added 5.0 g (20.0 mmol) of titanocene dichloride [bis(cyclopentadienyl)titanium dichloride] (Note 2). The flask is fitted with a rubber septum through which a large-gauge needle is passed to flush the system with dry nitrogen. After the vessel has been thoroughly purged, the nitrogen line flowing to the needle is opened to a mineral oil bubbler and 20 mL of a trimethylaluminum solution (2.0 *M* in toluene, 40 mmol) is added by a nitrogen-purged syringe (Note 3). Methane gas evolved by the reaction is allowed to vent as the resulting red solution is stirred at room temperature for 3 days. The Tebbe reagent[3] thus formed is used in situ by cooling the mixture in an ice-water bath (Note 4), then adding 4.0 g (20 mmol) of phenyl benzoate (Note 5) dissolved in 20 mL of dry tetrahydrofuran (Note 6) by syringe or cannula to the cooled stirring solution over 5–10 min. After the addition, the reaction mixture is allowed to warm to room temperature and is stirred for about 30 min. The septum is removed and 50 mL of anhydrous diethyl ether is added. To the stirring reaction mixture is gradually added 50 drops of an aqueous solution of 1 *M* sodium hydroxide over 10–20 min (Note 7). Stirring is continued until gas evolution essentially ceases; then to the resulting orange slurry are added a few grams of anhydrous sodium sulfate to remove excess water. The mixture is filtered through a Celite pad on a large coarse frit using suction and liberal amounts of diethyl ether to transfer the product and rinse the filter pad. Concentration of the filtrate with a rotary evaporator (Note 8) to 5–8 mL provides crude product, which is purified by column chromatography on basic alumina (150 g) eluting with 10% diethyl ether in pentane (Note 9). Fractions that contain product (Note 10) are combined and evaporated to give 2.69–2.79 g (68–70%) of the desired enol ether (Note 11) as a pale-yellow oil.

B. *3,4-Dihydro-2-methylene-2H-1-benzopyran.* Formation of the *exo*-methylene enol ether with

dihydrocoumarin is carried out as in the foregoing procedure except that the reaction solution is cooled with a dry ice–acetone bath before addition of the lactone. From 3.0 g (20 mmol) of dihydrocoumarin (Note 5) is obtained 1.85–1.97 g (63–67%) of the product (Note 12) as a pale-yellow oil, after column chromatography on basic alumina (150 g) eluting with 5% diethyl ether in pentane.

2. Notes

1. The checkers found that the acid ability of the enol ether products requires rigorous treatment of all glassware used for the reaction in order to avoid migration of the double bond in susceptible cases (e.g., dihydrocoumarin in Preparation B). Satisfactory results were obtained by treating the glassware sequentially with ethanolic 0.5 *M* solutions of hydrogen chloride and potassium hydroxide for approximately 1 hr, thoroughly rinsing with distilled water after each treatment, and finally oven-drying. This protocol is also effective for removing stubborn deposits on the glassware used for the reaction.
2. Titanocene dichloride was purchased from Aldrich Chemical Company, Inc. and used without further purification. This compound is normally obtained as bright red crystals. If its purity is in question Soxhlet extraction using dichloromethane is usually effective; titanocene dichloride is slightly soluble in dichloromethane and slowly dissolves from insoluble materials present.
3. Trimethylaluminum was purchased from Aldrich Chemical Company, Inc. and obtained as a 2.0 *M* solution in toluene sealed under nitrogen in a Sure/Seal bottle. Trimethylaluminum is pyrophoric and reacts violently with water and air; the syringe and needle used should be rinsed with toluene or hexenes immediately after addition. Note that the rinse, although dilute, contains pyrophoric material and should be handled accordingly.
4. Reaction with the ester is relatively exothermic. Sensitivity of the substrate product to heating varies and should be considered for each particular compound. Phenyl benzoate can be methylenated at room temperature with no significant decrease in product yield. By contrast, dihydrocoumarin (Preparation B) gives no product under these conditions and must be methylenated at −78°C to obtain a good yield. For most substrates it is satisfactory to carry out reactions at 0°C.
5. Substrate esters were purchased from Aldrich Chemical Company, Inc. and used without further purification.
6. Tetrahydrofuran was freshly distilled from the sodium ketyl of benzophenone.
7. Evolution of methane can be quite vigorous so that the reaction vessel must be large enough to prevent bubbling over. If the aqueous solution is delivered slowly in 10-drop increments over the addition period, a controlled quench of the reaction mixture is possible. Cooling slows gas evolution, but also greatly prolongs the hydrolysis step.
8. Methylene enol ethers are usually lower-boiling than their ester precursors. Low-molecular-weight products can be easily lost in evaporation; therefore, the toluene must be removed with care.
9. The checkers used Fisher Scientific basic alumina, Brockman activity I, 80–200 mesh. Neutral alumina and silica gel have also been used. Basic alumina minimizes the potential hazards of hydrolysis or proton-catalyzed isomerization of the carbon–carbon double bond in susceptible enol ethers. Gaseous trimethylamine has also been added to the eluent to minimize these problems during purification.
10. The checkers eluted the columns with a slight positive air pressure on the solvent reservoir to prevent formation of gas bubbles and cracks in the chromatographic medium. Fractions were collected in 25-mL test tubes (Note 1), analyzed by TLC on silica gel, eluting with the column solvent, and visualized with a phosphomolybdic acid solution. The checkers observed a nonvolatile hydrocarbon material (not substrate related) which was eluted in the fractions just prior to the products, which are quite nonpolar themselves and are eluted in the early fractions, ahead of any unreacted ester. Colored, metal-containing components usually remain near the top of the column, although some colored material may accompany the product if much toluene remains in the sample or if the sample is applied to the column in a more polar solvent.
11. The spectral properties for 1-phenoxy-1-phenylethene are as follows: IR (film) cm^{-1}: 1600, 1495, 1290, 1230; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 4.45 (d, 1 H, *J* = 2.3), 5.05 (d, 1 H, *J* = 2.3), 7.06–7.11 (m, 3 H), 7.29–7.38 (m, 5 H), 7.66–7.70 (m, 2 H).
12. While the submitters observed no complications, the checkers were unable, even after many trials, to obtain the dihydrocoumarin adduct completely free of what appears to be the product of double bond migration to give the endocyclic enol ether. Initial results were quite erratic. However, use of the glassware treatment described in Note 1, suggested by Professor Pine, has consistently provided the desired compound contaminated with only a few percent of the unwanted isomer. Spectral properties for

the 3,4-dihydro-2-methylene-2*H*-1-benzopyran are as follows: IR (film) cm^{-1}: 1665, 1595, 1500, 1470, 1250, 990, 770; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 2.57 (t, 2 H, *J* = 6.5), 2.80 (t, 2 H, *J* = 6.5), 4.14 (s, 1 H), 4.55 (s, 1 H), 6.85–6.92 (m, 1 H), 7.03–7.07 (m, 1 H), 7.11–7.18 (m, 1 H); impurity (partial) δ: 1.88 (bs, 3 H), 3.39 (bs, 2 H), 4.70 (bs, 1 H).
The submitters suggested that the use of $CDCl_3$ as the NMR solvent may be the cause of the appearance of unwanted double-bond isomer; they recommend CCl_4 as the solvent of choice.

3. Discussion

The formation of carbon–carbon bonds through the condensation of carbonyl compounds with phosphoranes (the Wittig reaction) is a very useful method in organic synthesis.[4 5] Allowing the convergence of a wide variety of substrates enables this reaction to provide considerable flexibility in product design. Yet, with limited exceptions,[6 7 8] this process has not been effective for the transfer of methylene or alkylidenes to the carbonyl group of esters or other carboxylic acid derivatives. However, reaction of the titanium–aluminum complex (the Tebbe reagent)[3] described here does transfer a methylene to the carbonyl group of esters, effecting the conversion of an ester to an enol ether.[9 10]

The Tebbe reagent functions as a nucleophilic carbenoid in its reactions with carbonyl groups. The carbenoid is activated in the presence of a Lewis base that presumably complexes with the aluminum atom. Tetrahydrofuran is the Lewis base in the reactions described above. If the reaction is performed in the absence of added tetrahydrofuran, the carbonyl oxygen atom can function as a weak Lewis base, although the methylenation process is considerably slower.

Vinyl ethers have also been prepared by addition of alkoxides to acetylene,[11,12,13] elimination from halo ethers and related precursors,[11,13] and vinyl exchange reactions.[13] Reaction of an electrophilic tungsten carbenoid with a methylene phosphorane or diazomethane also produces vinyl ethers.[14] Enol ethers have resulted from the reaction of some tantalum and niobium carbenoids with esters,[15] and the reaction of phosphoranes with electrophilic esters.[6,7,8]

Methylenation using the titanium–aluminum complex converts a variety of esters to enol ethers in good yields.[9,10] Lactones are converted to synthetically useful *exo*-methylene enol ethers. Carbon–carbon double bonds do not interfere with the methylenation reaction, although functional groups containing acidic hydrogen atoms do consume the reagent and should be protected. The carbonyl group of aldehydes and ketones reacts in preference to the ester carbonyl group in the methylenation process,[10] but those groups can also be selectively protected.

Because of the expense of obtaining the Tebbe reagent in its pure form,[16] an in situ method for its preparation and use was developed.[17] The presence of the excess Lewis acidic by-product, dimethylaluminum chloride, in the in situ preparation may cause reactivity at other sites in the substrate or lower yields of desired products (e. g., 70 vs. 94% for Preparation A, and 65 vs. 85% for Preparation B).[10] However, the overall simplicity of the method can be advantageous with readily obtained substrates.

This preparation is referenced from:

- Org. Syn. 79, 19

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium ketyl of benzophenone

titanocene dichloride [bis(cyclopentadienyl)titanium dichloride

acetylene (74-86-2)

hydrogen chloride (7647-01-0)

diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

aluminum (7429-90-5)

methane (7782-42-5)

potassium hydroxide (1310-58-3)

toluene (108-88-3)

Pentane (109-66-0)

dichloromethane (75-09-2)

Trimethylamine (75-50-3)

Diazomethane (334-88-3)

phenyl benzoate (93-99-2)

Tetrahydrofuran (109-99-9)

phosphomolybdic acid (51429-74-4)

trimethylaluminum (75-24-1)

titanium (7440-32-6)

1-Phenoxy-1-phenylethene, Ether, phenyl 1-phenylvinyl (19928-57-5)

Titanocene dichloride (1271-19-8)

dihydrocoumarin (119-84-6)

methylene phosphorane (61183-53-7)

dimethylaluminum chloride

3,4-Dihydro-2-methylene-2H-1-benzopyran, 2H-1-benzopyran, 3,4-dihydro-2-methylene- (74104-13-5)

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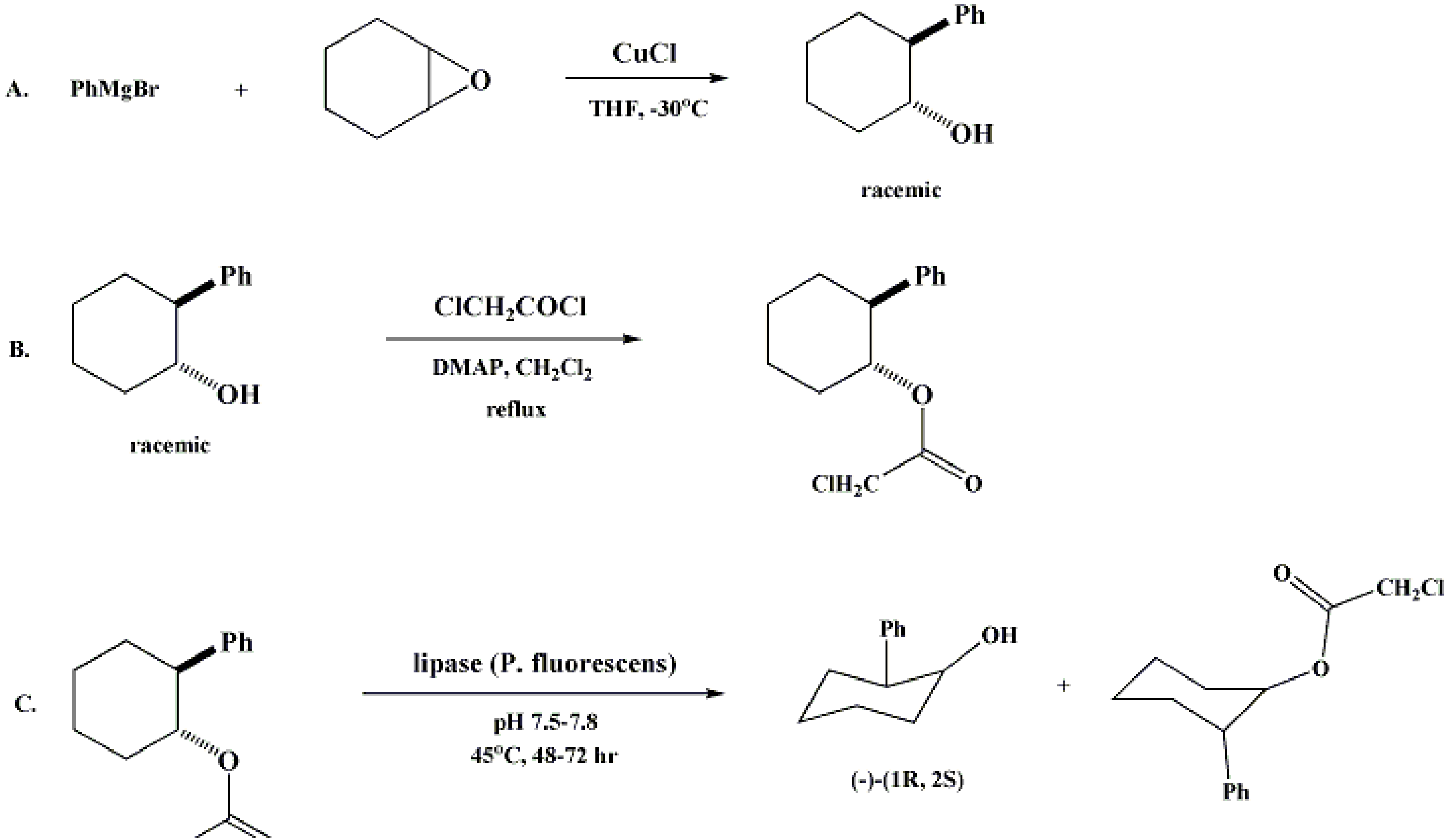
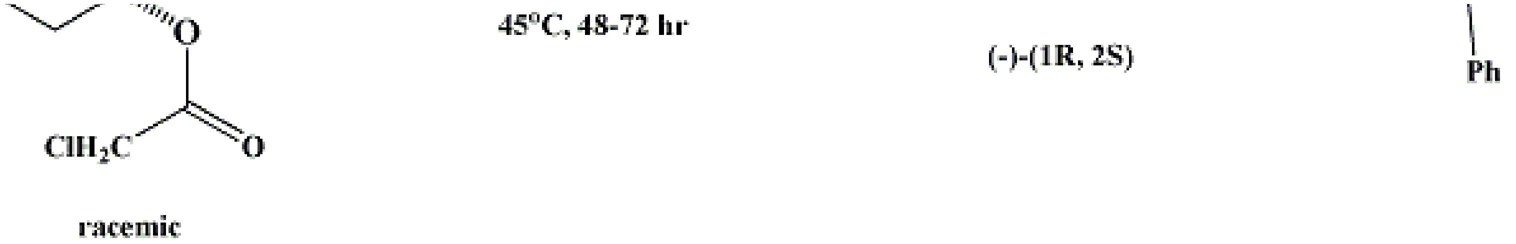
Organic Syntheses, CV 8, 516

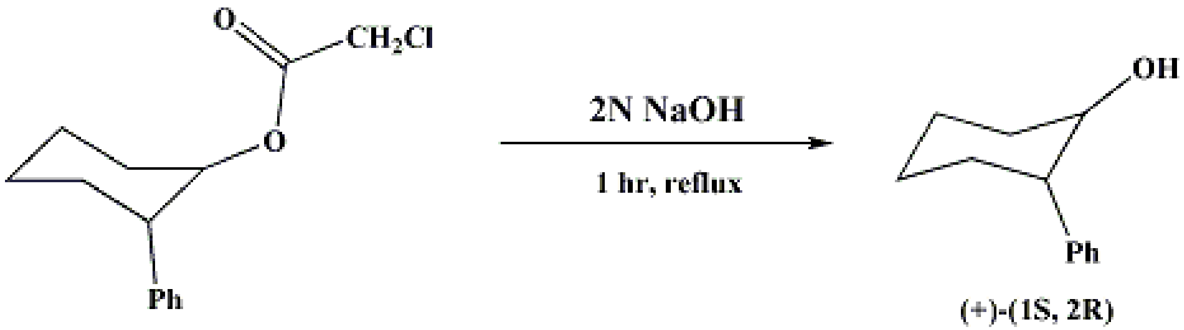
LIPASE-CATALYZED KINETIC RESOLUTION OF ALCOHOLS VIA CHLOROACETATE ESTERS: (–)-(1*R*,2*S*)-*trans*-2-PHENYLCYCLOHEXANOL AND (+)-(1*S*,2*R*)-*trans*-2-PHENYLCYCLOHEXANOL

[Cyclohexanol, 2-phenyl-, (1*R*-*trans*)- and cyclohexanol, 2-phenyl-, (1*S*-*trans*)-]





D.



Submitted by A. Schwartz[1], P. Madan[1], J. K. Whitesell[2], and R. M. Lawrence[2].
Checked by Robert E. Maleczka, Jr. and Leo A. Paquette.

1. Procedure

A. *Racemic trans-2-phenylcyclohexanol.* A 3-L, round-bottomed flask equipped with a mechanical stirrer, an addition funnel, a reflux condenser, and a nitrogen inlet is charged with 35.3 g (1.47 g-atom) of magnesium turnings (Note 1) and 170 mL of dry tetrahydrofuran (THF). To this stirred mixture a solution of 155 mL (1.47 mol) of bromobenzene (Note 2) in 250 mL of dry THF is added dropwise over a 1.5-hr period (Note 3) and (Note 4). After the addition of bromobenzene is complete, 1 L of dry THF is added. The solution is cooled to –30°C (dry ice–nitromethane slush bath) and 6.53 g (0.066 mol) of purified (Note 5) copper(I) chloride is added. The resulting mixture is stirred for 10 min, and then a solution of 101 mL (1.0 mol) of cyclohexene oxide (Note 6) in 100 mL of THF is added dropwise over a 1.5-hr period. On completion of the addition, the reaction mixture is allowed to warm to 0°C and stirred for 2 hr, then quenched by adding 500 mL of saturated ammonium sulfate [$(NH_4)_2SO_4$] solution (aqueous). The layers are separated and the organic layer is washed with 100 mL of saturated $(NH_4)_2SO_4$ (Note 7). The combined aqueous layers are extracted with ether, the organic layers are combined and dried over anhydrous $MgSO_4$, and the solvent is removed via rotary evaporator to give 175.5 g (99.6% crude) of the desired product as a light-yellow solid. The solid is recrystallized from pentane to give 142.3 g (80%), mp 55.5–57.0°C (lit.[3] 57–58°C) (Note 8).

B. *Racemic trans-2-phenylcyclohexyl chloroacetate.* A 1-L, round-bottomed flask equipped with a magnetic stirrer and a condenser is charged with 100 g (0.567 mol) of racemic *trans*-2-phenylcyclohexanol, 50 mL (0.625 mol) of chloroacetyl chloride (Note 9), 300 mg (0.0025 mol) of 4-dimethylaminopyridine (DMAP) (Note 10), and 250 mL of dichloromethane. This mixture is rapidly stirred and heated at reflux for 6 hr. The mixture is cooled and a solution of 350 mL of saturated sodium bicarbonate is carefully added to the rapidly stirring mixture (Note 11). Stirring is maintained for 3 hr (Note 12). The organic layer is separated and dried over anhydrous potassium carbonate. After filtration the filtrate is concentrated on a rotary evaporator (30°C) to a dark-brown oil. This oil is distilled through a 2- or 4-in. column packed with glass beads to give, after collecting a small forerun (ca. 2 g), 135 g (94%) of racemic *trans*-2-phenylcyclohexyl chloroacetate as a colorless liquid, bp 118–122°C at 0.3 mm.

C. *(–)-(1R,2S)-trans-2-Phenylcyclohexanol.* A 500-mL, three-necked Morton flask (Note 13) equipped with a mechanical stirrer, a pH probe (connected to a pH controller, (Note 14)), and a base inlet (connected to a syringe pump regulated by the pH controller and a calibrated 250-mL reservoir (Note 15) of 1 *N* sodium hydroxide) is charged with 106.0 g (0.419 mol) of racemic *trans*-2-phenylcyclohexyl chloroacetate, 10 mL of pH 7 buffer (Note 16), and 90 mL of deionized water. This heterogeneous mixture is rapidly stirred and heated to between 45° and 50°C using a constant temperature bath. The pH is adjusted to 7.5 with 1 *N* sodium hydroxide and after a steady pH reading is achieved (Note 17), 1 g of lipase (*P. fluorescens*, (Note 18)) is added. Immediately 1 *N* sodium hydroxide begins to flow into the reaction mixture as the pH begins to drop (indicating hydrolysis of the chloroacetate). The pH controller regulates the addition of base so as to maintain the pH between 7.5 and 7.8. After 2 hr, an additional 1.5 g of lipase is added to the reaction mixture and the rate of hydrolysis becomes noticeably faster (Note 19). After 45 hr, ca. 200 mL (95% of theory) of 1 *N* sodium hydroxide has been added and the rate of hydrolysis has become very slow. After ca. 50 hr, 210 mL of 1 *N* sodium hydroxide (0.21 mol, 100% of theory) has been added to the mixture and the rate of base addition has nearly stopped (Note 20). The mixture is cooled to room temperature and extracted with three 200-mL portions of ether. The organic layer is filtered through a small pad of Celite to remove traces of enzyme emulsion and the Celite is rinsed with three 100-mL portions of ether. The combined organic layers are dried over anhydrous sodium sulfate and after filtration are concentrated on a rotary evaporator (35°C) and finally dried at 0.5 mm for 1 hr to give 93 g of a colorless oil. Fractional crystallization from 100 mL of petroleum ether (30–60°C) at –20°C (freezer) overnight affords 19.8 g (53.5% of theory, (Note 21)) of (–)-(1*R*,2*S*)-*trans*-2-phenylcyclohexanol as colorless needles, mp 63–65°C, $[\alpha]_D^{25}$ –54.3° (methanol, *c* 18). An additional 15.8 g of the (–) alcohol is obtained by chromatography of the mother liquors (vide infra) to afford a total of 35.6 g (96.2% of theory, (Note 21) and (Note 22)).

The mother liquors are concentrated on a rotary evaporator (35°C) to give a colorless oil that is redissolved in 100 mL of hexanes and poured onto a 250-g pad of silica gel (Note 23) contained in a 500-mL sintered-glass funnel, preequilibrated with hexanes. Using this simple silica pad, 100-mL fractions are collected, diluting first with 1 L of hexanes, followed by 3 L of 9:1 hexanes: ethyl acetate, and finally with 600 mL of ethyl acetate. After TLC analysis of the eluants (Note 24), fractions 3–18 are combined and concentrated initially

on a rotary evaporator (40°C) and finally dried at 0.5 mm to afford 52.0 (98% of theory) of (–)-(1*S*,2*R*)-*trans*-2-phenylcyclohexyl chloroacetate as a colorless oil, $[\alpha]_D^{25}$ –14.3° (benzene, *c* 10). Fractions 20–28 are combined and concentrated as above to afford 15.8 g of the (–)-(1*R*,2*S*)-*trans*-2-phenylcyclohexanol, mp 62–65°C, $[\alpha]_D^{25}$ –54.9° (methanol, *c* 2.1).

D. *(+)-(1S,2R)-trans-2-Phenylcyclohexanol.* A 500-mL, round-bottomed flask is charged with a mixture of 52.0 g (0.206 mol) of (–)-(1*S*,2*R*)-*trans*-2-phenylcyclohexyl chloroacetate, 250 mL of 2 *N* sodium hydroxide, and 100 mL of methanol and then stirred at reflux for 3 hr. TLC analysis (Note 24) indicates complete reaction. The mixture is cooled to room temperature, adjusted to pH 7 with ca. 35 mL of 3 *N* sulfuric acid and poured into 500 mL of water. The mixture is extracted with two 150-mL portions of dichloromethane and the organic layer is dried over anhydrous sodium sulfate and concentrated on a rotary evaporator (35°C) to afford 37.0 g of a colorless solid. Recrystallization from 100 mL of petroleum ether (30–60°C) at –20°C gives in two crops, 35.8 g (96% of theory) of (+)-(1*S*,2*R*)-*trans*-2-phenylcyclohexanol as colorless needles, mp 60–62°C, $[\alpha]_D^{25}$ + 52.8° (methanol, *c* 5.4) (Note 25).

2. Notes

1. Magnesium turnings were purchased from Aldrich Chemical Company, Inc.
2. Bromobenzene was purchased from Fisher Scientific and used without further purification.
3. A small amount of 1,2-dibromoethane was used to initiate the reaction.
4. An ice bath was used to control the reaction temperature during Grignard formation.
5. Copper(I) chloride was purified via the procedure in *Inorganic Syntheses*.[4]
6. Cyclohexene oxide was purchased from Aldrich Chemical Company, Inc. and used without further purification.
7. The organic layer was washed until the aqueous layer no longer turned blue.
8. The spectral properties of the product are as follows: ^{1}H NMR (300 MHz) δ: 1.25–1.53 (bm, 4 H), 1.62 (s, 1 H), 1.76 (m, 1 H), 1.84 (m, 2 H), 2.11 (m, 1 H), 2.42 (ddd, 1 H, *J* = 16.5, 10.8, 5.4), 3.64 (ddd, 1 H, *J* = 10.8, 10.8, 5.4), 7.17–7.35 (m, 5 H); ^{13}C NMR (90 MHz) δ: 25.1 (t), 26.1 (t), 33.5 (t), 34.7 (t), 53.0 (d), 74.0 (d), 126.4 (d), 127.9 (d), 128.4 (d), 143.8 (s); IR cm^{-1}: 3592, 3461, 2941, 2863, 1604, 1497, 1451; MS 176 (M^+), 158, 143, 130, 117, 104, 91 (base).
9. Chloroacetyl chloride (99%) was purchased from Fluka and used without further purification.
10. 4-Dimethylaminopyridine was purchased from the Aldrich Chemical Company, Inc., and used without further purification.
11. Rapid addition of the bicarbonate solution may result in uncontrollable foaming.
12. Excess chloroacetyl chloride was slowly hydrolyzed to chloroacetic acid, which was neutralized.
13. A creased or Morton flask was preferable as the rate of hydrolysis of the chloroacetate increases with efficient agitation.
14. The pH controller used was a Horizon Model 5997 available from Cole-Parmer Instrument Co.
15. A 250-mL graduated cylinder, used as a reservoir, was capped with a septum through which base-stable, 1/32-in.-i.d. tubing was

run and connected to a peristaltic pump.
16. Fisher pH 7 buffer was used from the bottle as purchased.
17. Traces of chloroacetyl chloride are hydrolyzed to produce chloroacetic acid, producing a fluctuation in pH that will settle down within 5 min.
18. The lipase used was isolated from *Pseudomonas fluorescens* and was commercially available from Amano International Enzyme Co., Inc. (Troy, VA) as a powder, specific activity 32,000 units/g (P-30).
19. The rate enhancement was manifested by a more rapid base uptake.
20. If the hydrolysis was allowed to proceed, small additions of base (≤0.1 mL) occurred every 30 min or so.
21. If the hydrolysis was taken to 50% completion, the theoretical yield of each alcohol isomer was 36.96 g.
22. The (–)-(1*R*,2*S*) alcohol had an enantiomeric ratio of (–) : (+) 99.2: 0.8 corresponding to an enantiomeric excess (ee) of 98.4%. This determination resulted from GC analysis (50-m × 0.25-mm capillary column, OV-17 on fused silica, 250°C) of the α-methoxy-α-trifluoromethylphenylacetate (MTPA ester). The checkers determined the enantiomeric ratio to be 98.6: 1.4 (97.2% ee) by ^{1}H NMR analysis at 300 MHz of the MTPA ester that was prepared as follows. The sample alcohol (0.1 mmol) was placed in a vial along with a solution of (+)-α-methoxy-α-trifluoromethylphenylacetyl chloride (0.15 mmol) in 1 mL of dichloromethane, triethylamine (0.15 mmol), and a crystal of 4-dimethylaminopyridine, and stirred at room temperature overnight. The excess acid chloride was treated with dimethylaminopropylamine (0.1 mmol). The MTPA ester was isolated in pure form after passing the mixture through a 5-g plug of silica gel and elution with 4 : 1 hexanes : ethyl acetate.
23. The silica gel used was 70–230 mesh as purchased from E. Merck.
24. TLC was run on 10 × 20-mm silica plates (E. Merck): TLC solvent was 4 : 1 hexanes : ethyl acetate; visualization was with 5% $(NH_4)_2MoO_4$ in 10% aqueous sulfuric acid, with heat. In the event that any mixed fractions are obtained, these are combined and evaporated, and the residue is rechromatographed in the same manner.
25. By GC analysis of (+)-MTPA esters (see (Note 22)), an enantiomeric ratio of (+) : (–) 96.5 : 3.5, corresponding to 93% ee, was determined.

3. Discussion

The use of chiral auxiliaries to impart dissymmetry has become a powerful tool for controlling the stereochemical outcome of chemical transformations. Many of these auxiliaries have been drawn from the chiral pool of natural materials. While high levels of asymmetric induction have been achieved in many cases, none of these natural products has emerged as a general agent, in part because typically only one enantiomer of the auxiliary is readily available.

The procedure described here provides ready access to both the (+) and (–) antipodes of *trans*-2-phenylcyclohexanol, a useful chiral auxiliary in ene reactions of its glyoxylate ester[5] and its *N*-sulfinylcarbamate,[6] as well as in cycloaddition reactions of dienes with the *N*-

sulfinylcarbamate,[7] and olefins with ketenes.[8] This simple auxiliary appears to retain[5] many of the features of 8-phenylmenthol,[9] a powerful agent difficult to prepare on a large scale.[10] A modest-scale procedure for 8-phenylmenthol is included in this volume.[11]

Optically pure *trans*-2-phenylcyclohexanol can also be prepared by resolution of the phthalate esters using brucine to obtain the (+)-alcohol and strychnine to obtain the (–)-alcohol (after basic hydrolysis of their respective salts).[12] Enzyme-catalyzed kinetic resolution of the acetate esters using pig liver esterase[5] and pig liver acetone powder[3] has been used to prepare both enantiomers of this chiral auxiliary. The hydroboration of 1-phenylcyclohexene with isopinocampheylborane has been reported to give the chiral auxiliary in 97% enantiomeric excess.[13]

Racemic *trans*-2-phenylcyclohexanol has previously been prepared in a yield comparable to that realized in this procedure via copper-catalyzed phenyl Grignard addition to cyclohexene oxide using the more expensive copper(I) oxide.[14]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 258
- Org. Syn. 79, 93

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

hexanes

Racemic trans-2-phenylcyclohexanol

$(NH_4)_2SO_4$

Racemic trans-2-phenylcyclohexyl chloroacetate

(−)-(1S,2R)-trans-2-phenylcyclohexyl chloroacetate

$(NH_4)_2MoO_4$

N-sulfinylcarbamate

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

Benzene (71-43-2)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

magnesium turnings (7439-95-4)

sodium sulfate (7757-82-6)

chloroacetic acid (79-11-8)

copper(I) oxide

bromobenzene (108-86-1)

1,2-dibromoethane (106-93-4)

chloroacetyl chloride (79-04-9)

copper(I) chloride (7758-89-6)

Cyclohexene oxide (286-20-4)

ammonium sulfate (7783-20-2)

Pentane (109-66-0)

dichloromethane (75-09-2)

brucine

$MgSO_4$ (7487-88-9)

1-phenylcyclohexene (771-98-2)

strychnine

Tetrahydrofuran, THF (109-99-9)

triethylamine (121-44-8)

dimethylaminopropylamine (109-55-7)

4-dimethylaminopyridine (1122-58-3)

α-methoxy-α-trifluoromethylphenylacetate (56135-03-6)

(+)-α-methoxy-α-trifluoromethylphenylacetyl chloride

trans-2-Phenylcyclohexanol, (–)-(1R,2S)-trans-2-PHENYLCYCLOHEXANOL, Cyclohexanol, 2-phenyl-, (1R-trans)- (98919-68-7)

8-phenylmenthol

isopinocampheylborane

(+)-(1S,2R)-trans-2-PHENYLCYCLOHEXANOL, cyclohexanol, 2-phenyl-, (1S-trans)- (34281-92-0)

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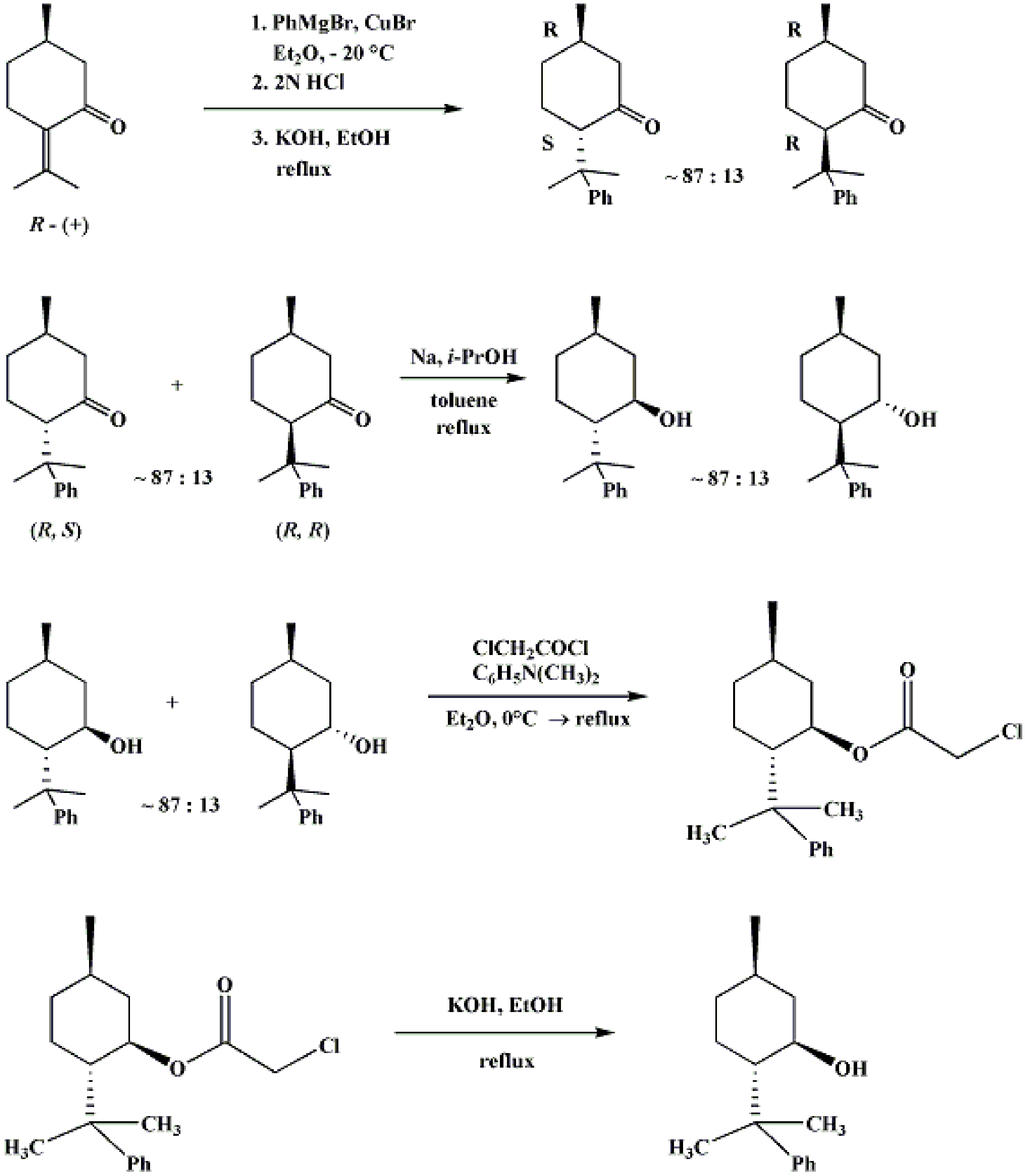
(–)-8-PHENYLMENTHOL

[Cyclohexanol, 5-methyl-2-(1-methyl-1-phenylethyl)-, [1*R*-(1α,2β,5α)]-]



Submitted by Oswald Ort[1]
Checked by Lalith R. Jayasinghe and James D. White.

1. Procedure

Caution! Chloroacetyl chloride is a strong lachrymator. N,N-Dimethylaniline is a severe poison.

Synthetic work with these substances should be performed in an efficient hood.

A. *(2RS,5R)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexanone* ***(2)***. (See (Note 1).)

a. GRIGNARD REAGENT FORMATION AND CONJUGATE ADDITION. In a nitrogen-flushed, 500-mL, two-necked, round-bottomed reaction flask fitted with a reflux condenser carrying a calcium chloride tube, a 250-mL pressure-equalizing dropping funnel, and a Teflon-coated magnetic stirring bar are placed 11.0 g (0.45 mol) of magnesium turnings and 50 mL of diethyl ether (Note 2). To this flask is added 10% of 78.5 g (0.5 mol) of bromobenzene in one portion (Note 3). The reaction mixture is heated to reflux without stirring to start Grignard reagent formation. When the reaction has started (Note 4), the rest of the bromobenzene in 100 mL of diethyl ether is added with stirring at such a rate that gentle reflux is maintained. After the addition is complete, the reaction mixture is heated to reflux for an additional 1 hr. The solution is cooled to room temperature and diethyl ether is added to give a total volume of about 300 mL (Note 5). The reflux condenser and the dropping funnel are replaced by a nitrogen inlet tube and a pierced rubber septum with Teflon tube inlet (Note 6).

In a second nitrogen-flushed, 500-mL, three-necked, round-bottomed reaction flask with a mechanical stirrer, a thermometer, and a two-way adapter carrying a calcium chloride tube and a rubber septum with a Teflon tube, connected to a reaction flask (.htm1 in Fig. 1), are placed 4.4 g (31 mmol) of copper(I) bromide (Note 7) and 70 mL of diethyl ether. The ethereal Grignard solution from the reaction flask (1) is added, through the Teflon tube by means of nitrogen pressure (see f.htmig. 1), to this vigorously stirred suspension at −20°C. After the addition is complete, the reaction mixture is stirred at −20°C for hr. The rubber septum is replaced by a 100-mL, pressure-equalizing dropping funnel containing 40.0 g (0.26 mol) of (*R*)-(+)-pulegone (Note 8) in 50 mL of diethyl ether. This solution is added with stirring at −20°C to the dark-green reaction mixture during ca. 2 hr. After the reaction mixture is kept overnight at −20°C, it is added to 300 mL of vigorously stirred ice-cold 2 N hydrochloric acid. The organic layer is separated and filtered with suction, and the residue on the funnel is washed twice with 20-mL portions of ether. The aqueous layer is saturated with ammonium chloride and extracted three times with 100-mL portions of ether. The combined organic phases are washed with saturated aqueous sodium hydrogen carbonate solution and the solvent is evaporated under reduced pressure. The crude oily product (ca. 62.4 g) is used for equilibration without further purification (Note 9).

Figure 1

Figure 1

b. EQUILIBRATION OF KETONES (**2**). A solution of 62.4 g of crude 2<.htm/A> in 600 mL of ethanol, 80 mL of water, and 70.0 g (1.2 mol) of potassium hydroxide is refluxed for 3 hr. The solution is concentrated on a rotary evaporator to a volume of about 200 mL, and 500 mL of water is added. This aqueous solution is saturated with sodium chloride and extracted with four 100-mL portions of ether. The combined organic layers are dried over anhydrous magnesium sulfate and the solvent is evaporated at reduced pressure. The remaining oily liquid is distilled under reduced pressure at 0.05 mm. Three fractions are collected; the first fraction (boiling range 40–80°C) is discarded. Fraction 2 (boiling range: 80–100°C; 120°C oil-bath temperature) consists mainly of biphenyl with small amounts of ketone **2** (Note 10). Fraction 3 (boiling range: 100–110°C; 140°C oil-bath temperature) contains the main quantity of ketone **2**. Fraction 3 and the decanted liquid of fraction 2 are combined to yield 47.3–54.5 g (79–91%) of pale-yellow oily **2** (Note 11).

B. *(1RS,2SR,5R)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexanol* ***(3/4)***. In a 500-mL, three-necked, round-bottomed reaction flask fitted with a reflux condenser carrying a calcium chloride tube, a 250-mL pressure-equalizing funnel, and a mechanical Hershberg stirrer[2] are placed 16.0 g (0.70 mol) of sodium and 220 mL of toluene (Note 12). The solution is heated to reflux and maintained at this temperature. By vigorous stirring a fine suspension of sodium is obtained. To this stirred suspension a solution of 54.5 g (0.24 mol) of equilibrated 2<.htm/A> in 40.8 g (0.68 mol) of 2-propanol (Note 13) is added dropwise at

such a rate that controlled refluxing is maintained. After the addition is complete, the reaction mixture is refluxed for an additional 8 hr and then cooled to 0°C. The mixture is diluted with 250 mL of ether (Note 14) and carefully poured into 260 mL of ice water. The organic layer is separated and the aqueous phase is saturated with sodium chloride and extracted 3 times with 100-mL portions of ether. The combined organic layers are washed with saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation. Fractional distillation of the concentrate gives 39.0–48.9 g (70–88%) of pale-yellow **3/4**, bp 103–107°C/0.01 mm (126°C oil-bath temperature) (Note 15).

C. *(1R,2S,5R)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl chloroacetate* **5** (Note 16). A 250-mL, three-necked, round-bottomed reaction flask fitted with a reflux condenser and a calcium chloride tube, a 50-mL pressure-equalizing funnel, a thermometer, and a Teflon-coated magnetic stirring bar is charged with 20.0 g (86 mmol) of 3/.htm4, 10.5 g (86 mmol) of *N,N*-dimethylaniline, and 30 mL of diethyl ether. This stirred mixture is cooled to 0°C and a solution of 10.5 g (93 mmol) of chloroacetyl chloride in 30 mL of diethyl ether is added at such a rate that this temperature is maintained. After the reaction is stirred at 0°C for an additional hr, the ice bath is removed and the reaction mixture is allowed to warm to room temperature, during which time *N,N*-dimethylaniline hydrochloride precipitates. The reaction is completed by heating to reflux for 3 hr (Note 17). The solvent is removed under reduced pressure using a rotary evaporator, and the crystalline white residue is dissolved in 60 mL of dichloromethane and 60 mL of water. The phases are separated and the organic phase is washed thoroughly with an equal volume of water; then it is washed until it is acid-free with a saturated aqueous sodium hydrogen carbonate solution. It is concentrated under reduced pressure to give about 25.0 g of a viscous oil, which crystallizes on addition of 30 mL of 90% aqueous ethanol. The crystals are filtered with suction to yield 18.6–21.8 g (70–82%) of the chloroacetate as a mixture of diastereomers. Diastereo- and enantiomerically pure chloroacetate **5** is obtained in 48% yield by two fractional crystallizations of the diastereomeric chloroacetates from ethanol, mp 82–83°C; $[\alpha]_D^{20}$ + 22.4° (CCl_4, *c* 2.29) (Note 18).

D. *(1R,2S,5R)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexanol* ***(3)***. In a 500-mL round-bottomed reaction flask, fitted with a reflux condenser and a Teflon-coated magnetic stirring bar, 12.8 g (41 mmol) of 5<.htm/A> (48%) is dissolved in a solution of 300 mL of ethanol, 40 mL of water, and 46 g (82 mmol) of potassium hydroxide. This solution is refluxed for 2 hr. The solution is concentrated at reduced pressure to a volume of ca. 50 mL and 200 mL of water and 100 mL of ether are added. After the ether layer is separated, the aqueous phase is saturated with sodium chloride and extracted with three 50-mL portions of ether. The combined organic layers are dried over anhydrous magnesium sulfate, filtered, and the solvent is evaporated. Kugelrohr distillation of the cloudy residual oil yields 8.9–9.2 g (92–97%) of **3**, bp 105–115°C at 0.01 mm; $[\alpha]_D^{20}$ –26.4° ± 0.1° (ethanol, *c* 1.97) (Note 19).

2. Notes

1. Parts A and B of this procedure are based on a communication by E. J. Corey and H. E. Ensley.[3] This protocol has been disclosed previously.[4]
2. The submitter used diethyl ether distilled from sodium wire.
3. Bromobenzene was purchased from Merck-Schuchardt and was used without further purification.
4. Sometimes it becomes necessary to add some single crystals of iodine to start the reaction.
5. The concentration of the ethereal Grignard solution was estimated to be 1.38 *N*, as determined by hydrolysis of an aliquot (1 mL taken by syringe) and titration with 0.1 *N* hydrochloric acid.
6. The Teflon tube was 3 mm in diameter.
7. Copper(I) bromide was purchased from Fluka AG, Buchs, Switzerland and was not further purified. In previous runs copper(I) iodide was used to give comparable yields.
8. (*R*)-Pulegone had $[\alpha]_D^{20}$ + 24.6° (ethanol, *c* 1.92) and was obtained from Haarmann & Reimer, Holzminden. The checkers used technical-grade (+)-pulegone (82% pulegone content) and obtained **2** in 67–70% isolated yield after equilibration. The submitters thank Haarmann & Reimer, Holzminden, Germany, for generous gifts of pure and technical-grade (+)-pulegone used in their

work.
9. An epimeric mixture of diasteromeric ratio 55:45 was determined by ^{13}C NMR spectroscopy.
10. The Grignard coupling product, biphenyl (mp 70°C, bp 250°C at 760 mm), crystallizes in the condenser and has to be liquified by warming with a heat gun.
11. The elemental and structural characterization of **2** is as follows. Anal. calcd. for $C_{16}H_{22}O$: C, 83.43; H, 9.63. Found: C, 83.61; H, 9.80; IR (liquid film) cm^{-1}: 1712 (C=O); ^{1}H NMR ($CDCl_3$) δ: 0.80–2.78 (m, 8 H), 0.90 (d, 3 H, *J* = 6, CH_3CH *cis*-**2**), 0.96 (d, 3 H, *J* = 6, CH_3CH *trans*-**2**), 1.42 (s, 3 H, CH_3CPh *trans*-**2**), 1.43 (s, 3 H, CH_3CPh *cis*-**2**), 1.48 (s, 3 H, CH_3CPh *cis/trans*-**2**), 7.00–7.44 (m, 5 H, aromatic H); ^{13}C NMR ($CDCl_3$), *trans*-**2** δ: 22.21 (CH_3), 23.52 (CH_3), 26.71 (CH_3), 28.89 (CH_2), 34.51 (CH_2), 36.02 (CH), 38.93 (C_{quat}), 52.13 (CH_2), 59.23 (CH), 125.37, 125.60, 127.87 and 149.71 (aromatic C), 210.31 (C=O); *cis*-**2** δ: 19.03 (CH_3), 23.67 (CH_3), 24.71 (CH_2), 27.23 (CH_3), 31.10 (CH_2), 32.00 (CH), 39.32 (C_{quat}), 50.07 (CH_2), 59.44 (CH), 125.44, 125.72, 128.65, 149.26 (aromatic C), 211.21 (C=O). An epimeric mixture of diastereomeric ratio 83:17 was determined by ^{13}C NMR spectroscopy. Ketones **2** have n_D^{20} 1.5270–1.5280.
12. Toluene was distilled from sodium.
13. 2-Propanol was refluxed with magnesium methoxide and fractionated.
14. Without this additional solvent the mixture is quite viscous.
15. ^{13}C NMR-spectroscopy indicated a **3/4** ratio of 87:13. Diastereomers **3/4** can be separated by careful medium-pressure silica gel chromatography (petroleum ether/ether; 95:5)[5] or by fractional crystallization of the diastereomeric chloroacetates (vide supra). For structural characterization, see (Note 19).

16. Part C is based on a report by G. Bergson and co-workers[6] and has been disclosed previously.[4] Compound **5** has also been prepared by using pyridine/4-dimethylaminopyridine in petroleum ether and chloroacetyl chloride in benzene.[7] Alternatively, chloroacetate **5** has been prepared according to a method by Herzog and Scharf.[8] A modification of Bergson's original procedure[6] has been published recently.[9]
17. The submitters suggest that a revised workup procedure as follows is preferable, but it was not checked. At this point 250 mL of ether and 60 mL of water are added to dissolve the salt. The phases are separated and the procedure as described is followed.
18. The structural and elemental characterization of **5** is as follows. Anal. calcd. for $C_{18}H_{25}ClO_2$: C, 70.00; H, 8.16. Found: C, 69.81; H, 8.20; IR (KBr) cm^{-1}: 1185 (COC), 1754 (C=O); ^{1}H NMR ($CDCl_3$) δ: 0.66–2.24 (m, 8 H), 0.90 (d, 3 H, *J* = 6, CH_3CH), 1.22 (s, 3 H, CH_3CPh), 1.33 (s, 3 H, CH_3CPh), 3.04, 3.43 (AB, 2 H, *J* = 15, CH_2Cl), 4.91 (dt, 1 H, *J* = 10.6, 4, HCO), 7.00–7.40 (m, 5 H, aromatic CH); ^{13}C NMR ($CDCl_3$) δ: 21.71 (CH_3), 22.72 (CH_3), 26.18 (CH_2), 29.67 (CH_3), 31.22 (CH), 34.37 (CH_2), 39.36 (C_{quat}), 40.66 (CH_2), 41.43 (CH_2), 50.20 (CH), 75.65 (CH), 124.93, 125.09, 127.79, 151.43 (aromatic C), 166.17 (C=O). The submitters report that **2** may be recovered from the mother liquors enriched in the unwanted diastereomer. The mother liquors were saponified to **3/4** as described in Section D, followed by dichromate oxidation to **2** in 77–81% yield according to a procedure given for menthone.[10] However, this recovery was not checked.
19. The optical rotation, $[\alpha]_D^{23}$ + 26.3° (ethanol, *c* 2.02), for the enantiomer of **3** is reported.[3] The elemental and structural characterization of **3** is as follows. Anal. calcd. for $C_{16}H_{24}O$: C, 82.70; H, 10.41. Found: C, 82.80; H, 10.27; IR (liquid film) cm^{-1}: 3420, 3570 (OH); ^{1}H NMR ($CDCl_3$) δ: 0.64–2.06 (m, 9 H), 0.87 (d, 3 H, *J* = 6, CH_3CH), 1.29 (s, 3 H, CH_3CPh), 1.42 (s, 3 H, CH_3CPh), 3.48 (dt, *J* = 10, 4, HCO), 6.97–7.46 (m, 5 H, aromatic H); ^{13}C NMR ($CDCl_3$) δ: 21.95 (CH_3), 25.93 (CH_3), 26.62 (CH_2), 27.33 (CH_3), 31.45 (CH), 34.81 (CH_2), 39.87 (C_{quat}), 45.62 (CH_2), 53.85 (CH), 72.52 (CH), 125.22, 125.52, 127.88, 150.83 (aromatic C). In our hands **3** is a stable compound. In contrast to another report[8] we encountered no difficulties in storing alcohol **3**.

3. Discussion

Since its introduction in 1975 by E. J. Corey and H. E. Ensley,[3] 8-phenylmenthol has found widespread use as a chiral auxiliary in organic syntheses.[3 5 6 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31] It has proved to be dramatically superior in diastereoface discriminating ability to the commonly used chiral auxiliaries such as menthol and borneol.

Starting from (*R*)-pulegone we present herein an efficient three-step synthesis furnishing (–)-8-phenylmenthol as an easily separable 87 : 13-mixture of diastereomers in 55–80% overall isolated yield. Separation of the isomers is achieved either by careful medium-pressure chromatography as reported by Corey and Ensley[3,5] or, less tediously for the preparation of larger amounts, by fractional crystallization of the chloroacetic acid esters[6] and successive saponification as described herein. After submission of this procedure for publication in *Organic Syntheses* **1987**, *65*, 203, a communication[8] was published independently that follows this methodology.[4]

Recently the isolation of (–)-8-phenylmenthol via its crystalline phenylcarbamate has been disclosed.[32]

Since the conversion of (–)-citronellol to (*S*)-pulegone is reported,[33 34 35] the enantiomeric (+)-8-phenylmenthol likewise may be synthesized. The latter should also be obtainable in a seven-step synthesis starting from (*R*)-pulegone (48% overall yield) as claimed by Corey and co-workers.[5]

A number of 8-arylmenthols substituted in the aryl moiety have also been synthesized[5,32] and their applicability has been studied in various diastereoselective reactions.[15,32]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 516

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

Grignard reagent

(–)-8-PHENYLMENTHOL

(–)-citronellol

(1RS,2SR,5R)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexanol

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether, diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

sodium hydrogen carbonate (144-55-8)

magnesium turnings (7439-95-4)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

chloroacetate (79-11-8)

iodine (7553-56-2)

pyridine (110-86-1)

potassium hydroxide (1310-58-3)

toluene (108-88-3)

sodium, sodium wire (13966-32-0)

2-propanol (67-63-0)

bromobenzene (108-86-1)

Biphenyl (92-52-4)

copper(I) bromide (7787-70-4)

chloroacetyl chloride (79-04-9)

N,N-dimethylaniline (121-69-7)

magnesium methoxide

menthol (15356-60-2)

menthone (1196-31-2)

dichloromethane (75-09-2)

copper(I) iodide (7681-65-4)

magnesium sulfate (7487-88-9)

N,N-dimethylaniline hydrochloride (5882-44-0)

borneol (6627-72-1)

4-dimethylaminopyridine (1122-58-3)

(+)-PULEGONE, pulegone (89-82-7)

8-phenylmenthol, (+)-8-phenylmenthol

(1R,2S,5R)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexanol, Cyclohexanol, 5-methyl-2-(1-methyl-1-phenylethyl)-, [1R-(1α,2β,5α)]- (65253-04-5)

(R)-(+)-pulegone, (R)-Pulegone

(1R,2S,5R)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl chloroacetate

(S)-pulegone

(2RS,5R)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexanone (57707-92-3)

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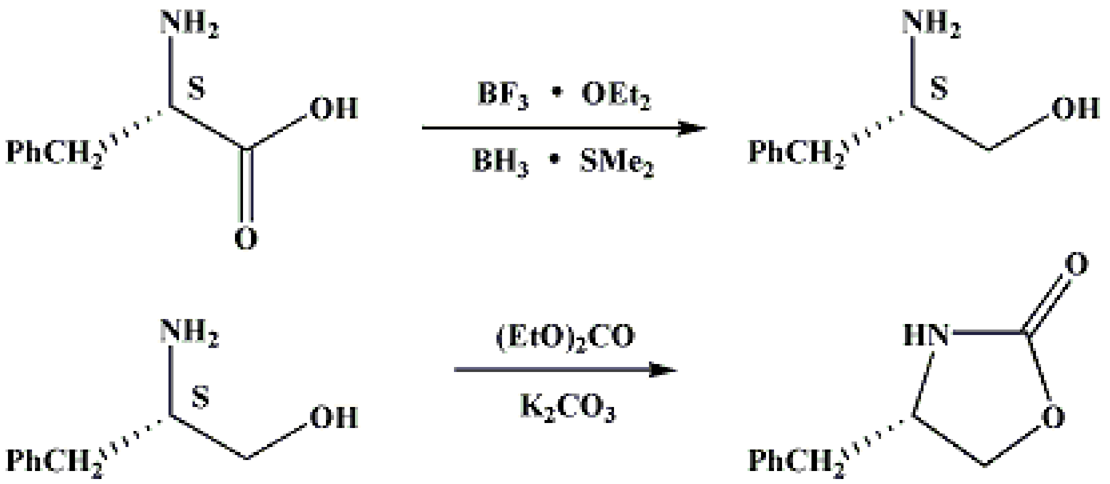
Organic Syntheses, CV 8, 528

(*S*)-4-(PHENYLMETHYL)-2-OXAZOLIDINONE

[2-Oxazolidinone, 4-(phenylmethyl)-, (*S*)-]



Submitted by James R. Gage and David A. Evans[1].
Checked by Philip G. Meister and Leo A. Paquette.

1. Procedure

Caution! This reaction should be carried out in a hood since dimethyl sulfide is liberated during the course of the reaction.

A. *(S)-Phenylalanol*. A dry, 3-L, three-necked flask is equipped with a mechanical stirrer and a reflux condenser connected to a mineral oil bubbler. The flask is loaded with 165 g (1.00 mol) of (*S*)-phenylalanine (Note 1), then equipped with a 250-mL pressure-equalized addition funnel capped with a rubber septum through which is inserted a nitrogen inlet needle. The flask is swept with nitrogen and filled with 500 mL of anhydrous tetrahydrofuran, and the addition funnel is charged with 123 mL (1.00 mol) of freshly distilled boron trifluoride etherate via cannula (Note 2). The boron trifluoride etherate is added dropwise to the phenylalanine slurry over a 30-min period with stirring, and the mixture is heated at reflux for 2 hr, resulting in a colorless, homogeneous solution. The addition funnel is then charged via cannula with 88 g (110 mL, 1.15 mol) of 20 *M* borane–dimethyl sulfide complex (Note 3), which is added carefully to the *vigorously* refluxing solution over a 100-min period. During the course of the addition there is continuous evolution of dimethyl sulfide and hydrogen gas, and the solution turns from orange to light brown. A vigorous exotherm occurs approximately half way through the addition period. *(Caution! See (Note 4))* The solution is heated at reflux for an additional 6 hr after the addition is complete (Note 5) and (Note 6), then allowed to cool to ambient temperature. The excess borane is quenched by the slow addition of 125 mL of a 1:1 tetrahydrofuran–water solution

followed by 750 mL of 5 *M* aqueous sodium hydroxide. The resulting two-phase mixture is heated at reflux for 12 hr, cooled to room temperature, and filtered through a coarse fritted funnel. The residual solids are washed with two 25-mL portions of tetrahydrofuran, and the filtrate is concentrated on a rotary evaporator to remove the bulk of the tetrahydrofuran. The resulting slurry is extracted with one 400-mL and three 200-mL portions of dichloromethane. The combined organic extracts are dried over anhydrous sodium sulfate, filtered, and concentrated by rotary evaporation, yielding 141–158 g (93–104%) of a white crystalline solid that is recrystallized from ca. 600 mL of ethyl acetate to give 111–113 g (73–75%) of the desired product as white needles in two crops, mp 88.5–91°C (Note 7).

B. *(S)-4-(Phenylmethyl)-2-oxazolidinone*. A dry, 1-L, three-necked flask is equipped with a mechanical stirrer and a 12-in. Vigreux column fitted with a distillation head and a 200-mL receiver flask connected to a nitrogen source and a bubbler. The flask is charged with 151 g (1.00 mol) of (*S*)-phenylalanol, 13.8 g (0.100 mol) of anhydrous potassium carbonate, and 250 mL (2.06 mol) of diethyl carbonate (Note 8). The mixture is lowered into an oil bath, preheated to 135°C, and is stirred until dissolution is achieved (ca. 5 min). The distillation receiver is cooled in an ice bath, and ca. 120 mL of ethanol is collected from the reaction over a 2.5-hr period. The oil bath is removed on cessation of the ethanol distillation. After the light-yellow solution is cooled to ambient temperature, it is diluted with 750 mL of dichloromethane, transferred to a separatory funnel, and washed with 750 mL of water. The organic phase is dried over anhydrous magnesium sulfate, filtered, and concentrated on the rotary evaporator affording 200 g (113%) of a white crystalline solid. This material is taken up into 600 mL of a hot 2:1 ethyl acetate–hexane solution, filtered while hot, then allowed to crystallize to afford 136–138 g (78–79%) of large white plates, mp 84.5–86.5°C (Note 9) and (Note 10).

2. Notes

1. (*S*)-Phenylalanine was obtained by the submitters from Ajinomoto Company, Inc. The starting material obtained by the checkers from Sigma Chemical Company was dried under reduced pressure over phosphorus pentoxide for 2 days.
2. Reagent-grade tetrahydrofuran (Fisher Scientific Company) was either freshly distilled from sodium metal and benzophenone or dried for at least 24 hr over activated Linde 4-Å molecular sieves. Boron trifluoride etherate was redistilled prior to use. Fresh bottles of redistilled born trifluoride etherate purchased from Aldrich Chemical Company, Inc. also usually give good results.
3. Borane–dimethyl sulfide (10 M) was purchased from Aldrich Chemical Company, Inc. and used as received.
4. The potential vigor of this exotherm cannot be overemphasized. It occurs later and is correspondingly stronger if vigorous reflux is not maintained during the addition. The reaction mixture should be watched closely throughout the addition of borane, and addition should be temporarily suspended at the onset of

the exotherm.
5. Dimethyl sulfide can be collected if desired by inserting a trap cooled in an acetone–dry ice bath into the hose leading to the bubbler.
6. Yields sometimes drop when an old bottle of borane–dimethyl sulfide is used. Reaction progress can be monitored by thin-layer chromatography (silica gel, eluting with 10 : 10 : 1 chloroform–methanol–concentrated ammonium hydroxide). Any remaining phenylalanine stains heavily when exposed to ninhydrin (R_f = 0.35). If phenylalanine is detected after 5 hr of reflux, an additional 10 mL (0.10 mol) of borane–dimethyl sulfide is added via syringe, and the solution is heated at reflux for an additional 1 hr.
7. The product has the following spectroscopic properties: IR (solution in dichloromethane) cm^{-1}: 3625, 3360, 3035, 2930, 2855, 1497, 1456, 1032; ^1H NMR ($CDCl_3$) δ: 1.5–2.0 (broad s, 3 H, NH_2, OH), 2.5 (dd, 1 H, $HCHC_6H_5$), 2.8 (dd, 1 H, $HCHC_6H_5$), 3.1 (m, 1 H, $CHNH_2$), 3.4 (dd, 1 H, HCHOH), 3.7 (dd, 1 H, HCHOH), 7.1–7.4 (m, 5 H, ArH); $[\alpha]_D$ –24.7° (ethanol, *c* 1.03). The checkers recorded $[\alpha]_D$ –22.4° (ethanol, *c* 1.03).
8. Diethyl carbonate (99%) was used as received from Aldrich Chemical Company, Inc.
9. The product has the following spectroscopic properties: IR (solution in dichloromethane) cm^{-1}: 3460, 3020, 1760, 1480, 1405, 1220; ^1H NMR ($CDCl_3$) δ: 2.9 (d, 2 H, $CH_2C_6H_5$), 4.0–4.6 (m, 3 H, $CHCH_2O$), 5.6 (broad s, 1 H, NH), 7.1–7.5 (m, 5 H, ArH); $[\alpha]_D$ +4.9° (ethanol, *c* 1.10).
10. The enantiomeric excess was determined to be >99% by capillary GLC analysis (30-m × 32-mm WCOT column coated with carbowax 20 M, hydrogen carrier gas, linear velocity ca. 94 cm/sec, oven temperature 225°C) of the imide derived from the Mosher acid chloride.[2]

3. Discussion

The utilization of α-amino acids and their derived β-amino alcohols in asymmetric synthesis has been extensive.[3] A number of procedures have been reported for the reduction of a variety of amino acid derivatives; however, the direct reduction of α-amino acids with borane has proved to be exceptionally convenient for laboratory-scale reactions.[4] These reductions characteristically proceed in high yield with no perceptible racemization. The resulting β-amino alcohols can, in turn, be transformed into oxazolidinones, which have proved to be versatile chiral auxiliaries. Besides the highly diastereoselective aldol addition reactions,[5] enolates of *N*-acyl oxazolidinones have been used in conjunction with asymmetric alkylations,[6] halogenations,[7] hydroxylations,[8] acylations,[9] and azide transfer processes,[10] all of which proceed with excellent levels of stereoselectivity.

The phenylalanine-derived oxazolidinone featured here enjoys three practical advantages over the valine-derived oxazolidinone developed earlier in this laboratory.[5]

First, both the intermediate β-amino alcohol and the derived oxazolidinone are crystalline solids that can be purified conveniently by direct crystallization. Second, the oxazolidinone contains a UV chromophore which greatly facilitates TLC or HPLC analysis when it is employed as a chiral auxiliary. Finally, both enantiomers of phenylalanine are readily available, enabling stereocontrol in either sense simply by using the oxazolidinone derived from the appropriate enantiomer.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 339

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Mosher acid chloride

phenylalanine-derived oxazolidinone

valine-derived oxazolidinone

ethanol (64-17-5)

potassium carbonate (584-08-7)

ethyl acetate (141-78-6)

methanol (67-56-1)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

Benzophenone (119-61-9)

sodium (13966-32-0)

ammonium hydroxide (1336-21-6)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

borane (7440-42-8)

dimethyl sulfide (75-18-3)

phenylalanine, (S)-Phenylalanine (63-91-2)

Tetrahydrofuran (109-99-9)

diethyl carbonate (105-58-8)

hexane (110-54-3)

boron trifluoride etherate (109-63-7)

ninhydrin (938-24-9)

phosphorus pentoxide (1314-56-3)

(S)-Phenylalanol (3182-95-4)

born trifluoride etherate

(S)-4-(Phenylmethyl)-2-oxazolidinone, 2-Oxazolidinone, 4-(phenylmethyl)-, (S)- (90719-32-7)

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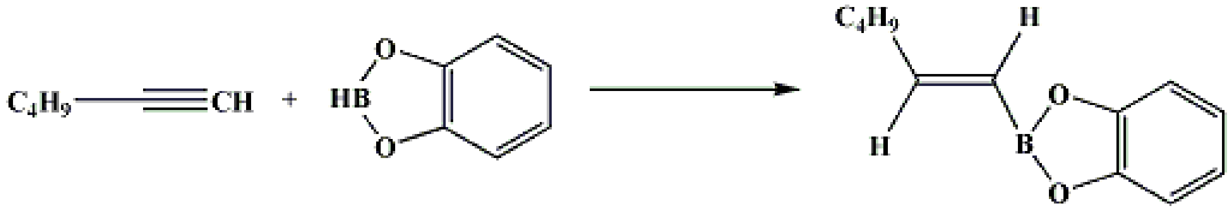
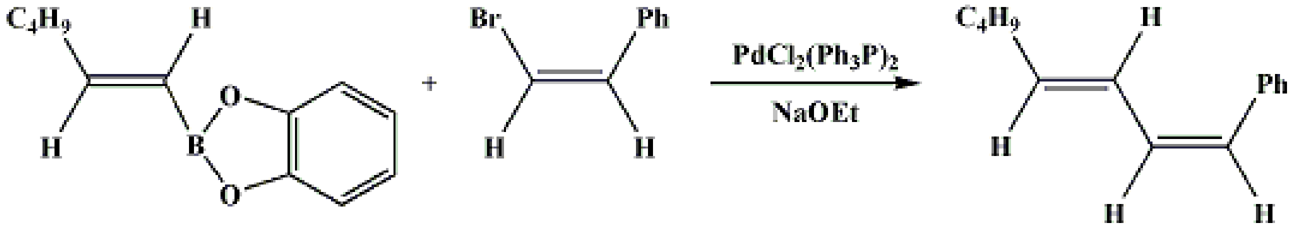
Organic Syntheses, CV 8, 532

PALLADIUM-CATALYZED REACTION OF 1-ALKENYLBORONATES WITH VINYLIC HALIDES: (1*Z*,3*E*)-1-PHENYL-1,3-OCTADIENE

[Benzene, 1,3-octadienyl-, (*Z*,*E*)-]





Submitted by Norio Miyaura and Akira Suzuki[1].
Checked by Albert L. Casalnuovo, Thomas S. Kline, Jr., and Bruce E. Smart.

1. Procedure

A. *(E)-1-Hexenyl-1,3,2-benzodioxaborole.* A 25-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, a thermometer, a rubber septum, a 10-mL addition funnel, and a reflux condenser. The apparatus is connected through the condenser to a nitrogen source and an oil bubbler (Note 1). The flask is charged with 4.9 g (60 mmol) of 1-hexyne (Note 2) through the addition funnel. While the solution is stirred slowly, 6.7 mL (60 mmol) of catecholborane (Note 3) is injected by syringe through the septum cap. The exothermic reaction is maintained at 60–70°C by intermittent cooling in an ice–water bath. The reaction mixture is allowed to cool to room temperature and is stirred for 15 min. The rubber septum is replaced by a glass stopper, and the mixture is heated to 60°C and stirred for an additional 2 hr. The flask is cooled to room temperature, the condenser is replaced by a short-path distillation head, and the mixture is distilled at reduced pressure to give 9.5–10.5 g (78–87%) of clear, colorless product, bp 75–76°C (0.10 mm) [lit.[2] bp 82°C (0.25 mm)] (Note 4).

B. *(1Z,3E)-1-Phenyl-1,3-octadiene.* A 500-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, a reflux condenser to which a nitrogen inlet tube and oil bubbler are attached, a glass stopper, and an addition funnel is flushed with nitrogen and charged with 9.5 g (47 mmol) of (*E*)-1-hexenyl-1,3,2-benzodioxaborole and 200 mL of benzene (Note 5). The solution is stirred and 8.4 g (46 mmol) of (*Z*)-β-bromostyrene (Note 6), 50 mL of 2 *M* sodium ethoxide in ethanol (Note 7), and finally 0.28 g (0.4 mmol) of dichlorobis(triphenylphosphine)palladium(II) (Note 8) are added. The mixture is refluxed for 3 hr. The light-brown solution containing a white precipitate of

sodium bromide is cooled to room temperature, treated with 60 mL of 3 *M* sodium hydroxide and 6 mL of 30% hydrogen peroxide, and stirred at room temperature for 1 hr (Note 9). The organic layer is separated, washed 4 times with 50 mL of 3 *M* sodium hydroxide (Note 10), and dried over anhydrous magnesium sulfate. The drying agent is removed by filtration and the filtrate is concentrated on a rotary evaporator. The residual oil is distilled under reduced pressure (Note 11) to give 7.0 g (82%) of (1*Z*,3*E*)-1-phenyl-1,3-octadiene as a clear, colorless liquid, bp 80°C (0.15 mm) (Note 12).

2. Notes

1. All glassware was predried in an oven at 130°C for 3 hr, assembled while hot, and allowed to cool under a stream of nitrogen.
2. The preparation of 1-hexyne is described in *Org. Synth., Coll. Vol. IV*, **1963**, 117. The checkers obtained 1-hexyne from Aldrich Chemical Company, Inc., and distilled it prior to use.
3. Catecholborane (1,3,2-benzodioxaborole) with a purity of 95% was purchased from Aldrich Chemical Company, Inc. and purified by distillation under nitrogen, bp 58°C (52 mm). For the distillation and handling of air and moisture-sensitive compounds, see [3,4,5]. Catecholborane is a liquid at room temperature, and the neat material is 9.0 *M* in catecholborane.[3] The preparation of catecholborane from borane and catechol has been reported.[3]
4. The submitters report bp 86–87°C (0.3 mm). (*E*)-1-Hexenyl-1,3,2-benzodioxaborole is quite air-stable, but it can slowly hydrolyze to boronic acid and turn brown on repeated use in air. The submitters recommend storing it at refrigerator temperature in a bottle purged with nitrogen and capped with a rubber septum. Alternatively, the crude 1-hexenyl-1,3,2-benzodioxaborole can be used the next coupling reaction without purification. In this case, the unreacted 1-hexyne should be removed under reduced pressure (0.1 mm for 30 min), because it also reacts with (*Z*)-β-bromostyrene to afford (1*Z*)-1-phenyl-1-octen-3-yne. In this manner the expected diene was obtained in a yield of 86%.
5. Benzene was obtained from Fisher Scientific Company and redistilled before use.
6. (*Z*)-β-Bromostyrene was prepared by the procedure described in *Org. Synth., Coll. Vol. VII*, **1990**, 172.
7. The sodium ethoxide solution was prepared by dissolving 2.3 g of sodium in 50 mL of anhydrous ethanol and was used immediately.
8. The palladium catalyst is prepared as follows. A 100-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar and a reflux condenser connected to a nitrogen inlet is flushed with nitrogen and charged with 1.00 g (5.64 mmol) of palladium chloride (Johnson Matthey, Inc.), 3.25 g (12.4 mmol) of triphenylphosphine (Aldrich Chemical Company, Inc.), and 30 mL of benzonitrile (Aldrich Chemical Company, Inc.). The mixture is stirred, gradually heated to 180°C, and held at that temperature for 20 min. The clear, red solution that results is allowed to cool slowly to room temperature and stand overnight. The bright-yellow crystals that precipitate are collected by filtration, washed with three 10-mL portions of ether, and dried at reduced pressure to give 3.90 g (5.55 mmol) of dichlorobis(triphenylphosphine)palladium(II).
9. This operation removes most of the palladium-containing compounds. Any unreacted 1-hexenylboronate is oxidized to hexenal.
10. Catechol must be washed out completely because it is difficult to remove by distillation. A solution of catechol in aqueous sodium hydroxide turns dark brown on treatment with

hydrogen peroxide or on standing in air.

11. The residual oil can be purified before distillation by filtering it through a short (20-cm) silica gel column (70–230 mesh) using hexanes as an eluant. This effectively removes traces of catechol and palladium-containing compounds.

12. Gas chromatographic analysis of the product (Hewlett-Packard fused silica, crosslinked, methylsilicone capillary column, 25 m × 20 mm, column temperature 100–270°C, injection temperature 250°C) shows that the product is over 99% chemically and isomerically pure. (*Z*, *E*)-1-Phenyl-1,3-octadiene shows the following spectral properties: IR (neat) cm^{-1}: 1640, 1595, 1490, 985; ^{1}H NMR ($CDCl_3$) δ: 0.89 (t, 3 H, *J* = 7.1), 1.25–1.45 (m, 4 H), 2.05–2.20 (m, 2 H), 5.87 (d of t, 1 H, *J* = 7.1, 15, PhC=C-C=CH), 6.21 (d of d, 1 H, *J* = 11.2, 11.6, PhC=CH), 6.30 (d, 1 H, *J* = 11.6, PhCH=C), 6.60 (d of d, 1 H, *J* = 11.2, 15, PhC=C-CH=C), and 7.15–7.40 (m, 5 H, aromatic).

3. Discussion

The procedure described here is an example of a general method for preparing conjugated alkadienes by the palladium-catalyzed reaction of 1-alkenylboranes or boronates with vinylic halides. Hydroboration of 1-alkynes with catecholborane is a standard method for obtaining (*E*)-1-alkenylboronates (**1**).[2,3] Several different types of alkenylboranes and boronates (**2–4**) are now available as reagents for the cross-coupling reaction with vinyl halides.

1 **2**[6,7] **3**[8] **4**[9]

These alkenylboron derivatives react not only with 1-alkenyl halides but also with a variety of other organic halides, including 1-bromo-1-alkynes,[6] aryl halides,[7,8,9] and allylic or benzylic halides,[10] in the presence of a palladium catalyst and base. Both $Pd(PPh_3)_4$ and $PdCl_2(PPh_3)_2$ are excellent catalysts for most of the reactions. A base is generally required for successful coupling. Sodium ethoxide (2 equiv) in ethanol–benzene, which is used in the procedure described here, gives high yields with most 1-bromo-1-alkenes. For 1-iodo-1-alkenes, aqueous sodium hydroxide in tetrahydrofuran[11] or aqueous 4 *M* potassium hydroxide (3 equiv) in benzene[8] can give better results. Alkoxides and hydroxides normally accelerate the reaction, but the choice of base depends on its compatibility with the particular organic halide. For the coupling reaction with 3-halo-2-cyclohexen-1-one[12] a relatively weak base, such as sodium acetate in methanol, works well. The reaction with 1-bromo-2-phenylthio-1-alkenes[13] is successfully carried out using aqueous potassium hydroxide. For the reaction of (*E*)-2-ethoxyvinylborane with aryl halides,[14] a suspension of sodium hydroxide in tetrahydrofuran gives better results than homogeneous base. The versatility of these methods has been reviewed.[15,16]

In addition to alkenylboron compounds, alkenylalane,[17 18 19] alkenylzirconium,[20 21] alkenyltin,[22] alkenylcopper,[23 24] and alkenylmagnesium[25] reagents are reported to undergo a related alkenyl–alkenyl coupling reaction to give 1,3-alkadienes.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

(E)-1-alkenylboronates

ethanol (64-17-5)

Benzene (71-43-2)

methanol (67-56-1)

ether (60-29-7)

sodium acetate (127-09-3)

benzonitrile (100-47-0)

sodium hydroxide (1310-73-2)

sodium bromide (7647-15-6)

nitrogen (7727-37-9)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

palladium (7440-05-3)

Catechol (120-80-9)

hydrogen peroxide (7722-84-1)

palladium chloride

magnesium sulfate (7487-88-9)

borane (7440-42-8)

Tetrahydrofuran (109-99-9)

1-Hexyne (693-02-7)

triphenylphosphine (603-35-0)

CATECHOLBORANE, 1,3,2-benzodioxaborole (274-07-7)

(Z)-β-Bromostyrene (103-64-0)

dichlorobis(triphenylphosphine)palladium(II) (13965-03-2)

1-hexenyl-1,3,2-benzodioxaborole

1-hexenylboronate

hexenal

(1Z,3E)-1-Phenyl-1,3-octadiene, (Z,E)-1-Phenyl-1,3-octadiene (39491-66-2)

Benzene, 1,3-octadienyl-, (Z,E)- (39491-66-2)

(E)-1-Hexenyl-1,3,2-benzodioxaborole (37490-22-5)

(1Z)-1-phenyl-1-octen-3-yne

(E)-2-ethoxyvinylborane

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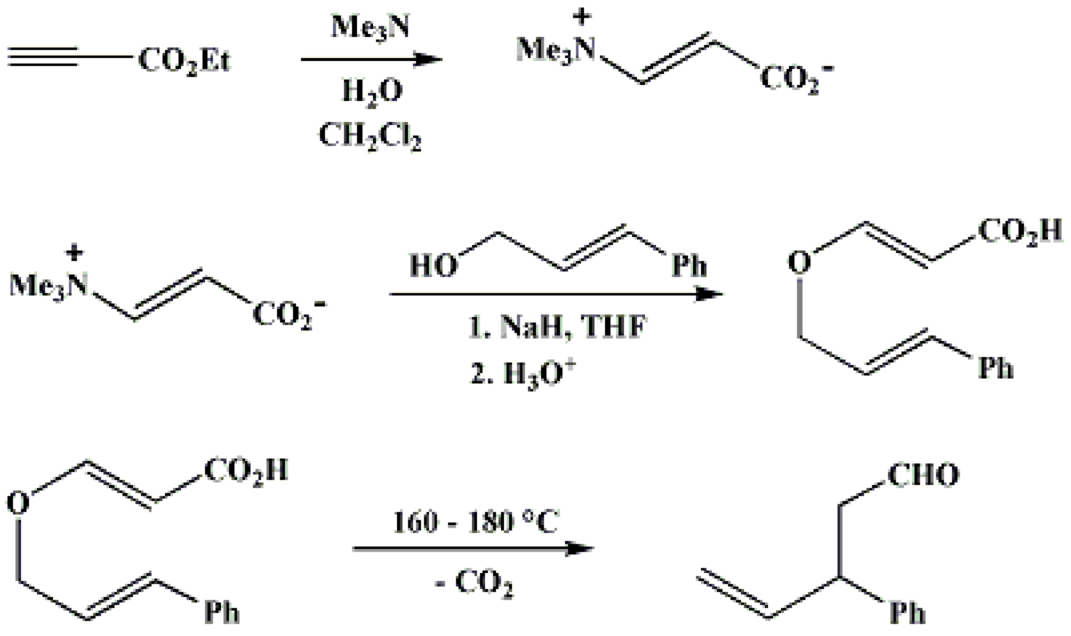
Organic Syntheses, CV 8, 536

α-UNSUBSTITUTED γ,δ-UNSATURATED ALDEHYDES BY CLAISEN REARRANGEMENT: 3-PHENYL-4-PENTENAL

[Benzenepropanal, β-ethenyl-]



Submitted by Dennis E. Vogel and George H. Büchi[1].
Checked by Tadahito Nobori and Ryoji Noyori.

1. Procedure

A. *(E)-(Carboxyvinyl)trimethylammonium betaine*. A 1-L, three-necked, round-bottomed flask is equipped with a mechanical stirrer, a dropping funnel, and a thermometer. The flask is charged with 25.0 g (0.255 mol) of ethyl propiolate (Note 1), 14 mL of dichloromethane, and 440 mL of water. The mixture is cooled to 5°C (Note 2) and 90 mL (0.35 mol) of an aqueous 25% solution of trimethylamine (Note 3) is added under vigorous stirring over a 30-min period. The reaction temperature remains between 0 and 5°C during the addition and then is allowed to warm to 25°C for 3 hr. The dichloromethane layer is separated and the aqueous layer is washed 3 times with 100-mL portions of dichloromethane. The aqueous layer is placed in a 1-L, round-bottomed flask and concentrated at 15 mm pressure with a rotary evaporator equipped with a dry-ice condenser. The flask is heated to approximately 45°C. When the residue gives the appearance of a wet solid, it is treated with 150 mL of dioxane and concentrated as described above. Dioxane treatment followed by concentration is repeated 3 more times with 150-mL portions of dioxane (Note 4). The yellow solid residue is triturated with acetonitrile (Note 5) until a white solid is obtained. The solid is collected and dried at 0.1 mm, 25°C for 14 hr to give 25.0–26.9 g (76–82% yield) of

(*E*)-(carboxyvinyl)trimethylammonium betaine, mp 176–177°C (dec) (Note 6).

B. *(E)-3-[(E)-3-Phenyl-2-propenoxy]acrylic acid.* An oven dried, 1-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, a dropping funnel, and a reflux condenser is purged with argon and charged with 8.20 g (0.171 mol) of 50% sodium hydride in oil (Note 7) and 90 mL of anhydrous tetrahydrofuran (Note 8). To this mixture is added a solution of 19.0 g (0.143 mol) of cinnamyl alcohol (Note 9) in 180 mL of anhydrous tetrahydrofuran. The mixture is stirred for 30 min at which point 25.0 g (0.194 mol) of (*E*)-(carboxyvinyl)trimethylammonium betaine is added and the reaction mixture is heated at a gentle reflux for 15 hr. The cooled reaction mixture is slowly added to a mixture of 600 mL of water and 220 mL of a saturated aqueous solution of sodium chloride (Note 10). The residual material is removed with wet ether (Note 11) and added to the aqueous solution. The aqueous layer is washed 3 times with 450 mL of ether and acidified with approximately 21 mL of concentrated hydrochloric acid to pH 1. This mixture is extracted 3 times with 700 mL of ether and the ether layer is dried with 20 g of anhydrous magnesium sulfate for 30 min. The mixture is filtered and the filtrate is concentrated, first with a rotary evaporator and then at 0.1 mm for 24 hr at 25°C to give crude (*E*)-3-[(*E*)-3-phenyl-2-propenoxy] acrylic acid. This material can be used in Part C without further purification. However, purification by trituration with approximately 30 mL of anhydrous ether gives 24.7–25.0 g (85% yield) of white crystalline product, mp 140–141.5°C (dec) (Note 12).

C. *3-Phenyl-4-pentenal.* In a 100-mL, round-bottomed flask equipped with a magnetic stirring bar is placed 20.1 g (0.098 mol) of (*E*)-3-[(*E*)-3-phenyl-2-propenoxy]acrylic acid from B (Note 13). The flask is fitted with a distillation head for vacuum distillation and heated at 0.1 mm pressure. The oil-bath temperature is maintained at 160–165°C while the mixture is stirred, until all the material melts. Once the initial reaction is under control, the oil bath is slowly heated to 180°C. The product is collected in a receiver flask cooled with a dry ice–acetone bath to give 13.3–14.3 g (84–91% yield) of 3-phenyl-4-pentenal, bp 114–115°C (15 mm) (Note 14).

2. Notes

1. Ethyl propiolate, purchased from Aldrich Chemical Company, Inc., is freshly distilled prior to use.
2. An ice–acetone bath is used to cool the reaction mixture.
3. An aqueous 25% solution of trimethylamine available from Aldrich Chemical Company, Inc. is used directly.
4. This procedure helps to concentrate further the product by forming an azeotrope with the water.
5. Continued trituration with small portions of acetonitrile (e.g., 8 times with 50-mL portions) eventually removes all traces of the yellow-colored impurity as well as any residual water.
6. The product exhibits the following spectral properties: IR (KBr) cm^{-1}: 1665, 1600, 1360; ^1H NMR (D_2O, DSS ref.) δ: 3.3 (br s, 9 H, $(CH_3)_3N$), 6.3 (br d, 1

H, *J* = 13, vinyl CH), 6.8 (br d, 1 H, *J* = 13, vinyl CH).

7. A suspension of 50% sodium hydride in mineral oil, purchased from Alfa Products, Johnson Mathey Co. or Nakarai Chemicals, Ltd., is used directly.

8. Anhydrous tetrahydrofuran is obtained by distillation from benzophenone ketyl prior to use.

9. Cinnamyl alcohol purchased from Aldrich Chemical Company, Inc. is freshly distilled before use. The checkers purchased it from Nakarai Chemicals, Ltd.

10. *Caution: Residual sodium hydride is present in the reaction mixture; however, it can be quenched safely by strict adherence to the procedure described.*

11. The use of wet ether has two purposes. Not only does the ether help wash residual product from the flask, but ether that has not been carefully dried contains traces of water, which allows for the safe quenching of the last traces of sodium hydride.

12. The product exhibits the following spectral properties: IR (KBr) cm^{-1}: 1680, 1615, 1600; ^{1}H NMR ($CDCl_3$ 60 MHz) δ: 4.5 (d, 2 H, *J* = 5.5, OCH_2CH=), 5.2 (d, 1 H, *J* = 12, $CH=CHCO_2H$), 6.5 (m, 2 H, PhCH=CH-), 7.2 (s, 5 H, Ph-), 7.5 (d, 1 H, *J* = 12, O-$CH=CHCO_2H$), 12.0 (s, 1 H, CO_2H).

13. The material obtained from trituration of the crude product in Part B can also be used at this point and gives similar results.

14. The product exhibits the following spectral properties: IR (neat) cm^{-1}: 2840, 2740, 1720, 1640, 1600; ^{1}H NMR ($CDCl_3$, 60 MHz) δ: 2.9 (d,d, 2 H, *J* = 2, 4, CH_2-CHO), 4.0 (q, 1 H, *J* = 7, Ph-CH), 5.0 (d, 1 H, *J* = 7, vinyl), 5.3 (s, 1 H, vinyl), 6.0 (m, 1 H, vinyl), 7.2 (s, 5 H, Ph), 9.5 (t, 1 H, *J* = 2, CHO).

3. Discussion

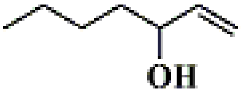
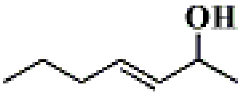
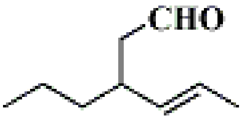
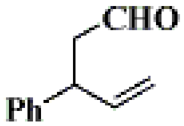
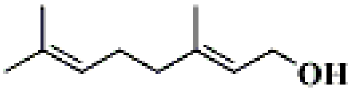
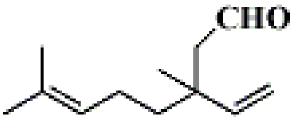
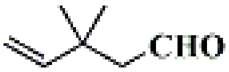
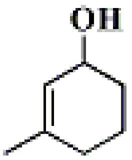
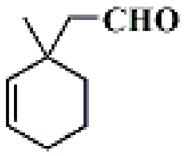
The procedure described[2] illustrates a new general synthetic method for the preparation of (*E*)-3-allyloxyacrylic acids and their conversion to α-unsubstituted γ,δ-unsaturated aldehydes by subsequent Claisen rearrangement–decarboxylation. Such aldehydes are traditionally prepared by Claisen rearrangements of allyl vinyl ethers.[3] Allyl vinyl ethers are typically prepared by either mercury-catalyzed vinyl ether exchange with allylic alcohols or acid-catalyzed vinylation of allylic alcohols with acetals. The basic conditions required for alkoxide addition to the betaine to produce carboxyvinyl allyl ethers, as described in this report, nicely complements these two methods. In addition, this Claisen rearrangement is an experimentally very simple procedure, since sealed-tube and other high-pressure vessels are not required. The allyloxyacrylic acids are heated neat (in most cases a small amount of hydroquinone is added) and, by adjusting the pressure at which the reaction is performed, the aldehyde products distill from the reaction mixture in analytically pure form.

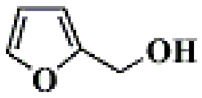
(*E*)-(Carboxyvinyl)trimethylammonium betaine is prepared by a modification of the procedure of McCulloch and McInnes.[4] They also reported the addition of simple alkoxides to this betaine, and that deuterium exchange is not observed when this reaction is performed with the deuterated betaine. We have also observed that

replacement of the betaine with propiolic acid leads to the formation of 3-alkoxyacrylic acids in significantly lower yields.[2] These observations are best accounted for by an addition–elimination process.

This procedure provides a variety of allyloxyacrylic acids; however, it is sensitive to steric hindrance. Tertiary allylic alcohols do not add to the betaine and sterically hindered secondary alcohols add with decreasing facility. Table I indicates the scope of this reaction.

TABLE I
PREPARATION AND REARRANGEMENT OF 3-ALLYLOXYACRYLIC ACIDS

Starting Material	Yield of Adduct, %	Product	Yield, %
	89		68
	84		78
	92		quant.
	62		quant.
	96		quant.
	53,77		quant.



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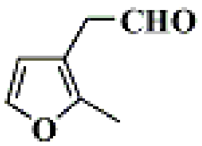

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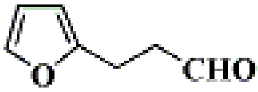

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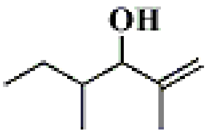

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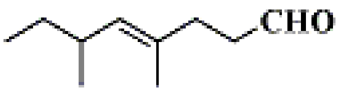

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

benzophenone ketyl

(E)-(Carboxyvinyl)trimethylammonium betaine

hydrochloric acid (7647-01-0)

ether (60-29-7)

acetonitrile (75-05-8)

hydroquinone (123-31-9)

sodium chloride (7647-14-5)

dichloromethane (75-09-2)

Trimethylamine (75-50-3)

magnesium sulfate (7487-88-9)

dioxane (5703-46-8)

Tetrahydrofuran (109-99-9)

cinnamyl alcohol (104-54-1)

sodium hydride (7646-69-7)

ethyl propiolate (623-47-2)

argon (7440-37-1)

deuterium (7782-39-0)

propiolic acid (471-25-0)

3-Phenyl-4-pentenal, Benzenepropanal, β-ethenyl- (939-21-9)

(E)-3-[(E)-3-Phenyl-2-propenoxy]acrylic acid (88083-18-5)

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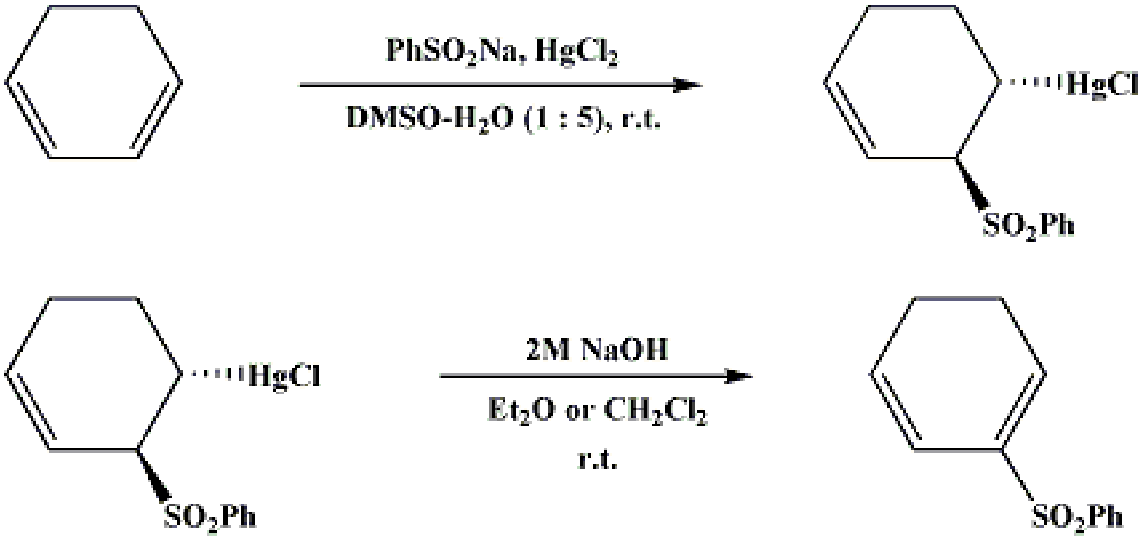
Organic Syntheses, CV 8, 540

2-(PHENYLSULFONYL)-1,3-CYCLOHEXADIENE

[Benzene, (1,5-cyclohexadien-1-ylsulfonyl)-]



Submitted by Jan-E. Bäckvall, Seppo K. Juntunen, and Ove S. Andell[1].
Checked by Willi-Kurt Gries and Larry E. Overman.

1. Procedure

A. *trans-3-(Phenylsulfonyl)-4-(chloromercuri)cyclohexene.* A 1-L, one-necked, round-bottomed flask equipped with a large magnetic stirring bar is charged with 32.6 g (120 mmol) of mercury(II) chloride (Note 1), 24.6 g (150 mmol) of sodium benzenesulfinate (Note 2), 80 mL of dimethyl sulfoxide, and 400 mL of water. The slurry is initially stirred at room temperature for 2 hr and then 10.6 g (132 mmol) of 1,3-cyclohexadiene (Note 3) is added dropwise under vigorous stirring at room temperature over a period of a few minutes. The reaction mixture is stirred for another 2 hr. The reaction flask is cooled with ice and the solid material collected by filtration using a Büchner funnel (Note 4), washed with 400 mL of water, and dried in a desiccator over calcium chloride at reduced pressure (oil pump), to give 53.0 g (97%) of essentially pure *trans*-3-(phenylsulfonyl)-4-(chloromercuri)cyclohexene (Note 5).

B. *2-(Phenylsulfonyl)-1,3-cyclohexadiene.* A 1-L, one-necked, round-bottomed flask, equipped with a magnetic stirring bar, is charged with 53.0 g (116 mmol) of *trans*-3-(phenylsulfonyl)-4-(chloromercuri)cyclohexene and 600 mL of diethyl ether (Note 6) at room temperature. The slurry is stirred for 5 min (Note 7) and 175 mL (350 mmol) of a 2 *M* aqueous solution of sodium hydroxide is added under vigorous stirring (Note 8). The reaction mixture immediately turns black and the vigorous stirring is continued for 30 min (Note 9). The two layers are separated and the aqueous phase is extracted three times with 50-mL portions of diethyl ether. The combined organic layers are filtered through a short column containing 10 g of silica gel and the column is washed

with 250 mL of diethyl ether. The ethereal solution is dried over anhydrous magnesium sulfate and filtered, and the solvent is removed at reduced pressure using a rotary evaporator to give 22.5–24.5 g (88–96%) of 2-(phenylsulfonyl)-1,3-cyclohexadiene as a colorless solid (Note 10).

2. Notes

1. Mercury(II) chloride was purchased from Merck & Company, Inc. and used as delivered. The checkers used material purchased from Mallinckrodt Inc.
2. Sodium benzenesulfinate (benzenesulfinic acid, sodium salt) was purchased from Aldrich Chemical Company, Inc. and used without further purification.
3. 1,3-Cyclohexadiene was obtained from Fluka Chemical Corporation and distilled before use. The distillation was performed at ambient temperature and reduced pressure (60–70 mm) and the diene was collected in a flask cooled with liquid nitrogen. The checkers used diene purchased from Aldrich Chemical Company, Inc.
4. A funnel with a fine frit must be used.
5. The crude product melts at 119–123°C and is sufficiently pure for use in the next step. Recrystallization from ethyl acetate provides material melting at 128°C (dec). NMR spectral properties are as follows: ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.92–2.12 (m, 3 H), 2.36–2.51 (m, 1 H), 2.95–3.05 (m, 1 H, H-4), 4.24–4.34 (m, 1 H, H-3), 5.57–5.81 (m, 1 H, =CH), 6.04–6.16 (m, 1 H, =CH), 7.53–7.65 (m, 3 H, ArH), 7.82–7.87 (m, 2 H, ArH); ^{13}C NMR (75 MHz/$CDCl_3$) δ: 26.5, 26.7, 44.1, 66.2, 119.6, 129.1, 129.3, 134.2, 135.4, 136.6.
6. The submitters report that dichloromethane can be used also as the solvent with similar results. This modification was not checked.
7. *trans*-3-(Phenylsulfonyl)-4-(chloromercuri)cyclohexene is only partly soluble in diethyl ether when the described proportions are used, whereas a clear solution is obtained when dichloromethane is used as solvent.
8. The submitters report that if dichloromethane is used as solvent, 250 mL (500 mmol) of aqueous 2 *M* sodium hydroxide is added at this point.
9. The submitters report that if dichloromethane is used as solvent, the reaction mixture is stirred for 1.5 hr.
10. The crude product melts at 60–63°C. The spectral properties of 2-(phenylsulfonyl)-1,3-cyclohexadiene are as follows: IR (KBr) cm^{-1}: 3060, 2982, 2923, 2880, 2830, 1585, 1450, 1305, 1150, 1090, 710, 690; ^{1}H NMR (250 MHz/$CDCl_3$) δ: 2.11–2.21 (m, 2 H), 2.35–2.45 (m, 2 H), 5.90–5.97 (m, 1 H, H-4), 6.07 (ddd, 1 H, J = 9.9, 3.6, 1.8, H-3), 6.91–6.95 (m, 1 H, H-1), 7.47–7.62 (m, 3 H, ArH), 7.84–7.88 (m, 2 H, ArH); ^{13}C NMR (75 MHz/$CDCl_3$) δ: 20.7, 22.3, 118.4, 127.7, 129.1, 130.0, 133.2, 134.8, 138.6, 139.8.

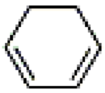
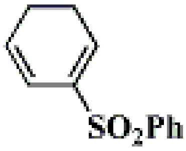
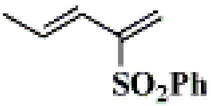
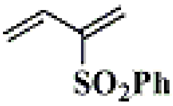
3. Discussion

This procedure[2,3; 4] illustrates a highly selective and facile method for introducing a

phenylsulfonyl group into the 2-position of 1,3-diene systems by using commercially available starting materials. The method can be applied to cyclic as well as acyclic systems giving 2-(phenylsulfonyl)-1,3-dienes. In an alternative synthesis[5]; [6] via condensation of allyl sulfone with aldehyde and subsequent acylation–elimination, the 2-(phenylsulfonyl)-1,3-dienes obtained are limited to acyclic systems.

The procedure described has been applied[2] to 4-methyl-1,3-pentadiene, 1,3-pentadiene and 1,3-butadiene (Table I). Caution must be taken in the handling of the sulfonyldiene products from the two latter dienes. They must be handled and stored in solution since they readily undergo Diels–Alder dimerization when concentrated. For the preparation of 2-(phenylsulfonyl)-1,3-pentadiene, final removal of solvent is never effected, giving a 10–50 m*M* solution of product in the preferred solvent. The solution can be stored at −20°C for several days (<5% dimerization), but the product was usually used within a few hours.

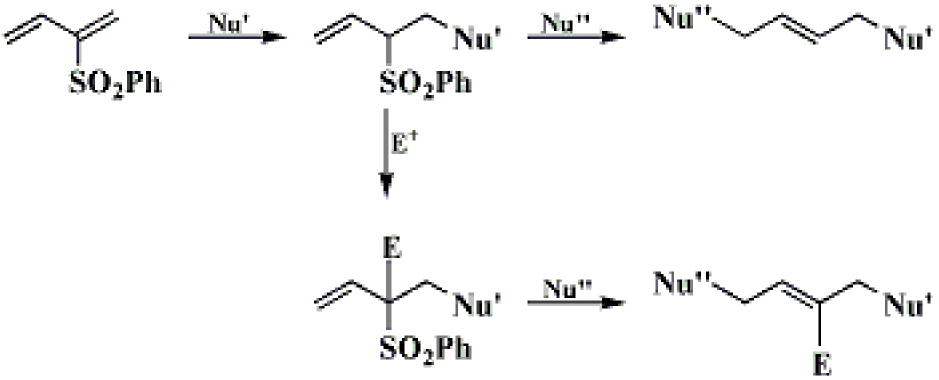
TABLE I
2-(PHENYLSULFONYL) 1,3-DIENES FROM1,3-DIENES

Olefin	Sulfonyl Diene	Yield(%)
		93[a]
		67[a]
		93[a]
		62[b]

[a]From [2] and [3,4].

[b]A modified procedure, compared to that in [2], was used. Acetone was used solvent in the first step and the reaction time was longer.

Phenylsulfonyl-1,3-dienes are versatile synthetic intermediates. They can participate in cycloaddition reactions and Michael-type additions[3,4,7,8], leading to adducts which can be further functionalized.[3,4,7,8] In the latter case the resulting allylic sulfone can be functionalized by electrophiles, nucleophiles, or both:



Electron-deficient 1,3-dienes are potentially interesting Diels–Alder dienes. In our study with different kinds of olefins, we observed that 2-(phenylsulfonyl)-1,3-dienes show a duality in their Diels–Alder cycloaddition reactions, giving [4+2] adducts with both electron-deficient and electron-rich olefins.[3,4] This dual reactivity of the 2-(phenylsulfonyl)-1,3-dienes in [4+2] cycloaddition increases the role they can play in organic synthesis.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

2-(phenylsulfonyl)-1,3-dienes

Phenylsulfonyl-1,3-dienes

calcium chloride (10043-52-4)

ethyl acetate (141-78-6)

diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

nitrogen (7727-37-9)

acetone (67-64-1)

mercury(II) chloride (7487-94-7)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

1,3-Butadiene (106-99-0)

sulfonyldiene, Sulfonyl Diene

4-methyl-1,3-pentadiene (926-56-7)

1,3-pentadiene (504-60-9)

dimethyl sulfoxide (67-68-5)

1,3-Cyclohexadiene (592-57-4)

sodium benzenesulfinate, benzenesulfinic acid, sodium salt

2-(Phenylsulfonyl)-1,3-cyclohexadiene, Benzene, (1,5-cyclohexadien-1-ylsulfonyl)- (102860-22-0)

allyl sulfone

2-(phenylsulfonyl)-1,3-pentadiene

trans-3-(Phenylsulfonyl)-4-(chloromercuri)cyclohexene

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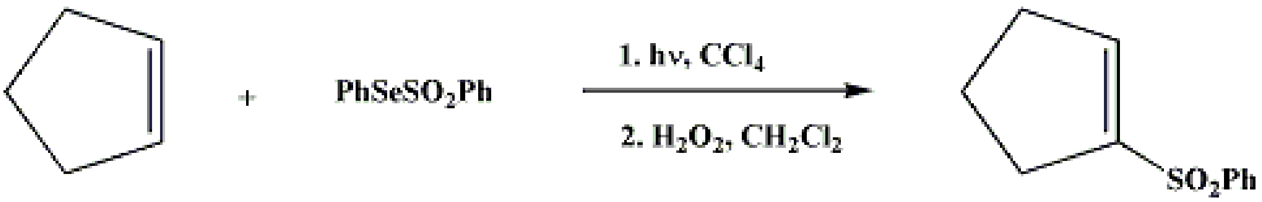
Organic Syntheses, CV 8, 543

DIENOPHILE ACTIVATION VIA SELENOSULFONATION: 1-(PHENYLSULFONYL) CYCLOPENTENE

[Benzene, (1-cyclopenten-1-ylsulfonyl)-]

$$PhSO_2NHNH_2 + PhSeO_2H \xrightarrow[25°C]{CH_2Cl_2} PhSeO_2Ph + N_2 + 2H_2O$$



Submitted by Ho-Shen Lin, Michael J. Coghlan, and Leo A. Paquette[1].
Checked by Tony Haight and Edwin Vedejs.

1. Procedure

A. *Phenyl benzeneselenosulfonate.* A 1-L, three-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar and a 250-mL addition funnel containing 17.2 g (100 mmol) of benzenesulfonyl hydrazide (Note 1) and 125 mL of dichloromethane is charged with 18.9 g (100 mmol) of phenylseleninic acid (Note 1) and 125 mL of dichloromethane. The seleninic acid is stirred at 25°C as the hydrazide slurry is added over 1 hr (Note 2). After an additional hour at 25°C, the reaction mixture is dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue is dissolved in 250 mL of hot methanol and the solution of selenosulfonate is cooled overnight at ca. 5°C in a refrigerator to induce crystallization. The yellow product that precipitates is filtered and recrystallized from methanol to afford 24.3–25.2 g (83–85%) of phenyl benzeneselenosulfonate, mp 56°C (Note 3).

B. *1-(Phenylsulfonyl)cyclopentene.* A one-necked, flat-bottomed, cylindrical flask (5 cm in diameter and 23 cm in height) equipped with a Teflon-coated magnetic stirring bar is charged in turn with phenyl benzeneselenosulfonate (15.0 g, 50.5 mmol), carbon tetrachloride (160 mL), and cyclopentene (11.1 mL, 126 mmol) (Note 4). The flask is equipped with a Friedrichs condenser and the stirred reaction mixture is blanketed with nitrogen. Following irradiation with 150-W sunlamp at room temperature for 45 min, the solution is transferred to a 500-mL, one-necked, round-bottomed flask and concentrated on a rotary evaporator.

A Teflon-coated magnetic stirring bar is placed atop the residue, which is dissolved in 140 mL of dichloromethane. The stirred solution is cooled in an ice–water bath to 0°C as

60 mL of 15% hydrogen peroxide is added dropwise via an addition funnel over 30 min (Note 5). Vigorous stirring is maintained at this temperature for 1.5 hr. The mixture is transferred to a 1-L separatory funnel, diluted with 400 mL of ethyl acetate and washed twice with 150-mL portions of water. The organic layer is dried over anhydrous magnesium sulfate, filtered, and freed of solvent under reduced pressure. The residual yellowish solid is dissolved in a small amount of dichloromethane and eluted with 5% ethyl acetate in dichloromethane through a column of 80 g of neutral alumina (activity III) to afford 8.28–9.19 g (79–87%) of colorless crystals, mp 65–66°C. ^{1}H NMR analysis shows this material to be of very high purity (Note 6).

2. Notes

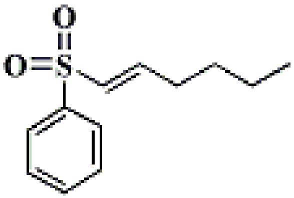
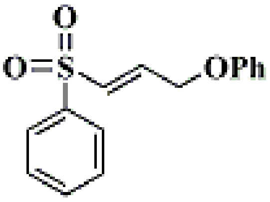
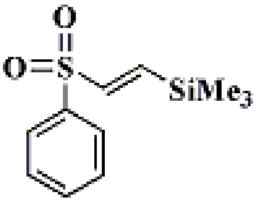
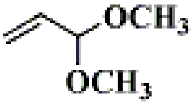
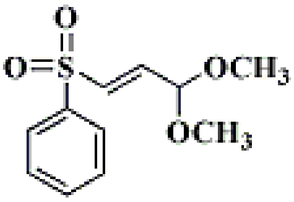
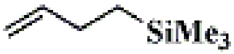
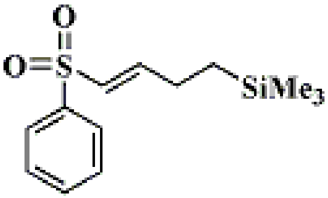
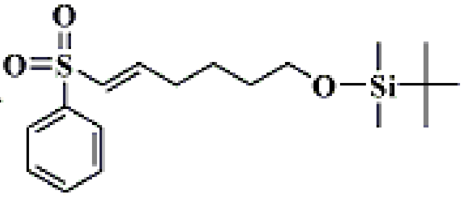
1. Benzenesulfonyl hydrazide is available from the Fluka Chemical Company, 255 Oser Avenue, Hauppauge, NY 11788.
2. This addition time ensures a slow, steady evolution of nitrogen during admixture of both slurried reactants.
3. Although this selenosulfonate is temperature- and light-sensitive, it can be stored indefinitely at refrigerator temperatures in an opaque glass container.[2]
4. Cyclopentene was purchased from the Aldrich Chemical Company, Inc. and used without further purification.
5. The peroxide is added at such a rate that the mildly exothermic oxidation–elimination reaction is well controlled. Faster addition of hydrogen peroxide can result in uncontrollable foaming.
6. The product has the following spectral properties: IR (KBr) cm^{-1}: 3060, 2960, 2920, 2840, 1610, 1580, 1440, 1300, 1150, 1085, 935, 825, 745, 710, 680, 600; ^{1}H NMR ($CDCl_3$) δ: 1.8–2.2 (m, 2 H, CH_2CH_2-CH_2), 2.2–2.6 (m, 4 H, CH_2C=), 6.6 (br s, 1 H, =CH), 7.3–8.0 (m, 5 H); *m/z* calcd. for $C_{11}H_{12}O_2S$: 208.0558. Found 208.0553. Anal. calcd. for $C_{11}H_{12}O_2S$: C, 63.43, H, 5.81. Found: C, 63.49; H, 5.83.

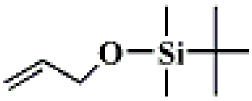
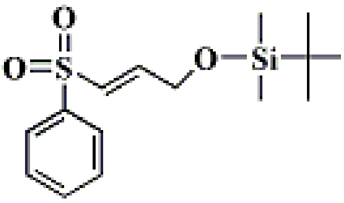
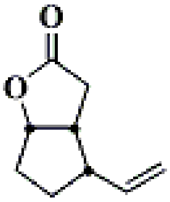
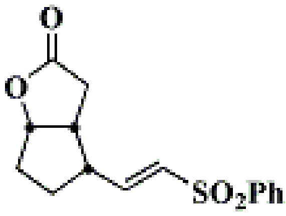
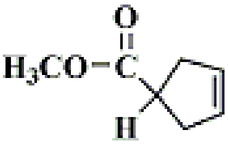
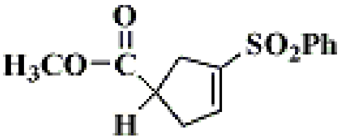
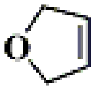
3. Discussion

Recent investigations into the chemistry of vinyl sulfones have revealed that they are versatile synthetic intermediates, serving either as dienophiles[3] or Michael acceptors.[4] Methods for the preparation of vinyl sulfones from unactivated olefins have customarily involved the catalyzed (boron trifluoride or benzoyl peroxide) addition of $PhSO_2X$ (X = Cl, Br, I, or SePh), followed by elimination of HX.[5] However, when phenylsulfonyl halides are employed, yields are variable, reactions are frequently incomplete, and the Lewis acid or free-radical catalyst employed can potentially interfere with any other functionality present. On the other hand, the selenosulfonation method, particularly when photochemically induced,[3,6] proceeds smoothly to completion in high yield and is compatible with several functional groups (Table I).[3] A further consequence of the *trans* disposition of the phenylselenenyl and phenylsulfonyl groups is invariant elimination to give the α,β-unsaturated sulfone.

TABLE I

PHOTOINDUCED SELENOSULFONATION–ELIMINATION OF OLEFINS

Olefin	Product	Yield(%)
		62
		89
		84
		73
		93
		89

		85
		72
		90
		75

This preparation is referenced from:

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethyl acetate (141-78-6)

methanol (67-56-1)

carbon tetrachloride (56-23-5)

nitrogen (7727-37-9)

hydrogen peroxide, peroxide (7722-84-1)

dichloromethane (75-09-2)

benzoyl peroxide (94-36-0)

magnesium sulfate (7487-88-9)

Cyclopentene (142-29-0)

boron trifluoride (7637-07-2)

vinyl (2669-89-8)

benzenesulfonyl hydrazide (80-17-1)

phenylsulfonyl

phenylselenenyl

phenylseleninic acid (6996-92-5)

1-(Phenylsulfonyl)cyclopentene, Benzene, (1-cyclopenten-1-ylsulfonyl)- (64740-90-5)

Phenyl benzeneselenosulfonate (60805-71-2)

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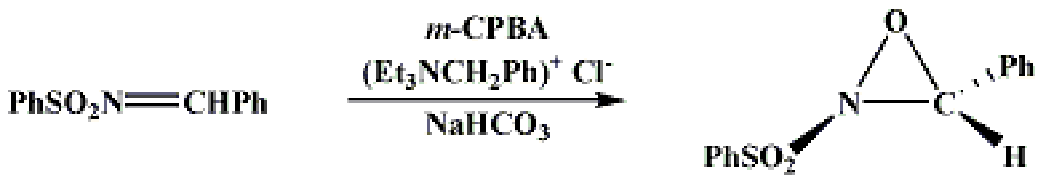
Organic Syntheses, CV 8, 546

(±)-*trans*-2-(PHENYLSULFONYL)-3-PHENYLOXAZIRIDINE

[Oxaziridine, 3-phenyl-2-(phenylsulfonyl)-]



Submitted by Lal C. Vishwakarma, Orum D. Stringer, and Franklin A. Davis[1].
Checked by James Pribish and Edwin Vedejs.

1. Procedure

A. *N-Benzylidenebenzenesulfonamide.* A 3-L, one-necked, round-bottomed flask is equipped with a mechanical stirrer (Note 1), Dean–Stark water separator (Note 2), a double-walled condenser attached to an argon gas inlet, and outlet needle connectors through a mineral oil bubbler. Into the flask are placed 150 g of Linde 5A powdered molecular sieves (Note 3), 2.0 g of Amberlyst 15 ion-exchange resin (Note 4), 157 g of benzenesulfonamide (Note 5), 1650 mL of dry toluene, and 107.5 g (1.014 mol) of freshly distilled benzaldehyde (Note 5). The reaction mixture is stirred and heated at reflux under an argon atmosphere. Water that separates during the reaction is periodically removed and refluxing is continued until water separation ceases (ca. 16 hr). The reaction mixture is cooled to room temperature without stirring and the insoluble materials are filtered through a 500-mL-capacity sintered-glass funnel of medium porosity. The residue in the filter funnel is washed thoroughly with another 700 mL of toluene in three portions. The collected filtrate is concentrated with a rotary evaporator to give a thick, yellow, oily residue that usually solidifies on standing. The residue is triturated with 800 mL of distilled pentane and the solid is broken into a powder with the aid of a flat-ended glass rod. The solid is separated by filtration through a 500-mL sintered-glass funnel of medium porosity, washed with distilled pentane (2 × 100 mL), and air-dried. The yield is 212 g (87%); mp 76–80°C (Note 6).

Although of sufficient purity for the next step, the sulfonimine can be further purified by recrystallization. In a 2-L Erlenmeyer flask containing 150 mL of ethyl acetate is dissolved, with warming, 212 g of the crude sulfonimine. After the mixture is cooled to room temperature, about 400 mL of pentane is added and the solution is allowed to stand at room temperature for 2–3 hr. The colorless crystalline product is collected by filtration, washed with 100 mL of pentane, and air-dried to give 191.5 g (78%), mp 78–80°C. The washings and filtrate are combined and the volume reduced by about one-

third using a rotary evaporator. A second crop of crystals, 20.2 g (8%), mp 75–79°C, was obtained on standing for several hours.

B. *(±)-trans-2-(Phenylsulfonyl)-3-phenyloxaziridine.* (See (Note 7).) A 5-L, three-necked flask is equipped with a mechanical stirrer and a 500-mL pressure-equalizing addition funnel. Into the flask are placed 500 mL of saturated aqueous sodium bicarbonate solution, 12.5 g (0.055 mol) of benzyltriethylammonium chloride (BTEAC), and 122.5 g (0.50 mol) of *N*-benzylidenebenzenesulfonamide dissolved in 380 mL of chloroform (Note 8). The reaction mixture is stirred vigorously at 0–5°C in an ice bath while a solution of 111.6 g (0.55 mol) of 85% *m*-chloroperoxybenzoic acid (MCPBA) dissolved in 1000 mL of chloroform is added dropwise. After the addition of the peracid, which takes about 1 hr, the reaction mixture is stirred for an additional hour at this temperature. A 3-L separatory funnel is used to separate the chloroform solution and wash it successively with 600 mL of cold water, 600 mL of aqueous 10% sodium sulfite, water (2 × 600 mL) and 250 mL of a saturated sodium chloride solution (Note 9). After the chloroform solution is dried over anhydrous potassium carbonate for 2 hr (Note 10), it is filtered and solvent is removed with a rotary evaporator, keeping the water-bath temperature below 40°C. The resulting white solid residue is washed with a small portion of pentane, dissolved in a minimum of ethyl acetate (about 700–800 mL) without heating, and filtered through fluted filter paper; 400 mL of pentane is added to the filtrate. After the white crystalline oxaziridine is cooled in the refrigerator overnight, it is separated by filtration, transferred to a 500-mL Erlenmeyer flask, washed with 200 mL of pentane, filtered, and air-dried for 1 hr. The yield is 83.5 g; mp 92–94°C. The mother liquor is reduced to about 300 mL and cooled in the refrigerator to give 36.6 g of a light-yellow solid; mp 87–90°C. This second crop is placed in a 250-mL Erlenmeyer flask and triturated with 50 mL of anhydrous ether followed by the addition of 60 mL of pentane. The oxaziridine is isolated by filtration to give 31.1 g; mp 94–95°C (dec) (Note 11) and (Note 12). The combined yield is 114.6 g (88%).

The 2-sulfonyloxaziridine can be stored in a brown bottle in the refrigerator. Storage at room temperature is potentially hazardous (Note 13).

2. Notes

1. A Teflon-coated, heavy duty, oval-shaped spin bar was used by the submitters for efficient stirring.
2. A Dean–Stark water separator equipped with a Teflon stopcock for water removal was used.
3. Linde powdered 5-Å molecular sieves were used as obtained from the supplier.
4. Amberlyst 15 ion-exchange resin is a strongly acidic, macroreticular resin purchased from Aldrich Chemical Company, Inc. The reaction fails in the absence of the acid catalysts.
5. Benzenesulfonamide, *m*-chloroperoxybenzoic acid, and benzaldehyde were obtained from the Aldrich Chemical Company, Inc. and, with the exception of

the latter, used without additional purification.

6. The ^{1}H NMR spectrum of *N*-benzylidenebenzenesulfonamide is as follows: ($CDCl_3$) δ: 7.6 (m, 6 H), 8.0 (m, 4 H), 9.05 (s, 1 H).

7. A more convenient oxidation method has since been developed.[2]

8. Analytical reagent-grade chloroform, Fisher Scientific Company, was used as obtained.

9. It is necessary to wash with a 10% $NaHCO_3$ solution, before the sodium chloride wash, if a large excess of *m*-chloroperoxybenzoic acid is used.

10. If the solution is dried for long times over potassium carbonate, decomposition of the oxaziridine sometimes occurs.

11. The ^{1}H NMR spectrum of *trans*-2-(phenylsulfonyl)-3-phenyloxaziridine is as follows: ($CDCl_3$) δ: 5.5 (s, 1 H), 7.4 (s, 5 H), 7.6–7.8 (m, 3 H), 8.05 (br d, 2 H, *J* = 7.1).

12. Careful recrystallization from ethyl acetate (saturated solution at 25°C; cool to −20°C) gave colorless crystals, ca. 20% recovery, mp 95–95.5°C.

13. Exothermic decomposition of a 500-g quantity after 2 weeks of storage at room temperature is reported by Dr. G. C. Crockett of Aldrich Chemical Company, Inc. Sufficient force was generated to shatter the container and char the oxaziridine.

3. Discussion

This procedure is representative of a general procedure for the synthesis of *trans*-2-sulfonyloxaziridines previously reported on a small scale (Table I).[3] *trans*-2-(Phenylsulfonyl)-3-(*p*-nitrophenyl)oxaziridine was prepared on a 0.16-molar scale in greater than 85% yield. The Baeyer–Villiger-type oxidation of the sulfonimine affords only the *trans*-oxaziridine. The synthesis of the sulfonimine ($PhSO_2N{=}CHPh$) directly from the sulfonamide and aromatic aldehyde is described here. This modification avoids use of the intermediate diethyl acetal used in earlier preparations of these compounds.[3]; [4]

2-Sulfonyloxaziridines are useful aprotic and neutral oxidizing reagents that, in general, afford greater selectivity for oxidations than do peracids. 2-Sulfonyloxaziridines have been employed in the oxidation of sulfides to sulfoxides,[5] disulfides to thiosulfinates,[5] selenides to selenoxides,[6] thiols to sulfenic acids (RSOH),[7] organometallic reagents to alcohols and phenols,[8] ketone and ester enolates to α-hydroxy carbonyl compounds,[9] in the epoxidation of alkenes,[10] and in the conversion of chiral amide enolates to optically active α-hydroxy carboxylic acids (93–99% ee).[11,12] These reagents can be used in the study of reactive oxidation intermediates and for mechanistic studies of oxygen-transfer reactions because of the ease with which the course of the oxidation can be monitored by proton NMR.

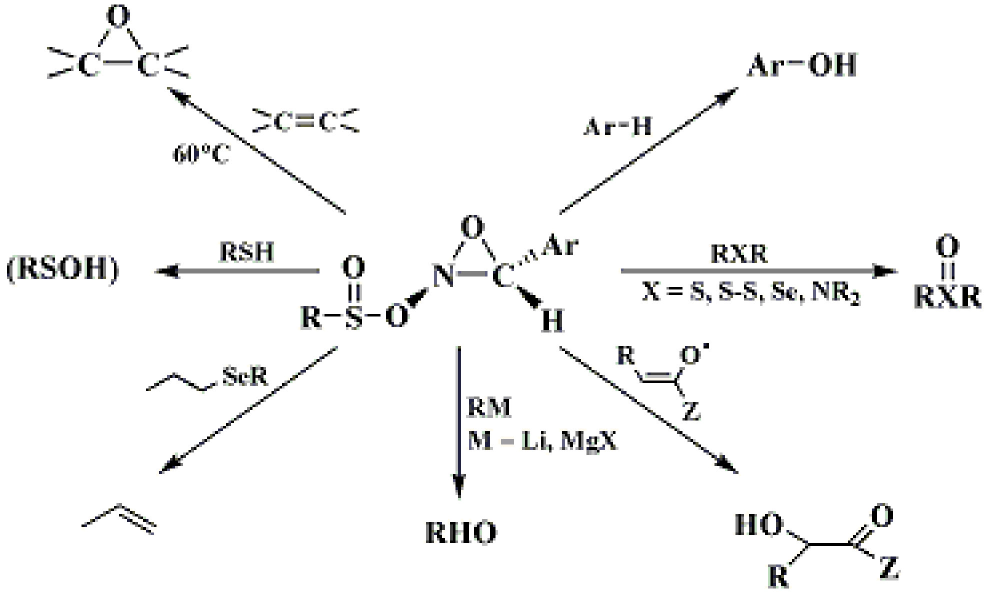
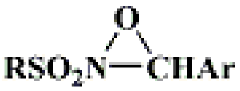
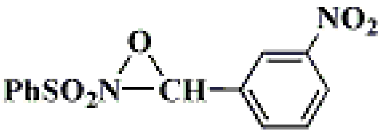
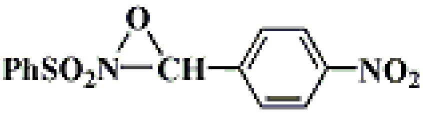
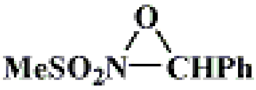


TABLE I

PREPARATION OF2-SULFONYLOXAZIRIDINES3[a,b]

	Yield (%)	mp (°C, dec)
 R = Ph, Ar = 3-NO_2Ph	83	113–115
 R = Ph, Ar = 4-NO_2Ph	80	134–136
 R = Me, Ar = Ph	85	59–61

R = $PhCH_2$, Ar = Ph	90	118–119

Oxidation of chiral sulfonimines ($R^*SO_2N{=}CHAr$)[13] and chiral sulfamylimines ($R^*RNSO_2N{=}CHAr$)[14] affords optically active 2-sulfonyloxaziridines and 2-sulfamyloxaziridines, respectively. These chiral, oxidizing reagents have been used in the asymmetric oxidation of sulfides to sulfoxides (15–68% ee),[13,14,15] selenides to selenoxides (8–9% ee),[16] enolates to α-hydroxycarbonyl compounds (8–37% ee),[17] and in the asymmetric epoxidation of alkenes (15–40% ee).[18] The synthetic applications of these reagents has been reviewed.[19]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

m-chloroperoxybenzoic acid (MCPBA)

Linde 5A

sulfonimine

benzyltriethylammonium chloride (BTEAC)

2-sulfonyloxaziridine

trans-2-sulfonyloxaziridines

diethyl acetal

2-Sulfonyloxaziridines

2-sulfamyloxaziridines

potassium carbonate (584-08-7)

ethyl acetate (141-78-6)

ether (60-29-7)

sodium sulfite (7757-83-7)

chloroform (67-66-3)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

benzaldehyde (100-52-7)

toluene (108-88-3)

Pentane (109-66-0)

Benzenesulfonamide (98-10-2)

oxaziridine, trans-oxaziridine

argon (7440-37-1)

Oxaziridine, 3-phenyl-2-(phenylsulfonyl)-, trans-2-(phenylsulfonyl)-3-phenyloxaziridine, (±)-trans-2-(Phenylsulfonyl)-3-phenyloxaziridine (63160-13-4)

m-chloroperoxybenzoic acid (937-14-4)

N-Benzylidenebenzenesulfonamide (13909-34-7)

trans-2-(Phenylsulfonyl)-3-(p-nitrophenyl)oxaziridine

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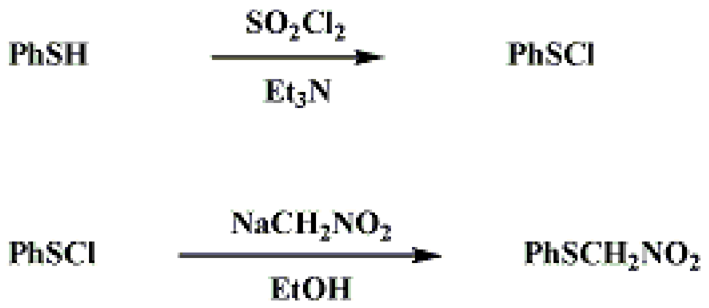
Organic Syntheses, CV 8, 550

(PHENYLTHIO)NITROMETHANE

[Benzene, [(nitromethyl)thio]-]



Submitted by Anthony G. M. Barrett, Dashyant Dhanak, Gregory G. Graboski, and Sven J. Taylor[1].
Checked by Zhou Zu-liang and Ekkehard Winterfeldt.

1. Procedure

Caution: Thiophenol (stench!!) and sulfuryl chloride are highly toxic. Steps A and B should be carried out in an efficient fume hood while wearing gloves and adequate eye protection. Sodium nitromethylate is explosive when dry and should be handled only as a slurry.

A. *Phenylsulfenyl chloride.* A 250-mL, three-necked, round-bottomed flask, fitted with a nitrogen inlet, a pressure-equalizing 125-mL dropping funnel, and a magnetic stirring bar, is charged with thiophenol (21 mL) (Note 1), dry triethylamine (0.25 mL), and dry pentane (100 mL) (Note 2) under a blanket of nitrogen. The remaining neck of the flask is stoppered and the nitrogen is allowed to sweep gently through the flask and out of the pressure-equalizing dropping funnel. The flask and its contents are cooled to 0°C with an ice bath and stirring is begun. The dropping funnel is charged with sulfuryl chloride (19 mL) (Note 1). The sulfuryl chloride is added dropwise over a 1-hr period to the chilled thiophenol solution with stirring. During this addition, a thick layer of white solid forms. It gradually dissolves as it is broken down. After the addition is complete, the ice bath is removed and the mixture is allowed to stir for 1 hr longer while slowly warming to room temperature. During the course of the addition and subsequent stirring, the clear, pale-yellow solution becomes dark orange-red. The dropping funnel is replaced with an outlet adapter connected to a vacuum pump and the nitrogen inlet is exchanged for a ground glass stopper. The pentane and excess sulfuryl chloride are removed under reduced pressure at room temperature. The outlet adapter is replaced by a short-path distillation apparatus adapted for use under reduced pressure. The oily red residue is distilled to give phenylsulfenyl chloride as a blood-red liquid (26 g, 87%), bp 41–42°C (1.5 mm) (Note 3). This compound is stored under nitrogen until used in Part B (Note 4).

B. *(Phenylthio)nitromethane.* Freshly cut sodium metal (4.8 g) is added to absolute ethanol (100 mL) in a 500-mL Erlenmeyer flask with a ground-glass joint and allowed to react until the metal is completely consumed (Note 5). To this mixture is added a solution of nitromethane (12 g) (Note 6) in absolute ethanol (100 mL) with swirling. The phenylsulfenyl chloride (prepared earlier) is quickly poured into a 1000-mL, three-necked, round-bottomed flask fitted with a mechanical stirrer, a nitrogen inlet/outlet adapter, and a calcium chloride drying tube, and is diluted with dry tetrahydrofuran (THF) (250 mL) (Note 7). Stirring is begun, the drying tube is removed, and the sodium nitromethane–ethanol slurry is added quickly in one portion to the THF solution (Note 8). The deep-red solution immediately turns yellow and stirring is continued for a further 10 min. The reaction mixture consists of solid and liquid. It is dissolved in 200 mL of a 1 *N* sodium hydroxide solution and poured into a 1000-mL separatory funnel. Dichloromethane (200 mL) is added (Note 9), the aqueous layer (lower layer) is separated, and the organic layer further extracted with 1 *N* sodium hydroxide (2 × 100 mL) (Note 10). The combined aqueous layers are washed with dichloromethane (500 mL) and acidified to pH 3 using 1 *N* hydrochloric acid. The brown organic layer that appears is separated, diluted with 50 mL of dichloromethane, dried over magnesium sulfate, filtered, and concentrated at water aspirator pressure to give 18–19 g (60–65%) of crude (phenylthio)nitromethane as an orange-red oil. This material is of sufficient purity for many purposes. Further purification may be effected by distilling at reduced pressure to give (phenylthio)nitromethane (14 g, 50%) as a pale-yellow oil, bp 85–95°C at 0.05 mm (Note 11),(Note 12),(Note 13),(Note 14).

2. Notes

1. Thiophenol (97%) and sulfuryl chloride (97%) were obtained from the Aldrich Chemical Company, Inc. and used without further purification.
2. Both pentane and triethylamine were obtained from the Aldrich Chemical Company, Inc. Before use they were dried over sodium wire and distilled from fresh sodium wire onto Linde 4A molecular sieves under an atmosphere of nitrogen.
3. The submitters report isolated yields of phenysulfenyl chloride of 82–92%.
4. Phenylsulfenyl chloride decomposes rapidly in moist air, and should be handled and stored under dry nitrogen.
5. The reaction is exothermic; cooling in an ice bath may be necessary to prevent the ethanol from refluxing.
6. Nitromethane was obtained from the Eastman Kodak Chemical Company and used without further purification.
7. Tetrahydrofuran was obtained from the Baker Chemical Company and distilled from sodium benzophenone ketyl before use.
8. The submitters preferred to transfer the phenylsulfenyl chloride via cannula. The sodium nitromethane–ethanol slurry is added by attaching the Erlenmeyer flask containing it to the reaction flask via an angle adapter and then simply inverting the Erlenmeyer flask. In either method additional absolute ethanol may

be necessary to complete the latter addition.
9. Dichloromethane was purchased from the Baker Chemical Company and used without further purification.
10. The checkers used sodium hydroxide (3 × 100 mL) in one run, which improved the yield by about 5%.
11. Gases are evolved during the distillation.
12. A pump of sufficient capacity must be used to maintain reduced pressure of at least 0.10 mm or extensive decomposition results.
13. (Phenylthio)nitromethane has the following properties: ^{1}H NMR ($CDCl_3$, 90 MHz) δ: 5.45 (s, 2 H, CH_2), 7.25–7.5 (m, 5 H, aromatic); IR (film) cm^{-1}: 3060 m, 3025 m, 2960 m, 2905 m, 1960 w, 1885 w, 1810 w, 1550 s, (NO_2), 1485 s, 1475 s, 1440 s, 1390 s, 1355 s, (NO_2), 1260 s, 1185 s, 1070 m, 1025 m, 1005 w, 900 m, 805 m, 745 s, 690 s.
14. *Storage and handling of (phenylthio)nitromethane*. Although (phenylthio)-nitromethane will slowly decompose at room temperature, the submitters have found that the compound may be stored essentially unchanged in a freezer at –25°C. Since it has an unpleasant odor, it is best handled in a well-ventilated hood; any spillage may be cleaned up with commercial bleach.

3. Discussion

(Phenylthio)nitromethane is a convenient reagent for the synthesis of derivatives of 3-methylfuran,[2] for the preparation of α-substituted phenylthio esters via the homologation of aldehydes,[3] and for the preparation of bicyclic β-lactams from monocyclic precursors.[4] This method is an adaption of Seebach's procedure.[5] Alternatively, (phenylthio)nitromethane may be prepared from the nitration of the dianion derived from (phenylthio)acetic acid[2] or from ethyl nitroacetate and *N*-(phenylthio)morpholine.[6] Neither of these procedures are as convenient on a large scale.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 82
- Org. Syn. Coll. Vol. 9, 207

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium benzophenone ketyl

phenysulfenyl chloride

phenylthio esters

sodium nitromethane

ethanol (64-17-5)

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

sodium hydroxide (1310-73-2)

nitrogen (7727-37-9)

sulfuryl chloride (7791-25-5)

sodium (13966-32-0)

Pentane (109-66-0)

Nitromethane (75-52-5)

dichloromethane (75-09-2)

Thiophenol (108-98-5)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

triethylamine (121-44-8)

ethyl nitroacetate (626-35-7)

3-Methylfuran (930-27-8)

Phenylsulfenyl chloride (931-59-9)

(Phenylthio)nitromethane, Benzene, [(nitromethyl)thio]-, (phenylthio)-nitromethane (60595-16-6)

Sodium nitromethylate

(phenylthio)acetic acid (103-04-8)

N-(phenylthio)morpholine

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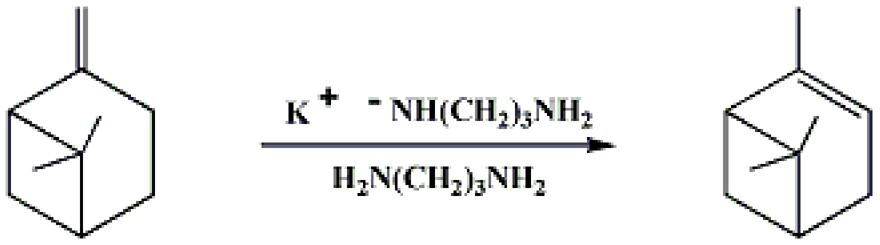
Organic Syntheses, CV 8, 553

(–)-α-PINENE BY ISOMERIZATION OF (–)-β-PINENE

$$KH + H_2N(CH_2)_3NH_2 \longrightarrow K^+ \; ^-NH(CH_2)_3NH_2 + H_2$$



(-) - β - pinene (-) - α - pinene

Submitted by Charles A. Brown[1] and Prabhakav K. Jadhav[2].
Checked by Janet W. Grissom and Edwin Vedejs.

1. Procedure

Caution! Potassium hydride[3] is highly reactive toward water. Material separated from protective oil or solvent should not be exposed to air, but should be kept under argon or nitrogen.

A. *Potassium 3-aminopropylamide (KAPA).* To a bottle of 22.4% potassium hydride in oil (Note 1) is added a Teflon-covered magnetic stirring bar. The contents are agitated by first shaking and then stirring until a visually uniform dispersion is attained. Then 17.8 g (0.10 mol) of the dispersion is transferred (Note 2) to an oven-dried 250-mL flask, fitted with a magnetic stirring bar (Note 3) and (Note 4), a septum-capped inlet, and an adapter connected to a pressure-relief bubbler (mercury or oil). The apparatus is purged with dry argon or nitrogen (Note 5). The flask is charged with 100 mL of dry pentane or other volatile hydrocarbon solvent, and the contents are stirred thoroughly. The stirrer is stopped to allow the potassium hydride to settle, assisted by gentle tapping on the flask, and the supernatant liquid is drawn off with a double-ended needle under inert-gas pressure. This procedure is repeated twice to complete removal of the oil. Residual solvent is then removed in a stream of dry gas. To the dry potassium hydride powder is added rapidly 100 mL of dry 3-aminopropylamine (Note 6). *Caution! Hydrogen gas evolution.* Hydrogen evolution commences immediately (Note 7) and subsides after 1.5–2 hr. Formation of KAPA is complete at this time.

B. *(–)-α-Pinene.* Concurrently, a 3-L, three-necked, round-bottomed flask (fitted with a septum-capped adapter, gastight mechanical stirrer, and a tube adapter connected to a gas bubbler) is purged with inert gas (Note 3) and (Note 4). The flask is then charged with 1588 mL of (–)-β-pinene (Note 8). To the vigorously stirred pinene at 25°C is added the KAPA (0.1 mol) prepared in part A, using a double-ended needle, over 15

min. The reaction mixture is stirred for 24 hr at 25°C and is then quenched by addition of 100 mL of ice-cold water. The reaction mixture is transferred to a separatory funnel, washed with two 100-mL portions of water, and dried with anhydrous calcium chloride. The crude pinene is decanted from the calcium chloride through a plug of glass wool and distilled at reduced pressure from lithium aluminium hydride (Note 8) and (Note 9). The yield of (−)-α-pinene, bp 72–73°C (46 mm), $[\alpha]_D^{23}$ −47.45° (neat, 92% ee), is 1264 g (93%). The chemical and isomeric purity is 99% by GLC (Note 10) and (Note 11).

2. Notes

1. Potassium hydride in oil is available from Aldrich Chemical Company, Inc. and Alfa Products, Morton/Thiokol, Inc. Material from both sources has been used successfully in this preparation.
2. Potassium hydride dispersion is transferred with a 20- or 30-mL syringe fitted with a 16-gauge needle. The plunger should be lubricated with mineral oil. The density of the potassium hydride dispersion is nearly 1.0 g/mL. Alternatively, a glove box or bag may be used for direct weighing.
3. Teflon is attacked superficially by KAPA with darkening of the surface and of the solution in contact with it. The reactivity of the KAPA is not affected. Polyethylene is not affected at all.
4. All equipment should be dried in an oven and cooled in a desiccator or under dry nitrogen.
5. From this point until the quenching of the final reaction operations must be carried out under argon or nitrogen.
6. For this reaction the amine (Aldrich Chemical Company, Inc.) from a freshly opened bottle is dried by distillation from active powdered calcium hydride. Addition over 1 min or less is required to avoid excessive foaming, which has been observed when slow or dropwise addition is used. Older samples of amine that contain water should be predried overnight with potassium hydroxide.
7. A cool (10–15°C) bath should be available to moderate the reaction if foaming occurs. Some samples of potassium hydride that have been exposed to air react sluggishly. Here application of a warm (35–40°C) bath is helpful.
8. The (−)-β-pinene used in this procedure was obtained from Glidden Organics. It was purified before use by distillation from lithium aluminium hydride; small increments of hydride were added to pinene stirred under nitrogen until an excess was present as determined by observing gas evolution on addition of a few drops of methanol to an aliquot of the slurry. The purified material had $[\alpha]_D^{23}$ −21.0° (neat, 92.1% ee). GLC analysis (10% SE-30 on Chromosorb W, 100°C) showed only one peak. Use of dry, peroxide-free pinene is critical to the success of this procedure. The (−)-β-pinene is also available from Aldrich Chemical Company, Inc. In separate experiments, (−)-β-pinene samples from Aldrich Chemical Company, Inc. and Fluka A. G. were used successfully. The checkers used Aldrich β-pinene and obtained product with $[\alpha]_D^{30}$ −46.3°.
9. Distillation from lithium aluminum hydride serves to remove completely all

traces of water and amine as is required for preparation of chiral organoboranes.
10. For GLC conditions, see Note 8.
11. The reaction has been carried out at 0°C on a 0.33-mol scale using a vigorous magnetic stirrer for 4 hr.[4] Under these conditions the isomeric purity was >99.5%. Because the reaction takes place in a two-phase system, the reaction rate appears to be stirrer-dependent and vigorous agitation is essential.

3. Discussion

β-Pinene is an important auxiliary for directed chiral syntheses. It has been used for preparation of mono- and diisopinocampheylborane[5] B-allyldiisopinocampheylborane,[6] B-pinanyl-9-bora[bicyclo]nonane,[5] *cis*-pinanediol,[7] and 2-hydroxypinan-3-one.[8]

Although both enantiomers of α-pinene occur in nature, only the (+)-enantiomer is commercially available with acceptable enantiomeric purity (92–95%). The (–)-enantiomer is readily available only with 80–85% enantiomeric purity, which is impractical for use in asymmetric syntheses via organoboranes.

Fortunately, (–)-β-pinene of high enantiomeric purity (90–95%) is commercially available and can be isomerized to the thermodynamically more stable (–)-α-pinene. The isomerization has been achieved by use of several acidic, basic, and metal catalysts.[4] These methods have various limitations such as partial racemization, low chemical yields, and vigorous reaction conditions. The current procedure is based on our earlier report using KAPA at 0°C on a much smaller scale.[4] The change to 25°C from 0°C was made to simplify the reaction conditions by eliminating the need for external cooling. The reaction has also been carried out on somewhat reduced scale (1–5 mol) using a magnetic stirrer in place of the mechanical stirrer.

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Appendix

Compounds Referenced (Chemical Abstracts Registry Number)

amine

(−)-α-PINENE

(−)-β-PINENE

Potassium 3-aminopropylamide (KAPA)

20- or 30-mL syringe

mono- and diisopinocampheylborane

calcium chloride (10043-52-4)

methanol (67-56-1)

hydrogen (1333-74-0)

nitrogen (7727-37-9)

mercury (7439-97-6)

potassium hydroxide (1310-58-3)

Pentane (109-66-0)

lithium aluminum hydride, lithium aluminium hydride (16853-85-3)

hydride

calcium hydride (7789-78-8)

argon (7440-37-1)

potassium hydride (7693-26-7)

α-pinene

pinene, β-pinene (18172-67-3)

3-aminopropylamine (109-76-2)

B-allyldiisopinocampheylborane

2-hydroxypinan-3-one

cis-pinanediol

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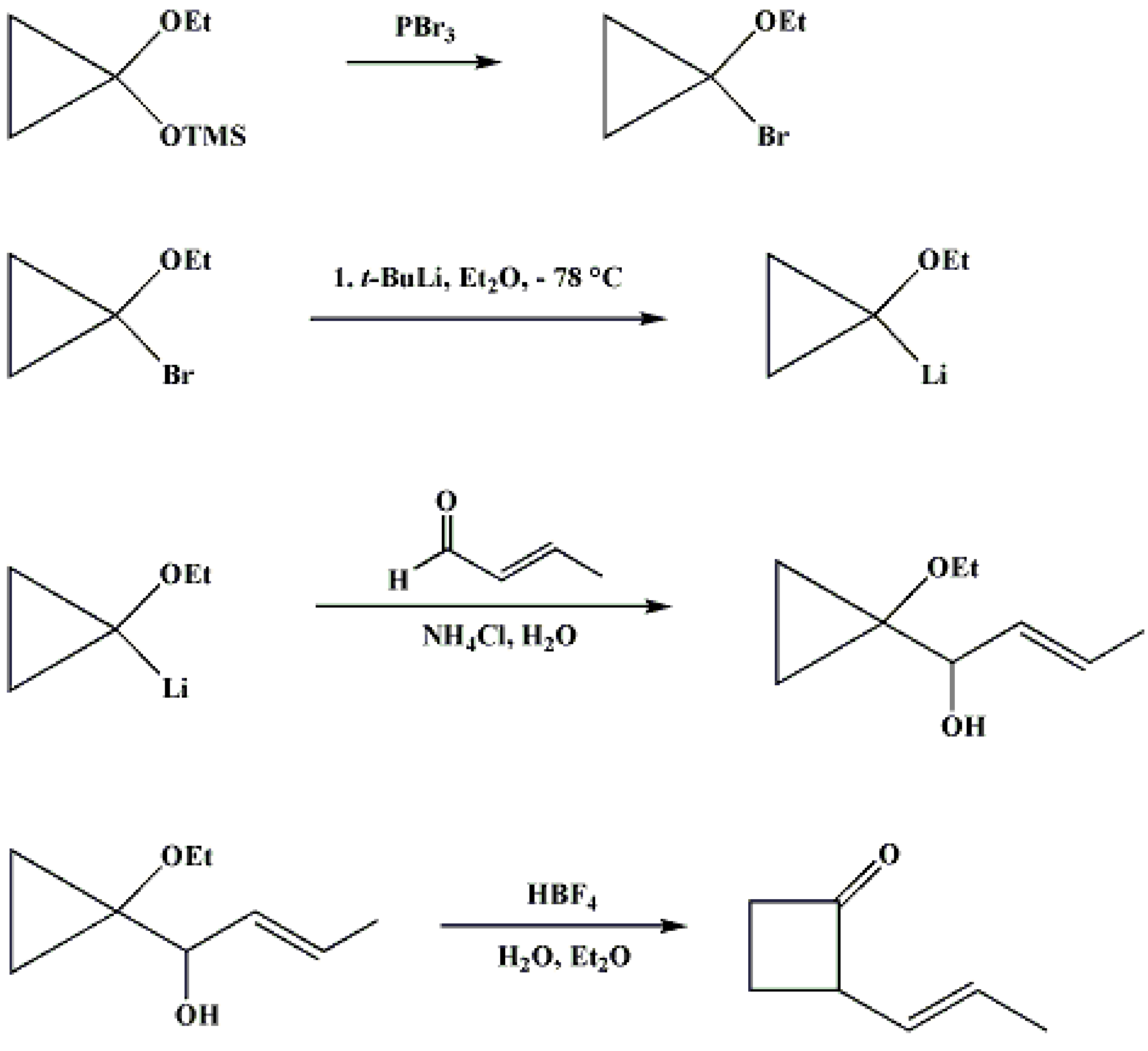
Organic Syntheses, CV 8, 556

SYNTHESIS OF CYCLOBUTANONES VIA 1-BROMO-1-ETHOXYCYCLOPROPANE: (*E*)-2-(1-PROPENYL) CYCLOBUTANONE

[Cyclobutanone, 2-(1-propenyl)-, (*E*)-]



Submitted by Scott A. Miller and Robert C. Gadwood[1].
Checked by Jeffrey A. McKinney and Leo A. Paquette.

1. Procedure

A. *1-Bromo-1-ethoxycyclopropane.*[2] A 500-mL, round-bottomed flask equipped with a magnetic stirring bar and a calcium sulfate drying tube is charged with 84.1 g (0.483 mol) of 1-ethoxy-1-trimethylsiloxycyclopropane.[3] Phosphorus tribromide (35.6 mL, 103 g, 0.379 mol) (Note 1) is added at room temperature with brisk stirring, followed

by a catalytic amount (0.5 ml) of 48% aqueous hydrobromic acid (Note 2). The resulting clear, pale-yellow solution is stirred for 6 hr (Note 3). After the stirring bar is removed, the reaction mixture is distilled by Kugelrohr apparatus at aspirator vacuum (10 mm) from 25 to 70°C to afford crude 1-bromo-1-ethoxycyclopropane (Note 4) and (Note 5). The crude product is dissolved in 300 mL of pentane in a 1-L Erlenmeyer flask and the resulting solution is chilled to −20°C in a dry ice–ethanol: water (30 : 70) bath. While the temperature of the solution is maintained below 25°C, 300 mL of saturated, aqueous sodium carbonate is carefully added (Note 6). The layers are carefully shaken and separated, and the aqueous phase is extracted with 100-mL of pentane. The organic layer is dried over magnesium sulfate, filtered, and most of the pentane is removed by distillation through a 15-cm Vigreux column at atmospheric pressure. The residue is transferred to a smaller distillation flask and distilled through the same column under aspirator vacuum to afford 47.0–57.6 g (59–72%) of 1-bromo-1-ethoxycyclopropane as a colorless liquid (bp 35–43°C, 10 mm) (Note 7) and (Note 8).

Caution! Because of the relatively large amount of pyrophoric tert-butyllithium involved, the following preparation should be performed in a hood behind a safety shield.

B. *(E)-1-Ethoxy-1-(1-hydroxy-2-butenyl)cyclopropane.* A 1-L, three-necked flask is equipped with a gas inlet adapter, a septum, a 250-mL graduated addition funnel capped with a septum, and a magnetic stirring bar (Note 9). The flask is charged with 500 mL of anhydrous diethyl ether (Note 10) and cooled to −78°C under a nitrogen atmosphere. The addition funnel is charged with 177 mL (19.2 g, 0.30 mol) of *tert*-butyllithium (Note 11), transferred from the reagent bottle via a stainless-steel cannula under positive nitrogen pressure. The *tert*-butyllithium is added dropwise to the stirred diethyl ether over approximately 20 min while the cooling bath is maintained at −78°C. After the addition is complete, 26.4 g (0.16 mol) of freshly prepared 1-bromo-1-ethoxycyclopropane is added to the reaction over about 5 min by syringe. The resulting cloudy, colorless, or light-yellow reaction mixture is stirred for 20–25 min, and a solution of 7.0 g (0.10 mol) of crotonaldehyde (Note 12) in 50 mL of anhydrous diethyl ether (chilled to −78°C) is added via a stainless-steel cannula under positive nitrogen pressure. The reaction mixture is stirred at −78°C for an additional 10 min, warmed to 0°C in an ice bath, and carefully quenched with 100 mL of saturated, aqueous ammonium chloride. The layers are shaken and separated and the aqueous phase is extracted with 100 mL of diethyl ether. The combined organic layers are dried over magnesium sulfate and filtered. After the crude adduct is concentrated on a rotary evaporator, it is filtered through a 10-cm pad of silica gel (Note 13) in a sintered-glass funnel with 10% ethyl acetate in hexane. After concentrating again on a rotary evaporator, the crude adduct is obtained as a pale-yellow oil (14.2–15.6 g) (Note 14). This material is not further purified, but is used directly in the next reaction.

C. *(E)-2-(1-Propenyl)cyclobutanone.* To a 1-L, round-bottomed flask equipped with a

magnetic stirring bar is added 15.3 g (0.098 mol) of (*E*)-1-ethoxy-1-(1-hydroxy-2-butenyl)cyclopropane, 500 mL of reagent-grade diethyl ether, and 6.6 mL (4.3 g, 0.049 mol) of 48% aqueous fluoboric acid (Note 15). After the reaction mixture is stirred for 15 min at room temperature, it is quenched with 60 mL (0.06 mol) of 1 *M* aqueous sodium carbonate. The layers are carefully shaken and separated, and the organic phase is washed with three 125-mL portions of water (Note 16). The combined aqueous layers are extracted with 100 mL of diethyl ether and the organic phase is dried over magnesium sulfate and filtered. The filtrate is concentrated on a rotary evaporator without external heating and the residue is distilled through a 10-cm Vigreux column under aspirator vacuum. The product, 7.2–8.3 g (66–75% yield from crotonaldehyde), is obtained as a colorless oil, bp 61–65°C (10 mm) (Note 17).

2. Notes

1. Phosphorus tribromide was obtained from the Aldrich Chemical Company, Inc. and used without further purification.
2. The addition of a catalytic amount of hydrobromic acid was frequently found to be necessary to initiate the reaction, especially if the phosphorus tribromide is of high purity. On addition of the hydrobromic acid, the reaction warms noticeably.
3. The course of the reaction is most conveniently followed by ^{1}H NMR analysis of a drop of the reaction mixture in carbon tetrachloride. The downfield quartet of the starting ketal (3.52 ppm) is replaced by a clean quartet at 3.62 ppm from the product. The checkers have found by this technique that reaction is complete in much less than 6 hr.
4. The crude product thus obtained also contains bromotrimethylsilane and hydrobromic acid.
5. *Caution! After distillation the Kugelrohr apparatus should first be cooled and then carefully vented to an atmosphere of nitrogen since traces of elemental phosphorus may be present in the pot residue and may ignite if exposed to air while still hot.*
6. This step neutralizes the hydrobromic acid and bromotrimethylsilane present in the product. Therefore, addition of the aqueous sodium carbonate solution is exothermic and causes vigorous carbon dioxide evolution. Cooling at this stage helps prevent hydrolysis of the product.
7. A low-boiling, silicon-containing fraction is also collected below 37°C (28 mm). The presence of a singlet at 0.10 ppm in the ^{1}H NMR of the product indicates contamination by this low-boiling fraction. Small amounts of this impurity do not seem to interfere in subsequent reactions of the 1-bromo-1-ethoxycyclopropane.
8. 1-Bromo-1-ethoxycyclopropane is relatively unstable at room temperature, but can be stored for several months at –20°C with only slight decomposition. Spectral data for 1-bromo-1-ethoxycyclopropane are as follows: IR (neat) cm^{-1}: 3100 (w), 2985 (s), 2935 (m), 2885 (m), 1445 (m), 1300 (s), 1160 (s), 1060 (s),

795 (s); ^{1}H NMR (CCl_4) δ: 1.17 (m, 7 H), 3.53 (q, 2 H, *J* = 8); MS (15 eV), *m/e* 164/166 (M^+), 136/138 (base), 85, 57.

9. The glassware was dried in an oven overnight at 110°C and assembled while hot under nitrogen flow.

10. Diethyl ether was dried by distillation from sodium metal/benzophenone.

11. *Caution! tert-Butyllithium is extremely pyrophoric and should be handled on a large scale only by experienced personnel.* *tert*-Butyllithium was obtained from the Aldrich Chemical Company, Inc. as a 1.7 *M* solution in pentane. In general, this material was used as received without titration.

12. Crotonaldehyde was obtained from The Matheson Company, Inc., and is also available (≥99% grade) from the Aldrich Chemical Company, Inc.

13. Merck Silica Gel 60 (230–400 mesh) was obtained from the Aldrich Chemical Company, Inc. Filtration through silica gel removes residual inorganic salts (mostly lithium chloride), which may interfere in the subsequent rearrangement step.

14. Spectral data for (*E*)-1-ethoxy-1-(hydroxy-2-butenyl)cyclopropane are as follows: ^{1}H NMR ($CDCl_3$) δ: 0.68 (m, 4 H), 1.12 (t, 3 H, *J* = 6), 1.64 (d, 3 H, *J* = 5), 2.46 (s, 1 H), 3.54 (m, 2 H), 4.15 (d, 1 H, *J* = 6), 5.52 (m, 2 H). Occasionally, a minor impurity is formed as a result of the addition of *tert*-butyllithium to crotonaldehyde (singlet at 0.89 ppm in the ^{1}H NMR). This side reaction occurs because of the presence of unreacted *tert*-butyllithium and is best avoided by using the indicated ratio of *tert*-butyllithium to 1-bromo-1-ethoxycyclopropane. The checkers were unable to remove this impurity by fractional distillation.

15. Fluoboric acid was obtained as a 48 wt% aqueous solution from the Aldrich Chemical Company, Inc. On the basis of its density, this solution was calculated to be approximately 7.4 *M* in HBF_4. The checkers used 5.4 mL (0.049 mol) of 60% fluoboric acid.

16. Washing with water helps to remove the ethanol generated in the course of the rearrangement. For higher-boiling cyclobutanones, where the ethanol can easily be removed during distillation, this step is unnecessary.

17. Spectral data for (*E*)-2-(1-propenyl)cyclobutanone are as follows: IR (CCl_4) cm^{-1}: 2960 (s), 1780 (s), 1660 (w), 1450 (m); ^{1}H NMR (CCl_4) δ: 1.62 (m, 3 H), 2.17 (m, 2 H), 2.88 (m, 2 H), 3.73 (m, 1 H), 5.37 (m, 2 H). The product was contaminated by an alcoholic impurity to the extent of 6–11%.

3. Discussion

Cyclobutanones have attained a position of considerable synthetic importance in recent years. In addition to being important synthetic targets themselves, they serve as useful precursors of five-,[4] six-,[5] and eight-membered[6] rings, as well as of a variety of highly functionalized acyclic fragments.[7,8]

In general, cyclobutanones are synthesized by either ketene cycloadditions or by ring expansions of cyclopropyl precursors. For the synthesis of simple α-substituted monocyclic cyclobutanones, the latter method is usually employed, and a variety of

approaches have been used to prepare the required cyclopropyl intermediates.

Vinylcyclopropanols have been prepared by the addition of alkenyl Grignard reagents to a variety of cyclopropanone equivalents.[9] On treatment with acid, the vinylcyclopropanols rearrange to α-substituted cyclobutanones. Alternatively, a variety of α-heteroatom-substituted cyclopropyllithium reagents have been developed. These react with aldehydes and ketones to afford cyclopropylcarbinols that also rearrange to cyclobutanones under acid catalysis.[8,10,11] Finally, vinylcyclopropanols and cyclopropylcarbinols have been prepared by the cyclopropanation of enol silyl ethers and allylic alcohols.[12]

There are several advantages to the procedure described here for the synthesis of α-substituted cyclobutanones. The preparation of 1-bromo-1-ethoxycyclopropane is convenient and can be accomplished in good overall yield in only two steps from commercially available ethyl 3-chloropropionate. Metalation of 1-bromo-1-ethoxycyclopropane is rapid and reproducible on a large scale, and (1-ethoxy) cyclopropyllithium adds cleanly to a wide variety of ketones and aldehydes. Finally, rearrangement of the cyclopropylcarbinol adducts occurs smoothly and in high yield.

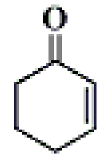
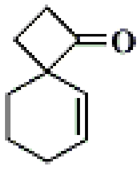
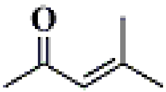
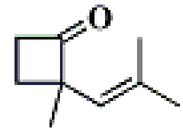
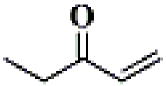
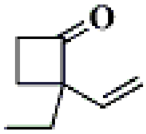
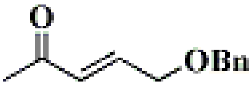
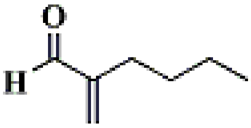
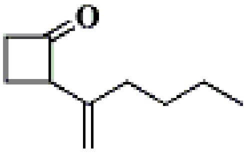
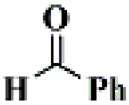
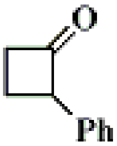
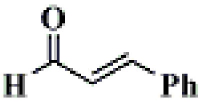
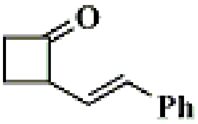
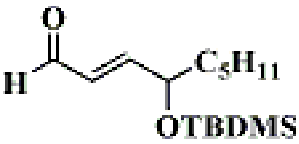
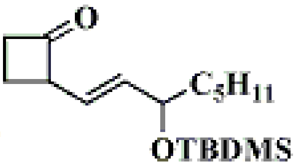
The preparation of 1-bromo-1-ethoxycyclopropane is based on a literature report of the synthesis of 1-bromo-1-methoxycyclopropane from 1-methoxy-1-trimethylsiloxycyclopropane using phosphorus tribromide in pyridine.[13] In our hands, reaction of 1-ethoxy-1-trimethylsiloxycyclopropane under these conditions afforded none of the bromide.

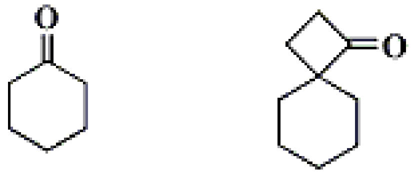
The title cyclobutanone has been prepared previously by the addition of (1-phenylthio) cyclopropyllithium to crotonaldehyde followed by rearrangement with anhydrous stannic chloride in methylene chloride.[11] However, in our experience, the procedure described here is much more convenient and reproducible on a large scale.

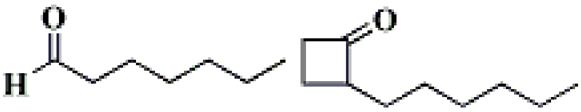
As shown in Table I, a wide variety of α-substituted cyclobutanones have been prepared by the general method described here.[14] The time required for rearrangement of the intermediate cyclopropylcarbinols varies from less than 5 min for entry 2 to 48 hr for entry 10. With most enones and enals, only 1,2-addition is observed, but in two cases (entries 3 and 4), a significant amount of the 1,4-adduct was also produced. The increased 1,4-addition seen in entry 3 apparently occurs because of steric factors, whereas that seen in entry 4 presumably occurs because of chelation of the organolithium to the benzyl ether oxygen.

TABLE I
CYCLOBUTANONE SYNTHESIS VIA 1-BROMO-1-ETHOXYCYCLOPROPANE

Entry	Ketone/aldehyde	Cyclobutanone	Yield(%)

1			97
2			86
3			40
4			30
5			65
6			71
7			79
8			74

9  81

10  81

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14. Entries 2, 9, and 10 of Table I have been reported previously.[2] Entry 1 was carried out by Amy J. DeWinter. Entry 3 was carried out by Scott A. Miller. Entry 4 was carried out by Mark R. Rubino. Entries 5–8 were carried out by Ishwar M. Mallick.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

fluoboric acid

ethanol (64-17-5)

ethyl acetate (141-78-6)

diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

HYDROBROMIC ACID (10035-10-6)

sodium carbonate (497-19-8)

PHOSPHORUS (7723-14-0)

phosphorus tribromide (7789-60-8)

carbon tetrachloride (56-23-5)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

pyridine (110-86-1)

Benzophenone (119-61-9)

sodium (13966-32-0)

Pentane (109-66-0)

methylene chloride (75-09-2)

stannic chloride (7646-78-8)

magnesium sulfate (7487-88-9)

hexane (110-54-3)

crotonaldehyde (123-73-9)

Lithium chloride (7447-41-8)

ethyl 3-chloropropionate (623-71-2)

Cyclobutanone (1191-95-3)

cyclopropylcarbinol (2516-33-8)

1-ethoxy-1-trimethylsiloxycyclopropane (27374-25-0)

tert-Butyllithium (594-19-4)

1-Bromo-1-ethoxycyclopropane (95631-62-2)

bromotrimethylsilane (2857-97-8)

(1-ethoxy)cyclopropyllithium

1-bromo-1-methoxycyclopropane

1-methoxy-1-trimethylsiloxycyclopropane

(1-phenylthio)cyclopropyllithium

benzyl ether oxygen

(E)-2-(1-Propenyl)cyclobutanone, Cyclobutanone, 2-(1-propenyl)-, (E)- (63049-06-9)

(E)-1-Ethoxy-1-(1-hydroxy-2-butenyl)cyclopropane (130719-17-4)

(E)-1-ethoxy-1-(hydroxy-2-butenyl)cyclopropane

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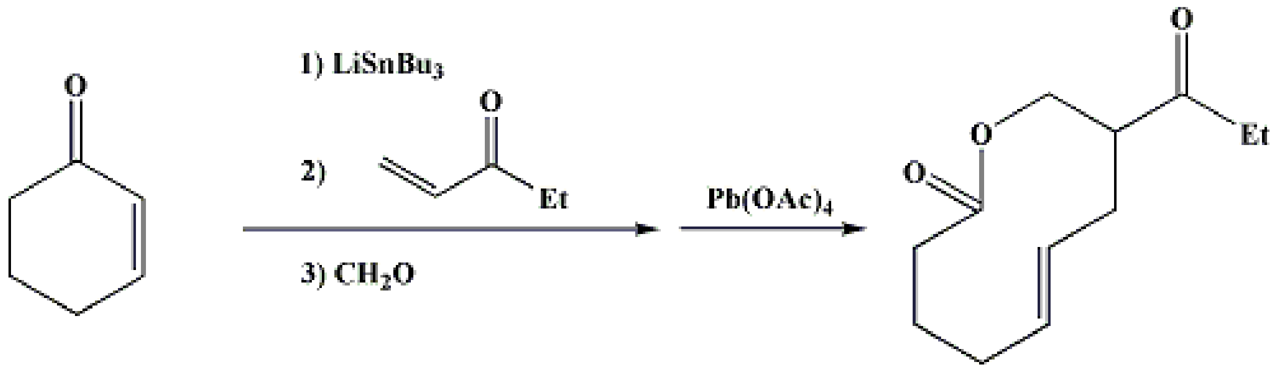
Organic Syntheses, CV 8, 562

A GENERAL METHOD FOR THE PREPARATION OF 9-, 10-, AND 11-MEMBERED UNSATURATED MACROLIDES: SYNTHESIS OF 8-PROPIONYL-(*E*)-5-NONENOLIDE

[2*H*-Oxecin-2-one, 3,4,5,8,9,10-hexahydro-9-(1-oxopropyl)-, (*E*)-]



Submitted by Kevin S. Webb, Edward Asirvatham, and Gary H. Posner[1].
Checked by Thais Sielecki and Albert I. Meyers.

1. Procedure

Caution! Benzene has been identified as a carcinogen: OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and gloves should be worn.

A flame-dried (Note 1), 500-mL, three necked, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar, rubber septa, and an argon inlet is charged with 75 mL of anhydrous tetrahydrofuran (Note 2) and 8.0 mL (57.1 mmol) of diisopropylamine (Note 3), then cooled to −10°C via an ice–salt bath. Next 34.8 mL (55.0 mmol) of butyllithium (1.58 *M*, (Note 4), in hexane) is added dropwise (over 4 min) to the vigorously stirred diisopropylamine solution, and stirred at −10°C for 20 min. Tributyltin hydride (15.2 mL, 55.0 mmol, (Note 5)) is added dropwise over 5 min to the solution, and the reaction mixture is stirred under argon at −10° to 0°C for an additional 30 min. The flask is cooled to −78°C and stirred for 20 min.

A flame-dried (Note 1), 100-mL, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar, a rubber septum, and an argon inlet is charged with 50 mL of anhydrous tetrahydrofuran (Note 2) and 4.85 mL (50.1 mmol) of 2-cyclohexen-1-one (Note 6), and cooled to −78°C. This solution (54.85 mL) is cannulated into the tributyltinlithium solution dropwise over 8 min (Note 7), and the solution is stirred at −78°C under argon for 25 min (Note 8). The same 100-mL, round-bottomed flask is charged with 50 mL of anhydrous tetrahydrofuran (Note 2) and 6.1 mL (59.4 mmol) of ethyl vinyl ketone (Note 9), and cooled to −78°C. This solution (56.1 mL) is cannulated into the 500-mL, round-

bottomed flask dropwise over 8 min (Note 10), and the solution is stirred for 1.5 hr (Note 11). The resulting solution is then transferred from a −78°C cold bath to a −23°C cold bath (Note 12) and stirred at this temperature for 30 min.

A flame-dried (Note 1), 100-mL, three-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar, a Teflon stopcock, rubber septa, and an argon inlet is charged with 6 g of paraformaldehyde (Note 13). The flask is heated to 165–170°C and the gaseous formaldehyde is bubbled into the −23°C solution (Note 14). After 15 min all of the paraformaldehyde is pyrolyzed (Note 15), and the solution becomes slightly cloudy and yellow. The 500-mL, three-necked, round-bottomed flask is transferred to a −40°C bath (maintained by a Flexicool cryostat) and allowed to stir under argon for 20 hr. The reaction mixture is quenched at −40°C with 7 mL of saturated ammonium chloride followed by 8 mL of distilled water. It is warmed to room temperature, poured into a 500-mL separatory funnel, and diluted with 75 mL of water; the organic layer is separated, and the aqueous layer is extracted with diethyl ether (2 × 100 mL). The combined organic layers are dried over anhydrous magnesium sulfate, filtered, and concentrated (Note 16) to afford 29.3 g of crude product.

A flame-dried (Note 1), 1000-mL, three-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar, rubber septa, a 24/40 condenser, and an argon inlet is charged with 300 mL of anhydrous benzene (Note 17) and 29.00 g (65.4 mmol) of lead tetraacetate (Note 18). The suspension is heated to 80°C and stirred vigorously under argon. A flame-dried (Note 1), 250-mL, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar, rubber septa, and an argon inlet is charged with 150 mL of anhydrous benzene (Note 17) and 29.3 g of the crude reaction mixture. This solution is cannulated into the lead tetraacetate suspension over 2 min (Note 19), and the suspension is allowed to reflux for 2.5 hr. The reaction flask is cooled to room temperature, quenched with 200 mL of distilled water, poured into a 2-L separatory funnel, and diluted with 1000 mL of diethyl ether (Note 29). The organic layer is washed with saturated sodium bicarbonate solution (3 × 200 mL), aqueous 5% hydrochloric acid (2 × 200 mL), distilled water (200 mL), and brine (200 mL). The organic layer is dried over anhydrous magnesium sulfate and filtered; solvent removal afforded 28.95 g of a crude oil. This crude residue (light-yellow-brown oil) is purified by short-path column chromatography (Note 21) to yield 4.37 g (41.5%) of 8-propionyl-(*E*)-5-nonenolide (Note 22) and (Note 23).

2. Notes

1. All glassware and Teflon-coated magnetic stirring bars were flame-dried under vacuum (0.5 mm) for 5 min, then back-filled with argon. The procedure was repeated a total of 3 times.
2. Baker reagent-grade tetrahydrofuran (99%, obtained from Aldrich Chemical Company, Inc.) was distilled over sodium metal spheres/benzophenone under an inert atmosphere and used immediately.
3. Diisopropylamine, 99%, was obtained form Aldrich Chemical Company, Inc., and allowed to reflux over calcium hydride (≥95%, obtained from Aldrich Chemical Company, Inc.) for 24 hr prior to use.
4. Butyllithium in hexane (1.6 *M*), obtained from Aldrich Chemical Company, Inc.,

was titrated (using 2,5-dimethoxybenzyl alcohol as the indicator[2]) just prior to use.
5. Tributyltin hydride, 97%, was obtained form Aldrich Chemical Company, Inc., and must be used quickly to ensure generation of the tributyltinlithium species. Two minutes after the initial addition of tributyltin hydride the colorless solution turned light yellow.
6. 2-Cyclohexen-1-one, 97%, was obtained from Aldrich Chemical Company, Inc., and was freshly distilled via short-path distillation.
7. After the 2-cyclohexenone addition was complete, the 100-mL, round-bottomed flask was washed with 10 mL of anhydrous tetrahydrofuran, and this wash was cannulated into the 500-mL flask (Note 2).
8. A small aliquot of the reaction mixture was removed after 15 min and analyzed by analytical TLC. The TLC was developed in 20% ethyl acetate:hexane and showed that the 1,4-conjugate addition had proceeded to completion (R_f = 0.58); the solution was colorless at this point of the reaction.
9. Ethyl vinyl ketone, 97%, was obtained from Aldrich Chemical Company, Inc., and used directly.
10. The reaction mixture turned slightly yellow during addition of ethyl vinyl ketone.
11. A small aliquot was removed from the reaction mixture and analyzed by analytical TLC (20% ethyl acetate:hexane) to ensure that the Michael addition had proceeded, R_f = 0.44, and R_f = 0.32 corresponding to the diastereomeric intermediates.
12. A −23°C bath was obtained from a mixture of dry ice/carbon tetrachloride. A temperature between −40° and −20°C is necessary.
13. Paraformaldehyde, 95%, was obtained from Aldrich Chemical Company, Inc., and used directly.
14. The argon inlet was equipped with a 16-gauge, 3-in. syringe needle; the transfer cannula was a flex-needle (Z10,091-9) obtained from Aldrich Chemical Company, Inc., and the outlet bubbler was equipped with a 16-gauge, 3-in., syringe needle.
15. A high-pressure stream of argon was needed to prevent the gaseous formaldehyde from polymerizing to paraformaldehyde in the transfer flex-needle.
16. The weight of 29.30 g was achieved by attaching the round-bottomed flask to a vacuum (1.5 mm) and heating via a water bath (55°C) for 4 hr.
17. Benzene (thiophene-free, ≥99%, 900 mL) was obtained from Aldrich Chemical Company, Inc., and washed with concentrated sulfuric acid (5 × 100 mL), distilled water (100 mL), aqueous 2% sodium hydroxide solution (100 mL), and distilled water (100 mL), and dried over anhydrous magnesium sulfate. It was then allowed to reflux over calcium hydride for 24 hr. The checkers found that the benzene needed to be distilled only from calcium hydride.
18. lead tetraacetate was purchased from Aldrich Chemical Company, Inc., and used directly.
19. The transfer cannula was a 12-in., 16-gauge, double-tipped syringe needle, and the 250-mL flask was washed with an additional 30 mL of anhydrous benzene (Note 17), which was cannulated into the 1000-mL flask.
20. The 1000-mL, round-bottomed flask was washed with diethyl ether (3 × 100 mL of the 1000 mL).
21. Working on one-half of the present scale, the checkers found that by using Amicon Grace Matrex Silica Gel, (60 Å, 20–45 m) and an eluting solvent of 10%

diethyl ether:hexane, 3.50 g (66.0%) of 8-propionyl-(*E*)-5-nonenolide was obtained. The white solid was further purified by recrystallization from 15 mL of hexane to yield 3.15 g (60.0%) as a white solid.

22. The physical properties are as follows: IR ($CHCI_3$) cm^{-1}; 2933, 1731, 1349, 1210, 1154, 979, 770, 746; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.05 (t, 2 H, *J* = 7.2), 1.12 (t, 1 H, *J* = 7.2), 1.70–3.00 (m, 11 H), 3.76–3.82 (m, 0.67 H), 4.15–4.21 (m, 0.33 H), 5.05–5.70 (m, 3 H). When the proton signals at 1.90–2.90 ppm were irradiated, the two olefinic multiplets collapsed into two doublets (*J* = 15.2). An analytical sample (4.37 g) was recrystallized from 20 mL of hexane (Fisher, certified) to yield 4.05 g (38.5%) was a white solid: mp 70–71°C. Anal. calcd. for $C_{12}H_{18}O_3$; C, 68.57; H. 8.57. Found: C, 68.47; H, 8.68.

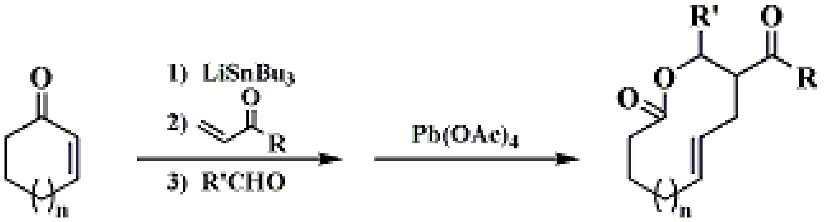
23. In order to determine whether the product was a mixture of geometrical isomers (e. g., differing by cis or trans geometry at the double bond) or conformers, it was necessary to obtain ^1H NMR spectra at various temperatures. The 400 MHz ^1H NMR (d_6-DMSO) at 100°C shows that the two triplets (δ 1.05, 1.12) start to collapse to one triplet, the multiplicity of the peaks in the region of δ 5.05–5.70 simplify greatly, and the initial peak ratios in the region of δ 3.70–4.20 change from 1:2 to 1:3. Therefore, the nonenolide is one pure isomer of only *trans* double-bond geometry and is able to exist as two stable conformers in solution. The glass capillary gas chromatograph (Hewlett Packard 5890) of 8-propionyl-(*E*)-5-nonenolide shows only one peak with a retention time of 4.21 min (injector temperature 175°C, detector temperature 225°C).

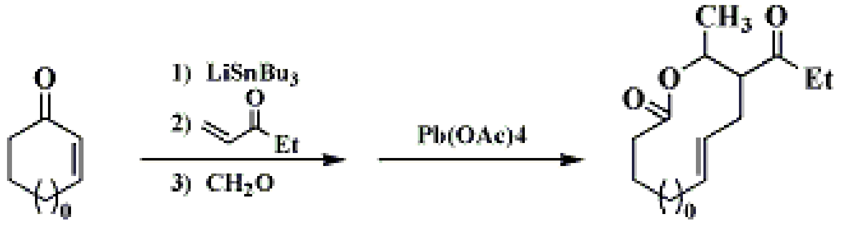
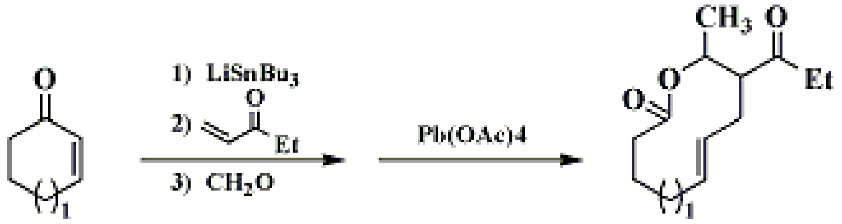
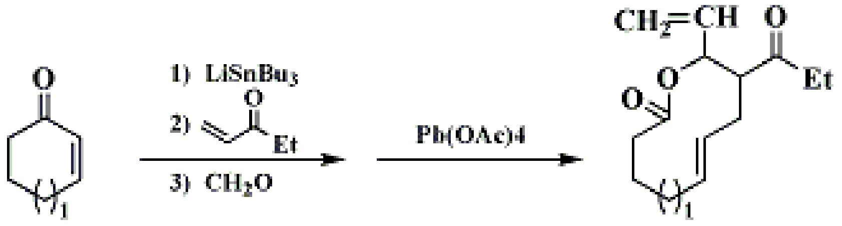
3. Discussion

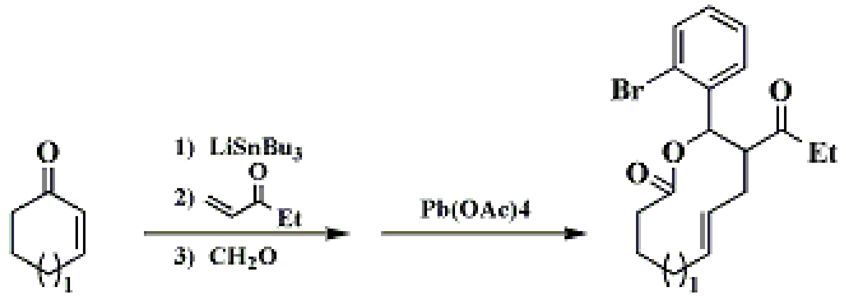
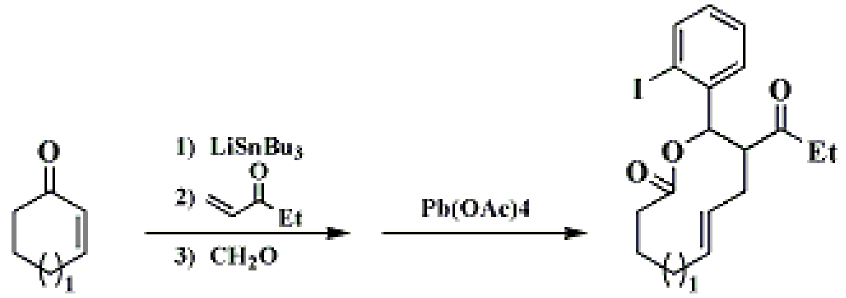
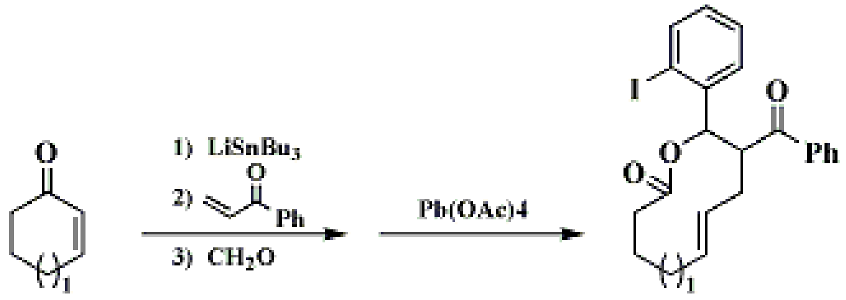
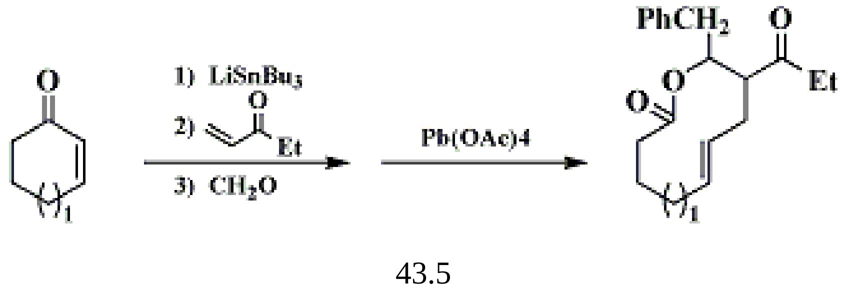
The procedure described is a simple, rapid, and convenient method for conversion of *n*-sized cycloalkenones into *n* + 4 alkenolides. Significant but limited progress has been reported in the recent literature toward the preparation of medium and large-ring lactones via ring-expansion reactions. One of the most notable and useful developments in this area involves conversion of a cycloalkanone into a bicyclic vinylic ether that is oxidatively cleaved to form a ring-enlarged keto lactone.[3,4; 5] Recently, several variations of this ring-enlargement reaction have been reported, including the scission of alkoxy radicals.[6,7,8,9,10,11,12,13,14] In most of these cases, a superfluous functional group (e.g., ketone, iodide), is produced during cleavage of the bicyclic system. Regiospecific conversion of such functional groups into a specific alkene structural unit is usually not possible because of the similar chemical environment α' to the functional group.[15] Because many regiospecifically unsaturated lactones are physiologically active natural products,[16,17,18,19] we have developed methodology to prepare unsaturated macrolides having a carbon–carbon double bond with specific geometry and at a specific position in the macrolide skeleton.

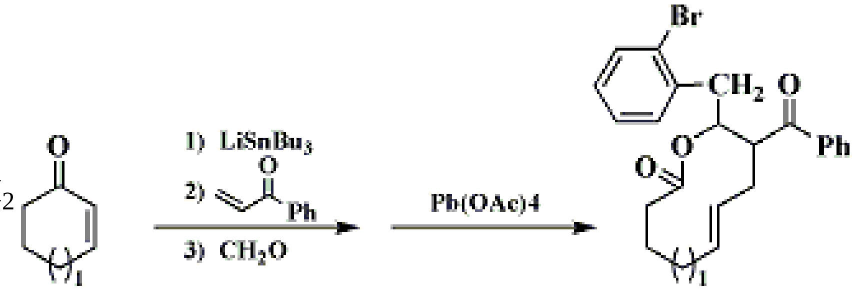
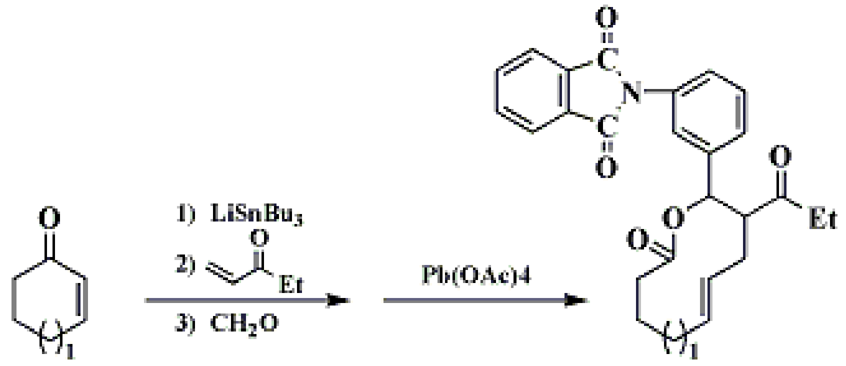
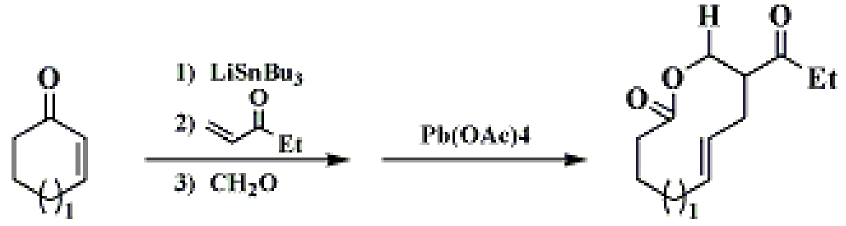
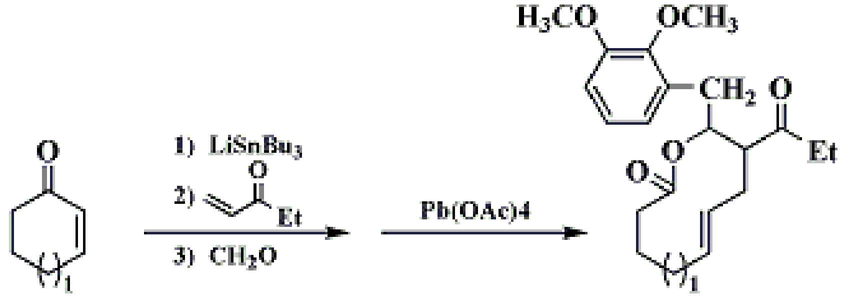
Because of our interest in one-pot, multicomponent annulations,[20,21,22,23,24,25,26] we envisioned a flexible and efficient protocol that would link the four different components via the formation of four new bonds (a–d, Eq. 1) in one reaction vessel. The intermediate γ-hydroxystannanes thus formed in Equation 1 could be oxidatively fragmented[27,28,29] to produce both ring enlargement and regiospecific formation of an alkenyl unit. This four-atom ring-expansion methodology of common side α,β-unsaturated ketones has led to the syntheses of many mono- and disubstituted 9-, 10-, and 11-membered unsaturated macrolides (Table I).

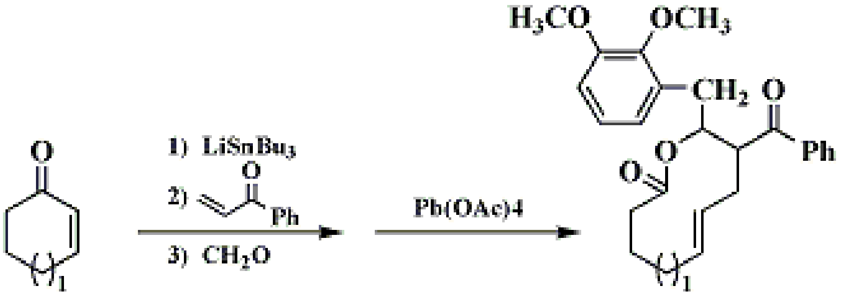
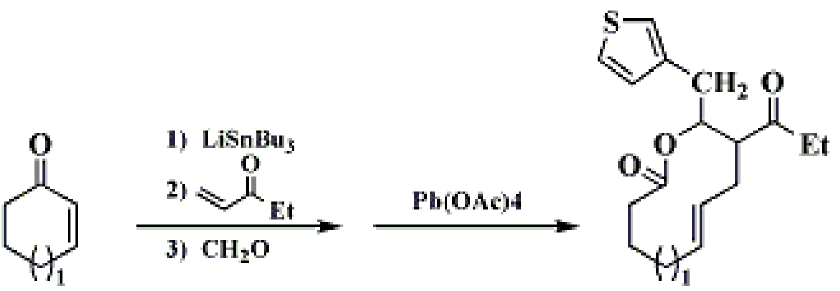
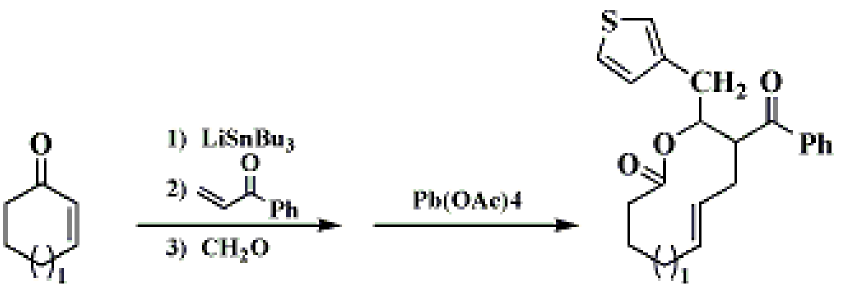
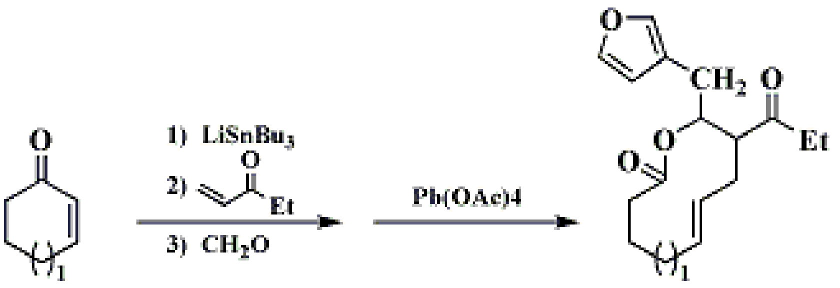
TABLE I

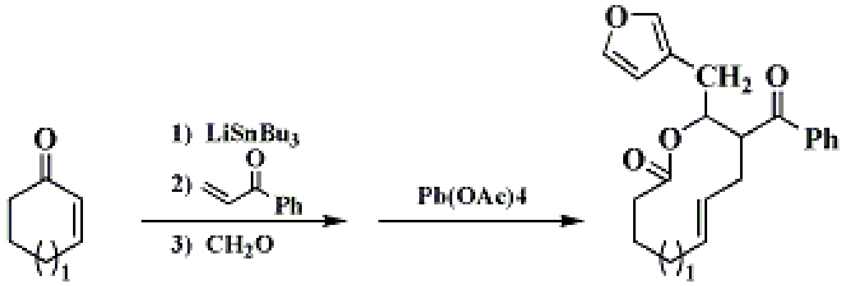
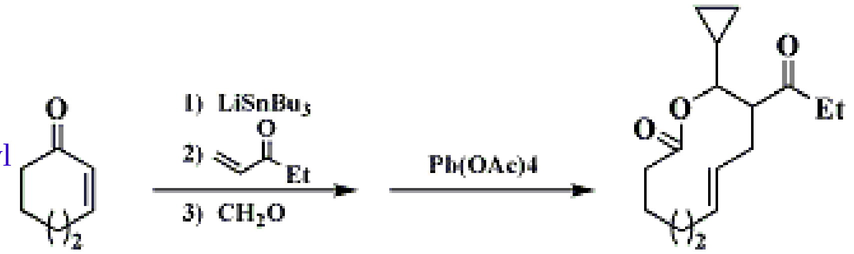
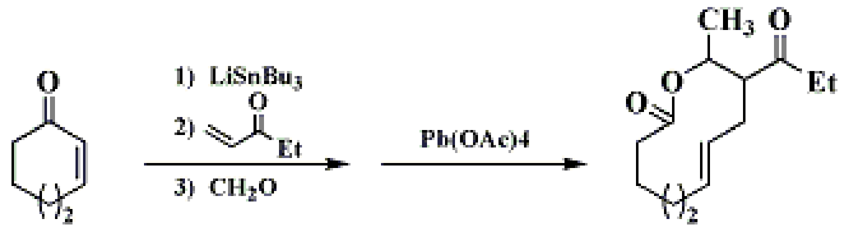
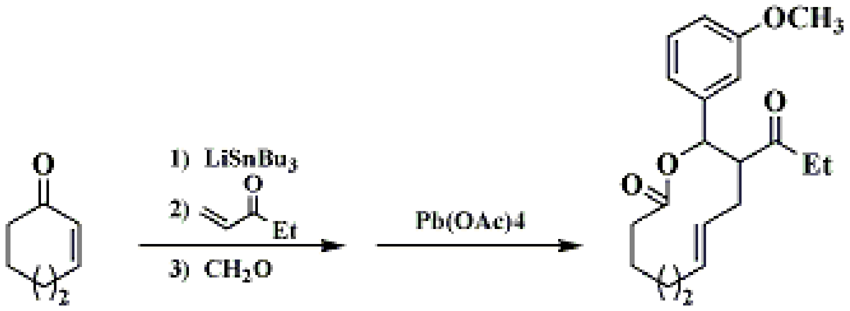


n	R	R'		Yield (%)	*trans: cis*
0	Et	CH_3		30.5	0.57
1	Et	CH_3		47	0.7
1	Et	CH_2=CH		39.5	2.6

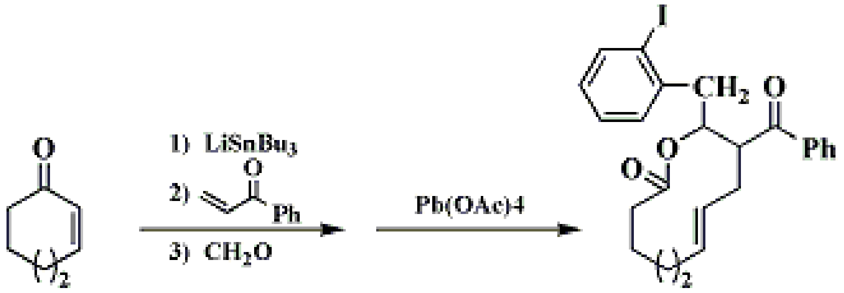
1Et	*o*-BrC_6H_4		5.3	47
1Et	*o*-IC_6H_4		2.6	37
1Ph	*o*-IC_6H_4		1.0	34
1Et	PhCH_2		1.5	43.5

1	Ph	*o*-$BrC_6H_4CH_2$		30	1.0
1	Et	*o*-N(phtl) C_6H_4		42	5.0
1	Et	H		41.5	—
1	Et	2,3-(MeO) $_2C_6H_3CH_2$		52	1.0

1	Ph	2,3-$(MeO)_2C_6H_3CH_2$		1.5	51
1	Et	3-ThienylCH$_2$		0.7	52
1	Ph	3-ThienylCH$_2$		1.8	52
1	Et	3-FurylCH$_2$		0.7	54

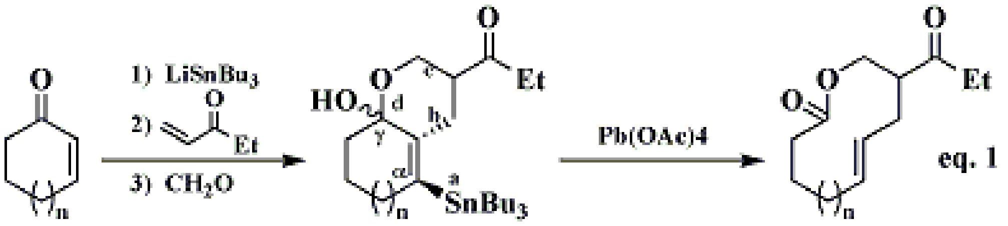
1	Ph	3-FurylCH_2		7.0
			40	
2	Et	Cyclopropyl		1.1
			53	
2	Et	CH_3		1.0
			40	
2	Et	3-(MeO) C_6H_4		1.5
			41.5	

2Ph *o*-$IC_6H_4CH_2$



1.9

38



Based on the data in Table I and on our published results,[20,21,22,23,24,25,26] it is clear that five-, six-, and seven-membered cycloalkenones undergo this four-atom ring enlargement reaction to produce medium ring, unsaturated lactones in overall yields of 30–54%. Permutations on this methodology include using either ethyl vinyl ketone or phenyl vinyl ketone as the third component, and either substituted acetaldehydes or substituted benzaldehydes as the last component. The geometrical assignment of the new carbon–carbon double bond was made from interpreting the 400 MHz ^{1}H NMR decoupled spectra in which each olefinic proton collapsed into a baseline-resolved doublet with coupling constants of J = 15–16. The proton decoupling experiments conducted to determine the relative stereochemistry of the vicinal substituents in the disubstituted macrolides were inconclusive; often the magnitude of the coupling constants were similar or not discernible from the spectra. Therefore, the relative stereochemistry of the vicinal substituents was established by examining the ^{1}H NMR spectra of the intermediate γ-hydroxystannanes (usually only two were isolated). The *trans*-hemiketals showed typical coupling constants of J = 8–13, while the *cis*-hemiketals showed coupling constants of J = 2–4. Separate lead tetraacetate oxidative fragmentation of these γ-hydroxystannanes produced two different ring-enlarged lactones, both with specific *trans* double-bond geometry and differing only in the relative stereochemistry of vicinal substituents.

This homologous Baeyer–Villiger-type oxidative ring expansion represents a conceptually new protocol illustrating the substantial value of one-pot, four-component annulations as a flexible and simple new synthetic method.

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

brine

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ethyl acetate (141-78-6)

diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

sodium hydroxide (1310-73-2)

formaldehyde (630-08-0)

sodium bicarbonate (144-55-8)

carbon tetrachloride (56-23-5)

Benzophenone (119-61-9)

sodium (13966-32-0)

magnesium sulfate (7487-88-9)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

hexane (110-54-3)

calcium hydride (7789-78-8)

2-Cyclohexenone, 2-cyclohexen-1-one (930-68-7)

argon (7440-37-1)

cyclopropyl (2417-82-5)

diisopropylamine (108-18-9)

tributyltin hydride (688-73-3)

2,5-dimethoxybenzyl alcohol (33524-31-1)

Tributyltinlithium

ethyl vinyl ketone (1629-58-9)

phenyl vinyl ketone (768-03-6)

8-Propionyl-(E)-5-nonenolide

2H-Oxecin-2-one, 3,4,5,8,9,10-hexahydro-9-(1-oxopropyl)-, (E)- (114633-68-0)

lead tetraacetate

paraformaldehyde (30525-89-4)

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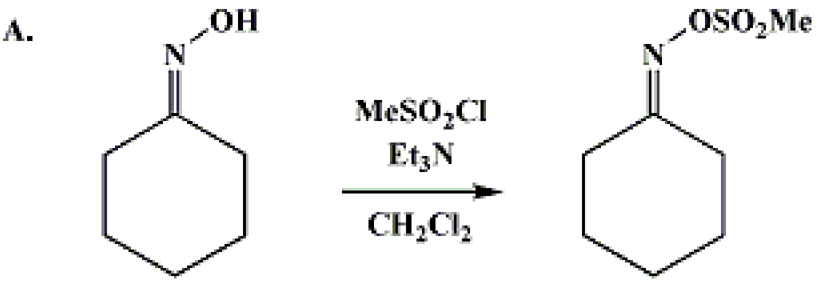
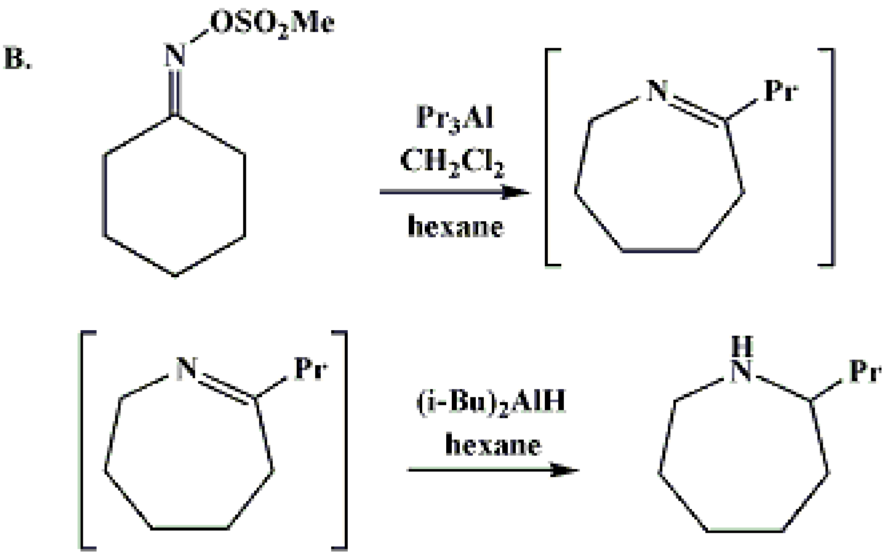
Organic Syntheses, CV 8, 568

2-PROPYL-1-AZACYCLOHEPTANE FROM CYCLOHEXANONE OXIME

[1*H*-Azepine, hexahydro-2-propyl-, (±)-]





Submitted by Keiji Maruoka, Shuichi Nakai, and Hisashi Yamamoto[1].
Checked by Jeffrey Doney and Clayton H. Heathcock.

1. Procedure

Caution! Part B of this procedure should be carried out in a well-ventilated hood to prevent exposure to methanethiol, a side product.

A. *Cyclohexanone oxime methanesulfonate.* A dry, 1-L, two-necked, round-bottomed flask is equipped with a gas inlet, a rubber septum, and a magnetic stirring bar. The flask is charged with 17.0 g (0.15 mol) of cyclohexanone oxime (Note 1) and flushed with argon, after which 300 mL of dichloromethane followed by 25 mL (0.18 mol) of triethylamine (Note 2) are injected through the septum into the flask. The solution is stirred and cooled to a temperature of –15 to –20°C in a dry ice–carbon tetrachloride bath, while 12.8 mL (0.165 mol) of methanesulfonyl chloride is added over a 20-min

period (Note 3) and (Note 4). The resulting mixture is stirred at this temperature for 15 min, and poured into 300 mL of ice water in a 1-L separatory funnel with the aid of three 30-mL portions of dichloromethane to rinse the flask. The lower organic layer is separated, and the aqueous layer is extracted with a 50-mL portion of dichloromethane. The combined extracts are washed successively with 250 mL of cold aqueous 10% hydrochloric acid, 250 mL of saturated sodium bicarbonate, and 250 mL of brine, and are dried over anhydrous sodium sulfate and concentrated with a rotary evaporator at room temperature to give 27.2–28.8 g of crude solid cyclohexanone oxime methanesulfonate (Note 5). This material is used in Part B without purification (Note 6).

B. *2-Propyl-1-azacycloheptane.* A dry, 2-L, three-necked, round-bottomed flask is equipped with a variable-speed mechanical stirrer, 300-mL pressure-equalizing dropping funnel bearing a gas inlet at its top, and a rubber septum. The apparatus is flushed with argon, after which 243 mL of hexane (Note 7) and 57 mL (0.3 mol) of tripropylaluminum (Note 8) are injected through the septum into the flask. The solution is stirred and cooled to a temperature of −73 to −78°C in a dry ice–methanol bath. The crude cyclohexanone oxime methanesulfonate prepared in Part A is dissolved in 100 mL of dichloromethane, transferred to the dropping funnel, and added to a 1 *M* solution of tripropylaluminum in hexane over a 30-min period (Note 9). The mixture is allowed to warm to 0°C and stirred for 1 hr, and 225 mL (0.225 mol) of 1 *M* solution of diisobutylaluminum hydride in hexane (Note 10) is added at 0°C and the mixture is further stirred at 0°C for 1 hr (Note 11). After addition of 100 mL of dichloromethane and 88.2 g (2.1 mol) of sodium fluoride, 28.4 mL (1.58 mol) of water is injected dropwise at 0°C (Note 12). Vigorous stirring of the resulting suspension is continued for 30 min at room temperature, and the contents of the flask are filtered with five 30-mL portions of dichloromethane (Note 13). The combined filtrates are evaporated under reduced pressure with a rotary evaporator. Distillation of the residual liquid under reduced pressure affords 11.3–12.2 g (53–58%) of 2-propyl-1-azacycloheptane as a colorless liquid, bp 79–81°C (18 mm) (Note 14) and (Note 15).

2. Notes

1. Reagent-grade cyclohexanone oxime, purchased from Wako Pure Chemical Industries, Ltd. (Japan), was used as received. The checkers used material obtained from the Aldrich Chemical Company, Inc. A suitable material may be prepared according to the procedures in *Organic Syntheses.*[2]
2. Both reagent-grade dichloromethane and triethylamine were dried and stored over Linde 4A molecular sieves.
3. The solution turns to a white suspension after half of the methanesulfonyl chloride is added; methanesulfonyl chloride, available from Tokyo Kasei Kogyo Company, Ltd. (Japan), was used without any purification.
4. The checkers found that an addition time of 40 min is required to maintain the temperature of the reaction mixture below −15°C.
5. If a crude oil was obtained at this stage, it can be solidified by cooling.

6. The reaction in Part A proceeds in almost quantitative yield.[3] Accordingly, the crude cyclohexanone oxime methanesulfonate can be used without any purification. Prolonged standing at room temperature may cause serious decomposition. The crude material may be stored in a freezer, or as a dichloromethane solution in a refrigerator, and can be recrystallized from ether-hexane to give the white solid (mp 43–45°C).[4]

7. Reagent-grade hexane was dried and stored over sodium.

8. Neat tripropylaluminum of 96% purity was supplied in a metal cylinder from Toso-Akzo Chemical Company, Ltd. (Japan). This reagent is contaminated by 1.2% of triethylaluminum, 2.2% of triisobutylaluminum, and other compounds. Neat tripropylaluminum is also available from Aldrich Chemical Company, Inc. Since neat tripropylaluminum is pyrophoric and reacts violently with oxygen and water, the syringe should be washed with hexane immediately after addition.

9. The checkers found that an addition time of 60 min is required to maintain the temperature of the reaction mixer below –73°C.

10. Diisobutylaluminum hydride in hexane was available from Aldrich Chemical Company, Inc. and Kanto Chemical Company, Inc. (Japan).

11. Methanethiol is generated as a side product by the reduction of the methanesulfonate with diisobutylaluminum hydride.

12. To avoid excessive foaming at the beginning of the hydrolysis, water should be added carefully by syringe. The rate of addition may be increased once the initially vigorous foaming subsides.

13. The sodium fluoride–water workup offers an excellent method for large-scale preparations and is generally applicable for product isolation in the reaction of organoaluminum compounds.[5]

14. The elemental analysis and the spectral properties of the product are as follows. Anal. calcd. for $C_9H_{19}N$: C, 76.61; H, 13.47; N, 9.92. Found: C, 76.75; H, 13.74; N, 9.51; IR (liquid film) cm^{-1}: 3320, 2860–2970, 1460, 1165; ^1H NMR ($CDCl_3$) δ: 0.87–0.94 (3 H, m, CH_3), 1.23–1.82 (13 H, m), 2.54–2.73 (2 H, m, CH_2N), 2.96–3.03 (1 H, m, CHN). A boiling point of 193–194°C at 750 mm has been reported for 2-propyl-1-azacycloheptane.[6]

15. Gas chromatographic analysis using a 25-m PEG-HT capillary column at 80°C indicated a purity of 97% (retention time: 8.1 min) based on tripropylaluminum of 96% purity (Note 8). The unrearranged product, cyclohexylpropylamine (retention time: 6.9 min), was less than 1%.

3. Discussion

This procedure illustrates a new, general method for the one-nitrogen ring expansion of cyclic ketoximes leading to α-alkylated, cyclic, secondary amines.[4,7] The key step in the sequence is the organoaluminum-promoted Beckmann rearrangement of ketoxime derivatives, in which the organoaluminum compounds are used as amphophilic reagents to induce the Beckmann rearrangement of oxime derivatives as well as to capture the intermediary imino carbocation by the alkyl group that is

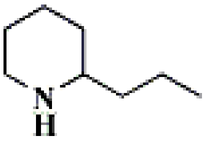
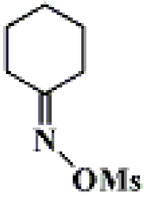
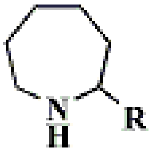
originally attached to aluminum. The conventional process for accomplishing this transformation consists of the following steps: (a) Beckmann rearrangement of ketoxime or its derivative to lactam; (b) conversion of the lactam to imino ether using trialkyloxonium tetrafluoroborate; (c) alkylation of the imino ether with alkyllithium or Grignard reagent to produce imine, which requires a considerably longer time for execution.[8]

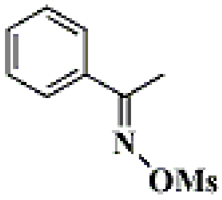
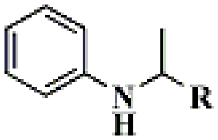
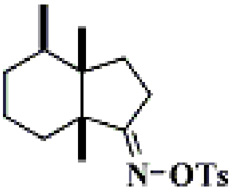
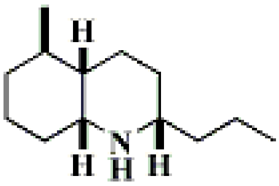
As oxime derivatives, oxime sulfonates can be used preferentially for the following reasons: (a) they are readily available from oximes using *p*-toluenesulfonyl chloride or methanesulfonyl chloride in the presence of base in almost quantitative yield; (b) they are easy to handle because of their fine crystalline properties; and (c) they are sufficiently reactive to initiate the rearrangement by organoaluminum reagents.

As shown in Table I, this reaction sequence has a wide generality and is readily applicable to the straightforward synthesis of various naturally occurring alkaloids such as coniine,[9] pumiliotoxin C,[10] and solenopsin A and B.[11] Oxime sulfonates of either linear or cyclic structures may be used. Obviously, the regioselectivity of the reaction follows the general rule of the Beckmann rearrangement,[12] and preferential migration of the group *anti* to the oxime sulfonate is observed. Diethylaluminum alkynides can be successfully used for the selective introduction of alkynyl groups to a substrate in preference to an ethyl group. Furthermore, the present procedure reduces the intermediate imine directly without isolation by using diisobutylaluminum hydride, thus excluding the troublesome isolation of unstable cyclic imino compound.

TABLE I

PREPARATION OF α-ALKYLATED AMINES FROM OXIME SULFONATES WITH TRIALKYLALUMINUM–DIISOBUTYLALUMINUM HYDRIDE

Oxime Sulfonate (mp, °C)	Trialkylaluminum	Amine	Yield (%)
(75-77)	Pr_3Al^a		55-58
 (43-45)	Me_3Al		70 (R = Me)
	$Et_2AlC≡CBu$		67 (R = C≡CBu)

 (64-65)	Me_3Al $Et_2AlC\equiv CBu$ $Et_2AlC\equiv CPh$		67 (R = Me) 83 (R = C≡CBu) 67 (R = C≡CPh)
 (67-71)	Pr_3Al^b		60

[a]Treatment with Pr_3Al at 40–80°C for 15–30 min.

[b]Treatment with Pr_3Al at 25°C for 30 min.

The organoaluminum-promoted Beckmann rearrangement–alkylation sequence represents a modern aspect of the classical Beckmann rearrangement, and has proved effective with other aluminum reagents of type R_2AlX (X = SR, SeR, CN) which would function in a similar way to trialkylaluminum compounds. Thus, a series of imino thioethers, selenoethers, and nitriles can be prepared with rigorous regioselectivity by using organoaluminum thiolates, selenolates, and cyanide, respectively.[4]

2-Propyl-1-azacycloheptane has been prepared by reduction of 2-aza-1-oxo-3-propylcycloheptane with lithium aluminum hydride,[6] and from azacycloheptane by conversion to its formamidine, alkylation with 1-iodopropane, and subsequent hydrazinolysis.[13]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

brine

2-aza-1-oxo-3-propylcycloheptane

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

oxygen (7782-44-7)

sodium (13966-32-0)

dichloromethane (75-09-2)

Cyclohexanone oxime (100-64-1)

methanethiol (74-93-1)

sodium fluoride (7681-49-4)

lithium aluminum hydride (16853-85-3)

hexane (110-54-3)

triethylamine (121-44-8)

triisobutylaluminum (100-99-2)

Methanesulfonyl chloride (124-63-0)

diisobutylaluminum hydride (1191-15-7)

triethylaluminum (97-93-8)

argon (7440-37-1)

p-Toluenesulfonyl chloride (98-59-9)

methanesulfonate

1-iodopropane (107-08-4)

azacycloheptane (111-49-9)

2-Propyl-1-azacycloheptane, 1H-Azepine, hexahydro-2-propyl-, (±)- (85028-29-1)

Cyclohexanone oxime methanesulfonate (80053-69-6)

tripropylaluminum

cyclohexylpropylamine

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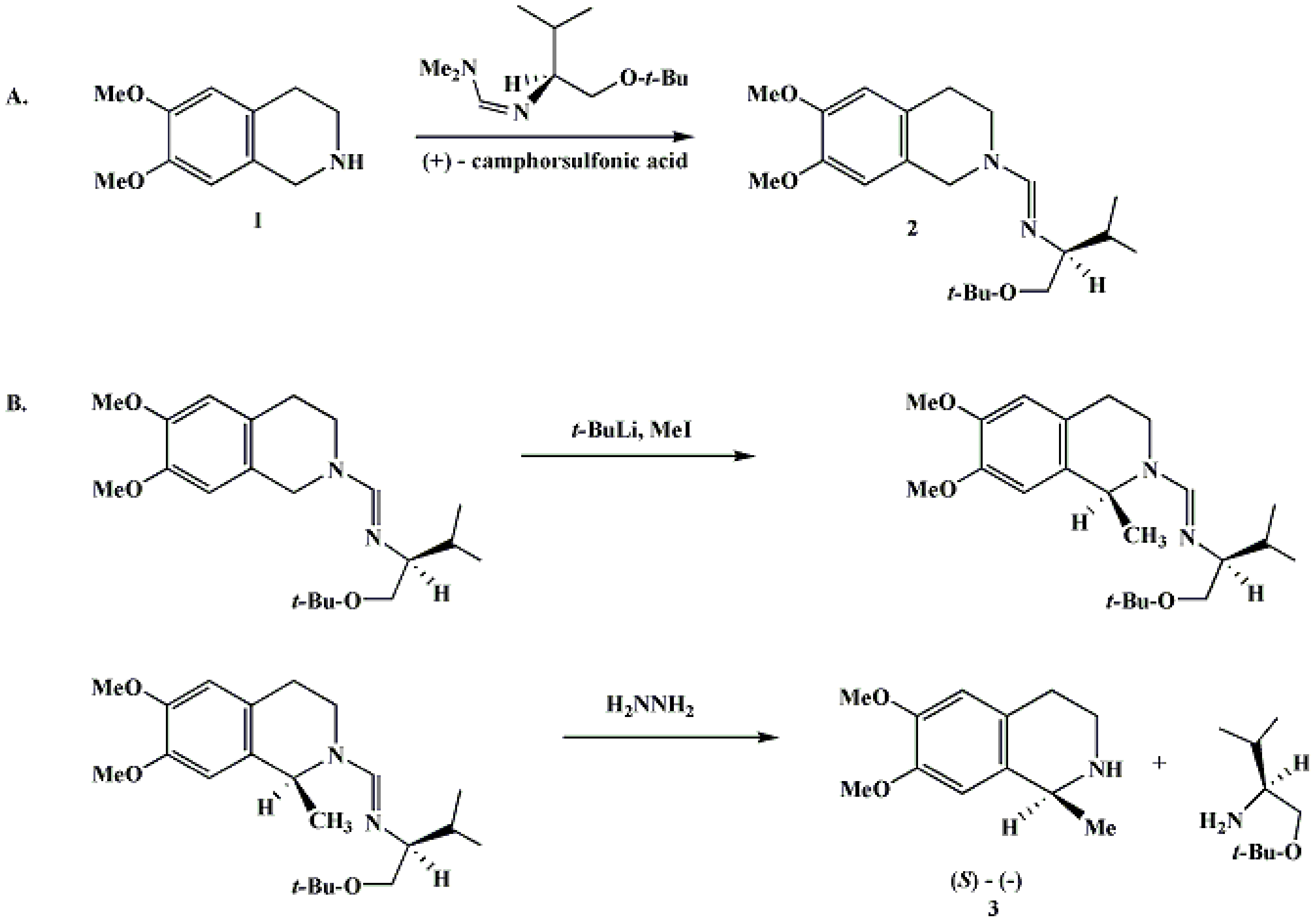
Organic Syntheses, *CV 8*, *573*

(–)-SALSOLIDINE

[Isoquinoline, 1,2,3,4-tetrahydro-6,7-dimethoxy-1-methyl-, (*S*)-]



Submitted by Albert I. Meyers[1], Michael Boes, and Daniel A. Dickman.
Checked by Melinda Gugelchuk and Leo A. Paquette.

1. Procedure

A. *6,7-Dimethoxy-1,2,3,4-tetrahydro-2-[(1-tert-butoxy-3-methyl)-2-butyliminomethyl]isoquinoline* ***(2)***. In a 250-mL, round-bottomed flask 10.0 g (51.7 mmol) of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline 1 (Note 1) is combined with 11.5 g (53.7 mmol) of (*S*)-*N*,*N*-dimethyl-*N'*-(1-*tert*-butoxy-3-methyl)-2-butylformamidine (Note 2), 50 mL of dry toluene, and 50 mg of (+)-camphorsulfonic acid (Note 3). The mixture is heated to reflux for 24 hr and allowed to cool to room temperature. Approximately 30 mL of toluene is removed by rotary evaporation and the residual solution is heated at reflux for an additional 2 days. After the reaction mixture is cooled, it is diluted with 50 mL of dichloromethane and washed with 50 mL of 1 *N* sodium hydroxide and 100 mL of brine and the organic layer is dried over anhydrous potassium carbonate, filtered, and concentrated by rotary evaporation. The residue is distilled (Kugelrohr 0.1 mm, 170°C bath temp.) to give 18.0 g (96%) of 2 as a pale-yellow oil (Note 4).

B. *(S)-6,7-Dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline*, *(–)-salsolidine* ***(3)***. A 500-mL, three-necked flask, containing a magnetic stirring bar, is equipped with a three-way stopcock, a low-temperature thermometer, and a rubber septum. The flask is charged with 15.0 g (41.4 mmol) of formamidine **2**, filled with argon, and kept under a pressure of ca. 100 mm against the atmosphere (Note 5). Through the septum, via a syringe, is added 300 mL of dry tetrahydrofuran (Note 6) and the solution is cooled to −75°C in a dry ice–acetone bath. A *tert*-butyllithium solution (21 mL of a 2.4 *M* solution, (Note 7)), is added dropwise within 5 min through the septum. After the deep-red solution is stirred at −75°C for 45 min, is cooled to −100°C in a liquid nitrogen–methanol bath and, after 15 min at −100°C, 3 mL of freshly distilled iodomethane (Note 8) dissolved in 10 mL of dry tetrahydrofuran is added by syringe at such a rate that the temperature of the reaction mixture does not rise above −90° C. Stirring is continued for 3 hr and the solution is poured into a 1-L separatory funnel containing 50 mL of water. This is extracted twice with 100 mL of dichloromethane and the combined organic layers are washed with 100 mL of brine, dried

over potassium carbonate, and filtered. Removal of the solvent on a rotary evaporator gives a cloudy yellow oil, which is dissolved in 100 mL of 60% ethanol. To this solution is added 4.5–5.0 mL of hydrazine (Note 9) followed by 3.0 mL of glacial acetic acid (pH 8–9). The mixture is stirred overnight at ambient temperature and diluted with 50 mL of water. It is extracted twice with 100 mL of dichloromethane, and the combined organic extracts are washed with 50 mL of water, dried (potassium carbonate), filtered, and concentrated at *ambient temperature under aspirator pressure*. The residue, which consists of valinol *tert*-butyl ether and salsolidine, is distilled bulb-to-bulb under aspirator pressure at 105°C (pot temperature). This removes the valinol *tert*-butyl ether (Note 10), leaving crude salsolidine as the pot residue. The residue is dissolved in 100 mL of ether and washed twice with 35-mL portions of ice water–3 *N* hydrochloric acid (1:4). The ether layer is discarded and the acidic aqueous layer is neutralized with cold (0–5°C) aqueous 25% sodium hydroxide until it is alkaline to pH paper. The creamy mixture is immediately extracted twice with 50 mL of dichloromethane and the organic layers are drawn off, combined, and dried over anhydrous potassium carbonate. After the drying agent is removed by filtration, it is washed twice with 5 mL of dichloromethane. The filtrate and wash are concentrated by rotoevaporation, leaving a yellow oil. Distillation (Kugelrohr) at a pot temperature of 120–125°C (0.01 mm) gives 5.1–5.3 g (60–63%) of (*S*)-6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline (salsolidine) **3** as a pale-yellow oil, which crystallizes on standing (Note 11), mp 47–49°C, (Note 12) and (Note 13).

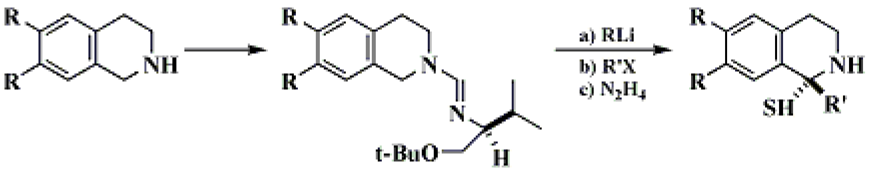
2. Notes

1. The tetrahydroisoquinoline hydrochloride was purchased from Aldrich Chemical Company, Inc. and treated with aqueous 5% sodium hydroxide, extracted with dichloromethane, dried over sodium sulfate, and distilled, bulb-to-bulb at 0.01 mm (58–60°C, bath temp.) to give a colorless oil. The compound solidifies to give an amorphous solid: mp 83.0–84.5°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.30 (br s, 1 H), 2.69, (t, 2 H, J = 6), 3.12 (t, 2 H, J = 6), 3.80 (s, 3 H), 3.82 (s, 3 H), 3.95 (s, 2 H), 6.50 (s, 1 H), 6.58 (s, 1 H).
2. See the previous procedure for preparation of this chiral formamidine; *Org. Synth., Coll. Vol. VIII* **1993**, 204.
3. (+)-10-Camphorsulfonic acid was purchased from Aldrich Chemical Company, Inc.
4. The physical properties are as follows: ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.87 (d, 3 H, J = 6.8), 0.87 (d, 3 H, J = 6.7), 1.14 (s, 9 H), 1.83 (hept, 1 H, J = 7), 2.68–2.81 (m, 3 H), 3.20 (dd, 1 H, J_1 = 8.8, J_2 = 7.1), 3.43–3.56 (m, 3 H), 3.83 (s, 3 H), 3.85 (s, 3 H), 4.40 (AB, 1 H, J = 17), 4.43 (AB, 1 H, J = 17), 6.60 (s, 1 H), 6.63 (s, 1 H), 7.40 (s, 1 H); $[\alpha]_D^{25}$ –30.3° ($CHCl_3$, c 2.7).
5. The flask was filled with argon by evacuating and pressurizing several times through the three-way stopcock.
6. Tetrahydrofuran was distilled from sodium wire and benzophenone.
7. *tert*-Butyllithium solution in pentane was purchased form Alfa Products, Morton/Thiokol, Inc.
8. Iodomethane was purchased from Aldrich Chemical Company, Inc.
9. Anhydrous hydrazine was purchased from Aldrich Chemical Company, Inc.
10. The spectral properties are as follows: ^{1}H NMR ($CDCl_3$) δ: 0.92 (d, 6 H, J = 6), 1.19 (s, 9 H), 1.61 (m, 1 H), 2.64 (m, 1 H), 3.12 (overlapping doublets, 1 H, J = 8, J = 9), 3.40 (dd, 1 H, J = 8, J = 9).
11. The checkers did not observe crystallization at this point when the reaction was run on a much smaller scale (8 mmol). Two runs, each starting with 3.05 g of **2**, gave rise to 0.88 g (51%) and 0.83 g (46%) of purified (–)-salsolidine.
12. The physical properties are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.41 (d, 3 H, J = 6.6), 1.78 (br s, 1 H), 2.65 (m, 1 H), 2.77 (m, 1 H), 3.01 (m, 1 H), 3.25 (m, 1 H), 3.822 (s, 3 H), 3.828 (s, 3 H), 3.89 (m, 1 H), 6.61 (s, 1 H), 6.55 (s, 1 H); $[\alpha]_D^{22}$ –53.9 to –54.0° (C_2H_5OH, c 3.8) (lit.[2] –59.5 ± 0.5°); (95–98% ee by Pirkle HPLC analysis, (Note 13)).
13. Enantiomeric purity determination was performed as follows. The (–)-salsolidine **3** (100 mg) was dissolved in 1 mL of dichloromethane and 0.05 mL of triethylamine. To this solution was added 150 mg of 1-naphthoyl chloride (Aldrich Chemical Company, Inc.) and the reaction mixture was stirred for 0.5 hr at room temperature, then poured into 5 mL of aqueous 20% sodium hydroxide solution. Extraction with 10 mL of dichloromethane was followed by separation of the organic layer, which was dried over potassium carbonate. The solvent was removed under reduced pressure and the crude naphthamide was purified by column chromatography on silica gel (ethyl acetate–hexane–dichloromethane, 1:4:5). Enantiomeric analysis was performed using a Waters Associates Model 440 high-pressure liquid chromatograph equipped with a Pirkle Covalent Phenylglycine Column (Baker Bond Chiral HPLC Column, DNBPG, J. T. Baker, Phillipsburg, NJ). The detector used was UV at 254 mm and the solvent for elution was 10% 2-propanol–hexane at 5 mL/min with a back pressure of 3500 psi. The peaks were baseline separated and electronically integrated.

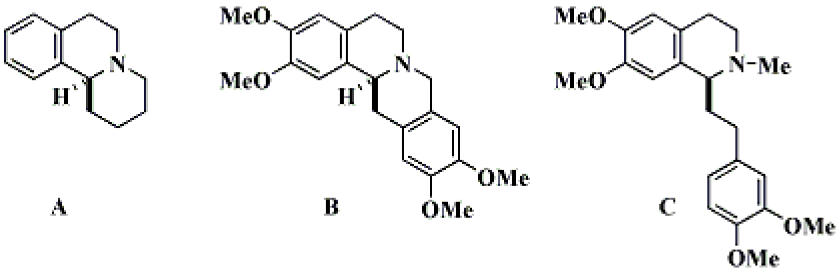
3. Discussion

This method of asymmetric alkylation has been performed in a number of other systems with equally good enantioselectivity. Tetrahydroisoquinolines have been alkylated[3] (Eq. 1) with various alkyl halides to give 1-substituted tetrahydroisoquinolines in 50–70% overall yields and with excellent ee values. Several naturally occurring isoquinoline alkaloids have also been prepared (compounds A–C) in 95–98.5% ee.[4] A number of chiral auxiliaries other than the valine-based *tert*-butyl ether also have been examined and gave 80–99% ee values after alkylation.[5] However, the authors consider the chiral auxiliary used in

the present procedure to be superior to the others.



In addition to isoquinolines, β-carbolines have been used to afford indole alkaloids, both natural and unnatural (Scheme 1), in high enantiomeric excess.[6] The indole nitrogen is protected as the methoxymethyl ether and later removed to provide the unsubstituted indole. In the absence of indole–nitrogen protection, the potassium salt is satisfactory but results in low asymmetric induction. However, if racemic products are desired, *N-tert*-butylformamidines can be used,[7] and smooth alkylation of the α-protons is achieved, thus obviating the need for protection of the indole nitrogen.



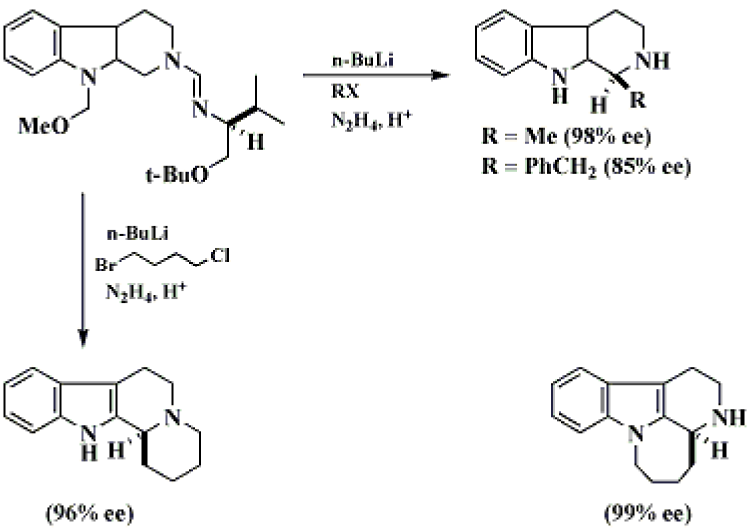
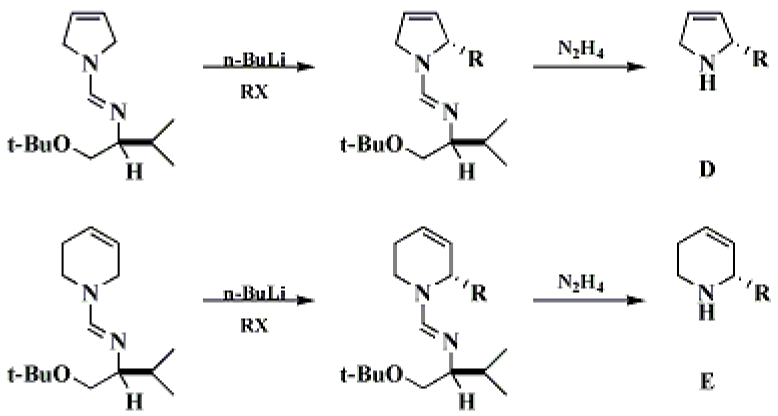


TABLE I

R,R	R'X	% ee
H	MeI	99
H	*n*-BuI	96
H	Allyl Br	96
H	$PhCH_2Cl$	98
MeO, MeO	3,4-$(MeO)_2PhCH_2Br$	99
MeO, MeO	3,4-$(MeO)_2PhCH_2CH_2I$	95

Asymmetric alkylations also are feasible, leading to the chiral dihydropyrrole (D) and the tetrahydropiperidine systems (E).[8] When the saturated analogs were employed (pyrrolidine and piperidine), no metalation could be effected in the presence of the chiral auxiliary, although metalation–alkylation proceeded normally when the *N-tert*-butylformamidines were employed.



This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 204

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

brine

(–)-SALSOLIDINE

6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline 1

(S)-N,N-dimethyl-N'-(1-tert-butoxy-3-methyl)-2-butylformamidine

N-tert-butylformamidines

ethanol (64-17-5)

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ethyl acetate (141-78-6)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium sulfate (7757-82-6)

toluene (108-88-3)

Benzophenone (119-61-9)

sodium (13966-32-0)

2-propanol (67-63-0)

piperidine, tetrahydropiperidine (110-89-4)

iodomethane (74-88-4)

Pentane (109-66-0)

hydrazine (302-01-2)

dichloromethane (75-09-2)

1-naphthoyl chloride (879-18-5)

naphthamide (2243-81-4)

Tetrahydrofuran (109-99-9)

pyrrolidine (123-75-1)

hexane (110-54-3)

triethylamine (121-44-8)

argon (7440-37-1)

Formamidine

tert-Butyllithium (594-19-4)

tetrahydroisoquinoline hydrochloride (14099-81-1)

dihydropyrrole

(+)-camphorsulfonic acid, (+)-10-Camphorsulfonic acid (3144-16-9)

Isoquinoline, 1,2,3,4-tetrahydro-6,7-dimethoxy-1-methyl-, (S)-, (S)-6,7-Dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline (493-48-1)

6,7-Dimethoxy-1,2,3,4-tetrahydro-2-[(1-tert-butoxy-3-methyl)-2-butyliminomethyl]isoquinoline (90482-03-4)

valinol tert-butyl ether

Salsolidine

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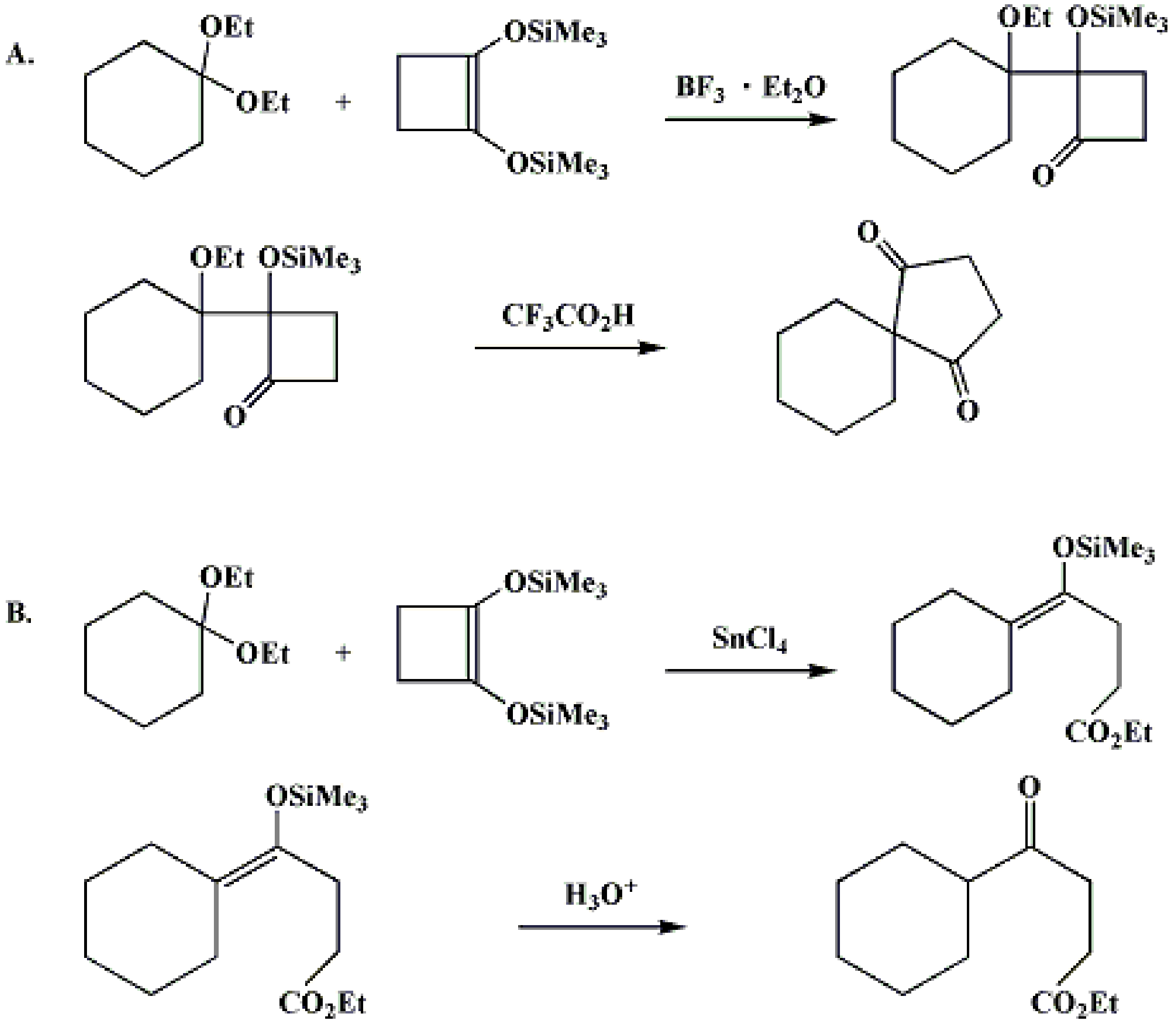
Organic Syntheses, CV 8, 578

RING EXPANSION AND CLEAVAGE OF SUCCINOIN DERIVATIVES: SPIRO[4.5]DECANE-1,4-DIONE AND ETHYL 4-CYCLOHEXYL-4-OXOBUTANOATE

[Cyclohexanebutanoic acid, γ-oxo-, ethyl ester]



Submitted by Eiichi Nakamura and Isao Kuwajima[1].
Checked by Jens Wolff and Ian Fleming.

1. Procedure

A. *Spiro[4.5]decane-1,4-dione* (**2**). In a dry, 200-mL, two-necked flask with one neck connected to a nitrogen source to maintain a positive pressure and the other neck covered with a rubber septum is placed a magnetic stirring bar. Boron trifluoride etherate (5.04 mL, 40.0 mmol) (Note 1) and 40 mL of dry methylene chloride (Note 2) are introduced with a hypodermic syringe and the solution is cooled to ca. –75°C with a dry ice/hexane bath. A mixture of cyclohexanone diethyl ketal (6.88 g, 40 mmol)

(Note 3) and 1,2-bis(trimethylsilyloxy)cyclobut-1-ene (9.20 g, 40 mmol) (Note 4) in 20 mL of dry methylene chloride is added during 10 min. The resulting yellow solution is stirred for 30 min at that temperature and 8 mL of trifluoracetic acid (Note 5) is added. The mixture is warmed to room temperature and stirred for 2 hr (Note 6) before addition of 40 mL of water. The mixture is extracted 3 times with 100 mL-portions of ether, and the combined extract is washed successively with a 30-mL portion of water, saturated aqueous sodium bicarbonate (2 × 45 mL), and 30 mL of saturated sodium chloride. The extract is dried over anhydrous magnesium sulfate, filtered, and concentrated on a rotary evaporator at aspirator pressure. The crude, viscous oily material is distilled at 0.05 mm with a Kugelrohr apparatus (Note 7) with an oven temperature at 75–80°C to obtain 5.40–6.00 g (81–90%) of spiro[4.5]decane-1,4-dione, which crystallizes on cooling to room temperature, mp 61–62°C (Note 8).

B. *Ethyl 4-cyclohexyl-4-oxobutanoate (**4**)*. In a dry, 100-mL, two-necked flask with one neck connected to a nitrogen source to maintain a positive pressure and with the other covered with a rubber septum is placed a magnetic stirring bar. Tin tetrachloride (7.50 g, 28.8 mmol) (Note 9) and 15 mL of dry methylene chloride (Note 2) are introduced with a hypodermic syringe and the solution is cooled to ca. −75°C with a dry ice/hexane bath. A mixture of cyclohexanone diethyl ketal (4.82 g, 28.0 mmol) (Note 3) and 1,2-bis(trimethylsilyloxy)cyclobut-1-ene (6.44 g, 28.0 mmol) (Note 4) in 10 mL of methylene chloride is added during 10 min. The yellow solution is stirred for 15 min at −75°C, and for 15 min at −30°C, during which period the solution turns heterogeneous (Note 10). Water (20 mL) and ether (50 mL) are added and the organic layer is separated. The aqueous layer is extracted twice with ether (50 mL) and the combined organic layers are washed successively with 3 × 10-mL portions of 1 *N* hydrochloric acid, and 20-mL portions each of water, aqueous sodium bicarbonate, and saturated sodium chloride. The oily product (6.30 g) obtained after drying (anhydrous magnesium sulfate) and concentration on a rotary evaporator is distilled to give an analytically pure keto ester (**4**) (5.27–5.44 g, 90–93%) as a fraction boiling at 110–112°C, 2.5 mm, or 84°C, 0.2 mm (Note 11).

2. Notes

1. Boron trifluoride etherate (Hashimoto Kasei Chemical, Osaka) was distilled before use.
2. Methylene chloride was distilled from phosphorus oxide and stored over molecular sieves.
3. Cyclohexanone diethyl ketal was prepared according to a procedure by Howard and Lorette; see *Org. Synth., Coll. Vol. V* **1973**, 292; bp 80–83°C, 18 mm. The checkers prepared it by keeping cyclohexanone (50 g), triethyl orthoformate (75 g) and concentrated hydrochloric acid (0.2 mL) in absolute ethanol (30 mL) for 10 hr at room temperature, followed by treatment with sodium hydroxide until the solution is basic.
4. 1,2-Bis(trimethylsiloxy)cyclobut-1-ene was prepared in ca. 80% yield on a

0.5-mol scale by Method 2 described by Bloomfield and Nelke; see *Org. Synth., Coll. Vol. VI* **1988**, 167.

5. Commercially available trifluoroacetic acid (Tokyo Kasei Co.) was used as received.

6. If trifluoroacetic acid treatment is omitted, the aldol-type adduct, 2-(1-ethoxycyclohexyl)-2-(trimethylsiloxy)cyclobutanone (**1**), is obtained in high (ca. 90%) yield; bp 85–90°C (bath temp.), 0.05 mm; IR (neat) cm^{-1}: 1789 (s, C=0); ^1H NMR (CCl_4) δ: 0.11 (s, 9 H), 0.9–2.2 (m, including t, *J* = 7 at δ 1.10), 2.2–2.9 (m, 3 H), 3.2–3.7 (AB part of ABX_3, 2 H). Treatment of purified **1** with trifluoroacetic acid gives **2** in nearly quantitative yield.

7. Kugelrohr distillation ovens are manufactured by Büchi Glasapparatefabrik.

8. The checkers found variable amounts (0–15%) of the ester (**4**) in the product. This could easily be removed by recrystallization of the diketone from light petroleum (bp 40–60°C) to give needles, mp 62–64°C. The product has the following spectral properties: IR (CCl_4) cm^{-1}; 1720 (vs); ^1H NMR (CCl_4) δ: 1.58 (br s, 10 H), 2.65 (s, 4 H); MS (70 eV) *m/e* (relative intensity) 166.0983 (M^+, 100, calcd. for $C_{10}H_{14}O_2$; 166.0994), 137 (24), 124 (36), 112 (87), 111 (83), 109 (27), 85 (38), 81 (48), 67 (95), 56 (48), 54 (45), 53 (42), 41 (58), 30 (64).

9. Tin tetrachloride (Yoneyama Yakuhin Co.) was distilled before use.

10. If the mixture is quenched with triethylamine before aqueous workup, the intermediate enol silyl ether **3** is obtained; bp 110–115°C (bath temp.), 0.04 mm; IR (neat) cm^{-1}: 1745 (s), 1680 (m); ^1H NMR (CCl_4) δ: 0.12 (s, 9 H), 1.3–2.6 (m, 14 H, including t, *J* = 7, at 1.26 and s at 2.36), 4.10 (q, *J* = 7). Addition of aldehydes, acetals, or phenylsulfenyl chloride at this stage gives the respective aldol and sulfenylated products.

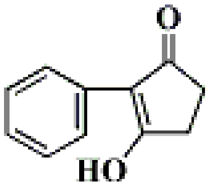
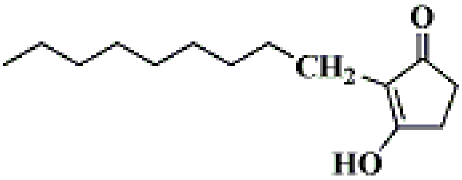
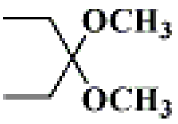
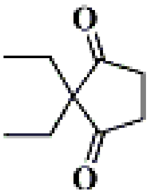
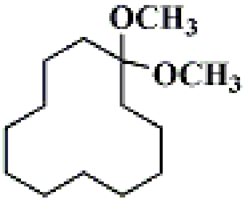
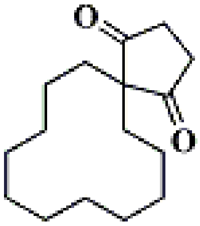
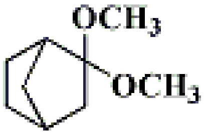
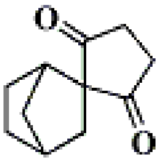
11. The product has the following spectral properties: IR (CCl_4), cm^{-1}: 1739 (s), 1713 (s); ^1H NMR (CCl_4) δ: 0.8–1.9 (m, 18 H, including t, *J* = 1.28, CH_2CH_3), 4.15 (q, *J* = 7, OCH_2CH_3); MS (70 eV) *m/e* (relative intensity) 212 (M^+, 5), 167 (20), 129 (55), 111 (28), 101 (80), 83 (100), 55 (72), 41 (37), 29 (34).

3. Discussion

The present reactions are based on the novel rearrangement of succinoin derivatives such as **1** which are obtainable in high yield by the reaction of 1,2-bis(trimethylsilyloxy)cyclobut-1-ene with carbonyl compounds. The first procedure, Part A, illustrates a general method for preparing a wide range of spiro[4.*n*]alkane-1,4-diones as well as useful 2-mono- and 2,2-disubstituted cyclopentane-1,3-diones (Table I).[2] The combination of an aldol reaction[3] and a skeletal rearrangement provides a highly efficient new approach to these synthetically interesting molecules.[4] The reaction can be performed either in a single pot or as a two-stage operation by isolating the initial aldol adduct **1**. The merit of the sequence as a spiro annelation method is illustrated by the synthesis of a 5,8-methanospiro[4.5]decanedione from norcamphor (Table I). γ-Keto acids and cyclopent-2-ene-1,4-diones also become available from

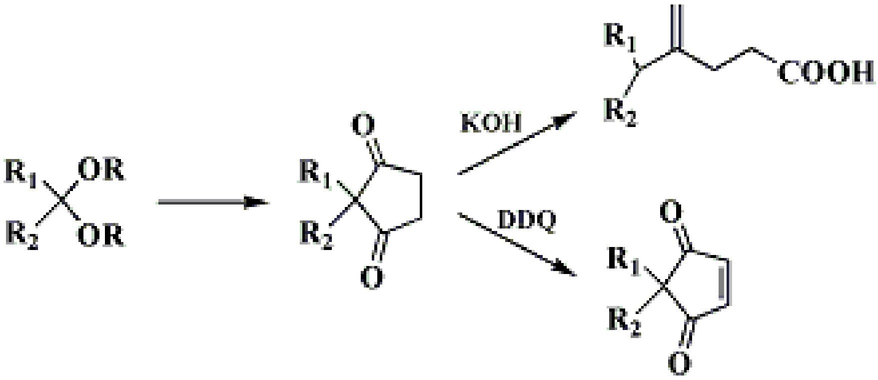
ketals in a few steps.

TABLE I
SYNTHESIS OF CYCLOPENTANE-1,3-DIONES

Acetal or Ketal	Product	Yield (aldol × rearrangement)[a]
$C_6H_5CH(OC_2H_5)_2$		94 × 97%
n-$C_9H_{19}CH(OCH_3)_2$		90 × 87%
		92 × 87%
		92 × 94% (91%)[b]
		60 × 92%

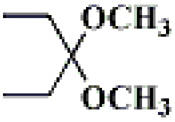
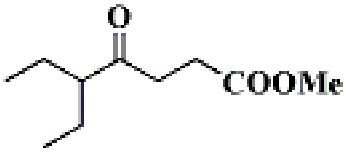
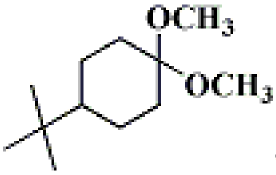
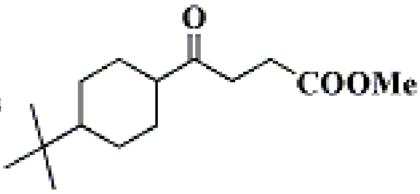
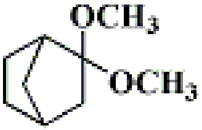
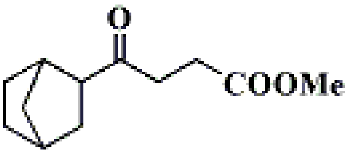
[a]The results in this table were obtained by the two-stage procedure (i.e., the isolation of the initial adduct, e.g., **1**, is involved).

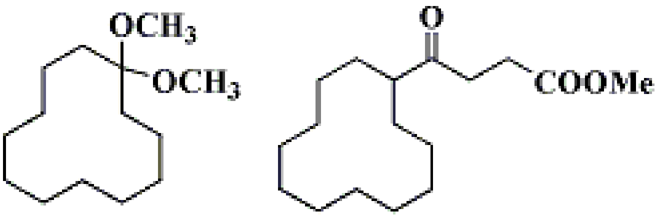
[b]Yield from the single-pot procedure as described in the text.



The second procedure, Part B, illustrates an easy synthesis of γ-keto esters by "reductive succinoylation" of a ketal function.[5] It is useful not only for the preparation of keto esters but also as a four-carbon chain-elongation reaction starting from ketones. The reaction is applicable to a diverse range of ketals as is shown in Table II. The enol silyl ether intermediate **3** can either be isolated or used in situ for further elaboration. Fluoride-[6] and Lewis-acid-catalyzed aldol reactions cleanly give aldol adducts,[6] and the reaction with phenylsulfenyl chloride gives α-phenylthio ketones in high yield.[5]

TABLE II
REDUCTIVESUCCINOYLATION

Ketal	Product	Yield
		87
		92
		90



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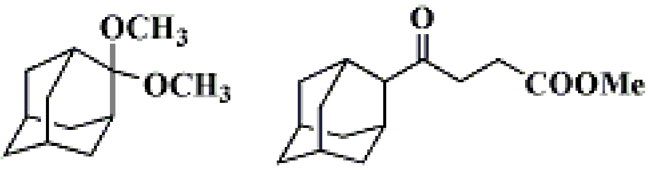

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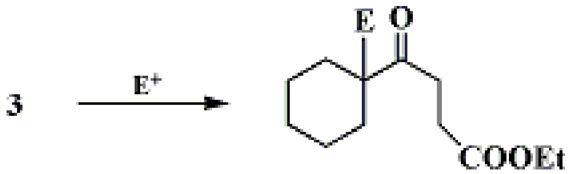

Cyclobutanone **1** is also useful for the stereoselective construction of quaternary carbon centers[7] and 2,3-substituted cyclopentenones.[8] The synthetic utility of the chemistry of **1** and related compounds has been reviewed.[7,9]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Spiro[4.5]decane-1,4-dione (2)

Ethyl 4-cyclohexyl-4-oxobutanoate (4)

ACETAL (105-57-7)

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

Cyclohexanone (108-94-1)

sodium chloride (7647-14-5)

triethyl orthoformate (122-51-0)

methylene chloride (75-09-2)

tin tetrachloride (7646-78-8)

magnesium sulfate (7487-88-9)

triethylamine (121-44-8)

boron trifluoride etherate (109-63-7)

trifluoroacetic acid, Trifluoracetic acid (76-05-1)

Phenylsulfenyl chloride (931-59-9)

Cyclobutanone (1191-95-3)

Norcamphor (497-38-1)

1,2-bis(trimethylsilyloxy)cyclobut-1-ene, 1,2-Bis(trimethylsiloxy)cyclobut-1-ene (17082-61-0)

silyl ether (13597-73-4)

phosphorus oxide (1314-56-3)

Spiro[4.5]decane-1,4-dione (39984-92-4)

Ethyl 4-cyclohexyl-4-oxobutanoate, Cyclohexanebutanoic acid, γ-oxo-, ethyl ester (54966-52-8)

cyclohexanone diethyl ketal (1670-47-9)

2-(1-Ethoxycyclohexyl)-2-(trimethylsiloxy)cyclobutanone (69152-09-6)

5,8-methanospiro[4.5]decanedione

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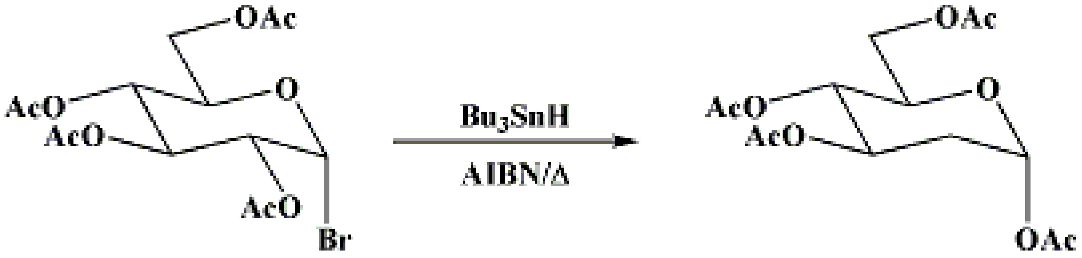
Organic Syntheses, CV 8, 583

1,3,4,6-TETRA-*O*-ACETYL-2-DEOXY-α-D-GLUCOPYRANOSE

[α-D-*arabino*-Hexopyranose, 2-deoxy-, tetracetate]



Submitted by Bernd Giese and Kay S. Gröninger[1].
Checked by Matthew R. Sivik and Leo A. Paquette.

1. Procedure

A 1-L, round-bottomed flask equipped with a magnetic stirring bar and a reflux condenser with a Claisen head on top fitted with a septum and a dry nitrogen inlet is charged with 20.6 g (50 mmol) of 2,3,4,6,-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (Note 1) and 400 mL of anhydrous toluene. The mixture is flushed with nitrogen and brought to reflux with a hot oil bath. A nitrogen atmosphere is maintained over the well-stirred reaction mixture during this and the ensuing steps. Meanwhile, a solution of 1.64 g (10 mmol) of azobisisobutyronitrile (AIBN) and 16.0 g (55 mmol) of tributylstannane in 90 mL of anhydrous toluene is prepared and filtered if necessary (Note 2). This solution is added to the refluxing, well-stirred reaction mixture during 6 hr by a syringe pump through a long needle that pierces the septum and ends at least 3 cm above the lower end of the cooling zone of the reflux condenser (Note 3). Ten minutes after all of the solution is added, the reaction mixture is cooled and the solvent is removed with a rotary evaporator (bath 40°C); 100 mL of hexane and 100 mL of acetonitrile are added, and the resulting two-phase solution is stirred vigorously for 5 min and then transferred to a separatory funnel. The lower, acetonitrile layer is separated and the hexane phase washed with 10 mL of acetonitrile (Note 4). This extraction of the combined acetonitrile solutions is repeated twice using 100 mL of hexane each time. The combined acetonitrile phases are then filtered and distilled (rotary evaporator, bath temp. 40°C). Coevaporation with 40 mL of hexane yields crude solid material that is dissolved in 120 mL of boiling *tert*-butyl methyl ether. Then 30 mL of hexane is added and the mixture is left for 4 hr at room temperature. To complete crystallization of the product, another 20 mL of hexane is added and the mixture is kept for 12 hr at 5°C. The long, colorless needles are filtered and washed once with 30 mL of hexane/*tert*-butyl methyl ether (2:1) and two times with 30 mL of pentane to yield 13.2–13.4 g (79–81%) of 1,3,4,6-tetra-*O*-acetyl-2-deoxy-α-D-

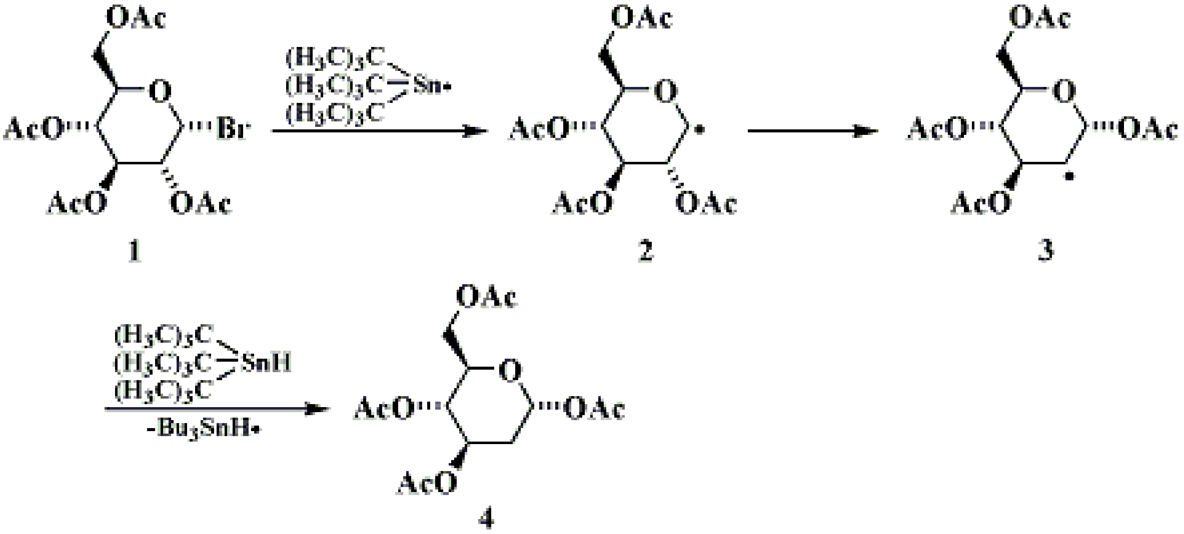
glucopyranose, mp 109–110°C; $[\alpha]_D^{20}$ + 113°C (C_2H_5OH, *c* 1.2).

2. Notes

1. This material was obtained form the Sigma Chemical Company and was recrystallized from diethyl ether/pentane before use. It can also be prepared by the procedure of Redemann, C. E.; Niemann, C. *Org. Synth., Coll. Vol. III,* **1955**, 11.
2. Azobisisobutyronitrile (AIBN) and tributylstannane were obtained from the Aldrich Chemical Company, Inc. The amount of AIBN can be reduced to 0.82 g (5 mmol) without affecting yields. A small excess (1.1–1.2 equiv) of tributylstannane must be used to ensure total consumption of starting material.
3. This method ensures that AIBN is not thermolyzed in the needle and that tributylstannane is diluted by the refluxing solvent before reaching the reaction mixture. It is also possible to add the tributylstannane solution by a dropping funnel (l drop every 2 sec) that replaces septum and syringe pump. This method gives only slightly lower yields (75%) if the stannane solution runs down slowly on the glass surface of the condenser and does not enter the reaction mixture undiluted.
4. By this procedure most of the tributylbromostannane and other stannyl compounds are removed. It is important to wait for complete separation of the phases.
5. The product is analytically pure. Anal. calcd. for $C_{14}H_{20}O_9$: C, 50.60; H. 6.07. Found: C, 50.71; H, 6.25. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.97 (ddd, 1 H, H-2a; $J_{1,2a}$ = 3.7, $J_{2a,2c}$ = 13.6, $J_{2a,3}$ = 11.6); 2.04, 2.05, 2.09, 2.14 (4 s, 12 H, acetyl); 2.28 (ddd, 1 H, H-2e, $J_{1,2e}$ = 1.4, $J_{2e,3}$ = 5.3); 4.00–4.11 (m, 2 H, H-5, H-6); 4.36 (m, 1 H, H-6"); 5.08 (t, 1 H, H-4, $J_{3,4}$ = $J_{4,5}$ = 9.7); 5.32 (ddd, 1 H, H-3); 6.26 (br d, 1 H, H-1).
6. Concentration of the mother liquors gives another 0.4–0.6 g of impure product that can be recrystallized from *tert*-butyl methyl ether/hexane to give another 0.3–0.5 g (2–3%) of analytically pure product.

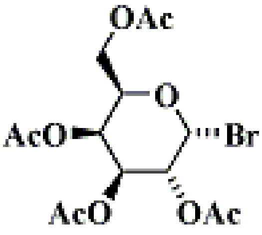
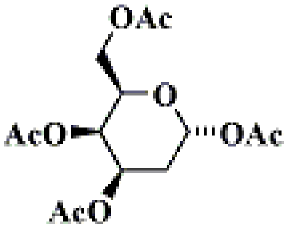
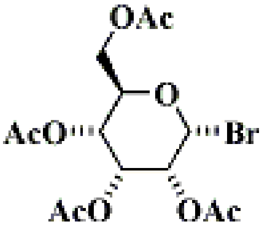
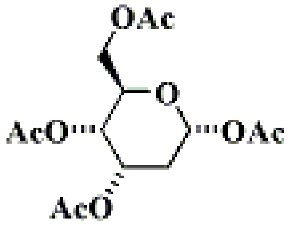
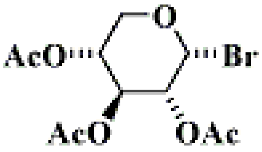
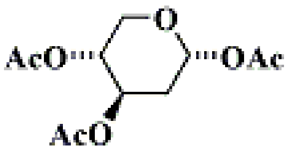
3. Discussion

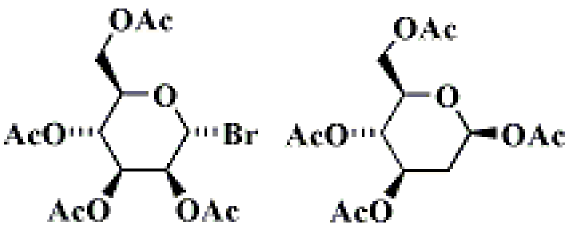
The main reaction step of this synthesis of 2-deoxy sugars is a radical rearrangement (**2** **3**).[2] Bromine abstraction from the glucosyl bromide **1** by tributyltin radicals yields glucosyl radical **2** that undergoes acetoxy migration and gives the rearranged radical **3**. This rearrangement is a stereoselective one-step reaction that occurs with rate coefficients of about 10^3 at 75°C in benzene.[3] The driving force of the rearrangement **2** **3** is the formation of the acetal structure at C-1 of **3**.[4] Hydrogen abstraction from tributyltin hydride yields 2-deoxy sugar **4** and the tributyltin radical that starts another chain.



This rearrangement offers a general synthesis of α- and β-2-deoxy sugars with pyranoid and furanoid ring systems (Table I).[5]

TABLE I
SYNTHESIS OF 2-DEOXY SUGARS VIA REDUCTIVE REARRANGEMENT OF GLYCOSYL DERIVATIVES[5]

Glycosyl Bromide	2-Deoxy Sugar	Yield(%)
		71
		70
		81



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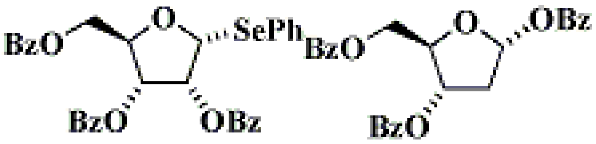

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Benzene (71-43-2)

diethyl ether (60-29-7)

hydrogen (1333-74-0)

acetonitrile (75-05-8)

bromine (7726-95-6)

nitrogen (7727-37-9)

toluene (108-88-3)

Pentane (109-66-0)

hexane (110-54-3)

tributyltin hydride, tributylstannane, tributyltin (688-73-3)

azobisisobutyronitrile (78-67-1)

tributylbromostannane (1461-23-0)

tert-butyl methyl ether (1634-04-4)

2,3,4,6,-tetra-O-acetyl-α-D-glucopyranosyl bromide

1,3,4,6-Tetra-O-acetyl-2-deoxy-α-D-glucopyranose

α-D-arabino-Hexopyranose, 2-deoxy-, tetracetate (16750-06-4)

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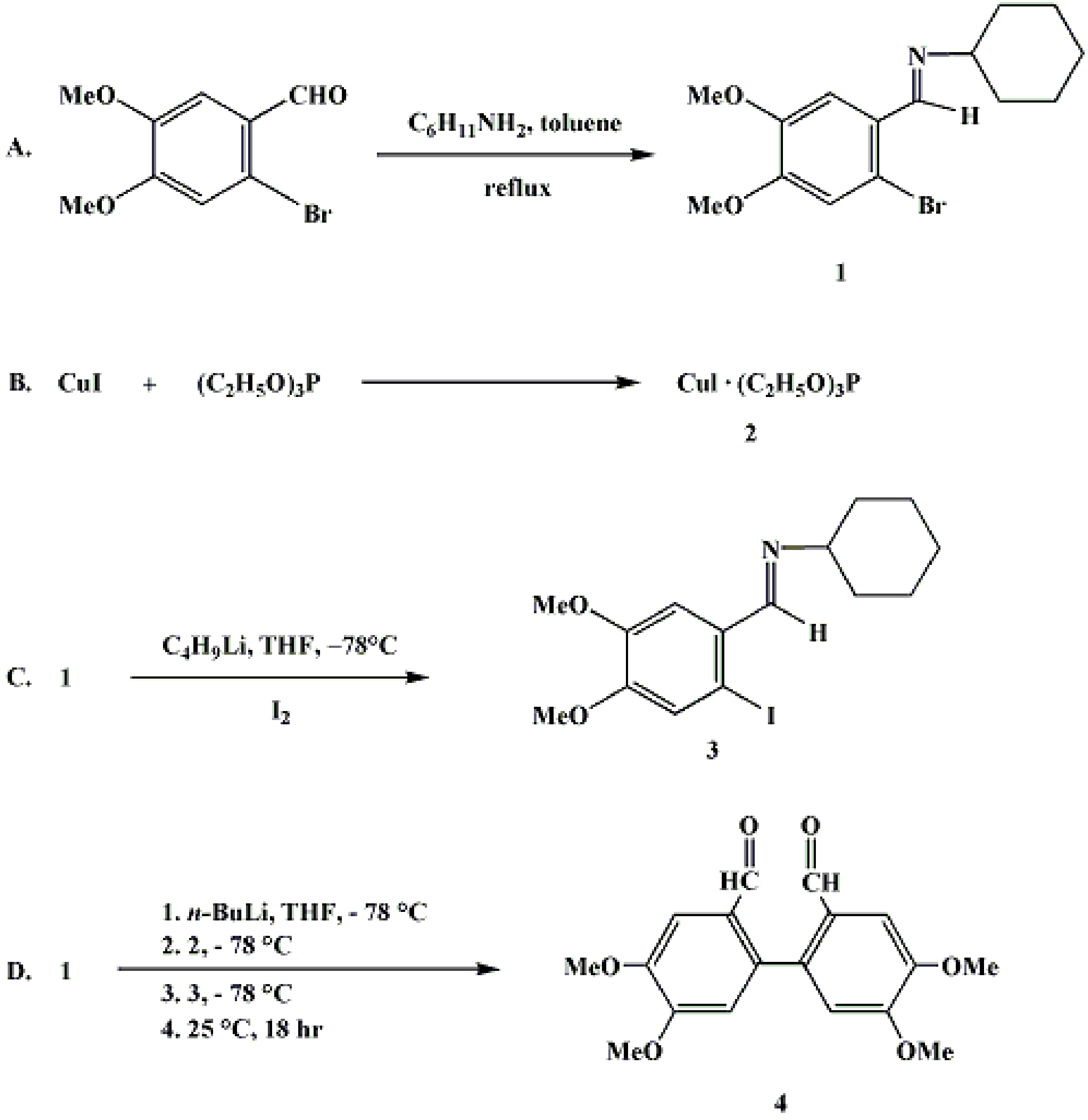
Organic Syntheses, *CV 8, 586*

AMBIENT-TEMPERATURE ULLMAN REACTION: 4,5,4',5'-TETRAMETHOXY-1,1'-BIPHENYL-2,2'-DICARBOXALDEHYDE

[1,1'-Biphenyl]-2,2'-dicarboxaldehyde, 4,4',5,5'-tetramethoxy-]



Submitted by F. E. Ziegler, K. W. Fowler, W. B. Rodgers, and R. T. Wester[1].
Checked by Tetsuji Oshima and Ryoji Noyori.

1. Procedure

Caution! Aqueous sodium cyanide is used in this procedure. All operations should be

conducted in a well-ventilated hood and rubber gloves should be worn.

A. *6-Bromo-3,4-dimethoxybenzaldehyde cyclohexylimine* ***(1)***. A 2-L, three-necked flask is equipped with a Dean–Stark trap, a reflux condenser, a magnetic stirrer, and a nitrogen inlet. The vessel is purged with nitrogen and charged with 40.0 g (0.16 mol) of 6-bromo-3,4-dimethoxybenzaldehyde (6-bromoveratraldehyde) (Note 1). 22.4 mL (0.20 mol) of cyclohexylamine (Note 2), and 800 mL of toluene. The mixture is refluxed for 16 hr (Note 3). The solution is cooled to room temperature and the solvent is removed on a rotary evaporator. The residual crystalline mass is recrystallized from a 3 : 1 hexane–methylene chloride mixture (1.5 L) to provide 48.4–51.4 g of the imine **1** as white crystals in two crops (mp 172–172.5°C)[2] (Note 4).

B. *Cuprous iodide-triethyl phosphite complex* (**2**). (Note 5). A 1-L, round-bottomed flask equipped with a magnetic stirrer and reflux condenser is flame-dried under nitrogen. The vessel is charged with 38.2 g (0.20mol) of cuprous iodide, 33.4 mL (0.20 mol) of triethyl phosphite (Note 6) and 400 mL of dry toluene (distilled from CaH_2). The mixture is stirred at 80°C for 8 hr, cooled to room temperature, and filtered under reduced pressure on a pad of Celite. The solvent is removed from the filtrate successively with a rotary evaporator and briefly (15 min) under high vacuum. The residual solid is recrystallized from ether (25 mL) to yield 41.1–49.9 g (57.4–69.8%) of cuprous iodidetriethyl phosphite complex in two crops, mp 114–115°C.

C. *6-Iodo-3,4-dimethoxybenzaldehyde cyclohexylimine* (**3**). A 1-L, three-necked flask is equipped with a Claisen adapter (Note 7), a Trubore stirrer, a nitrogen inlet, and glass stoppers. The flask is thoroughly flame-dried under nitrogen. To the cooled flask is added 14.0 g (0.043 mol) of cyclohexylimine **1** and the glass stoppers are replaced by an alcohol thermometer and a rubber septum. Tetrahydrofuran (400 mL) (Note 8) is added via syringe through the septum and the resultant mixture is stirred at room temperature (27°C) for 30 min to effect solution. The solution is cooled to −78°C in dry ice–acetone bath (Note 9). A solution of butyllithium in hexane (30.9 mL, 1.53 *M*, 0.047 mol) (Note 10) is added by syringe over 10 min at such a rate as to maintain the temperature below −75°C (Note 11). As the butyllithium is added the precipitate slowly dissolves, leaving a clear, golden-yellow solution that is stirred for 15 min after the addition is complete. A solution of 27.0 g (0.11 mol) of iodine dissolved in 50 mL of dry THF is added via syringe to the reaction mixture at such a rate as to maintain the temperature below −70°C. The iodine solution (20–25 mL) is added until the red iodine color persists; precipitation also occurs. The mixture is warmed to room temperature, poured into 400 mL of water, and extracted with methylene chloride (5 × 400 mL). The combined organic extracts are dried (anhydrous $MgSO_4$), filtered and concentrated on a rotary evaporator to 200 mL, and then washed with 200 mL of aqueous saturated sodium sulfite solution. The organic phase is redried, filtered, and concentrated. The solid residue is recrystallized from a 1:4 chloroform–hexane mixture (300 mL) to afford 12.6–13.5 g (78.6–85.0%) of 6-iodoveratraldehyde cyclohexylimine as white crystals, mp 180–181°C[2] (Note 4).

D. *4,5,4',5'-Tetramethoxy-1,1'-biphenyl-2,2'-carboxaldehyde* ***(4)***. The metalation procedure described in Section C is repeated using a 3-L flask, 18.4 g (0.056 mol) of 6-

bromoveratraldehyde cyclohexylimine (**1**), 575 mL of tetrahydrofuran, and 40.6 mL (1.53 *M*, 0.062 mol) of butyllithium. After the metalation is complete at −78°C, the septum is replaced by a glass stopper. Solid cuprous iodide–triethyl phosphite complex (30.3 g, 0.085 mol) is added to the vessel at −78°C in one portion, immediately giving a green solution. The mixture is stirred for an additional 30 min. After the first 15 min, the solution turns a brownish-orange to red color. Solid 6-iodoveratraldehyde cyclohexylimine **(3)** (21.0 g, 0.056 mol) is added in one portion to produce an orange suspension. The reaction mixture is allowed to warm to room temperature (27°C), during which time the mixture becomes dark brown. The reaction mixture is stirred for 18 hr at room temperature. The reaction mixture is diluted with 600 mL of methylene chloride and 850 mL of 15% aqueous acetic acid and stirred vigorously for 17 hr. The yellow solution is transferred to a 4-L separatory funnel and the layers are separated. The organic layer is dried (anhydrous magnesium sulfate), filtered, and concentrated on a rotary evaporator to 800 mL and then transferred to a 2-L separatory funnel. The organic solution is washed with 5% aqueous hydrochloric acid (5 × 100 mL) and saturated aqueous sodium bicarbonate solution (10 × 50 mL).

(Caution: The final washings must be alkaline to avoid the liberation of hydrogen cyanide in the subsequent step.) The organic layer is washed twice with 500 mL of 10% aqueous sodium cyanide solution, once with 500 mL of saturated aqueous sodium bicarbonate, and twice with 500 mL of water.

(Caution: The sodium cyanide washes should be bottled separately and labeled appropriately for approved disposal.) The organic layer is dried (anhydrous magnesium sulfate), filtered, and concentrated to provide 16.3–20.3 g of residue. Crystallization from a 1 : 3 methylene chloride–hexane mixture at 5°C affords 13.1–16.9 g (70.4–90.7%) of beige crystals of the biphenyl, mp 215–216°C (lit.[3] 214–215°C) after drying under high vacuum (0.1 mm) (Note 4).

2. Notes

1. 6-Bromo-3,4-dimethoxybenzaldehyde was purchased from the Aldrich Chemical Company, Inc. (Milwaukee) or readily prepared by bromination of veratraldehyde (Aldrich Chemical Company, Inc. or Tokyo Kasei).[4]
2. Cyclohexylamine (Aldrich Chemical Company, Inc. or Nakarai Chemicals) and all solvents and reagents (reagent grade) were used as received, unless otherwise specified.
3. The water level in the trap remains constant after this period of time.
4. Spectral characterization: ^{1}H NMR ($CDCl_3$). 6-Bromoveratraldehyde cyclohexylimine, δ: 1.07–1.82 (m, 10 H), 3.30 (m, 1 H, NCH), 3.89 (s, 3 H, OCH_3) 3.92 (s, 3 H, OCH_3), 6.97 (s, 1 H), 7.55 (s, 1 H), 8.54 (s, 1 H, N=CH); 6-Iodoveratraldehyde cyclohexylimine, δ: 1.07–1.82 (m, 10 H), 3.31 (m, 1 H, NCH), 3.88 (s, 3 H, OCH_3), 3.92 (s, 3 H, OCH_3), 7.22 (s, 1 H), 7.53 (s, 1 H), 8.32 (s, 1 H, N=CH). 4,5,4',5'-Tetramethoxy-1,1'-biphenyl-2,2'-dicarboxaldehyde, δ: 3.96 (s, 6 H, OCH_3), 4.01 (s, 6 H, OCH_3), 6.80 (s, 2 H), 7.56 (s, 2 H), and 9.67 (s, 2 H, CHO).
5. This method was adapted from the procedure of Nishizawa.[5] The complex is reported to have mp 109–110°C.[6]

6. Cuprous iodide was purchased from Alfa Products, Johnson Mathey Co., or Kishida Chemicals and triethyl phosphite from the Aldrich Chemical Company, Inc. or Nakarai Chemicals.
7. The offset neck of the adapter was fitted with the nitrogen inlet and the other neck with a glass stopper that was eventually replaced with a thermometer.
8. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl under nitrogen in all applications.
9. The bromide, **1**, precipitated during the cooling.
10. Butyllithium was purchased from Alfa Products, Johnson Mathey Co., or Mitsuwa Pure Chemicals and was standardized by the method of Kofron.[7]
11. Alcohol thermometers were found not to read temperatures accurately. A temperature of –78°C designates the lowest temperature to which a large dry ice–acetone bath cools the reaction mixture. The temperature –75°C signifies a 3° rise in temperature.

3. Discussion

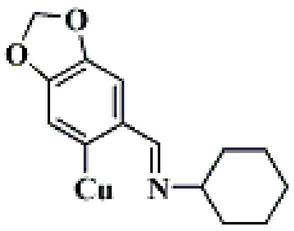
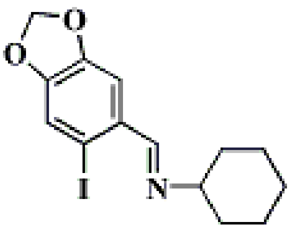
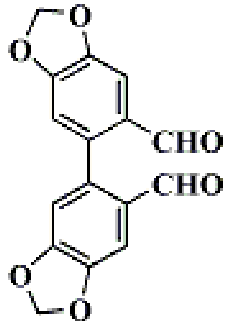
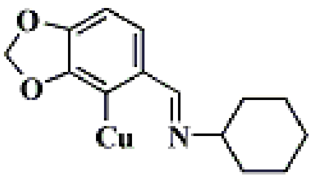
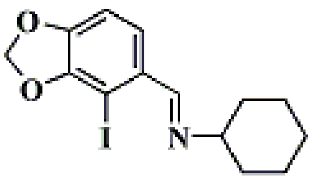
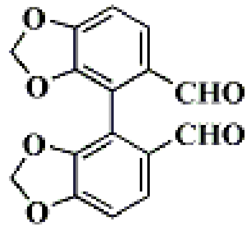
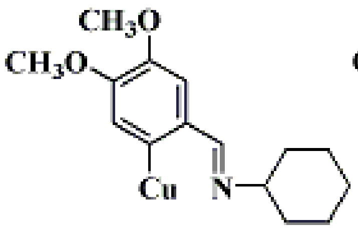
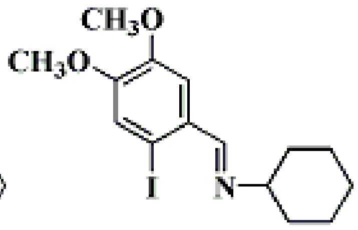
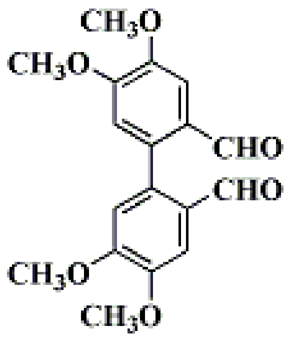
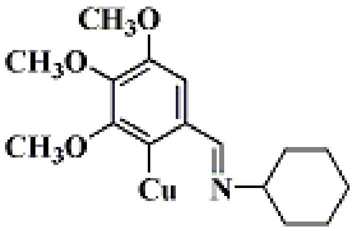
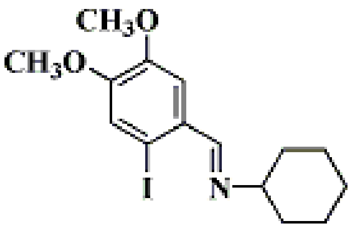
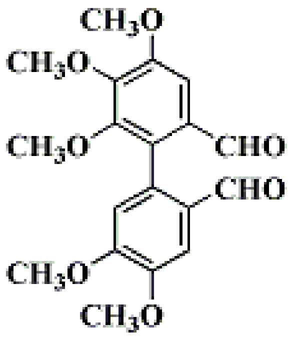
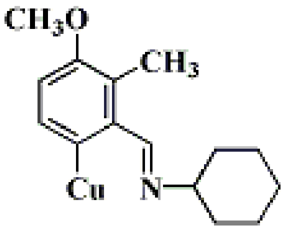
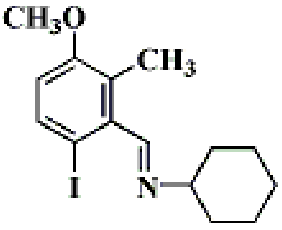
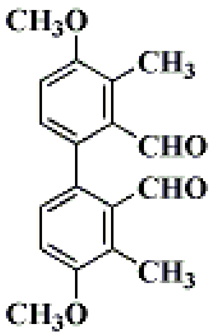
The Ullman reaction has been traditionally conducted at elevated temperatures (100–250°C), with or without solvent, in the presence of copper powder. Often the quality of copper can be extremely important to the success of the reaction.[8] Aromatic bromides and halides that bear *ortho*-substituted electron-withdrawing groups undergo coupling at the low end of the temperature range. Cross-coupling is best accomplished when only one of the aryl halides bears an electron-withdrawing group.[9] In such instances, an excess of the aryl halide without the electron-withdrawing group may have to be employed.[10]

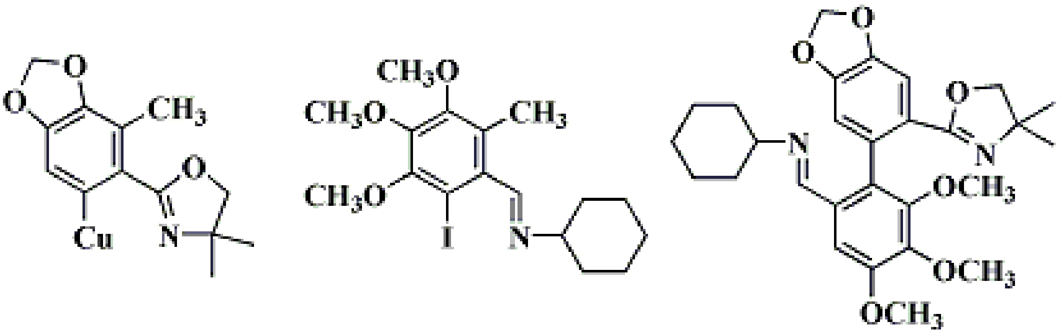
Nickel(0) reagents have been employed in the symmetric coupling of aryl halides in sterically unencumbered cases.[11,12] An efficient cross-coupling reaction between an arylzinc halide and an *ortho*-iodoarylimine under mild conditions mediated by Ni(0) has been reported.[13] Thallium(III) trifluoroacetate has been employed in the symmetrical coupling of aromatic ethers.[14] The use of diazonium salts in the formation of unsymmetric biphenyls has been reviewed.[15]

The present method permits both symmetric and unsymmetric coupling to occur at room temperature. It is necessary for a substitutent (nitrogen or sulfer) to be situated ortho to the halogen so that the heteroatom can chelate well with copper. This requirement must be fulfilled in both reacting partners. The organolithium species may be generated by metal–hydrogen or metal–halogen exchange. The coupling works well in sterically congested compounds, and only for aryl iodides. o-Iodoaldehydes may also be prepared by direct iodination of aromatic aldehydes.[12,16] Representative applications of this reaction are provided in Table I.

TABLE I
AMBIENT-TEMPERATURE ULLMAN REACTION

Organocopper	Iodide	Biphenyl	Yield (%)ref

			57[2]
			44[2]
			76 (62)[2]
			63[2]
			88[12]



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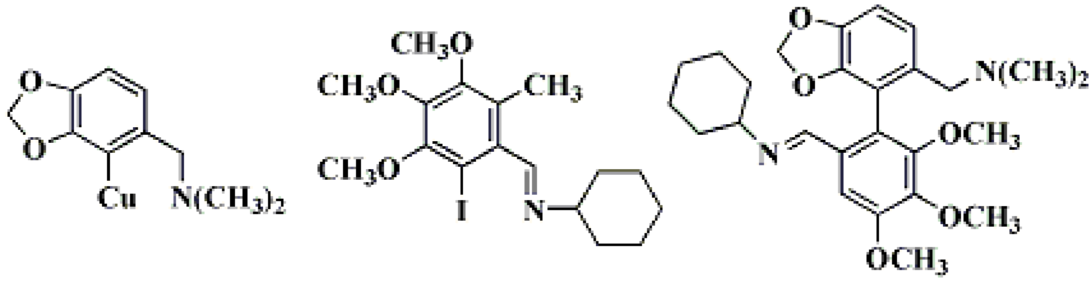

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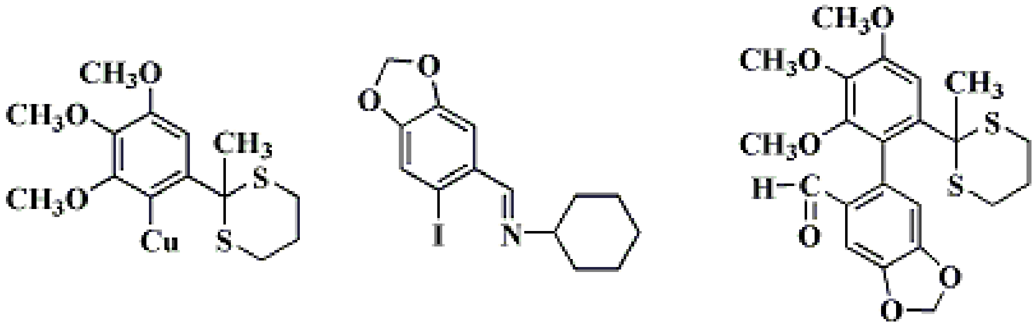

63[2]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium benzophenone ketyl

Cuprous iodide-triethyl phosphite complex

cuprous iodidetriethyl phosphite complex

4,5,4',5'-Tetramethoxy-1,1'-biphenyl-2,2'-carboxaldehyde

1,1'-Biphenyl]-2,2'-dicarboxaldehyde, 4,4',5,5'-tetramethoxy-

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ether (60-29-7)

sodium sulfite (7757-83-7)

chloroform (67-66-3)

sodium bicarbonate (144-55-8)

sodium cyanide (143-33-9)

hydrogen cyanide (74-90-8)

nitrogen (7727-37-9)

sulfer (7704-34-9)

copper (7440-50-8)

nickel(0) (7440-02-0)

iodine (7553-56-2)

toluene (108-88-3)

Biphenyl (92-52-4)

methylene chloride (75-09-2)

cuprous iodide (7681-65-4)

magnesium sulfate (7487-88-9)

Veratraldehyde (120-14-9)

iodide (20461-54-5)

cyclohexylamine (108-91-8)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

hexane (110-54-3)

Triethyl phosphite (122-52-1)

cyclohexylimine

thallium(III) trifluoroacetate (23586-53-0)

6-bromo-3,4-dimethoxybenzaldehyde, 6-bromoveratraldehyde (5392-10-9)

6-iodoveratraldehyde cyclohexylimine, 6-Iodo-3,4-dimethoxybenzaldehyde cyclohexylimine (61599-78-8)

6-bromoveratraldehyde cyclohexylimine, 6-Bromo-3,4-dimethoxybenzaldehyde cyclohexylimine (73252-55-8)

4,5,4',5'-TETRAMETHOXY-1,1'-BIPHENYL-2,2'-DICARBOXALDEHYDE (29237-14-7)

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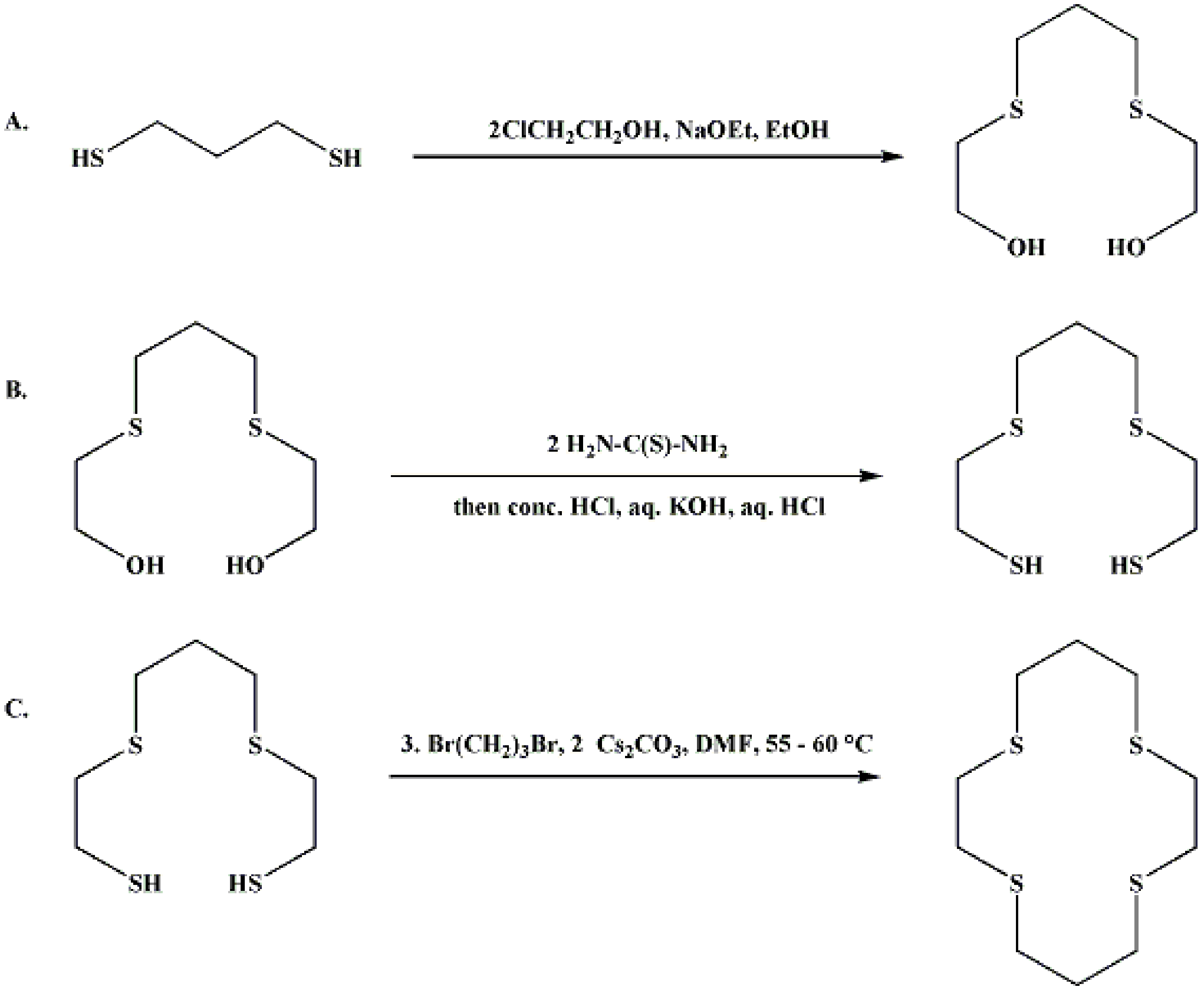
Organic Syntheses, *CV 8, 592*

SYNTHESIS OF MACROCYCLIC SULFIDES USING CESIUM THIOLATES: 1,4,8,11-TETRATHIACYCLOTETRADECANE



Submitted by J. Buter and Richard M. Kellogg[1].
Checked by Joseph M. Salvino and Bruce E. Smart.

1. Procedure

A. *3.7-Dithianonane-1,9-diol.*[2] A 500-mL, three-necked, round-bottomed flask is fitted with a mechanical stirrer, a reflux condenser attached to a nitrogen inlet, and a pressure-equalizing dropping funnel. The flask is flushed with nitrogen and charged with 250 mL of absolute ethanol. The ethanol is stirred and 5.75 g (0.25 mol) of sodium metal is cautiously added. After the sodium dissolves, the solution is warmed to 45–50°C and 13.5 g (0.125 mol) of 1,3-propanedithiol (Note 1) is added dropwise over a period of 15 min. To the resulting solution is added dropwise 20.1 g (0.25 mol) of 2-chloroethanol (Note 1) and the mixture is refluxed for 3–4 hr. The mixture is then allowed to cool to room temperature and is filtered. The filtrate is concentrated on a rotary evaporator to a viscous liquid, which is distilled to give 17.3–20.0 g (71–82%) of 3,7-dithianonane-1,9-diol, bp 200°C (1.5 mm) (Note 2).

B. *3,7-Dithianonane-1,9-dithiol.*[2] In a 1-L, round-bottomed flask equipped with a reflux condenser and a magnetic stirring bar are placed 35.0 g (0.178 mol) of 3,7-dithianonane-1,9-diol, 30.0 g (0.394 mol) of thiourea (Note 3), and 94 mL of concentrated hydrochloric acid. The mixture is stirred and refluxed for 12

hr. The resulting solution is cooled in an ice bath and 67 g (1.2 mol) of potassium hydroxide dissolved in 400 mL of water is added cautiously. The mixture is then refluxed for 3 hr. The resulting two-phase system is cooled to room temperature and the upper aqueous phase is decanted from the oily organic layer. The aqueous phase is acidified with dilute hydrochloric acid and extracted with 300 mL of ether. The ethereal extract is combined with the organic layer from the reaction mixture, and this solution is dried over anhydrous magnesium sulfate. The drying agent is removed by filtration and the filtrate is concentrated on a rotary evaporator. The residual liquid is distilled to give 21.4 g (53%) of 3,7-dithianonane-1,9-dithiol, bp 159–162°C (1.2 mm) (Note 4).

C. *1,4,8,11-Tetrathiacyclotetradecane.* A dry, 3-L, three-necked, round-bottomed flask is equipped with a double-necked adapter for a thermometer and the 250-mL addition funnel shown in f.htmigure 1 (Note 5), a reflux condenser, and a mechanical stirrer with a 7-cm blade of Teflon. The entire system is kept under positive nitrogen pressure. The flask is charged with 2.2 L of *N,N*-dimethylformamide and 13.04 g (40 mmol) of cesium carbonate (Note 6). The mixture is stirred and heated to 55–60°C.

Figure 1. Addition funnel.

Figure 1. Addition funnel.

A solution of 9.12 g (40 mmol) of 3,7-dithianonane-1,9-dithiol and 8.08 g (40 mmol) of 1,3-dibromopropane (Note 6) in 300 mL of *N,N*-dimethylformamide is prepared. Half of this solution is placed in the addition funnel and added to the well-stirred suspension of cesium carbonate in *N,N*-dimethylformamide over a period of 6–9 hr. The reaction mixture is then charged with another 13.04 g (40 mmol) of cesium carbonate and the second half of the solution of 3,7-dithianonane-1,9-dithiol and 1,3-dibromopropane is added over a period of 6–9 hr (Note 7). After the addition is complete, the reaction mixture is allowed to cool to room temperature. The *N,N*-dimethylformamide is distilled off as completely as possible under reduced pressure (Note 8). The residue is taken up in 300 mL of dichloromethane and washed once with 200 mL of a saturated solution of sodium chloride. The organic layer is dried over anhydrous magnesium sulfate. The drying agent is removed by filtration and the filtrate is concentrated on a rotary evaporator to a light-yellow crystalline mass. This is taken up in 200 mL of boiling 95% ethanol and the hot liquid is decanted. The remaining sediment is boiled with 125 mL of 95% ethanol and again decanted. The two ethanol solutions are combined and stored at 10°C overnight. The white crystalline product that separates is isolated by filtration and dried. The final product obtained is 6.20–6.60 g (58–62%) of 1,4,8,11-tetrathiacyclotetradecane, mp 118–119°C (lit.[2] mp 119–120°C) (Note 9).

2. Notes

1. 1,3-Propanedithiol and 2-chloroethanol were obtained from the Aldrich Chemical Company, Inc.
2. The submitters report obtaining 19.6–24.5 g (80–100%) of product, bp 179–181°C (0.5 mm). The product obtained by the checkers is pure by NMR and shows the following spectrum: ^{1}H NMR ($CDCl_3$) δ: 1.86 (quintet, 2 H, *J* = 7, CCH_2), 2.17 (br s, 2 H, OH), 2.65 (t, 4 H, *J* = 7, SCH_2), 2.73 (t, 4 H, *J* = 6, SCH_2), 3.73 (t, 4 H, *J* = 6, OCH_2).
3. The checkers purchased thiourea from the Aldrich Chemical Company, Inc.
4. The submitters report bp 159–161°C (0.5 mm) for the product and yields of 50–70% for reactions run with 0.1 mol of 3,7-dithianonane-1,9-diol and 0.2 mol of thiourea. The product obtained by the checkers is pure by NMR and shows the following spectrum: ^{1}H NMR ($CDCl_3$) δ: 1.63–2.07 (m, 4 H, CCH_2, SH), 2.50–2.83 (m, 12 H, SCH_2).
5. The device illustrated in f.htmigure 1 allows ready adjustment of addition rates without significant clogging. Component A is a conical ground-glass receiver for the ground-glass tapered end of a 7-mm-diameter glass rod. The rod is turned in the tapered receiver to attain the desired rate of addition. A ratchet device attached to the top of the addition funnel holds the rod in place and measures its rotation. Outlet B is connected to a mercury bubbler and nitrogen is introduced via C.

6. The checkers obtained *N,N*-dimethylformamide, cesium carbonate, and 1,3-dibromopropane from the Aldrich Chemical Company, Inc. The *N,N*-dimethylformamide was distilled and stored over molecular sieves (Linde 4A) prior to use.
7. The addition rate is sufficiently slow that virtually no starting material remains. The procedure avoids the need for excessively large volumes of solvent that are normally required in high dilution reactions.
8. A Büchi rotary evaporator attached to a vacuum pump is used. A pressure of 1–2 mm is maintained and the flask is heated in a water bath to a maximum temperature of 60°C.
9. The submitters report obtaining 6.97–8.00 g (65–70%) of product, mp 118–119.5°C. The product shows the following spectral properties: IR (KBr) cm^{-1}: 2930, 1430, 1338, 1270, 1205, 1138, 692; ^{1}H NMR ($CDCl_3$) δ: 1.90 (quintet, 4 H, *J* = 7, CCH_2), 2.65 (t, 8 H, *J* = 7, SCH_2CH_2), 2.77 (s, 8 H, SCH_2).

3. Discussion

The cyclic sulfide 1,4,8,11-tetrathiacyclotetradecane has been prepared in 7.5% yield by reaction of the bis-Na^{+} salt of 3,7-dithianonane-1,9-dithiol in boiling ethanol with 1,3-dibromopropane.[2] A marked improvement in yield by the use of cesium salts in *N,N*-dimethylformamide has been documented for other macrocyclic sulfides,[3] as well as macrocyclic lactones[4,5] and amines.[6] Moreover, the nucleophilic properties of cesium salts have been used to advantage in substitution reactions.[7]

Macrocyclic sulfides, including 1,4,8,11-tetrathiacyclotetradecane, are of interest, especially as ligands for transition-metal ions in a variety of different applications.[8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30] The methodology described here provides an efficient entry to many such macrocycles, including chiral ones that act as ligands in transition metal-catalyzed coupling reactions.[29]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

bis-Na^+ salt of 3,7-dithianonane-1,9-dithiol

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium chloride (7647-14-5)

1,3-dibromopropane (109-64-8)

nitrogen (7727-37-9)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

2-chloroethanol (107-07-3)

dichloromethane (75-09-2)

thiourea (62-56-6)

magnesium sulfate (7487-88-9)

N,N-dimethylformamide (68-12-2)

1,3-propanedithiol (109-80-8)

CESIUM (7440-46-2)

1,4,8,11-Tetrathiacyclotetradecane (24194-61-4)

3,7-Dithianonane-1,9-diol (16260-48-3)

3,7-Dithianonane-1,9-dithiol (25676-62-4)

cesium carbonate (29703-01-3)

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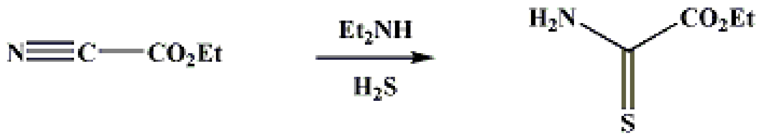
Organic Syntheses, CV 8, 597

PREPARATION AND INVERSE-ELECTRON-DEMAND DIELS–ALDER REACTION OF AN ELECTRON-DEFICIENT HETEROCYCLIC AZADIENE: TRIETHYL 1,2,4-TRIAZINE-3,5,6-TRICARBOXYLATE AND 2,3,6-TRICARBOETHOXYPYRIDINE

[1,2,4-Triazine-3,5,6-tricarboxylic acid, triethyl ester]

A.



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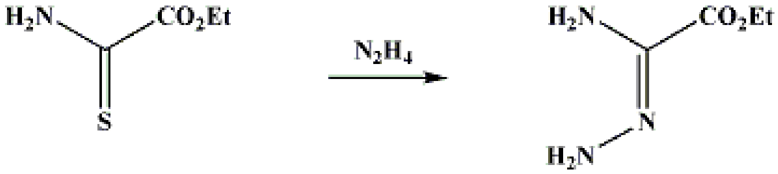

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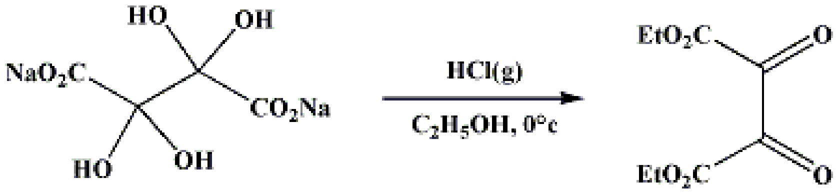

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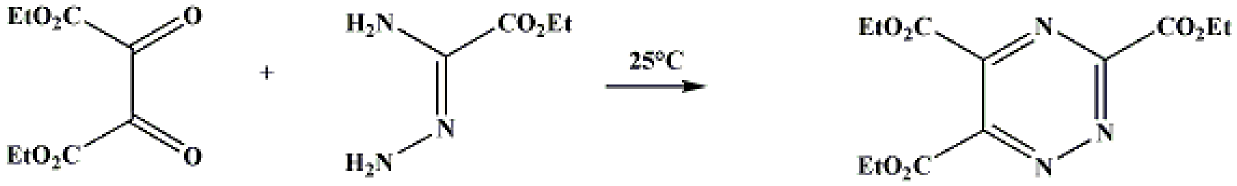

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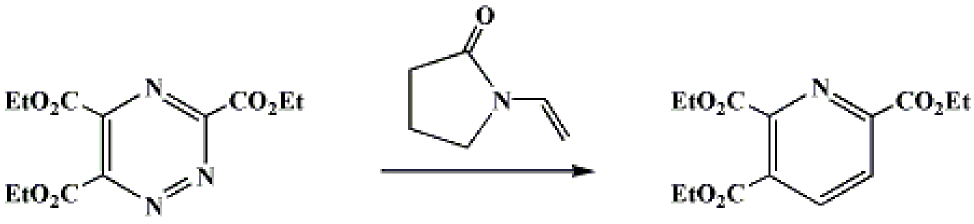


Submitted by Dale L. Boger, James S. Panek, and Masami Yasuda[1].
Checked by Pauline J. Sanfilippo and Andrew S. Kende.

1. Procedure

2

Caution! Hydrogen sulfide is highly toxic and a stench. Steps A and B must be run in an efficient fume hood.

A. *Ethyl thioamidooxalate.*[3] A 100-mL, round-bottomed flask is fitted with a magnetic stirring bar. Ethyl

cyanoformate (20 g, 0.20 mol, (Note 1)) in benzene (25 mL) is added to the reaction vessel and the mixture is cooled to 0°C with an ice bath. Diethylamine ((Note 2), 0.4 g, 5.5 mmol, 0.57 mL) is added to the stirring reaction mixture (0°C) and hydrogen sulfide (Note 3) is then bubbled into the reaction for an additional 15–20 min. The reaction mixture is allowed to stir at 25°C (14–16 hr). The crude product is collected by filtration (Note 4) and washed with benzene (2 × 3 mL) to give 20.96 g (78%) of pure ethyl thioamidooxalate. The filtrate is concentrated under reduced pressure and the crude product subjected to chromatography on silica gel (30% ether–hexane eluant) to give an additional 1.57 g of ethyl thioamidooxalate. The total amount of ethyl thioamidooxalate isolated as a bright-yellow solid is 22.53 g (84%); mp 63–66°C (Note 5).

B. *Ethyl oxalamidrazonate.* A 1-L, round-bottomed flask is equipped with a magnetic stirring bar and fitted with a 125-mL addition funnel. A solution of anhydrous hydrazine (4.8 g, 0.15 mol) in ethanol (75 mL) is added dropwise (10 min) to a stirred solution of ethyl thioamidooxalate (20.0 g, 0.15 mol) in ethanol (450 mL) at 25°C. The reaction mixture is stirred at 25°C (3.0 hr). The solvent is removed under reduced pressure and the reddish-orange solid is triturated with ethanol (350 mL). The ethanolic solution containing the oxalamidrazonate is concentrated under reduced pressure to afford 13.90 g (71%) of ethyl oxalamidrazonate as a yellow solid (Note 6).

C. *Diethyl dioxosuccinate.* A 1-L, round-bottomed flask equipped with a magnetic stirring bar is charged with dihydroxytartaric acid disodium salt hydrate (100 g, 0.44 mol, (Note 7)) and absolute ethanol (750 mL, (Note 8)). The suspension is cooled to 0°C with an ice bath and anhydrous hydrogen chloride gas (Note 9) is bubbled into the reaction mixture with stirring (0°C, ca. 30 min). The reaction mixture is stoppered and placed in the refrigerator for 72 hr. The mixture is filtered using a Büchner funnel and the filtrate is concentrated under reduced pressure. The crude diethyl dioxosuccinate is distilled under reduced pressure to afford 39.60 g (44%) of pure diethyl dioxosuccinate is (Note 10), bp 109–116°C (6–8 mm); lit.[4] bp 109–114°C (6 mm).

D. *Triethyl 1,2,4-triazine-3,5,6-tricarboxylate*. A 1-L, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, a 500-mL addition funnel, and a nitrogen inlet. A solution of ethyl oxalamidrazonate (11.6 g, 88.0 mmol) in absolute ethanol (350 mL) is added dropwise (40–45 mi) to a stirring solution of diethyl dioxosuccinate (23.1 g, 114.0 mmol) in absolute ethanol (86 mL) at 25°C under nitrogen. After the addition is complete, the reaction mixture is stirred at 25°C (16 hr). A reflux condenser is fitted onto the three-necked, round-bottomed flask and the reaction mixture is warmed at reflux for 2.0 hr. The reaction mixture is cooled and the solvent is removed under reduced pressure. Purification of the product is effected by gravity chromatography (Note 11) on a 5.20 × 40.0-cm column of silica gel (10–40% ether–hexane gradient elution), collecting 100-mL fractions. The fractions are analyzed by thin-layer chromatography on silica gel (40% ether–hexane eluant). The fractions containing product are combined and the solvent is removed under reduced pressure to afford 14.70 g (56%) of pure triethyl 1,2,4-triazine-3,5,6-tricarboxylate as a viscous, yellow oil[2,5] (Note 12).

E. *2,3,6-Tricarboethoxypyridine.* A 50-mL, round-bottomed flask is fitted with a magnetic stirring bar and a reflux condenser. Triethyl 1,2,4-triazine-3,5,6-tricarboxylate (1.49 g, 5.0 mmol) and chloroform (22.7 mL. (Note 13)) are added to the reaction vessel. *N*-Vinyl-2-pyrrolidone (2.22 g, 20 mmol, 2.3 mL, (Note 14)) is added to the solution and the reaction mixture is warmed at 60°C under an atmosphere of nitrogen for 26 hr. The solvent is removed under reduced pressure and the crude product subjected to gravity chromatography (Note 11) on a 2.7 × 32-cm column of silica gel (40–50% ether–hexane gradient elution), collecting 50-mL fractions. The fractions are analyzed by thin-layer chromatography on silica gel (50% ether–hexane eluant). The fractions containing product are combined and the solvent is removed under reduced pressure to afford 1.01–1.35 g (68–92%) of 2,3,6-tricarboethoxypyridine as a yellow oil (Note 15).

2. Notes

1. The submitters employed, without purification, ethyl cyanoformate purchased from Aldrich Chemical Company, Inc.
2. The submitters employed, without purification, diethylamine purchased from Aldrich Chemical Company, Inc.
3. Hydrogen sulfide gas was purchased from Burnox, Kansas City, MO. This reaction should be run in a fume hood.
4. In some instances, it is necessary to cool the flask (ice bath) containing the ethyl thioamidooxalate to promote crystallization of the product.

5. The product has the following spectral properties: ^{1}H NMR ($CDCl_3$) δ: 1.39 (t, 3 H, *J* = 8, CH_3), 4.33 (q, 2 H, *J* = 8, CH_2), 7.30–8.30 (br s, 2 H, NH_2), mp 63–66°C, lit.[2,5] mp 64–65°C.

6. *Caution: This reaction should be carried out in a fume hood. Ethyl oxalamidrazonate cannot be stored in solution for prolonged periods of time.*

7. The submitters employed dihydroxytartaric acid disodium salt hydrate purchased from Aldrich Chemical Company, Inc.

8. Ethanol was dried by distillation from magnesium turnings immediately before use.

9. Anhydrous hydrogen chloride gas purchased from Burnox, Kansas City, MO was employed.

10. The ^{1}H NMR spectrum of this compound is as follows: ^{1}H NMR ($CDCl_3$) δ: 1.36 (t, 3 H, *J* = 8, CH_3), 4.4 (q, 2 H, *J* = 8, CH_2).

11. The checkers used flash chromatography for these steps.

12. The spectral properties of this product (orange oil) are as follows: ^{1}H NMR ($CDCl_3$) δ: 1.45 (t, 3 H, *J* = 7, CH_3), 1.48 (t, 3 H, *J* = 7, CH_3), 1.51 (t, 3 H, *J* = 7, CH_3); 4.38–4.68 (3 overlapping q, 6 H, three CH_2); IR (film) cm^{-1}: 2986, 1757, 1738, 1518, 1468, 1408, 1383, 1302, 1217, 1177, 1155, 1099, 1017, 857.

13. The submitters employed chloroform obtained from Fisher Chemical Co.

14. The submitters employed, without purification, *N*-vinyl-2-pyrrolidone obtained from GAF Corporation.

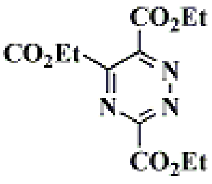
15. The spectral properties of the product are as follows: ^{1}H NMR ($CDCl_3$) δ: 1.38 (t, 3 H, *J* = 7, CH_3), 1.41 (t, 3 H, *J* = 7, CH_3), 1.43 (t, 3 H, *J* = 7, CH_3), 4.38 (q, 2 H, *J* = 7, CH_2), 4.44 (q, 2 H, *J* = 7, CH_2), 4.47 (q, 2 H, *J* = 7, CH_2), 8.16 (d, 1 H, *J* = 8, aromatic), 8.30 (d, 1 H, *J* = 8, aromatic); IR (film) cm^{-1}: 2986, 1728, 1586, 1570, 1468, 1455, 1406, 1387, 1370, 1321, 1283, 1239, 1152, 1071, 1021, 853, 762.

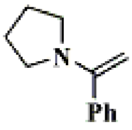
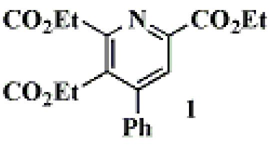
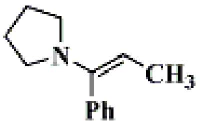
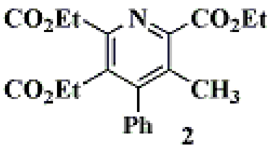
3. Discussion

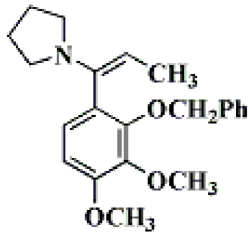
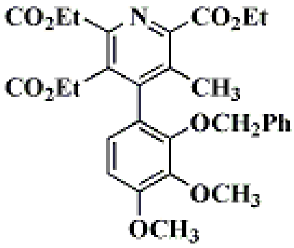
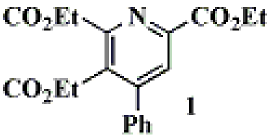
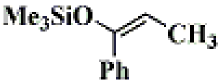
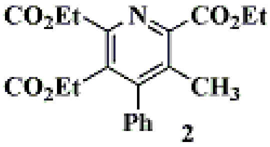
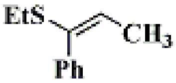
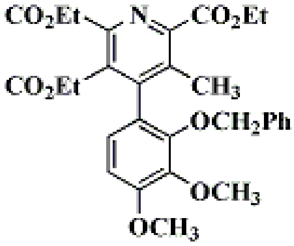
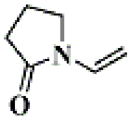
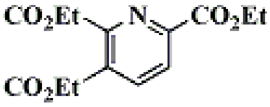
This procedure describes the preparation of an electron-deficient heterocyclic azadiene suitable for use in inverse-electron-demand ($LUMO_{diene}$ controlled)[6] Diels–Alder reactions with electron-rich dienophiles.

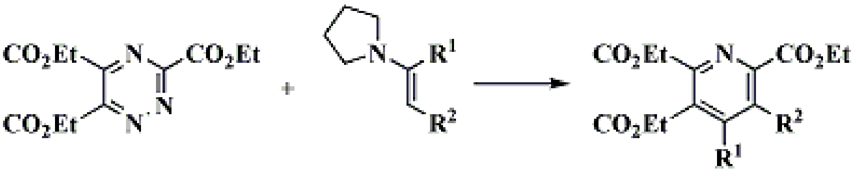
Table 1[6,7] details representative examples of the [4 + 2] cycloaddition of triethyl 1,2,4-triazine-3,5,6-tricarboxylate with pyrrolidine enamines and related electron-rich olefins. Cycloaddition occurs across carbon-3 and carbon-6 of the 1,2,4-triazine nucleus, and the nucleophilic carbon of the dienophile attaches to carbon-3 (Eq. 1). Loss of nitrogen from the initial adduct and aromatization with loss of pyrrolidine affords pyridine products.

TABLE 1
DIELS-ALDERREACTION OFTRIETHYL1,2,4-TRIAZINE-3,5,6-TRICARBOXYLATE

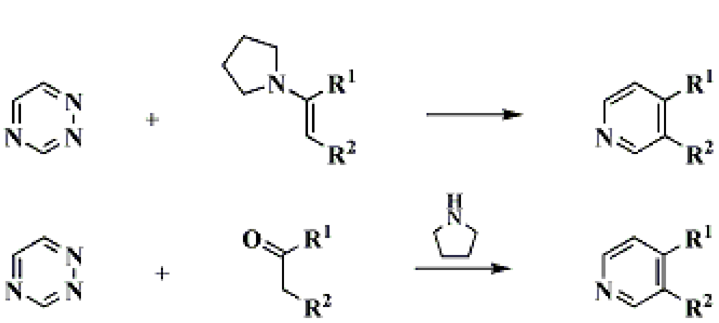


Dienophile	Conditions: Solv., Temp., Time	Product	Yield (%)
	$CHCl_3$ 60°C 18 hr		79
	$CHCl_3$ 45°C 8 hr		73

	$CHCl_3$ 45°C 3 hr	 3	59
	$CHCl_3$ 60°C 22 hr		84
	$CHCl_3$ 60°C 16 hr		0
	$CHCl_3$ 80-160°C 10-20 hr	 3	0
	$CHCl_3$ 60°C 26 hr		92



Similar reactivity and regioselectivity is observed with the parent system, 1,2,4-triazine (Eq. 2).[8] Reduction of this process to a catalytic Diels–Alder reaction with in situ generation of the pyrrolidine enamine does not alter these observations (Eq. 3).[9]



The number and position of electron-withdrawing substituents on the 1,2,4-triazine nucleus and the reactivity of

the electron-rich dienophile determine the mode of cycloaddition (additions across C-5/N-2 as well as C-3/C-6 of the 1,2,4-triazine nucleus have been observed) as well as the regioselectivity.[8,9,10] A survey of the reported Diels–Alder reactions of 1,2,4-triazines including triethyl 1,2,4-triazine-3,5,6-tricarboxylate has been compiled.[11]

12

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Ethyl thioamidooxalate

Ethyl oxalamidrazonate

ethanol (64-17-5)

hydrogen chloride (7647-01-0)

Benzene (71-43-2)

ether (60-29-7)

chloroform (67-66-3)

magnesium turnings (7439-95-4)

hydrogen sulfide (7783-06-4)

nitrogen (7727-37-9)

carbon (7782-42-5)

pyridine (110-86-1)

diethylamine (109-89-7)

hydrazine (302-01-2)

ethyl cyanoformate (623-49-4)

hexane (110-54-3)

Triethyl 1,2,4-triazine-3,5,6-tricarboxylate, 1,2,4-Triazine-3,5,6-tricarboxylic acid, triethyl ester (74476-38-3)

2,3,6-Tricarboethoxypyridine (122509-29-9)

dihydroxytartaric acid disodium salt hydrate

Diethyl dioxosuccinate (59743-08-7)

N-Vinyl-2-pyrrolidone (88-12-0)

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Organic Syntheses, CV 8, 602

CONVERSION OF ESTERS TO ALLYLSILANES: TRIMETHYL(2-METHYLENE-4-PHENYL-3-BUTENYL)SILANE

[Silane, trimethyl (2-methylene-4-phenyl-3-butenyl)-]

Submitted by William H. Bunnelle and B. A. Narayanan[1].
Checked by Jürgen Fischer and Ekkehard Winterfeldt.

1. Procedure

A 1-L, three-necked, round-bottomed flask with mechanical stirrer and vacuum outlet (Note 1) is charged with powdered cerium (III) chloride ($CeCl_3 \cdot 7H_2O$, 52.92 g, 0.142 mol) (Note 2). The flask is immersed to the necks in an oil bath and evacuated to 0.2 mm. The solid is agitated by stirring as the flask is heated to 150°C for 2 hr. After the flask is cooled to room temperature, it is vented to the atmosphere and quickly purged with a stream of dry nitrogen for 2 min. At this stage, the flask is fitted with a low-temperature thermometer and a graduated 250-mL addition funnel containing 300 mL of dry tetrahydrofuran (THF) (Note 3), and capped with a rubber septum. Connection to a dry nitrogen line with a pressure relief bubbler is made via a needle through the septum. Tetrahydrofuran is run into the flask with good stirring, so that an even suspension results (Note 4). The white suspension is stirred at room temperature for 2 hr. Meanwhile, the addition funnel is charged with trimethylsilylmethylmagnesium chloride (Me_3SiCH_2MgCl, 1 *M* solution in ethyl ether, 142 mL, 0.142 mol) (Note 5) and (Note 6), transferred via stainless-steel cannula. The contents of the flask are cooled to −65°C with a dry ice/2-propanol bath, and the Grignard solution is added dropwise over a period of 40–50 min, so that the temperature of the reaction mixture remains below −60°C. The addition funnel is removed from the setup, with the septum/nitrogen inlet connected directly to the flask. After the cold mixture is stirred for 15 min more, ethyl cinnamate (10.32 g, 0.0586 mol) (Note 7) is added via syringe over a 2–3-min period. Stirring is continued as the flask is allowed to warm slowly to room temperature (Note 8). The off-white to beige reaction mixture is cooled to <5°C (ice-water bath) and quenched by the portionwise addition of chilled 1 *M* hydrochloric acid (200 mL), so that the internal temperature remains below 20°C (Note 9). The layers are separated, and the aqueous phase is extracted twice with ethyl ether (100 mL each). The combined organic layers are washed with saturated sodium bicarbonate solution (Note 10) and dried over sodium sulfate, and the solvents are removed at a rotary evaporator (25°C at 60 mm). The residual oil is transferred to a 100-mL, round-bottomed flask and distilled bulb-to-bulb (Note 11). The product (9.69–9.85 g, 76.5–78%) (Note 12) is collected at an air-bath temperature of 110–112°C, 0.20 mm.

2. Notes

1. The vacuum outlet should be packed with glass wool to prevent loss of significant quantities of cerium salt during the drying process. During some runs, cerium salts worked into the stirrer shaft bearing, causing it to bind. This problem could be avoided by placing a straight adapter tube between the bearing and the flask, to distance the bearing from the reaction mixture. The checkers found that sublimation of the cerium salt occurred in all their runs, but did not appear to affect the yield.
2. Cerium(III) chloride heptahydrate was purchased from Aldrich Chemical Company, Inc., and ground with a mortar and pestle just before use.
3. Tetrahydrofuran was freshly distilled under nitrogen from sodium and benzophenone. The (nominal) 250-mL funnel holds the entire volume of solvent.
4. On one occasion, when the solvent was added without stirring, the solid formed a hard cake on the bottom of the flask and resisted attempts to bring it into suspension. The full 2-hr "aging" period is necessary for best results.
5. This clear, pale-yellow solution was purchased from the Aldrich Chemical Company, Inc. The Grignard solution may be prepared from trimethylsilylmethyl chloride.[2] Take care to prevent air oxidation in opened bottles of the Grignard reagent—these solutions deteriorate rapidly, and older samples are unsuitable for the present procedure.
6. The prescribed quantity of Grignard reagent (and cerium salt) is 25% more than stoichiometric. This excess is required to ensure complete consumption of the ester.
7. Ethyl cinnamate was purchased from Eastman Kodak Company, and was distilled at 110–111°C/0.75 mm

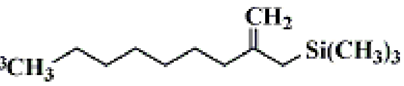
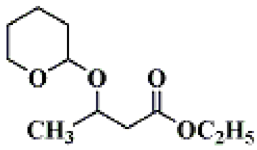
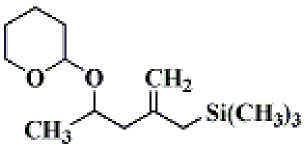
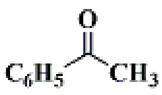
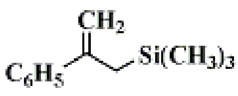
before use.
8. Warming takes approximately 3 hr. The reaction is complete by this time and can be worked up. Alternatively, the mixture may be stirred at room temperature for at least 12 hr (overnight) without any deleterious effect on yield.
9. If the reaction is allowed to become warm, substantial protodesilylation of the product takes place to give 3-methyl-1-phenyl-1,3-butadiene. The aqueous workup should be carried out rapidly to minimize this side reaction. The use of hydrochloric acid has a particular advantage since all of the salts dissolve, facilitating the extractions.
10. Some residual salts precipitate during this operation, but do not pose any handling difficulty.
11. Gas chromatographic analysis [0.53–mm i.d. × 10 m poly(dimethyl silicone) fused-silica column, temperature programmed from 140° to 220°C] indicates that this product is 98% pure, with < 1% 3-methyl-1-phenyl-1,3-butadiene and 1–2% of a less volatile, unidentified component. The checkers could obtain a very pure product by normal vacuum distillation. They found the impurities to be higher boiling compounds.
12. This material has the following spectral data: IR cm^{-1}: 3068, 1593, 872, 853, 838; ^{1}H NMR δ: 0.01 (s, 9 H), 1.80 (br, s, 2 H), 4.83 (br, s, 1 H), 5.00 (d, 1 H, *J* = 1), 6.45 (d, 1 H, *J* = 16), 6.77 (d, 1 H, *J* = 16), 7.1–7.4 (m, 5 H); ^{13}C NMR δ: –1.2, 22.2, 114.8, 126.4, 127.3, 128.6, 128.7, 132.0, 137.4, 143.8; MS (*m/e*, %): 216 (40%). 73 (100%).

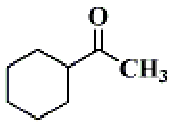
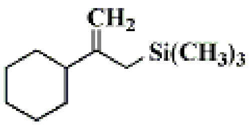
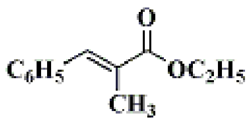
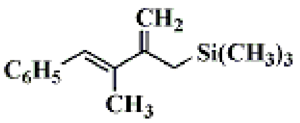
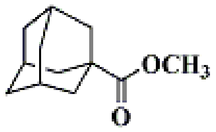
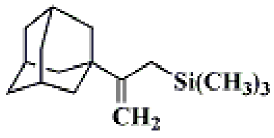
3. Discussion

Allylsilanes are exceptionally versatile compounds with a well-established function in organic synthesis.[3 4] General methods for their preparation, then, are valuable. The method described here is effective for elaboration of esters to allylsilanes. The transformation is conceptually straightforward: twofold addition of a trimethylsilylmethyl metal species to the ester, followed by Peterson-type elimination from the resultant bis(trimethylsilylmethyl)carbinol, leads to the allylsilanes.

The Grignard reagent Me_3SiCH_2MgCl has been used to effect this conversion with simple, unbranched esters, but the yields are only moderate (50%) and the process fails completely for more sterically congested esters.[5 6 7 8] In these cases, the α-silylketone intermediate resists further addition, instead suffering preferential enolization.[9] The use of organocerium reagents to circumvent this difficulty has been developed by two groups.[10,11] The reagent prepared from cerium(III) chloride and Me_3SiCH_2Li is quite effective for conversion of acid chlorides to allylsilanes, but does not react efficiently with esters.[10] Somewhat surprisingly in view of these results, a mixture of cerium(III) chloride with Me_3SiCH_2MgCl produces a powerful reagent for conversion of esters to allylsilanes in excellent yields.[11] Some examples, for reactions carried out on a 1-mmol scale, are collected in Table I.[11] Only the highly hindered methyl adamantanecarboxylate fails to react.

TABLE I

Ester	Allylsilane	Yield (%)
		95
		90[a]
		95

		77
		92
		0[b]

[a]Starting material and product each a 1 : 1 mixture of diastereoisomers.

[b]Starting material recovered quantitatively.

The protocol described above is a scaled-up modification of that reported earlier.[11] The title compound was prepared previously by a nickel-catalyzed cross-coupling,[12] and by the organocerium/acid chloride route.[10] The present procedure offers advantages in both convenience and yield compared to these other methods. Recently the method has been successfully applied to heteroatom-functionalized systems.[13]

This preparation is referenced from:

- Org. Syn. 76, 228

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Me_3SiCH_2Li

Me_3SiCH_2MgCl

hydrochloric acid (7647-01-0)

ethyl ether (60-29-7)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

Benzophenone (119-61-9)

sodium (13966-32-0)

Ethyl cinnamate (103-36-6)

Tetrahydrofuran (109-99-9)

cerium (III) chloride, cerium(III) chloride (7790-86-5)

methyl adamantanecarboxylate (711-01-3)

trimethylsilylmethyl chloride (2344-80-1)

Trimethylsilylmethylmagnesium chloride (13170-43-9)

Trimethyl(2-methylene-4-phenyl-3-butenyl)silane, Silane, trimethyl (2-methylene-4-phenyl-3-butenyl)- (80814-92-2)

Cerium(III) chloride heptahydrate (18618-55-8)

3-methyl-1-phenyl-1,3-butadiene

bis(trimethylsilylmethyl)carbinol

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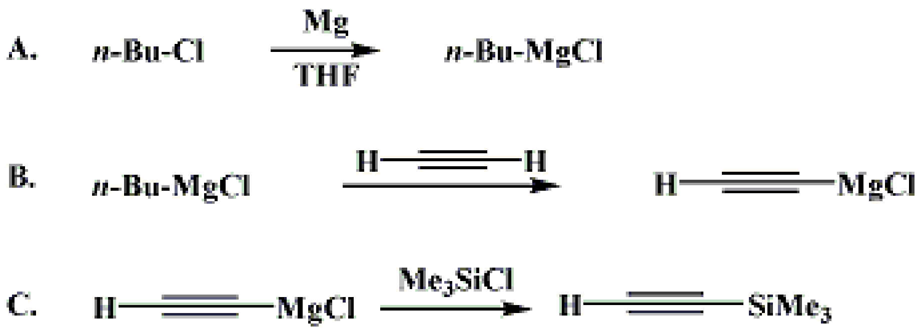
Organic Syntheses, CV 8, 606

TRIMETHYLSILYLACETYLENE

[Silane, ethynyltrimethyl-]



Submitted by Andrew B. Holmes and Chris N. Sporikou[1].
Checked by Dallas D. Crotts, Bruce E. Eaton, and Clayton H. Heathcock.

1. Procedure

A. *Butylmagnesium chloride.* A dry, 1-L, three-necked, round-bottomed flask is equipped with a sealed mechanical stirrer (Note 1), a 250-mL pressure-equalizing dropping funnel and a reflux condenser to the top of which is attached a T-piece connected at one end to a supply of dry nitrogen, and at the other to an oil or mercury bubbler. At the same time a dry, 2-L, three-necked, round-bottomed flask, fitted with a sealed mechanical stirrer and two swan-neck adapters, is prepared, with one adapter holding a gas inlet and a calcium chloride drying tube, and the other supporting a thermometer and a 1-L pressure-equalizing dropping funnel.

The 1-L flask is charged with magnesium turnings (39.6 g, 1.65 g-atom) (Note 2) and dry tetrahydrofuran (THF) (150 mL). The mixture is heated to reflux temperature under an atmosphere of dry nitrogen, and a crystal of iodine is added. The dropping funnel is filled with 1-chlorobutane (173 mL, 152.5 g, 1.65 mol) (Note 3) and a portion (15 mL) is added to the boiling THF mixture. The source of heat is removed. After the reaction has commenced, the THF begins to boil more vigorously and a further volume (400 mL) of THF is added to the reaction mixture. Then the remainder of the chlorobutane is added slowly at a rate sufficient to maintain the reaction under reflux. Finally, the reaction mixture is stirred and heated under reflux until all the magnesium has been consumed (0.5–1 hr).

B. *Ethynylmagnesium chloride.* While the butylmagnesium chloride is being prepared, the 2-L flask is filled with dry THF (500 mL), which is saturated by bubbling acetylene through it for 0.5–1 hr (Note 4). The warm (ca. 60°C) butylmagnesium chloride is rapidly poured under a liberal blanket of nitrogen into the 1-L dropping funnel, which is then flushed with nitrogen before being stoppered. The rapid flow of acetylene is maintained. The 2-L flask is cooled to −5°C in a dry ice–acetone bath, the

acetylene is bubbled rapidly through the THF (Note 4), and the butylmagnesium chloride is added dropwise to the stirred reaction mixture at a rate sufficient to maintain the temperature below 20°C (Note 5). This addition requires 1 hr; then acetylene is bubbled through the reaction mixture for a further 0.5 hr. (The mixture cools to about 5°C during this period.) The acetylene supply is disconnected and replaced by dry nitrogen.

C. *Trimethylsilylacetylene.* A solution of chlorotrimethylsilane (152 mL, 130 g, 1.197 mol) (Note 6) in dry THF (100 mL) is placed in the 1-L dropping funnel and is added (20 min) to the cooled and stirred solution of ethynylmagnesium chloride at a rate sufficient to maintain a reaction temperature of about 15–20°C (Note 7). Finally, the dropping funnel is replaced by an efficient double-surface condenser and calcium chloride drying tube, and the reaction mixture is heated under reflux for 1 hr (Note 8). The reflux condenser is replaced by a distillation head and a double surface condenser is connected to a receiver flask which is cooled in an ice bath (Note 9). The reaction mixture is distilled under nitrogen with stirring until all the azeotrope of trimethylsilylacetylene and THF (700–800 mL, bp ca. 66°C) has distilled (Note 10) and (Note 11). The distillate is washed with ice–water portions (10 × 500 mL) to remove the THF. Washing is continued until the organic layer stays constant in volume (Note 12). Distillation (Note 10) of the organic layer under an atmosphere of nitrogen through a short Vigreux column (Note 13) gives trimethylsilylacetylene, bp 50–52°C/760mm, n_D^{20} 1.391; (lit.[2,3,4] 53.5°C at 762 mm, n_D^{20} 1.3900; 52°C at 760 mm, n_D^{20} 1.3900; 52°C at 760 mm, n_D^{20} 1.3935) in yields ranging from 72.5 g (62%) to 87.5 g (75%) (Note 14) and (Note 15).

2. Notes

1. The checkers used an efficient magnetic stirrer.
2. The magnesium turnings for Grignard reactions were supplied by Fisons Scientific Apparatus, Loughborough. If less than 1.65 g-atom of magnesium is used, the final product will be contaminated with 1-chlorobutane.
3. It is essential that the 1-chlorobutane be free of 1-butanol. 1-Chlorobutane (Aldrich Chemical Company, Inc.) was purified by rapid passage through basic alumina (activity 1) before use.
4. Gaseous acetylene is introduced at the rate of about 20 L/hr and is purified by passage through a cold trap (–78°C), followed by bubbling through concentrated sulfuric acid and finally passage over sodium hydroxide pellets. These operations must be conducted in a well-ventilated fume hood. The checkers found that an insufficient acetylene flow rate in this and the next step results in the formation of butyltrimethylsilane and bis(trimethylsilyl)acetylene.
5. The temperature reaches 15°C after 0.5 hr, and 20°C after 0.8 hr. Ethynylmagnesium halides can rapidly disproportionate to bis (chloromagnesium)acetylene and acetylene at higher temperatures.[2] It is important to maintain the reaction mixture at or below 20°C and to have an

excess of acetylene in order to prevent formation of the bis(magnesium chloride). The checkers found that the ethynylmagnesium chloride can be formed at 10–15°C, thus minimizing the problem.

6. Commercial chlorotrimethylsilane is distilled from quinoline under nitrogen.

7. It is important that the addition be done fairly rapidly. The checkers found that slow addition (2 hr at 20°C) resulted in significant disproportionation of the ethynylmagnesium chloride.

8. It is essential to have an efficient condenser during the reflux and distillation stages because the product, trimethylsilylacetylene, is extremely volatile.

9. The receiver must be cooled to avoid serious loss of volatile product.

10. The hot distillation apparatus should be allowed to cool under a nitrogen atmosphere before being dismantled.

11. The submitters distilled the azeotrope immediately after heating the mixture to reflux. If it is allowed to stand and cool, it sets solid with magnesium chloride and subsequent distillation results in appreciably lower yields.

12. The presence of residual THF in the final product is easily detected by the characteristic ^1H NMR signals at δ 1.85 (4 H) and 3.75 (4 H). The checkers found GLC to be more convenient than ^1H NMR for analysis at this point. Either a 6-m × 2-mm glass column of 3% OV-101 on WHP 80/100 with 30 mL/min He or a 15-m × 0.25-mm fused-silica capillary column of DB-5 (cross linked phenylsilicone) with 1 mL/min H_2 proved sufficient to resolve butane, trimethylsilylacetylene, butyltrimethylsilane, THF, 1-chlorobutane, and bis(trimethylsilyl)acetylene.

13. The checkers used an 18-in. Vigreux column, equipped with an adjustable reflux ratio takeoff. The final product can be contaminated with up to several percent butane unless careful distillation is carried out.

14. Trimethylsilylacetylene displayed the following spectroscopic properties: IR (CCl_4) cm^{-1}: 3280 (s) and 2050 (s); ^1H NMR: ($CDCl_3$, 250 MHz) δ: 0.18 (s, 9 H, CH_3), 2.36 (s, 1 H, CH).

15. The submitters have carried out the preparation on twice the above scale with no reduction in yield.

3. Discussion

Trimethylsilylacetylene has been prepared by silylation of a variety of ethynyl metal derivatives.[2,3,4,5,6,7,8,9,10] The most useful methods are the silylation of ethynylmagnesium bromide[3,4,5] and chloride.[2,7,10] The use of ethynylmagnesium bromide has been reported to suffer from complicating side reactions,[2] and the results obtained in our hands were unreliable.

The present method is based on the silylation of ethynylmagnesium chloride as reported by Krüerke,[2] except that the Grignard reagent is prepared from 1-chlorobutane, rather than from the volatile (and therefore more difficult to manipulate) chloromethane. Although the preparation of ethynylmagnesium bromide is a well-

established *Organic Syntheses* procedure,[11] the use of ethynylmagnesium chloride has received little attention.[5] It does not seem to be widely appreciated that butylmagnesium chloride is much more soluble in THF than ethylmagnesium bromide, and its use in Grignard ethynylations is strongly recommended. The preparation of ethynylmagnesium chloride essentially follows the *Organic Syntheses* procedure laid down for the bromide.[11]

Trimethylsilylacetylene is an extremely versatile (and potentially nucleophilic) two-carbon building block. Applications in organic synthesis have been well documented in the literature.[12,13,14]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 63
- Org. Syn. Coll. Vol. 8, 609

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

bis(chloromagnesium)acetylene

sulfuric acid (7664-93-9)

acetylene (74-86-2)

sodium hydroxide (1310-73-2)

magnesium, magnesium turnings (7439-95-4)

nitrogen (7727-37-9)

chloromethane (74-87-3)

1-butanol (71-36-3)

iodine (7553-56-2)

1-chlorobutane, chlorobutane (109-69-3)

Quinoline (91-22-5)

ethylmagnesium bromide (925-90-6)

chloride

Tetrahydrofuran, THF (109-99-9)

ethynylmagnesium bromide

CHLOROTRIMETHYLSILANE (75-77-4)

bis(trimethylsilyl)acetylene (14630-40-1)

Trimethylsilylacetylene, Silane, ethynyltrimethyl- (1066-54-2)

Ethynylmagnesium chloride

Butylmagnesium chloride (693-04-9)

butyltrimethylsilane (1000-49-3)

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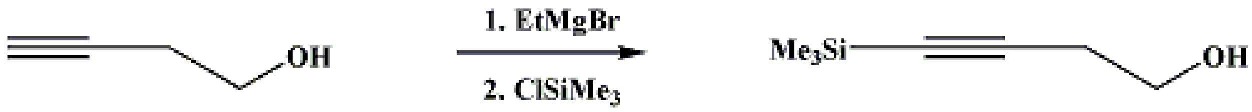
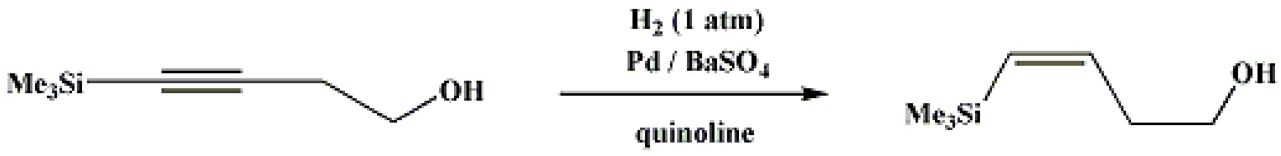
(*Z*)-4-(TRIMETHYLSILYL)-3-BUTEN-1-OL

[3-Buten-1-ol, 4-(trimethylsilyl)-, (*Z*)-]





Submitted by Larry E. Overman, Mark J. Brown, and Stephen F. McCann[1].
Checked by Ronald C. Newbold and Andrew S. Kende.

1. Procedure

A. *Preparation of 4-(trimethylsilyl)-3-butyn-1-ol*. A flame-dried, three-necked, 2-L, round-bottomed flask is fitted with a 1-L pressure-equalizing addition funnel, a mechanical stirrer, and a nitrogen inlet. The flask is flushed with dry nitrogen and charged with 3-butyn-1-ol (Note 1) (freshly distilled, 31.4 g, 0.448 mol) and 900 mL of anhydrous tetrahydrofuran (Note 2). The stirred solution is cooled to 0°C under nitrogen and to it is added over 1 hr a solution of ethylmagnesium bromide in tetrahydrofuran (493 mL of 2.0 *M* solution, 0.986 mol) (Note 1). The resulting heterogeneous mixture is rapidly stirred at 0°C for 1 hr, allowed to warm to room temperature for 1 hr, and then recooled to 0°C. To this mixture is slowly added over 30 min with rapid stirring freshly distilled (Note 3) chlorotrimethylsilane (125 mL, 0.986 mol). The mixture is stirred for 1 hr at 0°C and allowed to warm to room temperature over 1–2 hr. The entire reaction mixture is poured slowly with rapid stirring into a 4-L Erlenmeyer flask that contains 1 L of ice-cold 3 *M* hydrochloric acid, and is stirred at 25°C for an additional 2 hr. The organic phase is separated and the aqueous phase is extracted with three 200-mL portions of ether.

The combined organic phases are washed with two 200-mL portions of water, four 200-mL portions of saturated sodium bicarbonate solution, and two 200-mL portions of saturated sodium chloride. The organic phase is dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure at room temperature using a rotary evaporator. The crude product is distilled through a short-path distillation apparatus under reduced pressure to give 45.2 g (0.318 mol, 71% yield) of 4-(trimethylsilyl)-3-butyn-1-ol, bp 78–79°C (10 mm), as a colorless liquid (Note 4) and (Note 5).

B. *Preparation of (Z)-4-(trimethylsilyl)-3-buten-1-ol*. A dry, 250-mL, round-bottomed flask with a stirring bar is charged with 8.84 g (0.062 mol) of 4-(trimethylsilyl)-3-butyn-1-ol, 0.4 g of 5% palladium on barium sulfate (Note 6), 0.45 g of synthetic quinoline (Note 7), and 78 mL of methanol. The flask is placed in a hydrogenation apparatus equipped with a gas burette, and the stirred mixture is thoroughly purged with nitrogen. The nitrogen is then replaced by hydrogen and the reaction mixture is stirred at atmospheric pressure and room temperature until 1.46 L

(0.065 mol) of hydrogen is consumed. The flask is flushed with nitrogen and the solution is filtered through a thick pad of Celite. The filtrate is concentrated on a rotary evaporator at room temperature to afford 10–15 mL of an oil, which is diluted with 150 mL of ether. The ether solution is thoroughly washed once with 200 mL of ice-cold 0.2 *M* sulfuric acid, then once with 20 mL of 5% sodium bicarbonate solution. The ether layer is dried over anhydrous magnesium sulfate, filtered, and concentrated to yield 8.4 g (0.058 mol) of the crude buten-1-ol (Note 8). Short-path distillation under reduced pressure gives 7.60 g (0.0527 mol, 85% yield) of (*Z*)-4-(trimethylsilyl)-3-buten-1-ol, bp 95–100°C (25 mm) as a colorless liquid (Note 9) and (Note 10).

2. Notes

1. The reagents, 3-butyn-1-ol and 2.0 *M* ethylmagnesium bromide in tetrahydrofuran, were purchased from Aldrich Chemical Company, Inc. The ethylmagnesium bromide concentration can be easily checked by titration with menthol using 1,10-phenanthroline as indicator.[2]
2. Tetrahydrofuran was distilled from sodium and benzophenone under a nitrogen atmosphere.
3. Chlorotrimethylsilane was purchased from Aldrich Chemical Company, Inc., and was distilled from calcium hydride under an atmosphere of nitrogen immediately prior to use.
4. The product, 4-(trimethylsilyl)-3-butyn-2-ol, shows the following proton NMR spectrum at 300 MHz in $CDCl_3$ δ: 0.03 (s, 9 H, $SiCH_3$), 1.8 (broad s, 1 H, OH), 2.47 (t, 2 H, CH_2), 3.67 (m, 2 H, CH_2OH); and infrared spectrum (neat) cm^{-1}: 3350 (very broad), 2178, 1250, 1031, 894, 842, 760.
5. Similar yields can be obtained in this silylation by using the chloromagnesium salt (from butylmagnesium chloride) as described in *Org. Synth., Coll. Vol. VIII* **1993**, 606.
6. The 5% palladium on barium sulfate was purchased from Engelhard Industries, Newark, NJ.
7. Synthetic quinoline was purchased from Aldrich Chemical Company, Inc. and was distilled prior to use.
8. The proton NMR spectrum of the crude buten-1-ol was essentially identical to that of the distilled product, except for traces of solvent. This crude silylbuten-1-ol was of sufficient purity for the tetrahydropyridine synthesis described in the next procedure.
9. Distilled product showed a proton NMR at 250 MHz in $CDCl_3$ as follows δ: 0.14 (s, 9 H, $SiCH_3$), 1.61 (broad s, 1 H, OH), 2.37–2.46 (m, 2 H, CH_2CH_2OH), 3.68 (broadened t, 2 H, J = 6.5, CH_2OH), 5.66–5.71 (dt, 1 H, J = 14.1, J = 1.2, $Me_3SiCH{=}CHR$), 6.29 (overlapping dt, 1 H, J = 14.1, J = 7.1, $R_3SiCH{=}CHR$). Gas chromatographic analysis using a 25-m 5% methylphenylsilicone column showed that this sample was a 92:8 mixture of *Z* and *E* isomers and contained <2% of other impurities.
10. The submitters report that *Z*-4-(trimethylsilyl)-3-buten-1-ol of >98% isomeric purity can be obtained in ca. 60% overall yield by a more lengthy sequence involving hydroalumination–protonolysis[3] of the tetrahydropyranyl (THP) ether of 4-(trimethylsilyl)-3-butyn-1-ol[4] followed by cleavage[5] of the THP ether with pyridinium *p*-toluenesulfonate in methanol. This sequence is less convenient for the tetrahydropyridine synthesis described in the next procedure, since the isomeric purity of the vinylsilane is not important for the cyclization reaction.[6]

3. Discussion

The direct silylation of 3-butyn-1-ol follows the Danheiser modification[7] of the Westmuze–Vermeer[8] method. The subsequent semihydrogenation is a modification[9] of the Lindlar procedure and yields the *Z*-alkene isomer in >90% isomeric purity.

Another *Organic Syntheses* procedure[10] illustrates one[6] of the uses of the four-carbon organosilane intermediates described in this preparation.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 358

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

tetrahydropyranyl (THP) ether of 4-(trimethylsilyl)-3-butyn-1-ol

THP ether

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

methanol (67-56-1)

ether (60-29-7)

hydrogen (1333-74-0)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

barium sulfate (7727-43-7)

Benzophenone (119-61-9)

sodium (13966-32-0)

palladium (7440-05-3)

Quinoline (91-22-5)

menthol (15356-60-2)

ethylmagnesium bromide (925-90-6)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

calcium hydride (7789-78-8)

3-butyn-1-ol (927-74-2)

1,10-phenanthroline (66-71-7)

CHLOROTRIMETHYLSILANE (75-77-4)

TETRAHYDROPYRIDINE

vinylsilane (7291-09-0)

(Z)-4-(Trimethylsilyl)-3-buten-1-ol, 3-Buten-1-ol, 4-(trimethylsilyl)-, (Z)-, Z-4-(trimethylsilyl)-3-buten-1-ol (87682-77-7)

Butylmagnesium chloride (693-04-9)

4-(trimethylsilyl)-3-butyn-1-ol (2117-12-6)

4-(trimethylsilyl)-3-butyn-2-ol (6999-19-5)

pyridinium p-toluenesulfonate

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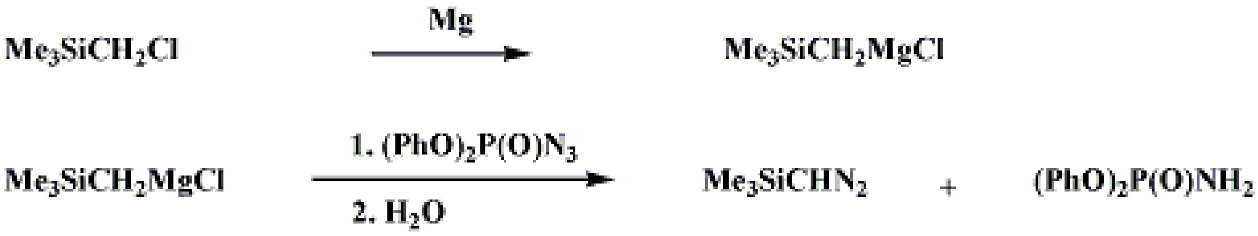
Organic Syntheses, CV 8, 612

TRIMETHYLSILYLDIAZOMETHANE

[Silane, (diazomethyl)trimethyl-]



Submitted by Takayuki Shioiri, Toyohiko Aoyama, and Shigehiro Mori[1].
Checked by George Maynard and Leo A. Paquette.

1. Procedure

A. *Trimethylsilylmethylmagnesium chloride*. Magnesium turnings (10.7 g, 0.44 g-atom) are placed in a dry, 300-mL, four-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar, a 200-mL pressure-equalizing dropping funnel capped with a rubber septum, a thermometer, another rubber septum, and a reflux condenser connected to an argon flow line. The apparatus is flushed with argon, and an argon atmosphere is maintained throughout the reaction. Anhydrous diethyl ether (40 mL) (Note 1) and 0.1 mL of 1,2-dibromoethane are placed in the reaction flask with a syringe, and the mixture is stirred at room temperature for 15 min. The dropping funnel is charged with a solution of 45.4 g (0.37 mol) of chloromethyltrimethylsilane (Note 2) in 100 mL of anhydrous diethyl ether with a syringe. With stirring, about 10 mL of this solution is added at once. When the reaction has started (Note 3), the remaining solution is added dropwise at such a rate that a gentle reflux is maintained throughout the addition (addition time ca. 2 hr). After the exothermic reaction subsides, the resulting solution is stirred at reflux by heating for an additional 1 hr. The reaction mixture is cooled to room temperature, and is used in step B.

B. *Trimethylsilyldiazomethane*. (See (Note 4).) A dry, 1-L, four-necked, round-bottomed flask is equipped with a liquid paraffin-sealed mechanical stirrer (Note 5), a rubber septum, 200-mL pressure-equalizing dropping funnel capped with another rubber septum, and a reflux condenser connected to an argon flow line. The apparatus is flushed with argon, and an argon atmosphere is maintained throughout the reaction. A solution of 91.2 g (0.33 mol) of diphenyl phosphorazidate (Note 6) in 350 mL of anhydrous diethyl ether is placed in the flask with a syringe. The rubber septum is quickly replaced by a low-temperature thermometer. The Grignard reagent prepared in Step A is transferred to the dropping funnel with a syringe. The flask is cooled with an ice–sodium chloride bath, and the stirring is started. When the internal temperature reaches –10°C, the Grignard reagent is added dropwise at such a rate that the internal temperature is maintained below 0°C (addition time ca. 1.5 hr) (Note 7). After the addition is complete, the ice–salt bath is replaced with an ice bath and the mixture is

stirred for 2 hr, then allowed to stand in the ice bath for 14–16 hr. The reaction mixture is cooled again to −15°C with an ice–sodium chloride bath. With vigorous stirring, 35 mL of cold water is carefully added dropwise at such a rate that the internal temperature is maintained below 0°C (addition time about 1 hr), and the stirring is continued for 0.5 hr (Note 8). The reaction mixture is then filtered by suction using a glass filter. The white solid is thoroughly washed with three 100-mL portions of diethyl ether. The combined filtrate is washed with two 100-mL portions of cold water and dried over anhydrous sodium sulfate. After the sodium sulfate is removed by filtration, the filtrate is placed in a 1-L, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar and a 30-cm Vigreux column (15-mm diameter). With constant stirring by a magnetic stirrer, the solution is slowly concentrated to a volume of about 200 mL by distillation at atmospheric pressure with the bath temperature below 45°C. The concentration time requires about 6 hr (Note 9) and (Note 10). The remaining deep-yellow solution is distilled through the same apparatus under reduced pressure between 100 mm at 0°C (bath temperature) and 15 mm at 40°C (bath temperature) until no more volatile material comes over, and the distillate is collected in a receiver cooled in a dry ice–acetone bath. The distillate is dried again over anhydrous sodium sulfate. The drying agent is removed by filtration, and 100 mL of hexane (Note 11) is added to the filtrate. In a manner similar to that described above, this solution is slowly concentrated by distillation at atmospheric pressure through a 30-cm Vigreux column (15-mm diameter). The color of the distillate gradually becomes yellow. Concentration is continued until the temperature of the vapor reaches 68°C (final oil-bath temperature 87°C). The concentration requires about 3 hr (Note 9). Approximately 80–110 mL of the remaining yellow hexane solution contains 220–230 mmol of trimethylsilyldiazomethane (67–70% yield based on diphenyl phosphorazidate) (Note 12) and (Note 13). This hexane solution can be stored without decomposition for periods exceeding 6 months at 0°C with protection from light.

2. Notes

1. Diethyl ether was distilled from lithium aluminum hydride under argon before use.
2. Chloromethyltrimethylsilane, obtained from Petrarch Systems Inc., was purified by distillation at 97°C under atmospheric pressure.
3. If the reaction does not start, the flask is gently heated by a heat gun.
4. *Trimethylsilyldiazomethane is both nonexplosive and nonmutagenic.*[2] *Therefore, the very careful operations*[3] *used for the preparation of diazomethane are not necessary.*
5. A glass or Teflon stirring rod should be used.
6. Diphenyl phosphorazidate, obtained from either Daiichi Pure Chemicals Co., Ltd. or Aldrich Chemical Company, Inc., was purified by distillation under reduced pressure; bp 134–136°C at 0.2 mm. It can be easily prepared according to *Org. Synth., Coll. Vol. VII* **1990**, 206.
7. After approximately two-thirds of the Grignard reagent is added, a large amount of white precipitate appears.
8. The mixture becomes yellow, which is the color of trimethylsilyldiazomethane.

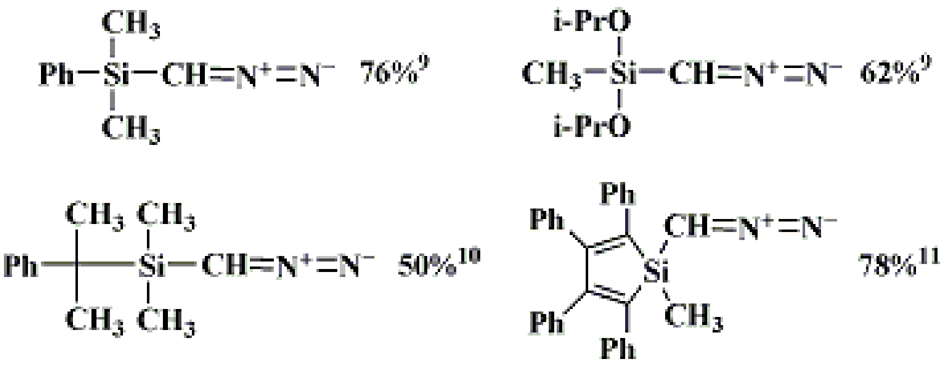
9. The color of the distillate is pale yellow because of codistillation of trimethylsilyldiazomethane. Therefore, the rate of concentration is very important. If the rate of concentration is more rapid, the yield of trimethylsilyldiazomethane will decrease.
10. The submitters report that when a 30-cm Widmer column is used, the concentration time required is shorter (ca. 4 hr).
11. Hexane was purified by distillation.
12. The infrared spectrum (hexane) has absorptions at 2075, 1260, and 885 cm^{-1}. The ^{1}H NMR spectrum is as follows (hexane) δ: 0.16 (s, 9 H), 2.58 (s, 1 H) (internal chloroform standard).
13. The ^{1}H NMR of the hexane solution showed the presence of a trace of diethyl ether. The concentration of trimethylsilyldiazomethane was determined by the ^{1}H NMR analysis as follows: Ninety-one milligrams of dibenzyl was dissolved in 1 mL of a hexane solution of trimethylsilyldiazomethane, and its ^{1}H NMR spectrum was determined. The concentration (x mmol/mL) of trimethylsilyldiazomethane was calculated as follows: $x = 2b/a$ (mmol/mL) where a = integral value (mm) of methylene protons (δ: 2.99) of dibenzyl b = integral value (mm) of the methine proton (δ: 2.58) of trimethylsilyldiazomethane

3. Discussion

Trimethylsilyldiazomethane, as a stable and safe substitute for hazardous diazomethane, is useful both as a reagent for introducing a C_1 unit and as a C-N-N synthon for the preparation of azoles.[4] Many methods are described in the literature for the preparation of trimethylsilyldiazomethane, including the trimethylsilylation of diazomethane (7–74%),[5] the alkaline decomposition of *N*-nitroso-*N*-(trimethylsilylmethyl)amides (25–61%),[2,6] and the diazo group transfer reaction of trimethylsilylmethyllithium with *p*-toluenesulfonyl azide (38%).[7] The present modified diazo group transfer method appears to be the most practical, high-yield, and large-scale procedure for the preparation of trimethylsilyldiazomethane.[8]

Diphenyl phosphorazidate can be replaced with diethyl phosphorazidate in the above procedure. Use of other azides such as *p*-toluenesulfonyl azide, *p*-methoxybenzyloxycarbonyl azide, diphenylphosphinic azide, or diphenylthiophosphinic azide is less satisfactory. No reaction occurs when trimethylsilyl azide, dimethylthiophosphinic azide, or alkaline azides are used, while decomposition of formed trimethylsilyldiazomethane seems to occur when methanesulfonyl azide is used.[9]

The present procedure affords a general method for preparing silyldiazomethanes from the corresponding chloromethylsilyl compounds. Typical examples are as follows:



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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

dibenzyl

diethyl ether (60-29-7)

magnesium turnings (7439-95-4)

sodium sulfate (7757-82-6)

1,2-dibromoethane (106-93-4)

Diazomethane (334-88-3)

lithium aluminum hydride (16853-85-3)

hexane (110-54-3)

argon (7440-37-1)

p-toluenesulfonyl azide (941-55-9)

TRIMETHYLSILYL AZIDE (4648-54-8)

Diphenyl phosphorazidate (26386-88-9)

chloromethyltrimethylsilane (2344-80-1)

Trimethylsilylmethylmagnesium chloride (13170-43-9)

Trimethylsilyldiazomethane, Silane, (diazomethyl)trimethyl- (18107-18-1)

trimethylsilylmethyllithium

diethyl phosphorazidate

diphenylphosphinic azide

diphenylthiophosphinic azide

dimethylthiophosphinic azide

methanesulfonyl azide

p-methoxybenzyloxycarbonyl azide (25474-85-5)

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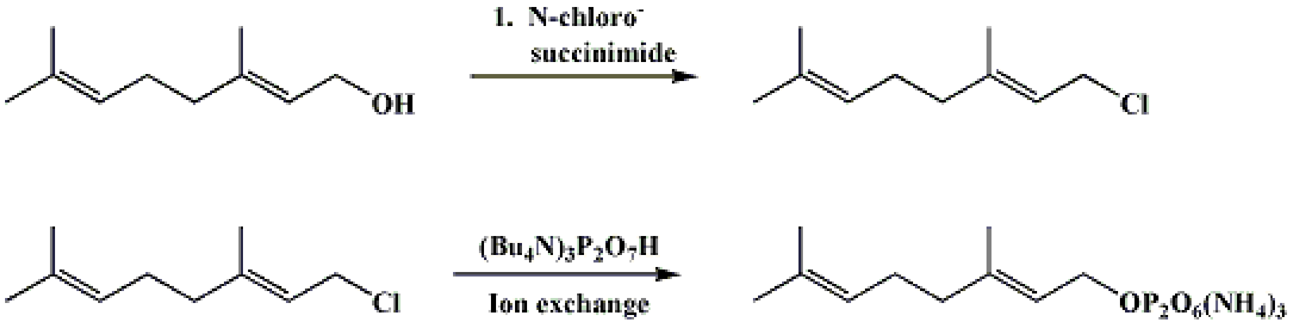
Organic Syntheses, *CV 8*, *616*

TRISAMMONIUM GERANYL DIPHOSPHATE

[Diphosphoric acid, mono(3,7-dimethyl-2,6-octadienyl) ester (*E*)-, trisammonium salt]



Submitted by Andrew B. Woodside, Zheng Huang, and C. Dale Poulter[1].
Checked by Pamela Seaton and James D. White.

1. Procedure

A. *Geranyl chloride.* To a flame-dried, 100-mL, three-necked, round-bottomed flask equipped with a magnetic stirrer, a low-temperature thermometer, a rubber septum, and a nitrogen inlet adapter is added 1.47 g (11 mmol) of *N*-chlorosuccinimide (Note 1). The powder is dissolved in 45 mL of dry dichloromethane (Note 2), and the resulting solution is cooled to −30°C with a dry ice–acetonitrile bath. Freshly distilled dimethyl sulfide (0.87 mL, 0.74 g, 12 mmol) is added dropwise by syringe. The mixture is warmed to 0°C with an ice–water bath, maintained at that temperature for 5 min, and cooled to −40°C. To the resulting milky white suspension is added dropwise by syringe 1.54 g (10 mmol) of geraniol (Note 3) dissolved in 5 mL of dry dichloromethane. The suspension is warmed to 0°C with an ice–water bath and stirred for 2 hr. The ice bath is then removed, and the reaction mixture is allowed to warm to room temperature. Stirring is continued for an additional 15 min. The resulting clear, colorless solution is poured into a 250-mL separatory funnel and washed with 25 mL of saturated sodium chloride. The aqueous layer is washed with two 20-mL portions of pentane. The pentane extracts and an additional 20-mL portion of pentane is added to the methylene chloride extract. The resulting solution is washed twice with 10 mL of saturated sodium chloride and dried over magnesium sulfate. Solid material is removed by vacuum filtration through a fritted-glass funnel, and most of the solvent is removed with a rotary evaporator at aspiratory pressure. The last traces of solvent are removed by pumping at high vacuum (0.2 mm) for 1.5 hr. The resulting pale-yellow oil (1.61 g, 9.3 mmol, 93%) is used directly in the next step (Note 4).

B. *Trisammonium geranyl diphosphate.* To a flame-dried, 100-mL, round-bottomed flask equipped with a magnetic stirrer and a nitrogen inlet adapter is added 9.14 g (9.3 mmol) of tris (tetrabutylammonium) hydrogen pyrophosphate trihydrate (Note 5). The flocculent white solid is dissolved in 20 mL of dry acetonitrile (Note 6). To the resulting milky-white suspension (Note 7) is added 0.83 g (4.8 mmol) of geranyl chloride. The mixture is allowed to stir at room temperature for 2 hr. solvent is then removed with a rotary evaporator using a 40°C water bath. The pale-yellow residue is dissolved in 3 mL of ion-exchange buffer (Note 8), and the resulting clear solution is loaded onto a 4 × 15-cm column of Dowex AG 50W-X8 (100–200-mesh) cation-exchange resin (ammonium form) (Note 9). The flask is washed twice with 5 mL of buffer and both washes are loaded into the column before elution with 360 mL (two column volumes) of ion-exchange buffer (Note 10). The eluant is collected in a 500-mL freeze-drying flask, frozen as described in Note 5, and

lyophilized for 18–24 hr (Note 11) to yield 2.57 g of a white solid. The material is dissolved in 5 mL of 0.05 *M* ammonium bicarbonate, and the clear solution is transferred to a 50-mL centrifuge tube. Then 20 mL of 1 : 1 (v/v) acetonitrile : isopropyl alcohol is added, and the contents are mixed thoroughly on a vortex mixer, during which time a white precipitate forms. The suspension is cleared by centrifugation for 5 min at 2000 rpm. The supernatant solution is removed with a pipette, and residue is suspended in 5 mL of 0.05 *M* ammonium bicarbonate, and the process is repeated. Three additional extractions are performed using 2 mL of 0.05 *M* ammonium bicarbonate and 8 mL of acetonitrile : isopropyl alcohol. The combined supernatant solutions (approximately 80 mL) are concentrated to approximately 5 mL with a rotary evaporator at 40°C (Note 12).

One-half of the concentrated extract, dissolved in an equal volume of chromatography buffer (Note 13), is loaded onto a 5.5 × 18-cm cellulose flash column[2] (Note 14). The flask is rinsed with three 5-mL portions of chromatography buffer and each is loaded onto the column. The column is then eluted with 900 mL of chromatography buffer. After a 50-mL forerun, twenty-eight 30-mL fractions are collected, and every second fraction is analyzed by thin-layer chromatography (Note 15). Fractions containing trisammonium geranyl diphosphate (typically 12–23) are pooled and concentrated to approximately 120 mL with a rotary evaporator at 40°C. The concentrate is transferred to a 250-mL freeze-drying flask and lyophilized for 18–24 hr as previously described in (Note 5). The resulting flocculent white solid is collected and stored at −78°C. The cellulose chromatography is repeated to yield a total of 1.51–1.55 g (85–87%) of trisammonium geranyl diphosphate from geraniol (Note 16).

2. Notes

1. *N*-Chlorosuccinimide (from the Aldrich Chemical Company, Inc.) is recrystallized from benzene *(Caution: Carcinogenic)*.
2. Methylene chloride is distilled from phosphorus pentoxide immediately before use.
3. Geraniol (from the Aldrich Chemical Company, Inc.) is distilled before use, bp 90–92°C at 3 mm.
4. The IR, ^{1}H NMR, and ^{13}C NMR spectra of this material are identical to those for distilled geranyl chloride (bp 49–51°C at 0.2 mm). Distillation on a small scale significantly reduces the yield, and there is no improvement in the yield of the phosphorylation reaction using distilled material. A synthesis of geranyl chloride was reported earlier in this series.[3] We find, however, that the procedure of Corey et al.[4] is more convenient.
5. Disodium dihydrogen pyrophosphate (3.13 g, 14 mmol) (from Sigma Chemical Co.) is dissolved in 25 mL of deionized water containing 1 mL of concentrated ammonium hydroxide. The resulting clear solution is loaded onto a 2 × 30-cm column of Dowex AG 50W-X8 cation exchange resin (100–200 mesh, H^{+}) and eluted with deionized water. The first 150 mL of eluant is collected in a 250mL freeze-drying flask. A magnetic stirring bar is added, and the solution is titrated to pH 7.3 by slow addition of tetrabutylammonium hydroxide (Aldrich Chemical Company, Inc.). The stirring bar is removed, and the flask is placed in a dry ice–propanol bath. The flask is spun slowly in a manner to uniformily freeze its contents to the walls. Water is removed by lyophilization for 24 hr. The resulting flocculant white solid (10.6 g, 83%) contains three to four waters of hydration and is used without further purification. The material is extremely hygroscopic and can be stored in a desiccator over phosphorus pentoxide.
6. Reagent-grade acetonitrile is distilled from phosphorus pentoxide immediately before use.
7. Clear solutions can be obtained by filtration. Residual water can be removed from freeze-dried salt by repeated evaporation of dry acetonitrile (rotary evaporator). This material is not noticeably more effective than the salt obtained after lyophilization.
8. Ammonium bicarbonate (2.0 g) is dissolved in 1 L of 2% (v/v) isopropyl alcohol/water. The

resulting solution is 25 m*M* in ammonium bicarbonate.

9. The ammonium form of the resin is generated by placing 188 mL of Dowex AG 50W-X8 (100–200 mesh, H^+ form) in an 1-L fritted-glass funnel and washing the material with four 200-mL portions of concentrated ammonium hydroxide. The resin is washed with 200-mL portions of deionized water until the pH of the filtrate drops to pH 7, then with two 200-mL portions of ion-exchange buffer. The washed resin is suspended in 200 mL of buffer and slurry-packed into the column.

10. Dowex AG 50W-X8 (100–200 mesh) from BioRad has a capacity of 1.7 meq per milliliter of resin bed. This represents approximately 10-fold excess of exchangeable ions in the resin over material loaded onto the column. However, the tetrabutylammonium cation has a lower affinity for the resin than the ammonium cation. To optimize the exchange, it is important to maintain a low concentration of ammonium ion in the exchange buffer, to elute the material slowly (less than 9 mL/min on the 4 × 15-cm column), and to elute with only two column volumes of exchange buffer; otherwise previously exchanged tetrabutylammonium cation will begin to elute from the column. Incomplete exchange dramatically reduces the efficiency of the subsequent purification on cellulose. The efficiency of the exchange can be determined by ^{1}H NMR.

11. Trisammonium geranyl diphosphate will decompose if left under vacuum for extended periods. It is important to remove the sample from the freeze drier within a few hours after water has been removed.

12. This material is stored at −20°C until chromatography on cellulose.

13. Chromatography buffer is prepared by dissolving 4.0 g of ammonium bicarbonate in 250 mL of deionized water and adding 500 mL of isopropyl alcohol and 250 mL of acetonitrile. The resulting solution is approximately 50 mM in ammonium bicarbonate.

14. Whatman CF11 fibrous cellulose powder is prepared for chromatography by the following procedure. Cellulose powder (1 L, dry volume) is mixed with 700 mL of deionized water in a 2-L beaker by vigorous stirring with a glass rod. The suspension is allowed to stand for 30 min, and the water is removed by decantation. The same procedure is followed as the cellulose is washed in succession with two 700-mL portions of 0.1 *N* hydrochloric acid, two 700-mL portions of deionized water, two 700-mL portions of 0.1 *N* sodium hydroxide, two 700-mL portions of deionized water, and two 700-mL portions of 1 : 1 (v/v) isopropyl alcohol : water. The material is stored at 4°C in 1 : 1 isopropyl alcohol : water until used. the column is slurry-packed in 1 : 1 isopropyl alcohol : water and washed with 1.3 L (approximately three column volumes) of acetonitrile. The column is then washed with 1.3 L of 1 : 1 isopropyl alcohol : water and equilibrated with 1.3 L of chromatography buffer (Note 13).

15. E. Merck cellulose thin-layer chromatography plates (available from American Scientific Products) are developed with chromatography buffer (Note 13) and visualized with sulfosalicylic acid/ferric chloride spray.[5] The system consists of a solution of 1.0 g of sulfosalicylic acid (from Aldrich Chemical Co., Inc.) dissolved in 100 mL of 3:2 (v/v) ethanol : water and a solution of 0.20 g of ferric chloride in 100 mL of 4:1 (v/v) ethanol : water. Plates are first sprayed with the sulfosalicylic acid solution (thoroughly wetted but not dripping) and allowed to air-dry. The ferric chloride solution is lightly sprayed onto the plates. Phosphate-containing compounds appear as white spots on a pink background. A second light spraying with ferric chloride may be necessary to make the spots pronounced. It is *important* to prepare both sprays freshly. Their shelf life is only about 6 hr. Under these conditions the trisammonium geranyl diphosphate has an R_f of 0.35. Residual tetrabutylammonium salt moves with the solvent front, and ammonium inorganic pyrophosphate remains at the origin.

16. This material migrates as a single spot on the cellulose thin-layer system and has no extraneous peaks in the ^{1}H, ^{13}C, and ^{31}P NMR spectra. The IR and NMR spectral properties of trisammonium geranyl diphosphate are as follows: IR (KBr) cm^{-1}: 3100–3500 (br), 2800, 2990 (br), 1650, 1450, 1400, 1200, 1120, 1080, 1015, 900; ^{1}H NMR (300 MHz, D_2O/

ND_4OD) δ: 1.62 (s, 3 H, methyl), 1.68 (s, 3 H, methyl) 1.72 (s, 3 H, methyl), 2.11 (m, 4 H, CH_2 at C_4 and C_5), 4.47 (t, 2 H, $J_{1H,1H}$ = 6.5, $J_{1H,31P}$ = 6.5, CH_2 at C_1), 5.22 (broad, 1 H, $J_{1H,1H}$ = 6.5, H at C_6), and 5.47 (t, 1 H, $J_{1H,1H}$ = 6.5, H at C_2); ^{13}C NMR (75 MHz, D_2O/ ND_4OD, ^1H decoupled: 18.28 (CH_3), 19.69 (CH_3), 27.55 (CH_3), 28.60 (CH_2), 41.55 (CH_2), 65.42 (CH_2, d, $J_{13C,31P}$ = 4.0), 122.85 (CH, d, $J_{13C,31P}$ = 7.5), 127.10 (CH), 136.68 (C), 145.76 (C); ^{31}P NMR (32 MHz, D_2O/ND_4OD, ^1H decoupled): −11.23 (d, 1 P $J_{31P,31P}$ = 20) and −9.10 (d, 1 P, P_2).

3. Discussion

Previous methods for the preparation of salts of geranyl diphosphate and other allylic isoprenoid diphosphates are based on condensation between the alcohol and inorganic phosphate by trichloroacetonitrile as originally reported by Cramer[6] and modified by Popjak.[7] The reaction generates a complex mixture of organic and inorganic polyphosphates that must be separated by chromatography. The desired diphosphate ester has been prepared on small scales in yields of up to 30%,[8] but in our experience, the yields of pure material obtained by this procedure are usually less than 10%.

The direct displacement reaction can be used to prepare many of the common diphosphate esters in the isoprene biosynthetic pathway,[9] including isopentenyl diphosphate.[10,11] The yields are typically 60–90% from the alcohol, and the absence of phosphate polymer found in the Cramer procedure simplifies the purification step. We have also used the displacement procedure to prepare radio-labeled material for biosynthetic studies.[12]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Diphosphoric acid, mono(3,7-dimethyl-2,6-octadienyl) ester (E)-, trisammonium salt

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

acetonitrile (75-05-8)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

isopropyl alcohol (67-63-0)

ferric chloride (7705-08-0)

ammonium hydroxide (1336-21-6)

sulfosalicylic acid

Pentane (109-66-0)

methylene chloride, dichloromethane (75-09-2)

trichloroacetonitrile (545-06-2)

magnesium sulfate (7487-88-9)

dimethyl sulfide (75-18-3)

ISOPRENE (78-79-5)

geraniol (106-24-1)

N-chlorosuccinimide (128-09-6)

Geranyl chloride (5389-87-7)

phosphorus pentoxide (1314-56-3)

tetrabutylammonium hydroxide (2052-49-5)

Trisammonium geranyl diphosphate

hydrogen pyrophosphate trihydrate

ammonium bicarbonate

Disodium dihydrogen pyrophosphate

geranyl diphosphate

isopentenyl diphosphate

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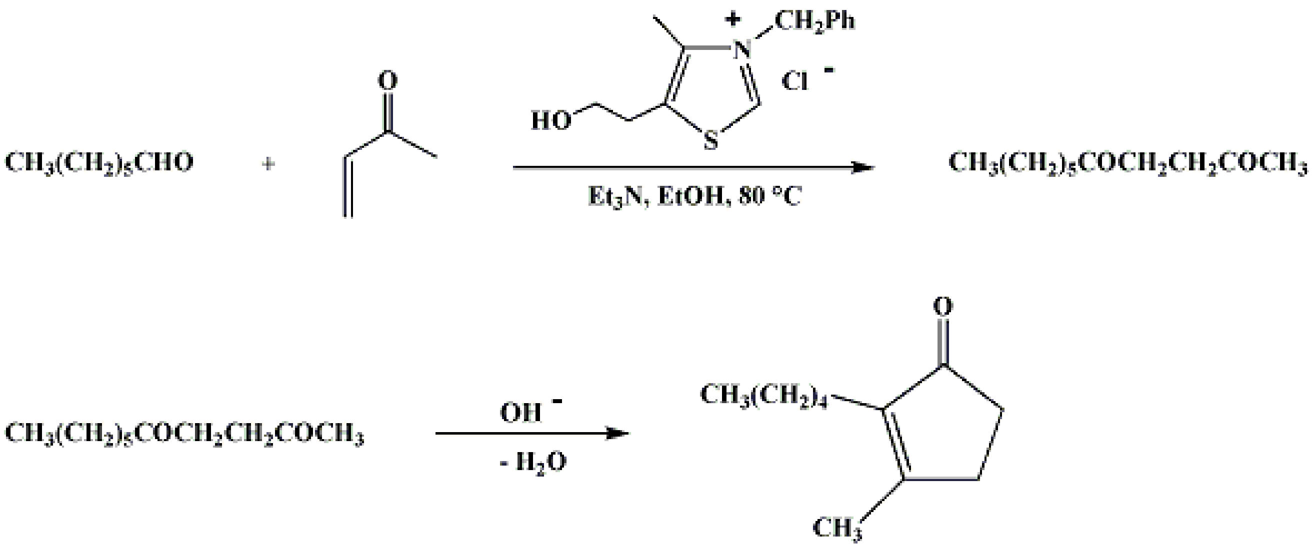
Organic Syntheses, CV 8, 620

THE STETTER REACTION: 2,5-UNDECANEDIONE AND 3-METHYL-2-PENTYL-2-CYCLOPENTEN-1-ONE (DIHYDROJASMONE)

[2-Cyclopenten-1-one, 3-methyl-2-pentyl-]



Submitted by H. Stetter, H. Kuhlmann, and W. Haese[1].
Checked by Rodney A. Badger and James D. White.

1. Procedure

A. *2,5-Undecanedione*. A 1000-mL, three-necked, round-bottomed flask equipped with a mechanical stirrer, a short gas inlet tube, and an efficient reflux condenser fitted with a potassium hydroxide drying tube is charged with 26.8 g (0.1 mol) of 3-benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium chloride (Note 1), 500 mL of absolute ethanol, 77.2 g (1.1 mol) of 3-buten-2-one (Note 2), 60.6 g (0.6 mol) of triethylamine (Note 3), and 114.2 g (1.0 mol) of heptanal (Note 4). A slow stream of nitrogen (Note 5) is started and the mixture is stirred and heated in an oil bath at 80°C. After 16 hr the reaction mixture is cooled to room temperature and concentrated by rotary evaporation. Then 500 mL of chloroform is added to the residue and the mixture is washed with 200 mL of dilute hydrochloric acid (5%), 200 mL of saturated sodium hydrogen carbonate solution, and, finally, with two 200-mL portions of water. After the solution is dried with anhydrous magnesium sulfate, the chloroform is distilled off and the residue is fractionated under reduced pressure through a 30-cm Vigreux column. The main fraction is collected at 80–82°C/0.3 mm. The yield is 130–138 g (71–75% based on heptanal) of a colorless distillate, which solidifies on standing at room temperature, mp 33–34°C (Note 6) and (Note 7).

B. *3-Methyl-2-pentyl-2-cyclopenten-1-one (Dihydrojasmone).* 2,5-Undecanedione (92.1 g, 0.5 mol) is added to a solution of 16.0 g (0.4 mol) of sodium hydroxide in 800 mL of water and 200 mL of ethanol in a 2000-mL round-bottomed flask. The mixture is refluxed for 6 hr, cooled to room temperature, and extracted with ether. The combined ether phases are dried with magnesium sulfate, and the solution is separated from the drying agent and concentrated at room temperature under reduced pressure. The residual oil is distilled through a 30-cm Vigreux column. the pure compound boils at 65–67°C/0.5 mm and weighs 70–73 g (84–88% based on the diketone) (Note 8).

2. Notes

1. 3-Benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium chloride is supplied by Fluka AG, Buchs,

Switzerland and by Tridom Chemical, Inc., Hauppague, New York. The thiazolium salt may also be prepared as described in *Org. Synth., Coll. Vol. VII,* **1990**, 95.

2. 3-Buten-2-one was used as obtained from Fluka AG, Buchs, Switzerland.

3. Triethylamine was dried with potassium hydroxide and distilled. Instead of triethylamine, sodium acetate (32.8 g, 0.4 mol), which has been dried under vacuum at 100°C for 1 day, can also be used.

4. Heptanal was supplied by Aldrich Chemical Company, Inc. It was freshly distilled before use.

5. The nitrogen flow rate should be one bubble per second.

6. A boiling point of 141°C at 14 mm and a melting point of 33°C is recorded.[2] The diketone exhibits the following spectral characteristics: IR ($CDCl_3$) cm^{-1}: 1710, ^1H NMR ($CDCl_3$) δ: 0.77–1.67 (m, 11 H, CH_2 and CH_3); 2.13 (s, 3 H, C-CH_3); 2.30–2.60 (m, 2 H, CH_2); 2.67 (s, 4 H, $COCH_2CH_2CO$).

7. The checkers obtained a second fraction from the distillation (13.5 g, 7.4%), bp 97–105°C at 0.15 mm, which solidified on cooling. Recrystallization of this material from hexane gave a colorless solid, mp 26–27°C, which was identified from its infrared, NMR, and mass spectra as 8-hydroxy-7-tetradecanone. This product arises via a "benzoin-type" condensation, catalyzed by the thiazolium salt, of heptanal.

8. A boiling point of 122–124°C at 12 mm is recorded.[2] The cyclopentenone exhibits the following spectral characteristics: IR (neat) cm^{-1}: 1695 and 1640; ^1H NMR ($CDCl_3$) δ: 0.77–1.50 (m, 9 H, CH_2 and CH_3); 2.03 (s, 3 H, CH_3); 2.13–2.57 (m, 6 H, CH_2). For fragrance it is advisable to destroy malodorous byproducts by the method described in (Note 9).

9. The use of sodium acetate instead of triethylamine (see (Note 3)) is an alternative and is followed by an oxidizing treatment of the diketone: 100 g of 2,5-undecanedione is dissolved in 500 mL of methylene chloride and treated with 10 g of an oxidizing reagent (Note 10). The mixture is refluxed for 3 hr, filtered, and washed with three 100-mL portions of water. The organic phase is dried with sodium sulfate and distilled. This material is converted into dihydrojasmone by Procedure B, and a last, efficient distillation (Fisher, slit-tube system, HMS 500) leads to chromatographic purity greater than 99%.

10. Oxidizing reagent:[3] To a solution of 500 g (0.5 mol) of chromium(VI) oxide and 300 mL of water is added 250 g of silica gel (silica gel 60, E. Merck, Darmstadt, Germany). The mixture is shaken at 30–35°C for 1 hr. After this, the water is removed on a rotary evaporator to yield a yellow-orange, free-flowing powder.

3. Discussion

2,5-Undecanedione and the cyclization to dihydrojasmone were first described by H. Hunsdiecker.[2] The natural jasmine odor components and the artificial substitutes have been the goal of many investigations.[4] Our method of preparing 2,5-undecanedione by addition of heptanal to 3-buten-2-one[5] is only one example of a wide range of reactions involving the conjugate addition to electron-deficient double bonds.[6]

A large variety of aldehydes has been used in the addition to butenone (we give some characteristic examples):

1. Simple straight-chain aliphatic aldehydes (C_2 to C_{12} tested) and mono α-branched aldehydes.[7]
2. Conjugated unsaturated aldehydes (e.g., citral, β,β-dimethylacrolein[8]).
3. Aldehydes that contain isolated double bonds, such as 10-undecenal, citronellal, 3-cyclohexene-1-carboxaldehyde, and norbornene carboxaldehyde.[8,9]
4. Aldehydes containing a variety of other functional groups, such as ether groups,[10] the phthalimido group,[11] and keto, ester, and nitrile groups.[12,13]
5. Heterocyclic and aromatic aldehydes[7,12] (e.g., furan-2-carboxaldehyde, thiophene-2-carboxaldehyde, and pyridinecarboxaldehydes, benzaldehyde, and diverse substituted benzaldehydes).

Variations have been made in the activated system also. Higher homologues of butenone (e.g., 1-penten-3-

one, *tert*-butyl vinyl ketone) react in the same manner as does phenyl vinyl ketone. The same variety of functional groups as shown before may be possible in the side chain of the ketone.[14]

Additions to acrylic esters and acrylonitrile[15] and to arylidene and alkylidene-β-dicarbonyl compounds[16] are possible.

The addition of aldehydes to α,β-unsaturated sulfones yields γ-diketones.[17]

The mechanism of the thiazolium ion-catalyzed conjugate addition reactions[6] is considered to be analogous to the Lapworth mechanism for the cyanide-catalyzed benzoin condensation, the thiazolium ylide playing the role of cyanide. The resulting intermediate carbanion is presumed to be the actual Michael donor. After conjugate addition to the activated olefin, the thiazolium ylide is eliminated to form the product and regenerate the catalyst.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium acetate (127-09-3)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium hydrogen carbonate (144-55-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

benzaldehyde (100-52-7)

Benzoin (119-53-9)

potassium hydroxide (1310-58-3)

furan-2-carboxaldehyde (98-01-1)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

chromium(VI) oxide (1333-82-0)

acrylonitrile (107-13-1)

hexane (110-54-3)

3-buten-2-one, butenone (78-94-4)

citral (5392-40-5)

thiophene-2-carboxaldehyde (98-03-3)

triethylamine (121-44-8)

Heptanal (111-71-7)

cyclopentenone (930-30-3)

3-cyclohexene-1-carboxaldehyde

citronellal (106-23-0)

3-benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium chloride

thiazolium ylide

1-penten-3-one (1629-58-9)

phenyl vinyl ketone (768-03-6)

2,5-Undecanedione (7018-92-0)

3-Methyl-2-pentyl-2-cyclopenten-1-one, 2-Cyclopenten-1-one, 3-methyl-2-pentyl- (1128-08-1)

8-hydroxy-7-tetradecanone

10-undecenal (112-45-8)

norbornene carboxaldehyde

Dihydrojasmone

tert-butyl vinyl ketone

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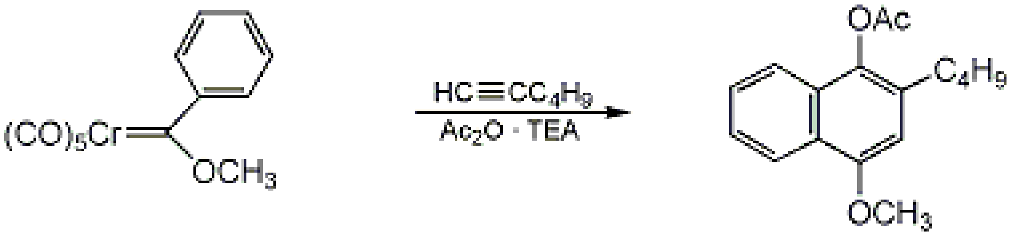
Organic Syntheses, CV 9, 1

SYNTHESIS OF 2-SUBSTITUTED NAPHTHALENEDIOL DERIVATIVES USING CHROMIUM CARBENE COMPLEXES: 1-ACETOXY-2-BUTYL-4-METHOXYNAPHTHALENE

[1-Naphthalenol, 2-butyl-4-methoxy-, acetate]



Submitted by Joseph M. Timko and Ayako Yamashita[1].
Checked by Paul A. Johnson and Albert I. Meyers.

1. Procedure

*Caution! All operations should be conducted in a well-ventilated hood with breathing protection. The chromium carbene complex generally is contaminated with the **very volatile and toxic** chromium hexacarbonyl, which is also generated as a by-product of the reaction.*

An oven-dried, 2-L, three-necked, round-bottomed flask, equipped with a nitrogen inlet, magnetic stirring bar, thermometer, and reflux condenser, under an inert nitrogen atmosphere (Note 1), is charged with 1.22 g (10 mmol) of 4-dimethylaminopyridine (Note 2), 500 mL of tetrahydrofuran (Note 3), 11.0 mL (95.7 mmol) of 1-hexyne (Note 4), 13.2 mL (140 mmol) of acetic anhydride (Note 5), 9.8 mL (70 mmol) of triethylamine (Note 2), 20.0 g (64.0 mmol) of pentacarbonyl[phenyl(methoxy) chromium]carbene (Note 1) and (Note 6), and a final 100-mL rinse of tetrahydrofuran. The solution is heated to reflux with an oil bath and heating is maintained until TLC indicates that the chromium complex is totally consumed (about 45–60 min, (Note 7)). The solution is then cooled to ambient temperature, 30 g of silica gel is added (Note 8), and volatile organic material is removed under reduced pressure (rotary evaporator). The green solids are transferred to a filter funnel and washed with hexane until TLC indicates that all products have been removed (5 × 100 mL) (Note 9). The hexane filtrate is then concentrated under reduced pressure to give crude product contaminated with chromium hexacarbonyl. To the mixture is added 20 mL of isopropyl alcohol and the insoluble chromium hexacarbonyl is removed by filtration (Note 9). The filtrate is concentrated under reduced pressure to give 14.0 g of crude product which is purified by silica gel chromatography (Note 10). Appropriate

fractions are combined and the solvent is removed under reduced pressure to give 1-acetoxy-2-butyl-4-methoxynaphthalene (11.8 g, >95% pure based on HPLC, 68% yield based on the carbene complex, (Note 6) and (Note 11)) as a light yellow oil which crystallizes on standing (Note 12). If desired, the product can be crystallized from isopropyl alcohol (2.5 mL/g) to give white crystals, mp 49–50°C (>99% pure based on HPLC).

2. Notes

1. Although slowly decomposed by exposure to air (oxygen), the chromium carbene complex is sufficiently stable to handle using ordinary nitrogen drybox techniques. The complex should be stored at refrigerator temperature. All solvents and liquid reagents were routinely deoxygenated prior to use with a slow stream of nitrogen.
2. 4-Dimethylaminopyridine and triethylamine were obtained from the Aldrich Chemical Company, Inc., and used without further purification. If 4-dimethylaminopyridine is omitted, the level of impurities rises.[2]
3. Tetrahydrofuran, UV grade, was obtained from Burdick and Jackson or Mallinkrodt Inc. and used after distillation from calcium hydride.
4. 1-Hexyne was obtained from Farchan Chemical Company or Aldrich Chemical Company, Inc., and used without further purification.
5. Acetic anhydride was obtained from Mallinckrodt Inc. or Aldrich Chemical Company, Inc., and used without further purification.
6. Pentacarbonyl[phenyl(methoxy)carbene]chromium was prepared by the checkers in 75% yield according to the literature: Hegedus, L. S.; McGuire, M. A.; Schultze, L. M. *Org. Synth., Coll. Vol. VIII* **1993**, 216. This material was stored under nitrogen at −30°C and purified immediately prior to use by filtration through a plug of Celite (hexane solvent). If the chromium carbene is purchased from Aldrich Chemical Company, Inc., the submitters found it was only 65% pure based on capillary GLC analysis.
7. Analytical thin layer chromatography (TLC) was conducted on 10 × 2.5-cm precoated glass plates (silica gel GF, 0.25-mm thickness, Analtech), eluted with 10% ethyl acetate in hexane, and visualized with both UV (254 nm) and aqueous 50% sulfuric acid spray/heating. The carbene complex moves as an orange spot on TLC; the reaction is complete when this spot is no longer visible.
8. The chromium complex degrades into chromium hexacarbonyl and an intractable green chromium tar. The addition of silica gel prior to solvent removal adsorbs this material before it can form a tar.
9. The solid material containing chromium waste was placed in a container for heavy metal wastes and disposed of by a commercial service according to approved procedures
10. Silica gel (obtained from E. Merck or Alfa Products, Morton/Thiokol Inc.) was used (420 g, 70–230 mesh) in a 5.5 × 60-cm column eluted with 10% ethyl acetate in hexane.

11. This reaction has been performed on a scale up to 20 times larger by the submitters (400 g of chromium carbene complex) with identical results.

12. The NMR spectrum was as follows: ^{13}C NMR (75 MHz, $CDCl_3$) δ: 17.3, 20.2, 23.1, 31.4, 67.4, 127.1, 127.2, 127.9, 128.2, 128.3, 128.6, 128.7, 130.1, 130.3, 141.2, 172.0, 216.1.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995. (See (Note 9)).

3. Discussion

The regioselective preparation of 2-substituted naphthalenediol derivatives having the diols differentially protected in a predictable and straightforward manner, previously not directly attainable, is readily accomplished using chromium carbene complexes. First prepared by E. O. Fischer, chromium carbene complexes react readily with alkynes (extensively investigated by K. H. Dötz, and others).[3] Steric effects dictate the substitution pattern observed[2,4] and the reaction mechanism has been widely studied.[2]

The title compound (U-66,858) and analogues are of interest as lipoxygenase inhibitors with potential application to the treatment of asthma and related disorders.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

30 g of silica gel

Pentacarbonyl[phenyl(methoxy)carbene]chromium

sulfuric acid (7664-93-9)

ethyl acetate (141-78-6)

acetic anhydride (108-24-7)

oxygen (7782-44-7)

nitrogen (7727-37-9)

isopropyl alcohol (67-63-0)

chromium (7440-47-3)

carbene (2465-56-7)

Tetrahydrofuran (109-99-9)

hexane (110-54-3)

1-Hexyne (693-02-7)

triethylamine (121-44-8)

calcium hydride (7789-78-8)

4-dimethylaminopyridine (1122-58-3)

chromium hexacarbonyl (13007-92-6)

chromium carbene

1-Acetoxy-2-butyl-4-methoxynaphthalene, 1-Naphthalenol, 2-butyl-4-methoxy-, acetate (99107-52-5)

pentacarbonyl[phenyl(methoxy)chromium]carbene

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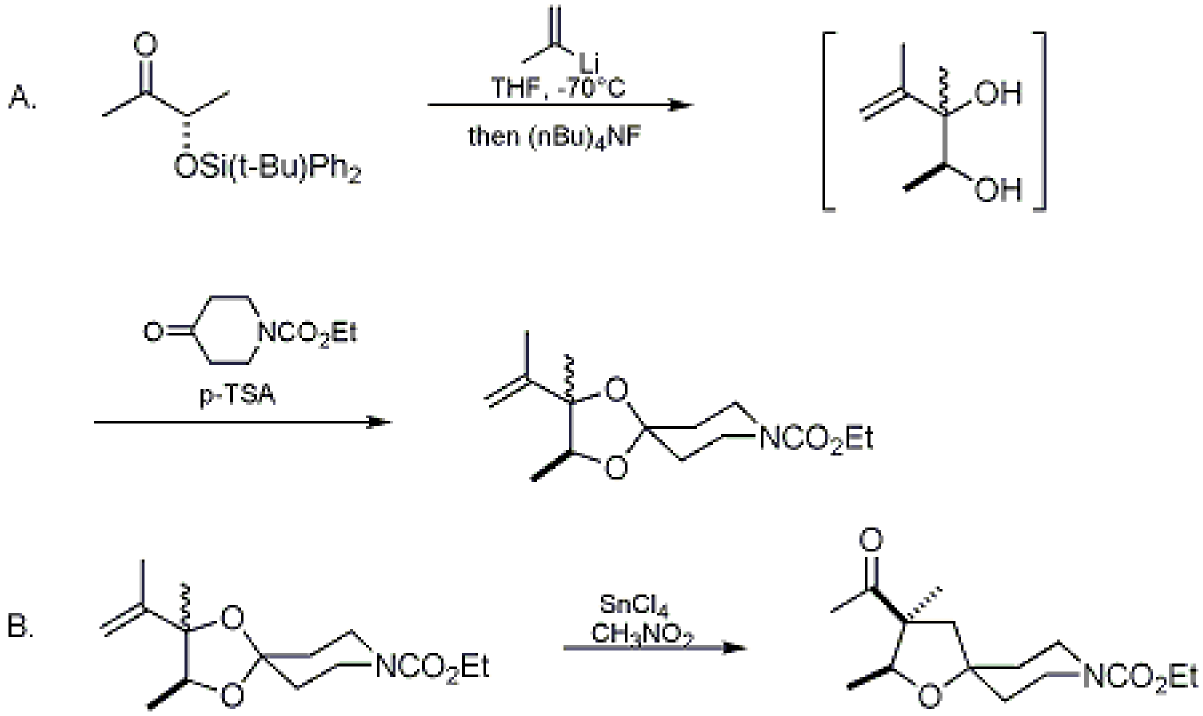
Organic Syntheses, CV 9, 4

STEREOCONTROLLED PREPARATION OF 3-ACYLTETRAHYDROFURANS FROM ACID-PROMOTED REARRANGEMENTS OF ALLYLIC KETALS: (2S,3S)-3-ACETYL-8-CARBOETHOXY-2,3-DIMETHYL-1-OXA-8-AZASPIRO[4.5]DECANE



Submitted by Larry E. Overman and Gilbert M. Rishton[1].
Checked by Takashi Ooi and Hisashi Yamamoto.

1. Procedure

A. *(2R,3S)- and (2S,3S)-1,4-Dioxa-2,3-dimethyl-2-(1-methylethenyl)-8-carboethoxy-8-azaspiro[4.5]decane*. An oven-dried, 500-mL, three-necked, round-bottomed flask is fitted with a mechanical stirrer, 100-mL addition funnel, and rubber septum, and then is charged with 100 mL of dry tetrahydrofuran (Note 1) and 7.7 mL (10.5 g, 86.7 mmol) of 2-bromopropene (Note 2). The solution is cooled to −70°C with mechanical stirring and a 1.9 M pentane solution of tert-butyllithium (92 mL, 175 mmol) is added by syringe over 20 min. The resulting yellow solution is stirred for an additional 10 min at −70°C and at this time a solution of 17.6 g (54.0 mmol) of 3-(S)-[(tert-butyldiphenylsilyl)oxy]-2-butanone[2] and 50 mL of dry tetrahydrofuran is added by dropping funnel over 20 min. The resulting solution is stirred for an additional 30 min at −70°C and at this time a 1.0 M tetrahydrofuran solution of tetrabutylammonium fluoride (163 mL, 163 mmol) is added in one portion and the resulting mixture is warmed to 23°C and stirred for 1 hr. At this time the contents of the flask are poured

into 200 mL of saturated aqueous ammonium chloride (NH_4Cl) and the resulting mixture is concentrated to remove tetrahydrofuran. The resulting aqueous suspension is diluted with 200 mL of brine and extracted twice with 200 mL of ethyl acetate (Note 3). The combined organic extracts are washed with five 100-mL portions of brine, dried over sodium sulfate, filtered, and then concentrated under reduced pressure using a rotary evaporator. The residue is subjected to short path vacuum distillation (150–160°C, 3 mm) to remove the less volatile tert-butyldiphenylsilyl by-product. The distillate contains ca. 10 g of a colorless oil that is comprised of the 2,3-dimethyl-1-pentene-3,4-diols as a 6:1 mixture of diastereomers and up to 30% of tributylamine (Note 4) and (Note 5).

1-Carbethoxy-4-piperidone (7.52 g, 43.9 mmol) (Note 6) and p-toluenesulfonic acid (5.0 g, 26 mmol) are added to a 250-mL, round-bottomed flask that contains the above distillate and a magnetic stir bar. The mixture is stirred under vacuum (20 mm) at 100°C for 90 min and the evolved water vapor is collected in a vacuum trap. The mixture is cooled to 23°C and subjected to flash chromatography on silica gel (250 g, 20 cm × 10 cm) using ethyl acetate:hexane (1:4) as the eluant (Note 7) to give 9.0 g (59% overall) of (2R,3S)- and (2S,3S)-1,4-dioxa-2,3-dimethyl-2-(1-methylethenyl)-8-carboethoxy-8-azaspiro[4.5]decane, a 6:1 mixture of diastereomers, as a pale yellow oil (Note 8).

B. *(2S,3S)-3-Acetyl-8-carboethoxy-2,3-dimethyl-1-oxa-8-azaspiro[4.5]decane*. Dry nitromethane (100 mL) (Note 9) is added through a rubber septum by syringe to a vacuum-dried, 500-mL, round-bottomed flask that contains the ketal mixture prepared in Step A (9.00 g, 31.8 mmol) and a magnetic stir bar. The solution is cooled to −23°C, tin(IV) chloride ($SnCl_4$) (11 mL, 94 mmol) is added by syringe and the solution is stirred for 30 min at −23°C (Note 10). At this time the brown solution is warmed to 23°C and stirring is continued for an additional 30 min. Saturated aqueous NH_4Cl (200 mL) is added and the mixture is concentrated under reduced pressure using a rotary evaporator to remove nitromethane. The resulting aqueous suspension is extracted with ethyl acetate (200 mL) and the organic extract is washed with brine (200 mL), dried over sodium sulfate (Na_2SO_4) and concentrated under reduced pressure using a rotary evaporator. The residue is subjected to flash chromatography on silica gel (250 g, 20 cm × 10 cm) using ethyl acetate:hexane (1:1) eluant (Note 7) to give 8.1 g (90%) of (2S,3S)-3-acetyl-8-carboethoxy-2,3-dimethyl-1-oxa-8-azaspiro[4.5]decane as a pale yellow oil (Note 11) and (Note 12).

2. Notes

1. Anhydrous tetrahydrofuran was prepared by distillation under argon from sodium benzophenone ketyl.
2. 2-Bromopropene, obtained from Aldrich Chemical Company, Inc., was distilled and then passed through a plug of activity IV basic alumina immediately before use.
3. The fine white emulsion formed at this stage was collected with the organic phase and was cleared in the subsequent brine washings.

4. This crude material was acceptable for use in the second step, although more p-toluenesulfonic acid will be required if large amounts of tributylamine are present. The diol mixture, free from tributylamine, can be obtained by careful chromatography on silica gel using ethyl acetate-hexane (1:1). The purified sample has the following characteristics: ^{1}H NMR (500 MHz, $CDCl_3$, major isomer) δ: 1.10 (d, 3 H, J = 6.5, CH_3), 1.37 (s, 3 H, CH_3), 1.80 (s, 3 H, CH_3), 2.21 (br s, 2 H, 2 × OH), 3.77 (q, 1 H, J = 5.6, CH), 4.89 (d, 1 H, J = 1.1, CH=C), 5.06 (s, 1 H, CH=C); IR (film) cm^{-1}: 3421, 3397, 3390, 3364, 2981, 2937, 1088; MS (Cl) m/z 113.0936 (113.0966 calcd for $C_7H_{14}O_2$, MH – H_2O).

5. The major isomer is assigned the 3R, 4S stereochemistry on the expectation that the addition would occur preferentially with Cram (Felkin-Ahn) selectivity.[3] This assignment was confirmed by ^{1}H NMR DNOE experiments on the isobutyraldehyde acetal.

6. 1-Carbethoxy-4-piperidone was obtained from Aldrich Chemical Company, Inc., and used as received.

7. A series of 200-mL fractions was collected during flash chromatography. The product was eluted in fractions 3–8 as indicated by TLC analysis using 4% ethanolic phosphomolybdic acid stain.

8. This sample has the following characteristics: ^{1}H NMR (500 MHz, $CDCl_3$, major isomer) δ: 1.17 (d, 3 H, J = 5.1, CH_3), 1.26 (t, 3 H, J = 7.1, OCH_2CH_3), 1.45 (s, 3 H, CH_3), 1.77 (s, 3 H, CH_3C=), 1.60–1.81 (m, 5 H, 2 × CH_2 and CH), 3.43–3.75 (m, 4 H, 2 × CH_2N), 4.13 (q, 2 H, J = 7.1, OCH_2CH_3), 4.96 (s, 2 H, CH_2=C); IR (film) cm^{-1}: 2977, 1702, 1433, 1238, 1122; MS (Cl) m/z 284.1850 (284.1861 calcd for $C_{15}H_{25}NO_4$, MH). Anal. Calcd for $C_{15}H_{25}NO_4$: C, 63.58; H, 8.89; N, 4.94. Found: C, 63.48; H, 8.90; N, 4.89.

9. Nitromethane was dried by distillation of a 10:1 mixture of nitromethane and trifluoroacetic anhydride and collection of the center fraction that distilled at 100°C.

10. Tin(IV) chloride ($SnCl_4$) was obtained from Aldrich Chemical Company, Inc., and handled under an atmosphere of argon.

11. Gas chromatographic analysis using a 25-m 10% SP 2100 silicone column showed that this sample was 94% pure and contained one major unidentified impurity. Bulb-to-bulb distillation (200°C, 0.6 mm) of a 7.4-g sample of the crude product afforded 7.0 g (85%) of the product as a pale yellow oil, which was shown by GLC analysis to be of 100% purity. This sample has the following spectral characteristics: $[\alpha]_D$ –79.1° (MeOH, *c* 1.0); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.17 (d, 3 H, J = 6.6, CH_3), 1.25 (m, 6 H, OCH_2CH_3 and CH_3), 1.70–1.90 (m, 4 H, 2 × CH_2), 2.19 (s, 3 H, CH_3CO), 1.57 (d, 1 H, J = 13.5) 2.36 (d, 1 H, J = 13.5), 3.38–3.70 (m, 4 H, 2 × CH_2N), 3.89 (q, 1 H, J = 6.6, CH) 4.12 (q, 2 H, J = 7.1, OCH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.5, 15.6, 22.5, 28.3, 36.0, 37.0, 40.7, 41.1, 47.3, 58.4, 61.0, 79.1, 81.0, 155.5, 210.3; IR (film) cm^{-1}: 2977, 2937, 1705, 1701, 1698, 1472, 1455, 1434, 1365, 1356, 1274, 1237; MS (Cl) m/z 284.1845 (284.1860 calcd for $C_{15}H_{25}NO_4$, MH). Anal. Calcd for

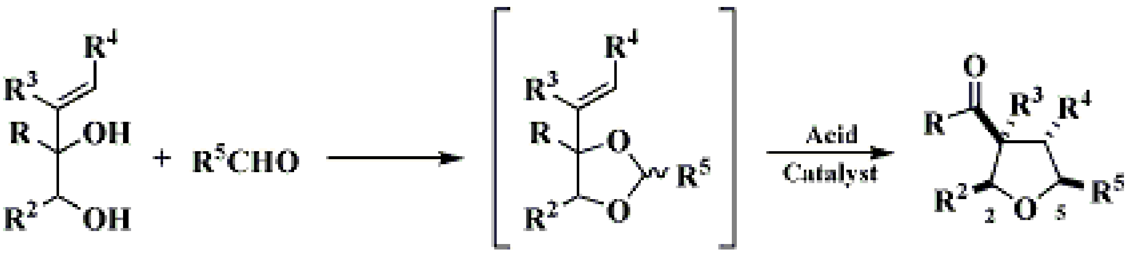
$C_{15}H_{25}NO_4$: C, 63.58; H, 8.89; N, 4.94. Found: C, 63.38; H, 8.87; N, 4.88.
12. The enantiomeric excess of the product is >96%. This was determined by treating a sample of the ketone with sodium borohydride/methanol ($NaBH_4$/MeOH) (23°C) and separating the resulting 3:2 mixture of alcohol diastereomers by flash chromatography (silica gel, 2:3 ethyl acetate-hexane). The major alcohol diastereomer was converted to its Mosher ester[4] [2.5 eq of (+)-α-methoxytrifluoromethylphenylacetic acid, 3 eq of dicyclohexylcarbodiimide, and 0.2 eq of 4-(dimethylamino)pyridine, CH_2Cl_2] and the crude esterification reaction mixture was analyzed using 500 MHz ^{1}H NMR. None of the minor diastereomer was observed while doping experiments established that 2% would have been detected [diagnostic signals: δ 1.80 (δ, J = 13.4, major ester diastereomer); δ 1.82 (δ, J = 14.1, minor ester diastereomer)].

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

This procedure illustrates a fundamentally new method for constructing substituted tetrahydrofurans.[5,6,7,8,9,10] This practical method assembles the tetrahydrofuran ring from allylic diol and carbonyl components and in the process forms three ring bonds: C(2)-C(3), C(4)-C(5) and O-C(5). Both aldehydes (eq 1) and ketones (illustrated in the present procedure) can be employed as the carbonyl component. Although it is often convenient to isolate the acetal intermediate, conversion to the 3-acyltetrahydrofuran can also be accomplished in many cases by the direct reaction of the diol and carbonyl components.[8] High cis stereoselectivity (at least 20:1) is observed in the preparation of tetrahydrofurans that contain single side chains at carbons 2 and 5 (eq. 1). The kinetically controlled product also has the cis relationship of these side chains and the 3-acyl substituent.

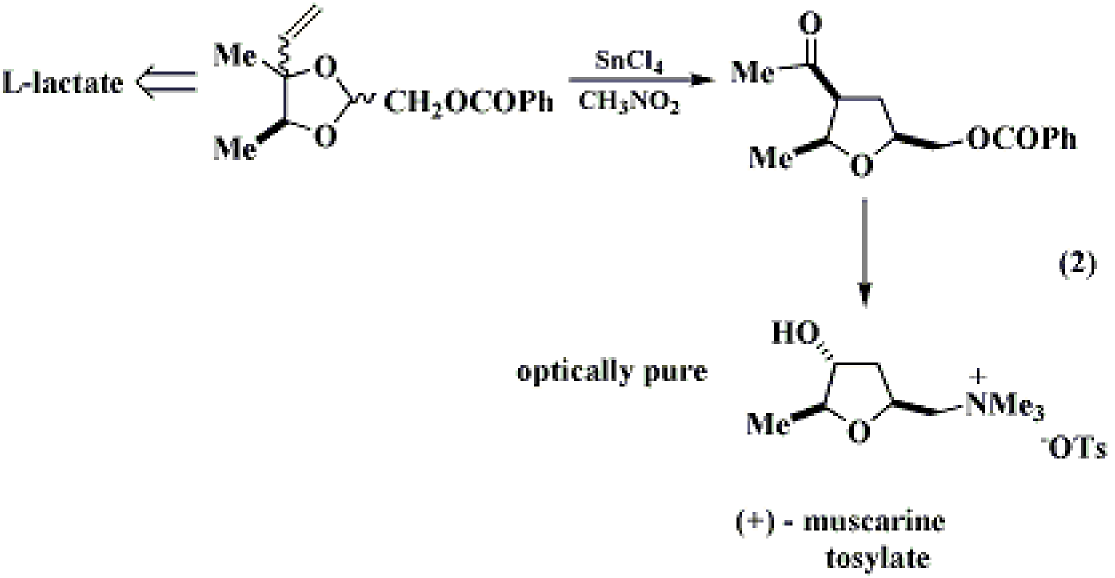


(1)

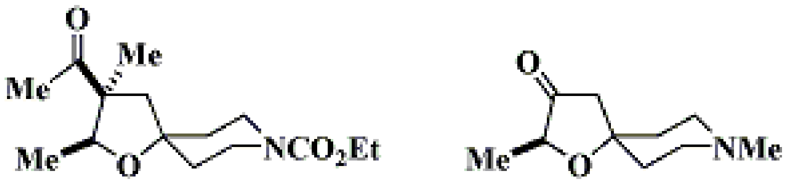
A definitive feature of this highly stereoselective new route to substituted tetrahydrofurans is that both syn and anti allylic diol stereoisomers typically afford identical tetrahydrofuran products. Thus, there is no need for stereoselective construction of the allylic diol reaction partner. The construction of substituted tetrahydrofurans in high enantiomeric purity from non-racemic allylic diol precursors has also been established.[5,7] The rearrangement illustrated in eq. 2 is the key step in a

recent synthesis of (+)-muscarine.

The scope and mechanism of the $SnCl_4$-promoted rearrangement of allylic acetals have been investigated in detail and these studies provide considerable guidance for using this new tetrahydrofuran synthesis.[5,6,7,8,9] Three major limitations emerge from studies conducted to date: (1) When the tetrahydrofuran construction involves a ketone, and thus forms a quaternary center at C(5), allylic diols with alkene substituents more nucleophilic than terminal vinyl rearrange in highest yield. (2) Allylic acetals that are reluctant to ring open in the presence of acid catalysts to generate oxocarbenium ions often undergo decomposition, rather than conversion to acyltetrahydrofuran products. (3) Allylic acetals that form highly stabilized oxocarbeniums (e.g., cinnamaldehyde-derived acetals) do not undergo conversion to 3-acyltetrahydrofurans.



This procedure illustrates the asymmetric synthesis of a spirobicyclic tetrahydrofuran from the reaction of readily available (S)-3-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-2-butanone[2] with cyclic ketones. The specific example described here affords an azaspirobicyclic tetrahydrofuran **1** that is structurally related to a recently reported class of powerful muscarinic agonists, exemplified by **2**.[10] Consistent with limitation (1) noted above, the related reaction of 3-methyl-4-pentene-2,3-diol (which contains a less-nucleophilic terminal vinyl participant) occurs in lower yield. As with other acetals that contain an electron-withdrawing heteroatom β or γ to the acetal carbon, the rearrangement described in this procedure is more efficient in nitromethane than in the less-ionizing solvent dichloromethane (CH_2Cl_2).[7]



1 1

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 139

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

brine

sodium benzophenone ketyl

(2R,3S)- and (2S,3S)-1,4-Dioxa-2,3-dimethyl-2-(1-methylethenyl)-8-carboethoxy-8-azaspiro[4.5]decane

2,3-dimethyl-1-pentene-3,4-diols

ethanolic phosphomolybdic acid

3-acyltetrahydrofuran

(+)-muscarine

ethyl acetate (141-78-6)

methanol (67-56-1)

ammonium chloride (12125-02-9)

sodium sulfate (7757-82-6)

Pentane (109-66-0)

Nitromethane (75-52-5)

dichloromethane (75-09-2)

tin(IV) chloride (7646-78-8)

Tetrahydrofuran (109-99-9)

hexane (110-54-3)

sodium borohydride (16940-66-2)

dicyclohexylcarbodiimide (538-75-0)

tributylamine (102-82-9)

trifluoroacetic anhydride (407-25-0)

argon (7440-37-1)

p-toluenesulfonic acid (104-15-4)

ethyl acetate-hexane (2639-63-6)

acetal carbon (463-57-0)

2-Bromopropene (557-93-7)

4-(dimethylamino)pyridine (1122-58-3)

tert-Butyllithium (594-19-4)

(+)-α-methoxytrifluoromethylphenylacetic acid (56135-03-6)

Tetrabutylammonium fluoride (429-41-4)

(2S,3S)-3-Acetyl-8-carboethoxy-2,3-dimethyl-1-oxa-8-azaspiro[4.5]decane (155534-75-1)

3-(S)-[(tert-Butyldiphenylsilyl)oxy]-2-butanone, (S)-3-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-2-butanone (135367-18-9)

tert-butyldiphenylsilyl

1-Carbethoxy-4-piperidone (29976-53-2)

isobutyraldehyde acetal

3-methyl-4-pentene-2,3-diol

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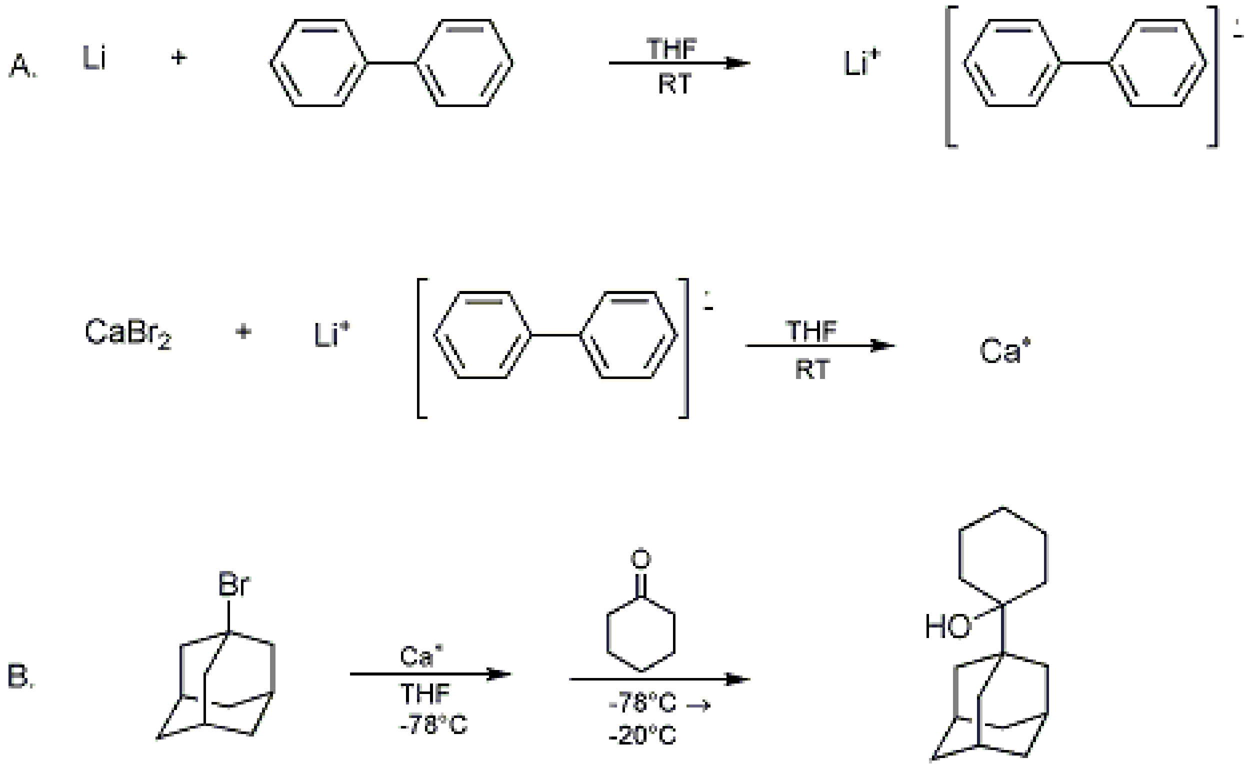
Organic Syntheses, CV 9, 9

HIGHLY REACTIVE CALCIUM FOR THE PREPARATION OF ORGANOCALCIUM REAGENTS: 1-ADAMANTYL CALCIUM HALIDES AND THEIR ADDITION TO KETONES: 1-(1-ADAMANTYL) CYCLOHEXANOL

[Cyclohexanol, 1-tricyclo[3.3.1.1^{3,7}]dec-1-yl]



Submitted by Reuben D. Rieke, Tse-Chong Wu, and Loretta I. Rieke[1].
Checked by Katsutaka Yasue and Hisashi Yamamoto.

1. Procedure

A. *Active calcium*. Freshly cut lithium (41.7 mg, 6.01 mmol) and biphenyl (1.020 g, 6.61 mmol) in freshly distilled tetrahydrofuran (THF, 15 mL) (Note 1) are vigorously stirred at room temperature under argon (Note 2) until the lithium is completely consumed (approx. 2 hr). The preformed lithium biphenylide is transferred via a cannula at room temperature to a well-dispersed suspension of calcium bromide ($CaBr_2$, 1.213 g, 6.07 mmol) (Note 3) in freshly distilled THF (15 mL). The reaction mixture is stirred for 1 hr at room temperature prior to use (Note 4).

B. *1-(1-Adamantyl)cyclohexanol*. Activated calcium prepared from preformed lithium

biphenylide and excess $CaBr_2$ in THF is cooled to −78°C (Note 5). 1-Bromoadamantane (543 mg, 2.52 mmol) (Note 6) in THF (10 mL) is added via a cannula at −78°C and the mixture is stirred at −78°C for 20 min (Note 7). Excess cyclohexanone (520 mg, 5.30 mmol) is added via a disposable syringe at −78°C. The resulting mixture is gradually warmed to −20°C and stirred at −20°C for 30 min. The reaction mixture is then quenched with water at −20°C (20 mL) and warmed to room temperature. At this temperature it is filtered through a small pad of Celite which is washed with diethyl ether (Et_2O, 100 mL). The aqueous layer is extracted with Et_2O (3 × 50 mL). The combined organic phases are washed with water (15 mL) and dried over anhydrous magnesium sulfate ($MgSO_4$). Removal of the solvent and flash-column chromatography on silica gel (150 g, 230–400 mesh, eluted sequentially with hexane/EtOAc [0% to 15%]) affords reasonably pure 1-(1-adamantyl)cyclohexanol as a white solid. 1-(1-Adamantyl)cyclohexanol is recrystallized from hexanes as follows: The white crystals are dissolved in a limited amount of dichloromethane (CH_2Cl_2), hexane (15 mL) is added, the solvent is evaporated to 8 mL, more hexane (15 mL) is added, the solvent is evaporated to about 15 mL, and the solution is gradually cooled and allowed to stand for 24 hr to afford 469–476 mg (80–82% yield) of product as colorless needles, mp 169–171°C (Note 8),(Note 9).

2. Notes

1. Lithium was weighed out and charged into reaction flasks under argon in a Vacuum Atmospheres Company dry box. (The checkers did not use a dry box: Lithium was freshly cut in air, rinsed in hexane, and charged into reaction flasks under argon.) Biphenyl was purchased from Aldrich Chemical Company, Inc. Tetrahydrofuran anhydrous, 99.9% purity, was purchased from Aldrich Chemical Company, Inc. It was freshly distilled over Na/K alloy under argon before use.
2. All glassware, syringes, needles, and cannulas were kept in a 120°C oven overnight prior to use. All manipulations were carried out on a dual manifold vacuum/argon system. The Linde prepurified grade argon was further purified by passing it through a 150°C catalyst column (BASF R3-11), a phosphorus pentoxide column, and a column of granular potassium hydroxide. (The checkers used argon as received.)
3. Anhydrous calcium(II) bromide was purchased from Cerac, Inc. Commercially available reagents were used as received unless specially noted.
4. Good stirring is important for the preparation of highly reactive calcium. A Schlenk tube is better than a flask for the reactor. Excess calcium salt was present during the oxidative addition reaction with 1-bromoadamantane.
5. Low-temperature reactions were performed using a Neslab endocal ULT-80 refrigerated circulating bath or a dry ice/acetone bath.
6. 1-Bromoadamantane, 99%, was purchased from Aldrich Chemical Company, Inc.
7. The reaction was checked by GC; all the starting material was consumed.
8. Melting points were determined on a Thomas Hoover melting point apparatus

or an Electrothermal melting point apparatus and are corrected.
IR spectra were taken on an Analect RFX-30 FTIR spectrophotometer neat between NaCl or KBr plates or as KBr disks. ^{1}H NMR spectra were recorded on a Nicolet NT-360 (360 MHz) or on a Varian VXR-200 (200 MHz) spectrometer. All chemical shifts are reported in parts per million (δ) downfield from internal tetramethylsilane. Fully decoupled ^{13}C NMR spectra and DEPT experiments were recorded on a Varian VXR-200 (50 MHz) spectrometer. The center peak of $CDCl_3$ (77.0 ppm) was used as the internal reference.

9. The physical properties are as follows: IR (KBr) cm^{-1}: 3465, 2931, 2902, 2844, 1448, 1344, 980, 955, 935; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.95–2.05 (m, 26 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 21.9, 26.0, 28.7, 29.8, 35.8, 37.3, 39.1, 74.6; MS (EI) m/e (relative intensity) 234 (M^{+}, 0.2), 135 (26.0), 98 (100.0); HRMS calcd for $C_{16}H_{26}O$ m/e 234.1984, found m/e 234.1982. Anal. Calcd: C, 81.99; H, 11.18. Found: C, 82.13; H, 11.41.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The development of organocalcium chemistry has been slow compared with the extensive studies of organometallic reagents of other light metals,[2] due in part to the lack of a facile method of preparing organocalcium compounds. Direct oxidative addition to calcium has been limited by the reduced reactivity of calcium metal with organic substrates, presumably because of surface poisoning. The organocalcium derivatives RCaX were formed most readily when X = I; the preparation of RCaX (X = Br, Cl) usually required activated calcium. Few examples have been reported and overall yields tend to be low.[2] Although simple primary and secondary alkyl iodides react with calcium in reasonable yields,[3 4] tertiary alkyliodocalcium compounds are very difficult to prepare and most workers have reported only trace amounts.[5 6] In contrast, the highly reactive calcium complexes reported here react readily with all these substrates to generate excellent yields of the corresponding organocalcium compounds.

Highly reactive calcium can be readily prepared by the reduction of calcium halides in tetrahydrofuran solution with preformed lithium biphenylide under an argon atmosphere at room temperature.[7] This colored calcium species seems to be reasonably soluble in THF. However, the reactive calcium complex prepared from preformed lithium naphthalenide was insoluble in THF solution and precipitated out of solution to give a highly reactive black solid. The exact nature of this black calcium complex has not been determined. Acid hydrolysis of the black material releases naphthalene as well as THF. Accordingly, the most likely structure of the black

material is a Ca-naphthalene-THF complex similar in nature to the soluble magnesium-anthracene complex recently reported.[8 9 10 11]

Highly reactive calcium was prepared by the lithium biphenylide reduction of calcium salts in THF. Both $CaBr_2$ and CaI_2 generate the reactive calcium species. The organocalcium compounds, prepared directly from this calcium complex and organic halides, were found to undergo Grignard-type reactions efficiently. Alkyl bromides and alkyl chlorides reacted rapidly with the calcium complex at temperatures as low as −78°C. 1-Chlorooctane gave 1-octylcyclohexanol in 83% yield.[7] Similar results were noted for secondary halides. Bromocyclohexane reacted readily with the calcium species at −78°C and the resulting organocalcium reagent underwent carbonyl addition to give the alcohol in 75% yield. Significantly, the highly reactive calcium complex reacted rapidly with tertiary bromides at −78°C. For example, the Grignard-type reaction of 1-bromoadamantane with the reactive calcium afforded 1-(1-adamantyl) cyclohexanol in 80% yield. The direct reaction of 1-bromoadamantane with metals is known to yield mainly reductive cleavage or dimerization.[12] Accordingly, this method represents a significant new approach to the 1-metalloadamantane.

Reactions of aryl halides with the reactive calcium required slightly higher temperatures, up to −30°C for aryl bromides and up to −20°C for aryl chlorides.[7] Surprisingly, the active calcium reacted readily with fluorobenzene at room temperature to form the corresponding organocalcium reagent in near quantitative yield.

Addition of copper(I) salts to the organocalcium reagents form novel organocalcium copper reagents that cross-couple with acid chlorides to yield ketones, and undergo conjugate addition to α,β-unsaturated ketones. The highly reactive calcium also reacts readily with 1,3-dienes to form bisorganocalcium complexes. Reaction of these calcium reagents with biselectrophiles generates a wide variety of complex cyclic hydrocarbons.[7]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

1-metalloadamantane

diethyl ether (60-29-7)

Cyclohexanone (108-94-1)

copper (7440-50-8)

calcium (7440-70-2)

Biphenyl (92-52-4)

Naphthalene (91-20-3)

bromocyclohexane (108-85-0)

dichloromethane (75-09-2)

lithium (7439-93-2)

magnesium sulfate (7487-88-9)

Fluorobenzene (462-06-6)

Tetrahydrofuran (109-99-9)

hexane (110-54-3)

1-bromoadamantane (768-90-1)

tetramethylsilane (75-76-3)

argon (7440-37-1)

1-ADAMANTYL CALCIUM

1-(1-Adamantyl)cyclohexanol, Cyclohexanol, 1-tricyclo[3.3.1.1^{3,7}]dec-1-yl (84213-80-9)

Lithium biphenylide (34467-57-7)

calcium bromide, calcium(II) bromide (7789-41-5)

lithium naphthalenide

1-Chlorooctane (111-85-3)

1-octylcyclohexanol

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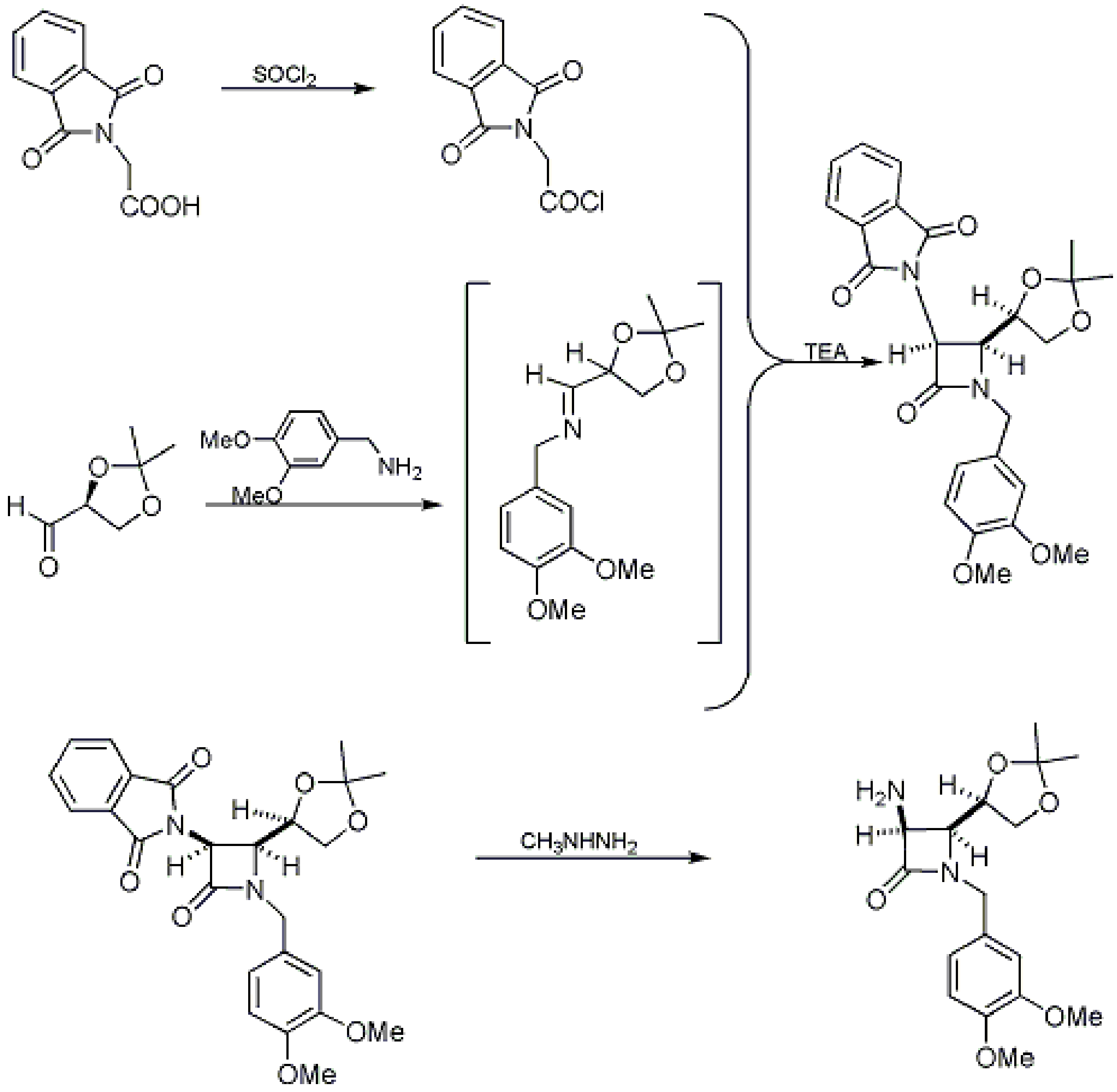
Organic Syntheses, *CV 9, 13*

(3S,4S)-3-AMINO-1-(3,4-DIMETHOXYBENZYL)-4-[(R)-2,2-DIMETHYL-1,3-DIOXOLAN-4-YL]-2-AZETIDINONE

[2-Azetidinone, 3-amino-1-[(3,4-dimethoxyphenyl)methyl]-4-(2,2-dimethyl-1,3-dioxolan-4-yl)-, [3S-[3a,4a(S*)]]-]



Submitted by Christian Hubschwerlen and Jean-Luc Specklin[1].
Checked by Julien G. Doyon and Leo A. Paquette.

1. Procedure

A. *Phthalylglycyl chloride*. Phthalylglycine (102.5 g, 0.5 mol; (Note 1)) is placed in a 750-mL, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar and a reflux condenser (Note 2). Thionyl chloride (109 mL, 1.5 mol, (Note 3)) is added in one portion

and the resulting suspension is stirred at reflux for 18 hr. The reaction mixture is cooled to room temperature before removing excess thionyl chloride under reduced pressure (Note 4). The residue is suspended in ether (100 mL, (Note 5)) and stirred for 1 hr at 0°C. The crystals are filtered by suction using a Büchner funnel (Note 6), washed with cold ether (50 mL), and dried under vacuum. Approximately 100 g of phthalylglycyl chloride (90% based on phthalylglycine) is obtained (Note 7).

B. *(3S,4S)-3-Amino-1-(3,4-dimethoxybenzyl)-4-[(R)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-azetidinone*. An aqueous solution of crude L-(S)-glyceraldehyde acetonide[2] (estimated content, 190 mmol) is placed in a 1000-mL, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar (32 mm) and a 100-mL, pressure-equalizing dropping funnel that is connected to an argon flow line. Dichloromethane (200 mL, (Note 5)) is added to the aqueous solution and the dropping funnel is charged with a solution of 3,4-dimethoxybenzylamine (31.1 g, 0.186 mol, (Note 8)) in dichloromethane (50 mL). The flask is flushed with argon and an argon atmosphere is maintained throughout the entire reaction sequence until the final work up. The solution is vigorously stirred and cooled to 10°C with an ice-water bath. The solution of 3,4-dimethoxybenzylamine is added dropwise over 5 min, the mixture is stirred for 20 min and then transferred into a 1000-mL separatory funnel. The organic phase is separated and the aqueous layer is extracted with dichloromethane (2 × 100 mL). The combined organic layers are collected in a 1000-mL Erlenmeyer flask and dried over magnesium sulfate under argon. After the magnesium sulfate is removed by filtration and thoroughly washed with three 100-mL portions of dichloromethane, the filtrate is placed in a 1000-mL, round-bottomed flask and concentrated to about 100 mL (Note 9). The solution is transferred to a 500-mL, two-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar, a thermometer, and a 250-mL, pressure-equalizing dropping funnel connected to an argon flow line. The solution is cooled to 0°C (ice-methanol bath) and treated with triethylamine (33.5 mL, 0.24 mol, (Note 10)). The dropping funnel is filled with a solution of phthalylglycyl chloride (41.5 g, 0.186 mol) in dichloromethane (75 mL). This solution is added dropwise over 45 min. The reaction mixture is stirred for 1 hr at room temperature, then transferred to a 1000-mL separatory funnel before sequentially washing with water (2 × 200 mL), cold 2 N hydrochloric acid (100 mL), saturated, aqueous sodium bicarbonate solution (100 mL), and brine (100 mL). The organic phase is dried over a mixture of magnesium sulfate and Fuller's earth (Fluka), filtered, and evaporated under reduced pressure. The resulting yellow syrup (72 g, 0.154 mol, 82% from 3,4-dimethoxybenzylamine, (Note 11)) is dissolved in 1,2-dichloroethane (200 mL, (Note 5)), treated with N-methylhydrazine (8.9 mL, 0.170 mol, (Note 12)) and refluxed for 60–80 min. The resulting suspension is cooled to room temperature and filtered by suction using a Büchner funnel. The crystals are thoroughly washed with two 100-mL portions of 1,2-dichloroethane and discarded. The combined organic solutions are evaporated to a heavy syrup under reduced pressure. The residue is dissolved in ethyl acetate (400 mL) and sequentially washed with water (2 × 150 mL) and aqueous 10% sodium chloride solution. The organic layer is dried over magnesium sulfate, filtered by suction using a Büchner funnel and evaporated. The resulting crystals are recrystallized from ethyl acetate/hexane (2:1). Approximately 30–32 g of (3S,4S)-3-amino-1-(3,4-dimethoxybenzyl)-4-[(R)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-azetidinone are obtained (49–52% from 3,4-

dimethoxybenzylamine; 54% from 5,6-O-isopropylidene-L-gulono-1,4-lactone[2]) as pale yellow crystals, mp. 101–103°C (Note 13).

2. Notes

1. Phthalylglycine was purchased from Fluka A.G and used without any purification.
2. The gas released during the reaction should be vented through a calcium chloride trap to the back of an efficient hood.
3. Thionyl chloride of technical grade was distilled prior to use.
4. The submitters used the following conditions: rotatory evaporator; water bath temperature, 60°C; pressure, 120 mm then 60 mm.
5. Diethyl ether, dichloromethane, and dichloroethane puriss p.a. were used as purchased from Fluka A.G.
6. The submitters filtered the suspension under a stream of argon.
7. Phthalylglycyl chloride is a colorless powder. It can be stored for several weeks at room temperature in the absence of moisture and air, mp 85–87°C (lit.[3] 85–86°C).
8. 3,4-Dimethoxybenzylamine was purchased from Aldrich Chemical Company, Inc., and used without any purification. It is air sensitive and decomposes on standing into a white solid (3,4-dimethoxybenzoic acid). The success of the cycloaddition depends on having stoichiometric quantities of reagents. The quantity of 3,4-dimethoxybenzylamine added (less than one equivalent) is related to the average quantity of glyceraldehyde acetonide present in the crude aqueous solution.
9. The submitters used the following conditions: rotatory evaporator, water bath temperature, 35°C; pressure: 500 mm. The quality of the imine solution is determined in the following way: an aliquot of the dichloromethane solution is further evaporated under reduced pressure and analyzed by ^{1}H NMR ($CDCl_3$). The ratio of integral value (height in mm) of the signal of the imine proton at δ 7.8 ppm to the signal of the three aromatic protons at δ 6.85 ppm gives a fairly good idea of the course of the reaction. The presence of an excess of 3,4-dimethoxybenzylamine in the solution leads to the formation of an insoluble by-product resulting from the reaction of 3,4-dimethoxybenzylamine with phthalimidoacetyl chloride. It renders the final purification more tedious.
10. Triethylamine (puriss. p.a.) was purchased from Fluka A.G. and used without any purification.
11. N-[(2R,3R)-cis-1-(3,4-Dimethoxybenzyl)-2-[(S)-2,2-dimethyl-1,3-dioxolan-4-yl]-4-oxo-3-azetidinyl]phthalimide can be purified at this stage by flash column chromatography (dichloromethane/ethyl acetate 9:1) but does not tend to crystallize. The ^{1}H NMR spectrum is as follows ($CDCl_3$) δ: 1.23 and 1.35 (2 s, 2 × 3 H), 3.39 (dd, 1 H, J = 6.5, 8.5), 3.66 (dd, 1 H, J = 6.5, 8.5), 3.79 (dd, 1 H, J = 5, 9), 3.89 and 3.91 (2 s, 2 × 3 H), 4.32 and 4.81 (2 × d, 2 × 1 H, J = 15), 4.36 (dt, 1 H, J = 6.5 and 9), 5.30 (d, 1 H, J = 5), 6.82–6.93 (m, 3 H), 7.76–7.90 (m, 4 H).
12. N-Methylhydrazine was purchased from Fluka and was used without any purification. All the operations should be carried out under a well-vented hood since N-methylhydrazine is a carcinogen.
13. An analytically pure sample can be obtained after a further recrystallization from ethyl acetate (mp 106–107°C). The ^{1}H NMR spectrum is as follows ($CDCl_3$) δ: 1.36

and 1.45 (2 s, 2 × 3 H), 1.86 (broad s, 2 H), 3.53 (t, 1 H, J = 7.5), 3.70 (dd, 1 H, J = 6, 10), 3.87 (2 s, 2 × 3 H), 4.06 and 4.80 (2 d, 2 × 1 H, J = 18), 4.15–4.30 (m, 3 H), 6.80–6.82 (m, 3 H).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Monocyclic azetidinones are useful building blocks in organic synthesis. Besides the wide use in the syntheses of monobactam antibiotics and nuclear analogues of natural bicyclic β-lactam antibiotics,[4] new applications have appeared with the syntheses of unnatural α-amino acids, amino sugars[5] and inhibitors of elastase.[6]

These building blocks can be obtained either by the Miller cyclization of β-hydroxy-α-amino acids[7] or by the Staudinger reaction[8 9] ([2+2] ketene-imine cycloaddition). The procedure reported here follows the second route and has the advantages of being diastereospecific and to proceed in high yield. For a large scale preparation, the harmful and toxic N-methylhydrazine can be replaced by N,N-dimethyl-1,3-propanediamine.[10] Further transformations of the key intermediate have been reported elsewhere.[8,11]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

brine

glyceraldehyde acetonide

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

ether, diethyl ether (60-29-7)

thionyl chloride (7719-09-7)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

1,2-dichloroethane (107-06-2)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

N-methylhydrazine (60-34-4)

hexane (110-54-3)

triethylamine (121-44-8)

dichloroethane (75-34-3)

argon (7440-37-1)

N,N-dimethyl-1,3-propanediamine (109-55-7)

ketene-imine (18295-52-8)

3,4-dimethoxybenzoic acid (93-07-2)

Morin

(3S,4S)-3-Amino-1-(3,4-dimethoxybenzyl)-4-[(R)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-azetidinone, 2-Azetidinone, 3-amino-1-[(3,4-dimethoxyphenyl)methyl]-4-(2,2-dimethyl-1,3-dioxolan-4-yl)-, [3S-[3a,4a(S*)]]- (159802-14-9)

Phthalylglycyl chloride (6780-38-7)

Phthalylglycine (4702-13-0)

3,4-dimethoxybenzylamine (5763-61-1)

5,6-O-isopropylidene-L-gulono-1,4-lactone

phthalimidoacetyl chloride

N-[(2R,3R)-cis-1-(3,4-Dimethoxybenzyl)-2-[(S)-2,2-dimethyl-1,3-dioxolan-4-yl]-4-oxo-3-azetidinyl]phthalimide (86418-70-4)

L-(S)-Glyceraldehyde acetonide (22323-80-4)

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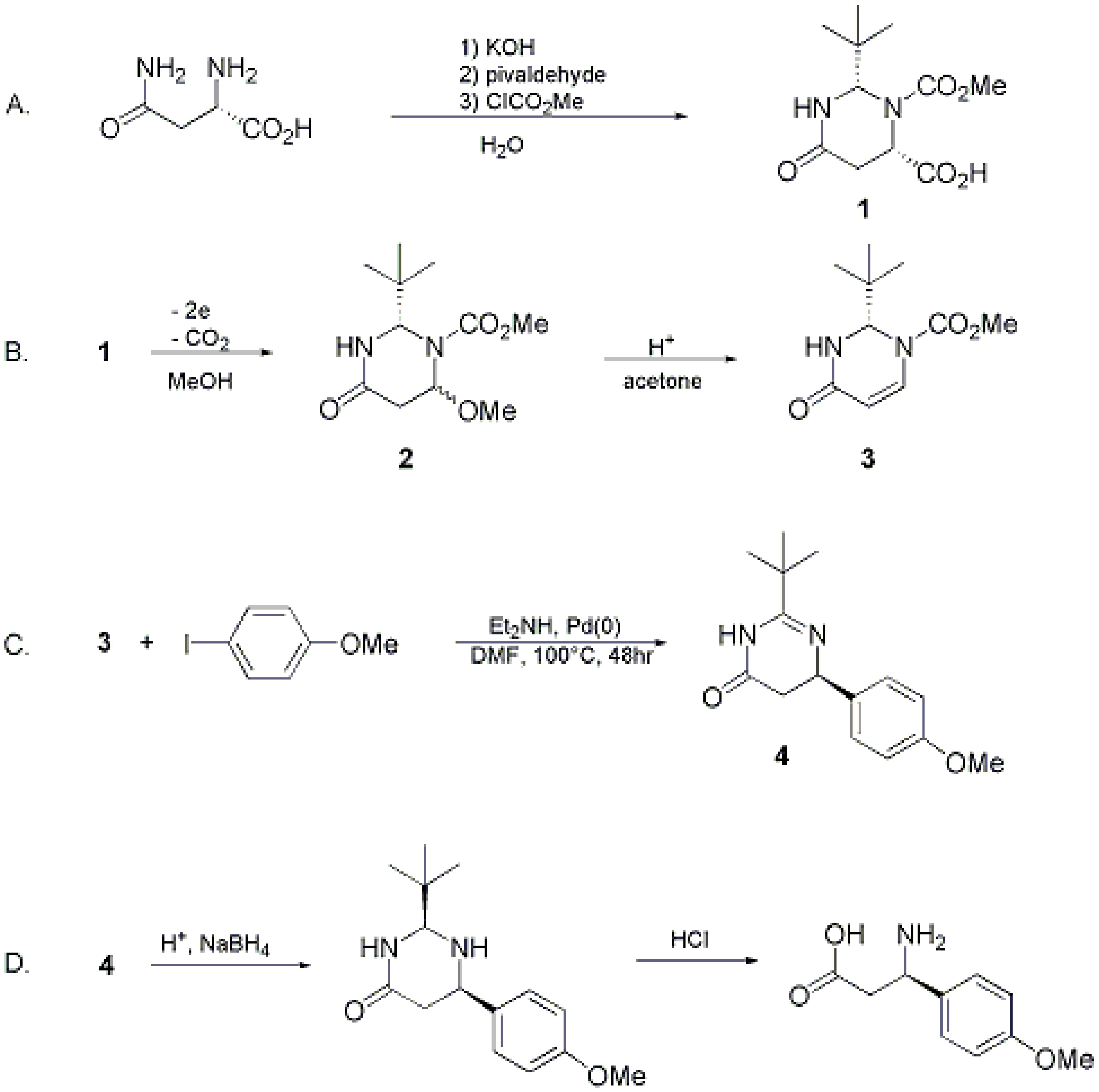
Organic Syntheses, CV 9, 17

ENANTIOMERICALLY PURE β-AMINO ACIDS FROM 2-*tert*-BUTYL-1-CARBOMETHOXY-2,3-DIHYDRO-4(1H)-PYRIMIDINONE: (R)-3-AMINO-3-(p-METHOXYPHENYL)PROPIONIC ACID

[1(2H)-Pyrimidinecarboxylic acid, 2-(1,1-dimethylethyl)-3,4-dihydro-4-oxo-, methyl ester, (R)- or (S)-]



Submitted by F. J. Lakner, K. S. Chu, G. R. Negrete, and J. P. Konopelski[1].
Checked by Pradeep B. Madan, George P. Yiannikouros, and David L. Coffen.

1. Procedure

A. *(S,S)-2-tert-Butyl-1-carbomethoxy-6-carboxy-2,3,5,6-tetrahydro-4(1H)-pyrimidinone*, **1**. An Erlenmeyer flask equipped with a magnetic stirring bar is charged with 21.8 g of potassium hydroxide (KOH, 85% assay, 0.33 mol) and 500 mL of deionized water. A 50-g portion of L-asparagine monohydrate (0.33 mol) is added with stirring, followed by the addition of 43.6 mL of pivalaldehyde (34.4 g, 0.4 mol) with vigorous stirring, after which the mixture becomes homogeneous (Note 1). At the end of 6 hr, the solution is chilled in an ice bath and 28.0 g of sodium bicarbonate ($NaHCO_3$, 0.33 mol) is added, followed by 25.8 mL of methyl chloroformate (0.33 mol) (Note 1). After 1 hr of vigorous stirring at ice temperature, an additional 8.5 g of $NaHCO_3$ (0.11 mol) and 7.5 mL of methyl chloroformate (0.11 mol) are added. The ice bath is removed and the solution is allowed to warm to room temperature for 2 hr. Precipitation of heterocycle **1** is accomplished by slow addition of 125 mL of 10% hydrochloric acid (0.44 mol). The resulting solids are collected by vacuum filtration, rinsed with 225 mL of ice water and dried in a vacuum desiccator yielding 62.1–67.1 g (72–79%) of heterocycle **1** as a white solid, mp 201°C (dec), $[\alpha]_D$-108.5° (CH_3OH, *c* 2.05) (Note 2).

B. *(S)-2-tert-Butyl-1-carbomethoxy-2,3-dihydro-4(1H)-pyrimidinone*, **3**. A 1-L, three-necked, round-bottomed flask is equipped with two electrodes, a thermometer, and a magnetic stirring bar (Note 3). The flask is charged with a solution of 60.0 g of heterocycle **1** (0.232 mol) in 620 mL of methanol (Note 4) and 3.2 mL (2.34 g, 23.2 mmol) of triethylamine (Note 5). The temperature is maintained at ≤20°C with a circulating water bath, while 0.60 amp is applied for 26 hr (Note 6). After transfer to a suitable vessel, the solvent is evaporated under reduced pressure providing heterocycle **2** as a clear, colorless syrup (Note 7). The residue is dissolved in 425 mL of acetone (Note 4), 20 g of cation exchange resin (Note 8) is added, and the suspension is then heated at reflux for 1 hr. The resin catalyst is collected by filtration and rinsed with an additional 100 mL of acetone, and the filtrate is concentrated under reduced pressure affording heterocycle **3** as a light yellow gum. The crude material is dissolved in 150 mL of ethyl acetate and washed twice with 50-mL portions of saturated aqueous sodium bicarbonate. The organic layer is dried with magnesium sulfate ($MgSO_4$), filtered, and crystallization is allowed to occur by slow evaporation of the solvent. The crystals are collected affording 30–46.8 g (48–68% from asparagine) of large, clear, colorless crystals of heterocycle **3**, mp 142–143°C, $[\alpha]_D$+416.6° (EtOAc, *c* 1.70) (Note 9).

C. *(R)-2-tert-Butyl-6-(4-methoxyphenyl)-5,6-dihydro-4(1H)-pyrimidinone*, **4**. Compound **3** (5.00 g, 23.6 mmol), 4-iodoanisole (5.52 g, 23.6 mmol), diethylamine (Et_2NH) (2.68 mL, 26.0 mmol), and tetrakis(triphenylphosphine)palladium(0) $[Pd(PPh_3)_4]$ (273 mg, 0.24 mmol) are dissolved in 25 mL of dimethylformamide (Note 10). The yellow-colored solution is transferred to a thick-walled Pyrex pressure tube and purged with argon. The tube is then sealed and suspended in a boiling water bath for 48 hr in the dark (Note 11). The tube is cooled in liquid nitrogen before opening (***Caution: pressure has developed***). The contents of the tube are transferred with the aid of 250 mL of ethyl acetate (EtOAc) to a wet packed approx. 40-mm × 50-mm bed of 17.5 g silica gel that is then rinsed with an additional 200 mL of EtOAc. After the solvent is removed under vacuum, the residue is dissolved in a mixture of 80 mL of water, 21.0 mL of 1.0 N hydrochloric acid solution,

and 50 mL of ether. The resulting solution is transferred to a 500-mL separatory funnel, washed twice with 100-mL portions of ether, and the ethereal washings are discarded. The aqueous layer is transferred to an Erlenmeyer flask, cooled in an ice bath, and 11.5 mL of 2 N aqueous sodium hydroxide solution is added in one portion with stirring to bring the solution to a pH of 8–9. The resulting precipitate (Note 12) is collected by suction filtration and air dried to give **4** as a yellowish solid (3.33–4.50 g, 55–75%), mp 118–120°C, $[\alpha]_D$ –20° ($CHCl_3$, *c* 3.3) (Note 13).

D. *(R)-3-Amino-3-(p-methoxyphenyl)propionic acid*.[2] A 125-mL Erlenmeyer flask containing a magnetic stirring bar is charged with 20 mL of tetrahydrofuran, 20 mL of 95% ethanol, and heterocycle **4** (2.39 g, 9.2 mmol). The mixture is stirred and cooled to –35°C to –45°C with an acetone-dry ice bath. About 0.6 mL of aqueous 9 N hydrochloric acid is added dropwise until a pH of approximately 7 is obtained as determined by pH paper. A solution of sodium borohydride, prepared by dissolving 0.5 g of sodium borohydride (13.0 mmol) in approximately 1.5 mL of water (minimum amount) containing 1 drop of 30% aqueous sodium hydroxide solution, is added dropwise alternately with 9 N hydrochloric acid to the stirred solution of **4** such that a pH of 6–8 is maintained. During the addition, the bath temperature should be maintained between –35°C and –45°C. After the addition of sodium borohydride solution is complete, the reaction mixture is stirred at –35°C for 1 hr. During this time, the reaction mixture is maintained at a pH of 7 by occasional addition of 9 N hydrochloric acid (about 0.4 mL additional is required). The reaction mixture is then stored at –20°C overnight. After warming to room temperature, the reaction mixture is transferred to a separatory funnel and the pH is raised to 9 by addition of aqueous 40% sodium hydroxide (1.5 mL). After dilution with 30 mL of water, the mixture is extracted three times with 20-mL portions of ether, and the combined ether extracts are washed with 10 mL of saturated sodium chloride. After the organic layer is dried over potassium carbonate, the solution is concentrated under reduced pressure giving 2.01 g (85%) of the acyl aminal as a slightly yellow solid that is used without further purification (Note 14).

An 0.80-g (3.0 mmol) portion of the crude aminal above is dissolved in 8 mL of 4.5 N hydrochloric acid solution and heated to 100°C in a boiling water bath for 2.5 hr. The clear liquid reaction mixture is transferred to an evaporating dish and left to evaporate in a fume hood. The residue is dissolved in 2 mL of 2 N hydrochloric acid solution and the pH of the solution is adjusted to 7 by slow addition of 30% aqueous sodium hydroxide with swirling, at which time the whole mixture solidifies. The solid mixture is kept at –20°C overnight, followed by addition of 10 mL of water and stirring with a glass rod. The solids are collected by suction affording 0.38–0.41 g (63–69%) of the β-amino acid of 85% purity as a slightly yellow crystalline solid, mp 235°C (dec); $[\alpha]_D$ –4° (1 N HCl, *c* 1.86) (Note 15).

2. Notes

1. L-Asparagine monohydate, pivalaldehyde, and methyl chloroformate were purchased from the Aldrich Chemical Company, Inc. and used without purification.

2. An extra 8.0 g may precipitate by saturation of the filtrate with sodium chloride and storing the solution in a refrigerator overnight. This material is of significantly inferior chemical and diastereomeric purity. The initial precipitate, however, is usually 92% optically pure as compared to the material obtained by recrystallization from 1:4 ethanol/water, and exhibits constant rotation upon further recrystallization. The rotation for twice recrystallized **1** is $[\alpha]_D$ −115° (CH_3OH, *c* 2.05). However, this purification procedure (recrystallization) is not necessary, since heterocycle **3** is easily crystallized to ≥99% ee as the final isolation step. Spectral characteristics for pure **1** are: ^1H NMR (400 MHz, D_2O/K_2CO_3, 10 mg/mL) δ: 1.16 (s, 9 H), 2.87–2.96 (m, 2 H), 3.83 (s, 3 H), 4.58 (m, 1 H), 5.33 (s, 1 H); IR (KBr) cm^{-1}: 3283, 2966, 1719, 1631, 1314, 1220, 1090, 779.

3. The flask possesses three vertical side necks of equal height. The middle neck and one side neck were fitted with 1-hole septa pierced by 1-cm diameter cylindrical graphite electrodes (Sargent Welch). The electrodes were inserted 7 cm into the solution, supplying a working electrode surface of 23 cm^2, and were 5 cm apart. A thermometer was inserted through the third neck with room to vent gases. A power supply (Southwest Technical Products Corp.) is attached to the electrodes with alligator clips. These conditions provide 34–37 V at 0.60 A.

4. Methanol was purchased from Fisher Scientific Company and used without further purification.

5. Triethylamine was purchased from the Aldrich Chemical Company, Inc., distilled, and stored over KOH pellets.

6. This represents the time necessary to pass 2.5 F/mol for the quantity stated at 0.60 A.

7. Methoxylated product **2** consists of diastereomers in a 3:1 ratio, the main proton resonances [^1H NMR (400 MHz, $CDCl_3$)] being δ: 0.95 and 1.02 (s, 9 H), 2.6–2.9 (m, 2 H), 3.35 and 3.39 (s, 3 H), 3.77 (s, 3 H), 5.17–5.29 (m, 1 H), 8.07–8.1 (s (br), 1 H).

8. Dowex 50W-X8 cation exchange resin, 200–400 mesh, in the hydrogen form was purchased from J. T. Baker Chemical Company. It was placed in a sintered-glass funnel and washed with three bed-volumes each of 10% hydrochloric acid, water, methanol, and acetone, and then dried under vacuum. The checkers recommend Soxhlet extraction of the resin for complete recovery of product **3**.

9. Product **3** has the following spectral properties: ^1H NMR (400 MHz, $CDCl_3$) δ: 0.95 (s, 9 H), 3.83 (s, 3 H), 5.15–5.45 (m, 2 H), 7.2–7.5 (m, 1 H), 8.0–8.5 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$)δ: 25.5, 40.7, 54.0, 72.0, 104.8, 137.5, 153.3, 164.6; IR (thin film) cm^{-1}: 3201, 2966, 1731, 1666, 1443, 1331, 1249. The submitters report an optical rotation for **3** of $[\alpha]_D$ +434° (EtOAc, *c* 1.70). Enantiomeric purity of **3** has been established by acylation of **3** with (s)-O-methylmandelic acid chloride followed by ^1H NMR analysis. Integration of the GC traces reveals that the resulting diastereomeric purity is equivalent to the enantiomeric purity of the mandelate (99%).

10. All glassware was oven dried at 120°C prior to use. Diethylamine was distilled from calcium hydride. Palladium(II) acetate, $Pd(OAc)_2$ (53 mg, 0.24), (cancer suspect agent), without added triarylphosphine, gave **4** at a slightly lower yield as compared to $Pd(PPh_3)_4$.

11. During the course of the reaction, the solution is black. When the reaction is complete, the solution is clear brown with some black precipitate.
12. Some decomposition of the product, which appeared to be the major side reaction in this procedure, may occur in this step. The submitters found that decomposition is significant when the temperature is ≥20°C, and the desired material is left in contact with the basic solution for extended periods of time. This procedure is the most efficient for larger amounts of material. For smaller amounts, base can be added to the aqueous layer in a separatory funnel and the resulting solution can be extracted with methylene chloride. In many cases the submitters have obtained material directly from this extraction that was suitable for further transformations.
13. The compound appears to be capable of isolation by sublimation, but this has not been checked. The submitters report obtaining **4** having mp 123–125°C and $[\alpha]_D$ −47° ($CHCl_3$, *c* 3.3). The reasons for the discrepancy in rotation have not been determined. The spectral properties of pure **4** are as follows: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.27 (s, 9 H), 2.35 (dd, 1 H, J = 16.5, 12.0), 2.72 (dd, 1 H, J = 16.5, 5.7), 3.80 (s, 1 H), 4.71 (dd, 1 H, J = 12.0, 5.7), 6.89 (d, 2 H, J = 9), 7.3 (d, J = 9), 8.66 (s (br), 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 27.7, 37.6, 55.4, 56.7, 114.0, 127.5, 134.8, 158.8, 160.2, 171.7; IR (KBr) cm^{-1}: 3237, 3000, 1702, 1662, 1508 1254, 1135, 920, 832.
14. The properties of pure saturated heterocycle are as follows: mp 136–138°C, $[\alpha]_D$ +27.67° (CH_2Cl_2, *c* 1.2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.99 (s, 9 H), 2.33–2.72 (m, 2 H), 3.82 (s, 3 H), 3.97–4.04 (m, 1 H), 4.12 (s, 1 H), 6.03 (s (br), 1 H), 6.9 (d, 2 H, J = 10), 7.3 (d, 2 H, J = 10); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.9, 34.5, 39.8, 55.0, 55.4, 76.0, 114.1, 127.4, 134.2, 159.2, 171.6; IR (KBr) cm^{-1}: 3190, 2954, 1655, 1514, 1472, 1243, 1173.
15. Further purification including removal of the slight yellow color could be effected by recrystallization from boiling water. Physical properties of the purified amino acid product are as follows: mp 239°C (dec), $[\alpha]_D$ −4.35° (1 N HCl, *c* 1.86); ^{1}H NMR (400 MHz, D_2O) δ: 3.02–3.25 (m, 2 H), 3.83 (s, 3 H), 4.90 (m, 1 H), 7.03 (d, 2 H, J = 10), 7.45 (d, 2 H, J = 10); ^{13}C NMR (100 MHz, D_2O) δ: 38.7, 52.1, 56.6, 115.9, 128.7, 129.8, 160.8, 174.5; IR (KBr) cm^{-1}: 2960, 2364, 2150, 1615, 1518, 1404, 1250, 1184.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Chemical methods for the production of enantiomerically pure α-amino acids have been extensively investigated in recent years.[3] Conversely, there are relatively few methods for the synthesis of chiral, nonracemic β-amino acids,[4 5] although there is considerable interest in these compounds as precursors to β-lactams,[6 7 8 9 10,11 12] as components of

natural products,[13 14 15 16 17] and as reactive molecules in their own right.[18]

The procedure given here stems from our synthetic effort toward (+)-jasplakinolide[19 20 21,22,23 24 25 26] that contains the β-amino acid (R)-β-tyrosine.[27] This protocol permits the introduction of the desired *carbon substitutent* at the β-site in an enantioselective manner. This approach contrasts with previous methodologies, which develop the chiral center via conjugate addition of an amine to an α,β-unsaturated system,[28 29 30 31 32 33 34 35 36] reduction of a C=C or C=N functionality,[37 38 39 40 41] or C-C bond formation involving imines and enolate derivatives.[42 43 44 45 46 47 48 49 50 51 52]

The key element in this technology is heterocycle **3**. Although asparagine has been cyclized with acetone,[53] cyclocondensation with aldehydes has not been described in detail, except for tetrahydropyrimidinone formation using formaldehyde.[54] Electrochemical oxidative decarboxylation, on the other hand, is a well-known procedure[55] with broad applicability.[56] Our initial synthesis of **3** was accomplished with lead(IV) acetate;[57,58] the two-step method described here is cleaner and the cost and hazards of using and disposing of lead are precluded. Furthermore, the acid catalyst is easily recyclable. The two enantiomers of **3** are easily prepared from the corresponding enantiomers of asparagine which are readily available and inexpensive. The intermediate **3** and analogues are highly crystalline, stable, and possess large specific rotations which allows determination of the enantiomeric purity.

In addition, the protocol for the transformation of **3** to **4** has been modified from our original publication. We have found that the use of Et_2NH instead of triethylamine (Et_3N) as base gives a more reproducible reaction and, at the same time, all but eliminates the formation of biaryl material as a side product. The synthesis of **4** with Et_3N as base has been the subject of a mechanistic study and our results have been communicated.[58] Whether or not the mechanism is as we propose when Et_2NH is employed is not known.

Recently, we have demonstrated that **3** functions as an attractive chiral auxiliary for the synthesis of scalemic α-substituted carboxylic acids.[59] In addition, we have extended the scope of the β-amino acid synthesis to include alkyl groups through a protected derivative of heterocycle **3**.[60] Thus, a unified approach to the synthesis of enantiomerically pure β-amino acids has been developed from **3**. Recent efforts by Seebach, Juaristi, and co-workers[61 62 63] on a saturated analog of **3** have developed routes to products substituted at C_5 (α to the carbonyl).

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

amine

β-AMINO ACIDS

1(2H)-Pyrimidinecarboxylic acid, 2-(1,1-dimethylethyl)-3,4-dihydro-4-oxo-, methyl ester, (R)- or (S)-

β-amino acid

L-Asparagine monohydate

β-amino acid (R)-β-tyrosine

ethanol (64-17-5)

potassium carbonate (584-08-7)

hydrochloric acid, HCl (7647-01-0)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether (60-29-7)

sodium hydroxide (1310-73-2)

formaldehyde (630-08-0)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

acetone (67-64-1)

carbon (7782-42-5)

potassium hydroxide (1310-58-3)

diethylamine (109-89-7)

methylene chloride (75-09-2)

amino (15194-15-7)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

methyl chloroformate (79-22-1)

dimethylformamide (68-12-2)

asparagine (70-47-3)

triethylamine (121-44-8)

calcium hydride (7789-78-8)

sodium borohydride (16940-66-2)

argon (7440-37-1)

pivalaldehyde (630-19-3)

palladium(II) acetate (3375-31-3)

tetrakis(triphenylphosphine)palladium(0) (14221-01-3)

lead(IV) acetate (546-67-8)

2-tert-Butyl-1-carbomethoxy-2,3-dihydro-4(1H)-pyrimidinone (131791-81-6)

(R)-3-Amino-3-(p-methoxyphenyl)propionic acid (131690-57-8)

(S,S)-2-tert-Butyl-1-carbomethoxy-6-carboxy-2,3,5,6-tetrahydro-4(1H)-pyrimidinone (138723-45-2)

L-asparagine monohydrate (5794-13-8)

(S)-2-tert-Butyl-1-carbomethoxy-2,3-dihydro-4(1H)-pyrimidinone (131791-75-8)

(R)-2-tert-Butyl-6-(4-methoxyphenyl)-5,6-dihydro-4(1H)-pyrimidinone (131791-77-0)

4-iodoanisole (696-62-8)

(S)-O-methylmandelic acid chloride

tetrahydropyrimidinone (1852-17-1)

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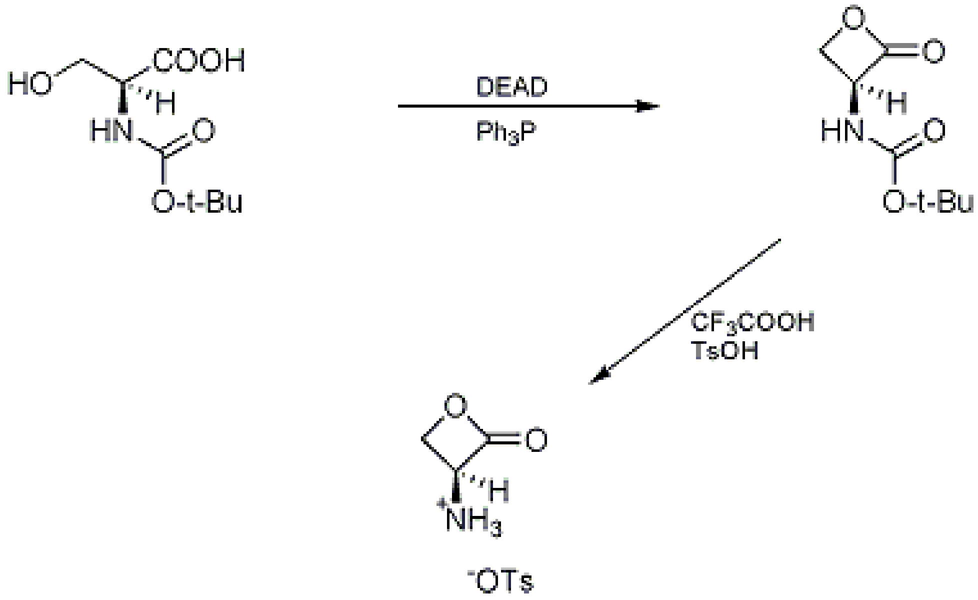
N-tert-BUTOXYCARBONYL-L-SERINE β-LACTONE AND (S)-3-AMINO-2-OXETANONE p-TOLUENESULFONIC ACID SALT

[(Carbamic acid, (2-oxo-3-oxetanyl)- 1,1-dimethylethyl ester, (S)-) and (2-Oxetanone, 3-amino-, (S)-, 4-methylbenzenesulfonate)]



Submitted by Sunil V. Pansare, Lee D. Arnold, and John C. Vederas[1].
Checked by P. S. Manchand, P. Mastrodonato-DeLora, and David L. Coffen.

1. Procedure

A. *N-(tert-Butoxycarbonyl)-L-serine β-lactone*.[2 3] A 2-L, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, an argon inlet adaptor, a low temperature thermometer, and a rubber septum (Note 1). The flask is charged with tetrahydrofuran (1.1 L) and triphenylphosphine (42.1 g, 160 mmol) (Note 2). The triphenylphosphine is dissolved with stirring, and the flask is cooled to −78°C with a dry ice-acetone bath maintained at that temperature (Note 3). Distilled diethyl azodicarboxylate (DEAD) (27.86 g, 160 mmol) is then added dropwise with a syringe over 10 min (Note 4). The resulting pale yellow solution is stirred at −75°C to −78°C for 10 min, at which point a milky slurry is obtained. The rubber septum on the flask is quickly replaced with a 1-L, pressure-equalizing dropping funnel containing a solution of N-(tert-butoxycarbonyl)-L-serine (32.8 g, 160 mmol) in tetrahydrofuran (240 mL), (Note 2) and (Note 5) which is then added dropwise to the mixture over 30 min. After completion of the addition, the mixture is stirred at −75°C to −78°C for 20 min, the cooling bath is removed, and the mixture is slowly warmed with stirring to room temperature over 2.5 hr (Note 6). The solvent is removed on a rotary evaporator at 35°C. The residual pale yellow syrup is suspended in hexane/ethyl acetate (85/15, 20 mL), slurried, and the solid is removed by filtration. The

filtrate is diluted with ethyl acetate (30 mL) to give a solution which is applied to a 10 × 23-cm column of flash silica gel[4] (800 g) packed in hexane/ethyl acetate (85/15). The flask and the sides of the column are rinsed with additional ethyl acetate (20 mL), which is added to the column that is then eluted with hexane/ethyl acetate (85/15, 2.7 L). The solvent is changed to hexane/ethyl acetate (7/3) and 500-mL fractions are collected. Concentration of fractions 6–12 on a rotary evaporator gives 12.07 (40%) of pure N-(tert-butoxycarbonyl)-L-serine β-lactone (Note 7) and (Note 8).

B. *(S)-3-Amino-2-oxetanone p-toluenesulfonic acid salt*.[5] A 500-mL, single-necked, round-bottomed flask is equipped with a magnetic stirring bar and an argon inlet adaptor (Note 1). The flask is charged with a mixture of N-(tert-butoxycarbonyl)-L-serine β-lactone (14.0 g, 74.8 mmol) and anhydrous p-toluenesulfonic acid (13.5 g, 78.5 mmol) (Note 9). The argon inlet adaptor is replaced with a rubber septum and an argon inlet and the flask is cooled in an ice bath for ca. 15 min. Anhydrous trifluoroacetic acid (200 mL, (Note 10)) is added by cannula along the sides of the flask over 20 min (stirring is initiated when possible). The pale yellow solution is stirred at 0°C for 10 min, the trifluoroacetic acid is removed on a rotary evaporator at below 30°C, and the resulting syrup is placed under high vacuum (0.2 mm) for ca. 1 hr. Anhydrous ether (200 mL, (Note 11)) is added to the resulting solid, the mixture is triturated to break up lumps, and the suspension is filtered. The solid thus obtained is washed with ether (100 mL), air dried (5 min), and then dried under reduced pressure (0.2 mm) overnight to give 18.4 g (95% yield) of (S)-3-amino-2-oxetanone p-toluenesulfonic acid salt (Note 12).

2. Notes

1. The glass components of the apparatus are dried overnight in a 120°C oven, and then assembled and maintained under an atmosphere of dry nitrogen or argon before use.
2. Triphenylphosphine (obtained from Aldrich Chemical Company, Inc.) and N-(tert-butoxycarbonyl)-L-serine (obtained from U.S. Biochemical Corporation) were dried over P_2O_5 for 72 hr and 24 hr, respectively. Tetrahydrofuran was distilled from sodium benzophenone ketyl directly into the glassware (under argon) the day before and stored under argon overnight until used.
3. The temperature of the solution should be about −75°C before the diethyl azodicarboxylate is added.
4. Diethyl azodicarboxylate was obtained from Fluka AG. (*See warning*, p. 837.htm). The material used was distilled, bp 82–83°C at 2 mm, in the hood behind a safety shield. It is important that the addition of this compound to the reaction mixture be done at a constant rate without interruption because of its tendency to freeze in the syringe needle. Dimethyl azodicarboxylate (17.7 mL, 160 mmol; δ = 1.33 g/mL at 25°C; bp 71–72°C at 2 mm) can be used in place of diethyl azodicarboxylate. This compound is manfactured by Tokyo Kasei Kogyo Co. and is available from CTC Organics. The use of a very slight excess of azodicarboxylate ester (a few percent relative to triphenylphosphine) prevents reaction of triphenylphosphine with the β-lactone product.[6]

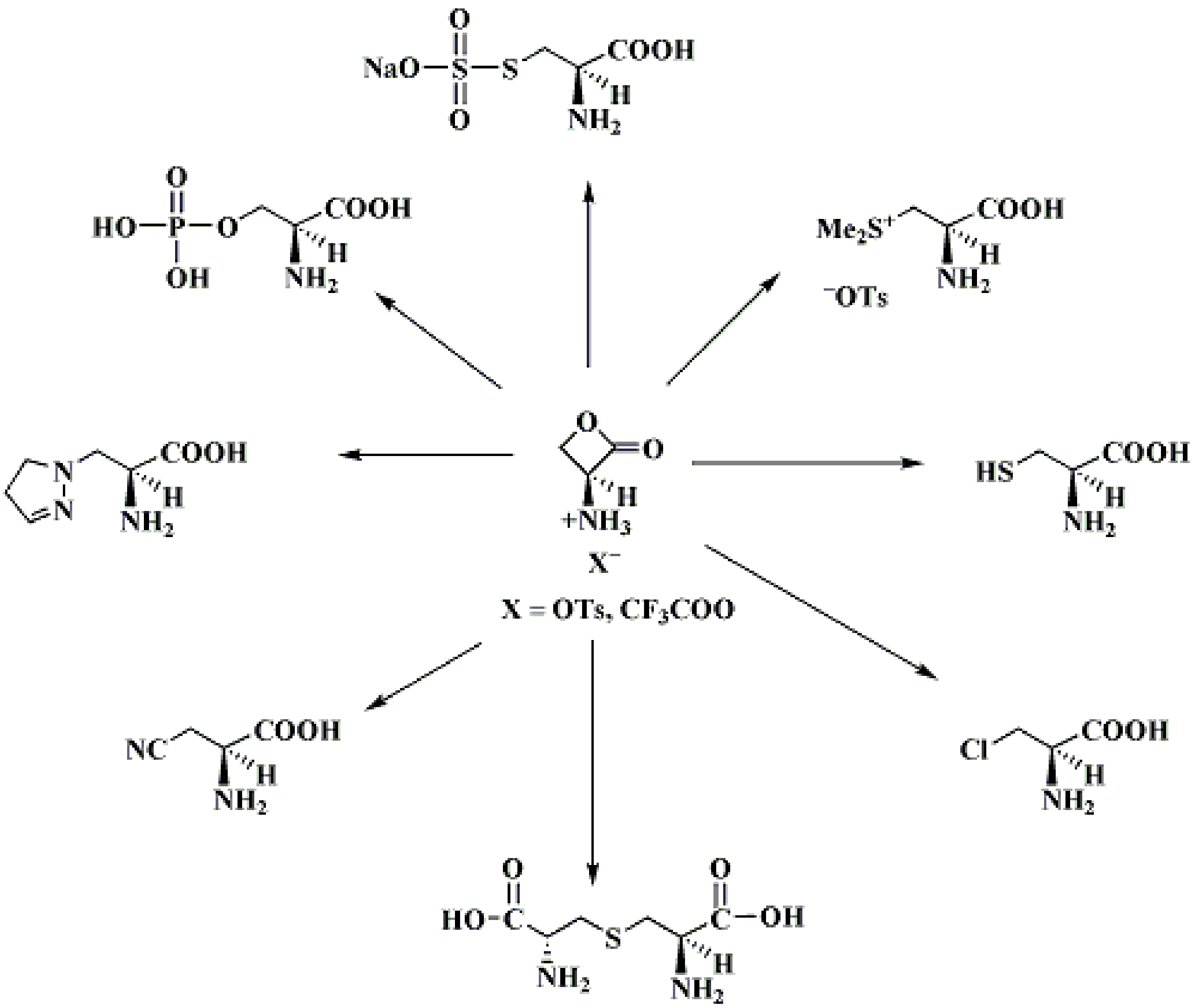
5. The solution of dried N-(tert-butoxycarbonyl)-L-serine was made up separately in an addition funnel under an atmosphere of argon. This avoids complications that may arise if the funnel is prefitted on the reaction vessel.
6. The reaction vessel was placed in a water bath at room temperature after the temperature of the mixture was ca. 15°C.
7. The reaction usually works better on a smaller scale (25 mmol) where a yield of 70% or greater can be obtained. The flash column was eluted such that the solvent level dropped 1 cm/13 sec. This corresponds to an approximate rate of 362 mL/min. The concentration and purification of the reaction mixture should be done as quickly as possible on the same day. Although storage of the concentrated reaction mixture at −20°C overnight results in substantial decomposition of the lactone, column fractions containing pure lactone (after chromatography) can be stored at 4°C overnight and concentrated on the following day.
The β-lactone is readily visualized by TLC (Merck, Kieselgel 60 F_{254}, 0.25 mm thickness, hexane/ethyl acetate (65/35) as solvent system) by staining in iodine or by using bromocresol green spray (0.04% in EtOH, made blue by NaOH) followed by heating the plate to detect the lactone as a yellow spot on a blue background.
8. The product exhibits the following properties: mp 119.5–120.5°C; $[\alpha]_D^{24}$ −26.2° (CH_3CN, *c* 1); IR cm^{-1}: 3358, 1836, 1678, 1533, 1290, 1104; ^1H NMR (360 MHz, CD_2Cl_2) δ: 1.45 (s, 9 H, $-C(CH_3)_3$), 4.4–4.45 (m, 2 H, CH_2), 4.95–5.05 (m, 1 H, NH-CH), 5.2–5.4 (br s, 1 H, NH); MS (CI, NH_3), m/z 205 (M · NH_4 , 100%). Anal. Calcd for $C_8H_{13}NO_4$: C, 51.33; H, 6.99; N, 7.48. Found: C, 51.28; H, 7.01; N, 7.42.
9. Anhydrous p-toluenesulfonic acid was prepared from the monohydrate (obtained from Aldrich Chemical Company, Inc.) by solution in hot benzene with the aid of ethyl acetate and azeotropic distillation to 50% volume to remove water. The solution was then concentrated to a syrup on a rotary evaporator. The syrup was dissolved in a minimum volume of acetone and excess benzene was added to precipitate the anhydrous acid. This material was recrystallized from acetone/benzene and dried at 50°C for 12 hr. It was stored under reduced pressure over anhydrous $CaSO_4$. The material used melted at 104–105°C.
10. Trifluoroacetic acid (obtained from Aldrich Chemical Company, Inc.) was refluxed over P_2O_5 for ca. 3 hr and then distilled from P_2O_5 under an atmosphere of argon. The material used distilled at 68–71°C. All manipulations involving trifluoroacetic acid (except removal on a rotary evaporator) were done in a fume hood.
11. Commercially available anhydrous ether (obtained from Fisher Scientific Company) was used directly from a freshly opened can.
12. The product exhibits the following properties: mp (4°C/min) 133–135°C (darkens), 173°C (dec) (rapid); $[\alpha]_D^{24}$ −15.8° (DMF, *c* 2.2); IR (Fluorolube mull) cm^{-1}: 3040, 1833, 1547; ^1H NMR (360 MHz, d_7 DMF) δ: 2.3 (s, 3 H, $ArCH_3$), 4.66 (m, 1 H, CHHO), 4.74 (m, 1 H, CHHO), 5.54 (dd, 1 H, J = 4.6, 6.5, CH), 7.15 (d, 2 H, J = 8, m-ArH), 7.64–7.7 (d, 2 H, J = 8, o-ArH); FAB MS (glycerol) m/z 260 (MH). Anal. Calcd for $C_{10}H_{13}NO_5S$: C, 46.32; H, 5.05; N, 5.40; S, 12.37. Found: C, 46.44; H, 5.14; N, 5.24; S, 12.41.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Recent work has shown that a large variety of carbon, nitrogen, oxygen, sulfur, and halogen nucleophiles attack chiral N-protected serine β-lactones at the β-carbon to give optically pure N-protected α-amino acids.[2,3,5] However, in certain cases (e.g., β-azidoalanine[7]) these products are unstable to most common deprotection conditions. The procedure given here describes the preparation of (S)-3-amino-2-oxetanone p-toluenesulfonic acid salt, a compound which reacts with a variety of nucleophiles to afford unprotected, optically pure α-amino acids directly (Scheme 1).[8] This salt has a long shelf life (many months) at room temperature provided that it is stored dry. It reacts rapidly with water (t□□ 2.5 hr in unbuffered water; t□□ 10 min in 50 mM potassium phosphate at pH 6.8). However, good nucleophiles such as thiols afford high yields of sulfur-containing amino acids in water if the pH is kept at 5.0–5.5.[7] Since both enantiomers of serine are relatively inexpensive, and L-serine is readily available in isotopically labeled form, this approach should prove useful for syntheses of sensitive D-amino acids as well as for preparation of the labeled L-isomers.



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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

benzophenone ketyl

2-Oxetanone, 3-amino-, (S)-, 4-methylbenzenesulfonate

Benzene (71-43-2)

ethyl acetate (141-78-6)

ether (60-29-7)

nitrogen (7727-37-9)

iodine (7553-56-2)

acetone (67-64-1)

sodium (13966-32-0)

D-amino (15194-15-7)

Tetrahydrofuran (109-99-9)

diethyl azodicarboxylate (1972-28-7)

hexane (110-54-3)

serine, L-serine (56-45-1)

trifluoroacetic acid (76-05-1)

triphenylphosphine (603-35-0)

argon (7440-37-1)

p-toluenesulfonic acid (104-15-4)

dimethyl azodicarboxylate (2446-84-6)

(S)-3-AMINO-2-OXETANONE p-TOLUENESULFONIC ACID SALT (112839-95-9)

N-tert-Butoxycarbonyl-L-serine β-lactone, N-(tert-Butoxycarbonyl)-L-serine β-lactone, Carbamic acid, (2-oxo-3-oxetanyl)- 1,1-dimethylethyl ester, (S)- (98541-64-1)

N-(tert-Butoxycarbonyl)-L-serine

azodicarboxylate

potassium phosphate (7778-53-2)

(benzyloxycarbonyl)-β-(pyrazol-1-yl)-L-alanine

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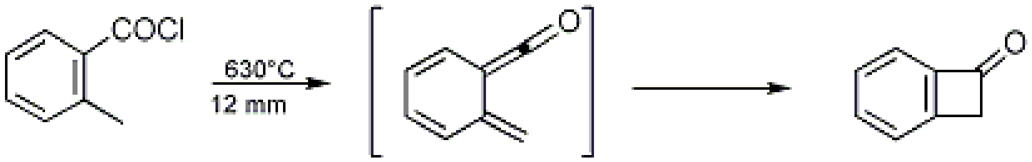
Organic Syntheses, CV 9, 28

BENZOCYCLOBUTENONE BY FLASH VACUUM PYROLYSIS

[Bicyclo[4.2.0]octa-1,3,5-trien-7-one]



Submitted by Peter Schiess, Ppatibha V. Barve, Franz E. Dussy, and Andreas Pfiffner[1].
Checked by Nobuyoshi Nomura and Hisashi Yamamoto.

1. Procedure

For flash vacuum pyrolysis experiments on a preparative scale the apparatus shown in f.htmigure 1 is used.[2] It consists of a vertically-mounted assembly of fused silica and Pyrex tubing 3.2 cm in diameter. The high temperature section **A**, 45 cm in length, is made from fused silica. It carries inner 29/32 ground glass joints. The upper evaporation section **B**, 25 cm in length, is made of Pyrex. It is fitted with two outer 29/32 ground glass joints (Note 1). Both tubes are loosely filled with Raschig rings cut from thin-walled, fused silica tubing 1 cm in diameter. The evaporation zone is heated by glass fiber heating tape (180 × 1 cm) controlled by a variac transformer. Heat for the pyrolysis section is provided by an electric tube furnace (Note 2). The temperature is measured with a thermocouple fixed on the surface of the silica tube in the middle of the hot reaction zone. The substance to be pyrolyzed is added to the evaporator under reduced pressure and at a constant drop rate from a 250-mL, pressure-equalizing dropping funnel **C** (Note 3). A 250-mL, long-necked, round-bottomed flask **D** cooled to −78°C serves as a receiver. (*Caution! Flask **D** (Note 4) must be checked by visual inspection at regular intervals. If condensed product accumulates in the entrance neck, the cooling bath level must be lowered to prevent clogging. Flask **D** must always be cooled to the neck of the flask. Otherwise material might be transferred from the receiver into trap **E**, which might then become plugged).* Flask **D** is connected by a wide glass tube (Note 4) to a cooling trap **E** kept at liquid nitrogen temperature (Note 5).

Figure 1

Figure 1

At a pyrolysis oven temperature of 630°C, an evaporator temperature of 200°C, and a pressure of 12 mm, 2-toluic acid chloride (240 g, 1.55 mol) (Note 6) is added in about 2.5 hr at a constant rate of 40–60 drops/min (Note 7). The pressure should be monitored in the addition funnel **C** during the pyrolysis. A sudden rise in pressure indicates that a restriction is building up between the pyrolysis reactor and the pump. In this case addition of reactant must be stopped. Ten minutes after the addition is complete the apparatus is flushed with nitrogen. The dark brown, oily condensate in the receiver is dissolved in 500 mL of acetone and diluted with 250 mL of cold water (Note 8) and (Note 9). The homogeneous solution is stirred at room

temperature for 1 hr. It then is separated into two phases by the addition of 500 mL of 2 N sodium carbonate solution and 250 mL of ether. The aqueous layers are extracted twice with 250-mL portions of ether. The ether extracts are washed with 2 N sodium carbonate solution and with saturated sodium chloride solution. The combined ether layers are dried over sodium sulfate. Removal of the solvent and distillation of the residue yields 65 g of a yellow oil, bp 87–90°C/13 mm, with the following composition: Benzocyclobutenone (97%), benzyl chloride (3%) (Note 10). Fractionation at 12 mm through a 25-cm spinning band column (Note 11) gives 58 g of benzocyclobutenone (>99%) as a colorless oil, bp 84–86°C/12 mm (Note 12) and (Note 13). The product crystallizes at 0°C and then melts at 10–15°C (Note 14).

Most of the acetone is removed from the combined aqueous layers by distillation. Upon acidification with concentrated hydrochloric acid a thick precipitate forms. Filtration and drying leads to 106 g of almost colorless 2-toluic acid, mp 103–107°C. This material is of sufficient purity for conversion into the acid chloride and for subsequent flash vacuum pyrolysis.

2. Notes

1. Teflon sleeves are used to assure the vacuum tight connection between the ground joints subjected to heat. The checkers used clear-seal joints in all of the glass connections.
2. Electric tube furnaces of appropriate dimensions are available from various manufacturers. A model RO 4/25 by Heraeus GmbH, Hanau, FRG is suitable. However, a very satisfactory furnace can be built by any well equipped laboratory workshop at little cost and effort. The material required consists of thin walled ceramic tubing, 3.5 cm i.d., nichrome resistance wire, heat resistant insulation, and ordinary hardware material. A technical drawing will be provided by the submitters upon request. The temperature of the furnace can be adjusted by an electronic temperature controller using a thermocouple sensor. A 1.5 kW-Variac transformer and any high temperature thermometer would do as well for the budget-minded chemist.
3. A dropping funnel with a needle valve, NORMAG type 8056, manufactured by NORMAG GmbH, D-6238 Hofheim, FRG, has been used by the submitters. The checkers used a standard pressure-equalizing dropping funnel with a Teflon stopcock.
4. Receiver **D** is a 250-mL, round-bottomed flask with two, 15-cm long necks with a diameter of 3.5 to 5 cm (entrance neck) and 2.5 cm (exit neck) (see f.htmigure 1). If a receiver **D** with a narrower entrance neck than indicated is used the neck can become plugged by condensate. A wide-bore connection is used between receiver **D** and the cold trap **E** to prevent a pressure drop during pyrolysis, which might be caused by a restriction in the HCl-gas flow.
5. *Caution!* Hydrogen chloride (bp –84.9°C) is condensed in trap **E**. Exercise care in its disposal.
6. 2-Toluic acid chloride (bp 213–214°C) is prepared from 2-toluic acid (EGA Chemie, Steinheim, FRG) by treatment with thionyl chloride ($SOCl_2$). The checkers purchased the acid chloride from Tokyo Chemical Co.
7. The pyrolysis temperature and the rate of addition are chosen such that about 50% of the acid chloride is recovered as 2-toluic acid after hydrolysis. Under these conditions only a small amount of benzyl chloride and polymeric material is formed in addition to benzocyclobutenone. The percentage of reactant conversion depends not only on the pyrolysis temperature, but also on the pressure in the reactor and on the rate of reactant

addition. It is advisable, therefore, to optimize the pyrolysis temperature in trial runs keeping the other variables constant.
In the runs carried out by the checkers, conversion of reactant was slightly lower than 50% as shown by the recovery of 2-toluic acid in 63–74% yield. In these runs benzocyclobutenone was obtained in 17–20% yield only. However, the yield calculated with respect to reactant consumed and not recovered as 2-toluic acid amounted to 56–64% and thus did not differ significantly from the value given in the procedure.
8. If separation into two phases occurs, acetone is added until a homogeneous solution results.
9. Hydrolysis of unreacted acid chloride is carried out without neutralization of the acid generated. In the presence of a base such as sodium carbonate or sodium bicarbonate the anhydride of 2-toluic acid would be formed, in addition to the sodium salt of the free acid. This anhydride is much less reactive toward hydrolysis than the acid chloride.
10. VPC analyses were performed using a PEG column of 25 m × 0.25 mm.
11. A 25-cm spinning band column of 12 theoretical plates, manufactured by NORMAG GmbH, D-6238 Hofheim, FRG, has been used by the submitters. The checkers found a 30-cm Vigreux distillation column just as suitable for the separation.
12. A forerun, 4.9 g of a yellow oil, bp 52–85°C/12 mm, consisting of a mixture of benzyl chloride and benzocyclobutenone, is discarded.
13. This corresponds to a yield of benzocyclobutenone, >99% homogeneous by VPC, of 32% with respect to the 2-toluic acid chloride subjected to pyrolysis, and of 63% with respect to the 2-toluic acid chloride consumed in the reaction.
14. The spectral properties are as follows: ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 4.00 (s, 2 H), 7.34–7.45 (m, 2 H), 7.50–7.57 (m, 2 H); IR (liquid film) cm^{-1}: 3060, 2920, 1780, 1760, 1585, 955, and 755.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

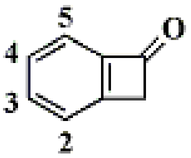
3. Discussion

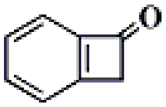
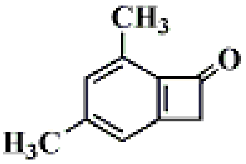
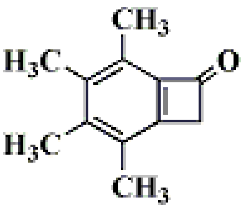
Benzocyclobutenone was first prepared from 1-bromobenzocyclobutene by hydrolysis followed by chromium trioxide oxidation.[3 4,5] More recent procedures involve hydrolysis of 1,1-dichloro- or 1,1-dimethoxybenzocyclobutene which in turn have been obtained through cycloaddition of the appropriate 1,1-disubstituted ethylenes to benzyne generated either from anthranilic acid through diazotization[6,7] or from bromobenzene through sodium amide treatment.[8,9] Benzocyclobutenone has also been obtained through flash vacuum pyrolysis from homophthalic anhydride,[10] from indane-1,2-dione,[11] and from 2-trimethylsilylmethylbenzoyl chloride.[12]

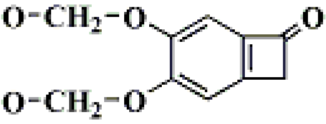
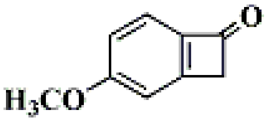
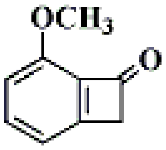
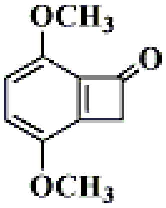
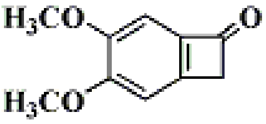
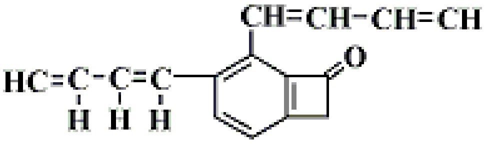
The present pyrolytic method is based on a communication by the authors[13] with some modifications of the pyrolysis apparatus for preparative scale.[14] This method is applicable to the preparation of benzocyclobutenones carrying various substituents on the aromatic ring (see Table). Its merit lies in its simplicity for generating the strained bicyclic ring system from inexpensive precursors. Benzocyclobutenones in general are thermolabile, losing carbon

monoxide at higher temperature.[11] It therefore is advisable to keep thermolytic conversion below 100%. Unconverted starting material can be recovered after hydrolysis of the crude reaction mixture as carboxylic acid and reused for the conversion to acid chloride without further purification. Gas phase pyrolysis has been available as a preparative method in organic chemistry for a long time.[15] Various procedures using this method have been described in previous volumes of *Organic Syntheses*.[16 17 18 19 20 21 22 23] Several reviews describing applications of the pyrolytic method in preparative organic chemistry have appeared in recent years.[24 25]

TABLE
BENZOCYCLOBUTENONES PREPARED THROUGH FLASH VACCUM PYROLYSIS OF 2-METHYLBENZOIC ACID CHLORIDES[14,16,17,18,19,20,21,22,23]



2	3	4	5	Reaction Conditions (°C/mm)	Acid Recovered, %	Yield[a] %	mp (°C)
H 	H	H	H	630/13	50	65	10–15
H 	CH_3	H	CH_3	560/13	5	77	47–48
CH_3 	CH_3	CH_3	CH_3	550/13	-	83	156–157

H							
	O-CH_2-O		H	570/13	12	81	122–124
H							
	OCH_3	H	H	570/13	41	67	49–50
H							
	H	H	OCH_3	590/0.1	51	63	32–33
OCH_3							
	H	H	OCH_3	590/0.1	20	63	106–107
H							
	OCH_3	OCH_3	H	530/13	57	37	142–143
H							
	H	CH=CH-CH=CH	550/13	11	82	96–97	

[a]Yield of purified ketone with respect to acid chloride consumed and not recovered as acid after hydrolysis.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

1,1-dichloro- or 1,1-dimethoxybenzocyclobutene

hydrogen chloride, hydrochloric acid (7647-01-0)

benzyne (71-43-2)

ether (60-29-7)

carbon monoxide (630-08-0)

thionyl chloride (7719-09-7)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

acetone (67-64-1)

benzyl chloride (100-44-7)

bromobenzene (108-86-1)

Anthranilic Acid (118-92-3)

chloride

chromium trioxide (1333-82-0)

sodium amide (7782-92-5)

1-bromobenzocyclobutene

Benzocyclobutenone

Bicyclo[4.2.0]octa-1,3,5-trien-7-one (3469-06-5)

2-toluic acid chloride (933-88-0)

2-toluic acid (118-90-1)

indane-1,2-dione

2-trimethylsilylmethylbenzoyl chloride

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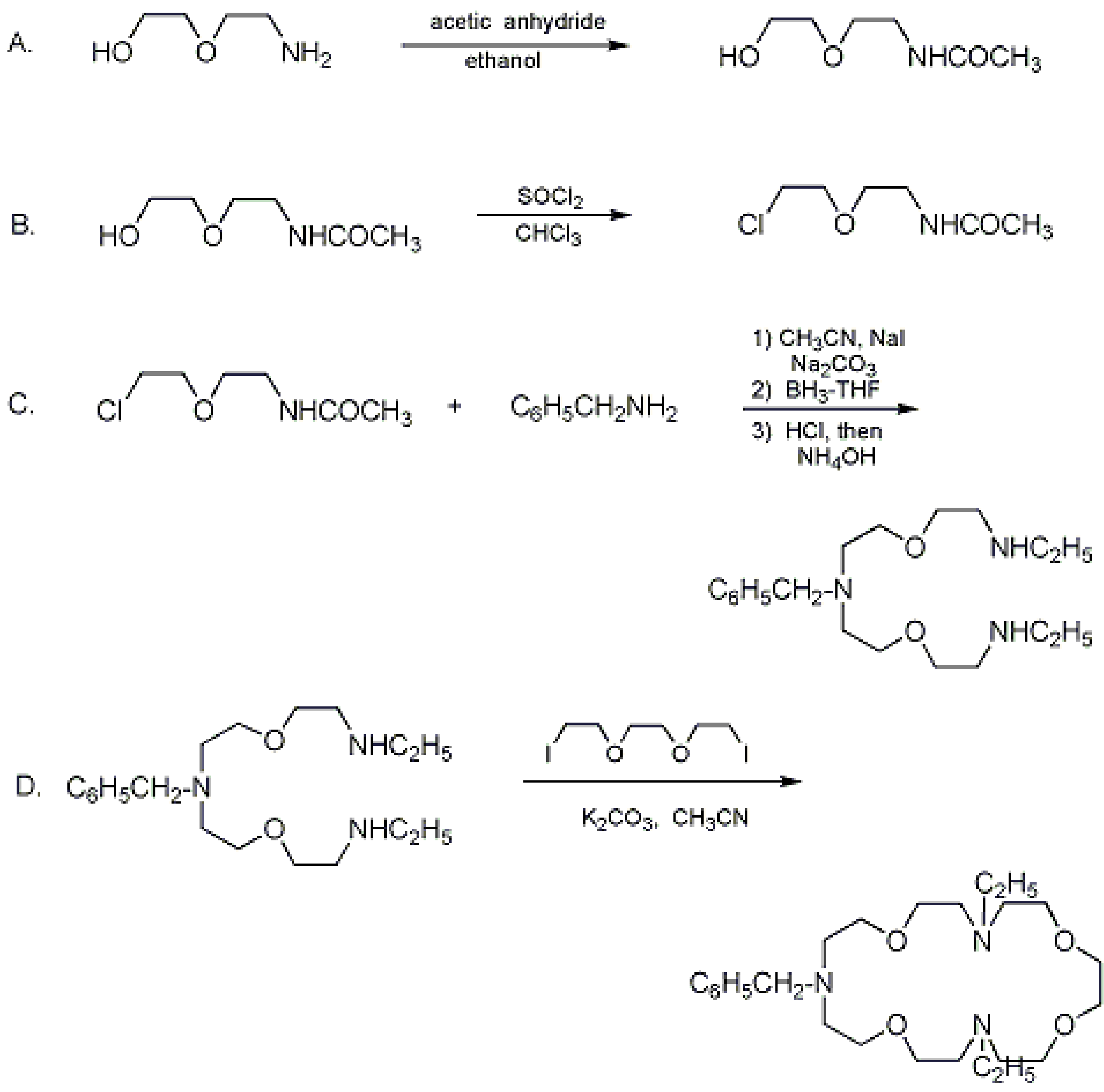
Organic Syntheses, CV 9, 34

4-BENZYL-10,19-DIETHYL-4,10,19-TRIAZA-1,7,13,16-TETRAOXACYCLOHENEICOSANE (TRIAZA-21-CROWN-7)



Submitted by Krzysztof E. Krakowiak[1] and Jerald S. Bradshaw[2].
Checked by Hyunik Shin and James D. White.

1. Procedure

A. *N-[2-(2-Hydroxyethoxy)ethyl]acetamide*. Into an oven-dried, 100-mL, three-necked, round-bottomed flask that contains a magnetic stirring bar, 25-mL addition funnel, condenser, and thermometer, is placed 15.75 g (0.15 mol) of 2-(2-aminoethoxy)ethanol (Note 1) in 20 mL of anhydrous ethanol (Note 2). Acetic anhydride (15.75 g, 0.154

mol) (Note 1) is slowly dripped into this stirring solution while the temperature is kept at or below 40°C. The resulting mixture is stirred under reflux for 15 min. The mixture is evaporated on a rotary evaporator to give a pale yellow oil that is distilled through a short path apparatus containing a 2-cm Vigreux column to give 20.3–21.5 g (92–97%) of product, bp 135–139°C/0.12 mm (Note 3).

B. *N-[2-(2-Chloroethoxy)ethyl]acetamide*. N-[2-(2-Hydroxyethoxy)ethyl]-acetamide (20.58 g, 0.14 mol) in 30 mL of chloroform (Note 4) is placed in an oven-dried, 250-mL, three-necked, round-bottomed flask that contains a magnetic stirring bar, pressure-equalizing dropping funnel, condenser that is connected by a polyethylene tube to a glass funnel, and a thermometer (Note 2). The flask is cooled in an ice bath and the glass funnel is immersed in a beaker of water. Thionyl chloride (28 g, 0.24 mol) (Note 1) in 25 mL of chloroform is added dropwise to the stirring mixture at 10–15°C. The mixture is then stirred at room temperature for 30 min and under reflux for 20 min (Note 5). It is immediately cooled to 30°C and the solvent and excess thionyl chloride are removed on a rotary evaporator (Note 6). The residue is immediately distilled through an 8-cm Vigreux column using an oil bath (Note 7) to give 17–18 g (73–77%) (Note 8) of N-[2-(2-chloroethoxy)ethyl]acetamide, bp 105–108°C/0.1 mm (Note 3).

C. *9-Benzyl-3,9,15-triaza-6,12-dioxaheptadecane*. A mixture of 17.5 g (0.105 mol) of N-[2-(2-chloroethoxy)ethyl]acetamide, 200 mL of acetonitrile (Note 9), 22 g (0.21 mol) of anhydrous sodium carbonate (Note 10), 16.5 g (0.11 mol) of sodium iodide (Note 1) and (Note 11) and 5.35 g (0.05 mol) of benzylamine (Note 1) is added to an oven-dried, 250-mL, three-necked flask that contains a magnetic stirring bar and condenser. The mixture is refluxed for 48 hr, cooled to room temperature and filtered under vacuum. The solid in the filter is washed twice with 70-mL portions of methylene chloride (Note 12). The combined filtrate and methylene chloride mixture are evaporated on a rotary evaporator until all of the solvents are removed. The residue is dissolved in 70 mL of water and transferred to an extraction funnel. The aqueous solution is extracted with three 200-mL portions of methylene chloride (Note 12). The combined methylene chloride extracts are dried over anhydrous magnesium sulfate (Note 13). The mixture is filtered under vacuum and the solid is washed with 100 mL of methylene chloride. The solvents are evaporated on a rotary evaporator. The residue is dissolved in 80 mL of tetrahydrofuran (Note 14) and transferred to a dropping funnel equipped with an anhydrous calcium sulfate drying tube. This solution is slowly dripped into 300 mL of cold, stirring 1 N borane-THF (Note 1) and (Note 15) in an oven-dried, 1-L, one-necked, round-bottomed flask containing a magnetic stirring bar. The addition funnel is removed, a condenser equipped with an anhydrous calcium sulfate drying tube is connected, and the stirring mixture is refluxed for 16 hr. The mixture is cooled and 20 mL of distilled water is slowly dripped into it from a dropping funnel (Note 16). The solvents are then removed on a rotary evaporator. The residue is cooled in an ice water bath and 300 mL of aqueous 18% hydrochloric acid (Note 17) is slowly added to the stirring mixture. The resulting mixture is stirred for 16 hr, first at room temperature, and then warmed until the solvent just reaches the boiling point. The solution is cooled and the solvents are completely removed on a rotary evaporator. To the residue is added 50 mL of water. The aqueous mixture is stirred (Note 18) and filtered under vacuum. The

solid is washed with 15 mL of water, and 150 mL of ammonium hydroxide (Note 19) is added to the filtrate (Note 2). The resulting solution is extracted three times with 300-mL portions of chloroform (35 g of sodium chloride is added to the aqueous solution before the third extraction). The chloroform layers are combined and dried over anhydrous magnesium sulfate. The solution is filtered under vacuum, the solid is washed with 50 mL of chloroform, and the solvent is removed on a rotary evaporator. The residue is distilled slowly through a short path apparatus that contains a 2-cm Vigreux column to give 11.6–12.6 g (69–75%) of 9-benzyl-3,9,15-triaza-6,12-dioxaheptadecane as a light yellow oil, bp 144–152°C/0.085 mm (Note 3).

D. *4-Benzyl-10,19-diethyl-4,10,19-triaza-1,7,13,16-tetraoxacycloheneicosane* (*triaza-21-crown-7*). A mixture of 10 g (0.03 mol) of 9-benzyl-3,9,15-triaza-6,12-dioxaheptadecane and 600 mL of acetonitrile (Note 9) is placed in an oven-dried, 1-L, three-necked, round-bottomed flask equipped with a condenser, an efficient mechanical stirrer and a rubber septum. Argon gas is flushed through the flask using a needle through the septum before and during the reaction. To the above mixture, while stirring at room temperature, is added 50 g (0.36 mol) of anhydrous powdered potassium carbonate (Note 20) and the mixture is stirred for 15 min; then 11.5 g (0.031 mmol) of 1,2-bis(2-iodoethoxy)ethane (Note 1) is added. The resulting mixture is stirred under reflux for 24 hr. The cooled mixture is filtered under vacuum and the solid is washed with 100 mL of acetonitrile. The solvent is removed from the filtrate on a rotary evaporator. Methylene chloride (160 mL) (Note 12) is added to the residue and the resulting mixture is stirred (Note 18). The mixture is filtered under vacuum and the solid is washed with two 20-mL portions of methylene chloride (Note 12). The combined organic layers are evaporated on a rotary evaporator to give a brown oil. The oil is purified by chromatography on 300 g of alumina (Note 21) using 1000 mL of toluene/ethanol: 50:1 as the eluant. The first 120–150 mL of eluant is removed. The remainder of the eluant is evaporated in a rotary evaporator to give 9.6–10 g (72–75%) of the triaza-21-crown-7 as a light yellow oil (Note 22),(Note 23),(Note 24).

2. Notes

1. 2-(2-Aminoethoxy)ethanol, acetic anhydride (99+%), thionyl chloride (99+%), benzylamine (99%), 1,2-bis(2-iodoethoxy)ethane (98%), anhydrous sodium iodide (99+%) and borane-tetrahydrofuran complex (1.0 M solution in tetrahydrofuran) were purchased from Aldrich Chemical Company, Inc. and were used without further purification.
2. The reaction must be carried out in an efficient hood.
3. The IR and NMR spectra in reference [3] were consistent with the proposed structure.
4. Chloroform ("Chrom Pure") manufactured by American Burdick & Jackson (distributed by American Scientific Products) was used.
5. The reaction also can be carried out at room temperature for 48 hr.
6. A rotary evaporator that has a safety flask in the vacuum line was used. The water bath temperature was not higher than 50°C.

7. The submitters prefer to use an oil bath rather than a heating mantle because control of pot temperature is essential so that no polymers can form. There is a loss of vacuum at the beginning of the distillation because of various gases in the product.

8. The yield from a seven times larger reaction was 85%.[3]

9. Acetonitrile ("Chrom Pure") manufactured by American Burdick & Jackson (distributed by American Scientific Products) was used.

10. Sodium carbonate (anhydrous A.C.S. certified) distributed by Fisher Scientific was used.

11. In reference [3], xylene was used as the solvent instead of acetonitrile and sodium iodide was not used. The yield in that case was lower.

12. Methylene chloride ("Chrom Pure") manufactured by American Burdick & Jackson (distributed by American Scientific Products) was used.

13. Magnesium sulfate (anhydrous, powder) distributed by EM Science was used.

14. Tetrahydrofuran (HPLC quality), manufactured by Mallinckrodt Inc., was used.

15. When fresh lithium aluminum hydride was used instead of the borane-tetrahydrofuran complex,[3] the reduction gave low yields and the product was more difficult to purify.

16. The first drops of water are added very slowly because the reaction causes considerable foaming.

17. Analytical reagent grade hydrochloric acid, manufactured by Mallinckrodt Inc., was used for the preparation of the 18% solution.

18. The mixture was stirred until the solid was completely suspended.

19. Analytical reagent grade ammonium hydroxide (NH_3 = 29.6%), manufactured by Mallinckrodt Inc., was used.

20. "Baker Analyzed" reagent grade potassium carbonate (anhydrous, granular) was used.

21. Activated, neutral, 150 mesh alumina (Brockman 1 standard grade), sold by Aldrich Chemical Company, Inc., was used in a 5-cm diameter column for the purification of the triaza-crown. Alumina TLC plates (Aluminum oxide 60_{F254} neutral (Type E), manufactured by E. Merck, distributed by EM Science) were used to monitor the purification process (toluene/ethanol = 20:1, using iodine as an indicator).

22. The product is nearly 98% pure as determined by GC using a Carlo Erba 5160 Mega instrument, flame ionization detection, with H_2 as the carrier gas (50 cm/sec). The column was a 10-m × 200-•m i.d. fused silica column coated at a 0.15-•m film thickness with SE-33 (methyl silicone). The split injector was kept at 300°C, the detector at 280°C, and the column at 230°C. The product gave the correct elemental analysis and has the following spectral properties: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.0 (t, 6 H), 2.55 (m, 4 H), 2.72 (m, 12 H), 3.6 (m, 18 H), 7.35 (m, 5 H); IR (neat) cm^{-1}: 2860, 1440, 1340, 1110; MS (20 eV) m/e 160, 275, 336, 451 (100%).

23. The crown can be distilled under high vacuum in a short path distillation apparatus using an oil bath, bp 188–190°C/0.05 mm.

24. The product should be stored under argon at 0°C in a dark bottle to prevent decomposition.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The procedure described here illustrates a new "building block" method for the preparation of per-N-alkyl-substituted polyaza-crown compounds.[3,4,5] The key building block, N-[2-(2-chloroethoxy)ethyl]acetamide and its benzamide analog,[3] allows the preparation of a variety of tri- and tetraamino compounds capable of ring closure reactions to form a variety of polyaza-crowns.[3,4] Polyaza-crowns containing a secondary amine side chain (mono lariat ether),[5] a hydroxyalkyl side chain,[6] and very large polyaza-crowns (30–36 ring members)[3] have been prepared using these procedures. The triaza-18-crown-6 analog was prepared in an overall yield of 25% by treating 9-benzyl-3,9,15-triaza-6,12-dioxaheptadecane with 3-oxapentanedioyl dichloride followed by reduction.[3,4]

The procedures previously used to prepare N-peralkylated polyaza-crowns required the use of nitrogen protecting groups that must subsequently be removed and the alkyl groups added.[7,8,9,10,11] These added steps greatly reduced the overall yields of the polyaza-crowns. Polyaza-crowns are important for complexing certain "soft" heavy metals,[12,13,14,15,16] and anions,[17,18,19,20] and as enzyme mimics in certain biological systems.[21] It is important to note that the N-peralkylated polyaza-crowns have about the same affinity for metal cations as the unsubstituted aza-crowns.[15] We have prepared 26 new N-peralkylated polyaza-crowns using this new method.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

4-Benzyl-10,19-diethyl-4,10,19-triaza-1,7,13,16-tetraoxacycloheneicosane (Triaza-21-crown-7)

ethanol (64-17-5)

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

acetic anhydride (108-24-7)

acetonitrile (75-05-8)

thionyl chloride (7719-09-7)

chloroform (67-66-3)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

iodine (7553-56-2)

toluene (108-88-3)

ammonium hydroxide (1336-21-6)

xylene (106-42-3)

sodium iodide (7681-82-5)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

benzylamine (100-46-9)

borane (7440-42-8)

aluminum oxide (1344-28-1)

Tetrahydrofuran, THF (109-99-9)

lithium aluminum hydride (16853-85-3)

argon (7440-37-1)

1,2-bis(2-iodoethoxy)ethane (36839-55-1)

4-BENZYL-10,19-DIETHYL-4,10,19-TRIAZA-1,7,13,16-TETRAOXACYCLOHENEICOSANE

TRIAZA-21-CROWN-7

N-[2-(2-Hydroxyethoxy)ethyl]acetamide, N-[2-(2-Hydroxyethoxy)ethyl]-acetamide (118974-46-2)

2-(2-aminoethoxy)ethanol (929-06-6)

N-[2-(2-Chloroethoxy)ethyl]acetamide (36961-73-6)

9-Benzyl-3,9,15-triaza-6,12-dioxaheptadecane (118974-42-8)

triaza-18-crown-6

3-oxapentanedioyl dichloride (21062-20-4)

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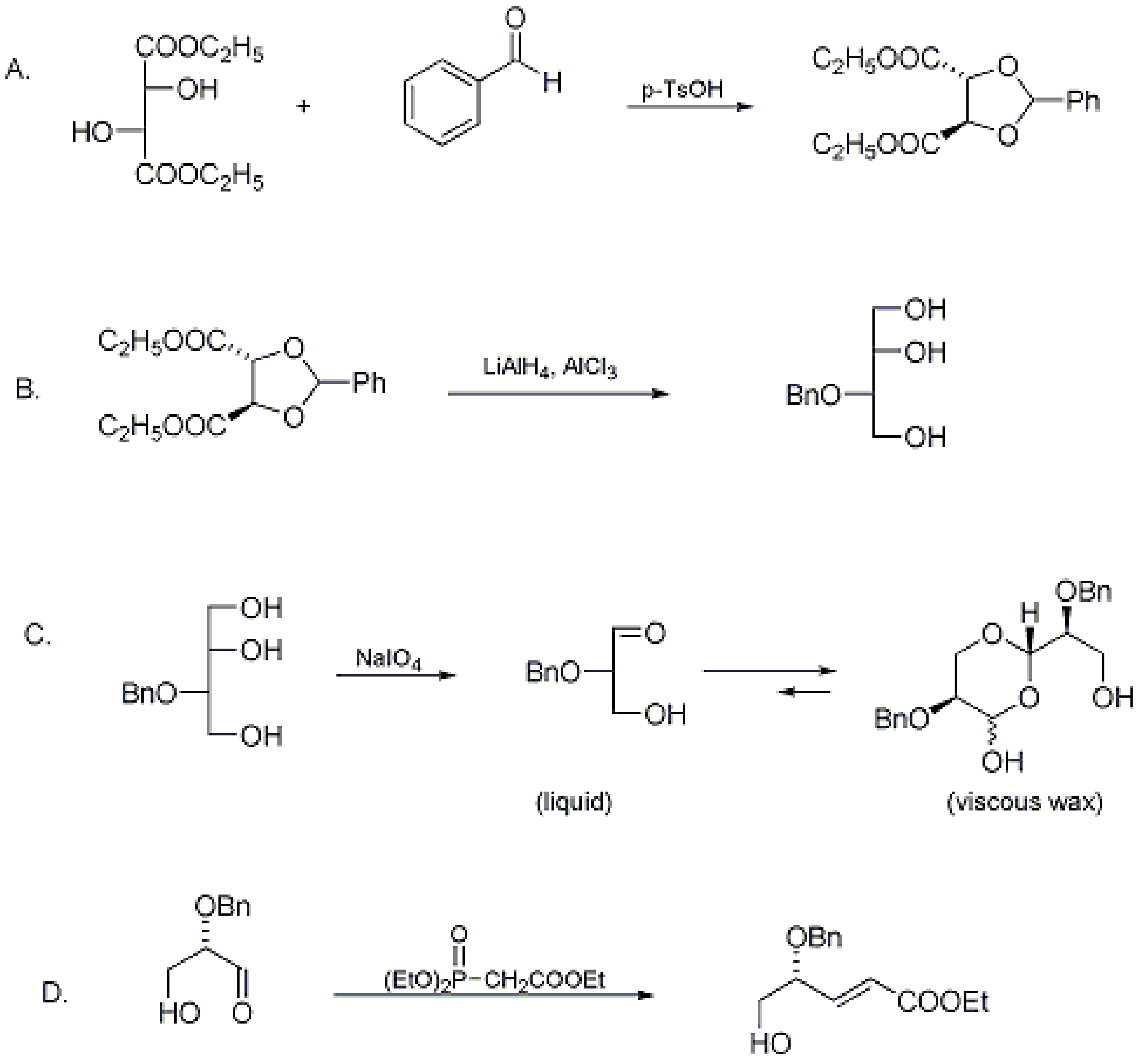
(–)-2-O-BENZYL-L-GLYCERALDEHYDE AND ETHYL (R,E)-4-O-BENZYL-4,5-DIHYDROXY-2-PENTENOATE

[Propanal, 3-hydroxy-2-(phenylmethoxy)-, (R)- and 2-Pentenoic acid, 5-hydroxy-4-(phenylmethoxy)-, ethyl ester, [R-(E)]-]



Submitted by B. Steuer, V. Wehner, A. Lieberknecht, and V. Jäger[1].
Checked by Joseph P. Bullock and Louis S. Hegedus.

1. Procedure

Caution: Lithium aluminum hydride is sensitive to mechanical shock and very reactive towards moisture and other protic substances; its dust is very irritating to skin and mucous membranes. It should not be allowed to come into contact with metallic species or apparatus, including metal spatulas, because of the potential danger of metal ion-

promoted detonation.

A. *Diethyl (–)-2,3-O-benzylidene-L-tartrate*. A 1-L, round-bottomed flask equipped with a Dean-Stark trap is charged with 103 g (500 mmol) of diethyl L-tartrate (Note 1), 53.1 g (500 mmol) of benzaldehyde (Note 2), 600 mL of cyclohexane and 2.80 g (14.7 mmol) of p-toluenesulfonic acid monohydrate (Note 3). The stirred mixture is heated with azeotropic removal of water (Note 4). The solution is allowed to cool to room temperature and then is concentrated by rotary evaporation (30 mm, 30°C). The residual yellow oil is dissolved in 400 mL of diethyl ether (Note 5), transferred to a 1-L separatory funnel, and washed with saturated aqueous potassium bicarbonate (200 mL) , and with water (2 × 200 mL). The ethereal layer is dried over magnesium sulfate and filtered. The solution is concentrated by rotary evaporation (30 mm, 30°C), followed by removal of solvent at 0.02 mm at room temperature. The solid crude product is collected by suction filtration through a sintered-glass funnel to give diethyl (–)-2,3-O-benzylidene-L-tartrate as yellow crystals. Trituration of the crude solid product with 150 mL of hexanes and collection of the purified product by suction filtration through a sintered-glass funnel gives 105 g (71%) of purified product, mp 47°C (Note 6).

B. *(+)-2-O-Benzyl-L-threitol*.[2] A 2-L, three-necked, round-bottomed flask is oven-dried (140°C) and flushed with nitrogen. The flask is equipped with an efficient mechanical stirrer, a 250-mL pressure-equalizing addition funnel, and a reflux condenser equipped with a mineral oil bubbler that is connected to a nitrogen source. A slight pressure of gas is maintained in the apparatus throughout the course of the reaction. The flask is charged with 16.5 g (434 mmol) of lithium aluminum hydride (Note 7), and cooled to –30°C using an isopropyl alcohol-dry ice bath. Then 167 mL of dry diethyl ether (Note 8) is added with vigorous stirring and a solution of 57.8 g (434 mmol) of aluminum chloride in 134 mL of dry diethyl ether (Note 8), (Note 9) is added dropwise during 40 min. Dry dichloromethane (134 mL) (Note 10) is placed in the addition funnel and added rapidly, while the temperature is allowed to rise to 0°C. A solution of 64.7 g (220 mmol) of diethyl (–)-2,3-O-benzylidene-L-tartrate in dry dichloromethane (134 mL) is added dropwise during 30 min (Note 11). The mixture is stirred for 1 hr at room temperature and heated to reflux for an additional 2 hr. The mixture is cooled to –20°C as above, and 14 mL of de-ionized water, followed by a solution of 31.5 g (561 mmol) of potassium hydroxide in 46 mL of de-ionized water, is added cautiously. The cooling bath is removed and the mixture is stirred at room temperature until the grey color (probably due to unreacted lithium aluminum hydride) has completely disappeared (Note 12). Efficient stirring is required throughout to ensure good yields. The mixture is filtered through a glass-sintered funnel containing a 2-cm pad of Celite, and the inorganic precipitate is extracted with 0.5 L of dichloromethane in a Soxhlet apparatus for 3 days. The combined extracts and filtrate are evaporated under reduced pressure (30 mm, 30°C). After drying over phosphorus pentoxide (P_4O_{10}) in an evacuated (1 mm) desiccator, 42.4 g (91%) of colorless crystals, mp 71–73°C, are obtained and used as such for step C. Recrystallization from dichloromethane (Note 10) gives 37.4 g (80%) of (+)-2-O-benzyl-L-threitol, mp 75–76°C (Note 13).

C. *(–)-2-O-Benzyl-L-glyceraldehyde.*[3] A solution of 9.22 g (43.4 mmol) of (+)-2-O-benzyl-L-threitol (Note 14) in 100 mL of water is stirred vigorously, while 9.28 g (43.4 mmol) of sodium periodate (Note 15) is added in ca. 1-g portions over 40 min. The mixture is stirred for 2 hr at room temperature, then the pH is adjusted to 7.0 by addition of solid potassium carbonate (Note 16). The mixture is transferred to a 500-mL separatory funnel and extracted with dichloromethane (3 × 150 mL). The combined organic layers are dried over magnesium sulfate for 15 min and concentrated on a rotary evaporator (30 mm, 30°C). The remaining pale-yellow crude oil is transferred to a 25-mL round-bottomed flask and purified by short-path distillation in a preheated oil bath (0.025 mm, 160°C) (Note 17), to yield 6.32 g (80%) of (–)-2-O-benzyl-L-glyceraldehyde, a colorless oil that on standing turns more and more viscous, and after several weeks at room temperature forms a waxy solid (Note 18).

D. *Ethyl (–)-[R-(E)]-4-O-benzyl-4,5-dihydroxy-2-pentenoate*. To a 500-mL, round-bottomed, two-necked flask, fitted with a nitrogen inlet (Note 19) and a stopper, is added 3.32 g of a suspension of sodium hydride in paraffin, containing 65% sodium hydride. The suspension is washed three times with 40 mL and once with 20 mL of hexanes (Note 20) to remove the paraffin. The residue is freed from remaining hexanes under vacuum (0.01 mm) to give ca. 2.16 g (ca. 90 mmol) of sodium hydride. The flask is fitted with a magnetic stirring bar and the stopper is exchanged for a septum. Then 100 mL of tetrahydrofuran (Note 21) is added and the suspension is cooled to 0°C. Triethyl phosphonoacetate (22.87 g, 102 mmol) (Note 22) is added to the stirred sodium hydride/tetrahydrofuran suspension by means of a 50-mL syringe over a period of 20 min. The mixture is cooled to –78°C (acetone/dry ice) and a solution of 10.81 g (60 mmol) of (–)-2-O-benzyl-L-glyceraldehyde in 80 mL of tetrahydrofuran (Note 21) is added by means of a syringe over 20 min. (The checkers transferred this solution via a cannula.) The mixture is stirred for an additional 15 min at –78°C. The temperature is allowed to rise to 0°C within 30 min, and finally is kept at room temperature for an additional 45 min. The reaction is quenched with 150 mL of saturated ammonium chloride solution and extracted three times with ether (500, 200, 200 mL). The combined organic layers are washed with a mixture of saturated sodium bicarbonate/brine (1:1, 160 mL). The aqueous layer is washed with ether (3 × 100 mL). The combined organic layers are dried over magnesium sulfate, filtered, and evaporated to dryness to give a pale yellow oil. The crude product is purified by column chromatography over silica gel (Note 23) with petroleum ether/ethyl acetate 1/1 as eluent (Note 24), to yield 11.7 g (78%) of analytically pure ethyl (–)-[R-(E)]-4-O-benzyl-4,5-dihydroxy-2-pentenoate (Note 25).

2. Notes

1. Diethyl L-tartrate (99%) was obtained from Janssen Chimica, Brüggen, Germany or Aldrich Chemical Company, Inc.
2. Benzaldehyde (99+%) from Aldrich Chemical Company, Inc., was used as received.
3. p-Toluenesulfonic acid monohydrate (99%) was obtained from Fluka Feinchemikalien GmbH, Neu-Ulm, Germany or from Aldrich Chemical Company,

Inc.

4. The mixture becomes homogeneous at reflux temperature. The reaction usually takes about 16 hr at an 0.5 mole-scale as indicated by the amount of water separated.

5. Diethyl ether (technical grade) was distilled over potassium hydroxide.

6. The spectral properties of diethyl (–)-2,3-O-benzylidene-L-tartrate are as follows: ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.32, 1.35 (2 t, 6 H, J = 7.1, 2 CH_2CH_3), 4.23, 4.28 (2 q, 4 H, J = 7.1, 2 CH_2CH_3), 4.83, 4.95 (2 d, 2 H, J = 4.0, 2 CHO), 6.16 (s, 1 H, CHPh), 7.40, 7.58 (2 m, 5 H, C_6H_5),[4] $[\alpha]_D^{20}$ –30.7° ($CHCl_3$, *c* 2.20),[5] mp 45°C.[4,5]

7. Lithium aluminum hydride was obtained in 25-g samples (98%) from Merck-Schuchardt, Hohenbrunn, Germany or Aldrich Chemical Company, Inc.

8. Diethyl ether was dried first by distillation over potassium hydroxide, then by distillation from lithium aluminum hydride.

9. In order to dissolve aluminum chloride in dry diethyl ether, a flask is charged with the aluminum chloride and the diethyl ether is added in 10-mL portions with vigorous mechanical stirring to give a dark solution. The flask must be cooled in an ice bath.

10. Dichloromethane (technical grade) was distilled over phosphorus pentoxide.

11. If lithium aluminum hydride and aluminum chloride are not of high purity, an excess of 10% of each should be used. Otherwise a mixture with products of incomplete reduction is obtained.

12. The reaction mixture is heated to reflux with 200 mL of tetrahydrofuran; the precipitate then obtained is very easy to filter off.

13. The spectral properties of (+)-2-O-benzyl-L-threitol are as follows: ^{1}H NMR (250 MHz, $CDCl_3$) δ: 2.58, 2.76, 2.98 (bs, 3 H, 3 OH), 3.44–3.88 (m, 6 H, 2 CH_2OH, H-2, H-3), 4.56, 4.69 (AB, 2 H, J = 11.6, $CH_2C_6H_5$), 7.16–7.34 (m, 5 H, C_6H_5), $[\alpha]_D^{25}$ +17.5° (EtOH, *c* 1.14).[5]

14. In several experiments it was found that the yield of (–)-2-O-benzyl-L-glyceraldehyde is somewhat lower when the reaction is performed on a larger scale.

15. Sodium periodate (98%) was obtained from Fluka Feinchemikalien GmbH, Neu-Ulm, Germany or from Fisher Scientific Company.

16. The pH was controlled with Merck Universal-Indikatorpapier or pHydrion Vivid 1–11 Jumbo pH paper, Micro Essential Laboratory, Brooklyn, NY, USA.

17. A silicone-oil bath is preheated to 160°C (the checkers used a sand bath). The flask of the evacuated apparatus filled with the crude product is immersed totally in the bath until no more distillate is collected. For optimum results, the distillation should be performed within 10 to 15 min. Slower distillation leads to lower yields because of thermal decomposition.

18. It is not possible to give exact spectral properties of (–)-2-O-benzyl-L-glyceraldehyde because of rapid di- and/or oligomerization. In order to check the optical purity of the product, it is convenient to compare the equilibrium value of specific rotation, as obtained after 6 days in ethanol solution at room temperature; $[\alpha]_D^{22}$ –33.2° (EtOH, *c* 0.083). In succeeding reactions (see Discussion and Step D), it was determined from NMR shift experiments that these products [e.g., (i) the

Z-selective Wittig enoate product (with ethoxycarbonylmethylene-triphenylphosphorane) and the penten-5-olide therefrom (after acid-catalyzed lactonization,[4,6]] and (ii) the E-enoate (Horner product)[4,6] contained enantiomers in ratios of >96:4.

19. Nitrogen was dried by means of a Sicapent® (E. Merck) drying tube. The checkers used argon.

20. The checkers used hexanes (technical grade) distilled over 3 Å molecular sieves. The submitters used pentane distilled from sodium.

21. Tetrahydrofuran was purified by distillation under nitrogen from a purple solution of sodium and benzophenone.

22. Triethyl phosphonoacetate was purified by distillation (bp 143°C, 9 mm). The checkers obtained this compound (99%) from Aldrich Chemical Company, Inc., and used it as received.

23. The submitters used 28 g of Kieselgel 60, E. MERCK, 0.040–0.063 mm (250–400 mesh); column: 28 cm × 2.5 cm. The checkers used 100 g of silica gel, 0.032–0.063 mm, Selecto Scientific, Norcross, GA, USA, catalog # 162824; column: 40 cm × 5.5 cm.

24. Ethyl acetate and petroleum ether (technical grade; boiling range 40–80°C) were purified by distillation. The checkers used ethyl acetate/hexanes 10/90 followed by ethyl acetate/hexanes 35/65 as eluent; ethyl acetate (HPLC grade) was obtained from Mallinckrodt Specialty Chemicals Company, Paris, KY, USA and hexanes (technical grade) were distilled over 3 Å molecular sieves.

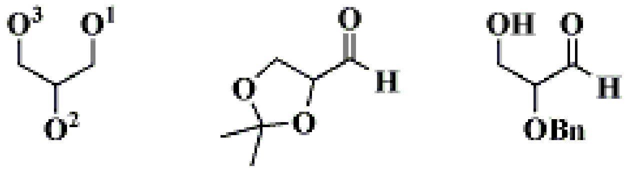
25. The analytical data (after chromatography) were as follows: Calcd. for $C_{14}H_{18}O_4$ (250.29): C, 67.18; H, 7.25. Found: C, 67.00; H. 7.20. The E/Z ratio was found to be >97:3 (determined by HPLC). Rt_E = 3.72 min; Rt_Z = 4.28 min, eluent petroleum ether/ethyl acetate 6/4 (LiChrosorb Si 60 column, E. Merck]. TLC: R_f = 0.34 (petroleum ether/ethyl acetate 1/1). GLC analysis: Column PS086/.32 mm × 20 m glass capillary, 95:5 methyl/phenylsilicone. Program: T_1, 40°C/(1 min), rate 10°C/min, T_2, 300°C, 0.5 bar hydrogen pressure; Rt_Z = 16.47 min; Rt_E = 17.25 min. E/Z ratio was found to be >97:3 (determined by GLC). $[\alpha]_D^{22}$ −75.8° ($CHCl_3$, *c* 1.192, E/Z >97:3), bp 125–130°C (0.001 mm). ^{13}C NMR (63 MHz, $CDCl_3$) δ: 14.2 (OCH_2CH_3), 60.7 (OCH_2CH_3), 64.6 (C-5), 71.5 (CH_2Ph), 79.0 (C-4), 123.9 (C-2), 127.9, 128.0, 128.3, 128.6, 137.6 (C_6H_5), 144.3 (C-3), 165.9 (C-1); ^1H NMR (250 MHz, $CDCl_3$), δ: 1.30 (t, 3 H, J = 7.1, CH_3), 2.32 (dd, 1 H, J = 5.2, 7.9, OH), 3.65 (m, 2 H, CH_2OH), 4.14 (m, 1 H, 4-H), 4.22 (q, 2 H, J = 7.1, OCH_2CH_3), 4.41, 4.45 (AB, 2 H, J = 11.6, CH_2Ph), 6.11 (dd, 1 H, J = 1.3, 15.8, 2-H), 6.85 (dd, 1 H, J = 6.1, 15.8, 3-H), 7.34 (m, 5 H, C_6H_5).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995 and "Neue Datenblätter für gefährliche Arbeitsstoffe nach der Gefahrstoffverordnung", Welzbacher, U. (Ed.); WEKA Fachverlage, Kissing, 1991.

3. Discussion

Optically active C_3-building blocks of type **1** are key starting compounds in organic synthesis.[7 8 9 10 11 12] The most important member of this class is 2,3-O-isopropylideneglyceraldehyde **2**.[7,8,9,10,11,12,13 14 15]



1 2 3

Both enantiomers of **2** are readily available from D-mannitol and from L-gulonolactone, respectively, and have been used in many reactions in a straightforward manner, because of the free aldehyde and the protected hydroxy functions. Unfortunately, **2** tends to trimerize and partial racemization has often been encountered on prolonged storage, thus preventing shipping/commercialization.[16] A recent paper on large-scale preparation of glyceraldehyde acetonide **2**, however, indicates suitable stability even at room temperature when certain precautions are met.[17 18 19]

Glyceraldehyde derivatives with one protected and one free hydroxy function could, in principle offer new options because 2O/3O are more strongly differentiated, and further, since the free hydroxy group does or may cause different regio- and stereoselectivity in the next or subsequent steps. 2-O-Benzylglyceraldehyde, **3**, because of its di- or oligomeric form, is configurationally stable at room temperature.[6] The D-form has previously been prepared from D-mannitol in four steps, with an overall yield of 5%,[20] or in 9 steps with 4%,[21] and from D-glucose in six steps with an overall yield of 50%.[22]

As described here, both enantiomers of **3** can be prepared in three steps from commercially available diethyl D- and L-tartrate in up to 70% over-all yield.[2,3,4,6] Procedures to obtain the benzylidene acetal,[23,24] with the ensuing reduction step,[23,24] are based on previous literature reports. Both enantiomers of **3** have been used in highly stereoselective nitroaldol additions.[4,25] Imines, nitrones, oximes, and nitrile oxides derived therefrom were recently employed in a variety of additions/cycloadditions.[26 27 28,29 30 31 32 33] (−)-2-O-Benzyl-L-glyceraldehyde has further been used for the preparation of protected (2S,4R)-4-hydroxyornithine, via a Horner-Emmons reaction to the corresponding α,β-didehydroamino acid derivatives and subsequent diastereoselective hydrogenation.[34] Transformation of aldehyde **3** in Z-selective Wittig or E-selective Horner reactions[4,6,35] (see Step D[36]), formation of the dimethyl acetal[5,37] or of the corresponding nitro compound by oxidation of the oxime,[5,37] represent further recent uses of **3**.

This preparation is referenced from:

- Org. Syn. 78, 123

References and Notes

1. Institut für Organische Chemie und Isotopenforschung der Universität Stuttgart, Pfaffenwaldring 55, D-70569 Stuttgart. Work carried out before 1993 was done at Universität Würzburg.
2. (+)-2-O-Benzyl-L-threitol is available from Fluka Feinchemikalien GmbH at ca. DM 60/g;
3. 2-O-Benzylglyceraldehyde is available from Merck-Schuchardt, D- and L- at a price of ca. DM 140/g.
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36. We thank Mr. Timo Gräther for experimental assistance concerning Step D.
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

hexanes

brine

dimethyl acetal

glyceraldehyde acetonide

(–)-2-O-BENZYL-L-GLYCERALDEHYDE

ETHYL (R,E)-4-O-BENZYL-4,5-DIHYDROXY-2-PENTENOATE

Diethyl (–)-2,3-O-benzylidene-L-tartrate

Ethyl (–)-[R-(E)]-4-O-benzyl-4,5-dihydroxy-2-pentenoate

sodium hydride in paraffin

penten-5-olide

diethyl D- and L-tartrate

benzylidene acetal

methylsilicone

phenylsilicone

ethanol (64-17-5)

potassium carbonate (584-08-7)

ethyl acetate (141-78-6)

ether, diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

sodium bicarbonate (144-55-8)

nitrogen (7727-37-9)

cyclohexane (110-82-7)

benzaldehyde (100-52-7)

acetone (67-64-1)

aluminum chloride (3495-54-3)

potassium hydroxide (1310-58-3)

Benzophenone (119-61-9)

sodium (13966-32-0)

Pentane (109-66-0)

d-Glucose (492-62-6)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

sodium hydride (7646-69-7)

potassium bicarbonate (298-14-6)

argon (7440-37-1)

triethyl phosphonoacetate (867-13-0)

Sodium periodate (7790-28-5)

diethyl L-tartrate

ethoxycarbonylmethylene-triphenylphosphorane (1099-45-2)

phosphorus pentoxide (1314-56-3)

D-mannitol (69-65-8)

p-toluenesulfonic acid monohydrate (6192-52-5)

2-O-Benzylglyceraldehyde

Propanal, 3-hydroxy-2-(phenylmethoxy)-, (R)-

2-Pentenoic acid, 5-hydroxy-4-(phenylmethoxy)-, ethyl ester, [R-(E)]- (119770-84-2)

(+)-2-O-Benzyl-L-threitol

2,3-O-isopropylideneglyceraldehyde (22323-80-4)

L-gulonolactone

(2S,4R)-4-hydroxyornithine

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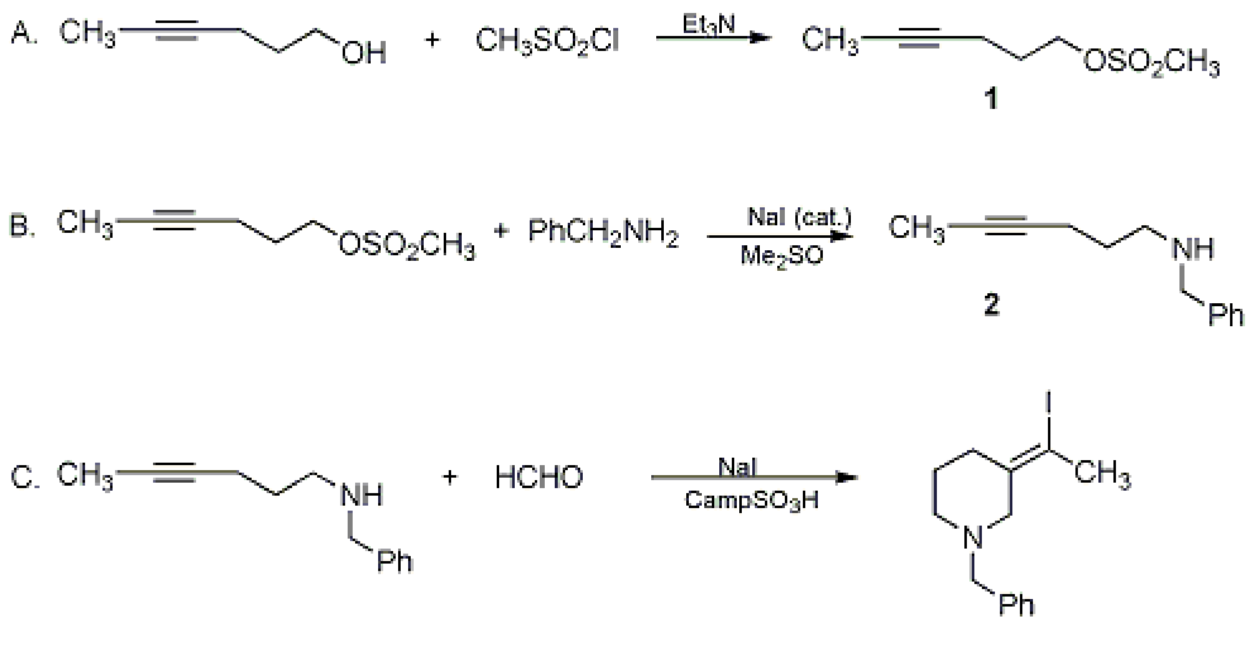
(E)-1-BENZYL-3-(1-IODOETHYLIDENE)PIPERIDINE: NUCLEOPHILE-PROMOTED ALKYNE-IMINIUM ION CYCLIZATIONS

[Piperidine, 3-(iodoethylidene)-1-(phenylmethyl)-(E)-]



Submitted by H. Arnold, L. E. Overman, M. J. Sharp, and M. C. Witschel[1].
Checked by Antje Grützmann, Thomas Hache, and Ekkehard Winterfeldt.

1. Procedure

A. *4-Hexyn-1-yl methanesulfonate* (**1**). An oven-dried, 500-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar is flushed with argon and 260 mL of dichloromethane is added (Note 1). The flask is sealed with a rubber septum inlet and cooled to ca. −10°C in an ice-salt bath. To this flask are added via syringe 11 mL (80 mmol) of triethylamine, 5.0 g (51 mmol) of 4-hexyn-1-ol (Note 2), and 4.3 mL (56 mmol) of methanesulfonyl chloride (Note 3). The resulting solution is stirred for an additional 30 min and then quenched by adding 30 mL of ice-water. The organic layer is separated and washed successively with 1 M hydrochloric acid solution (30 mL), saturated aqueous sodium bicarbonate solution (30 mL), and brine (30 mL). The organic layer is dried over magnesium sulfate, filtered, and concentrated with a rotary evaporator to give 8.3–9.0 g (93–100%) of crude 4-hexyn-1-yl methanesulfonate (**1**) which was used directly in the next step (Note 4).

B. *N-Benzyl-4-hexyn-1-amine* (**2**). An oven-dried, 100-mL, one-necked, round-bottomed flask containing a magnetic stirring bar and a rubber septum inlet is flushed with argon and charged with 200 mg of sodium iodide. The crude mesylate **1**, 40 mL of dimethyl sulfoxide (Note 5) and 10.9 g (102 mmol) of benzylamine are added via syringe. The resulting solution is heated in an oil bath at 47–53°C for 5 hr (Note 6) and then allowed to cool to room

temperature. The reaction solution is poured into a separatory funnel containing 200 mL of aqueous 1% sodium hydroxide solution and the resulting mixture is extracted with ether (3 × 100 mL). The combined ether extracts are washed with brine (50 mL), dried over magnesium sulfate, filtered, and concentrated with a rotary evaporator. The residue (ca. 9 g) is purified by flash chromatography (ca. 300 g of silica gel using 1:1 hexane-ether containing 5% triethylamine as the eluent) (Note 7) to give 7.2–7.5 g (75–79% overall) of **2** as a colorless liquid (Note 8).

C. *(E)-1-Benzyl-3-(1-iodoethylidene)piperidine* (**3**). A 250-mL, one-necked, round-bottomed flask containing a magnetic stirring bar and a reflux condenser topped with a rubber septum inlet is flushed with argon and charged with 4.0 g (21 mmol) of alkynylamine **2**, 11 g (73 mmol) of sodium iodide (Note 9), 35 mL of 37% w/w formaldehyde solution, 5.4 g (22 mmol) of camphorsulfonic acid monohydrate (Note 10) and 80 mL of water. The resulting mixture is heated at reflux under an argon atmosphere for 15 min (Note 11) and then allowed to cool to room temperature. This solution is made basic by adding 5 M aqueous potassium hydroxide solution and then poured into a separatory funnel where it is extracted with dichloromethane (3 × 50 mL) (Note 12). The combined organic layers are dried over sodium sulfate, filtered, and concentrated with a rotary evaporator. The resulting residue is purified by flash chromatography (ca. 150 g of silica gel, 1:1 hexane-ethyl ether containing 5% triethylamine as eluent) to give 5.4–6.2 g (79–90%) of **3** as a colorless oil (Note 13) and (Note 14).

2. Notes

1. Dichloromethane is distilled from calcium hydride (CaH_2) and added directly from the still to the reaction flask.
2. This alcohol is readily prepared in standard fashion from the tetrahydropyranyl ether of 4-pentyn-1-ol and iodomethane: A hexane solution of butyllithium (46 mL of a 2.2 M solution, 100 mmol) is added dropwise under an argon atmosphere to a dry ice-cooled solution of tetrahydro-2-(4-pentynyloxy)-2H-pyran (14.4 g, 84 mmol, prepared from commercially available 4-pentyn-1-ol[2]) in 100 mL of dry tetrahydrofuran. After 10 min, 7.0 mL (110 mmol) of iodomethane is added dropwise to the dry ice-cooled, stirring solution of the alkynyllithium intermediate. The reaction mixture is maintained at dry ice temperature for 1 hr, and, after warming to room temperature, the tetrahydrofuran is removed by mild rotary evaporation (or distillation at atmospheric pressure). The crude product is dissolved in 100 mL of ether and washed with brine (50 mL), and the aqueous phase is back-extracted with ether (25 mL). The combined organic phases are concentrated and the residue is dissolved in 200 mL of methanol. p-Toluenesulfonic acid (4 g) is added and the resulting solution is heated at reflux for 3 hr. The solvent is removed by distillation through an 8–10 cm Vigreux column, the residue is dissolved in 100 mL of ether and this solution is extracted with 25 mL of aqueous 10% sodium carbonate solution. After the solution is dried over $MgSO_4$, the solvent is removed by distillation and the residue is distilled through a 50-cm concentric tube column. The fraction boiling at 92–93°C (10 mm Hg) is collected to give 7.8 g (94%) of 4-hexyn-1-ol, which is >95% pure by GC analysis (30 m, Supelco SPB-5 capillary column).

3. Triethylamine, distilled from CaH_2, and methanesulfonyl chloride, vacuum distilled at ca. 60°C (20 mm), are employed.
4. The spectrum is as follows: ^1H NMR (300 MHz, $CDCl_3$) δ: 1.78 (t, 3 H, J = 2.5), 1.91 (apparent pentaplet, 2 H, J = 6.5), 2.25–2.35 (m, 2 H), 3.03 (s, 3 H), 4.35 (t, 2 H, J = 6.1).
5. Dimethyl sulfoxide, distilled at 20 mm from CaH_2, and benzylamine, freshly distilled at 20 mm, are employed.
6. The reaction is easily monitored by TLC (silica gel, 1:1 ether-ethyl acetate): mesylate R_f = 0.9, amine R_f = 0.4.
7. This material can also be purified by vacuum distillation; however, some decomposition results.
8. This material is 97% pure by capillary GC analysis (30 m, J & W DB-5 fused silica column). Spectral data are as follows: IR (film) cm^{-1}: 3330, 1453, 1120, 736; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.69 (apparent pentaplet, 2 H, J = 7), 1.77 (t, 3 H, J = 2.5), 2.15–2.25 (m, 2 H), 2.73 (t, 2 H, J = 7.0), 3.80 (s, 2 H), 7.2–7.4 (m, 5 H); MS (isobutane CI): 188 (MH), 172, 120, 91; high resolution MS (70 eV, EI) 187.1331 (187.1261 Calcd for $C_{13}H_{17}N$).
9. Fisher *Certified* sodium iodide is used as received.
10. Fisher *Certified* A.C.S. formaldehyde solution is used as received. Aldrich Chemical Company, Inc., camphorsulfonic acid monohydrate is recrystallized from ethyl acetate prior to use.
11. This conversion is easily monitored by TLC (silica gel, 1:1 hexane-ethyl acetate containing 5% triethylamine): **2**, R_f = 0.4, **3**, R_f = 0.7.
12. The free base of this iodoamine darkens slowly when exposed to room light. The isolation procedure should be conducted rapidly or the separatory funnel and rotary evaporator bulb should be wrapped in aluminum foil to exclude room light.
13. This material is at least 95% pure by capillary GC analysis (30 m, J & W DB-5 fused silica column); a small unknown impurity (ca. 2%) with characteristic ^1H NMR signals at δ 3.41, 4.77 and 4.92 is apparent in some chromatography fractions. Spectral data for **3** are as follows: IR (film) cm^{-1}: 1646, 1228, 1138, 1119, 1061, 739; ^1H NMR δ: 1.55–1.8 (m, 2 H), 2.40 (t, 2 H, J = 6.3), 2.45 (s, 3 H), 2.56 (t, 2 H, J = 5.5), 3.10 (s, 2 H), 3.57 (s, 2 H), 7.2–7.4 (m, 5 H); MS (isobutane CI): 328 (MH), 202, 200, 112, 110, 92. High resolution MS (70 eV, EI): 327.0465 (327.0484 calcd for $C_{14}H_{18}NI$).
14. The maleate salt is prepared in good yield and crystallizes as fine needles (ca. 1 g of salt/10 mL) from absolute ethanol: mp 143–144°C. This salt can be stored at room temperature in room light with no noticeable decomposition. Anal. Calcd. for $C_{18}H_{22}INO_4$: C, 48.77; H, 5.00; N, 3.16. Found: C, 48.70; H, 5.00; N, 3.09.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

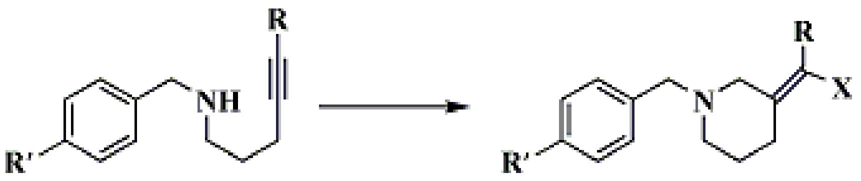
Simple alkynes do not undergo intramolecular reactions with weakly electrophilic iminium ions in the absence of strong external nucleophiles.[3] For example, the formaldiminium ion

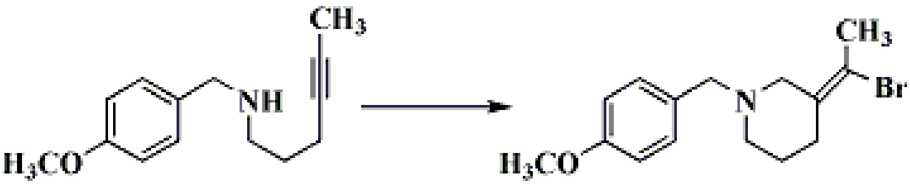
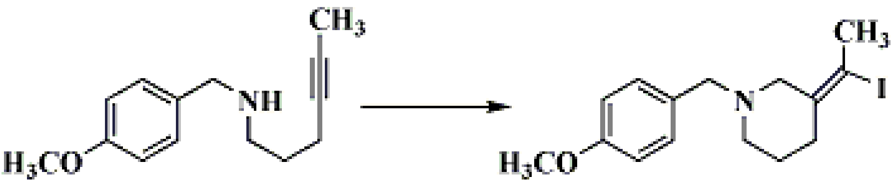
derived from 4-hexynylamine, formaldehyde, and camphorsulfonic acid does not cyclize when maintained in acetonitrile at 100°C for 1 hr.[3] Iminium ion-alkyne cyclizations do take place in nucleophilic solvents such as H_2O[4] or in non-nucleophilic solvents when a strong nucleophile is present.[3]

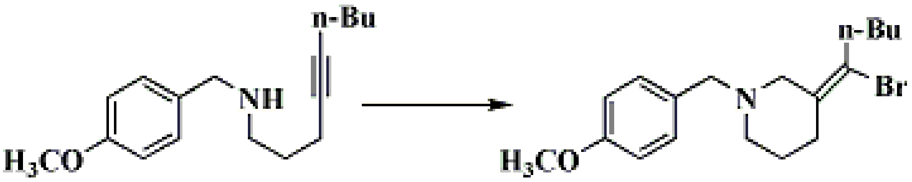
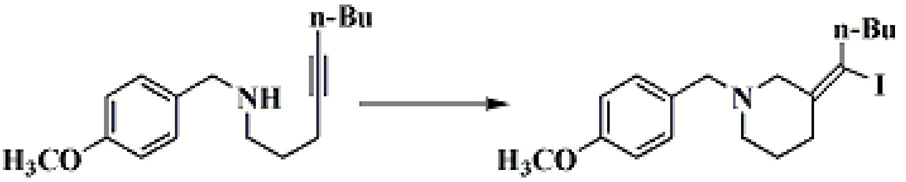
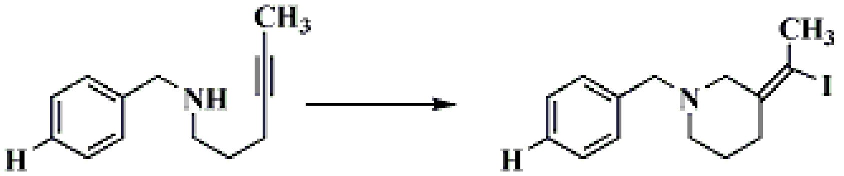
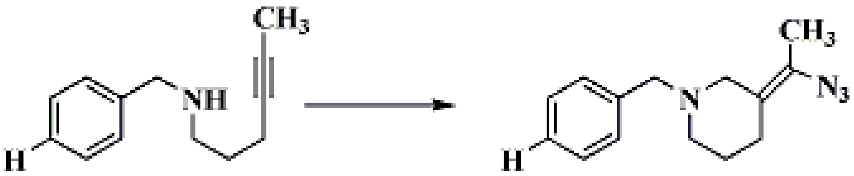
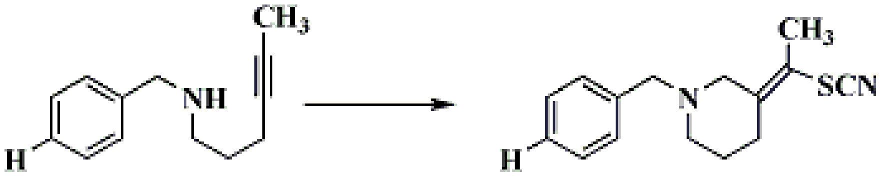
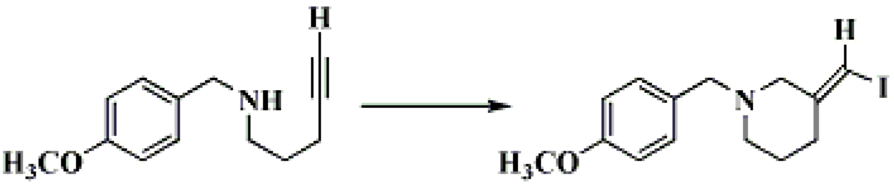
The present procedure illustrates the use of added iodide anion to promote the Mannich cyclization of an alkyne to afford 3-alkylidenepiperidines. As illustrated in Table I a variety of nonbasic nucleophiles with nucleophilic constants[5] η-CH_3I >5.8 are useful promoters of formaldiminium ion-alkyne cyclizations.[3] Piperidines containing both endocyclic and exocyclic allylic unsaturation can be efficiently assembled in this way from readily available alkynol precursors (see Table I).[3] To the limits of ^1H NMR detection at 500 MHz all nucleophile-promoted cyclizations that form 3-alkylidenepiperidines occur with complete anti-stereoselectivity.

TABLE I

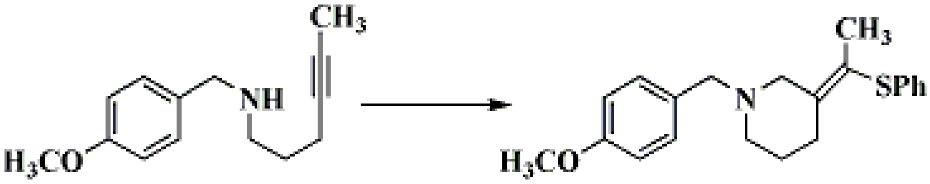
NUCLEOPHILE-PROMOTEDIMINIUMION-ALKYNECYCLIZATIONS[3]



R'	R	X	Yield
OCH_3	CH_3	Br	 89%
OCH_3CH_3	CH_3	I	 80%

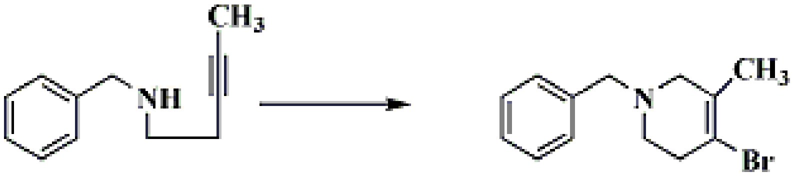
OCH_3	n-Bu	Br		63%[6]
OCH_3	n-Bu	I		76%[6]
H	CH_3	I		81-90%
H	CH_3	N_3		72%
H	CH_3	SCN		82%
OCH_3	H	I		56%

OCH_3 CH_3 SPh



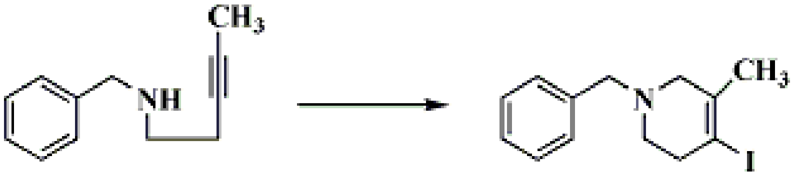
<15%

CH_3 Br



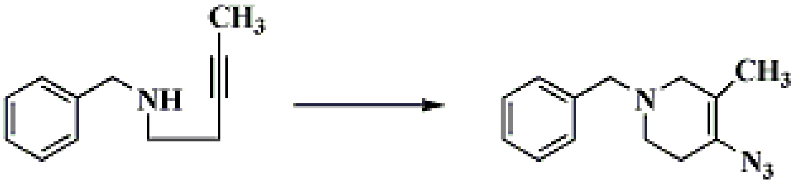
75%

CH_3 I



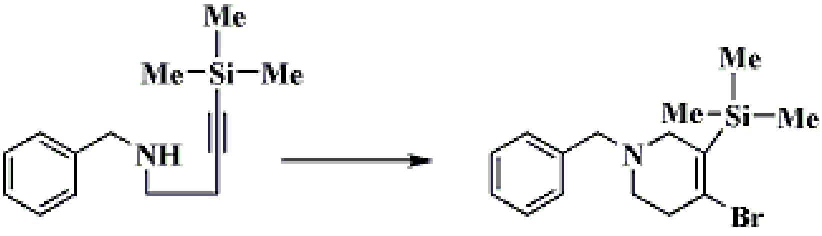
90%

CH_3 N_3



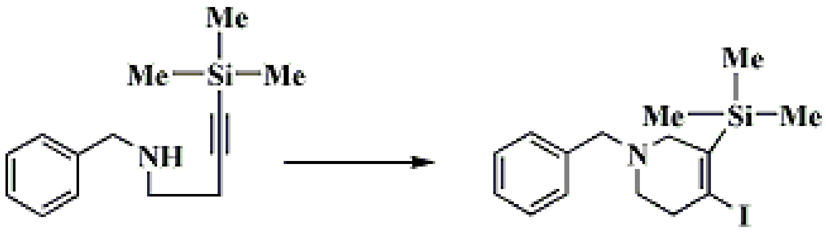
40%

Me_3Si Br



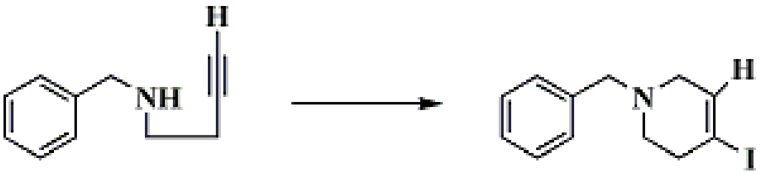
44%

Me_3Si I



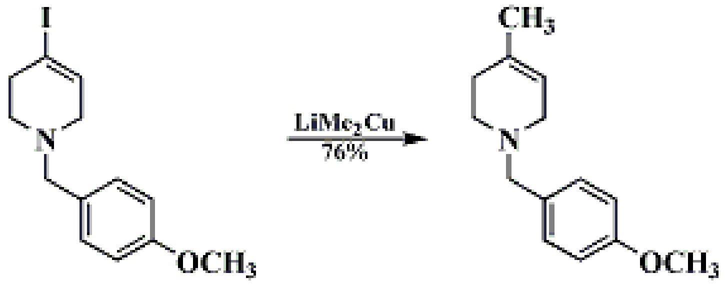
60%

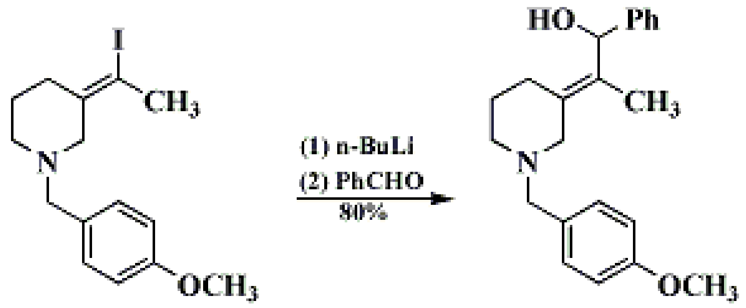
H I

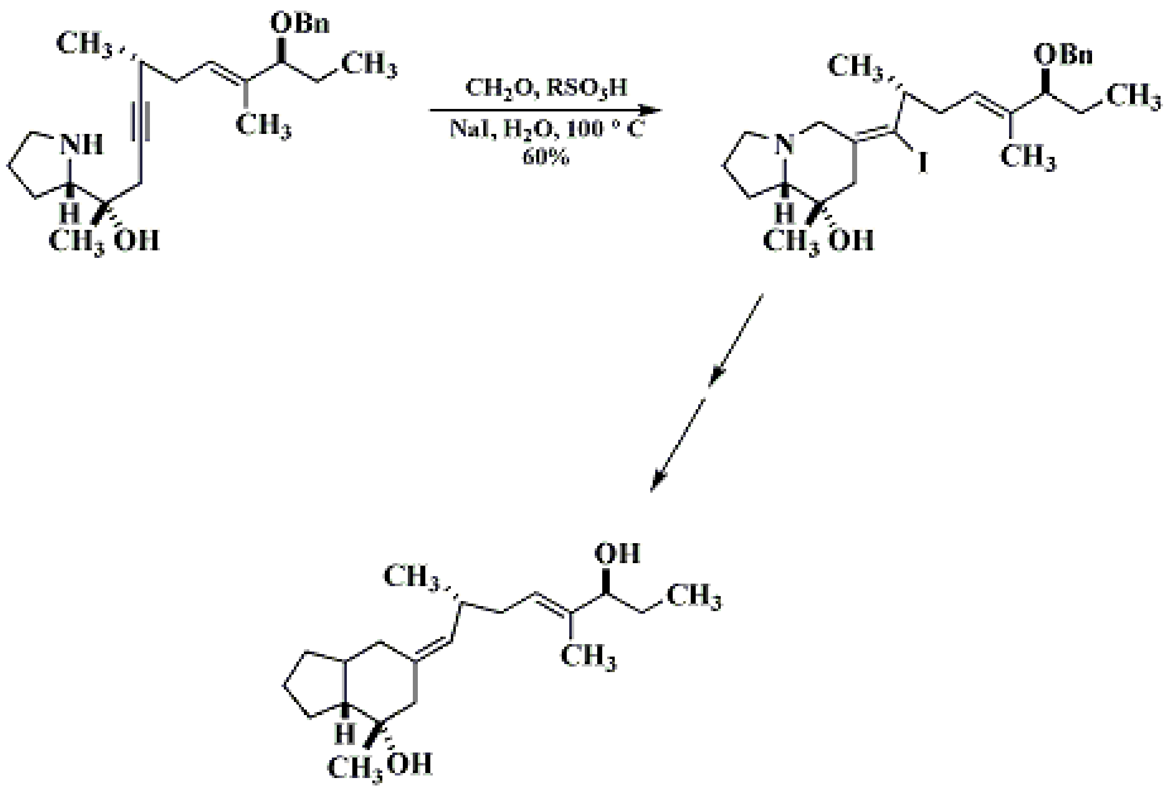


87%

The usefulness of nucleophile-promoted iminium ion-alkyne cyclizations derives from the ready availability of alkynylamines and the subsequent transformations of the cyclization products made possible because of their vinylic functionality (e.g., equations 1 and 2). Equation 2 illustrates use of this chemistry to elaborate an exocyclic tetrasubstituted double bond with complete stereocontrol. Net "reductive" iminium ion alkyne cyclizations can be accomplished by dehalogenation of vinyl halide cyclization products. The conversion illustrated in equation 3 is a key step in an efficient, practical synthesis of the cardiotonic frog alkaloid pumiliotoxin A.[7]







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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

brine

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether, ethyl ether (60-29-7)

acetonitrile (75-05-8)

sodium hydroxide (1310-73-2)

formaldehyde (630-08-0)

sodium bicarbonate (144-55-8)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

aluminum (7429-90-5)

potassium hydroxide (1310-58-3)

iodomethane (74-88-4)

sodium iodide (7681-82-5)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

benzylamine (100-46-9)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

hexane (110-54-3)

dimethyl sulfoxide (67-68-5)

triethylamine (121-44-8)

calcium hydride (7789-78-8)

Methanesulfonyl chloride (124-63-0)

mesylate (75-75-2)

4-Pentyn-1-ol (5390-04-5)

camphorsulfonic acid (5872-08-2)

argon (7440-37-1)

p-toluenesulfonic acid (104-15-4)

(E)-1-Benzyl-3-(1-iodoethylidene)piperidine (146980-71-4)

Piperidine, 3-(iodoethylidene)-1-(phenylmethyl)-(E)-

4-Hexyn-1-yl methanesulfonate (68275-05-8)

4-hexyn-1-ol (928-93-8)

N-Benzyl-4-hexyn-1-amine (112069-91-7)

camphorsulfonic acid monohydrate (5872-08-2)

tetrahydro-2-(4-pentynyloxy)-2H-pyran (62992-46-5)

iodoamine

4-hexynylamine

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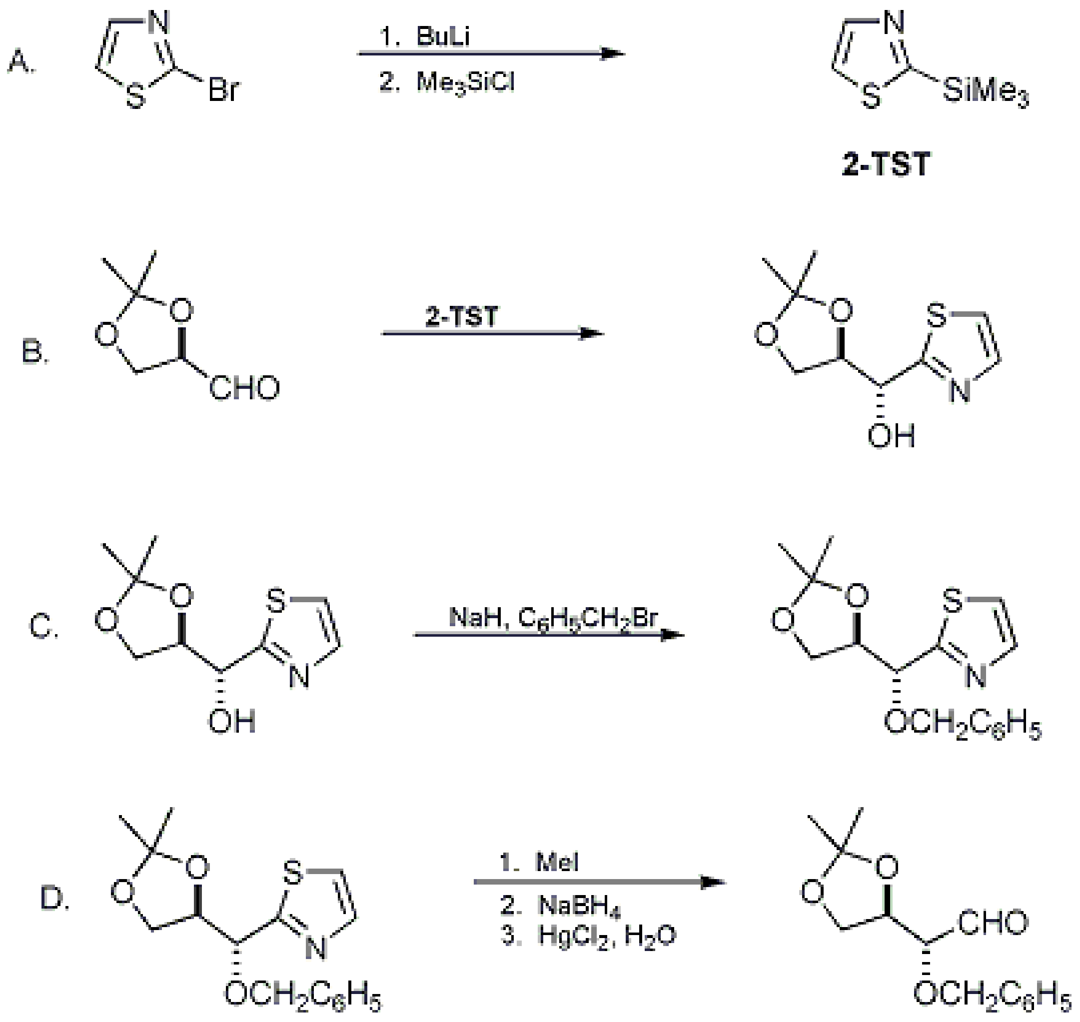
Organic Syntheses, CV 9, 52

DIASTEREOSELECTIVE HOMOLOGATION OF D-(R)-GLYCERALDEHYDE ACETONIDE USING 2-(TRIMETHYLSILYL)THIAZOLE: 2-O-BENZYL-3,4-ISOPROPYLIDENE-D-ERYTHROSE

[1,3-Dioxolane-4-acetaldehyde, 2,2-dimethyl- α-(phenylmethoxy)-, [R-(R*,R*)]-]



Submitted by Alessandro Dondoni and Pedro Merino[1].
Checked by Gregory P. Brengel and Albert I. Meyers.

1. Procedure

A. *2-(Trimethylsilyl)thiazole (2-TST)*. A 500-mL, four-necked, round-bottomed flask, containing a magnetic stirring bar, is equipped with two 100-mL, pressure-equalizing dropping funnels and a low-temperature thermometer (Note 1). The dry apparatus is filled with argon and kept under a slightly positive pressure (ca. 100 mm) of this gas for the entire reaction time. The flask is charged with 200 mL of freshly distilled

diethyl ether (Note 2) and 111 mL of a 1.5 M solution of butyllithium (0.167 mol) in hexane (Note 3) and (Note 4). One of the two dropping funnels is charged with 25 g (0.152 mol) of 2-bromothiazole (Note 5) in 50 mL of diethyl ether (Note 2) and the other with 16.5 g (0.152 mol) of chlorotrimethylsilane (Note 6) in 50 mL of diethyl ether (Note 2). The reaction flask is cooled to −78°C in a dry ice-acetone bath. While the solution in the flask is stirred, 2-bromothiazole is added dropwise over a period of 1 hr. After 20 min additional stirring, chlorotrimethylsilane is added dropwise over 30 min and stirring is continued for 1 hr at −78°C. The resulting mixture is then allowed to warm up to room temperature. A saturated aqueous sodium bicarbonate solution (200 mL) is added and the mixture is transferred into a 1-L separatory funnel. After the mixture is shaken, the organic layer is recovered and the aqueous layer is extracted with diethyl ether (200 mL). The combined organic layers are dried over anhydrous sodium sulfate, filtered, and concentrated at reduced pressure by rotary evaporation with the external bath temperature not higher than 40°C. The residue is distilled from a 100-mL flask at reduced pressure in a Claisen apparatus equipped with a 10-cm Vigreux column (Note 7). The distillation, after a forerun at 40–65°C (15 mm) consisting mainly of bromobutane, gives 20.2 g (85%) of 2-(trimethylsilyl)thiazole as a colorless liquid, bp 88–91°C (16–17 mm) (Note 8).

B. *(1R)-2,3-Di-O-isopropylidene-1-(2-thiazolyl)-D-glycitol*. A 100-mL, three-necked, round-bottomed flask, containing a magnetic stirring bar, is equipped with a 50-mL pressure-equalizing dropping funnel and a low-temperature thermometer (Note 1). The dry apparatus is filled with argon and kept under an inert gas pressure of ca. 100 mm for the entire reaction time. The flask is charged with 2.0 g (0.0154 mol) of D-glyceraldehyde acetonide (Note 9) in 25 mL of dichloromethane (Note 10) and the dropping funnel is filled with 2.4 g (0.0153 mol) of 2-TST in 25 mL of dichloromethane (Note 10). The reaction flask is cooled to 0°C in an ice bath. While the solution is stirred, 2-TST is added dropwise over a period of 15 min. After the reaction is stirred for 12 hr at room temperature, it is complete as shown by TLC (silica, diethyl ether – petroleum ether 1:1). Dichloromethane (ca. 40 mL) is removed under reduced pressure and the residue is treated with tetrabutylammonium fluoride (14 mL of a 1.1 M solution in tetrahydrofuran, 0.0154 mol) (Aldrich Chemical Company, Inc.) Desilylation is complete as shown by TLC (silica, diethyl ether – petroleum ether, 1:1) in 10 min. Volatile material is removed under reduced pressure and the residue is treated with 50–60 mL of water. The mixture is extracted with dichloromethane (3 × 50 mL) and the combined dichloromethane solutions are dried with anhydrous sodium sulfate. The solvent is removed under reduced pressure and the solid residue (3.14 g) is flash chromatographed (silica, diethyl ether – petroleum ether, 3:2) to give 2.85 g (84%) of the alcohol as a white solid, mp 114–116°C (from dichloromethane-hexane) (Note 11).

C. *(1R)-O-Benzyl-2,3-di-O-isopropylidene-1-(2-thiazolyl)-D-glycitol*. A 250-mL, two-necked, round-bottomed flask containing a magnetic stirring bar, is equipped with a 50-mL pressure-equalizing dropping funnel. The dry apparatus is filled with argon and kept under an inert gas pressure of ca. 100 mm greater than the atmosphere until the

aqueous work-up (Note 1). The flask is charged with 2.6 g (0.012 mol) of the alcohol (from Step B) in 100 mL of tetrahydrofuran (Note 12) and the dropping funnel is filled with 2.06 g (0.012 mol) of benzyl bromide (Note 13) in 10 mL of tetrahydrofuran (Note 12). Sodium hydride (0.0145 mol, 0.69 g of a 50% dispersion in oil) (Note 14) is added in portions to the flask and, after gentle reflux for 20 min, the mixture is cooled to room temperature and the solution of benzyl bromide is added dropwise via the addition funnel (10–15 min). Tetrabutylammonium iodide (0.48 g, 0.0013 mol) is added in one portion and the solution is stirred overnight at room temperature (Note 15). The solvent is removed under reduced pressure (water aspirator) and the residue is treated with 50 mL of saturated sodium chloride (NaCl) solution. The mixture is extracted with dichloromethane (3 × 50 mL) (dilution of the aqueous phase with water to avoid emulsions may be necessary) and the combined extracts are dried over anhydrous sodium sulfate. The solvent is removed under reduced pressure using a rotatory evaporator and the residue is flash chromatographed (silica, diethyl ether – petroleum ether 1:1) to give 3.53 g (96% yield) of product as an oil (Note 16).

D. *Thiazolyl-to-formyl deblocking*. The protected 1-(2-thiazolyl)-D-glycitol (3.5 g, 0.0115 mol) is dissolved in 70 mL of acetonitrile (Note 17), methyl iodide (24.7 g, 0.173 mol, purified by passing through neutral alumina) is added and the resulting mixture is heated to reflux until N-methylation of thiazole is complete (at least 24 hr) as shown by TLC (Note 15) and (Note 18). The solvent is removed under reduced pressure and the residue (Note 19) is dissolved in at least 70 mL of methanol. The solution is cooled to 0°C in an ice bath and sodium borohydride (0.65 g, 0.0172 mol) is added in portions while the solution is stirred vigorously. After the solution is stirred for 30 min at 0°C, it is treated with 2 mL of acetone, and the solvent is removed under reduced pressure. The residue is treated with a saturated solution of sodium chloride (50 mL) and extracted with dichloromethane (3 × 50 mL). The combined extracts are dried over anhydrous sodium sulfate and the solvent is removed under reduced pressure. The resulting oil (Note 20) is dissolved in acetonitrile (5 mL) and the solution is slowly added to a vigorously stirred solution of mercury chloride (3.7 g, 0.0136 mol) in a 4:1 mixture of acetonitrile – water (50 mL). After being stirred at room temperature for 15 min, the reaction mixture is filtered on a Büchner funnel through Celite and the sticky inorganic residue is rinsed with diethyl ether. The combined ethereal extracts are added to the filtered solution and the mixture is concentrated to ca. 10 mL by evaporation of the solvent under reduced pressure. The residue is treated with a saturated solution of potassium chloride (KCl) (50 mL), extracted with dichloromethane (3 × 50 mL), and the combined extracts are dried over anhydrous sodium sulfate (Note 21). Removal of volatile material under reduced pressure gives an oil that is flash chromatographed (silica, diethyl ether – petroleum ether 1:1) to afford 1.77 g (62%) of 2-O-benzyl-3,4-isopropylidene-D-erythrose (Note 22).

2. Notes

1. The glass components of the apparatus were dried overnight in a 150°C-oven and allowed to cool in a desiccator over a drying agent before assembly.
2. Diethyl ether was distilled from sodium wire under a nitrogen atmosphere immediately prior to use.
3. A 1.5 M solution of butyllithium in hexane was purchased from Aldrich Chemical Company, Inc. Aliquots were transferred to a 100-mL graduated cylinder, stoppered with a rubber septum using a 15-gauge cannula and argon.
4. The slight excess of butyllithium with respect to chlorotrimethylsilane is used to avoid acid-catalyzed protodesilylation of 2-TST during the work-up operations.
5. 2-Bromothiazole, available from Aldrich Chemical Company, Inc., was distilled prior to use.
6. Chlorotrimethylsilane was obtained from Fluka Chemical Corporation and distilled before use.
7. The Claisen distillation head was filled with glass wool to avoid formation of foam. The checkers found that constant heating of the distillation apparatus with a heat gun greatly facilitates the rate of distillation and minimizes the column holdup.
8. The product showed the following spectroscopic properties: ^{1}H NMR (80 MHz, $CDCl_3$, TMS) δ: 0.40 (s, 9 H), 7.40 (d, 1 H, J = 3.0), 8.01 (d, 1 H, J = 3.0); ^{13}C NMR (75.5 MHz, $CDCl_3$, TMS) δ: –1.20 (q), 121.3 (d), 145.8 (d), 174.3 (s). Other physical properties includes $n^{22.5}_D$ 1.4975 and d = 0.987.
9. The aldehyde was freshly distilled material prepared according to the *Organic Syntheses* procedure.[2]
10. Dichloromethane was freshly distilled under a nitrogen atmosphere from calcium hydride.
11. This product (anti-adduct) was ≥95% diastereomerically pure based on comparison of the ^{1}H NMR spectrum with that of the syn-adduct.[3] Physical properties and spectral data are as follows: $[\alpha]_D$ –1.2° to –1.5° (MeOH, *c* 1.0) ^{1}H NMR (80 MHz, $CDCl_3$-D_2O, TMS) δ: 1.40 (s, 3 H), 1.47 (s, 3 H), 4.0 (m, 2 H), 4.45 (m, 1 H), 5.07 (d, 1 H, J = 5.1), 7.30 (d, 1 H, J = 3.2), 7.73 (d, 1 H, J = 3.2); ^{13}C NMR (75.5 MHz, $CDCl_3$, TMS) δ: 25.16 (q), 26.69 (q), 65.38 (t), 71.77 (d), 78.42 (d), 110.54 (s), 120.33 (d), 142.96 (d), 170.95 (s).
12. Tetrahydrofuran was distilled from lithium aluminum hydride under a nitrogen atmosphere immediately prior to use.
13. Benzyl bromide was purchased from Aldrich Chemical Company, Inc., and purified by passing through neutral alumina.
14. Sodium hydride, 60% dispersion in mineral oil from Aldrich Chemical Company, Inc., was used as obtained.
15. The reaction appeared complete by TLC (silica, diethyl ether – petroleum ether, 1:1); R_f alcohol = 0.15, R_f O-benzyl derivative = 0.27.
16. Physical properties and spectral data are as follows: $[\alpha]_D$ +53.7° to +59.6° ($CHCl_3$, *c* 1.66); ^{1}H NMR (270 MHz, $CDCl_3$, TMS) δ: 1.34 (s, 3 H), 1.39 (s, 3 H), 4.02 (dd, 1 H, J = 4.9, 1.2), 4.52–4.70 (m, 3 H), 4.83 (d, 1 H, J = 5.5), 7.33–

7.35 (m, 5 H), 7.39 (d, 1 H, J = 3.2), 7.81 (d, 1 H, J = 3.2); ^{13}C NMR (75.5 MHz, $CDCl_3$, TMS) δ: 25.39 (q), 26.54 (q), 56.31 (t), 72.81 (t), 78.65 (d), 79.09 (d), 110.67 (s), 120.73 (d), 128.74 (d), 128.86 (d), 129.20 (d), 138.0 (s), 143.5 (s) 170.55 (s).

17. Reagent grade acetonitrile from Carlo Erba was used as obtained.

18. The R_f of the N-methylthiazolium salt is zero.

19. A sample of this material obtained in a separate experiment was crystallized from methanol – diethyl ether to give the pure N-methylthiazolium iodide as white crystals, mp 181–183°C (dec); ^{1}H NMR (80 MHz, CD_3OD, TMS) δ: 1.33 (s, 3 H), 1.51 (s, 3 H), 3.95–4.51 (m, 3 H), 4.17 (s, 3 H), 4.79 (br d, 2 H), 5.36 (d, 1 H, J = 7.2), 7.34 (s, 5 H), 8.27 (m, 2 H).

20. A sample of this material obtained in a separate experiment was purified by chromatography (silica, dichloromethane – diethyl ether 85:5) to give the pure thiazolidine as 1:1 mixture of diastereoisomers : oil; ^{1}H NMR (80 MHz, $CDCl_3$, TMS) δ: 1.36 (s, 3 H), 1.42 (s, 3 H), 2.31 (s, 1.5 H), 2.33 (s, 1.5 H), 2.77–3.25 (m, 4 H), 3.66 (m, 1 H), 3.90–4.55 (m, 4 H), 4.77 (s, 2 H), 7.32 (s, 5 H).

21. The solid residue contains mercury salts and should be disposed of by procedures used for heavy metal residues.

22. The product showed the following properties: oil; $[\alpha]_D$ +36.8° to +37.1° ($CHCl_3$, *c* 1.70); IR (film) cm^{-1}: 2720, 1734; ^{1}H NMR (270 MHz, $CDCl_3$, TMS) δ: 1.35 (s, 3 H), 1.43 (s, 3 H), 3.81 (dd, 1 H, J = 6.8, 2.5), 3.92 (dd, 1 H, J = 6.1, 9.6), 4.07 (dd, 1 H, J = 9.2, 7.3), 4.35 (m, 1 H), 4.67 (AB quartet, 2 H, J = 11.6), 7.3–7.38 (m, 5 H), 9.70 (d, 1 H, J = 2.5); ^{13}C NMR (75.5 MHz, $CDCl_3$, TMS) δ: 25.22 (q), 26.55 (q), 66.37 (t), 73.51 (t), 75.22 (d), 83.31 (dd), 110.24 (s), 128.38 (d), 128.75 (d), 137.23 (s), 201.4 (d).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995. See (Note 21).

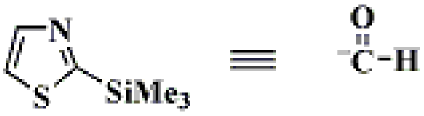
3. Discussion

2-(Trimethylsilyl)thiazole (2-TST)[4] is used as a stable and convenient substitute for 2-lithiothiazole for introducing various substituents at C-2 of the thiazole ring (f. htmigure 1). Reactions of 2-TST with various carbon electrophiles[5] occur readily under mild conditions without the need for any catalyst to give the corresponding 2-substituted thiazoles in fair yields. As has been already pointed out,[5] the multigram preparation of 2-TST from 2-bromothiazole via halogen-metal exchange is much more convenient and practical than the procedure[6] employing the highly volatile and expensive unsubstituted thiazole.

Figure 1. Synthesis of 2-Substituted Thiazoles from 2-TST

Figure 1. Synthesis of 2-Substituted Thiazoles from 2-TST

The procedure presented here illustrates the use of 2-TST as a one-carbon homologating reagent of a chiral α,β-dialkoxy aldehyde.[3,7] The protocol is based on three essential key operations, i.e., the anti-stereoselective addition (ds ≥ 95%) of 2-TST to the aldehyde (Step B), the protection of the hydroxy group at the newly formed stereogenic center (Step C), and the liberation of the formyl group from the thiazole ring (Step D). This step involves a sequence of three reactions (N-methylation of the thiazole ring, reduction, and hydrolysis) that occurs under almost neutral conditions and leaves unaltered the asymmetric centers in the chiral compounds. The procedure for the N-methylation appears more practical than an earlier method[8] employing trimethyloxonium fluoroborate in liquid sulfur dioxide.[9] Overall, 2-TST appears to serve as an equivalent to the formyl anion synthon. The iterative application of this principle over several consecutive cycles produces a series of homologues of D-glyceraldehyde up to a nine-carbon chain and with an all-*anti* configuration of the vicinal hydroxy groups.[3] This linear iterative one-carbon extension technology was successfully applied to L-threose acetonide,[3] dialdoses,[3,10] and α-amino aldehydes.[11]



2-TST

Although various compounds are known to act as synthetic equivalents to the formyl anion synthon,[12] the advantages that appear to be associated with the use of 2-TST warrant comment. First, 2-TST is a readily available, relatively cheap, and storable reagent; second, it reacts promptly and stereoselectively with aldehydes under neutral conditions; third, it gives high yields of products that are stable to isolation and purification and nevertheless can be readily transformed into aldehydes.

This preparation is referenced from:

- Org. Syn. 77, 78

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

D-glyceraldehyde acetonide

(1R)-2,3-Di-O-isopropylidene-1-(2-thiazolyl)-D-glycitol

(1R)-O-Benzyl-2,3-di-O-isopropylidene-1-(2-thiazolyl)-D-glycitol

2-O-Benzyl-3,4-isopropylidene-D-erythrose

D-(R)-GLYCERALDEHYDE ACETONIDE

1,3-Dioxolane-4-acetaldehyde, 2,2-dimethyl- α-(phenylmethoxy)-, [R-(R*,R*)]-

2-(Trimethylsilyl)thiazole (2-TST)

Thiazolyl-to-formyl deblocking

1-(2-thiazolyl)-D-glycitol

L-threose acetonide

methanol (67-56-1)

diethyl ether (60-29-7)

acetonitrile (75-05-8)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

sulfur dioxide (7446-09-5)

bromobutane (109-65-9)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

acetone (67-64-1)

sodium (13966-32-0)

hydroxy (3352-57-6)

mercury chloride (7487-94-7)

Methyl iodide (74-88-4)

dichloromethane (75-09-2)

potassium chloride (7447-40-7)

D-glyceraldehyde (56-82-6)

benzyl bromide (100-39-0)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

thiazole (288-47-1)

sodium hydride (7646-69-7)

hexane (110-54-3)

calcium hydride (7789-78-8)

sodium borohydride (16940-66-2)

argon (7440-37-1)

trimethyloxonium fluoroborate (420-37-1)

CHLOROTRIMETHYLSILANE (75-77-4)

Tetrabutylammonium fluoride (429-41-4)

tetrabutylammonium iodide (311-28-4)

2-(Trimethylsilyl)thiazole (79265-30-8)

2-bromothiazole (3034-53-5)

N-methylthiazolium

N-methylthiazolium iodide

thiazolidine (504-78-9)

2-lithiothiazole

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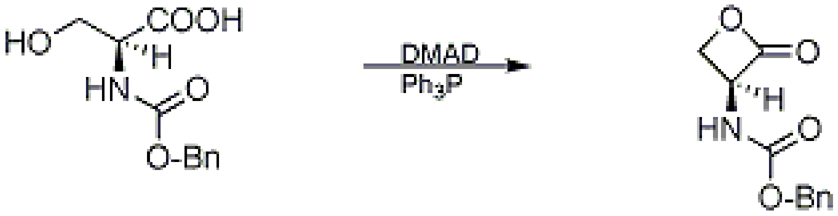
Organic Syntheses, CV 9, 58

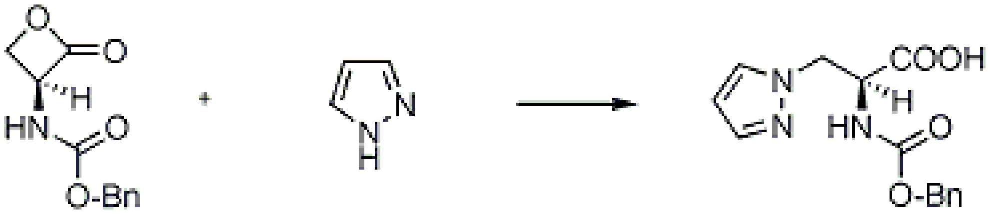
SYNTHESIS OF N-PROTECTED α-AMINO ACIDS FROM N-(BENZYLOXYCARBONYL)-L-SERINE VIA ITS β-LACTONE: Nα-(BENZYLOXYCARBONYL)-β-(PYRAZOL-1-YL)-L-ALANINE

[Serine, N-carboxy-, β-lactone, benzyl ester, L-]

A.



B.



Submitted by Sunil V. Pansare, Gregory Huyer, Lee D. Arnold, and John C. Vederas[1].
Checked by M. Jones, G. L. Olson, and David L. Coffen.

1. Procedure

A. *N-(Benzyloxycarbonyl)-L-serine β-lactone*.[2] [3] A 2-L, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, an argon inlet adaptor, a low temperature thermometer, and a rubber septum (Note 1). The flask is charged with tetrahydrofuran (1.1 L) and triphenylphosphine (42.1 g, 160 mmol, (Note 2)). The triphenylphosphine is dissolved with stirring and the flask is then cooled to −78°C with a dry ice-acetone bath (Note 3). Distilled dimethyl azodicarboxylate (17.7 mL, 160 mmol, d = 1.33 g/mL at 25°C) is added dropwise with a syringe over 10 min (*Caution*, (Note 4)). The resulting pale yellow solution is stirred at −75° to −78°C for 10 min, at which point a milky white slurry is obtained. The rubber septum on the flask is quickly replaced with a 1-L, pressure-equalizing dropping funnel containing a solution of N-(benzyloxycarbonyl)-L-serine (38.3 g, 160 mmol) in tetrahydrofuran (240 mL), (Note 2), (Note 5) which is added dropwise to the mixture over 30 min. After completion of the addition, the mixture is stirred at −75° to −77°C for 20 min, the cooling bath is removed, and the mixture is slowly warmed with stirring to room temperature over 2.5 hr (Note 6). The solvent is removed on a rotary evaporator at 35°

C. The residual pale yellow syrup is dried briefly (15 min) under high vacuum (0.2 mm) and suspended in hexane/ethyl acetate (4/1, 20 mL). Ethyl acetate (30 mL) is added to give a solution which is applied to a 10 × 23-cm column of flash silica gel[4] (800 g) packed in hexane/ethyl acetate (4/1). The flask and the sides of the column are rinsed with additional ethyl acetate (20 mL), and this is added to the column which is then eluted with hexane/ethyl acetate (4/1, 2.6 L). The solvent is changed to hexane/ ethyl acetate (3/2) and 500-mL fractions are collected. Concentration of fractions 6–10 on a rotary evaporator gives 15.5 g (44%) of analytically pure N-(benzyloxycarbonyl)-L-serine β-lactone (Note 7). Fractions 11–14 contain slightly impure β-lactone. The solid obtained from concentration of these fractions on a rotary evaporator is dissolved in dichloromethane (50 mL) and precipitated by addition of hexane (50 mL) followed by cooling to −20°C (0.5 hr). The process is repeated twice to afford additional β-lactone (1.25 g). The total yield is 16.8 g (47%) (Note 8).

B. *N^{α}-(Benzyloxycarbonyl)-β-(pyrazol-1-yl)-L-alanine.*[2,3,5 6 7] A 500-mL, single-necked, round-bottomed flask is equipped with a magnetic stirring bar, a rubber septum and an argon inlet (Note 1). The flask is charged with N-(benzyloxycarbonyl)-L-serine β-lactone (15 g, 68 mmol) and anhydrous acetonitrile (240 mL, (Note 2)). The cloudy mixture is stirred and solid pyrazole (4.9 g, 72 mmol) (Note 9) is added. The rubber septum is quickly replaced with a reflux condenser and an argon inlet adaptor, and the reaction mixture is heated in an oil bath at 52–54°C for 24 hr. The solvent is removed on a rotary evaporator to leave a white solid that is dried under vacuum for 30 min. Sodium hydroxide (1 N, 69 mL) is added, the suspension is diluted with distilled water (350 mL) and the mixture is stirred vigorously for 5 min. It is then extracted with dichloromethane (3 × 100 mL) to remove unreacted pyrazole and side products. The aqueous phase is cooled in an ice bath to ca. 4°C, and concentrated hydrochloric acid is added with stirring to bring the pH to 1 (about 10 mL required). The resulting precipitate is filtered, washed with water (ca. 75 mL), air dried, and then completely dried in a desiccator over phosphorus oxide (P_2O_5) at 0.2 mm for 12 hr. This material is recrystallized from ethyl acetate (350 mL) to give 7.3 g of pure product (37% yield). Concentration of the mother liquor on a rotary evaporator and recrystallization from the minimum volume of ethyl acetate gives an additional 1.1 g of analytically pure N^{α}-(benzyloxycarbonyl)-β-(pyrazol-1-yl)-L-alanine. The total yield is 8.4 g (43%) (Note 10).

2. Notes

1. The glass components of the apparatus are dried overnight in a 120°C oven, and then assembled and maintained under an atmosphere of dry argon or nitrogen before use. It is essential to complete the purification of the β-lactone as rapidly as possible because this compound is unstable in the crude reaction mixture.
2. Triphenylphosphine (obtained from General Intermediates of Canada) and N-(benzyloxycarbonyl)-L-serine (obtained from Sigma Chemical Company) were

dried under reduced pressure over P_2O_5 for 72 hr and 24 hr, respectively. Acetonitrile was refluxed over calcium hydride (CaH_2) for ca. 10 hr and distilled from CaH_2 before use. Tetrahydrofuran was distilled from sodium benzophenone ketyl directly into the glassware (under argon) the day before and stored under argon overnight until used.

3. The temperature of the solution should be about −75°C before dimethyl azodicarboxylate is added.

4. Dimethyl azodicarboxylate (manufactured by Tokyo Kasei Kogyo Co., Japan) was purchased from CTC Organic, 792 Windsor Street, Atlanta, GA 30315. (See warning, p. 837.htm). *Overheating of dimethyl azodicarboxylate should be avoided because of the danger of explosion*. Distillation should be conducted from a temperature-controlled bath in the hood behind a safety shield. The material used distilled at 71–72°C (2 mm), at a bath temperature of 84–86°C. It is important that the addition of this compound to the reaction mixture be carried out at a constant rate without interruption because it tends to freeze in the syringe needle. The checkers explored the use of diethyl azodicarboxylate because of its lower cost and wider availability. However, the corresponding hydrazine derivative is more difficult to separate from the β-lactone product of this step. The use of a very slight excess of azodicarboxylate ester (a few percent relative to triphenylphosphine) prevents reaction of triphenylphosphine with the β-lactone product.[8]

5. The solution of dried N-(benzyloxycarbonyl)-L-serine was made up separately in an addition funnel under an atmosphere of argon. This avoids complications that may arise if the funnel is prefitted on the reaction vessel.

6. The reaction vessel was placed in a water bath at room temperature after the temperature of the mixture was ca. 15°C.

7. The reaction usually works better on a small scale (25 mmol) and a yield of 60% or more is usually obtained. The flash chromatography column was eluted so that the solvent level dropped 1 cm/13 sec. This corresponds to an approximate rate of 362 mL/min. The concentration and purification of the reaction mixture should be carried out as quickly as possible on the same day. Although storage of the concentrated reaction mixture at −20°C overnight results in substantial decomposition of the β-lactone, column fractions containing pure β-lactone (after chromatography) can be stored at 4°C overnight and concentrated on the following day.

The β-lactone is readily visualized by TLC (Merck, Kieselgel 60 F_{254}, 0.25-mm thickness, hexane/ethyl acetate (55/45) as solvent system) under UV, or by using bromocresol green spray (0.04% in EtOH, made blue by NaOH) followed by heating of the plate to detect the β-lactone as a yellow spot on a blue background.

8. The product exhibits the following properties: mp 133–134°C; $[\alpha]_D^{22}$ −26.5° (CH_3CN, *c* 1); IR cm^{-1}: 3355, 1847, 1828, 1685, 1530, 1268; ^1H NMR (360 MHz, CD_2Cl_2) δ: 4.4 (m, 2 H, CH-CH_2-O), 5.0–5.1 (m, 1 H, N-CH-CO), 5.12 (s, 2 H, OCH_2Ph), 5.5–5.7 (br, s, 1 H, NH), 7.3–7.4 (s, 5 H, ArH); EI-MS: M^+

221.0681 (221.0688 calcd for $C_{11}H_{11}NO_4$). Anal. Calcd for $C_{11}H_{11}NO_4$: C, 59.71; H, 4.97, 6.33. Found: C, 59.66; H, 4.92; N, 6.32.

The optical purity was determined as previously described,[3] and corresponds within experimental error to that of the starting material. N-(Benzyloxycarbonyl)-L-serine obtained from Sigma typically contains 0.75–2.80% of the D-isomer.

9. Pyrazole was obtained from Aldrich Chemical Company, Inc.

10. The reaction usually is more successful on a smaller scale and yields up to 70% can be obtained. The product exhibits the following properties: mp 168–169°C, $[\alpha]_D^{22}$ –53.5°; (DMF, *c* 1); IR (KBr disc) cm^{-1}: 3350, 1745, 1696, 1534, 1260; ^1H NMR (360 MHz, CD_3OD) δ: 4.4–4.5 (m, 1 H, CH), 4.60–4.70 (m, 2 H, CH_2N), 5.08 (s, 2 H, OCH_2Ph), 6.25 (t, 1 H), 7.3 (s, 5 H, -Ph), 7.48 (d, 1 H), 7.52 (d, 1 H); MS: FAB MS in glycerol m/z 290 (MH^+, 36%). Anal. Calcd for $C_{14}H_{15}N_3O_4$: C, 58.13; H, 5.23; N, 14.53. Found: C, 57.86; H, 5.25; N, 14.36.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

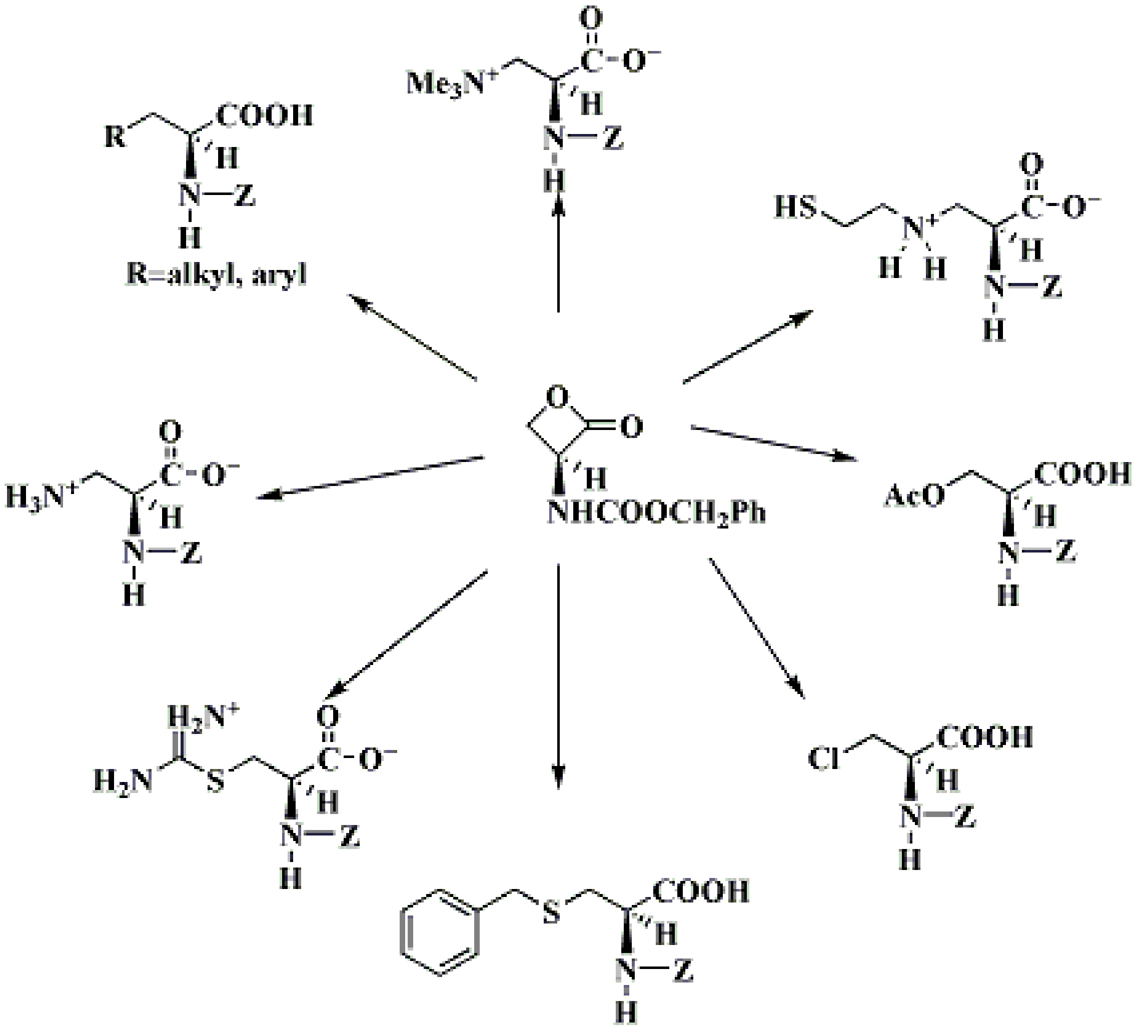
3. Discussion

A large number of α-amino acids with interesting biological properties occur in nature.[9 10 11] This fact, together with the utility of amino acids as chiral synthons, catalysts, and auxiliaries,[12 13 14] has stimulated extensive interest in their chemical synthesis.[15] Serine is an especially attractive starting material for preparation of other amino acids because both enantiomers are commercially available (in both free and various N-protected forms) with high optical purity at relatively low cost. Recent work has shown that chiral N-protected serine β-lactones are readily formed under modified Mitsunobu conditions and that they react readily with a variety of carbon, nitrogen, oxygen, sulfur, and halogen nucleophiles to afford optically pure N-protected α-amino acids (Scheme 1).[2,3,16 17]

The procedure given here describes the preparation and use of N-(benzyloxycarbonyl)-L-serine β-lactone for the synthesis of a protected β-substituted alanine, N^{α}-(benzyloxycarbonyl)-β-(pyrazol-1-yl)-L-alanine. This compound occurs in watermelon seeds,[18] and has been used as a histidine analog.[6] Its synthesis illustrates how serine β-lactones can provide convenient access to other β-substituted alanines such as mimosine, willardiine, quisqualic acid, and stizolobic acid which occur in higher plants.[9,19] Many previous chemical syntheses of racemic pyrazolylalanine have been published; the best of these routes appear to be from acetamidoacrylic acid (94–96% yield)[20] and from O-acetylserine (40–45%).[7] The racemate has been resolved.[6] The β-(pyrazol-1-yl)-L-alanine synthase enzyme has been purified and used to make the

chiral material from O-acetyl-L-serine.[21]

The crystalline N-(benzyloxycarbonyl)-serine β-lactone is easily handled in air at room temperature and can be stored dry at −20°C for many months without decomposition. Solutions of this compound in non-nucleophilic organic solvents (e.g., chloroform, ethyl acetate) or in neutral or slightly acidic water (pH 3–6) are stable for several days. Aqueous base rapidly hydrolyzes the β-lactone.[3,16,17]



Scheme 1

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 24

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

N^{α}-(Benzyloxycarbonyl)-β-(pyrazol-1-yl)-L-alanine

sodium benzophenone ketyl

quisqualic acid

stizolobic acid

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

acetonitrile (75-05-8)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

oxygen (7782-44-7)

nitrogen (7727-37-9)

sulfur (7704-34-9)

carbon (7782-42-5)

dichloromethane (75-09-2)

bromocresol

Tetrahydrofuran (109-99-9)

diethyl azodicarboxylate (1972-28-7)

hexane (110-54-3)

pyrazole (288-13-1)

calcium hydride (7789-78-8)

triphenylphosphine (603-35-0)

argon (7440-37-1)

dimethyl azodicarboxylate (2446-84-6)

phosphorus oxide (1314-56-3)

N-(BENZYLOXYCARBONYL)-L-SERINE (1145-80-8)

pyrazolylalanine

acetamidoacrylic acid (5429-56-1)

O-acetylserine, O-acetyl-L-serine (5147-00-2)

N-(Benzyloxycarbonyl)-L-serine β-lactone, N-(benzyloxycarbonyl)-serine β-lactone, Serine, N-carboxy-, β-lactone, benzyl ester, L- (26054-60-4)

β-(pyrazol-1-yl)-L-alanine

mimosine

willardiine

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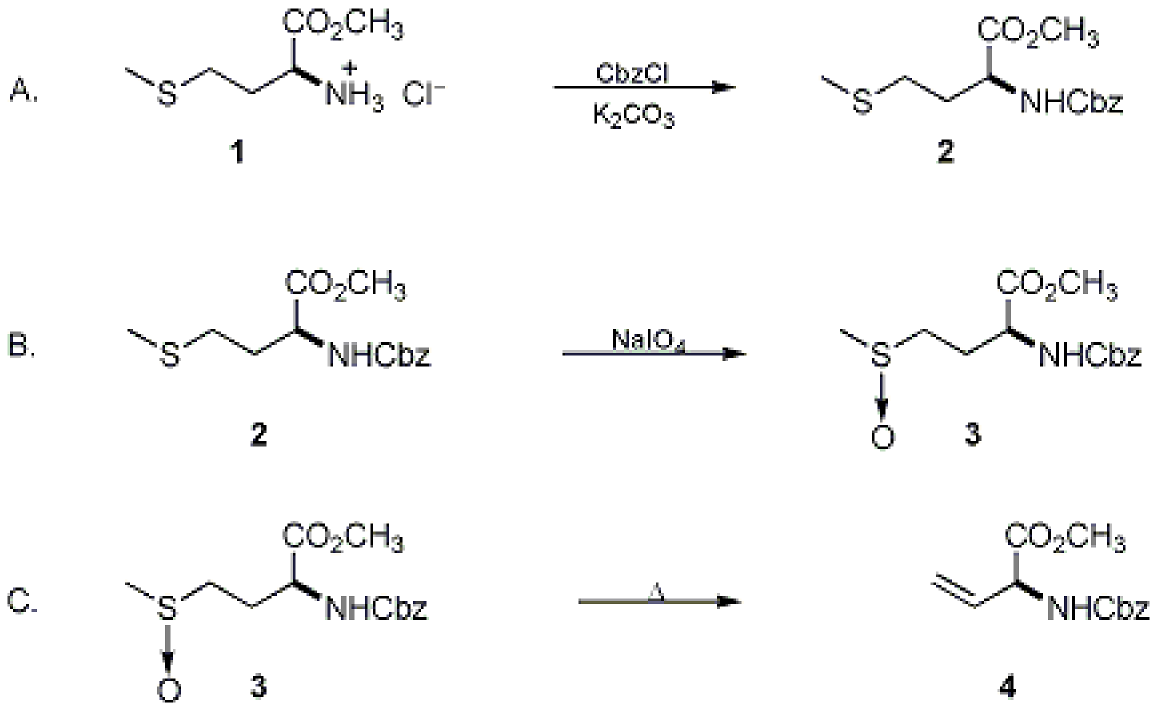
N-(BENZYLOXYCARBONYL)-L-VINYLGLYCINE METHYL ESTER

[3-Butenoic acid, 2-[[(phenylmethoxy)carbonyl]amino]-, methyl ester, (S)-]



Submitted by Michael Carrasco, Robert J. Jones, Scott Kamel, H. Rapoport[1], and Thien Truong.
Checked by Antje Grützmann and Ekkehard Winterfeldt.

1. Procedure

A. *N-(Benzyloxycarbonyl)-L-methionine methyl ester* **(2)**. A 3-L, three-necked, Morton flask equipped with an efficient mechanical stirrer, thermometer, and a dropping funnel is charged with L-methionine methyl ester hydrochloride (117.6 g, 0.56 mol) (Note 1), potassium bicarbonate (282.3 g, 2.82 mol, 500 mol %), water (750 mL), and ether (750 mL), and the solution is cooled to 0°C. Benzyl chloroformate (105 g, 88.6 mL, 0.62 mol, 110 mol %, Aldrich Chemical Company, Inc.) is added dropwise over 1 hr, the cooling bath is removed, and the solution is stirred for 5 hr. Glycine (8.5 g, 0.11 mol, 20 mol %, Aldrich Chemical Company, Inc.) is added (to scavenge excess chloroformate) and the solution is stirred for an additional 18 hr. The organic layer is separated, and the aqueous layer is extracted with ether (2 × 200 mL). The combined organic layers are washed with 0.01 M hydrochloric acid (2 × 500 mL), water (2 × 500 mL), and saturated brine (500 mL), and then dried (Na_2SO_4), filtered, and evaporated on a rotary evaporator. The resulting oil is further dried in a Kugelrohr oven (50°C, 0.1

mm, 12 hr) to leave product **2** as a clear oil that solidifies upon cooling: 165–166 g (98–99%), mp 42–43°C.

B. *Methyl L-2-(benzyloxycarbonylamino)-4-(methylsulfinyl)butanoate* **(3)**. A 5-L, three-necked, Morton flask equipped with an efficient mechanical stirrer, thermometer, and dropping funnel is charged with 2 (166.0 g, 0.56 mol) and methanol (1.5 L), and the solution is cooled to 0°C. A solution of sodium periodate ($NaIO_4$) (131.4 g, 0.61 mol, 110 mol %) in water (2 L) is added dropwise over a period of 1.5 hr. The cooling bath is removed and the mixture is stirred for 18 hr. The product is vacuum-filtered through Celite and divided into two portions. Each portion is extracted with chloroform (6 × 200 mL), washed with water (300 mL) and brine (300 mL), dried (Na_2SO_4), filtered, and evaporated by rotary evaporation (bath temperature <30°C). The resulting oils are combined and further dried in a Kugelrohr oven (30°C, 0.1 mm, 12 hr), yielding the product as a waxy solid: 173.2 g, 99%.

C. *N-(Benzyloxycarbonyl)-L-vinylglycine methyl ester* **(4)**. Sulfoxide 3 (35.0 g, 0.11 mol) and Pyrex helices (35 g) are placed in a 1-L, round-bottomed flask, thoroughly mixed by shaking, and distilled from a preheated rocking Kugelrohr apparatus (195–200°C, 0.1–0.3 mm, 1 hr) into a chilled receiving flask cooled in powdered dry ice to afford a yellow oil (Note 2) and (Note 3). Low pressure chromatography (LPC) of the crude oil gives the N-protected vinylglycine methyl ester **4** (17.4 g, 62%) of 95% purity (Note 4) and (Note 5). Medium pressure liquid chromatography (MPLC) of the crude oil provides pure **4** in 60% yield from **3** (Note 6). L-Vinylglycine hydrochloride can be obtained from **4** in almost quantitative yield by refluxing in 6 N hydrochloric acid for 1 hr.[2]

2. Notes

1. L-Methionine methyl ester hydrochloride is commercially available (Aldrich Chemical Company, Inc.); however, it is prepared easily as follows: A 3-L, three-necked, Morton flask is equipped with an efficient mechanical stirrer. The flask is charged with L-methionine (100.0 g, 0.67 mol) and methanol (0.7 L), the solution is cooled to 0°C, and hydrogen chloride gas is bubbled through the mixture for 15 min (in about 2 min the solution becomes homogeneous). The cooling bath is removed, the solution is stirred for 18 hr, and the solvent is evaporated. Further drying under reduced pressure gives L-methionine methyl ester hydrochloride as a white solid (132.5 g, 99%), that is suitable for most purposes. It can be recrystallized by dissolving in hot methanol (500 mL) and precipitating with ether (1 L) to give the pure hydrochloride: 117.6 g, 88%, mp 152–153°C.
2. *Caution: Stench. The entire reaction apparatus—Kugelrohr oven, vacuum pump, and subsequent chromatography—should be kept in an efficient fume hood.*
3. TLC of the distillate shows **4** (2/1, hexanes/ethyl acetate; visualization by staining with 5% ethanolic molybdophosphoric acid and charring) as the major

product (R_f 0.37) along with minor amounts of the (E)- and (Z)-α,β-unsaturated isomer (R_f 0.40 and 0.30).

4. LPC conditions are as follows: 9-cm diameter column; 800 mL of 230–400 mesh EM Science silica gel; 4/1, hexanes/ethyl acetate (1.8 L) to 2/1, hexanes/ethyl acetate.

5. The ^1H NMR spectrum of **4** is as follows: ($CDCl_3$) δ: 3.77 (s, 3 H, CO_2CH_3), 4.94 (m, 1 H, α-H), 5.13 (s, 2 H, CH_2PH), 5.28 (dd, 1 H, J = 1.2, 10.3, H_{cis}), 5.36 (dd, 1 H, J = 1.4, 17.1, H_{trans}), 5.47 (bd, 1 H, NH), 5.91 (m, 1 H, H_{vinyl}), 7.35 (s, 5 H, ArH).

6. MPLC conditions are as follows: 40 cm × 6-cm column; 230–400 mesh EM Science silica gel; flow rate 18 mL/min; model 153 Altex UV Detector; retention time ca. 100 min; 4/1, hexanes/ethyl acetate. The distillate was chromatographed in 2.5-g batches. The checkers experienced significant losses in this step, which may be highly sensitive to the type of silica and the apparatus used. In any case the material obtained after the first chromatography will be acceptable for most purposes.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Vinylglycine is a natural amino acid found in mushrooms.[3] It is an inhibitor of pyridoxal-linked aspartate aminotransferase,[4 5] and has also been postulated as an intermediate in the enzymatic conversion of homoserine to threonine[6] and α-ketobutyrate.[7] Protected vinylglycine is also a versatile asymmetric starting material for synthesis.[8] Variants have been prepared in racemic,[9,10,11,12,13,14] optically active,[15] optically pure,[2,16,17,18] and isotopically labeled form.[5,19,20,21] This procedure is derived from our earlier publication[2] and contains improvements in procedure and scale-up.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica

hexanes

brine

hydrogen chloride, hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether (60-29-7)

chloroform (67-66-3)

Glycine (513-29-1)

L-Methionine (63-68-3)

benzyl chloroformate (501-53-1)

threonine (72-19-5)

potassium bicarbonate (298-14-6)

Sodium periodate (7790-28-5)

Molybdophosphoric acid (51429-74-4)

N-(Benzyloxycarbonyl)-L-vinylglycine methyl ester

3-Butenoic acid, 2-[[(phenylmethoxy)carbonyl]amino]-, methyl ester, (S)- (75266-40-9)

N-(Benzyloxycarbonyl)-L-methionine methyl ester (56762-93-7)

L-methionine methyl ester hydrochloride (2491-18-1)

Methyl L-2-(benzyloxycarbonylamino)-4-(methylsulfinyl)butanoate

L-Vinylglycine hydrochloride

Vinylglycine

homoserine (672-15-1)

α-ketobutyrate

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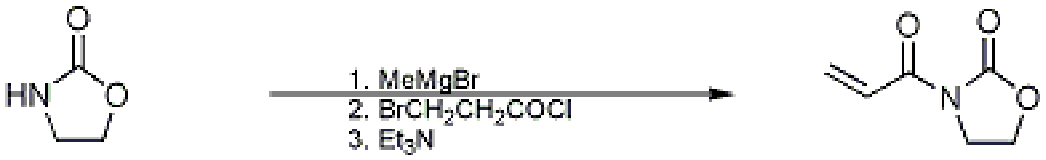
Organic Syntheses, CV 9, 67

ENANTIOSELECTIVE, CATALYTIC DIELS-ALDER REACTION: (1S-endo)-3-(BICYCLO[2.2.1]HEPT-5-EN-2-YLCARBONYL)-2-OXAZOLIDINONE

[2-Oxazolidinone, 3-bicyclo[2.2.1]hept-5-en-2-ylcarbonyl)-, (1S-endo)-]

A.

B.



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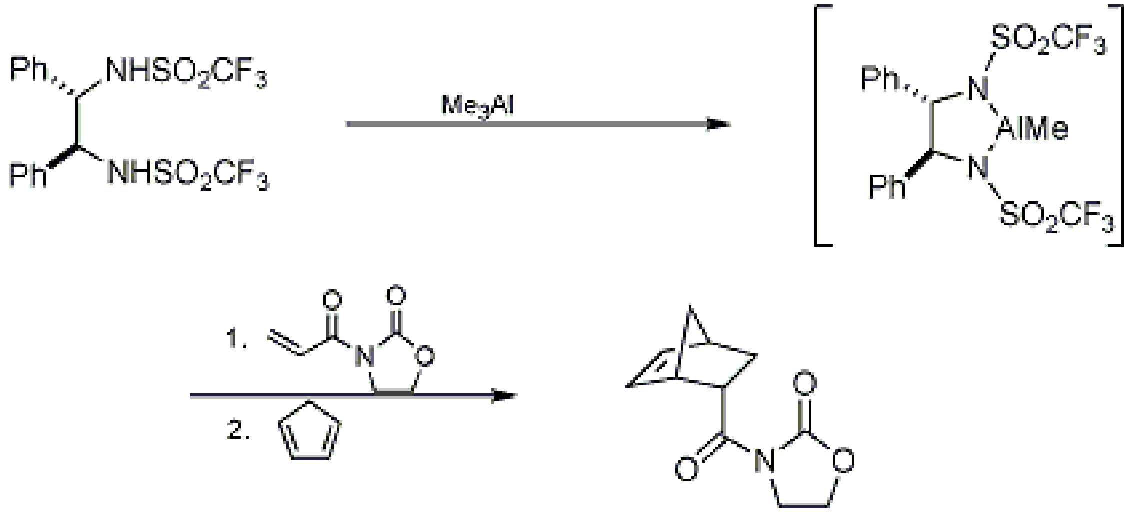

Submitted by S. Pikul[1] and E. J. Corey[2].
Checked by Scott Jeffrey and James D. White.

1. Procedure

A. *Bistriflamide of (1S,2S)-1,2-diphenylethylenediamine*. A 50-mL, one-necked, round-bottomed flask, equipped with a magnetic stirring bar, is charged with 1.06 g (5 mmol) of (1S,2S)-1,2-diphenylethylenediamine,[3] 2.1 mL (15 mmol) of triethylamine (Note

1), 12.2 mg (0.1 mmol) of 4-dimethylaminopyridine (DMAP) (Note 2) and 25 mL of methylene chloride (Note 3). The mixture is stirred to dissolve the solids, cooled to –78°C with a solid carbon dioxide/acetone bath, and 3.39 g (12 mmol) of trifluoromethanesulfonic anhydride (Note 4) is added dropwise. The cooling bath is removed and the mixture is allowed to warm to ambient temperature over 30 min. The mixture is then poured into 4% aqueous sodium bicarbonate, the phases are separated, and the aqueous phase is washed with 15 mL of methylene chloride. The combined organic phases are washed with 1 N hydrochloric acid, with brine, and then dried over anhydrous sodium sulfate and filtered. The filtrate is concentrated under reduced pressure and the residue is subjected to flash chromatography[4] on 100 g of silica gel (Note 5) (15% ethyl acetate-hexane, v/v) to give 1.64 g (69%) of the bistriflamide of (1S,2S)-1,2-diphenylethylenediamine as colorless crystals, mp 213–214°C (Note 6).

B. *Acryloyl-2-oxazolidinone (Note 7).* A flame-dried, 1-L, one-necked, round-bottomed flask, equipped with a magnetic stirring bar, is charged with 8.71 g (100 mmol) of 2-oxazolidinone (Note 2), flushed with argon (Note 8), and then 500 mL of tetrahydrofuran (Note 9) is introduced. The mixture is stirred to dissolve solids, cooled to 0°C, and 33.3 mL (100 mmol) of 3 M methylmagnesium bromide in ether (Note 2) is slowly added. After the solution is stirred for 10 min at 0°C, 11.6 mL (115 mmol) of 3-bromopropionyl chloride (Note 10) is added dropwise. The cooling bath is removed and the mixture is allowed to warm to ambient temperature over 30 min. The mixture is diluted with 600 mL of peroxide-free ether (Note 11) and washed with saturated aqueous ammonium chloride. The organic phase is dried over magnesium sulfate and filtered. To the filtrate, stirred at ambient temperature, is added 69 mL (500 mmol) of triethylamine (Note 1). A colorless precipitate forms immediately and the resulting slurry is stirred at ambient temperature for 3 hr, then poured into a 1:1 mixture of saturated aqueous ammonium chloride and 1 N aqueous hydrochloric acid. The aqueous layer is extracted with 200 mL of peroxide-free ether (Note 11), and the combined organic phases are dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue is subjected to flash chromatography[4] on 150 g of silica gel (Note 5) (35% ethyl acetate-hexane, v/v) to give 5.81 g (41%) of acryloyl-2-oxazolidinone as colorless crystals, mp 82–83°C (Note 12).

C. *Diels-Alder reaction.* All reagents and glassware are dried rigorously. A flame-dried, 250-mL, three-necked, round-bottomed flask, equipped with a magnetic stirring bar and a reflux condenser, is charged with 1.31 g (2.75 mmol) of bistriflamide of (1S,2S)-1,2-diphenylethylenediamine (dried at 80°C and 1 mm) and placed under dry argon (Note 8). 1,2-Dichloroethane (20 mL) (Note 13) is added, the mixture is heated to 80°C with stirring to effect solution, cooled to ambient temperature, and treated dropwise with 1.37 mL (2.74 mmol) of 2 M trimethylaluminum in toluene (Note 2). After the evolution of gases ceases, the homogeneous mixture is heated to 80°C (oil bath) for 3 hr. The heating bath is removed, the mixture is cooled to ambient temperature, the reflux condenser is replaced by a glass stopper, and the solvent is removed under reduced pressure (oil pump) that is maintained for an additional 30 min. The resulting solid is dissolved in 10 mL of dry methylene chloride (Note 3) and

overlayered with 50 mL of dry heptane. Colorless crystals are deposited after 20 hr. The supernatant liquid is drawn off by syringe and the residual solid is dissolved in 50 mL of methylene chloride (Note 3). The solution is cooled to −78°C and a solution of 7.76 g (55 mmol) of acryloyl-2-oxazolidinone in 50 mL of methylene chloride (Note 3) is introduced through a cannula. The mixture is stirred for 5 min at −78°C and then 5.7 mL (71 mmol) of neat, cold (−78°C) cyclopentadiene (Note 14) is slowly introduced through a cannula (Note 15) along the cooled sides of the flask. Stirring is continued for another 15 min. The mixture is poured into 1 N aqueous hydrochloric acid, the phases are separated, and the aqueous phase is washed with 25 mL of methylene chloride. The combined organic phases are washed successively with aqueous sodium bicarbonate and brine, dried over anhydrous sodium sulfate, and filtered. The filtrate is concentrated under reduced pressure and the residue is subjected to flash chromatography[4] on 150 g of silica gel (Note 5) (hexane-ethyl acetate 2:1, v/v) to give 10.1 g (89%) of the cycloadduct as colorless crystals, mp 68–69°C (Note 16) and (Note 17).

2. Notes

1. Triethylamine (99+%) was purchased from the Aldrich Chemical Company, Inc., and stored over sodium hydroxide.
2. 4-Dimethylaminopyridine (DMAP) (99%), 2-oxazolidinone (98%), methylmagnesium bromide (3 M in ether), and trimethylaluminum (2 M in toluene) were purchased from the Aldrich Chemical Company, Inc., and used as received.
3. Methylene chloride (A.C.S. reagent) was distilled from calcium hydride prior to use.
4. Trifluoromethanesulfonic anhydride was purchased from the Aldrich Chemical Company, Inc., and used as received. It can also be prepared from the acid according to the *Organic Syntheses* procedure.[5]
5. Kieselgel 60 (230–400 mesh) was purchased from EM Science, an affiliate of E. Merck, Darmstadt.
6. The product has the following properties: $[\alpha]_D$ −6.6° ($CHCl_3$, *c* 1.4); ^1H NMR ($CDCl_3$) δ: 4.81 (s, 2 H), 6.80 (bs, 2 H), 7.25 (6 H), 7.0 (4 H); ^{13}C NMR ($CDCl_3$) δ: 63.7, 127.0, 129.1 (2 C), 135.1.
7. This procedure is essentially the same as that described in the literature.[6]
8. This procedure involves three consecutive evacuations of the flask and fillings with dry argon.
9. Reagent grade tetrahydrofuran, purchased from J. T. Baker Chemical Company, was freshly distilled from sodium metal and benzophenone.
10. 3-Bromopropionyl chloride (tech) was purchased from the Aldrich Chemical Company, Inc., and distilled prior to use.
11. Anhydrous diethyl ether was freshly distilled from sodium metal and benzophenone.

12. The product has the following properties: R_f = 3.1 (35% ethyl acetate in hexane, v/v); IR cm^{-1}: 1785, 1675, 1419, 1396, 1321, 1258, 1220, 1024, 1008, 982, 752; ^1H NMR ($CDCl_3$) δ: 4.09 (t, 2 H, J = 8.0), 4.45 (t, 2 H, J = 8.0), 5.90 (dd, 1 H, J = 10.4, 1.6), 6.56 (dd, 1 H, J = 17.1, 1.6), 7.49 (dd, 1 H, J = 17.1, 10.4); ^{13}C NMR ($CDCl_3$) δ: 42.6, 62.1, 127.0, 131.6, 153.6, 165.0.

13. 1,2-Dichloroethane (99%, A.C.S. reagent) was freshly distilled from calcium hydride.

14. Cyclopentadiene was prepared by thermal cracking of dicyclopentadiene available from the Aldrich Chemical Company, Inc., following the literature procedure.[7]

15. Because of the high rate of the cycloaddition reaction it is very important that the cyclopentadiene solution enter the reaction flask and mix with the acrylate solution at as low a temperature as possible. For this reason it is beneficial to use a short cannula and to introduce the cyclopentadiene solution onto the wall of the flask that is deeply immersed in a solid CO_2 bath.

16. The product has the following properties: $[\alpha]_D$ –152.0° ($CHCl_3$, *c* 1.5; ee 89%), (lit.[7] $[\alpha]_D$ –65° ($CHCl_3$, *c* 1.5; ee 38%); R_f = 0.23 (hexane-ethyl acetate 2:1, v/v); IR cm^{-1}: 2975, 1775, 1696, 1386, 1337, 1279, 1253, 1226, 1111, 1039, 761, 704; ^1H NMR ($CDCl_3$) δ: 1.39–1.50 (m, 3 H), 1.95 (ddd, 1 H, J = 12.6, 9.3, 3.7), 2.93 (m, 1 H), 3.30 (m, 1 H), 3.91–4.00 (m, 3 H), 4.35–4.41 (m, 2 H), 5.87 (dd, 1 H, J = 5.5, 2.8), 6.24 (dd, 1 H, J = 5.5, 3.1); ^{13}C NMR ($CDCl_3$) δ: 29.5, 42.9 (2 C), 43.2, 46.4, 50.2, 61.9, 131.6, 138.1, 153.4, 174.7.

17. The endo-exo selectivity of the cycloaddition reaction is higher than 50:1, since no signals corresponding to the exo product are observed in the 500 MHz ^1H NMR spectrum of the crude or chromatographed product. The optical purity is 89% ee based on comparison with an authentic sample and the literature data.[8] The optical purity is confirmed by a 500 MHz ^1H NMR spectrum of the corresponding Mosher ester prepared in two steps: 1. Lithium aluminum hydride ($LiAlH_4$) reduction in tetrahydrofuran at room temperature; 2. esterification of the resulting primary alcohol with (R)-(+)-α-methoxy-α-(trifluoromethyl) phenylacetyl chloride[9] in the presence of triethylamine and DMAP in methylene chloride at room temperature.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The design and application of chiral, non-racemic Lewis acids for the asymmetric Diels-Alder reaction has recently been a subject of considerable interest.[10 11] Several

methods have been developed in many laboratories[8,12 13 14 15 16 17 18 19 20 21 22 23 24] but catalysts are still needed that are more efficient in governing the stereochemical course of the cycloaddition reaction.

This procedure describes the preparation and application of an effective chiral catalyst for the enantioselective Diels-Alder reaction.[25] The catalyst is derived from optically active 1,2-diphenylethylenediamine, the preparation of which (either antipode) is described (p. 387). The aluminum-based Lewis acid also catalyzes the cycloaddition of crotonoyl oxazolidinones with cyclopentadiene,[25] and acryloyl derivatives with benzyloxymethylenecyclopentadiene. The latter reaction leads to optically pure intermediates for synthesis of prostaglandins.[25]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

brine

2-Oxazolidinone, 3-bicyclo[2.2.1]hept-5-en-2-ylcarbonyl)-, (1S-endo)-

Bistriflamide of (1S,2S)-1,2-diphenylethylenediamine

DMAP

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

ether, diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

1,2-dichloroethane (107-06-2)

toluene (108-88-3)

Benzophenone (119-61-9)

sodium (13966-32-0)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

methylmagnesium bromide (75-16-1)

Tetrahydrofuran (109-99-9)

heptane (142-82-5)

lithium aluminum hydride (16853-85-3)

hexane (110-54-3)

triethylamine (121-44-8)

CYCLOPENTADIENE (542-92-7)

dicyclopentadiene

2-Oxazolidinone (497-25-6)

calcium hydride (7789-78-8)

argon (7440-37-1)

ethyl acetate-hexane (2639-63-6)

Trifluoromethanesulfonic anhydride (358-23-6)

trimethylaluminum (75-24-1)

4-dimethylaminopyridine (1122-58-3)

(1S,2S)-1,2-diphenylethylenediamine (35132-20-8)

Acryloyl-2-oxazolidinone (2043-21-2)

3-bromopropionyl chloride (15486-96-1)

1,2-diphenylethylenediamine

benzyloxymethylenecyclopentadiene

(1S-endo)-3-(Bicyclo[2.2.1]hept-5-en-2-ylcarbonyl)-2-oxazolidinone (109299-97-0)

(R)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride

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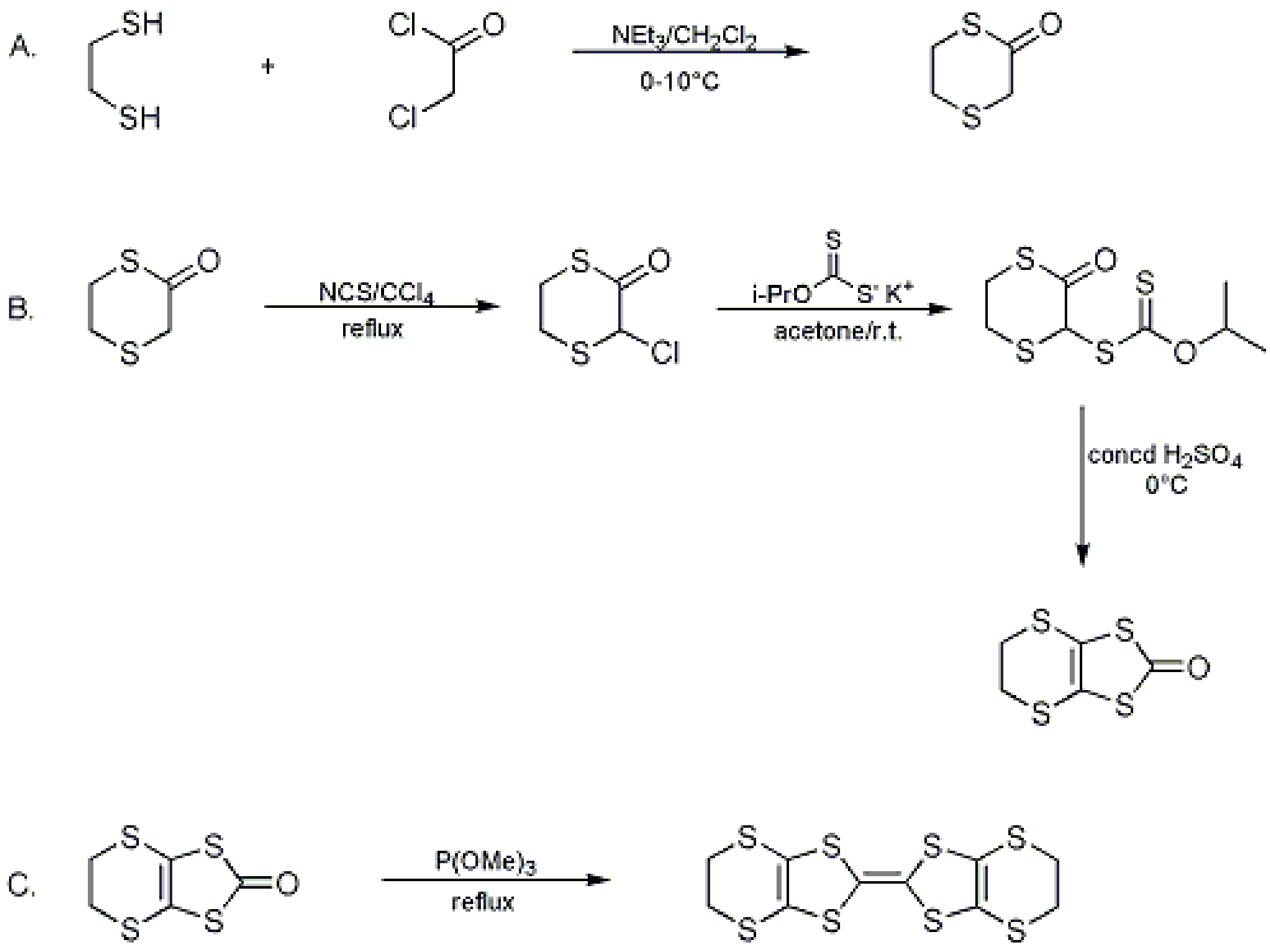
2,2'-BI-5,6-DIHYDRO-1,3-DITHIOLO[4,5-b][1,4] DITHIINYLIDENE (BEDT-TTF)

[1,3-Dithiolo[4,5-b][1,4]dithiin, 2-(5,6-dihydro-1,3-dithiolo- [4,5-b][1,4] dithiin-2-ylidene)-5,6-dihydro-]



Submitted by Jan Larsen[1] and Christine Lenoir[2].
Checked by Mathew Carson and David L. Coffen.

1. Procedure

Caution! This preparation should be conducted in an efficient hood because of the obnoxious odor of 1,2-ethanedithiol.

A. *2-Oxo-1,4-dithiane*. A 4-L, four-necked, round-bottomed flask equipped with a mechanical stirrer, 500-mL pressure-equalizing dropping funnel, thermometer, and reflux condenser provided with a calcium chloride drying tube, is charged with 1 L of dichloromethane, 1,2-ethanedithiol (102 mL, 1.2 mol) (Note 1), and triethylamine (336 mL, 2.4 mol). The mixture is cooled while it is stirred in an ice-acetone bath to 0–10°C while a solution of chloroacetyl chloride (96 mL, 1.2 mol) (Note 2) in 400 mL of dichloromethane is added over a period of 1.5 hr, during which time a thick white precipitate of triethylamine

hydrochloride is formed. After the addition is complete, stirring is continued for another 2 hr at ambient temperature. To the stirred mixture is added 500 mL of ice water. During the addition all the precipitated triethylamine hydrochloride is dissolved and a two-phase system is formed. The organic phase is washed with four 200-mL portions of water and dried over anhydrous magnesium sulfate ($MgSO_4$). The drying agent is removed by filtration, and the dichloromethane is evaporated using a rotary evaporator at ca. 13 mm. The residue is distilled at 0.7 mm using an oil bath with the temperature set at 120–130°C (Note 3) and 2-oxo-1,4-dithiane is distilled at 92–93°C; yield, 96 g (60%) (Note 4), (Note 5).

B. 3-Chloro-2-oxo-1,4-dithiane. A 250-mL, round-bottomed flask, equipped with a magnetic stirring bar and a reflux condenser provided with a nitrogen bubbler, is flushed with nitrogen and charged with 150 mL of carbon tetrachloride (CCl_4), 2-oxo-1,4-dithiane (10.0 g, 0.075 mol), and N-chlorosuccinimide (11.0 g, 0.083 mol) (Note 6), (Note 7). The mixture is refluxed for 30 min. After cooling to 0°C the precipitated succinimide is removed by filtration and washed with 20 mL of CCl_4 (Note 8). The solution is filtered directly into a 1-L, conical flask equipped with a magnetic stirring bar, charged with a suspension of potassium O-(2-propyl) dithiocarbonate (13.1 g, 0.075 mol) (Note 9) in 300 mL of dry acetone, and stirred at ambient temperature for 0.5 hr. The precipitate is removed by filtration and the solvent is evaporated at ambient temperature using a rotary evaporator at ca. 13 mm. 2-Oxo-3-(2-propoxythiocarbonylthio)-1,4-dithiane is obtained in quantitative yield as a slightly brown oil and used in the following step without further purification (Note 10).

2-Oxo-5,6-dihydro-1,3-dithiolo[4,5-b][1,4]dithiin. A 1-L conical flask, equipped with a magnetic stirring bar, is charged with 500 mL of concentrated sulfuric acid (H_2SO_4), and cooled to 0°C; 45 mL of ether is added dropwise. 2-Oxo-3-(2-propoxythiocarbonylthio)-1,4-dithiane is added in a thin stream during 10 min using an additional 5 mL of ether to complete the transfer. During the addition the sulfuric acid becomes dark. After 1.5 hr the reaction mixture is poured onto 3 kg of ice, at which time a sticky mass appears. The mixture is filtered by suction through a sintered glass funnel (D = 10 cm) charged with a layer of 2 cm of Celite. The Celite is washed with four 150-mL portions of water. A first crop is obtained by combining the water phase and leaving it for 5–7 days at room temperature. During this time the solution first becomes turbid and then clear, at which time 2-oxo-5,6-dihydro-1,3-dithiolo[4,5b][1,4]dithiin has separated as slightly yellow crystals. The water is removed by filtration, the product is washed with four 50-mL portions of water, and with two 20-mL portions of methanol, and dried under reduced pressure at ambient temperature.

The gummy mass isolated on the Celite is dissolved by washing with four 100-mL portions of dichloromethane. The organic phase is washed with three 100-mL portions of water and dried over anhydrous $MgSO_4$. The drying agent is removed by filtration and the solvent is evaporated using a rotary evaporator at ca. 13 mm. The residue is purified by filtration on silica gel (Note 11) with toluene. Toluene is evaporated using a rotary evaporator at ca. 13 mm. The residue is combined with the first crop and purified by recrystallization from absolute ethanol to yield 2-oxo-5,6-dihydro-1,3-dithiolo[4,5b][1,4]dithiin as white crystals (yield 7.8–9.4 g, 50–60% based on 2-oxo-1,4-dithiane); mp 126–127°C (Note 12).

C. *2,2'-Bi-5,6-dihydro-1,3-dithiolo[4,5-b][1,4]dithiinylidene(BEDT-TTF)*. A 250-mL,

round-bottomed flask equipped with a magnetic stirring bar and reflux condenser provided with a nitrogen bubbler is charged with 100 mL of freshly distilled trimethyl phosphite and 2-oxo-5,6-dihydro-1,3-dithiolo[4,5-b][1,4]dithiin (5.0 g, 0.024 mol). The solution is heated to reflux by immersing the flask in an oil bath preheated to 125°C (Note 13) for 2–3 hr. During this time bright orange-red crystals of product precipitate. The mixture is cooled to room temperature and the solid is filtered, and washed with four 20-mL portions of methanol and with four 20-mL portions of ether and dried under reduced pressure at ambient temperature to provide BEDT-TTF. Recrystallization from 300 mL of chlorobenzene affords 4.3 g (93%) of BEDT-TTF as bright red needles; mp 245–247°C (dec).

2. Notes

1. 1,2-Ethanedithiol (99%) is available from Aldrich Chemical Company, Inc., and is used without further purification.
2. Chloroacetyl chloride (98%) is available from Aldrich Chemical Company, Inc., and is used without further purification.
3. The use of an electric heating mantle results in local overheating of the initially formed poly- or oligomeric products giving red, foul-smelling products instead. The product distills rather slowly (2–4 hr).
4. The product was pure by NMR spectroscopy. ^{1}H NMR ($CDCl_3$/TMS) δ: 3.2 (m); ^{13}C NMR ($CDCl_3$/TMS) δ: 25.82 (CH_2), 31.02 (CH_2), 35.25 (CH_2), 197.11 (C=O).
5. 2-Oxo-1,4-dithiane can be stored for a long time at −20°C, at which temperature the product crystallizes.
6. N-Chlorosuccinimide (98%) is available from Aldrich Chemical Company, Inc., and is used without further purification.
7. The use of N-bromosuccinimide instead of N-chlorosuccinimide affords a dark, tarry mass.
8. 3-Chloro-2-oxo-1,4-dithiane can be obtained by removing the solvent at ambient temperature using a rotary evaporator at ca. 13 mm. The product was pure by NMR spectroscopy. ^{1}H NMR ($CDCl_3$/TMS) δ: 3.2 (m, 4 H, CH_2), 5.37 (s, 1 H, CH); ^{13}C NMR ($CDCl_3$/TMS) δ: 24.52 (CH_2), 30.18 (CH_2), 61.91 (CH), 188.27 (C=O). The product becomes black in a few days, even when stored at −20°C.
9. Potassium O-(2-propyl) dithiocarbonate can be prepared in the following manner: With heating, 42 g (0.75 mol) of potassium hydroxide is dissolved in 400 mL of 2-propanol. The solution is then cooled in an ice bath, and the temperature is kept below 10°C while carbon disulfide (46 mL, 0.75 mol) is added dropwise with stirring. The potassium xanthate is collected by suction filtration and washed with four 100-mL portions of ether and dried under reduced pressure at ambient temperature; yield 111 g (85%).
10. The product was pure by NMR spectroscopy. ^{1}H NMR ($CDCl_3$/TMS) δ: 1.40 (d, 6 H, CH_3), 3.41 (m, 4 H, CH_2), 5.62 (s, 1 H, CH), 5.70 (sept, 1 H, CH); ^{13}C NMR ($CDCl_3$/TMS) δ: 21.00 (CH_3), 27.70 (CH_2), 31.74 (CH_2), 54.17 (CH), 79.53 (CH), 191.58 (C=O), 207.71 (C=S).
11. Silicagel 60, 55 g, was used on a 5-cm column.
12. The product showed the following NMR data: ^{1}H NMR ($CDCl_3$/TMS) δ: 3.43 (s,

4 H, CH_2); ^{13}C NMR ($CDCl_3$/TMS) δ: 31.08 (CH_2), 113.41 (C=C), 188.72 (C=O).
13. It is essential that the mixture be heated rapidly, otherwise the yield decreases dramatically.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

BEDT-TTF [Bis(ethylenedithio)tetrathiafulvalene] has been synthesized by a variety of methods, mostly by reduction of carbon disulfide with alkali metals,[3,4,5] or electrochemically,[6] followed by alkylation of the formed disodium 4,5-dimercapto-1,3-dithiole-2-thione with 1,2-dibromoethane,[3,4,5] The thione is converted to 2-oxo-5,6-dihydro-1,3-dithiolo[4,5-b][1,4]dithiin by oxidation with mercuric acetate.[4] Finally coupling with triethyl phosphite,[4,7,8] or direct coupling of the thione with triethyl phosphite[5,9,10] or with triethyl phosphite under photochemical conditions[11] or with triethyl phosphite under high pressure[12] yields BEDT-TTF. Coupling has also been effected by alkylating the thione followed by electrochemical reduction of the formed 2-alkylthio-1,3-dithiolium salt.[13] Pyrolysis then yields the final product.

BEDT-TTF was also obtained by selective ring opening of 1,3,4,6-tetrathiapentalen-2,6-dione and alkylation with 1,2-dibromoethane followed by coupling with triethyl phosphite.[7,8]

The present procedure, which is based on those of Schumaker[8] and Larsen and Lenoir,[14] is simple and avoids the use of the troublesome and sometimes hazardous reduction of carbon disulfide with alkali metals. On several occasions a violent explosion has occurred in our laboratories during this reaction.

The present method gives high yields of BEDT-TTF in excellent purity. Actual investigation of super-conducting salts of BEDT-TTF show that BEDT-TTF made by the present route gives material of superior purity.[15] Also by the present method BEDT-TTF is obtained from readily available starting materials.

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

2-Oxo-3-(2-propoxythiocarbonylthio)-1,4-dithiane

2,2'-BI-5,6-DIHYDRO-1,3-DITHIOLO[4,5-b][1,4]DITHIINYLIDENE (BEDT-TTF)

2-oxo-5,6-dihydro-1,3-dithiolo[4,5b][1,4]dithiin

2,2'-Bi-5,6-dihydro-1,3-dithiolo[4,5-b][1,4]dithiinylidene(BEDT-TTF)

BEDT-TTF

Silicagel

BEDT-TTF [Bis(ethylenedithio)tetrathiafulvalene]

disodium 4,5-dimercapto-1,3-dithiole-2-thione

ethanol (64-17-5)

sulfuric acid (7664-93-9)

methanol (67-56-1)

ether (60-29-7)

carbon tetrachloride, CCl_4 (56-23-5)

nitrogen (7727-37-9)

mercuric acetate (1600-27-7)

acetone (67-64-1)

chlorobenzene (108-90-7)

potassium hydroxide (1310-58-3)

toluene (108-88-3)

2-propanol (67-63-0)

carbon disulfide (75-15-0)

1,2-dibromoethane (106-93-4)

chloroacetyl chloride (79-04-9)

dichloromethane (75-09-2)

Succinimide (123-56-8)

magnesium sulfate, $MgSO_4$ (7487-88-9)

N-bromosuccinimide (128-08-5)

potassium xanthate

triethylamine (121-44-8)

N-chlorosuccinimide (128-09-6)

Triethylamine hydrochloride (554-68-7)

Triethyl phosphite (122-52-1)

1,2-ethanedithiol (540-63-6)

trimethyl phosphite (121-45-9)

2-Oxo-1,4-dithiane (74637-14-2)

3-Chloro-2-oxo-1,4-dithiane (88682-21-7)

potassium O-(2-propyl) dithiocarbonate (140-92-1)

1,3-Dithiolo[4,5-b][1,4]dithiin, 2-(5,6-dihydro-1,3-dithiolo- [4,5-b][1,4]dithiin-2-ylidene)-5,6-dihydro- (66946-48-3)

1,3,4,6-tetrathiapentalen-2,6-dione

2-Oxo-5,6-dihydro-1,3-dithiolo[4,5-b][1,4]dithiin (74962-29-1)

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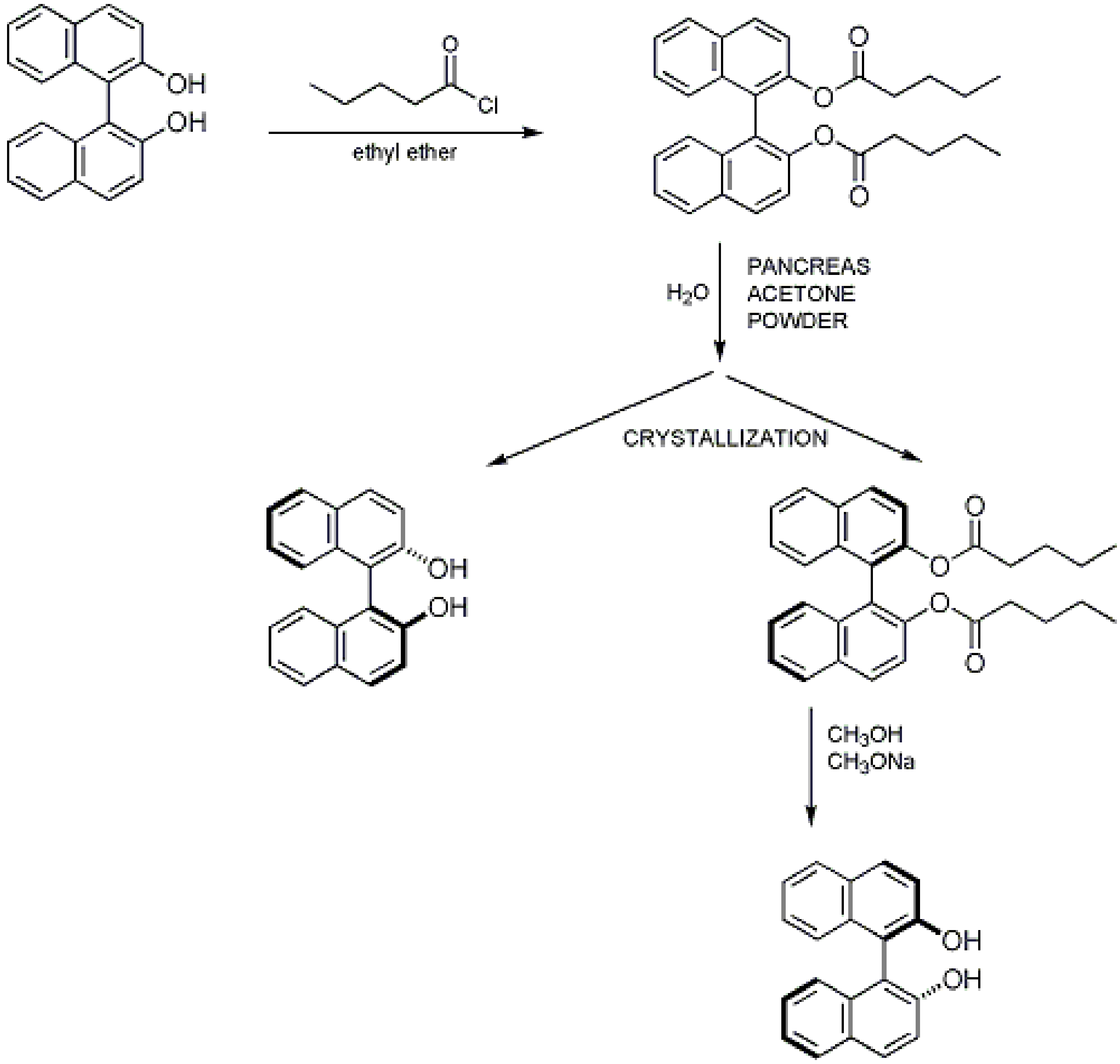
Organic Syntheses, CV 9, 77

(S)-(–)- AND (R)-(+)-1,1'-BI-2-NAPHTHOL

[[1,1'-Binaphthalene]-2,2'-diol, (S)- and [1,1'-Binaphthalene]-2,2'-diol, (R)-]



Submitted by Romas J. Kazlauskas[1]
Checked by Mark R. Sivik and Leo A. Paquette.

1. Procedure

A. *Racemic 1,1'-bi-2-naphthyl pentanoate*. A suspension of 203 g (0.71 mol) of racemic 1,1'-bi-2-naphthol (Note 1) and 215 mL (1.54 mol) of triethylamine in 2 L of ethyl ether is stirred magnetically in a 4-L Erlenmeyer flask. Over a period of 20 min 185 mL (1.56 mol) of pentanoyl chloride is added (Note 2) and the suspension is stirred for an additional hour to ensure complete reaction (Note 3). The mixture is poured into a 6-L separatory funnel and

washed twice with 2-L portions of aqueous 1 M sodium bicarbonate and once with a 2-L portion of water resulting in a clear yellow-orange ether solution.

B. *(S)-(−)-1,1'-Bi-2-naphthol*. In a 12-L, round-bottomed flask the above ether solution is diluted to 4 L with additional ethyl ether. A 5.0-mL aliquot of this solution is used to assay the enzyme (Note 4). The remaining ether solution is stirred using an overhead stirrer with 4 L of aqueous 0.1 M phosphate buffer (pH 7.5) containing 60 g of crude sodium taurocholate (Note 5). An opaque emulsion forms. The reaction is started by adding 2000 units of cholesterol esterase activity (100–150 g of bovine pancreas acetone powder, (Note 4)). Stirring is continued at 25°C and the flask is stoppered to minimize evaporation of ether. The pH of the emulsion is measured occasionally and readjusted to 7.2 ± 0.3 by adding aqueous 1 M sodium hydroxide. Approximately 250 mL of base is consumed during the first 3 hr; an additional 400 mL is consumed over the next 20 hr. Although the consumption of base virtually ceases after 24 hr, stirring is continued for a total of 3 days (Note 6).

To break the emulsion 400 mL of ethanol is added and the mixture is transferred to separatory funnels and allowed to settle for 4 hr. Three layers form: at the top—a clear yellow ether phase, at the bottom—a brown aqueous phase and in between—an opaque emulsion layer. The brown aqueous layer is discarded. The emulsion layer (1 L) is transferred to a flask and broken up by addition of 200 g of magnesium sulfate in portions. Heat is evolved, the ether boils and two layers form. This ether layer is combined with the first ether layer, dried over 50 g of magnesium sulfate, filtered and concentrated by rotary evaporation to 300 mL of an orange oil. Toluene (500 mL) is added and the solution cooled to 4°C overnight. Fine white crystals (70–71 g) are collected by filtration and washed twice with 20-mL portions of cold toluene (Note 7). The filtrate is concentrated to 600 mL by rotary evaporation and cooled once again to 4°C. The additional 10 g of crystals which form are collected by filtration and washed twice with 20-mL portions of toluene. Recrystallization of the combined crystals from 375–400 mL of toluene yields 65–68 g (64–67%) of white crystals, mp 211–213.5°C; $[\alpha]_D^{19}$ −33.2 ± 0.8° (THF, *c* 0.2); >99% diol (see (Note 3)), >99.9% enantiomeric purity (Note 8).

C. *(R)-(+)-1,1'-Bi-2-naphthol*. Toluene in the above filtrate is removed by rotary evaporation, and the residue is recrystallized from methanol (500 mL) overnight at 4°C. Yellow crystals (125–141 g) form and are collected by filtration and washed twice with 20 mL of hexane. Recrystallization from 500 mL of methanol yields pure (R)-binaphthol dipentanoate [mp 63–65°C, 89–102 g, >99% ee (R), $[\alpha]_D^{19}$ +15.0 ± 0.3° ($CHCl_3$, *c* 0.4), (Note 9)]. If desired, an additional 25 g of dipentanoate can be isolated from the filtrate by column chromatography on 1 kg of silica gel eluted with methylene chloride followed by crystallization (Note 9).

The crystalline dipentanoate (89–102 g, 0.20 mol) is dissolved in 1 L of methanol containing 6.6 g (0.12 mol) of sodium methoxide. After 4 hr at room temperature, analysis of the solution by thin layer chromatography (Note 3) shows only traces of the mono- and diester. The solution is neutralized to pH <7 (test paper) with 10 mL of concd hydrochloric acid. The solution is diluted with 1 L of 0.1 M phosphate buffer (pH 7), transferred to a 4-L

separatory funnel and extracted with a mixture of 1 L of ethyl ether and 500 mL of toluene. The organic layer is washed with a 1-L portion of water, dried over magnesium sulfate, concentrated to 300 mL and cooled to 4°C. White crystals (48–64 g) separate and are collected by filtration and washed twice with 20-mL portions of cold toluene, mp 211–213.5°C; $[\alpha]_D^{19}$ +33.9 ± 0.2° (THF, *c* 0.2); 99% chemical purity (Note 3), >99% enantiomeric purity (Note 8).

2. Notes

1. (±)-1,1'-Bi-2-naphthol was purchased from Aldrich Chemical Company, Inc. or prepared by oxidative coupling of 2-naphthol.[2]
2. The initial suspension is thick and can sometimes be difficult to stir magnetically. In this case, occasional swirling by hand is sufficient. The mixture thins as the reaction proceeds. *Caution: This exothermic reaction causes the ether to boil; pentanoyl chloride should be added slowly, allowing the heat of reaction to dissipate.* The checkers cooled the reaction mixture in an ice bath during addition of the acid chloride. Pentanoyl chloride was obtained from Aldrich Chemical Company, Inc.
3. To ensure high enantiomeric purity of the product there should be <0.5% 1,1'-bi-2-naphthol or its monoester in this solution. The relative amounts of binaphthol species can be accurately determined by HPLC on a reverse-phase column eluted with a water-acetonitrile gradient (50–100% over 10 min). Both 1,1'-bi-2-naphthol and its dipentanoate have equal (within 2%) extinction coefficients at 254 nm. The monopentanoate absorbs more strongly: the relative extinction coefficient at 254 nm is 1.13. Alternatively, the solution composition can be estimated using thin layer chromatography: silica gel eluted with 1:4 ethyl acetate/cyclohexane: 1,1'-bi-2-naphthol, R_f 0.39; monopentanoate, R_f 0.56; dipentanoate, R_f 0.71.
4. The catalyst for this reaction is the enzyme cholesterol esterase (EC 3.1.1.13). Bovine pancreas acetone powder (Sigma Chemical Company), a crude extract from pancreas, is an inexpensive source of cholesterol esterase activity. This extract contains 15 units of cholesterol esterase activity/gram; unit = •mol of ester hydrolyzed/min. To measure the activity, the ethereal aliquot of binaphthol dipentanoate is stirred rapidly using a magnetic stirrer with 5.0 mL of 10 mM phosphate buffer (pH 7.0) containing 75 mg of crude sodium taurocholate (Sigma Chemical Company). Approximately 200 mg of acetone powder is added and the pH of the emulsion is monitored with a pH meter and maintained at 7.0 by addition of aqueous 0.1 M sodium hydroxide in portions of 50 •L until 200 •L has been added, 70 min. The slope of a plot of •moles of base consumed vs. time gives the activity of the acetone powder. (The amount of base needed to readjust the pH to 7.0 after the addition of the slightly acidic acetone powder is ignored in the activity calculation.)
5. Directions for the preparation of this buffer solution are given in reference [3].
6. After 24 hr, analysis by HPLC shows 37% binaphthol, 10% monopentanoate and 53% dipentanoate, after an additional 2 days of stirring, analysis shows 45%, 3%, and 52%. Isolation of binaphthol and diester by crystallization is substantially more difficult and less efficient from reaction mixtures containing <40 mol % binaphthol.
7. Binaphthol may not crystallize if the solution is wet. If no crystals form, water can be removed by rotary evaporation of the water-toluene azeotrope.

8. Enantiomeric purity of binaphthol is determined using chiral stationary phase HPLC: Pirkle Type 1-A column (Regis Chemical Company) eluted with 20:1 hexane/2-propanol[4] or poly(triphenylmethyl)methacrylate on silica gel (Chiralpak OT, Daicel Chemical Industries, LTD) eluted with methanol.[5] To determine enantiomeric purities >99% ee an HPLC trace of the unknown is compared to the HPLC trace of unknown containing 0.2% deliberately-added racemic material.

9. Crystallization of (R)-binaphthyl dipentanoate increases its enantiomeric purity from 92% ee in the reaction mixture to >99% ee. The enantiomeric purity of the final product, binaphthol, is not increased by crystallization. The recrystallization step for the dipentanoate ensures high enantiomeric purity. Usually crystallization from methanol must be induced by scratching the side of the flask with a glass rod. The enantiomeric purity of the dipentanoate is determined after cleavage to binaphthol. A sample of dipentanoate is treated with an equivalent of sodium methoxide in methanol. After 30 min the solution is neutralized with excess acetic acid and analyzed by HPLC as in (Note 8).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Enantiomerically pure binaphthol is used as a chiral auxiliary.[6] For example, it has been used to prepare chiral aluminum hydride reducing agents,[7] chiral Lewis acids catalysts,[8] and chiral crown ethers.[9]

The best previous resolution of binaphthol uses fractional crystallization of the diastereomeric cinchonine salts of binaphthol cyclic phosphate ester.[10] The resolution using cholesterol esterase involves fewer manipulations and thus is simpler and faster than the cinchonine method. Fewer manipulations also enable the resolutions using cholesterol esterase to be carried out on a larger scale. The high enantioselectivity of cholesterol esterase assures high ee for the (S)-enantiomer, while crystallization of (R)-binaphthyl dipentanoate assures high enantiomeric purity for the (R)-enantiomer.

Octahydrobinaphthol and several spirobiindanols can also be resolved using this method, but several bromo-substituted binaphthols could not be resolved because their esters were not hydrolyzed.[11]

This preparation is referenced from:

- Org. Syn. 76, 1

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2K6 Canada. Initial work was done at General Electric Company, Corporate Research and Development, Schenectady, NY.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

(S)-(−)- AND (R)-(+)-1,1'-BI-2-NAPHTHOL

poly(triphenylmethyl)methacrylate

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether, ethyl ether (60-29-7)

acetonitrile (75-05-8)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

2-naphthol (135-19-3)

cyclohexane (110-82-7)

sodium methoxide (124-41-4)

toluene (108-88-3)

2-propanol (67-63-0)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

hexane (110-54-3)

triethylamine (121-44-8)

binaphthol

(R)-(+)-1,1'-Bi-2-naphthol, 1,1'-bi-2-naphthol, [1,1'-Binaphthalene]-2,2'-diol, (R)-, (±)-1,1'-bi-2-naphthol, [1,1'-Binaphthalene]-2,2'-diol, (S)-, (S)-(–)-1,1'-Bi-2-naphthol (18531-99-2)

1,1'-bi-2-naphthyl pentanoate (110902-38-0)

pentanoyl chloride (638-29-9)

sodium taurocholate

binaphthol dipentanoate, (R)-binaphthol dipentanoate

(R)-binaphthyl dipentanoate

Octahydrobinaphthol

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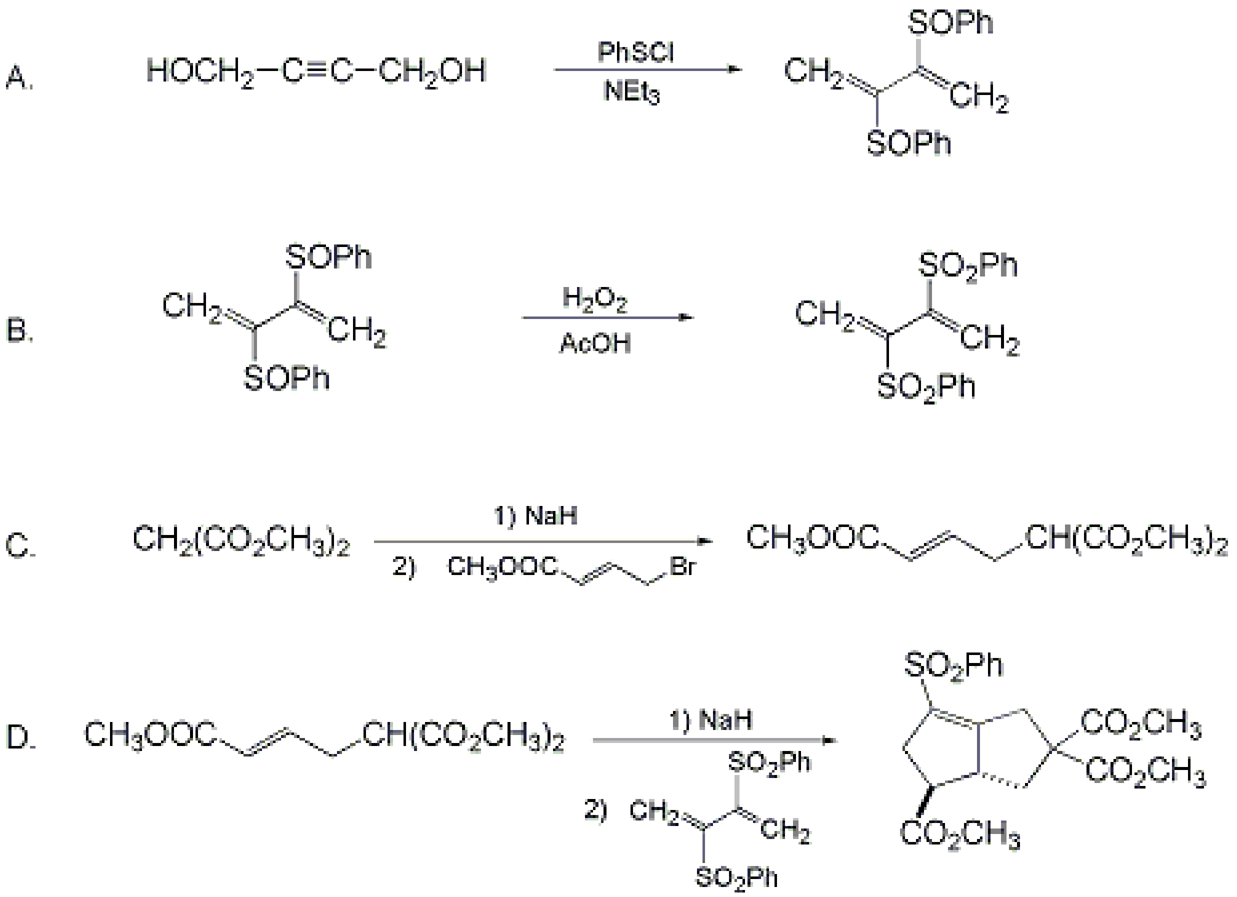
Organic Syntheses, CV 9, 82

[3+2]-ANIONIC ELECTROCYCLIZATION USING 2,3-BIS(PHENYLSULFONYL)-1,3-BUTADIENE: trans-4,7,7-TRICARBOMETHOXY-2-PHENYLSULFONYLBICYCLO[3.3.0]OCT-1-ENE

[Benzene, 1,1'-[[1,2-bis(methylene)-1,2-ethanediyl]bis(sulfonyl)]bis-]



Submitted by Albert Padwa[1], Scott H. Watterson, and Zhijie Ni.
Checked by David Young, Michael Rupp, Dan Kuzmich, and David J. Hart.

1. Procedure

A. *2,3-Bis(phenylsulfinyl)-1,3-butadiene*. In a 2-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, 25-mL dropping funnel, and a nitrogen inlet, are placed 7.75 g (0.09 mol) of 2-butyne-1,4-diol (Note 1), 37.6 mL (0.27 mol) of triethylamine, and 700 mL of dichloromethane. After the diol is completely dissolved, the mixture is cooled to −78°C. To this solution is added 26.0 g (0.18 mol) of phenylsulfenyl chloride (Note 2) over a 30-min interval. The mixture is gradually warmed to room temperature and stirred for an additional 12 hr. The solution is then washed with 100 mL each of water, saturated ammonium chloride solution, saturated

sodium bicarbonate solution, and brine, and dried over sodium sulfate. After filtration and concentration, the residue is recrystallized from methanol-ether (1:1) to give 20.1 g (74%) of 2,3-bis(phenylsulfinyl)-1,3-butadiene as a 1.1:1 mixture of diastereomers (Note 3).

B. *2,3-Bis(phenylsulfonyl)-1,3-butadiene* **(1)**. A solution of 17.0 g of 2,3-bis (phenylsulfinyl)-1,3-butadiene (56.3 mmol) and 34 mL of hydrogen peroxide (30–35%) (Note 4) in 170 mL of glacial acetic acid is placed in a 500-mL, three-necked flask equipped with a reflux condenser and thermometer. The solution is warmed using an oil bath such that a reaction temperature of 90°C is maintained for 5 hr (Note 5). To the hot solution is added 40 mL of water and the mixture is allowed to stand at room temperature for 12 hr. The resulting precipitate is collected, washed with water (50 mL), cold methanol (30 mL), and ether (100 mL). The filter cake (13.9 g) is dissolved in 100 mL of hot dichloromethane and 100 mL of hexane is added slowly. After standing at 25°C for 1 day, the crystalline solid is collected and washed with 100 mL of ether to give 11.6 g (61%) of 2,3-bis(phenylsulfonyl)-1,3-butadiene (Note 6).[2] Concentration and recrystallization of the mother liquor affords an additional 1.7 g (9%) of the disulfone.

C. *Dimethyl (E)-5-methoxycarbonyl-2-hexenedioate*. Into a flame-dried, 500-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, a 100-mL dropping funnel, and a nitrogen inlet, is placed 4.2 g of sodium hydride (60% in oil, 105 mmol) which has been washed twice with 50 mL of hexane and then suspended in 400 mL of anhydrous tetrahydrofuran (THF). The mixture is cooled to 0°C with an ice bath and a solution containing 13.7 mL (15.8 g, 120 mmol) of dimethyl malonate in 30 mL of anhydrous THF is added over a 30-min interval. After being stirred for an additional 20 min at 0°C, the mixture is transferred by cannula into an ice-cold solution containing 19.9 g (110 mmol) of methyl 4-bromocrotonate (Note 7) in 300 mL of THF in a 1-L, round-bottomed flask fitted with a nitrogen inlet. Stirring is continued for an additional 20 min and the reaction is quenched by the addition of 100 mL of a saturated ammonium chloride solution. The solvent is removed with a rotary evaporator at aspirator vacuum, and the aqueous layer is extracted three times with ether (200 mL). The organic layer is washed with 100 mL each of water and brine, and dried over sodium sulfate. After filtration and concentration, the resulting residue is distilled using a 5-cm Vigreux column under reduced pressure to give 8.8 g (38%) of dimethyl (E)-5-methoxycarbonyl-2-hexenedioate (Note 8).

D. *trans-4,7,7-Tricarbomethoxy-2-phenylsulfonylbicyclo[3.3.0]oct-1-ene*. In a flame-dried, 2-L, three-necked, round-bottomed flask equipped with a magnetic stirrer, dropping funnel, and nitrogen inlet, is placed 1.44 g of sodium hydride (60% in oil, 36.0 mmol) which has been washed twice with 50 mL of hexane and then suspended in 500 mL of anhydrous THF. After 7.59 g (33.0 mmol) of dimethyl (E)-5-methoxycarbonyl-2-hexenedioate in 50 mL of THF is added to the above mixture, it is stirred at 0°C for 30 min. Then a solution containing 10.02 g (30.0 mmol) of 2,3-bis

(phenylsulfonyl)-1,3-butadiene in 900 mL of anhydrous THF is added over 30 min. The solution is stirred for 10 min at 0°C and then quenched with 100 mL of a saturated aqueous ammonium chloride solution. The solvent is removed under reduced pressure, and the residue is extracted three times with 300 mL of dichloromethane. The organic phase is washed with 100 mL each of water, brine, and dried over sodium sulfate. The filtrate is concentrated under reduced pressure and the residue is chromatographed on 350 g of silica gel eluting with 4 L of a 2:1-hexane/ethyl acetate mixture to give 9.54 g (75%) of trans-4,7,7-tricarbomethoxy-2-phenylsulfonylbicyclo[3.3.0]oct-1-ene as a clear oil (Note 9).

2. Notes

1. 2-Butyne-1,4-diol, sodium hydride (60% in oil) and dimethyl malonate were purchased from Aldrich Chemical Company, Inc. and used without further purification. Triethylamine and dichloromethane were distilled from calcium hydride prior to use.
2. Phenylsulfenyl chloride was prepared according to the known literature procedure.[3]
3. This product is a 1.1:1 mixture of two diastereoisomers, mp 127–129°C, and was used in the next step without further purification. The product has the following spectral properties: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 5.6, 5.85, 6.18, 6.22 (four s, 4 H), 7.1–7.5 (m, 10 H).
4. Hydrogen peroxide (30–35%) and glacial acetic acid were purchased from Fisher Scientific Company and were used without further purification.
5. The yield is considerably reduced if the reaction temperature is allowed to exceed 90°C. Yields as high as 80% have been obtained with careful monitoring of the temperature.
6. The product has the following physical properties: mp 181–183°C (lit.[2] 183–185°C); IR (KBr) cm^{-1}: 3120, 1580, 1441, 1302, 1140, 1067, 744, 685; ^{1}H NMR (300 MHz, $CDCl_3$) d: 6.61 (s, 2 H), 6.74 (s, 2 H), 7.20–7.30 (m, 4 H), 7.42–7.51 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 128.4 (d), 129.1 (d), 130.8 (t), 133.7 (d), 137.1 (s), 140.8 (s). Anal. Calcd for $C_{16}H_{14}O_4S_2$: C, 57.46; H, 4.22; S, 19.18. Found: C, 57.39; H, 4.23; S, 19.08.
7. Methyl 4-bromocrotonate was purchased from Lancaster Synthesis Inc. and distilled before use.
8. Dimethyl (E)-5-methoxycarbonyl-2-hexenedioate[4] has the following physical properties: bp 144–146°C (2.0 mm); IR (neat) cm^{-1}: 3004, 2947, 1737, 1431, 1268, 1033, 727; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.79 (t, 2 H, J = 7.2), 3.51 (t, 1 H, J = 7.2), 3.70 (s, 3 H), 3.74 (s, 6 H), 5.98 (d, 1 H, J = 15.6), 6.86 (dt, 1 H, J = 15.6, 7.2); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 30.9, 50.1, 51.3, 52.6, 123.3, 143.7, 166.1, 168.5. This compound has also been prepared by the ozonolysis of dimethyl allylmalonate followed by reaction with methyl (triphenylphosphoranylidene)acetate.[5] While this procedure is reported to afford

the triester in 60–65% overall yield, we found the above method to be simpler and more convenient for the preparation of larger quantities of material.

9. trans-4,7,7-Tricarbomethoxy-2-(phenylsulfonyl)bicyclo[3.3.0]oct-1-ene has the following spectral properties: IR (neat) cm^{-1}: 3004, 2947, 1730, 1438, 1147, 1075, 727; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.86 (t, 1 H, J = 12.3), 2.56 (dd, 1 H, J = 13.2, 7.8), 2.79–2.99 (m, 3 H), 3.17 (brd, 1 H, J = 21.0), 3.34 (brd, 1 H, J = 21.0), 3.4–3.7 (m, 1 H), 3.56 (s, 3 H), 3.65 (s, 3 H), 3.67 (s, 3 H), 7.47 (t, 2 H, J = 7.5), 7.56 (t, 1 H, J = 7.2), 7.78 (d, 2 H, J = 7.5); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 33.2, 37.4, 39.4, 48.9, 51.9, 52.8, 53.0, 54.7, 63.1, 127.3, 129.0, 129.1, 133.4, 139.7, 161.0, 170.7, 171.2, 172.4; HRMS Calcd for $C_{20}H_{22}O_8S$: m/e 422.1035. Found m/e 422.1030.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

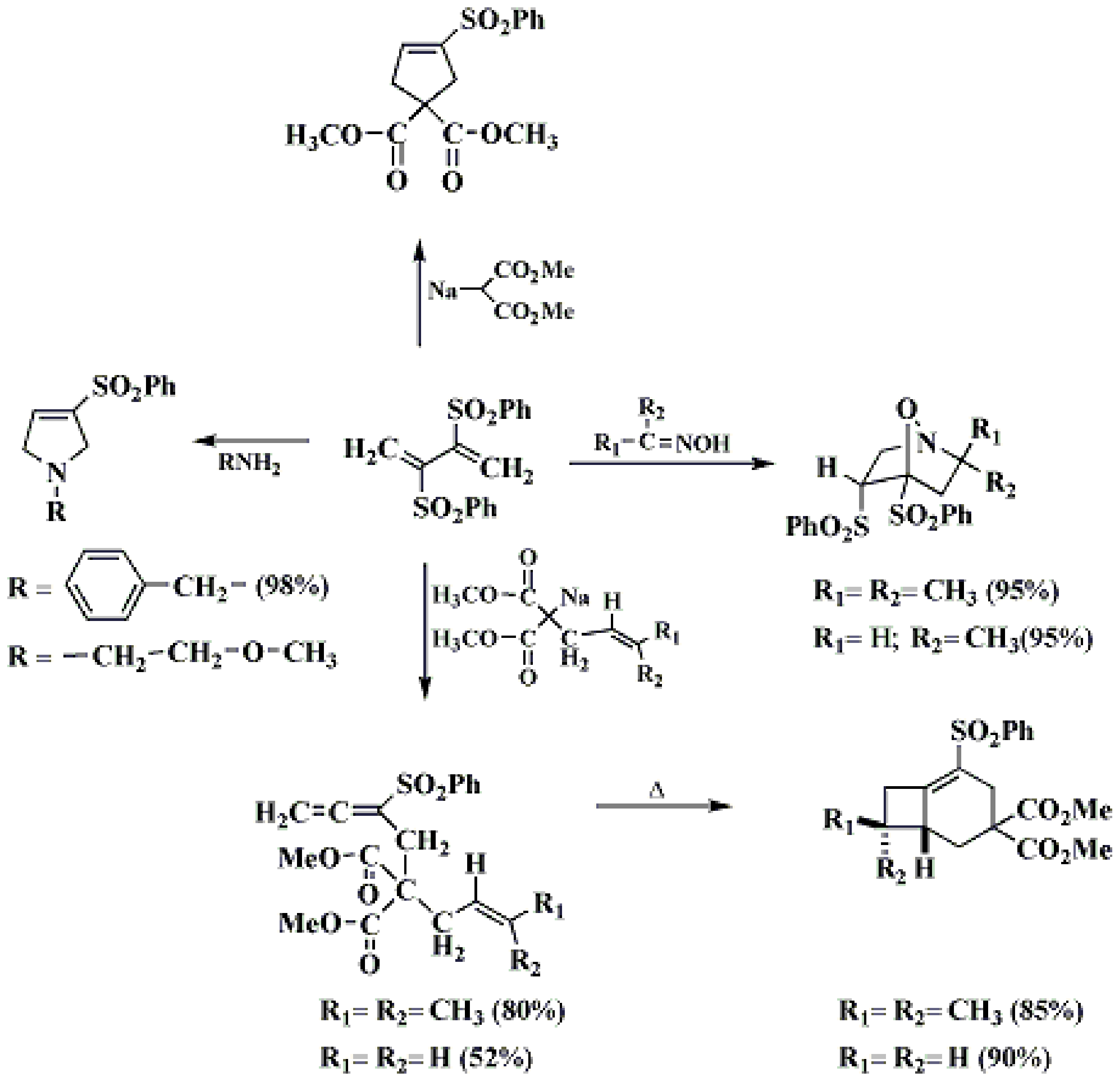
3. Discussion

The chemistry of phenylsulfonyl-substituted 1,3-butadienes is receiving increasing attention because of their synthetic versatility and the efficient π-bond activation by the sulfonyl group.[6,7,8,9,10] Some of the procedures currently available for their preparation include phenylsulfonyl-mercuration of 1,3-dienes,[11] condensation of allyl sulfones with aldehydes followed by acetylation and subsequent elimination,[12] thermal SO_2 extrusion from 2-(arylsulfonyl)sulfolenes,[13,14] cheletropic ring-opening of sulfolanes,[15] palladium(II)-catalyzed chloroacetoxylation of 1,3-dienes,[16] and the 2-tosylvinyl sulfone coupling with vinylstannanes.[17] Methods of preparing bis (phenylsulfonyl)-substituted 1,3-dienes, however, are limited to relatively few routes.[18] In spite of its simplicity and its obvious potential as an activated diene, 2,3-bis (phenylsulfonyl)-1,3-butadiene **(1)** has not been used extensively in organic synthesis. This reagent was prepared by a modification of the procedure of Jeganathan and Okamura in multigram quantities.[2] Treatment of 2-butyne-1,4-diol with benzenesulfenyl chloride produces the disulfenate ester as a transient species, which rapidly undergoes a series of 2,3-sigmatropic rearrangements to give 2,3-bis (phenylsulfinyl)-1,3-butadiene. This material is readily oxidized with hydrogen peroxide to the bis(phenylsulfonyl)diene **1** in 70–80% yield.

Over the past several years, the submitter has demonstrated the use of diene **1** as a versatile building block in organic synthesis, particularly for [4+2]-cycloaddition chemistry.[19] In an early report, the cycloaddition of this diene with various oximes as a method for piperidine formation was described.[20] In subsequent investigations, disulfone **1** was demonstrated to undergo cycloaddition to a variety of simple imines[21]

and enamines[22] under mild conditions producing novel rearranged heterocycles. This diene also played an important role in the successful outcome of the submitter's [4+1]-annulation strategy for pyrrolidine formation, since it is highly activated toward nucleophilic addition.[23] More recently, disulfone **1** was found to undergo a [4+1]-annulation reaction with a variety of soft carbanions to give phenylsulfonyl-substituted cyclopentenes in good yield.[24] The pivotal step in this reaction involves addition of a stabilized carbanion onto the highly activated π-bond of diene **1** followed by $PhSO_2$-elimination to give a phenylsulfonyl-substituted allene as a key intermediate. Further reaction of the allene with benzenesulfinate anion eventually provides the five-membered ring. Several phenylsulfonyl alkenyl-substituted allenes were also prepared and found to undergo a highly chemo- and stereospecific intramolecular [2+2]-cycloaddition reaction to give bicyclo[4.2.0]oct-1-enes in high yield.[25]

The procedure described here provides a simple and general approach for the construction of bicyclo[3.3.0]oct-1-enes using 2,3-bis(phenylsulfonyl)-1,3-butadiene **(1)** as a key reagent. The [3+2]-cycloaddition of an allyl anion with an activated olefin to give cyclopentyl anion has been an active area of investigation for many years.[26] The synthetic potential of disulfone **1** for [3+2]-cyclization chemistry is demonstrated here by taking advantage of two properties of the molecule: (1) the ability of the phenylsulfonyl group to activate the double bond toward Michael addition with soft β-dicarbonyl anions and (2) the facility with which the phenylsulfonyl group can be eliminated. Thus, conjugate addition of the anion derived from dimethyl (E)-5-methoxycarbonyl-2-hexenedioate to diene **1** is followed by a series of consecutive tandem Michael additions to the activated π-bonds.[27] Eventual phenylsulfinate elimination produces the bicyclo[3.3.0]oct-1-ene skeleton. Since disulfone **1** can react with a variety of β-dicarbonyl anions, a wide assortment of bicyclo[3.3.0]octenes is easily available. This strategy can clearly be applied to more complex targets.



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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

brine

acetic acid (64-19-7)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether (60-29-7)

ammonium chloride (12125-02-9)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

piperidine (110-89-4)

hydrogen peroxide (7722-84-1)

dichloromethane (75-09-2)

Tetrahydrofuran, THF (109-99-9)

pyrrolidine (123-75-1)

sodium hydride (7646-69-7)

hexane (110-54-3)

triethylamine (121-44-8)

calcium hydride (7789-78-8)

Benzenesulfenyl chloride, Phenylsulfenyl chloride (931-59-9)

dimethyl malonate (108-59-8)

methyl 4-bromocrotonate (1117-71-1)

methyl (triphenylphosphoranylidene)acetate (2605-67-6)

Palladium(II)

2-butyne-1,4-diol (110-65-6)

2,3-Bis(phenylsulfonyl)-1,3-butadiene, Benzene, 1,1'-[[1,2-bis(methylene)-1,2-ethanediyl]bis(sulfonyl)]bis- (85540-20-1)

trans-4,7,7-Tricarbomethoxy-2-phenylsulfonylbicyclo[3.3.0]oct-1-ene, trans-4,7,7-Tricarbomethoxy-2-(phenylsulfonyl)bicyclo[3.3.0]oct-1-ene

2,3-Bis(phenylsulfinyl)-1,3-butadiene (85540-18-7)

Dimethyl (E)-5-methoxycarbonyl-2-hexenedioate (93279-60-8)

dimethyl allylmalonate (40637-56-7)

2-tosylvinyl sulfone

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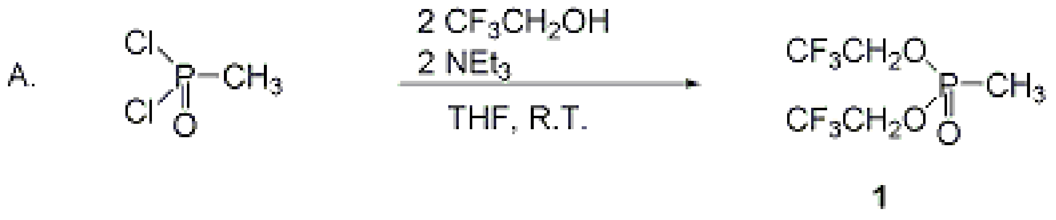
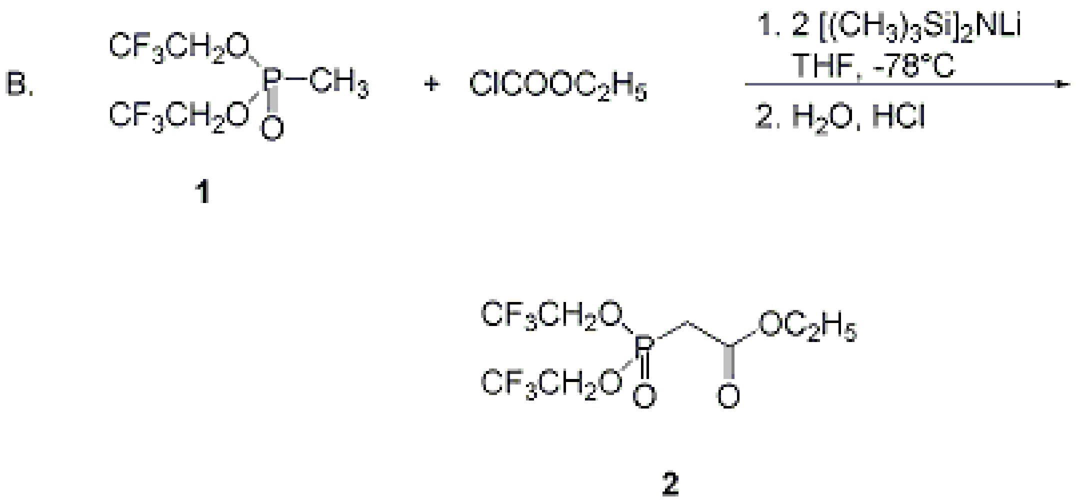
Organic Syntheses, CV 9, 88

BIS(TRIFLUOROETHYL) (CARBOETHOXYMETHYL)PHOSPHONATE

[Acetic acid, [bis(2,2,2-trifluoroethoxy)phosphinyl]-, ethyl ester]





Submitted by Carl Patois[1], Philippe Savignac[1], Elie About-Jaudet[2], and Noël Collignon[2].
Checked by Andrzej R. Daniewski, Bryon K. Tilley, and David L. Coffen.

1. Procedure

A. *Bis(trifluoroethyl) methylphosphonate* **1**. All glassware is oven-dried. A 1-L, four-necked, round-bottomed flask is fitted with an efficient mechanical stirrer, a thermometer, reflux condenser with a bubbler, and a 200-mL, pressure-equalizing dropping funnel with a nitrogen inlet. Under a gentle flow of nitrogen, the flask is charged with 300 mL of anhydrous tetrahydrofuran (THF) (Note 1), 42 g (0.42 mol) of trifluoroethanol (Note 2), and 42.4 g of triethylamine (Note 2). Stirring is started, and the flask is immersed in a cool (10°C) water bath. The dropping funnel is charged with a solution of 26.6 g (0.2 mol) of methylphosphonic dichloride (Note 3) in 100 mL of THF, that is subsequently added at a constant rate over 30 min. The internal temperature rises to 20–30°C, and a white solid precipitates. After the addition is complete, the water bath is removed, and the resulting mixture is stirred at room temperature for 2 hr. The organic salts are removed by suction filtration through a

glass funnel, and the filter cake is washed with three 50-mL portions of THF. The solvent is completely removed under reduced pressure on a rotary evaporator. The residue is dissolved in 100 mL of dry ether and filtered to remove insoluble triethylamine hydrochloride, using an additional 40 mL of ether to aid the filtration/transfer. Solvent is again completely evaporated under reduced pressure. Crude product **1**, thus obtained, is transferred to a 100-mL pear-shaped flask, fitted with a short distillation column (Note 4), and distilled under reduced pressure to afford 45.3–48.0 g (89–93%) of pure bis(trifluoroethyl) methylphosphonate (**1**) as a colorless liquid, bp 88–91°C (14 mm), which affords white crystals on standing in the freezer (Note 5). When sufficiently pure, **1** will crystallize on standing at room temperature.

B. *Bis(trifluoroethyl) (carboethoxymethyl)phosphonate* (**2**). An oven-dried, 1-L, four-necked, round-bottomed flask is fitted as above (Part A), flushed with nitrogen, and charged with 131 mL (0.210 mol) of a solution of butyllithium (1.6 M in hexane) (Note 6). The solution is cooled with stirring to approximately −20°C in a dry ice-acetone bath, and the dropping funnel is charged with a solution of 34 g (0.212 mol) of hexamethyldisilazane (Note 7) in 110 mL of tetrahydrofuran (THF) (Note 1). The contents of the addition funnel are added dropwise over 15 min during which time the yellow color practically disappears. A fine white suspension forms when the resulting solution is cooled to −78°C. A solution of 26 g (0.1 mol) of 1 and 11.5 g (0.106 mol) of ethyl chloroformate (Note 7) in 60 mL of THF is then added dropwise over 15 min via the addition funnel. During the course of the addition, the temperature rises to between −75° and −65°C, and the solution becomes clear. The reaction mixture is stirred at −70°C for an additional 15 min; the flask containing the reaction mixture is securely stoppered and stored overnight at −20°C in a freezer (Note 8). The cold (−20°C) reaction mixture is poured into a stirred mixture of 170 mL of 2 M hydrochloric acid and an equal volume of crushed ice, and 150 mL of methylene chloride. The organic layer is separated, and the aqueous layer is extracted twice with 50 mL of methylene chloride (Note 9). The combined organic extracts are diluted with 200 mL of hexane to facilitate drying, and then dried for 12 hr over anhydrous magnesium sulfate (Note 10). After removal of the magnesium sulfate by filtration, the solvents are evaporated under reduced pressure using a rotary evaporator to give crude **2** as a pale yellow liquid. Subsequent distillation of this crude material in a short path distillation apparatus (Note 11) under reduced pressure gives, after a small forerun (Note 12), 25.5–26.3 g (77–79%) of bis(trifluoroethyl) (carboethoxymethyl)phosphonate (**2**) as a colorless oil, bp 88–97°C (0.04 mm) (Note 13).

2. Notes

1. Tetrahydrofuran available from SDS Company was purified by distillation from sodium and benzophenone.
2. The submitters used 99+% 2,2,2-trifluoroethanol, and 99% triethylamine, purchased from Janssen Chimica, without purification. The checkers used the same grade materials purchased from Aldrich Chemical Company, Inc., and

Eastman Kodak, respectively.
3. Methylphosphonic dichloride (98%) can be purchased from Aldrich Chemical Company, Inc., or prepared according to a reported procedure.[3]
4. For the distillation, the submitters used a 14-cm fractional distillation column equipped with an 8-cm condenser.
5. The product displays the following spectroscopic data: ^{31}P ($CDCl_3$) δ: +35.0; ^{1}H ($CDCl_3$) δ: 1.68 (d, 3 H, J = 18.2), 4.35–4.42 (m, 4 H); ^{13}C (CDCl3) δ: 10.9, 61.8, 122.6; IR (film) cm^{-1}: 1415, 1317, 1292, 1258, 1186, 1169, 1111, 1075, 966, 922, 901, 845.
6. The submitters used 140 mL of 1.5 M butyllithium in hexane available from Janssen Chimica, standardized before use by titration against a solution of benzyl alcohol in toluene and 2,2'-biquinoline. The checkers used material from Aldrich Chemical Company, Inc.
7. The submitters used 98% 1,1,1,3,3,3-hexamethyldisilazane and 99% ethyl chloroformate purchased from Janssen Chimica and used without purification.
8. *Yields are low and erratic if the overnight cold storage is omitted!*
9. Prolonged exposure to work-up conditions should be avoided to prevent hydrolysis at phosphorus at this step.
10. In some cases, the organic extracts are contaminated with a salt resulting from partial hydrolysis at phosphorus. The salt precipitates slowly overnight and is removed together with the magnesium sulfate by filtration prior to the removal of the solvents.
11. A Büchi GKR-50 Kugelrohr distillation apparatus with three flasks was used by the submitters. The flask containing the crude product was in the upper part of the oven, and the collecting flask was just outside.
12. The forerun consisted mainly of siloxanes and other by-products.
13. The product displays the following NMR and physical data: ^{31}P ($CDCl_3$) δ: +24.0; ^{1}H ($CDCl_3$) δ: 1.29 (t, 3 H, J = 7.1), 3.14 (d, 2 H, J = 21.2), 4.21 (q, 2 H, J = 7.2), 4.45 (m, 4 H); ^{13}C ($CDCl_3$) δ: 14.1, 34.2, 62.8, 62.5, 122.7, 164.7. Anal. Calcd for $C_8H_{11}F_6O_5P$: C, 28.93; H, 3.34; F, 34.32; P, 9.33. Found: C, 29.10; H, 3.49; F, 34.20; P, 9.16.

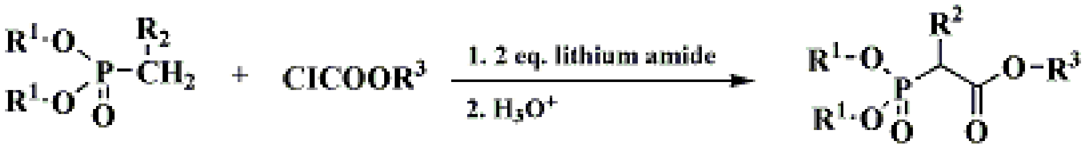
Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Ethyl bis(trifluoroethyl) phosphonoacetate was introduced to synthesis by Still and Gennari in 1983.[4] It is a very useful reagent for the preparation of Z-acrylates by means of a Wittig-Hürner olefination. The procedure described here illustrates a general method for the one-pot formation of phosphonocarboxylates and enolates. The key step in the sequence is the formation of an α-lithiomethyl phosphonate in the presence of two equivalents of a hindered lithium amide, which promotes the direct

generation of the enolate.[5] The present procedure has several advantages: 1) easy availability of reagents, 2) the possibility to extend the reaction to various carboxylate groups by the choice of the chloroformates (e.g., $ClCO_2R^3$; R^3 = Me, Et, i-Pr, tert-Bu), 3) the possibility to extend the reaction to α-alkylated phosphonocarboxylates by the choice of the starting alkylphosphonate $(R^1O)_2P(O)CH_2R^2$ (R^2 = H, Me, Et, Pr, etc.), and 4) high yields of the phosphonates, simplicity, and ease of isolation of the products.



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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

ether (60-29-7)

PHOSPHORUS (7723-14-0)

nitrogen (7727-37-9)

toluene (108-88-3)

Benzophenone (119-61-9)

sodium (13966-32-0)

Benzyl alcohol (100-51-6)

methylene chloride (75-09-2)

ethyl chloroformate (541-41-3)

magnesium sulfate (7487-88-9)

butyllithium (109-72-8)

Tetrahydrofuran, THF (109-99-9)

hexane (110-54-3)

triethylamine (121-44-8)

Triethylamine hydrochloride (554-68-7)

hexamethyldisilazane

Bis(trifluoroethyl) (carboethoxymethyl)phosphonate, Acetic acid, [bis(2,2,2-trifluoroethoxy)phosphinyl]-, ethyl ester, bis(trifluoroethyl) (carboethoxymethyl) phosphonate (124755-24-4)

Bis(trifluoroethyl) methylphosphonate

trifluoroethanol

methylphosphonic dichloride (3279-26-3)

2,2,2-trifluoroethanol (75-89-8)

2,2'-biquinoline (119-91-5)

1,1,1,3,3,3-hexamethyldisilazane (999-97-3)

Ethyl bis(trifluoroethyl) phosphonoacetate

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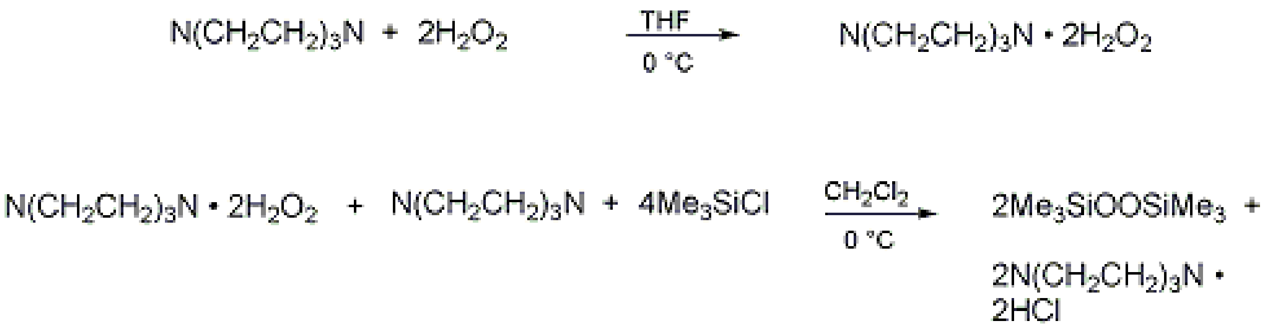
Organic Syntheses, CV 9, 91

BIS(TRIMETHYLSILYL) PEROXIDE (BTMSPO)

[Silane, dioxybis[trimethyl-]



Submitted by P. Dembech[1], A. Ricci, G. Seconi, and M. Taddei.
Checked by Christopher S. Brook, Mark Guzman, and Amos B. Smith, III.

1. Procedure

Caution! The possibility of explosions when handling bis(trimethylsilyl) peroxide (BTMSPO) has been reported,[2] especially in the presence of metal needles, cannulas, etc., although the product was prepared using a different procedure that included the use of 85% H_2O_2 and pyridine. Our method never gave rise to explosions in the general practice of an organic chemistry laboratory. Nevertheless all the reactions were carried out in safety cupboards and behind blast shields(Note 1).

A. *Diazabicyclooctane-hydrogen peroxide (DABCO · $2H_2O_2$) complex*. A 1-L, two-necked flask, fitted with a dropping funnel, 3-cm stirring bar, and a thermometer, is charged with diazabicyclooctane (DABCO) (28.05 g, 0.25 mol) (Note 2) dissolved in commercial grade tetrahydrofuran (THF) (375 mL) (Note 3). The flask is cooled to 0°C (internal temperature, ice-salt bath), and hydrogen peroxide (49 mL of a 35% solution, 0.5 mol) (Note 4) is slowly added at such a rate that the temperature remains constant, under vigorous stirring. A precipitate appears immediately and, after completing the addition of hydrogen peroxide, stirring is continued at 0°C for 1 hr. The mixture is then filtered through a Büchner funnel and the collected precipitate washed with cold THF (3 × 50 mL) and dried under reduced pressure (2 mm, 35–40°C) in a flask for 2 hr. The yield of DABCO · $2H_2O_2$ obtained is 28.3 g (63%), m.p. 102–105°C (sealed tube) with decomposition, softness at 80°C (lit.[3] m.p. 112°C) (Note 5).

B. *Bis(trimethylsilyl) peroxide (BTMSPO)*. A 2-L, three-necked flask, containing a 3-cm stirring bar, and a thermometer, dropping funnel, and an argon inlet adapter, is maintained under a slight pressure of argon. The flask is charged with the DABCO · $2H_2O_2$ complex (28.3 g, 0.157 mol) and DABCO (28 g, 0.25 mol). Dry dichloromethane (700 mL) (Note 6) is added and the mixture is cooled to 0°C. Chlorotrimethylsilane (80 mL, 0.628 mol) (Note 7) is added dropwise, maintaining the temperature at 0°C, and the resulting mixture

is stirred for 5 hr at room temperature. The mixture is filtered through a sintered Büchner funnel and the precipitate is washed with pentane (2 × 25 mL). The solution, transferred to a 2-L flask fitted with a vacuum-jacketed, packed column (70 cm long, 4-cm i.d.) and a distillation head equipped with a dry ice/acetone cold finger (Note 8), is concentrated to ca. 80 mL under reduced pressure (Note 9). Pentane (25 mL) is added to the mixture, the additional precipitate is filtered off, and the solution is transferred to a smaller flask, (500 mL). It is concentrated under reduced pressure with the distillation apparatus previously employed to give a residue of 40.1 g (71% yield) of BTMSPO as a clear colorless liquid. It is shown (Note 10) from multinuclear NMR to be contaminated by ca. 8% of hexamethylsiloxane (Note 11).

For synthetic purposes the BTMSPO obtained can be used without further purification; on the other hand, distillation (40°C/30 mm) or column chromatography (Florisil–eluent pentane) does not seem to improve the grade of purity (Note 12). The compound can be stored under nitrogen in a refrigerator for months without any appreciable decomposition.

2. Notes

1. Because of the reported[4] instability of the DABCO · $2H_2O_2$ complex, the checkers found it prudent to use new glassware for each run.
2. Diazabicyclooctane (DABCO) was used as purchased from Aldrich Chemical Company, Inc.
3. In the preparation of the complex the use of THF, miscible with water, produced a fine precipitate.
4. Hydrogen peroxide, 35% m/v, 120 volumes, from Aldrich Chemical Company, Inc., was used without titration.
5. The submitters ran this procedure on twice the scale (i.e., 0.5 mol of DABCO) in 59% yield. The complex is hygroscopic and can be stored in a desiccator overnight, but decomposes over long storage.
6. DABCO is previously dried at 20–27°C (room temperature) under reduced pressure (2 mm) Dichloromethane was used as purchased from Aldrich Chemical Company, Inc., (99.9%).
7. Trimethylchlorosilane was used as purchased from Aldrich Chemical Company, Inc.
8. If the solvent is removed with a rotary evaporator, considerable loss of product results from codistillation with dichloromethane. The checkers found that if this exact distillation set-up was not used the yield of BTMSPO decreased substantially (30–40%) because of the codistillation of CH_2Cl_2 and BTMSPO (observed in distillate by ^1H NMR). The distillation set-up requires use of a "walk-in" hood (see diagram).

9. Important points of this procedure are the temperature of the pot, which never must exceed 0°C, the temperature of the cooled head of the column, which should vary in the range of −5–0°C, and the vacuum, which throughout the distillation has been kept in the range of 90–100 mm (90–100 drops/min). These conditions apply

to CH_2Cl_2 removal, whereas for pentane distillation a pressure of about 200 mm is recommended. To remove the last traces of solvent at the very end of the fractionation, the pot temperature was raised to 15–20°C and the pressure decreased to 40 mm.

10. The submitters ran this procedure on twice the scale (i.e., 0.28 mol of DABCO · $2H_2O_2$) and report a yield of 94%. The checkers found that the final stillpot residue still contained some DABCO · HCl salt that had to be filtered to obtain pure BTMSPO. Filtration was done via a fluted filter paper.

11. A typical NMR spectroscopic analysis was as follows: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.187 ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ: −1.40

12. Recently another procedure has appeared,[4] dealing with the large scale preparation of BTMSPO. The costs and the yield of the two procedures are comparable, calculated on the amount of H_2O_2-base complex used, but the present procedure avoids the *potential* danger of violent decomposition[2] of the silylated peroxide during its distillation.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The procedure described here, based on a modification of that of A. G. Davies,[5] provides the first large scale preparation of BTMSPO, a reagent widely used for synthetic purposes over the last few years. The present method is characterized by high reliability; the low concentration of H_2O_2, high yields, and the safe procedure are further major advantages.

BTMSPO has been mainly employed as a reagent for the transformation of carbanions into the corresponding trimethylsiloxy or hydroxy derivatives,[6 7] and in the hydroxylation of neutral aromatic systems[8] (in the presence of TfOH).

It has, for example, been used in the preparation of 3-trimethylsiloxyfuran,[9] and to prepare stereochemically pure E- or Z-silyl enol ethers starting from the corresponding E- or Z-vinyl bromides[10] or vinylstannanes.[6,7]

It can also be used as a mild aprotic oxidizing agent (soluble in all common organic solvents), for the transformation of sulfides into the corresponding sulfoxides,[11 12] phosphines into phosphine oxides,[13. 14] in the oxidation of alcohols to aldehydes[15] (as cooxidant of CrO_3 · Py), in the Baeyer-Villiger reaction[16] (in the presence of $TfOSiMe_3$). It has also been employed in the transformation of acetylenes to the corresponding iodoacetylenes.[17]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Florisil

BIS(TRIMETHYLSILYL) PEROXIDE (BTMSPO)

Diazabicyclooctane-hydrogen peroxide (DABCO · $2H_2O_2$) complex

DABCO · $2H_2O_2$

DABCO · $2H_2O_2$ complex

DABCO

BTMSPO

DABCO · HCl

TfOH

nitrogen (7727-37-9)

pyridine (110-86-1)

hydrogen peroxide (7722-84-1)

Pentane (109-66-0)

dichloromethane (75-09-2)

Tetrahydrofuran, THF (109-99-9)

argon (7440-37-1)

CHLOROTRIMETHYLSILANE, trimethylchlorosilane (75-77-4)

hexamethylsiloxane (107-46-0)

Silane, dioxybis[trimethyl- (5796-98-5)

diazabicyclooctane

3-trimethylsiloxyfuran

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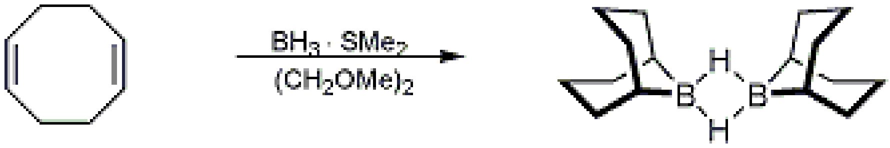
Organic Syntheses, CV 9, 95

9-BORABICYCLO[3.3.1]NONANE DIMER

[9-Borabicyclo[3.3.1]nonane, dimer]



Submitted by John A. Soderquist[1] and Alvin Negron.
Checked by Daniel M. Berger and Larry E. Overman.

1. Procedure

CAUTION! The manipulation and handling of air-sensitive compounds requires the use of special techniques. While no difficulties have been encountered with the present procedures, the preparer should consult References [3] and [2] prior to carrying out these syntheses.

A 2-L, three-necked, round-bottomed flask containing a magnetic stirring bar is fitted with a 250-mL addition funnel and a distillation assembly set for downward distillation to a 500-mL receiver flask. Rubber septa are used to isolate the system from atmospheric contact. Under a nitrogen purge, vented to an exhaust hood through a mercury bubbler, the entire system is thoroughly flame-dried (Note 1). After the 2-L flask is cooled to room temperature, it is charged with 500 mL of pure, dry 1,2-dimethoxyethane (Note 2) and 153 mL (1.53 mol) of borane-methyl sulfide complex (Note 3) employing a double-ended needle to effect the transfer. With a similar technique, 164 g (1.52 mol) of 1,5-cyclooctadiene (Note 4) is transferred to the addition funnel. To the stirred borane solution, 1,5-cyclooctadiene is added dropwise over ca. 1 hr to maintain a reaction temperature of 50–60°C during which time a small amount of dimethyl sulfide (bp 38°C) distills slowly from the reaction mixture. After the addition is completed, the addition funnel is replaced with a glass stopper and approximately 300 mL of the solution is distilled to reach a final distillation temperature of 85°C, indicating the complete removal of dimethyl sulfide from the reaction mixture (Note 5). If the distillate temperature does not reach 85°C, 150 mL of additional 1,2-dimethoxyethane is added and the distillation is continued until the distillate temperature reaches 85°C. The distillation assembly is replaced with a rubber septum and 1,2-dimethoxyethane is added to the reaction flask to bring the total liquid volume to 1 L. The mixture is warmed to effect the dissolution of the solid and allowed to cool very slowly to 0°C, which results in the formation of crystalline 9-borabicyclo[3.3.1]nonane (9-BBN) dimer. The supernatant liquid is decanted from the product using a double-ended needle and the 9-BBN dimer is dissolved in 1 L of fresh 1,2-dimethoxyethane. After the flask is cooled to 0°C, the supernatant liquid is removed as above and the large needles are dried under reduced pressure for 12 hr at

0.1 mm to give 158–165 g (85–89%) of product (mp 152–154°C, sealed capillary) (Note 6),(Note 7),(Note 8).

2. Notes

1. Alternatively, the apparatus can be dried for 4 hr at 150°C, assembled hot and purged with dry nitrogen.
2. 1,2-Dimethoxyethane, available from the Aldrich Chemical Company, Inc., was predried over calcium hydride and distilled from sodium/benzophenone prior to use. The solvent was used directly after purification or stored in an ampule bottle, available from the Aldrich Chemical Company, Inc., under a nitrogen atmosphere.
3. Borane-methyl sulfide complex, obtained from the Aldrich Chemical Company, Inc., was used directly without additional purification. However, titration of the reagent was carried out with glycerol as described[3] to determine its actual molarity. Older samples of this reagent can be distilled under aspirator vacuum to obtain pure reagent.
4. 1,5-Cyclooctadiene, obtained from the Aldrich Chemical Company, Inc., was distilled under aspirator pressure from lithium aluminum hydride prior to use.
5. Failure to remove the dimethyl sulfide from the reaction mixture increases the solubility of the 9-BBN dimer and lowers the overall yield to ca. 65%.
6. The spectra of the product are as follows: ^{1}H NMR (300 MHz, C_6D_6) δ: 1.44–1.57 (m, 4 H), 1.58–1.74 (m, 12 H), 1.83–2.07 (m, 12 H). A standard HETCOR experiment revealed that protons on each of the methylene carbons were superimposed upon one another to give rise to these downfield multiplets; ^{13}C NMR (75 MHz, C_6D_6) δ: 20.2 (br, C-1,5), 24.3 (C-3,7), 33.6 (C-2,4,6,8); ^{11}B NMR (96 MHz, C_6D_6) δ: 28.
7. The 9-BBN dimer so prepared is reasonably air-stable so that exposure to the atmosphere for 1 month lowered the mp to ca. 146–151°C.
8. Purification of commercial 9-BBN and other samples can be effected by recrystallization from 1,2-dimethoxyethane. Insoluble impurities can be removed from hot 1,2-dimethoxyethane solutions of 9-BBN by decantation of the solution to a second dry flask. To prevent clogging of the double-ended needle during the transfer process it is important to keep the ends of needle below the liquid surfaces. We have found that the receiver vessel should be charged with a small quantity of fresh, hot 1,2-dimethoxyethane prior to decantation and that a portion of this material should be transferred under a positive pressure of nitrogen to the 9-BBN solution to warm initially the transfer needle. Subsequently, the hot 9-BBN solution can be transferred without difficulty.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

9-Borabicyclo[3.3.1]nonane (9-BBN) has been prepared by the thermal redistribution of 9-n-propyl-9-BBN,[4] and the hydroboration of 1,5-cyclooctadiene with borane-tetrahydrofuran complex followed by thermal isomerization of the mixture of dialkylboranes at 65°C.[5] Solutions of 9-BBN have been prepared from the hydroboration of 1,5-cyclooctadiene with borane-methyl sulfide in solvents other than THF.[6] The present procedure involves the cyclic hydroboration of 1,5-cyclooctadiene with borane-methyl sulfide in 1,2-dimethoxyethane.[7] Distillative removal of the dimethyl sulfide in this special solvent system provides a medium that gives high purity, large needles of crystalline 9-BBN dimer in excellent yield. The material can be handled in air for brief periods without measurable decomposition.

As a dialkylborane, 9-borabicyclo[3.3.1]nonane (9-BBN) is unrivaled in both stability and selectivity.[8] It has been distilled (bp 195°C, 12 mm) and exhibits a strong characteristic IR absorption band at 1560 cm^{-1} (B-H-B) for the bridged dimeric structure.[5] The crystal structure of 9-BBN dimer has been determined[9] and the drawing above approximates the conformational features of this compound. The ^{13}C NMR properties of 9-BBN adducts have been studied extensively.[10]

Since the 9-methoxy derivative of 9-BBN is a common by-product of several reactions of 9-BBN,[11] its efficient conversion back to 9-BBN has been described.[12] Such a process enables one to recycle 9-BBN in reactions which require its high regioselectivity in hydroboration reactions and the related organoborane conversions.

The selective transformations of 9-BBN are numerous and varied, with derivatives being readily prepared through both hydroboration and organometallic methodology.[8] It has been used for the preparation of isomerically-pure boracycles,[11,13] the highly enantioselective reduction of aldehydes and ketones,[14] the preparation of new selective borohydride reducing agents,[15] C-C bond-forming transformations,[16] and radiopharmaceutical labeling.[17] Its reactivity has made it the reagent of choice for many organoborane conversions.[18] The stability and distinctive spectral properties of 9-BBN have provided the initial key information to unravel the details of hydroboration reactions.[8,19]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 107
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

9-BBN

9-Borabicyclo[3.3.1]nonane dimer

9-Borabicyclo[3.3.1]nonane, dimer

9-borabicyclo[3.3.1]nonane (9-BBN) dimer

9-BBN dimer

9-Borabicyclo[3.3.1]nonane (9-BBN)

9-n-propyl-9-BBN

9-BB

glycerol (56-81-5)

nitrogen (7727-37-9)

Benzophenone (119-61-9)

sodium (13966-32-0)

borane (7440-42-8)

dimethyl sulfide (75-18-3)

THF (109-99-9)

lithium aluminum hydride (16853-85-3)

calcium hydride (7789-78-8)

1,2-dimethoxyethane (110-71-4)

1,5-cyclooctadiene

borane-tetrahydrofuran complex (14044-65-6)

borane-methyl sulfide complex, borane-methyl sulfide (13292-87-0)

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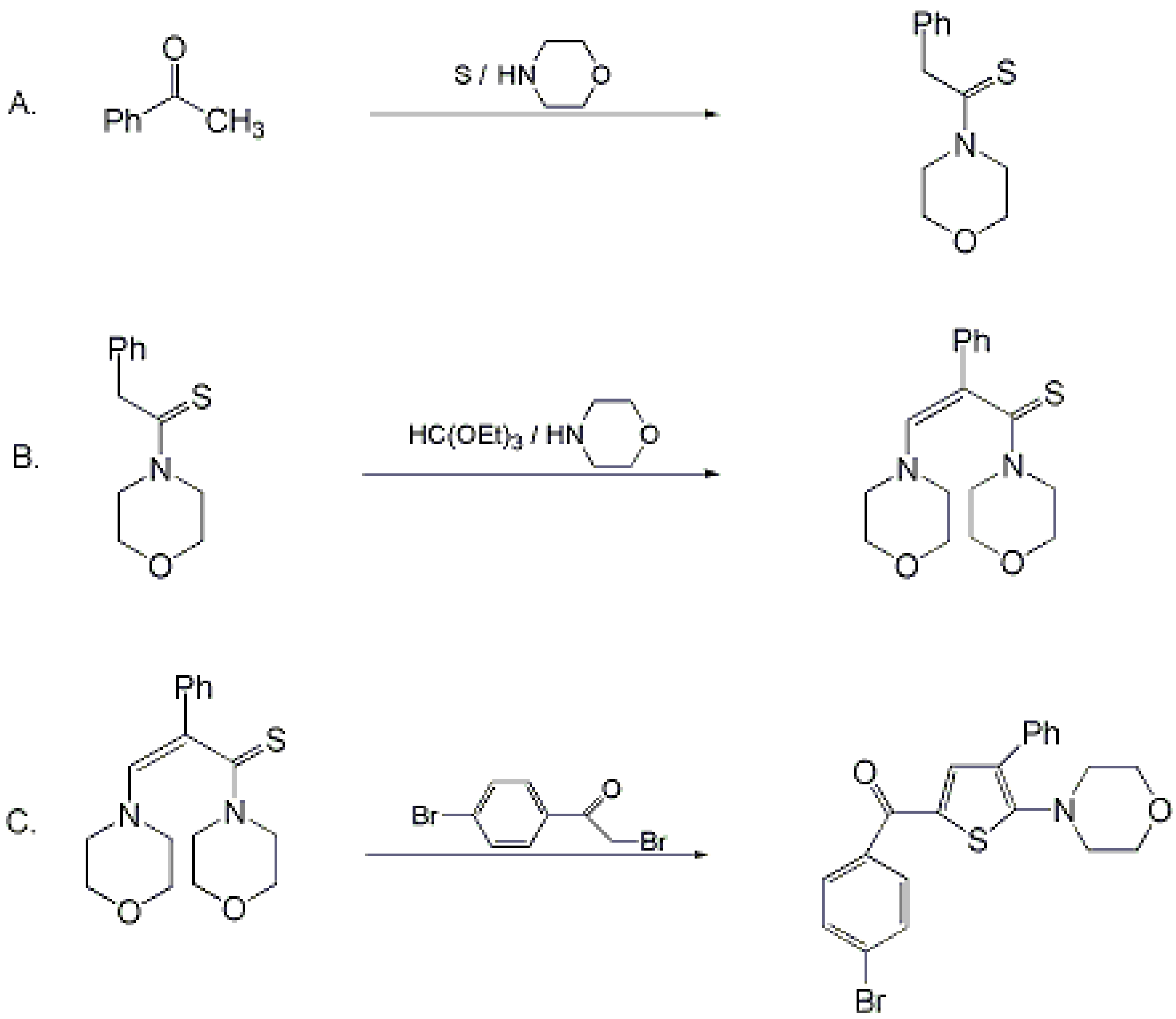
Organic Syntheses, CV 9, 99

3-MORPHOLINO-2-PHENYLTHIOACRYLIC ACID MORPHOLIDE AND 5-(4-BROMOBENZOYL-2-(4-MORPHOLINO)-3-PHENYLTHIOPHENE

[(Morpholine, 4-[3-(4-morpholinyl)-2-phenyl-1-thioxo-2-propenyl]-,) and (Thiophene, 5-(4-bromobenzoyl)-2-(4-morpholino)-3-phenyl-)]



Submitted by Andreas Rolfs and Jürgen Liebscher[1].
Checked by Andrew B. Benowitz and Amos B. Smith, III.

1. Procedure

Caution! Part A should be carried out in an efficient hood to avoid exposure to noxious vapors (hydrogen sulfide).

A. *Phenylthioacetic acid morpholide.* A 100-mL, round-bottomed flask is charged with 24.0 g (0.2 mol) of acetophenone, 1 g of p-toluenesulfonic acid monohydrate,

36.0 g (0.41 mol) of morpholine, and 6.4 g (0.2 mol) of sulfur (Note 1). The flask is equipped with a reflux condenser and is heated at reflux for 3 hr (Note 2). The resulting reddish-brown solution is poured into 100 mL of stirred hot methanol (55–60°C). The wall of the beaker is scratched with a glass rod for seeding. The beaker is sealed with aluminum foil and put into a refrigerator for 6 hr (Note 3). The resulting crystalline product is filtered and washed twice with ice-cold methanol (10 mL). The material (22.2 g, mp 69–79°C, almost colorless) is recrystallized by adding 25 mL of methanol and 25 mL of water and heating at reflux, followed by slow addition of methanol (about 58 mL) until complete solution is obtained. After the sides of the flask are scratched, the solution is cooled in a refrigerator for about 10 hr; 21.9 g (49.5%) (Note 4) of the pure product is obtained, mp 77.5–79°C.

B. *3-Morpholino-2-phenylthioacrylic acid morpholide*. A distillation apparatus (250-mL, round-bottomed flask, distillation head, thermometer, condenser and receiver) equipped with a magnetic stirrer is charged with 22.3 g (0.1 mol) of phenylthioacetic acid morpholide, 26.1 g (0.3 mol) of morpholine and 67 mL (0.4 mol) of triethyl orthoformate (Note 5). The flask is heated in a heating bath (bath temperature 160°C) for 8 hr. During this time, ethanol is distilled continuously from the reaction (about 18 mL). Further raising the temperature of the bath to 180°C gives rise to the distillation of excess morpholine and triethyl orthoformate (38 mL, bp 128–130°C) from the orange solution within 30 min (Note 6). The mixture is evaporated under reduced pressure (rotary evaporator, bath temperature 80°C). The remaining crystalline material is dissolved in 30 mL of chloroform and 150 mL of hot methanol (about 60°C). The solution is allowed to cool to room temperature (Note 7) and is put into a freezer (–24°C) for 12 hr. The light yellow product is filtered and washed with methanol (30 mL) followed by diethyl ether (30 mL). After drying in the open air for 18 hr, 29.4 g (92%) (Note 8) of pure material is obtained, mp 156–156.5°C (Note 9).

C. *5-(4-Bromobenzoyl)-2-morpholino-3-phenylthiophene*. A mixture of 3.18 g (0.01 mol) of 3-morpholino-2-phenylthioacrylic acid morpholide, 2.8 g (0.01 mol) of 4-bromophenacyl bromide, and 50 mL of methanol is heated to boiling. After the addition of a solution of 1.01 g (0.01 mol) of triethylamine in 10 mL of methanol to the mixture, the reaction is allowed to heat at reflux for 10 min. The reaction mixture is then cooled to 0°C in a refrigerator for 1 hr. The yellow crystalline product is collected by filtration and washed with 20 mL of cold methanol. After drying in the open air for 18 hr, 4.15 g (97%) of analytically pure product is obtained, mp 176–177°C (mp[2] 175°C) (Note 10). Although not necessary, the material can be recrystallized from acetonitrile.

2. Notes

1. All chemicals were obtained from the Aldrich Chemical Company, Inc. It is advisable to distill acetophenone and morpholine. The sulfur should be small particles and must not form lumps. Excess morpholine is generally

recommended in Willgerodt-Kindler reactions.
2. The reflux condenser should be connected by a gas outlet and tubing directly to the hood pipe to prevent hydrogen sulfide from entering the laboratory atmosphere.
3. If crystallization fails, a small amount of the solution is evaporated, cooled in an ice/sodium chloride bath, and scratched with a glass rod. The resulting crystals are used to seed the main solution.
4. a) The reported yield[3] of 94% could not be achieved. The amount of sulfur can be increased to 12.4 g (0.2 mol) giving a higher yield of phenylthioacetic acid morpholide that contains some unreacted sulfur and a yellow impurity (2-morpholin-4-yl-1-phenyl-2-thioxoethanone) that is difficult to remove. b) Spectral data: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.37 (m, 2 H), 3.61 (m, 2 H), 3.72 (m, 2 H), 4.34 (s, 2 H), 4.34 (m, 2 H), 7.23 (m, 1 H), 7.31 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 50.06, 50.50, 50.70, 65.99, 66.21, 127.01, 127.01, 127.66, 128.84, 135.70, 199.91.
5. Triethyl orthoformate was distilled. Trimethyl orthoformate can not be used since no reaction occurs. Excess morpholine and triethyl orthoformate are used as solvents to achieve smooth solution. The amounts of both of these reagents can be increased without affecting the yield.
6. TLC of the remaining solution (0.25-mm Whatman precoated silica gel plate, 33% ethyl acetate in hexanes) does not show any starting phenylthioacetic acid morpholide.
7. Crystallization of the pure product begins after slight cooling.
8. Additional product can be obtained by evaporating the combined mother liquor, adding 25 mL of methanol to the remaining oil, and cooling the resulting solution to –24°C.
9. The product consists of a mixture of E/Z isomers[4] in an approximate ratio of 15:85; R_f = 0.35 and 0.25 (0.25-mm Whatman precoated silica gel plate, 33% ethyl acetate in hexanes). Anal. Calcd for $C_{17}H_{22}N_2O_2S$: C, 64.12; H, 6.96; N, 8.80; S, 10.07, Found: C, 64.38; H, 6.99; N, 8.80; S, 10.18. IR (KBr) cm^{-1}: 1611, 1586, 1440, 1429, 1413, 1236, 1226, 1116; Z-isomer (major isomer); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 124.8, 128.5 (C2',C3'-C_6H_5), 125.3 (C4'-C_6H_5), 139.3 (C1'-C_6H_5), 112.6 (C2), 137.5 (C3), 198.9 (C1); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.07 (s, HC=C); E-isomer (minor isomer); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 126.4 (C4'-C_6H_5), 128.1, 129.9 (C2',C3'-C_6H_5), 138.3 (C1'-C_6H_5), 115.2 (C2), 147.4 (C3), 203.3 (C1).
10. The spectral data for the title compound are as follows: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.05 (m, 4 H), 3.71 (m, 4 H), 7.21 (dddd, 1 H), 7.35 (m, 2 H), 7.46 (s, 1 H), 7.50–7.53 (m, 2 H), 7.57 (ddd, 2 H), 7.65 (ddd, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 51.79, 66.11, 126.21, 126.28, 127.29, 127.67, 128.13, 130.08, 130.31, 131.57, 135.51, 137.12, 138.64, 162.80, 185.84.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

3-Aminothioacrylic acid amides are versatile β-dicarbonyl derivatives that have found widespread use as C-C-C and C-C-C-S building blocks in the synthesis of heterocyclic and open chain products.[5,6] To date, 2-arylthioacrylmorpholides with mainly a 3-dimethylamino leaving group have been prepared by the Vilsmeier-Haack reaction of arylthioacetic acid amides with DMF/$POCl_3$.[7,8] This synthesis is not convenient since the resulting 3-dimethylaminothioacrylic acid morpholides must be isolated as hydroperchlorates, the yields are occasionally low, and in a number of cases (especially if other amino groups beside the morpholino or dimethylamino are found in the products, or if the aryl group is ortho-substituted) no stable crystalline material is obtained. With the present procedure,[9] a very reliable synthesis of 3-morpholinothioacrylic acid amides with a wide variety of 2-aryl substituents has been elaborated. Instead of triethyl orthoformate/morpholine, the non-commercially available trismorpholinomethane[10] can be used,[9] also enabling the synthesis of the 2-unsubstituted 3-morpholinothioacrylic acid morpholide. In addition to the well known Willgerodt-Kindler reaction,[11] the starting thioacetamides can also be obtained by other methods such as reaction of styrenes with sulfur and amines,[12] and the reaction of arylthioacetic acid thiol ester with amines.[13] Furthermore the thioamide amino group of the synthesized 3-morpholinothioacrylic acid amides can also be monosubstituted. Through the use of pyrrolidine, 3-pyrrolidinothioacrylic acid amides can be obtained. Generally the procedure is very simple and safe. Scale-up can be effected without incident and very pure products are obtained. Since the 3-morpholino substituent usually acts as a leaving group in further synthetic applications, the same reactivity is found as in the well investigated 2-aryl-3-dimethylaminothioacrylic acid morpholides.

The mechanism of the formation of 3-aminothioacrylic amides from arylthioacetic acid amides and ortho ester amine is likely to resemble similar aminomethinylation reactions of other CH-acidic substrates.[14]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hexanes

$POCl_3$

3-Morpholino-2-phenylthioacrylic acid morpholide

3-MORPHOLINO-2-PHENYLTHIOACRYLIC ACID MORPHOLIDE AND 5-(4-BROMOBENZOYL-2-(4-MORPHOLINO)-3-PHENYLTHIOPHENE

(Morpholine, 4-[3-(4-morpholinyl)-2-phenyl-1-thioxo-2-propenyl]-

Thiophene, 5-(4-bromobenzoyl)-2-(4-morpholino)-3-phenyl-)

ethanol (64-17-5)

ethyl acetate (141-78-6)

methanol (67-56-1)

diethyl ether (60-29-7)

acetonitrile (75-05-8)

chloroform (67-66-3)

hydrogen sulfide (7783-06-4)

sulfur (7704-34-9)

Acetophenone (98-86-2)

triethyl orthoformate (122-51-0)

DMF (68-12-2)

pyrrolidine (123-75-1)

morpholine (110-91-8)

triethylamine (121-44-8)

trimethyl orthoformate (149-73-5)

p-toluenesulfonic acid monohydrate (6192-52-5)

5-(4-Bromobenzoyl)-2-morpholino-3-phenylthiophene (86673-62-3)

Phenylthioacetic acid morpholide (949-01-9)

4-bromophenacyl bromide (99-73-0)

2-morpholin-4-yl-1-phenyl-2-thioxoethanone

trismorpholinomethane

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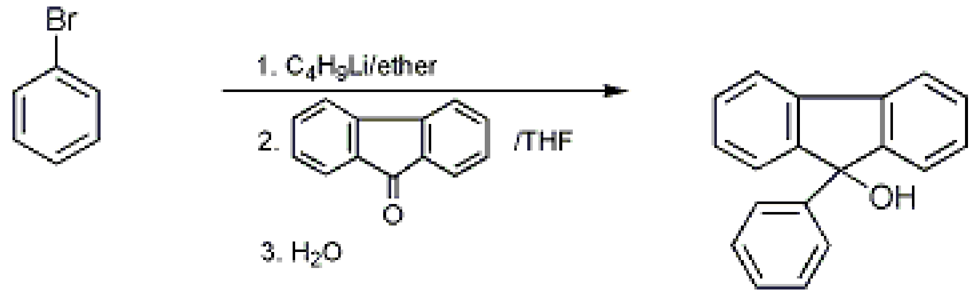
Organic Syntheses, CV 9, 103

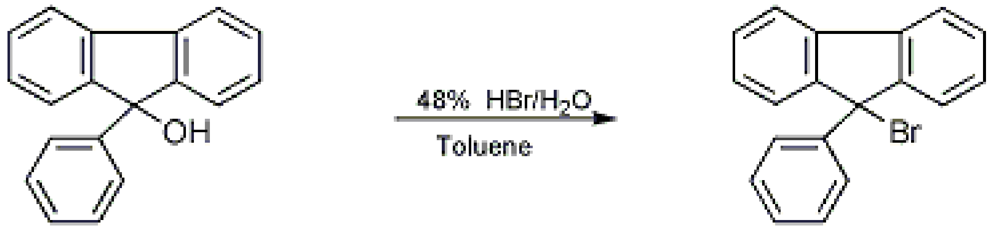
9-BROMO-9-PHENYLFLUORENE

[9H-Fluorene, 9-bromo-9-phenyl-]

A.



B.



Submitted by T. F. Jamison, W. D. Lubell, J. M. Dener, M. J. Krisché, and H. Rapoport[1].
Checked by Carol M. Taylor and Amos B. Smith, III.

1. Procedure

CAUTION! Butyllithium is an air-sensitive, pyrophoric material and should be kept under an inert atmosphere at all times. Persons following this procedure should be thoroughly familiar with the handling of air-sensitive solutions(Note 1). Bromobenzene is an irritant and a potential carcinogen.

A. *9-Phenyl-9-fluorenol.* A flame-dried, 3-L, three-necked, round-bottomed flask equipped with an overhead stirrer, rubber septum, and glass stopper, under a nitrogen atmosphere, is charged with bromobenzene (158 mL, 1.5 mol, (Note 2)) and ethyl ether (800 mL, (Note 2)). The solution is cooled in an ice bath and stirred at 0°C. A flame-dried, 1-L, graduated cylinder fitted with a rubber septum is filled with 767 mL of a 1.5 M solution of butyllithium in hexane (1.15 mol, (Note 3)) under a nitrogen atmosphere. The butyllithium solution is then added to the 0°C ether solution over 30 min via a Teflon cannula with a positive nitrogen pressure. After the addition is complete, the solution is stirred for 20 min at 0°C and a solution of fluorenone (180 g, 1 mol, (Note 4)) in tetrahydrofuran (THF) (300 mL, (Note 5)) is added over 25 min via a Teflon cannula using positive nitrogen pressure. The ice bath is removed, the mixture is allowed to reach room temperature (24°C), and stirred for 2 hr. During this

time, lithium bromide precipitates out of the reaction mixture. Water (250 mL) is added to dissolve the precipitate, the layers are separated, and the organic layer is washed with 800 mL of water and 800 mL of brine. The brine wash is discarded, and the other aqueous layers are combined and extracted with ethyl ether (2 × 200 mL). The combined organic layers are evaporated on a rotary evaporator at an initial bath temperature of 30–35°C and, when most of the volatile material has been removed, at a bath temperature of 70–75°C until a yellow solid is obtained (Note 6).

B. 9-Bromo-9-phenylfluorene. The yellow solid obtained in Step A is dissolved in toluene (800 mL, (Note 7)) and transferred to a three-necked, 2-L Morton flask (Note 8) equipped with an overhead stirrer, a nitrogen-filled balloon, and a glass stopper. Aqueous hydrobromic acid (HBr) (48%, 400 mL, (Note 9)) is added, and the heterogeneous mixture is vigorously stirred at room temperature (ca. 20–25°C) for 24 hr (Note 10). The layers are separated, the aqueous layer is extracted with toluene (400 mL), the combined organic layers are dried over sodium sulfate (Na_2SO_4) and filtered. The filter cake is washed with ethyl acetate (2 × 50 mL), and the combined organic filtrate and washings are evaporated to a yellow solid. Recrystallization from isooctane (1.25 L, (Note 7)) gives 270 g (84%) of 9-bromo-9-phenylfluorene (Note 11),(Note 12),(Note 13),(Note 14).

2. Notes

1. A pamphlet describing techniques for the handling of air-sensitive solutions can be ordered from Aldrich Chemical Company, Inc.
2. Bromobenzene and ethyl ether were obtained from the Fisher Scientific Company. Bromobenzene was distilled from calcium hydride (CaH_2) under vacuum, and ethyl ether was distilled from sodium/benzophenone. Each liquid was transferred to the reaction vessel via glass syringe or Teflon cannula under a positive nitrogen pressure.
3. Butyllithium was obtained as a solution in hexane from Foote Mineral Ltd. and titrated with 0.5 M 2-propanol in tetrahydrofuran (THF) with 1,10-phenanthroline as the indicator. The butyllithium was transferred via Teflon cannula under positive nitrogen pressure. The checkers used a 1.6 M solution of butyllithium purchased from Aldrich Chemical Company, Inc.
4. Fluorenone was obtained from Chemical Dynamics Corporation or Fluka Chemical Corporation and recrystallized from absolute ethanol to remove fluorene.
5. Tetrahydrofuran was obtained from the Fisher Scientific Company and distilled from lithium aluminum hydride ($LiAlH_4$). (See warning: *Org. Synth., Coll. Vol. V* **1973**, 976).
6. The physical properties of 9-phenyl-9-fluorenol, which was recrystallized from isooctane to give pale yellow, translucent needles, are as follows: ^{13}C NMR (Nicolet, 200 MHz) δ: 83.5, 120.0, 124.7, 125.3, 127.1, 128.1, 128.4, 129.0, 139.5, 143.1, 150.3; mp 107–108°C (lit. mp 85°C,[2] 107°C[3]). The

checkers observed mp 85–86°C. Anal. Calcd for $C_{19}H_{14}O$: C, 88.34; H, 5.46. Found: C, 88.39; H, 5.60.

7. Toluene and isooctane (2,2,4-trimethylpentane) were obtained from the Fisher Scientific Company and used without further purification.

8. Use of a Morton flask and an overhead stirrer allows for better mixing of the two-phase system and gives conversion to product faster than does use of a standard round-bottomed flask with an overhead stirrer.

9. Aqueous hydrobromic acid (HBr) (48%) was obtained from the J. T. Baker Chemical Company.

10. The relative amounts of 9-phenyl-9-fluorenol and 9-bromo-9-phenylfluorene were determined as follows: A ^{13}C NMR spectrum ($CDCl_3$ solution, Bruker 400 MHz) of an authentic sample of 9-bromo-9-phenylfluorene was recorded and then doped in 1% increments with authentic 9-phenyl-9-fluorenol. A ^{13}C NMR spectrum ($CDCl_3$ solution, Bruker 400 MHz) was recorded after each doping, and the heights of the peaks at 120.3 ppm (bromide) and 120.0 ppm (alcohol) were monitored. These spectra were compared with a ^{13}C NMR spectrum ($CDCl_3$ solution, Bruker 400 MHz) of the sample in question. Application of this technique to an evaporated aliquot of the reaction mixture in Step B, indicated >97% conversion of alcohol to bromide after 24 hr.

11. 9-Bromo-9-phenylfluorene is greater than 99% pure as shown by ^{13}C NMR, (determined by the procedure in (Note 10)); mp 99°C (lit.[4] mp 99°C).

12. The physical properties of 9-bromo-9-phenylfluorene, which was recrystallized from isooctane to give light-yellow, lustrous flakes, are as follows: ^{13}C NMR δ: 67.5, 120.3, 126.1, 127.4, 128.0, 128.3, 128.5, 129.0, 138.1, 141.1, 149.6; mp 99°C (lit.[4] mp 99°C); IR ($CHCl_3$) cm^{-1}: 3060 (m), 3000 (m), 1600 (w), 1485 (m), 1445 (s), 1150 (m), 830 (w), 690 (m), 620 (m); UV (EtOH) λ, nm, (ε): 310 (8,000), 276 (29,000), 238 (59,000), 230 (70,000), 213 (78,000). Anal. Calcd. for $C_{19}H_{13}Br$: C, 71.04; H, 4.08; Br, 24.88. Found: C, 71.11; H, 4.13; Br, 25.07.

13. The submitters report that 9-bromo-9-phenylfluorene of poorer quality can also be prepared on an identical scale in a lower yield using phenyllithium (obtained from Aldrich Chemical Company, Inc.) following the procedure given in Step A with minor modifications: A black solution of phenyllithium (632 mL, 1.14 mol, (Note 14)) was added to a 0°C solution of fluorenone (180.2 g, 1 mol, (Note 4)) in THF (1360 mL, (Note 5)) over 30 min, and the solution was stirred for 2 hr at room temperature (24°C). Isolation as described in Step A and conversion to the bromide as described in Step B, afforded 234 g (72.8%) of 9-bromo-9-phenylfluorene as an orange/yellow solid (mp 98°C, lit.[4] mp 99°C); >99% pure [^{13}C NMR (Note 10)] that was contaminated with approximately 20 g of a black solid; mp 91–94.5°C. This alternative procedure was not checked by the checkers.

14. Phenyllithium ("2.0 M" in cyclohexane/ether, 70/30, found to be 1.8 M by titration as described in (Note 3)) was obtained from the Aldrich Chemical

Company, Inc., as a black solution and was added to the solution of fluorenone via Teflon cannula under positive nitrogen pressure.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Alkylation of α-amino esters with 9-bromo-9-phenylfluorene serves as the principal step in the preparation of N-(9-phenylfluoren-9-yl)-α-amino carbonyl compounds which are useful chiral educts for asymmetric synthesis. A discussion of the synthetic utility of N-9-phenylfluoren-9-yl derivatives of amino acids and amino acid esters appears on p. 348.

The preparation reported here is based on the method of Christie and Rapoport.[5] 9-Bromo-9-phenylfluorene has also been prepared by a light-initiated reaction of bromine and 9-phenylfluorene in carbon disulfide,[4] by addition of phenylmagnesium bromide to fluorene[3] followed by treatment with acetyl bromide,[6] and by treatment of 9-phenylfluorene with N-bromosuccinimide.[7]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

brine

ethanol (64-17-5)

ethyl acetate (141-78-6)

ether, ethyl ether (60-29-7)

HYDROBROMIC ACID (10035-10-6)

bromine (7726-95-6)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

cyclohexane (110-82-7)

toluene (108-88-3)

Benzophenone (119-61-9)

sodium (13966-32-0)

2-propanol (67-63-0)

bromobenzene (108-86-1)

carbon disulfide (75-15-0)

Phenylmagnesium bromide (100-58-3)

Phenyllithium (591-51-5)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

acetyl bromide (506-96-7)

lithium aluminum hydride (16853-85-3)

N-bromosuccinimide (128-08-5)

hexane (110-54-3)

fluorenone (486-25-9)

calcium hydride (7789-78-8)

isooctane (592-27-8)

1,10-phenanthroline (66-71-7)

lithium bromide (7550-35-8)

9-Bromo-9-phenylfluorene, 9-bromo-9-phenyl-fluorene, 9H-Fluorene, 9-bromo-9-phenyl- (55135-66-5)

9-Phenyl-9-fluorenol (25603-67-2)

2,2,4-trimethylpentane (540-84-1)

9-phenylfluorene (789-24-2)

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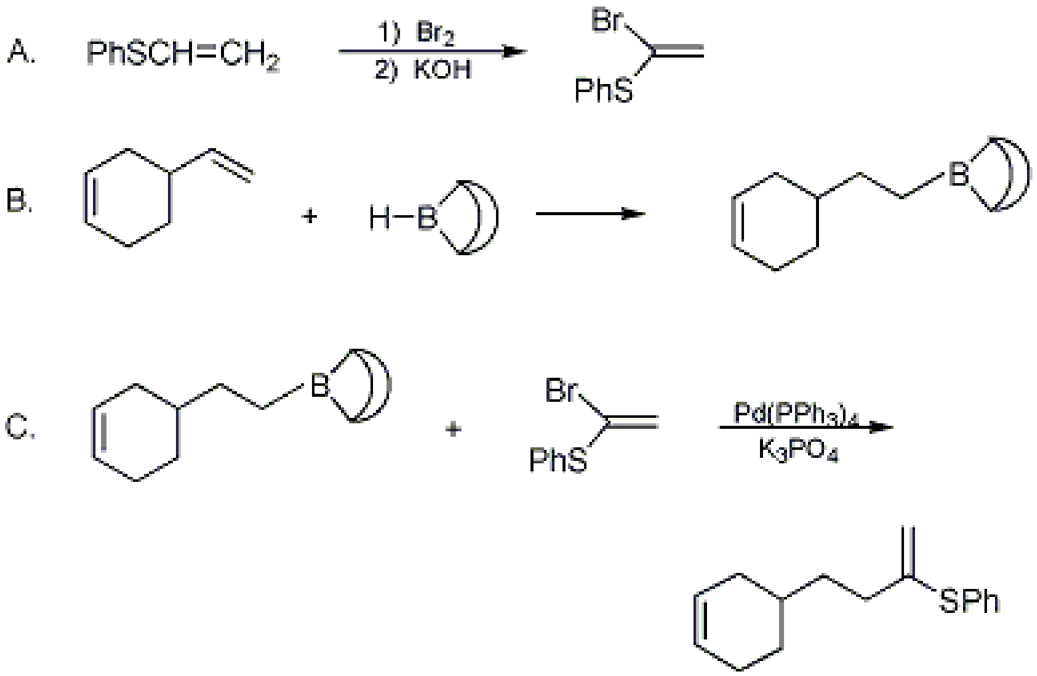
Organic Syntheses, CV 9, 107

PALLADIUM(0)-CATALYZED REACTION OF 9-ALKYL-9-BORABICYCLO[3.3.1]NONANE WITH 1-BROMO-1-PHENYLTHIOETHENE: 4-(3-CYCLOHEXENYL)-2-PHENYLTHIO-1-BUTENE



Submitted by Tatsuo Ishiyama, Norio Miyaura, and Akira Suzuki[1].
Checked by Ron J. Graham and Leo A. Paquette.

1. Procedure

A. *1-Bromo-1-phenylthioethene.* A 300-mL, two-necked, round-bottomed flask is fitted with a magnetic stirring bar, pressure-equalizing dropping funnel, and a reflux condenser to which a nitrogen inlet tube and an oil bubbler are attached, and flushed with nitrogen (Note 1). In the flask are placed 13.6 g (100 mmol) of phenyl vinyl sulfide (Note 2) and 80 mL of ether (Note 3), which are then cooled to ca. −78°C with a dry ice-methanol bath. Bromine (16.0 g, 100 mmol) is added dropwise over 30 min to the stirred solution. After the solution is warmed to room temperature, 40 mL of absolute ethanol, followed by a solution of 8.0 g (140 mmol) of potassium hydroxide in 80 mL of absolute ethanol is added dropwise to the resulting slightly red solution over 30 min. The light brown solution containing a white precipitate of potassium bromide is stirred at room temperature for 2 hr. The precipitate is removed by filtration and the filtrate is concentrated by rotary evaporation. The residue is treated with 200 mL of ether and 200 mL of water. The organic layer is separated, washed with brine (50 mL), and dried over anhydrous magnesium sulfate. After rotary evaporation of the solvent, the residual oil is distilled under reduced pressure to give 17.2 g (80% yield)

of 1-bromo-1-phenylthioethene (Note 4) as a colorless liquid, bp 49–50°C (0.07 mm).

B. *9-[2-(3-Cyclohexenyl)ethyl]-9-BBN.* A 500-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, thermometer, reflux condenser, and a pressure-equalizing addition funnel capped with a rubber septum. The apparatus is connected through the condenser to a nitrogen source and an oil bubbler and flushed with nitrogen. The flask is charged with 35 mL of tetrahydrofuran (Note 5) and 8.32 g (77.0 mmol) of 4-vinyl-1-cyclohexene (Note 6) and cooled to 0°C. A 0.5 M solution of 9-BBN (9-borabicyclo[3.3.1]nonane) in tetrahydrofuran (154 mL, 77.0 mmol) (Note 7) is transferred via cannula to the addition funnel and is added dropwise with stirring over 1 hr maintaining the temperature at 0–5°C. The reaction mixture is stirred for 1 hr at 0°C and for 1.5 hr at room temperature. The solution obtained is used in the next step without further treatment (Note 8).

C. *4-(3-Cyclohexenyl)-2-phenylthio-1-butene*. To the above solution of the borane derivative, 0.809 g (0.700 mmol) of tetrakis(triphenylphosphine)palladium(0) (Note 9), 1.47 g (5.60 mmol) of triphenylphosphine (Note 10), 35 mL of 3 M potassium phosphate in water (Note 11), and finally 15.1 g (70.0 mmol) of 1-bromo-1-phenylthioethene are added and the resulting mixture is heated at reflux for 3 hr with stirring. The light brown solution is cooled to room temperature and treated with 6.4 g (100 mmol) of ethanolamine (Note 12) for 1 hr. Then 100 mL of hexane and 100 mL of water are added. The organic layer is separated, washed with 100 mL of water, and dried over anhydrous magnesium sulfate. The drying agent is removed by filtration and the filtrate is concentrated by rotary evaporation. The addition of 250 mL of hexane to the residual viscous oil, containing some solid, precipitates the 9-BBN/ethanolamine complex. The solid is removed by filtration and is washed with hexane (50 mL × 3), and the filtrate is concentrated using a rotary evaporator. The crude product is passed through a short silica gel column (60–200 mesh, 60 g) using hexane as an eluent (Note 13). After removal of the hexane, the residue is distilled under reduced pressure to give 12.5–13.9 g (73–81%) of 4-(3-cyclohexenyl)-2-phenylthio-1-butene as a colorless liquid, bp 114–116°C (0.04 mm) (Note 14).

2. Notes

1. All glassware was pre-dried in an oven at 120°C for 2 hr, assembled while hot, and allowed to cool under a stream of nitrogen.
2. The preparation of phenyl vinyl sulfide is described *Org. Synth., Coll. Vol. VII* **1990**, 453 and in this volume on pp. 662. The compound is also available from Aldrich Chemical Company, Inc.
3. Ether was distilled from benzophenone ketyl under nitrogen before use.
4. The product is labile at room temperature and should be stored in a freezer. Spectral data are as follows: IR (neat) cm^{-1}: 3076, 3060, 1583, 1477, 1440, 1069, 752, 689; ^1H NMR (300 MHz, $CDCl_3$) δ: 5.73 (d, 1 H, J = 2.3), 5.83 (d, 1 H, J = 2.3), 7.23–7.46 (m, 5 H).
5. Tetrahydrofuran is distilled from benzophenone ketyl under nitrogen before

use.
6. 4-Vinyl-1-cyclohexene was obtained from Aldrich Chemical Company, Inc., and distilled it prior to use.
7. A 0.5 M solution of 9-BBN in tetrahydrofuran was purchased from Aldrich Chemical Company, Inc., and was used without additional purification. The preparation[2] of the reagent by hydroboration of 1,5-cyclooctadiene with borane/tetrahydrofuran complex is reported.

8. If necessary, 9-[2-(3-cyclohexenyl)ethyl]-9-BBN[3] can be purified by removal of the solvent and vacuum distillation under nitrogen [bp 103°C (0.035 mm)].

9. The preparation of tetrakis(triphenylphosphine)palladium(0) is described.[4] It is also available from Aldrich Chemical Company, Inc.
10. Triphenylphosphine was obtained from Nakarai Chemicals, Japan. When the reaction is carried out without additional triphenylphosphine, the yield of coupling product may drop to 60–70% and the product is accompanied by the by-products, phenyl vinyl sulfide and 4-vinyl-1-cyclohexene, derived from β-hydride elimination.
11. The solution is prepared by dissolving 22.3 g (105 mmol) of potassium phosphate (Nakarai Chemicals, Japan) in water and adjusting the final volume to 35 mL. The original method[5] used sodium hydroxide as base; potassium phosphate is desirable for the extension of the present procedure to base-sensitive compounds. Under such conditions, the reaction with 9-(10-carbomethoxydecanyl)-9-BBN proceeds similarly without saponification of the ester group.
12. Ethanolamine was purchased from Nakarai Chemicals, Japan. The reagent reacts with the resulting 9-BBN residue to give an air stable 1:1 adduct[6] that is insoluble in hexane.
13. This operation effectively removes the remaining palladium-containing compounds, phosphine derivatives, and borane residues.
14. Gas chromatographic analysis of the product (Finnigan ITD 800-fused silica capillary, SE 30 column, 0.35 mm × 25 m, column temperature 80–250°C, injection temperature 250°C) shows that the chemical purity is 94–98.5%. The spectral data are as follows: IR (neat) cm^{-1}: 3030, 2920, 1615, 1590, 1480, 1440, 750, 690; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.00–1.90 (m, 6 H), 1.90–2.20 (m, 3 H), 2.20–2.50 (m, 2 H), 4.88 (s, 1 H), 5.15 (s, 1 H), 5.64 (s, 2 H), 7.20–7.50 (m, 5 H). The product deteriorates at room temperature and should be stored in the freezer.

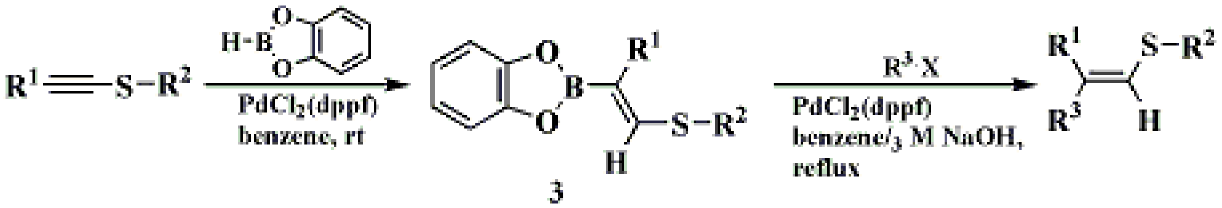
Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

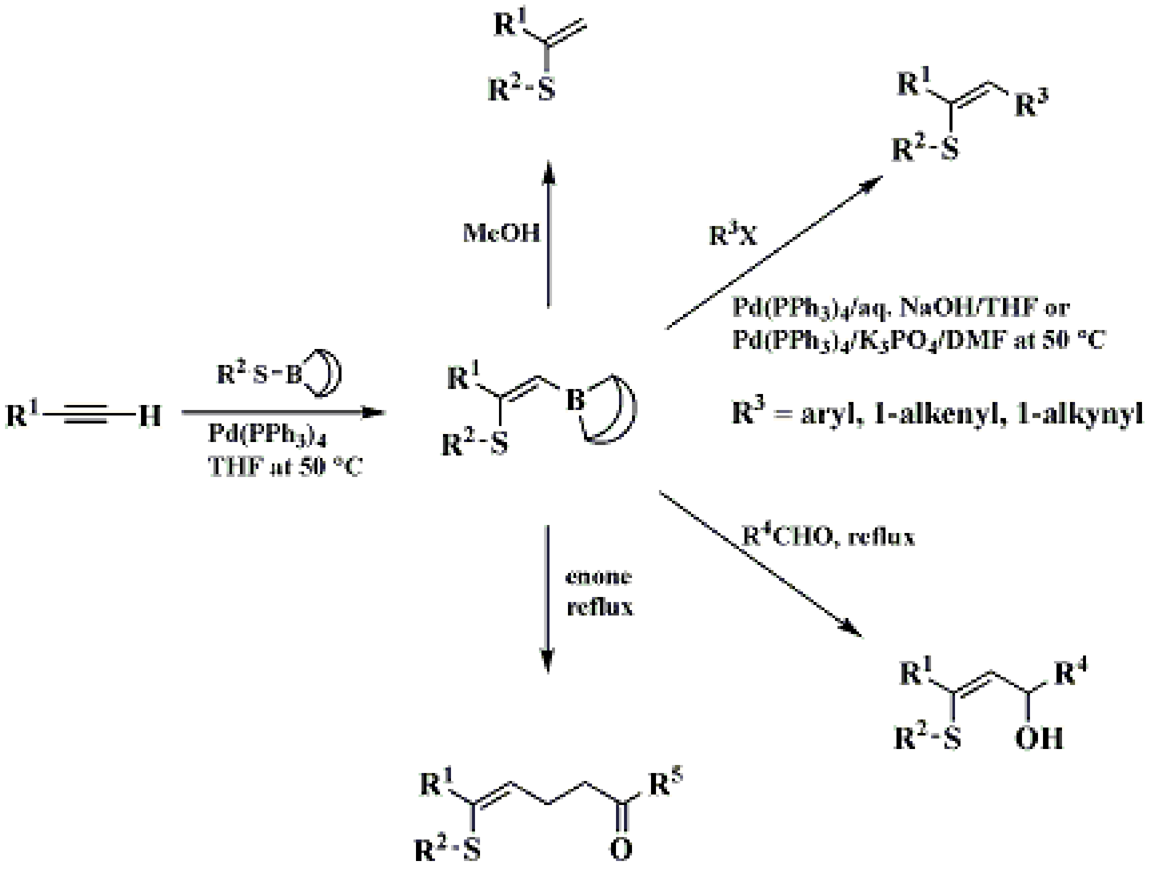
The reaction described here is a method for the synthesis of alkenyl sulfides via the palladium-catalyzed cross-coupling reaction of 9-alkyl-9-BBN.[5] Bromo(phenylthio)ethene has several advantages in terms of its practical use for the cross-coupling reaction. The coupling occurs at the bromine position, but no coupling products at the sulfur position are obtained even under conditions using an excess of 9-alkyl-9-BBN. Thus, the formation of dialkylation products is completely avoided. The reaction is highly stereoselective and readily extended to the coupling with (E)- and (Z)-2-bromo-1-phenylthio-1-alkenes (**1** and **2**).[7] The reactions of (E)-, (Z)-1-alkenyl, or 1,3-alkadienylboronic esters with **1** or **2** provide simple routes for the stereoselective syntheses of 1,3-alkadienyl and 1,3,5-alkatrienyl phenyl sulfides.[8] Another route to vinylic sulfides involves the cross-coupling of 1-alkenyl halides with lithium, tin, and boron thioalkoxides.[9] These routes are convenient when the corresponding alkenyl halides are easily available.

The ready availability of 2-(organothio)-1-alkenylboron compounds, obtained by the catalytic hydroboration of 1-organothio-1-alkynes (eq. 1) or the thioboration of 1-alkynes (Scheme 1), may offer other flexible and reliable routes to such stereodefined alkenyl sulfides in combination with the cross-coupling reaction with organic halides. The catalytic hydroboration of thioalkynes with catecholborane in the presence of $NiCl_2$(dppe) or $PdCl_2$(dppf) regio- and stereoselectively gives **3**. [10]The sequential catalytic hydroboration and cross-coupling reactions with a common palladium catalyst allows the one-pot synthesis of 1-alkenyl sulfides (eq. 1).[11]



When a solution of terminal alkyne and 9-RS-9-BBN in THF is heated at 50°C for 3 hr in the presence of $Pd(PPh_3)_4$ (3 mol %), the cis-addition of the B-S bond to alkyne proceeds regio- and stereoselectively (Scheme 1).[12] The adduct **4** is susceptible to C-B bond breaking or stereochemical isomerization, but the in situ preparation and subsequent cross-coupling with organic halides gives a variety of alkenyl sulfides retaining the original configuration of **4**. The vinylboranes thus obtained have unusually high nucleophilicity due to the activation by an electron-donating β-organothio group. The protodeboronation proceeds instantaneously with methanol to provide the thiol adducts. The addition to aldehydes and the Michael addition to α,β-unsaturated ketones or aldehydes at the refluxing temperature of THF afford various vinyl sulfides.[13]

The synthesis of vinylic sulfides via the cross-coupling reaction of organoboron compounds and other related reactions were recently reviewed.[14]



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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

benzophenone ketyl

brine

9-BBN

9-[2-(3-Cyclohexenyl)ethyl]-9-BBN

9-BBN (9-borabicyclo[3.3.1]nonane)

9-(10-carbomethoxydecanyl)-9-BBN

NiCl

PdCl

$Pd(PPh_3)_4$

ethanolamine complex

ethanol (64-17-5)

methanol (67-56-1)

ether (60-29-7)

sodium hydroxide (1310-73-2)

bromine (7726-95-6)

nitrogen (7727-37-9)

sulfur (7704-34-9)

potassium hydroxide (1310-58-3)

palladium (7440-05-3)

potassium bromide (7758-02-3)

magnesium sulfate (7487-88-9)

ethanolamine (141-43-5)

borane (7440-42-8)

Tetrahydrofuran, THF (109-99-9)

hexane (110-54-3)

triphenylphosphine (603-35-0)

1,5-cyclooctadiene

4-vinyl-1-cyclohexene

CATECHOLBORANE (274-07-7)

tetrakis(triphenylphosphine)palladium(0) (14221-01-3)

Phenyl vinyl sulfide (1822-73-7)

potassium phosphate (7778-53-2)

1-BROMO-1-PHENYLTHIOETHENE (80485-53-6)

4-(3-Cyclohexenyl)-2-phenylthio-1-butene (155818-88-5)

Bromo(phenylthio)ethene

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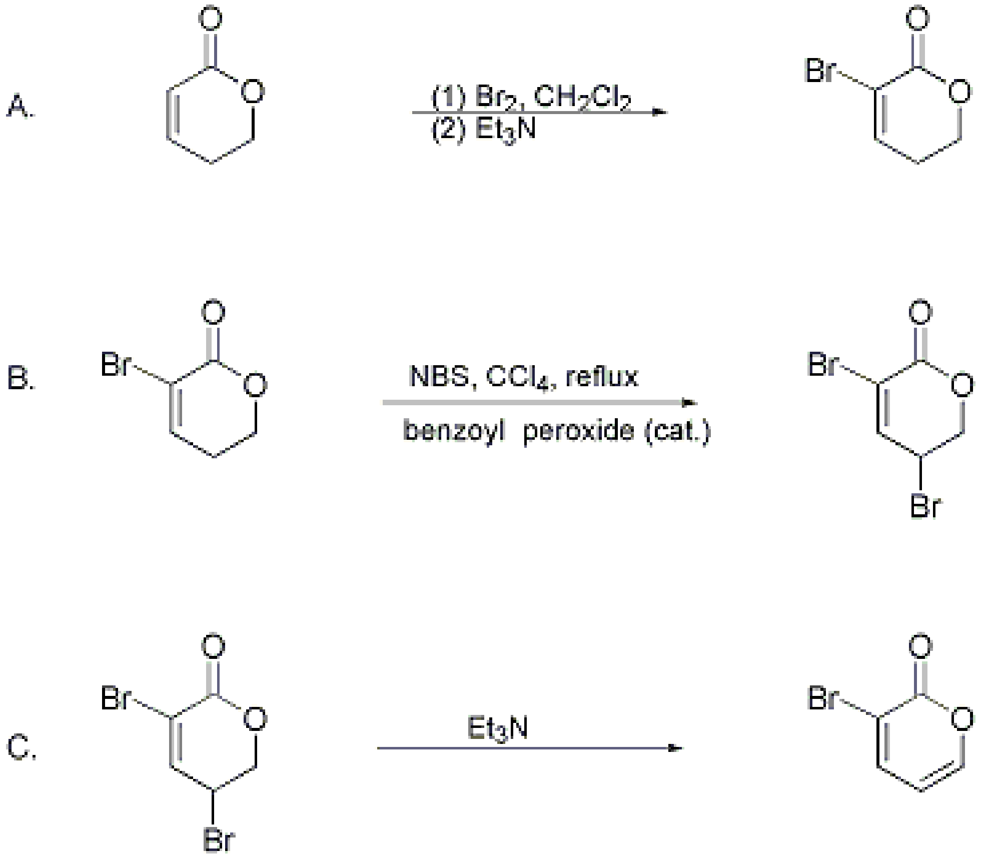
Organic Syntheses, CV 9, 112

AN IMPROVED PREPARATION OF 3-BROMO-2H-PYRAN-2-ONE: AN AMBIPHILIC DIENE FOR DIELS-ALDER CYCLOADDITIONS

[2H-Pyran-2-one, 3-bromo-]



Submitted by G. H. Posner, K. Afarinkia, and H. Dai[1].
Checked by Alyx-Caroline Guevel and David J. Hart.

1. Procedure

A. *3-Bromo-5,6-dihydro-2H-pyran-2-one*. A 1-L, three-necked, round-bottomed flask, equipped with a magnetic stirring bar, a pressure-equalizing addition funnel, a drying tube that contains sodium hydroxide pellets, and a thermometer, is charged with 10.15 g (0.103 mol) of 5,6-dihydro-2H-pyran-2-one (Note 1) and 350 mL of methylene chloride (Note 2). The addition funnel is charged with a solution of 16.7 g (0.105 mol) of bromine (Note 3) in 130 mL of methylene chloride. The bromine solution is added over a period of 4 hr (Note 4) in 10–15-mL portions (*Caution! Exothermic reaction. External cooling may be necessary*). After the addition of the last portion of bromine, the reaction is analyzed by TLC and NMR (Note 5) and (Note 6). The resulting pale orange solution is stirred for 2 hr until the color has almost faded. The addition funnel is replaced by a rubber septum, and the reaction mixture is cooled by means of an ice

bath. Via syringe, 15.0 mL (0.107 mol) of triethylamine is added through the rubber septum over 2 min (*Caution! Exothermic reaction*). The colorless solution is stirred for 40 min and then the contents of the flask are transferred to a 1-L separatory funnel and washed twice with 150 mL of water. The organic phase is dried over anhydrous sodium sulfate and filtered through a pad of silica gel (Note 7) and the pad rinsed with 700 mL of methylene chloride. The combined filtrates are concentrated at reduced pressure (20 mm) and the last traces of solvent are removed under high vacuum at ambient temperature to afford 16.3 g (89%) of 3-bromo-5,6-dihydro-2H-pyran-2-one as an amber-colored mobile liquid that solidifies when stored overnight at −4°C. This material is sufficiently pure for use in the next step. An analytically pure sample may be prepared by Kugelröhr distillation at 1.0 mm (pot temperature 100°C) (Note 8).

B. *3,5-Dibromo-5,6-dihydro-2H-pyran-2-one*. A flame-dried, 1-L, round-bottomed flask, equipped with a magnetic stirring bar and an efficient water-cooled condenser fitted with a nitrogen inlet, is placed under a nitrogen atmosphere and charged with 15.8 g (0.089 mol) of 3-bromo-5,6-dihydro-2H-pyran-2-one, 16.5 g (0.093 mol) of N-bromosuccinimide (Note 1), 0.8 g (3.3 mmol) of benzoyl peroxide (Note 1), and 455 mL of freshly distilled carbon tetrachloride. The reaction flask is immersed in a preheated oil bath (100°C) and the contents are refluxed vigorously for 4.5 hr (Note 9) and (Note 10); the reaction mixture is cooled and allowed to stand at room temperature for 4.5 hr. The precipitate (9.5 g) is collected by suction filtration, the filtrate is concentrated under reduced pressure at 50–60°C (20 mm), and the last traces of solvent are removed under high vacuum (1 mm) at room temperature over 2.5 hr affording 21.5 g (94%) of crude 3,5-dibromo-5,6-dihydro-2H-pyran-2-one as an amber liquid which is sufficiently pure for use in the next step (Note 11). This crude material may be further purified by chromatography (Note 12).

C. *3-Bromo-2H-pyran-2-one*. A 1-L, one-necked, round-bottomed flask, equipped with a magnetic stirring bar, and rubber septum through which a needle-tipped inert gas line is inserted (vented through a mineral oil bubbler), is charged with 20.3 g of crude 3,5-dibromo-5,6-dihydro-2H-pyran-2-one, as prepared above, and 360 mL of methylene chloride (Note 1). Via syringe, 14.0 mL (0.1 mol) of triethylamine (Note 2) is added over a 5-min period at room temperature. During the addition, the reaction mixture becomes dark brown. After 24 hr, analysis by TLC and NMR indicates the reaction to be complete. The reaction mixture is transferred to a 1-L separatory funnel and washed three times with 140 mL of water. The organic phase is dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure at 50–60°C (20 mm). The last traces of solvent and triethylamine are removed by brief exposure (10 min) to high vacuum at ambient temperature (Note 13). The residue is purified by chromatography on a 5.0 cm-in-diameter column of 150 g of silica gel packed in hexane. The crude material is dissolved in a minimum amount of methylene chloride and applied to the column. Elution with 800 mL of 10% ethyl acetate in hexane followed by 1300 mL of 20% ethyl acetate in hexane, using analytical TLC to monitor fractions, affords in sequence 1.97 g (14%) of 5-bromo-2-pyrone as a light-brown solid with mp 54–56°C (lit.[2] mp 60–61°C) (Note 14), and 6.06 g (43%) of 3-bromo-2-

pyrone as a tan solid with mp 59.5–61°C (lit.[3,4] mp 63.5–65°C), 36% yield overall from 5,6-dihydro-2H-pyran-2-one (Note 15) and (Note 16).

2. Notes

1. All commercially available reagents were used as received without further purification. Benzoyl peroxide was 95% pure by iodometric titration.

2. All common reagents were dried according to recommended procedures[5] and were redistilled prior to use.

3. The weight of bromine should be measured by addition to a cooled, pre-weighed Erlenmeyer flask containing methylene chloride. *Caution: bromine is toxic and should always be handled in a well-ventilated fumehood*.

4. The rate of addition is determined by the temperature of the reaction mixture and the quality of the starting pyrone. In a duplicate run, starting from redistilled starting material, addition took only 2 hr.

5. TLC analysis was carried out on precoated plastic silica gel plates (with fluorescent indicator) using diethyl ether as eluant. With this eluant, the R_f of starting material is 0.50 and the R_f of 3,4-dibromo-3,4,5,6-tetrahydro-2H-pyran-2-one is 0.83. In addition to these two spots, a third spot, $R_f = 0.55$, corresponding to 3-bromo-5,6-dihydro-2H-pyran-2-one was detected. TLC analysis is not always reliable and it is better to analyze a small aliquot by NMR.

6. More bromine may be necessary. *Avoid addition of more bromine if the starting material has already been consumed*.

7. A pad of 100 g of flash silica gel (1.5 cm thick and 11 cm diameter) was used.

8. Distillation of 1.71 g of crude material afforded 1.50 g of pure 3-bromo-5,6-dihydro-2H-pyran-2-one as a colorless oil which solidifies at –4°C (mp 27–30°C), and which slowly turns yellow upon standing at room temperature. The spectral data for 3-bromo-5,6-dihydro-2H-pyran-2-one are as follows: ^1H NMR (400 MHz, $CDCl_3$) δ: 2.58 (dt, 2 H, J = 6.1, 4.6), 4.49 (t, 2 H, J = 6.1), 7.30 (t, 1 H, J = 4.6); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 26.5, 66.7, 113.3, 146.2, 159.1; IR (neat) cm^{-1}: 1733, 1615; Mass spectrum (m/z) (EI, 70 eV) 177.9 and 176.9 (M^+, 42). Anal. Calcd for $C_5H_5O_2Br$: C, 33.91; H, 2.85; Br, 45.16. Found C, 33.99; H, 2.88; Br, 45.08.

9. Shortly after refluxing begins, the reaction mixture turns dark orange; however, the color dissipates by the end of the reaction period.

10. Completion of the reaction was checked by TLC analysis (Note 5). The R_f of the product is 0.60 with diethyl ether as eluant.

11. The crude material is contaminated with starting bromide, small amounts of succinimide and aromatic material, as well as other minor impurities as indicated by ^1H NMR.

12. Chromatography of 1.17 g of this material on 50 g of silica gel with elution by a gradient of 20–50% ethyl acetate in hexane gave 0.90 g (77%) of 94% pure 3,5-dibromo-5,6-dihydro-2H-pyran-2-one as a yellow oil that crystallized

on standing (mp 60.5–62.5°C; lit.[3] mp 64–65°C). The spectral data for 3,5-dibromo-5,6-dihydro-2H-pyran-2-one are as follows: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.62–4.67 (m, 1 H), 4.76–4.81 (m, 2 H), 7.37 (d, 1 H, J = 5.7). This material was contaminated with 6% of 3-bromo-5,6-dihydro-2H-pyrone as indicated by ^{1}H NMR.

13. 3-Bromo-2-pyrone sublimes in high vacuum at relatively low temperature. Thus, the material should not be subjected to high vacuum for long periods of time.

14. The spectral data for 5-bromo-2-pyrone are as follows: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.31 (dd, 1 H, J = 9.8, 1.1), 7.38 (dd, 1 H, J = 9.8, 2.7), 7.62 (dd, 1 H, J = 2.7, 1.1); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 100.7, 117.4, 145.9, 149.6, 159.3.

15. The spectral data for 3-bromo-2-pyrone are as follows: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.15 (dd, 1 H, J = 6.9, 5.0), 7.51 (dd, 1 H, J = 5.0, 1.9), 7.69 (dd, J = 6.9, 1.9); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 106.5, 112.6, 144.0, 150.1, 158.0.

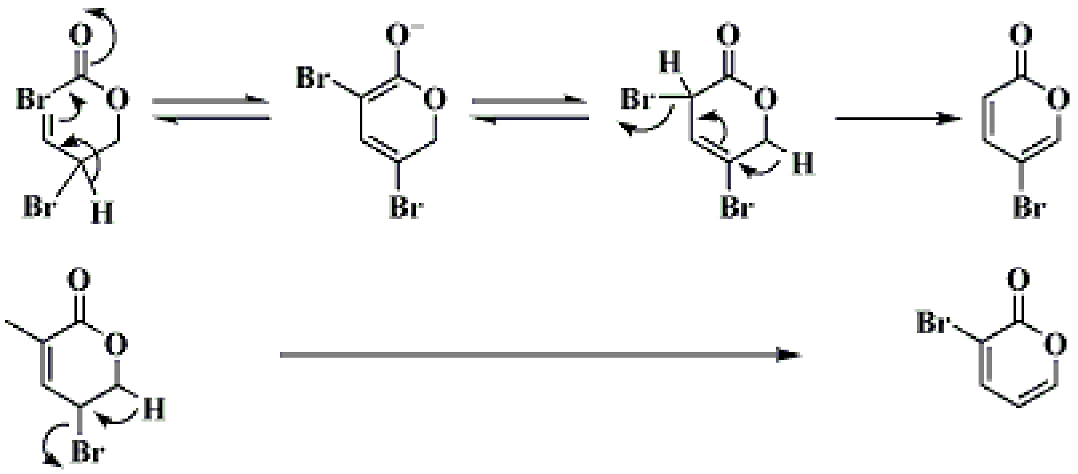
16. The checkers also isolated 0.7 g (3%) of 3,5-dibromo-2-pyrone as a brown solid, mp 55.5–58.5°C (lit.[2] mp 66–67°C), from the fractions preceding the 5-bromo-2H-pyrone

Waste Disposal Information

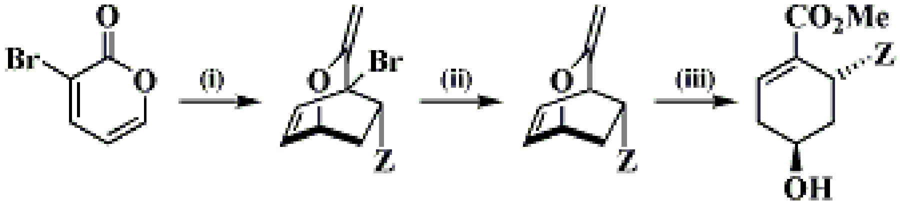
All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The procedure described above allows a more efficient and convenient synthesis of 3-bromo-2-pyrone than previously described in the literature.[4] This procedure avoids making and handling 2-pyrone, a sensitive compound.[6] The major by-product of the reaction is 5-bromo-2-pyrone. We postulate that the formation of this by-product results from prototropic migration in basic medium followed by elimination of HBr (Scheme 1).



3-Bromo-2-pyrone is not only a valuable precursor for the synthesis of various 3-substituted 2-pyrones,[7,8] but it is also a reactive unsymmetrical diene.[9,10,11,12,13] 3-Bromo-2-pyrone undergoes Diels-Alder cycloadditions with a regioselectivity and stereoselectivity that is superior to that of 2-pyrone. Furthermore, 3-bromo-2-pyrone is a chameleon (i.e., ambiphilic) dienophile, undergoing cycloaddition to both electron deficient and electron rich dienophiles. The cycloadducts of bromopyrone with dienophiles are isolable and are useful in the synthesis of diastereomerically pure cyclohexene carboxylates (Scheme 2).[9,10,11,12,13]



Z = CH_2OSiMe_2-t-Bu: (i) Acrolein (10 equiv), 90°C, 96 hr, 70%; then $NaBH_4$, MeOH, 0°C, 15 min (80%); then TSDMSTf, Et_3N, CH_2Cl_2, 30 min (90%); (ii) Bu_3SnH, AIBN, benzene, reflux 2 hr (99%); (iii) MeONa, MeOH, 0°C, 92%.

Z = $OSiPh_2Me$: (i) CH_2=$CHOSiPh_2Me$ (10 equiv), 90°C, 140 hr, 44%; (ii) Bu_3SnH, AIBN, benzene, reflux 2 hr (47%); (iii) MeOLi, MeOH, 0°C, 90%.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

TSDMSTf

Et_3N

Bu_3SnH

AIBN

MeONa

MeOLi

Benzene (71-43-2)

ethyl acetate (141-78-6)

MeOH (67-56-1)

diethyl ether (60-29-7)

Acrolein (107-02-8)

bromide (24959-67-9)

HBr (10035-10-6)

bromine (7726-95-6)

sodium sulfate (7757-82-6)

carbon tetrachloride (56-23-5)

nitrogen (7727-37-9)

methylene chloride, CH_2Cl_2 (75-09-2)

benzoyl peroxide (94-36-0)

N-bromosuccinimide (128-08-5)

hexane (110-54-3)

triethylamine (121-44-8)

$NaBH_4$ (16940-66-2)

2-pyrone (504-31-4)

3-Bromo-2H-pyran-2-one, 3-bromo-2-pyrone, 2H-Pyran-2-one, 3-bromo- (19978-32-6)

3-Bromo-5,6-dihydro-2H-pyran-2-one, 3-bromo-5,6-dihydro-2H-pyrone (104184-64-7)

5,6-Dihydro-2H-pyran-2-one (3393-45-1)

3,5-Dibromo-5,6-dihydro-2H-pyran-2-one (56207-18-2)

5-bromo-2-pyrone, 5-bromo-2H-pyrone (19978-33-7)

3,4-dibromo-3,4,5,6-tetrahydro-2H-pyran-2-one

3,5-dibromo-2-pyrone

vitamin D_3

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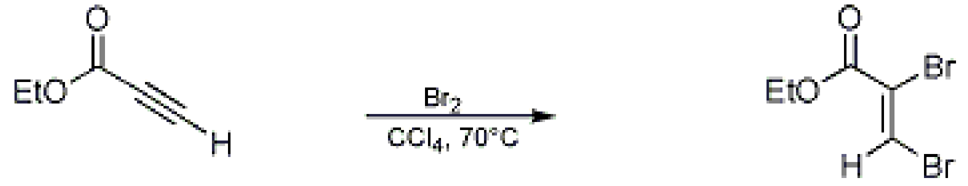
Organic Syntheses, CV 9, 117

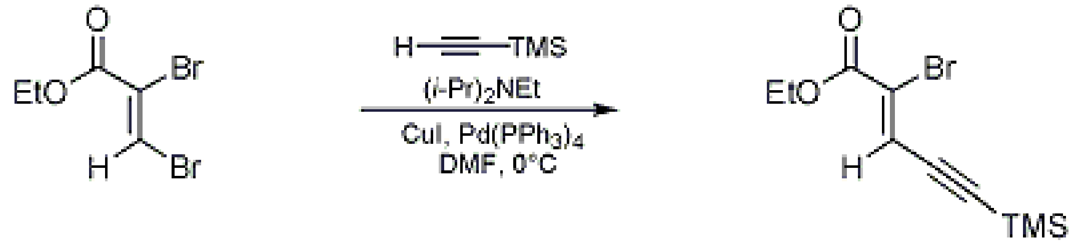
SYNTHESIS OF FUNCTIONALIZED ENYNES BY PALLADIUM/COPPER-CATALYZED COUPLING REACTIONS OF ACETYLENES WITH (Z)-2,3-DIBROMOPROPENOIC ACID ETHYL ESTER: (Z)-2-BROMO-5-(TRIMETHYLSILYL)-2-PENTEN-4-YNOIC ACID ETHYL ESTER

[2-Penten-4-ynoic acid, 2-bromo-5-(trimethylsilyl)-, ethyl ester, (Z)-]

A.



B.



Submitted by Andrew G. Myers and Peter S. Dragovich[1].
Checked by Rhonda A. Musselman and Robert K. Boeckman, Jr..

1. Procedure

A. *(Z)-2,3-Dibromo-2-propenoic acid ethyl ester*.[2] Ethyl propiolate (9.01 g, 91.8 mmol) and carbon tetrachloride (75 mL) are added in sequence to a 250-mL, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar (Note 1). The flask is fitted with a 30-mL, pressure-equalizing addition funnel to which elemental bromine (5.00 mL, 97.0 mmol) is added by transfer pipette (Note 2). The flask is partially immersed in an oil bath heated to 70°C. After 10 min for temperature equilibration, dropwise addition of bromine is initiated and completed within 10 min. Complete bromine transfer is achieved by rinsing the addition funnel with a 5-mL portion of carbon tetrachloride. The red-brown solution is heated at 70°C for 30 min, allowed to cool to ambient temperature, and carbon tetrachloride and excess bromine are removed by rotary evaporation. The pale yellow concentrate is applied to the top of a short column of flash-grade silica gel (150 g, 7-cm diam × 10 cm) loaded with 5%

ethyl acetate-hexanes solution; the product dibromide elutes rapidly with this solvent system (< 1 L total solvent volume, 150-mL fractions, (Note 3)). Fractions containing the dibromide (R_f = 0.66, 5% ethyl acetate-hexanes) are combined and concentrated. The last traces of solvent are removed at 1 mm (0.5 hr) to afford (Z)-2,3-dibromo-2-propenoic acid ethyl ester (21.5–22.0 g, 91–93%) as a colorless liquid (Note 4), (Note 5).

B. *(Z)-2-Bromo-5-(trimethylsilyl)-2-penten-4-ynoic acid ethyl ester*. An oven-dried, 500-mL, modified Schlenk flask (Kjeldahl shape with 24/40 female top), equipped with a Teflon-coated magnetic stirring bar and rubber septum, is connected at the side-arm to a source of argon and vacuum. The flask is charged with (Z)-2,3-dibromo-2-propenoic acid ethyl ester prepared in part A (21.5 g, 83.4 mmol) and N,N-dimethylformamide (150 mL). With efficient stirring, it is alternately evacuated and flushed with argon at ambient temperature to deoxygenate the solution (Note 6), (Note 7). The flask is cooled in ice and (trimethylsilyl)acetylene (20.0 mL, 142 mmol) and N,N-diisopropylethylamine (24.7 mL, 142 mmol) are added in sequence (Note 8). The resulting pale yellow solution is deoxygenated as above. Cuprous iodide (3.18 g, 16.7 mmol) and tetrakis(triphenylphosphine)palladium (4.82 g, 4.17 mmol) are added, followed by a third deoxygenation cycle (Note 9). The brown reaction mixture is maintained at 0°C while the progress of reaction is monitored by thin layer chromatography (TLC), as follows: An aliquot (ca. 0.1 mL) of the reaction mixture is withdrawn with an argon-flushed hypodermic syringe and is injected into a small test tube containing ethyl ether (0.25 mL) and water (0.5 mL). After the biphasic mixture is swirled briefly, the ether layer is allowed to separate and is analyzed by TLC using 20% ethyl ether-hexanes as eluent (R_f of the starting dibromide = 0.67, of the product = 0.76, visualization with ultraviolet light). When TLC analysis indicates consumption of the starting dibromide, typically 3–6 hr at 0°C, the reaction mixture is poured into a 1-L separatory funnel containing water (300 mL), saturated aqueous ammonium chloride solution (75 mL), and the tetrasodium salt of ethylenediaminetetraacetic acid (4.50 g, (Note 10)). The resulting brown suspension is extracted with four 150-mL portions of 50% ethyl acetate-hexanes. The organic layers are combined and washed with three 100-mL portions of water, then dried over sodium sulfate and concentrated. The brown oil thus obtained is filtered through a short column of flash-grade silica gel (150 g, 7-cm diam × 10 cm), using 20% toluene-hexanes as eluent (< 1.5 L total solvent volume, 150-mL fractions). Fractions containing product (R_f = 0.23, 20% toluene-hexanes) are combined and concentrated. The light brown concentrate is combined with silicone oil (7.0 g) in a 250-mL, 14/20 round-bottomed flask. An insulated 6-in Vigreux column and a short-path distillation head are affixed for vacuum distillation. The system is evacuated (0.9 mm) and the pot is heated to 110°C whereupon bis(trimethylsilyl)butadiyne sublimes from the mixture. A heat gun is used to assist in the transfer of this component; the flow of condenser water is initiated only after this phase of the distillation. A liquid forerun is collected (ca. 0.5 mL, head temperature 94°C, pot temperature 125°C) prior to collection of the product. (Z)-2-Bromo-5-(trimethylsilyl)-2-penten-4-ynoic acid ethyl ester is collected (bp 105–108°

C, 0.9 mm, pot temperature < 125°C) as a pale yellow oil (10.95–12.85 g, 48–56%) and is shown by capillary GC to be 87–94% pure (contaminants include bis (trimethylsilyl)butadiyne, <2% and (E)-2-[(trimethylsilyl)ethynyl]-5-(trimethylsilyl)-2-penten-4-ynoic acid ethyl ester, 6–11%; (Note 11),(Note 12),(Note 13)).

2. Notes

1. Ethyl propiolate was used as received from Aldrich Chemical Company, Inc. (pure by 400 MHz ^{1}H NMR analysis). Carbon tetrachloride was spectrophotometric grade and was used without purification.
2. Elemental bromine was used as received from EM Science.
3. Although the crude dibromide is essentially pure, the submitters found the subsequent coupling reaction to be more reproducible and to proceed in higher yield when this simple purification procedure is employed.
4. The purified compound displayed the following characteristics: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.35 (t, 3 H, J = 7.1, CH_3), 4.31 (q, 2 H, J = 7.1, CH_2), 8.23 (s, 1 H, HC=C); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.0, 63.0, 122.6, 126.4, 160.7; IR (thin film) cm^{-1}: 3072, 2983, 1732, 1569, 1253, 1213, 1037, 737; HRMS calcd for $C_5H_6Br_2O_2$: 255.8735, found: 255.8739. A trace impurity is visible in the ^{1}H NMR spectrum (δ 6.35, s). This impurity is tentatively identified as 2,2,3,3-tetrabromopropanoic acid ethyl ester and is estimated by integration to constitute less than 2 mol percent of the mixture.
5. The checkers found three distinct signals due to impurities at δ 7.74 (s), 7.14 (q), 6.34 (s) which totaled 4–7% by NMR integration.
6. N,N-Dimethylformamide was distilled from calcium sulfate under reduced pressure (40 mm) and was stored over 4 Å molecular sieves under argon.
7. Typically three to five evacuation/argon flush cycles are employed. This deoxygenation protocol is simpler and faster than a freeze-pump-thaw procedure.
8. (Trimethylsilyl)acetylene was used as received from Aldrich Chemical Company, Inc. N,N-Diisopropylethylamine was distilled from calcium hydride (atmospheric pressure) and stored over 4 Å molecular sieves under argon.
9. Cuprous iodide (EM Science) was purified by continuous extraction (12 hr) with tetrahydrofuran in a Soxhlet apparatus. The purified compound was stored in a brown bottle and was light grey in appearance. Tetrakis(triphenylphosphine) palladium, $Pd(PPh_3)_4$, was prepared according to a published procedure[3] and was stored in a dry box under a nitrogen atmosphere. It was a bright yellow solid. The purity of this reagent is crucial for the stoichiometry and reaction times reported to be observed. It must be handled with care to avoid exposure to air. Dark colored or yellow-green samples of $Pd(PPh_3)_4$ are not suitable.
10. For optimum results, it is important to monitor the reaction carefully. Extended reaction times lead to formation of bis-coupled product. Optimum results are obtained when the dibromide (Note 3) and the palladium catalyst (Note 9) are prepared as described.
11. Capillary gas chromatography is conducted with a cross-linked phenyl

methyl silicone stationary phase (5%, 25 m × 0.2 mm × 0.5 •m film thickness, injector temp. 225°C, detector temp. 250°C, column temp. 40–200°C, 15°C/min after 1 min initial time). (Z)-2-Bromo-5-(trimethylsilyl)-2-penten-4-ynoic acid ethyl ester is observed to have a retention time of 14.0 min. GC data for bis (trimethylsilyl)butadiyne is as follows: retention time 10.0 min, response factor (GC area produced relative to an equimolar quantity of (Z)-2-bromo-5-(trimethylsilyl)-2-penten-4-ynoic acid ethyl ester) 1.29. For (E)-2-[(trimethylsilyl)ethynyl]-5-(trimethylsilyl)-2-penten-4-ynoic acid ethyl ester the retention time is 17.0 min, the response factor 1.19.

12. The purified product displays the following characteristics: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.25 (s, 9 H, $SiCH_3$), 1.34 (t, 3 H, J = 7.1, CH_3), 4.30 (q, 2 H, J = 7.1, CH_2), 7.29 (s, 1 H, HC=C); ^{13}C NMR (100 MHz, $CDCl_3$) δ: –0.6, 14.0, 62.6, 100.4, 111.9, 123.7, 124.6, 161.7; IR (CH_2Cl_2 solution) cm^{-1}: 2964, 1723, 1584, 1252, 1082, 1044, 850; HRMS calcd for $C_{10}H_{15}BrO_2Si$: 274.0025, found: 274.0024. Additional purification of the distilled product (1.09 g) by silica gel chromatography (5 cm diam × 14-cm column, 100 g of silica gel, eluent, 20% toluene-hexanes) provided an analytical sample (1.02 g, 94% recovery) that was shown to be >99% pure by capillary GC analysis. Anal. Calcd for $C_{10}H_{15}BrO_2Si$: C, 43.64; H, 5.49. Found: C, 43.74; H. 5.26.

13. The fractions containing the product were combined and analyzed by capillary GC, which showed them to be 87–94% pure with the major impurity (6–11%) being the bis-coupled product.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The procedure outlined above describes the selective, retentive, β-coupling of (Z)-2,3-dibromopropenoic acid ethyl ester with (trimethylsilyl)acetylene employing the palladium-modified version of the Castro-Stephens reaction.[4,5,6,7] The dibromide starting material is readily available by bromination of ethyl propiolate (Procedure A), as described by Trippett and Hall.[2] The coupling product has been shown to be a versatile precursor for the synthesis of variously substituted enynes and enediynes. For example, a second acetylene may be introduced into the α-position under modified coupling conditions. Alternatively, reduction of the ester with diisobutylaluminum hydride and protection of the resultant alcohol with tert-butyldiphenylsilyl chloride affords a vinyl bromide that can be metalated and trapped with various electrophiles. These procedures have been used on the gram and multigram scale.[7]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hexanes

phenyl methyl silicone

ethyl acetate (141-78-6)

ether, ethyl ether (60-29-7)

ammonium chloride (12125-02-9)

bromine (7726-95-6)

sodium sulfate (7757-82-6)

carbon tetrachloride (56-23-5)

nitrogen (7727-37-9)

calcium sulfate (7778-18-9)

toluene (108-88-3)

palladium (7440-05-3)

cuprous iodide (7681-65-4)

Tetrahydrofuran (109-99-9)

N,N-dimethylformamide (68-12-2)

calcium hydride (7789-78-8)

diisobutylaluminum hydride (1191-15-7)

ethyl propiolate (623-47-2)

argon (7440-37-1)

N,N-diisopropylethylamine (7087-68-5)

Tetrakis(triphenylphosphine)palladium (14221-01-3)

bis(trimethylsilyl)butadiyne (4526-07-2)

(Trimethylsilyl)acetylene (1066-54-2)

(Z)-2-Bromo-5-(trimethylsilyl)-2-penten-4-ynoic acid ethyl ester, 2-Penten-4-ynoic acid, 2-bromo-5-(trimethylsilyl)-, ethyl ester, (Z)- (124044-21-9)

(Z)-2,3-Dibromo-2-propenoic acid ethyl ester, (Z)-2,3-dibromopropenoic acid ethyl ester (26631-66-3)

(E)-2-[(trimethylsilyl)ethynyl]-5-(trimethylsilyl)-2-penten-4-ynoic acid ethyl ester

2,2,3,3-tetrabromopropanoic acid ethyl ester

tert-butyldiphenylsilyl chloride (58479-61-1)

tetrasodium salt of ethylenediaminetetraacetic acid (10378-23-1)

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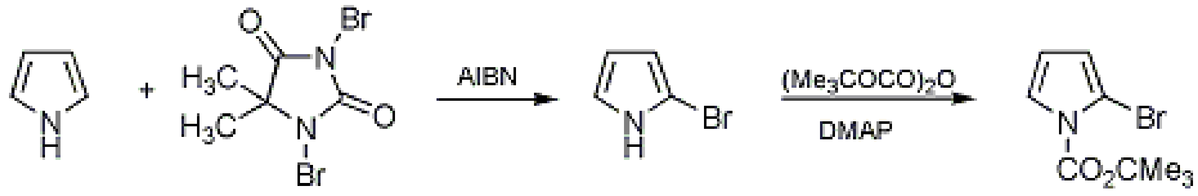
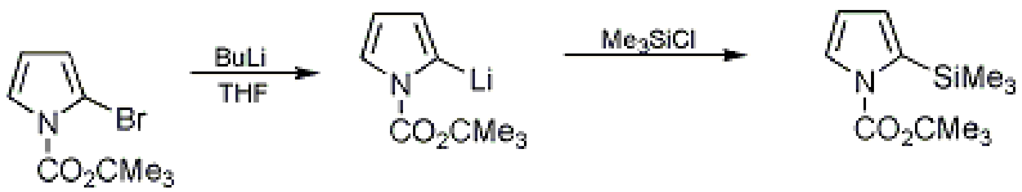
Organic Syntheses, *CV 9, 121*

2-SUBSTITUTED PYRROLES FROM N-tert-BUTOXYCARBONYL-2-BROMOPYRROLE: N-tert-BUTOXYCARBONYL-2-TRIMETHYLSILYLPYRROLE

A.


B.


Submitted by Wha Chen, E. Kyle Stephenson, Michael P. Cava[1], and Yvette A. Jackson[2].
Checked by Wei He and Leo A. Paquette.

1. Procedure

A. *N-tert-Butoxycarbonyl-2-bromopyrrole*. A dry, 500-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, two solid addition funnels, and a three-way stopcock attached to a balloon filled with nitrogen. To the flask are added 4.5 g (67.2 mmol) of pyrrole (Note 1) and 180 mL of tetrahydrofuran (Note 2). The flask is evacuated and purged with nitrogen (Note 3). The stirred solution is cooled to −78°C with a dry ice-acetone bath (Note 4) and a catalytic amount (ca. 0.1 g) of azoisobutyronitrile (AIBN) (Note 5) is added via a solids addition funnel. After 5 min, 9.57 g (33.6 mmol) of 1,3-dibromo-5,5-dimethylhydantoin (Note 6) is added over a 20-min period via a solids addition funnel. The light-green mixture is stirred for an additional 10 min, then allowed to stand for 2 hr, keeping the temperature below −50°C. The solution is filtered by suction into a dry, 500-mL, round-bottomed flask that has been cooled to −78°C in a dry ice-acetone bath. The flask is equipped with a magnetic stirring bar and a three-way stopcock attached to a balloon filled with nitrogen. To the stirred dark-green solution is added 2.71 g (26.9 mmol) of triethylamine followed immediately by addition of 20.4 g (93.9 mmol) of di-tert-butyl dicarbonate and a catalytic amount (ca. 0.1 g) of 4-dimethylaminopyridine (Note 7). The flask is evacuated and purged with nitrogen (Note 3). The mixture is stirred for 8 hr while it is allowed to warm to room temperature (Note 8). The solvent is removed under reduced pressure at room temperature and 100 mL of hexane is added to the crude product, which is washed with deionized water (3 × 100 mL), dried over sodium sulfate, and concentrated under reduced pressure at room temperature. The crude product is purified by chromatography on amine-treated neutral silica (270 g) using hexane as the

eluent (Note 9). The fractions containing the product are identified by TLC, combined, and concentrated under reduced pressure at room temperature to yield compound **1** as a colorless oil (13.5–14.7 g, 82–89%) (Note 10).

B. *N-tert-Butoxycarbonyl-2-trimethylsilylpyrrole*. A solution of N-tert-butoxycarbonyl-2-bromopyrrole (13.5 g, 54.9 mmol) in 40 mL of hexane is added to 200 mL of tetrahydrofuran (Note 2) in a dry, 500-mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar, rubber septum, and a three-way stopcock attached to a balloon of nitrogen. The flask is evacuated and purged with nitrogen (Note 3). The stirred mixture is cooled to −78°C and 34.3 mL of 1.6 M butyllithium in hexane (Note 10) is added slowly via syringe over a 10-min period, during which time the colorless solution becomes brown. After an additional 10 min, 13.4 g (124 mmol) of chlorotrimethylsilane (Note 11) in 10 mL of tetrahydrofuran (Note 3) is added via syringe over a 10-min period. Stirring is continued and the mixture is allowed to warm to −30°C over a 1-hr period. The reaction mixture is quenched with saturated aqueous sodium bicarbonate (10 mL) at which point a dark red-purple color develops. After warming to 0°C, the solvent is removed under reduced pressure and the product is extracted into 300 mL of hexane. The organic layer is washed twice with 150 mL of water and then dried over anhydrous sodium sulfate. The solvent is removed under reduced pressure, and the residue is distilled twice using a Kugelrohr oven at 85°C and 0.15 mm to give the pure product **2** (10.5–11.1 g, 80–85%) (Note 12).

2. Notes

1. Pyrrole (Aldrich Chemical Company, Inc.) was freshly distilled before use.
2. Tetrahydrofuran was distilled from sodium benzophenone ketyl.
3. The apparatus is maintained under a nitrogen atmosphere during the course of the reaction.
4. The level of the reaction mixture must remain below the level of the cooling bath to avoid partial decomposition of the bromination product.
5. Azoisobutyronitrile (AIBN) (Fluka) was used as received.
6. Commercial 1,3-dibromo-5,5-dimethylhydantoin (Aldrich Chemical Company, Inc.) (22.0 g) was stirred for 12 hr at room temperature with 400 mL of 5% aqueous sodium bicarbonate, then stirred with 400 mL of deionized water for 8 hr, filtered, washed with 500 mL of deionized water and dried over phosphorus pentoxide to constant weight. The checkers used the commercial brominating agent as received from Aldrich Chemical Company, Inc.
7. Di-tert-butyl dicarbonate (Aldrich Chemical Company, Inc.) and 4-dimethylaminopyridine (Aldrich Chemical Company, Inc.) were used as received.
8. The checkers found that the reaction mixture must be stirred at room temperature for at least 2 hr prior to workup. It is advisable to monitor the progress of reaction by TLC.
9. The column is packed with hexane and pretreated with 500 mL of 5% triethylamine in hexane, then washed with 700 mL of hexane before addition of the compound.
10. Although this N-Boc derivative is far more stable than 2-bromopyrrole, it is best stored as a 20–25% solution in hexane at −10°C. Under these conditions, solutions show no sign of decomposition after many months. The product shows the following

spectrum: ^{1}H NMR ($CDCl_3$) δ: 1.61 (s, 9 H), 6.14 (t, 1 H, J = 3.5), 6.29 (dd, 1 H, J = 2.0, 3.5), 7.30 (dd, 1 H, J = 2.0, 3.5).

11. Butyllithium solution (Aldrich Chemical Company, Inc.) and chlorotrimethylsilane (Aldrich Chemical Company, Inc.) were used as received.

12. The spectral properties for 2-trimethylsilyl-N-Boc pyrrole are as follows: ^{1}H NMR ($CDCl_3$) δ: 0.27 (s, 9 H), 1.60 (2, 9 H), 6.21 (t, 1 H, J = 3.0), 6.46 (dd, 1 H, J = 1.5, 3.0), 7.38 (dd, 1 H, J = 1.5, 3.0).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Whereas 2-lithiothiophene and 2-lithiofuran are readily prepared from butyllithium and the parent heterocycles by lithium-hydrogen exchange, a similar exchange with pyrrole affords only N-lithiopyrrole. A study of the lithium-hydrogen exchange of several N-blocked pyrroles with strong bases concluded that synthetically useful lithium-hydrogen exchange at the 2-position could best be effected using as the substrate N-tert-butoxycarbonylpyrrole, but only in conjunction with the very hindered and costly base lithium tetramethylpiperidide.[3]

In the present procedure, pyrrole is brominated under mild conditions to the very labile 2-bromopyrrole using 1,3-dibromo-5,5-dimethylhydantoin: the latter reagent gives better results than the previously employed N-bromosuccinimide.[4] Direct conversion of 2-bromopyrrole to its more stable N-tert-butoxycarbonyl derivative (**1**) affords a substrate which readily undergoes lithium-halogen exchange with butyllithium at −78°C. Subsequent reaction with an electrophile is exemplified by the reaction with chlorotrimethylsilane to give N-tert-butoxycarbonyl-2-trimethylsilylpyrrole (**2**). Other electrophiles (e.g., dimethyl disulfide, methyl chloroformate) have also been employed successfully.[5] In addition, a similar procedure has been used to convert pyrrole into N-tert-butoxy-2,5-disubstituted pyrroles.[5]

The N-tert-butoxycarbonyl protecting group of substituted pyrroles can be removed readily by methoxide ion[3] or, when electron-withdrawing substituents are present, by mild thermolysis.[6]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium benzophenone ketyl

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

Pyrrole (109-97-7)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

methyl chloroformate (79-22-1)

N-bromosuccinimide (128-08-5)

hexane (110-54-3)

triethylamine (121-44-8)

dimethyl disulfide (624-92-0)

CHLOROTRIMETHYLSILANE (75-77-4)

N-lithiopyrrole

2-lithiothiophene

4-dimethylaminopyridine (1122-58-3)

phosphorus pentoxide (1314-56-3)

2-Lithiofuran

azoisobutyronitrile (78-67-1)

N-tert-Butoxycarbonyl-2-bromopyrrole (117657-37-1)

1,3-dibromo-5,5-dimethylhydantoin (77-48-5)

N-tert-Butoxycarbonyl-2-trimethylsilylpyrrole, 2-trimethylsilyl-N-Boc pyrrole (75400-57-6)

2-bromopyrrole

N-tert-butoxycarbonylpyrrole (5176-27-2)

lithium tetramethylpiperidide

Di-tert-butyl dicarbonate (24424-99-5)

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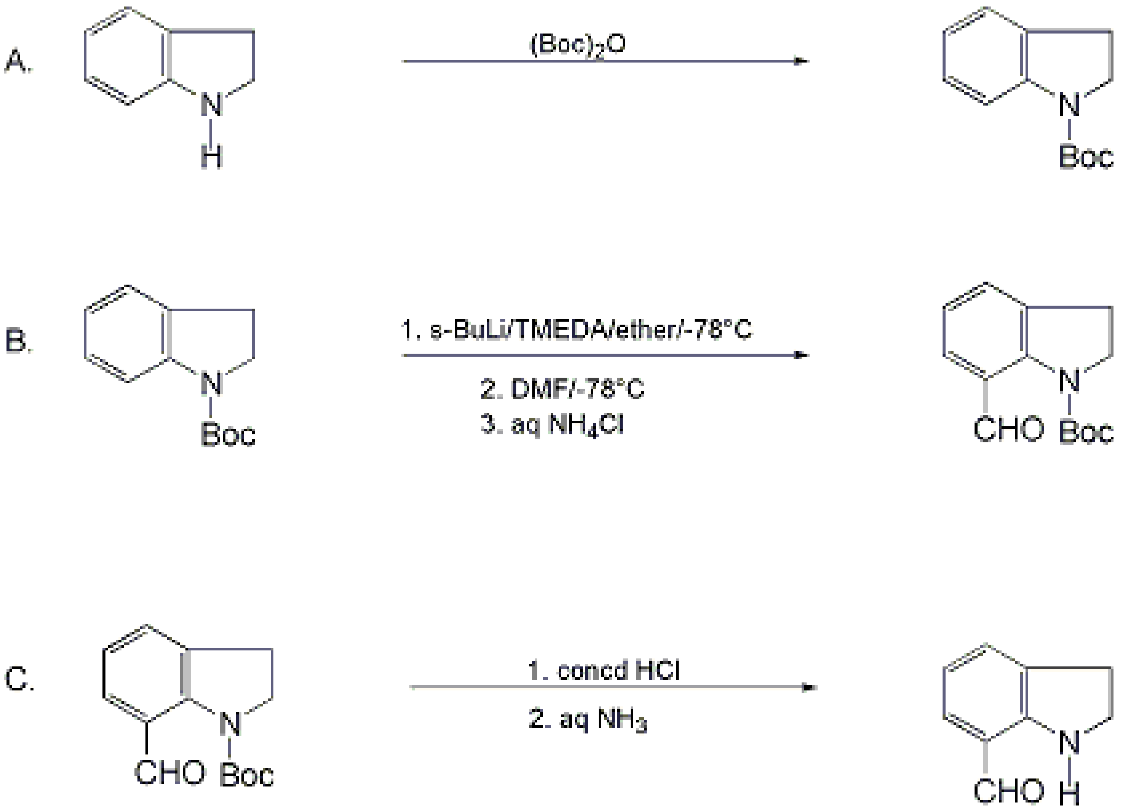
SYNTHESIS OF 7-SUBSTITUTED INDOLINES via DIRECTED LITHIATION OF 1-(tert-BUTOXYCARBONYL)INDOLINE: 7-INDOLINECARBOXALDEHYDE



Submitted by Masatomo Iwao and Tsukasa Kuraishi[1].
Checked by Jeff Crowley and Stephen F. Martin.

1. Procedure

Caution! Part C of this procedure should be carried out in an efficient hood to avoid exposure to noxious vapors (hydrogen chloride and ammonia).

A. *1-(tert-Butoxycarbonyl)indoline*. A 1-L, two-necked, round-bottomed flask, equipped with a reflux condenser fitted with a calcium chloride-filled drying tube, a pressure-equalizing addition funnel, and a magnetic stirring bar, is charged with 113.5 g (0.52 mol) of di-tert-butyl dicarbonate (Note 1) and 200 mL of tetrahydrofuran. Through the dropping funnel, 59.6 g (0.50 mol) of indoline is added to the reaction mixture with stirring over 30 min which maintains a steady evolution of carbon dioxide (Note 2). The reaction mixture is stirred at room temperature for an additional 3 hr followed by removal of the solvent with a rotary evaporator. The residual liquid is distilled under reduced pressure to give 107.6–107.8 g of 1-(tert-butoxycarbonyl)

indoline (98% yield) as a colorless oil, bp 83–84°C at 0.1 mm, which on standing solidifies, mp 42–45°C (Note 3).

B. *1-(tert-Butoxycarbonyl)-7-indolinecarboxaldehyde*. An oven-dried, 2-L, three-necked, round-bottomed flask, equipped with an argon inlet, 200-mL pressure-equalizing dropping funnel fitted with a rubber septum, a low temperature thermometer, and a 4.5-cm egg-shaped magnetic stirring bar (Note 4), is flushed with argon and charged with 32.9 g (0.15 mol) of 1-(tert-butoxycarbonyl)indoline, 27.2 mL (0.18 mol) of N,N,N',N'-tetramethylethylenediamine (TMEDA) (Note 5), and 750 mL of anhydrous ether (Note 6). The dropping funnel is charged with 167 mL (0.18 mol) of a 1.08 M solution of sec-butyllithium in cyclohexane via syringe (Note 7). Under a positive pressure of argon, the flask is immersed in a dry ice-acetone bath. When the internal temperature has reached ca. –70°C, a white precipitate of the starting material appears. The solution of sec-butyllithium is added dropwise to this suspension with rapid stirring over 30 min while keeping the internal temperature below –70°C. The dropping funnel is rinsed with 10 mL of anhydrous ether. The light brown mixture is stirred for an additional 2 hr at –78°C, during which time the precipitate completely dissolves and the color of the reaction mixture becomes deep brown. After the 2 hr has elapsed, 17.0 mL (0.22 mol) of N,N-dimethylformamide (DMF) is added dropwise through the addition funnel over a 10-min period (Note 8). After stirring the resulting mixture for 30 min at –78°C, 50 mL of saturated aqueous ammonium chloride solution is added through the dropping funnel over 15 min, and the cooling bath is removed (Note 9). When the internal temperature of the reaction mixture has reached –50°C, 50 mL of water is added dropwise, whereupon the deep orange color becomes light yellow. The reaction mixture is allowed to warm to 0°C and then poured into a 2-L separatory funnel containing water (200 mL). After thorough mixing, the layers are separated, and the aqueous phase is extracted with two 200-mL portions of ether. The combined organic layers are washed twice with 200 mL of saturated aqueous sodium chloride solution, dried over sodium sulfate, filtered, and concentrated under reduced pressure on a rotary evaporator followed by exposure to oil pump vacuum to remove as much of the volatiles as possible. The residue is chromatographed on 750 g of silica gel (Note 10), using a carefully packed 8-cm diameter glass column, and a mixture of toluene and ethyl acetate (30:1) as the eluent (Note 11). The appropriate fractions are combined and concentrated to give crude 1-(tert-butoxycarbonyl)-7-indolinecarboxaldehyde (23.6–25.5 g, 64–69% yield) as a light yellow solid. Recrystallization of this solid from a mixture of ethyl acetate and hexane affords the pure aldehyde (20.5–21.1 g, 55–57% yield in two crops) as practically colorless needles, mp 86.5–87.5°C (Note 12).

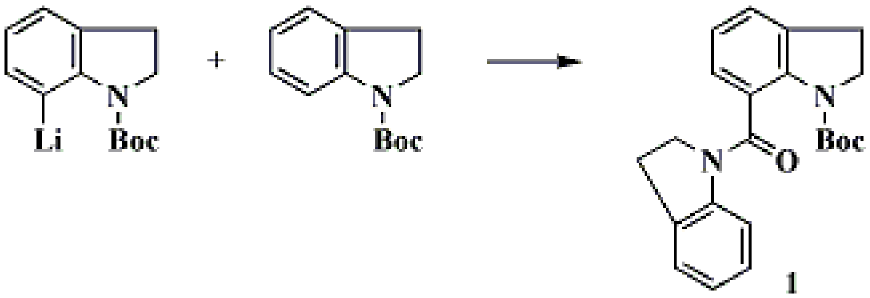
C. *7-Indolinecarboxaldehyde*. A 300-mL Erlenmeyer flask fitted with a magnetic stirring bar is charged with 150 mL of concentrated (36%) hydrochloric acid. To this magnetically stirred solution, 19.8 g (0.08 mol) of finely powdered 1-(tert-butoxycarbonyl)-7-indolinecarboxaldehyde is added portionwise over 15 min at room temperature. The starting material gradually dissolves accompanied by gas evolution.

After 2 hr, the resulting orange-colored solution is poured into a 2-L beaker containing crushed ice (500 g). To this mixture, 120 mL of 28% aqueous ammonia solution is added slowly with stirring, and the resulting mixture containing a yellow precipitate is transferred to a 2-L separatory funnel and extracted with four 100-mL portions of dichloromethane. The combined extracts are washed with 100 mL of saturated aqueous sodium chloride solution, dried over sodium sulfate, filtered, and concentrated on a rotary evaporator. The resulting yellowish brown oil is passed through 300 g of silica gel (Note 10) packed in an 8-cm diameter glass column using a mixture of toluene and ethyl acetate (30:1) as an eluent. The yellow eluates are combined, and the solvent is removed to give pure 7-indolinecarboxaldehyde (10.6–11.2 g, 90–95% yield) as a yellow solid, mp 48.5–49°C (Note 13).

2. Notes

1. Di-tert-butyl dicarbonate was purchased from Wako Pure Chemical Industries, Ltd. and used without further purification.
2. Indoline was purchased from Tokyo Kasei Kogyo Co., Ltd. and distilled under reduced pressure before use.
3. The spectral data for 1-(tert-butoxycarbonyl)indoline are as follows: IR (KBr) cm^{-1}: 1700 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.56 (s, 9 H), 3.07 (t, 2 H, J = 8.5), 3.96 (t, 2 H, J = 8.5), 6.91 (dt, 1 H, J = 7.5, 1.0), 7.11–7.17 (m, 2 H), 7.4–8.0 (extremely broad, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 27.3, 28.5, 47.6, 80.8, 114.7, 122.1, 124.7, 127.4, 131.1, 142.8, 152.7.
4. For efficient stirring, a powerful magnetic stirrer should be used. The submitters employed Super Stirrer Model MS-2 manufactured by Ishii Laboratory Works Co., Ltd.
5. N,N,N',N'-Tetramethylethylenediamine was distilled from powdered calcium hydride and stored under argon.
6. Ether was distilled from sodium benzophenone ketyl under nitrogen.
7. sec-Butyllithium was purchased from Kanto Chemical Co., Inc. and used after titration with 2,5-dimethoxybenzyl alcohol.[2]
8. N,N-Dimethylformamide was distilled from powdered calcium hydride and stored over 3 Å molecular sieves under argon.
9. When the reaction mixture was warmed to room temperature (4 hr – stirring after removal of cooling bath) before quenching with aqueous ammonium chloride solution, 7-indolinecarboxaldehyde (9.8–10.1 g, 44–46%) was obtained directly after silica gel column chromatography (SiO_2, 750 g, toluene elution).[3] However, the product was contaminated by small amounts of impurities, and attempted purification by recrystallization (ether-pentane) caused considerable loss of the main product.
10. Merck silica gel 60 (230–400 mesh) (No. 9385) was used.
11. Compound **1**, a major by-product of this reaction, was eluted after 1-(tert-butoxycarbonyl)-7-indolinecarboxaldehyde on chromatography (ca. 10% yield). This compound could be formed by condensation of the C-7 lithiated 1-(tert-

butoxycarbonyl)indoline with the non-lithiated starting material. Compound **1** has mp 192–195°C (decomp.) after recrystallization from ethyl acetate.



1

The submitters attempted inverse addition of 1-(tert-butoxycarbonyl)indoline to the ether solution of sec-BuLi-TMEDA complex at −78°C in order to suppress this side reaction. Formation of **1** was certainly decreased, but C-2 lithiation was observed as the other side reaction.

12. Spectral data of 1-(tert-butoxycarbonyl)-7-indolinecarboxaldehyde are as follows: IR (KBr) cm^{-1}: 1700, 1675 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.51 (s, 9 H), 3.07 (t, 2 H, J = 8.0), 4.17 (t, 2 H, J = 8.0), 7.10 (t, 1 H, J = 7.5), 7.36 (dq, 1 H, J = 7.5, 1.0), 7.64 (dd, 1 H, J = 7.5, 1.0), 10.11 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.2, 49.9, 82.5, 124.0, 125.0, 126.1, 129.2, 134.5, 143.7, 153.9, 189.6.

13. Spectral data of 7-indolinecarboxaldehyde are as follows: IR (KBr) cm^{-1}: 1650 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.05 (t, 2 H, J = 8.5), 3.78 (t, 2 H, J = 8.5), 6.60 (dd, 1 H, J = 8.0, 7.0), 7.17 (dq, 1 H, J = 7.0, 1.0), 7.27 (dd, 1 H, J = 8.0, 1.0), 9.82 (s, 1 H) (NH absorption not observed); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 27.8, 47.1, 116.0, 116.1, 129.2, 130.7, 131.1, 153.5, 192.4.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The procedure described here offers a general route to 7-substituted indolines.[3] The method is based on the directed ortho-lithiation of N-(tert-butoxycarbonyl)aniline derivatives.[4 5 6 7] The tert-butoxycarbonyl group seems to be essential for C-7 selective lithiation, since other directing groups so far reported promote C-2 or C-3 metalation on the indoline ring.[8 9 10] The C-7 selective lithiation of 1-(tert-butoxycarbonyl)indoline is in contrast to the C-2 selective lithiation of 1-(tert-butoxycarbonyl)indole.[11]

The C-7 lithio species reacts successfully with a wide range of electrophiles (chlorotrimethylsilane, tributyltin chloride, diphenyl disulfide, iodine, 1,2-

dibromoethane, hexachloroethane, iodomethane, carbon dioxide, DMF, aromatic and aliphatic aldehydes).[3] Lithiation occurs selectively at C-7 even in the presence of moderately ortho-directing methoxy or chloro groups on the aromatic ring.[3] The tert-butoxycarbonyl group is a well-established protective group for amine functionality and can be easily removed under a variety of reaction conditions.[12] Since indolines are readily oxidized to indoles,[13] [14] this method should be useful for the preparation of 7-substituted indoles, which are not readily prepared by using conventional methodologies.[15] [16] [17] [18] [19]

Two other methods for the C-7 selective functionalization of indoline have been reported. Somei developed C-7 selective thallation of 1-acetylindoline and applied it to the synthesis of 7-substituted indoles.[20] [21] [22] [23] Lo reported a synthesis of 7-benzoylindoline[24] by using Sugasawa's boron trichloride-mediated ortho-acylation of aniline derivatives.[25] The present method is superior to these procedures since a greater diversity of functionality can be introduced, the metalation exhibits high regioselectivity, and the use of highly toxic reagents such as thallium tris (trifluoroacetate) can be avoided.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium benzophenone ketyl

lithiated 1-(tert-butoxycarbonyl)indoline

TMEDA

hydrogen chloride, hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ethyl acetate (141-78-6)

ether (60-29-7)

ammonium chloride (12125-02-9)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

cyclohexane (110-82-7)

iodine (7553-56-2)

toluene (108-88-3)

1,2-dibromoethane (106-93-4)

iodomethane (74-88-4)

Pentane (109-66-0)

dichloromethane (75-09-2)

Tetrahydrofuran (109-99-9)

N,N-dimethylformamide, DMF (68-12-2)

hexane (110-54-3)

calcium hydride (7789-78-8)

argon (7440-37-1)

diphenyl disulfide (882-33-7)

hexachloroethane (67-72-1)

CHLOROTRIMETHYLSILANE (75-77-4)

thallium tris(trifluoroacetate) (23586-53-0)

sec-butyllithium, sec-BuLi (598-30-1)

indoline (496-15-1)

2,5-dimethoxybenzyl alcohol (33524-31-1)

tributyltin chloride (1461-22-9)

1-(tert-Butoxycarbonyl)indoline (143262-10-6)

7-Indolinecarboxaldehyde (143262-21-9)

1-(tert-Butoxycarbonyl)-7-indolinecarboxaldehyde (174539-67-4)

N,N,N',N'-tetramethylethylenediamine (110-18-9)

1-(tert-butoxycarbonyl)indole (75400-67-8)

1-acetylindoline (16078-30-1)

7-benzoylindoline

Di-tert-butyl dicarbonate (24424-99-5)

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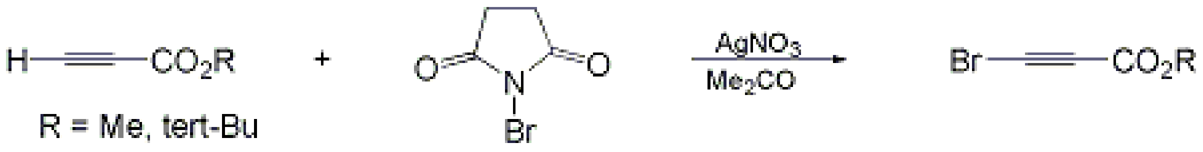
Organic Syntheses, CV 9, 129

PREPARATION OF 3-BROMOPROPIOLIC ESTERS: METHYL AND tert-BUTYL 3-BROMOPROPIOLATES

[2-Propynoic acid, 3-bromo-, methyl and 1,1-dimethylethyl esters]



Submitted by J. Leroy[1]
Checked by Paul N. Devine and Ichiro Shinkai.

1. Procedure

CAUTION! Propiolates and their bromo derivatives are lachrymators and must be handled under an efficient hood. Distillation of bromopropiolates should be carried out behind a safety shield (Note 1).

Methyl 3-bromopropiolate. A 250-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar is charged with 100 mL of acetone (Note 2) and 4.0 g (47.6 mmol) of methyl propiolate (Note 3). To the stirred solution at room temperature is added 0.8 g (4.7 mmol) of silver nitrate. After 5 min, 9.8 g of N-bromosuccinimide (55 mmol) is added at once. The homogeneous mixture becomes cloudy and a grayish precipitate develops. Stirring is continued for 2 hr (Note 4). The solids are filtered through a pad of Celite, which is rinsed with acetone (30–50 mL). After careful rotary evaporation of the acetone at ≈20°C under 20 mm, the oily residue is bulb-to-bulb distilled at room temperature under reduced pressure (≈0.1 mm), affording methyl 3-bromopropiolate as a colorless liquid (7.0–7.5 g, 42.9–46.0 mmol, 90–97%) solidifying in the refrigerator (mp ≈20°C) (Note 5).

tert-Butyl 3-bromopropiolate. tert-Butyl propiolate (Note 6) (5.42 g, 42.8 mmol) dissolved in 150 mL of acetone is treated as above with 0.8 g of silver nitrate (4.7 mmol) and, after 5 min of stirring at room temperature, with 9.8 g (55 mmol) of N-bromosuccinimide introduced at once into the suspension. Stirring is continued for 90 min. The solids are filtered through a pad of Celite, rinsed with acetone (30–50 mL) and the filtrate is concentrated at 20–25°C (20 mm) to give a white pasty solid. Water (80 mL) is added and the mixture is extracted with ether (3 × 80 mL). The ethereal layer is dried over anhydrous magnesium sulfate and the solvent is evaporated, leaving a semi-solid residue which is bulb-to-bulb distilled in an oil-bath at 45–50°C (≈0.1 mm) to give tert-butyl 3-bromopropiolate as a white semi-solid (8.51 g, 41.5 mmol, 97%) (Note 7).

2. Notes

1. Explosions during distillation of certain bromoalkynes have been reported.[2] Although methyl 3-bromopropiolate was not specifically cited, precautionary measures are recommended. The tert-butyl ester is a new compound[3] and must be handled like the methyl ester.
2. Acetone may be redistilled before use to remove the eventual autocondensation product, 4-hydroxy-4-methyl-2-pentanone (diacetone alcohol, bp 166°C). The submitter used, as received, fresh 99% pure acetone from Prolabo.
3. Methyl propiolate 99%, N-bromosuccinimide 99%, and silver nitrate were obtained from Janssen Chimica and used as received.
4. One hour of stirring is usually sufficient for completion of the reaction, but this time can be exceeded; longer reaction times improve the succinimide particle size, which aids the subsequent filtration. The product seems to adhere to the succinimide.
5. Depending on the conditions of the preliminary evaporation this product is contaminated with up to 5% of residual acetone. Nevertheless, it can be considered as pure enough for certain uses. Complete removal of acetone may be obtained by distillation in a small Vigreux column, although a yellowing of the distillate is observed: bp 86–88°C/100 mm (lit.[2] 88°C/100 mm and lit.[4] 40–45°C/5 mm). The spectral and analytical properties of methyl 3-bromopropiolate are as follows: ^{1}H NMR (200 MHz, $CDCl_3$) d: 3.73 (s, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 52.8 (C-3), 52.9 (CH_3), 72.4 (C-2), 152.8 (C-1). Anal. Calcd for $C_4H_3BrO_2$ (undistilled sample): C, 29.48; H, 1.86; Br, 49.03. Found: C, 29.11; H, 1.92; Br 48.79.
6. tert-Butyl propiolate was prepared from propiolic acid and isobutene in the presence of sulfuric acid.[5] It is now commercially available from Fluka Chemical Corp. and Aldrich Chemical Company, Inc.
7. Although pure enough to be used as obtained, tert-butyl 3-bromopropiolate may be distilled in a Vigreux column at 75–77°C (15 mm) to give a colorless oil crystallizing as plates: mp 25–27°C. The spectral and analytical properties of tert-butyl 3-bromopropiolate are as follows: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.46 (s, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 27.8 (CH_3), 50.0 (C-3), 73.9 (C-2), 84.0 (CMe_3), 151.3 (C-1). Anal. Calcd for $C_7H_9BrO_2$ (undistilled sample): C, 41.00; H, 4.42; Br, 38.48. Found: C, 40.48, H, 4.40; Br, 38.10.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Methyl 3-bromopropiolate has been prepared by esterification of 3-bromopropiolic acid with methanol and sulfuric acid for 6 days (75% yield),[4] the starting bromo acid being prepared by bromination of propiolic acid with aqueous potassium hypobromite.[6] This reaction is particularly delicate to control, giving erratic results. Moreover, direct bromination of methyl propiolate with sodium hypobromite[2] could not be reproduced.

Bromination of 1-alkynes with N-bromosuccinimide in the presence of catalytic amounts of silver nitrate, was used first for the bromination of 17-ethynyl steroids.[7] Similarly, N-iodosuccinimide led to 17-iodoethynyl steroids. Iodination of propiolates in this way has not been studied. A recent method of preparation of 1-iodoalk-1-ynes under phase-transfer conditions involves molecular iodine and copper(I) iodide as catalyst, in the presence of potassium or sodium carbonate as a base. Ethyl 3-iodopropiolate was prepared by this route in 80% yield.[8]

The present procedure provides ready access to 3-bromopropiolic esters, the methyl ester requiring adapted work up, because of its low boiling point. Less volatile esters, like tert-butyl, can be conveniently isolated by a standard aqueous-extraction work up.

Methyl 3-bromopropiolate has been used in Diels-Alder reactions either as a methoxycarbonyl ketene equivalent[9 10] or for the synthesis of functionalized naphthalenes.[11]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

METHYL AND tert-BUTYL 3-BROMOPROPIOLATES

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

methanol (67-56-1)

ether (60-29-7)

silver nitrate (7761-88-8)

sodium carbonate (497-19-8)

iodine (7553-56-2)

acetone (67-64-1)

4-hydroxy-4-methyl-2-pentanone (123-42-2)

sodium hypobromite

copper(I) iodide (7681-65-4)

magnesium sulfate (7487-88-9)

isobutene (9003-27-4)

potassium hypobromite

N-bromosuccinimide (128-08-5)

methyl propiolate (922-67-8)

N-Iodosuccinimide (516-12-1)

propiolic acid (471-25-0)

Methyl 3-bromopropiolate, 2-Propynoic acid, 3-bromo-, methyl ester (23680-40-2)

tert-Butyl propiolate (13831-03-3)

tert-Butyl 3-bromopropiolate, 2-Propynoic acid, 3-bromo-, 1,1-dimethylethyl ester

3-bromopropiolic acid

Ethyl 3-iodopropiolate

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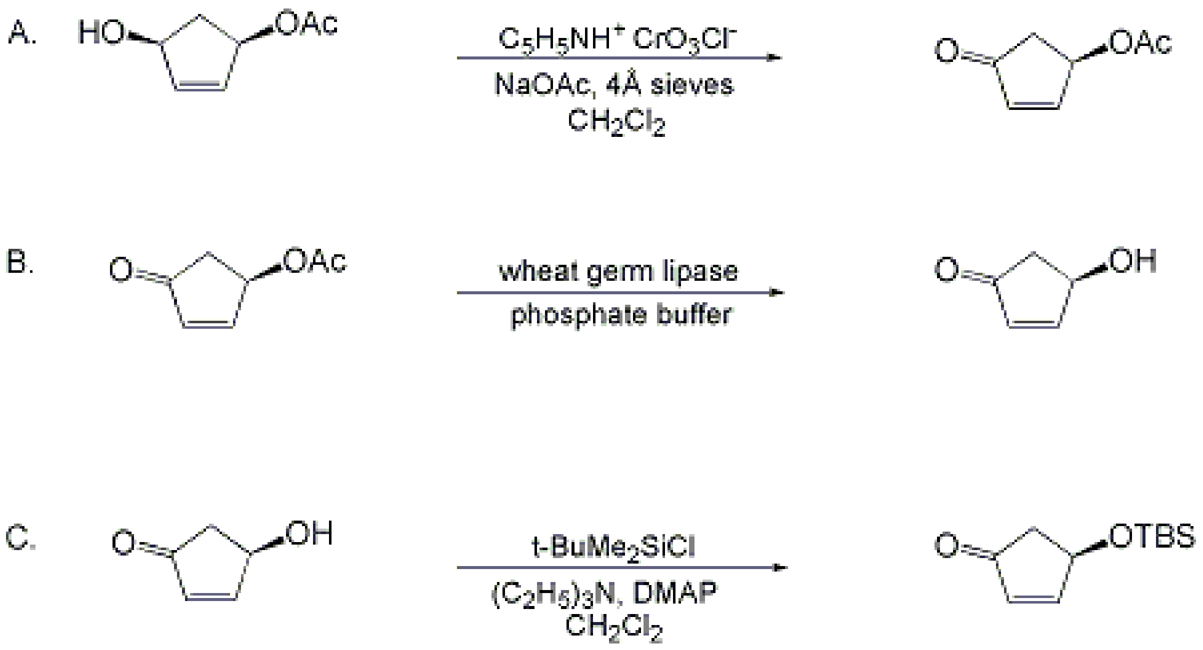
Organic Syntheses, CV 9, 132

(4R)-(+)-tert-BUTYLDIMETHYLSILOXY-2-CYCLOPENTEN-1-ONE

[2-Cyclopenten-1-one, 4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-, (R)-]



Submitted by Leo A. Paquette, Martyn J. Earle, and Graham F. Smith[1].
Checked by Thomas Kirrane and Albert I. Meyers.

1. Procedure

A. *(4R)-(+)-Acetoxy-2-cyclopenten-1-one*. A flame-dried, 2-L, three-necked, round-bottomed flask, equipped with a Teflon-coated magnetic stirring bar, is purged with nitrogen and charged with 1.0 L of dry dichloromethane (Note 1), 1.5 g of anhydrous sodium acetate (Note 2), 70 g of 4 Å molecular sieves (Note 3), and 23 g (162 mmol) of (1R,4S)-(+)-4-hydroxy-2-cyclopentenyl acetate (Note 4). Finely powdered pyridinium chlorochromate (50 g, 240 mmol) is added portionwise over a period of 5 min, and the mixture is stirred at room temperature for 3 hr (Note 5), then filtered through a pad of Florisil. The filtrate is concentrated on a rotary evaporator, and the residual dark oil is purified by flash chromatography on silica gel with elution by 20% ethyl acetate in petroleum ether (bp 35–60°C) (Note 6) to give 18.9 g (83%) of (4R)-(+)-acetoxy-2-cyclopenten-1-one as a colorless oil (Note 7).

B. *(4R)-(+)-Hydroxy-2-cyclopenten-1-one*. A 2-L, one-necked, round-bottomed flask, fitted with a Teflon-coated magnetic stirring bar, is charged with 1.5 L of 0.05 M phosphate buffer (Note 8) and 18.8 g (134 mmol) of (4R)-(+)-acetoxy-2-cyclopenten-1-one. A 4.0-g lot of wheat germ lipase (Note 9) is added slowly with rapid stirring.

Once the enzyme is dispersed, the speed of the stirrer is reduced and the flask is sealed with a glass stopper prior to being stirred at room temperature for 7 days (Note 10). The stopper is removed and the contents of the flask are transferred to the body of a lighter than water continuous extraction apparatus whose pot is charged with 1 L of ethyl acetate. After extraction for 3 days, the ethyl acetate solution is concentrated on a rotary evaporator, and the residue is subjected to flash chromatography on silica gel using 30% ethyl acetate in petroleum ether (bp 35–60°C) as eluent (Note 11). After recovery of 4.60 g (25%) of the less polar, unreacted acetoxy ketone (Note 12), 7.80 g (60%) of the colorless, oily (R)-(+)-hydroxy ketone is obtained (Note 13).

C. *(4R)-(+)-tert-Butyldimethylsiloxy-2-cyclopenten-1-one*. A 500-mL, three-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar, pressure-equalizing addition funnel, and nitrogen inlet, is flame-dried under a stream of dry nitrogen. The apparatus is charged with 7.7 g (78 mmol) of (4R)-(+)-hydroxy-2-cyclopenten-1-one, 0.96 g (10 mol %) of 4-dimethylaminopyridine (Note 14), 20 g (200 mmol) of triethylamine (Note 2), and 150 mL of dry dichloromethane (Note 1). The dropping funnel is charged with a solution of 14.2 g (94 mmol) of tert-butyldimethylsilyl chloride (Note 14) in 50 mL of dry dichloromethane. Magnetic stirring is initiated, the reaction mixture is cooled in an ice-water bath, and the silyl chloride solution is added dropwise during 10 min. The ice-water bath is removed, and the mixture is stirred at room temperature for 3 hr; then 100 mL of deionized water is added with stirring. After the organic layer is separated, the aqueous phase is extracted three times with 50 mL of dichloromethane and the combined organic solutions are dried over anhydrous magnesium sulfate, filtered, and concentrated on a rotary evaporator. The residue is filtered through a short column of silica gel with elution by 5% ethyl acetate in petroleum ether (bp 35–60°C). After concentration of the fractions containing the product, the resulting oil is distilled in a short path distillation apparatus (bp 60°C at 0.1 mm) to give 13.2 g of a colorless oil. Crystallization of this material from pentane with cooling by an acetone-dry ice bath gives 10.6 g (64%) of colorless needles, mp 27–28°C, $[\alpha]_D^{20}$ +65.3° (CH_3OH, *c* 0.4) (Note 15) and (Note 16).

2. Notes

1. Dichloromethane is distilled from calcium hydride prior to use.
2. Sodium acetate and triethylamine were purchased from the J. T. Baker Chemical Company. Sodium acetate is used without further purification; triethylamine is distilled from calcium hydride prior to use.
3. The 4 Å molecular sieves were purchased from the Aldrich Chemical Company, Inc., and activated by drying in a vacuum oven at 150°C for 24 hr prior to storing in an oven at 140°C. Both powdered and pelletized forms of the sieve were used without affecting the yield of product.
4. High purity (≥99% ee) (1R,4S)-4-hydroxy-2-cyclopentenyl acetate exhibiting $[\alpha]_D^{23}$ values of +71.1° to +71.3° in $CHCl_3$ can be obtained by enzymatic hydrolysis of the racemic diacetate (*Org. Synth., Coll. Vol. IX* **1998**, 487)[2,3,4]

with electric eel acetyl cholinesterase[4] or with A.K. lipase (Amano International Enzyme Company).[5]

5. The progress of this reaction is conveniently monitored by TLC. The silica gel plates are eluted with 50% ethyl acetate in petroleum ether (bp 35–60°C). Under these conditions, the alcohol exhibits an R_f of 0.45 and the acetate an R_f of 0.80.

6. The column consists of 300 g of silica gel; 100-mL sized fractions are collected. Since release of the product from the chromium salts occurs slowly, fractions 5–20 are found to contain the acetoxy ketone and are combined.

7. The spectral data for (4R)-(+)-acetoxy-2-cyclopenten-1-one are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.06 (s, 3 H), 2.29 (dd, 1 H, J = 2.2, 18.7), 2.78 (dd, 1 H, J = 6.4, 18.7), 5.81 (m, 1 H), 6.29 (dd, 1 H, J = 1.3, 5.7), 7.53 (dd, 1 H, J = 2.4, 5.7); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.7, 40.9, 71.9, 136.9, 158.8, 170.3, 204.7; IR ($CHCl_3$) cm^{-1}: 2950, 1740, 1720, 1600, 1375, 1355, 1190, 795; $[\alpha]_D^{20}$ +96.1° (CH_3OH, *c* 0.17) [lit.[6] $[\alpha]_D^{22}$ +97° (CH_3OH, *c* 0.1].

8. The buffer is prepared by dissolving 27.2 g of potassium dihydrogen phosphate in 4.0 L of deionized water and titrating with 1 M sodium hydroxide until pH 5.0 is reached.

9. Wheat germ lipase was purchased from the Sigma Chemical Company.

10. The reaction rate decreased significantly toward the end of the hydrolysis. The level of conversion can be improved either by increasing the amount of enzyme or by lengthening the reaction time. The course of the reaction can be monitored by TLC on silica gel (elution with 50% ethyl acetate in petroleum ether). The product has an R_f of 0.20 and the starting material an R_f of 0.40.

11. The column consists of 200 g of silica gel; 100-mL sized fractions are collected. The starting material was recovered in fractions 2–5 while the product was recovered from fractions 7–20.

12. This material can be recycled in future reactions.

13. The spectral data for (4R)-(+)-hydroxy-2-cyclopenten-1-one are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.27 (dd, 1 H, J = 3.0, 18.0), 2.78 (dd, 1 H, J = 6.0, 18.0), 3.27 (br s, 1 H), 4.88–5.22 (m, 1 H), 6.25 (d, 1 H, J = 6.0), 7.60 (dd, 1 H, J = 2.0, 6.0); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 44.1, 70.1, 134.7, 164.0, 207.3; $[\alpha]_D^{20}$ +78.1° (CH_3OH, *c* 2.03).

14. 4-Dimethylaminopyridine and tert-butyldimethylsilyl chloride were purchased from the Aldrich Chemical Company, Inc., and used without purification.

15. The spectral data for (4R)-(+)-tert-butyldimethylsiloxy-2-cyclopenten-1-one are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.12 (s, 3 H), 0.13 (s, 3 H), 0.91 (s, 9 H), 2.23 (dd, 1 H, J = 2.3, 18.2), 2.69 (dd, 1 H, J = 6.0, 18.2), 4.98 (m, 1 H), 6.17 (dd, 1 H, J = 1.2, 5.7), 7.44 (dd, 1 H, J = 2.3, 5.7); ^{13}C NMR (75 MHz, $CDCl_3$) δ: –4.76, –4.74, 18.0, 25.7, 44.9, 70.9, 134.4, 163.7, 206.3.

16. The reported optical rotations are $[\alpha]_D^{21}$ +66.6° (CH_3OH, *c* 1.0),[7] $[\alpha]_D^{21}$ +67.0° (CH_3OH, *c* 0.12),[6] and $[\alpha]_D^{21}$ +67.3° (CH_3OH, *c* 0.82).[8]

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

As a direct consequence of the quest for optically active prostaglandins,[9] derivatives of (R)-4-hydroxy-2-cyclopenten-1-one have come to be regarded as important chiral building blocks. Initial efforts to obtain these compounds in enantiomerically pure form involved the chemical modification of D-tartaric acid,[10] degradation of the fungal metabolite terrein,[11] ring contraction of 2,4,6-trichlorophenol with resolution,[9,12] chromatography of diastereomeric[13] or racemic hydroxy-protected derivatives,[14] and a multi-step conversion from glucose.[15] Subsequent discoveries that excellent kinetic resolution can be achieved either by asymmetric BINAL-H reduction of 4-cyclopentene-1,3-dione[16] or by enzymatic hydrolysis of the acetate[17] proved to be major advances.

More recently, the desymmetrization of cis-3,5-diacetoxycyclopent-1-ene by enantioselective monohydrolysis in the presence of various enzymes has been intensively investigated.[18,19,20,21,22,23] This approach is readily adaptable to a laboratory setting, is inexpensive, and is capable of straightforwardly delivering multigram quantities of high quality (>99% ee) product.

The reaction sequence shown here, which has been adapted from earlier literature reports, permits the convenient acquisition of (4R)-(+)-tert-butyldimethylsiloxy-2-cyclopenten-1-one, perhaps the most useful of the possible derivatives for further synthetic elaboration.[24] The companion synthesis of the useful (4S) enantiomer from the same starting material is also described.[25]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 136

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

ethyl acetate (141-78-6)

sodium acetate (127-09-3)

sodium hydroxide (1310-73-2)

nitrogen (7727-37-9)

acetate

Pentane (109-66-0)

glucose (492-62-6)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

potassium dihydrogen phosphate (7778-77-0)

triethylamine (121-44-8)

calcium hydride (7789-78-8)

phosphate

4-cyclopentene-1,3-dione (930-60-9)

pyridinium chlorochromate (26299-14-9)

4-dimethylaminopyridine (1122-58-3)

(4R)-(+)-tert-BUTYLDIMETHYLSILOXY-2-CYCLOPENTEN-1-ONE (61305-35-9)

2-Cyclopenten-1-one, 4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-, (R)-

(4R)-(+)-Acetoxy-2-cyclopenten-1-one (59995-48-1)

(1R,4S)-(+)-4-Hydroxy-2-cyclopentenyl acetate (60410-16-4)

(4R)-(+)-Hydroxy-2-cyclopenten-1-one

acetoxy ketone

tert-butyldimethylsilyl chloride (18162-48-6)

(R)-4-hydroxy-2-cyclopenten-1-one

D-tartaric acid (147-71-7)

2,4,6-trichlorophenol (88-06-2)

cis-3,5-diacetoxycyclopent-1-ene (54664-61-8)

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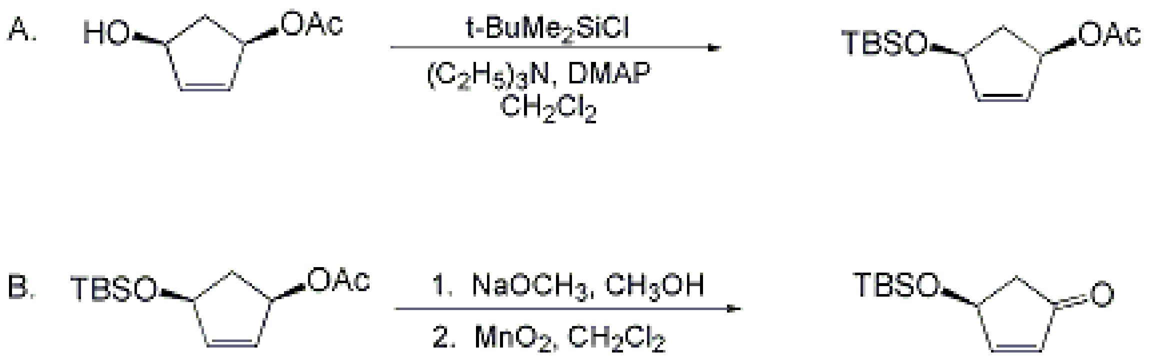
(4S)-(−)-tert-BUTYLDIMETHYLSILOXY-2-CYCLOPENTEN-1-ONE

[(4S)-(−)-tert-Butyldimethylsiloxy-2-cyclopenten-1-one]



Submitted by Leo A. Paquette and Todd M. Heidelbaugh[1].
Checked by Thomas Kirrane and Albert I. Meyers.

1. Procedure

A. *(1R,4S)-(−)-4-tert-Butyldimethylsiloxy-2-cyclopentenyl acetate*. A dry, 500-mL, three-necked, round-bottomed flask, equipped with a Teflon-coated magnetic stirring bar, rubber septum, and nitrogen inlet, is purged with nitrogen and charged with 7.67 g (54 mmol) of (1R,4S)-(+)-4-hydroxy-2-cyclopentenyl acetate (Note 1), 660 mg (5.4 mmol) of 4-dimethylaminopyridine (Note 2), 17 mL (122 mmol) of triethylamine (Note 3), and 175 mL of dichloromethane (Note 3). The reaction mixture is cooled to 0°C in an ice-water bath, and tert-butyldimethylsilyl chloride (10.24 g, 68 mmol) (Note 2) is introduced in one portion. The ice-water bath is removed and the mixture is allowed to warm to room temperature and stir for 3 hr. At this point, more silyl chloride is added if necessary (Note 4). After 5 hr, 200 mL of water is added, the mixture is transferred to a separatory funnel and the organic phase separated. The aqueous phase is extracted with three 100-mL portions of dichloromethane. The combined organic layers are washed with 100 mL of saturated sodium bicarbonate solution and 100 mL of brine prior to drying over anhydrous magnesium sulfate. After filtration and solvent removal with a rotary evaporator, the residual solids are removed by filtration (Note 5), and the resulting yellow oil is purified by bulb-to-bulb distillation at 0.4–0.6 mm (pot temperature 80–100°C) to give 10.67–11.08 g (77–80%) of (1R,4S)-(−)-4-tert-butyldimethylsiloxy-2-cyclopentenyl acetate as a colorless liquid, $[\alpha]_D^{20}$ −1.32° (CH_3OH, *c* 1.52) (Note 6).

B. *(4S)-(−)-tert-Butyldimethylsiloxy-2-cyclopenten-1-one*. A dry, 500-mL, one-necked, round-bottomed flask, equipped with a Teflon-coated magnetic stirring bar, is purged with nitrogen and charged with 11.7 g (45.6 mmol) of (1R,4S)-(−)-tert-butyldimethylsiloxy-2-cyclopentenyl acetate and 250 mL of anhydrous methanol

(Note 7) to which 4.94 g (91.5 mmol) of powdered sodium methoxide (Note 8) is added. The reaction mixture is stirred for 15 min at ambient temperature, freed of most of the methanol using a rotary evaporator, and taken up in 400 mL of dichloromethane. The solution is washed with three 200-mL portions of water, dried over anhydrous magnesium sulfate, filtered, and concentrated using a rotary evaporator, giving 11.2 g of crude allylic alcohol which is carried into the next reaction without further purification.

A 500-mL, round-bottomed flask, equipped with a Teflon-coated magnetic stirring bar, is charged with the 11.2 g of crude allylic alcohol obtained above and 300 mL of dichloromethane, and the resulting vigorously stirred solution is treated with 33 g of active manganese dioxide (380 mmol) (Note 9). Additional 2–5 g lots of the oxidant are added every 2–3 hr until the reaction is complete (Note 10). The reaction mixture is vacuum-filtered through a pad of diatomaceous earth, and the pad is washed with 200 mL of dichloromethane. The resulting clear filtrate is concentrated carefully using a rotary evaporator, and the residual oil is purified by bulb-to-bulb distillation at 0.3 mm (pot temperature 100°C) affording 8.43–8.71 g (87–90%) of enone as a pale yellow oil that solidifies when cooled below 15°C. Crystallization of the crude product from pentane at −70°C gives (4S)-(−)-tert-butyldimethylsiloxy-2-cyclopenten-1-one as colorless needles having mp 32–33°C, $[\alpha]_D^{23}$ −65.1° (CH_3OH, *c* 0.94) (Note 11).

2. Notes

1. High purity (≥99% ee) (1R,4S)-4-hydroxy-2-cyclopentenyl acetate exhibiting $[\alpha]_D^{20}$ values of +71.1 to +71.3° in $CHCl_3$ can be obtained by enzymatic hydrolysis of the racemic diacetate[2,3,4] either with electric eel cholinesterase[2] or with A.K. lipase (Amano International Enzyme Company).[5] The checkers employed the EEAC procedure.[2]
2. 4-Dimethylaminopyridine and tert-butyldimethylsilyl chloride were purchased from the Aldrich Chemical Company, Inc. and used without further purification.
3. Triethylamine and dichloromethane were distilled from calcium hydride before use.
4. The progress of the reaction is easily monitored by TLC analysis. Silyl chloride is added until the starting hydroxy acetate is no longer detected.
5. Filtration is performed only to prevent bumping during the ensuing distillation.
6. The spectral data are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.09 (s, 6 H), 0.90 (s, 9 H), 1.57–1.65 (m, 1 H), 2.04 (s, 3 H), 2.75–2.85 (dt, 1 H, J = 7.3, 3.8), 4.69–4.73 (m, 1 H), 5.44–5.48 (m, 1 H), 5.87–5.98 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: −4.7, −4.6, 18.2, 21.1, 25.9, 41.2, 74.9, 77.4, 131.2, 138.9, 170.9; IR (neat) cm^{-1}: 2940, 2870, 1740, 1610, 1375, 1250.
7. The methanol was refluxed over magnesium turnings and a crystal of iodine under nitrogen for 3 hr prior to use.

8. Sodium methoxide was freshly prepared by adding sodium metal to methanol (*Caution: hydrogen evolution*), evaporation of the solvent, and vacuum drying of the white solid.

9. Manganese dioxide was prepared as described.[6]

10. The time required to achieve complete reaction varies from 20–48 hr depending on the activity of the manganese dioxide. The progress of the oxidation is easily monitored by TLC analysis on silica gel.

11. The spectral data are identical to those reported for the (4R) enantiomer.[7]

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Although (1R,4S)-(+)- and (1S,4R)-(–)-4-hydroxy-2-cyclopentenyl acetate are both available by enzyme-promoted enantioselective hydrolysis,[8,9] different enzymes are, of course, required to achieve this stereochemical divergence. Economy would be realized if one of these enantiomeric products could serve as the starting point for the preparation of both antipodal forms of structurally more advanced intermediates. The importance of (4R)-(+)-[10,11] and (4S)-(–)-tert-butyldimethylsiloxy-2-cyclopenten-1-one[12] to prostaglandin synthesis is well established. The latent potential of these highly functionalized building blocks for the enantiospecific synthesis of other natural products is beginning to emerge.[13,14,15] Use of the present procedure makes possible the direct, efficient acquisition of the 4S enantiomer from the same hydroxy acetate that serves as a convenient progenitor to the 4R isomer.[7] The synthetic route is closely similar to that outlined earlier by Danishefsky, Cabal, and Chow.[13]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

brine

(4S)-(−)-tert-BUTYLDIMETHYLSILOXY-2-CYCLOPENTEN-1-ONE

(1R,4S)-(−)-4-tert-Butyldimethylsiloxy-2-cyclopentenyl acetate

(1R,4S)-(−)-tert-butyldimethylsiloxy-2-cyclopentenyl acetate

(1R,4S)-(+)- and (1S,4R)-(−)-4-hydroxy-2-cyclopentenyl acetate

methanol (67-56-1)

hydrogen (1333-74-0)

sodium bicarbonate (144-55-8)

magnesium turnings (7439-95-4)

nitrogen (7727-37-9)

iodine (7553-56-2)

sodium methoxide (124-41-4)

sodium (13966-32-0)

manganese dioxide (1313-13-9)

Pentane (109-66-0)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

triethylamine (121-44-8)

calcium hydride (7789-78-8)

4-dimethylaminopyridine (1122-58-3)

(1R,4S)-(+)-4-Hydroxy-2-cyclopentenyl acetate (60410-16-4)

tert-butyldimethylsilyl chloride (18162-48-6)

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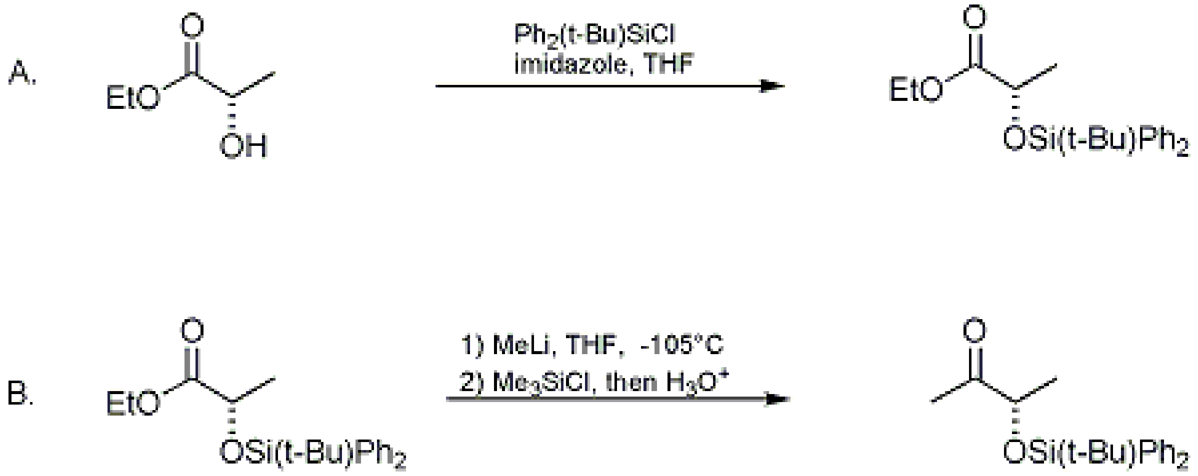
3-(S)-[(tert-BUTYLDIPHENYLSILYL)OXY]-2-BUTANONE

[2-Butanone, 3-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-, (S)-]



Submitted by Larry E. Overman and Gilbert M. Rishton[1].
Checked by Takashi Ooi and Hisashi Yamamoto.

1. Procedure

A. *Ethyl 2-(S)-[(tert-butyldiphenylsilyl)oxy]propanoate*. An oven-dried, 500-mL, round-bottomed flask is equipped with a magnetic stirring bar and purged with dry argon. The flask is charged with 10.0 g (84.6 mmol) of (S)-(−)-ethyl lactate, 23.3 g (84.6 mmol) of tert-butyldiphenylsilyl chloride, 14.4 g (211 mmol) of imidazole, and 50 mL of dry tetrahydrofuran (Note 1). The resulting white suspension is stirred vigorously at 23°C for 2 hr. (At the beginning of the stirring, a heated water bath is useful to maintain the reaction temperature.) The mixture is then filtered through glass wool into 400 mL of water and the solids are washed with two 25-mL portions of tetrahydrofuran. The filtrate is concentrated to remove tetrahydrofuran under reduced pressure using a rotary evaporator. The resulting aqueous suspension is transferred to a 1-L separatory funnel and is extracted with 400 mL of ethyl acetate. The organic phase is washed with two 400-mL portions of water, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure using a rotary evaporator to give 30.0 g (99%) of ethyl 2-(S)-[(tert-butyldiphenylsilyl)oxy]propanoate as a clear colorless oil (Note 2).

B. *3-(S)-[(tert-Butyldiphenylsilyl)oxy]-2-butanone*. An oven-dried, 1-L, three-necked, round-bottomed flask is charged with 20.0 g (56.2 mmol) of ethyl 2-(S)-[(tert-butyldiphenylsilyl)oxy]propanoate and the flask is fitted with a mechanical stirrer, a 100-mL addition funnel, and a rubber septum. A low temperature thermometer (Note 3) is inserted through the rubber septum and 250 mL of dry tetrahydrofuran (Note 1) is

injected with a syringe. The mechanically stirred solution is cooled to −105°C (Note 4) and maintained until the temperature has stabilized. The addition funnel is charged with 52 mL of a 1.4 M ether solution of halide-free methyllithium (73 mmol) and this solution is added dropwise with mechanical stirring over 35–40 min. The internal temperature is never allowed to rise above −100°C (Note 5). When addition is complete, 20 mL (158 mmol) of trimethylsilyl chloride (Note 6) is injected and the resulting clear solution is warmed to room temperature over 20 min with the aid of a water bath. At this time 200 mL of 1 N hydrochloric acid is added and vigorous stirring is continued for 1 hr (Note 7). The mixture is poured slowly into a 2-L Erlenmeyer flask containing 30 g of solid sodium bicarbonate and then concentrated to remove tetrahydrofuran under reduced pressure using a rotary evaporator. The resulting aqueous suspension is transferred to a 1-L separatory funnel and extracted with 400 mL of ethyl acetate. The organic layer is washed with two 400-mL portions of water, dried over anhydrous sodium sulfate, filtered, and concentrated using a rotary evaporator to give 18.2 g (99%) of 3-(S)-[(tert-butyldiphenylsilyl)oxy]-2-butanone as a clear colorless oil (Note 8) and (Note 9).

2. Notes

1. (S)-Ethyl lactate, $[\alpha]_D^{14}$ −10° (neat) and other chemicals employed in this procedure were obtained from Aldrich Chemical Company, Inc. Anhydrous tetrahydrofuran was prepared by distillation under argon from sodium benzophenone ketyl.

2. Gas chromatographic analysis using a 25-m 10% SP 2100 silicone column showed that this sample was >95% pure and contained one major unidentified impurity. Material of this purity is acceptable for use in the second step. A sample showing no detectable impurities by GLC analysis can be obtained by flash chromatography on silica gel (5:95 ethyl acetate-hexane). This sample has the following spectral characteristics: $[\alpha]_D$ −45.1° (MeOH, *c* 1.0); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.09 (s, 9 H, t-Bu), 1.14 (t, 3 H, J = 7.1, OCH_2CH_3), 1.37 (d, 3 H, J = 6.7, CH_3), 3.99–4.04 (m, 2 H, OCH_2CH_3), 4.27 (q, 1 H, J = 6.7, CH), 7.36–7.41 (m, 6 H, Ph), 7.65–7.69 (m, 4 H, Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.0, 19.2, 21.2, 26.8, 60.5, 68.9, 127.6, 129.7, 133.1, 133.5, 135.7, 135.8, 173.6; IR (film) cm^{-1}: 2980, 2933, 2859, 1753, 1735, 1429, 1198, 1139, 1112, 1081, 823, 739, 702, 690, 611. Anal. Calcd for $C_{21}H_{28}O_3Si$: C, 70.74; H, 7.92. Found: C, 70.94; H, 7.89.

3. An OMEGA 450 ATT (Type T) thermocouple thermometer was used.

4. A minimum amount of liquid nitrogen contained in a 1-L Dewar bowl was used to cool the solution to −105°C.

5. It is crucial that the internal temperature of the reaction mixture never exceed −100°C during the addition of the methyllithium solution. If the temperature begins to rise, the dropwise addition of the reagent should be slowed. Periodic addition of a small amount of liquid nitrogen to the cooling bath may also be necessary.

6. Trimethylsilyl chloride is distilled from calcium hydride and stored under argon or nitrogen in a stoppered bottle over polyvinylpyridine.
7. Hydrolysis of the reaction mixture may be accomplished by addition of 200 mL of water instead of 200 mL of 1 N hydrochloric acid. In the former case complete hydrolysis requires 5 hr and in the latter hydrolysis is complete within 1 hr.
8. Gas chromatographic analysis using a 25-m 10% SP 2100 silicone column showed that this sample was >95% pure and contained one major unidentified impurity. A sample of 100% purity may be obtained by flash chromatography on silica gel (1:9 ethyl acetate-hexane). This sample has the following spectral characteristics: $[\alpha]_D$ −3.1° (MeOH, *c* 1.0); ^{1}H NMR (300 MHz, $CDCl_3$): δ: 1.10 (s, 9 H, t-Bu), 1.19 (d, 3 H, J = 6.8, CH_3), 2.16 (s, 3 H, $COCH_3$), 4.17 (q, 1 H, J = 6.8, CH), 7.36–7.40 (m, 6 H, Ph), 7.60–7.66 (m, 4 H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 19.2, 20.6, 24.9, 26.9, 75.7, 127.6, 127.8, 129.9, 135.7, 211.7; IR (film) cm^{-1}: 2961, 2933, 2859, 1719, 1428, 1114, 823, 741, 703, 691; MS (Cl) m/z 327.1760 (327.1780 calcd for $C_{20}H_{26}O_2Si$, MH). Anal. Calcd for $C_{20}H_{26}O_2Si$: C, 73.57; H, 8.03. Found: C, 73.52; H, 8.07.
9. The enantiomeric excess of the product is >96%. This was determined by treating a sample of the ketone sequentially with methyllithium and tetrabutylammonium fluoride (THF, −78°C). The resulting diol was converted to its Mosher diester[2 3] [2.5 eq of (+)-α-methoxytrifluoromethylphenylacetic acid, 3 eq of dicyclohexylcarbodiimide, and 0.2 eq of 4-(dimethylamino)pyridine, CH_2Cl_2] and the crude esterification reaction mixture was analyzed using 500 MHz ^{1}H NMR. None of the minor diastereomer was observed; doping experiments established that 2% of the minor diastereomer would have been detected [diagnostic signals: d 5.03 (q, J = 6.2, major diastereomer); δ 5.17 (q, J = 6.1, minor diasteromer)].

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The sequence detailed here provides 3-(S)-((tert-butyldiphenylsilyl)oxy)-2-butanone in high purity and on a preparative scale from inexpensive (S)-ethyl lactate. This optically active ketone should be a useful intermediate for the preparation of a variety of enantiomerically pure materials. It has been used in our laboratory for an asymmetric synthesis of (+)-muscarine[4] and in the preparation of various other optically active tetrahydrofurans.[5] Mitsunobu inversion of (S)-ethyl lactate followed by protection to provide 2-(R)-((tert-butyldiphenylsilyl)oxy)propanoate[6] affords, by this method, ready access to the enantiomer of the title compound.

Conversions of carboxylic acids to ketones are typically performed in stepwise fashion[7] via intermediates such as acid chlorides,[8 9 10 11] anhydrides,[12] thioesters,[13] or N-alkoxy amides,[14 15] or by the direct reaction of carboxylic acids with lithium reagents.[16] In this latter method trimethylsilyl chloride has been shown to be an effective reagent for trapping the tetrahedral alkoxide intermediates and for quenching excess organolithium reagent.

The addition of trimethylsilyl chloride proved crucial to the success of the procedure described here. Use of aqueous ammonium chloride as a quenching reagent (instead of trimethylsilyl chloride) resulted in a reaction mixture that contained up to 30% of the corresponding tertiary alcohol.

Preliminary investigations into the generality of this synthesis of lactate-derived ketones using other alkyl lithium reagents including butyllithium and phenyllithium have not been as successful. Product mixtures were typically contaminated with significant amounts of both the tertiary alcohol and the starting ester.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 4

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium benzophenone ketyl

(+)-muscarine

(S)-(−)-ethyl lactate

polyvinylpyridine

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

ether (60-29-7)

ammonium chloride (12125-02-9)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

Phenyllithium (591-51-5)

lithium (7439-93-2)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

Imidazole (288-32-4)

Methyllithium (917-54-4)

calcium hydride (7789-78-8)

dicyclohexylcarbodiimide (538-75-0)

argon (7440-37-1)

trimethylsilyl chloride (75-77-4)

ethyl acetate-hexane (2639-63-6)

4-(dimethylamino)pyridine (1122-58-3)

(+)-α-methoxytrifluoromethylphenylacetic acid (56135-03-6)

Tetrabutylammonium fluoride (429-41-4)

3-(S)-[(tert-Butyldiphenylsilyl)oxy]-2-butanone, 3-(S)-((tert-butyldiphenylsilyl)oxy)-2-butanone, 2-Butanone, 3-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-, (S)- (135367-18-9)

tert-butyldiphenylsilyl chloride (58479-61-1)

Ethyl 2-(S)-[(tert-butyldiphenylsilyl)oxy]propanoate (102732-44-5)

(S)-ethyl lactate (97-64-3)

2-(R)-((tert-butyldiphenylsilyl)oxy)propanoate

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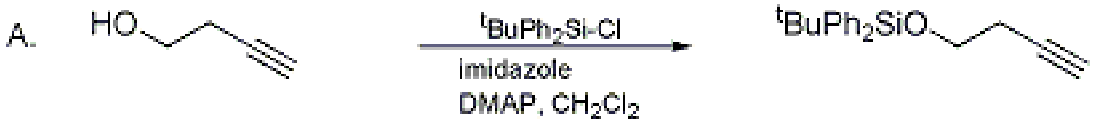
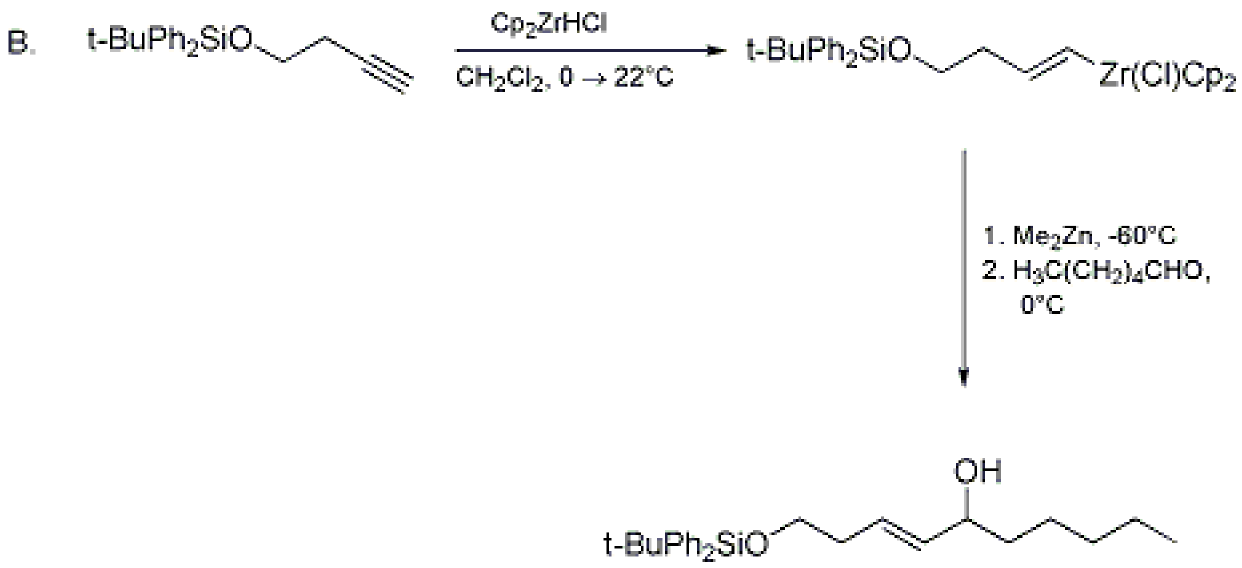
Organic Syntheses, CV 9, 143

ALLYLIC ALCOHOLS BY ALKENE TRANSFER FROM ZIRCONIUM TO ZINC: 1-[(tert-BUTYLDIPHENYLSILYL)OXY]-DEC-3-EN-5-OL





Submitted by Peter Wipf and Wenjing Xu[1].
Checked by Thomas Wynn and Louis S. Hegedus.

1. Procedure

A. *tert-Butyl(but-3-ynyloxy)diphenylsilane.* A dry, 250-mL, round-bottomed flask is fitted with a rubber septum and a magnetic stirring bar. The flask is charged with 3-butyn-1-ol (2.1 g, 30 mmol) (Note 1) and dry dichloromethane (60 mL) (Note 2). After addition of 8.5 g (31 mmol) of tert-butyldiphenylchlorosilane (Note 3), the reaction flask is immersed in a water bath and imidazole (2.86 g, 42 mmol) is added in one portion followed by 4-dimethylaminopyridine (0.37 g, 3 mmol). The water bath is removed and the reaction mixture is stirred at room temperature overnight. The white precipitate is filtered through a sintered glass funnel (`M' frit). The precipitate is washed with cold dichloromethane (50 mL). The combined filtrates are transferred to a 500-mL separatory funnel and washed with 1 M aqueous hydrochloric acid solution

(50 mL) and water (100 mL), successively. The organic layer is dried over magnesium sulfate and concentrated by rotary evaporator. Bulb-to-bulb distillation of the residue (bp 150–152°C/1 mm) gives 8.90 g (96%) of tert-butyl(but-3-ynyloxy)diphenylsilane as a colorless oil (Note 4).

B. *1-[(tert-Butyldiphenylsilyloxy)]-dec-3-en-5-ol*. A flame-dried, 250-mL, round-bottomed flask equipped with a gas inlet stopcock (f.htmigure 1) is fitted with a rubber septum and a magnetic stirring bar, and flushed with nitrogen. The flask is charged with tert-butyl(but-3-ynyloxy)diphenylsilane (5.55 g, 18 mmol) and dry dichloromethane (60 mL), immersed in a cold water bath and stirred. Within 20 min, 5.10 g (19.8 mmol) of zirconocene hydrochloride (Note 5) is added in five portions. The water bath is removed and the reaction mixture is stirred at room temperature until a homogenous solution forms. The resulting golden-yellow solution is stirred for another 20 min (Note 6) and then cooled to –60°C. By syringe, dimethylzinc (2.0 M solution in toluene, 10.4 mL, 20.8 mmol) (Note 1) is added dropwise over 45 min while the bath temperature is kept at –60°C. The resulting orange-yellow solution is stirred for an additional 10 min at –60°C after the addition is completed. The reaction flask is immersed in an ice bath, and a solution of 2.16 g (21.6 mmol) of hexanal (Note 1) in dry dichloromethane (10 mL) is added via syringe over 45 min. The reaction mixture is stirred at 0°C for another 6 hr. The yellow solution is poured slowly into a beaker containing ice-cold aqueous 5% sodium bicarbonate solution (200 mL) and vigorous stirring is continued at room temperature until gas evolution subsides. The mixture is transferred to a 1-L separatory funnel and is extracted with diethyl ether (3 × 200 mL) (Note 7). The combined extracts are washed with a saturated aqueous sodium chloride solution (300 mL) and dried over sodium sulfate. The cloudy solution is filtered through a pad of Florisil (Note 8) loaded on a sintered glass funnel (`M' frit). The clear filtrate solution is concentrated by rotary evaporator. The residue is layered on a column of silica gel (150 g, column diameter: 6.0 cm) and eluted (ethyl acetate/hexane, 1:30 to 1:15 as eluents) to give 4.90 g (66%) of 1-[(tert-butyldiphenyl-silyl)oxy]-dec-3-en-5-ol as a colorless oil (Note 9).

Figure 1

Figure 1

2. Notes

1. 3-Butyn-1-ol, dimethylzinc and hexanal were obtained from Aldrich Chemical Company, Inc., and used without purification.
2. Solvent grade dichloromethane was dried over calcium hydride, refluxed and distilled freshly before use.
3. tert-Butyldiphenylchlorosilane was obtained from United Chemical Technologies, Inc. or Aldrich Chemical Company, Inc., and used without purification.
4. The product has the following spectral properties: ^{1}H NMR (300 MHz,

$CDCl_3$) δ: 1.06 (s, 9 H), 1.95 (t, 1 H, J = 2.6), 2.45 (dt, 2 H, J = 7.1, 2.7), 3.79 (t, 2 H, J = 7.1), 7.36–7.46 (m, 6 H), 7.67–7.70 (m, 4 H).

5. Zirconocene hydrochloride was prepared according to Buchwald's procedure[2] and stored in a Schlenk filter flask under argon in a freezer at −20°C or obtained from Aldrich Chemical Company, Inc., and used without further purification.

6. The reaction is conveniently monitored by TLC (silica gel, 4:1 hexane-ethyl acetate) with anisaldehyde stain (alkyne stains as a red spot, while the hydrozirconation product shows a blue color).

7. Significant amounts of white foam form between the ether and aqueous layers during extraction. Separation of these layers can be improved by the addition of 1–2 spoonfuls of solid sodium chloride.

8. Florisil (100–200 mesh) was obtained from Fisher Scientific Company.

9. The product has the following spectral data: IR (neat) cm^{-1}: 3350, 2912, 1454, 1417, 1099, 733, 698, 609; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.88 (t, 3 H, J = 6.7), 1.05 (s, 9 H), 1.34–1.51 (m, 9 H), 2.26–2.33 (m, 2 H), 3.71 (t, 2 H, J = 6.6), 4.00–4.03 (m, 1 H), 5.49 (dd, 1 H, J = 15.5, 6.8), 5.64 (dt, 1 H, J = 15.5, 6.7), 7.35–7.46 (m, 6 H), 7.66–7.69 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ: 14.1, 19.2, 22.6, 25.2, 26.9, 31.8, 35.6, 37.2, 63.6, 73.1, 127.7, 128.2, 129.6, 133.9, 135.2, 135.6; MS (EI) m/e (relative intensity) 353 ([M-tert-butyl]+, 4), 335 (20), 229 (25), 199 (100), 135 (20), 91 (15), 57 (10); HRMS (EI) m/e calcd. for $C_{22}H_{29}O_2Si$ ($M-C_4H_9$): 353.1937, found: 353.1833.

Waste Disposal Information

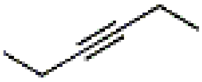
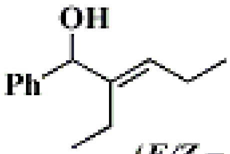
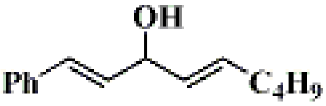
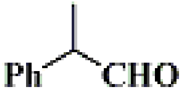
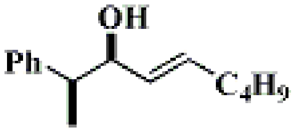
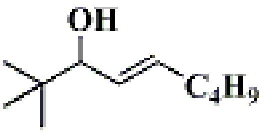
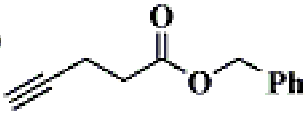
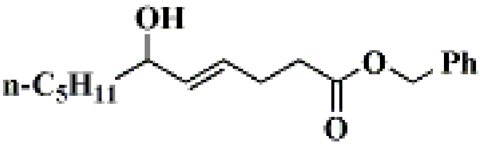
All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Organometallic derivatives of zirconium(IV) are readily obtained by hydrozirconation of alkenes and alkynes with Cp_2ZrHCl (Schwartz reagent). Because of the relatively low reactivity of the resulting organozirconocenes, transmetalation protocols are frequently applied for further carbon-carbon formation.[3,4] Transmetalation of alkenylzirconocenes to the corresponding organozinc compounds occurs rapidly at low temperature in the presence of stoichiometric amounts of commercially available dimethyl- or diethylzinc. Subsequent addition of aldehydes provides an in situ protocol for the conversion of alkynes into allylic alcohols in good to excellent yields.[5] Compared to standard organometallic methods applying lithium or Grignard reagents for this transformation, the use zirconocenes tolerates the presence of a wide range of functional groups in the substrate (Table). The zirconium □ zinc transmetalation is related in scope to the boron □ zinc transmetalation, which can also be applied for the conversion of alkynes to allylic alcohols.[6,7]

TABLE I

REACTION OF *IN SITU* GENERATED ALKENYLALKYLZINC REAGENTS WITH ALDEHYDES

Aldehyde	Alkyne	Time (h)	Product	yield (%)
PhCHO		1		93
PhCHO		2		89
PhCHO		5	 (*E/Z* = 2.5:1)	78
		1.5		94
		1.5	 (*syn:anti* = 85:15)	92
		2		54
		2		72#

On 5 g scale, this product was isolated in 68% yield.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

zirconocene hydrochloride

dimethyl- or diethylzinc

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

ether, diethyl ether (60-29-7)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

PhCHO (100-52-7)

toluene (108-88-3)

zinc (7440-66-6)

dichloromethane (75-09-2)

lithium (7439-93-2)

magnesium sulfate (7487-88-9)

Imidazole (288-32-4)

hexane (110-54-3)

zirconium

carbon-carbon

calcium hydride (7789-78-8)

argon (7440-37-1)

3-butyn-1-ol (927-74-2)

Hexanal (66-25-1)

4-dimethylaminopyridine (1122-58-3)

tert-butyldiphenylchlorosilane (58479-61-1)

1-[(tert-Butyldiphenylsilyloxy)]-dec-3-en-5-ol, 1-[(tert-butyldiphenyl-silyl)oxy]-dec-3-en-5-ol, 1-[(tert-BUTYLDIPHENYLSILYL)OXY]-DEC-3-EN-5-OL (190072-44-7)

tert-Butyl(but-3-ynyloxy)diphenylsilane

dimethylzinc (544-97-8)

zirconium(IV)

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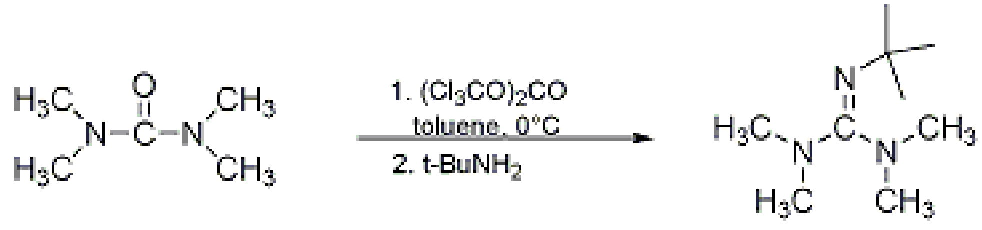
Organic Syntheses, CV 9, 147

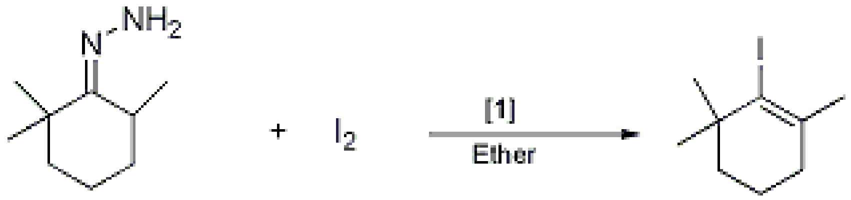
PREPARATION AND REACTIONS OF 2-tert-BUTYL-1,1,3,3-TETRAMETHYLGUANIDINE: 2,2,6-TRIMETHYLCYCLOHEXEN-1-YL IODIDE

A.



1

B.



2

Submitted by Derek H. R. Barton, Mi Chen, Joseph Cs. Jászberényi, and Dennis K. Taylor[1].
Checked by Richard A. Hartz and Amos B. Smith, III.

1. Procedure

CAUTION! These reactions, which involve toxic reagents, must be carried out (including workup) in an efficient fume hood.

A. *2-tert-Butyl-1,1,3,3-tetramethylguanidine* **(1)**. To an oven-dried, 500-mL, three-necked, round-bottomed flask, equipped with a nitrogen inlet with gas bubbler, magnetic stirring bar, thermometer, condenser, and a 250-mL dropping funnel, are added triphosgene (14.8 g, 0.05 mol) (Note 1), and anhydrous toluene (120 mL) (Note 2). The mixture is kept under argon and cooled to ≈10°C with the aid of an external ice bath. A solution of N,N,N',N'-tetramethylurea (18.0 mL, 0.15 mol) (Note 3) in dry toluene (50 mL) is slowly added to the mixture over 30 min (Note 4). After the addition is complete, the mixture is allowed to warm to ambient temperature, and stirring of the mixture is continued for an additional hour. During this time a white precipitate forms (Note 5). tert-Butylamine (47.3 mL, 0.45 mol) (Note 6) is slowly added to the mixture over 30 min (Note 7). After the addition is complete, the mixture is heated under reflux for 5 hr and then cooled to room temperature. Anhydrous ether (200 mL) (Note 8) is added and the white precipitate is quickly removed by filtration

(Note 9). The precipitate is washed with a further quantity of anhydrous ether (300 mL) (Note 10) and immediately dissolved in aqueous 25% sodium hydroxide solution (100 mL). The mixture is then extracted with three portions of ether (300 mL). The combined organic layers are dried (potassium carbonate), filtered, and the solvent is removed under reduced pressure. The resulting colorless liquid is purified by distillation (bp 88–89°C/36 mm) to afford 18.7 g (73%) of 2-tert-butyl-1,1,3,3-tetramethylguanidine **1** (Note 11).

B. *2,2,6-Trimethylcyclohexen-1-yl iodide* **(2)**. To an oven-dried, 500-mL, three-necked, round-bottomed flask, equipped with a nitrogen inlet with gas bubbler, magnetic stirring bar, and a 250-mL dropping funnel, are added 2,2,6-trimethylcyclohexanone hydrazone (4.6 g, 0.03 mol) (Note 12), anhydrous ether (100 mL) (Note 8), and 2-tert-butyl-1,1,3,3-tetramethylguanidine **(1)** (46.25 g, 0.27 mol). The mixture is kept under argon at ambient temperature and an ethereal solution (100 mL) of iodine (15.25 g, 0.06 mol) is added to the mixture over 40 min with vigorous stirring. (Note 13). After the addition is complete, stirring is continued for an additional 30 min. The ether is removed under reduced pressure (Note 14) and the residue is heated at 90°C for 30 min (Note 15) under an inert atmosphere. The reaction mixture is allowed to attain ambient temperature. Ether (100 mL) is added and the organic phase is washed twice with 2 N hydrochloric acid (30 mL), aqueous sodium thiosulfate solution (30 mL), aqueous sodium bicarbonate solution (30 mL) and saturated sodium chloride solution (30 mL). The organic phase is dried (sodium sulfate) and the solvent is removed under reduced pressure to afford crude iodide **(2)**. Purification of **2** can be achieved by flash chromatography (Note 16) affording pure iodide **(2)** (6.34 g, 85%) as a colorless oil. (Note 17).

2. Notes

1. Triphosgene was purchased from the Aldrich Chemical Company, Inc., and used as received.
2. Toluene is distilled from calcium hydride (CaH_2) under argon just prior to use.
3. N,N,N',N'-Tetramethylurea was purchased from the Aldrich Chemical Company, Inc., and purified by distillation prior to use.
4. Although no major temperature increase is observed, the reaction proceeds best with slow addition.
5. This salt is the corresponding Vilsmeier salt. See reference [2].
6. tert-Butylamine was purchased from the Aldrich Chemical Company, Inc., and dried prior to use by distillation from CaH_2 under argon.
7. No major temperature increase is observed.
8. Diethyl ether is distilled from sodium under argon just prior to use.
9. The white precipitate should be collected as quickly as possible to avoid hydrolysis to the starting urea. The precipitate turns pale yellow if hydrolysis is occurring. Additional ether (300 mL) may be needed to ensure complete transfer of the solids to the filtration apparatus.

10. The filtrate must be colorless, indicating that all impurities have been removed.
11. Distillation is not neccessary if the solids are washed correctly. Spectral data for **1** are as follows: IR (neat) cm^{-1}: 1620; ^{1}H NMR ($CDCl_3$) δ: 1.22 (s, 9 H), 2.67 (s, 12 H). **1** should be stored under argon in the refrigerator to prevent hydrolysis. The purity is estimated to be ≈95% by NMR and TLC analysis. The impurity is the starting urea and could not be avoided.
12. The hydrazone of 2,2,6-trimethylcyclohexanone is prepared according to a procedure outlined in reference [3]. To a solution of absolute ethanol (37 mL), hydrazine (26.0 g, 25.40 mL), and triethylamine (6.8 g, 9.43 mL) is added 2,2,6-trimethylcyclohexanone (6.3 g, 7.0 mL). The mixture is heated to 100°C for 2–3 days, cooled to ambient temperature, and the solvent removed under reduced pressure. Recrystallization of the residue from hexanes affords the hydrazone as white needles (4.85 g, 70%, mp 48–49°C). The spectra are as follows: ^{1}H NMR ($CDCl_3$) δ: 1.0–1.2 (m, 9 H), 1.40–1.92 (m, 6 H), 2.95 (m, 1 H), 4.51 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ: 17.18, 17.39, 26.51, 28.92, 29.48, 31.68, 37.61, 40.43, 162.47.
13. Vigorous stirring is required as large quantities of precipitate form during the addition.
14. The nitrogen inlet is removed and replaced with a line to a water pump.
15. Heating causes most of the solids to liquify. The temperature refers to the outside oil bath temperature.
16. Flash chromatography was performed on standard Silica Gel 60Å, (230–400 mesh) with hexane, $R_f = 0.75$.
17. Spectral data for **2** are as follows: ^{1}H NMR ($CDCl_3$) δ: 1.09 (s, 6 H), 1.53–1.72 (m, 4 H), 1.87 (s, 3 H), 2.12 (t, 2 H); ^{13}C NMR ($CDCl_3$) d: 19.40, 31.08, 31.56, 33.69, 37.86, 39.51, 117.36, 137.70. Compound **2** deteriorates rapidly at ambient temperature, but is stable for several weeks if stored under argon in the refrigerator. The purity is estimated to be >98% by NMR and TLC analysis. No microanalytical data was obtained because of the instability of **2**.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

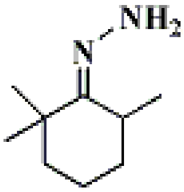
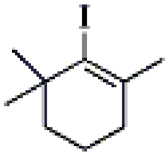
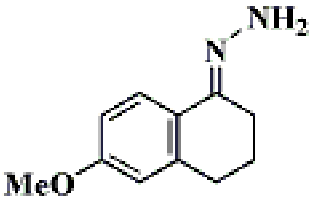
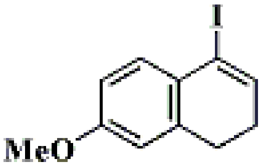
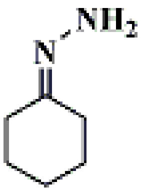
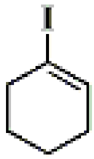
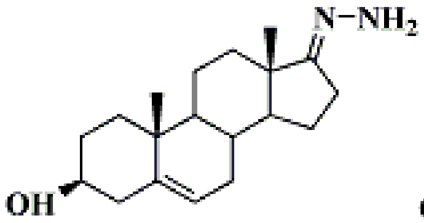
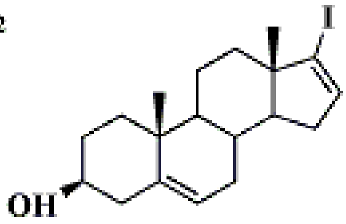
The procedure described here allows the convenient preparation of large quantities of the strong, non-nucleophilic base 2-tert-butyl-1,1,3,3-tetramethyl-guanidine **(1)**. This reagent provides an inexpensive alternative to the amidine bases, 1,5-diazabicyclo [4.3.0]non-5-ene (DBN) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), which suffer from being easily alkylated.[4] Additionally, the hazards of using phosgene in the previous preparations of **1**[2,4,5] have been greatly reduced by employing triphosgene as

a phosgene equivalent.[6]

The synthetic utility of this base **(1)** was demonstrated in the preparation of vinyl iodides in high yields from simple ketohydrazones and iodine (Table), a process that normally gives mixtures of vinyl iodides and geminal diiodides if less hindered bases are employed.[5] This base has also been used in the elimination of sulfonic acids from the corresponding sulfonates, the alkylation of compounds containing active methylene groups, the conversion of hydrazones to vinyl selenides, and the preparation of esters from sterically hindered acids.[4,5]

TABLE

PREPARATION OF VINYL IODIDES FROM HYDRAZONES

Entry	Hydrazone	Vinyl Iodide	% Yield
1			73
2			70
3			91
4			95

Other inexpensive, sterically hindered guanidine bases have also been synthesized and their reactivity is comparable to that described here.[2,4]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrazone of 2,2,6-trimethylcyclohexanone

ethanol (64-17-5)

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

ether, diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

sodium thiosulfate (7772-98-7)

iodine (7553-56-2)

toluene (108-88-3)

sodium (13966-32-0)

phosgene (75-44-5)

hydrazine (302-01-2)

guanidine (113-00-8)

hexane (110-54-3)

triethylamine (121-44-8)

calcium hydride (7789-78-8)

argon (7440-37-1)

2-tert-Butyl-1,1,3,3-tetramethylguanidine, 2-tert-butyl-1,1,3,3-tetramethyl-guanidine (34331-58-3)

2,2,6-TRIMETHYLCYCLOHEXEN-1-YL IODIDE (189633-81-6)

triphosgene (32315-10-9)

N,N,N',N'-tetramethylurea (632-22-4)

tert-Butylamine (75-64-9)

2,2,6-trimethylcyclohexanone hydrazone (189633-82-7)

2,2,6-trimethylcyclohexanone (2408-37-9)

1,5-diazabicyclo[4.3.0]non-5-ene

1,8-diazabicyclo[5.4.0]undec-7-ene (6674-22-2)

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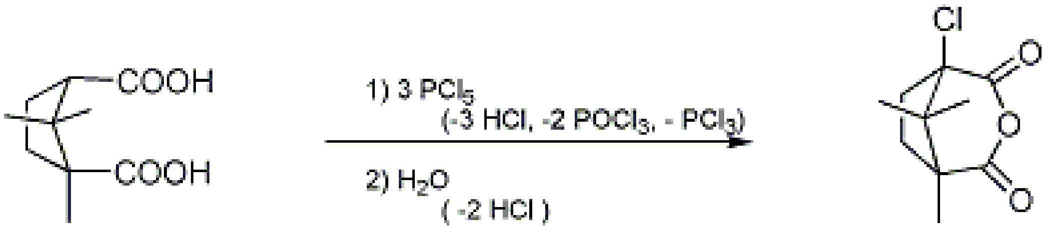
(–)-(1S,4R)-CAMPHANOYL CHLORIDE

[2-Oxabicyclo[2.2.1]heptane-1-carbonyl chloride, 4,7,7-trimethyl-3-oxo-, (1S)-)]

A.



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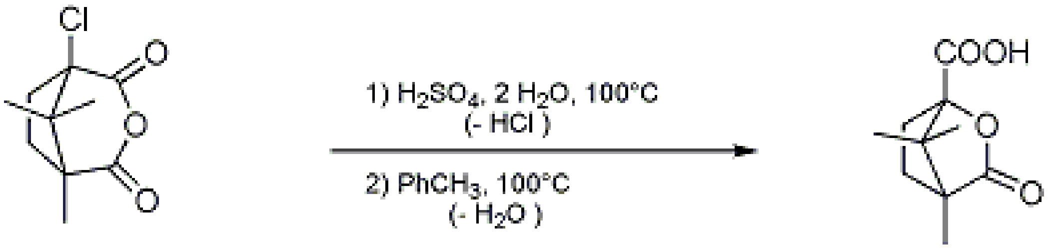
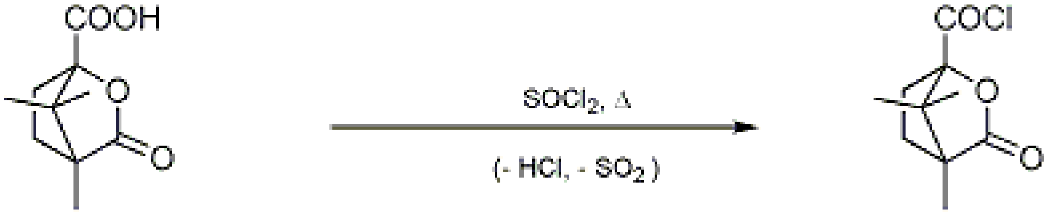


C.



Submitted by Hans Gerlach[1], Dag Kappes, Robert K. Boeckman, Jr.[2], and Graham N. Maw.
Checked by D. Zhao, D. Hughes, and I. Shinkai.

1. Procedure

A. *(–)-(1R,3R)-3-Chlorocamphoric anhydride.* (+)-(1R,3S)-Camphoric acid (Note 1), (125 g, 0.625 mol) is added in small portions to a 1000-mL, three-necked flask charged with 455 g of phosphorus pentachloride (2.19 mol) and equipped with a ground glass adaptor connected to a T-tube with one outlet open to the atmosphere and the remaining outlet connected to a gas trap (Note 2). The mildly exothermic reaction is controlled by gently swirling the flask in an ice bath as required (Note 3). After the addition is complete, the flask is equipped with a reflux condenser topped by a calcium chloride ($CaCl_2$) drying tube, and the reaction mixture is heated under reflux (using an oil bath at 125°C) for 12 hr. The reaction mixture is cooled to room temperature and the volatile material is removed by distillation using a bath temperature of 50°C under

aspirator vacuum with the distillate boiling at 30–35°C (Note 4). The residual liquid is then added to a mechanically-stirred mixture of ice (2 kg) and dimethylformamide (DMF, 125 ml), and stirring is continued until all the ice has melted. The resulting waxy white precipitate is collected by vacuum filtration while cold (2°C), washed with three, 500-mL portions of cold water, and dried under vacuum (Note 5). The crude white solid, (–)-(1R,3R)-3-chlorocamphoric anhydride (122 g, 90%), is of sufficient purity to be used in the next step (Note 6) and (Note 7).

B. *(–)-(1S,4R)-Camphanic acid.* A 2000-mL, three-necked round-bottomed flask equipped with a magnetic stirrer and reflux condenser is charged with 1000-mL of 0.1 N sulfuric acid and heated by means of an oil bath to 80°C. Finely powdered (–)-(1R,3R)-3-chlorocamphoric anhydride (115 g, 0.53 mol) is added in portions over about 10 min to the stirred acid solution, the necks are sealed with glass stoppers and the resulting suspension is brought to a gentle reflux (Note 2). After all the solids have dissolved (4–6 hr), the resulting solution is refluxed for an additional 2 hr (Note 8). The solution is allowed to cool to room temperature with stirring overnight (12 hr), and the resulting off-while solid is collected by vacuum filtration and washed with water (3 × 250 mL). The remaining camphanic acid is obtained by extraction of the aqueous filtrate with three 250-mL portions of chloroform (Note 9). After evaporation of the combined organic phases, the combined vacuum-dried solids are added to a 1000-mL, round-bottomed flask containing 500 mL of toluene, a condenser is added and the mixture is brought to gentle reflux until dissolution is complete (Note 2). The water/toluene azeotrope (85°C) is removed by distillation until no further water is obtained (Note 10). Distillation of the toluene (110°C) is then continued until the residual volume has been reduced to 350 mL (Note 10) and (Note 11). The resulting solution is allowed to cool to room temperature during which time the acid crystallizes. After 4 hr at room temperature, the solids are collected by vacuum filtration and air-dried, affording (–)-(1S,4R)-camphanic acid (76 g, 72%) as colorless needles, mp 197–201°C, of sufficient purity for use in the next step (Note 12) and (Note 13).

C. *(–)-(1S,4R)-Camphanoyl chloride*. A 500-mL, three-necked, round-bottomed flask, equipped for magnetic stirring and protected from moisture by a reflux condenser topped by a $CaCl_2$ drying tube, is charged with 200 mL of thionyl chloride using a graduated cylinder. (–)-(1S,4R)-Camphanic acid (63.8 g, 0.322 mol) is added in portions using a powder funnel over 30 min, and the reaction mixture is heated under reflux for 3 hr, then allowed to cool to room temperature (Note 2). Excess thionyl chloride is removed by rotary evaporation (Note 14) to afford a solid that is freed of any residual thionyl chloride by the addition of toluene (500 mL) and subsequent evaporation under reduced pressure (repeated three times). The resulting solids are dried under high vacuum (Note 5) to afford 69 g of (–)-(1S,4R)-camphanoyl chloride (99%) as an off-white solid, mp 69–71°C (Note 15) and (Note 16).

2. Notes

1. (+)-(1R,3S)-Camphoric acid (99% purity) was obtained from Aldrich Chemical Company, Inc.
2. The acidic gases may be absorbed in 10% NaOH solution using the absorption trap as described in *Org. Synth., Coll. Vol. I* **1941**, 97.
3. The reactants initially form a paste that may form sizable lumps upon agitation, but the mixture liquifies upon further reaction as the result of the production of phosphorus oxychloride ($POCl_3$) and phosphorus trichloride (PCl_3).
4. The resulting liquid sometimes contains small amounts of white solid, but this solid does not require removal by filtration.
5. A freeze dryer (lyophilizer) was employed for vacuum drying (23°C at 0.05 mm).
6. If desired, a pure sample of the anhydride (mp 225–229°C) can be obtained by recrystallization of the crude anhydride from carbon tetrachloride (CCl_4) (1 g/5 mL).
7. Spectroscopic data for the purified anhydride are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.07 (s, 3 H), 1.14 (s, 3 H), 1.36 (s, 3 H), 2.11 (m, 2 H), 2.50 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 16.0, 17.9, 18.7, 31.5, 35.2, 48.7, 54.1, 166.0, 170.3; IR (cm^{-1}): 3019, 1821, 1773, 1215; $[\alpha]_D^{25}$ –17.6° (chloroform, *c* 2.04).
8. A total period of heating of 6–8 hr at 80–100°C was required.
9. Alternatively, a second crop of material can be obtained from the aqueous filtrate after several hours. However, a considerable amount of camphanic acid still remains in the aqueous layer; thus chloroform extraction of the aqueous phase as described is recommended. *To avoid undue exposure to the chloroform vapor, these extractions should be performed in a fume hood*.
10. The volume of toluene required will depend on the amount of water in the crude material. Additional toluene should be added as required, so that the final, residual volume of dry toluene solution is 350 mL as described.
11. Colored impurities, if produced, can be removed by treatment of the solution, prior to cooling, with charcoal (Norit) followed by filtration.
12. If desired, pure acid (mp 201–204°C) can be obtained by recrystallization of the crude acid from hot toluene.
13. Spectroscopic data for the purified acid are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.03 (s, 3 H), 1.11 (s, 3 H), 1.15 (s, 3 H), 1.74 (ddd, 1 H, J = 4.3, 9.3, and 13.2), 1.98 (ddd, 1 H, J = 4.5, 10.6, and 13.2), 2.11 (ddd, 1 H, J = 4.5, 9.3, and 13.5), 2.48 (ddd, 1 H, J = 4.2, 10.6, and 13.5), 8.80 (br, 1 H, (s)); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 9.60, 16.70, 16.73, 29.02, 30.73, 54.60, 55.11, 90.89, 172.41, 177.90; (IR cm^{-1}):3418, 3019, 1785, 1716, 1215; $[\alpha]_D^{25}$ –20.4° (dioxane, *c* 1.71).
14. Corrosive thionyl chloride may destroy the rubber vacuum seals of a rotary evaporator. Thionyl chloride can also be removed by vacuum distillation.
15. (–)-(1S,4R)-Camphanoyl chloride produced in this manner is of sufficient

purity to be used directly in most acylation reactions. However, pure acid chloride (mp 69–71°C) can be conveniently obtained by recrystallization of the crude acid chloride from cold CCl_4 (1 g/1 mL, 75% recovery).

16. Spectroscopic data for the purified acid chloride are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.06 (s, 3 H), 1.12 (s, 3 H), 1.15 (s, 3 H), 1.76 (ddd, 1 H, J = 4.2, 9.3, and 13.3), 1.99 (ddd, 1 H, J = 4.6, 10.6, and 13.3), 2.18 (ddd, 1 H, J = 4.6, 9.3, and 13.6), 2.52 (ddd, 1 H, J = 4.2, 10.6, and 13.6); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 9.55, 16.55, 16.64, 28.76, 31.46, 55.40, 55.52, 94.86, 170.87, 176.52; IR (cm^{-1}): 2975, 1794, 1231; $[\alpha]_D^{25}$ −24.7° (chloroform, *c* 3.57).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995. (See (Note 2).)

3. Discussion

The resolution of alcohols by fractional crystallization or chromatography of diastereoisomeric esters with (–)-camphanic acid was introduced some time ago.[3] The method has proven to be both convenient and efficient. A substructure search in the Chemical Abstracts Service (CAS) registry file has shown that more than 500 camphanic acid derivatives have been described in the last two decades. Besides resolution, camphanic acid esters of primary alcohols have been used to distinguish the signals of diastereotopic α-hydrogen atoms in ^{1}H NMR spectra and to determine the optical purity of α-deutero primary alcohols.[4] Camphanoates are well suited for characterizing alcohols. They are easily prepared with camphanoyl chloride in pyridine and generally have high melting points.

Because both enantiomers, (+)- and (–)-camphoric acid, are available by oxidation either from natural (+)-D-camphor or from natural (–)-L-borneol, both enantiomers of camphanoyl chloride can be prepared conveniently.[3,5] The corresponding enantiomers of camphanic acid were described for the first time by Wreden[6] and Aschan.[7] The three-step procedure, described above is an adaptation of procedures described by Aschan,[8] Zelinsky et al.,[9] Meyer et al.,[10] and Gerlach.[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 275

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1. Laboratorium für Organische Chemie, Universität Bayreuth, Postfach 10 12 51, D-8580 Bayreuth, West Germany.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

(–)-(1S,4R)-CAMPHANOYL CHLORIDE

2-Oxabicyclo[2.2.1]heptane-1-carbonyl chloride, 4,7,7-trimethyl-3-oxo-, (1S)-)

(–)-(1R,3R)-3-Chlorocamphoric anhydride

(–)-(1S,4R)-Camphanic acid

(–)-camphanic acid

(+)- and (–)-camphoric acid

(–)-L-borneol

sulfuric acid (7664-93-9)

phosphorus pentachloride (10026-13-8)

thionyl chloride (7719-09-7)

chloroform (67-66-3)

carbon tetrachloride (56-23-5)

Phosphorus Oxychloride (21295-50-1)

pyridine (110-86-1)

toluene (108-88-3)

phosphorus trichloride (7719-12-2)

dioxane (5703-46-8)

(+)-D-camphor (21368-68-3)

dimethylformamide (68-12-2)

(+)-(1R,3S)-Camphoric acid

camphanic acid

camphanoyl chloride

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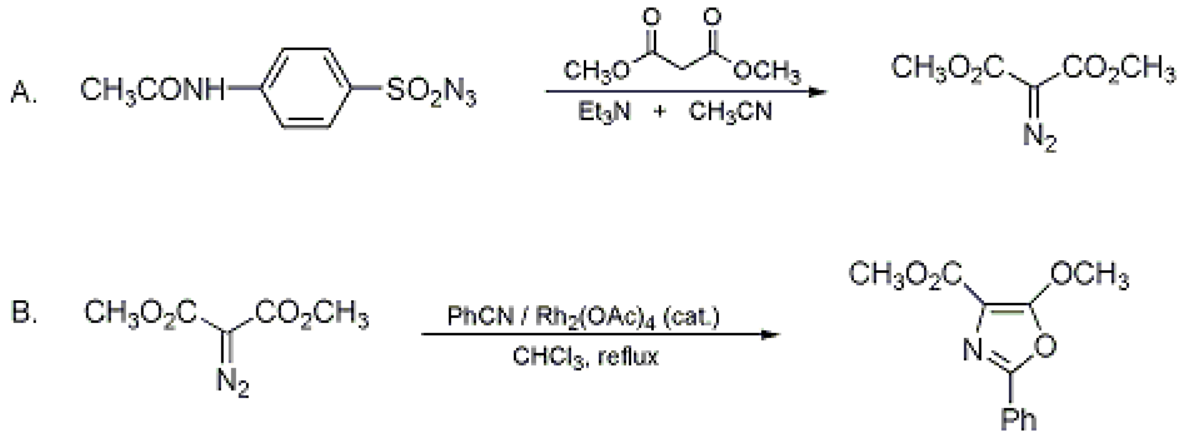
RHODIUM-CATALYZED HETEROCYCLOADDITION OF A DIAZOMALONATE AND A NITRILE: 4-CARBOMETHOXY-5-METHOXY-2-PHENYL-1,3-OXAZOLE

[4-Oxazolecarboxylic acid, 5-methoxy-2-phenyl-, methyl ester]



Submitted by Joshua S. Tullis and Paul Helquist[1].
Checked by Anne K. Courtney and Stephen F. Martin.

1. Procedure

CAUTION! This experiment should be conducted behind an auxiliary safety shield in a closed fume hood because of the explosive nature of diazo and azide compounds.

A. *Dimethyl diazomalonate*. Into a 500-mL, round-bottomed flask is placed a large magnetic stirring bar (Note 1), 4-acetamidobenzenesulfonyl azide (72.3 mmol, 17.36 g, (Note 2)), acetonitrile (250 mL, (Note 3)), and triethylamine (76.5 mmol, 7.74 g, (Note 4)). The reaction mixture is cooled to 0°C, and dimethyl malonate (72.0 mmol, 9.51 g, (Note 4)) is slowly added over 3–5 min by a syringe. The reaction mixture is kept at 0°C for 10 min then stirred at room temperature for 17 hr. A thick white precipitate that forms during the reaction is removed by filtration through a Büchner filter. The filter cake is washed with a 1:1 mixture of petroleum ether and ethyl ether (200 mL, (Note 5)). The resulting filtrates are concentrated by rotary evaporation under reduced pressure giving a yellow oil with some visible precipitate of sulfonamide. Repeated trituration and filtration of this oil with 1:1 petroleum ether and ethyl ether (6 × 50 mL, (Note 5)) to remove the solid 4-acetamidobenzenesulfonamide, followed by concentration of all filtrates by rotary evaporation under reduced pressure, gives 10.92 g of the crude diazo product as a yellow oil (96%). The crude product is purified by distillation to provide 8.26 g (73%) of dimethyl diazomalonate as a bright yellow oil (Note 6).

B. *4-Carbomethoxy-5-methoxy-2-phenyl-1,3-oxazole*. In an oven-dried, 100-mL, round-bottomed flask is placed a small magnetic stirring bar (Note 7), rhodium(II) acetate dimer, $Rh_2(OAc)_4$, (0.230 mmol, 0.102 g, (Note 4)), benzonitrile (19.5 mmol, 2.011 g, (Note 8)), and

chloroform ($CHCl_3$, 5 mL, (Note 9)). The flask is placed in an oil bath and fitted with a 30-cm reflux condenser. On top of the condenser is placed a three-way stopcock having horizontal and vertical tubulations. A source of nitrogen (N_2) is connected to the system via the horizontal tubulation of the stopcock, and a septum is placed over the vertical tubulation. The entire system is flushed several times with N_2, and the solution is heated to reflux (68°C) during which time it becomes deep purple.

Into a dry, 50-mL, conical vial is placed dimethyl diazomalonate (29.4 mmol, 4.65 g) and 25 mL of chloroform (Note 9). The solution is taken up into a syringe (Note 10) fitted with a 30-cm needle. The needle is inserted about half way into the septum on the stopcock so that the needle tip extends down into the condenser. The syringe is placed on a syringe pump (Note 11) which is set to add the solution at a rate of 1.17 mL/hr over a period of about 25 hr. After the addition is complete, the syringe is again filled with 2 mL of $CHCl_3$, which is added to the system via the septum. The needle is removed, and the stopcock plug is rotated so that the septum is closed off from the system while the N_2 inlet remains open. The solution is allowed to continue stirring at reflux for another 20 hr. It is then concentrated by rotary evaporation under reduced pressure to yield a brownish-purple oil containing crude product. The crude oxazole is purified using flash column chromatography (silica gel, 40% ethyl acetate in hexane, (Note 12), (Note 13), (Note 14)) to yield 2.73–2.96 g (60–65%) of 4-carbomethoxy-5-methoxy-2-phenyl-1,3-oxazole as white needles (Note 15).

2. Notes

1. An egg-shaped stirring bar ca. 2.5 cm in length is recommended for stirring the suspension that is produced during the reaction.
2. 4-Acetamidobenzenesulfonyl azide is obtained from Aldrich Chemical Company, Inc., and used without further purification. In addition, 4-acetamidobenzenesulfonyl azide can be synthesized from the precursor, 4-acetamidobenzenesulfonyl chloride.[2]
3. The checkers used standard reagent grade acetonitrile from EM Science.
4. Triethylamine, dimethyl malonate, and rhodium(II) acetate dimer were purchased from Aldrich Chemical Company, Inc., and used without further purification.
5. Standard reagent grade ether and petroleum ether are used during workups.
6. Crude dimethyl diazomalonate is distilled under reduced pressure using a vacuum pump and a short-path distillation apparatus equipped with a Vigreux fractionating column measuring 8–10 cm. The apparatus is wrapped in glass wool and aluminum foil to minimize heat loss. Pure dimethyl diazomalonate[3 4 5] is a bright yellow oil: bp 60°C, ca. 0.65 mm (lit.[5] bp 45°C, 0.2 mm); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.79 (s, 6 H, $COOCH_3$; lit.[5] δ 3.76); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 52.4, 65.6, 161.3; IR (neat) cm^{-1}: 3006 (m), 2958 (s), 2849 (w), 2138 (s), 1760 (s), 1738 (s), and 1696 (s); (lit.[3,4,5] IR).
7. The specific size of the stirring bar is not important, but the stirring rate should be adjusted so that the $Rh_2(OAc)_4$ catalyst remains suspended in solution. It should not be resting on the bottom of the round-bottomed flask, nor should it be splashed onto the sides of the flask.
8. Benzonitrile is available from Aldrich Chemical Company, Inc. and is distilled at reduced pressure (0.5 mm, 75°C) using a short-path distillation apparatus.
9. Spectroscopic grade chloroform is obtained from J. T. Baker, Inc., (99+% purity) and used without further purification.

10. The syringe used is a 50-mL, gas-tight syringe (Model #1050) available from Hamilton Company. It is very important that a gas-tight syringe be used during the addition because of the tendency of chloroform to leak with loss of starting material from other types of syringes.
11. The syringe pump used is available from Sage Instruments, Model Number 341B. *NOTE*: The slow addition of the dimethyl diazomalonate is of key importance to the success of the reaction. When scaling this reaction up or down, the rate of addition should be altered so that the addition time remains constant at ca. 25 hr. For example, in the reaction described here, there is ca. 30 mL of solution containing dimethyl diazomalonate, and it is added over 25 hr at a rate of 1.17 mL/hr. If the reaction were at 20% scale, the rate of addition would be 0.23 mL/hr.
12. On one occasion, crude product was a solid and was dissolved in a minimum amount of eluent and added to the top of the silica column.
13. To purify the product on this scale, a 35-mm wide column with a 500-mL glass bulb on top and a glass frit at the base is used. It is packed with 25–30 cm silica gel 60 (230–400 mesh, available from EM Science) and eluted with solvent to remove any air bubbles. The purification is monitored by TLC (silica gel, 40% ethyl acetate in hexanes; $R_f = 0.35$).
14. Usually, the purification leads to several fractions containing a mixture of the product and the starting material, dimethyl diazomalonate, ($R_f = 0.43$). In this event, an alternative to performing another column chromatography has been developed based on trituration according to the following procedure. All fractions that contain the mixture are combined in a round-bottomed flask, and the solvent is removed by rotary evaporation under reduced pressure. The mixture should appear to be a yellow oil mixed with the crystalline oxazole. With an ice bath, the mixture is cooled along with a separate flask containing 10–15 mL ether. Using a pipette, 2–3 mL of the cold ether is transferred to the mixture. The mixture is swirled, and the solvent is removed with a pipette. This procedure is repeated several times until only white crystals remain. It is important to keep both flasks cool throughout the procedure so that loss of the product is minimized.
15. The product, 4-carbomethoxy-5-methoxy-2-phenyl-1,3-oxazole, is obtained as colorless needles: mp 92–95°C (lit.[6] mp 98–99°C); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.86 (s, 3 H, $COOCH_3$), 4.20 (s, 3 H, $C{=}COCH_3$), 7.36–7.39 (m, 3 H, Ar-H), 7.89–7.93 (m, 2 H, Ar-H); ^{13}C NMR[6] (125 MHz, $CDCl_3$) δ: 51.7 ($COOCH_3$), 59.7 ($C{=}COCH_3$), 107.4 (C-4), 125.8 (C-3', C-5'), 126.2 (C-1'), 128.6 (C-2', C-6'), 130.3 (C-4'), 150.8 (C-5), 161.7, 161.8 ($COOCH_3$, C-2); IR ($CDCl_3$) cm^{-1}: 1713 ($COOCH_3$), 1619 ($C{=}COCH_3$); mass spectrum[6] (Cl, argon) m/e (rel intensity) 233 (M^+, 27), 173 (11), 146 (15), 105 (100), 77 (24). Anal Calcd for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.75. Found: C, 61.53; H, 4.75.

Waste Disposal Information

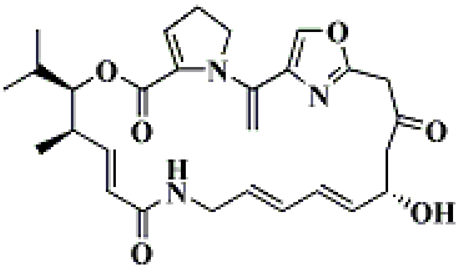
All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

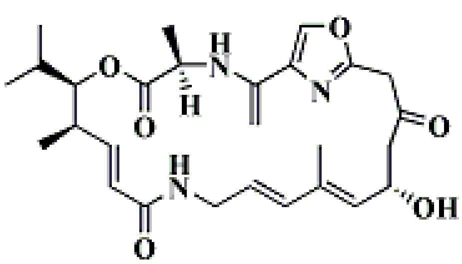
Oxazoles are well-investigated compounds. The occurrence, uses, and synthesis of oxazole derivatives have been the subjects of extensive reviews.[7 8 9 10] The heterocyclic oxazole unit

is seen with various substitution patterns in a large number of naturally occurring compounds. Furthermore, oxazoles serve as synthetic intermediates leading to many other systems.[7,8,9,10,11,12,13,14,15,16,17] In this context, oxazoles have seen, for example, numerous applications as "2-azadiene" components in 4+2 cycloadditions with several types of dienophiles. Further transformations of the products then lead to a number of other nitrogen- or oxygen-containing heterocyclic products.[11,12]

Of the many specific types of oxazoles, those bearing a 4-carboxy-derived group are of considerable importance. Among these compounds are several natural products, including many which contain this moiety, or the analogous thiazole group. Two examples, from the type A streptogramin family, include virginiamycin M_1 and madumycin I.[18,19,20,21,22,23,24,25,26]

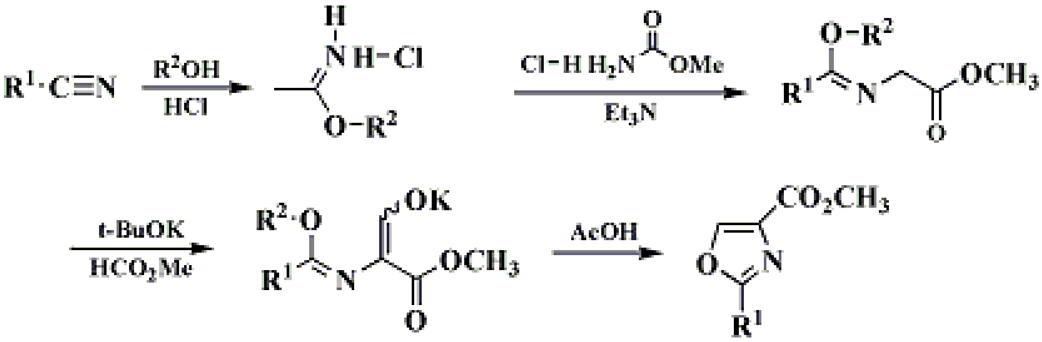


Virginiamycin M_1



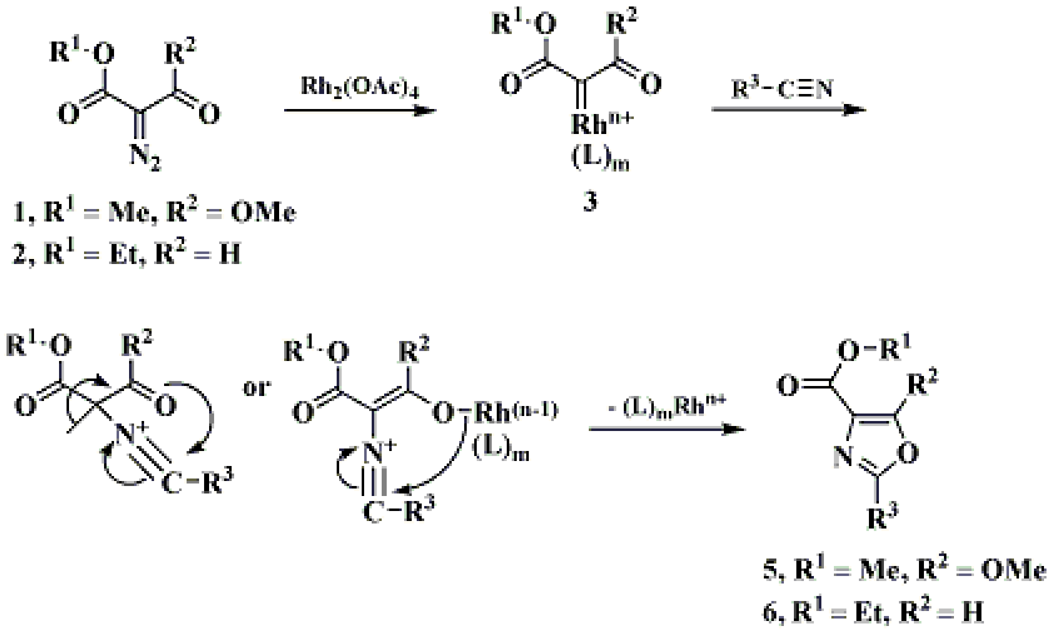
Madumycin I

Because of the many roles that these compounds play in natural products and synthetic organic chemistry, many methods have been developed for the preparation of 4-carboxy derivatives of oxazoles.[7,8,9,10,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46] A well-established, classical method is the Cornforth oxazole synthesis (Scheme 1). This method has been shown to be widely applicable, although it employs a complex, multi-step pathway.[47]



In consideration of conceivable strategies for the more direct construction of these derivatives, nitriles can be regarded as simple starting materials with which the 3+2 cycloaddition of acylcarbenes would, in a formal sense, provide the desired oxazoles. Oxazoles, in fact, have previously been obtained by the reaction of diazocarbonyl compounds with nitriles through the use of boron trifluoride etherate as a Lewis acid promoter. Other methods for attaining oxazoles involve thermal, photochemical, or metal-catalyzed conditions.[48,49,50,51,52,53,54,55,56] Several recent studies have indicated that many types of rhodium-catalyzed reactions of diazocarbonyl compounds proceed via formation of electrophilic rhodium carbene complexes as key intermediates rather than free carbenes or other types of reactive intermediates.[57,58,59,60] If this postulate holds for the reactions described here, then the mechanism outlined in Scheme 2 may be proposed, in which the carbene complex **3** and the adduct **4** are formed as

intermediates.[61 62 63]



The particular reaction described in Scheme 2 using dimethyl diazomalonate produces oxazoles **5** that bear a methoxy group at C-5. If desired, this substituent may be removed in some cases by reductive cleavage using $LiB(Et)_3H$ to give the 5-unsubstituted oxazoles **6**.[3,4,5,64] Alternatively, the 5-unsubstituted derivatives **6** may be obtained directly through the use of diazo formylacetate **(2)** in place of dimethyl diazomalonate **(1)**.[3,4,5,64] Some additional, representative examples of the use of **1** and **2** are shown below in the Table.

TABLE
ADDITIONAL EXAMPLES OF OXAZOLE FORMATION USING DIMETHYL DIAZOMALONATE 1 AND DIAZO FORMYLACETATE 2[a]

Nitrile	Method	Product Compound	Yield
p-ClC	1	[illegible]	96
CH	[illegible]	[illegible]	93
Ph-CN	2	[illegible]	45

PhCH 2 CN 65

64 Ref

Results taken from references

In conclusion, the rhodium-catalyzed reaction of diazo dicarbonyl compounds with nitriles provides direct access to useful classes of functionalized oxazoles. This direct, one-step pathway provides a significant improvement over past preparations.

Acknowledgment. We wish to express our appreciation to the National Institutes of Health and the National Science Foundation for providing generous financial support for this work.

This preparation is referenced from:

- Org. Syn. 79, 244

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

rhodium(II) acetate dimer

$Rh_2(OAc)_4$

$3\text{-}ClC_6H_4CN$

$4\text{-}CH_3C_6H_4CN$

Ph-CN

ethyl acetate (141-78-6)

ether, ethyl ether (60-29-7)

acetonitrile (75-05-8)

benzonitrile (100-47-0)

4-acetamidobenzenesulfonyl chloride (121-60-8)

chloroform, $CHCl_3$ (67-66-3)

nitrogen (7727-37-9)

aluminum (7429-90-5)

hexane (110-54-3)

triethylamine (121-44-8)

boron trifluoride etherate (109-63-7)

dimethyl malonate (108-59-8)

oxazole, 1,3-oxazole (288-42-6)

4-Carbomethoxy-5-methoxy-2-phenyl-1,3-oxazole, 4-Oxazolecarboxylic acid, 5-methoxy-2-phenyl-, methyl ester (53872-19-8)

Dimethyl diazomalonate (6773-29-1)

4-acetamidobenzenesulfonyl azide (2158-14-7)

4-acetamidobenzenesulfonamide (121-61-9)

rhodium carbene

diazo formylacetate

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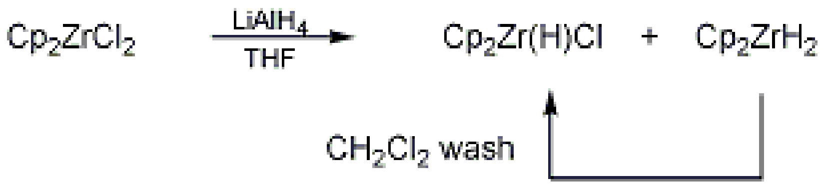
Organic Syntheses, CV 9, 162

SCHWARTZ'S REAGENT

[Zirconium, chlorobis(η5-2,4-cyclopentadien-1-yl)hydro-]



Submitted by Stephen L. Buchwald[1], Susan J. LaMaire, Ralph B. Nielsen, Brett T. Watson, and Susan M. King.
Checked by Daniel J. Keavy and Robert K. Boeckman, Jr..

1. Procedure

CAUTION! The washing procedure described in (Note 8) should be followed carefully. On one occasion, allowing a contact time of ca. 1 hr while attempting to use a cannula filter to remove the methylene chloride led to an exothermic decomposition reaction.

To a dry, 1-L Schlenk flask equipped with a magnetic stirring bar is added under argon zirconocene dichloride (100 g, 0.342 mol) (Note 1), followed by dry tetrahydrofuran (650 mL) (Note 2). Dissolution of the solid is accomplished by gentle heating with a heat gun. To the solution at 35°C (Note 3) is added dropwise, over a 45-min period, a filtered solution (Note 4),(Note 5) of lithium aluminum hydride (3.6 g, 94 mmol) (Note 4) in ethyl ether (100 mL) (Note 6),(Note 7). The resulting suspension is stirred at room temperature for 90 min. The mixture is then Schlenk-filtered (f.htmigure 1) under argon using a "D" frit. The resulting white solid is washed with tetrahydrofuran (4 × 75 mL), methylene chloride (2 × 100 mL) (Note 8) with stirring or agitation of the stirbar immersed in the slurry, and then with ether (4 × 50 mL). The resulting white solid is dried under reduced pressure to give a white powder (Note 9), 66 g, 75% yield (Note 10).

Figure 1

Figure 1

2. Notes

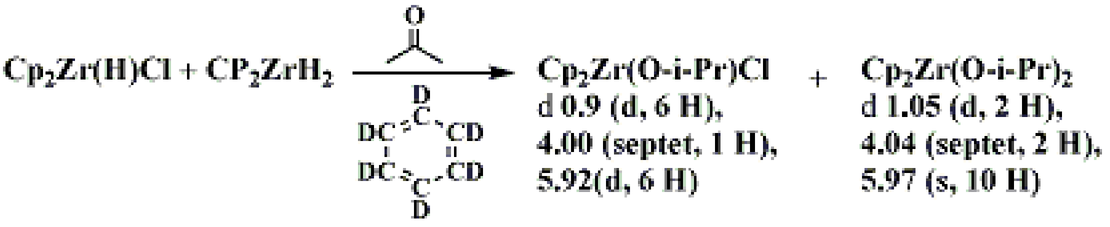
1. Zirconocene dichloride is purchased from Boulder Scientific Co., and used without any further purification.
2. Tetrahydrofuran is distilled from sodium/benzophenone ketyl under argon at

atmospheric pressure immediately before use.
3. Crystallization occurs if the temperature is allowed to fall below 35°C. The reaction can be conducted successfully even if a small amount of solid forms.
4. This solution is prepared by adding lithium aluminum hydride to ethyl ether, stirring the suspension for 10 min, and allowing the undissolved material to settle to the bottom of the flask. The clear solution is then filtered under argon using a modified cannula (f.htmigure 2) fitted with a piece of glass fiber filter (Number 34 Glass, 24 mm, purchased from Schleicher & Schuell); a Schlenk-filtered or commercial clear solution would work as well.

Figure 2

Figure 2

5. Lithium aluminum hydride (95%) is purchased from Alfa Products, Morton/Thiokol, Inc.
6. A slightly exothermic reaction results that maintains the temperature of the reaction mixture at 35°C during the addition.
7. Ethyl ether is distilled from sodium/benzophenone ketyl under argon at atmospheric pressure immediately before use.
8. Methylene chloride is distilled from calcium hydride under argon at atmospheric pressure immediately before use. It is important to keep the methylene chloride wash in contact with the Schwartz's Reagent for a maximum period of 10 min; use of a frit filter is essential.
9. Schwartz's Reagent is an air, moisture, and moderately light sensitive compound that should be dried in the dark, and protected from moisture and light during storage.
10. A small sample of the hydride is suspended in benzene-d_6 and assayed in a 5-mm NMR tube by treatment with a known amount of excess acetone (Equation 1). The relative areas of the signal for the mono- and diisopropoxides are determined by ^{1}H NMR (300 MHz, C_6D_6 integrating the methyl doublets): $Cp_2Zr(H)Cl$: 94–96%, Cp_2ZrH_2: 4–6%.[2]



Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Schwartz's Reagent[3] is available commercially (from the Aldrich Chemical Company, Inc.) although it is quite expensive. Two literature preparations of this important reagent are available. The first utilizes $LiAl(OtBu)_3H$ to reduce zirconocene dichloride.[4 5] The second method utilizes sodium bis(2-methoxyethoxy) aluminum hydride (RED-AL) as the reducing agent.[2] The disadvantages of these procedures have been discussed.[3]

Wailes, in his original report on the preparation of $Cp_2Zr(H)Cl$, investigated the lithium aluminum hydride reduction of zirconocene dichloride and found that this leads to considerable overreduction to give Cp_2ZrH_2.[4,5] Later it was found that treatment of Cp_2ZrH_2 with methylene chloride converts the dihydride into Schwartz's Reagent.[3]

In the procedure described here, zirconocene dichloride is reduced to a mixture of $Cp_2Zr(H)Cl$, and Cp_2ZrH_2 using a solution of lithium aluminum hydride. Washing the mixture with methylene chloride converts the Cp_2ZrH_2 into the desired $Cp_2Zr(H)Cl$. This method circumvents the need for expensive reducing agents and the use of the filtered lithium aluminum hydride solution substantially simplifies the product isolation. The procedure can be performed in 3–4 hr and does not require the use of a glove box thus making it an experimentally simple, inexpensive preparation for large scale batches of Schwartz's Reagent.

The utility of Cp_2ZrHCl for hydrozirconation was discovered by Schwartz.[2,6 7 8 9] Many subsequent applications of this useful reagent have been documented.[10] One such application is illustrated in the conjugate addition of a vinylzirconium reagent to form 3-(1-octen-1-yl)cyclopentanone.[11] In some cases Schwartz's Reagent (or its equivalent) can be prepared and used in situ.[12]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 143
- Org. Syn. Coll. Vol. 9, 640

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

benzophenone ketyl

SCHWARTZ'S REAGENT

Zirconium, chlorobis(η^5-2,4-cyclopentadien-1-yl)hydro-

zirconocene dichloride

$Cp_2Zr(H)Cl$

Cp_2ZrH_2

Cp_2ZrHCl

ether, ethyl ether (60-29-7)

acetone (67-64-1)

sodium (13966-32-0)

methylene chloride (75-09-2)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

calcium hydride (7789-78-8)

argon (7440-37-1)

sodium bis(2-methoxyethoxy) aluminum hydride

3-(1-Octen-1-yl)cyclopentanone (64955-00-6)

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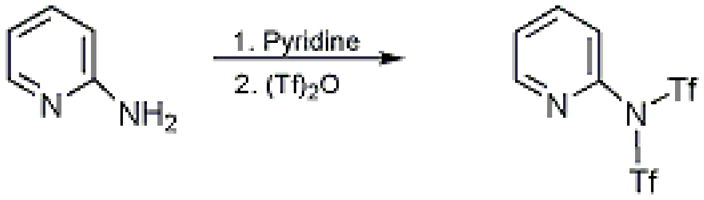
Organic Syntheses, CV 9, 165

PYRIDINE-DERIVED TRIFLATING REAGENTS: N-(2-PYRIDYL)-TRIFLIMIDE AND N-(5-CHLORO-2-PYRIDYL)TRIFLIMIDE

[Methanesulfonamide, 1,1,1-trifluoro-N-2-pyridinyl-N-[(trifluoromethyl)sulfonyl]-] and Methanesulfonamide, N-(5-chloro-2-pyridinyl)-1,1,1-trifluoro-N-[(trifluoromethyl)sulfonyl]-]



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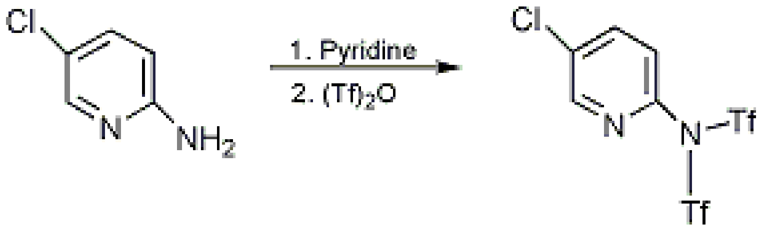


2

Submitted by Daniel L. Comins, Ali Dehghani, Christopher J. Foti, and Sajan P. Joseph[1].
Checked by Maria A. Cichy and Amos B. Smith, III.

1. Procedure

A. *N-(2-Pyridyl)triflimide* **(1)**. A 2-L, two-necked, round-bottomed flask equipped with a mechanical stirrer (Note 1) and a rubber septum is charged with 2-aminopyridine (19.859 g, 0.211 mol) (Note 2) and pyridine (35.04 g, 35.88 mL, 0.443 mol) (Note 3) in 800 mL of dichloromethane (CH_2Cl_2) (Note 4) under an argon atmosphere. The reaction mixture is cooled to −78°C and a solution of triflic anhydride (125 g, 74.54 mL, 0.443 mol) (Note 5) in 150 mL of CH_2Cl_2 is added dropwise via a cannula over 3.5 hr with vigorous stirring. After the solution is stirred for 2 hr at −78°C, the cooling bath is removed and stirring is continued at room temperature for 19 hr. The reaction mixture is quenched with 50 mL of cold water and the layers are separated. The aqueous layer is extracted with CH_2Cl_2 (4 × 50 mL). The combined organic extracts are washed with cold aqueous 10% sodium hydroxide (1 ×

150 mL), cold water (1 × 100 mL), brine (1 × 100 mL) and dried over magnesium sulfate. After filtration, the solvent is removed under vacuum to give 69 g of the crude product. After Kugelrohr distillation (Note 6), 61 g (81%) of pure N-(2-pyridyl) triflimide (bp 85–100°C/0.25 mm, mp 41–42°C) (Note 7) is obtained as a white solid.

B. *N-(5-Chloro-2-pyridyl)triflimide* **(2)**. Using the same procedure as described above, 2-amino-5-chloropyridine (27.13 g, 0.211 mol) (Note 8) is converted to N-(5-chloro-2-pyridyl)triflimide (mp 47–48°C) (61.84 g, 75%, bp 88–100°C/0.15 mm) (Note 9).

2. Notes

1. A magnetic stirrer can be used with a large stirrer bar and 1.5 L of dichloromethane.
2. 2-Aminopyridine was purchased from Aldrich Chemical Company, Inc., and used without further purification.
3. Anhydrous pyridine was purchased from Aldrich Chemical Company, Inc., and kept over 3 Å molecular sieves for two days prior to use.
4. Anhydrous dichloromethane was purchased from Aldrich Chemical Company, Inc., and used without further purification.
5. Triflic anhydride was purchased from Aldrich Chemical Company, Inc., and used as such.
6. Sometimes a second distillation is needed to obtain pure compound.
7. The spectral properties of N-(2-pyridyl)triflimide are as follows: IR (nujol) cm^{-1}: 1590, 1570, 1460, 1220, 1215, 1120, 1040, 990, 940, 910, 880, 735, 710; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.46–7.55 (m, 2 H), 7.91–7.97 (dt, 1 H, J = 8.06, 2.2), 8.63 (dd, 1 H, J = 4.4, 1.46); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 112.80, 117.10, 121.39, 125.50, 125.69, 126.79, 139.71, 145.98, 150.31.
8. 2-Amino-5-chloropyridine was purchased from Aldrich Chemical Company, Inc., and used without further purification.
9. The spectral properties of N-(5-chloro-2-pyridyl)triflimide are as follows: IR (nujol) cm^{-1}: 1570, 1460, 1230, 1215, 1125, 1010, 925, 905, 745, 730; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.42 (d, 1 H, J = 8.8), 7.90 (dd, 1 H, J = 8.8, 2.2), 8.58 (d, 1 H, J = 2.93); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 112.77, 117.06, 121.36, 125.66, 126.18, 135.84, 139.33, 143.82, 149.31.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

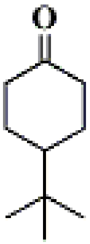
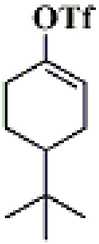
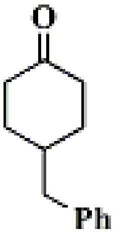
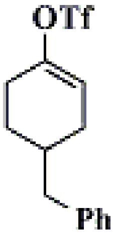
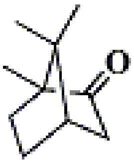
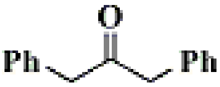
3. Discussion

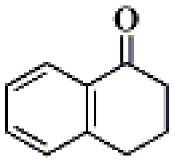
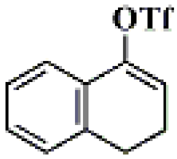
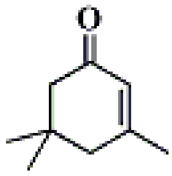
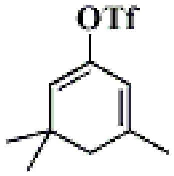
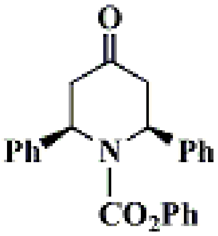
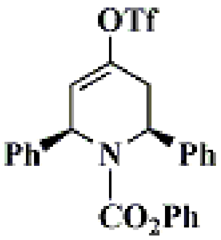
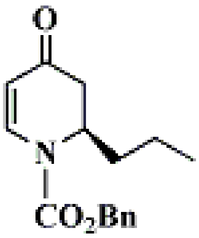
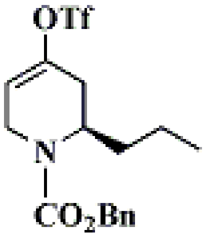
Vinyl triflates are important intermediates, since they can be used as synthetic precursors for vinyl cations and alkylidene carbenes, and as substrates for regiospecific coupling reactions.[2 3,4 5 6 7 8 9 10] Vinyl triflates are also valuable

intermediates in a mild, two-step procedure for the deoxygenation of ketones.[11,12,13] These new triflating reagents are highly reactive and easy to prepare and handle.[14] When compared with other triflating reagents, the vinyl triflate can in most cases be made at lower temperatures, and any excess reagent and by-products can be removed by washing with cold aqueous 5% sodium hydroxide solution. The utility of the pyridine-derived triflating reagents is illustrated by the examples in the Table.[14] Recently reagent **2** has been used in the total syntheses of (−)-porantheridine[15] and trans-decahydroquinoline alkaloid (+)-219 A.[16]

TABLE[14]

PREPARATION OF VINYL TRIFLATES FROM KETONE ENOLATES

Ketone	Base; Reagent; Condition	Product	Yield, %
	NaHMDS; **2** −78°C, 2 hr		92
	LDA; **1** −78°C, 3 hr		76
	LDA; **2** −78°C, 2 hr		77
	LDA; **2** −78°C, 3 hr		79

	LDA; **1** −78°C, 2 hr; −23°C, 4 hr; −16°C, 12 hr		76
	LDA; **2** −78°C, 2 hr		86
	LDA; **2** −78°C, 2 hr		88
	L-Selectride; **2** −23°C, 2 hr		80

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

brine

Methanesulfonamide, 1,1,1-trifluoro-N-2-pyridinyl-N-[(trifluoromethyl)sulfonyl]-]

(−)-porantheridine

sodium hydroxide (1310-73-2)

pyridine (110-86-1)

dichloromethane, CH_2Cl_2 (75-09-2)

2-aminopyridine (504-29-0)

magnesium sulfate (7487-88-9)

argon (7440-37-1)

triflic anhydride (358-23-6)

vinyl triflate

N-(2-Pyridyl)triflimide, N-(2-PYRIDYL)-TRIFLIMIDE (145100-50-1)

N-(5-Chloro-2-pyridyl)triflimide, Methanesulfonamide, N-(5-chloro-2-pyridinyl)-1,1,1-trifluoro-N-[(trifluoromethyl)sulfonyl]- (145100-51-2)

2-amino-5-chloropyridine (1072-98-6)

trans-decahydroquinoline

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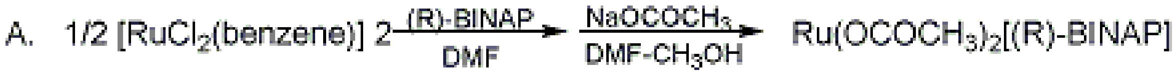
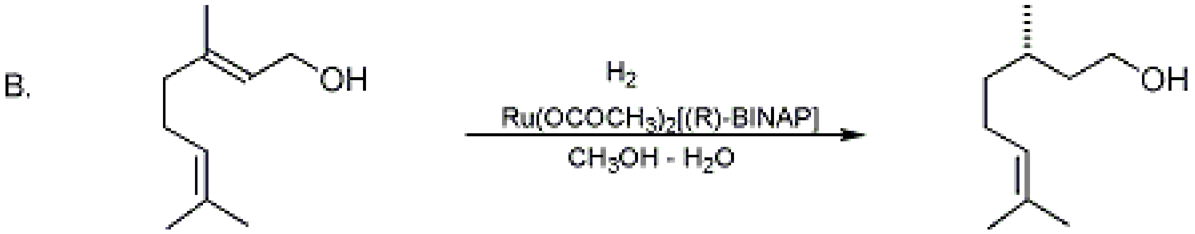
Organic Syntheses, CV 9, 169

ASYMMETRIC HYDROGENATION OF ALLYLIC ALCOHOLS USING BINAP-RUTHENIUM COMPLEXES: (S)-(−)-CITRONELLOL

[6-Octen-1-ol, 3,7-dimethyl, (S)-]





Submitted by Hidemasa Takaya[1], Tetsuo Ohta[1], Shin-ichi Inoue[2], Makoto Tokunaga[2], Masato Kitamura[2], and Ryoji Noyori[2].
Checked by Andrew Madin and Larry E. Overman.

1. Procedure

Caution! BINAP-Ru complexes are rapidly oxidized in solution in the presence of air, and all procedures should be carried out under anaerobic conditions using degassed solvents.

A. *[(R)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl]ruthenium diacetate, Ru(OCOCH$_3$)$_2$[(R)-BINAP].* A dry, 150-mL Schlenk tube (Note 1) connected to a supply of argon (Note 2) is equipped with a Teflon-coated magnetic stirring bar and a glass stopper. The vessel is charged with benzeneruthenium(II) chloride dimer, [RuCl$_2$(benzene)]$_2$, (800 mg, 1.60 mmol) (Note 3) and (R)-BINAP (1.89 g, 3.04 mmol) (Note 4), evacuated, and then filled with argon. N,N-Dimethylformamide (DMF) (30 mL) (Note 5) is introduced with a hypodermic syringe under the stream of argon. The reddish brown suspension is stirred at 100°C for 10 min (Note 6) and the resulting clear reddish brown solution (Note 7) is cooled. Another dry, 60-mL Schlenk tube is charged with sodium acetate (5.20 g, 63.4 mmol) and methanol (50 mL) (Note 8) and the solution is degassed by three freeze-thaw cycles. It is transferred into the DMF solution of BINAP-Ru(II) complex prepared above via cannula and the solution is stirred at 25°C for 5 min. To the solution are added water (50 mL) and toluene (25

mL) under argon and the resulting two layers are mixed by vigorous stirring. The upper organic layer is transferred into another 200-mL Schlenk tube (Note 9) using a cannula. The aqueous layer is vigorously mixed with toluene (25 mL) and the upper organic layer is again transferred into the Schlenk tube. This procedure is repeated once more. The combined organic layers are washed with four 10-mL portions of water (Note 10). Removal of the solvent at 1 mm and 40°C for 30 min with vigorous stirring (Note 11) and evacuation at 0.1 mm and 25°C for 12 hr gives 2.54–2.67 g of solid Ru(OCOCH$_3$)$_2$ [(R)-BINAP] (99–104% crude yield based on BINAP) (Note 12). It is dissolved in toluene (20–25 mL) with heating. Hexane (80–100 mL) is added very carefully to the solution down the side of the flask to form two layers. The solution is left at 25°C for 12 hr and then at 4°C for 3 days to give solid material. Removal of the mother liquor is followed by washing with hexane (20 mL) and drying under reduced pressure to afford 1.8–2.2 g (71–85% yield) of pure Ru(OCOCH$_3$)$_2$ [(R)-BINAP] as fine yellow needles or powdery crystals; mp 188–190°C dec (Note 13).

B. *(S)-(−)-Citronellol*. Geraniol (12.9 mL, 74 mmol) (Note 14) and 95% methanol (15 mL) (Note 15) are placed in a dry, 80-mL Schlenk tube and the mixture is degassed by five freeze-thaw cycles. Another dry, 80-mL Schlenk tube, equipped with a rubber septum and a magnetic stirring bar and filled with argon, is charged with Ru(OCOCH$_3$)$_2$ [(R)-BINAP] (45 mg, 53 •mol) (Note 16). The system is evacuated and refilled with argon three times. By use of a cannula, the solution of geraniol in methanol is introduced into the Schlenk tube containing the ruthenium complex under argon. The resulting light yellow solution (Note 17) is then transferred with a cannula into a 100-mL, stainless steel autoclave equipped with a glass vessel (Note 18) and a magnetic stirring bar by use of a slight positive pressure of argon. The autoclave is connected to a hydrogen source (Note 19) using the arrangement shown in f.htmigure 1, and the air originally present in the gas-inlet tube is replaced by hydrogen (Note 20). Valve A is opened and hydrogen is introduced until pressure gauge B indicates 100 atm. The solution is stirred at 20°C for 8–16 hr (Note 21). During hydrogenation, the hydrogen pressure is kept above 90 atm by the occasional introduction of hydrogen from the cylinder (Note 22). When consumption of hydrogen ceases, the gas-inlet tube is disconnected. Excess hydrogen is carefully released by opening valve A and then the apparatus is disassembled. The yellowish brown contents (Note 23) are transferred to a 50-mL flask and the solvent is removed by a rotary evaporator. The residue (Note 24) is distilled under reduced pressure to give 10.7–11.2 g (93–97% yield) of (S)-(−)-citronellol in 98% ee (Note 25) and (Note 26); bp 58–62°C/0.01 mm.

Figure 1

Figure 1

2. Notes

1. Before use, all apparatus is dried overnight in a 120°C oven.

2. Argon (99.998%) is purified by passing through a BASF catalyst RC-11 column at 80°C and then through 4 Å molecular sieves.
3. $[RuCl_2(benzene)]_2$, available from Aldrich Chemical Company, Inc., is used without purification.
4. BINAP [2,2'-bis(diphenylphosphino)-1,1'-binaphthyl] is commercially available or can be prepared according to a literature procedure.[3] The diphosphine is slowly oxidized in air to give the corresponding mono- and diphosphine oxides that can be removed by column chromatography (silica gel, benzene) under an inert atmosphere.
5. Guaranteed grade DMF, available from NACALAI TESQUE, Inc., is distilled over 4 Å molecular sieves under argon before use and stored in a 100-mL Schlenk tube. It is degassed by three freeze-thaw cycles.
6. Reaction at a higher temperature for a longer period leads to formation of the ruthenium carbonyl complex [IR(KBr) 1964 cm^{-1}].
7. The solution may be a crude mixture of cationic BINAP-Ru(II) complexes such as $[RuCl(BINAP)(DMF)_3]Cl$ and $[Ru(BINAP)(DMF)_4]Cl_2$. Physical properties include conductivity, 27 Scm^2/mol (DMF); ^{31}P NMR (4:1 DMF-$CDCl_3$) δ: 60.6 (d, J = 46), 61.4 (d, J = 46), 61.8 (s). The (R)-BINAP-Ru(II) complex obtained by removal of the solvent can catalyze hydrogenation of geraniol (98.7% pure commercial geraniol containing 1.3% of nerol, distilled from 4 Å molecular sieves). However, in addition to (S)-citronellol in 95–96% ee, dihydrocitronellol, an overreduction product, is obtained in 3–7% yield (1.1 M substrate in 95% aqueous methanol, 1.7 mM catalyst, 100 atm of H_2, 20°C, 8 hr).
8. Guaranteed grade methanol is distilled under argon.
9. The diameter is about 4 cm.
10. The extraction procedure must be carried out under an argon atmosphere.
11. Under reduced pressure, the solution sometimes foams. This can be avoided by heating the top part of the Schlenk tube with a hot air gun.
12. Crude BINAP-Ru complex with consistent spectral characteristics can be used for hydrogenation of geraniol (98.7% pure commercial geraniol containing 1.3% of nerol, distilled from 4 Å molecular sieves, 4.7 M substrate in 95% aqueous methanol, 2.8 mM $Ru(OCOCH_3)_2$ [(R)-BINAP], 100 atm of H_2, 20°C, 8 hr), to give (S)-citronellol in 96% ee, 97% isolated yield.
13. The product has the following spectral properties: ^1H NMR ($CDCl_3$) δ: 1.80 (s, 2 $OCOCH_3$), 6.47–7.84 (m, aromatic protons); ^{31}P NMR ($CDCl_3$) δ: 65.13 (s); ^{13}C NMR ($CDCl_3$) δ:23.50, 125.2–138.3, 188.1; IR (CH_2Cl_2) cm^{-1}: 1452, 1518. An analytical sample is prepared by drying at 110°C and 0.01 mm for 12 hr: Calcd for $C_{48}H_{38}O_4P_2Ru$: C, 68.5; H, 4.6. Found: C, 68.4; H, 4.5.
14. Pure geraniol is obtained by fractional distillation using a 1000 theoretical plate column. The checkers obtained geraniol, > 99.5% purity by GC analysis, from Fluka Chemical Company and used it directly.
15. The 95% methanol is prepared by mixing distilled, guaranteed methanol (95 mL) and water (5 mL). If absolute methanol or 90% aqueous methanol is used

as solvent, somewhat longer reaction times are needed.

16. The complex can be stored under argon without noticeable loss of catalytic activity. It is weighed under an argon atmosphere.

17. The ruthenium complex is moderately soluble in methanol. Ultrasonic stirring is employed for complete solution.

18. A glass vessel is used for keeping the reaction mixture away from the stainless steel wall. The reaction system is evacuated and filled with argon three times before use.

19. The purity of hydrogen (Nippon Sanso Co.) used by the submitters is 99.99999%. The checkers used hydrogen of 99.99% purity.

20. The gas-inlet tube is attached to the autoclave and then the main valve of the cylinder is opened. After closing the main valve of the cylinder, the connector of the gas-inlet tube is loosened to release hydrogen pressure and tightened immediately. This procedure is repeated five times.

21. To maintain an internal temperature of 20°C the checkers placed the autoclave in a 18°C bath. Reactions terminated after 8 hr by the checkers showed the presence of unreacted geraniol (2–4%).

22. Enantioselectivity is very dependent on hydrogen pressure. Optical purities of citronellol products are 70% and 95% at 4 and 30 atm, respectively. Thus, hydrogen pressure greater than 90 atm is required for high optical yields.

23. In air, the color gradually changes to dark green.

24. Gas chromatographic analysis indicates that this consists of 97–99% of citronellol and 1–3% of dihydrocitronellol; column, SHIMADZU HiCap-CBP20, 25 m × 0.2-mm fused silica; column temperature, 140°C; injection temperature 160°C; helium pressure as carrier gas, 1.0 kg/cm^2; t_R of geraniol, citronellol, and dihydrocitronellol are 16.2, 13.7, and 8.6 min, respectively.

25. The product has the following spectral properties; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.89 (d, J = 6.6, $CH_2CH(CH_3)CH_2$), 1.18 (m, $CH_2CHHCH(CH_3)CH_2$), 1.36 (m, $CH_2CHHCH(CH_3)CHH$), 1.57 (m, $CH_2CH(CH_3)CHH$), 1.59 (s, $(CH_3)_2C{=}CH$), 1.67 (s, $(CH_3)_2C{=}CH$), 1.71 (s, CH_2CH_2OH), 1.97 (m, $(CH_3)_2C{=}CHCH_2$), 3.66 (m, CH_2CH_2OH), 5.08 (t, J = 6.96, $(CH_3)_2C\text{-}CH$), $[\alpha]_D^{29}$ −4.5° to −4.7° (neat) [lit.[4] $[\alpha]_D^{20}$ −4.76° (neat)]. The submitters determined the enantiomeric excess by HPLC analysis of the diastereomeric amide prepared by condensation of citronellic acid (Note 27), obtained by the Jones oxidation of the alcohol, and (R)-1-(1-naphthyl)ethylamine (Note 28). HPLC analysis of this amide (column, TOYO SODA SILICA-60, 4.6 × 500 mm, a 3:7 ether-hexane mixture; flow rate 1 mL/min; detection 254 nm light) showed two peaks with t_R at 33.0 and 36.0 min in 1:99 ratio assignable to the R,R- and R,S-diastereomers, respectively.

26. With a commercially available 98.7:1.3 mixture of geraniol and nerol as substrate, (S)-citronellol in 96% ee is obtained. See also (Note 7).

27. In a 100-mL, round-bottomed flask equipped with a magnetic stirring bar are placed β-citronellol (1.63 g, 10.4 mmol) and acetone (25 mL). To this is slowly added Jones reagent [$Na_2Cr_2O_7$ (0.73 M in H_2O)/H_2SO_4 (concn = 1/4.2 v/v)] at

0–5°C until the orange color remains unchanged. To this mixture is added 2-propanol (5 mL) to decompose excess Jones reagent. After the orange color disappears, insoluble material is filtered off and the solvent is removed under reduced pressure. The residue is dissolved in ether (10 mL) and the solution is washed with brine (10 mL). The water layer is extracted with ether and the combined organic layers are extracted with 1 N aqueous sodium hydroxide (50 mL) at 0°C. The alkaline aqueous layer is acidified and extracted with three, 20-mL portions of ether at 0°C. The combined ether layers are dried over anhydrous magnesium sulfate and the solvent is evaporated. To the residue is added a small amount of benzene; the benzene is then removed under reduced pressure to give 977 mg (55% yield) of citronellic acid.

28. In a 50-mL, round-bottomed flask, equipped with a rubber septum and a magnetic stirring bar and filled with argon, are placed citronellic acid (112 mg, 0.658 mmol) and a solution of (R)-1-(1-naphthyl)ethylamine (140 mg, 0.818 mmol) (Note 29) in dry DMF (4 mL) (Note 5). To this mixture in an ice bath are added a solution of diethyl cyanophosphonate (224 mg, 1.37 mmol) (Note 30) in dry DMF (2 mL) and then dry triethylamine (0.1 mL). The mixture is stirred and the reaction is followed by TLC. When the carboxylic acid has been consumed, which takes approximately 2 hr at room temperature, the reaction mixture is dissolved in a mixture of benzene (5 mL) and ethyl acetate (5 mL). The mixture is washed successively with cold 5% hydrochloric acid, ice-water, saturated sodium hydrogen carbonate solution, and brine, dried over anhydrous sodium sulfate, and finally concentrated under vacuum to give 207 mg (97% yield) of the amide.

29. (R)-(+)-1-(1-Naphthyl)ethylamine is purchased from Aldrich Chemical Company, Inc. The reagent is purified by recrystallization of its tartaric acid salt three times from 94% aqueous methanol followed by treatment with base and distillation of the free amine.

30. Commercial grade diethyl cyanophosphonate is distilled under argon before use.

Waste Disposal Information

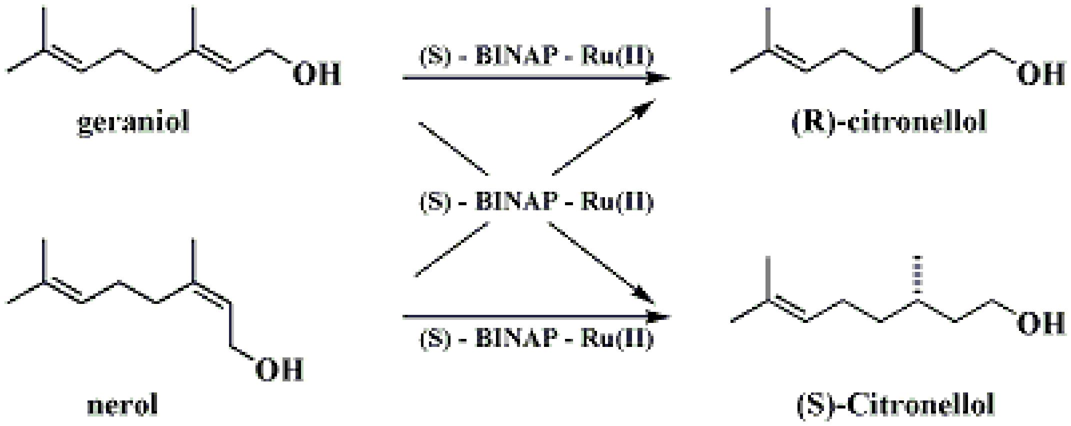
All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The procedure for the synthesis of the title compound is a representative example of asymmetric hydrogenation in the presence of BINAP-Ru(II) diacetate.[5] The method is based on the synthesis of BINAP-Ru(II) dicarboxylate complexes[6] and enantioselective hydrogenation of geraniol.[7] The present method provides the first practical means for asymmetric synthesis of (S)- and (R)-citronellol. (S)-(−)-Citronellol of optical purity up to 92% can be obtained in a limited quantity from rose

oil. A microbiological reduction of geraniol was reported to give enantiomerically pure (R)-(+)-citronellol.[8]

Nerol can also be used as a substrate. The stereochemical outcome is shown in Scheme 1, which indicates that the BINAP-Ru species differentiates the C(2) enantiofaces. The C(6)-C(7) double bonds are left intact. Thus, both R and S enantiomers are accessible by either variation of allylic olefin geometry or choice of handedness of the catalysts.



The complex formulated as $Ru(OCOCF_3)_2$ (BINAP), that is prepared from $Ru(OCOCH_3)_2$ (BINAP) and excess trifluoroacetic acid, shows high catalytic activity (S/C = 50000, 20°C, 100 atm, 96% ee). The cationic complex [RuI(BINAP)(p-cymene)] I[9] also acts as an efficient catalyst (96% ee). In the presence of the catalyst system derived from $Ru(OCOCH_3)_2$(BINAP) and 1 equiv of aqueous perchloric acid, hydrogenation proceeds very rapidly (S/C = 2000, completion after 15 min), but results in low enantioselectivity (94% ee). TolBINAP[10] [2,2'-bis(di-p-tolylphosphino)-1,1'-binaphthyl] can also be used. Hydrogenation of geraniol using Ru_2Cl_4 [(R)-BINAP]$_2$[N(C_2H_5)$_3$][11] as catalyst (6:1 ethanol-dichloromethane, H_2, 40 atm, 24°C, 90 hr) gives (S)-citronellol in 47% yield and 93% ee (92% conversion) in addition to dihydrocitronellol (40% yield) (see also (Note 7)).

This procedure has been successfully applied to the asymmetric synthesis of (3R,7R)-3,7,11-trimethyldodecanol, a versatile intermediate for synthesis of α-tocopherol (vitamin E). Hydrogenation of homogeraniol also proceeds smoothly to give 4,8-dimethylnon-7-enol in 92% ee in 96% yield. Hydrogenation of racemic allylic secondary alcohols in the presence of BINAP-Ru(II) diacetate brings about a high level of kinetic enantiomer selection.[12] This method provides a practical route to (R)-4-hydroxy-2-cyclopentenone, an important building block for the three-component prostaglandin synthesis.[13] A useful intermediate for synthesis of 1β-methylcarbapenems can be prepared by the hydrogenation of a chiral allylic alcohol.[14]

BINAP-ruthenium dicarboxylate complexes are also efficient catalysts for asymmetric hydrogenation of enamides, α,β– and β,γ-unsaturated carboxylic acids, α-amino ketones, and α-acylaminoacrylic acids.[5,15]

A detailed procedure for the asymmetric hydrogenation of β-ketoesters using a BINAP-ruthenium complex may be found on p. 589.[16]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 589

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

brine

Homogeraniol

(S)-(−)-CITRONELLOL

[(R)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl]ruthenium diacetate, $Ru(OCOCH_3)_2$ [(R)-BINAP]

benzeneruthenium(II) chloride dimer

BINAP-Ru(II) complex

$Ru(OCOCH_3)_2$ [(R)-BINAP]

ruthenium complex

BINAP [2,2'-bis(diphenylphosphino)-1,1'-binaphthyl]

ruthenium carbonyl complex

BINAP-Ru(II) diacetate

(S)- and (R)-citronellol

$Ru(OCOCF_3)_2$ (BINAP)

$Ru(OCOCH_3)_2$ (BINAP)

$Ru(OCOCH_3)_2$(BINAP)

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether (60-29-7)

sodium acetate (127-09-3)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

sodium hydrogen carbonate (144-55-8)

allylic alcohol (107-18-6)

sodium sulfate (7757-82-6)

acetone (67-64-1)

toluene (108-88-3)

2-propanol (67-63-0)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

N,N-dimethylformamide, DMF (68-12-2)

hexane (110-54-3)

geraniol (106-24-1)

triethylamine (121-44-8)

perchloric acid (7601-90-3)

trifluoroacetic acid (76-05-1)

helium (7440-59-7)

argon (7440-37-1)

nerol

citronellol, dihydrocitronellol, β-citronellol (106-22-9)

(R)-4-hydroxy-2-cyclopentenone

(S)-Citronellol, 6-Octen-1-ol, 3,7-dimethyl, (S)- (7540-51-4)

citronellic acid (502-47-6)

(R)-1-(1-naphthyl)ethylamine, (R)-(+)-1-(1-Naphthyl)ethylamine (42882-31-5)

diethyl cyanophosphonate (2942-58-7)

(R)-(+)-citronellol

(3R,7R)-3,7,11-trimethyldodecanol

4,8-dimethylnon-7-enol (163182-73-8)

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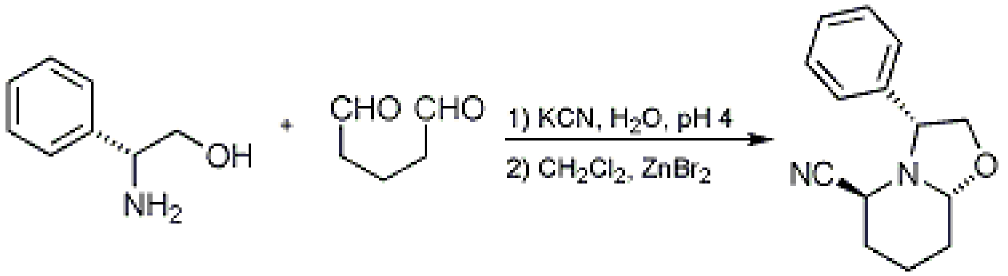
Organic Syntheses, CV 9, 176

A STABLE CHIRAL 1,4-DIHYDROPYRIDINE EQUIVALENT FOR THE ASYMMETRIC SYNTHESIS OF SUBSTITUTED PIPERIDINES: 2-CYANO-6-PHENYLOXAZOLOPIPERIDINE

[5H-Oxazolo[3,2-a]pyridine-5-carbonitrile, hexahydro-3-phenyl-, [3R-(3α,5β,8aβ)]]



1 2

Submitted by Martine Bonin, David S. Grierson, Jacques Royer, and Henri-Philippe Husson[1].
Checked by Gilbert Rishton and Larry E. Overman.

1. Procedure

CAUTION! Aqueous potassium cyanide is used in this procedure. All operations should be conducted in a well-ventilated hood and rubber gloves should be worn.

2-Cyano-6-phenyloxazolopiperidine. A 2-L, round-bottomed flask is charged with 10 g (0.073 mol) of (−)-phenylglycinol (Note 1) and 40 g of citric acid in 1 L of distilled water. The mixture is stirred magnetically until complete dissolution is achieved and is then cooled to 0–5°C (ice-water bath). The flask is equipped with a dropping funnel and 45 mL of an aqueous 24% glutaraldehyde solution (0.11 mol) is added dropwise over 20 min and the resultant cloudy solution is stirred for an additional 30 min at 0°C. The cooling bath is removed and a solution of 7.15 g (0.11 mol) of potassium cyanide in 20 mL of water is carefully added in one portion followed by 200 mL of methylene chloride. The resulting two-phase reaction system is stirred for 3 hr at room temperature, then the aqueous phase is neutralized (Note 2) by addition of sodium bicarbonate and the two layers are separated. The water layer is extracted with three 200-mL portions of methylene chloride (Note 3) and the combined methylene chloride layers are dried over sodium sulfate and concentrated on a rotary evaporator to a volume of 500 mL. Zinc bromide (2 g) is added in small portions over 5 min to this solution and vigorous stirring under nitrogen is continued for 3 hr (Note 4). The reaction mixture is concentrated to a volume of approximately 150 mL (Note 5) and

the resultant mixture is applied to a 10-cm diameter flash chromatography column prepared using hexane-ether (2:1) as the eluant. The desired product is eluted first (Note 6), (Note 7). By recrystallization from hexane, the product [10.8–11.6 g (65–70%)] is obtained analytically pure; mp 79–81°C, $[\alpha]_D^{23}$ −280° ($CHCl_3$, *c* 1.0) (Note 8).

2. Notes

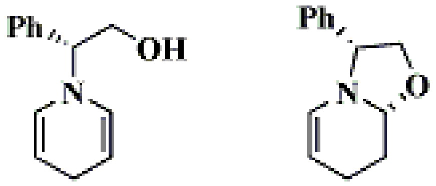
1. The checkers used (R)-(−)-2-phenylglycinol [98%, $[\alpha]_D^{24}$ −31.7° (1 N HCl, *c* 0.76)] purchased from Aldrich Chemical Company, Inc. The submitters employed material [mp 78°C, $[\alpha]_D^{20}$ −26.5° (MeOH, *c* 0.7)] prepared by lithium aluminum hydride reduction of (−)-phenylglycine and report that the yield of 2-cyano-6-phenyloxazolopiperidine prepared from this material is 75–83%.
2. Extraction at pH greater than 9 led to the formation of by-products (2,6-dicyanopiperidines)[2] and consequently to a lower yield of the desired product.
3. The aqueous layer containing residual potassium cyanide is destroyed by addition of potassium permanganate.
4. The reaction must be carried out in a well-ventilated hood as hydrogen cyanide may be evolved.
5. Complete evaporation of the solvent gives a viscous oil which is only slightly soluble in either the elution solvent or methylene chloride. Significant loss of material thus occurs during the purification process.
6. R_f = 0.6 (SiO_2, hexane-ether : 2–1) for the product.
7. Further elution permits the isolation of a mixture of two other isomers (0.3 g, 3.6%).
8. The product obtained by this procedure shows the following spectral data: IR ($CHCl_3$) cm^{-1}: 2100; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.5–2.0 (m, 5 H), 2.13 (dd, 1 H, J = 11.5, J' = 1.5), 3.74 (t, 1 H, J = 7.8), 3.85 (bd, 1 H, J = 7.1), 3.90 (t, 1 H, J = 8.0), 4.12 (dd, 1 H, J = 9.7, J' = 2.8), 4.25 (t, 1 H, J = 7.9), 7.4 (m, 5 H); ^{13}C NMR (15 MHz, $CDCl_3$) δ: 19.3, 28.0, 30.0, 47.4, 63.9, 73.0, 89.9, 116.0, 128.2, 128.6, 129.0, 137.4.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995. See (Note 3).

3. Discussion

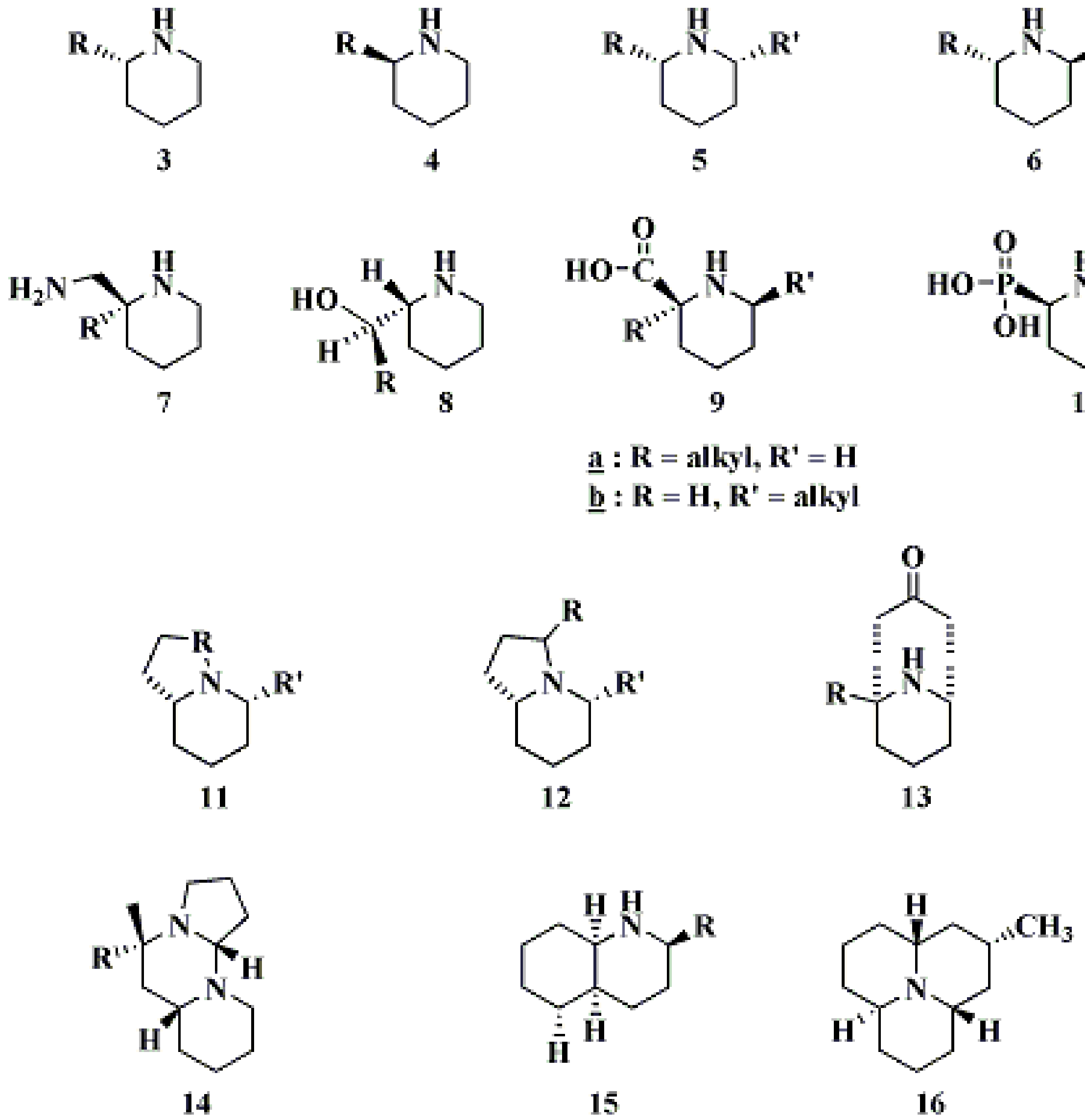
The preparation described here is an improvement of the previous procedure.[3] The double condensation of glutaraldehyde with the amino group of (R)-(−)-phenylglycinol (related to the Robinson-Schopf condensation) probably leads to the expected product via the formation of an intermediate of type A[4] and/or B.



A B

Trapping intermediate B with cyanide ion would lead to the final product. Formation of the four possible product isomers has been observed after short reaction periods, and equilibration of this mixture to the described product **2** has been demonstrated. In the original procedure compound **2** was obtained in 50–60% yield after prolonged (72 hr) reaction in water. In the present procedure equilibration of all intermediates and/or product isomers to the observed, thermodynamically more stable form of compound **2** is accelerated and the yield improved considerably through the use of zinc bromide as a catalyst in an organic medium.

2-Cyano-6-phenyloxazolopiperidine, **2**, is a stable, chiral, 1,4-dihydropyridine equivalent, useful for the asymmetric synthesis of piperidines. Synthon **2** has been used for the asymmetric synthesis of several alkaloids or structural analogs in this laboratory and by others.[5,6] A sequence of reactions involving alkylation at the α-aminonitrile center (LDA, RX), elimination of the cyano group with concomitant opening of the oxazolidine ring ($NaBH_4$), and finally debenzylation (H_2, Pd/C) permits the preparation of α-alkylated piperidine **3** in 90 % overall yield (ee ≥95 %).[7] From the same synthon **2**, enantiomeric **4** can also be prepared.[7] A regio- and chemoselective elimination of the cyano group is also possible giving an oxazolopiperidine intermediate which can further be used to prepare the cis- and trans-2,6-disubstituted piperidines **5**[7] and **6**.[8]



The possibility to create an R or S chiral center by substituting the CN group in **2** led us to call this methodology the CN(R,S) method, in recognition of the Centre National de la Recherche Scientifique (CNRS) which supported this work.

This methodology was extented to enantiospecific synthesis of generally less accessible or more complex piperidine derivatives :

a) 2-(1-aminomethyl)piperidines **7**.[9]

b) Amino-alcohols **8**[10] and other β-amino-alcohols reported in the literature.[5,6]

c) Pipecolic acid and 2- or 6-alkylated derivatives **9**.[11]

d) (R)-Enantiomer of piperidin-2-yl phosphonic acid **10**.[12]

e) Alkaloids **11**[13], **12**[3], **13**[14], **14**[15], **15**[16], and the symmetric molecule **16**.[17]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

2-Cyano-6-phenyloxazolopiperidine

5H-Oxazolo[3,2-a]pyridine-5-carbonitrile, hexahydro-3-phenyl-, [3R-(3α,5β,8aβ]

(−)-phenylglycinol

(−)-phenylglycine

(R)-(−)-phenylglycinol

HCl (7647-01-0)

ether (60-29-7)

citric acid (77-92-9)

sodium bicarbonate (144-55-8)

potassium permanganate (7722-64-7)

hydrogen cyanide (74-90-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

potassium cyanide (151-50-8)

methylene chloride (75-09-2)

lithium aluminum hydride (16853-85-3)

zinc bromide (7699-45-8)

hexane (110-54-3)

glutaraldehyde (111-30-8)

1,4-DIHYDROPYRIDINE

Pipecolic acid (535-75-1)

piperidin-2-yl phosphonic acid

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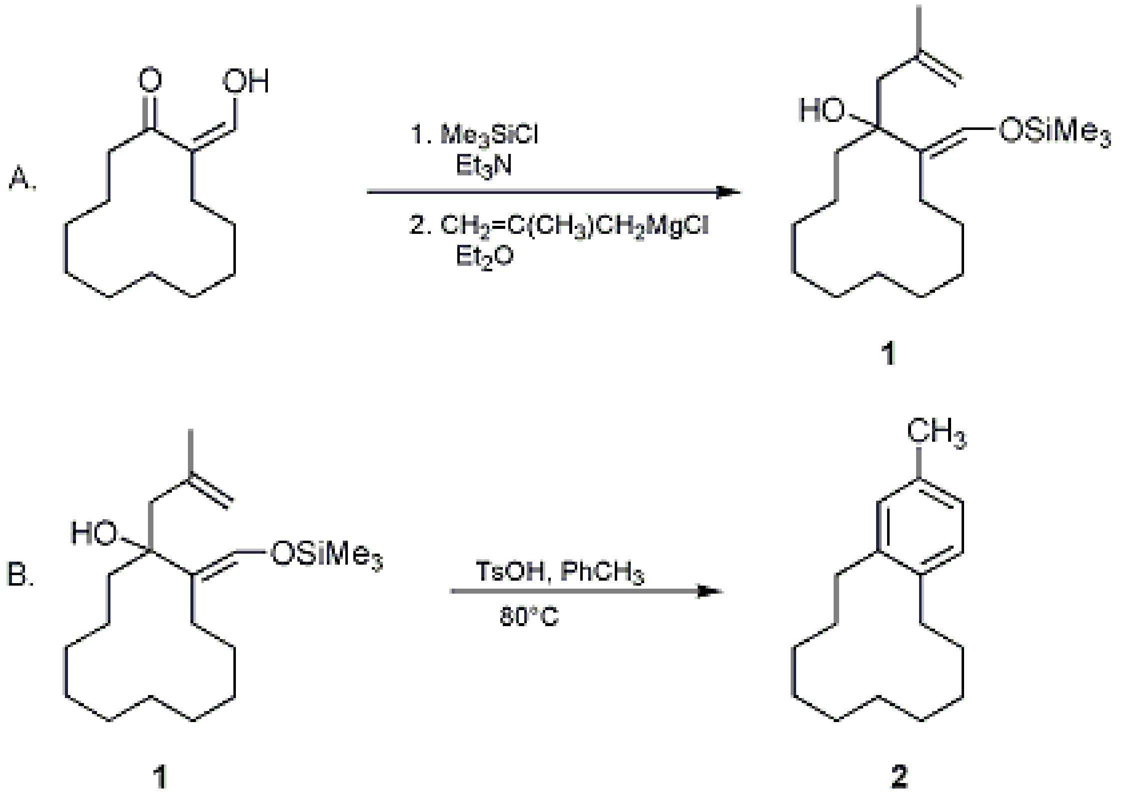
Organic Syntheses, CV 9, 180

BENZOANNELATION OF KETONES: 3,4-CYCLODODECENO-1-METHYLBENZENE

[Benzocyclododecene, 5,6,7,8,9,10,11,12,13,14-decahydro-2-methyl-]



Submitted by Marcus A. Tius and G. S. Kamali Kannangara[1].
Checked by Annapoorna Akella and James D. White.

1. Procedure

A. *1-(2-Methylallyl)-2-(trimethylsiloxy)methylenecyclododecanol.* A dry, 2-L, three-necked, round-bottomed flask connected to a nitrogen bubbler and equipped with a mechanical stirrer with ground glass shaft and bearing a 100-mL pressure-equalizing dropping funnel and a septum inlet is charged with 45.4 g (1.89 mol) of magnesium turnings (Note 1) and flushed for 5 min with nitrogen. Anhydrous ether, 450 mL, (Note 2) is added and the flask is cooled to 0°C in an ice bath. Methallyl chloride, 64.6 mL (0.65 mol, (Note 3)) is added dropwise from the addition funnel to the stirred magnesium turnings during 45 min. *(Caution! The reaction is exothermic and care must be exercised to add the methallyl chloride at a moderate rate with adequate stirring and cooling of the reaction mixture).* During this time the reaction mixture turns to a gray heterogeneous slurry. Stirring is continued at 0°C for 1.5 hr and at 22°C for 1.5 hr.

In a separate, dry, 1-L, two-necked, round-bottomed flask fitted to a nitrogen bubbler

and equipped with a magnetic stirring bar and a septum inlet is added a solution of 12.6 g (60.0 mmol) of 2-(hydroxymethylene)cyclododecanone (Note 4) in 500 mL of anhydrous ether. The stirred ethereal solution of the hydroxymethylene ketone is treated at 22°C with 33 mL of a freshly prepared mixture (1/1, v/v) of chlorotrimethylsilane and triethylamine (Note 5). An immediate reaction takes place with deposition of a white precipitate. The mixture is stirred thoroughly at 22°C for 15 min to insure complete conversion to the silyl enol ether.

The heterogeneous mixture of the silyl enol ether and triethylamine hydrochloride is transferred to the solution of the Grignard reagent at 0°C by means of a large-bore cannula (Note 6) during 15 min. The efficient transfer of the silyl enol ether is accomplished with the aid of nitrogen pressure. The flask containing the silyl enol ether is rinsed with 50 mL of ether that is transferred to the Grignard solution. Stirring at 0°C is continued for 15 min. The reaction is then quenched by slow addition of saturated aqueous sodium chloride solution until the reaction mixture becomes clear. *(Caution! The septa are removed from the flask in order to vent the pressure)*. The solution is allowed to warm to 22°C and the ether layer is decanted from the magnesium salt and the unreacted magnesium. The residue is diluted with 100 mL of saturated aqueous sodium chloride solution and extracted with ether (3 × 50 mL). The combined ether extracts are washed with brine (2 × 50 mL), dried over anhydrous magnesium sulfate and concentrated at reduced pressure. The product that is obtained is used in the next step without purification.

B. *3,4-Cyclododeceno-1-methylbenzene*. A 1-L, two-necked, round-bottomed flask equipped with a reflux condenser, septum inlet, and a magnetic stirring bar is fitted to a nitrogen bubbler. The flask is charged with 200 mL of toluene (Note 7) and 4.6 g (24 mmol) of p-toluenesulfonic acid monohydrate (Aldrich Chemical Company, Inc.). The solution is warmed to 80°C in a heating mantle. Tertiary alcohol **1** from the preceding step is dissolved in 150 mL of toluene and transferred to the flask by cannula. The progress of the reaction can be monitored by silica gel TLC eluting with 20% ethyl acetate in hexane (Note 8). After 3 hr the reaction mixture is cooled to 22°C and washed with saturated aqueous sodium bicarbonate (2 × 100 mL). The aqueous phase is extracted with ether (4 × 100 mL) and the combined organic extracts are dried over anhydrous magnesium sulfate. The solvents are removed under reduced pressure and the residue is purified by flash column chromatography on silica gel, eluting with hexane. The benzoannelated product is obtained as a pale yellow oil in 86% overall yield (12 g; (Note 9)).

2. Notes

1. Magnesium turnings (98%) from Aldrich Chemical Company, Inc. were used after drying in a beaker at 110°C overnight. The Grignard reaction took place without need of an initiator.
2. Reagent grade ether was dried by distillation under argon from a purple solution of sodium benzophenone ketyl.

3. Methallyl chloride (obtained from Aldrich Chemical Company, Inc.) was distilled (bp 71–72°C) from phosphorus pentoxide prior to use.

4. See, Ainsworth, C. *Org. Synth., Coll. Vol. IV* **1963**, 536 and Woodward, R. B.; Pachter, I. J.; Scheinbaum, M. L. *Org. Synth., Coll. Vol. VI* **1988**, 590. The following modified procedure was used: To a 1-L, three-necked, round-bottomed flask equipped with a septum inlet, mechanical stirrer, nitrogen inlet, and pressure-equalizing dropping funnel was added 3.0 g (92 mmol) of sodium hydride (obtained from Aldrich Chemical Company, Inc.). The mineral oil was removed from the sodium hydride by washing with hexane. Ether was added (250 mL) and the reaction mixture cooled to 0°C. A mixture of 14 g (77 mmol) of cyclododecanone (obtained from Aldrich Chemical Company, Inc.) and 6.8 mL (85 mmol) of ethyl formate (obtained from Aldrich Chemical Company, Inc., and distilled from phosphorus pentoxide) in 75 mL of ether was added through the dropping funnel over 45 min. Next, 4 mL of methanol was cautiously added. After 30 min the reaction became heterogeneous. Further addition of 4 mL of methanol allowed stirring to take place. The reaction mixture was then stirred for 4 hr at 0°C. The cooling bath was removed and stirring was continued for 8 hr at 23°C. The reaction was worked up by collecting the light yellow solid and dissolving it in 150 mL of water. The aqueous layer was washed once with ether to remove unreacted ketone and residual mineral oil. Careful acidification with 1 N hydrochloric acid to pH 6 was followed by extraction with ether (6 × 50 mL). The ether extracts were washed with brine (2 × 50 mL), dried ($MgSO_4$) and concentrated to produce 11.5 g of the hydroxymethylene ketone, which was used in the next step without purification. The spectrum was as follows: ^1H NMR (300 MHz, $CDCl_3$) δ: 1.30–1.39 (m, 12 H), 1.50–1.58 (br m, 2 H), 1.78–1.80 (br m, 2 H), 2.26 (t, 2 H, J = 6.9), 2.35 (t, 2 H, J = 7.5), 8.58 (d, 1 H, J = 3.6).

5. Chlorotrimethylsilane (obtained from Aldrich Chemical Company, Inc.) and triethylamine (obtained from Aldrich Chemical Company, Inc.) were mixed in equal volumes in dry, stoppered tubes. These were centrifuged briefly and the supernatant was transferred through a septum by syringe.

6. A suitable cannula was made by filing the ends of a 45-cm long aluminum tube of 2-mm internal diameter to points.

7. Reagent grade toluene (obtained from Fisher Scientific Company) was degassed with a nitrogen stream.

8. The reaction was most easily monitored by noting the disappearance of the highly uv absorbing unsaturated aldehyde intermediate at R_f = 0.41 (20% ethyl acetate in hexane eluant).

9. The physical properties are as follows: ^1H NMR (300 MHz, $CDCl_3$) δ: 1.39–1.44 (m, 8 H), 1.51–1.54 (m, 4 H), 1.65–1.76 (m, 4 H), 2.29 (s, 3 H), 2.62 (t, 4 H, J = 7.5), 6.93–7.09 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 20.95, 22.84, 22.85, 25.54 (two peaks overlap), 26.25, 26.30, 28.93, 29.29, 29.89, 29.98, 126.52, 129.45, 130.21, 134.91, 137.86, 140.74; IR (neat) cm^{-1}: 2940, 2880, 1510, 1475, 1450, 830, 810; mass spectrum m/e 230 (M^+, 82%), 215 (4%), 173

(8%), 159 (20%), 145 (50%), 119 (100%), 105 (42%), 91 (20%), 40 (37%).

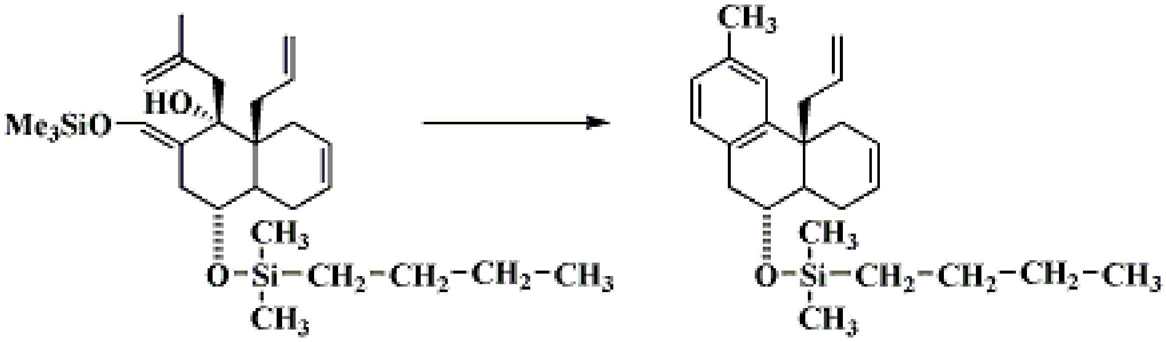
Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

This preparation describes a highly practical and efficient method for the benzoannelation of ketones. The classical approach to the synthesis of aromatic compounds has been to start with a commercially available aromatic compound and make use of traditional substitution reactions in order to introduce appendages and functionality. This strategy has served well, but it is limiting for multistep organic synthesis because it normally requires that the aromatic substitution chemistry be carried out at the very beginning of a sequence. The method described here provides an alternative strategy in which a non-aromatic compound can serve as a precursor to an aromatic molecule.

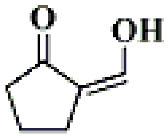
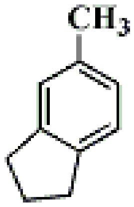
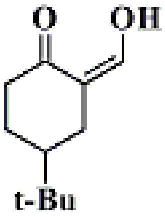
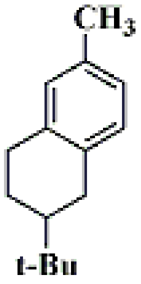
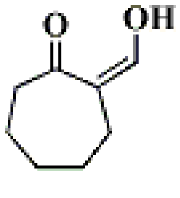
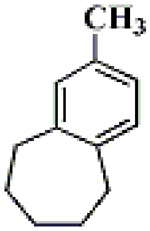
The present method is successful with a wide variety of ketones (see Table). Cyclic ketones (entries 1–4, 8) produce benzoannelated products in excellent overall yields. There is no need to purify the intermediate; both the nucleophilic addition of methallylmagnesium chloride and the aromatic cyclization take place cleanly. Acyclic ketones (entries 5–7) also provide high yields of benzoannelated product. Aromatic ketones are particularly interesting substrates for this reaction since they provide substituted biphenyls, which are potentially useful materials for liquid crystal synthesis and whose preparation through classical methodology is often not straightforward. The conditions for the cationic cyclization step can be modified to accommodate acid-sensitive functionality. For example, cyclization of **3** to **4**, the latter a precursor for 3-methyl-8,14-dehydromorphinan, was accomplished in 77% yield by treatment of **3** at 23°C for 12 hr with pyridinium tosylate in benzene.[2] This is an extraordinarily mild procedure for an aromatic annelation. The method is not limited to the preparation of methyl-substituted aromatics. By using benzylmagnesium bromide instead of methallyl Grignard reagent, a naphthalene can be appended onto the ketone.[3] Similarly, phenanthrenes[3] and m-terphenyls[4] can be obtained conveniently and in high yield. In the absence of a cation-stabilizing group at C-2 of the Grignard reagent, the yield for cyclization is diminished.[5] A similar effect has been noted in related work.[6] Unsubstituted, benzoannelated products are nevertheless accessible from cyclization of the adducts of [2-(trimethylsilyl)-2-propenyl]magnesium chloride.[5]

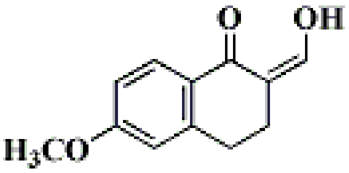
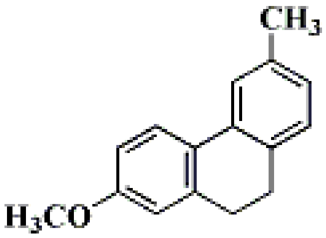
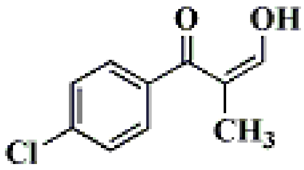
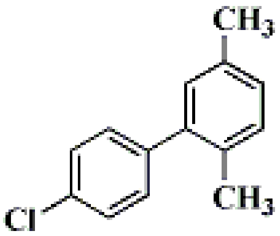
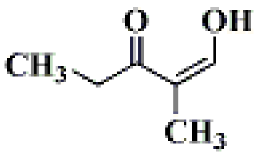
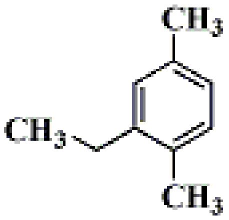
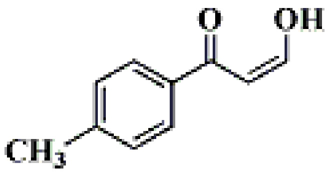
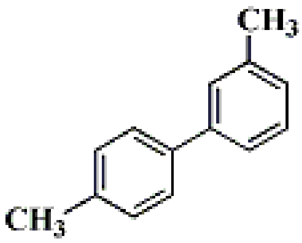
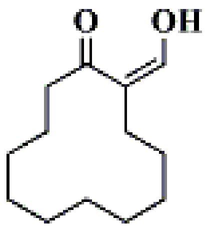
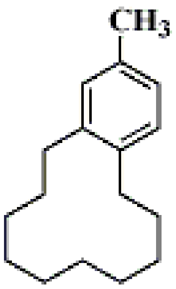


3 4

3 4

TABLE
BENZOANNELATION OFKETONES

Entry	2-Hydroxymethylene ketone	Product	Overall yield (%)
1			52[a]
2			76[b]
3			79[c]

4			74[d]
5			66[e]
6			89[f]
7			65[g]
8			86

Several related methods for benzoannelation have been reported.[7 8 9 10] Most provide aromatic sulfides or phenols that require additional manipulation. The present method provides convenient and highly efficient access to structurally diverse benzoannelated products. The ease of the reactions, the high yields, and the convenience recommend its use.

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

brine

sodium benzophenone ketyl

3,4-Cyclododeceno-1-methylbenzene

Tertiary alcohol

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether (60-29-7)

sodium bicarbonate (144-55-8)

magnesium, magnesium turnings (7439-95-4)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

toluene (108-88-3)

Naphthalene (91-20-3)

ethyl formate (109-94-4)

magnesium sulfate (7487-88-9)

benzylmagnesium bromide (1589-82-8)

sodium hydride (7646-69-7)

hexane (110-54-3)

triethylamine (121-44-8)

Triethylamine hydrochloride (554-68-7)

methallyl chloride (563-47-3)

cyclododecanone (830-13-7)

argon (7440-37-1)

CHLOROTRIMETHYLSILANE (75-77-4)

phosphorus pentoxide (1314-56-3)

p-toluenesulfonic acid monohydrate (6192-52-5)

Benzocyclododecene, 5,6,7,8,9,10,11,12,13,14-decahydro-2-methyl- (81857-28-5)

1-(2-Methylallyl)-2-(trimethylsiloxy)methylenecyclododecanol (155727-13-2)

2-(hydroxymethylene)cyclododecanone (949-07-5)

methallylmagnesium chloride

pyridinium tosylate

[2-(trimethylsilyl)-2-propenyl]magnesium chloride

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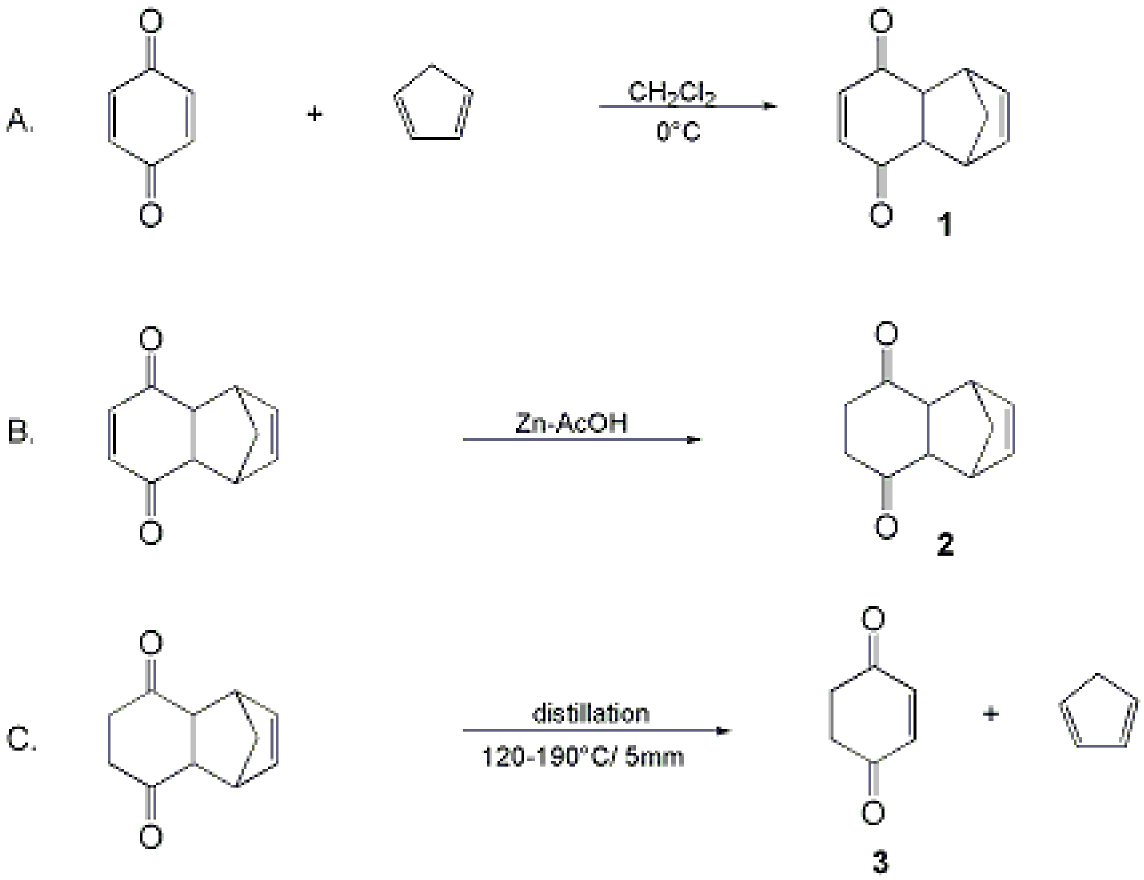
Organic Syntheses, CV 9, 186

2-CYCLOHEXENE-1,4-DIONE



Submitted by Masaji Oda, Takeshi Kawase, Tomoaki Okada, and Tetsuya Enomoto[1].
Checked by Kazushige Kajita and Amos B. Smith, III.

1. Procedure

A. *endo-Tricyclo[6.2.1.0^{2,7}]undeca-4,9-diene-3,6-dione* **1**. A 1-L, three-necked, round-bottomed flask, equipped with a mechanical stirrer, 100-mL pressure-equalizing dropping funnel, and a thermometer, is charged with 108.1 g (1.0 mol) of 1,4-benzoquinone (Note 1) and 350 mL of dichloromethane (Note 2). The flask is cooled to 0°C with an ice bath. Via the addition funnel, 41.5 mL of cyclopentadiene (34.2 g, 0.52 mol) (Note 3) is added dropwise over a 45-min period with stirring at such a rate that the internal temperature remains below 8°C (Note 4). A second 41.5-mL portion (34.2 g, 0.52 mol) of cyclopentadiene is added in a similar way (Note 5). The resulting mixture is stirred for 1 hr in the ice bath, for 0.5 hr at room temperature, and then is transferred to a 1-L, pear-shaped flask by rinsing with a small amount of dichloromethane. Most of the solvent is removed by rotary evaporation under reduced pressure, and 200 mL of hexane is added to the residue. The flask is cooled in an ice bath for 0.5 hr. The pale yellow solids are collected by suction filtration, washed with three 30-mL portions of hexane, and air-dried to afford 150–155 g of the Diels-Alder

adduct **1** (D-A adduct) of sufficient purity for use in the next step (Note 6). Concentration of the filtrate to about half the volume and cooling affords 12–15 g of a second crop of **1**. The combined yield of **1** is 164–169 g (94–97%).

B. *endo-Tricyclo[6.2.1.$0^{2,7}$]undec-9-ene-3,6-dione* **2**. A 3-L, three-necked, round-bottomed flask, equipped with a mechanical stirrer, thermometer, and heating mantle, is charged with 166 g (0.95 mol) of the crude D-A adduct 1 and 1.3 L of acetic acid (Note 7). Portionwise, 228.8 g (3.5 mol) of zinc dust (Note 8) is added to the mixture with stirring. The temperature rises to about 70°C over a 10-min period and then drops. The resulting mixture is then heated at 70–80°C for 1 hr, followed by addition of a further 32.7 g (0.5 mol) of zinc powder and continued heating and stirring for an additional 1.5 hr. After the mixture has cooled to room temperature, the gray solids are collected by suction filtration, and washed with 200 mL of acetic acid (Note 9). The dark yellowish filtrate is then concentrated by rotary evaporation under reduced pressure (Note 10), the residue diluted with 600 mL of water, and the resulting mixture extracted with three 300-mL portions of toluene (Note 11). The combined toluene extracts are washed with two 100-mL portions of water, 100 mL of aqueous 10% sodium hydroxide solution, two 100-mL portions of brine, and dried over sodium sulfate, and filtered into a 500-mL round-bottomed flask. Removal of the solvent by rotary evaporation under reduced pressure yields 148–155 g of crude diketone **2**, sufficiently pure for further transformation, as a reddish liquid that solidifies on cooling (Note 12).

C. *2-Cyclohexene-1,4-dione* **3** (Note 13) and (Note 14). The 500-mL, round-bottomed flask containing 150 g of crude diketone 2 from Part B is equipped with a magnetic stirring bar and fitted with a Claisen-type short path distillation head leading to a condenser and a 200-mL, round-bottomed receiver. Two cold traps are placed between the receiver and a vacuum pump. The first trap is cooled in a dry ice-ethanol bath and the second trap in liquid nitrogen (Note 15). The system is evacuated and the distillation pot is placed in an oil bath and heated rapidly to 140–180°C with magnetic stirring, whereupon diketone **2** distills fairly rapidly into the receiver to afford a mixture of diketone **2** and 2-cyclohexene-1,4-dione **3**, bp 80–140°C (most at 130–140°C) at 4–7 mm (bath temperature 140–180°C), as a pale yellow oil (Note 16), (Note 17) and (Note 18).

The 200-mL, round-bottomed receiver, containing a mixture of diketone **2** and 2-cyclohexene-1,4-dione **3**, is then fitted with a long path (25 cm) distillation head packed with Pyrex glass helices or chips, an air condenser (25 cm), and a 200-mL, two-necked, round-bottomed receiver with one neck connected to the vacuum pump via the traps described earlier. The distillation pot is placed in an oil bath, the system is evacuated, and the receiver is immersed in an ice bath. The bath is heated to 120°C and the mixture of diketone **2** and 2-cyclohexene-1,4-dione **3** is redistilled at 4–8 mm while the bath temperature is gradually increased from 120°C to 190°C. Early in the distillation, the enedione **3**, which is already present, distills smoothly, then the rate of dissociation of **2** becomes rate-determining. The bath temperature is maintained at 180–190°C so as to keep the boiling point nearly constant (87°C/6 mm). Care is taken

to assure that any enedione **3** that crystallizes in the condenser or receiver is quickly melted with an efficient heat gun to avoid occlusion of the distillation path (Note 19). A total of 73–80 g of crude yellow solid enedione **3** is obtained containing a small amount of diketone **2**.

The resulting crude solid enedione **3** is melted at 60–70°C in a water bath and 35 mL of carbon tetrachloride is added (Note 20). The mixture is cooled in an ice bath, 18 mL of hexane is added (Note 21), and the resulting mixture is gently stirred with a glass rod. After cooling for 20–30 min, the resulting pale yellow crystals are collected by suction filtration, washed with 20–30 mL of a cold mixture of carbon tetrachloride and hexane (1:1 v/v), and then with 40 mL of hexane. Brief air drying affords 65–71 g of almost pure enedione **3**, mp 54–54.5°C (Note 21) and (Note 22). Concentration of the filtrate to about 15 mL, addition of 8 mL of hexane, and cooling the mixture furnishes a further 1.5–2.5 g of **3**. In total, 67.0–72.5 g (61–66% from 1,4-benzoquinone) of nearly pure **3** is obtained (Note 23), (Note 24) and (Note 25).

2. Notes

1. Reagent-grade 1,4-benzoquinone was purchased from Wako Pure Chemical Industries, LTD and was used without additional purification.
2. Dichloromethane was distilled from phosphorus pentoxide.
3. Cyclopentadiene is prepared according to the procedure in *Org. Synth., Coll. Vol. VII* **1990**, 339.
4. At higher temperatures, 1:2 adducts[2] between 1,4-benzoquinone and cyclopentadiene are formed as by-products. Separation of the 1:1 adduct and 1:2 adducts is not easy on a large scale. If the material is contaminated by a small amount of the 1:2 adduct, it is best to carry the procedure on to the last step (see (Note 23)).
5. Cyclopentadiene was added in two portions to minimize dimerization during warming to room temperature. If a dropping funnel with cooling jacket is available, it is not necessary to divide the cyclopentadiene into two portions.
6. Recrystallization of a portion of the product from hexane-dichloromethane furnishes pure **1**, mp 78–79°C which exhibits the following spectral data: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.39 (d, 1 H, J = 9), 1.51 (d, 1 H, J = 9), 3.19 (s(br), 2 H), 3.51 (s(br), 2 H), 6.03 (s(br), 2 H), 6.54 (s, 2 H); ^{13}C (125 MHz, $CDCl_3$) δ: 48.31, 48.69, 48.74, 135.26, 142.02, 199.39; IR ($CHCl_3$) cm^{-1}: 3000, 2940, 2870, 1675, 1604, 1450, 1335, 1295, 12.75, 1230, 1120, 1105, 1050, 990, 960, 940, 910, 855.
7. Commercial reagent grade acetic acid was used as purchased.
8. Commercial reagent grade zinc dust was used immediately after opening.
9. The gray solids should be added to water as soon as possible after filtration and washing; otherwise, the solids become hot, probably because of air oxidation.
10. Do not distil to dryness.

11. Diethyl ether may be substituted for toluene.

12. Crude diketone **2** may contain some toluene. Chromatography of a portion of the material on silica gel furnishes pure diketone **2**, mp 22°C which exhibits the following spectra data: ^1H NMR (500 MHz, $CDCl_3$) δ: 1.32 (d, 1 H, J = 8), 1.44 (d, 1 H, J = 8), 2.10–2.30 (m, 2 H), 2.50–2.60 (m, 2 H), 3.18 (s(br), 2 H), 3.42 (d, 2 H, J = 1.8), 6.14 (d, 2 H, J = 1.8); ^{13}C (125 MHz, $CDCl_3$) δ: 37.89, 47.38, 48.68, 51.77, 136.58, 209.48; IR ($CHCl_3$) cm^{-1}: 3000, 2940, 2865, 1710, 1415, 1330, 1250, 1220, 1150, 1100, 1050, 995, 895.

13. It is desirable that the following procedures be completed smoothly in one day to avoid possible isomerization of enedione **3** to hydroquinone. If two days are required, the distillate from the first distillation can be stored without change in a freezer in the dark.

14. All glassware used in these procedures should be free of acids or bases.

15. It is important that the first trap be of sufficient size to accommodate liberated cyclopentadiene.

16. A silicone oil bath was used for the pyrolytic distillations.

17. The ratio of diketone **2** to enedione **3** varies with the precise conditions of distillation with **2** being the major product.

18. Rapid distillation serves to eliminate possible contamination of diketone **2** with trace amounts of acids or bases.

19. Toward the end of the pyrolytic distillation enedione **3** often crystallizes on the walls of the distillation head and condenser.

20. Spectrophotometric grade carbon tetrachloride was used without causing isomerization of enedione **3** to hydroquinone.

21. Enedione **3** crystallizes fairly rapidly; stirring controls the crystal size to some extent. Since enedione **3** sublimes easily, drying under reduced pressure is not appropriate.

22. Pure enedione **3** has the following spectral data: ^1H NMR (500 MHz, $CDCl_3$) δ: 2.84 (s, 4 H), 6.66 (s, 2 H); ^{13}C (125 MHz, $CDCl_3$) δ: 36.52, 141.05, 197.21; IR ($CHCl_3$) cm^{-1}: 3020, 2970, 2905, 1690, 1600, 1420, 1370, 1300, 1280, 1225, 1140, 1095, 1000, 985, 935, 845.

23. If D-A adduct **1** contains some 1:2 adducts as impurities, 1,4-benzoquinone is formed by a retro-Diels-Alder reaction during the pyrolytic distillations. In this case, a dark yellow solid of benzoquinone can be seen on the walls of the air condenser, and the distillate has a deeper yellow color. Contamination with a small amount of 1,4-benzoquinone apparently does not interfere with photochemical [2+2] cycloadditions of enedione **3** with alkenes and alkynes, an important application of **3**. Fractional distillation of the benzoquinone-contaminated **3** as described for the second distillation of **3** can remove the benzoquinone with some loss of enedione **3**. The benzoquinone deposits initially as a dark yellow solid on the walls of the distillation head and air condenser during early fractions.

24. Enedione **3** as a crystalline solid can be stored indefinitely below 0°C in a glass container in the dark.

25. Experiments starting from 1.5 mol of 1,4-benzoquinone gave similar results.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

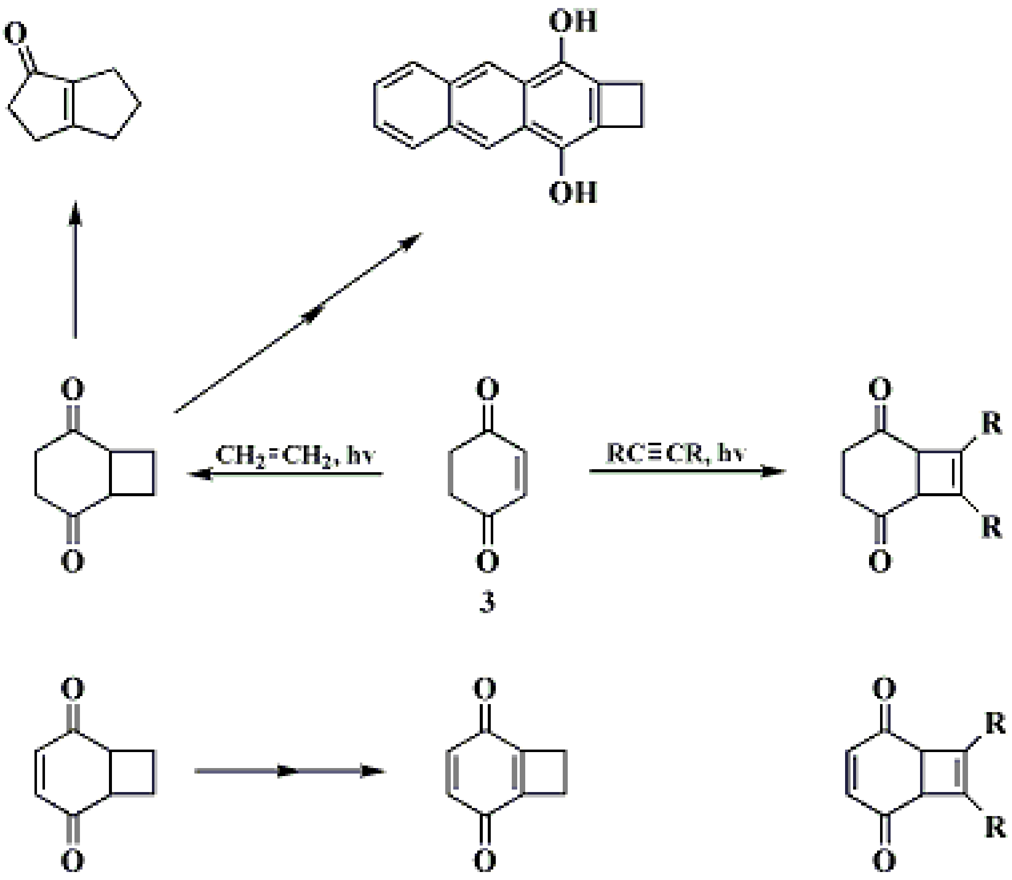
3. Discussion

2-Cyclohexene-1,4-dione **3** was first synthesized by careful acid hydrolysis of its monoacetal.[3] Because of the high sensitivity of **3** to acids and bases, this method is not suitable for large-scale preparations. The present method is essentially identical to that reported by Chapman, et al.,[4] with modifications for large-scale and minimal solvent use. Alkyl substituted 2-cyclohexene-1,4-diones can be prepared similarly.[4]

The 1,4-benzoquinone-cyclopentadiene Diels-Alder adduct **2** is well known.[5] The procedure described here is adapted for large-scale preparation. For the zinc reduction, aqueous acetic acid has also been used.[4] The present procedure allows recovery of most of the acetic acid. The entire procedure can be completed in 3–4 days.

The most useful application of **3** is its use in photochemical [2+2] cycloadditions with alkenes and alkynes at the carbon-carbon double bond to afford bicyclo[4.2.0]octane-2,5-diones and bicyclo[4.2.0]oct-7-ene-2,5-diones in good to excellent yield.[6] Since selenium dioxide oxidation of the resulting adducts furnishes the corresponding 3-ene-2,5-diones, diketone **3** can be regarded as a 1,4-benzoquinone equivalent leading to [2+2] cycloadducts at the carbon-carbon double bond.

Some typical applications are shown below.[6,7]



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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

endo-Tricyclo[6.2.1.0^{2,7}]undeca-4,9-diene-3,6-dione

brine

1,4-benzoquinone-cyclopentadiene

acetic acid (64-19-7)

diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium sulfate (7757-82-6)

carbon tetrachloride (56-23-5)

nitrogen (7727-37-9)

selenium dioxide (7446-08-4)

toluene (108-88-3)

zinc, zinc powder (7440-66-6)

1,4-benzoquinone, benzoquinone (106-51-4)

dichloromethane (75-09-2)

hexane (110-54-3)

CYCLOPENTADIENE (542-92-7)

phosphorus pentoxide (1314-56-3)

2-Cyclohexene-1,4-dione (4505-38-8)

endo-Tricyclo[6.2.1.$0^{2,7}$]undec-9-ene-3,6-dione (21428-54-6)

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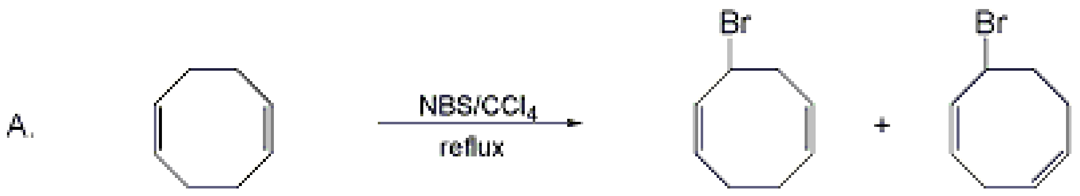
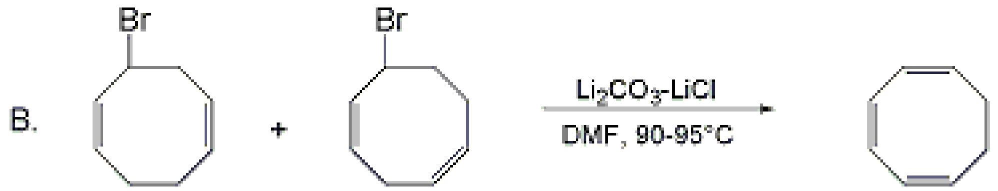
Organic Syntheses, CV 9, 191

1,3,5-CYCLOOCTATRIENE





Submitted by Masaji Oda, Takeshi Kawase, and Hiroyuki Kurata[1].
Checked by Daniel V. Paone and Amos B. Smith, III.

1. Procedure

CAUTION. The handling of carbon tetrachloride must be done in a well-ventilated hood using glass. It must be disposed of properly. See Waste Disposal Information.

A. *Allylic bromination of 1,5-cyclooctadiene*. A 2-L, three-necked, round-bottomed flask, equipped with a mechanical stirrer, reflux condenser, and a heating mantle, is charged with 216.4 g (2.0 mol) of 1,5-cyclooctadiene (Note 1), 44.5 g (0.25 mol) of N-bromosuccinimide (NBS), 0.5 g of benzoyl peroxide, and 700 mL of carbon tetrachloride. The mixture is heated to gentle reflux with stirring. When the reaction starts, a rapid reflux is observed. Three more 44.5-g portions (0.25 mol) of NBS are added at 30-min intervals (total 178 g, 1.0 mol). Heating is continued for 1.5 hr after addition of the final portion of NBS. The mixture is cooled to room temperature and suction filtered and the filter cake is washed with 150 mL of carbon tetrachloride (Note 2). The filtrate is washed once with 150 mL of water, dried over calcium chloride, and filtered with suction. A vacuum distillation apparatus consisting of a 500-mL, two-necked, round-bottomed flask, a stoppered pressure-equalizing dropping funnel, a distilling head (25 cm long) packed with Pyrex glass tips or helices, a condenser, and receivers is assembled (Note 3). The dried carbon tetrachloride solution is transferred to the dropping funnel, the system is evacuated to 150 mm, and the solution is introduced continuously from the dropping funnel resulting in removal of the bulk of the solvent (Note 4). The pale yellow residue is then fractionally distilled first at 30 mm to remove the unreacted 1,5-cyclooctadiene (Note 5), and then at 5 mm to distill the bromocyclooctadienes to give 113–121 g (60–65%) of a mixture

of 3-bromo-1,5-cyclooctadiene and 6-bromo-1,4-cyclooctadiene,[2] bp 66–69°C at 5 mm (Note 6),(Note 7),(Note 8).

B. *1,3,5-Cyclooctatriene*. A 1-L, three-necked, round-bottomed flask, equipped with a magnetic stirring bar, pressure-equalizing dropping funnel, immersion thermometer, and a condenser bearing a gas inlet vented through a mineral oil bubbler, is charged with 25.9 g (0.35 mol) of lithium carbonate, 2.0 g (0.047 mol) of lithium chloride (Note 9), and 400 mL of dry dimethylformamide (DMF) (Note 10). The magnetically stirred mixture is heated to 90°C in an oil bath (Note 11) and 113.5 g (0.607 mol) of the bromocyclooctadiene mixture (Part A) is added dropwise via the dropping funnel over 50 min. During the addition, rapid evolution of gas (carbon dioxide) is observed via the bubbler. After completion of the addition, heating is continued for 1 hr at 90–95°C. The mixture is cooled to room temperature, diluted with 1 L of ice water, and the mixture extracted twice with 200-mL portions of pentane. The combined organic phase is washed twice with 100-mL portions of water, dried over sodium sulfate, and filtered. The filtrate is distilled at atmospheric pressure to remove the pentane, and the residue is distilled under reduced pressure, employing a short (12 cm) Vigreux column, to give 54–58 g (84–90%) of almost pure 1,3,5-cyclooctatriene, bp 63–65°C at 48 mm (Note 12).

2. Notes

1. All reagents and solvents are commercially available and are used without further purification.
2. The solids consisted of 94.0 g of succinimide (0.95 mol, 95% of theoretical).
3. The distillation system was connected to a closed-tube manometer and a Cartesian diver-type pressure regulator employed to control the pressure.
4. When a rotary evaporator was used for the concentration, the recovery of 1,5-cyclooctadiene decreased substantially.
5. Approximately 88.5 g (0.82 mol, 82% of theoretical) of 1,5-cyclooctadiene, bp 55–57°C at 30 mm, is recovered and can be recycled.
6. Care must be taken during fractionation of 1,5-cyclooctadiene and the bromocyclooctadienes, because contamination of the bromide with 1,5-cyclooctadiene leads to contamination of 1,3,5-cyclooctatriene with the diene. A 1–2-mL intermediate fraction effects clean separation. The distillation took the checkers 6–8 hr. The bromides are extremely light sensitive, turning yellow to red-brown quickly. To avoid product coloration all product receiving flasks were wrapped in aluminum foil.
7. When NBS was added in two portions instead of four, the yield of bromocyclooctadienes decreased slightly to 60%. A preparation using 500 g (2.80 mol) of NBS (five-portion addition) gave a higher yield (78%).
8. The spectral data for the mixture of bromocyclooctadienes is as follows: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.7–3.4 (m, 12 H), 4.6–5.25 (m, 2 H), 5.3–5.9 (m, 8 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 25.0, 27.7, 28.3, 28.7, 34.3, 36.8, 48.0,

49.9, 124.7, 127.0, 128.3, 128.8, 129.2, 130.4, 130.6, 131.7; IR (thin film) cm^{-1}: 3000, 2940, 2890, 2820, 1640, 1480, 1450, 1440, 1420, 1220, 1150, 1140, 990, 910, 860, 805, 670.

9. Lithium carbonate and lithium chloride were dried under reduced pressure at 80–100°C for 3 hr before use.

10. DMF dried azeotropically with benzene is sufficient for the present reaction.

11. The checkers employed a heating mantle.

12. 1,3,5-Cyclooctatriene exists in equilibrium with bicyclo[4.2.0]octa-2,4-diene, its valence isomer (ratio = 7:1).[3 4 5 6] 1,3,5-Cyclooctatriene exhibits the following spectral data: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.43 (s, 4 H), 5.50–6.00 (m, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 28.0, 125.9, 126.7, 135.5; IR (thin film) cm^{-1}: 3000, 2920, 2875, 2830, 1635, 1605, 1445, 1425, 1220, 690, 635. Signals for the minor valence isomer may be observed. No signals for 1,3,6-cyclooctatriene, another possible isomer, are observed.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Mixtures of 1,3,5- and 1,3,6-cyclooctatriene were obtained by partial reduction of cyclooctatetraene in ways such as protonation of cyclooctatetraene dianion[6,7] and reduction with zinc-alkali.[2,8] 1,3,6-Cyclooctatriene is the major product in these reductions. However, since 1,3,6-cyclooctatriene isomerizes to 1,3,5-cyclooctatriene on treatment with base, quenching cyclooctatetraene dianion with methanol and subsequent heating affords 1,3,5-cyclooctatriene in an 80% yield.[6] Reduction of cyclooctatetraene with sodium hydrazide and hydrazine also produces 1,3,5-cyclooctatriene.[9] Therefore, when cyclooctatetraene is available in quantity, these procedures are the methods of choice.

The present two-step procedure for the synthesis of 1,3,5-cyclooctatriene uses commercially available 1,5-cyclooctadienes as starting material. Although allylic bromination of 1,5-cyclooctadiene with N-bromosuccinimide produces a mixture of 3-bromo-1,5-cyclooctadiene and 6-bromo-1,4-cyclooctadiene,[2] dehydrobromination of this mixture with LiCl-Li_2CO_3/DMF affords only 1,3,5-cyclooctatriene, which is in equilibrium with its valence isomer bicyclo[4.2.0]octa-2,4-diene.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

NBS

1,3,5- and 1,3,6-cyclooctatriene

LiCl

Li_2CO_3

calcium chloride (10043-52-4)

Benzene (71-43-2)

methanol (67-56-1)

bromide (24959-67-9)

sodium sulfate (7757-82-6)

carbon tetrachloride (56-23-5)

aluminum (7429-90-5)

carbon dioxide (124-38-9)

Pentane (109-66-0)

hydrazine (302-01-2)

benzoyl peroxide (94-36-0)

Succinimide (123-56-8)

dimethylformamide, DMF (68-12-2)

N-bromosuccinimide (128-08-5)

lithium carbonate (554-13-2)

Lithium chloride (7447-41-8)

1,5-cyclooctadiene

sodium hydrazide

1,3,5-Cyclooctatriene (1871-52-9)

cyclooctatetraene

3-Bromo-1,5-cyclooctadiene (23346-40-9)

6-Bromo-1,4-cyclooctadiene (23359-89-9)

bromocyclooctadiene

bicyclo[4.2.0]octa-2,4-diene

1,3,6-cyclooctatriene

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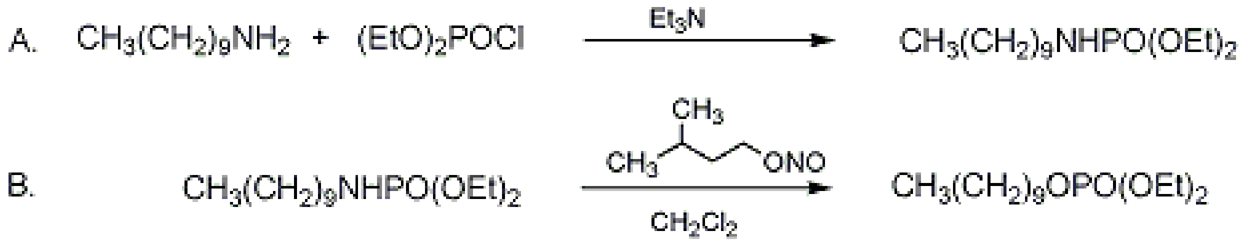
Organic Syntheses, CV 9, 194

CONVERSION OF AMINES TO PHOSPHO ESTERS: DECYL DIETHYL PHOSPHATE

[Phosphoric acid, decyl diethyl ester]



Submitted by Nick Nikolaides, Ioanna Schipor, and Bruce Ganem[1].
Checked by Susumu Saito and Hisashi Yamamoto.

1. Procedure

A. *Diethyl decylphosphoramidate.* An oven-dried (Note 1), three-necked, septum-capped, 250-mL, round-bottomed flask containing a 1-inch magnetic stirring bar is flushed with argon and charged with 10.0 mL (0.05 mol) of decylamine (Note 2) and 35 mL (0.25 mol) of triethylamine (Note 3). The solution is cooled to 0°C in an ice bath with stirring. Using a 10-mL, gas-tight syringe, 7.4 mL (0.05 mol) of diethyl chlorophosphate (Note 4) is added dropwise, whereupon a voluminous white precipitate forms. Upon completion of addition, vigorous stirring is maintained for 30 min at 0°C. The mixture is diluted with 100 mL of ice-cold, anhydrous diethyl ether (Note 5) and filtered through a sintered glass funnel (Note 6) layered with ca. 1 in. of Celite. The solid residue is washed with ca. 50 mL of fresh, cold ether, and the filtrate is concentrated by rotary evaporation (room temperature under aspirator pressure) to give a cloudy white suspension. Another aliquot of cold ether (50 mL) is added and the process of filtration through Celite is repeated at least three times (Note 7). Concentration by rotary evaporation followed by drying under reduced pressure for 1 hr at 0.1 mm provides 14.0–14.5 g (95–99% yield) of a clear, pale yellow oil (Note 8) . This compound is stored under argon until used in part B.

B. *Decyl diethyl phosphate.* An oven-dried (Note 1), three-necked, septum-capped, 250-mL, round-bottomed flask containing a 1-in. magnetic stirring bar is flushed with argon and charged with 14 g (0.048 mol) of diethyl decylphosphoramidate and 125 mL of dichloromethane (Note 9). Using a 20-mL gas-tight syringe, 31.9 mL (0.24 mol) of isoamyl nitrite (Note 10) is added successively in two portions (20 mL, 11.9 mL) at 33°C (oil bath) and stirring is continued for 18 hr. At this time, nitrogen evolution is no longer observed and thin layer chromatography (eluting with 3:2 hexanes:ethyl acetate, (Note 11)) indicates the complete disappearance of starting phosphoramidate (R_f = 0.1) and the appearance of a major product spot (R_f = 0.3). The

solvent is removed by rotary evaporation (40–50°C under aspirator pressure) to produce 17 g (>100%) of a viscous yellow oil that still contains traces of isoamyl nitrite and other impurities. The crude product is redissolved in 20 mL of ethyl acetate, loaded onto a 1" × 6" column of Silica Gel 60 (Note 12) and eluted under pressure (Note 13) with 150 mL of ethyl acetate into a 500-mL, round-bottomed flask. The solvent is removed by rotary evaporation (room temperature under aspirator pressure), the product is transferred to an ammonia-washed (Note 14), oven-dried, 50-mL, round-bottomed flask and distilled under vacuum to yield 7.7–8.8 g (54–60%) of the phospho triester as a clear, colorless oil (bp 95–105°C/0.15 mm) (Note 15) and (Note 16)).

2. Notes

1. All glassware was oven-dried for at least 24 hr at 130°C, assembled hot, and cooled under a stream of argon.[2]
2. Decylamine was obtained from Aldrich Chemical Company, Inc., and was distilled under reduced pressure prior to use (bp 70°C at 1.9 mm).
3. Reagent grade triethylamine was obtained from Mallinckrodt Inc. and distilled from barium oxide immediately prior to use (bp 87°C at 1 atm).
4. Diethyl chlorophosphate (97%) was obtained from Aldrich Chemical Company, Inc., and distilled before use (bp 58–60°C at 2 mm). This material is a highly toxic acetylcholinesterase inhibitor and must be handled with caution.
5. Diethyl ether was distilled from sodium benzophenone ketyl immediately before use.
6. A grade D (10–20 m) sintered glass funnel from Ace Glass Corporation was used.
7. Insufficient filtrations led to solid precipitates after rotary evaporation.
8. The product exhibits the following spectral properties: IR (film) cm^{-1}: 3220, 2970, 2880, 1470, 1240, 1060, 1040; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.78 (t, 3 H, J = 6.4, CH_3), 1.17–1.25 (m, 20 H, -$[CH_2]_7$ -OCH_2CH_3), 1.39 (m, 2 H, CH_2CH_2N), 2.79 (m, 3 H, NH, CH_2N), 3.96 (m, 4 H, OCH_2CH_3); CIMS (isobutane) m/z 294 (M+1, 100%).
9. Dichloromethane was dried and distilled over calcium hydride immediately prior to use.
10. Isoamyl nitrite (97%) was obtained from either Aldrich Chemical Company, Inc., or Fluka AG and used without further purification. Five equivalents of isoamyl nitrite were optimal for complete consumption of starting phosphoramidate. Use of three equivalents of isoamyl nitrite necessitated much longer reaction times (2–3 days) and resulted in incomplete conversions.
11. ACS reagent grade hexanes and ethyl acetate were obtained from Aldrich Chemical Company, Inc. Thin layer chromatography was performed on Silica Gel 60 F-254 precoated plates. Chromatograms were visualized with phosphomolybdic acid reagent from Aldrich Chemical Company, Inc.
12. Silica Gel 60 (230–400 mesh) was obtained from Merck & Company, Inc.
13. The published procedure of flash chromatography was employed.[3]

14. The distillation flask was rinsed with 28% ammonium hydroxide solution to neutralize the acidic glass surface, then placed directly in the oven (i.e., with no aqueous rinse).
15. The product exhibits the following spectral properties: IR (film) cm^{-1}: 2940, 2860, 1470, 1395, 1275, 1040, 755; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.82 (t, 3 H, J = 6.8, CH_3), 1.24–1.33 (m, 20 H, $-[CH_2]_7$, $-OCH_2CH_3$), 1.63 (m, 2 H, CH_2CH_2OP), 3.96–4.13 (m, 6 H, OCH_2-); CIMS (isobutane) m/z 295 (M+1, 50%), 155 (100%).
16. The checkers isolated decyl isoamyl ether as a side-reaction product in 2.0–2.3 g (18–20%) yield. This product exhibits the following spectral properties: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.80–1.05 (m, 9 H, $C[CH_3]_2$, $-CH_3$), 1.12–1.80 (m, 19 H, $[CH_2]_8$, -OC $-CH_2CH$), 3.41 (q, 4 H, J = 6.6, OCH_2); (bp 80–85°C/0.5 mm).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Phospho esters are important components of nucleic acids, lipids, and other biologically significant substances. Most existing phospho ester syntheses rely on the direct phosphorylation of alcohols.[4] Here, a general procedure for the conversion of amines into phospho esters is described,[5] based on the well-known thermal decomposition of N-nitroso carboxamides to carboxylic esters, that represents one of the few useful synthetic methods for replacing an amine group with oxygen-based functionality.[6,7 8 9,10 11 12 13] Besides complementing existing methods for synthesizing phospho triesters, the nitrosation of phosphoramidates makes available unnatural phosphates derived from naturally-occurring amino sugars, alkaloids, and amino acids. Phospho monoesters may similarly be prepared by hydrogenolysis of the corresponding alkyl dibenzyl phosphates.[14]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hexanes

sodium benzophenone ketyl

ethyl acetate (141-78-6)

ether, diethyl ether (60-29-7)

barium oxide

nitrogen (7727-37-9)

ammonium hydroxide (1336-21-6)

dichloromethane (75-09-2)

Isoamyl nitrite (110-46-3)

decylamine (2016-57-1)

triethylamine (121-44-8)

calcium hydride (7789-78-8)

argon (7440-37-1)

diethyl chlorophosphate (814-49-3)

phosphomolybdic acid (51429-74-4)

Decyl diethyl phosphate, Phosphoric acid, decyl diethyl ester (20195-16-8)

Diethyl decylphosphoramidate (53246-96-1)

decyl isoamyl ether

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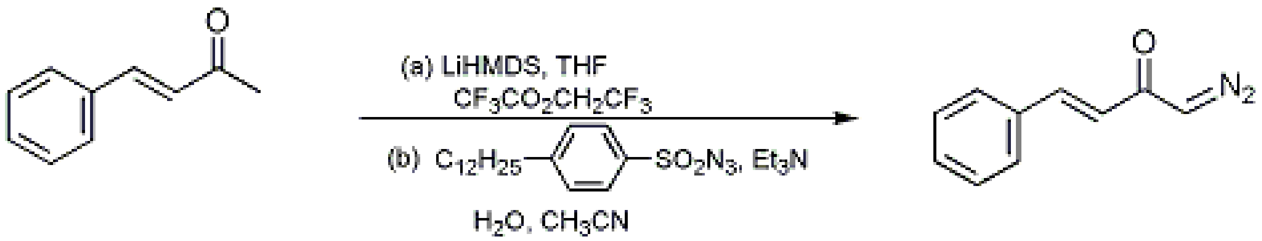
DETRIFLUOROACETYLATIVE DIAZO GROUP TRANSFER: (E)-1-DIAZO-4-PHENYL-3-BUTEN-2-ONE

[3-Buten-2-one, 1-diazo-4-phenyl-]



Submitted by Rick L. Danheiser, Raymond F. Miller, and Ronald G. Brisbois[1].
Checked by Cameron Clark and Stephen F. Martin.

1. Procedure

Caution! Diazo compounds are presumed to be toxic and potentially explosive and therefore should be handled with caution in a fume hood. Although in carrying out this reaction numerous times we have never observed an explosion, we recommend that this preparation be conducted behind a safety shield.

A 500-mL, three-necked, round-bottomed flask is equipped with a mechanical stirrer, nitrogen inlet adapter, and 150-mL pressure-equalizing dropping funnel fitted with a rubber septum (Note 1). The flask is charged with 70 mL of dry tetrahydrofuran (Note 2) and 15.9 mL (0.075 mol) of 1,1,1,3,3,3-hexamethyldisilazane (Note 3), and then cooled in an ice-water bath while 28.8 mL (0.072 mol) of a 2.50 M solution of butyllithium in hexane (Note 4) is added dropwise over 5–10 min. After 10 min, the resulting solution is cooled at –78°C in a dry ice-acetone bath, and a solution of 10.0 g (0.068 mol) of trans-4-phenyl-3-buten-2-one (Note 5) in 70 mL of dry tetrahydrofuran is added dropwise over 25 min. The dropping funnel is washed with two 5-mL portions of tetrahydrofuran and then replaced with a rubber septum. The yellow reaction mixture is allowed to stir for 30 min at –78°C, and then 10.1 mL (0.075 mol) of 2,2,2-trifluoroethyl trifluoroacetate (TFEA, (Note 6)) is added rapidly in one portion via syringe (over 5 sec). After 10 min, the reaction mixture is poured into a 1-L separatory funnel containing 100 mL of diethyl ether and 200 mL of 5% aqueous hydrochloric acid. The aqueous layer is separated and extracted with 50 mL of diethyl ether. The combined organic layers are washed with 200 mL of saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure using a rotary evaporator to afford 18.61 g of a yellow oil. This yellow oil is immediately dissolved in 70 mL of acetonitrile (Note 7) and transferred to a 500-mL, one-necked flask equipped with a magnetic stirring bar and a 150-mL pressure equalizing dropping funnel fitted with a nitrogen inlet adapter. Water (1.2 mL,

0.069 mol), triethylamine (14.3 mL, 0.103 mol) (Note 8), and a solution of 4-dodecylbenzenesulfonyl azide[2] (35.74 g, 0.103 mol) (Note 9) in 10 mL of acetonitrile are then sequentially added (each over 1–2 min) via the dropping funnel. The resulting yellow solution is allowed to stir at room temperature for 6.5 hr and then is poured into a 1-L separatory funnel containing 100 mL of diethyl ether and 200 mL of aqueous 5% sodium hydroxide (NaOH). The organic layer is separated, washed successively with three 200-mL portions of 5% aq NaOH, four 200-mL portions of water, 200 mL of saturated sodium chloride, dried over anhydrous sodium sulfate, filtered, and concentrated at reduced pressure using a rotary evaporator to yield 23.17 g of crude reaction product as a light brown oil. The crude reaction product is purified by column chromatography on 230–400 mesh silica gel (30 times by weight, elution with 5–10% diethyl ether-hexane) to furnish 9.54–9.80 g (81–83%) of (E)-1-diazo-4-phenyl-3-buten-2-one (mp 68–69°C) as a bright yellow solid (Note 10), (Note 11)).

2. Notes

1. The apparatus is flame-dried under reduced pressure and then maintained under an atmosphere of nitrogen during the course of the reaction.
2. Tetrahydrofuran was distilled from sodium benzophenone ketyl immediately before use.
3. 1,1,1,3,3,3-Hexamethyldisilazane was purchased from Aldrich Chemical Company, Inc., and was distilled from calcium hydride prior to use.
4. Butyllithium was purchased from Aldrich Chemical Company, Inc., and was titrated prior to use according to the the method of Watson and Eastham.[3]
5. trans-4-Phenyl-3-buten-2-one was purchased from Aldrich Chemical Company, Inc., and used without further purification.
6. 2,2,2-Trifluoroethyl trifluoroacetate was purchased from Aldrich Chemical Company, Inc., and used without further purification.
7. Acetonitrile was distilled from calcium hydride immediately prior to use.
8. Triethylamine was purchased from Fisher Chemical Company and distilled from calcium hydride before use.
9. The submitters originally used methanesulfonyl azide,[4 5 6] but the Board of Editors of *Organic Syntheses* requested substitution of the much less shock sensitive reagent 4-dodecylbenzenesulfonyl azide. The use of methanesulfonyl azide has previously been recommended,[4] since excess reagent as well as certain formamide by-products can be easily separated from the desired diazo ketone product during workup by extraction into dilute aqueous base.
10. The product has the following spectral properties: IR (CCl_4) cm^{-1}: 3150–3000, 2090, 1645, 1600, 1445, 1360, 1180, 1140, 1095, 1070, 970, 690; ^1H NMR (300 MHz, $CDCl_3$) δ: 5.54 (s, 1 H), 6.60 (d, 1 H, J = 15.8), 7.30–7.34 (m, 3 H), 7.46–7.49 (m, 2 H), 7.57 (d, 1 H, J = 15.8); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.8, 123.5, 127.8, 128.5, 129.9, 134.0, 140.1, 184.0; Anal. Calcd for $C_{10}H_8N_2O$: C, 69.76; H, 4.68; N, 16.27. Found: C, 69.65; H, 4.84; N, 16.32.

11. When 4-dodecylbenzenesulfonyl azide is used for the diazo transfer reaction, the crude reaction product is contaminated with by-products that cannot be separated during basic workup, and consequently column chromatography is required for the purification of the diazo ketone. Use of mesyl azide for the diazo transfer reaction allows purification of the crude reaction product by recrystallization from diethyl ether-pentane to obtain 10.11 g (86%) of the desired diazo ketone.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The importance of α-diazo ketones as synthetic intermediates has led to the development of a number of general methods for their preparation.[7 8] Particularly popular approaches include the acylation of diazo alkanes and the base-catalyzed "diazo group transfer" reaction of sulfonyl azides with β-dicarbonyl compounds.[9 10 11,12 13 14] While *direct* diazo transfer to ketone enolates is usually not a feasible process,[15,16]diazo transfer to simple ketones can be achieved in two steps by employing an indirect "deformylative diazo transfer" strategy in which the ketone is first formylated under Claisen condensation conditions, and then treated with a sulfonyl azide reagent such as p-toluenesulfonyl azide.[9,11,16,17 18 19 20,21 22,]

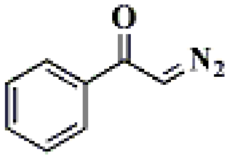
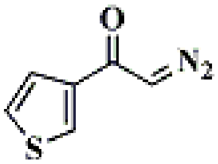
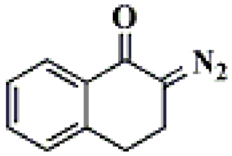
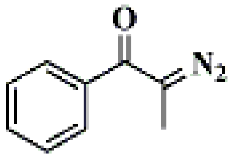
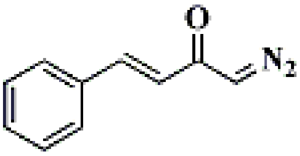
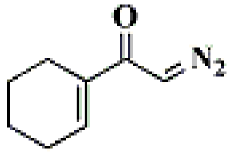
Unfortunately, several important classes of α-diazo ketones cannot be prepared in good yield via these standard methods. α'-Diazo derivatives of α,β-unsaturated ketones, for example, have previously proved to be particularly difficult to prepare.[22,23 24 25 26 27] The acylation of diazomethane with α,β-unsaturated acid chlorides and anhydrides is generally not a successful reaction because of the facility of dipolar cycloaddition to conjugated double bonds, which leads in this case to the formation of mixtures of isomeric pyrazolines. Also problematic are diazo transfer reactions involving base-sensitive substrates such as certain α,β-enones and heteroaryl ketones. Finally, the relatively harsh conditions and lack of regioselectivity associated with the thermodynamically controlled Claisen formylation step in the "deformylative" diazo transfer procedure limit the utility of this method when applied to the synthesis of diazo derivatives of many enones and unsymmetrical saturated ketones.

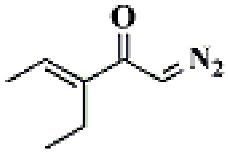
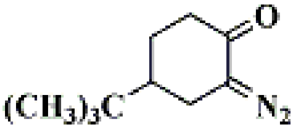
The *detrifluoroacetylative* diazo transfer procedure described here[28] is more general than the classical deformylative strategy, and as indicated in the Table, gives superior results when applied to a variety of ketone substrates. The new method has proved particularly valuable in the preparation of diazo derivatives of α,β-enones. In the case of saturated ketones such as 4-tert-butylcyclohexanone, both methods give comparable results, although the new procedure is more convenient to carry out, and has the advantage of providing a regioselective means of effecting diazo transfer to

unsymmetrical ketones.

TABLE

SYNTHESIS OF α-DIAZOKETONES

Entry	α-Diazo Ketone	Diazo Transfer Procedure[a] (Isolated Yield, %) via Formylation	via Trifluoroacetylation
1		73	95
2		57	92
3		56	81
4		71	63, 90[b]
5		17	83[c], 86
6		45	87

7		44	84
8		68	61

[a]Diazo transfer reactions were carried out using methanesulfonyl azide unless otherwise indicated. [b]The yield is corrected for recovered propiophenone. [c]4-Dodecylbenzenesulfonyl azide was employed for this diazo transfer reaction.

A key feature of the new procedure is the activation of the ketone starting material as the corresponding α-trifluoroacetyl derivative. To our knowledge, the use of TFEA to activate ketones in this fashion has not previously been reported, although Doyle has employed a similar strategy to achieve diazo transfer to a base sensitive N-acyloxazolidone derivative.[29] In our experience, TFEA has proved superior to other trifluoroacetylating agents [e.g. CF_3CO_2Et, $(CF_3CO)_2O$] for this transformation; the reaction of ketone enolates with this ester takes place essentially instantaneously at −78°C. By contrast, the formylation of ketone enolates with ethyl formate is usually carried out using sodium hydride or sodium ethoxide as base and generally requires 12 to 48 hr at room temperature for complete reaction.

Only one equivalent of base is required for the trifluoroacetylation step; apparently the chelated tetrahedral intermediate is stable at −78°C and the β-dicarbonyl product is not generated until workup. Crucial to the success of the trifluoroacetylation reaction in some cases is the selection of lithium hexamethyldisilazide (LiHMDS) for the generation of the ketone enolate; under otherwise identical conditions diazo transfer to several aryl ketones proceeds in dramatically reduced yield when lithium diisopropylamide is employed as base.

In summary, the method described here provides an efficient and convenient route to a variety of α-diazo ketones including unsaturated derivatives that were not previously available by diazo transfer. α-Diazo ketones serve as key intermediates in a number of important synthetic methods including the Arndt-Eistert homologation, the photo-Wolff ring contraction strategy, and the carbenoid-mediated cyclopropanation reaction. We anticipate that improved access to α-diazo ketones will serve to enhance the utility of these valuable synthetic strategies.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 322

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium benzophenone ketyl

lithium hexamethyldisilazide (LiHMDS)

hydrochloric acid (7647-01-0)

diethyl ether (60-29-7)

acetonitrile (75-05-8)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

Acetophenone (98-86-2)

sodium ethoxide (141-52-6)

ethyl formate (109-94-4)

lithium (7439-93-2)

benzyl (2154-56-5)

diazo

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

sodium hydride (7646-69-7)

hexane (110-54-3)

diethyl oxalate (95-92-1)

triethylamine (121-44-8)

calcium hydride (7789-78-8)

α-diazoacetophenone (3282-32-4)

diethyl ether-pentane

lithium diisopropylamide (4111-54-0)

4-tert-Butylcyclohexanone (98-53-3)

p-toluenesulfonyl azide (941-55-9)

diethyl ether-hexane

methanesulfonyl azide, mesyl azide

1,1,1,3,3,3-hexamethyldisilazane (999-97-3)

(E)-1-Diazo-4-phenyl-3-buten-2-one

3-Buten-2-one, 1-diazo-4-phenyl- (24265-71-2)

trans-4-phenyl-3-buten-2-one

2,2,2-trifluoroethyl trifluoroacetate (407-38-5)

4-Dodecylbenzenesulfonyl azide (79791-38-1)

2,4,6-triisopropylphenylsulfonyl azide (36982-84-0)

p-nitrobenzenesulfonyl azide

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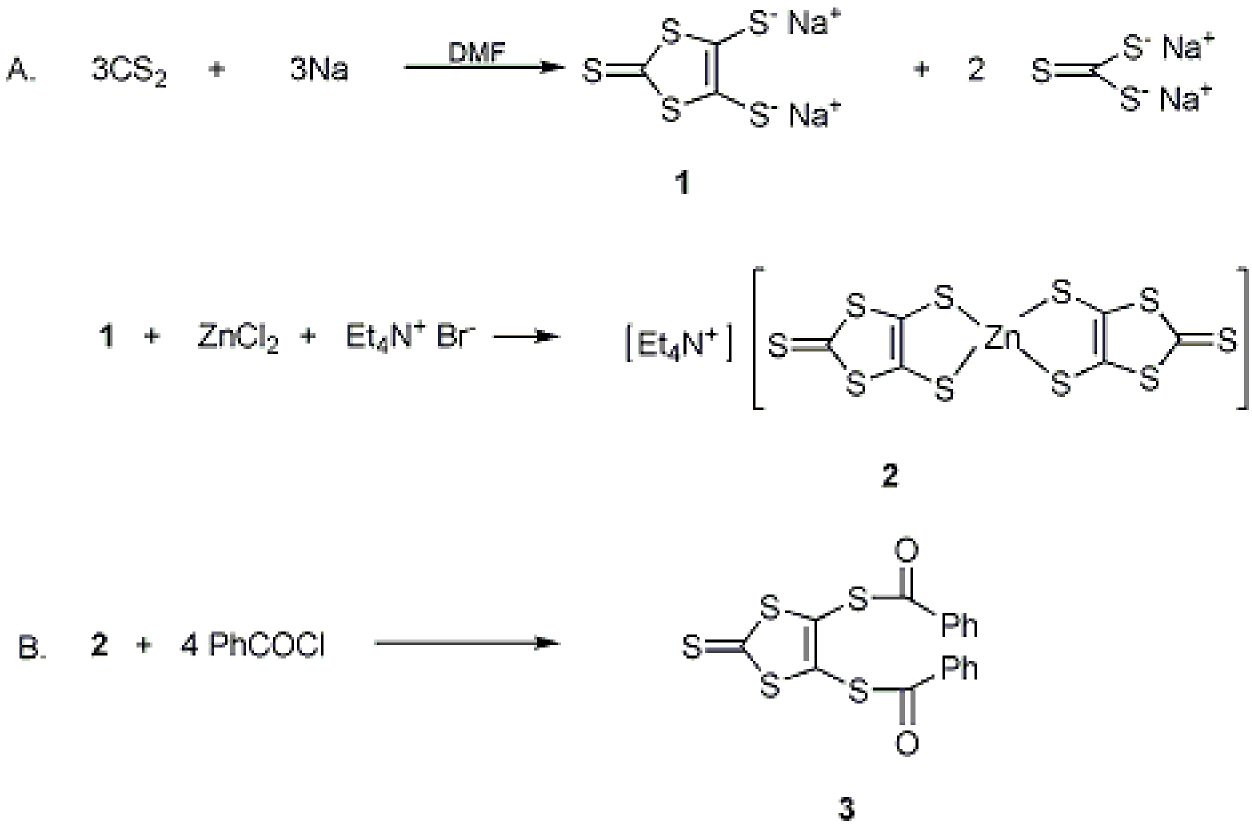
4,5-DIBENZOYL-1,3-DITHIOLE-1-THIONE

[Benzenecarbothioic acid, S,S'-(2-thioxo-1,3-dithiole-4,5-diyl) ester]



Submitted by Thomas K. Hansen[1], Jan Becher[1], Tine Jørgensen[1], K. Sukumar Varma[2], Rajesh Khedekar[3], and Michael P. Cava[3].
Checked by John Hynes and Amos B. Smith, III.

1. Procedure

CAUTION! The preparation should be carried out in an efficient hood, since carbon disulfide is both toxic and easily ignited.

A. *Tetraethylammonium bis(1,3-dithiole-2-thione-4,5-dithiol) zincate* **(2)**. An oven-dried (105°C for 6 hr) apparatus consisting of a 3-L, round-bottomed flask, equipped with a mechanical stirrer (Note 1), a 250-mL pressure-equalizing dropping funnel, and a gas inlet tube, is connected to nitrogen (N_2) via a Firestone valve (Note 2). To avoid water condensing on the surfaces, N_2 should be allowed to flow through the flask and out of the dropping funnel while the glassware is still hot. While the dropping funnel is temporarily removed, the flask is charged with 23.0 g of sodium shavings (1.0 mol) (Note 3) via a solids addition funnel (Note 4) and (Note 5) and, after reassembly, the apparatus is flushed with N_2 for 5 min and placed in an ice-water bath. Carbon

disulfide (CS_2, 180 mL, 3.0 mol) (Note 6) is introduced into the flask through the dropping funnel, after which the dropping funnel is immediately loaded with 200 mL of dimethylformamide (DMF) (Note 7), the system is closed, and the N_2 atmosphere is maintained throughout the reaction by adjusting the Firestone valve to a slightly positive pressure (Note 8). The DMF is added dropwise with stirring over 4 hr during which a red color appears (after addition of several mL of DMF). During the addition, the temperature of the reaction mixture is maintained with ice-water cooling. Upon completion of the addition, the reaction mixture is allowed to warm to room temperature and stir overnight, during which time it becomes increasingly deep red/violet. The reaction mixture is visually inspected for residual sodium (Note 9). As a precaution, ice is added to the cooling bath and 50 mL of methanol is added slowly through the dropping funnel (Note 9). A mixture of 400 mL methanol and 500 mL of deionized water, which is degassed by applying vacuum, is then added rapidly through the dropping funnel. A solution of 20 g (0.15 mol) of zinc chloride ($ZnCl_2$) in a mixture of 500 mL of concentrated aqueous ammonium hydroxide and 500 mL of methanol is then added through the dropping funnel (Note 10). A solution of 53 g (0.25 mol) of tetraethylammonium bromide in 250 mL of deionized water is added dropwise via the dropping funnel with vigorous stirring over at least 4 hr, and the solution is stirred overnight. A large amount of red precipitate develops in the flask overnight. This salt is collected by suction on a Büchner funnel and washed immediately with 500 mL of deionized water, then with 400-mL portions of isopropyl alcohol until the filtrate is colorless, and finally once with 200 mL of diethyl ether. The product is then dried in a desiccator under vacuum affording 74–76 g (83–84%) of zincate **2** as a red powder. The product is sufficiently pure for further reactions including alkylation and acylation (Note 11) and (Note 12).

B. *4,5-Dibenzoylthio-1,3-dithiole-1-thione* **(3)**. A 1-L, round-bottomed flask, equipped for magnetic stirring, is charged with 400 mL of acetone (Note 13) and 16 g (0.0223 mol) of tetraethylammonium bis(1,3-dithiole-2-thione-4,5-dithio) zincate **(2)**. Magnetic stirring is initiated, 40 mL (48.4 g, 0.345 mol) of benzoyl chloride (Note 14) is added via a dropping funnel over 4 hr, and the mixture is left overnight. The resulting yellow-light brown precipitate is collected by suction and washed on the filter with 500 mL of deionized water and 300 mL of acetone. This crude material is dissolved in 350 mL of chloroform, 0.5 g of Norit is added and the mixture heated under reflux for 10 min (Note 15). The mixture is filtered while still hot, and the filter cake washed with an additional 50 mL of hot chloroform to dissolve any residual product on the filter. The combined chloroform solutions are concentrated to 150 mL by use of a rotary evaporator. The resulting mixture is warmed to effect complete solution of diester **3** and 50 mL of methanol is added portionwise with stirring. The solution is then left overnight in the refrigerator. The resulting crystalline precipitate is collected by suction and air-dried, affording 11.8–12.0 g (65–66%) of dibenzoyl ester **3** (mp 143–144°C) (Note 16)

2. Notes

1. The mechanical stirrer must be made of inert material (glass or Teflon).
2. If a Firestone valve (Ace Glass Inc., Vineland NJ) is not available, a bubbler connected to the N_2 inlet tube via a T-adapter is sufficient.
3. Sodium shavings (23.0 g, 1 mol) are conveniently prepared in the following way: A clean piece of sodium, 40–60 g, is weighed. Shavings are prepared from this using a commercial household grater directly into a beaker containing dry ether. The weight of shavings is determined by differential weighing of the remaining piece of sodium. *CAUTION: Sodium is a corrosive and potentially flammable solid. Handle with care using appropriate gloves for protection in a hood avoiding contact with moisture.*
4. *Extreme caution is necessary during the preparation and transfer of the sodium shavings because of the large amount of sodium placed in the flask*. The flask must be free of flaws and sodium waste must be carefully destroyed with ethanol.
5. Decanting the ether off immediately before addition is recommended to avoid oxidation of the shavings. If the shavings are a little wet from ether this does not harm the reaction.
6. The CS_2 was HPLC grade obtained from Aldrich Chemical Company, Inc. and used without purification. Lower grades of CS_2 can be used; however, a minor decrease in yield will occur.
7. The DMF used was obtained from Fisher Scientific Company (certified A.C.S.) and used without further purification.
8. It is important that the stirrer assembly be nearly gas tight, so that only small amounts of N_2 and CS_2 are lost.
9. Normally there will not be any sodium metal left, but small pieces of sodium may have adhered to the walls of the flask above the liquid level. These pieces of residual sodium metal must be destroyed with methanol. If any sodium is left, gas evolution is seen and the mixture is left for 1 hr with cooling and stirring.
10. This is most easily accomplished by adding the $ZnCl_2$ in portions to the rapidly stirred ammonium hydroxide followed by addition of the methanol.
11. Recrystallization of the zinc complex can be carried out as follows: Dissolve 20 g of the salt in 300 mL of warm acetone and add 0.5 g of Norit. Heat at reflux for 10 min, filter the hot mixture to remove the Norit, concentrate the filtrate under reduced pressure to one half the original volume, and add 100 mL of isopropyl alcohol. Collect the resulting precipitate by suction and wash the precipitate with ether. Provides 15.8 g (80% recovery) of pure salt (mp 206–208°C).
12. The product exhibits the following properties: IR (KBr) cm^{-1}: 1460, 1410, 1165, 1050, 986, 878, 775, 450; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 7.9, 53.2, 136.3, 209.5.
13. Commercial acetone was first dried with $CaCl_2$, then distilled.
14. Benzoyl chloride was obtained from Merck & Company, Inc., and used without purification.
15. Any brand of decolorizing charcoal may be used.

16. The product exhibits the following properties: IR ($CHCl_3$) cm^{-1}: 3001, 1695, 1601, 1586, 1450, 1200, 1179, 1068, 880, 660, 637; ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 127.8, 129.0, 133.5, 134.6, 134.8, 185.2, 212.1.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

This synthesis provides easy and inexpensive access to the 4,5-dithio-1,3-dithiole-2-thione system. By alkylation with 1,2-dibromoethane, 4,5-ethylenedithio-1,3-dithiole-2-thione, a key intermediate in the synthesis of bis(ethylenedithio)tetrathiofulvalene (BEDT-TTF) is obtained.[4,5] BEDT-TTF forms charge-transfer salts, many of which are conducting and superconducting, and known as "organic metals". Extensive reviews on the synthesis and properties of BEDT-TTF[6] and other TTF derivatives have been published.[7]

Originally, the reduction of carbon disulfide was carried out electrochemically, but this procedure is not practical for preparative amounts of material.[8] In 1979, a chemical reduction method was discovered by Steimecke.[9] The present procedure is based on that 1979 report, but sodium is substituted for potassium (which presents an explosive hazard).[10] Practical improvements have allowed the development of a one-pot procedure that is easily scaled up to provide 70–80 g of material.

Complexation with zinc effectively separates the C_3S_5 dianion from the trithiocarbonate ion in high yield, and the material obtained is sufficiently pure for further reactions. The quaternary ammonium zincate salt is alkylated slowly but smoothly by many halides at room temperature in solvents such as acetone or tetrahydrofuran. Reaction of the zincate with benzoyl chloride followed by cleavage of the resulting benzoate by sodium ethoxide in ethanol provides the much more reactive species $Na_2C_3S_5$. The sodium salt is, however, very air sensitive,[5] whereas the zinc salt is completely stable.

An alternative to this synthesis is provided by Shumaker via tetrathiapentalene.[11] For most purposes, this procedure offers no advantages and requires more expensive starting materials. The procedure described here is applicable not only for the preparation of BEDT-TTF, but intermediates **2** and **3** may also be used for the synthesis of a variety of BEDT-TTF analogs.[12 13]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Tetraethylammonium bis(1,3-dithiole-2-thione-4,5-dithiol) zincate

BEDT-TTF

tetraethylammonium bis(1,3-dithiole-2-thione-4,5-dithio) zincate

ethanol (64-17-5)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

chloroform (67-66-3)

nitrogen (7727-37-9)

acetone (67-64-1)

Norit (7782-42-5)

benzoyl chloride (98-88-4)

zinc (7440-66-6)

sodium (13966-32-0)

isopropyl alcohol (67-63-0)

sodium ethoxide (141-52-6)

carbon disulfide (75-15-0)

1,2-dibromoethane (106-93-4)

zinc chloride (7646-85-7)

ammonium hydroxide (1336-21-6)

potassium (7440-09-7)

Tetrahydrofuran (109-99-9)

dimethylformamide, DMF (68-12-2)

tetraethylammonium bromide (71-91-0)

4,5-Dibenzoyl-1,3-dithiole-1-thione

4,5-ethylenedithio-1,3-dithiole-2-thione

bis(ethylenedithio)tetrathiofulvalene

4,5-Dibenzoylthio-1,3-dithiole-1-thione

Benzenecarbothioic acid, S,S'-(2-thioxo-1,3-dithiole-4,5-diyl) ester (68494-08-6)

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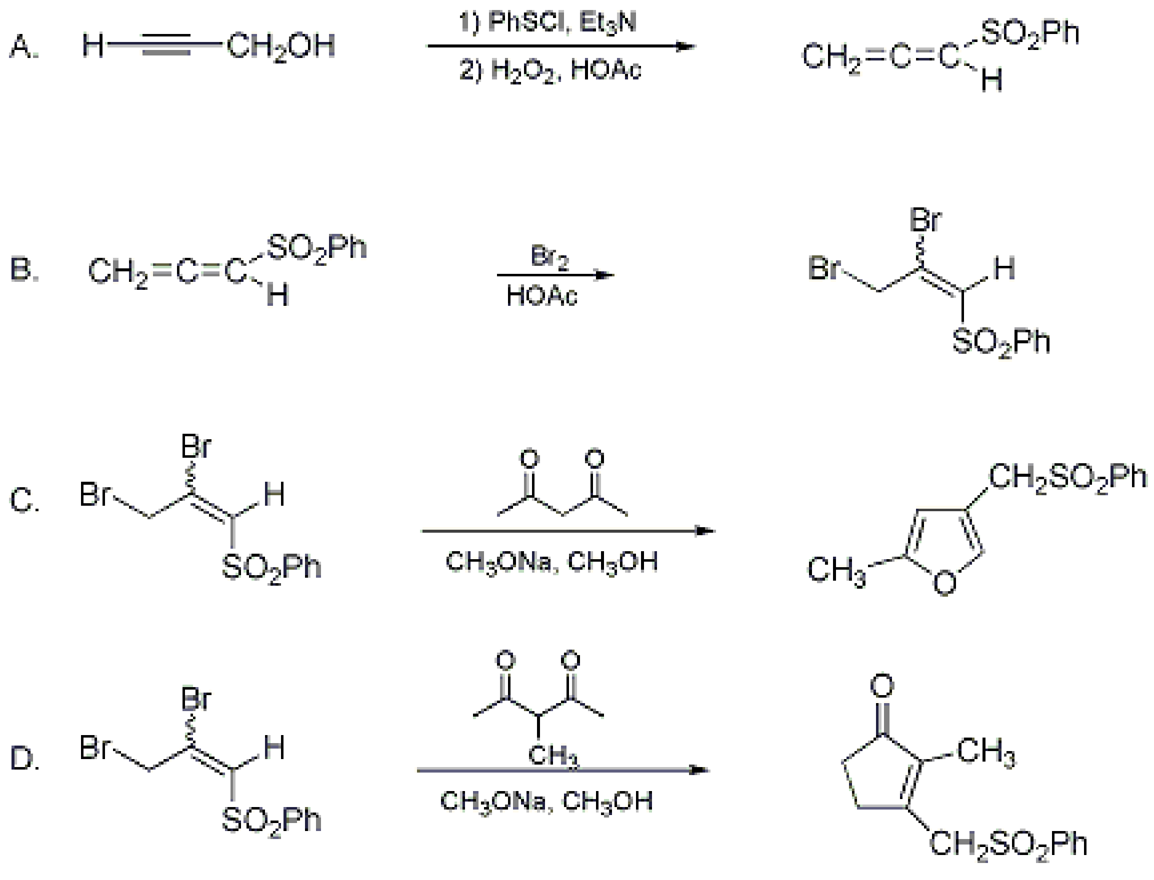
Organic Syntheses, CV 9, 207

2,3-DIBROMO-1-(PHENYLSULFONYL)-1-PROPENE AS A VERSATILE REAGENT FOR THE SYNTHESIS OF FURANS AND CYCLOPENTENONES: 2-METHYL-4-[(PHENYL-SULFONYL)METHYL]FURAN AND 2-METHYL-3-[(PHENYLSULFONYL)METHYL]-2-CYCLOPENTEN-1-ONE

[Benzene, [(2,3-dibromo-1-propenyl)sulfonyl]-, Furan, 2-methyl-4-[(phenylsulfonyl)methyl]-, and 2-Cyclopenten-1-one, 2-methyl-3-[(phenylsulfonyl)methyl]-]



Submitted by Scott H. Watterson, Zhijie Ni, Shaun S. Murphree, and Albert Padwa[1].
Checked by Huguette Vanlierde, Amy Dekoker, and Leon Ghosez.

1. Procedure

A. *1-(Phenylsulfonyl)-1,2-propadiene*. In a 1-L, three-necked, round-bottomed flask equipped with a magnetic stirring bar, 100-mL addition funnel, and a septum fitted with a nitrogen inlet, are placed 10.5 mL (0.18 mol) of propargyl alcohol (Note 1),

30.1 mL (0.22 mol) of triethylamine, and 700 mL of dichloromethane. The flask is cooled with an ice-water bath and 26.0 g (0.18 mol) of phenylsulfenyl chloride (Note 2) in 50 mL of dichloromethane is added under a nitrogen atmosphere from the addition funnel. After the solution is warmed to room temperature and stirred for 3 hr, the mixture is washed with water (2 × 200-mL) and then concentrated under reduced pressure. The resulting residue (ca. 37 g) is dissolved in 100 mL of acetic acid in a 500-mL, round-bottomed flask fitted with a magnetic stirring bar, an addition funnel, and a thermometer. The solution is heated to 95°C and then 40 mL of hydrogen peroxide (30–35%) (Note 3) is slowly added over a 20-min period maintaining the internal temperature in the flask below 95°C. The mixture is heated for an additional 10 hr, maintaining the external temperature at 95°C (Note 4). After being cooled to 25°C, the mixture is poured into 200 mL of water, and extracted with dichloromethane (3 × 100 mL). The organic layer is washed with water (2 × 100 mL) followed by saturated sodium bicarbonate solution (100 mL), dried over magnesium sulfate, and filtered. The filtrate is concentrated to give 28.1 g (68%) of 1-(phenylsulfonyl)-1,2-propadiene as an oil, which is used in the next step (Note 5), (Note 6).

B. *2,3-Dibromo-1-(phenylsulfonyl)-1-propene*. To a solution containing 25.4 g (0.14 mol) of 1-(phenylsulfonyl)-1,2-propadiene in 100 mL of acetic acid in a 250-mL, round-bottomed flask fitted with a dropping funnel is added 8.0 mL (0.14 mol) of bromine over a period of 30 min. The solution is stirred at room temperature for 8 hr, poured into 200 mL of water, and extracted with dichloromethane (3 × 100 mL). The dichloromethane layer is washed with 50 mL of a 1.0 M aqueous sodium thiosulfate solution, water (2 × 100 mL) and saturated sodium bicarbonate solution (100 mL). The organic phase is dried over anhydrous magnesium sulfate, filtered under reduced pressure through a 60-mL fritted funnel containing 4.0 g of Celite topped with 6.0 g of silica gel. The mixture is concentrated under reduced pressure to give 41.5 g (87%) of 2,3-dibromo-1-(phenylsulfonyl)-1-propene (Note 7), which is used in the next step without further purification.

C. *2-Methyl-4-[(phenylsulfonyl)methyl]furan*. Into a flame-dried, 1-L, round-bottomed flask equipped with an addition funnel fitted with a nitrogen inlet are placed 20.0 g (58.8 mmol) of 2,3-dibromo-1-(phenylsulfonyl)-1-propene and 6.1 mL (59.4 mmol) of 2,4-pentanedione in 300 mL of methanol (Note 8). The flask is blanketed with nitrogen and cooled using an ice-water bath. To this mixture is added 140 mL (70.0 mmol) of a 0.5 N methanolic solution of sodium methoxide (Note 9) dropwise over 30 min. The solution is stirred at 25°C for 12 hr and cooled to 0°C. Another 140 mL (70.0 mmol) of the 0.5 N methanolic solution of sodium methoxide is added over 20 min. After being stirred at 25°C for 10 hr, the reaction is quenched by the addition of 50 mL of saturated ammonium chloride solution. The solvent is removed with a rotary evaporator at aspirator vacuum and the resulting residue is taken up in 100 mL of water and 200 mL of dichloromethane. The aqueous layer is extracted with dichloromethane (2 × 200 mL). The organic layer is washed with water (100 mL) and brine (100 mL) and then dried over anhydrous magnesium sulfate. After filtration and concentration, the residue is recrystallized from ethyl acetate to give 5.6 g (59%) of 2-

methyl-4-[(phenylsulfonyl)methyl]furan (Note 6), (Note 10).

D. *2-Methyl-3-[(phenylsulfonyl)methyl]-2-cyclopenten-1-one*. In a flame-dried, 1-L, round-bottomed flask equipped with an addition funnel under a nitrogen atmosphere are placed 20.0 g (58.8 mmol) of 2,3-dibromo-1-(phenylsulfonyl)-1-propene and 7.0 mL (60.0 mmol) of 3-methyl-2,4-pentanedione in 300 mL of methanol (Note 8). The flask is cooled using an ice-water bath. To this mixture is added 140 mL (70.0 mmol) of a 0.5 N methanolic solution of sodium methoxide (Note 9) dropwise over 30 min. The solution is stirred at 25°C for 5 hr and cooled to 0°C. Another 140-mL (70.0 mmol) portion of the 0.5 N methanolic solution of sodium methoxide is added over 20 min. After being stirred at 25°C for 10 hr, the reaction is quenched by the addition of 50 mL of saturated ammonium chloride solution. The solvent is removed with a rotary evaporator at aspirator vacuum and the resulting residue is taken up in 100 mL of water and 200 mL of dichloromethane. The aqueous layer is extracted with dichloromethane (2 × 200 mL). The organic layer is washed with water (100 mL) and brine (100 mL) and then dried over anhydrous magnesium sulfate. After filtration and concentration, the residue is recrystallized from ethyl acetate to give 6.5 g (44%) of 2-methyl-3-[(phenylsulfonyl)methyl]-2-cyclopenten-1-one (Note 6), (Note 11).

2. Notes

1. Propargyl alcohol, 2,4-pentanedione and 3-methyl-2,4-pentanedione were purchased from Aldrich Chemical Company, Inc., and were used without further purification. Dichloromethane and triethylamine were distilled from calcium hydride prior to use. Methanol was dried and distilled from magnesium-iodine.
2. Phenylsulfenyl chloride was prepared according to the procedure of Barrett, A. G. M.; Dhanak, D.; Graboski, G. G.; Taylor, S. J. *Org. Synth., Coll. Vol. VIII* **1993**, 550.
3. Hydrogen peroxide (30–35%), glacial acetic acid, and bromine were purchased from Fisher Scientific Company and were used without further purification.
4. For the next 30–60 min the internal temperature should not be allowed to exceed 95°C.
5. The submitters were able to obtain most of this product as a crystalline solid that could be recrystallized from ether at –20°C, mp 44–45°C [lit.[2] mp 44–45°C]. It has the following spectral properties: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.40 (d, 2 H, J = 6.3), 6.21 (t, 1 H, J = 6.3), 7.47–7.87 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 84.0, 100.7, 127.3, 129.0, 133.4, 140.9, 209.2.
6. The checkers were not able to purify the crude oil. As a result their overall yield of final product was 40%. The submitters obtained a 71% overall yield using the crystalline material.
7. This product contains a mixture of E- and Z-isomers in a 7:3 ratio, which could be separated by flash chromatography on silica gel eluting with hexane: ethyl acetate (4:1). The spectral properties of both isomers are as follows: E-

isomer: mp 62–63°C (recrystallized from ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.96 (s, 2 H), 6.78 (s, 1 H), 7.50–8.15 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 29.8, 127.8, 129.6, 133.7, 134.4, 137.6, 139.6; Anal. Calcd for $C_9H_8Br_2O_2S$: C, 31.79; H, 2.37. Found: C, 31.86; H, 2.36. Z-Isomer (oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.20 (s, 2 H), 7.31 (s, 1 H), 7.50–7.95 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 35.7, 127.9, 128.5, 129.1, 133.8, 134.0, 139.4.

8. Both isomers gave similar yields. If the crystalline E-isomer was used, it took about 30 min for the solid to dissolve.

9. This solution was prepared from sodium and methanol and could be stored in a plastic bottle over a period up to several months without any effect on the reaction.

10. The product has the following spectral properties; mp 91–92°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.22 (s, 3 H), 4.10 (s, 2 H), 5.91 (s, 1 H), 7.01 (s, 1 H), 7.50–7.95 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 12.9, 53.0, 106.9, 112.5, 127.9, 128.3, 133.1, 137.3, 140.3, 152.6. Anal. Calcd for $C_{12}H_{12}O_3S$: C, 61.00; H, 5.12. Found: C, 60.91; H, 5.12.

11. The product has the following spectral properties; mp 166–167°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.26 (s, 3 H), 2.45 (m, 2 H), 2.73 (m, 2 H), 4.15 (s, 2 H), 7.40–7.95 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 7.2, 29.4, 33.7, 57.9, 127.5, 128.9, 133.7, 137.7, 142.4, 155.8, 207.8. Anal. Calcd. for $C_{13}H_{14}O_3S$: C, 62.38, H, 5.64. Found: C, 62.14, H, 5.47.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Many methods have been devised for the formation of multicyclic furans[3] and cyclopentenones[4] because of their importance in organic synthesis. The procedure described here provides a simple and general approach for the construction of 2-methyl-4-[(phenylsulfonyl)methyl]furan and 2-methyl-3-[(phenylsulfonyl)methyl]-2-cyclopenten-1-one using 2,3-dibromo-1-(phenylsulfonyl)-1,2-propene (DBP) as the key reagent.[5] Addition of bromine to 1-(phenylsulfonyl)-1,2-propadiene proceeds smoothly at 25°C and can be controlled so that the reaction may be terminated after 1 equiv of bromine is consumed. The resulting dibromide is a stable, crystalline solid, requiring no special precautions to prevent decomposition.[6] This dibromosulfone can be viewed as a multielectrophilic reagent with great potential as a nucleophilic acceptor for sequential addition. Functionalized allylic reagents that contain both a leaving group and a π-activating substituent have been used extensively in organic synthesis.[7,8,9,10] These substituted 1-propenes have been referred to as multicoupling reagents.[8] Because of the molecular weight and stability of the phenylsulfonyl group,

the carbon backbone of DBP is very small, without the drawback of volatility or thermal lability seen in other synthetic intermediates with the same carbon skeleton. The synthetic potential of DBP is demonstrated here by taking advantage of two properties of the molecule: 1) the ability of the phenylsulfonyl group to activate the double bond toward Michael addition with soft dicarbonyl anions and 2) the facility with which both bromides can be displaced.

Treatment of 1,3-dicarbonyl compounds with DBP in a methoxide/methanol system affords 2-alkyl-4-[(phenylsulfonyl)methyl]furans, where reaction proceeds by initial addition-elimination on the vinyl sulfone moiety. In contrast, silyl enol ethers in the presence of silver tetrafluoroborate resulted in products derived from S_N2 displacement at the allylic site.[11] Anions derived from 1,3-dicarbonyls substituted at the C-2 position are found to induce a complete reversal in the mode of ring closure.[12] The major products obtained are 3-[(phenylsulfonyl)methyl]-substituted cyclopentenones. The internal displacement reaction leading to the furan ring apparently encounters an unfavorable $A_{1,3}$-interaction in the transition state when a substituent group is present at the 2-position of the dicarbonyl compound. This steric interaction is not present in the transition state leading to the cyclopentenone ring.

Since DBP can react with a variety of β-dicarbonyl anions, a wide assortment of furans and cyclopentenones is available. In addition to its ease of removal,[13] the pendant sulfone also offers a convenient and versatile site for further elaboration (via alkylation[14] or Julia coupling[15]). This strategy toward furans and cyclopentenones can clearly be applied to more complex targets.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

brine

Benzene, [(2,3-dibromo-1-propenyl)sulfonyl]-, Furan, 2-methyl-4-[(phenylsulfonyl) methyl]-, and 2-Cyclopenten-1-one, 2-methyl-3-[(phenylsulfonyl)methyl]-

2,3-dibromo-1-(phenylsulfonyl)-1,2-propene (DBP)

acetic acid (64-19-7)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether (60-29-7)

ammonium chloride (12125-02-9)

sodium bicarbonate (144-55-8)

bromine (7726-95-6)

sodium thiosulfate (7772-98-7)

nitrogen (7727-37-9)

sodium methoxide (124-41-4)

carbon (7782-42-5)

sodium (13966-32-0)

hydrogen peroxide (7722-84-1)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

2,4-pentanedione (123-54-6)

hexane (110-54-3)

triethylamine (121-44-8)

calcium hydride (7789-78-8)

propargyl alcohol (107-19-7)

Phenylsulfenyl chloride (931-59-9)

3-methyl-2,4-pentanedione (815-57-6)

silver tetrafluoroborate (14104-20-2)

2,3-Dibromo-1-(phenylsulfonyl)-1-propene (132604-65-0)

2-METHYL-4-[(PHENYL-SULFONYL)METHYL]FURAN, 2-Methyl-4-[(phenylsulfonyl)methyl]furan (128496-98-0)

2-METHYL-3-[(PHENYLSULFONYL)METHYL]-2-CYCLOPENTEN-1-ONE

1-(Phenylsulfonyl)-1,2-propadiene (2525-42-0)

magnesium-iodine

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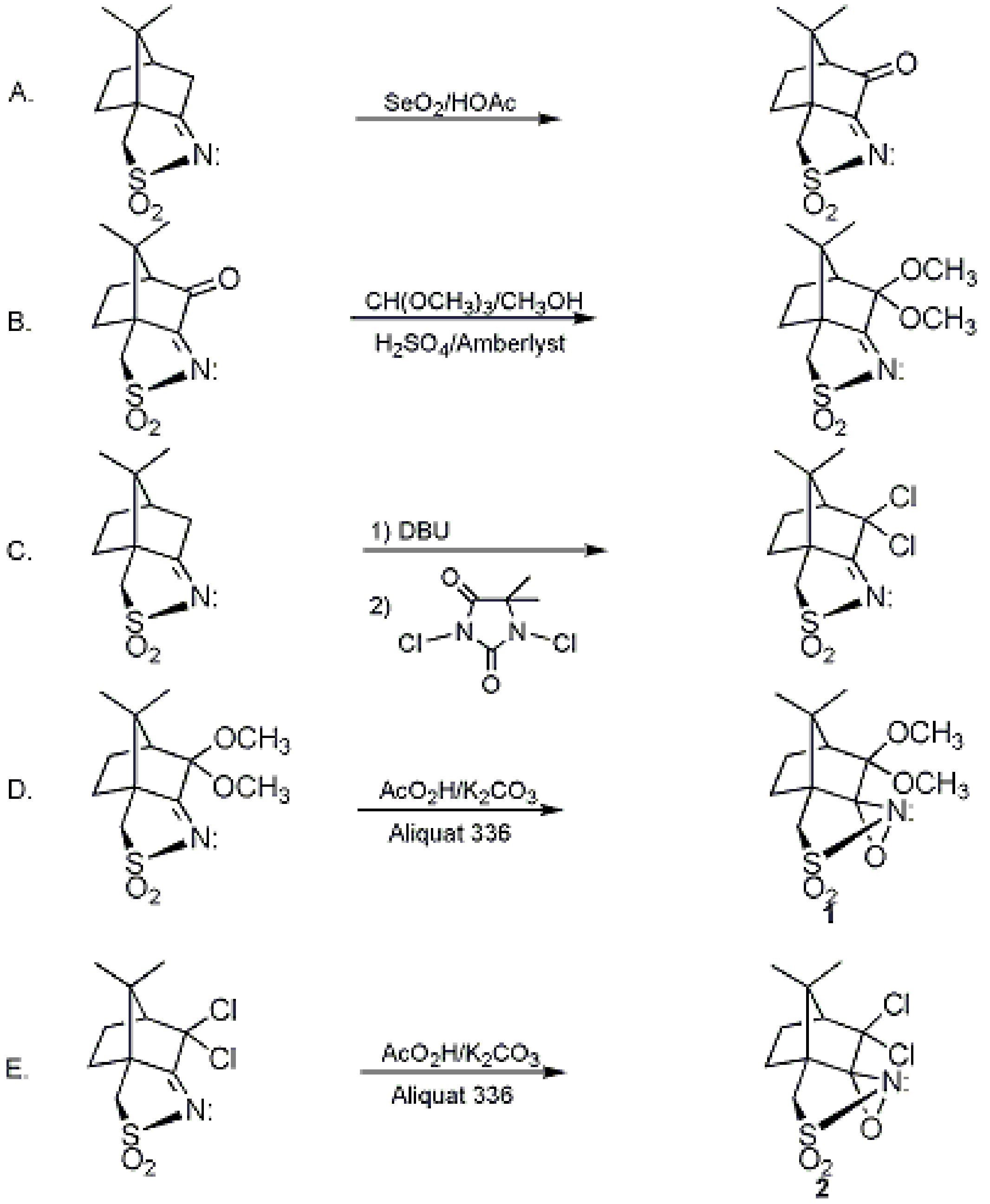
(+)-(2R,8aR)-[(8,8-DIMETHOXYCAMPHORYL) SULFONYL]OXAZIRIDINE AND (+)-(2R,8aR)-[(8,8-DICHLOROCAMPHORYL)SULFONYL]OXAZIRIDINE

[[4H-4a,7-Methanooxazirino[3,2-i][2,1]benzisothiazole, tetrahydro-8,8-dimethoxy-9,9-dimethyl-, 3,3-dioxide], [2R-(2α,4aα,7α,8aR)]- and [4H-4a,7-Methanooxazirino[3,2-i][2,1]benzisothiazole, 8,8-dichlorotetrahydro-9,9-dimethyl-, 3,3-dioxide, [2R-(2α,4aα,7α,8aR)]]



Submitted by Bang-Chi Chen[1], Christopher K. Murphy[1], Anil Kumar[1], R. Thimma Reddy[1], Charles Clark[1], Ping Zhou[1], Bryan M. Lewis[1], Dinesh Gala[2],

Ingrid Mergelsberg[3], Dominik Scherer[3], Joseph Buckley[2], Donald DiBenedetto[2], and Franklin A. Davis[1,4].
Checked by Thanh H. Nguyen and Albert I. Meyers.

1. Procedure

A. *(−)-(3-Oxocamphorylsulfonyl)imine*. A 2-L, single-necked, round-bottomed flask, equipped with a condenser and magnetic stirring bar, is charged with 42.6 g (0.2 mol) of (−)-(camphorylsulfonyl)imine (Note 1), 30.0 g (0.27 mol) of selenium dioxide (Note 2), and 500 mL of reagent grade acetic acid (Note 3). The mixture is stirred at reflux for 14 hr (Note 4), and the black selenium metal that separates is removed by suction filtration of the hot reaction mixture using a 250-mL porcelain filter funnel. The funnel, flask and residue are washed with 50 mL of acetic acid. Removal of solvent using a rotary evaporator gives 43.0–47.0 g of crude (−)-(3-oxocamphorylsulfonyl)imine as a dark orange solid that is dried under reduced pressure overnight in a desiccator (Note 5) and (Note 6). This product is suitable for further reaction without purification.

B. *(+)-[(7,7-Dimethoxycamphoryl)sulfonyl]imine*. A 500-mL, single-necked, round-bottomed flask, equipped with a condenser, magnetic stirring bar, and nitrogen inlet, is charged with 22.8 g (0.1 mol) of the crude (−)-(3-oxocamphorylsulfonyl)imine prepared above, 125 mL of trimethyl orthoformate, 68 mL of methanol, and 5 mL of concd sulfuric acid. The mixture is heated to 85–90°C in an oil bath (Note 7) and (Note 8). After heating for 4 hr, during which time precipitation of the product is observed, the reaction mixture is cooled to room temperature, and an additional 30 mL of trimethyl orthoformate and 10 mL of methanol are added. Heating is continued for an additional hour, after which the reaction mixture is cooled to room temperature and transferred with the aid of 250 mL of methylene chloride to a 500-mL separatory funnel. The solution is washed successively with water (100 mL), aqueous 20% sodium bicarbonate solution (100 mL), water (4 × 100 mL), and brine (100 mL), and dried over anhydrous magnesium sulfate. Filtration and removal of the solvent under reduced pressure affords 22.8–23.0 g (83–85%) of the crude (+)-(7,7-dimethoxy camphorylsulfonyl)imine as a light pink solid, mp 179–184°C ((Note 9) and (Note 10)). This product is suitable for further reaction without purification.

C. *(+)-[(7,7-Dichlorocamphoryl)sulfonyl]imine*. A 1-L, three-necked, round-bottomed flask, equipped with a mechanical stirrer or magnetic stirring bar, thermometer, and 250-mL pressure-equalizing addition funnel with a nitrogen inlet, is placed under a nitrogen atmosphere and charged with a solution of 50 g (0.235 mol) of (−)-(camphorsulfonyl) imine (Note 1) in 250 mL of ethyl acetate. To this solution is added 71 g (0.47 mol) of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (Note 11) over 30 min, and the reaction mixture is stirred for 30 min at room temperature. To the resulting mixture is then added 51.5 g (0.26 mol) of 1,3-dichloro-5,5-dimethylhydantoin (Note 12) in portions over 90 min while maintaining the reaction temperature at 20–25°C by cooling with an ice-water bath. When the reaction is complete, typically 30–60 min as determined by HPLC or TLC (Note 13) and (Note 14), 400 mL of water is slowly added while keeping the temperature at 20–25°C. The pH of the reaction mixture is adjusted to 7–7.5 by the

addition of 25 mL of concd hydrochloric acid, and the ethyl acetate solvent is removed on the rotary evaporator at a maximum bath temperature of 60°C (Note 15). The resulting suspension is stirred for 1 hr at room temperature, then the solids are collected by suction filtration, washed with 500 mL of water, and dried in a draft oven at 50°C to a constant weight affording 62.0–63.0 g (94–95%) of white solid (+)-(7,7-dichlorocamphorylsulfonyl)imine (mp 170–175°C) (Note 16) and (Note 17). This product is suitable for further reaction without purification.

D. *(+)-(2R,8aR)-[(8,8-Dimethoxycamphoryl)sulfonyl]oxaziridine* (**1**). In a 500-mL, three-necked, Morton flask, equipped with a mechanical stirrer with a Teflon stirring blade and stirrer bearing, a thermometer, and a 250-mL pressure-equalizing addition funnel, is charged with 20.9 g (0.077 mol) of crude (+)-(7,7-dimethoxy camphorylsulfonyl)imine, 175 mL of methylene chloride, and 1.6 g of Aliquat 336 (Note 18). The reaction mixture is cooled in an ice bath to 0°C, efficient stirring is initiated, and a solution of 63 g (0.38 mol) of potassium carbonate in 120 mL of water is added at 0–10°C followed by 27.2 g (0.114 mol) of 32% peracetic acid (Note 19) dropwise such that the temperature is maintained at 3–5°C. After the addition is completed, the reaction mixture is allowed to warm to room temperature and stirred until reaction is complete (typically 40 hr) as determined by ^{1}H NMR (Note 4) and (Note 20). On completion, 0.6 g of sodium sulfite is added, the reaction mixture is stirred for 30 min, and 5 mL of aqueous 30% sodium hydroxide is introduced. The reaction mixture is transferred to a 500-mL separatory funnel with the aid of 50 mL of methylene chloride, the phases are separated, and the aqueous phase is extracted twice with 50 mL of methylene chloride. The combined organic extracts are washed successively with a saturated solution of sodium bicarbonate (50 mL) and water (2 × 50 mL), and then dried over anhydrous magnesium sulfate. The solvents are removed under reduced pressure while maintaining the temperature below 40°C which affords an off-white solid that is suspended in 100 mL hexane and collected by suction. The solids are washed on the filter with two additional 100-mL portions of hexane to give 15.1 g of (+)-(2R,8aR)-[(8,8-dimethoxycamphoryl)sulfonyl]oxaziridine (**1**) having mp 184–186°C (dec.) and $[\alpha]_D^{25}$ +91.6° ($CHCl_3$, *c* 3.39) (Note 21). A second crop is obtained by evaporating the filtrate to dryness and repeating the process which affords a total of 19.2–19.8 g (86–90%) of the oxaziridine (mp 184–186°C (dec.)). The product may be used as obtained for oxidations, but may be further purified, if desired, by recrystallization from 1400 mL of 95% ethanol.

This oxaziridine can also be prepared in 4 hr by oxidation of the corresponding imine using 3-chloroperbenzoic acid (Note 22).

The antipode, (−)-(2S,8aR)-[(8,8-dimethoxycamphoryl)sulfonyl]oxaziridine, (mp 189°C (dec.); $[\alpha]_D^{20}$ −91.3° ($CHCl_3$, *c* 0.5)) was prepared in a similar manner starting from (+)-(camphorylsulfonyl)imine.

E. *(+)-(2R,8aR)-[(8,8-Dichlorocamphoryl)sulfonyl]oxaziridine* (**2**). A 1-L, three-necked, Morton flask, equipped with a mechanical stirrer with a Teflon stirring blade and stirrer

bearing or a magnetic stirring bar, a thermometer, and a 250-mL pressure-equalizing addition funnel is charged with a solution of 48 g (0.17 mol) of (+)-[(7,7-dichlorocamphoryl)sulfonyl]imine in 300 mL of methylene chloride and 3.5 g of Aliquat 336 (Note 18). After cooling the resulting mixture to 0°C with an ice-bath, a solution of 119 g (0.86 mol) of potassium carbonate in 250 mL of water is added to the rapidly stirring reaction mixture while maintaining the temperature between 0–10°C. Then 45 g (0.188 mol) of 32% peracetic acid (Note 19) is added dropwise at such a rate (30 min) that the temperature is maintained between 0–5°C. When the oxidation is complete, as determined by TLC (normally after stirring overnight) (Note 23), 1.3 g (0.099 mmol) of sodium sulfite is added between 0–10°C. After stirring for 30 min, 8 mL of 30% aqueous sodium hydroxide solution is added and the reaction mixture is warmed to room temperature. The organic phase is separated, the aqueous phase is extracted with methylene chloride (2 × 25 mL), and the combined organic phases are washed with saturated sodium bicarbonate solution (25 mL) and water (2 × 25 mL) (Note 24), and dried over anhydrous sodium sulfate. Approximately 210 mL of methylene chloride is evaporated from the organic phase under reduced pressure while maintaining the bath temperature below 40°C. During removal of the solvent crystallization occurs. The resulting slurry is diluted with 125 mL of hexane, cooled in an ice bath (0–5°C), and stirred for 1 hr. The product is collected by suction filtration, washed with hexane (100 mL), and dried at a maximum of 40°C in an air draft oven to yield 45.5–48.0 g (90–95%) of (+)-(2R,8aR)-[(8,8-dichlorocamphoryl)sulfonyl] oxaziridine (**2**) (mp 182–186°C; $[\alpha]_D^{20}$ +91.4° ($CHCl_3$, *c* 0.5)) ((Note 25) and (Note 26)).

The antipode (–)-(2S,8aR)-[(8,8-dichlorocamphoryl)sulfonyl]oxaziridine (mp 182–186°C; $[\alpha]_D^{20}$ –92.3° ($CHCl_3$, *c* 0.5)) was prepared in a similar manner starting from (+)-(camphorylsulfonyl)imine.

2. Notes

1. (–)-(Camphorylsulfonyl)imine may be purchased from Aldrich Chemical Company, Inc., or prepared according to reference [5].
2. Selenium dioxide was purchased from Aldrich Chemical Company, Inc.
3. Reagent grade acetic acid was purchased from Aldrich Chemical Company, Inc.
4. The progress of the reaction was monitored using ^1H NMR by observing the disappearance of the two methyl absorptions of (–)-(camphorylsulfonyl)imine at δ 0.88, and 1.09 in a sample obtained from a 0.5-mL aliquot which is concentrated to dryness on a rotary evaporator.
5. The crude product is of sufficient purity for the next step even if trace amounts of acetic acid and selenium dioxide are present. The material can be purified by crystallization from chloroform to provide product with mp 189–190°C (Lit.[6] mp 190–191°C) and $[\alpha]_D^{20}$ –178.5° (acetone, *c* 2.2).
6. The spectral properties of (–)-[(3-oxocamphoryl)sulfonyl]imine are as follows: ^1H NMR (300 MHz, $CDCl_3$) δ: 0.95 (s, 3 H), 1.13 (s, 3 H), 1.76–1.87 (m, 1 H), 1.92–2.02 (m, 1 H), 2.16–2.36 (m, 2 H), 2.74 (d, 1 H, J = 4.8), 3.20 (d, 1 H, J =

13.5), 3.42 (d, 1 H, J = 13.5); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 18.41, 20.19, 22.28, 28.00, 44.65, 50.07, 59.04, 62.74, 181.38, 197.71; IR (KBr) cm^{-1}: 2950, 1761, 1654, 1340, 1166, 741.

7. Within 30 min of heating to 85–90°C, vigorous evolution of gas ensues.

8. The reaction was monitored using ^{1}H NMR by observing the disappearance of the two methyl absorptions at δ 0.95 and 1.13 of (−)-(3-oxocamphorylsulfonyl)imine.

9. This material can be purified by crystallization from absolute ethanol to give product with mp 186–7°C and $[\alpha]_D^{20}$ +7.2° ($CHCl_3$, *c* 3.6).

10. The spectral properties of (+)-[(7,7-dimethoxycamphoryl)sulfonyl]imine are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.94 (s, 3 H), 1.04 (s, 3 H), 1.73–2.02 (m, 4 H), 2.29 (d, 1 H, J = 1.4), 2.93 (d, 1 H, J = 13.3), 3.12 (d, 1 H, J = 13.3), 3.30 (s, 3 H), 3.39 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.4, 20.5, 20.6, 29.2, 46.0, 48.8, 50.3, 50.5, 52.0, 64.2, 103.0, 188.8; IR (KBr) cm^{-1}: 1620, 1340, 1160.

11. DBU was purchased from Fluka Chemie AG, Air Products, or Aldrich Chemical Company, Inc.

12. 1,3-Dichloro-5,5-dimethylhydantoin (DCDMH) was purchased from Aldrich Chemical Company and used without additional purification.

13. HPLC conditions were as follows: C_{18}-Novapak (Waters), 5•; UV detector at 210 nm; mobile phase: acetonitrile/water (55/45) at a flow rate of 1 mL/min. Alternately, this reaction can be monitored by TLC: R_f = 0.42 using CH2Cl2 and 10% molybdophosphoric acid in ethanol as the developer.

14. During the reaction, the suspended solids dissolve giving a clear solution.

15. In the event that foaming takes place a few drops of 2-octanol are added.

16. This solid can be purified by crystallization from 2-propanol to give product with mp 177–179°C, and $[\alpha]_D^{20}$ +7.9° ($CHCl_3$, *c* 2.1), $[\alpha]_D^{20}$ +97.8° (CH_3CN, *c* 1).

17. The spectral properties of (+)-[(7,7-dichlorocamphoryl)sulfonyl]imine are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.12 (s, 3 H), 1.17 (s, 3 H), 1.75–1.93 (m, 1 H), 1.96–2.20 (m, 2 H), 2.23–2.38 (m, 1 H), 2.75 (d, 1 H, J = 3.5), 3.24 (d, 1 H, J = 13.5), 3.42 (d, 1 H, J = 13.5); ^{13}C NMR (75 MHz, CDCl3) δ: 21.8, 25.1, 27.4, 47.8, 50.8, 61.2, 64.1, 81.9, 189.2.

18. Aliquat 336 (tricaprylylmethylammonium chloride) was purchased from Aldrich Chemical Company, Inc.

19. Peracetic acid, 32% in acetic acid, was purchased from Aldrich Chemical Company, Inc.

20. The reaction was monitored using ^{1}H NMR by observing the disappearance of the two methyl absorptions at δ 0.94 and 1.04 of (−)-(7,7-dimethoxycamphoryl sulfonyl)imine.

21. The spectral properties of (+)-(2R,8aR)-[(8,8-dimethoxycamphoryl)sulfonyl] oxaziridine are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ:1.02 (s, 3H), 1.28 (s, 3H), 1.70–1.95 (m, 4 H), 2.24 (d, 1 H, J = 4.0), 3.03 (d, 1 H, J = 14), 3.23 (s, 3 H), 3.24 (d, 1 H, J = 14), 3.30 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.5, 21.6, 28.1, 45.1, 47.4, 50.5, 50.8, 52.9, 54.6, 97.6, 102.8; IR (KBr) cm^{-1}: 1356, 1165.

22. Biphasic basic oxidation using technical grade (50–60%) 3-chloroperbenzoic acid affords this oxaziridine in 4 hr: In a 2-L, three-necked, Morton-flask equipped with a mechanical stirrer was placed 22.6 g (0.083 mol) of crude (+)-[(7,7-dimethoxycamphoryl)sulfonyl]imine, 42.6 g (0.13 mol) of 3-chloroperoxybenzoic acid (50–60%) in 450 mL of methylene chloride, and 450 mL of saturated potassium carbonate solution. The reaction mixture was stirred vigorously until the oxidation was complete as indicated by TLC (Note 27) at which time 500 mL of water was added, the organic layer was separated and the aqueous layer was extracted with methylene chloride (2 × 500 mL). The combined organic extracts were washed with saturated sodium sulfite (300 mL) and water (300 mL), and dried over anhydrous magnesium sulfate.

23. The reaction was monitored by TLC using silica gel plates (Kieselgel-60F, 254 nm, Merck), developing with CH_2Cl_2; for visualization spray with 5% molybdophosphoric acid in ethanol and heat.

24. The aqueous phases are monitored with Merckoquant 10011 test strips for their peroxide content prior to their disposal. The residual peroxide is neutralized (<1 ppm, the detection limit of the paper) by the addition of saturated sodium sulfite solution.

25. The spectral properties of (+)-(2R,8aR)-[(8,8-dichlorocamphoryl)sulfonyl]oxaziridine are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.16 (s, 3 H), 1.48 (s, 3 H), 1.86–2.18 (m, 3 H), 2.30–2.40 (m, 1 H), 2.73 (d, 1 H, J = 3.9), 3.23 (d, 1 H, J = 14), 3.45 (d, 1 H, J = 14); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.9, 23.31, 25.3, 26.8, 47.3, 49.4, 54.6, 62.5, 86.1, 99.1.

26. The product can be recrystallized from ethanol/ethyl acetate (1.5:1).

27. A 1-mL aliquot was removed from the organic layer, diluted with 2 mL of methylene chloride, and analyzed by TLC eluting with methylene chloride (I_2 visualization); imine R_f = 0.34, oxaziridine R_f = 0.51.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

In the Radex study, samples of oxaziridine **2** were heated in open glass tubes at 60°C/hr from ambient temperature to 260°C under atmospheric conditions. It was found that there is a strong exotherm with an onset at 165°–190°C (neat), at 135–158°C upon addition of stainless steel, and at 73°–84°C upon addition of $FeCl_3 \cdot H_2O$. Furthermore, the onset temperature in the $FeCl_3 \cdot H_2O$ study was found to be dependent on the concentration of ferric ion. In each case as the exotherm occurred, each sample frothed violently out of the sample tube as a gas was produced.

3. Discussion

(−)-[(3-Oxocamphoryl)sulfonyl]imine has been prepared independently by Glahsl and Herrmann in 70% yield in a similar manner using dioxane as solvent, but the reaction

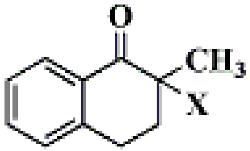
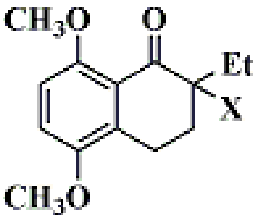
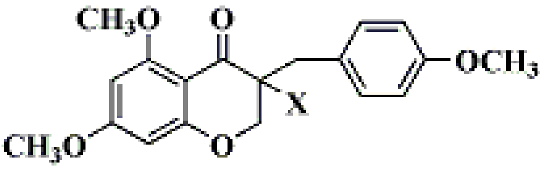
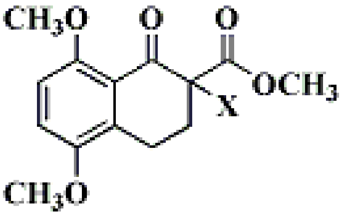
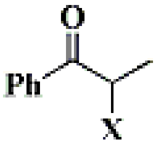
required two weeks for completion.[7] The submitters observed that using acetic acid as the solvent dramatically reduces the time to 14 hr and improves the yield to 90%.[6] (+)-[(7,7-Dimethoxycamphoryl)sulfonyl]imine has been prepared in a similar manner in 70% yield.[8] This procedure affords this material in 83–88% yield.[6] Chlorination of the aza enolate of (+)-(camphorylsulfonyl)imine, prepared by treatment with sodium bis (trimethylsilyl)amide, with N-chlorosuccinimide affords (+)-[(7,7-dichlorocamphoryl) sulfonyl]imine in 74% yield.[9] The procedure described here uses inexpensive DBU and 1,3-dichloro-5,5-dimethylhydantoin to give this imine in 95% yield and is applicable to large scale preparations.[10]

Oxidation of (+)-[(7,7-dimethoxycamphoryl)sulfonyl]imine (96%)[6] and (+)-[(7,7-dichlorocamphoryl)sulfonyl]imine (98%)[10] with 3-chloroperbenzoic acid has been reported. The procedure described here uses less hazardous and less expensive peracetic acid with the aid of Aliquat 336.[10] However, this system requires 40 hr vs. 4 hr using 3-chloroperbenzoic acid for oxidation of (+)-[(7,7-dimethoxycamphoryl)sulfonyl]imine to the oxaziridine.

N-Sulfonyloxaziridines are an important class of selective, neutral, and aprotic oxidizing reagents.[11 12] Enantiopure N-sulfonyloxaziridines have been used in the asymmetric hydroxylation of enolates to enantiomerically enriched α-hydroxy carbonyl compounds,[9,11,12,13,14] the asymmetric oxidation of sulfides to sulfoxides,[15,16] selenides to selenoxides,[17] sulfenimines to sulfinimines,[18] and the epoxidation of alkenes.[19]

(+)-(2R,8aR)-[(8,8-Dimethoxycamphoryl)sulfonyl]oxaziridine (**1**) and (+)-(2R,8aR)-[(8,8-dichlorocamphoryl)sulfonyl]oxaziridine (**2**) are most effective for the hydroxylation of 2-substituted 1-tetralone enolates to 2-substituted 2-hydroxy-1-tetralones. The former oxaziridine, **1**, gives higher ee's (>90%) with tetralones having an 8-methoxy group, while the dichloro reagent **2** is more effective with those enolates lacking this substituent. For example (+)-**1** has been employed in highly enantioselective syntheses of (+)- and (–)-5,7-O-dimethyleucomol (>96% ee),[20] the AB-ring segments for γ-rhodomycinone and α-citromycinone (94% ee),[6] and (R)-(–)-2-acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol (>95% ee), a key intermediate in the synthesis of anthracyclinones.[21] The asymmetric synthesis of the AB ring of aklavinone (>95% ee)[22] and the homoisoflavanoids (+)-O-trimethylsappanone (94% ee) and (+)-O-trimethylbrazilin (92% ee) used oxaziridine (+)-**2**. Some representative examples using these reagents are given in the Table.

TABLE
ASYMMETRIC HYDROXYLATION OF TETRALONE AND PROPIOPHENONE ENOLATES USING (CAMPHORYLSULFONYL)OXAZIRIDINES 1 AND 2

Oxaziridine	Ketone (X=H)	Base	Temp. (°C)	α-Hydroxy Tetralone (X=OH) % Yield[a]	%ee (Config.)	Ref.
(+)–1		NHMDS[a]	–78	66	36(R)	6,9,22
(+)–2		NHMDS	–78	66	>95(R)	6,9,22
(+)–1		NHMDS	–78	58	60(R)	6,22
		LDA[b]	0	66	94(R)	
(+)–2		LDA	–78	55	73(R)	
(+)–1		NHMDS	–78	75	77(R)	20
		LDA	–78	72	≥96(R)	
(+)–2		NHMDS	–78	66	88(R)	
(+)–1		NHMDS	0	73	56(S)	21
		LDA	0		No Reaction	
		KHMDS[c]	–78	70	≥95(S)	
(+)–2		NHMDS	0	63	47(S)	
(+)–1		NHMDS	–78	73	79(S)	6,9,22
(+)–2		NHMDS	–78	70	95(S)	9

[a]Isolated yields. [b]NHMDS = Sodium bis(trimethylsilyl)amide. [b]LDA = Lithium diisopropylamide. [c]KHMDS = Potassium bis(trimethylsilyl)amide.

This preparation is referenced from:

- Org. Syn. 76, 37

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

(−)-(Camphorsulfonyl)imine

(+)-[(7,7-Dimethoxycamphoryl)sulfonyl]imine

(+)-[(7,7-Dichlorocamphoryl)sulfonyl]imine

[4H-4a,7-Methanooxazirino[3,2-i][2,1]benzisothiazole, tetrahydro-8,8-dimethoxy-9,9-dimethyl-, 3,3-dioxide], [2R-(2α,4aα,7α,8aR)]-

[4H-4a,7-Methanooxazirino[3,2-i][2,1]benzisothiazole, 8,8-dichlorotetrahydro-9,9-dimethyl-, 3,3-dioxide, [2R-(2α,4aα,7α,8aR)]

(−)-(3-Oxocamphorylsulfonyl)imine

(−)-(camphorylsulfonyl)imine

(+)-(7,7-dimethoxy camphorylsulfonyl)imine

(+)-(7,7-dichlorocamphorylsulfonyl)imine

(−)-(2S,8aR)-[(8,8-dimethoxycamphoryl)sulfonyl]oxaziridine

(+)-(camphorylsulfonyl)imine

(−)-(2S,8aR)-[(8,8-dichlorocamphoryl)sulfonyl]oxaziridine

(−)-[(3-oxocamphoryl)sulfonyl]imine

DBU

(−)-(7,7-dimethoxycamphoryl sulfonyl)imine

$FeCl_3 \cdot H_2O$

(−)-5,7-O-dimethyleucomol

(R)-(−)-2-acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol

(+)-O-trimethylsappanone

(+)-O-trimethylbrazilin

ethanol (64-17-5)

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ethyl acetate (141-78-6)

methanol (67-56-1)

acetonitrile (75-05-8)

sodium sulfite (7757-83-7)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

selenium dioxide (7446-08-4)

2-propanol (67-63-0)

methyl (2229-07-4)

methylene chloride (75-09-2)

2-Octanol (123-96-6)

Propiophenone (93-55-0)

magnesium sulfate (7487-88-9)

dioxane (5703-46-8)

selenium

tetralone (529-34-0)

peracetic acid (79-21-0)

hexane (110-54-3)

N-chlorosuccinimide (128-09-6)

1,3-dichloro-5,5-dimethylhydantoin (118-52-5)

Molybdophosphoric acid (51429-74-4)

lithium diisopropylamide (4111-54-0)

tricaprylylmethylammonium chloride (5137-55-3)

trimethyl orthoformate (149-73-5)

1,8-diazabicyclo[5.4.0]undec-7-ene (6674-22-2)

(+)-(2R,8aR)-[(8,8-DIMETHOXYCAMPHORYL)SULFONYL]OXAZIRIDINE (131863-82-6)

(+)-(2R,8aR)-[(8,8-DICHLOROCAMPHORYL)SULFONYL]OXAZIRIDINE, (+)-(2R,8aR)-[(8,8-dichlorocamphoryl)sulfonyl] oxaziridine (127184-05-8)

3-chloroperoxybenzoic acid, 3-chloroperbenzoic acid (937-14-4)

Sodium bis(trimethylsilyl)amide (1070-89-9)

Potassium bis(trimethylsilyl)amide (40949-94-8)

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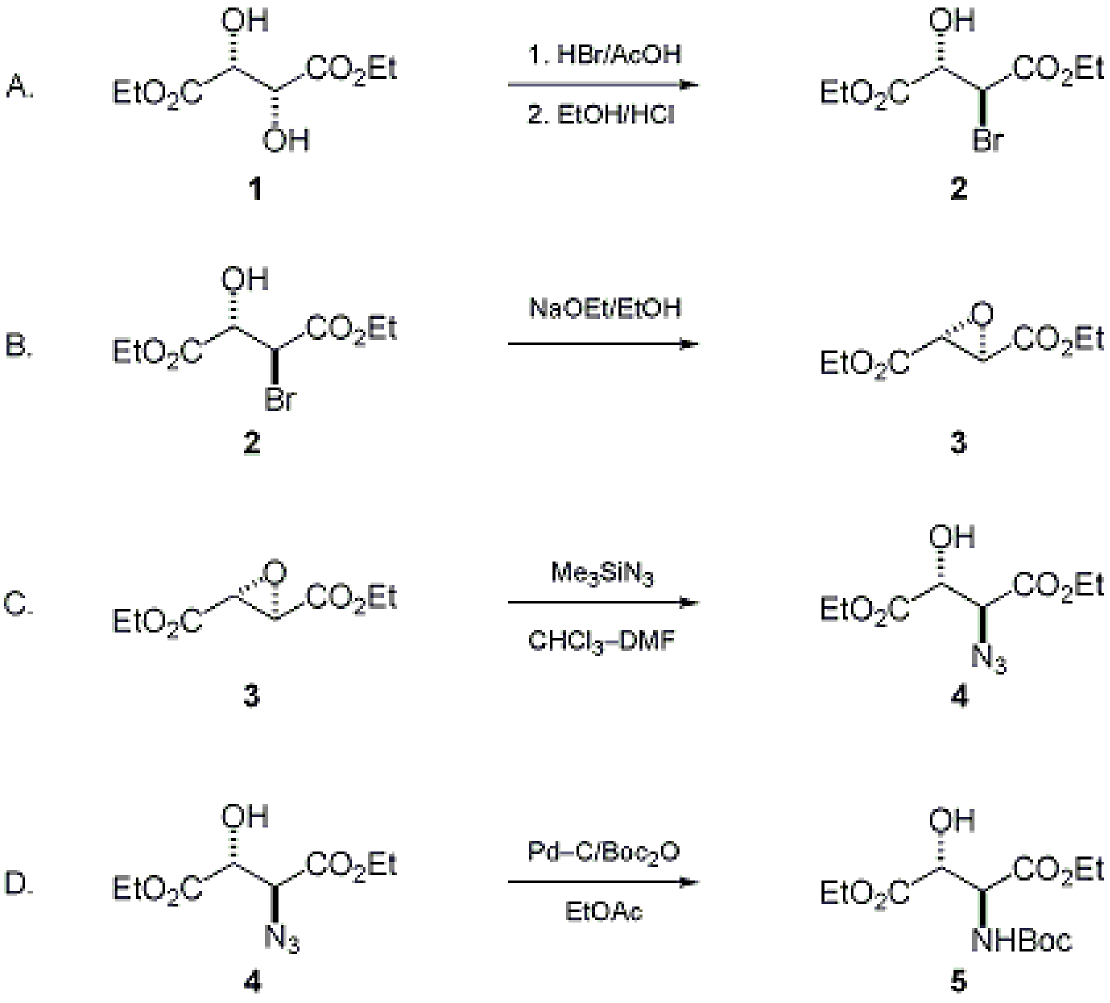
Organic Syntheses, CV 9, 220

DIETHYL (2S,3R)-2-(N-tert-BUTOXYCARBONYL) AMINO- 3-HYDROXYSUCCINATE

[D-Aspartic acid, N-[(1,1-dimethylethoxy)carbonyl]-3-hydroxy-, diethyl ester, threo-]



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Checked by Martin Fox and Larry E. Overman.

1. Procedure

Caution! Parts A and C of this procedure should be carried out in a well-ventilated hood since toxic hydrogen bromide and azidotrimethylsilane are handled and toxic hydrogen azide is liberated during the course of the reaction.

A. *Diethyl (2S,3S)-2-bromo-3-hydroxysuccinate* (**2**). In an oven-dried, 300-mL, round-bottomed flask containing a Teflon-coated stirring bar is placed 26.0 g (0.126 mol) of diethyl L-tartrate (Note 1). A pressure-equalizing dropping funnel containing 100 mL

(0.504 mol) of 30% hydrobromic acid (HBr) in acetic acid (Note 2) is mounted on the flask and the top of the funnel is fitted with a nitrogen inlet vented through an oil bubbler. The system is placed under a nitrogen atmosphere, magnetic stirring is initiated, and contents of the flask are cooled in an ice-water bath. The contents of the dropping funnel are added to the cooled tartrate during 30 min and the yellow mixture is stirred for an additional 15 min after completion of the addition. The cooling bath is removed and the reaction mixture is allowed to reach 25°C and stir for an additional 10 hr or until disappearance of the tartrate as judged by TLC analysis (Note 3). The light brown reaction mixture is poured into 500 g of ice, and the resulting mixture is transferred to a 1-L separatory funnel and extracted four times with 80 mL of ether. The combined ether extracts are washed successively three times with 60 mL of water, and then 100 mL of brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure using a rotary evaporator to give a pale yellow oil.

A single-necked, 300-mL, round-bottomed flask, equipped with a Teflon-coated stirring bar and an efficient reflux condenser bearing a drying tube packed with blue indicator silica gel beads, is charged with the yellow oil obtained above and 140 mL of ethanol (Note 4) to which is cautiously added 4 mL of acetyl chloride with stirring (Note 5). The mixture is heated under gentle reflux for 7 hr, then cooled to room temperature, the condenser is removed, and the mixture is concentrated under reduced pressure at 50–60°C using a rotary evaporator to give a yellow oil. The crude product is transferred to a silica gel column (Note 6) with the aid of a small amount of hexane-ethyl acetate (4:1) and eluted with the same mixed solvent in 60-mL fractions. Fractions 5 to 15 (Note 7) are combined and concentrated on a rotary evaporator to give a colorless oil, which, upon vacuum distillation, affords 24.36–25.73 g (72–76%) of 99% pure (GLC) diethyl (2S,3S)-2-bromo-3-hydroxysuccinate, bp 93–94°C (0.2 mm) [lit.[2] bp 123–125°C (0.6 mm)], $[\alpha]^{25.6}_{D}$ −16.8° (EtOH, *c* 5.70), $[\alpha]^{27}_{D}$ −35.72° (neat) [lit.[2] $[\alpha]^{21}_{D}$ −28.9° (neat)] (Note 8),(Note 9).

B. *Diethyl (2R,3R)-2,3-epoxysuccinate* (**3**). An oven-dried, 300-mL, round-bottomed flask, equipped with a Teflon-coated stirring bar and a rubber septum through which is inserted a large bore, needle-tipped nitrogen line vented through an oil bubbler, is charged with 29.7 g (0.110 mol) of diethyl (2S,3R)-2-bromo-3-hydroxy succinate and 80 mL of dry ethanol (Note 10). In a separate, oven-dried, 250-mL, round-bottomed flask, capped with a rubber septum and vented though a bubbler as described above, a solution of sodium ethoxide in ethanol is prepared from 3.05 g of sodium (0.132 mol) and 120 mL of dry ethanol (Note 10). (*Caution: This operation should be conducted in a well-ventilated hood. Sodium is a highly reactive metal, avoid exposure to moisture. Hydrogen gas, which is highly flammable and forms explosive mixtures with air, is rapidly evolved. External cooling may be necessary.*) The two flasks are placed under a nitrogen atmosphere, and connected by means of a long double needle-tipped cannula. Magnetic stirring is initiated, and the ethanolic solution of the succinate **2** is cooled in an ice-water bath for 15 min followed by dropwise addition of the solution of sodium ethoxide in ethanol which is transferred via the cannula under a very slight positive pressure of nitrogen (Note 11). Complete transfer of the base should require 2 hr (Note

12). The reaction mixture is stirred for an additional 20 min at 0–10°C (bath temperature) and then quenched by the addition of 1.43 mL (0.025 mol) of acetic acid. The reaction mixture is diluted with 900 mL of water, transferred to a 2-L separatory funnel, and extracted four times with 100 mL of dichloromethane. The combined organic phases are washed with 100 mL of brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure using a rotary evaporator to give a colorless oil. Vacuum distillation of this crude product affords 17.7–18.7 g (85–90%) of diethyl (2R,3R)-2,3-epoxysuccinate (**3**), bp 97–98°C (0.9 mm) [lit.[2] bp 100–104°C (4 mm)], $[\alpha]_D^{25}$ −110° (EtOH, *c* 5.09), $[\alpha]_D^{28}$ −115° (neat) [lit.[2] $[\alpha]_D^{21.5}$ −88.47° (ether, *c* 1.030)] which is homogeneous by GLC analysis (Note 9), and (Note 13),(Note 14),(Note 15).

C. *Diethyl (2S,3R)-2-azido-3-hydroxysuccinate* (**4**). An oven-dried, 200-mL, round-bottomed flask, containing a Teflon-coated stirring bar, is capped with a septum while hot, and purged with nitrogen until cool via insertion through the septum of a needle-tipped nitrogen line (vented through an oil bubbler) and an open needle. The open needle is removed and the flask is charged with a solution of 3.45 g (0.0282 mol) of 4-(dimethylamino)pyridine (DMAP) in 17 mL of N,N-dimethylformamide (DMF) (Note 16) and (Note 17) and 1.93 mL (0.0329 mol) of dry ethanol (Note 11) through the septum via syringe. Stirring is initiated and the mixture is cooled in an ice-water bath. To this cold solution is added 17.1 mL (0.122 mol) of azidotrimethylsilane (Note 18) dropwise at 0°C by means of a syringe (Note 19). The heterogeneous mixture is stirred for 15 min at room temperature (25°C) and then a solution of 17.7 g (0.0940 mol) of diethyl (2R,3R)-2,3-epoxysuccinate (**3**) in 50 mL of chloroform (Note 20), prepared in a septum-capped, oven-dried, 100-mL, round-bottomed flask, is rapidly transferred via cannula with the aid of a positive nitrogen pressure as above (Part B). The mixture is stirred at 25°C until epoxide **3** can no longer be detected upon TLC analysis of the reaction mixture (40 hr). The mixture is then diluted with 300 mL of water, transferred to a 1-L separatory funnel, and the organic phase separated. The aqueous phase is extracted four times with 60 mL of a hexane-ether mixture (1:1 v/v). The combined organic phases are added to 20 mL of a magnetically stirred 2.3 N solution of hydrogen chloride in ethanol (Note 21), followed by dilution of the resulting mixture with an additional 50 mL of ethanol and continued stirring at room temperature for 30 min (Note 22). After transfer to a separatory funnel, the solution is washed successively with four 50-mL portions of water, 50 mL of saturated aqueous sodium bicarbonate solution, and 50 mL of saturated aqueous sodium chloride solution, dried over sodium sulfate, and concentrated under reduced pressure using a rotary evaporator followed by exposure to high vacuum affording 18.6 g (86%) of 96–98% pure diethyl (2S,3R)-2-azido-3-hydroxysuccinate (**4**) as a pale yellow oil, $[\alpha]_D^{20}$ +31.8° (EtOH, *c* 18.1), as judged by NMR analysis (Note 23) and (Note 24). This material contains 2–4% of the inseparable (2R,3R)-diastereomer (Note 24).

D. *Diethyl (2S,3R)-2-(N-tert-butoxycarbonyl)amino-3-hydroxysuccinate* (**5**). A 500-mL, single-necked, round-bottomed flask, equipped with a Teflon-coated stirring bar, is charged with a suspension of 0.91 g of 10% palladium on carbon catalyst (Note 25) in

100 mL of ethyl acetate (Note 26). The flask is connected to a normal pressure hydrogenation apparatus (Note 27) and the catalyst is saturated with hydrogen. After removal of the hydrogen, a solution of 18.2 g (0.0785 mol) of 4 and 20.6 g (0.0942 mol) di-tert-butyl dicarbonate (Note 28) in 80 mL of ethyl acetate (Note 26) is added to the suspension of catalyst, a hydrogen atmosphere reestablished, and the suspension is stirred at room temperature under a slight positive pressure of hydrogen for 4–6 hr (Note 29). The suspension is filtered through a Celite pad, and the pad is rinsed with several portions of ethyl acetate. The combined ethyl acetate solutions are concentrated on a rotary evaporator and finally under high vacuum to give a pale yellow oil that is initially purified by means of a column packed with silica gel (100 g) using hexane-ethyl acetate (6:1) as eluent (Note 30). Fractions containing the product are combined and concentrated on a rotary evaporator to give 23.3 g of crude **5** as a colorless oil. The oily crude **5** is dissolved in 70 mL of hexane-ether (3:1), and the solution is cooled to –30°C, seeded, and kept overnight at that temperature (freezer) to allow crystallization (Note 31). The mother liquor is siphoned out while the mixture is kept at –30°C (dry ice-acetone bath). The crystals are washed with several portions of hexane-ether (3:1) at –30°C, then dried under high vacuum to provide 12.2–12.7 g of diastereomerically and enantiomerically pure diethyl (2S,3R)-2-(N-tert-butoxycarbonyl)amino-3-hydroxysuccinate (**5**) as colorless prisms, mp 33–34°C; $[\alpha]_D^{24}$ +13.1° (EtOH, *c* 6.32); $[\alpha]_D^{24}$ +28.7° ($CHCl_3$, *c* 6.05) (Note 32). The combined mother liquor and the hexane–ether (3:1) washings are concentrated on a rotary evaporator to give a colorless oil, which upon crystallization as above provides an additional 2.7–3.8 g of product **5** (Note 33). The combined yield of crystalline **5** is 15.9–16.5 g (66–73%).

2. Notes

1. Diethyl L-tartrate was usually purchased from Aldrich Chemical Co., Ltd. The diester was also prepared from L-tartaric acid by the procedure of Kocienski[3] (triethyl orthoformate–ethanol–acetyl chloride) or Seebach[4] [ethanol–acidic ion-exchange resin (Lewatit 3333)].
2. A solution of HBr (30%) in acetic acid (d = 1.31 g/mL) was purchased from Kishida Chemical Co., Ltd. (Japan). When 3 equiv of HBr rather than 4 equiv was employed, the yield of **2** dropped by more than 40%.
3. Using Merck precoated silica gel plates (0.25-mm thickness) with elution by hexane-EtOAc (2:1), after this time period, the starting tartrate ester (R_f = 0.14) was absent. Three spots with R_f values of 0.53 (the largest), 0.36 (half of the largest), and 0.21 (trace) were observed upon visualization. See discussion for the structure of these products.
4. Commercial reagent grade ethanol was used as received.
5. Acetyl chloride was purchased from Kishida Chemical Co. Ltd. (Japan), and used as received.
6. A column (350 mm × 50 mm) packed with Merck silica gel 60 (230–400 mesh ASTM) was used. Elution was facilitated by the action of an air pump for tropical fish tanks available from supermarkets. After use, the column was washed

successively with methanol (500 mL), ethyl acetate (400 mL), and hexane (400 mL). Such a washing operation reactivates the column enough for reuse to purify the epoxide (**3**), if necessary (see (Note 15)). Thus the submitters can employ the same column repeatedly for the purification of **2** and **3** (over 10 times). The checkers recommend purification by flash chromatography using a 350-mm × 50-mm column.

7. Fractions 17 to 27, 25–27 eluted with hexane-ethyl acetate (1:2), afforded recovered diethyl L-tartrate (3.1 g).

8. The spectral data for **2** are as follows: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.31 (t, 6 H, J = 7.1), 3.42 (d, 1 H, J = 7.5), 4.21–4.35 (m, 4 H), 4.66 (dd, 1 H, J = 7.5, 4.1), 4.71 (d, 1 H, J = 4.1); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 13.7, 13.8, 47.4, 62.3, 62.6, 72.3, 166.5, 170.1; IR (film) cm^{-1}: 3480, 2909, 2873, 1739, 1371, 1302, 1286, 1220, 1161, 1113, 1024.

9. A Simadzu GC-8A gas chromatograph equipped with a flame ionization detector and ULBON HR-101 capillary column (23 m × 0.25 mm) was used.

10. Ethanol was freshly distilled from magnesium ethoxide.

11. If it proves difficult to control the rate of addition by adjusting the nitrogen pressure, a static positive pressure of nitrogen can be employed and the flask containing the sodium ethoxide solution can be moved up or down slightly to regulate the rate of addition.

12. More rapid addition of the base results in a lower yield of **3**.

13. The spectral data for **3** are as follows: ^{1}H NMR (300 MHz, CDCl3) δ: 1.31 (t, 6 H, J = 7.1), 3.66 (s, 2 H), 4.21–4.32 (m, 4 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 13.9, 51.9, 62.1, 166.6; IR (film) cm^{-1}: 2988, 1751, 1372, 1330, 1200, 1029.

14. Epoxide **3** should be free from **2** because **2**, if subjected to the next step (**3** **4**), leads to the (2R,3R)-diastereoisomer via an S_N2 displacement process. If **3** is contaminated with **2**, the distillate can be purified using the same column as above (Note 6), employing hexane–ether (5:1) as eluent and 60-mL fractions. In the checkers' hands a trace of **2** was always present. Therefore, the checkers recommend that the crude product be purified by flash chromatography (as in step A) to remove residual **2** prior to distillation.

15. The literature values[2] for the antipode (95% pure by GLC analysis) are as follows: bp 98–99°C (3 mm) and $[\alpha]_D^{23}$ +105.49° (ether, *c* 1.413).

16. DMAP was purchased from Nacalai Tesque, Inc. (Japan) and used as received.

17. N,N-Dimethylformamide was distilled from calcium hydride.

18. Azidotrimethylsilane was purchased from Aldrich Chemical Co., Ltd. (95% pure) and used as received.

19. The reaction of azidotrimethylsilane and ethanol, which gives hydrogen azide and ethoxytrimethylsilane, is exothermic and the hydrogen azide immediately forms a salt with 4-(dimethylamino)pyridine, a part of which cannot be dissolved in N,N-dimethylformamide and precipitates.

20. Commercial, reagent grade chloroform was used as received.

21. The solution was prepared by carefully mixing 3.28 mL acetyl chloride with sufficient dry ethanol to reach a final volume of 20 mL.

22. This operation transforms any diethyl (2S,3R)-2-azido-3-(trimethylsiloxy) succinate present to the desired diethyl (2S,3R)-2-azido-3-hydroxysuccinate.

23. The optical rotation of 4 is highly dependent both on solvent and sample concentration. For example, $[\alpha]_D$ values observed in chloroform vary as follows: +1.43° (*c* 3.25) , +3.69° (*c* 6.61), and +5.68° (*c* 16.7).

24. The spectral data for 4 are as follows: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.30 (t, 3 H, J = 7.1), 1.31 (t, 3 H, J = 7.1), 3.38 (d, 1 H, J = 5.4), 4.20–4.34 (m, 5 H), 4.63 (dd, 1 H, J = 5.4, 2.7); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 13.90, 13.94, 62.3, 62.6, 64.3, 72.0, 166.9, 170.7; IR (film) cm^{-1}: 3480, 2989, 2943, 2910, 2877, 2120, 1751, 1724, 1209, 1114, 1028. The signal corresponding to C_3 proton of the (2R,3R) diastereoisomer appears at δ 4.73 (dd, J = 5.6, 2.4).

25. 10% Palladium on carbon catalyst was purchased from Ishizu Seiyaku Co., Ltd. (Japan) and employed as received.

26. Commercial reagent-grade ethyl acetate was used as received. Ethyl acetate is the best choice of solvent with regard to reaction time. Alcohols such as methanol or ethanol should be avoided because di-tert-butyl dicarbonate is decomposed by these solvents.

27. An MRK catalytic hydrogenation apparatus (Mitamura Riken Co., Japan) was used.

28. Di-tert-butyl dicarbonate (97% pure) was purchased from Wako Pure Chemical Industries, Ltd. (Japan) and used as received.

29. The time required for completion of the reaction depends on the activity of the palladium catalyst employed.

30. This solvent system is convenient to separate less polar contaminants such as tert-butyl acetate or unchanged di-tert-butyl dicarbonate.

31. The seeds required for crystallization are available by cooling a small portion (1 mL) of the hexane–ether solution to −78°C and scratching the highly viscous gum that separates with a glass rod. The rate of crystallization is very slow and additional ether is sometimes required when an oil phase appears on cooling instead of development of crystals.

32. When commercial chloroform (stabilized with 0.3–1% of ethanol) was used as received for optical rotation measurements, the submitters obtained $[\alpha]_D^{24}$ +19.3° (*c* 6.05). However, chloroform passed through a silica gel column prior to the measurement gave a much higher value as indicated. The optical rotation of **5** observed with commercial ethanol was ($[\alpha]_D^{24}$ +19.3° (EtOH, *c* 6.32)), while that determined using absolute EtOH [distilled from $Mg(OEt)_2$] led to a much lower value $[\alpha]_D^{24}$ +7.19° (EtOH, *c* 6.32). The spectral properties for pure **5** are as follows: ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.25 (t, 3 H, J = 7.1), 1.32 (t, 3 H, J = 7.1), 1.46 (s, 9 H), 3.47 (s (br), 1 H), 4.14–4.34 (m, 4H), 4.50 (s (br), 1 H), 4.83 (dd, 1 H, J = 7.9, 1.3), 5.51 (d, 1 H, J = 7.9); ^{13}C NMR ($CDCl_3$, 50 MHz) δ:13.9, 14.0, 28.2, 56.9, 61.8, 62.1, 72.0, 80.3, 155.5, 168.5, 171.5; IR (film) cm^{-1}: 3450 (br), 2983, 1720, 1507, 1369, 1241, 1218, 1188, 1117, 1059, 1029.

33. After isolation of the second crop, the recovered oily product mixture should be purified, if required, by column chromatography (100 g of silica gel/g oil)

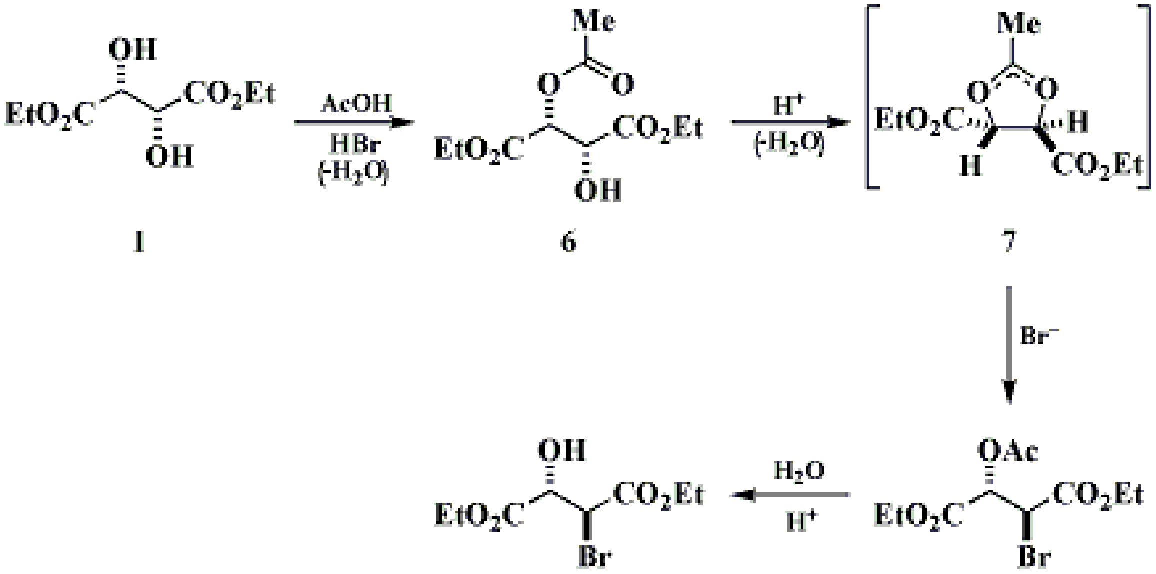
using hexane–ethyl acetate (8:1). The rate of crystallization for the third crop becomes much slower, requiring 2 to 3 days at −30°C; cooling at −78°C results in oil separation. Careful chromatography on silica gel of the oily residue remaining after concentration of the mother liquors of the third crystallization affords the pure 2R,3R diastereomer. Spectral data for diethyl (2R,3R)-2-(N-tert-butoxycarbonyl)amino-3-hydroxysuccinate are as follows: ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.30 (t, 3 H, J = 6.9), 1.31 (t, 3 H, J = 7.0), 1.41 (s, 9 H), 3.45 (d, 1 H, J = 5.0), 4.22–4.30 (m, 4 H), 4.68 (d (br), 1 H, J = 3.3), 4.78 (d (br), 1 H, J = 8.3), 5.26 (d (br), 1H, J = 9.3); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 13.9, 14.0, 28.0, 56.0, 61.9, 62.4, 71.1, 80.0, 155.2, 169.4, 171.9.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Optically active β-hydroxy-α-amino acids are important not only as constituents of biologically active peptides,[5 6] but also as precursors to β-lactam antibiotics.[7 8 9 10] Various synthetic approaches to compounds of this class have been reported involving the traditional resolution of racemic compounds,[11] asymmetric syntheses,[12 13 14 15 16 17 18] or the derivatization of appropriate chiral templates.[19 20 21 22] The procedure described here is a practical preparation of diethyl erythro-3-hydroxy-N-(tert-butoxycarbonyl)-L-aspartate (**5**) in high optical purity, amenable to large scale preparation. The synthetic route involves the transformation of diethyl L-tartrate to diethyl (2S,3S)-2-bromo-3-hydroxysuccinate (**2**),[2] preparation of diethyl (2R,3R)-2,3-epoxysuccinate (**3**),[2] nucleophilic cleavage of the epoxide by azide to give diethyl (2S,3R)-2-azido-3-hydroxysuccinate (4),[9f] and the single-pot transformation of the azido group into the N-(tert-butoxycarbonyl)amino group[23] to give **5** in high enantiomeric and diastereomeric purity.



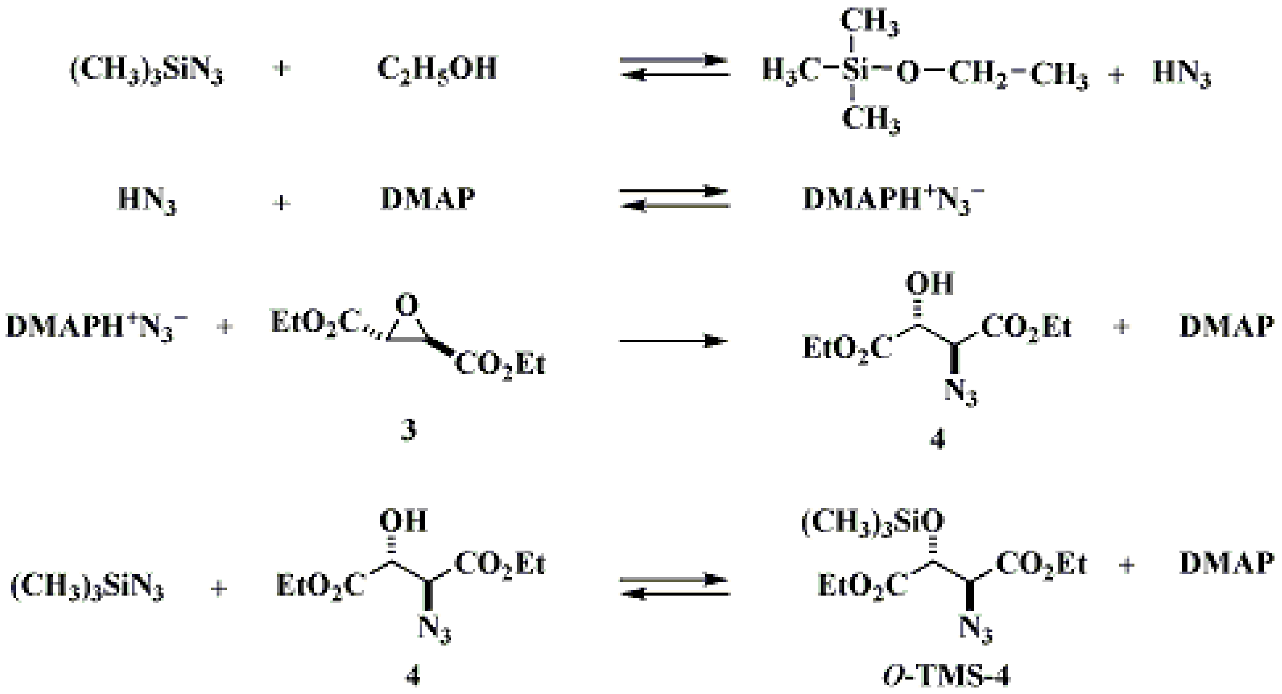
1 6 7 2 8

The first and second steps are examples of a standard method for the stereospecific synthesis of epoxides via vicinal acetoxy bromides from vicinal diols.[24 25] Based upon kinetic studies, the stereochemical outcome, and the observation of an intermediate carbocation by NMR spectroscopy,[24] the mechanism of the first step has been rationalized to involve monoacetylation of the diol, cyclization to a 1,3-dioxolan-2-ylium ion, and capture of this intermediate by bromide ion. If this mechanism is valid for the present case, the reaction can be illustrated as shown in Scheme 1. The experimental findings (Note 3) correspond reasonably with this mechanistic scheme. Reaction of **1** with 30% HBr in acetic acid proceeded, as shown by both TLC and isolation experiments, with the initial formation of **8** (R_f = 0.53) followed by the gradual increase in the formation of **2** (R_f = 0.36) because of increase in the content of water liberated in the medium. At complete consumption of **1**, an additional minor product **6** (R_f = 0.21) was detected by TLC. The presence of **6** may result from competition by the increasing concentration of water as the reaction progresses for **7** relative to bromide. Thus, although **1** had been completely consumed as observed by TLC, the subsequent transesterification process (ethanol/HCl) gives rise to a mixture of **2** and a small amount of **1** (derived from **6**) which are easily separated by column chromatography on silica gel.

The optimal base for closure to epoxide **2** is sodium ethoxide in ethanol, as potassium hydroxide in ethanol, sodium or potassium carbonate in ethanol, or benzyltrimethylammonium hydroxide in ethanol resulted in the formation of a complex mixture of decomposition products arising mainly from deprotonation at carbon.

For the azide cleavage of chiral 2,3-epoxy diester **3**, the submitter's earlier procedure[9f] was modified to reduce the amount of azide reagent (azidotrimethylsilane, $TMSN_3$) and lower the reaction temperature. This effort, coupled with the submitter's recent finding that such a reaction can be accelerated in the presence of amines,[18,9i] led to the use of the system described above. The reaction may proceed by the pathway shown in Scheme 2. The reactive azide species could be DMAPH + N_3^- formed from DMAP and

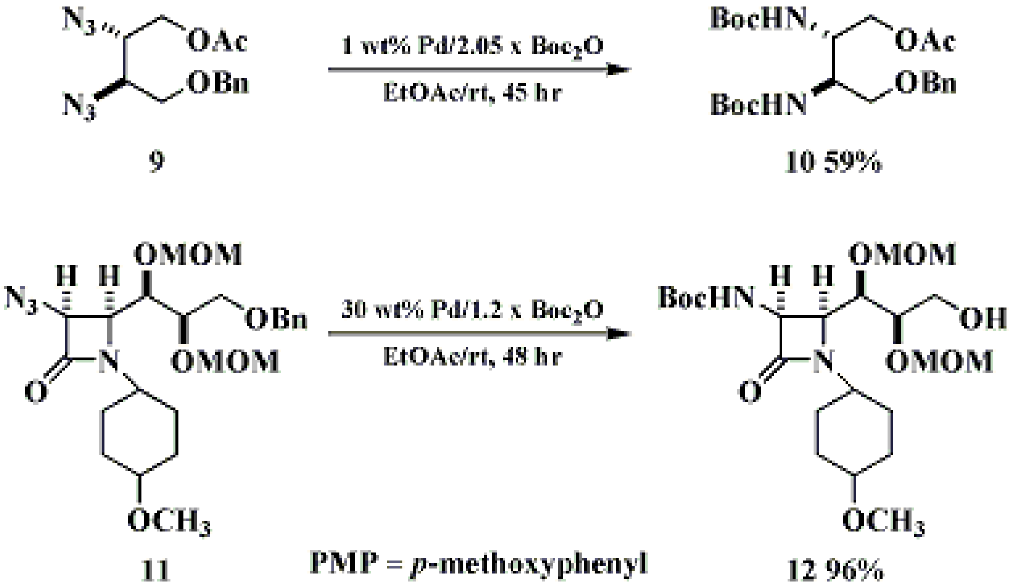
HN_3 which are, in turn, initially generated by the exothermic reaction of $TMSN_3$ and ethanol, or later catalytically from reaction of $TMSN_3$ with the desired product 4. The reaction occurs with these reagents at a practical rate at 25°C, in sharp contrast to the previous more vigorous conditions (2 equiv or more of $TMSN_3$-CH_3OH (1:1) at 60°C in DMF).[9f] In addition, this reaction does not require any special precautions other than use of a well-ventilated hood since the generation a high concentration of the hazardous, free HN_3 is avoided.[18],[9i] The initial product is a mixture of 4 and its O-silylated derivative (O-TMS-**4**). The latter is converted to 4 upon treatment of the mixture with HCl in ethanol affording 4 in over 85% yield.



The final one-pot, two-stage conversion of azide to an amino group and then to the related tert-butoxycarbonyl derivative was effected as before.[23] Catalytic hydrogenolysis of 4 over 10% Pd-carbon in ethyl acetate in the presence of di-tert-butyl dicarbonate for 4 hr at room temperature provides a crude product consisting of **5** and its (2R,3R)-isomer (in the same ratio as that observed for 4 and its (2R,3R)-isomer) that can be separated by fractional crystallization from a hexane–ether mixed solvent at −30°C.

This procedure has been used by Ohfune[26] to convert N-(benzyloxycarbonyl)amino groups to N-(tert-butoxycarbonyl)amino groups in one pot, the Cbz to Boc switching protocol. This procedure is efficient because no tedious isolation of the intermediate amine is required. The following examples illustrate the advantages of this one-pot procedure. In addition, the amount of palladium catalyst employed controls the chemoselectivity of the transformation. For instance, employing 1–2 wt% Pd/g of substrate, the 1,2-diazide **9** can be changed to the corresponding, protected 1,2-diamine derivative **10**, while the O-benzyl group is kept unchanged.[9i] On the other hand, employing 30 wt% Pd/g of substrate, both the azido and O-benzyl groups of **11** can be transformed to N-(tert-butoxycarbonyl)amino and hydroxyl groups, (**12**) respectively

(Scheme 3).[27]



A recent report by Evans[28] of azide reduction by $SnCl_2$ in aqueous dioxane and in situ amine protection by addition of Boc_2O has demonstrated that other methods of reduction of azides may be feasible if catalytic reduction of the azide is precluded because of the presence of protective groups sensitive to hydrogenolysis.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

brine

D-Aspartic acid, N-[(1,1-dimethylethoxy)carbonyl]-3-hydroxy-, diethyl ester, threo-

diethyl erythro-3-hydroxy-N-(tert-butoxycarbonyl)-L-aspartate

Pd-carbon

ethanol (64-17-5)

potassium carbonate (584-08-7)

hydrogen chloride, HCl (7647-01-0)

acetic acid (64-19-7)

ethyl acetate, EtOAc (141-78-6)

methanol (67-56-1)

ether (60-29-7)

hydrogen (1333-74-0)

acetyl chloride (75-36-5)

chloroform (67-66-3)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

HYDROBROMIC ACID, hydrogen bromide, HBr (10035-10-6)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

carbon (7782-42-5)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

palladium (7440-05-3)

L-tartaric acid (87-69-4)

triethyl orthoformate (122-51-0)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

dioxane (5703-46-8)

N,N-dimethylformamide (68-12-2)

magnesium ethoxide (2414-98-4)

benzyltrimethylammonium hydroxide (100-85-6)

hexane (110-54-3)

calcium hydride (7789-78-8)

hydrogen azide

azidotrimethylsilane (4648-54-8)

diethyl L-tartrate

4-(dimethylamino)pyridine (1122-58-3)

Diethyl (2S,3S)-2-bromo-3-hydroxysuccinate (80640-14-8)

Diethyl (2R,3R)-2,3-epoxysuccinate (74243-85-9)

diethyl (2S,3R)-2-bromo-3-hydroxy succinate

Diethyl (2S,3R)-2-azido-3-hydroxysuccinate (101924-62-3)

Diethyl (2S,3R)-2-(N-tert-butoxycarbonyl)amino-3-hydroxysuccinate, DIETHYL (2S,3R)-2-(N-tert-BUTOXYCARBONYL)AMINO- 3-HYDROXYSUCCINATE (174682-54-3)

ethoxytrimethylsilane (1825-62-3)

diethyl (2S,3R)-2-azido-3-(trimethylsiloxy)succinate

diethyl (2R,3R)-2-(N-tert-butoxycarbonyl)amino-3-hydroxysuccinate

Di-tert-butyl dicarbonate (24424-99-5)

(2S,3S)-2-bromo-3-hydroxysuccinate

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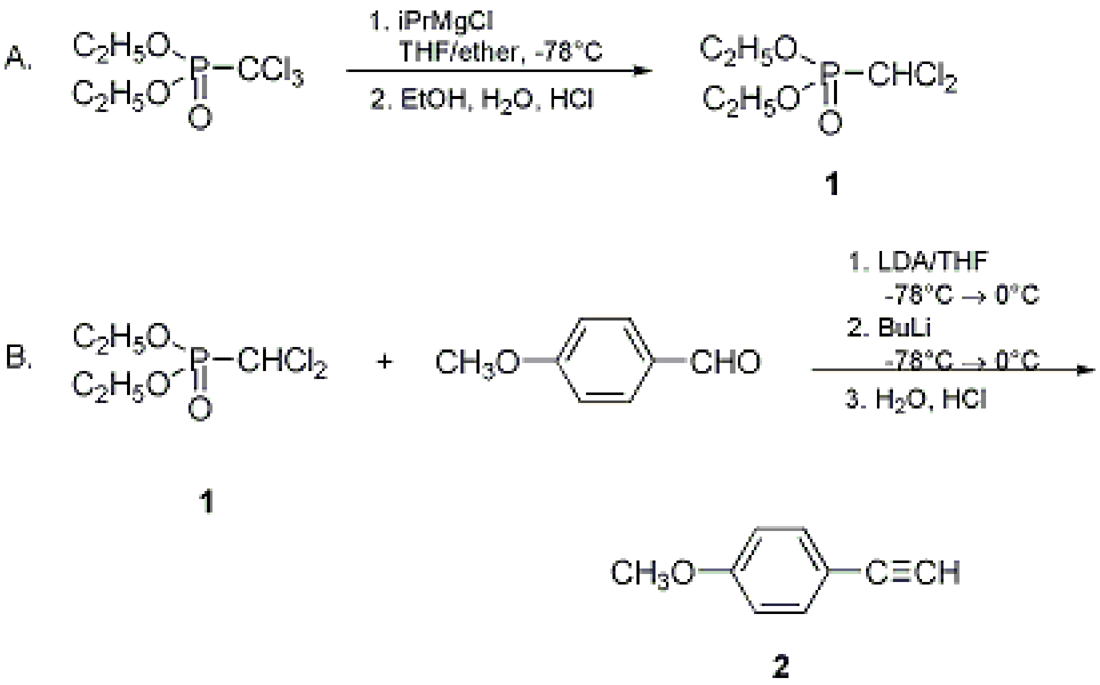
Organic Syntheses, CV 9, 230

DIETHYL (DICHLOROMETHYL)PHOSPHONATE. PREPARATION AND USE IN THE SYNTHESIS OF ALKYNES: (4-METHOXYPHENYL)ETHYNE

[Phosphonic acid, (dichloromethyl)-, diethyl ester to prepare Benzene, 1-ethylnyl-4-methoxy-]



Submitted by Angela Marinetti and Philippe Savignac[1].
Checked by Catherine Dubuisson and Louis S. Hegedus.

1. Procedure

A. *Diethyl (dichloromethyl)phosphonate*, **1**. An oven-dried, 1-L, four-necked, round-bottomed flask (or a 1-L, three-necked flask with a Claisen head fitted in a side neck) is fitted with an efficient mechanical stirrer, thermometer, reflux condenser with a bubbler, and a 200-mL, pressure-equalizing addition funnel with a nitrogen inlet. Under a gentle flow of nitrogen the flask is charged with 400 mL of tetrahydrofuran (THF) (Note 1). The addition funnel is charged with a 1.9 M solution of isopropylmagnesium chloride in diethyl ether (83 mL, 0.158 mol) (Note 2). The mixture is cooled to −78°C with a dry ice/acetone bath (Note 3), and isopropylmagnesium chloride is added over a few minutes with stirring. At this temperature, a solution of diethyl (trichloromethyl)phosphonate (38.3 g, 0.150 mol) (Note 4) in tetrahydrofuran (50 mL) is added dropwise over 15 min. The resulting solution is stirred for an additional 15 min at −78°C producing a clear orange solution. Anhydrous ethanol (12 g, 0.260 mol) in tetrahydrofuran (15 mL) is added dropwise at

–78°C, producing a clear yellow solution. The resulting mixture is stirred for a few minutes, then allowed to warm slowly to –40°C. The reaction mixture is poured into a beaker containing a stirred mixture of 3 M hydrochloric acid (70 mL), and an equal volume of crushed ice and dichloromethane (70 mL). The yellow color initially dissipates, but the solution becomes yellow orange upon warming to room temperature. The organic layer is separated, and the aqueous layer is extracted with dichloromethane (2 × 60 mL). The extracts are combined and dried over anhydrous magnesium sulfate. After the filtration, the solvents are evaporated on a rotary evaporator. The bright yellow, crude liquid (36.3 g) is transferred to a pear-shaped flask fitted with a 10-cm Vigreux column and distilled under reduced pressure to give 26.6 g (80%) of diethyl (dichloromethyl)phosphonate, **1**, as a pale yellow liquid, bp 115–119°C/9 mm, >90% pure by ^{1}H, ^{13}C and ^{31}P NMR spectroscopy (Note 5) and (Note 6).

B. *(4-Methoxyphenyl)ethyne*, **2**. An oven-dried, 1-L, four-necked, round-bottomed flask is fitted as above, flushed with nitrogen, and charged with a solution of butyllithium in hexane (1.56 M, 92 mL, 0.143 mol) (Note 7). The solution is cooled with stirring to –20°C with a dry ice/acetone bath and a solution of diisopropylamine (15.1 g, 0.149 mol) (Note 8) in tetrahydrofuran (220 mL) (Note 1), is added dropwise over 15 min. The resulting clear solution is cooled to –78°C and treated by the dropwise addition of a solution of 1 (30 g, 0.136 mol) and 4-methoxybenzaldehyde (18.1 g, 0.133 mol) (Note 8) in tetrahydrofuran (60 mL) over 30 min. The resulting brown solution is stirred at –78°C for an additional 30 min, then allowed to warm slowly to 0°C over 60 min. The resulting mixture is then cooled to –78°C and a solution of butyllithium (1.56 M in hexane, 183 mL, 0.285 mol) (Note 7) is added dropwise over 20 min. The resulting brown solution is stirred at –78°C for an additional 30 min, then allowed to warm slowly to 0°C over 60 min. At this temperature, the reaction mixture is quenched by the dropwise addition of 3 M hydrochloric acid to pH 5–6 (125–130 mL). The brown color has practically disappeared and the solution is yellow orange. The organic layer is separated and the aqueous layer is extracted with diethyl ether (3 × 50-mL). The extracts are combined, washed with water (3 × 10 mL), and dried over anhydrous magnesium sulfate. Magnesium sulfate is removed by filtration and the solvents are evaporated on a rotary evaporator. The residue is dissolved in hexane (200 mL) and filtered after 30 min. Solvent is again completely evaporated under reduced pressure. Crude product **2** thus obtained is purified by column chromatography on silica gel (Note 9) to afford 11.0 g (63%) of pure (4-methoxyphenyl)ethyne as a colorless liquid, bp 70–72°C (3 mm) that gives white crystals on standing in the freezer (Note 10).

2. Notes

1. Tetrahydrofuran is obtained from S.D.S. Company and is purified by distillation from sodium and benzophenone.
2. Isopropylmagnesium chloride (2 M in diethyl ether) is available from Aldrich

Chemical Company, Inc., and is standardized before use by titration against a solution of benzyl alcohol in toluene with cuproine (2,2'-biquinoline).

3. An alternative cooler was also used by the submitters consisting of a Dewar partially filled with liquid nitrogen.

4. Diethyl (trichloromethyl)phosphonate (97%) either purchased from Aldrich Chemical Company, Inc., or prepared according to a described procedure[2] is used.

5. The crude liquid could be distilled using a Kugelrohr apparatus. The main fraction (27.5 g, 83% yield) consists of a clear orange liquid that was collected at 145–155°C (oven temperature)/9–10 mm. ^{1}H NMR (200 MHz, $CDCl_3$) indicates that this material is of the same purity as that from conventional distillation.

6. The product displays the following spectroscopic data: ^{31}P NMR (81 MHz, $CDCl_3$) δ: +10.9; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.29 (t, 6 H, CH_3), 4.22 (dq, 4 H, CH_2), 5.6 (d, 1 H, $^{2}J_{H-P}$ = 2, CH); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 16.2 (d, J_{C-P} = 5.9, CH_3), 60.7 (d, J_{C-P} = 178, CH), 65.0 (d, J_{C-P} = 7.4, CH_2) ppm.

7. Butyllithium (1.6 M solution in hexane) is available from Janssen Chimica or Aldrich Chemical Company, Inc., and is standardized before use by titration against a solution of benzyl alcohol in toluene with cuproine (2,2'-biquinoline) or with (±)-2-butanol and 1,10-phenanthroline in diethyl ether.

8. Diisopropylamine (99%) and 4-methoxybenzaldehyde (98%) were purchased from Aldrich Chemical Company, Inc., and used without purification.

9. The crude product is purified by chromatography (200 g of silica gel, Silitech 32–63 •m, purchased from ICN Biomedicals; column diameter, 5.5 cm). Elution is performed first with hexanes (200 mL) and then with hexanes-diethyl ether (20:1). Alternatively, the submitters purified the product by distillation from a pear-shaped flask using an 8-cm fractionating column.

10. The product displays the following spectroscopic data: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.02 (s, 1 H), 3.80 (s, 3 H), 6.8 (AA'BB', 2 H), 7.4 (AA'BB', 2 H); ^{13}C NMR (50, MHz, $CDCl_3$) δ: 55.2 (OCH_3), 75.8 (CCH), 83.6 (CCH), 113.9 [CH (Ar)], 114.0 (C-C□CH), 133 [CH (Ar)], 159.9 (COCH-3) ppm.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The procedure described in Part A represents a convenient synthesis ofdiethyl (dichloromethyl)phosphonate, **1**, for large-scale preparations (up to 1 mol). The use of isopropylmagnesium chloride instead of butyllithium[3,4] reduces the amount of by-products,[5] simplifies the purification step, and improves the yield. An alternative

synthetic method for **1** is chlorination of diethyl (chloromethyl)phosphonate;[6,7] however, yields and selectivities are lower than in the procedure described here. Diethyl (dichloromethyl)phosphonate, **1**, or the corresponding lithiated derivative, are useful intermediates in organic synthesis: 1,1-dichloroalkenes[3,4,6] as well as terminal alkynes[4] have been prepared.

Part B shows the use of **1** as starting material for the synthesis of (4-methoxyphenyl) ethyne. The generation of the phosphorylated carbanion is performed through metalation with lithium diisopropylamide (LDA). A mixture containing the phosphorus reagent **1** and the aldehyde is added directly to LDA, in order to trap the unstable phosphorylated, lithiated carbanion, thus preventing decomposition and side reactions. The formation of (4-methoxyphenyl)ethyne described here is an example of a general synthetic method for the conversion of aldehydes into acetylenes, on a large scale, by means of diethyl (dichloromethyl)phosphonate, **1**. The methodology is well suited for the synthesis of a wide variety of acetylenic compounds, such as $C_9H_{19}C$ CH, $(C_2H_5)_2CHC$ CH, $C_6H_5CH=CHC$ CH,[4] and analogous terminal alkynes. Several methods for the preparation of alkynes based on phosphorus reagents have been reported previously. Each of these procedures can be regarded as an extension of the Wittig-Horner olefin synthesis. In the final step the olefins are converted into the corresponding alkynes. The first method that employed the PPh_3-CBr_4 couple (or PPh_3- CBr_4- zinc dust) was introduced by Corey and Fuchs[8] (1972). The amounts of PPh_3 involved (2 or 4 equiv and of PPh_3O formed during the reaction, are obstacles for large scale synthesis. Dimethyl diazomethylphosphonate first prepared by Seyferth[9] in 1971 was shown, by Colvin and Hamill[10] in 1977, then by Gilbert and Weerasooriya[11] in 1982, to be an effective reagent for the transformation of aldehydes, alkyl aryl ketones or diaryl ketones into alkynes. However, this reagent is rather difficult to prepare (four steps, 46% yield), and very hazardous to handle (explosive decomposition on distillation), and therefore is unsuitable for preparative scale synthesis.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Benzene, 1-ethylnyl-4-methoxy-

sodium and benzophenone

cuproine

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

diethyl ether (60-29-7)

nitrogen (7727-37-9)

toluene (108-88-3)

zinc (7440-66-6)

Benzyl alcohol (100-51-6)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

isopropylmagnesium chloride (1068-55-9)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

hexane (110-54-3)

(±)-2-butanol (78-92-2)

lithium diisopropylamide (4111-54-0)

1,10-phenanthroline (66-71-7)

diisopropylamine (108-18-9)

4-methoxybenzaldehyde (123-11-5)

Dimethyl diazomethylphosphonate

2,2'-biquinoline (119-91-5)

Diethyl (dichloromethyl)phosphonate, Phosphonic acid, (dichloromethyl)-, diethyl ester (3167-62-2)

(4-Methoxyphenyl)ethyne (768-60-5)

diethyl (trichloromethyl)phosphonate (866-23-9)

diethyl (chloromethyl)phosphonate (3167-63-3)

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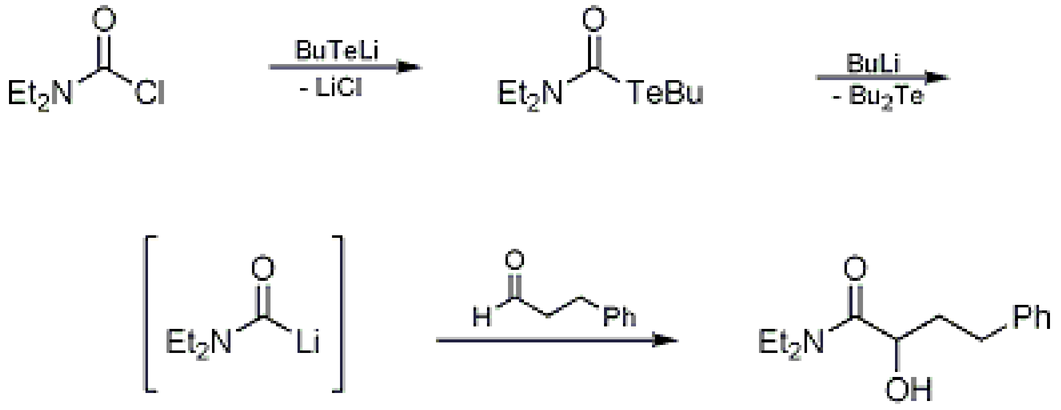
Organic Syntheses, CV 9, 234

GENERATION OF N,N-DIETHYLCARBAMOYLLITHIUM VIA LITHIUM-TELLURIUM EXCHANGE AND ITS REACTION WITH 3-PHENYLPROPANAL: N,N-DIETHYL-2-HYDROXY-4-PHENYLBUTANAMIDE

[Benzenebutanamide, N,N-diethyl-α-hydroxy-]



Submitted by Nobuaki Kambe, Toru Inoue, and Noboru Sonoda[1].
Checked by Thomas G. Gant and Albert I. Meyers.

1. Procedure

Finely ground elemental tellurium (13.40 g, 105 mmol) (Note 1) and tetrahydrofuran (THF, 400 mL) (Note 2) are placed under nitrogen (N_2) in a flame-dried, 1-L, three-necked, round-bottomed flask equipped with a N_2 inlet, 100-mL pressure-equalizing dropping funnel, and a rubber septum. Into the mixture is added ca. 65.5 mL (1.6 N in hexane, ca. 105 mmol) of butyllithium (Note 3) dropwise with a syringe through the septum with stirring at room temperature until the mixture becomes a pale yellow homogeneous solution (Note 4). The solution is stirred for 10 min, then cooled to −78°C. Diethylcarbamoyl chloride (12.7 mL, 13.56 g, 100 mmol) (Note 5) is injected through the septum with a syringe, and the solution is stirred at −78°C for 10 min. The cold bath is removed and the solution is allowed to warm to room temperature, then stirred for 1 hr. It is cooled again to −78°C, and 62.5 mL (1.6 N, 100 mmol) of butyllithium (Note 3) is injected over a 3-min period. After the solution is stirred at −78°C for 5 min, 13.42 g (100 mmol) of 3-phenylpropanal (Note 6) in 50 mL of THF is added from the dropping funnel over a 5-min period. The mixture is stirred for 10 min, warmed to room temperature, and stirred for 1 hr. The mixture is poured into 200 mL of a saturated ammonium chloride solution and extracted with diethyl ether (Et_2O) three times, 30 mL each. The combined organic layers are dried over anhydrous magnesium sulfate, and concentrated on a rotary evaporator at ca. 5 mm. The residual

yellowish brown oil is chromatographed (silica gel, 50 mm × 25 cm) (Note 7). The first, pale yellow fraction eluted with ca. 400 mL of hexane contains dibutyl telluride (23.62 g, 93% based on tellurium used) (Note 8). The next 500-mL fraction (eluted with hexane/Et_2O, 10/1) contains by-products (Note 9). The desired product is eluted in the third fraction (ca. 500 mL of Et_2O) that is concentrated on a rotary evaporator and distilled to afford 19.35 g of N,N-diethyl-2-hydroxy-4-phenylbutanamide as a pale yellow viscous oil (bp 155–156°C at 0.6 mm, 82%) (Note 10),(Note 11),(Note 12).

2. Notes

1. The submitters used tellurium pieces from Aldrich Chemical Company, Inc., that were ground with a mortar and pestle just before use. The checkers found that direct use of tellurium powder (–60 mesh, Aldrich Chemical Company, Inc.) gave similar results.
2. THF purchased from Wako Pure Chemical Industries, Ltd. (Japan) was used after distillation from Drynap. Drynap is a registered trademark of an alloy of sodium (above 8 wt%) and lead (90 wt%) produced by Dojin Chemical Research Center, Ltd. (Japan). Although Drynap is not essential and any procedure can be used for drying THF provided that the THF is sufficiently dry for the usual reactions of organolithium compounds, the submitters often use this drying reagent when a large amount of solvent is needed since it is mild, much safer than sodium, and is easy to handle.
3. The submitters used butyllithium (1.6 M in hexane) from Nacalai Tesque Company, Ltd. (Japan). The checkers used butyllithium (1.6 M in hexane) from Aldrich Chemical Company, Inc.
4. The reaction is slightly exothermic. At this stage, lithium butanetelluroate (BuTeLi) is formed. (The checkers noted a deep red color as the BuLi was added.) BuTeLi should be prepared slightly in excess to the carbamoyl chloride. The subsequent step produces carbamoyllithium that may react with any excess carbamoyl chloride to give an undesired oxamide by-product.
5. The submitters used diethylcarbamoyl chloride from Aldrich Chemical Company, Inc., after fractional distillation. The checkers used the reagent without further purification with similar results.
6. The submitters used 3-phenylpropanal from Wako Pure Chemical Industries, Ltd., after distillation. The checkers used reagent obtained from Lancaster Synthesis without further purification with similar results.
7. The submitters used silica gel (mesh 100–200, BW-820 MH) from Fuji Davison Chemical, Ltd. (Japan). The checkers used radial chromatography (silica gel 60 PF 254 with gypsum, EM Science) with hexane/ethyl acetate (4/1) as eluent for small scale reactions. The checkers used flash chromatography (240 g of silica gel, grade 633, 47 × 61 microns, Davison Chemical) with hexane (1.5 L), hexane/ether (10/1, 1.5 L), and ether (1.5 L) as eluent for large scale reactions (100 mmol).
8. Elemental tellurium can be recovered from dibutyl telluride by the following procedure. Under nitrogen, naphthalene (4.0 g) and dry THF (100 mL) are

placed in a flame-dried, 200-mL, three-necked, round-bottomed flask equipped with a N_2 inlet, reflux condenser, and rubber septum. Sodium pieces (4.28 g, 186 mmol) are added to the solution slowly with stirring. After the solution turns deep blue, 4.50 g (18.6 mmol) of dibutyl telluride is added over a 3-min period with a syringe at room temperature. The rubber septum is replaced with a glass stopper and the mixture is refluxed for 2 days. The mixture is cooled to room temperature and ethanol is added very slowly until the sodium completely disappears. Air is bubbled into the solution with stirring for one day. The black solids that are obtained by filtration are washed well with Et_2O and dried (0.2 mm, 250°C, 4 hr) to give 2.22 g of elemental tellurium (93%, based on dibutyl telluride used). These conditions have not been optimized.

9. This fraction contains 3-phenylpropanal and 1-phenylheptan-3-ol that is formed by the addition of butyllithium to 3-phenylpropanal.

10. The physical properties are as follows: ^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.09 (t, 3 H, J = 6.9), 1.10 (t, 3 H, J = 6.9), 1.72–1.94 (m, 2 H), 2.72–2.87 (m, 2 H), 2.98–3.13 (m, 2 H), 3.25 (dq, 1 H, J = 13.8, 6.9), 3.52 (dq, 1 H, J = 13.8, 6.9), 3.87 (d, 1 H, J = 7.8), 4.24 (ddd, 1 H, J = 7.8, 7.8, 2.9), 7.16–7.37 (m, 5 H); ^{13}C NMR (68 MHz, $CDCl_3$) δ: 12.8, 14.0, 31.3, 37.4, 40.2, 40.8, 67.0, 120.0, 128.5, 128.6, 141.4, 173.6; IR (NaCl, neat) cm^{-1}: 3408, 1636. Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.45; H, 9.00; N, 5.95. Found: C, 71.17; H, 9.08; N, 6.01.

11. Glassware is cleaned by soaking it overnight in a concd nitric acid bath.

12. When methyl benzoate was used as an electrophile instead of 3-phenylpropanal, N,N-diethylphenylglyoxylamide [$Et_2NC(O)C(O)Ph$] was obtained in a similar manner as a pale yellow viscous oil (bp 118–120°C at 0.2 mm, 13.40 g, 65 mmol, 65%), ^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.15 (t, 3 H, J = 7.2), 1.29 (t, 3 H, J = 7.2), 3.24 (q, 2 H, J = 7.2), 3.56 (q, 2 H, J = 7.2), 7.50 (t, 2 H, J = 7.3), 7.63 (t, 1 H, J = 7.3), 7.94 (d, 2 H, J = 7.3); IR (NaCl, neat) cm^{-1}: 1681, 1636, 1448, 1232, 721.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

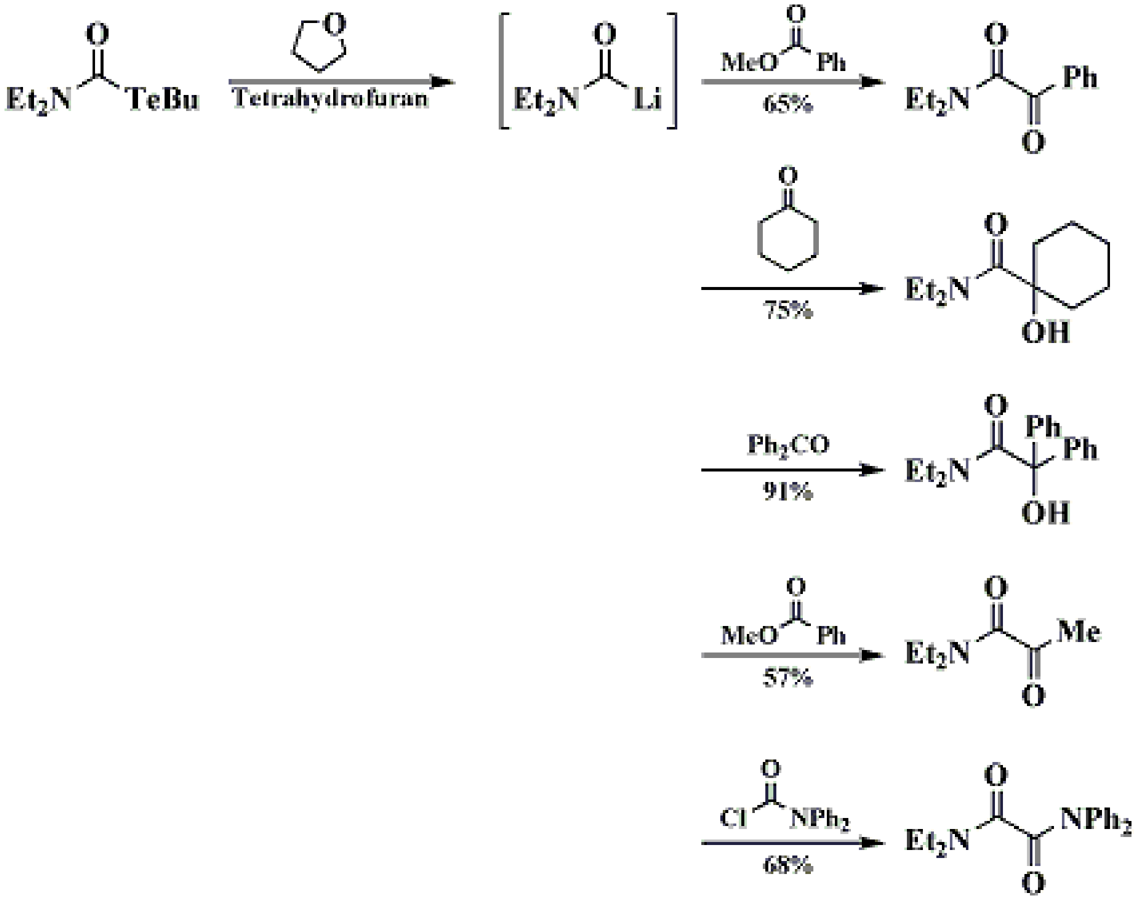
3. Discussion

Organic tellurium compounds react readily with organolithium reagents to give the thermodynamically more stable organolithium compounds via tellurium ate complexes. The lithium-tellurium exchange reaction proceeds quite rapidly at low temperatures, and can be used for the generation of a variety of organolithium compounds,[2,3,4,5] including very reactive umpolung species, such as acyl-,[3] aroyl-,[3] and carbamoyllithiums.[4] Among these, acyl- and aroyllithiums are kinetically very unstable, even at low temperatures, and dimerize quickly unless a suitable electrophile is present when generated. In contrast N,N-dialkylcarbamoyllithiums are potentially

useful synthetically since they are stable in THF at −78°C and can be efficiently trapped with various electrophiles.[4]

Carbamoyllithiums are attractive umpolung species that enable the straightforward introduction of carbamoyl moieties into organic molecules as nucleophiles. Although several methods have been reported for the generation of carbamoyllithiums, such as abstraction of the formyl hydrogen,[6] insertion of carbon monoxide into lithium amides[7] or lithium diaminocuprates,[8] and transmetalation of a biscarbamoylmercury,[9] these procedures have some disadvantages. Very few examples of hydrogen abstraction are reported, and satisfactory yields of the addition products are obtained only in the case of N,N-diisopropylcarbamoyllithium, or when the reaction is conducted in the presence of an electrophile. Reaction of carbon monoxide (CO) with lithium amides often gave complex results arising from the incorporation of two CO molecules. Diaminocuprates do not react satisfactorily with CO under atmospheric pressure.

The lithium-tellurium exchange reaction illustrated here provides a useful alternative to known methods. The reaction can be used to produce various α-hydroxyamides by using aldehydes and ketones as the electrophiles. Trapping the generated carbamoyllithium compounds with esters affords α-ketoamides in good yields (Scheme 1). α-Ketoamides with an aliphatic substituent on the carbonyl carbon cannot be obtained by palladium-catalyzed double carbonylation.[10] Successful trapping of N, N-diethylcarbamoyllithium with N,N-diphenylcarbamoyl chloride to give an unsymmetrical oxamide demonstrates a synthetic use of carbamoyllithiums as the umpolung species of carbamoyl halides. A limitation of this procedure may arise from elimination of CO from the carbamoyllithiums. This becomes appreciable when a carbamoyl halide with an aromatic substituent on the nitrogen is used as a starting material. A variety of N,N-dialkylcarbamoyllithiums, such as N,N-diethyl-, N,N-dimethyl-, and N,N-pentamethylenecarbamoyllithiums can, however, be generated efficiently by the lithium-tellurium exchange reactions and trapped with various electrophiles to give the corresponding adducts in good yields.[2]



The present procedure provides a convenient method for the generation of carbamoyllithiums from carbamoyl halides and is very useful synthetically for the introduction of carbamoyl groups into organic molecules.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

BuTeLi

Et_2O

ethanol (64-17-5)

ethyl acetate (141-78-6)

ether, diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

hydrogen (1333-74-0)

carbon monoxide, formyl hydrogen (630-08-0)

nitric acid (7697-37-2)

nitrogen (7727-37-9)

sodium (13966-32-0)

Naphthalene (91-20-3)

methyl benzoate (93-58-3)

magnesium sulfate (7487-88-9)

butyllithium (109-72-8)

Tetrahydrofuran, THF (109-99-9)

hexane (110-54-3)

3-phenylpropanal (104-53-0)

tellurium, tellurium powder

N,N-Diethylcarbamoyllithium

LITHIUM-TELLURIUM

N,N-Diethyl-2-hydroxy-4-phenylbutanamide, Benzenebutanamide, N,N-diethyl-α-hydroxy- (134970-54-0)

Diethylcarbamoyl chloride (88-10-8)

dibutyl telluride (38788-38-4)

Lithium butanetelluroate

1-phenylheptan-3-ol

N,N-diethylphenylglyoxylamide (34906-86-0)

biscarbamoylmercury

N,N-diisopropylcarbamoyllithium

N,N-diphenylcarbamoyl chloride (83-01-2)

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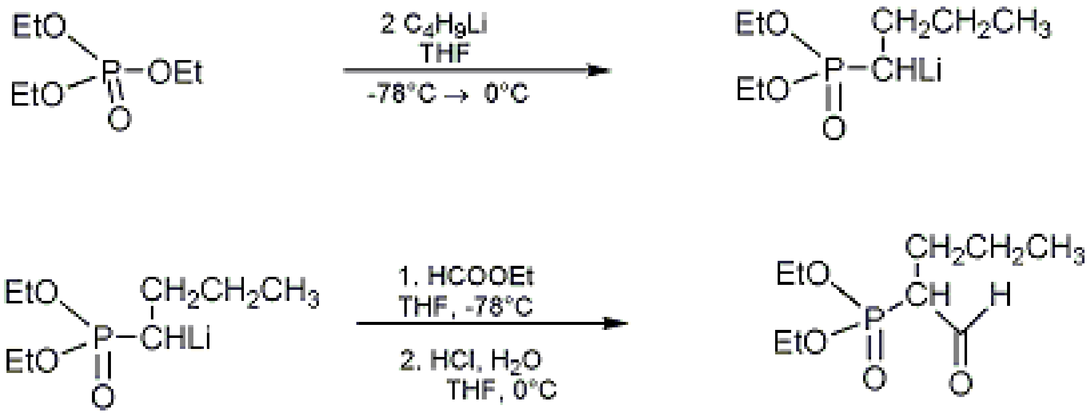
Organic Syntheses, CV 9, 239

DIETHYL 1-PROPYL-2-OXOETHYLPHOSPHONATE

[Phosphonic acid (1-formylbutyl)-, diethyl ester]



Submitted by Philippe Savignac and Carl Patois[1].
Checked by David R. Jones and Amos B. Smith, III.

1. Procedure

A four-necked, 500-mL, round-bottomed flask is fitted with an efficient mechanical stirrer, thermometer, reflux-condenser with a bubbler, and a 200-mL, pressure-equalizing dropping funnel with a nitrogen inlet. The flask is flame-dried, flushed with nitrogen (the checkers used argon throughout), and charged with 100 mL of tetrahydrofuran (THF) (Note 1). The dropping funnel is charged with 140 mL of a 1.5 M solution of butyllithium in hexane (0.210 mol) (Note 2). The flask is cooled to −20°C with a dry ice/acetone bath (Note 3), stirring is started, and butyllithium is added to tetrahydrofuran over a few minutes. The resulting yellow solution is cooled to −78°C. The cooling bath is then kept just below the bottom of the flask while a solution of triethyl phosphate (18.2 g, 0.1 mol) (Note 4) in tetrahydrofuran (50 mL) is added dropwise from the dropping funnel over 15 min at such a rate that the temperature of the reaction mixture slowly rises to 0°C (Note 5). The resulting solution is stirred for an additional 15 min at 0°C. By this time, the yellow color has practically disappeared and the solution is clear. The reaction mixture is cooled to −78°C and a solution of ethyl formate (7.9 g, 0.107 mol) (Note 6) in tetrahydrofuran (20 mL) is added dropwise at this temperature. The reaction mixture is stirred for 30 min, then allowed to warm up slowly to 0°C, and quenched by the dropwise addition of 80 mL of 3 M hydrochloric acid. The organic layer is separated, and the aqueous phase is extracted with three 50-mL portions of dichloromethane. The extracts are combined with the original organic layer, and dried over anhydrous magnesium sulfate. The magnesium sulfate is removed by filtration, and the solvents are removed on a rotary evaporator. The yellow, crude liquid is distilled through a short column (Note 7) to give 21.0 g (94%) of diethyl 1-propyl-2-oxoethylphosphonate (Note 8) as a pale yellow oil (Note

9), bp 110–115°C/0.05 mm (Note 10).

2. Notes

1. Tetrahydrofuran available from S.D.S. Company was purified by distillation from sodium and benzophenone.
2. The submitters used butyllithium in hexane available from Janssen Chimica and standardized before use by titration against a solution of benzylic alcohol in toluene and cuproine (2,2'-biquinoline). The checkers used butyllithium (1.6 M in hexane) available from Aldrich Chemical Company, Inc., which was standardized before use by titration with diphenylacetic acid in THF.
3. An alternative cooler was used by the submitters, consisting of a Dewar partially filled with liquid nitrogen.
4. The submitters used triethyl phosphate, 99%, available from Janssen Chimica without further purification. The checkers used triethyl phosphate (99+ %) available from Aldrich Chemical Company, Inc., without further purification.
5. The reaction mixture must be only slightly cooled by placing it just above the cooling bath, so that the reaction proceeds smoothly.
6. The submitters used ethyl formate, 97%, available from Janssen Chimica, without further purification. Dimethylformamide (DMF) can be used instead of ethyl formate with the same operating conditions. The checkers used ethyl formate (99%), available from Aldrich Chemical Company, Inc., without further purification.
7. The submitters used an 8-cm fractionating column equipped with a condenser for distillation.
8. The product displays the following spectroscopic data: m/e = 222; ^{31}P NMR ($CDCl_3$) δ: +19.4 (CHO form), +24.2 (=CHOH form); ^{1}H NMR ($CDCl_3$) δ: 0.88 (t, 3 H), 1.30 (t, 6 H), 1.1–2.3 (m, 4 H), 2.9 (m, 1 H), 4.1 (dq, 4 H), 9.6 (d, 1 H). In the presence of the enol form, the ^{1}H spectrum is more complex and exhibits the signal of the aldol proton at 7.3 ppm. ^{13}C NMR ($CDCl_3$) δ: 13.7 (CH_3-CH_2), 15.8 (CH_3-CH_2-O), 21.3 (CH_2), 25.5 (CH_2), 52.6 (d, J_{PC} 126.0, P-CH, CHO form), 61.0 and 62.6 (O-CH_2), 99.2 (d, J_{PC} 195.7, P-C=C, CHOH form), 156.6 (d, J_{PC} 29.0, P-C=C, CHOH form), 196.0 (C=O). When several grains of solid potassium carbonate were added to the NMR sample, the ^{1}H and ^{13}C NMR spectra were consistent with the spectral data provided by the submitters for the keto form of the title compound.
9. The distilled product was found to be slightly yellow. It should be stored at 0° C; under these conditions, the purified product is stable for at least several months.
10. The large temperature range is due to the distillation of a mixture of the keto-enol tautomers.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the

Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

This procedure, based on the alkylation-metalation of a trialkyl phosphate by alkyllithiums,[2] illustrates a general route to diethyl 1-formylalkylphosphonates. The method is general and characterized by good yields, mild conditions, and easy preparation of phosphonic aldehydes in pure form starting from readily available materials. It has been shown to be applicable to a wide variety of organolithium reagents, linear (MeLi, EtLi, PrLi) or branched (i-BuLi, isopentyllithium). It is superior to the multistep synthesis previously described which includes an Arbuzov reaction with a protected aldehyde, acidic hydrolysis, enaminophosphonate alkylation, and acidic hydrolysis.[3] Diethyl 1-formylalkylphosphonates are useful intermediates in the Wittig-Horner synthesis of α,β-unsaturated aldehydes and in the synthesis of aminoalkylphosphonates by reductive amination.[4]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium and benzophenone

i-BuLi

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

nitrogen (7727-37-9)

toluene (108-88-3)

benzylic alcohol (100-51-6)

Diphenylacetic acid (117-34-0)

ethyl formate (109-94-4)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

dimethylformamide (68-12-2)

hexane (110-54-3)

argon (7440-37-1)

triethyl phosphate (78-40-0)

2,2'-biquinoline (119-91-5)

Diethyl 1-propyl-2-oxoethylphosphonate, Phosphonic acid (1-formylbutyl)-, diethyl ester (112292-30-5)

isopentyllithium

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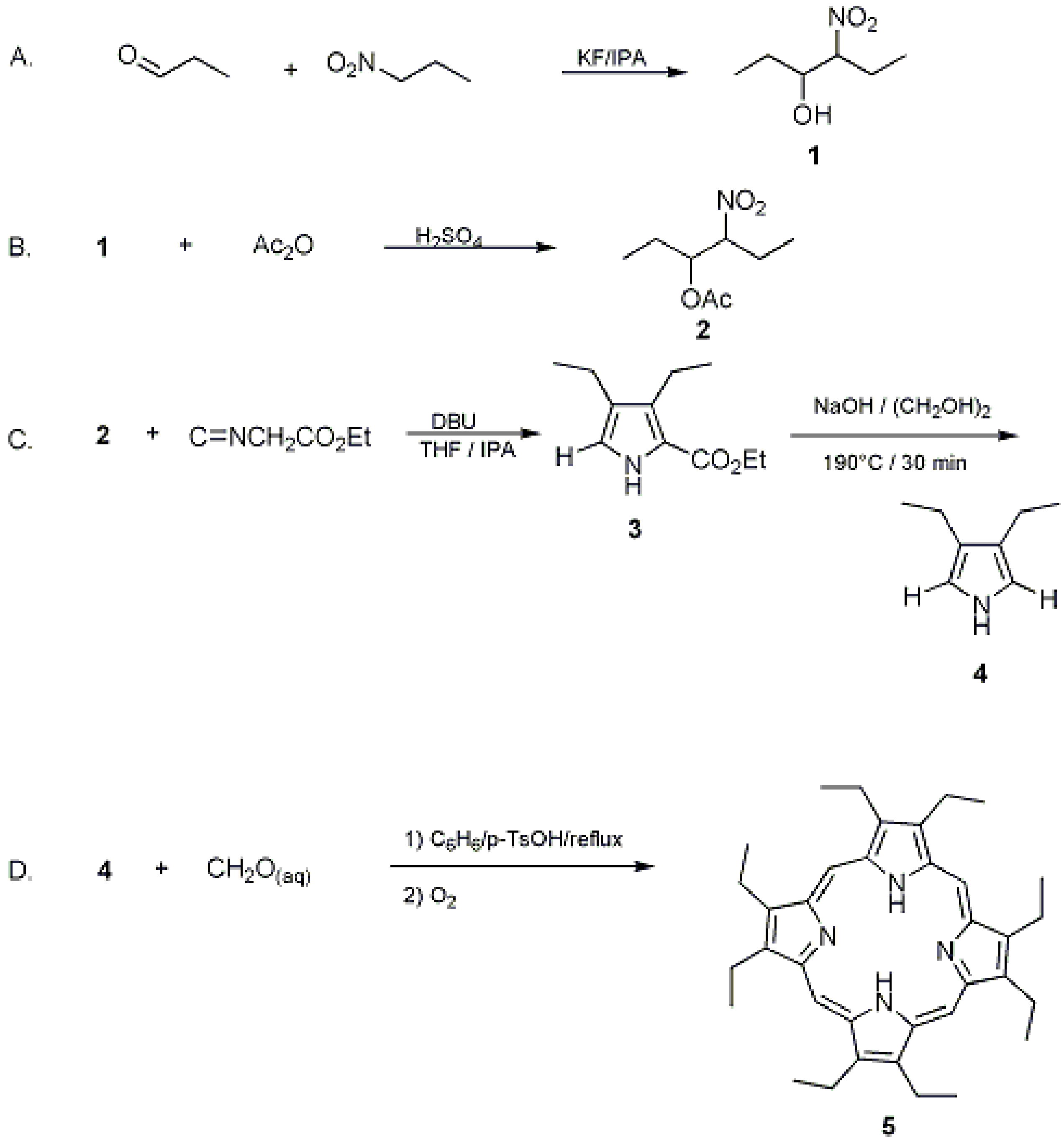
Organic Syntheses, CV 9, 242

3,4-DIETHYLPYRROLE AND 2,3,7,8,12,13,17,18-OCTAETHYLPORPHYRIN

[Pyrrole, 3,4-diethyl and 21H,23H-Porphine, 2,3,7,8,12,13,17,18-octaethyl-]



Submitted by Jonathan L. Sessler[1], Azadeh Mozaffari, and Martin R. Johnson.
Checked by Jürgen Fischer and Ekkehard Winterfeldt.

1. Procedure

A. *4-Nitro-3-hexanol* **(1)**.[2] To a 2-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, thermometer, dropping funnel, and drying tube are added propionaldehyde (174 g, 3 mol) and isopropyl alcohol (IPA) (450 mL) (Note 1). The solution is stirred while finely ground potassium fluoride (25 g, 0.15 mol) is added to the flask. 1-Nitropropane (267.3 g, 3 mol) (Note 1) is then added dropwise with stirring, and the temperature is kept below 40°C with the aid of an ice bath (Note 2). The ice bath is removed about 30 min after the addition of 1-nitropropane is complete. The flask contents are stirred for an additional 18 hr. The catalyst is then removed by filtration and the filtrate is concentrated under reduced pressure. The residue is poured into water (500 mL) and the oil is extracted with ether (3 × 300 mL). The ethereal layer is dried over anhydrous sodium sulfate (Na_2SO_4), and the solvent is removed under reduced pressure. The remaining liquid is distilled under reduced pressure and the fraction boiling at 88–90°C/2 mm is collected in a tared, 1-L round-bottomed flask, yielding 3-nitro-4-hexanol (330 g, 2.24 mol, 65%) (Note 3). The flask containing the product is used directly in the next step.

B. *4-Acetoxy-3-nitrohexane* **(2)**.[3] To the above flask, containing 3-nitro-4-hexanol (330 g, 2.24 mol), is added a magnetic stirring egg and 1 mL of concd sulfuric acid. The contents of the flask are stirred in an ice bath and acetic anhydride (240 g, 2.35 mol) is added in portions, keeping the temperature of the reactants below 60°C. After the addition of the acetic anhydride is complete, the contents of the flask are stirred for 1 hr. The flask is then equipped for vacuum distillation. The lower boiling components (Ac_2O and AcOH) are removed at 25 mm by gently heating the stirred contents of the flask (≤ 100°C bath temperature). After these reagents have been removed, the system is cooled, attached to a vacuum pump, and carefully heated. The fraction boiling at 105–107°C/10 mm is collected, affording 4-acetoxy-3-nitrohexane (379 g, 2.0 mol, 90%) (Note 4).

C. *Ethyl 3,4-diethylpyrrole-2-carboxylate* **(3)**[4] *and 3,4-Diethylpyrrole* **(4)**. A 1-L, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, dropping funnel, thermometer, and drying tube, and charged with 4-acetoxy-3-nitrohexane (103 g, 0.54 mol), ethyl isocyanoacetate (50.7 g, 0.45 mol, (Note 5)), anhydrous tetrahydrofuran (320 mL), and anhydrous isopropyl alcohol (IPA) (130 mL) (Note 1). 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU, 152 g, 1 mol) (Note 6) & (Note 7) is then added, taking care to maintain the temperature at 20°C to 30°C at all times with the aid of an ice bath (Note 8). When addition of DBU is complete, the orange solution is stirred for 4 hr at room temperature. The solvent is completely removed under reduced pressure (50°C bath temp, 20–40 mm) and the residue is poured into a 1-L beaker and diluted with warm water (300 mL). To this biphasic mixture is added diethyl ether (300 mL). The contents of the beaker are poured into a separatory funnel. The aqueous layer is drawn off and extracted with an additional two portions of ether (300 mL). The ether layers are combined and washed with aqueous 10% hydrochloric acid (2 × 300 mL) and dried over magnesium sulfate ($MgSO_4$). The ether is removed under reduced pressure in a 1-L round-bottomed flask, leaving approximately 95 g of crude ethyl 3,4-diethylpyrrole-2-carboxylate **(3)** (Note 7). This material is not isolated, but is decarboxylated directly as follows: To the crude product **3** (95 g) is added sodium hydroxide (30 g, 0.75 mol) and ethylene glycol (300

mL). The contents are held at reflux under nitrogen for 1 hr, cooled, transferred to a 2-L separatory funnel, and diluted with water (500 mL) and hexane (600 mL). The layers are separated, and the aqueous layer is extracted further with hexane (3 × 300 mL). The hexane layers are combined, dried over $MgSO_4$, and concentrated under reduced pressure. The residue is distilled under reduced pressure, and the fraction boiling at 100°C/25 mm is collected, yielding 3,4-diethylpyrrole (21.14–22.00 g, 0.17–0.177 mol, 38.1–40%) (Note 9).

D. *2,3,7,8,12,13,17,18-Octaethylporphyrin* **(5)**. A 500-mL, round-bottomed flask is wrapped with aluminum foil and equipped with a reflux condenser with a Dean-Stark trap, mechanical stirrer, and nitrogen inlet. The flask is charged with 3,4-diethylpyrrole (1 g, 8.1 mmol), benzene (300 mL) (Note 10), a 37% solution of aqueous formaldehyde (0.73 mL, 8.9 mmol), and *p*-toluenesulfonic acid (0.03 g, 1.7 mmol). The mixture is stirred and heated at reflux under nitrogen using an oil bath, and the water is removed by means of the Dean-Stark trap. After 8 hr, the solution is cooled, and the Dean-Stark trap and condenser are replaced with a fritted glass aerator/bubbler. Oxygen is bubbled through the brown mixture while it is stirred for 12–24 hr. Benzene is removed from the flask by distillation under reduced pressure, and the residue is dissolved in chloroform (20 mL) (Note 11). The solution is washed with 1 N sodium hydroxide (40 mL) and water (2 × 20 mL). The chloroform solution is concentrated to 5 mL in a 100-mL, round-bottomed flask, carefully layered over with methanol (≈70 mL), and allowed to stand for 48 hr. The resulting solid is collected by filtration and dried under reduced pressure for 24 hr. The crude material is recrystallized twice from chloroform-hexanes [effected by dissolving in chloroform (≈10 mL), layering over with hexanes (≈70 mL), and allowing to stand overnight]. The final precipitate is collected by filtration and dried under reduced pressure for 48 hr to yield analytically pure 2,3,7,8,12,13,17,18-octaethylporphyrin (720 mg, 1.34 mmol, 66.4%) as a purple, amorphous powder (Note 12).

2. Notes

1. Propionaldehyde and 1-nitropropane were obtained from Aldrich Chemical Company, Inc., and used as received. Isopropyl alcohol and tetrahydrofuran were obtained from J.T. Baker and used as received.
2. It is necessary to cool the reaction vessel to prevent the volatile propionaldehyde from evaporating.
3. The literature boiling point is reported[2] as 89°C (2 mm).
4. The spectral and analytical properties are as follows: ^1H NMR (300 MHz, $CDCl_3$) δ: 0.99 (m, 6 H, CH_3), 1.62 and 1.80 (2 × m, 2 H, $O_2NCHCH_2CH_3$), 1.99 and 2.12 (2 × m, 2 H, $CH_3CO_2CHCH_2CH_3$), 2.06 (m, 3 H, CH_3CO_2), 4.56 (m, 1 H, $CHNO_2$), 5.16 and 5.24 (2 × m, 1 H, CH_3CO_2CH); C.I. MS, $(M+1)^+$ 190 (calcd for $C_8H_{15}NO_4{\cdot}H$: 190). Anal. Calcd for $C_8H_{15}NO_4$: C, 50.78; H, 7.99; N, 7.40. Found: C, 50.98; H, 8.14; N, 7.01.
5. A disadvantage of the present procedure is that it requires the use of the relatively foul-smelling substance, ethyl isocyanoacetate. Although this material is commercially available (from, e.g., Aldrich Chemical Company, Inc.), it is

moderately expensive. The authors have found that the existing preparative procedure (Hartman, G. D.; Weinstock, L. M. *Org. Synth., Coll. Vol VI* **1988**, 620) can be improved by the use of trichloromethyl chloroformate (Kurita, K.; Iwakura, Y. *Org. Synth., Coll. Vol. VI* **1988**, 715) rather than phosphoryl chloride. This substitution simplifies purification of the isocyanoacetate by eliminating the aqueous portion of the workup.

6. DBU was obtained from Aldrich Chemical Company, Inc. and used as received.

7. Two equivalents of DBU are used here. One equivalent of DBU eliminates acetate from one of the reactants to form 3-nitro-3-hexene in situ, which goes on to form the pyrrole. The intermediate ethyl 3,4-diethylpyrrole-2-carboxylate can also be prepared directly from ethyl isocyanoacetate and 3-nitro-3-hexene in good yield (86%) under conditions similar to those outlined here.[5] Although this alternative requires a further manipulative step, it requires only half as much DBU.

8. It is important not to allow the temperature to drop below 20°C because the reaction slows down considerably. Unreacted DBU then builds up. As a result, when the temperature does climb, it does so rapidly (often to as high as 65°C). This results in a significantly lower yield.

9. The spectral and physical properties are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.16 (t, 6 H, CH_2CH_3), 2.47 (q, 4 H, CH_2CH_3), 6.42 (d, 2 H, pyrrole CH), 7.65 (s, 1 H, pyrrole NH); MS m/e (relative intensity) 123 (46), 108 (100), 93 (37); bp 100°C/25 mm; 69°C/7 mm (lit.[6] bp, 83°C/10 mm).

10. Benzene is a known carcinogen. Follow manufacturer's recommended procedures for handling, storage, and disposal.

11. Chloroform is a suspected carcinogen. Follow manufacturer's recommended procedures for handling, storage, and disposal.

12. The spectral and analytical properties are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ: –3.72 (s, 2 H, NH), 1.95 (t, 24 H, CH_2CH_3), 4.12 (q, 16 H, CH_2CH_3), 10.12 (s, 4 H, meso CH); HRMS, M^+ 534.37351 (calcd for $C_{36}H_{46}N_4$: 534.37225). Anal. Calcd for $C_{36}H_{46}N_4$: C, 80.85; H, 8.67; N, 10.48. Found: C, 80.89; H, 8.56; N, 10.37; UV-vis ($CHCl_3$-MeOH 95:5 vv.) λ_{max} (log ε): 398 (5.20), 498 (4.10), 533 (4.00), 565 (3.79), 618 (3.68) nm.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Octaethylporphyrin (OEP) and tetraphenylporphyrin (TPP) remain among the most widely used of an increasingly diverse set of available synthetic porphyrins. The inherently high symmetry and relatively good solubility properties of these systems often combine to make them the models of choice for a wide range of biological modeling and inorganic chemical applications.[7] Recently, an optimized synthesis of TPP and related tetraarylporphyrins has been developed by Lindsey and co-workers.[8 9 10] At present, however, the synthesis of OEP **(5)** remains problematic: Although numerous strategies

have been reported,[5,11 12,13,14,15,16,17 18,19] no convenient, high-yield procedure currently exists.

Traditionally, octaethylporphyrin has been prepared by the self-condensation of 2-N,N'-diethylaminomethyl-3,4-diethylpyrrole,[11,12,13] ethyl 5-N,N'-diethylaminomethyl-3,4-diethylpyrrole-2-carboxylate,[14,15] or 3,4-diethyl-5-hydroxymethylpyrrole-2-carboxylic acid under oxidative conditions.[16] It has also been prepared on a small scale directly from 3,4-diethylpyrrole in 65% yield by condensation with aqueous formaldehyde under acid-catalyzed conditions,[17,18] using conditions similar to those which have proved useful for preparing the corresponding octamethylporphyrin analogue.[20] All of these syntheses derive from the same, initial pyrrole precursor, namely, ethyl 3,4-diethyl-5-methylpyrrole-2-carboxylate, prepared from the classic, reverse-sense Knorr reaction of ethyl propionylacetate with 2,4-pentanedione, and they require several steps before the ultimate porphyrin-forming condensation. Octaethylporphyrin has also been prepared recently by the reduction of 2,8,12,18-tetraacetyl-3,7,13,17-tetraethylporphyrin by diborane,[17,18] and by the condensation of 3,4-diethylpyrrole-N-carboxylic acid with formaldehyde in refluxing acetic acid/pyridine.[19] Neither of these procedures, however, truly overcomes the problem associated with preparing the initial pyrrole.

The synthesis reported here circumvents many of the problems associated with existing preparative methods. Specifically, it makes use of a new procedure of Barton and Zard[4] in the key pyrrole-forming step. This method, which gives an α-unsubstituted pyrrole ester (e.g., **3**) directly in good yield, provides a substantial saving in labor when compared to the Knorr approach, and it is very flexible with regard to the kinds of β-substitution allowed. Since the remaining α-ester group can be conveniently removed by saponification and subsequent decarboxylation (often, as is the case here, without isolation of the initial pyrrole product), this method provides a quick and easy means of preparing 3,4-dialkylated pyrroles. Simple acid-catalyzed condensation of the resulting 3,4-dialkylpyrroles with formaldehyde and subsequent oxidation is then all that is required to complete the synthesis of an octaalkylporphyrin.[21,22] We have found that these latter transformations may be readily effected using aqueous formaldehyde under acid-catalyzed dehydrating conditions, followed by simple air-induced oxidation. In the specific case of octaethylporphyrin, when the reaction is run on a 1-g scale, a 75% yield of analytically pure product is obtained following workup and purification (which involves only simple recrystallizations and no chromatographic separations). This procedure can be conveniently scaled up by a factor of ten. Under these conditions, it still gives a good yield (55%) of pure product. It does, however, require relatively large amounts of benzene (3 L for a reaction carried out with 10 g of 3,4-diethylpyrrole), which could present a health hazard. However, if due caution is exercised with regard to this point, the present method provides an easy way to prepare large quantities of octaethylporphyrin. As such it represents a considerable advance over earlier methods in terms of both ease and convenience.

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21. Alternatively, the ethyl 3,4-diethylpyrrole-2-carboxylate may be carried on directly to give octaethylporphyrin,[5] although the yields reported (ca. 40%) are not quite as good as those obtained by the present procedure. Similarly, this substance or the 3,4-diethylpyrrole produced by the present procedure could conceivably serve as the basis for an an improved synthesis via a Mannich base-type approach such as that outlined in refs. 9–12.
22. The procedure reported here appears to be quite general. We have, for example, used it to prepare a β-substituted tetrakis-fused cyclohexylporphyrin (1,2,3,4,8,9,10,11,15,16,17,18,22, 23,24,25-hexadecahydro-29H,31H-tetrabenzo[BGLQ] porphine) in 51% overall yield starting from 1-nitrocyclohexene.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hexanes

diborane

2,3,7,8,12,13,17,18-Octaethylporphyrin

DBU

Pyrrole, 3,4-diethyl and 21H,23H-Porphine, 2,3,7,8,12,13,17,18-octaethyl-

Octaethylporphyrin (OEP)

tetraphenylporphyrin (TPP)

TPP

octaethylporphyrin

ethyl 5-N,N'-diethylaminomethyl-3,4-diethylpyrrole-2-carboxylate

2,8,12,18-tetraacetyl-3,7,13,17-tetraethylporphyrin

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

acetic anhydride (108-24-7)

sodium hydroxide (1310-73-2)

formaldehyde (630-08-0)

chloroform (67-66-3)

sodium sulfate (7757-82-6)

oxygen (7782-44-7)

Propionaldehyde (123-38-6)

nitrogen (7727-37-9)

aluminum (7429-90-5)

pyridine (110-86-1)

isopropyl alcohol (67-63-0)

ethylene glycol (107-21-1)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

2,4-pentanedione (123-54-6)

potassium fluoride (7789-23-3)

hexane (110-54-3)

1-nitropropane (108-03-2)

p-toluenesulfonic acid (104-15-4)

Trichloromethyl chloroformate (503-38-8)

phosphoryl chloride (10025-87-3)

Ethyl isocyanoacetate (2999-46-4)

1,8-diazabicyclo[5.4.0]undec-7-ene (6674-22-2)

3,4-Diethylpyrrole (16200-52-5)

4-Nitro-3-hexanol, 3-nitro-4-hexanol (5342-71-2)

4-Acetoxy-3-nitrohexane (3750-83-2)

Ethyl 3,4-diethylpyrrole-2-carboxylate (97336-41-9)

3-nitro-3-hexene (4812-22-0)

3,4-diethyl-5-hydroxymethylpyrrole-2-carboxylic acid

ethyl 3,4-diethyl-5-methylpyrrole-2-carboxylate (16200-50-3)

ethyl propionylacetate (4949-44-4)

3,4-diethylpyrrole-N-carboxylic acid

1-nitrocyclohexene

2-N,N'-diethylaminomethyl-3,4-diethylpyrrole

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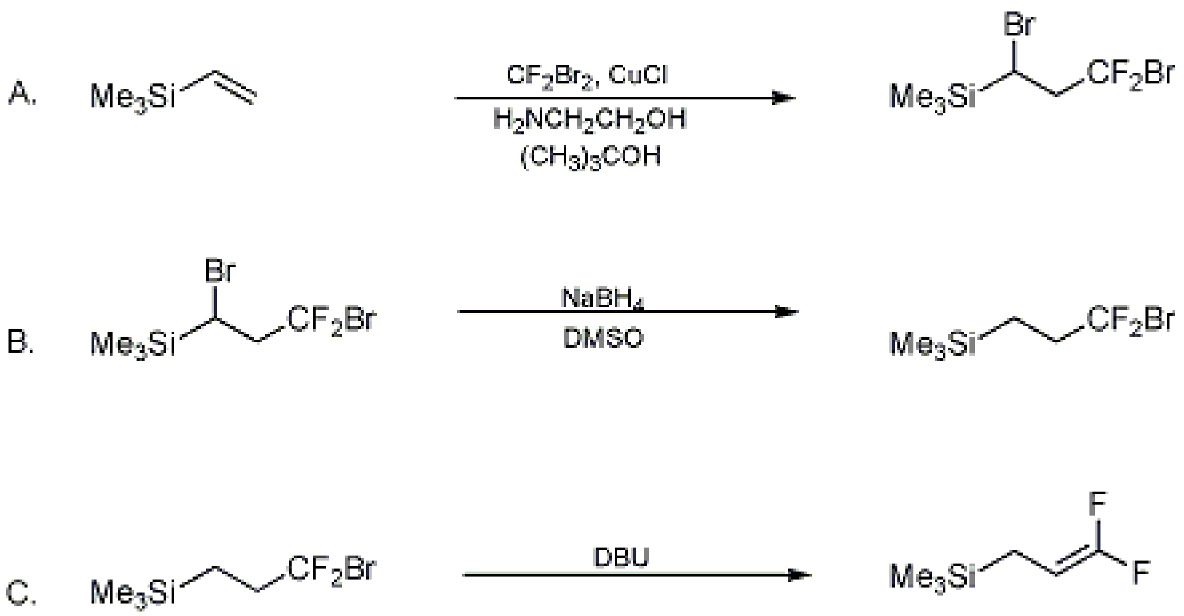
(3,3-DIFLUOROALLYL)TRIMETHYLSILANE

[Silane, (3,3-difluoro-2-propenyl)trimethyl-]



Submitted by Javier Gonzalez, Matthew J. Foti, and Seth Elsheimer[1].
Checked by Louis Portland, Tai-Nang Huang, and David L. Coffen.

1. Procedure

A. *(1,3-Dibromo-3,3-difluoropropyl)trimethylsilane* (Note 1). A 250-mL pressure tube (Note 2) equipped with a magnetic stirring bar is charged with vinyltrimethylsilane (20 g, 30.8 mL, 0.20 mol), ethanolamine (6.11 g, 6.04 mL, 0.10 mol), dibromodifluoromethane (83.9 g, 36.5 mL, 0.4 mol), copper(I) chloride (0.18 g, 1.8 mmol), and tert-butyl alcohol (15 mL) (Note 3) and (Note 4). The tube is sealed and stirred for 20 hr in an oil bath at 90°C (Note 5). The reaction mixture is combined with that from another run at the same scale and diluted with 40 mL of hexane (the mixture separates into a cloudy supernatant and a brown resin). The hexane layer is separated and the resinous precipitate extracted with two 20-mL portions of hexane. The combined solutions are filtered through a bed of silica gel on a 60-mL fritted glass funnel and the resulting clear filtrate is concentrated by rotary evaporation using a water aspirator. The crude material is fractionally distilled to afford 71.9–78.3 g (58–61%) of the dibromide as a colorless oil, bp 78–79°C (12 mm) [lit.[2] bp 95°C (25 mm)] (Note 6).

B. *(3-Bromo-3,3-difluoropropyl)trimethylsilane*. A 1-L, four-necked flask is equipped with a mechanical stirrer, thermometer, Claisen adapter, septum inlet, reflux condenser (the top of which is connected to a calcium chloride drying tube), and a solid addition funnel. The flask is charged with (1,3-dibromo-3,3-difluoropropyl)trimethylsilane

(78.3 g, 0.25 mol), and anhydrous dimethyl sulfoxide (200 mL), and the solid addition funnel is charged with sodium borohydride (11.5 g, 0.30 mol) (Note 7) and (Note 8). The stirred solution is warmed to 80°C, and sodium borohydride is added at a rate sufficient to maintain a reaction temperature of 80–90°C (Note 9). Toward the end of the addition, an additional portion of dimethyl sulfoxide (200 mL) is added via syringe to lower the viscosity of the reaction mixture. After the addition is complete, the mixture is cooled in an ice-water bath, diluted with 100 mL of pentane, and *cautiously* quenched with 12 M hydrochloric acid until no further gas evolution occurs. The mixture is transferred to a separatory funnel and washed with three 100-mL portions of 5% brine. The pentane extract is dried over calcium chloride and the solvent removed through a 15-cm Vigreux column. Further fractionation yields 41.5 g (72%) of 3-bromo-3,3-difluoropropyltrimethylsilane, bp 139–141°C (Note 10).

C. *(3,3-Difluoroallyl)trimethylsilane*. A 100-mL, three-necked, round-bottomed flask is equipped with a magnetic stirrer, short-path distillation head, and an electric heating mantle. The flask is charged with 30.99 g (0.13 mol) of (3-bromo-3,3-difluoropropyl) trimethylsilane and 29.1 g (0.19 mol) of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (Note 11). Stirring and gradual heating are begun and the reaction mixture becomes thick with precipitate (Note 12). The product distilling from the mixture is collected from 80–100°C giving 11.88 g of colorless liquid.

Additional product is obtained by extractive workup of the residue. The cooled residue is acidified by adding 50 mL of 3 N hydrochloric acid and the resulting solution is extracted with 50 mL of pentane. The pentane layer is washed with 2 × 50 mL of water, dried over sodium sulfate, filtered and concentrated at 35°C under ca. 30 mm vacuum. The remaining liquid is distilled using a short-path distillation head to afford an additional 1.77 g of product (bp 86–95°C). The combined product, weighing 13.65 g (70% yield), has a purity of 85–90% based on NMR and capillary GC analysis (Note 13).

2. Notes

1. This procedure is based on a report by Burton and Kehoe.[3]
2. An Ace Model # 8648-83 tube with a FETFE O-ring was used.
3. Vinyltrimethylsilane, ethanolamine, copper(I) chloride (98+% ACS reagent grade), and dibromodifluoromethane were obtained from Aldrich Chemical Company, Inc. tert-Butyl alcohol was obtained from Fisher Scientific Company.
4. Dibromodifluoromethane (bp 22°C) was chilled and handled as a liquid.
5. The bottom third of the tube was immersed. The reaction mixture changed color from blue-green to brown during this period.
6. This material is 95–98% pure by GLC analysis (20% DC 200 on 80-100 mesh Chromosorb P, 4' × 0.25" column, 200°C). The presence of a lower-boiling impurity, 3-bromo-3,3-difluoro-1-propenyltrimethylsilane, does not affect the yield of the subsequent steps.
7. Dimethyl sulfoxide (99+% anhydrous grade) and sodium borohydride were

purchased from Aldrich Chemical Company, Inc.
8. Other polar aprotic solvents (HMPA, DMPU) were used successfully in place of DMSO in small-scale runs.
9. Shortly after starting the addition, the exothermic reaction causes an increase in temperature, and external heating is discontinued. Care should be taken not to add the sodium borohydride too rapidly, as temperatures above 92°C have resulted in the formation of an over-reduced product, 3,3-difluoropropyltrimethylsilane. It is advisable to have an ice bath available in case the reaction requires external cooling.
10. This compound has the following spectral properties: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.02 (s, 9 H, Me_3Si), 0.72–0.83 (m, 2 H, H-1), 2.14–2.38 (m, 2 H, H-2); ^{13}C NMR δ: –1.94 (Me_3Si), 10.8 (C-1), 40.0 (t, C-2, J = 22.6), 125.4 (t, J = 307, CF_2Br).
11. The 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was purchased from Aldrich Chemical Company, Inc.
12. On a smaller scale the reaction was run in a round-bottomed flask and the product isolated at this stage by direct distillation of the reaction mixture through a short-path distillation head.
13. This product has the following spectroscopic properties: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.00 (s, 9 H, Me_3Si), 1.2 (dt, $^3J_{HH}$ = 8.9, $^4J_{FH}$ = 1.5, 2 H, CH_2), 4.1 (dtd, $^3J_{FH}$ (trans) = 25.2, $^3J_{HH}$ = 8.9, $^3J_{FH}$ (cis) = 2.7, 1 H, =CH); ^{13}C NMR δ: –2.25 (Me_3Si), 10.8 (unresolved m, CH_2), 74.6 (t, $^2J_{FC}$ = 23.0, =CH), 156.3 (dd, $^1J_{FC}$ = 284, CF_2); IR (film) cm^{-1}: 1740 s (C=CF_2). The ^{1}H NMR and IR data are consistent with those previously reported.[4]

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Radical addition of dibromodifluoromethane to alkenes followed by sodium borohydride reduction is a convenient two-step method for the introduction of the difluoromethyl group.[5] Either one or both carbon-bromine bonds in the intermediate dibromides may be reduced, depending on the reaction conditions. In the case of *acyclic* dibromodifluoromethane-alkene adducts, the reduction occurs *regioselectively* to yield the relatively inaccessible bromodifluoromethyl-substituted alkanes. The latter are potential building blocks for other fluorinated compounds. For example, they may be dehydrohalogenated to 1,1-difluoroalkenes; an example of this methodology is illustrated in this synthesis of (3,3-difluoroallyl)trimethylsilane.

(3,3-Difluoroallyl)trimethylsilane was first prepared in low yield from the high-temperature reaction of vinyltrimethylsilane with chlorodifluoromethane.[6] An

improved synthesis involving the insertion of difluorocarbene into the requisite β-silyl ylide has been reported.[4] Although the yield is excellent, the reaction consumes a mole of the valuable Wittig reagent (it forms the phosphonium salt which must be recycled) in generating difluorocarbene from chlorodifluoromethane. Other (3,3-difluoroallyl) silanes have been synthesized via the S_N2' reactions of silyl anions with 3,3,3-trifluoropropenes.[7]

(3,3-Difluoroallyl)silanes are of interest as carbon-carbon bond forming building blocks in organofluorine chemistry.[4,7,8]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

brine

HMPA

DMPU

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

sodium sulfate (7757-82-6)

copper(I) chloride (7758-89-6)

Pentane (109-66-0)

ethanolamine (141-43-5)

hexane (110-54-3)

dimethyl sulfoxide, DMSO (67-68-5)

tert-butyl alcohol (75-65-0)

sodium borohydride (16940-66-2)

1,8-diazabicyclo[5.4.0]undec-7-ene (6674-22-2)

(3,3-Difluoroallyl)trimethylsilane, Silane, (3,3-difluoro-2-propenyl)trimethyl- (40207-81-6)

(1,3-Dibromo-3,3-difluoropropyl)trimethylsilane (671-80-7)

Vinyltrimethylsilane (754-05-2)

dibromodifluoromethane (75-61-6)

(3-Bromo-3,3-difluoropropyl)trimethylsilane, 3-bromo-3,3-difluoropropyltrimethylsilane (134134-62-6)

3-bromo-3,3-difluoro-1-propenyltrimethylsilane

3,3-difluoropropyltrimethylsilane

chlorodifluoromethane (75-45-6)

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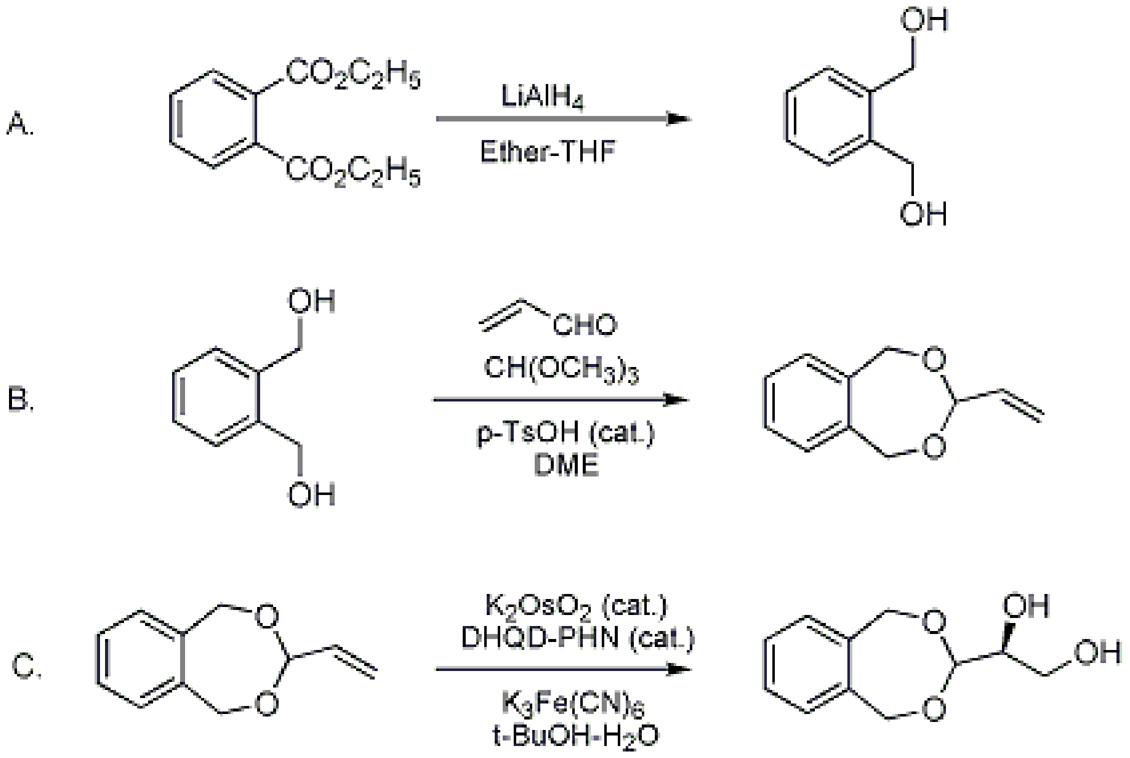
3-[(1S)-1,2-DIHYDROXYETHYL]-1,5-DIHYDRO-3H-2,4-BENZODIOXEPINE

[1,2-Ethanediol, 1-(1,5-dihydro-2,4-benzodioxepin-3-yl)-, (S)-]



Submitted by Ryu Oi[1] and K. Barry Sharpless[2].
Checked by Michelle A. Laci and Robert K. Boeckman, Jr..

1. Procedure

CAUTION: Lithium aluminum hydride is a flammable solid which evolves hydrogen, a highly flammable and potentially explosive gas, upon contact with moisture. Potassium osmate is highly toxic as are any residues containing osmium and should be handled with care. All operations should be conducted in an efficient fume hood.

A. *1,2-Benzenedimethanol*. An oven-dried, 2-L, three-necked, round-bottomed flask, equipped for mechanical stirring, and outfitted with a reflux condenser bearing an argon inlet/outlet vented through a mineral oil bubbler, and a 250-mL, pressure-equalizing addition funnel, is placed under an argon atmosphere and charged with 20.94 g (0.552 mol) of lithium aluminum hydride ($LiAlH_4$), and 850 mL of anhydrous diethyl ether (Note 1) and (Note 2). A solution of 87.46 mL (97.78 g, 0.44 mol) of diethyl phthalate (Note 1) in 170 mL of anhydrous tetrahydrofuran (THF) is added dropwise via the addition funnel over 1.5 hr with efficient mechanical stirring, at a rate of addition adjusted to maintain a gentle reflux (Note 3). After the addition is

complete, the mixture is heated to reflux by means of a heating mantle for 1.5 hr. The mechanically stirred reaction mixture is then cooled to 0°C in an ice-water bath, and quenched by *cautious* sequential addition of 21 mL of water, 21 mL of aqueous 15% sodium hydroxide solution, and 63 mL of water (Note 4). While stirring is continued, the mixture is held for 30 min at 0°C then allowed to warm to room temperature. The resulting white solids are collected by vacuum filtration and washed on the filter using a total of 1 L of ether in 100-mL portions (Note 5). Concentration of the filtrate, under reduced pressure, affords 56.64 g (93%) of 1,2-benzenedimethanol as a white solid, mp 62–64°C, which is sufficiently pure for further transformation (Note 6).

B. *3-Vinyl-1,5-dihydro-3H-2,4-benzodioxepine*. An oven-dried, 2-L, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, a calcium chloride drying tube, and two rubber septa. The flask is charged with 41.45 g (0.3 mol) of 1,2-benzenedimethanol, 5.71 g (0.03 mol) of p-toluenesulfonic acid monohydrate (Note 1), and 600 mL of dry 1,2-dimethoxyethane (Note 1) and (Note 7). Stirring is initiated, and 49.2 mL (0.45 mol) of trimethyl orthoformate (Note 1) and 30.1 mL (0.45 mol) of acrolein (Note 1) are then added sequentially via syringe. The reaction mixture is stirred at room temperature for 5 hr (Note 8), then poured into a mixture of ice and 150 mL of aqueous 10% sodium bicarbonate solution in a 2-L separatory funnel using 90 mL of ether to rinse the flask. After thorough mixing, the organic phase is separated and the aqueous phase is extracted with 300 mL of ether. The combined organic layers are washed sequentially with 90 mL of cold aqueous 10% sodium bicarbonate solution and 90 mL of brine, dried over anhydrous sodium sulfate (Na_2SO_4), filtered, and concentrated under reduced pressure to give 52 g (99%) of crude acetal. Distillation of the residual liquid under reduced pressure affords 39.6–40.4 g (75–77%) of 3-vinyl-1,5-dihydro-3H-2,4-benzodioxepine as a colorless liquid, bp 116–118°C (5 mm), that may crystallize on standing, mp 30°C (Note 9) and (Note 10).

C. *3-[(1S)-1,2-Dihydroxyethyl)]-1,5-dihydro-3H-2,4-benzodioxepine*. A 2-L, three-necked, round-bottomed flask is equipped with a mechanical stirrer, a thermometer, and a rubber septum. The flask is charged with dihydroquinidine 9-O-(9'-phenanthryl) ether (Note 1) and (Note 11), [0.75 g, (1.5 mmol, 1 mol%, 0.0057 M in the organic phase)], 148.2 g (0.45 mol) of potassium ferricyanide (Note 1), 62.2 g (0.45 mol) of potassium carbonate (Note 1), 264 mL of tert-butyl alcohol (tert-BuOH) (Note 1), and 264 mL of distilled water. Mechanical stirring is initiated, 0.11 g (0.3 mmol, 0.2 mol %) of potassium osmate (VI) dihydrate, which generates a 0.0011 M solution of OsO_4 in the organic phase (Note 1), is added, and the mixture is stirred at room temperature for 0.5 hr, resulting in an orange suspension. The flask is immersed in a 0°C cooling bath, and the mixture stirred for 1 hr (Note 12). Over a period of 24 hr at 0°C, 26.25 g (0.16 mol) of 3-vinyl-1,5-dihydro-3H-2,4-benzodioxepine is added dropwise via syringe (Note 13), and the reaction mixture is stirred an additional 24 hr at 0°C (Note 14). After the required time period has elapsed, 30.25 g (0.24 mol) of solid sodium sulfite (Na_2SO_3) is added in portions, the reaction mixture is stirred for an additional 1

hr at room temperature, poured into a 3-L beaker, and allowed to stand for another 1 hr at room temperature (Note 1). After the organic phase is decanted, the aqueous phase is diluted with 300 mL of water to dissolve the salts, and poured into a 2-L separatory funnel using 90 mL of dichloromethane (CH_2Cl_2) to rinse the flask and beaker. The aqueous phase is extracted three times with 150 mL of CH_2Cl_2. The organic extracts are combined with the decanted organic phase, dried over Na_2SO_4, filtered, and concentrated, under reduced pressure, to afford 33.1 g (104%) of crude product, as a pale yellow liquid (Note 15) that crystallizes rapidly. The ee of the crude 3-[(1S)-1,2-dihydroxyethyl)]-1,5-dihydro-3H-2,4-benzodioxepine is determined by HPLC analysis of the derived bis-Mosher ester to be 84% (Note 16).

A 2-L Erlenmeyer flask is charged with 33.1 g of the crude protected diol which is dissolved in 600 mL of hot ethyl acetate (EtOAc), and the solution is allowed to stand at room temperature for 3 hr and at 0°C to −5°C for 24 hr (Note 17). The resulting white precipitate is collected by suction filtration through a 10-cm Büchner funnel (Note 18), and the mother liquor is concentrated under reduced pressure to afford 21.15 g of a pale yellow liquid that slowly crystallizes (Note 19). The residual liquid is placed in a 500-mL Erlenmeyer flask, dissolved in 150 mL of hot toluene (Note 20), and allowed to stand for 24 hr at 0°C to −5°C. The slightly yellow precipitate is collected by suction filtration through a 10-cm Büchner funnel and dried under reduced pressure to give 16.0–17.4 g (50–55%) of 3-[(1S)-1,2-dihydroxyethyl)]-1,5-dihydro-3H-2,4-benzodioxepine, mp 73–75°C, $[\alpha]_D^{23}$ −12.4° ($CHCl_3$, *c* 2.62) (Note 21). The ee of the product is determined by HPLC analysis of the derived bis-Mosher ester to be 97% (Note 16).

The mother liquor is then concentrated to afford 2.4 g of a brown yellow liquid (Note 22). Flash chromatography of this material on 30 g of SiO_2 with elution by EtOAc then by EtOAc:MeOH (5:1 v/v) affords 0.63 g (2%) of 3-[(1S)-1,2-dihydroxyethyl)]-1,5-dihydro-3H-2,4-benzodioxepine and 0.69 g (92% recovery) of dihydroquinidine 9-O-(9'-phenanthryl) ether.

2. Notes

1. This reagent was purchased from Aldrich Chemical Company, Inc., and used without further purification.
2. Anhydrous ether was purchased from J. T. Baker Chemical Company and used as received.
3. Tetrahydrofuran was purchased from J. T. Baker Chemical Company and dried and deoxygenated prior to use by distillation from sodium-benzophenone ketyl under argon.
4. During the initial stages of the addition of water, care must be exercised to control the vigorous exothermic reaction by use of efficient cooling and agitation along with careful regulation of the rate of addition. This procedure must be conducted in an efficient fume hood since a considerable volume of hydrogen gas is produced that must be vented.

5. Since the solids have a tendency to occlude significant amounts of the diol, efficient washing of the solids is essential to obtain good yields. Warm solvent can be employed to assist in removal of the product.

6. 1,2-Benzenedimethanol (lit.[3] mp 63–65°C) has the following spectral characteristics: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.97 (s, 2 H), 4.61 (s, 4 H), 7.30 (s, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 63.8, 128.5, 129.6, 139.3; IR ($CHCl_3$) cm^{-1}: 3279, 2890, 1454, 1214, 1182, 1110, 1036, 1005, 758.

7. A freshly opened bottle of reagent grade 1,2-dimethoxyethane (Aldrich Chemical Company, Inc.) was used without further purification.

8. The reaction mixture was monitored by TLC analysis on silica gel (4:1 EtOAc:hexane v/v). 3-Methoxy-1,5-dihydro-3H-2,4-benzodioxepine (R_f = 0.5) is first produced by transesterification with trimethyl orthoformate, and is then transformed to the final product (R_f = 0.6).

9. Slightly impure forerun, 6–9 g, was separated from the main fraction. After the distillation was stopped, approximately 6–9 g of residue remained.

10. The spectroscopic data and elemental analysis of the product are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.91 (q, 4 H, J = 14.2), 5.33–5.38 (m, 2 H), 5.53 (dt, 1 H, J = 17.4, 1.4), 5.90–5.99 (m, 1 H), 7.10–7.25 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 70.0, 104.2, 118.4, 127.0, 127.2, 134.7, 138.8; IR (neat) cm^{-1}: 3068, 3024, 2950, 2860, 1769, 1725, 1497, 1445, 1412, 1376, 1353, 1291, 1268, 1221, 1210, 1150, 1123, 1094, 1046, 1032, 944, 932, 749; m/z Calcd. for Cs^{+}-$C_{11}H_{12}O_2$: 308.9892; Found 308.9892; Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86; O, 18.16. Found: C, 75.12; H, 6.84; O, 18.26.

11. Dihydroquinidine 9-O-(9'-phenanthryl) ether[4] (Aldrich, Cat. No. 38195-0: Hydroquinidine 9-phenanthryl ether) gave the highest enantioselectivity compared with several other commercially available dihydroquinidine derivatives; 34% ee with dihydroquinidine 4-chlorobenzoate (Aldrich, Cat. No. 33648-3: Hydroquinidine 4-chlorobenzoate) and 61% ee with dihydroquinidine-9-O-(4'-methyl-2'-quinolyl) ether (Aldrich, Cat. No. 38194-2: Hydroquinidine 4-methyl-2-quinolyl ether). The submitters report that the reaction can be run on 0.5-mol scale using this procedure to afford comparable yields and enantiomeric purity of the diol product.

12. Upon cooling, the mixture becomes a viscous suspension, and vigorous stirring is required. At temperatures below –5°C, the reaction mixture starts to freeze, thereby precluding efficient mixing.

13. Neat 3-vinyl-1,5-dihydro-3H-2,4-benzodioxepine was added by syringe drive (Syringe Infusion Pump 22, Harvard Apparatus, South Natick, MA) using a gas-tight syringe. If the material has crystallized, it is liquified by gentle warming (30°C) and 2 mL of t-BuOH-H_2O is added before placing the material in the syringe. The tip of the syringe needle is 15 cm above the reaction surface to prevent freezing of the liquid which occurs around 5°C. Careful temperature control is required to prevent the mixture from freezing during the slow addition. Without slow addition, the ee of the product drops to 67%. The ee also deteriorates if the mixture is allowed to freeze during addition, permitting

unreacted olefin to accumulate prior to warming enough to achieve efficient stirring.

14. Reaction progress was monitored by TLC on silica gel (5:1 EtOAc:MeOH v/v). As the reaction neared completion, the color of the reaction mixture turned yellow.

15. The oil contained 5–10% t-BuOH by weight. 3-[(1R)-1,2-Dihydroxyethyl)]-1,5-dihydro-3H-2,4-benzodioxepine was produced with 84% ee when dihydroquinine-9-O-(9'-phenanthryl) ether (Aldrich, Cat. No. 38197-7: Hydroquinine 9-phenanthryl ether) (Note 1) was used instead of dihydroquinidine 9-O-(9'-phenanthryl) ether.[5]

16. The ee was determined by HPLC analysis (Chemcosorb 3Si, Chemco, Japan) of the corresponding bis-Mosher[6] ester eluted with 5% EtOAc in hexane (2 mL/min, (R)-diol: t_R = 14.8 min, (S)-diol: t_R = 18.2 min). The checkers employed a 25 × 10-mm Prep Nova-Pak HR Silica Column (particle size 6 mm, 60 Å) with UV detection at 220 nm and elution by 10% diethyl ether/hexane at 12 mL per min flow rate (R-diol: t_R = 12.6 min and S-diol: t_R = 15.1 min).

17. Ethyl acetate is preferable to aromatic hydrocarbon solvents such as benzene or toluene because of the high solubility of the diol in EtOAc; this results in higher recovery of the enantomerically enriched diol from the mother liquor.

18. The white precipitate was dried under reduced pressure to afford 8.7–11.1 g (28–35%) of 3-[(1S)-1,2-dihydroxyethyl)]-1,5-dihydro-3H-2,4-benzodioxepine (55–60% ee).

19. The ee of this crude mixture before recrystallization was 97%.

20. Aromatic hydrocarbon solvents such as toluene or benzene are preferable to several other solvents such as EtOAc or ethanol because of efficient recovery of the diol and better separation of the diol from the ligand.

21. The melting point of the racemic diol was 110–113°C. The spectral data and elemental analysis of the diol are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.13 (t, 1 H, J = 6.4), 2.57 (d, 1 H, J = 4.2), 3.73 (m, 1 H), 3.80 (dd, 2 H, J = 6.4, 4.2), 4.93–5.01 (m, 5 H), 7.20–7 30 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 62.42, 72.17, 72.86, 73.23, 108.20, 127.73, 127.79, 138.89, 138.93; IR ($CHCl_3$) cm^{-1}: 3575, 3018, 2966, 2892, 2855, 1456, 1446, 1375, 1294, 1265, 1138, 1103, 1083, 1048; m/z Calcd. for Na^+-$C_{11}H_{14}O_4$: 233.0790; Found 233.0970; Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71; Found: C, 62.78; H, 6.57.

22. The oil contained 10–30% toluene by weight.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

This procedure describes a convenient preparation of highly enantiomerically enriched

3-(1,2-dihydroxyethyl)-1,5-dihydro-3H,2,4-benzodioxepine,[5] a chiral glyceraldehyde equivalent, on a 0.5-mol scale and illustrates the utility of catalytic asymmetric dihydroxylation (ADH)[7] on a large scale. The merits of the diol compared with other chiral derivatives of glyceraldehyde, e.g., 2,3-O-isopropylidene-, 2,3-O-cyclohexylidene-, or 2,3-di-O-acylated glyceraldehyde[8 9] include its ease of handling, its low volatility and high stability at ambient temperature, and its UV chromophore that facilitates TLC or HPLC analysis. In addition, this seven-membered ring acetal can be deprotected easily under mild, neutral conditions by catalytic hydrogenolysis.[5,10 11] A variety of selective nucleophilic substitution reactions on derivatives easily obtained from this new C-3 chiral building block can be envisioned.[5]

The ADH at higher substrate concentrations is more practical for large scale applications. Unfortunately, high concentration of olefin in the reaction mixture is detrimental to the catalytic cycle responsible for asymmetric induction as the ee dropped to 67% at high olefin concentration (0.57 M in t-BuOH) compared with 86% at low concentrations (0.13 M in t-BuOH). However, in the more concentrated case, slow addition of the olefin raised the ee from 67% to 84%. The mechanistic rationale for the deleterious effect of high olefin concentration in this Os/$K_3Fe(CN)_6$ system[12 13] is not yet clear, but in any case the slow addition used here keeps the olefin concentration low.

Of the three types of racemates,[14] conglomerate, racemic compound, and solid solution, 3-(1,2-dihydroxyethyl)-1,5-dihydro-3H-2,4-benzodioxepine shows melting point behavior characteristic of a racemic compound. The racemic diol is much higher melting than the enantiomerically enriched diol as shown in the f.htmigure 1. Therefore the diol of lower ee precipitates first during recrystallization and the enantiomerically enriched diol remains in the mother liquor. High ee diol (97% ee) is then obtained upon recrystallization of this mother liquor.

Figure 1 Relationship between enantiopurity and melting point.

Figure 1 Relationship between enantiopurity and melting point.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

brine

SiO_2

3-[(1S)-1,2-Dihydroxyethyl)]-1,5-dihydro-3H-2,4-benzodioxepine

potassium osmate

dihydroquinidine 9-O-(9'-phenanthryl) ether

ethyl acetate (EtOAc)

sodium-benzophenone ketyl

dihydroquinidine-9-O-(4'-methyl-2'-quinolyl) ether

t-BuOH-H_2O

t-BuOH

3-[(1R)-1,2-Dihydroxyethyl)]-1,5-dihydro-3H-2,4-benzodioxepine

dihydroquinine-9-O-(9'-phenanthryl) ether

2,3-O-isopropylidene-, 2,3-O-cyclohexylidene-, or 2,3-di-O-acylated glyceraldehyde

ethanol (64-17-5)

potassium carbonate (584-08-7)

Benzene (71-43-2)

ethyl acetate, EtOAc (141-78-6)

MeOH (67-56-1)

ether, diethyl ether (60-29-7)

hydrogen (1333-74-0)

sodium sulfite (7757-83-7)

sodium hydroxide (1310-73-2)

Acrolein (107-02-8)

sodium bicarbonate (144-55-8)

sodium sulfate, Na_2SO_4 (7757-82-6)

toluene (108-88-3)

dichloromethane, CH_2Cl_2 (75-09-2)

Acrolein acetal

potassium ferricyanide (13746-66-2)

glyceraldehyde (56-82-6)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

hexane (110-54-3)

diethyl phthalate (84-66-2)

tert-butyl alcohol (75-65-0)

1,2-dimethoxyethane (110-71-4)

argon (7440-37-1)

osmium

trimethyl orthoformate (149-73-5)

glycidol (556-52-5)

p-toluenesulfonic acid monohydrate (6192-52-5)

3-[(1S)-1,2-Dihydroxyethyl]-1,5-dihydro-3H-2,4-benzodioxepine, 1,2-Ethanediol, 1-(1,5-dihydro-2,4-benzodioxepin-3-yl)-, (S)- (142235-22-1)

1,2-Benzenedimethanol (612-14-6)

3-Vinyl-1,5-dihydro-3H-2,4-benzodioxepine (142169-23-1)

3-Methoxy-1,5-dihydro-3H-2,4-benzodioxepine (67461-24-9)

dihydroquinidine 4-chlorobenzoate, Hydroquinidine 4-chlorobenzoate

Hydroquinine 9-phenanthryl ether

3-(1,2-dihydroxyethyl)-1,5-dihydro-3H,2,4-benzodioxepine, 3-(1,2-dihydroxyethyl)-1,5-dihydro-3H-2,4-benzodioxepine

phenanthryl ether

Hydroquinidine 9-phenanthryl ether

Hydroquinidine 4-methyl-2-quinolyl ether

potassium osmate (VI) dihydrate (19718-36-3)

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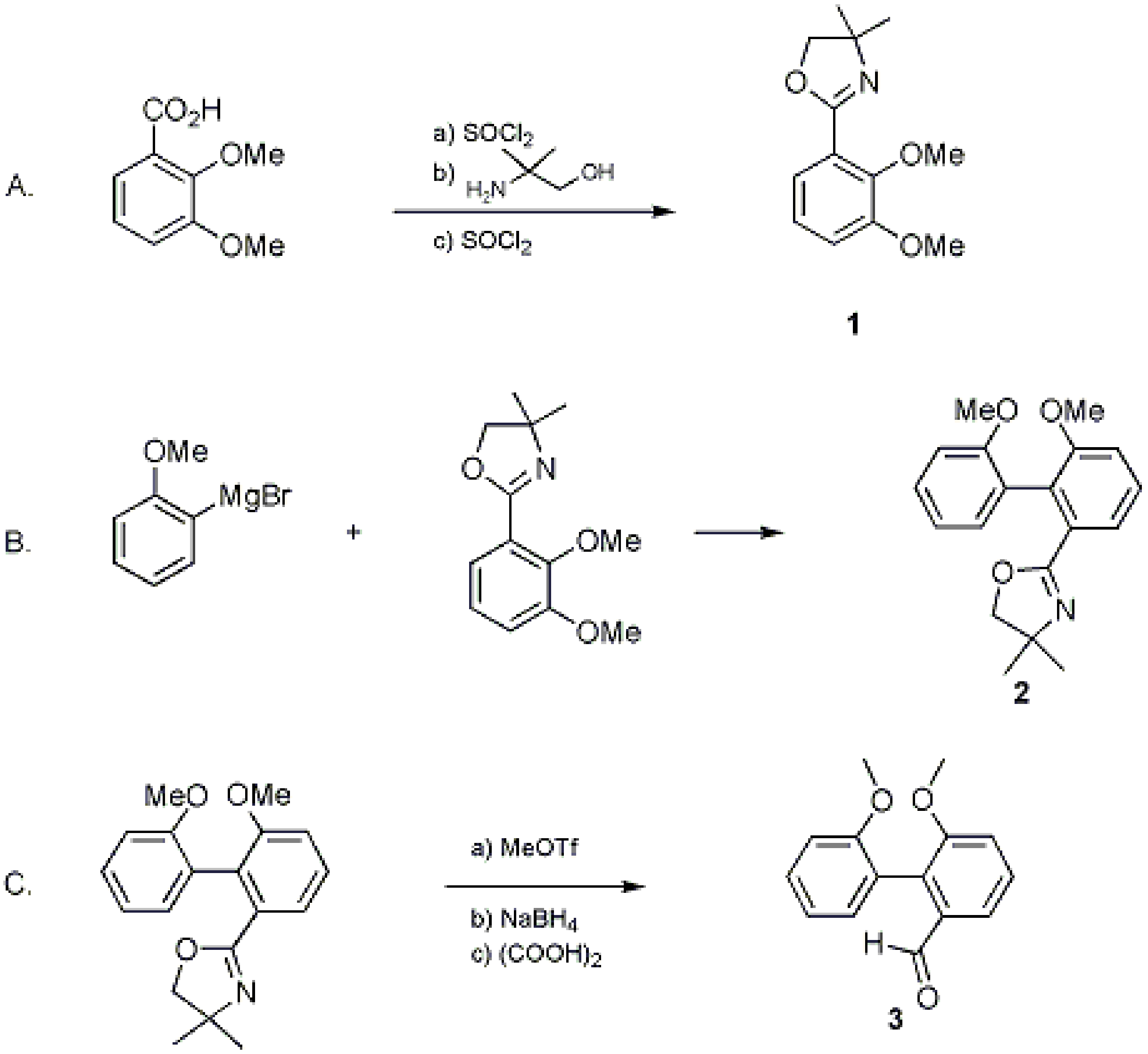
2,2'-DIMETHOXY-6-FORMYLBIPHENYL

[(1,1'-Biphenyl)-2-carboxaldehyde, 2',6-dimethoxy-]



Submitted by Albert I. Meyers and Mark E. Flanagan[1].
Checked by Chris H. Senanayake and Ichiro Shinkai.

1. Procedure

Caution! This procedure should be performed in a well-ventilated hood.

A. *2-(2,3-Dimethoxyphenyl)-4,4-dimethyl-2-oxazoline*. To a 100-mL, round-bottomed flask, fitted with a magnetic stirring bar and a reflux condenser and placed in an ice-water bath, is added 24.5 g (0.206 mol) of thionyl chloride (Note 1). To this is added 12.2 g (0.067 mol) of 2,3-dimethoxybenzoic acid (Note 2). The resulting mixture is stirred at 0°C for 1 hr and then at room temperature for 24 hr. Excess thionyl chloride is

removed by rotary evaporation (HOOD!) and the residue is distilled using a Kugelrohr apparatus at 105°C (0.05 mm) to give 12.7–13.1 g of 2,3-dimethoxybenzoyl chloride, which crystallizes on cooling (Note 3).

The acid chloride, 12.7 g, is dissolved in 60 mL of dichloromethane and transferred to a 300-mL, round-bottomed flask fitted with a magnetic stirring bar and a 100-mL, pressure-equalizing dropping funnel. The solution is cooled to 0°C in an ice bath. 2-Amino-2-methyl-1-propanol (12.5 g, 0.140 mol) dissolved in 50 mL of dichloromethane is added dropwise to the cold solution over 15 min. The reaction mixture is allowed to warm to room temperature and stirring is continued for 2 hr. The white precipitate (Note 4) is removed by filtration and the mother liquor is removed by rotary evaporation to afford 15.7 g of the amido alcohol (Note 5). The amido alcohol is redissolved in 100 mL of dichloromethane and added to a 300-mL round-bottomed flask fitted with a reflux condenser and a magnetic stirring bar. Thionyl chloride (24.5 g, 0.206 mol) is added dropwise and the resulting mixture is stirred at room temperature for 1.5 hr (Note 6). The reaction mixture is cooled to 0°C (ice-water bath) and to it is added slowly 50 mL of cold water followed by approximately 50 mL of aqueous 40% sodium hydroxide solution, which basifies the reaction mixture to approximately pH 11. Saturated sodium chloride solution (approximately 50 mL) is added and the contents of the flask are transferred to a 1-L separatory funnel. The lower phase (CH_2Cl_2 solution) is removed and set aside while the upper, aqueous phase is extracted once with 50 mL of dichloromethane. The dichloromethane extracts are combined and dried over magnesium sulfate. The solution is then filtered through Celite and concentrated under reduced pressure to leave crude 2-(2,3-dimethoxyphenyl)-4,4-dimethyl-2-oxazoline **(1)**. The latter is distilled in a Kugelrohr apparatus at 110°C (0.05 mm) to give 12.7–13.3 g (81–85%) (Note 7).

B. *2,2'-Dimethoxy-6-(4",4"-dimethyloxazolinyl)biphenyl*. Magnesium turnings (3.3 g, 0.14 g-atom, (Note 8)) and 100 mL of dry ether (Note 9) are added to a flame-dried, 1-L, round-bottomed flask under a nitrogen atmosphere. The flask is fitted with a 250-mL addition funnel, reflux condenser, and magnetic stirring bar, and placed under a slow nitrogen flow. A few crystals of iodine are added to the reaction vessel followed by dropwise addition of 18 g (0.12 mol) of 2-bromoanisole (Note 10) in 150 mL of anhydrous ether (Note 11). When the addition is complete, the reaction mixture is stirred for 2 hr at room temperature. When it is apparent that formation of the Grignard solution has consumed most of the magnesium turnings, a solution of the dimethoxyphenyloxazoline, 11.2 g (0.048 mol) in 300 mL of anhydrous tetrahydrofuran (Note 12), is added dropwise at room temperature to the stirred Grignard solution. After addition is complete, stirring of the dark solution is continued for 24 hr or until reaction is complete (Note 13). The reaction mixture is quenched by careful addition of saturated ammonium chloride (50 mL) followed by addition of 50 mL of water. The contents are transferred to a 1-L separatory funnel and the lower aqueous phase is separated while the upper organic phase is set aside. The aqueous phase is returned to the separatory funnel and extracted once with 50 mL of ether; both ethereal phases are then combined, dried over magnesium sulfate, and filtered and concentrated under reduced pressure.

There is obtained 19.2 g of a yellow solid that contains, in addition to the biphenyl, some anisole and other contaminants (e.g., starting materials). The volatile impurities are removed by Kugelrohr or other short path distillation (105°C, 0.05 mm, 15 min) to leave 14.2 g (96%) of crude biphenyl product. Purification is performed by recrystallization from ethyl acetate-hexane (1:1) to give 12.2–13.0 g (80–85%) of pure material (Note 14), (Note 15).

C. *2,2'-Dimethoxy-6-formylbiphenyl*. To a flame-dried, 1-L, round-bottomed flask, under nitrogen, and fitted with a magnetic stirring bar is added 12.2 g (0.039 mol) of pure biphenyloxazoline 2 in 300 mL of dry dichloromethane (Note 16). To this is added 7.9 g (0.048 mol) of methyl trifluoromethanesulfonate (Note 17) and the chilled solution is stirred at room temperature for 2–3 hr (Note 18). The solution of quaternized oxazoline is cooled to 0°C in an ice-water bath. Separately, 3.3 g (0.87 mol) of sodium borohydride is slurried at 0°C with 125 mL of absolute ethanol. The chilled slurry is added slowly, to control foaming, to the reaction mixture. When the addition is complete, the mixture is stirred at 0°C for 45 min and the contents of the flask are evaporated under reduced pressure. The resulting solid residue is dissolved in 400 mL of 4:1 tetrahydrofuran-water and 19.5 g (0.217 mol) of oxalic acid is added in portions (exotherm). The mixture is stirred at room temperature for 16–18 hr (Note 19). Tetrahydrofuran is removed under rotary evaporation to leave behind an aqueous slurry that is washed in a separatory funnel with pentane-ether (1:1, 2 × 100 mL). The upper layer is removed and the aqueous layer is extracted again with 50 mL of pentane-ether. The organic layers are combined and washed with 50 mL of aqueous 10% sodium bicarbonate and then with 50 mL of saturated brine. The aqueous washes are also back-extracted with pentane-ether which is combined with the other organic solutions. The organic layers are dried over sodium sulfate (anhydrous) and the solution is filtered through Celite. Concentration of the solution under reduced pressure gives 7.5 g (75–83%) of the final biphenyl aldehyde, mp 65–67°C. Recrystallization from 2-propanol gives 6.5 g of pure material (Note 20), (Note 21).

2. Notes

1. Thionyl chloride was purchased from Fisher Scientific Company.
2. 2,3-Dimethoxybenzoic acid was used as received from Aldrich Chemical Company, Inc.
3. The melting point was 53–54°C.
4. This is the hydrochloride of 2-amino-2-methyl-1-propanol.
5. The melting point was 77–80°C after air drying for several hours.
6. The formation of the 2,3-dimethoxyphenyloxazoline **(1)** can be readily followed by removing aliquots, neutralizing with aqueous sodium hydroxide, and checking on TLC using silica gel and eluting with hexane-acetone, 85:15; R_f is 0.29.
7. The physical properties are as follows: mp 44–46°C, ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 1.36 (s, 6 H), 3.83 (s, 6 H), 4.08 (s, 2 H), 6.96 (dd, 1 H, J = 8.2, 1.9), 7.02 (dd, 1 H, J = 8.2, 7.5), 7.29 (dd, 1 H, J = 7.5, 1.9).

8. Magnesium turnings were purchased from J. T. Baker Chemical Company.
9. Ether was distilled from benzophenone ketyl under nitrogen. The checkers used ether dried over 4 Å molecular sieves, under nitrogen, for 2 days and obtained the same results.
10. 2-Bromoanisole was purchased, and used without further purification, from Aldrich Chemical Company, Inc.
11. Warming of the reaction vessel with a water bath (30°C) tends to expedite the initiation of the Grignard reagent.
12. Anhydrous tetrahydrofuran (THF) was distilled from benzophenone ketyl under nitrogen. The checkers used THF dried over 4 Å molecular sieves, under nitrogen, for 2 days and obtained the same results.
13. The reaction is followed by TLC (silica, hexane-acetone, 85:15) and shows the disappearance of the dimethoxyphenyloxazoline **1** at R_f 0.29 and the appearance of the biphenyl **2** at R_f 0.18.
14. The physical properties are as follows: mp 127–129°C; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.18 (s, 3 H), 1.19 (s, 3 H), 3.59 (d, 1 H, J = 8.1), 3.72 (d, 1 H, J = 8.1), 3.75 (s, 6 H), 6.98 (om, 2 H), 7.05 (dd, 1 H, J = 7.1, 2.4), 7.15 (dd, 1 H, J = 7.4, 1.7), 7.29 (dd, 1 H, J = 7.6, 1.8), 7.34–7.39 (om, 2 H).
15. If crude material is used in Step C, the yield of final product is approximately 50–58%.
16. Dichloromethane was dried by distilling from calcium hydride. The checkers used dichloromethane (reagent grade) kept over 4 Å molecular sieves for 2 days to obtain the same results.
17. Methyl trifluoromethanesulfonate was purchased from Aldrich Chemical Company, Inc.
18. Stirring is continued until quaternization of the oxazoline **2** is complete. This is easily monitored by TLC which shows only baseline salt (silica, hexane-acetone) and complete absence of the biphenyloxazoline at R_f 0.18.
19. The checkers report that the reaction can be followed by TLC, indicating disappearance of starting material and appearance of the aldehyde (R_f = 0.75, hexane-ethyl acetate, 75:25).
20. The physical properties are as follows: mp 75–76°C; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 3.74 (s, 3 H), 3.78 (s, 3 H), 7.01 (d, 1 H, J = 8.3), 7.06 (m, 1 H), 7.22 (dd, 1 H, J = 7.9, 17), 7.23 (dd, 1 H, J = 7.4, 1.8), 7.39–7.49 (om, 2 H), 7.63 (dd, 1 H, J = 7.8, 1.0), 9.68 (d, 1 H, J = 0.8).
21. The submitters report that this procedure can also produce the corresponding biphenyl carboxylic acid by omitting the quaternization-reduction step and subjecting the biphenyloxazoline **2** to hydrolysis as follows:
A slurry of **2** (0.1 M) in 4 M hydrochloric acid is heated at reflux for 16 hr. The solution is concentrated to dryness by rotary evaporation and the crude carboxylic acid, derived from **2**, is recrystallized from hexane-ethyl acetate-isopropyl alcohol (2:1:1) furnishing pure material in 80% yield, mp 196–197°C.

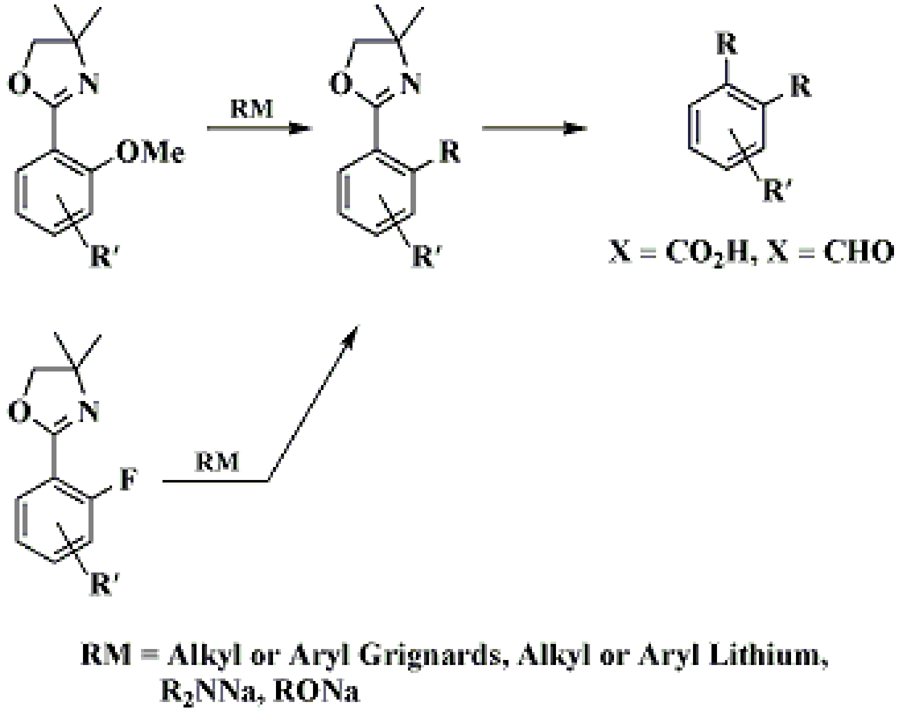
Waste Disposal Information

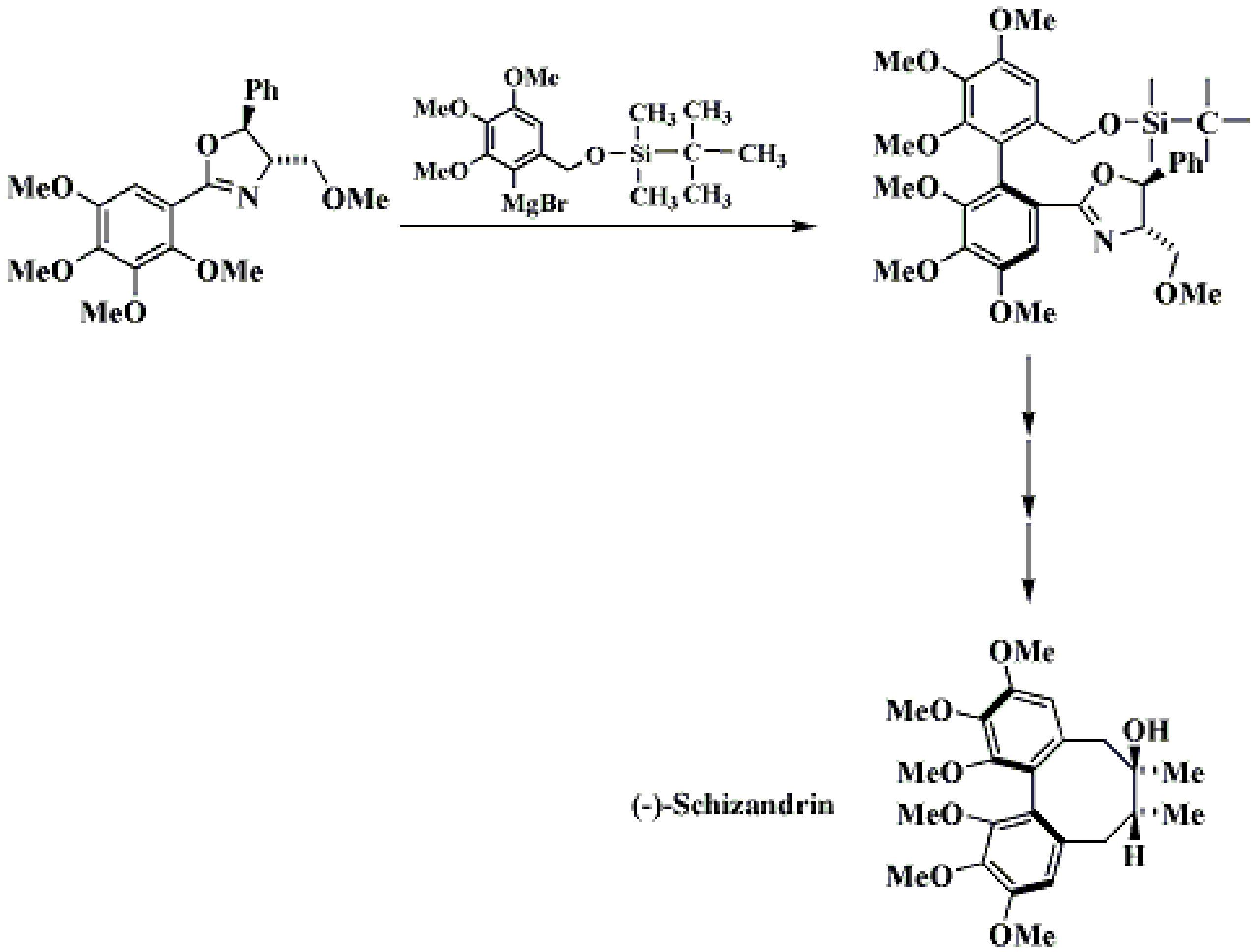
All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The use of oxazolines in aromatic substitution is a valuable synthetic tool.[2] The o-methoxy- or o-fluorophenyloxazoline reacts readily with a variety of organolithium or Grignard reagents to displace only the ortho substituent. In this fashion a number of ortho-substituted benzoic acids, benzaldehydes, and unsymmetrical biphenyls are accessible. The reaction takes place under very mild conditions, usually at or below room temperature, and thus allows a number of other sensitive groups to be present.

In addition to the simple substitutions shown in Scheme 1, this reaction has been used in a variety of complex systems as a route to optically active substances. For example, use of chiral oxazolines in this coupling process has led to an asymmetric synthesis of (−)-steganone,[3] podophyllotoxin,[4] (−)-schizandrin,[5] and (+)-phylictralin.[6] The synthesis of (−)-schizandrin is sketched in Scheme 2.





This method described here for preparing unsymmetrical biphenyls compares favorably with other recent and classical routes.[7,8,9,10]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

benzophenone ketyl

silica

brine

2,2'-Dimethoxy-6-(4",4"-dimethyloxazolinyl)biphenyl

o-methoxy- or o-fluorophenyloxazoline

(−)-steganone

podophyllotoxin

(−)-schizandrin

(+)-phylictralin

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

ether (60-29-7)

ammonium chloride (12125-02-9)

sodium hydroxide (1310-73-2)

thionyl chloride (7719-09-7)

sodium bicarbonate (144-55-8)

magnesium turnings (7439-95-4)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

Oxalic acid (144-62-7)

nitrogen (7727-37-9)

iodine (7553-56-2)

acetone (67-64-1)

isopropyl alcohol, 2-propanol (67-63-0)

Pentane (109-66-0)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

2-amino-2-methyl-1-propanol (124-68-5)

hexane (110-54-3)

calcium hydride (7789-78-8)

sodium borohydride (16940-66-2)

ethyl acetate-hexane (2639-63-6)

2,3-dimethoxybenzoic acid (1521-38-6)

methyl trifluoromethanesulfonate (333-27-7)

2,2'-Dimethoxy-6-formylbiphenyl, (1,1'-Biphenyl)-2-carboxaldehyde, 2',6-dimethoxy- (87306-84-1)

2-(2,3-Dimethoxyphenyl)-4,4-dimethyl-2-oxazoline (57598-32-0)

2,3-dimethoxybenzoyl chloride

2-bromoanisole (578-57-4)

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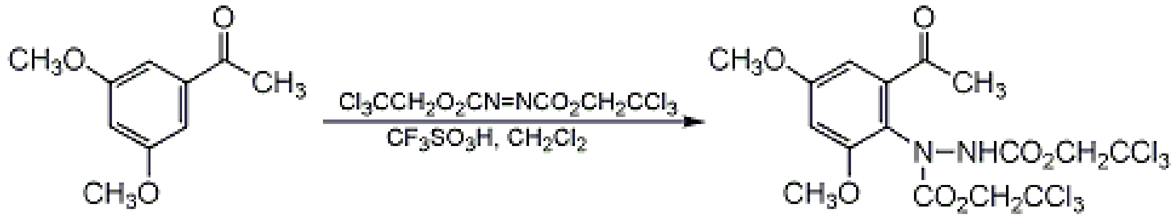
Organic Syntheses, CV 9, 264

5,7-DIMETHOXY-3-METHYLINDAZOLE FROM 3,5-DIMETHOXYACETOPHENONE

[1H-Indazole, 5,7-dimethoxy-3-methyl-]

A.



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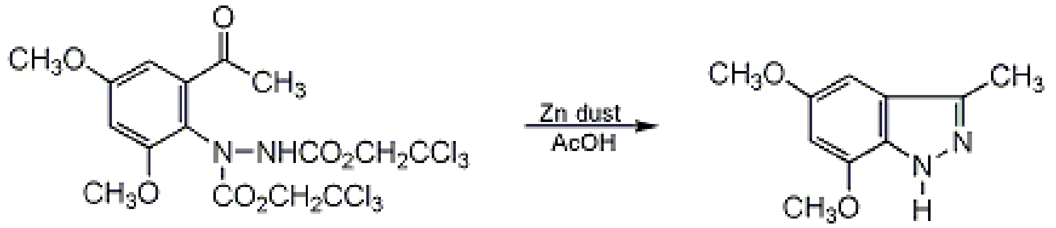


Submitted by Nicolas Boudreault and Yves Leblanc[1].
Checked by John A. McCauley and Amos B. Smith, III..

1. Procedure

A. *1-(2-Acetyl-4,6-dimethoxyphenyl)-1,2-hydrazinedicarboxylic acid bis(2,2,2-trichloroethyl) ester*. A 2-L, round-bottomed flask, equipped with a magnetic stirrer, thermometer, and an ice bath is charged with 3,5-dimethoxyacetophenone (20.00 g, 111.0 mmol) (Note 1) and dichloromethane (CH_2Cl_2, 555 mL) (Note 1). At 0–5°C, under nitrogen, trifluoromethanesulfonic acid (980 •L, 11.1 mmol) (Note 1) is added in one portion. To the resulting yellow solution, bis(2,2,2-trichloroethyl) azodicarboxylate (BTCEAD) (50.70 g, 133.3 mmol) (Note 2) is gradually introduced over 15 min in order to maintain an internal temperature between 0–5°C.

The orange-yellow solution is stirred for 5.5 hr at room temperature until complete reaction has taken place. The reaction mixture is poured into saturated aqueous sodium bicarbonate ($NaHCO_3$) solution (100 mL) at 0°C. The organic phase is separated and the aqueous phase is reextracted with CH_2Cl_2 (30 mL). The combined organic layers are washed with water (H_2O) (2 × 50 mL), dried over anhydrous sodium sulfate, filtered, concentrated and placed on a vacuum pump to afford a pale yellow foam. Ethyl acetate (85 mL) is added and the crude mixture is heated under reflux until complete dissolution occurs. At reflux hexane (85 mL) is added and the solution is allowed to stand at room temperature. After a period of 15 hr the flask containing a mass of solid is cooled in an ice bath for 1.5 hr. The solid is collected by filtration and washed with a cold ethyl acetate-hexane mixture (1:4) (50 mL). The hydrazide is dried under high vacuum at 45°C for 3 days (Note 3) to provide 52.0 g (84%) of a white solid sufficiently pure for the next step (Note 4). From the mother liquor, an additional 3.8 g (6.0%) of material is recovered by flash chromatography (20% ethyl acetate in hexane) followed by recrystallization from ethyl acetate-hexane (1:1 mixture, 20 mL).

B. *5,7-Dimethoxy-3-methylindazole*. A 2-L, round-bottomed flask, equipped with a magnetic stirrer and a thermometer is charged with the hydrazide (54.0 g, 96.3 mmol) and acetic acid (480 mL). To the suspension at 16°C is added zinc dust (35.6 g, 544 mmol) (Note 5) portionwise over 5 min. After a period of 10 min, the cooling bath is removed to allow the internal temperature to reach 35°C. The mixture is stirred for about 3 hr until no hydrazide is detected by TLC (30% ethyl acetate in hexane, R_f = 0.3). The mixture is filtered over Celite and washed carefully with CH_2Cl_2 (15 × 40 mL). After removal of the solvents under reduced pressure, the brown mixture is dissolved in CH_2Cl_2 (800 mL) and saturated aqueous $NaHCO_3$ solution (600 mL). Additional solid $NaHCO_3$ is then added until pH 8 is attained. The resulting milky mixture is filtered over Celite, washed carefully with CH_2Cl_2 (10 × 100 mL), and the organic phase separated. The water phase is reextracted with CH_2Cl_2 (2 × 100 mL) and the combined organic layers are dried over sodium sulfate. After evaporation under reduced pressure, the resulting green residue is dissolved in hot CH_2Cl_2 (80 mL) and purified by flash chromatography (200 g of silica gel) (5% CH_2Cl_2/30% ethyl acetate/hexane). The indazole (14.02 g) is obtained as a yellowish solid. Crude product is recrystallized twice from ethyl acetate (100 mL) to provide 9.6 g of pure indazole (52%) as white crystals (Note 6). An additional 2.8 g (15%) of pure material is recovered from the mother liquor after recrystallization.

2. Notes

1. 3,5-Dimethoxyacetophenone 97%, anhydrous CH_2Cl_2, and trifluoromethanesulfonic acid were purchased from Aldrich Chemical Company, Inc., and used as received.
2. Bis(2,2,2-trichloroethyl) azodicarboxylate was purchased from Aldrich Chemical Company, Inc. It can also be prepared as described in reference [2,3]. See Hazard Index, p. 837.htm.
3. The ground hydrazide was dried in order to remove trapped ethyl acetate.
4. An analytical sample was obtained by recrystallization from ethyl acetate to afford a white solid, containing 0.5 equiv of ethyl acetate, mp 137–139°C. The hydrazide exhibits the following spectral properties. IR (KBr) cm^{-1}: 3240, 1765, 1735, 1595; ^{1}H NMR (400 MHz, acetone-d_6,325 K) δ: 2.65 (s, 3 H), 3.89 (s, 3 H), 3.90 (s, 3 H), 4.80 (s, 2 H), 4.90 (bs, 2 H), 6.76 (d, 1 H), 6.81 (d, 1 H), 8.91 (bs, 1 H); ^{13}C NMR (100 MHz, acetone-d_6,325 K) δ: 56.19, 56.81, 75.44, 76.47, 96.00, 96.35, 102.39, 105.61, 121.48, 140.99, 154.57, 155.34, 158.03, 161.84, 200.40. Anal. Calcd for $C_{16}H_{16}Cl_6N_2O_7$· $C_4H_8O_2$: C, 35.70; H, 3.30; N, 4.62. Found C, 35.83; H, 3.14; N, 4.54. High-resolution mass spectrum, m/z calcd for $C_{16}H_{17}Cl_6N_2O_7$ $(M+H)^+$ 558.9167. Found 558.9166.
5. Zinc dust was purchased from Anachemia. Excess zinc was used to ensure completion of the reaction. The reactivity of the zinc dust should be verified on a small scale first. Lower reactivity has been observed with another substrate using zinc dust from Aldrich Chemical Company, Inc.
6. 5,7-Dimethoxy-3-methylindazole has the following physical properties. mp 158°C. IR (KBr) cm^{-1}: 3315, 1600; ^{1}H NMR (400 MHz, acetone-d_6) δ: 2.44 (s, 3 H), 3.82 (s, 3 H), 3.94 (s, 3 H), 6.45 (d, 1 H), 6.65 (d, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 12.02, 55.47, 55.74, 90.84, 98.48, 123.41, 129.41, 142.64, 145.67, 155.26. Anal Calcd for $C_{10}H_{12}N_2O_2$: C, 62.49; H, 6.29; N, 14.57. Found C, 62.54; H, 6.32; N, 14.57. High-resolution mass spectrum, m/e calcd for $C_{10}H_{13}N_2O_2$ $(M+H)^+$ 193.0977. Found 193.0976.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

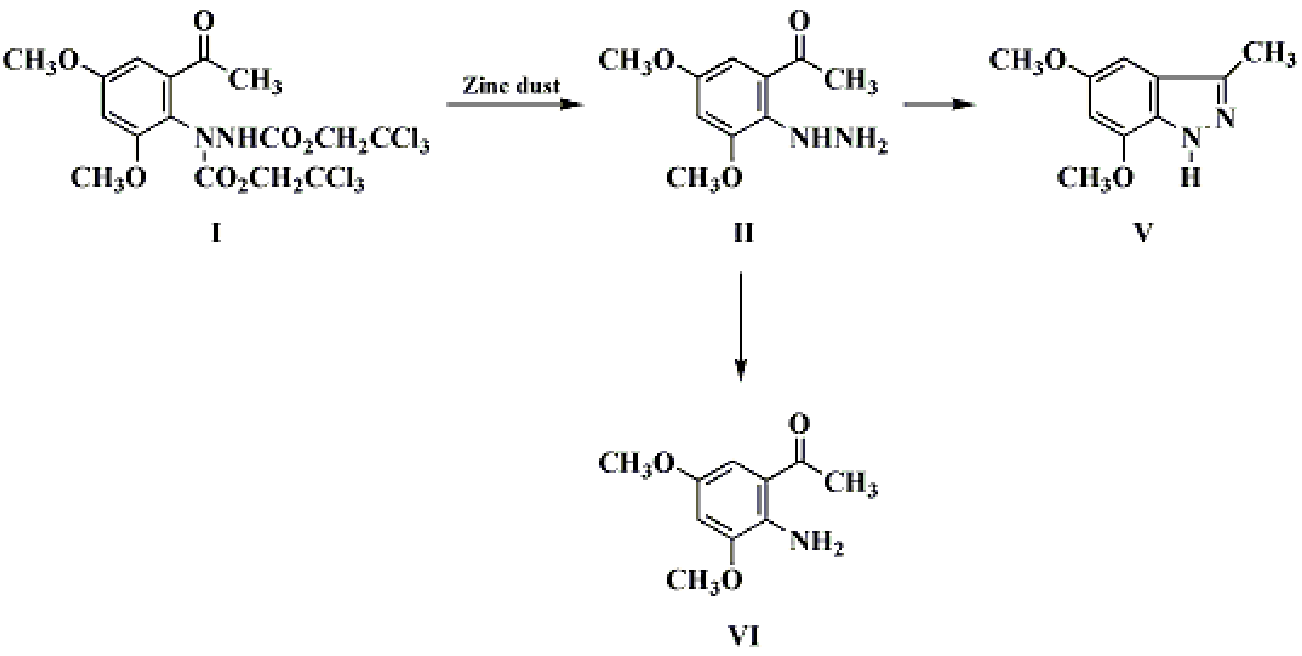
3. Discussion

The electrophilic, aromatic substitution of electron-rich arenes with the electron-deficient azodicarboxylate BTCEAD is a powerful method for the introduction, in a single operation, of a masked hydrazine or amino group.[4,5] Several activators can be used for this amination reaction; $ZnCl_2$,[5] $BF_3 \cdot Et_2O$,[5] $LiClO_4$,[4] and here, trifluoromethanesulfonic acid.[6] Trifluoromethanesulfonic acid dramatically increases the rate of the amination reaction and makes possible the use of this methodology with poorly reactive substrates.

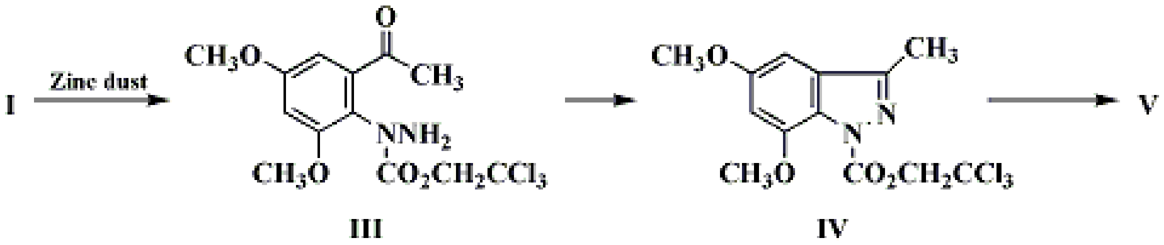
The present, straightforward, two-step synthesis of 5,6-dimethoxyindazole from 3,5-dimethoxyacetophenone illustrates the usefulness of this amination reaction. With standard chemistry the introduction of a hydrazine group into the acetophenone molecule would have required four steps: 1) nitration, 2) reduction of the nitro group to the aniline, 3) diazotization and 4) reduction of the diazonium compound to the hydrazine.

A plausible mechanism for the formation of the indazole is illustrated below. Based on our previous observations that aryltrichlorohydrazides are readily converted to anilines, via the aryl hydrazines, it is unlikely that formation of the indazole ring **5** arises from the free hydrazine intermediate **2** since the corresponding aniline **6** was not detected at all in this case. This would suggest that the terminal trichloro ester group is selectively removed to give **3**, followed by cyclization to **4** and cleavage of the second ester unit. Intermediate **4** was isolated and characterized during a probe reaction for which an equimolar amount of zinc dust was used. However, this intermediate does not accumulate to more than 1%. It appears that cleavage of the second ester group is relatively rapid after cyclization. Traces of compound **4** have also been detected during preparation of the hydrazide **1**, presumably from acid hydrolysis.

PATHWAY A



PATHWAY B



References and Notes

1. Merck Frosst Centre for Therapeutic Research, P.O. Box 1005, Pointe Claire-Dorval, Québec, Canada H9R 4P8.
2. Mackay, D.; Pilger, C. W.; Wong, L. L. *J. Org. Chem.* **1973**, *38*, 2043;
3. Little, R. D.; Venegas, M. G. *Org. Synth., Coll. Vol. VII* **1990**, 56.
4. Mitchell, H.; Leblanc, Y. *J. Org. Chem.* **1994**, *59*, 682.
5. Zaltsgendler, I.; Leblanc, Y.; Bernstein, M. A. *Tetrahedron Lett.* **1993**, *34*, 2441.
6. For other examples in which trifluoromethanesulfonic acid and trifluoroacetic acid are used Leblanc, Y.; Boudreault, N. *J. Org. Chem.* **1995**, *60*, 4268.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

3,5-DIMETHOXYACETOPHENONE

Aldrich Chemical Company, Inc

$ZnCl_2$

$BF_3 \cdot Et_2O$

$LiClO_4$

acetic acid (64-19-7)

ethyl acetate (141-78-6)

sodium bicarbonate, $NaHCO_3$ (144-55-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

zinc (7440-66-6)

dichloromethane, CH_2Cl_2 (75-09-2)

hexane (110-54-3)

trifluoroacetic acid (76-05-1)

trifluoromethanesulfonic acid (1493-13-6)

Bis(2,2,2-trichloroethyl) azodicarboxylate (38857-88-4)

5,7-Dimethoxy-3-methylindazole, 1H-Indazole, 5,7-dimethoxy-3-methyl- (154876-15-0)

1-(2-Acetyl-4,6-dimethoxyphenyl)-1,2-hydrazinedicarboxylic acid bis(2,2,2-trichloroethyl) ester

5,6-dimethoxyindazole

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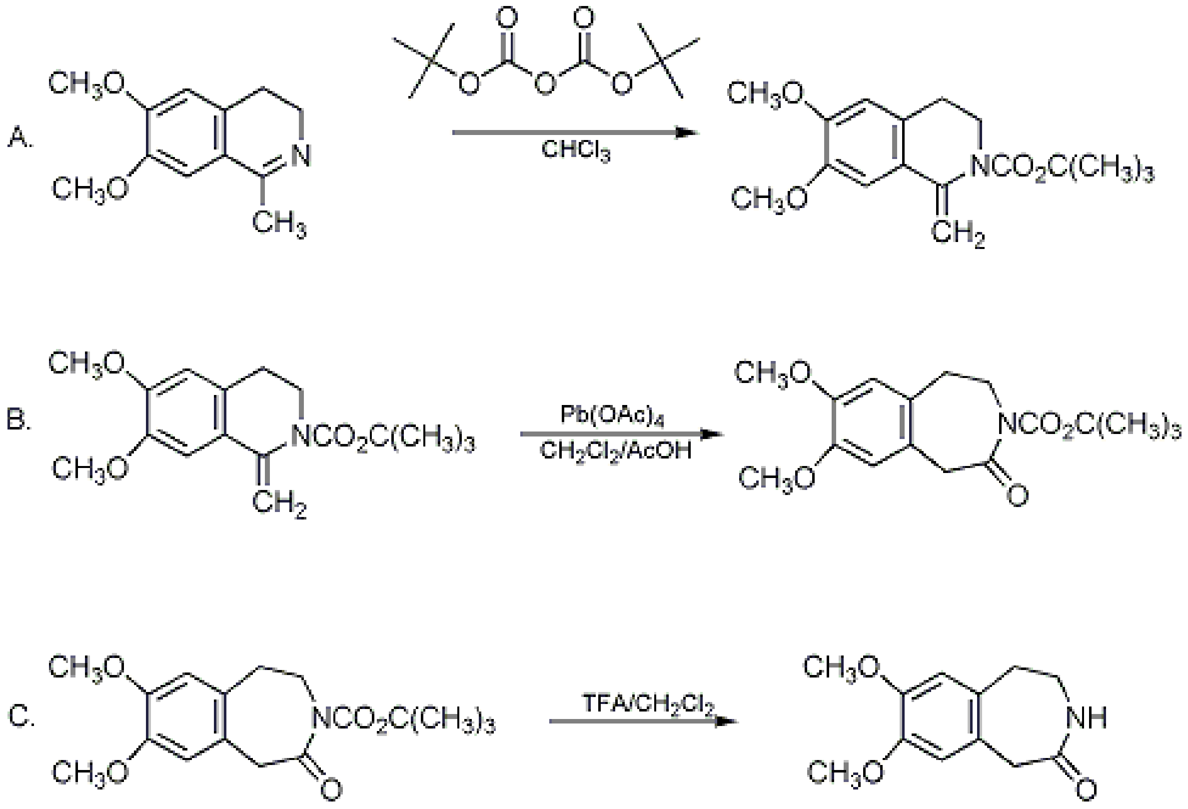
Organic Syntheses, CV 9, 268

TETRAHYDRO-3-BENZAZEPIN-2-ONES BY LEAD TETRAACETATE OXIDATION OF ISOQUINOLINE ENAMIDES: 7,8-DIMETHOXY-1,3,4,5-TETRAHYDRO-2H-3-BENZAZEPIN-2-ONE

[2H-3-Benzazepin-2-one, 1,3,4,5-tetrahydro-7,8-dimethoxy-]



Submitted by George R. Lenz and Ralph A. Lessor[1].
Checked by Shaowo Liang and Leo A. Paquette.

1. Procedure

A. *N-(tert-Butoxycarbonyl)-6,7-dimethoxy-1-methylene-1,2,3,4-tetrahydroisoquinoline*. A 1-L, three-necked, round-bottomed flask is equipped with a thermometer, magnetic stirring bar, nitrogen inlet with gas bubbler, and a pressure-equalizing dropping funnel (Note 1). The flask is charged with 102.6 g (500 mmol) of 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline (Note 2) and 150 mL of alcohol-free chloroform (Note 3). The mixture is warmed to 50°C with stirring. The dropping funnel is charged with a solution of 136.9 g (627 mmol) of di-tert-butyl pyrocarbonate (Note 4) in 50 mL of alcohol-free chloroform. The nitrogen is turned off, and the solution of di-tert-butyl pyrocarbonate is added to the mixture at such a rate as to maintain steady but controlled gas evolution (Note 5). The stirred reaction mixture is heated at 60–65°C until gas evolution ceases, then allowed to cool to room temperature with stirring.

Solvent is removed on a rotary evaporator at reduced pressure, and the resulting crude pink solid is dried overnight under high vacuum. The yield of slightly pink solid is 176.5–180 g (Note 6), (Note 7).

B. *N-(tert-Butoxycarbonyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one* A 1-L, three-necked, round-bottomed flask is equipped with a nitrogen inlet, mechanical stirrer, thermometer, and a pressure-equalizing dropping funnel (Note 8). The flask is charged with 93 g (210 mmol) of lead tetraacetate (Note 9) and 250 mL of glacial acetic acid. Stirring is started, the flask is immersed in an ice-water bath, and the funnel is charged with a solution of 61 g (200 mmol) of N-(tert-butoxycarbonyl)-6,7-dimethoxy-1-methylene-1,2,3,4-tetrahydroisoquinoline (Note 10) in 250 mL of methylene chloride. This solution is added at such a rate that a temperature of 19–23°C is maintained throughout the addition, typically over a period of 15 to 20 min. The cooling bath is removed, and the mixture is stirred at room temperature for 1 hr. Glycerol (4 mL) is added to quench unreacted lead tetraacetate, and the mixture is stirred for an additional 10 min.

The mixture is poured into 750 mL of water in a 2-L separatory funnel and shaken thoroughly. The phases are separated, and the aqueous phase is extracted with two 100-mL portions of methylene chloride. The combined organic layers are washed with 700 mL of water, followed by successive 100-mL portions of saturated aqueous sodium bicarbonate until no further effervescence is observed. The organic layer is dried over magnesium sulfate, filtered, and evaporated at reduced pressure to give a yellow-orange solid, which is dissolved in 100 mL of boiling acetone and allowed to cool slowly to room temperature, then kept overnight at –20°C. Filtration affords a cream-colored solid in a yield of 51.2–52.2 g (Note 11), (Note 12). A second crop is obtained by evaporation of the mother liquors, dissolution in a minimal amount of boiling acetone, cooling and seeding. The total yield is brought to 58–59 g (90–92%).

C. *7,8-Dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one*. A 250-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, thermometer, and pressure-equalizing dropping funnel. The flask is charged with 32.1 g (100 mmol) of recrystallized N-(tert-butoxycarbonyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one and 100 mL of methylene chloride. The flask is immersed in an ice-water bath and stirred until the internal temperature reaches 5°C. The dropping funnel is charged with 40 mL of trifluoroacetic acid, which is added dropwise at a rate such that the temperature of the reaction mixture does not exceed 10°C (Note 13). When addition is complete, the cooling bath is removed, and the mixture is stirred for 3 hr (Note 14).

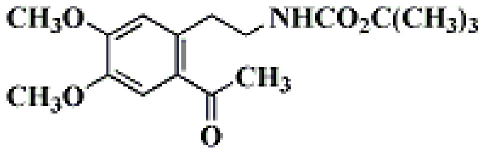
The mixture is diluted with an additional 700 mL of methylene chloride and poured into a separatory funnel containing 500 mL of water. The funnel is shaken thoroughly, and the phases are separated. The organic layer is washed with 500 mL of water, followed by successive washes with 200-mL portions of saturated aqueous sodium bicarbonate until no further effervescence is observed (Note 15). The organic phase is dried over sodium sulfate and evaporated under reduced pressure to give 24.8–25.2 g of crude product. The crude material is dissolved in a minimal amount of boiling methylene chloride, and then diluted with an equal volume of ethyl acetate. The mixture is boiled down to approximately two thirds of its starting volume, by which time crystallization has begun, then allowed to cool slowly to room temperature. After storage at –20°C overnight, filtration affords 17.5–18.0 g (79–81%) of product, mp 194–195°C (Note 16), (Note 17)).

2. Notes

1. The glassware is dried in an oven at 110°C and assembled while still hot, then allowed to cool while a slow stream of nitrogen is passed through the apparatus.

2. 6,7-Dimethoxy-1-methyl-3,4-dihydroisoquinoline was prepared according to an *Organic Syntheses* procedure: Brossi, A.; Dolan, L. A.; Teitel, S. *Org. Synth., Coll. Vol. VI* **1988**, 1.
3. The submitters used J. T. Baker Chemical Company hydrocarbon-stabilized chloroform containing 0.015% amylene stabilizer. The checkers used chloroform of comparable quality purchased from Aldrich Chemical Company, Inc.
4. The submitters used commercially available tert-butyl pyrocarbonate from either Fluka or Aldrich Chemical Company, Inc. Alternatively, the reagent can be prepared according to Pope, B. M.; Yamamoto, Y.; Tarbell, D. S. *Org. Synth., Coll. Vol. VI* **1988**, 418.
5. The addition typically took 1.5 to 2 hr. The bubbler on the nitrogen line used to flush the flask is conveniently used to monitor the evolution of carbon dioxide as the reaction proceeds.
6. This material is pure enough for use in the next step. The impurities of tert-butyl alcohol and a small amount of unreacted tert-butyl pyrocarbonate do not interfere with the oxidation.
7. If desired, the material can be recrystallized from methanol; under these circumstances, 146–149 g of white solid, mp 101–102°C, is returned. The spectral characteristics of recrystallized material are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.49 (s, 9 H), 2.78 (t, 2 H, J = 5.9), 3.77 (t, 2 H, J = 5.9), 3.86 (s, 3 H), 3.89 (s, 3 H), 5.31 (s, 1 H), 5.50 (s, 1 H), 6.56 (s, 1 H), 7.11 (s, 1 H); IR (KBr) cm^{-1}: 1690, 1630, 1605, 1510, 1390, and 1170; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 28.38, 28.96, 43.51, 55.89, 56.02, 80.47, 101.86, 107.46, 110.77, 124.84, 127.72, 139.99, 147.51, 149.22, 153.83. Anal. Calcd. for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 67.02; H, 7.48; N, 4.65.
8. The glassware is assembled hot under nitrogen as for the previous step. The nitrogen inlet and stirrer are mounted on a Claisen adapter, and the thermometer is removed during the flushing period, then reinserted.
9. The submitters used lead tetraacetate from Aldrich Chemical Company, Inc., which was dried under reduced pressure at room temperature for 10 min prior to use to remove any acetic acid present. Alternatively, lead tetraacetate still containing acetic acid may be used successfully if a slight excess is used.
10. If crude material containing tert-butyl alcohol and unreacted pyrocarbonate is used in this step, the amount of starting material present is calculated based on the mass balance for the first step, assuming a quantitative conversion, and 1.05 equivalents of lead tetraacetate are used. The checkers used only pure material and advise against carrying forward less pure carbamate.
11. This material may be used directly in the following step. If desired, the material can be recrystallized from acetone, mp 116.5–118°C. The spectral characteristics of the recrystallized material are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.52 (s, 9 H), 3.14 (t, 2 H, J = 6.0), 3.84 (s, 6 H), 3.92 (s, 2 H), 4.18 (t, 2 H, J = 6.0), 6.56 (s, 1 H), 6.57 (s, 1 H); IR (KBr) cm^{-1}: 1715, 1610, 1525, 1370, 1255, 1110, and 1060; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 28.03, 32.83, 43.42, 45.21, 55.94, 55.97, 83.18, 113.25, 114.28, 121.92, 127.09, 147.41, 148.38, 152.08, 171.33. Anal. Calcd. for $C_{17}H_{23}NO_5$: C, 63.54; H, 7.21; N, 4.36. Found: C, 63.36; H, 7.30; N, 4.16.
12. If insufficient lead tetraacetate is used in the oxidation, unoxidized starting enamide is hydrolyzed during the workup to tert-butyl 2-(2-acetyl-3,4-dimethoxyphenyl) ethyl carbamate, mp 111.5–112.5°C (cf. ref. in (Note 2)): ^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.42 (s, 9 H), 2.58 (s, 3 H), 3.03 (t, 2 H), 3.37 (q, 2 H), 3.92 (s, 3 H), 6.76 (s, 1 H), 7.23 (s, 1 H); IR (FTIR) cm^{-1}: 1707, 1674, 1604, 1517, 1266, 1212, 1152. Anal. Calcd for $C_{17}H_{25}NO_5$: C, 63.13; H, 7.79; N, 4.33. Found: C, 63.24; H, 7.91; N, 4.28. The hydrolyzed material co-migrates with the oxidation product in a variety of TLC systems, and also co-crystallizes with it. It is, however, removed during the trifluoroacetic acid (TFA) cleavage to form the

benzazepinone (Step C). The presence of any hydrolyzed material is readily detected by the presence of the acetyl resonance (δ 2.58) in the NMR spectrum.



13. After approximately 25 mL of the trifluoroacetic acid have been added, gas evolution begins. This can be quite vigorous if the temperature is not kept below 10°C.
14. The progress of the reaction can be monitored by thin layer chromatography on silica gel plates, using a 95:5:0.5 mixture of chloroform:methanol:concentrated ammonium hydroxide as the developing solvent.
15. Foaming can be quite vigorous, especially if the reaction mixture is not washed first with water prior to the use of sodium bicarbonate solution.
16. A small second crop of impure material can be obtained from the mother liquors.
17. The product exhibited the following spectral characteristics: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.03 (t, 2 H, J = 6.0), 3.52–3.60 (m, 2 H), 3.75 (s, 2 H), 3.83 (s, 3 H), 3.84 (s, 3 H), 6.34 (br s, 1 H), 6.59 (s, 1 H), 6.62 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 33.03, 40.62, 41.71, 55.77 (2C), 112.96, 113.53, 123.19, 128.39, 147.09, 147.72, 174.49; IR (KBr) cm^{-1}: 1675, 1220, 1125, 1100, and 1010.

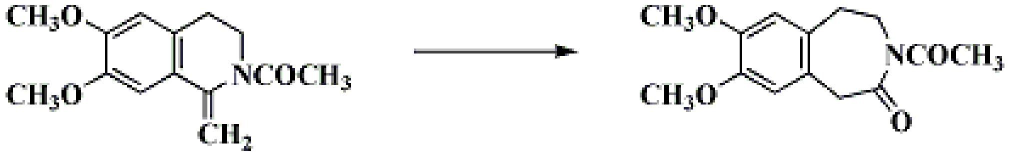
Waste Disposal Information

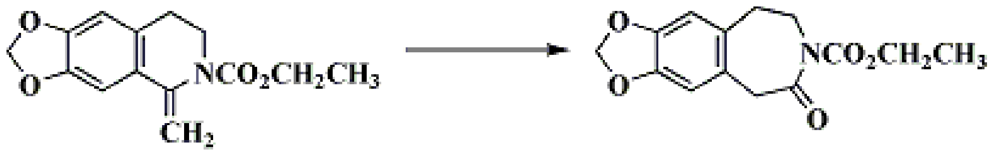
All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

This procedure illustrates a general route to tetrahydro-3-benzazepin-2-ones from readily available dihydroisoquinolines.[2] The benzazepine ring system exists in various classes of isoquinoline-derived alkaloids,[3 4 5] while other members of this class are being developed as pharmaceutical agents.[6] The present procedure takes advantage of ready formation of enamides from dihydroisoquinolines and carboxylic acid anhydrides, acid chlorides, carbonic anhydrides and chlorides and their facile oxidation to differentially functionalized benzazepinones (Table I). The mechanism has been described and involves migration of the isoquinoline aromatic ring to the exocyclic methylene group.[2]

TABLE I
LEAD TETRAACETATE OXIDATIVE RING EXPANSION OF ISOQUINOLINE ENAMIDES

	Yield (%)
	



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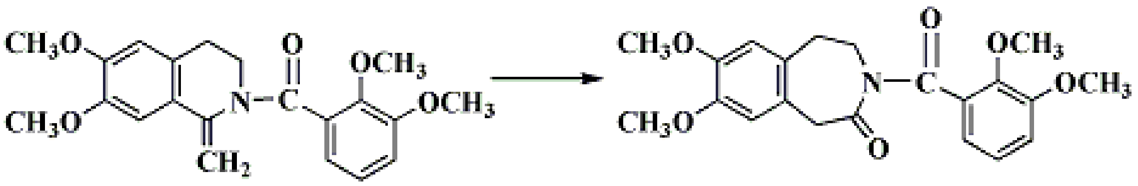

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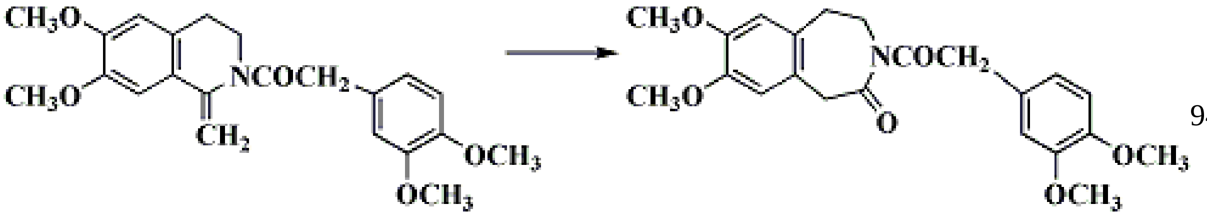

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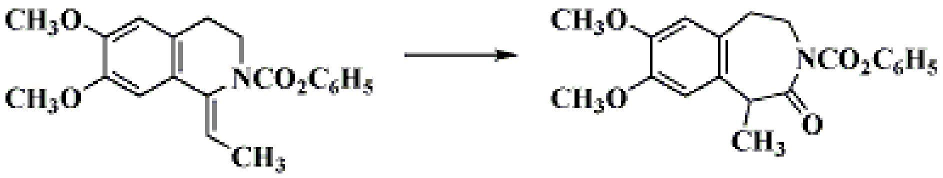

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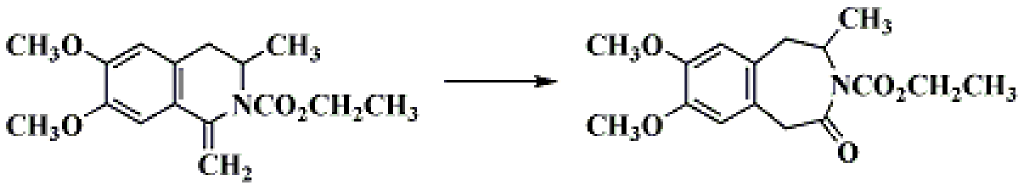

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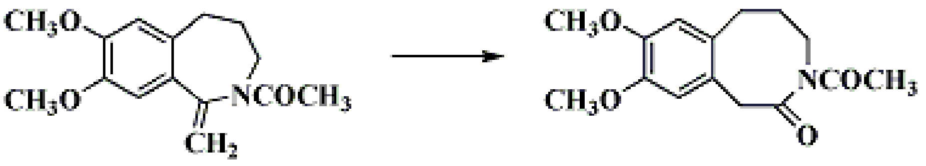
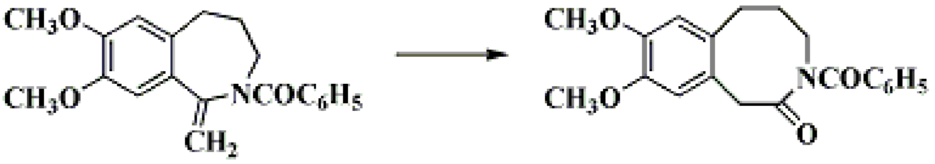
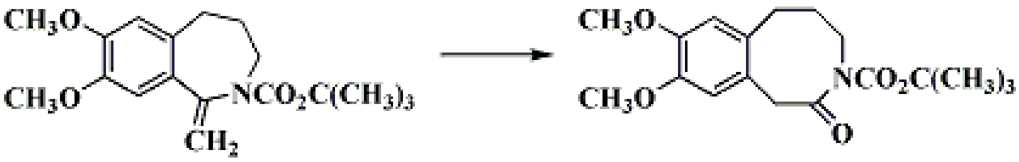
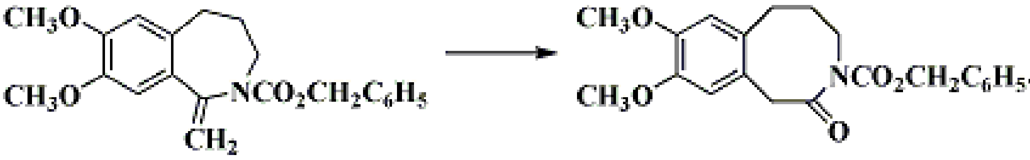
Several approaches to the synthesis of the tetrahydrobenzazepine ring system have been described,[7] and excellent methods exist for the preparation of aryl substituted tetrahydrobenzazepines.[6] However, benzazepines that are either unsubstituted or alkyl-substituted on the azepine ring are much less readily obtainable. For instance, the benzazepinone, synthesized by this procedure, was originally isolated, in low yield, from the mixture of photoproducts obtained from the irradiation of N-[3-(3,4-dimethoxyphenyl)]propyl chloroacetamide.[8] [9] Preparative approaches to the benzazepinones have required multiple steps starting from an N-phenylethylacetamide and involving chloromethylation, cyanide displacement, nitrile solvolysis, hydrolysis to the amino acid and cyclization.[10] [11] The 1-alkyl derivatives are subsequently prepared by alkylation of the parent compound.[12] The current procedure reduces the preparation of the tetrahydrobenzazepinone ring system to two straightforward steps.

Ring expansion of the isoquinoline enamides is insensitive to the type of acyl functionality used to form the enamide.[13] The reaction occurs when the isoquinoline aromatic ring is unsubstituted, or contains electron releasing substituents. The reaction is sensitive, however, to the degree and type of substitution on the exocyclic methylene group. Oxidative ring expansion occurs when the

double bond is either unsubstituted or monoalkyl substituted. Phenyl substitution yields differing products depending on a number of variables.[13] When the exocyclic double bond is disubstituted, oxidation with lead tetraacetate proceeds readily, but does not lead to ring expansion.[14] The ring expansion reaction works equally well for the preparation of tetrahydrobenzazocinones from tetrahydrobenzazepine enamides (Table II).[15]

TABLE II
LEAD TETRAACETATE OXIDATIVE RING EXPANSION OF BENZAZEPINE ENAMIDES

	Yield(%)
	76
	83
	73
	78

The acid-catalyzed cleavage of the tert-butoxycarbonyl group is the best method to form the parent benzazepinone. Other methods used have been the Pd/C hydrogenolysis of a benzyloxycarbonyl group,[2,15,16] and zinc mediated reductive cleavage of trichloroethoxy and trichloro-tert-butoxy carbonyl groups.[15]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

trifluoroacetic acid (TFA)

Pd/C

acetic acid (64-19-7)

ethyl acetate (141-78-6)

methanol (67-56-1)

chloroform (67-66-3)

glycerol (56-81-5)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

acetone (67-64-1)

zinc (7440-66-6)

ammonium hydroxide (1336-21-6)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

amylene

tert-butyl alcohol (75-65-0)

trifluoroacetic acid (76-05-1)

N-phenylethylacetamide (877-95-2)

6,7-Dimethoxy-1-methyl-3,4-dihydroisoquinoline (4721-98-6)

BOC

7,8-Dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one, 2H-3-Benzazepin-2-one, 1,3,4,5-

tetrahydro-7,8-dimethoxy- (20925-64-8)

N-(tert-Butoxycarbonyl)-6,7-dimethoxy-1-methylene-1,2,3,4-tetrahydroisoquinoline (82044-08-4)

di-tert-butyl pyrocarbonate (24424-99-5)

N-(tert-Butoxycarbonyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one (146858-74-4)

tert-butyl pyrocarbonate

tert-butyl 2-(2-acetyl-3,4-dimethoxyphenyl) ethyl carbamate

N-[3-(3,4-dimethoxyphenyl)]propyl chloroacetamide

lead tetraacetate

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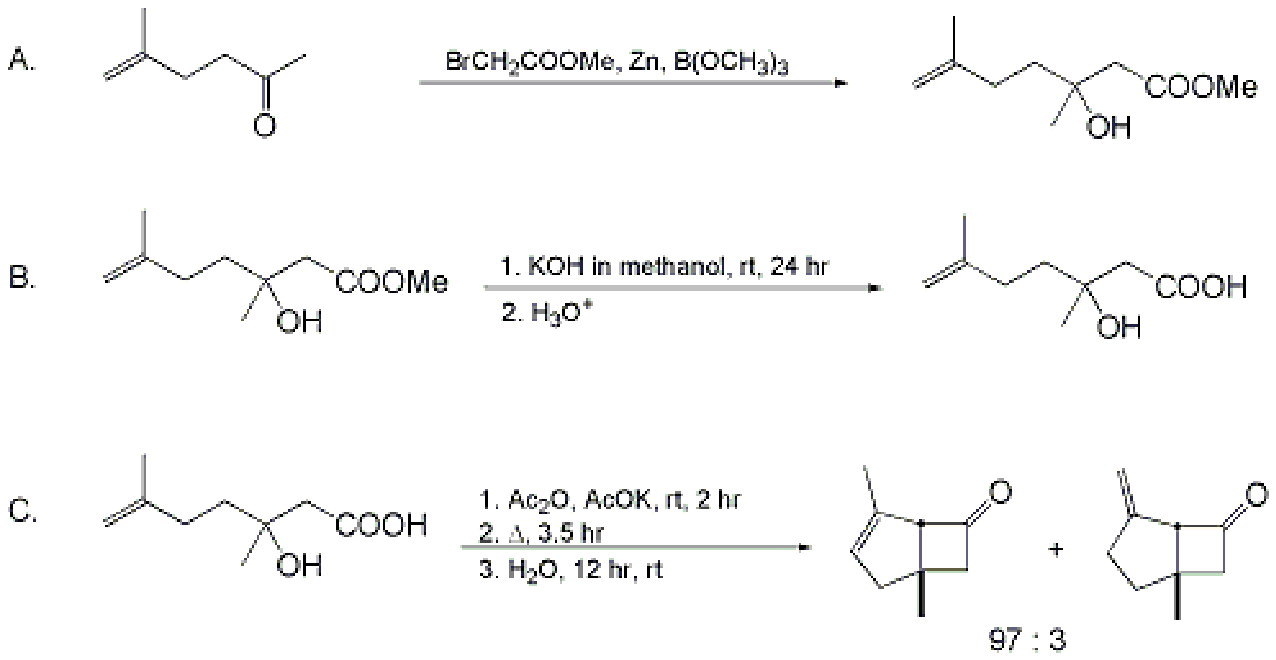
Organic Syntheses, *CV 9, 275*

PREPARATION OF BICYCLO[3.2.0]HEPT-3-EN-6-ONES: 1,4-DIMETHYLBICYCLO[3.2.0]HEPT-3-EN-6-ONE

[Bicyclo[3.2.0]hept-3-en-6-one, 1,4-dimethyl-, cis-(±)-]



Submitted by Goffredo Rosini[1], Giovanni Confalonieri[2], Emanuela Marotta[1], Franco Rama[2], and Paolo Righi[1].
Checked by Jian-Ping Chao and Robert K. Boeckman, Jr..

1. Procedure

A. *Methyl 3,6-dimethyl-3-hydroxy-6-heptenoate* (Note 1). An oven-dried, three-necked, 500-mL, round-bottomed flask, is fitted with an efficient mechanical stirrer, a Claisen adapter bearing a reflux condenser with a nitrogen inlet and rubber septum, and a thermometer. The flask is maintained under a static nitrogen pressure and charged with 5-methyl-5-hexen-2-one (24.20 g, 0.216 mol) (Note 2), trimethyl borate (60 mL) (Note 3), tetrahydrofuran (60 mL) (THF) (Note 4), and freshly activated 20-mesh zinc granules (16.96 g, 0.259 g-atom) (Note 5). The reaction flask is immersed in an oil bath at 25°C. Stirring is initiated and methyl bromoacetate (39.65 g, 0.259 mol) (Note 6) is added in a single portion through the septum. After an induction time (Note 7), a white precipitate starts to form and an increase of the internal temperature, up to reflux, is observed (Note 8). The mixture is stirred for 3 hr, after which time starting material is completely consumed (Note 9). The reaction is quenched by the sequential addition of glycerol (60 mL) and saturated aqueous ammonium chloride (60 mL), then is transferred to a separatory funnel using 120 mL of diethyl ether. The aqueous layer is separated and extracted again with diethyl ether (3 × 60 mL). The combined ether extracts are washed with aqueous 30% ammonium hydroxide solution (3 × 30 mL) and then with saturated sodium chloride

solution (2 × 30 mL). The organic extracts are dried over magnesium sulfate ($MgSO_4$) and concentrated at reduced pressure with a rotary evaporator to afford 37.32–38.92 g of crude β-hydroxy ester (93–97% yield) (Note 10).

B. *3,6-Dimethyl-3-hydroxy-6-heptenoic acid*. In a 500-mL flask, the crude ester prepared in Part A (37.00 g, 0.199 mol) is dissolved in a 2 N solution of potassium hydroxide (KOH) in methanol (130 mL, 0.260 mol). The solution is stirred at 25°C and disappearance of the starting material is monitored by GLC (Note 9). After 5 hr saponification is complete and the methanol is evaporated at reduced pressure (Note 11). The residue is taken up with water (500 mL), extracted with diethyl ether (3 × 100 mL), and the organic phase is discarded. The aqueous phase is acidified (pH 2.5 on universal pH indicator paper) with 6 N hydrochloric acid (about 60 mL) and extracted with diethyl ether (5 × 100 mL). These latter ethereal extracts are washed with water (2 × 30 mL) and then with saturated sodium chloride (2 × 30 mL). The organic phase is dried over sodium sulfate, and filtered. Evaporation at reduced pressure affords crude 3,6-dimethyl-3-hydroxy-6-heptenoic acid as a viscous yellow oil that can be used in Part C without further purification. Evacuation at 0.5 mm at room temperature with internal magnetic stirring for 24 hr gives 28.07–29.40 g (82–86% yield) of a solvent-free material (Note 12) and (Note 13).

C. *1,4-Dimethylbicyclo[3.2.0]hept-3-en-6-one*. A three-necked, 500-mL, round-bottomed flask, equipped with a condenser fitted with a calcium chloride tube, an efficient mechanical stirrer, and an immersion thermometer, is charged with crude 3,6-dimethyl-3-hydroxy-6-heptenoic acid (29.40 g, 0.171 mol), acetic anhydride (185 mL) (Note 14) and potassium acetate (40.28 g, 0.410 mol). The reaction mixture is stirred for 2 hr at room temperature. During this time, an exotherm is observed (up to 50°C) followed by a slow return to room temperature, and the suspension becomes thicker. The reaction is brought to reflux (in ca. 20 min) by means of a heating mantle and stirring is continued for another 3.5 hr. A two-necked, 2-L, round-bottomed flask fitted with a condenser and magnetic stirrer is charged with crushed ice (400 g) and water (100 g), and the hot mixture is added carefully with good stirring. Light petroleum ether (500 mL) is added and the mixture is stirred for 12 hr at room temperature. The reaction mixture is transferred into a 2-L separatory funnel and the aqueous layer is separated and extracted with light petroleum ether (4 × 100 mL). The combined organic layers are washed with saturated sodium bicarbonate solution (3 × 50 mL) and saturated sodium chloride solution (2 × 30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated at ambient pressure to give the crude product as a dark oil. Final purification is achieved by distillation under reduced pressure (Note 15) affording 17.70–18.86 g (76–81% yield) of a 99% pure mixture (97:3) of the keto olefin isomers as a colorless oil, bp 84–85°C/26–28 mm (Note 16).

2. Notes

1. This procedure is essentially that of Rathke and Lindert.[3]
2. The submitters used freshly distilled ketone prepared according to the *Organic Syntheses* procedure.[4] 5-Methyl-5-hexen-2-one is also available from Aldrich Chemical Company, Inc., and can be used as purchased.
3. Trimethyl borate was distilled from calcium hydride and stored under nitrogen.

4. Tetrahydrofuran (reagent grade) was dried by distillation from sodium/benzophenone ketyl and freshly distilled before use.
5. Zinc granules (20-mesh, 99.8%, A.C.S. reagent grade, Pb ≤ 0.01%, Fe ≤ 0.01%) obtained from Aldrich Chemical Company, Inc., were activated according to the procedure of Newman and Evans.[5] About 25 g of 20-mesh zinc was covered with 5% hydrochloric acid (30 mL) and stirred vigorously for 3 min. The zinc was washed by decantation with distilled water (3 × 30 mL), with acetone (2 × 20 mL), with diethyl ether (2 × 20 mL), and finally dried and stored in a vacuum desiccator.
6. Methyl bromoacetate was distilled and stored under nitrogen. Ethyl bromoacetate can also be used: in this case a mixture of ethyl and methyl esters is obtained.
7. Induction times from 15 to 45 min have been observed. In one instance, the reaction did not start even after 1.5 hr, and required the mixture to be heated to 60°C for several minutes until a white precipitate began to form. The checkers observed induction periods of 25–35 min.
8. On some occasions, the exotherm induced a vigorous reflux that was difficult to control. In such cases, stirring had to be stopped occasionally to control the reflux rate. Although the use of 20-mesh zinc granules reduces the possibility of hard-to-control exotherms, a cold water bath was kept ready to provide cooling if needed. The checkers did not observe an uncontrollable exotherm, but this type of reaction is well-known to be susceptible to such a problem. The checkers recommend that the mesh size not be reduced further without first testing the procedure on smaller scale. The checkers successfully performed this reaction at twice the reported scale without event and obtained the same yield (93%).
9. Progress of the reactions and analysis of the products was monitored by GLC using a Hewlett Packard 5890 Series II gas chromatograph equipped with an HP 3396 Series II Integrator and a Quadrex 007 Series bonded-phase fused silica capillary column (methyl 5% phenyl silicone; length 25 m; internal diameter 0.25 mm; film thickness 0.25 •m; carrier gas: nitrogen 75 kPa). Injector: 200°C; detector (FID): 250°C; Temperature program: 75°C (2 min); 15°/min, 250°C (3 min). Retention times (min): methyl bromoacetate, 2.24 (2.54); 5-methyl-5-hexen-2-one, 2.68 (2.94); 1,4-dimethylbicyclo[3.2.0]hept-3-en-6-one, 4.42 (4.77); 1-methyl-4-methylidenebicyclo[3.2.0]heptan-6-one, 4.73 (5.08); methyl 3,6-dimethyl-3-hydroxy-6-heptenoate, 7.05 (7.44). The checkers employed a similar column 30 m in length with the same stationary phase and observed the retention times shown above in parentheses.
10. The crude ester so obtained is greater than 97% pure by GLC analysis and is used in the next step without further purification. The checkers determined that the remainder of the material (3%) is unreacted methyl bromoacetate. Spectral data for the crude ester are as follows: IR (neat) cm^{-1}: 3516, 2951, 1735, 1649, 1439, 1216; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.22 (s, 3 H), 1.70 (m, 2 H), 1.75 (s, 3 H), 2.11 (m, 2 H), 2.48 (d, 1 H, J = 17.2), 2.54 (d, 1 H, J = 17.2), 3.52 (s, 1 H, disappears after D_2O exchange), 3.73 (s, 3 H), 4.70 (s, 2 H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ: 23.07 (CH_3), 27.04 (CH_3), 32.43 (CH_2), 40.33 (CH_2), 45.16 (CH_2), 52.12 (CH_3), 71.26 (C), 110.2 (CH_2), 146.2 (C), 173.8 (C).
11. The submitters employed a 1 N solution of KOH in methanol and observed the saponification to be complete in 24 hr. The checkers observed that the saponification

required 48 hr for completion under these conditions. The checkers employed a 2 N solution of KOH in methanol and observed that saponification was complete in 5 hr.

12. The submitters reported 87–92% yields of the acid. In the hands of the checkers, the yield of this reaction appears to be scale dependent. At one half the reported scale, the yield was reduced by 10–12%. This variation appears to result from losses during the isolation procedure. The acid has a very disagreeable butyric acid-like odor. The checkers recommend that all manipulations of this material be performed in a good hood, and that all apparatus employed be kept in the hood until base washed.

13. Spectral data for the crude acid are as follows: IR (neat) cm^{-1}: 3380, 2971, 1707, 1646, 1222, 888; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.30 (s, 3 H), 1.67 (m, 2 H), 1.72 (s, 3 H), 2.10 (m, 2 H), 2.55 (d, 1 H, J = 17.1), 2.60 (d, 1 H, J = 17.1), 4.70 (s, 2 H), 6.61 [s (broad), 2 H]; ^{13}C NMR (50.3 MHz, $CDCl_3$) δ: 23.11 (CH_3), 26.33 (CH_3), 32.40 (CH_2), 40.18 (CH_2), 45.13 (CH_2), 71.84 (C), 110.5 (CH_2), 146.0 (C), 177.9 (C).

14. Acetic anhydride was distilled from anhydrous sodium acetate and stored under nitrogen.

15. To control foaming, the submitters recommend the use of a distillation flask larger than usual. In this instance, they used a 250-mL flask fitted with a Claisen adapter.

16. The product is about 99% pure by GLC analysis (Note 9), containing about 1% of an unknown impurity having a retention time of 8.01 min. The ratio of the olefin isomers, 1,4-dimethylbicyclo[3.2.0]hept-3-en-6-one and 1-methyl-4-methylenebicyclo-[3.2.0]heptan-6-one, was determined to be 97:3. Spectral data for the major isomer are as follows: IR (neat) cm^{-1}: 1770; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.35 (s, 3 H), 1.73 (s, 3 H), 2.55 (m, 2 H), 2.87 (dd, 1 H, J = 17.8, 4.7), 3.03 (dd, 1 H, J = 17.8, 2.9), 3.58 (m, 1 H), 5.45 (m, 1 H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ: 15.34 (CH_3), 24.03 (CH_3), 35.35 (C), 47.08 (CH_2), 58.81 (CH_2), 79.94 (CH), 126.8 (CH), 135.2 (C), 207.9 (C).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

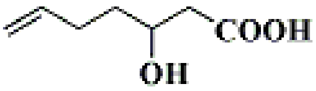
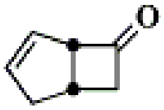
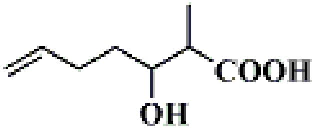
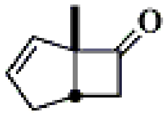
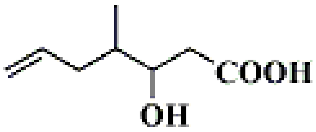
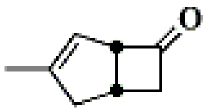
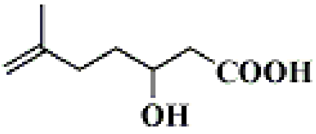
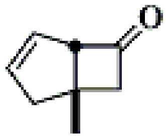
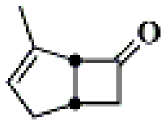
3. Discussion

Bicyclo[3.2.0]hept-3-en-6-ones are fused ring compounds that offer different functionalities in each ring, and have different ring size. They are suitable for chemo-, regio- and stereo-controlled manipulations and are useful for the assembly of more complex structures in a predictable fashion. The preparation reported here illustrates the simplicity of the procedure and the selectivity by which the thermodynamically more stable isomer can be prepared in high purity and good yield. Both yield and stereoselectivity are superior to those observed in the syntheses of 1,4-dimethylbicyclo[3.2.0]hept-3-en-6-one previously reported in the literature.[6,7] This process involves the generation of an α,β-unsaturated ketene intermediate that undergoes intramolecular [2+2] cyclization to give a

bicyclo[3.2.0]hept-3-en-6-one. An equilibrium among the possible isomers of the α,β-unsaturated ketene intermediate could account for the good yield as well as the high selectivity in generating the thermodynamically more stable endo-ene isomer.[8]

This foregoing procedure is rather general as demonstrated by the preparation of a number of bicyclo[3.2.0]hept-3-en-6-ones by the bicyclization of a variety of secondary and tertiary 3-hydroxy-6-alkenoic acids (Table). The use of bicyclo[3.2.0]hept-3-en-6-ones as starting materials has been reported in the synthesis of racemic grandisol,[9] lineatin,[1,2,4] filifolone,[10] and several intermediates[5,11] in Curran's synthesis of linear condensed sesquiterpenes such as hirsutene,[12,13] δ2-capnellene,[14] hypnophilin[15] and coriolin.[15] The successful use of these intermediates in the previously mentioned applications, and their unusual reactivity,[16] suggest the broad usefulness of the bicyclo[3.2.0]hept-3-en-6-ones made readily available by the present procedure. Some bicyclo[3.2.0]hept-3-en-6-ones have been obtained enantiomerically pure[17] by the oxidation of the enantiomers of bicyclo[3.2.0]hept-3-en-6-endo-ols, resolved using (−)-(1S,4R)-camphanic acid chloride.[18]

TABLE I
PREPARATION OF BICYCLO[3.2.0]HEPT-3-EN-6-ONES

Starting Material	Product	Yield (%)
		62
		63
		63
		78
		79

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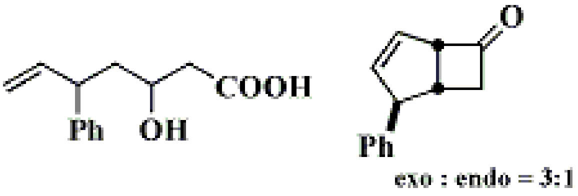

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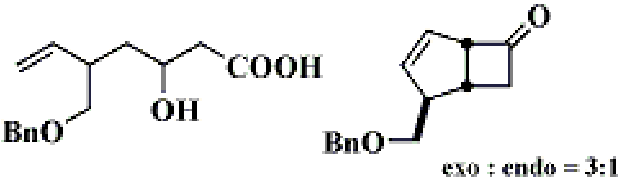
48



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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

sodium/benzophenone ketyl

coriolin

grandisol

lineatin

filifolone

hirsutene

δ^2-capnellene

hypnophilin

(−)-(1S,4R)-camphanic acid chloride

hydrochloric acid (7647-01-0)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

acetic anhydride (108-24-7)

ammonium chloride (12125-02-9)

sodium acetate (127-09-3)

glycerol (56-81-5)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

acetone (67-64-1)

potassium hydroxide, KOH (1310-58-3)

zinc (7440-66-6)

ammonium hydroxide (1336-21-6)

magnesium sulfate (7487-88-9)

potassium acetate (127-08-2)

Ethyl bromoacetate (105-36-2)

Tetrahydrofuran (109-99-9)

calcium hydride (7789-78-8)

5-Methyl-5-hexen-2-one (3240-09-3)

trimethyl borate (121-43-7)

methyl bromoacetate (96-32-2)

1,4-Dimethylbicyclo[3.2.0]hept-3-en-6-one (133700-21-7)

3,6-Dimethyl-3-hydroxy-6-heptenoic acid

1-methyl-4-methylidenebicyclo[3.2.0]heptan-6-one, 1-methyl-4-methylenebicyclo-[3.2.0]heptan-6-one

Methyl 3,6-dimethyl-3-hydroxy-6-heptenoate

Bicyclo[3.2.0]hept-3-en-6-one, 1,4-dimethyl-, cis-(±)-

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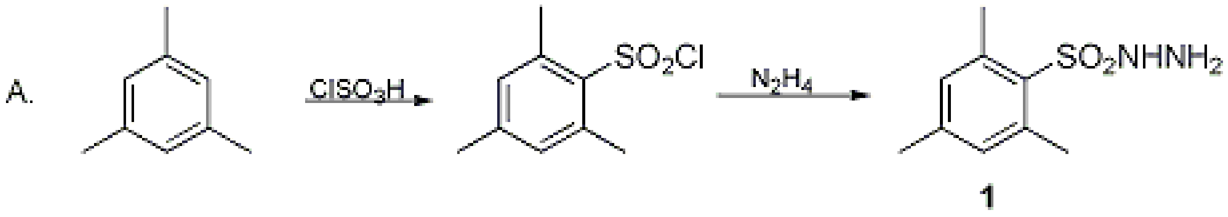
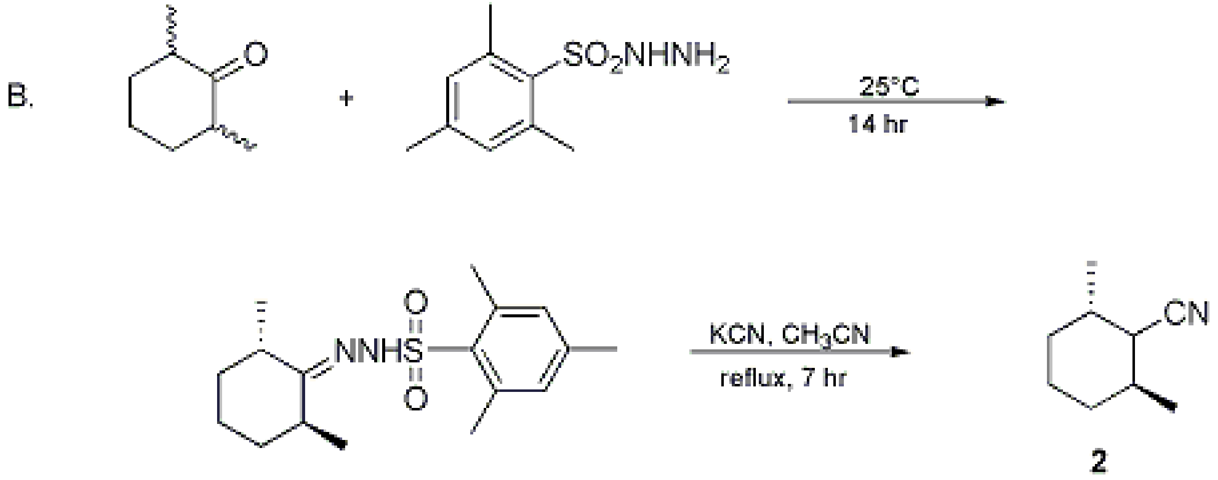
Organic Syntheses, CV 9, 281

MESITYLENESULFONYLHYDRAZINE, AND (1α,2α,6β)-2,6-DIMETHYLCYCLOHEXANECARBONITRILE AND (1α,2β,6α)-2,6-DIMETHYLCYCLOHEXANECARBONITRILE AS A RACEMIC MIXTURE

[Benzenesulfonic acid, 2,4,6-trimethyl-, hydrazide]





Submitted by Jack R. Reid, Richard F. Dufresne, and John J. Chapman[1].
Checked by Michael P. Dwyer and Stephen F. Martin.

1. Procedure

Caution! Mesitylene is an irritant, potassium cyanide is highly toxic, chlorosulfonic acid is corrosive, hydrazine monohydrate is a toxic, cancer-suspect agent, and dichloromethane is an irritant and should be handled in a well-ventilated hood.

A. *Mesitylenesulfonylhydrazine* (**1**). A 500-mL, three-necked, round-bottomed flask is assembled as shown in f.htmigure 1 (Note 1). The equipment consists of a 250-mL

constant pressure addition funnel, a thermometer, and an air-cooled Friedrichs condenser attached to a gas inlet-outlet adapter. A 250-mL vacuum flask is equipped with a gas delivery tube that is inserted through a single-holed rubber stopper and positioned 1 cm above the bottom of an aqueous 20% sodium hydroxide solution. This assembly is used as a gaseous hydrogen chloride (HCl) trap (Note 2). The flask is charged with mesitylene (Note 3) (76.0 g, 0.630 mol) and its contents cooled to between −10°C and 0°C in a wet ice–acetone bath while stirring (Note 4). When the contents of the flask and HCl trap are between −10°C and 0°C, a 6-mL portion of the total quantity of the chlorosulfonic acid (Note 3) (161.0 g, 92.1 mL, 1.39 mol) is added to initiate the reaction. After HCl gas evolution begins, the remaining chlorosulfonic acid is added at a rate such that the reaction temperature remains below 60°C (Note 5). After the chlorosulfonic acid is added, the reaction mixture is heated to 60°C to disperse and dissolve any precipitated salts (Note 6) and then allowed to cool to room temperature. The reaction mixture is poured into 250 mL of ice water with stirring, and the crude crystals are recovered by suction filtration. The crystals are washed with generous portions of ice-cold water. The crude product is taken up in 125 mL of dichloromethane and a 50-mL upper aqueous layer is removed. The aqueous layer is extracted with one 50-mL portion of methylene chloride. The combined organic fractions are dried over sodium sulfate (Note 7) with vigorous stirring, filtered and then concentrated on a rotary evaporator. Crude mesitylenesulfonyl chloride (109.7 g, 80%) is recovered as an oil that solidifies into off-white crystals, mp 54–56°C (Note 8). If used immediately, no additional purification is necessary (Note 9).

Figure 1

Figure 1

Using the equipment in f.htmigure 1, but without the HCl gas trap attached, mesitylenesulfonyl chloride (109.7 g, 0.503 mmol, (Note 7)) is dissolved in 175 mL of dry tetrahydrofuran (THF) and cooled to between −10°C and 0°C in a wet ice–acetone bath. Hydrazine monohydrate (63.0 g, 61.0 mL, 1.26 mol) (Note 3) is dissolved in 30 mL of ice-cold water and added so that the temperature remains below 25°C (Note 10). After the addition is completed, the mixture is stirred for an additional 45 min at room temperature and poured into 250 mL of ice water with stirring. Crude mesitylenesulfonylhydrazine is recovered by suction filtration and then dissolved in 500 mL of dichloromethane. A 150- to 175-mL portion of water separates. The water layer is removed, and the organic layer is washed with one 50-mL portion of ice-cold water, dried over sodium sulfate, filtered, and the solvent is removed on a rotary evaporator. The crystals are triturated in 250 mL of cold hexane, and the fluffy white product (95.4 g, 89%, (Note 11)) is recovered by suction filtration ((Note 12) and (Note 13)).

B. *(1α,2α,6β)-2,6-Dimethylcyclohexanecarbonitrile* and *(1α,2β,6α)-2,6-Dimethylcyclohexanecarbonitrile* (**2**). The apparatus depicted in f.htmigure 1 lacking

the HCl trap and with a glass stopper in place of the thermometer is used for this procedure. The 1-L reaction flask is charged with mesitylenesulfonylhydrazine (56.0 g, 0.262 mol) (Note 1) and 175 mL of acetonitrile. The mixture is stirred at room temperature until solution is attained (Note 14). 2,6-Dimethylcyclohexanone (Note 3) (32.2 g, 0.255 mol) is added in one portion and the reactants are stirred an additional 10 min. A 10-drop portion of concentrated sulfuric acid is added and the mixture is stirred at room temperature for 12 to 18 hr to facilitate complete hydrazone formation (Note 15). Water is circulated through the reflux condenser that is already attached to the flask, and potassium cyanide (27.2 g, 0.418 mol) is added (Note 3). The reaction mixture is gradually heated to reflux over 2 hr and then gently refluxed for 10 to 12 hr (Note 16). The contents of the flask are cooled to room temperature and water (125 mL), 20% aqueous sodium hydroxide solution (25 mL), hexane (175 mL), and ether (75 mL) are added in succession with vigorous mixing. The mixture is stirred for 15 min, and the lower aqueous layer is separated (Note 17). The aqueous layer is extracted with a 7:3 hexane-ether mixture (2 × 75 mL). The combined organic layers are washed with two 25-mL portions of aqueous 10% sodium hydroxide solution and dried over sodium sulfate. The organic layer is filtered and concentrated on a rotary evaporator, and the crude yellow residual oil is distilled at 100–102°C at 39 mm to give 25.5 g (73%) of colorless **2** ((Note 18) and (Note 19)).

2. Notes

1. The submitters ran the reaction on a scale four times that described. The submitters also note that the reaction may be successfully carried out in a 2-L Erlenmeyer flask equipped with a thermometer to monitor the internal reaction temperature and a large magnetic stirring assembly. The gas delivery tube and rubber stopper, used in f.htmigure 1, is placed in the mouth of the flask, and the HCl gas is forced into a base trap or disposed of through an aspirator.
2. The HCl trap is charged with 150 mL of aqueous 20% sodium hydroxide solution and cooled in an ice-water or wet ice-acetone bath.
3. Mesitylene (1,3,5-trimethylbenzene), chlorosulfonic acid, hydrazine monohydrate, 2,6-dimethylcyclohexanone and potassium cyanide were purchased from Aldrich Chemical Company, Inc., and used without further purification.
4. A 250-g quantity of wet ice and 250 mL of acetone give a bath temperature between −15°C to −20°C. The bath generally does not need to be recharged.
5. After half of the chlorosulfonic acid has been added, the exothermic reaction and gas evolution decrease considerably. If the temperature is allowed to rise above 60°C, the yield decreases and the final product is slightly discolored.
6. Briefly warming the reaction mixture solubilizes all the mesitylenesulfonic acid and drives the reaction to completion. Mesitylenesulfonic acid is less soluble than mesitylenesulfonyl chloride. Therefore, after everything dissolves, conversion of the acid to the acid chloride is complete. The product is partially hydrolyzed if it is poured into water while it is still hot.
7. Methylene chloride partitions water from the crude product in this step and

greatly reduces the drying time. However, the mixture is stirred rapidly to bring the water that naturally partitions to the top of the methylene chloride layer in contact with the drying agent that is on the bottom of the flask.

8. The spectral properties of the product are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.35 (s, 3 H), 2.73 (s, 6 H), 7.03 (s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.2, 22.9, 132.3, 139.5, 140.2, 145.3; mp 54–56°C.

9. If mesitylenesulfonyl chloride is prepared without delay, the damp crystals may be used in the next step without further drying. If the product is to be stored for long periods of time, it is necessary to remove the last traces of water. This is also a convenient place to stop if the reaction will not be completed in a single day.

10. Temperature control and efficient stirring are more important here than in the preparation of mesitylenesulfonyl chloride. Better yields are obtained when the temperature is kept below 25°C. Gas evolution accompanied by some decomposition occurs at elevated temperatures.

11. The spectral and physical properties are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.31 (s, 3 H), 2.65 (s, 6 H), 3.61 (br s, 2 H), 5.75 (br s, 1 H), 6.99 (s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.0, 22.9, 130.0, 132.1, 140.7, 143.3; mp 114–116°C (lit.[5] mp 115–116°C).

12. Additional product separates from the filtrate upon standing. Excessive work-up water results in product loss. The crude product can hold considerable volatile material. The weight of the product is usually greater than theoretical prior to thorough air or vacuum drying. Mesitylenesulfonylhydrazine must be completely dry before it is used in a reaction.

13. Mesitylenesulfonylhydrazine should be stored in a brown bottle in an area protected from light. Refrigeration of the product, though not required, tends to increase the shelf life.

14. The checkers noted that gentle warming of the solution with a heat gun greatly facilitated the dissolution of mesitylenesulfonylhydrazine.

15. A catalytic amount of sulfuric acid greatly facilitates formation of the hydrazone which precipitates from solution as it is formed. The checkers found that the reaction mixture must be stirred at room temperature for 14–18 hr to ensure complete formation of the hydrazone. It is advisable to monitor the reaction by TLC. The submitters noted that formation of the hydrazone can be reduced to several hours when the reaction mixture is heated at 40°C.

16. Unsolvated potassium cyanide and hydrazone dissolve as the reactants are converted to the thermodynamically favored trans-nitrile. Shortly after all of the solid dissolves, a second solid precipitates from solution. This solid is presumed to be potassium mesitylenesulfinate and is usually accompanied by some foaming. An oversize flask used with efficient stirring keeps the reaction mixture from foaming into the condenser.

17. Commercial Clorox, with an activity of 5.25%, is used to destroy excess potassium cyanide prior to disposing of the aqueous mixture.

18. A rotary evaporator water bath setting is kept at room temperature during the concentration of the product.

19. The spectral properties of the product are as follows: IR ($CHCl_3$) cm^{-1}: 2933, 2236, 1459, 1384, 1230; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.99 (d, 3 H, J = 7.1), 1.02 (d, 3 H, J = 7.1), 1.37–1.48 (m, 4 H), 1.67–1.72 (m, 1 H), 1.86–1.93 (m, 1 H), 2.00–2.03 (m, 1 H), 2.29–2.33 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 16.5, 19.2, 19.3, 28.9, 30.0, 30.5, 31.2, 40.4, 121.0.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995. See (Note 17).

3. Discussion

This is a simplified procedure that uses much less chlorosulfonic acid than previous methods,[2,3] while obtaining a better yield of mesitylenesulfonylhydrazine[4,5,6] via mesitylenesulfonyl chloride. Mesitylenesulfonylhydrazine is used for preparing medium-size cycloalkanones by the Eschenmoser fragmentation reaction,[7] diazo compounds,[8] regiospecific alkylations,[9] and hydrogenations.[5] The hydrolysis of mesitylenesulfonyl chloride and the decomposition of mesitylenesulfonylhydrazine is rather slow at low temperatures and short contact times; therefore, the preparations are conveniently worked-up in ice water. However, if damp crystals of mesitylenesulfonylhydrazine are stored at room temperature for extended periods, an odor of SO_2 becomes evident. Therefore, an alternative procedure for working up very dry mesitylenesulfonyl chloride and mesitylenesulfonylhydrazine was developed. This is especially useful if the reaction will not be completed in one session or if the material will be stored for an extended period. The hydrazine prepared in the first step is used to prepare the racemic product (1α,2α,6β)- and (1α,2β,6α)-2,6-dimethylcyclohexanecarbonitrile via the corresponding hydrazone in good to excellent yield. This procedure represents a simple, stereoselective, large-scale, one-pot conversion of a moderately hindered ketone to the next higher nitrile analog. The crude product contains small amounts of olefin and starting ketone that can be removed by distillation. Ketones with α,α'-alkyl substituents may be used as diastereomeric mixtures, since they equilibrate to one pair of enantiomers during hydrazone formation, and this stereoselectivity is preserved during the cyanide anion reaction. A minimum of the toxic reagent potassium cyanide is used and evolution of hydrogen cyanide is avoided. The use of oxidizing agents such as bromine and strong bases such as sodium methoxide in methanol are avoided, making this method more tolerant of other substituents on the ketone such as olefins.[10,11,12,13,14] The reagent 2,4,6-triisopropylbenzenesulfonylhydrazine is less effective for converting moderately hindered ketones to nitriles, more difficult to prepare, and more expensive to purchase. The nitrile products are useful intermediates in the synthesis of acids by saponification, aldehydes by reduction with diisobutylaluminum hydride (DIBAL), and ketones by reaction with Grignard reagents.[15,16,17] The scope of this procedure is indicated by the modestly hindered nitriles shown in Table.

TABLE I
KETONES TO NITRILES VIA MESITYLENESULFONYLHYDRAZINE

Entry	Ketone	Nitrile	Yield,[a] %	Solvent[c]	BP (°C/mm)
1	4-tert-Butylcyclohexanone	4-tert-Butylcyclohexanecarbonitrile	73.0–76.7	B	140–142/30
2	4,4-Dimethylcyclohexanone	4,4-Dimethylcyclohexanecarbonitrile	73.8	B	95–97/30
3	4-Isopropylcyclohexanone	4-Isopropylcyclohexanecarbonitrile	73.0–83.0	B	130–131/35
4	Pinacolone	2,3,3-Trimethylbutanenitrile	60.3	A	54–57/33
5	3,4,4-Trimethylcyclohexanone	3,4,4-Trimethylcyclohexanecarbonitrile	80.5	B	127–130/30
6	3,3,5-Trimethylcyclohexanone	3,3,5-Trimethylcyclohexanecarbonitrile	72.6	A	110–118/26
7	3-tert-Butylcyclopentanone	3-tert-Butylcyclopentanecarbonitrile	78.7	A	117–121/28
8	2,6-Dimethylcyclohexanone	2,6-Dimethylcyclohexanecarbonitrile	73.5[b]	A	97–99/35

[a]Satisfactory analytical data, ± 0.3% C, H, were obtained for all of the products.

[b]The product is 90+% the racemic, and between 1% and 5% the meso nitriles.

[c]Solvent or solvent system used in the reaction: A = acetonitrile; B = 7:1 acetonitrile: 2-methoxyethanol.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

(1α,2α,6β)- and (1α,2β,6α)-2,6-Dimethylcyclohexanecarbonitrile

Mesitylene (1,3,5-trimethylbenzene)

sulfuric acid (7664-93-9)

HCl (7647-01-0)

methanol (67-56-1)

ether (60-29-7)

acetonitrile (75-05-8)

sodium hydroxide (1310-73-2)

chlorosulfonic acid (7790-94-5)

hydrogen cyanide (74-90-8)

bromine (7726-95-6)

sodium sulfate (7757-82-6)

potassium cyanide (151-50-8)

acetone (67-64-1)

sodium methoxide (124-41-4)

Pinacolone (75-97-8)

Mesitylene (108-67-8)

hydrazine monohydrate (7803-57-8)

hydrazine (302-01-2)

mesitylenesulfonic acid

methylene chloride, dichloromethane (75-09-2)

chloride

Tetrahydrofuran (109-99-9)

hexane (110-54-3)

diisobutylaluminum hydride (1191-15-7)

3,3,5-trimethylcyclohexanone (873-94-9)

4-tert-Butylcyclohexanone (98-53-3)

2,4,6-triisopropylbenzenesulfonylhydrazine (39085-59-1)

Mesitylenesulfonylhydrazine

Benzenesulfonic acid, 2,4,6-trimethyl-, hydrazide (16182-15-3)

Mesitylenesulfonyl chloride (773-64-8)

2,6-Dimethylcyclohexanecarbonitrile

2,6-Dimethylcyclohexanone (2816-57-1)

potassium mesitylenesulfinate

(1α,2α,6β)-2,6-DIMETHYLCYCLOHEXANECARBONITRILE

(1α,2β,6α)-2,6-DIMETHYLCYCLOHEXANECARBONITRILE

4-tert-Butylcyclohexanecarbonitrile

4,4-Dimethylcyclohexanone (4255-62-3)

4,4-Dimethylcyclohexanecarbonitrile

4-Isopropylcyclohexanone (5432-85-9)

4-Isopropylcyclohexanecarbonitrile

2,3,3-Trimethylbutanenitrile

3,4,4-Trimethylcyclohexanone

3,4,4-Trimethylcyclohexanecarbonitrile

3,3,5-Trimethylcyclohexanecarbonitrile

3-tert-Butylcyclopentanone

3-tert-Butylcyclopentanecarbonitrile

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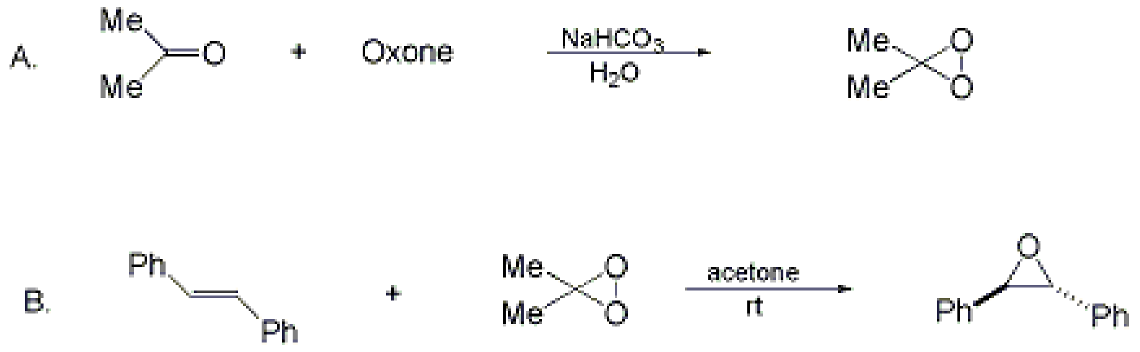
SYNTHESIS OF EPOXIDES USING DIMETHYLDIOXIRANE: trans-STILBENE OXIDE

[Dioxirane, dimethyl- and Oxirane, 2,3-diphenyl-, trans]



Submitted by Robert W. Murray and Megh Singh[1].
Checked by Thomas G. Marron, Lance A. Pfeifer, and William R. Roush.

1. Procedure

CAUTION! Dimethyldioxirane is a volatile peroxide and should be treated as such. The preparation and all reactions of the dioxirane should be carried out in a hood.

A. *Dimethyldioxirane* (See f.htmigure 1). A 2-L, three-necked, round-bottomed flask containing a mixture of water (80 mL), acetone (50 mL, 0.68 mol), and sodium bicarbonate (96 g), is equipped with a magnetic stirring bar and a pressure equalizing addition funnel containing water (60 mL) and acetone (60 mL, 0.82 mol) (Note 1). A solid addition flask containing Oxone (180 g, 0.29 mol) is attached to the reaction vessel via a rubber tube (Note 2). An air condenser (20 cm length) loosely packed with glass wool is attached to the reaction vessel. The outlet of the air condenser is connected to a 75 × 350-mm Dewar condenser filled with dry ice-acetone that is connected to a receiving flask (100 mL) cooled in a dry ice-acetone bath. The receiving flask is also connected in series to a second dry ice-acetone cold trap, a trap containing a potassium iodide solution, and a drying tube. A gas inlet tube is connected to the reaction flask and a stream of nitrogen gas is bubbled through the reaction mixture (Note 3). The Oxone is added in portions (10–15 g) while the acetone-water mixture is simultaneously added dropwise (Note 4). The reaction mixture is stirred vigorously throughout the addition of reagents (ca. 30 min). A yellow solution of dimethyldioxirane in acetone collects in the receiving flask. Vigorous stirring is continued for an additional 15 min while a slight vacuum (ca. 30 mm, water aspirator) is applied to the cold trap (Note 5). The yellow dioxirane solution (62–76 mL, (Note 6)) is dried over sodium sulfate (Na_2SO_4), filtered and stored in the freezer (–25°C) over Na_2SO_4. The dioxirane content of the solution is assayed using phenyl methyl sulfide and the GLC method ((Note 7) and (Note 8)). Generally concentrations in the range of 0.07–0.09 M are obtained.

Figure 1

Figure 1

B. *trans-Stilbene oxide*. To a magnetically stirred solution of trans-stilbene (0.724 g, 4.02 mmol) (Note 9) in 5 mL of acetone is added a solution of 0.062 M dimethyldioxirane in acetone (66 mL, 4.09 mmol) at room temperature. The progress of the reaction is followed by GLC (Note 10), which analysis indicates that trans-stilbene is converted to the oxide in 6 hr (Note 11). Removal of solvent on a rotary evaporator gives a white crystalline solid. The solid is dissolved in dichloromethane (CH_2Cl_2) (30 mL) and dried with anhydrous Na_2SO_4. The drying agent is filtered off and washed with CH_2Cl_2. The solvent is removed on a rotary evaporator. Remaining solvent is removed under reduced pressure to give an analytically pure sample of the oxide (0.788 g, 100% yield). Recrystallization from aqueous ethanol gives white plates/prisms, mp 69–70°C ((Note 12), (Note 13)).

2. Notes

1. A mechanical stirrer may also be used.
2. The submitters used Oxone supplied by DuPont, whereas the checkers used Oxone purchased from Aldrich Chemical Company, Inc.
3. The submitters recommended that a stream of helium be passed through the reaction system during the course of the experiment. The checkers substituted nitrogen for helium with no decrease in yield . In addition, on several occasions the checkers did not use a gas purge and there was no decrease in yield. Therefore, use of a gas purge is viewed as optional, not mandatory. It is noted that other investigators have reported dimethyldioxirane preparations that do not require use of a gas purge.[2]
4. The procedure followed was generally that contained in the original publication.[3] See an alternative procedure, by Adam.[2]
5. The submitters recommended that the distillation be performed at ca. 30 mm. By using this procedure the checkers obtained an average of 67 mL (range: 62–76 mL) of dioxirane solution with an average concentration of 0.077 M (range: 0.068–0.087 M) over 10 repetitions of the procedure. When the distillation was performed at 80 mm for up to 90 min, greater volumes of dimethyldioxirane solution were obtained (84–89 mL), but with a corresponding decrease in the reagent concentration (0.053–0.066 M).
6. The submitters reported that 80–90 mL of dimethyldioxirane solution is obtained.
7. Determination of dimethyldioxirane concentration by the GLC method is as follows: A standard solution of thioanisole (phenyl methyl sulfide) is prepared. The solution is usually 0.2 M in acetone, but other concentrations may be used. It is important to keep the sulfide in excess so that oxidation by the dioxirane will produce largely or exclusively the sulfoxide and not the sulfone.
A standard solution of an internal standard (dodecane or hexadecane) is also prepared in acetone. This solution should be at the same concentration as that of the sulfide.

To determine the dioxirane concentration 1 mL each of the dioxirane, sulfide, and internal standard solutions are combined in a vial. The GLC analysis is then carried out using the following: Column: DB 210; temp 1 = 60°C, time 1 = 5 min, rate 1 = 20°/min; temp 2 = 200°C, time 2 = 5 min. The analysis is conducted on 1 •L of solution. The analysis is made quantitative by determining the response factors of the sulfide and internal standard in the usual manner. The dimethyldioxirane concentration is determined by measuring the sulfide concentration before and after adding the dioxirane. Under these conditions the following retention times are observed: dodecane, 7.15 min; sulfide, 8.2 min; sulfoxide, 12.9 min.

8. Generally concentrations in the range of 0.07–0.09 M are obtained. The submitters reported a concentration range of 0.05–0.10 M.

9. trans-Stilbene was purchased from Eastman Organic Chemical Co. The purity of the sample was 99%. Sample purity was also checked by GLC and GC-MS. The GC-MS analysis suggests that the sample contains bibenzyl (<1%) as an impurity.

10. Gas chromatographic conditions are as follows: Column DB-210 (30 m × 0.318 mm × 0.5 •m, fused silica capillary column), column temp 1 = 100°C, time 1 = 5 min, rate = 20°/min; temp 2 = 200°C, time 2 = 7 min, injector temp 250°C, detector temp 250°C, inlet P, 24 psi, retention times: trans-stilbene 11.4 min, trans-stilbene oxide 11.9 min.

11. In 2 hr, 96% conversion had occurred.

12. The checkers obtained 790 mg (100%) of crude trans-stilbene oxide that was recrystallized from aqueous ethanol to give 744 mg (95%; two crops) of analytically pure trans-stilbene oxide.

13. trans-Stilbene oxide has the following properties: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.86 (s, 2 H, 2 × -CH-), 7.26–7.45 (m, 10 H, 2 × C_6H_5-); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 62.81 (-CH-); 125.4 (C-4, Ar), 128.19 (C-3,5, Ar), 128.44 (C-2,6, Ar), 136.99 (C-1, ipso C of phenyl); IR ($CHCl_3$) cm^{-1}: 3076, 3036, 2989, 1603, 1497, 1457, 870, 698; high resolution mass spectrum, Calcd. for $C_{14}H_{12}O$, 196.0888. Found 196.0896. Anal. Calcd. for $C_{14}H_{12}O$: C, 85.68; H, 6.16. Found: C, 85.76; H, 6.05.

Waste Disposal Information

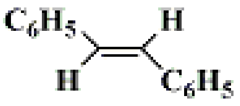
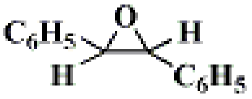
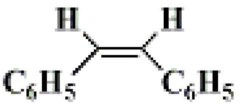
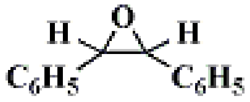
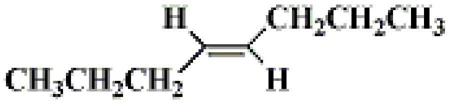
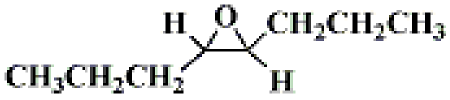
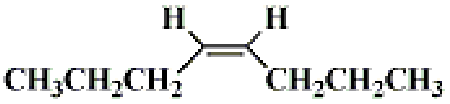
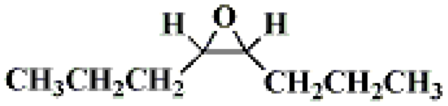
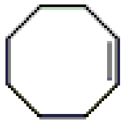
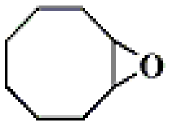
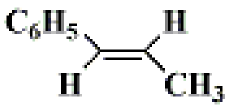
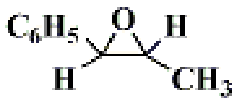
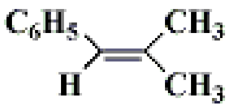
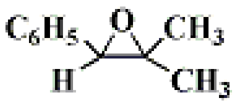
All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

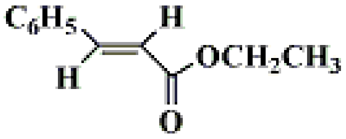
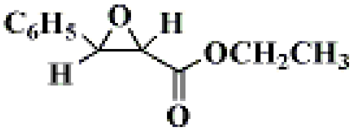
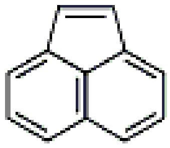
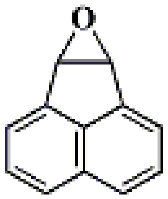
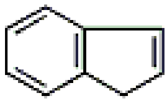
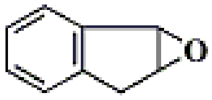
3. Discussion

For most epoxidations dimethyldioxirane (DMD) is the reagent of choice. The reaction is usually carried out at room temperature or below and in neutral solution. The reaction is stereospecific, proceeds rapidly, and generally in essentially quantitative yield. The procedure is remarkably convenient. In many cases removal of the solvent gives the pure product. The reaction is applicable to a variety of unsaturated systems (Table). The data given in the Table also compare yields with the commonly used epoxidation reagent m-chloroperbenzoic acid (MCPBA). In almost every case use of DMD gave a higher yield than did MCPBA. In many cases the difference is dramatic (see entries 1 and 2, for example). The use of MCPBA frequently leads to opening of sensitive epoxides under the

acidic conditions of the reaction. This problem is conveniently avoided when using DMD. In a growing number of cases DMD has successfully given an epoxide when other methods fail. A particularly pleasing example[4] of this is the preparation of the 8,9-epoxide of the mycotoxin, aflatoxin B_1.

TABLE I
EPOXIDATION OF OLEFINS WITH DIMETHYLDIOXIRANE

Entry	Olefin	Equiv.	Time hr	Product	Yield (a, ref)
1		1	6		100 (55,[5] 90[6])
2		1	8		99 (52,[5] 55[6])
3		1	3		74 (70[6])
4		1	1		81 (60[6])
5		1	20 min		97
6		1	1		98 (90,[7] b)
7		1	1		99 (95[8])

8		2	24		100 (47[9])
9		1	1		97 (100, [7]b)
10		1	1		96 (91[7])

(a) % Yield by MCPBA oxidation; (b) NMR yield.

Linear free energy relationship studies[10,11] have demonstrated that DMD is an electrophilic reagent. This property is demonstrated in the Table where substrates with electron-withdrawing substituents require longer reaction times (compare entries 1 and 2 with 4, for example). This is particularly noticeable in entry 8 where the substrate contains a strong electron-withdrawing substituent. The previously reported[10] faster rates for DMD epoxidation of cis-alkenes compared to their trans stereoisomers is seen in the longer reaction times required for the trans isomers (compare entries 1 and 2, and 3 and 4). This difference in rates is taken as support for a spiro transition state[10] for epoxidation. A number of reviews[12,13,14,15,16] of the chemistry of DMD, including its use as an epoxidizing reagent, have been published.

Acknowledgment We gratefully acknowledge support of this work by the National Institute of Environmental Health Sciences through Grant No. ES01984.

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

oxone (37222-66-5)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

acetone (67-64-1)

peroxide (7722-84-1)

dichloromethane (75-09-2)

Hexadecane (544-76-3)

bibenzyl (103-29-7)

helium (7440-59-7)

thioanisole, phenyl methyl sulfide (100-68-5)

Dimethyldioxirane, Dioxirane, dimethyl- (74087-85-7)

trans-Stilbene oxide, Oxirane, 2,3-diphenyl-, trans (1439-07-2)

trans-Stilbene (103-30-0)

Dodecane (112-40-3)

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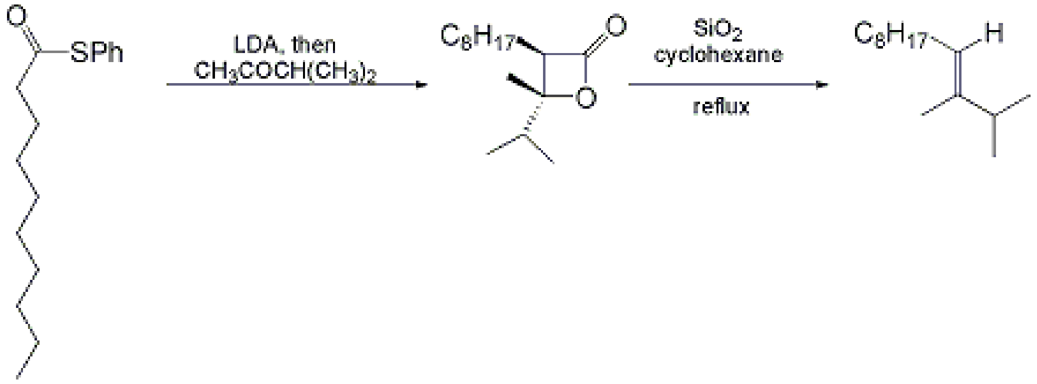
Organic Syntheses, CV 9, 293

SYNTHESIS OF β-LACTONES AND ALKENES VIA THIOL ESTERS: (E)-2,3-DIMETHYL-3-DODECENE



Submitted by Rick L. Danheiser, James S. Nowick, Janette H. Lee, Raymond F. Miller, and Alexandre H. Huboux[1].
Checked by David J. Mathre and Ichiro Shinkai.

1. Procedure

A 1-L, three-necked, round-bottomed flask is equipped with a mechanical stirrer, nitrogen inlet adapter, and a 150-mL, pressure-equalizing dropping funnel fitted with a rubber septum (Note 1). The flask is charged with 225 mL of dry tetrahydrofuran (THF) (Note 2) and 26.5 mL (0.189 mol) of diisopropylamine (Note 3), and then is cooled in an ice-water bath while 70.4 mL (0.178 mol) of a 2.53 M solution of butyllithium in hexane (Note 4) is added dropwise over 5–10 min. After 10 min, the resulting solution is cooled to −78°C (Note 5) in a dry ice-acetone bath and a solution of 45.0 g (0.17 mol) of S-phenyl decanoate (Note 6) in 75 mL of dry tetrahydrofuran is added dropwise over 1 hr (the dropping funnel is washed with two 5-mL portions of tetrahydrofuran). The yellow reaction mixture is allowed to stir for 30 min at −78°C, and then 18.2 mL (0.17 mol) of 3-methyl-2-butanone (Note 7) is added via a syringe pump or funnel over 7.5 min (Note 8). After 30 min, the reaction mixture is allowed to warm gradually to 0°C over 1.5 hr (Note 9) and then is quenched by the addition of 225 mL of a half-saturated aqueous ammonium chloride solution. The resulting mixture is poured into a 1-L separatory funnel containing 150 mL of hexane and 150 mL of water. The aqueous layer is separated and washed with 50 mL of hexane. The combined organic layers are washed successively with three 200-mL portions of aqueous 10% sodium carbonate and 200 mL of saturated sodium chloride (NaCl) solution, dried over anhydrous sodium sulfate, filtered, and concentrated at reduced pressure using a rotary evaporator to afford 41.5 g of the β-lactone as a yellow oil which is used in the next step without further purification (Note 10).

A 500-mL, one-necked, round-bottomed flask, equipped with a magnetic stirring bar and a condenser fitted with a nitrogen inlet adapter, is charged with the 41.5 g of crude β-lactone prepared above, 200 mL of cyclohexane (Note 11), and 41.5 g of 230-400 mesh silica gel (Note 12). The resulting yellow mixture is heated at reflux for 1 hr (water may be observed collecting in the condenser) and then allowed to cool to room temperature. Activated charcoal (6 g) is added (Note 13), and the resulting mixture is stirred for 5 min and filtered. The residue is washed with an additional 50 mL of cyclohexane and the combined filtrates are concentrated at reduced pressure using a rotary evaporator to afford 31.5 g of a yellow oil. This crude material is applied to the top of a 4.8-cm × 30-cm column of 210 g of 230-400 mesh silica gel 60 (Note 14) and eluted with hexane (20 mL per min, 120-mL fractions) (Note 15). Concentration of fractions 3–5 using a rotary evaporator and then high vacuum (0.1 mm) affords 22.0–23.0 g (66–69% overall yield) of (E)-2,3-dimethyl-3-dodecene as a clear, colorless oil ((Note 16),(Note 17),(Note 18)).

2. Notes

1. The apparatus is oven-dried at 110°C or flame-dried under reduced pressure and maintained under an atmosphere of nitrogen during the course of the reaction.

2. Tetrahydrofuran was distilled from sodium benzophenone ketyl immediately before use. The checkers used tetrahydrofuran (E. Merck) dried over 4 Å molecular sieves and purged with dry nitrogen (water content <10 •g/mL by Karl Fischer titration).

3. Diisopropylamine was purchased from Aldrich Chemical Company, Inc., and distilled from calcium hydride prior to use. The checkers used diisopropylamine (Aldrich Chemical Company, Inc.) dried over 3 Å molecular sieves and purged with dry nitrogen (water content <35 •g/mL by Karl Fisher titration).

4. n-Butyllithium was purchased from Aldrich Chemical Company, Inc., and titrated according to the the method of Watson and Eastham.[2]

5. The checkers monitored the internal temperature of the reaction with a Teflon-coated J-type thermocouple.

6. S-Phenyl decanethioate was prepared by the following procedure:[3 4] A 500-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, glass stopper, nitrogen inlet adapter, and a 50-mL pressure-equalizing addition funnel fitted with a rubber septum is charged with 250 mL of methylene chloride, 17.6 mL (0.171 mol) of thiophenol, and 13.9 mL (0.172 mol) of pyridine (Note 19). The reaction mixture is cooled in an ice-water bath and 35.4 mL (0.171 mol) of decanoyl chloride (Note 19) is added dropwise via the addition funnel over 20 min. The resulting suspension of white solid is stirred for an additional 10 min at 0°C, at room temperature for 1 hr, and then is poured into 210 mL of water. The organic phase is separated and washed, successively with 210 mL of 10% hydrochloric acid and 210 mL of saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered, and concentrated at reduced pressure using a rotary evaporator, then under high vacuum (0.1 mm), to provide 44.8 g of a clear, colorless oil. Distillation of this material through an 8-cm Vigreux column affords 41.7–44.0 g (93–98%) of S-phenyl decanoate as a clear, colorless oil, bp 95–125°C (0.04 mm). [Note: it appears that some of the product may decompose during the distillation based on capillary GC analysis (crude product, distilled fractions, and pot residue) and the wide temperature range for the distillation even though the pressure appeared to remain constant.]

7. 3-Methyl-2-butanone was purchased from Eastman Chemical Products, Inc. and distilled prior to use. It appeared that water was azeotropically removed during the distillation, and thus a significant fore-run was discarded.

8. The submitters employed an addition funnel and conducted the addition over 7.5 min.

9. This is best accomplished by periodically adding room temperature acetone to the cooling bath over the course of 1.5 hr. More rapid warming results in dramatically reduced yields of β-lactone.

10. A pure sample of the β-lactone was obtained by vacuum distillation through an 8-cm Vigreux column (bp 43–80°C, 0.25 mm) followed by column chromatography on silica gel and exhibited the following spectral characteristics: IR (neat) cm^{-1}: 2960, 2930, 2860, 1830, 1465, 1390, 1220, 1095, 1020, 810; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.88 (t, 3 H, J = 7), 0.93 (d, 3 H, J = 7), 1.02 (d, 3 H, J = 7), 1.20–1.50 (m, 15 H), 1.50–1.65 (m, 1 H), 1.65–1.90 (m, 1 H), 1.99 (sept, 1 H, J = 7), 3.13 (t, 1 H, J = 8); ^{13}C NMR 75 MHz, $CDCl_3$) δ: 14.0, 14.9, 17.0, 17.5, 22.6, 25.0, 27.5, 29.1, 29.2, 29.4, 31.8, 37.5, 56.2, 85.0, 171.9. Anal. Calcd for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74. Found: C, 75.17; H, 11.57. Only the trans-substituted β-lactone could be detected by NMR and NOE analysis.

11. Cyclohexane was purchased from Mallinckrodt Inc. and used without further purification.

12. Silica gel (230-400 mesh) was obtained from J. T. Baker, Inc., or E. Merck. Less silica gel (e. g., 10% wt. equiv) can be used in this step, although in this case longer reflux times are necessary to complete the decarboxylation. Note that the use of completely anhydrous silica gel (e.g., silica gel flame-dried under reduced pressure) was found to catalyze olefin isomerization in some cases and should be avoided.

13. Activated charcoal (20-40 mesh) was used as received from Matheson, Coleman, & Bell or Darco (G-60). Addition of charcoal at this stage removes reduces the amount of malodorous thiol impurities.
14. The submitters silica gel (J. T. Baker, Inc.) column (8-cm × 10-cm) was packed as a slurry in petroleum ether (Mallinkrodt Inc., bp 35–60°C). The column was eluted using petroleum ether (20 mL/min, collecting 70-mL fractions). The fractions were analyzed by capillary GC, and those containing the product (fractions 4–9) were combined.
15. Elution of the silica gel column with additional hexane afforded thiophenol (5.0 g), diphenyl disulfide (0.2 g), and BHT (0.1 g, stabilizer from the THF). Continued elution with increasing amounts of ethyl acetate (hexane:EtOAc from 100:0 to 80:20) afforded dinonyl ketone (2.4 g, 10%), S-phenyl decanoate (0.8 g, 2%), and the enol of 2-methyl-3,5-diketotetradecane (2.4 g, 6%; the amount is probably greater).
16. Alternatively, the alkene can be purified by distillation through an 8-cm Vigreux column (Note 20) to furnish 11.8–13.0 g (53–59% overall yield) of (E)-2,3-dimethyl-3-dodecene as a clear, colorless oil, bp 52°C (0.03 mm) The yield of alkene is considerably reduced if the distillation is carried out at higher temperature.
17. The olefin thus obtained was found by ^{1}H NMR and gas chromatographic analysis to consist of a 25-27:1 mixture of E and Z isomers. The major product was identified as the trans isomer by ^{1}H NMR NOE analysis. Gas chromatographic analysis was carried out on a 0.25-mm × 30-m DB-1701-coated fused silica capillary column, column temperature 125°C, flow rate 1 mL/min, retention times: Z isomer 9.09 min, E isomer 9.30 min.
18. The product has the following spectral properties: IR (neat) cm^{-1}: 2970, 2940, 2870, 1465, 1380; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.87 (t (br), 3 H), 0.95 (d, 6 H, J = 6.5), 1.25 (s (br), 12 H), 1.55 (s, 3 H), 1.95 (m, 2 H), 2.20 (m, 1 H), 5.15 (t (br), 1 H, J = 6.9); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.3, 14.1, 21.5, 22.7, 27.8, 29.4, 29.6, 30.0, 32.0, 36.8, 122.3, 140.6; Z isomer impurity (partial) δ: 5.05 (t (br), J = 6.5), 2.8 (m), 1.60 (m), 0.95 (d). Anal. Calcd for $C_{14}H_{28}$: C, 85.71; H, 14.29. Found: C, 85.55; H, 14.38. The major product was determined to be the trans isomer by NOE analysis.
19. Methylene chloride was purchased from Mallinckrodt Inc. and used without further purification. Thiophenol was purchased from Fluka Chemical Co. and used without further purification. Pyridine was purchased from Mallinckrodt Inc. and was distilled from calcium hydride. Decanoyl chloride was purchased from the Aldrich Chemical Company, Inc., and used without further purification.
20. In order to reduce foaming, enough glass wool is added to the distillation flask just to cover the surface of the liquid.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

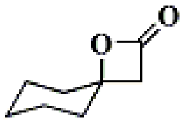
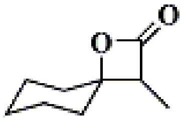
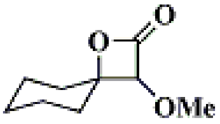
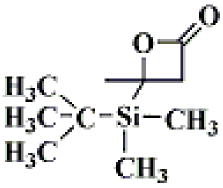
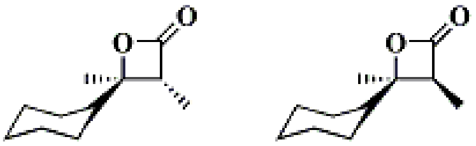
3. Discussion

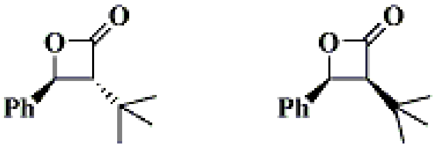
The procedure described here illustrates a practical and convenient method for the synthesis of β-lactones.[3,4] In conjunction with the stereospecific decarboxylation of the β-lactone products, it provides an attractive strategy for the synthesis of substituted alkenes. The new method is based on the addition of lithium enolate derivatives of thiol esters to ketones and aldehydes at −78°C as originally described by Wemple.[5] The submitters have found that gradual warming (generally to 0°C) of the resulting aldolates produces β-lactones in good to excellent yield. The facility and generality of this spontaneous lactonization process had not been noted previously. Low-temperature quenching of the aldol addition reaction affords only the expected β-hydroxy thiol esters, although Masamune has shown that cyclization of the thiol ester aldol products can be effected as a separate operation by treatment with excess mercury (II) methanesulfonate and disodium phosphate (Na_2HPO_4) in acetonitrile.[6]

Both ketones and aldehydes, as well as acylsilanes can be employed as carbonyl substrates in the new β-lactone synthesis (Table). Reactions involving ketones are most conveniently carried out by adding the neat carbonyl compound to the thiol ester enolate solution. Under these conditions aliphatic aldehydes react to form substantial quantities of 2:1 adducts; however, formation of these side products can be suppressed simply by slowly adding the aldehyde component as a precooled (−78°C) solution to the reaction mixture. Wide variation is also possible in the thiol ester component, although a few limitations of the method have been noted. For example, α,β-unsaturated ketones such as methyl vinyl ketone and cyclohexenone fail to yield β-lactones, and attempts to generate β-lactones with severe steric crowding have also met with limited success.[3,4]

TABLE I

PREPARATION OF β-LACTONES VIA THIOL ESTERS

Entry	Carbonyl Compound	Thiol Ester	β-Lactone	% Isolated Yield
1	Cyclohexanone	CH_3COSPh		86
2	Cyclohexanone	CH_3CH_2COSPh		92
3	Cyclohexanone	$MeOCH_2COSPh$		78
4	n-Octanal	$Me_2CHCOSPh$		54
5	CH_3COSi-t-$BuMe_2$	CH_3COSPh		55
6	Acetylcyclohexane	CH_3CH_2COSPh	 29:1	75

7	n-Octanal	CH_3CH_2COSPh	2.5:1	42
8	Benzaldehyde	$t\text{-}BuCH_2COSPh$	 34:1	85

Not surprisingly, thiol ester enolates combine with ketones (and many aldehydes) to form predominantly the less sterically crowded β-lactone diastereomers, in some cases with excellent stereoselectivity. However, the stereochemical course of reactions involving aldehydes has proved to be rather complicated, and further studies are required to clarify the factors that control the stereochemical outcome of these reactions.

As described here, the new β-lactone synthesis also provides the basis for a very attractive approach to the synthesis of substituted alkenes. Since the 19th century it has been known that, upon heating, β-lactones undergo a facile [2+2] cycloreversion to generate alkenes and carbon dioxide.[7 8] This stereospecific process[9] generally takes place at temperatures between 80° and 160°C, with the rate of reaction being highly dependent on the nature of substituents present at the C-4 (β) position of the lactone ring. The reaction often proceeds in nearly quantitative yield, and in recent years has been applied to the synthesis of a variety of types of substituted and functionalized alkenes. In this work, two experimental protocols were employed to effect the cycloreversion step. Alkenes boiling at 200°C or lower were best generated by Kugelrohr distillation at 80–110°C from a mixture of the lactone and 10 weight % of silica gel[10] at a pressure such that the alkene product distilled as it was generated, leaving the less volatile β-lactone behind in the distillation flask. As described in the above procedure, alkenes with boiling points of ca. 250°C or greater were prepared by heating a benzene or cyclohexane solution of the requisite β-lactone at reflux in the presence of an equal weight of chromatographic silica gel.

The synthesis of β-lactones has received considerable attention[7,8] since the first representative of this class of heterocycles was prepared in 1883. Classical routes to β-lactones generally involved the cyclization of β-halocarboxylate salts[7,8] and the related "deaminative cyclization" that occurs upon diazotization of β-amino acids.[11] β-Hydroxy acids undergo a similar cyclization under Mitsunobu conditions,[12 13 14] and the halolactonization of α,β-unsaturated acids[15 16] is a related process of some interest. Although these classical methods have been successfully employed for the preparation of a variety of β-lactones, their utility is often limited by side reactions including β-elimination (to form α,β-unsaturated acids) and decarboxylative elimination (to generate alkenes).

The strategy described here should find considerable use as a method for the stereoselective synthesis of alkenes. Although this olefination strategy involves one more step than the classic Wittig reaction, in many cases it may prove to be the more practical method. Finally, the scope, overall efficiency, and stereoselectivity of the β-lactone route compares favorably to the Wittig, Julia-Lythgoe, and related established strategies for the synthesis of tri- and tetrasubstituted alkenes.

This preparation is referenced from:

- Org. Syn. 75, 116

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

sodium benzophenone ketyl

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ethyl acetate (141-78-6)

ammonium chloride (12125-02-9)

acetonitrile (75-05-8)

Cyclohexanone (108-94-1)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

cyclohexane (110-82-7)

benzaldehyde (100-52-7)

acetone (67-64-1)

pyridine (110-86-1)

methylene chloride (75-09-2)

Thiophenol (108-98-5)

magnesium sulfate (7487-88-9)

Disodium Phosphate (7558-79-4)

3-methyl-2-butanone (563-80-4)

butyllithium, n-butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

hexane (110-54-3)

methyl vinyl ketone (78-94-4)

calcium hydride (7789-78-8)

cyclohexenone (930-68-7)

diphenyl disulfide (882-33-7)

acetylcyclohexane (823-76-7)

n-Octanal (124-13-0)

diisopropylamine (108-18-9)

(E)-2,3-Dimethyl-3-dodecene (174783-19-8)

S-phenyl decanoate

decanoyl chloride (112-13-0)

dinonyl ketone (504-57-4)

mercury(II) methanesulfonate (29526-41-8)

S-Phenyl decanethioate (51892-25-2)

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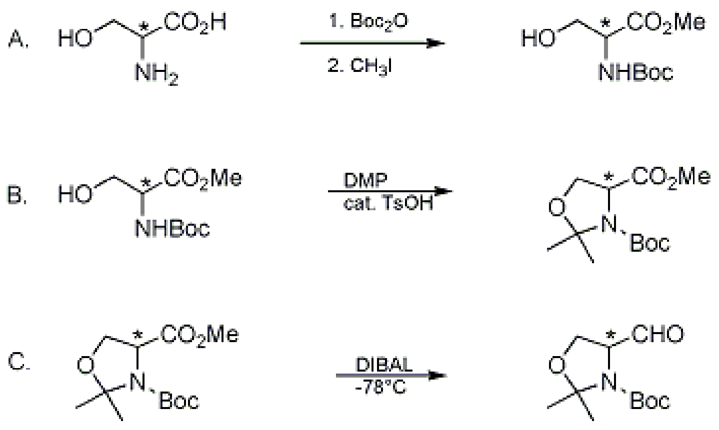
Organic Syntheses, CV 9, 300

1,1,-DIMETHYLETHYL (S)- OR (R)-4-FORMYL-2,2-DIMETHYL-3-OXAZOLIDINECARBOXYLATE: A USEFUL SERINAL DERIVATIVE

[3-Oxazolidinecarboxylic acid, 4-formyl-2,2-dimethyl-, 1,1-dimethylethyl ester, (S)- or (R)-]



Submitted by Philip Garner and Jung Min Park[1].
Checked by Mayumi Takasu and Hisashi Yamamoto.

1. Procedure

A. *N-[(1,1-Dimethylethoxy)carbonyl]-L-serine methyl ester*. A solution of di-tert-butyl dicarbonate [$(Boc)_2O$] (78.4 g, 0.36 mol, (Note 1)) in dioxane (280 mL, (Note 2)) is added to an ice-cold, magnetically stirred solution of L-serine (31.7 g, 0.30 mol, (Note 3)) in 1 N sodium hydroxide (620 mL) by means of an addition funnel. The two-phase mixture is stirred at 5°C for 30 min, then allowed to warm to room temperature over 3.5 hr at which time TLC analysis shows the reaction to be complete (Note 4). The mixture is concentrated to half its original volume by rotary evaporation at 35°C, cooled in an ice-water bath, acidified to pH 2–3 by the slow addition of 1 N potassium bisulfate (620 mL), and then extracted with ethyl acetate (3 × 1000 mL). The combined extracts are dried over magnesium sulfate, filtered and concentrated to give N-Boc-L-serine (63.0 g) as a colorless, sticky foam which is used without further purification.

To a cold solution of N-Boc-L-serine (32.4 g, 0.16 mol, (Note 5)) in dimethylformamide (150 mL) is added solid potassium carbonate (24.3 g, 0.176 mol). After stirring for 10 min in an ice-water bath, methyl iodide (20.0 mL, 46.3 g, 0.32 mol – *CAUTION! Methyl iodide is toxic and a suspected carcinogen that should be handled in a well-ventilated fume hood.*) is added to the white suspension and stirring continued at 0°C for 30 min whereupon the mixture solidifies. The reaction is warmed to room temperature and stirred for an additional hour or so at which point TLC analysis indicates complete formation of the methyl ester (Note 6). The reaction mixture is filtered by suction and the filtrate partitioned between ethyl acetate (300 mL) and water (300 mL). The organic phase is washed with brine (2 × 300 mL), dried with magnesium sulfate, filtered and concentrated to give 29.8 g (86% yield) of N-Boc-L-serine methyl ester as a pale amber oil which is used without further purification (Note 7) and (Note 8).[2]

B. *3-(1,1-Dimethylethyl) 4-methyl (S)-2,2-dimethyl-3,4-oxazolidinedicarboxylate*. To a 2-L, three-necked, round-bottomed flask, equipped with a magnetic stirring bar, Claisen distilling head, thermometer, and reflux condenser protected from moisture by a calcium sulfate-filled drying tube are added a solution of N-Boc-L-serine methyl ester (48.5 g, 0.22 mol) in benzene (770 mL), 2,2-dimethoxypropane (55 mL, 47 g, 0.45 mol), and p-toluenesulfonic acid monohydrate (0.593 g, 3.1 mmol, (Note 9). The colorless solution is heated under reflux (oil bath temperature, 110°C) for 30 min, then slowly distilled until a volume of 660 mL is collected over 4 hr when the reaction is judged to be complete by TLC (Note 10) and (Note 11). The cooled, amber solution is partitioned between saturated sodium bicarbonate solution (200 mL) and ethyl ether (2 × 500 mL). The organic layer is washed with brine (200 mL), then dried over magnesium sulfate, filtered and concentrated to give the crude product as an amber oil. This material is vacuum distilled through a 10-cm Vigreux column to give 40.3–50.9 g (70–89% yield) of oxazolidine methyl ester as a very pale yellow liquid, bp 101–102°C (2 mm) (Note 12).

C. *1,1-Dimethylethyl (S)-4-formyl-2,2-dimethyl-3-oxazolidinecarboxylate*. A dry (Note 13), 1-L, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, rubber septa, three-way balloon adapter, and a low temperature thermometer. After the flask is purged with nitrogen (Note 14), a solution of the oxazolidine ester (40.2 g, 0.15 mol) in dry toluene (300 mL, (Note 15)) is added via cannula (using positive nitrogen pressure) and cooled to −78°C with an acetone-dry ice bath. To this cooled solution is added a −78°C solution of 1.5 M diisobutylaluminum hydride in toluene (175 mL, (Note 16)) via cannula (using positive nitrogen pressure). The rate of addition is adjusted so as to keep the internal temperature below −65°C and takes

approximately 1 hr to complete. The reaction mixture is stirred for an additional 2 hr at −78°C under an atmosphere of nitrogen when TLC anlaysis shows the reaction to be complete (Note 17). The reaction is quenched by slowly adding 60 mL of cold (−78° C) methanol (*Evolution of hydrogen occurs!*)—again keeping the internal temperature below −65°C. The resulting white emulsion is slowly poured into 1000 mL of ice-cold 1 N hydrochloric acid with swirling over 15 min, and the aqueous mixture is then extracted with ethyl acetate (3 × 1000 mL). The combined organic layers are washed with brine (1000 mL), dried over magnesium sulfate, filtered and concentrated to give 33.6 g of crude product as a colorless oil. This material is vacuum distilled through a 10-cm Vigreux column to give 26.9 g (76% yield) of oxazolidine aldehyde as a colorless liquid, bp 83–88°C (1.0–1.4 mm) (Note 18).

2. Notes

1. The submitters used di-tert-butyl dicarbonate from Aldrich Chemical Company, Inc., and also available from Wako Pure Chemical Industries, LTD.
2. Unless stated otherwise in the procedure, all solvents and reagents were used as purchased without further purification.
3. The submitters used L-serine (and D-serine) from United States Biochemical Corporation, and also available from Tokyo Kasei Kogyo Co., LTD.
4. TLC analysis on Merck silica gel 60F-254 plates eluting with (8:1:1) n-BuOH-H_2O-AcOH showed the clean formation of a product with R_f 0.65 (visualized with 0.3% ninhydrin in (97:3) n-BuOH-AcOH) at the expense of starting amino acid at the origin. If starting material remained, more $(Boc)_2O$ (13.1 g, 0.060 mol) was added.
5. The submitters have also found commercially available N-Boc-L-serine (United States Biochemical Corporation) to be an entirely satisfactory starting material. However, for the unnatural D-series, they find that it is more economical to prepare N-Boc-D-serine as described.
6. TLC analysis on Merck silica gel 60F-254 plates eluting with (1:1) ethyl acetate-hexanes showed the clean formation of ester, R_f 0.38 (visualized with 0.5% phosphomolybdic acid in 95% ethanol), at the expense of starting material at the origin.
7. Optical measurements on this material were not very useful since they were in general low and quite variable. Furthermore, no literature values could be found for comparison. IR (neat) cm^{-1}: 3400, 1720 (br); ^1H NMR (200 MHz, C_6D_6, 17°C) δ: 1.41 (s, 9 H), 2.50 (br, s, H, exchanged with D_2O), 3.26 (s, 3 H), 3.66 (dd, H, J = 11 and 4), 3.76 (dd, H, J = 11 and 4), 4.40 (m, H), 5.60 (m, H, exchanged with D_2O).
8. *Alternatively, the methyl ester could be prepared as follows:* N-Boc-serine (63 g, 0.31 mol) was dissolved in ethyl ether (600 mL) in a 2-L Erlenmeyer flask equipped with a magnetic stirring bar, cooled in an ice-water bath and treated with ten 50-mL aliquots of cold ethereal (approximately 0.6 M) diazomethane prepared from N-nitroso-N-methylurea according to Arndt's procedure.[3] After 30 min at 0°C, TLC analysis showed the reaction to be complete (Note 6). Excess diazomethane was destroyed with acetic acid (the yellow color disappears) and the resulting solution was extracted with half-saturated sodium bicarbonate solution (300 mL), then washed with brine (200 mL), dried with magnesium sulfate, filtered and concentrated to give 60.1 g (91% over 2 steps) of N-Boc-serine methyl ester as a colorless, sticky foam which was used without further purification. *CAUTION! N-Nitroso-N-methylurea is suspected of being a carcinogen and diazomethane is highly toxic. The utmost care must be used when handling these substances; diazomethane solutions should be restricted to a well-ventilated fume hood at all times.*
9. Moriwake et al. have reported that boron trifluoride etherate can also be used as the acid catalyst for this reaction.[4]
10. TLC analysis on Merck silica gel 60F-254 plates eluting with (1:1) ethyl acetate-hexanes showed the clean formation of product, R_f 0.78 (visualized with 0.5% phosphomolybdic acid in 95% ethanol), at the expense of starting material at R_f 0.23.
11. If starting material remained at this time, more 2,2-dimethoxypropane (14 mL, 12 g, 0.11 mol) and benzene (310 mL) were added and the procedure was repeated, collecting 250 mL of distillate, at which time the TLC analysis generally showed the reaction to be complete.
12. The optical rotation of the L-oxazolidine methyl ester was −46.7° ($CHCl_3$, *c* 1.30). An essentially identical procedure emanating from N-Boc-D-serine methyl ester gave the corresponding D-oxazolidine methyl ester in 80% yield with a rotation of +53°. In either case further purification could be achieved with flash chromatography to give product with a maximum rotation of 57° although we have found distilled material to be entirely satisfactory for our purposes: IR (neat) cm^{-1}: 1760, 1704; ^1H NMR (200 MHz, C_6D_6, 75°C) δ: 1.41 (s, 9 H), 1.53 (br s, 3 H), 1.81 (br s, 3 H), 3.35 (s, 3 H), 3.75 (dd, H, J = 8.5 and 8.1), 3.81 (dd, H, J = 8.5 and 3.5), 4.26 (m, H). (The oxazolidine derivatives exist as slowly interconverting rotamers on the NMR time scale and samples require heating to obtain averaged spectra.)
13. All the glassware (except the low-temperature thermometer) was oven-dried (>100°C) and quickly assembled before use.
14. The checkers used argon.
15. Toluene was distilled from sodium-benzophenone ketyl.
16. The diisobutylaluminum hydride solution (1.5 M in toluene, Aldrich Chemical Company, Inc.) was transferred to a dry, 250-mL, graduated cylinder equipped with a rubber septum and drying tube via cannula (using positive nitrogen pressure). The graduated cylinder was then placed in a Dewar flask and cooled to −78°C with an acetone-dry ice bath.

17. TLC analysis on Merck silica gel 60F-254 plates eluting with (4:1) hexanes-ethyl acetate showed the formation of product, R_f 0.33 (visualized with 0.5% phosphomolybdic acid in 95% ethanol), with only a trace of starting material remaining at R_f 0.41. Some over-reduced product arising within the TLC capillary may be evident at this stage.

18. The optical rotation of the L-oxazolidine aldehyde was −91.7° ($CHCl_3$, *c* 1.34). An identical procedure emanating from the D-oxazolidine methyl ester gave D-oxazolidine aldehyde in 85% yield having a rotation of +95°. These distilled products contained up to 5% of the starting material as judged by their NMR spectra, but were suitable for use without further purification. Homogeneous samples could be obtained in either case by flash chromatography on silica gel eluting with (4:1) hexanes-ethyl acetate and showed a maximum optical rotation of 105°. This material can be stored indefinitely provided it is kept cold (≤ 5°C) and moisture-free. IR (neat) cm^{-1}: 1735, 1705; ^1H NMR (200 MHz, C_6D_6, 60°C) δ: 1.34 (s, 9 H), 1.40 (br s, 3 H), 1.59 (br s, 3 H), 3.52 (dd, H, J = 8.7 and 8.3), 3.65 (dd, H, J = 8.7 and 2.9), 3.90 (m, H), 9.34 (br s, H).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

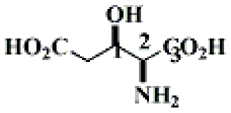
3. Discussion

Since its preparation and use was first reported by us,[5] the title compound has been gaining favor as a chiral, nonracemic synthon for the asymmetric synthesis of a variety of amino alcohol- and amino acid-containing targets. Among the virtues of this oxazolidine aldehyde over previously reported N-acylated serinal derivatives are its ease of preparation on a large scale and its configurational stability. The procedure described here provides material that has been determined to be 95% enantiomerically pure by Mosher ester analysis.[6] Homologation (C-C bond formation) of this serinal derivative can be achieved without competing racemization using both olefination[4,7,8,9,10,11,12] and nucleophilic addition[5,13,14,15,16,17,18,19,20,21,22,23,24,25,26] protocols. The latter process can be made to occur with good to excellent diastereoselectivity (i.e., 1,2-asymmetric induction) by simply choosing reagents/conditions so as either to preclude or favor chelation-control. Protocols for diasteroselective additions to the oxazolidine-appended olefins are also known. Once the rest of the target molecule's structure is in place, the oxazolidine can be unravelled to give either an aminoethanol group or, after oxidation of the primary alcohol, an α-amino acid moiety. The products so produced are typically >98% enantiomerically pure. Thus the title compound can serve not only as a serinal derivative but as a penaldic acid equivalent as well. Representative examples of the use of 1,1-dimethylethyl (S)- and (R)-4-formyl-2,2-dimethyl-3-oxazolidinecarboxylate as a chiral synthon for natural product synthesis are collected in the Table.

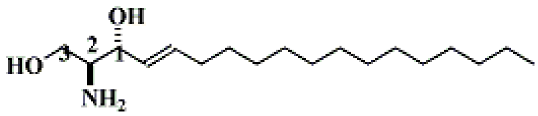
This preparation is referenced from:

- Org. Syn. 77, 64

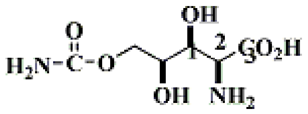
TABLE
SELECTED EXAMPLES OF THE USE OF 1,1-DIMETHYL(S)- AND (R)-4-FORMYL-2,2-DIMETHYL-3-OXAZOLIDINECARBOXYLATE FOR NATURAL PRODUCT SYNTHESIS: THE C-3 SUBUNITS EMANATING FROM SERINE ARE NUMBERED ACCORDINGLY



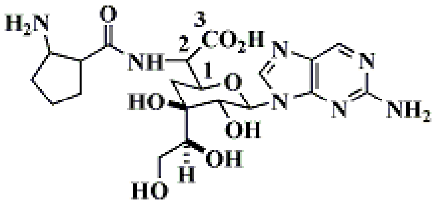
threo-β-hydroxy-L-glutamic acid (ref. 4)



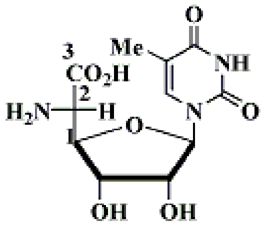
D-*erythro*-sphingosine (refs. 8-10, 12, 13)



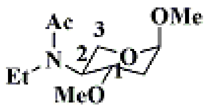
5-carbamoylpolyxamic acid (ref. 11)



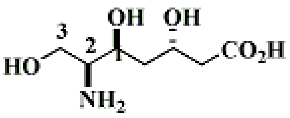
Amipurimycin studies (ref. 5)



Thymine polyoxin C (ref. 16)



Calicheamycin fragment (ref. 19)



(-)-Galantic acid (ref. 26)

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

hexanes

brine

sodium-benzophenone ketyl

1,1,-DIMETHYLETHYL (S)- OR (R)-4-FORMYL-2,2-DIMETHYL-3-OXAZOLIDINECARBOXYLATE

$(Boc)_2O$

D-oxazolidine methyl ester

ethanol (64-17-5)

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

ethyl acetate (141-78-6)

methanol (67-56-1)

ethyl ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

nitrogen (7727-37-9)

potassium bisulfate (7646-93-7)

toluene (108-88-3)

Methyl iodide (74-88-4)

magnesium sulfate (7487-88-9)

dioxane (5703-46-8)

Diazomethane (334-88-3)

dimethylformamide (68-12-2)

serine, L-serine (56-45-1)

boron trifluoride etherate (109-63-7)

diisobutylaluminum hydride (1191-15-7)

2,2-dimethoxypropane (77-76-9)

argon (7440-37-1)

phosphomolybdic acid (51429-74-4)

ninhydrin (938-24-9)

p-toluenesulfonic acid monohydrate (6192-52-5)

N-Boc-L-serine, N-Boc-serine

Di-tert-butyl dicarbonate (24424-99-5)

N-[(1,1-Dimethylethoxy)carbonyl]-L-serine methyl ester, N-Boc-L-serine methyl ester, N-Boc-serine methyl ester (2766-43-0)

3-(1,1-Dimethylethyl) 4-methyl (S)-2,2-dimethyl-3,4-oxazolidinedicarboxylate (108149-60-6)

1,1-Dimethylethyl (S)-4-formyl-2,2-dimethyl-3-oxazolidinecarboxylate, 3-Oxazolidinecarboxylic acid, 4-formyl-2,2-dimethyl-, 1,1-dimethylethyl ester, (S)-, 1,1,-DIMETHYLETHYL (S)-4-FORMYL-2,2-DIMETHYL-3-OXAZOLIDINECARBOXYLATE (102308-32-7)

D-serine (312-84-5)

N-Boc-D-serine (6368-20-3)

N-nitroso-N-methylurea (684-93-5)

N-Boc-D-serine methyl ester (95715-85-8)

(R)-4-formyl-2,2-dimethyl-3-oxazolidinecarboxylate

1,1,-DIMETHYLETHYL (R)-4-FORMYL-2,2-DIMETHYL-3-OXAZOLIDINECARBOXYLATE, 3-Oxazolidinecarboxylic acid, 4-formyl-2,2-dimethyl-, 1,1-dimethylethyl ester, (R)-, 1,1-dimethylethyl (R)-4-formyl-2,2-dimethyl-3-oxazolidinecarboxylate (95715-87-0)

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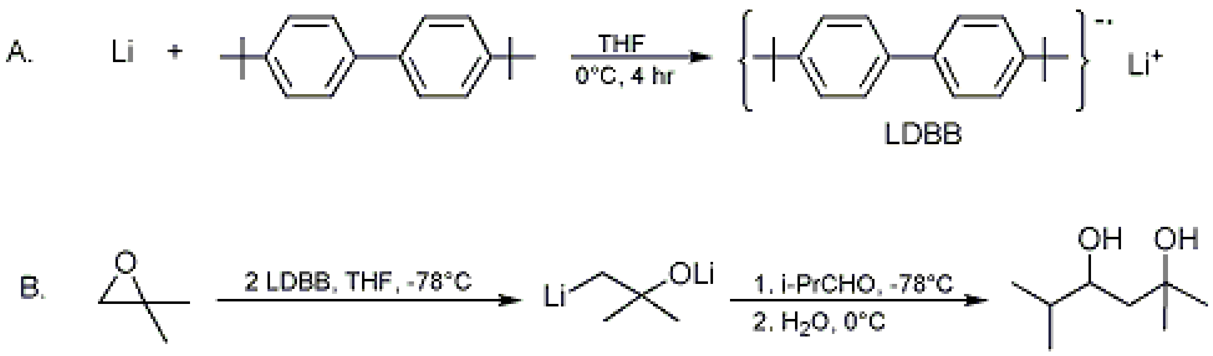
Organic Syntheses, CV 9, 306

1,3-DIOLS FROM LITHIUM β-LITHIOALKOXIDES GENERATED BY THE REDUCTIVE LITHIATION OF EPOXIDES: 2,5-DIMETHYL-2,4-HEXANEDIOL

[2,4-Hexanediol, 2,5-dimethyl-]



Submitted by Boguslaw Mudryk and Theodore Cohen[1].
Checked by Hiroaki Hibino and Hisashi Yamamoto.

1. Procedure

A. *Lithium 4,4'-di-tert-butylbiphenylide (LDBB).*[2] An oven-dried, three-necked round-bottomed, 1-L flask, equipped with a Teflon-coated magnetic stirring bar (Note 1), small, pressure-equalizing funnel, low temperature thermometer, and a gas inlet, is flushed with dry argon. The apparatus is charged with 600 mL (Note 2) of dry tetrahydrofuran (THF) (Note 3) and 56 g (0.21 mol) of 4,4'-di-tert-butylbiphenyl (DBB) (Note 4). Lithium pieces (1.5 g, 0.22 M) (Note 5) are then introduced under argon into the well-stirred DBB solution in THF at room temperature. As soon as the dark blue-greenish color of the LDBB solution appears, the flask is immersed in an ice-cold bath (Note 6) and the solution is vigorously stirred for 4 hr at 0°C. The LDBB solution so prepared is ready for further use.

B. *2,5-Dimethyl-2,4-hexanediol*. Isobutylene oxide (7.2 g, 0.10 mol) (Note 7) is added dropwise from the pressure-equalizing funnel to the LDBB solution in THF at −78°C at such a rate (the addition lasts for 8–12 min) that the temperature inside the flask does not exceed −78° C. After all the epoxide has been added (8–11 min), the solution becomes deep red. After 5 more minutes of stirring, isobutyraldehyde (7.2 g, 0.10 mol) (Note 8) is added dropwise within 5 min. The mixture is stirred for 1 hr at −78°C; it is allowed to reach 0°C by removing the cold bath, and finally is quenched with water (100 mL). After the mixture is extracted with ether (1 × 300 mL, 2 × 100 mL), the combined organic layers are dried with anhydrous magnesium sulfate ($MgSO_4$) and the solvents are evaporated under reduced pressure. The addition of cold methanol (250 mL) results in precipitation of most of the DBB as a white solid. The latter is crushed in methanol to a fine powder with a spatula and the methanolic suspension is placed in a freezer for 1 hr. The solid is filtered, washed with 50–250 mL of ice-cold methanol and air-dried; the yield is 49.1 g (88% recovery). The methanol is evaporated under reduced pressure and the product is isolated by flash chromatography (25% ethyl acetate in hexane as the

eluent); yield 11.3–12.3 g (77–88%). An additional vacuum distillation at 104–105°C/13 mm provides >99% pure product, yield 9.2 g (62–66%) ((Note 9),(Note 10)).

2. Notes

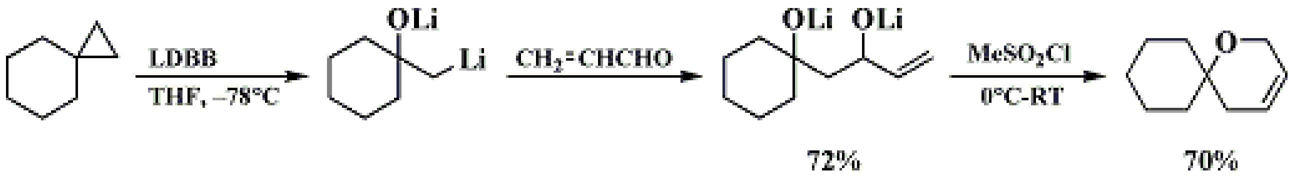
1. A large size, football-shaped stirring bar is required to provide effective stirring.
2. At least this amount of THF is needed to ensure that the final LDBB concentration is below 0.4 M. More concentrated solutions solidify at −78°C.
3. Tetrahydrofuran was purchased from Wako Pure Chemical Industries, Ltd., Osaka, Japan (also available from Fisher Scientific Co.) and distilled from potassium benzophenone ketyl before use.
4. 4,4'-Di-tert-butylbiphenyl (97%) was used as purchased from Aldrich Chemical Company, Inc.
5. The submitters used lithium (99.9%, Alfa Products) as a ribbon (0.28 mm thick, 25 mm wide). [The checkers used lithium (99.9%, Aldrich Chemical Company, Inc.) as a wire (3.2 mm diam. in mineral oil).] Its surface was cleaned by scraping off the lithium oxide and nitride with an X-Acto knife under mineral oil. The ribbon was then cut into 20–30 mg pieces that were rinsed with pentane before use.
6. A 2.5-L Dewar flask (I.D. = 170 mm) was employed for the 0°C and −78°C cooling baths.
7. Isobutylene oxide was used as purchased from Tokyo Kasei Kogyo Co., Ltd., Tokyo, Japan (also available from TCI America).
8. Isobutyraldehyde purchased from Wako Pure Chemical Industries, Ltd., Osaka, Japan (also available from Aldrich Chemical Company, Inc.) was purified by distillation immediately before use.
9. The diol was characterized by ^{1}H NMR and ^{13}C NMR; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.92 (d, J = 6.8) and 0.93 (d, J = 6.8) (6 H), 1.28 (s) and 1.31 (s) (6 H), 1.49 (dd, 1 H, J = 2.5 and 14.5), 1.57–1.69 (m, 2 H), 3.00 (s, 2 H), 3.77 (ddd, 1 H, J = 2.5, 5.4 and 10.3); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 17.4, 17.6, 27.0, 31.5, 33.7, 43.2, 71.0, 73.8.
10. The submitters have employed the procedure described above for some other epoxides. The yields of diols resulting from trapping the intermediate β-lithioalkoxides with aldehydes were generally lower than in the small-scale experiments.[3] This may be caused in part by the longer period of addition of the epoxide that is required to maintain a low temperature, thus allowing more time for destruction of the dianion that is being generated. In cases where the alkoxide group is not tertiary, the product yield is lowered by transfer of the carbinol hydride ion to the aldehyde to produce a new alkoxide and an enolate ion. Thus, propylene oxide, after reductive cleavage with LDBB and trapping with isobutyraldehyde or *p*-anisaldehyde, provided 5-methyl-2,4-hexanediol in 40–50% yield or 1-p-anisyl-1,3-butanediol in 44% yield, respectively (in both cases about equal mixtures of diastereoisomers were obtained). The cyclohexene oxide-derived dianion, when trapped with isobutyraldehyde, gave 2-(1-hydroxy-2-methylpropyl)cyclohexanol in 71% yield as a mixture of only partially separable isomers in the ratio 15:11:39:35.

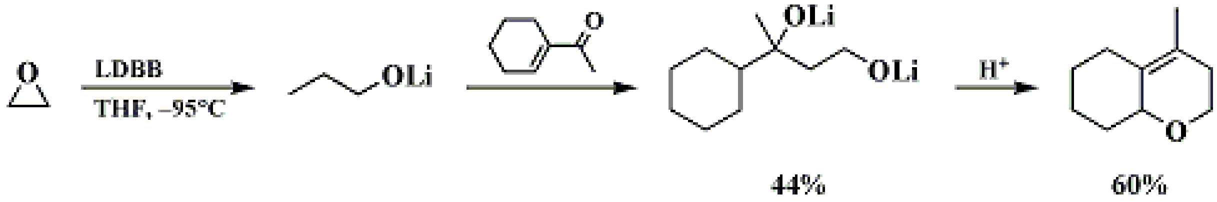
Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The present example represents a larger-scale version of a recently described synthesis of 1,3-diols from aldehydes and lithium β-lithioalkoxides.[3,4] These useful dianions can be conveniently generated from epoxides at −78°C in THF by the reductive cleavage of the carbon-oxygen bond using the powerful reducing agent LDBB. Previously reported reductions of epoxides with alkali metals were carried out in protic media and therefore the intermediate dianions were immediately destroyed by protonation by the solvent.[5 6 7 8] The reductive opening of 2,2-dialkyl epoxides is highly regioselective and always leads to the less-substituted organolithium and the more-substituted alcoholate.[3,9] The procedure can also be useful for monosubstituted epoxides, provided that they are employed in excess toward the aldehyde. They are cleaved mainly to produce the primary organolithiums, but they do undergo a minor degree of ring cleavage yielding the secondary organolithiums, which are known to expel lithium oxide rapidly[10 11 12] to form easily removable olefins. Lithium β-lithioalkoxides can be trapped at −78°C with a variety of aldehydes and ketones yielding 1,3-diols with different substitution patterns.[3] When conjugated enones are employed as electrophiles, unsaturated cyclic ethers can be produced in one pot by activating the allylic hydroxyl group toward displacement by the other hydroxyl group with allylic inversion:[3]





Although lithium β-lithioalkoxides can also be generated from β-halo alcohols by deprotonation and subsequent reductive lithiation of the carbon-halogen bond[10,13] or from β-halo ketones by organolithium addition to the carbonyl group followed by reductive lithiation,[13] the current method is more direct as well as more convenient, since epoxides are readily available either commercially or by a variety of procedures.

Despite the lack of diastereoselectivity and the moderate yields, the present procedure complements other syntheses of 1,3-diols such as hydride reductions of β-diketones,[14 15] β-hydroxy ketones[16 17 18 19 20 21] and β-keto esters,[22] or the opening of 2,3-epoxy alcohols[23 24 25 26] and 3,4-epoxy alcohols[27] with Lipshutz cuprates.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

potassium benzophenone ketyl

ethyl acetate (141-78-6)

methanol (67-56-1)

ether (60-29-7)

propylene oxide (75-56-9)

Pentane (109-66-0)

lithium (7439-93-2)

magnesium sulfate (7487-88-9)

isobutyraldehyde (78-84-2)

Tetrahydrofuran (109-99-9)

isobutylene oxide (558-30-5)

hexane (110-54-3)

argon (7440-37-1)

p-anisaldehyde (123-11-5)

2,5-Dimethyl-2,4-hexanediol, 2,4-Hexanediol, 2,5-dimethyl- (3899-89-6)

Lithium 4,4'-di-tert-butylbiphenylide (61217-61-6)

4,4'-di-tert-butylbiphenyl (1625-91-8)

lithium oxide

5-methyl-2,4-hexanediol

1-p-anisyl-1,3-butanediol

2-(1-hydroxy-2-methylpropyl)cyclohexanol

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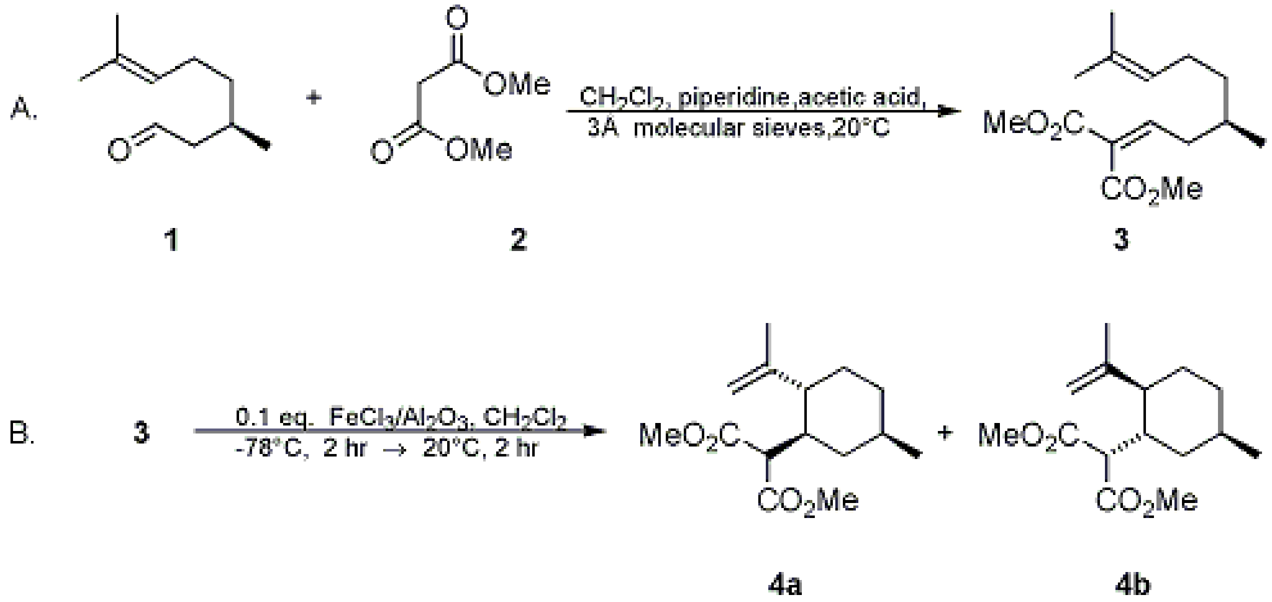
Organic Syntheses, *CV 9, 310*

DIASTEREOSELECTIVE FORMATION OF trans-1,2-DISUBSTITUTED CYCLOHEXANES FROM ALKYLIDENEMALONATES BY AN INTRAMOLECULAR ENE REACTION: DIMETHYL (1'R,2'R,5'R)-2-(2'-ISOPROPENYL-5'-METHYLCYCLOHEX-1'-YL)-PROPANE-1,3-DIOATE

[Propanedioic acid, [5-methyl-2-(1-methylethenyl)cyclohexyl]-, dimethyl ester, [1R-(1α,2β,5α)]-]



Submitted by L. F. Tietze and U. Beifuss[1].
Checked by David Rawson and Albert I. Meyers.

1. Procedure

A. *Methyl (5R)-2-(methoxycarbonyl)-5,9-dimethyldeca-2,8-dienoate*, **3**.[2] A dry, 250-mL, two-necked, round-bottomed flask, equipped with a magnetic stirring bar, calcium chloride drying tube, and rubber septum, is charged with 50 mL of dry dichloromethane (Note 1), R-citronellal **1** ((Note 2), 15.4 g, 18.0 mL, 100 mmol), dimethyl malonate, **2** ((Note 3), 14.5 g, 12.5 mL, 110 mmol) and 3 Å molecular sieves ((Note 4), 9.0 g). To the vigorously stirred mixture, piperidine ((Note 5), 0.86 g, 1.00 mL, 10.0 mmol) and acetic acid ((Note 6), 0.63 g, 0.6 mL, 10.0 mmol) are added simultaneously by syringes within a few seconds at room temperature. The reaction mixture is stirred for 30 min, another portion of molecular sieves ((Note 4), 9.0 g) is added, and stirring is continued for another 2 hr (Note 7). After the solvent is removed on a rotary evaporator at 25°C, the resulting slurry is diluted with 30 mL of diethyl ether and the resulting mixture is filtered with suction using a Büchner funnel.

The residue is washed with diethyl ether (4 × 30 mL), and the combined organic layers are washed with water (3 × 30 mL), 1 N hydrochloric acid (3 × 30 mL), saturated sodium bicarbonate solution (3 × 30 mL), water (30 mL), and brine (3 × 30 ml), and finally dried over anhydrous sodium sulfate. Filtration and removal of the solvent on a rotary evaporator at 25°C yields 24.1–25.5 g (90–95%) of the Knoevenagel product as a colorless oil. The crude product is pure enough to be used in the ene reaction. An analytically pure sample of 3 (Note 8) is obtained by column chromatography (SiO_2) (Note 9) with petroleum ether/acetone, 98:2. Compound 3 is acid- and base-sensitive and should be stored under argon in a freezer.

B. *Dimethyl (1'R,2'R,5'R)-2-(2'-isopropenyl-5'-methylcyclohex-1'-yl)propane-1,3-dioate*, **4a**.[2] A dry, 500-mL, three-necked, round-bottomed flask, equipped with a circular magnetic stirring bar, two rubber septa, and a three-way stopcock connected to an argon line and a vacuum line, respectively, is charged with ferric chloride on alumina ((Note 10), 9.25 g, 9.50 mmol of ferric chloride). An argon atmosphere is established in the reaction flask by repeated cycles of evacuation and refilling with argon. Through use of a syringe, 210 mL of dry dichloromethane is added to the reaction flask. Under a positive argon stream, one rubber septum is replaced by a thermometer (–110°C to +30°C) and the other rubber septum is replaced by an argon-flushed, pressure-equalizing dropping funnel sealed with a rubber septum and charged with a solution of 3 (25.5 g, 95.0 mmol) in 40 mL of dry dichloromethane (Note 1). The reaction flask is cooled to −78°C and the solution of **3** in dichloromethane is added dropwise over a period of 30–45 min with stirring at this temperature. Stirring is continued for 2 hr at −78°C and the mixture is allowed to warm to room temperature during 2 hr by taking away the dry ice-acetone bath. The solvent is removed on a rotary evaporator and the remaining brown slurry is treated with diethyl ether (50 mL); the resulting suspension is then filtered with suction using a Büchner funnel. The residue is washed with four 50-mL portions of diethyl ether and the combined organic layers are washed with water (50 mL), saturated sodium bicarbonate solution (50 mL), 1 N hydrochloric acid (50 mL), water (50 mL), and brine (50 mL). The ethereal phase is dried over anhydrous sodium sulfate, filtered, and concentrated on a rotary evaporator to give 24.9 g (98%) of crude 4a/**4b** as a yellowish oil in a 98.8:1.2 ratio. (The checkers determined the composition of 4a/**4b** to be 97.4–97.8/2.6–2.2 by GC/MS.) The oil is purified by short path distillation under reduced pressure to yield 17.1–19.7 g 71–77%) of 4a/**4b** as a clear, colorless, analytically pure liquid (Note 11). Analytically pure samples of 4a/**4b** can also be obtained by flash column chromatography of the crude material on SiO_2 (Note 12) with diethyl ether/petroleum ether, 1:4) in 87% yield.

2. Notes

1. Dichloromethane is freshly distilled from phosphorus pentoxide or calcium hydride.
2. (R)-Citronellal purchased from Aldrich Chemical Company, Inc., Dragoco, Holzminden, or Takasago, Perfumery Co., Ltd., Tokyo was used as received. (R)-Citronellal can also be synthesized from pulegone with ee >99%.[3] The optical purity of citronellal can be determined by GLC after conversion to the acetal of (–)-

(2R,4R)-pentanediol[4] or by HPLC of the amide of citronellic acid and (R)-(+)-1-(1-naphthyl)ethylamine.[4] The chemical purity was checked by TLC. We are grateful to Dr. Brunke, Dragoco, Holzminden, Dr. Kumobayashi, Takasago, Tokyo and Dr. Nürrenbach, BASF, Ludwigshafen for gifts of (+)- and (±)-citronellal.

3. Dimethyl malonate was purified by distillation.

4. Molecular sieves (3 Å) were finely ground and dried under reduced pressure at 100°C for 24 hr prior to use.

5. Piperidine was purified by distillation prior to use.

6. Acetic acid was purified by distillation.

7. The final stirring period can be shortened to 1 hr if an additional 0.6 mL of acetic acid and 1 mL of piperidine are added at this point.

8. The physical properties of 3 are as follows: R_f 0.51 (ether/hexane, 1:1); HPLC 3.4 min (Nucleosil CN-10; ether/hexane, 1:2; flow 1.5 mL/min); IR (film, cm^{-1}: 1730, 1645, 1260, 1225, 1060; UV sh 210 (4.13); ^1H NMR (100 MHz, C_6D_6) δ: 0.78 (d, 3 H, J = 6.5, 5-CH_3), 0.94–1.46 (m, 3 H, 5-H, 6-H_2), 1.53 (s br, 3 H, 10-H_3), 1.66 (s br, 3 H, 9-CH_3), 1.91 (q m, 2 H, J = 7, 7-H_2), 2.13 (multiplet centered, 2 H, 4-H_2), 3.39 (s, 3 H, OCH_3), 3.51 (s, 3 H, OCH_3), 5.10 (tm, 1 H, J = 7, 8-H), 7.06 (t, 1 H, J = 8, 3-H); ^{13}C NMR (20 MHz, C_6D_6) δ: 17.66 (C-10), 19.59 (5-CH_3), 25.81 (9-CH_3), 25.81 (C-7), 32.68 (C-5), 36.99 and 37.03 (C-4 and C-6), 51.69 and 51.81 (OCH_3), 124.89 (C-8), 129.80 (C-2), 131.25 (C-9), 148.48 (C-3), 164.20 (2-CO), 165.76 (C-1); MS m/z 268 (1, M^+), 237 (2, M-CH_3O), 136 (47, $C_{10}H_{16}$). Anal. Calcd for $C_{15}H_{24}O_4$: C, 67.14; H, 9.01. Found: C, 67.19; H, 9.03.

9. Compound 3 is isolated in 82% yield by flash chromatography on SiO_2; SiO_2 is Silica Woelm 32–63 active, Fa. Woelm Pharma, Eschwege or Aldrich Grade 951.

10. Iron(III) chloride on alumina is prepared as follows: A two-necked, round-bottomed flask is equipped with a circular magnetic stirring bar, a rubber septum, and an argon inlet adapter. The flask is flushed with argon and an argon atmosphere is maintained during the reaction. By use of a syringe the reaction flask is charged with dry dichloromethane (160 mL, (Note 1)). Iron(III) chloride from Merck AG, Darmstadt or Fluka Chemie AG, Buchs (10.0 g, 61.6 mmol) is added under argon and the suspension is vigorously stirred. Chromatography-grade neutral or basic alumina from Woelm Pharma, Eschwege (50.0 g) is added in small portions under argon. Stirring is continued for 1 hr to achieve homogeneous adsorption and the solvent is then removed on a rotary evaporator under reduced pressure at room temperature. The rotary evaporator is carefully flushed with argon. After drying under reduced pressure (0.01 atm) for 12 hr, 60 g of alumina-supported iron(III) chloride is obtained that can be stored under argon for several months without substantial loss of catalytic activity.

11. The physical properties of **4a**/**4b** are as follows: R_f 0.56 (diethyl ether/hexane, 1:1); GLC t**(4a)** 16.88 min, t**(4b)** 17.11 min (Chrompack 0.13 •m CpSil 5, 0.32 mm × 25 m; 100°C, 5°C/min), **4a**/**4b** = 98.82: 1.18 ± 0.043, bp 128–129°C/0.5 mbar; $[\alpha]^{20}_D$ –34.6° (CH_3CN, *c* 1,2); IR (film, cm^{-1}) 3065, 1750, 1735, 1645, 1155, 1035, 1020, 895; ^1H NMR (200 MHz, $CDCl_3$) δ: 0.91 (d, 3 H, J = 6.5, 5'-CH_3), 0.95 (dq, 1 H, J = 3.5, 12, 4'-H ax), 1.11 (q, 1 H, J = 11.5, 6'-H ax), 1.24–1.57 (m, 2 H, 3'-H ax,

5'-H ax), 1.65 (multiplet centered, 3 H, 2"-CH_3), 1.57–1.94 (m, 3 H, 3'-H eq, 4'-H eq, 6'-H eq), 2.05 (dt, 1 H, J = 3.0, 11.5, 2'-H), 2.13 (tt, 1 H, J = 3.5, 11.5, 1'-H), 3.56 (d, 1 H, J = 3.5, 2-H), 3.73 (s, 6 H, OCH_3), 4.74 (multiplet centered, 1 H, 1"-H), 4.79 (m, 1 H, 1"-H); double resonance experiment, irradiation at δ 2.13 (1'-H), 3.56 (2-H), 4.79 (1"-H); significant change at δ 3.56 (s, 2-H) and 1.11 (t, 6'-H ax) 2.13 (1'-H), 1.65 (d, 2"-CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) of **4a**/**4b**, δ 18.96/19.36 (C-3"), 22.54/17.89 (5'-CH_3), 32.35/26.27 (C-3'), 32.73/27.32 (C-5'), 34.68/31.09 (C-4'), 36.59/33.47 (C-6'), 39.88/34.33 (C-1'), 48.68 (C-2'), 51.80 and 52.22 (OCH_3), 53.22/53.14 (C-2), 112.43/112.22 (C-1"), 147.52 (C-2"), 169.03 and 170.11/169.95 (C-1 and C-3); MS m/z 268 (4, M^+), 136 (100, $C_{10}H_{16}$). Anal. Calcd for $C_{15}H_{24}O_4$: C, 67.14, H, 9.01. Found: C, 67.22; H, 9.07.

12. A mixture of 4a/**4b** is isolated in 87% yield by flash chromatography on SiO_2; SiO_2 is Silica Woelm 32–63 active, Woelm Pharma, Eschwege or Aldrich Grade 951. Diastereomers 4a and **4b** can be separated by chromatography, (diethyl ether/ petroleum ether, 1:9) which, however, causes loss of material; it is also possible to separate the corresponding diols, that can be obtained by reduction with lithium aluminum hydride ($LiAlH_4$), by crystallization from diethyl ether.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The domino-Knoevenagel-ene reaction is a powerful tool to synthesize five- and six-membered carbocycles.[2,5] The process is exemplified by the diastereoselective synthesis of 4a. Compound 4a has been obtained in both enantiomeric forms and as a racemate according to the procedure described here. The sequence includes the Knoevenagel reaction of citronellal, **1**, and dimethyl malonate, **2**, followed by the intramolecular ene cyclization of the chiral 1,7-diene 3 to yield the trans 1,2-disubstituted products 4a and **4b**. Whereas the thermal cyclization of 3 at 180°C provides 4a and **4b** in a ratio of only 89.7 : 10.3, the Lewis acid promoted reaction can be performed at a lower temperature and shows a much higher diastereoselectivity.[2] If ferric chloride adsorbed on aluminum oxide is used, the reaction can be carried out at −78°C to give 4a and **4b** in a ratio of 98:2 in 87% yield.[2] It should be stressed that $FeCl_3/Al_2O_3$ is employed as a catalyst using about 0.1 equiv. In the ene reaction other Lewis acids such as diethylaluminum chloride (Et_2AlCl) and zinc bromide ($ZnBr_2$) may be used; however, they have to be added in at least equimolar amounts.[2] Compound 4a has been used in the synthesis of terpenoid natural products.[6]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alumina

petroleum ether

brine

(+)- and (±)-citronellal

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ether, diethyl ether (60-29-7)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

acetone (67-64-1)

piperidine (110-89-4)

ferric chloride, iron(III) chloride (7705-08-0)

dichloromethane (75-09-2)

aluminum oxide (1344-28-1)

lithium aluminum hydride (16853-85-3)

zinc bromide (7699-45-8)

hexane (110-54-3)

calcium hydride (7789-78-8)

argon (7440-37-1)

diethylaluminum chloride

citronellal (106-23-0)

dimethyl malonate (108-59-8)

phosphorus pentoxide (1314-56-3)

pulegone (89-82-7)

(R)-(+)-1-(1-Naphthyl)ethylamine (42882-31-5)

Methyl (5R)-2-(methoxycarbonyl)-5,9-dimethyldeca-2,8-dienoate (106431-76-9)

R-citronellal, (R)-Citronellal (2385-77-5)

Dimethyl (1'R,2'R,5'R)-2-(2'-isopropenyl-5'-methylcyclohex-1'-yl)propane-1,3-dioate, DIMETHYL (1'R,2'R,5'R)-2-(2'-ISOPROPENYL-5'-METHYLCYCLOHEX-1'-YL)-PROPANE-1,3-DIOATE

dimethyl malonate, 2

Propanedioic acid, [5-methyl-2-(1-methylethenyl)cyclohexyl]-, dimethyl ester, [1R-(1α,2β,5α)]- (106431-81-6)

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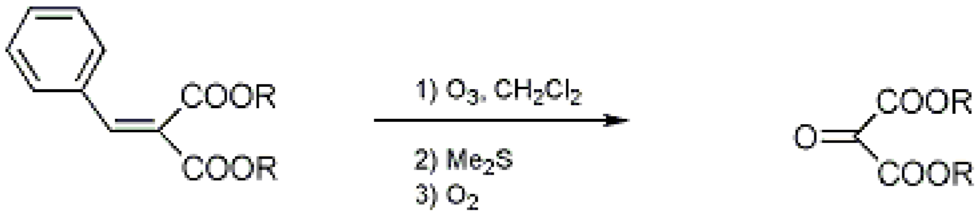
Organic Syntheses, CV 9, 314

DIALKYL MESOXALATES BY OZONOLYSIS OF DIALKYL BENZALMALONATES: DIMETHYL MESOXALATE

[Propanedioic acid, oxo-, dimethyl ester]



Submitted by Lutz F. Tietze and Matthias Bratz[1].
Checked by Makoto Kaino and Hisashi Yamamoto.

1. Procedure

A 300-mL wash bottle with an inlet tube fitted with a wide pore glass frit and equipped with a stirring bar is charged with 40.0 g (0.18 mol) of dimethyl benzalmalonate (Note 1) dissolved in 150 mL of dichloromethane. The cooled solution (0°C, ice bath) is purged with argon (10 min) and then a stream of ozone is passed through with vigorous stirring for 4.5 hr (Note 2). After the reaction is complete (TLC, silica gel, diethyl ether/petroleum ether = 1:1), excess ozone is removed by purging with argon (10 min) and 15 mL of dimethyl sulfide (Note 3) is slowly added at 0°C (ice bath). Stirring is continued for 1 hr at this temperature and 2 hr at ambient temperature. Finally, air is blown through the solution for 12 hr (Note 4) and the residue is distilled at 20 mm, boiling range 90–100°C (Note 5) to give a yellow liquid that is further purified by filtration through 150 g of silica gel (SiO_2) (Note 6) (elution with diethyl ether). The solvent is removed under reduced pressure and the residue is recrystallized from ethyl acetate to give 23.9 g (80%) of the dimethyl mesoxalate hydrate as colorless crystals (Note 7). Dehydration of the product is accomplished by azeotropic removal of water. The hydrate is dissolved in dichloromethane (150 mL) and heated for 12 hr in a Soxhlet apparatus (Note 8) equipped with a thimble containing layers of phosphorus pentoxide and basic alumina. The solvent is then evaporated and the residue distilled at reduced pressure to give 20.1 g (76%) of the ester as a yellow liquid [bp 94°C (20 mm)].

2. Notes

1. Dimethyl benzalmalonate and the corresponding esters of other alcohols can be prepared according to an Organic Syntheses procedure or as described in standard textbooks.[2 3]

2. A Fischer Ozonizator 502 was used. The flow was adjusted to about 70 L/hr and the ozone content to 2–3 vol.%. The checkers used Japan Ozone Co. Ltd. 0–3–2 Ozonator. The flow was adjusted to about 1.3 mmol/min. Efficiency of stirring affects the yield greatly.
3. Dimethyl sulfide (Me_2S) was purchased from Tokyo Kasei; it is also available from Aldrich Chemical Company, Inc.
4. By this procedure the benzaldehyde is oxidized to benzoic acid, which is easily removed from the products.
5. Esters of higher alcohols may be filtered directly through silica gel and further purified by recrystallization.
6. Silica gel is 60 mesh.
7. All ester hydrates prepared were crystalline and can be stored without decomposition.
8. A 250-mL Soxhlet apparatus was used.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The method described is an improved procedure based on a work appearing in the patent literature.[4] Mesoxalates have been prepared by direct oxidation of malonates with selenium dioxide (SeO_2) or nitrogen dioxide (N_2O_4),[5 6 7] by thermolysis of brominated malonates,[8 9] or by oxidative cleavage of malonates with ozone[10 11] or singlet oxygen.[12] Diethyl mesoxalate is commercially available.

The procedure described has advantages over previously published methods. The starting material is easily obtained on a large scale at low cost. The ozonolysis can be conducted even on a large scale (150 g) and the workup is simple since the benzoic acid that is also formed can be removed by distillation, chromatography, or crystallization. The method is general and can be applied to different esters including chiral derivatives such as dimenthyl mesoxalate (see Table).

TABLE
PREPARATION OF DIALKYL MESOXALATES

R	Ester Hydrate		Ester b.p. [°C]
	Yield [%]	m.p.°C (Solvent)	
Me	77	76 (ethyl ether)	110/17 mm
i-Pr	70	56–57 (t-BuOMe/pet. ether)	96/10 mm
Benzyl	86	55–57 (t-BuOMe/pet. ether)	

(–) Menthyl	74	115 (Et_2O/pet. ether)
(–)-Bornyl	42	93–95 (Et_2O/pet. ether)

Mesoxalates are highly reactive substrates because of their strongly polarized carbon-oxygen bond. They have been used in pericyclic processes (e.g. Diels-Alder reactions,[13 14 15 16 17] ene reactions,[18 19] [3+2][20] and [2+2][21] cycloadditions), in aldol[22] and Wittig as well as Friedel-Crafts reactions.[23] Further applications arise from the use of the corresponding imines in hetero Diels-Alder reactions[24 25] and electrophilic cyclizations.[26 27 28 29 30]

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Appendix

Compounds Referenced (Chemical Abstracts Registry Number)

alumina

silica gel

petroleum ether

ethyl acetate (141-78-6)

ethyl ether, diethyl ether (60-29-7)

oxygen (7782-44-7)

Benzoic acid (65-85-0)

benzaldehyde (100-52-7)

selenium dioxide (7446-08-4)

nitrogen dioxide (10102-44-0)

dichloromethane (75-09-2)

ozone (10028-15-6)

dimethyl sulfide (75-18-3)

argon (7440-37-1)

phosphorus pentoxide (1314-56-3)

Dimethyl mesoxalate, Propanedioic acid, oxo-, dimethyl ester (3298-40-6)

dimethyl benzalmalonate (6626-84-2)

dimethyl mesoxalate hydrate

Diethyl mesoxalate (609-09-6)

dimenthyl mesoxalate

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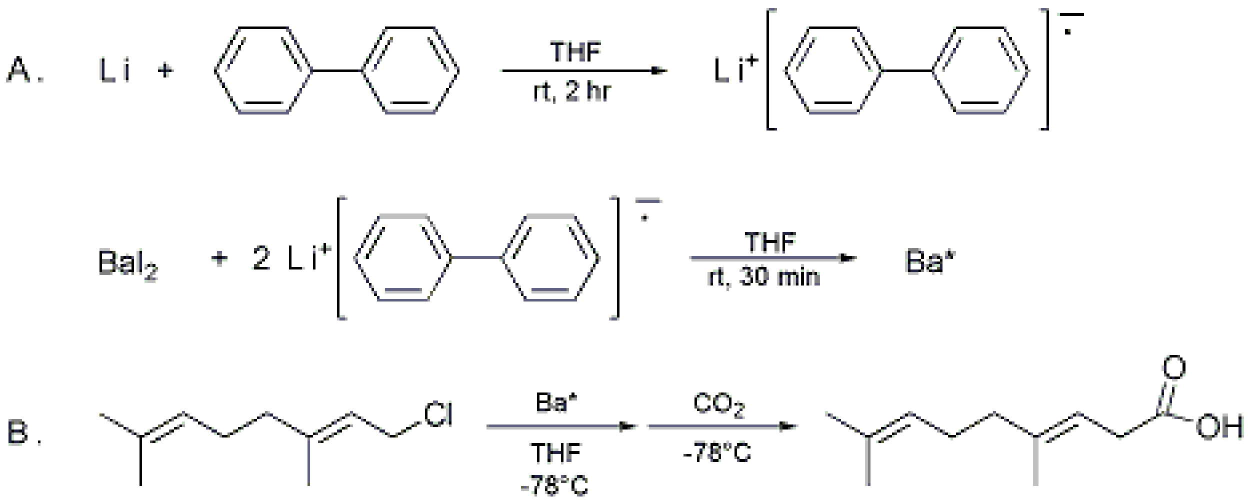
Organic Syntheses, CV 9, 317

REGIO- AND STEREOSELECTIVE CARBOXYLATION OF ALLYLIC BARIUM REAGENTS: (E)-4,8-DIMETHYL-3,7-NONADIENOIC ACID

[3,7-Nonadienoic acid, 4,8-dimethyl-, (E)-]



Submitted by Akira Yanagisawa, Katsutaka Yasue, and Hisashi Yamamoto[1].
Checked by D. Scott Coffey and William R. Roush.

1. Procedure

A. *Active barium*. An oven-dried, three-necked, round-bottomed, 300-mL flask, equipped with a Teflon-coated magnetic stirring bar, is flushed with argon (Note 1). Freshly cut lithium (210 mg, 30.3 mmol) and biphenyl (4.7 g, 30.5 mmol) are placed in the apparatus and covered with dry tetrahydrofuran (THF) (80 mL) (Note 2), and the mixture is stirred for 2 hr at room temperature (Note 3). In a separate, oven-dried, three-necked, round-bottomed, 500-mL flask, equipped with a Teflon-coated magnetic stirring bar and a 100-mL addition funnel, is placed anhydrous barium iodide (BaI_2) (6.0 g, 15.3 mmol) ((Note 4), (Note 5)) under an argon atmosphere; this is covered with dry THF (80 mL), and stirred for 5 min at room temperature. To the resulting yellowish solution of BaI_2 in THF is added at room temperature a solution of the lithium biphenylide through a stainless steel cannula under an argon stream. The reaction mixture is stirred for 1 hr at room temperature, and the resulting dark brown suspension of active barium thus prepared is ready for further use.

B. *(E)-4,8-Dimethyl-3,7-nonadienoic acid*. To the suspension of active barium in THF is added dropwise over 20 min a solution of geranyl chloride (1.19 g, 6.89 mmol) (Note 6) in THF (40 mL) from the 100-mL dropping funnel at −78°C (Note 7), and the

mixture is stirred at this temperature for 30 min (Note 8). An excess of dry ice (ca. 10 g) (Note 9) is added at −78°C and stirring continued for 10 min. The reaction mixture is quenched with 1 N hydrochloric acid (HCl) (40 mL) at −78°C, warmed to room temperature, and poured into a mixture of water (H_2O) (200 mL) and ethyl acetate (EtOAc) (200 mL). After the organic layer is shaken vigorously, it is separated and washed with dilute sodium thiosulfate solution (200 mL). The two aqueous layers are combined, acidified (pH <3) with concd HCl, and extracted twice with EtOAc (2 × 100 mL). The combined organic extracts are washed with H_2O (200 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue is then dissolved in methanol (MeOH) (10 mL) by gentle heating and placed in a freezer (0°C) for over 1 hr to crystallize the biphenyl. The white solid is filtered off (Note 10), washed with cold MeOH (0°C, 40 mL), and the filtrate is concentrated under reduced pressure. The residual oil is purified by flash-column chromatography on silica gel (70 g, (Note 11)) using 2% EtOAc/hexane (500 mL), 20% EtOAc/hexane (600 mL), and then 30% EtOAc/hexane (1 L) as eluant, to afford the crude β,γ-unsaturated carboxylic acid (1.43 g). An additional vacuum distillation (106°C/0.4 mm, (Note 12)) provides pure (E)-4,8-dimethyl-3,7-nonadienoic acid (0.91–0.96 g, 72–76% yield, (Note 13), (Note 14), (Note 15)) as a colorless oil. The isomeric purity is determined to be ≥ 97 : 3 [(E/Z) of 98 : 2 and α:γ of >99 : 1] by GC analysis after conversion to the corresponding methyl ester (Note 16).

2. Notes

1. The submitters used standard grade argon gas (oxygen <10 ppm) which was further purified by passing through a GAS CLEAN column (GC-RX, NIKKA SEIKO Co.) to remove traces of oxygen. The checkers used UHP/Zero grade argon that was passed through a tube of Dri-Rite before use. However, no special precautions were made to remove oxygen.

2. Lithium (wire, 99.9%) was purchased from Aldrich Chemical Company, Inc., (submitters) or EM Science (checkers). The wire was cut into 20–30-mg pieces that were rinsed with dry hexane before use. Biphenyl (guaranteed reagent) was used as purchased from Nacalai Tesque (submitters) or EM Science (checkers). The submitters used dry THF as purchased from Aldrich Chemical Company, Inc. (anhydrous, 99.9%). The checkers used THF (99.5%, EM Science) that was distilled from benzophenone ketyl.

3. The submitters reported that lithium was completely consumed within 2 hr at room temperature (20 25°C). However, the checkers found that a small amount of Li (ca. 20–40 mg) remained at the end of the reaction.

4. The submitters report that $BaI_2 \cdot 2H_2O$ purchased from Nacalai Tesque (extra pure reagent), Aldrich Chemical Company, Inc., Fluka Chemical Corp., Kishida Chemical, or Wako Pure Chemical can be used with equal efficiency. The checkers used $BaI_2 \cdot 2H_2O$ purchased from Aldrich Chemical Company, Inc.

5. The submitters prepared anhydrous BaI_2 by drying $BaI_2 \cdot 2H_2O$ at 150°C for 2 hr under reduced pressure (<10 mm). However, the checkers were unsuccessful

in attempts to generate active barium from BaI_2 that was dried according to these specifications. The checkers obtained good results when finely ground $BaI_2·2H_2O$ was dried at 150°C (1–2 mm) for 12–24 hr while being stirred (see (Note 13)). The color of the $BaI_2·2H_2O$ changes from light yellow to white during the first 1–2 hr, with no subsequent color changes observed.

6. Geranyl chloride (95%, Aldrich Chemical Company, Inc.) was purified by distillation immediately before use.

7. A 5-L Dewar flask (I.D. 200 mm) was employed for the −78°C cooling bath (dry ice/methanol).

8. A dark red suspension or wine-red solution is obtained.

9. Dry ice was cut into appropriate size pieces and added from the middle inlet of the three-necked, round-bottomed flask. The checkers obtained good results (65–74%) by bubbling carbon dioxide (CO_2) gas (Air Products and Chemicals, Inc.) vigorously into the reaction mixture through an 18-gauge needle for 20 min. The CO_2 was dried by passing through sulfuric acid and then through a drying tube packed with Dri-Rite.

10. After recrystallization (methanol) ca. 2.8 g of biphenyl was recovered (60%).

11. Silica gel 60 (E. Merck 9385, 230–400 mesh) was used.

12. A bulb to bulb distillation apparatus was used. The checkers found the bp to be 104–110°C/0.4 mm.

13. The checkers obtained 0.93 g of product (74% yield) with isomeric purity of 97 : 3 from an experiment run with 210 mg of lithium (Li), BaI_2 that was dried for 24 hr (see (Note 5)), and CO_2 gas. The yield was 62–65% (isomeric purity 97 : 3) from experiments run with 230 mg of Li and BaI_2 that was dried for only 12–14 hr; one experiment was quenched with dry ice and the other with CO_2 gas.

14. The physical properties of (E)-4,8-dimethyl-3,7-nonadienoic acid are as follows: TLC R_f = 0.50 (1:1 ethyl acetate/hexane); bp 106°C/0.4 mm; IR (neat) cm^{-1}: 2969, 2919, 1713, 1416, 1300, 1225, 1156, 1109, 941, 831; ^1H NMR (200 MHz, $CDCl_3$) δ: 1.60 (s, 3 H, CH_3), 1.65 (s, 3 H, CH_3), 1.68 (s, 3 H, CH_3), 2.07 (m, 4 H, 2 CH_2), 3.10 (d, 2 H, J = 7.0, CH_2), 5.05–5.13 (m, 1 H, vinyl), 5.31 (t, 1 H, J = 7.0, vinyl), 10.2–11.4 (br, 1 H, CO_2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 16.4, 17.7, 25.7, 26.4, 33.5, 39.5, 114.9, 123.9, 131.7, 139.8, 178.8; MS (EI) m/e (rel intensity): 170 (5.86, M-12), 149 (7.45), 139 (17.87), 122 (9.11), 69 (62.75); MS (FAB) m/e 183 (M^++1). Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.51; H, 10.20.

15. The checkers performed this procedure on five times the reported scale and obtained 2.6 g (41%) of crude (impure) (E)-4,8-dimethyl-3,7-nonadienoic acid following chromatographic purification.

16. GC analysis was performed on a Shimadzu GC-8A instrument equipped with a flame ionization detector and a capillary column of PEG-HT (0.25 × 25000 mm) using nitrogen as carrier gas.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the

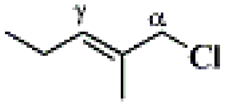
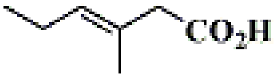
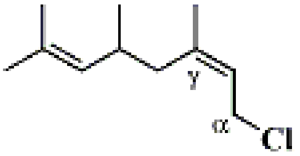
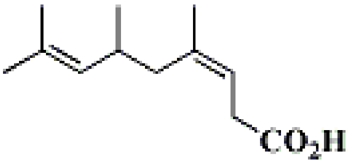
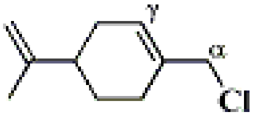
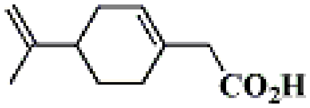
Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

β,γ-Unsaturated carboxylic acids and their derivatives are valuable synthetic intermediates for various natural products. Two typical multi-step processes for the synthesis of β,γ-unsaturated acids, Knoevenagel reaction/isomerization with base[2 3 4 5 6] and allylic cyanide/hydrolysis,[7 8 9 10 11 12] are those most commonly used. Other new methods have been developed;[13,14,15 16 17 18 19 20,21] however, there is a problem with E/Z stereoselectivity. One straightforward way to obtain β,γ-unsaturated acids is by the carboxylation of an allyl metal intermediate. In the substituted allylic series, the reaction usually occurs at the more sterically hindered terminus.[22] A stereospecific route for the synthesis of homogeranic acid and homoneric acid by carboxylation of the lithiated allylic sulfone has also been reported.[23] In contrast, we have found that allylic barium reagents are prepared directly by reaction of in situ generated barium metal with various allylic chlorides, and react with carbonyl compounds or allylic halides in a highly α-selective manner without loss of the double bond geometry.[24 25] As illustrated in the present procedure, treatment of the allylic barium reagent with excess carbon dioxide results in α-carboxylation, whereas γ-carboxylation occurred with allylic magnesium reagent.[22] Results of carboxylation of allylic barium reagents are summarized in the Table.[26 27] The characteristic features of the reaction are as follows: (1) Allylic barium reagents generated from a variety of γ-mono- and γ-disubstituted allyl chlorides showed high α-selectivities without exception. (2) The double-bond geometry of the allyl chloride precursor was completely retained in each case. (3) The alkyl substituent at the β-position of an allylic barium reagent had no effect on the regioselectivity.

TABLE
REGIO- AND STEREOSELECTIVE CARBOXYLATION OF ALLYLIC BARIUM REAGENTS

Allylic chloride[a]	Product	Yield, %[b]	α : γ[X]	E : Z[c]
(E)-$C_7H_{15}\overset{\gamma}{C}H=CH\overset{\alpha}{C}H_2Cl$	(E)-$C_7H_{15}CH=CHCH_2CO_2H$	82	98 : 2	99 : 1
(Z)-$C_7H_{15}\overset{\gamma}{C}H=CH\overset{\alpha}{C}H_2Cl$	(Z)-$C_7H_{15}CH=CHCH_2CO_2H$	65	82 : 18	1 : 99

		58	95 : 5	99 : 1
γ α $(CH_3)_2C=CHCH_2Cl$	$(CH_3)_2C=CHCH_2CO_2H$	59	>99 : 1	
		51	>99 : 1	<1 : 99
		79	98 : 2	

[a]Stereochemically pure (>99%) allylic chloride was used. [b]Isolated yield. [c]Determined by GC analysis after conversion to methyl ester.

In conclusion, this is one of the most straightforward and practical methods available for the regioselective and stereospecific synthesis of β,γ-unsaturated carboxylic acids.

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

benzophenone ketyl

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ethyl acetate, EtOAc (141-78-6)

methanol (67-56-1)

oxygen (7782-44-7)

sodium thiosulfate (7772-98-7)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

Biphenyl (92-52-4)

barium (7440-39-3)

lithium (7439-93-2)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

hexane (110-54-3)

argon (7440-37-1)

Geranyl chloride (5389-87-7)

Lithium biphenylide (34467-57-7)

diethyl oxomalonate (609-09-6)

(E)-4,8-Dimethyl-3,7-nonadienoic acid, 3,7-Nonadienoic acid, 4,8-dimethyl-, (E)- (459-85-8)

barium iodide (13718-50-8)

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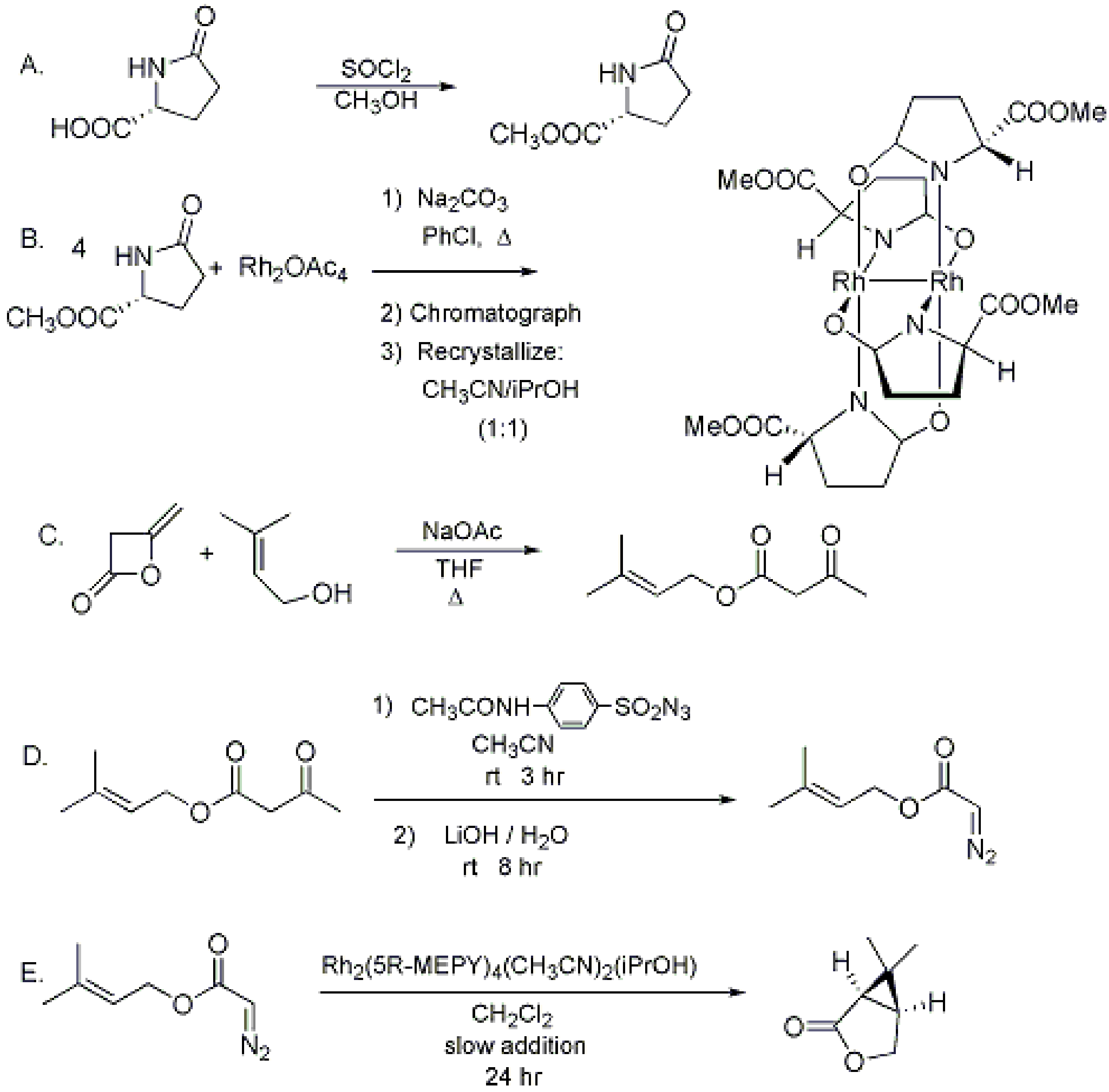
Organic Syntheses, *CV 9, 322*

(1R,5S)-(−)-6,6-DIMETHYL-3-OXABICYCLO[3.1.0] HEXAN-2-ONE. HIGHLY ENANTIOSELECTIVE INTRAMOLECULAR CYCLOPROPANATION CATALYZED BY DIRHODIUM(II) TETRAKIS[METHYL 2-PYRROLIDONE-5(R)-CARBOXYLATE]

[3-Oxabicyclo[3.1.0]hexan-2-one, 6,6-dimethyl-, (1R-cis)-]



Submitted by Michael P. Doyle, William R. Winchester, Marina N. Protopopova, Amy P. Kazala, and Larry J. Westrum[1].
Checked by Robert K. Boeckman, Jr., Jacqueline C. Bussolari, and Michael R. Reeder.

1. Procedure

Caution! Thionyl chloride is a reactive substance that must be handled in a fume hood.

A. *(−)-Methyl 2-pyrrolidone-5(R)-carboxylate*. A 500-mL, single-necked, round-bottomed flask, equipped with a Teflon-coated magnetic stirring bar, loose fitting rubber septum, and a needle for nitrogen inlet which is vented through a mineral oil bubbler, is flushed with nitrogen and charged with 6.60 g (51.1 mmol) of (R)-(+)-2-pyrrolidone-5-carboxylic acid (Note 1) and 200 mL of methanol (Note 2). Thionyl chloride (0.50 mL, 6.8 mmol) is added cautiously by syringe over a 0.5-min period to the rapidly stirring solution at room temperature. The reaction flask is sealed with the septum and the nitrogen inlet removed after addition is complete, and the resulting solution is stirred continuously at room temperature for 24 hr. The flask is uncapped, and aqueous, saturated sodium carbonate is added with stirring until the reaction solution is pH 7 to litmus paper (Note 3). After removal of the methanol at room temperature under reduced pressure by rotary evaporator, the residue is dissolved in 50 mL of dichloromethane and washed with 10 mL of aqueous, saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue is distilled through a short-path distillation apparatus to afford 5.60 g (75% yield) of colorless methyl (R)-2-pyrrolidone-5-carboxylate, bp 83°C (0.25 mm), $[\alpha]_D^{24}$ −8.6° (EtOH, *c* 1.13) (Note 4).

B. *(+)-Dirhodium(II) tetrakis[methyl 2-pyrrolidone-5(R)-carboxylate] acetonitrile-isopropanol solvate*, (+)-Rh_2 [(5R)-MEPY]$_4$ $(CH_3CN)_2$ (*i*-PrOH). A 50-mL, single-necked, round-bottomed flask, equipped with a Teflon-coated stirring bar and nitrogen inlet, is flushed with nitrogen and charged with 200 mg (0.452 mmol) of rhodium(II) acetate (Note 5), 1.02 g (7.13 mmol) of methyl 2-pyrrolidone-5(R)-carboxylate, and 20 mL of chlorobenzene (Note 6). The flask is fitted with a Soxhlet extraction apparatus (Note 7) into which is placed a thimble containing 5 g of an oven-dried mixture of 2 parts sodium carbonate and 1 part of sand (Note 8). The initially green rhodium acetate, upon mixing with the pyrrolidonecarboxylate forms a blue solution, which is heated at reflux under nitrogen for 6 hr (Note 9); removal of the solvent under reduced pressure using a rotary evaporator yields a blue, glass-like solid. The solid is dissolved in a minimal volume of methanol and purified by chromatography on a column containing J.T. Baker BAKERBOND Cyano 40 •m prep LC pacKing (10 g) in methanol. The dirhodium(II) product forms a broad blue band across the top of the column, which moves imperceptively with methanol. However, the excess ligand moves rapidly as a yellow/brown band in methanol and may be collected with the first 100 mL of eluent (Note 10). Subsequent elution with 1.0 vol % acetonitrile in methanol causes an instantaneous color change from blue to red and rapid elution. The entire red band is collected as one fraction, and the solvent is removed under reduced pressure (Note 11), (Note 12). The resulting blue, glass-like solid (380 mg) is recrystallized by dissolving the solid in 1.0 mL of acetonitrile per 100 mg of solid and then adding an equivalent amount of isopropyl alcohol. Bright red crystals of Rh_2 (5R-MEPY)$_4$ $(CH_3CN)_2$ (i-PrOH) form overnight, and are collected by suction, washed with isopropyl alcohol and air-dried to yield 240 mg (0.262 mmol, 58% yield) (Note 13).

C. *3-Methyl-2-buten-1-yl acetoacetate*. A 500-mL, three-necked, round-bottomed flask, equipped with a Teflon-coated magnetic stirring bar, stoppered pressure-equalizing addition funnel and a reflux condenser bearing a drying tube, is charged with a solution of 21.5 g (0.250 mol) of 3-methyl-2-buten-1-ol in 70 mL of anhydrous tetrahydrofuran and 1.20 g (0.015 mol) of sodium acetate (Note 14). The reaction mixture is heated at reflux with continuous magnetic stirring, and a solution of 23.5 g (0.280 mol) of freshly distilled diketene in 30 mL of tetrahydrofuran is added dropwise via the addition funnel over 1 hr (Note 15). The reaction mixture is heated at reflux for an additional 30 min upon completion of the addition. The brown reaction mixture is cooled to room temperature, transferred to a separatory funnel containing 300 mL of ether and 50 mL of saturated aqueous sodium chloride solution, mixed thoroughly, and the aqueous layer withdrawn. The aqueous layer is extracted twice with 50-mL portions of ether, and the combined ether solution is washed twice with 50-mL portions of saturated aqueous sodium chloride solution. After the organic layer is dried over anhydrous magnesium sulfate, the solvent is removed under reduced pressure, and the brown residue is distilled (bp 85°C, 0.15 mm) to afford 28.9 g (68% yield) of 3-methyl-2-buten-1-yl acetoacetate as a colorless liquid (Note 16).

D. *3-Methyl-2-buten-1-yl diazoacetate*. A 1-L, three-necked, round-bottomed flask, equipped with a Teflon-coated magnetic stirring bar and a stoppered, pressure-equalizing addition funnel is charged with a solution of 30.5 g (0.179 mmol) of 3-methyl-2-buten-1-yl acetoacetate and 23.3 g (0.231 mol) of triethylamine> in 150 mL of anhydrous acetonitrile (Note 16). A solution of 55.85 g (0.233 mol) of p-acetamidobenzenesulfonyl azide in 150 mL of acetonitrile is added dropwise over 30 min with continuous magnetic stirring (Note 17). A white precipitate of p-acetamidobenzenesulfonamide is observed after 30 min (additional acetonitrile is added if necessary to facilitate stirring). The resulting heterogeneous yellow mixture is maintained at room temperature for an additional 2.5–3 hr (Note 18). A solution of 24.6 g (0.586 mol) of lithium hydroxide ($LiOH·H_2O$) in 200 mL of water is added to the reaction mixture (the precipitate dissolves), and the resulting light brown mixture is stirred for 8 hr (Note 19). The reaction mixture is extracted with two 50-mL portions of 2:1 ether:ethyl acetate. The combined organic phases are washed with one 25-mL portion of saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, and the solvent is removed under reduced pressure. The resulting orange liquid, containing some solid sulfonamide, is purified by flash column chromatography on silica (200 g) with 1:10 ethyl acetate:hexane as the eluent. Collection of the yellow band and concentration under reduced pressure affords 22.39 g (81% yield) of 3-methyl-2-butenyl diazoacetate as a yellow oil (Note 20).

E. *(1R,5S)-(−)-6,6-Dimethyl-3-oxabicyclo[3.1.0]hexan-2-one*. A 1-L, three-necked, round-bottomed flask, equipped with a stoppered pressure-equalizing addition funnel and a reflux condenser bearing a drying tube and a nitrogen inlet vented through a mineral oil bubbler, is charged with a solution of 0.203 g (0.221 mmol) of Rh_2 (5R-MEPY)$_4$ (CH_3CN)$_2$ (i-PrOH) in 150 mL of freshly distilled, anhydrous dichloromethane (Note 21). The apparatus is flushed with nitrogen and the reaction mixture is heated at reflux during the dropwise addition of a solution of 14.9 g (96.7 mmol) of 3-methyl-2-buten-1-yl diazoacetate in 450 mL of anhydrous dichloromethane over a 30-hr period. The slow flow of external inert gas

is terminated after 1 hr, and the evolution of nitrogen from the reaction solution is used to monitor the progress of the reaction. After the addition is complete, the blue reaction mixture is heated at reflux for an additional hour, cooled to room temperature, and the solvent is removed from the green reaction mixture under reduced pressure. Kugelrohr distillation of the residue (80°C, 0.15 mm) affords 12.1 g of a nearly colorless liquid that upon chromatographic purification on silica-alumina (100 g) with hexane:ethyl acetate (80:20 to 70:30) affords 10.2–10.7 g (84–88% yield) of >99% pure (1R,5S)-(−)-6,6-dimethyl-2-oxabicyclo- [3.1.0]hexan-2-one, bp 70°C (0.15 mm), $[\alpha]_D^{24}$ −81.2° ($CHCl_3$, *c* 2.4) (Note 22), whose optical purity was determined on a Chiraldex B-PH capillary column to be 92–93% ee (Note 23). The solid residue remaining after Kugelrohr distillation is dissolved in a minimal volume of methanol and purified by chromatography, as described in Part B. Isolation of the red band affords 0.098–0.099 g (49%) of recovered catalyst (Note 24).

2. Notes

1. (R)-(+)-2-Pyrrolidone-5-carboxylic acid [Fluka Chemika-BioChemika, D-pyroglutamic acid, $[\alpha]_D^{22}$ +9±1° (H_2O, *c* 5)] was recrystallized from ethanol/ether (2/1), $[\alpha]_D^{22}$ +10° (H_2O, *c* 0.97), prior to use.

2. HPLC grade methanol (Aldrich Chemical Company, Inc.) was used without further purification.

3. This titration generally requires the addition of 8 mL of aqueous, saturated sodium carbonate solution.

4. The literature value for this ester is reported to be $[\alpha]_D$ −8.7° (EtOH, *c* 1.13).[2] The NMR spectra are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.18–2.56 (m, 4 H), 3.78 (s, 3 H), 4.26 (dd, 1 H, J = 8.5, 5.1), 6.25 (s(br), 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 25.3, 29.9, 53.1, 56.1, 173.3, 179.1.

5. Rhodium(II) acetate is obtained commercially (Degussa Corporation, Aldrich Chemical Company, Inc., AESAR/Johnson Matthey, or Johnson Matthey/Alfa Products) or prepared from rhodium(III) chloride hydrate (Johnson Matthey) by the standard literature procedure.[3]

6. Chlorobenzene was distilled under nitrogen from calcium hydride (−4 to +40 mesh) prior to use.

7. A micro Soxhlet extraction apparatus (Ace Glass, Inc.) consisting of the extractor, a 50-mL round-bottomed flask, and an Allihn condenser fitted with a 10 × 50 mm thimble is used.

8. Sodium carbonate is used to trap acetic acid liberated in the ligand exchange reaction. Sand is included to maintain the porosity of the solid. A layer of sand at the top of the carbonate mixture prevents sodium carbonate from entering the reaction flask.

9. When the reaction is followed by HPLC using a •-Bondapak-CN column with 2% acetonitrile in methanol as the eluent, two bands are observed initially: a broad band eluting with the solvent front [chlorobenzene and excess methyl 2-pyrrolidone-5(R)-carboxylate] and a second band at 1.6 min when the flow rate is 1.5 mL/min [rhodium(II) acetate]. As the reaction progresses, the rhodium(II) acetate band

diminishes and is replaced by several bands with longer retention volumes until one major band, in addition to that for chlorobenzene and ligand, is observed at about 4 min. Only minor impurities elute at intermediate times. A brown-black material, insoluble in all common solvents, is observed in some preparations. The origin of this material is unknown, but its presence decreases product yield by 25%.

10. Unreacted methyl 2-pyrrolidone-5(R)-carboxylate may be reisolated by distillation (70% recovery) without loss of optical purity.

11. This material is >95% pure by HPLC analysis.

12. Direct recrystallization is an alternative to chromatography, but decreased yields result because of the large amount of unreacted ligand present. In this procedure 1 mL of acetonitrile is added to the crude, blue glass-like solid. The resulting solution is filtered through glass wool and 5 mL of isopropyl alcohol is added. Overnight refrigeration gives a 38% yield of red crystals that are identical with those described in the procedure.

13. This procedure produced analytically pure crystals with the following physical properties: Anal. Calcd for $C_{31}H_{46}N_6O_{13}Rh_2$: C, 40.63; H, 5.06; N, 9.17. Found: C, 40.37, H, 5.11; N, 9.12; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.21 (d, 6 H, J = 6.1), 1.35 (d, 1 H, J = 4.4), 1.8–2.4 (m, 12 H), 2.26 (s, 6 H), 2.55–2.70 (m, 4 H), 3.68 (s, 6 H), 3.70 (s, 6 H), 3.95 (dd, 2 H, J = 8.6, 2.1), 3.96–4.08 (m, 1 H), 4.32 (dd, 2 H, J = 8.8, 3.0); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 2.9, 25.0, 25.2, 26.0, 31.2, 31.4, 51.6, 51.9, 64.0, 66.4, 66.6, 114.9, 175.5, 175.7, 188.3, 188.5. $[\alpha]_D^{24}$ +270.6° (CH_3CN, *c* 0.112).

14. Tetrahydrofuran was distilled from lithium aluminum hydride.

15. This reaction has an induction period. If too much diketene is added before condensation begins, an exotherm may result. Reaction onset is evident by a color change and a significant increase in temperature.

16. The NMR spectra are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.72 (s, 3 H), 1.79 (s, 3 H), 2.27 (s, 3 H), 3.45 (s, 2 H), 4.64 (d, 2 H, J = 7.3), 5.32–5.40 (m, 1 H); enol form at 1.96 (s) and 4.99 (s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 18.5, 26.2, 30.5, 50.5, 62.6, 118.6, 140.2, 167.7, 201.2 (minor amounts of the enol tautomer may also be present).

17. Commercially available p-acetamidobenzenesulfonyl azide (Aldrich Chemical Company, Inc.) was preferred over p-dodecylbenzenesulfonyl azide (Danheiser, R. L.; Miller, R. F.; Brisbois, R. G. *Org. Synth., Coll. Vol. IX* **1998**, 197, Note 9; Ref. 4a), or methanesulfonyl azide[4] for reasons of safety, yield, and ease of manipulation. See also Davies, H. M. L.; Cantrell, Jr., W. R.; Romines, K. R.; Baum, J. S. *Org. Synth., Coll. Vol. IX* **1998**, 422.

18. After this time, no starting β-keto ester is observed upon analysis by TLC.

19. The principal reaction competing with deacylation is ester hydrolysis.

20. The spectral properties are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.72 (s, 3 H), 1.77 (s, 3 H), 4.66 (d, 2 H, J = 7.3), 4.74 (s, 1 H), 5.32–5.39 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 18.4, 26.2, 46.6, 62.2, 119.2, 139.7, 167.4; IR (thin film) cm^{-1}: 2109 ($C=N_2$), and 1694 (C=O).

21. Dichloromethane was distilled from phosphorus pentoxide and stored under nitrogen. All glassware was oven dried.

22. The NMR spectra are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.17 (s, 3 H),

1.18 (s, 3 H), 1.93 (d, 1 H, J = 6.2), 2.04 (dd, 1 H, J = 6.2, 5.5), 4.13 (d, 1 H, J = 9.8), 4.35 (dd, 1 H, J = 9.8, 5.5); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.2, 25.0, 29.9, 30.3, 66.4, 174.9. Enantiomerically pure (1R,5S)-(−)-6,6-dimethyl-3-oxabicyclo[3.1.0] hexan-2-one is reported to have $[\alpha]^{25}_{D}$ −89.9° ($CHCl_3$, *c* 1.4) (calculated).[5]

23. A 30 m × 0.32 mm ID Chiraldex B-PH (β-cyclodextrin) column was used under isothermal conditions at 120°C. Retention time of the (1R,5S)-enantiomer was 16.9 min, while the (1S,5R)-enantiomer eluted at 17.9 min. The submitters report that separation also occurred on a 30-m Chiraldex γ-cyclodextrin trifluoroacetate column operated at 140°C; retention times were 14.2 min (1R,5S-enantiomer) and 18.9 min (1S,5R-enantiomer).

24. The submitters report that the recovered catalyst can be reused in the same reaction; (1R,5S)-(−)-6,6-dimethyl-3-oxabicyclo[3.1.0]hexan-2-one was formed in 83% yield and 88% ee.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

This is the first detailed procedure for the synthesis of a chiral dirhodium(II) carboxamide catalyst and its application to intramolecular cyclopropanation. The preparation of the ligand, methyl 2-pyrrolidone-5(R)-carboxylate, is adapted from the procedure of Ackermann, Matthes, and Tamm.[2] The method for ligand displacement from dirhodium(II) tetraacetate is an extension of that reported for the synthesis of dirhodium(II) tetraacetamide.[6] The title compound, (1R,5S)-(−)-6,6-dimethyl-3-oxabicyclo[3.1.0]hexan-2-one, is a synthetic precursor to (1R,3S)-(+)-cis-chrysanthemic acid.[5]

Dirhodium(II) tetrakis[methyl 2-pyrrolidone-5(R)-carboxylate], Rh_2 (5R-MEPY)$_4$, and its enantiomer, Rh_2 (5S-MEPY)$_4$, which is prepared by the same procedure, are highly enantioselective catalysts for intramolecular cyclopropanation of allylic diazoacetates (65-≥94% ee) and homoallylic diazoacetates (71–90% ee),[7,8] intermolecular carbon-hydrogen insertion reactions of 2-alkoxyethyl diazoacetates (57–91% ee)[9] and N-alkyl-N-(tert-butyl) diazoacetamides (58–73% ee),[10] intermolecular cyclopropenation of alkynes with ethyl diazoacetate (54–69% ee) or menthyl diazoacetates (77–98% diastereomeric excess, de),[11] and intermolecular cyclopropanation of alkenes with menthyl diazoacetate (60–91% de for the cis isomer, 47–65% de for the trans isomer).[12] Their use in ≤1.0 mol % in dichloromethane solvent effects complete reaction of the diazo ester and provides the carbenoid product in 43–88% yield. The same general method used for the preparation of Rh_2 (5R-MEPY)$_4$ was employed for the synthesis of their isopropyl[7] and neopentyl[9] ester analogs.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica-alumina

(1R,5S)-(−)-6,6-DIMETHYL-3-OXABICYCLO[3.1.0]HEXAN-2-ONE

DIRHODIUM(II) TETRAKIS[METHYL 2-PYRROLIDONE-5(R)-CARBOXYLATE

(−)-Methyl 2-pyrrolidone-5(R)-carboxylate

(+)-Dirhodium(II) tetrakis[methyl 2-pyrrolidone-5(R)-carboxylate]

(1R,5S)-(−)-6,6-dimethyl-2-oxabicyclo- [3.1.0]hexan-2-one

dirhodium(II) tetraacetamide

ethanol (64-17-5)

acetic acid (64-19-7)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether (60-29-7)

sodium acetate (127-09-3)

acetonitrile (75-05-8)

thionyl chloride (7719-09-7)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

nitrogen (7727-37-9)

diketene (674-82-8)

chlorobenzene (108-90-7)

isopropyl alcohol (67-63-0)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

ethyl diazoacetate (623-73-4)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

hexane (110-54-3)

triethylamine (121-44-8)

calcium hydride (7789-78-8)

lithium hydroxide (1310-65-2)

phosphorus pentoxide (1314-56-3)

rhodium(II) acetate

methanesulfonyl azide

p-Acetamidobenzenesulfonyl azide (2158-14-7)

p-acetamidobenzenesulfonamide (121-61-9)

p-dodecylbenzenesulfonyl azide (79791-38-1)

Menthyl

3-Oxabicyclo[3.1.0]hexan-2-one, 6,6-dimethyl-, (1R-cis)- (71565-25-8)

Methyl (R)-2-pyrrolidone-5-carboxylate, Methyl 2-pyrrolidone-5(R)-carboxylate (64700-65-8)

(R)-(+)-2-pyrrolidone-5-carboxylic acid, D-pyroglutamic acid (4042-36-8)

rhodium acetate

3-Methyl-2-buten-1-yl acetoacetate (21597-32-0)

3-methyl-2-buten-1-ol (556-82-1)

3-Methyl-2-buten-1-yl diazoacetate, 3-Methyl-2-butenyl diazoacetate (72800-60-3)

rhodium(III) chloride hydrate

dirhodium(II) tetraacetate (15956-28-2)

(1R,3S)-(+)-cis-chrysanthemic acid

menthyl diazoacetate

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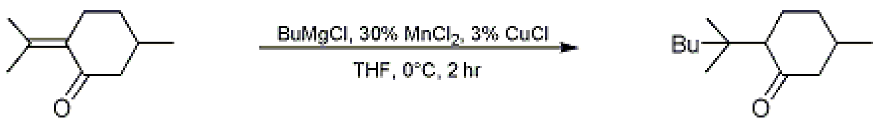
MANGANESE-COPPER-CATALYZED CONJUGATE ADDITION OF ORGANOMAGNESIUM REAGENTS TO α,β-ETHYLENIC KETONES: 2-(1,1-DIMETHYLPENTYL)-5-METHYL-CYCLOHEXANONE FROM PULEGONE

[Cyclohexanone, 2-(1,1-dimethylpentyl)-5-methyl-]



Submitted by S. Marquais, M. Alami, and G. Cahiez[1].
Checked by Todd Gane and Stephen F. Martin.

1. Procedure

A 500-mL, three-necked, round-bottomed flask is equipped with a mechanical stirrer, 100-mL, pressure-equalizing dropping funnel, and a Claisen head fitted with a low-temperature thermometer and a nitrogen inlet (Note 1). The flask is charged with 80 mL of anhydrous tetrahydrofuran (THF, (Note 2)), 1.9 g (15 mmol) of anhydrous manganese chloride (Note 3), 0.15 g (1.5 mmol) of cuprous chloride (Note 4), 1.28 g (30 mmol) of lithium chloride (Note 5), and 7.61 g (50 mmol) of (R)-(+)-pulegone (Note 6). The mixture is stirred at room temperature until dissolution of the salts is complete (1 to 2 hr) (Note 7), then a solution of butylmagnesium chloride (58 mmol) in THF (Note 8) is added dropwise at 0°C over a 25–30 min period. Stirring is continued for 1.5 hr at 0°C. The reaction mixture is hydrolyzed by dropwise addition of 2 M hydrochloric acid (HCl, 100 mL). After addition of 80 mL of petroleum ether (35–60°C) and decantation (Note 9), the aqueous layer is extracted three times with 100-mL portions of petroleum ether (35–65°C). The combined organic layers are successively washed with 50 mL of 1 M HCl, 50 mL of a diluted ammonium chloride/ammonium hydroxide (NH_4Cl/NH_4OH) solution and 50 mL of a saturated sodium bicarbonate solution, then dried over magnesium sulfate. After filtration, the solvents are removed with a rotary evaporator (20 mm, room temperature). The product is obtained in crude form in almost quantitative yield as a 61.5:38.5 mixture of diastereoisomers, purity > 96% (Note 10). Distillation under reduced pressure affords 9.85 g of pure 2-(dimethylpentyl)-5-methylcyclohexanone (94%, (Note 12)), bp 101–105°C (3 mm).

2. Notes

1. The apparatus is flame-dried under a stream of dry nitrogen or argon. Later a slight positive nitrogen pressure is maintained with an oil bubbler throughout the reaction.
2. THF is freshly distilled from sodium benzophenone ketyl under a nitrogen atmosphere.
3. Manganese chloride, 98%, was purchased from Aldrich Chemical Company, Inc., or from Janssen Chimica. It must be finely pulverized, then dried by heating at 180°-200°C (0.1 mm to 0.01 mm) for 6 hr (for example, in a vacuum oven) prior to use. The anhydrous salt is very hygroscopic and must be protected against moisture (a well-closed bottle is convenient). It can, however, be handled *very quickly* without any special precaution.
4. Pulverized cuprous chloride purchased from Aldrich Chemical Company, Inc., was used.
5. Anhydrous lithium chloride purchased from Aldrich Chemical Company, Inc., was used. It is finely pulverized, then dried by heating at 200°C (0.1 mm to 0.01 mm) for 6 hr (vacuum oven) before use. The salt is hygroscopic and must be handled *very quickly*. The reaction can be achieved by using only 1.2 equiv of lithium chloride (18 mmol) instead of 2 equiv.
6. (R)-(+)-Pulegone available from Fluka AG (puriss; 99%), was distilled before use.
7. Generally a green-brown solution is obtained; this color is primarily due to the presence of the copper salt. However, the rate of dissolution (formation of the ate-complex $MnCl_4Li_2$) is very dependent on both the grain size of the two salts ($MnCl_2$ and LiCl) and on their purity. When unpulverized Aldrich or Janssen material is used it is necessary to stir for at least 4 hr to obtain complete dissolution. On the other hand, with finely pulverized anhydrous manganese chloride obtained by drying an analytical grade manganese chloride tetrahydrate (e.g., manganese chloride tetrahydrate p.a., Janssen Chimica), it is possible to obtain complete dissolution after only 5 to 10 min. Moreover, formation of the ate-complex is exothermic.
8. THF solutions of butylmagnesium chloride purchased from Aldrich Chemical Company, Inc., or, preferably, freshly prepared from butyl chloride and magnesium under a nitrogen atmosphere (Note 11), were used. They were standardized immediately before use according to the titration procedure of Watson and Eastham[2] (see also (Note 6), Gall, M.; House, H. O. *Org. Synth., Coll. Vol. VI* **1988**, 121). During addition of the butylmagnesium chloride solution (about 1.5 M) a brownish color appears, indicating the formation of the intermediate organomanganese reagent. Magnesium-manganese exchange occurs instantaneously.
9. Metallic copper can be filtered off (on Celite) before decantation.

10. Purity was determined by capillary GC analysis, OV-1, 25 m × 0.33 mm i.d., 0.5 •m film thickness.
11. To prepare a THF solution of butylmagnesium chloride from butyl chloride, the procedure described by Olah and Arvanaghi (Olah, G. A.; Arvanaghi, M. *Org. Synth., Coll. Vol. VII* **1990**, 451) for the preparation of 2-phenylethylmagnesium chloride ($PhCH_2CH_2MgCl$) is convenient. However one should adjust the addition rate of the THF solution of butyl chloride to keep the temperature of the reaction mixture between 40°C to 45°C, then stir for 6 hr at this temperature.
12. Yields of 92 to 95% were obtained on several runs. The spectra are as follows: ^{13}C NMR ($CDCl_3$) δ (the values separated by a slash correspond to the diastereoisomers): 14.20, 19.45/22.40, 23.60, 24.60/24.95, 25.05/25.25, 26.05, 24.15/28.25, 31.50/34.05, 34.60/34.90, 32.35/36.45, 40.35/40.55, 50.50/52.55, 57.25/57.30, 212.25/213.20; IR (neat) cm^{-1}: 1710.

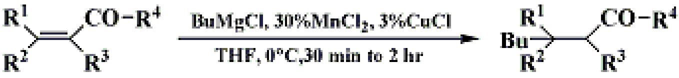
Waste Disposal Information

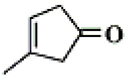
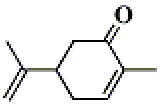
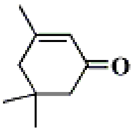
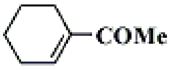
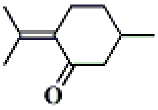
All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Manganese-copper-catalyzed conjugate addition of organomagnesium reagents to α,β-enones is a general synthetic method. Table I shows that the reaction can be successfully performed even with enones of low reactivity. 30% Manganese chloride is necessary to obtain good yields. In most cases, however, 0.1% cuprous chloride is sufficient.[3]

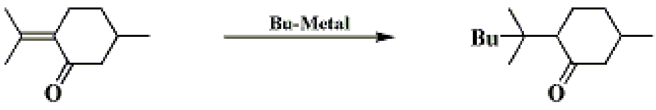
TABLE I
MANGANESE-COPPER-CATALYZED CONJUGATE ADDITION OF ORGANOMAGNESIUM CHLORIDES TO α,β-ETHYLENIC KETONES IN THF AT 0°C

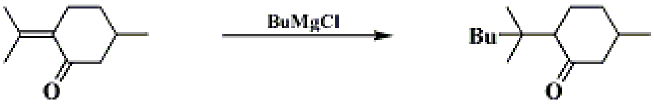
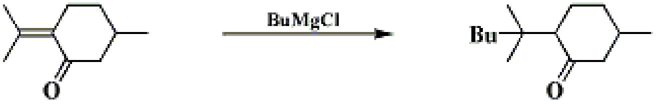
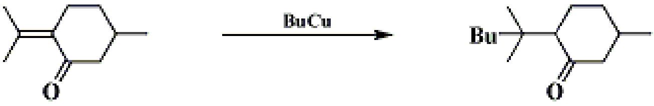
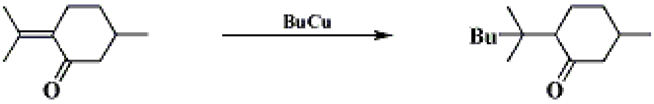
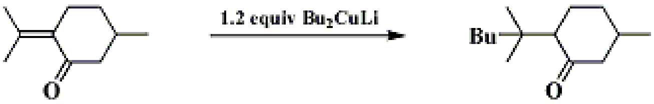
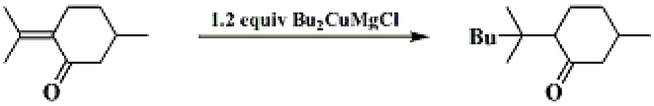


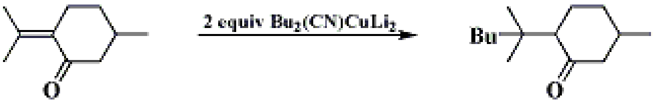
α-Enone	Isolated Yield %	α-Enone	Isolated Yield %
$Me_2C{=}CHCOMe$	94		81
	87		93
	87		94

This manganese-copper-catalyzed conjugate addition reaction compares favorably with the classical copper-catalyzed reaction. The two reactions are easily and similarly carried out under mild conditions, but the first one gives higher yields. This difference, already observed in the case of β-monosubstituted α,β-ethylenic ketones, is especially noticeable with β,β-disubstituted or α,β,β-trisubstituted α,β-ethylenic ketones which are known to be less reactive.[4] Thus, in the case of the title compound, the manganese-copper catalyzed reaction is clearly superior (see Table II).

TABLE II
CONJUGATE ADDITION OF BU-METAL COMPOUNDS TO PULEGONE



	Bu-Metal	Reaction Conditions	Isolated Yield (%)[a]
	BuMgCl	30% $MnCl_2$-3% CuCl THF, 0°C, 2 hr	94
	BuMnCl	3% CuCl; THF, 0°C, 1 hr	95
	BuMgCl	5% CuCl; THF, 0°C	51[b]
	BuCu	Ether-Me_2S, −50°C to −10° C	43[c]
	BuCu	1.1 equiv Me_3SiCl; ether, −10°C	70[c]
	Bu(CN)CuLi	Ether, −50°C to −10°C	13
	0.6 equiv Bu_2CuLi	Ether, −78°C to −30°C	33
	1.2 equiv Bu_2CuLi	Ether, −50°C to −10°C	85[d]
	1.2 equiv $Bu_2CuMgCl$	THF; −50°C to −10°C	47[d]

 Ether, −78°C, 5 hr then 0°C 69[d,e]

2 equiv $Bu_2(CN)CuLi_2$

(a) All reactions have been performed on a 30-mmol scale. (b) Conjugate addition of copper-catalyzed butylmagnesium halide to pulegone gives a better yield in THF than in ether. (c) BuCu from CuBr-Me_2S. (d) Yield based on the starting enone. (e) There is some 1,2-addition.

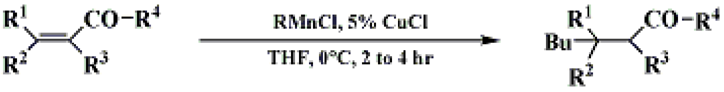
A comparison with various organocopper or cuprate reagents is also favorable since the procedure described here gives higher yields. In addition, the reaction is simpler and more economic, since it is performed at 0°C, using only 1 equiv of organometallic reagent, and no special additive such as HMPA, Bu_3P, BF_3-Et_2O or Me_3SiCl is required. (See ref. [3] for a comparison with the case of the mesityl oxide.)

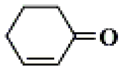
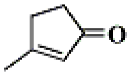
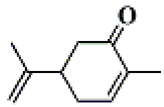
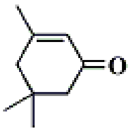
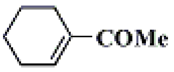
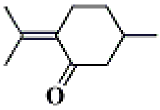
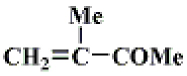
Manganese chloride is inexpensive and the work-up is easier with manganese than with copper. This is an advantage, especially for large-scale preparations.

The procedure described here is a variant of the copper-catalyzed conjugate-addition of organomanganese reagents to α,β-ethylenic ketones. Thus, alkyl, alkenyl, or arylmanganese chloride reagents react with a vast array of α,β-ethylenic ketones in THF[3] and in the presence of copper chloride to give 1,4-addition products in high yields (see Table III).

Table III

COPPER-CATALYZEDCONJUGATEADDITION OFORGANOMANGANESECHLORIDES,[a]RMnCl TOα,β-ETHYLENICKETONES INTHF AT0°C



α-Enone	R	Isolated Yield %	α-Enone	R	Isolated yield %
	Bu	95			
Ph Me_2C=CH	94 92	Bu	90		
	Bu	98		Bu	95
	Bu	86[b]		Bu	88[d]
CH_2=CHCOMe	C_7H_{15}	90[c]	Me_2C=CHCOC_7H_{15}Me		82
	Bu	94			
C_7H_{15} PrCH=CH	89 91	Me_2C=CHCOMe	Ph	89	
Bu	90				

PentCH=CHCOMe	Me	85	Bu	90
$Me_2C=CH$	81			

(a) Unless otherwise stated 1.05 equiv of RMnCl was used. Organomanganese reagents RMnCl were prepared from RLi or RMgX (X = Cl, Br, I). (b) 1.5 equiv of BuMnCl was used. With 1.05 equiv of BuMnCl the yield drops to 77%. (c) The reaction was performed in the presence of 1.2 equiv of Me_3SiCl to trap the intermediate enolate to prevent its addition to the starting methyl vinyl ketone (Micheal addition or aldol condensation). A mixture THF/AcOEt 50:50 was used as solvent. (d) A mixture THF/AcOEt 50:50 was used as solvent (an 82% yield was obtained in THF alone).

The scope of the reaction has been successfully extended to α,β-ethylenic aldehydes,[5] esters,[6] and amides[7] as well as to α,β-acetylenic ketones[8] (see Table IV). With esters, the reaction must be performed in the presence of chlorotrimethylsilane (Me_3SiCl) to avoid the Claisen reaction by trapping the intermediate enolate. In most cases the organomanganese procedure is simpler and more efficient than the organocopper procedure.

TABLE IV
COPPER-CATALYZEDCONJUGATEADDITION OFORGANOMANGANESECHLORIDES, RMnCl, TOα,β-UNSATURATEDCARBONYLSUBSTRATES INTHF

α,β-Unsaturated Carbonyl Substrates	RMnCl	Yield (%) of 1,4-Addition Product
$Me_2C=CHCHO$	$C_7H_{15}MnCl$	80[a]
MeCH=CHCOOEt	i-PrMnCl	96[b]
$MeCH=CHCONEt_2$	BuMnCl	87[b]
$C_5H_{11}C$[illegible]CCOBu	BuMnCl	79[c]
$Me_2C=C(COOEt)_2$	PrCH=CH	92[d]
$Me_2C=C(COOEt)_2$	Ph	87[e]

(a) 3% CuCl, 1.2 equiv Me_3SiCl, –30°C. (b) 3% CuCl, 1.2 equiv Me_3SiCl, 0°C. (c) 3% CuCl, –20°C. (d) 3% CuCl, 0°C to 20°C. (e) Without CuCl, 20°C.

Good yields of 1,4-addition products have also been obtained with alkylidene malonate esters which generally react with organomanganese reagents in the absence of copper salts[9] (see Table IV).

In conclusion, copper-manganese-catalyzed organomagnesium reagents and copper-catalyzed organomanganese reagents are a simple, efficient, and economic alternative to copper-catalyzed organomagnesium reagents and especially to organocopper or cuprate reagents for conjugate addition reactions to α,β-unsaturated carbonyl compounds.

Organomanganese reagents have also been used to prepare numerous simple or functionalized ketones in high yields.[10] They can be also used to carry out in high yields, at room temperature, various chemoselective 1,2-addition reactions, for example to keto aldehydes.[11]

References and Notes

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9. Cahiez, G.; Alami, M. *Tetrahedron* **1989**, *45*, 4163.
10. Cahiez, G.; Laboue, B. *Tetrahedron Lett.* **1989**, *30*, 7369 and references therein.
11. Cahiez, G.; Figadère, B. *Tetrahedron Lett.* **1986**, *27*, 4445.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

sodium benzophenone ketyl

hydrochloric acid, HCl (7647-01-0)

ether (60-29-7)

ammonium chloride (12125-02-9)

sodium bicarbonate (144-55-8)

magnesium (7439-95-4)

nitrogen (7727-37-9)

copper (7440-50-8)

Butyl chloride (109-69-3)

cuprous chloride (7758-89-6)

copper chloride (7758-89-6)

ammonium hydroxide (1336-21-6)

Mesityl oxide (141-79-7)

chloride

magnesium sulfate (7487-88-9)

manganese (7439-96-5)

Tetrahydrofuran (109-99-9)

methyl vinyl ketone (78-94-4)

Lithium chloride (7447-41-8)

argon (7440-37-1)

CHLOROTRIMETHYLSILANE (75-77-4)

pulegone (89-82-7)

Butylmagnesium chloride (693-04-9)

2-(1,1-DIMETHYLPENTYL)-5-METHYL-CYCLOHEXANONE, 2-(dimethylpentyl)-5-methylcyclohexanone, Cyclohexanone, 2-(1,1-dimethylpentyl)-5-methyl- (109539-17-5)

manganese chloride (7773-01-5)

(R)-(+)-pulegone

manganese chloride tetrahydrate

2-phenylethylmagnesium chloride

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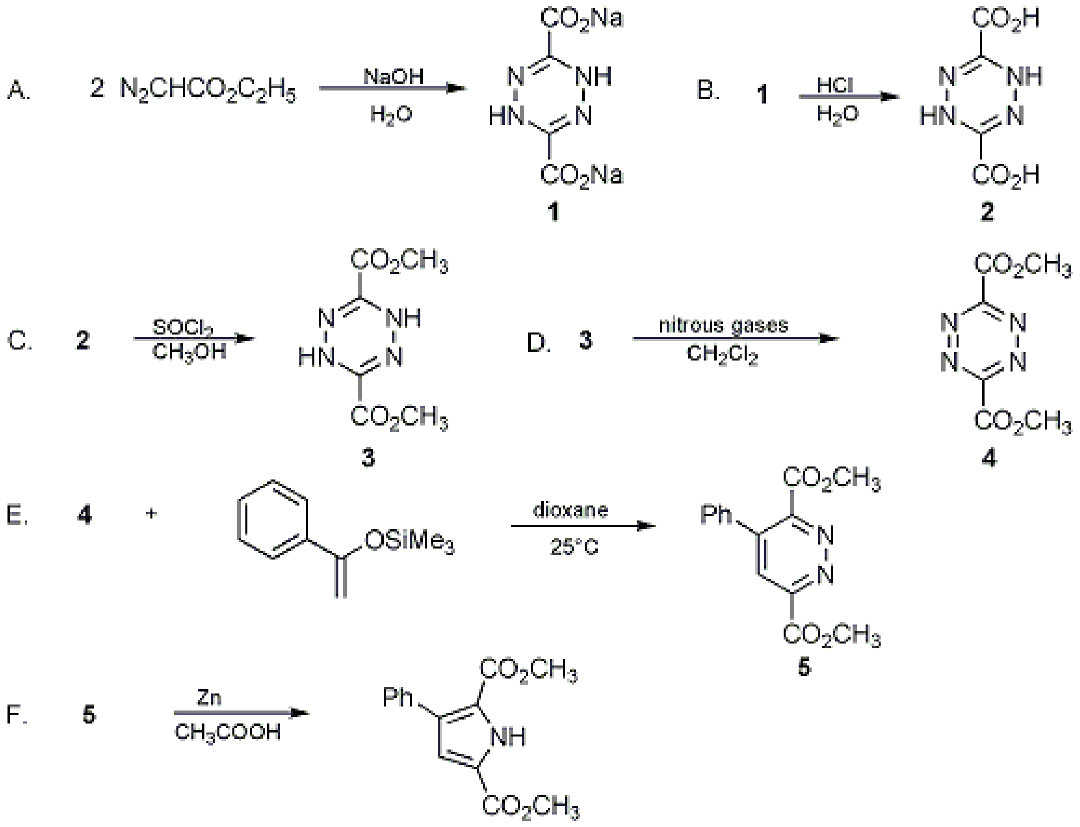
Organic Syntheses, CV 9, 335

PREPARATION AND DIELS-ALDER REACTION OF A REACTIVE, ELECTRON-DEFICIENT HETEROCYCLIC AZADIENE: DIMETHYL 1,2,4,5-TETRAZINE-3,6-DICARBOXYLATE. 1,2-DIAZINE (DIMETHYL 4-PHENYL-1,2-DIAZINE-3,6-DICARBOXYLATE) AND PYRROLE (DIMETHYL 3-PHENYLPYRROLE-2,5-DICARBOXYLATE) INTRODUCTION

[1,2,4,5-Tetrazine-3,6-dicarboxylic acid, dimethyl ester; 3,6-Pyridazinedicarboxylic acid, 4-phenyl-, dimethyl ester; 1H-Pyrrole-2,5-dicarboxylic acid, 3-phenyl-, dimethyl ester]



Submitted by Dale L. Boger, James S. Panek, and Mona Patel[1].
Checked by Richard Hutchings and Albert I. Meyers.

1. Procedure

2 3 4

A. *Disodium dihydro-1,2,4,5-tetrazine-3,6-dicarboxylate*. A 2-L, three-necked, round-bottomed flask is equipped with an overhead stirrer, thermometer, and a 500-mL addition funnel. Sodium hydroxide (320 g, 8 mol) and 500 mL of water are added. Ethyl diazoacetate (200 g, 1.75 mol, (Note 1)) is placed in the addition funnel and added dropwise to the stirred sodium hydroxide solution so as to maintain the temperature of the reaction mixture between 60°C and 80°C (approximately 1.5 hr, (Note 2)). After the reaction slurry is cooled to room temperature, it is poured into 2 L of 95% ethanol, mixed well, and the liquid is decanted. This washing procedure is repeated five times using 1.5 L of 95% ethanol each time. The precipitate is collected by filtration using a Büchner funnel, the collected solid is washed with 1 L of absolute ethanol and 1 L of ether, and dried (12 hr) in the air to afford 160–184 g (85–97%) of disodium dihydro-1,2,4,5-tetrazine-3,6-dicarboxylate as yellow brown solid.

B. *Dihydro-1,2,4,5-tetrazine-3,6-dicarboxylic acid*. A 2-L, three-necked, round-bottomed flask is equipped with

an overhead stirrer and a 100-mL addition funnel. Disodium dihydro-1,2,4,5-tetrazine-3,6-dicarboxylate (90.37 g 0.42 mol) in 100 mL of water and 100 g of crushed ice are added. The resulting slurry is cooled with an ice/sodium chloride bath and a solution of concentrated hydrochloric acid (84 mL of 36–38%) is added dropwise with stirring over 45 min. The reaction mixture is washed five times with 200 mL of dry ether and the ether layer is decanted. The product is immediately collected by filtration using a Büchner funnel. Drying the collected solid at room temperature under reduced pressure affords 51.6–53.06 g (72–74%) of dihydro-1,2,4,5-tetrazine-3,6-dicarboxylic acid as a yellow powder: mp 144–148°C (Note 3).

C. *Dimethyl dihydro-1,2,4,5-tetrazine-3,6-dicarboxylate*. Absolute methanol (700 mL, (Note 4)) is placed in a dry, 2-L, round-bottomed flask fitted with an overhead stirrer, thermometer, and a 100-mL addition funnel and is cooled to −30°C. Thionyl chloride (62.12 g, 0.522 mol, 38.1 mL, (Note 5)) is added carefully with stirring and the reaction mixture is allowed to stir at −30°C for 30 min. Dihydro-1,2,4,5-tetrazine-3,6-dicarboxylic acid (45.00 g, 0.261 mol) is added as a solid in portions over 30 min to the cooled, stirred thionyl chloride-methanol solution (Note 6). The reaction mixture is allowed to warm to room temperature (1 hr) and is subsequently warmed to 35–40°C (internal temperature) for 2 hr. The reaction mixture is cooled to −30°C and the precipitate is collected by filtration using a Büchner funnel. The collected solid is washed with ether (115 mL, (Note 7)) and the filtrate is concentrated under reduced pressure to give an orange-brown oil (ca. 15 g). The collected solid is triturated with methylene chloride (2.0 L) and the insoluble inorganic salts are removed by filtration using a Büchner funnel. The orange-brown oil (ca. 15 g) is taken up in water (150 mL) and extracted with methylene chloride (6 × 270 ml). The combined methylene chloride extracts and methylene chloride triturate are dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford 23–31 g (44–51%) of pure dimethyl dihydro-1,2,4,5-tetrazine-3,6-dicarboxylate as an orange-yellow powder: mp 171–172°C (Note 8).

D. *Dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate*. Dimethyl dihydro-1,2,4,5-tetrazine-3,6-dicarboxylate (20 g, 0.1 mol) is slurried in 800 mL of methylene chloride (Note 9) in a 2-L, round-bottomed flask fitted with a magnetic stirring bar and the mixture is cooled with an ice/water bath. A stream of nitrous gases (Note 10) is bubbled into the reaction mixture with stirring for 15 min. The color of the reaction mixture changes from orange to bright red during the addition. Stirring is continued for 1.5 hr as the reaction mixture is allowed to warm to room temperature. The solvent and excess nitrous gases are removed under reduced pressure to afford dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (19.7 g, 99%) as a bright red, crystalline solid: mp 173–175°C (Note 11).

E. *Dimethyl 4-phenyl-1,2-diazine-3,6-dicarboxylate*. A 50-mL, round-bottomed flask equipped with a magnetic stirring bar is charged with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (1.0 g, 0.005 mol) and 1,4-dioxane (20 mL, (Note 12)). 1-Phenyl-1-(trimethylsiloxy)ethylene (1.07 g, 0.0056 mol, 1.14 mL, (Note 13)) is added and the reaction mixture is stirred under nitrogen at room temperature for 8 hr. The solvent is removed under reduced pressure to give a viscous oil that is triturated with anhydrous ether (2–3 mL). The solid product is collected by vacuum filtration and recrystallized from ethyl acetate/hexane to give 1.23–1.30 g (90–96%) of dimethyl 4-phenyl-1,2-diazine-3,6-dicarboxylate as a light yellow solid, mp 95.5–96°C (Note 14).

F. *Dimethyl 3-phenylpyrrole-2,5-dicarboxylate*. A 250-mL, round-bottomed flask equipped with a magnetic stirring bar is charged with dimethyl 4-phenyl-1,2-diazine-3,6-dicarboxylate (1.36 g, 0.005 mol) and glacial acetic acid (55 mL, (Note 15)). Zinc dust (3.25 g, 0.05 mol, (Note 16)) is added and the reaction mixture is stirred at room temperature for 6 hr. A second portion of zinc dust (3.25 g, 0.05 mol) is added and the reaction mixture is stirred for an additional 18 hr. The zinc dust is removed by filtration through a pad of Celite and the residue is washed with ether (100 mL). The filtrate and washes are combined, made basic (pH 10) with the addition of saturated sodium bicarbonate, and extracted with ether (2 × 100 mL). The combined ether extracts are dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Purification of the product is effected by flash chromatography on a 4.5 × 9-cm column of silica gel (Aldrich 951, CH_2Cl_2 eluant), collecting 20-mL fractions. The fractions are analyzed by thin-layer chromatography (Kieselgel 60, CH_2Cl_2 eluant) and those containing product are combined and concentrated in vacuo to give 0.676 g (52%) of dimethyl 3-phenylpyrrole-2,5-dicarboxylate as a white solid: mp 122–123°C (ethyl acetate-hexane, (Note 17)).

2. Notes

1. The submitters employed, without purification, ethyl diazoacetate obtained from Aldrich Chemical Company, Inc.

2. A time lag (10–15 min) is observed before the exothermic reaction begins. Addition of ethyl diazoacetate is then maintained at such a rate that the reaction temperature does not rise above 80°C. The checkers had to heat the mixture to 60°C.

3. Drying of the free acid should be rapid with a large surface area since traces of hydrochloric acid promote hydrolysis of the product to hydrazine salts. Slight warming (≤ 60°C) during drying accelerates the drying process. The IR spectrum is as follows: IR (KBr) γ_{max} cm^{-1}: 3700–3100, 3320, 3000–1850, 1710, 1630. The checkers found that this step does not work as well on a smaller scale (0.14 mol).

4. Methanol is distilled from magnesium turnings immediately before use.

5. The submitters employed, without purification, thionyl chloride obtained from Fisher Scientific Company. The procedure should be performed in a well-ventilated hood since thionyl chloride is a lachrymator. The yield of dimethyl ester was found to be lower in instances when the thionyl chloride-methanol solution was not allowed to stir (30 min, –30°C) prior to the addition of dihydro-1,2,4,5-tetrazine-3,6-dicarboxylic acid.

6. The temperature is maintained at –30°C during the additions.

7. The submitters employed ether distilled from sodium benzophenone ketyl.

8. The spectral properties of the product are as follows: ^{1}H NMR ($CDCl_3$) δ: 3.92 (s, 6 H, CO_2CH_3), 7.42 (br s, 2 H, NH); IR (KBr) ν_{max} cm^{-1}: 3160, 3050, 1740, 1720.

9. The submitters employed methylene chloride from Fisher Scientific Company, which was distilled before use.

10. Nitrous gases are generated in a separate vessel by the disproportionation of nitrous acid (HONO): 200 mL of 6 N $NaNO_2$ (1.2 mol) is added dropwise to 125 mL of concentrated hydrochloric acid (1.5 mol) in a 500-mL, three-necked, round-bottomed flask fitted with a nitrogen inlet, a 500-mL addition funnel, and an outlet tube leading to the reaction flask. The brown gases evolved are bubbled directly into the reaction mixture through a 5-mm (inside diameter) glass tube (smaller inlet tubes occasionally became plugged) using a nitrogen stream. *CAUTION: all operations involving nitrous gases should be conducted in a well-ventilated hood because of the toxicity of these gases.*

11. The checkers observed some starting material in the product which depressed the mp. It could be removed by crystallization from ethyl acetate to give pure 3, mp 176–177°C, but with significant loss of product. The spectral properties of the product are as follows: ^{1}H NMR ($CDCl_3$) δ: 4.22 (s, 6 H, CO_2CH_3); IR (KBr) η_{max} cm^{-1}: 2970, 1752, 1445, 1385, 1219, 1175, 1082, 960, 912; UV (dioxane) λ_{max}(log ε) 520 nm (2.754).

12. The submitters employed 1,4-dioxane obtained from Fisher Scientific Company and distilled before use.

13. The submitters employed, without purification, 1-phenyl-1-(trimethylsiloxy)ethylene obtained from Aldrich Chemical Company, Inc.

14. The elemental analysis and the spectral analysis of the product are as follows: Anal. Calcd for $C_{14}H_{12}N_2O_4$: C, 61.76; H, 4.44; N, 10.29. Found: C, 62.01; H, 4.50; N, 10.19; ^{1}H NMR ($CDCl_3$) δ: 3.89 (s, 3 H, CO_2CH_3), 4.12 (s, 3 H, CO_2CH_3), 7.40–7.60 (m, 5 H, Ph), 8.27 (s, 1 H, C5-H); IR (KBr) ν_{max} cm^{-1}: 2955, 1742, 1584, 1447, 1399, 1287, 1244, 1142, 766; EI-MS (70 eV): m/e (relative intensity) 272 (M^+, 9), 242 (7), 241 (6), 214 (34), 182 (10), 155 (base), lit[3] mp 94–95.5°C.

15. The submitters employed, without purification, glacial acetic acid obtained from Fisher Scientific Company.

16. Zinc dust obtained from Fisher Scientific Company was activated prior to use following an established procedure.[5]

17. The elemental analysis and the spectral analysis of the product are as follows: Anal. Calcd for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40. Found: C, 65.10; H, 4.99; N, 5.48; ^{1}H NMR ($CDCl_3$) δ: 3.82 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 6.94 (d, 1 H, J = 3, C4-H), 7.30–7.60 (m, 5 H, Ph), 9.80 (br, s, 1 H, NH); IR (KBr) ν_{max} cm^{-1}: 3314, 2958, 1726, 1564, 1464, 1436, 1270, 1096, 1008, 940, 846, 762, 696. The additional formation of methyl 3-phenyl-5-carboxamidopyrrole-2-carboxylate in 32% yield is observed. The spectral properties of the product are as follows: ^{1}H NMR ($CDCl_3$) δ: 1.75 (br s, 2 H), 3.92 (s, 3 H), 7.14 (s, 1 H), 7.40–7.60 (m, 5 H); IR (KBr) $\nu_{max}$$cm^{-1}$: 3442, 3346, 2950, 1708, 1642, 1580, 1528, 1476, 1366, 1280, 1132, 1022, 936, 808, 728, 618; CI-MS (70 eV): m/e (relative intensity) 245 (M^+ + H, base).

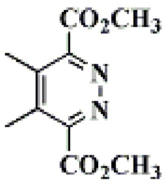
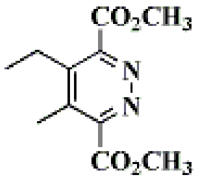
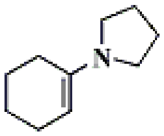
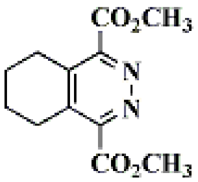
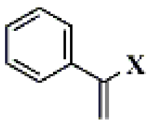
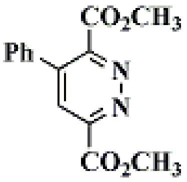
Waste Disposal Information

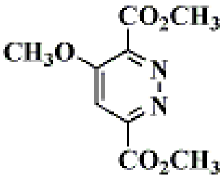
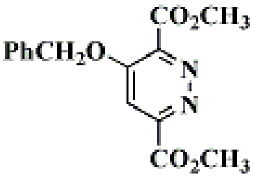
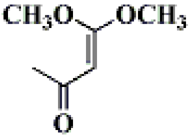
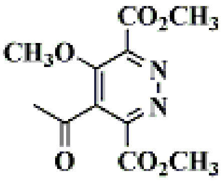
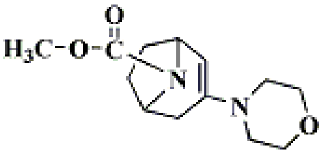
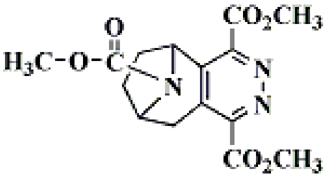
All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The procedure describes the preparation and use of a reactive, electron-deficient heterocyclic azadiene suitable for Diels-Alder reactions with electron-rich, unactivated, and electron-deficient dienophiles.[6 7 8 9 10 11] Dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate, because of its electron-deficient character, is ideally suited for use in inverse electron demand ($LUMO_{diene}$-controlled)[12] Diels-Alder reactions. Table I and Table II detail representative examples of the reaction of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate with electron-rich carbon dienophiles[13] and heterodienophiles,[6,7,8] respectively. Complete surveys of the reported Diels-Alder reactions of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate have been compiled.[6,7,8,9,10,11] Reductive ring contraction of the substituted dimethyl 1,2-diazine-3,6-dicarboxylate [4 + 2] cycloadducts effected by zinc in acetic acid provides the corresponding substituted dimethyl pyrrole-2,5-dicarboxylates.[13,14] Table III details representative examples of this general reductive ring contraction reaction.[14,15]

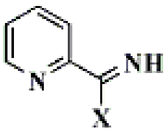
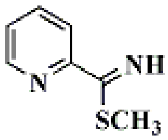
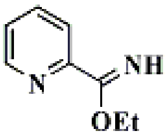
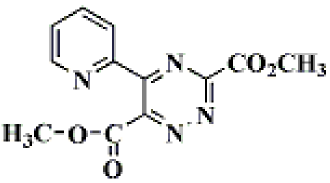
TABLE I
DIELS-ALDER REACTIONS OF DIMETHYL 1,2,4,5-TETRAZINE-3,6-DICARBOXYLATE: 1,2-DIAZINE INTRODUCTION[13]

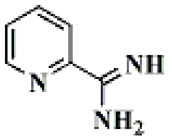
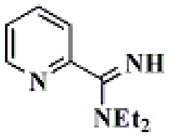
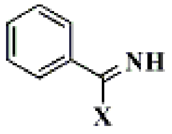
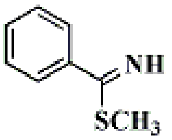
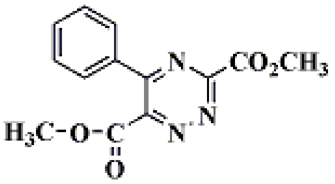
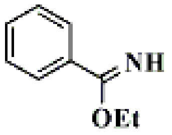
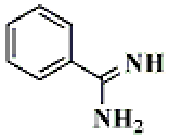
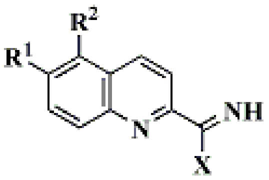
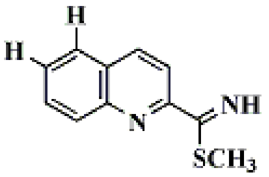
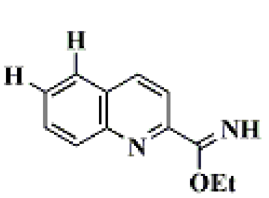
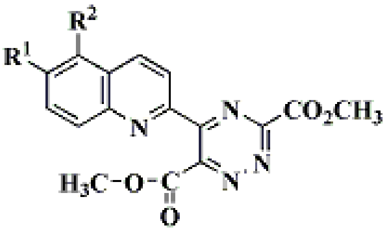
Entry		Dienophile	Conditions[a] Equiv. Temp °C (time hr)	1,2-Diazine	%Yield
1			1.5,25(12)		1 87
2			2-6,25(12)		1 trace
3	X = morpholine		2,25(48)		2 70
4	= pyrrolidine		2,25(48)		trace
5			1.5,25(12)		3 85
6	X = $OSi(CH_3)_3$		1,25(5)		4 92
7	= morpholine		1.2,25(1.5)		87
8	= pyrrolidine		1.5,25(12)		trace

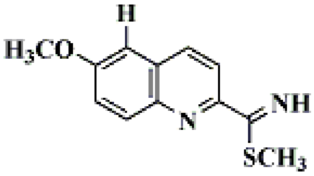
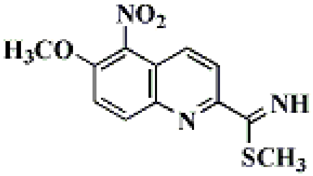
9			1.5,25(0.5)		5	65
10	R = Si(Me)$_2$-t-Bu		1.5,5-25(0.5)		6	33
11			2-3,25(6)		6	82
12			2.5,101(3)		7	71
13		1,25(5)		8	69	

(a) All Diels-Alder reactions were carried out in dioxane.

TABLE II
IELS-ALDERREACTIONS OFDIMETHYL1,2,4,5-TETRAZINE-3,6-DICARBOXYLATE WITHC=N HETERODIENOPHILES[16][17][18]

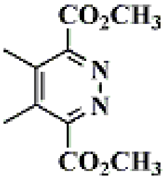
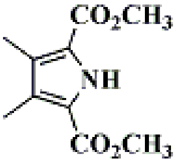
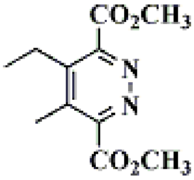
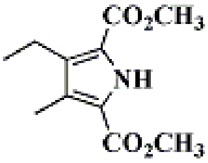
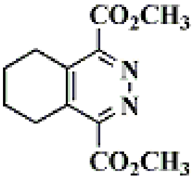
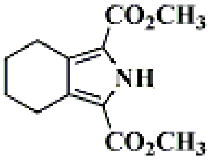
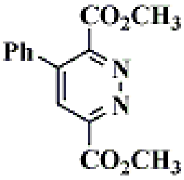
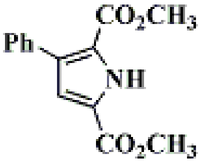
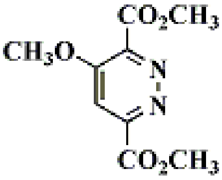
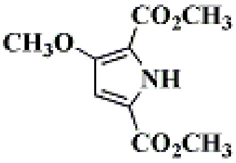
Dienophile	Conditions Temp °C (time hr)^a	Product	% Yield
			
	80(20)		68
	80(8-12)		37

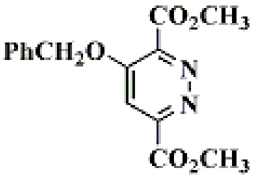
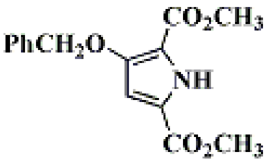
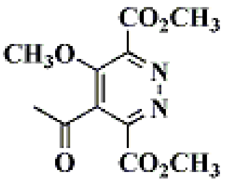
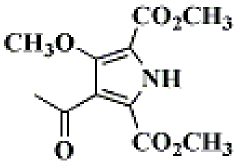
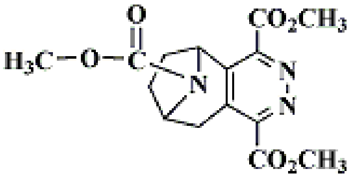
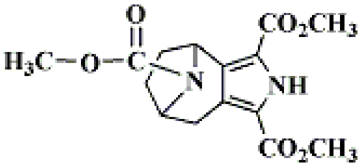
	25(5)		-
	25-50(25)		-
			
	80(24)		65
	60(10)		27
	25(5)		-
			
		80(4)	70
		80(20)	33

	80(4)	78
	80(20-24)	82

(a) All Diels-Alder reactions were carried out in dioxane.

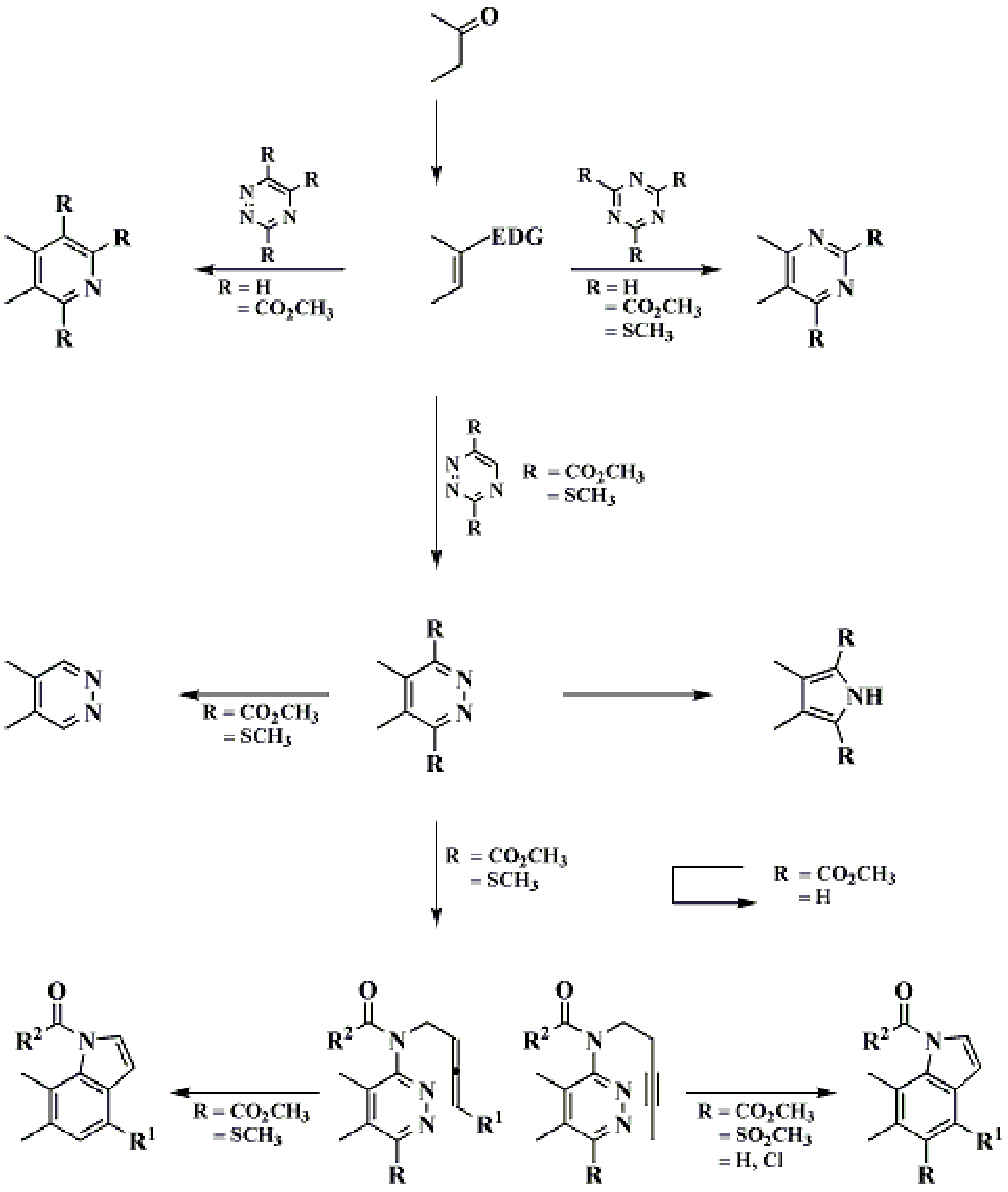
TABLE III
REDUCTIVE RING CONTRACTION OF SUBSTITUTED DIMETHYL 1,2-DIAZINE-3,6-DICARBOXYLATES: PYRROLE INTRODUCTION[13]

Entry	1,2-Diazine	Conditions[a] Temp °C (time hr)	Pyrrole	%Yield
1		25(24)		63
2		25(24)		70
3		25(22)		52
4		25(9)		65
5		25(24)		67

6		25(24)		62
7		25(24)		56
8		25(36)		48

(a) All zinc (9-20 molar equiv) reductions were carried out in acetic acid (0.09 M in substrate).

This approach to 1,2-diazine and pyrrole introduction based on the inverse electron demand Diels-Alder reaction of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate complements the [4 + 2] cycloaddition reactions of a range of electron-deficient heterocyclic azadienes which permits the divergent preparation of a range of heterocyclic agents employing a common dienophile precursor, Scheme I.



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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium benzophenone ketyl

1,2-DIAZINE (DIMETHYL 4-PHENYL-1,2-DIAZINE-3,6-DICARBOXYLATE)

PYRROLE (DIMETHYL 3-PHENYLPYRROLE-2,5-DICARBOXYLATE)

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether (60-29-7)

sodium hydroxide (1310-73-2)

thionyl chloride (7719-09-7)

sodium bicarbonate (144-55-8)

magnesium (7439-95-4)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

nitrous acid (7782-77-6)

carbon (7782-42-5)

zinc (7440-66-6)

methylene chloride (75-09-2)

Pyrrole (109-97-7)

magnesium sulfate (7487-88-9)

ethyl diazoacetate (623-73-4)

Dihydro-1,2,4,5-tetrazine-3,6-dicarboxylic acid (3787-09-5)

hexane (110-54-3)

1,4-dioxane (123-91-1)

1,2-DIAZINE (289-80-5)

Dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate, 1,2,4,5-Tetrazine-3,6-dicarboxylic acid, dimethyl ester (2166-14-5)

Dimethyl 4-phenyl-1,2-diazine-3,6-dicarboxylate, 3,6-Pyridazinedicarboxylic acid, 4-phenyl-, dimethyl ester (2166-27-0)

Dimethyl 3-phenylpyrrole-2,5-dicarboxylate, 1H-Pyrrole-2,5-dicarboxylic acid, 3-phenyl-, dimethyl ester (92144-12-2)

Disodium dihydro-1,2,4,5-tetrazine-3,6-dicarboxylate (96898-32-7)

Dimethyl dihydro-1,2,4,5-tetrazine-3,6-dicarboxylate (3787-10-8)

1-Phenyl-1-(trimethylsiloxy)ethylene (13735-81-4)

methyl 3-phenyl-5-carboxamidopyrrole-2-carboxylate

dimethyl 1,2-diazine-3,6-dicarboxylate

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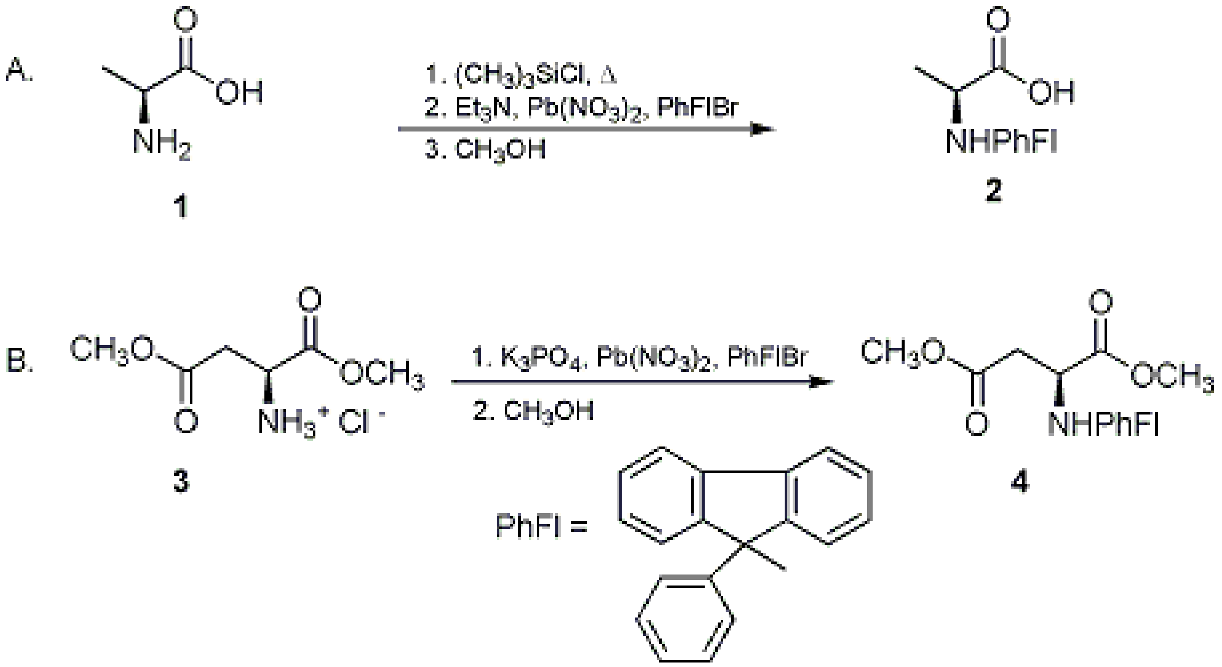
Organic Syntheses, CV 9, 344

(S)-N-(9-PHENYLFLUOREN-9-YL)ALANINE AND (S)-DIMETHYL N-(9-PHENYLFLUOREN-9-YL) ASPARTATE

[L-Alanine, N-(9-phenyl-9H-fluoren-9-yl)- and L-Aspartic acid, N-(9-phenyl-9H-fluoren-9-yl-, dimethyl ester]



Submitted by T. F. Jamison[1] and H. Rapoport[2].
Checked by Carol M. Taylor and Amos B. Smith, III.

1. Procedure

Caution! Chlorotrimethylsilane is moisture-sensitive and should be kept under an inert atmosphere at all times. Persons following this procedure should be thoroughly familiar with the handling of moisture-sensitive materials. Lead nitrate [$Pb(NO_3)_2$] is toxic (1), and it and tripotassium phosphate (K_3PO_4) are hygroscopic.

A. *(S)-N-(9-Phenylfluoren-9-yl)alanine* (**2**).[3] A 1-L, flame-dried, three-necked Morton flask (Note 1) equipped with an overhead stirrer, rubber septum, and reflux condenser (equipped with a rubber septum) under a nitrogen atmosphere is charged with L-alanine (**1**, 13.5 g, 150 mmol, (Note 2)), chloroform (375 mL, (Note 3)), acetonitrile (75 mL, (Note 4)), and chlorotrimethylsilane (19.04 mL, 150 mmol, (Note 5)). The rubber septum in the neck of the Morton flask is replaced with a glass stopper, and the mixture is heated at reflux for 2 hr with vigorous stirring under an inert atmosphere (Note 6). The mixture is cooled to room temperature under a stream of nitrogen,

triethylamine (46.0 mL, 330 mmol, (Note 7)) is added via syringe at a rate sufficient to maintain a gentle reflux, and the mixture is stirred for 15 min after which $Pb(NO_3)_2$ (33.1 g, 100 mmol, (Note 8)) is added. The glass stopper is replaced with a rubber septum, and a solution of 9-bromo-9-phenylfluorene (57.8 g, 180 mmol, (Note 9)) in chloroform (180 mL, (Note 3)) is added via a Teflon cannula with a positive nitrogen pressure. The reflux condenser is replaced with a glass stopper, and an 18-gauge syringe needle equipped with an argon-filled balloon is inserted in the rubber septum. The heterogeneous, off-white mixture is stirred vigorously under this inert atmosphere for 48 hr. After about 20 hr, the reaction mixture becomes orange and darkens over time. Methanol (15.2 mL, 375 mmol, (Note 10)) is then added, and the mixture is stirred an additional 30 min.

The mixture is filtered using a sintered glass filter, the filter cake is washed by stirring with chloroform (3 × 50 mL), and the dark orange filtrate is evaporated to a residue that is partitioned between ether (750 mL, (Note 11)) and aqueous 5% citric acid (750 mL, (Note 12)). The layers are separated, and the aqueous layer is extracted with ether (4 × 250 mL). The combined organic solutions are extracted with 1 M sodium hydroxide (300 mL). The aqueous solution is washed with 300 mL of ether, cooled to 0°C with stirring using a magnetic stir bar, and the pH is adjusted to 7 by the dropwise addition of glacial acetic acid (approximately 17 mL, (Note 13)). The mixture now containing an off-white precipitate is extracted with 25% 2-propanol (Note 14) in chloroform (3 × 300 mL). The combined organic solutions are washed with 150 mL of saturated sodium chloride solution, dried (Na_2SO_4), filtered, and evaporated to a light yellow foam that is dried under reduced pressure to give 39.2 g (80% yield) of (S)-N-(9-phenylfluoren-9-yl)alanine (2) (Note 15).

B. *(S)-Dimethyl N-(9-phenylfluoren-9-yl)aspartate* (**4**).[4] A 1-L, flame-dried, three-necked Morton flask (Note 1) equipped with an overhead stirrer and two rubber septa under a nitrogen atmosphere is charged with $Pb(NO_3)_2$ (28.2 g, 85.0 mmol, (Note 8)), K_3PO_4 (44.6 g, 210 mmol, (Note 16)), and acetonitrile (250 mL, (Note 4)). (S)-Dimethyl aspartate hydrochloride (**3**, 19.8 g, 100 mmol, (Note 17)) is added, followed by 9-bromo-9-phenylfluorene (40.15 g, 125 mmol, (Note 9)). The off-white, heterogeneous mixture is stirred vigorously for 22 hr, and to the mixture is added methanol (40.5 mL, 1.00 mol, (Note 10)); the mixture is stirred an additional 30 min and filtered through approximately 20 g of diatomaceous earth ("Celite") on a sintered glass funnel. The filter cake is washed by stirring with portions of chloroform until no UV chromophore can be detected in the filtrate (Note 18). Silica (60 g, (Note 19)) is added to the combined organic solutions, and the solvent is removed (rotary evaporator), leaving a dry powder. This powder is added to a column of silica (800 g, (Note 19)) and the column is eluted with 10% ethyl acetate in hexanes (Note 20) to give 9-methoxy-9-phenylfluorene (5.30 g, 19.5 mmol, (Note 21)) and then 9-phenyl-9-fluorenol (2.00 g, 7.7 mmol, (Note 22)). A 1/1 mixture of 9-phenyl-9-fluorenol and 4 is eluted next (2.13 g). After all the 9-phenyl-9-fluorenol has been eluted, the eluting solvent is changed to 25% ethyl acetate in hexanes (Note 20). The combined solutions

of pure 4 are evaporated (rotary evaporator), yielding (S)-dimethyl N-(9-phenylfluoren-9-yl)aspartate (4) as a light yellow solid (36.1 g, 90 mmol, 90% yield, (Note 23)) after drying for 1 day at 0.1 mm. The 2.13-g mixture of 4 and 9-phenyl-9-fluorenol can be rechromatographed (100 g of silica, 10–25% ethyl acetate in hexane) to give an additional 0.8 g (3.1 mmol) of 9-phenyl-9-fluorenol (for a total of 2.80 g, 10.8 mmol) and 1.3 g (3.2 mmol, 3.2% yield) of 4, for a total of 37.4 g (93% yield) of 4.

2. Notes

1. Use of a Morton flask and an overhead stirrer allows for better mixing of the heterogenous system and gives conversion to product faster than does use of a standard round-bottomed flask with an overhead stirrer.
2. L-Alanine was purchased from Fisher Scientific company and used without further purification.
3. Chloroform was purchased from Fisher Scientific Company and distilled from phosphorus oxide (P_2O_5) immediately before use and added to the reaction mixture via syringe.
4. Acetonitrile was purchased from EM Science, distilled from calcium hydride (CaH_2) immediately before use and added to the reaction mixture via syringe.
5. Chlorotrimethylsilane was purchased from Aldrich Chemical Company, Inc., distilled from CaH_2 immediately before use, and added to the reaction mixture via syringe.
6. A syringe needle equipped with an argon-filled balloon should be inserted through the rubber septum on the reflux condenser. In addition, while the mixture is refluxing, the apparatus should be checked frequently for leaks.
7. Triethylamine was purchased from Fisher Scientific Company and distilled from barium oxide (BaO) immediately before use and added to the reaction mixture via syringe.
8. Lead nitrate (toxic!) was purchased from Fisher Scientific Company, dried in an oven at 160°C for 4 days, and cooled in a desiccator, yielding a freely-flowing, white granular solid. The checkers dried it at 100°C under 1.5 mm vacuum for 4 days.
9. 9-Bromo-9-phenylfluorene was prepared as described.[5]
10. Methanol was purchased from Fisher Scientific Company and used without further purification.
11. Ethyl ether was purchased from Fisher Scientific Company and used without further purification.
12. An insoluble brownish-orange polymer formed was carefully excluded from the organic extractions. Leaching of this material into the organic layer produces colored product.
13. Glacial acetic acid was purchased from Fisher Scientific Company and used without further purification. Near pH 7, much of the product precipitated, and the off-white mixture became difficult to stir. Distribution of the acetic acid was accomplished by manually swirling the flask.
14. 2-Propanol was purchased from Fisher Scientific Company and used without

further purification.

15. Compound 2[3] thus obtained was of sufficient purity (>97%, as determined by elemental analysis) for direct use; but was contaminated by a small amount of highly colored impurities. IR cm^{-1}: 3070 (m), 3005 (m), 2905 (m), 1765 (m), 1735 (m), 1640 (m), 1590 (m), 1450 (s), 1390 (s), 1375 (s), 1355 (s), 690 (m), 605 (m). 2 can be recrystallized (1:1 EtOAc/hexane) to give a white solid,[3] mp 158–161°C. [α] –63.0° (EtOH, *c* 1.4); ^{1}H NMR δ: 1.09 (d, 3 H, J = 7.2), 2.70 (q, 1 H, J = 7.2), 7.36 (m, 11 H), 7.71 (m, 2 H); ^{13}C NMR δ: 19.2, 52.9, 73.0, 120.19, 120.21, 125.5, 125.7, 125.9, 127.6, 128.2, 128.6, 129.1, 140.5, 140.6, 141.8, 145.9, 146.5, 176.5 (Four ^{13}C NMR signals appear to be missing, possibly due to overlapping of signals.); TLC R_f 0.25 (8:1 EtOAc/hexane); UV (EtOH) λ, nm (ε): 310 (9,600), 298 (5,000), 266 (14,000), 238 (23,000), 209 (47,000). Anal. Calcd for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81; N, 4.25. Found: C, 80.4; H, 5.6; N, 4.2.

16. Potassium phosphate was obtained from Mallinckrodt Chemical and was dried at >500°C for > 12 hr, cooled in a desiccator, ground to a *fine powder* with a mortar and pestle, and stored in a desiccator before use. It must be weighed quickly, as it is hygroscopic.

17. (S)-Dimethyl aspartate hydrochloride was prepared as described[4] and recrystallized from acetone to give a white crystalline solid (mp 114.5–115°C, lit.[6] mp 116–117°C), which was stored in a vacuum desiccator before use.

18. Eight or nine 100-mL portions of chloroform, obtained from EM Science and used without further purification, were required.

19. Silica gel of 230–400 mesh was obtained from EM Science. The checkers used silica gel from J. T. Baker.

20. Both ethyl acetate and hexanes were obtained from Fisher Scientific Company and used without further purification.

21. The physical properties of 9-methoxy-9-phenylfluorene are as follows:[7] mp 93–94°C (lit.[7] mp 94–95°C), ^{1}H NMR δ: 2.96 (s, 3 H), 7.2–7.4 (m, 11 H), 7.7 (m, 2 H); ^{13}C NMR δ: 51.3, 89.0, 119.9, 125.3, 125.5, 127.1, 128.0, 128.1, 128.9, 140,8, 143.4, 146.8; TLC (1/3 EtOAc/hexane, aluminum backed silica) R_f 0.85.

22. The properties of 9-phenyl-9-fluorenol are as follows: TLC (1/3 EtOAc/hexane, aluminum backed silica) R_f 0.67; see ref. [5] for additional spectral and physical data.

23. The physical properties of (S)-dimethyl N-(9-phenylfluoren-9-yl)aspartate (4) are as follows:[4] mp 58–59.5°C (sometimes 4 does not solidify); $[\alpha]_D$ –264° ($CHCl_3$, *c* 3.3); IR ($CHCl_3$) cm^{-1}: 3320 (w), 3005 (m), 2950 (m), 1740 (s), 1600 (w), 1440 (s), 1365 (m), 1340 (m), 1170 (m), 1010 (m), 1000 (m), 900 (w), 690 (m), 610 (w); UV (EtOH) λ (ε): 310 (9,600), 298 (8,700), 276 (22,100), 239 (43,700), 231 (50,700), 211 (66, 200); ^{1}H NMR δ: 2.35 (dd, 1 H, J = 15, 5.4), 2.52 (dd, 1 H, J = 15, 6.8), 3.01 (m, 1 H), 3.3 (br s, 1 H), 3.34 (s, 3 H), 3.65 (s, 3

H), 7.15–7.4 (m, 11 H), 7.7–7.8 (m, 2 H); ^{13}C NMR δ: 39.7, 51.5, 51.8, 52.7, 72.7, 119.7, 119.9, 125.4, 125.8, 125.9, 127.2, 127.4, 127.7, 128.2, 128.3, 139.7, 141.1, 144.4, 148.3, 148.5, 170.8, 174.6 (Note: Three ^{13}C NMR signals appear to be missing, possibly due to overlapping of signals.); TLC (1/3 EtOAc/hexane, aluminum backed silica) R_f 0.52. Anal. Calcd for $C_{25}H_{23}NO_4$: C, 74.8; H, 5.8; N, 3.5. Found: C, 74.6; H, 5.8; N, 3.4.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Procedures A and B illustrate the two current methods for preparation of N-9-phenylfluoren-9-yl derivatives of amino acids and amino acid esters. Free carboxylate (as in alanine in Step A) or free hydroxyl (e.g., serine[8]) functions can be blocked for the duration of the reaction as trimethylsilyl (TMS) esters or ethers, respectively, by treatment with chlorotrimethylsilane and triethylamine. The TMS group(s) are then removed by methanolysis from carboxylic acids (as in Step A) and mild acidic hydrolysis from hydroxyl groups, both being accomplished during product isolation. In addition to **2**, the N-9-phenylfluoren-9-yl derivatives of serine,[8] glutamic acid γ-methyl ester,[9] and aspartic acid β-methyl ester[4,10] have been prepared in this manner.

Substrates whose only reactive nucleophile is an amino group can be alkylated with 9-bromo-9-phenylfluorene using the method described in Step B. In addition to 4, the N-9-phenylfluoren-9-yl derivatives of glutamate diesters,[9] aziridines,[11] and N-alkyl aspartate diesters[4,12,13] have been prepared by this method.

Exclusion of moisture from the reagents and apparatus is most important, as 9-bromo-9-phenylfluorene hydrolyzes to 9-phenyl-9-fluorenol, which is unreactive toward free amines. Accordingly, all glassware, K_3PO_4, $Pb(NO_3)_2$ (which scavenges bromide ion), and substrates must be dried thoroughly (as described above) and kept under an inert atmosphere prior to use. In addition, solvents must be distilled immediately before use and transferred to the reaction vessel under an inert atmosphere.

The methanol quench in Step B facilitates chromatographic purification by forming the known 9-methoxy-9-phenylfluorene,[7] which is less polar than 9-phenyl-9-fluorenol, from 9-bromo-9-phenylfluorene (but not from 9-phenyl-9-fluorenol). Both 9-methoxy-9-phenylfluorene and 9-phenyl-9-fluorenol can be converted to 9-bromo-9-phenylfluorene by treatment with 48% hydrobromic acid (HBr).[5]

Both the stability[14] and rigid steric bulk of the 9-phenylfluoren-9-yl group have increased significantly the utility of amino acids N-protected in this way as chiral

educts for asymmetric synthesis. N-(9-Phenylfluoren-9-yl)-α-amino aldehydes maintain configurational stability at the αcarbon during treatment with silica gel or triethylamine and on treatment with Wittig and organometallic reagents.[3,8,15,16] N-(9-Phenylfluoren-9-yl)-α-amino ketones and esters behave similarly under these conditions, and they can also be regioselectively enolized and subsequently alkylated with a variety of electrophiles in good to excellent yield with modest to excellent diastereoselectivity, no detectable racemization, and no detectable alkylation on nitrogen or at the carbon corresponding to the αcarbon of the starting amino acid.[4,9,10,11,12,13,15,16] Consequently, these N-(9-phenylfluoren-9-yl)-α-amino carbonyl compounds have enabled the enantiospecific syntheses of many important compounds, including cyclosporin's unique amino acid MeBmt,[16] other unusual amino acids,[9,10] α-amino aldehydes,[3,8,15,16] vinca alkaloids,[4,12] (−)-vindoline,[13,17] α-alkyl branched carboxylic acids,[15] and the core nuclei of two antineoplastic agents.[11]

Removal of the 9-phenylfluoren-9-yl group has been accomplished by three different procedures: acidolysis with trifluoroacetic acid,[3,9,11,12,13] catalytic hydrogenolysis,[4,8,10,15,16] and dissolving metal reduction.[16]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 103

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

silica

L-Aspartic acid, N-(9-phenyl-9H-fluoren-9-yl-, dimethyl ester

acetic acid (64-19-7)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether, ethyl ether (60-29-7)

acetonitrile (75-05-8)

sodium hydroxide (1310-73-2)

citric acid (77-92-9)

chloroform (67-66-3)

sodium chloride (7647-14-5)

alanine, L-alanine (56-41-7)

HYDROBROMIC ACID (10035-10-6)

barium oxide

nitrogen (7727-37-9)

aluminum (7429-90-5)

acetone (67-64-1)

carbon (7782-42-5)

2-propanol (67-63-0)

lead nitrate (10099-74-8)

hexane (110-54-3)

serine (56-45-1)

triethylamine (121-44-8)

calcium hydride (7789-78-8)

trifluoroacetic acid (76-05-1)

CHLOROTRIMETHYLSILANE (75-77-4)

phosphorus oxide (1314-56-3)

potassium phosphate, tripotassium phosphate (7778-53-2)

9-Bromo-9-phenylfluorene (55135-66-5)

9-Phenyl-9-fluorenol (25603-67-2)

(S)-N-(9-Phenylfluoren-9-yl)alanine, L-Alanine, N-(9-phenyl-9H-fluoren-9-yl)- (105519-71-9)

(S)-Dimethyl N-(9-phenylfluoren-9-yl)aspartate (120230-62-8)

9-methoxy-9-phenylfluorene

(S)-Dimethyl aspartate hydrochloride

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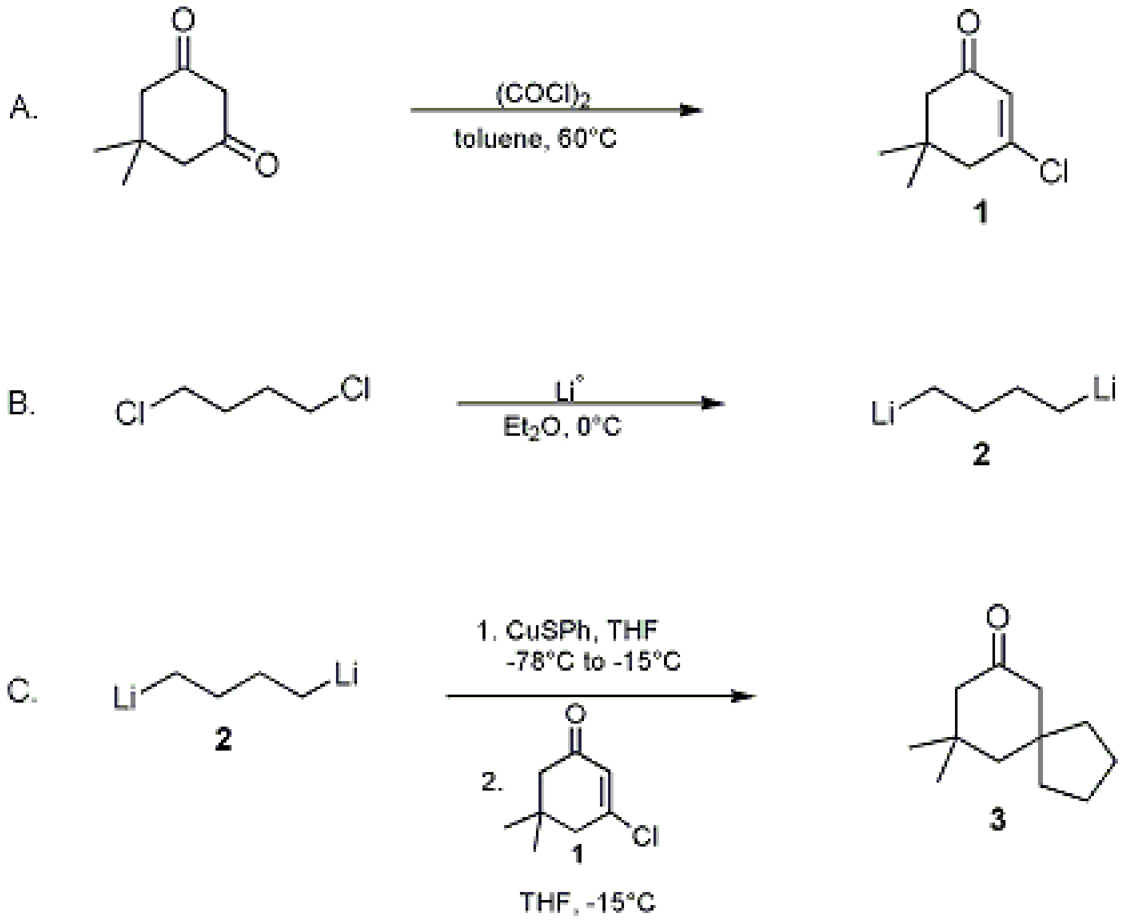
Organic Syntheses, CV 9, 350

SPIROANNELATION VIA ORGANOBIS(CUPRATES): 9,9-DIMETHYLSPIRO[4.5]DECAN-7-ONE

[Spiro[4.5]decan-7-one, 9,9-dimethyl-]



Submitted by Paul A. Wender[12], Alan W. White[1], and Frank E. McDonald[2].
Checked by Naoki Hirayama and Hisashi Yamamoto.

1. Procedure

Note: All reactions should be conducted in an efficient fume hood.

A. *3-Chloro-5,5-dimethylcyclohex-2-en-1-one* (**1**)[3,4] (Note 1). An oven-dried, 250-mL, one-necked, round-bottomed flask is equipped with a magnetic stirring bar and graduated addition funnel topped with a nitrogen inlet. The flask is charged with dimedone (28.1 g, 200 mmol) and toluene (100 mL) (Note 2). The suspension is stirred while oxalyl chloride (35 mL, 400 mmol) is slowly added via the addition funnel over a 10-min period (Note 3). After the addition is complete and gas evolution has subsided, the addition funnel is quickly exchanged for a reflux condenser topped with a nitrogen inlet. The mixture is then heated at 60–70°C for 30 min, or until no

more suspended dimedone remains and gas evolution has ceased. (Additional oxalyl chloride may be added until dimedone has completely reacted.) The reaction is allowed to cool and concentrated by rotary evaporation at reduced pressure. The crude red oil is distilled through a short path apparatus to give 3-chloro-5,5-dimethylcyclohex-2-en-1-one (**1**) (29.3 g, 93% yield) as a colorless oil, bp 68–71°C (6.0 mm) (Note 4).

B. *1,4-Dilithiobutane* (**2**).[5,6,7] (All transfers are conducted under dry nitrogen; reagents are introduced into reaction vessels through rubber septa using a cannula or syringe.) An oven-dried, 1-L, three-necked, round-bottomed flask is equipped with a large magnetic stirring bar and glass beads (ca. 3-mm diameter), graduated addition funnel, stopper, and large diameter nitrogen inlet (at least 2 mm in diameter). The flask is purged with nitrogen, charged with anhydrous diethyl ether (250 mL) (Note 2), and cooled to 0°C. The stopper is removed from the flask and replaced with a conical funnel while a rapid flow of dry nitrogen is passed through the flask. Lithium wire, 1% Na (9.48 g, 1.36 mol, 4.5 eq.) (Note 5), prewashed with hexanes, is held with forceps over the funnel and cut with clean scissors into pieces no larger than 2 mm in length (Note 6) so that the freshly cut lithium pieces drop directly into the anhydrous ether. 1,4-Dichlorobutane (33.5 mL, 300 mmol) (Note 2) is then dissolved in anhydrous diethyl ether (85 mL) and introduced into the addition funnel; approximately 10% of this solution is introduced into the lithium/ether suspension, and the reaction is initiated by vigorous stirring. A white precipitate (LiCl) signaling initiation of the reaction should be apparent within 5 to 15 min, at which time the remainder of the solution is added dropwise over a 1 to 2-hr period (Note 7). The white suspension is rapidly stirred for 20 hr at 0°C.

The mixture is most conveniently filtered by gravity filtration through an oven-dried coarse (15 •M) sintered glass frit (Note 8), (Note 9). The concentration of 1,4-dilithiobutane (**2**) in ether is determined by titration with sec-butyl alcohol using 1,10-phenanthroline as indicator. The molarity of the solution obtained under these optimized conditions is approximately 1.7 M in "RLi", i.e., 0.9 M in 1,4-dilithiobutane (**2**) (Note 10). This solution is stable for several months when stored at −10°C under nitrogen.

C. *9,9-Dimethylspiro[4.5]decan-7-one* (**3**).[6,7] (All transfers are conducted under dry nitrogen; reagents are introduced into reaction vessels through rubber septa using a cannula or syringe.) An oven-dried, 2-L, three-necked, round-bottomed flask is equipped with a graduated addition funnel, overhead mechanical stirrer, and a nitrogen inlet. The flask is purged with nitrogen and charged with copper(I) thiophenoxide (36.7 g, 212 mmol) and anhydrous tetrahydrofuran (400 mL) (Note 2), and the heterogeneous suspension is mechanically stirred while cooling in a −78°C cold bath (dry ice-acetone). 1,4-Dilithiobutane (**2**), 0.87 (± 0.02) M in diethyl ether (122 mL, 106 mmol) is added via the addition funnel over 5 min, and then the reaction mixture is allowed to slowly warm to −15°C (Note 11) over a 20 to 45-min period, during

which time the initial yellow color changes to brown-red with concomitant dissolution of copper thiophenoxide. The addition funnel is washed with a few milliliters of anhydrous tetrahydrofuran, and a solution of 3-chloro-5,5-dimethylcyclohex-2-en-1-one (**1**) (15.85 g, 100 mmol) in anhydrous tetrahydrofuran (250 mL) is added dropwise over a 1 to 2-hr period, while the temperature of the cold bath is maintained at −15°C to −20°C. The reaction turns olive-green and then black as the chloroenone is added. After the addition is complete, the cold bath is removed and the reaction flask is allowed to warm to room temperature.

After 30 to 45 min, the reaction mixture is opened to the air and poured into approximately 500 mL of saturated aqueous ammonium chloride solution, diluted with approximately 500 mL of diethyl ether washings, and allowed to stir for 10 to 15 min. The resulting mixture is filtered through a Büchner funnel, washing with small portions of diethyl ether (Note 12). The layers are separated in a separatory funnel, the aqueous layer is extracted with diethyl ether, and the combined organic layers are washed with water, saturated aqueous sodium bicarbonate, and saturated aqueous sodium chloride, dried over approximately 100 g of sodium sulfate, filtered through a Büchner funnel, and concentrated by rotary evaporation. The concentrated product may still contain solid diphenyl disulfide that can now be efficiently removed by chromatography of the neat crude product mixture through a 5-cm diameter × 10-cm height silica gel column and elution with hexane-diethyl ether (7:1) (Note 13). Evaporation of solvent by rotary evaporation at reduced pressure gives 13.28 g (74% yield) of 9,9-dimethylspiro[4.5]decan-7-one (**3**) as a pale yellow to colorless oil (Note 14).

2. Notes

1. This procedure is identical to that originally published by Heathcock and Clark,[3,4] except that toluene has been substituted for benzene and chloroform as the solvent, because of the relative health hazards associated with the latter two solvents.
2. Dimedone, oxalyl chloride, 1,4-dichlorobutane, and copper thiophenoxide were purchased from Fluka Chemical Corporation, and were used without further purification. The checkers purchased dimedone, oxalyl chloride and 1,4-dichlorobutane from Nacalai Tesque, Inc., Kyoto, Japan and Tokyo Kasei Kogyo Co., LTD, Japan, and prepared copper thiophenoxide from thiophenol and copper(I) oxide. Toluene, diethyl ether and tetrahydrofuran were distilled from sodium-benzophenone ketyl immediately prior to use.
3. The addition of oxalyl chloride was accompanied by much gas evolution, but no apparent exothermic reaction. Two equivalents of oxalyl chloride were required in order to consume completely the dimedone.[3,4]
4. The spectral properties of **1** were as follows: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.10 (s, 6 H), 2.26 (s, 2 H), 2.57 (d, 2 H, J = 1.4), 6.23 (t, 1 H, J = 1.4); IR (film) cm^{-1}: 2980 (m), 1680 (s), 1616 (m), 1346 (m), 1300 (m), 1276 (m), 1008 (m).

The submitters obtained 30.1 g (95% yield) of **1**, bp 79–80°C (7.5 mm).

5. Lithium wire was obtained from Aldrich Chemical Company, Inc. The use of 4.5 equiv of lithium represented a 12.5% excess. The use of only 4 equiv of lithium gave a lower titer of 1,4-dilithiobutane (**2**), and a small amount of unreacted lithium always remained even after prolonged reaction times.

6. The lithium wire must be freshly cut and in pieces not exceeding 2 mm in length. The yield dropped sharply when the average length of lithium wire was increased to 5 mm. The preparation of 1,4-dilithiobutane (**2**) from 1,4-dichlorobutane failed with the use of lithium shot[5] or low-sodium (<0.8% Na) lithium wire.

7. We have not yet observed an exothermic reaction in the initiation of this reaction, although maintaining the temperature at 0°C might help to control safely the lithiation reaction as well as to maximize the yield of 1,4-dilithiobutane (**2**).

8. Gravity filtration was preferred over vacuum filtration, since the latter method tended to pull LiCl through the frit. Small amounts of LiCl did not interfere with the formation or reaction of the biscuprate generated in Section C. The checkers used this solution without filtration.

9. In order to quench the small amount of unreacted lithium wire remaining in the reaction flask, the stopper was replaced by a reflux condenser open to the atmosphere at the top. Approximately 100 mL of diethyl ether was added to the reaction flask containing the lithium and the flask was cooled to 0°C under a stream of nitrogen. A 4:1 mixture of t-butyl alcohol : water was then added dropwise via the addition funnel until all of the lithium wire was consumed. *Caution: The quench is exothermic and is accompanied by the evolution of large amounts of hydrogen gas.* The mixture was then transferred to a separatory funnel for separation of the organic and aqueous layers followed by disposal.

10. Significant amounts of ether solvent are lost presumably by evaporation during the nitrogen flush and/or filtration steps. Thus, the molarity of the 1,4-dilithiobutane (**2**) solution is not an accurate indication of yield. The submitters titrated with menthol instead of with sec-butyl alcohol

11. Temperature control of the cold bath at −15°C was accomplished by addition of small amounts of dry ice to acetone and monitoring with a low-temperature thermometer. A slurry of dry ice in ethylene glycol was occasionally used as a −15°C cold bath.

12. The omnipresent solid contaminant was diphenyl disulfide, which was sparingly soluble in diethyl ether. Each filtration noted in the text was necessary for a successful workup on this large scale. The submitters used a medium (90 •m) sintered glass frit for these filtrations. The attempted removal of product **3** by distillation from diphenyl disulfide was largely unsuccessful because of efficient entrainment of **3** in diphenyl disulfide.

13. Pure **3** is best obtained by chromatography. Product **3** could also be purified by vacuum distillation through a 10-cm Vigreux column, bp 100–103°C (2.2 mm). However, distillation did not efficiently separate **3** from diphenyl

disulfide, and bumping was often a serious problem.

14. The spectral properties of **3** were as follows: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.02 (s, 6 H), 1.42–1.68 (m, 8 H), 1.70 (s, 2 H), 2.18 (s, 2 H); IR (film) cm^{-1}: 2950 (s), 1710 (s), 1450 (m), 1370 (m), 1280 (m), 1230 (m). The submitters obtained 13.01 g (72% yield) of **3**.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

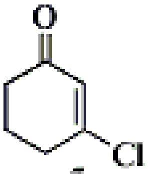
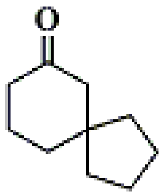
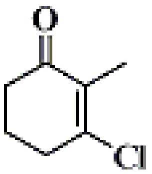
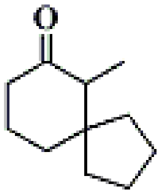
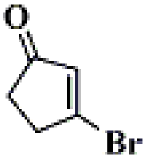
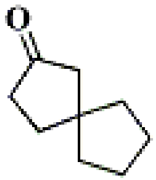
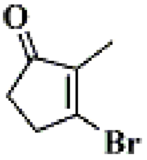
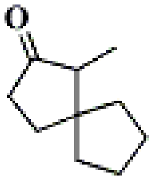
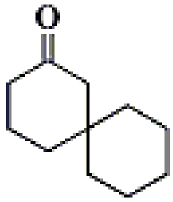
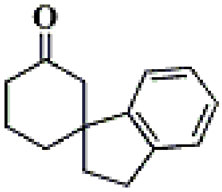
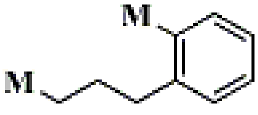
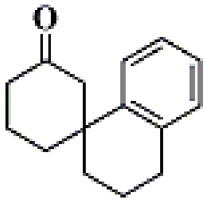
The procedure in Section C is representative of the synthesis of spirobicyclic systems featuring the reaction of bis(nucleophile) reagents with geminal bis(electrophile) acceptors. This strategy provides for formation of both carbon-carbon bonds of the new ring in a single step.

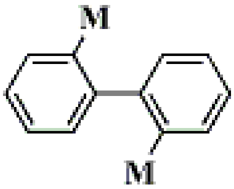
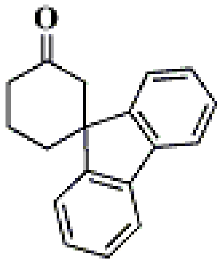
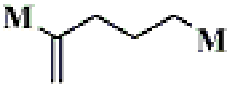
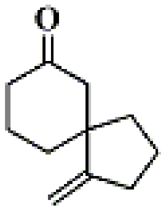
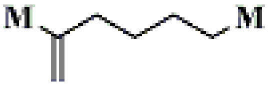
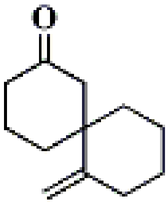
The starting material 3-chloro-5,5-dimethylcyclohex-2-en-1-one (**1**) is easily synthesized from dimedone by the general methodology developed by Clark and Heathcock.[3,4] The β-chlorine can also be replaced with a variety of carbon- and heteronucleophiles,[8] and β-chloroenones can be easily reduced by zinc/silver couple to the corresponding enone.[4]

The formation of 1,4-dilithiobutane (2) was first described by West and Rochow.[9] The original procedure was modified by Whitesides, et al., in their pioneering studies on the synthesis and reactivity of metallocyclopentanes.[5,10] The methodology described in Section B is general for the synthesis of a variety of 1,4- and 1,5-dilithioalkanes, as evident in the Table below.[6,7]

TABLE I
SPIROANNELATION USING ORGANOBIS(CUPRATES)

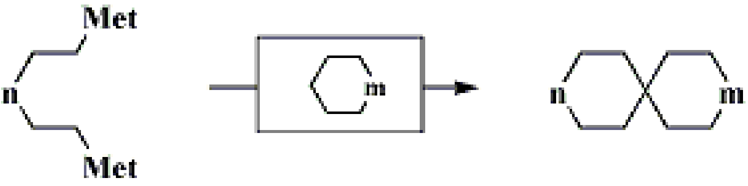
Reagent M = CuSPh	Equiv.	Substrate	Product	Time hr	Yield %
4	1.1	**1**	**3**	1	(96)

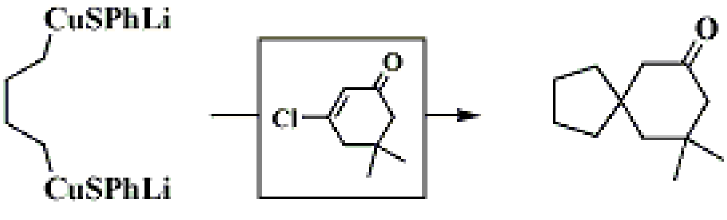
4	1.1	 **5**		1	(85)
4	1.1			1	(80)
	1.1			18	(93)
4	1.1			1	(87)
4	1.1			1	(76)
	4.0	**5**		1	(74)
	1.2	**5**		1	(49)
	3.0	**5**		2	88

	3.0	5		2	39
	10.0			2	94
	1.1	5		0.5	(66)
	4.0	5		0.5	(56)

Yields in parantheses were determined by internal standard gas chromatographic analysis.

The synthesis of 9,9-dimethylspiro[4.5]decan-7-one (**3**) uses the organobis(cuprate) derived from 1,4-dilithiobutane (**2**) as a bis(nucleophile) component, which is added to the bis(electrophile) 3-chloro-5,5-dimethylcyclohex-2-en-1-one (**1**).





2-(CuSPh)$_2$ **1** **3**

This methodology provides for spiroannelation at a carbon beta to the ketone, and is a complementary protocol for the cyclization of α,ω-dihaloalkanes to the kinetic enolates of 1,3-cycloalkanedione enol ethers (at the alpha position).[11]

The methodology has been successfully extended with modifications to both the bis (nucleophile) and the bis(electrophile) components, as shown in the Table.[6,7]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium-benzophenone ketyl

chloroenone

β-chlorine

β-chloroenones

organobis(cuprate)

Benzene (71-43-2)

ether, diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

hydrogen (1333-74-0)

chloroform (67-66-3)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

acetone (67-64-1)

copper(I) oxide

toluene (108-88-3)

zinc (7440-66-6)

sodium (13966-32-0)

ethylene glycol (107-21-1)

menthol (15356-60-2)

Thiophenol (108-98-5)

silver (7440-22-4)

lithium (7439-93-2)

dimedone (126-81-8)

Tetrahydrofuran (109-99-9)

1,4-dichlorobutane (110-56-5)

oxalyl chloride (79-37-8)

hexane (110-54-3)

t-butyl alcohol (75-65-0)

diphenyl disulfide (882-33-7)

sec-butyl alcohol (78-92-2)

1,10-phenanthroline (66-71-7)

copper(I) thiophenoxide (34012-88-9)

9,9-Dimethylspiro[4.5]decan-7-one, Spiro[4.5]decan-7-one, 9,9-dimethyl- (63858-64-0)

3-Chloro-5,5-dimethylcyclohex-2-en-1-one (17530-69-7)

1,4-Dilithiobutane

copper thiophenoxide

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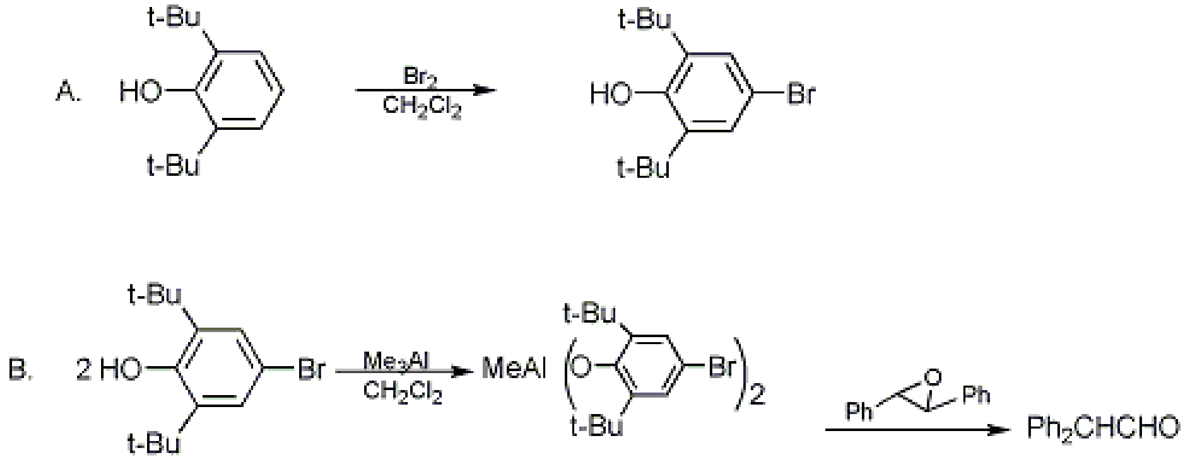
Organic Syntheses, CV 9, 356

REARRANGEMENT OF trans-STILBENE OXIDE TO DIPHENYLACETALDEHYDE WITH CATALYTIC METHYLALUMINUM BIS(4-BROMO-2,6-DI-tert-BUTYLPHENOXIDE)

[Oxirane, 2,3-diphenyl-, trans- to Benzeneacetaldehyde, α-phenyl-]



Submitted by Takashi Ooi, Keiji Maruoka, and Hisashi Yamamoto[1].
Checked by Catherine Gasparski and Larry E. Overman.

1. Procedure

A. *4-Bromo-2,6-di-tert-butylphenol*. A dry, 1-L, three-necked, round-bottomed flask is fitted with a gas inlet, rubber septum, pressure-equalizing dropping funnel, magnetic stirring bar, and a gas outlet tube that is connected to a gas trap containing 0.5 M sodium hydroxide (NaOH). The flask is charged with 103.2 g (500 mmol) of 2,6-di-tert-butylphenol (Note 1) and flushed with argon, after which 200 mL of dry dichloromethane (Note 2) is added. The dropping funnel is charged with 28.2 mL (550 mmol) of bromine and 20 mL of dry dichloromethane. The reaction vessel is immersed in an ice-water bath, stirring is initiated, and bromine in dichloromethane is added over 1 hr. The reaction mixture is stirred at 0°C for 10–20 min (Note 3). Then 60 mL of saturated aqueous sodium sulfite is added slowly at 0°C and stirring is continued at room temperature until the light orange color of bromine is discharged, The mixture is poured into a 1-L separatory funnel containing 400 mL of saturated aqueous sodium bicarbonate (Note 4). The heavier organic layer is separated and the aqueous layer is extracted with two 75-mL portions of dichloromethane. The combined extracts are dried over sodium sulfate and concentrated with a vacuum rotary evaporator. The residue is recrystallized twice from ethanol-water (first with 130 mL of ethanol and 18 mL of water, then with 110 mL of ethanol and 11 mL of water) to furnish 109 g (76% yield) of 4-bromo-2,6-di-tert-butylphenol (Note 5) as light yellow crystals, mp 83–85°C. Pure 4-bromo-2,6-di-tert-butylphenol is reported to melt at 81–82°C.[2]

B. *Diphenylacetaldehyde*. A dry, 1-L, three-necked, round-bottomed flask is equipped with a gas inlet, rubber septum, pressure-equalizing dropping funnel, and a magnetic stirring bar. The flask is charged with 3.42 g (12 mmol) of 4-bromo-2,6-di-tert-butylphenol and flushed with argon, after which 600 mL of freshly distilled dichloromethane is added. The mixture is stirred, degassed under

vacuum, flushed with argon, and 3 mL (6 mmol) of a 2 M hexane solution of trimethylaluminum (Me_3Al, (Note 6)) is injected through the septum to the flask at room temperature. The resulting solution is stirred at this temperature for 1 hr to give methylaluminum bis(4-bromo-2,6-di-tert-butylphenoxide) almost quantitatively (Note 7). The reaction vessel is cooled to a temperature of −20°C in a dry ice/o-xylene bath (Note 8). Then 11.8 g (60 mmol) of trans-stilbene oxide (Note 9) is dissolved in 25 mL of dry dichloromethane, transferred to the dropping funnel, and added over 15–20 min at −20°C. The mixture is stirred at −20°C for 4 hr. After addition of 1.01 g (24 mmol) of sodium fluoride, 324 •L (18 mmol) of water is injected dropwise at −20°C (Note 10). The entire mixture is vigorously stirred at −20°C for 5 min and at 0°C for 30 min. The contents of the flask are filtered with the aid of three 50-mL portions of dichloromethane (Note 11),(Note 12),(Note 13),(Note 14),(Note 15). The combined filtrates are concentrated to ca. 100 mL under reduced pressure with a rotary evaporator. Silica gel (35 g) is added and the remainder of the dichloromethane is removed using a rotary evaporator. The residue is layered on a column of silica gel (500 g, column diameter: 9.5 cm) (Note 12) and eluted (ether/dichloromethane/hexane, 1:2:20 to 1:1:10 as eluants) to give 10.3 g (87%) of diphenylacetaldehyde as a colorless oil (Note 16) and (Note 17).

2. Notes

1. 2,6-Di-tert-butylphenol was obtained from Nacalai Tesque Co. and used without any purification.
2. Solvent grade dichloromethane was dried and stored over Linde type 4 Å molecular sieves.
3. The reaction is conveniently followed by TLC (silica gel, 10:1:1 hexane-CH_2Cl_2-ether).
4. The extractive workup is performed carefully to avoid vigorous evolution of carbon dioxide gas.
5. The product has the following spectral properties: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.39 (s, 18 H, 2 t-Bu), 5.15 (s, 1 H, OH), 7.24 (s, 2 H, Ar-H).
6. Neat trimethylaluminum was obtained from Toso-Akzo Chemical Company Ltd. (Japan) and used as a 2 M hexane solution. The checkers used similar material obtained from Aldrich Chemical Company, Inc.
7. During this operation, nearly 2 equiv of methane gas are evolved per 1 equiv of trimethylaluminum.
8. o-Xylene is recommended as refrigerant in place of carbon tetrachloride.
9. trans-Stilbene oxide was obtained from Aldrich Chemical Company, Inc., and used without any purification.
10. To avoid excessive foaming on hydrolysis water should be added carefully by syringe.
11. The sodium fluoride-water workup offers an excellent method for large-scale preparations, and is generally applicable to product isolation in the reaction of organoaluminum compounds.[3]
12. The checkers report that GLC analysis (Note 13) at this point shows that the product is contaminated with ca. 4% of trans-stilbene oxide and <1% of the Tischenko product (Note 14).
13. Gas chromatography conditions are as follows: Supelco fused silica capillary SPB-1 column (30 m, 0.32-mm ID, 0.25 micrometers df), 100°C initial temperature, 280°C final temperature, 10°C/min. The following retention times were obtained: diphenylacetaldehyde (6.7 min), trans-stilbene oxide (7.4 min), Tischenko product (18.2 min).
14. The Tischenko product, $Ph_2CHCO_2CH_2CHPh_2$, has the following properties: mp, 95–98°C, ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.35 (t, 1 H, J = 7.5), 4.70 (d, 2 H, J = 7.5), 4.92 (s, 1 H), 7.11–7.40 (m, 20 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 49.7, 57.2, 67.4, 126.8, 127.1, 128.2,

128.47, 128.53, 138.3, 140.8, 172.2; HRMS (CI, isobutane) Calcd for $C_{28}H_{24}O_2$: 393.1854 (MH); Found: 393.1829; IR (CCl_4) cm^{-1}: 3094–2906, 1737, 1600, 1494, 1450, 1144.

15. Merck Kieselgel 60 (Art. 9385) was used. The checkers found that loading the column in this way avoids precipitation of a by-product during column elution. The chromatography removes a few percent of remaining epoxide and 4-bromo-2,6-di-tert-butylphenol.

16. The product is >99% pure by capillary GLC analysis (Note 13) and has the following spectral characteristics: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 4.92 (d, 1 H, J = 2.6, CH), 7.20–7.49 (m, 10 H, 2 Ph), 9.98 (d, 1 H, J = 2.6, CHO).

17. The rearrangement is considerably faster when the reaction solution is more concentrated. If 480 mL of dichloromethane is used, the rearrangement is complete within 20 min at −20°C. However, the checkers found that the crude product is contaminated with 3–10% of the Tischenko product (Note 14), which is difficult to remove by chromatography. This by-product can be removed by vacuum distillation (bp 136–144°C, 2 mm). Using this combined purification procedure, the checkers obtained 9.6 g (81%) of diphenylacetaldehyde of >99% purity by capillary GLC analysis (Note 13).

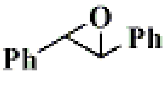
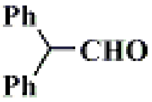
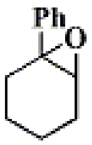
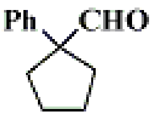
Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

This catalytic procedure illustrates a general method for preparing a wide range of carbonyl compounds by the selective rearrangement of epoxides under the influence of the exceptionally bulky, oxygenophilic methylaluminum bis(4-bromo-2,6-di-tert-butylphenoxide) (MABR) as catalyst.[4] The advantages of catalytic versions include economy, ease of large-scale preparation and isolation, and the synthetic potential for in situ derivatization of the carbonyl products. Use of a sodium fluoride-water (NaF-H_2O) workup[3] further simplifies the experimental operation. As revealed in Tables I and II, the amount of the catalyst varies from 5 to 20 mol% depending on the epoxy substrates. Yields when MABR is used stoichiometrically are also included for comparison. Certain epoxy substrates require stoichiometric MABR. Neither epoxides derived from monsubstituted olefins nor from certain internal dialkyl-substituted olefins can be rearranged by MABR, however, even using two equivalents.

TABLE I
MABR-CATALYZED REARRANGEMENT OF EPOXIDES

Epoxide	MABR (mol %)	Product	Yield (%)
	200		93
	10		95
	200		98
	10		96
	5		91
	200		87

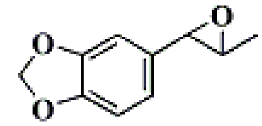
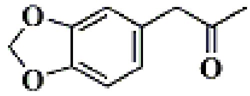
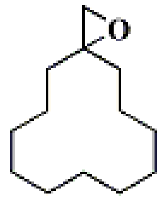
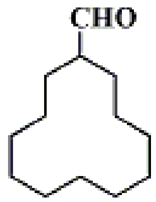
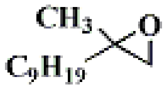
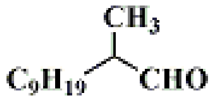
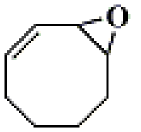
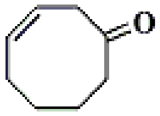
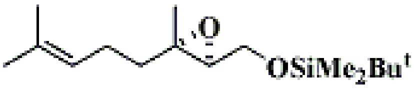
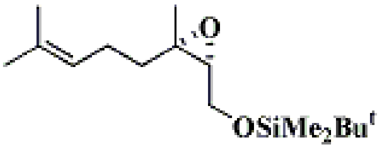
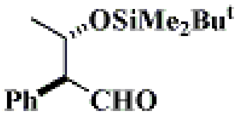
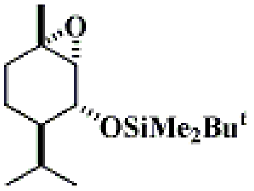
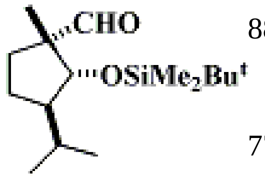
	10 5		90 84
	200 20		94 58
	200 20		96 0
	200 20		73 0

TABLE II
MABR-CATALYZED REARRANGEMENT OF CHIRAL EPOXY SILYL ETHERS

Epoxy Silyl Ether	MABR (mol %)	β-Siloxy Aldehyde	Yield (%)
	200 20 10		99 82 74
	200 20 10		98 79 68
	200 20 10		87 74 71
	200 20		88 77

The MABR-promoted rearrangement, when applied to optically active epoxy substrates, has been

shown to proceed with rigorous transfer of the epoxide chirality. Accordingly, used in combination with the Sharpless asymmetric epoxidation of allylic alcohols,[5] this rearrangement represents a new approach to the synthesis of various optically active β-siloxy aldehydes, useful intermediates in natural product synthesis (Table II).[4,6]

The stronger coordination of a carbonyl oxygen than an epoxide oxygen to an aluminum reagent requires the stoichiometric use of MABR at low temperature. The key element of the present modification is the use of a higher reaction temperature (though still at or below 0°C) than the previously reported conditions[7] in order to induce dissociation of the aluminum reagent-carbonyl complex, thereby allowing regeneration of MABR as catalyst for further use in the catalytic cycle of the reaction. The facile dissociation of the organoaluminum-carbonyl complex as well as the smooth rearrangement of epoxides is apparently ascribable to the exceptional bulkiness of MABR compared to other ordinary Lewis acids.[8] The less bulky methylaluminum bis(4-bromo-2,6-diisopropylphenoxide) was found to be totally ineffective for the rearrangement of the tert-butyldimethylsilyl ether of epoxy geraniol.

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

methylaluminum bis(4-bromo-2,6-di-tert-butylphenoxide) (MABR)

Dry Ice

ethanol (64-17-5)

ether (60-29-7)

sodium sulfite (7757-83-7)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

bromine (7726-95-6)

sodium sulfate (7757-82-6)

oxygen (7782-44-7)

carbon tetrachloride (56-23-5)

carbon dioxide (124-38-9)

methane (7782-42-5)

dichloromethane (75-09-2)

sodium fluoride (7681-49-4)

hexane (110-54-3)

Diphenylacetaldehyde, Benzeneacetaldehyde, α-phenyl- (947-91-1)

argon (7440-37-1)

trimethylaluminum (75-24-1)

trans-Stilbene oxide, Oxirane, 2,3-diphenyl-, trans- (1439-07-2)

Methylaluminum bis(4-bromo-2,6-di-tert-butylphenoxide) (118495-99-1)

4-Bromo-2,6-di-tert-butylphenol (1139-52-2)

2,6-di-tert-butylphenol (128-39-2)

o-Xylene (95-47-6)

Methylaluminum bis(4-bromo-2,6-diisopropylphenoxide)

tert-butyldimethylsilyl ether

epoxy geraniol

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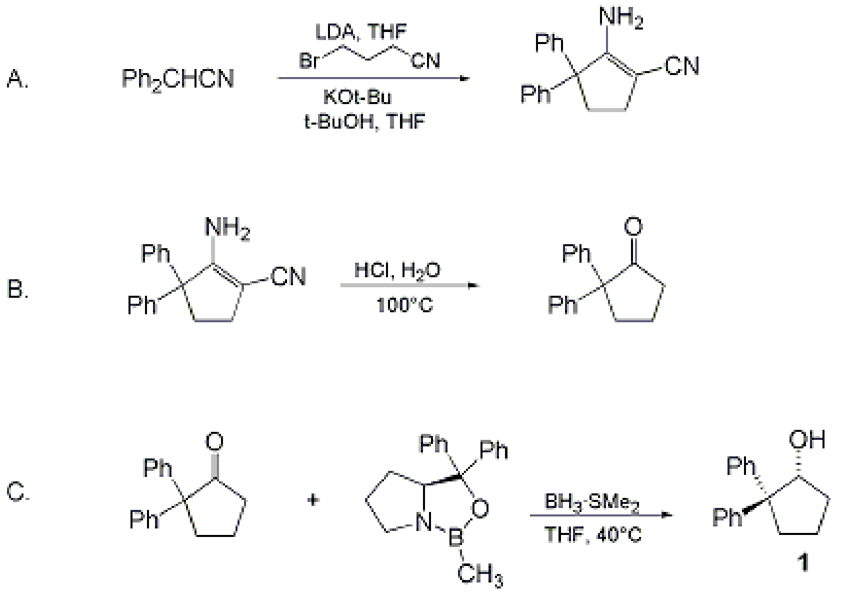
Organic Syntheses, CV 9, 362

(R)-(–)-2,2-DIPHENYLCYCLOPENTANOL

[Cyclopentanol, 2,2-diphenyl-, (R)-]



Submitted by Scott E. Denmark, Lawrence R. Marcin, Mark E. Schnute, and Atli Thorarensen[1].
Checked by David J. Mathre, Khateeta M. Emerson, and Ichiro Shinkai.

1. Procedure

A. *2-Amino-3,3-diphenyl-1-cyclopentene-1-carbonitrile*. To a 2-L, three-necked, round-bottomed flask equipped with a 250-mL, pressure-equalizing addition funnel, magnetic stirrer, nitrogen/vacuum adapter, and a thermometer is added 39.9 mL (0.29 mol) of diisopropylamine and 200 mL of tetrahydrofuran (THF) (Note 1), (Note 2). The solution is cooled to 0°C, and 101.6 mL of butyllithium (2.55 M in hexane, 0.26 mol) is added slowly (Note 3). After 10 min, a solution of 50.0 g (0.26 mol) of diphenylacetonitrile (Note 4) in 200 mL of THF is added over 30 min forming a deep yellow solution. A solution of 28.3 mL (0.29 mol) of 4-bromobutyronitrile (Note 5), (Note 6) in 200 mL of THF is then added over 20 min. The resulting bright-yellow solution is allowed to warm slowly to room temperature overnight (10 hr) (Note 7). The reaction mixture is quenched by the slow addition of water (25 mL) and then is diluted with 400 mL of tert-butyl methyl ether (MTBE), and washed with water (2 × 100 mL) and brine (100 mL). The aqueous layers are back-extracted with MTBE (100 mL). The combined organic layers are dried with sodium sulfate (Na_2SO_4), concentrated on a rotary evaporator, and the resulting crude dinitrile is placed under high vacuum (0.2 mm) for 1 hr. The dinitrile is transferred to a 2-L, three-necked, round-bottomed flask equipped with a reflux condenser, magnetic stirrer, nitrogen/vacuum adapter, and a thermometer and is dissolved in a mixture of tert-butyl alcohol (400 mL) and THF (200 mL). To the solution is added 23.25 g (0.21 mol) of potassium tert-butoxide, and the suspension is heated at 60°C (internal temperature) for 2 hr. After the reaction mixture is cooled to room temperature, it is quenched with water (25 mL), diluted with MTBE (500 mL), and washed with water (100 mL) and brine (3 × 100 mL). The aqueous layers are back-extracted with MTBE (100 mL), and the combined organic layers are dried (Na_2SO_4) and concentrated on a rotary evaporator to afford an off-white granular solid. The crude product is suspended in MTBE (75 mL), cooled (0°C), filtered, and

recrystallized from absolute ethanol (400 mL). The mother liquor is concentrated on a rotary evaporator, purified by column chromatography on silica gel (330 g) (Note 8) eluting with hexane/EtOAc (4/1), and recrystallized from absolute ethanol to afford a combined yield of 57.7 g (86%) of the enaminonitrile as a white solid (Note 9),(Note 10).

B. *2,2-Diphenylcyclopentanone*. To a 3-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, thermometer, and wide inner-spiral reflux condenser (Note 11) is added 57.5 g (0.22 mol) of the enaminonitrile from step A and 800 mL of concd hydrochloric acid (HCl, (Note 12)). The mixture is stirred for 5 min, and 800 mL of water is added. The reaction mixture is heated to reflux (heating mantle, 110°C internal temperature) with vigorous stirring for 4 days (Note 13), (Note 14), (Note 15). The reaction mixture is cooled to room temperature, and extracted with dichloromethane (CH_2Cl_2, 5 × 200 mL). The organic layers are washed with saturated aqueous sodium bicarbonate ($NaHCO_3$, 100 mL) and brine (100 mL), and the aqueous layers are back-extracted with dichloromethane (100 mL). The combined organic layers are dried ($MgSO_4$) and concentrated on a rotary evaporator. The crude product is recrystallized from MTBE (300 mL). The mother liquor is concentrated on a rotary evaporator, and purified by column chromatography on silica gel (250 g) eluting with hexane/EtOAc (4/1), decolorized with carbon, and recrystallized from MTBE to afford a combined yield of 48.2 g (92%, (Note 16)) of the ketone as a white solid (Note 17), (Note 18)).

C. *(R)-(–)-2,2-Diphenylcyclopentanol* **1**. In a 500-mL, three-necked, round-bottomed flask, equipped with a 125-mL graduated, pressure-equalizing addition funnel, 30-mm, egg-shaped magnetic stir bar, nitrogen/vacuum adapter, and an internal temperature probe is placed 1.76 g (6.34 mmol) of the B-methyloxazaborolidine catalyst (Note 1), (Note 19), (Note 20). The apparatus is evacuated, flushed with nitrogen, charged with 86 mL of dry THF and 6.34 mL (63.4 mmol) of borane-methyl sulfide complex, and then warmed to 40°C (internal temperature) (Note 21). In a 250-mL, three-necked, round-bottomed flask, equipped with a nitrogen/vacuum adapter and magnetic stirrer is placed 15 g (63.4 mmol) of 2,2-diphenylcyclopentanone. The flask is evacuated, flushed with nitrogen, and charged with 111 mL of dry THF. After dissolution, the ketone solution is transferred to the addition funnel via cannula and added dropwise over 8 hr to the stirred catalyst solution maintained at 40°C (Note 22). After complete addition, the funnel is rinsed into the reaction vessel with 10 mL of dry THF, and the resulting reaction mixture is stirred at 40°C for an additional 30 min. Finally, the reaction mixture is cooled to 0–5°C and carefully quenched by the dropwise addition of 100 mL of methanol (*CAUTION: considerable hydrogen evolution occurs after a short induction period*) (Note 23). The cold bath is removed and the reaction is stirred until gas evolution ceases (Note 24). The resulting solution is poured into a 1-L, round-bottomed flask and the reaction vessel is rinsed with 50 mL of methanol. A simple distillation head is attached to the 1-L flask and 100 mL of solvent is distilled (*CAUTION: the distillate contains malodorous methyl sulfide*). An additional 100 mL of fresh methanol is added and 100 mL of solvent is again distilled. The residue is cooled to room temperature and concentrated on a rotary evaporator to afford a slightly yellow oil. The oil is dissolved in MTBE (250 mL), washed with aqueous 0.1 N aqueous hydrochloric acid (3 × 100 mL), and the combined acidic, aqueous phases are back-extracted with MTBE (100 mL). The combined organic phases are washed with water (100 mL) and brine (100 mL), dried (Na_2SO_4), filtered, and concentrated on a rotary evaporator to afford 15.1 g of an off-white solid. The solid is purified by bulb-to-bulb distillation (bp 180°C/0.2 mm) to afford 14.7 g (97%) of (R)-(–)-2,2-diphenylcyclopentanol (92% ee) as an analytically-pure, white solid (Note 25), (Note 26). Multiple recrystallizations of the product from hexane afford 11.3 g (75%) of (R)-(–)-2,2-diphenylcyclopentanol (>97% ee) (Note 26), (Note 27), (Note 28). To recover the catalyst precursor, (S)-α,α-diphenyl-2-pyrrolidinemethanol, the acidic, aqueous phase is made basic (blue to litmus) by addition of 25 mL of aqueous 25% sodium hydroxide solution. The aqueous phase is extracted with dichloromethane (3 × 100 mL), and the combined organic phases are washed with brine (100 mL), dried (Na_2SO_4), filtered, and concentrated on a rotary evaporator to afford a clear oil that crystallizes under high vacuum (0.1 mm, several hours). The solid is recrystallized from hexane to afford 1.5 g (93% recovery) of (S)-α,α-diphenyl-2-pyrrolidinemethanol as a white crystalline solid (Note 29).

2. Notes

1. All glassware was dried in an oven (140°C) and after assembly was allowed to cool under an atmosphere of dry nitrogen.
2. THF was freshly distilled from sodium/benzophenone. tert-Butyl alcohol was purchased from Aldrich Chemical Company, Inc., and was used without further purification. Solvents for extraction and chromatography were technical grade and distilled from the indicated drying agents: hexane ($CaCl_2$); dichloromethane ($CaCl_2$); tert-butyl methyl ether (MTBE) ($CaSO_4/FeSO_4$); ethyl acetate (K_2CO_3).
3. Butyllithium was freshly titrated by the method of Gilman.[2] Excess strong base, either butyllithium or lithium diisopropylamide (LDA), (exceeding 1 equiv per diphenylacetonitrile) should be avoided since the resulting Thorpe-Ziegler cyclization product is susceptible to fragmentation under the reaction conditions to afford 1,1-

dicyano-4,4-diphenylbutane.

4. Diphenylacetonitrile was purchased from Aldrich Chemical Company, Inc., and recrystallized from hexane (mp 73–75°C).

5. 4-Bromobutyronitrile was purchased from Aldrich Chemical Company, Inc., and was freshly distilled (bp 95–98°C, 15 mm).

6. 4-Iodobutyronitrile may also be used as a less expensive alternative available from 4-chlorobutyronitrile[3] by a modification of the above procedure. The increased reactivity of the iodide, however, requires a more tedious procedure, but is provided as follows:

A. *4-Iodobutyronitrile*. To a 1-L, three-necked, round-bottomed flask equipped with a mechanical stirrer and a reflux condenser is placed a solution of 70 mL (0.77 mol) of 4-chlorobutyronitrile in 420 mL of acetone. To the solution is added 123.4 g (0.82 mol) of sodium iodide, and the resulting clear solution is heated to reflux for 23 hr. Over time, the formation of large amounts of a white precipitate is observed. The resulting suspension is cooled to room temperature, filtered, and the filter cake is washed with dichloromethane (200 mL). The combined organic layers are concentrated on a rotary evaporator. The residue is redissolved into dichloromethane (200 mL), washed with saturated aqueous sodium thiosulfate ($Na_2S_2O_3$, 50 mL) and brine (50 mL), dried (Na_2SO_4), and concentrated on a rotary evaporator. The resulting oil is distilled (bp 80–92°C/0.8 mm) to afford 141.6 g (92%) of 4-iodobutyronitrile as a clear colorless oil.

B. *2-Amino-3,3-diphenyl-1-cyclopentene-1-carbonitrile*. In a 1-L, three-necked, round-bottomed flask, a solution of 53.8 mL (0.38 mol) of diisopropylamine in 250 mL of dry THF is cooled to –70°C. To the solution is slowly added 118 mL of butyllithium (2.95 M in hexane, 0.34 mol) at such a rate that the internal temperature never exceeds –50°C. The resulting solution is cooled to –70°C, and a solution of 67.5 g (0.34 mol) of diphenylacetonitrile in 250 mL of dry THF is added over 30 min forming a black solution that is stirred an additional 20 min. In a 2-L, three-necked, round-bottomed flask, a solution of 4-iodobutyronitrile (74.9 g, 0.38 mol) in 250 mL of dry THF is cooled to –77°C. Using a Teflon cannula (0.5-cm diameter) the anion of diphenylacetonitrile is added very rapidly to the 4-iodobutyronitrile solution (internal temperature rose by only 3°C). The resulting light-yellow solution is stirred for 80 min at –78°C, warmed to 0°C for 60 min, and allowed to stir at room temperature for 30 min. The reaction mixture is quenched with water (34 mL), diluted with MTBE (500 mL), and washed with water (2 × 250 mL) and brine (250 mL). The aqueous layers are back-extracted with MTBE (200 mL), and the combined organic layers are dried (Na_2SO_4) and concentrated on a rotary evaporator. The resulting crude dinitrile is dissolved in a mixture of tert-butyl alcohol (540 mL) and THF (270 mL). To the solution is added 31.0 g (0.28 mol) of potassium tert-butoxide, and the suspension is heated at 60°C (internal temperature) for 2 hr. After the reaction mixture is cooled to room temperature, it is diluted with MTBE (600 mL), and washed with water (150 mL) and brine (3 × 150 mL). The aqueous layers are back-extracted with MTBE (150 mL), and the combined organic layers are dried ($MgSO_4$) and concentrated on a rotary evaporator. The crude product is suspended in MTBE (75 mL), cooled, filtered, and recrystallized from absolute ethanol (600 mL) to afford 67.5 g of pure ketone. The mother liquor is concentrated on a rotary evaporator, purified by column chromatography [hexane/EtOAc (8/1, 4/1)], and crystallized from absolute ethanol to afford 8.6 g (9.5%) of additional material for a combined yield of 76.1 g (84%) of analytically pure enaminonitrile as a white solid giving identical spectral data to that reported above (Anal. Calcd for $C_{18}N_{16}N_2$: C, 83.04; H, 6.20; N, 10.76. Found: C, 83.06; H, 6.20; N, 10.74).

7. The following reverse-phase HPLC assay was developed to monitor steps A-C. Column: YMC J'Sphere H80 (4.6 × 250 mm); eluent: 45:55 H_2O (20 mM H_3PO_4)/MeCN; flow rate: 1.0 mL/min; column temp.: 45°C; detection: UV (210 nm). Retention times: "diphenylprolinol" (1.85 min, with solvent front); 4-bromobutyronitrile (4.0 min); "enaminoamide" (6.1 min); "dinitrile" (11.4 min); diphenylacetonitrile (12.0 min); "cyanoketone" (12.5 min); diphenylcyclopentanol (13.1 min); "enaminonitrile" (14.4 min); "diphenylcyclopentanone" (19.5 min).

8. Kieselgel 60 (230–400 mesh) was purchased from EM Science.

9. Rather than purifying the mother liquors by column chromatography, the checkers obtained a second crop of crystals for a combined yield of 57.3 to 60.3 g (85–89%). The checkers also note that the crude product can be used "as is" in the next step after being suspended and washed with cold MTBE.

10. The physical properties are as follows: mp 145–148°C; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.46 (dd, 2 H, J = 6.8, 5.6), 2.63 (dd, 2 H, J = 7.6, 6.3), 4.38 (br, 2 H, NH_2), 7.23–7.37 (m, 10 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 27.94, 41.48, 62.76, 76.19, 118.77, 127.08, 128.19, 128.40, 142.82, 164.78; IR (CCl_4) cm^{-1}: 3490 (w), 3395 (w), 3063 (w), 2954 (w), 2863 (w), 2197 (m), 1643 (s), 1595 (m); MS (EI, 70 eV) 260 (M^+, 100), 259 (31), 183 (49), 182 (36); TLC R_f = 0.38 (hexane/EtOAc, 4/1). Anal. Calcd for $C_{18}H_{16}N_2$: C, 83.05; H, 6.19; N, 10.76. Found: C, 83.34; H, 6.07; N, 10.84.

11. The product may sublime into the condenser causing it to become clogged. This can be prevented by periodically washing down the solids with 6 N HCl.

12. To ensure complete consumption of the intermediate cyano ketone, the ratio of enaminonitrile to solvent volume cannot be altered.

13. Efficient stirring and heating to a vigorous reflux is crucial for complete consumption of the intermediate cyano ketone.

14. The reaction progress can be monitored by ^{1}H NMR integration of the signals of the ketone (dt, 1.95 ppm, 2 H) and the cyano ketone intermediate (t, 3.43 ppm, 1 H) determined from a crude reaction sample following the same work-up as reported above. Spectral data for 2-cyano-5,5-diphenylcyclopentanone are as follows: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.22 (m, 1 H), 2.47 (m, 1 H), 2.70 (ddd, 1 H, J = 12.5, 9.8, 6.1), 2.90 (dt, 1 H, J_d = 12.5, J_t = 6.1), 3.43 (t, 1 H, J = 9.0), 7.15–7.40 (m, 10 H). Alternatively, high pressure liquid chromatography (HPLC) analysis may be used employing a Supelco LC-Si (5•, 250 × 4.5 mm) column (hexane/EtOAc, 9/1, 1.5 mL/min, detector λ = 254 nm); R_t: "ketone" (4.6 min, response factor = 1.50), R_t: "cyano ketone" (16.8 min, response factor = 0.76).

15. The progress of the reaction was monitored by HPLC. The checkers found the reaction to take from 4 to 7 days to reach > 99% completion.

16. Yields ranged from 84% to 92%.

17. Rather than purifying the mother liquors by column chromatography, the checkers obtained a second crop of crystals for a combined yield of 87–95%.

18. The physical properties are as follows: mp 85–88°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.95 (dt, 2 H, J_d = 13.4, J_t = 7.3) 2.46 (t, 2 H, J = 7.7), 2.73 (t, 2 H, J = 6.6), 7.21–7.32 (m, 10 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 18.79, 38.07, 38.16, 62.44, 126.69, 127.96, 128.31, 142.02, 217.77; IR (CCl_4) cm^{-1}: 3061 (m), 3033 (m), 2969 (m), 2886 (m), 1744 (s), 1494 (s), 1446 (m), 1406 (m), 1143 (m), 1104 (m); MS (EI, 70 eV) 236 (M^+, 47), 208 (11), 180 (100), 179 (37), 178 (25), 165 (43); TLC R_f = 0.48 (hexane/EtOAc, 8/1). Anal. Calcd for $C_{17}H_{16}O$: C, 86.41; H, 6.82. Found: C, 86.57; H, 6.75.

19. A Baxter Diagnostics Inc. Type K Thermo-Couple Thermometer was used to monitor the internal temperature of the reaction solution.

20. (S)-Tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaborole was prepared from (S)-proline in two steps according to the literature procedure[4] and purified by bulb-to-bulb distillation (170°C, 0.2 mm). The enantiomeric purity of the intermediate, (S)-α,α-diphenyl-2-pyrrolidinemethanol, was determined to be >99% ee by chiral HPLC analysis of its corresponding N-p-toluenesulfonamide derivative (DIACEL Chiralcel OD column; hexane/ethanol, 92/8; 1.0 mL/min; R_t(S) 8.6 min; R_t(R) 12.8 min). The checkers used the crystalline β-methyloxazaborolidine-borane complex (1.84 g, 6.34 mmol) as the catalyst.

21. Borane-methyl sulfide complex was purchased from Aldrich Chemical Company, Inc., and was used without purification.

22. Addition of the ketone solution over a 6-hr period affords almost identical results. However, variation of the reaction temperature can have a dramatic effect on product ee.[5]

23. Anhydrous, reagent-grade methyl alcohol was purchased from Mallinckrodt Inc. and used without purification.

24. Hydrogen evolution stops after 2–3 hr; however, for convenience the reaction can be allowed to stand at room temperature overnight with no deleterious effect on yield or enantioselectivity.

25. Anal. Calcd for $C_{17}H_{18}O$: C, 85.67; H, 7.61. Found: C, 85.65; H, 7.63.

26. Enantiomeric excess is determined by chiral HPLC analysis (DIACEL Chiralcel OJ column; hexane/ethanol, 70/30; 1.0 mL/min; R_t: S-isomer (8.8 min); R_t: R-isomer (17.9 min).

27. The checkers determined enantiomeric purity by supercritical fluid chromatography (SFC) using a Chiralpak AD (4.6 × 250 mm) column. Eluent: carbon dioxide (300 Bar); modifier: methanol (24%); flow rate: 1.5 mL/min; detection: UV (210 nm). Retention times were as follows: "diphenylcyclopentanone" (3.9 min); (R)-diphenylcyclopentanol (5.9 min); (S)-diphenylcyclopentanol (10.4 min).

28. The product is recrystallized two times by dissolution in boiling hexane (60 mL and 50 mL) and cooling to room temperature to provide 9.8 g of material with greater than 97% ee. The mother liquors are then combined, concentrated and recrystallized four times from hexane (20 mL, 15 mL, 10 mL and 10 mL) to provide 1.5 g of additional (R)-(−)-2,2-diphenylcyclopentanol with greater than 97% ee. The physical properties are as follows: mp 76–77°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.28 (dd, 1 H, J = 4.9, 0.7), 1.55–1.75 (m, 2 H), 1.93 (m, 1 H), 2.10 (m, 1 H), 2.32 (ddd, 1 H, J = 12.9, 8.7, 3.3), 2.66 (dt, 1 H, J_t = 12.9, J_d = 8.9), 4.88 (dd, 1 H, J = 9.7, 4.8), 7.14–7.33 (m, 10 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.95, 31.67, 34.60, 59.71, 77.57, 125.89, 126.33, 126.92, 128.17, 128.44, 128.53, 144.26, 146.87; MS (EI, 70 eV) 239 (8), 238 (M^+, 44), 78 (12), 167 (100), 115 (16), 91 (11); IR (CCl_4) cm^{-1}: 3585 (m), 3061 (m), 3025 (w), 2967 (s), 2916 (w), 1495 (s), 1446 (s), 1288 (w), 1094 (m), 1074 (m), 1034 (m), 1015 (m); $[\alpha]_D^{26}$ −114.8° (EtOH, *c* 1.17). Anal. Calcd for $C_{17}H_{18}O$: C, 85.67; H, 7.61. Found: C, 85.65; H, 7.59.

29. The solid is recrystallized by dissolution in boiling hexane (20 mL) and cooling to 0°C to afford 1.37 g of (S)-α,α-diphenyl-2-pyrrolidinemethanol. The mother liquor is then concentrated and recrystallized from hexane (10 mL) to afford an additional 0.13 g of material. The physical properties are as follows: mp 75–76°C; ^{1}H NMR (400

MHz, $CDCl_3$) 1.58–1.74 (m, 4 H), 2.96 (m, 1 H), 3.02 (m, 1 H), 4.26 (t, 1 H, J = 7.6), 7.14–7.59 (m, 10 H).

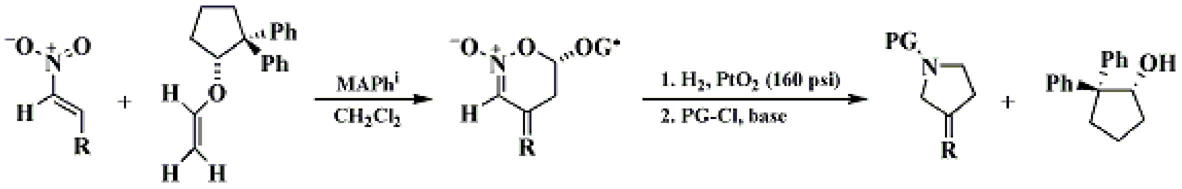
Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995. The malodorous, methanol distillate resulting from the borane reduction was first treated with commercial bleach before disposal.

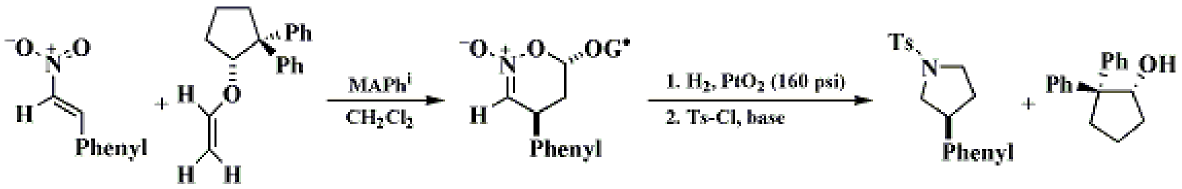
3. Discussion

(R)-(–)-2,2-Diphenylcyclopentanol **(1)** is a highly effective chiral auxiliary in asymmetric synthesis. Hydrogenation of chiral β-acetamidocrotonates derived from this alcohol has afforded the corresponding β-amido esters with high diastereoselectivity (96% de).[6] In addition, (R)-**1** has been used as a chiral auxiliary in Mn(III)-based oxidative free-radical cyclizations to provide diastereomerically enriched cycloalkanones (60% de).[7] Our interest in (R)-(–)-2,2-diphenylcyclopentanol is its utility as a chiral auxiliary in Lewis acid-promoted, asymmetric nitroalkene [4+2] cycloadditions. The 2-(acetoxy)vinyl ether derived from alcohol (R)-**1** is useful for the asymmetric synthesis of 3-hydroxy-4-substituted pyrrolidines from nitroalkenes (96% ee).[8] In a similar fashion, a number of enantiomerically enriched (71–97% ee) N-protected, 3-substituted pyrrolidines have been prepared in two steps from 2-substituted 1-nitroalkenes and (R)-2,2-diphenyl-1-ethenoxycyclopentane **(2)** (see Table).[9]

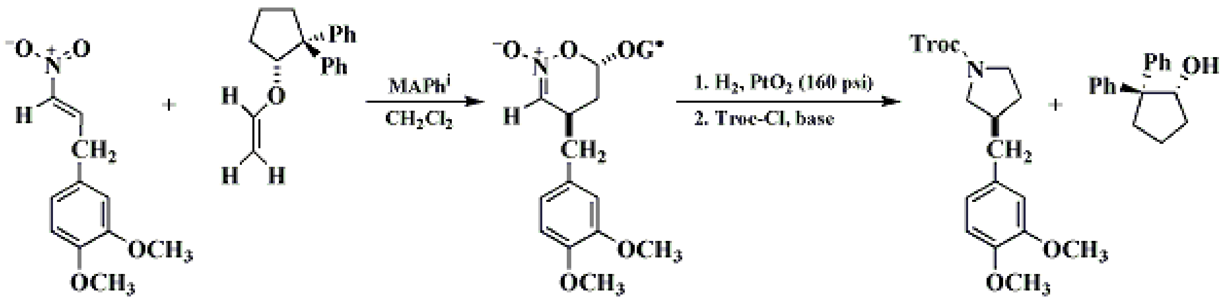
TABLE I
SYNTHESIS OF OPTICALLY ACTIVE 3-SUBSTITUTED PYRROLIDINES



2 3 4

R	Yield 3, %	PG	Base	Yield 4, %	ee, %
phenyl  2 3 4	89	Ts	Et_3N	80	91

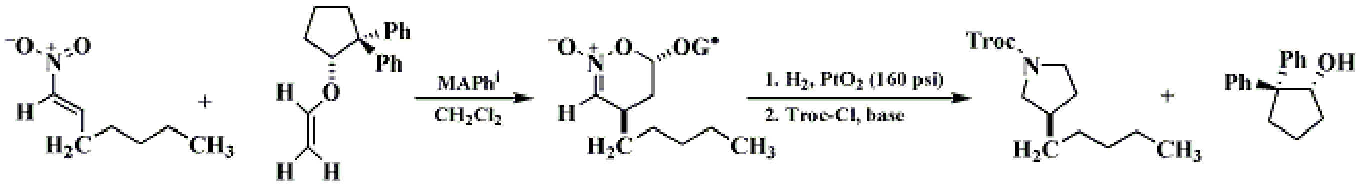
veratryl



2 3 4

91 Trocpyridine 76 71

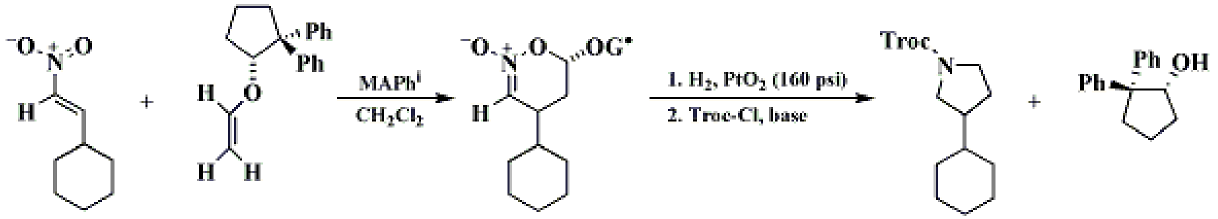
pentyl



2 3 4

88 Trocpyridine 72 93

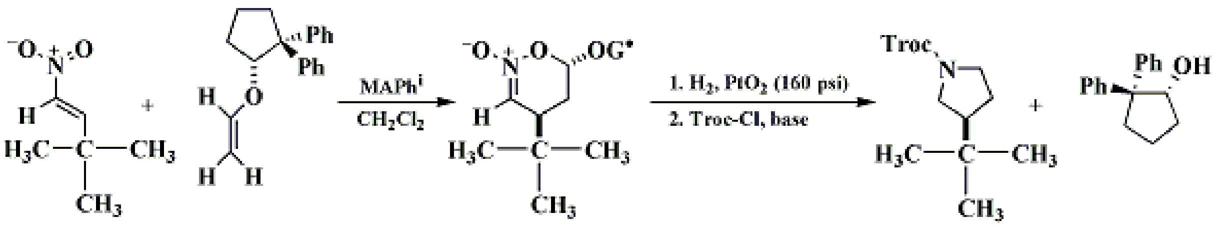
cyclohexyl



2 3 4

84 Trocpyridine 79 91

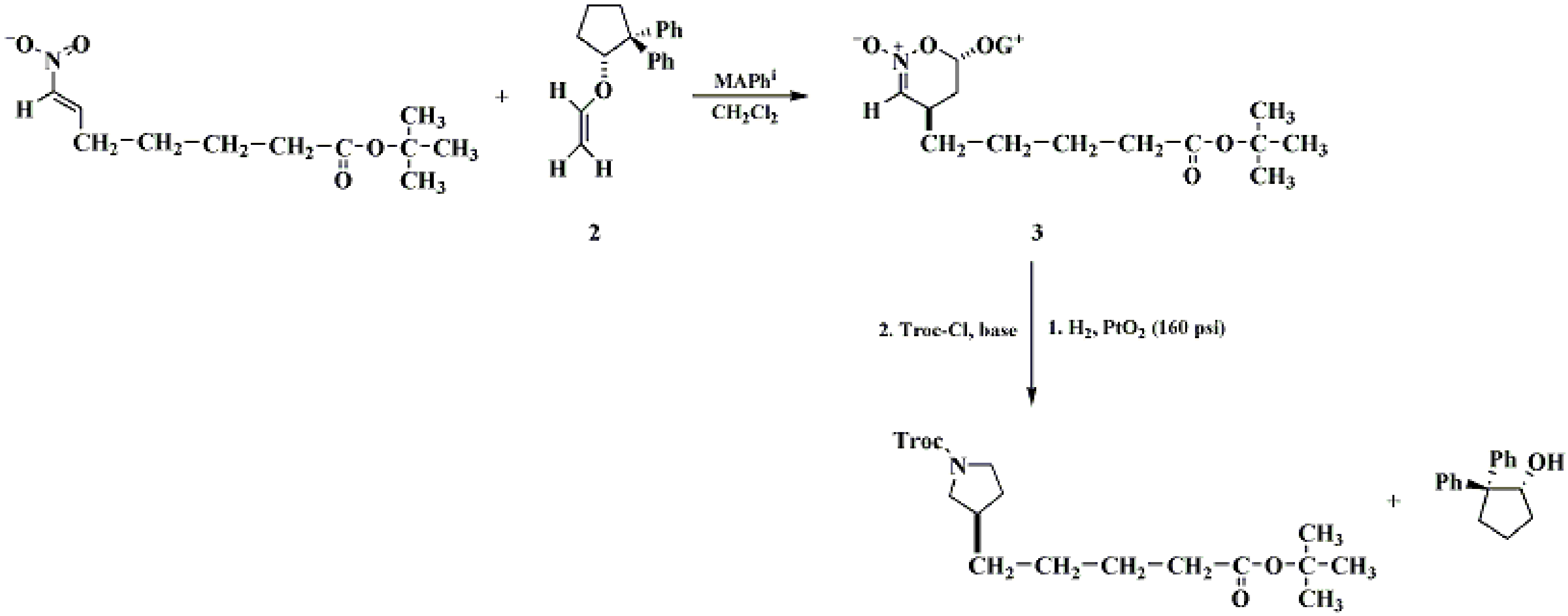
tert-butyl



2 3 4

91 Trocpyridine 80 77

-$(CH_2)_4CO_2$-tert-Bu



2 3 4

92 Trocpyridine 69 97

i) Methylaluminum bis-2,6-diphenylphenoxide.

2,2-Diphenylcyclopentanone previously has been synthesized several times employing three general approaches.[10 11 12 13,14 15,16] The most common approach involves alkylation of diphenylacetonitrile with a 4-halobutyronitrile followed by Thorpe-Ziegler cyclization and acid hydrolysis to afford the ketone.[10,11,12,13] One- and two-step preparations of the enaminonitrile have been reported. The best results have been obtained by using sodium amide in liquid ammonia (70% yield).[11] Acid hydrolysis (H_2SO_4) of the enaminonitrile is

reported to afford the desired ketone in only moderate yields employing tedious procedures. Alternatively, the ketone is available by allylation of diphenylacetic acid followed by Lewis acid promoted Friedel Crafts acylation to afford the 5,5-diphenyl-2-cyclopentenone.[14,15] Subsequent reduction provided the ketone, however, only in 20% overall yield.[15] A more recent and more conceptually attractive approach involves the one step diphenylation of cyclopentanone trimethylsilyl enol ether with diphenyliodonium fluoride (DIF) giving the desired ketone in 51% yield.[16] The disadvantage of this approach lies in the preparation of the DIF reagent, available in one step from very expensive diphenyliodonium iodide or in five steps from inexpensive, available starting materials.

The procedure described here represents a reliable modification of the alkylation/Thorpe-Ziegler approach to 2,2-diphenylcyclopentanone applicable to large-scale preparations. The use of LDA as the alkylation base, in exact stoichiometry, has been found to avoid over-reaction and the undesired fragmentation pathway of the enaminonitrile observed with sodium amide. The Thorpe-Ziegler cyclization proceeds smoothly employing modified literature conditions[10] with potassium tert-butoxide as the base. Hydrolysis of the enaminonitrile with hydrochloric acid,[17] was found to be superior to previously reported methods, which led to incomplete consumption of the intermediate cyano ketone in our hands. The ratio of solvent volume to enaminonitrile is very important and more concentrated reaction mixtures result in incomplete conversion of the cyano ketone even after prolonged heating.

Asymmetric reduction of the ketone on a 1.0-g (4.0-mmol) scale to provide (R)-(–)-2,2-diphenylcyclopentanol (96% ee) has been reported employing (+)-β-chlorodiisopinocampheylborane; however, the reaction is extremely slow and inefficient [70% yield, 5 days, 2.6 equiv of (+)-β-chlorodiisopinocampheylborane].[6] Other efforts to obtain enantiomerically pure **1** by means of enzymatic hydrolysis of the corresponding racemic acetates using horse liver acetone powder (HLAP) and pig liver acetone powder (PLAP) have been only moderately successful and are of limited utility [4.0-mmol scale, 28% yield, 96.5% ee (R)].[18]

The oxazaborolidine-catalyzed borane reduction of 2,2-diphenylcyclopentanone provides an efficient and useful alternative for the asymmetric synthesis of (R)-**1** on a preparative scale. Variation of several reaction parameters such as catalyst loading, solvent, temperature, and addition order, have led to the development of an optimized procedure for this reduction. To achieve a selectivity of >90% ee, the reaction requires the use of 10 mol% of the oxazaborolidine catalyst, which is easily prepared in two steps from natural proline[4] or in one step from commercially available (S)-α,α-diphenylpyrrolidinemethanol. When using a smaller catalyst loading a significant decrease in selectivity is observed [5 mol% cat. provides 87% ee (R)-**1**]. The oxazaborolidine catalyst used in these experiments was purified by bulb-to-bulb distillation prior to use and quickly weighed in the open atmosphere. Examination of the purified catalyst by ^{1}H NMR confirmed the presence of B-methyloxazaborolidine as well as varying amounts of the hydrated adduct (approximately 7–20%).[4] Unfortunately, it is not clear whether the hydrated adduct was the result of trace amounts of water in the NMR solvent, exposure to atmospheric moisture, or simply insufficient purification. Regardless, the use of different batches of the catalyst provided reproducible results that are within experimental error [(R)-**1** with 91–94% ee]. Several solvents such as toluene, dichloromethane and THF have been reported to be useful in oxazaborolidine reductions;[19] however, for the reduction of 2,2-diphenylcyclopentanone the use of THF was found to provide the highest enantioselectivity. An extremely important parameter in this reaction is temperature. The reaction displays an inverse temperature effect with respect to enantioselectivity, where decreased selectivity is observed at lower temperatures. This interesting phenomenon in oxazaborolidine-catalyzed reductions has precedents,[5] and can be attributed to the slow breakdown of the catalyst-product complex at low temperatures. The catalyst-product complex is a highly active but less selective catalyst for the reduction of the starting ketone.[20] Accumulation of this undesired intermediate can be avoided by running the reaction at higher temperatures (40°C) as well as using a slow inverse addition of the ketone to the catalyst-borane mixture.

The oxazaborolidine-catalyzed borane reduction to prepare (R)-**1** is an improvement over existing methods such as the β-chlorodiisopinocampheylborane reduction,[6] and enzymatic resolution[18] for several reasons. First, the reaction uses an easily obtained *catalytic* reducing agent that provides the chiral alcohol in 92% ee. Secondly, the reaction proceeds at a reasonable rate (6–8 hr) and affords the chiral alcohol (92% ee) in nearly quantitative yield (97%). Finally, the work-up, isolation and purification of the product is straightforward and requires no column chromatography, only bulb-to-bulb distillation and recrystallization, affording (R)-**1** in 75% yield with 97% ee. In addition, the catalyst precursor, (S)-α,α-diphenylpyrrolidinemethanol, can be easily recovered in excellent yield.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

(+)-β-chlorodiisopinocampheylborane

β-chlorodiisopinocampheylborane

brine

(R)-(–)-2,2-DIPHENYLCYCLOPENTANOL

Methylaluminum bis-2,6-diphenylphenoxide

β-methyloxazaborolidine

ethanol (64-17-5)

hydrochloric acid, HCl (7647-01-0)

ammonia (7664-41-7)

ethyl acetate (141-78-6)

methyl alcohol, methanol (67-56-1)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

sodium thiosulfate (7772-98-7)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

acetone (67-64-1)

carbon (7782-42-5)

pyridine (110-86-1)

toluene (108-88-3)

Benzophenone (119-61-9)

sodium (13966-32-0)

4-chlorobutyronitrile (628-20-6)

Diphenylacetic acid (117-34-0)

sodium iodide (7681-82-5)

dichloromethane (75-09-2)

borane (7440-42-8)

methyl sulfide (75-18-3)

sodium amide (7782-92-5)

butyllithium (109-72-8)

proline, (S)-proline (147-85-3)

Tetrahydrofuran (109-99-9)

4-bromobutyronitrile (5332-06-9)

Diphenylacetonitrile (86-29-3)

DIPHENYLIODONIUM IODIDE (2217-79-0)

hexane (110-54-3)

tert-butyl alcohol (75-65-0)

cyano ketone (1115-12-4)

lithium diisopropylamide (4111-54-0)

diisopropylamine (108-18-9)

Cyclopentanol, 2,2-diphenyl-, (R)- (126421-67-8)

2-Amino-3,3-diphenyl-1-cyclopentene-1-carbonitrile (3597-67-9)

tert-butyl methyl ether (1634-04-4)

potassium tert-butoxide (865-47-4)

2,2-Diphenylcyclopentanone (15324-42-2)

B-methyloxazaborolidine

1,1-dicyano-4,4-diphenylbutane

4-Iodobutyronitrile (6727-73-7)

diphenylcyclopentanol

2-cyano-5,5-diphenylcyclopentanone (2674-76-2)

(S)-Tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaborole (112022-81-8)

N-p-toluenesulfonamide (70-55-3)

2-(acetoxy)vinyl ether

5,5-diphenyl-2-cyclopentenone

diphenyliodonium fluoride

oxazaborolidine

(S)-α,α-diphenyl-2-pyrrolidinemethanol

(R)-diphenylcyclopentanol

(S)-diphenylcyclopentanol

(R)-2,2-diphenyl-1-ethenoxycyclopentane

(S)-α,α-diphenylpyrrolidinemethanol

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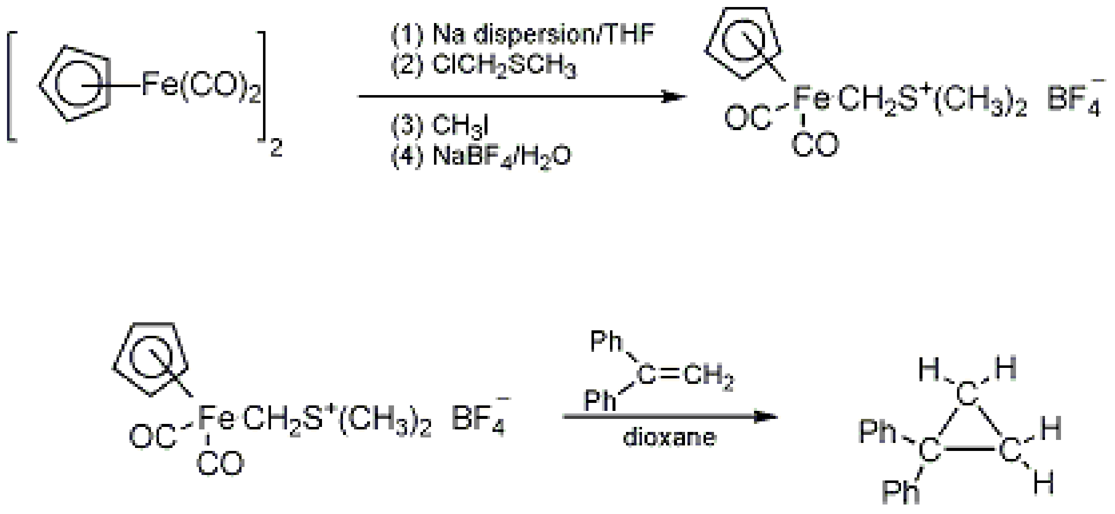
CYCLOPROPANATION USING AN IRON-CONTAINING METHYLENE TRANSFER REAGENT: 1,1-DIPHENYLCYCLOPROPANE

[Iron (1+), dicarbonyl(η5-2,4-cyclopentadien-1-yl)(dimethylsulfonium η-methylide)-, tetrafluoroborate (1-) and Benzene, 1,1'-cyclopropylidenebis-]



Submitted by Matthew N. Mattson[1], Edward J. O'Connor[2], and Paul Helquist[1].
Checked by Jörn-Bernd Pannek and Ekkehard Winterfeldt.

1. Procedure

CAUTION! This experiment should be performed in an efficient fume hood because of the unpleasant odors of sulfide-containing materials. In addition, the first part of this procedure should be conducted behind a safety shield because of the use of highly reactive sodium metal.

Into a dry, one-necked, 2000-mL, round-bottomed flask is placed a medium-sized magnetic stirring bar (Note 1) and cyclopentadienyliron dicarbonyl dimer $[C_5H_5(CO)_2Fe]_2$, (0.50 mol equiv, 0.21 mol, 74.4 g; (Note 2) and (Note 3)). Sodium dispersion (40% by weight) in light mineral oil (1.25 mol equiv, 0.52 mol, 30.1 g; (Note 4) and (Note 5)) is weighed into the flask (Note 6). The flask is then equipped with a reflux condenser topped with a three-way stopcock (Note 7) having a vertical tubulation capped with a septum through which solvents and reagents can be introduced with long needles or cannulas. By evacuation through the other tubulation of the stopcock, the apparatus is evacuated and filled with nitrogen twice, then placed under vacuum (≤0.1 mm) for 1 to 2 hr to remove the bulk of the mineral oil. The flask is filled with nitrogen, and tetrahydrofuran (THF; 850 mL; (Note 8)) is transferred into the flask.

Rapid stirring is begun and maintained while an oil bath or a heating mantle is employed to heat the mixture at reflux for ≥ 18 hr.

The flask is cooled to 0°C in an ice bath, and chloromethyl methyl sulfide (1.00 mol equiv, 0.42 mol, 35.2 ml) is added dropwise with a syringe over 25 min (Note 9) and (Note 10). After residues of the sulfide are rinsed into the flask with additional THF (ca. 5–10 mL), the mixture is stirred at 0°C for 1 hr and then at 25°C for 1 hr (Note 11). Iodomethane (1.30 mol equiv, 0.55 mol, 34.0 mL; (Note 12)) is added over 5 min using a syringe. After residues of iodomethane are rinsed into the flask with THF (5–10 mL), the mixture is stirred at 25°C for ≥ 15 hr. Stirring is stopped (Note 13), and the volatile materials are removed under vacuum (≤0.1 mm) using a large, liquid nitrogen-cooled trap (Note 14). The vacuum in the apparatus is relieved with nitrogen, and the three-way stopcock is removed from the top of the condenser, exposing the reaction mixture to air.

In a 2000-mL Erlenmeyer flask containing a magnetic stirring bar, a solution of sodium tetrafluoroborate (6.00 mol equiv, 2.52 mol, 277 g) in water (1200 mL total volume of solution) is prepared and heated to 95°C while being stirred. A 1000-mL portion of the hot sodium tetrafluoroborate solution solution is slowly poured down the condenser into the reaction mixture which is kept at ca. 95°C while being stirred. At the same time, a 350-mL, medium-frit, sintered-glass Büchner funnel is prepared with a 2.5-cm layer of diatomaceous earth and a 1-cm layer of sand covered with a piece of filter paper with holes punched in it, and the funnel is preheated by passage, with suction, of 700–1000 mL of hot, distilled water which is then discarded. The condenser is removed from the reaction flask, and the contents are suction-filtered through the hot funnel into a heated, 2000-mL filter flask (Note 15). The remaining hot sodium tetrafluoroborate solution is used to rinse the reaction flask and the hot funnel. The combined filtrates are swirled while being cooled. If necessary, a seed crystal can be added. The filtration flask is placed in an ice bath while swirling is continued. After the temperature reaches 0°C, the flask is placed in a freezer at ca. –10°C for 1–3 hr. The product is collected by suction filtration using a large, chilled Büchner funnel (Whatman no. 1 filter paper) and is rinsed with ice-cold distilled water (150 mL) and cold diethyl ether (1500 mL). The filter cake is broken up, and the crystals are dried in a stream of air overnight. There is obtained 100.6 g (70.4%) of $(\eta^5\text{-}C_5H_5)(CO)_2FeCH_2S^+(CH_3)_2\ BF_4^-$ as free-flowing, flake-like, amber crystals (Note 16),(Note 17),(Note 18). The yields were found to be considerably lower on runs of smaller scale (Note 19).

Into a 200-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar are placed the crystalline reagent (35 g, 0.10 mol; (Note 20)), 1,1-diphenylethene (9.1 mL, 9.3 g, 0.05 mol; (Note 21)), and dioxane (25 mL; (Note 22) and (Note 23)). The flask is equipped with a reflux condenser topped with a stopcock, and a nitrogen atmosphere (Note 24) is established within the apparatus. While being stirred vigorously, the heterogeneous mixture is heated to reflux in an oil bath (120°C) for 14 hr (Note 25). The brown mixture is removed from the oil bath and allowed to cool sufficiently to permit the addition of hexane (75 mL, (Note 26)) to the flask. The

mixture is stirred in the air until the flask reaches 25°C. The supernatant liquid containing the product is poured from the flask and filtered through Whatman no. 1 filter paper. The remaining solid is repeatedly suspended and washed with several portions of hexane (ca. 1000 mL total; (Note 27)). The combined filtrates are filtered through a pad of silica gel in a sintered glass Büchner funnel and are then concentrated by rotary evaporation. The residual dark brown oil is dissolved in methanol (200 mL) to give an orange-brown solution which immediately becomes dark green when solid ferric chloride (7 g; (Note 28)) is added at 25°C. The mixture is stirred for 15 min and then concentrated by rotary evaporation. The residual dark green oil is extracted with two 200-mL portions of hexane, and the combined extracts are filtered through a pad of silica gel and concentrated by rotary evaporation. The colorless oil that remains is distilled through a short-path apparatus to give 8.76 g (88%) of 1,1-diphenylcyclopropane as a clear, colorless liquid, bp 89°C (0.8 mm; lit[3] 110–111°C, 1.3 mm; (Note 29)). The checkers obtained 65–77% yield of product on roughly half the scale.

2. Notes

1. The stirring bar must be able to stir the heterogeneous reaction mixture rapidly. Very good stirring is required for the metallic sodium dispersion to react efficiently. A medium-sized, egg-shaped stirring bar (32 × 16 mm, available from Fisher Scientific Company) was found to be particularly effective.
2. Cyclopentadienyliron dicarbonyl dimer $[C_5H_5(CO)_2Fe]_2$ can be purchased from Alfa Products, Morton/Thiokol Inc. or Aldrich Chemical Company, Inc. Alternatively, it is easily and inexpensively prepared by heating dicyclopentadiene with iron pentacarbonyl. Our yield (80–90%) of this reagent is considerably higher than that reported in the literature procedure.[4]
3. In order to allow for proper placement of the sodium dispersion in the flask later (Note 5), the $[C_5H_5(CO)_2Fe]_2$ was neatly piled in a mound on top of the stirring bar in the middle of the bottom of the flask.
4. The 40% (by weight) sodium dispersion in light mineral oil was used as obtained from Aldrich Chemical Company, Inc., except for thorough shaking immediately prior to transfer of the dispersion.
5. A 1-cm diameter glass tube narrowed to a tip at one end and equipped with a pipet bulb was used to transfer the dispersion which was carefully placed around the perimeter of the mound of $[C_5H_5(CO)_2Fe]_2$. After evaporation of the oil, the stirring bar should rest in the center of the ring of sodium without contacting it. In this way, the reaction mixture can subsequently be stirred more efficiently. Also, all of the sodium should lie below the surface of the tetrahydrofuran solution formed, so that the mixture reacts efficiently upon being heated at reflux.
6. The procedure described here for reductive cleavage of this compound with sodium dispersion[5] to give sodium cyclopentadienyldicarbonylferrate is considerably more convenient and less hazardous than the more traditional use

of sodium amalgam that was reported previously.[6 7 8]

7. The stopcock used in this procedure is of the design shown in f.htmigure 1. A source of inert gas and vacuum can be attached to the horizontal tubulation. The vertical tubulation is capped with a septum to allow introduction of liquid reagents and solvents through use of a long syringe needle or cannula inserted through the septum and down through the body of the stopcock. In order to avoid air leaks through the septum into the reaction apparatus when reagents are not being added, the stopcock is normally turned to close off the vertical tubulation, but to leave the flask open to the nitrogen/vacuum source.

Figure 1

Figure 1

8. Commercial, anhydrous-grade tetrahydrofuran (THF) is further purified by distillation from a dark blue or purple solution of sodium benzophenone ketyl or dianion under nitrogen. One method for transferring the THF into the reaction flask is through the use of cannulas. The cannulas (available from Aldrich Chemical Company, Inc.) are constructed from 60-cm sections of 18-gauge stainless steel tubing with a needle tip at each end. It is perhaps more convenient to use two short sections of needle tubing (each having a needle point at only one end) joined with 25–50 cm of small-diameter Teflon tubing. Transfer through the cannula is facilitated by applying a slight vacuum to the reaction apparatus while maintaining a positive pressure of nitrogen in the flask originally containing the distilled THF. Alternatively, the THF can be distilled directly into the reaction flask.

9. Chloromethyl methyl sulfide was obtained from Aldrich Chemical Company, Inc. and distilled under nitrogen prior to use, although direct use of the commercial material without distillation had little effect on the overall efficiency of this procedure.

10. *WARNING:* Chloromethyl methyl sulfide has a very unpleasant, penetrating odor and should be handled in a properly ventilated fume hood. Also, because of its structural similarity to chloromethyl methyl ether which is highly toxic and an OSHA-regulated carcinogen, this sulfide should be handled as a substance having potentially similar toxic properties.

11. The product of this alkylation step is $(\eta^5\text{-}C_5H_5)(CO)_2FeCH_2SCH_3$ which is used directly in the next step but which, if desired, can be isolated as a dark yellow-brown, somewhat air-sensitive oil in greater than 90% yield.[9,10 11]

12. Iodomethane (99%) was used as obtained from Aldrich Chemical Company, Inc. Excess iodomethane is used to quench any unreacted sodium metal.

13. At this point, the flask can be swirled so that any small amounts of sodium adhering to the wall of the flask above the solution level can be coated with the reaction mixture.

14. Trapping of the unreacted chloromethyl methyl sulfide in the cold trap is recommended because of the problems summarized in (Note 10).

15. In order for this filtration to proceed smoothly, the funnel and its contents

must remain hot to avoid premature crystallization of the product and clogging of the funnel. Minor clogging can be remedied by addition of a 100-mL portion of boiling distilled water to the funnel. Major clogging may require addition of boiling water and agitation of the filtration media with a spatula. This addition, however, may reduce the yield of the crystallized product.

16. Physical data for this compound are the following: mp 129–130°C (corrected); IR (KBr pellet) cm^{-1}: 3120, 3035, 2040, 1955, 1417, 1328, 1280, 1055, 852; ^1H NMR (80 MHz, CD_3NO_2) δ: 2.72 (s, 2 H, CH_2), 3.00 (s, 6 H, 2 CH_3), 5.34 (s, 5 H, C_5H_5); ^{13}C NMR (20 MHz, CD_3NO_2) 13.35 (CH_2), 31.20 (CH_3), 87.88 (C_5H_5), 215.56 (CO).

17. This material is satisfactory for alkene cyclopropanation reactions, although recrystallization can be effected very easily by dissolving the crude product in nitromethane at 25°C in the air and by slowly cooling the filtered solution to –70°C. The recrystallization recovery is greater than 80% and provides large, "gem-like," amber-colored crystals. Acetone can also be used as the recrystallization solvent.

18. This reagent can be stored in ordinary flasks or bottles in the air, but it should be protected from bright light, which leads to slow decomposition. Storage in a dark brown bottle is recommended.

19. The checkers' yields ranged from 25–46% in preparations that were run on one-fourth to one-half of the scale used by the submitters.

20. A two-fold excess of the iron reagent is employed to assure high conversion of the alkene to the cyclopropane. Equimolar amounts of the starting materials can be used, but the cyclopropane yield is ca. 20% lower.

21. 1,1-Diphenylethene is obtained from Aldrich Chemical Company, Inc. and is used without further purification.

22. 1,4-Dioxane is distilled from sodium benzophenone ketyl under nitrogen.

23. Nitromethane is also a good solvent for this reaction, and in some cases gives somewhat higher yields of cyclopropanes. Also, the reaction times are reduced to 2–4 hr when nitromethane is used. Before use, this solvent is purified according to a published procedure.[12] Commercially obtained solvent is first dried over anhydrous magnesium sulfate and then over anhydrous calcium sulfate. The solvent is filtered into a flask containing activated 3 Å molecular sieves and is heated at 60°C for 8 hr while being stirred. Nitromethane is distilled from the powdered molecular sieves under reduced pressure (bp 58°C, 150 mm; lit.[12] 58°C, 160 mm) directly into a flask containing additional 3 Å molecular sieves. The purified solvent is stored in the dark. When "wet" nitromethane from commercial sources is used directly as the reaction solvent, the percent conversions of alkenes to cyclopropanes are reduced substantially. *CAUTION*: Distillations of nitromethane and reactions using this solvent at elevated temperature should be conducted behind a safety shield.

24. When the cyclopropanation reactions are run in the presence of air, the yields are slightly reduced.

25. Vigorous stirring is necessary for a reasonable rate of reaction. The mixture remains heterogeneous both before and after the iron reagent melts. Monitoring

of the reaction by GLPC (2-m 5% OV-1 or SE-30) is recommended to assure maximum conversion before the reaction is stopped.
26. The function of the hexane (or pentane) is to promote precipitation of organometallic byproducts.
27. The solid is bright yellow after these washings and consists primarily of $[C_5H_5(CO)_2FeS(CH_3)_2]^+ BF_4^-$ and some unreacted cyclopropanation reagent. The latter can be recovered if desired by recrystallization of this mixture from acetone.
28. Ferric chloride destroys ferrocene, a contaminating side product that is difficult to remove by physical means because of its hydrocarbon-like characteristics.
29. The purity of this product is greater than 98% as determined by GLPC (2-m 5% OV-1 or SE-30). The spectral properties are as follows: ^{1}H NMR (300 MHz, $CDCl_3$, cf. lit.[3]) δ: 1.30 (s, 4 H, 2 cyclopropyl CH_2), 7.12–7.40 (m, 10 H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 16.33 (cyclopropyl CH_2), 29.97 (quaternary cyclopropyl C), 125.9 (para C), 128.2, 128.4 (ortho and meta C), 145.8 (ipso C); MS (EI, 70 eV) m/e (rel intensity) 194 (M+, 86), 193 (100), 178 (64), 115 (9).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Despite their high ring strain, cyclopropanes are commonly encountered among naturally occurring as well as synthetic compounds. Cyclopropanes are most commonly synthesized by addition of alkylidene units to alkenes.[13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32] These reactions employ various types of carbenes, carbenoids, or diazo compounds. One particularly important method is the Simmons-Smith reaction[14] which, according to the original procedure, involves the treatment of diiodomethane with zinc-copper couple to generate a reactive intermediate that serves as a cyclopropanation reagent. Several modifications of this procedure have been reported more recently. Another common approach is to employ a dihalocarbene to give a 1,1-dihalocyclopropane which is treated subsequently with a reducing agent to effect replacement of the halide substituents by hydrogen.

In the mid-1960's, transition metal carbene complexes were first reported by E. O. Fischer.[33 34 35 36 37 38 39 40 41 42 43 44] Although their structures may be suggestive of classical carbene-like behavior, relatively few of these complexes serve as useful cyclopropanation reagents.[45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78] Rather, these compounds exhibit their own characteristic types of reactions, many of which are useful in synthetic transformations other than cyclopropanations. Contrary to this more general case, Pettit[79 80] and then Green[81]

reported some early findings that indicated the possible utility of certain iron carbene complexes for three-membered ring construction. Their studies were followed by investigations of iron complexes by many others,[25,82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100] among which has been the recent work of Brookhart[101 102 103 104] and Casey.[105 106 107]

Helquist has focused efforts on developing synthetically useful cyclopropanation reagents based upon the use of stable organoiron compounds which may be regarded, at least formally, as direct precursors of reactive carbene complexes. Sulfonium derivatives[11,108 109 110 111 112 113] and alkenyl complexes[114 115] have proven to be useful in this regard. The presently described methylene transfer reagent[11,108,109] and a related ethylidene transfer reagent[110,111] are included among the former sulfonium salt complexes. Among the many compounds reported by Brookhart is a useful silyl ether-based reagent for ethylidene transfer[101] as well as a reagent for asymmetric cyclopropanations.[102] Helquist[114,115] and Casey[105,106,107] have also reported complexes for transfer of several more complex types of alkylidene units.

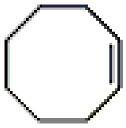
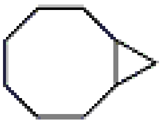
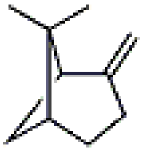
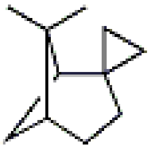
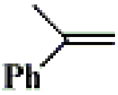
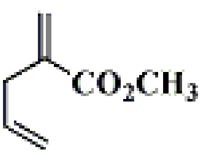
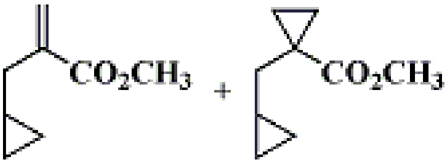
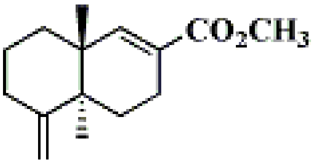
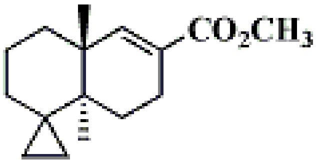
An important advantage of the presently described procedure is that the cyclopropanation reagent is unusually stable for an organometallic compound. Not only is the solid reagent stable to air indefinitely, but its crystallization is accomplished from hot aqueous solutions. Samples of this reagent have been stored in ordinary laboratory reagent bottles for more than five years with no noticeable decomposition. This stability is in contrast to typical Simmons-Smith intermediates and diazoalkanes. Another advantage of the present reagent is that once it has been prepared, its subsequent use in cyclopropanation reactions is trivially straightforward. The reagent can be handled as an ordinary laboratory reagent and combined with an alkene substrate and a suitable solvent in an ordinary flask. Although an inert atmosphere is specified for the present cyclopropanation, these reactions have also been performed routinely in the air with only small reductions in yields.

1,1-Diphenylcyclopropane has been prepared previously by (1) the Simmons-Smith procedure (24% yield)[14,116] and modified versions of this method (up to 72%),[117 118] (2) sulfonium ylide addition to 1,1-diphenylethene (61% yield),[119 120] (3) reduction of 1,1-diphenyl-2,2-dihalocyclopropanes with sodium in ammonia (47% yield),[121 122] with sodium and tert-butyl alcohol (80%),[3] or with diethyl lithiomethanephosphonate (62%),[123] (4) base-promoted cyclization of trimethyl(3,3-diphenylpropyl)ammonium iodide (78%),[124 125] (5) boron trifluoride-promoted cyclization of a corresponding 3-hydroxypropylstannane (97%),[126] (6) reaction of 3,3-diphenylpropenoic acid with lithium aluminum hydride (62%),[127] (7) reaction of diphenylmethane with $NaAlH_2(OCH_2CH_2OCH_3)_2$ (20%),[128] (8) decomposition of the pyrazoline (unspecified yield) obtained by addition of diazomethane to 1,1-diphenylethene,[129 130] (9) thermolysis of

a corresponding acyldiazene (43%),[131] (10) photolysis of 2,2-diphenylcyclobutanone (19%),[131] and (11) decarboxylation of 1,1-diphenyl-2-carboxycyclopropane (unspecified yield).[132]

The Table summarizes some of the other examples of cyclopropanations that have been performed by the presently described procedure.[11,108,110,133]

TABLE I
OTHER CYCLOPROPANATIONS USING $C_5H_5(CO)_2FeCH_2S^+(CH_3)_2BF_4^-$

Alkene	Cyclopropane Product(s)	Consumption of Alkene (%)[a]	Yield (%)[b]
		96	92
		81	70
		100	58
		86	96
		99	62 + 5
		100	86[c]

[a]The % consumption values were determined by quantitative GLPC measurement of unreacted alkenes using an internal standard. [b]The yields were determined by quantitative GLPC using an internal standard and are corrected for unreacted alkenes. The reactions were typically run on 1-mmol scales. [c]Taken from ref. [133].

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

BF_4

sodium benzophenone ketyl

Ferrocene

Iron (1+), dicarbonyl(η^5-2,4-cyclopentadien-1-yl)(dimethylsulfonium η-methylide)-, tetrafluoroborate (1-)

cyclopentadienyliron dicarbonyl dimer

sodium cyclopentadienyldicarbonylferrate

1,1-diphenyl-2,2-dihalocyclopropanes

acyldiazene

ammonia (7664-41-7)

methanol (67-56-1)

diethyl ether (60-29-7)

hydrogen (1333-74-0)

iron (7439-89-6)

sulfonium ylide (7783-06-4)

nitrogen (7727-37-9)

calcium sulfate (7778-18-9)

acetone (67-64-1)

sodium, metallic sodium (13966-32-0)

Diphenylmethane (101-81-5)

ferric chloride (7705-08-0)

iodomethane (74-88-4)

1,1-diphenylethene (530-48-3)

Pentane (109-66-0)

Nitromethane (75-52-5)

diiodomethane (75-11-6)

chloromethyl methyl ether (107-30-2)

cyclopropane (75-19-4)

magnesium sulfate (7487-88-9)

dioxane (5703-46-8)

Diazomethane (334-88-3)

zinc-copper

methylene, carbene (2465-56-7)

boron trifluoride (7637-07-2)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

hexane (110-54-3)

sodium tetrafluoroborate (13755-29-8)

ethylidene

dicyclopentadiene

tert-butyl alcohol (75-65-0)

iron pentacarbonyl

1,1-Diphenylcyclopropane, Benzene, 1,1'-cyclopropylidenebis- (3282-18-6)

3,3-diphenylpropenoic acid (606-84-8)

trimethyl(3,3-diphenylpropyl)ammonium iodide

pyrazoline

cyclopropyl (2417-82-5)

1,4-dioxane (123-91-1)

chloromethyl methyl sulfide (2373-51-5)

diethyl lithiomethanephosphonate

3-hydroxypropylstannane

2,2-diphenylcyclobutanone

1,1-diphenyl-2-carboxycyclopropane

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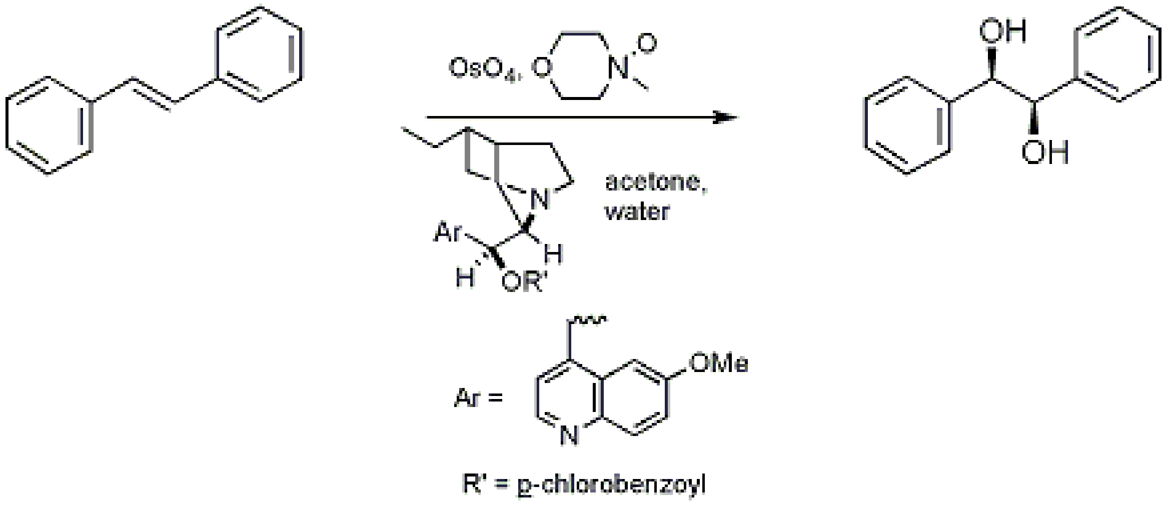
(R,R)-1,2-DIPHENYL-1,2-ETHANEDIOL (STILBENE DIOL)

[1,2-Ethanediol, 1,2-diphenyl-[R-(R,R)]-]



Submitted by Blaine H. McKee[1], Declan G. Gilheany[2], and K. Barry Sharpless[1].
Checked by Aaron Balog and Robert K. Boeckman, Jr..

1. Procedure

To a 3-L, three-necked, round-bottomed flask equipped with a mechanical stirrer and two glass stoppers at room temperature are added (E)-1,2-diphenylethene (trans-stilbene) (180.25 g, 1.0 mol, 1.0 equiv) (Note 1), 4-methylmorpholine N-oxide (NMO) [260 mL of a 60% by wt. aqueous solution (1.5 mol, 1.5 equiv) (Note 1) and (Note 2)], dihydroquinidine 4-chlorobenzoate (23.25 g, 0.05 mol, 0.05 equiv) (Note 3) and (Note 4), 375 mL of acetone and 7.5 mL water. [The solution is 0.1 M in alkaloid (Note 5), 2 M in olefin, and the solvent is 25% water/75% acetone (v/v) (Note 6)]. The flask is immersed in a 0°C cooling bath and stirred for 1 hr. Osmium tetroxide (1.0 g, 4.0 mmol, 4.0 × 10^{-3} equiv) is added in one portion, producing a milky brown-yellow suspension (Note 7). The reaction mixture is then stirred at 0°C for 33 hr and monitored by silica TLC (3:1 CH_2Cl_2:Et_2O v/v) until complete. At this point, the mixture is warmed to room temperature, diluted with 500 mL of dichloromethane, and sodium metabisulfite (285 g, 1.5 mol) is added in several portions while the internal temperature is maintained at room temperature with an ice bath as needed. After addition is complete and the exothermic reaction has subsided, stirring is continued at room temperature for 1 hr (Note 8). Anhydrous sodium sulfate (50 g) is added and the mixture is stirred at room temperature overnight (Note 9). The suspension is filtered through a 20-cm Büchner funnel, the filtrand is rinsed thoroughly with acetone (3 × 250 mL), and the filtrate is concentrated to a brown paste (Note 10). The paste is

dissolved in 3.5 L of ethyl acetate, transferred to a 6-L separatory funnel, and washed sequentially with water (2 × 500 mL) (Note 11), 0.25 M sulfuric acid (2 × 500 mL) (Note 12), and brine (1 × 500 mL). The initial, aqueous washes are kept separate from the subsequent acid washes which are retained for alkaloid recovery (Note 13) and (Note 14). The organic layer is dried (Na_2SO_4), and concentrated to give the crude diol in quantitative yield (222.7 g, 1.04 mol, 104%). The ee of the crude product is determined by ^1H NMR analysis of the derived bis-Mosher ester to be 90%. One recrystallization[3] from hot aqueous 95% ethanol (3 mL/g) affords 155–162 g (72–75%) of enantiomerically pure stilbene diol as a white solid, mp 144.5–146.5°C, $[\alpha]_D^{25}$ 90.0° (abs EtOH, *c* 1.96) (Note 15).

2. Notes

1. trans-Stilbene and N-methylmorpholine N-oxide were obtained from the Aldrich Chemical Company, Inc.
2. This solution contains 173.7 g of NMO and 117.5 mL of water. Its density is 1.130 g/mL.
3. Dihydroquinidine 4-chlorobenzoate is available from the Aldrich Chemical Company, Inc. The optical rotation of the commercial sample employed by the checkers had an $[\alpha]_D^{25}$ of –68.9° (EtOH, *c* 0.95).
4. Many other dihydroquinidine derivatives have been assayed in the catalytic, asymmetric dihydroxylation reaction (ADH)[4] and the submitters have recently found that the benzoate and 2-naphthoate esters are slightly better for aryl-substituted alkenes while certain ethers are better for other substrates.[5] However, since the level of asymmetric induction is already high, there is little advantage to be gained from their use in this case.
5. When the alkaloid concentration is increased to 0.25 M there is a slight increase in ee; when the concentration is decreased below 0.067 M there is a drastic decrease in ee.[6 7]
6. These solvent conditions have been optimized. The low solubility of stilbene in the reaction mixture approximates "slow addition" conditions.[8]
7. Osmium tetroxide is volatile and toxic and therefore should be used only in a well-ventilated hood. On a 1-mole scale, osmium tetroxide was added as a solid. On a smaller scale, it was added as a solution (ca. 0.5 M) in toluene.[6]
8. The checkers noted a significant exotherm upon addition of the sodium metabisulfite and warming to room temperature that caused the temperature of the methylene chloride solution to rise to the boiling point. Addition of the bisulfite in small portions at 0°C had no beneficial effect in moderating the exotherm that occurred after warming to room temperature.
9. This time can be reduced to 30 min without any deleterious effects.[8]
10. The filtrate is concentrated on a rotary evaporator with slight heating (bath temperature 30–40°C). In some runs with other substrates, stronger heating (bath temperature 70–80°C) caused the reaction mixture to turn black. However, there was no significant effect on either yield or enantiomeric excess in those

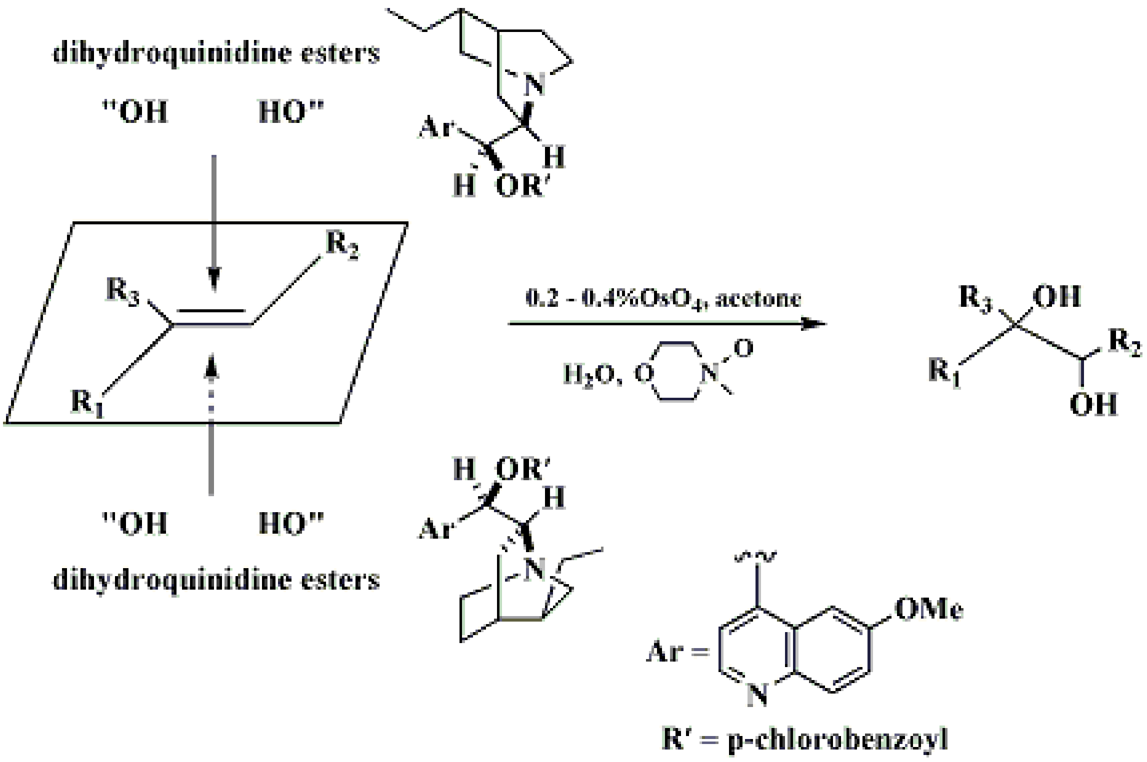
cases.
11. These washes remove 4-methylmorpholine as well as any remaining acetone. Subsequent contact of the diol with acetone should be avoided to prevent any chance of acetonide formation.
12. It is important to use sulfuric acid at this point to ensure efficient extraction. The sulfate salt of the alkaloid is more soluble in water and less soluble in organic solvents than the hydrochloride salt. In the ADH of other alkenes the preferred system is sulfuric acid/diethyl ether. However, stilbene diol is only sparingly soluble in diethyl ether, which necessitates the use of ethyl acetate. Chlorinated hydrocarbon solvents should be avoided since both alkaloid salts have appreciable solubility in them. When diethyl ether is used as the organic phase, not all of the reaction mixture dissolves in it, but the material that remains undissolved is derived solely from 4-methylmorpholine.
13. Back extraction of the acid layer yields an insignificant amount of diol in this case. However, it may be necessary for more water-soluble diols. For example, in the case of the diol from methyl 2-octenoate the yield is increased by 30% with one back extraction, while styrene glycol requires repeated prolonged extraction.
14. The alkaloid was recovered by raising the pH of the acidic washes to 11 with sodium carbonate, transferring the solution to a 6-L separatory funnel and extracting with methylene chloride (3 × 500 mL). The alkaloid was recovered in 84–85% yield as a white foam and was used without further purification in subsequent dihydroxylations. The use of recovered alkaloid by the checkers resulted in a decrease in the ee of the crude diol to 80%. The submitters, however, report ee's of 90% from repeated use of recovered alkaloid. Note that the alkaloid is stable for several days in the acidic aqueous extract. Once the solution is made alkaline, however, it should be extracted immediately.
15. Optically pure S,S-stilbene diol can be similarly obtained in 66% yield using dihydroquinine-4-chlorobenzoate. The crude ee before recrystallization is 74%.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The present procedure describes a convenient preparation of threo-stilbene diol on a 1-mole scale and illustrates the utility of the catalytic, asymmetric dihydroxylation (ADH) of solid substrates on a large scale. Note that this procedure calls for more water than initially reported.[6] The extra water leads to higher ee (90% cf. 78%[6]) by better approximating the slow addition conditions that are now almost always used for liquid olefins.[8,9] In the meantime a new procedure employing the $(DHQD)_{22}$-PHAL ligand has been developed to perform the oxidation on a 1 kilo scale.[10]



Recently reported uses of optically pure stilbene diol in asymmetric synthesis include. (1) the dimethyl ether as a ligand for effecting enantioselective conjugate addition;[10] (2) the preparation of α,β-unsaturated ketals for achieving diastereoselective Simmons–Smith cyclopropanation;[11] (3) the preparation of enantiomercially pure β-halohydrins;[12] and (4) the preparation of chiral crown ethers.[13]

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References and Notes

1. Department of Chemistry, Massachusetts Institute of Technology, Cambridge, MA 02139.
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium metabisulfite

brine

(R,R)-1,2-DIPHENYL-1,2-ETHANEDIOL (STILBENE DIOL)

(E)-1,2-diphenylethene (trans-stilbene

dihydroquinine-4-chlorobenzoate

ethanol (64-17-5)

sulfuric acid (7664-93-9)

ethyl acetate (141-78-6)

diethyl ether (60-29-7)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

dimethyl ether (115-10-6)

acetone (67-64-1)

toluene (108-88-3)

methylene chloride, dichloromethane (75-09-2)

stilbene

osmium tetroxide (20816-12-0)

styrene glycol

dihydroquinidine 4-chlorobenzoate

trans-Stilbene (103-30-0)

STILBENE DIOL, S,S-stilbene diol

1,2-Ethanediol, 1,2-diphenyl-[R-(R,R)]- (52340-78-0)

4-methylmorpholine N-oxide, N-methylmorpholine N-oxide (80913-66-2)

4-methylmorpholine (109-02-4)

methyl 2-octenoate

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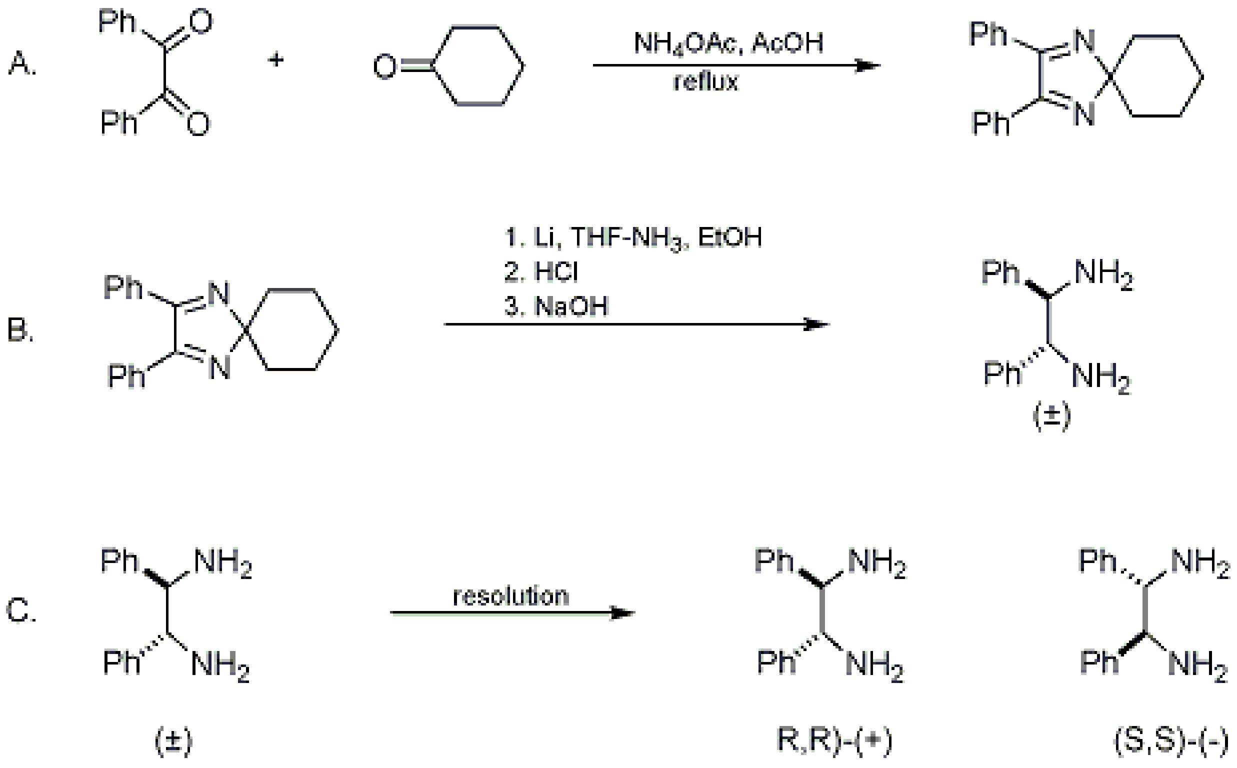
Organic Syntheses, CV 9, 387

(1R,2R)-(+)- AND (1S,2S)-(–)- 1,2-DIPHENYL-1,2-ETHYLENEDIAMINE

[1,2-Ethanediamine, 1,2-diphenyl-, [R-(R,R)]- and [S-(R,R)]-]



Submitted by S. Pikul[1] and E. J. Corey[2].
Checked by Scott C. Jeffrey and James D. White.

1. Procedure

CAUTION! Parts A and B of this procedure should be carried out in an efficient hood to avoid exposure to noxious vapors (acetic acid, ammonia).

A. *2,2-Spirocyclohexane-4,5-diphenyl-2H-imidazole* (Note 1). A 2-L, three-necked, round-bottomed flask equipped with a mechanical stirrer and a reflux condenser is charged with 1.0 L of glacial acetic acid (Note 2), 158 g (0.75 mol) of benzil (Note 2), 400 g of ammonium acetate (Note 2) and 80 mL (0.77 mol) of cyclohexanone (Note 2). The mixture is stirred and heated at reflux temperature for 1.5 hr (Note 3) and then, while hot, poured into 3 L of vigorously stirred water. The mixture is left overnight to cool to ambient temperature, the crystals are collected by filtration, washed 4 times with 300 mL of water, crushed in a mortar and dried under reduced pressure to give 205–210 g (95–97%) of the imidazole as yellowish-green crystals, mp 105–106°C, lit.[3] mp 107–108°C (Note 4).

B. *(±)-1,2-Diphenyl-1,2-ethylenediamine*. A 2-L, four-necked, round-bottomed flask equipped with a mechanical stirrer, thermometer and dry ice condenser is charged with 72.0 g (0.250 mol) of 2,2-spirocyclohexane-4,5-diphenyl-2H-imidazole. The flask is flushed with argon, and 400 mL of tetrahydrofuran (Note 5) is added. The mixture is stirred until all solids dissolve, cooled to −78°C (dry ice/acetone bath) and treated with a stream of gaseous ammonia (Note 6) until the volume of liquid increases by about 400 mL (Note 7). One of the side necks is then equipped with a solids addition funnel and 6.94 g (1.00 mol) of lithium (Note 8) is slowly introduced by cutting the wire with scissors in a gentle stream of argon. The rate of lithium addition is such that the temperature does not rise above –65°C. Following the addition of lithium, the mixture is stirred for 30 min and 30 mL (1.0 mol) of ethanol (Note 9) is slowly added. The mixture is stirred for an additional 20 min and 70 g of ammonium chloride is added. The cooling bath is removed, the mixture is allowed to warm to 0°C, 400 mL of water is carefully introduced, and the phases are separated. The aqueous phase is washed 3 times with 300 mL of ether and the combined organic extracts are washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated with a rotary evaporator to about 200 mL. The solution is transferred to a 1-L, one-necked, round-bottomed flask equipped with a mechanical stirrer, cooled to 0°C and treated with 300 mL of 2 N aqueous hydrochloric acid. The biphasic mixture is vigorously stirred at ambient temperature for 1 hr, 500 mL of water is added and phases are separated. The organic phase is washed with 150 mL of water and the combined aqueous phases are extracted with 300 mL of dichloromethane. The aqueous solution is then carefully treated with 300 mL of 2 N aqueous sodium hydroxide and the mixture is extracted 4 times with 150 mL of methylene chloride. The combined organic extracts are washed with brine, dried over anhydrous sodium sulfate, and filtered. Removal of volatile material under reduced pressure (water aspirator) gives 47–50 g (89–94%) of racemic diamine as a pale yellow solid, mp 81–82°C, lit.[4] mp 82°C corr. (Note 10).

C. *(1S,2S)-(–)- and (1R,2R)-(+)-1,2-Diphenyl-1,2-ethylenediamine* (Note 11). A 1-L, round-bottomed flask equipped with a mechanical stirrer is charged with 42.5 g (0.200 mol) of the racemic diamine and 230 mL of ethanol (Note 9). The solids are dissolved by heating the mixture to 70°C whereupon a hot (70°C), homogeneous solution, of 30.0 g (0.200 mol) of L-(+)-tartaric acid (Note 12) in 230 mL of ethanol is added (Note 13). The tartrate salts precipitate immediately, and after the mixture is cooled to ambient temperature, the crystals are collected by filtration, washed twice with 60 mL of ethanol, and dried under reduced pressure. The solids are dissolved in 230 mL of boiling water, 230 mL of ethanol is added and the homogeneous solution is allowed to cool slowly to room temperature. The crystals are collected by filtration, washed with 40 mL of ethanol and dried under reduced pressure. The recrystallization procedure is then repeated twice using the same volumes of solvents (230 mL of water and 230 mL of ethanol) to give 23–25 g (63–69%) of the tartrate salt as colorless crystals, $[\alpha]_D^{23}$ −10.8 ± 0.2° (H_2O, *c* 1.3), lit.[5] $[\alpha]_D^{23}$ −11° (H_2O).

The salt is transferred to a 1-L, one-necked, round-bottomed flask equipped with a

magnetic stirring bar and suspended in 300 mL of water. After the mixture is vigorously stirred and then cooled to 0–5°C, 23 mL of 50% aqueous sodium hydroxide is added dropwise followed by 150 mL of dichloromethane, and stirring is continued for 30 min. The phases are separated, the aqueous phase is washed twice with 50 mL of dichloromethane and the combined organic extracts are washed with brine, dried over anhydrous sodium sulfate and filtered. Removal of the volatile material under reduced pressure gives a colorless solid that is recrystallized from hexane to yield 12–14 g (57–66%) of (S,S)-(−)-diamine as colorless crystals, $[\alpha]_D^{23}$ −106 ± 1° (MeOH, *c* 1.1) lit.[6] $[\alpha]_D^{23}$ −106.5° (MeOH, *c* 1.09) (Note 14).

The filtrates from all crystallizations are combined and the solvent is evaporated on a rotary evaporator under vacuum (water aspirator). The residual solid is transferred to a 1-L, one-necked, round-bottomed flask equipped with a magnetic stirring bar, and suspended in 250 mL of water. To this vigorously stirred mixture is slowly added 25 mL of aqueous 50% sodium hydroxide followed by 200 mL of dichloromethane and the stirring is continued for 30 min. The phases are separated, the aqueous phase is washed twice with 50 mL of dichloromethane and the combined organic extracts are washed with brine, dried over anhydrous sodium sulfate and filtered. Removal of volatile material under reduced pressure gives 24–27 g of the enriched (R,R)-diamine as pale yellow crystals. This material is treated with D-(−)-tartaric acid (Note 12) and the resulting salt is recrystallized in exactly the same manner as described for the other enantiomer to give 29–31 g (80–85%) of colorless crystals, $[\alpha]_D^{23}$ +4 ± 0.5 ° (H_2O, *c* 1.3). (The checkers found that the salt from (−)-tartaric acid was optically impure even after five recrystallizations. However, this did not affect the optical purity of the (R,R)-(+)-diamine.) Treatment with sodium hydroxide, as described above, followed by crystallization from hexane gives 11.5–13 g (54–61%) of (R,R)-(+)-diamine as colorless crystals, $[\alpha]_D^{23}$ +106 ± 1° (MeOH, *c* 1.1) (Note 14).

2. Notes

1. Step A is a modified literature procedure.[3]
2. Glacial acetic acid (99.8%), benzil (99%), anhydrous ammonium acetate (A.C. S.) and cyclohexanone (99.8%) were obtained from the Aldrich Chemical Company, Inc., and used as received.
3. As the reaction progresses there is a change of color from light yellow to dark green.
4. This material is pure enough for use in the next step. If necessary, it can be recrystallized from hexane or methanol-water. The properties of 2,2-spirocyclohexane-4,5-diphenyl-2H-imidazole are as follows: R_f = 0.48 (hexane-ether 1:1, v/v; ^1H NMR ($CDCl_3$) δ: 1.65–1.92 (m, 6 H), 1.95–2.00 (m, 4 H), 7.33–7.53 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ: 24.1, 25.7, 34.7, 104.1, 128.3, 128.9, 129.9, 133.1, 164.0.
5. Reagent grade tetrahydrofuran purchased from J. T. Baker Chemical Co., was freshly distilled from sodium metal and benzophenone.

6. Anhydrous ammonia (99.98%) was obtained from Matheson Gas Products, Inc., and used as received.
7. The mixture stays homogeneous when cooled to −78°C.
8. Lithium wire (99% with 1% of sodium) was purchased from the Aldrich Chemical Company, Inc. The mineral oil is wiped off with a paper towel before use.
9. Absolute ethanol (200 proof) was obtained from Aaper Alcohol and Chemical Co. and used as received.
10. The racemic diamine contains 5–10% of an impurity (by ^{13}C NMR analysis) that does not interfere with the subsequent resolution. The product has the following spectral properties: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.59 (bs, 4 H), 4.10 (s, 2 H), 7.2–7.3 (m, 10 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 61.9, 126.8, 126.9, 128.2, 143.4.
11. This resolution procedure is essentially the same as described in the literature.[5]
12. L-(+)- and D-(–)-Tartaric acids (99+ and 99%, respectively) were obtained from the Aldrich Chemical Company, Inc., and used as received.
13. The tartaric acid solution should be added slowly to avoid spontaneous boiling of ethanol.
14. The spectral properties of this product are the same as that of the racemate (see (Note 10)). The optical purity is higher than 98% as confirmed by ^{1}H NMR of its salt with L-mandelic acid.[7]

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Enantiomerically pure (+)- and (–)-diphenylethylenediamines have recently been used for highly stereoselective Diels-Alder,[8] aldol,[8] allylation,[9] osmylation,[10] and epoxidation[11] reactions. Other synthetic applications involve enantioselective Michael addition[12] and asymmetric hydrogenation.[13]

The present two-step procedure for preparation of the racemic diphenylethylenediamine is significantly shorter and more suitable for scale-up than that described in the literature.[4] The resolution of the racemate has also been reported using the commercially available enantiomers of mandelic acid.[6]

This preparation is referenced from:

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

brine

2,2-Spirocyclohexane-4,5-diphenyl-2H-imidazole

(1R,2R)-(+)- AND (1S,2S)-(−)- 1,2-DIPHENYL-1,2-ETHYLENEDIAMINE

1,2-Ethanediamine, 1,2-diphenyl-, [R-(R,R)]- and [S-(R,R)]-

(1S,2S)-(−)- and (1R,2R)-(+)-1,2-Diphenyl-1,2-ethylenediamine

(S,S)-(−)-diamine

(R,R)-diamine

D-(−)-tartaric acid

(−)-tartaric acid

(R,R)-(+)-diamine

L-(+)- and D-(−)-Tartaric acids

(+)- and (−)-diphenylethylenediamines

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ammonia (7664-41-7)

methanol (67-56-1)

ether (60-29-7)

ammonium acetate (631-61-8)

ammonium chloride (12125-02-9)

sodium hydroxide (1310-73-2)

Mandelic acid, L-mandelic acid (90-64-2)

Cyclohexanone (108-94-1)

sodium sulfate (7757-82-6)

Benzil (134-81-6)

Benzophenone (119-61-9)

sodium (13966-32-0)

tartaric acid, L-(+)-tartaric acid (87-69-4)

methylene chloride, dichloromethane (75-09-2)

lithium (7439-93-2)

Tetrahydrofuran (109-99-9)

Imidazole (288-32-4)

hexane (110-54-3)

argon (7440-37-1)

(±)-1,2-Diphenyl-1,2-ethylenediamine

diphenylethylenediamine

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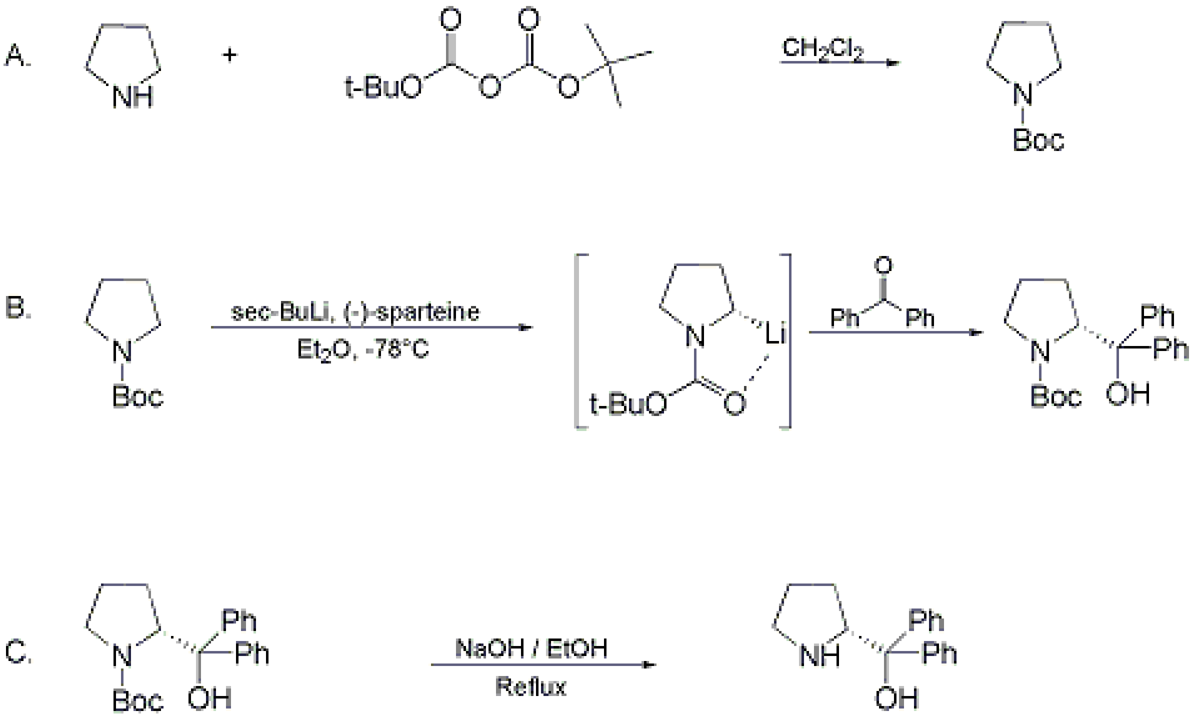
Organic Syntheses, CV 9, 391

(R)-(+)-2-(DIPHENYLHYDROXYMETHYL)PYRROLIDINE

[2-Pyrrolidinemethanol, α,α-diphenyl-, (R)-]



Submitted by Nikola A. Nikolic and Peter Beak[1].
Checked by Michael R. Reeder and Robert K. Boeckman, Jr..

1. Procedure

A. *N-(tert-Butoxycarbonyl)pyrrolidine*. A 500-mL round-bottomed flask, equipped with magnetic stirring bar, is charged with dichloromethane (CH_2Cl_2) (120 mL) and pyrrolidine (11.3 mL, 133 mmol) (Note 1). The flask is fitted with a 60-mL, pressure-equalizing addition funnel vented through a mineral oil bubbler and charged with a solution of di-tert-butyl dicarbonate (24.6 g, 112 mmol) in CH_2Cl_2 (35 mL) . After the pyrrolidine solution is cooled to 0°C in ice, the colorless dicarbonate solution is added dropwise over a period of 30 min, and the resulting solution is stirred at room temperature for 3 hr (Note 2). The solvents are then removed under reduced pressure, and two consecutive Kugelrohr distillations of the residual oil (oven temperature 80°C at 0.2 mm) afford 16.6 g (87%) of N-Boc-pyrrolidine as a colorless oil (Note 3).

B. *(R)-(+)-2-(Diphenylhydroxymethyl)-N-(tert-butoxycarbonyl)pyrrolidine*. An oven-dried, 2-L, three-necked flask, equipped with a magnetic stirring bar and a thermocouple (Note 4), is charged with (–)-sparteine (30.2 mL, 131 mmol) (Note 5), N-Boc-pyrrolidine (15.0 g, 87.6 mmol), and anhydrous ether (900 mL) (Note 6). The solution is cooled to –70°C (dry ice/ acetone bath) (Note 4). To this solution is added sec-butyllithium (96 mL, 1.16 M in cyclohexane, 111 mmol) (Note 7) and (Note 8) dropwise over a period of 35 min (Note 9). The reaction is then stirred at –70°C for 5.5 hr (Note 10).

After this interval, a solution of benzophenone (25.5 g, 140 mmol) (Note 11) in anhydrous ether (200 mL) is added dropwise over a period of 1.25 hr (Note 9). The dark green to greenish-yellow suspension is maintained at −70°C for 2.0 hr, and the reaction is then quenched by dropwise addition of glacial acetic acid (8.5 mL, 150 mmol) over a period of 15 min. The resulting lemon-yellow suspension is allowed to warm slowly to room temperature over a period of 12 hr, during which time the mixture becomes cream colored.

After the solution is warmed to 25°C, 5% phosphoric acid (H_3PO_4) (150 mL) is added to the reaction mixture, and the resulting biphasic mixture is stirred for 20 min. The layers are partitioned and the organic phase is washed with additional 5% H_3PO_4 (3 × 150 mL). Combined aqueous phases are extracted with ether (3 × 200 mL). The original organic phase and the ethereal extracts are combined, washed with brine (200 mL), dried over magnesium sulfate ($MgSO_4$), filtered, and the solvents are removed under reduced pressure to afford crude product as an off-white solid. The crude (R)-(+)-2-(diphenylhydroxymethyl)-N-(tert-butoxycarbonyl)pyrrolidine is purified by recrystallization from a mixture of hexanes-ethyl acetate (675 mL, 20 : 1, v/v) affording in two crops 20.9–22.0 g (73–74%) of analytically pure product as a white solid (Note 12) having greater than 99.5% ee (Note 13).

Sparteine is recovered by making the aqueous phases basic with aqueous 20% sodium hydroxide (NaOH) (160 mL) (Note 14). The aqueous phase is extracted with Et_2O (4 × 150 mL), and the combined organic phases are dried over potassium carbonate (K_2CO_3), filtered, and the solvents removed under reduced pressure to afford 30.3 g (98%) of crude, recovered sparteine as a pale yellow oil (Note 15). Fractional distillation of the residual oil from calcium hydride (CaH_2) (Note 5) affords 27.0 g of sparteine (88%) suitable for reuse.

C. *(R)-(+)-2-(Diphenylhydroxymethyl)pyrrolidine*. A 1-L, round-bottomed flask, equipped with a magnetic stirring bar, is charged with 325 mL of absolute ethanol and NaOH (27.0 g, 675 mmol). The NaOH is dissolved with vigorous stirring, and (R)-(+)-2-(diphenylhydroxymethyl)-N-(tert-butoxycarbonyl)pyrrolidine (22.0 g, 62.3 mmol) is added (Note 16). The flask is fitted with a reflux condenser, and the resulting milky white suspension is heated to reflux for 2.5 hr. The suspension is cooled to room temperature, and the solvents are removed under reduced pressure. To the residual off-white solids are added ether (800 mL) and deionized water (400 mL). The suspension is stirred until the solids are dissolved, and the resulting biphasic mixture is transferred to a 2-L separatory funnel. The layers are partitioned, and the aqueous phase is extracted with ether (4 × 200 mL). The organic phases are combined, dried over K_2CO_3 (ca. 100 g), filtered, and the solvents are removed under reduced pressure (Note 17) to afford 14.5–15.8 g (92–100%) of the pure title compound as a white solid (Note 18).

2. Notes

1. Dichloromethane was obtained from Mallinckrodt Inc., and was used without further purification. Pyrrolidine and di-tert-butyl dicarbonate were obtained from Aldrich Chemical Company, Inc., and used as received.
2. Toward the end of the addition, gas evolution (CO_2) occurs. Care should be taken to provide adequate venting to avoid pressure buildup.
3. The product, N-Boc-pyrrolidine, has the following spectral characteristics: ^1H NMR

($CDCl_3$, 300 MHz) δ: 1.43 (s, 9 H), 1.81 [s (br), 4 H], 3.27 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.78, 25.54, 28.32, 45.38, 45.71, 78.57, 154.41; IR (film) cm^{-1}: 2974, 2875, 1698, 1403, 1168, 877, 772.

4. The internal temperature was monitored throughout the reaction with an Omega D730 or equivalent thermocouple.

5. Sparteine is liberated from the commercially available sulfate salt (Aldrich Chemical Company, Inc.) as follows: Sparteine sulfate pentahydrate (100 g, 240 mmol) is dissolved in deionized water (125 mL), and to this solution is slowly added aqueous 20% NaOH (100 mL). The resulting milky-white, oily mixture is then extracted with ether (4 × 150 mL). The combined ethereal extracts are dried over anhydrous K_2CO_3, filtered, and the solvent is removed under reduced pressure. Vacuum distillation of the residual oil from CaH_2 affords 52 g (92%) of sparteine as a clear, colorless to slightly yellow, viscous oil (bp 115–120°C/0.3 mm). The sparteine free base readily absorbs atmospheric carbon dioxide (CO_2) and should be stored under argon at –20°C in a freezer.

6. Anhydrous ethyl ether was obtained by distillation under nitrogen from sodium benzophenone ketyl.

7. sec-Butyllithium (1.3 M in cyclohexane) was titrated in toluene immediately before use using a standard solution (1 M) of sec-butyl alcohol in o-xylene with 0.2% 2,2'-biquinoline in toluene as the indicator according to Watson and Eastham.[2]

8. The checkers found that the yields obtained in this procedure are critically dependent on the quality of the sec-butyllithium employed. Best results are obtained with fresh (< 3 months shelf life) commercial samples (FMC Lithium Division, and Aldrich Chemical Company, Inc.) that are colorless to deep yellow, largely free of precipitated salts, and that have been kept refrigerated and have not been exposed to traces of moisture or oxygen by extensive previous sampling. Samples of sec-butyllithium that contain alkoxide or hydroxide undergo alkoxide/hydroxide-catalyzed decomposition to butene and lithium hydride (LiH), particularly when stored at room temperature; the latter cannot be readily removed. In the hands of the checkers, such aged sec-butyllithium samples provide the N-Boc amino alcohol of comparable enantiomeric purity in 5–15% lower yield.

9. During the addition, the internal temperature of the reaction did not exceed –68°C.

10. The reaction mixture became milky white during this interval.

11. Commercially available benzophenone (Aldrich Chemical Company, Inc., 99+ %) was used without further purification.

12. The product has the following characteristics: ^1H NMR (300 MHz, $CDCl_3$) δ 0.65–0.80 (m, 1 H), 1.40–1.60 (s, 11 H), 1.82–1.95 (m, 1 H), 1.98–2.14 (m, 1 H), 2.75–2.90 (m, 1 H), 3.20–3.45 (m, 1 H), 4.86 (dd, 1 H, J_1 = 8.9, J_2 = 3.8), 7.20–7.45 (m, 10 H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.84, 28.29, 29.67, 47.77, 65.50, 80.54, 81.62, 126.96, 127.00, 127.27, 127.61, 127.77, 128.14, 143.72, 146.41, 159.00; IR (film) cm^{-1}: 3370, 2979, 1659, 1415, 1164, 763, 70. Anal. Calcd for $C_{22}H_{27}NO_3$: C, 74.76; H, 7.70; N, 3.96. Found: C, 74.62; H, 7.72; N, 4.13. $[\alpha]_D^{25}$ +150° ($CHCl_3$, *c* 3.62); mp 150.5–152°C. The checkers found $[\alpha]_D^{25}$ +144° ($CHCl_3$, *c* 3.89).

13. The enantiomeric excess was determined by alkaline ethanolysis of the Boc group followed by conversion of the amine to the 3,5-dinitrobenzamide. HPLC analysis of a saturated solution of the benzamide in 5% 2-propanol in hexane using a Pirkle Covalent S-N1N-Naphthylleucine Column (Regis Chemical Company) with 5% 2-propanol in

hexane as the eluent, and a flow rate of 1.5 mL/min indicates a single peak with retention time of 35 min. HPLC analysis of the corresponding racemic benzamide affords two peaks at 27 and 32 min corresponding to the (S)- and (R)-enantiomers respectively. The differences in retention times arise from the size of sample that was injected; the ^{1}H NMR of the racemic and enantio-enriched benzamides were identical.
14. The aqueous solution was brought to ca. pH 11 as tested by Hydrion Paper (Micro Essential Laboratories, Brooklyn, NY).
15. The ^{1}H NMR of the recovered (−)-sparteine was identical to that of pure (−)-sparteine.

16. The concentration of the reactants is 0.2 M. If more dilute solutions of base are employed (0.01 M), the checkers found that the reaction required at least 24 hr to completion and that impure product was obtained. At higher dilution, formation of significant amounts of the cyclic urethane was observed, and this by-product required removal by chromatography.
17. The residual, colorless, viscous oil solidified slowly upon exposure to high vacuum.
18. The title compound has the following characteristics: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40–1.95 (m, 5 H), 2.89–3.05 (m, 2 H), 4.23 (t, 1 H, J = 7.4), 4.55 [(s (br), 1 H], 7.10–7.35 (m, 4 H), 7.45–7.60 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.47, 26.23, 46.71, 64.42, 76.65, 125.47, 125.80, 126.29, 126.40, 127.91, 128.17, 145.36, 148.13; IR (film) cm^{-1}: 3352, 2968, 1598, 1492, 1448, 1173, 748, 701. Anal. Calcd for $C_{17}H_{19}NO$: C, 80.60; H, 7.56; N, 5.53. Found: C, 80.56; H, 7.60; N, 5.68. $[\alpha]_D^{25}$ +73.8° ($CHCl_3$, *c* 3.37); mp 76–77°C; R_f = 0.13 (CH_2Cl_2 : MeOH, 95 : 5). The checkers found $[\alpha]_D^{25}$ +67.9° ($CHCl_3$, *c* 3.37)

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

α,α-Diaryl-2-pyrrolidinemethanols represent an important class of ligands for asymmetric synthesis.[3] For example, reaction of these amino alcohols with boranes affords oxazaborolidinones that are effective enantioselective reagents for asymmetric reduction of ketones.[3,4,5,6,7,8,9,10,11,12] The chiral non-racemic amino alcohols have been prepared through addition of organometallic agents to enantio-enriched proline,[3,7,8,9,10,11,12,13] or by resolution of racemic pyrrolidinemethanols.[11] The procedure reported here describes a new approach to the synthesis of the title compound based on an asymmetric lithiation/substitution sequence.[14,15]

Treatment of Boc-pyrrolidine with sec-butyllithium in the presence of (−)-sparteine affords the putative enantio-enriched organolithium reagent. This organolithium reagent can be quenched with electrophiles to afford 2-substituted-Boc-pyrrolidines.[14,15] This approach offers several advantages over existing methodologies. First, the use of the (−)-sparteine ligand affords 2-substituted pyrrolidines with high enantioselectivity. Second, the ligand can be recovered and purified in high yields; [in this example, (−)-sparteine was recovered and purified in 88% yield]. Third, this approach obviates the preparation of enolizable proline derivatives that have

been shown to racemize.[3] Finally, this two-step approach affords the (R)-α,α-diphenylpyrrolidine enantiomer that has previously been obtained from relatively expensive "unnatural" D-proline.

The approach reported here should facilitate the preparation of α,α-disubstituted-pyrrolidinemethanol analogs. By using this methodology, a single enantio-enriched organolithium intermediate can be treated with a variety of electrophiles (e.g., diaryl ketones) to afford aryl-substituted analogs of the title compound. Previously reported syntheses involve a variety of nucleophilic organometallic reagents that must be prepared and treated with proline derivatives.

An interesting feature of this study is the enantiomeric purity analysis of the products. By converting the amine functionality of the pyrrolidine to a 3,5-dinitrobenzamide, the substrate can be analyzed by chiral HPLC. To date, the 3,5-dinitrobenzamide of 2-substituted pyrrolidines that the submitters have prepared have been baseline-resolved by the Pirkle S-N1N-Naphthylleucine column. This approach obviates the need for MPTA-derivativization which has been previously employed in enantiomeric purity determinations.[3,7,8,9,10,11,12]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 676

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hexanes

brine

sodium benzophenone ketyl

(−)-sparteine

Sparteine

Sparteine sulfate pentahydrate

ethanol (64-17-5)

potassium carbonate (584-08-7)

acetic acid (64-19-7)

ethyl acetate (141-78-6)

ether, ethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

oxygen (7782-44-7)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

cyclohexane (110-82-7)

benzamide (55-21-0)

toluene (108-88-3)

Benzophenone (119-61-9)

2-propanol (67-63-0)

phosphoric acid (7664-38-2)

butene (106-98-9)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

urethane (51-79-6)

pyrrolidine (123-75-1)

hexane (110-54-3)

calcium hydride (7789-78-8)

argon (7440-37-1)

sec-butyl alcohol (78-92-2)

lithium hydride (7580-67-8)

2-Pyrrolidinemethanol

sec-butyllithium (598-30-1)

BOC

2,2'-biquinoline (119-91-5)

Di-tert-butyl dicarbonate (24424-99-5)

o-Xylene (95-47-6)

oxazaborolidine

(R)-(+)-2-(Diphenylhydroxymethyl)pyrrolidine (22348-32-9)

N-(tert-Butoxycarbonyl)pyrrolidine, N-Boc-pyrrolidine, Boc-pyrrolidine (86953-79-9)

(R)-(+)-2-(Diphenylhydroxymethyl)-N-(tert-butoxycarbonyl)pyrrolidine (137496-68-5)

N-Boc amino alcohol (36016-38-3)

3,5-dinitrobenzamide (121-81-3)

D-proline (344-25-2)

(R)-α,α-diphenylpyrrolidine

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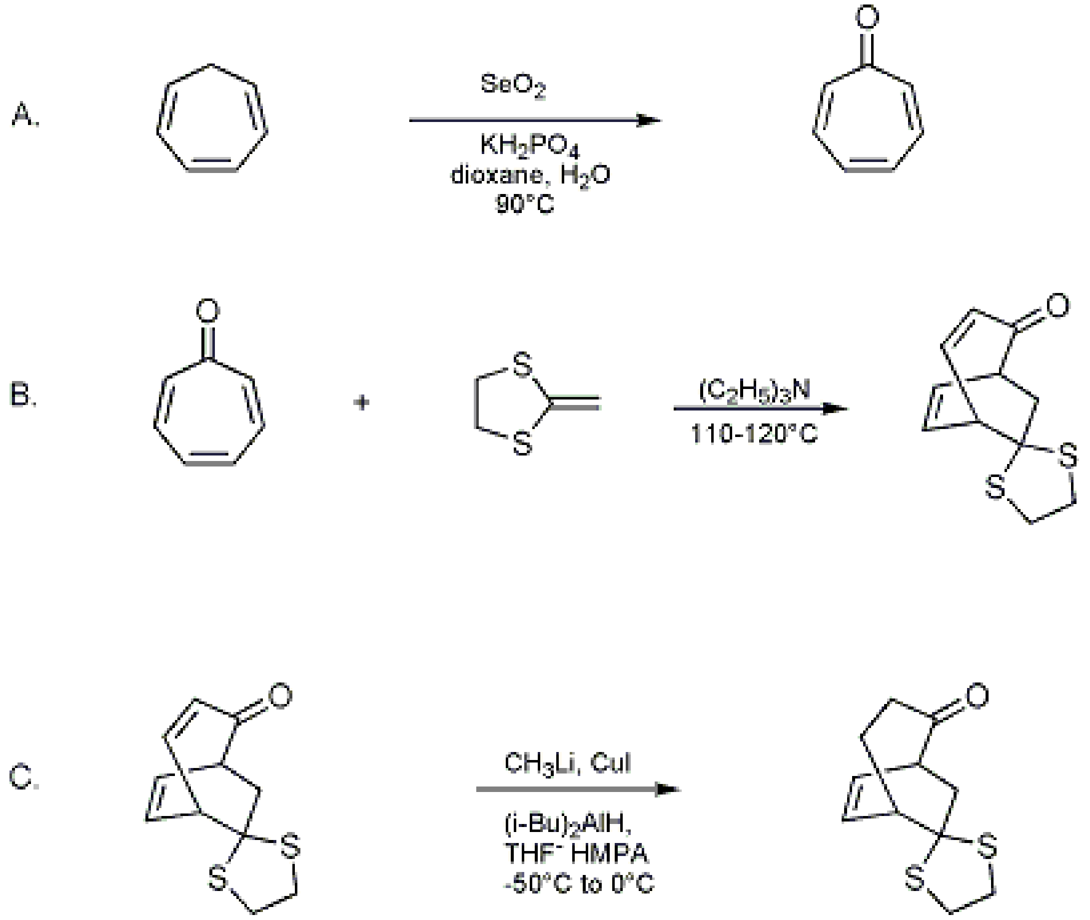
Organic Syntheses, CV 9, 396

INVERSE ELECTRON-DEMAND DIELS-ALDER CYCLOADDITION OF A KETENE DITHIOACETAL. COPPER HYDRIDE-PROMOTED REDUCTION OF A CONJUGATED ENONE. 9-DITHIOLANOBICYCLO [3.2.2]NON-6-EN-2-ONE FROM TROPONE



Submitted by Karl R. Dahnke and Leo A. Paquette[1].
Checked by Antonino Focella, Mittira Amornmarn, and David L. Coffen.

1. Procedure

A. *Tropone*. A 5-L, three-necked, Morton flask, equipped with a reflux condenser, thermometer, nitrogen inlet, and mechanical stirrer is charged with 81 g (0.59 mol) of potassium dihydrogen phosphate, 200 mL of water, and 2 L of p-dioxane. With vigorous mechanical stirring, 258 g (2.80 mol) of cycloheptatriene (Note 1) is added, followed by 318 g (2.87 mol) of selenium dioxide (Note 2). The mixture is heated to 90°C and maintained with vigorous stirring for 20 hr. After the black suspension is cooled to room temperature, 1 L of water is added and the mixture is filtered over Celite (Note 3). The solution is divided into two halves and each is extracted with

dichloromethane (2 × 1.5 L). Each organic extract is washed with saturated sodium bicarbonate solution (500 mL) and the solvent is removed under reduced pressure. The combined, crude, black oil is subjected to bulb-to-bulb distillation (20–110°C at 0.05 mm) with dry ice cooling. The resulting light brown liquid is fractionally redistilled (62–65°C at 0.25 mm) to give 147 g (50%) of tropone as a pale yellow oil (Note 4).

B. *9-Dithiolanobicyclo[3.2.2]nona-3,6-dien-2-one*. A 50-mL, three-necked, round-bottomed flask, equipped with a reflux condenser, nitrogen inlet, and magnetic stirring bar is charged with 8.23 g (77.6 mmol) of tropone, 0.75 mL of triethylamine (Note 5), and 11.0 g (93.1 mmol) of 2-methylene-1,3-dithiolane (Note 6). After the system is flushed with nitrogen, the mixture is heated to 110–120°C for 10 hr. The resulting dark oil is cooled to room temperature and purified by column chromatography on silica gel (Note 7). Elution with petroleum ether (1 L) followed by dichloromethane affords 9-dithiolanobicyclo[3.2.2]nona-3,6-dien-2-one as an orange oil that solidifies (10.3 g, 59%), mp 56–58°C (Note 8).

C. *9-Dithiolanobicyclo[3.2.2]non-6-en-2-one*. (*Caution! Hexamethylphosphoric triamide (HMPA) is toxic and must be handled with gloves.*) A 500-mL, three-necked, round-bottomed flask, equipped with an argon inlet, stirring bar, thermometer, and rubber septum is charged with 0.80 g (4.2 mmol) of copper(I) iodide (Note 9) and 150 mL of dry tetrahydrofuran (Note 10). The resulting slurry is cooled to −50°C and treated in turn with 3.2 mL of 1.4 M methyllithium in ether (4.5 mmol), 40 mL of hexamethylphosphoramide (Note 11) and (Note 12), and 50 mL of a 1.0 M solution of diisobutylaluminum hydride in hexanes (Note 13), all via syringe. After 1.5 hr at –50°C, 7.4 g (33 mmol) of 9-dithiolanobicyclo[3.2.2]nona-3,6-dien-2-one (Note 14) in 30 mL of tetrahydrofuran is added over 10 min via syringe. The mixture is allowed to warm gradually to 0°C over a 4-hr period and quenched with 75 mL of 1.6 N hydrochloric acid. The organic layer is separated and the aqueous layer is extracted with ether (3 × 100 mL). The combined organic layers are washed with 1.6 N hydrochloric acid (75 mL), water (3 × 150 mL), and brine (150 mL), prior to drying over magnesium sulfate. Evaporation of the solvent under reduced pressure yields an orange oil which solidifies on standing for a short time (Note 15). The solid 9-dithiolanobicyclo[3.2.2]non-6-en-2-one thus obtained is vacuum dried to give 6.9 g (92%) of material, mp 68–71°C, as one spot on TLC, with no starting material detectable upon NMR analysis (Note 16).

2. Notes

1. Cycloheptatriene was purchased from the Aldrich Chemical Company, Inc., and was washed with 10% sodium hydroxide solution, dried over magnesium sulfate, and distilled prior to use.
2. Selenium dioxide was obtained from Alfa Products, Morton/Thiokol Inc. and used without purification.
3. The solid material containing selenium waste was placed in a container for heavy metal wastes and disposed of by a commercial service according to

approved procedures.

4. Spectral characteristics are as follows: IR ($CHCl_3$) cm^{-1}: 3000, 1630, 1580, 1515, 1470, 1210; ^1H NMR (300 MHz, $CDCl_3$) δ: 6.88–7.11 (series of m, 6 H).

5. Triethylamine was distilled from calcium hydride prior to use.

6. 2-Methylene-1,3-dithiolane was prepared by the procedure of Dahnke and Paquette, *Org. Synth., Coll. Vol. IX* **1998**, 585.

7. The R_f for this adduct is 0.6 in CH_2Cl_2. Its presence is clearly visible when anisaldehyde is employed as the staining agent.

8. The adduct exhibits the following spectral properties: IR ($CHCl_3$) cm^{-1}: 2930, 1665, 1603, 1380, 1165; ^1H NMR (300 MHz, $CDCl_3$) δ: 2.72 (d, 1 H, J = 15.5), 2.87 (dd, 1 H, J = 6.8, 15.5), 3.21–3.45 (m, 5 H), 3.66 (t, 1 H, J = 7.7), 5.77 (dd, 1 H, J = 2.0, 11.1), 6.13 (t, 1 H, J = 7.9), 6.60 (dt, 1 H, J = 0.8, 7.6), 6.92 (dd, 1 H, J = 8.5, 11.1); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 40.2, 40.6, 42.9, 51.9, 52.1, 70.8, 126.5, 129.4, 139.4, 150.6, 196.3. A sample recrystallized from hexane afforded off-white crystals with mp 62–63°C. As an alternative to chromatography, the Diels-Alder adduct can be purified by pouring the cooled, crude product into 100 mL of ether and rinsing the dark viscous gum with additional ether (2 × 25 mL). The material obtained from evaporation of the combined ethereal extracts is then subjected to bulb-to-bulb distillation. After removal of the volatile impurities, the product distils during the ramping of the temperature from 110–165°C at 0.5 mm. This modification affords a comparable yield of adduct on a 6-fold scale.

9. Copper iodide was purified prior to use by the method of Kauffman.[2]

10. Tetrahydrofuran was distilled from sodium-benzophenone ketyl before use.

11. Hexamethylphosphoramide (HMPA) was distilled from calcium hydride and stored over molecular sieves before use.

12. Attempts were made to substitute other polar solvents for HMPA in this reduction. Under similar reaction conditions but with substitution of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU) no reaction took place, and the starting material was recovered unchanged. The slightly more polar 1,3-dimethyl-2-imidazolidinone (DMI) allowed reduction to take place, but with only 80% conversion to a mixture of 1,2- and 1,4-reduction products after 10 hr. With L-selectride in tetrahydrofuran (THF) at −78°C, 1,4-reduction was achieved in 30–60% yield alongside competitive 1,2-reduction.

13. Diisobutylaluminum hydride was purchased from the Aldrich Chemical Company, Inc. and used as received.

14. Before use, this material should be thoroughly dried by heating to 50°C under high vacuum to constant weight (1–2 hr).

15. The R_f of this product is 0.6 in CH_2Cl_2. Anisaldehyde was employed as the staining agent.

16. Spectral characteristics are as follows: IR ($CHCl_3$) cm^{-1}: 2930, 2860, 1700, 1425; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.82–1.94 (m, 1 H), 2.28–2.38 (m, 1 H), 2.52–2.70 (m, 3 H), 2.83–2.94 (m, 2 H), 3.10 (t, 1 H, J = 7.3), 3.22–3.48 (m, 4

H), 6.14 (t, 1 H, J = 7.9), 6.51 (t, 1 H, J = 8.2); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 27.1, 38.1, 39.4, 39.8, 42.9, 46.8, 49.1, 69.9, 127.3, 137.3, 206.9. An analytical sample recrystallized from ether melts at 74–75°C. Anal. Calcd for $C_{11}H_{14}OS_2$: C, 58.37; H, 6.23; S, 28.33. Found: C, 58.32, H, 6.22; S, 28.63.

Waste Disposal Information

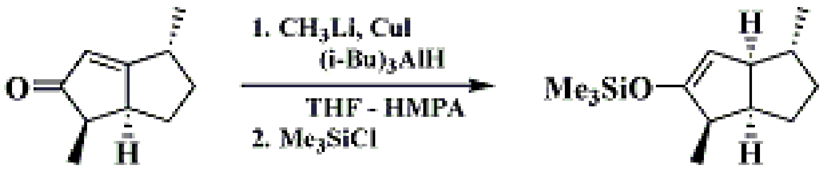
All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Although examples of inverse electron-demand Diels-Alder reactions involving ketene thioacetals and α,β-unsaturated aldehydes, ketones, and esters abound,[3] the formation of six-membered carbocyclic products is rarely encountered. Isoquinolinium salts and 4a-azoniaanthracenes are recognized as good 2π acceptors,[4] but the use of positively charged reaction partners is not necessary as the condensation with tropone illustrates. An important advantage of such cycloadditions is their ability to distinguish two carbonyl groups from the outset. Furthermore, the example provided illustrates the regiospecificity with which carbon-carbon bond formation occurs.

The methodology employed for the oxidation of cycloheptatriene is based on an original report by Radlick[5] as subsequently improved by Rigby and Wilson.[6]

The second stage of the procedure describes a method for the fully regiocontrolled saturation of conjugated double bonds in the presence of isolated pi bonds. The agent perhaps responsible for this discrimination is a coordinated form of copper hydride. Although "CuH" has been generated in several different ways, the diisobutylaluminum hydride-methyl copper-HMPA complex developed by Tsuda and Saegusa[7] is especially attractive because of its quantitative capacity for 1,4-reduction and its ease of generation.[8] This chemistry results in regiospecific enolate anion formation and permits ready trapping of these intermediates as illustrated below:[9]



Consequently, this mild, conjugate reduction may become a powerful tool in synthetic organic chemistry.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 585

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

brine

9-Dithiolanobicyclo[3.2.2]nona-3,6-dien-2-one

9-Dithiolanobicyclo[3.2.2]non-6-en-2-one

sodium-benzophenone ketyl

diisobutylaluminum hydride-methyl copper-HMPA

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

nitrogen (7727-37-9)

selenium dioxide (7446-08-4)

dichloromethane (75-09-2)

copper(I) iodide (7681-65-4)

magnesium sulfate (7487-88-9)

potassium dihydrogen phosphate (7778-77-0)

selenium

Tetrahydrofuran (109-99-9)

copper iodide (7681-65-4)

hexane (110-54-3)

Methyllithium (917-54-4)

triethylamine (121-44-8)

calcium hydride (7789-78-8)

diisobutylaluminum hydride (1191-15-7)

cycloheptatriene (544-25-2)

hexamethylphosphoric triamide, hexamethylphosphoramide (680-31-9)

p-dioxane (123-91-1)

Tropone (492-37-5)

1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (7226-23-5)

anisaldehyde (123-11-5)

KETENE DITHIOACETAL

2-Methylene-1,3-dithiolane (26728-22-3)

1,3-dimethyl-2-imidazolidinone (80-73-9)

copper hydride

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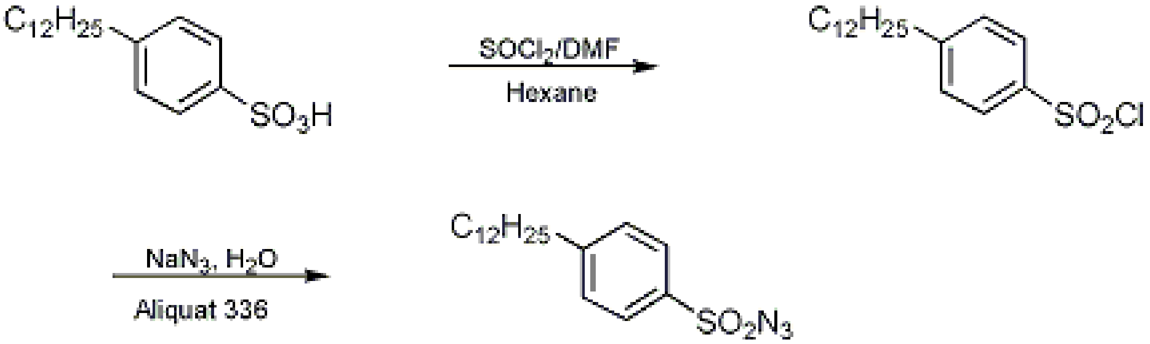
Organic Syntheses, CV 9, 400

4-DODECYLBENZENESULFONYL AZIDES

[Benzenesulfonyl azides, 4-dodecyl-]



Submitted by G. G. Hazen, F. W. Bollinger, F. E. Roberts, W. K. Russ, J. J. Seman, and S. Staskiewicz[1].
Checked by Mark Spaller and Stephen F. Martin.

1. Procedure

Caution! Although the mixture of dodecylbenzenesulfonyl azides is the safest of a group of diazo transfer reagents,[2] one should keep in mind the inherent instability, shock sensitivity, and explosive power of azides. All users should exercise appropriate caution.

4-Dodecylbenzenesulfonyl chlorides. A 250-mL, three-necked, round-bottomed flask, equipped with a mechanical overhead stirrer, a Claisen adapter bearing an immersion thermometer, a pressure-equalizing addition funnel, and reflux condenser, is charged with a solution of 60.00 g (0.184 mol) of dodecylbenzenesulfonic acids (Note 1) and 8.64 mL of dimethylformamide (DMF) in 60 mL of hexane . Stirring is initiated while the mixture is heated to 70°C using a heating mantle, and 22.1 mL (36.24 g, 0.304 mol) of thionyl chloride (Note 2) is added at a rate to maintain controlled reflux (Note 3). The required addition time is about 1 hr. The dark solution is heated an additional 2 hr at 70°C and cooled to 40°C (Note 4). While still warm (□40°C), the mixture is transferred to a 250-mL separatory funnel, and the dark lower layer is separated from the hexane solution (Note 5). The hexane layer is cooled to 25°C and washed with 60 mL of aqueous 5% sodium bicarbonate solution (Note 6). The bicarbonate wash is back extracted with 36 mL of hexane and the combined hexane layers are treated with 3 g of carbon (Note 7), (Note 8) and stirred for 2 hr at 25°C. The carbon is removed by filtration and the cake is washed with three portions (12-mL each) of hexane. The combined hexane layers plus the hexane washes are used to prepare the azide.

4-Dodecylbenzenesulfonyl azides. A 500-mL, three-necked, round-bottomed flask fitted with a mechanical overhead stirrer is charged with the hexane solution from step

A. To this solution is added a solution of 11.6 g (0.178 mol based on the total solids from the sulfonyl chlorides above) of sodium azide (NaN_3) in 100 mL of water and 2.0 g of phase transfer catalyst (Aliquat 336) (Note 9). Stirring is initiated, and the reaction progress is monitored by thin layer chromatography (Note 10). Approximately 4 hr at 25°C is required to complete the reaction. The two-phase mixture is transferred to a 500-mL separatory funnel and the aqueous layer is removed. The hexane layer is washed with 100 mL of aqueous 5% sodium bicarbonate solution and dried over 28 g of anhydrous sodium sulfate. The drying agent is removed by suction filtration, and the cake is washed with 20 mL of hexane. The concentration and purity of the 4-dodecylbenzenesulfonyl azides are best determined by evaporation of a small sample to an oil of constant weight with visible spectrophotometric assay for the azide (Note 11). The hexane solution of dodecylbenzenesulfonyl azides, when standardized as above (Note 11), can be used as obtained for most applications. However, if desired, *careful concentration of the hexane solution under reduced pressure at room temperature* affords 58.2–61.4 g (90–95%) of the oily mixture of dodecylbenzenesulfonyl azides; corrected for the assay of the azides the yield is usually 95% (Note 12) and (Note 13).

2. Notes

1. Dodecylbenzenesulfonic acids, a 97% mixture of branched chain isomers, was purchased from Spectrum Chemical Mfg. Corp.
2. Reagent grade thionyl chloride from Fisher Scientific Co. was used.
3. An excess of thionyl chloride–dimethylformamide catalyst is used to prevent formation of sulfonic anhydrides. A stoichiometric amount of thionyl chloride gives a much reduced yield.
4. The progress of the reaction is monitored by thin layer chromatography. A 0.1-mL sample is removed, evaporated to dryness and dissolved in 2 mL of hexane. The solution is spotted on an Analtech silica GF plate (8 cm × 2.5 cm) and developed in hexane/methylene chloride (4/1). Visualization by UV light shows R_f = 0.4 for the sulfonyl chlorides.
5. If allowed to cool to 25°C, the dark layer may solidify, hampering the separation. This very acidic layer is the excess thionyl chloride/DMF complex. It should be handled with proper protection in a ventilated area To facilitate visual identification of the layers, the checkers added about 25 mL of hexane.
6. The pH of the bicarbonate wash is a reflection of the efficiency with which the dark lower layer has been removed. In the course of a dozen runs, this pH ranged from 5.5 to 7.1. If the pH of the wash is below 5.5, a second wash with bicarbonate is necessary.
7. Nuchar SA carbon from Westvaco Co. was used.
8. It is essential that the carbon treatment be carried out within a few hours. Experiments where this treatment was delayed for 16 hr invariably produced an azide mixture of lower purity (85%) and lower yield (80%). Although the sulfonyl chlorides hydrolyze only slightly (1–2%) in wet hexane in 24 hr, that amount of sulfonic acids in the presence of the phase transfer agent catalyzes the

hydrolysis of sulfonyl chlorides. After treatment with carbon, the hexane solution of sulfonyl chlorides can be stored for several weeks in the refrigerator with little or no adverse effect on the next step.

9. Aliquat 336 (tri-n-alkylmethylammonium chloride) was obtained from Aldrich Chemical Company, Inc. The material is a mixture of C_8 and C_{10} chains with C_8 predominating. There is a slight initial exothermic reaction on adding the phase transfer catalyst. Intermittent cooling with a cold water bath is required to keep the temperature below 35°C.

10. A sample of the hexane layer from the reaction mixture is diluted 10 fold with hexane, spotted and developed as described in (Note 4). Visualization by UV light shows R_f = 0.3 for sulfonyl azides.

11. The assay for sulfonyl azides is adapted from the method of Siewinski, et al.[3] The azide content of the hexane solution was assayed as follows to determine the contained yield:

1. Standard Curve:

Stock solution: 80 mg of NaN_3 diluted to the mark in a 100-mL volumetric flask with 0.1 N NaOH-MeOH.

Procedure: Into a series of four, 100-mL volumetric flasks, transfer 5, 7, 10 and 15 mL respectively of the stock solution. Into a 100-mL volumetric labelled blank, pipet 10 mL of 0.1 N NaOH-MeOH solution. To all add 2 drops of 0.1% ethanolic phenolphthalein indicator solution, and 20 mL of aqueous 1.5% sodium sulfate (Na_2SO_4). Acidify each, in turn, to the phenolphthalein end point with 1 N hydrochloric acid and immediately add 25 mL of 1 M ferric ammonium sulfate [$Fe(NH_4)(SO_4)_2$] solution. Dilute to the mark with 1.5% Na_2SO_4. Let stand 10 min, then read absorbance at 458 nm. Plot absorbance vs. concentration.

2. Sample:

Pipet 5 mL of the hexane solution containing 4-dodecylbenzenesulfonyl azides into a 100-mL volumetric flask and dilute to the mark with methanol. Pipet 5 mL of this solution into a small stoppered flask. Add 2 mL of aqueous 1 N potassium hydroxide solution and heat at 75°C for 20 min. Allow to cool to room temperature, add 2 drops of 0.1% phenolphthalein solution, and 10 mL of 1.5% Na_2SO_4. Shake, then transfer quantitatively to a 60-mL separatory funnel. Add 10 mL of butanol (or isoamyl alcohol) to the sample flask, shake, then transfer to the separatory funnel. Shake the funnel, let the layers separate, then remove the bottom (H_2O) layer into a 100-mL volumetric flask. Add an additional 10 mL of 1.5% Na_2SO_4 to the alcohol layer in the separatory funnel, shake, let the layers separate, then transfer the water layer to the volumetric flask. Neutralize the combined water layers to the phenolphthalein end point with 1 N hydrochloric acid, then immediately add 25 mL of $Fe(NH_4)(SO_4)_2$. Dilute to the mark with 1.5% Na_2SO_4 solution, let stand 10 min, then read absorbance at 458 nm. Read azide concentration against the NaN_3 calibration curve.

12. The checkers determined the yield by evaporation of the hexane solution to

constant weight (3–10 hr at 0.1 mm). The yields cited are based on the assumption that the 3% impurity in the starting sulfonic acids is not present in the final product. The checkers found the material obtained upon concentration, to be sufficiently pure for use without further purification.

13. The spectroscopic data for the mixture of four isomeric secondary dodecylbenzenesulfonyl azides (2.5:1.6:1.6:1.0) is as follows: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.70–1.00 (m, 6 H), 1.00–1.50 (m, 12 H), 1.50–1.80 (m, 6 H), 2.90–2.50 (m, 1H), 7.25–7.45 (m 2 H), 7.87 (m 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 12.07, 13.94, 14.02, 14.05, 14.07, 14.10, 20.63, 21.89, 22.50, 22.61, 22.63, 22.65, 22.69, 27.18, 27.48, 27.52, 27.58, 29.15, 29.26, 29.30, 29.32, 29.44, 29.46, 29.49, 29.51, 29.57, 29.61, 29.72, 31.69, 31.82, 31.83, 31.88, 31.91, 36.21, 36.34, 36.60, 36.61, 36.64, 38.06, 38.85, 40.24, 46.11, 46.38, 48.15, 127.55, 127.66, 128.33, 128.93, 129.01, 135.82, 135.85, 154.56, 154.82, 154.87, 156.09; IR (film) 2126 cm^{-1}.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

4-Dodecylbenzenesulfonyl chlorides have been prepared from the corresponding acids using chlorosulfonic acid,[4] phosphorus oxychloride,[2] and thionyl chloride.[5] The use of catalytic amounts of DMF in conjunction with thionyl chloride is based on the work of H. Bosshard, et al.[6] The insolubility of the DMF/thionyl chloride complex in the reaction solvent permits easy removal at the end of reaction. Extraction with dilute base removes the last trace of acids and the solution is pure enough for the next step.

The method described above for the preparation of the mixture of 4-dodecylbenzenesulfonyl azides is new and based on the work of Bollinger and Hazen.[5,7] Sulfonyl azides have been prepared by diazotizing substituted sulfonyl hydrazides,[8] and treating sulfonyl halides in methanol-water,[9] ethanol-water,[10] acetone,[2,5,7] or acetone-water solutions[11] with aqueous or solid sodium azide.[5,7,12] Use of phase transfer catalysis for the preparation of sulfonyl azides is new, simple and effective. It avoids solvent changes and permits isolation of a hexane solution of sulfonyl azides without concentration.

The use and advantages of 4-dodecylbenzenesulfonyl azides as a diazo transfer agent are fully discussed by Hazen, Weinstock, Connell, and Bollinger.[7] In contrast to p-toluenesulfonyl azide, that has the shock sensitivity of tetryl (N-methyl-N-2,4,6-tetranitroaniline) and the explosiveness of TNT, the mixture of 4-dodecylbenzenesulfonyl azides exhibits no shock sensitivity at the highest test level (150 kg cm) and 24% of the heat of decomposition measured in cal/g. p-

Toluenesulfonyl azide appears as a diazo transfer agent in *Org. Synth., Coll. Vol. V* **1973**, 179; *VI*, **1988**, 389, 414 and its preparation is reported in the first of these. Two explosions during its preparation have been reported.[13,14]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 197

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sulfonyl chlorides

H_2O

4-DODECYLBENZENESULFONYL AZIDES

Benzenesulfonyl azides, 4-dodecyl-

dodecylbenzenesulfonyl azides

4-Dodecylbenzenesulfonyl chlorides

dodecylbenzenesulfonic acids

sulfonyl azides

ethanolic phenolphthalein

tetryl (N-methyl-N-2,4,6-tetranitroaniline

hydrochloric acid (7647-01-0)

methanol (67-56-1)

chlorosulfonic acid (7790-94-5)

thionyl chloride (7719-09-7)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

butanol (71-36-3)

acetone (67-64-1)

carbon (7782-42-5)

Phosphorus Oxychloride (21295-50-1)

potassium hydroxide (1310-58-3)

sodium azide (26628-22-8)

methylene chloride (75-09-2)

phenolphthalein (77-09-8)

isoamyl alcohol (123-51-3)

azide

dimethylformamide, DMF (68-12-2)

hexane (110-54-3)

p-toluenesulfonyl azide (941-55-9)

ferric ammonium sulfate

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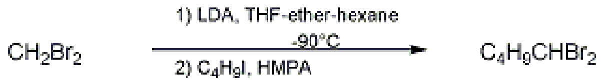
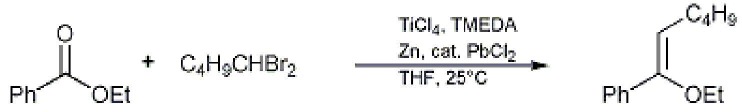
Organic Syntheses, CV 9, 404

ALKYLIDENATION OF ESTER CARBONYL GROUPS: (Z)-1-ETHOXY-1-PHENYL-1-HEXENE

A.



B.



Submitted by Kazuhiko Takai[1], Yasutaka Kataoka, Jiro Miyai, Takashi Okazoe, Koichiro Oshima, and Kiitiro Utimoto[2].
Checked by Stephen T. Wrobleski, Alan T. Johnson, and Robert K. Boeckman, Jr..

1. Procedure

Caution! Hexamethylphosphoric triamide (HMPA) is toxic and must be handled with gloves.

A. *1,1-Dibromopentane*(Note 1). A dry, 3-L, three-necked, round-bottomed flask is equipped with a mechanical stirrer, nitrogen inlet, rubber septum, and a 200-mL, graduated, pressure-equalizing addition funnel that is sealed with a rubber septum. After placing the system under a nitrogen atmosphere, the flask is charged with 280 mL of dry tetrahydrofuran (Note 2), 400 mL of dry diethyl ether (Note 2), and 20 g (0.20 mol) of dry diisopropylamine (Note 3). Stirring is initiated, and the contents of the flask are cooled to −10°C (dry ice-acetone bath). After transfer of 120 mL (0.20 mol) of 1.7 M butyllithium in hexane (Note 4) to the addition funnel by syringe, the solution of alkyllithium is slowly added to the stirred solution at such a rate as to maintain a temperature of −10°C. After the addition is complete, 10 mL of dry THF is introduced via syringe to rinse the walls of the addition funnel and then added to the reaction mixture. The mixture is stirred at −10°C for 15 min and cooled to −90°C (toluene-liq. nitrogen bath). The addition funnel is charged by syringe with a solution of 15 mL (38 g, 0.22 mol) of dibromomethane (Note 5) in 100 mL of dry THF, which is then added at such a rate that the temperature does not exceed −85°C (Note 6). The mixture is stirred for 15 min. A solution of 22 mL (37 g, 0.20 mol) of 1-iodobutane (Note 7) in 100 mL of THF, and 120 mL of hexamethylphosphoric triamide (Note 8) are successively added by syringe at such a rate (over an 25 min period) that the temperature of the reaction mixture does not exceed −85°C (Note 6). After the addition is complete, the reaction mixture is stirred at −90°C (toluene-liq. nitrogen bath) for 2 hr, −78°C (dry ice-acetone bath) for 1 hr, −48°C (dry ice-acetonitrile bath) for 2 hr, and −23°C (dry ice-carbon tetrachloride bath) for 3 hr (Note 6) and (Note 9). The solution is poured into 200 mL of 1 M hydrochloric acid solution and transferred to a 2-L separatory funnel. The resulting mixture is extracted with three 100-mL portions of hexane. The organic extracts are combined and washed with three 300-mL portions of water, 100 mL of saturated aqueous sodium sulfite solution, and 100 mL of brine. The organic layer is dried over anhydrous magnesium sulfate and then concentrated with a rotary evaporator (0°C water bath, trapping at −78°C with a dry ice-acetone condenser) at aspirator pressure. The brown liquid residue is distilled to afford 27–32 g (59–70%) of 1,1-dibromopentane as a colorless liquid, bp 70–72°C (15 mm) (Note 10).

B. *(Z)-1-Ethoxy-1-phenyl-1-hexene*. A dry, 3-L, three-necked, round-bottomed flask is equipped with a mechanical stirrer, nitrogen inlet, rubber septum, and a 200-mL, pressure-equalizing addition funnel that is sealed with rubber septum. After placing the system under a nitrogen atmosphere, the flask is charged with 350 mL of dry tetrahydrofuran (Note 2). The contents of the flask are cooled to 0°C with an ice bath, and 140 mL (0.28 mol) of a 2.0 M solution of titanium tetrachloride in dichloromethane (Note 11) is added slowly by syringe to the stirred THF over a period of 10 min. To the yellow solution at 0°C is added slowly 84 mL (0.56 mol) of tetramethylethylenediamine> (Note 12) by syringe. After being stirred at 0°C for 20 min, 41 g (0.63 mol) of zinc dust (Note 13) is added to the reaction mixture at 0°C in five portions in such a manner that the temperature remains at 0°C (Note 14), followed by addition of 0.88 g (3.2 mmol) of lead (II) chloride (Note 13) and (Note 15), and then the resulting suspension is warmed to 25°C. The color of the suspension turns from brownish yellow to dark greenish blue while being stirred at 25°C for 30 min. The addition funnel is then charged by syringe with a solution of 11 g (70 mmol) of ethyl benzoate (Note 12) and 35 g (0.15 mol) of 1,1-dibromopentane (part A) in 100 mL of dry THF. The resulting solution is then added to the stirred reaction mixture over a period of 10 min at 25°C and stirring is continued for 3.5–4.5 hr. The color of the resulting mixture gradually turns dark brown as the reaction proceeds (Note 16),(Note 17),(Note 18). The reaction mixture is then cooled to 0°C and 70 mL of triethylamine (Note 12) and 91 mL of saturated aqueous potassium carbonate solution are successively added slowly at 0°C by syringe.

After stirring at 0°C for an additional 15 min, 200 mL of ether-triethylamine (200/1, v/v) is added to the reaction mixture. The entire reaction mixture is then passed rapidly through a thin pad of activity III basic alumina (Note 19) on a 1-L glass filter using 500 mL of ether-triethylamine (200/1, v/v) as eluent. The filtrate is concentrated with a rotary evaporator (25°C, water bath). If a white solid appears at this point, the mixture is diluted with 100 mL of hexane-triethylamine (200/1, v/v) and the mixture is again filtered through a thin pad of basic alumina (Akt. III). The pad is washed with 100 mL of hexane-triethylamine (200/1, v/v) and the total eluent is concentrated again with a rotary evaporator. The resulting crude material is then vacuum distilled to give 11.0–11.4 g (77–80%) of a 93:7 mixture of (Z)- and (E)-1-ethoxy-1-phenyl-1-hexene, bp 73–75°C (0.20 mm) (Note 20) and (Note 21).

2. Notes

1. This procedure was reported by J. Villieras, C. Bacquet, and J. F. Normant.[3]
2. Tetrahydrofuran and diethyl ether were distilled from sodium and benzophenone just before use.
3. Diisopropylamine was distilled from calcium hydride, bp 84°C.
4. A 1.7 M hexane solution of butyllithium was obtained from Kanto Chemical Co. It may be standardized; however, the submitters chose to use a fresh reagent and forego the titration. The checkers employed a 1.6 M solution of n-butyllithium in hexane obtained from Lithco Inc., which was standardized before use.
5. Dibromomethane was freshly distilled, bp 96–97°C. The checkers noted some variability in the yield which in part appeared to be associated with the source of the dibromomethane.
6. The checkers monitored the internal temperature of the reaction mixture via thermocouple using an immersion well. The checkers observed that accurate temperature control is essential to obtain the reported yields reproducibly.
7. 1-Iodobutane was freshly distilled, bp 129°C.
8. Hexamethylphosphoric triamide is toxic and a cancer-suspect agent. It was distilled from calcium hydride, bp 68–69°C at 1 mm.
9. The color of the mixture changed from brown to white after 30-min stirring at −90°C. Then the color of the mixture changed gradually from white to light brown at −23°C.
10. The infrared spectrum (neat) has absorptions at 2956, 2930, 2860, 1465, 1431, 1238, 1158, 927, 732, 667, 596 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 0.95 (t, 3 H, J = 7.2), 1.28–1.61 (m, 4 H), 2.41 (dt, 2 H, J = 8.4, 6.2), 5.72 (t, 1 H, J = 6.2); ^{13}C NMR ($CDCl_3$) δ: 13.8, 21.4, 30.1, 45.1, 46.2.
11. Freshly distilled titanium tetrachloride (bp 136°C) was diluted with dichloromethane to afford a 2.0 M solution. All residues of titanium tetrachloride were destroyed with acetone from a wash bottle.
12. Tetramethylethylenediamine was freshly distilled from potassium hydroxide, bp 46–47°C (47 mm). Ethyl benzoate was distilled before use. Triethylamine was distilled from potassium hydroxide before use.
13. Zinc dust purchased from Wako Pure Chemical Industries, Ltd. (GR grade) was activated by washing several times with 5% hydrochloric acid washing in turn with water, methanol, and ether, and drying in vacuo according to Fieser and Fieser.[4] The lots employed by the submitters were found to contain □0.05 mol% Pb based on the Zn content by X-ray fluorescence analysis (Note 15). The checkers employed Zn dust (−325 mesh, 99.998% purity) obtained from Aldrich Chemical Company, Inc.
14. The reduction is a slightly exothermic process.
15. Addition of a catalytic amount of $PbCl_2$ (Rare Metallic Co., 99.999% purity) to a commercial lot of Zn dust (Aldrich Chemical Company, Inc. (99.998% purity) or Rare Metallic Co. (99.999% purity)) has shown reproducible results as were previously reported.[5,6] The yield of (Z) and (E)-1-ethoxy-1-phenyl-1-hexene fell to 10–15% ((Z)/(E) = 92/8–95/5) without the addition of $PbCl_2$.[7]
16. The consumption of ethyl benzoate was checked by tlc analysis.
17. The following ratios of reactants, ester/1,1-dibromoalkane/zinc/$TiCl_4$/$PbCl_2$/TMEDA = 1/2.2/9/4/0.045/8, gave the best results. When the amount of the reagent was reduced to 1/1.1/4.5/2/0.023/4, only 44% of the 1-ethoxy-1-phenyl-1-hexene was isolated under the same reaction conditions and 44% of ethyl benzoate remained.
18. Under the reaction conditions for alkylidenation, compounds containing the following functional groups were found to be stable: trimethylsilyl ethers of alcohols, olefins, primary alkyl iodides, and ethylene acetals of aldehydes.
19. Basic alumina (ICN alumina B-Act. I) was purchased from ICN Biochemical GmbH and pretreated by shaking with 6% of water to change its activity (Act I □ III).
20. The infrared spectrum (neat) has absorptions at 2924, 2870, 1649, 1492, 1446, 1266, 1072, 768, 696 cm^{-1}; ^1H NMR ((Z) isomer) ($CDCl_3$) δ: 1.00 (t, 3 H, J = 6.9), 1.23–1.45 (m, 7 H), 2.32–2.39 (m, 2 H), 3.76 (q, 2 H, J = 7.0), 5.38 (t, 1 H, J = 7.3), 7.23–7.50 (m, 5 H); ^1H NMR ((E) isomer) ($CDCl_3$) δ: 0.87 (t, 3 H, J = 7.0), 1.23–1.45 (m, 7 H), 2.00–2.13 (m, 2 H), 3.80 (q, 2 H, J = 7.0), 4.74 (t, 1 H, J = 7.4), 7.23–7.50 (m, 5 H); ^{13}C NMR ((Z) isomer) ($CDCl_3$) δ: 14.0, 15.3, 22.5, 25.4, 32.0, 65.8, 115.4, 125.8, 127.5, 128.2, 136.7, 153.2. MS m/z (%): 204 (M^+, 48), 161 (100), 133 (55), 55 (49). Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.47; H, 10.04.
21. The ratio of the geometric isomers of the product ((Z)/(E)) was determined by ^1H NMR since isomerization has been shown to occur under GLC conditions.[8]

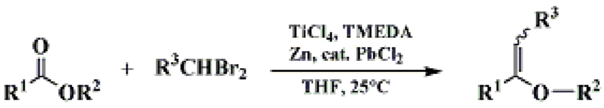
Waste Disposal Information

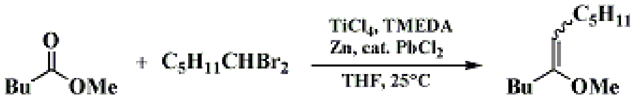
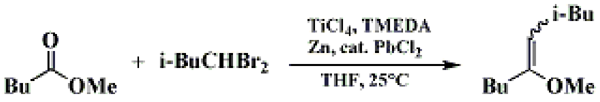
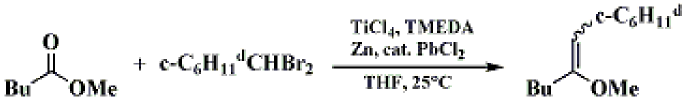
All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

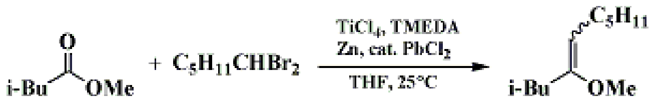
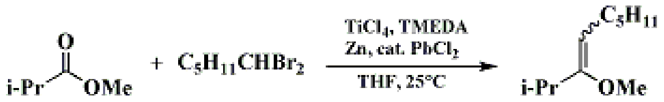
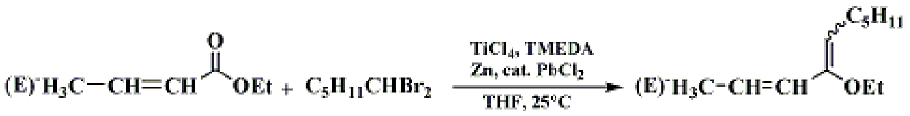
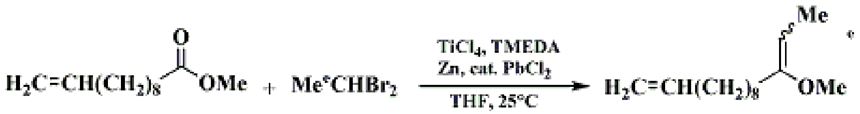
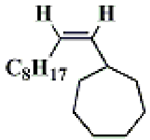
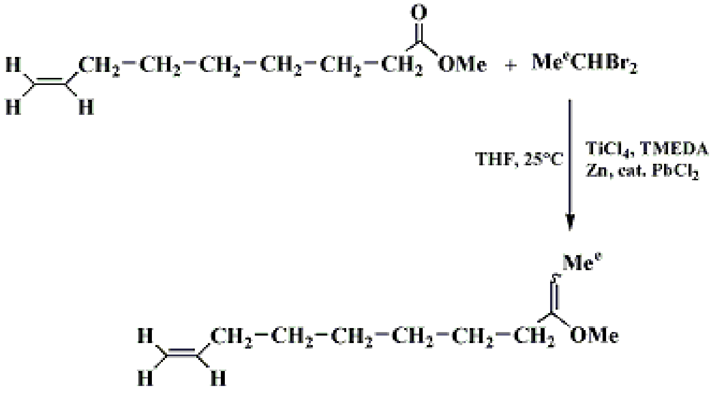
3. Discussion

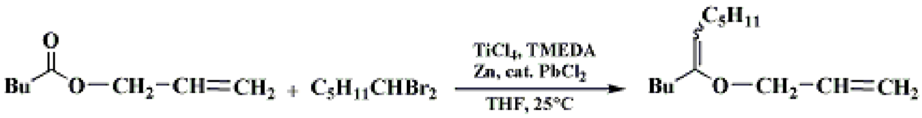
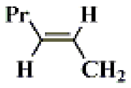
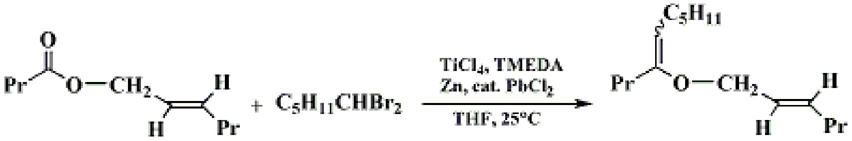
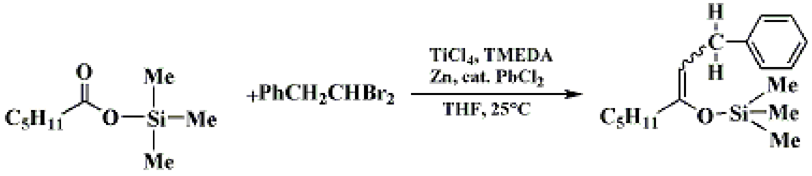
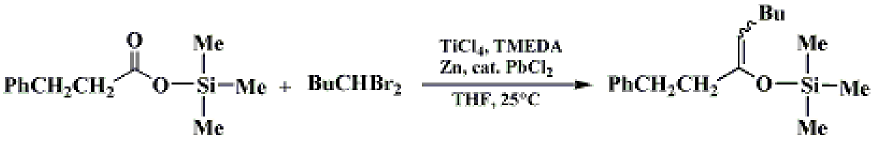
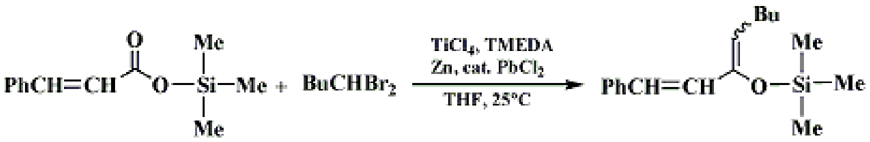
The procedure described here provides a convenient method for the conversion of esters to Z-alkenyl ethers.[5] The results in the Table show the wide applicability and high Z selectivity of the process. As the substituents R^1 or R^3 become bigger, or R^2 becomes smaller, higher Z selectivity is observed. The stereochemistry of the isomers (Table, cases 1–10) was determined by ^{13}C NMR.[8] Since isomerization of alkenyl ethers has been reported to take place under GLC conditions, the remaining Z/E ratios were measured by ^{1}H NMR (200 MHz) analysis. Esters having terminal double bonds reacted to afford the corresponding alkenyl ethers in about 50% yield (cases 7 and 9). Esters with internal double bonds gave better yields and the stereochemistry of double bonds of the reactants was retained except in the instance of case 8 where partial isomerization of the isolated cis double bond occurred. Thus, the reaction provides a convenient and stereoselective access to allyl vinyl ethers (cases 9 and 10) and oxygen-substituted dienes (case 6). Z-Isomers of silyl enol ethers (cases 11–13) and an alkenyl sulfide (case 14) are also produced under good stereocontrol from the corresponding carboxylic acid derivatives.

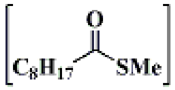
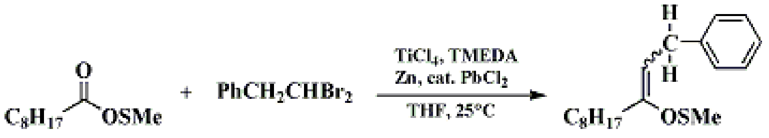
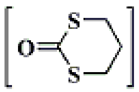
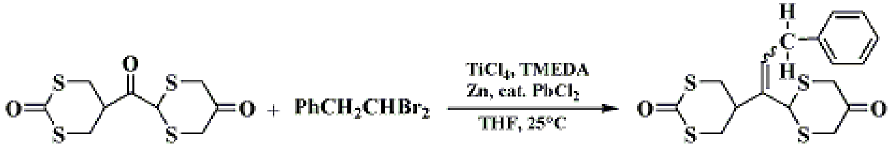
TABLE
ALKYLIDENATION OF CARBOXYLIC ACID DERIVATIVES[a]



Case	R^1	R^2	R^3	Yield(%)[b]	Z/E[c]
1	Bu	Me	C_5H_{11}	 96	91/9
2	Bu	Me	i-Bu	 95	93/7
3	Bu	Me	c-C_6H_{11}[d]	 69	93/7

4	i-Bu	Me	C_5H_{11}	 88	92/8
5	i-Pr	Me	C_5H_{11}	 89	100/0
6	(E)-MeCH=CH	Et	C_5H_{11}	 90	94/6
7	CH_2=CH $(CH_2)_8$	Me	Me[e]	 53	89/11
8		Me	Me[e]	 70[f]	90/10

9	Bu	$CH_2=CHCH_2$	C_5H_{11}		52	92/8
10	Pr		C_5H_{11}		85	94/6
11	C_5H_{11}	Me_3Si	$PhCH_2$		76[g]	89/11
12	$PhCH_2CH_2$	Me_3Si	Bu		80[g]	84/16
13	PhCH=CH	Me_3Si	Bu		79[g]	100/0

14		$PhCH_2$	 87[g]	90/10
15		$PhCH_2$	 87[h]	—

[a]The carboxylic acid derivatives (1–2 mmol scale) are treated with 1,1-dibromoalkane (2.2 equiv), Zn (9.0 equiv), $TiCl_4$ (4.0 equiv), $PbCl_2$ (0.045 equiv), and TMEDA (8.0 equiv) in THF at 25°C for 0.5–3 hr. [b]Products are isolated by column chromatography on alumina unless otherwise noted. [c]See the text. [d]Prepared from cyclohexanecarbaldehyde[9] [e]Commercially available at Tokyo Kasei Kogyo Co., Japan. [f]The cis/trans ratio of the double bond at C-11 of the resultant ether was 87/13. [g]Isolated by column chromatograpy on silica gel (70–230 mesh ATSM, MERCK). [h]The product was isolated by Kugelrohr distillation.bp 150–152°C (bath temperature, 0.2 mm).

The preparation of alkenyl ethers is limited to methods which use as starting materials either acetals[10] or acetylenes.[11,12] It is usually difficult to prepare the alkenyl ethers, especially trisubstituted ones, in a regio- and stereoselective manner by these methods. Alkylidenation of carboxylic acid derivatives does not proceed with the Wittig reagent.[13] Methylene transfer (C=O □ C=CH_2) of such electron-rich carbonyl compounds has been achieved with the Tebbe reagent[14] or dimethyltitanocene.[15,16] Alkylidenation by using the Schrock-type metal carbene complex of Ta, Ti, Zr, or W has been reported.[17 18 19] However, the method using the Schrock complexes has several drawbacks. For example, i) the preparation of the complex usually requires special techniques and some restrictions exist on the nature of the substitutents R^1 and/or R^2. ii) The alkylidenation reaction using the Schrock complexes does not provide alkenyl ethers with good control over olefin geometry. The present procedure offers an experimentally simple and stereoselective preparation of alkenyl ethers. The reactants, 1,1-dibromoalkanes, are readily prepared from either iodoalkanes (vide supra) or aldehydes[20 9,21 22] and it is not necessary to isolate the reactive organometallic compound.

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

alumina

brine

(Z) and (E)-1-ethoxy-1-phenyl-1-hexene

$PbCl_2$

Zn

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

sodium sulfite (7757-83-7)

lead (II) chloride

nitrogen (7727-37-9)

acetone (67-64-1)

potassium hydroxide (1310-58-3)

Benzophenone (119-61-9)

zinc (7440-66-6)

sodium (13966-32-0)

ethyl benzoate (93-89-0)

dibromomethane (74-95-3)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

cadmium (7440-43-9)

butyllithium, n-butyllithium (109-72-8)

Tetrahydrofuran, THF (109-99-9)

hexane (110-54-3)

titanium tetrachloride (7550-45-0)

triethylamine (121-44-8)

cyclohexanecarbaldehyde (2043-61-0)

calcium hydride (7789-78-8)

hexamethylphosphoric triamide (680-31-9)

diisopropylamine (108-18-9)

tetramethylethylenediamine (20485-44-3)

1-iodobutane (542-69-8)

(Z)-1-Ethoxy-1-phenyl-1-hexene (174866-87-6)

1,1-Dibromopentane (13320-56-4)

(E)-1-ethoxy-1-phenyl-1-hexene

1-ethoxy-1-phenyl-1-hexene

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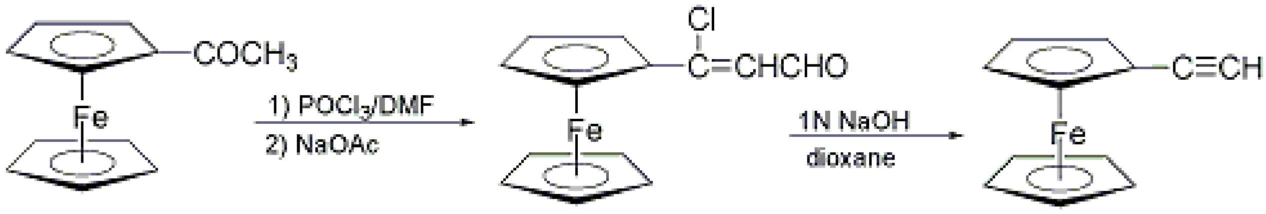
Organic Syntheses, CV 9, 411

CONVERSION OF METHYL KETONES INTO TERMINAL ACETYLENES: ETHYNYLFERROCENE

[Ferrocene, ethynyl]



Submitted by Johann Polin and Herwig Schottenberger[1].
Checked by Bruce Anderson and Stephen F. Martin.

1. Procedure

(2-Formyl-1-chlorovinyl)ferrocene: A dry, 1-L, three-necked, round-bottomed flask, equipped with a magnetic stirring bar, an inlet valve for inert gas, a pressure-equalizing addition funnel, and an outlet valve vented through a mercury bubbler, is charged with 22.8 g (0.1 mol) of acetylferrocene (Note 1) and 25 mL (0.32 mol) of N,N-dimethylformamide (DMF) (Note 2). The system is flushed with argon, cooled to 0°C by means of an ice bath, and the brown reaction mixture is stirred well for several minutes (Note 3). Separately, a dry, 100-mL, graduated cylinder bearing a standard taper ground joint with an argon inlet/outlet, is purged with nitrogen and charged with 25 mL (0.32 mol) of DMF. The DMF is cooled in crushed ice and agitated by hand during the cautious addition of 25 mL (0.27 mol) of phosphorus oxychloride (Note 4). The resulting viscous, red complex is transferred to the dropping funnel and added to the magnetically stirred mixture of acetylferrocene and DMF dropwise over 30 min (Note 5). Complete addition is assured by washing the addition funnel and walls of the flask with a small amount of DMF using a pipette. The mixture is stirred at 0°C for 2 hr during which time the color of the reaction mixture changes from dark brown to olive and ultimately to deep blue. Prior to neutralization, the dropping funnel is replaced by a reflux condenser (Note 6). A 75-mL portion of diethyl ether is added, and the viscous mixture is stirred vigorously for several minutes (Note 7).

Under a positive pressure of argon with continued ice cooling, 116 g (0.85 mol) of sodium acetate trihydrate is cautiously added to the reaction mixture in one portion through a powder funnel followed by cautious addition of 10 mL of water with vigorous stirring (Note 8). The ice bath is removed whereupon the organic layer undergoes a striking color change from colorless to ruby red indicating the formation of the formyl derivative. After 1 hr, an additional 10 mL of ether is added, and stirring is continued for 3 hr at room temperature to ensure complete quenching. The reaction mixture is transferred to a 2-L separatory funnel with ether and water and mixed thoroughly, and the organic phase is separated. The aqueous phase is extracted several times with 100-mL portions of ether (Note 9). The combined organic phases are carefully washed twice with 100-mL portions

of saturated aqueous sodium bicarbonate solution (*CAUTION: gas evolution*) and then with 100 mL of water (Note 10). The organic phase is dried over sodium sulfate, filtered, and concentrated using a rotary evaporator affording 23.4–25.6 g (85–93%) of (2-formyl-1-chlorovinyl)ferrocene (homogeneous by TLC analysis) as deep purple crystals (mp 76–77°C) after drying under high vacuum (Note 11).

Ethynylferrocene: A dry, 1-L, three-necked, round-bottomed flask, equipped with a magnetic stirring bar, reflux condenser, and inlet/outlet valves for maintenance of an inert atmosphere as described above, is flushed with argon, charged with 26.0 g (95.0 mmol) of (2-formyl-1-chlorovinyl)ferrocene and 300 mL of anhydrous 1,4-dioxane (Note 12), and the apparatus is placed in an oil bath. The reaction mixture is heated to reflux and after 5 min at reflux, 250 mL of a boiling 1 N solution of sodium hydroxide (a 2.5-fold excess) is cautiously added as rapidly as possible in one portion (Note 13), and the mixture is heated at reflux for another 25 min (Note 14). The oil bath is removed and the reaction mixture is allowed to cool to room temperature.

The reaction mixture is cautiously poured into ice and neutralized with 1 N hydrochloric acid. After transfer to a 1-L separatory funnel, the aqueous mixture is extracted five times with 100 mL of hexane (Note 15). After the combined organic extracts are successively washed twice with 100-mL portions of saturated aqueous sodium bicarbonate solution and water, the organic phase is dried over sodium sulfate, filtered, and concentrated using a rotary evaporator affording an orange residue of crude ethynylferrocene. The crude product is purified by flash chromatography (Silica G-60, 5 × 15 cm column) with elution by hexane (Note 16). Concentration of the fractions containing the product and drying under high vacuum affords 14.8–15.0 g (74–75%) of pure ethynylferrocene which crystallizes as an orange solid, mp 53°C (lit.[2] 52–53.5°C) upon seeding (Note 17).

2. Notes

1. Acetylferrocene, $C_{12}H_{12}FeO$, 95% (FW (228.07), mp 85–86°C) is available from Aldrich Chemical Company, Inc. or Lancaster Synthesis Ltd., and is used without further purification (*CAUTION: highly toxic*). Acetylferrocene should be carefully triturated before use. The analytical data are as follows: ^{1}H NMR (100 MHz, CCl_4) δ: 2.25 (s, 3 H), 4.08 (s, 5 H), 4.30 (s, 2 H), 4.61 (s, 2 H); ^{13}C NMR (22.6 MHz) δ: 26.9, 69.2, 69.5, 71.8, 79.3, 200.1; IR (CCl_4) cm^{-1}: 3100, 1675.

2. N,N-Dimethylformamide (DMF), 99% (C_3H_7NO, FW (73.10), mp −61°C, bp 153°C, d = 0.944, n_D^{20} 1.4305) was purchased from Fluka Chemie AG, and used without further purification. *CAUTION: DMF is a cancer suspect agent*.

3. The best results were obtained in an argon atmosphere, although from the stability of the product it seems most likely that an inert gas atmosphere is not essential. Care must be taken to stir the entire system, particularly for large-scale syntheses.

4. Phosphorus oxychloride ($POCl_3$), 99% (FW 153.33, mp 1.25°C, bp 105.8°C, d = 1.645) available from Fluka Chemie AG, was used as purchased. $POCl_3$ is highly toxic and moisture sensitive.

5. *CAUTION: The formation of the complex is highly exothermic! Be aware of the hazards of phosphorus oxychloride.*

6. This is a safety measure in case the neutralization should become too exothermic.
7. If the ethereal layer turns orange, it is removed and replaced with 75 mL of fresh ether. This procedure removes any traces of unreacted acetylferrocene or ferrocene impurities. The use of a pipette is recommended to replace the organic layer, if necessary.
8. Sodium acetate trihydrate ($CH_3CO_2Na \cdot 3\ H_2O$) 99%, available from Fluka Chemie AG, was used. Anhydrous sodium acetate (CH_3CO_2Na) 99% is only appropriate, if sufficient amounts of water are present.
9. Initially the phase separation is hard to discern. Extraction is continued until the organic phase is nearly colorless.
10. Additional sodium acetate trihydrate is added to the combined aqueous phases, which after some time, affords a small amount of additional product upon ether extraction. Careful extraction and washing of the organic phases prevents undesired polymerization. The yield and quality of the product obtained are largely dependent on the care taken in the extraction procedure.
11. (2-Formyl-1-chlorovinyl)ferrocene ($C_{13}H_{11}ClFeO$) has the following spectroscopic characteristics: ^1H NMR (300 MHz, $CDCl_3$) δ: 4.24 (s, 5 H), 4.57 (s, 2 H), 4.75 (s, 2 H), 6.40 (d, 1 H, J = 6.7), 10.09 (d, 1 H, J = 6.7); IR (CCl_4) cm^{-1}: 2851, 1671.
12. 1,4-Dioxane, 99% ($C_4H_8O_2$, FW (88.11), mp 11.8°C, bp 100–102°C, n_D^{20} 1.4225, d = 1.034) was purchased from Aldrich Chemical Company, Inc. and distilled from sodium benzophenone ketyl before use. *CAUTION: dioxane is a cancer suspect agent and a flammable liquid*. Attempts to use other solvents failed, and despite subsequent addition of aqueous sodium hydroxide, prior distillation of the dioxane from sodium benzophenone ketyl seems to be essential.
13. A solution of aqueous sodium hydroxide is prepared by dissolving 10 g of sodium hydroxide pellets, 97% (Fluka Chemie AG) in 250 mL of water. The solution is heated to boiling before addition.
14. After this time, TLC analysis (hexane as eluent) indicates essentially complete conversion to ethynylferrocene and an impurity with an R_f value near zero.
15. A pH of 6–7 should be maintained. The phase boundary of the organic and aqueous phases is often difficult to discern, but separation is most satisfactory if the organic/aqueous mixture is filtered through a pad of Celite to remove an oily third phase prior to separation of the aqueous and organic layers. After the final extraction, the organic layer should be nearly colorless.
16. Silica Gel 60741 from Fluka Chemie AG was used. The impurities remain at the top of the 5 × 15-cm column when hexane is used as eluent.
17. The spectroscopic data for ethynylferrocene are as follows: ^1H NMR (300 MHz, $CDCl_3$) δ: 2.71 (s, 1 H), 4.19 (m, 2 H), 4.21 (s, 5 H), 4.46 (m, 2 H); ^{13}C NMR (75 MHz) δ: 63.5, 68.3, 69.6, 71.2; IR (CCl_4) cm^{-1}: 3311, 2112.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The two-step synthesis of ethynylferrocene described here follows essentially the scale-sensitive route reported by Rosenblum, et al.[2] Although various intermediates have been evaluated,[3,4] (2-formyl-1-chlorovinyl)ferrocene is the most successful precursor in the synthesis of ethynylferrocene. Treatment of acetylferrocene with phosphorus oxychloride in dimethylformamide leads to mixtures of (2-formyl-1-chlorovinyl)ferrocene and the more unstable (1-chlorovinyl)ferrocene, with the ratio of products depending on the stoichiometry.[2] However, production of (1-chlorovinyl)ferrocene can be effectively suppressed by employing an excess of phosphorus oxychloride. Using dimethylformamide as solvent leads to satisfactory results only for small-scale preparations. However, modification of the stoichiometry and experimental conditions led to the above described procedure which is useful for large-scale preparations. Use of conditions employing a comparatively small excess of dimethylformamide and phosphorus oxychloride resulting in a heterogeneous reaction mixture, as well as use of solid sodium acetate trihydrate surmount the problems of scale up and enable the removal of organic impurities. The purity and yield of the intermediate (2-formyl-1-chlorovinyl)ferrocene are substantially improved using the present procedure, and this intermediate is obtained in pure form without need of chromatography .

The procedure for the final elimination reaction is essentially that of Rosenblum, et al.[2] A more detailed procedure is provided which improves reproducibility. Treatment of an ethereal solution of (2-formyl-1-chlorovinyl)ferrocene with sodium amide in liquid ammonia under anhydrous conditions is also an acceptable method,[5] along with the method described which employs base-induced elimination using aqueous sodium hydroxide in dioxane.[2,6] Compounds of the α-haloferrocene type are converted more or less quantitatively into alkynes by dehydrochlorination using potassium tert-butoxide in dimethyl sulfoxide.[7] This alternative method for converting the β-chloroaldehyde might also be useful, but lower yields (15–20% less) make the conventional method[2] more efficient for the synthesis of ethynylferrocene.

With respect to cost and ease of accessibility, the procedure described above is superior to other, more recent synthetic methods.[8,9,10,11,12] However, the most convenient alternative synthesis of ethynylferrocene is that of Doisneau, et al.[11] Some procedures[11,12] also permit the synthesis of 1,1'-diethynylferrocene derivatives. Diethynylmetallocenes represent versatile precursors for the preparation of oligometallocenes.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

H_2O

sodium benzophenone ketyl

Ferrocene

(2-Formyl-1-chlorovinyl)ferrocene

Ethynylferrocene

Ferrocene, ethynyl

acetylferrocene

(1-chlorovinyl)ferrocene

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ether, diethyl ether (60-29-7)

sodium acetate (127-09-3)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

Phosphorus Oxychloride (21295-50-1)

dioxane (5703-46-8)

sodium amide (7782-92-5)

N,N-dimethylformamide, dimethylformamide, DMF (68-12-2)

sodium acetate trihydrate (6131-90-4)

hexane (110-54-3)

dimethyl sulfoxide (67-68-5)

argon (7440-37-1)

1,4-dioxane (123-91-1)

potassium tert-butoxide (865-47-4)

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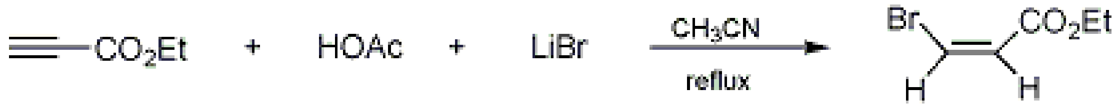
Organic Syntheses, *CV 9*, *415*

STEREOSPECIFIC SYNTHESIS OF ETHYL (Z)-3-BROMO-2-PROPENOATE

[2-Propenoic acid, 3-bromo-, ethyl ester, (Z)-]



Submitted by Shengming Ma and Xiyan Lu[1].
Checked by Qingzhi Gao and Hisashi Yamamoto.

1. Procedure

Ethyl (2Z)-3-bromopropenoate. To a three-necked, round-bottomed flask are added lithium bromide (10.0 g, 0.115 mol, (Note 1)), acetonitrile (100 mL, (Note 2)), acetic acid (7.0 g, 0.116 mol, (Note 3)), and ethyl 2-propynoate (9.0 g, 0.092 mol, (Note 4), (Note 5)) under nitrogen. The reaction is carried out with magnetic stirring under reflux and monitored by GLC (Note 6). The reaction is complete after 24 hr. The reaction is cooled, water (20 mL) is added to the flask, and the mixture is cautiously neutralized with solid potassium carbonate, added in portions (Note 3). The organic layer is separated, and the aqueous layer is extracted with ether (3 × 20 mL) (Note 3). The combined organic layers are dried with magnesium sulfate and filtered. After removal of the solvent, ethyl (2Z)-3-bromopropenoate is obtained by vacuum distillation (14.0 g, yield, 85%, (Note 7)).

2. Notes

1. Lithium bromide (reagent grade) was dried over phosphorus pentoxide (P_2O_5) with heating at 100°C under vacuum.
2. Acetonitrile was distilled from P_2O_5 before use.
3. Acetic acid, potassium carbonate and ether are reagent grade.
4. The optimum ratio of starting materials for this reaction is LiBr : CH_3CO_2H : 2-propynoate = 1.25 : 1.25 : 1.
5. Ethyl 2-propynoate is available from Aldrich Chemical Company, Inc.
6. GLC was performed on a 2-m column (10% OV-1 supported on 102 silanized white support, 60–80 mesh) at 90°C.
7. Ethyl (2Z)-bromopropenoate boils at 92–93°C/40 mm. Isomerization was not detected during careful distillation (bath temperature: <115°C). The spectral data are as follows: IR (neat) cm^{-1}: 1730, 1605, 1200, 1185; MS m/e: 181 [M^+(^{81}Br)+1]/179 [M^+(^{79}Br)+1]: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.31 (t, 3 H, J = 7.0), 4.24 (q, 2 H, J = 6.2), 6.61 (d, 1 H, J = 8.4), 6.99 (d, 1 H, J = 8.4). No E isomer was detected by ^{1}H NMR, GLC (Note 6), or TLC on silica gel (eluent:

petroleum ether : CH_3CO_2Et = 10:1).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

3-Halopropenoic acids and their derivatives are valuable intermediates in organic synthesis because three functional groups are present: the C-X bond, the conjugated C=C bond, and the carbonyl group. These compounds can be used to react with nucleophiles,[2] and, as vinyl halides, to introduce a cis olefinic moiety into an organic molecule using organometallic methods, for the synthesis of (2Z)-en-4-ynoic and (2Z,4Z)- and (2Z,4E)-dienoic acid derivatives.[3] Usually such compounds are prepared as a Z and E isomeric mixture. Only a few stereoselective synthetic methods have been reported, most of which are for E isomers. For example, the title compound was reported to be prepared as a Z and E isomeric mixture via the reaction of ethyl 2-propynoate with hydrogen bromide in acetic acid.[4] The only possible route for its synthesis is by esterification of (2Z)-3-bromopropenoic acid[5] according to the method for methyl (2Z)-3-chloropropenoate, but isomerization may occur during the prolonged heating of esterification.[6] No one-step method for the synthesis of the pure Z isomer is available. The stereospecific method described here can also be applied to the synthesis of (2Z)-3-halopropenoic acids,[7,8] (2Z)-3-halopropenoates,[7,8,9] (2Z)-3-halo-propenamides,[8] and (2Z)-3-halopropenenitriles[8] (X=I, Br, Cl). In the case of the iodide, sodium iodide and lithium iodide gave similar results, but it is necessary to carry out the reaction under N_2.[9] With the bromide and chloride, lithium salts gave higher yields than sodium salts. The mechanism of this reaction is believed to involve nucleophilic addition of halide anion to the electron-deficient, carbon-carbon triple bond. The stability of a termolecular transition state or stereoelectronic stabilization of the anion intermediate formed in situ by the nucleophilic addition might be responsible for the high stereospecificity.[8]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 510

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

petroleum ether

P_2O_5

LiBr

CH_3CO_2H

CH_3CO_2Et

potassium carbonate (584-08-7)

acetic acid (64-19-7)

ether (60-29-7)

acetonitrile (75-05-8)

hydrogen bromide (10035-10-6)

nitrogen (7727-37-9)

sodium iodide (7681-82-5)

magnesium sulfate (7487-88-9)

ethyl 2-propynoate (623-47-2)

lithium iodide (10377-51-2)

lithium bromide (7550-35-8)

phosphorus pentoxide (1314-56-3)

2-propynoate

Ethyl (2Z)-3-bromopropenoate, ETHYL (Z)-3-BROMO-2-PROPENOATE, 2-Propenoic acid, 3-bromo-, ethyl ester, (Z)- (31930-34-4)

Ethyl (2Z)-bromopropenoate

(2Z)-3-bromopropenoic acid (1609-92-3)

methyl (2Z)-3-chloropropenoate

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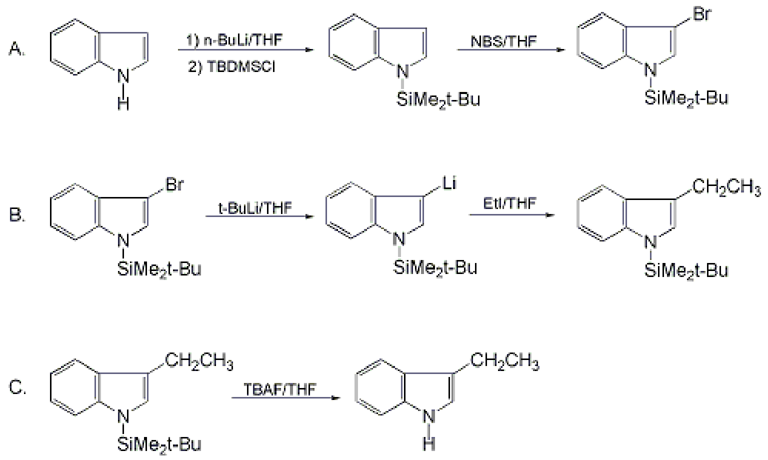
Organic Syntheses, CV 9, 417

REGIOSELECTIVE SYNTHESIS OF 3-SUBSTITUTED INDOLES: 3-ETHYLINDOLE

[1H-Indole, 3-ethyl-]



Submitted by Mercedes Amat, Sabine Hadida, Swargam Sathyanarayana, and Joan Bosch[1].
Checked by Ji Liu, Chris H. Senanayake, and Ichiro Shinkai.

1. Procedure

CAUTION: tert-Butyllithium is extremely pyrophoric.

A. *3-Bromo-1-(tert-butyldimethylsilyl)indole*. An oven-dried, 500-mL, three-necked, round-bottomed flask, equipped with a magnetic stirring bar, 100-mL pressure-equalizing addition funnel, and an argon inlet and outlet, is charged with indole (8.0 g, 0.068 mol) (Note 1) and tetrahydrofuran (200 mL) (Note 2). The solution is stirred and cooled to −78°C with a dry ice/acetone bath, and a solution of butyllithium in hexane (47 mL of a 1.6 M solution, 0.075 mol) (Note 3) is added dropwise via cannula. The mixture is warmed to −10°C, stirred for 15 min, and cooled to −50°C. A solution of tert-butyldimethylsilyl chloride (11.6 g, 0.077 mol) (Note 3) in tetrahydrofuran (60 mL) is added dropwise to this mixture. The temperature is raised to 0°C and after 3 hr the reaction mixture is cooled to −78°C. Freshly crystallized N-bromosuccinimide (12.18 g, 0.0684 mol) (Note 4) is added via a solid-addition funnel and the resulting mixture is stirred in the dark at −78°C for 2 hr and allowed to warm to room temperature. Hexane (100 mL) and pyridine (1 mL) are added and the resulting suspension is filtered through a Celite pad. The filtrate is evaporated under reduced pressure. The crude residue is purified (Note 5) by flash chromatography on silica gel (Note 6) (350 g, 30 cm × 6 cm) (100% hexane) to give 17.8 g (84%) of 3-bromo-1-(tert-butyldimethylsilyl)indole as a colorless solid (Note 7).

B. *1-(tert-Butyldimethylsilyl)-3-ethylindole*. An oven-dried, 500-mL, three-necked, round-bottomed flask, equipped with a magnetic stirring bar, 50-mL pressure-equalizing addition funnel, and an argon inlet and outlet, is charged with 3-bromo-1-(tert-butyldimethylsilyl)indole (10 g, 0.032 mol) and tetrahydrofuran (100 mL). The mixture is stirred and cooled to −78°C with a dry ice/acetone bath. A solution of tert-butyllithium (Note 8) (41.7 mL of a 1.7 M solution in pentane, 0.071 mol) is transferred slowly to the above mixture from a graduated tube via a stainless steel cannula under positive argon pressure. The reaction mixture becomes yellow. Stirring is continued at −78°C for 10 min. A solution of ethyl iodide (5.2 mL, 0.065 mol) (Note 9) in tetrahydrofuran (20 mL) is added dropwise over 15 min to the resulting 1-(tert-butyldimethylsilyl)-3-lithioindole. The reaction mixture becomes colorless, and after 15 min it is allowed to reach room temperature, poured into a cold saturated sodium carbonate solution (200 mL), and extracted with methylene chloride (3 × 100 mL). The combined organic layers are washed with water (100 mL), dried over sodium sulfate, and evaporated under reduced pressure to give 8.0 g (96%) of 1-(tert-butyldimethylsilyl)-3-ethylindole as a light pink oil (Note 10).

C. *3-Ethylindole*. An oven-dried, 250-mL, round-bottomed flask, equipped with a magnetic stirring bar, rubber septum, and an argon inlet and outlet, is charged with 1-(tert-butyldimethylsilyl)-3-ethylindole (8 g, 0.031 mol) and tetrahydrofuran (100 mL). The mixture is stirred and a 1 M solution of tetrabutylammonium fluoride (TBAF) in tetrahydrofuran (31 mL, 0.031 mol) (Note 11) is added. After the solution is stirred for 10 min at room temperature, it is poured into a saturated solution of sodium carbonate (200 mL) and extracted with dichloromethane (3 × 100 mL). The combined organic layers are washed with water (100 mL), dried over sodium sulfate, and evaporated under reduced pressure. The residue is subjected to flash chromatography on silica gel (175 g, 32 cm × 4.5 cm) (25% dichloromethane-hexane, v/v) to give 4.1 g (92%) of 3-ethylindole as colorless plates (Note 12).

2. Notes

1. Indole was obtained from Fluka Chemie AG, and was crystallized from hexane and dried over phosphorus pentoxide (P_2O_5) before use.
2. Tetrahydrofuran was distilled from sodium benzophenone ketyl immediately before use.
3. Butyllithium and tert-butyldimethylsilyl chloride were obtained from Fluka Chemie AG and used as received.

4. N-Bromosuccinimide was obtained from Fluka Chemie AG, and crystallized from water and dried over P_2O_5 before use.
5. Chromatographic purification of the reaction mixture must be effected as soon as possible after workup in order to separate traces of contaminating 3-bromoindole, which promotes rapid decomposition. Pure 3-bromo-1-(tert-butyldimethylsilyl)indole can be stored under argon at 4°C without appreciable decomposition.
6. Silica gel (35–70 mesh) was used as received.
7. The spectral properties for 3-bromo-1-(tert-butyldimethylsilyl)indole are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.60 (s, 6 H), 0.93 (s, 9 H), 7.17 (s, 1 H), 7.20 (m, 2 H), 7.48 (m, 1 H), 7.54 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: –4.0 (CH_3Si), 19.3 [$C(CH_3)_3$], 26.2 [$C(CH_3)_3$], 93.6 (C-3), 114.0 (C-7), 119.1 (C-4), 120.5 (C-5), 122.5 (C-6), 129.6 (C-2), 129.8 (C-3a), 140.2 (C-7a). Anal Calcd for $C_{14}H_{20}BrNSi$: C, 54.18; H, 6.50; Br, 25.75; N, 4.51. Found: C, 54.21; H, 6.60; Br, 25.52; N, 4.62. Attempts to crystallize 3-bromo-1-(tert-butyldimethylsilyl)indole were unsuccessful.
8. tert-Butyllithium (1.7 M solution in pentane) was obtained from Aldrich Chemical Company, Inc., and used as received.
9. Ethyl iodide was obtained from Fluka Chemie AG and distilled prior to use.
10. NMR spectrum shows the presence of less than 3% of 1-(tert-butyldimethylsilyl)indole. Crude 1-(tert-butyldimethylsilyl)-3-ethylindole can be purified by flash column chromatography on silica gel (35-70 mesh) (350 g, 30 cm × 6 cm) (100% hexane) to give pure 1-(tert-butyldimethylsilyl)-3-ethylindole as a colorless oil in about 90% yield. The spectral properties are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.57 (s, 6 H), 0.92 (s, 9 H), 1.32 (t, 3 H, J = 7.5), 2.76 (g, 2 H, J = 7.5), 6.92 (s, 1 H), 7.12 (m, 2 H), 7.47 (m, 1 H), 7.58 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: –3.9 (CH_3Si), 14.5 (CH_3CH_2), 18.4 (CH_2CH_3), 19.5 [$C(CH_3)_3$], 26.3 [$C(CH_3)_3$], 113.8 (C-7), 118.8 (C-4), 119.2 (C-5), 119.8 (C-3), 121.3 (C-6), 126.9 (C-2), 130.9 (C-3a), 141.6 (C-7a). Anal. Calcd for $C_{16}H_{25}NSi$: C, 74.06; H, 9.71; N, 5.40. Found: C, 74.18; H, 9.73; N, 5.46.
11. Tetrabutylammonium fluoride in tetrahydrofuran (1 M solution) was obtained from Fluka Chemie AG and used as received.
12. The spectral properties for 3-ethylindole are as follows: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.37 (t, 3 H, J = 7.5), 2.82 (q, 2 H, J = 7.5), 6.98 (br s, 1 H), 7.18 (m, 2 H), 7.37 (d, 1 H, J = 7.5), 7.66 (d, 1 H, J = 7.8), 7.85 (br s, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 15.0 (CH_3CH_2), 18.9 (CH_2CH_3), 111.6 (C-7), 119.3 (C-3), 119.5 (C-4), 119.6 (C-5), 121.1 (C-6), 122.4 (C-2), 128.0 (C-3a), 136.9 (C-7a).

Waste Disposal Information

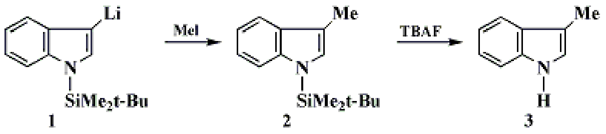
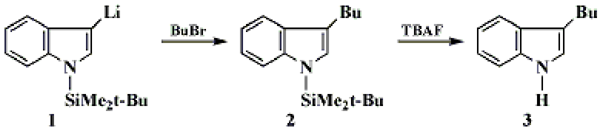
All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

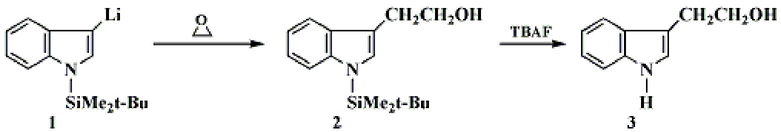
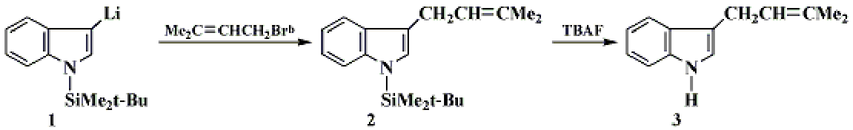
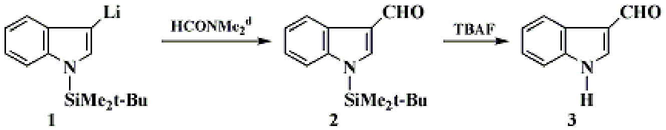
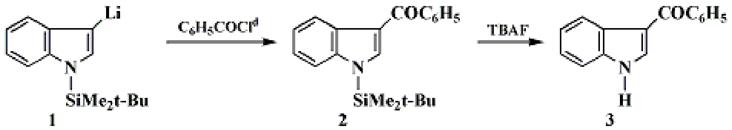
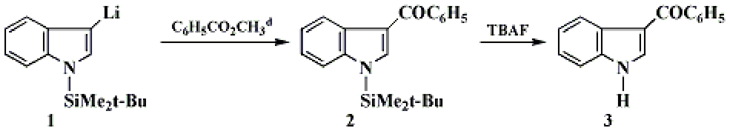
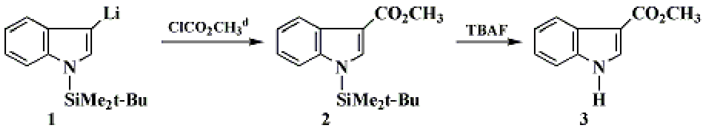
3. Discussion

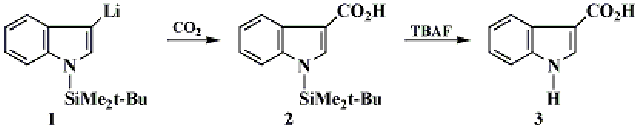
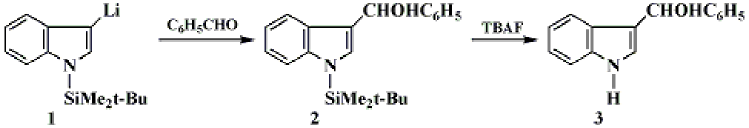
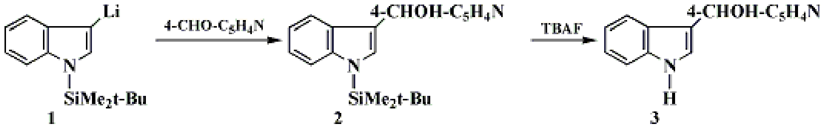
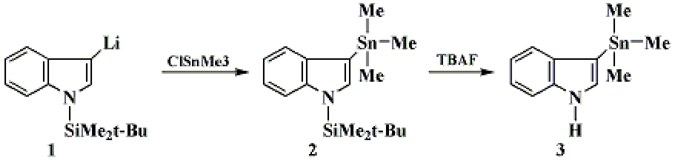
Although there are many studies about the preparation and synthetic applications of N-protected 2-lithioindoles,[2] their isomers, the 3-lithioindoles, have received little attention. Thus, the only indole protecting group used for the preparation of simple 3-lithioindoles is the benzenesulfonyl group. 1-(Benzenesulfonyl)-3-lithioindole is prepared at −100°C by halogen-metal exchange with tert-butyllithium from the corresponding 3-iodo-[3] or 3-bromoindole.[4] At higher temperatures it rearranges to the thermodynamically more stable 2-lithio isomer. On the other hand, some 2-substituted 1-(benzenesulfonyl)-3-lithioindoles undergo ring fragmentation to give 2-aminophenylacetylene derivatives.[5] The change of the benzenesulfonyl protecting group for a trialkylsilyl group allows the preparation of 3-lithioindoles that are relatively stable species even at room temperature.

In the present procedure, indole is protected with a tert-butyldimethylsilyl group and further brominated with N-bromosuccinimide in a one-pot reaction. 3-Bromo-1-(tert-butyldimethylsilyl)indole readily undergoes halogen-lithium exchange with tert-butyllithium at −78°C. Subsequent reaction with an electrophile is exemplified by the reaction with ethyl iodide to give 1-(tert-butyldimethylsilyl)-3-ethylindole. Other electrophiles such as alkyl or allyl halides, ethylene oxide, acylating reagents, carbon dioxide, aromatic aldehydes, and trimethyltin chloride have also been employed successfully in a 500 mg scale (see Table).[6] The reactions regioselectively lead to 3-substituted indoles. 2-Substituted indoles were not detected, indicating that 1-(tert-butyldimethylsilyl)-3-lithioindole **(1)** does not undergo rearrangement to the 2-lithio isomer. Products arising from a ring fragmentation were not detected either. When the reactions of **1** with ethyl iodide and methyl iodide were carried out at room temperature, the yields of the respective 3-alkylindoles were similar to those obtained when operating at −78°C. Finally, the 1-tert-butyldimethylsilyl protecting group can be readily removed by treatment with TBAF under mild conditions.

TABLE
SYNTHESIS OF 3-SUBSTITUTED INDOLES

Entry	Electrophile	R	**2** Yield(%)	**3** Yield(%)[a]
a	MeI	Me	 90	85
b	BuBr	Bu	 64	61

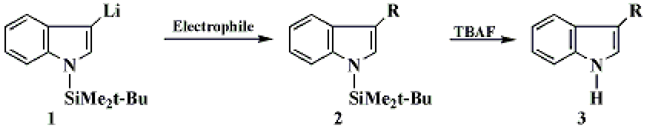
c	$(CH_2CH_2)O$	CH_2CH_2OH	 63	62
d	$Me_2C{=}CHCH_2Br$[b]	$CH_2CH{=}CMe_2$		 69[c]
e	$HCONMe_2$[d]	CHO	e	 94
f	C_6H_5COCl[d]	COC_6H_5	e	 84
g	$C_6H_5CO_2CH_3$[d]	COC_6H_5	 69	58
h	$ClCO_2CH_3$[d]	CO_2CH_3	 84	80

i	CO_2	CO_2H	 94	70[f]
j	C_6H_5CHO	$CHOHC_6H_5$	 67	g
k	4-CHO-C_5H_4N	4-CHOH-C_5H_4N	 55	g
l	$ClSnMe_3$	$SnMe_3$	 94	h

[a]Overall yield after purification by column chromatography. [b]The 3-lithioindole **1** was converted into a cuprate by addition of 1 equiv of $CuBr·SMe_2$. [c]An 85:15 mixture of **3d** and the isomer in which R is $CMe_2CH=CH_2$, respectively, is obtained. [d]The best yields were obtained by reverse addition of the lithium derivative **1** to a THF solution of the electrophile at −78°C. [e]The corresponding 3-acyl derivatives undergo partial desilylation during the work-up. [f]This desilylation was best effected by using CsF instead of TBAF. [g]These carbinols were obtained as pink oils, which partially decomposed during purification by column chromatography. [h]Attempts to deprotect the tin derivative **2l** afforded only indole.

The triisopropylsilyl group gave comparable satisfactory results.[7]

As a further synthetic application, 3-lithioindole **1** was converted to 1-(tert-butyldimethylsilyl)-3-indolylzinc chloride, which has been successfully employed in the heteroarylation of the indole 3-position by a palladium(0)-catalyzed cross-coupling reaction.[8]



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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

P_2O_5

sodium benzophenone ketyl

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

carbon dioxide (124-38-9)

pyridine (110-86-1)

palladium (7440-05-3)

Ethylene oxide (75-21-8)

Methyl iodide (74-88-4)

Pentane (109-66-0)

methylene chloride, dichloromethane (75-09-2)

Ethyl iodide (75-03-6)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

N-bromosuccinimide (128-08-5)

Indole (120-72-9)

hexane (110-54-3)

argon (7440-37-1)

phosphorus pentoxide (1314-56-3)

tert-Butyllithium (594-19-4)

Tetrabutylammonium fluoride (429-41-4)

trimethyltin chloride (1066-45-1)

tert-butyldimethylsilyl chloride (18162-48-6)

3-Ethylindole, 1H-Indole, 3-ethyl- (1484-19-1)

3-Bromo-1-(tert-butyldimethylsilyl)indole (153942-69-9)

1-(tert-Butyldimethylsilyl)-3-ethylindole (153942-71-3)

1-(tert-butyldimethylsilyl)-3-lithioindole

3-bromoindole

1-(tert-butyldimethylsilyl)indole

1-(Benzenesulfonyl)-3-lithioindole

3-lithioindole

1-(tert-butyldimethylsilyl)-3-indolylzinc chloride

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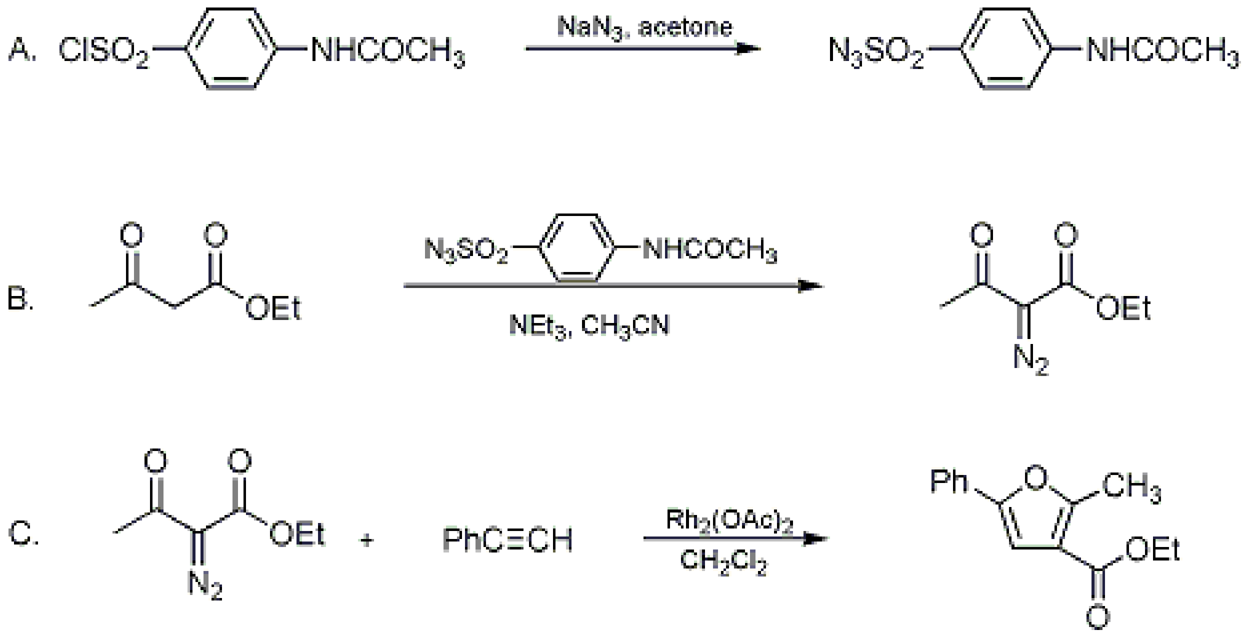
Organic Syntheses, CV 9, 422

SYNTHESIS OF FURANS VIA RHODIUM(II) ACETATE-CATALYZED REACTION OF ACETYLENES WITH α-DIAZOCARBONYLS: ETHYL 2-METHYL-5-PHENYL-3-FURANCARBOXYLATE

[3-Furancarboxylic acid, 2-methyl-5-phenyl-, ethyl ester]



Submitted by Huw M. L. Davies[1], William R. Cantrell, Jr.[1], Karen R. Romines[1], and Jonathan S. Baum[2].
Checked by Frank Stappenbeck and James D. White.

1. Procedure

CAUTION! These reactions, which involve toxic reagents, should be carried out in an efficient hood. Although p-acetamidobenzenesulfonyl azide exhibited no impact sensitivity,[3] proper caution should be exercised with all azide compounds.

A. *p-Acetamidobenzenesulfonyl azide.*[3] A 2-L Erlenmeyer flask equipped with a magnetic stirrer is charged with 117.0 g (0.50 mol) of p-acetamidobenzenesulfonyl chloride (Note 1) and 1 L of acetone. A solution of 39.0 g (0.60 mol) of sodium azide in 300 mL of water is added with stirring and the resulting mixture is left to stir for 12 hr. Three 2-L beakers equipped with magnetic stirrers are charged with 1.5 L each of water. The reaction mixture is divided into three portions and poured into the beakers with stirring. After the mixture is stirred for 1 hr, the white precipitate is filtered (Note 2) and dried in a desiccator over sodium hydroxide for 24 hr. Recrystallization of this

material in four portions from toluene (1.5 L each portion), while the temperature is maintained below 80°C (Note 3), affords 88.9 g (74%) of p-acetamidobenzenesulfonyl azide as white crystals, mp 113°-115°C (Note 4).

B. *Ethyl diazoacetoacetate*.[3] A 2-L, round-bottomed flask equipped with a magnetic stirrer is charged with 26.0 g (0.20 mol) of ethyl acetoacetate, 49.0 g (0.20 mol) of p-acetamidobenzenesulfonyl azide and 1.5 L of acetonitrile. The reaction vessel is cooled in an ice bath, and 60.6 g (0.60 mol) of triethylamine is added to the stirring mixture in one portion. The reaction mixture is warmed to room temperature and stirred for 12 hr. The solvent is removed under reduced pressure, and the residue is triturated with 500 mL of a 1:1 mixture of ether/petroleum ether. The mixture is filtered to remove the sulfonamide by-product, and the filtrate and wash are concentrated under reduced pressure. The crude product is purified by chromatograpy on silica gel (130 g, (Note 5)) with ether/petroleum ether (1:4) as eluant to yield 28.5 g (91%) of ethyl diazoacetoacetate as a yellow oil (Note 6).

C. *Ethyl 2-methyl-5-phenyl-3-furancarboxylate*.[4] A 1-L, three-necked, round-bottomed flask equipped with a magnetic stirrer, an addition funnel, and a reflux condenser is flushed with argon (Note 7). The reaction vessel is charged with 44.35 g of phenylacetylene (0.44 mol, (Note 8)), 0.38 g of rhodium(II) acetate dimer (0.00087 mol), and 100 mL of dichloromethane and the mixture is heated to reflux under an argon atmosphere. The addition funnel is charged with 13.57 g of ethyl diazoacetoacetate (0.087 mol) and 200 mL of dichloromethane, and this solution is added dropwise over 1.5 hr to the reaction mixture. After the reaction mixture is heated under reflux for an additional 12 hr, it is cooled and the solvent is removed under reduced pressure. The crude product is purified by chromatography on silica gel (110 g) with ether/petroleum ether (1:19) as eluant, followed by vacuum distillation (10-cm Vigreux column, 130°C, 0.1 mm) to yield 9.95 g (50%) of the furan as a pale yellow liquid (Note 9).

2. Notes

1. The following chemicals were obtained from the Aldrich Chemical Company, Inc., and were used without further purification: p-acetamidobenzenesulfonyl chloride, 97%; acetone, 99.9+%, HPLC grade; sodium azide, 99%; ethyl acetoacetate, 99%; triethylamine, 99%; rhodium(II) acetate dimer; phenylacetylene, 98%. The following solvents were obtained from Fisher Scientific and were used without further purification: toluene, certified A. C. S.; ethyl ether (Solvent grade, Concentrated); petroleum ether, certified A. C. S. Dichloromethane was distilled from calcium hydride.
2. The filtrate contains excess sodium azide which should be destroyed prior to disposal.
3. The azide partially decomposes at temperatures exceeding 80°C, and the resulting crystals appear slightly brown.

4. Data for p-acetamidobenzenesulfonyl azide are as follows: R_f = 0.49 (ether/ petroleum ether (1:4)); ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.23 (s, 3 H), 7.75–7.89 (m, 4 H), 8.02 (s, 1 H); IR (nujol) cm^{-1}: 3250, 2110, 1665, 1580. Anal. Calcd for $C_8H_8N_4O_3S$: C, 40.00; H, 3.36; N, 23.32; S, 13.35. Found: C, 40.10; H, 3.40; N, 23.26; S, 13.40.
5. Silica gel 60 230–400 mesh ASTM was used. Whatman 250-mm layer, UV254, silica gel TLC plates with polyester backing were used to analyze the fractions.
6. Spectral data for ethyl diazoacetoacetate are as follows: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.29 (t, 3 H, J = 7.1), 2.43 (s, 3 H), 4.26 (q, 2 H, J = 7.1); IR (neat) cm^{-1}: 2970, 2130, 1700, 1650.
7. The glassware in this reaction is dried with a heat gun and placed in a drying oven for 1 hr prior to use.
8. A smaller amount of phenylacetylene results in inefficient capture of the carbenoid intermediate, leading to lower yields.
9. Data for ethyl 2-methyl-5-phenyl-3-furancarboxylate are as follows: R_f = 0.51 (ether/petroleum ether (1:9)); ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.35 (t, 3 H, J = 7.1), 2.63 (s, 3 H), 4.30 (q, 2 H, J = 7.1), 6.87 (s, 1 H), 7.24–7.40 (m, 3 H), 7.60–7.65 (m, 2 H); IR (neat) cm^{-1}: 3080, 3000, 1725, 1610, 1590, 1565. Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13. Found: C, 73.17; H, 6.09.

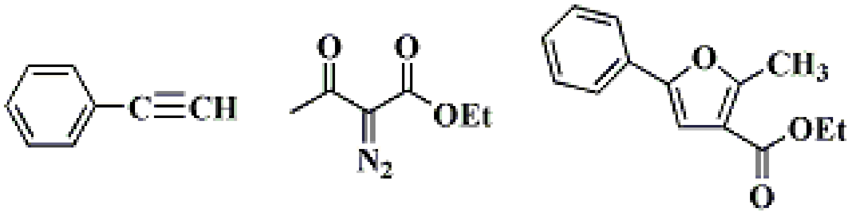
Waste Disposal Information

Excess sodium azide in the filtrate was destroyed by treatment with ammonium cerium (IV) nitrate solution according to the procedure described by Lunn, G.; Sansone, E. B., In "Destruction of Hazardous Chemicals in the Laboratory"; Wiley: New York, 1990; p. 44.

3. Discussion

The procedure described here provides a direct synthesis of highly substituted furans (see Table). Reaction of keto carbenoids with acetylenes is normally an efficient method to prepare cyclopropenes.[5] In numerous systems, however, the formation of furans was observed as a competing side reaction.[6 7 8 9] Furan formation is particularly favored when the carbenoid is a pyruvate[10] or contains two electron-withdrawing groups,[4,11] and when electron-donating groups are present on the acetylene.[4,11]

TABLE
RHODIUM(II) ACETATE-CATALYZED REACTION OF ACETYLENES WITH DIAZO CARBONYL COMPOUNDS[4]



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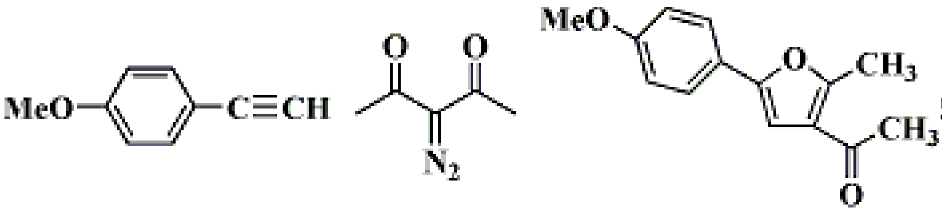

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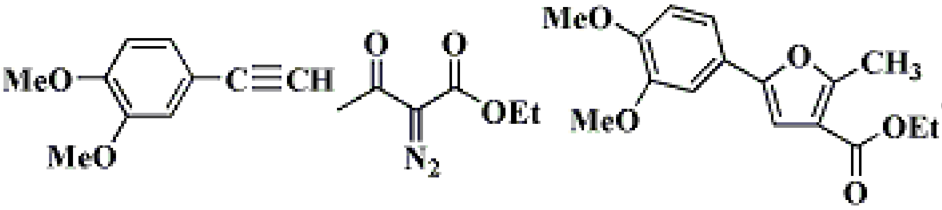

69

The diazo transfer reaction with sulfonyl azides has been used extensively for the preparation of diazo compounds.[12] Toluenesulfonyl azide is the standard reagent used,[13] but because of safety problems resulting from its potentially explosive nature, and because of the difficulty of product separation, several alternative reagents have been developed recently. n-Dodecylbenzenesulfonyl azide[14] has been reported to be very effective for the preparation of crystalline diazo compounds, while p-naphthalenesulfonyl azide[14] has been used for fairly non-polar compounds. Other useful reagents are methanesulfonyl azide[15] and p-carboxybenzenesulfonyl azide.[16] p-Acetamidobenzenesulfonyl azide[3] offers the advantages of low cost, safety, and ease of removal of the sulfonamide by-product through a simple trituration.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 322

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

petroleum ether

rhodium(II) acetate dimer

p-naphthalenesulfonyl azide

ether, ethyl ether (60-29-7)

acetonitrile (75-05-8)

sodium hydroxide (1310-73-2)

p-acetamidobenzenesulfonyl chloride (121-60-8)

acetone (67-64-1)

toluene (108-88-3)

Ethyl acetoacetate (141-97-9)

sodium azide (26628-22-8)

dichloromethane (75-09-2)

Phenylacetylene (536-74-3)

triethylamine (121-44-8)

calcium hydride (7789-78-8)

argon (7440-37-1)

ammonium cerium(IV) nitrate

p-carboxybenzenesulfonyl azide (17202-49-2)

rhodium(II) acetate

methanesulfonyl azide

p-Acetamidobenzenesulfonyl azide (2158-14-7)

n-Dodecylbenzenesulfonyl azide (79791-38-1)

Ethyl 2-methyl-5-phenyl-3-furancarboxylate, 3-Furancarboxylic acid, 2-methyl-5-phenyl-, ethyl ester (29113-64-2)

Ethyl diazoacetoacetate (2009-97-4)

Toluenesulfonyl azide

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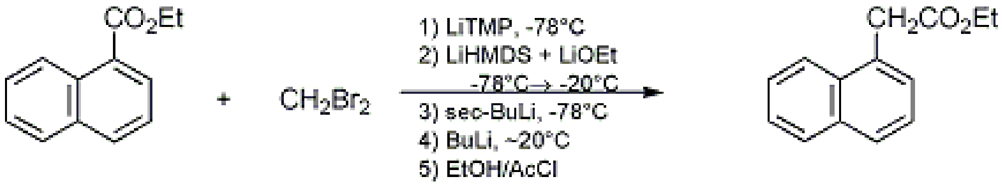
Organic Syntheses, CV 9, 426

ETHYL 1-NAPHTHYLACETATE: ESTER HOMOLOGATION VIA YNOLATE ANIONS

[1-Naphthaleneacetic acid, ethyl ester]



Submitted by Rajarathnam E. Reddy and Conrad J. Kowalski[1].
Checked by Chang Y. Hong and Larry E. Overman.

1. Procedure

A. *Preparation of lithium 2,2,6,6-tetramethylpiperidide (LiTMP)*. An oven-dried, 500-mL, round-bottomed flask, equipped with a magnetic stirring bar, nitrogen inlet, and septum, is filled with a nitrogen atmosphere and charged via syringe with 40.5 mL (33.9 g, 0.240 mol) of 2,2,6,6-tetramethylpiperidine (Note 1) and 250 mL of anhydrous tetrahydrofuran (Note 2). The rapidly stirred solution is cooled with an ice bath and 88.0 mL (0.220 mol) of 2.5 M butyllithium in hexanes (Note 3) is added via syringe over a 20-min period. This solution of lithium 2,2,6,6-tetramethylpiperidide is stirred with continued ice bath cooling for a period of about 30 min while the next reaction is readied.

B. *In situ lithiodibromomethane preparation/addition*. An oven-dried, 2-L, round-bottomed flask with three vertical necks, containing 20.0 g (0.100 mol) of ethyl 1-naphthoate (Note 4), is equipped with a 2-1/2 × -inch, egg-shaped magnetic stirring bar (Note 5), a −100°C to +50°C thermometer (Note 6) and a rubber septum. The apparatus is flushed with nitrogen and a nitrogen atmosphere is maintained throughout the reaction using a nitrogen bubbler system that allows pressure release. The flask is charged through the septum (via syringe) with 200 mL of anhydrous tetrahydrofuran and 15.5 mL (38.3 g, 0.220 mol) of dibromomethane (Note 1). The thermometer (in a side neck) is adjusted so that the bulb is submerged when the liquid is stirred. The flask is immersed almost to the necks in a dry ice-acetone bath using about 2 L of acetone, and the contents are stirred vigorously for good heat transfer.

The lithium tetramethylpiperidide solution from Part A is cooled with a dry ice-acetone bath. When the solution of ethyl 1-naphthoate and dibromomethane has cooled to −74°C or below (internal solution temperature), addition of the dry ice-acetone cooled solution of lithium tetramethylpiperidide is begun. Addition is made via a double-ended (16 gauge) needle over a 40 to 50-min period using a slight positive nitrogen pressure in the 500-mL flask (Note 7). During this time, the addition rate is slowed or stopped as needed to maintain the reaction temperature below −67°C.

C. *Preparation of lithium hexamethyldisilazide(LiHMDS)/lithium ethoxide*. As the addition of Part B above is progressing, an oven-dried, 500-mL, round-bottomed flask, equipped with a magnetic stirring bar, nitrogen inlet, and septum, is filled with a nitrogen atmosphere and charged via syringe with 42.1 mL (32.2 g, 0.200 mol) of 1,1,1,3,3,3-hexamethyldisilazane (Note 1), 5.9 mL (4.6 g, 0.100 mol) of absolute ethanol, and 160 mL of anhydrous tetrahydrofuran. The rapidly stirred solution is cooled with an ice bath and 120 mL (0.300 mol) of 2.5 M butyllithium in hexanes is added via syringe over a 20-min period. The resulting solution of lithium hexamethyldisilazide and lithium ethoxide is stirred with continued cooling for a period of about 30 min and is then cooled with a dry ice-acetone bath (Note 8).

D. *Base and butyllithium addition*. Ten minutes after the addition of lithium tetramethylpiperidide to the

main reaction is complete, the cold (ca. −70°C) solution of lithium hexamethyldisilazide and lithium ethoxide is added (via a double-ended needle) over a 15 to 20-min period, while maintaining the reaction mixture temperature below −65°C. Five minutes after the addition is complete, the dry ice-acetone cooling bath is removed and the reaction mixture is allowed to warm. When the internal temperature of the solution has reached −20°C (after about 15 min), the reaction mixture is again cooled with a dry ice-acetone bath (Note 9), (Note 10). When the internal reaction temperature has reached −70°C or below, 308 mL (0.400 mol) of 1.3 M sec-butyllithium in cyclohexane (Note 11) is added via syringe over a 30 to 40-min period so that the internal temperature is maintained below −60°C. Five minutes after the addition is complete, the dry ice-acetone cooling bath is removed and the reaction mixture is allowed to warm. After the internal temperature has gradually reached ca. −10°C (Note 12), the reaction mixture is warmed to 20°C with a 25°C water bath. A solution of butyllithium (80 mL, 0.200 mol) in hexanes is then added using a syringe pump over a 30 to 40-min period while the internal temperature is maintained between 20–25°C (Note 13), (Note 14). The reaction mixture is then allowed to stir for 30 min at room temperature (Note 15).

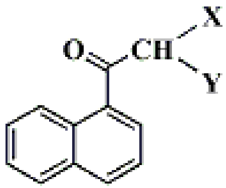
E. *Quench and purification*. While the butyllithium addition is taking place, an acidic ethanol quench solution is prepared in a 3-L, two-necked, round-bottomed flask, equipped with a mechanical stirrer and a 250-mL, pressure-equalizing dropping funnel. The flask is charged with 1 L of absolute ethanol and the funnel with 250 mL of acetyl chloride. The ethanol is stirred rapidly and the flask is cooled with an ice bath as the acetyl chloride is added over a 30–40-min period and then the cooling bath is removed and stirring is continued for 20–30 min. After the main reaction mixture has been stirred for 30 min at room temperature, it is cooled with a dry ice-acetone bath. The acidic ethanol solution is cooled with an ice bath and the cold, main reaction mixture is quenched by addition (via a double-ended needle) into the rapidly stirred, cold, acidic ethanol solution over a 3 to 3.5 hr period (Note 16).

After the quench is complete, the mixture is diluted with 2 L of ether and washed in a separatory funnel with 1.25 L of aqueous 10% hydrochloric acid. The aqueous layer is reextracted with a 2-L portion of ether. The combined ethereal layers are washed with 1.25 L of saturated brine solution and dried over anhydrous magnesium sulfate. After filtration and removal of solvent using a rotary evaporator there remains 26 g of crude product as a reddish-brown oil. Distillation of this material under reduced pressure through an unpacked, 2-inch distillation apparatus affords 17.3 g (81%) of ethyl 1-naphthylacetate as a yellow liquid, (bp 134–138°C, 0.2 mm) (Note 17), (Note 18).

2. Notes

1. 2,2,6,6-Tetramethylpiperidine, dibromomethane (99%) and 1,1,1,3,3,3-hexamethyldisilazane (98%) were purchased from Aldrich Chemical Company, Inc., and used without further purification. Use of less hindered secondary amines (such as diisopropylamine) in place of tetramethylpiperidine results in lower yields because of the formation of carboxamide by-products.
2. Reagent grade tetrahydrofuran was freshly distilled under nitrogen from a purple solution of sodium and benzophenone.
3. Solutions of butyllithium in hexanes and sec-butyllithium in cyclohexane were purchased from the Aldrich Chemical Company, Inc. It is recommended that only freshly opened bottles or extremely well protected solutions be used as the presence of lithium butoxide in partially decomposed bottles results in formation of the corresponding butyl ester as an undesired by-product.
4. Ethyl 1-naphthoate was purchased from Lancaster Synthesis, Inc., P.O. Box 1000, Windham, NH 03087, and used without purification. The checkers found that the purity of the ester was 95% by capillary GC analysis.
5. Good stirring is important to the success of this reaction, in order to provide efficient heat transfer during the addition of lithium tetramethylpiperidide and sec-butyllithium. The 2-1/2 × inch stirring bar used is available from Aldrich Chemical Company, Inc.

6. The submitters recommend calibrating the thermometer to ca. –78°C when immersed in a dry ice-acetone bath. The thermometer used for these runs (Catalog #Z11,011-6) was purchased from Aldrich Chemical Company, Inc. Three different thermometers (two Fisher 15-035 and one Ertco X7048) were found that read from –86°C to –96°C when immersed in a dry ice-acetone bath! The checkers used a digital thermometer, model 450-ATT, purchased from OMEGA Engineering, Inc., Stamford, CT 05907.
7. At a very low temperature the lithium tetramethylpiperidide solution may become too thick for smooth addition. If that occurs, the dry ice-acetone cooling bath is either partially or completely removed for a short period until addition can take place. The checkers warmed this mixture to –20°C to –10°C (whereupon it became a clear solution) prior to addition.
8. While it is important for all ester substrates that lithium hexamethyldisilazide be added before warming in order to avoid yield loss, the addition of lithium ethoxide (LiOEt) is specific for the naphthyl ester and is not generally necessary (see Discussion). Thus for other esters the ethanol can be omitted in this step and the amount of butyllithium can be reduced to 0.20 mol.
9. The reaction mixture turns from a yellow-orange color to a dark brown/black during the warming process, at ca. –35° to –25°C.
10. It is helpful to withdraw about a 0.20-mL aliquot of the reaction mixture after the warming-recooling process, to quench it in about 1.5 mL of a 1:5 mixture of acetyl chloride and absolute ethanol, and then to add about 1 mL of ethyl acetate and 0.5 mL of water. The mixture is shaken and most of the organic layer is transferred via pipette to a tube containing anhydrous magnesium sulfate for drying. GC analysis of this material (at a convenient time) on a 50 m × 0.32 mm i.d. capillary column of cross-linked methylsilicone, at 40 psi of pressure for the helium carrier gas, and at a temperature raised from 100°C to 300°C at a rate of 15°C/min should show no remaining starting ester (ret. time = 6.5 min); instead it should show dibromo ketone **Ia** (X = Br, Y = Br) at a ret. time = 9.0 min, monobromo ketone **Ib** (X = H, Y = Br) at a ret. time = 7.7 min and monochloro ketone **Ic** (X = H, Y = Cl) at a ret. time = 7.1 min (resulting from halogen exchange during the quench) in a ratio of about 3.9:4.2:1.



11. Use of butyllithium in place of sec-butyllithium at this point results in formation of some α-butylated ester by-product later upon warming, while use of sec-butyllithium in greater excess results in formation of methyl ketone **Id** (X, Y = H) in the final product.
12. *CAUTION:* A pressure buildup can occur on this scale if the reaction mixture is warmed from –78°C to –10°C too rapidly and if the nitrogen inlet/pressure release system has very narrow constrictions. The initial warming is best done without a bath and takes about 15 min.
13. The internal temperature is maintained between 20°C to 25°C during the addition with a cold water bath.
14. For non-aromatic esters, this addition can be carried out more conveniently by adding the butyllithium over 5–10 min (without cooling) once the internal temperature has reached –20°C, and then warming to room temperature using a 20–25°C bath. For ethyl 1-naphthoate, however, addition of butyllithium at a lower temperature, or too quickly at a higher temperature, results in formation of ca. 3.2% of methyl ketone **Id** (X = Y = H). This lowers the yield and this compound is difficult to separate from the product.
15. It is wise to remove, quench, and analyze an aliquot from the reaction (as described in (Note 10). At this point there should be no dibromo ketone **Ia** (X, Y = Br, ret. time = 9.0 min) or monobromo ketone (X = H, Y = Br, ret time = 7.7 min), but instead a strong peak for product at a ret. time = 6.8 min. If any monobromo or dibromo ketone is present in the 30-min aliquot, a longer time should be allowed for stirring at room temperature and/or slightly more butyllithium should be added.

16. It is important to quench the reaction *into*the acidic ethanol. If the quench solution is added to the reaction mixture, very little product is obtained.
17. The pot material in this distillation is rather viscous and tends to bump, so good stirring and extra care should be employed to avoid this problem. A low-boiling fraction (0.67–0.78 g, 95–133°C, 0.2 mm) is collected that is mostly a mixture of hydrocarbons and ethyl 1-naphthylacetate (ca. 1% yield). More than 90% of the product distils at 134–138°C, 0.2 mm. For the final few drops of product the bath temperature must be raised by 15–20°C, resulting in a slight rise in product boiling point; however, all the remaining distillate obtained is desired product.
18. G/C analysis (as in (Note 10)) of the final product, shows a single peak with retention time of 6.8 min. This material has the following spectral properties: IR (neat) cm^{-1}: 2981, 1730, 1598, 1512, 1445, 1174, 792, 780; ^{1}H NMR ($CDCl_3$) δ: 1.19 (t, 3 H, J = 7.0), 4.04 (s, 2 H), 4.13 (q, 2 H, J = 7.1), 7.39–7.51 (m, 4 H), 7.76 (dd, 1 H, J = 2.4, 7.1), 7.84 (d, 1 H, J = 7.9), 7.98 (d, 1 H, J = 8.3).

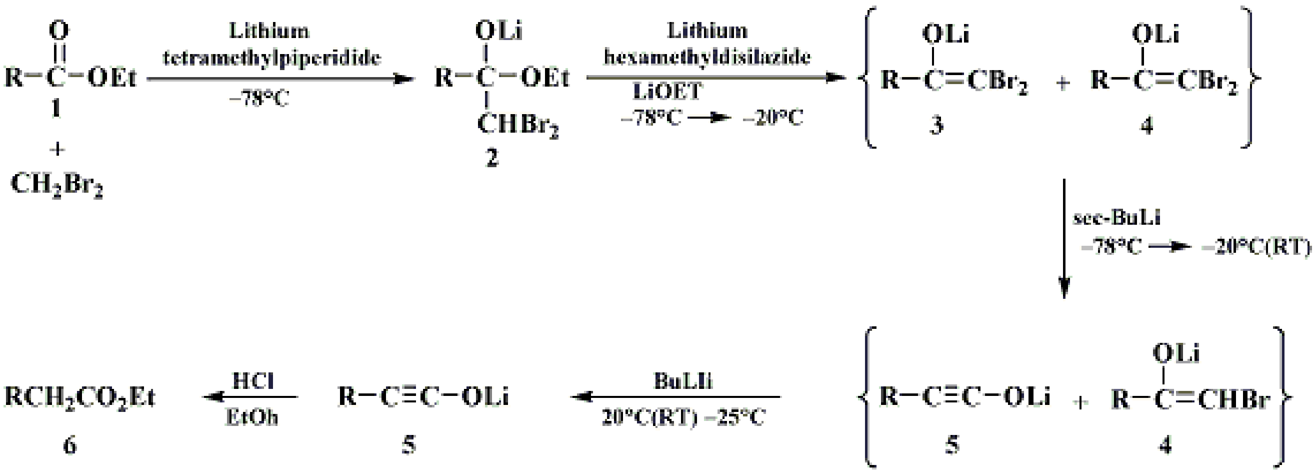
Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

This procedure illustrates a general method for the direct homologation of common esters, that represents a convenient, safer alternative to the classical Arndt-Eistert approach. Ethyl 1-naphthylacetate was selected for this demonstration since its preparation via the classical procedure has appeared previously in *Organic Syntheses*,[2] thus offering a direct comparison. In the earlier work, 1-naphthoyl chloride was prepared from the corresponding acid and converted using diazomethane to 1-(diazoacetyl)naphthalene. Preparation of multigram quantities of hazardous diazomethane was required, and the 1-(diazoacetyl)naphthalene produced was a severe skin irritant that had to be recrystallized in order to achieve the desired overall yield. Freshly prepared silver benzoate was then used to catalyze the Wolff rearrangement, providing the final ethyl 1-naphthylacetate in 78% overall yield (from the acid chloride). A modified Arndt-Eistert procedure using trimethylsilyldiazomethane has also been used to effect transformation of 1-naphthoyl chloride to ethyl 1-naphthylacetate in 66% yield on a 3-mmol scale.[3]

The current procedure starts with the ester, ethyl 1-naphthoate, and converts it into homologated product in 81% yield without isolation of any intermediates. Safe, commercially available materials are employed. Based on a recently published variation[4] of our original homologation methods,[5] it represents a general procedure applicable to esters **1** bearing aryl, alkenyl, alkynyl and primary, secondary or tertiary alkyl attachments R. Yields range from 67–90% (on a 25-mmol scale) and like the Arndt-Eistert sequence this procedure affords retention of stereochemistry for the attachment R. It is also worth noting that this chemistry proceeds through the intermediacy of ynolate anions **5** that are useful for other processes,[6 7] including the preparation of silyloxyacetylenes.[8]



Parts A and B of the procedure correspond to preparation of lithium tetramethylpiperidide, and its use in the in situ preparation[9] and addition of dibromomethyllithium to the ester **1** producing tetrahedral intermediate **2**. In Part C a mixture of lithium hexamethyldisilazide and lithium ethoxide is prepared for addition in Part D to the solution of **2**. The silazide base serves to deprotonate the mono and dibromo ketones that are formed on initial warming of the reaction to −20°C, thus protecting them as the enolate anions **4** and **3**. Addition of the sec-butyllithium in Part D effects the key metal-halogen exchange/ rearrangement of **3** at −78°C, converting it to the ynolate anion **5** (and producing sec-butyl bromide that does not alkylate the ynolate anion on subsequent warming). Addition of butyllithium, also in Part D, provides a source of base (regenerated lithium tetramethylpiperidide) to deprotonate enolate **4** at room temperature and initiate rearrangement to ynolate **5**. The Part E quench then affords final product **6**.

Two modifications were made to our general procedure,[4] specifically to suit the ethyl 1-naphthoate case in this preparation, that are not necessary for most other compounds. For most ynolate anions, **5**, the inverse quench into acidic ethanol described here is sufficient to eliminate significant formation of dimeric products resulting from ynolate anion reaction with the ketene intermediate. In the naphthalene case, however, about 3% of dimeric material (which complicates the distillation) is formed, possibly because of tighter aggregation of the ynolate anions via π-stacking. This was eliminated by adding an equivalent of lithium ethoxide (Parts C and D) to provide more ethoxide as an internal nucleophile/ aggregate companion to trap effectively all the ketene formed in the quench. This ethoxide is not generally required for other substrates (Note 8).

It was also found for the naphthalene case (and to a lesser extent for phenyl), that small amounts of metal-halogen exchange can take place between bromoenolate **4** and butyllithium at room temperature, affording about 3% of acetonaphthone after quench. Thus the butyllithium addition was carried out slowly enough at room temperature so that no buildup of butyllithium would occur; under these conditions, the lithium tetramethylpiperidide deprotonation of **4** was occurring sufficiently fast to generate tetramethylpiperidine and to protonate the butyllithium as it was being added. For non-aromatic R groups on **4**, this competitive metal-halogen exchange was not a problem and the butyllithium need not be added slowly at room temperature (Note 14).

Ethyl 1-naphthoate thus represents one of the more difficult homologation cases, requiring the two modifications above. For most other compounds these are unnecessary and the procedure can be simplified as noted. On untried compounds one should always test the chemistry first on a small (2 mmol) scale, monitoring the quenched aliquots (as in (Note 10) and (Note 15)) to ensure that minor adjustments to the stoichiometry are not needed (e.g., a larger excess of dibromomethyllithium in the first step to consume all the starting ester and/or more butyllithium in the final step to deprotonate/rearrange all the bromoenolate **4**). No such changes have been required for any of the esters that we have investigated to date,[4] however, indicating that this procedure represents a quite general method for the direct homologation of common esters.

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9. This preparation is patterned after the in situ preparation of dibromomethyllithium for addition to ketones using lithium dicyclohexylamide, as reported by Taguchi, H.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1974**, *96*, 3010.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

Lithium 2,2,6,6-tetramethylpiperidide

brine

Lithium hexamethyldisilazide

lithium 2,2,6,6-tetramethylpiperidide (LiTMP)

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

ether (60-29-7)

acetyl chloride (75-36-5)

sec-Butyl bromide (78-76-2)

nitrogen (7727-37-9)

cyclohexane (110-82-7)

acetone (67-64-1)

Benzophenone (119-61-9)

sodium (13966-32-0)

Naphthalene (91-20-3)

dibromomethane (74-95-3)

magnesium sulfate (7487-88-9)

Diazomethane (334-88-3)

ethyl 1-naphthoate (3007-97-4)

1-naphthoyl chloride (879-18-5)

acetonaphthone (941-98-0)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

helium (7440-59-7)

lithium ethoxide

diisopropylamine (108-18-9)

2,2,6,6-tetramethylpiperidine (768-66-1)

Ethyl 1-naphthylacetate (3121-70-8)

1-Naphthaleneacetic acid, ethyl ester (2122-70-5)

1-(Diazoacetyl)naphthalene (4372-76-3)

silver benzoate (532-31-0)

sec-butyllithium (598-30-1)

Trimethylsilyldiazomethane (18107-18-1)

1,1,1,3,3,3-hexamethyldisilazane (999-97-3)

lithium tetramethylpiperidide

lithiodibromomethane, Dibromomethyllithium

tetramethylpiperidine

lithium butoxide (2698-11-5)

lithium dicyclohexylamide

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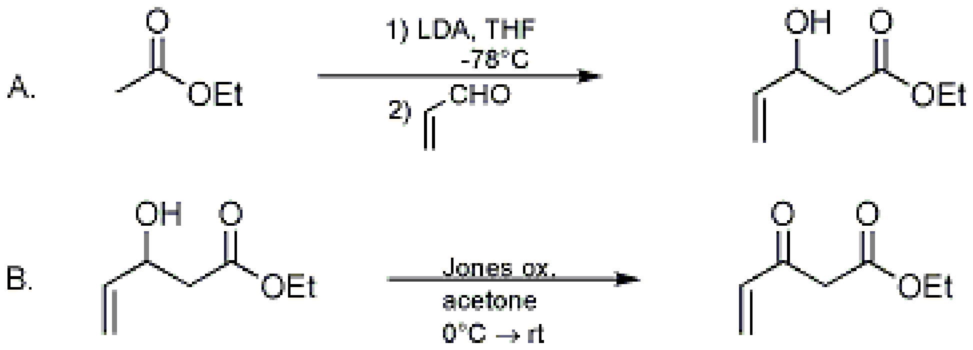
Organic Syntheses, *CV 9, 432*

ETHYL 3-OXO-4-PENTENOATE (NAZAROV'S REAGENT)

[4-Pentenoic acid, 3-oxo-, ethyl ester]



Submitted by R. Zibuck[1] and J. Streiber.
Checked by Michael D. Gaul and Robert K. Boeckman, Jr..

1. Procedure

CAUTION: Acrolein is highly toxic and a lachrymator. Handle in a well-ventilated fume hood!

A. *Ethyl 3-hydroxy-4-pentenoate* A dry, 2-L, two-necked, round-bottomed flask, capped with septa and equipped with a thermometer (Note 1), magnetic stirring bar, and an argon inlet is flushed with argon and charged with dry tetrahydrofuran (400 mL, (Note 2)) and diisopropylamine (30.8 mL, 220 mmol, (Note 3)). The solution is cooled to –30°C and butyllithium (BuLi) (93.2 mL, 220 mmol, 2.36 M solution in hexanes, (Note 4)) is added. The reaction is stirred for 15 min and cooled to –76° to –78°C. Dry ethyl acetate (19.5 mL, 200 mmol, (Note 5)) is added dropwise so that the internal reaction temperature remains below –66°C (addition time 10–15 min). When addition of the ethyl acetate is complete, the reaction is stirred for 50 min at –70° to –78°C. A solution of freshly distilled acrolein (13.4 mL, 200 mmol, (Note 6)) and 100 mL of dry tetrahydrofuran is then added rapidly via a cannula. The reaction is stirred for 5 min and quenched by the rapid addition of saturated aqueous ammonium chloride (NH_4Cl), (100 mL). The reaction mixture is poured immediately into a 2-L separatory funnel containing 500 mL of diethyl ether. The reaction flask is rinsed with 100 mL of distilled water and 100 mL of diethyl ether. After thorough mixing, the layers are separated and the aqueous layer is extracted with diethyl ether (three, 100-mL portions). The combined organic layers are washed with brine (200 mL), dried over magnesium sulfate ($MgSO_4$), filtered, and evaporated under reduced pressure (Note 7). Crude ethyl 3-hydroxy-4-pentenoate is used in the next step (Note 8).

B. *Ethyl 3-oxo-4-pentenoate*. A 1-L, round-bottomed flask equipped with a magnetic stirring bar and pressure-equalizing dropping funnel is charged with ethyl 3-hydroxy-4-pentenoate (Part A) and 400 mL of acetone. The mixture is cooled in an ice bath and Jones reagent (175 mL, (Note 9)) is added dropwise via the dropping funnel (addition time is approximately 30–40 min). When addition of the Jones reagent is complete, the reaction mixture is allowed to warm slowly to room temperature and is stirred overnight (10–20 hr). Methanol (20 mL) is added to quench excess Jones reagent and the reaction mixture is poured into a 2-L separatory funnel containing diethyl ether (800 mL). After thorough mixing, the layers are separated and the aqueous layer is extracted with diethyl ether (three 200-mL portions) (Note 10). The combined organic layers are washed with brine (two 200-mL portions), dried over $MgSO_4$, filtered, and the solvent is removed by simple distillation (Note 11). Final purification is accomplished by Kugelrohr distillation (Note 12) at 0.60 mm (oven temp 45°C) with a 250-mL receiving bulb cooled to −78°C using a dry ice/isopropyl alcohol cold bath. The purified product (14.9 g, 52%) (Note 13) can be stored at −20°C for several months without decomposition.

2. Notes

1. A Fluke 51 K/J digital thermometer with temperature probe is used to monitor internal reaction temperature.
2. Tetrahydrofuran is distilled from sodium-benzophenone ketyl under argon. The reaction may be carried out using a freshly opened can of anhydrous diethyl ether from Fisher Scientific or Mallinckrodt without further purification.
3. Diisopropylamine is purified by heating to reflux over sodium hydroxide (NaOH) for 3–12 hr, followed by simple distillation from NaOH.
4. Butyllithium in hexanes (2.5 M) is purchased from Aldrich Chemical Company, Inc., and titrated using diphenylacetic acid.[2]
5. Ethyl acetate (500 mL) is purified by washing with 100 mL of 5% sodium carbonate solution, followed by 100 mL of saturated sodium chloride solution, drying over potassium carbonate and filtering. It is then heated at reflux over phosphorus oxide (P_2O_5) for 3–12 hr and distilled from P_2O_5.[3]
6. Acrolein is purchased from Aldrich Chemical Company, Inc. It is freshly distilled under reduced pressure (20 mm) employing a dry ice/isopropyl alcohol cooled-receiver.
7. The rotary evaporator bath temperature should not exceed 40°C.
8. If desired, ethyl 3-hydroxy-4-pentenoate can be purified by Kugelrohr distillation at 0.60 mm (oven temperature 57°C) using a dry ice/isopropyl alcohol cold bath to cool the receiver (79% yield). Spectral properties are as follows: IR (film) cm^{-1}: 3437, 2984, 2938, 1732, 1373, 1275, 1030; ^1H NMR (300 MHz $CDCl_3$) δ 1.22 (t, 3 H, J = 6.7, OCH_2CH_3), 2.4–2.6 (m, 2 H, C(OH) $CH_2C(O)$), 3.15–3.25 (br m, 1 H, OH), 4.10 (q, 2 H, J = 6.7, OCH_2CH_3), 4.44–4.57 (m, 1 H, HC(OH)), 5.05–5.35 (m, 2H), 5.78–5.90 (m, 1H); MS, m/z 145

(MH^+).
9. Jones reagent is prepared by dissolving chromium oxide (CrO_3) (23.5 g) in concd sulfuric acid (21 mL) with cooling and then diluting with distilled water to give a total volume of 175 mL.[4]
10. Aqueous chromium waste must be bottled, labeled, and given to the waste management technical personnel.
11. The simple distillation is accomplished by using a rotary evaporator at atmospheric pressure and bath temperature ≤50°C. The last traces of solvent are removed under reduced pressure with an ambient temperature bath. *CAUTION: the product is volatile and will be lost by evaporation if care is not taken.* If water should be present, the compound can be dissolved in diethyl ether, dried again over $MgSO_4$, filtered and distilled.
12. During the Kugelrohr distillation a forerun of 3–4 mL is collected and discarded.
13. The spectral properties of ethyl 3-oxo-4-pentenoate, which exists as a mixture of keto and enol forms, are: IR (film) cm^{-1}: 2984, 1741, 1659, 1588, 1423, 1242, 1150, 1038, 812; ^{1}H NMR ($CDCl_3$) δ 1.2–1.3 (overlapping t, 3 H), 3.6 (s, ketonic H at C(2)), 4.1–4.3 (m, 2 H), 5.05 (s, enolic H at C(2)), 5.50 (app t, 1 H), 5.91–6.43 (m, 2 H), 11.8 (s, enol OH); ^{13}C NMR δ 14.02, 14.19, 46.43, 60.23, 61.43, 91.84, 122.53, 130.16, 131.20; 135.74, 167.14, 168.61, 172.70, 192.62. Minor peaks are observed which may be the E enol form. The mass spectrum shows m/z 143 (MH^+).

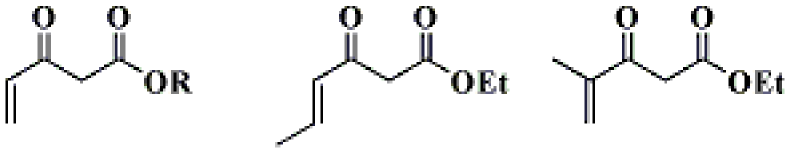
Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Ethyl 3-oxo-4-pentenoate (Nazarov's reagent) is a well known annelating agent that has been used in several terpene[5] and alkaloid[6] syntheses.

Other preparations of Nazarov's reagent and its analogs have been reported,[7] but many of the procedures are labor-intensive and/or require special apparatus. The reported preparation of ethyl 3-oxo-4-pentenoate is facile (2 steps) and efficient (52% overall yield). All starting materials are commercially available, relatively inexpensive, and easily purified. The synthesis is also amenable to scale up and has been carried out successfully on a 1-mol scale. Other esters have also been synthesized by this method with overall yields ranging from 45–58% (see Scheme 1).[8] Finally, methacrolein and crotonaldehyde are also suitable reactants (see Scheme 1).



48% 37%

R = Me 45%
Et 67%
i-Pr 58%
t-Br 47%
(-)-bornyl 56%

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

P_2O_5

brine

sodium-benzophenone ketyl

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

ethyl acetate (141-78-6)

methanol (67-56-1)

diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

sodium hydroxide (1310-73-2)

Acrolein (107-02-8)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

acetone (67-64-1)

Diphenylacetic acid (117-34-0)

magnesium sulfate, $MgSO_4$ (7487-88-9)

chromium (7440-47-3)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

crotonaldehyde (123-73-9)

chromium oxide (1308-38-9)

methacrolein (78-85-3)

argon (7440-37-1)

diisopropylamine (108-18-9)

phosphorus oxide (1314-56-3)

ETHYL 3-OXO-4-PENTENOATE, 4-Pentenoic acid, 3-oxo-, ethyl ester (22418-80-0)

Ethyl 3-hydroxy-4-pentenoate (38996-01-9)

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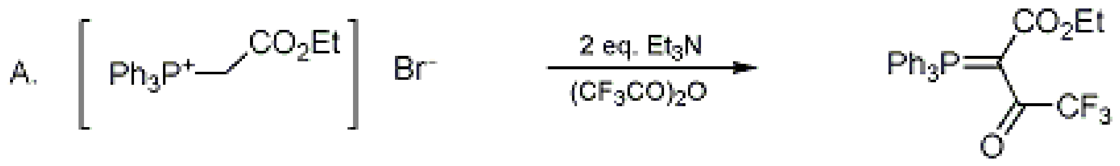
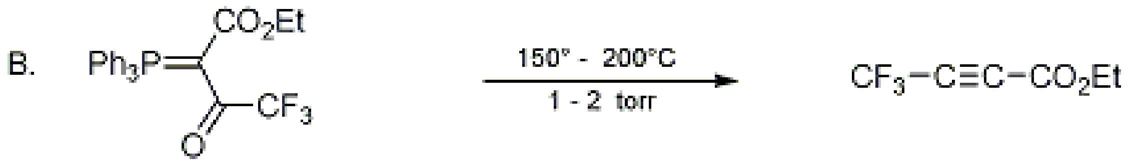
Organic Syntheses, CV 9, 436

α-ACETYLENIC ESTERS FROM α-ACYLMETHYLENEPHOSPHORANES: ETHYL 4,4,4-TRIFLUOROTETROLATE

[2-Butynoic acid, 4,4,4-trifluoro-, ethyl ester]





Submitted by B. C. Hamper[1]
Checked by T. Harrison and Larry E. Overman.

1. Procedure

A. *Ethyl 4,4,4-trifluoro-2-(triphenylphosphoranylidene)acetoacetate*. A 2-L, four-necked, round-bottomed flask is equipped with a nitrogen line attached to a bubbler, a 250-mL pressure-equalizing funnel, an overhead stirrer and a thermometer. The flask is charged with 215 g (0.5 mol) of (carbethoxymethyl)triphenylphosphonium bromide and 1.1 L of anhydrous tetrahydrofuran (THF) (Note 1) and (Note 2). The stirred suspension is cooled in an ice water bath and treated with 150 mL (1.1 mol) of triethylamine (Note 3) added dropwise over 5 min. After the mixture is stirred for an additional 30 min at 5°C, it is treated dropwise with 78 mL (116 g, 0.55 mol) of trifluoroacetic anhydride (Note 4) in such a manner that the reaction temperature is maintained between 5–10°C, which results in a total addition time of approximately 1 hr. The mixture is allowed to stir for 2 hr and subsequently filtered, the precipitate is washed three times with cold THF and the filtrate is concentrated under reduced pressure to afford a yellow oily residue. Trituration of the residue with 600 mL of water affords a crystalline product which is collected, washed three times with 100 mL of water, and dried by suction to afford 208 g of a yellowish colored solid (Note 5). The solid is dissolved in 900 mL of hot methanol; the solution is filtered, treated with 500 mL of water, and placed in a refrigerator overnight. The crystalline product is collected, washed three times with 100 mL of cold water and dried under reduced pressure to afford 200–208 g (89–93%) of ethyl 4,4,4-trifluoro-2-(triphenylphosphoranylidene)acetoacetate as a very pale-yellow,

crystalline solid (Note 6).

B. *Ethyl 4,4,4-trifluorotetrolate*. A 1-L, three-necked, round-bottomed flask is equipped with an efficient magnetic stirrer, a heating mantle, a thermocouple (Note 7) and a large bore gas exit tube (f.htmigure 1, (Note 8)). To this flask are added 200 g (0.45 mol) of ethyl 4,4,4-trifluoro-2-(triphenylphosphoranylidene)acetoacetate and 40 g of potassium carbonate (Note 9). The gas exit tube is connected to a Dewar condenser, modified with a side arm connection, which has a round-bottomed flask for collection of the product in a dry ice-acetone bath. A second trap is placed between the reaction setup and the vacuum pump, all the traps are cooled with dry ice-acetone, and the system is evacuated to 1–2 mm. The reaction flask is carefully heated to 150°C (Note 10) at which point the phosphorane melts and the acetylene evolution begins. The molten phosphorane is stirred and heated from 160°C to 220°C over a period of 5 hr. Heating is carefully increased during the reaction in order to control the rate of distillation of the acetylenic product. From the round-bottomed flask in the cold trap is obtained 65–67 g (87–89%) of a clear, slightly yellow, liquid. The thermolysis product is dried with magnesium sulfate and filtered through Celite. Distillation at atmospheric pressure through a short-path distillation apparatus affords about 1.0 g of forerun and 59–61 g (79–82%) of ethyl 4,4,4-trifluorotetrolate as an analytically pure, colorless liquid, bp_{760} 97–100°C (Note 11).

Figure 1

Figure 1

2. Notes

1. Anhydrous tetrahydrofuran was obtained from Aldrich Chemical Company, Inc., in SureSeal bottles and was used without further purification. (Carbethoxymethyl)triphenylphosphonium bromide may be obtained from Aldrich Chemical Company Inc., or prepared as described in *Org. Synth., Coll. Vol. VII* **1990**, 232. The in situ preparation described in (Note 2) was used by the checkers.

2. We have found it more convenient to prepare (carbethoxymethyl) triphenylphosphonium bromide in situ in the same reaction vessel from triphenylphosphine and ethyl bromoacetate. This effectively provides a one-pot preparation for the α-acylmethylenephosphorane from triphenylphosphine and allows facile incorporation of various esters, by employing different bromoacetate esters, in the acetylenic product. The yield and purity of the resultant phosphorane is unaffected by the following one-pot procedure.

A 2-L, four-necked, round-bottomed flask is equipped with a nitrogen line attached to a bubbler, a 250-mL pressure-equalizing funnel, an overhead stirrer and a thermometer. The flask is charged with 132 g of triphenylphosphine (0.503 mol) and 500 mL of anhydrous tetrahydrofuran and cooled in an ice water bath to 5°C. The stirred solution is treated dropwise with 56 mL of ethyl bromoacetate (84 g, 0.503 mol) added at such a rate that the temperature is maintained between

8°C and 10°C. The total addition time is about 15 min. After the mixture is stirred overnight, it is diluted with an additional 600 mL of anhydrous tetrahydrofuran and the precipitate is washed from the sides of the flask. The resultant suspension of (carbethoxymethyl)triphenylphosphonium bromide is cooled in an ice-water bath and used directly in the same pot to prepare α-acylmethylenephosphoranes as detailed in section A.

3. Triethylamine was supplied by Eastman Kodak Company and Fisher Scientific Company.

4. Trifluoroacetic anhydride was obtained from Aldrich Chemical Company, Inc.

5. The yellow crystalline solid is analytically pure (>95% by NMR and HPLC analysis), mp 124–127°C. We have found that the yield of the acetylenes can be adversely affected by small amounts of impurities in the α-acylmethylenephosphoranes and prefer to recrystallize the phosphoranes prior to thermolysis. The yield from the recrystallization step is greater than 95%.

6. The phosphorane softens above 120°C and melts between 125–130°C (lit.[2,3] mp 125–127°C). Spectral properties of the phosphorane are as follows: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.87 (t, 3 H, J = 7.2), 3.81 (q, 2 H, J = 7.2), 7.49 (dt, 6 H, J = 7.9, 3.3), 7.57 (m, 3 H), 7.67 (dd, 6 H, J = 12.9, 7.9); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.5, 59.8, 70.1 (d, $^{1}J_{CP}$ = 110), 117.9 (dd, $^{1}J_{CF}$ = 288, $^{3}J_{CP}$ = 14.6), 123.7 (d, $^{1}J_{CP}$ = 93.3), 128.8 (d, $^{2}J_{CP}$ = 13.0), 132.2 (d, $^{4}J_{CP}$ = 3.0), 133.2 (d, $^{3}J_{CP}$ = 10.0), 165.6 (d, $^{2}J_{CP}$ = 13.0), 174.4 (dd, $^{2}J_{CF}$ = 34.0, $^{2}J_{CP}$ = 5.8); ^{31}P NMR (202 MHz, $CDCl_3$) δ: 19.8. Anal. Calcd for $C_{24}H_{20}O_3F_3P$: C, 64.87; H, 4.54. Found: C, 64.96; H, 4.60.

7. A stainless steel-covered thermocouple is preferred since it is less likely to break than a mercury thermometer. As the phosphorane begins to melt, large chunks of solid remain as the mixture is initially stirred, and these can lodge between a thermometer and the walls of the flask. The thermocouple has the added advantage that the steel rod can be used to help break up the melting phosphorane, taking care to avoid breaking the flask.

8. The large bore gas exit tube (f.htmigure 1) used between the reaction flask and the Dewar condenser is a glass tee equipped with the appropriate 24/40 ground glass joints. Alternatively, the connection can be made using large bore, thick wall Tygon or vacuum tubing.

9. In the absence of potassium carbonate, the thermolysis product is slightly acidic and the pH of a water wash of freshly collected product is about 1.

10. *CAUTION! Care must be taken not to heat the phosphorane too rapidly, particularly before the solid has melted. The temperature of the molten material is not at equilibrium until the mixture has completely melted. If it is heated too rapidly, it is difficult to control the rate of acetylene production. It is best to heat slowly until a stirred, molten material is obtained and to continue heating at such a rate as to control acetylene formation.* We have obtained excellent results applying initially 30 volts to a 380-watt, 115-volt, 1-L heating mantle obtained from Glas-Col Apparatus Company. Alternatively, more even and controlled heating can be obtained by using a large oil bath.

11. Previous literature reports[3] bp 96–98°C. Spectral properties of the acetylene

are as follows: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.34 (t, 3 H, J = 7.1), 4.32 (q, 2 H, J = 7.1); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.8, 63.5, 69.9 (q, $^{2}J_{CF}$ = 54.0), 75.5 (q, $^{3}J_{CF}$ = 6.0), 113.4 (q, $^{1}J_{CF}$ = 259), 150.7; IR (neat) cm^{-1}: 2987, 2275 (w); 1731. Anal. Calcd for $C_6H_5O_2F_3$: C, 43.49; H, 3.03. Found: C, 43.14; H, 3.07.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

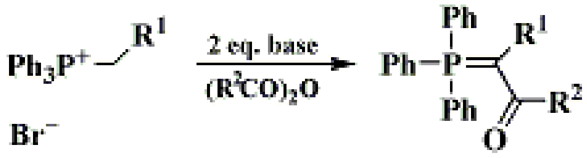
Thermolysis of α-acylmethylenephosphoranes is the most convenient method for preparation of acetylenes with perfluoroalkyl substituents.[3,4] Many of these acetylenes, particularly the trifluoromethyl analogs, are particularly volatile and thermolysis allows preparation and collection of material which is free of solvents or impurities of similar boiling point. In addition, the acetylenes are prepared from readily available starting materials with overall conversions for the two steps of greater than 75% in many cases. Attempts to prepare trifluorotetrolic acid by carbonylation of the lithium acetylenide of 3,3,3-trifluoropropyne have been unsuccessful.[5] However, the treatment of lithium acetylenides with chloroformates affords perfluoroalkyl-substituted propiolates (the perfluoroalkyl group is a C_4 chain length or longer) in 38–43% yield along with an unusual by-product.[6] Benzyl trifluorotetrolate, which was employed in the synthesis of a trifluoromethyl analog of geraniol, has been prepared from ethyl trifluoroacetoacetate via a pyrazolone in an overall yield of 55%.[7] A number of (difluoroalkyl)propiolates, employed in Diels-Alder cycloaddition reactions, have been prepared by treatment of the corresponding ketones with diethylaminosulfur trifluoride (DAST).[8] The corresponding (difluoroalkyl)propiolic acids have also been prepared by carbonylation of the magnesium bromoacetylenide.[9]

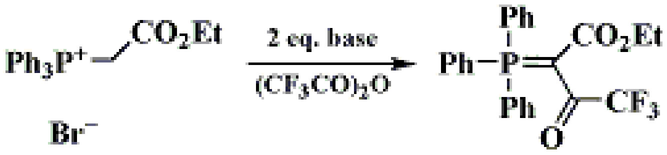
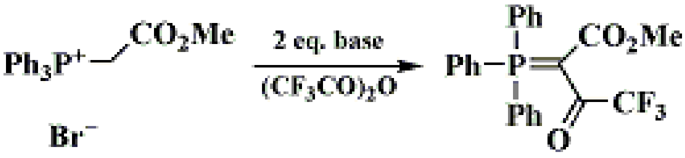
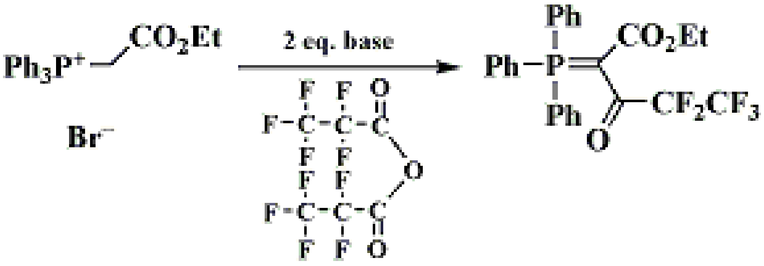
The utility of the phosphorane route to electron-deficient acetylenes depends on the facile synthesis of the α-acylmethylenephosphorane intermediates. Previously they had been prepared by a two-step procedure from the available phosphonium salts, requiring isolation of the Wittig reagent [e.g., (ethoxycarbonylmethylene)triphenylphosphorane] intermediate.[3,4] Acylation of the Wittig reagent affords, via transylidation,[10] a 1:1 mixture of components which must be separated prior to thermolysis. In addition, at least half of the Wittig reagent is lost by conversion to the starting phosphonium salt. The addition of a suitable base, such as triethylamine, to the reaction mixture avoids the undesired transylidation reaction and affords complete conversion to the desired α-acylmethylenephosphorane. For acyl halides which have an acidic hydrogen α to the carbonyl group, treatment with base can give rise to ketenes which readily react with Wittig reagents to afford allenes.[11] This route, using triethylamine as a base, has been explored to prepare allenes that are either substituted or unsubstituted in the α-position.

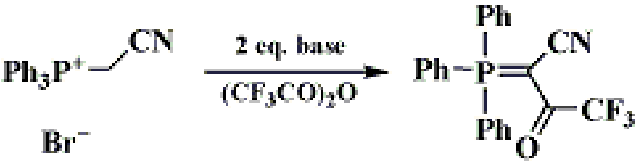
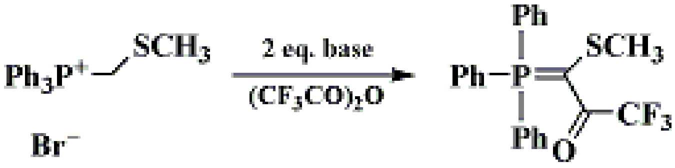
For acyl halides or anhydrides which do not afford ketenes in the presence of base (such as perfluoroacyl halides), however, the α-acylmethylenephosphoranes can be prepared directly in one step from the phosphonium salts by using two equivalents of base by the present procedure (Table I).[2] Both tetrahydrofuran and methylene chloride have been used as solvents; in the case of the title compound, tetrahydrofuran provides the best results. Good yields of the phosphoranes are generally obtained when R^1 is an electron-withdrawing group such as ester or nitrile. The yields of phosphoranes obtained for the thiomethyl or phenyl cases can be improved by using 1,4-diazabicyclo[2.2.2]octane (DABCO) rather than triethylamine as the base.

TABLE I

Preparation of (α-Acylmethylene)Phosphoranes From α-Substituted Methylphosphonium Salts[2]



R^1	R^2	Solvent	Base	Yield (%)
CO_2Et	CF_3	CH_2Cl_2	Et_3N	 54
CO_2Me	CF_3	THF	Et_3N	 99
CO_2Et	CF_2CF_3	THF	Et_3N	 69

CN	CF_3	THF	Et_3N		75
SCH_3	CF_3	THF	Et_3N		49
Ph	CF_3	CH_2Cl_2	Et_3N		24
Ph	CF_3	CH_2Cl_2	DABCO		57

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

potassium carbonate (584-08-7)

acetylene (74-86-2)

methanol (67-56-1)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

Ethyl bromoacetate (105-36-2)

Tetrahydrofuran, THF (109-99-9)

geraniol (106-24-1)

triethylamine (121-44-8)

triphenylphosphine (603-35-0)

trifluoroacetic anhydride (407-25-0)

1,4-diazabicyclo[2.2.2]octane (280-57-9)

Diethylaminosulfur trifluoride (38078-09-0)

(ethoxycarbonylmethylene)triphenylphosphorane (1099-45-2)

Ethyl 4,4,4-trifluorotetrolate, 2-Butynoic acid, 4,4,4-trifluoro-, ethyl ester (79424-03-6)

Ethyl 4,4,4-trifluoro-2-(triphenylphosphoranylidene)acetoacetate (83961-56-2)

(carbethoxymethyl)triphenylphosphonium bromide (1530-45-6)

trifluorotetrolic acid

lithium acetylenide

3,3,3-trifluoropropyne (661-54-1)

Benzyl trifluorotetrolate

ethyl trifluoroacetoacetate

magnesium bromoacetylenide

METHYLPHOSPHONIUM

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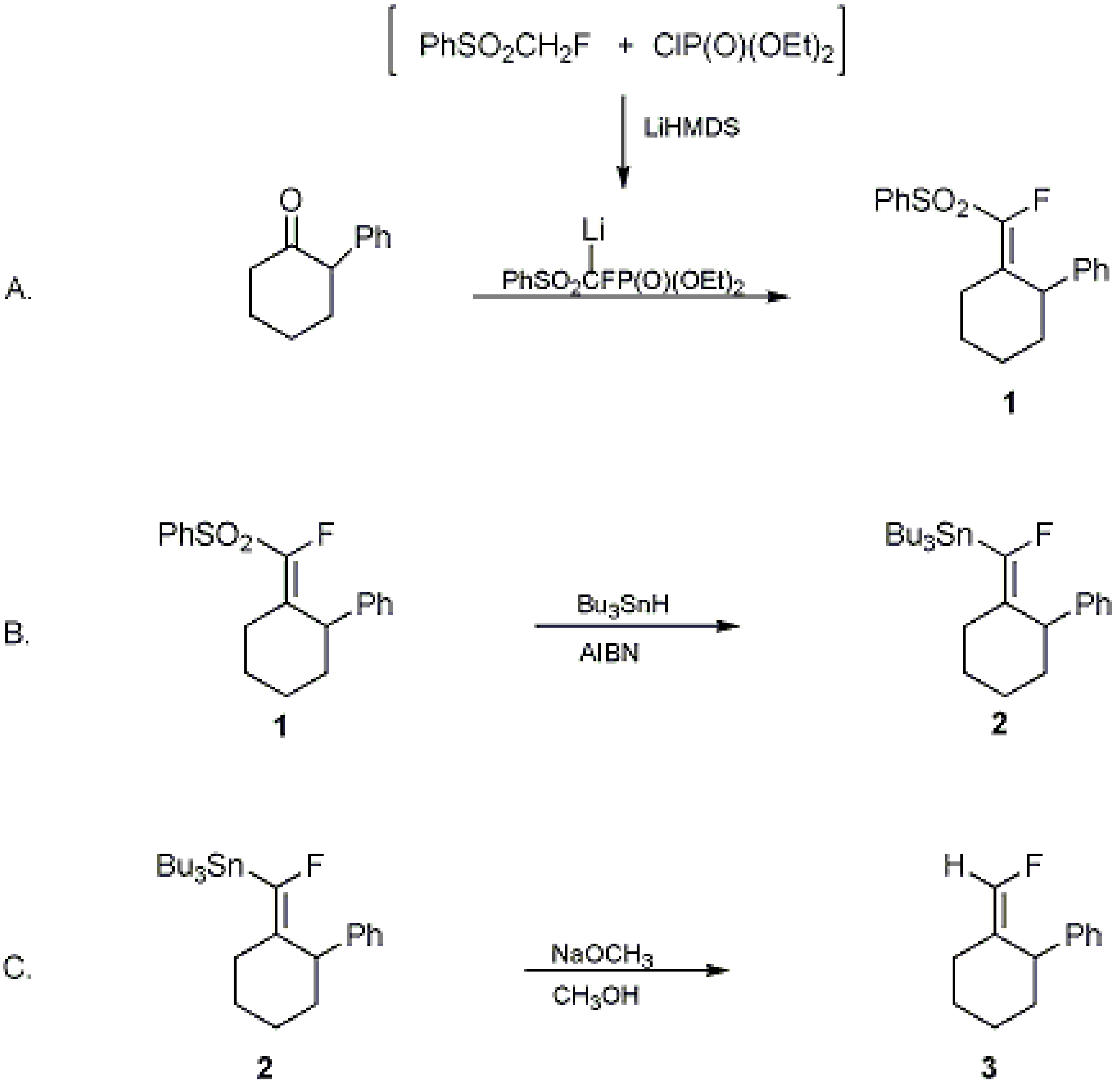
Organic Syntheses, CV 9, 442

STEREOSELECTIVE SYNTHESIS OF 2,2-DISUBSTITUTED 1-FLUORO-ALKENES: (E)-[[FLUORO(2-PHENYLCYCLOHEXYLIDENE)-METHYL]SULFONYL]BENZENE AND (Z)-[2-(FLUOROMETHYLENE)-CYCLOHEXYL]BENZENE

[Benzene, [fluoro(2-phenylcyclohexylidene)methyl]sulfonyl]-, (E)-(±)- and Benzene, [2-(fluoromethylene)cyclohexyl]-, (Z)-(±)-]



Submitted by James R. McCarthy, Donald P. Matthews, and John P. Paolini[1].
Checked by Carmen M. Simone and Albert I. Meyers.

1. Procedure

CAUTION! All reactions should be conducted in an efficient fume hood.

A. *(E)-[[Fluoro(2-phenylcyclohexylidene)methyl]sulfonyl]benzene* ***(1)***. To an oven-dried, 1-L, three-necked, round-bottomed flask, equipped with a nitrogen inlet with gas bubbler, thermometer, magnetic stirring bar, and a 500-mL addition funnel with side arm and septum, are added 25.0 g (0.14 mol) of fluoromethyl phenyl sulfone (Note 1), diethyl chlorophosphate (24.8 g, 0.14 mol) (Note 2), and anhydrous tetrahydrofuran (THF) (300 mL). The solution is kept under a nitrogen atmosphere and cooled to −70°C with a dry ice-acetone bath. A solution of 1 M lithium bis(trimethylsilyl)amide (LiHMDS) in THF (310 mL, 0.31 mol) (Note 3) is transferred via cannula to the dropping funnel and added over 15 min. After the reaction mixture is stirred for 1 hr at ≤ −70°C (Note 4), the addition funnel is replaced with a septum. 2-Phenylcyclohexanone (17.4 g, 0.10 mol) (Note 5) is dissolved in THF (65 mL) and added via a syringe. The reaction mixture is allowed to warm to ambient temperature. Stirring is continued for 2 hr at room temperature and, during this time, a white precipitate forms in solution. The reaction mixture is poured into an ice-cold mixture of ethyl acetate (250 mL), saturated aqueous ammonium chloride (250 mL), and concd hydrochloric acid (30 mL). The organic layer is collected and the aqueous layer is extracted with ethyl acetate (250 mL). The combined organic layers are washed with saturated aqueous sodium chloride (100 mL) and dried (magnesium sulfate). The solvent is removed under reduced pressure and the resulting orange-brown oil is purified by flash chromatography[2] (1.25 L of 230–400 mesh silica gel) using ether/hexane (1:10) to provide 23 g of colorless oil (Note 6). The oil is dissolved in hot ethanol (200 mL) and the solution is cooled in the freezer. The shiny white crystals that form are collected by filtration and dried under reduced pressure to afford 19.5–23.1 g (59–70%) of **1**, mp 75–78°C (Note 7).

B. *(E)-Tributyl[fluoro(2-phenylcyclohexylidene)methyl]stannane* ***(2)***. To a 1-L, round-bottomed flask with reflux condenser, magnetic stirring bar, and nitrogen inlet with gas bubbler are added fluorovinyl sulfone 1 (22.0 g, 0.067 mol), tributyltin hydride (42.0 g, 38.9 mL, 0.14 mol), azobisisobutyronitrile (AIBN) (500 mg) (Note 8) and benzene (700 mL) (Note 9). The solution is refluxed for 3 hr under a nitrogen atmosphere (Note 10), cooled to room temperature, and 125 mL of silica gel (230–400 mesh) is added. The mixture is concentrated on a rotary evaporator to a white powder (Note 11) and applied to the top of a flash silica gel column[2] (1.3 L) packed with hexane. The column is eluted with hexane and fractions containing **2** (Note 12) are combined and concentrated on a rotary evaporator to give 23.4–27.5 g (74–87% yield) of **2** as a colorless oil (Note 13).

C. *(Z)-[2-(Fluoromethylene)cyclohexyl]benzene* ***(3)***. To a solution of (fluorovinyl) stannane 2 (26.0 g, 0.054 mol) in dry THF (150 mL) is added 65 mL of 1 M sodium methoxide in methanol (prepared by the addition of 1.50 g (0.065 g-atom) of sodium to 65 mL of methanol). The solution is refluxed for 18 hr under nitrogen (Note 14), cooled to ambient temperature and concentrated on a rotary evaporator. The residue is

partitioned between water (200 mL) and hexane (200 mL). The aqueous layer is separated and extracted with hexane (100 mL). The combined organic layers are dried (magnesium sulfate) and concentrated on a rotary evaporator to give a colorless oil (30 g). Kugelrohr distillation gives 10.0–10.2 g (97–100%) of fluoro olefin **3** (bp 85–90°C, 0.4 mm) as a colorless oil (Note 15).

2. Notes

1. See McCarthy, J. R.; Matthews, D. P.; Paolini, J. P. *Org. Synth., Coll. Vol. IX* **1998**, 446.
2. Diethyl chlorophosphate was purchased from Aldrich Chemical Company, Inc., and distilled before use; bp 60°C (2 mm). This reagent is a highly toxic acetylcholinesterase inhibitor and should be handled with care.
3. 1 M Lithium bis(trimethylsilyl)amide in THF was purchased from Aldrich Chemical Company, Inc.
4. Formation of the carbanion of diethyl 1-fluoro-1-(phenylsulfonyl) methanephosphonate is followed by gas chromatography, by quenching a small aliquot of the reaction in ether/saturated aqueous ammonium chloride. The carbanion forms in ca. 85% to 95% yield after 1 hr.
5. 2-Phenylcyclohexanone was purchased from Aldrich Chemical Company, Inc., and used without further purification.
6. Alternatively, the orange-brown oil can be crystallized twice from ethanol (200 mL, 150 mL) (seed crystal) to provide 16.6 g (50%) of off-white crystals of **1**, mp 75–78°C. The checkers observed mp 68–70°C for this material.
7. Spectral and elemental analysis data for **1** are the following: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.3–2.1 (m, 6 H), 2.46 (d, 1 H, J = 14.3), 3.61 (dd, 1 H, J = 3.5, 14.2), 4.22 (s, 1 H), 7.0–8.1 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.76, 23.34, 27.17 (d, $^{3}J_{F,CH2}$ = 2.2), 29.42, 38.45 (d, $^{3}J_{F,CH}$ = 7.5), 126.35, 127.11, 127.96, 128.65, 129.34, 134.07, 134.96 (d, $^{2}J_{F,C}$ = 6.7), 139.46, 139.67, 147.80 (d, $^{1}J_{F,C}$ = 280.1); ^{19}F NMR (282 MHz, $CDCl_3$) δ: –123.4 (s); MS (CI/CH_4) m/z 331 (MH^+). Anal. Calcd for $C_{19}H_{19}FO_2S$: C, 69.06; H, 5.80. Found: C, 68.88; H, 5.86. The structure for **1** was confirmed by X-ray crystallography.[3]
8. Azobisisobutyronitrile (AIBN) was purchased from Aldrich Chemical Company, Inc. and used as received.
9. *Benzene is a known carcinogen*. Follow manufacturer's recommended procedures for handling, storage, and disposal. Cyclohexane was found to be a suitable alternate solvent for other examples of this reaction.
10. Progress of the reaction is followed by either gas chromatography or thin layer chromatography (silica gel, hexane) since the time required for completion of the reaction can vary up to 16 hr. An additional 500 mg of AIBN is added to the reaction mixture after 3 hr if starting material is still present.
11. An adapter tube containing a fritted disc prevents loss of silica gel into the condenser of the rotary evaporator. These tubes are available from Aldrich Chemical Company, Inc. Alternatively, the checkers found that the silica gel can

be added to the crude mixture after removal of benzene.

12. Fractions containing **2** of ca. ≥90% purity by gas chromatography (flame ionization detector) were combined.

13. In some runs, material (≤5%) with the retention time of tributyltin hydride is present in product **2**. This impurity does not interfere in the last step of the reaction sequence. Spectral and elemental analysis data for **2** are the following: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.91 (t, 9 H, J = 7.0), 1.0–1.1 (m, 6 H), 1.2–2.0 (m, 19 H), 2.41 (d, 1 H, J = 13.9), 4.4 (m, 1 H), 7.2 (m, 1 H), 7.3–7.4 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 10.44, 13.74, 21.68, 26.75 (d, $^{3}J_{F,CH2}$ = 11.8), 27.23, 28.37 (d, $^{4}J_{F,CH2}$ = 2.7), 29.06, 29.52, 36.31 (d, $^{3}J_{F,CH}$ = 15.0), 125.42, 127.60, 128.21, 135.37, 142.02 (d, $^{2}J_{F,C}$ = 5.2), 163.34 (d, $^{1}J_{F,C}$ = 306.2); ^{19}F NMR (282 MHz, $CDCl_3$) δ: –110.52 (84%, m) (16%, dm, J = 282); MS (CI/ CH_4) m/z 461 (MH^+ -HR). Anal. Calcd for $C_{25}H_{41}FSn$: C, 62.65; H, 8.62. Found: C, 62.43; H, 8.61. Proton-fluorine NOE difference spectroscopy ($CDCl_3$) showed an enhancement in the fluorine signal (δ – 110.5) when the benzylic proton (δ 4.4) was irradiated and showed no enhancement when the allylic protons (δ 2.41, equatorial proton and δ 1.77, axial proton) were irradiated. See reference [4] for a discussion of this technique.

14. Progress of the reaction is followed by either gas chromatography or thin layer chromatography (silica gel, hexane).

15. Spectral and elemental analysis data for **3** are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.2–2.0 (m, 7 H), 2.37 (d, 1 H, J = 13.2), 4.2 (m, 1 H), 6.6 (dm, 1 H, J = 87.1), 7.2 (m, 1 H), 7.25–7.35 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.72, 25.06 (d, $^{3}J_{F,CH2}$ = 6.9), 27.71 (d, $^{4}J_{F,CH2}$ = 2.8), 29.74, 36.13 (d, $^{3}J_{F,CH}$ = 5.2), 123.18 (d, $^{2}J_{F,C}$ = 3.8), 125.73, 127.54, 128.31, 141.55, 142.19 (d, $^{1}J_{F,C}$ = 252.6); ^{1}9F NMR (282 MHz, $CDCl_3$) δ: – 139.64 (dd, J = 3.4, 86.8); MS (CI/ CH_4) m/z 191 (MH^+). Anal. Calcd for $C_{13}H_{15}F$: C, 82.07; H, 7.95. Found: C, 82.13; H, 8.15.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The procedure described here provides a stereospecific synthesis of (E)- and (Z)-fluoroalkenes from the corresponding (E)- and (Z)-fluorovinyl sulfones. Fluorovinyl sulfones obtained from ketones are, in most cases, readily separable into (E) and (Z) isomers either by crystallization or by chromatography.[5] In the example described, only the (E)-fluorovinyl sulfone **1** is formed (which is converted into the (Z)-fluoroalkene **3** with complete retention of configuration). The reaction sequence has been used for the stereospecific synthesis of fluoroalkene nucleosides[6] as well as for 1-

deutero-1-fluoroalkenes. In the case of fluoroalkenes obtained from aldehydes, conversion of the intermediate monosubstituted fluorovinyl sulfones to (fluorovinyl) stannanes does not proceed with retention of configuration.[7] However, subsequent cleavage of the vinyltributyltin group with either sodium methoxide, cesium fluoride or methanolic ammonia does proceed with retention of configuration. Since (E)- and (Z)-vinylstannanes are usually separable, this method also provides a route to stereochemically-pure, terminal, mono-substituted fluoroalkenes.[4] A significant property of the intermediate (fluorovinyl)stannanes is their ability to act as fluorovinyl carbanion equivalents. Thus, treatment of (fluorovinyl)stannanes with acid chlorides in the presence of a palladium(0) catalyst provides α-fluoro-α,β-unsaturated ketones with complete retention of configuration.[4] Iodine reacts with (fluorovinyl)stannanes to give 1-iodo-1-fluoroalkenes with complete retention of configuration.[7,4]

It should be noted that addition of the tributyltin radical to 1-fluoro-1-(phenylsulfonyl) ethene provides phenyl vinyl sulfone as the only isolated product. However, 2-trimethylsilyl-1-fluoro-1-(phenylsulfonyl)ethene reacts with tributyltin hydride in the presence of AIBN to provide (E)-2-trimethylsilyl-1-fluoro-1-tributylvinylstannane. The vinylstannane is an equivalent for the synthon "$H_2C{=}CF^-$" providing a convenient route to 2-fluoro-1-alkenes.[8] The trimethylsilyl group can be removed with potassium fluoride in dimethyl sulfoxide-water or oxalic acid-methanol at the end of the reaction sequence.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 446

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

AIBN

Benzene, [fluoro(2-phenylcyclohexylidene)methyl]sulfonyl]-, (E)-(±)-

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

Benzene (71-43-2)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether (60-29-7)

ammonium chloride (12125-02-9)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

cyclohexane (110-82-7)

iodine (7553-56-2)

sodium methoxide (124-41-4)

sodium (13966-32-0)

palladium(0) (7440-05-3)

magnesium sulfate (7487-88-9)

Tetrahydrofuran, THF (109-99-9)

potassium fluoride (7789-23-3)

hexane (110-54-3)

dimethyl sulfoxide (67-68-5)

2-phenylcyclohexanone (1444-65-1)

diethyl chlorophosphate (814-49-3)

lithium bis(trimethylsilyl)amide (4039-32-1)

cesium fluoride (13400-13-0)

tributyltin hydride (688-73-3)

azobisisobutyronitrile (78-67-1)

(E)-[[Fluoro(2-phenylcyclohexylidene)methyl]sulfonyl]benzene, (E)-[[FLUORO(2-PHENYLCYCLOHEXYLIDENE)-METHYL]SULFONYL]BENZENE (135790-01-1)

(Z)-[2-(Fluoromethylene)cyclohexyl]benzene, (Z)-[2-(FLUOROMETHYLENE)-CYCLOHEXYL]BENZENE, Benzene, [2-(fluoromethylene)cyclohexyl]-, (Z)-(±)- (135790-02-2)

Fluoromethyl phenyl sulfone (20808-12-2)

(E)-Tributyl[fluoro(2-phenylcyclohexylidene)methyl]stannane (135789-96-7)

diethyl 1-fluoro-1-(phenylsulfonyl)methanephosphonate

1-fluoro-1-(phenylsulfonyl)ethene

2-trimethylsilyl-1-fluoro-1-(phenylsulfonyl)ethene

(E)-2-trimethylsilyl-1-fluoro-1-tributylvinylstannane

oxalic acid-methanol

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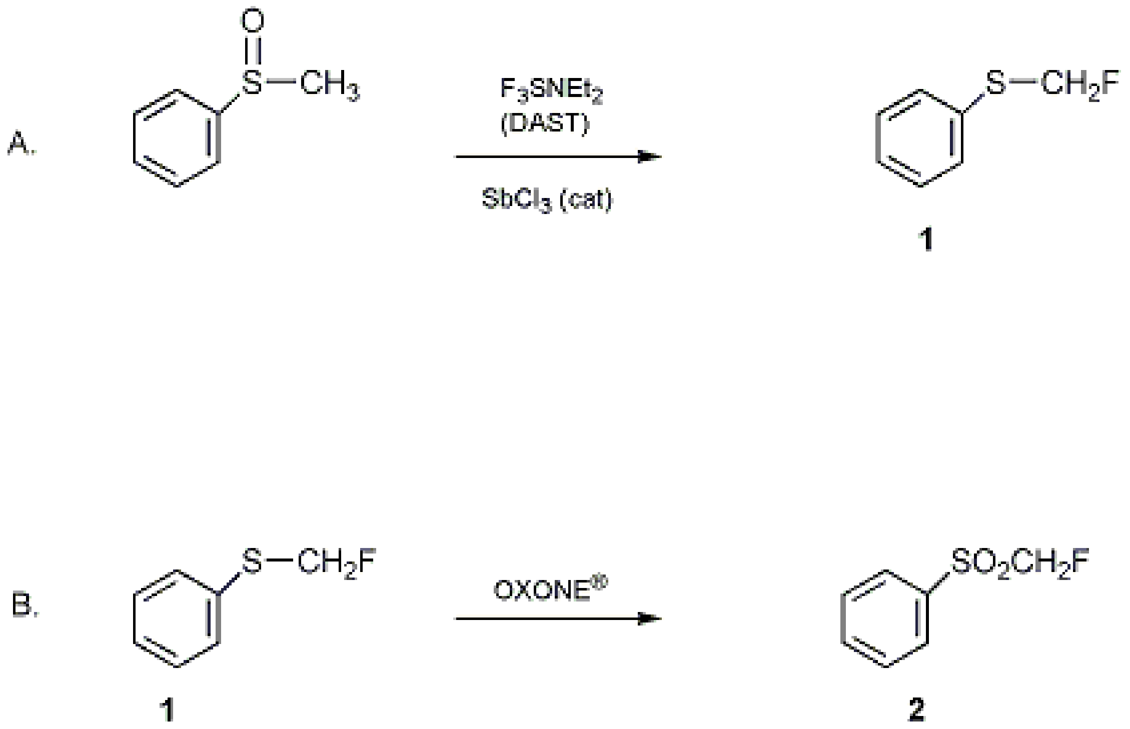
Organic Syntheses, CV 9, 446

REACTION OF SULFOXIDES WITH DIETHYLAMINOSULFUR TRIFLUORIDE: FLUOROMETHYL PHENYL SULFONE, A REAGENT FOR THE SYNTHESIS OF FLUOROALKENES

[Benzene, [(fluoromethyl)sulfonyl]-]



Submitted by James R. McCarthy, Donald P. Matthews, and John P. Paolini[1].
Checked by Carmen M. Simone and Albert I. Meyers.

1. Procedure

CAUTION! All reactions should be conducted in an efficient fume hood.

A. *Fluoromethyl phenyl sulfide* ***(1)***. To a 1-L, three-necked, round-bottomed flask, equipped with a magnetic stirring bar, air condenser and thermometer are added methyl phenyl sulfoxide (25.2 g, 0.18 mol) (Note 1) and chloroform (150 mL) (Note 2). The flask is placed in a cooling bath containing 3 L of water kept at 20°C (Note 3). Diethylaminosulfur trifluoride (DAST) (38.5 g, 31.6 mL, 0.24 mol) (Note 4) is added to the flask, followed by antimony trichloride (0.50 g, 0.0022 mol) (Note 5), and an additional 50 mL of chloroform. The light yellow reaction mixture is stirred under an argon atmosphere. After 2 to 8 hr, an exothermic reaction is observed and the solution turns dark orange (Note 6). The reaction mixture is poured slowly with stirring into 600 mL of ice-cold, saturated, aqueous sodium bicarbonate containing 10 g (0.25 mol)

of sodium hydroxide (*CAUTION: gas evolution*). After 10 min, the chloroform layer is separated and the remaining aqueous layer is extracted with additional chloroform (3 × 100 mL). The combined organic layers are washed with saturated aqueous sodium bicarbonate (250 mL), saturated aqueous sodium chloride, and dried over potassium carbonate. The chloroform is removed with a rotary evaporator at 30–40°C and the crude fluoromethyl phenyl sulfide **1** (ca. 29 g), obtained as a yellow orange oil, is used immediately in the next step (Note 7) and (Note 8).

B. *Fluoromethyl phenyl sulfone* ***(2)***. To a 3-L, three-necked, round-bottomed flask, equipped with an overhead stirrer, thermometer, and 1-L addition funnel with sidearm are added Oxone (221.0 g, 0.36 mol) (Note 9) and water (700 mL). The mixture is cooled to 5°C and a solution of the crude fluoromethyl phenyl sulfide **(1)** in methanol (700 mL) is placed in the addition funnel and added in a slow stream to the stirring slurry. After addition of the sulfide, the reaction mixture is stirred at room temperature for 4 hr, (Note 10) and the methanol is removed on a rotary evaporator at 40°C. The remaining solution is extracted with methylene chloride (2 × 500 mL). The combined organic layers are dried over magnesium sulfate, concentrated to ca. 150 mL, filtered through a plug of silica gel (230–400 mesh, 300 mL, 10 × 6.5 cm), and washed with an additional 500 mL of methylene chloride (Note 11). The colorless filtrate is concentrated and the resulting oil or solid is dried under vacuum (0.1 mm) at room temperature to provide 29 g of crude fluoromethyl phenyl sulfone **(2)** as a solid white mass. The solid is recrystallized from 250 mL of hot hexane (forms two layers) by cooling the two phase solution to room temperature with vigorous stirring and adding a seed crystal. The resulting white crystals of fluoromethyl phenyl sulfone **(2)** (25.0–28.5 g, 80–90%) are collected by filtration, mp 53–55°C (Note 12) and (Note 13).

2. Notes

1. Methyl phenyl sulfoxide was purchased from Aldrich Chemical Company, Inc., and used as received.
2. *Chloroform is a suspected carcinogen*. Follow manufacturer's recommended procedures for handling, storage, and disposal.
3. Both a sizable head space and a large heat sink are essential for this reaction since a vigorous, but latent, exothermic reaction occurs (see (Note 5)). This reaction was run twelve times without incident on a 25–125-g scale following these precautions.
4. Diethylaminosulfur trifluoride (DAST) should be handled using appropriate safety equipment (rubber gloves and goggles). DAST was purchased from Carbolabs, Inc., and used as received.
5. Antimony trichloride was purchased from Aldrich Chemical Company, Inc. and used as received. Excess antimony trichloride can cause a vigorous reaction.
6. Progress of the reaction can be followed by gas chromatography, TLC (ethyl acetate/hexane 1:5) or ^{1}H NMR. (Probe reactions can be carried out in $CDCl_3$ in an NMR tube).
7. Alternatively, the chloroform solution can be treated with 2 equiv of 3-

chloroperbenzoic acid (MCPBA) to provide fluoromethyl phenyl sulfone (see reference [2]).
8. The crude sulfide is readily purified by Kugelrohr distillation (bp 80–90°C, 0.8 mm), but the colorless liquid polymerizes to a white solid on standing overnight. A solution of the sulfide in chloroform was stored at −10°C for 2 days on one occasion with no decomposition, ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.72 (d, 2 H, J = 52.9), 7.29–7.52 (m, 5).
9. Oxone (potassium peroxymonosulfate, 2 $KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) was purchased from Aldrich Chemical Company, Inc.
10. Progress of the oxidation can be followed by TLC (ethyl acetate/hexane 1:5). The checkers found that the product crystallized from water when the methanol was removed.
11. Alternatively, the organic layer is concentrated to an oil and **2** is purified by Kugelrohr distillation, bp 120–125°C (1 mm).
12. The two step reaction was run on a 125-g scale with an overall yield of 88%.
13. The physical properties are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.15 (d, 2 H, J = 47.1), 7.60–8.00 (m, 5 H); ^{19}F NMR (282 MHz, $CDCl_3$) δ: –211.2 (t, J = 47.4); MS (EI) m/z 175 ($M^{+}\cdot$); Anal. Calcd for $C_7H_7FO_2S$: C, 48.26; H, 4.05. Found: C, 48.35, H, 3.94.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The first step of the present procedure is an example of the fluoro Pummerer or DAST Pummerer reaction[3] and describes a convenient method for the synthesis of α-fluoro sulfides. α-Fluoro sulfides can subsequently be oxidized to the corresponding sulfoxide or sulfone. For aromatic sulfoxides, use of the 4-anisyl group can dramatically improve the yield and facility of the reaction. The submitters originally found that zinc iodide catalyzes the reaction.[3] Recently, Robins and co-workers[4,5] have reported that antimony trichloride is a superior catalyst for this transformation, eliminating the need for a 4-methoxy group for the conversion of aryl sulfoxides to α-fluoro sulfides. The submitters have subsequently utilized this catalyst in place of zinc iodide.[2,6]

In most cases, the fluoro Pummerer reaction can be carried out with 1.33 to 2.0 equiv of DAST and a "catalytic" amount of antimony trichloride in either refluxing methylene chloride or chloroform at room temperature or 50°C. In the synthesis of fluoromethyl phenyl sulfide, however, the induction period makes room temperature conditions the preferred method for large scale synthesis.

Electron-withdrawing groups decrease the rate of the fluoro Pummerer reaction, which, in certain cases,[7] allows a DAST-mediated deoxygenation to compete with the introduction of fluorine alpha to sulfur. The reaction is compatible with a number of functional groups and can readily be carried out with nucleosides. Robins and co-workers[4] reported the synthesis of a 5'-fluoro-5'-S-phenyladenosine analog using antimony trichloride as catalyst at room temperature. It should be noted that α-fluoro sulfoxides provide a convenient entry to terminal fluoroalkenes.[3,8,9,10]

In most cases, introduction of fluorine adjacent to sulfur can be monitored by proton NMR for small-scale probe reactions run in $CDCl_3$. The CHF peaks in the proton NMR are generally found between δ 5 and 6 ppm (with proton-fluorine coupling constants around 55) and fall below the range for protons on DAST.

For the synthesis of the title compound, Oxone or 3-chloroperbenzoic acid[2] can be used to oxidize the sulfide to the sulfone. The title compound is a key reagent for the preparation of fluoroalkenes from aromatic[11] and aliphatic[2] aldehydes. Recently, a stereospecific method to (E)- and (Z)-fluoroalkenes was reported using this reagent.[12,13,14]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 442

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

DAST

3-chloroperbenzoic acid (MCPBA)

Oxone (potassium peroxymonosulfate, 2 $KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$)

potassium carbonate (584-08-7)

ethyl acetate (141-78-6)

methanol (67-56-1)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

oxone (37222-66-5)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

antimony trichloride

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

hexane (110-54-3)

zinc iodide

argon (7440-37-1)

Methyl phenyl sulfoxide (1193-82-4)

Diethylaminosulfur trifluoride (38078-09-0)

3-chloroperbenzoic acid (937-14-4)

Fluoromethyl phenyl sulfone, Benzene, [(fluoromethyl)sulfonyl]- (20808-12-2)

Fluoromethyl phenyl sulfide (60839-94-3)

5'-fluoro-5'-S-phenyladenosine

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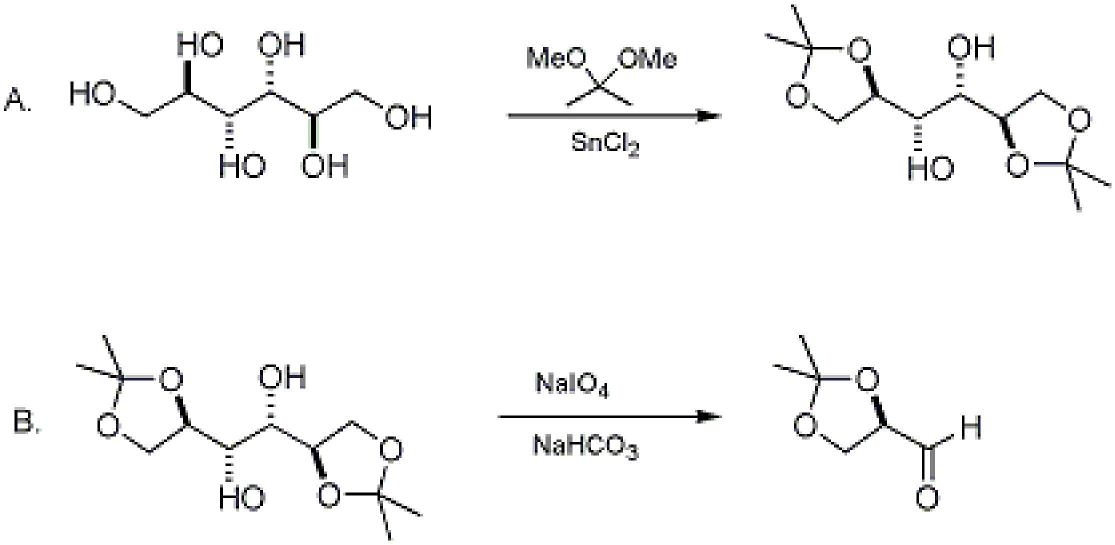
Organic Syntheses, CV 9, 450

D-(R)-GLYCERALDEHYDE ACETONIDE

[1,3-Dioxolane-4-carboxaldehyde, 2,2-dimethyl-, (R)-]



Submitted by Christopher R. Schmid and Jerry D. Bryant[1].
Checked by Marc J. McKennon and Albert I. Meyers.

1. Procedure

A. *1,2:5,6-Diisopropylidene-D-mannitol*. A 1-L, three-necked flask equipped with overhead stirrer, heating mantle, and condenser with drying tube is charged with 100 g of D-mannitol (0.549 mol), 240 mL of freshly-distilled 1,2-dimethoxyethane (Note 1), and 160 mL of 2,2-dimethoxypropane (1.3 mol). Stirring is begun and 0.1 g of stannous chloride is added. The remaining neck is capped with a septum and the stirred slurry is heated to reflux. Reflux is maintained until the mixture becomes clear (30–50 min) and is continued for 30 min after clarity is attained. The heating mantle is removed and the solution is cooled below reflux. Pyridine (200 •L) is added through the septum via syringe. After the solution is cooled to room temperature, it is transferred to a tared, 1-L, one-necked flask, and the contents are concentrated on a rotary evaporator, beginning at room temperature and increasing the temperature to 95–100°C. The flask contents are held at that temperature until no more evaporate is collected (15–30 min). The semi-solid is then cooled to room temperature, to yield 130–160 g of crude solid product of 50–55% purity (72–80 g, 50–56% yield) as assayed by ^{1}H NMR against dichloromethane (Note 2).

B. *2,3-O-Isopropylidene-D-glyceraldehyde*. A large, magnetic stir bar is added to the flask that contains the crude solid diacetonide from procedure A above and 700–800 mL of dichloromethane (10 mL/g of diacetonide) is added. The flask is equipped with a condenser and heating mantle, and the slurry is stirred vigorously and heated to reflux until the solids are digested to an even consistency. The mantle is removed, the

slurry is allowed to cool below reflux, and Celite (10 g) is added with stirring. The contents are further cooled to room temperature and vacuum-filtered through a pad of Celite on a glass frit filter into a three-necked, 2-L vessel. The flask is rinsed with 50 mL of dichloromethane and the rinse is filtered through the funnel. The 2-L vessel is then equipped with an overhead stirrer, thermometer, and water bath, and stirring is begun at 300–350 rpm. A solution of 30–40 mL of saturated aqueous sodium bicarbonate (0.4 mL/g of diacetonide) is added with stirring, followed by 130–140 g of sodium metaperiodate (2.0 mol equiv), added portionwise over 2–3 min. The resulting mixture is stirred while the internal temperature is maintained below 35°C with water bath cooling. After the solution is stirred for 2 hr, 35–50 g of magnesium sulfate (0.5 g/g of diacetonide) is added and stirring is continued for 20 min. The slurry is vacuum-filtered through a glass frit filter into a 2-L, one-necked, round-bottomed flask. The filter cake is removed, transferred back into the three-necked vessel, 200 mL of dichloromethane is added, and the resulting slurry is stirred for 10 min. The slurry is vacuum-filtered (Note 3) and the filtrate is added to the one-necked flask (Note 4).

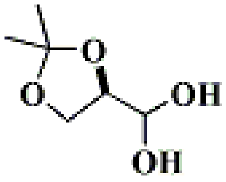
The filtrate-containing flask is equipped with a 12"-Vigreux column, distillation head, receiver, and heating mantle, and dichloromethane is removed by distillation (head temperature to 40°C) (Note 5). The residual oil is cooled and transferred to a 250-mL, round-bottomed flask and the flask is equipped with a simple distillation head, cow receiver, and heating mantle. After a brief forerun (2–3 g), product is collected by distillation at 30 mm (65–120°C) into a chilled receiver (5°C) to afford 54–68 g (75–85%) of crude 2,3-O-isopropylidene-D-glyceraldehyde (Note 6). The crude product is transferred to a 100-mL, round-bottomed flask equipped with a 6"-Vigreux column, cow receiver, and heating mantle, and redistilled (Note 7) at 30 mm, collecting the fraction distilling at 67–73°C into a chilled receiver to afford 50–64 g of product (70–80%, 34–45% overall, (Note 8)).

2. Notes

1. Commercial samples of 1,2-dimethoxyethane were found to contain trace impurities that inactivate the stannous chloride catalyst. Simple distillation affords purified solvent.[2]
2. Samples of about 50 mg are weighed and dissolved in 0.5 mL of (methyl sulfoxide)-d_6(DMSO-d_6) and 10 •L of dichloromethane is added. A small portion of this solution is then withdrawn and diluted in an NMR tube with DMSO-d_6. ^{1}H NMR integration parameters are as follows: 32K data points, recycle delay of 5 s, 30° pulse angle. Measurement is against the hydroxyl proton doublet (2 H) at δ 4.63. If the hydroxyl doublet is not satisfactorily resolved, additional dilution is performed.
Physical data for material purified by slurry in dichloromethane followed by recrystallization from butyl ether is as follows: mp 121.8–123.4°C (lit.[3] mp 118–120°C); $[\alpha]_D^{23}$ +1.9° (CH_3OH, *c* 1.74), lit.[4] $[\alpha]_D^{20}$ +1.9° (CH_3OH, *c* 2); ^{1}H NMR ($CDCl_3$) δ: 1.36 (s, 6 H), 1.42 (s, 6 H), 2.70 (d, 2 H, J = 6.7), 3.75

(approx. t, 2 H, J = 6.2), 3.98 (dd, 2 H, J = 8.4, 5.4), 4.10–4.22 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ: 25.19, 26.72, 66.74, 71.16, 76.22, 109.39; IR (KBr) cm^{-1}: 3400, 3292, 2980, 2933, 2895, 1386, 1372, 1265, 1212, 1070, 859. Anal. Calcd. for $C_{12}H_{22}O_6$: C, 54.95; H, 8.45. Found: C, 54.80; H, 8.50.

3. In the presence of water, 2,3-O-isopropylidene-D-glyceraldehyde forms the highly water soluble hydrate **1**. Failure to dry the reaction and reslurry the filter cake results in loss of about 10% yield.



1

4. On standing, the filtered solids take on a color characteristic of iodine; the solids can be decomposed by treatment in water with sodium thiosulfate or bisulfite to a negative starch-iodide endpoint.

5. Removal of dichloromethane (CH_2Cl_2) in the final step was performed by the checkers using a rotary evaporator. The pressure was monitored during evaporation and was not allowed to drop below 100 mm. In this fashion the same yield of material was obtained as reported.

6. On standing, both the initially distilled and redistilled material may deposit a small amount of flocculent solid or gel characteristic of polymerized material, which results in some thickening of the product oil.

7. The checkers found that a single distillation of the final product was sufficient to obtain pure material.

8. The physical characteristics are as follows: $[\alpha]_D^{23}$ +70–80° (*c* 1.0–1.5, benzene, taken immediately upon completion of distillation); ^1H NMR ($CDCl_3$) δ: 1.40 (s, 3 H), 1.47 (s, 3 H), 4.12 (m, 2 H), 4.36 (m, 1 H), 9.70 (d, 1 H, J = 1.9); ^{13}C NMR ($CDCl_3$) δ: 24.73, 25.84, 65.11, 79.49, 110.79, 201.38; IR (neat) cm^{-1}: 2990, 2940, 2890, 2820, 1730, 1375, 1250, 1215, 1150, 1070, 840. Material obtained from this scale procedure is approximately 90% monomeric; the presence of polymeric material is shown in the ^1H NMR by broad signals at δ 4.7, 3.9 and 1.23.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

2,3-O-Isopropylidene-D-glyceraldehyde has been obtained from D-mannitol by a bis-ketalization/glycol cleavage sequence using a number of ketalizing reagents,[3 5 6 7 8 9 10 11] and either lead tetraacetate[11],[12] or lead periodate[13 14 15 16 17 18 19 20] to effect

glycol cleavage. The compound has also been prepared using alternative methodology,[21] and from other chiral pool sources.[22] This procedure represents recently disclosed[2] optimization efforts on previously reported syntheses of 1,2:5,6-diisopropylidene-D-mannitol[3] and 2,3-O-isopropylidene-D-glyceraldehyde.[20]

A review article reports information regarding the preparation, handling, and storage of this important 3-carbon chiral source.[23] Our experience with the compound demonstrates that it tends to polymerize and readily adds water to form hydrate **1** in aqueous solution, from which it is extracted only with difficultly. Both hydrated and polymerized aldehyde can contaminate samples and result in lowered optical rotation values, even though no racemization has occurred. The present procedure provides anhydrous aldehyde, that polymerizes on standing. Polymerized material can be cracked by redistillation (threshold temperature ca. 90°C) at reduced pressure to provide monomer without compromise of enantiomeric integrity; monomeric aldehyde has been obtained routinely in our labs by distillation from still pots that contain substantially polymerized material. Although polymeric material can be stored for months at room temperature in sealed containers and recracked to provide monomer with good recovery, refrigerated storage retards polymerization rates and probably extends the useful lifetime of the compound, as polymerized material failed in some instances to recrack to monomer. Other workers have recommended storage in a frozen benzene matrix,[24] and a report on successful recracking of refrigerated polymerized material has appeared.[25] We recommend the use of freshly-distilled material in synthetic applications.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 52
- Org. Syn. Coll. Vol. 9, 454
- Org. Syn. 75, 139

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

1,2:5,6-Diisopropylidene-D-mannitol

D-(R)-GLYCERALDEHYDE ACETONIDE

DMSO-d_6

sodium thiosulfate or bisulfite

Benzene (71-43-2)

sodium bicarbonate (144-55-8)

stannous chloride

iodine (7553-56-2)

pyridine (110-86-1)

butyl ether (142-96-1)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

1,2-dimethoxyethane (110-71-4)

2,2-dimethoxypropane (77-76-9)

sodium metaperiodate (7790-28-5)

D-mannitol (69-65-8)

2,3-O-Isopropylidene-D-glyceraldehyde (22323-80-4)

1,3-Dioxolane-4-carboxaldehyde, 2,2-dimethyl-, (R)- (15186-48-8)

lead tetraacetate

lead periodate

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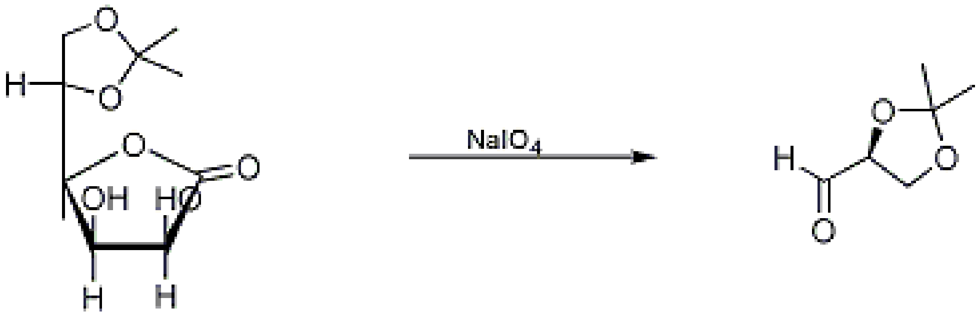
Organic Syntheses, CV 9, 454

L-(S)-GLYCERALDEHYDE ACETONIDE

[1,3-Dioxolane-4-carboxaldehyde, 2,2-dimethyl-, (S)-]



Submitted by Christian Hubschwerlen, Jean-Luc Specklin, and J. Higelin[1].
Checked by Todd M. Heidelbaugh and Leo A. Paquette.

1. Procedure

A 500-mL, four-necked, reaction flask, equipped with a mechanical stirrer, thermometer, and glass pH electrode combined with an automatic titrator (Note 1), is charged with sodium (meta)periodate (85.5 g, 0.4 mol) (Note 2) and water (200 mL). The suspension is cooled to 0°C in an ice bath and 3 N sodium hydroxide (about 133 mL, 0.4 mol) is added dropwise at a rate such that the temperature does not exceed 7°C. The final pH of the suspension is 5.5. The cooling bath is removed and finely powdered 5,6-O-isopropylidene-L-gulono-1,4-lactone (Note 3) (43.6 g, 0.2 mol) is added in one portion. The temperature of the mixture is kept below 30°C (Note 4). The pH of the suspension is maintained at 5.5 during the course of the reaction by addition of aqueous 15% sodium carbonate (about 15 mL). The suspension is further stirred at room temperature for 30 min, saturated with sodium chloride (105 g), and filtered by suction using a Büchner funnel. The white solid (Note 5) is washed thoroughly with two 50-mL portions of brine and the pH of the combined aqueous layers is adjusted to 6.7 with aqueous 15% sodium carbonate before extraction with dichloromethane (6 × 100 mL) (Note 6). The combined organic extracts are dried over magnesium sulfate (25 g). The magnesium sulfate is removed by filtration and washed with two 50-mL portions of dichloromethane. The organic solutions are combined and slowly concentrated to about 50 mL under reduced pressure (Note 7). The remaining solution is placed in a 100-mL, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar and a 10-cm, vacuum-jacketed, Claisen-Vigreux column (10-mm diameter). With constant stirring by a magnetic stirrer, the solution is further concentrated by distillation under reduced pressure (400 mbar) at 35°C (bath temperature) (Note 8). The temperature of the oil bath is then gradually increased to 80°C and the glyceraldehyde acetonide is distilled between 51°C and 52°C. The distillate is collected in a receiver cooled with an ice-methanol bath (Note 9). Approximately 14.5 g of L-(S)-glyceraldehyde acetonide (56% based on 5,6-O-

isopropylidene-L-gulono-1,4-lactone) is obtained.

2. Notes

1. A 200-mm Radiometer combined glass/reference electrode (Ag/AgCl) was used. To control the pH the submitters used a Radiometer standard pH meter PHM82 coupled to a TTT80 titrator. The end point was set to pH 5.5. If an automatic delivery system is not used the pH range should be kept between 4 and 6 during the oxidation process. Low pH values favor hydrolysis of the acetonide protective group, high pH values lead to epimerization of the aldehyde. The checkers did not use an automatic titrator. The pH was adjusted manually; 1.25 hr was required to bring the solution to pH 5.5.
2. Sodium (meta)periodate (puriss. p.a.) was purchased from Fluka Chemical Corporation and used without any purification.
3. 5,6-O-Isopropylidene-L-gulono-1,4-lactone was purchased from Fluka Chemical Corporation and used without any purification. It can also be synthesized from ascorbic acid in a two-step procedure.[2]
4. The temperature of the solution was kept between 20°C and 30°C by occasional cooling with an ice-water bath.
5. The white solid is mainly sodium iodate and sodium chloride.
6. GLC analysis of a sample of the crude, aqueous solution indicates the presence of 95% of the theoretical amount of glyceraldehyde acetonide. This crude, aqueous solution can be used for further chemical transformations,[2] but was not stored for more than 6 hr at 0°C. GLC analysis of the aqueous layer after dichloromethane extraction still indicates the presence of about 30% of the total amount of glyceraldehyde acetonide in the aqueous solution.
7. The submitters used the following conditions: rotatory evaporator bath temperature: 35°C, cooling water temperature: –5°C; pressure: 500 mbar.
8. In the condenser, the cooling water was replaced by a methanol-ice mixture.
9. (S)-Glyceraldehyde acetonide is an unstable liquid that starts to polymerize on standing even at low temperature. It can be depolymerized by distillation before use. The ^{1}H NMR spectrum is as follows ($CDCl_3$) δ: 1.43 and 1.49 (2 s, 2 × 3 H), 4.08–4.21 (2 dd, 2 × 1 H, J = 4.4, 7.6), 4.38 (ddd, 1 H, J = 2, 4.4, 7.6), 9.72 (d, 1 H, J = 2), internal tetramethylsilane standard). The optical rotation is $[\alpha]_D^{20}$ –75.4° (benzene, *c* 8) [lit. $[\alpha]_D^{20}$ –67.9°/69.7° (benzene, *c* 8/2.2)[3,4]].

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Optically pure glyceraldehyde acetonides are widely used in the synthesis of enantiomerically pure compounds (EPC synthesis).[5] Whereas D-(R)-glyceraldehyde

acetonide is easily obtained from the inexpensive D-mannitol,[6,7] there are only a limited number of practical syntheses of the enantiomeric L-(S)-glyceraldehyde acetonide.[8,9] Difficulties arise from different sources: 1) availability of the starting material diisopropylidene-L-mannitol; 2) length of the synthesis;[10] 3) nature of the reactants used : mercury acetate, mercaptans, lead tetraacetate, ozone at –78°C, 4) moderate yields.[11,12,13,14]

The procedure reported here is practical, uses readily available, non-toxic starting materials, and can be easily scaled up. No harmful by-products are formed during the synthesis, and sodium iodate, generated during the periodate cleavage, can be recycled into sodium metaperiodate.[15]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 13

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

brine

D-(R)-GLYCERALDEHYDE ACETONIDE

(S)-Glyceraldehyde acetonide

Benzene (71-43-2)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

mercury acetate (1600-27-7)

dichloromethane (75-09-2)

ozone (10028-15-6)

magnesium sulfate (7487-88-9)

sodium metaperiodate, sodium (meta)periodate (7790-28-5)

sodium iodate (7681-55-2)

ascorbic acid

D-mannitol (69-65-8)

5,6-O-isopropylidene-L-gulono-1,4-lactone

L-(S)-Glyceraldehyde acetonide (22323-80-4)

1,3-Dioxolane-4-carboxaldehyde, 2,2-dimethyl-, (S)- (22323-80-4)

diisopropylidene-L-mannitol

lead tetraacetate

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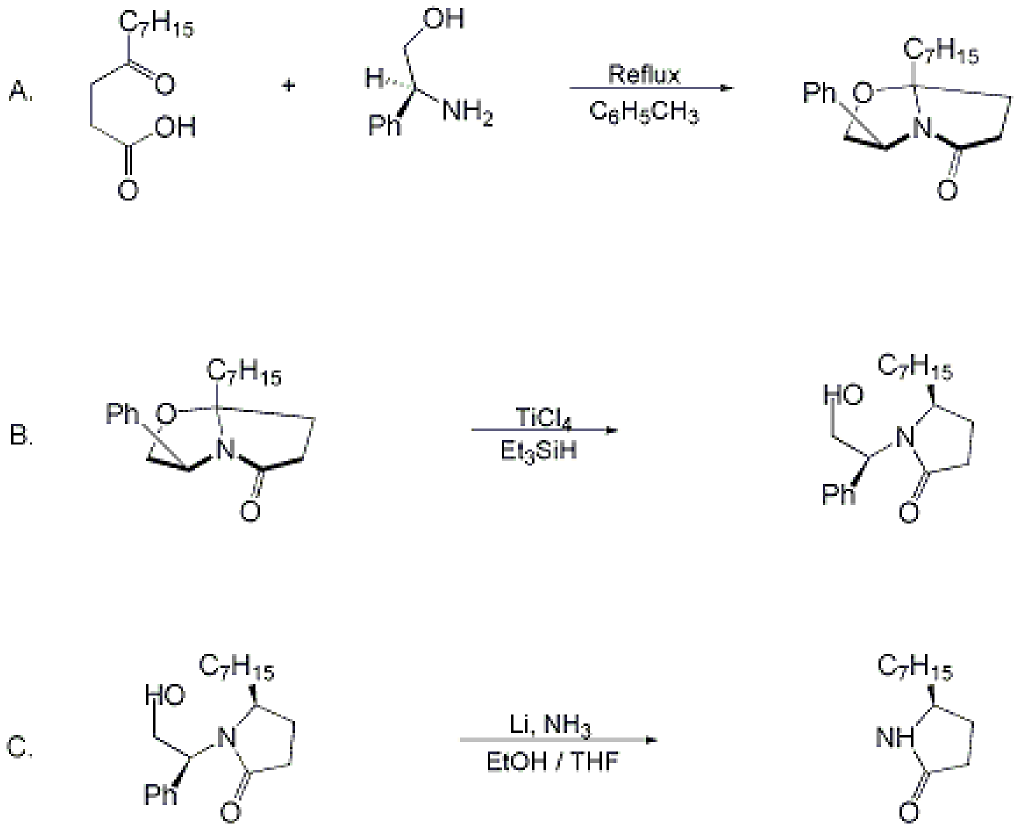
Organic Syntheses, CV 9, 457

S-(–)-5-HEPTYL-2-PYRROLIDINONE. CHIRAL BICYCLIC LACTAMS AS TEMPLATES FOR PYRROLIDINES AND PYRROLIDINONES

[2-Pyrrolidinone, 5-heptyl-, (S)-]



Submitted by M. A. Tschantz, L. E. Burgess, and A. I. Meyers[1].
Checked by J. Madalengoitia and L. E. Overman.

1. Procedure

A. *(+)-3-Phenyl-5-oxo-7a-heptyl-2,3,5,6,7,7a-hexahydropyrrolo[2,1-b]oxazole*. A clean, 500-mL, round-bottomed flask, equipped with a magnetic stirring bar and a Dean-Stark trap, is charged with 12.5 g of 4-ketoundecanoic acid (62.4 mmol) (Note 1), 8.56 g of (S)-(+)-2-Phenylglycinol (62.4 mmol) (Note 2), and 150 mL of toluene. The solution is heated at reflux with stirring for 20 hr and then cooled to room temperature. The solution is concentrated at reduced pressure, and the residual yellow oil is purified by flash chromatography on silica gel (Note 3) employing 3:1 hexane/ethyl acetate as the eluent to provide 14.5–16.2 g of the bicyclic lactam (77–86%) as a light yellow oil (Note 4).

B. *(+)-N-[2-(1-Hydroxy-2-phenethyl)]-5-heptyl-2-pyrrolidinone*. An oven-dried, 1-L, one-necked, round-bottomed flask, equipped with a magnetic stirring bar and fitted with a rubber septum, is flushed with argon and charged with 14.1 g of the bicyclic lactam (46.7 mmol) prepared above and 270 mL of dry dichloromethane (Note 5). The resulting solution is cooled to −78°C, using an external dry ice-acetone bath, and stirred for 15 min. Then 13.4 mL of triethylsilane (84.1 mmol) (Note 6) and 93 mL (93 mmol) of a 1.0 M solution of titanium tetrachloride in CH_2Cl_2 (Note 7) are successively added dropwise via syringe under an argon atmosphere (Note 8). The solution is stirred at −78°C for 1.5 hr and then allowed to warm to room temperature and stir at that temperature for 1 hr. The mixture is recooled

to 0°C and carefully quenched with saturated ammonium chloride via syringe (*CAUTION: vigorous reaction!*). The resulting solution is diluted with 120 mL of water, transferred to a 1-L separatory funnel, and extracted with three 75-mL portions of dichloromethane. The combined organic extracts are dried over sodium sulfate (Na_2SO_4), filtered, and concentrated under reduced pressure to afford a crude mixture containing the product. Purification of the product by flash chromatography, using 1:1 (v/v) hexane/ethyl acetate as eluent, provides the hydroxypyrrolidinone (12.6 g, 89%) as a pale yellow oil (Note 9).

C. *S-(–)-5-Heptyl-2-pyrrolidinone*. An oven-dried, 1-L, two-necked, round-bottomed flask, equipped with a glass-covered stirring bar, is charged with 12.4 g of (+)-N-[2-(1-hydroxy-2-phenethyl)]-5-heptyl-2-pyrrolidinone (40.8 mmol), 24 mL of anhydrous ethyl alcohol (410 mmol), and 100 mL of dry tetrahydrofuran (THF). One neck is fitted with an acetone-dry ice cooled cold finger condenser bearing an argon inlet/outlet vented through a mineral oil bubbler, and the other neck with a second gas inlet valve. With stirring, the solution is cooled to –78°C using an external acetone-dry ice bath, and ammonia (200 mL) is condensed into the flask through the gas inlet valve. The gas inlet is replaced with a stopper, the acetone-dry ice bath is removed, and 2.83 g of lithium wire (408 mmol) (Note 10) is added in small portions by removal of the stopper. The resulting blue solution is allowed to stir and reflux for 30 min (Note 11). The reaction mixture is carefully quenched with a small amount of ammonium chloride (solid) until disappearance of the blue color. The cold finger is removed, and the resulting solution is allowed to warm to room temperature over 4 hr (*CAUTION: ammonia is evolved*). The residual milky solution is concentrated under reduced pressure, and the remaining semisolid is diluted with water (100 mL) and dichloromethane (150 mL) and stirred for 30 min. The two layers are separated, and the aqueous layer is extracted four times with 50-mL portions of dichloromethane. The combined organic phases are dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The yellow residue is subjected to flash chromatography (Note 3) and (Note 12), employing a 4:1 hexane/ethyl acetate solution as eluent, to afford 4.64 g (62%) of the desired pyrrolidinone as a pale yellow solid, mp 43–44°C (Note 13). *CAUTION: The minor reaction by-product, phenethyl alcohol, which has a distinct benzene-like odor, is an inhibitor of DNA and RNA synthesis in vitro.*

2. Notes

1. Tschantz, M. A.; Burgess, L. E.; Meyers, A. I. *Org. Synth., Coll. Vol. IX* **1998**, 530.
2. (S)-(+)-2-Phenylglycinol is commercially available, or may be prepared by reducing (S)-(+)-2-phenylglycine as follows: A 1-L, three-necked, round-bottomed flask is charged with 200 mL of dry THF under an argon atmosphere. Portionwise, 10.01 g of sodium borohydride (264.6 mmol) is added, followed by the dropwise addition of 65.1 mL of boron trifluoride etherate (528.7 mmol). The colorless suspension is stirred for 15 min, followed by portionwise addition of 20.00 g of (S)-(+)-2-phenylglycine (132.2 mmol). (*CAUTION: exotherm and gas evolution!*). The resulting suspension is heated at reflux for 12 hr and then is allowed to cool to room temperature followed by quenching with methanol until gas evolution ceases. The reaction mixture is concentrated under reduced pressure to yield a colorless solid that is taken up in 400 mL of 20% aqueous sodium hydroxide solution. The basic solution is extracted three times with 200-mL portions of dichloromethane, the combined organic layers are dried over sodium sulfate, and concentrated under reduced pressure to yield 14.72 g (81%) of (S)-(+)-2-phenylglycinol as a colorless solid: mp 72–74°C, $[\alpha]_D$ +32.2°; ^1H NMR (300 MHz, $CDCl_3$) δ: 3.52 (dd, 1 H, J = 10.7, 8.3), 3.71 (dd, 1 H, J = 10.7, 4.4), 4.01 (dd, 1 H, J = 8.2, 4.4), 7.23–7.35 (m, 5 H).
3. Merck 951 grade silica gel was used. Chromatography was performed in the manner described by Still[2] using 20:1 (w/w) of silica gel to crude product.
4. The spectral data of the purified bicyclic lactam are as follows: ^1H NMR (300 MHz, $CDCl_3$) δ: 0.85 (t, 3 H, J = 6.4), 1.13–1.72 (m, 12 H), 2.13 (m, 1 H), 2.33 (ddd, 1 H, J = 13.4, 9.7, 2.5), 2.57 (ddd, 1 H, J = 17.3, 10.2, 2.5), 2.81 (m, 1 H), 4.05 (dd, 1 H, J = 8.7, 7.3), 4.62 (t, 1 H, J = 8.5),

5.17 (t, 1 H, J = 7.7), 7.20–7.36 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 14.0, 22.5, 23.9, 29.1, 29.5, 30.9, 31.6, 33.3, 36.3, 57.5, 72.8, 102.7, 125.4, 127.3, 128.6, 140.1, 179.3; IR (thin film) cm^{-1}: 2954–2856, 2362, 1715, 1458, 1364, 1031, 699.

5. Dichloromethane was freshly distilled over calcium hydride.

6. Triethylsilane was purchased from Aldrich Chemical Company, Inc. and used without further purification.

7. Titanium tetrachloride was purchased from Fluka Chemical Corporation and used without further purification.

8. The checkers used an internal thermometer and maintained the reaction temperature between –78° and –70°C during the addition.

9. The spectral data of the purified hydroxyalkyl lactam are as follows: ^{1}H NMR (300 MHz, $CDCl_3$, 5 mg/mL) δ: 0.86 (t, 3 H, J = 6.6), 1.05–1.40 (m, 11 H), 1.58 (m, 1 H), 1.75 (m, 1 H), 2.07 (m, 1 H), 2.40–2.59 (m, 2 H), 2.95 (s (br), 1 H), 3.33 (m, 1 H), 3.95 (dd, 1 H, J = 12.3, 3.3), 4.22 (dd, 1 H, J = 12.3, 7.8), 4.41 (dd, 1 H, J = 7.8, 3.3), 7.20–7.37 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 14.0, 22.6, 24.1, 24.5, 29.1, 29.4, 31.3, 31.7, 32.3, 59.3, 62.3, 64.1, 127.2, 127.8, 128.7, 137.5, 176.8; IR (thin film) cm^{-1}: 3377 (br), 2959–2856, 1668, 1451, 1420, 1285, 1064, 702. The ^{1}H NMR signal for the proton of the OH group (δ 2.95) was found to be concentration dependent.

10. Lithium wire was purchased from Aldrich Chemical Company, Inc., and was cut into small pieces.

11. The solution should remain blue for the duration (30 min). More lithium may be added if necessary.

12. The final product is difficult to visualize during TLC analysis. Ninhydrin (5% w/v in ethanol) or ceric ammonium nitrate (5 g in 100 mL of aqueous 1 M H_2SO_4) are effective.

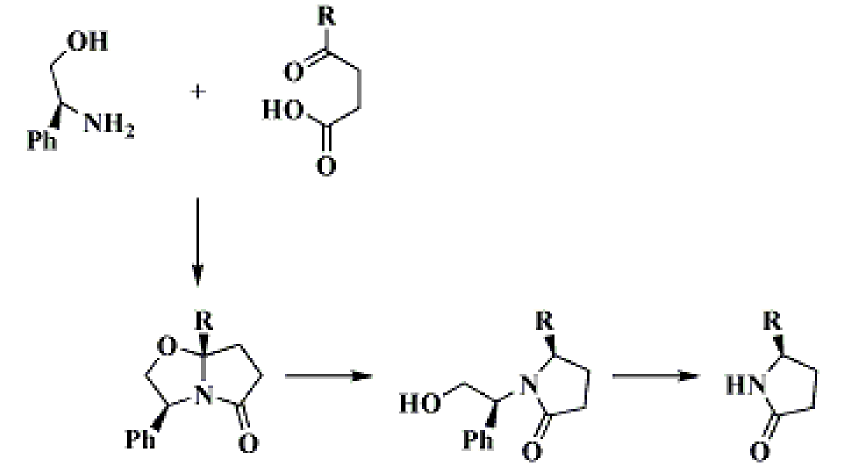
13. The spectral data for the purified pyrrolidinone are as follows: ^{1}H NMR (300 MHz, $CDCl_3$, 5 mg/mL) δ: 0.86 (t, 3 H, J = 6.4), 1.25–1.75 (m, 13 H), 2.20–2.35 (m, 3 H), 3.61 (quintet, 1 H, J = 6.9), 6.09 (s (br), 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 14.0, 22.6, 25.8, 27.3, 29.1, 29.4, 30.2, 31.7, 36.7, 54.7, 178.2; IR (thin film) cm^{-1}: 3204 (br), 2956–2856, 1700, 1463, 1387, 1311, 1266. $[\alpha]_D$ –9.7° ($CHCl_3$, *c* 1.1).

Waste Disposal Information

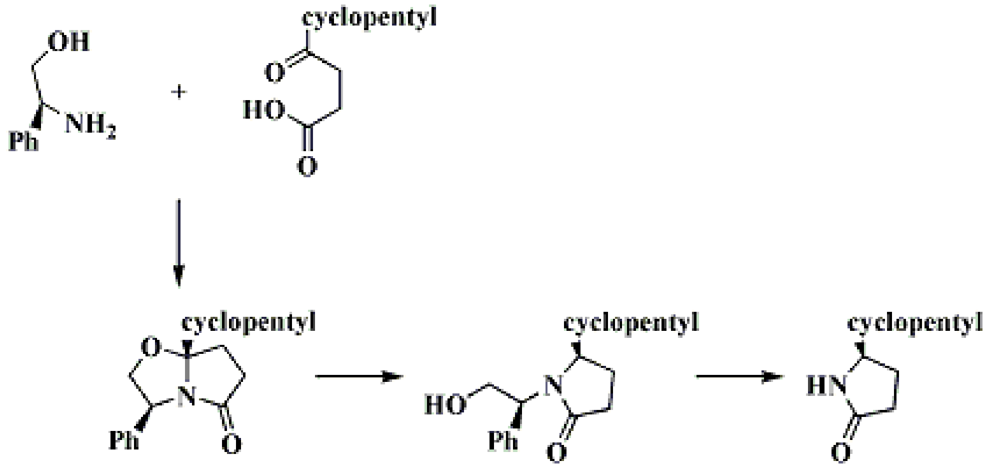
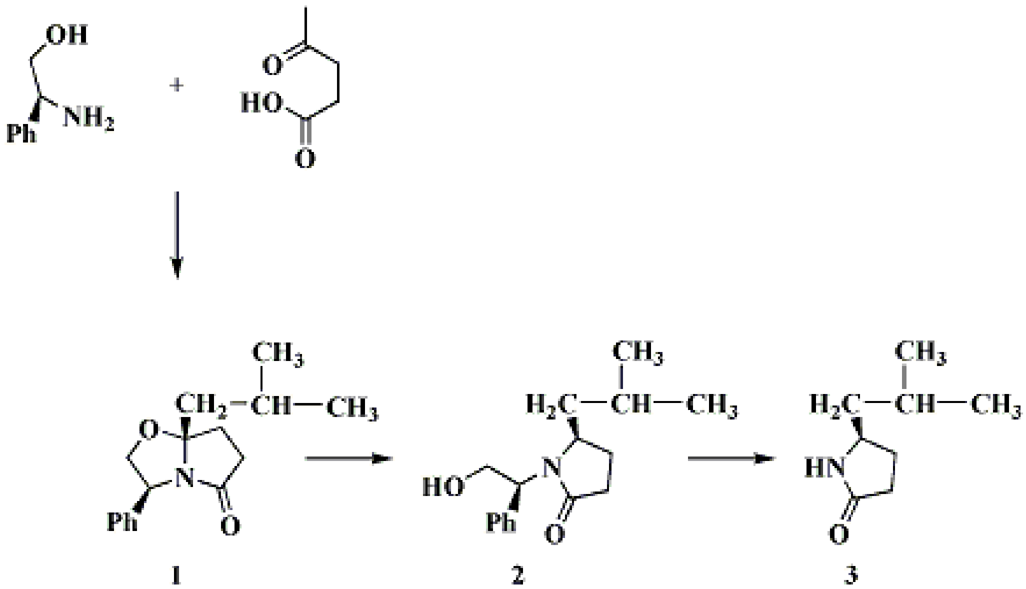
All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

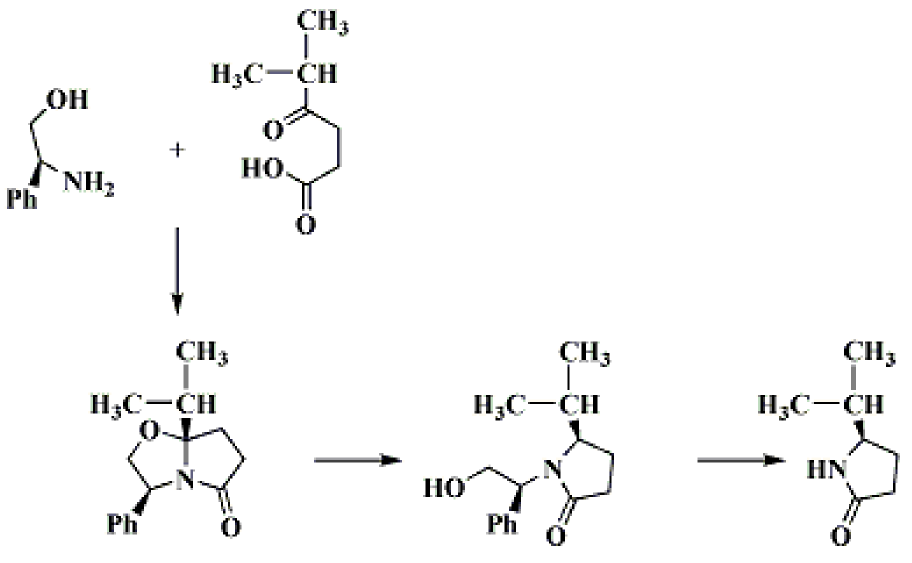
3. Discussion

Chiral bicyclic lactams are excellent precursors to a wide variety of chiral, non-racemic carbocycles including cyclopentenones, cyclohexenones, cyclopropanes, indanones, naphthalenones, and asymmetric keto acids.[3 4] Recently they have been applied to the synthesis of chiral, non-racemic pyrrolidines and pyrrolidinones,[5 6 7 8] that are medicinally and synthetically important molecules.[9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37] The three-step procedure described here provides an efficient route (overall yield: 46%) to (S)-5-heptyl-2-pyrrolidinone of high enantiomeric purity. The scheme below illustrates this reaction.



TABLE

R	Yield of **1**	Yield of **2**	Yield of **3**
 1 2 3	83%	88%	89%
 1 2 3	89%	85%	65%



84% 94% 81%

The first step is the formation of the chiral bicyclic lactam **1** involving the cyclodehydration of a 4-keto acid (p. 530) and (S)-2-phenylglycinol. Interestingly only a single diastereomer (NMR) of **1** is formed. The second step, the crucial reduction of the N,O-ketal, probably proceeds via an N-acyl iminium ion in which allylic 1,3-interactions dictate the facial selectivity of hydride delivery.[6,7] The resulting N-substituted 5-alkylpyrrolidinones **2** were typically obtained in >94% diastereomeric excess as determined by the isolation of each diastereomer via flash chromatography. The final step, cleavage of the chiral auxiliary, takes advantage of the benzylic C-N bond to expose the free amide by dissolving metal reduction. Although the chiral "auxiliary" is destroyed, the relatively low cost of both antipodes of phenylglycine make this procedure attractive as a preparative method for both antipodes of the pyrrolidinones.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

(+)-N-[2-(1-Hydroxy-2-phenethyl)]-5-heptyl-2-pyrrolidinone

S-(−)-5-HEPTYL-2-PYRROLIDINONE

H_2SO_4

ethyl alcohol, ethanol (64-17-5)

ammonia (7664-41-7)

ethyl acetate (141-78-6)

methanol (67-56-1)

ammonium chloride (12125-02-9)

sodium hydroxide (1310-73-2)

sodium sulfate (7757-82-6)

toluene (108-88-3)

dichloromethane (75-09-2)

phenethyl alcohol (60-12-8)

lithium, Lithium wire (7439-93-2)

magnesium sulfate (7487-88-9)

Tetrahydrofuran, THF (109-99-9)

(S)-(+)-2-phenylglycine (2935-35-5)

hexane (110-54-3)

titanium tetrachloride (7550-45-0)

phenylglycine (103-01-5)

boron trifluoride etherate (109-63-7)

calcium hydride (7789-78-8)

sodium borohydride (16940-66-2)

argon (7440-37-1)

ninhydrin (938-24-9)

ceric ammonium nitrate

TRIETHYLSILANE (617-86-7)

(S)-5-heptyl-2-pyrrolidinone, 2-Pyrrolidinone, 5-heptyl-, (S)- (152614-98-7)

(+)-3-Phenyl-5-oxo-7a-heptyl-2,3,5,6,7,7a-hexahydropyrrolo[2,1-b]oxazole (132959-41-2)

4-Ketoundecanoic acid (22847-06-9)

(S)-(+)-2-Phenylglycinol, (S)-2-phenylglycinol (20989-17-7)

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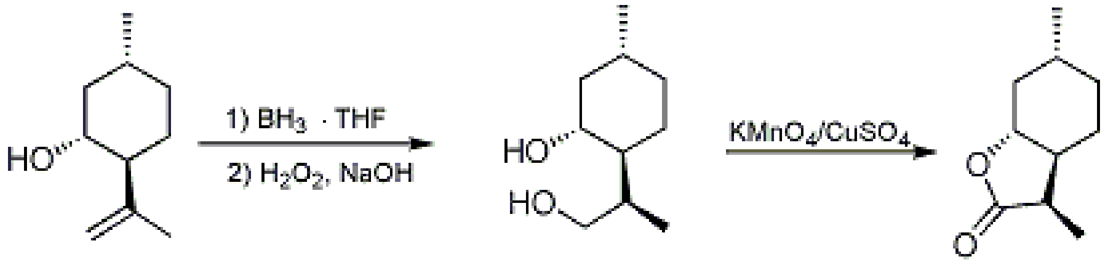
Organic Syntheses, CV 9, 462

A SELECTIVE, HETEROGENEOUS OXIDATION USING A MIXTURE OF POTASSIUM PERMANGANATE AND CUPRIC SULFATE: (3aS,7aR)-HEXAHYDRO-(3S,6R)-DIMETHYL-2(3H)-BENZOFURANONE

[2(3H)-Benzofuranone, hexahydro-3,6-dimethyl-, [3R-(3α,3aβ,6β,7aα)]-]



Submitted by Charles W. Jefford, Yun Li, and Ying Wang[1].
Checked by Timothy J. Watson and Leo A. Paquette.

1. Procedure

A. *(–)-(1R,3R,4S,8R)-p-Menthane-3,9-diol*. To a dry, 2-L, three-necked flask equipped with a gas outlet, an overhead stirrer, and a 500-mL pressure-equalizing dropping funnel with a gas inlet, is added a solution of 31 g (0.20 mol) of isopulegol (Note 1) in 550 mL of tetrahydrofuran (THF) (Note 2) under nitrogen. From the funnel, 230 mL of a 1.0 M diborane solution (Note 3) is added dropwise with stirring at room temperature at such a rate to insure that gas evolution is not violent. When the addition is complete, the clear solution is stirred for 3 hr at room temperature. The dropping funnel is removed and 100 mL of aqueous 3 N sodium hydroxide is added slowly; the solution is then warmed to 60°C on the steam bath for 2 hr. The gas outlet is replaced by a thermometer and the septum is replaced by another dropping funnel charged with 120 mL of aqueous 30% hydrogen peroxide and the reaction flask is placed in an ice bath. Hydrogen peroxide is then added and the reaction temperature is maintained between 30–50°C by carefully controlling the rate of addition (the reaction is strongly exothermic at the beginning). When the addition is complete, the ice bath is removed and the reaction mixture is stirred at 50°C for 2 hr. The bulk of the THF is removed under reduced pressure and the residue is diluted with 200 mL of ether and washed with brine. The aqueous layer is extracted with two 50-mL portions of ether; the resulting extracts are combined and dried over anhydrous sodium sulfate for several hours and filtered. The filtrate is concentrated using a rotary evaporator. The resulting oil is dissolved in 100 mL of hot hexane, allowed to cool slowly, and stored at 0°C for

2 days. The supernatant mother liquor is decanted, 100 mL of fresh hexane is added, the crystalline mass is swirled for 2–3 min and the product is separated by filtration. After vacuum drying, 17.6 g (51%) of (−)-(1R,3R,4S,8R)-p-menthane-3,9-diol is obtained as colorless crystals, mp 105–107°C (Note 4).

B. *(+)-(3aS,7aR)-Hexahydro-(3S,6R)-dimethyl-2(3H)-benzofuranone*. To a 1-L round-bottomed flask equipped with an efficient magnetic stirrer is added 10 g (58 mmol) of (−)-(1R,3R,4S,8R)-p-menthane-3,9-diol and 400 mL of dichloromethane. The resulting suspension is stirred until all the solid dissolves at which time a mixture of powdered potassium permanganate and copper sulfate ($CuSO_4 \cdot 5H_2O$) (Note 5) is added in one portion. The reaction mixture is then stirred at 25°C between 6 and 8 hr depending upon the quality of the oxidant (Note 6), 400 mL of ether is added, and stirring is continued for an additional 20 min. The suspension is transferred with the aid of a small amount of ether onto a fritted-disk Büchner funnel containing 50 g of silica gel and a little ether. The spent manganese salt is mixed with some of the silica gel, using a spatula, to insure that all the solution is absorbed. The resulting filter-cake is washed with 500 mL of ether (Note 7). Upon removal of the solvent, the crude product is obtained as a clear, colorless oil. More product is recovered by taking the filter-cake from the funnel and placing it in a 2-L beaker containing 100 mL of ether and a solution of 270 g of sodium metabisulfite in 1 L of water that is cooled in an ice bath (Note 8). The cake is broken up with a glass rod and stirred. To the resulting slurry, 150 mL of aqueous 10% hydrochloric acid is added in portions with stirring until the color turns from dark gray to pale yellow and all the solid material, except the silica, is dissolved. The resulting mixture is filtered and the filtrate is extracted with three 150-mL portions of ether. The ether extracts are combined and washed twice with water and once with brine. The ethereal solution is dried by shaking with 30 g of anhydrous sodium sulfate and filtered. The filtrate is concentrated to about 150 mL and stirred with 10 g of Amberlyst-15 for 3 hr (Note 9). After another filtration, the solvent is evaporated and the residual oil is combined with that previously obtained. Purification by vacuum distillation gives 4.8–5.0 g (49–51% yield) of 3aS,7aR-hexahydro-3S,6R-dimethyl-2(3H)-benzofuranone as a colorless oil, bp 110°C (0.05 mm) (Note 10).

2. Notes

1. Isopulegol (Tech. as obtained from Aldrich-Chemie GmbH & Company KG, D-7924 Steinheim, Federal Republic of Germany) contains about 65–70% (−)-isopulegol according to its NMR spectrum. It has an optical rotation of $[\alpha]_D^{20}$ −4.6° (neat), while $[\alpha]_D^{20}$ −22° is reported[2] for the pure material. The technical grade product was used without further purification. Pure (−)-isopulegol can be prepared in a highly stereoselective manner from (+)-citronellal.[3]

2. Tetrahydrofuran (THF) was dried with and distilled from sodium in the presence of benzophenone.

3. Diborane was obtained as a 1.0 M THF solution from Aldrich Chemical

Company, Inc.

4. The NMR spectrum of the diol obtained was identical to that already reported:[2] ^{1}H NMR (360 MHz, $CDCl_3$) δ: 0.86–0.99 (m, 2 H), 0.92 (d, 3 H, J = 6.6), 0.96 (d, 3 H, J = 7.5), 1.17–1.29 (m, 1 H), 1.32–1.49 (m, 2 H), 1.57 (m, 1 H), 1.64 (m, 1 H), 1.85 (m, 1 H), 1.96 (m, 1 H), 3.29 (br, s, 2 H), 3.47 (t, d, 1 H, J = 10.4, 4.2), 3.60 (dd, 1 H, J = 10.6, 3.5), 3.66 (dd, 1 H, J = 10.6, 5.4). Its optical rotation ($[\alpha]_D^{20}$ −18.7° ($CHCl_3$, *c* 10)) was identical to that reported.[2] The checkers recorded an $[\alpha]_D^{20}$ of −20.7° ($CHCl_3$, *c* 10).

5. The oxidant was prepared from 130 g of crystalline potassium permanganate ($KMnO_4$) and 25 g of $CuSO_4 \cdot 5H_2O$ by grinding them together in a mortar until a fine powder was obtained.

6. The progress of the oxidation can be monitored by the disappearance of the diol using TLC (eluent, hexane:ethyl acetate, 2:7).

7. It is essential to mix thoroughly the spent oxidant and the silica gel with a spatula while washing. This process does not cause any manganese salt to pass into the filtrate.

8. The quality of the $KMnO_4$ and $CuSO_4 \cdot 5H_2O$ varies with the supplier and affects the yield. Consequently, some hydroxy acid, instead of the lactone, may be formed. In such a case, treatment with sodium metabisulfite solution followed by acidification converts any free acid retained on the filter cake into lactone.

9. Amberlyst-15, a cation exchange resin, was supplied by Fluka Chemical Corporation.

10. The lactone is identical to that previously reported[4] and has the following spectral data: IR (neat) cm^{-1}: 1770, 1453, 1375, 1290, 1190, 1096, 847; ^{1}H NMR (360 MHz, $CDCl_3$) δ: 0.99–1.38 (m, 3 H), 1.02 (d, 3 H, J = 6.5), 1.15 (d, 3 H, J = 7.6), 1.59 (m, 1 H), 1.78 (m, 2 H), 1.92 (m, 1 H), 2.25 (m, 1 H), 2.64 (quint., 1 H, J = 7.6), 4.00 (dt, 1 H, J = 11, 4); ^{13}C NMR (360 MHz, $CDCl_3$) δ: 9.57, 21.99, 23.77, 31.25, 34.15, 38.72 (2 carbons), 47.09, 81.38, 180.27. It has $[\alpha]_D^{20}$ +106.2° ($CHCl_3$, *c* 0.6). The checkers recorded $[\alpha]_D^{25}$ of +72 to +88° ($CHCl_3$, *c* 0.6). If the temperature of the distillation exceeds 110°C, a decrease in $[\alpha]_D$ might be observed because of epimerization α to the lactone carbonyl. If the pure diastereomer is required, it is recommended that purification be effected by column chromatography over silica gel (eluent, pentane:ethyl acetate 20:1). Typically, the lactone is obtained in a yield of 55% with an $[\alpha]_D^{20}$ +149° ($CHCl_3$, *c* 1.1).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

There are few oxidants that oxidize primary alcohols faster than secondary ones. We have demonstrated that a solid mixture of $KMnO_4$ and $CuSO_4 \cdot 5H_2O$ treated with base can bring about such selectivity.[4] The present procedure illustrates a general and convenient method for the oxidation of α,ω-diols to give lactones, that is typified by procedure B, where base is not necessary since ideally no acid is produced. When conducted on a 1-g scale and using pure (−)-isopulegol, overall yields were as high as 89%. In the present instance, starting with pure diol in 10-g lots, maximum yields of only 55% were attained. The reason for the lower yield on larger scale is unclear, although the formation of hydroxy acid rather than lactone may account for some loss. Nonetheless, the procedure has undeniable advantages, including, the formation of a single lactone retaining the initial stereochemistry at C(3). Although Jones oxidation of the diol[5] is reported to give the product lactone in 89% yield, repetition of the experiment reveals that only 38% is found in practice, the balance of material being two other related, but different products.[4] Other routes[6,7] to this lactone, because of the conditions, give most probably the 3R epimer as evidenced by the NMR spectral data.

References and Notes

1. Department of Organic Chemistry, University of Geneva, 30 quai Ernest Ansermet, 1211 Geneva 4, Switzerland. We thank the Swiss National Science Foundation for the support of this work (Grant No. 2.812–0.85).
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium metabisulfite

brine

diborane

(−)-(1R,3R,4S,8R)-p-Menthane-3,9-diol

(−)-isopulegol

$KMnO_4$

$CuSO_4 \cdot 5H_2O$

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

ether (60-29-7)

sodium hydroxide (1310-73-2)

potassium permanganate (7722-64-7)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

copper sulfate, cupric sulfate (7758-98-7)

Benzophenone (119-61-9)

sodium (13966-32-0)

hydrogen peroxide (7722-84-1)

Pentane (109-66-0)

dichloromethane (75-09-2)

Tetrahydrofuran, THF (109-99-9)

hexane (110-54-3)

(+)-citronellal (106-23-0)

(3aS,7aR)-HEXAHYDRO-(3S,6R)-DIMETHYL-2(3H)-BENZOFURANONE, 3aS,7aR-hexahydro-3S,6R-dimethyl-2(3H)-benzofuranone, (+)-(3aS,7aR)-Hexahydro-(3S,6R)-dimethyl-2(3H)-benzofuranone (79726-51-5)

isopulegol (89-79-2)

2(3H)-Benzofuranone, hexahydro-3,6-dimethyl-, [3R-(3α,3aβ,6β,7aα)]-

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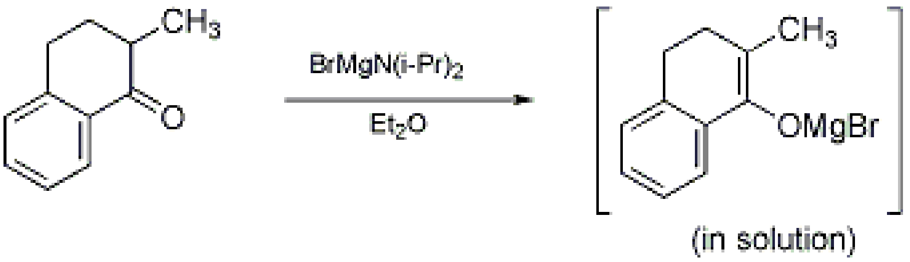
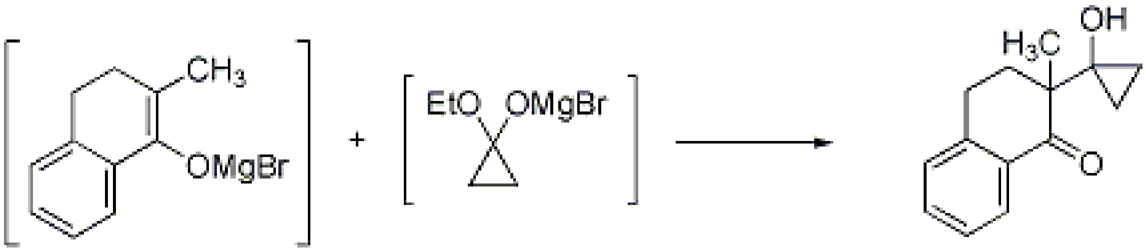
Organic Syntheses, CV 9, 466

CYCLOPENTANONE ANNULATION VIA CYCLOPROPANONE DERIVATIVES: (3aβ,9bβ)-1,2,3a,4,5,9b-HEXAHYDRO-9b-HYDROXY-3a-METHYL-3H-BENZ[e]INDEN-3-ONE

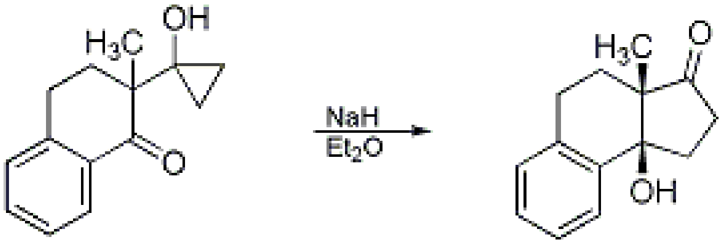
A.



B.



C.



Submitted by Michael J. Bradlee and Paul Helquist[1].
Checked by Steve Berberich and Stephen F. Martin.

1. Procedure

A. *Magnesium enolate of 2-methyl-1-tetralone*. Into a 500-mL, round-bottomed flask equipped with a magnetic stirring bar is placed 6.72 g of magnesium bromide diethyl etherate ($MgBr_2 \cdot Et_2O$) (26.0 mmol) under nitrogen (Note 1). Anhydrous ether, 350 mL, (Note 2) is added with a syringe, and the mixture is stirred at 25°C for a few minutes to dissolve the solid. Using an air-tight syringe, 11.2 mL of a 3.0 M solution of methylmagnesium bromide in ether (34 mmol, (Note 3)) is added to the slightly turbid solution at 25°C over a period of a few minutes. N,N-Diisopropylamine, 4.46 mL (34 mmol, (Note 4)) is added over 5 min, and the mixture is stirred for 16–18 hr, during which time a fine white precipitate forms (Note 5). The mixture is cooled to 0°

C, and a solution of 5.28 g of 2-methyl-1-tetralone (33 mmol, (Note 6)) in 20 mL of anhydrous ether is added with a cannula over a 10-min period. The mixture becomes a bright yellow solution during the addition, and after 45 min of additional stirring, it becomes pale yellow.

B. *2-(1-Hydroxycyclopropyl)-2-methyl-1-tetralone*. Simultaneously with the above operations, a separate 2-L, three-necked, round-bottomed flask is equipped with a mechanical stirrer, reflux condenser, nitrogen inlet, and a septum, and the flask is placed under a nitrogen atmosphere. Anhydrous ether, 600 mL, and 20 mL of a 3.0 M solution of methylmagnesium bromide in ether (60 mmol, (Note 3)) are added to the flask with a cannula and a syringe, respectively, and the solution is cooled to 0°C. A solution of 6.12 g of cyclopropanone ethyl hemiketal[2] (60.0 mmol, (Note 7)) in 20 mL of anhydrous ether is added with vigorous stirring over several minutes with a cannula. During this addition, gas evolution is observed, and a fine white precipitate forms. After the mixture is stirred for 15 min, the solution of the enolate of 2-methyl-1-tetralone is added using a wide gauge cannula (ca. 1 mm id) over several minutes. The resulting turbid, light yellow solution is heated at reflux for 4 hr. The resulting clear, yellow solution is cooled to 25°C and diluted with 200 mL of ether. The organic solution is washed with saturated aqueous ammonium chloride (3 × 200 mL) and saturated aqueous sodium chloride (200 mL) and dried over anhydrous magnesium sulfate. The drying agent is removed by filtration and the filtrate is concentrated by rotary evaporation under reduced pressure to give 7.92 g of crude 2-(1-hydroxycyclopropyl)-2-methyl-1-tetralone (Note 8) as a clear yellow oil that is used in the next step without further purification.

C. *(3aβ,9bβ)-1,2,3a,4,5,9b-Hexahydro-9b-hydroxy-3a-methyl-3H-benz[e]inden-3-one*.[3] The yellow oil from Part B is dissolved in 100 mL of anhydrous ether in a 100-mL round-bottomed flask at 25°C under nitrogen. Into a separate 250-mL flask containing a magnetic stirring bar are placed 4.0 g of powdered sodium hydride (166 mmol, (Note 9)), and 100 mL of anhydrous ether at 25°C under nitrogen. The solution of the yellow oil is added with stirring over a period of a few minutes using a cannula. The mixture is stirred at 25°C for 3 hr, during which time it becomes yellow-orange. The reaction is quenched by adding 100 mL of ice-cold saturated aqueous ammonium chloride and 100 mL of ether. The organic layer is washed with saturated aqueous ammonium chloride (3 × 100 mL) and saturated aqueous sodium chloride (100 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation under reduced pressure. The crude product is obtained as 5.8 g of yellow-orange crystals. The solid is dissolved in about 150 mL of warm ether, and 100 mL of hexanes is added. The mixture is concentrated to ca. 100 mL in a heating bath (or on a steam bath), and the resulting cloudy solution is cooled slowly to 0°C. An initial crop of 4.73 g (67%) of pale yellow crystals is obtained and the mother liquor is decanted from the solid and concentrated by rotary evaporation under reduced pressure to ca. 5 mL to give 0.39 g (5%) of pale yellow crystals as a second crop. The mother liquor may then be concentrated and the residue purified by flash chromatography[4] on silica

gel using 1:1 ether/hexane to give 0.29 g (4%) of additional product (R_f = 0.33) as yellow crystals after washing with warm 1:1 ether/hexane. The total combined yield of (3aβ,9bβ)-1,2,3a,4,5,9b-hexahydro-9b-hydroxy-3a-methyl-3H-benz[e]inden-3-one is 5.41 g (76%) (Note 10).

2. Notes

1. The $MgBr_2 \cdot Et_2O$ was obtained from Aldrich Chemical Company, Inc., as a white solid in the form of a powder mixed with lumps. The solid was transferred to the 250-mL, round-bottomed flask in a nitrogen-filled glove box and carefully crushed with a glass stirring rod until the solid was a uniform powder. The flask was then equipped with a septum, taken out of the glove box, and attached to a standard nitrogen/vacuum double manifold system to maintain an inert, dry atmosphere of prepurified nitrogen in the flask throughout the remainder of the reaction sequence.
2. Anhydrous diethyl ether and anhydrous tetrahydrofuran (THF) were obtained from Fisher Scientific Company. They were redistilled under nitrogen from dark blue or purple solutions of sodium benzophenone ketyl immediately prior to use. All transfers of these and other anhydrous materials were performed with syringes or stainless steel cannulas while carefully maintaining a nitrogen atmosphere.
3. Methylmagnesium bromide was purchased from Aldrich Chemical Company, Inc., as a solution in ether, and the solution was used as obtained without titration.
4. N,N-Diisopropylamine was purchased from Aldrich Chemical Company, Inc., and distilled under nitrogen from calcium hydride prior to use.
5. The submitters observed the fine white precipitate after 12 hr of stirring.
6. 2-Methyl-1-tetralone was purchased from Aldrich Chemical Company, Inc., and used without further purification.
7. Cyclopropanone ethyl hemiketal is contaminated with 8–9% of the cyclopropanone methyl hemiketal as a result of exchange with the solvent.[2] The calculated number of mmoles of total cyclopropanone hemiketal is based upon this composition.
8. ^{1}H NMR analysis of the crude product indicated greater than 90% conversion of the starting 2-methyl-1-tetralone to 2-(1-hydroxycyclopropyl)-2-methyl-1-tetralone: IR ($CHCl_3$) cm^{-1}: 3485 (O-H), 3067 (aromatic C-H), 2972 (aliphatic C-H), 1670 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ:0.49–0.72 (m, 4 H, cyclopropyl CH_2CH_2), 1.20 (s, 3 H, CH_3), 1.61–1.71 (dt, 1 H, J = 13.4, 4.5, CHH), 2.03–2.15 (m, 1 H, CHH), 2.88–3.04 (m, 2 H, benzylic CH_2), 3.68 (s, 1 H, OH), 7.15–7.96 (m, 4 H, aromatic CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 9.0, 10.4 (cyclopropyl CH_2CH_2), 18.2 (CH_3), 25.5 (CH_2), 31.0 (benzylic CH_2), 48.0 (CC=O), 59.3 (cyclopropyl COH), 126.7, 127.8, 128.7, 131.7 (aromatic CH), 133.6, 143.4 (ipso aromatic C), 204.0 (C=O).
9. Sodium hydride was obtained as a powder of 95% purity grade from Aldrich

Chemical Company, Inc. A nitrogen-filled glove box was used to weigh the reagent and transfer it into the reaction flask.

10. Yields of the product ranged from 67 to 81% over a series of several runs. For (3aβ,9bβ)-1,2,3a,4,5,9b-hexahydro-9b-hydroxy-3a-methyl-3H-benz[e]inden-3-one, mp 117–118°C; IR ($CHCl_3$) cm^{-1}: 3466 (O-H), 3066, 3070 (aromatic C-H), 2976 (aliphatic C-H), 1736 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.14 (s, 3 H, CH_3), 1.58–1.67 (m, 1 H), 1.80 (s, 1 H, OH), 1.87–1.99 (m, 1 H), 2.20–2.41 (m, 3 H), 2.48–2.61 (m, 1 H), 2.66–2.76 (m, 1 H), 2.84–2.97 (m, 1 H), 7.08–7.68 (m, 4 H, aromatic CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.5 (CH_3), 25.0 (CH_2), 29.1 (CH_2COH), 34.9 ($CH_2C{=}O$), 36.1 (benzylic CH_2), 52.5 (CCH_3), 79.8 (benzylic COH), 126.6, 126.9, 127.5, 128.5 (aromatic CH), 134.6, 140.5 (ipso aromatic C), 204.5 (C=O); CIMS, m/e (rel intensity) 217 (10%, MH^+), 199 (100%, MH^+ –18); Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 78.00; H, 7.60.

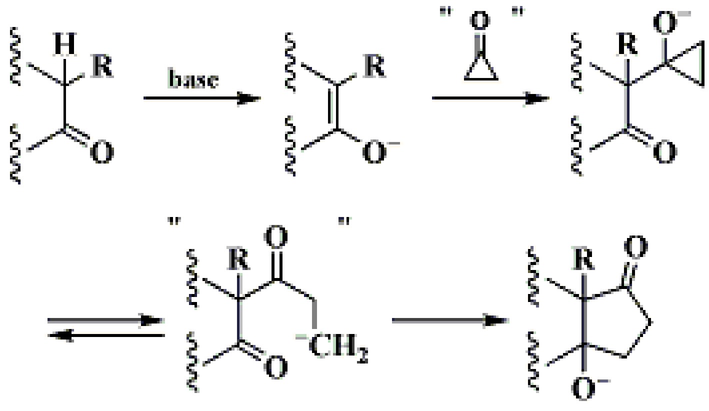
Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

A large number of methods have been developed for the construction of five-membered carbocyclic systems. These methods are too numerous to review here, but a number of key references are cited.[5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21]

The method that is used in the present preparation is based upon the *formal concept* of employing cyclopropanone in an aldol condensation with an enolate of another ketone. The resulting aldolate exhibits characteristics of a "homoenolate" and may undergo a second carbonyl addition reaction to form a five-membered ring as suggested in the following generalized pathway:

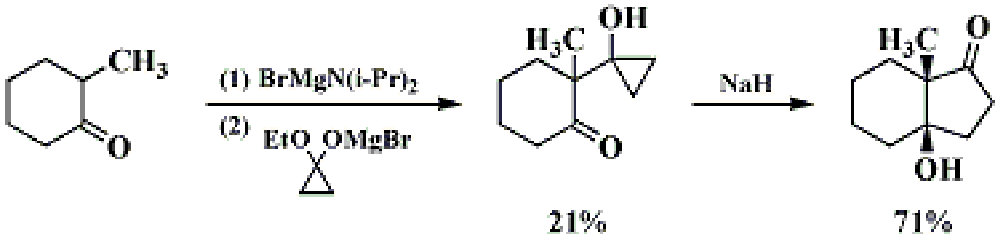


The homoenolate is not necessarily an intermediate in this pathway, but rather, it is shown only to illustrate the basic concept.

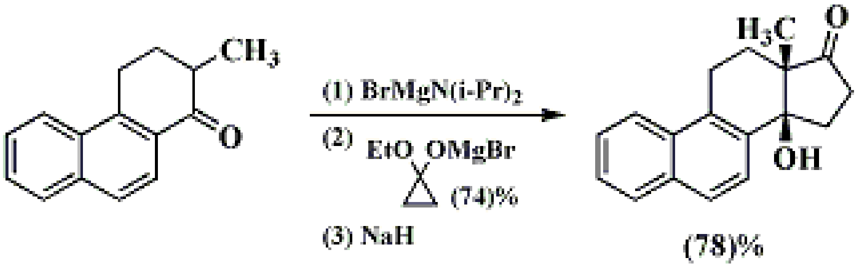
Cyclopropanone itself is a very unstable compound that has been isolated only at low

temperature. Its chemistry has been studied thoroughly during the past several years.[22,23,24,25,26,27] Various forms of homoenolates have also been investigated, and their applications in synthesis are being actively developed.[28,29,30,31,32,33,34,35,36,37,38,39,40,41,42] The combination of cyclopropanone and homoenolate chemistry employed here is most closely related to studies of Narasimhan[43,44] and follows from a series of studies in the laboratory of the submitters.[3,45,46,47,48,49] Whether free cyclopropanone or the homoenolate form of the aldol adduct are produced as actual species in the above pathway is uncertain, but at least the formal concept of their hypothetical intermediacy and expected reactivity patterns have proven useful in the design of the annulation method employed in the present preparation. The cyclopropanone hemiketal used in this work could conceivably undergo ethoxide elimination to produce cyclopropanone in situ which would then serve as a very reactive acceptor for nucleophilic addition,[2,22,23,24,25,26,27,50] but other mechanistic pathways may also be consistent with the observed reaction sequence.

An attractive feature of this procedure is the directness with which the annulation of 3-hydroxycyclopentanone systems onto preexisting ketone skeletons can be accomplished to give usefully functionalized products. However, this method does have important limitations in its scope. The most common difficulty is that the "cyclopropanone" condensation with a wide range of ketone enolates often occurs in only low to modest yields. A two-fold excess of the cyclopropanone hemiketal is therefore used to provide at least some improvement in the yields of this step. In contrast, the subsequent "homoenolate" cyclization generally occurs in quite acceptable yields. A simpler representative example that illustrates the contrasting yields in the two steps is the following:[46]



On the other hand, the parent, unsubstituted cyclohexanone enters into an apparently much more complex reaction pathway leading to the formation of a tricyclic, cycloheptanone-containing product.[45] Also, cycloheptanones as starting materials give annulation products that undergo a subsequent retro-aldol/re-aldol sequence to give rearranged hydrazulenones as the final isolated products. In fact, the best cases of the present cyclopentanone annulation sequence are limited to benzo-fused cyclohexanones bearing an additional α-alkyl substituent. In addition to the preparation described here, another important example is the following (yields are not optimized as in the present preparation):[46]



Although the limitations in the cases that provide good yields may appear to be very restrictive, this last example is suggestive of the potential applications of this procedure. Rather obvious possibilities that follow from this case include derivatives of the equilinin steroidal hormone system,[51] and of the steroidal cardiotonic agents, e. g., the cardenolides, digitoxigenin, bufadienolides, etc.[52]

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52. See "Natural Products Chemistry", Nakanishi, K.; Goto, T.; Ito, S.; Natori, S.; Nozoe, S., Eds.; Academic Press: New York, 1974; Vol. 1, pp 462–476.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium benzophenone ketyl

magnesium bromide diethyl etherate

ether, diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

magnesium (7439-95-4)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

Cyclopentanone (120-92-3)

magnesium sulfate (7487-88-9)

methylmagnesium bromide (75-16-1)

Tetrahydrofuran (109-99-9)

sodium hydride (7646-69-7)

hexane (110-54-3)

calcium hydride (7789-78-8)

N,N-Diisopropylamine (108-18-9)

CYCLOPROPANONE (5009-27-8)

cyclopropanone ethyl hemiketal (13837-45-1)

cyclopropanone methyl hemiketal

cyclopropanone hemiketal

2-methyl-1-tetralone (1590-08-5)

2-(1-Hydroxycyclopropyl)-2-methyl-1-tetralone

(3aβ,9bβ)-1,2,3a,4,5,9b-hexahydro-9b-hydroxy-3a-methyl-3H-benz[e]inden-3-one

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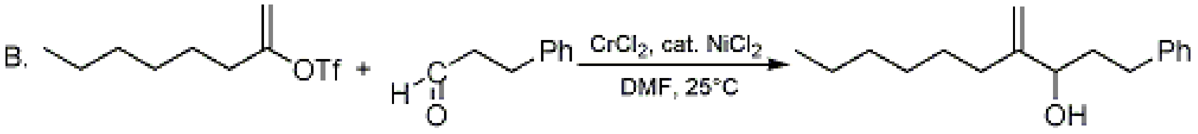
Organic Syntheses, CV 9, 472

PREPARATION AND REACTIONS OF ALKENYLCHROMIUM REAGENTS: 2-HEXYL-5-PHENYL-1-PENTEN-3-OL



Submitted by Kazuhiko Takai[1], Koichi Sakogawa, Yasutaka Kataoka, Koichiro Oshima, and Kiitiro Utimoto[2].
Checked by Tadahiro Takemoto and Larry E. Overman.

1. Procedure

A. *1-Hexylethenyl triflate* (Note 1). A dry, 300-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, nitrogen inlet, rubber septum, and a 100-mL, graduated, pressure-equalizing addition funnel that is sealed with a rubber septum. The flask is charged with 1-octyne (11 g, 0.10 mol, (Note 2)) and dry hexane (100 mL, (Note 3)). The contents of the flask are cooled to −30°C (dry ice-methanol). The addition funnel is charged with neat trifluoromethanesulfonic acid (TfOH, 4.9 mL, 55 mmol, (Note 4)) which is then added dropwise at −30°C to the stirring solution over a period of 30 min. The addition funnel is rinsed with dry hexane (10 mL). The dark brown solution is warmed to 0°C and stirred at 0°C for 10 min. Saturated sodium bicarbonate ($NaHCO_3$) solution (20 mL) is introduced at 0°C to the reaction mixture. The organic layer is separated, washed with additional $NaHCO_3$ solution (2 × 50 mL), and then dried over potassium carbonate. The solvent is removed with a rotary evaporator. The crude product is distilled using a short-path still to give 9.6–10.4 g (67–73%) of 1-hexylethenyl triflate (Note 5), bp 97–98°C at 19 mm.

B. *2-Hexyl-5-phenyl-1-penten-3-ol*. A dry, 500-mL, four-necked, round-bottomed flask is equipped with a mechanical stirring bar, nitrogen inlet, rubber septum, and a 100-mL, graduated, pressure-equalizing addition funnel that is sealed with a rubber septum. In the flask are placed anhydrous chromium(II) chloride ($CrCl_2$) (10 g, 80 mmol, (Note 6)) and anhydrous nickel(II) chloride ($NiCl_2$) (52 mg, 0.40 mmol, (Note 7)) under an argon atmosphere. The flask is cooled to 0°C and dry, oxygen-free N,N-dimethylformamide (DMF, 250 mL, (Note 8)) is added to the flask with stirring. The salts are dissolved in a slightly exothermic process. The mixture is stirred at 0°C for 10 min. To the $CrCl_2$-$NiCl_2$ reagent at 25°C is added a solution of 3-phenylpropanal (2.7 g, 20 mmol, (Note 9)) in DMF (20 mL) by syringe. A solution of 1-hexylethenyl triflate (10 g, 40 mmol, (Note 5)) in DMF (60 mL) is added at 25°C through the addition funnel over a period of 5 min. The entire mixture is stirred at 25°C for 30 min. The reaction mixture is diluted with ether (200 mL), poured into ice-cooled water (400 mL), and extracted with ether (3 × 200 mL) repeatedly. The combined extracts are washed with aqueous sodium chloride solution (150 mL), dried over anhydrous sodium sulfate, and concentrated with a rotary evaporator (25°C, water bath). The crude product is distilled using a short-path still to give 4.0–4.6 g (82–94%) of 2-hexyl-5-phenyl-1-penten-3-ol, bp 109–111°C at 0.11 mm (Note 10) and (Note 11).

2. Notes

1. This procedure was reported by Stang and Summerville.[3]
2. 1-Octyne was distilled, bp 125–126°C.
3. Hexane was freshly distilled from sodium or calcium hydride.
4. Trifluoromethanesulfonic acid was distilled, bp 72–73°C at 20 mm.
5. The distilled triflate contained 3–9% of isomers, that were confirmed by capillary GLPC (Silicone OV-17, 50 m, 105°C, 1-hexylethenyl triflate: t_R = 11.1 min; isomers: t_R = 11.4 and 12.4 min) and ^{1}H NMR analysis. Because the isomers did not interfere with the second reaction, the triflate was employed without further purification. Spectral data of the distilled triflate was as follows: IR (neat) cm^{-1}: 2954, 2930, 2858, 1671, 1419, 1250, 1213, 1141, 943, 899, 703, 610; ^{1}H NMR ($CDCl_3$) δ: 0.89 (t, 3 H, J = 6.9), 1.2–1.4 (m, 6 H), 1.5–1.6 (m, 2 H), 2.34 (t, 2 H, J = 7.5), 4.93 (dt, 1 H, J = 3.5, 1.0), 5.08 (d, 1 H, J = 3.5), ^{1}H NMR peaks of the impurities appeared at δ 2.05–2.20 and 5.18–5.55; ^{13}C NMR ($CDCl_3$) δ: 13.9, 22.4, 25.9, 28.3, 31.3, 33.8, 103.9, 118.5 (q, J = 320, CF_3), 157.1.
6. Chromium(II) chloride (95% purity) was purchased from Aldrich Chemical Company, Inc., and used without further purification. The salt is easily oxidized and should be handled under an inert atmosphere.
7. Anhydrous nickel(II) chloride was purchased from Nacalai Tesque Co. and used without further purification. The salt is hygroscopic and should be handled under an inert atmosphere.
8. N,N-Dimethylformamide was refluxed in the presence of calcium sulfate under reduced pressure and distilled with nitrogen bubbling from a capillary, bp 76°C at 39 mm.
9. 3-Phenylpropanal was freshly distilled, bp 97–98°C at 12 mm.
10. The pot residue can be bulb-to-bulb distilled to give an additional 0.5–1 g of product to bring the combined yields to 94–95%. 2-Hexyl-5-phenyl-1-penten-3-ol has the following properties: R_f = 0.29 (ethyl acetate/hexane = 1/10); IR (neat) cm^{-1}: 3340, 3024, 2924, 2854, 1647, 1600, 1497, 1456, 1017, 900, 741, 697; ^{1}H NMR ($CDCl_3$) δ: 0.88 (t, 3 H, J = 6.8), 1.2–1.4 (m, 8 H), 1.7–2.2 (m, 5 H), 2.62 (ddd, 1 H, J = 6.6, 9.6, 13.9), 2.74 (ddd, 1 H, J = 6.1, 9.6, 13.9), 4.10 (dd, 1 H, J = 5.1, 7.5), 4.87 (d, 1 H, J = 1.5), 5.04 (s 1 H), 7.1–7.4 (m, 5 H). ^{13}C NMR ($CDCl_3$) δ: 14.1, 22.6, 27.9, 29.2, 31.4, 31.7, 31.9, 37.0, 74.7, 109.3, 125.7, 128.3, 128.4, 142.0, 152.0.
11. The following ratio of reactants, aldehyde/alkenyl triflate/$CrCl_2$/$NiCl_2$ = 1/2/4/0.02 gave the best results. When the ratio of reagents was reduced to aldehyde/alkenyl triflate/$CrCl_2$/$NiCl_2$ = 1/1/2/0.01, the reaction proceeded slowly. When the reaction was carried out at 25°C for 2 hr, 65% of the 2-hexyl-5-phenyl-1-penten-3-ol was isolated and 14% (GLPC analysis) of the 3-phenylpropanal remained.

Waste Disposal Information

Compounds of chromium and nickel are toxic. The aqueous layers from Step B and any other waste materials should be disposed of properly (see "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995).

3. Discussion

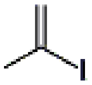
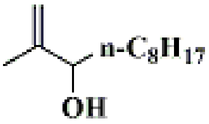
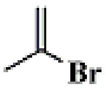
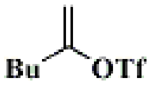
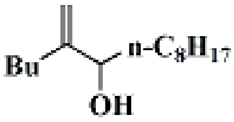
In the synthesis of a complex molecule, it is sometimes necessary to prepare an organometallic reagent under mild conditions. Because of the strong basicity and nucleophilicity of alkenyllithium and alkenylmagnesium compounds, only a few electrophilic functional groups are stable under the reaction conditions.[4] In contrast, the alkenylchromium reagents described here react with aldehydes

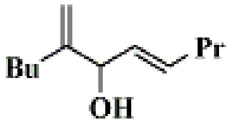
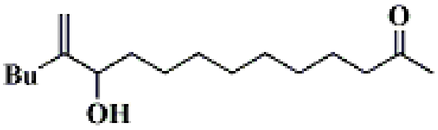
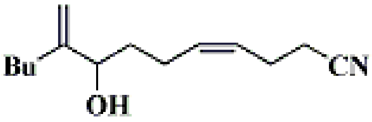
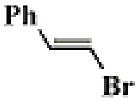
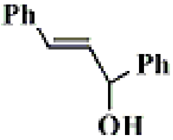
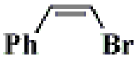
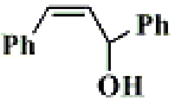
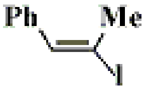
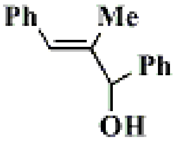
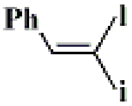
to give adducts in good to excellent yields in the presence of ketones, esters, amides, acetals, ethers, silyl ethers, and nitriles.[5,6,7] The method is especially effective for highly oxygenated molecules.[6] Intramolecular cyclization of iodo aldehydes leading to 13-membered lactones has also been reported.[8]

Addition of a catalytic amount of $NiCl_2$ to $CrCl_2$ is essential for the formation of alkenylchromium reagents.[5,6,7] However, a substantial amount of 1,3-diene, the coupling product of the alkenyl iodide, is produced if a higher content of $NiCl_2$ is employed.[9,10]

Reduction of alkenyl iodides and bromides to alkenylchromium reagents with $CrCl_2$ proceeds smoothly under the same conditions.[5,6,7] Several examples of the Grignard-type addition of alkenyl halides and triflates to aldehydes with the combination of $CrCl_2$ and $NiCl_2$ are shown in the Table. Iodoalkenes are more reactive than bromoalkenes (compare run 1 and 2). In the case of an α,β-unsaturated aldehyde, the 1,2-addition product is the main product (run 4). The alkenylchromium reagent adds to an aldehyde group selectively (runs 5–7), as do allyl-[11] and alkynylchromium reagents.[12] Steric interaction of substituents at a position cis to halogen causes cis-trans isomerization in some cases.[10] For example, while the reaction of (E)- and (Z)-2-bromostyrene and benzaldehyde proceeded stereospecifically (runs 8 and 9), both (E)- and (Z)-2-iodo-1-phenyl-1-propene reacted with benzaldehyde to give (E)-1,3-diphenyl-2-methyl-2-propen-1-ol as the sole product (runs 10 and 11). The regiochemistry of double bonds is maintained during the coupling reaction. The $CrCl_2$-$NiCl_2$ system is also effective for the addition of iodobenzene to an aldehyde (run 12).[7]

TABLE
GRIGNARD-TYPE COUPLING BETWEEN ALKENYL HALIDES (OR TRIFLATES) AND ALDEHYDES, MEDIATED BY THE $CrCl_2$-$NiCl_2$ SYSTEM[a]

Run	Alkenyl Halide (or Triflate)	Aldehyde	Time hr	Product	Yield %
1		n-C_8H_{17}CHO	0.25		100
2		n-C_8H_{17}CHO	3		62
3		n-C_8H_{17}CHO	3		81

4		(E)-PrCH=CHO	4		64
5			1		87
6			2		78
7		PhCOMe	6	(recovery of PhCOMe, 87%)	
8		PhCHO	1		82
9		PhCHO	1		78
10		PhCHO	3		91[d]
11		PhCHO	3		90[d]
12	PhI	n-C_8H_{17}CHO	3		83

[a]A mixture of an alkenyl halide (or alkenyl triflate, 2.0 mmol) and an aldehyde (1.0 mmol) was treated at 25°C with $CrCl_2$ (4.0 mmol) and $NiCl_2$ (0.02 mmol) in DMF. [b]Products are isolated by column chromatography on silica gel. [c]The reaction mixture was heated at 60°C. [d]The absence of (Z)-isomer was confirmed by GLPC (Silicone SE-30) and NMR analysis.

References and Notes

1. Department of Applied Chemistry, Faculty of Engineering, Okayama University, Tsushima, Okayama 700, Japan.
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

oxygen-free N,N-dimethylformamide

$CrCl_2$-$NiCl_2$

$NiCl_2$

$CrCl_2$

(E)- and (Z)-2-bromostyrene

(E)- and (Z)-2-iodo-1-phenyl-1-propene

n-C_8H_{17}CHO

Phl

potassium carbonate (584-08-7)

ethyl acetate (141-78-6)

ether (60-29-7)

sodium bicarbonate, $NaHCO_3$ (144-55-8)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

benzaldehyde, PhCHO (100-52-7)

calcium sulfate (7778-18-9)

nickel(0) (7440-02-0)

sodium (13966-32-0)

Iodobenzene (591-50-4)

N,N-dimethylformamide, DMF (68-12-2)

hexane (110-54-3)

chromium(II) chloride (10049-05-5)

calcium hydride (7789-78-8)

nickel(II) chloride (7718-54-9)

argon (7440-37-1)

1-OCTYNE (629-05-0)

triflate

trifluoromethanesulfonic acid (1493-13-6)

3-phenylpropanal (104-53-0)

2-Hexyl-5-phenyl-1-penten-3-ol (187821-45-0)

1-Hexylethenyl triflate (98747-02-5)

(E)-1,3-diphenyl-2-methyl-2-propen-1-ol

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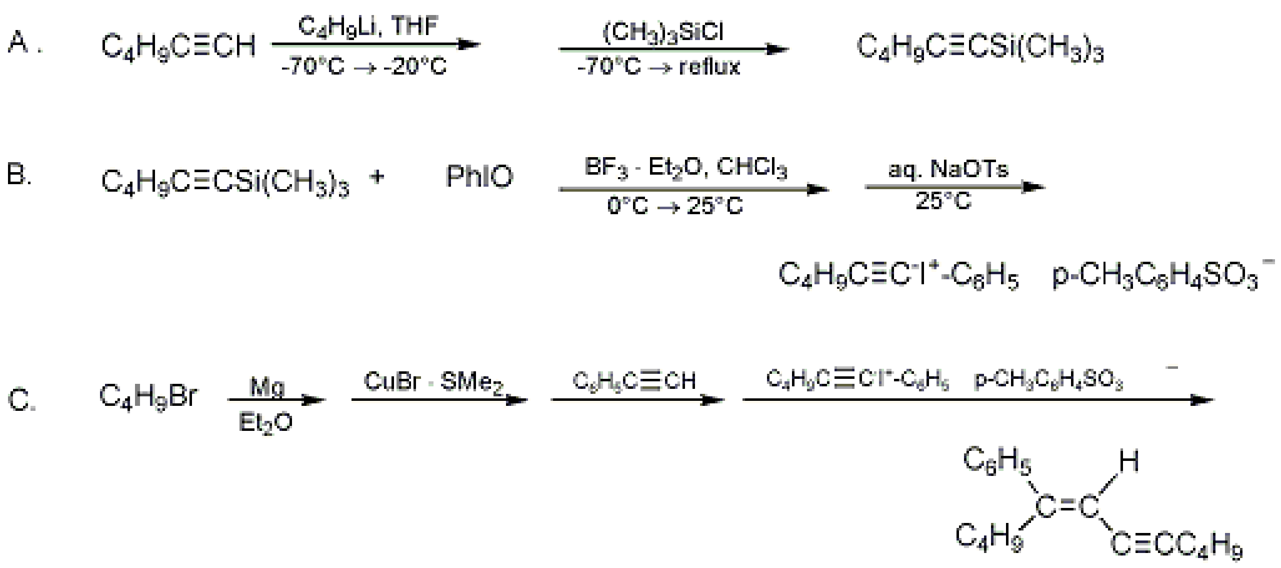
ALKYNYL(PHENYL)IODONIUM TOSYLATES: PREPARATION AND STEREOSPECIFIC COUPLING WITH VINYLCOPPER REAGENTS. FORMATION OF CONJUGATED ENYNES. 1-HEXYNYL(PHENYL) IODONIUM TOSYLATE AND (E)-5-PHENYLDODEC-5-EN-7-YNE

[Iodine, 1-hexynyl(4-methylbenzenesulfonato-O)phenyl- and Benzene, (1-butyl-1-octen-3-ynyl)-, (E)-]



Submitted by Peter J. Stang and Tsugio Kitamura[1].
Checked by Kazuaki Ishihara and Hisashi Yamamoto.

1. Procedure

A. *1-Trimethylsilyl-1-hexyne* (Note 1). A dry, 500-mL, three-necked, round-bottomed flask (equipped with a magnetic stirrer system) is fitted with one 50-mL and one 125-mL pressure-equalizing addition funnel and a reflux condenser. The top of the condenser is mounted with a T-piece connected at one end to an argon outlet and at the other end to an oil bubbler. The apparatus is purged with dry argon and the reaction is carried out under an argon atmosphere. The flask is charged with 16.4 g (0.20 mol) of 1-hexyne (Note 2) and 200 mL of tetrahydrofuran (THF, (Note 3)), and the mixture is cooled to approximately −70°C with a dry ice-2-propanol slush bath. The 125-mL dropping funnel is filled with 80 mL (0.20 mol) of 1.63 M butyllithium in hexane (Note 4) which is added over a period of 30 min to the stirred, cold (−70°C) 1-hexyne in THF. After addition is complete the flask is gradually warmed over a 3-hr period to −20°C, then recooled to −70°C with the dry ice-2-propanol slush bath. Chlorotrimethylsilane (Note 5), 25.3 mL (0.20 mol), is placed in the 50-mL dropping funnel and added over a period of 15 min to the stirred, cooled reaction mixture. After the addition is complete the slush bath is removed and the mixture is first stirred at room temperature for 16 hr, then heated under reflux for 1 hr (Note 6). The mixture is cooled to 0°C with an ice-water

bath and then 50 mL of water is carefully added. The entire reaction mixture is transferred to a 1-L separatory funnel and extracted with 200 mL of pentane. The organic phase is separated, washed successively with three 100-mL portions of water followed by 100 mL of saturated sodium chloride solution and then dried over anhydrous magnesium sulfate. After filtration the solvent is distilled off through a 15-cm Vigreux column. The pale yellow residue is transferred to a 100-mL round-bottomed flask and distilled through a 15-cm Vigreux column to give 25.0–27.5 g (81–89%) of 1-trimethylsilyl-1-hexyne as a clear, colorless liquid, bp 149–156°C, that can be used as is in the subsequent step.

B. *1-Hexynyl(phenyl)iodonium tosylate*. The center neck of a dry, 500-mL, three-necked, round-bottomed flask (equipped with a magnetic stirrer system) is fitted with a 50-mL pressure-equalizing addition funnel One side neck is fitted with a glass stopper and the other with a gas inlet to which is attached a T-piece connected to an argon supply and an oil bubbler. After the flask is purged with dry argon, it is charged with 22.0 g (0.10 mol) of finely ground iodosobenzene (Note 7), 200 mL of chloroform (Note 8) and 17.0 g (0.11 mol) of 1-trimethylsilyl-1-hexyne, and the entire mixture is cooled to 0°C with an ice-water bath. Boron trifluoride etherate (Note 9), 13.0 mL (0.11 mol), is added dropwise over a period of about 5 min to the stirred, cooled reaction mixture (Note 10). After the addition is complete the mixture is stirred at room temperature for about 16 hr (Note 11).

To a 1-L beaker are added 76.1 g (0.4 mol) of p-toluenesulfonic acid monohydrate (Note 12) and 400 mL of water. To this solution is carefully added 21.2 g (0.2 mol) of anhydrous sodium carbonate and then the entire solution is purged with argon for about 15 min to replace all air. This solution of sodium toluenesulfonate (NaOTs), along with the contents of the reaction flask, are placed in a 1-L separatory funnel and the mixture is vigorously shaken for a period of about 10 min (Note 13). The organic phase is separated and the aqueous phase is extracted with 50 mL of methylene chloride. The combined organic phases are dried over anhydrous magnesium sulfate, filtered and the solvent evaporated on a rotary evaporator. To the residual yellow-brown oil is added a mixture of 75 mL of diethyl ether and 75 mL of pentane resulting, after stirring, in fine white crystals. The powdery white crystals are filtered, washed with two 50-mL portions of a diethyl ether/pentane (1:1 v/v) mixture, air dried, then dried under reduced pressure. The resulting white crystalline solid, 27–34 g (60–75%), mp 77–80°C, (dec) is essentially pure and ready for most uses (Note 14).

C. *(E)-5-Phenyldodec-5-en-7-yne*. *CAUTION: Dimethyl sulfide is a volatile, very smelly irritant. This reaction must be conducted in a hood!*

A dry, 100-mL, three-necked, round-bottomed flask (equipped with a magnetic stirrer system) is fitted with a 25-cm Liebig condenser, a 25-mL pressure-equalizing dropping funnel topped off with a gas-inlet, and a glass stopper. After the flask is purged with argon, it is charged with 0.90 g (37.5 mmol) of magnesium turnings and 15 mL of anhydrous ether. To the dropping funnel is added a solution of 4.0 mL (37.5 mmol) of 1-bromobutane (Note 15) in 20 mL of anhydrous ether. This solution is added to the reaction flask at such a rate (approximately 1 hr) that after the Grignard reaction is initiated a gentle reflux is maintained. After the addition is complete the mixture is stirred for an additional 30 min.

The center neck of a dry, 250-mL, three-necked, round-bottomed flask (equipped with a magnetic stirrer system) is fitted with a 50-mL pressure-equalizing dropping funnel topped off with a rubber septum and an argon inlet. The side necks are fitted with a glass stopper and a

rubber septum, respectively. The apparatus is purged with argon and to the flask are added 7.7 g (37.5 mmol) of copper(I) bromide-dimethyl sulfide complex (Note 16), 60 mL of anhydrous ether, and 38 mL of dimethyl sulfide (Note 17). The mixture is cooled to −70°C with a dry ice-2-propanol slush bath. The previously prepared butyl Grignard reagent is transferred to the addition funnel via a double-ended needle with a positive argon pressure. The Grignard reagent is added dropwise, over a 30-min period, to the cooled reaction mixture (Note 18). After the addition is complete the reaction is maintained between −40°C to −50°C for 2 hr, then recooled to −70°C. Phenylacetylene (Note 19), 4.1 mL (37.1 mmol), is slowly added via a syringe through the rubber septum. After addition, the reaction mixture is maintained at −30°C to −25°C for 2 hr (Note 20), then recooled to −70°C and 6.8 g (15 mmol) of the previously prepared iodonium tosylate is added, in the solid form, through the side neck, over a positive argon pressure. The stirring reaction mixture is gradually warmed to room temperature and stirred for an additional 12 hr at room temperature. The mixture is poured into a 1-L beaker containing 200 mL of saturated ammonium chloride solution and stirred vigorously. The undissolved materials are filtered off and the organic phase is separated. The aqueous phase is extracted with three 50-mL portions of ether. The combined organic phase are washed with 100 mL of water followed by 100 mL of saturated sodium chloride solution, and dried over anhydrous magnesium sulfate and filtered. The solvent is removed on a rotary evaporator in the hood and the residual oil chromatographed (4 × 50 cm column) on alumina (600 g, (Note 21)). The column is successively eluted with 1 L of hexane, 750 mL of 10% dichloromethane-hexane, 500 mL of 20% dichloromethane-hexane and 250 mL of 30% dichloromethane-hexane. The fractions are analyzed by TLC on silica gel (Note 22) using 10% dichloromethane-hexane as eluent and the product-containing fractions (Note 23) are combined. The solvent is evaporated on a rotary evaporator and the residual yellow-brown oil (5.8 g) (Note 24) is distilled under reduced pressure, bp 135–143°C (3–4 mm), to give 2.3 g of crude product. Redistillation under reduced pressure affords 1.9–2.1 g (53–58%) of product as a pale yellow liquid, bp 143–144°C (1 mm) (Note 25).

2. Notes

1. Many 1-trimethylsilylalkynes are commercially available from Aldrich, Petrarch and other vendors of silicon compounds. Alternatively they are readily made from 1-alkynes and chlorotrimethylsilane as described in part A.
2. 1-Hexyne was obtained from Tokyo Kasei Kogyo Co., Ltd. or Aldrich Chemical Company, Inc. and used without purification.
3. Tetrahydrofuran was obtained from Wako Pure Chemical Industries, Ltd., and distilled from potassium benzophenone ketyl immediately before use.
4. Butyllithium in hexane (2.6 M) was obtained from Mitsuwas Pure Chemical or Aldrich Chemical Company, Inc. and a freshly opened sample was used without assay or purification.
5. Chlorotrimethylsilane was obtained from Shin-ETSU Silicon Chemicals or PCR Research Chemicals, Inc., and distilled prior to use.
6. During this period copious amounts of a white precipitate (LiCl) is formed.
7. Iodosobenzene was purchased by the checkers from Tokyo Kasei Kogyo Co., Ltd. and dried under reduced pressure prior to use.
8. Chloroform was distilled from phosphorus oxide (P_2O_5) and passed through an alumina column prior to use.
9. Boron trifluoride etherate (98%) was obtained from Wako Pure Chemical Industries,

Ltd., or MC and B Manufacturing Chemists, and distilled from granular calcium hydride prior to use.
10. The pale yellow suspension turns to a deeper yellow suspension during addition.
11. Iodosobenzene is a polymer and depolymerizes as it reacts, forming a clear, yellow-light brown, homogeneous solution during the course of the reaction. It is not ready for work-up until a clear homogeneous solution is obtained.
12. p-Toluenesulfonic acid monohydrate was obtained from Wako Pure Chemical Industries, Ltd., or MC and B Manufacturing Chemists, and used without further purification.
13. Care must be taken to release periodically the pressure formed. It is advisable to chill both solutions prior to mixing and shaking.
14. The spectral properties of 1-hexynyl(phenyl)iodonium tosylate are as follows: IR (nujol) cm^{-1}: 2185 (m, C≡C), 1225 (s), 1175 (m), 1145 (vs), 1115 (m), 1025 (m), 1000 (s), 985 (m, sh), 807 (m), 730 (m), 675 (s); FAB-MS m/z 285 (n, BuC≡CIPh$^+$); ^1H NMR ($CDCl_3$) δ 0.73–0.92 (m, CH_3), 1.12–1.58 (m, CH_2CH_2), 2.30 (s, $ArCH_3$), 2.30–2.50 (m, CH_2), 6.98–7.60 (m, ArH), 7.92–8.05 (m, ArH).
15. 1-Bromobutane was obtained from Wako Pure Chemical Industries, Ltd., or Eastman Kodak Company, and distilled through a 10-cm Vigreux column prior to use.
16. Copper(I) bromide-dimethyl sulfide complex, ($CuBr{\cdot}SMe_2$), 99%, was obtained from Aldrich Chemical Company, Inc. and purified prior to use as follows: 10 g of $CuBr{\cdot}SMe_2$ was dissolved in 20 mL of dimethyl sulfide and triturated with 30 mL of pentane. The resulting white crystals were filtered, washed with three 20-mL portions of pentane and dried under reduced pressure.
17. Dimethyl sulfide, 99+%, anhydrous, was obtained from Tokyo Kasei Kogyo Co., Ltd., or Aldrich Chemical Company, Inc.
18. The white suspension turned to an orange suspension during the course of the addition.
19. Phenylacetylene was obtained from Tokyo Kasei Kogyo Co., Ltd., or Farchan Laboratories and distilled through a 15-cm Vigreux column prior to use.
20. During this period the color changed from orange through brown to black.
21. Unactivated alumina from J. T. Baker Chemical Company was used.
22. TLC silica gel $60F_{254}$ sheets were obtained from Merck & Company, Inc.
23. The desired product appears as the second spot on TLC with an R_f = 0.42–0.45 with 10% dichloromethane-hexane.
24. The major by-product is 5,8-diphenyldodeca-5,7-diene, which can be separated by distillation.
25. GC analysis of the product on a 10% UCW-982 Chromosorb W column (0.25 in × 6 ft) at 200°C showed a single isomer with a purity of 99%. The spectral properties of the product are as follows: IR (neat) cm^{-1}: 3070 (m, sh), 3050 (m), 3015 (m), 2950 (vs), 2925 (vs), 2855 (s), 2200 (w), 1595 (m), 1570 (w), 1490 (m), 1465 (s), 1442 (s), 1375 (m), 1325 (m), 847 (m), 752 (vs), 690 (vs), MS (EI) m/z: 240 M^+, 57%, 141 (100%), 105 (53%); ^1H NMR ($CDCl_3$) δ 0.81–1.00 (m, CH_3), 1.21–1.59 (m, CH_2CH_2), 2.30–2.46 (m, CH_2), 2.67–2.84 (m, CH_2), 5.74 (t, J = 2, C=CH), 7.14–7.51 (m, ArH): ^{13}C NMR (300 MHz, $CDCl_3$) δ 13.52 (CH_3), 13.81 (CH_3), 19.35 (CH_2), 21.91 (CH_2), 22.50 (CH_2), 30.50 (CH_2) 30.96 (CH_2), 31.70 (CH_2), 78.93 (C≡C), 95.47 (C≡C), 107.42 (C=CH), 125.78, 127.44, 128.24, 140.52 (aromatic), 151.88 (C=CH).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The only known alternative procedure for the preparation of alkynyl(phenyl)iodonium arylsulfonates, the latest member of the family[2] of polyvalent iodine compounds, involves the reaction of [hydroxy(tosyloxy)iodo]benzene, PhIOH·OTs, with terminal alkynes as first reported by Koser[3] and elaborated by us.[4] This procedure has a number of shortcomings. Formation of the desired alkynyliodonium salt is usually accompanied by a related vinyl species, R(TsO)C=CHIPh·OTs, that both decreases the yields and causes purification problems. Furthermore, when the alkyl substituent of the starting alkyne is small, such as CH_3, n-Pr, n-Bu, etc., this procedure gives either no product[3] or low yields[4] at best.

The present procedure, similar to that of Fujita[5] for the preparation of alkynyl(phenyl) iodonium tetrafluoroborates, RC□CIPh·BF_4, is simpler, much more general and in most cases gives significantly better yields.[6] Table I gives yields of alkynyl(phenyl)iodonium sulfonates prepared by this procedure.

TABLE I
ALKYNYL(PHENYL)IODONIUMSULFONATES

Starting Alkyne	Product	Yields (%)	M.P. (dec.) °C
CH_3C□CH	CH_3C□CIPh·OTs	62	123–125
EtC□CH	EtC□CIPh·OTs	81	108–110
n-PrC□CH	n-PrC□CIPh·OTs	89	93–95
Me_3SiC□CSiMe_3	Me_3SiC□CIPh·OTs	70	107–109
PhC□CH	PhC□CIPh·OTs	61	128–133[4]
t-BuC□CH	t-BuC□CIPh·OTs	67	118–124[4]

Alkynyl(phenyl)iodonium sulfonates are stable, microcrystalline substances that can be stored and used indefinitely with little or no decomposition. They have been employed in the formation of aryl (2-furyl)iodonium tosylates,[7] alkynyl sulfonate,[4] carboxylate[8] and phosphate[9] esters, tricoordinate vinyliodinane species,[10] and alkylidenecarbene-iodonium ylides.[11]

The stereoselective formation of conjugated enynes has been reported[12] via the coupling of vinylcopper reagents with alkynyl(phenyl)iodonium tosylates. A representative example of this process is described in part C of the present procedure. This method[12] affords stereoisomerically pure 1,1-disubstituted conjugated 1,3-enynes with a trisubstituted olefin component with complete control of olefin geometry. The simplicity of the procedure, mild reaction conditions, reasonable yields (46–94%) and total stereocontrol[12] should make this an attractive alternative and complement to the known[13,14] Pd-catalyzed olefin-alkyne couplings for the synthesis of this important class of aliphatic compounds.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

potassium benzophenone ketyl

(LiCl)

$CH_3C{\equiv}CH$

$CH_3C{\equiv}CIPh\cdot OTs$

$EtC{\equiv}CH$

n-$PrC{\equiv}CH$

n-$PrC{\equiv}CIPh\cdot OTs$

$Me_3SiC{\equiv}CSiMe_3$

$PhC{\equiv}CH$

$PhC{\equiv}CIPh\cdot OTs$

t-$BuC{\equiv}CH$

t-$BuC{\equiv}CIPh\cdot OTs$

Iodine, 1-hexynyl(4-methylbenzenesulfonato-O)phenyl-

ether, diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

chloroform (67-66-3)

magnesium turnings (7439-95-4)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

1-bromobutane (109-65-9)

Pentane (109-66-0)

methylene chloride, dichloromethane (75-09-2)

Phenylacetylene (536-74-3)

magnesium sulfate (7487-88-9)

dimethyl sulfide (75-18-3)

butyllithium (109-72-8)

Tetrahydrofuran, THF (109-99-9)

Iodosobenzene (536-80-1)

hexane (110-54-3)

1-Hexyne (693-02-7)

boron trifluoride etherate (109-63-7)

calcium hydride (7789-78-8)

argon (7440-37-1)

CHLOROTRIMETHYLSILANE (75-77-4)

phosphorus oxide (1314-56-3)

p-toluenesulfonic acid monohydrate (6192-52-5)

1-Trimethylsilyl-1-hexyne (3844-94-8)

1-Hexynyl(phenyl)iodonium tosylate (94957-42-3)

(E)-5-Phenyldodec-5-en-7-yne, Benzene, (1-butyl-1-octen-3-ynyl)-, (E)- (111525-79-2)

sodium toluenesulfonate

iodonium tosylate

5,8-diphenyldodeca-5,7-diene

copper(I) bromide-dimethyl sulfide complex (54678-23-8)

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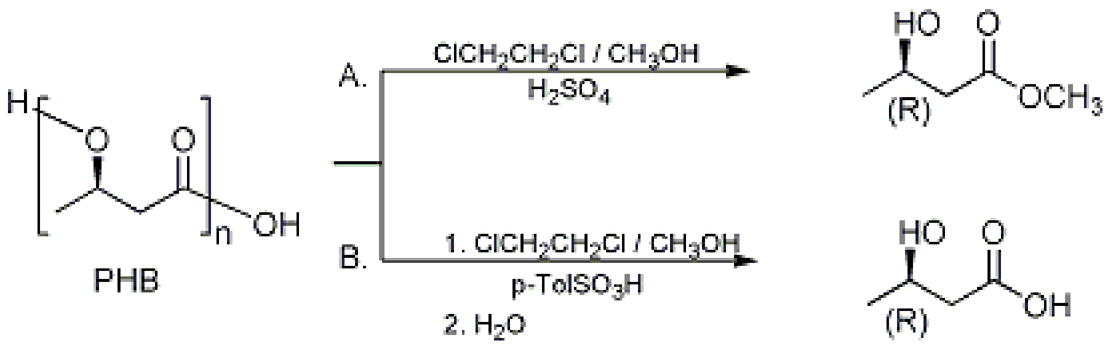
Organic Syntheses, CV 9, 483

DIRECT DEGRADATION OF THE BIOPOLYMER POLY[(R)-3-HYDROXYBUTYRIC ACID] TO (R)-3-HYDROXYBUTANOIC ACID AND ITS METHYL ESTER

[Butanoic acid, 3-hydroxy-, (R)-, homopolymer to Butanoic acid, 3-hydroxy-, (R)- and Butanoic acid, 3-hydroxy-, methyl ester, (R)-]



Submitted by Dieter Seebach, Albert K. Beck, Richard Breitschuh, and Kurt Job[1].
Checked by Eugene R. Hickey and Leo A. Paquette.

1. Procedure

A. *(R)-(–)-Methyl 3-hydroxybutanoate*. A 2-L, round-bottomed flask is charged with 50 g (0.58 mol) of poly-[(R)-3-hydroxybutyric acid] (PHB) (Note 1) and 500 mL of absolute 1,2-dichloroethane. The flask is equipped with a reflux condenser, and the mixture is heated at reflux for 1 hr. A solution of 10 mL of concd sulfuric acid in 200 mL of absolute methanol is added and the reaction mixture is heated at reflux for 3 days. During this time the mixture becomes homogeneous.

After the reaction mixture is cooled to room temperature, 100 mL of half-saturated brine is added to the reaction mixture, which is stirred for 10 min before the layers are separated. The aqueous layer is extracted three times with 200 mL each of chloroform. The combined organic layers are washed with 100 mL of brine, 100 mL of saturated sodium bicarbonate solution, and 100 mL of brine. After the solution is dried over magnesium sulfate and removed in a rotary evaporator, a residue of 59 g is isolated.

This crude product is distilled under reduced pressure to give 48 g (70%) of pure (R)-(–)-methyl 3-hydroxybutanoate (bp 61–62°/18 mm) with a specific rotation of $[\alpha]_D^{RT}$ –47.6° ($CHCl_3$, *c* 1.0) (Note 2).

B. *(R)-(–)-3-Hydroxybutanoic acid*. In a 1-L, two-necked, round-bottomed flask, fitted

with a precision-ground stirrer and a coil condenser bearing a distillation bridge, are placed 200 mL of 1,2-dichloroethane and 50 g (0.58 mol) of PHB (Note 1). The mixture is stirred and heated at 150°C until a milky solution is formed (Note 3). p-Toluenesulfonic acid monohydrate (2.5 g, 0.013 mol) is added and the solution heated an additional 30 min at 150°C. A total amount of 9.3 g (11.8 mL, 0.29 mol) of methanol is then added carefully through the condenser to the boiling solution in approx 1-mL portions (Note 4). The light brown, cloudy solution is heated at reflux (oil bath, 140°C) for another 48 hr (Note 5). The oil bath temperature is reduced to 130°C and 60 mL of water is carefully added. The resulting two-phase mixture is heated for another 4 hr (Note 6). Methanol, 1,2-dichloroethane, and approx 150 mL of water are removed by distillation through the condenser within 1–2 hr (Note 7). During the distillation nine 30-mL portions of water are added; the resulting homogeneous aqueous solution is heated at reflux for another 4 hr. During this period the temperature of the oil bath is increased to 180°C. Methanol/water (50 mL) is removed by distillation and, after the addition of 50 mL of water (Note 8), the solution is again heated at reflux for 15 hr. The reaction mixture is cooled to about 30°C, followed by the addition of 0.6 g (0.015 mol) of sodium hydroxide in 10 mL of water. Water is first removed in a rotary evaporator at a maximum temperature of 30°C, 15 mm, followed by drying at 0.1 mm (Note 9). The residue is dissolved in 250 mL of ether, the solution is dried over magnesium sulfate, filtered, concentrated in a rotary evaporator and dried at 0.1 mm. The resulting light-brown clear oil (Note 10) is distilled at 80–100°C (air bath)/10^{-3}mm by bulb to bulb distillation (Note 11). The crude product is either crystalline or a colorless oil that crystallizes upon standing at room temperature. After the crystals are crushed in a mortar, they are dried for 2 days in a desiccator over phosphorus pentoxide (P_2O_5) (Note 12), to yield 32 g (53%) of (R)-3-hydroxybutanoic acid, mp 44–46°C, $[\alpha]_D^{RT}$ −24.7° (H_2O, *c* 5.0 (Note 13), (Note 14), (Note 15).

2. Notes

1. The submitters used PHB=Poly-(R)-3-hydroxybutyric acid obtained from Marlborough Biopolymers Ltd., Rudby Hall, Hutton Rudby, Yarm, Cleveland, England, PHB homopolymer, BX GO4, technical grade powder, MBL 100/703. The checkers used PHB from Fluka Chemie AG, CH-8470 Buchs, Switzerland. The submitters report that the procedure works well on batch sizes of 200–250 g.
2. The spectroscopic properties are as follows: IR (neat) cm^{-1}: 1735 (C=O); ^1H NMR (90 MHz, $CDCl_3$) δ: 1.25 (d, 3 H, CH_3), 2.45 (d, 2 H, CH_2), 3.00 (br s,1 H, OH), 3.75 (s, 3 H, OCH_3), 4.20 (m, 1 H, CH). For further data see ref. [2].
3. The submitters used an oil bath to insure vigorous reflux. The time required to obtain the desired solution consistency depends on the PHB used (30 min to over 2 hr).
4. The reaction solution should be maintained at a vigorous reflux. Should the solution cool during the addition a white flaky precipitate may form that redissolves upon extended heating (up to 4 hr at 140°C).
5. This results in a mixture of oligomeric methyl esters with an average degree

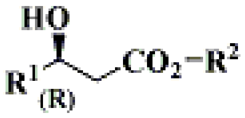
of polymerization of 2.1–2.3, according to ^{1}H NMR analysis (ratio of the CH_3C-signals vs. CH_3O-signals of the esters).
6. Most of the methyl ester groups are saponified with release of methanol.
7. It is crucial that all the methanol and 1,2-dichloroethane be removed from the reaction mixture to insure that all the oligomers are in the aqueous phase.
8. Newly formed methanol is removed at this stage. Only a small amount of methyl esters remains in the mixture at this point.
9. Low temperature during evaporation avoids condensation back to oligomers.
10. According to ^{1}H NMR analysis the crude product consists of more than 93% monomeric (R)-3-hydroxybutanoic acid, contaminated by 1–2% of methyl (R)-3-hydroxybutanoate and less than 0.2% of crotonic acid.
11. The crude product is placed in a 1-L, round-bottomed flask and distilled in an Aldrich Kugelrohr apparatus, heated with an air bath, the receiver bulb being cooled with ice water. Partial condensation of (R)-3-hydroxybutanoic acid to oligomers occurs if the temperature is too high during distillation (Note 12).
12. Drying in an evacuated desiccator over P_2O_5 removes water as well as methyl (R)-3-hydroxybutanoate and crotonic acid.
13. The spectra are as follows: IR (neat) cm^{-1}: 1710 (C=O); ^{1}H NMR (90 MHz, $CDCl_3$) δ: 1.25 (d, 3 H, CH_3), 2.50 (d, 2 H, CH_2), 4.20 (m, 1 H, CH), 7.70 (br s, 2 H, OH). For further data see ref. [2].
14. The distillation residue (8–9 g) consists of water-soluble oligomers that can be saponified without loss of optical purity by heating at reflux with aqueous acid for 15 hr.
15. The submitters report a yield of 45–48 g (74.5–79%) using PHB obtained from Marlborough Biopolymers. The checkers verified this result using PHB obtained from the submitters. The yield reported here represents the checker's results with PHB obtained from Fluka Chemie.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

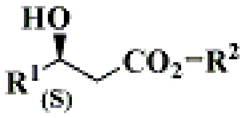
Optically active 3-hydroxybutanoic acid and its methyl ester were first prepared by McKenzie, Magnus-Levy, and Emil Fischer.[3] The biopolymer PHB and mixed polymers containing (R)-3-hydroxybutanoate and (R)-3-hydroxypentanoate were also discovered long ago,[4,5] and are now produced on an industrial scale.[6,7 8] As described here, depolymerization by transesterification [H^+ or $Ti(OR)_4$ catalysis], or by hydrolysis, produces[9,10 11 12] the corresponding monomeric (R)-esters and (R)-acids **1**. The 3-hydroxybutanoic acid can also be prepared by hydrolysis of the ester.[2,13]



1

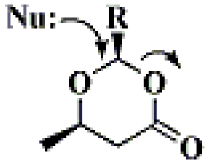
$R^1 = CH_3, C_2H_5$

$R^2 = H, CH_3, C_2H_5$



ent-1

The enantiomeric compounds, ent-**1**, are available from **1** by inversion through sulfonates[14] or through β-lactones.[15 16] Ethyl (S)-3-hydroxybutanoate of 86–95 % ee has also been made by yeast reduction of acetoacetate.[17] Either the ester **1** or ent-**1** can be prepared by enantioselective hydrogenation of the methyl acetoacetate with a Ru-BINAP catalyst.[18]



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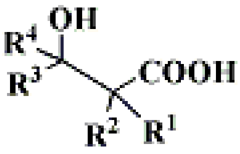

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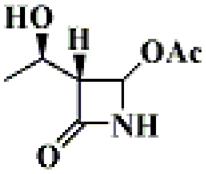

4

The hydroxy acid derivatives **1** are most versatile auxiliaries and building blocks for the synthesis of enantiomerically pure products.[7,11,19] Thus, in an improvement of Johnson´s method,[20] the dioxanones **2** can be used for overall enantioselective nucleophilic additions to aldehydes.[21] Through open-chain[22] or cyclic[23] lithium enolates derived from **1** and, through dioxinones,[24] new substituents can be introduced at carbons (2), (3) and (4) of hydroxybutanoic or hydroxypentanoic acid to give enantiomerically pure products[25,26] of type **3**. Another application is the incorporation of (R)-3-hydroxybutanoic acid into the antibiotic thienamycin[27] through the β-lactam **4**.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

H_2O

P_2O_5

brine

(R)-(−)-Methyl 3-hydroxybutanoate

(R)-(−)-3-Hydroxybutanoic acid

PHB

POLY[(R)-3-HYDROXYBUTYRIC ACID]

homopolymer to Butanoic acid, 3-hydroxy-, (R)-

poly-[(R)-3-hydroxybutyric acid]

sulfuric acid (7664-93-9)

methanol (67-56-1)

ether (60-29-7)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium bicarbonate (144-55-8)

1,2-dichloroethane (107-06-2)

magnesium sulfate (7487-88-9)

crotonic acid (3724-65-0)

Methyl acetoacetate (105-45-3)

3-Hydroxybutanoic acid (300-85-6)

phosphorus pentoxide (1314-56-3)

p-toluenesulfonic acid monohydrate (6192-52-5)

(R)-3-Hydroxybutanoic acid, Butanoic acid, 3-hydroxy-, (R)- (625-72-9)

methyl (R)-3-hydroxybutanoate, Butanoic acid, 3-hydroxy-, methyl ester, (R)-, (R)-3-hydroxybutanoic acid, methyl ester (3976-69-0)

(R)-3-hydroxybutanoate

(R)-3-hydroxypentanoate

Ethyl (S)-3-hydroxybutanoate (56816-01-4)

hydroxypentanoic acid (13392-69-3)

(S)-3-hydroxybutanoic acid (6168-83-8)

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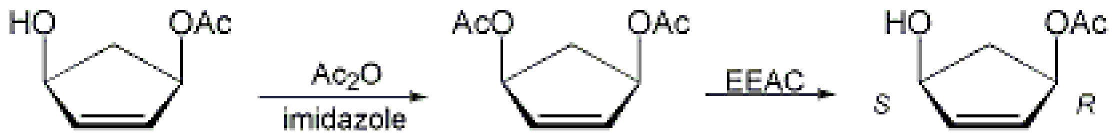
ENANTIOSELECTIVE HYDROLYSIS OF cis-3,5-DIACETOXYCYCLOPENTENE: (1R,4S)-(+)-4-HYDROXY-2-CYCLOPENTENYL ACETATE

[4-Cyclopentene-1,3-diol, monoacetate, (1R-cis)-]



(±)-**1** **2** (+)-**1**

Submitted by Donald R. Deardorff, Colin Q. Windham, and Chris L. Craney[1].
Checked by Renaud Beaudegnies and Leon Ghosez.

1. Procedure

A. *cis-3,5-Diacetoxycyclopentene.* A flame-dried, 100-mL, single-necked, round-bottomed flask is equipped with a serum cap, Teflon-coated magnetic stirring bar, and an 18-gauge needle attached to a dry source of argon vented through a mineral oil bubbler. The apparatus is flushed with argon and charged with 16.70 g (118 mmol) of (±)-cis-4-acetoxy-1-hydroxycyclopent-2-ene [(±)-**1**] (Note 1) and 20 mL of methylene chloride (Note 2). To this stirred solution is added 8.81 g (129 mmol) of imidazole in one portion (Note 3). When dissolution is complete, the reaction mixture is cooled to 0°C with the aid of an ice-water bath. Acetic anhydride (13.20 g, 12.20 mL, 129 mmol) (Note 4) is added dropwise over 5 min by means of an oven-dried syringe and needle. The cooling bath is removed and the reaction is allowed to stir at ambient temperature until judged complete by TLC analysis (Note 5). The contents of the flask are transferred to a 250-mL separatory funnel and diluted with 60 mL of reagent grade ethyl ether. The contents of the separatory funnel are washed with 60 mL of ice-cold 1 N hydrochloric acid which results in noticeable removal of all color from the organic phase. The acidic aqueous phase is back-extracted with two 50-mL portions of ether (Note 6). The combined organic phases are washed with a single 50-mL portion of saturated sodium bicarbonate solution followed by back-extraction of the aqueous phase with three 50-mL portions of ether (Note 6). The combined organic extracts are dried over anhydrous magnesium sulfate, filtered, and concentrated under rotary evaporation at 30 mm. The resulting viscous tan oil is distilled through a 10-cm Vigreux column to afford 20.9–21.1 g (96–98%) of cis-3,5-diacetoxycyclopentene **(2)** (Note 7) as a colorless liquid, bp 55–56°C at 0.1 mm.

B. *(1R,4S)-(+)-4-Hydroxy-2-cyclopentenyl acetate.* A rigorously clean 1-L Erlenmeyer flask, equipped with a 2-in. long Teflon-coated stirring bar (Note 8), is charged with

320 mL of a 1.45 M sodium dihydrogen phosphate buffer concentrate (Note 9). The solution is diluted to a final volume of 800 mL with the addition of 480 mL of glass-distilled water. To the gently stirred solution (Note 10) is added 78 mg of sodium azide (Note 11) followed by 18.6 mg (200 units/mg) of lyophilized electric eel acetyl cholinesterase (EEAC) (Note 12). The enzyme completely dissolves within 5 min after which time 16.01 g (87.0 mmol) of cis-3,5-diacetoxycyclopentene is added in one portion. A few extra mL of distilled water are used to facilitate a quantitative transfer of the diacetate. Parafilm is placed over the mouth of the flask and the two-phase system (Note 13) is allowed to stir at room temperature (Note 14). The progress of the reaction is conveniently monitored by periodic TLC analysis. The reaction is terminated when only a trace of diacetate remains and the corresponding diol begins to appear (Note 15). The aqueous phase is first extracted three times with 150-mL portions of ether followed by fifteen 150-mL extractions with a 1:1 mixture of ether/ethyl acetate (Note 16). The organic extracts are combined, dried over anhydrous magnesium sulfate, and concentrated by rotory evaporation at 30 mm (Note 17). The residue is passed through a 60-g plug of silica gel (Note 18) with approximately 750 mL of ether. Removal of the solvent by rotary evaporation followed by exposure to oil pump vacuum affords 11.32 g of nearly colorless material [mp 43–49°C (corrected)]. Vacuum distillation (Note 19) of the product through a short-path apparatus at 64°C/0.060 mm furnishes 10.64–10.76 g (86–87%, 96% e.e.) of colorless solid (+) hydroxy acetate **1** (mp 44.5–49.5°C (corrected), $[\alpha]_D^{23}$ +62.9° (chloroform, *c* 1.465)) (Note 20). A sample recrystallized from 1:1 pentane/ether (approximately 5 mL/g) provides high purity (≥99% e.e.), colorless needles of **1** (mp 50.7–51.3°C (corrected), $[\alpha]_D^{23}$ +73.8° (chloroform, *c* 1.25) [lit.[2] mp 49° – 51°C, $[\alpha]_D^{23}$ +68.0° (chloroform, *c* 1.64)] (Note 21).

2. Notes

1. (±)-cis-4-Hydroxy-2-cyclopentenyl acetate [(±)-**1**] was prepared according to the method described in *Org. Synth.*[3] This material must be recrystallized (1:1 ether-pentane) before use to remove impurities (e.g., trans-monoacetate) that otherwise lead to reduced optical rotations in the final product [(+)-**1**]. The submitters have found that material having a melting point of 37–39°C is of satisfactory purity. The racemic monoacetate is hygroscopic so the proper precautions should be taken to prevent exposure to moisture. The NMR spectrum is as follows: ^{1}H NMR of (±) **1** (200 MHz, $CDCl_3$) δ: 1.64 (dt, 1 H, J = 14.7, 3.7), 2.02 (s, 3 H), 2.78 (overlapping dt, 1 H, J = 14.7, 7.5), 4.70 (overlapping s, 1 H and broad s), 5.45 (m, 1 H), 5.95 (m, 1H), 6.10 (m, 1H); ^{13}C NMR of (+) **1** (50 MHz, $CDCl_3$) δ: 21.2, 40.5, 74.9, 77.0, 132.6, 138.5, 170.8.

2. HPLC grade methylene chloride was purchased from Fisher Scientific Company and distilled from calcium hydride through a Vigreux column prior to use.

3. Imidazole (99% indicated purity) was purchased from Aldrich Chemical

Company, Inc., and used without any further purification.

4. Acetic anhydride (98% indicated purity) was purchased from Aldrich Chemical Company, Inc., and distilled from phosphorus pentoxide through a Vigreux column prior to use.

5. Thin layer chromatographic (TLC) analysis was performed on Baker Si250F precoated plates with ethyl ether as the solvent. The approximate R_f values for the monoacetate and diacetate under these conditions are 0.44 and 0.72, respectively. The compounds were visualized using p-anisaldehyde stain.

6. This step is necessary to retrieve the slightly water-soluble product diester that migrates into the aqueous layer during the wash process. The meso-diester is easily detected in the water phase by TLC analysis (see (Note 5)).

7. cis-3,5-Diacetoxycyclopentene has the following spectral data: ^{1}H NMR of **2** (200 MHz, $CDCl_3$) δ: 1.74 (dt, 1 H, J = 15, 3.85), 2.05 (s, 6 H), 2.87 (overlapping dt, 1 H, J = 15, 7.6), 5.55 (m, 2 H), 6.1 (s, 2 H); ^{13}C NMR of **2** (50 MHz, $CDCl_3$) δ: 21.1, 37.1, 76.6, 134.6, 170.7.

8. The stirring bar should be free of any slivers of magnetic material or heavy metals that could inactivate the enzyme.

9. The buffer was prepared by dissolving 100 g of sodium dihydrogen phosphate monohydrate (Alfa Johnson Matthey) into 200 mL of glass-distilled water. The pH of the solution was adjusted to 6.9 with the addition of concentrated sodium hydroxide solution (MCB Reagent) and verified with a pH meter recently calibrated between 4–7 pH units using Fisher standards. The buffer solution was diluted to a final volume of 500 mL (1.45 M) and stored in a clean plastic bottle.

10. The stirring rate was adjusted so as to minimize the size of the vortex, which would introduce air into the solution and jeopardize the enzyme.

11. Sodium azide (Sigma Chemical Company) was used to protect the solution's components from microbial attack during the prolonged reaction period.

12. Lyophilized electric eel acetyl cholinesterase (C-3389, EC 3.1.1.7) was purchased from Sigma Chemical Company and stored below 0°C.

13. As the reaction nears completion, all the diacetate dissolves.

14. The success of this reaction may be temperature dependent. Shortly after starting this reaction on a particularly hot day, the building air conditioning failed. The temperature of the reaction flask quickly reached 28.7°C. The optical rotation of the distilled product was 4° off and the melting point was lower than expected. In all reactions prior to or since that incident the reaction temperatures never climbed above 23°C and the results have been uniformly superior.

15. Under these conditions, the reaction lasts 9–12 hr with a final pH of approximately 6.5. Nonspecific hydrolysis of **2** over this time accounts for less than 0.5% of the product as measured by control experiments. If cost is of little concern, the reaction time can be shortened dramatically by the addition of extra enzyme. cis-3,5-Dihydroxycyclopentene has an R_f value in ether of approximately 0.1.

16. HPLC grade ethyl acetate was purchased from J. T. Baker Inc. and distilled from phosphorus pentoxide prior to use. Although the product, (1R,4S)-(+)-4-hydroxy-2-cyclopentenyl acetate [(+)-**1**], is more soluble in ethyl acetate,

emulsion concerns dictated the use of pure ether for the first three extractions and then a 1:1 ether/ethyl acetate mixture for all subsequent extractions. When emulsions did occur during the extraction process, the unemulsified portion of the aqueous phase was drained and a few mL of brine solution was added to the emulsified phase. Two or three quick shakes alleviated the problem.

17. The residual oil may crystallize during this process. If so, it will be necessary to dissolve the solid in about 10 mL of ether (with the aid of a hot air gun) prior to passing the material through the silica gel plug.

18. Baker Analyzed Reagent silica gel 40-140 mesh was used in a 4.5-cm diameter column. This step removes the small amounts of diol present. TLC analysis was helpful in determining when all the monoacetate had been stripped from the plug.

19. The receiving flask should be submerged in an ice-water bath since the product has a considerable vapor pressure under these conditions. It is wise to have a heat gun nearby in the event that the condensate begins to crystallize in the condenser.

20. The enantiomeric excess was unambiguously determined via gas chromatographic separation of diastereomers obtained from derivatization of the chiral alcohol with Mosher's reagent,[4] (R)-(+)-α-methoxy-α-(trifluoromethyl) phenylacetic acid, (MTPA) 99% (Aldrich Chemical Company, Inc.). The checkers used the procedure of Noyori: Kitamura, M.; Tokunaga, M.; Ohkuma, T., Noyori, R. *Org. Synth., Coll. Vol. IX* **1998**, 592 for derivatization with Mosher's reagent. The MTPA esters derived from the (−)- and (+)-monoacetate enantiomers have retention times of 108 and 111.5 min, respectively, on a 25-m OV-101, crosslinked, methylsilicone capillary column operating at 150°C and flow rate of 22 cm/sec. Although less reliable than GC, the ratio of MTPA esters can be estimated via the use of high field (≥200 MHz) NMR in $CDCl_3$ solvent.[5]

21. One paper reports5 an optical rotation of $[\alpha]_D^{22}$ +75.0° (chloroform, *c* 1.16) for crystals of (+)-**1** melting at only 47.5–48°C. We find these data to be inconsistent with our own experience and with the absolute values of the reported rotations for optically pure (−)-**1**. The polarimeter used in the submitter's analysis, a JACSO DIP-360, had been previously calibrated with NBS Standard Reference Sucrose 17d in accordance with NBS guidelines.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

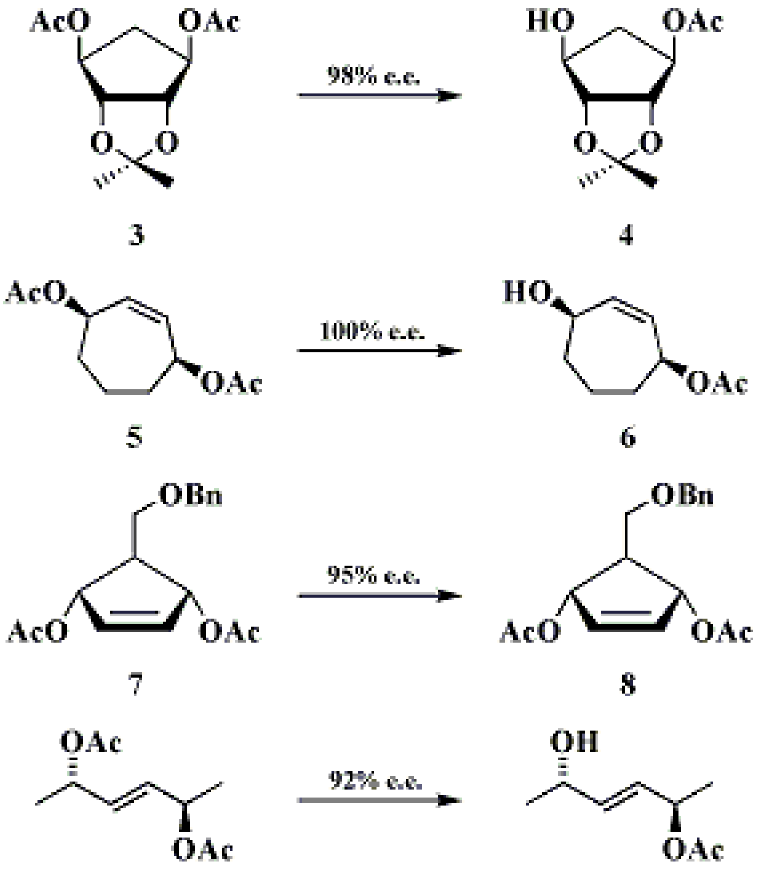
In the 1980's there was a great increase in the development and use of enzymatic procedures by synthetic chemists.[6,7,8,9,10,11] Previously regarded more as scientific curiosities of limited scope than of practical utility, biological-chemical transformations are now used regularly by synthetic chemists. The ability to induce optical activity in molecules where none existed before is the most useful property of

these chiral catalysts. Hydrolase enzymes are generally preferred over other kinds of enzymes for transformations of this nature because they are more easily handled and do not require cofactors for activity. In cases where enantiotopic differentiation between ester functions is desired, prochiral meso diesters are more efficient substrates than racemic esters. In the former case it is possible for all starting material to be converted into a single enantiomer, whereas in the latter example only enzymatic resolution is possible.

(1R,4S)-(+)-4-Hydroxy-2-cyclopentenyl acetate [(+)-**1**] is an important synthetic precursor. It provides optically active starting material, via the versatile intermediate 4-oxo-2-cyclopentenyl acetate,[12] for important cyclopentanoids such as the prostaglandins[13] and carbocyclic nucleosides.[14] Because of the medicinal significance of these compounds, more efficient routes with better enantioselectivities have been devised to nonracemic **1**. Enzymatic catalysis has become the dominant methodology for induction of this optical activity.

In addition to the title procedure,[15] other enzymatic preparations of nearly optically pure (1R,4S)-(+)-4-hydroxy-2-cyclopentenyl acetate [(+)-**1**][5,21] and its optical antipode (–)-**1**[16,17,18,19,20] are known. These enzyme-catalyzed procedures are derivatives of two basic strategies: (1) the enantioselective hydrolysis of the meso-diacetate **2**,[5,15,21,16,17] or (2) the enantioselective transacetylation of the parent meso-diol.[18,19,20] Although (–)-**1** has been successfully prepared by either route, the (+)-enantiomer is available only via the hydrolytic approach.

The other enzymatic routes[5,21] to (+)-**1** follow roughly similar procedures. Both employ pH 7 buffer solutions of the hydrolytic enzyme porcine pancreas lipase (PPL) as opposed to electric eel acetyl cholinesterase (EEAC) used here. Although EEAC does afford better enantioselection than PPL (96% vs. 92% e.e.[21]), this apparent advantage may be viewed as somewhat tenuous since (+)-**1** can be optically enriched via repeated recrystallizations. However, EEAC is clearly superior to PPL in terms of chemical yield. PPL mediated hydrolyses lead to yields of (+)-**1** in the 50% range (plus recovered starting material), while the EEAC conversion rate is 90–95%. More importantly, the EEAC route eliminates the need to recycle starting material.



EEAC has been used successfully in other enantiotopic differentiations. Johnson, et al.[22] have reported that diester **3** can be readily transformed into hydroxy acetate **4** via this enzymatic process in 98% e.e. and an 80% chemical yield. Similarly, hydroxy acetate **6** was prepared from its parent diester **5** by Pearson, et al.[23] in 100% e.e., although in 39% yield (50–55% recovered starting material). The enzyme also appears effective on 4-substituted cis-3,5-diacetoxycyclopentenes as Danishefsky[24] demonstrated with the conversion of **7** into **8** in 95% yield and 95% e.e. Finally, the successful enantioselective hydrolysis of **9** into **10** (77%, 92% e.e.) extends the range of useful EEAC substrates to acyclic cases.[25]

Immobilized EEAC (Sigma Chemical Company) has been found equally effective and allows economical, large-scale hydrolyses of **2**. The immobilized enzyme, which is covalently bonded to agarose beads, is easily recovered through centrifugation. Reuse does not compromise the enantioselectivity (unpublished results).

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 132
- Org. Syn. Coll. Vol. 9, 136

References and Notes

1. Department of Chemistry, Occidental College, Los Angeles, CA 90041. We gratefully acknowledge the National Science Foundation (CHE-8908212, CHE-8804037 & DMB-9005512) for financial support of this work. C. Q. W. wishes to thank the Ford Foundation for his summer undergraduate research stipend.
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

brine

acetyl cholinesterase

EEAC

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

ether, ethyl ether (60-29-7)

acetic anhydride (108-24-7)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium bicarbonate (144-55-8)

sucrose

Pentane (109-66-0)

sodium azide (26628-22-8)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

Imidazole (288-32-4)

sodium dihydrogen phosphate (7558-80-7)

calcium hydride (7789-78-8)

argon (7440-37-1)

phosphorus pentoxide (1314-56-3)

p-anisaldehyde (123-11-5)

4-oxo-2-cyclopentenyl acetate (768-48-9)

(1R,4S)-(+)-4-Hydroxy-2-cyclopentenyl acetate, 4-Cyclopentene-1,3-diol, monoacetate, (1R-cis)-, (±)-cis-4-Hydroxy-2-cyclopentenyl acetate (60410-16-4)

cis-3,5-Diacetoxycyclopentene (54664-61-8)

(±)-cis-4-acetoxy-1-hydroxycyclopent-2-ene (60410-18-6)

sodium dihydrogen phosphate monohydrate (10049-21-5)

cis-3,5-Dihydroxycyclopentene

(R)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (20445-31-2)

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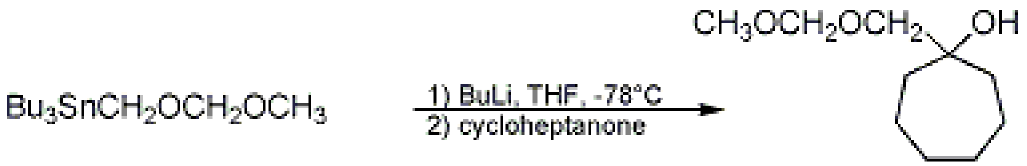
PREPARATION AND USE OF (METHOXYMETHOXY) METHYLLITHIUM: 1-(HYDROXYMETHYL) CYCLOHEPTANOL

[Cycloheptanemethanol, 1-hydroxy-]

A.


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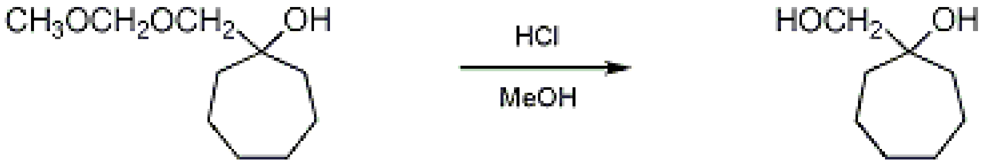

Submitted by Carl R. Johnson[1], John R. Medich[2], Rick L. Danheiser[3], Karen R. Romines[3], Hiroo Koyama[3], and Stephen K. Gee[3].
Checked by Darius J. Robinson and Amos B. Smith, III.

1. Procedure

A. *1-[(Methoxymethoxy)methyl]cycloheptanol*. A 250-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, a rubber septum, an argon inlet adapter, and a thermometer port. The apparatus is flame dried under reduced pressure and evacuated; the vacuum is broken with argon. The flask is charged with tributyl[(methoxymethoxy)methyl]stannane[4] (10.5 g, 28.7 mmol) and evacuated for 15 min; the vacuum is broken with argon. The flask is charged with 40 mL of dry tetrahydrofuran (Note 1), a low temperature thermometer is set into the flask and the solution is cooled to –78°C using a dry ice-acetone bath. A solution of butyllithium (2.5 M in hexanes, 11.2 mL, 28.0 mmol) (Note 2) is added via a syringe over a period of 5 min while maintaining a reaction temperature below –60°C. Stirring is continued for no more than 5 min (Note 3), at which time cycloheptanone (2.70 g, 24.0 mmol) (Note 4) is added neat via a syringe. After the solution is stirred for 30 min at –78°C, the dry ice-acetone bath is removed and the reaction mixture is diluted with 40 mL of saturated aqueous ammonium chloride. The resulting mixture is stirred for 30 min and then extracted with three 40-mL portions of ethyl acetate. The combined organic layers are washed with 20 mL of saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, filtered, and concentrated at reduced pressure using a rotary evaporator to provide 12.8 g of crude product. The crude product is purified by

flash chromatography on a 70-mm diameter column packed with 130 g of silica gel (Note 5) using 5% ethyl acetate/hexane to elute the tin by-products and 30% ethyl acetate/hexane to elute the title compound. The product fractions are combined and concentrated at reduced pressure using a rotary evaporator to provide 1-[(methoxymethoxy)methyl]cycloheptanol (4.1–4.3 g, 91–95% based on cycloheptanone) as a colorless liquid (Note 6).

B. *1-(Hydroxymethyl)cycloheptanol*. To a 100-mL round-bottomed flask equipped with a stirring bar and a reflux condenser are added 1-[(methoxymethoxy)methyl] cycloheptanol (3.90 g, 20.7 mmol), methanol (50 mL), and hydrochloric acid (12.1 N, 0.75 mL). The reaction mixture is heated to 55°C for 1.5–2 hr (Note 7). After completion of the reaction, as indicated by TLC (Note 7), the reaction mixture is cooled to ambient temperature and carefully diluted with 35 mL of saturated aqueous sodium bicarbonate and stirred for 30 min. The methanol is removed under reduced pressure using a rotary evaporator and the remaining aqueous mixture is extracted with three 40-mL portions of ethyl acetate. The combined organic layers are washed once with 15 mL of saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, filtered, and concentrated at reduced pressure using a rotary evaporator to afford 2.9 g of crude product as a pale yellow oil. The crude product is purified by flash chromatography on a 40-mm diameter column packed with 70 g of silica gel (Note 5), using 40% ethyl acetate-hexane to elute the product. The desired fractions are combined and concentrated under reduced pressure using a rotary evaporator to provide 1-[hydroxymethyl)cycloheptanol (2.3–2.4 g, 76–80% yield) as a white solid (mp 52–53°C) (Note 8).

2. Notes

1. Tetrahydrofuran was distilled from sodium benzophenone ketyl immediately before use.
2. Butyllithium was purchased from Aldrich Chemical Company, Inc. and titrated using a solution of 2-butanol (1.0 M in p-xylene) with 1,10-phenanthroline as the end-point indicator.
3. In some cases the submitters have noticed that when the transmetalation mixture was allowed to stir for 15 min or more prior to addition of the carbonyl compound, the expected addition product was contaminated with material resulting from addition of butyllithium.
4. Cycloheptanone was purchased from Aldrich Chemical Company, Inc. and distilled under aspirator vacuum through a 6-in. Vigreux column prior to use.
5. Merck 230–400 mesh silica gel 60 was used for the column chromatography.
6. 1-[(Methoxymethoxy)methyl]cycloheptanol has the following spectral properties: IR (neat) cm^{-1}: 3460, 2930, 2860, 1460, 1445, 1405, 1212, 1198, 1150, 1112, 1042, 965, 920; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.35–1.69 (m, 12 H), 2.40 (s, 1 H), 3.35 (s, 2 H), 3.35 (s, 3 H), 4.63 (s, 2 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ: 22.3, 30.0, 37.6, 55.2, 74.6, 76.1, 97.0. Anal. Calcd for $C_{10}H_{20}O_3$: C, 63.80; H, 10.71. Found: C, 63.73; H, 10.82.

7. Progress of the reaction should be monitored periodically during the 2 hr to determine when the starting material is consumed in order to avoid unnecessary heating, which leads to the formation of by-products. TLC can be used: 50% ethyl acetate/hexane, silica gel stained with phosphomolybdic acid.

8. 1-(Hydroxymethyl)cycloheptanol has the following spectral properties: IR (KBr) cm^{-1}: 3370, 2920, 2858, 1465, 1445, 1375, 1341, 1230, 1190, 1075, 1029, 991, 961, 935, 920, 890, 850, 800, 710; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.3–1.8 (m, 12 H); 2.98 (s, 1 H), 3.38 (d, 2 H), 3.52 (t, 1 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ: 22.4, 30.2, 37.2, 69.6, 76.0. Anal. Calcd for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.35; H, 11.39.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The utility of α-alkoxyorganostannanes as precursors to α-alkoxyorganolithiums has been demonstrated by several groups.[5,6,7,8,9,10,11] Primary α-alkoxyorganostannanes[8,9,10,11] have been used as hydroxymethyl anion equivalents.[12,13,14,15] Direct hydroxymethylation of carbonyl compounds was achieved by Seebach and Meyers,[16] who treated tributylstannylmethanol with two equivalents of butyllithium (BuLi) to produce the dianion of methanol. The dianion added to carbonyl compounds to give diols directly. The usefulness of this method, however, is limited because of the instability of the reagent and the moderate yields of addition products. Still prepared tributyl[(ethoxy)(methyl)methoxy]stannnane and (benzyloxymethyl)tributylstannane.[9] These compounds, upon treatment with one equivalent of BuLi, gave α-alkoxyorganolithiums, which added in high yields to carbonyl compounds to provide monoprotected diols. The former reagent results in the introduction of a new chiral center and the latter results in a protected diol that must be unmasked by hydrogenolysis. The related "MOM" reagent described here was foreseen as fulfilling a need for an acid-sensitive protecting group that would not introduce new diastereomers.

Tributyl[(methoxymethoxy)methyl]stannane in tetrahydrofuran readily transmetalates with BuLi and the resulting (methoxymethoxy)methyllithium adds in high yield to carbonyl compounds, providing monoprotected diols.[11] The reagent can also be added in a conjugate fashion to enones, albeit in moderate yield,[11] using the copper methodology of Fuchs and Hutchinson.[17] Deprotection of the alcohol can be achieved in high yield by simple acid hydrolysis.[18]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 704

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium benzophenone ketyl

1-[hydroxymethyl)cycloheptanol

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

methanol (67-56-1)

ammonium chloride (12125-02-9)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

tin (7440-31-5)

p-xylene (106-42-3)

butyllithium, BuLi (109-72-8)

Tetrahydrofuran (109-99-9)

hexane (110-54-3)

Cycloheptanone (502-42-1)

argon (7440-37-1)

2-Butanol (78-92-2)

phosphomolybdic acid (51429-74-4)

1,10-phenanthroline (66-71-7)

(Methoxymethoxy)methyllithium (115384-62-8)

1-(Hydroxymethyl)cycloheptanol, Cycloheptanemethanol, 1-hydroxy- (74397-19-6)

1-[(Methoxymethoxy)methyl]cycloheptanol (115384-52-6)

Tributyl[(methoxymethoxy)methyl]stannane (100045-83-8)

tributylstannylmethanol (27490-33-1)

(benzyloxymethyl)tributylstannane

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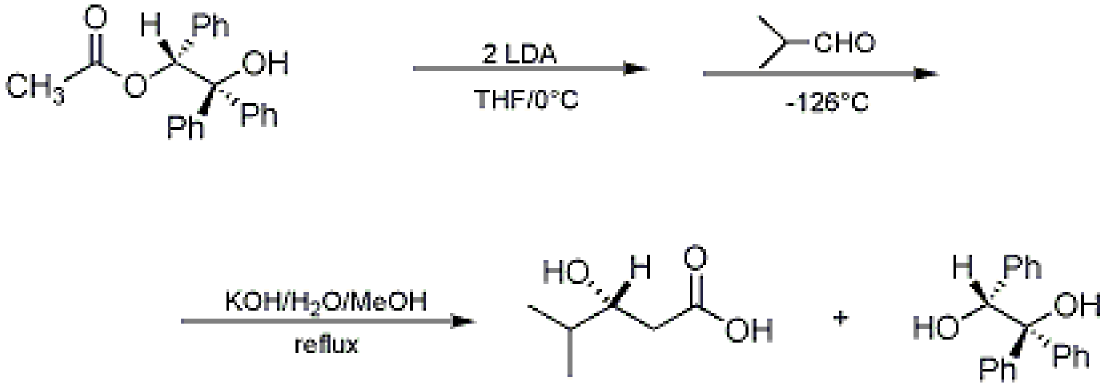
Organic Syntheses, CV 9, 497

STEREOSELECTIVE ALDOL REACTION OF DOUBLY DEPROTONATED (R)-(+)-2-HYDROXY-1,2,2-TRIPHENYLETHYL ACETATE (HYTRA): (R)-3-HYDROXY-4-METHYLPENTANOIC ACID

[Pentanoic acid, 3-hydroxy-4-methyl-, (R)-]



Submitted by Manfred Braun and Silke Gräf[1].
Checked by K. Ryan, J. Lynch, and I. Shinkai.

1. Procedure

A 500-mL, two-necked, round-bottomed flask is equipped with a magnetic stirrer, septum, and a connection to a combined vacuum/nitrogen line (Note 1). The air in the flask is replaced by nitrogen by repeated evacuation and flushing with nitrogen, the pressure of which is maintained during the reaction at ca. 70 mm above atmospheric pressure with a mercury bubbler. Dry tetrahydrofuran (100 mL) (Note 2) and 38.4 mL (0.269 mol) of diisopropylamine (Note 3) are injected with syringes through the septum. The mixture is cooled to −78°C by means of a dry ice/acetone bath and treated with stirring with 165 mL (0.264 mol) of a 15% solution of butyllithium in hexane. The dry ice/acetone bath is replaced with an ice bath, and stirring is continued for 30 min. A 2-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, septum, and a connection to the combined vacuum/nitrogen line (Note 1) is charged with 40.0 g (0.120 mol) of (R)-(+)-2-hydroxy-1,2,2-triphenylethyl acetate [(R)-HYTRA].[2] The air in the flask is replaced with nitrogen, and 400 mL of dry tetrahydrofuran is added via a cannula with 1.2 mm inside diameter, whereby the flask is slightly evacuated. The suspension is stirred at −78°C in a dry ice/acetone bath. The ice-cold solution of lithium diisopropylamide, prepared as described above, is added via a cannula under vigorous stirring, whereby the 2-L flask is slightly evacuated. The reaction mixture is stirred at 0°C for 60 min to complete the double deprotonation. A clear orange solution forms that is cooled, below −70°C (dry ice/acetone bath). Thereafter, 900 mL of dry 2-methylbutane (Note 4) is added via a cannula. A

thermocouple, connected to a resistance thermometer (Note 5), is introduced via the septum. The reaction flask is plunged into a bath of liquid nitrogen, the depth of immersion being 0.5–1 cm (Note 6). When the temperature of the suspension has reached −128°C, a solution of 18.3 mL (0.200 mol) of 2-methylpropanal in 5 mL of dry tetrahydrofuran is added dropwise via syringe through the septum at such a rate that the temperature does not rise above −126°C. Stirring is continued for 90 min at −128°C to −106°C (Note 7). The mixture is treated with 500 mL of a saturated aqueous solution of ammonium chloride and allowed to reach room temperature.

The organic layer is separated and washed twice with a total of 200 mL of water. The aqueous reaction layer is extracted five times with a total of 600 mL of chloroform. The organic extracts are washed twice with a total amount of 250 mL of water. The combined organic layers are dried with magnesium sulfate and evaporated to dryness. The residual solid product is carefully dried under reduced pressure to yield 48–50 g (≥ 100%) (Note 8).

The crude product is transferred to a 2-L, round-bottomed flask equipped with a magnetic stirrer and a condenser. Methanol (1.4 L), water (0.4 L), and 66.6 g of potassium hydroxide are added and the mixture is refluxed for 3 hr. After the solution is cooled to room temperature, the organic solvent is removed on a rotary evaporator. The residual aqueous alkaline suspension is filtered through a suction filter. The solid (Note 9) is washed carefully with 250 mL of water. In a separatory funnel the combined aqueous layers are washed three times with a total of 300 mL of methylene chloride. The aqueous solution is transferred to a 2-L, round-bottomed flask, immersed in an ice bath, and acidified to pH 2.5 by cautious addition of 6 N hydrochloric acid. The mixture is stirred vigorously with a magnetic stirrer, and the pH is controlled carefully to avoid over-acidification. The clear solution is again poured into a separatory funnel, saturated with sodium chloride, and extracted with five 100-mL portions of diethyl ether. The pH of the aqueous layer is controlled and readjusted to pH 2.5 by addition of 6 N hydrochloric acid, if necessary. The combined organic layers are dried with magnesium sulfate and concentrated in a rotary evaporator without heating. The yellow syrupy residue is dried carefully at room temperature under reduced pressure (10^{-3} mm) to yield 9.7–12.4 g (61–78%) (76 mmol; 63%) of (R)-(+)-3-hydroxy-4-methylpentanoic acid in 86–92% optical purity (Note 10), $[\alpha]_D^{20}$ +32° to +37° (99% chloroform, *c* 0.11) [lit.[2] $[\alpha]_D^{20}$ +40.5° (chloroform, *c* 0.0063); lit.[3] $[\alpha]_D^{20}$ +40.14° (chloroform, *c* 1.22)].

2. Notes

1. Alternatively, the flask can be closed with a three-way stop-cock to maintain connections to a vacuum pump and to a nitrogen line.
2. Tetrahydrofuran is distilled first from sodium wire and then under nitrogen from lithium aluminum hydride. 2-Methylbutane (purchased from Aldrich Chemical Company, Inc.) and petroleum ether (low-boiling fraction, bp 30–37°

C) are distilled from lithium aluminum hydride under nitrogen. The solvents are stored under nitrogen, and can be taken from the receiving flasks, closed with septa, with syringes or cannulas.

3. Diisopropylamine (Merck AG, D-Darmstadt) is distilled from calcium hydride and stored over molecular sieves (3 Å). Butyllithium (15% solution in hexane) was purchased from Merck AG, D-Darmstadt.

4. Instead of 2-methylbutane, a low-boiling fraction of petroleum ether (bp 30–37°C), but not pure pentane, can be used (cf. (Note 2)).

5. Because of the inaccuracy of alcohol thermometers it is strongly recommended that one monitor those reactions that are run below –80°C with a resistance thermometer. The submitters used an apparatus purchased from Ebro, D-Ingolstadt.

6. The submitters used a 2-L Dewar cylinder of 20 cm inner depth, covered with aluminum foil. The mixture should be stirred very vigorously to avoid solidification.

7. When the addition of the aldehyde is complete, liquid nitrogen is removed from the Dewar cylinder.

8. ^{1}H NMR ($CDCl_3$/TMS/300 MHz) δ: 0.82 (d, 3 H, J = 6.9, CH_3), 0.83 (d, 3 H, J = 6.7, CH_3), 1.53 (m, 1 H, $CH(CH_3)_2$), 2.35 (m, 2 H, CH_2), 3.56 (m, 1 H, CH (OH), 6.72 (s, 1 H, CHPh), 7.11 (m, 10 H, Ar-H), 7.32 (m, 3 H, Ar-H); 7.63 (m, 2 H, Ar-H); $[\alpha]_D^{20}$ +159° to 171° (99% chloroform, *c* 1); mp 178° to 190°C. The optical rotation is influenced by the diastereomeric ratio and by traces of HYTRA, if present. Those traces can be detected by TLC on silica gel (R_f = 0.2, chloroform).

9. Colorless, crystalline, optically pure (R)-(+)-1,1,2-triphenyl-1,2-ethanediol can be recovered in >95% yield after recrystallization from methanol,[2] mp 124°C, $[\alpha]_D^{20}$ +224° (95% aqueous ethanol, *c* 0.984).

10. The optical purity of 3-hydroxy-4-methylpentanoic acid is determined by shift measurements on the methyl ester. Chemical purity exceeds 98% according to GC. The submitters report consistent ee of 92–94%; the checker's experience is recorded in the procedure.

Waste Disposal Information

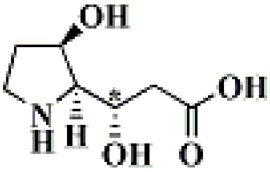
All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The addition of doubly deprotonated HYTRA to achiral[4,5] as well as to enantiomerically pure aldehydes[6] enables one to obtain non-racemic β-hydroxycarboxylic acids. Thus, the method provides a practical solution for the stereoselective aldol addition of α-unsubstituted enolates, a long-standing synthetic problem.[7] As opposed to some other chiral acetate reagents,[7] both enantiomers of

HYTRA are readily available. Furthermore, the chiral auxiliary reagent, 1,1,2-triphenyl-1,2-ethanediol, can be recovered easily. Aldol additions of HYTRA have been used in syntheses of natural products and biological active compounds, and some of those applications are given in Table I. (The chiral center, introduced by a stereoselective aldol addition with HYTRA, is marked by an asterisk.)

TABLE I
NATURAL PRODUCTS AND BIOLOGICALLY ACTIVE ANALOGUES PREPARED BY STEREOSELECTIVE ALDOL ADDITION OF DOUBLY DEPROTONATED (R)- AND (S)-HYTRA



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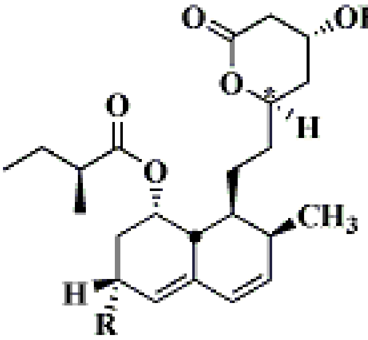

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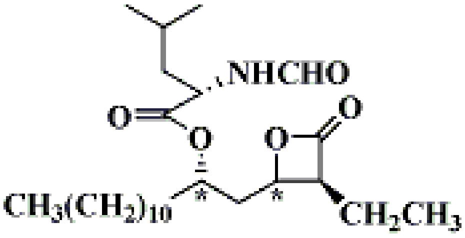

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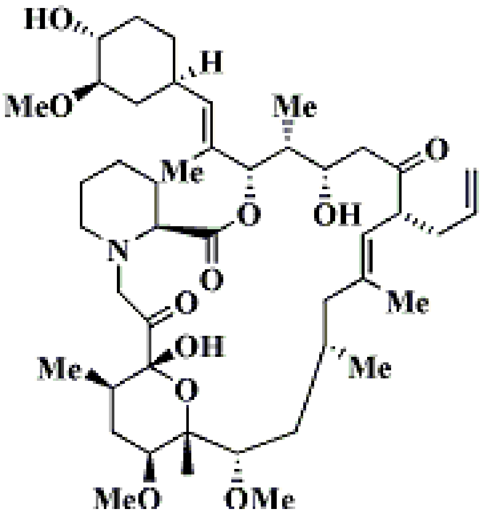

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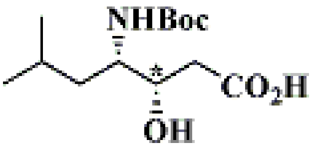

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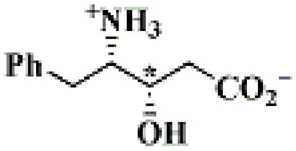

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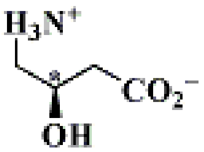

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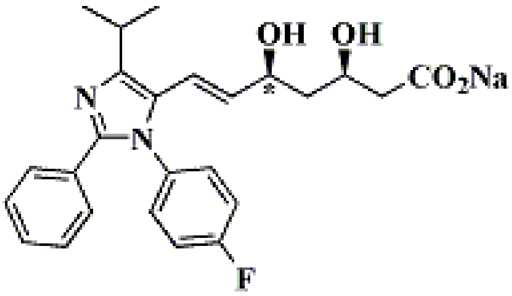

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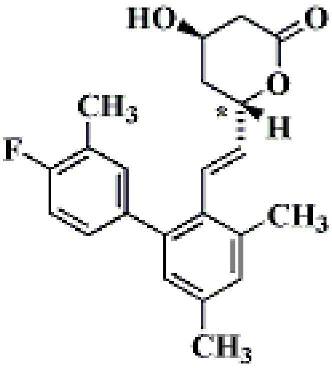

16 17

Preparation of (R)-(+)-3-hydroxy-4-methylpentanoic acid has been reported previously by the submitters.[5] Alternative syntheses of (R)-(+)- or (S)-(−)-3-hydroxy-4-methylpentanoic acid rely on aldol reactions of chiral ketone, ester, or amide enolates,[3,18,19,20] or Lewis-acid mediated additions of chiral silyl ketene acetals to isobutyraldehyde.[21,22] Since both enantiomers of HYTRA are readily available this method enables one to prepare (S)-3-hydroxy-4-methylpentanoic acid as well.

This preparation is referenced from:

- Org. Syn. 77, 45

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

petroleum ether

(R)-(+)- or (S)-(−)-3-hydroxy-4-methylpentanoic acid

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

methanol (67-56-1)

diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

chloroform (67-66-3)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

aluminum (7429-90-5)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

Pentane (109-66-0)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

isobutyraldehyde, 2-methylpropanal (78-84-2)

2-methylbutane (78-78-4)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

hexane (110-54-3)

calcium hydride (7789-78-8)

lithium diisopropylamide (4111-54-0)

diisopropylamine (108-18-9)

(R)-3-Hydroxy-4-methylpentanoic acid, (R)-(+)-3-hydroxy-4-methylpentanoic acid, Pentanoic acid, 3-hydroxy-4-methyl-, (R)- (77981-87-4)

(R)-(+)-1,1,2-triphenyl-1,2-ethanediol (95061-46-4)

3-hydroxy-4-methylpentanoic acid

1,1,2-triphenyl-1,2-ethanediol

(S)-3-hydroxy-4-methylpentanoic acid

(R)-(+)-2-Hydroxy-1,2,2-triphenylethyl acetate (95061-47-5)

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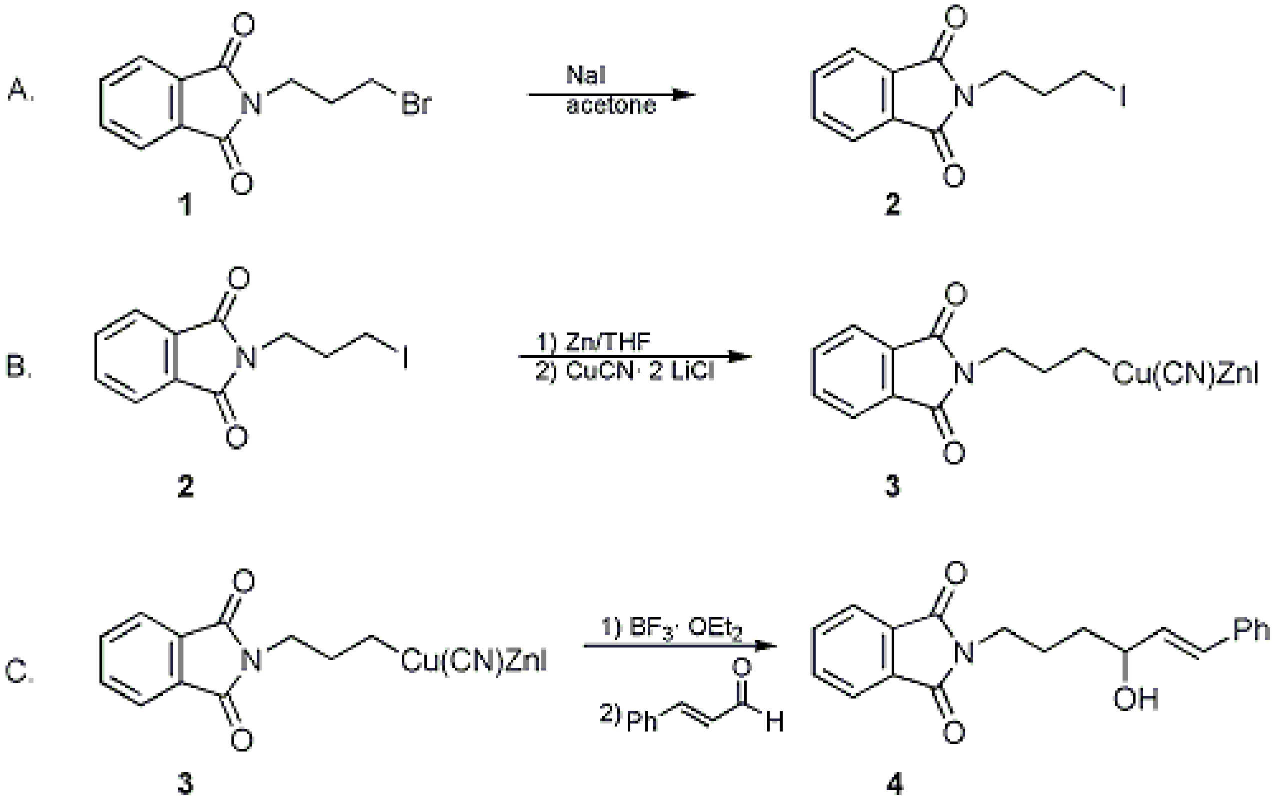
Organic Syntheses, CV 9, 502

1,2-ADDITION OF A FUNCTIONALIZED ZINC-COPPER ORGANOMETALLIC [RCu(CN)ZnI] TO AN α,β-UNSATURATED ALDEHYDE: (E)-2-(4-HYDROXY-6-PHENYL-5-HEXENYL)-1H-ISOINDOLE-1,3(2H)-DIONE

[1H-Isoindole-1,3(2H)-dione, 2-(4-hydroxy-6-phenyl-5-hexenyl)-]



Submitted by Ming Chang P. Yeh, Huai Gu Chen, and Paul Knochel[1].
Checked by Thomas Wagler, Brian E. Jones, Thomas C. Zebovitz, and David L. Coffen.

1. Procedure

A. *2-(3-Iodopropyl)-1H-isoindole-1,3(2H)-dione* **2**. A dry, one-necked, 500-mL, round-bottomed flask equipped with a magnetic stirring bar and a reflux condenser with a gas inlet at the top, is charged with 13.4 g (50 mmol) of 2-(3-bromopropyl)-1H-isoindole-1,3(2H)-dione **1** (Note 1), 17.95 g (120 mmol) of sodium iodide (Note 2), and 100 mL of acetone. The reaction mixture is stirred at reflux under nitrogen for 21 hr (Note 3). The solvent is removed on a rotary evaporator and the resulting solid is dissolved in 300 mL of dichloromethane and 200 mL of water. The two layers are separated in a separatory funnel and the aqueous layer is extracted with two 100-mL portions of dichloromethane. The combined organic extracts are washed successively with 100 mL of an aqueous 10% solution of sodium thiosulfate, three 100-mL portions of water and 150 mL of brine. The organic layer is dried over anhydrous magnesium sulfate. After filtration, the solvent is

removed on a rotary evaporator. The crude white solid is dried for several hours at room temperature under reduced pressure to remove traces of solvent [15.0–15.5 g (47.6–49.2 mmol) 95–98% yield]. This material can be used directly in the next step (Note 4).

B. *Formation of the copper-zinc organometallic* **3** *from 2-(3-iodopropyl)-1H-isoindole-1,3 (2H)-dione*. A dry, 100-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, 50-mL pressure-equalizing addition funnel bearing a rubber septum, three-way stopcock, and a thermometer. The air in the flask is replaced by dry argon and the flask is charged with 4.71 g (72 mmol) of cut zinc (ca. 1.5 × 1.5 mm; (Note 5)). The flask is again flushed three times with argon. 1,2-Dibromoethane (Note 6), (0.2 mL, 2.3 mmol) and 3 mL of tetrahydrofuran (THF) (Note 7) are successively injected into the flask which is then heated gently with a heat gun until ebullition of solvent is observed; the zinc suspension is stirred a few minutes and heated again. The process is repeated three times; 0.15 mL (1.2 mmol) of chlorotrimethylsilane[2 3 4] is then injected into the addition funnel. The cut zinc foil turns grey. After 15 min the reaction mixture is heated to 30°C with an oil bath and 18.9 g (60 mmol) of iodide 2 dissolved in 30 mL of THF is added dropwise over 40 min. After addition, the reaction mixture is stirred for 4 hr at 43°C to give a dark brown-yellow solution of the zinc reagent (Note 8). A second, dry, 250-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, three-way stopcock connected to vacuum and an argon source, and two glass stoppers. The flask is charged with 4.59 g (108 mmol) of lithium chloride (Note 9). The flask is heated with an oil bath at 130°C (oil bath temperature) under vacuum (0.1 mm) for 2 hr to dry the lithium chloride. The reaction flask is then cooled to 25° C and flushed with argon. The two glass stoppers are replaced by a low temperature thermometer and a rubber septum and 4.84 g (54 mmol) of copper cyanide (Note 10) is added. The flask is flushed three times with argon and 40 mL of freshly-distilled THF (Note 7) is added to give, after 15 min, a clear yellow-green solution of the complex $CuCN\cdot 2LiCl$ (Note 11). This solution is cooled to ca. –40°C and the two flasks are connected via a stainless steel cannula. The solution of the zinc reagent is transferred to the THF solution of copper cyanide and lithium chloride (Note 12). The resulting dark green solution is warmed to 0°C within 5 min and is ready to use in the next step after 5 min of stirring at this temperature.

C. *(E)-2-(4-Hydroxy-6-phenyl-5-hexenyl)-1H-isoindole-1,3(2H)-dione* **4**. The THF solution of the copper-zinc reagent is cooled to –78°C and 19.9 mL (162 mmol) of boron trifluoride etherate (Note 13) is added dropwise. The reaction mixture is warmed to –30°C and stirred for 30 min, then cooled to –60°C. (E)-Cinnamaldehyde (5.71 g, 43.2 mmol) is added slowly via a syringe. The reaction mixture is allowed to stir at –30°C for 14 hr (Note 14) and for 30 min at 0°C. After this time, conversion is complete as indicated by GLC analysis and the reaction mixture is poured into an Erlenmeyer flask containing 500 mL of ethyl acetate, 100 mL of a saturated aqueous solution of ammonium chloride and 5 mL of ammonium hydroxide. The mixture is filtered by suction through 10 g of Celite on a sintered glass funnel, the contents of the funnel are washed twice with 50 mL of ethyl acetate and the filtrate is separated into two layers. The organic layer is washed successively with 100 mL of aqueous 10% sodium thiosulfate, and twice with 100 mL of a saturated aqueous solution of ammonium chloride. The combined aqueous phases are extracted with 100 mL of ethyl acetate and the combined organic phases are washed with 100 mL of a saturated aqueous

sodium chloride solution, then dried over magnesium sulfate. After filtration, the solvent is removed on a rotary evaporator (ca. 10 mm) to afford 19.85 g of a crude yellowish oil. Flash chromatography separation[5] of the oil using silica gel (230-400 mesh, 570 g) and ethyl acetate/hexane (1:2) gives 6.92 g (50% yield) of the 1,2-addition product 4 as a pale yellow solid, mp 87–88°C, after removal of the solvents (Note 15).

2. Notes

1. The N-(3-bromopropyl)phthalimide **1** was purchased from Aldrich Chemical Company, Inc. or from Lancaster Synthesis Ltd.
2. Sodium iodide (Analytical Reagent) was purchased from Mallinckrodt, Inc.
3. A GLC analysis (Megabore Column (DB5)) shows a conversion of 95%. The remaining bromide 1 is converted to the iodide 2 during the formation of the zinc organometallic (next reaction step).
4. The iodide 2 can be recrystallized from hexane/dichloromethane to give white needles; mp 87–88°C.[6] The spectra are as follows: IR (CH_2Cl_2) cm^{-1}: 3054.6 (m), 2892.5 (w), 1773.8 (m), 1716.1 (s), 1435.8 (s), 1396.3 (m), 1265.6 (s); ^1H NMR (360 MHz, $CDCl_3$) δ: 2.25 (m, 2 H), 3.16 (t, 2 H, J = 7.2), 3.78 (t, 2 H, J = 3.6), 7.34 (dd, 2 H, J = 6.0 and 3.1); 7.86 (dd, 2 H, J = 6.0 and 3.1); ^{13}C NMR (90.5 MHz, $CDCl_3$) δ: 2.1, 32.6, 38.2, 132.7, 134.8, 168.4.
5. This procedure uses cut zinc foil purchased from Alfa Products, Morton/Thiokol Inc. (foil, 0.25 mm thick, 30 cm wide, 99.9% purity). However, zinc dust can also be used. The reaction time using zinc dust is shorter and a lower reaction temperature may be possible. After formation of the zinc organometallic, the zinc dust is allowed to settle and the THF solution of the zinc organometallic is transferred via a syringe to the THF-solution of the complex CuCN·2LiCl. The checkers obtained a 51–56% yield of product, melting at 80–90°C.
6. 1,2-Dibromoethane and the chlorotrimethylsilane are purchased from Aldrich Chemical Company, Inc.
7. All the tetrahydrofuran used in this procedure was freshly distilled over sodium/benzophenone before use.
8. A GLC analysis of hydrolyzed aliquots allows one to check the completion of the reaction. Less than 7% of the starting iodide 2 and more than 93% of N-propylphthalimide can be detected. A yield of 90% of the zinc reagent is assumed. The zinc reagent has also been formed at a reaction temperature of 33°C. A reaction time of 16 hr is then required.
9. Anhydrous lithium chloride is purchased from Aldrich Chemical Company, Inc.
10. Copper cyanide, purchased from Aldrich Chemical Company, Inc., is not a hygroscopic salt and does not need to be dried before use.
11. A very small amount of undissolved lithium chloride may still be present and will dissolve after the addition of the zinc reagent.
12. To effect the transfer, the argon pressure in the flask containing the copper salt is reduced by inserting a needle through the septum and by shutting off the argon gas entry. Washing the remaining zinc foil with 5 mL of dry THF allows one to transfer the zinc reagent almost quantitatively.
13. Boron trifluoride etherate is purchased from Aldrich Chemical Company, Inc., and

is manipulated under argon.

14. An immersion cooler (Cryocool/Neslab) is used to maintain the temperature at –30°C.

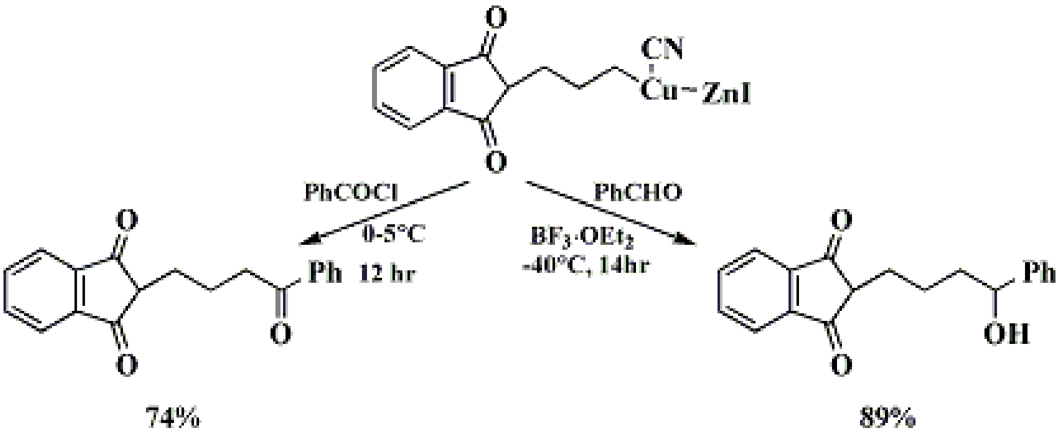
15. A portion of this product is crystallized from 1:1 ethyl acetate:hexane to yield analytically pure product, mp 92–93°C (Anal. Calcd for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36. Found: C, 74.52; H, 6.03; N, 4.29). The spectra are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.67–1.81 (m, 4 H), 3.75 (t, 2 H, J = 6.9), 4.34 (m, 1 H), 6.19 (dd, 1 H, J = 15.9 and 6.8), 6.56 (d, 1 H, J = 15.9), 7.22–7.36 (m, 5 H), 7.70 (m, 2 H), 7.82 (m, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 24.6, 34.1, 37.7, 72.4, 123.1, 126.4, 127.6, 128.4, 128.5, 130.5, 131.9, 132.0, 133.8, 168.3; IR (CH_2Cl_2) cm^{-1}: 3489.5 (br), 3058.2 (m), 3024.8 (m), 2942.8 (m), 1771.3 (s), 1709.9 (s), 1467.6 (m), 1438.8 (s), 1398.8 (s), 1337.1 (s), 1266.2 (s), 1069.3 (m), 969.0 (m). MS (EI) m/e 321 (M^+, 45), 304 (5), 263 (2), 216 (24), 189 (20), 174 (87), 160 (89), 156 (25), 148 (33), 133 (100), 115 (30), 105 (41), 91 (44), 77 (45); High resolution MS. Anal. Calcd for $C_{20}H_{19}NO_3$: 321.1365. Found: 321.1369.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Organometallic compounds are among the most versatile intermediates for the formation of carbon-carbon bonds, but their high reactivity allows preparation of only relatively unfunctionalized reagents. In contrast, organozinc halides with a less reactive carbon-metal bond, display a high functional group tolerance, and can include a variety of functional groups such as esters,[7 8 9,10 11 12 13] enoates,[8,14] ketones,[7,15,16] nitriles,[17 18 19 20] halides,[21 22] amino groups,[14,23 24] phosphonates,[25] thioethers,[26] sulfoxides,[26] and sulfones.[26] A transmetallation of these zinc organometallics to the corresponding copper compounds, carried out using the THF-soluble copper salt CuCN·2LiCl, affords highly reactive copper reagents [RCu(CN)ZnX]. In this procedure, we describe the synthesis of an alkylzinc iodide with a phthalimido group at the γ-position, its conversion to the corresponding copper derivative, and its regiospecific 1,2-addition to cinnamaldehyde in the presence of boron trifluoride etherate. Copper reagent **3** reacts with several other electrophiles in excellent yields (see Scheme). This preparation illustrates the convenient synthesis of highly functionalized organozinc halides in THF[27] and their high synthetic potential.



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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

brine

ethyl acetate (141-78-6)

ammonium chloride (12125-02-9)

sodium chloride (7647-14-5)

sodium thiosulfate (7772-98-7)

nitrogen (7727-37-9)

copper (7440-50-8)

acetone (67-64-1)

Benzophenone (119-61-9)

zinc (7440-66-6)

sodium (13966-32-0)

1,2-dibromoethane (106-93-4)

ammonium hydroxide (1336-21-6)

sodium iodide (7681-82-5)

cinnamaldehyde

dichloromethane (75-09-2)

copper cyanide (544-92-3)

magnesium sulfate (7487-88-9)

iodide (20461-54-5)

Tetrahydrofuran (109-99-9)

hexane (110-54-3)

Lithium chloride (7447-41-8)

boron trifluoride etherate (109-63-7)

argon (7440-37-1)

CHLOROTRIMETHYLSILANE (75-77-4)

phthalimido

(E)-2-(4-Hydroxy-6-phenyl-5-hexenyl)-1H-isoindole-1,3(2H)-dione

1H-Isoindole-1,3(2H)-dione, 2-(4-hydroxy-6-phenyl-5-hexenyl)- (121883-31-6)

2-(3-Iodopropyl)-1H-isoindole-1,3(2H)-dione (5457-29-4)

2-(3-bromopropyl)-1H-isoindole-1,3(2H)-dione, N-(3-bromopropyl)phthalimide (5460-29-7)

N-propylphthalimide (5323-50-2)

(E)-Cinnamaldehyde (104-55-2)

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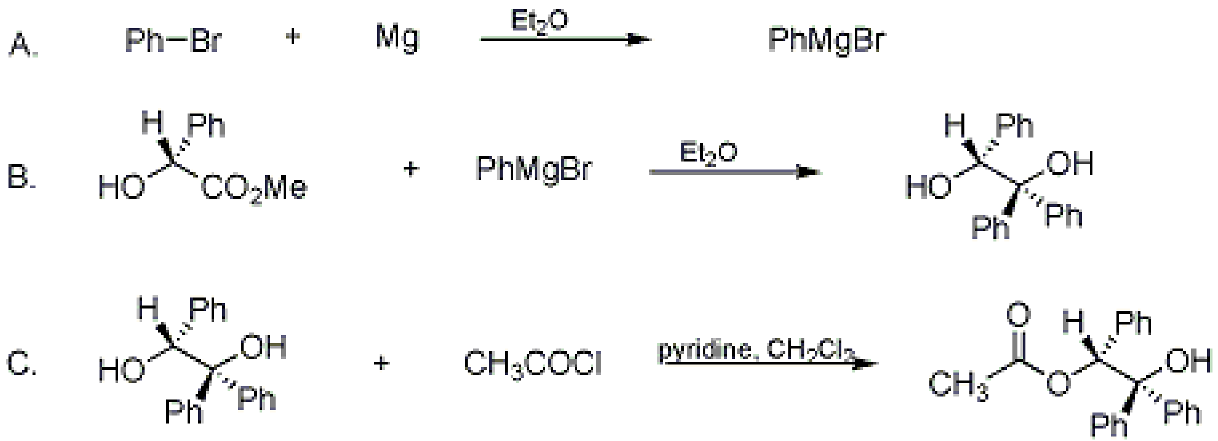
Organic Syntheses, CV 9, 507

(R)-(+)-2-HYDROXY-1,2,2-TRIPHENYLETHYL ACETATE

[1,2-Ethanediol, 1,1,2-triphenyl-, 2-acetate, (R)-]



Submitted by Manfred Braun, Silke Gräf, and Sabine Herzog[1].
Checked by Joseph Lynch and Ichiro Shinkai.

1. Procedure

A. *Phenylmagnesium bromide* (Note 1). Ether (100 mL) is added to magnesium (Mg) turnings (74.6 g, 3.07 mol) in a dry, 5-L flask equipped with an overhead stirrer, reflux condenser, and addition funnel. Iodine (several crystals) is added and the mixture is stirred for several minutes (the color dissipates). Bromobenzene (9.23 mL, 13.76 g, 87.64 mmol) is added and the mixture is heated with a heat gun to initiate the reaction. A solution of bromobenzene (322.8 mL, 481 g, 3.06 mol) in ether (600 mL) is added dropwise over 2.75 hr, maintaining a gentle reflux. The dark brown mixture is stirred an additional 3 hr at ambient temperature under nitrogen and then cooled in an ice/methanol bath to 0°C.

B. *(R)-(+)-1,1,2-Triphenylethanediol*. A solution of methyl (R)-(−)-mandelate (92.3 g, 0.556 mol) (Note 2) in ether (500 mL) (Note 3) is added dropwise to the cold solution of phenylmagnesium bromide prepared in Step A at a rate such that the temperature does not rise above 10°C (1.25 hr required). The mixture is then allowed to stir an additional 2 hr with cooling (final temp 6°C) before heating to reflux. After 3 hr at reflux the solution is allowed to stand overnight at ambient temperature under nitrogen. The solution (*CAUTION: Contains benzene*) is poured onto 1 kg of ice contained in a 5-L, round-bottomed flask placed in an ice bath and equipped with an overhead stirrer and reflux condenser. A solid mass results that is broken up with a spatula so that it is partly stirrable. Hydrochloric acid (6 N, 516 mL) is added dropwise, while monitoring the pH, to a pH of 3.9. The two-phase, liquid mixture is stirred for 1 hr at ambient temperature. The layers are separated and the aqueous layer

is extracted with methylene chloride (CH_2Cl_2) (3 × 250 mL). The combined organic layers are dried ($MgSO_4$), filtered, and concentrated to a thick caramel-like oil (179 g). Methanol (300 mL) is added causing crystallization and the mixture is heated to reflux to give a clear yellow solution. The solution is allowed to cool to room temperature over several hours. It is then cooled in an ice bath to 0°C and aged for 1 hr. The product is collected on a filter and washed with cold (–10°C) methanol (200 mL). The solid is dried under reduced pressure at 50°C (106.6 g, 66%), mp 123–127°C, $[\alpha]_D^{20}$ +220° (95% ethanol, *c* 1). Liquid chromatographic (LC) analysis shows 96.6% purity with 3.2% benzoin contamination (area %, uncorrected for relative response).

C. *(R)-(+)-2-Hydroxy-1,2,2-triphenylethyl acetate [(R)-HYTRA]*. Acetyl chloride (32.6 mL, 0.458 mol) in CH_2Cl_2 (85 mL) is added dropwise to R-(+)-triphenylethanediol (103.04 g, 0.355 mol) and pyridine (46.4 mL, 0.574 mol) in CH_2Cl_2 (860 mL) at 0°C (ice/methanol bath). The rate is controlled so that the temperature does not exceed 5° C. After the addition is complete, the mixture is allowed to warm to ambient temperature and aged for 4 hr. LC assay shows 1% unreacted diol. Water (430 mL) is added and the mixture is stirred vigorously for 30 min (pH was 3.5). The mixture is concentrated on a rotary evaporator until second phase CH_2Cl_2 is no longer observed in the distillate or in the reaction mixture. Water (100 mL) is used to aid transfer of the solids to a filter, the filter cake is washed with water (600 mL), and air dried (with suction) overnight. The resulting wet cake is transferred to a 3-L flask equipped with an overhead stirrer, a distillation head, and an addition funnel. Toluene (2 L) is added and the azeotrope is removed by atmospheric distillation. After 480 mL of distillate is collected (80 mL of second phase water), 300 mL of toluene is added; an additional 460 mL of distillate is collected and fresh toluene (500 mL) is added. After 100 mL of clear distillate is collected, fresh toluene (200 mL) is added a third time and the mixture is finally distilled to a 1.5-L mark on the flask (a total of 1620 mL of distillate, including 90 mL of second phase water, is collected). The mixture is allowed to cool overnight with stirring and then cooled to 0°C and aged for 2 hr. The product is collected on a filter, washed with toluene (room temperature, 400 mL) and dried under reduced pressure at 60°C for 7 hr (Note 4); 108.91 g (92.3%), mp 249–251°C, $[\alpha]_D^{25}$ +213° (pyridine, *c* 1), $[\alpha]_D^{20}$ +218° (pyridine, *c* 1). LC analysis shows 100.0% pure (Note 5) and (Note 6).

2. Notes

1. The preparation of phenylmagnesium bromide follows approximately the procedure of Allen, C. F. H.; Converse, S. *Org. Synth., Coll. Vol. I* **1941**, 226.

2. Commercial methyl (R)-(–)-mandelate can be used. The submitters prepared it from (R)-(–)-mandelic acid (BASF AG, D-Ludwigshafen), $[\alpha]_D^{20}$ –154.9° (water, *c* 2): A 2-L, round-bottomed flask equipped with a condenser with a drying tube and a magnetic stirrer is charged with 100 g (0.66 mol) of (R)-(–)-mandelic acid and 500 mL of dry methanol. One milliliter of sulfuric acid is added and the mixture is heated under reflux for 2 hr. (LC analysis showed a 97:3 ratio of ester to acid which did not change after 2 hr further reflux). The

flask is cooled in an ice bath and 50 mL of water and 7 g (83 mmol) of sodium bicarbonate ($NaHCO_3$) are added under stirring, which is continued until the pH rises to 7.6 The mixture is filtered and concentrated on a rotary evaporator at 50° C. On cooling the two-phase liquid mixture a solid mass is obtained that is broken up with a spatula; water (200 mL) is added and the slurry is stirred for 2 hr. The product is collected on a filter, washed with water and dried under reduced pressure to give 93.0 g (85%) of white solid, mp 56–58°C, $[\alpha]_D^{25}$ −133° (95% ethanol, *c* 1) [lit.[2] $[\alpha]_D^{25}$ −128.6° (ethanol, *c* 1)].

3. Molten methyl mandelate dissolves readily in diethyl ether.

4. Careful drying is strongly recommended, since methanol is retained tenaciously by crystalline 1,1,2-triphenyl-1,2-ethanediol. Material containing minor amounts of methanol can be used in the following step provided that the acylation is performed with a 50% excess of acetyl chloride.

5. (R)- and (S)-HYTRA are commercially available from Merck AG, D-Darmstadt.

6. The spectral properties are as follows: ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.96 (s, 3 H, CH_3), 2.78 (s, 1 H, OH), 6.68 (s, 1 H, PhCH), 7.05–7.40 (m, 13 H, ArH), 7.54–7.57 (m, 2 H, ArH).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

(R)-(+)-1,1,2-Triphenyl-1,2-ethanediol is available from methyl[3] and ethyl[4] (R)-(−)-mandelate by treatment with phenylmagnesium bromide. The synthesis of (R)-(+)-2-hydroxy-1,2,2-triphenylethyl acetate [(R)-HYTRA] has been reported previously by the submitters.[5,6] (S)-(−)-2-Hydroxy-1,2,2-triphenylethyl acetate is available according to this procedure starting from the enantiomeric methyl (S)-(+)-mandelate or (S)-(+)-mandelic acid, respectively, both of which are commercially available. Doubly deprotonated HYTRA can be used to introduce an acetate moiety into achiral as well as chiral aldehydes in an enantioselective manner.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 497
- Org. Syn. 77, 45

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

(R)-(+)-2-hydroxy-1,2,2-triphenylethyl acetate [(R)-HYTRA]

methyl (R)-(−)-mandelate

(R)-(−)-mandelic acid

(S)-(−)-2-Hydroxy-1,2,2-triphenylethyl acetate

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

acetyl chloride (75-36-5)

sodium bicarbonate (144-55-8)

magnesium (7439-95-4)

nitrogen (7727-37-9)

iodine (7553-56-2)

pyridine (110-86-1)

Benzoin (119-53-9)

toluene (108-88-3)

bromobenzene (108-86-1)

Phenylmagnesium bromide (100-58-3)

methylene chloride (75-09-2)

(R)-(+)-1,1,2-triphenyl-1,2-ethanediol, (R)-(+)-1,1,2-Triphenylethanediol (95061-46-4)

1,1,2-triphenyl-1,2-ethanediol

(R)-(+)-2-Hydroxy-1,2,2-triphenylethyl acetate (95061-47-5)

1,2-Ethanediol, 1,1,2-triphenyl-, 2-acetate, (R)- (95061-47-5)

R-(+)-triphenylethanediol

methyl mandelate (4358-87-6)

methyl (S)-(+)-mandelate (771-90-4)

(S)-(+)-mandelic acid (17199-29-0)

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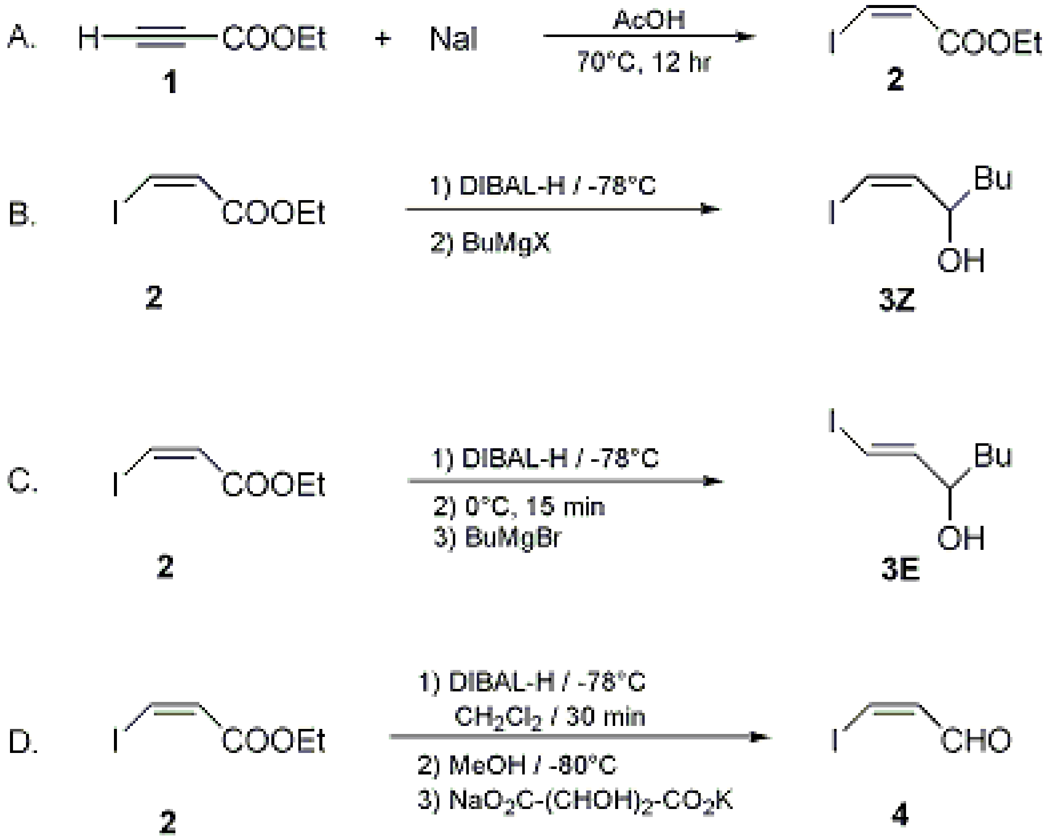
Organic Syntheses, CV 9, 510

A SIMPLE AND CONVENIENT METHOD FOR THE PREPARATION OF (Z)-β-IODOACROLEIN AND OF (Z)- OR (E)-γ-IODO ALLYLIC ALCOHOLS: (Z)- AND (E)-1-IODOHEPT-1-EN-3-OL

[2-Propenal, 3-iodo-, (Z)- and 1-Hepten-3-ol, 1-iodo-, (Z)- and (E)-]



Submitted by Ilane Marek, Christophe Meyer, and Jean-F. Normant[1].
Checked by David A. Favor and Amos B. Smith, III.

1. Procedure

A. *Ethyl (Z)-β-iodoacrylate* (Note 1). A 250-mL, round-bottomed flask equipped with a magnetic stirring bar and nitrogen gas inlet is charged with 30.6 g (204 mmol) of dry sodium iodide (Note 2) and 100 mL of glacial acetic acid. To the stirred solution is added in one portion 20.6 mL (204 mmol) of ethyl propiolate (Note 2) and the resulting mixture is heated with an oil bath (bath temperature 70°C) for 12 hr. The brown solution is cooled to room temperature, and 100 mL of water and 100 mL of ether are added. The organic layer is separated and the aqueous layer is extracted with ether (2 × 20 mL). The combined organic layers are treated with 3 M aqueous potassium hydroxide (ca. 150 mL in 50-mL portions) until the aqueous phase becomes

neutral (pH = 7), washed with 50 mL of brine, and dried over anhydrous magnesium sulfate. After evaporation of the solvent, the residual brown oil is distilled to give 40.6 g (88% yield) of ethyl (Z)-β-iodoacrylate (Note 3) as a pale yellow liquid, bp 57°C/0.1 mm.

B. *(Z)-1-Iodohept-1-en-3-ol*. A 100-mL, dry (Note 4), four-necked, round-bottomed flask equipped with a mechanical stirrer, an internal thermometer, a rubber septum, and a nitrogen gas inlet, is charged with 2.26 g (10 mmol) of ethyl (Z)-β-iodoacrylate, 2, and 20 mL of anhydrous dichloromethane (Note 5). The stirred solution is cooled to −78°C by means of a liquid nitrogen bath and 10 mL (10 mmol) of a 1 M solution of diisobutylaluminum hydride in hexane (Note 6) is added dropwise with a syringe at such a rate that the temperature does not exceed −75°C. After stirring for 30 min at −78°C (Note 7) 11 mL (11 mmol, 1 M solution in Et_2O) of a butylmagnesium bromide solution in ether (Note 8) is added dropwise at −70°C with a syringe through the septum. The cooling bath is removed and the reaction mixture is allowed to warm to room temperature. Hydrolysis is carried out at −20°C by dropwise addition of 20 mL of a 1 M aqueous solution of hydrochloric acid, followed by addition of 30 mL of ether. The organic layer is separated, the aqueous layer is extracted with ether (2 × 20 mL), and the combined extracts are dried over magnesium sulfate. After rotary evaporation of the solvents, the residual pale yellow oil is purified by chromatography through 1.85 g of silica (Note 9) packed in a 4-cm diameter column and eluted with 15% ethyl acetate in hexane, to give 1.7 g of (Z)-1-iodohept-1-en-3-ol, **2**, (71% yield) as a pale yellow liquid (Note 10).

C. *(E)-1-Iodohept-1-en-3-ol*. A 100-mL, dry (Note 4) four-necked, round-bottomed flask equipped with a mechanical stirrer, an internal thermometer, a rubber septum, and a nitrogen gas inlet, is charged with 2.26 g (10 mmol) of ethyl Z-β-iodoacrylate, 2, and 20 mL of anhydrous dichloromethane (Note 5). The stirred solution is cooled to −78°C by means of a liquid nitrogen bath and 10 mL (10 mmol) of a 1 M solution of diisobutylaluminum hydride in hexane (Note 6) is added dropwise with a syringe at such a rate that the temperature does not exceed −75°C. After the mixture is stirred for 30 min at −78°C (Note 7), it is allowed to warm slowly to 0°C in 45 min, stirred for 15 min at this temperature, and then cooled to −20°C; 11 mL (11 mmol, 1 M solution in Et_2O) of a butylmagnesium bromide solution in ether (Note 8) is added dropwise at −20°C with a syringe through the septum. The reaction mixture is allowed to warm to room temperature and worked up, as described for the Z isomer. (E)-1-Iodohept-1-en-3-ol (1.9 g) is obtained as a colorless liquid (79% yield) (Note 11) with an E/Z ratio of 96/4 .

D. *(Z)*-β-*Iodoacrolein*, **4**. A 100-mL, dry (Note 4), four-necked, round-bottomed flask equipped with a mechanical stirrer, an internal thermometer, a rubber septum, and a nitrogen gas inlet, is charged with 2.26 g (10 mmol) of ethyl (Z)-β-iodoacrylate, 2, and 20 mL of anhydrous dichloromethane (Note 5). The stirred solution is cooled to −78°C in a liquid nitrogen bath and 10 mL (10 mmol) of a 1 M solution of

diisobutylaluminum hydride in hexane (Note 6) is added dropwise with a syringe at such a rate that the temperature does not exceed −75°C. After the solution is stirred at −78°C (Note 7), 5 mL of cold methanol (Note 12) is added dropwise through the septum with a syringe at −80°C. Immediately after this addition, 25 mL of aqueous 20% potassium sodium tartrate is added to the cold reaction mixture in one portion, which causes the temperature to reach 0°C within a few seconds. The cooling bath is removed and 20 mL of ether is added to the hydrolyzed reaction mixture, which is further stirred for 20 min at room temperature (Note 13). It is then filtered through a pad of Celite and extracted with 30 mL of ether. The organic layer is washed with brine and dried over potassium carbonate. After careful rotary evaporation of the solvents, 1.6 g of (Z)-β-iodoacrolein is obtained as a yellow liquid (88%) (Note 14), which can be handled easily as ether or dichloromethane solutions, and can be stored in the refrigerator for a few weeks without decomposition or isomerization.

2. Notes

1. Part A of the procedure should be carried out in an efficient fume hood to avoid exposure to noxious vapor (acetic acid) and to lachrymatory ethyl propiolate.
2. Sodium iodide, 99%, was purchased from Janssen Chimica and used as received. Glacial acetic acid, 99%, was purchased from Prolabo. Ethyl propiolate was obtained from Janssen Chimica and used as received.
3. The product exhibits the following physical and spectral properties: IR (film) cm^{-1}: 3080, 2940, 1735, 1640, 1425, 1365, 1230, 1170, 1020, 925, 730; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.32 (t, 3 H, J = 7.15, $C\mathbf{H}_3CH_2$), 4.25 (q, 2 H, J = 7.14, $OC\mathbf{H}_2$), 6.89 (d, 1 H, J = 9.34, =C**H**-CO_2Et), 7.44 (d, 1 H, J = 9.34, =C**H**I); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.2, 60.8, 94.6, 129.9, 164.6.
4. All glassware is oven dried at 140°C overnight and assembled while hot under a nitrogen atmosphere.
5. Dichloromethane was distilled from calcium hydride and stored over 4 Å molecular sieves.
6. Diisobutylaluminum hydride was purchased from Aldrich Chemical Company, Inc.
7. At this point, TLC analysis of a hydrolyzed (1 M aqueous hydrochloric acid) aliquot, eluted with 10% ethyl acetate in hexane, indicated that the reaction is complete.
8. Butylmagnesium bromide was prepared from the corresponding butyl bromide and magnesium turnings in anhydrous ether.[2]
9. Silica gel was purchased from Merck: Geduran SI 60.
10. The product exhibits the following spectral properties: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.90 (t, 3 H, J = 7.15, $C\mathbf{H}_3$), 1.31–1.36 (m, 4 H), 1.51–1.63 (m, 2 H), 1.7 (s, 1 H, O**H**), 4.4 (m, 1 H, C**H**OH), 6.20 (t, 1 H, J = 7.69, =C**H**), 6.33 (d, 1 H, J = 7.69, =C**H**I); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.0, 22.6, 27.1, 35.6, 74.4

(CHOH), 82.2 (=CI), 143.4 (=CH).

11. The product exhibits the following spectral properties: IR (film) cm^{-1}: 3350, 3060, 2950, 2920, 2850, 1605, 1450, 1265, 1165, 1015, 930; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.90 (t, 3 H, J = 7.15, C**H**$_3$), 1.31–1.36 (m, 4 H), 1.51–1.63 (m, 2 H), 1.71 (s, 1 H), 4.1 (m, 1 H, C**H**OH), 6.34 (dd, 1 H, J = 14.3, 1.1, =C**H**I), 6.58 (dd, 1 H, J = 14.3, 6.6, =C**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.9, 22.5, 27.2, 36.2, 74.6 (CHOH), 77.2 (=CI), 148.6 (=CH).

12. Methanol was obtained from Merck & Company, Inc., and used as received.

13. The workup should be carried out under an efficient fume hood since the title compound is a lachrymator.

14. The (Z)-β-iodoacrolein exhibits the following spectral properties: IR (CCl_4) cm^{-1}: 3050, 2820, 2730, 1675, 1610, 690; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.77 (dd, 1 H, J = 8.25, 6.6, =C**H**-CHO), 7.79 (d, 1 H, J = 8.25, =C**H**I), 9.67 (d, 1 H, J = 6.6, C**H**O); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 103.0 (=CHI), 136.4 (=CH), 195.4 (C=O).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The present procedure illustrates the simplest convenient method for the preparation of (Z)- or (E)-γ-iodo allylic alcohols and (Z)-β-iodoacrolein. It uses ethyl propiolate as a unique starting material: ethyl propiolate and ethyl tetrolate can be hydroiodinated regio- and stereospecifically (Z > 99%) by reaction with inexpensive sodium iodide in acetic acid[3 4 5 6 7 8] (Scheme 1). The same methodology has been applied recently to the synthesis of enantiomerically pure (Z)-2-haloalkenyl sulfoxides.[9] By reaction of 2 with diisobutylaluminum hydride at low temperature, and subsequent reaction with a Grignard reagent, one can obtain, very easily, the secondary (Z)-γ-iodo allylic alcohols with good chemical yield and exclusive Z stereochemistry of the double bonds (Table I). This one-pot "reduction-C-alkylation" sequence of the ester group allows the preparation of very sensitive derivatives (entry 5 or 6), which are difficult to prepare by usual methods.[10 11 12 13]

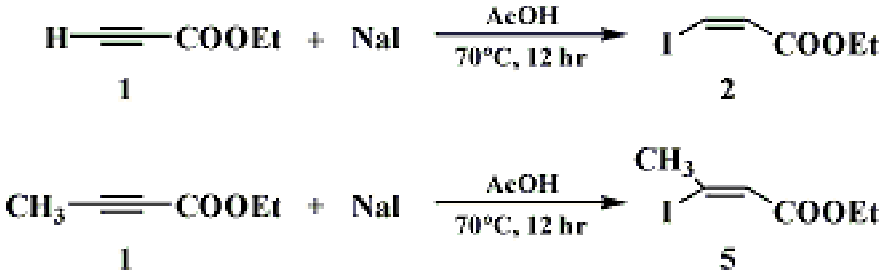
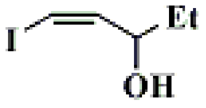
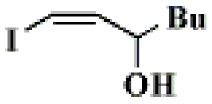
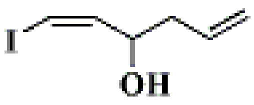
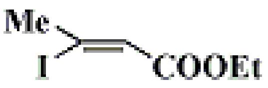
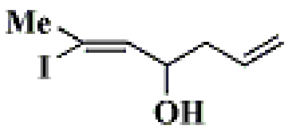
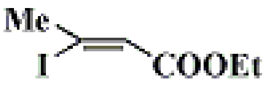
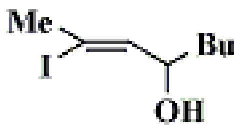


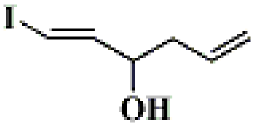
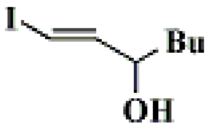
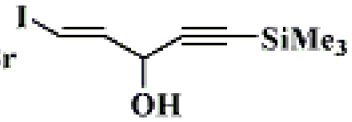
TABLE I

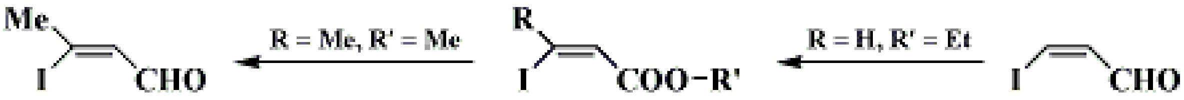
Starting Ester	Grignard Reagents	Products	Yield
2	EtMgBr		88%
2	BuMgBr		79%
2	PhMgBr		85%
2			72%
2			81%
2			63%
			65%
	BuMgBr		81%

However, reaction of ethyl (Z)-β-iodoacrylate with DIBAL-H at low temperature (−78°C, 15 min) followed by warming to 0°C and addition of a Grignard reagent (−20°C to 0°C) now leads to the E isomers of the secondary γ-iodo allylic alcohols with an E/Z

ratio of 96/4 (Table II). This isomerization can be rationalized as occurring by the influence of the weak Lewis acid, $Al(iBu)_2OEt$, generated by α-elimination of the thermally labile aluminooxyacetal.[14] The (Z)-β-iodoacrolein **4** and crotonaldehyde **6** (Scheme 2) are also easily obtained by dropwise addition of an excess of methanol to the aluminooxyacetal at low temperature, immediately followed by alkaline hydrolysis. (3Z)-Iodopropenals are valuable intermediates in organic synthesis because of the presence of three functional groups on three carbon atoms.[14,15]

TABLE II

Starting Ester	Grignard Reagents	Products	Yield
			80%
	BuMgBr		86%
			72%



6 4

Starting from ethyl (Z)-β-iodoacrylate, (E)- or (Z)-γ-iodo allylic alcohols are easily obtained in a highly stereoselective manner by a "reduction-C-alkylation" of the ester group without alteration of the nature or geometry of the iodo vinylic part. (Z)-β-Iodoacrolein can be easily isolated in good yields, and gives rise to various derivatives.

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

silica

brine

1-Hepten-3-ol, 1-iodo-, (Z)- and (E)-

(Z)-ß-bromoacrolein

(Z)-ß-chloroacrolein

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether (60-29-7)

magnesium (7439-95-4)

Butyl bromide (109-65-9)

nitrogen (7727-37-9)

carbon (7782-42-5)

potassium hydroxide (1310-58-3)

sodium iodide (7681-82-5)

Butylmagnesium bromide (693-03-8)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

hexane (110-54-3)

crotonaldehyde (123-73-9)

calcium hydride (7789-78-8)

diisobutylaluminum hydride (1191-15-7)

ethyl propiolate (623-47-2)

Ethyl tetrolate (4341-76-8)

(E)-1-Iodohept-1-en-3-ol (151160-08-6)

(Z)-β-IODOACROLEIN, 2-Propenal, 3-iodo-, (Z)- (138102-13-3)

(Z)-1-Iodohept-1-en-3-ol (138102-06-4)

potassium sodium tartrate (304-59-6)

Ethyl (Z)-β-iodoacrylate, ethyl Z-β-iodoacrylate (31930-36-6)

β-Iodoacrolein

γ-iodo allylic alcohols

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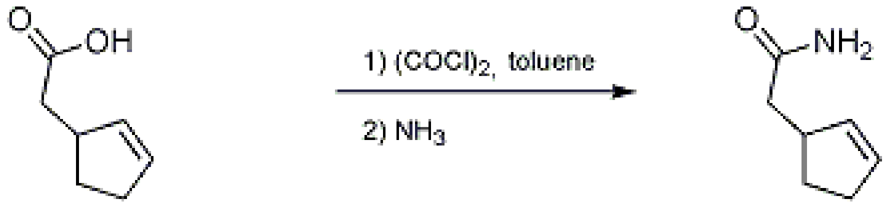
Organic Syntheses, CV 9, 516

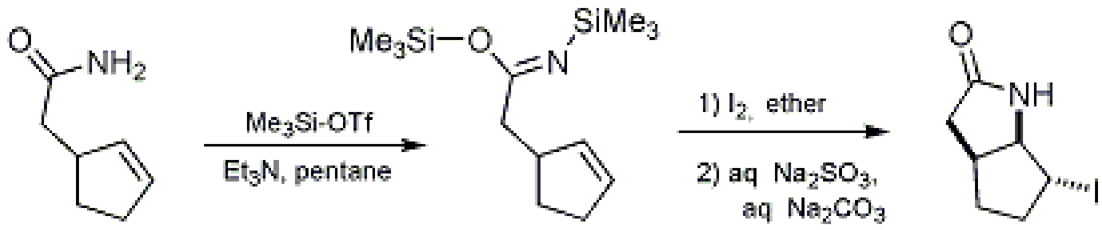
IODOLACTAMIZATION: 8-exo-IODO-2-AZABICYCLO[3.3.0]OCTAN-3-ONE

[Cyclopenta[b]pyrrol-2(1H)-one, hexahydro-6-iodo-, (3aα,6α,6aα)-]

A.



B.



Submitted by Spencer Knapp and Frank S. Gibson[1].
Checked by Chris Melville and James D. White.

1. Procedure

CAUTION! The following operations produce lachrymatory and corrosive vapors and must be carried out in a well-ventilated fume hood.

A. *2-Cyclopentene-1-acetamide*. A dry, 250-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, serum stopper, 25-mL pressure equalizing addition funnel, and an argon atmosphere with provision for venting gaseous reaction products (Note 1). The vessel is charged with 20 g (152 mmol) of 2-cyclopentene-1-acetic acid (Note 2) and 25 mL of dry toluene (Note 3). Oxalyl chloride (17.3 mL, 1.3 equiv) is added slowly over a 30-min period by means of the addition funnel, taking care to release any pressure buildup. (*Caution: gaseous hydrogen chloride evolution!*.) The dark reaction mixture is stirred for an additional 20 min while the second reaction vessel is assembled, then concentrated to about 2/3 volume at the vacuum pump (Note 4).

A 250-mL, three-necked, round-bottomed flask equipped with magnetic stirring bar, serum stopper, dry ice condenser, and argon atmosphere is cooled by means of a dry ice/acetone bath and charged with approximately 150 mL of dry liquid ammonia. The 2-(2-cyclopentenyl)acetyl chloride reaction mixture is added carefully but steadily (Note 5) to the cold and rapidly stirred ammonia by syringe. (*Caution: vigorous*

exothermic reaction!). Residual acid chloride is transferred by rinsing the first vessel with 5 mL of toluene. After the addition the mixture is stirred for an additional 5 min, then 60 mL of dichloromethane is added. The cold bath is removed and the excess ammonia is allowed to escape into the fume hood by stirring the open vessel overnight.

The crude reaction mixture is filtered and the filtrate is reserved. The solids are triturated by stirring vigorously with 100 mL of methanol for 20 min with gentle warming to about 40°C. The solids are filtered and triturated again in the same way. The three organic filtrates are combined and concentrated to near dryness. The resulting semi-solid is redissolved in 100 mL of dichloromethane, filtered to remove residual ammonium chloride, and concentrated to a light brown solid, 18.9 g. The crude product is dissolved in 60 mL of boiling tetrahydrofuran and allowed to crystallize in a –6°C freezer overnight. The amide is collected by filtration, washed with 5 mL of cold ether, and dried under reduced pressure, giving 15.77 g of white flakes, mp 128–129°C. The filtrate is concentrated to about 8 mL, brought to the cloud point by the addition of a few drops of hexane, and cooled in the freezer. Filtration as before gives a second crop of white flakes, 1.46 g, mp 128–129°C (total yield 17.23 g, 90.6%) (Note 6).

B. *8-exo-Iodo-2-azabicyclo[3.3.0]octan-3-one*. A dry, 500-mL, three-necked, round-bottomed flask equipped with magnetic stirring bar, serum stopper, 50-mL pressure-equalizing addition funnel, cold water bath, and argon atmosphere is charged with 12.5 g (100 mmol) of 2-cyclopentene-1-acetamide, 29.2 mL (210 mmol) of triethylamine (Note 7), and 80 mL of dry pentane (Note 8). By means of the addition funnel, 41 mL (210 mmol) of trimethylsilyl trifluoromethanesulfonate (Note 9) is slowly added to the cooled and rapidly stirred amide suspension over a 50-min period. After the addition is complete, the reaction mixture is stirred for an additional 20 min at room temperature, then the stirring is stopped, and the two layers are allowed to separate.

A second, dry, 500-mL, three-necked, round-bottomed flask is equipped with magnetic stirring bar, serum stopper, vacuum pump connection, and argon atmosphere. The (top) pentane layer from the first flask, which contains the bis (trimethylsilyl)imidate, is carefully transferred to the second flask by cannula, maintaining the argon atmosphere, and leaving the oily triethylammonium trifluoromethanesulfonate layer behind. This remaining salt is triturated with 30 mL of a dry 2:1 pentane/ether mixture by stirring for 15 min, allowing the layers to separate, then transferring the extract to the second flask as before. The trituration is repeated with a 30-mL portion of anhydrous ether, and the combined extracts in the second flask are concentrated with stirring to about 1/3 volume using the vacuum pump (Note 10).

A third, dry, 500-mL, three-necked, round-bottomed flask equipped with an addition funnel, magnetic stirring bar, serum stopper, cold water bath, and argon atmosphere is charged with 53.3 g (210 mmol) of molecular iodine and 140 mL of anhydrous ether. The mixture is allowed to stir for 10 min to dissolve most of the iodine. The concentrated organic extract in the second flask is now added to the iodine solution

with stirring and cooling over 15 min. The reaction mixture warms slightly during the addition, but should not reach reflux. An additional 10 mL of anhydrous ether is used to complete the transfer of the bis(trimethylsilyl)imidate. Near the end of the addition, the oily black layer (which contains the cyclized iminium salt) solidifies, leaving a clear light brown ether supernatant. The serum stopper is carefully removed and the solid residue gently broken up using a spatula. The stopper is replaced and the reaction mixture is allowed to stand for an additional 45 min with occasional swirling by hand. The reaction is quenched by removing the addition funnel and stopper and slowly adding 20 mL of saturated aqueous sodium carbonate. (*Caution: vigorous gas evolution!*). At this point stirring can be resumed. A 20-mL portion of saturated aqueous sodium sulfite is added slowly (*more gas evolution*), and the process is repeated until 100 mL each of saturated aqueous sodium carbonate and sulfite have been added. The reaction mixture is filtered, the crude solid iodolactam is reserved, and the organic layer is separated and reserved. The aqueous layer is saturated with sodium chloride and extracted with four, 100-mL portions of dichloromethane. The five organic extracts are combined, dried over anhydrous sodium sulfate, and concentrated to a light brown solid. This residue is dissolved in 20 mL of tetrahydrofuran and hexane is added to the cloud point. Cooling in the freezer gives colorless needles, which are collected and dried under reduced pressure to afford 1.60 g of iodolactam, mp 138–139°C.

The reserved solid from filtration is dried under reduced pressure, dissolved in 65 mL of hot tetrahydrofuran and filtered. The solution is allowed to cool, first at room temperature, then in the freezer. The product (16.77 g, mp 138–139°C) is collected as before. The mother liquor is concentrated to about 10 mL, brought to the cloud point by the addition of hexane, and cooled in the freezer, resulting in an additional crop of 1.70 g, mp 138–139°C. The total amount of iodolactam is 19.80 g, representing a 79% yield from the amide (Note 11).

2. Notes

1. All reaction glassware was oven dried at 120°C and assembled hot. The submitters used three evacuate/fill cycles from an argon-filled balloon fitted on a three-way stopcock to provide the inert atmosphere.
2. 2-Cyclopentene-1-acetic acid (96%) was purchased from Aldrich Chemical Company, Inc., and used as received.
3. Toluene was dried by distillation from –40 mesh calcium hydride. Unless otherwise specified, reagents in this procedure were obtained commercially and used as received.
4. In series with the usual (500 mL) dry ice/acetone trap, a trap filled with solid sodium hydroxide was used to protect the pump from acidic vapors.
5. Continuous addition of the carboxylic acid chloride solution is required to prevent clogging the syringe needle.
6. The spectral properties are as follows: FT-IR (KBr) cm^{-1}: 3360, 3355, 1663, 1634; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.42–1.49 (m, 1 H), 2.07–2.35 (m, 5 H), 3.06–3.09 (m, 1 H), 5.66 (br s, 1 H), 5.75 (app dd, 1 H, J = 2, 5), 5.76 (app dd, 1

H, J = 2.5, 4.5), 5.94 (br s, 1 H); ^{13}C NMR δ: 29.6, 31.8, 42.0, 42.3, 131.7, 133.7, 175.0.

7. Triethylamine was dried by distillation from –40 mesh calcium hydride.

8. Pentane was dried by distillation from –40 mesh calcium hydride.

9. Trimethylsilyl trifluoromethanesulfonate (99%) was purchased from Aldrich Chemical Company, Inc., and used as received.

10. Any adventitious water introduced during these operations results in a decreased yield of iodo lactam and the formation of iodo lactone as an undesired side product.

11. The spectral properties are as follows: FT-IR (KBr) cm^{-1}: 3189, 3078, 3034, 1680; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.55–1.60 (m, 1 H), 1.99–2.06 (m, 1 H), 2.10–2.20 (m, 2 H), 2.33–2.45 (m, 1 H), 2.70 (dd, 1 H, J = 18, 10), 3.05–3.13 (m, 1 H), 4.16 (br s, 1 H), 4.40 (d, 1 H, J = 7.2), 5.75–5.85 (br s, 1 H); ^{13}C NMR δ: 32.3, 32.9, 35.0, 35.5, 38.2, 69.8, 178.6.

Waste Disposal Information

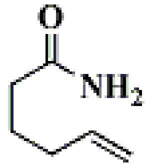
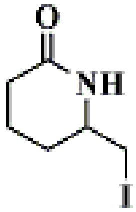
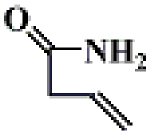
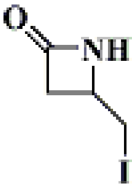
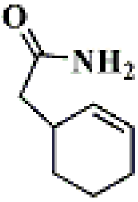
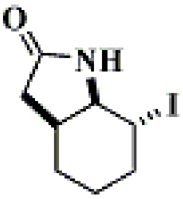
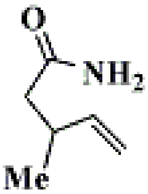
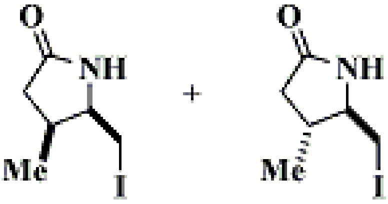
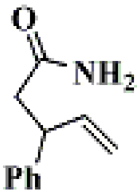
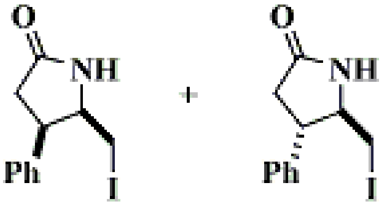
All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

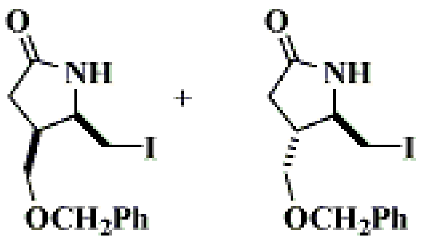
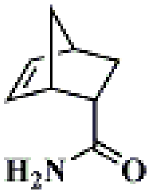
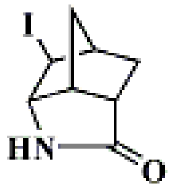
3. Discussion

This "iodolactamization" procedure has been optimized for the present example. Related reaction conditions have been used to generate a series of iodo lactams from the corresponding unsaturated amides (Table).[2,3] For these (smaller scale) examples, the cyclization was carried out in tetrahydrofuran solution, and isolation was by column chromatography. The lactams in entries 3, 4, and 8 have also been prepared by the submitters in 81%, 82%, and 78% yields, respectively, using the procedure described herein. Cyclization in ether solution rather than in tetrahydrofuran avoids the formation of iodobutanol,[3] which must then be separated from product.

Iodo lactams are a useful, new class of difunctional compounds.[2] Conversions of iodo lactams to N-acylaziridines,[3,4] unsaturated lactams,[3,5] azido lactams,[3,4] amino lactams,[3,4] hydroxy lactams,[3] seleneno lactams,[6 7] annulated lactams,[3,6,7,8] and other derivatives[2] have been described. Syntheses of ezoaminuroic acid[5] and slaframine[6,7] have used halo lactamizations for key steps. Halo lactams have also been prepared from aspartic acid[8] and glutamic acid,[9] from N-substituted unsaturated amides[10,11 12 13,14] and imidates,[15,16,17] and from unsaturated amides whose competing O-cyclization reaction is less favored.[18,19 20]

TABLE
PREPARATION OF IODO LACTAMS

Entry	Unsaturated Amide	Iodo Lactam(s)	% Yield (cis/trans)
1			35[a]
2			35[b]
3			86
4			88
5			84 (3:1)
6			88 (2:1)

7			86 (1:1)
8			80[c]

[a]10–20% of starting amide was also recovered. [b]54% of crotonamide was also isolated. [c]Overall yield after separate desilylation.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium carbonate and sulfite

ezoaminuroic acid

hydrogen chloride (7647-01-0)

ammonia (7664-41-7)

methanol (67-56-1)

ether (60-29-7)

ammonium chloride (12125-02-9)

sodium sulfite (7757-83-7)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

iodine (7553-56-2)

toluene (108-88-3)

Glutamic Acid (56-86-0)

Pentane (109-66-0)

dichloromethane (75-09-2)

Tetrahydrofuran (109-99-9)

oxalyl chloride (79-37-8)

hexane (110-54-3)

aspartic acid (56-84-8)

triethylamine (121-44-8)

calcium hydride (7789-78-8)

iodo

argon (7440-37-1)

Trimethylsilyl trifluoromethanesulfonate (27607-77-8)

8-exo-Iodo-2-azabicyclo[3.3.0]octan-3-one (100556-58-9)

2-Cyclopentene-1-acetamide (72845-09-1)

2-cyclopentene-1-acetic acid

2-(2-Cyclopentenyl)acetyl chloride

iodobutanol

crotonamide (23350-58-5)

Cyclopenta[b]pyrrol-2(1H)-one, hexahydro-6-iodo-, (3aα,6α,6aα)-

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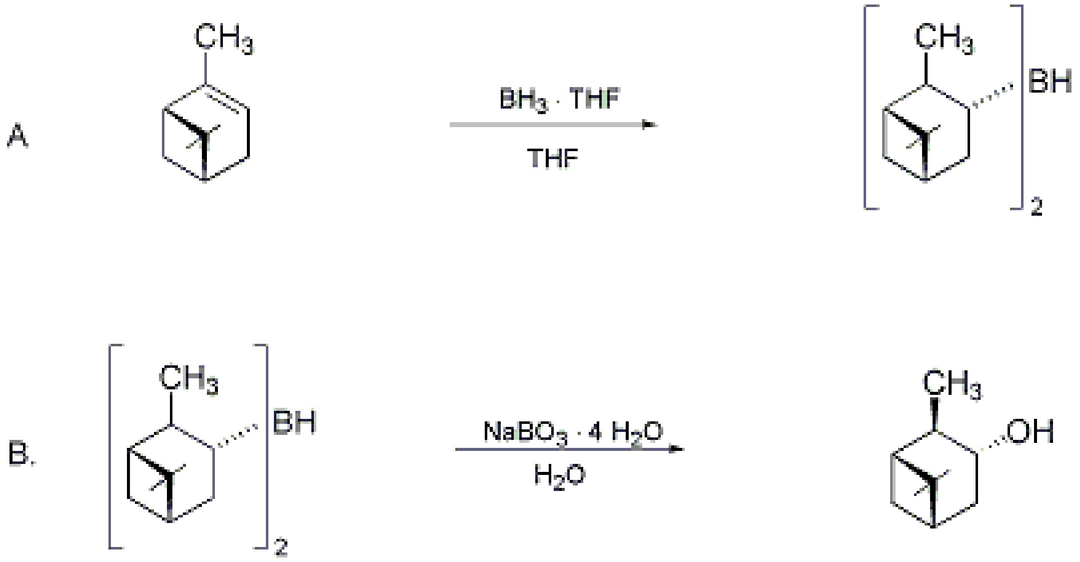
Organic Syntheses, CV 9, 522

A SIMPLE AND CONVENIENT METHOD FOR THE OXIDATION OF ORGANOBORANES USING SODIUM PERBORATE: (+)-ISOPINOCAMPHEOL

[Bicyclo[3.1.1]heptan-3-ol, 2,6,6-trimethyl-, [1S-(1α,2β,3α,5α)]-]



Submitted by George W. Kabalka, John T. Maddox, Timothy Shoup, and Karla R. Bowers[1].
Checked by C. Huart and Leon Ghosez.

1. Procedure

CAUTION! This procedure should be conducted in an efficient fume hood to assure the adequate removal of hydrogen, a flammable gas which forms explosive mixtures with air.

A. *(+)-Diisopinocampheylborane*. A dry, 250-mL, three-necked, round-bottomed flask, equipped for magnetic stirring, and with a nitrogen inlet vented through a mercury bubbler, a rubber septum, and a thermometer, is flushed with nitrogen and charged with 13.75 g (0.101 mol) of (−)-α-pinene and 25 mL of tetrahydrofuran (Note 1),(Note 2),(Note 3)). The mixture is cooled to 0°C in an ice-water bath, magnetic stirring is initiated, and 58.0 mL (0.055 mol) of 0.95 M borane-tetrahydrofuran solution (Note 4) is added via syringe at a rate such that the temperature of the reaction mixture remains below 5°C. After the addition is complete, the cooling bath is removed. The reaction mixture is allowed to warm to room temperature and stir for 2 hr to ensure complete reaction.[2]

B. *(+)-Isopinocampheol*. To the stirred solution of (+)-diisopinocampheylborane in

tetrahydrofuran, prepared above, 50 mL of distilled water is *slowly* added dropwise via syringe [*CAUTION!*] (Note 5) followed by the slow addition of 16.41 g (0.107 mol) of solid sodium perborate tetrahydrate (Note 6) through an appropriate addition funnel at a rate such that the temperature of the reaction mixture does not exceed 35°C (Note 7). Stirring is continued at room temperature (22°C) for 2 hr to ensure completion of the oxidation reaction. The contents of the flask are then poured into 70 mL of ice-cold water in a separatory funnel. After thorough mixing, the organic layer is removed and the aqueous layer is extracted twice with 25 mL of ether. The combined ether extracts are washed twice with 20-mL portions of water and then with 50 mL of saturated aqueous sodium chloride solution. The ether layer is dried over anhydrous magnesium sulfate, filtered, and concentrated on a rotary evaporator. The crude product is purified by short-path vacuum distillation to give 14.1–14.3 g (91–92%) of isopinocampheol, bp 68°C (0.7 mm), as white needles (mp 53–55°C) that crystallize in the receiving flask (Note 8). Recrystallization from pentane gives pure isopinocampheol as needles, mp 54–55°C (uncorrec.), $[\alpha]_D^{25}$ 34.4° (benzene, *c* 10) indicating 96.4% enantiomeric purity based on the highest reported literature value of 35.7° (Note 9).[3]

2. Notes

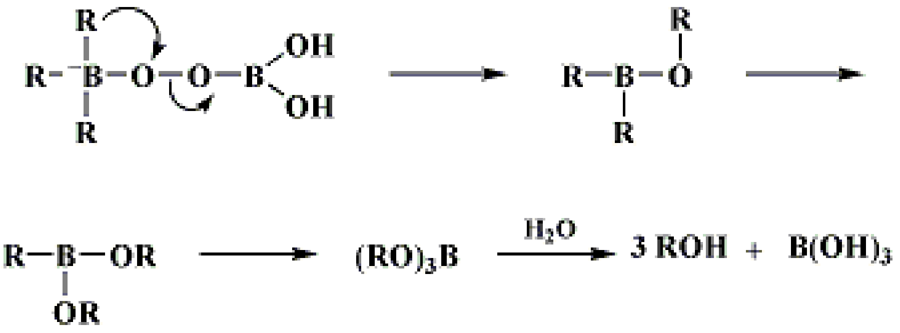
1. All glassware was predried at 140°C for at least 4 hr, assembled hot, flame dried, and cooled under a stream of nitrogen.
2. (1S)-(−)-α-Pinene [99%, 98% optical purity, $[\alpha]_D^{25}$ −50.6° neat] was purchased from Aldrich Chemical Company, Inc., and distilled under reduced pressure from lithium aluminum hydride before use.[2]
3. Tetrahydrofuran was distilled under nitrogen from sodium benzophenone ketyl.
4. Borane-tetrahydrofuran complex (1.0 M) was obtained from Aldrich Chemical Company, Inc., and the concentration of the solution determined using the literature procedure.[4]
5. *Since the hydroboration only proceeds to the dialkylborane stage, a large amount of hydrogen is evolved on hydrolysis. Very slow dropwise addition of water and adequate ventilation are recommended.*
6. Sodium perborate tetrahydrate was purchased from Aldrich Chemical Company, Inc. and used as received.
7. During the addition of sodium perborate the reaction flask is kept in a water bath (25°C).
8. An air condenser is employed for the distillation. The receiving flask is immersed in an ice bath.
9. The product exhibits the following spectral properties: IR (melt) cm^{-1}: 3300 (OH), 2930, 1472, 1450, 1384, 1367, 1050, 1015; ^1H NMR (250 MHz, $CDCl_3$) δ: 0.92 (s, 3 H), 1.04 (d, 1 H, J = 9), 1.13 (d, 3 H, J = 7), 1.22 (s, 3 H), 1.67–2.11 (m, 5 H), 2.30–2.58 (m, 2 H), 4.06 (dt, 1H); ^{13}C NMR (62.87 MHz, $CDCl_3$) δ: 20.7, 23.7, 27.7, 34.4, 38.1, 39.1, 41.8, 47.8, 47.9, 71.7.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

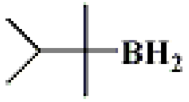
This procedure illustrates the simplest and most convenient method for oxidizing organoboranes, in the present example a dialkylborane. It uses sodium perborate,[5] an inexpensive, safe, and easily handled reagent, as the oxidizing agent. The reaction proceeds under mild conditions and the yield of the product alcohol is generally as high or higher than that obtained in the sodium hydroxide/hydrogen peroxide oxidation procedure.[6] Thus, the sodium perborate method is an attractive alternative to the base/hydrogen peroxide oxidation procedure. In the case described above, the perborate procedure produces higher yields of (−)-isopinocampheol than the sodium hydroxide/hydrogen peroxide procedure with comparable stereoselectivity.[7] Although the mechanism of the oxidation has not been investigated in detail, sodium perborate does not appear to be acting as a simple mixture of hydrogen peroxide and sodium borate.[8,9,10,11] Presumably, borate is a more effective leaving group (Scheme 1) than hydroxide ion which is generated during oxidation by hydrogen peroxide .

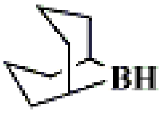
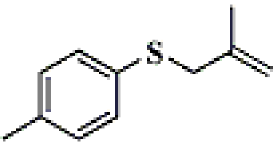
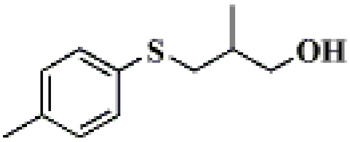
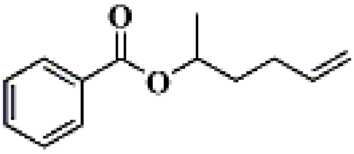
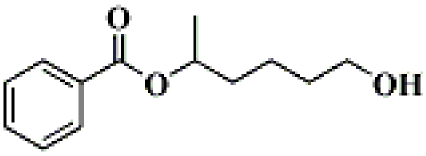
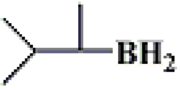
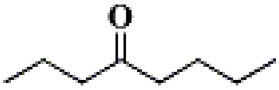
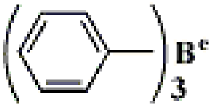
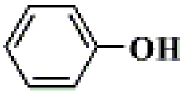


Sodium perborate, owing to its stability, commercial availability, and ease of handling, should prove to be a popular reagent for oxidizing organoboranes. Some representative examples of the oxidation of organoboranes bearing a variety of alkyl and aryl groups are listed in Table I.[12] [13]

TABLE I

SODIUMPERBORATEOXIDATION OFORGANORANES[a]

Alkene	Reagent	Product	Yield (%)[b]
			93

			99
	BH_3		92
	BH_3		86
			84
			87

[a]The organoboranes were formed via the hydroboration of the alkene listed. [b]Isolated yield. [c]One equivalent of 2,3-dimethyl-2-butanol was isolated in addition to 2 equiv of 2-hexanol. [d]One equivalent of 1,4-cyclooctanediol was isolated in addition to the 1-hexanol. [e]Triphenylborane was purchased from Aldrich Chemical Company, Inc.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium benzophenone ketyl

(−)-α-PINENE

(−)-ISOPINOCAMPHEOL

(1S)-(−)-α-Pinene

Benzene (71-43-2)

ether (60-29-7)

hydrogen (1333-74-0)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

hydrogen peroxide (7722-84-1)

Pentane (109-66-0)

magnesium sulfate (7487-88-9)

borane (7440-42-8)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

sodium borate

sodium perborate tetrahydrate (10486-00-7)

Isopinocampheol, (+)-Isopinocampheol (27779-29-9)

(+)-Diisopinocampheylborane (21947-87-5)

SODIUM PERBORATE

Bicyclo[3.1.1]heptan-3-ol, 2,6,6-trimethyl-, [1S-(1α,2β,3α,5α)]- (24041-60-9)

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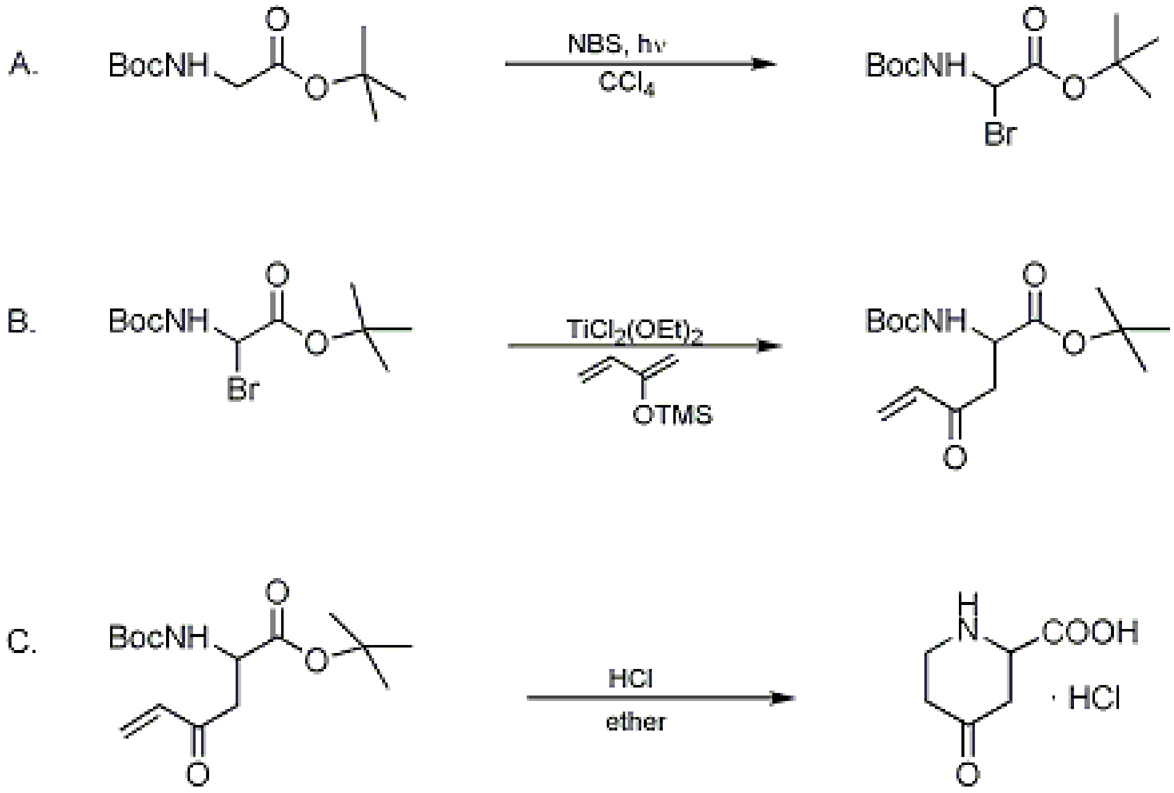
Organic Syntheses, CV 9, 526

TITANIUM-MEDIATED ADDITION OF SILYL DIENOL ETHERS TO ELECTROPHILIC GLYCINE: 4-KETOPIPECOLIC ACID HYDROCHLORIDE

[Pipecolic acid, 4-oxo-, hydrochloride]



Submitted by Clarisse Mühlemann, Peter Hartmann, and Jean-Pierre Obrecht[1].
Checked by Eugene Ho and David L. Coffen.

1. Procedure

A. *2-Bromo-N-Boc-glycine tert-butyl ester*. In a 1-L, round-bottomed flask are placed 20.0 g (0.0865 mol) of N-Boc-glycine tert-butyl ester (Note 1) and 16.2 g (0.0912 mol) of N-bromosuccinimide (Note 2). Carbon tetrachloride (350 mL, (Note 3)) is added, the flask is connected to a clean rotatory evaporator (Note 4) and the apparatus is flushed with argon. The flask is cooled, while being rotated, by means of a water bath and is irradiated with two 150-W tungsten lamps (Note 5) for 1 hr. The colorless solution becomes dark red and a precipitate forms. The suspension is filtered through a Schlenk tube and the carbon tetrachloride (CCl_4) is evaporated under reduced pressure. The remaining yellowish oil is employed in the next step without purification (Note 6).

B. *tert-Butyl [1-(tert-butoxycarbonyl)-3-oxo-4-pentenyl]carbamate*. The crude

bromination product from the previous step is taken up in 240 mL of dry tetrahydrofuran (THF) (Note 7) and transferred to a 1000-mL flask equipped with a stirrer, thermometer, dropping funnel, and argon inlet. The solution is cooled to −78°C and a solution of 42 g (0.20 mol) of dichlorodiethoxytitanium [$TiCl_2$ $(OEt)_2$] in 80 mL of dry THF (Note 8) is added at such a rate that the internal temperature does not exceed −72°C. When the addition is complete, the reaction mixture is stirred at −78°C for 10 min and then 24 g (0.170 mol) of 2-trimethylsiloxybutadiene (Note 9) in 100 mL of THF is added dropwise, causing only a slight increase in temperature (−72°C). The reaction mixture is allowed to warm to room temperature overnight and poured into 700 mL of ice-cooled, saturated sodium bicarbonate solution. After filtration through Celite, the aqueous phase is extracted with three 200-mL portions of ether. The combined organic layers are washed twice with water, dried over magnesium sulfate ($MgSO_4$), filtered, and concentrated. The remaining dark oil (29 g) is subjected to flash chromatography (20-cm column diameter, ether/hexane 1:3); 8.44–8.73 g (33–36%) (Note 10) of the product is obtained as a slightly yellowish oil (Note 11).

C. *4-Ketopipecolic acid hydrochloride*. tert-Butyl [1-(tert-butoxycarbonyl)-3-oxo-4-pentenyl]carbamate, 8.73 g (0.0308 mol), is dissolved in 280 mL of an ice-cooled, saturated solution of hydrogen chloride in ether. The solution is kept without stirring at room temperature overnight. The resulting suspension is filtered and the filter cake is immediately washed with dry ether (Note 12). The washing with ether is repeated four times and, after drying under reduced pressure, 5.48 g (99%) of 4-ketopipecolic acid hydrochloride is obtained as a colorless powder, mp 139–142°C dec (Note 13).

2. Notes

1. Boc-Glycine tert-butyl ester can be prepared by treatment of glycine tert-butyl ester hydrochloride (Aldrich Chemical Company, Inc.) with di-tert-butyl dicarbonate (Fluka Chemical Corporation) and triethylamine in THF.[2]
2. N-Bromosuccinimide was purchased from Fluka Chemical Corporation, recrystallized from water, and dried well in a vacuum desiccator.
3. Carbon tetrachloride is toxic and should only be handled in a well-ventilated hood.
4. The rotatory evaporator was washed with ethanol and ether. Bromination on a smaller scale can be carried out in a three-necked, round-bottomed flask with a thermometer, argon inlet, and stirring bar. External cooling with a water bath to keep the internal temperature between 15° and 20°C is important. The use of more concentrated solutions should be avoided, since dimerization instead of bromination becomes the dominant reaction.
5. The water bath was coated with aluminum foil in order to increase the efficiency of the irradiation.
6. TLC (ethyl acetate/hexane 1:3; vanillin/concd. H_2SO_4/heat) reveals complete consumption of the starting material and only small amounts of impurities. The crude product is stable for several weeks at −20°C under argon.[2]

7. THF was distilled from potassium and benzophenone.

8. Tetraethyl orthotitanate, 22.9 g (0.100 mol), (Fluka Chemical Corporation, bulb-to-bulb-distilled at 110–115°C/0.1 mm) is dissolved in 80 mL of dry THF. Titanium chloride ($TiCl_4$) (Fluka Chemical Corporation), 19.0 g (0.100 mol, distilled at 136°C/atmospheric pressure) was added dropwise while cooling with an acetone/dry ice bath to keep the temperature below 0°C. Alternatively, $TiCl_4$ may be added to a solution of $Ti(OEt)_4$ (obtained from Aldrich Chemical Company, Inc.) in hexane at 0°C; the solvent is evaporated and replaced by THF.[3]

9. Trimethylsiloxybutadiene was purchased from Petrarch Systems, Inc., and employed without further purification. The checkers attempted to use the more stable triethylsiloxybutadiene without success.

10. In an experiment on one tenth the scale, the yield was 57%.[4]

11. The physical properties are as follows: ^{1}H-NMR ($CDCl_3$) δ: 1.44 (s, 18 H), 3.08 (dd, 1 H, J = 4 and 18), 3.28 (dd, 1 H, J = 4 and 18), 4.45 (m, 1 H), 5.48 (d, 1 H, J = 8, N-H), 5.91 (dd, 1 H, J = 2 and 10), 6.25 (dd, 1 H, J = 2 and 18), 6.34 (dd, 1 H, J = 10 and 18); IR ($CHCl_3$) cm^{-1}: 3430, 3000, 2980, 2930, 1740, 1720, 1710, 1630, 1500.

12. When the filter cake contains hydrogen chloride, it is very hygroscopic. It should therefore be covered immediately with dry ether after the ethereal hydrogen chloride solution has been aspirated.

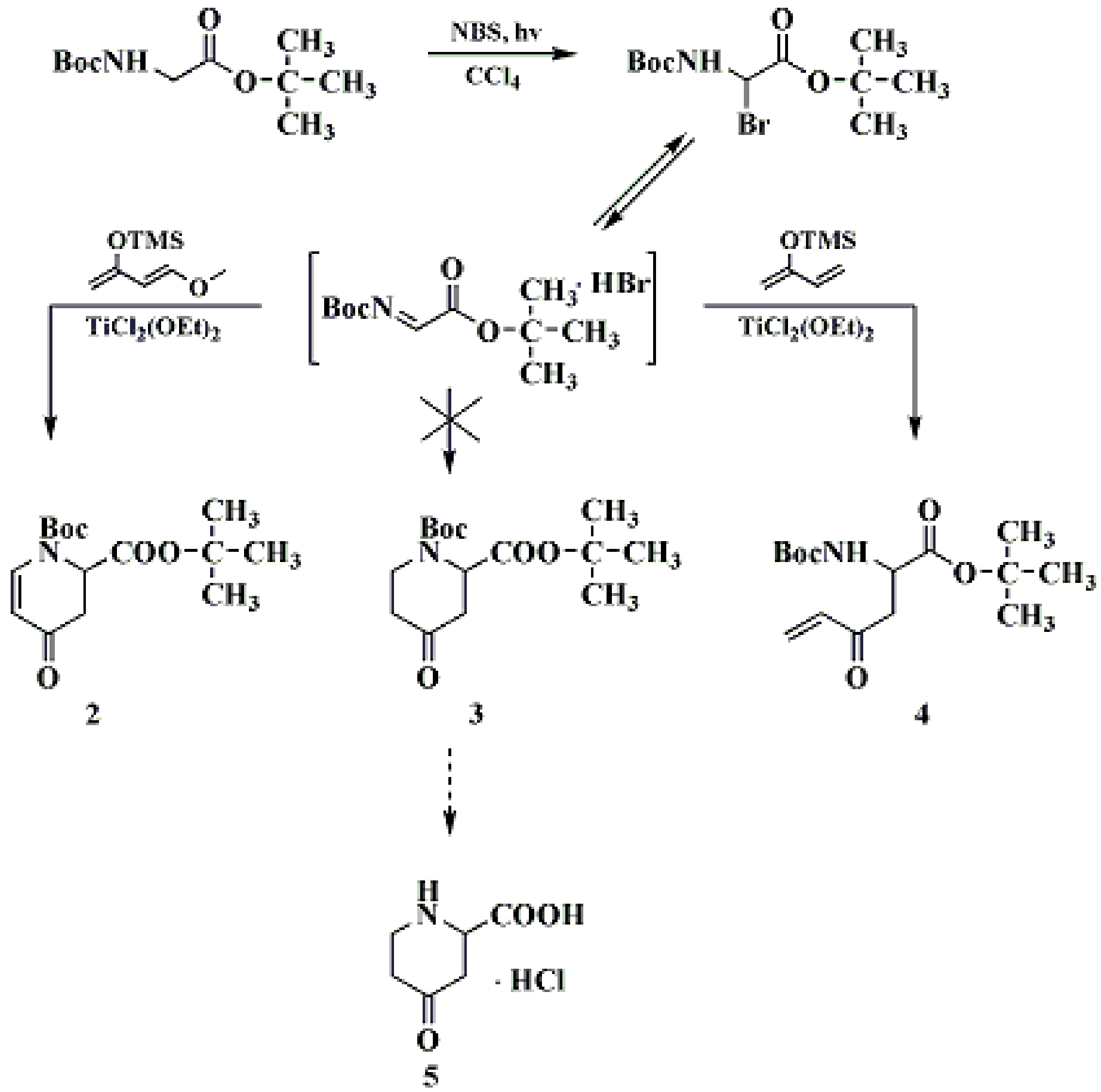
13. The physical properties are as follows: ^{1}H NMR (MeOD) δ: 3.05 (dt, 2 H, J = 2 and 6), 3.20 (dd, 1 H, J = 7 and 20), 3.29 (dd, 1 H, J = 4 and 20), 3.79 (t, 2 H, J = 6), 4.30 (dd, 1 H, J = 4 and 7); IR (nujol) cm^{-1}: 3300–2300 broad, 3060, 2960, 2920, 2860, 1740, 1725, 1600, 1570.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

N-Boc-2-Bromoglycine tert-butyl ester (**1**), introduced by Steglich and co-workers, is a versatile synthon for electrophilic glycine,[5] an important tool in the synthesis of non-proteinogenic amino acids.



Elimination of HBr leads to an acylimino acetate that should be able to undergo an aza-Diels–Alder reaction with dienes to give pipecolic acid derivatives not readily accessible by other methods. Indeed, **1**, in the presence of $TiCl_2(OEt)_2$, reacts with Danishefsky's diene between −78°C and room temperature to give the cyclic compound **2** in 72% yield. In a thermal reaction of 2-trimethylsiloxybutadiene with another electrophilic glycine equivalent, Jung and co-workers[6] isolated a cyclic product of type **3**. Under the reaction conditions described here, the reaction product is not **3** but the enone **4**, which by itself is an interesting bifunctional intermediate. However, upon deprotection the anticipated ring closure takes place in a very clean fashion. Pure 4-ketopipecolic acid hydrochloride crystallizes out of the ethereal hydrogen chloride solution in quantitative yield, which illustrates the advantage of the use of **1** in amino acid synthesis, i.e., the ease of deprotection, often a critical step.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

ethanol (64-17-5)

hydrogen chloride (7647-01-0)

ethyl acetate (141-78-6)

ether (60-29-7)

sodium bicarbonate (144-55-8)

carbon tetrachloride (56-23-5)

aluminum (7429-90-5)

Benzophenone (119-61-9)

potassium (7440-09-7)

Glycine (513-29-1)

magnesium sulfate (7487-88-9)

vanillin (121-33-5)

Tetrahydrofuran (109-99-9)

N-bromosuccinimide (128-08-5)

hexane (110-54-3)

titanium chloride (7550-45-0)

triethylamine (121-44-8)

argon (7440-37-1)

2-trimethylsiloxybutadiene (38053-91-7)

Di-tert-butyl dicarbonate (24424-99-5)

4-Ketopipecolic acid hydrochloride, Pipecolic acid, 4-oxo-, hydrochloride (99979-55-2)

2-Bromo-N-Boc-glycine tert-butyl ester, N-Boc-2-Bromoglycine tert-butyl ester

N-Boc-glycine tert-butyl ester, Boc-Glycine tert-butyl ester (111652-20-1)

tert-Butyl [1-(tert-butoxycarbonyl)-3-oxo-4-pentenyl]carbamate (117833-62-2)

dichlorodiethoxytitanium (3582-00-1)

glycine tert-butyl ester hydrochloride (27532-96-3)

Tetraethyl orthotitanate (3087-36-3)

Trimethylsiloxybutadiene

triethylsiloxybutadiene

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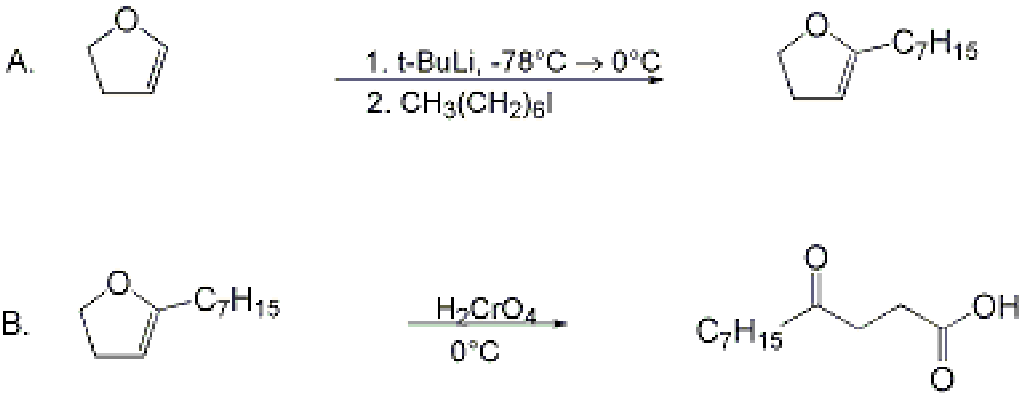
Organic Syntheses, CV 9, 530

4-KETOUNDECANOIC ACID

[Undecanoic acid, 4-oxo-]



Submitted by M. A. Tschantz, L. E. Burgess, and A. I. Meyers[1].
Checked by T. M. Kamenecka and L. E. Overman.

1. Procedure

A. *2-Heptyl-4,5-dihydrofuran*. An oven-dried, 1-L, round-bottomed flask, equipped with a magnetic stirring bar, and fitted with a rubber septum, is flushed with argon and charged with 8.00 mL of 2,3-dihydrofuran (105.8 mmol) (Note 1) and 600 mL of dry tetrahydrofuran (THF) (Note 2). The solution is stirred and cooled to −78°C using an external acetone–dry ice bath. After stirring at −78°C for 30 min, 50.0 mL of a solution of tert-butyllithium in pentane (2.60 M in pentane, 130 mmol) (Note 3) is added dropwise via syringe over 60 min. The acetone–dry ice bath is replaced by an ice–water bath for 30 min, at which time the reaction mixture is recooled to −78°C. A solution of 17.35 mL of 1-iodoheptane (105.8 mmol) (Note 4) in 30 mL of dry tetrahydrofuran is added dropwise via syringe, and the resulting solution is allowed to warm to room temperature and stir for 60 min. The solution is recooled to 0°C and quenched by the careful addition of 100 mL of 50% aqueous ammonium chloride. The contents are transferred to a 1-L separatory funnel, and the organic phase separated. The aqueous phase is extracted three times with 100-mL portions of pentane–ether (1:1 v/v), and the combined organic phases are dried over Na_2SO_4, filtered, and concentrated under reduced pressure without heating to afford crude 2-heptyl-4,5-dihydrofuran (17.77 g, 100%) as a yellow oil (Note 5). This crude material is used directly in the next step.

B. *4-Ketoundecanoic acid*. A 2-L, round-bottomed flask, equipped with a magnetic stirring bar and a 250-mL addition funnel, is charged with 17.77 g of the crude 2-heptyl-4,5-dihydrofuran (105.8 mmol) and 400 mL of tetrahydrofuran (Note 6). The resulting solution is cooled to 0°C using an external ice bath, and 117.5 mL of a 2.7 M solution of aqueous chromic acid (317.4 mmol) (Note 7) is added dropwise via the

addition funnel over 90 min, and the solution is allowed to stir overnight (Note 8). The reaction mixture is diluted with 300 mL of diethyl ether and 300 mL of water, and the resulting mixture is allowed to stir vigorously for 30 min. The reaction mixture is transferred to a separatory funnel, and the organic phase is separated (Note 9). The aqueous phase is extracted four times with 200-mL portions of diethyl ether. The combined organic phases are washed with three times with 100-mL portions of water (Note 10), followed by extraction three times with 150-mL portions of 10% aqueous sodium hydroxide solution. The combined basic extracts are acidified with 6 N hydrochloric acid to pH 1 (*CAUTION:* Exothermic reaction!). The cloudy mixture is extracted 4 times with 150 mL of dichloromethane, and the combined organic extracts are dried over $MgSO_4$, followed by concentration under reduced pressure to afford crude 4-ketoundecanoic acid (12.4–14.7 g, 59–69%) as a white solid: mp 74–77° C (Note 11).

2. Notes

1. 2,3-Dihydrofuran was purchased from Fluka Chemical Corporation and used without further purification.
2. Tetrahydrofuran was freshly distilled over sodium/benzophenone prior to use.
3. tert-Butyllithium was purchased from Lithco Chemical Corporation (the checkers used tert-butyllithium purchased from Aldrich Chemical Company, Inc.) and titrated prior to use.
4. 1-Iodoheptane was purchased from Fluka Chemical Corporation and passed through activated basic aluminum oxide prior to use.
5. Because of the product's volatility, a hot water bath should not be used during solvent evaporation. GC and GC/MS analysis of an aliquot indicate that the product ranges in purity from 75–95% with unreacted 1-iodoheptane also present. The addition of 0.5 equiv of hexamethylphosphoramide (HMPA) prior to addition of the iodoheptane was found to improve the yield of this alkylation. The addition of 0.5 to 2.0 equiv of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU) did not improve the yield. The checkers found the following GC conditions useful for monitoring the alkylation reaction: initial column temperature, 40°C; heating increment, 10°C/min; iodoheptane R_f = 3.3 min, product R_f = 5.7 min. Column specifications were as follows: SPB-1 (stationary phase), fused silica gel capillary column, 30 m × 0.32 mm ID, 0.25-mm film thickness.
6. Acetone is commonly used as a solvent in Jones oxidations; however, the desired keto acid tends to be retained by the chromium salts during work-up. A benzene/THF solution has also been employed for the oxidation, but this modification did not seem to have much effect on the overall yield.
7. Aqueous chromic acid solution (the Jones reagent) was prepared according to "Reagents in Organic Syntheses", Fieser & Fieser; J. Wiley, 1967; Vol. 1, p. 142.
8. Chromium salts may precipitate upon addition of the Jones reagent. A minimal amount of water may be added to dissolve them.

9. Additional water may be added to facilitate separation of layers.
10. At this point, it is important to remove as much of the blue chromium impurities from the organic phase as possible.
11. The product may be recrystallized from hexanes to mp 79–80°C. The spectral data of the recrystallized material are as follows: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.86 (t, 3 H, J = 7.0), 1.30 (s, 8 H), 1.57 (quintet, 2 H, J = 7.3), 2.43 (t, 2 H, J = 7.5), 2.61 (dd, 2 H, J = 6.23, 5.87), 2.71 (dd, 2 H, J = 6.60, 6.23); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.0, 22.6, 23.8, 27.7, 29.0, 29.1, 31.6, 36.7, 42.7, 178.5, 208.9; IR (thin film) cm^{-1}: 3056, 2987, 2957, 2933, 2873, 2858, 1710, 1421, 1265, 748. Other electrophiles were used to give the corresponding keto acids as shown below:

Electrophile	Keto Acid Yield
C_4H_9I	64%
$C_{11}H_{23}I$	82%
$C_6H_5CH_2Br$	62%

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Because of a long standing research program centering on chiral bicyclic lactams, the submitter's laboratories have required a variety of 4-keto acids as precursors to these versatile intermediates.[2 3] Generally these acids are useful for the preparation of many important compounds.[4 5 6 7 8 9 10 11 12] A general route to 4-keto acids is the Larson procedure involving the C-silylation of butyrolactone followed by Grignard addition, elimination and in situ oxidation.[13 14 15 16 17] However, the major disadvantage to this process is the need for stoichiometric amounts of the expensive chlorodiphenylmethylsilane.

The procedure described here involves the metallation of dihydrofuran and subsequent alkylation with an alkyl iodide (bromides are much less reactive).[18 19 20] The resulting substituted dihydrofuran, the intermediate postulated in the Larson procedure, is then treated with chromic acid to hydrolyze the enol ether and oxidize the resulting primary alcohol to the corresponding carboxylic acid as in the Larson procedure. The isolated oxidation product is of suitable purity for subsequent reactions, but if necessary, recrystallization from hexanes is readily accomplished .

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 457

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

ether, diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

sodium hydroxide (1310-73-2)

acetone (67-64-1)

Benzophenone (119-61-9)

sodium (13966-32-0)

chromic acid (7738-94-5)

Pentane (109-66-0)

dichloromethane (75-09-2)

chromium (7440-47-3)

keto

aluminum oxide (1344-28-1)

Tetrahydrofuran (109-99-9)

Butyrolactone (96-48-0)

hexamethylphosphoramide (680-31-9)

argon (7440-37-1)

1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (7226-23-5)

tert-Butyllithium (594-19-4)

4-Ketoundecanoic acid, Undecanoic acid, 4-oxo- (22847-06-9)

2-Heptyl-4,5-dihydrofuran

2,3-dihydrofuran, dihydrofuran (1191-99-7)

1-iodoheptane, iodoheptane (4282-40-0)

chlorodiphenylmethylsilane (144-79-6)

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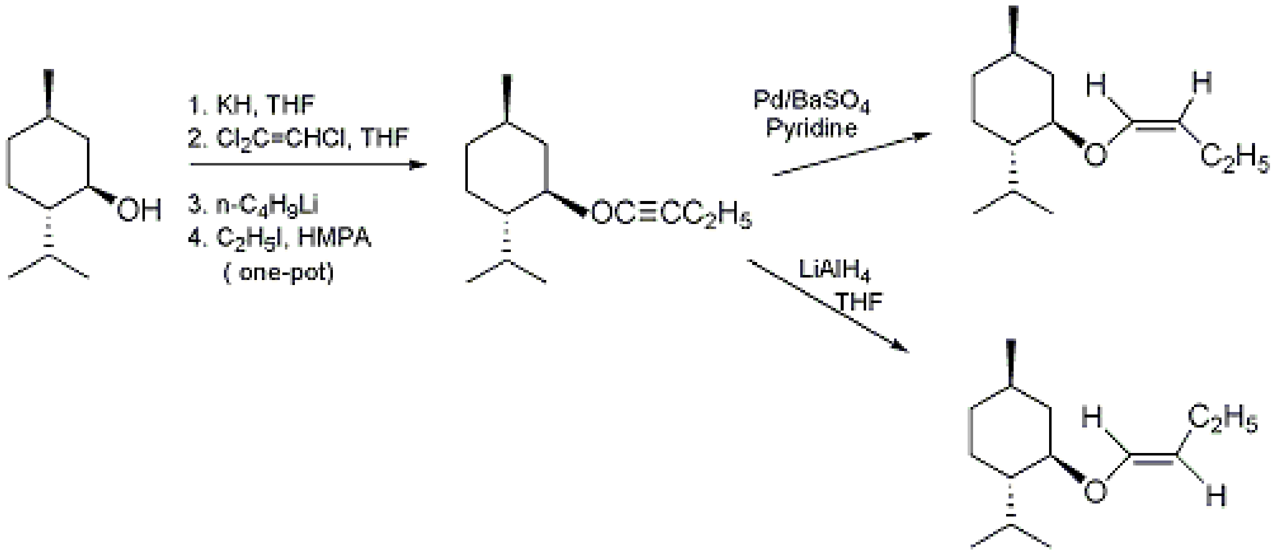
Organic Syntheses, CV 9, 533

ACETYLENIC ETHERS FROM ALCOHOLS AND THEIR REDUCTION TO Z- AND E-ENOL ETHERS: PREPARATION OF 1-MENTHOXY-1-BUTYNE FROM MENTHOL AND CONVERSION TO (Z)- AND (E)-1-MENTHOXY-1-BUTENE

[[Cyclohexane, 2-(1-butynyloxy)-4-methyl-1-(1-methylethyl)-[1S-(1α,2β,4β)]-], and [[[Cyclohexane, 2-(1-butenyloxy)-4-methyl-1-(1-methylethyl)-, [1S-[1α,2β(Z),4β]]- and [1S-[1α,2β(E),4β]]-]



Submitted by Nina Kann, Vania Bernardes, and Andrew E. Greene[1].
Checked by Rodolphe Tamion and Leon Ghosez.

1. Procedure

CAUTION! These transformations should be carried out in an efficient hood and only by persons familiar with the handling of air-sensitive and toxic materials. Hexamethylphosphoric triamide (HMPA) is toxic and must be handled with gloves.

A. *1-Menthoxy-1-butyne*. A dry, 500-mL, one-necked, round-bottomed flask (Note 1), equipped with a Teflon-covered magnetic stirring bar, is flushed with argon and charged with 13.2 g (115 mmol) of a 35% suspension of potassium hydride in mineral oil (Note 2). The mineral oil is removed by washing with pentane (3 × 30 mL) and the potassium hydride is suspended in 100 mL of anhydrous tetrahydrofuran (Note 3). The flask is capped with a rubber septum and is connected to a Nujol-filled bubbler by means of a syringe needle. A solution of 12.0 g (76.8 mmol) of (−)-menthol (Note 2) in 120 mL of anhydrous tetrahydrofuran is then added dropwise by syringe over 20 min. The mixture is stirred until hydrogen evolution is complete (ca. 20 min) and cooled to −50°C by means of an acetone-liquid nitrogen bath. A solution of trichloroethylene (7.58 mL, 84.4 mmol) (Note 3) in 75

mL of anhydrous tetrahydrofuran is added dropwise by syringe over 15 min, after which the reaction mixture is allowed to warm to room temperature and is stirred for 1 hr. The resulting brown solution is then cooled to −70°C and treated dropwise with 67.6 mL (169 mmol) of 2.5 M butyllithium in hexanes (Note 2). After the reaction mixture is stirred for 30 min at −70°C, it is warmed to −40°C over 30 min (Note 4) and treated dropwise with a solution of ethyl iodide (18.5 mL, 230 mmol) (Note 5) in 25 mL of hexamethylphosphoramide (Note 3), (Note 6). The solution is stirred at room temperature for 3 hr, whereupon it is quenched by slow addition of 15 mL of methanol and poured into 300 mL of cold aqueous saturated ammonium chloride. The phases are separated and the aqueous phase is extracted with pentane (3 × 200 mL). The combined organic phases are washed with water (4 × 150 mL), dried over sodium sulfate, and filtered. Concentration by rotary evaporation affords 17.1 g of dark brown oil, which is purified by bulb-to-bulb distillation (0.02 mm, oven temperature 70–90°C) to yield 14.9 g (93%) of 1-menthoxy-1-butyne as a colorless oil (Note 7).

B. *(Z)-1-Menthoxy-1-butene*. A dry, 250-mL, one-necked, round-bottomed flask (Note 1), equipped with a Teflon-covered magnetic stirring bar, is charged with 14.0 g (67.2 mmol) of 1-menthoxy-1-butyne, 0.7 g of 10% palladium on barium sulfate and 180 mL of pyridine (Note 8). The flask is capped with a rubber septum and by means of syringe needles is degassed and connected to a hydrogen-filled balloon. The mixture is stirred for 6 hr (Note 9), whereupon the hydrogen is replaced with argon, and the reaction mixture is filtered through a glass frit under water aspirator pressure. The filtrate is diluted with 300 mL of pentane and washed first with saturated copper sulfate solution (5 × 120 mL) and then with water (1 × 200 mL). The organic phase is dried over sodium sulfate and the solvent is removed by rotary evaporation to give 15.8 g of a yellow oil. Bulb-to-bulb distillation (0.02 mm, oven temperature 70–90°C) provides 12.7 g (90%) of (Z)-1-menthoxy-1-butene as a colorless oil (Note 10).

C. *(E)-1-Menthoxy-1-butene*. A dry, 500-mL, one-necked, round-bottomed flask (Note 1), equipped with a Teflon-covered magnetic stirring bar, is flushed with argon and charged with 7.65 g (202 mmol) of lithium aluminum hydride (Note 11) and 325 mL of anhydrous tetrahydrofuran (Note 3) and then capped with a rubber septum and connected by means of a syringe needle to an argon-filled balloon. To the stirred slurry is added dropwise by syringe neat 1-menthoxy-1-butyne (14.0 g, 67.2 mmol), followed by 2 mL of tetrahydrofuran wash. The septum is replaced with a reflux condenser connected to an argon-filled balloon and the mixture is refluxed for 4 hr. After the flask is allowed to cool to room temperature, it is placed in an ice bath and the reaction mixture is quenched by the slow addition (*CAUTION!* (Note 12)) of 12.5 mL of aqueous 10 % sodium hydroxide, followed by 15.5 mL of water. The resulting mixture is stirred for 30 min, after which anhydrous sodium sulfate (ca. 60 g) is added and the solid material is removed by filtration through a 1-cm pad of Celite, which is then rinsed with diethyl ether (4 × 100 mL) . Concentration of the combined filtrates yields 14.7 g of a pale yellow oil, which is purified by filtration through a 4-cm (80-g) pad of silica gel pretreated with triethylamine (2.5% v/v, (Note 13)) using hexane as the eluant. Concentration gives 13.3 g (94%) of (E)-1-menthoxy-1-butene as a colorless oil (Note 14).

2. Notes

1. All glassware was flame-dried and allowed to cool in a desiccator before use.
2. Potassium hydride (35% in mineral oil) and (−)-menthol (99%) were purchased from the Aldrich Chemical Company, Inc., and butyllithium (2.5 M in hexanes) was obtained from Janssen Chimica.
3. Pentane and trichloroethylene were distilled from calcium chloride, tetrahydrofuran from the sodium ketyl of benzophenone, and hexamethylphosphoramide from calcium hydride under reduced pressure.
4. Quenching the reaction at this stage with methanol, followed by the work-up described below and bulb-to-bulb distillation (0.02 mm, oven temperature 60–80°C), gave 12.5 g (90%) of menthoxyacetylene as a colorless oil: $[\alpha]_D^{25}$ −74° (cyclohexane, *c* 0.76); IR (film) cm^{-1}: 3340, 2960, 2940, 2870, 2150, 1450, 1370, 1100, 940, 890, 840; ^1H NMR (200 MHz, $CDCl_3$) δ: 0.68–1.54 (m, 5 H; CH and CH_2), 0.81 (d, 3 H, J = 6.9, CH_3), 0.90 (d, 3 H, J = 7.0, CH_3), 0.94 (d, 3 H, J = 6.4, CH_3), 1.49 (s, 1 H, C CH), 1.57–1.74 (m, 2 H), 2.00–2.33 (m, 2 H), 3.83 (app td, 1 H, J = 10.9, 4.5, CH-O-); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ: 16.3 (CH_3), 20.5 (CH_3), 22.0 (CH_3), 23.3 (CH_2), 25.9 (CH), 27.1 (C), 31.6 (CH), 33.9 (CH_2), 39.4 (CH_2), 46.7 (CH), 88.2 (CH), 89.7 (CH); mass spectrum (chemical ionization), m/e 181 (M^+ + 1, 5%), 156 (100%), 139 (58%); analytical TLC (pentane): Rf 0.54 (single spot). Proton NMR confirmed the complete absence (<1%) of menthol. Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: 79.72; H, 10.98.
5. Ethyl iodide (99%) was purchased from Prolabo (Paris, France) and was washed with saturated aqueous sodium thiosulfate solution, dried over anhydrous sodium sulfate and then sodium metal, and distilled prior to use.
6. Dimethylpropyleneurea (75 mL) can be used in place of hexamethylphosphoramide; however, a small amount (5–10%) of menthoxyacetylene contaminates the final product.
7. Data for 1-menthoxy-1-butyne are as follows: $[\alpha]_D^{25}$ −78° (cyclohexane, *c* 0.69); IR (film) cm^{-1}: 2950, 2925, 2870, 2280, 1460, 1390, 1370, 1250, 1230, 1210, 980, 950, 910, 840; ^1H NMR (200 MHz, $CDCl_3$) δ: 0.75–1.20 (m, 3 H, CH and CH_2), 0.80 (d, 3 H, J = 6.9, CH_3), 0.89 (d, 3 H, J = 7.1, CH_3), 0.93 (d, 3 H, J = 6.4, CH_3), 1.08 (t, 3 H, J = 7.5, CH_2CH_3), 1.27–1.51 (m, 2 H), 1.64 (br d, 2 H), 2.11 (q, 2 H, J = 7.5, CH_2CH_3), 2.12–2.25 (m, 2 H), 3.69 (app td, 1 H, J = 10.9, 4.5, CHO); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ: 11.0 (CH_2), 15.1 (CH_3), 16.2 (CH_3), 20.5 (CH_3), 21.9 (CH_3), 23.2 (CH_2), 25.7 (CH), 31.5 (CH), 34.0 (CH_2), 39.6 (2C: C and CH_2), 46.8 (CH), 86.9 (CH), 87.4 (C); mass spectrum (chemical ionization), m/e 209 (M^+ + 1, 4%), 156 (100%), 139 (26%); analytical TLC (pentane): R_f 0.54 (single spot). Proton NMR indicated a complete absence (<1%) of both menthol and menthoxyacetylene. Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.70; H, 11.55.
8. 10% Palladium on barium sulfate was purchased from Fluka Chemie AG and pyridine (99.5%) was obtained from Chimie-Plus Laboratories (St.-Priest, France) and dried over calcium hydride before use.
9. The reaction was followed by IR analysis of worked-up aliquots (disappearance of band at 2280 cm^{-1}).
10. Data for (Z)-1-menthoxy-1-butene are as follows: $[\alpha]_D^{25}$ −18° (cyclohexane, *c*

0.11); IR (film) cm^{-1}: 3030, 2970, 2920, 2870, 1660, 1460, 1380, 1350, 1250, 1140, 1110, 1090, 1070, 1050; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.72–1.08 (m, 3 H, CH and CH_2), 0.80 (d, 3 H, J = 7.0, CH_3), 0.92 (d, 3 H, J = 7.1, CH_3), 0.93 (d, 3 H, J = 6.5, CH_3), 0.97 (t, 3 H, J = 7.5, CH_2CH_3), 1.22–1.46 (m, 2 H), 1.56–1.70 (m, 2 H), 1.85–2.21 (m, 4 H), 3.35 (app td, 1 H, J = 10.7, 4.3, CHOCH=CH), 4.32 (app q, 1 H, J = 7.1, OCH=CH), 5.97 (d, 1 H, J = 6.2, -OCH=CH); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ: 14.6 (CH_3), 16.5 (CH_3), 17.5 (CH_2), 20.7 (CH_3), 22.2 (CH_3), 23.6 (CH_2), 25.8 (CH), 31.5 (CH), 34.5 (CH_2), 41.6 (CH_2), 47.9 (CH), 81.3 (CH), 108.2 (CH), 143.6 (CH); mass spectrum (electron impact) m/e 210 (M^+, 14%), 138 (32%), 83 (100%); analytical TLC (pentane): R_f 0.59 (major spot). Proton NMR indicated a complete absence (<1%) of menthol, menthoxybutyne, and menthoxybutane, but the presence of ca. 3% of the E -isomer. Anal. Calcd for $C_{14}H_{26}O$: C, 79.94; H, 12.46. Found: C, 79.84; H, 12.55.

11. Lithium aluminum hydride (95+%) was purchased from Janssen Chimica. Lesser amounts led to incomplete reaction under the stated conditions.

12. *CAUTION! Quenching should be performed very carefully as a rapid, exothermic evolution of hydrogen occurs during the initial phase. Flushing with argon throughout the quenching is recommended.* Toward completion of the sodium hydroxide addition, a thick slurry is produced, which makes stirring difficult. This difficulty is alleviated, however, upon the addition of water.

13. Silica gel (70-230 mesh) was treated with triethylamine (2.5% v/v) and then shaken to achieve homogeneity.

14. Data for (E)-1-menthoxy-1-butene are as follows: $[\alpha]_D^{25}$ –37° (cyclohexane, *c* 0.80); IR (neat) cm^{-1}: 2960, 2910, 2860, 1670, 1650, 1450, 1180, 1140, 920; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.71–1.08 (m, 3 H, CH and CH_2), 0.75 (d, 3 H, J = 7.0, CH_3), 0.87 (d, 3 H, J = 7.1, CH_3), 0.89 (d, 3 H, J = 6.5, CH_3), 0.94 (t, 3 H, J = 7.4, CH_2CH_3), 1.19–1.46 (m, 2 H), 1.54–1.70 (m, 2 H), 1.90 (app quint d, 2 H, J = 7.3, 1.3), 1.96–2.21 (m, 2 H), 3.36 (app td, 1 H, J = 10.6, 4.3, CHOCH=CH), 4.88 (dt, 1 H, J = 12.3, 7.0, OCH=CH), 6.06 (dt, 1 H, J = 12.3, 1.3, OCH=CH); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ: 15.2 (CH_3), 16.3 (CH_3), 20.8 (CH_3), 21.0 (CH_2), 22.2 (CH_3), 23.4 (CH_2), 25.7 (CH), 31.5 (CH), 34.4 (CH_2), 41.1 (CH_2), 47.8 (CH), 80.0 (CH), 107.5 (CH), 144.8 (CH); mass spectrum (electron impact), m/e 210 (M^+, 4%), 83 (100%), 69 (40%); analytical TLC (pentane): R_f 0.53 (single spot). Proton NMR confirmed the complete absence (<1%) of menthol, menthoxybutyne, menthoxybutane, and the Z-isomer. Anal. Calcd for $C_{14}H_{26}O$: C, 79.94; H, 12.46. Found: C, 79.91; H, 12.41.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The conversion of menthol to 1-menthoxy-1-butyne described in Part A illustrates an efficient, one-pot preparation of acetylenic ethers from alcohols that is relatively inexpensive and requires only common reagents and standard laboratory equipment. It is substantially

higher-yielding and more direct and generally applicable than other available approaches to these versatile[2] compounds, which generally involve base treatment of haloalkenyl ethers, dihaloalkyl ethers, haloacetals, or related compounds.[2] The conversion in this procedure is an optimized example of a method that has previously been applied with success to a wide range of secondary alcohols.[3] Several primary alcohols have also been transformed to acetylenic ethers through this method.[4]

Parts B and C exemplify efficient procedures for the stereoselective reduction of acetylenic ethers to the corresponding Z- and E-enol ethers, synthetically useful intermediates.[5] These procedures, which are optimized versions of previously described methods,[3,6] also require only common reagents and standard laboratory equipment. Alternatively, acetylenic ethers can be converted stereoselectively to E-enol ethers under Birch conditions[3] and to Z- (or E-) enol ethers with Red-Al.[7]

Other known methods for preparing O-alkyl enol ethers include, most notably, alcohol elimination from acetals, double bond isomerization in allylic ethers, reduction of alkoxy enol phosphates, and phosphorane-based condensation approaches.[5] These methods, however, suffer from poor stereoselectivity, low yields, or lack of generality, if not a combination of these drawbacks.

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

sodium ketyl of benzophenone

(–)-Menthol

(Z)- AND (E)-1-MENTHOXY-1-BUTENE

[Cyclohexane, 2-(1-butynyloxy)-4-methyl-1-(1-methylethyl)-[1S-(1α,2β,4β)]-]

[[[Cyclohexane, 2-(1-butenyloxy)-4-methyl-1-(1-methylethyl)-, [1S-[1α,2β(Z),4β]]- and [1S-[1α,2β(E),4β]]-

calcium chloride (10043-52-4)

methanol (67-56-1)

diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

sodium sulfate (7757-82-6)

sodium thiosulfate (7772-98-7)

copper sulfate (7758-98-7)

cyclohexane (110-82-7)

barium sulfate (7727-43-7)

pyridine (110-86-1)

sodium (13966-32-0)

palladium (7440-05-3)

Pentane (109-66-0)

menthol (15356-60-2)

Ethyl iodide (75-03-6)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

hexane (110-54-3)

trichloroethylene (79-01-6)

triethylamine (121-44-8)

calcium hydride (7789-78-8)

1-Adamantanol (768-95-6)

hexamethylphosphoric triamide, hexamethylphosphoramide (680-31-9)

argon (7440-37-1)

2-cyclohexylethanol (4442-79-9)

decanol (112-30-1)

potassium hydride (7693-26-7)

dimethylpropyleneurea (7226-23-5)

1-Menthoxy-1-butyne (108266-28-0)

(E)-1-MENTHOXY-1-BUTENE, (Z)-1-Menthoxy-1-butene (107941-62-8)

menthoxyacetylene

menthoxybutyne

menthoxybutane

adamantyloxyacetylene

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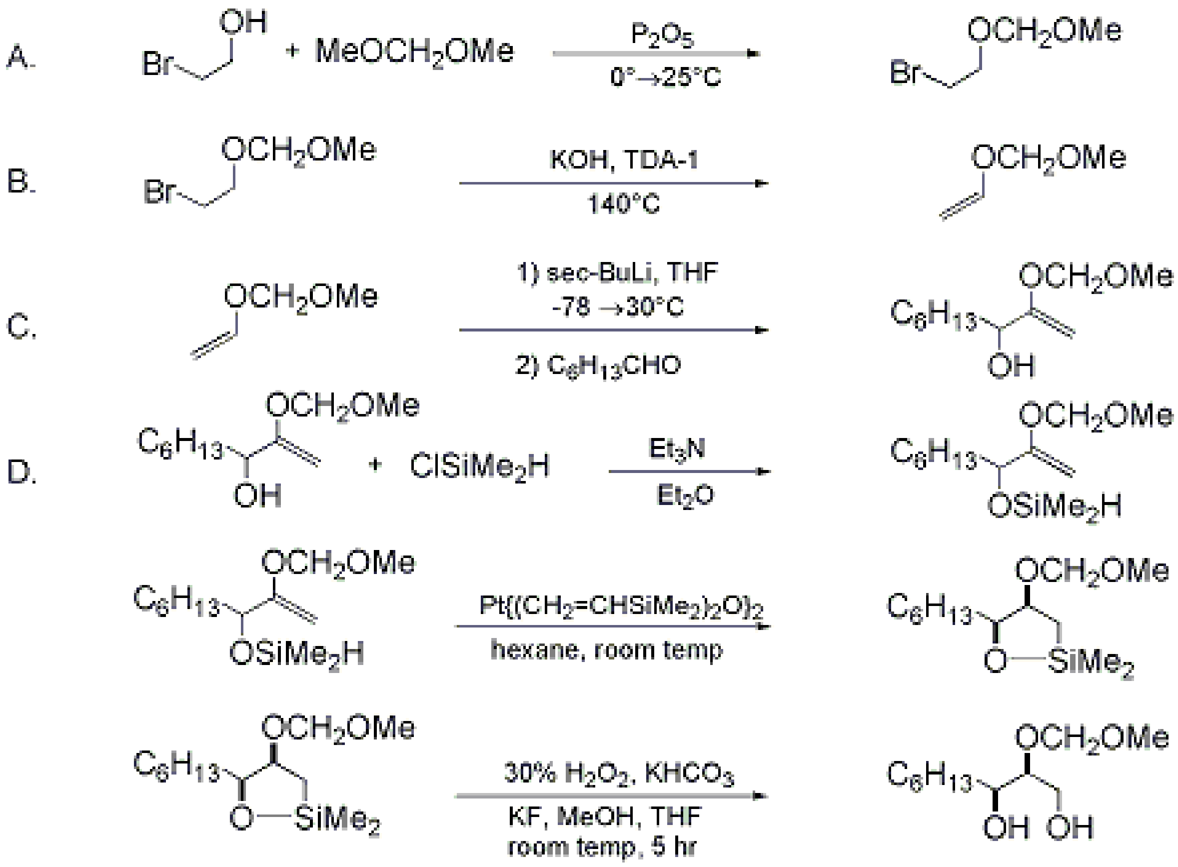
Organic Syntheses, CV 9, 539

REGIO- AND STEREOSELECTIVE INTRAMOLECULAR HYDROSILYLATION OF α-HYDROXY ENOL ETHERS: 2,3-syn-2-METHOXYMETHOXY-1,3-NONANEDIOL

[1,3-Nonanediol, 2-(methoxymethoxy)-, (R,R)-(±)-]



Submitted by Kohei Tamao[1], Yoshiki Nakagawa[2], and Yoshihiko Ito[2].
Checked by Michael R. Reeder, Lisa M. Reeder, and Robert K. Boeckman, Jr..

1. Procedure

A. *2-Bromoethyl methoxymethyl ether*. A 1-L, single-necked, round-bottomed flask is equipped with a magnetic stirring bar and a gas inlet valve (Note 1). The flask is purged with argon, and charged with 125.0 g of 2-bromoethanol (1.00 mol), and 500 mL of dimethoxymethane (Note 2) and (Note 3). The resulting mixture is cooled to 0°C in an ice-water bath. As a single portion, 71.0 g (0.5 mol) of solid phosphorus pentoxide (P_2O_5) is added with stirring (Note 4). The resulting mixture, which becomes quite viscous because of the insoluble P_2O_5, is stirred at 0°C for 10 min, then warmed to room temperature and stirred for an additional 7 hr during which time the viscosity of the mixture decreases. The mixture is transferred to a 2-L separatory

funnel, 200 mL of water is added, and the resulting mixture is extracted three times with 50 mL of ether. The combined organic extracts are washed successively with 100 mL of water and 100 mL of saturated aqueous sodium carbonate solution, dried over magnesium sulfate, filtered, and carefully concentrated with a rotary evaporator under reduced pressure (20–30 mm) at room temperature. The residue is distilled under reduced pressure to afford 131.3 g (78%) of 2-bromoethyl methoxymethyl ether as a colorless liquid, bp 74–78°C (40 mm) (Note 5).

B. *Methoxymethyl vinyl ether*. A 200-mL, two-necked, round-bottomed flask is equipped with a stopper, magnetic stirring bar (Note 6), and an efficient reflux condenser that is attached through a thick rubber tube to a clean trap, cooled in a dry ice-acetone bath, whose outlet is equipped with a calcium chloride drying tube. The flask is charged with 74.2 g (440 mmol) of 2-bromoethyl methoxymethyl ether, 58 g (880 mmol) of 85% potassium hydroxide pellets (Note 7), and 7.09 g (2.2 mmol) of tris [2-(2-methoxyethoxy)ethyl]amine (TDA-1) (Note 8). The mixture is heated to 140°C with stirring. The clear liquid phase gradually becomes cloudy and begins to reflux. After heating for 27 hr, consumption of the starting material is confirmed by GLC (Note 9). The calcium chloride tube is replaced with an additional cold trap that is attached to a water aspirator. The reaction mixture is cooled to 110°C and a vacuum is applied using the water aspirator for 2 hr, during which time volatile material is collected in the first cold trap. After the flask is cooled to room temperature, the first trap is disconnected and allowed to warm to room temperature. The liquid is transferred to a 50-mL, round-bottomed flask. A small amount of water (about 1 mL) is usually present and is removed with a syringe. The organic layer is distilled at atmospheric pressure into an ice-cooled receiver to afford 26.6–28.2 g (69–72%) of methoxymethyl vinyl ether as a colorless liquid, bp 64–70°C (Note 10). The product is dried and kept over 4 Å molecular sieves.

C. *2-Methoxymethoxy-1-nonen-3-ol*. A 500-mL, two-necked, round-bottomed flask is equipped with a rubber septum, a magnetic stirring bar, and a pressure-equalizing dropping funnel bearing a three-way stopcock connected to a mineral oil bubbler. The flask is evacuated, purged with nitrogen, and charged with 200 mL of dry tetrahydrofuran (THF) (Note 11) and 8.83 g of methoxymethyl vinyl ether (100 mmol). The solution is cooled to −78°C with a dry ice-acetone bath, and then 88.7 mL (100 mmol) of sec-butyllithium (1.13 M in cyclohexane) is added dropwise over 15 min with stirring via syringe. After the addition is complete, the yellow mixture is allowed to warm to −30°C over 30 min and stir for 1 hr. The mixture is recooled to −78°C and 11.44 g (100 mmol) of heptanal is added dropwise over 5 min through the dropping funnel. The reaction mixture is allowed to warm to room temperature over 30 min and to stir for 3 hr. A 100-mL portion of saturated aqueous sodium chloride solution is added, the mixture is transferred to a 1-L separatory funnel, mixed thoroughly, and the organic layer separated. The aqueous layer is extracted three times with 50 mL of diethyl ether. The combined organic phases are dried over sodium sulfate (Na_2SO_4), filtered, and concentrated under reduced pressure with a rotary evaporator. The residue is distilled under reduced pressure to afford 12.6–13.1 g (62–65%) of 2-methoxymethoxy-1-nonen-3-ol as a colorless liquid, bp 82–84°C (0.4 mm)

(Note 12).

D. *2-Methoxymethoxy-1,3-nonanediol*. A 500-mL, single-necked, round-bottomed flask, equipped with a three-way stopcock connected to a bubbler as above and a magnetic stirring bar, is charged with 14.79 g (73.1 mmol) of 2-methoxymethoxy-1-nonen-3-ol (Note 6). The flask is evacuated, then purged with nitrogen, and charged with 350 mL of dry diethyl ether and 8.88 g (87.7 mmol) of triethylamine (Note 13). After the mixture is cooled to 0°C in an ice-water bath, 8.30 g (87.7 mmol) of chlorodimethylsilane is added slowly with stirring. A large quantity of salt appears immediately. The white suspension is stirred at room temperature for 1 hr. The resulting mixture is then filtered through a sintered-glass Büchner funnel and the filter cake is washed thoroughly with dry hexane (Note 14). The combined filtrate and washings are concentrated under reduced pressure with a rotary evaporator. Some salts usually remain in the residue and are removed by dilution of the residue with an additional 50 mL of dry hexane followed by filtration, washing the filter cake with hexane, and concentration of the combined filtrate and washings as above. This procedure for removal of salts is repeated two to three times until the colorless residual liquid remains clear after concentration (Note 15). The residual liquid is finally subjected to high vacuum (0.4 mm) for 2 hr to complete removal of volatile material, and then transferred to a 300-mL, round-bottomed flask, equipped with a three-way stopcock and a magnetic stirring bar. The flask is evacuated, purged with nitrogen, and charged with 73 mL of dry hexane. To this mixture is added 1.21 mL (0.35 mmol) of the previously prepared platinum catalyst solution (Note 16) at room temperature with stirring. An exothermic reaction ensues almost immediately and the temperature of the mixture rises to about 30°C in 15 min, during which time the color of the clear mixture changes to yellow. The exothermic reaction ceases in about 1 hr. After the reaction mixture is stirred for an additional 1.5 hr at room temperature, completion of the reaction is confirmed by analysis by ^{1}H NMR (Note 17). A 7.3-g portion of activated carbon powder is then added to the lightly colored mixture to effect removal of organoplatinum species (Note 18). The black suspension is stirred for about 12 hr, and suction filtered through Celite into a 500-mL, two-necked, round-bottomed flask. The filter cake is washed with dry hexane, and the combined filtrate and washings are concentrated by rotary evaporation (Note 19). The flask containing the residue is equipped with a magnetic stirring bar and a thermometer, and is kept open to the air throughout subsequent manipulations. The flask is charged with 73 mL of THF, 73 mL of methanol (Note 20), 7.32 g (73.1 mmol) of solid potassium hydrogen carbonate, and 8.5 g (146 mmol) of solid potassium fluoride (Note 21). To the stirred mixture is added 29.7 mL (263 mmol) of 30% hydrogen peroxide slowly at room temperature (Note 22). A somewhat cloudy upper organic layer and a milky white lower aqueous layer result. After several minutes, an exothermic reaction begins which is controlled by intermittent, brief cooling with a water bath to maintain the temperature at about 40°C. The exothermic reaction ceases in about 2 hr. The mixture is stirred at room temperature for an additional 3 hr (Note 23). The excess hydrogen peroxide is decomposed by careful dropwise addition of a 50% aqueous sodium thiosulfate

pentahydrate solution (20 mL) with stirring over 20 min during which time the temperature is maintained near 30°C by intermittent cooling with an ice bath (Note 24). A negative starch-iodide test is observed after addition is complete (Note 25). The mixture is concentrated by rotary evaporator at 40–50°C under reduced pressure (water aspirator). To the residual aqueous suspension is added 150 mL of anhydrous ethanol and the mixture is stirred vigorously until the sticky, pale yellow precipitate becomes granular. The mixture is concentrated as above to give a pale yellow solid. The ethanol addition and evaporation procedure is repeated once more to insure thorough removal of water. The residue is then diluted with 150 mL of diethyl ether, the mixture is filtered with suction, and the filter cake is washed well with two 100-mL portions of diethyl ether. The combined filtrate and washings are concentrated by rotary evaporation. The residual, crude product is purified by chromatography on 250 g of silica gel with hexane/ethyl acetate (1:1 v/v) as eluent to give 9.34–10.62 g (58–66%) of 2-methoxymethoxy-1,3-nonanediol (R_f = 0.2) as a colorless liquid (Note 26). The syn and anti isomers cannot be separated by column chromatography. However, separation can be effected by GLC which showed the isomer ratio to be 98:2 syn/anti (Note 27).

2. Notes

1. A powerful magnetic stirrer and a large rugby ball-shaped stirring bar can be used. The checkers suggest use of an overhead mechanical stirrer because of the viscosity of the mixture in the initial stages of the reaction, which makes efficient magnetic stirring difficult.
2. 2-Bromoethanol was obtained from Aldrich Chemical Company, Inc., and was distilled prior to use.
3. Dimethoxymethane was purchased from the Aldrich Chemical Company, Inc., and used as received.
4. Reagent grade phosphorus pentoxide was obtained from the J. T. Baker Chemical Company and used as received.
5. 2-Bromoethyl methoxymethyl ether exhibits the following spectral properties: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.38 (s, 3 H), 3.49 (t, 2 H, J = 6.2), 3.85 (t, 2 H, J = 6.2), 4.66 (s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 30.74, 55.45, 67.79, 96.54; IR (neat) cm^{-1}: 2952, 2900, 1148, 1118, 1072, 1036. Anal. Calcd for $C_4H_9BrO_2$: C, 28.43; H, 5.37. Found: C, 28.39; H, 5.36.
6. A powerful magnetic stirrer and a large rugby ball-shaped stirring bar can be used. The checkers suggest use of an overhead mechanical stirrer because of the large quantity of salts produced in the reaction, which makes efficient magnetic stirring difficult.
7. Potassium hydroxide pellets are better than finely ground powder, because the powder readily solidifies into a mass upon heating causing the reaction to slow down. Sonication does not facilitate the reaction.
8. TDA-1 is not essential, but accelerates the reaction considerably.
9. Isothermal GLC analysis was performed on a 30-m × 0.32-mm ID HP-5 capillary column containing 5% phenylmethylsilicone as a stationary phase at

50°C (retention time of the bromo ether is 3.8 min).

10. Methoxymethyl vinyl ether exhibits the following spectral properties: ^{1}H NMR (200 MHz, C_6D_6) δ: 3.11 (s, 3 H), 4.09 (dd, 1 H, J = 6.6, 1.4), 4.54 (s, 2 H), 4.61 (dd, 1 H, J = 14.2, 1.4), 6.32 (dd, 1 H, J = 14.2, 6.6); ^{13}C NMR (50 MHz, C_6D_6) δ: 55.37, 90.71, 95.28, 149.94.

11. Tetrahydrofuran was distilled from sodium benzophenone ketyl.

12. Since 2-methoxymethoxy-1-nonen-3-ol tends to decompose on attempted GLC analysis, the purity is best checked by ^{1}H NMR. 2-Methoxymethoxy-1-nonen-3-ol exhibits the following spectral properties: ^{1}H NMR (200 MHz, C_6D_6) δ: 0.91 (t (br), 3 H, J = 7), 1.20–1.95 (m, 11 H), 3.17 (s, 3 H), 4.02 (q (br), 1 H, J = 5), 4.35 (s, 2 H), 4.75 (d, 1H, J = 6), 4.78 (d, 1 H, J = 6); ^{13}C NMR (50 MHz, C_6D_6) δ: 14.27, 22.99, 25.88, 29.64, 32.20, 35.73, 55.71, 72.95, 84.21, 93.87, 162.63; IR (neat) cm^{-1}: 3448, 2940, 2864, 1644, 1156, 1096, 1020. Anal. Calcd for $C_{11}H_{22}O_3$: C, 65.31; H, 10.96. Found: C, 65.48; H, 11.17.

13. Triethylamine was distilled from calcium hydride. Freshly distilled triethylamine should be used, because any impurities in aged triethylamine may poison the catalyst in the next step.

14. Hexane was distilled from sodium.

15. Since the O-silylated product is somewhat sensitive to moisture, the filtration process should be performed quickly.

16. Platinum catalyst preparation: a mixture of 1 g of chloroplatinic acid hexahydrate, 12.4 mL (22 equiv) of 1,3-divinyltetramethyldisiloxane (an excess), and 1.2 mL of water is heated to 65–70°C for 3.5 hr with stirring.[3] [4] The initial mixture becomes homogeneous after 30 min. The solution is then cooled to room temperature, and 5 mL of aqueous saturated sodium bicarbonate ($NaHCO_3$) solution is added. The upper, yellow-orange, organic layer was separated, dried over Na_2SO_4, and filtered affording a solution (0.29 M) of the platinum catalyst in disiloxane that was stored in the refrigerator until use.

17. An aliquot is taken into an NMR tube, solvent is removed under reduced pressure, C_6D_6 is added and the sample is analyzed by ^{1}H-NMR. The following spectral and analytical data for the cyclic siloxanes were obtained. The syn/anti ratio (95/5) was determined by capillary GLC (Note 9) except that a temperature program was employed [100°C for 2 min, then increased 15°C/min to 250°C (retention times 6.46 min (anti), 6.66 min (syn)]. Each isomer was isolated by preparative GLC: Syn: ^{1}H NMR (200 MHz, C_6D_6) δ: 0.17 (s, 3 H), 0.29 (s, 3 H), 0.78 (dd, 1 H, J = 15, 5.5), 0.92 (t (br), 3 H, J = 7), 1.03 (dd, 1 H, J = 15, 5), 1.20–1.65 (m, 7 H), 1.65–2.00 (m, 3 H), 3.23 (s, 3 H), 3.89 (dt (br), 1 H, J = 9, 4), 4.12 (q (br), 1 H, J = 5), 4.48 (d, 1 H, J = 7), 4.65 (d, 1 H, J = 7); ^{13}C NMR (50 MHz, C_6D_6) δ: 0.28, 1.14, 14.30, 18.39, 23.04, 26.72, 29.96, 32.18, 32.33, 55.28, 77.91, 80.91, 95.16; IR (neat) cm^{-1}: 2963, 2864, 1470, 1254, 1150, 1102, 1046, 872. Anti: ^{1}H NMR (200 MHz, C_6D_6) δ: 0.15 (s, 3 H), 0.23 (s, 3 H), 0.83 (dd, 1 H, J = 14.2, 7.8), 0.91 (t (br), 3 H, J = 6), 1.18 (dd, 1 H, J = 14, 6), 1.25–

1.85 (m, 10 H), 3.26 (s, 3 H), 3.90–4.14 (m, 2 H), 4.57 (d, 1 H, J = 7), 4.73 (d, 1 H, J = 7). Anal. Calcd for $C_{13}H_{28}O_3Si$ (isomeric mixture): C, 59.95, H, 10.84. Found: C, 59.67; H, 11.02.

18. It is essential to remove all organoplatinum species since these species rapidly decompose hydrogen peroxide in the next oxidation step.

19. The filtrate is ordinarily colorless but may possibly be brown, owing to the presence of trace amounts of organoplatinum species.

20. Commercial reagent grade THF and methanol are used without further purification.

21. Reagent grade anhydrous potassium fluoride was purchased from J. T. Baker Chemical Company. This material must be weighed quickly because it is highly hygroscopic.

22. Slow, not vigorous, evolution of small bubbles of oxygen due to a trace amount of residual organoplatinum species may be observed.

23. Since the hydrosilylation products decompose on silica gel, consumption of the starting material cannot be monitored by TLC. Only the formation of the product diol can be detected (R_f = 0.2, hexane/ethyl acetate 1:1).

24. *CAUTION: The thiosulfate solution* ***MUST NOT*** *be added in one portion; since a sudden, violent, uncontrollable reaction could occur.*

25. If the starch-iodide test is still positive for the presence of peroxide, additional thiosulfate solution should be added until a negative starch-iodide test is obtained.

26. The major syn isomer of 2-methoxymethoxy-1,3-nonanediol exhibits the following spectral properties: ^1H NMR (200 MHz, $CDCl_3$) δ: 0.86 (t (br), 3 H, J = 7), 1.18–1.50 (m, 10 H), 2.52 (d, 1 H, J = 5), 2.95 (dd, 1 H, J = 8, 4), 3.35–3.50 (m, 4 H, including a sharp singlet at 3.44), 3.55–3.82 (m, 3 H), 4.71 (d, 1 H, J = 7), 4.80 (d, 1 H, J = 7); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 14.02, 22.54, 25.43, 29.23, 31.72, 33.31, 55.89, 63.22, 71.80, 84.12, 97.43; IR (neat) cm^{-1}: 3428, 2936, 1470, 1154, 1108, 1032. Anal. Calcd for $C_{11}H_{24}O_4$ (isomer mixture): C, 59.97; H, 10.98. Found: C, 59.78; H, 11.04.

27. The syn/anti ratio (98:2) was determined by capillary GLC on a 30-m × 0.32-mm ID HP-5 capillary column containing 5% phenylmethylsilicone as the stationary phase using the following temperature program: 100°C for 2 min, then increase 15°C/min to 250°C (retention times 6.96 min (anti), 7.55 min (syn)). The submitters report that the syn/anti ratio can be determined after conversion to the acetonide by treatment with excess dimethoxypropane and catalytic acid. By this procedure, the isomer ratio was found to be 94.4:5.6 (syn/anti). The submitters also report that the isomers can be separated easily by chromatography on silica gel: R_f = 0.31 for the syn isomer and R_f = 0.45 for the anti isomer (hexane/ethyl acetate 1:1). The acetonides exhibit the following spectral properties: syn: ^1H NMR (200 MHz, $CDCl_3$) δ: 0.85 (t (br), 3 H, J = 7), 1.15–1.75 (m, 16 H, including two sharp singlets at 1.41 and 1.42), 3.33 (q, 1 H, J = 2.0), 3.39 (s, 3 H), 3.80–4.04 (m, 3 H), 4.64 (d, 1 H, J = 7.1), 4.78 (d, 1 H, J = 7.1); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 14.01, 18.89, 22.53, 24.92, 29.17, 31.05, 31.72, 55.71, 62.82, 70.00, 71.30, 95.29, 98.52 (Only five signals are observed

for the hexyl group). Anal. Calcd for $C_{14}H_{28}O_4$: C, 64.58; H, 10.84. Found: C, 64.42; H, 11.11. Anti: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.81 (t (br), 3 H, J = 6.5), 1.10–1.80 (m, 16 H, including two sharp singlets at 1.30 and 1.38), 3.23–3.38 (m, 4 H, including a sharp singlet at 3.29), 3.50–3.68 (m, 2 H), 3.90 (dd, 1 H, J = 11.4, 5.2), 4.54 (d, 1 H, J = 6.8), 4.59 (d, 1 H, J = 6.8); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 14.08, 19.76, 22.62, 25.06, 28.23, 29.24, 31.83, 32.34, 55.62, 63.39, 72.11, 74.48, 96.49, 98.60. The checkers found the determination of the syn/anti ratio by this procedure to be unreliable because of the presence of interfering impurities formed during conversion to the acetonide.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

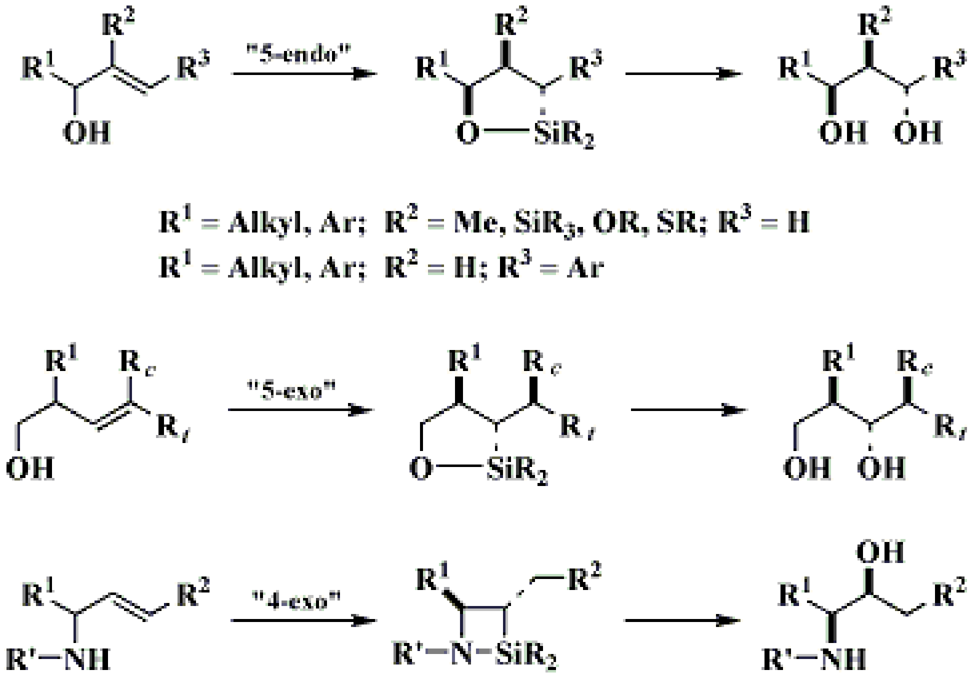
This procedure for the preparation of 2-methoxymethoxy-1,3-nonanediol is a modification of that reported by the submitters.[5] Among a wide variety of methodologies for stereoselective construction of polyoxygenated skeletons, the most straightforward is the stereoselective introduction of two oxygen functionalities onto carbon-carbon double bonds, as represented by the Sharpless epoxidation[6] or osmium tetroxide oxidation of allyl alcohols.[7] An alternative route may be envisioned by anti-Markovnikov hydration of enol ether derivatives, as in the present method, but such an approach has so far been rarely studied. The only other reported method is hydroboration which affords syn/anti ratios in the range of 83/17 to 3/97 in essentially the same systems as those examined in this procedure.[8] The method described here is a highly stereoselective route to 2,3-syn isomers of 1,2,3-triol skeletons from α-hydroxy enol ethers.

This procedure consists of the synthesis of a precursor, methoxymethyl vinyl ether, an α-hydroxy enol ether, and the intramolecular hydrosilylation of the latter followed by oxidative cleavage of the silicon-carbon bonds. The first step, methoxymethylation of 2-bromoethanol, is based on Fujita's method.[9] The second and third steps are modifications of results reported by McDougal and his co-workers.[10] Dehydrobromination of 2-bromoethyl methoxymethyl ether to methoxymethyl vinyl ether[10] was achieved most efficiently with potassium hydroxide pellets[10,11] rather than with potassium tert-butoxide as originally reported for dehydrobromination of the tetrahydropyranyl analog.[12] Potassium tert-butoxide was effective for the dehydrobromination, but formed an adduct of tert-butyl alcohol with the vinyl ether as a by-product in substantial amounts. Methoxymethyl vinyl ether is lithiated efficiently with sec-butyllithium in THF[10] and, somewhat less efficiently, with butyllithium in tetrahydrofuran. Since lithiation of simple vinyl ethers such as ethyl vinyl ether

requires tert-butyllithium,[13] metalation may be assisted by the methoxymethoxy group in the present case.

In the final step for this large scale preparation, the hydroxyl group is silylated with chlorodimethylsilane and triethylamine to effect introduction of the dimethylsilyl group. Alternatively, (diethylamino)dimethylsilane (HMe_2SiNEt_2) or 1,1,3,3-tetramethyldisilazane $(HMe_2Si)_2NH$ in the presence of a catalytic amount of ammonium chloride as a promoter can also be used. In these cases, the filtration step can be omitted since removal of the generated amine and the excess silylamine affords the crude oily product that can be directly employed in the hydrosilylation step.[5,14] Intramolecular hydrosilylation of α-hydroxy enol ethers proceeds readily with a neutral platinum catalyst such as the vinylsiloxane/platinum(0) complex[3,4] since the most commonly used catalyst, chloroplatinic acid hydrate ($H_2PtCl_6 \cdot 6H_2O$), is not suitable for use with acid-sensitive enol ethers. Similar regio- and stereoselective intramolecular hydrosilylations can also be achieved with rhodium catalysts.[15] For removal of organoplatinum species prior to the oxidation, activated carbon seems to be more efficient than the disodium salt of ethylenediaminetetraacetic acid (EDTA·2Na) originally used.[5] Oxidative cleavage of the silicon-carbon bond is performed under standard conditions.[16 17 18]

Finally, the regio- and stereoselectivities of the intramolecular hydrosilylation of allyl alcohols, homoallyl alcohols, and allylamines are summarized in Scheme 1. While these results have been obtained with the dimethylsilyl (HMe_2Si) group in the presence of a platinum catalyst, stereoselectivity, but not regioselectivity, can be controlled by other silyl groups such as the diphenyl (HPh_2Si) or di(isopropyl)silyl [H(i-Pr)$_2$Si] groups.



In the allylic alcohol series having a terminal olefin, the reaction proceeds in the 5-

endo fashion to give five-membered ring compounds selectively with the syn stereoisomer being predominant, regardless of the nature of the catalyst, platinum or rhodium.[19 20,21] Stereoselectivity increases with an increase in bulk of the allylic substituent. In addition, much higher selectivities are attained with enol ethers (R^2 = OMOM, OTHP, SR)[5] in comparison to other systems [(R^2 = Me, $SiMe_2$(O-i-Pr)[22]]. Stereoselectivities in cyclic enol ethers appear to be sensitive to the reaction conditions.[23] It has also been shown that the 5-endo cyclization proceeds smoothly with allyl alcohols with a terminal aryl group (R^3 = Ar), but not with an alkyl group.[24] In homoallyl alcohols, the 5-exo type of intramolecular hydrosilylation proceeds to form five-membered cyclic compounds and eventually 1,3-diols by oxidative cleavage. Two types of 1,2-stereoselection are possible, one being anti-controlled by the allylic substituent and, the other depending upon the olefin geometries, anti to the cis substituent R_c and syn to the trans R_t.[19,20] Catalytic, asymmetric, intramolecular hydrosilylation is also possible with rhodium catalysts in the presence of optically active phosphine ligands.[15,24] In contrast, allylamines form four-membered cyclic products via 4-exo ring closure in the platinum-catalyzed hydrosilylation from which syn-1,2-amino alcohols are obtained highly stereoselectively after oxidative cleavage.[25]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

sodium benzophenone ketyl

2,3-syn-2-Methoxymethoxy-1,3-nonanediol

(diethylamino)dimethylsilane (HMe_2SiNEt_2)

chloroplatinic acid hydrate ($H_2PtCl_6 \cdot 6H_2O$)

EDTA·2Na

ethanol (64-17-5)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

PHOSPHORUS (7723-14-0)

sodium sulfate (7757-82-6)

oxygen (7782-44-7)

nitrogen (7727-37-9)

platinum, platinum(0) (7440-06-4)

cyclohexane (110-82-7)

carbon (7782-42-5)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

2-BROMOETHANOL (540-51-2)

hydrogen peroxide, peroxide (7722-84-1)

thiosulfate

Dimethoxymethane (109-87-5)

magnesium sulfate (7487-88-9)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

potassium fluoride (7789-23-3)

hexane (110-54-3)

triethylamine (121-44-8)

ethyl vinyl ether (109-92-2)

potassium hydrogen carbonate (298-14-6)

Heptanal (111-71-7)

calcium hydride (7789-78-8)

bromo ether

argon (7440-37-1)

rhodium (7440-16-6)

sodium thiosulfate pentahydrate

sec-butyllithium (598-30-1)

homoallyl (2154-62-3)

phosphorus pentoxide (1314-56-3)

tert-Butyllithium (594-19-4)

potassium tert-butoxide (865-47-4)

2-Methoxymethoxy-1,3-nonanediol

2-Bromoethyl methoxymethyl ether (112496-94-3)

Methoxymethyl vinyl ether (63975-05-3)

tris[2-(2-methoxyethoxy)ethyl]amine (70384-51-9)

2-Methoxymethoxy-1-nonen-3-ol (114675-31-9)

chlorodimethylsilane (1066-35-9)

1,3-divinyltetramethyldisiloxane (2627-95-4)

dimethoxypropane (4744-10-9)

1,1,3,3-tetramethyldisilazane (15933-59-2)

1,3-Nonanediol, 2-(methoxymethoxy)-, (R,R)-(±)- (114675-32-0)

disodium salt of ethylenediaminetetraacetic acid

vinylsiloxane

chloroplatinic acid hexahydrate (16941-12-1)

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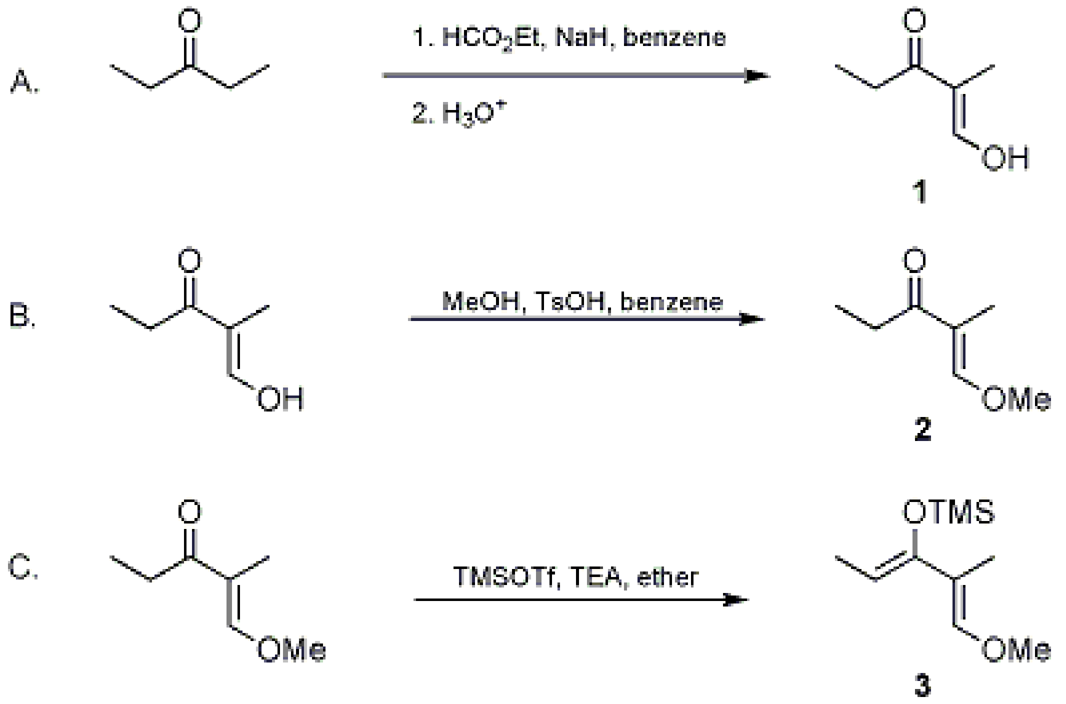
Organic Syntheses, CV 9, 548

(E,Z)-1-METHOXY-2-METHYL-3-(TRIMETHYLSILOXY)-1,3-PENTADIENE

[Silane, [[1-(2-methoxy-1-methylethenyl)-1-propenyl]oxy] trimethyl-, (Z,E)-]



Submitted by David C. Myles and Mathew H. Bigham[1,2].
Checked by David I. Magee and Robert K. Boeckman, Jr..

1. Procedure

CAUTION! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A. A 5-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, calcium sulfate drying tube, and 500-mL pressure equalizing addition funnel is charged with 2.4 L of dry benzene (Note 1), 81.7 g (2.04 mol) of 60% sodium hydride dispersion in benzene (Note 2), and 1.9 mL (0.05 mol) of methyl alcohol (Note 3). The flask is immersed in an ice bath and the addition funnel is charged with a mixture (Note 4) of 222 mL (172 g, 2 mol) of 95% 3-pentanone and 163 mL (148 g, 2 mol) of 99% ethyl formate (Note 5). This mixture is added dropwise to the cooled, stirred suspension over 1.5 hr. During the addition, there is a visible evolution of gas, the mixture darkens, and a paste-like precipitate forms. At the completion of the addition, the ice bath is removed and the mixture is stirred an additional 1.5 hr, until gas

evolution has ceased. The stirred reaction mixture is then diluted with 1.5 L of anhydrous ether (Note 6). The suspension is filtered through an 18.5-cm Büchner funnel fitted with two Whatman 1 filter papers and the solid is washed with two 500-mL portions of anhydrous ethyl ether. The solid is transferred to a 19 × 10-cm evaporating dish and dried under reduced pressure in a vacuum desiccator to afford crude sodium salt of **1** (270–280 g) as a colorless or slightly tan hygroscopic solid. The material is carried on directly in the continuation of this procedure.

A 4-L Erlenmeyer flask equipped with a 2-in Teflon-coated magnetic stirbar is charged with 1.5 L of deionized water and placed in an ice bath. To the stirring water is added in small portions (*CAUTION*, (Note 7)) the crude sodium salt of **1**. When all of the salt has dissolved, the cooled, dark brown solution is acidified to pH 5 (Hydrion paper) by dropwise addition of concd hydrochloric acid. The resultant two-phase mixture is poured into a 3-L separatory funnel and the Erlenmeyer flask is washed with two 100-mL portions of ethyl ether which are added to the separatory funnel. An additional 800 mL of ether is added to the mixture. The upper (organic) and lower (aqueous) phases are separated. The aqueous phase is extracted six additional times (Note 8) with 400 mL of ether each time. The combined organic phases are dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure at 10°C to afford approximately 250 mL of crude **1** as a clear amber oil. This is distilled (Note 9) under reduced pressure (bp 58.5°C, 20 mm) to afford 125–137 g (55–60% yield) of **1** as a slightly yellow oil which solidifies on standing. An analytical sample of **1** was prepared by recrystallization from pentane (mp 42–43°C) (Note 10).

B. A 3-L, three-necked, round-bottomed flask is equipped (see f.htmigure 1) with a 2-in Teflon-coated magnetic stirring bar, a 150-mm Vigreux column topped by a 500-mL pressure-equalizing addition funnel and calcium sulfate drying tube, a short path distillation apparatus, and a ground glass stopper. The flask is charged with 1 L of benzene and 0.5 L of a 60:40 mixture of benzene/methanol (Note 11). To this solution is added 114 g (1.0 mol) of 1-hydroxy-2-methylpent-1-en-3-one **(1)** in a small amount of benzene and 0.95 g (0.005 mol) of p-toluenesulfonic acid monohydrate. The addition funnel is charged with 500 mL of the 60:40 benzene/methanol mixture. The magnetically stirred solution is warmed to a gentle reflux at which time the solution begins to darken to a light brown color. The distillation temperature rises to 59°C (the boiling point of the benzene/methanol azeotrope) and stabilizes. The distillate volume is monitored throughout the course of the reaction. When 250 mL of distillate has collected, the reaction vessel is replenished with 250 mL of fresh benzene/methanol mixture. This cycle is repeated 6 times until starting material is consumed (Note 12). At this time any residual benzene/methanol mixture in the addition funnel is discarded and the funnel is charged with 500 mL of benzene. The reaction volume is maintained by the addition of benzene as the boiling point of the distillate rises to 79°C. In this way, a total of 750 mL of benzene is distilled out of the reaction mixture as the reaction is driven to completion. The reaction mixture is allowed to cool to room temperature and is quenched by the addition of 500 mL of 1.0 M aqueous sodium bicarbonate solution. The two phase mixture is stirred for 5 min and then transferred to

a 2-L separatory funnel. The phases are separated and the aqueous (lower) phase is extracted two times with 500 mL of ether each time. The combined organic phases are dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to give crude **2** as a brown oil. The oil is fractionally distilled under reduced pressure (bp 94–96°C, 22 mm) to afford 90–96 g (70–75%) of **2**. Assay of this material by GLC shows it to be ca. 95% pure (Note 13).

Figure 1

Figure 1

C. A 2-L, round-bottomed flask equipped with a 2-in Teflon-coated magnetic stirring bar is charged with 750 mL of anhydrous ether, 102 g (1.0 mol) of 99% triethylamine (Note 14) and 96 g (0.75 mol) of 1-methoxy-2-methylpent-1-en-3-one **(2)**. The flask is capped with a rubber septum equipped with a 16-gauge needle connected to a dry nitrogen source. The magnetically stirred solution is cooled in an ice bath and 167 g (0.75 mol) of trimethylsilyl trifluoromethanesulfonate (Note 15) is added via an 18-gauge cannula over 10 min. The cooled mixture is stirred for 30 min, during which time a red-brown oily precipitate forms. The reaction mixture is transferred to a 2-L separatory funnel and the red-brown (lower) phase is separated and discarded. The remaining ethereal phase is washed with 500 mL of 1.0 M aqueous sodium bicarbonate solution and separated. The aqueous (lower) phase is extracted with 500 mL of ether, separated and discarded. The combined organic phases are dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to yield crude diene **3** as a yellow oil. This is fractionally distilled through a 150-mm Vigreux column at reduced pressure (bp 83–85°C, 22 mm) to afford 121–131 g (81–87%) of **3** as a colorless or slightly yellow liquid. Assay of this material by GLC shows it to be ca. 95% pure (Note 16).

2. Notes

1. Unless otherwise indicated, the solvents are reagent grade and are used without further purification.
2. Commercially available (Aldrich Chemical Company, Inc.) 60% sodium hydride dispersed in mineral oil is dispersed in benzene in the following manner: 81.7 g of 60% sodium hydride mineral oil dispersion is suspended in 100 mL of benzene in a 500-mL Erlenmeyer flask equipped with a Teflon-coated magnetic stirbar. The suspension is vigorously stirred for 1 hr until all of the lumps are gone. The suspension is then transferred to the reaction vessel with a small amount of benzene.
3. Methyl alcohol functions as a catalytic base in this reaction.
4. The efficiency of the procedure is enhanced by complete premixing of the 3-pentanone and ethyl formate.
5. 3-Pentanone and ethyl formate were purchased from Aldrich Chemical Company, Inc. and used without further purification.

6. Efficient mixing is essential during the addition of the ether to ensure the formation of a flocculent precipitate. Inadequate agitation results in the formation of large clumps of product.
7. *CAUTION: Small amounts of sodium hydride from the previous step may remain in the solid. The addition should be carried out slowly enough to allow any residual sodium hydride to quench completely before the next portion of solid is added.*
8. TLC analysis (Merck 0.25-mm silica gel plates with 254 nm UV indicator, 1:4 ethyl acetate:hexanes) of the organic phase of each extraction reveals the presence of **1** (R_f = 0.32). Extraction is continued until **1** is no longer seen in the organic extracts.
9. Crude **1** may solidify in the pot as any remaining solvent evaporates, but can be reliquified by gentle heating. Stirring is facilitated by a powerful magnetic stirrer and 2-in Teflon-coated magnetic stirbar. To prevent solidification of the distillate on the condenser, the water temperature through the condenser is maintained at 25°C. To minimize product loss, all fractions were collected in a receptacle cooled with an ice bath.
10. The ^{1}H-NMR spectrum of **1** is as follows: (90 MHz, $CDCl_3$, TMS = 0 ppm) δ: 1.13 (t, 3 H, J = 7), 1.79 (s, 3 H), 2.46 (q, 2 H, J = 7), 7.45 (s, 1 H), 7.57 (s, 1 H).
11. The composition of the binary azeotrope of benzene and methanol is 60.5% benzene, 39.5% methanol.
12. The progress of the reaction is monitored by TLC (R_f of **1** = 0.32, R_f of **2** = 0.25; 1:4 ethyl acetate:hexanes). A non-UV absorbing spot (R_f = 0.29) is seen to form as an intermediate between **1** and **2**. This is presumed to be the 1,1-dimethyl acetal of **1**. When this spot is nearly gone, the reaction is presumed to be complete.
13. The ^{1}H-NMR of **2** is as follows: (90 MHz, $CDCl_3$, TMS) δ: 1.10 (t, 3 H, J – 7.4), 1.71 (s, 3 H), 2.52 (q, 2 H, J = 7.4), 3.86 (s, 3 H), 7.23 (bs, 1 H).
14. Triethylamine was purchased from Aldrich Chemical Company, Inc. and was used without further purification.
15. Trimethylsilyl trifluoromethanesulfonate was purchased from Petrarch Systems and was used without further purification.
16. The ^{1}H-NMR of **3** is as follows: (90 MHz, $CDCl_3$, $CHCl_3$, δ 7.27) δ: 0.23 (s, 9 H), 1.63 (d, 3 H, J = 7), 1.70 (s, 3 H), 3.66 (s, 3 H), 4.75 (q, 1 H, J = 7), 6.35 (s, 1 H).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Siloxy dienes have been shown to be highly effective in both the Diels-Alder[3 4]

reaction and the hetero Diels-Alder (diene-aldehyde cyclocondensation)[5] reactions. Diene **3** has been used in the synthesis of several important natural products including zincophorin,[6] rifamycin,[7] and the Prelog-Djerassi lactone.[8] Recently, under the aegis of chiral catalysts, **3** has been shown to participate in the diene-aldehyde cyclocondensation reaction with several aldehydes to afford cycloadducts of very high enantiomeric excess.[9 10]

The procedure described here allows the convenient preparation of large quantities of diene **3** and has several advantages over previously published sequences. 1-Methoxy-2-methylpenten-3-one **(2)** can be prepared in ca. 90-g lots and can be stored for several months at 0°C under argon. The earlier procedure for the synthesis of **2**[11] relies on dimethyl sulfate as the methylating reagent in the formation of the methyl enol ether moiety. The high toxicity of this reagent renders this strategy unattractive for routine use. The published procedure for the conversion of **2** to 1-methoxy-2-methyl-3-(trimethylsiloxy)-1,3-pentadiene **(3)**[3] uses trimethylsilyl chloride, triethylamine and a catalytic amount of zinc chloride in benzene (40°C, ca. 12 hr) for the silylation. This mixture results in the formation of copious quantities of triethylamine hydrochloride, which greatly complicates the work up and purification. This new procedure, using trimethylsilyl trifluoromethanesulfonate and triethylamine, allows the convenient separation of the amine salt and significantly shortens the reaction time (30 min vs 12 hr). The silylation can be carried out on scales ranging from 0.10 mol to 0.75 mol with consistently good yields. Diene **3** can be stored for several months at 0°C under argon without significant decomposition.

References and Notes

1. Department of Chemistry, Yale University, New Haven, CT 06511.
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hexanes

1,1-dimethyl acetal

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ethyl acetate (141-78-6)

methyl alcohol, methanol (67-56-1)

ether, ethyl ether (60-29-7)

sodium bicarbonate (144-55-8)

ethyl (2025-56-1)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

dimethyl sulfate (77-78-1)

zinc chloride (7646-85-7)

ethyl formate (109-94-4)

Pentane (109-66-0)

magnesium sulfate (7487-88-9)

3-pentanone (96-22-0)

sodium hydride (7646-69-7)

triethylamine (121-44-8)

Triethylamine hydrochloride (554-68-7)

argon (7440-37-1)

trimethylsilyl chloride (75-77-4)

Trimethylsilyl trifluoromethanesulfonate (27607-77-8)

p-toluenesulfonic acid monohydrate (6192-52-5)

(E,Z)-1-Methoxy-2-methyl-3-(trimethylsiloxy)-1,3-pentadiene, Silane, [[1-(2-methoxy-1-methylethenyl)-1-propenyl]oxy]trimethyl-, (Z,E)- (72486-93-2)

1-Hydroxy-2-methylpent-1-en-3-one (50421-81-3)

1-Methoxy-2-methylpent-1-en-3-one, 1-Methoxy-2-methylpenten-3-one

1-methoxy-2-methyl-3-(trimethylsiloxy)-1,3-pentadiene

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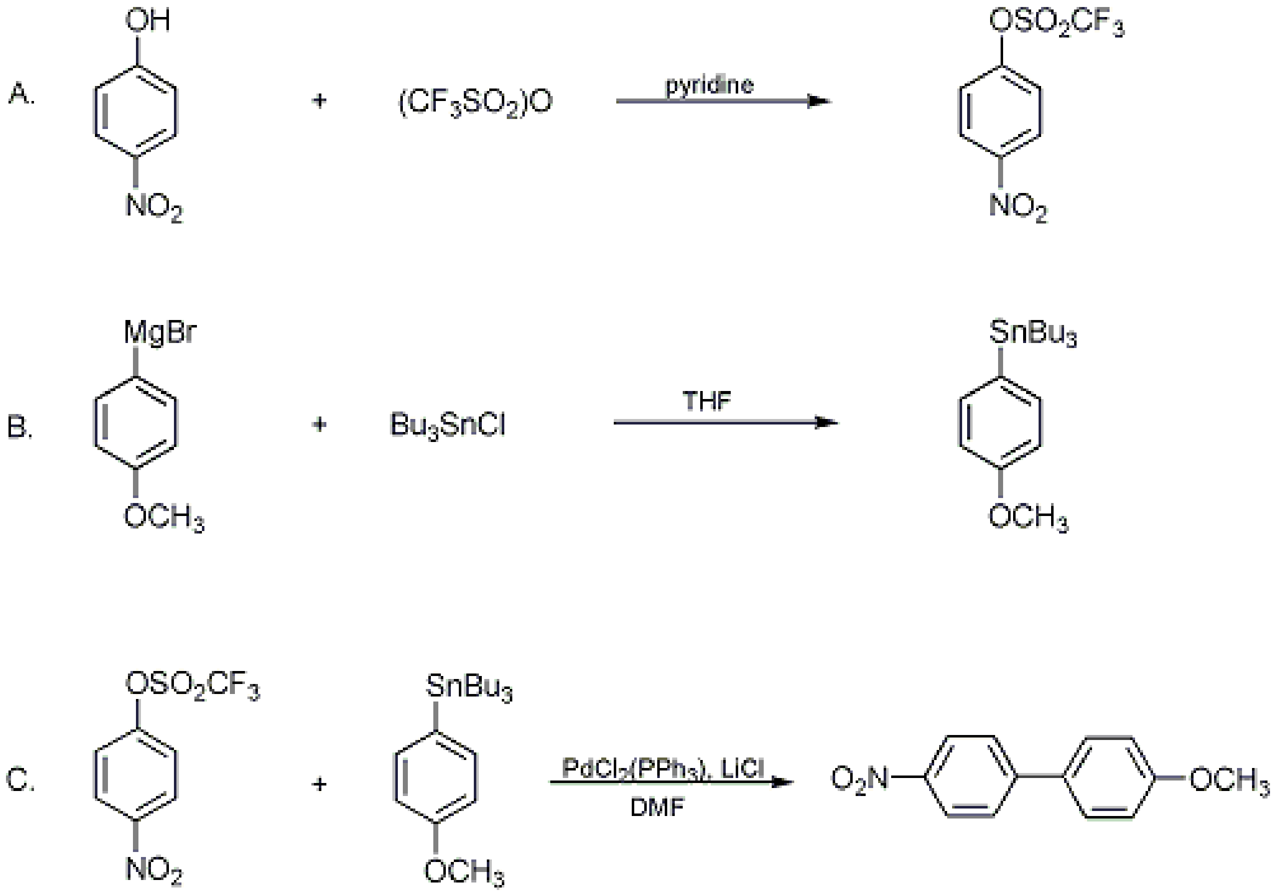
Organic Syntheses, *CV 9, 553*

4-METHOXY-4'-NITROBIPHENYL

[1,1'-Biphenyl, 4-methoxy-4'-nitro-]



Submitted by J. K. Stille, Antonio M. Echavarren, Robert M. Williams, and James A. Hendrix[1].
Checked by Bryon A. Merrill and Larry E. Overman.

1. Procedure

CAUTION! Many organotin compounds are toxic.[2] Their preparation and use should be carried out in a well-ventilated hood.

A. *4-Nitrophenyl trifluoromethanesulfonate* **(1)**. A dry, 100-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, nitrogen gas inlet, and rubber septum (Note 1) is charged sequentially with 10.0 g (71.9 mmol) of 4-nitrophenol and 38 mL of pyridine (Note 2). The stirred solution is cooled to 0°C and 13.5 mL (80 mmol) of trifluoromethanesulfonic anhydride (Note 3) is added through the septum via a syringe. The rate of addition is such that the internal temperature of the flask never exceeds 25°C (Note 4). The solution is allowed to warm slowly to room temperature and is maintained at room temperature for 25 hr. The reaction is quenched by pouring it into a 250-mL separatory funnel that contains 100 mL of water and 50 mL of diethyl ether. The two phases are

separated and the aqueous phase is extracted with four additional 50-mL portions of diethyl ether. The combined organic fractions are dried over magnesium sulfate, filtered, and concentrated to provide 18.7 g of crude **1** as a yellow, crystalline, solid.

The crude product is dissolved in 50 mL of diethyl ether and adsorbed onto 20 g of Celite 521 by evaporation of the diethyl ether under reduced pressure. The dry Celite 521 is then added to the top of a column containing 200 g of silica gel (32–63 micron) and the column is eluted with a mobile phase of 9:1 hexanes-ethyl acetate. The fractions containing the product (R_f = 0.50, 9:1 hexanes-ethyl acetate) are collected and concentrated under reduced pressure to yield 17.7 g (91%) of **1** as a colorless, crystalline, solid (Note 5).

B. *Tributyl(4-methoxyphenyl)stannane* **(2)**. A dry, 250-mL, three-necked, round-bottomed flask, equipped with a reflux condenser, magnetic stirring bar, and nitrogen gas inlet, is charged with 2.91 g (120 mmol) of magnesium turnings (Note 1) and (Note 6). The flask is fitted with a rubber septum and charged sequentially via syringe with 85 mL of tetrahydrofuran (Note 7), 14.0 mL (112 mmol) of 4-bromoanisole (Note 8), and 0.05 mL of methyl iodide (Note 9). The rubber septum is immediately replaced with a Teflon stopper. Within 5 min, the reaction spontaneously warms to reflux temperature and continues to boil for approximately 10 min. The reaction is stirred an additional 2 hr without external heating or cooling. The flask is fitted with a rubber septum and 30.5 mL (112 mmol) of tributyltin chloride is added to the green solution via a syringe (Note 10). The septum is again replaced with a Teflon stopper and the reaction is heated at reflux for 12 hr.

Upon cooling to room temperature, a gray precipitate forms and the reaction is quenched with 220 mL of saturated, aqueous ammonium chloride. The resulting mixture is poured into a 1-L separatory funnel and extracted with 220 mL of diethyl ether. The organic fraction is washed two times with 100 mL of water, and once with 100 mL of brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide 44.1 g of crude product as a pale yellow oil. Purification of this material by bulb-to-bulb distillation (140–145°C, 0.5 mm) (Note 11) into a chilled (–78°C) receiving flask yields 41.0 g (92%) of **2** as a clear, colorless oil (Note 12).

C. *4-Methoxy-4'-nitrobiphenyl* **(3)**. A dry, 500-mL, three-necked, round-bottomed flask equipped with a reflux condenser, magnetic stirring bar, nitrogen gas inlet, and rubber septum (Note 1) is charged sequentially with 300 mL of anhydrous N,N-dimethylformamide (Note 13), 15.0 g (55.4 mmol) of 4-nitrophenyl trifluoromethanesulfonate **(1)**, 27.8 g (70.0 mmol) of tributyl(4-methoxyphenyl)stannane **(2)** (Note 14), 7.5 g of dry lithium chloride (Note 15), and 1.6 g (4 mol percent) of bis(triphenylphosphine)palladium(II) chloride (Note 16). The rubber septum is replaced with a Teflon stopper and the yellow mixture is heated at 100–105°C for 2.5 hr. After approximately 20 min, the reaction turns dark brown.

The reaction mixture is cooled to room temperature and then vacuum-filtered through a 350-mL, medium frit, sintered-glass Büchner funnel that is filled to a height of 4 cm with ethyl acetate-impregnated Celite 521. Four 100-mL portions of ethyl acetate are used to wash the pad of Celite 521. The filtrate is partially concentrated by removal of ethyl acetate under reduced pressure. The resulting brown liquid is slowly poured into 1.5 L of water. After standing for 8 hr, the precipitate is collected by vacuum filtration and air dried. The solid is dissolved in 500 mL of acetonitrile, the resulting solution is poured into a 1-L separatory

funnel, and is washed with three 300-mL portions of hexanes. The acetonitrile layer is concentrated to provide 24 g of crude product as a brown solid.

The crude product is dissolved in a minimum amount of dichloromethane and adsorbed onto 25 g of silica gel (32–63 micron) by subsequent evaporation of the dichloromethane under reduced pressure. The sample of dry, dark brown silica gel is added to the top of a column containing 500 g of silica gel (32–63 micron) with a mobile phase of hexanes. The polarity of the mobile phase is gradually increased from hexanes to 95:5 hexanes-ethyl acetate. The fractions containing the desired product (R_f = 0.26, 95:5 hexanes-ethyl acetate) are combined and concentrated under reduced pressure to yield 6.9 g of **3** as a yellow solid. Additional purification is required to remove traces of tin by-products. Compound **3** is dissolved in 70 mL of ethyl acetate and stirred over 70 mL of saturated, aqueous potassium fluoride for 24 hr. The two phases are separated and the organic phase is dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting yellow solid is recrystallized from ethyl alcohol to provide 6.1 g (48%, 2 crops) of **3** as yellow needles (Note 17), (Note 18), and (Note 19).

2. Notes

1. All glassware is oven-dried at 140°C overnight and assembled while hot under a nitrogen atmosphere.
2. 4-Nitrophenol (99%+) is purchased from the Aldrich Chemical Company, Inc., as a golden yellow solid and used as received. Pyridine is freshly distilled from calcium hydride.
3. Trifluoromethanesulfonic anhydride is purchased from the Aldrich Chemical Company, Inc., and used as received. It may also be prepared from trifluoromethanesulfonic acid.[3]
4. The reaction turns deep red upon addition of the anhydride.
5. 4-Nitrophenyl trifluoromethanesulfonate exhibits the following properties: mp 54–55°C (lit.[4] 53°C); IR (KBr) cm^{-1}: 3125, 3094, 1625, 1590, 1537, 1487, 1423, 1352, 1253, 1214, 1137, 1012, 900, 862, 759, 744, 692, 613; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.50 (d, 2 H, J = 9.2), 8.37 (d, 2 H, J = 9.2); high resolution mass spectrum (isobutane CI): 271.9848 (271.9840 calcd for $C_7H_5F_3NO_5S$).
6. Magnesium turnings (99.99%) are purchased from Johnson Matthey/Alfa Products and used as received.
7. Tetrahydrofuran is freshly distilled from sodium benzophenone ketyl.
8. 4-Bromoanisole is purchased from the Aldrich Chemical Company, Inc., and used as received.
9. Methyl iodide is purchased from the Aldrich Chemical Company, Inc., and used as received. Methyl iodide is used as a catalyst to initiate the Grignard reaction.
10. Tributlytin chloride is purchased from the Aldrich Chemical Company, Inc., and used as received. The reaction warms upon the introduction of tributyltin chloride, but it does not boil spontaneously .
11. Tributyl(4-methoxyphenyl)stannane is reported to boil at 158–160°C (0.5 mm).[5]
12. Tributyl(4-methoxyphenyl)stannane exhibits the following properties: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.88 (t, 9 H, J = 7.3), 1.02 (m, 6 H), 1.33 (m, 6 H), 1.53 (m, 6

H), 3.80 (s, 3 H), 6.90 (d, 2 H, J = 8.5), 7.37 (d, 2 H, J = 8.5). The peaks at 1.02 and 7.37 ppm show coupling with tin; mass spectrum (isobutane CI) 399, 397, 395, 291, 289, 287. The product is at least 97% pure by GC analysis (30 m, Supelco SPB-1 fused silica column).

13. Anhydrous N,N-dimethylformamide (water <0.005%) is purchased from the Aldrich Chemical Company, Inc., and transferred via cannula directly from the Sure/Seal bottle into the reaction flask. The solvent is deoxygenated by bubbling nitrogen through it for 45 min prior to the addition of compound **2**.

14. Tributyl(4-methoxyphenyl)stannane **(2)** is added to the reaction flask via a 30-mL syringe.

15. Lithium chloride is dried by heating at 130°C under reduced pressure (0.5 mm) for 24 hr.

16. Bis(triphenylphosphine)palladium(II) chloride (98%) is purchased from the Aldrich Chemical Company, Inc., and used as received.

17. 4-Methoxy-4'-nitrobiphenyl **(3)** has the following properties: mp 109–110°C (lit.[6] 111°C); IR (KBr) cm^{-1}: 3062, 2968, 2838, 1600, 1509, 1487, 1345, 1253, 1034, 1017, 857, 845, 830, 817, 757, 724, 696; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.88 (s, 3 H), 7.01 (d, 2 H, J = 8.7), 7.58 (d, 2 H, J = 8.7), 7.68 (d, 2 H, J = 8.7) 8.26 (d, 2 H, J = 8.7); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 55.4, 114.5, 124.1, 127.0, 128.5, 131.0, 146.4, 147.1, 160.4; mass spectrum (isobutane CI): 230 (MH). Anal. Calcd for $C_{13}H_{11}NO_3$: C, 68.10; H, 4.84; N, 6.11. Found: C, 67.99; H, 4.87; N, 6.13.

18. The checkers also recover 170 mg (2%) of 4,4'-dimethoxybiphenyl **(4)** (R_f = 0.38, 95:5 hexanes-ethyl acetate) and 310 mg (3%) of 4-amino-4'-methoxybiphenyl **(5)** (R_f = 0.28, 4:1 hexanes-ethyl acetate) as minor byproducts. Compound **5** is recovered from the column by increasing the eluent polarity to 4:1 hexanes-ethyl acetate.

4,4'-Dimethoxybiphenyl **(4)** has the following properties: mp 175–177°C (lit.[7] 176–178°C); IR (KBr) cm^{-1}: 2958, 2914, 2840, 1608, 1503, 1277, 1251, 1184, 1042, 1012, 825, 810; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.85 (s, 6 H), 6.96 (d, 4 H, J = 8.7), 7.48 (d, 4 H, J = 8.7); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 55.3, 114.1, 127.7, 133.5, 158.7; high resolution mass spectrum (70 eV, EI): 214.0993 (214.0994 calcd for $C_{14}H_{14}O_2$).

4-Amino-4'-methoxybiphenyl **(5)** has the following properties: mp 143–144°C (lit.[8] 144–145.5°C): IR (KBr) cm^{-1}: 3396, 3334, 3224, 3033, 2965, 2837, 1636, 1608, 1500, 1270, 1241, 1181, 1035, 1015, 817; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.69 (broad s, 2 H), 3.84 (s, 3 H), 6.75 (d, 2 H, J = 8.5), 6.95 (d, 2 H, J = 8.8), 7.37 (d, 2 H, J = 8.4); 7.46 (d, 2 H, J = 8.8); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 55.3, 114.1, 115.4, 127.4, 127.6, 131.3, 133.8, 145.2, 158.4; high resolution mass spectrum (70 eV, EI): 199.0990 (199.0997 calcd for $C_{13}H_{13}NO$).

19. The checkers found that using tetrakis(triphenylphosphine)palladium(0) as the catalyst and dioxane as the solvent resulted in significant reduction of the nitro-substituent in the coupled product.[9] Biphenyls **3** and **5** are obtained in ratios as high as one to one under these conditions.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the

Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The introduction of a bond between two aromatic rings is a familiar problem in organic synthesis. A wide variety of classical and non-classical methods are available for the preparation of unsymmetrical biaryl compounds.[10] However, many of these methods are non-selective and require harsh conditions in order to obtain reasonable yields. A relatively mild and versatile method for the formation of carbon-carbon bonds is the palladium-catalyzed coupling of functionalized organostannanes with organic electrophiles.[11 12,13 14 15] Aryl halides[16 17 18] and aryl trifluoromethanesulfonates (triflates)[9,19 20] couple with organostannanes to provide a selective method for the formation of aryl-aryl bonds. Aryl triflates are especially important starting materials because of their stability and ease of formation.[21,22]

The palladium-catalyzed cross-coupling reaction featured in this procedure occurs under neutral conditions in the presence of many synthetically useful functional groups (e.g. alcohol, ester, nitro, acetal, ketone, and aldehyde). The reaction works best in N,N-dimethylformamide with bis(triphenylphosphine)palladium(II) chloride, $PdCl_2(PPh_3)_2$, as the catalyst. Lithium chloride is added to prevent decomposition of the catalyst.[19,20] It is presumed that conversion of the intermediate aryl palladium triflate to an aryl palladium chloride is required for the transmetallation step to proceed.[9]

In a recent study examining ligand effects on the palladium-catalyzed cross-coupling reaction between aryl triflates and vinylstannanes, tri-2-furylphosphine and triphenylarsine were observed to provide significant rate enhancements (10^2-10^3 greater than with triphenylphosphine-based catalysts).[23 24] Although not reported, these ligands may also be useful for aryl-aryl cross-coupling reactions.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 258
- Org. Syn. 75, 53
- Org. Syn. 78, 23

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

nitro, acetal, ketone

hexanes

brine

sodium benzophenone ketyl

Tributlytin chloride

ethyl alcohol (64-17-5)

ethyl acetate (141-78-6)

diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

acetonitrile (75-05-8)

magnesium turnings (7439-95-4)

nitrogen (7727-37-9)

pyridine (110-86-1)

Methyl iodide (74-88-4)

dichloromethane (75-09-2)

palladium chloride

magnesium sulfate (7487-88-9)

dioxane (5703-46-8)

Tetrahydrofuran (109-99-9)

potassium fluoride (7789-23-3)

N,N-dimethylformamide (68-12-2)

Lithium chloride (7447-41-8)

calcium hydride (7789-78-8)

Triphenylarsine (603-32-7)

trifluoromethanesulfonic acid (1493-13-6)

Trifluoromethanesulfonic anhydride (358-23-6)

4-bromoanisole (104-92-7)

tetrakis(triphenylphosphine)palladium(0) (14221-01-3)

tributyltin chloride (1461-22-9)

4-Methoxy-4'-nitrobiphenyl, 1,1'-Biphenyl, 4-methoxy-4'-nitro- (2143-90-0)

4-Nitrophenyl trifluoromethanesulfonate (17763-80-3)

4-nitrophenol (100-02-7)

Tributyl(4-methoxyphenyl)stannane (70744-47-7)

bis(triphenylphosphine)palladium(II) chloride

4,4'-dimethoxybiphenyl (2132-80-1)

4-amino-4'-methoxybiphenyl

palladium triflate

tri-2-furylphosphine (5518-52-5)

4-nitrophenyl fluorosulfonate

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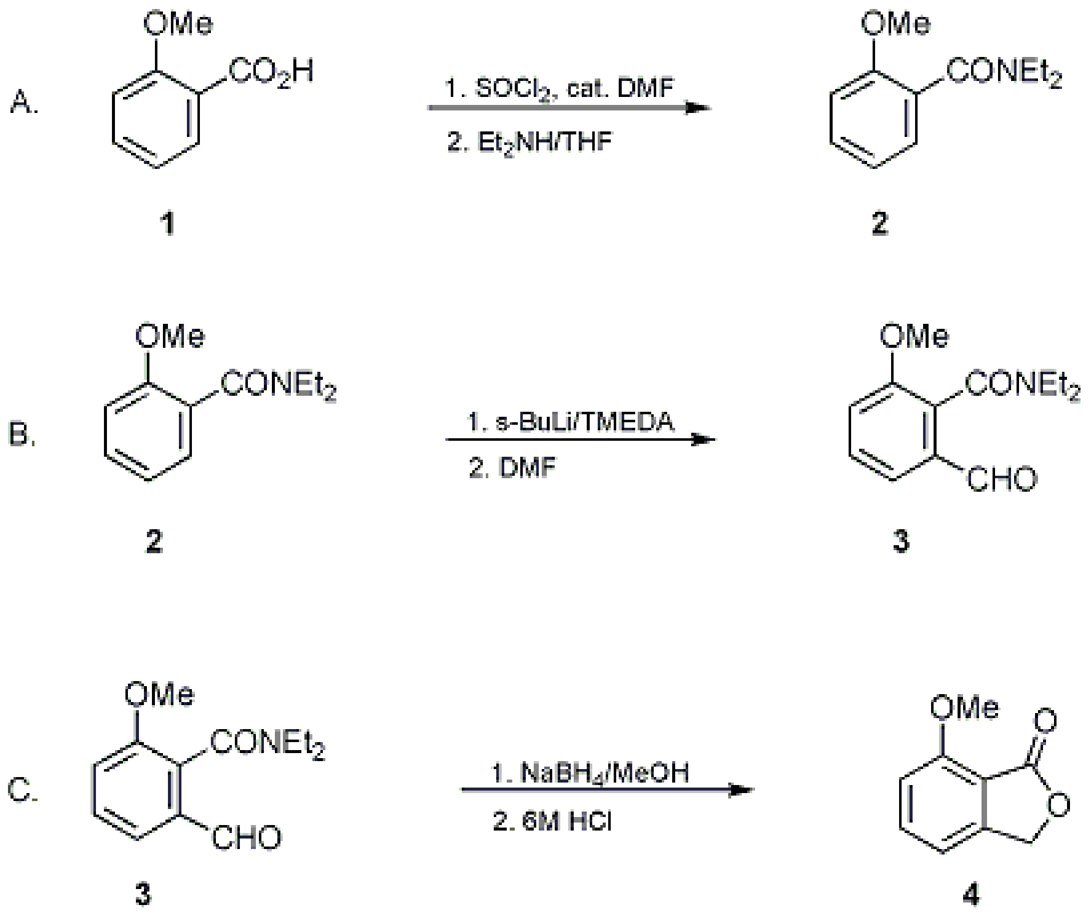
Organic Syntheses, CV 9, 559

7-METHOXYPHTHALIDE

[1(3H)-Isobenzofuranone, 7-methoxy-]



Submitted by X. Wang, S. O. de Silva, J. N. Reed, R. Billadeau, E. J. Griffen, A. Chan, and V. Snieckus.[1].
Checked by Chris Limberakis and Stephen F. Martin.

1. Procedure

A. *N,N-Diethyl-2-methoxybenzamide* **(2)**. An oven-dried, two-necked, 500-mL flask equipped with a septum cap, nitrogen bubbler, and magnetic stirrer is charged with 2-methoxybenzoic acid (20 g, 0.13 mol) (Note 1) under nitrogen. Thionyl chloride (135 mL, 220 g, 1.85 mol) (Note 2) is added with stirring, resulting in slow effervescence. Dimethylformamide (DMF, 0.34 mL, 320 mg, 4.4 mmol) (Note 3),(Note 4) is added dropwise via syringe after which effervescence becomes much more vigorous *(CAUTION: Sulfur dioxide and hydrogen chloride are evolved)*. The solution is stirred for 0.5 hr, at which time no further effervescence is visible. Half of the thionyl chloride is removed under reduced pressure on a rotary evaporator, toluene (100 mL) is added, and the mixture is evaporated to dryness. A further 100 mL of toluene is added and the process of evaporation is repeated twice more to ensure complete

removal of all excess thionyl chloride (Note 5). The colorless oil is dissolved in dry tetrahydrofuran (THF, 150 mL) (Note 6), the resulting solution is cooled in an ice water bath, and treated slowly with diethylamine (50 mL, 35.3 g, 0.48 mol) (Note 7), with stirring to prevent the reaction from becoming too vigorous. A copious white precipitate forms.

When all the diethylamine has been added the mixture is stirred for a further 10 min and then concentrated under reduced pressure. The residue is dissolved in methylene chloride (200 mL), washed with water (2 × 200 mL) and saturated brine (2 × 50 mL), and concentrated under reduced pressure to give an orange oil. The oil is distilled at reduced pressure to give 23.5–24.5 g (86–90%) of N,N-diethyl-2-methoxybenzamide (118–120°C/0.1 mm) as a straw-colored liquid.

B. *N,N-Diethyl-2-formyl-6-methoxybenzamide* **(3)**. An oven-dried, three-necked, 1-L flask equipped with a 100-mL, pressure-equalizing, dropping funnel, nitrogen bubbler, internal low temperature thermometer pocket, and overhead stirrer is flamed under reduced pressure and allowed to cool under a stream of nitrogen. The flask is charged with 500 mL of THF (Note 6) and cooled to an internal temperature of −72°C. N,N,N',N'-Tetramethylethylenediamine (TMEDA) (Note 8) (23.5 mL, 0.156 mol) followed by 128.7 mL (0.157 mmol) of 1.22 M sec-butyllithium in cyclohexane (Note 9) are then added. The internal temperature rises a little as the reagents are added. The fluorescent yellow solution is allowed to recool to an internal temperature of −73°C. N,N-Diethyl-2-methoxybenzamide **(2)** 24.9 g (0.121 mmol) is dissolved in 100 mL of THF and added dropwise via the dropping funnel, while the internal temperature is maintained below −68°C. The solution is stirred for 1 hr during which time the color changes from fluorescent yellow to yellow with a white precipitate. Dimethylformamide (DMF, 11.2 mL) is added via the dropping funnel, and the cooling bath is removed after 2 min. The solution is allowed to warm to room temperature over 16 hr after which time the solution is yellow. The reaction mixture is concentrated under reduced pressure to 150 mL, and the residue is cooled to 0°C and made acidic (pH 4–5) by the addition of 90 mL of 6 M aqueous hydrochloric acid. The solution is extracted with ethyl acetate (5 × 100 mL) (Note 10), the combined organic layers are washed with water (100 mL) and brine (2 × 200 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residual, yellow oil is dried overnight under reduced pressure to give 26.9 g of crude product [2](Note 11).

C. *7-Methoxyphthalide* **(4)**. The crude product from Step B (26.9 g), in a 1-L, one-necked, round-bottomed flask with a magnetic stirring bar, is dissolved in 465 mL of absolute methanol (Note 12). To this solution, cooled to 0°C, is added 7.4 g (0.20 mol) of powdered sodium borohydride, in small portions (Note 13), and the mixture is stirred at room temperature for 18 hr. The reaction mixture is cooled in an ice water bath and taken to pH 4–5 with about 35 mL of 6 M aqueous hydrochloric acid. A further 48 mL (0.288 mol) of 6 M hydrochloric acid is added, the flask is fitted with a reflux condenser and the reaction mixture is heated under reflux for 12 hr. The reaction mixture is then allowed to cool to room temperature and most of the methanol

is evaporated under aspirator pressure. The residue is dissolved in 400 mL of methylene chloride, the phases are separated, and the organic fraction is washed with saturated ammonium chloride (3 × 200 mL) and water (1 × 100 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The pale yellow solid is recrystallized from ethyl acetate-hexane (1:1) (Note 10) to give 15.4 g (81% overall from **2**) of 7-methoxyphthalide, mp 106–108°C, lit[3] mp 107–109°C (Note 14).

2. Notes

1. 2-Methoxybenzoic acid, purchased from Lancaster Synthesis Ltd., was used as received.
2. Thionyl chloride, purchased from J.T.Baker Ltd., was used as received.
3. Dimethylformamide was distilled from calcium hydride and stored over 4 Å molecular sieves under nitrogen.
4. The use of DMF to accelerate the formation of acid chlorides from carboxylic acids has been reviewed previously,[4] and is believed to occur via an imidoyl chloride intermediate.[5]
5. The removal of excess thionyl chloride by formation of an azeotrope with benzene was used in a previous *Organic Syntheses* procedure;[6] however, toluene is much less toxic than benzene and is therefore recommended.
6. Tetrahydrofuran was freshly distilled from sodium/benzophenone ketyl at atmospheric pressure under nitrogen.
7. The use of acid chlorides in the preparation of amides has been reviewed.[7] The diethylamine was distilled from calcium hydride prior to use.
8. N,N,N',N'-Tetramethylethylenediamine was distilled from calcium hydride and stored under nitrogen.
9. sec-Butyllithium purchased from Aldrich Chemical Company, Inc., was standardized by titration using 2,5-dimethoxybenzyl alcohol as indicator.[8]
10. Reagent grade ethyl acetate, methylene chloride, and hexane purchased from British Drug House, Inc., were distilled before use.
11. N,N-Diethyl-2-formyl-6-methoxybenzamide may be purified by silica gel (mesh 230-400) column chromatography using ethyl acetate-hexane (1:1) eluent. The compound shows the following physical and spectral data: bp 134–136°C (0.05 mm); IR ($CHCl_3$) ν (max) cm^{-1}: 1705, 1620 ; ^1H NMR ($CDCl_3$) δ: 1.01 (t, 3 H, J = 7.2), 1.29 (t, 3 H, J = 7.2), 3.11 (q, 2 H, J = 7.2), 3.49–3.61 (m, 1 H), 3.67–3.82 (m, 1 H), 3.86 (s, 3 H), 7.16 (dd, 1 H, J = 1.3, 7.8), 7.43–7.55 (m, 2 H), 9.99 (s, 1 H); MS, m/z (rel intensity) 235 (M^+, 5), 206 (100); Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 67.44; H, 7.69; N, 5.75.
12. Absolute methanol, purchased from British Drug House, Inc., was used as received.

13. Sodium borohydride, purchased from Aldrich Chemical Company, Inc., was used as received.
14. 7-Methoxyphthalide shows the following spectral data : IR ($CHCl_3$) ν (max) cm^{-1}: 1755; ^1H NMR ($CDCl_3$) δ: 4.01 (s, 3 H), 5.23 (s, 2 H), 6.95 (d, 1 H, J = 8.2), 7.01 (d, 1 H, J = 8.2), 7.65 (t, 1 H, J = 8.2).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

7-Methoxyphthalide has also been prepared by nonregioselective bromination of substituted benzenes,[9] by L-Selectride reduction[10,11] of 3-methoxyphthalic anhydride,[12,13] by metalation of 3-methoxybenzyl alcohol[14,15] and its chromium tricarbonyl complex,[15,16] by metalation of N,N-dimethyl-3-methoxybenzylamine,[17,18] and by Diels-Alder reaction of methoxycyclohexadiene with propargylic esters.[19] The isomeric 4-methoxyphthalide, that is also available by the present method,[2] has been prepared by methods that, in part, overlap those used for the synthesis of 7-methoxyphthalide: by bromination of o-toluic acids and o-xylenes,[9,19,20] by metal hydride reduction[21] of 3-methoxyphthalic anhydride, and by metalation of 3-methoxyphenyloxazoline.[22] Some of these methods[19,23,24] as well as others, have been used for the preparation of a variety of other methoxy-substituted phthalides.

The directed ortho metalation reaction has been widely applied for the preparation of phthalides.[25,26,27] Since it lends itself well to the regiospecific construction of contiguously substituted aromatic compounds, the approach via metalation of N,N-diethylbenzamides has been particularly extensively adapted.[28,29] The present procedure uses a readily available and inexpensive starting benzoic acid, proceeds in reproducible, high yields, does not require chromatographic separation, and furnishes usually crystalline phthalide products in high purity. A comparison of yields shows that 7-methoxyphthalide has been obtained by metalation of 3-methoxybenzyl alcohol (78%),[14] Diels-Alder reaction of methoxycyclohexadiene with a propargylic ester (55%),[19] and reduction of 3-methoxyphthalic anhydride (quantitative).[10] The latter two methods are lengthy and require a several stage synthesis of precursors. The metalation method complements the present procedure, but has not been optimized. Based on the reported preparation of 4-methoxyphthalide,[22] the synthesis of 7-methoxyphthalide via metalation of 2-methoxyphenyloxazoline would undoubtedly be successfully achieved, but would require the more expensive oxazoline.

Phthalides constitute a relatively minor class of natural products.[25,30] However, their value as synthetic intermediates is shown by an extensive list of applications. The use of phthalides derived from metalation of N,N-diethylbenzamides in the synthesis of anthraquinones, anthracyclones, isocoumarins, fluorenones, phenanthrenes, several classes of alkaloids, and polycyclic aromatic hydrocarbons has been summarized.[27] Phthalides derived by other methods have served as intermediates in the construction of anthraquinones,[15,20,31,32,33] benzophenones,[34] cervicarcin,[35] dibenzofurans,[36,37] lignans,[22] naphthalenes and naphthoquinones,[15,24,38,39,40,41] and polyketides.[14,42,43]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

benzophenone ketyl

brine

imidoyl chloride

o-toluic acids

o-xylenes

N,N-diethylbenzamides

anthraquinones

anthracyclones

isocoumarins

fluorenones

phenanthrenes

benzophenones

cervicarcin

dibenzofurans

naphthalenes

naphthoquinones

hydrogen chloride, hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ethyl acetate (141-78-6)

methanol (67-56-1)

ammonium chloride (12125-02-9)

thionyl chloride (7719-09-7)

sulfur dioxide (7446-09-5)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

Benzoic acid (65-85-0)

cyclohexane (110-82-7)

toluene (108-88-3)

sodium (13966-32-0)

diethylamine (109-89-7)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

dimethylformamide (68-12-2)

hexane (110-54-3)

oxazoline

calcium hydride (7789-78-8)

sodium borohydride (16940-66-2)

ethyl acetate-hexane (2639-63-6)

sec-butyllithium (598-30-1)

methoxycyclohexadiene

chromium tricarbonyl

2,5-dimethoxybenzyl alcohol (33524-31-1)

N,N,N',N'-tetramethylethylenediamine (110-18-9)

7-Methoxyphthalide, 1(3H)-Isobenzofuranone, 7-methoxy- (28281-58-5)

N,N-Diethyl-2-methoxybenzamide (51674-10-3)

2-methoxybenzoic acid (579-75-9)

N,N-Diethyl-2-formyl-6-methoxybenzamide (70946-17-7)

4-methoxyphthalide

3-methoxyphthalic anhydride

3-methoxybenzyl alcohol (6971-51-3)

2-methoxyphenyloxazoline

N,N-dimethyl-3-methoxybenzylamine (15184-99-3)

3-methoxyphenyloxazoline

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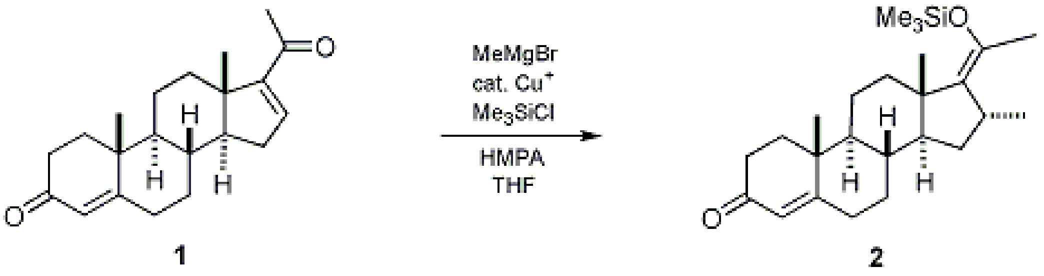
Organic Syntheses, CV 9, 564

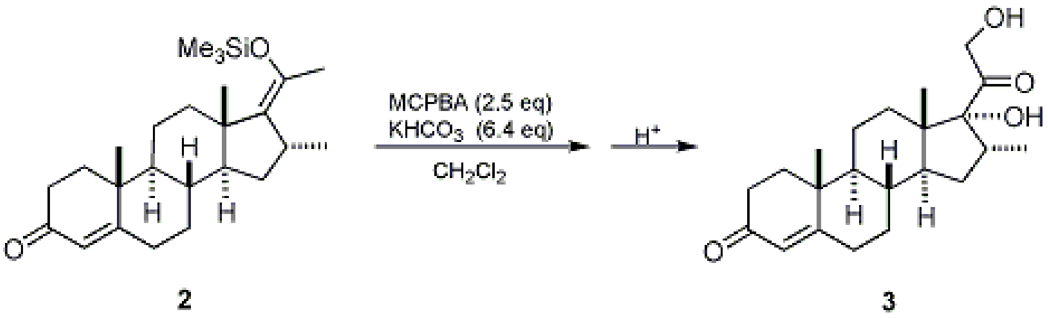
DOUBLE HYDROXYLATION REACTION FOR CONSTRUCTION OF THE CORTICOID SIDE CHAIN: 16α-METHYLCORTEXOLONE

[Pregn-4-ene-3,20-dione, 17,21-dihydroxy-16-methyl-, (16α)-(±)-]

A.



B.



Submitted by Yoshiaki Horiguchi, Eiichi Nakamura, and Isao Kuwajima[1].
Checked by Ronald W. Regenye, Miguel Pagan, and David L. Coffen.

1. Procedure

CAUTION: Hexamethylphosphoramide (HMPA) has been identified as a carcinogen. Glove protection is required during the handling in Part A. In addition, the column chromatography in Part B using chloroform as the eluent should be conducted in a well-ventilated hood.

A. *(Z)-16α-Methyl-20-trimethylsiloxy-4,17(20)-pregnadien-3-one* **(2)**. (All transfers are conducted under dry nitrogen; reagents are introduced into reaction vessels through rubber septa using a syringe.) An oven-dried, 300-mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar, nitrogen-vacuum inlet, and rubber septum is charged with 6.25 g (20 mmol) of 16-dehydroprogesterone **(1)** and 0.20 g (1.0 mmol) of cuprous bromide-dimethyl sulfide complex (Note 1). After the apparatus is flushed with nitrogen, 100 mL of tetrahydrofuran (THF) and 7.7 mL (44 mmol) of hexamethylphosphoramide are added (Note 1). The resulting clear solution, upon cooling to −78°C, becomes a white slurry to which 5.1 mL (40 mmol) of chlorotrimethylsilane is added dropwise (Note 1). To the resulting yellow solution is added 23.7 mL (22 mmol) of a 0.93 M solution of methylmagnesium bromide in THF (Note 2) over a 30-min period. The resulting yellow slurry is then stirred at −55 to −60°C (Note 3) for 12 hr followed by addition of 5.6 mL (40 mmol) of triethylamine dropwise (Note 1). The reaction mixture is then poured into a vigorously stirred mixture of 50 mL of saturated aqueous sodium bicarbonate, 50 g of ice, and 200 mL of hexane. After stirring for 15 min, the mixture is transferred to a 1-L separatory funnel, and the organic phase is separated. The remaining aqueous phase is extracted three times with 50-mL portions of hexane. The combined organic phases are washed successively with 50 mL of water and 50 mL of brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give 6.84–8.67 g of crude (Z)-16α-methyl-20-trimethylsiloxy-4,17(20)-pregnadien-3-one **(2)** as an amorphous white solid. Analysis of crude **2** by ^{1}H NMR

indicates a chemical purity of 90–95% and a geometrical ratio of >95% (Z) (Note 4).

B. *16α-Methylcortexolone* **(3)**. An oven-dried, 1-L, three-necked, round-bottomed flask, equipped with a magnetic stirring bar, nitrogen-vacuum inlet, 200-mL addition funnel topped with a nitrogen inlet, and a rubber septum, is charged with 7.20 g of the crude (Z)-16α-methyl-20-trimethylsiloxy-4,17(20)-pregnadien-3-one **(2)**. The apparatus is flushed with nitrogen and 200 mL of methylene chloride (CH_2Cl_2) is added (Note 1). Quickly under nitrogen flow, the rubber septum is removed from the flask and 12.8 g (128 mmol) of finely powdered, dry potassium bicarbonate (Note 5) is added to the solution, and the flask is resealed with the rubber septum. The flask is then immersed in an ice bath. With vigorous stirring of the mixture, 100 mL of a 0.5 M solution (50 mmol) of m-chloroperoxybenzoic acid (MCPBA) in CH_2Cl_2 is added dropwise via the addition funnel over a 2.5-hr period followed by a few mL of $CH_2Cl_2$to rinse the addition funnel (Note 6). TLC is used to monitor the progress of the reaction (Note 7). After stirring the reaction mixture for an additional 10 min after the addition is complete, the addition funnel, nitrogen-vacuum inlet, and rubber septum are removed and 100 mL of aqueous 0.5 M sodium thiosulfate solution is added, vigorous stirring is maintained at room temperature for 30 min. The mixture is then transferred to a 1-L separatory funnel, and the organic phase is separated. The aqueous phase is extracted three times with 50 mL of CH_2Cl_2. The combined organic extracts are concentrated on a rotary evaporator. The residue is dissolved in 100 mL of THF, and the solution is acidified to pH 1 by addition of 10 mL of 1 N hydrochloric acid (HCl) to effect desilylation of the 21-trimethylsilyl ether of 16α-methylcortexolone **(6)** (Note 8). The homogeneous solution is allowed to stand at room temperature for 30 min and then most of the solvent is removed by rotary evaporation under reduced pressure. The residue is dissolved in 300 mL of CH_2Cl_2, transferred into a 1-L separatory funnel, and the solution washed with 50 mL of saturated aqueous sodium bicarbonate solution. After separation of the organic phase, the aqueous phase is extracted three times with 50-mL portions of CH_2Cl_2. The combined organic extracts are washed with 50 mL of brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give 6.0 g of a white solid. Chromatographic purification on silica gel (300 g) with 30 40% ethyl acetate/chloroform eluent gives 2.92 g (40.5%, 2 steps) of 16α-methylcortexolone **(3)** (Note 9).

2. Notes

1. 16-Dehydroprogesterone **(1)** was purchased from Sigma Chemical Company and used without further purification. Cuprous bromide-dimethyl sulfide complex was prepared according to House's procedure.[2] Hexamethylphosphoramide, chlorotrimethylsilane, and triethylamine were purchased from Tokyo Kasei Kogyo Co., Ltd., Japan and distilled from calcium hydride (CaH_2). Tetrahydrofuran (THF) was distilled from sodium-benzophenone ketyl immediately prior to use. Methylene chloride was distilled from phosphorus pentoxide (P_2O_5).
2. A THF solution of methylmagnesium bromide was purchased from Tokyo Kasei Kogyo Co., Ltd., Japan and titrated with sec-butyl alcohol using 1,10-phenanthroline as indicator. Rapid addition might raise the internal temperature and use of excess methylmagnesium bromide would cause undesired methylation of the A-ring enone.
3. The reaction temperature was controlled by an electric cooling system. A higher reaction temperature would cause undesired methylation of the A-ring enone.
4. Crude **2** is free from HMPA. The spectral properties of **2** were as follows: IR (neat) cm^{-1}: 1670, 1610, 1265, 1250, 1230; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.19 (s, 9 H), 0.90 (s, 3 H), 0.99 (d, 3 H, J = 7.1), 1.09–2.71 (m including two s at 1.19 and 1.79, 25 H), 5.73 (s (br), 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 1.07, 17.1, 17.3, 20.6, 21.3, 22.1, 32.1, 32.9, 33.5, 34.0, 34.2, 34.3, 35.6, 37.3, 38.7, 44.0, 52.1, 54.1, 123.6, 132.5, 139.9, 171.3, 199.2. The geometry was determined based on observed NOEs from 20-methyl to 16β-H and 16α-methyl.
5. Potassium bicarbonate was purchased from Koso Chemical Co., Ltd., Japan. It was finely powdered and dried under reduced pressure (0.1 mm) at ambient temperature over P_2O_5.
6. m-Chloroperoxybenzoic acid (MCPBA) of 85% purity was purchased from Aldrich Chemical Company, Inc. and purified according to Schwartz's procedure[3] to remove any remaining m-

chlorobenzoic acid. Slow addition of MCPBA is required to avoid hydrolysis of the transient, intermediate epoxide **4** by rapid formation of free m-chlorobenzoic acid.
7. Progress of the double hydroxylation reaction can be monitored by TLC analysis. The R_f values of the products with 30% ethyl acetate/hexanes as the eluent are as follows: 0.70 for **2**, 0.59 for **5**, 0.29 for **6**, and 0.18 for **7**. Additional MCPBA may be added until the intermediate hydroxy enol silyl ether **5** has completely reacted.
8. Desilylation of **6** can be monitored by TLC analysis. The R_f values of **3** and **6** are 0.32 and 0.67, respectively, with 50% ethyl acetate/hexanes as the eluent.
9. A portion of this compound is recrystallized from 1:1 ethyl acetate/hexanes to yield white plates with mp 194–197°C (Anal. Calcd for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95. Found: C, 73.24; H, 8.98). The spectral properties were as follows: IR ($CDCl_3$) cm^{-1}: 3650–3100, 1705, 1660, 1615; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.79 (s, 3 H), 0.93 (d, 3 H, J = 7.3), 0.97–2.49 (m including s at 1.18), 2.62 (s, 1 H), 2.94–3.14 (m, 1 H), 3.20 (s (br), 1 H), 4.30 (dd, 1 H, J = 20, 4.8), 4.62 (dd, 1 H, J = 20, 4.8), 5.73 (s (br), 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.8, 15.2, 17.4, 20.5, 30.4, 32.0, 32.5, 32.8, 33.9, 35.6, 35.7, 36.8, 38.6, 49.7, 49.8, 53.3, 67.8, 90.5, 123.8, 170.8, 199.3, 212.4. The stereochemistry of the 16- and 17-positions were determined based on the observed NOEs from the 18-methyl (δ 0.79, s) to both 16β-H (δ 2.94–3.14, m) and 21-H (δ 4.63, dd). The submitters obtained an overall yield of 68%

Waste Disposal Information

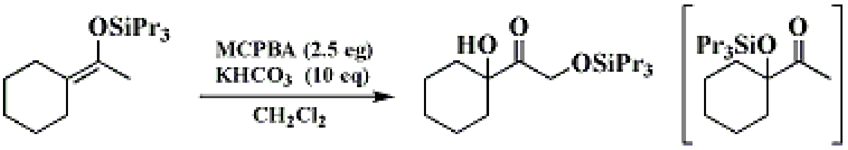
All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The present procedure is an efficient two-step preparation of the 17-dihydroxyacetone side chain with a 16α-methyl substituent from the 16-dehydro-17-acetyl substructure.[4] The D-ring substructure of the product is of pharmaceutical importance as seen in synthetic corticoids such as betamethasone.[5] The two-step conversion consists of 1) conjugate addition of a methyl group into the 16-position and 2) a novel, double hydroxylation of the resultant enol silyl ether.

Although the chlorotrimethylsilane-accelerated conjugate addition of the catalytic methylcopper reagent[6] proceeds at the sterically less congested D-ring enone in a highly chemoselective manner under the reaction conditions discussed in the procedure, a higher reaction temperature and/or use of excess methylmagnesium bromide might cause undesired methylation of the A-ring enone.

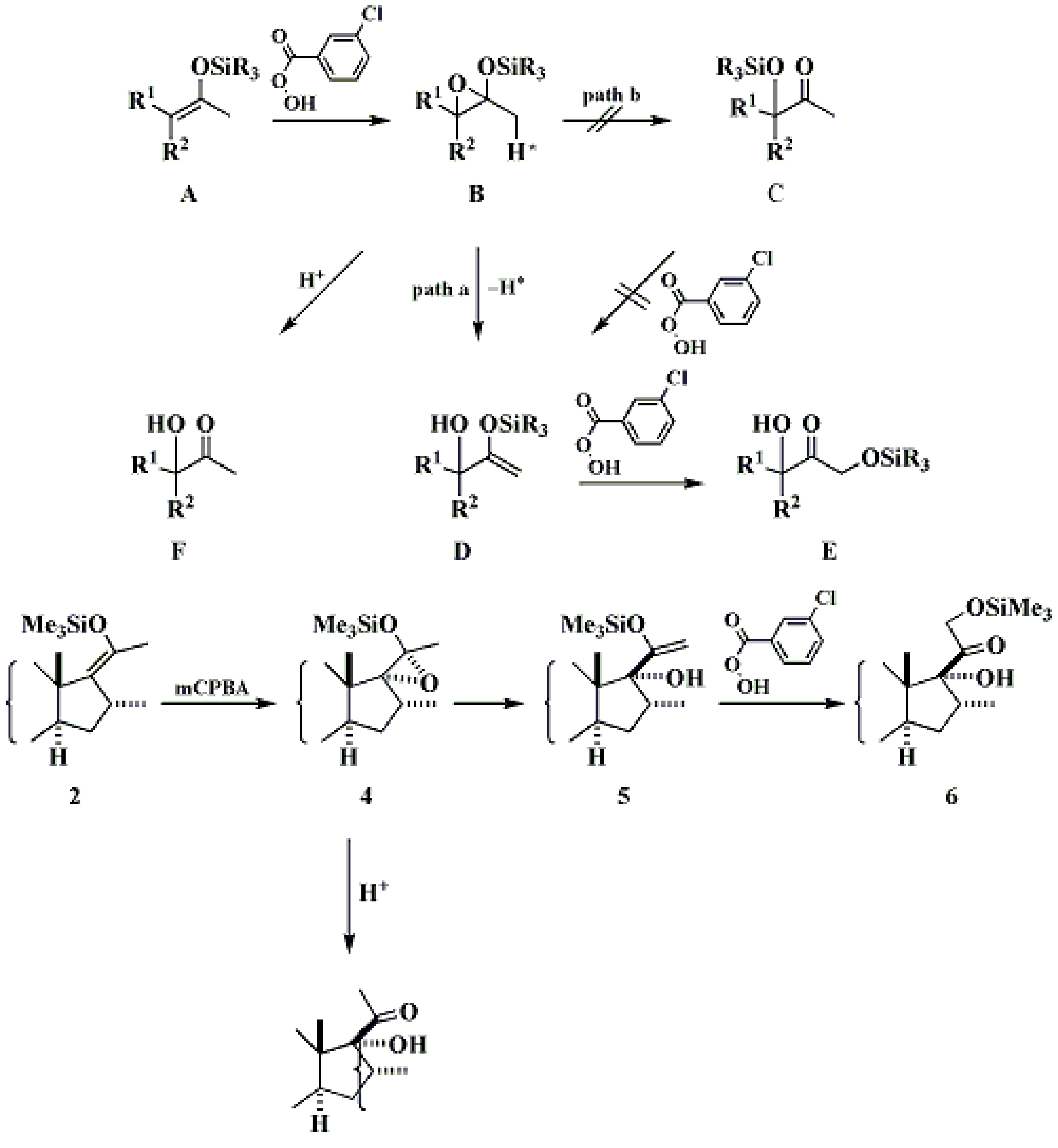
Since Hassner's initial report in 1975,[7] oxidation of an enol silyl ether with peracid has been a reliable method for the preparation of α-siloxy and α-hydroxy ketones. However, the submitters have found that, if the enol silyl ether possesses certain structural features, the reaction, with more than two equivalents of the oxidant, affords α,α'-dihydroxylated ketones (i.e., introduction of two oxygen atoms in a single-step) instead of the expected monohydroxylated compounds.[8]



Mechanistic investigations carried out in some depth suggested an interesting reaction pathway (*path a*, Scheme I), in which rearrangement of the intermediate epoxide **B** to the hydroxy enol silyl ether **D** (with loss of H*) represents the crucial step. In the normal Hassner reaction (*path b*), rearrangement of epoxide **B** to the siloxy ketone **C** proceeds through migration of the silyl group from the enol oxygen to the epoxide oxygen. The inertness of **C** under the reaction conditions indicated that *path a* and *path b* are independent reactions. The hydroxy enol silyl ether **D** has been shown to be the primary product of the reaction by its isolation upon use of only one equivalent of the oxidant, and its subsequent conversion to **E** upon addition of another

equivalent of the oxidant.

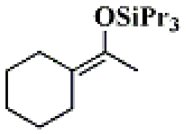
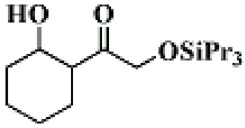
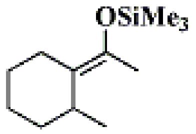
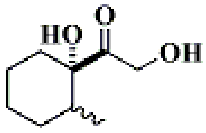
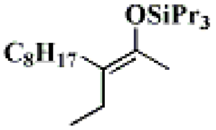
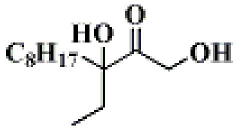
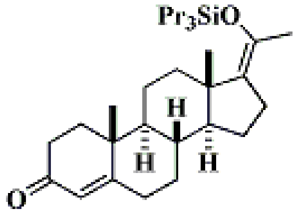
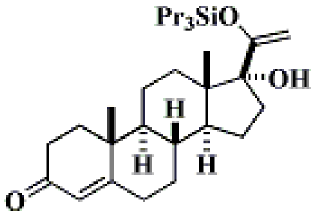
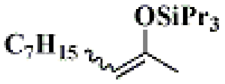
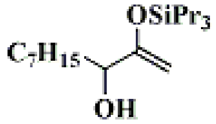
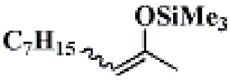
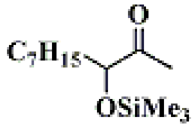
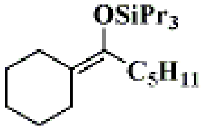
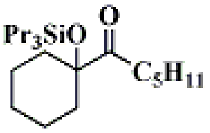
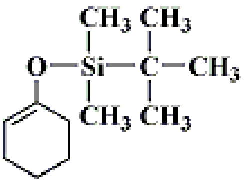
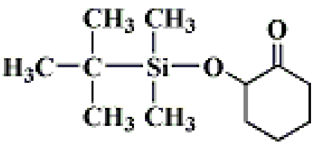
Scheme 1

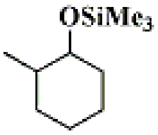
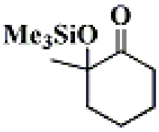


The major by-product in the double hydroxylation reaction is the α-hydroxy ketone **F** which forms presumably by protiodesilylation of the transient, intermediate epoxide **B**. In order to exclude free m-chlorobenzoic acid that might cause this side reaction, MCPBA is purified and added very slowly to the substrate in the presence of excess, finely powdered potassium bicarbonate. In the case of the example presented above, the mechanism presumably is as follows:

Examples of the double hydroxylation reaction observed for several representative substrates illustrate the scope of this reaction (Table). *Path a* is generally preferred by the internal olefinic isomer of the enol silyl ether of methyl alkyl ketones (entries 1–4, and 9) among which methyl sec-alkyl ketones (entries 1–3, and 9) overwhelmingly prefer the *path a*. Choice of the silyl group substantially affects *path a* vs. *path b* ratio: *path a* becomes the favored pathway when the bulky tripropylsilyl group was used in place of the trimethylsilyl group (cf. entries 4 and 5). Thus steric hindrance at the site of the initial oxidation, the nature of the site of the proton removal (i.e., H* in **B**), and the steric effect of the silyl group all contribute to the relative amounts of the two pathways.

TABLE
DOUBLEHYDROXYLATION OFENOLSILYLETHERS

Entry	Substrate	MCPBA, equiv	Path a: Path b	Combined %Yield	Major product
1		2.5	100:0	72	
2		2.5	100:0	79[a]	
3		3.3	100:0	74[a]	
4		1.0	100:0	91	
5		1.0	63:35	75	
6		1.0	32:68	94	
7		2.0	25:75	88	
8		2.0	0:100	nd[b]	

9		2.0	0:100	nd[b]	

[a]Isolated after acidic workup.
[b]Not determined. A major portion of the initial monooxygenation product was lost by further oxidation with excess MCPBA.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hexanes

brine

sodium-benzophenone ketyl

16-dehydroprogesterone

cuprous bromide-dimethyl sulfide

17-dihydroxyacetone

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

chloroform (67-66-3)

sodium bicarbonate (144-55-8)

oxygen (7782-44-7)

sodium thiosulfate (7772-98-7)

nitrogen (7727-37-9)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

methylmagnesium bromide (75-16-1)

Tetrahydrofuran (109-99-9)

hexane (110-54-3)

triethylamine (121-44-8)

potassium bicarbonate (298-14-6)

calcium hydride (7789-78-8)

hexamethylphosphoramide (680-31-9)

sec-butyl alcohol (78-92-2)

1,10-phenanthroline (66-71-7)

CHLOROTRIMETHYLSILANE (75-77-4)

silyl ether (13597-73-4)

phosphorus pentoxide (1314-56-3)

m-chloroperoxybenzoic acid (937-14-4)

m-chlorobenzoic acid (535-80-8)

(Z)-16α-Methyl-20-trimethylsiloxy-4,17(20)-pregnadien-3-one (122315-01-9)

16α-Methylcortexolone, Pregn-4-ene-3,20-dione, 17,21-dihydroxy-16-methyl-, (16α)-(±)- (122405-63-4)

21-trimethylsilyl ether of 16α-methylcortexolone

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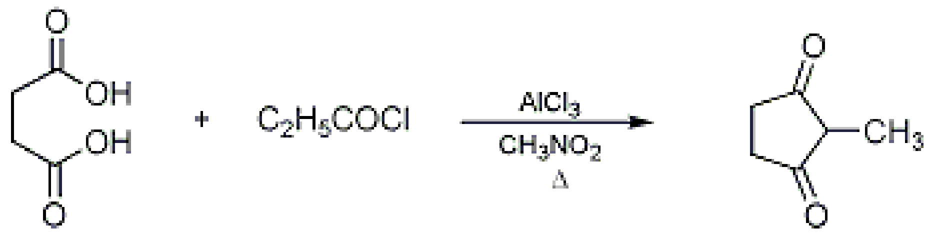
Organic Syntheses, CV 9, 570

2-METHYL-1,3-CYCLOPENTANEDIONE

[1,3-Cyclopentanedione, 2-methyl-]



Submitted by Philip G. Meister, Matthew R. Sivik, and Leo A. Paquette[1].
Checked by David L. Coffen

1. Procedure

CAUTION! These operations result in the evolution of considerable amounts of hydrogen chloride and should therefore be performed in a well-ventilated hood

A dry, 5-L, three-necked, round-bottomed flask equipped with a nitrogen inlet, mechanical stirrer (Note 1), and an efficient reflux condenser (Note 2) is charged with 500 mL of dry nitromethane (Note 3). Stirring is begun and 1000 g (7.50 mol) of anhydrous aluminum chloride (Note 4) is added, followed by an additional 500 mL of dry nitromethane. After the reaction mixture cools to room temperature, the gas inlet is replaced with a Gooch tube attached to a 500-mL filter flask containing 295 g (2.5 mol) of powdered succinic acid (Note 5). The nitrogen line is now attached to the sidearm of this flask. The succinic acid is introduced in portions during 1.5 hr *(CAUTION: This process evolves a large volume of hydrogen chloride gas which may cause the mixture to foam. Small quantities of the acid should be added at a time and the foaming should be allowed to subside prior to introduction of the next amount).* The mixture is stirred for 2 hr and the Gooch tube is replaced by a 500-mL pressure-equalizing addition funnel equipped with a nitrogen inlet. Propionyl chloride (650 mL, 694 g, 7.5 mol) (Note 6) is added dropwise during 30 min and the reaction mixture is brought to reflux for 2 hr, cooled, and poured onto 4 L of crushed ice. After the precipitated brown solid is cooled in an ice bath, it is separated by filtration (Note 7) and washed with 250 mL of brine and 250 mL of cold (0°C) toluene. The material is dissolved in 7 L of boiling water containing 20 g of decolorizing carbon, then filtered while still hot (Note 8). The filtrate is concentrated to a volume of 5 L, then cooled in an ice bath. The crystals are collected by suction filtration and air-dried to give 157–171 g (56–61%) of 2-methyl-1,3-cyclopentanedione (Note 9). The mother liquors are concentrated to approximately 1.5 L by rotary evaporation. The solution is boiled until crystals form, cooled in ice, and filtered to give an additional 20–23 g (7–8%) of product (63–69% overall yield).

2. Notes

1. Efficient stirring is mandatory.
2. The top of the condenser is equipped with a gas outlet leading via an oil bubbler into a large alkali bath or to a water aspirator. A steady stream of nitrogen should be maintained at all times.
3. Commercial nitromethane was dried over calcium chloride, filtered, and distilled. The forerun was discarded. The checker used 96% spectrophotometric grade as received from Aldrich Chemical Company, Inc.
4. Aluminum chloride, which was obtained from Fluka Chemical Corporation, generates heat during dissolution.
5. Succinic acid was obtained in powdered form from Fluka Chemical Corporation. If granular succinic acid is to be used, it should be pulverized to aid in dissolution.
6. Propionyl chloride was purchased from Fluka Chemical Corporation and Aldrich Chemical Company, Inc.
7. Two 17-cm Büchner funnels should be used simultaneously. However, if left to digest overnight, the mixture can be conveniently filtered using a 3-L sintered glass funnel.
8. Use of a 17-cm Büchner funnel preheated with hot tap water has proven most convenient for this purpose. The checker used an oven-heated, 3-L sintered glass funnel layered with Celite.
9. The crystals are off-white to tan, mp 211–212°C. It appears to exist in the enol form: ^{1}H NMR (200 MHz, $CDCl_3/d_6$-DMSO) δ: 1.05 (s, 3 H), 2.0 (s, 4 H), 10.7 (s, 1 H).

Waste Disposal Information

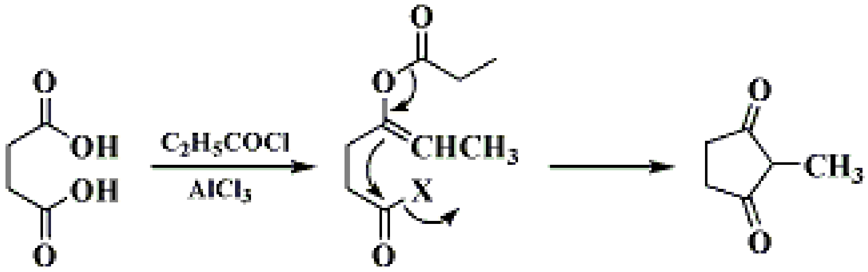
All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

A variety of methods have been published to achieve the preparation of 2-methyl-1,3-cyclopentanedione.[2,3,4,5,6] The present method, which was first reported by Schick, Lehmann, and Hilgetag,[4] provides for the acquisition of large amounts of the product in a single step from inexpensive starting materials. The alternative multistep procedures are appreciably more laborious and costly.

The importance of the title compound as an intermediate in organic synthesis goes unquestioned, having been produced on an industrial scale. The syntheses and reactions of this class of compounds have recently been summarized in an extensive review of the subject.[7]

The success of the present process appears to rest on the facility with which intermediate **1** is produced and its capacity for ready intramolecular cyclization.[4]



(X = $OCOC_2H_5$ or Cl)

1

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

brine

calcium chloride (10043-52-4)

hydrogen chloride (7647-01-0)

nitrogen (7727-37-9)

Succinic acid (110-15-6)

carbon (7782-42-5)

aluminum chloride (3495-54-3)

toluene (108-88-3)

Nitromethane (75-52-5)

propionyl chloride (79-03-8)

1,3-Cyclopentanedione, 2-methyl-, 2-Methyl-1,3-cyclopentanedione (765-69-5)

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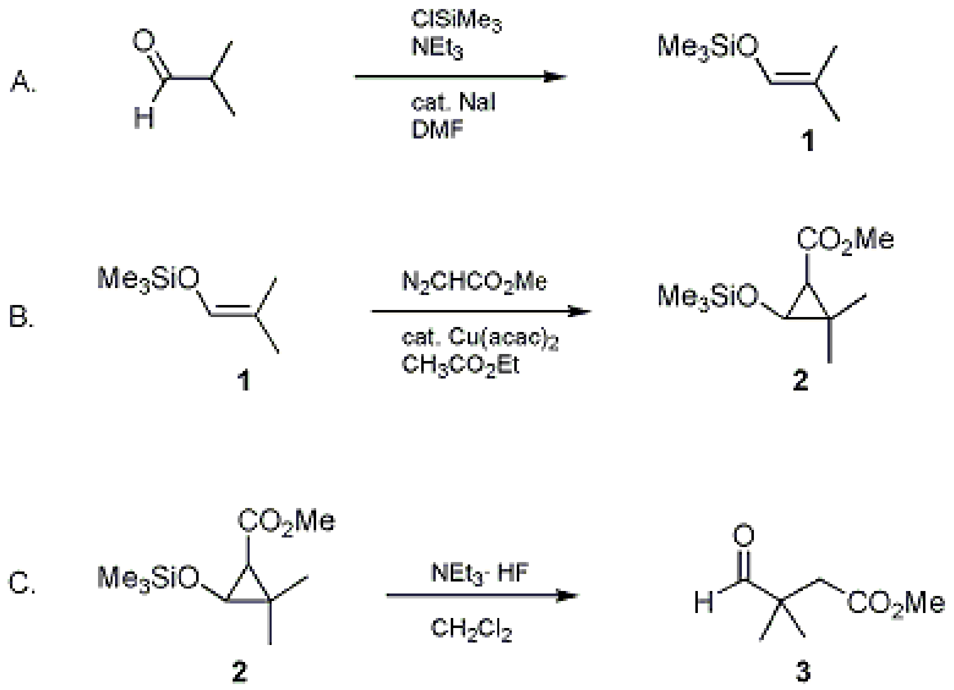
Organic Syntheses, CV 9, 573

METHOXYCARBONYLMETHYLATION OF ALDEHYDES VIA SILOXYCYCLOPROPANES: METHYL 3,3-DIMETHYL-4-OXOBUTANOATE

[Butanoic acid, 3,3-dimethyl-4-oxo-, methyl ester]



Submitted by Hans-Ulrich Reissig[1], Ingrid Reichelt[2], and Thomas Kunz[2].
Checked by Lawrence Snyder and Albert I. Meyers.

1. Procedure

A. *2-Methyl-1-(trimethylsiloxy)propene* (**1**). A dry, 1-L, three-necked flask, equipped with an efficient mechanical stirrer, reflux condenser with nitrogen inlet, and a pressure-equalizing dropping funnel, is charged with 230 mL of dry dimethylformamide (Note 1), 7.5 g (50 mmol) of dry sodium iodide (Note 2), and 119 g (1.18 mol) of triethylamine (Note 3) under a nitrogen atmosphere. Chlorotrimethylsilane (Note 4), 64.3 g (0.592 mol) and 36.0 g (0.500 mol) of freshly distilled isobutyraldehyde are added sequentially to this stirred mixture via the dropping funnel at room temperature. Under vigorous stirring the resulting mixture is heated to 120°C (oil bath temperature) for 8 hr, then cooled to room temperature and poured into 400 mL of saturated aqueous sodium bicarbonate ($NaHCO_3$) solution. The mixture is extracted with three 200-mL portions of pentane, the combined organic phases are washed four times with 60 mL of ice-cold 2 N hydrochloric acid (Note 5) and finally with 100 mL of saturated $NaHCO_3$ solution, dried with magnesium sulfate ($MgSO_4$), filtered, and the pentane is removed at atmospheric pressure to provide crude product (80 g). This material is carefully distilled at atmospheric pressure through a column packed with glass beads (30 cm). Silyl enol ether **1** is the fraction boiling at 94–108°C; the yield is 48.8 g (67%, (Note 6)).

B. *Methyl 2,2-dimethyl-3-(trimethylsiloxy)-1-cyclopropanecarboxylate* (**2**). *CAUTION: This step should be performed behind a safety shield.* A 500-mL flask, equipped with a magnetic stirring

bar and a reflux condenser that contains at its head a pressure-equalizing dropping funnel connected to a gas bubbler, is charged with 1.04 g (4.00 mmol) of copper(II) acetylacetonate [Cu (acac)$_2$] (Note 7) and 28.8 g (200 mmol) of silyl enol ether **1**. The suspension is heated to 90–100°C (oil bath temperature) and a solution of 24.0 g (240 mmol) of methyl diazoacetate (Note 8) dissolved in 250 mL of dry ethyl acetate (Note 9) is added dropwise within 3–4 hr (Note 10). After a short induction period, vigorous nitrogen evolution is observed and the suspension turns from blue to brownish-yellow. Addition of the diazo compound is regulated so that continuous liberation of nitrogen is observed at the gas bubbler. After the resulting black-brown suspension is cooled to room temperature, the solvent is removed on a rotary evaporator (bath temperature below 35°C). The residue is treated with 50 g of alumina (Note 11) and 100 mL of pentane; the slurry is filtered and placed on a column that contains 200 g of alumina. Elution with pentane is accelerated by applying a slight pressure of nitrogen at the top of the column. Concentration of the colorless solution obtained (Note 12) provides crude **2** (55 g) that is distilled (bp 86–88°C, 12 mm) to give 35.0 g (81%, (Note 13)) of pure cyclopropane derivative **2** as a mixture of cis/trans isomers (Note 14).

C. *Methyl 3,3-dimethyl-4-oxobutanoate* (**3**). A 50-mL flask, connected to a gas bubbler and equipped with a magnetic stirring bar, is charged with 20 mL of dichloromethane (or tetrahydrofuran), 2.16 g (10.0 mmol) of siloxycyclopropane **2** and 3.64 g (30.0 mmol) of triethylamine hydrofluoride ($NEt_3 \cdot HF$) prepared in situ (Note 15). This mixture is stirred for 1 hr at room temperature (Note 16) and diluted with 20 mL of water. The aqueous phase is extracted with three 20-mL portions of dichloromethane. The combined organic phases are dried with magnesium sulfate, filtered, and concentrated on a rotary evaporator (bath temperature below 40°C). Crude product **3** is distilled with a Kugelrohr oven (oven temperature 105°C, 10 mm) to provide 1.26 g (87%) of pure **3** as a colorless liquid (Note 17).

2. Notes

1. Dimethylformamide (Aldrich Chemical Company, Inc.) was distilled from phosphorus pentoxide and stored over molecular sieves.

2. The procedure described is a slight variation of the published method.[3] We found addition of ca. 10% sodium iodide to be advantageous in terms of reaction times and yields. Sodium iodide was dried at 120°C/0.2 mm for 6 hr.

3. Triethylamine was distilled from calcium hydride (CaH_2) and stored over molecular sieves.

4. Chlorotrimethylsilane (obtained from Fluka Chemical Company or Janssen) was distilled from calcium hydride.

5. The washing process was performed until the aqueous phase was acidic to pH paper. The checkers found that gas pressure build-up was common, so the separatory funnel should be vented frequently during acidification.

6. The fraction boiling at 94–108°C was found to be 99% pure by GLC and contained a trace of hexamethyldisiloxane. The impurity does not affect the outcome of the next step. The NMR spectrum was as follows: ^{1}H NMR (270 MHz, $CDCl_3$) δ: 0.14 (s, 9 H), 1.52 (s, 3 H), 1.57 (s, 3 H), 5.98 (m, 1 H).

7. Copper(II) acetylacetonate, as supplied by Dynamit Nobel or by other commercial sources, was used.

8. Methyl diazoacetate was obtained according to a procedure for ethyl diazoacetate (Searle, N.E. *Org. Synth., Coll. Vol. IV* **1963**, 42). Although the experiments were usually

performed with distilled methyl diazoacetate (bp 43°C at 25 mm, bath temperature below 60°C) without any problems, the cyclopropanation reaction described works equally well with undistilled diazo compound. If distilled diazo compound is desired, the submitters have stated that "a spatula of K_2CO_3 is added to the crude diazo ester to trap traces of acid and then distill behind a safety shield". The checkers did not evaluate this aspect of the procedure.

Crude methyl diazoacetate contains up to 20% of the solvent dichloromethane, which has to be taken into account when calculating the stoichiometry. The checkers had no problems in preparing, handling, and using undistilled methyl diazoacetate; however, it must be emphasized that this compound is a potential explosive and all operations should be performed behind an efficient safety shield.

9. Our first experiments were performed with benzene as solvent, which generally provides very good yields.[4] Use of the less hazardous solvent ethyl acetate gives inferior yields if the silyl enol ether contains triethylamine. Ethyl acetate was distilled from potassium carbonate.

10. If the solution of methyl diazoacetate is dropped through the condenser the diazo compound is further diluted by the refluxing solvent. This simple technique diminishes formation of dimethyl fumarate and dimethyl maleate as side products. For small scale experiments a motor driven syringe pump may replace the dropping funnel with good success.

11. Neutral aluminum oxide (activity III, Woelm) was used.

12. Siloxycyclopropane **2** is eluted very quickly. Final fractions contain dimethyl fumarate and maleate. If mixtures of **2** with these carbene dimers are obtained, the filtration through alumina has to be repeated.

13. Yields of 75–85% have been obtained in several experiments on this scale.

14. The cis/trans ratio is 25:75. The spectra are as follows: IR (CCl_4) cm^{-1}: 1728 (CO_2Me); ^1H NMR (270 MHz, $CDCl_3$) δ: 0.12 (s, 9 H, $SiCH_3$), 1.04, 1.15, 1.19, 1.30 (4 s, 6 H, 2-CH_3 of cis-**2** and trans-**2**), 1.35, 3.42 (2 d, J = 7, 0.25 H each, 1-H and 3-H of cis-**2**), 1.43, 3.60 (2 d, J = 3, 0.75 H each, 1-H and 3-H of trans-**2**), 3.63 (s, 3 H, CO_2CH_3). For ^{13}C NMR data, mass spectrum, and combustion analysis see reference [4].

15. The reagent was generated in situ by sequential addition of 1.63 mL of triethylamine trishydrofluoride (obtained from Riedel deHaen, Merck, or Aldrich Chemical Company, Inc.) and 2.80 mL of triethylamine to the solution of **2**. The procedure reported in reference [15] provides a reagent with an approximate stoichiometry of $NEt_3 \cdot 2HF$ that can also be used for the purpose described.[5]

16. A short period of gas evolution is observed. This is probably fluorotrimethylsilane (Me_3SiF).

17. This procedure can be performed without any problems on a larger scale (2.6 g, 90% yield was obtained by checkers). However, aldehyde **3** is of limited stability and should be stored with exclusion of oxygen at low temperature. It is advantageous to generate only the amount of **3** required for subsequent reactions and to use it immediately. The physical properties are as follows: IR (CCl_4) cm^{-1}: 1739, 1730 (CO_2Me, CO); ^1H NMR (270 MHz, $CDCl_3$) δ: 1.13 (s, 6 H, 3-CH_3), 2.52 (s, 2 H, CH_2), 3.63 (s, 3 H, CO_2CH_3), 9.53 (s, 1 H, CHO). Anal. Calcd for $C_7H_{12}O_3$: C, 58.32; H, 8.39. Found: C, 58.59; H, 8.77.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory";

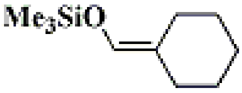
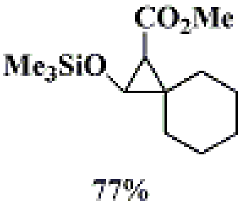
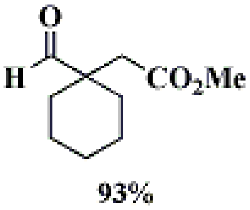
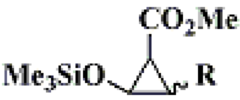
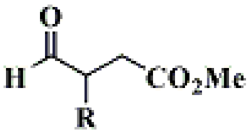
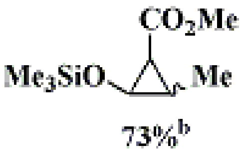
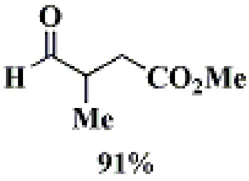
National Academy Press; Washington, DC, 1995.

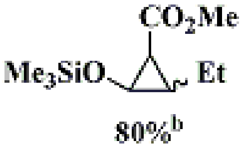
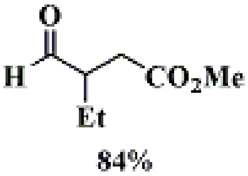
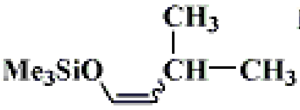
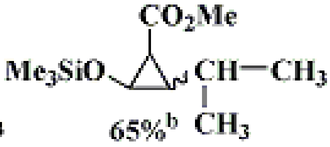
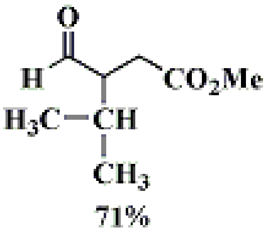
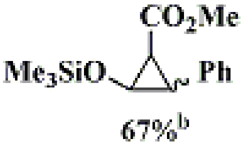
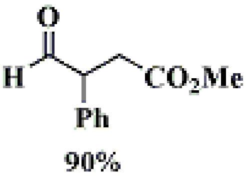
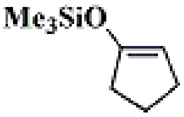
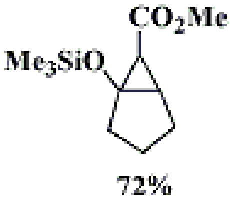
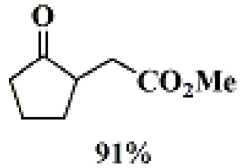
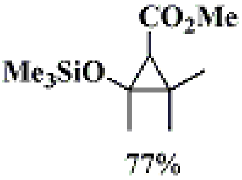
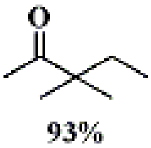
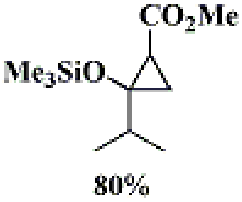
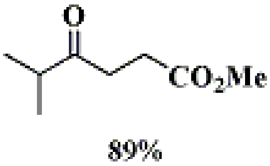
3. Discussion

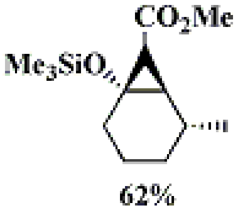
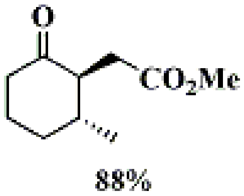
This sequence illustrates a very general method for the synthesis of methyl γ-oxoalkanoates which are valuable intermediates in organic synthesis.[4,6] The scope of the cyclopropanation reaction is very broad; only functional groups interacting with the carbenoid generated from methyl diazoacetate are not compatible. Use of $Rh_2(OAc)_4$ instead of $Cu(acac)_2$ as catalyst did not afford better yields.[4] The cyclopropanation reaction has been performed with similar efficiency on scales from 4 mmol up to 500 mmol.

Silyl enol ethers derived from aldehydes (see Table, entries 1–5) or ketones (entries 6–9) can be used. If unsymmetrical ketones are used as starting material, the regiochemistry established at the silyl enol ether stage is cleanly transferred to the siloxycyclopropanes and eventually to the methyl γ-oxoalkanoates (entries 7–9). For some chiral silyl enol ethers, high stereoselectivities can be attained in the [2+1]-cycloaddition. Because of the very mild conditions for the ring opening step, using the only weakly acidic fluoride reagent, the stereoselectivity is transmitted to the γ-oxoalkanoate without accompanying epimerization (entry 9).[5,7] This mild, ring-opening procedure that uses $NEt_3 \cdot HF$ is essential for preparation of the β-formyl esters as described in the procedure and for entries 1–5 in the Table. For simple ketone-derived products ring cleavage can also be effected with 2 N hydrochloric acid.[5]

TABLE
SYNTHESIS OFSILOXYCYCLOPROPANES ANDγ-OXOALKANOATES

Entry	Silyl Enol Ether	Siloxycyclopropane[a] (% yield)	γ-Oxoalkanoate (% yield)
1		 77%	 93%
			
2		 73%	 91%

3		 80%	 84%
4		 65%	 71%
5		 67%	 90%
6		 72%	 91%
7		 77%	 93%
8		 80%	 89%

9		 62%	 88%

[a]Cis/trans isomers in all examples.

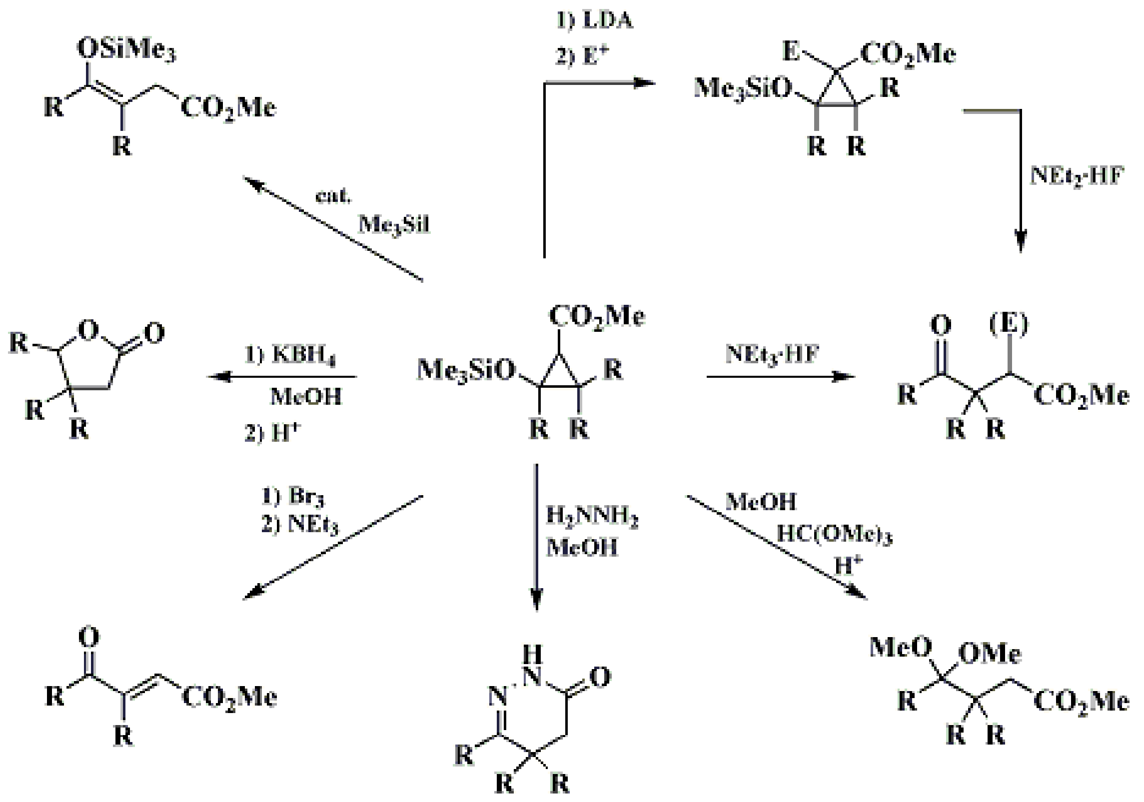
[b]Mixture of all four diastereomers.

[c]Trans compound >95% (racemic mixture).

The methyl γ-oxoalkanoates shown are not available by alternative methods with similar efficiency and flexibility. Although the reaction of enamines with alkyl α-bromoacetates proceeds well in some cases, yields are only moderate in many examples.[8] A further drawback is that the methods for enamine generation lack the high degree of selectivity and mildness that is characteristic of the preparation of silyl enol ethers. Related alkylations of lithium enolates often afford low yields or polyalkylated products, and are in general very inefficient when aldehydes are utilized as the starting materials.[9]

An alternative method to prepare β-formyl esters uses different building blocks to assemble the 1,4-dicarbonyl system and is complementary in many cases.[10] Base-catalyzed addition of nitromethane to α,β-unsaturated esters, followed by a variation of the Nef reaction, provides γ-dialkoxy-substituted esters. The scope of this sequence has not yet been explored. Another approach involves cuprate additions to norephedrine-derived 2-alkenyloxazolidines; this process allows small-scale synthesis of several β-formyl esters in optically active form (ee up to 95%).[11]

A major advantage of the sequence presented here is that the aldehyde group is protected at the siloxycyclopropane stage, which allows convenient storage of this stable intermediate. Of equal importance is the valuable carbanion chemistry that can be carried out α to the ester function. Efficient substitution can be achieved by deprotonation with LDA and subsequent reaction with electrophiles.[12,13,6] This process makes several α-substituted β-formyl esters available. Other ring opening variants of siloxycyclopropanes—mostly as one-pot-procedures—are contained in Scheme I. They underscore the high versatility of these intermediates for the synthesis of valuable compounds.[6] Chiral formyl esters (see Table, entries 2–5) are of special interest as starting materials for chelate-controlled synthesis of disubstituted γ-lactones.[14]



15

References and Notes

1. Institut für Organische Chemie, Technische Universität Dresden, Mommsenstr. 13, D-01062 Dresden, Germany;
2. Institut für Organische Chemie, Technische Hochschule Darmstadt, Petersenstrasse 22, D-6100 Darmstadt, Germany.
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

copper(II) acetylacetonate

dimethyl fumarate and maleate

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ethyl acetate (141-78-6)

sodium bicarbonate (144-55-8)

oxygen (7782-44-7)

nitrogen (7727-37-9)

sodium iodide (7681-82-5)

Pentane (109-66-0)

Nitromethane (75-52-5)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

aluminum oxide (1344-28-1)

ethyl diazoacetate (623-73-4)

isobutyraldehyde (78-84-2)

Tetrahydrofuran (109-99-9)

dimethylformamide (68-12-2)

triethylamine (121-44-8)

calcium hydride (7789-78-8)

Dimethyl fumarate (624-49-7)

CHLOROTRIMETHYLSILANE (75-77-4)

siloxycyclopropane

hexamethyldisiloxane (107-46-0)

fluorotrimethylsilane (420-56-4)

phosphorus pentoxide (1314-56-3)

dimethyl maleate (624-48-6)

Methyl 3,3-dimethyl-4-oxobutanoate, Butanoic acid, 3,3-dimethyl-4-oxo-, methyl ester (52398-45-5)

2-Methyl-1-(trimethylsiloxy)propene (6651-34-9)

Methyl 2,2-dimethyl-3-(trimethylsiloxy)-1-cyclopropanecarboxylate (77903-45-8)

methyl diazoacetate

triethylamine hydrofluoride

triethylamine trishydrofluoride (73602-61-6)

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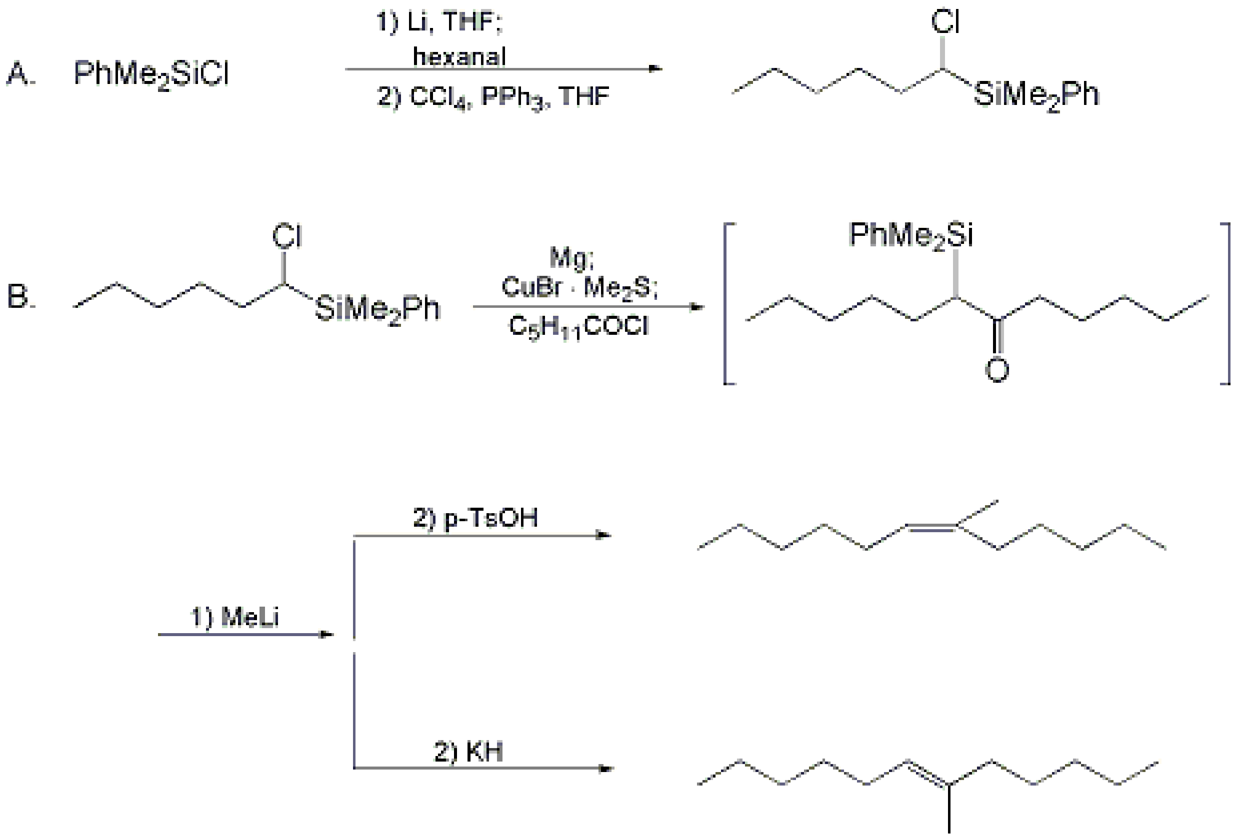
Organic Syntheses, CV 9, 580

STEREOSELECTIVE ALKENE SYNTHESIS via 1-CHLORO-1-[(DIMETHYL)PHENYLSILYL]ALKANES AND α-(DIMETHYL)PHENYLSILYL KETONES: 6-METHYL-6-DODECENE



Submitted by Anthony G. M. Barrett, John A. Flygare, Jason M. Hill, and Eli M. Wallace[1].
Checked by Shuyong Chen and Amos B. Smith, III.

1. Procedure

A. *1-Chloro-1-[(dimethyl)phenylsilyl]hexane*. An oven-dried, 500-mL, round-bottomed flask, equipped with a magnetic stirring bar and a rubber septum, is purged with argon via an inlet hose equipped with a needle and an outlet hose equipped with a needle leading to an oil bubbler. The flask is charged with 250 mL of dry tetrahydrofuran (THF) (Note 1) and 7.37 g of lithium wire (1.06 mol) cut into small pieces (Note 2). After cooling the reaction mixture to 0°C in a CryoCool bath (Note 3), 30 g (29.1 mL, 176 mmol) of phenyldimethylsilyl chloride is added via syringe and the reaction mixture is stirred at 0°C for 16 hr (Note 4).[2] Within 0.5 hr, the reaction mixture turns from clear and colorless to dark red. An oven-dried, 1-L, round-bottomed flask, equipped with a magnetic stirring bar and a rubber septum, is purged with argon via an inlet needle and an outlet needle to an oil bubbler, charged with

16.78 g (20.0 mL, 167.5 mmol) of hexanal and 400 mL of dry THF (Note 5), and cooled to −78°C with a dry ice-acetone bath. The solution of phenyldimethylsilyllithium in THF prepared above is then added via cannula. After addition, the red reaction mixture is warmed to 0°C and stirred for 1 hr. A saturated aqueous ammonium chloride solution (250 mL) is then added in one portion and the resulting mixture is poured into a 2-L separatory funnel containing 250 mL of diethyl ether. The organic layer is washed with saturated aqueous ammonium chloride (3 × 250-mL) and brine (250 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Purification via flash column chromatography (silica gel 230-400 mesh, 450 g of oil, loaded with hexanes, eluant 10:1 hexanes:diethyl ether) yields a total of 32.6 g (82%) of 1-[(dimethyl)phenylsilyl]-1-hexanol as a colorless oil (a second column with 250 g of silica gel may be required for rechromatography of tailing fractions).

An oven-dried, 1-L, round-bottomed flask, equipped with a magnetic stirring bar, is charged with 500 mL of dry THF and 1-[(dimethyl)phenylsilyl]-1-hexanol (32.6 g, 138 mmol). Carbon tetrachloride (53.20 g, 33.4 mL, 345.9 mmol) and triphenylphosphine (54.30 g, 207 mmol) are added and the flask is equipped with a condenser and a rubber septum and purged with argon via inlet needle and outlet needle to an oil bubbler.[3] The reaction mixture is heated to reflux under argon for 12 hr. After the reaction mixture is allowed to cool to room temperature, the volatiles are removed under reduced pressure, and the residue is triturated with hexanes (3 × 300-mL). Concentration of the extracts under reduced pressure and purification via flash column chromatography (silica gel 230-400 mesh, 450 g, eluant hexanes) yields 30.4–31.7 g of 1-chloro-1-[(dimethyl)phenylsilyl]hexane (71–74% from hexanal) as a colorless oil (Note 6)

B. *6-Methyl-6-dodecene*. An oven-dried, 1-L, three-necked, round-bottomed flask is equipped with a condenser, a 125-mL, pressure-equalizing addition funnel, a magnetic stirring bar, and a rubber septum. The flask is purged with argon and charged with 96.23 g (373 mmol) of magnesium bromide etherate ($MgBr_2{\cdot}Et_2O$) (Note 2) and 250 mL of dry THF. A total of 26.67 g (682 mmol) of potassium metal, freshly rinsed with 60 mL of dry THF, is added piecewise (Note 7). The reaction mixture is heated at reflux with stirring for 3 hr, at which time the activated magnesium has formed as a finely divided black powder (Note 8). The activated magnesium is allowed to cool and settle. The supernatant THF layer is carefully transferred via cannula into a 500-mL Erlenmeyer flask containing 250 mL of isopropyl alcohol. The activated magnesium is rinsed with dry diethyl ether (2 × 200-mL) and diluted with 100 mL of dry diethyl ether all via cannula. The crude 1-chloro-1-[(dimethyl)phenylsilyl]hexane (31.58 g, 124 mmol) is diluted with 100 mL of dry diethyl ether and transferred via cannula to the addition funnel. The ethereal solution of the α-silyl chloride is added to the activated magnesium slurry in diethyl ether slowly in portions causing the reaction mixture to reflux gently (Note 9). Upon completion of the addition, the reaction mixture is stirred for 15 min (Note 10).

An oven-dried, 1-L, round-bottomed flask is equipped with a magnetic stirring bar and a rubber septum. The flask is charged with 25.61 g of copper bromide-dimethyl sulfide complex (124 mmol) and 250 mL of dry diethyl ether, and the resulting slurry is cooled to −78°C with a dry ice-acetone bath. The Grignard reagent solution prepared above is added to the copper bromide-dimethyl sulfide slurry via cannula (Note 11). The residual activated magnesium is rinsed once with 200 mL of dry diethyl ether, and the supernatant layer is transferred via cannula to the copper bromide-dimethyl sulfide slurry (Note 12). The reaction mixture is slowly warmed to −10°C, and then 16.78 g (17.42 mL, 125 mmol) of hexanoyl chloride is added dropwise via syringe after which the reaction mixture is warmed to room temperature. After stirring for 3 hr, the reaction mixture is filtered through a 75-g layer of Celite 545 (Note 13) and the filter cake rinsed with three 100-mL portions of diethyl ether. Concentration of the filtrate under reduced pressure yields the α-silyl ketone which is utilized without further purification (Note 14).

(1) Acidic Elimination:

An oven-dried, 1-L, three-necked, round-bottomed flask is equipped with a 125-mL pressure-equalizing addition funnel, a magnetic stirring bar, and a rubber septum, and the system is purged with argon. The flask is charged with the crude α-silyl ketone prepared above and 500 mL of dry THF. Via cannula, a 125-mL (175 mmol) portion of a 1.4 M solution of methyllithium in hexanes is transferred to the addition funnel . After the α-silyl ketone solution is cooled to −78°C with a dry ice-acetone bath, the methyllithium solution is added dropwise over approximately 1 hr, and the reaction mixture is stirred for 0.5 hr at −78°C. A second, oven-dried, 1-L, round-bottomed flask is equipped with a magnetic stirring bar and a rubber septum. The second flask is charged with 47.39 g (249 mmol) of p-toluenesulfonic acid monohydrate and 100 mL of dry THF, and purged with argon. The β-alkoxysilane solution prepared above is transferred to the flask containing the solution of p-toluenesulfonic acid monohydrate in THF via cannula and stirred for 2 hr. The reaction mixture is then poured into a separatory funnel containing a biphasic mixture of 500 mL of saturated aqueous sodium bicarbonate and 250 mL of diethyl ether. The resulting organic layer is washed with saturated aqueous sodium bicarbonate (3 × 250-mL) and brine (250 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the residue via flash column chromatography (silica gel 230-400 mesh, 450 g, eluant hexanes) yields 11.31–11.75 g of (Z)-6-methyl-6-dodecene (50–52% from the α-silyl chloride) as a 92:8 Z/E ratio of isomers (Note 15) and (Note 16).

(2) Basic Elimination:

An oven-dried, 1-L, three-necked flask is equipped with a 125-mL pressure-equalizing addition funnel, a magnetic stirring bar, and a rubber septum. The flask is purged with argon and is charged with the crude α-silyl ketone (from 30.00 g, 118 mmol of α-silyl chloride) and dry THF (500 mL). Methyllithium (1.4 M, 118 mL, 165 mmol) is added to the addition funnel via cannula. The α-silyl ketone solution is cooled to −78°C with

a dry ice-acetone bath, and methyllithium is added dropwise over approximately 1 hr after which the reaction mixture is stirred for 0.5 hr. A second, oven-dried, 1-L, round-bottomed flask, equipped with a magnetic stirring bar and a rubber septum, is charged with 27 g of potassium hydride (35% wt/wt dispersion in oil which is rinsed with three 100-mL portions of dry diethyl ether), and diluted with 100 mL of dry THF, and 0.200 g of 18-crown-6 (0.76 mmol) is added. The β-alkoxysilane solution prepared above is added to the potassium hydride slurry via cannula, and the mixture is stirred for 16 hr.

Excess potassium hydride is quenched with isopropyl alcohol (50 mL) until no further hydrogen gas is evolved (Note 17). Saturated aqueous ammonium chloride (250-mL) is added to the reaction mixture which is then combined with 250 mL of diethyl ether in a separatory funnel. The organic layer is washed successively with three 250-mL portions of saturated aqueous ammonium chloride and 250 mL of brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the residue via flash column chromatography (silica gel 230-400 mesh, 450 g, eluant hexanes) provides 11.19–11.62 g (E)-6-methyl-6-dodecene, (52–54% from the α-silyl chloride) as a 95:5 E/Z ratio of isomers (Note 15) and (Note 18).

2. Notes

1. Both THF and diethyl ether were obtained from Mallinckrodt Inc. Before use they were dried by distillation from sodium metal and benzophenone under an atmosphere of nitrogen.
2. Lithium wire (3.2 mm diam.), carbon tetrachloride, triphenylphosphine, $MgBr\cdot Et_2O$, copper bromide-dimethyl sulfide complex, hexanoyl chloride, methyllithium, p-toluenesulfonic acid monohydrate, potassium hydride, and 18-crown-6 were purchased from Aldrich Chemical Company, Inc. and used without further purification.
3. The CryoCool bath may be obtained from CryoCool CC-80II Neslab Instruments, Inc. Portsmouth, N.H. 03801, USA. The reaction may be run in an ice bath under supervision.
4. Phenyldimethylsilyl chloride was purchased from the Petrarch Chemical Company and used without further purification.
5. Hexanal was purchased from the Aldrich Chemical Company Inc. and distilled (bp 131°C) before use.
6. The product exhibits the following properties: IR (film) cm^{-1}: 3016, 2968, 2940, 2866, 1465, 1430, 1253, 1117; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.40 (s, 3 H), 0.41 (s, 3 H), 0.85 (t, 3 H, J = 7.1), 1.17–1.34 (m, 5 H), 1.58–1.68 (m, 3 H), 3.42 (dd, 1 H, J = 2.9, 11.2), 7.35–7.39 (m, 3 H), 7.54–7.56 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: –5.7, –4.6, 14.0, 22.5, 27.4, 31.0, 33.1, 51.2, 127.8, 129.5, 134.1, 136.0; high resolution mass spectrum (CI, NH_3) m/z 272.1615 $[(M^{+}NH_4)^{+}]$; calcd for $C_{14}H_{27}NSiCl$: 272.1602].
7. Potassium metal, purified, was purchased from J.T. Baker Chemical Company. *CAUTION: Potassium metal is pyrophoric and reacts violently with*

water.

8. Activated magnesium is prepared as described in *Org. Synth., Coll. Vol. VI* **1988**, 845.

9. *CAUTION: The reaction is exothermic.*

10. The Grignard solution may be stored overnight under argon.

11. Care should be taken not to add excess activated magnesium, although a small amount does not seem to affect cuprate formation.

12. Activated magnesium is quenched by the addition of isopropyl alcohol until hydrogen gas is no longer evolved. *CAUTION: Hydrogen gas is flammable and should be vented into a fume hood.*

13. The Celite used is NOT the acid-washed reagent. Acid-washed Celite will cause some desilylation of the α-silyl ketone intermediate.

14. The α-silyl ketone may be stored overnight either under vacuum or under argon at –20°C.

15. The ratio of isomers was determined by GC/MS (Hewlett Packard 5890 Series II Gas Chromatograph/5870 Series Mass Selective Detector).

16. The product exhibits the following properties: IR (film) cm^{-1}: 2966, 2935, 2867, 1460, 1379; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.89 (t, 3 H, J = 7.1, overlapping 0.88 (t, 3 H, J = 6.9)), 1.23–1.39 (m, 12 H), 1.58 (s, 0.26 H, E-methyl), 1.67 (s, 2.74 H, Z-methyl), 1.94–2.01 (m, 4 H), 5.11 (t, 1 H, J = 7.1); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.10, 22.63, 22.64, 23.40, 27.75, 27.77, 29.80, 31.60, 31.70, 31.80, 125.30, 135.40; high resolution mass spectrum (CI, NH_3) m/z 182.2029 $[(M)^+]$; calcd for $C_{13}H_{26}$: 182.2035].

17. *CAUTION: Hydrogen gas is flammable and should be vented into a fume hood.*

18. The product exhibits the following properties: IR (film) cm^{-1}: 2968, 2936, 2867, 1460, 1380; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.89 (t, 6 H, J = 7.0), 1.21–1.41 (m, 12 H), 1.58 (s, 2.73 H, E-methyl), 1.67 (s, 0.27 H, Z-methyl), 1.94–1.99 (m, 4 H), 5.11 (t, 1 H, J = 7.1); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.1, 15.8, 22.6, 27.7, 27.9, 29.6, 29.9, 31.6, 31.7, 31.8, 39.7, 124.6, 135.1; high resolution mass spectrum (CI, NH_3) m/z 182.2026 $[(M)^+]$; calcd for $C_{13}H_{26}$: 182.2035].

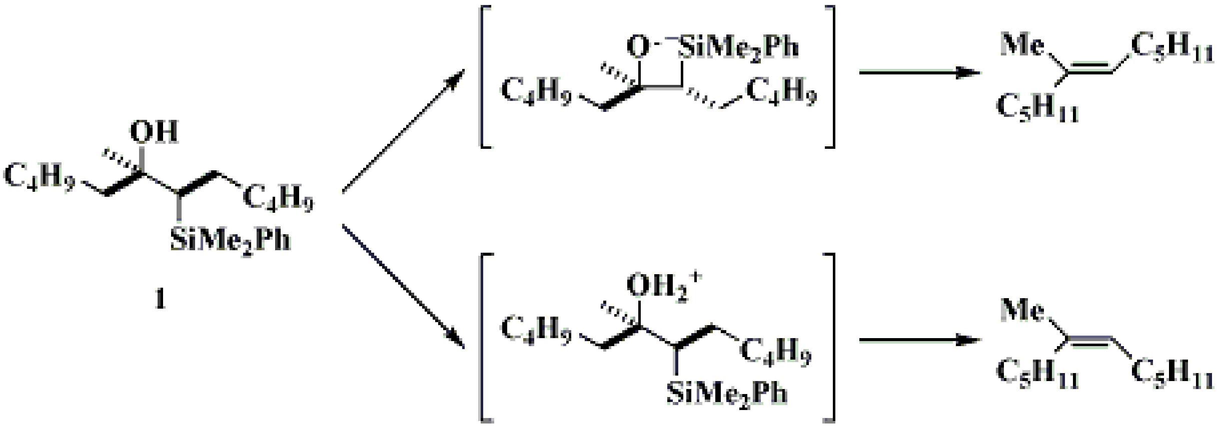
Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The acid or base elimination of a diastereoisomerically pure β-hydroxysilane, **1**, (the Peterson olefination reaction[4] For reviews see: [5,6,7,8,9]) provides one of the very best methods for the stereoselective formation of alkenes. Either the E- or Z-isomer may be prepared with excellent geometric selectivity from a single precursor (Scheme 1). The widespread use of the Peterson olefination reaction in synthesis has been limited,

however, by the fact that there are few experimentally simple methods available for the formation of diastereoisomerically pure β-hydroxysilanes.[10,11,12,13] Also see: [14,15,16,17,18,19] One reliable route is the Cram controlled addition of nucleophiles to α-silyl ketones,[18,19] but such an approach is complicated by difficulties in the preparation of (α-silylalkyl)lithium species or the corresponding Grignard reagents. These difficulties have been resolved by the development of a simple method for the preparation and reductive acylation of (α-chloroalkyl)silanes.[20]



The procedure shown here describes the preparation of α-silyl ketones from aldehydes and acyl chlorides. The α-silyl ketones undergo Cram addition of various nucleophiles to produce diastereoselectively β-hydroxysilanes. These compounds are then subjected directly to elimination in situ under basic or acidic conditions to produce the corresponding alkenes.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hexanes

brine

diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

hydrogen (1333-74-0)

sodium bicarbonate (144-55-8)

magnesium (7439-95-4)

carbon tetrachloride (56-23-5)

nitrogen (7727-37-9)

Benzophenone (119-61-9)

sodium (13966-32-0)

isopropyl alcohol (67-63-0)

potassium (7440-09-7)

lithium (7439-93-2)

Tetrahydrofuran (109-99-9)

Methyllithium (917-54-4)

hexanoyl chloride (142-61-0)

triphenylphosphine (603-35-0)

magnesium bromide etherate

argon (7440-37-1)

α-silyl chloride (13465-78-6)

18-Crown-6 (17455-13-9)

potassium hydride (7693-26-7)

Hexanal (66-25-1)

p-toluenesulfonic acid monohydrate (6192-52-5)

α-silyl ketone

6-METHYL-6-DODECENE

phenyldimethylsilyl chloride (768-33-2)

phenyldimethylsilyllithium

1-[(Dimethyl)phenylsilyl]-1-hexanol (125950-71-2)

1-Chloro-1-[(dimethyl)phenylsilyl]hexane (135987-51-8)

(Z)-6-Methyl-6-dodecene (101165-44-0)

(E)-6-methyl-6-dodecene (101146-61-6)

copper bromide-dimethyl sulfide (54678-23-8)

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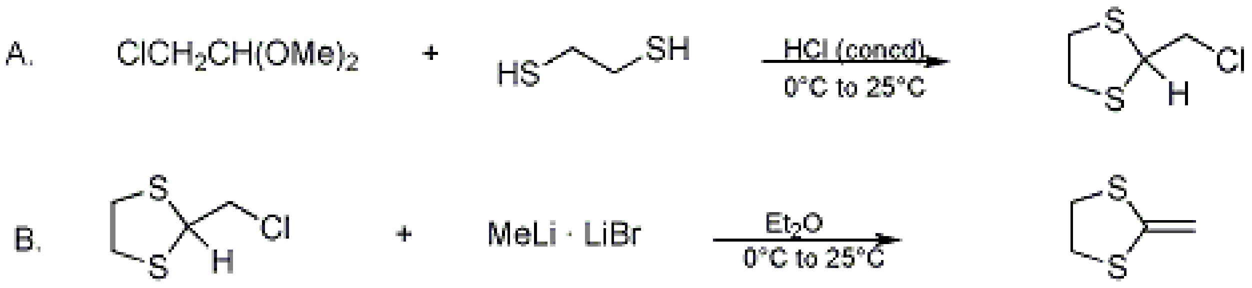
Organic Syntheses, CV 9, 585

2-METHYLENE-1,3-DITHIOLANE

[1,3-Dithiolane, 2-methylene-]



Submitted by Karl R. Dahnke and Leo A. Paquette[1].
Checked by M. Amornmarn, A. Focella, and David L. Coffen.

1. Procedure

A. *2-Chloromethyl-1,3-dithiolane*. A 500-mL, three-necked, round-bottomed flask equipped with a dropping funnel and magnetic stirrer is charged with 59.5 mL (0.71 mol) of 1,2-ethanedithiol (Note 1) and 50 mL of concd hydrochloric acid. This mixture is cooled to 0°C and 89 mL (0.78 mol) of chloroacetaldehyde dimethyl acetal (Note 2) is added via the dropping funnel over 2 hr (Note 3). After an additional 30 min, the ice bath is removed and the reaction mixture is stirred for 3 hr at room temperature. The resulting two-phase mixture is partitioned between dichloromethane (100 mL) and water (100 mL). The organic phase is separated and the aqueous phase is extracted with dichloromethane (100 mL). The combined organic layers are washed with water (100 mL), saturated sodium bicarbonate solution (100 mL), and brine (100 mL), then dried over magnesium sulfate. After removal of the solvent under reduced pressure, the viscous, colored residue (111 g) is subjected to bulb-to-bulb distillation using 500-mL and 250-mL collector bulbs and a 500-mL flask to hold the crude product. The oven temperature is initially 20°C and is gradually increased to 120°C. Pressure is maintained at 0.25 mm. Initially *only* the bulb remote from the oven is cooled, using an acetone/dry ice bath. Solvent and volatile impurities are collected in this bulb. The product is then condensed in the bulb nearest the oven by placing a dry ice/acetone bath under this bulb after the higher boiling material begins to distill. The clear colorless oil thus obtained consists of fairly pure 2-chloromethyl-1,3-dithiolane (59.3–65.0 g, 54–59%) (Note 4), (Note 5) and (Note 6).

B. *2-Methylene-1,3-dithiolane*. A 1-L, three-necked, round-bottomed flask equipped with a pressure-equalizing dropping funnel, thermometer, magnetic stirrer, and nitrogen inlet is charged with 33.0 g (0.213 mol) of 2-chloromethyl-1,3-dithiolane and diethyl ether (400 mL) (Note 7). After the flask is flushed with nitrogen, the solution is cooled to 0°C. Methyllithium-lithium bromide complex in diethyl ether (156 mL of 1.5 M solution, 0.235 mol) (Note 8) is transferred into the dropping funnel via cannula

and added dropwise over 2 hr. After an additional 30 min, the ice bath is removed and the mixture is allowed to warm gradually to room temperature. After 2 hr at room temperature when methane evolution has ceased, the mixture is recooled to 0°C and quenched by dropwise addition of 50 mL of saturated ammonium chloride solution followed by sufficient water to just dissolve the salts. The organic layer is separated, washed with water (3 × 100 mL), saturated sodium bicarbonate solution (100 mL), and brine (100 mL), then dried over magnesium sulfate. The solvent is removed under reduced pressure and the residue is distilled through a short-path distillation apparatus (34–40°C at 1.0 mm) (Note 9) to give 20.6–21.6 g (82–86%) of 2-methylene-1,3-dithiolane as a light yellow oil (Note 10).

2. Notes

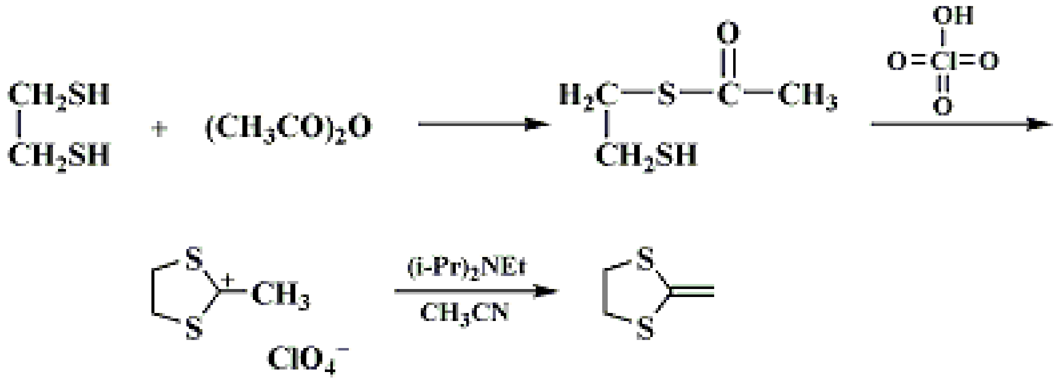
1. 1,2-Ethanedithiol was purchased from the Aldrich Chemical Company, Inc., and used without further purification.
2. Chloroacetaldehyde dimethyl acetal was obtained from the Elanco Company and used as received.
3. The addition was performed sufficiently slowly to maintain a temperature of 5–10°C.
4. During the thioketalization and distillation, thermal extrusion of HCl and isomerization to 2,3-dihydro-1,4-dithiin is observed[2] and the product of Step A typically contains ca. 10% of this impurity.
5. Storage of this material in a freezer is recommended.
6. Spectral characteristics are as follows: IR ($CHCl_3$) cm^{-1}: 3000, 2910, 1430, 1260; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.22 (s, 4 H), 3.61 (d, 2 H, J = 7.2), 4.63 (t, 1 H, J = 7.2); ^{13}C NMR ($CDCl_3$) δ: 38.36, 49.64, 54.23. Peaks arising from the 1,4-dithiin impurity appear at 3.18 and 6.08 ppm in the ^{1}H NMR.
7. Ether was distilled from sodium-benzophenone ketyl before use.
8. Methyllithium-lithium bromide complex was purchased from the Aldrich Chemical Company, Inc., and was titrated prior to use.
9. The receiver was cooled to −78°C and a small amount of triethylamine was added to the cold solution to stabilize the product against acid-catalyzed polymerization. As an added precaution, all glassware was base-washed prior to use.
10. Spectral characteristics are as follows: IR ($CHCl_3$) cm^{-1}: 3000, 2930, 1675, 1575, 1525, 1425, 1285; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.37 (s, 4 H), 5.13 (s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 38.47, 99.60, 144.50. Peaks attributable to the 1,4-dithiin impurity carried through from Step A also appear in the ^{1}H NMR spectrum.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Despite the latent reactivity of ketene thioacetals,[3,4] some members of this class such as the title compound have been little studied, perhaps because of preparative inaccessibility. The only previously reported route to 2-methylene-1,3-dithiolane involves monoacetylation of 1,2-ethanedithiol, cyclization to 2-methyl-1,3-dithiolan-2-yl perchlorate, and exposure of this salt to diisopropylethylamine in acetonitrile:[5]



The process requires vast amounts of solvent, proceeds in low yield, and is plagued by the need to isolate and handle a potentially explosive intermediate.

Herein is described a much simpler dehydrohalogenation alternative that had been earlier applied successfully to the preparation of ketene acetals[6,7] and 2-alkylidene-1,3-dithianes.[8] This route appears not to have been examined for preparing the title compound because of an early report that 2-lithio-1,3-dithiolanes undergo ready fragmentative elimination to form ethylene and dithiocarbonate unlike their stable 1,3-dithiane homologues.[8] In point of fact, the loss of chloride ion from lithiated 2-chloromethyl-1,3-dithiolane is the kinetically-favored elimination reaction. Use of the present two-step procedure makes possible the safe, direct acquisition of 2-methylene-1,3-dithiolane in unlimited quantities.

One of the uses of this reactive intermediate is illustrated on page 396.[9]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 396

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

brine

sodium-benzophenone ketyl

2-lithio-1,3-dithiolanes

hydrochloric acid (7647-01-0)

ether, diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

acetonitrile (75-05-8)

sodium bicarbonate (144-55-8)

nitrogen (7727-37-9)

methane (7782-42-5)

ethylene (9002-88-4)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

triethylamine (121-44-8)

1,2-ethanedithiol (540-63-6)

1,3-Dithiane (505-23-7)

diisopropylethylamine (7087-68-5)

Methyllithium-lithium bromide

2-Methylene-1,3-dithiolane, 1,3-Dithiolane, 2-methylene- (26728-22-3)

2-Chloromethyl-1,3-dithiolane (86147-22-0)

chloroacetaldehyde dimethyl acetal (97-97-2)

2,3-dihydro-1,4-dithiin

2-methyl-1,3-dithiolan-2-yl perchlorate

dithiocarbonate

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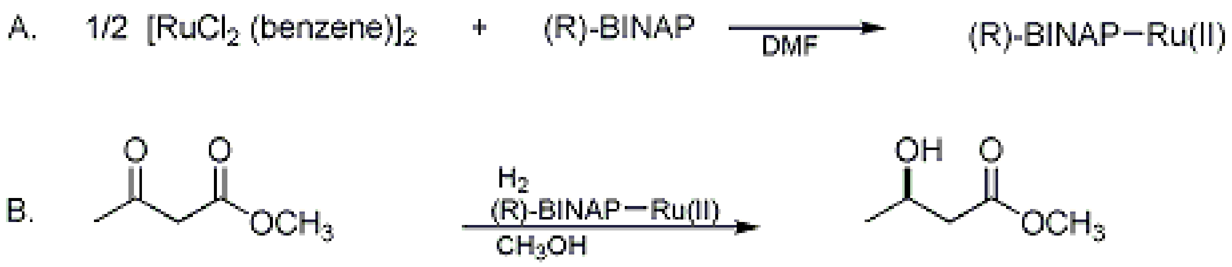
Organic Syntheses, CV 9, 589

ASYMMETRIC HYDROGENATION OF 3-OXO CARBOXYLATES USING BINAP-RUTHENIUM COMPLEXES: (R)-(−)-METHYL 3-HYDROXYBUTANOATE

[Butanoic acid, 3-hydroxy-, methyl ester, (R)-]



Submitted by Masato Kitamura, Makoto Tokunaga, Takeshi Ohkuma, and Ryoji Noyori[1].
Checked by Jaechul Shim and Larry E. Overman.

1. Procedure

CAUTION! BINAP-Ru complexes are rapidly oxidized in solution in the presence of air and all procedures should be carried out under anaerobic conditions using degassed solvents.

A. *[(R)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl]ruthenium(II) complex*. A dry, 80-mL Schlenk tube (Note 1) connected to a supply of argon (Note 2) is equipped with a Teflon-coated magnetic stirring bar and a glass stopper. The flask is charged with $[RuCl_2(benzene)]_2$ (130.5 mg, 0.261 mmol) (Note 3), (R)-BINAP (341 mg, 0.548 mmol) (Note 4), and then is evacuated and filled with argon. N,N-Dimethylformamide (DMF) (9 mL) (Note 5) is introduced with a hypodermic syringe under a stream of argon and the inlet is sealed by a glass stopper using silicon grease. The suspension is stirred at 100°C for 10 min under argon (Note 6), giving a clear reddish brown solution (Note 7). The reaction mixture is cooled and concentrated at 1 mm at 50°C with vigorous stirring and then at 0.1 mm for 1 hr to give 500 mg of (R)-BINAP-Ru (II) complex (Note 8) as a reddish brown solid, which is used as the hydrogenation catalyst.

B. *(R)-Methyl 3-hydroxybutanoate*. A 200-mL, dry Schlenk tube is charged with methyl 3-oxobutanoate (50.0 g, 0.431 mol) (Note 9) and methanol (50 mL) (Note 10) via hypodermic syringes. To this mixture is added the in situ prepared (R)-BINAP-Ru (II) complex (175 mg) (Note 11) under a stream of argon. The resulting yellowish orange solution (Note 12) is further degassed by two freeze-thaw cycles and then

transferred by cannula to a dry, argon-filled, 500-mL glass autoclave equipped with a gas inlet tube, a septa-covered stop valve, and pressure gauge (Note 13). The gas inlet tube is attached to a hydrogen source (Note 14) and the air originally present in this tube and the autoclave is replaced by evacuation (to ca. 20 mm) and refilling with hydrogen five times. Hydrogen is introduced into the reaction vessel until the pressure gauge indicates 3 atm. The pressure is carefully released to 1 atm by opening the stop valve. This procedure is repeated three times, and finally hydrogen is pressurized to 4 atm (Note 15). The yellowish orange solution is vigorously stirred at 100°C for 6 hr during which time the hydrogen cylinder is kept connected. After the main valve of the hydrogen cylinder is closed, the reaction mixture is allowed to cool to room temperature, excess hydrogen is carefully bled off, and the apparatus is disassembled. The deep reddish orange contents (Note 16) are placed in a 300-mL, round-bottomed flask, and the glass autoclave is rinsed with three 20-mL portions of dichloromethane. The solvent is removed by a rotary evaporator, and the residue (Note 17) is distilled to give 47–49 g (92–96% yield) of (R)-(−)-methyl 3-hydroxybutanoate in 97–98% ee as a fraction boiling at 40°C, 2 mm (Note 18).

2. Notes

1. All the apparatus is dried overnight in a 120°C oven before use.
2. Argon gas (99.998%) is purified by passing through the BASF catalyst R3-11 column at 80°C and then through 4 Å molecular sieves.
3. $[RuCl_2(benzene)]_2$, available from Aldrich Chemical Company, Inc., is used without purification.
4. BINAP is 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl.[2]
5. Guaranteed grade DMF, available from NACALAI TESQVE, Inc. (the checkers used DMF, Certified A.C.S., from Fisher Scientific Company), is distilled over 4 Å molecular sieves under argon before use and stored in a 100-mL Schlenk tube. It is degassed by three freeze-thaw cycles.
6. Reaction at a higher temperature for a longer period leads to formation of the ruthenium carbonyl complex [IR(KBr) 1964 cm^{-1}]. This undesired reaction is suppressed under the present conditions. Use of commercial $[RuCl_2(1,5\text{-cyclooctadiene})]_n$ or readily available $RuCl_2[Sb(C_6H_5)_3]_3$[3] gives similar results on heating in DMF at 160°C for 20 min or in o-dichlorobenzene at 160°C for 10 min. N,N-Dimethylacetamide can be used in place of DMF.
7. The solution is probably a crude mixture of cationic BINAP-Ru(II) complexes such as $[RuCl(BINAP)(DMF)_3]Cl$ and $[Ru(BINAP)(DMF)_4]Cl_2$. The physical properties are as follows: conductivity 27 Scm^2/mol (DMF); ^{31}P NMR (4:1 DMF-$CDCl_3$) δ: 60.6 (d, J = 46), 61.4 (d, J = 46), 61.8 (s). The DMF solution can be used directly for hydrogenation although the reactivity is one-half that of the dried material (Note 8).
8. This complex is probably a mixture of neutral BINAP-Ru(II) complexes such as $RuCl_2(BINAP)(DMF)_2$ and $[RuCl_2(BINAP)(DMF)]_n$. The physical

properties are as follows: conductivity 0.4 Scm^2/mol (CH_2Cl_2); ^{31}P NMR ($CDCl_3$) δ: 53.7 (d, J = 41), 54.5 (d, J = 42), 54.8 (d, J = 39), 57.4 (d, J = 41), 59.7 (d, J = 42), 61.5 (d, J = 39).

9. Methyl 3-oxobutanoate, available from NACALAI TESQVE, Inc. (the checkers used ester purchased from Aldrich Chemical Company, Inc.), is distilled over 4 Å molecular sieves under argon and stored in a 200-mL Schlenk tube. It is degassed by three freeze-thaw cycles before use.

10. Guaranteed-grade methanol is dried and degassed at refluxing temperature over magnesium methoxide (from magnesium turnings) under a stream of argon for 6 hr and distilled into a 2-L Schlenk flask. It is further degassed by three freeze-thaw cycles before use.

11. The complex is weighed quickly in the air.

12. The ruthenium complex is moderately soluble in methanol. Suspension in an ultrasonic cleaning bath is employed to achieve complete solution.

13. The glass autoclave is evacuated and filled with argon five times before use. The apparatus is shown in f.htmigure 1. Inside diameter and length are 7 and 14 cm. A Teflon-coated stirring bar of ca. 2 by 4 cm is recommended. The submitters report that vigorous stirring and use of a wide-shaped autoclave (Figure 1) are important in obtaining high yields.

Figure 1. A low-pressure hydrogenation apparatus.

Figure 1. A low-pressure hydrogenation apparatus.

14. Hydrogen of 99.99999% purity (Nippon Sanso) is used. The checkers employed 99.99% grade hydrogen.

15. Satisfactory results are not obtained at atmospheric hydrogen pressure, with slow conversion even at 100°C.

16. The color changes gradually to dark green in the air.

17. Gas chromatographic analysis indicates that the yield of methyl 3-hydroxybutanoate is 98%: column, PEG-20M on Chromosorb WAW (Stainless steel 3 m × 3 ϕ, Gasukuro Kogyo); column temperature, 120°C; injector temperature, 160°C, carrier nitrogen pressure, 1.2 kg/cm^2; t_R of methyl 3-oxobutanoate, methyl 3,3-dimethoxybutanoate, and methyl 3-hydroxybutanoate are 31.5, 34.0 and 41.7 min, respectively.

18. The product has the following spectral properties: ^1H NMR (270 MHz, $CDCl_3$) δ: 1.24 (d, 3, J = 6.3, CH_3CHOH), 2.43 (dd, 1, J = 8.3 and 16.5, CHH), 2.52 (dd, 1, J = 4.3 and 16.5, CHH), 3.01 (br s, 1, OH), 3.72 (s, 3, CH_3O), 4.2–4.3 (m, 1, CHOH); IR ($CHCl_3$) cm^{-1}: 3450, 2980, 1735, 1440, 1380, 1285, 1180, 1070, 1005; $[\alpha]_D^{25}$ −23.1° to −23.6° (neat) [lit.[4] $[\alpha]_D^{22}$ −23.5° (neat)]. The enantiomeric excess is determined to be 97–98% by HPLC analysis after converting an aliquot of the product to the (R)-α-methoxy-α-trifluoromethylphenylacetate [(R)-MTPA ester]. An aliquot of the crude reaction

product (17.5 mg, 148 •mol) is dissolved in dichloromethane (0.5 mL). To this solution are added (S)-MTPACI (75.0 mg, 297 •mol) (Note 19) and pyridine (50 •L) and the mixture is kept at 20°C for 12 hr. To this are added ether (2 mL) and water (1 mL) and the mixture is vigorously stirred for 15 min. The aqueous layer is extracted with two 2-mL portions of ether and the combined organic layers are successively washed with 1 N hydrochloric acid (3 mL), 1 N sodium hydroxide (3 mL), water (3 mL), and brine (3 mL). Drying over anhydrous sodium sulfate, evaporation of the solvent under reduced pressure, and purification by flash chromatography [silica gel (Fuji Davison BW 300), 2 g; eluent, 1:20 and then 1:7 ether-hexane mixture] afford 45 mg (91% yield) of the (R)-MTPA ester. ^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.34 (d, 3, J = 6.3, CH_3), 2.57 (dd, 1, J = 4.6 and 16.2, CHH), 2.74 (dd, 1, J = 8.6 and 16.2, CHH), 3.53 (br s, 3, J = 1.3, CH_3OCCF_3), 3.67 (s, 3, CH_3OCO), 5.55 (ddq, 1, J = 4.6 and 8.6 and 6.3, CHOCO), 7.3–7.6 (m, 5, aromatic). HPLC analysis of this ester [column, YMC 003-3 SIL (250 mm × 4.6 mm) and 002-3 SIL (150 mm × 4.6 mm); eluent, 1:5 ether-hexane mixture] shows two signals with t_R of 18.6 and 20.7 min in a 98.9:1.1 ratio assignable to the (R,R-) and (R,S)-diastereomers, indicating 98% ee. The checkers used a SUPELCOCIL LC-SI column (250 mm × 4.6 mm); eluent 7:1 hexane-ethyl acetate with RI detection and observed two signals (t_R, 13.7 and 15.0 min) with 98.6:1.4 ratio, indicating 97% ee.

19. The (S)-MTPACI is prepared by Mosher's method[5] from (R)-α-methoxy-α-(trifluoromethyl)phenylacetic acid purchased from Aldrich Chemical Company, Inc.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Optically pure alkyl (R)-3-hydroxybutanoates can be obtained by alcoholysis of poly-(R)-3-hydroxybutanoate, a fermentation product of fructose by *Alcaligenes eutrophus*.[4] (S)-Ethyl 3-hydroxybutanoate in 84–87% ee can be synthesized in 57–67% yield on a decagram-scale by an *Organic Syntheses* procedure[6] using bakers' yeast reduction of ethyl 3-oxobutanoate with the aid of sucrose.[7] In order to obtain enantioselectivity as high as 95–97% ee, the substrate concentration should be kept below 1 g/L.[8]

Among some syntheses of optically active 3-hydroxy carboxylates including optical resolution,[9] enantioselective aldol reactions between aldehydes and chirally-modified enolates,[10] cinchona alkaloid-catalyzed [2+2] cycloaddition between aldehydes and ketene,[11] enantioselective hydride reduction[12] or hydrogenation[13,14] of 3-oxo

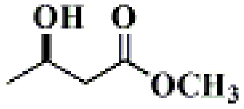
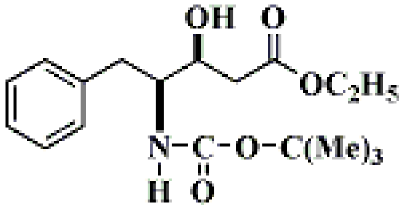
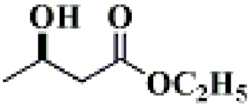
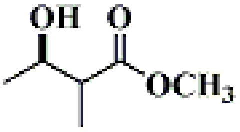
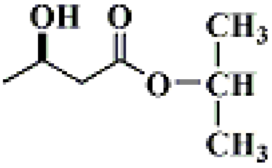
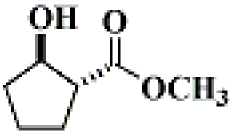
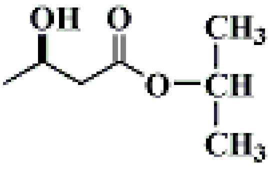
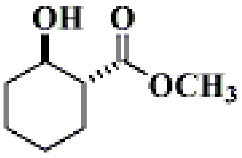
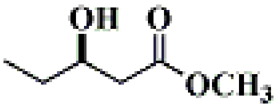
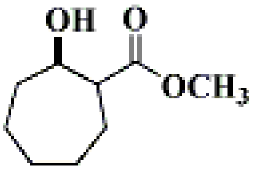
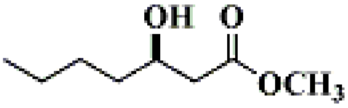
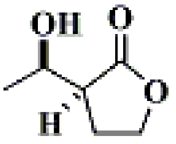
carboxylic acid derivatives, the most simple and most desirable would be asymmetric hydrogenation of 3-oxo carboxylates aided by chiral metal catalysts. Methyl 3-oxobutanoate can be hydrogenated by using a homogeneous chiral phosphine rhodium complex[13] and heterogeneous Raney nickel catalyst modified by tartaric acid and sodium bromide,[14] affording methyl 3-hydroxybutanoate in up to 71% ee and 87% ee, respectively.

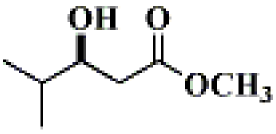
Hydrogenation of 3-oxobutanoic acid esters catalyzed by $Ru(OCOCH_3)_2$ [(R)-BINAP][15] proceeds slowly and in very low optical yield. However, addition of two equivalents of hydrogen chloride to the ruthenium complex facilitates the hydrogenation of methyl 3-oxobutanoate in methanol under the 100-atm, room temperature conditions to give the corresponding (R)-hydroxy ester in 97% isolated yield and in greater than 99% ee. RuX_2(BINAP) (empirical formula, X = Cl, Br, or I),[16] is prepared by mixing Ru $(OCOCH_3)_2$ (BINAP) and hydrogen chloride, hydrogen bromide, hydrogen iodide, or iodotrimethylsilane in a 1:2 mole ratio followed by removal of the solvent. [RuCl (benzene)(BINAP)]Cl[17] or $Ru_2Cl_4(BINAP)_2[N(C_2H_5)_3]$[18] are also usable as catalyst precursor. The present crude BINAP-Ru(II) complexes prepared by high-temperature ligand exchange[19] possess reactivities and selectivities comparable to these materials. In research laboratories, one may conduct relatively small-scale reactions in a Parr apparatus or an ordinary thickwalled glass vessel equipped with a Young's tap under pressure as low as 4 atm and at 80–100°C.[20] Large-scale reactions are performed conveniently under high pressure by using a stainless steel autoclave at room temperature.

The present catalytic, asymmetric hydrogenation using BINAP-Ru(II) complexes is the first practical chemical procedure for the preparation of (R)- or (S)-3-hydroxybutanoates. Characteristic features of this method include high chemical and optical yields, high efficiency of chiral multiplication (a substrate to catalyst mol ratio of >1000), easy access to both antipodes, clean reactions with high (up to 50%) substrate concentrations, and simple isolation of products by distillation. Some examples of the high-pressure, enantioselective hydrogenation of 3-oxo carboxylates using halogen-containing preformed BINAP-Ru(II) complexes are given in the Table.[21]

TABLE
OPTICALLY ACTIVE 3-HYDROXY CARBOXYLATES OBTAINED BY (R)-BINAP-Ru-CATALYZED ASYMMETRIC HYDROGENATION OF 3-OXO CARBOXYLATES[a]

Product	% ee	Product	%ee

	>99	 syn/anti = >99:1	99
	99	 syn/anti = 51:49	syn, 97 anti, 98
	98	 trans/cis = 99:1	92[c]
	98		
 trans/cis = 95:5	100		90[c]
 trans/cis = 93:7	98		93[c]
 syn/anti = 98:2	>99		



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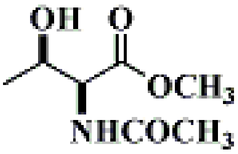

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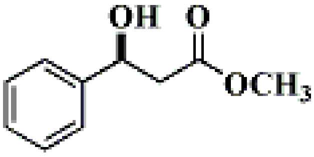

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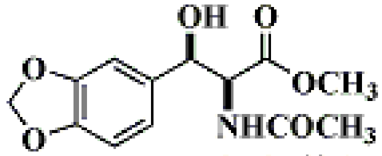

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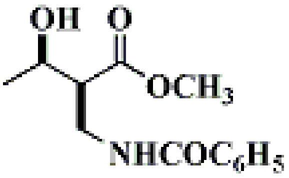
98[c]

98[b]



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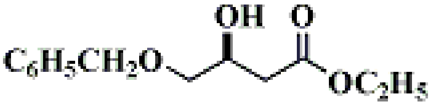
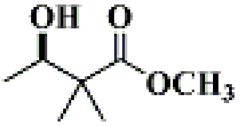
94[c]



97[b]



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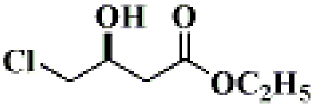
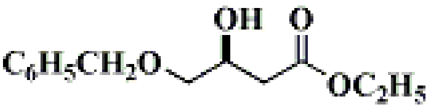


98[c]

99



96

[a]Hydrogenation catalyzed by performed RuX_2 (BINAP) (X = Cl, Br, or I) at room temperature at 100 atm of hydrogen. [b]100° C. [c]In CH_2Cl_2.

This method has been used to effect practical asymmetric syntheses of carnitine[22] and statine,[23] important, unusual amino acids. Highly stereoselective hydrogenation via dynamic kinetic resolution has been realized with chirally-labile, racemic, 2-

substituted 3-oxo carboxylic esters,[24,25,26] allowing stereocontrolled synthesis of natural and unnatural threonine, DOPS (anti-Parkinsonian agent), a useful intermediate for the synthesis of compounds such as carbapenems or carbocyclic analogues of prostacyclin. This methodology can be further extended to a variety of functionalized ketones that have directive groups such as dialkylamino, hydroxyl, alkoxyl, siloxyl, keto, alkoxycarbonyl, alkylthiocarbonyl, (dialkylamino)-carbonyl, carboxyl, dialkoxyphosphoryl, and halogen.[27]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 169
- Org. Syn. Coll. Vol. 9, 483
- Org. Syn. Coll. Vol. 9, 487

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

BINAP

(R)-(−)-Methyl 3-hydroxybutanoate

[(R)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl]ruthenium(II) complex

(R)-BINAP

(R)-BINAP-Ru(II) complex

hydrogen chloride, hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

magnesium turnings (7439-95-4)

hydrogen bromide (10035-10-6)

sodium bromide (7647-15-6)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

sucrose

Raney nickel (7440-02-0)

pyridine (110-86-1)

hydrogen iodide (10034-85-2)

tartaric acid (87-69-4)

ethyl 3-oxobutanoate (141-97-9)

magnesium methoxide

dichloromethane (75-09-2)

fructose

N,N-dimethylformamide (68-12-2)

hexane (110-54-3)

methyl 3-oxobutanoate (105-45-3)

threonine (72-19-5)

3-oxobutanoic acid (541-50-4)

argon (7440-37-1)

ruthenium (7440-18-8)

N,N-dimethylacetamide (127-19-5)

Iodotrimethylsilane (16029-98-4)

o-dichlorobenzene (95-50-1)

methyl 3-hydroxybutanoate

2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (76189-56-5)

(R)-Methyl 3-hydroxybutanoate, Butanoic acid, 3-hydroxy-, methyl ester, (R)- (3976-69-0)

(S)-Ethyl 3-hydroxybutanoate (56816-01-4)

phosphine rhodium

carnitine

(R)-α-methoxy-α-(trifluoromethyl)phenylacetic acid, (R)-α-methoxy-α-trifluoromethylphenylacetate (20445-31-2)

methyl 3,3-dimethoxybutanoate

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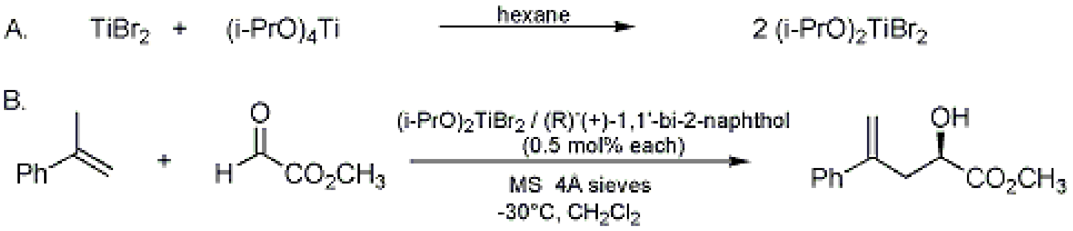
Organic Syntheses, CV 9, 596

ASYMMETRIC CATALYTIC GLYOXYLATE-ENE REACTION: METHYL (2R)-2-HYDROXY-4-PHENYL-4-PENTENOATE

[Benzenebutanoic acid, α-hydroxy-γ-methylene, methyl ester, (R)-]



Submitted by Koichi Mikami, Masahiro Terada, Satoshi Narisawa, and Takeshi Nakai[1].
Checked by Masami Okabe, Ruen-Chu Sun, and David L. Coffen.

1. Procedure

A. *Diisopropoxytitanium(IV) dibromide* (Note 1). A 50-mL, two-necked, round-bottomed pre-weighed flask equipped with a magnetic stirring bar, a rubber septum, and an argon inlet is charged with 20 mL of hexane (Note 2) and titanium(IV) bromide (7.3 g, 20 mmol) (Note 3). To the red-brown suspension is added titanium (IV) isopropoxide (5.9 mL, 20 mmol) (Note 4) slowly (7 min) at ambient temperature from a syringe. The addition of titanium(IV) isopropoxide causes the mixture to warm to about 37°C. After stirring for 10 min, the now yellow solution is allowed to stand for 6 hr at room temperature, and the pale yellow precipitate that forms is isolated by removing the supernatant liquid with a syringe. The solid residue is then washed with hexane (5 mL × 2) and recrystallized from hexane (10 mL). Recrystallization is carried out in the same flask by heating the solution to reflux and then leaving it at room temperature overnight. Again the supernatant liquid is removed with a syringe and the crystalline residue is vacuum dried to give 5.7 g (44%) of yellow, *highly moisture sensitive* product. While still in the original flask, this product is dissolved in 88 mL of dry toluene to give a 0.2 M solution (Note 5).

B. *Methyl (2R)-2-hydroxy-4-phenyl-4-pentenoate*. A 100-mL, four-necked, round-bottomed flask equipped with a magnetic stirring bar, thermometer, two dropping funnels, and an argon inlet is charged with 20 mL of methylene chloride (Note 6) and (R)-(+)-1,1'-bi-naphthol (Note 7) (100 mg, 0.35 mmol). The suspension is stirred until the binaphthol is completely dissolved. Powdered molecular sieves 4 Å (2 g) (Note 8) are then added. To the resultant suspension is added a 0.2 M toluene solution of diisopropoxytitanium dibromide (1.75 mL, 0.35 mmol) by syringe at room temperature. After stirring for 1 hr at room temperature, the reaction mixture is cooled to −35°C. To the reaction mixture is added dropwise a mixture of α-methylstyrene (14 mL, 108 mmol) and methylene chloride (5 mL) followed by a solution of freshly distilled methyl glyoxylate (Note 9) (6.16 g, 70.0 mmol) in methylene chloride (20 mL) over 30 min. The mixture is stirred at −35° to −30°C (Note 10) for 6 hr. Progress of the reaction is monitored by thin layer chromatography (Note 11). Even after 6 hr, a small amount of unreacted methyl glyoxylate is detected. The solution is poured into saturated sodium hydrogen carbonate (30 mL). The molecular sieves are removed by filtration through a pad of Celite, and the filtrate is extracted with ethyl acetate (80 mL × 3). The combined organic layers are washed with brine (50 mL × 2). The extract is dried over magnesium sulfate and evaporated under reduced pressure. Fractional distillation gives 12.1 g (84%) of methyl 2-hydroxy-4-phenyl-4-pentenoate (Note 12) and (Note 13). The enantiomeric purity is 93–95% ee by HPLC analysis using a chiral column (Note 14) or by lanthanide induced shift (LIS) NMR measurement with (+)-Eu(dppm)$_3$ (Note 15) after conversion to the α-methoxy ester (Note 16).

2. Notes

1. Diisopropoxytitanium(IV) dibromide is prepared following the preparative procedure for diisopropoxytitanium(IV) dichloride.[2]
2. Hexane is freshly distilled from calcium hydride (CaH_2) or dried over 4 Å molecular sieves.
3. Titanium(IV) bromide is purchased from Aldrich Chemical Company, Inc. This material is very moisture sensitive and is therefore weighed and transferred under an argon blanket.
4. Titanium(IV) isopropoxide is purchased from Tokyo Kasei Co., Ltd. or Aldrich Chemical Company, Inc.
5. Storage of the solution in a refrigerator is recommended.
6. Methylene chloride is freshly distilled from CaH_2 or dried over 4 Å molecular sieves.
7. (R)-(+)-1,1'-Bi-2-naphthol is purchased from Wako Pure Chemical Industries Ltd. or Aldrich Chemical Company, Inc.
8. Molecular sieves 4 Å (activated powder) are purchased from Aldrich Chemical Company, Inc.
9. Methyl glyoxylate can be prepared following a literature procedure.[3] The checkers used commercial material supplied by Hoechst Celanese, Specialty Chemicals. Immediately before use, the material is depolymerized by vacuum distillation from phosphorus pentoxide (P_2O_5) (10% weight); bp 62°C/60 mm.
10. In order to achieve high chemical and optical yields, the reaction temperature must be kept in the range of −30 to −35°C.
11. E. Merck silica gel 60 F-254 plates are used, with 2:1 v/v hexane:ethyl acetate as eluent, R_f = 0.4 and iodine vapor for visualization.
12. The product has the following spectral and physical characteristics: IR (neat, KBr) cm^{-1}: 3450 (br, s), 2940 (s), 1730 (s), 1440 (m), 1030 (m), 910 (m), 780 (s), 710 (s); ^1H NMR (200 MHz, $CDCl_3$) δ: 2.76 (bs, 1 H, OH), 2.88 (dd, 1 H, J = 8.1, 13.5, CCH_2CH), 3.13 (dd, 1 H, J = 4.5, 13.5, CCH_2CH), 3.68 (s, 3 H, OCH_3), 4.33 (dd, 1 H, J = 4.5, 8.1, CHOH), 5.28 (m, 1 H, $C{=}CH_2$), 5.48 (m, 1 H, $C{=}CH_2$), 7.3–7.5 (m, 5 H, Ar); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 40.4 (t), 52.2 (q), 69.2 (d), 116.5 (t), 126.6 (d), 127.9 (d), 128.6 (d), 140.4 (s), 143.7 (s), 175.1 (s); $[\alpha]_D^{23}$ −30.55° ($CHCl_3$, *c* 4.83) for 97% ee R); m/z: Found M^+ 206.0936, $C_{12}H_{14}O_3$ requires M^+, 206.0943; mp 36–38°C.
13. Fractional distillation is carried out as follows: bp 105–106°C/0.2 mm; first fraction: 0.7 g, 5% (< 105°C); main fraction: 12.1 g, 84% (105–106°C); last fraction: 0.3 g, 2% (> 106°C).
14. SUMICHIRAL OA-2500I is available from Sumitomo Chemical Co., Ltd. The eluent was hexane/1,2-dichloroethane/ethanol, 200:40:1, with a flow rate of 0.5 mL/min, and detection by 254 nm light. The t_R of the (R)-isomer (16.8 min) is shorter than that of the (S)-isomer (18.3 min). The checkers used a CHIRACEL OC column supplied by Daicel Chemical Industries, Ltd., with 10% isopropyl alcohol/heptane as the mobile phase.
15. The shift reagent $Eu(dppm)_3$ (30 w/v% CCl_2FCClF_2 solution) is available from Daiichi Kagaku Yakuhin Co.[4]
A 10-•L sample of the α-methoxy ester is dissolved in 0.5 mL of $CDCl_3$ and transferred to an NMR tube. A 5-•L portion of (+)-$Eu(dppm)_3$ (30 w/v% CCl_2FCClF_2 solution) is added to the α-methoxy ester sample. The mixture is shaken well, and the ^1H NMR spectrum is recorded. Additional portions of the shift reagent solution are added in 5-•L portions until the methyl ether resonance shifts downfield beyond that of the methyl ester and shows baseline resolution of the methyl ester and methyl ether resonances from the two enantiomers. (Four singlets should be observed). In total 15–20 •L of the shift reagent solution should be required to achieve the desired shift. At that point, a chemical shift difference of the methyl esters (about 0.1 ppm) should be observed. The % ee is obtained by integration of the two methyl ester peaks. The chemical shifts of the α-methoxy groups of (R)-methoxy esters are lower than those of the (S)-isomers, and in contrast those of the methyl ester groups of (R)-methoxy esters are higher than those of the (S)-isomers.
16. The α-methoxy ester is prepared following a literature procedure:[5] To a mixture of methyl iodide (0.3 mL) and the ene product (104 mg, 0.50 mmol) in ether (1–2 mL) is added silver(I) oxide (0.23 g). The reaction mixture is stirred for 1 day at room temperature. The suspension is filtered through a pad of Celite and the filtrate is evaporated under reduced pressure. Chromatographic purification of the residue gives the α-methoxy ester in quantitative yield (110 mg).

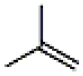
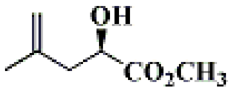
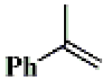
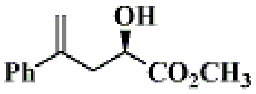
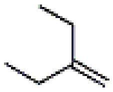
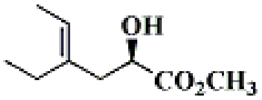
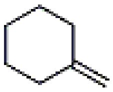
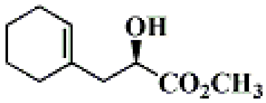
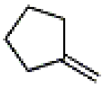
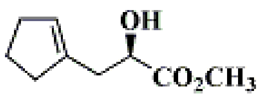
Waste Disposal Information

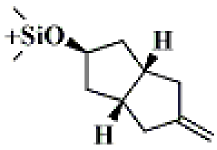
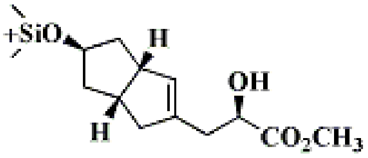
All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

A full account[5] describes the enantioselective carbonyl-ene reaction of glyoxylate esters catalyzed by a binaphthol-derived chiral titanium complex that is potentially useful for the asymmetric synthesis of α-hydroxy esters of biological and synthetic importance.[6,7,8,9] The present procedure is applicable to a variety of 1,1-disubstituted olefins to provide ene products in extremely high enantiomeric purity by the judicious choice of the dichloro or dibromo chiral catalyst (see Table). In certain glyoxylate-ene reactions involving removal of a methyl hydrogen, the dichloro catalyst is superior to the dibromo catalyst in enantioselectivity, although lower in reactivity (see Table, entries A and B). In reactions involving removal of a methylene hydrogen, the dibromo catalyst is superior in both enantioselectivity and reactivity (see Table, entries C, D, and E); the dibromo catalyst provides a higher % ee, while both catalysts provide equally high (ca. 90%) E selectivity (see Table, entry C). Since both (R)- and (S)-binaphthol are commercially available in optically pure form, the present asymmetric process allows the synthesis of both enantiomers of α-hydroxy esters and their derivatives.

TABLE
ASYMMETRICCATALYTICGLYOXYLATE-ENEREACTIONS WITH1,1-DISUBSTITUTEDOLEFINS[a]

Entry	Olefin	$(i\text{-}PrO)_2TiX_2$	Catalyst mol%	Time hr	Product	% Yield	%ee$_b$
A		Cl	10	8		72	95 R
						68	95 S[c]
		Br	10	3		87	94 R
B		Cl	1.0	8		97	97 (R)
		Br	1.0	3		98	95 (R)
C		Cl	10	8		68[d]	94[e](R)
		Br	5	3		73[f]	98[e](R)
D		Cl	10	8		82	97 (R)
		Br	5	3		89	98 (R)
E		Cl	10	8		93	88 (R)
		Br	5	3		92	89 (R)

F		Cl	10	3		77[g]	99[h](R)
		Br	10	3		100[g]	99[h](R)

[a]All reactions were run on scale pf 1 mmol of methyl glyoxylate by the representative procedure described in the text. [b]Determined as described in (Note 14) and/or (Note 15). The configuration in parenthesis could be assigned by the similarity in shift pattern seen in the LIS-NMR spectra using (+)-Eu(dppm)$_3$ as a chiral shift reagent. [c](S)-BINOL was used instead of the (R)-counterpart. [d]Combined yield of the (E)- and (Z)-isomer (E/Z = 89 : 11). [e]Refers to the optical purity of the major (E)-product. [f]Combined yield of the (E)- and (Z)-isomer (E/Z = 91 : 9). [g]Combined yield of the diastereomeric

mixture (96 : 4). [h]Refers to the optical purity of the major isomer.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

GLYOXYLATE-ENE

brine

methylene hydrogen

ethanol (64-17-5)

ethyl acetate (141-78-6)

ether (60-29-7)

sodium hydrogen carbonate (144-55-8)

silver(I) oxide (20667-12-3)

1,2-dichloroethane (107-06-2)

iodine (7553-56-2)

methyl hydrogen (7782-42-5)

toluene (108-88-3)

isopropyl alcohol (67-63-0)

Methyl iodide (74-88-4)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

heptane (142-82-5)

hexane (110-54-3)

α-methoxy (2143-68-2)

calcium hydride (7789-78-8)

α-methylstyrene (98-83-9)

argon (7440-37-1)

phosphorus pentoxide (1314-56-3)

titanium(IV) isopropoxide (546-68-9)

binaphthol

(R)-(+)-1,1'-Bi-2-naphthol (18531-99-2)

Methyl (2R)-2-hydroxy-4-phenyl-4-pentenoate, Benzenebutanoic acid, α-hydroxy-γ-methylene, methyl ester, (R)- (119072-58-1)

Diisopropoxytitanium(IV) dibromide, diisopropoxytitanium dibromide

titanium(IV) bromide (7789-68-6)

(R)-(+)-1,1'-bi-naphthol

methyl glyoxylate (922-68-9)

methyl 2-hydroxy-4-phenyl-4-pentenoate

diisopropoxytitanium(IV) dichloride

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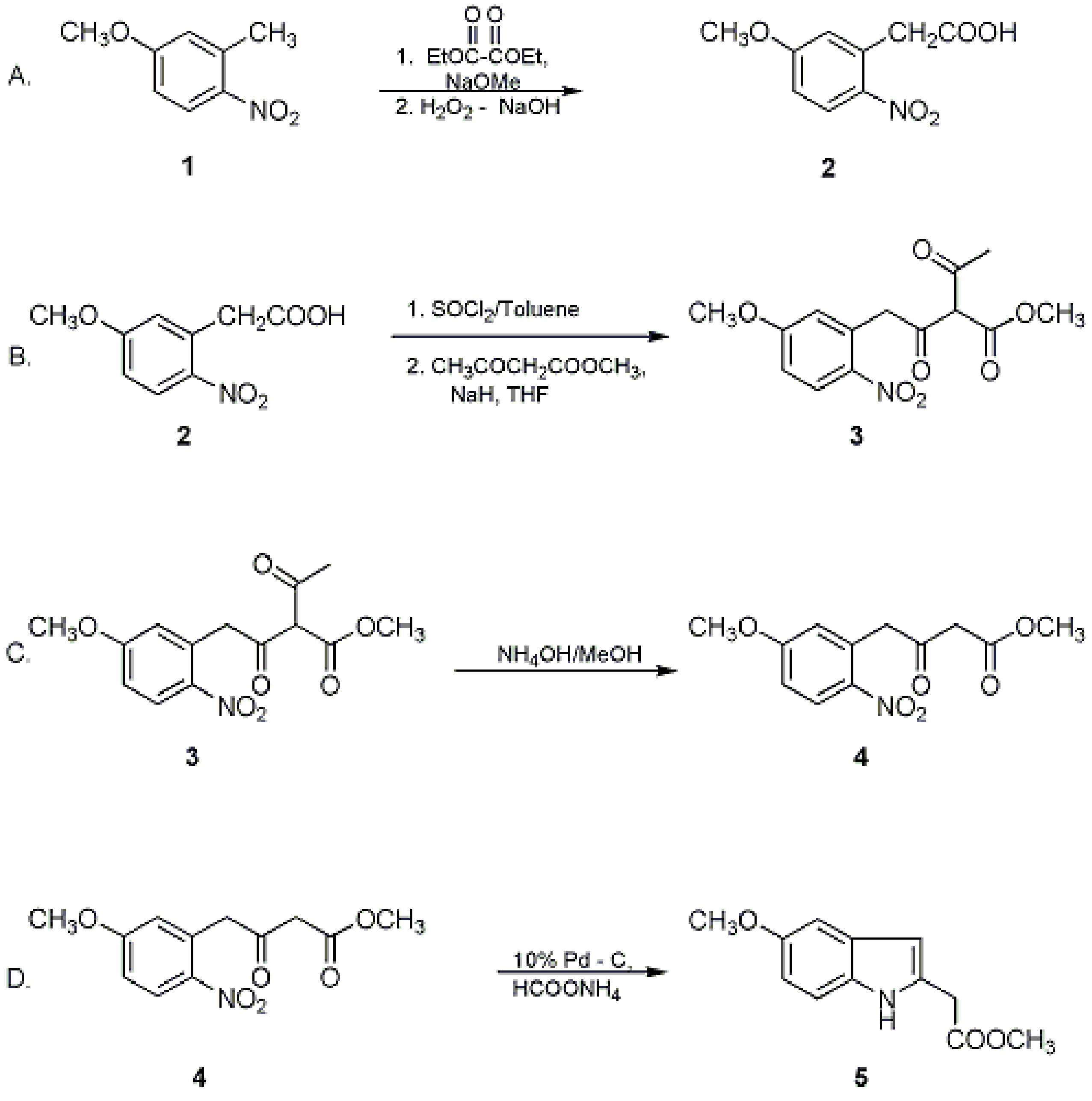
Organic Syntheses, *CV 9*, *601*

INDOLE-2-ACETIC ACID METHYL ESTERS: METHYL 5-METHOXYINDOLE-2-ACETATE

[1H-Indole-2-acetic acid, 5-methoxy-, methyl ester]



Submitted by Sandeep P. Modi[1], R. Christopher Oglesby[2], and Sydney Archer[1].
Checked by Katerina Matcheva and Ekkehard Winterfeldt.

1. Procedure

A. *5-Methoxy-2-nitrophenylacetic acid*, **2**.[3,4] A 1-L, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, 50-mL addition funnel, and a reflux condenser fitted with an inert gas (argon) inlet tube that is attached to a mineral oil bubbler. The system is

flushed with argon, flame dried, cooled to room temperature, and maintained under a positive pressure of argon. The reaction flask is charged with 18.8 g (0.34 mol) of anhydrous powdered sodium methoxide (Note 1) in 60 mL of anhydrous diethyl ether (Note 2). The flask is cooled in an ice bath and 47.5 mL (0.35 mol) of diethyl oxalate (Note 1) is added over 5 min from the addition funnel. The ice bath is removed and the resulting mixture is stirred at room temperature for 15 min. At the end of this time a pale yellow, thick suspension results, to which 50 g (0.3 mol) of anhydrous powdered 3-methyl-4-nitroanisole, **1**, (Note 1) is added, followed by 75 mL of anhydrous ether (Note 2). The orange-red mixture is heated to reflux for 4 hr. After the flask is cooled to room temperature approximately 1 L of water is added to dissolve the resulting thick orange precipitate (Note 3). The red solution is transferred to a 4-L beaker and kept cold using an ice-water mixture. Alternate portions of 30% hydrogen peroxide (Note 1) and 10 N sodium hydroxide (Note 4) are added to the cold red solution. Addition of hydrogen peroxide bleaches the solution and addition of sodium hydroxide restores the red color. This procedure is repeated 3 to 4 times until further addition of 10 N sodium hydroxide solution does not result in a color change (Note 5). The yellow brown solid is collected by filtration; it is impure starting material (wt 6–10 g) (Note 6). The filtrate is poured into a 4-L beaker, cooled to 0°C, and acidified with concentrated hydrochloric acid (Note 2) to precipitate 5-methoxy-2-nitrophenylacetic acid. The solid is collected on a Büchner funnel, washed with cold water until the filtrate is neutral, and then dried to give 45.3–48.5 g (70–75%) of an almost colorless product, mp 172–176°C (Note 7). Two recrystallizations in methanol give colorless product, mp 175–176°C (Note 8).

B. *Methyl (5-methoxy-2-nitrophenylacetyl)acetoacetate*, **3** (*CAUTION*, see (Note 13)). A 2-L, three-necked, round-bottomed flask equipped with a magnetic stirring bar, inert gas inlet, and two stoppers is flame dried and cooled to room temperature under an atmosphere of argon. The flask is charged with 42.5 g (0.20 mol) of **2** in 480 mL of anhydrous toluene (Note 2). To the resulting suspension is added 15.3 mL (0.21 mol) of thionyl chloride (Note 9) followed by 2 mL of anhydrous N,N-dimethylformamide (DMF) (Note 2). As soon as the DMF is added the color of the mixture turns light red. The mixture is stirred at room temperature overnight (Note 10). A 1-L, three-necked, round-bottomed flask equipped with a magnetic stirring bar, 250-mL pressure-equalizing funnel, and an inert gas inlet is flame dried and allowed to cool to room temperature under argon. The flask is charged with 10.1 g (0.49 mol) of 97% sodium hydride (Note 1) in 280 mL of dry tetrahydrofuran (THF) (Note 11) and then cooled to 0°C in an ice bath. A solution of 45.3 mL (0.42 mol) of methyl acetoacetate (Note 1) in 160 mL of dry THF (Note 11) is placed in the addition funnel and added dropwise to the reaction flask over a period of 45–50 min. After the addition is complete the light gray-colored solution is quickly transferred to a dried, 500-mL addition funnel (Note 12). The funnel is mounted on the flask containing the acid chloride solution. The solution of methyl acetoacetate anion is added to the crude acid chloride solution (Note 13) over 5 min and the resulting mixture is stirred overnight at room temperature. Water (350 mL) is added to the reaction mixture and the mixture is stirred for 15 min before being poured into a 2-L separatory funnel. The layers are separated and the aqueous layer is extracted with ether (2 × 150 mL). The combined organic layers are washed with brine and dried over sodium sulfate (Note 1). The filtered organic layer is concentrated under reduced pressure and the residue is dissolved in 100 mL

of methanol. After cooling in the freezer overnight, the yellow crystals that separate are collected and dried to give 34.8–37.3 g (56–60%) of **3** (Note 14), (Note 15), suitable for use in the next step.

C. *Methyl 4-(5-methoxy-2-nitrophenyl)-3-oxobutyrate*, **4**. A 1-L, three-necked flask equipped with a magnetic stirring bar, an inert gas inlet, and a stopper is charged with 25.2 g (0.08 mol) of **3** in 200 mL of reagent grade methanol (Note 2) followed by 20 mL of ammonium hydroxide (Note 2). The beige suspension turns red as soon as ammonium hydroxide is added. After about 15 min a white solid precipitates (Note 16). The mixture is stirred at room temperature for 30 min, filtered and the solid is washed with 10–15 mL of cold methanol. The filtrate is concentrated under reduced pressure and the residue is collected on a filter. This procedure is repeated once more (Note 17). After three filtrations the combined solid weighs 16.3–17.4 g (75–80%), which is suitable for use in the next step. Recrystallization from methanol gives a colorless product (Note 18).

D. *Methyl 5-methoxyindole-2-acetate*, **5**. A flame dried, 1-L, three-necked, round-bottomed flask equipped with a magnetic stirring bar and a condenser under argon is charged with 19.6 g (0.07 mol) of **4** followed by 450 mL of anhydrous methanol (Note 2). A slurry of 1.9 g of 10% palladium over activated carbon (Note 1) in 20 mL of anhydrous methanol is added to the flask (Note 19) followed by 53.5 g (0.8 mol) of ammonium formate (Note 1), (Note 20). The reaction mixture is stirred at room temperature for 1 hr (Note 21) and then filtered through a bed of Celite. The Celite is washed with 100 mL of anhydrous methanol and the solvents are removed under reduced pressure to give a beige solid. The residue is triturated with 350 mL of cold water and the insoluble material (Note 22) is filtered and then dried to give 13.5–14.3 g (84–89%) of **5** (Note 23).

2. Notes

1. Sodium methoxide, 3-methyl-4-nitroanisole, diethyl oxalate, 30% hydrogen peroxide, 97% sodium hydride, methyl acetoacetate, sodium sulfate, 10% palladium on activated carbon, ammonium formate, and 5-methoxy-2-nitrophenylacetic acid were purchased from Aldrich Chemical Company, Inc., and were used without further purification.
2. Anhydrous solvents such as diethyl ether, N,N-dimethylformamide, toluene, and methanol were purchased from Mallinckrodt Inc. and were used without further drying. Concentrated hydrochloric acid and ammonium hydroxide were also purchased from Mallinckrodt Inc.
3. Water was added in portions of 300–400 mL each to the reaction flask. The mixture was stirred for 5–10 min and the red solution was decanted into a separate flask. This procedure was repeated until all the solid went into solution.
4. Sodium hydroxide was purchased from Fischer Scientific Company.
5. The total amounts of 30% hydrogen peroxide and 10 N sodium hydroxide used were 60–70 mL and 20–25 mL, respectively.
6. The melting point of the crude compound is 50–60°C; the NMR and IR correspond to starting material.
7. The physical properties are as follows: m.p. 175–176°C (lit value:[3] 174–176°C); IR (KBr) cm^{-1}: 3140–2740, 2660, 1715, 1620, 1580, 1510, 1410, 1340, 1320, 1290,

1260, 1200, 1175, 1090, 1040, 955, 850, 830, 760, 710, 630; NMR (DMSO-d_6) δ: 3.86 (s, 3 H, OCH_3), 3.97 (s, 2 H, CH_2), 7.04–7.10 (m, 2 H, H_4, H_6), 8.13 (d, 1 H, J = 8.8, H_3); MS m/e 212 (M+1).

8. It is essential to have compound **2** as a colorless product; otherwise the yield in the next step is poor.

9. Thionyl chloride was purchased from Aldrich Chemical Company, Inc., and distilled prior to use.

10. If a clear solution did not result at the end of 16–18 hr, the mixture was warmed at 35–40°C for 1 hr or until a clear solution resulted; then it was cooled to room temperature.

11. Reagent grade tetrahydrofuran was purchased from Mallinckrodt Inc. and freshly distilled from sodium metal and benzophenone.

12. A 500-mL, pressure-equalizing funnel was oven-dried and then cooled under argon.

13. 5-Methoxy-2-nitrophenylacetyl chloride was never isolated from the reaction mixture. It is known[5,6] that 2-nitrophenylacetyl chloride is a potentially explosive material, but it is not documented that the 5-methoxy derivative is also hazardous. 5-Methoxy-2-nitrophenylacetyl chloride was also prepared as described by Rosenmund and his co-workers,[7] and was used in the crude form.

14. Depending on the purity of the starting material, the yield of **3** has been as high as 80%.

15. The analytical sample melted at 78–79°C after crystallization from methanol. The spectra are as follows: IR (KBr) cm^{-1}: 2960, 2850, 1710, 1620–1390, 1350–1250, 1190, 1090, 1035, 950, 910, 890, 840, 760, 730, 630; NMR ($CDCl_3$) δ: 2.40 (s, 3 H, $COCH_3$), 3.84 (s, 3 H, $COOCH_3$), 3.99 (s, 3 H, OCH_3), 4.50 (s, 2 H, CH_2), 6.77 (d, 1 H, J = 2.6, H_6), 6.90 (dd, 1 H, J = 2.8, 9.0, H_4), 8.19 (d, 1 H, J = 9.0, H_3); MS m/e 310 (M+1).

16. If there is no precipitate, a few crystals of starting material **3** are added to the reaction flask to initiate crystallization.

17. After a total of three filtrations, the filtrate contained 5-methoxy-2-nitrophenyl-acetamide and 4-(5-methoxy-2-nitrophenyl)-4-oxobutyramide as the by-products in varying amounts.

18. The physical properties are as follows: mp 85–87°C; IR (KBr) cm^{-1}: 3470, 3130, 2980, 2850, 1710, 1590, 1500, 1440, 1400, 1200, 1065, 1010, 865, 850, 760, 750, 700, 630, 620; NMR ($CDCl_3$) δ: 3.66 (s, 2 H, CH_2), 3.77 (s, 3 H, $COOCH_3$), 3.87 (s, 3 H, OCH_3), 4.20 (s, 2 H, $ArCH_2$), 6.73 (d, 1H, J=2.8, H_6), 6.89 (dd, 1 H, J = 2.8, 9.2, H_4), 8.19 (d, 1 H, J = 9.2, H_3); MS m/e 268 (M+1).

19. Excess ammonium formate was necessary for completion of the reaction.

20. The slurry was prepared by adding ice-cold methanol to 10% palladium on activated charcoal. The slurry was transferred to the reaction flask with a pipet.

21. The reaction was monitored by TLC, using silica gel plates and 2:1 ethyl acetate–hexane.

22. If an oil resulted, it was taken up in ethyl acetate (150 mL) and the two layers were separated. The aqueous layer was extracted with ethyl acetate (2 × 50 mL); the organic layers were combined, dried (Na_2SO_4) and concentrated under reduced

pressure at 35–40°C to give 12.7–13.5 g (80–85%) of product **5** as an oil that solidifies on cooling in the freezer.

23. The physical properties are as follows: mp 96–98°C; IR (KBr) cm^{-1}: 3370, 3020, 2970, 2840, 1720, 1595, 1485, 1445, 1395, 1330, 1205, 1120, 1035, 1010, 980, 950, 845, 810, 770, 735, 695, 625^{-1}; NMR ($CDCl_3$) δ: 3.74 (s, 3 H, $COOCH_3$), 3.82 (s, 2 H, CH_2), 3.83 (s, 3 H, CH_3), 6.27 (d, 1 H, J = 1.0, H_3), 6.81 (dd, 1 H, J = 2.4, 8.8, H_6), 7.01 (d, 1 H, J = 2.4, H_4), 7.23 (d, 1 H, J = 8.8, H_7), 8.53 (s, 1 H, NH); MS m/e 220 (M+1). The product must be stored in the freezer; on the bench top it turns red.

24. The physical properties for methyl (2-nitrophenylacetyl)acetoacetate are as follows: mp 82–83°C; IR (KBr) cm^{-1}: 2960, 1705, 1515, 1400, 1335, 1080, 860, 790, 720 cm−1; NMR ($CDCl_3$) δ: 2.41 (s, 3 H, $COCH_3$), 3.85 (s, 3 H, $COOCH_3$), 4.20 (s, 2 H, CH_2), 4.50 (s, 2 H, CH_2), 7.36–7.65 (m, 3 H), 8.16 (t, 1 H).

25. The physical properties for methyl 4-(2-nitrophenyl)-3-oxobutyrate are as follows: mp 50–51°C; IR (KBr) cm^{-1}: 2960, 1750, 1715, 1610, 1575, 1520, 1440, 1340, 1265, 1200, 1070, 1010, 795, 730, 705 cm^{-1}; NMR ($CDCl_3$) δ: 3.66 (2 H, $COCH_2COOMe$), 3.76 (s, 3 H, $COOCH_3$), 4.25 (s, 2 H, Ar-CH_2), 7.30 (d, 1 H, J = 7.2), 7.50 (t, 1 H), 7.6 (t, 1 H), 8.10 (d, 1 H, J = 6.8).

26. The physical properties for methyl indole-2-acetate are as follows: mp 71–74°C; IR (KBr) cm^{-1}: 3430, 3405, 3320, 3220, 1740, 1720, 1660, 1620, 1565, 1525, 1430, 1340, 1300, 1280, 1190, 1170, 1030, 860, 820, 790, 780, 730, 700 cm^{-1}; NMR ($CDCl_3$) δ: 3.61 (s, 3 H, $COOCH_3$), 3.71 (s, 2 H, CH_2), 7.42–7.58 (m, 4 H), 7.93 (m, 1 H), 7.97 (d, 1 H, J = 1.8).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Compound **5** and its 5-H-analog can be prepared in one to two steps from the known intermediates 5-methoxyindole-2-acetonitrile and indole-2-acetic acid, respectively. 5-Methoxyindole-2-acetonitrile is obtained in very poor overall yield when the patented procedure is followed.[8] Indole-2-acetic acid is prepared from indole-2-carboxylic acid[9,10] in five steps or from indole[11,12] in three steps. The first method involves six steps for the one carbon homologation and the overall yield is 23%. The second method involves protection and deprotection of the indole nitrogen. In addition the reaction conditions for the lithiation step require a very low (–78°C) temperature and for the Wolff-Kishner step a very high (180°C) temperature. The procedure described here illustrates a general synthetic method for the preparation in three steps of substituted indole-2-acetic acid methyl esters from o-nitrophenylacetic acid and its derivatives. The overall yields are 30–40% and the reactions can be carried out on a large scale. The purity of the intermediates and the products is greater than 90% as determined by NMR. One of the intermediates, o-nitrophenylacetyl chloride, is considered to be a potentially explosive material; therefore it is never isolated, but is used in its crude form. Although it is not known whether 5-

methoxy-2-nitrophenylacetyl chloride is an explosive material, it is also prepared and used in its crude form.

Compound **5** and its 5-H-analog are useful intermediates in preparing a number of 5-substituted 6H-pyrido[4,3-b]carbazoles.[9,10,13] These pyridocarbazoles are potential antitumor agents.

The corresponding 5-H analogs of the title compound are prepared using the procedure described for compounds **3**, **4**, and **5** in 55–61%, 65–70%, and 80–86% yield, respectively.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

palladium over activated carbon

palladium on activated carbon, ammonium formate

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

thionyl chloride (7719-09-7)

sodium sulfate (7757-82-6)

sodium methoxide (124-41-4)

toluene (108-88-3)

Benzophenone (119-61-9)

sodium (13966-32-0)

palladium on activated charcoal (7440-05-3)

hydrogen peroxide (7722-84-1)

ammonium hydroxide (1336-21-6)

ammonium formate (540-69-2)

Tetrahydrofuran (109-99-9)

N,N-dimethylformamide (68-12-2)

sodium hydride (7646-69-7)

Indole (120-72-9)

indole nitrogen

indole-2-carboxylic acid (1477-50-5)

hexane (110-54-3)

Methyl acetoacetate (105-45-3)

diethyl oxalate (95-92-1)

argon (7440-37-1)

INDOLE-2-ACETIC ACID METHYL ESTERS, methyl indole-2-acetate, indole-2-acetic acid methyl ester

Methyl 5-methoxyindole-2-acetate, 1H-Indole-2-acetic acid, 5-methoxy-, methyl ester (27798-66-9)

5-Methoxy-2-nitrophenylacetic acid (20876-29-3)

3-methyl-4-nitroanisole (5367-32-8)

Methyl (5-methoxy-2-nitrophenylacetyl)acetoacetate (130916-40-4)

methyl acetoacetate anion

Methyl 4-(5-methoxy-2-nitrophenyl)-3-oxobutyrate (130916-41-5)

5-Methoxy-2-nitrophenylacetyl chloride

2-nitrophenylacetyl chloride, o-nitrophenylacetyl chloride (22751-23-1)

5-methoxy-2-nitrophenyl-acetamide

4-(5-methoxy-2-nitrophenyl)-4-oxobutyramide

methyl (2-nitrophenylacetyl)acetoacetate (160206-92-8)

methyl 4-(2-nitrophenyl)-3-oxobutyrate (119209-56-2)

5-methoxyindole-2-acetonitrile

indole-2-acetic acid

o-nitrophenylacetic acid (3740-52-1)

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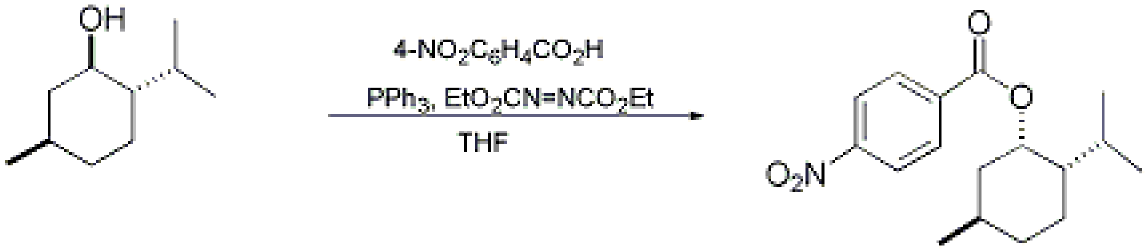
Organic Syntheses, CV 9, 607

A GENERAL PROCEDURE FOR MITSUNOBU INVERSION OF STERICALLY HINDERED ALCOHOLS: INVERSION OF MENTHOL. (1S,2S,5R)-5-METHYL-2-(1-METHYLETHYL)CYCLOHEXYL 4-NITROBENZOATE

[Cyclohexanol, 5-methyl-2-(1-methylethyl)-, 4-nitrobenzoate, [1S-(1α,2α,5β)]-]



Submitted by Jeffrey A. Dodge, Jeffrey S. Nissen, and Misti Presnell[1].
Checked by Masami Okabe, Ruen Chu Sun, and David Coffen.

1. Procedure

(1S,2S,5R)-5-Methyl-2-(1-methylethyl)cyclohexyl 4-nitrobenzoate. A 250-mL, three-necked, round-bottomed flask is equipped with a stirring bar, nitrogen inlet, rubber septum, and thermometer. The flask is charged with 3.00 g of (1R,2S,5R)-(−)-menthol (19.2 mmol), 12.9 g of 4-nitrobenzoic acid (77.2 mmol), 20.1 g of triphenylphosphine (PPh_3) (76.6 mmol) (Note 1), and 150 mL of tetrahydrofuran (Note 2). The flask is immersed in an ice bath, and 12.1 mL of diethyl azodicarboxylate (77 mmol) is added dropwise at a rate such that the temperature of the reaction mixture is maintained below 10°C (Note 3). Upon completion of the addition (Note 4), the flask is removed from the ice bath and the solution is allowed to stir at room temperature overnight (14 hr) and subsequently at 40°C for 3 hr (Note 5). The reaction mixture is cooled to room temperature, diluted with 150 mL of ether, and washed twice with 100 mL portions of saturated aqueous sodium bicarbonate solution. The aqueous layers are combined and back-extracted with 100 mL of ether. The combined organic layers are dried over sodium sulfate. Excess solvent and other volatile reaction components are completely removed under reduced pressure initially on a rotary evaporator and then under high vacuum (approximately 0.2 mm for 3 hr at 30°C) (Note 6). The resulting semi-solid is suspended in 40 mL of ether and the suspension is allowed to stand at room temperature overnight (Note 7). The mixture is stirred while 20 mL of hexanes is slowly added (Note 8). The resulting white solid is filtered under vacuum and the filter cake is washed with 200 mL of 50% (v/v) ether-hexanes. The solvent is removed from

the filtrate on a rotary evaporator under reduced pressure to give a yellow oil that is dissolved in 10 mL of methylene chloride (Note 9) and diluted with 40 mL of 8% ether-hexanes. The solution is applied to a flash chromatography column (Note 10) and eluted with 8% ether-hexanes to give 5.03 g (85.6%) of pure nitrobenzoate ester as a white crystalline solid (Note 11).

2. Notes

1. (1R,2S,5R)-(−)-Menthol, 4-nitrobenzoic acid, triphenylphosphine, and diethyl azodicarboxylate were purchased from Aldrich Chemical Company, Inc., and used without further purification.

2. Anhydrous tetrahydrofuran (THF) was purchased from Aldrich Chemical Company, Inc. (Sure/Seal™ bottle). The checkers used a freshly opened bottle of certified grade THF from Fisher Scientific Company.

3. Since diethyl azodicarboxylate decomposes when warmed, the reaction temperature is maintained at < 10°C during the addition of this reagent at which time a slight exothermic reaction occurs. [See Hazard Index, p. 837.htm.]

4. 4-Nitrobenzoic acid is not entirely soluble in the tetrahydrofuran solution, resulting in a heterogeneous mixture. Upon addition of diethyl azodicarboxylate the reaction becomes homogeneous within several minutes and turns yellow-orange.

5. Shorter reaction times (2–5 hr) result in slightly decreased yields (65–75%) of inverted product. Lower yields (73–75%) were realized by the checkers when stirring at 40°C was omitted.

6. Removal of all residual tetrahydrofuran is critical to the success of the subsequent precipitation. The submitters recommend high vacuum removal of the solvent. Use of "house vacuum" (4–10 mm) also proved effective if applied to the crude sample for several hours.

7. Precipitation of the undesired reaction by-products (reduced diethyl azodicarboxylate, triphenylphosphine oxide) occurs after the product mixture is suspended in ether.

8. Extractive workup can be deleted, in which case sonication is required at this stage. Sonication appears to initiate further crystallization of by-products, as well as minimizing the amount of oil formed during the addition of hexanes.

9. The yellow oil is not sufficiently soluble in the chromatographic eluant (8% ether in hexanes) to provide efficient loading of the sample on the column. Thus, the crude material is initially dissolved in a small amount of dichloromethane.

10. Chromatography was performed via the method of Still[2] using an 80-mm i.d. column of 300 g of silica gel (230–400 mesh).

11. The physical properties are as follows: mp 93–95°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.87–1.23 (m, 12 H), 1.44–1.56 (m, 2 H), 1.64–1.70 (m, 1 H), 1.71–1.90 (m, 2 H), 2.05–2.13 (m, 1 H), 5.50 (s, 1 H), 8.20 (d, 2 H, J = 8.5), 8.29 (d, 2 H, J = 8.9); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.0, 20.8, 22.0, 25.3, 26.7, 29.0, 29.3, 34.6, 46.8, 73.0, 123.4, 130.5, 136.3, 150.3, 163.8; IR ($CDCl_3$) cm^{-1}:

1726, 1540, 1293.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Since its introduction in 1967,[3] the Mitsunobu reaction has been widely used in the refunctionalization of alcohols, in particular, for inversion. However, Mitsunobu inversions of hindered alcohols have been problematic resulting in low yields or unused starting material. A simple modification of the standard Mitsunobu procedure using 4-nitrobenzoic acid (instead of benzoic or acetic acid) results in significantly improved yields of inverted product for sterically hindered alcohols.[4] The procedure outlined here provides experimental details for the inversion of menthol, a representative, hindered, secondary alcohol, using 4-nitrobenzoic acid as the acidic coupling partner in the Mitsunobu process. The experimental procedure is a modification of that reported by Martin and Dodge.[4] Improvements in the solvent (tetrahydrofuran rather than benzene) and a practical method for the removal of undesired by-products (e.g., $EtCO_2NHNHCO_2Et$ and triphenylphosphine oxide) have led to optimization of reaction conditions.

Previously documented methods for menthol inversion under standard Mitsunobu conditions (benzoic acid, PPh_3, diethyl azodicarboxylate) result in low yields[4] (27%). More effective methods have been reported using extended reaction periods in refluxing toluene via a formic acid/N,N'-dicyclohexylcarbodiimide-mediated transformation[5] (20–92 hr, 80%). For hindered alcohols in general, representative methods for inverting alcohol stereochemistry necessitate conversion of the alcohol to a leaving group such as a mesylate or triflate, followed by S_N2 displacement with a carboxylate nucleophile (typically cesium acetate or propionate).[6] Other prevalent methods include (a) oxidation followed by stereoselective reduction and (b) intramolecular delivery (for suitably functionalized substrates) of the requisite oxygen functionality. One inherent advantage of the Mitsunobu reaction is compatibility with a diverse array of functional groups, due in large part to the mild, essentially neutral reaction conditions.

References and Notes

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210, 1986; *Chem. Abstr*. **1987**, *106*, 32087g.
6. For example, Torisawa, Y.; Okabe, H.; Ikegami, S. *Chem. Lett.* **1984**, 1555.

Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

hexanes

Cyclohexanol, 5-methyl-2-(1-methylethyl)-, 4-nitrobenzoate, [1S-(1α,2α,5β)]-

(1R,2S,5R)-(−)-menthol

$EtCO_2NHNHCO_2Et$

PPh_3

acetic acid (64-19-7)

Benzene (71-43-2)

ether (60-29-7)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

formic acid (64-18-6)

Benzoic acid (65-85-0)

toluene (108-88-3)

menthol (15356-60-2)

methylene chloride, dichloromethane (75-09-2)

Tetrahydrofuran, THF (109-99-9)

diethyl azodicarboxylate (1972-28-7)

triphenylphosphine (603-35-0)

N,N'-dicyclohexylcarbodiimide (538-75-0)

triphenylphosphine oxide (791-28-6)

4-nitrobenzoic acid (62-23-7)

cesium acetate

(1S,2S,5R)-5-Methyl-2-(1-methylethyl)cyclohexyl 4-nitrobenzoate (27374-00-1)

cesium propionate

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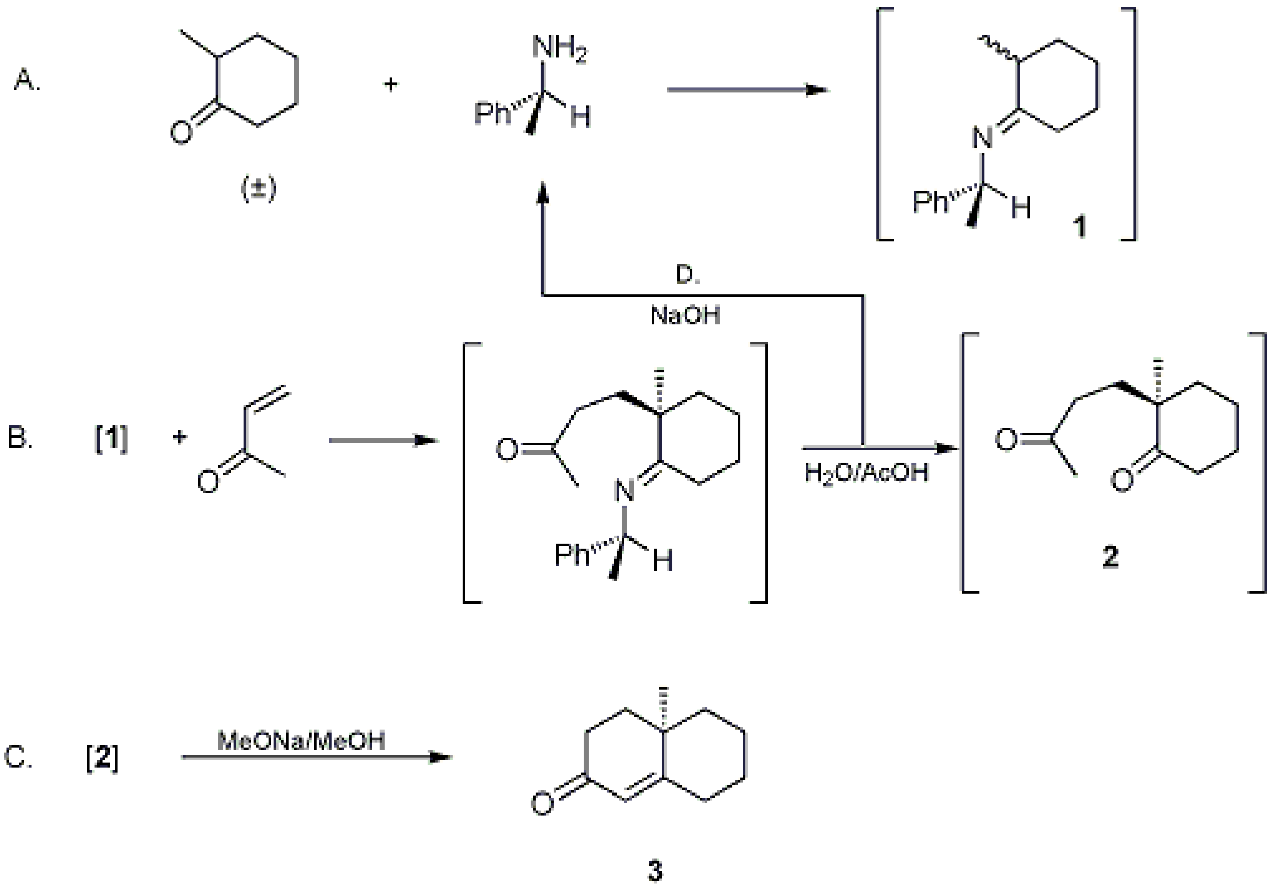
Organic Syntheses, CV 9, 610

(R)-(–)-10-METHYL-1(9)-OCTAL-2-ONE

[2(3H)-Naphthalenone, 4,4a,5,6,7,8-hexahydro-4a-methyl-, (R)-]



Submitted by G. Revial and M. Pfau[1].
Checked by Graham N. Maw and Robert K. Boeckman, Jr..

1. Procedure

A. *Imines* **(1)**. In a 1000-mL, round-bottomed flask, fitted with a toluene-filled Dean-Stark water separator, 100.0 g (0.825 mol) of (S)-(–)-α-methylbenzylamine (Note 1), 92.5 g (0.825 mol) of 2-methylcyclohexanone (Note 2) and 100 mL of toluene are heated at reflux temperature under a nitrogen atmosphere. After 24 hr, ca. 15 mL of water (ca. 100% theor.) has been removed azeotropically.

B. *(R)-(+)-2-Methyl-2-(3-oxobutyl)cyclohexanone* **(2)**. The solution of imines **1** is cooled in an ice bath and 72.5 mL (61.0 g, 0.870 mol, ca. 1.05 equiv) of freshly distilled methyl vinyl ketone (Note 3) is added with a syringe, with magnetic stirring, under a nitrogen atmosphere. The flask is then heated at ca. 40°C for 24 hr.

The slightly yellow solution is cooled in an ice bath and 60 mL of glacial acetic acid (ca. 1 mol) and 50 mL of water are added. Hydrolysis is achieved by stirring the heterogeneous mixture at room temperature for 2 hr. The now clear solution is poured into a 2000-mL separatory funnel containing 100 mL of brine and 160 mL of water and is extracted five times

with a 50:50 mixture of ether-petroleum ether (35–60°C) (1000-mL total amount). The organic phase is washed efficiently with 20 mL of 10% hydrochloric acid, 20 mL of water, and two 10-mL portions of brine.

The aqueous layer is kept for recovery of the amine (see D below).

The pale yellow organic layer is dried over a small amount of anhydrous magnesium sulfate and filtered. The solvents are removed with a rotary evaporator at ca. 40°C and the crude diketone **2** (ca. 145 g) is used directly for the next step.

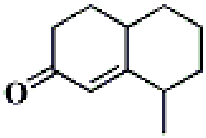
C. *(R)-(−)-10-Methyl-1(9)-octal-2-one* **(3)**. Dry methanol (600 mL) is added to the crude diketone **2** contained in a 2000-mL, round-bottomed flask and a rubber septum is fitted. The solution is stirred at room temperature for 15 min under a slight stream of nitrogen to remove traces of oxygen. A 25 wt. % solution of sodium methoxide in methanol (Note 4) is then introduced dropwise with a syringe, under stirring, until a slightly red color develops (Note 5). At this point, 15 mL (ca. 0.07 mol) of the sodium methoxide solution is added and the mixture is heated at 60°C for 10 hr under a nitrogen atmosphere. The solution is cooled and the now deep red solution is neutralized with glacial acetic acid (ca. 4.5 mL) until the color turns yellow. Methanol is removed with a rotary evaporator until a thick paste (sodium acetate) results; this is dissolved with 200 mL of water. Extraction is effected in a 2000-mL separatory funnel using four portions of a 50:50 mixture (1000 mL total amount) of ether-petroleum ether (35–60°C). The pale orange organic phase is washed twice with 40 mL of water, then twice with 20 mL of brine. The organic layer is dried over a small amount of anhydrous magnesium sulfate and filtered. The solvents are removed with a rotary evaporator at ca. 40°C and the red oily residue of crude octalone **3** is distilled under reduced pressure to afford ca. 110 g of a colorless oil, bp 70°C (2 mm) (Note 6). The oil is purified by recrystallization at a low temperature with an apparatus designed for this purpose.[2] The oil is dissolved with stirring in a 1000-mL, round-bottomed flask with 370 mL of pentane under a nitrogen atmosphere. The flask is then cautiously cooled in a Dewar flask containing liquid nitrogen until the solution is solid. The Dewar flask is removed and the temperature is allowed to rise, while magnetic stirring is resumed. When a crystalline mass in suspension appears suddenly (Note 7), an acetone bath adjusted to about −10°C is installed. When only a few crystals remain in suspension, the bath temperature is slowly lowered to −35°C, inducing crystallization. After the mixture has been kept at −35°C for 15 min, magnetic stirring is stopped and efficient filtration is performed through the filter stick. Still at −35°C, the compound is washed with 40 mL of pentane. The solution is stirred vigorously for 5 min and filtered as before. The washing operation is repeated two more times. The flask is warmed to room temperature and the oil is distilled as before, bp 70°C (2 mm), to afford 60–65 g (44–48% overall yield from 2-methylcyclohexanone) of methyloctalone **3** [>99% chemical purity, capillary GLC (Note 6)], $[\alpha]_D^{20}$ −210° (ethanol, *c* 1.00), optical purity 96% (Note 8).

D. *Recovery of (S)-(−)-α-methylbenzylamine*. The aqueous layer (see above, *B*, 3rd paragraph) contained in a 1000-mL flask is cooled in an ice bath under a nitrogen atmosphere. An aqueous 10% sodium hydroxide solution is added with stirring until a pH of 12–14 (Note 9) is reached. The mixture is transferred to a 2000-mL separatory funnel and extracted three times with ether (1000-mL total amount). The organic phase is washed twice with 100 mL of water and twice with 30 mL of brine, then dried over potassium carbonate and filtered. The solution is concentrated at room temperature with a rotary evaporator and

distilled under reduced pressure to afford 85–90 g (85–90% yield) of the amine, bp 70°C (15 mm), the specific rotation of which is the same as that of the original starting material.

2. Notes

1. (S)-(–)-α-Methylbenzylamine (95.8% optical purity) and its (R)-(+)-enantiomer (93.4% optical purity) were purchased from Aldrich Chemical Company, Inc. and used without further purification. *CAUTION: These amines are toxic.* Air must be excluded to prevent formation of carbonates.
2. 2-Methylcyclohexanone was purchased from Aldrich Chemical Company, Inc., and used without further purification.
3. Methyl vinyl ketone, purchased from Aldrich Chemical Company, Inc., is dried over anhydrous potassium carbonate for 0.5 hr. The now slightly-colored oil is filtered and distilled under a nitrogen atmosphere at reduced pressure, bp 55°C (260 mm). *The colorless center of the distillate is collected over a few milligrams (ca. 0.05% concentration) of hydroquinone.*
4. A 25 wt % solution of sodium methoxide in methanol (4.6 M) was purchased from Aldrich Chemical Company, Inc.
5. Any acetic acid present is thus neutralized (a few drops are usually sufficient). Confirm that a basic pH has been reached by testing a drop of the solution, removed by syringe.
6. Although a TLC test (silica gel Merck 60 F_{254}, ethyl acetate/hexane 20:80 elution, UV and chromic-sulfuric acid visualization) of this oil reveals only one spot (R_f 0.6), capillary GLC (Hewlett-Packard HP-5, 25 m × 0.2 mm × 0.5 •m, 200°C) shows in addition to methyloctalone **3** (retention time, 10.9 min), an 8% impurity (retention time, 11.7 min) which is probably the regioisomer **4**.



4

A chemically pure sample of methyloctalone **3**, $[\alpha]_D^{20}$ –190° (ethanol, *c* 1.00) is obtained by preparative GLC (3 m × ", 5% carbowax 20 M on Aeropak 30, 180°C, retention time 12.4 min) of a distillate sample. The impurity has a 13.2-min retention time under these conditions. A good approximation of the reaction ee is calculated as follows, taking into account the optical purity of the starting amine (95.8%) and the $[\alpha]_D^{20}$ –219° (ethanol, *c* 1.00) value (Note 8) for optically pure methyloctalone 3: ee = 100 × 190 × 100/95.8 × 219 91%.
7. If no crystalline mass is formed but instead an emulsion of the two liquid phases appears, the entire solidification must be repeated (liquid nitrogen cooling).
8. Chiral capillary GLC (OV-1701 + trimeb/2), 25 m × 0.3 mm, He, 65 kPa, 130°C: (R)-(–)-**3**, 58.3 min (98%); (S)-(+)-**3**, 62.0 min (2%). Optically pure methyloctalone **3** is obtained by recrystallizing a sample of the purified compound several times until a constant $[\alpha]_D^{20}$ –219° (ethanol, *c* 1.00 or methanol, *c* 1.10) is observed. As chiral capillary GLC shows only (R)-(–)-**3**, the $[\alpha]_D^{20}$ –219° (methanol, *c* 1.1) value from the literature[3] is confirmed.
9. If a pH lower than 12 is used, recovery of the amine is poor.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

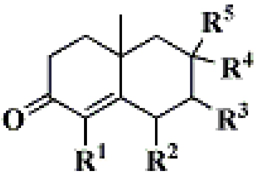
Optically active methyloctalone **3** (or its enantiomer) has been obtained by resolution[3,4] and by asymmetric synthesis.[5] Both enantiomers are also available commercially. The synthesis described here is by far the most simple and gives the best yield. It is an application of the general method reported for the enantioselective elaboration of quaternary carbon centers through Michael-type alkylation of chiral imines.[6 7 8 9 10 11 12 13 14]

This general method has the following advantages: very simple procedures, very mild conditions involving moderate reaction temperatures and no acids, bases, catalysts, etc., allowing the use of labile reactants, excellent regio- and enantioselectivities as well as high chemical yields, and creation of useful chiral building blocks with quaternary carbon centers involving functionalized chains, allowing one to devise syntheses of natural compounds of various types (terpenes, steroids, alkaloids, etc.). As both optically active amines are commercially available, targets with either desired absolute configuration can be synthesized. Easy recovery of the auxiliary chiral moiety is possible.

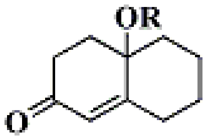
Racemic methyloctalone **3** has been used as a starting material for many transformations as well as for syntheses of racemic natural compounds. In the following examples, the absolute configuration of the methyloctalone that would be required to obtain the natural enantiomer is indicated in parentheses: β-gorgonene[15] (S), widdrol[16,17] (R), thujopsene[16,18] (R), 7-hydroxycostal[19,20] (R), β-selinene[21,22] (R), costol, costal and costic acid[21] (R), norketoagarofuran[23,24] (R), β-eudesmol[21,22,23,25] (R), taxane model[26] (S), polygodial[27] (S), warburganal[27] (S).

(R)-Methyloctalone **3** itself has been used to synthesize a pasmalinine model,[28] a subunit of penitrem D,[29] and several biologically active decalin derivatives.[30]

The following key-intermediates have been prepared by a procedure similar to the one described above, generally with excellent chemical and optical yields :

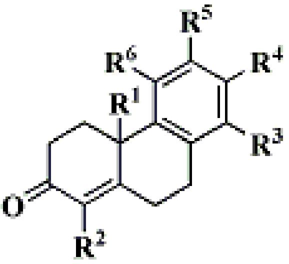


5: R^1 = Me; R^2 = R^3 = R^4 = H (R and S)[23]
6: R^1 = R^3 = R^4 = H; R^2 = Me (S,S)[23]
7: R^1 = R^2 = R^4 = H; R^3 = $C(=CH_2)Me$(R,R and 7 R, 10 S)[24]
8: R^1 = Me; R^2 = R^4 = H; R^3 = $C(=CH^2)Me$(R.R)[25]
9: R^1 = R^2 = R^3 = H; R^4R^4 = $O(CH_2)_4O$(R)[26]
10: R^1 = Me; R^2 = R^3 = H; R^4R^4 = $O(CH_2)_2O$(R)[27]



R = Me[28]

R = CH_2Ph (R)[28]



R^1 = Me; R^2 = R^3 = R^4 = R^5 = R^6 = H(R)[29]

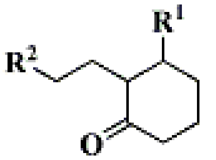
11: R^1 = Me; R^2 = R^4 = R^5 = H; R^3 = $(CH_2)_2COOH$; R^6 = OMe(S)[29]

12: R^1 = Me; R^2 = R^4 = R^5 = R^6 = H; R^3 = OMe(S)[30]

13: R^1 = R^2 = Me; R^3 = R^4 = R^6 = H; R^5 = OMe(R and S)[31]

14: R^1 = R^2 = Me; R^3 = R^5 = H; R^4 = OMe(S)[32]

15: R^1 = CH_2COO-t-Bu; R^2 = R^3 = R^4 = R^6 = H; R^5 = OMe(S)[33]



16: R^1 = Me; R^2 = COOMe(R)[6a,b]

17: R^1 = Et; R^2 = COOMe(S)[34]

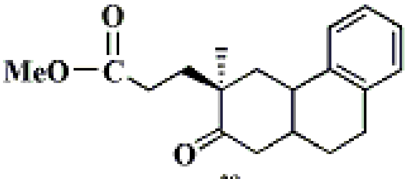
R^1 = Me(R) or OMe(S); R^2 = CN[35]

R^1 = OMe or OCH_2Ph; R^2 = COOMe(R)[28]

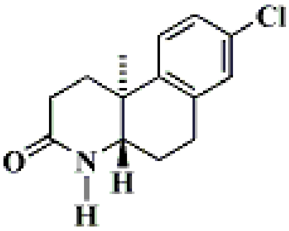
R^1 = R^2 = COMe(S)[36]

R^1 = COOEt; R^2 = COOMe(S),[37] COOEt(R)[36](S),[37]
COO-t-Bu(S),[37] CN(S) (18),[38] COMe(R)[36]

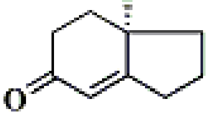
R^1 = COOMe; R^2 = SO_2Ph(S)[39]



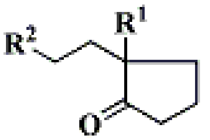
ref. [29]



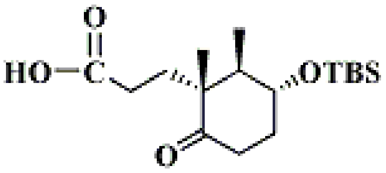
19 (R and S)



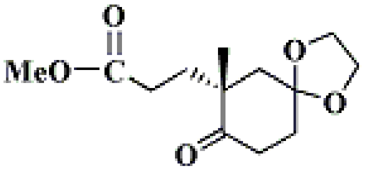
ref. [6a,b]



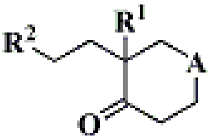
R^1 = Me; R^2 = COOMe(R)[6a,b]
21: R^1 = Et; R^2 = COOMe(S)[42]
R^1 = CH_2COOMe; R^2 = SO_2Ph(S)[43]
R^1 = COOME; R^2 = CN(S),[38] COOMe,[37]
COOEt,[37] COO-t-Bu(S) (22)[37]
23: R^1 = COOMe; R^2 = $(CH_2)_2CO(CH_2)_5Me$(S)[44]



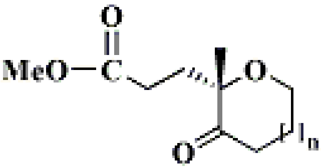
20[41]



ref. 26

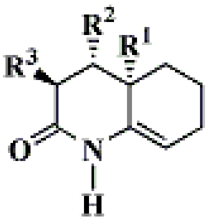


A = NMe; R^1 = R^2 = COOMe or CN(S)[45]
24: A = NBn; R^1 = Me; R^2 = COMe(R and S)[46]
A = S; R^1 = Me or allyl (R and S), Pr(S); R^2 = COOMe[47]
A = S; R^1 = Me, Pr, allyl; R^2 = COMe(R and S)[47]

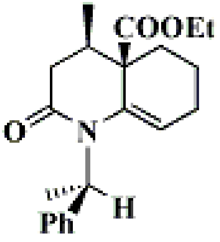


25: n=0[48]
26: n=1[49]

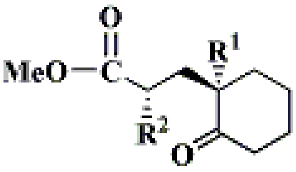
The use of substituted acrylic acid derivatives shows that besides the high enantioselectivity usually observed, the process is also highly diastereoselective, leading to compounds such as **27-32**.



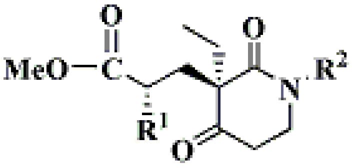
27: R^1=R^2=Me; R^3=H[50]
28: R^1=R^3=Me; R^2=H[50]



29[51]



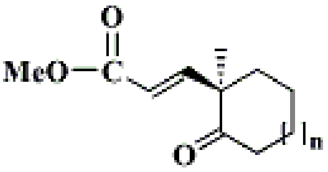
30: R^1=Me; R^2=Me[50], OAc[52]
31: R^1=COOMe; R^2=Me[53]



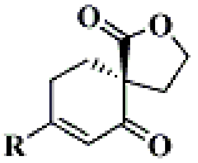
32: R^1=OAc; R^2=Tr[54]
33: R^1=H; R^2=Tr(34)[54] or i-Pr[55]

An acetylenic electrophile such as methyl propiolate leads to unsaturated compounds **35** and **36**.

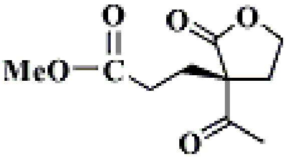
Linear β-ketoesters and lactones lead to compounds such as **37-39**.



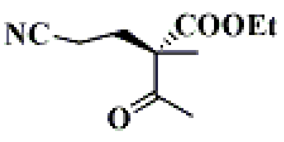
35: n=1[56]
36: n=0[57]



37: R=H, Me[58a]

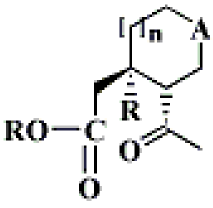


38[58a]

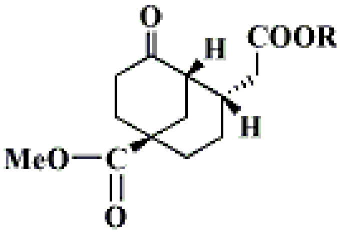


39[58b]

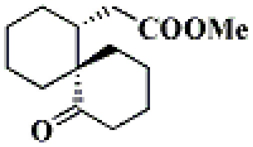
Compounds **40-45** arise from an analogous but intramolecular reaction. A special application of the chiral imine procedure, i.e., the use of an oxaziridine rather than an electrophilic olefin, yielding compound **46**, has been reported.



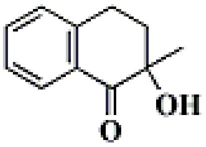
40: n=1; A = NCH_2Ph; R = Et (R,R) and (S,S)[59a,b,d,f]
41: n=1; A = CH_2; R = Me[60]
42: n=0; A = NCH_2Ph[59c,d,f] or NCH_2Tr,[59e,f] R = Et(R,R) and (S,S)
43: n=0; A = CH_2; R = Me[60]



44: R=Me, Bn[61]



45[62]



46: (-)[63]

Several of these chiral non racemic compounds were used for the synthesis of bilogically active products. Thus, (R)- and (S)-dimethyloctalones **5** lead respectively to natural and ent-geosmin.[31] The (R)-enantiomer is also a precursor for the formal synthesis of isocostic and 3-isocostic acid[32] while the (S)-enantiomer would lead to tuberiferine[33] and was actually used to synthesize (–)-TMD, a specific inhibitor of the cholesterol biosynthesis.[34] (S,S)-Dimethyloctalone **6** (a natural compound) leads to a natural octalin[31] and would lead to α-vetispirene[35] while the (R,R)-enantiomer would lead to frullanolide.[36] Compound **7** (R,R) is a precursor for the formal synthesis of muzigadial[27] while the (S,S)-enantiomer would lead to polygodial[27] and warburganal.[27] (+)-α-Cyperone **8** has been widely used as a starting material for the synthesis of many other sesquiterpenes[37] and was in particular converted to ent-allohedycaryol.[38] Compound **9** was transformed into a C_2-symmetric chiral dione[39] while compound **10** was the starting material for the synthesis of (–)-polywood.[34] Tricyclic compounds **11** and **12** were used respectively to synthesize a ring C aromatic steroid[40] and a key [ABC] steroid intermediate[41] while compounds **13** were transformed into isosteres of aphidicolin as potential antiherpes agents.[42] Methoxyketone **14** was converted to a precursor of bruceantin[43] and compound **15** was used for the preparation of a 14-hydroxymorphinan derivative.[44] (R)-Ketoester **16** is a key building block for the synthesis of (+)-cassiol,[45] a potent antiulcerogenic agent, tridensone,[46] and (–)-19-noraspidospermidine,[47] while **17** led to (+)-aspidospermidine.[48] Compound **18** was converted to (–)-nitramine.[49,14] Lactams **19** show potent inhibition of the recombinant human type-1 steroid 5α-reductase. Compound **20** was used to perform the first synthesis of (+)-petasine and (+)-isopetasine, potent antiinflammatory and spasmolytic agents.[50] Ketoester **21** is an intermediate for the formal

total synthesis of vallesamidine.[51] Ketodiesters **22** or **23** led to the marine antibiotic (–)-malyngolide.[52] Aza-heterocycles **24** were used to synthesize substituted isoquinoline derivatives which were evaluated as potential inhibitors of 2,3-oxidosqualene lanosterol cyclase[53] while oxo-heterocycles **25** and **26** have been used respectively for the synthesis of the mycotoxin, (–)vertinolide[54] and of a subunit of marine polyethers toxins[55] as well as to advanced intermediates for the synthesis of the anti-fertility agent, zoapatanol.[56] Compounds **32** and **34** lead to precursors of *Vinca* and *Hunteria* alkaloids.[57] Ethylenic compounds **35** and **36** were used respectively for the total synthesis of both riccardiphenols A and B[58] and isocuparene.[59] Acyclic compound **39** was converted to a nipecotic acid derivative.[60] (R,R)-**40** is a common intermediate in the total synthesis of (–)-ajmalicine and (–)-tetrahydroalstonine[61,62,63] as well as of (+)-yohimbine,[64,62,63] (–)-ochropposinine,[63] and (–)-emetine[62,63] while (S,S)-**40** leads to (–)-(10R)-hydroxydihydroquinine.[61,62,63]

656667686970717273747576777879808182838485868 7

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

petroleum ether

brine

(S)-(−)-α-methylbenzylamine

β-gorgonene

widdrol

thujopsene

7-hydroxycostal

β-selinene

costol

costal

costic acid

norketoagarofuran

β-eudesmol

polygodial

warburganal

penitrem D

isocostic and 3-isocostic acid

tuberiferine

(–)-TMD

octalin

α-vetispirene

frullanolide

muzigadial

(+)-α-Cyperone

ent-allohedycaryol

bruceantin

(+)-cassiol

tridensone

(–)-19-noraspidospermidine

(+)-aspidospermidine

(–)-nitramine

5α-reductase

(+)-petasine

(+)-isopetasine

vallesamidine

(–)-malyngolide

2,3-oxidosqualene lanosterol cyclase

mycotoxin

(–)vertinolide

zoapatanol

isocuparene

(–)-ajmalicine

(–)-tetrahydroalstonine

(–)-ochropposinine

(–)-emetine

(–)-(10R)-hydroxydihydroquinine

ethanol (64-17-5)

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether (60-29-7)

sodium acetate (127-09-3)

sodium hydroxide (1310-73-2)

hydroquinone (123-31-9)

oxygen (7782-44-7)

nitrogen (7727-37-9)

sodium methoxide (124-41-4)

toluene (108-88-3)

Pentane (109-66-0)

magnesium sulfate (7487-88-9)

hexane (110-54-3)

methyl vinyl ketone (78-94-4)

2-methylcyclohexanone (583-60-8)

oxaziridine

methyl propiolate (922-67-8)

(R)-(–)-10-METHYL-1(9)-OCTAL-2-ONE, 2(3H)-Naphthalenone, 4,4a,5,6,7,8-hexahydro-4a-methyl-, (R)- (63975-59-7)

(R)-(+)-2-Methyl-2-(3-oxobutyl)cyclohexanone (91306-30-8)

(+)-yohimbine

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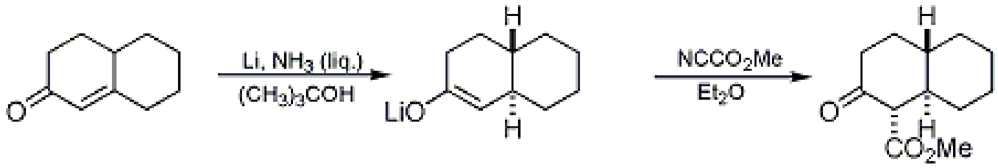
Organic Syntheses, CV 9, 619

SYNTHESIS OF β-KETO ESTERS BY C-ACYLATION OF PREFORMED ENOLATES WITH METHYL CYANOFORMATE: PREPARATION OF METHYL (1α,4aβ,8aα)-2-OXODECAHYDRO-1-NAPHTHOATE



1 **2** **3**

Submitted by Simon R. Crabtree, Lewis N. Mander, and S. Paul Sethi[1].
Checked by Thierry Vandenheste and Leo A. Paquette.

1. Procedure

CAUTION! Cyanide salts are formed in this procedure. All procedures should be conducted in a well-ventilated hood and rubber gloves should be worn.

Liquid ammonia (350 mL) is dried over sodium amide for 20 min (Note 1), then distilled under a positive pressure of dry nitrogen into a flame-dried, 1-L, three-necked, round-bottomed flask equipped with a dry ice condenser, rubber septum and magnetic stirring bar. The flask is cooled to −78°C and small pieces of lithium (1.11 g, 0.16 mol) (Note 2) are added over 10 min to afford a deep blue solution. A solution of enone **1** (10.08 g, 0.07 mol) (Note 3) in tert-butyl alcohol (5.10 g, 0.07 mol) (Note 4) and ether (40 mL) (Note 5) is added dropwise over a 15-min period at −78°C, and then sufficient isoprene (Note 6) is added dropwise to discharge the residual blue color of the reaction mixture. The ammonia is allowed to evaporate under a stream of dry nitrogen and the ether is removed under reduced pressure to leave a white foam. After a further 5 min under high vacuum, the nitrogen atmosphere is restored, the lithium enolate **2** is suspended in dry ether (80 mL) at −78°C by vigorous stirring, and methyl cyanoformate (6.73 g, 0.08 mol) (Note 7) is added over a 5-min period. Stirring is maintained at this temperature for a further 40 min and then the mixture is allowed to warm to 0°C. Water (500 mL) and ether (200 mL) are added and the mixture is stirred vigorously until the precipitate has dissolved. After separation of the organic layer, the aqueous phase is extracted with ether (2 × 300 mL), the combined extracts are washed with water (200 mL) and brine (200 mL) (Note 8), and then dried over anhydrous magnesium sulfate. Removal of solvent under reduced pressure furnishes a pale yellow oil which is dissolved in hexane (200 mL); the solution is kept in the freezer (−28°C) for approximately 1.5 hr, after which time very pale yellow crystals of the β-keto ester **3** are deposited. These are collected by filtration at low temperature and after concentration of the mother liquors, two further crops are collected. Flash chromatography (ethyl acetate/hexane, 13:87) on silica gel (140 g) (Note 9) of the residue (3.5 g) from the remaining mother liquor followed by two recrystallizations affords further **3**. The total quantity of **3** obtained is 11.5–11.8 g (81–84% yield) (Note 10).

2. Notes

1. Sodium amide is generated in situ from sodium metal and a crystal of ferric nitrate. Sodium metal by itself is not an effective drying agent.
2. Lithium wire was purchased from Merck Schuchardt.
3. Enone **1** was prepared according to the procedure of Augustine, R. L.; Caputo, J. A. *Org. Synth., Coll. Vol. V* **1973**, 869.
4. tert-Butyl alcohol was purchased from Ajax Chemicals and was freshly distilled from calcium hydride.
5. Diethyl ether was purchased from Ajax Chemicals and was freshly distilled from sodium and

benzophenone.
6. Isoprene was purchased from Eastman Kodak, Ltd.
7. Methyl cyanoformate was purchased from the Aldrich Chemical Company, Inc. The ethyl and benzyl analogues are also available. Small quantities up to 30 g are conveniently prepared by the method of Childs and Weber,[2] but several workers have found it to be unsatisfactory on a larger scale because of the generation of inseparable impurities.
8. The aqueous washings contain toxic lithium cyanide and should be treated with a strong oxidizing agent (e.g., potassium permanganate) before disposal.
9. Merck Kieselgel 60 silica gel was used.
10. A sample recrystallized twice from hexane had mp 48–49°C (Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.53; H. 8.63%; Found C, 68.59; H, 8.93). The spectroscopic properties of this product are as follows: IR ($CHCl_3$) cm^{-1}: 3026, 2931, 2859, 1744, 1710, 1454, 1447, 1437, 1364, 1348, 1340, 1155, 1112; ^1H NMR ($CDCl_3$) δ: 1.00–1.50 (m, 6 H), 1.65–1.8 (m, 5 H), 1.9–2.0 (m, 1 H CH), 2.30–2.50 (m, 2 H, CH_2), 3.12 (d, 1 H, J = 12), 3.76 (s, 3 H, OMe). ^{13}C NMR ($CDCl_3$) δ: 25.4, 25.9, 32.6, 32.9, 33.3, 40.5, 41.4, 45.5, 51.8, 53.8, 170.2, 205.6; MS (m/z): 210 (M^+, 34.6%), 192 (72), 122 (66), 108 (59), 95 (68), 94 (94), 81 (100), 79 (53), 67 (77), 51 (61).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995. See (Note 8).

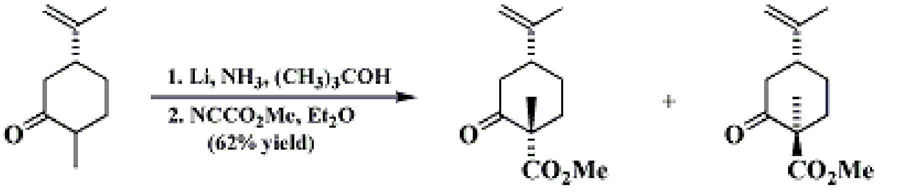
3. Discussion

The present procedure provides an example of the regiospecific synthesis of β-keto esters by the C-acylation of preformed lithium enolates with cyanoformate esters.[3] The enolates can be generated in a variety of ways, including direct enolization of ketones with suitable bases, liberation from silyl enol ethers and acetates, conjugate additions of cuprates to α,β-unsaturated enones and by the reduction of enones by lithium in liquid ammonia, as in the example described above. The more traditional acylating agents (acyl halides and anhydrides) afford variable amounts of O-acylated products[4] and although the use of reaction temperatures of −100°C is reported to obviate this problem with some substrates,[5] the method does not appear to be general. The classical solution has been to use carbon dioxide followed by esterification,[6] but yields rarely exceed 50%, indicating, *inter alia*, that the formation of enol carbonates probably occurs to a significant extent and that these unstable intermediates decompose to ketones on work up.[7] There is also the problem of handling thermally unstable β-keto acids. Carbon disulfide[8] and carbon oxysulfide[9] have been used instead of carbon dioxide, and the products methylated in situ to form dithio and thio esters, respectively. These can subsequently be converted into methyl esters by mercury(II) diacetate-catalyzed transesterification in methanol, but the methods are elaborate and do not appear to have found general use. Diethyl dicarbonate and its analogues show promise as possible alternatives to cyanoformates, but the reported yields to date are inferior.[10]

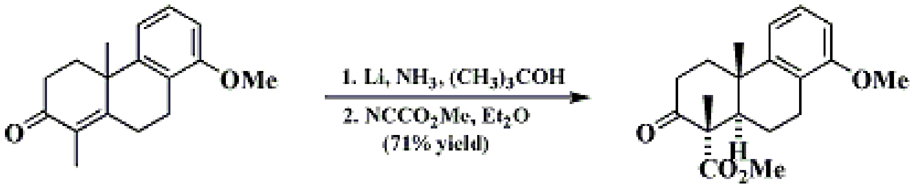
In the early investigations of this reaction it was found that in one comparative study of lithium, sodium and potassium enolates, only the lithium derivatives reacted satisfactorily,[3] although sodium enolates have subsequently been used successfully.[11] A range of cyanoformates can be employed, but the tert-butyl derivatives have been reported to be too unreactive. However, a satisfactory substitute which affords esters that can be de-alkylated with comparable facility is the p-methoxybenzyl analogue,[12 13] although it is prepared with some difficulty. In general, benzyl derivatives seem to give slightly better yields, possibly due to the more efficient isolation of products from substrates with lower molecular weights. Optically active cyanoformates derived from (+)-menthol, (−)-borneol, and the Oppolzer alcohol were reported to furnish good chemical yields, but the level of stereoselectivity was disappointingly low.[14]

For more conformationally-constrained chiral substrates, however, diastereoselectivity can be expected to be good to excellent. Lithium enolates derived from sterically unencumbered cyclohexanones undergo preferential axial acylation as illustrated by the reductive acylation of (R)-(−)-carvone **4** to afford a 3:1 mixture of esters **5**

and **6**, whereas equatorial acylation is favored in compounds that possess an alkyl substituent in a 1,3-syn-axial relationship to the reacting center, as in the conversion of tricyclic enone **7** to ester **8** (epimeric with the product from the more traditional sequence of acylation followed by alkylation).[15] (In substrates of this kind it is assumed that the transition state structure is based on a twist-boat conformation which permits the reagent to approach along an axial-like trajectory on the less encumbered, lower face of the substrate.)[16]

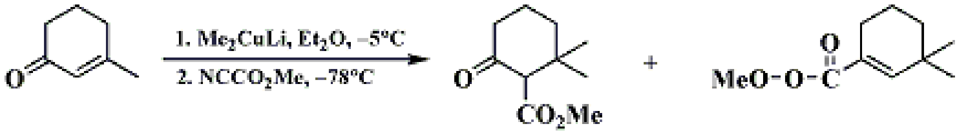


4   5 (75% ds)   6 (25% ds)



7   8 (>98% ds)

For compounds in which the β-carbon of the enolate is sterically hindered, this problem can normally be eliminated by the use of diethyl ether as the solvent. In several cases a switch from exclusive O-acylation in tetrahydrofuran to complete C-acylation in ether has been observed, and the conversion of **7** into **8** provides a typical illustration. When 3-methyl-2-cyclohexen-1-one **9** is converted into **10** by the addition of lithium dimethyl cuprate followed by in situ reaction with methyl cyanoformate, however, enol carbonate **11** accounts for 6% of the products. This can be avoided if the intermediate enolate is trapped as the enol trimethylsilyl ether and the enolate reliberated by treatment with butyllithium (note that the traditional reagent, methyllithium, is ineffective in ether as a solvent), but the overall yield is reduced.

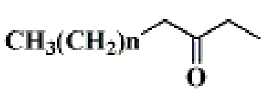
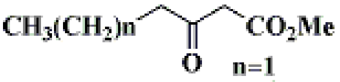


9   10 (78% yield)   11 (6% yield)

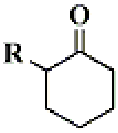
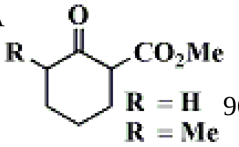
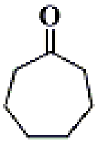
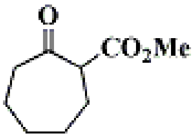
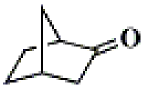
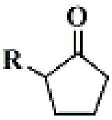
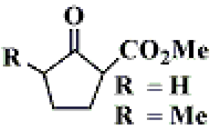
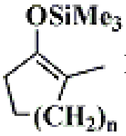
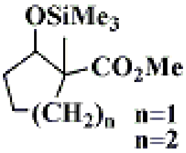
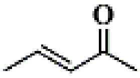
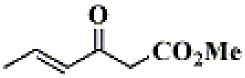
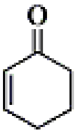
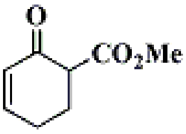
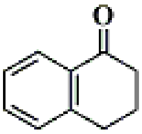
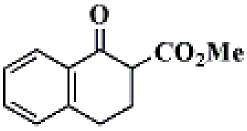
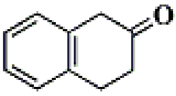
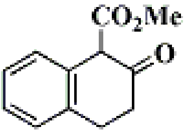
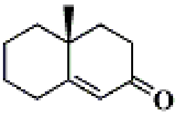
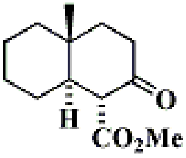
Quite apart from the issue of regioselectivity, the present method is exceptionally reliable and makes it possible to prepare β-keto esters from ketones under especially mild conditions. It is not only the method of choice with sensitive substrates, but will often ensure superior results with more stable intermediates as well.[8,17] A wide range of examples is provided in the Table, while further examples have been reported elsewhere.[18 19 20] The methodology has also been applied to esters,[12,13] lactones,[21] phosphonates,[22 23] imines[24] and the N-acylation of lactams.[25] The formation of β-diketones by the treatment of lithium enolates with alkanoyl and aroyl nitriles has also been described.[26]

TABLE

PREPARATION OF β-KETO-ESTERS BY THE KINETICALLY CONTROLLED C-ACYLATION OF LITHIUM ENOLATES WITH METHYL CYANOFORMATE

Entry	Substrate	Procedure‡	Product	Yield (%)	
1		A	 n=1 n=4	84	86

8686

2		A		96
3		A		
4		A		85
5		A		71 75
6		B		7268
7		A		65
8		A		84
9		A		92
10		A		92
11		C		85

‡Procedures: **A**: Reference; **B**: Lithium enolates generated by addition of methyllithium in THF at −78°C; **C**: As described for the conversation of enone **1** into β-keto ester **3**.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

carbon oxysulfide

brine

(R)-(−)-carvone

(−)-borneol

lithium dimethyl cuprate

ammonia (7664-41-7)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether, diethyl ether (60-29-7)

potassium permanganate (7722-64-7)

nitrogen (7727-37-9)

mercury(II) diacetate (1600-27-7)

carbon dioxide (124-38-9)

Benzophenone (119-61-9)

sodium (13966-32-0)

carbon disulfide (75-15-0)

(+)-menthol (15356-60-2)

lithium (7439-93-2)

magnesium sulfate (7487-88-9)

sodium amide (7782-92-5)

butyllithium (109-72-8)

Tetrahydrofuran, THF (109-99-9)

ferric nitrate

ISOPRENE (78-79-5)

hexane (110-54-3)

Methyllithium (917-54-4)

tert-butyl alcohol (75-65-0)

calcium hydride (7789-78-8)

3-methyl-2-cyclohexen-1-one

lithium cyanide

METHYL CYANOFORMATE (17640-15-2)

Methyl (1α,4aβ,8aα)-2-oxodecahydro-1-naphthoate (147086-16-6)

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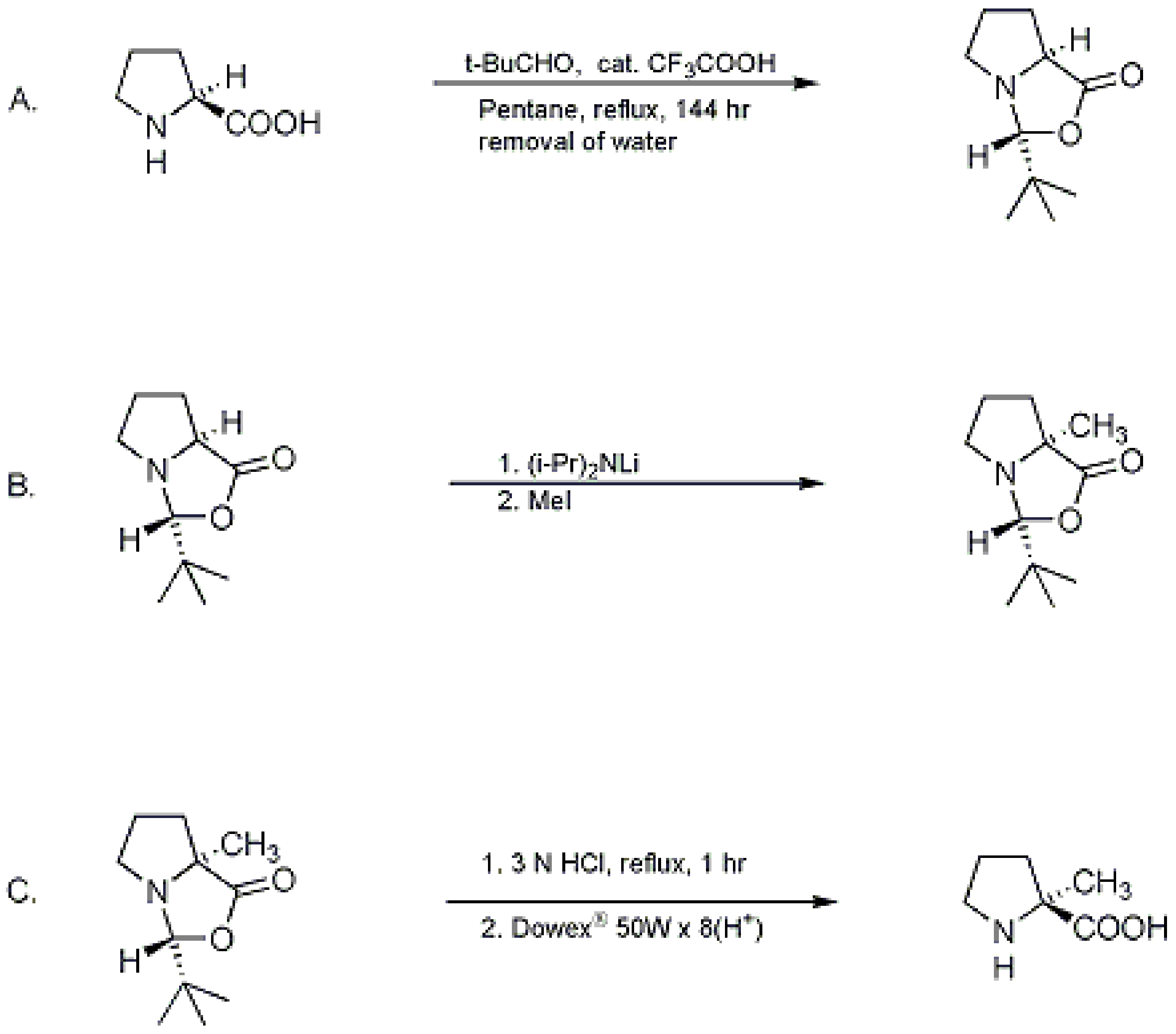
Organic Syntheses, CV 9, 626

SYNTHESIS OF (S)-2-METHYLPROLINE: A GENERAL METHOD FOR THE PREPARATION OF α-BRANCHED AMINO ACIDS

[L-Proline, 2-methyl-]



Submitted by A. K. Beck, S. Blank, K. Job, D. Seebach, and Th. Sommerfeld[1].
Checked by Frank Narjes and Larry E. Overman.

1. Procedure

A. *(2R,5S)-2-tert-Butyl-1-aza-3-oxabicyclo[3.3.0]octan-4-one*. To a suspension of 40.0 g (0.347 mol) of (S)-proline (Note 1) in 1400 mL of pentane (Note 2) in a 2.5-L, round-bottomed flask are added 225 mL (2.072 mol) of pivalaldehyde (Note 3) and 3.0 mL (38.9 mmol) of trifluoroacetic acid. The mixture is heated at reflux for 72 hr with azeotropic removal of the water formed (Dean-Stark trap). After the addition of another 40.0 mL (0.368 mol) of pivalaldehyde, 1 mL of trifluoroacetic acid (13.0

mmol), and 200 mL of pentane (Note 4), refluxing is continued for an additional 72 hr. Water, 5.4 mL total, is collected. After the reaction mixture is cooled to room temperature, it is filtered under argon (Note 5). The resulting clear solution is concentrated in a 1000-mL flask under reduced pressure. The residue is distilled in a Kugelrohr oven (70°C/0.0005 mm) (Note 6) and (Note 7) to afford 42.5–47.0 g (0.232–0.257 mol, 67–74%) of the desired product as a colorless oil (Note 8) and (Note 9).

B. *(2R,5S)-2-tert-Butyl-5-methyl-1-aza-3-oxabicyclo[3.3.0]octan-4-one*. In a 250-mL, round-bottomed flask equipped with a magnetic stirrer, 18.3 mL (0.131 mol) of diisopropylamine (Note 10) is mixed with 120 mL of dry tetrahydrofuran (THF, (Note 11)) under argon. At −78°C bath temperature, 88.6 mL of a 1.6 M solution of butyllithium (0.142 mol) in hexane is added and the mixture is allowed to warm to room temperature for 20 min. After the mixture is recooled to −78°C, the lithium diisopropylamide (LDA) solution is added over a period of 20 min (Note 12) to a solution of 20.0 g (0.109 mol) of (2R,5S)-2-tert-butyl-1-aza-3-oxabicyclo[3.3.0]octan-4-one in 600 mL of dry THF in a 1-L, round-bottomed flask, precooled to −78°C. Tetrahydrofuran (20 mL) is used to rinse the 250-mL flask. After keeping the resulting solution at −78°C for 45 min, 8.8 mL (0.142 mol) of iodomethane (Note 13) is added over a period of 10 min. The resulting mixture is allowed to warm to 0°C over a period of 3 hr, and 300 mL of a saturated aqueous solution of ammonium chloride is added. After separation, the organic layer is washed with 300 mL each of saturated aqueous solutions of sodium carbonate and brine. Each aqueous layer is extracted twice with 200 mL of ethyl acetate. The combined organic layers are dried over magnesium sulfate and the solvent is removed in a rotary evaporator at ca. 15 mm. Traces of solvent are removed by drying the residue at 60°C/0.05 mm for 2 hr under an oil pump vacuum to yield 19.8–20.5 g (0.100–0.104 mol, 93–95%) of the desired product. It is used directly in the next step (Note 14).

C. *(S)-2-Methylproline*. In a 1-L, round-bottomed flask, 20.1 g (0.102 mol) of (2R,5S)-2-tert-butyl-5-methyl-1-aza-3-oxabicyclo[3.3.0]octan-4-one in 400 mL of 3 N hydrochloric acid (HCl) is heated to reflux for 1 hr. The water is removed under reduced pressure in a rotary evaporator (ca. 15 mm). The dark residue is treated with 400 mL of 3 N HCl and extracted four times with 200 mL each of dichloromethane (CH_2Cl_2). The combined organic layers are washed once with 200 mL of 3 N HCl. The combined aqueous layers are concentrated and dried under reduced pressure in a rotary evaporator at elevated temperature (60°C at 15 mm). The residue is suspended in 50 mL of water and adsorbed on 600 g of Dowex 50W × 8 (H^+ form) (Note 15) in a 50 × 380-mm column. Water is passed through the column. After 200 mL of effluent, the pH changes to 2; after another 700 mL, the pH of the effluent is 7. The amino acid is then eluted with 3 N aqueous ammonia. After 500 mL of effluent, the developing hot front reaches the outlet. The following 2000 mL are collected and yield 12.0–12.3 g of the amino acid, free of inorganic salts, after removal of the water (Note 16) and (Note 17). The 500 mL of water collected subsequently contains another 0.34 g, yielding altogether 93–98 mmol [85–90% from (2R,5S)-2-tert-butyl-1-aza-3-

oxabicyclo[3.3.0]octan-4-one] of (S)-2-methylproline, $[\alpha]_D^{RT}$ −71.1° to −72.1° (MeOH, *c* 1.0), mp 248–252°C (dec). The enantiomeric excess (ee) of a sample with a rotation of −72.1° was shown to be 99.0 ± 0.5% by capillary gas chromatographic analysis of a derivative (Note 18) using a chiral column (Note 19) (see f.htmigure 1).

Figure 1. Gas chromatograms for the determination of the enantiomeric purity of the derivatives of 2-methylproline (Note 18) and (Note 19): A) (R)- and (S)-2-methylproline; B) (S)-2-methylproline; (C) (R)-2-methylproline; D) 1% (R)- in (S)-2-methylproline.

Figure 1. Gas chromatograms for the determination of the enantiomeric purity of the derivatives of 2-methylproline and : A) (R)- and (S)-2-methylproline; B) (S)-2-methylproline; (C) (R)-2-methylproline; D) 1% (R)- in (S)-2-methylproline.

2. Notes

1. (S)-Proline was used as commercially available. The submitters obtained (S)-proline from Degussa AG (D-Hanau), while the checkers used material from Aldrich Chemical Company, Inc.
2. When higher boiling solvents such as cyclohexane are used, the reaction is complete earlier, but side-products can be detected that are difficult to remove from the reaction mixture and that tend to catalyze decomposition of the desired product.
3. Commercially available material can be used. As pure pivalaldehyde is expensive, the submitters used technical grade as provided by BASF AG (D-Ludwigshafen). The material was washed with water (to remove alcohol impurities) and distilled before use. The checkers used material from Aldrich Chemical Company, Inc., without purification.
4. Pentane has to be replenished since some is lost from the reaction mixture because of its low boiling point and the prolonged heating period.
5. Since the product is extremely sensitive to hydrolysis, contact with air and moisture have to be avoided. Thus, the reaction mixture was filtered through a funnel under a stream of argon.
6. The use of an Aldrich Kugelrohr oven allowed for distillation in a large flask. This is advantageous, since decomposition may ensue above 100°C.[2] For this reason distillation has to be carried out at as low a pressure as possible. In most cases the submitters used a turbo pump, but application of a normal high

vacuum pump with a distillation temperature of 90°C at 0.04 mm is also possible.

7. To recover part of the excess pivalaldehyde, the material that was collected in the cooling trap used with the rotary evaporator and with the Kugelrohr oven can be distilled through a 35-cm Vigreux column; this yielded 150 mL of recovered pivalaldehyde.

8. The spectrum is as follows: ^1H NMR (200 MHz, $CDCl_3$) δ: 1.55–2.25 (m, 4 H), 2.98 [(m (centered), 2 H)], 3.78 (dd, 1 H, J = 9, 5), 4.49 (s, 1 H). Additional analytical data are given in ref. [3].

9. As described in (Note 5) above, the product hydrolyzes on contact with moisture (the clear liquid turns milky at the surface). Therefore any transfer of this compound must be carried out under argon and the product must be stored under an inert atmosphere in a refrigerator.

10. Diisopropylamine was distilled over calcium hydride and stored under argon before use.

11. THF was freshly distilled under argon over potassium or sodium/ benzophenone.

12. For addition of the LDA solution, either a bowed metal needle or a Teflon cannula (2 mm diameter) can be used. See ref. [4] for a diagram of the set up.

13. Iodomethane was filtered through neutral aluminum oxide (the submitters used Alumina Woelm B, Akt. I) directly before use to remove moisture and decomposition products. (A layer of brown material was found on top of the aluminum oxide when the iodomethane had not been freshly distilled.)

14. A pure sample for determining the analytical data of this bicyclic product was obtained by Kugelrohr distillation (bp 85°C at 0.05 mm). The spectrum is as follows: ^1H NMR (200 MHz, $CDCl_3$) δ: 0.88 (s, 9 H), 1.36 (s, 3 H), 1.60–1.90 (m, 3 H), 2.10–2.25 (m, 1 H), 2.75–2.90 (m, 1 H), 3.05–3.20 (m, 1 H), 4.24 (s, 1 H). Further data for this compound are available in Ref. [3].

15. Dowex 50W × 8 (Na^+ form), as purchased from Fluka AG or recovered from previous use, is stirred for 30 min with ca. 6 N HCl, washed until nearly neutral, stirred with ca. 6 N ammonium hydroxide, washed with water, then stirred a second time with ca. 6 N HCl and washed until neutral (pH 7). The resin thus obtained is used directly.

16. Though yellow-colored, the 2-methylproline thus obtained is spectroscopically pure (according to the ^1H and ^{13}C NMR spectra, see (Note 17)). It can be further purified by dissolution in methanol with 5% w/w activated charcoal and filtration of the resulting suspension through Celite. In spite of the poor crystallizing tendency of most amino acids, 2-methylproline can be recrystallized from methanol/ethyl acetate to yield colorless platelets.

17. The spectra are as follows: ^1H NMR (200 MHz, D_2O, HDO = 4.80) δ: 1.52 (s, 3 H), 1.75–2.40 (m, 4 H), 3.20–3.45 (m, 2 H); ^{13}C NMR (50 MHz, D_2O) δ: 23.99, 25.85, 38.27, 48.06, 73.21, 179.87.

18. For gas chromatography, derivatives of the two enantiomers of the amino acid (the isopropyl amido isopropyl amides) were obtained according to the

procedure developed by König:[5 6 7] In a 1-mL, sealed flask, 5 mg of the amino acid is treated with 0.3 mL of CH_2Cl_2 and 0.3 mL of isopropyl isocyanate at 100°C for 15 min. After the solution is cooled, both CH_2Cl_2 and excess isopropyl isocyanate are driven out by a strong stream of dry air. The residue is treated with 1 mL of diethyl ether and the resulting suspension is filtered through cotton wool. The solution can be used directly for determination of the ee by GC. This analysis was not checked by the checkers.

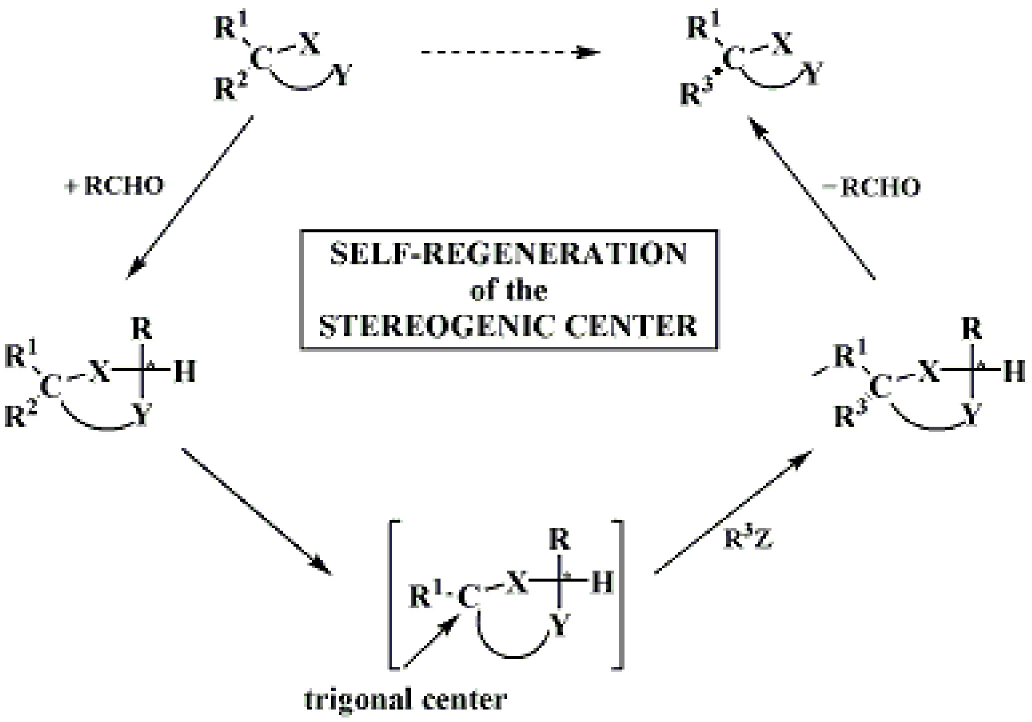
19. The solution, 10 •L, prepared as outlined in (Note 18) was loaded on a Chirasil-Val fused-silica capillary column of Machery-Nagel (25 m, 0.4 mm) in a Carlo-Erba-Fraktovap 4160 HR GC. After 5 min at 160°C, the column temperature was increased by 2°C per min up to 200°C.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

rac-2-Methylproline has been obtained previously by Ellington and Honigberg[8] from 5-(3-hydroxypropyl)-5-methylhydantoin. For other preparations of enantiopure 2-methylproline see references [9 10] and [11]. Methylation of proline with retention of configuration as described here is an example of a general principle that has been applied to chiral α- and β-HX-substituted carboxylic acids (X = NH, O, S).[12 13 14 15 16 17 18 19,20 21 22,23 24] It involves a three-step sequence: diastereoselective conversion of the enantiopure carboxylic acid to a cyclic acetal derivative, diastereoselective replacement of one of the substituents on the original asymmetric carbon atom, and cleavage of the acetal. Since no chiral auxiliary molecule is employed in the procedure, in which the one and only chirality center of the starting material is temporarily eliminated (i.e., converted to a trigonal center), the overall transformation has been called self-regeneration of a stereogenic center,[25 26 27] as shown in the accompanying scheme.



The intermediate trigonal center may be cationic, radical, anionic, or part of a double bond. By this methodology, the large supply of simple, mostly naturally occurring enantiopure compounds ("chiral pool"[28]) can be used in many ways.[12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27]

α-Methylproline is an especially interesting α-branched amino acid for the synthesis of peptides and proteins that show an unusual stability to proteases.[29] Moreover incorporation of α-methylproline into a peptide to replace proline in a β-turn causes a significant increase in stability of this particular structural element.[30,31 32 33 34]

Following exactly the same procedure, Parts A, B and C, but starting with (R)-proline gives (R)-2-methylproline, $[\alpha]_D^{RT}$ +73.1° (MeOH, *c* 1.7) in an overall yield of 55%.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

brine

LDA

(R)- and (S)-2-methylproline

rac-2-Methylproline

hydrochloric acid, HCl (7647-01-0)

ammonia (7664-41-7)

ethyl acetate (141-78-6)

methanol (67-56-1)

diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

sodium carbonate (497-19-8)

cyclohexane (110-82-7)

Benzophenone (119-61-9)

sodium (13966-32-0)

ammonium hydroxide (1336-21-6)

potassium (7440-09-7)

iodomethane (74-88-4)

Pentane (109-66-0)

dichloromethane, CH_2Cl_2 (75-09-2)

magnesium sulfate (7487-88-9)

aluminum oxide (1344-28-1)

butyllithium (109-72-8)

proline, (S)-proline (147-85-3)

Tetrahydrofuran, THF (109-99-9)

hexane (110-54-3)

calcium hydride (7789-78-8)

trifluoroacetic acid (76-05-1)

argon (7440-37-1)

lithium diisopropylamide (4111-54-0)

diisopropylamine (108-18-9)

pivalaldehyde (630-19-3)

isopropyl isocyanate (1795-48-8)

(R)-proline (344-25-2)

(S)-2-Methylproline, 2-methylproline, (R)-2-methylproline, L-Proline, 2-methyl- (42856-71-3)

(2R,5S)-2-tert-Butyl-1-aza-3-oxabicyclo[3.3.0]octan-4-one (81286-82-0)

(2R,5S)-2-tert-Butyl-5-methyl-1-aza-3-oxabicyclo[3.3.0]octan-4-one (86046-11-9)

5-(3-hydroxypropyl)-5-methylhydantoin

α-Methylproline (475-11-6)

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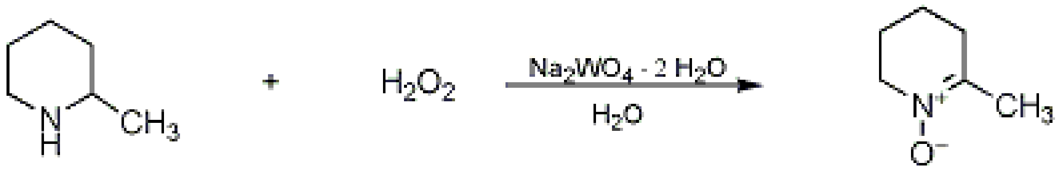
Organic Syntheses, CV 9, 632

OXIDATION OF SECONDARY AMINES TO NITRONES: 6-METHYL-2,3,4,5-TETRAHYDROPYRIDINE N-OXIDE

[Pyridine, 2,3,4,5-tetrahydro-6-methyl-, 1-oxide]



Submitted by Shun-Ichi Murahashi, Tatsuki Shiota, and Yasushi Imada[1].
Checked by Gary C. Look and Larry E. Overman.

1. Procedure

In a 500-mL, three-necked, round-bottomed flask equipped with a 100-mL pressure-equalizing dropping funnel, a thermometer, and a magnetic stirring bar is placed 2.64 g (8.00 mmol) of sodium tungstate dihydrate (Note 1). After the flask is flushed with nitrogen, 40 mL of water and 23.5 mL (200 mmol) of 2-methylpiperidine (Note 2) are added. The flask is cooled with an ice-salt bath to −5°C (internal temperature) and 45.0 mL (440 mmol) of 30% aqueous hydrogen peroxide solution (Note 3) is added dropwise over a period of ca. 30 min. During the period of addition the reaction mixture should be carefully kept at a temperature below 20°C (Note 4). The cooling bath is removed, and the mixture is stirred for 3 hr (Note 5). Excess hydrogen peroxide is decomposed by adding ca. 3 g of sodium hydrogen sulfite with ice cooling (Note 6). The solution is saturated by adding ca. 25 g of sodium chloride and extracted with ten 200-mL portions of dichloromethane (Note 7). Combined organic extracts are dried over anhydrous sodium sulfate. The drying agent is removed by filtration, and the solvent is removed by a rotary evaporator keeping the temperature at 40°C (Note 8) to give a pale yellow oil (20.0–22.0 g), which may be sufficiently pure for some applications (Note 9). Purification of the nitrone is achieved by column chromatography on 300 g of silica gel packed in 97:3 chloroform/methanol in a 4.8-cm × 70-cm column (Note 10). The product is applied to the column in 10 mL of chloroform and the column is eluted with 97:3 chloroform/methanol. After twenty 100-mL fractions are collected, the eluent is changed to 8:2 chloroform/methanol, and another ten 100-mL fractions are collected and analyzed by thin layer chromatography (Note 11). Combination of fractions 16–30 and evaporation provides 14.0–15.7 g (62–70%) of pure 6-methyl-2,3,4,5-tetrahydropyridine N-oxide as a pale yellow oil (Note 12) and (Note 13).

2. Notes

1. Sodium tungstate dihydrate was purchased from Wako Pure Chemical Ind., Ltd. and used without further purification. The checkers employed material purchased from Mallinckrodt, Inc.
2. 2-Methylpiperidine purchased from Nacalai Tesque, Inc. was distilled prior to use (bp 119–120°C). The checkers employed 2-methylpiperidine purchased from Aldrich Chemical Company, Inc.
3. The 30% aqueous solution of hydrogen peroxide was purchased from Mitsubishi Gas Chemical Company, Inc. or Fisher Scientific. Ten percent excess of hydrogen peroxide is used to complete the reaction within an appropriate time.
4. This is an exothermic reaction. Higher reaction temperatures cause partial decomposition of the product.
5. The reaction mixture consists of the desired nitrone and 6–15% of isomeric 2-methyl-2,3,4,5-tetrahydropyridine N-oxide: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.53 (d, 3 H, J = 6.9, $-CH_3$), 7.14 (t, 1 H, J = 3.9, -CH=N-).
6. The presence of hydrogen peroxide is detected with potassium iodide-starch test paper.
7. Extraction with five 200-mL portions of dichloromethane gives 20–21 g of the product. Oxidation of secondary amines which have low molecular weights requires water as solvent. The nitrones thus obtained are highly soluble in water, and many extractions are required. However, other nitrones can be isolated easily by simple extraction.
8. Higher temperatures cause decomposition of the desired product, and lower temperatures retard the decomposition of the undesired nitrone to give the dimeric compound.
9. The crude nitrone consists of the desired nitrone (85–70%), the 1:1 adduct of the less substituted nitrone with the desired nitrone [(3,14-dimethyl-2,9-dioxa-1,8-diazatricyclo[8.4.0.0^{3,8}]tetradecane) (15–30%), R_f = 0.39 (TLC glass plate silica gel 60 F_{254}, obtained from E. Merck, 9:1 chloroform/methanol); m/e = 226.1681 ($C_{12}H_{22}N_2O_2$)], and the dimer of the desired nitrone [(3,10-dimethyl-2,9-dioxa-1,8-diazatricyclo[8.4.0.0^{3,8}]tetradecane) (< 1%), mp 87.5–88.0°C; R_f = 0.46 (under the same conditions); m/e = 226.1664]. The checkers found that the crude product decomposed noticeably when stored overnight at –20°C.
10. Silica gel 60 (70-230 mesh) was purchased from E. Merck. The checkers employed flash chromatography using a 20-cm × 7-cm column and 230-400 mesh EM silica gel 60. With this silica gel it is essential to have 1% triethylamine in the eluent.
11. The R_f value of the nitrone is 0.37 (under the same conditions described above).
12. The product has the following spectral characteristics: IR (neat) cm^{-1}: 2945, 1627, 1448, 1190, 1165, 951, 872, 750, a strong OH stretch at 3400 cm^{-1} is also apparent; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.71-1.77 (m, 2 H, H-4), 1.92–1.97 (m, 2 H, H-3), 2.11 (overlapping tt, 3 H, J = 1.5, 1.0, CH_3), 2.42–2.47 (m, 2 H, H-5), 3.78–3.83 (m, 2 H, H-2); ^{13}C NMR ($CDCl_3$, 68 MHz) δ: 18.0 (CH_3), 18.2, 22.7, 30.0 (C-5), 57.3 (C-2), 145.1 (C-6); UV (EtOH) 235 nm (e 6910).

13. The nitrone slowly dimerizes at room temperature. It should be stored as a solution in a solvent such as dichloromethane to prevent dimerization.

Waste Disposal Information

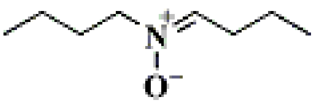
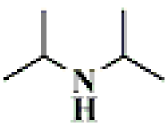
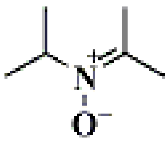
All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

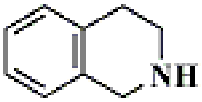
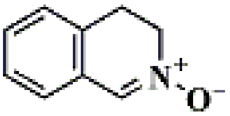
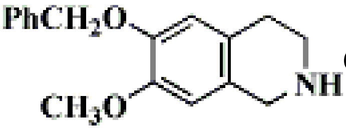
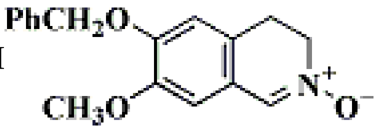
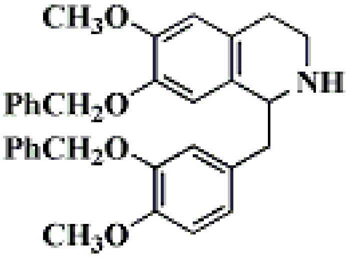
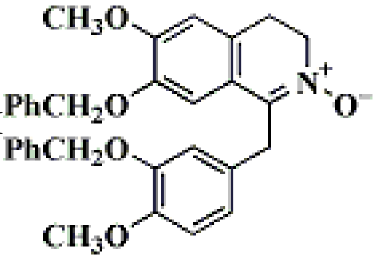
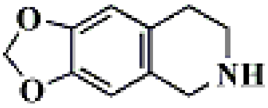
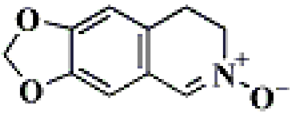
3. Discussion

Nitrones are highly versatile synthetic intermediates and excellent spin trapping reagents.[2 3 4] In particular, nitrones are excellent 1,3-dipoles[5 6 7] and have been used for the synthesis of various nitrogen-containing biologically active compounds.[5,6] The preparation of nitrones has been performed either by condensation of aldehydes or ketones with hydroxylamines,[8] or by oxidation of the corresponding hydroxylamines.[9] The difficulty of these methods is in the preparation of the starting hydroxylamines. For example, cyclic hydroxylamines are prepared from the corresponding cyclic amines via thermal decomposition of the corresponding tertiary amine N-oxides.[10 11]

The present procedure provides a single step synthesis of nitrones from secondary amines.[12] Typical results of the preparation of nitrones are summarized in Table I. If necessary, the nitrones are easily purified by distillation, recrystallization, or column chromatography. Selenium dioxide is also an effective catalyst for the oxidation of secondary amines with hydrogen peroxide to give nitrones.[13] 1,3-Dipolar cycloadducts are obtained directly by the oxidation of secondary amines in the presence of alkenes.

TABLE I
CATALYTIC OXIDATION OF SECONDARY AMINES WITH HYDROGEN PEROXIDE

Amine	Solvent	Product	Yield %
	CH_3OH		89
	CH_3OH		74

	CH_3OH		85
	CH_3OH		85
	CH_3OH		86
	CH_3OH		60
	CH_3OH		62
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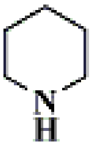
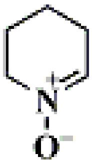
	H_2O		40

The reaction of nitrones with various nucleophiles provides a powerful strategy for the introduction of a substituent at the α-position of secondary amines.[14 15] The reaction of nitrones with Grignard reagents or organolithium compounds affords various α-substituted hydroxylamines, which can be converted into α-substituted secondary amines by catalytic hydrogenation. The nucleophilic reaction with potassium cyanide

gives α-cyanohydroxylamines which are useful precursors for amino acids and N-hydroxyamino acids.[16]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

methanol (67-56-1)

chloroform (67-66-3)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

potassium cyanide (151-50-8)

sodium hydrogen sulfite (7631-90-5)

selenium dioxide (7446-08-4)

hydrogen peroxide (7722-84-1)

dichloromethane (75-09-2)

triethylamine (121-44-8)

sodium tungstate dihydrate (10213-10-2)

6-Methyl-2,3,4,5-tetrahydropyridine N-oxide, Pyridine, 2,3,4,5-tetrahydro-6-methyl-, 1-oxide (55386-67-9)

2-methylpiperidine (109-05-7)

2-methyl-2,3,4,5-tetrahydropyridine N-oxide

3,14-dimethyl-2,9-dioxa-1,8-diazatricyclo[8.4.0.0^{3,8}]tetradecane

3,10-dimethyl-2,9-dioxa-1,8-diazatricyclo[8.4.0.0^{3,8}]tetradecane

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Organic Syntheses, CV 9, 636

NITROACETALDEHYDE DIETHYL ACETAL

[Ethane, 1,1-diethoxy-2-nitro-]

1

Submitted by V. Jäger and P. Poggendorf[1].
Checked by E. Jnoff and Leon Ghosez.

1. Procedure

CAUTION! Distillation of nitromethane and reactions using it as a solvent or a reactant at an elevated temperature, as well as reactions of nitroalkanes in general, should be conducted behind a safety shield. In one instance a minor deflagration was observed upon erroneously aerating the distillation residue while it was still hot. The apparatus, therefore, should only be ventilated after cooling to ambient temperature, and nitrogen, not air, is recommended for this purpose.

A 500-mL, round-bottomed flask, equipped with a magnetic stirring bar, 20-cm Vigreux column, column head, Claisen distilling head, and thermometer, is charged with 89.3 g (602 mmol) of triethyl orthoformate (Note 1), 180 g (2.95 mol) of nitromethane (Note 2), and 5.00 g (36.6 mmol) of anhydrous zinc chloride. The solution is heated to 90°C (oil bath temperature, (Note 3)). After 16 hr (overnight) ca. 30 mL of ethanol is collected (Note 4). The remaining mixture, a brown suspension, is cooled to room temperature, and filtered by suction through a sintered glass funnel. The brown liquid obtained is distilled from a 100-mL, round-bottomed flask through a 20-cm Vigreux column at reduced pressure. First, excess nitromethane is removed (bp ca. 30°C/35 mm), then the fraction boiling at 58–60°C/1 mm (Note 3) is collected to afford 39–41 g (40–42% yield) of nitroacetaldehyde diethyl acetal **1** as a colorless liquid (Note 4), (Note 5).

2. Notes

1. All reagents were purchased from Fluka Feinchemikalien GmbH, Neu-Ulm, Germany and used without further purification.
2. Nitromethane, 98% purity, was used.
3. The rate of heating depends on the type of Vigreux column used, in this case a 20-cm, silver-plated Vigreux column with 4-cm outer and 1 1/2-cm inner diameter. The bath temperature should not be raised above 110°C when using this type of column, to avoid co-distillation of nitromethane (bp at 760 mm, 101°C). Ethanol should be distilled off at a rate of about 10 drops/min.

4. The spectroscopic properties of nitroacetaldehyde diethyl acetal are as follows: IR (film) ν_{max} cm^{-1}: 2970 (CH), 2920 (CH), 2880 (CH), 1550 (N=O), 1365 (N=O), 1340, 1120 (C-O), 1060; ^1H NMR (250 MHz, $CDCl_3$) δ: 1.15 (t, 6 H, CH_2CH_3), 3.56 and 3.67 (2 q, 4 H, J = 7.1, 2 CH_2CH_3), 4.44 ("d", 2 H, J = 5.8, CH_2NO_2), 5.09 ("t", 1 H, J = 5.8, CH); ^{13}C NMR (63 MHz, $CDCl_3$) δ: 15.0 (q, CH_2CH_3), 63.3 (t, CH_2CH_3), 76.8 (t, CH_2NO_2), 98.7 [d, $CH(OEt)_2$].

5. This reaction was carried out in the submitter's group more than 30 times, with yields ranging from 32–41% (lit.[2]: 49%). The purity of this material was repeatedly determined by gas chromatographic analysis to be >98%. GLC analysis: Column PS 086/.30 mm × 20 m glass capillary, 95:5 methyl/phenylsilicone. Program T_1, 40°C (1 min), rate 10°C/min; T_2, 300°C, 0.4 mm hydrogen pressure; R_t = 9.37 min.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

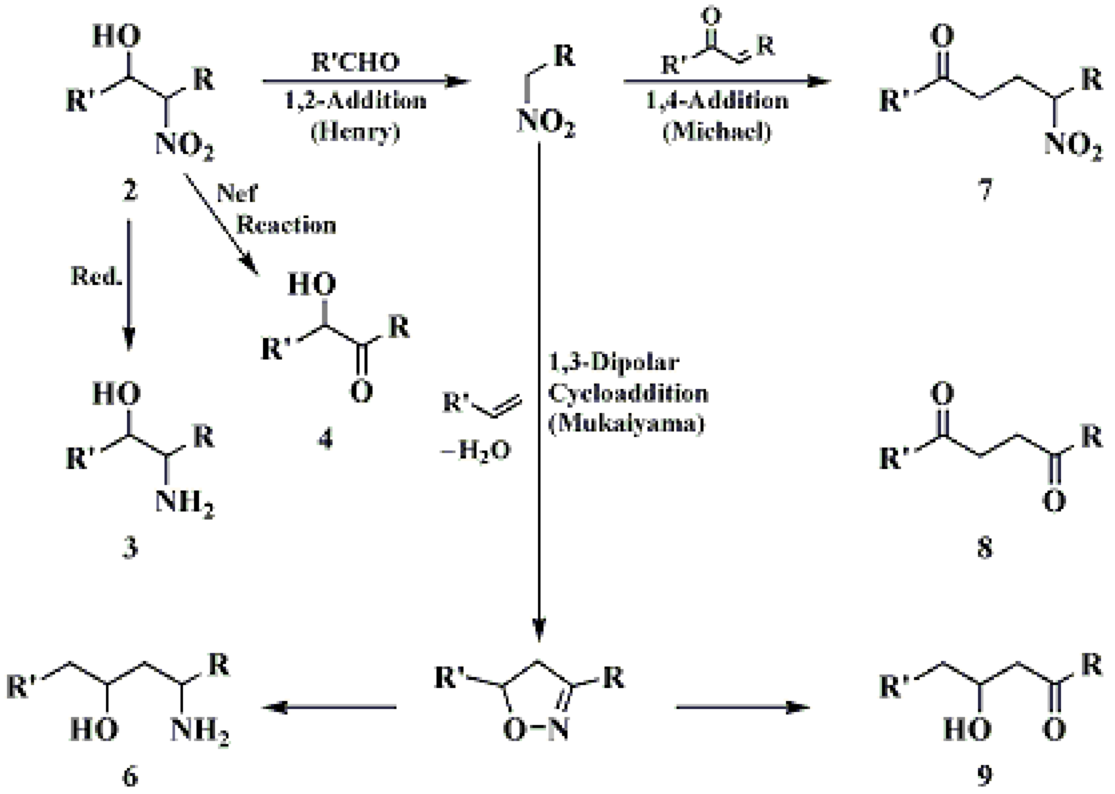
3. Discussion

This procedure describes the preparation of nitroacetaldehyde diethyl acetal **1** according to the method of René and Royer.[2]

Two other procedures for the preparation of **1** are known, i.e., by treatment of chloroacetaldehyde diethyl acetal with silver nitrite,[3] and by the reaction of α,α-diethoxymethyltriethylammonium tetrafluoroborate and nitromethane.[4] These alternate methods are less suited and less economic for preparation of **1** on a large scale. The dimethyl acetal has been obtained by treatment of 1-chloro-2-nitroethene with sodium methoxide.[5]

Diethyl acetal **1** has been used to obtain various other acetals by transacetalization,[6,7] such as the dimethyl, the ethyleneglycol, and the neopentylglycol acetal (2,2-dimethyl-1,3-propylidene acetal).

Aliphatic nitro compounds are highly versatile building blocks in organic synthesis[8 9 10 11,12 13] (see Scheme 1). For example, the nitroaldol addition (Henry reaction)[14] leads to the formation of 1,2-nitro alcohols, **2**, which are easily transformed into 1,2-amino alcohols, **3**, by reduction, and into α-hydroxycarbonyl compounds, **4**, by hydrolysis[15] (Nef reaction). The former process, mostly using nitromethane, has been widely employed in carbohydrate chemistry.[16 17 18 19 20 21 22]



Dehydration of primary nitro compounds (Mukaiyama reaction)[23] affords nitrile oxides, which may dimerize to yield furoxans, or otherwise be trapped by suitable dipolarophiles such as double or triple bond systems, leading to the formation of various heterocyclic systems, **5**.[24,25] The latter have been used for further derivatization in the heterocyclic series, or in "return" as precursors of acyclic products after ring cleavage,[11,26,27,7] for example, 1,3-amino alcohols **6** or β-hydroxycarbonyl compounds, **9**.

Both nitroaldol[28,29] and 1,3-dipolar cycloaddition products (e.g., isoxazolines, from alkenes)[24,25,26,27,7] have shown that nitroacetaldehyde diethyl acetal **1** constitutes a versatile C_2 building block in organic synthesis, notably what concerns amino sugar target structures. Recent work both on nitroaldol and nitroalkane derived dipolar additions has concentrated on the study and elaboration of stereoselective C-C forming steps with nitroalkanes.

Further uses of nitroalkanes are in 1,4-additions (Michael reaction) to α,β-unsaturated carbonyl compounds and the like. Recent reports deal with transformations of 1,4-nitro ketones, **7**, into 1,4-keto aldehydes, **8**, and cyclization to cyclopentenones.[30,31]

This preparation is referenced from:

- Org. Syn. 77, 236

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

dimethyl, the ethyleneglycol

neopentylglycol acetal (2,2-dimethyl-1,3-propylidene acetal)

ethanol (64-17-5)

hydrogen (1333-74-0)

nitrogen (7727-37-9)

sodium methoxide (124-41-4)

zinc chloride (7646-85-7)

triethyl orthoformate (122-51-0)

Nitromethane (75-52-5)

silver nitrite (7783-99-5)

chloroacetaldehyde diethyl acetal (621-62-5)

Nitroacetaldehyde diethyl acetal, Ethane, 1,1-diethoxy-2-nitro- (34560-16-2)

α,α-diethoxymethyltriethylammonium tetrafluoroborate

1-chloro-2-nitroethene

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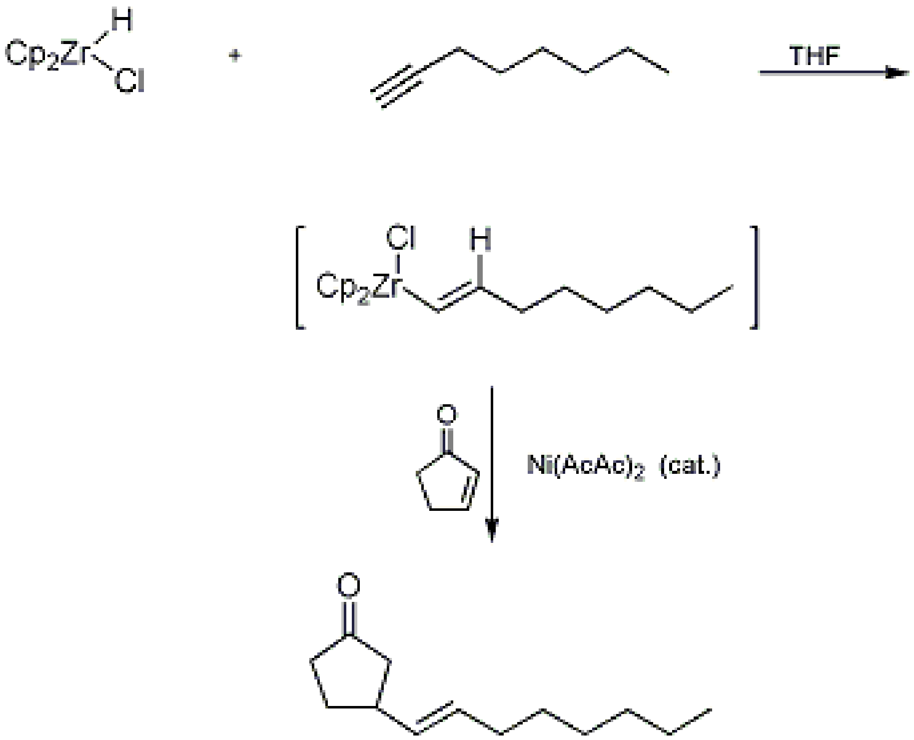
Organic Syntheses, CV 9, 640

CONJUGATE ADDITION OF A VINYLZIRCONIUM REAGENT: 3-(1-OCTEN-1-YL)CYCLOPENTANONE

[Cyclopentanone, 3-(1-octenyl)-, (E)-]



Submitted by Ruen Chu Sun[1], Masami Okabe[1], David L. Coffen[1], and Jeffrey Schwartz[2].
Checked by Daniel J. Keavy and Robert K. Boeckman, Jr..

1. Procedure

3-(1-Octen-1-yl)cyclopentanone.[3] A 38.7-g quantity (0.150 mol) of chlorobis(η^5-cyclopentadienyl)hydridozirconium, Schwartz's reagent, (Note 1) is weighed into an oven-dried, 250-mL, three-necked flask. The flask, equipped with argon inlet and exit tubes, a thermometer and magnetic stirrer, is placed in an ice/water cooling bath. Under an atmosphere of argon, 50 mL of dry tetrahydrofuran (Note 2) and 23.6 mL (0.16 mol) of freshly distilled 1-octyne (Note 3) are added. The ice/water cooling bath is used to keep the temperature between 15°C and 25°C during the addition. Stirring is continued in the ice bath for 2 hr to control a mildly exothermic reaction; then the flask is wrapped in aluminum foil and stirred overnight at room temperature (elapsed time is 18 hr). At this point, 10.9 mL (0.130 mol) of freshly distilled 2-cyclopentenone (Note 3) is added and the reaction mixture is chilled in an ice bath for 10 min. To the cooled reaction mixture a total of 3.34 g (0.0130 mol) of vacuum-sublimed (at 180°C), powdered, solid nickel acetylacetonate (Note 3),(Note 4) is added in three portions at

10-min intervals, keeping the temperature of the reaction mixture below 50°C (Note 5), (Note 6).

The mixture is stirred for 2 hr in the ice bath and for 2 hr at room temperature, then poured into a large Erlenmeyer flask containing 150 mL of 1 N hydrochloric acid and 200 mL of ice/water mixture. Hexane (400 mL) is added and the quenched reaction mixture is stirred for 30 min. Solid material is removed by vacuum filtration (Note 7) and the solids are washed with hexane (3 × 70 mL). The combined filtrates are transferred to a separatory funnel and the organic layer is removed. The aqueous layer (Note 7) is extracted with 300 mL of hexane and the extract is combined with the original organic layer. After the organic layer is washed successively with 300-mL portions of saturated sodium bicarbonate solution and brine, it is dried over sodium sulfate and concentrated under reduced pressure to give 24.8 g of crude product. The crude product is placed on a chromatography column prepared from 550 g of silica gel and hexane. The column is eluted with 2% ethyl acetate in hexane until 3.5 L of eluant has been collected. Then 4% ethyl acetate in hexane is used. The fractions containing the product (TLC) are combined and evaporated, finally under high vacuum, to afford 15.4 g (61%) of a very pale yellow liquid (Note 8). GC analysis of this product on an OV17 50-m capillary column (100°C to 200°C at 5°C/min) shows it to be 98.2% pure.

The material is distilled in a Kugelrohr apparatus at 0.15 mm and an oven temperature of 95–105°C to give 15.0 g (59% overall yield) of material with GC purity of 98.3% (Note 9).

2. Notes

1. Chlorobis(η^5-cyclopentadienyl)hydridozirconium was prepared by lithium aluminum hydride reduction of the dichloro compound using the procedure of Buchwald and co-workers.[4] When carried out using chlorobis(η^5-cyclopentadienyl)-hydridozirconium obtained from a commercial source, the procedure afforded only a 28% yield of final product.
2. Tetrahydrofuran was distilled from sodium/benzophenone before use.
3. 1-Octyne, cyclopentenone, and nickel acetylacetonate were purchased from the Aldrich Chemical Company, Inc. The checkers recrystallized the latter compound from anhydrous methanol followed by azeotropic drying with hot toluene.
4. For some applications of this chemistry, it may be preferable first to reduce the nickel catalyst with DIBAL.[3]
5. The checkers observed a significant induction period prior to onset of the exothermic reaction. Care must be taken to avoid addition of the nickel acetylacetonate too rapidly initially or temperature control becomes difficult.
6. In several separate small scale experiments, it was noted that the coupling reaction was not impeded by adding pyridine, triethylamine, t-butyl alcohol, chlorotrimethylsilane, or diisopropylamine to the reaction mixture before adding the nickel catalyst. These results suggest that a variety of functional groups can

be present in the enone partner of the coupling reaction. In addition toluene can be used instead of tetrahydrofuran as the solvent.

7. Disposal of waste materials containing nickel salts should be carried out in an environmentally acceptable manner.

8. The checkers employed a flash chromatography technique, and 4% ethyl acetate/hexanes as the TLC solvent system to monitor the chromatographic separation.

9. The NMR spectrum of the product [^{1}H NMR ($CDCl_3$) δ] showed a characteristic set of multiplets from 0.8 to 2.9 ppm and olefinic protons at 5.43 (dd, 1 H, J = 15.4 and 6.4) and 5.49 ppm (dt, 1 H, J = 15.4 and 5.8); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.0, 22.6, 28.7, 29.3, 29.9, 31.6, 32.4, 38.1, 39.7, 44.9, 130.6, 131.9, 219.0; IR (neat) cm^{-1}: 1743; MS m/e 194 (M^+). Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 80.40; H, 11.35. The checkers employed a 30-m Durawax DX3 column for the GC analysis and found a purity of 97%.

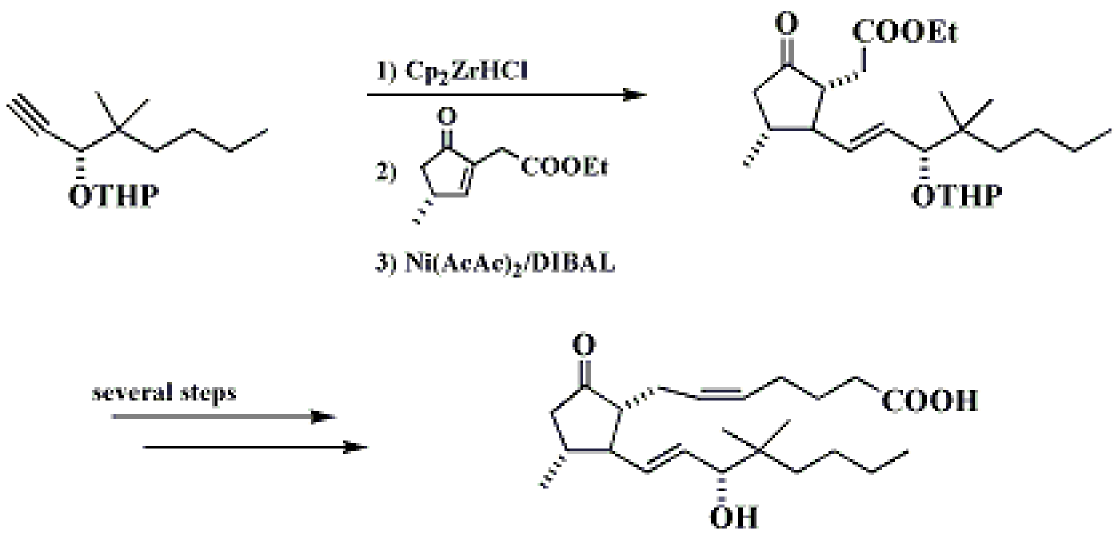
Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

This example does not illustrate the highest yield application of this chemistry. Coupling of 1-octyne and cyclopentenone was selected because these materials are commercially available and because this coupling exemplifies, in a prototypical fashion, the application of this powerful chemistry to prostaglandin synthesis. Several additional examples are presented in the original publication.[3]

A closely related coupling reaction is a key step in a synthesis of the anti-ulcer prostaglandin **1**, a synthesis that was developed for large scale preparation of this compound.[5]



1

The simplicity of operation and flawless rendering of (E)-geometry make this an attractive alternative to vinylcuprate additions.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 162

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hexanes

brine

chlorobis(η^5-cyclopentadienyl)hydridozirconium, Schwartz's reagent

Chlorobis(η^5-cyclopentadienyl)hydridozirconium

chlorobis(η^5-cyclopentadienyl)-hydridozirconium

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

methanol (67-56-1)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

aluminum (7429-90-5)

nickel (7440-02-0)

pyridine (110-86-1)

toluene (108-88-3)

Benzophenone (119-61-9)

sodium (13966-32-0)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

hexane (110-54-3)

triethylamine (121-44-8)

t-butyl alcohol (75-65-0)

2-Cyclopentenone, cyclopentenone (930-30-3)

argon (7440-37-1)

1-OCTYNE (629-05-0)

diisopropylamine (108-18-9)

CHLOROTRIMETHYLSILANE (75-77-4)

3-(1-Octen-1-yl)cyclopentanone (64955-00-6)

Cyclopentanone, 3-(1-octenyl)-, (E)- (64955-00-6)

nickel acetylacetonate (3264-82-2)

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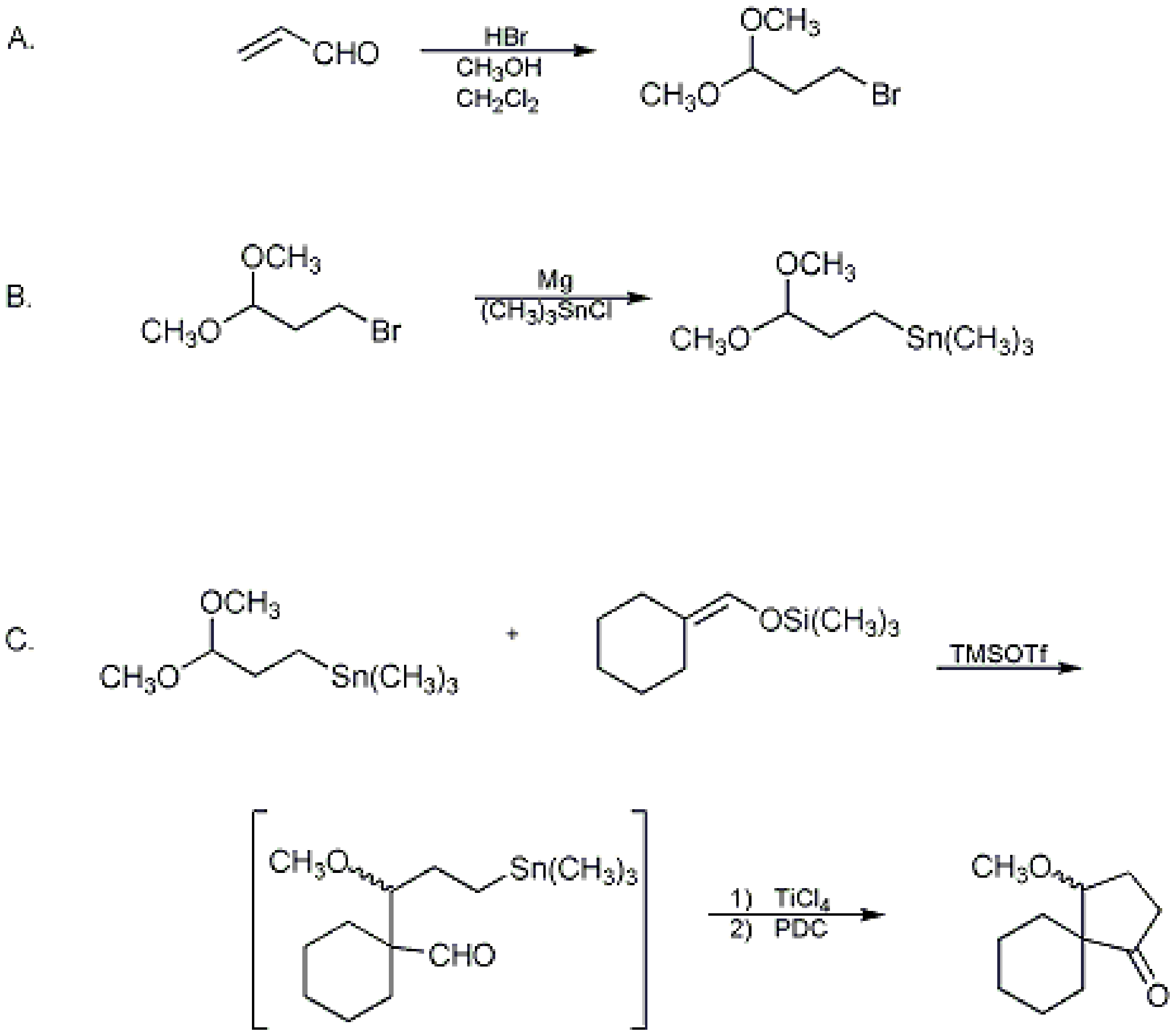
Organic Syntheses, CV 9, 643

SPIROANNELATION OF ENOL SILANES: 2-OXO-5-METHOXYSPlRO[5.4]DECANE

[Spiro[4.5]decan-1-one, 4-methoxy-]



Submitted by Thomas V. Lee[1] and John R. Porter[2].
Checked by Joseph L. Kent and Robert K. Boeckman, Jr..

1. Procedure

CAUTION! Many organotin compounds are known to be highly toxic[3] (Note 1), and hydrogen bromide (HBr), titanium tetrachloride ($TiCl_4$), and trimethylsilyl trifluoromethanesulfonate (TMSOTf) are corrosive. Steps A-C should be performed in an efficient fume hood while wearlng gloves and adequate eye protection.

A. *1-Bromo-3,3-dimethoxypropane*(Note 2). Into a flame-dried, tared, 1-L, round-

bottomed flask containing 500 mL of methylene chloride (CH_2Cl_2) (Note 3) at 0°C is bubbled anhydrous hydrogen bromide for approximately 15 min (33.0 g, 0.408 mol of HBr absorbed) (Note 4),(Note 5). Acrolein (22.9 g, 27.2 mL, 0.408 mol) is added rapidly (30 sec) via syringe to the stirred solution (Note 6). After 2 min, a solution of 86.6 g (89.3 mL, 0.816 mol) of trimethyl orthoformate (Note 7) in methanol (100 mL) is introduced into the reaction mixture via cannula over 5 min. The reaction mixture is stirred for 10 min at 0°C, and solid anhydrous calcium carbonate (12.0 g, 0.120 mol) is then added in one portion. The reaction mixture is stirred for an additional 1 hr, the solution is filtered, and the filtrate concentrated under reduced pressure to ca. 50 mL. The residue is distilled through a 25-cm Vigreux column under reduced pressure to give, after a forerun of variable amount (10 mL) (Note 8), 38.8 g (52%) of 1-bromo-3,3-dimethoxypropane as a colorless liquid, bp 67–69°C at 24 mm (Note 9).

B. *1-Trimethylstannyl-3,3-dimethoxypropane*. An oven-dried, 500-mL, three-necked, round-bottomed flask fitted with a reflux condenser, nitrogen inlet tube, pressure-equalizing addition funnel, and rubber septum is charged with magnesium turnings (1.34 g, 55.2 mmol). The apparatus is carefully flame-dried under a flow of nitrogen and allowed to cool to room temperature. Tetrahydrofuran (5 mL) (Note 10) is added to the flask and a solution of 1-bromo-3,3-dimethoxypropane (10.10 g, 55.2 mmol) in tetrahydrofuran (10 mL) is added to the dropping funnel. A small portion (0.5 mL) of the solution of 1-bromo-3,3-dimethoxypropane is added to the flask along with 3 drops of 1,2-dibromoethane, with warming (Note 11), until reaction commences. Stirring is begun and the remainder of the bromide solution is added dropwise to the reaction mixture. After ca. 5 min the reaction becomes vigorous and a further 35 mL of tetrahydrofuran is added via a syringe. The reaction is allowed to stir at room temperature for 1 hr after addition is complete, by which time all the magnesium has been consumed. A solution of chlorotrimethylstannane (11.0 g, 55.2 mmol) (Note 12) in tetrahydrofuran (50 mL) is then added rapidly to the reaction mixture which is allowed to stir for 18 hr at room temperature before being poured into water (100 mL). The aqueous phase is washed with diethyl ether (3 × 100 mL), the combined organic phases are dried over anhydrous magnesium sulfate, and the solvent is removed under reduced pressure to afford a yellow liquid (14.18 g).

The crude product is dissolved in petroleum ether (10 mL) (Note 13) and poured onto a column (45-mm diameter) filled with 350 g of silica gel (Merck 230–400 mesh) for flash chromatography. Elution under pressure (Note 14), initially with 2% diethyl ether in petroleum ether (Note 15) and then with increasing amounts of diethyl ether (up to 10%) in petroleum ether, gives, after removal of the solvent under reduced pressure, 1-trimethylstannyl-3,3-dimethoxypropane as a colorless liquid (11.9 g; 81%).

C. *2-Oxo-5-methoxyspiro[5.4]decane*. An oven-dried, 1-L, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, nitrogen inlet tube, pressure-equalizing dropping funnel, and a rubber septum, and allowed to cool under a flow of dry nitrogen. The flask is charged with 1-trimethylstannyl-3,3-dimethoxypropane (8.69 g, 32.6 mmol), [(1-trimethylsilyloxy)methylene]cyclohexane (6.0 g, 32.6 mmol)

(Note 16) and dichloromethane (100 mL) (Note 17). The mixture is stirred and cooled to −78°C using an acetone-dry ice bath, and trimethylsilyl trifluoromethanesulfonate (1.47 g; 6.6 mmol) (Note 18) is added dropwise. After 1.5 hr all starting materials have been consumed (Note 19), and a solution of titanium tetrachloride (7.40 g, 39.0 mmol) (Note 20) in dichloromethane (10 mL) is added dropwise at −78°C with stirring. On completion of the reaction, which requires 2 hr (Note 19), dichloromethane (250 mL) is added slowly so that the temperature does not rise above −70°C. Pyridinium dichromate (PDC) (20.32 g, 54.0 mmol) (Note 21) is added in 2-g portions. Stirring is then continued overnight while the reaction is allowed to warm to room temperature. Sodium-dried diethyl ether (300 mL) is added and the reaction mixture filtered through a short column of Celite. The solid residues are washed thoroughly with diethyl ether (5 × 50 mL), and the combined filtrates are concentrated under reduced pressure (Note 22), redissolved in diethyl ether, washed with 10% aqueous HCl (1 × 100 mL), brine (1 × 100 mL), saturated aqueous sodium hydrogen carbonate solution (1 × 100 mL), dried over anhydrous magnesium sulfate, and the solvent is removed under reduced pressure to afford a yellow liquid (8.20 g).

The crude product is dissolved in diethyl ether/petroleum ether (1:5) (5 mL) and poured onto a column (45-mm diameter) filled with 200 g of silica gel (Merck 230–400 mesh for flash chromatography). Elution (Note 23) under pressure (Note 14) with diethyl ether/petroleum ether (1:5) gives 2-oxo-5-methoxyspiro[5.4]decane as a colorless liquid (4.43 g; 75%) (Note 24).

2. Notes

1. *Because of the highly toxic nature of many tin compounds all tin residues from these reactions, including those extracted by aqueous washing, were collected together by the submitters and dispatched to a licensed chemical waste disposal unit for burning in a chemical incinerator, equipped with an afterburner and scrubbers.*

2. This procedure is essentially that of Battersby and co-workers.[4]

3. Reagent grade methylene chloride was distilled from calcium hydride (CaH_2) prior to use.

4. A steady stream of HBr was introduced via a Pasteur pipette with the tip extending into the solution.

5. The solution is almost saturated after 15 min as judged by evolution of HBr.

6. Acrolein was obtained from the Aldrich Chemical Company, Inc., and distilled before use.

7. Trimethyl orthoformate was obtained from the Aldrich Chemical Company, Inc., and used as received.

8. The forerun consists primarily of methanol and trimethyl orthoformate.

9. The checkers found that commercially available 3-bromo-1,1-dimethoxypropane (Aldrich Chemical Company, Inc.) was unsatisfactory, even after purification, for preparation of the stannane in part B, resulting in greatly

diminished yields.
10. Tetrahydrofuran was distilled under nitrogen from sodium/benzophenone ketyl radical immediately prior to use.
11. Warming was achieved by use of a water bath at 40°C.
12. Chlorotrimethylstannane was obtained from the Aldrich Chemical Company, Inc. and was used without further purification.
13. Petroleum ether boiling at 40–60°C was distilled immediately prior to use.
14. The submitters used a compressed air line at a pressure that maintained a flow rate of 5 mL min^{-1}.
15. Preliminary elution allows removal of hexamethyldistannoxane, formed as a by-product in the reaction, which slowly precipitates from the elution solvent as a white solid. A total of 1200 mL of solvent was collected in 30-mL fractions.
16. [(1-Trimethylsilyloxy)methylene]cyclohexane was prepared from the corresponding carboxaldehyde according to the method of House.[5 6] Cyclohexane carboxaldehyde was obtained from the Aldrich Chemical Company, Inc., and purified by distillation at atmospheric pressure (bp 160–164°C).
17. Dichloromethane was distilled from CaH_2 immediately prior to use.
18. Trimethylsilyl trifluoromethanesulfonate was obtained from the Aldrich Chemical Company, Inc., and was purified by distillation under nitrogen (bp 142°C/760 mm), immediately prior to use.
19. The progress of the reaction is conveniently monitored by TLC on Kieselgel 60 F_{254} eluting, for the first bond-forming reaction, with diethyl ether:petroleum ether (1:9). The intermediate aldehyde had an R_f of 0.5, and the starting acetal an R_f = 0.45. The second bond-forming reaction was monitored by elution with diethyl ether:petroleum ether (2:3), and the R_f of the product was 0.4.
20. Titanium tetrachloride was obtained from the Aldrich Chemical Company, Inc., and was purified by distillation under nitrogen (bp 136°C/700 mm) immediately prior to use.
21. Pyridinium dichromate was prepared by the method of Corey.[7] The checkers employed PDC, obtained from the Aldrich Chemical Company, Inc., that was used as received.
22. This evaporation removes dichloromethane used in the original reaction, and assists isolation of the product.
23. A total of 600 mL of solvent was collected in 30-mL fractions.
24. The purity of the product was found to be 97% by high-field NMR (270 MHz). Physical properties are as follows: Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95%. Found: C, 72.60; H, 9.94%. ν_{max} 1720 (C=O), 1100 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.2–1.8 (10 H, m, CH_2), 1.81–2.40 (4 H, m, CH_2), 3.38 (3 H, s, OCH_3), 3.78 (1 H, m, CH-OCH_3); ^{13}C NMR ($CDCl_3$) δ: 22.13, 22.40, 22.77, 25.64, 25.94, 31.25, 34.12 (all t, CH_2), 54.11 (s, quat C), 56.92 (q, OCH_3), 83.87 (d, C-OCH_3), 221.30; m/z 182 (M^+).

Waste Disposal Information

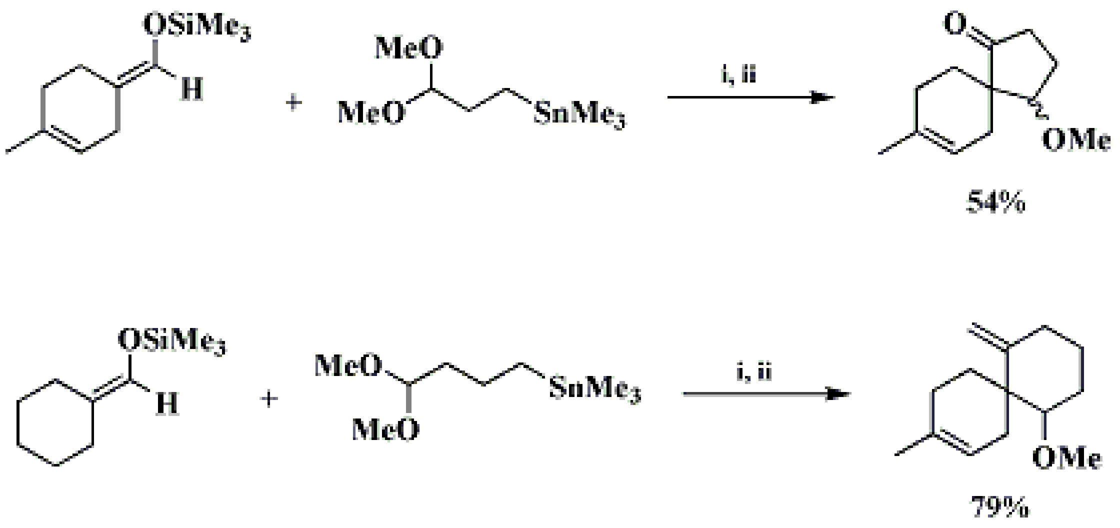
All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995. See (Note 1).

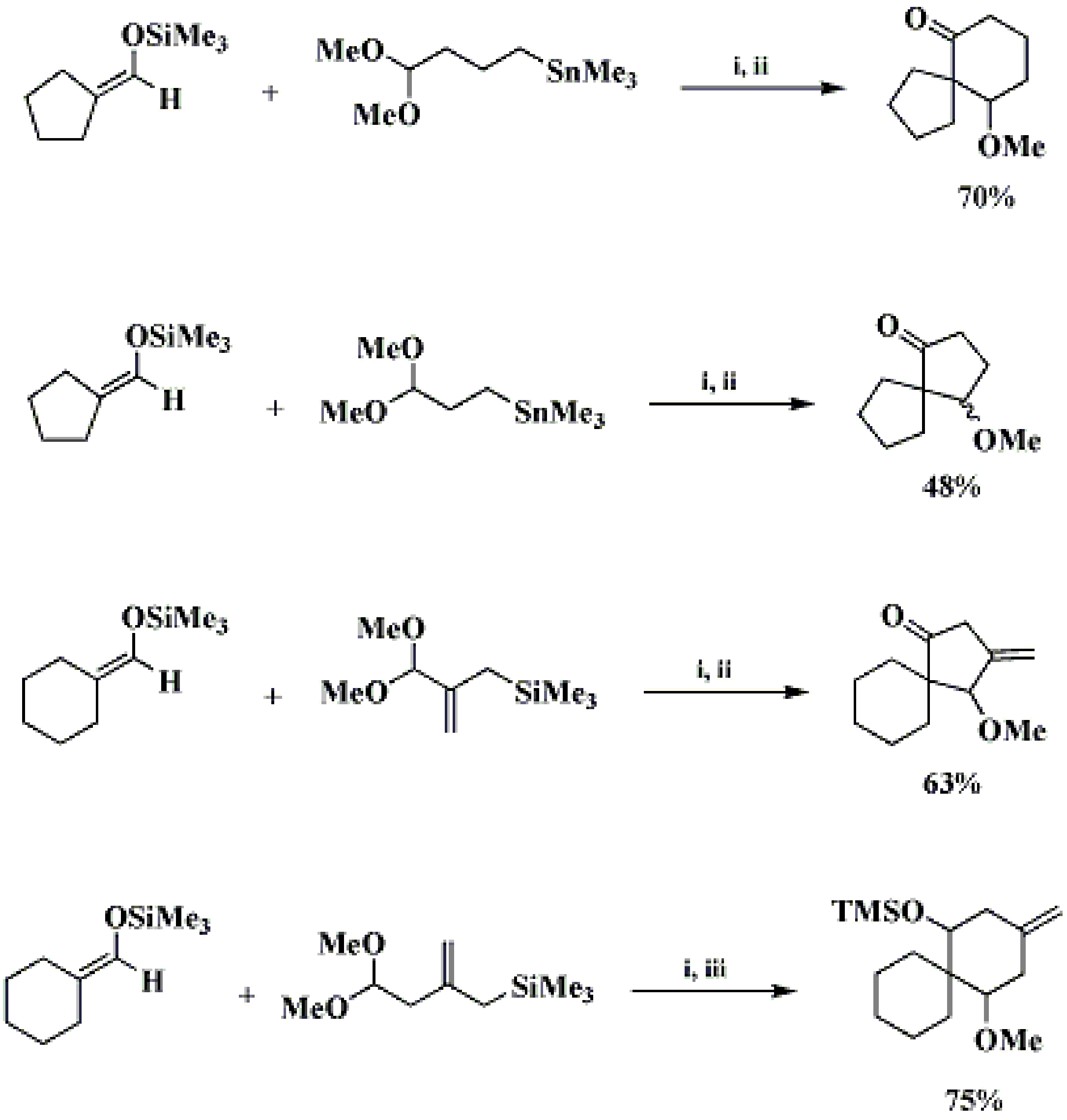
3. Discussion

The synthesis of spirocyclic compounds and quaternary carbon centers in general has been an area of intense synthetic activity,[8] because of the widespread occurrence of such products in nature, and because of the challenge they present to synthetic methodology. The reaction described here is a very simple method for constructing such systems in a single step, a two-bond forming, annelation process, using readily available starting materials. This new process involves the chemoselective[9] *intermolecular* reaction of the acetal function of a bifunctional alkyl stannane or allyl silane with an enol silane, followed by *intramolecular* ring closure to give an annelated product. By using a range of bifunctional reagents of this type, a highly efficient single-step construction of fused five-,[10,11] six-,[12] seven-,[12] eight-,[13] and nine-membered rings,[13] and of five-, six-, and seven-membered spirocyclic ring systems has been developed.[14,15]

The new spiroannelation method gives, by use of both the tin and silicon chemistry, ready access to [4.4], [4.5], [5.5], [4.6], and [5.6] spirocyclic systems as well as five-, six-, and seven-membered rings possessing a quaternary center. An in situ oxidation, or protection of an initially formed crude secondary alcohol increases the ease of isolation of the product and leads to improved overall yields. Furthermore, for symmetrical substrates, this chemodifferentiates two oxygen functionalities at equivalent carbon atoms. This makes the reaction potentially stereoconvergent at the newly formed quaternary center (see Table).

TABLE
SPIROCYCLIC COMPOUNDS





i. TMSOTf - $TiCl_4$; ii. PDC; iii. TMSOTMS/DMAP

Probably the best alternative to the present procedure, in terms of generality, is the use of a cycloaddition strategy that can give access to a wide range of different sized spirocyclic molecules.[16]

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

benzophenone ketyl

brine

2-OXO-5-METHOXYSPlRO[5.4]DECANE

Sodium-dried diethyl ether

methanol (67-56-1)

diethyl ether (60-29-7)

Acrolein (107-02-8)

sodium hydrogen carbonate (144-55-8)

magnesium, magnesium turnings (7439-95-4)

hydrogen bromide, HBr (10035-10-6)

oxygen (7782-44-7)

nitrogen (7727-37-9)

tin (7440-31-5)

calcium carbonate (471-34-1)

carbon (7782-42-5)

sodium (13966-32-0)

1,2-dibromoethane (106-93-4)

methylene chloride, dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

titanium tetrachloride (7550-45-0)

Cyclohexane carboxaldehyde (2043-61-0)

calcium hydride (7789-78-8)

silicon

pyridinium dichromate (20039-37-6)

trimethyl orthoformate (149-73-5)

Trimethylsilyl trifluoromethanesulfonate (27607-77-8)

chlorotrimethylstannane (1066-45-1)

Spiro[4.5]decan-1-one, 4-methoxy- (108264-15-9)

1-Bromo-3,3-dimethoxypropane, 3-bromo-1,1-dimethoxypropane (36255-44-4)

1-Trimethylstannyl-3,3-dimethoxypropane (102402-80-2)

2-Oxo-5-methoxyspiro[5.4]decane

hexamethyldistannoxane

[(1-Trimethylsilyloxy)methylene]cyclohexane

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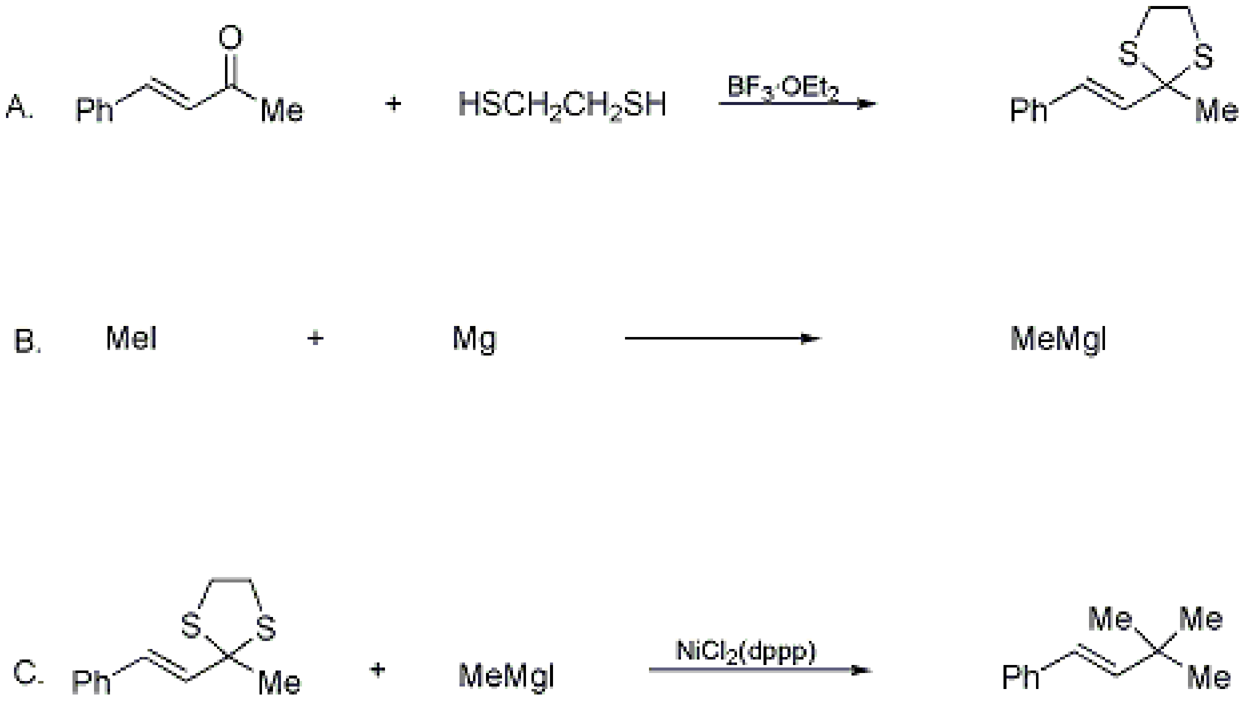
Organic Syntheses, CV 9, 649

NICKEL-CATALYZED, GEMINAL DIMETHYLATION OF ALLYLIC DITHIOACETALS: (E)-1-PHENYL-3,3-DIMETHYL-1-BUTENE

[Benzene, (3,3-dimethyl-1-butenyl)- (E)-]



Submitted by Tien-Min Yuan and Tien-Yau Luh[1].
Checked by Yugang Liu and Robert K. Boeckman, Jr..

1. Procedure

CAUTION! 1,2-Ethanedithiol has a powerful stench. Steps A and C should be performed in a well-ventilated hood.

A. *(E)-2-Methyl-2-(2-phenylethenyl)-1,3-dithiolane*. In a 500-mL, round-bottomed flask equipped with a magnetic stirring bar are placed 29.2 g (0.2 mol) of (E)-4-phenyl-3-buten-2-one (Note 1) and 20.7 g (0.22 mol) of 1,2-ethanedithiol in 200 mL of methanol. To the stirred solution is added 11 mL (12.4 g, 0.087 mol) of boron trifluoride etherate. The mixture is stirred at room temperature for 45 min. To the mixture is added 50 mL of aqueous 10% sodium hydroxide, and the methanol is removed under reduced pressure. Dichloromethane (300 mL) is introduced and the solution is washed with aqueous 10% sodium hydroxide solution (2 × 100 mL). The aqueous layer is extracted with dichloromethane (3 × 200 mL). The combined organic layers are washed with 200 mL of water, dried over anhydrous magnesium sulfate, and filtered. The solvent is removed under reduced pressure and the residue is fractionally

distilled to give 24.9–27.1 g (56–61%) of (E)-2-methyl-2-(2-phenylethenyl)-1,3-dithiolane (Note 2) and (Note 3) as a yellowish liquid, bp 109–112°C (0.16 mm), that solidifies on standing, mp 52–53°C.

B. *Methylmagnesium iodide*. A 500-mL, three-necked, round-bottomed flask containing 9.7 g (0.4 g-atom) of magnesium turnings is equipped with a rubber septum, reflux condenser, an addition funnel, and a magnetic stirring bar. The system is flame-dried and flushed with nitrogen. Anhydrous ether (20 mL, (Note 4)) is introduced to cover the magnesium. As the contents of the flask are stirred, iodomethane (56.7 g, 0.4 mol) in 180 mL of anhydrous ether is added dropwise through the addition funnel. The addition requires about 2 hr; the mixture is then stirred for an additional 30 min.

C. *(E)-1-Phenyl-3,3-dimethyl-1-butene*. In a 1-L, two-necked, round-bottomed flask fitted with a reflux condenser, rubber septum, and a magnetic stirring bar are placed 17.8 g (0.08 mol) of 2-methyl-2-(2-phenylethenyl)-1,3-dithiolane and 2.17 g (0.004 mol) of [1,3-bis(diphenylphosphino)propane]nickel(II) chloride [$NiCl_2$(dppp)] (Note 5). The flask is evacuated and flushed with nitrogen three times. To the above mixture is added 300 mL of anhydrous tetrahydrofuran (Note 6). The ether solution of methylmagnesium iodide prepared in Step B is introduced with a double-ended needle in one portion (Note 7). The mixture is heated under reflux for 24 hr, cooled to room temperature, and treated with 200 mL of saturated ammonium chloride solution. The organic layer is separated and the aqueous layer is extracted with ether (3 × 200-mL). The combined organic layers are washed twice with aqueous 10% sodium hydroxide solution (100 mL) and with brine (100 mL). The organic solution is dried over anhydrous magnesium sulfate. The solvent is removed under reduced pressure and the residue is filtered through a short column packed with 30 g of silica gel (Note 8) and flushed under a positive nitrogen pressure with 350 mL of hexane. After the solvent is evaporated under reduced pressure, the yellowish residue is distilled through a spinning band (Note 9) to give 10.4 g (81%) of (E)-1-phenyl-3,3-dimethyl-1-butene (Note 10) as a colorless liquid, bp 91–93°C/30 mm.

2. Notes

1. (E)-4-Phenyl-3-buten-2-one was purchased from Division of Janssen Pharmaceutica and used directly.
2. A 6-cm Vigreux column was employed for fractional distillation.
3. The spectral properties of the (E)-2-methyl-2-(2-phenylethenyl)-1,3-dithiolane are as follows: IR (neat) cm^{-1}: 3025, 2922, 1637, 1600, 1494, 1446, 1275, 1065, 964, 754, 692; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.01 (s, 3 H), 3.33–3.46 (m, 4 H), 6.47 (d, 1 H, J = 15.5), 6.63 (d, 1 H, J = 15.5), 7.21–7.43 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 29.6, 40.1, 65.4, 126.6, 127.0, 127.5, 128.4, 135.0, 136.4; MS m/e (rel) 222 (M^+, 100), 207 (17), 194 (59), 161 (44), 129 (45), 117 (39); HRMS calcd for $C_{12}H_{14}S_2$: 222.0537. Found 222.0546.

4. Ethyl ether is distilled from sodium-benzophenone ketyl before use.
5. [1,3-Bis(diphenylphosphino)propane]nickel(II) chloride was purchased from Aldrich Chemical Company, Inc., and used without further purification. The catalyst can also be prepared according to literature procedures.[2]
6. Tetrahydrofuran is distilled from sodium-benzophenone ketyl before use.
7. An excess of the Grignard reagent is required to maximize the yield; otherwise the reaction is incomplete.
8. Silica gel (230–400 mesh) was purchased from E. Merck Co.
9. A spinning band distillation setup is employed (800 Mirco Still, B/R Instrument Corporation, 3000 rpm, theoretical plates 23–26). The mixture was heated under reflux for 3 hr to reach equilibrium before distillation (reflux/distillation ratio = 5–10/1).
10. The spectral properties of the product are as follows: IR (neat) cm^{-1}: 3027, 2960, 1648, 1598, 1493, 1362, 1266, 968, 746, 693; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.16 (s, 9 H), 6.30 (d, 1 H, J = 16.2), 6.34 (d, 1 H, J = 16.2), 7.18–7.41 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 29.6, 33.3, 124.6, 126.0, 126.7, 128.4, 138.1, 141.8; MS m/e (rel) 160 (M^+, 35), 145 (100), 117 (21), 105 (11), 103 (11), 91 (25), 77 (12); HRMS calcd for $C_{12}H_{16}$: 160.1252, Found 160.1250.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Geminal dimethylation at a carbon center is useful in organic synthesis. Much effort has been devoted to the attachment of a tert-butyl group or a quarternary carbon center to olefinic carbon atom(s) in order to synthesize crowded olefins.[3 4 5 6 7] Although Tebbe-like reagents are effective for converting a carbonyl group into a gem-dimethyl substituent, their application to an allylic carbonyl substrate is limited by poor regioselectivity.[8,9,10,11,12,13] The present procedure is based on a series of reports on the nickel-catalyzed cross coupling reactions of dithioacetals with Grignard reagents.[14,15,16,17,18,19,20] α,β-Unsaturated aldehydes or ketones react as the dithioacetal in a polar solvent (such as tetrahydrofuran) or non-polar aromatic solvent (such as benzene or toluene) with methylmagnesium iodide in the presence of a catalytic amount $NiCl_2$ (dppp) or [1,2-bis(diphenylphosphino)ethane]nickel(II) chloride [$NiCl_2$ (dppe)], under a nitrogen atmosphere to give the corresponding geminal dimethylation products.[15,16,17] Substrates with structural variety react smoothly.[15,16,17] Allylic orthothioesters, on the other hand, give the corresponding trimethylation products with different regioselectivity.[16]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

brine

sodium-benzophenone ketyl

$NiCl_2$ (dppp)

Benzene (71-43-2)

methanol (67-56-1)

ether, ethyl ether (60-29-7)

ammonium chloride (12125-02-9)

sodium hydroxide (1310-73-2)

magnesium, magnesium turnings (7439-95-4)

nitrogen (7727-37-9)

toluene (108-88-3)

iodomethane (74-88-4)

methylmagnesium iodide (917-64-6)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

hexane (110-54-3)

boron trifluoride etherate (109-63-7)

1,2-ethanedithiol (540-63-6)

(E)-4-phenyl-3-buten-2-one

(E)-1-Phenyl-3,3-dimethyl-1-butene, Benzene, (3,3-dimethyl-1-butenyl)- (E)- (3846-66-0)

(E)-2-Methyl-2-(2-phenylethenyl)-1,3-dithiolane (107389-59-3)

2-methyl-2-(2-phenylethenyl)-1,3-dithiolane

[1,3-Bis(diphenylphosphino)propane]nickel(II) chloride (15629-92-2)

[1,2-bis(diphenylphosphino)ethane]nickel(II) chloride (15793-01-8)

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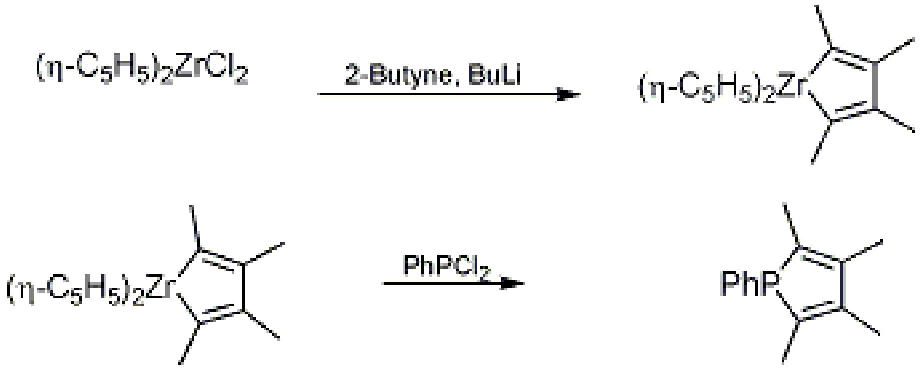
Organic Syntheses, CV 9, 653

1-PHENYL-2,3,4,5-TETRAMETHYLPHOSPHOLE

[1H-Phosphole, 2,3,4,5-tetramethyl-1-phenyl-]



Submitted by Paul J. Fagan and William A. Nugent[1].
Checked by Mark S. Jensen and James D. White.

1. Procedure

A 500-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, rubber septum-capped pressure-equalizing addition funnel on the center neck, rubber septum on one side neck, and a nitrogen inlet with stopcock on the other side neck is charged in a nitrogen-filled glove box (Note 1) with 27.0 g (92.5 mmol) of zirconocene dichloride [(η-$C_5H_5)_2ZrCl_2$] (Note 2), 150 mL of tetrahydrofuran (Note 3), and 16.0 mL (204 mmol) of 2-butyne (Note 4) added via syringe. The apparatus is removed from the glove box and attached via the nitrogen stopcock to a nitrogen bubbler. The flask is cooled to −78°C (dry ice-acetone bath) and 108 mL of 1.72 M butyllithium (186 mmol) in hexane (Note 5) is added via syringe to the addition funnel through the septum. The butyllithium solution is added dropwise to the stirred mixture in the flask. After the addition is complete, the reaction mixture is stirred at −78°C for 10 min (Note 6). The flask is allowed to warm by removing the dry ice-acetone bath, and the reaction mixture is stirred at room temperature for 2.5 hr at which point the mixture is dark orange-red (Note 7). The flask is again cooled to −78°C, and 17.5 mL (129 mmol) of dichlorophenylphosphine (Note 8) is added in a slow stream via syringe through the septum on the flask. The dry ice-acetone bath is removed and the flask is allowed to warm to room temperature. After 1 hr the orange-red color has dissipated and the septa are replaced with glass stoppers. The nitrogen inlet is connected to a vacuum line (0.1 mm) and the solvent is removed under reduced pressure. The stopcock is closed and the apparatus is placed in a nitrogen-filled glove box (Note 1). The reaction residue is extracted three times with 30-mL portions of hexane, each of which is filtered from the precipitate of (η-$C_5H_5)_2ZrCl_2$ and combined. The hexane is removed under reduced pressure (0.5 mm), and the oily liquid that remains is transferred into a 100-mL round-bottomed flask. The flask is attached to a vacuum distillation apparatus with a 10-cm Vigreux column. The distillation apparatus is

removed from the glove box and attached to a vacuum line. Distillation at 0.35 mm yields a fraction which is collected between 40–92°C and discarded. A second fraction boiling between 92–104°C (Note 9) is collected; the clear oily liquid is 1-phenyl-2,3,4,5-tetramethylphosphole [14.9–15.5 g, 75–78% based on $(\eta\text{-}C_5H_5)_2ZrCl_2$)] (Note 10). The compound is air-sensitive and should be stored under nitrogen.

2. Notes

1. A nitrogen-filled glove bag may also be used.
2. Zirconocene dichloride was obtained from Aldrich Chemical Company, Inc. and used without further purification.
3. Tetrahydrofuran was distilled from sodium benzophenone ketyl before use.
4. 2-Butyne was obtained from Farchan Chemical Company and dried over 4 Å molecular sieves before use.
5. Butyllithium was obtained from Foote Mineral Co. The molarity was checked by titration of 2.00 mL of the butyllithium solution in 10 mL of diethyl ether with dry 2-butanol using 1,10-phenanthroline as indicator.
6. The reaction mixture may become thick with a white solid at this point. The solid can be loosened by manually shaking the flask, or with the aid of an external permanent magnet using the magnetic stirring bar to break up the solid. The solid loosens some more upon warming, and stirring is not a problem.
7. If desired, the zirconium metallacycle can be isolated at this point: The flask is attached to a vacuum line via the nitrogen inlet, and solvents are removed from the flask under reduced pressure. With the aid of a 40°C water bath, the reaction residue is thoroughly dried. The flask is sealed and placed in a nitrogen-filled glove box (Note 1). The residue is extracted with small portions of toluene (total of 50 mL), each portion being filtered and combined. Toluene is removed from the filtrate under reduced pressure. Hexane (20 mL) is added to the solid residue, and after trituration, the solid is collected by filtration, and washed once with 10 mL of hexane. It is dried under reduced pressure to yield 26.0 g (85%) of crystalline, orange-red $(\eta\text{-}C_5H_5)_2ZrC_4(CH_3)_4$ which is >95% pure by spectroscopic analysis. This compound is very stable thermally both in solution and in the solid state; however, it is air-sensitive and should be handled under nitrogen. It can be used as obtained as a reagent in the synthesis of other heterocycles. The NMR spectrum is as follows: ^{1}H NMR (300 MHz, THF-d_8) δ: 1.54 (s, 6 H, CH_3), 1.57 (s, 6 H, CH_3), 6.15 (s, 10 H, h$\eta\text{-}C_5H_5$).
8. Dichlorophenylphosphine (Strem Chemicals, Inc.) was vacuum distilled and placed under a nitrogen atmosphere before use.
9. The boiling point has been reported previously as 105–110°C at 0.5 mm.[2]
10. The product has the following spectral properties: ^{1}H NMR (300 MHz, THF-d_8) δ: 1.89 (d, 6 H, J = 10.6, CH_3), 1.93 (s, 6 H, CH_3), 7.24 (m, 5 H, phenyl); ^{13}C NMR (75.5 MHz, THF-d_8) δ: 12.9 (dq, J_{CH} = 126, J_{PC} = 22, CH_3), 13.9 (q, J_{CH} = 126, CH_3), 129.2 (dt, J_{CH} = 160 and 6, J_{PC} = 8, phenyl), 129.6 (dt, J_{CH} = 162 and 6, phenyl), 134.3 (ddt, J_{CH} = 161 and 5, J_{PC} = 20, phenyl), 134.7 (d, J_{PC}

= 15), 136.4 (s, C=C), 143.4 (m, J_{PC} = 11); ^{31}P {^{1}H} NMR (121.7 MHz, THF-d_8) δ: 14 (s). Exact mass: Calcd. for $C_{14}H_{17}P$: m/e = 216.1068. Found: 216.1127.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Phospholes and other related heterocycles are an important class of main group compounds. The chemistry of phospholes and their preparation has been reviewed extensively by Mathey.[3] We provide details here for a simple, one-pot procedure for the preparation of 1-phenyl-2,3,4,5-tetramethylphosphole applying zirconocene chemistry.[4] The procedure involves reduction of $(\eta\text{-}C_5H_5)_2ZrCl_2$ with butyllithium in the presence of 2-butyne which (as reported initially by Negishi, et al.[5]) forms a zirconium metallacycle. Addition of dichlorophenylphosphine to this reaction mixture produces the phosphole. One other procedure for the preparation of 1-phenyl-2,3,4,5-tetramethylphosphole has been reported by Nief, et al.[2] That procedure involved aluminum chloride-coupling of 2-butyne, followed by reaction with dichlorophenylphosphine to form a chlorophospholium tetrachloroaluminate which was then reduced with tributylphosphine to produce the phosphole in 68% yield.

Using a procedure similar to that described here, or using isolated zirconium metallacycles as reagents, we have been able to prepare not only phospholes, but also arsoles, stiboles, bismoles, siloles, germoles, stannoles, galloles, thiophenes, selenophenes, and borole Diels-Alder dimers.[4] Since a number of other titanium and zirconium metallacycles are readily available,[4] these reagents should be useful in the preparation of a variety of heterocycles.

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium benzophenone ketyl

zirconocene dichloride

η-$C_5H_5)_2ZrCl_2$

η-$C_5H_5)_2ZrC_4(CH_3)_4$

diethyl ether (60-29-7)

nitrogen (7727-37-9)

toluene (108-88-3)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

hexane (110-54-3)

zirconium

2-butyne (503-17-3)

dichlorophenylphosphine (644-97-3)

2-Butanol (78-92-2)

tributylphosphine (998-40-3)

1,10-phenanthroline (66-71-7)

titanium (7440-32-6)

1-Phenyl-2,3,4,5-tetramethylphosphole, 1H-Phosphole, 2,3,4,5-tetramethyl-1-phenyl- (112549-07-2)

chlorophospholium tetrachloroaluminate

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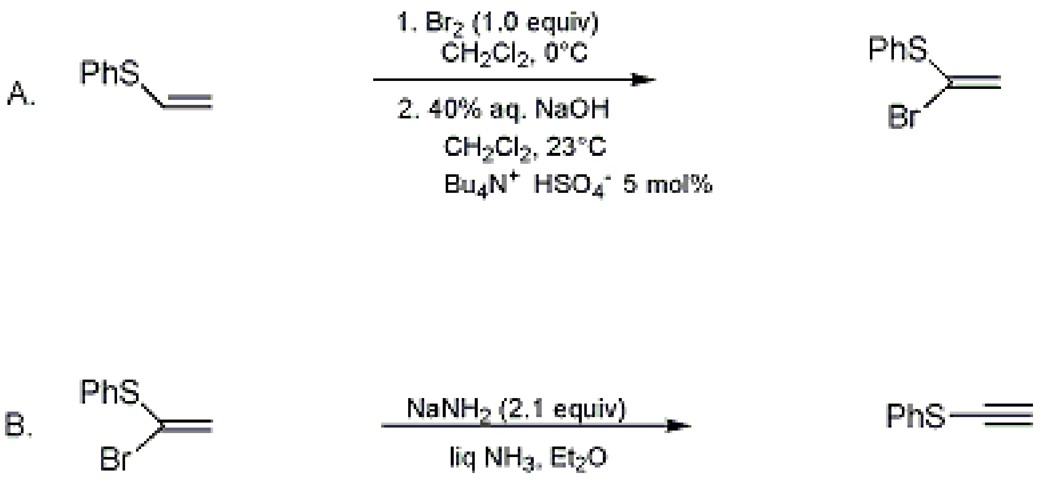
Organic Syntheses, CV 9, 656

PHENYLTHIOACETYLENE

[Benzene, (ethynylthio)-]



Submitted by Plato A. Magriotis and John T. Brown[1].
Checked by Armin Walser, Carl Mason, and David L. Coffen.

1. Procedure

CAUTION! These operations involve reagents and solvents with potentially harmful vapors (Br_2, NH_3) and therefore should be conducted in an efficient hood. The use of disposable gloves is highly recommended.

A. *1-Bromovinyl phenyl sulfide*. A 1-L, round-bottomed flask is equipped with a 1.5-in egg-shaped magnetic stirring bar and a 100-mL, pressure-equalizing, addition funnel fitted with a Claisen adapter that contains a drying tube and stopper. The flask is charged with 40.8 g (0.30 mol) of phenyl vinyl sulfide (Note 1) and 250 mL of dichloromethane (Note 2). The resulting solution is cooled to 0°C and 49.6 g (0.31 mol) of bromine (Note 3) is added dropwise over approximately 1 hr through the funnel, until a bright red color persists. The intermediate product, phenylthio-1,2-dibromoethane (Note 4), is then treated at 0°C with 250 mL of aqueous 40% sodium hydroxide followed by 5.1 g (15 mmol, 5 mol%) of the phase-transfer catalyst tetrabutylammonium hydrogen sulfate. Vigorous stirring is continued at ambient temperature for 2–3 hr until TLC (10% benzene, 90% hexane) indicates that dehydrobromination is complete (Note 5). The organic layer is separated and the aqueous layer is extracted with two 200-mL portions of dichloromethane. The combined organic extracts are washed with a saturated solution of sodium bisulfite (250 mL), water (250 mL), and brine (250 mL) and dried over sodium sulfate. Excess dichloromethane is removed under reduced pressure on a rotary evaporator and the resulting dark brown oil is distilled under vacuum (1.5 mm) to provide 51.5–58.0 g

(80–90%) of pure 1-bromovinyl phenyl sulfide as a pale yellow liquid, bp 76–78°C (Note 6) and (Note 7).

B. *Phenylthioacetylene*. An oven-dried, 2-L, three-necked, round-bottomed flask is equipped with a mechanical stirrer (Note 8), an acetone-dry ice condenser with a drying tube containing potassium hydroxide pellets, and a gas inlet. The flask is placed in an acetone-dry ice bath (–40°C, bath temperature) and 450 mL of anhydrous ammonia (Note 9) is condensed into the flask. Upon addition of a small piece of sodium metal (ca. 0.6 g) to the liquid ammonia the characteristic deep blue color develops. A catalytic amount of anhydrous ferric chloride (0.25 g, 1.5 mmol; 0.3 mol %) is added with continued stirring (Note 10) and the color of the reaction mixture turns gray. The remaining sodium metal (10.0 g, 0.46 g-atom total) is added in 0.6-g pieces over ca. 1 hr, since the blue color must be discharged before each new addition of sodium. A gray suspension of sodium amide is obtained upon completion of this addition. The temperature of the cooling bath is adjusted to −50°C and the gas inlet is replaced with a 250-mL, pressure-equalizing addition funnel containing 49.5 g (0.23 mol) of 1-bromovinyl phenyl sulfide in 100 mL of anhydrous ether (Note 11). This solution is added dropwise to the freshly generated sodium amide over 20 min, while the temperature of the acetone-dry ice bath is maintained at –50°C. Stirring is continued (Note 8) at this temperature for 0.5 hr, the brown-red reaction mixture is allowed to warm to reflux temperature (–33°C) during 1 hr, and then is recooled to –60°C (bath temperature). Solid ammonium chloride is added slowly (Note 12) to quench the sodium phenylthioacetylide, the cooling bath is removed, and the ammonia is allowed to evaporate. During evaporation, 400 mL of anhydrous ether (Note 13) is added dropwise through the addition funnel to replace ammonia. The resulting mixture is filtered at ambient temperature and reduced pressure through a coarse, Celite-packed, fritted-glass filter to remove the inorganic salts that are subsequently washed three times with 50 mL of anhydrous ether. The combined ethereal filtrate and washes are concentrated on a rotary evaporator and the dark brown residue (Note 14) is transferred to a 100-mL, round-bottomed flask fitted with a short-path distillation head. Pure product (Note 15) is distilled at 1.5 mm pressure (bp 48–50°C, (Note 16)) into an ice-cooled receiver. In this way, 21.6–24.7 g (70–80% yield) of phenylthioacetylene (Note 17) is obtained as a pale yellow liquid, which turns brown-red upon storage at −10°C (freezer) within a few hours (Note 18). Phenylthioacetylene stored under these conditions is stable for several months.

2. Notes

1. Phenyl vinyl sulfide is prepared from thiophenol and 1,2-dibromoethane according to the procedure described by Paquette and Carr; see: *Org. Synth., Coll. Vol. VII* **1990**, 453. An alternative preparation may be found on p. 662. An earlier, three-step synthesis employing 2-chloroethanol instead of 1,2-dibromoethane is available.[2]

2. Dichloromethane (A.C.S. certified) was obtained from Fisher Scientific

Company and used as received.
3. Bromine (A.C.S. certified) was purchased from Aldrich Chemical Company Inc., used as received, and measured with a 50-mL graduated cylinder in the hood.
4. At this point crude phenylthio-1,2-dibromoethane can be isolated by separation of the organic phase, extraction of the aqueous layer with dichloromethane, washing of the combined extracts with saturated sodium bisulfite solution, drying ($MgSO_4$), and concentration (95% crude yield): ^1H NMR (270 MHz, $CDCl_3$) δ: 3.75 (dd, 1 H, J = 11.0, 8.6), 3.94 (dd, 1 H, J = 11.0, 5.5), 5.39 (dd, 1 H, J = 8.6, 5.5), 7.20–7.70 (m, 5 H). This dibromide is relatively unstable giving rise to a streak on silica gel TLC (10% benzene, 90% hexanes; R_f of the streak front is ca. 0.35, anisaldehyde detection). It has been reported that a 2:1–3:1 ratio of cis- and trans-2-bromovinyl phenyl sulfide is obtained upon distillation of the above dibromide.[2]
5. Neither a streak nor any significant by-product is detected (UV and anisaldehyde) by TLC analysis (Merck 0.25-mm thickness silica gel plates with 254 nm UV indicator).
6. Assay of this material by GC/MS (HP 5970 Mass Selective Detector equipped with a 50-m HP-1 capillary column) shows it to be ca. 96% pure (R_t = 3.6 min; 80–280°C, 20°C/min). The spectral and analytical properties are as follows: ^1H NMR (270 MHz, $CDCl_3$) δ: 5.83 (d, 1 H, J = 2.2), 5.93 (d, 1 H, J = 2.2), 7.35–7.55 (m, 5 H); MS m/e (relative intensity) 216 (M^+, 17), 214 (16), 135 (100), 109 (15). Anal. Calcd for C_8H_7BrS: C, 44.67; H, 3.28; S, 14.91. Found: C, 44.30; H, 3.46; S, 15.23.
7. The literature boiling point is reported as 70–73°C (2 mm). 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) in ether has been employed to effect this elimination.[3] However, the procedure reported here is more amenable to large scale preparation because of its lower cost.
8. The stirring blade should be glass because sodium in ammonia solution attacks Teflon.
9. Commercial anhydrous ammonia is employed without further drying.
10. Stirring is maintained at a rate such that splattering of the reaction mixture on the upper parts of the flask's side-wall is minimized (see also ref 4, Chapter I, pp 1–4).
11. Ether is distilled from sodium-benzophenone ketyl under argon just prior to use.
12. A total of 35 g of solid ammonium chloride is added in portions of ca. 1 g with a spatula.
13. Anhydrous ether (A.C.S. certified) was obtained from Fisher Scientific Company and used as received.
14. TLC analysis (10% benzene, 90% hexanes) of the crude reaction mixture (95% yield) indicates complete conversion of vinyl bromide (R_f = 0.5) to phenylthioacetylene (R_f = 0.6). A minor product, which can be purified by flash column chromatography and identified as cis-1,2-bis(phenylthio)ethylene,[4 5 6 7]

[8 9] is also detected (R_f = 0.3) in variable amounts (5–15% yield) depending on the run.
15. Assay of this material by GC/MS shows it to be >98% pure (R_t = 3.0 min; 80–280°C, 15°C/min).
16. Four literature boiling points are reported: 78–79°C (7 mm),[5] 86–88°C (14 mm),[2] 61–62°C (5 mm),[2] and 48°C (0.8 mm).[10]
17. Spectral and analytical properties for phenylthioacetylene are as follows: IR (neat) cm^{-1}: 3285, 2040, 1585; ^1H NMR (270 MHz, $CDCl_3$) δ: 3.26 (s, 1 H), 7.20–7.50 (m, 5 H), ; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ: 70.0, 87.0, 126.5, 126.7, 129.2, 131.4; MS m/e (relative intensity) 134 (M^+, 100), 90 (24), 89 (26), 51 (44). Anal. Calcd for C_8H_6S: C, 71.60; H, 4.51; S, 23.89. Found: C, 71.77; H, 4.63; S, 24.31.
18. It has been reported that methyl phenyl sulfide acts as a stabilizer; phenylthioacetylene did not tend to darken in its presence.[5]

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

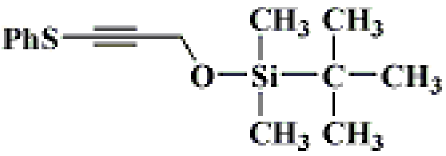
Phenylthioacetylene has been prepared by elimination of thiophenol and dehydrobromination of cis-1,2-bis(phenylthio)ethylene[4,5,6,7,8,9] and cis-1-bromo-2-phenylthioethylene,[2,11 12] respectively. The latter was obtained by addition of thiophenol to propiolic acid in ethanol and subsequent one-pot bromine addition, decarboxylative dehalogenation, and careful distillation to remove the trans isomer.[2,11,12] On the other hand, cis-1,2-bis(phenylthio)ethylene was prepared by double addition of thiophenol to cis-1,2-dichloroethylene.[4,5,6,7] Although these procedures can provide useful amounts of phenylthioacetylene, they were found to be somewhat less satisfactory in our hands as far as operation and/or overall yields are concerned. Furthermore, we have encountered problems with regard to the reproducibility of one-pot dehydrobrominations of phenylthio-1,2-dibromoethane.[10 13 14 15] However, the stepwise execution of the double dehydrobromination, as described in the modified procedure reported here, provides preparatively useful quantities of phenylthioacetylene in a practical manner.

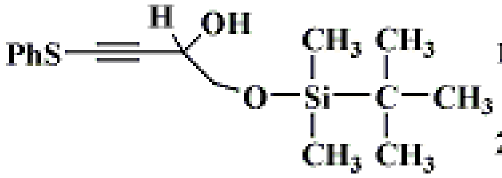
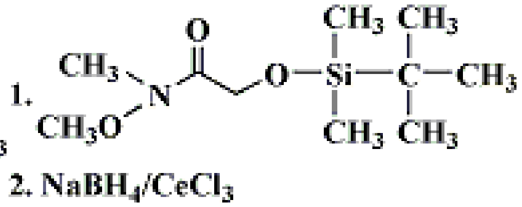
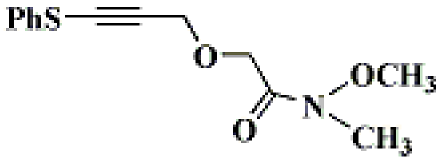
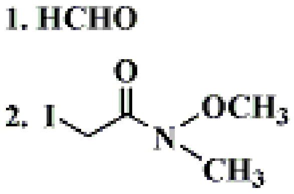
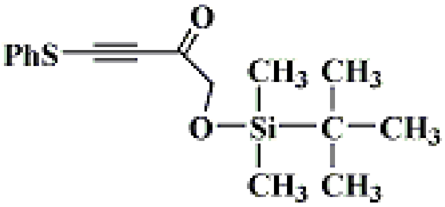
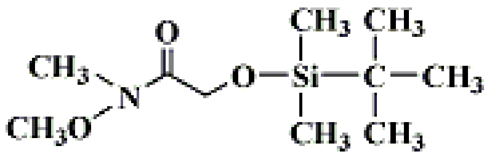
A reported procedure based on lithium diisopropylamide induced double elimination of ethanol from bromoacetaldehyde diethyl acetal also was not very effective for the large scale preparation of phenylthioacetylene.[16] Another more recent synthesis of the title compound relies on the reaction of dimethyl(chloroethynyl)carbinol with an alkali

metal phenylthiolate, followed by elimination of acetone under basic conditions.[17] Finally, synthesis of phenylthioacetylene has been achieved by the reaction of lithium trimethylsilyl acetylide with either phenylsulfinyl chloride[18] or the relatively expensive (>$10/1 g, Fluka Chemical Corp.) phenyl benzenethiosulfonate[15,19] and subsequent desilylation.

A large variety of phenylthio-substituted alkynes can be conveniently prepared from phenylthioacetylene as the nucleophilic component (Table I).[20 21 22 23] This type of construction is more flexible than the one based on nucleophilic substitution of a terminal alkali metal acetylide on phenyl benzenethiosulfonate, phenyl sulfinyl chloride, and/or diphenyl disulfide.[24,25] Regio- and stereoselective syntheses of functionalized vinyl sulfides[26 27 28 29 30] are accomplished by Pd(0)-catalyzed hydrostannation,[22] hydroboration,[31] treatment with low-valent tantalum,[32] and stannylcupration[15,33] of 1-phenylthio-1-alkynes. In turn, vinyl sulfides are very useful intermediates in organic synthesis not only as carbonyl-masking moieties,[34 35 36 37 38] but also in a variety of other transformations,[39 40 41 42 43] including the Ni(0)-catalyzed cross-coupling reactions with alkyl, aryl, and alkenyl Grignard reagents.[44 45 46 47] The important role of the phenylthio group and its higher oxidation states in activating and directing olefins in cycloaddition reactions[48 49 50] has been reviewed.[48]

TABLE
PREPARATION OFPHENYLTHIOALKYNES FROMPHENYTHIOACETYLENE1

Entry	Phenylthioalkyne[a]	Electrophile[b]	% Yield[c]
1.		1. HCHO 2. t-BuMe$_2$SiCI	82
2.		HCHO	86
3.		MeI	89

4.			70
		2. $NaBH_4/CeCl_3$ 1. HCHO	
5.			78
6.		$ClCO_2Et$	85
7.			75
8.		PhI	73
9.		BuI	80
10.		Me_3SiCl	90

[a]All Phenylthio alkyne products exibited spectral properties (^1H NMR, IR, and GC/MS) in accord with the assigned structures. [b]The electrophile employed in entries 4 and 7 was prepared from glycolic acid by reaction of its bis(*tert*-butyldimethylsilyl) derivative with oxalyl chloride followed by N,O-dimethylhyroxylamine hydrochloride.[51] Entry 8 involved Pd(O)- and Cu(I)-catalyzed coupling. [c]Isolated yield after preparative TLC, silica flash chromatography, or short-path distillation.

Finally, useful stereoselectivities have been recorded for the heteroconjugate addition

of organometallic reagents to 1-silyl substituted vinyl sulfones.[52 53] The synthesis of such sulfones can be achieved starting from phenylthioacetylene.[15,19,54] The synthesis of the dicobalt hexacarbonyl complex[55] and the polymerization of phenylthioacetylene[56] have been described.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hexanes

brine

HCHO

sodium-benzophenone ketyl

N,O-dimethylhyroxylamine hydrochloride

t-BuMe$_2$SiCI

MeI

CICO$_2$Et

PhI

BuI

Me_3SiCI

ethanol (64-17-5)

ammonia (7664-41-7)

Benzene (71-43-2)

ether (60-29-7)

ammonium chloride (12125-02-9)

sodium hydroxide (1310-73-2)

bromine (7726-95-6)

sodium sulfate (7757-82-6)

sodium bisulfite (7631-90-5)

acetone (67-64-1)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

1,2-dibromoethane (106-93-4)

ferric chloride (7705-08-0)

2-chloroethanol (107-07-3)

dichloromethane (75-09-2)

Thiophenol (108-98-5)

tantalum (7440-25-7)

sodium amide (7782-92-5)

hexane (110-54-3)

argon (7440-37-1)

diphenyl disulfide (882-33-7)

phenylsulfinyl chloride, phenyl sulfinyl chloride (4972-29-6)

methyl phenyl sulfide (100-68-5)

lithium diisopropylamide (4111-54-0)

bromoacetaldehyde diethyl acetal (2032-35-1)

propiolic acid (471-25-0)

tetrabutylammonium hydrogen sulfate (32503-27-8)

Phenyl vinyl sulfide (1822-73-7)

anisaldehyde (123-11-5)

1-Bromovinyl phenyl sulfide (80485-53-6)

cis- and trans-2-bromovinyl phenyl sulfide

1,8-diazabicyclo[5.4.0]undec-7-ene (6674-22-2)

Phenylthioacetylene, Benzene, (ethynylthio)- (6228-98-4)

phenylthio-1,2-dibromoethane

sodium phenylthioacetylide

cis-1,2-bis(phenylthio)ethylene

cis-1,2-dichloroethylene (156-59-2)

dimethyl(chloroethynyl)carbinol

lithium trimethylsilyl acetylide

phenyl benzenethiosulfonate

cis-1-bromo-2-phenylthioethylene

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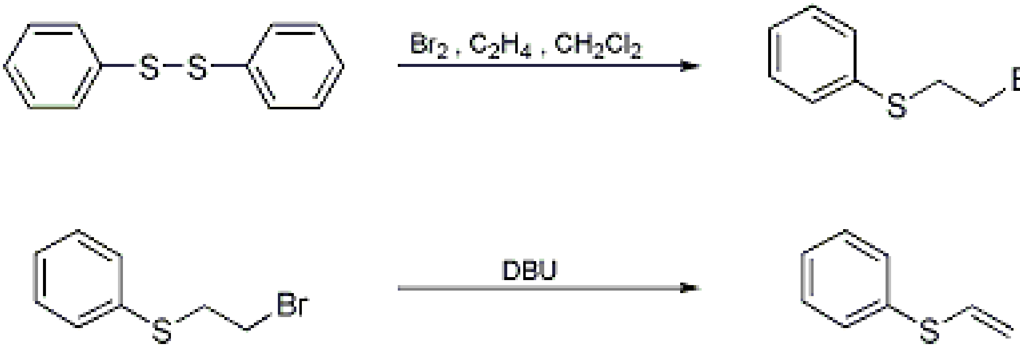
Organic Syntheses, CV 9, 662

PHENYL VINYL SULFIDE

[Benzene, (ethenylthio)-]



Submitted by Daniel S. Reno[1] and Richard J. Pariza[2].
Checked by David A. Barda and William R. Roush.

1. Procedure

CAUTION! The intermediate, 1-phenylthio-2-bromoethane, produced in the first step of this one pot reaction sequence is a strong alkylating agent, and some bromine escapes from the reaction vessel. Therefore the reaction should be run in a properly operating ventilation hood, and care must be exercised to avoid exposure to these substances.

A 2-L, three-necked, round-bottomed flask fitted with a reflux condenser, an addition funnel, a magnetic stirring bar, thermometer, and nitrogen inlet is charged with diphenyl disulfide (200 g, 917 mmol) and dichloromethane (320 mL) (Note 1). The addition funnel is charged with bromine (161 g, 52 mL, 1.01 mol). After the diphenyl disulfide dissolves, the nitrogen inlet is replaced with a calcium sulfate-packed drying tube, and the flask is fitted with a gas-dispersion tube. Ethylene (73.1 g, 2.61 mol) (Note 2), (Note 3) is slowly bubbled into the solution through a gas dispersion tube, and the bromine is added in 2–3-mL portions over 5 hr (Note 4), (Note 5). After addition of the bromine and ethylene is complete, the drying tube is replaced with the nitrogen inlet, and the flask is fitted with a clean addition funnel. The addition funnel is charged with 1,8-diazabicyclo[5.4.0]undec-7-ene, DBU, (306 g, 300 mL, 2.01 mol) (Note 6). DBU is added at a rate such that the temperature of the reaction mixture does not exceed 55°C. After the DBU is added the reaction mixture is maintained at about 50°C for 15–18 hr. A 1.0 M ammonium hydroxide solution (600 mL) is added to the reaction mixture, and the mixture is transferred to a separatory funnel. The layers are separated, and the aqueous layer is extracted with 300 mL of dichloromethane. The organic fractions are combined, washed with water (600 mL), and dried with 10 g of magnesium sulfate. The mixture is filtered, and the solvent is evaporated under

reduced pressure. Distillation of the residue affords 162–184 g (65–74%) of phenyl vinyl sulfide, bp 80–84°C/11–12 mm (Note 7), (Note 8), (Note 9) and (Note 10). The purity is greater than 98% by GC analysis (Note 11), (Note 12).

2. Notes

1. All the materials used in this process were obtained from the Aldrich Chemical Company, Inc., and were used as received.
2. Initiation of the ethylene addition should precede the introduction of the first portion of bromine by 2–4 min. Ethylene is then added continuously at a slow rate until all the bromine is consumed (see (Note 4)).
3. The submitters reported that use of less than 1.41 equiv (2.62 mol) of ethylene reduces the yield of product. The checkers used a 145–174-•m fritted gas dispersion tube, and up to 1.84 equiv of ethylene (3.38 mol) was required to consume all the bromine (see (Note 4)). However, on one occasion the checkers obtained excellent results (83% yield) using only 1.26 equiv of ethylene (2.30 mol). In this instance, a 25–50-•m fritted gas dispersion tube was used, which permitted a slower and more efficient rate of ethylene introduction.
4. The first 2–3-mL portion of bromine is added until the reaction mixture is intensely violet. Subsequent portions of bromine are added when the reaction mixture fades to an amber color. After all the bromine has been added, ethylene addition is continued until the color fades to amber.
5. A competing process involving halogenation of the phenyl substituent occurs when the bromine concentration becomes too high. The slow addition of bromine specified here minimizes the competing aromatic bromination.
6. The submitters report that use of less than this amount of DBU reduces the yield of phenyl vinyl sulfide.
7. The checkers obtained 204–207 g (82–84%) of phenyl vinyl sulfide, bp 83–84°C/11–12 mm.
8. Phenyl vinyl sulfide has the following spectral properties: EI MS 136; ^{1}H NMR (400 MHz, $CDCl_3$) δ:5.35 (d, 1 H, J = 16.9), 5.36 (d, 1 H, J = 9.8), 6.55 (dd, 1 H, J = 9.8, 16.9), 7.22–7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 115.4, 127.1, 129.1, 130.4, 131.8, 134.2.
9. Phenyl vinyl sulfide prepared using this procedure is stable at room temperature under a nitrogen atmosphere for months. The submitters have kept samples for over nine months at ambient temperature without any visible degradation.
10. This procedure was used by the submitters to prepare 97 kg of phenyl vinyl sulfide from 100 kg of diphenyl disulfide (78% yield).
11. The GC analysis was performed with a Hewlett-Packard, HP-1 column (10 m × 0.53 mm × 2.65 •m). The temperature program was as follows: initial temperature, 50°C; initial time, 2.0 min; rate, 20°C/min; final temperature, 250°C; final time, 8 min.
12. The checkers identified the two major impurities as p-bromophenyl vinyl

sulfide (see (Note 5)) and 2-chloroethyl phenyl sulfide by GCMS analysis.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Phenyl vinyl sulfide possesses a number of synthetically useful attributes. It participates as an electron-rich alkene in 1+2,[3] 2+2,[4] 3+2,[5] and 4+2[6] cycloaddition reactions. Deprotonation of phenyl vinyl sulfide with strong base affords an α-metallated sulfide that reacts with electrophiles.[7] The metallation-electrophile sequence and the cycloaddition reactions afford products amenable to further synthetic manipulation via the sulfide functionality. Furthermore, phenyl vinyl sulfide is a convenient precursor to the synthetically useful phenyl vinyl sulfoxide and phenyl vinyl sulfone.[8]

The procedure described here affords phenyl vinyl sulfide in a high yield using common reagents and mild conditions. The material obtained via this procedure is stable at room temperature under a nitrogen atmosphere for months. As indicated in (Note 10), this process is readily scaled up. Other methods either afford lower yields,[8,9,10] less stable product,[8] or require more extreme conditions.[11,12]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 107
- Org. Syn. Coll. Vol. 9, 656

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

DBU

bromine (7726-95-6)

nitrogen (7727-37-9)

ethylene (9002-88-4)

ammonium hydroxide (1336-21-6)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

diphenyl disulfide (882-33-7)

Phenyl vinyl sulfone (5535-48-8)

1-Phenylthio-2-bromoethane (4837-01-8)

Phenyl vinyl sulfide, Benzene, (ethenylthio)- (1822-73-7)

Phenyl vinyl sulfoxide (20451-53-0)

1,8-diazabicyclo[5.4.0]undec-7-ene (6674-22-2)

p-bromophenyl vinyl sulfide

2-chloroethyl phenyl sulfide (5535-49-9)

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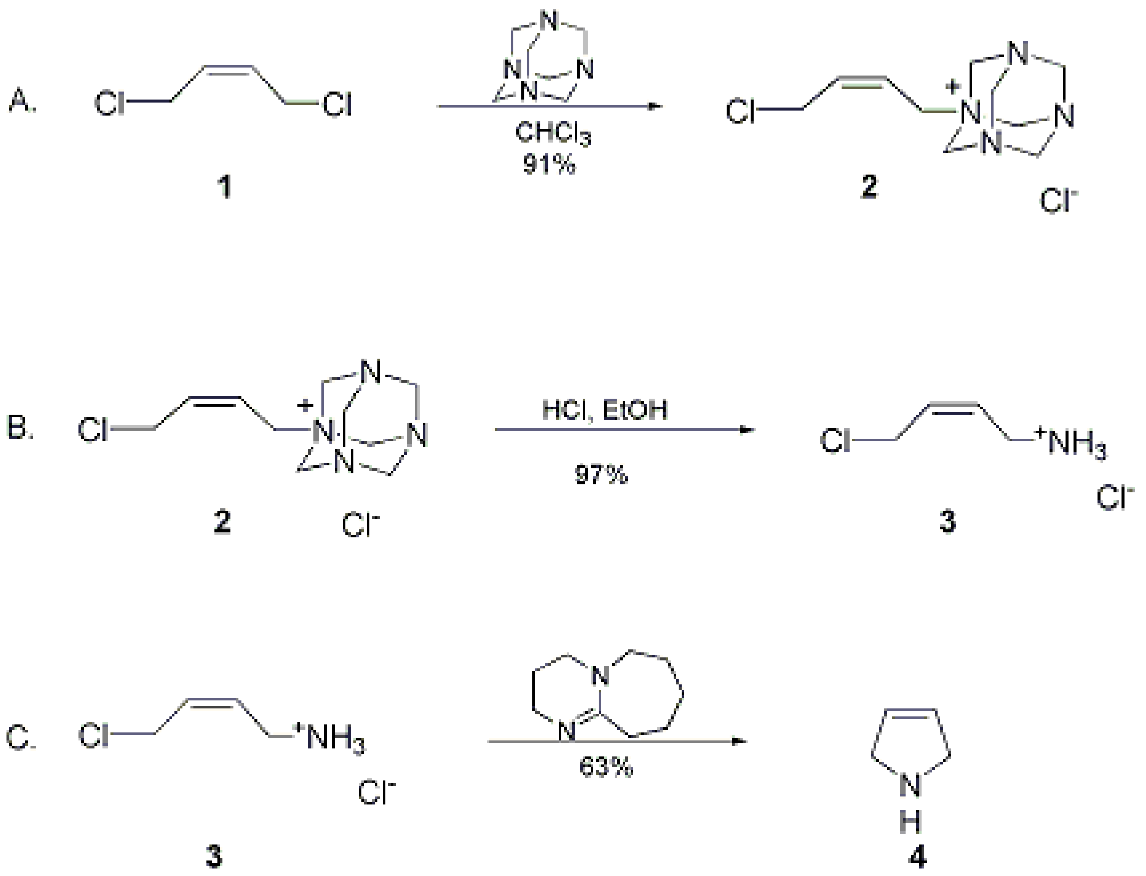
Organic Syntheses, CV 9, 666

3-PYRROLINE

[1H-Pyrrole, 2,5-dihydro-]



Submitted by Albert I. Meyers[1], Joseph S. Warmus, and Garrett J. Dilley.
Checked by Kevin W. Gillman and David J. Hart.

1. Procedure

A. *1-[(Z)-4-Chloro-2-butenyl]-1-azonia-3,5,7-triazatricyclo[3.3.1.1^{3,7}]decane chloride* (**2**). A 1-L, single-necked, round-bottomed flask is charged with 34.4 g (246 mmol) of hexamethylenetetramine and 500 mL of chloroform ($CHCl_3$) (Note 1). cis-1,4-Dichlorobut-2-ene (30.2 g, 242 mmol) is added, the flask is fitted with a reflux condenser (Note 2), and the mixture is heated to reflux with a heating mantle. After 4 hr, the mixture is cooled to room temperature, and filtered through a sintered glass funnel (10–20 • porosity). The resulting white solid, quaternary salt **2**, is washed with two 100-mL portions of $CHCl_3$, and the filtrate is heated to reflux for an additional 18 hr, cooled, and filtered. The resulting light brown solid **2** is washed twice with 50-mL portions of $CHCl_3$. The combined solids are dried in a desiccator under reduced pressure (1 mm) to afford 58.6 g (91%) of **2** (Note 3).

B. *(Z)-4-Chloro-2-butenylammonium chloride* (**3**). A 1-L, single-necked, round-

bottomed flask, equipped for magnetic stirring, is charged with 400 mL of 95% ethanol (EtOH) and 70 mL of concd hydrochloric acid (HCl) is slowly added (slightly exothermic reaction). To the still warm solution is added solid 2 (58.5 g, 221 mmol) in one portion. The reaction initially becomes homogeneous and slightly orange colored, then after 45 min a precipitate begins to form. The reaction mixture is allowed to stir at room temperature for 18 hr, cooled to 0°C, and the precipitate (NH_4Cl) is collected by filtration using a 10–20 • porosity sintered glass funnel. The collected solid is washed on the funnel twice with 100 mL of cold 95% EtOH. The filtrate is concentrated by rotary evaporation, and the remaining semisolid is taken up in 40 mL of cold 95% EtOH. The resulting precipitate (NH_4Cl) is again collected on the filter and washed with cold 95% EtOH (2 × 20 mL). This procedure (rotary evaporation, solution in 95% EtOH, cooling, filtration) is repeated once more.

The solid remaining upon concentration of the filtrate from the final filtration is dissolved in 80 mL of warm ethyl acetate (EtOAc). Upon cooling, the product crystallizes. Hexane is added (30 mL) and the crystals are collected on a 10–20 • porosity sintered-glass funnel. The solid is washed with 60 mL of hexane. The filtrate is concentrated by rotary evaporation to give an additional amount of solid that is recrystallized from a minimum amount of EtOAc and hexane as before. The combined solids are dried in a desiccator under reduced pressure (1 mm) for 2 hr to give 28.1–30.4 g (90–96%) of **3** as a light yellow crystalline solid (Note 4).

C. *3-Pyrroline* (**4**). A 200-mL round-bottomed flask, equipped with a reflux condenser, is charged with 66.4 g (437 mmol) of 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU) which is cooled to 0°C in an ice bath while 3 (30.3 g, 213 mmol) is added in portions through the top of the condenser. Toward the end of the addition, the resulting slurry becomes orange, gas is evolved, and mixture begins to reflux (the reaction is exothermic). Any remaining salt **3** is added, and, when boiling subsides, a short-path distillation head wrapped in glass wool is put in place (Note 5). A 50-mL receiving flask is totally immersed in a –78°C bath (dry ice-isopropyl alcohol). The orange solid mixture is heated using a heating mantle during which time the solid liquifies and 3-pyrroline (**4**) distills at 85–92°C at atmospheric pressure. (*CAUTION: some foaming occurs initially, but subsides during the reaction)*. Heating is continued until no more 3-pyrroline distills, affording 11.05 g (75%) of 3-pyrroline as a clear oil (Note 6), (Note 7).

2. Notes

1. Hexamethylenetetramine and cis-1,4-dichloro-2-butene (95%) were obtained from Aldrich Chemical Company, Inc., and were not purified before use. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU), chloroform, ethyl acetate, and hexane were distilled prior to use.
2. The mixture is left open to air.
3. All physical data for **2** are consistent with that given in reference [2]: mp 160–170°C dec; ^{1}H NMR (D_2O) δ: 3.54 (dd, 2 H, J = 7.9, 0.5), 4.10 (dd, 2 H, J = 8.1,

0.5), 4.43 (d, 3 H, J = 12.9), 4.58 (d, 3 H, J = 12.9), 5.01 (s, 6 H), 5.67 (m, 1 H), 6.23 (complex m, 1 H); ^{13}C NMR (D_2O) δ: 40.5, 55.4, 73.0, 81.1, 119.6, 140.9. The yield of the first crop is 81–82%. The second crop contains a minor impurity as indicated by a doublet at δ 3.79 in the ^{1}H NMR, but is used in the next step.

4. The physical properties of **3** are as follows: mp 117–120°C dec; ^{1}H NMR (D_2O) δ: 3.63 (d, 2 H, J = 7.3), 4.07 (d, 2 H, J = 8.0), 5.58 (m, 1 H), 5.89 (m, 1 H); ^{13}C NMR (D_2O) δ: 38.8, 41.4, 127.5, 134.9. This material is easily stored without any special precautions.

5. The distillation should be carried out under an inert atmosphere.

6. The 3-pyrroline (**4**), prepared as described above, is estimated to be >95% pure. A sample was stored at 0°C in a stoppered, round-bottomed flask for six months with very little oxidation or decomposition; the compound, however, had yellowed. For prolonged storage, a sealed ampoule is recommended. The checkers obtained a somewhat lower yield of **4**using an oil bath at 200°C for the distillation, whereas the submitters employed a heat gun and obtained a 63% yield of **4** (bp 80–85°C).

7. The NMR spectra of 3-pyrroline (**4**) are as follows: ^{1}H NMR ($CDCl_3$) δ: 1.93 (s (broad), 1 H), 3.71 (s, 4 H), 5.84 (s (broad), 2 H); ^{13}C NMR ($CDCl_3$) δ: 53.6, 128.2.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

3-Pyrroline is a desirable starting material for alkylation of heterocycles. 1-(Methoxycarbonyl)-3-pyrroline[3] has been used to prepare 2,5-dialkylated pyrrolines,[4] which resulted in the synthesis of the Pharaoh ant trail pheromone[5] and gephyrotoxin 223.[6] Alkylation of 3-pyrrolines has also led to the synthesis of 12-azaprostaglandins.[7] The submitters have used a formamidine derived from 3-pyrroline to provide access to 2-substituted pyrrolines and pyrrolidines,[8 9] which has led to the synthesis of the unnatural (+)-anisomycin.[10]

Recently, Brown has shown the feasibility of a one-carbon homologation procedure using a chiral non-racemic boronate derived from the hydroboration of 3-pyrroline.[11 12] Pyrrole-containing nucleosides have been prepared from the pyrroline nucleoside by photodehydrogenation.[13 14]

Pure 3-pyrroline has been difficult to obtain. Commercially available 3-pyrroline was at one time supplied in 85% purity, the remaining 15% being pyrrolidine.[15] It is now

supplied in only 65% purity. Material of 97% purity is available; however, the cost ($51/g) is excessively high, limiting its use as a starting material.[15,16]

Preparation of N-alkyl-3-pyrrolines has been accomplished by treatment of cis-1,4-dihalo-2-butene with the appropriate amine.[17 18 19] However, synthesis of the parent 3-pyrroline by condensation of cis-1,4-dihalo-2-butene with ammonia is a very low-yielding process.[18]

Reduction of pyrrole by zinc/hydrochloric acid (Zn/HCl) leads to various amounts of pyrrolidine as overreduced material.[20 21] Other preparations of pure 3-pyrroline were found to be difficult or of low yield.[20 21 22 23 24 25] Separation of 3-pyrroline from pyrrolidine is difficult, as they differ in boiling points by only 1.5°C.[21] Crystallization of their hydrochloride salts,[21] or urethanes,[26] is possible, but only with significant losses.

A three-step preparation, based on the Delépine reaction,[2] describes the synthesis of this compound in high purity.[27] However, some difficulties were encountered in the hands of the submitters following this procedure.[28] Several modifications have now led to an efficient preparation of 3-pyrroline in high purity, and to a procedure that is readily amenable to large scale synthesis.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

(NH_4Cl)

ethanol, EtOH (64-17-5)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ethyl acetate, EtOAc (141-78-6)

chloroform (67-66-3)

hexamethylenetetramine (100-97-0)

Pyrrole (109-97-7)

pyrrolidine (123-75-1)

hexane (110-54-3)

Formamidine

3-Pyrroline, 1H-Pyrrole, 2,5-dihydro-

1,8-diazabicyclo[5.4.0]undec-7-ene, 1,8-diazabicyclo[5.4.0] undec-7-ene (6674-22-2)

cis-1,4-Dichlorobut-2-ene, cis-1,4-dichloro-2-butene (1476-11-5)

(Z)-4-Chloro-2-butenylammonium chloride (7153-66-4)

1-(Methoxycarbonyl)-3-pyrroline

1-[(Z)-4-Chloro-2-butenyl]-1-azonia-3,5,7-triazatricyclo[3.3.1.1^{3,7}]decane chloride (117175-09-4)

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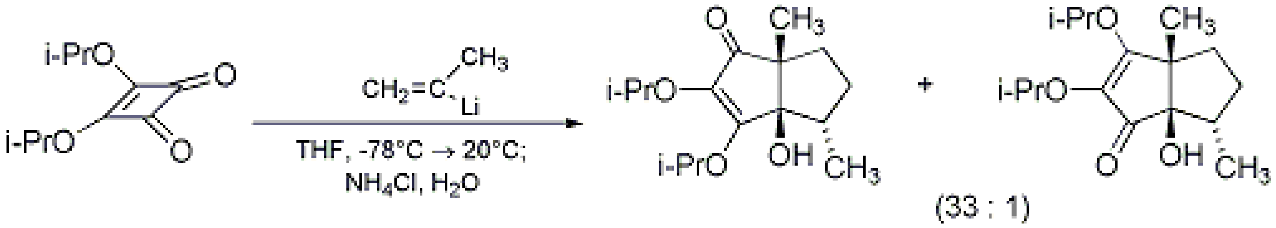
Organic Syntheses, CV 9, 670

PREPARATION OF POLYQUINANES BY DOUBLE ADDITION OF VINYL ANIONS TO SQUARATE ESTERS: 4,5,6,6a-TETRAHYDRO-3a-HYDROXY-2,3-DIISOPROPOXY-4,6a-DIMETHYL-1(3aH)-PENTALENONE



Submitted by Tina Morwick and Leo A. Paquette[1].
Checked by Lisa Frey and Ichiro Shinkai.

1. Procedure

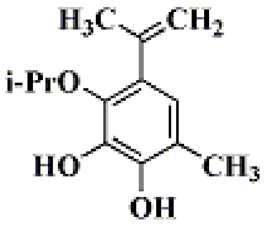
A 1000-mL, two-necked, round-bottomed flask (Note 1) is equipped with a rubber septum, magnetic stirring bar, and gas inlet connected to a vacuum/argon line via a Firestone valve. The flask is flame-dried under vacuum, then filled with argon. Ten cycles of evacuation and argon fill are carried out. The flask, in which a positive flow of argon is maintained throughout the entire procedure, is charged with 6.66 mL (75 mmol) of 2-bromopropene (Note 2) dissolved in dry tetrahydrofuran (250 mL) (Note 3). The solution is cooled to −78°C by a dry ice/acetone bath, at which point 88 mL of 1.7 M tert-butyllithium in pentane (150 mmol) is introduced dropwise in three roughly equal portions from a 50-mL syringe (Note 4) during 45 min. The colorless reaction mixture is allowed to stir at −78°C for approximately 30 min (Note 5).

A 250 mL, two-necked, round-bottomed flask, equipped with a rubber septum and gas inlet, is flame-dried under vacuum, filled with argon, and charged with a solution of diisopropyl squarate (5.94 g, 30 mmol) (Note 6) in dry tetrahydrofuran (150 mL). The solution is cooled to −78°C and cannulated rapidly into the reaction flask (Note 7). After completion of the addition, the mixture is stirred for 2 hr at 0°C, then for an additional 15 hr at room temperature. Following recooling to 0°C, 180 mL of saturated ammonium chloride solution (Note 8) is added via syringe, the ice bath is removed, and stirring is continued for an additional 7 hr.

The reaction mixture is poured into a 2000-mL separatory funnel containing water (300 mL) and ether (300 mL). After thorough mixing, the aqueous layer is separated and extracted with ether (2 × 200 mL). The combined ethereal solutions are washed with water (300 mL) and brine (300 mL), dried over magnesium sulfate, and evaporated under reduced pressure to leave 8.5 g of a pale yellow oil. This material is subjected to flash chromatography on silica gel using 20% ethyl acetate in hexanes as the mobile phase (Note 9). The minor diquinane (230 mg, (Note 10)) is eluted first. A mixed fraction of the two isomers follows (570 mg, (Note 11)) in advance of the pure title compound (6.36 g, (Note 12), (Note 13)).

2. Notes

1. All apparatus was washed with base and oven-dried overnight.
2. 2-Bromopropene was purchased from the Aldrich Chemical Company, Inc., and used as received.
3. Tetrahydrofuran was freshly distilled from sodium benzophenone ketyl.
4. tert-Butyllithium was purchased from the Aldrich Chemical Company, Inc., and titrated before use with diphenylacetic acid according to an established procedure.[2] The syringe and needle were oven-dried overnight prior to use. The plunger is rotated slowly and continuously throughout the addition to avoid loss of mobility brought on by the adventitious formation of lithium hydroxide. *This alkyllithium is extremely pyrophoric and must be treated cautiously to avoid exposure to the atmosphere.*
5. tert-Butyllithium forms a yellow complex with tetrahydrofuran at low temperatures. When all of this reagent is consumed, the yellow color disappears and a colorless solution of the vinyl anion is obtained. If the color continues the remaining tert-butyllithium can be consumed by the slow addition of a few drops of 2-bromopropene until a colorless solution results.
6. Diisopropyl squarate, available from the Aldrich Chemical Company, Inc., can be readily prepared from squaric acid according to the procedure reported by Liebeskind.[3]
7. An oven-dried, 18-gauge cannula wrapped with glass wool and aluminum foil was used.
8. This solution was deoxygenated by bubbling argon through it for a period of 15 min immediately before use.
9. The dimensions of the column were 6.5 cm by 36 cm. The relevant R_f values of the isomers are 0.34 and 0.26.
10. This product, which can be recrystallized from hexane (colorless crystals, mp 110–111°C), exhibits the following spectral properties: IR ($CHCl_3$) cm^{-1}: 3560, 2980, 1650, 1600; ^1H NMR (300 MHz, C_6D_6) δ: 0.92–1.12 (m, 1 H), 1.02 (d, 3 H, J = 6.0), 1.03 (d, 3 H, J = 6.0), 1.05 (d, 3 H, J = 6.0), 1.10 (d, 3 H, J = 7.0), 1.15 (d, 3 H, J = 6.0), 1.26 (s, 3 H), 1.25–1.35 (m, 1 H), 1.42–1.50 (m, 1 H), 1.92–2.07 (m, 2 H), 3.08 (s, 1 H), 5.20 (hep, 1 H, J = 6.0), 5.31 (hep, 1 H, J = 6.0); ^{13}C NMR (75 MHz, C_6D_6) δ: 15.3, 19.9, 22.3 (2C), 22.6, 22.8, 30.8, 34.3, 46.6, 52.8, 71.1, 73.4, 83.9, 131.4, 171.9, 199.9.
11. Assay of this fraction by VPC (SE-30, 70–250°C/min) showed its composition to consist of 8% of the less polar isomer and 92% of the more polar product. The overall yields are consequently 2.5% and 81%, respectively.
12. The title compound was obtained as a colorless oil that slowly crystallized on standing, mp 52–53°C. Its spectral characteristics are as follows: IR ($CHCl_3$) cm^{-1}: 3589, 2979, 1697, 1616; ^1H NMR (300 MHz, C_6D_6) δ: 0.84–0.98 (m, 1 H), 1.01 (d, 3 H, J = 7.0), 1.07 (d, 3 H, J = 6.0), 1.09 (d, 3 H, J = 6.0), 1.10 (d, 3 H, J = 6.0), 1.11 (d, 3 H, J = 6.0), 1.28 (s, 3 H), 1.23–1.43 (m, 2 H), 1.86–1.94 (m, 1 H), 2.18–2.24 (m, 2 H), 5.24–5.38 (m, 2 H); ^{13}C NMR (75 MHz, C_6D_6) δ: 15.5, 19.6, 22.5, 22.6 (2 C), 22.9, 31.3, 35.0, 46.9, 56.7, 71.2, 73.6, 83.1, 132.5, 165.4, 202.7.
13. The checkers isolated an additional side product **A**, not observed by the submitters, in 2% yield; its structure is based upon NMR $^1H/^{13}C$ correlations and NOE data:



A

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.2 [(d, 6 H) ($OCH(CH_3)_2$)], 2.08 [(m, 3 H) (CH_2=C-CH_3)], 2.4 [(s, 3 H) (ar-CH_3)], 4.3 [(m, 1 H) ($OCH(CH_3)_2$)], 5.08 (m, 2 H, =CH_2), 5.2 (s, 1 H, 3-OH), 5.6 (s, 1 H, 2-OH), 6.5 (s, 1 H, ar-H).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

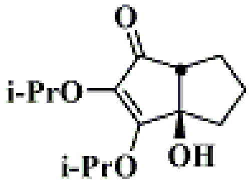
Twofold addition of the same or different vinyl anions to squarate esters leads to polyquinane products.[4] The principal pathway involves trans-1,2-addition of the organometallic reagent to generate a cyclobutene dialkoxide such as **1**. Ring strain and electrostatic factors promote the rapid conrotatory opening of **1** in that sense leading to outward splaying of the oxido functional groups.[5] The resultant doubly-charged 1,3,5,7-octatetraenes shown by **2**, undergo symmetry-controlled 8π electrocyclization from a coiled conformation, thereby giving rise to cyclooctenyl dienolates **3**. In symmetrical examples such as that illustrated, protonation at either available reactive center delivers **4**, and sets the stage for intramolecular aldolization via transannular cyclization. In unsymmetrical cases, both aldols are sometimes produced, with steric discrimination occurring.[6] A strong interdependence of the efficiency in this cascade process and vinyl anion substitution has been noted.[6] 2-Propenyllithium is particularly conducive to product formation in good yields, presumably because the presence of methyl groups at C-2 and C-7 in **2** favors the adoption of the conformer shown over others less conducive to the conrotatory requirements for the conversion to **3**.

The cascade sequence associated with this remarkable series of chemical events is tolerant of structurally varied vinyl anions provided that steric bulk is not excessive. The end result is the potential for establishing many stereogenic centers from a triad of achiral reactants in a single laboratory operation. The very substantial increase in complexity attainable from these tandem stereoregulated chemical events is shown in the Table.

TABLE
POLYQUINANES PRODUCED FROM DIISOPROPYL SQUARATE VIA AN ELECTROCYCLIC CASCADE

First Anion	Second Anion	Product (isolated yield)

CH_2=CHLi



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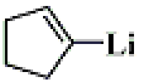

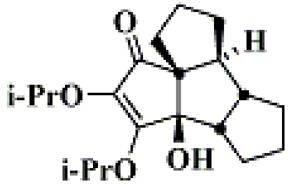

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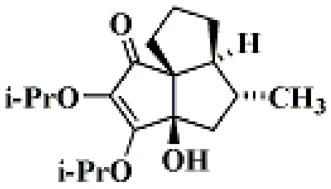

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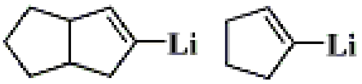

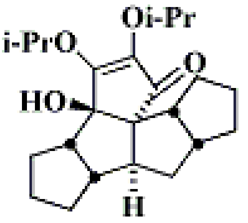

(38%)

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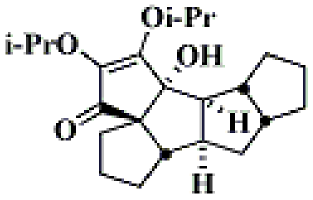
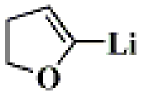
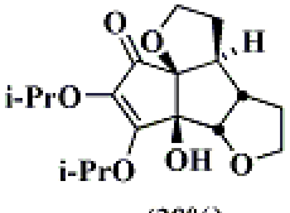


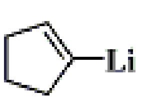
(27%)

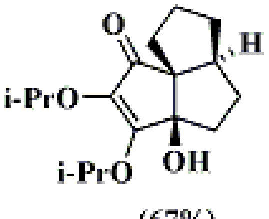




(38%)

CH_2=CHLi





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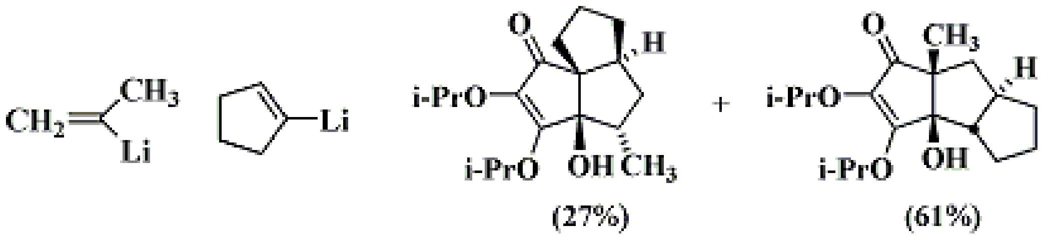
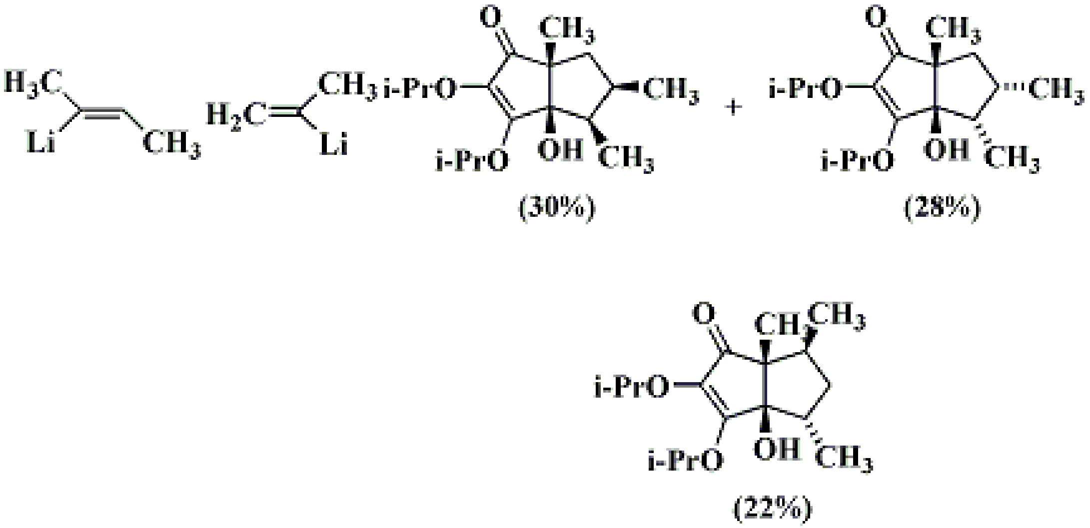
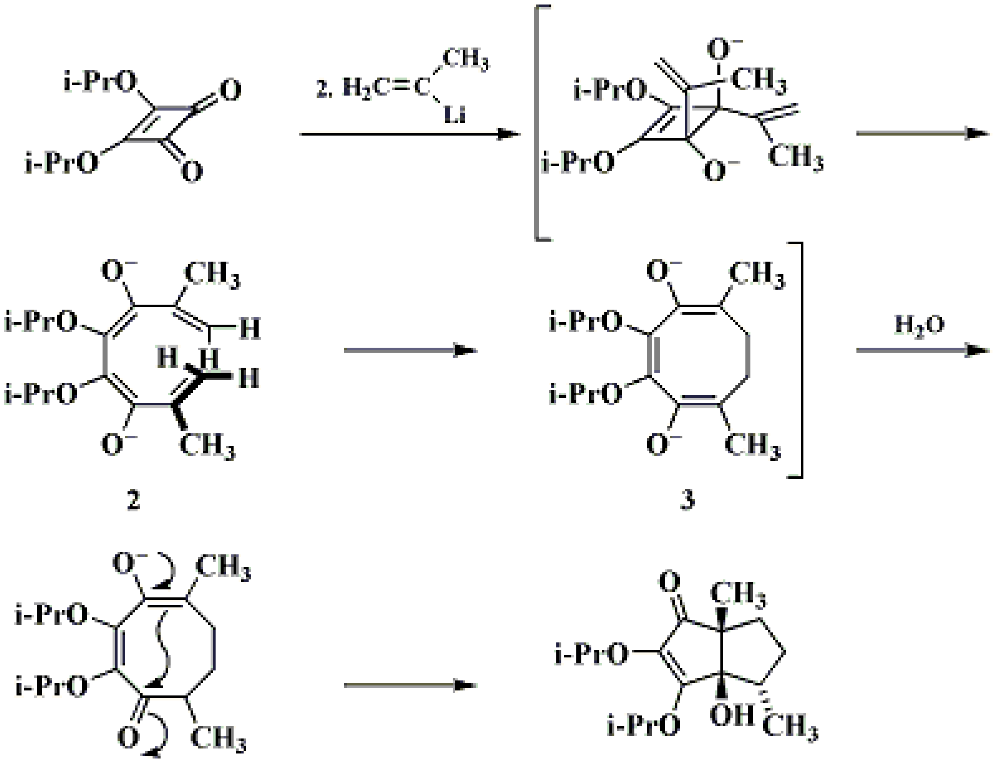


(27%)
(61%)

(73%)



(30%)
(28%)
(22%)



Two minor processes sometimes operate competitively with that illustrated in the scheme. One of these involves 1,4-addition of the second vinyl anion to give a reactive intermediate that differs structurally from **1**, but is capable of setting into motion a closely related sequence of chemical events leading to an isomeric diquinane.[4] This is the route followed to produce the minor product characterized here. The other option consists of cis-1,2-addition, an event that is followed by a dianionic oxy-Cope rearrangement via a boat-like transition state.[4] When sufficient substitution is present to allow the installation of multiple stereogenic centers, the adoption of this pathway is easily distinguished from the electrocyclic alternative since a cis relationship between relevant substituents is in place, instead of the trans arrangement required by the electrocyclization cascade.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

brine

sodium benzophenone ketyl

diquinane

ethyl acetate (141-78-6)

ether (60-29-7)

ammonium chloride (12125-02-9)

Diphenylacetic acid (117-34-0)

Pentane (109-66-0)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

hexane (110-54-3)

argon (7440-37-1)

2-Propenyllithium

lithium hydroxide (1310-65-2)

2-Bromopropene (557-93-7)

tert-Butyllithium (594-19-4)

diisopropyl squarate

4,5,6,6a-TETRAHYDRO-3a-HYDROXY-2,3-DIISOPROPOXY-4,6a-DIMETHYL-1(3aH)-PENTALENONE

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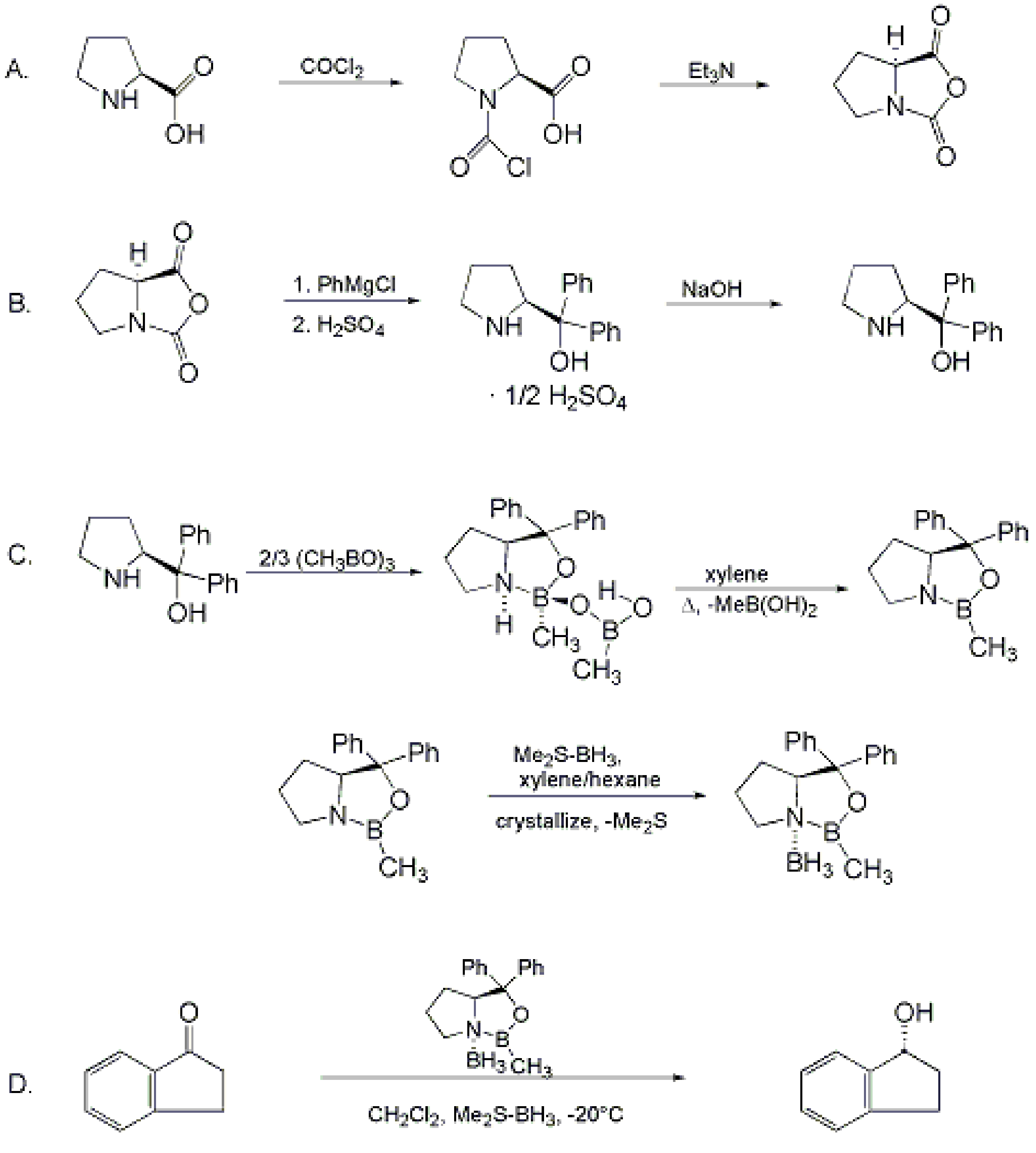
Organic Syntheses, CV 9, 676

(S)-TETRAHYDRO-1-METHYL-3,3-DIPHENYL-1H,3H-PYRROLO-[1,2-*c*][1,3,2]OXAZABOROLE-BORANE COMPLEX

[Boron, trihydro(tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo-[1,2-*c*][1,3,2]oxazaborole-N7)-, [I-4-(3aS-cis)]-]



Submitted by Lyndon C. Xavier, Julie J. Mohan, David J. Mathre, Andrew S. Thompson, James D. Carroll, Edward G. Corley, and Richard Desmond[1].
Checked by Peter G. Dormer and Amos B. Smith, III.

1. Procedure

CAUTION! This reaction should be carried out in a fume hood since phosgene is an insidious poison.

A. *(S)-Proline-N-carboxyanhydride*. A dry, 3-L, three-necked flask, fitted with a mechanical stirrer, nitrogen inlet tube, 500-mL, pressure-equalized addition funnel and a Teflon-coated thermocouple probe, containing dry tetrahydrofuran (THF) (600 mL) is charged with (S)-proline (60.0 g, 0.521 mol) (Note 1). To the cooled (15–20°C) suspension is added phosgene (324 mL, 0.625 mol, 1.93 M in toluene), via a pressure-equalized addition funnel, over a 0.5–1.0 hr period maintaining a temperature of 15–20°C (Note 2). The reaction mixture is then aged for 0.5–0.75 hr at 30–40°C. The reaction mixture should become homogeneous as the proline reacts with the phosgene to afford the intermediate N-carbamoyl chloride. Once homogeneous, the reaction mixture is aged an additional 0.5 hr, then concentrated under reduced pressure (15–20°C, 1000 down to 50 mBar) to a volume of 80 mL (Note 3). Dry tetrahydrofuran (600 mL, KF < 50 •g/mL) is added to the mixture and it is cooled to 0–5°C. Dry triethylamine (72.6 mL, 0.521 mol, KF < 50 •g/mL) is added over 0.25 hr (Note 4). The mixture is aged for 0.5 hr at 0–5°C, then filtered through an enclosed, 2-L, medium-frit Schlenk funnel under an atmosphere of nitrogen (with careful exclusion of moisture). The triethylammonium hydrochloride cake is washed with dry tetrahydrofuran (3 × 105 mL, KF < 50 •g/mL). The filtrate and washes are combined and used as is in the next reaction (Note 5) and (Note 6).

Caution! Benzene is generated in this reaction. Benzene is a known carcinogen.

B. *(S)-1,1-Diphenylprolinol*. A 3-L, three-necked flask, fitted with a mechanical stirrer, nitrogen inlet tube, 1-L addition funnel and Teflon-coated thermocouple probe, is charged with phenylmagnesium chloride (0.80 L, 1.6 mol, 2.0 M in tetrahydrofuran) (Note 7) and cooled to −10°C (Note 8). To the suspension is added, with stirring, the tetrahydrofuran solution of (S)-proline-N-carboxyanhydride over a 1-hr period maintaining the temperature at −15° to −10°C (Note 9). After the addition is complete, the reaction mixture is aged for 3 hr at −15°C, then 1 hr at 0°C (Note 10). The reaction is quenched into a 5-L, mechanically-stirred flask containing 2 M aqueous sulfuric acid (1.05 L, 2.1 mol) (0°C) over a 0.5–1.0 hr period (Note 11). The reaction mixture is aged for 1 hr at 0–5°C, filtered, and the magnesium sulfate cake washed with tetrahydrofuran (3 × 500 mL) (Note 12). The filtrate and tetrahydrofuran washes are combined and concentrated (1 atm) to a volume of 1.0 L (Note 13). The mixture is cooled to 0°C, aged 1 hr, and then filtered. The cake is washed with water (5°C, 2 × 100 mL) and ethyl acetate (3 × 180 mL) (Note 14). The cake is dried under reduced pressure (40°C, 50 mBar) to yield 79–88 g (50–56% based on proline) of (S)-diphenylprolinol sulfate as a free-flowing white crystalline solid, mp 275–290°C (Note

15).

A 3-L, three-necked flask, fitted with a mechanical stirrer, nitrogen inlet tube, and Teflon-coated thermocouple, is charged with (S)-diphenylprolinol sulfate (81.0 g, 0.268 mol), tetrahydrofuran (268 mL), and 2 M aqueous sodium hydroxide (268 mL). The mixture is stirred at 20–25°C until all the solid dissolves (0.5 hr) (Note 16). Toluene (1.1 L) is added and the mixture is aged 0.5 hr. The two-phase mixture is filtered through a medium frit sintered glass funnel and partitioned (Note 17). The upper layer is washed with water (130 mL) and the toluene is removed under reduced pressure to afford a light-tan colored oil that crystallizes upon standing at ambient temperature (Note 18). Recrystallization of the resulting light-tan crystals from heptane (ca. 2 mL of heptane per gram of prolinol) affords (S)-1,1-diphenylprolinol; [yield 64–68 g (94–99% yield based upon diphenylprolinol sulfate)] as white crystals, mp 76–78°C, >98% ee (Note 19),(Note 20)).

Caution! Neat (10 M) borane-methyl sulfide is an air- and moisture-sensitive flammable liquid. Dimethyl sulfide has a noxious odor. All reactions should be conducted in an efficient fume hood.

C. *(S)-Tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaborole-borane complex*. A 500-mL, four-necked, round-bottomed flask (Note 21) is equipped with a Teflon-coated thermocouple probe, 60-mL pressure-equalizing addition funnel, nitrogen inlet, mechanical stirrer, and distillation head connected to a wide-bore, air-cooled condenser. The flask is charged with 200 mL of xylenes (Note 22) and (S)-diphenylprolinol (50.0 g, 198 mmol). To the vigorously stirred solution at 20°C is added a 50% (w/w) solution of trimethylboroxine (TMB) in tetrahydrofuran (38 g, containing 19 g, 152 mmol of TMB) (Note 23) dropwise over a 15-min period. The addition funnel is rinsed with dry xylenes (10 mL). During the addition an exothermic reaction occurs (warming the mixture to ca. 35°C) resulting in the formation of the bismethylboronic acid adduct as a white precipitate (Note 24). After the addition, the mixture is stirred for 0.5 hr, then heated and concentrated by distillation (1 atm) (Note 25) to a volume of ca. 100 mL (Note 26). The mixture is allowed to cool to ca. 60°C, and is charged with additional dry xylenes (200 mL) (Note 22). The distillation and nitrogen sweep are continued, this time until essentially all the solvent is removed. The mixture is then heated so that the internal temperature is maintained between 160–180°C for a 0.5-hr period. The pale yellow oil (free oxazaborolidine) is cooled to 20°C (Note 26) and (Note 27), and diluted with dry xylenes (Note 22) to a volume of 100 mL. The distillation head is replaced with a 500-mL, pressure-equalizing addition funnel. At this point, the nitrogen sweep is discontinued; however, the vessel is maintained under a static atmosphere of nitrogen for the remainder of the reaction. To the well stirred solution is added neat (10 M) borane-methyl sulfide (21 mL, 210 mmol) (Note 23) over a 5-min period via syringe. The mixture is stirred for 0.5 hr at 20°C, then slowly diluted with dry hexane to a volume of 450 mL over a 1–2 hr period (Note 28). After the addition is complete, the mixture is aged for 1 hr at 20°C, cooled

to –10°C, and then aged for 2 hr at –10°C. The mixture is filtered in an enclosed Schlenk filter (Note 29). The cake is washed with dry hexane (3 × 50 mL) (Note 30). The product is dried under reduced pressure (100 mBar, nitrogen sweep, 20°C) for 1 hr to afford 51–53 g of the title compound as a free-flowing white crystalline solid (Note 31),(Note 32).

Caution! Neat (10 M) borane-methyl sulfide is an air- and moisture-sensitive flammable liquid. Dimethyl sulfide has a noxious odor. All reactions should be conducted in an efficient fume hood.

D. *(R)-2,3-Dihydro-1H-inden-1-ol*. A 250-mL, three-necked, round-bottomed flask (Note 33) is equipped with a Teflon-coated thermocouple probe, a 125-mL pressure-equalizing addition funnel, nitrogen inlet, and Teflon-coated magnetic stirring bar. The flask is charged with the (S)-oxazaborolidine-borane complex (2.91 g, 10.0 mmol) (Note 34), purged with nitrogen, and charged with dry dichloromethane (10 mL) (Note 35). To the stirred solution is added borane-methyl sulfide (10 M, 20 mL, 200 mmol) (Note 36). The solution is cooled to –20°C (Note 37) and the addition funnel charged with a solution of 1-indanone (26.4 g, 200 mmol) (Note 38) in dry dichloromethane (75 mL) (Note 35). The 1-indanone solution is then added dropwise over a 4–6 hr period while maintaining the internal temperature of the reaction mixture at –20±5°C. After the addition is complete, the reaction mixture is stirred for 2 hr at –20°C (Note 39). After the reaction is complete, the mixture is cautiously poured into a 1-L flask containing magnetically-stirred, pre-cooled (–20°C) methanol (300 mL) (Note 40). The cooling bath is removed, and the stirred mixture allowed to warm to room temperature (20–25°C). After evolution of hydrogen ceases, the mixture is concentrated by distillation (1 atm) to a volume of ca. 50 mL. Methanol (200 mL) is added, and the distillation repeated (Note 41). The residue containing the product and diphenylprolinol is diluted with methanol (100 mL) and then loaded onto a 2.5 × 30-cm column packed with Amberlyst 15 (NH_4^+) (Note 42) at ca. 2.5 mL/min, collecting 40-mL fractions. The column is rinsed with methanol until the product is eluted (Note 43). The column is then rinsed with 1 M methanolic ammonia until the diphenylprolinol is eluted. The fractions containing the product (2–15) are combined, and then concentrated under reduced pressure (40°C, 100 mm) to give 26.2 g of crude product as a white crystalline solid (Note 44). The crude product is dissolved in hexane (260 mL) at 50–60°C in a 500-mL, round-bottomed flask fitted with a mechanical stirrer. The product is allowed to crystallize as the stirred mixture is slowly cooled to 20–25°C. The mixture is stirred for 4 hr at 20–22°C, filtered, and the cake washed with hexane (2 × 25 mL). The product is dried in a vacuum oven (30°C, 10 mm) to constant weight to yield 24.1–25.2 g (90–94%) of the title compound as a white crystalline solid (Note 45) and (Note 46).

2. Notes

1. The submitters used reagent grade tetrahydrofuran (EM Science) dried over 4

Å or 5 Å molecular sieves (Aldrich Chemical Company, Inc.), and determined the water content in the solvents by Karl Fisher titration (KF). The submitters report that the tetrahydrofuran should be dry (KF < 50 •g/mL) and *MUST NOT* contain any DMF (≤ 1 ppm). Also, the KF of the tetrahydrofuran/proline suspension should be < 50 •g/mL. The submitters used (S)-proline obtained from Ajinomoto while the checkers used (S)-proline from Aldrich Chemical Company, Inc. The proline should be milled and/or delumped prior to use, if necessary, to insure complete reaction. The enantiomeric purity of the (S)-proline should be > 99.5%, and can be assayed via the procedure of Marfey.[2] The checkers used HPLC grade THF (Fisher Scientific Company) that was dried over 4 Å molecular sieves.

2. Phosgene (1.93 M in toluene) was obtained from Fluka Chemical Company. Neat phosgene (Matheson Gas Products) and triphosgene (Aldrich Chemical Company, Inc.) (98%) can also be used. *Phosgene is an insidious poison so all manipulations with it must be performed in a fume hood with good ventilation. Any excess phosgene should be CAREFULLY decomposed in cold aqueous sodium hydroxide or aqueous ammonia*. Since the addition is slightly exothermic, the rate of addition and external cooling is adjusted to maintain the internal temperature at 15–20°C.

3. The vacuum is decreased gradually in order to prevent bumping as the hydrogen chloride, excess phosgene, and tetrahydrofuran are removed. The checkers concentrated the reaction mixture using a rotary evaporator (a drying tube was placed in-line between the water aspirator and the rotary evaporator) under aspirator pressure (bath temp < 30°C), in an efficient fume hood The temperature must be maintained < 20°C during the concentration. At a volume of 80 mL the mixture is viscous but can still be stirred. The reaction can be assayed at this point by ^{1}H NMR; an aliquot withdrawn (ca. 30 mg) and dissolved in $CDCl_3$ (0.6 mL) giving ^{1}H NMR (250 MHz, $CDCl_3$) δ: 2.35 (s, toluene), 1.83–2.44 (m, 4 H, C-3-H_2 and C-4-H_2), 3.54–3.86 (m, 2 H, C-5-H_2), 4.47–4.52 (dd, 0.6 H, C-2-H rotamer),4.58–4.61 (dd, 0.4 H, C-2-H rotamer), 7.12–7.29 (m, toluene), 10.6–10.8 (br s, CO_2H). The ^{1}H NMR spectrum should not contain resonances at δ 4.9 (dd, 0.4 H, C-2-H) and 4.7 (dd, 0.6 H, C-2-H) (i. e., those corresponding to the N-carbamoyl chloride, acid chloride derivative of proline).

4. Triethylamine obtained from J. T. Baker Inc. was dried over 4 Å or 5 Å molecular sieves to a KF < 50 •g/mL. The checkers used triethylamine (Fisher Scientific Company) dried over 4 Å molecular sieves. The reaction is slightly exothermic so the rate of addition and external cooling are adjusted to maintain the internal temperature at 0–5°C. During the addition, a white precipitate of triethylammonium hydrochloride is formed.

5. The tetrahydrofuran solution of the proline-N-carboxyanhydride must be used immediately since on standing the material can polymerize and release CO_2. The reaction can be assayed at this point by ^{1}H NMR: (1.0 mL of the THF solution is concentrated under reduced pressure, and the residue dissolved in 0.6

mL of $CDCl_3$) δ: 1.83–2.39 (m, 4 H), 3.29–3.39 (m, 1 H, C-5-H), 3.70–3.81 (m, 1 H, C-5-H), 4.35–4.39 (dd, 1 H, C-2-H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 26.7, 27.2, 46.2, 62.8, 154.6, 168.8. The amount of triethylammonium hydrochloride, δ3.12 (q, 6 H) and 1.4 (t, 9 H), should be less than 5 mol%.

6. Alternate work-up: The filtered tetrahydrofuran solution is concentrated under reduced pressure (20°C, 50 mm) to a volume of 80 mL. Dry hexane (KF < 50 •g/mL, 600 mL) is slowly added with stirring. The product should begin to crystallize during the addition; seed if necessary. The mixture is stirred at 20–25°C for 1 hr, then filtered. The cake is washed with dry hexane (2 × 25 mL). Filtration is performed in an enclosed, medium-frit Schlenk funnel, under an atmosphere of nitrogen (with careful exclusion of moisture). The cake is dried under reduced pressure (30°C, < 100 mm) for 2 hr to yield 70.5 g (95%) as a free-flowing white crystalline solid, mp 51.5–52°C. The product should be stored cool, protected from moisture. By microanalysis, the product contains 1–4 wt% of triethylammonium hydrochloride. It is also possible to concentrate the THF to precipitate the product as a white solid.

7. Phenylmagnesium chloride (2.0 M in tetrahydrofuran) was obtained from Aldrich Chemical Company, Inc. The vessel must be dry and flushed with nitrogen prior to the addition of the phenylmagnesium chloride.

8. The reaction should not be cooled lower than −10°C because the Grignard reagent can crystallize. This can cause the stir shaft to break. It is best to add a small portion of the proline-N-carboxyanhydride, slurry the solution, and then cool to −10°C. Crystallization of the Grignard reagent does not affect the reaction yield.

9. The reaction is exothermic; therefore the rate of addition and external cooling are adjusted to maintain the internal temperature at −15 to −10°C.

10. The checkers allowed the reaction mixture to warm to ambient temperature overnight before quenching the reaction. If desired, the progress of the reaction may be monitored by the following HPLC assay. An aliquot (0.5 mL, accurately measured) is quenched into water (5 mL) containing 6 M aqueous sulfuric acid (200 •L). The solution is diluted to 100 mL with 1:1 H_2O/MeCN and analyzed by HPLC. The checkers did not monitor the reaction by HPLC. Column: 4.6 × 250-mm ZORBAX RX ; Eluent A: H_2O (0.01 M KH_2PO_4); Eluent B: MeCN; Linear Gradient: 80:20 (A:B) to 20:80 over 12 min; Flow Rate: 1.0 mL/min; Injection: 10.0 •L; Detection: UV (210 nm); Retention Times: Proline, N-benzamide 4.82 min; Diphenylprolinol 6.68 min; Benzene 11.45 min; Triphenylmethanol 14.66 min.

11. Sulfuric acid (Mallinckrodt Inc.) is diluted to the desired concentration with deionized water. Since the quench is exothermic the rate of addition and external cooling are adjusted to maintain the internal temperature below 20°C. During the quench a white precipitate of magnesium sulfate is formed. The amount of water and sulfuric acid used is important. Insufficient water results in the product (sulfate salt) precipitating with the magnesium sulfate. Excess water reduces the amount of magnesium removed. Insufficient sulfuric acid results in non-filterable gels of magnesium hydroxide. Excess sulfuric acid increases the

solubility of the diphenylprolinol sulfate, therefore reducing the yield of isolated product.

12. A large sintered glass funnel is required because of the amount of magnesium sulfate solution produced (□700 mL). Analysis of the magnesium sulfate cake by HPLC detected < 1 g of diphenylprolinol.

13. During concentration, a precipitate of diphenylprolinol sulfate and triphenylmethanol is formed. *CAUTION: Benzene (43 g), formed during the quench of the excess phenylmagnesium chloride, is removed during the concentration.*

14. Water is used to remove excess sulfuric acid, and ethyl acetate to remove triphenylmethanol, benzophenone and the N-benzamide derivative of proline.

15. Assay for enantiomeric purity: To a magnetically stirred suspension of diphenylprolinol sulfate (30 mg) in tetrahydrofuran (1 mL) is added 1 M aqueous sodium hydroxide (210 •L). The mixture is stirred for 15 min, then (R)-Mosher acid chloride (20 •L) is added. By TLC (EM Si-60, 8:2 hexane/EtOAc, R_f diphenylprolinol = 0.05, R_f Mosher amide = 0.4) the reaction is complete in 1 hr. The reaction mixture is diluted into hexane (9 mL), then eluted through a Baker Silica SPE (1 g) column (previously washed with hexane). The column was eluted with additional 9:1 hexane/tetrahydrofuran (5 mL). The combined eluates were than analyzed by capillary GC: Column: 0.33 mm × 30 m DB-23 (J&W Scientific); Oven Temperature: 250°C; Injector/Detector Temperature: 275°C; Carrier Gas: Helium (21 lbs/in^2), ca. 30:1 split; Injection: 1 •L; Detection: FID; Retention Times: (R,R)-Mosher amide 25.9 min; (R,S)-Mosher amide 29.6 min. The enantiomeric purity is 99:1.

16. There are occasions when a small amount of material does not dissolve. This does not affect the reaction.

17. Filtration is necessary to remove a small amount of polymeric solid that interferes with the phase separation.

18. Toluene is removed with a rotary evaporator (water aspirator, 40°C bath temperature). If desired, a toluene flush (300 mL) may be employed to remove residual traces of water. Concentration serves both to remove THF and azeotropically dry the solution. The last traces of solvent are removed by placing the oil under high vacuum (ca. 1 mBar) at room temperature overnight.

19. The physical properties are as follows: lit. mp: 76.5–77.5°C;[2] ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.57–1.79 (m, 4 H, C-3-H_2, C-4-H_2), 2.93–2.98 (m, 1 H, C-5-H), 3.02–3.07 (m, 1 H, C-5-H), 4.27 (t, J = 7.6, C-2-H), 7.16–7.21 (m, 2 H, Ar-H), 7.28–7.34 (m, 4 H, Ar-H), 7.53–7.72 (m, 4 H, Ar-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 25.4, 26.3 (C-3, C-4), 46.7 (C-5), 64.5 (C-2), 125.5, 125.8, 126.3, 126.4, 127.9, 128.2, (C-2'-C-6', C-2"-C-6"), 145.4 (C-1"), 148.1 (C-1').

20. If desired, the diphenylprolinol may be assayed for enantiomeric purity as described in (Note 15).

21. The glassware was oven-dried (110°C) before use. The 500-mL round-bottomed flask was graduated in 100-mL increments. The checkers used argon in place of nitrogen.

22. The xylenes (EM Science) were dried over 4 Å molecular sieves. Residual water content < 20 •g/mL by Karl Fisher titration. The checkers dried hexanes (Fisher Scientific Company), tetrahydrofuran, and xylenes over 4 Å molecular sieves. The checkers did not measure the residual water content of the solvents.
23. Trimethylboroxine (as a 50 wt% solution in THF) and borane-methyl sulfide (10 M) were obtained from Callery Chemical Company. The checkers employed 50 wt% trimethylboroxine/THF solution (prepared from neat trimethylboroxine (Aldrich Chemical Company, Inc.) and dry THF). The checkers used borane-methyl sulfide obtained from Aldrich Chemical Company, Inc.
24. The submitters report that a two-stage exotherm occurs during the addition. The first exotherm occurs as the trimethylboroxine reacts with the diphenylprolinol, and the second occurs as the intermediate bismethylboronic acid adduct crystallizes. Typically, the intermediate begins to crystallize after ca. one third of the trimethylboroxine is added. The reaction should not be run more concentrated. The checkers observed an exothermic reaction (warming from 20 to 45°C) after approximately one half to two thirds of the trimethylboroxine/ THF solution was added.
25. The vessel is swept with a gentle stream of nitrogen during the distillation and subsequent operation to ensure the complete removal of the reaction by-products. The condenser should be air-cooled during the initial stages of the distillation to prevent it from being plugged with methylboronic acid. The checkers heated the stirred mixture rapidly to the boiling point (over ca. 20–30 min period) and used an argon sweep in place of nitrogen during the distillation.
26. The essentially pure free oxazaborolidine will slowly solidify on standing (mp 79–81°C). Although this material can be stored and used "as is" if scrupulously protected from adventitious moisture, the submitters recommend that it be converted to the more stable borane complex.
27. The physical properties are as follows: mp 80–83°C (corr); ^{1}H NMR (500 MHz, 0.15 M in $CDCl_3$) δ: 0.46 (s, 3 H, B-CH_3), 0.85–0.93 (m, 1 H, C-4-H), 1.64–1.85 (m, 3 H, C-4-H, C-5-H_2), 3.08–3.13 (m, 1 H, C-6-H), 3.38–3.43 (m, 1 H, C-6-H), 4.40–4.43 (dd, 1 H, J = 5.5, 9.8, C-3a-H), 7.23–7.43 (m, 8 H, Ar-H), 7.59–7.61 (m, 2 H, Ar-H); ^{11}B NMR (64.2 MHz, 0.15 M in $CDCl_3$) δ: 34.6; ^{13}C NMR (125 MHz, $CDCl_3$) δ: –5.7 (br, B-CH_3), 26.3 (C-5), 30.1 (C-4), 42.8 (C-6), 72.6 (C-3a), 87.7 (C-3), 126.1, 126.2, 126.5, 127.0, 127.6, 128.0 (C-3', C-3", C-4', C4", C-5', C-5"), 143.9, 147.5 (C-1', C-1"); IR (CCl_4) cm^{-1}: 3060, 3025, 2980, 2875, 1445, 1335, 1315, 1235, 995, 695; low-resolution EIMS: m/z 277.2 $[M]^+$. The solvent used for the NMR spectra must be dry and free of HCl or DCl (molecular sieves and/or anhydrous potassium carbonate).
28. During the addition, the oxazaborolidine-borane complex crystallizes. A slow addition of dry hexane favors the formation of larger crystals.
29. During the filtration it is important to keep the operation under an atmosphere of dry nitrogen to prevent moisture from condensing on the product. The submitters have also isolated the product in a 600-mL, sintered-glass funnel contained in a large bag maintained under an atmosphere of dry nitrogen. The checkers performed the filtration in a 600-mL, medium-frit sintered glass funnel

contained in a large plastic glove bag maintained under an argon atmosphere.

30. The three hexane washes are first used to rinse product remaining in the reaction vessel.

31. The physical properties are as follows: mp 124–127°C (dec); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.77 (s, 3 H, B-CH_3), 1.0–1.9 (very br s, 3 H), 1.28–1.37 (m, 1 H, C-4-H), 1.56–1.68 (m, 1 H, C-5-H_2), 1.89–2.0 (m, 2 H, C-5-H_2), 3.19–3.24 (m, 1 H, C-6-H), 3.37–3.43 (m, 1 H, C-6-H), 4.66 (t, 1 H, J = 7.9, C-3a-H), 7.2–7.4 (m, 8 H, Ar-H), 7.6 (m, 2 H, Ar-H); ^{11}B NMR ($CDCl_3$) δ: 34.5 (oxazaborolidine-B), –14.5 (complexed H_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ: –3.9 (br, B-CH_3), 24.9 (C-5), 31.4 (C-4), 57.7 (C-6), 76.2 (C-3a), 90.6 (C-3), 125.0 (C-2", C-6"), 125.4 (C-2', C-6'), 127.1 (C-4"), 127.3 (C-4'), 128.1 (C-3", C-5"), 128.2 (C-3', C-5'), 143.5 (C-1"), 144.6 (C-1'). Anal. Calcd for $C_{18}H_{23}B_2NO$: C, 74.29, H, 7.97; N, 4.81. Found: C, 74.34; H, 8.00; N, 4.69.

32. The product is stored at room temperature protected from moisture. A nitrogen atmosphere is recommended for long term storage. Unlike the free oxazaborolidine that readily reacts with and is decomposed by atmospheric moisture, the oxazaborolidine-borane complex is significantly more stable, allowing it to be handled briefly in the open.

33. The glassware was oven-dried (110°C) before use. The checkers used argon in place of nitrogen.

34. The checkers observed gas evolution upon dissolution of the (S)-oxazaborolidine-borane complex in dichloromethane (CH_2Cl_2) at room temperature.

35. Dichloromethane (Fisher Scientific Company) was dried over 4 Å molecular sieves before use (water content < 20 mg/mL by Karl Fisher titration). The checkers did not measure the residual water content of the solvent.

36. Borane-methyl sulfide (10 M) was obtained from Callery Chemical Company. The checkers purchased borane-methyl sulfide (10 M) from Aldrich Chemical Company, Inc.

37. The reaction temperature was controlled using a cooling bath of methanol/ice and sufficient dry ice to maintain the indicated temperature.

38. 1-Indanone (Aldrich Chemical Company, Inc., 99+%) was used as received.

39. The progress of the reaction was followed by capillary GC. An aliquot (50 •L) is quenched into methanol (5 mL) and then analyzed using a 30-m × 0.32-mm DB-23 (J&W Associates) column (He carrier, 15 Ibs/in^2; ca. 30:1 split; oven temp: 50 to 150°C at 10°C/min; injector/detector temp: 250°C). 1-Indanol (t_R 10.9 min); 1-indanone (t_R 11.1 min).

40. *CAUTION: Hydrogen is evolved during the quench. The flask should be flushed with nitrogen. The reaction mixture is added at a rate to control the foaming.*

41. Methanol distillation serves to remove the majority of the boron species, as $B(OMe)_3$and $MeB(OMe)_2$

42. The Amberlyst (NH_4+) resin column is prepared as follows: Amberlyst 15 (H^+) (56 g, 100 mL dry, Rohm & Haas Co.) is suspended in an open beaker

containing methanol (100 mL). [*CAUTION: the slurry exotherms to ca. 40°C without external cooling, and expands to ca. 1.5 times its initial volume.*] The slurry is poured into a 2.5 × 30-cm column and is eluted with 1 M methanolic ammonia (ca. 1 L) until a sample of the eluent diluted 1:1 with water is basic. The resin is then eluted with methanol (ca. 0.5 L) until a sample of the eluent diluted 1:1 with water is neutral. Once prepared, the column can be reused multiple times.

43. The progress of the column is monitored by UV (260 nm) or capillary GC (Note 39).

44. Chiral HPLC assay (4.6 × 250-mm Chiralcel-OB, 90:10 hexane/isopropyl alcohol, 0.5 mL/min, UV 254 nm): 1-indanone (t_R 29.6 min, < 0.1%), (R)-carbinol (t_R 10.3 min, 98.9%), (S)-carbinol (t_R 15.3 min, 1.1%). The sample was taken as a homogenous solution in methanol (prior to crystallization) to avoid enantiomeric enrichment. The checker's weight of crude (R)-1-indanol (prior to recrystallization); was 26 g, ca. 90% ee. The checkers also recovered crude (S)-diphenylprolinol (1.9 g) from the column.

45. The physical properties are as follows: Mp 73.0–73.5°C [lit.[3] 72.0°C]; HPLC (Chiralcel-OB) (R)-carbinol (t_R 10.3 min, > 99.9%), (S)-carbinol (t_R 15.3 min, <0.1%); $[\alpha]_D^{29}$ –45.5° (MeOH, *c* 1.184) [lit.[4] (S)-carbinol $[\alpha]_D^{25}$ +22.6° ($CHCl_3$, *c* 4.2) reported for the enantiomer]; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.2–2.25 (br s, 1 H, OH), 1.91–1.98 (m, 1 H, C-2-H), 2.46–2.53 (m, 1 H, C-3-H), 2.81–2.87 (m, 1 H, C-3-H), 3.04–3.10 (m, 1 H, C-3-H), 5.23 (t, 1 H, J = 6.0, C-1-H), 7.27–7.45 (m, 4 H, Ar-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 29.7, 35.7, 76.2, 124.1, 124.7, 126.5, 128.1, 143.2, 144.9. Checkers yield of (R)-2,3-dihydro-1H-inden-1-ol after recrystallization was 19.6–20.3 g (73–76%); mp (corr): 73–74°C, $[\alpha]_D^{29}$ –18.1° (MeOH, *c* 1.3).

46. From the mother liquors was obtained an additional 1.75 g (6.5%) of 1-indanol of lower enantiomeric purity (HPLC: 85:15 R/S). The checkers concentrated the mother liquors to afford additional (R)-1-indanol (6.5–6.9 g) of lower enantiomeric purity (60–70% ee).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

A-B. Enantiomerically pure (R)- and (S)-α,α-diaryl-2-pyrrolidinemethanols are precursors to several useful asymmetric catalysts,[5 6 7 8 9] including the corresponding oxazaborolidines.[19 10 11 12 13 14 15] Although several routes have been reported for making these compounds, none were suitable for our purposes (poor yields, multiple steps, difficult isolations).[16 17,18,20 21,22,23] We therefore developed a practical two-step synthesis of (R)-α, α-diaryl-2-pyrrolidinemethanols from (R)- or (S)-proline

based on the addition of proline-N-carboxyanhydride to phenylmagnesium chloride.[24,25 26 27] This investigation led to the development of a reliable procedure for oxazaborolidine preparation based on the reaction of trimethylboroxine with diphenylprolinol.[24] Using this the submitters prepared a series (see Table) of enantiomerically pure α,α-diphenyl-2-pyrrolidinemethanols and their corresponding B-alkyl- and B-aryloxazaborolidines beginning with either (R)- or (S)-proline.

TABLE
α,α-DIARYL-2-PYRROLIDINEMETHANOLS

Entry	R	Yield[a]	e.e.[b]
1	Phenyl	73%	99.4%
2	4-Fluorophenyl	89%	99.4%
3	4-Chlorophenyl	59%	99.4%
4	4-Methylphenyl	57%	99.4%
5	4-(CF_3)-Phenyl	46%	99.4%
6	4-tert-Butylphenyl	50%	99.4%
7	4-Methoxyphenyl	53%	99.4%
8	3-Chlorophenyl	62%	99.4%
9	3,5-Dichlorophenyl	68%	99.4%
10	3,5-Dimethylphenyl	60%	99.4%
11	2-Naphthyl	64%	99.4%

[a]Isolated yield. [b]Enantiomeric excess (e.e.) determined by capillary GC analysis of the (R)-α-methoxy-α-(trifluoromethyl)phenylacetic acid amide derivative.

The yield obtained for the preparation of (S)-α,α-diaryl-2-pyrrolidinemethanol was 67% at −10°C. It was found that addition of the Grignard reagent to the proline-N-carboxyanhydride resulted in a lower yield; therefore the proline-N-carboxyanhydride is added to the Grignard. The reaction is successful with meta- and para-substituted aryl Grignards, but with ortho-substituted aryl Grignard reagents only one equivalent adds, affording an unstable ketone intermediate too hindered for further addition. Alkyl Grignards do not afford the desired product so the submitters recommend the procedure described by Enders.[23]

The methods reported for the preparation of the oxazaborolidine include the reaction of diphenylprolinol with methylboronic acid 1) in toluene at 23°C for 1.5 hr with 4 Å molecular sieves present and 2) in toluene at reflux for 3 hr using a Dean-Stark trap, both followed by evaporation of solvent and molecular distillation (0.1 mm, 170°C).[19] An alternate method involved heating a toluene solution of 2-naphthylprolinol and methylboronic acid at reflux for 10 hr using a Soxhlet extractor containing 4 Å molecular sieves.[12] These methods afforded erratic results. The submitters therefore developed an alternate synthesis.

During their investigations they isolated the methylboronic acid adduct and the water adduct of the catalyst. The submitters found, by NMR experiments, that these were the compounds giving rise to spurious signals that were attributed to a "dimer". It was shown that the methylboronic acid adduct could be synthesized directly by treating 0.667 equiv of methylboronic acid with (S)-α,α-diphenyl-2-pyrrolidinemethanol. Heating at reflux in toluene yielded the catalyst free of any spurious signals. The catalyst prepared this way reproducibly afforded high levels of enantioselection. The oxazaborolidine must, however, be protected from moisture in order to retain high levels of enantioselection.

C. The reported procedure provides a practical preparation of (S)-tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo[1,2-*c*][1,3,2]oxazaborole and conversion to its more stable borane complex.[28 29] The oxazaborolidine-borane complex has also been prepared by treatment of a toluene solution of the free oxazaborolidine with gaseous diborane followed by recrystallization from a dichloromethane-hexane bilayer.[30] This and other chiral oxazaborolidines have been used to catalyze the enantioselective reduction of prochiral ketones.[31 32 33 34] The yield and enantioselectivity of reductions using catalytic amounts of the oxazaborolidine-borane complex are equal to or greater than those obtained using the free oxazaborolidine.[28,29]

D. The use of chiral oxazaborolidines as enantioselective catalysts for the reduction of prochiral ketones, imines, and oximes, the reduction of 2-pyranones to afford chiral biaryls, the addition of diethylzinc to aldehydes, the asymmetric hydroboration, the Diels-Alder reaction, and the aldol reaction has recently been reviewed.[32,34] The yield and enantioselectivity of reductions using stoichiometric or catalytic amounts of the oxazaborolidine-borane complex are equal to or greater than those obtained using the free oxazaborolidine.[28,29] The above procedure demonstrates the catalytic use of the oxazaborolidine-borane complex for the enantioselective reduction of 1-indanone. The enantiomeric purity of the crude product is 97.8%. A single recrystallization from hexane then affords enantiomerically pure (> 99.8% ee) 1-indanol in 90–94% overall yield.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 362
- Org. Syn. 79, 72

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22. Addition of N-(benzyloxycarbonyl)-(S)-proline methyl ester to phenylmagnesium chloride to give (S)-α,α-diphenyl-2-pyrrolidinemethanol (3 steps, 5 isolations, 0–50% yield from (S)-proline): ref. [9] and [10]. It should be noted that 6–10 equiv of the Grignard reagent are required to drive this reaction to completion. Quenching the excess phenylmagnesium bromide affords benzene—an environmental and health hazard.
23. Addition of N-benzyl-(S)-proline ethyl ester to phenylmagnesium chloride followed by catalytic hydrogenolysis affords (S)-α,α-diphenyl-2-pyrrolidinemethanol (4 steps, 3 isolations, 51% yield from (S)-proline: Enders, D.; Kipphardt, H.; Gerdes, P.; Brena-Valle, L. J.; Bhushan, V. *Bull. Soc. Chim. Belg.* **1988**, *97* , 691–704. This method has also been used to prepare other (S)-α,α-diaryl-2-pyrrolidinemethanols: ref. [12].
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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

H_2O

hexanes

(S)-Proline-N-carboxyanhydride

(S)-Tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo-[1,2-c][1,3,2]oxazaborole-borane complex

N-carbamoyl chloride

(S)-Tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaborole-borane complex

xylenes

proline-N-carboxyanhydride

N-benzamide

Trimethylboroxine

pyrroglutamic acid

(R)- or (S)-α,α-diphenyl-2-pyrrolidinemethanol

(R)- or (S)-proline

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

hydrogen chloride, HCl (7647-01-0)

ammonia (7664-41-7)

Benzene (71-43-2)

ethyl acetate (141-78-6)

methanol (67-56-1)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

magnesium (7439-95-4)

nitrogen (7727-37-9)

toluene (108-88-3)

Benzophenone (119-61-9)

isopropyl alcohol (67-63-0)

phosgene (75-44-5)

phenylmagnesium chloride (100-59-4)

magnesium hydroxide

Phenylmagnesium bromide (100-58-3)

dichloromethane (75-09-2)

diethylzinc (557-20-0)

triphenylmethanol (76-84-6)

magnesium sulfate (7487-88-9)

borane (7440-42-8)

1-Indanone (83-33-0)

methyl sulfide, dimethyl sulfide (75-18-3)

proline, (S)-proline (147-85-3)

Tetrahydrofuran, THF (109-99-9)

heptane (142-82-5)

hexane (110-54-3)

triethylamine (121-44-8)

helium (7440-59-7)

argon (7440-37-1)

DCl (7698-05-7)

α,α-diphenyl-2-pyrrolidinemethanol (112068-01-6)

N-nitrosopyrrolidine (930-55-2)

triphosgene (32315-10-9)

(S)-Tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaborole (112022-81-8)

oxazaborolidine

triethylammonium hydrochloride

(S)-1,1-Diphenylprolinol, diphenylprolinol, (R)-diphenylprolinol, (S)-α,α-diphenyl-2-pyrrolidinemethanol, (S)-diphenylprolinol

(S)-diphenylprolinol sulfate, diphenylprolinol sulfate

(R)-2,3-Dihydro-1H-inden-1-ol, (R)-1-indanol (697-64-3)

methylboronic acid (13061-96-6)

1-Indanol (6351-10-6)

2-naphthylprolinol

methyl pyroglutamate (4931-66-2)

(S)-proline methyl ester hydrochloride

N-(benzyloxycarbonyl)-(S)-proline methyl ester

N-benzyl-(S)-proline ethyl ester

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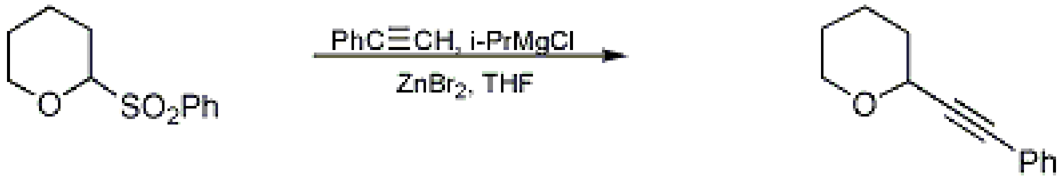
Organic Syntheses, CV 9, 688

SUBSTITUTION REACTIONS OF 2-BENZENESULFONYL CYCLIC ETHERS: TETRAHYDRO-2-(PHENYLETHYNYL)-2H-PYRAN

[2H-Pyran, tetrahydro-2-(phenylethenyl)-]



Submitted by Dearg S. Brown and Steven V. Ley[1].
Checked by David J. Mathre and Ichiro Shinkai.

1. Procedure

An oven-dried, three-necked, 1-L, round-bottomed Morton flask equipped with a mechanical stirrer, gas bubbler outlet, 125-mL, pressure-equalizing addition funnel fitted with a rubber septum, and a nitrogen inlet (Note 1) is charged with 11.2 g (110 mmol) of phenylacetylene (Note 2) and 60 mL of dry tetrahydrofuran (THF) (Note 3). The addition funnel is charged with 60 mL of 2 M isopropylmagnesium chloride (Note 4) which is then added over a 5-min period (Note 5). The addition funnel is rinsed with 10 mL of dry THF and the solution is stirred at room temperature for 1 hr. The addition funnel is charged with 72 mL of 1 M anhydrous zinc bromide in THF (Note 6) which is then added to the light-grey solution over a 5-min period (Note 7). The addition funnel is rinsed with 10 mL of dry THF, and the mixture is stirred for a further 30 min at room temperature (Note 8). The addition funnel is charged with a solution of 22.6 g (100 mmol) of 2-(phenylsulfonyl)tetrahydro-2H-pyran (Note 2) dissolved in 100 mL of dry THF, which is then added over a 5-min period (Note 9). The resulting grey solution is stirred at room temperature for 18 hr and then quenched with 300 mL of 1 M hydrochloric acid (Note 10). The mixture is transferred to a single necked, 1-L, round-bottomed flask and concentrated under reduced pressure (40°C, 100 mm) to remove the THF. The residue is transferred to a 1-L separatory funnel and extracted with 300 mL of isopropyl acetate (i-PrOAc). The extract is sequentially washed with water (150 mL), 1 M aqueous dibasic potassium phosphate (3 × 150 mL), and brine (150 mL). The extract is dried over anhydrous sodium sulfate, filtered through a sintered glass funnel, washing the residue with more i-PrOAc, and then concentrated under reduced pressure (40°C, 10 mm) to give 19.6 g of crude product as a pale yellow liquid (Note 11). This is distilled under reduced pressure to afford 18.3 g (98%) of tetrahydro-2-(phenylethynyl)-2H-pyran as a colorless liquid, bp 110–115°C (0.01 mm) (Note 12).

2. Notes

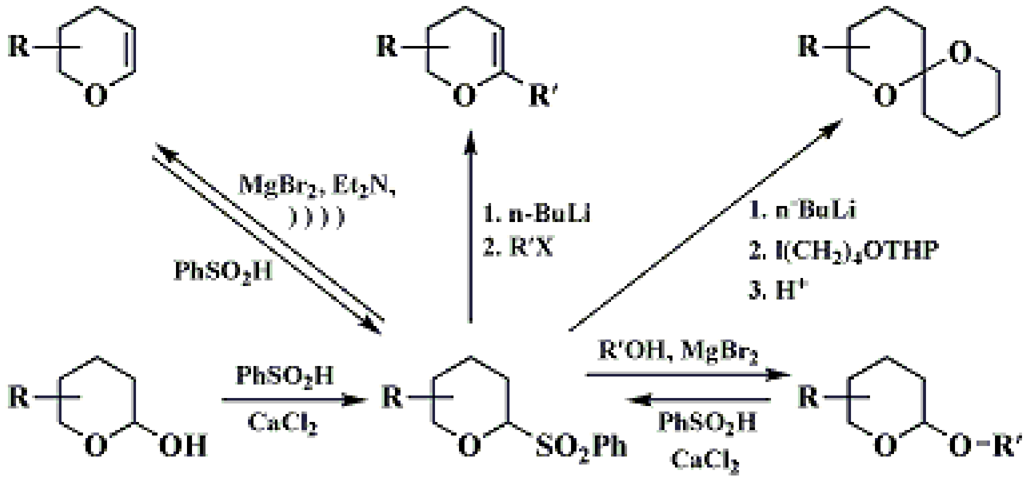
1. A constant stream of anhydrous nitrogen (dried over molecular sieves) was maintained throughout the reaction.
2. All the chemicals used in this procedure were purchased from Aldrich Chemical Company, Inc., and were used without further purification unless otherwise stated.
3. Tetrahydrofuran was dried over 3Å molecular sieves (residual water content <20 •g/mL) and purged with nitrogen prior to use.
4. Isopropylmagnesium bromide can also be used in this type of experiment.
5. The reaction is exothermic, the internal temperature rising from 20°C to 44°C. *CAUTION: Do not run the reaction under more concentrated conditions, or on a larger scale without providing external cooling.*
6. Zinc bromide (100 g, 440 mmol) (98+%, (Note 2)) was dissolved in dry THF bringing the volume to 440 mL (exothermic heat of solution). The initial water content (1.2 mg/mL) was reduced to <50 •g/mL by drying the solution with 3Å molecular sieves (50 g) for 24 hr.
7. The reaction is exothermic, the internal temperature rising from 20°C to 34°C. See (Note 5).
8. On addition of zinc bromide a fine white precipitate is sometimes formed (observed by checkers).
9. The reaction is exothermic, raising the internal temperature from 20°C to 32°C. See (Note 5).
10. The quench is exothermic during addition of the first ca. 25 mL of the aqueous hydrochloric acid, the internal temperature rising from 20°C to 30°C.
11. HPLC analysis is as follows: 94.1 wt% product, 2.4 wt% phenylacetylene, remainder i-PrOAc. HPLC conditions are as follows: [4.6 × 250 mm Zorbax RX; 40:60 H_2O (0.01 M KH_2PO_4)/MeCN; 1.5 mL/min; UV 210 nm] phenylsulfinic acid (2.6 min), 2-(phenylsulfonyl)tetrahydro-2H-pyran (4.7 min, decomposes in solution), phenylacetylene (6.1 min), tetrahydro-2-(phenylethynyl)-2H-pyran (9.2 min).
12. The physical properties are as follows: literature bp 149°C (8 mm);[2] HPLC analysis: >99 wt% product, <0.1% phenylacetylene; ^{1}H NMR ($CDCl_3$) δ: 1.50–2.00 (m, 6 H, C3-H_2, C4-H_2, C5-H_2), 3.53–3.66 (m, 1 H, C6-H), 4.00–4.13 (m, 1 H, C6-H), 4.52 (dd, 1 H, J = 2.8, 7.4, C2-H), 7.26–7.35 (m, 3 H, Ar-H), 7.41–7.51 (m, 2 H, Ar-H); ^{13}C NMR ($CDCl_3$) δ: 21.8 (t), 25.7 (t), 32.2 (t), 66.6 (t), 67.5 (d), 85.2 (s), 88.1 (s), 122.8 (s), 128.2 (d), 128.3 (d), 131.8 (d).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

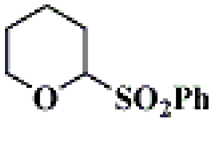
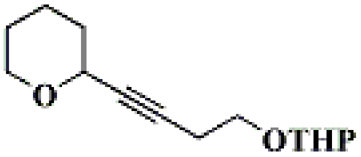
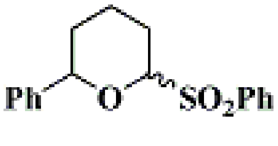
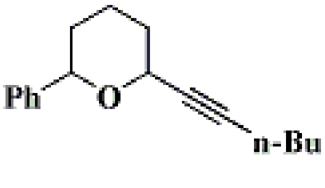
3. Discussion

Methods for forming carbon-carbon bonds at the anomeric position of cyclic ethers are important processes in organic synthesis. We have shown how lactols and their derivatives can be readily converted into the corresponding 2-benzenesulfonyl cyclic ethers.[3,4] These versatile intermediates can then be transformed into the corresponding dihydropyrans,[3] 2-substituted dihydropyrans,[4] spiroacetals,[4,5] and tetrahydropyranyl ethers[6] (Scheme 1).



The procedure illustrated here is representative of a general and versatile method for the preparation of 2-substituted tetrahydrofurans and tetrahydropyrans from cyclic ether sulfones and the appropriate alkynyl, vinyl, or aryl Grignard reagent. From the examples shown in the Table and others previously reported,[3,7] a selectivity for the trans-product is observed with 6-substituted tetrahydropyrans irrespective of the initial geometry of the sulfone. This implies the presence of a common reaction intermediate such as an oxonium ion which is trapped by preferred axial bond formation at the 2-position. For 5-substitued tetrahydrofurans, significant trans-selectivity is only observed with large substituents.

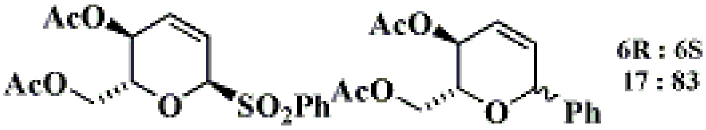
TABLE
SUBSTITUTIONREACTIONS OF2-BENZENESULFONYLCYCLICETHERS

Sulfone	Product(s)	Yield (%)
		83
		81

91

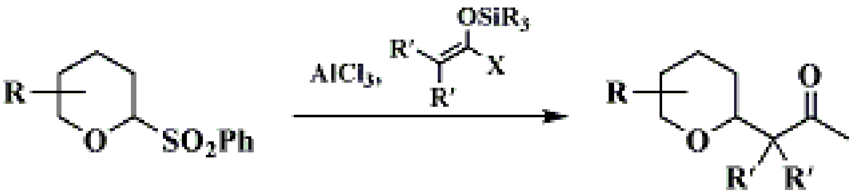
95

82



54

The benzenesulfones also undergo nucleophilic displacement with silyl enol ethers and ketene silyl acetals in the presence of a Lewis acid such as aluminum trichloride (Scheme 2).[8]



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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

brine

hydrochloric acid (7647-01-0)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

aluminum trichloride (3495-54-3)

Ketene (463-51-4)

Phenylacetylene (536-74-3)

isopropylmagnesium bromide (920-39-8)

isopropylmagnesium chloride (1068-55-9)

Tetrahydrofuran (109-99-9)

zinc bromide (7699-45-8)

phenylsulfinic acid (618-41-7)

isopropyl acetate (108-21-4)

silyl (13765-44-1)

potassium phosphate (7778-53-2)

Tetrahydro-2-(phenylethynyl)-2H-pyran (70141-82-1)

2H-Pyran, tetrahydro-2-(phenylethenyl)-

2-(phenylsulfonyl)tetrahydro-2H-pyran (96754-03-9)

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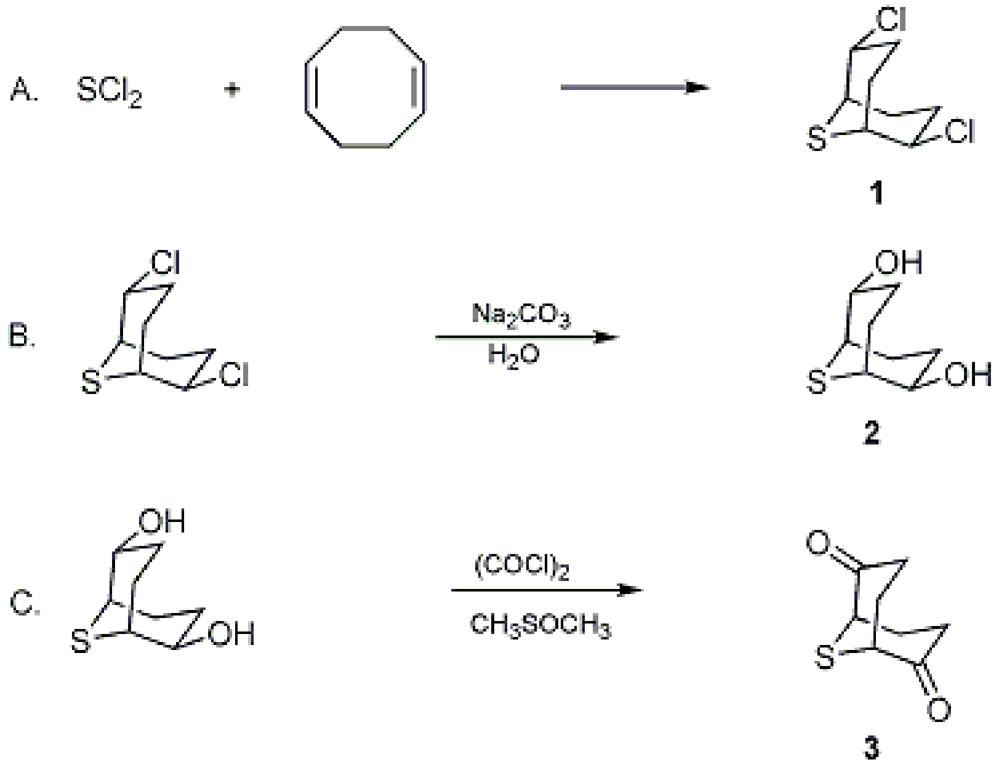
Organic Syntheses, CV 9, 692

9-THIABICYCLO[3.3.1]NONANE-2,6-DIONE



Submitted by Roger Bishop[1]
Checked by Graham N. Maw and Robert K. Boeckman, Jr..

1. Procedure

A. *(1α,2α,5α,6α)-2,6-Dichloro-9-thiabicyclo[3.3.1]nonane* **(1)**. *(CAUTION! Preparation A should be carried out in a well-ventilated hood).* A dry, 2-L, four-necked, round-bottomed flask is equipped with a sealed mechanical stirrer (Note 1), 1-L pressure-equalizing funnel fitted with a drying tube, low temperature thermometer, and a nitrogen inlet. The flask is charged with 125 mL (1.02 mol) of 1,5-cyclooctadiene (Note 2) and 1 L of reagent dichloromethane, cooled to –50 to –60°C using an external acetone-dry ice bath, and the solution placed under a slow stream of dry nitrogen. To the vigorously stirred solution is added slowly over a period of 2 hr a solution of 65 mL (1.02 mol) of freshly purified sulfur dichloride (Note 3) in 500 mL of dichloromethane while maintaining the temperature at, or below, –50°C. The cloudy solution is allowed to warm to room temperature and filtered to remove a small amount of white solid. The filtrate is transferred to a 3-L separatory funnel, washed with brine (3 × 100 mL), and dried (Na_2SO_4). Solvent is removed from the filtrate under reduced pressure with a rotary evaporator to afford 201.4–210.8 g (94–98%) of (1α,2α,5α,6α)-2,6-dichloro-9-thiabicyclo[3.3.1]nonane (1) as a faintly yellow solid, mp 97.5–99°C (Note 4).

B. *(endo,endo)-9-Thiabicyclo[3.3.1]nonane-2,6-diol* **(2)**. To a 1-L, round-bottomed flask, equipped with a magnetic stirring bar, is added 21.12 g (0.10 mol) of the dichloride (1), 100 mL of acetone, and a solution of 34.33 g (0.12 mol) of sodium carbonate decahydrate (Note 5) in 200 mL of water. A condenser is attached to the flask, the contents are stirred gently and then heated to reflux. After 1 hr at reflux (bath temperature ca. 85°C) the clear solution is allowed to cool to room temperature and the stirrer bar is removed (Note 6). Solvent is removed under reduced pressure using a rotary evaporator until the aqueous slurry of white solid is reduced to roughly 25 mL and then the solid is removed by suction filtration at room temperature. The dried, crude diol is heated with 300 mL of methanol and the hot solution filtered directly into a 500-mL, round-bottomed flask, thereby removing small quantities of solid impurity (Note 7). A rotary evaporator is used to concentrate the solution to a volume of ca. 40 mL, and the resulting slurry is filtered to yield 15.2–16.2 g (87–93%) of (endo,endo)-9-thiabicyclo[3.3.1]nonane-2,6-diol (2) as a white solid (Note 8), (Note 9).

C. *9-Thiabicyclo[3.3.1]nonane-2,6-dione* **(3)**.*(CAUTION! Oxalyl chloride and dimethyl sulfoxide are reported to react explosively at room temperature. Preparation C should be carried out in a well-ventilated hood since a co-product of the reaction is dimethyl sulfide).* To a 1-L, three-necked flask equipped with a magnetic stirring bar, low temperature thermometer, dropping funnel protected from moisture by a drying tube, and a second drying tube, is added 13.5 mL (0.16 mol) of oxalyl chloride and 350 mL of dichloromethane. The solution is stirred and cooled to −78°C using an external acetone-dry ice bath. A solution of 22.0 mL (0.31 mol) of dry dimethyl sulfoxide (Note 10) in 75 mL of dichloromethane is added over 10 min ensuring that the reaction temperature does not exceed −60°C. After a further 10 min a solution of 13.07 g (0.08 mol) of (endo,endo)-9-thiabicyclo[3.3.1]nonane-2,6-diol (2) in 30 mL of dry dimethyl sulfoxide is added rapidly from the dropping funnel to the stirred solution at −78°C (Note 11). Final traces of the solution are washed into the reaction using a further 10 mL of dry dimethyl sulfoxide. The reaction is stirred for 25 min at −78°C after addition of diol 2 is complete and then 105 mL of redistilled triethylamine is added dropwise. After a further 15 min at −78°C the cooling bath is removed and the reaction is allowed to warm to room temperature whereupon 300 mL of water is added. The material is transferred to a 2-L separatory funnel, the dichloromethane layer is separated, and the aqueous layer is extracted with two 100-mL portions of dichloromethane. The combined dichloromethane extracts are washed successively with 1 L of 1% hydrochloric acid, 300 mL of 5% aqueous sodium carbonate, and two 300-mL portions of water. After the extracts are dried (anhydrous sodium sulfate), the pale yellow filtrate is evaporated to give 11.9–12.4 g of crude 9-thiabicyclo[3.3.1]nonane-2,6-dione (3) as a slightly yellow solid. Thin layer chromatography (silica/dichloromethane) indicates the presence of a small quantity of colored polar impurity, which is not easily removed by recrystallization. The crude solid is dissolved in ca. 300 mL of hot 1:1 ethyl ether/benzene containing 0.5 g of activated charcoal, then filtered through a short plug of Celite filter aid. The plug is washed with further hot solvent and the combined filtrates are evaporated to give 11.3–11.7 g (88–92%) of 9-

thiabicyclo[3.3.1]nonane-2,6-dione (3) as a faintly off-white solid of ca. 99% purity. Analytically pure material is obtained by recrystallization from 2:1 light petroleum/chloroform or from 1:1 light petroleum/dichloromethane. Alternatively, the product is sublimed under reduced pressure (ca. 160°C/30 mm) (Note 12).

2. Notes

1. A magnetic stirring bar may be used provided that *vigorous* mixing of the solution is possible.
2. 1,5-Cyclooctadiene purchased from the Aldrich Chemical Company, Inc. was purified by elution of the neat liquid through a short column of activated alumina immediately prior to use.
3. Sulfur dichloride partially decomposes on standing to chlorine and sulfur monochloride and so should always be purified before use. Commercial sulfur dichloride of approximately 80% purity (Aldrich Chemical Company, Inc.) was purified in a hood following the procedure described by Brauer.[2] Phosphorus trichloride (2 mL) was added to crude sulfur dichloride (200 mL) contained in a flask set up for a standard distillation and protected from the atmosphere by a silica gel drying tube. The fraction boiling between 55–63°C was collected in a receiving flask containing phosphorus trichloride (5 drops). A second distillation using the same technique gave pure sulfur dichloride of bp 59–60°C/atmospheric pressure. Material stabilized with a few drops of phosphorus trichloride may be stored for a few days in a sealed container without significant decomposition.
4. Compound 1 has the following spectral properties. IR (paraffin mull) cm^{-1}: 1245 (m), 1160 (m), 1000 (w), 950 (w), 890 (w), 815 (s), 755 (m), 735 (m); ^{1}H NMR ($CDCl_3$) δ: 2.18–2.38 (6 H, m), 2.65–2.70 (2 H, m), 2.85–2.88 (2 H, m), 4.68–4.75 (2 H, m); ^{13}C NMR ($CDCl_3$) δ: 28.3 (t), 32.6 (t), 37.3 (d), 62.5 (d). The crude product is sufficiently pure for most purposes, but analytically pure material is colorless, lit.[3] mp 98.1–99.6°C. This may be obtained by trituration of the crude product with a little ethyl ether (which removes a small quantity of yellowish oil) followed by filtration. Alternatively it may be purified by sublimation under reduced pressure (48°C/0.05 mm)[3] or recrystallized from benzene.[4]
5. The checkers employed anhydrous sodium carbonate.
6. The checkers filtered the solution at this point to remove small amounts of a brown solid.
7. (endo,endo)-9-Thiabicyclo[3.3.1]nonane-2,6-diol (2) is remarkably insoluble in the solvents normally used for extraction of organic materials from aqueous solutions.
8. Compound (2) has the following spectral properties. IR (paraffin mull) cm^{-1}: 3300 (s), 1025 (s), 990 (m), 950 (w), 900 (w), 880 (m): ^{1}H NMR (d^{6}-DMSO) δ: 1.55–1.93 (6 H, m), 2.28–2.50 (4 H, m), 3.91 (2 H, m), 4.91 (2 H, d, J = 6); ^{13}C

NMR (d^6-DMSO) δ: 26.4 (t), 30.8 (t), 37.0 (d), 70.7 (d).

9. Lautenschlaeger[5] has reported that diol 2 can be obtained in polymorphic forms with melting points between 188°C and 257°C according to the history of the sample. Determination of the mp is therefore not necessarily a good indicator of purity in this particular case, and the spectroscopic methods quoted are recommended. Crystals from methanol had mp 250–253°C (lit.[4] 249–250.5°C) but these rapidly became opaque and eventually crumbled to a white powder with lower mp. Samples of diol 2 prepared by the method described here melted indistinctly about 220–225°C.

10. Dimethyl sulfoxide was stirred and heated at ca. 100°C with powdered calcium hydride for 2 hr, distilled under reduced pressure, and used at once.

11. Care must be taken to ensure that the liquid from the funnel drops directly into the reaction and not onto the walls of the flask where it will solidify.

12. The physical properties of the product are as follows: mp 140–142°C; lit.[6] 140–142°C. IR (paraffin mull) cm^{-1}: 1690 (s), 1260 (m), 1215 (m), 1125 (m), 1095 (w), 1035 (w), 935 (w); ^1H NMR ($CDCl_3$) δ: 2.47–2.69 (6 H, m), 2.82–2.89 (2 H, m), 3.37–3.38 (2 H, m); ^{13}C NMR ($CDCl_3$) δ: 31.1 (t), 36.6 (t), 44.7 (d), 205.2 (s).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The addition of sulfur dichloride and 1,5-cyclooctadiene to produce (1α,2α,5α,6α)-2,6-dichloro-9-thiabicyclo[3.3.1]nonane (1) has been described by several workers.[3,4,5,7] Determination of the stereochemistry of the product has been carried out using ^1H NMR methods,[3] and by means of the X-ray crystal structure of the corresponding sulfone derivative.[8] The procedure described here as step A is that due to Corey and Block.[3]

Hydrolysis of the dichloride (1) to yield (endo,endo)-9-thiabicyclo[3.3.1]nonane-2,6-diol (2) has been carried out using water,[4] aqueous sodium hydroxide,[4] aqueous sodium hydrogen carbonate,[5] and aqueous sodium carbonate.[5] Step B is an improved version of the latter reaction. The (endo,endo)-stereochemistry was originally inferred from IR evidence,[4] and subsequently confirmed by NMR work and the crystal structure of the related compound 2,6-dinitrato-9-thiabicyclo[3.3.1]nonane 9,9-dioxide.[9] Both the high lability of the dichloride (1) and the stereochemistry resulting from hydrolysis arise from neighboring group participation of the sulfur atom to form intramolecular sulfonium ion intermediates.[3,4] These processes have been studied in

detail by Vincent and co-workers[10] using ^{13}C NMR spectroscopy.

The diketone (3) is a versatile intermediate for the preparation of 9-thiabicyclo[3.3.1] nonane derivatives[6,11,12,13] and provides a simple synthetic entry to a number of other heterocycles such as the 2-thiaadamantane,[13,14] thiacyclohexane,[15] thiacycloheptane,[15] 2,6-dithiaadamantane,[16] and 2-thiabrexane[17] ring systems. Only one previous procedure for its preparation has been published.[6] This method involves the oxidation of diol (2) with chromium trioxide in pyridine and dichloromethane to yield 9-thiabicyclo[3.3.1]nonane-2,6-dione (3) in 65% yield. In practice this reaction is difficult to carry out reproducibly because of precipitation of tarry chromium salts which make adequate stirring and extraction of the product very difficult. Consequently the dione (3) is often accompanied by partly oxidized material and/or material where the sulfur atom has been oxidized. The method reported here avoids these technical difficulties and affords a considerably increased yield.

More generally, the procedure described in step C illustrates how the Swern oxidation method[18,19,20] can be employed for the selective oxidation of an alcohol functionality in the presence of a sulfur moiety. A drawback of the original Swern oxidation is the lack of solubility of some substrates in the dichloromethane solvent at low temperatures, which results in a serious reduction of yield. In the past this has been avoided by carrying out the oxidation step at −10°C. This once again gave excellent yields, but this procedure required the use of twice the stoichiometric amount of oxidant.[19] The method described here as step C demonstrates that this is not necessary, and that the oxidation of insoluble materials can be carried out following the routine procedure provided that the substrate is added as a solution in dry dimethyl sulfoxide.

Step C has been carried out on three times the described scale without any deleterious effects being noted.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica

brine

2,6-dinitrato-9-thiabicyclo[3.3.1]nonane 9,9-dioxide

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

methanol (67-56-1)

ethyl ether (60-29-7)

diketone (107-22-2)

sodium hydroxide (1310-73-2)

sodium hydrogen carbonate (144-55-8)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

acetone (67-64-1)

pyridine (110-86-1)

chlorine (7782-50-5)

phosphorus trichloride (7719-12-2)

sodium carbonate decahydrate (6132-02-1)

sulfur monochloride

dichloromethane (75-09-2)

chromium trioxide (1333-82-0)

sulfur dichloride (10545-99-0)

dimethyl sulfide (75-18-3)

oxalyl chloride (79-37-8)

dimethyl sulfoxide (67-68-5)

triethylamine (121-44-8)

calcium hydride (7789-78-8)

1,5-cyclooctadiene

9-Thiabicyclo[3.3.1]nonane-2,6-dione (37918-35-7)

(endo,endo)-9-Thiabicyclo[3.3.1]nonane-2,6-diol (22333-35-3)

2-thiaadamantane (281-25-4)

thiacyclohexane (1613-51-0)

thiacycloheptane (4753-80-4)

2,6-dithiaadamantane

(1α,2α,5α,6α)-2,6-Dichloro-9-thiabicyclo[3.3.1]nonane (10502-30-4)

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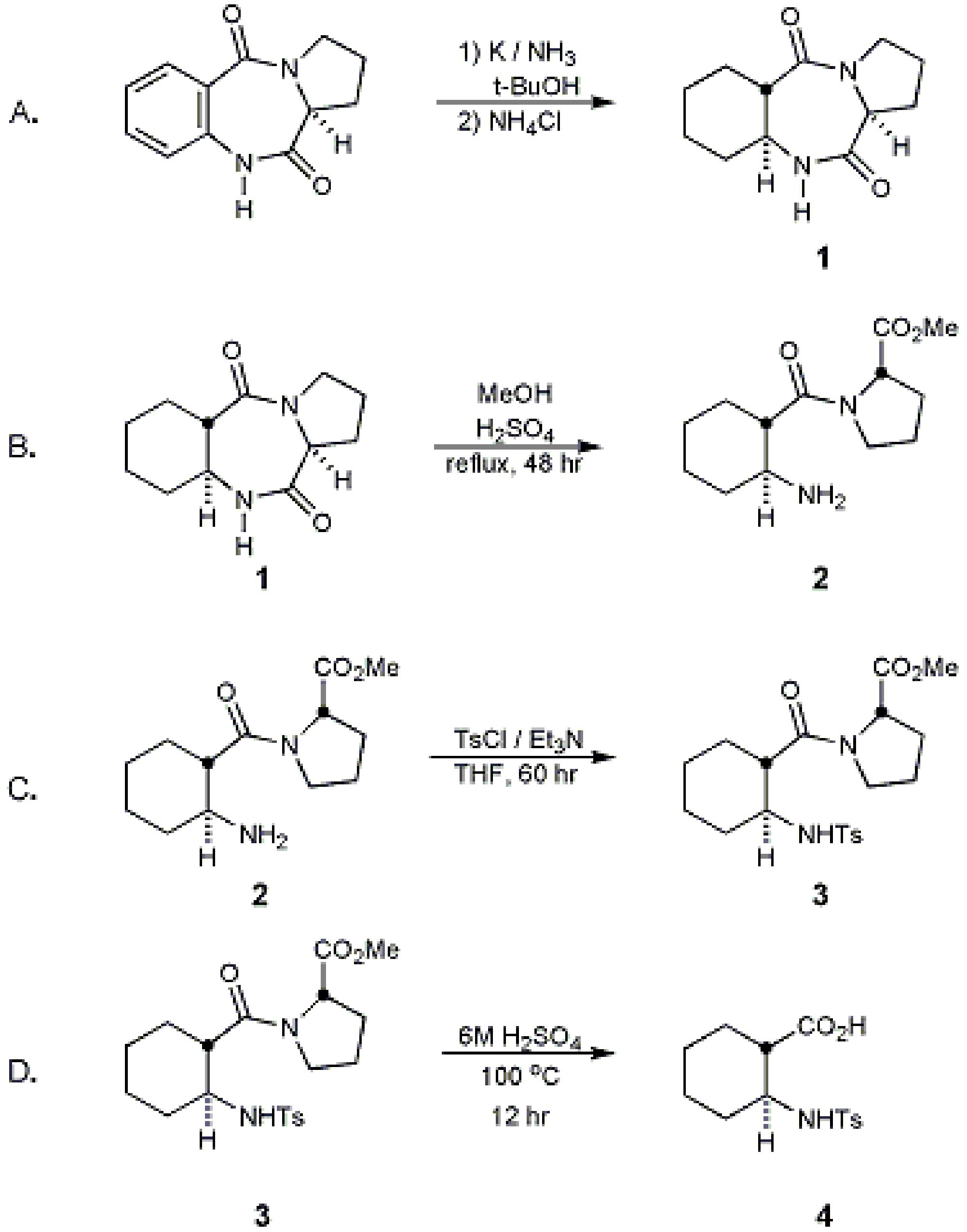
ASYMMETRIC SYNTHESIS OF trans-2-AMINOCYCLOHEXANECARBOXYLIC ACID DERIVATIVES FROM PYRROLOBENZODIAZEPINE-5,11-DIONES: (1S,2S)-2-(N-TOSYLAMINO) CYCLOHEXANECARBOXYLIC ACID



Submitted by Arthur G. Schultz and Carlos W. Alva[1].
Checked by Steven S. Henry and Albert I. Meyers.

1. Procedure

A. *(5aS,9aS,11aS)-Perhydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine-5,11-dione* **(1)**. A 3-L, three-necked, round-bottomed flask, equipped with a mechanical stirrer bearing a glass paddle, a dry ice/acetone-cooled cold-finger condenser bearing a nitrogen inlet/outlet valve vented through a mineral oil bubbler, and a gas inlet (Note 1) is placed under a nitrogen atmosphere, and charged with 25.0 g (0.116 mol) of 99% pure (S)-(+)-2,3-dihydro-1H-pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)dione (Note 2) and a solution of 42.2 g (0.570 mol) of tert-butyl alcohol in 150 mL of dry tetrahydrofuran (THF) (Note 3). The mixture is cooled to −78°C (dry ice/acetone bath) and 2 L of dry ammonia is distilled into the mixture (Note 4). After stirring is initiated, a total of 35.7 g (0.912 mol) of potassium metal is added to the reaction mixture in small chunks at −78°C, and the resulting blue-colored solution is stirred for 1 hr. The reaction is then carefully quenched at −78°C by the addition of 61 g (1.14 mol) of solid ammonium chloride (Note 5). The cooling bath and condenser are removed, and the ammonia is allowed to evaporate overnight. The residue is suction filtered, and the filter cake is washed with 100 mL of chloroform. The filtrate is diluted with 200 mL of water, transferred to a 1-L separatory funnel, the organic phase is separated, and the aqueous phase is extracted three times with 100 mL of chloroform. The combined organic layers are dried over anhydrous sodium sulfate (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue is crystallized from ethyl acetate, and the mother liquor purified by chromatography (Note 6) to give a total of 17.8 g (69%) of **1** (R_f 0.31, EtOAc/MeOH, 9:1) as a colorless solid, mp 225–227°C, $[\alpha]_D^{23}$ +55° ($CHCl_3$, *c* 0.61) (Note 7) and (Note 8).

B. *(1S,2S)-2-Amino-1-[((2S)-2-carbomethoxypyrrolidinyl)carbonyl]cyclohexane* **(2)**. A 250-mL, single-necked, round-bottomed flask equipped with a condenser bearing a nitrogen inlet/outlet valve as above (Part A) and a magnetic stirring bar, is charged with a solution of 20.0 g (90.0 mmol) of **1**, 100 mL of anhydrous methanol, and 18.4 g (180 mmol) of concentrated sulfuric acid, placed under a nitrogen atmosphere, and heated at reflux (oil bath temperature at 80–85°C) for 48 hr or until TLC analysis indicates the disappearance of **1**. The solution is concd under reduced pressure, 100 mL of dichloromethane (CH_2Cl_2) is added, and the mixture is cooled to 0°C. A total of 150 mL of saturated aqueous sodium bicarbonate solution is added in small portions with good stirring, followed by 10–12 mL of concd ammonium hydroxide until a pH of 10 is reached (Note 9). After thorough mixing, the organic phase is separated and the aqueous phase is extracted twice with 50 mL of CH_2Cl_2. The combined organic phases are dried over Na_2SO_4, concentrated, and the resulting crude amine **2** used immediately in the next step (Note 10).

C. *(1S,2S)-2-(N-Tosylamino)-1-[((2S)-2-carbomethoxypyrrolidinyl)carbonyl] cyclohexane* **(3)**. Approximately 22.9 g (90 mmol) of crude amine **2** (prepared above in part B), 13.66 g (135 mmol) of triethylamine, and 100 mL of dry THF are placed in a 300-mL, round-bottomed flask, equipped with a pressure-equalizing dropping funnel, a magnetic stirring bar, and a nitrogen inlet. The dropping funnel is

charged with a solution of 18.9 g (99.1 mmol) of p-toluenesulfonyl chloride (Note 11) in 50 mL dry THF. The reaction mixture is cooled to 0°C with magnetic stirring, and the solution of p-toluenesulfonyl chloride is delivered dropwise over a 30-min period. The resulting cloudy solution is stirred for 60 hr at ambient temperature. After this time period, the reaction mixture is diluted with 50 mL of saturated sodium chloride solution and 50 mL of ethyl acetate, transferred to a 500-mL separatory funnel, mixed thoroughly, and the organic phase separated. The aqueous phase is extracted twice with 50 mL of ethyl acetate. The combined organic layers are dried (Na_2SO_4), filtered, concentrated under reduced pressure, and the resulting residue purified by chromatography (Note 12) to give 22.43 g (61% from **1**) of **3** (R_f 0.34, $CHCl_3$/EtOAc, 1:1) as a colorless solid, mp 144–146°C (Note 13).

D. *(1S,2S)-2-(N-Tosylamino)cyclohexanecarboxylic acid* **(4)**. A 250-mL round-bottomed flask, equipped with a water-cooled condenser, is charged with 28.8 g (70.5 mmol) of **3** and 120 mL of 6 M sulfuric acid. The resulting heterogeneous mixture is heated at reflux (oil bath temperature 110–115°C) for 14 hr. After several hours at reflux, suspended solids are observed. The mixture is cooled to room temperature, transferred to a 500-mL separatory funnel, and extracted three times with 100 mL of CH_2Cl_2. The combined organic layers are dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to afford **4** as a colorless solid. Recrystallization of the crude solid **4** from CH_2Cl_2 and ethyl acetate affords 12.16 g (58%) of pure **4**(R_f 0.29, $CHCl_3$/EtOAc, 1:1) as colorless needles, mp 175–177°C, $[\alpha]_D^{20}$ +35° ($CHCl_3$, *c* 0.50) (Note 14) and (Note 15).

2. Notes

1. All glassware is flame dried and cooled under a stream of anhydrous nitrogen. All reactions are carried out under a positive pressure of nitrogen except for step D.
2. (S)-(+)-2,3-Dihydro-1H-pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione was purchased from the Aldrich Chemical Company, Inc. Other reagents, solvents, and drying agents were obtained from either Aldrich Chemical Company, Inc. or Fisher Scientific Company.
3. tert-Butyl alcohol is distilled prior to use. THF is distilled immediately before use from sodium benzophenone ketyl.
4. The ammonia is dried thoroughly over sodium metal before distillation into the reaction flask. If this step is not performed, a mixture of products may be obtained.[2]
5. Ammonium chloride is introduced as rapidly as possible, but with great care to avoid splashing and violent evaporation of the ammonia. The coloration of the reaction mixture will change from dark blue to colorless within 5–10 min.
6. As much product as possible is crystallized from the residue obtained from the organic extracts. The mother liquor from the crystallization is chromatographed on a column filled with neutral alumina (available from J. T. Baker Chemical Company, powder, Brockmann Activity Grade 1) using 20 g of

alumina per gram of residue (elution with $CHCl_3$/EtOAc, 1:1). Chromatography removes an impurity that makes crystallization difficult. Material purified by chromatography is also crystallized from ethyl acetate.

7. TLC analyses were performed on Macherey-Nagel Polygram SIL G UV/254 plates that were stained with a solution of phosphomolybdic acid in 95% ethanol.

8. Purified **1** has the following spectral data: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.18–1.43 (m, 4 H), 1.69–1.93 (m, 4 H), 1.95–2.08 (m, 2H), 2.19 (dt, 1 H, J = 11.3, 3.3), 2.43–2.53 (m, 1 H), 2.58 (m, 1 H), 3.46–3.69 (m, 3 H), 4.54 (t, 1 H, J = 6.8), 5.95 (s (br), 1 H); ^{13}H NMR (75 MHz, $CDCl_3$) δ: 22.2, 25.0, 25.6, 27.9, 29.7, 32.4, 48.8, 51.7, 52.5, 56.2, 170.9, 171.2; IR (KBr) cm^{-1}: 3215, 1678, 1587; chemical ionization mass spectrum, m/z (relative intensity) M^+ + 1 (100). Anal. Calcd for $C_{12}H_{18}N_2O_2$: C, 64.85; H, 8.15. Found: C, 64.74; H, 8.14.

9. The aqueous layer must be strongly alkaline to enable extraction of the amine.

10. The free amine cyclizes to the diamide **1** upon standing.

11. p-Toluenesulfonyl chloride is recrystallized from chloroform prior to use.

12. Column chromatography is performed using 30 g of silica per gram of residue and $CHCl_3$/EtOAc (1:1) as the eluent. The resulting clear solution is concentrated and the product crystallizes slowly upon standing.

13. The N-tosylamino derivative **3** has the following spectral data: ^{1}H NMR (300 MHz, $CDCl_3$) (4:1 mixture of rotamers) δ: 1.05–1.27 (m, 2 H), 1.35–1.54 (m, 1 H), 1.59–1.78 (m, 4 H), 1.80–2.34 (m, 5 H), 2.39 (s, 3 H), 2.61 (dt, 1 H, J = 11.5, 3.2), 3.05 (m, 1 H), 3.49 (m, 1 H), 3.71 (s, 0.6 H, minor rotamer), 3.78 (s, 2.4 H, major rotamer), 3.89 (m, 1 H), 4.48 (dd, 0.8 H, J = 8.5, 4.4, major rotamer), 4.53 (d, 0.2 H, J = 8, exchanges with D_2O, minor rotamer), 4.80 (dd, 0.2 H, J = 8.5, 3.0, minor rotamer), 5.41 (d, 0.8 H, J = 2, exchanges with D_2O, major rotamer), 7.25 (d, 2 H, J = 8, overlapping minor and major rotamers), 7.69 (d, 0.4 H, J = 8 minor rotamer), 7.74 (d, 1.6 H, J = 8, major rotamer); IR (KBr) cm^{-1}: 3260, 1740, 1611, 1417; chemical ionization mass spectrum, m/z (relative intensity) M^+ + 1 (100). Anal. Calcd for $C_{20}H_{28}N_2O_5S$: C, 58.82; H, 6.90. Found: C, 58.92; H, 6.92.

14. The submitters obtained yields of **4** as high as 92% after recrystallization in some runs.

15. The carboxylic acid **4** has the following spectral data: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.08–1.30 (m, 4 H), 1.48 (dd, 1 H, J = 24.5, 11.8), 1.56–1.68 (m, 3 H), 1.88–2.00 (m, 2 H), 2.28 (dt, 1 H, J = 11.1, 3.7), 2.38 (m, 4 H), 3.34 (m, 1 H), 5.27 (d, 1 H, J = 8, exchanges with D_2O), 7.26 (d, 2 H, J = 8), 7.70 (s (br), 1 H, exchanges with D_2O), 7.73 (d, 2 H, J = 8); IR (KBr) cm^{-1}: 3310, 1674, 1152; chemical ionization mass spectrum, m/z (relative intensity) 298 (M^+ + 1, 30), 280 (100). Anal. Calcd for $C_{14}H_{19}NO_4S$: C, 56.56; H, 6.44. Found: C, 56.60; H, 6.42.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the

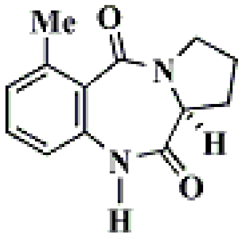
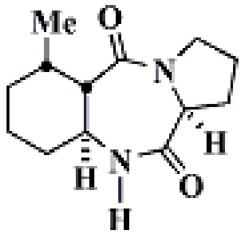
Laboratory"; National Academy Press; Washington, DC, 1995.

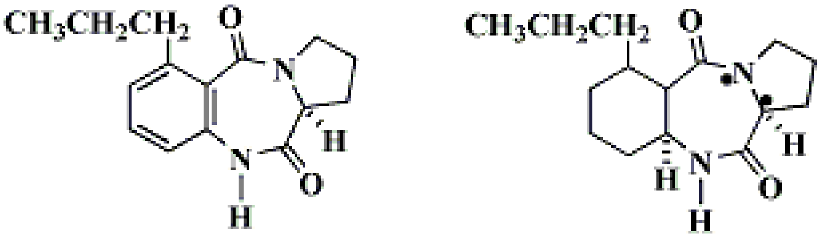
3. Discussion

Alkali metal in ammonia reductions of pyrrolobenzodiazepine-5,11-diones give trans-2-aminocyclohexanecarboxylic acid derivatives (e.g., **4**) in enantiomerically pure form.[2,3] A method for preparation of cis-2-aminocyclohexanecarboxylic acids related to **4** is based on the enantioselective hydrolysis of symmetrical diesters with pig liver esterase.[4] cis-2-Aminocyclohexane derivatives have been used for syntheses of aminocyclitol antibiotics.[4,5] 6-Alkyl-cis-2-aminocyclohexanecarboxylic acids can be prepared by alkali metal in ammonia reduction of pyrrolobenzodiazepine-5,11-diones followed by olefin hydrogenation; the cis-decahydroquinoline alkaloid (+)-pumiliotoxin C has been prepared by this methodology.[2]

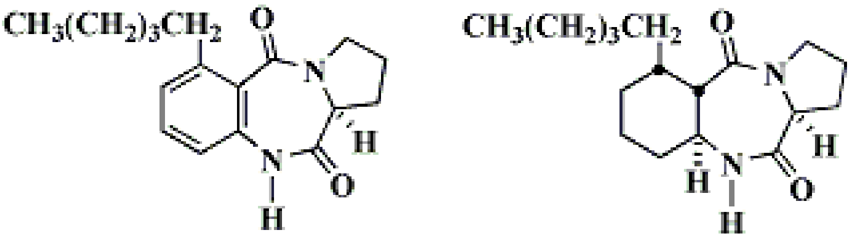
The preparation of **4** described here can be modified to provide a range of substitution patterns as shown in the Table. Some of the derivatives have been used for enantioselective syntheses of poison frog alkaloids that possess the trans-decahydroquinoline ring system.[3,6] The 6-alkyl substituted pyrrolobenzodiazepine-5,11-diones shown in the Table were prepared by metallation of the 6-methylpyrrolobenzodiazepine-5,11-dione with 2 equiv of butyllithium followed by addition of the appropriate alkylation reagent.[3,6] The highly stereoselective alkali metal in ammonia reductions of pyrrolobenzodiazepine-5,11-diones are a special application of a quite general method for enantioselective synthesis of chiral cyclohexanes from benzoic acid derivatives.[7]

TABLE
CHIRAL CYCLOHEXANE DERIVATIVES

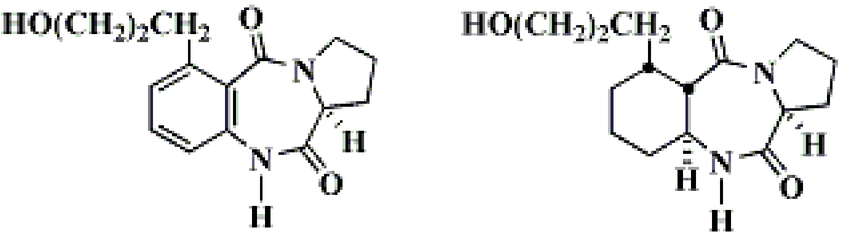
Substrate	Product	Yield (%)
		91[a]



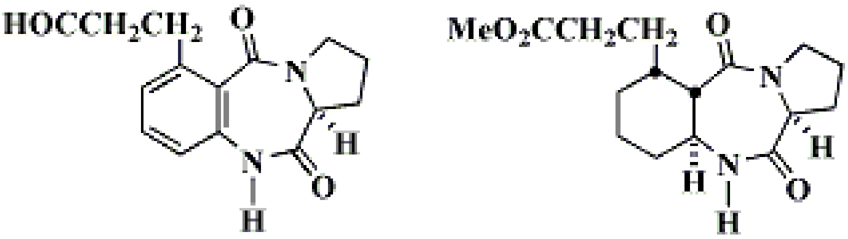
83[b]



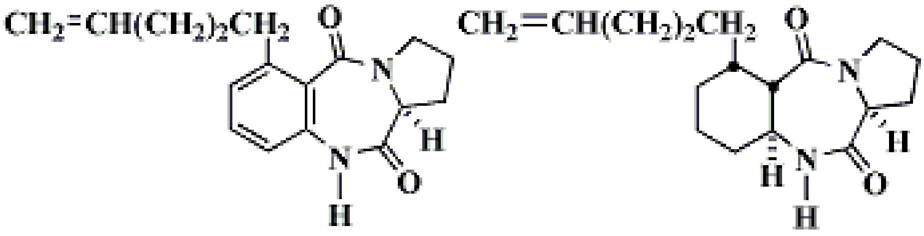
90[c]



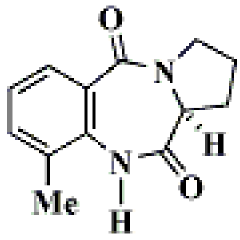
92[d]

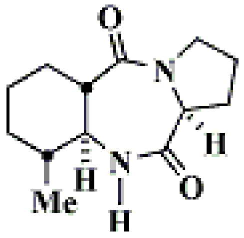


52[e,f]



90[c]





80[a]

[a]See ref. 2. [b]See ref. 3. [c]See ref. 4. [d]Unpublished work of C. Alva. [e]Unpublished work of L. Waykole. [f]The alkali metal in ammonia reduction product was treated with diazomethane.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

amine

sodium benzophenone ketyl

pyrrolobenzodiazepine-5,11-diones

6-methylpyrrolobenzodiazepine-5,11-dione

ethanol (64-17-5)

sulfuric acid (7664-93-9)

ammonia (7664-41-7)

ethyl acetate (141-78-6)

methanol (67-56-1)

ammonium chloride (12125-02-9)

chloroform (67-66-3)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

sodium (13966-32-0)

ammonium hydroxide (1336-21-6)

potassium (7440-09-7)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

triethylamine (121-44-8)

tert-butyl alcohol (75-65-0)

phosphomolybdic acid (51429-74-4)

p-Toluenesulfonyl chloride (98-59-9)

(1S,2S)-2-(N-Tosylamino)cyclohexanecarboxylic acid (110456-11-6)

(5aS,9aS,11aS)-Perhydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine-5,11-dione (110419-86-8)

(S)-(+)-2,3-dihydro-1H-pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)dione, (S)-(+)-2,3-Dihydro-1H-pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione

(1S,2S)-2-Amino-1-[((2S)-2-carbomethoxypyrrolidinyl)carbonyl]cyclohexane (174624-00-1)

(1S,2S)-2-(N-Tosylamino)-1-[((2S)-2-carbomethoxypyrrolidinyl)carbonyl] cyclohexane (110419-91-5)

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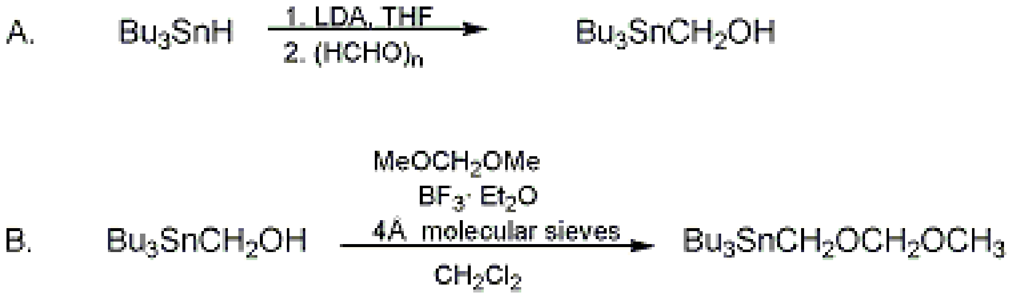
Organic Syntheses, CV 9, 704

A HYDROXYMETHYL ANION EQUIVALENT: TRIBUTYL[(METHOXYMETHOXY)METHYL] STANNANE

[Stannane, tributyl[(methoxymethoxy)methyl]-]



Submitted by Rick L. Danheiser[1], Karen R. Romines[1], Hiroo Koyama[1], Stephen K. Gee[1], Carl R. Johnson[2], and John R. Medich[2].
Checked by Darius J. Robinson and Amos B. Smith, III.

1. Procedure

A. *(Tributylstannyl)methanol*. A 500-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, a rubber septum, an argon inlet adapter, and a 150-mL, pressure-equalizing, dropping funnel fitted with a rubber septum (Note 1). The flask is charged with 13.7 mL (0.098 mol) of diisopropylamine (Note 2) and 120 mL of dry tetrahydrofuran (Note 3), and then cooled with an ice-water bath while 58.4 mL (0.093 mol) of a 1.60 M solution of butyllithium in hexane (Note 4) is added dropwise via syringe over 15 min. After 30 min, a solution of 24.75 g (0.0850 mol) of tributyltin hydride (Note 5) in 50 mL of tetrahydrofuran is added dropwise via the addition funnel over 50 min. After 30 min, 3.57 g (0.119 mol) of paraformaldehdye (Note 6) is added in one portion, the ice bath is removed, and the heterogeneous yellow reaction mixture is stirred for 3 hr at room temperature. The resulting clear, colorless solution is diluted with 500 mL of petroleum ether and washed with 300 mL of water. The aqueous phase is separated and extracted with 150 mL of petroleum ether, and the combined organic layers are washed with 200 mL of saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and concentrated at reduced pressure using a rotary evaporator to afford approximately 30 g of (tributylstannyl)methanol as a colorless oil, which was used in the next step without further purification (Note 7).

B. *Tributyl[(methoxymethoxy)methyl]stannane*. A 1-L, three-necked, round-bottomed flask is equipped with a mechanical stirrer, an argon inlet adapter, and a rubber septum (Note 1). The flask is charged with the (tributylstannyl)methanol prepared in the previous reaction, 190 mL of dichloromethane (Note 8), 280 mL (3.16 mol) of

dimethoxymethane (Note 9), and 50 g of powdered 4 Å molecular sieves (Note 10). Boron trifluoride etherate (13.0 mL, 0.106 mol) (Note 11) is added dropwise over 2 min via syringe to the vigorously stirred reaction mixture, and the resulting orange suspension is stirred at room temperature for 13 hr, and then filtered through a 2-cm pad of Celite in a sintered-glass funnel. The filter cake is washed with 250 mL of dichloromethane, and the combined filtrates are washed with two 250-mL portions of saturated sodium bicarbonate solution. The combined aqueous layers are extracted with 250 mL of dichloromethane, and the combined organic phases are then washed with 250 mL of saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and concentrated at reduced pressure using a rotary evaporator. The residual pale yellow oil (30 g) is dissolved in 20 mL of hexane and applied to 150 g of alumina (Note 12) packed in a 4.5-cm diameter column. The column is eluted with 1.3 L of 1% ethyl acetate-hexane (Note 13). The total eluant is concentrated at reduced pressure using a rotary evaporator, and the residual colorless oil is transferred to a 100-mL, round-bottomed flask and distilled through a 10-cm Vigreux column to furnish 23 g (74% overall yield based on tributyltin hydride) of tributyl[(methoxymethoxy)methyl]stannane as a colorless liquid, bp 117°C (0.34 mm) ((Note 14) and (Note 15)).

2. Notes

1. The glass components of the apparatus are immersed in a solution of 19.8 g of potassium hydroxide in 20 mL of water and 88 mL of ethanol for 20 min, dried overnight in a 150°C oven, and then assembled and maintained under an atmosphere of argon during the course of the reaction. This procedure removes traces of materials that otherwise can catalyze decomposition of the organotin reagents employed in the reaction.

2. Diisopropylamine was purchased from Aldrich Chemical Company, Inc. and distilled from calcium hydride before use.

3. Tetrahydrofuran was distilled from sodium benzophenone ketyl immediately before use.

4. Butyllithium was purchased from Aldrich Chemical Company, Inc. and titrated using the method of Watson and Eastham.[3]

5. Tributyltin hydride was freshly prepared by the method of Hayashi et al.[4] Commercial tributyltin hydride (Aldrich Chemical Company, Inc.) can also be used, but in this case the yield of product is 5–7% lower.

6. Paraformaldehyde was obtained from Aldrich Chemical Company, Inc. and dried overnight in a desiccator over phosphorus pentoxide at 0.3 mm.

7. If desired, the product can be purified by column chromatograpy on 230–400 mesh silica gel (50 times by weight, elution with 5–10% ethyl acetate-hexane). (Tributylstannyl)methanol exhibits the following spectral properties: IR (film) cm^{-1}: 3320, 2970, 2940, 2880, 2860, 1465, 1440, 1380, 1360, 1345, 1295, 1255, 1185, 1155, 1075, 1045, 1025, 985, 875; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.8–1.1 (m, 15 H), 1.2–1.7 (m, 13 H), 4.02 (d, 2 H, J = 4.5).

8. Dichloromethane was distilled from calcium hydride immediately before use.

9. Dimethoxymethane was obtained from Aldrich Chemical Company, Inc. and distilled from sodium before use.
10. Linde type 4 Å molecular sieve pellets were crushed using a mortar and pestle and then dried under vacuum (0.3 mm) at 300°C[5] for 15 hr prior to use.
11. Boron trifluoride etherate ($BF_3 \cdot Et_2O$) was purchased from Aldrich Chemical Company, Inc. and distilled at 20 mm from calcium hydride. The overall yield for the reaction is reduced by ca. 10% if less $BF_3 \cdot Et_2O$ (1.1 equiv) or less dimethoxymethane (20 equiv) is employed.
12. EM Science 80-325 mesh alumina was used for this filtration.
13. Filtration of the crude product through alumina prior to distillation is necessary to obtain pure material. If the filtration step is omitted, product of only 85–90% purity is obtained.
14. The purity of this material was determined to be >99% by gas chromatographic analysis (0.25 mm × 30 m DB-1701 fused silica capillary column, 12 psi column pressure, 120°C for 2 min, 120–250°C at 10°C/min, then 250°C; retention time 13.1 min).
15. The product has the following spectral properties: IR (film) cm^{-1}: 2970, 2930, 2880, 2770, 1465, 1420, 1395, 1380, 1345, 1295, 1245, 1205, 1150, 1100, 1040, 965, 930, 875, 730; ^1H NMR (250 MHz, $CDCl_3$) δ: 0.8–1.1 (m, 15 H), 1.2–1.7 (m, 12 H), 3.33 (s, 3 H), 3.74 (s, 2 H), 4.52 (s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 8.9, 13.6, 27.3, 29.1, 54.9, 57.6, 99.4. Anal. Calcd for $C_{15}H_{34}O_2Sn$: C, 49.34; H, 9.39. Found: C, 49.68, H, 9.56.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Hydroxymethyl anion equivalents play an important role as building blocks in the synthesis of complex organic compounds.[6] Still[7] has previously demonstrated the utility of $Bu_3SnCH_2OCH(OEt)CH_3$ as a hydroxymethyl anion equivalent. The preparation of this reagent involves the addition of tributylstannyllithium to paraformaldehyde followed by the protection of the resultant alcohol with α-chloroethyl ethyl ether. Transmetalation of the organostannane with one equivalent of butyllithium then furnishes an α-alkoxymethyllithium reagent which adds to carbonyl compounds in good yield. Hydrolysis of the ethoxyethyl protective group provides the desired primary alcohols.

Like Still's reagent, tributyl[(methoxymethoxy)methyl]stannane incorporates an alcohol protective group that can be conveniently unmasked under mild acidic conditions. However, an advantageous feature of this MOM ether derivative is that, in contrast to Still's reagent, it is achiral. In many applications the introduction of an additional chiral center into synthetic intermediates is undesirable because of the

complications associated with the manipulation, analysis, and purification of diastereomeric mixtures.

Methoxymethylation of alcohols is generally achieved through alkylation with chloromethyl methyl ether. The procedure described here for the preparation of $Bu_3SnCH_2OCH_2OCH_3$ avoids the use of the highly toxic chloromethyl ether by employing an acid-catalyzed acetal exchange reaction with dimethoxymethane for the key protection step. Two related procedures have been developed for the methoxymethylation of (tributylstannyl)methanol based on this strategy.[8,9,10] The protocol described here employs BF_3-etherate and molecular sieves[8,11] to promote the acetal exchange and results in a higher yield of product compared to the alternative Fujita procedure[12] that uses phosphorus pentoxide. In this fashion the title compound is obtained in excellent purity in 74% overall yield from tributyltin hydride. An application of this organotin compound which illustrates its use as a hydroxymethyl anion equivalent may be found on p. 493.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 493

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

petroleum ether

sodium benzophenone ketyl

paraformaldehdye

ethanol (64-17-5)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

Dimethoxymethane (109-87-5)

dichloromethane (75-09-2)

chloromethyl ether (542-88-1)

chloromethyl methyl ether (107-30-2)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

hexane (110-54-3)

boron trifluoride etherate (109-63-7)

calcium hydride (7789-78-8)

α-chloroethyl ethyl ether (51202-81-4)

argon (7440-37-1)

p-toluenesulfonic acid (104-15-4)

diisopropylamine (108-18-9)

ethyl acetate-hexane (2639-63-6)

tributyltin hydride (688-73-3)

phosphorus pentoxide (1314-56-3)

Tributyl[(methoxymethoxy)methyl]stannane, Stannane, tributyl[(methoxymethoxy)methyl]- (100045-83-8)

(Tributylstannyl)methanol (27490-33-1)

tributylstannyllithium

paraformaldehyde (30525-89-4)

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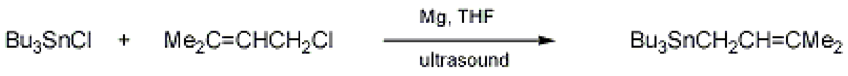
Organic Syntheses, CV 9, 707

TRIBUTYL(3-METHYL-2-BUTENYL)TIN

[Stannane, tributyl(3-methyl-2-butenyl)-]



Submitted by Yoshinori Naruta, Yutaka Nishigaichi, and Kazuhiro Maruyama[1].
Checked by Bruce M. Branan and Leo A. Paquette.

1. Procedure

CAUTION! This experiment should be perfomed with gloves in an efficient hood in order to avoid the contact of toxic tributyltin derivatives with the skin and to avoid their unpleasant odor. One should wear earmuffs during operation of an ultrasound processor.

A dry, 500-mL, three-necked flask appropriately shaped to accommodate the horn of an ultrasonic processor is equipped with a thermometer and a pressure-equalizing dropping funnel to which a nitrogen inlet is attached. A nitrogen atmosphere is established in the flask, which is charged with 100 mL of anhydrous tetrahydrofuran (THF) (Note 1), 3.04 g (0.125 mol) of magnesium (Mg) turnings (Note 2), 32.5 g (0.100 mol) of tributyltin chloride (Note 2), and a small piece of iodine (optional), and then immersed in an ice-salt bath. After the temperature of the solution falls below 15°C, 13.4 mL (0.120 mol) of 1-chloro-3-methyl-2-butene (Note 3) in 50 mL of THF is added dropwise over 30–60 min while maintaining the temperature at less than 20°C (Note 4) under sonication at an output power of 30–75W (Note 5). After the addition is complete, sonication is continued for a further 30–45 min (Note 6) to complete the reaction. The reaction mixture is poured into 400 g of ice water and the mixture is extracted with three 100-mL portions of ether. The combined ethereal solutions are washed with 50 mL of water and 50 mL of brine, dried over anhydrous magnesium sulfate, and evaporated under aspirator pressure to yield a colorless oil. This oil is further evacuated (1 mm) at room temperature for 1 hr (Note 7) to give 36 g (100%) of tributyl(3-methyl-2-butenyl)tin. This material is sufficiently pure for direct use in most reactions, but can be purified by distillation to afford 33.2 g (92%) of colorless oil, bp 105–107°C (0.01 mm) (Note 8),(Note 9),(Note 10).

2. Notes

1. THF is distilled from benzophenone ketyl and stored over sodium wire under a nitrogen atmosphere. For the drying procedure and caution, see *Org. Synth., Coll. Vol. VII* **1990**, 451 and *Org. Synth., Coll. Vol. V* **1973**, 976, respectively.
2. Magnesium turnings were purchased from Wako Pure Chemical Industries and the Aldrich Chemical Company, Inc. Tributyltin chloride was obtained from Tokyo Kasei Kogyo and the Aldrich Chemical Company, Inc. They were used without further purification.
3. As purchased from the Aldrich Chemical Company, Inc., this chloride contains 5–10% of 3-chloro-3-methyl-1-butene. Contamination by this isomeric chloride does not affect the yield of tributyl(3-methyl-2-butenyl)tin.
4. The reaction temperature should be kept below 20°C to prevent side reactions. If the temperature exceeds 20°C, one should stop both the addition of the prenyl chloride and the ultrasound irradiation, and wait for the reaction temperature to fall below 15°C.
5. The submitters used Heat Systems-Ultrasonics Model W-220 (maximum output power 200W) with a standard horn. The checkers used a Sonics and Materials Inc. Vibra-Cell High Intensity Ultrasonic Processor (maximum power outlet 600W) fitted with a 13-in extender probe. If the applied ultrasonic processor does not have a power meter, one can judge the applied power by the occurrence of vigorous stirring of the Mg turnings around the immersed ultrasonic horn. If the Mg turnings settle to the bottom of the flask, the applied sonication power is insufficient.
For reaction on a 10-mmol scale, an ultrasonic cleaner with sufficient output power (e.g., Branson Model B-220) can be used for external irradiation.
6. After completion of the reaction, ultrasonic irradiation for an unnecessarily long period causes decomposition of the allyltributyltin. The end of the reaction can be determined by a faint turbidity in the solution and by darkening of the brilliant Mg surface.
7. Through this treatment, most of the low-boiling impurity can be removed.
8. Good purity (95–98%) is observed by GLC (glass capillary column, OV-101, 0.33 mm × 25 m) at an oven temperature of 200°C.
9. Because of modest thermal instability of the material, one should distill at a bath temperature below 150°C. When the bath temperature exceeds 150°C, considerable decomposition of the allylic tributyltin occurs and a poorer yield is realized. The checkers measured a bp of 100°C at 0.1 mm.
10. The spectrum is as follows: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.83 (m, 6 H, $SnCH_2$), 0.89 (t, 9 H, J = 7, CH_3 of Bu), 1.29 (m, 6 H, $SnCH_2CH_2$), 1.47 (m, 6 H, CH_2CH_3), 1.57 (s, 3 H, cis-CH_3), 1.64 (d, 2 H, J = 9, $CH_2CH{=}C$), 1.67 (s, 3 H, trans-CH_3), 5.28 (broad t, 1 H, J = 9, CH=C); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 9.4, 10.7, 13.7, 17.4, 25.5, 27.4, 29.3, 123.0, 125.3; ^{119}Sn NMR (120 MHz, $CDCl_3$) δ: −13.4.

Waste Disposal Information

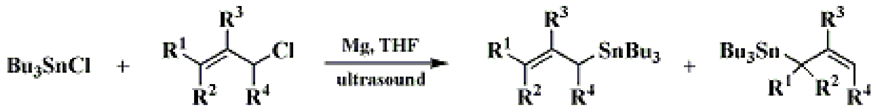
All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

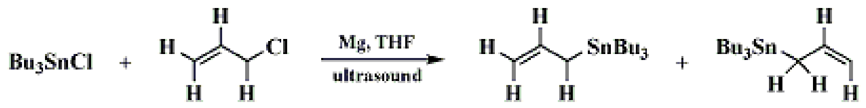
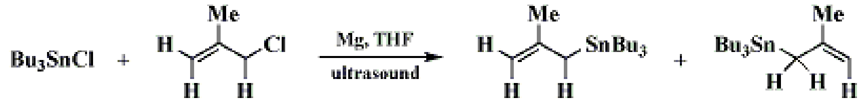
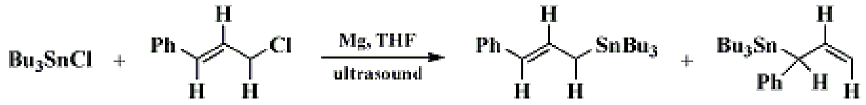
3. Discussion

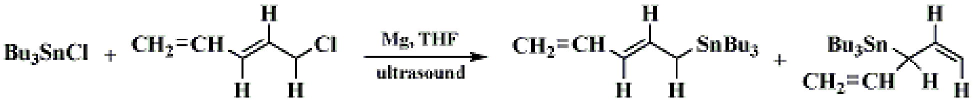
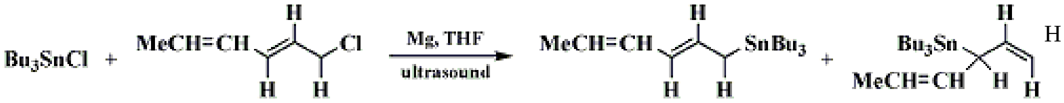
This procedure describes ultrasound-promoted Barbier-type cross coupling of an allylic chloride with tributyltin chloride.[2] Allylic trialkyltin derivatives have also been prepared by (i) a coupling reaction of a trialkyltin chloride with an allyl Grignard reagent[3,4,5] or allyllithium,[6,7] and allyl derivatives with stannyl metals,[8,9,10,11,12] (ii) stannylation of allylic sulfides,[12] sulfones,[13,14] selenoxides,[15] alcohols,[16] and allyl palladium.[17,18,19] The method with an allylic Grignard reagent prepared in advance of the coupling reaction is an alternative to this method, but the ultrasonic procedure is more convenient and effective. For the preparation of simple allyltributyltin or its homologues, the present method has advantages over other methods, especially because of easy manipulation and scale-up, reproducibility, and yield.

This procedure is representative of a general and versatile method for the preparation of allylic tributyltins. Other allylstannanes prepared using this method are shown in the Table.

TABLE
COUPLING OF ALLYLIC HALIDES WITH TRIBUTYLTIN CHLORIDE>[a]



R1	R2	R3	R4	Total Yield, % (α- + γ-isomers)	Isomeric ratio, α : γ
H 	H	H	H	100	–
H 	H	Me	H	96	–
Me	H	H	H	100	1 : 1[b]
Me	H	H	Me	52[c]	–
Ph 	H	H	H	100[d]	1 : 0

CH_2=CH 	H	H	H	96[e]	1 : 0
MeCH=CH 	H	H	H	100[f]	1 : 0

[a]All reactions were performed on a 10-mmol scale.

[b]The α-adduct is a mixture of trans:cis = 55:45.

[c]Pure trans-2-chloro-3-pentene was used. The α-adduct is a mixture of trans:cis = 55:45.

[d]No cis isomer is formed.

[e]The stereoisomer ratio is trans:cis = 92:8.

[f]The trans,trans-isomer is obtained in >90% purity.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 741
- Org. Syn. 75, 12

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

benzophenone ketyl

brine

magnesium (Mg) turnings

Mg turnings

ether (60-29-7)

magnesium turnings (7439-95-4)

nitrogen (7727-37-9)

iodine (7553-56-2)

sodium (13966-32-0)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

tributyltin (688-73-3)

tributyltin chloride (1461-22-9)

Tributyl(3-methyl-2-butenyl)tin, Stannane, tributyl(3-methyl-2-butenyl)- (53911-92-5)

1-chloro-3-methyl-2-butene, prenyl chloride (503-60-6)

3-chloro-3-methyl-1-butene (2190-48-9)

trans-2-chloro-3-pentene

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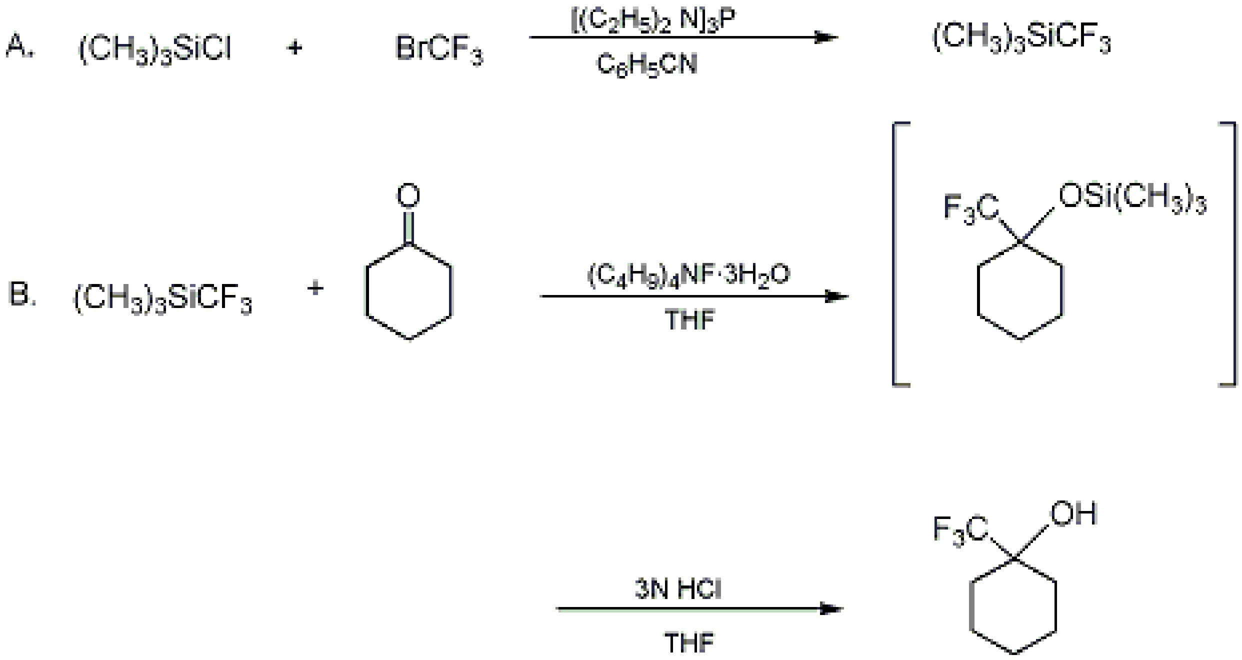
Organic Syntheses, *CV 9, 711*

1-TRIFLUOROMETHYL-1-CYCLOHEXANOL

[Cyclohexanol, 1-(trifluoromethyl)-]



Submitted by Pichika Ramaiah, Ramesh Krishnamurti, and G. K. Surya Prakash[1].
Checked by Zhen-Yu Yang and Bruce E. Smart.

1. Procedure

CAUTION! All operations should be performed in a well ventilated hood. Hexaethylphosphorous triamide is potentially toxic and should be handled with protective gear.

A. *(Trifluoromethyl)trimethylsilane*. A 2-L, three-necked flask is fitted with an efficient, overhead, sealed mechanical stirrer, a cold-finger condenser (30-cm in length and 8-cm in diameter) and a rubber septum (Note 1). The top outlet of the condenser is attached to an oil bubbler. The flask is flushed with dry nitrogen and charged with 118.8 g (1.09 mol) of chlorotrimethylsilane (Note 2) in 100 mL of anhydrous benzonitrile (Note 3). The septum is replaced quickly under dry nitrogen with a 500-mL Ace dry ice gas condenser trap (15-cm in length and 8-cm in diameter) (Note 4). The outlet of the trap is protected from moisture by a tube packed with potassium hydroxide and the inlet is connected by tygon tubing to a cylinder of bromotrifluoromethane (Note 5). The 2-L flask is immersed in a dry ice-acetone bath maintained at –30°C (Note 6) and the condensers are filled with dry ice-acetone mixture (–78°C). The cylinder is opened and 250 mL (d = 1.94 g/mL,[2] 485 g, 3.25

mol) of bromotrifluoromethane is condensed into the 500-mL Ace reservoir (Note 7). Stirring is started, and the condensed liquid bromotrifluoromethane is gradually added to the vessel at −30°C by slowly warming the reservoir to −45°C to −50°C. The resulting white slurry is further cooled to −60°C (Note 6) and (Note 8). The Ace dry ice gas condenser trap is disconnected under dry nitrogen and replaced with a 600-mL, pressure-equalizing dropping funnel containing a solution of 325.0 g (1.31 mol) of hexaethylphosphorous triamide (Note 9) in 250 mL of dry benzonitrile. This solution is added with stirring at −60°C to the white slurry mixture over a period of 2.5 hr. After the addition is complete, the reaction mixture is stirred for an additional hour at −60°C (Note 10), and then allowed to warm gradually to room temperature (25°C) over a period of 14 hr, during which time it turns clear yellow (Note 11). The condenser and dropping funnel are removed and replaced by a glass stopper and joint adapter with its glass tube connected to two, 250-mL, dry ice/acetone-cooled traps; then aspirator vacuum (ca. 20 mm) is applied. The reaction flask is gently warmed to 50°C during which time (3 hr) all the volatile material collects in the cooled traps (Note 12). The cooling baths are removed and the material in the traps is brought to 0° C. The colorless liquid is transferred quickly to a 250-mL separatory funnel, washed rapidly with ice cold water (3 × 100 mL), and the top organic product layer is separated (Note 13). The product is dried over 5 g of anhydrous magnesium sulfate, and the dry liquid is decanted into a 250-mL flask. The product is fractionally distilled through a 15-cm column packed with glass helices. Three fractions are collected. The first minor fraction (bp 45–54°C) and the second major fraction (bp 54–55°C) contain the main quantity of (trifluoromethyl)trimethylsilane. The third minor fraction (bp 55–65°C) consists mainly of hexamethyldisiloxane with a small quantity of product (trifluoromethyl)trimethylsilane (Note 14). The first and second fractions are combined to yield 116.9 g (75%) of clear liquid product (Note 15) and (Note 16), bp 54–55°C (Note 17).

B. *1-Trifluoromethyl-1-cyclohexanol*. A 250-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, rubber septum, and a reflux condenser is attached to a nitrogen source to maintain a positive pressure and the other neck is closed with a glass stopper. Tetrahydrofuran (70 mL) (Note 18) and 19.2 g (0.13 mol) of (trifluoromethyl)trimethylsilane are introduced into the flask through the septum using dry syringes (Note 19). The flask is immersed in an ice-water bath (0°C), and a solution of 10.2 g (0.104 mol) of cyclohexanone (Note 20) in 50 mL of tetrahydrofuran is added to the stirred solution of (trifluoromethyl)trimethylsilane using a syringe. Tetrabutylammonium fluoride trihydrate (33 mg) catalyst (Note 21), (Note 22) is transferred into the reaction vessel. As the exothermic reaction proceeds, a yellowish brown color develops with the initial evolution of fluorotrimethylsilane (Note 23). The reaction mixture is stirred at 0°C for 30 min and then the cooling bath is removed. The reaction mixture is brought to room temperature and stirred for an additional hour. The reaction mixture is periodically analyzed by GC-MS and the reaction is complete within 1 hr at 25°C (Note 24). To the reaction mixture that contains crude 1-trifluoromethyl-1-O-(trimethylsilyl)cyclohexane are added 25 mL of

tetrahydrofuran and 40 mL of 3 N hydrochloric acid. The mixture is stirred at room temperature for 8 hr and then transferred to a 500-mL separatory funnel containing 50 mL of water. The product is extracted with 50 mL of ether. The organic layer is separated and the aqueous layer is reextracted with 30 mL of ether. The combined organic layers are washed with 50 mL of water, dried over 10 g of anhydrous magnesium sulfate, and filtered. The residue is repeatedly washed with dry ether (3 × 20 mL). The solvent is removed on a rotary evaporator and the residue is dried to give a semi-solid that is purified by sublimation under vacuum (Note 25) to furnish 13.9–14.3 g (79–82%) of 1-trifluoromethyl-1-cyclohexanol as a white waxy solid, mp 60.8°C (Note 26).

2. Notes

1. All glass apparatus is dried in an oven at 100°C and assembled while still hot under dry nitrogen flow. All ground glass joints are tightly sealed with a Teflon tape and then wrapped with parafilm.
2. Chlorotrimethylsilane (98%) was obtained from the Aldrich Chemical Company, Inc. and was distilled over calcium hydride under a static atmosphere of dry nitrogen just prior to use.
3. Anhydrous benzonitrile (99+%) was purchased from the Aldrich Chemical Company, Inc. and used without further purification.
4. The trap was built in house. A 1000-mL Ace trap is available from the Aldrich Chemical Company, Inc.

5. Bromotrifluoromethane, bp −57°C, was supplied by E.I. du Pont de Nemours & Co., Inc.
6. A temperature of –30°C to –60°C was maintained by adding dry ice to excess acetone.
7. The rate of bromotrifluoromethane transfer was monitored by a Nujol bubbler. A mark is made on the Ace reservoir trap to indicate the 250-mL volume.
8. If the temperature falls below –60°C, the reaction mixture solidifies but returns to a liquid upon warming. The inverse addition, i.e., addition of chlorotrimethylsilane to bromotrifluoromethane, causes formation of a solid block that impedes stirring.
9. Hexaethylphosphorous triamide (97%) was obtained from the Aldrich Chemical Company, Inc., and used as received. It can be prepared from diethylamine and phosphorus trichloride following the literature procedure.[3 4]
10. An exothermic reaction usually begins after all the hexaethylphosphorous triamide is introduced, and some of the bromotrifluoromethane escapes through the bubbler.
11. To recover excess unreacted bromotrifluoromethane, a dry ice-acetone cooled trap is connected to the condenser outlet before the reaction mixture is

warmed to room temperature.
12. The proton NMR of the distillate shows the two methyl group absorptions of (trifluoromethyl)trimethylsilane and chlorotrimethylsilane in a ratio of about 85:15. The material solidifies in a dry ice-acetone cooled trap.
13. The distillate is shaken well with water to convert chlorotrimethylsilane to hexamethyldisiloxane.
14. The product from the third fraction could not be isolated pure by redistillation.
15. The yield is based on chlorotrimethylsilane. A comparable yield of 77% was obtained when the reaction was repeated on one-third the scale. GC and NMR analyses show the product to be 98–99% pure.
16. (Trifluoromethyl)trimethylsilane has the following spectroscopic properties: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.25 (s, 9 H, $Si(CH_3)_3$); ^{13}C NMR (50.0 MHz, $CDCl_3$) δ: 131.7 (q, $^{1}J^{13}C\text{-}^{19}F$ = 321.9), –5.2 (CH_3-Si); ^{19}F NMR (188.0 MHz, $CDCl_3$, $CFCl_3$ external) d: –66.1; ^{29}Si NMR (39.7 MHz, $CDCl_3$) δ: +4.7 (q, ^{2}J ($^{29}Si\text{-}^{19}F$) = 37.9). MS (m/z) 123 (M^+-19).
17. The boiling point for (trifluoromethyl)trimethylsilane is reported as 45°C.[5] The submitters report a boiling point of 55.5°C.
18. Reagent grade tetrahydrofuran was purchased from the Fisher Scientific Company and freshly distilled from sodium benzophenone ketyl under dry nitrogen atmosphere.
19. Prior to use, the hypodermic syringes and needles were dried for several hours in an oven at 100°C and allowed to cool to ambient temperature in a desiccator.
20. Cyclohexanone (99%) was purchased from the Aldrich Chemical Company, Inc., and used as such.
21. Tetrabutylammonium fluoride (TBAF) trihydrate (99%) was purchased from the Aldrich Chemical Company, Inc.
22. TBAF trihydrate acts as an initiator and the water of hydration in TBAF does not pose any problem.
23. Bubbles of fluorotrimethylsilane are seen escaping during the initial stages of the reaction.
24. Progress of the reaction can be monitored by GC-MS using a Finnigan Model Incos-50 GC-MS spectrometer: Column: DB-5; temperature program: 50°C (4.5 min), 30°C/min, 250°C (30 min). Retention time: Cyclohexanone, 7.44 min. and 1-trifluoromethyl-O-(trimethylsilyl)cyclohexane, 11.20 min.
25. The product was sublimed at 2 mm at a bath temperature of 100°C. The receiver is cooled to 0°C, using an ice-bath.
26. The submitters report a melting point of 61.6°C. The product is pure (GC-MS) and has the following spectroscopic and analytical data : IR (KBr) cm^{-1}: 3364(s), 1255(s), 1146(s); ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.00–1.90 (m,10 H), 1.93 (br, 1 H, OH); ^{13}C NMR (50.0 MHz, $CDCl_3$) δ: 20.2, 25.0, 29.8, 72.6 (q, $^{2}J_{C\text{-}F}$ = 28.2), 126.4 (q, $^{1}J_{C\text{-}F}$ = 284.5 Hz, CF_3); ^{19}F NMR (188 MHz, $CDCl_3$, $CFCl_3$, external) δ: –85.0; MS (m/z): 149 (M^+ -19, 0.57), 125 (1.25), 112 (1.23),

99 (100), 92 (1.50), 81 (66.79), 69 (10.49), 55 (26.01), 41 (37.26). Anal. Calcd for $C_7H_{11}F_3O$: C, 50.00; H, 6.59. Found: C, 49.69; H, 6.51.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

(Trifluoromethyl)trimethylsilane has been prepared by a modification[6 7] of the procedure originally published by Ruppert.[5] The optimized yield is 75%. Other less convenient methods are also available for its preparation.[8 9] (Trifluoromethyl)trimethylsilane acts as an in situ trifluoromethide equivalent under nucleophilic initiation and reacts with a variety of electrophilic functional groups. Carbonyl compounds such as aldehydes, ketones and lactones react rather readily[6,7,10] with (trifluoromethyl)trimethylsilane under fluoride initiation. The reagent also reacts with oxalic esters,[11] sulfonyl fluorides,[12] α-keto esters,[13] fluorinated ketones,[14] and sulfoxides.[15] Homologous trifluoromethyltrialkylsilanes have also been used as nucleophilic trifluoromethylating agents.[16] In the presence of copper(I) iodide (CuI), homologous (trifluoromethyl)triethylsilane reacts with aromatic, allylic and benzylic halides to provide the corresponding trifluoromethyl derivatives.[17] The synthetic applications of trifluoromethyltrimethylsilane have been reviewed.[18 19]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

sodium benzophenone ketyl

1-Trifluoromethyl-1-O-(trimethylsilyl)cyclohexane

Tetrabutylammonium fluoride (TBAF) trihydrate

1-trifluoromethyl-O-(trimethylsilyl)cyclohexane

trifluoromethide

hydrochloric acid (7647-01-0)

ether (60-29-7)

benzonitrile (100-47-0)

Cyclohexanone (108-94-1)

nitrogen (7727-37-9)

acetone (67-64-1)

potassium hydroxide (1310-58-3)

phosphorus trichloride (7719-12-2)

diethylamine (109-89-7)

copper(I) iodide (7681-65-4)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

calcium hydride (7789-78-8)

Hexaethylphosphorous triamide (2283-11-6)

CHLOROTRIMETHYLSILANE (75-77-4)

hexamethyldisiloxane (107-46-0)

fluorotrimethylsilane (420-56-4)

Tetrabutylammonium fluoride trihydrate (87749-50-6)

1-Trifluoromethyl-1-cyclohexanol, Cyclohexanol, 1-(trifluoromethyl)- (80768-55-4)

bromotrifluoromethane (75-63-8)

(Trifluoromethyl)trimethylsilane, trifluoromethyltrimethylsilane (81290-20-2)

(trifluoromethyl)triethylsilane (120120-26-5)

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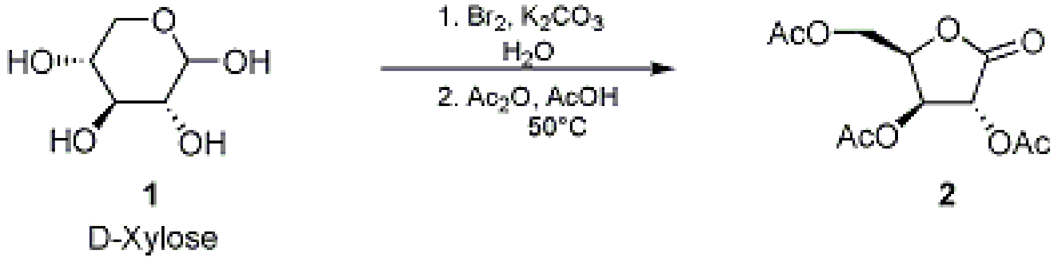
Organic Syntheses, CV 9, 717

(2S,4S)-2,4,5-TRIHYDROXYPENTANOIC ACID 4,5-ACETONIDE METHYL ESTER

[D-erythro-Pentonic acid, 3-deoxy-4,5-O-(1-methylethylidene)-, methyl ester]

A.



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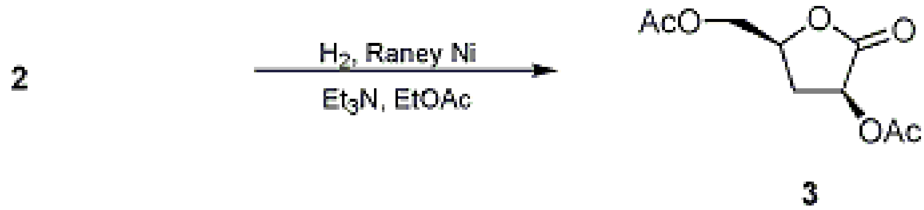

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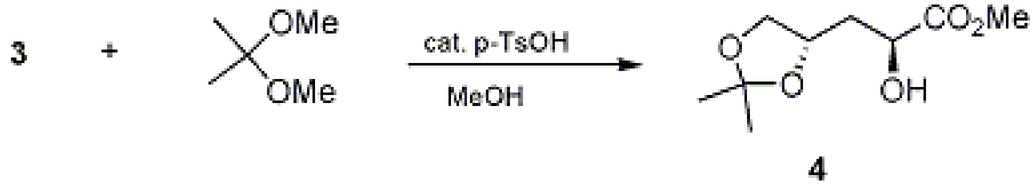


Submitted by Ruen Chu Sun and Masami Okabe[1].
Checked by Timothy C. Gahman and Larry E. Overman.

1. Procedure

A. *Tri-O-acetyl-D-xylono-1,4-lactone* **2**. a) Bromine oxidation. A 250-mL, three-necked, round-bottomed reaction flask equipped with a magnetic stirrer, thermometer, and an addition funnel is charged with 30.0 g (0.20 mol) of D-xylose and 80 mL of water. After the clear aqueous solution is cooled with an ice-water bath, 34.0 g (0.23 mol) of potassium carbonate is added in portions, keeping the temperature below 20°C. After the mixture is cooled to below 5°C, 12 mL (0.22 mol) of bromine is added dropwise over 90 min, keeping the temperature of the reaction mixture below 10°C (Note 1). The orange solution is stirred at that temperature for 30 min, then at room temperature overnight. The reaction is quenched by careful addition of 88% formic

acid (2.5 mL) to afford a colorless solution (Note 2). The solution is concentrated at 50°C on a rotary evaporator and 20 mL of acetic acid is added. The mixture is concentrated again at 50°C to remove any residual water (Note 3).

b) Acetylation. The residual white semi-solid is transferred to a 500-mL, three-necked, round-bottomed reaction flask with the aid of warm acetic acid (40 mL). The flask is equipped with a mechanical stirrer, thermometer, and an addition funnel. After the suspension is warmed to 50°C, 180 mL (1.9 mol) of acetic anhydride is added dropwise over 90 min, keeping the temperature between 50–55°C. After the mixture is stirred at that temperature overnight and then cooled to room temperature, 200 mL of water is added. The mixture is extracted with 200 mL of dichloromethane (CH_2Cl_2). The organic layer is washed with 200 mL of water. The combined aqueous layers are back-extracted with 100 mL of CH_2Cl_2. The combined organic layers are placed in a 1-L Erlenmeyer flask. After the solution is cooled with an ice-water bath, 200 mL of 2 N sodium hydroxide is added and the mixture is stirred for 30 min. The aqueous layer is separated and back-extracted with 50 mL of CH_2Cl_2. The combined organic layers are washed with 200 mL of brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue (54 g) is suspended in 50 mL of ethyl acetate. To the stirred suspension, 70 mL of hexane is added dropwise. After stirring at room temperature for 1 hr, the mixture is cooled with an ice-water bath for 30 min. The precipitate is filtered and washed with a cold 1:2 ethyl acetate/hexane mixture (2 × 60 mL) to yield 39.3–40.7 g (71.6–74.2%) of **2** as light beige crystals, mp 96–97°C (lit.[2] mp 94–95°C) (Note 4).

B. *Di-O-acetyl-3-deoxy-D-arabino-1,4-lactone* **3** (Note 5). A 300-mL, bench-top, high-pressure reactor (Note 6) is charged with 9.83 g (35.8 mmol) of **2**, 1 g of Raney nickel (Note 7), and 65 mL of ethyl acetate. After 7.5 mL (73 mmol) of triethylamine is added, the pressure in the bomb is immediately raised to 1000 psi with hydrogen. After the mixture is *stirred vigorously* (see (Note 6)) at room temperature (15°C) for 3 hr, the temperature is adjusted to 30°C, and the stirring is continued for 24 hr. The pressure is released, and the bomb is flushed with nitrogen. The catalyst is removed by filtration and washed with ethyl acetate (*CAUTION! Fire hazard!* See (Note 7)). The combined filtrate and washes are washed with 75 mL of water. The aqueous layer is back-extracted with 25 mL of ethyl acetate. The combined organic layers are then washed with 75 mL of 1 N hydrochloric acid. The aqueous layer is back-extracted again with 25 mL of ethyl acetate and this extract is combined with the original organic layer. After washing with 75-mL portions of saturated sodium bicarbonate solution, and brine, the organic layer is dried over sodium sulfate and the solvent is removed to give ca. 6.5 g of crude product (Note 8). The crude product is dissolved in 7 mL of warm ethyl acetate. Cooling to room temperature with stirring results in crystallization of **3**. Hexane (13 mL) is added dropwise to the slurry. After the mixture is stirred at room temperature for 1 hr, it is stored in a refrigerator overnight. The precipitate is filtered and washed with a cold 1:4 ethyl acetate/hexane mixture (6 mL) to yield 5.8 g (75%) of **3** as a white solid, mp 68–70°C (lit.[2] mp 69–71°C) (Note 9).

C. *(2S,4S)-2,4,5-Trihydroxypentanoic acid 4,5-acetonide methyl ester* **4**. A 100-mL, round-bottomed reaction flask equipped with a magnetic stirrer, reflux condenser, and an argon inlet tube is charged with 5.4 g (25 mmol) of the diacetate **3**, 0.5 g (2.5 mmol) of p-toluenesulfonic acid monohydrate, and 5 mL of methanol. After the mixture is refluxed for 3 hr and cooled to room temperature, 18 mL (140 mmol) of 2,2-dimethoxypropane is added. After 3 hr of stirring, sodium acetate (powder, 0.41 g, 5 mmol) is added and the mixture is stirred for 20 min to quench the reaction. Ethyl acetate (50 mL) and saturated sodium bicarbonate solution (50 mL) are added to the reaction mixture. The organic layer is removed and the aqueous layer is back-extracted twice with 25-mL portions of ethyl acetate. The combined organic layers are washed with 25 mL of brine, dried over sodium sulfate, and concentrated to afford 5.5 g of a colorless oil. Distillation through a short path distillation apparatus (with no forerun) gives 4.6 g of **4** (90% yield) as a colorless oil, bp 71–78°C (0.1 mm) (Note 10).

GC analysis of the product on a capillary column shows the diastereomeric purity to be 98.9% (Note 11). Enantiomeric integrity is confirmed after conversion to the corresponding p-phenylbenzoate by HPLC analysis on a chiral column (Note 12).

2. Notes

1. Since the reaction is exothermic at the beginning, one must avoid the accumulation of bromine in the reaction mixture.
2. A negative potassium iodide-starch test is obtained.
3. To remove the last traces of water and acetic acid the checkers found it most convenient to place the residue on a high vacuum line overnight.
4. The elemental analysis and the spectral properties of the product **2** are as follows: Anal. Calcd for $C_{11}H_{14}O_8$: C, 48.18; H, 5.15. Found: C, 47.97; H, 5.01. IR (KBr) cm^{-1}: 1805, 1792, 1750; ^{1}H NMR ($CDCl_3$) δ: 2.13 (s, 3 H), 2.14 (s, 3 H), 2.19 (s, 3 H), 4.27 (dd, 1 H, J = 12.8 and 2.9), 4.39 (dd, 1 H, J = 12.8 and 2.9), 5.00 (dt, 1 H, J = 7.7 and 2.9), 5.62 (t, 1 H, J = 7.8), 5.69 (d, 1 H, J = 7.9).
5. This is a modification of the procedure described by Bock, Lundt, and Pedersen.[2]
6. The checkers used a Parr model 4022 stirred pressure reactor. Rapid stirring is essential to ensure that hydrogenation takes place more rapidly than elimination; otherwise a number of side reactions, e.g., deoxygenation at C(5), occur. Deoxygenation was observed by the checkers if the stirring rate was less than maximum or if the reactor was filled to a higher level, e.g., when the reaction was conducted on twice the scale described. Using industrial hydrogenation equipment with stirring at 500 rpm, the submitters report that this step can be conducted on a 1-mol scale with identical yield.
7. *Caution! The catalyst is extremely pyrophoric when exposed to the air in a dry condition; it should be kept wet with solvent at all times*. The catalyst (Raney 2800 Grade Active Nickel Catalyst in Water) is purchased from Davison Chemical, and is weighed out while it is wet. The catalyst is washed by suspension in methanol and decanted to remove water. It is further washed with

ethyl acetate prior to use. The checkers obtained similar results with Raney nickel (50% slurry in water) catalyst purchased from Aldrich Chemical Company, Inc.

8. The crude diacetate contains a small amount of the epimeric acetate, as detected by NMR (m, 4.88 ppm, $CDCl_3$), that can be produced by isomerization of **3** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dichloromethane (CH_2Cl_2).

9. The elemental analysis and the spectral properties of product **3** are as follows: Anal. Calcd for $C_9H_{12}O_6$: C, 50.00; H, 5.59. Found: C, 50.11, H. 5.59. IR (KBr) cm^{-1}: 1791, 1745; ^{1}H NMR ($CDCl_3$) δ: 2.07 (dt, 1 H, J = 12.8 and 10.3), 2.12 (s, 3 H), 2.18 (s, 3 H), 2.78 (ddd, 1 H, J = 12.8, 8.8, and 6.0), 4.19 (dd, 1 H, J = 12.5 and 5.8), 4.38 (dd, 1 H, J = 12.5 and 3.1), 4.68 (m, 1 H), 5.51 (dd, 1 H, J = 10.3 and 8.8).

10. The elemental analysis and the spectral properties of product **4** are as follows: Anal. Calcd for $C_9H_{16}O_5$: C, 52.93; H, 7.90. Found: C, 52.83; H, 7.96; $[\alpha]_D$ +3.0° (MeOH, *c* 1.0). IR (neat) cm^{-1}: 3455, 1742, 1378, 1368; ^{1}H NMR ($CDCl_3$) δ: 1.37 (s, 3 H), 1.43 (s, 3 H), 1.81 (ddd, 1 H, J = 13.9, 9.3, and 4.5), 2.11 (ddd, 1 H, J = 13.9, 8.4, and 3.1), 3.01 (d, 1 H, J = 5.9), 3.60 (dd, 1 H, J = 8.2 and 6.8), 3.80 (s, 3 H), 4.11 (dd, 1 H, J = 8.2 and 6.0), 4.32 (m, 1 H), 4.39 (m, 1 H).

11. The retention time of **4** is 5.1 min, and that of the (2R,4S)-isomer is 4.7 min (on an OV-101, 12.5-m capillary column: 100°C to 140°C at 4°C/min). ^{1}H NMR ($CDCl_3$) of the (2R,4S)-isomer δ: 1.34 (s, 3 H), 1.40 (s, 3 H), 2.05 (t, 2 H, J = 6.1), 3.15 (d, 1 H, J = 3.8), 3.64 (dd, 1 H, J = 8.2 and 6.7), 3.80 (s, 3 H), 4.10 (dd, 1 H, J = 8.2 and 6.1), 4.31 (m, 1 H), 4.35 (m, 1 H).

12. A small amount of **4** is treated with p-phenylbenzoyl chloride (1.2 equiv) and triethylamine (2 equiv) in CH_2Cl_2 at room temperature overnight. After aqueous workup, the crude product is purified by chromatography on silica gel, eluting with 15% ethyl acetate in hexane. The fractions containing the product are combined and concentrated. The residue is dissolved in 5% 2-methyl-1-propanol/heptane (ca. 1 mg/2 mL). The corresponding diastereomeric mixture is prepared via isomerization of **3** with DBU, and the (2R,4R)-isomer (enantiomer) is prepared from L-xylose. HPLC analysis of the solution on Chiralcel OC 250 mm × 5 mm (purchased from Daicel Chemical), eluting with 5% 2-methyl-1-propanol in heptane (1 mL/min), reveals no detectable amount of the enantiomer [0.24% of the (2R,4S)-isomer was detected]. The retention times of the (2S,4S)-, (2R,4R)-, and (2R,4S)-isomers are 33.2, 45.3, and 54.0 min, respectively. Alternatively a Chiracel OD column can be employed.

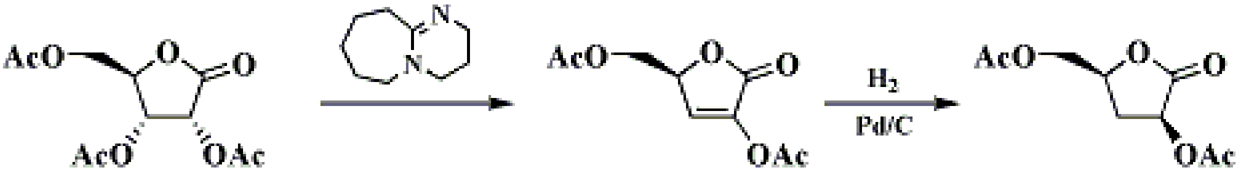
Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The present procedure for the preparation of (2S,4S)-2,4,5-trihydroxypentanoic acid 4,5-acetonide methyl ester is a slight modification of a method previously reported by the submitters.[3] The hydrogenation step is based on the method of Bock, Lundt, and Pedersen,[2] in which the 3-acetoxy group is eliminated and the resulting unsaturated lactone is simultaneously reduced with high stereoselectivity to afford di-O-acetyl-3-deoxy-D-arabino-1,4-lactone. A cleaner reaction was achieved by using Raney-Ni (instead of using palladium on carbon). When platinum catalysts are employed, the corresponding 2,3-dideoxy sugar lactones are obtained.[4]

A two-step sequence to prepare di-O-acetyl-3-deoxy-D-arabino-1,4-lactone from tri-O-acetyl-D-ribono-1,4-lactone has also been reported, but in a low yield of 46% because of the difficulty of controlling the elimination of the 3-acetoxy group, since the 2,3-unsaturated lactone also undergoes further elimination.[5] Furthermore, partial racemization of the enolizable 2,3-unsaturated lactone could occur during treatment with DBU.[6]



The ready availability of the selectively protected 2,4,5-trihydroxypentanoic acid derivatives of defined stereochemistry, such as (2S,4S)-2,4,5-trihydroxypentanoic acid 4,5-acetonide methyl ester described here, coupled with Mitsunobu inversion,[3,7] provide chiral synthons with the promise of broad utility.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

brine

(2S,4S)-2,4,5-Trihydroxypentanoic acid 4,5-acetonide methyl ester

Di-O-acetyl-3-deoxy-D-arabino-1,4-lactone

D-erythro-Pentonic acid, 3-deoxy-4,5-O-(1-methylethylidene)-, methyl ester

(2S,4S)-2,4,5-trihydroxypentanoic acid 4,5-acetonide methyl

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ethyl acetate (141-78-6)

methanol (67-56-1)

acetic anhydride (108-24-7)

sodium acetate (127-09-3)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

bromine (7726-95-6)

sodium sulfate (7757-82-6)

formic acid (64-18-6)

nitrogen (7727-37-9)

platinum (7440-06-4)

nickel, Raney nickel (7440-02-0)

palladium on carbon (7440-05-3)

dichloromethane (75-09-2)

2-methyl-1-propanol (78-83-1)

heptane (142-82-5)

hexane (110-54-3)

triethylamine (121-44-8)

d-xylose

2,2-dimethoxypropane (77-76-9)

p-toluenesulfonic acid monohydrate (6192-52-5)

1,8-diazabicyclo[5.4.0]undec-7-ene (6674-22-2)

Tri-O-acetyl-D-xylono-1,4-lactone

p-phenylbenzoate

p-phenylbenzoyl chloride (14002-51-8)

L-xylose (5328-37-0)

tri-O-acetyl-D-ribono-1,4-lactone

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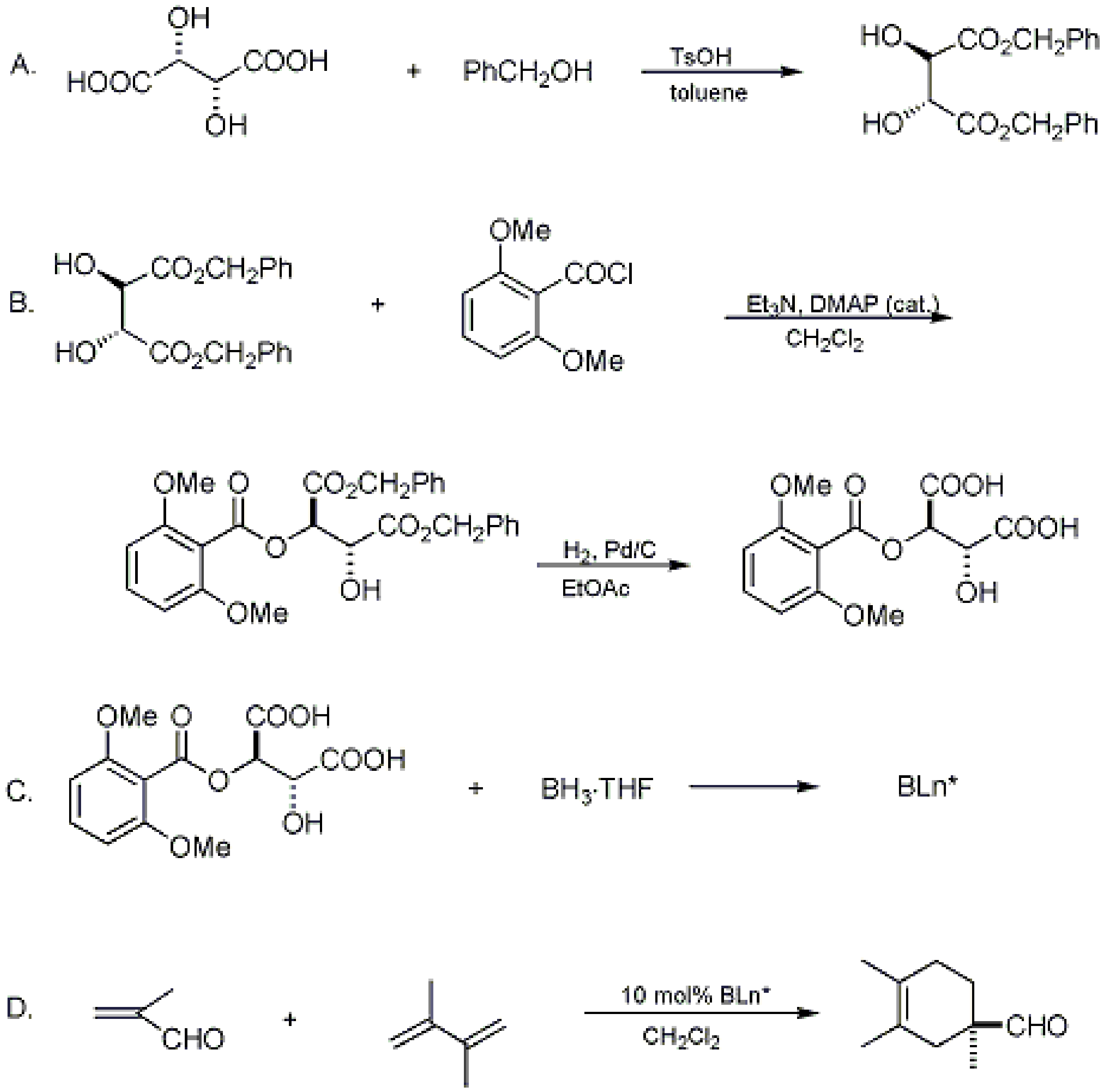
Organic Syntheses, CV 9, 722

CHIRAL (ACYLOXY)BORANE COMPLEX-CATALYZED ASYMMETRIC DIELS-ALDER REACTION: (1R)-1,3,4-TRIMETHYL-3-CYCLOHEXENE-1-CARBOXALDEHYDE

[3-Cyclohexene-1-carboxaldehyde, 1,3,4-trimethyl-, (–)-]



Submitted by Kyoji Furuta, Qing-Zhi Gao, and Hisashi Yamamoto[1].
Checked by Stephane Borrelly and Leo A. Paquette.

1. Procedure

A. *(–)-Dibenzyl tartrate*. A 300-mL, one-necked, round-bottomed flask is equipped

with a magnetic stirrer, Dean-Stark trap, and a reflux condenser. The flask is charged with 3.0 g (20 mmol) of L-(+)-tartaric acid, 6.5 g (60 mmol) of benzyl alcohol, 47.5 mg (0.25 mmol) of p-toluenesulfonic acid monohydrate, and 40 mL of toluene (Note 1). The mixture is heated under reflux in an oil bath (about 130°C) for 13 hr. During this period the theoretical amount of water (0.62 mL) is collected. The mixture is allowed to cool to ambient temperature, diluted with ether, and poured into 50 mL of aqueous, saturated sodium bicarbonate. The organic phase is separated and the aqueous phase is extracted twice with 20 mL of ether. The combined organic phases are dried over sodium sulfate. The solvent is removed with a rotary evaporator, and the resulting crude product is triturated with hexane-ether (20:1, 210 mL) to give white crystals of (−)-dibenzyl tartrate. The precipitate is collected by filtration and washed with hexane-ether (20:1). The filtrate is further concentrated to give a second crop. The total yield is 6.2 g (94%), mp 49–50°C (Note 2).

B. *Mono(2,6-dimethoxybenzoyl)tartaric acid*. In a 250-mL, three-necked, round-bottomed flask, equipped with a nitrogen inlet, a reflux condenser and a magnetic stirring bar are placed 6.1 g (18.5 mmol) of dibenzyl tartrate, 100 mL of dry dichloromethane, 4 mL (28.8 mmol) of triethylamine and 50 mg (0.4 mmol) of 4-(dimethylamino)pyridine. The stirred mixture is cooled to 0°C and 3.65 g (18.2 mmol) of 2,6-dimethoxybenozyl chloride (Note 3) is added portion-wise over 1 hr. The reaction mixture is then warmed to room temperature and refluxed for 12 to 18 hr (the reaction is easily monitored by TLC). The reaction mixture is then allowed to cool down to room temperature and poured in 100 mL of water, The aqueous phase is extracted with 2 × 75 mL of dichloromethane. The organic phases are combined, dried over sodium sulfate, filtered and concentrated to give a viscous oil. This is purified by column chromatography on silica gel using a mixture of hexane, ether and dichloromethane (3:1:5) as eluent (Note 4) to afford 7.1–7.5 g (78–82%) of a clear oil identified as dibenzyl mono(2,6-dimethoxybenzoyl)tartrate (Note 5). A 200-mL, pressure bottle is flushed with dry argon and charged with 5.8 g (11.7 mmol) of the above tartrate, 100 mL of ethyl acetate, and 580 mg of 10% palladium on charcoal (Note 6). The argon is then replaced by hydrogen and the reaction mixture is shaken on a Parr apparatus at 20 psi and room temperature for several hours (Note 7). The mixture is filtered through a pad of Celite and the filtrate is concentrated with a rotary evaporator, and dried completely under vacuum (80°C, ≤ 1 mm, overnight) (Note 8) to afford 3.5 g (97%) of mono(2,6-dimethoxybenozyl)tartaric acid as colorless solid, mp 184–186°C (Note 9). This material is practically pure and is used in Parts C, D without purification.

C. D. *(1R)-1,3,4-Trimethyl-3-cyclohexene-1-carboxaldehyde*. A 100-mL, three-necked, round-bottomed flask containing a magnetic stirring bar is equipped with a rubber septum and a three-way stopcock with an argon inlet. The air is displaced by repeated flushing with dry argon. The flask is charged with 1.57 g (5 mmol) of mono (2,6-dimethoxybenzoyl)tartaric acid obtained in Part B and 50 mL of dry dichloromethane (Note 10), and cooled in an ice bath. Through the septum, with a

syringe, is added dropwise 3.57 mL (5 mmol) of borane-THF solution (1.40 M) at 0°C over a period of 30 min (Note 11). The reaction mixture is stirred for 15 min at 0°C and then cooled to −78°C in a dry ice-methanol bath. To this solution is added 4.14 mL (50 mmol) of freshly distilled methacrolein (Note 12) via a syringe dropwise. After the addition is complete, 8.49 mL (75 mmol) of 2,3-dimethyl-1,3-butadiene (Note 13) is introduced to the solution at the same temperature and the mixture is stirred for 12 hr. The cold reaction mixture is poured into 150 mL of ice-cold saturated sodium bicarbonate and the product is extracted with three 200-mL portions of hexane (Note 14). The combined organic phases are washed with brine (2 × 200 mL) (Note 15), dried over sodium sulfate, filtered, and concentrated at atmospheric pressure. The residue is distilled at reduced pressure to afford 6.53 g (86%) of (1R)-1,3,4-trimethyl-3-cyclohexene-1-carboxaldehyde as a colorless liquid, bp 92–93°C (23 mm) (Note 16).

2. Notes

1. L-(+)-Tartaric acid, benzyl alcohol, and p-toluenesulfonic acid monohydrate were purchased from Wako Pure Chemical Industries, Ltd. (Japan). Guaranteed-grade toluene was dried and stored over sodium metal.

2. The physical properties are as follows: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.15 (d, 2 H, J = 7.5), 4.6 (d, 2 H, J = 7.5), 5.27 (s, 4 H), 7.35 (s, 10 H); $[\alpha]_D^{24}$ −10.2° ($CHCl_3$, *c* 1.03).

3. 2,6-Dimethoxybenzoyl chloride was purchased from the Aldrich Chemical Company, Inc. and was used without purification.

4. The purity of the ligand depends largely on the purity of the dibenzyl ester. Flash chromatography was carried out with silica gel purchased from Merck (Kieselgel 60, Art. 9385). For TLC analysis, Merck silica gel F-254 TLC plates were used, with 3:1:5 hexane-ether-dichloromethane as eluent. Dibenzyl mono (2,6-dimethoxybenzoyl)tartrate has an R_f of ca. 0.35 in this solvent system.

5. The physical properties are as follows: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.24 (d, 1 H, J = 9), 3.7 (s, 6 H), 4.89 (dd, 1 H, J = 2.5 and 9), 5.08–5.34 (4 H), 5.99 (d, 1 H, J = 2.5), 6.53 (d, 2 H, J = 8.5), 7.25–7.4 (m, 11 H); $[\alpha]_D^{24}$ −60.1° ($CHCl_3$, *c*., 1.15).

6. Ethyl acetate was obtained from Wako Pure Chemical Industries and was used without purification. The 10% palladium on charcoal was purchased from Aldrich Chemical Company, Inc.

7. This requires 4–12 hr, depending on catalyst conditions. Progress of the reaction can be monitored by TLC.

8. Thorough drying is essential to obtain the % ee as described.

9. The physical properties are as follows: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.63 (s, 6 H), 4.61 (d, 1 H, J = 2), 5.61 (d, 1 H, J = 2), 6.38 (d, 2 H, J = 9), 7.13 (t, 1 H, J = 9); $[\alpha]_D^{24}$ −73.0° (EtOH, *c* 1.03).

10. Dichloromethane was purchased from Wako Pure Chemical Industries and was dried over Linde-type 4 Å molecular sieves.

11. Borane–THF complex was obtained from Toso-Akzo Chemical Company,

Ltd. in Japan and should be titrated before use. Vigorous evolution of hydrogen is observed during addition of borane–THF solution to the reaction mixture.
12. Methacrolein from Tokyo Kasei Kogyo Company, Ltd. was dried with calcium sulfate and distilled through a 20-cm Vigreux column under argon prior to use.
13. 2,3-Dimethyl-1,3-butadiene was purchased from Tokyo Kasei Kogyo Company, Ltd. and was distilled before use.
14. The tartaric acid ligand can be recovered (1.52 g, 97%) from the aqueous phase by an acidification-extraction (4 N HCl-ethyl acetate) sequence. The material is essentially pure for future use.
15. Careful washing with brine is important to avoid foaming during distillation.
16. The physical properties are as follows: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.99 (s, 3 H), 1.3–2.1 (m, 5 H), 1.56 (s, 3 H), 1.61 (s, 3 H), 2.23 (br d, 1 H, J = 17), 9.43 (s, 1 H); $[\alpha]_D^{23}$ −64.1° ($CHCl_3$, *c* 1.0). The optical purity of this adduct was 95% as determined by 200 MHz ^{1}H NMR spectroscopy and GC analysis (capillary column PEG, 0.25 mm × 25 m, purchased from Gaskuro Kogyo Company, Ltd. in Japan) after conversion to the corresponding chiral acetal as follows: A solution of the adduct, (2R,4R)-(−)-pentanediol (1.2 equiv, obtained from Wako Pure Chemical Industries), triethyl orthoformate (1.2 equiv), and p-toluenesulfonic acid monohydrate (as a 5 mM solution) in dry benzene is stirred at ambient temperature for 3 hr. The mixture is poured into saturated sodium bicarbonate and the product is extracted with ether. The combined organic phases are dried over sodium sulfate and concentrated on a rotary evaporator. The residue is purified by flash column chromatography on silica gel using hexane-ethyl acetate (25:1) as eluent to give the acetal quantitatively; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.83 (s, 3 H), 1.15 (d, 3 H, J = 6), 1.28 (d, 3 H J = 6.5), 1.56 (s, 6 H), 1.2–2.06 (m, 8 H), 3.86 (m, 1 H), 4.27 (m, 1 H), 4.42 (s, 1 H; diastereomer at 4.45).

Waste Disposal Information

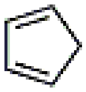
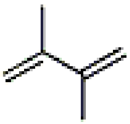
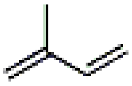
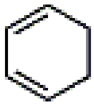
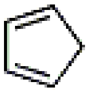
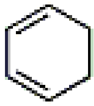
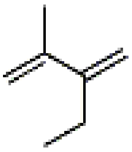
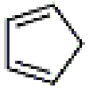
All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

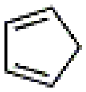
3. Discussion

The procedure described here provides a simple and general method for the construction of optically active 3-cyclohexene-1-carboxaldehydes.[2 3] The reaction has been applied successfully to a series of α,β-unsaturated aldehydes with dienes (Table). Several methods are described in the literature for asymmetric Diels-Alder reactions of chiral α,β-unsaturated esters or amides;[4 5 6 7] little is reported, however, for the reaction of achiral, simple aldehydes.[8 9 10 11 12] The present method is characterized as a true catalytic process (only 10 mol % of chiral catalyst is needed), with good chemical and high optical yields, simple operation, preparation of both enantiomers

with equal ease, and the ready availability of the starting materials.

TABLE
ChiralAcyloxyboraneCatalyzedAsymmetricDiels-AlderReaction

Dienophile	Diene	Temp (°C)	Yield (%)	Isomers endo/exo	ee (%)
		–78	85	11/89	96
		–78	84[a]	10/90	96
		–78	61	-	97
		–78	38	97/3[b]	93
		–40	65	98/2[b]	91
	–20	40	93/7	82	
		–78	90	88/12	84
		–78	46	>99/1	80
		–78	53	-	84
		–78	53	90/10	2

		–78	91	3/97	90

[a](2S,3S)-Tartaric acid derivative was used as a chiral ligand.

[b]Ratio of regioisomers.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

brine

palladium on charcoal

3-Cyclohexene-1-carboxaldehyde, 1,3,4-trimethyl-, (–)-

(–)-Dibenzyl tartrate

2,6-dimethoxybenozyl chloride

mono(2,6-dimethoxybenozyl)tartaric acid

(2R,4R)-(–)-pentanediol

Benzene (71-43-2)

ethyl acetate (141-78-6)

ether (60-29-7)

hydrogen (1333-74-0)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

calcium sulfate (7778-18-9)

toluene (108-88-3)

sodium (13966-32-0)

Benzyl alcohol (100-51-6)

tartaric acid, L-(+)-tartaric acid (87-69-4)

triethyl orthoformate (122-51-0)

dichloromethane (75-09-2)

borane (7440-42-8)

tartrate

THF (109-99-9)

2,3-DIMETHYL-1,3-BUTADIENE (513-81-5)

hexane (110-54-3)

triethylamine (121-44-8)

methacrolein (78-85-3)

argon (7440-37-1)

4-(dimethylamino)pyridine (1122-58-3)

p-toluenesulfonic acid monohydrate (6192-52-5)

dibenzyl tartrate (622-00-4)

Mono(2,6-dimethoxybenzoyl)tartaric acid (116212-44-3)

dibenzyl mono(2,6-dimethoxybenzoyl)tartrate (158732-36-6)

(1R)-1,3,4-Trimethyl-3-cyclohexene-1-carboxaldehyde (130881-20-8)

2,6-Dimethoxybenzoyl chloride (1989-53-3)

Mono(2,6-dimethoxybenzoyl)tartrate

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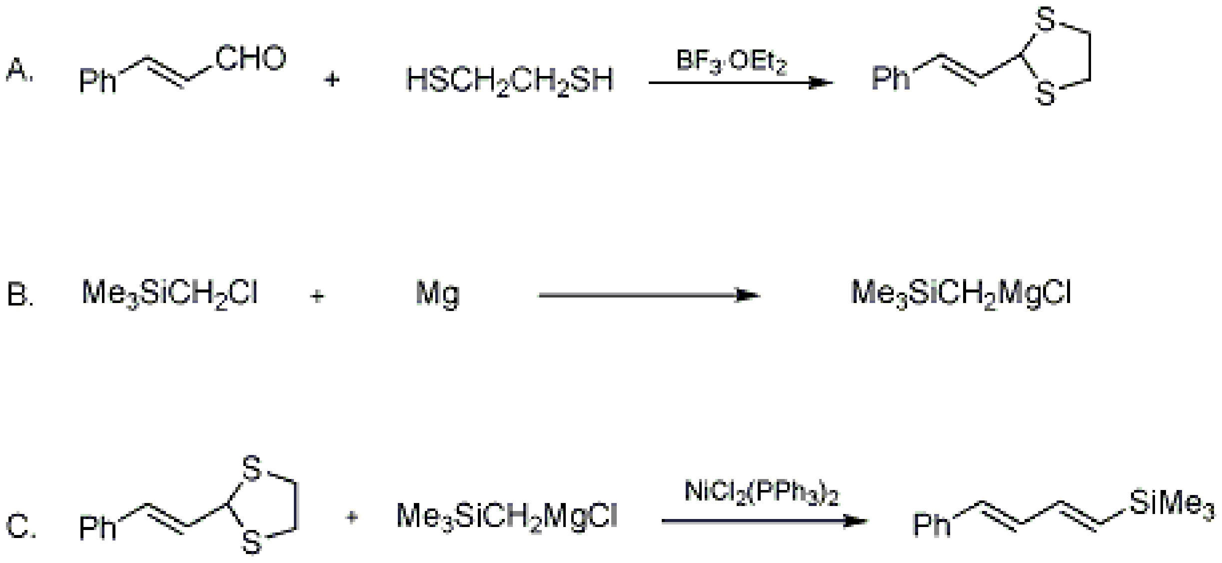
Organic Syntheses, CV 9, 727

NICKEL-CATALYZED SILYLOLEFINATION OF ALLYLIC DITHIOACETALS: (E,E)-TRIMETHYL(4-PHENYL-1,3-BUTADIENYL)SILANE

[Silane, trimethyl (4-phenyl-1,3-butadienyl)-, (E,E)-]



Submitted by Zhi-Jie Ni and Tien-Yau Luh[1].
Checked by Shigeki Habaue and Hisashi Yamamoto.

1. Procedure

CAUTION! 1,2-Ethanedithiol has a powerful stench. Steps A and C should be performed in a well-ventilated hood.

A. *2-(2-Phenylethenyl)-1,3-dithiolane*. In a 1-L, round-bottomed flask equipped with a magnetic stirring bar are placed 26.8 g (0.2 mol) of freshly distilled (E)-3-phenyl-2-propenal and 20.1 g (0.21 mol) of 1,2-ethanedithiol in 400 mL of chloroform. To the stirred solution is added 10 mL (11.3 g, 0.080 mol) of boron trifluoride etherate in one portion. The mixture is stirred at room temperature for 2 hr. The chloroform solution is washed with two 100-mL portions of 10% aqueous sodium hydroxide. The aqueous layer is extracted twice with 100 mL of chloroform. The combined organic layers are washed twice with 200 mL of water, dried over anhydrous magnesium sulfate, and filtered. The filtrate is concentrated under reduced pressure to give 40.6 g (97%) of a white solid which is sufficiently pure for the next operation.

B. *(Trimethylsilyl)methylmagnesium chloride*. A 500-mL, three-necked, round-bottomed flask containing 5.2 g (0.22 g-atom) of magnesium turnings is equipped with a rubber septum, a reflux condenser, an addition funnel and a magnetic stirring bar.

The system is flame-dried and flushed with nitrogen. A few crystals of iodine and 150 mL of anhydrous ether (Note 1) are introduced. As the contents of the flask are stirred, 25.8 g (0.21 mol) of (chloromethyl)trimethylsilane (Note 2) is added in small portions until the reaction begins, and then at such a rate as to maintain gentle refluxing of the ether. The addition requires about 30 min, after which the mixture is heated under reflux for an additional 30 min. The solution is cooled to room temperature and is used directly for the next reaction.

C. *(E,E)-Trimethyl(4-phenyl-1,3-butadienyl)silane*. In a 1-L, two-necked, round-bottomed flask fitted with a reflux condenser, rubber septum, and a magnetic stirring bar are placed 14.6 g (0.070 mol) of 2-(2-phenylethenyl)-1,3-dithiolane and 2.3 g (0.0035 mol) of dichlorobis(triphenylphosphine)nickel (Note 3). The flask is evacuated and flushed with nitrogen three times. To the above mixture is added 200 mL of anhydrous tetrahydrofuran (Note 4); then it is cooled in an ice bath. The ether solution of (trimethylsilyl)methylmagnesium chloride prepared above is introduced with a double-ended needle in one portion (Note 5). The mixture is refluxed for 10 hr, cooled to room temperature, and treated with 200 mL of saturated ammonium chloride solution. The organic layer is separated and the aqueous layer is extracted with three, 200-mL portions of ether. The combined organic layers are washed twice with 100 mL of aqueous 10% sodium hydroxide solution and twice with 100 mL of brine. The organic solution is dried over anhydrous magnesium sulfate. The solvent is removed under reduced pressure and the residue is filtered through a short column packed with 30 g of silica gel (Note 6) and flushed under a positive nitrogen pressure with 300 mL of hexane. After evaporation of the solvent under reduced pressure, the yellowish residue is distilled to give 12.9 g (91%) of (E,E)-trimethylsilyl(4-phenyl-1,3-butadienyl)silane (Note 7) as a colorless liquid, bp 99–101°C (0.6 mm), which solidifies on standing, mp <37°C.

2. Notes

1. Ethyl ether is distilled from sodium-benzophenone ketyl before use.
2. (Chloromethyl)trimethylsilane, also available from Aldrich Chemical Company, Inc., was purchased from Wako Pure Chemical Industries, LTD. and used directly.
3. Dichlorobis(triphenylphosphine)nickel, also available from Aldrich Chemical Company, Inc., was purchased from Fluka AG, and used without further purification. The catalyst can also be prepared according to literature procedures.[2 3]
4. Tetrahydrofuran is distilled from sodium-benzophenone ketyl before use.
5. An excess of the Grignard reagent is required to maximize the yield; otherwise, the reaction is incomplete.
6. Silica gel (230–400 mesh) was purchased from E. Merck Co.
7. The spectral properties of the product are as follows: IR (neat) cm^{-1}: 3040, 1605, 1450, 1250, 1000, 870, 840, 730, 690; ^{1}H NMR ($CDCl_3$) δ: 0.13 (s, 9 H, -

$Si(CH_3)_3$), 6.01 (d, 1 H, J = 17.6, =CHTMS), 6.58 (d, 1 H, J = 15.2, PhCH=), 6.69 (dd, 1 H, J = 9.8 and 17.6, =CH=CHTMS), 6.83 (dd, 1 H, J = 9.8 and 15.2, PhCH=CH-), 7.20–7.40 (m, 5 H, aromatic) (The assignments for olefinic protons are based on simulation results); ^{13}C NMR ($CDCl_3$) δ: −1.5, 126.7, 127.8, 128.7, 131.8, 133.0, 135.2, 137.4, 144.3; exact mass calcd for $C_{13}H_{18}Si$: 202.1178; found 202.1185.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Trimethyl(4-phenyl-1,3-butadienyl)silane can be prepared by the reaction of bis (trimethylsilyl)methyllithium with cinnamaldehyde[4] or 1,3-bis(trimethylsilyl) propenyllithium with benzaldehyde.[5,6] The reaction of 1-bromo-2-phenylthioethene with (E)-2-trimethylsilylethenylmagnesium bromide in the presence of a palladium catalyst gives the corresponding dienyl sulfide which serves as a precursor for the preparation of butadienylsilanes.[7] However, the starting materials in most of these syntheses are not readily available.

The procedure described here is based on a series of reports on the nickel-catalyzed coupling reactions of dithioacetals with Grignard reagents.[8,9,10,11,12] The method offers a new, very efficient and convenient route to the substituted butadienylsilanes.[8] The starting materials are easily accessible and the operation is very simple. The reaction in general is highly stereoselective, if not stereospecific. The phenyl substituent can be replaced with simple alkyl groups and yields essentially remain unchanged.[8] The extension of this method to the synthesis of trienylsilanes has proved successful.[8] Since vinylsilanes can be converted into α,β-unsaturated aldehydes,[13,14,15,16,17] the combination of these latter procedures with the method described here can be used in the homologation of enals. (E)-β-Arylvinylsilanes are synthesized stereospecifically in a similar manner from benzylic dithioacetals.[9]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

silica gel

brine

sodium-benzophenone ketyl

ether, ethyl ether (60-29-7)

ammonium chloride (12125-02-9)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

magnesium (7439-95-4)

nitrogen (7727-37-9)

benzaldehyde (100-52-7)

iodine (7553-56-2)

palladium (7440-05-3)

cinnamaldehyde

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

hexane (110-54-3)

boron trifluoride etherate (109-63-7)

1,2-ethanedithiol (540-63-6)

dichlorobis(triphenylphosphine)nickel (14264-16-5)

(chloromethyl)trimethylsilane (2344-80-1)

1-bromo-2-phenylthioethene

(E,E)-Trimethyl(4-phenyl-1,3-butadienyl)silane, Silane, trimethyl (4-phenyl-1,3-butadienyl)-, (E,E)- (70960-88-2)

2-(2-Phenylethenyl)-1,3-dithiolane (5616-58-0)

(E)-3-phenyl-2-propenal (104-55-2)

(Trimethylsilyl)methylmagnesium chloride

(E,E)-trimethylsilyl(4-phenyl-1,3-butadienyl)silane

Trimethyl(4-phenyl-1,3-butadienyl)silane

bis(trimethylsilyl)methyllithium

(E)-2-trimethylsilylethenylmagnesium bromide

1,3-bis(trimethylsilyl)propenyllithium

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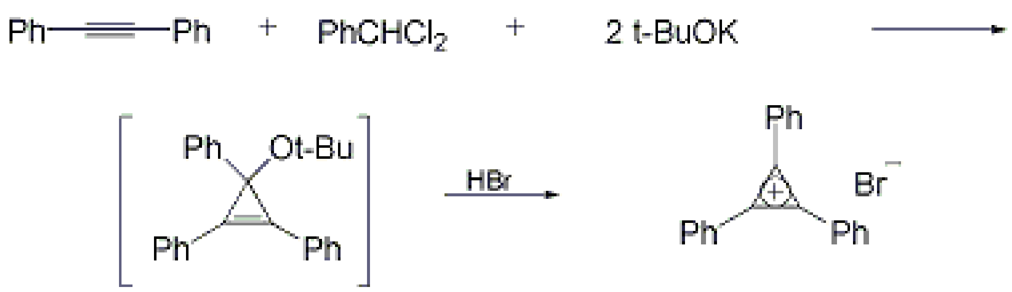
Organic Syntheses, CV 9, 730

1,2,3-TRIPHENYLCYCLOPROPENIUM BROMIDE

[Cyclopropenylium, triphenyl-, bromide]



Submitted by Ruo Xu and Ronald Breslow[1].
Checked by Rebecca Calvo and Robert K. Boeckman, Jr..

1. Procedure

1,2,3-Triphenylcyclopropenium bromide. A flame-dried, 500-mL, three-necked, round-bottomed flask, equipped with a magnetic stirring bar and a reflux condenser fitted with an argon inlet vented through a mineral oil bubbler, glass stopper, and rubber septum, is flushed with argon and charged with a solution of diphenylacetylene (3.92 g, 0.022 mol) (Note 1) and potassium tert-butoxide (9.97 g, 0.089 mol) in dry benzene (100 mL) (Note 2). Efficient magnetic stirring is initiated, and 5.8 mL of α,α-dichlorotoluene (7.2 g, 0.045 mol) (Note 3) is added dropwise over 5 min via a syringe under argon (Note 4). The reaction mixture is then heated under reflux for 3 hr during which time the precipitate dissolves (Note 5). After the reaction mixture is cooled to room temperature, 100 mL of water is added to remove inorganic salts. The organic layer is separated and the aqueous layer is extracted with portions of ether (2 × 50-mL). The organic layers are combined, dried over magnesium sulfate, and filtered. The filtrate is saturated with anhydrous hydrogen bromide (Note 6), whereupon a light yellow precipitate forms that is collected to afford 6.8–7.2 g (89–93%) of essentially pure triphenylcyclopropenium bromide (Note 7). The material prepared in this manner provides a satisfactory elemental analysis,[2] but it can be further purified by recrystallization from acetonitrile, if desired.

2. Notes

1. Diphenylacetylene, potassium tert-butoxide, and α,α-dichlorotoluene were purchased from Aldrich Chemical Company, Inc. and used without further purification.
2. Benzene is obtained from the Fisher Scientific Company and purified by distillation from CaH_2.
3. An excess of α,α-dichlorotoluene and potassium tert-butoxide is necessary to

ensure high conversion of diphenylacetylene. When 1 equiv of α,α-dichlorotoluene and 2 equiv of potassium tert-butoxide are used, only 60% conversion of diphenylacetylene is achieved and the remainder is recovered during the workup. Nonetheless, the yield corrected for recovered diphenylacetylene is still more than 90%.

4. The reaction mixture is observed to bubble, fume, become brown in color, and deposit a precipitate. When the reaction is carried out in the air rather than under argon, the conversion is only 50%.

5. Slightly lower conversion is consistently realized when the reflux period is shortened to 1 hr.

6. When the usual preparative procedure was interrupted before the addition of water, and the inorganic material was removed by filtration, concentration of the solution and addition of dry hexane caused crystallization of 1,2,3-triphenylcyclopropenyl tert-butyl ether as white prisms.[2] The checkers did not observe reprecipitation of the salts upon cooling the reaction mixture.

7. The crude product is quite pure and has the following spectral characteristics: ^{1}H NMR (300 MHz, CD_3NO_2) δ: 7.99 (t, 6 H, J = 8), 8.12 (t, 3 H, J = 8), 8.71 (d, 6 H, J = 8); ^{13}C NMR (75 MHz, CD_3NO_2) δ: 119.65, 130.18, 135.40, 138.18, 155.26; IR ($CHCl_3$) cm^{-1}: 3382, 1712, 1594, 1505, 1410. On heating it decomposes without a defined melting point.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

This is the procedure first reported in 1961.[2] It involves generation of phenylchlorocarbene, or more likely a related carbenoid, which adds to the acetylene to form triphenylcyclopropenium chloride. This chloride reacts with tert-butoxide ion to form the covalent tert-butyl ether, which can be isolated. With water, this ether hydrolyzes to bis(triphenylcyclopropenyl) ether, but either of these compounds is converted to the ionic bromide salt with HBr.

According to this procedure, with proper choice of reaction conditions, a sizeable amount of diphenylacetylene can be converted quantitatively to triphenylcyclopropenium bromide in a few hours. The reaction is of wide generality and can be applied to p-anisylphenylacetylene and to di-p-anisylacetylene, or with p-anisal chloride instead of α,α-dichlorotoluene, to prepare p-methoxy derivatives of the title compound.[2] Since the initial preparation of this derivative of the cyclopropenyl cation by a less efficient procedure,[3] many aryl-, alkyl- and heteroatom-substituted derivatives of this simplest cyclic aromatic system have been synthesized,[4 5 6]

including the parent cyclopropenyl cation itself.[7] They have been used for various physical studies,[8] and for the preparation of derivatives such as covalent cyclopropenes and metal coordination complexes.[9,10]

The cyclopropenyl cation is the simplest aromatic system, and thus of some theoretical interest. In addition, the chemistry of cyclopropene derivatives is full of interesting rearrangements to other novel structures,[11] reflecting the great strain energy of the cyclopropene ring.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

CaH_2

acetylene (74-86-2)

Benzene (71-43-2)

ether (60-29-7)

acetonitrile (75-05-8)

hydrogen bromide, HBr (10035-10-6)

α,α-dichlorotoluene (98-87-3)

magnesium sulfate (7487-88-9)

Diphenylacetylene (501-65-5)

hexane (110-54-3)

argon (7440-37-1)

phenylchlorocarbene

potassium tert-butoxide (865-47-4)

1,2,3-TRIPHENYLCYCLOPROPENIUM BROMIDE (4919-51-1)

Cyclopropenylium, triphenyl-, bromide, Triphenylcyclopropenium bromide (4919-51-1)

1,2,3-triphenylcyclopropenyl tert-butyl ether

triphenylcyclopropenium chloride (58090-78-1)

tert-butyl ether (6163-66-2)

bis(triphenylcyclopropenyl) ether

p-anisylphenylacetylene

di-p-anisylacetylene

p-anisal chloride

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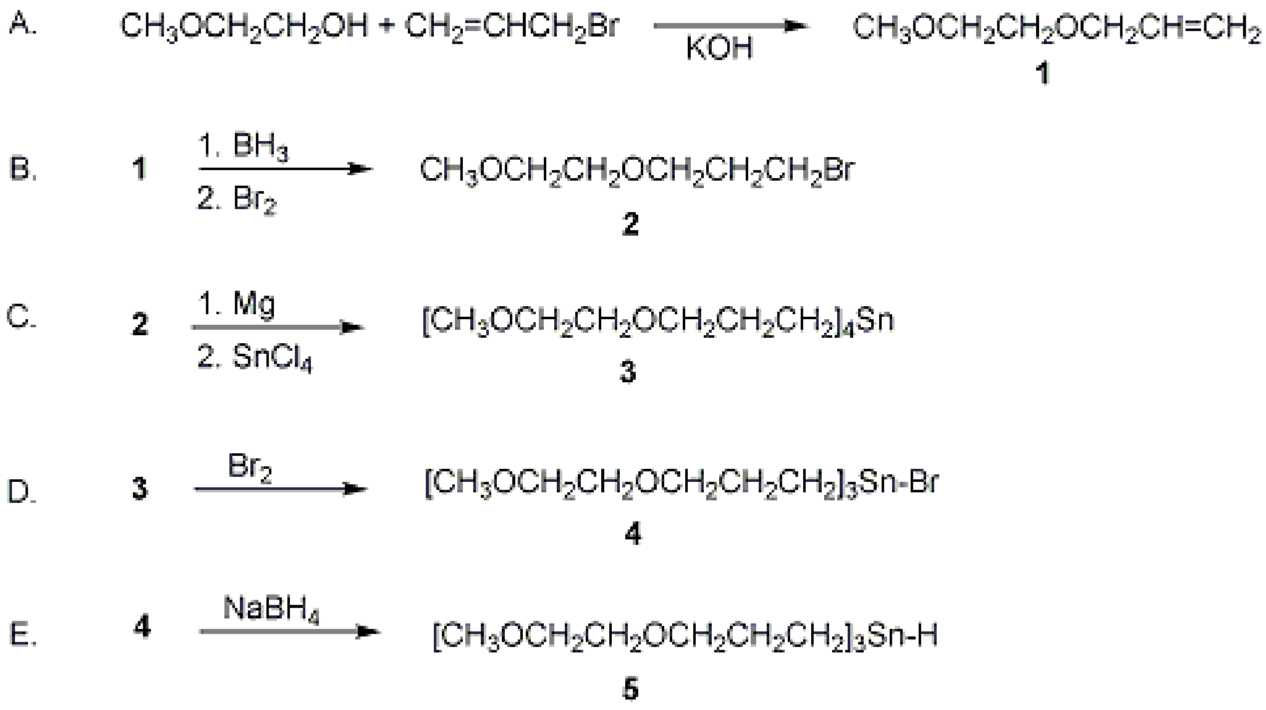
Organic Syntheses, CV 9, 733

A WATER-SOLUBLE TIN HYDRIDE: TRIS[3-(2-METHOXYETHOXY)PROPYL]STANNANE

[2,5,13,16-Tetraoxa-9-stannaheptadecane, 9-[3-(2-methoxyethoxy)propyl]-]



Submitted by James Light and Ronald Breslow[1].
Checked by Scott R. Breining and Robert K. Boeckman, Jr..

1. Procedure

A. *3-(2-Methoxyethoxy)propene* **(1)**. A three-necked, 1000-mL flask equipped with a thermometer, mechanical stirrer, and dropping funnel is charged with 51 g (0.9 mol) of potassium hydroxide (KOH, (Note 1)) and 65 mL (62.3 g, 0.82 mol) of dry 2-methoxyethanol (Note 2). The resulting mixture is cooled in an ice bath, efficient stirring is begun, and 72 mL (100 g, 0.82 mol) of allyl bromide (Note 2) is added dropwise, keeping the internal temperature below 10°C (Note 3). After the solution is stirred overnight, the sticky white solid is collected by suction filtration and the collected solids are washed with 300 mL of hexanes. The combined yellow filtrate and washings are dried thoroughly over sodium sulfate (Na_2SO_4), and the whole mixture is distilled from calcium hydride (CaH_2) through a 6-in. Vigreux column (Note 4). The product (67–69 g, 70–73%) is collected from 115–129°C with the bulk of the material distilling at bp 117–127°C, and is 94% pure (as judged by gas chromatography, (Note 5),(Note 6),(Note 7)).

B. *1-Bromo-3-(2-methoxyethoxy)propane* **(2)**. A flame-dried, three-necked, 1000-mL flask that is equipped for magnetic stirring, and has a dry addition funnel and a

thermometer, is placed under an inert atmosphere and charged with 209 mL (250 g, 0.209 mol) of a 1.0 M solution of borane-tetrahydrofuran complex (Note 2). The resulting solution is cooled to –10°C using a dry ice/ethylene glycol bath and 3-(2-methoxyethoxy)propene (**1**, 60 g, 0.52 mol) is added dropwise over 1 hr keeping the internal temperature of the reaction mixture at or below 0°C. Methanol (1.5 mL) is added to destroy any excess borane, and the reaction mixture is stirred an additional 1 hr below 10°C.

After the reaction mixture is recooled to –15°C (internal temperature), 35 mL (107.8 g, 0.67 mol) of bromine (Br_2) is added dropwise over 1 hr, keeping the reaction temperature between –10° and 0°C. The mixture is stirred a further 1.5 hr at 0°C then recooled to –15°C. While cooling is maintained, 210 mL of a 4 M solution of sodium methoxide (0.84 mol) in methanol (freshly prepared from sodium metal) is added dropwise over 1.5 hr, keeping the reaction temperature between –15° and 0°C. The resulting orange brown solution and white precipitate are slowly warmed to room temperature and stirred overnight (16 hr).

Hexane (100 mL) is added to the reaction mixture causing more white precipitate to form. The mixture is filtered by suction, and the collected solids are washed with two 50-mL portions of hexane. The combined filtrate and washings are partitioned with 200 mL of a mixture (1:3 v/v) of saturated potassium carbonate solution and water (Note 8). The aqueous phase is extracted with three 200-mL portions of hexane. The combined organic phases are partitioned with 100 mL of saturated sodium chloride, dried thoroughly over anhydrous sodium sulfate and concentrated under reduced pressure to afford 65–75 g of crude product. A small amount of additional crude material can be isolated by continuously extracting the combined aqueous layers with hexane for 3 hr.

Distillation of the crude product through a 6-in. Vigreux column at 0.6 mm into a dry ice/acetone-cooled receiver affords 55–70 g of material bp >40°C/0.6 mm that is 83% pure (as judged by gas chromatography, (Note 6)). To obtain material of greater purity (94%) suitable for further transformation, a second distillation through a 6-in. Vigreux column packed with glass beads is required to afford 53–57 g (52–56%) of the bromide as a colorless liquid, bp 55–65°C/0.6 mm (Note 9).

C. *Tetra[3-(2-methoxyethoxy)propyl]stannane* **(3)**. A 500-mL, three-necked flask is fitted with a thermometer and a dried addition funnel, charged with 9.1 g (0.375 mol) of magnesium metal turnings (Note 2) and heated with a flame or heat gun while purging with argon. After the flask is cooled, 50 mL of dry tetrahydrofuran (THF) and a crystal of iodine are added, and the addition funnel is charged with 40 mL (52 g, 0.264 mol) of 1-bromo-3-(2-methoxyethoxy)propane (2<.htm/A>, (Note 10)). Approximately 2 mL of the bromide is added to the reaction mixture, and the internal temperature of the mixture is monitored. When the temperature rises slightly (3°C) and the iodine color is discharged indicating that formation of the Grignard reagent has begun, the reaction mixture is immediately cooled to –15°C in a dry ice/ethylene glycol bath, 100 mL of dry THF (Note 10) is added to the addition funnel, and 150 mL of dry THF (Note 10) is

directly added to the reaction mixture. The bromide solution is added dropwise over 2 hr while keeping the reaction temperature between –15° and 5°C (Note 11).

The concentration of the Grignard reagent solution is determined by titration. An oven-dried, 10-mL flask with septum is charged with 1 mg of phenanthroline and 3.0 mL of the reaction mixture. 2-Methylpropanol is added until the red-purple color is dissipated and a yellow endpoint is reached. The yield of Grignard reagent is 0.184 mol (70%).

A dry, 1000-mL flask is placed under a nitrogen atmosphere, charged with 4.9 mL (0.042 mol) of tin(IV) chloride ($SnCl_4$, (Note 1)), and cooled to –78°C in a dry ice/acetone bath with swirling. After the $SnCl_4$ solidifies on the walls of the flask, the flask is equipped for magnetic stirring. The previously prepared Grignard solution is added to the $SnCl_4$ as a slow stream via cannula and the reaction mixture is allowed to warm to room temperature with stirring overnight (20 hr). After the solution is stirred at room temperature for 20 hr, the addition funnel is replaced by a reflux condenser, and the reaction mixture is heated at reflux for 4 hr by means of a heating mantle (Note 12). After the solution is cooled, the solvent is removed under reduced pressure, 300 mL of water is added, and the resulting mixture (a heavy precipitate results) is continuously extracted with 750 mL of hexane for 12–24 hr. The hexane solution is dried over magnesium sulfate ($MgSO_4$), and the volatile material is removed under reduced pressure, to afford 23.6–24 g (96–97% based on $SnCl_4$) of the tetraalkylstannane that is not homogeneous as judged by NMR integration. Pure stannane suitable for further transformation is obtained by removal of a low boiling impurity (bp 90–100°C/0.6 mm) under high vacuum to afford 21–23 g of purified stannane. Stannane (bp 210–215°C at 0.005 mm) of even higher purity can be obtained by short-path distillation with some loss due to decomposition (Note 13).

D. *Bromotris[3-(2-methoxyethoxy)propyl]stannane* **(4)**. A dry, 50-mL, round-bottomed flask is placed under a nitrogen atmosphere and charged with 8.25 g (14.0 mmol) of tetra[3-(2-methoxyethoxy)propyl]stannane **(3)**, and 40 mL of dry carbon tetrachloride (CCl_4) (Note 1). After the mixture is cooled to 0°C in an ice-water bath, 14 mL of a 1 M solution of bromine (0.014 mol) in CCl_4 is added dropwise (Note 14). The mixture is allowed to warm slowly to room temperature and stand overnight. The solvent is removed under reduced pressure, and the residual brown liquid is purified by Kugelrohr distillation at 0.1 mm. A low boiling fraction (bp <70°C) that contains alkyl bromide is discarded, and the residual material is distilled to afford 6.9–7.4 g (90–96%) of the bromotrialkylstannane (bp 100–110°C) as a pale tan viscous oil that is homogeneous as judged by NMR spectroscopy and of sufficient purity for further transformation (Note 15),(Note 16),(Note 17).

E. *Tris[3-(2-methoxyethoxy)propyl]stannane* **(5)**. A 100-mL, round-bottomed flask equipped for magnetic stirring is placed under an inert atmosphere and charged with 5.0 g (4.5 mmol) of freshly distilled bromotris[3-(2-methoxyethoxy)propyl]stannane **(4)** and 40 mL of dry 1,2-dimethoxyethane (Note 10). To the stirred solution is added 2.0 g (54 mmol) of sodium borohydride ($NaBH_4$) (Note 2) at room temperature in portions at such a rate as is required to control foaming. The resulting white suspension is stirred at room

temperature for 2.5 hr (the reaction appears complete nearly instantaneously) and then concentrated under reduced pressure. The residue is taken up in 50 mL of ether, suction filtered through a bed of Celite, and concentrated under reduced pressure to afford 3.47–3.64 g (82–86%) of the trialkyltin hydride as a clear colorless oil that is homogeneous by NMR. The trialkyltin hydride is pure enough for most purposes, but further purification is possible by short-path distillation to afford pure trialkyltin hydride bp 100–120°C (pot temperature) at 0.005–0.01 mm (Note 18).

2. Notes

1. Potassium hydroxide was A.C.S. reagent grade obtained from J. T. Baker Chemical Company and used as received.
2. 2-Methoxyethanol was research grade obtained from Aldrich Chemical Company, Inc., and used as received.
3. The reaction is exothermic, and temperature control is required for control of the reaction. Good agitation is essential to avoid occlusion of unreacted starting materials in the sticky precipitate.
4. Substantial amounts (grams) of CaH_2 may be required (care should be taken on addition because of foaming) if predrying with Na_2SO_4 is incomplete.
5. The boiling range is broad because of codistillation of the product with small amounts of allyl bromide and 2-methoxyethanol.
6. Analysis was performed on a 25-m fused silica capillary column with DX-3 (polymethylsiloxane) stationary phase and a temperature program from 50°C-150°C.
7. The spectra are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.39 (s, 3 H), 3.59–3.61 (m, 4 H), 4.03 (dt, 2 H, J = 5.7, 1.6), 5.18 (dq, 1 H, J = 10.3, 1.6), 5.28 (dq, 1 H, J = 17.2, 1.6),5.92 (ddt, 1 H, J_1 = 17.2, J_2 = 10.3, J_1 = 5.7); ^{13}C NMR (75.43 MHz, $CDCl_3$) δ: 58.64, 69.03, 71.70, 71.95, 116.62, 134.55.
8. Three phases may result. If three phases are present, add the minimum amount of additional water that affords two phases. Addition of large amounts of water should be avoided because of the significant water solubility of the product.
9. The spectra as as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.18 (quintet, 2 H), 3.42 (s, 3 H), 3.54–3.68 (m, 8 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 30.57, 32.71, 58.99, 68.61, 70.23, 71.81. The checkers noted a larger variability in yield (38–56%).
10. Tetrahydrofuran and 1,2-dimethoxyethane were dried and deoxygenated by distillation from sodium benzophenone ketyl under argon.
11. Inadequate temperature control leads to the formation of by-products resulting from elimination.
12. Magnetic stirring is difficult because of the formation of a sticky precipitate. A very vigorous reaction ensues upon heating the mixture to reflux if inadequate agitation occurs during addition of the Grignard reagent or if the $SnCl_4$ is allowed to solidify in a pool in the bottom of the flask.
13. The spectra are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.77 (m, 8 H, apparent t within a doublet), 1.78 (m, 8 H), 3.39 (s, 12 H), 3.39 (t, 8 H), 3.55 (AA'BB' m, 16 H); in D_2O, d_4-TSP ref. δ: 0.89 (m, 8 H), 1.84 (m, 8 H), 3.64 (m,

16 H), 3.53 (t, 8 H), 3.40 (s, 12 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 4.44, 26.69, 59.00, 69.95, 71.90, 74.82 (apparent ^{13}C-^{119}Sn ^{1}J = 322, ^{2}J = 19, ^{3}J = 66); ^{119}Sn NMR 111.86 MHz (200 mg/mL) $CDCl_3$, Me_4Sn ref. δ: –3.8 ppm (inverse gated decoupled).

14. Discharge of the yellow color is instantaneous until >13 mL of the bromine solution is added. A persistent yellow color was not observed until 1 equiv of bromine had been added.

15. No unreacted tetraalkylstannane is observed when a full equivalent of bromine is employed.

16. The bromotrialkylstannane is stable to storage under argon in the freezer, and can be converted to the tin hydride as needed.

17. The spectra are as follows: ^{1}H NMR (300 MHz, C_6D_6) δ: 1.38 (br t, 6 H), 1.95 (br quintet, 6 H), 3.14 (s, 9 H), 3.25 (m, 12 H), 3.35 (m, 6 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 15.06 ppm (apparent ^{13}C-^{119}Sn ^{1}J = 413, ^{3}J = 64), 26.04, 58.90, 70.06, 71.71, 73.44; ^{119}Sn NMR 111.86 MHz (200 mg/mL), Me_4Sn ref. δ: +60.0 ppm (inverse gated decoupled). CI MS with NH_3 gave peaks at m/e 471 (base peak) and m/e 433 with the isotopic distribution expected for Sn and Br.

18. The spectra are as follows: ^{1}H NMR (300 MHz, C_6D_6) δ: 0.94 (td, 6 H, J = 8, J_{HSnCH} = 1.8), 1.85 (quintet, 6 H, J_{avg} = 7), 3.15 (s, 9 H), 3.36 (t, 6 H, J = 6.4), 3.40–3.52 (m, AA'BB', 12 H),5.17 (br septet, 1 H, J<2); ^{13}C NMR (75.4 MHz, C_6D_6) δ: 4.87, 27.54, 58.28, 70.00, 71.97, 74.03, (apparent ^{13}C-^{119}Sn ^{1}J = 354, ^{2}J = 22, ^{3}J = 52, apparent ^{13}C-^{117}Sn ^{1}J = 336, ^{2}J = 22, ^{3}J = 52); ^{119}Sn NMR 111.86 MHz (200 mg/mL), C_6D_6, Me_4Sn standard δ –82.4 ppm (d of septets, $^1J_{Sn\text{-}H}$ = 1612, $^2J_{Sn\text{-}H}$ = 55); IR (film on NaCl) cm^{-1}: 3500 weak, 2970–2930 strongest absorption, $\nu_{Sn\text{-}H}^{1}$ 1810, 1452, 1358, 1300, 1285, 1245, 1200, 1140-1100 broad, 1040, 985, 925, 885, 850, 715, 685.

Anal: Calcd for $C_{18}H_{40}SnO_6$, MW 471.19: C, 45.88; H, 8.56; Sn, 25.19. Found: C, 45.74, 45.76; H, 8.71, 8.36; Sn, 25.08, 25.17.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Tributyltin hydride is a common reagent, used extensively in free radical chemistry.[2] However, it is soluble only in typical organic solvents. The tin hydride reagent prepared here[3] can be used in free radical chemistry in many solvents. It is soluble in organic media, but also has sufficient water solubility (30 mM at room temperature, more on warming) to be useful in aqueous reactions. This reagent is not only of interest for use with water-soluble biomolecules but there is also increasing interest in the special effects of water as solvent on organic reactions.[4,5,6] In addition, the reaction product of this reagent is the corresponding tin oxide species that can be easily recovered and recycled,

and that is sometimes more easily removed from organic products than is the corresponding product from tributyltin hydride. Most notably, this reagent is non-volatile and odorless.

This procedure illustrates the bromopropylation of an alcohol by allylation and then hydroboration/bromination,[7] a clean, selective procedure compared with other approaches via 3-substituted propyl bromide derivatives. Conversion to the tetraalkyl tin, then brominative cleavage, is the standard sequence for preparation of trialkyl tin derivatives.[8] The standard lithium aluminum hydride ($LiAlH_4$) reduction of the tin bromide was not usable here because of contamination of the product by $LiAlH_4$ by-products that were not easily separated, and the polymethylhydrosiloxane reduction method[9] was not successful. However, use of $NaBH_4$ in 1,2-dimethoxyethane was effective and convenient.[10]

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

D_2O

sodium benzophenone ketyl

potassium carbonate (584-08-7)

methanol (67-56-1)

ether (60-29-7)

magnesium (7439-95-4)

sodium chloride (7647-14-5)

bromine (7726-95-6)

Allyl bromide (106-95-6)

sodium sulfate (7757-82-6)

carbon tetrachloride (56-23-5)

nitrogen (7727-37-9)

iodine (7553-56-2)

sodium methoxide (124-41-4)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

2-Methylpropanol (78-83-1)

magnesium sulfate (7487-88-9)

borane (7440-42-8)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

hexane (110-54-3)

2-methoxyethanol (109-86-4)

calcium hydride (7789-78-8)

1,2-dimethoxyethane (110-71-4)

phenanthroline

argon (7440-37-1)

tin oxide

tributyltin hydride (688-73-3)

TIN HYDRIDE

Tris[3-(2-methoxyethoxy)propyl]stannane, 2,5,13,16-Tetraoxa-9-stannaheptadecane, 9-[3-(2-methoxyethoxy)propyl]- (130691-03-1)

1-Bromo-3-(2-methoxyethoxy)propane (59551-75-6)

3-(2-Methoxyethoxy)propene (18854-48-3)

Tetra[3-(2-methoxyethoxy)propyl]stannane (130691-01-9)

Bromotris[3-(2-methoxyethoxy)propyl]stannane (130691-02-0)

borane-tetrahydrofuran complex (14044-65-6)

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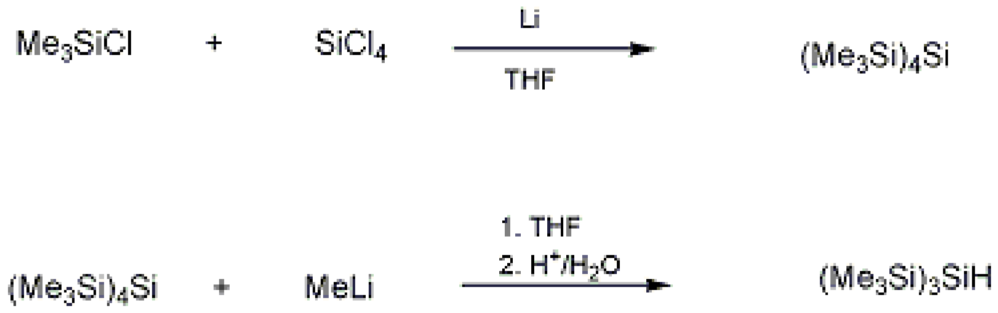
Organic Syntheses, CV 9, 738

TRIS(TRIMETHYLSILYL)SILANE

[Trisilane, 1,1,1,3,3,3-hexamethyl-2-(trimethylsilyl)-]



Submitted by Joachim Dickhaut and Bernd Giese[1].
Checked by George A. O'Doherty and Leo A. Paquette.

1. Procedure

Lithium powder (7.55 g, 1.07 mol) is placed in a 500-mL, four-necked flask equipped with a condenser, mechanical stirrer, dropping funnel, and low-temperature thermometer (Note 1) and (Note 2). The apparatus is carefully flushed several times with nitrogen followed by the addition of 50 mL of anhydrous tetrahydrofuran (THF). The reaction flask is cooled to approximately −60°C in a dry ice-acetone bath, and a mixture of freshly distilled (from CaH_2) chlorotrimethylsilane (54.8 mL, 47.1 g, 0.43 mol) and tetrachlorosilane (Note 3) (10.1 mL, 15.0 g, 0.09 mol) in 140 mL of anhydrous THF is added over 1 hr by dropping funnel so that the temperature of the reaction mixture never exceeds −30°C. After addition is complete, stirring is continued for 0.5 hr with cooling (Note 4). The gold-brown suspension is allowed to warm to room temperature and stirred for 12 hr, during which time the color becomes more intense (Note 5). The thermometer is removed and the mixture is heated to reflux for 2 hr to destroy the remaining chlorotrimethylsilane. After the condenser is cooled to room temperature, it is replaced with a nitrogen bubbler and gas inlet. Methyllithium-lithium bromide complex (66 mL, 99 mmol, 1.5 M in ether) is added over 3 hr to the grey-brown mixture with vigorous stirring (Note 6). During the addition a continuous stream of nitrogen is bubbled through the reaction mixture. After the reaction mixture is stirred for an additional 16 hr at room temperature, it acquires a greenish tint. Hydrolysis is carried out by the careful addition of the reaction mixture to 400 mL of ice-cold 2 N hydrochloric acid. [*CAUTION: The solid residue may be highly pyrophoric. The checkers blanketed the flask with argon prior to the introduction of ether (100 mL) and poured the vigorously stirred slurry into the cold hydrochloric acid. This rinse procedure was repeated twice more.*] The aqueous phase is extracted four times with 200-mL portions of pentane, the combined organic phases are dried over magnesium sulfate and the solvents removed under reduced pressure. Distillation under reduced pressure (1 mm, 38°C) affords 13.4–17.2 g of the product as a clear oil

(60–77% yield).

2. Notes

1. The checkers used a three-necked flask having one arm equipped with a Claisen head.
2. All reagents were purchased from Fluka Chemical Corporation, except the methyllithium-lithium bromide complex, which was purchased from Aldrich Chemical Company, Inc., and were used without further purification. The lithium powder can be weighed in air; however, the use of a dust mask is recommended.
3. As tetrachlorosilane smokes strongly when exposed to air, introduction to the addition funnel is best carried out using a syringe.
4. If the temperature falls below –60°C, the mixture may solidify, but returns to a liquid upon warming.
5. The synthesis should be carried out over three days, stirring the mixture overnight. The stirring times reported should be considered a minimum, and need not be followed exactly.
6. A clean dropping funnel should be used for the addition of the methyllithium solution, and should be filled with rigorous exclusion of air. It is simpler to employ a syringe pump, and replace the dropping funnel with a septum. In this case the stream of nitrogen can be introduced by a needle through the septum.

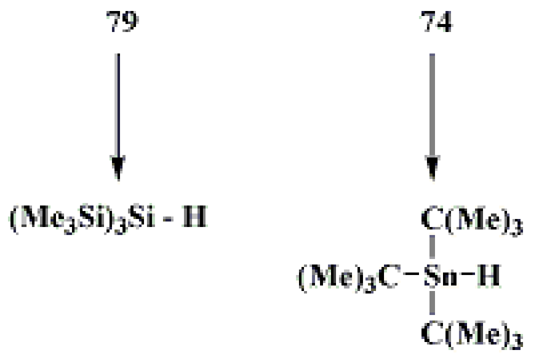
Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

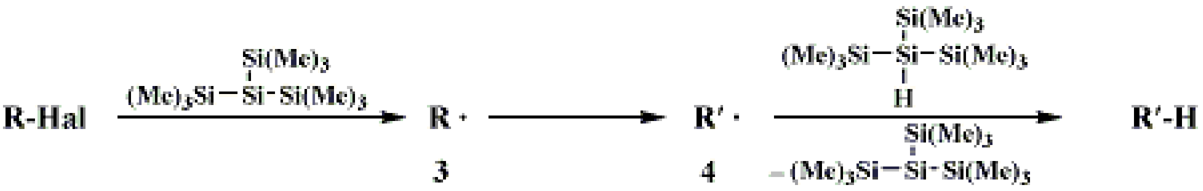
Tris(trimethylsilyl)silane **1** can be substituted for toxic stannanes like tributyl-stannane **2** in organic syntheses which involve radicals,[2] because: a) silyl radicals are as efficient as stannyl radicals in the radical-forming step,[3] and b) the Si-H bond strength in tris(trimethylsilyl)silane 1 is only slightly higher than the Sn-H bond strength in tributylstannane 2.[4]

Bond energy (kcal/mol):



1 2

Thus, heating a mixture of an organic bromide or iodide with equimolar amounts of silane 1 and catalytic amounts of a radical initiator like azobisisobutyronitrile gives organic radicals **3** that can undergo addition, cyclization or rearrangement reactions[2] (**3** **4**) before hydrogen abstraction[5] yields the product.



Tris(trimethylsilyl)silane **1**is a mediator in this reaction. In contrast to the reported method,[6] the synthesis described in this procedure gives silane 1 in high yields in a one-pot reaction.

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

hydrochloric acid (7647-01-0)

ether (60-29-7)

hydrogen (1333-74-0)

nitrogen (7727-37-9)

Pentane (109-66-0)

lithium (7439-93-2)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

Methyllithium (917-54-4)

argon (7440-37-1)

tetrachlorosilane (10026-04-7)

CHLOROTRIMETHYLSILANE (75-77-4)

tributylstannane, tributyl-stannane (688-73-3)

Methyllithium-lithium bromide

azobisisobutyronitrile (78-67-1)

Tris(trimethylsilyl)silane, Trisilane, 1,1,1,3,3,3-hexamethyl-2-(trimethylsilyl)- (1873-77-4)

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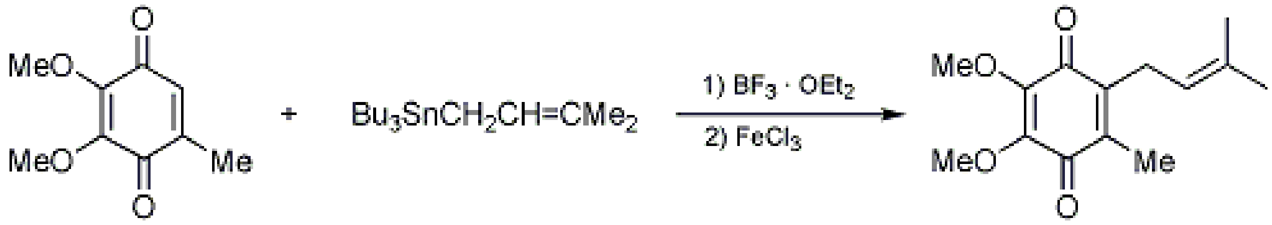
Organic Syntheses, CV 9, 741

UBIQUINONE-1

[2,5-Cyclohexadiene-1,4-dione, 2,3-dimethoxy-5-methyl-6-(3-methyl-2-butenyl)-]



Submitted by Yoshinori Naruta and Kazuhiro Maruyama[1].
Checked by Steven W. Elmore and Leo A. Paquette.

1. Procedure

CAUTION! This experiment should be performed with gloves in an efficient hood in order to avoid the contact of toxic tributyltin derivatives with the skin and to avoid their unpleasant odor.

A 500-mL, three-necked, round-bottomed flask fitted with a low-temperature thermometer, 125-mL pressure-equalizing dropping funnel, and nitrogen gas inlet is flame-dried under vacuum, cooled to room temperature, and flushed with nitrogen. The flask is charged with 5.00 g (27.4 mmol) of 2,3-dimethoxy-5-methyl-1,4-benzoquinone (Note 1) as a solid followed by 100 mL of dry dichloromethane (Note 2) via syringe. The addition funnel is charged with 11.8 g (32.9 mmol) of tributyl(3-methyl-2-butenyl)tin (Note 3) in 100 mL of dry dichloromethane. The flask is immersed in an acetone/dry ice bath, the solution cooled to −78°C, and 10.1 mL (82.3 mmol) of boron trifluoride etherate (Note 4) is added dropwise from a syringe. Next, the stannane solution is added dropwise over a 30-min period. Following completion of the addition, the cooling bath is removed and the reaction mixture is allowed to warm to room temperature. At −40°C, the color of the solution turns from deep red to yellow. When the reaction mixture reaches 0°C, it is treated with 100 mL of 10% hydrochloric acid, stirred for 5 min, and allowed to stand. The aqueous phase that separates is washed with dichloromethane (2 × 20 mL) and the combined organic layers are washed with water (2 × 20 mL) and brine (2 × 20 mL), dried over anhydrous magnesium sulfate, and concentrated. The residual yellow oil is dissolved in 200 mL of ether and this solution is added to 37.1 g (137 mmol) of ferric chloride hexahydrate ($FeCl_3 \cdot 6\ H_2O$) in 200 mL of water in a 500-mL conical flask. The resulting mixture is stirred for 8 hr at room temperature. The layers are then separated, the aqueous phase is extracted with ether (2 × 50 mL), and the combined organic solutions are stirred with 100 mL of 10% aqueous potassium fluoride for 2 hr (Note 5). The insoluble tin salts are separated by filtration (Note 6). The organic phase in the filtrate is washed with water (3 × 20 mL) and brine (3 × 20 mL), dried over anhydrous magnesium sulfate, and concentrated to give a deep red oil, that is purified by column chromatography (Note 7). The red-orange band is collected (1600–

3000 mL) to give 6.15 g (90%) of 2,3-dimethoxy-5-methyl-6-(3-methyl-2-butenyl)-1,4-benzoquinone as a deep red oil (Note 8).

2. Notes

1. Commercial 2,3-dimethoxy-5-methyl-1,4-benzoquinone (Aldrich Chemical Company, Inc.) was used without further purification.
2. Dichloromethane was distilled from phosphorus pentoxide.
3. Tributyl(3-methyl-2-butenyl)tin was prepared by the procedure on p. 707.
4. Boron trifluoride etherate was purchased from Nacalai Tesque or Aldrich Chemical Company, Inc. and used without further purification. Since the purity of the BF_3 complex affects the yield of the quinone, reagent stored for a long period should be distilled prior to its use.
5. This facile method for removing organotin impurities was developed by Keck.[2]
6. Tin wastes are collected and disposed of in an environmentally safe manner. (See Waste Disposal Information below.)
7. A gravity column (7 cm × 15 cm) was packed with 60-230 mesh silica gel. Elution was effected with 10% ethyl acetate in petroleum ether.
8. Spectroscopic data are as follows: ^1H NMR (400 MHz, $CDCl_3$) δ: 1.68 (s, 3 H, cis-CH_3), 1.74 (s, 3 H, trans-CH_3), 2.20 (s, 3 H, ring CH_3), 3.17 (d, 2 H, J = 7.0, CH_2), 3.98 (s, 3 H, CH_3O), 3.99 (s, 3 H, CH_3O), 4.94 (t, 1 H, J = 7.0, C=CH); IR (neat) cm^{-1}: 2790, 1650, 1617, 1455, 1329, 1262, 1555, 1102, 1013.

Waste Disposal Information

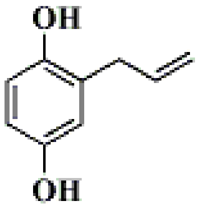
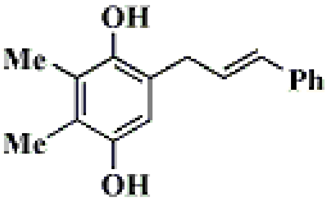
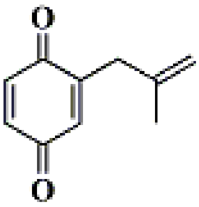
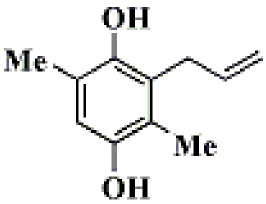
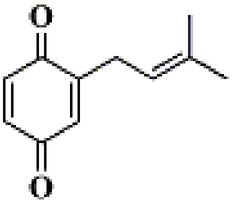
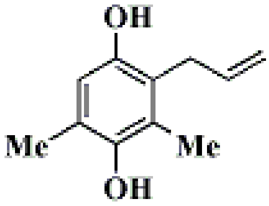
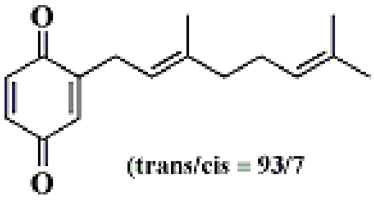
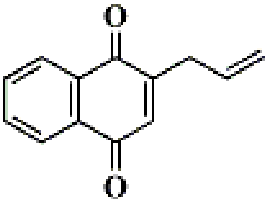
A chloroform solution of toxic tributyltin fluoride was placed in a round-bottomed flask equipped with a reflux condenser, and bromine (3 equiv per Bu_3SnF) was added all at once. After the mixture was stirred for 2–3 days at room temperature, aqueous sodium thiosulfate was added until the brown color of bromine disappeared. The aqueous layer containing inorganic tin compounds was disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

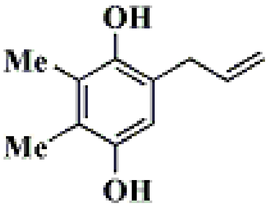
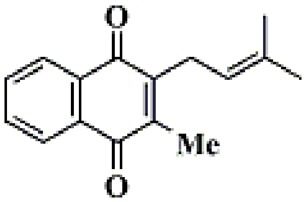
3. Discussion

Ubiquinones are synthesized by the introduction of an isoprenyl side chain to the corresponding quinone or hydroquinone using several compounds: Lewis acid-isoprenyl alcohols,[3] π-allylnickel bromides,[4,5] isoprenyltrialkyltins,[6] N-sulfinylamideisoprenyl alcohols,[7] amalgamated zinc-isoprenyl bromides,[8] and Claisen rearrangement of isoprenyl aryl ethers.[9] Among these procedures, the isoprenyltin method is superior to the others with respect to yield, simplicity of manipulation, and purity of product. This method can be also applied to the synthesis of the higher homologues of ubiquinone-n (n = 2–10). In general, synthesis of allylated quinones or hydroquinones can be performed by the reaction with allylborane,[10] π-allylnickel complexes,[11] allyltrimethylsilane,[12] or allyltrialkyltins.[6,13,14] Direct allylation to the quinone is considered to be the best procedure compared with stepwise methods including protection/deprotection of quinone.[15] The present method is applicable to a broad range of quinones and allylated trialkyltins to give the corresponding

hydroquinone (or quinone after oxidation) in good to excellent yields. Several other examples are shown in the Table. In this reaction, boron trifluoride plays two roles: activation of the quinones resulting in 1,2-addition and acceleration of dienone-phenol rearrangement of the allylic group.[8] In addition this method can be applied to the synthesis of many other polyprenylated quinones,[6,13] including naturally occurring quinones, plastoquinone-n, phylloquinone (vitamin K_1), and menaquinone-n (vitamin $K_{2(n)}$). The polyprenyl side chain can be stereoselectively introduced into a quinone nucleus without formation of the corresponding chromanol or other side chain-cyclized products. Other methods of polyprenyl group introduction to quinones or their protected forms are known: a Friedel-Crafts alkylation,[16] a free-radical alkylation,[17] and coupling reactions with organometallic reagents including lithium,[18] magnesium,[19,20] and tin.[21]

TABLE
PREPARATION OF ALLYLATED QUINONES FROM QUINONES AND ALLYLATED TRIBUTYLTINS

	Yield (%)		Yield (%)
	68		81
	45[a]		90
	55[a]		82
	58[a]		42[a]

 72  78[a]

[a]isolated after oxidation in ether with aqueous $FeCl_3$ solution

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

H_2O

brine

plastoquinone-n

phylloquinone (vitamin K_1)

menaquinone-n (vitamin $K_{2(n)}$)

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

ether (60-29-7)

chloroform (67-66-3)

magnesium (7439-95-4)

bromine (7726-95-6)

sodium thiosulfate (7772-98-7)

nitrogen (7727-37-9)

tin (7440-31-5)

Quinone (106-51-4)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

boron trifluoride (7637-07-2)

ferric chloride hexahydrate (10025-77-1)

potassium fluoride (7789-23-3)

boron trifluoride etherate (109-63-7)

tributyltin (688-73-3)

phosphorus pentoxide (1314-56-3)

allyltrimethylsilane (762-72-1)

tributyltin fluoride

stannane (7440-31-5)

Tributyl(3-methyl-2-butenyl)tin (53911-92-5)

2,3-dimethoxy-5-methyl-1,4-benzoquinone

2,3-dimethoxy-5-methyl-6-(3-methyl-2-butenyl)-1,4-benzoquinone, 2,5-Cyclohexadiene-1,4-dione, 2,3-dimethoxy-5-methyl-6-(3-methyl-2-butenyl)- (727-81-1)

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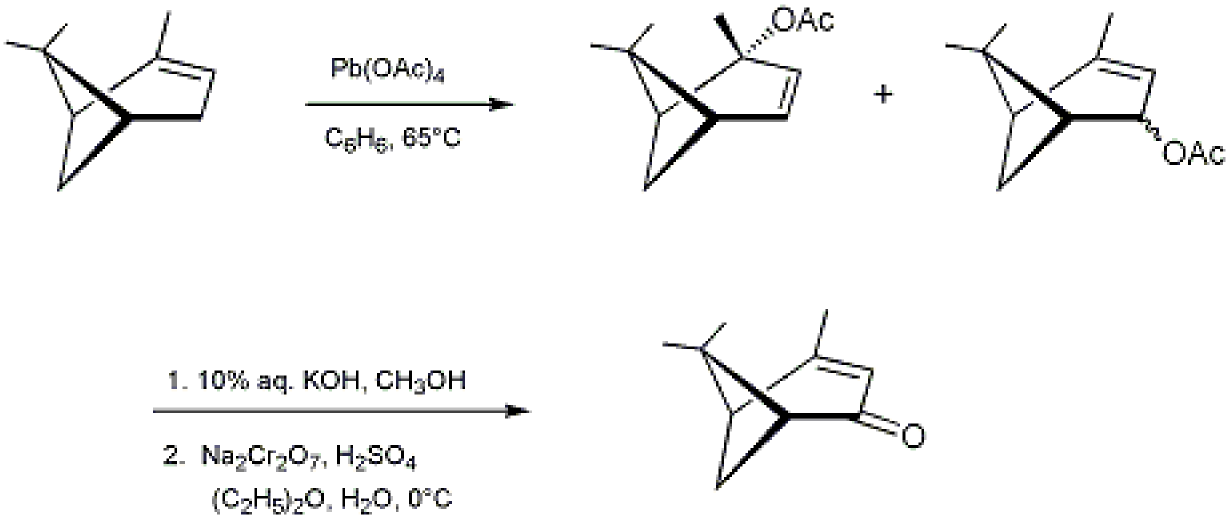
Organic Syntheses, CV 9, 745

(1R,5R)-(+)-VERBENONE OF HIGH OPTICAL PURITY

[Bicyclo[3.1.1]hept-3-en-2-one-, 4,6,6-trimethyl-, (1R)-]



Submitted by Mark R. Sivik, Kenetha J. Stanton, and Leo A. Paquette[1].
Checked by Bradley J. Newhouse and Albert I. Meyers.

1. Procedure

(1R)-(+)-α-Pinene (25.0 g, 0.183 mol, $[\alpha]_D^{20}$ +50.9° (neat), 98.6% ee) (Note 1) and 350 mL of dry benzene (Note 2) are placed in a base-washed, 1000-mL Morton flask fitted with a mechanical stirrer, condenser, internal thermometer, and gas inlet. The flask is set in a heating mantle and warmed to 65°C, at which point lead tetraacetate (77.8 g, 0.175 mol) is added via Gooch tubing over 20 min (Note 3). The reaction mixture becomes bright yellow, this color slowly changing to tan after heating at 65°C with stirring for 1 hr. The solution is cooled to room temperature and filtered through a 1-in pad of Celite. The Celite is washed with several 50-mL portions of benzene. To the filtrate is added 300 mL of water, at which point brown-black lead oxide precipitates (Note 4). The two-phase system is swirled vigorously at 10-min intervals for an hour and then filtered through a 1-in pad of Celite. The layers of the filtrate are separated and the aqueous phase is extracted with three 150-mL portions of ether. The combined organic fractions are dried over magnesium sulfate, filtered, and concentrated by rotary evaporation at room temperature to give a mixture of acetates as a colorless liquid (Note 5).

Without purification, the mixture of acetates is placed in a 250-mL, round-bottomed flask and 150 mL of a 10% potassium hydroxide solution in aqueous methanol is introduced at room temperature. After 24 hr of stirring, the brown mixture is poured into a separatory funnel, diluted with 200 mL of water, and extracted with four 150-

mL portions of ether. The combined ethereal fractions are dried over anhydrous magnesium sulfate, filtered, and concentrated to give a mixture of alcohols (Note 6) as a light yellow oil.

The mixture of alcohols is placed in a 1000-mL round-bottomed flask, dissolved in 300 mL of ether, and cooled to 0°C. To this solution is added via an addition funnel over a 30-min period a mixture of sodium dichromate dihydrate (27.5 g, 0.092 mol), 100 mL of water, and 10.2 mL of concd sulfuric acid. The mixture is stirred at 0°C for 1 hr, warmed to room temperature where stirring is maintained overnight, diluted with 200 mL of water, and poured into a separatory funnel. The layers are separated and the aqueous phase is extracted with ether (3 × 200 mL). The combined organic layers are washed with saturated sodium bicarbonate solution (200 mL) and brine (200 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation to give 16.8–17.8 g (61–65%) of verbenone (Note 7). Final purification is achieved by distillation of the oil through a 5-in Vigreux column at reduced pressure (dry ice-acetone cooled receiver); 13.1 g (47%), bp 108–110°C (5 mm) (Note 8).

2. Notes

1. (1R)-(+)-α-Pinene was purchased from the Aldrich Chemical Company, Inc. The optical purity of the starting material is based on the maximum reported rotation for the dextrorotatory enantiomer: $[\alpha]_D^{20}$ +51.6° (neat).[2] The levoratory form is also available from the same vender in high optical purity.
2. Benzene is reagent grade quality and distilled from sodium/benzophenone ketyl. *This solvent is a suspect carcinogen and should be handled in a well-ventilated hood.*
3. Lead tetraacetate was purchased from the Sigma Chemical Company. *This reagent is highly toxic and should be handled in a well-ventilated hood with gloves.*
4. The checkers did not observe a precipitate on this scale, but it was observed on smaller-scale runs.
5. The tertiary acetate is formed initially[3,4] and constitutes the major component of the mixture that may also contain residual amounts of benzene. Failure to remove all the lead oxide can induce further isomerization to the secondary acetate. To avoid this, a second filtration may be necessary. Although further purification is unnecessary, results in lower yields, and is not recommended, distillation at this point will give 26.8 g (75%) of a colorless oily acetate mixture.
6. Decomposition and lower yields result if this mixture is distilled, since the tertiary isomer loses water on attempted purification.[5] Both alcohols yield the same ketone in the oxidation step.
7. The undistilled product is sufficiently pure for most purposes.
8. The verbenone is clear on distillation but yellows slightly on exposure to air. This does not affect its quality. Radial chromatography (4-mm plate, 10% ethyl acetate/hexane) of a 1-g sample yielded 900 mg of pure verbenone, $[\alpha]_D$ 222.0° (EtOH, *c* 2.00). Column chromatography (200 g of m, 10% ethyl acetate/

hexane) was used to purify verbenone from the small scale preparation. A 43% overall yield was obtained, $[\alpha]_D$ 202.5° (EtOH). The optical rotation of high quality verbenone has been reported by several groups as neat samples.[6,7,8] The percent of enantiomeric excess in the present example is correlated directly to the optical purity of the starting α-pinene.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995. Particular care must be taken in the disposal of waste materials containing lead and chromium compounds.

3. Discussion

In recent years, verbenone has been used with increasing frequency as a convenient "chiral pool" starting material for enantiospecific natural product synthesis[9] and for the preparation of chiral ligands for transition metals.[10] However, a serious deterrent to the use of verbenone in this capacity is the rather low enantiomeric purity of commercially available material (customarily 55–60% ee). The short sequence outlined here provides a ready and convenient means for obtaining (1R, 5R)-(+)-verbenone in high optical purity. Since several firms offer both enantiomers of the α-pinene precursor in high quality (> 98% ee), the present procedure is a direct method for obtaining either essentially pure verbenone enantiomer in reasonable quantities. The possibility of upgrading the optical purity of lower grade α-pinene in advance of its oxidation also exists.[2]

The reaction sequence is based on the readiness with which α-pinene undergoes oxidation predominantly to the tertiary acetate with $Pb(OAc)_4$.[3,4] Dichromate oxidation of the derived alcohol proceeds by way of a second allylic rearrangement to give verbenone without affecting the neighboring stereogenic centers.

References and Notes

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Appendix
Compounds Referenced (Chemical Abstracts Registry Number)

benzophenone ketyl

brine

sulfuric acid (7664-93-9)

Benzene (71-43-2)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether (60-29-7)

sodium bicarbonate (144-55-8)

lead oxide

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

magnesium sulfate (7487-88-9)

chromium (7440-47-3)

sodium dichromate dihydrate (10588-01-9)

hexane (110-54-3)

α-pinene

(1R,5R)-(+)-Verbenone, verbenone, (1R, 5R)-(+)-verbenone (18309-32-5)

Bicyclo[3.1.1]hept-3-en-2-one-, 4,6,6-trimethyl-, (1R)-

lead tetraacetate

(1R)-(+)-α-Pinene

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